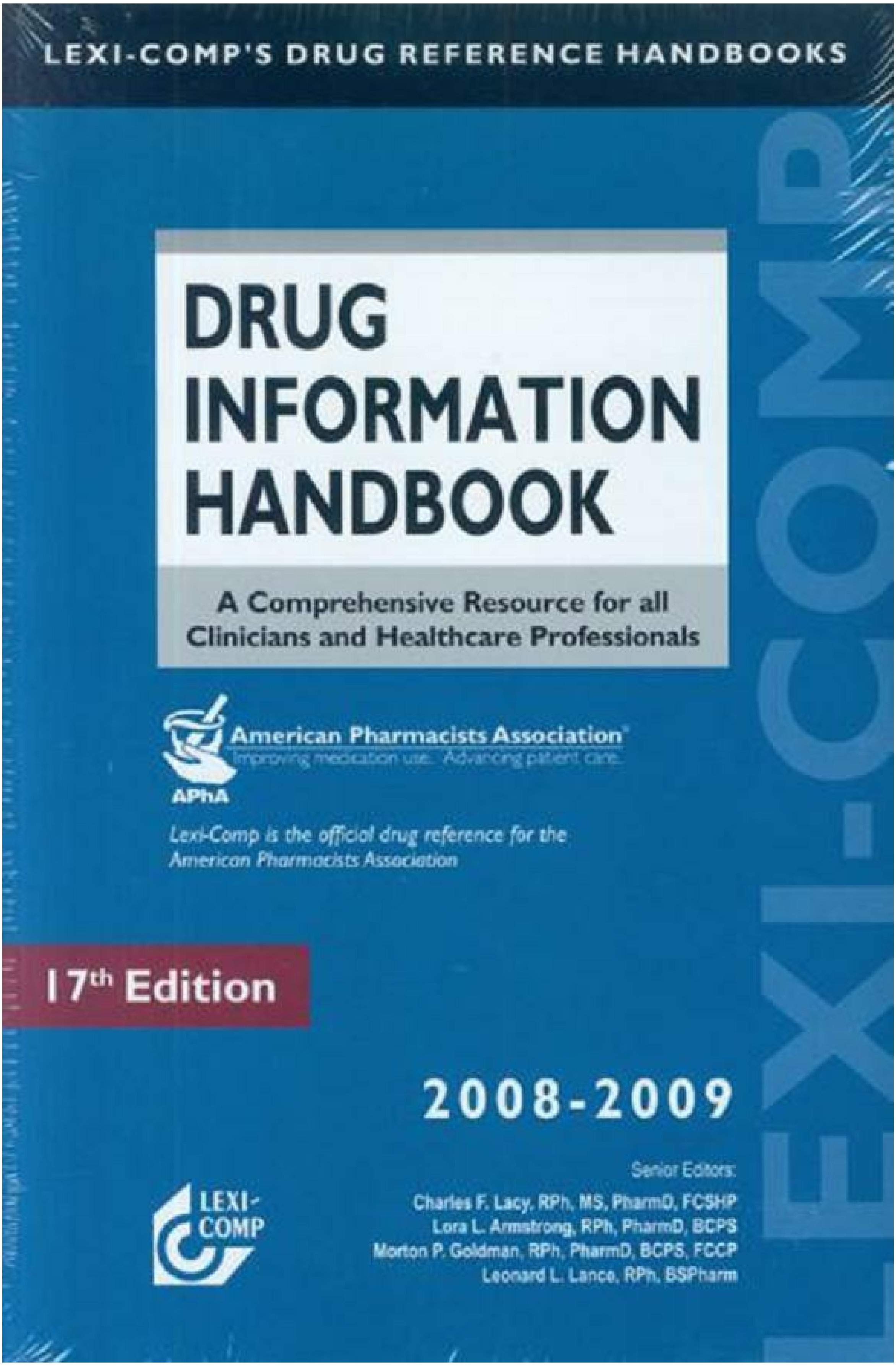

LEXI-COMP'S DRUG REFERENCE HANDBOOKS

DRUG INFORMATION HANDBOOK

A Comprehensive Resource for all Clinicians and Healthcare Professionals

American Pharmacists Association
Improving medication use. Advancing patient care.
APhA

Lexi-Comp is the official drug reference for the American Pharmacists Association

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This data is intended to serve the user as a handy reference and not as a complete drug information resource. It does not include information on every therapeutic agent available. The publication covers over 1700 commonly used drugs and is specifically designed to present important aspects of drug data in a more concise format than is typically found in medical literature or product material supplied by manufacturers.

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PREFACE

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We are fortunate to live in an age where medications are readily available to prevent, treat, and cure a wide variety of conditions. Drugs can also improve the quality of life and prolonging independence. Pharmaceutical innovation continues, and new medications will continue to play an important role in improving the health.

However, new discoveries continue to increase the complexity of medical treatment, as well as monitoring of response. This complexity of therapy often increases the potential for interactions, adverse reactions, and medication errors. Healthcare providers must continually assess the potential risks and benefits of individual medications, as well as the complete therapeutic regimen as it relates to an individual patient.

New molecular entities, new warnings, new interactions and additional drug experience continue to expand, presenting a challenge to maintain a current knowledge base concerning medications. It remains the goal of the authors of Lexi-Comp, Inc to provide you, the user, with the critical information regarding pharmacology and the therapeutic use of drugs in a concise compendium, designed for ease of use by a variety of healthcare professionals. We trust you find the information useful and balanced, and further hope it will assist you in your therapeutic decision-making and drug-therapy monitoring.

DESCRIPTION OF FIELDS

Lexi-Drugs Online

Generic Name	U.S. or Canadian adopted name.
ALERT: U.S. Boxed Warning	The FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.
Special Alerts	Important information (new warnings, adverse reactions, etc) to be conveyed to clinicians expeditiously.
Medication Safety Issue	In an effort to promote the safe use of medications, this field is intended to highlight possible sources of medication errors such as sound-alike/look-alike drugs or highly concentrated formulations which require vigilance on the part of healthcare professionals. In addition, medications which have been associated with severe consequences in the event of a medication error are also identified in this field.
Pronunciation	Phonetic pronunciation guide.
Brand Names	
U.S. Brand Names	Trade names found in the United States (manufacturer-specific).
Canadian Brand Names	Trade names found in Canada.
Pharmacologic Category	Unique systematic classification of medications.
Uses	
Use: Labeled Indications	Information pertaining to approved FDA- or Canadian-approved indications for the drug.
Use: Unlabeled/Investigational	Information pertaining to unlabeled or investigational indications of the drug.
Use: Dental	Information pertaining to appropriate dentistry-specific indications of the drug.
Dosages	
Dosing: • Adults • Elderly • Pediatric • Renal Impairment • Hepatic Impairment	The amount of the drug to be typically given or taken during therapy for children and adults; also includes any dosing adjustment/comments for renal impairment or hepatic impairment and other suggested dosing adjustments (eg, hematological toxicity). Combination regimens identify how the drug may be used in combination with other agents for the treatment of neoplastic disease. Calculations relevant

• Adjustment for Toxicity • Combination Regimens • Calculations	to dosing are also provided.
Oncology: Bone Marrow - High Dose	Chemotherapy doses 1.5- to 30-fold greater than standard dosages. Nonhematologic adverse reactions are dose-limiting.
Administration and Storage Issues	
Administration: • I.M. • I.V. • I.V. Detail • Oral • Inhalation • Topical • Other	Information regarding the recommended final concentrations, rates of administration for parenteral drugs, or other guidelines when giving the medication.
Dietary Considerations	Specific dietary modifications and/or restrictions.
Storage Reconstitution Compatibility	Information regarding storage and stability of product and reconstitution guidance (where necessary). Provides the time and conditions for which a solution or mixture will maintain full potency. For example, some solutions may require refrigeration after reconstitution while stored at room temperature prior to preparation. Also includes compatibility information, when available, for admixtures, Y-site administration, and syringe storage.
Extemporaneously Prepared	Directions for preparing liquid formulations from solid drug products. May include stability information and references.
Warnings & Precautions	
Restrictions	The controlled substance classification from the Drug Enforcement Agency (DEA). U.S. schedules are I-V. Schedules vary by country and sometimes state (eg, Massachusetts uses I-VI). May also include restricted availability information.
Contraindications	Information pertaining to inappropriate use of the drug as dictated by approved labeling.
Allergy Considerations	Information relating to spectrum of reactions noted with a true drug allergy; also describes timing of reactions, potential for cross-hypersensitivity, and patient management considerations.
Warnings/Precautions	Precautionary considerations, hazardous conditions related to use of the drug, and disease states or patient populations in which the drug should be cautiously used. Boxed warnings, when present, are clearly identified and are adapted from the FDA approved labeling. Consult the product labeling for the exact black box warning through the manufacturer's or

	the FDA website.
Geriatric Considerations	Pertinent information specific to older adults.
Pregnancy & Lactation	
Pregnancy Risk Factor	Five categories established by the FDA to indicate the potential of a systemically absorbed drug for causing risk to fetus.
Pregnancy Considerations	A summary of human and/or animal information pertinent to or associated with the use of the drug as it relates to clinical effects on the fetus, newborn, or pregnant women.
Lactation	Indicates if the drug listed in the monograph is present in breast milk and the manufacturers recommendation for use while breast-feeding (where recommendation of American Academy of Pediatrics differs, notation is made).
Breast-feeding Considerations	Information pertinent to or associated with the human use of the drug as it relates to clinical effects on the nursing infant or postpartum woman.
Pregnancy & Lactation, In-Depth	Detailed information on the effects of the medication on the fetus, newborn, and/or breast-feeding infant, as well as use of the drug in pregnant and postpartum women.
Adverse Reactions	
Adverse Reactions	Side effects are grouped by percentage of incidence (if known) and/or body system, <1% effects are grouped only by percentage (Note: Includes postmarketing and/or case report information if available).
Oncology-related Reactions	
Oncology: Vesicant	Indicates whether the drug is considered to be a vesicant and likely to cause significant morbidity if the infusion infiltrates soft tissues.
Oncology: Emetic Potential	Likelihood that the drug will cause nausea or vomiting.
Oncology: Bone Marrow - Unique Toxicity	Nonhematologic adverse reactions that occur commonly with, or are unique to, high-dose chemotherapy administration.
Interactions	
Metabolism/Transport Effects	If a drug has demonstrated involvement with cytochrome P450 enzymes, or other metabolism or transport proteins, this field will identify the drug as an inhibitor, inducer, or substrate of the specific enzyme(s) (eg, CYP1A2 or UGT1A1). CYP450 isoenzymes are identified as substrates (minor or major), inhibitors (weak, moderate, or strong), and inducers (weak or strong).
	This field presents a description of the interaction

Drug Interactions	between the drug listed in the monograph and other drugs or drug classes. Following a description of the interaction for a drug class, any drugs from that class which are NOT likely to cause a similar interaction with the monograph drug are listed as exceptions. Lastly, the significance of the interaction is identified in the form of a risk rating. A brief description of the rating system is as follows (please note that the risk levels of *A* and *B* exist, reflecting no known interactions or clinically-insignificant interactions, respectively; however, for brevity, these interactions are not displayed in printed form: *Risk C: Monitor therapy* – data demonstrate that the specified agents may interact with each other in a clinically-significant manner, but the benefits of concomitant use usually outweigh any risks. An appropriate monitoring plan should be implemented to identify potential negative effects and dosage adjustments may be needed in a minority of patients. *Risk D: Consider therapy modification* - data demonstrate that the specified agents may interact with each other in a clinically-significant manner and patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize toxicity of concomitant use. *Risk X: Avoid combination* - data demonstrate that the specified agents may interact with each other in a clinically-significant manner and the risk generally outweighs any potential benefit. Concurrent use of these agents is generally considered contraindicated.
Ethanol/Nutrition/Herb Interactions	Presents a description of the interaction between the drug listed in the monograph and ethanol, food, or herb/nutraceuticals.
Test Interactions	Listing of assay interferences when relevant.
Patient & Therapy Management	
Monitoring Parameters	Laboratory tests and patient physical parameters that should be monitored for safety and efficacy of drug therapy.
Reference Range	Therapeutic and toxic serum concentrations listed including peak and trough levels.
Nursing Considerations	
Nursing: Physical Assessment/Monitoring	Monitoring guidelines for laboratory tests and patient physical parameters; includes caregiver guidance relating to administration issues and patient teachings that facilitate safe and efficacious therapy.
Monitoring: Lab Tests	Suggested laboratory tests to monitor for safety and efficacy of the drug.
Patient Education	Specific information pertinent for the patient.
Preparations	
Product Availability	Provides availability information on products that have been approved by the FDA, but not yet available for use. Estimates for when a product may be available are included, when this information is known. May

	also provide any unique or critical drug availability issues (eg, drug shortage of a critical drug).
Dosage Forms	Information with regard to form, strength, and availability of the drug. Note: Additional formulation information (eg, excipients, preservatives) is included when available. Please consult product labeling for further information.
Generic Available	Indicates availability of generic product(s).
Manufacturer	Identifies product manufacturer only if there is a sole supplier.
Pricing: U.S. (www.drugstore.com)	Third party supplier of drug pricing based on estimated average retail prices.
Pharmacology & Pharmacokinetics	
Mechanism of Action	How the drug works in the body to elicit a response.
Pharmacodynamics/Kinetics	The magnitude of a drug's effect depends on the drug concentration at the site of action. The pharmacodynamics are expressed in terms of onset of action and duration of action. Pharmacokinetics are expressed in terms of absorption, distribution (including appearance in breast milk and crossing of the placenta), protein binding, metabolism, bioavailability, half-life, time to peak serum concentration, and elimination.
Pearls and Related Information	
Related Information	Cross-reference links to other pertinent, related drug information.
Pharmacotherapy Pearls	Information about sodium content and/or pertinent information about specific brands.
Dental Info	
Dental Health Professional Considerations	Pharmacology-related comments and considerations relevant to the dental professional.
Dental Health: Effects on Dental Treatment	Specific information for the dental professional on how drug therapy affects the dental treatment/diagnosis with suggested management approaches.
Dental Health: Vasoconstrictor/Local Anesthetic Precautions	Specific information for the dental health professional to prevent potential drug interactions related to anesthesia.
Mental Health Info	
Mental Health: Effect on Mental Status	Specific information for the mental health professional indicating pertinent drug effects which may affect or alter a patient's mental status.
Mental Health: Effect on Psychiatric Treatment	Specific information for the mental health professional relative to the impact on psychiatric treatment.

Mental Health: Child/Adolescent Considerations	Specific information for the mental health professional relative to clinical trials for children and adolescent patients.
Cardiovascular Considerations	This field provides a focused summary of some of the important issues concerning cardiovascular applications, outcomes, side effects, interactions, and recent developments relevant to the drug.
Anesthesia and Critical Care Concerns/Other Considerations	This field provides a focused summary of some of the important issues concerning anesthesia and critical care applications relevant to the drug; other additional information may be included.
Oncology: Bone Marrow Comments	Additional information relating to myelosuppressive toxicities anticipated with the drug.
Index Terms	Other names or accepted abbreviations of the generic drug.
References	Literature or source used in preparing the monograph.
International Brand Names	Trade names found throughout various international markets.

The following countries are included in the International Brand Names field and are abbreviated as follows:

Argentina (AR)

Australia (AU)

Austria (AT)

Belgium (BE)

Brazil (BR)

Bulgaria (BG)

Canada (CA)

Chile (CL)

China (CN)

Colombia (CO)

Costa Rica (CR)

Croatia / Hrvatska (HR)

Czech Republic (CZ)

Denmark (DK)

Egypt (EG)

Finland (FI)

France (FR)

Germany (DE)

Great Britain [UK] (GB)

Greece (GR)

Hong Kong (HK)

Hungary (HU)

Iceland (IS)

India (IN)

Ireland (IE)

Israel (IL)

Italy (IT)

Japan (JP)

Jordan (JO)

Korea [South] (KR)

Kuwait (KW)

Lebanon (LB)

Malaysia (MY)

Mexico (MX)

Monaco (MC)

Netherlands (NL)

New Zealand [Aotearoa] (NZ)

Norway (NO)

Poland (PL)

Portugal (PT)

Puerto Rico (PR)

Romania (RO)

Russian Federation (RU)

Singapore (SG)

Slovak Republic (SK)

Slovenia (SI)

South Africa (ZA)

Spain (ES)

Sweden (SE)

Switzerland (ST)

Syria (SY)

Taiwan (TW)

Thailand (TH)

Turkey (TR)

Ukraine (UA)

United States (US)

Venezuela (VE)

Yugoslavia (YU)

FDA PREGNANCY CATEGORIES

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Throughout this book there is a field labeled Pregnancy Risk Factor and the letter A, B, C, D, or X immediately following which signifies a category. The FDA has established these five categories to indicate the potential of a systemically absorbed drug for causing birth defects. The key differentiation among the categories rests upon the reliability of documentation and the risk:benefit ratio. Pregnancy Category X is particularly notable in that if any data exists that may implicate a drug as a teratogen and the risk:benefit ratio is clearly negative, the drug is contraindicated during pregnancy.

These categories are summarized as follows:

A	Controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester with no evidence of risk in later trimesters. The possibility of fetal harm appears remote.
B	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters.
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in

	women, or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

SAFE WRITING

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Health professionals and their support personnel frequently produce handwritten copies of information they see in print; therefore, such information is subjected to even greater possibilities for error or misinterpretation on the part of others. Thus, particular care must be given to how drug names and strengths are expressed when creating written healthcare documents.

The following are a few examples of safe writing rules suggested by the Institute for Safe Medication Practices, Inc.[1]

1. There should be a space between a number and its units as it is easier to read. There should be no periods after the abbreviations mg or mL.

Correct	Incorrect
10 mg	10mg
100 mg	100mg

2. Never place a decimal and a zero after a whole number (2 mg is correct and 2.0 mg is **incorrect**). If the decimal point is not seen because it falls on a line or because individuals are working from copies where the decimal point is not seen, this causes a tenfold overdose.
3. Just the opposite is true for numbers less than one. Always place a zero before a naked decimal (0.5 mL is correct, .5 mL is **incorrect**).
4. Never abbreviate the word unit. The handwritten U or u, looks like a 0 (zero), and may cause a tenfold overdose error to be made.
5. IU is not a safe abbreviation for international units. The handwritten IU looks like IV. Write out international units or use int. units.
6. Q.D. is not a safe abbreviation for once daily, as when the Q is followed by a sloppy dot, it looks like QID which means four times daily.
7. O.D. is not a safe abbreviation for once daily, as it is properly interpreted as meaning “right eye” and has caused liquid medications such as saturated solution of potassium iodide and Lugol's solution to be administered incorrectly. There is no safe abbreviation for once daily. It must be written out in full.
8. Do not use chemical names such as 6-mercaptopurine or 6-thioguanine, as sixfold overdoses have been given when these were not recognized as chemical names. The proper names of these drugs are mercaptopurine or thioguanine.
9. Do not abbreviate drug names (5FC, 6MP, 5-ASA, MTX, HCTZ, CPZ, PBZ, etc) as they are misinterpreted and cause error.
10. Do not use the apothecary system or symbols.
11. Do not abbreviate microgram as µg; instead use mcg as there is less likelihood of misinterpretation.
12. When writing an outpatient prescription, write a complete prescription. A complete prescription can prevent the prescriber, the pharmacist, and/or the patient from making a mistake and can eliminate the need for further clarification. The legible prescriptions should contain:
    a. patient's full name
    b. for pediatric or geriatric patients: their age (or weight where applicable)
    c. drug name, dosage form and strength; if a drug is new or rarely prescribed, print this information
    d. number or amount to be dispensed
    e. complete instructions for the patient, including the purpose of the medication
    f. when there are recognized contraindications for a prescribed drug, indicate to the pharmacist that you are aware of this fact (ie, when prescribing a potassium salt for a patient receiving an ACE inhibitor, write “K serum level being monitored”)

[1] From “Safe Writing” by Davis NM, PharmD and Cohen MR, MS, Lecturers and Consultants for Safe Medication Practices, 1143 Wright Drive, Huntington Valley, PA 19006. Phone: (215) 947-7566.

FDA NAME DIFFERENTIATION PROJECT: THE USE OF TALL-MAN LETTERS

Lexi-Drugs Online

Confusion between similar drug names is an important cause of medication errors. For years, The Institute For Safe Medication Practices (ISMP), has urged generic manufacturers to use a combination of large and small letters as well as bolding (ie, chlorpro**MAZINE** and chlorpro**PAMIDE**) to help distinguish drugs with look-alike names, especially when they share similar strengths. Recently the FDA's Division of Generic Drugs began to issue recommendation letters to manufacturers suggesting this novel way to label their products to help reduce this drug name confusion. Although this project has had marginal success, the method has successfully eliminated problems with products such as diphenhydr**AMINE** and dimenhy**DRINATE**. Hospitals should also follow suit by making similar changes in their own labels, preprinted order forms, computer screens and printouts, and drug storage location labels.

Lexi-Comp Medical Publishing will use “Tall-Man” letters for the drugs suggested by the FDA or recommended by ISMP.

The following is a list of generic product names and recommended revisions.

Drug Product	**Recommended Revision**
acetazolamide	aceta**ZOLAMIDE**
acetohexamide	aceto**HEXAMIDE**
alprazolam	**ALPRAZ**olam
amiloride	a**MIL**oride
amlodipine	am**LODIP**ine
azacitidine	aza**CITID**ine
azathioprine	aza**THIO**prine
bupropion	bu**PROP**ion
buspirone	bus**PIR**one
carbamazepine	car**BAM**azepine
carboplatin	**CARBO**platin
cefazolin	ce**FAZ**olin
ceftriaxone	cef**TRIAX**one
chlordiazepoxide	chlordiaze**POXIDE**
chlorpromazine	chlorpro**MAZINE**
chlorpropamide	chlorpro**PAMIDE**
cisplatin	**CIS**platin
clomiphene	clomi**PHENE**
clomipramine	clomi**PRAMINE**
clonazepam	clonaze**PAM**

clonidine	clo**NID**ine
cycloserine	cyclo**SERINE**
cyclosporine	cyclo**SPORINE**
dactinomycin	**DACTIN**omycin
daptomycin	**DAPTO**mycin
daunorubicin	**DAUNO**rubicin
dimenhydrinate	dimenhy**DRINATE**
diphenhydramine	diphenhydr**AMINE**
dobutamine	**DOBUT**amine
dopamine	**DOP**amine
doxorubicin	**DOXO**rubicin
duloxetine	**DUL**oxetine
ephedrine	e**PHED**rine
epinephrine	**EPINEPH**rine
fentanyl	fenta**NYL**
fluoxetine	**FLU**oxetine
glipizide	glipi**ZIDE**
glyburide	gly**BURIDE**
guaifenesin	guai**FEN**esin
guanfacine	guan**FACINE**
hydralazine	hydr**ALAZINE**
hydrocodone	**HYDRO**codone
hydromorphone	**HYDRO**morphone
hydroxyzine	hydr**OXY**zine
idarubicin	**IDA**rubicin
infliximab	in**FLIX**imab
lamivudine	lami**VUD**ine

lamotrigine	lamo**TRI**gine
lorazepam	**LOR**azepam
medroxyprogesterone	medroxy**PROGESTER**one
metformin	met**FORMIN**
methylprednisolone	methyl**PREDNIS**olone
methyltestosterone	methyl**TESTOSTER**one
metronidazole	metro**NIDAZOLE**
nicardipine	ni**CAR**dipine
nifedipine	**NIFE**dipine
nimodipine	ni**MOD**ipine
olanzapine	**OLANZ**apine
oxcarbazepine	**OX**carbazepine
oxycodone	oxy**CODONE**
paroxetine	**PAR**oxetine
pentobarbital	**PENT**obarbital
phenobarbital	**PHEN**obarbital
prednisolone	predniso**LONE**
prednisone	predni**SONE**
quetiapine	**QUE**tiapine
quinidine	qui**NID**ine
quinine	qui**NINE**
rituximab	ri**TUX**imab
sitagliptin	sita**GLIP**tin
sufentanil	**SUF**entanil
sulfadiazine	sulf**ADIAZINE**
sulfisoxazole	sulfi**SOXAZOLE**

sumatriptan	**SUMA**triptan
tiagabine	tia**GAB**ine
tizanidine	ti**ZAN**idine
tolazamide	**TOLAZ**amide
tolbutamide	**TOLBUT**amide
tramadol	tra**MAD**ol
trazodone	tra**ZOD**one
vinblastine	vin**BLAS**tine
vincristine	vin**CRIS**tine

Institute for Safe Medication Practices. “New Tall-Man Lettering Will Reduce Mix-Ups Due to Generic Drug Name Confusion,” *ISMP Medication Safety Alert*, September 19, 2001. Available at: http://www.ismp.org.

Institute for Safe Medication Practices. “Prescription Mapping, Can Improve Efficiency While Minimizing Errors With Look-Alike Products,” *ISMP Medication Safety Alert*, October 6, 1999. Available at: http://www.ismp.org.

Institute for Safe Medication Practices. "Use of Tall Man Letters Is Gaining Wide Acceptance," *ISMP Medication Safety Alert*, July 31, 2008. Available at: http://www.ismp.org.

U.S. Pharmacopeia, “USP Quality Review: Use Caution-Avoid Confusion,” March 2001, No. 76. Available at: http://www.usp.org.

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid
Regimen UseLeukemia, acute myeloid (induction)
Index TermsCytarabine-Daunorubicin (5 + 2); Daunorubicin-Cytarabine (5 + 2)
Regimen

Cytarabine: I.V.: 100-200 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 500-1000 mg/m^2]

with

Daunorubicin: I.V.: 45 mg/m^2/day days 1 and 2

[total dose/cycle = 90 mg/m^2]

References

Rai KR, Holland JF, Glidewell OJ, et al, âTreatment of Acute Myelocytic Leukemia: A Study by Cancer and Leukemia Group B,â *Blood*, 1981, 58(6):1203-12.[PubMed 6946847]

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7 + 3 (Daunorubicin)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid

Regimen UseLeukemia, acute myeloid (induction)

Index TermsCytarabine-Daunorubicin (7 + 3)

Regimen

Cytarabine: I.V.: 100 mg/m^2/day continuous infusion days 1 to 7

[total dose/cycle = 700 mg/m^2]

Daunorubicin: I.V.: 45 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 135 mg/m^2]

Administer one cycle only

References

Dilman RO, Davis RB, Green MR, et al, “A Comparative Study of Two Different Doses of Cytarabine for Acute Myeloid Leukemia: A Phase III Trial of Cancer and Leukemia Group B,” *Blood*, 1991, 78(10):2520-6. [PubMed 1824249]

Preisler H, Davis RB, Kirschner J, et al, “Comparison of Three Remission Induction Regimens and Two Postinduction Strategies for the Treatment of Acute Nonlymphocytic Leukemia: A Cancer and Leukemia Group B Study,” *Blood*, 1987, 69(5):1441-9. [PubMed 3552076]

Rai KR, Holland JF, Glidewell OJ, et al, “Treatment of Acute Myelocytic Leukemia: A Study by Cancer and Leukemia Group B,” *Blood*, 1981, 58(6):1203-12. [PubMed 6946847]

Vogler WR, Velez-Garcia E, Weiner RS, et al, “A Phase III Trial Comparing Idarubicin and Daunorubicin in Combination With Cytarabine in Acute Myelogenous Leukemia: A Southeastern Cancer Study Group Study,” *J Clin Oncol*, 1992, 10(7):1103-11. [PubMed 1607916]

Yates J, Glidewell O, Wiernik P, et al, “Cytosine Arabinoside With Daunorubicin or Adriamycin® for Therapy of Acute Myelocytic Leukemia: A CALGB Study,” *Blood*, 1982, 60(2):454-62. [PubMed 6953986]

Yates JW, Wallace HJ Jr, Ellison RR, et al, “Cytosine Arabinoside (NSC-63878) and Daunorubicin (NSC-83142) Therapy in Acute Nonlymphocytic Leukemia,” *Cancer Chemother Rep*, 1973, 57(4):485-8.[PubMed 4586956]

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7 + 3 (Idarubicin)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid
Regimen UseLeukemia, acute myeloid (induction)
Index TermsCytarabine-Idarubicin (7 + 3)

Regimen

Cytarabine: I.V.: 100-200 mg/m^2/day continuous infusion days 1 to 7

[total dose/cycle = 700 - 1400 mg/m^2]

Idarubicin: I.V.: 12 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 36 mg/m^2]

Administer one cycle only

References

Vogler WR, Velez-Garcia E, Weiner RS, et al, âA Phase III Trial Comparing Idarubicin and Daunorubicin in Combination With Cytarabine in Acute Myelogenous Leukemia: A Southeastern Cancer Study Group Study,â *J Clin Oncol*, 1992, 10(7):1103-11.[PubMed 1607916]

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7 + 3 (Mitoxantrone)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid

Regimen UseLeukemia, acute myeloid (induction)

Index TermsCytarabine-Mitoxantrone (7 + 3)

Regimen

Cytarabine: I.V.: 100-200 mg/m^2/day continuous infusion days 1 to 7

[total dose/cycle = 700-1400 mg/m^2]

Mitoxantrone: I.V.: 12 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 36 mg/m^2]

Administer one cycle only

References

Arlin Z, Case DC Jr, Moore J, et al, âRandomized Multicenter Trial of Cytosine Arabinoside With Mitoxantrone or Daunorubicin in Previously Untreated Adult Patients With Acute Nonlymphocytic Leukemia (ANLL),â Lederle Cooperative Group, *Leukemia*, 1990, 4(3):177-83.[PubMed 2179638]

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Leukemia, Acute Myeloid]

Regimen UseLeukemia, acute myeloid

Index TermsCytarabine-Daunorubicin-Etoposide (7 + 3 + 7)

Regimen

Cytarabine: I.V.: 100 mg/m^2/day continuous infusion days 1 to 7

[total dose/cycle = 700 mg/m^2]

Daunorubicin: I.V.: 50 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 150 mg/m^2]

Etoposide: I.V.: 75 mg/m^2/day days 1 to 7

[total dose/cycle = 525 mg/m^2]

Repeat cycle every 21 days; up to 3 cycles may be given based on individual response

References

Bishop JF, Lowenthal RM, Joshua D, et al, âEtoposide in Acute Nonlymphocytic Leukemia, Australian Leukemia Study Group,â *Blood*, 1990, 75(1):27-32.[PubMed 2403818]

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8 in 1 (Brain Tumors)

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Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Brain Tumors

Regimen Use Brain tumors

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Methylprednisolone: I.V.: 300 mg/m^2 every 6 hours day 1 (3 doses)

[total dose/cycle = 900 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2 (maximum 2 mg) day 1

Lomustine: Oral: 75 mg/m^2 day 1

Procarbazine: Oral: 75 mg/m^2 day 1; 1 hour after methylprednisolone and vincristine

Hydroxyurea: Oral: 3000 mg/m^2 day 1; 2 hours after methylprednisolone and vincristine

Cisplatin: I.V.: 90 mg/m^2 day 1; 3 hours after methylprednisolone and vincristine

Cytarabine: I.V.: 300 mg/m^2 day 1; 9 hours after methylprednisolone and vincristine

Dacarbazine: I.V.: 150 mg/m^2 day 1; 12 hours after methylprednisolone and vincristine

Repeat cycle every 14 days

Variation 2:

Methylprednisolone: I.V.: 300 mg/m^2 every 6 hours day 1 (3 doses)

[total dose/cycle = 900 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2 (maximum 2 mg) day 1

Lomustine: Oral: 75 mg/m^2 day 1

Procarbazine: Oral: 75 mg/m^2 day 1; 1 hour after methylprednisolone and vincristine

Hydroxyurea: Oral: 3000 mg/m^2 day 1; 2 hours after methylprednisolone and vincristine

Cisplatin: I.V.: 60 mg/m^2 day 1; 3 hours after methylprednisolone and vincristine

Cytarabine: I.V.: 300 mg/m^2 day 1; 9 hours after methylprednisolone and vincristine

Cyclophosphamide: I.V.: 300 mg/m^2 day 1; 12 hours after methylprednisolone and vincristine

Repeat cycle every 14 days

References

Pendergrass TW, Milstein JM, Geyer JR, et al, âEight Drugs in One Day Chemotherapy for Brain Tumors: Experience in 107 Children and Rationale for Preradiation Chemotherapy,â *J Clin Oncol*, 1987, 5(8):1221-31.[PubMed 3040919]

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8 in 1 (Retinoblastoma)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Retinoblastoma]

Regimen UseRetinoblastoma

Regimen

Vincristine: I.V.: 1.5 mg/m^2 day 1

Methylprednisolone: I.V.: 300 mg/m^2 day 1

Lomustine: Oral: 75 mg/m^2 day 1

Procarbazine: Oral: 75 mg/m^2 day 1

Hydroxyurea: Oral: 1500 mg/m^2 day 1

Cisplatin: I.V.: 60 mg/m^2 day 1

Cytarabine: I.V.: 300 mg/m^2 day 1

Repeat cycle every 28 days

References

Doz F, Khelfaoui F, Mosseri V, et al, âThe Role of Chemotherapy in Orbital Involvement of Retinoblastoma. The Experience of a Single Institution With 33 Patients,â *Cancer*, 1994, 74(2):722-32.[PubMed 8033054]

AAV (DD)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Wilms' Tumor

Regimen Use Wilms' tumor

Regimen

Dactinomycin: I.V.: 15 mcg/kg/day days 1 to 5 of weeks 0, 13, 26, 39, 52, and 65

[total dose/cycle = 450 mcg/kg]

Doxorubicin: I.V.: 20 mg/m^2/day days 1, 2, and 3 of weeks 6, 19, 32, 45, and 58

[total dose/cycle = 300 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2 day 1 of weeks 0-10, 13, 14, 26, 27, 39, 40, 52, 53, 65, and 66

[total dose/cycle = 31.5 mg/m^2]

References

D'Angio GJ, Breslow N, Beckwith JB, et al, “Treatment of Wilms' Tumor. Results of the Third National Wilms' Tumor Study,” *Cancer*, 1989, 64(2):349-60.[PubMed 2544249]

Abacavir, Lamivudine, and Zidovudine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Abacavir and Abacavir-Containing Products: Boxed Warning Update Concerning Increased Risk of Hypersensitivity Reactions in Patients with *HLA-B*5701* Allele - July 2008

The Food and Drug Administration (FDA) is requesting the manufacturer of abacavir and abacavir-containing products to update the boxed warning concerning serious hypersensitivity reactions. The update includes a recommendation to test all patients for the presence of the *HLA-B*5701* allele prior to initiating therapy or resuming therapy in patients of unknown *HLA-B*5701* status, including patients previously tolerating therapy. Patients testing positive for the presence of this genotype are at an increased risk for serious hypersensitivity reactions. If a patient tests positive for the presence of the *HLA-B*5701* allele, abacavir is **not** recommended and an alternative agent should be selected. If a suspected abacavir hypersensitivity reaction occurs during therapy, regardless of *HLA-B*5701* status, abacavir should be discontinued immediately and permanently.

Additional information may be found at http://www.fda.gov/medwatch.safety/2008/safety08.htm#Abacavir

Abacavir-Containing Products: Increased Risk of Myocardial Infarction Observed; Health Canada Issues Alert to Canadian Healthcare Professionals - June 2008

The Canadian Dear Healthcare Provider letter can be found at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/abacavir_hpc-cps-eng.php

FDA Early Communication: Increased Risk of Myocardial Infarction Observed - March 2008

The Food and Drug Administration (FDA) has issued an Early Communication to patients, caregivers, and healthcare professionals informing them of new evidence regarding the use of abacavir (Ziagen®) and didanosine (Videx®) and the risk of myocardial infarction (MI). Analysis from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study, an observational study aimed at investigating the adverse effects of certain nucleoside reverse transcriptase inhibitors (NRTI) involving over 33,000 patients, suggests that patients taking Ziagen® or Videx® appear to be at an increased risk for MI in comparison to other NRTIs. The risk of MI appears to be greatest with recent use (within 6 months) and in patients with existing risk factors for heart disease (eg, hypercholesterolemia, hypertension, diabetes, smoking, and age). In addition, the risk of MI appears to be reversible upon discontinuation of the offending agents. Patients taking abacavir (Ziagen®) may have up to a 90% increase in their risk of MI according to study results.

The FDA emphasizes that these are preliminary results of the D:A:D study and urges healthcare providers to weigh the potential risks and benefits of every treatment option until further results become available.

Additional information is available at http://www.fda.gov/cder/drug/early_comm/abacavir.htm

Pronunciation(a BAK a veer, la MI vyoo deen, & zye DOE vyoo deen)

U.S. Brand NamesTrizivir®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)

Use: Labeled IndicationsTreatment of HIV infection (either alone or in combination with other antiretroviral agents) in patients whose regimen would otherwise contain the components of Trizivir®

Dosing: AdultsHIV treatment: Oral: 1 tablet twice daily. **Note:** Not recommended for patients <40 kg.

Dosing: ElderlyUse with caution.

Dosing: PediatricHIV treatment: Adolescents: Refer to adult dosing (not recommended for patients <40 kg).

Dosing: Renal ImpairmentCl_{cr} ≤50 mL/minute: Avoid use.

Dosing: Hepatic ImpairmentUse contraindicated.

Calculations

- Creatinine Clearance: Adults

Administration: OralAdminister without regard to food or water.

Dietary ConsiderationsMay be taken without regard to food or water.

StorageStore at room temperature 15°C to 30°C (59°F to 86°F).

RestrictionsAn FDA-approved medication guide and warning card (summarizing symptoms of hypersensitivity) must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to abacavir, lamivudine, zidovudine, or any component of the formulation; hepatic impairment. Do not rechallenge patients who have experienced hypersensitivity to abacavir.

Allergy Considerations

- Abacavir Allergy
- LamiVUDine Allergy
- Zidovudine Allergy

Warnings/Precautions

Boxed warnings:

- Chronic hepatitis B: See “Disease-related concerns” below.
- Hematologic toxicity: See “Concerns related to adverse effects” below.
- HIV: Appropriate use: See “Disease-related concerns” below.
- Hypersensitivity reactions: See “Concerns related to adverse effects” below.
- Lactic acidosis/hepatomegaly: See “Concerns related to adverse effects” below.
- Myopathy: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Hematologic toxicity: **[U.S. Boxed Warning]: Zidovudine has been associated with hematologic toxicities (eg, neutropenia, anemia);** use with caution in patients with bone marrow compromise.
- Hypersensitivity reactions: **[U.S. Boxed Warning]: Fatal hypersensitivity reactions have occurred in patients taking abacavir (in Trizivir®).** Patients testing positive for the presence of the *HLA-B*5701* allele are at an increased risk for hypersensitivity reactions. Screening for *HLA-B*5701* allele status is recommended prior to initiating abacavir-containing therapy or reinitiating therapy in patients of unknown status, including patients who previously tolerated abacavir therapy. Trizivir® is **not** recommended in patients testing positive for the *HLA-B*5701* allele. Patients exhibiting symptoms of fever, skin rash, fatigue, respiratory symptoms (eg, pharyngitis, dyspnea, cough) and/or GI symptoms (eg, abdominal pain, nausea, vomiting, diarrhea) should discontinue therapy immediately and call for medical attention. Trizivir® should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible and regardless of *HLA-B*5701* status. Trizivir® SHOULD NOT be restarted because more severe symptoms may occur within hours, including LIFE-THREATENING HYPOTENSION AND DEATH. Fatal hypersensitivity reactions have occurred following the reintroduction of abacavir in patients whose therapy was interrupted (eg, interruption in drug supply, temporary discontinuation while treating other conditions). Reactions occurred within hours. In some cases, signs of hypersensitivity may have been previously present, but attributed to other medical conditions (eg, acute onset respiratory diseases, gastroenteritis, reactions to other medications). If Trizivir® is to be restarted following an interruption in therapy, first evaluate the patient for previously unsuspected symptoms of hypersensitivity. Do not restart if hypersensitivity is suspected or cannot be ruled out. To report these events on Trizivir® hypersensitivity, a registry has been established (1-800-270-0425).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).
- Myopathy: **[U.S. Boxed Warning]: Prolonged use of zidovudine has been associated with symptomatic myopathy and myositis.**

Disease-related concerns:

- Chronic hepatitis B: **[U.S. Boxed Warning]: Exacerbation of hepatitis B has been reported with discontinuation of lamivudine in coinfected HIV/HBV patients;** monitor hepatic function closely for several months after discontinuing Trizivir® in coinfected patients.
- Coronary heart disease: Use caution in patients with risks for coronary heart disease; modifiable risk factors (eg, hypertension, hyperlipidemia, diabetes mellitus, and smoking) should be minimized prior to use.
- HIV: Appropriate use: **[U.S. Boxed Warning]: This combination should only be used as part of a multidrug regimen for which the individual components are indicated.**
- Renal impairment: Trizivir®, as a fixed-dose combination tablet, should not be used in patients with Cl_{cr} ≤50 mL/minute.

Concurrent drug therapy issues:

- Interferon alfa: Use with caution in combination with interferon alfa with or without ribavirin in HIV/HBV coinfected patients; monitor closely for hepatic decompensation, anemia, or neutropenia; dose reduction or discontinuation of interferon and/or ribavirin may be required if toxicity evident.

Special populations:

- Adults <40 kg: Trizivir®, as a fixed-dose combination tablet, should not be used in patients <40 kg or those requiring dosage adjustment.

- Pediatrics: Trizivir®, as a fixed-dose combination tablet, should not be used in children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsSee individual agents.

LactationSee individual agents.

Breast-Feeding ConsiderationsSee individual agents.

Adverse ReactionsFatal hypersensitivity reactions have occurred in patients taking abacavir (in Trizivir®). If Trizivir® is to be restarted following an interruption in therapy, first evaluate the patient for previously unsuspected symptoms of hypersensitivity. Do not restart if hypersensitivity is suspected or if hypersensitivity cannot be ruled out.

The following information is based on CNA3005 study data concerning effects noted in patients receiving abacavir, lamivudine, and zidovudine. See individual agents for additional information.

>10%:

Central nervous system: Headache (13%), malaise (12%), fatigue (12%)

Gastrointestinal: Nausea (19%)

1% to 10%:

Central nervous system: Fever/chills (6%), depression (6%), anxiety (5%)

Dermatologic: Rash (5%)

Endocrine & metabolic: Triglycerides increased (2% grade 3-4)

Gastrointestinal: Nausea and vomiting (10%), diarrhea (7%), amylase increased (2%)

Hematologic: Neutropenia (5%)

Hepatic: ALT increased (6%)

Neuromuscular & skeletal: CPK increased (7%)

Miscellaneous: Hypersensitivity (2% to 9% based on abacavir component), ear/nose/throat infection (5), viral infection (5%)

Other (frequency unknown): Pancreatitis, GGT increased, fat redistribution, immune reconstitution syndrome

Drug Interactions

Acyclovir-Valacyclovir: May enhance the CNS depressant effect of Zidovudine. *Risk C: Monitor therapy*

DOXOrubicin: May enhance the adverse/toxic effect of Zidovudine. DOXOrubicin may diminish the therapeutic effect of Zidovudine. *Risk D: Consider therapy modification*

DOXOrubicin (Liposomal): May enhance the adverse/toxic effect of Zidovudine. DOXOrubicin (Liposomal) may diminish the therapeutic effect of Zidovudine. *Risk D: Consider therapy modification*

Emtricitabine: LamiVUDine may enhance the adverse/toxic effect of Emtricitabine. *Risk X: Avoid combination*

Fluconazole: May decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Ganciclovir-Valganciclovir: May enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. *Risk D: Consider therapy modification*

Interferons: May enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Methadone: May increase the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Probenecid: May decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the serum concentration of Abacavir. *Risk C: Monitor therapy*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Zidovudine. **Exceptions:** Rifabutin. *Risk D: Consider therapy modification*

Stavudine: Zidovudine may diminish the therapeutic effect of Stavudine. *Risk D: Consider therapy modification*

Trimethoprim: May decrease the excretion of LamiVUDine. *Risk C: Monitor therapy*

Valproic Acid: May decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Zalcitabine: LamiVUDine may diminish the therapeutic effect of Zalcitabine. *Risk D: Consider therapy modification*

Monitoring ParametersCBC with differential, serum creatine kinase, CD4 count, HIV RNA plasma levels, bilirubin, serum transaminases, triglycerides, serum amylase; *HLA-B*5701* genotype status prior to initiation of therapy and prior to reinitiation of therapy in patients of unknown *HLA-B*5701* status; signs and symptoms of hypersensitivity, particularly in patients untested for the *HLA-B*5701* allele; signs and symptoms of pancreatitis; observe for appearance of opportunistic infections

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsCBC with differential, serum creatine kinase, CD4 count, HIV RNA plasma levels, bilirubin, serum transaminases, triglycerides, serum amylase; *HLA-B*5701* genotype status prior to initiation of therapy and prior to reinitiation of therapy in patients of unknown *HLA-B*5701* status

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Trizivir®: Abacavir 300 mg, lamivudine 150 mg, and zidovudine 300 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Trizivir)

300-150-300 mg (60): $1271.45

Mechanism of ActionThe combination of abacavir, lamivudine, and zidovudine is believed to act synergistically to inhibit reverse transcriptase via DNA chain termination after incorporation of the nucleoside analogue as well as to delay the emergence of mutations conferring resistance.

Pharmacodynamics/KineticsBioavailability studies of Trizivir® show no difference in AUC or C_{max} when compared to abacavir, lamivudine, and zidovudine given together as individual agents. See individual agents.

Related Information

- Abacavir
- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- LamiVUDine
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV
- Zidovudine

Pharmacotherapy PearlsHypersensitivity testing (*HLA-B*5701*): Prevalence of hypersensitivity reactions has been estimated at 5% to 8% in Caucasians and 2% to 3% in African-Americans. Pretherapy identification of *HLA-B*5701*-positive patients, and subsequent avoidance of abacavir therapy in these patients has been shown to reduce the occurrence of abacavir-mediated hypersensitivity reactions. A skin patch test is in development for clinical screening purposes; however, only PCR-mediated genotyping methods are currently in clinical practice use for documentation of this susceptibility marker.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia

Mental Health: Effects on Psychiatric TreatmentGastrointestinal side effects are common; these effects may be additive with concurrent use of SSRIs, lithium, or valproate. The hypnotic effect of the benzodiazepines may be diminished. Valproic acid may decrease the clearance of zidovudine. Increase in triglycerides is common and may be additive with clozapine, olanzapine, or quetiapine. May cause pancreatitis; use caution with valproic acid and atypical antipsychotics. May increase GGT; use caution with olanzapine and valproic acid. May cause aplastic anemia; use caution with clozapine and carbamazepine. Suspected Stevens-Johnson syndrome (SJS) has been reported in patients receiving abacavir in combination with medications known to be associated with SJS (lamotrigine).

Index Terms3TC, Abacavir, and Zidovudine; Azidothymidine, Abacavir, and Lamivudine; AZT, Abacavir, and Lamivudine; Compound S, Abacavir, and Lamivudine; Lamivudine, Abacavir, and Zidovudine; ZDV, Abacavir, and Lamivudine; Zidovudine, Abacavir, and Lamivudine

References

“Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection,” January 29, 2008. Available at http://www.aidsinfo.nih.gov

Lucas A, Nolan D, and Mallal S, “HLA-B*5701 Screening for Susceptibility to Abacavir Hypersensitivity,” *J Antimicrob Chemother*, 2007, 59(4):591-3.[PubMed 17317695]

“Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States,” October 12, 2006. Available at: http://www.aidsinfo.nih.gov.

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” February 28, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesTricivir (AR, CN); Trivudin (AR); Trizivir (AT, AU, BE, BG, CH, CL, CO, CR, CZ, DE, DK, FI, FR, GB, GR, HK, HN, IE, IL, IT, MX, NL, NO, PE, PT, RU, SE, TR, TW, UY, VE)

Abacavir and Lamivudine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Abacavir and Abacavir-Containing Products: Boxed Warning Update Concerning Increased Risk of Hypersensitivity Reactions in Patients with *HLA-B*5701* Allele - July 2008

The Food and Drug Administration (FDA) is requesting the manufacturer of abacavir and abacavir-containing products to update the boxed warning concerning serious hypersensitivity reactions. The update includes a recommendation to test all patients for the presence of the *HLA-B*5701* allele prior to initiating therapy or resuming therapy in patients of unknown *HLA-B*5701* status, including patients previously tolerating therapy. Patients testing positive for the presence of this genotype are at an increased risk for serious hypersensitivity reactions. If a patient tests positive for the presence of the *HLA-B*5701* allele, abacavir is **not** recommended and an alternative agent should be selected. If a suspected abacavir hypersensitivity reaction occurs during therapy, regardless of *HLA-B*5701* status, abacavir should be discontinued immediately and permanently.

Additional information may be found at http://www.fda.gov/medwatch.safety/2008/safety08.htm#Abacavir

Abacavir-Containing Products: Increased Risk of Myocardial Infarction Observed; Health Canada Issues Alert to Canadian Healthcare Professionals - June 2008

The Canadian Dear Healthcare Provider letter can be found at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/abacavir_hpc-cps-eng.php

FDA Early Communication: Increased Risk of Myocardial Infarction Observed - March 2008

The Food and Drug Administration (FDA) has issued an Early Communication to patients, caregivers, and healthcare professionals informing them of new evidence regarding the use of abacavir (Ziagen®) and didanosine (Videx®) and the risk of myocardial infarction (MI). Analysis from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study, an observational study aimed at investigating the adverse effects of certain nucleoside reverse transcriptase inhibitors (NRTI) involving over 33,000 patients, suggests that patients taking Ziagen® or Videx® appear to be at an increased risk for MI in comparison to other NRTIs. The risk of MI appears to be greatest with recent use (within 6 months) and in patients with existing risk factors for heart disease (eg, hypercholesterolemia, hypertension, diabetes, smoking, and age). In addition, the risk of MI appears to be reversible upon discontinuation of the offending agents. Patients taking abacavir (Ziagen®) may have up to a 90% increase in their risk of MI according to study results.

The FDA emphasizes that these are preliminary results of the D:A:D study and urges healthcare providers to weigh the potential risks and benefits of every treatment option until further results become available.

Additional information is available at http://www.fda.gov/cder/drug/early_comm/abacavir.htm

Pronunciation(a BAK a veer & la MI vyoo deen)

U.S. Brand NamesEpzicom®

Canadian Brand NamesKivexa™

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)

Use: Labeled IndicationsTreatment of HIV infections in combination with other antiretroviral agents

Dosing: AdultsHIV: Oral: One tablet (abacavir 600 mg and lamivudine 300 mg) once daily

Dosing: Renal ImpairmentCl_{cr} <50 mL/minute: Use not recommended

Dosing: Hepatic ImpairmentUse contraindicated.

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

RestrictionsAn FDA-approved medication guide and warning card (summarizing symptoms of hypersensitivity) must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to abacavir, lamivudine, or any component of the formulation; hepatic impairment. Do not rechallenge patients who have experienced hypersensitivity to abacavir.

Allergy Considerations

- Abacavir Allergy
- LamiVUDine Allergy

Warnings/Precautions

Boxed warnings:

- Chronic hepatitis B: See “Disease-related concerns” below.
- HIV: Appropriate use: See “Disease-related concerns” below.
- Hypersensitivity reactions: See “Concerns related to adverse effects” below.
- Lactic acidosis/hepatomegaly: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Hypersensitivity reactions: **[U.S. Boxed Warning]: Fatal hypersensitivity reactions have occurred in patients taking abacavir (in Epzicom®).** Patients testing positive for the presence of the *HLA-B*5701* allele are at an increased risk for hypersensitivity reactions. Screening for *HLA-B*5701* allele status is recommended prior to initiating abacavir-containing therapy or reinitiating therapy in patients of unknown status, including patients who previously tolerated abacavir therapy. Epzicom® is **not** recommended in patients testing positive for the *HLA-B*5701* allele. Patients exhibiting symptoms of fever, skin rash, fatigue, respiratory symptoms (eg, pharyngitis, dyspnea, cough) and/or GI symptoms (eg, abdominal pain, nausea, vomiting, diarrhea) should discontinue therapy immediately and call for medical attention. Epzicom® should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible and regardless of *HLA-B*5701* status. Epzicom® SHOULD NOT be restarted because more severe symptoms may occur within hours, including LIFE-THREATENING HYPOTENSION AND DEATH. Fatal hypersensitivity reactions have occurred following the reintroduction of abacavir in patients whose therapy was interrupted (eg, interruption in drug supply, temporary discontinuation while treating other conditions). Reactions occurred within hours. In some cases, signs of hypersensitivity may have been previously present, but attributed to other medical conditions (eg, acute onset respiratory diseases, gastroenteritis, reactions to other medications). If Epzicom® is to be restarted following an interruption in therapy, first evaluate the patient for previously unsuspected symptoms of hypersensitivity. Do not restart if hypersensitivity is suspected or cannot be ruled out. To report these events on Epzicom® hypersensitivity, a registry has been established (1-800-270-0425).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).

Disease-related concerns:

- Coronary heart disease: Use caution in patients with risks for coronary heart disease; modifiable risk factors (eg, hypertension, hyperlipidemia, diabetes mellitus, and smoking) should be minimized prior to use.
- Chronic hepatitis B: **[U.S. Boxed Warning]: Following discontinuation of lamivudine, severe acute exacerbations of hepatitis B in patients coinfected with HBV and HIV have been reported.** Monitor patients closely for several months following discontinuation of therapy for chronic hepatitis B; clinical exacerbations may occur.
- HIV: Appropriate use: **[U.S. Boxed Warning]: This combination should only be used as part of a multidrug regimen for which the individual components are indicated.**
- Renal impairment: Due to fixed dose of combination product, use is not recommended with renal impairment (Cl_{cr} <50 mL/minute).

Concurrent drug therapy issues:

- Interferon alfa: Use with caution in combination with interferon alfa with or without ribavirin in HIV/HBV coinfected patients; monitor closely for hepatic decompensation, anemia, or neutropenia; dose reduction or discontinuation of interferon and/or ribavirin may be required if toxicity evident.

Special populations:

- Pediatrics: Due to fixed dose of combination product, use is not recommended in children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsSee individual agents.

LactationSee individual agents.

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV. See individual agents.

Adverse ReactionsSee individual agents.

Postmarketing and/or case reports: Alopecia, anaphylaxis, anemia, aplastic anemia, breath sounds abnormal, CPK increased, erythema multiforme, fat redistribution, hepatic steatosis, hepatitis B exacerbation, hyperglycemia, hypersensitivity reaction, lactic acidosis, lymphadenopathy, muscle weakness, pancreatitis, paresthesia, peripheral neuropathy, rhabdomyolysis, seizure, splenomegaly, Stevens-Johnson syndrome, stomatitis, urticaria, weakness, wheezing

Drug Interactions

Emtricitabine: LamiVUDine may enhance the adverse/toxic effect of Emtricitabine. *Risk X: Avoid combination*

Ganciclovir-Valganciclovir: May enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the serum concentration of Abacavir. *Risk C: Monitor therapy*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Trimethoprim: May decrease the excretion of LamiVUDine. *Risk C: Monitor therapy*

Zalcitabine: LamiVUDine may diminish the therapeutic effect of Zalcitabine. *Risk D: Consider therapy modification*

Monitoring ParametersAmylase, bilirubin, liver enzymes, hematologic parameters, viral load, and CD4 count; *HLA-B*5701* genotype status prior to initiation of therapy and prior to reinitiation of therapy in patients of unknown *HLA-B*5701* status; signs and symptoms of hypersensitivity, particularly in patients untested for the *HLA-B*5701* allele

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsAmylase, bilirubin, liver enzymes, hematologic parameters, viral load, and CD4 count,*HLA-B*5701* genotype status prior to initiation of therapy and prior to reinitiation of therapy in patients of unknown *HLA-B*5701* status

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Epzicom®: Abacavir 600 mg and lamivudine 300 mg

Generic AvailableNo

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Tablets (Epzicom)

600-300 mg (30): $870.93

Mechanism of ActionNucleoside reverse transcriptase inhibitor combination.

Abacavir is a guanosine analogue which is phosphorylated to carbovir triphosphate which interferes with HIV viral RNA-dependent DNA polymerase resulting in inhibition of viral replication.

Lamivudine is a cytosine analog. After lamivudine is triphosphorylated, the principle mode of action is inhibition of HIV reverse transcription via viral DNA chain termination; inhibits RNA-dependent DNA polymerase activities of reverse transcriptase.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Abacavir
- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- LamiVUDine
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV

Pharmacotherapy PearlsA high rate of early virologic nonresponse was observed when abacavir, lamivudine, and tenofovir were used as the initial regimen in treatment-naive patients. Use of this combination is not recommended; patients currently on this regimen should be closely monitored for modification of therapy.

Hypersensitivity testing (*HLA-B*5701*): Prevalence of hypersensitivity reactions has been estimated at 5% to 8% in Caucasians and 2% to 3% in African-Americans. Pretherapy identification of *HLA-B*5701*-positive patients, and subsequent avoidance of abacavir therapy in these patients has been shown to reduce the occurrence of abacavir-mediated hypersensitivity reactions. A skin patch test is in development for clinical screening purposes; however, only PCR-mediated genotyping methods are currently in clinical practice use for documentation of this susceptibility marker.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, abnormal dreams, dizziness, depression, fatigue, lethargy, malaise, insomnia, and headache

Mental Health: Effects on Psychiatric TreatmentSide effects mimic depressive symptoms; use caution with benzodiazepines, CNS depressants, or antidepressants. May rarely cause neutropenia; use caution with clozapine and carbamazepine.

Index TermsAbacavir Sulfate and Lamivudine; Lamivudine and Abacavir

References

"Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection," January 29, 2008. Available at http://www.aidsinfo.nih.gov

Lucas A, Nolan D, and Mallal S, "HLA-B*5701 Screening for Susceptibility to Abacavir Hypersensitivity," *J Antimicrob Chemother*, 2007, 59(4):591-3.[PubMed 17317695]

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection," February 28, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesKivexa (AR, AT, AU, BE, BG, CH, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, MX, NL, NO, PT, RU, SE, TH, TR, TW, UY)

Abacavir

Lexi-Drugs Online

English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Abacavir and Abacavir-Containing Products: Boxed Warning Update Concerning Increased Risk of Hypersensitivity Reactions in Patients with *HLA-B*5701* Allele - July 2008

The Food and Drug Administration (FDA) is requesting the manufacturer of abacavir and abacavir-containing products to update the boxed warning concerning serious hypersensitivity reactions. The update includes a recommendation to test all patients for the presence of the *HLA-B*5701* allele prior to initiating therapy or resuming therapy in patients of unknown *HLA-B*5701* status, including patients previously tolerating therapy. Patients testing positive for the presence of this genotype are at an increased risk for serious hypersensitivity reactions. If a patient tests positive for the presence of the *HLA-B*5701* allele, abacavir is **not** recommended and an alternative agent should be selected. If a suspected abacavir hypersensitivity reaction occurs during therapy, regardless of *HLA-B*5701* status, abacavir should be discontinued immediately and permanently.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Abacavir

Abacavir-Containing Products: Increased Risk of Myocardial Infarction Observed; Health Canada Issues Alert to Canadian Healthcare Professionals - June 2008

The Canadian Dear Healthcare Provider letter can be found at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/abacavir_hpc-cps-eng.php

FDA Early Communication: Increased Risk of Myocardial Infarction Observed - March 2008

The Food and Drug Administration (FDA) has issued an Early Communication to patients, caregivers, and healthcare professionals informing them of new evidence regarding the use of abacavir (Ziagen®) and didanosine (Videx®) and the risk of myocardial infarction (MI). Analysis from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study, an observational study aimed at investigating the adverse effects of certain nucleoside reverse transcriptase inhibitors (NRTI) involving over 33,000 patients, suggests that patients taking Ziagen® or Videx® appear to be at an increased risk for MI in comparison to other NRTIs. The risk of MI appears to be greatest with recent use (within 6 months) and in patients with existing risk factors for heart disease (eg, hypercholesterolemia, hypertension, diabetes, smoking, and age). In addition, the risk of MI appears to be reversible upon discontinuation of the offending agents. Patients taking abacavir (Ziagen®) may have up to a 90% increase in their risk of MI according to study results.

The FDA emphasizes that these are preliminary results of the D:A:D study and urges healthcare providers to weigh the potential risks and benefits of every treatment option until further results become available.

Additional information is available at http://www.fda.gov/cder/drug/early_comm/abacavir.htm

Pronunciation(a BAK a veer)

U.S. Brand NamesZiagen®

Canadian Brand NamesZiagen®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)

Use: Labeled IndicationsTreatment of HIV infections in combination with other antiretroviral agents

Dosing: AdultsHIV treatment: Oral: 300 mg twice daily or 600 mg once daily in combination with other antiretroviral agents

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricHIV treatment: Oral: 3 months to 16 years: 8 mg/kg body weight twice daily (maximum: 300 mg twice daily) in combination with other antiretroviral agents

Dosing: Hepatic Impairment

Mild dysfunction (Child-Pugh score 5-6): 200 mg twice daily (oral solution is recommended)

Moderate-to-severe dysfunction: Use is contraindicated by the manufacturer

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore oral solution and tablets at controlled room temperature of 20°C to 25°C (68°F to 77°F). Oral solution may be refrigerated; do not freeze.

RestrictionsAn FDA-approved medication guide and warning card (summarizing symptoms of hypersensitivity) must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to abacavir or any component of the formulation (do not rechallenge patients who have experienced hypersensitivity to abacavir); moderate-to-severe hepatic impairment

Allergy Considerations

- Abacavir Allergy

Warnings/Precautions

Boxed warnings:

- Hypersensitivity reactions: See "Concerns related to adverse effects" below.
- Lactic acidosis/hepatomegaly: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Hypersensitivity reactions: **[U.S. Boxed Warning]: Serious and sometimes fatal hypersensitivity reactions have occurred.** Patients testing positive for the presence of the *HLA-B*5701* allele are at an increased risk for hypersensitivity reactions. Screening for *HLA-B*5701* allele status is recommended prior to initiating therapy or reinitiating therapy in patients of unknown status, including patients who previously tolerated therapy. Therapy is **not** recommended in patients testing positive for the *HLA-B*5701* allele. Patients exhibiting symptoms from two or more of the following: Fever, skin rash, constitutional symptoms (malaise, fatigue, aches), respiratory symptoms (eg, pharyngitis, dyspnea, cough), and GI symptoms (eg, abdominal pain, diarrhea, nausea, vomiting) should discontinue therapy immediately and call for medical attention. Abacavir should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible and regardless of *HLA-B*5701* status. Abacavir SHOULD NOT be restarted because more severe symptoms may occur within hours, including LIFE-THREATENING HYPOTENSION AND DEATH. Fatal hypersensitivity reactions have occurred following the reintroduction of abacavir in patients whose therapy was interrupted (ie, interruption in drug supply, temporary discontinuation while treating other conditions). Reactions occurred within hours. In some cases, signs of hypersensitivity may have been previously present, but attributed to other medical conditions (eg, acute onset respiratory diseases, gastroenteritis, reactions to other medications). If abacavir is restarted following an interruption in therapy, evaluate the patient for previously unsuspected symptoms of hypersensitivity. Do not restart if hypersensitivity is suspected or if hypersensitivity cannot be ruled out. To report these events on abacavir hypersensitivity, a registry has been established (1-800-270-0425).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).

Disease-related concerns:

- Coronary heart disease: Use caution in patients with risks for coronary heart disease; modifiable risk factors (eg, hypertension, hyperlipidemia, diabetes mellitus, and smoking) should be minimized prior to use.
- Hepatic impairment: Use with caution in patients with mild hepatic dysfunction (contraindicated in moderate-to-severe dysfunction).
- HIV: Appropriate use: Abacavir should always be used as a component of a multidrug regimen.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <3 months of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsIt is not known if abacavir crosses the human placenta. No increased risk of overall birth defects has been observed following 1st trimester exposure according to data collected by the antiretroviral pregnancy registry. Cases of lactic acidosis/hepatic steatosis syndrome have been reported in pregnant women receiving nucleoside analogues. It is not known if pregnancy itself potentiates this known side effect; however, pregnant women may be at increased risk of lactic acidosis and liver damage. Hepatic enzymes and electrolytes should be monitored frequently during the 3rd trimester of pregnancy in women receiving nucleoside analogues. Dose adjustment is not needed for pregnancy. The Perinatal HIV Guidelines Working Group considers abacavir to be an alternative NRTI in dual nucleoside combination regimens. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse ReactionsHypersensitivity reactions (which may be fatal) occur in ~5% of patients (see Warnings/Precautions). Symptoms may include anaphylaxis, fever, rash (including erythema multiforme), fatigue, diarrhea, abdominal pain; respiratory symptoms (eg, pharyngitis, dyspnea, cough, adult respiratory distress syndrome, or respiratory failure); headache, malaise, lethargy, myalgia, myolysis, arthralgia, edema, paresthesia, nausea and vomiting, mouth ulcerations, conjunctivitis, lymphadenopathy, hepatic failure, and renal failure.

Note: Rates of adverse reactions were defined during combination therapy with other antiretrovirals (lamivudine and efavirenz **or** lamivudine and zidovudine). Only reactions which occurred at a higher frequency in adults (except where noted) than in the comparator group are noted.

Adverse reaction rates attributable to abacavir alone are not available.

>10%:

- Central nervous system: Headache (7% to 13%)
- Gastrointestinal: Nausea (7% to 19%, children 9%)

1% to 10%:

- Central nervous system: Depression (6%), fever/chills (6%, children 9%), anxiety (5%)
- Dermatologic: Rash (5% to 6%, children 7%)
- Endocrine & metabolic: Triglycerides increased (2% to 6%)
- Gastrointestinal: Diarrhea (7%), vomiting (children 9%), amylase increased (2%)
- Hematologic: Thrombocytopenia (1%)
- Hepatic: AST increased (6%)
- Neuromuscular & skeletal: Musculoskeletal pain (5% to 6%)
- Miscellaneous: Hypersensitivity reactions (2% to 9%; may include reactions to other components of antiretroviral regimen), infection (EENT 5%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Erythema multiforme, fat redistribution, GGT increased, hepatic steatosis, hepatomegaly, hepatotoxicity, lactic acidosis, MI, pancreatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Drug Interactions

Ganciclovir-Valganciclovir: May enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the serum concentration of Abacavir. *Risk C: Monitor therapy*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Ethanol may increase the risk of toxicity.

Monitoring ParametersCBC with differential, serum creatine kinase, CD4 count, HIV RNA plasma levels, serum transaminases, triglycerides, serum amylase; *HLA-B*5701* genotype status prior to initiation of therapy and prior to reinitiation of therapy in patients of unknown *HLA-B*5701* status; signs and symptoms of hypersensitivity, particularly in patients untested for the *HLA-B*5701* allele

Nursing: Physical Assessment/MonitoringAssess closely for any previous exposure/allergy to abacavir and evaluate risk factors for heart disease prior to beginning treatment. Assess other pharmacological or herbal products patient may be taking for potential interactions or toxicity; dosing adjustments may be necessary. A list of medications that should not be used is available in each bottle and patients should be provided with this information. **Note:** Patient must be closely monitored for any sign of hypersensitivity reaction which can occur within hours or at any time and may be fatal (can occur also at reintroduction with patients who have no history of previous reaction) (See Warnings/Precautions). Assess results of laboratory tests and effectiveness of therapy (decrease in infections and progress of disease; viral load and CD4 count) periodically during therapy. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions, and importance of immediately reporting any sign of hypersensitivity or myocardial infarction.

Monitoring: Lab TestsCBC with differential, serum creatine kinase, CD4 count, HIV RNA plasma levels, serum transaminases, triglycerides, serum amylase; *HLA-B*5701* genotype status prior to initiation of therapy and prior to reinitiation of therapy in patients of unknown *HLA-B*5701* status

Patient EducationYou will be provided with a medication guide (identifying medications that should not be used during therapy) and a warning card (summarizing symptoms of hypersensitivity). Do not take any new prescriptions, over-the-counter medications, or herbal products (even if they are not on the list) without consulting prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. This drug is prescribed as one part of a multidrug combination; take exactly as directed for full course of therapy. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. Avoid alcohol to decrease risk of hypersensitivity reaction. You may be susceptible to infection; avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber. Frequent blood tests may be required with prolonged therapy. May cause dizziness or weakness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea and vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). **Note:** Seek immediate emergency care if you experience unusual chest pain, palpitations, erratic heart beat or if you suspect you are having a heart attack. Stop drug and report immediately symptoms of hypersensitivity (eg, fever; rash; fatigue, malaise, lethargy; persistent nausea, vomiting, diarrhea, abdominal pain; mouth sores; sore throat, cough, difficulty breathing; headache; swelling of face, mouth or throat; numbness or loss of sensation; pain, tingling, or numbness in toes, feet, muscles or joints; swollen glands; alterations in urinary pattern; swelling of extremities or weight gain). Do not restart without specific instruction by your prescriber. If you are instructed to stop the medication, do not restart in the future. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral:

- Ziagen®: 20 mg/mL (240 mL) [strawberry-banana flavor]

Tablet:

- Ziagen®: 300 mg

Generic AvailableNo

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Solution (Ziagen)

20 mg/mL (240): $125.04

Tablets (Ziagen)

300 mg (60): $514.18

Mechanism of ActionNucleoside reverse transcriptase inhibitor. Abacavir is a guanosine analogue which is phosphorylated to carbovir triphosphate which interferes with HIV viral RNA-dependent DNA polymerase resulting in inhibition of viral replication.

Pharmacodynamics/Kinetics

Absorption: Rapid and extensive absorption

Distribution: V_d: 0.86 L/kg

Protein binding: 50%

Metabolism: Hepatic via alcohol dehydrogenase and glucuronyl transferase to inactive carboxylate and glucuronide metabolites

Bioavailability: 83%

Half-life elimination: 1.5 hours

Time to peak: 0.7-1.7 hours

Excretion: Primarily urine (as metabolites, 1.2% as unchanged drug); feces (16% total dose)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV

Pharmacotherapy PearlsA high rate of early virologic nonresponse was observed when abacavir, lamivudine, and tenofovir were used as the initial regimen in treatment-naive patients. Use of this combination is not recommended; patients currently on this regimen should be closely monitored for modification of therapy.

Hypersensitivity testing (*HLA-B*5701*): Prevalence of hypersensitivity reactions has been estimated at 5% to 8% in Caucasians and 2% to 3% in African-Americans. Pretherapy identification of *HLA-B*5701*-positive patients, and subsequent avoidance of abacavir therapy in these patients has been shown to reduce the occurrence of abacavir-mediated hypersensitivity reactions. A skin patch test is in development for clinical screening purposes; however, only PCR-mediated genotyping methods are currently in clinical practice use for documentation of this susceptibility marker.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue, lethargy, malaise, insomnia, and headache

Mental Health: Effects on Psychiatric TreatmentSide effects mimic depressive symptoms; caution with benzodiazepines or other CNS depressants and antidepressants

Index TermsAbacavir Sulfate; ABC

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Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection," July 29, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesAbamune (IN); Ampi-quim (MX); Filabac (AR); Zepril (AR); Ziagen (AT, AU, BB, BE, BG, BM, BS, BZ, CH, CL, CN, CO, CR, CZ, DE, DK, DO, ES, FI, FR, GB, GR, GT, GY, HK, HN, IE, IL, IT, JM, KP, NI, NL, NO, PA, PE, PL, PT, RU, SE, SG, SR, SV, TR, TT, TW, VE); Ziagenavir (AR, BR, MX, TH, UY)

Abatacept

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Orencia® may be confused with Oracea™

Pronunciation(ab a TA sept)

U.S. Brand NamesOrencia®

Canadian Brand NamesOrencia®

Pharmacologic CategoryAntirheumatic, Disease Modifying

Use: Labeled Indications

Treatment of moderately- to severely-active adult rheumatoid arthritis (RA); may be used as monotherapy or in combination with other DMARDs

Treatment of moderately- to severely-active juvenile idiopathic arthritis (JIA); may be used as monotherapy or in combination with methotrexate

Note: Abatacept should **not** be used in combination with anakinra or TNF-blocking agents

Dosing: Adults **Rheumatoid arthritis:** I.V.: Dosing is according to body weight. Repeat dose at 2 weeks and 4 weeks after initial dose, and every 4 weeks thereafter:

<60 kg: 500 mg

60-100 kg: 750 mg

>100 kg: 1000 mg

Dosing: ElderlyRefer to adult dosing. Due to potential for higher rates of infections and malignancies, use caution.

Dosing: Pediatric**JIA:** I.V.:

Children ≥6 years and <75 kg: 10 mg/kg, repeat dose at 2 and 4 weeks after initial infusion, and every 4 weeks thereafter; Maximum dose: 1000 mg

Children ≥6 years and >75 kg: **Note:** Dosage is according to body weight. Repeat dose at 2 weeks and 4 weeks after initial dose and every 4 weeks thereafter:

75-100 kg: 750 mg

>100 kg: 1000 mg

Dosing: Adjustment for ToxicityWithhold therapy for patients with serious infections.

Administration: I.V.Infuse over 30 minutes. Administer through a 0.2-1.2 micron low protein-binding filter

Administration: I.V. DetailpH: 7-8

StoragePrior to reconstitution, store at 2°C to 8°C (36°F to 46°F); protect from light. After dilution, may be stored for up to 24 hours at room temperature or refrigerated at 2°C to 8°C (36°F to 46°F). Must be used within 24 hours of reconstitution.

ReconstitutionReconstitute each vial with 10 mL SWFI using the provided silicone-free disposable syringe (discard solutions accidentally reconstituted with siliconized syringe as they may develop translucent particles). Inject SWFI down the side of the vial to avoid foaming. The reconstituted solution contains 25 mg/mL abatacept. Further dilute (using a silicone-free syringe) in 100 mL NS to a final concentration of ≤10 mg/mL. Prior to adding abatacept to the 100 mL bag, the manufacturer recommends withdrawing a volume of NS equal to the abatacept volume required, resulting in a final volume of 100 mL. Mix gently; do not shake.

CompatibilityStable in NS.

ContraindicationsThere are no contraindications listed within the FDA-approved labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Rare cases of hypersensitivity, anaphylaxis, or anaphylactoid reactions have been reported; medication for the treatment of hypersensitivity reactions should be available for immediate use.
- Infections: Caution should be exercised when considering the use in patients with a history of new/recurrent infections, with conditions that predispose them to infections, or with chronic, latent, or localized infections. Patients who develop a new infection while undergoing treatment should be monitored closely. If a patient develops a serious infection, therapy should be discontinued.
- Malignancy: Use may affect defenses against malignancies (via T cell inhibition); impact on the development and course of malignancies is not fully defined. As compared to the general population, an increased risk of lymphoma and lung cancer has been

noted in clinical trials; however, rheumatoid arthritis has been previously associated with an increased rate of lymphoma.

Disease-related concerns:

- COPD: Use caution with chronic obstructive pulmonary disease (COPD), higher incidences of adverse effects (COPD exacerbation, cough, rhonchi, dyspnea) have been observed; monitor closely.

Concurrent drug therapy issues:

- Anakinra: The manufacturer does not recommend concurrent use with anakinra.

- TNF-blocking agents: Adult patients receiving therapy in combination with TNF-blocking agents had higher rates of infections (including serious infections) than patients on TNF-blocking agents alone. Concurrent use with TNF-blocking agents is not recommended. Monitor for signs and symptoms of infection when transitioning from TNF-blocking agents to abatacept.

Special populations:

- Elderly: Use with caution, higher incidences of infection and malignancy were observed in the elderly.

- Pediatrics: Not FDA approved for use in children <6 years of age.

- Tuberculosis-positive patients: Safety has not been established in tuberculosis-positive patients; screen patients for latent tuberculosis infection prior to initiating therapy. Treat patients testing positive according to standard therapy prior to initiating abatacept.

Dosage form specific issues:

- Maltose: May contain maltose, which may result in falsely-elevated serum glucose readings on the day of infusion.

Other warnings/precautions:

- Hepatitis screening: Patients should be screened for viral hepatitis prior to use; antirheumatic therapy may cause reactivation of hepatitis B.

- Immunizations: Patients should be brought up to date with all immunizations before initiating therapy. Live vaccines should not be given concurrently or within 3 months of discontinuation of therapy; there is no data available concerning secondary transmission of live vaccines in patients receiving therapy.

Geriatric ConsiderationsThe number of elderly (≥65 years of age) were insufficient to draw significant clinical conclusions. The studies to date have not demonstrated any differences in safety and efficacy between young adults and elderly. However, the frequency of infections and malignancy was higher in those >65 years of age than those <65 years. Since elderly experience a higher incidence of infections and malignancies, use abatacept with caution in this population.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Due to the potential risk for development of autoimmune disease in the fetus, use during pregnancy only if clearly needed. A pregnancy registry has been established to monitor outcomes of women exposed to abatacept during pregnancy (1-877-311-8972).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for adverse reactions and possible effects on the developing immune system, breast-feeding is not recommended.

Adverse Reactions**Note:** Percentages not always reported; COPD patients experienced a higher frequency of COPD-related adverse reactions (COPD exacerbation, cough, dyspnea, pneumonia, rhonchi)

>10%:

Central nervous system: Headache (≤18%)

Gastrointestinal: Nausea

Respiratory: Nasopharyngitis (12%), upper respiratory tract infection

Miscellaneous: Infection (adults 54%; children 36%), antibody formation (2% to 41%)

1% to 10%:

Cardiovascular: Hypertension (7%)

Central nervous system: Dizziness (9%), fever

Dermatologic: Rash (4%)

Gastrointestinal: Dyspepsia (6%), abdominal pain, diarrhea

Genitourinary: Urinary tract infection (6%)

Neuromuscular & skeletal: Back pain (7%), limb pain (3%)

Respiratory: Cough (8%), bronchitis, pneumonia, rhinitis, sinusitis

Miscellaneous: Infusion-related reactions (2% to 9%), herpes simplex, influenza

<1%, postmarketing, and/or case reports: Acute lymphocytic leukemia, anaphylaxis, anaphylactoid reactions, cellulitis, COPD exacerbation,

disease flare, diverticulitis, dyspnea, flushing, hypersensitivity, hypotension, joint wear, lung cancer, lymphoma; malignancies (including bile duct, bladder, breast, cervical, melanoma, myelodysplastic syndrome, prostate, renal, skin, thyroid and uterine); ovarian cyst, pruritus, pyelonephritis, rhonchi, urticaria, varicella infection, wheezing

Drug Interactions

Anti-TNF Agents: May enhance the adverse/toxic effect of Abatacept. An increased risk of serious infection during concomitant use has been reported. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid echinacea (has immunostimulant properties; consider therapy modifications).

Test InteractionsContains maltose; may result in falsely elevated blood glucose levels with dehydrogenase pyrroloquinolinequinone or glucose-dye-oxidoreductase testing methods on the day of infusion. Glucose monitoring methods which utilize glucose dehydrogenase nicotine adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase are recommended.

Monitoring ParametersSigns and symptoms of infection, signs and symptoms of infusion reaction; hepatitis and TB screening prior to therapy initiation

Nursing: Physical Assessment/MonitoringMonitor therapeutic response and adverse reactions. Perform testing for tuberculosis prior to initiating therapy. Assess for infection prior to initiating infusion. Teach patient appropriate interventions to reduce side effects and adverse symptoms to report.

Monitoring: Lab TestsHepatitis and TB screening prior to therapy initiation

Patient EducationThis drug can only be administered by infusion. You may be more susceptible to infections. Report signs of infection. Avoid immunizations unless approved by prescriber. May cause falsely elevated blood glucose readings on day of infusion. You may experience headache, sore throat, and nausea. Report immediately respiratory difficulty, hives, dizziness, nausea, flushing, cough, or wheezing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Orencia®: 250 mg [contains maltose]

Generic AvailableNo

ManufacturerBristol-Myers Squibb Company

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Orencia)

250 mg (1): $511.47

Mechanism of ActionSelective costimulation modulator; inhibits T-cell (T-lymphocyte) activation by binding to CD80 and CD86 on antigen presenting cells (APC), thus blocking the required CD28 interaction between APCs and T cells. Activated T lymphocytes are found in the synovium of rheumatoid arthritis patients.

Pharmacodynamics/Kinetics

Distribution: V_{ss}: 0.02-0.13 L/kg

Half-life elimination: 8-25 days

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause nausea; concomitant use with SSRIs, lithium, valproic acid, and carbamazepine may produce additive effects

Index TermsCTLA-4Ig

References

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International Brand Names Orencia (AR, CH, CZ, DE, DK, EE, GB, IE, NO, SE)

Abciximab

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ab SIK si mab)

U.S. Brand NamesReoPro®

Canadian Brand NamesReopro®

Pharmacologic CategoryAntiplatelet Agent, Glycoprotein IIb/IIIa Inhibitor

Use: Labeled IndicationsPrevention of acute cardiac ischemic complications in patients at high risk for abrupt closure of the treated coronary vessel and patients at risk of restenosis; an adjunct with heparin to prevent cardiac ischemic complications in patients with unstable angina not responding to conventional therapy when a percutaneous coronary intervention (PCI) is scheduled within 24 hours

Use: Unlabeled/InvestigationalAcute MI - combination regimen of abciximab (full dose), tenecteplase (half dose), and heparin (unlabeled dose)

Dosing: Adults

Prevention of restenosis (patients at high risk for abrupt closure): I.V.: 0.25 mg/kg bolus administered 10-60 minutes before the start of intervention followed by an infusion of 0.125 mcg/kg/minute (maximum: 10 mcg/minute) for 12 hours

Patients with unstable angina not responding to conventional medical therapy and with planned percutaneous coronary intervention within 24 hours: I.V.: 0.25 mg/kg intravenous bolus followed by an 18- to 24-hour intravenous infusion of 10 mcg/minute, concluding 1 hour after the percutaneous coronary intervention.

Acute MI combination regimen (unlabeled): Half-dose tenecteplase (15-25 mg based on weight), abciximab 0.25 mg/kg bolus then 0.125 mcg/kg/minute (maximum: 10 mcg/minute) for 12 hours and heparin dosing as follows: Concurrent bolus of 40 units/kg (maximum: 3000 units), then 7 units/kg/hour (maximum: 800 units/hour) as continuous infusion. Adjust to aPTT target of 50-70 seconds.

Dosing: ElderlyRefer to adult dosing.

Calculations

- Abciximab

Administration: I.V.Abciximab is intended for coadministration with aspirin postangioplasty and heparin infused and weight adjusted to maintain a therapeutic bleeding time (eg, ACT 300-500 seconds). Solution must be filtered prior to administration. Do not shake the vial.

Administration: I.V. Detail

Bolus dose: Aseptically withdraw the necessary amount of abciximab for the bolus dose into a syringe using a 0.2 or 5 micron low protein-binding syringe filter (or equivalent); the bolus should be administered 10-60 minutes before the procedure

Continuous infusion: Aseptically withdraw amount required of abciximab for the infusion through a 0.2 or 5 micron low protein-binding syringe filter into a syringe; inject this into 250 mL of NS or D_5W to make solution. If a syringe filter was not used when preparing the infusion, administer using an in-line 0.2 or 0.22 micron low protein-binding filter. **Note:** Alternatively, a standard concentration of 7.2 mg in 250 mL of NS or D_5W may also be prepared for all patients and administered at the standard dose (0.125 mcg/kg/minute; maximum: 10 mcg/minute) with a variable rate in mL/hour. Infuse for 12-24 hours via pump after bolus dose; length of therapy dependent on indication.

StorageVials should be stored at 2°C to 8°C. Do not freeze or shake. After admixture, the prepared solution is stable for 12 hours.

CompatibilityAbciximab should be administered in a separate intravenous line. No incompatibilities have been observed with glass bottles or PVC bags.

ContraindicationsHypersensitivity to abciximab, to murine proteins, or any component of the formulation; active internal hemorrhage or recent (within 6 weeks) clinically-significant GI or GU bleeding; history of cerebrovascular accident within 2 years or cerebrovascular accident with significant neurological deficit; clotting abnormalities or administration of oral anticoagulants within 7 days unless prothrombin time (PT) is ≤1.2 times control PT value; thrombocytopenia (<100,000 cells/µL); recent (within 6 weeks) major surgery or trauma; intracranial tumor, arteriovenous malformation, or aneurysm; severe uncontrolled hypertension; history of vasculitis; use of dextran before PTCA or intent to use dextran during PTCA; concomitant use of another parenteral GP IIb/IIIa inhibitor

Allergy Considerations

- Glycoprotein (GP) IIb/IIIa Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Administration may result in human antichimeric antibody formation that can cause hypersensitivity reactions (including anaphylaxis).

- Bleeding: The most common complication is bleeding, including retroperitoneal, pulmonary, and spontaneous GI and/or GU bleeding; watch closely for bleeding, especially the arterial access site for the cardiac catheterization. Use with extreme caution in patients with platelet counts <150,000/mm^3, patients with hemorrhagic retinopathy, previous history of GI disease, recent thrombolytic therapy and in chronic dialysis patients. Use caution with administration of other drugs affecting hemostasis. Minimize other procedures including arterial and venous punctures, I.M. injections, nasogastric tubes, etc. Increased risk of hemorrhage during or following angioplasty is associated with unsuccessful PTCA, PTCA procedure >70 minutes duration, or PTCA performed within 12 hours of symptom onset for acute myocardial infarction.

- Thrombocytopenia: Administration may result in human antichimeric antibody formation that can cause thrombocytopenia; readministration within 30 days or in patients with human antichimeric antibodies (HACA) increases the incidence and severity of thrombocytopenia.

Special populations:

- Elderly: Use with caution in patients >65 years of age; increased risk of bleeding.

- Low weight patients: Use with caution in patients weighing <75 kg; increased risk of bleeding.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Diminished efficacy: Administration may result in human antichimeric antibody formation that can cause diminished efficacy.

- Sheath removal: Prior to pulling the sheath, heparin should be discontinued for 3-4 hours and ACT ≤175 seconds or aPTT ≤50 seconds. Use standard compression techniques after sheath removal. Watch the site closely afterwards for further bleeding.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. *In vitro* studies have shown only small amounts of abciximab to cross the placenta. It is not known whether abciximab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsAs with all drugs which may affect hemostasis, bleeding is associated with abciximab. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the concurrent use of multiple agents which alter hemostasis and patient susceptibility.

>10%:

Cardiovascular: Hypotension (14%), chest pain (11%)

Gastrointestinal: Nausea (14%)

Hematologic: Minor bleeding (4% to 17%)

Neuromuscular & skeletal: Back pain (18%)

1% to 10%:

Cardiovascular: Bradycardia (5%), peripheral edema (2%)

Central nervous system: Headache (7%)

Gastrointestinal: Vomiting (7%), abdominal pain (3%)

Hematologic: Major bleeding (1% to 14%), thrombocytopenia: <100,000 cells/mm^3 (3% to 6%); <50,000 cells/mm^3 (0.4% to 2%)

Local: Injection site pain (4%)

<1% (Limited to important or life-threatening): Abnormal thinking, abnormal vision, agitation, allergic reactions/anaphylaxis (possible), anemia, anxiety, arteriovenous fistula, bronchitis, bronchospasm, bullous eruption, cellulitis, coma, complete AV block, confusion, cystalgia, diabetes mellitus, diaphoresis increased, diarrhea, diplopia, dizziness, dyspepsia, dysuria, embolism, gastroesophageal reflux, hyperkalemia, hypertonia, hypoesthesia, ileus, incomplete AV block, inflammation, intracranial hemorrhage, leukocytosis, muscle contractions, myalgia, nodal arrhythmia, pain, palpitation, peripheral coldness, petechiae, pleural effusion, pneumonia, prostatitis, pruritus, pseudoaneurysm, pulmonary embolism, stroke, thrombophlebitis, urinary incontinence, urinary retention, ventricular tachycardia, weakness, xerostomia

Drug Interactions

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Dextran: May enhance the anticoagulant effect of Abciximab. *Risk X: Avoid combination*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Monoclonal Antibodies: Abciximab may enhance the potential for allergic or hypersensitivity reactions to Monoclonal Antibodies. Also may cause thrombocytopenia or diminished therapeutic effects. **Exceptions:** Alefacept. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Monitoring ParametersProthrombin time, activated partial thromboplastin time (aPTT), hemoglobin, hematocrit, platelet count, fibrinogen, fibrin split products, transfusion requirements, signs of hypersensitivity reactions, guaiac stools, Hemastix® urine. Platelet count should be monitored at baseline, 2-4 hours following bolus infusion, and at 24 hours (or prior to discharge, if before 24 hours). To minimize risk of bleeding:

Abciximab initiated 18-24 hours prior to PCI: Maintain aPTT between 60-85 seconds during the heparin/abciximab infusion period

During PCI: Maintain ACT between 200-300 seconds

Following PCI (if anticoagulation is maintained): Maintain aPTT between 50-75 seconds

Sheath removal should not occur until aPTT is ≤50 seconds or ACT ≤175 seconds.

Maintain bleeding precautions, avoid unnecessary arterial and venous punctures, use saline or heparin lock for blood drawing, assess sheath insertion site and distal pulses of affected leg every 15 minutes for the first hour and then every 1 hour for the next 6 hours. Arterial access site care is important to prevent bleeding. Care should be taken when attempting vascular access that only the anterior wall of the femoral artery is punctured, avoiding a Seldinger (through and through) technique for obtaining sheath access. Femoral vein sheath placement should be avoided unless needed. While the vascular sheath is in place, patients should be maintained on complete bedrest with the head of the bed at a 30° angle and the affected limb restrained in a straight position.

Observe patient for mental status changes, hemorrhage; assess nose and mouth mucous membranes, puncture sites for oozing, ecchymosis, and hematoma formation; and examine urine, stool, and emesis for presence of occult or frank blood; gentle care should be provided when removing dressings.

Nursing: Physical Assessment/MonitoringMonitor vital signs and laboratory results prior to, during, and after therapy. Assess infusion insertion site and peripheral pulses during and after therapy. Observe and teach patient bleeding precautions (avoid invasive procedures and activities that could result in injury). Monitor closely for signs of excessive bleeding. **Pregnancy risk factor C.** Note breast-feeding caution.

Monitoring: Lab TestsProthrombin time, activated partial thromboplastin time (aPTT), hemoglobin, hematocrit, platelet count, fibrinogen, fibrin split products, transfusion requirements, signs of hypersensitivity reactions, guaiac stools, Hemastix® urine. Platelet count should be monitored at baseline, 2-4 hours following bolus infusion, and at 24 hours (or prior to discharge, if before 24 hours). To minimize risk of bleeding:

Abciximab initiated 18-24 hours prior to PCI: Maintain aPTT between 60-85 seconds during the heparin/abciximab infusion period

During PCI: Maintain ACT between 200-300 seconds

Following PCI (if anticoagulation is maintained): Maintain aPTT between 50-75 seconds

Sheath removal should not occur until aPTT is ≤50 seconds or ACT ≤175 seconds.

Patient EducationThis medication can only be administered I.V. You will have a tendency to bleed easily following this medication; use caution to prevent injury (use electric razor, soft toothbrush, and use caution with knives, needles, or anything sharp). If bleeding occurs, apply pressure to bleeding spot until bleeding stops completely. Report unusual bruising or bleeding; blood in urine, stool, or vomitus; bleeding gums; or vision changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

ReoPro®: 2 mg/mL (5 mL)

Generic AvailableNo

Mechanism of ActionFab antibody fragment of the chimeric human-murine monoclonal antibody 7E3; this agent binds to platelet IIb/IIIa receptors, resulting in steric hindrance, thus inhibiting platelet aggregation

Pharmacodynamics/KineticsHalf-life elimination: ~30 minutes

Related Information

- Glycoprotein Antagonists

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: As with all anticoagulants, bleeding is a potential adverse effect of abciximab during dental surgery; risk is dependent on multiple variables, including the intensity of anticoagulation and patient susceptibility. Medical consult is suggested. It is unlikely that ambulatory patients presenting for dental treatment will be taking intravenous anticoagulant therapy.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular Considerations

Acute Coronary Syndrome (ACS): The 2002 ACC/AHA guidelines for unstable angina/non-ST-segment elevation myocardial infarctions (UA/NSTEMI) recommend administration of intravenous glycoprotein IIb/IIIa inhibitors (along with ASA and heparin) in patients with non-ST-segment elevation ACS who are expected to undergo catheterization and PCI. In such patients in which PCI in **not** expected, eptifibatide or tirofiban should be administered (along with ASA and either heparin or LMWH) if high-risk features (eg, positive biochemical markers of infarction, ST-segment depression, sustained VT, >75 years of age, or signs of LV dysfunction) or refractory ischemia are present.

Percutaneous Coronary Intervention (PCI): A glycoprotein IIb/IIIa inhibitor is recommended for patients who will undergo PCI, especially those with unstable angina or other high risks for postprocedure ischemic complications. In the TARGET trial, abciximab (FDA-approved dose) and tirofiban (10 mcg/kg bolus; infusion of 0.15 mcg/kg/minute for 18-24 hours) were compared to each other in patients undergoing coronary stenting. The primary endpoint was death, nonfatal MI, or urgent target vessel revascularization at 30 days. Abciximab improved outcome to a greater extent than tirofiban did primarily by reducing nonfatal MI. Follow-up at 6 months revealed no significant difference in primary outcomes between treatments, but a trend existed in favor of abciximab reducing the occurrence of MIs.

STEMI: Adjunct to Thrombolysis: In the GUSTO V trial, patients with acute MI were randomized to standard-dose reteplase or half-dose reteplase (two boluses of 5 units each, 30 minutes apart) and full-dose abciximab. Mortality at 30 days (primary endpoint) was similar in both groups. The combination treatment group had significantly fewer reinfarctions or recurrent episodes of ischemia. Combination treatment was also associated with less need for urgent revascularization. More bleeding occurred in the combination treatment group, but the incidence of nonfatal disabling stroke and stroke of any type were similar in both groups. Overall, no difference in intracranial hemorrhages was observed between the two treatments, but a trend towards an increased incidence occurred in patients >75 years of age who received combination treatment. Patients with acute MI were randomized in an open-label study to full-dose tenecteplase and enoxaparin, half-dose tenecteplase with low-dose, weight-based heparin and a 12-hour infusion of abciximab or full-dose tenecteplase with weight-based heparin (ASSENT-3 Investigators, 2001). The primary endpoint (30 days) was mortality, in-house reinfarction, and in-house refractory ischemia. The abciximab arm and the enoxaparin arm had significantly less mortality, reinfarction, and refractory ischemia than in the unfractionated heparin/full-dose tenecteplase. One year mortality (secondary endpoint) was similar in all three treatment arms (Sinnaeve PR, 2004). However, the 1-year outcome tended to be worse with abciximab in patients with diabetes. The 2004 ACC/AHA guidelines for STEMI recommend that pharmacologic reperfusion with abciximab and half-dose reteplase or tenecteplase may be considered in patients <75 years of age with anterior wall infarctions and no risk factors for bleeding.

Platelet Effects: Abciximab has a long duration of action and platelet effects reverse slowly. It can take 24-48 hours for platelet function to return to normal after discontinuation of infusion making it difficult to use in patients likely to need CABG. Antiplatelet effects can be reversed with platelet transfusions. Platelet count monitoring is recommended 2-4 hours after initiation, and at 24 hours or prior to discharge, whichever is first. Acute profound thrombocytopenia with abciximab occurs within 24 hours of administration and may be treated by discontinuing the infusion (if still running) and administering platelets. Platelet counts should recover rapidly after discontinuation.

Anesthesia and Critical Care Concerns/Other Considerations**Platelet Effects:** Abciximab has a long duration of action and platelet effects reverse slowly. It can take 24-48 hours for platelet function to return to normal after discontinuation of infusion making it difficult to use in patients likely to need CABG. Antiplatelet effects can be reversed with platelet transfusions. Platelet count monitoring is recommended 2-4 hours after initiation, and at 24 hours or prior to discharge, whichever is first. Acute profound thrombocytopenia with abciximab occurs within 24 hours of administration and may be treated by discontinuing the infusion (if still running) and administering platelets. Platelet counts should recover rapidly after discontinuation.

Index Terms7E3; C7E3

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Berkowitz SD, Harrington RA, Rund MM, et al, “Acute Profound Thrombocytopenia After C7E3 Fab (Abciximab) Therapy,” *Circulation*, 1997, 95(4):809-13. [PubMed 9054735]

Braunwald E, Antman EM, Beasley JW, et al, “ACC/AHA 2002 Guideline Update for the Management of Patients With Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction - Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina),” *J Am Coll Cardiol*, 2002, 40(7):1366-74. Available at: http://www.acc.org/clinical/guidelines/unstable/incorporated/index.htm. Accessed May 20, 2003. [PubMed 12383588]

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Angioplasty for Acute Myocardial Infarction," ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) Investigators, *Circulation*, 1998, 98(8):734-41.

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Lincoff AM, Califf RM, Van de Werf F, et al, "Mortality at 1 Year With Combination Platelet Glycoprotein IIb/IIIa Inhibition and Reduced-Dose Fibrinolytic Therapy vs Conventional Fibrinolytic Therapy for Acute Myocardial Infarction: GUSTO V Randomized Trial," *JAMA*, 2002, 288(17):2130-5. [PubMed 12413372]

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Smith SC Jr, Dove JT, Jacobs AK, et al, "ACC/AHA Guidelines of Percutaneous Coronary Interventions (Revision of the 1993 PTCA Guidelines) - Executive Summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty)," *J Am Coll Cardiol*, 2001, 37(8):2215-39. [PubMed 11419905]

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International Brand NamesReoPro (AR, AT, AU, BE, BR, CH, CN, CZ, DE, DK, ES, FI, FR, GB, GR, IE, IN, IT, KP, LU, MX, MY, NL, NO, PE, PK, PL, PT, SE, SG, TH, TW, ZA)

ABVD

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lymphoma, Hodgkin's Disease

Regimen Use Lymphoma, Hodgkin's disease

Regimen

Doxorubicin: I.V.: 25 mg/m^2/day days 1 and 15

[total dose/cycle = 50 mg/m^2]

Bleomycin: I.V.: 10 units/m^2/day days 1 and 15

[total dose/cycle = 20 units/m^2]

Vinblastine: I.V.: 6 mg/m^2/day days 1 and 15

[total dose/cycle = 12 mg/m^2]

Dacarbazine: I.V.: 375 mg/m^2/day days 1 and 15

[total dose/cycle = 750 mg/m^2]

Repeat cycle every 28 days

References

Bonadonna G, Zucali R, DeLena M, et al, “Combined Chemotherapy (MOPP or ABVD) - Radiotherapy Approach in Advanced Hodgkin's Disease,” *Cancer Treat Rep*, 1977, 61(5):769-77.[PubMed 70270]

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AC/Paclitaxel (Sequential)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer

Regimen Use Breast cancer

Regimen

Variation 1: AC + Paclitaxel (conventional):

Doxorubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 21 days for 4 cycles

followed by

Paclitaxel: I.V.: 175 mg/m^2 day 1

[total dose/cycle = 175 mg/m^2]

Repeat cycle every 21 days for 4 cycles

Variation 2: AC + Paclitaxel (dose dense):

Doxorubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Filgrastim: SubQ: 5 mcg/kg/day days 3 to 10

[total dose/cycle = 40 mcg/kg]

Repeat cycle every 14 days for 4 cycles

followed by

Paclitaxel: I.V.: 175 mg/m^2 day 1

[total dose/cycle = 175 mg/m^2]

Filgrastim: SubQ: 5 mcg/kg/day days 3 to 10

[total dose/cycle = 40 mcg/kg]

Repeat cycle every 14 days for 4 cycles

References

Variation 1:

Henderson IC, Berry DA, Demetri GD, et al, “Improved Outcomes From Adding Sequential Paclitaxel but not From Escalating Doxorubicin Dose in an Adjuvant Chemotherapy Regimen for Patients With Node-Positive Primary Breast Cancer,” *J Clin Oncol*, 2003, 21(6):976-83.[PubMed 12637460]

Variation 2:

Citron ML, Berry DA, Cirrincione C, et al, “Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer Leukemia Group B Trial 9741,” *J Clin Oncol*, 2003, 21(8):1431-9.[PubMed 12668651]

AC-Paclitaxel-Trastuzumab

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Doxorubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 21 days for 4 cycles

followed by

Paclitaxel: I.V.: 175 mg/m^2 day 1

[total dose/cycle = 175 mg/m^2]

Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1 (cycle 1 only)

[total dose/cycle = 4 mg/kg]

followed by I.V.: 2 mg/kg/day days 8 and 15 (cycle 1)

[total dose/cycle = 4 mg/kg]

then I.V.: 2 mg/kg/day days 1, 8, and 15 (cycles 2, 3, and 4)

[total dose/cycle = 6 mg/kg]

Repeat cycle every 21 days for 4 cycles

followed by

Trastuzumab: I.V.: 2 mg/kg weekly for 40 weeks

Variation 2:

Doxorubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 21 days for 4 cycles

followed by

Paclitaxel: I.V.: 80 mg/m^{2}day 1 week 13

[total dose/cycle = 80 mg/m^2]

Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1 week 13 only

[total dose/cycle = 4 mg/kg]

followed by

Paclitaxel: I.V.: 80 mg/m^2 weekly

[total dose/cycle = 80 mg/m^2]

Trastuzumab: I.V.: 2 mg/kg /weekly

[total dose/cycle = 2 mg/kg]

Repeat cycle every week for 11 cycles

followed by

Trastuzumab: I.V.: 2 mg/kg /weekly for 40 weeks

References

Romond EH, Perez EA, Bryant J, et al, âTrastuzumab Plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer,â *N Engl J Med*, 2005, 353(16):1673-84.[PubMed 16236738]

AC

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer

Regimen Use Breast cancer

Regimen NOTE: Multiple variations are listed below.

Variation 1: AC (conventional):

Doxorubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Cyclophosphamide: Oral: 200 mg/m^2/day days 3 to 6

[total dose/cycle = 800 mg/m^2]

Doxorubicin: I.V.: 40 mg/m^2 day 1

[total dose/cycle = 40 mg/m^2]

Repeat cycle every 3 weeks for 3 cycles, then every 4 weeks

References

Variation 1:

Fisher B, Brown AM, Dimitrov NV, et al, “Two Months of Doxorubicin-Cyclophosphamide With and Without Interval Reinduction Therapy Compared With 6 Months of Cyclophosphamide, Methotrexate, and Fluorouracil in Positive-Node Breast Cancer Patients With Tamoxifen-Nonresponsive Tumors: Results From the National Surgical Adjuvant Breast and Bowel Project B-15,” *J Clin Oncol*, 1990, 8(9):1483-96. [PubMed 2202791]

Variation 2:

Jones SE, Durie BG, and Salmon SE, “Combination Chemotherapy With Adriamycin and Cyclophosphamide for Advanced Breast Cancer,” *Cancer*, 1975, 36(1):90-7.[PubMed 1203853]

English

Jump To Field (Select Field Name)

Pronunciation(a kam PROE sate)

U.S. Brand NamesCampral®

Canadian Brand NamesCampral®

Pharmacologic CategoryGABA Agonist/Glutamate Antagonist

Use: Labeled IndicationsMaintenance of alcohol abstinence

Dosing: AdultsAlcohol abstinence: Oral: 666 mg 3 times/day (a lower dose may be effective in some patients).

Adjustment in patients with low body weight (unlabeled): A lower dose (4 tablets/day) may be considered in patients with low body weight (eg, <60 kg).

Note: Treatment should be initiated as soon as possible following the period of alcohol withdrawal, when the patient has achieved abstinence.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 30-50 mL/minute: Initial dose should be reduced to 333 mg 3 times/day.

Cl_{cr} <30 mL/minute: Contraindicated in severe renal impairment.

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered without regard to meals. Tablet should be swallowed whole; do not crush or chew.

Dietary ConsiderationsMay be taken without regard to meals. Each 333 mg tablet contains 33 mg of elemental calcium.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to acamprosate or any component of the formulation; severe renal impairment (Cl_{cr} <30 mL/minute)

Warnings/Precautions

Concerns related to adverse effects:

- Suicidal ideation/attempt: Attempted and completed suicides have occurred in acamprosate-treated patients; use with caution in suicidal ideation. Monitor for depression and/or suicidal thinking.

Disease-related concerns:

- Alcohol dependence: Appropriate use: Should be used as part of a comprehensive program to treat alcohol dependence. Treatment should be initiated as soon as possible following the period of alcohol withdrawal, when the patient has achieved abstinence. Acamprosate does not eliminate or diminish the symptoms of alcohol withdrawal.

- Renal impairment: Use with caution in patients with moderate renal impairment (Cl_{cr} 30-50 mL/minute).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Sulfites: Traces of sulfites may be present in the formulation.

Geriatric ConsiderationsInitial studies did not include sufficient geriatric patients to be able to derive sufficient data to compare elderly to younger adults. Only 41 out of 4234 patients in clinical trials were ≥65 years of age with none ≥75 years. However, since this medication is cleared renally exclusively, caution should be used since many elderly have Cl_{cr} 30-50 mL/minute where dosage reduction is required (see Dosage).

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic in animal studies. No adequate or well-controlled studies in pregnant women; use only if potential benefit outweighs possible risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

Note: Many adverse effects associated with treatment may be related to alcohol abstinence; reported frequency range may overlap with placebo.

>10%: Gastrointestinal: Diarrhea (10% to 17%)

1% to 10%:

Cardiovascular: Syncope, palpitation, edema (peripheral)

Central nervous system: Insomnia (6% to 9%), anxiety (5% to 8%), depression (4% to 8%), dizziness (3% to 4%), pain (2% to 4%), paresthesia (2% to 3%), headache, somnolence, amnesia, tremor, chills

Dermatologic: Pruritus (3% to 4%), rash

Endocrine & metabolic: Weight gain, libido decreased

Gastrointestinal: Anorexia (2% to 5%), flatulence (1% to 3%), nausea (3% to 4%), abdominal pain, dry mouth (1% to 3%), vomiting, dyspepsia, constipation, appetite increased, taste perversion

Genitourinary: Impotence

Neuromuscular & skeletal: Weakness (5% to 7%), back pain, myalgia, arthralgia

Ocular: Abnormal vision

Respiratory: Rhinitis, dyspnea, pharyngitis, bronchitis

Miscellaneous: Diaphoresis (2% to 3%), suicide attempt

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Angina, asthma, exfoliative dermatitis, gastrointestinal hemorrhage, hallucinations, hypothyroidism, MI, ophthalmitis, pancreatitis, photosensitivity, psychosis, pulmonary embolus, renal calculus, renal failure, seizure, suicidal ideation, suicide attempts, suicide completion

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb Interactions

Ethanol: Abstinence is required during treatment. Ethanol does not affect the pharmacokinetics of acamprosate; however, the continued use of ethanol will decrease desired efficacy of acamprosate.

Food: Food decreases absorption of acamprosate (not clinically significant).

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and potential interactions. May cause depression. Monitor for suicide ideation.

Patient EducationTaking this medication helps maintain abstinence only when used as part of a treatment program that includes counseling and support. Swallow tablet whole. Do not chew or crush. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake by prescriber. Can cause drowsiness (use caution when driving or engaging in activities requiring alertness until response to drug is known). You may experience diarrhea (buttermilk, boiled milk, or yogurt may help), peripheral edema, insomnia, anxiety, depression, and generalized weakness. Report persistent diarrhea, excessive or sudden weight gain, swelling of extremities, respiratory difficulties, fainting, or thoughts of suicide. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber before breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, enteric coated, delayed release, as calcium:

Campral®: 333 mg [contains calcium 33 mg and sulfites]

Generic AvailableNo

ManufacturerForest Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablet, EC (Campral)

333 mg (180): $136.08

Tablet, EC (Campral Dose Pak)

333 mg (180): $150.10

Mechanism of ActionMechanism not fully defined. Structurally similar to gamma-amino butyric acid (GABA), acamprosate appears to increase the activity of the GABA-ergic system, and decreases activity of glutamate within the CNS, including a decrease in activity at N-methyl D-aspartate (NMDA) receptors; may also affect CNS calcium channels. Restores balance to GABA and glutamate activities which appear to be disrupted in alcohol dependence. During therapeutic use, reduces alcohol intake, but does not cause a disulfiram-like reaction following alcohol ingestion.

Pharmacodynamics/Kinetics

Distribution: V_d: 1 L/kg

Protein binding: Negligible

Metabolism: Not metabolized

Bioavailability: 11%

Half-life elimination: 20-33 hours

Excretion: Urine (as unchanged drug)

Related Information

- Addiction Treatments

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation) and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Index Terms Acamprosate Calcium; Calcium Acetylhomotaurinate

References

Brasser SM, McCaul ME, and Houtsmuller EJ, “Alcohol Effects During Acamprosate Treatment: A Dose-Response Study in Humans,” *Alcohol Clin Exp Res*, 2004, 28(7):1074-83. [PubMed 15252294]

Graham R, Wodak AD, and Whelan G, “New Pharmacotherapies for Alcohol Dependence,” *Med J Aust*, 2002, 177(2):103-7. [PubMed 12098353]

Overman GP, Teter CJ, and Guthrie SK, “Acamprosate for the Adjunctive Treatment of Alcohol Dependence,” *Ann Pharmacother*, 2003, 37(7-8):1090-9.[PubMed 12841823]

International Brand Names Acampral (KP); Aotal (FR); Campral (AR, AT, AU, BE, BG, BR, CH, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, MX, NL, NO, PL, PT, RU, SE, TR)

Acarbose

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Precose® may be confused with PreCare®

International issues:

Precose® may be confused with Precosa® which is a brand name for *Saccharomyces boulardii* in Denmark, Finland, Norway, and Sweden

Pronunciation(AY car bose)
U.S. Brand NamesPrecose®
Canadian Brand NamesGlucobay™
Pharmacologic CategoryAntidiabetic Agent, Alpha-Glucosidase Inhibitor
Use: Labeled IndicationsAdjunct to diet and exercise to lower blood glucose in patients with type 2 diabetes mellitus (noninsulin dependent, NIDDM)
Dosing: AdultsType 2 diabetes: Oral:

Initial: 25 mg 3 times/day with the first bite of each main meal; to reduce GI effects, some patients may benefit from initiating at 25 mg once daily with gradual titration to 25 mg 3 times/day as tolerated

Maintenance dose: Should be adjusted at 4- to 8-week intervals based on 1-hour postprandial glucose levels and tolerance until maintenance dose is reached; maintenance dose: 50-100 mg 3 times/day. Dosage must be individualized on the basis of effectiveness and tolerance while not exceeding the maximum recommended dose.

Maximum:

≤60 kg: 50 mg 3 times/day

>60 kg: 100 mg 3 times/day

Patients receiving sulfonylureas or insulin: Acarbose given in combination with a sulfonylurea or insulin will cause a further lowering of blood glucose and may increase the hypoglycemic potential of the sulfonylurea or insulin. If hypoglycemia occurs, appropriate adjustments in the dosage of these agents should be made.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal Impairment

Cl_{cr} <25 mL/minute: Peak plasma concentrations were 5 times higher and AUCs were 6 times larger than in volunteers with normal renal function.

Significant renal dysfunction (S_{cr} >2 mg/dL): Use is not recommended.

Administration: OralShould be **administered with the first bite of each main meal.**
Dietary ConsiderationsTake with food (first bite of meal).
StorageStore at <25°C (77°F). Protect from moisture.
ContraindicationsHypersensitivity to acarbose or any component of the formulation; patients with diabetic ketoacidosis or cirrhosis; patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, or in patients predisposed to intestinal obstruction; patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption, and in patients who have conditions that may deteriorate as a result of increased gas formation in the intestine
Warnings/Precautions

Concerns related to adverse effects:

- Elevated serum transaminases: Treatment-emergent elevations of serum transaminases (AST and/or ALT) occurred in up to 14% of acarbose-treated patients in long-term studies. These serum transaminase elevations appear to be dose related. At doses >100 mg 3 times/day, the incidence of serum transaminase elevations greater than 3 times the upper limit of normal was 2-3 times higher in the acarbose group than in the placebo group. These elevations were asymptomatic, reversible, more common in females, and, in general, were not associated with other evidence of liver dysfunction. Fulminant hepatitis has been reported rarely.

Disease-related concerns:

- Renal impairment: Use not recommended in patients with significant impairment (S_{cr} >2 mg/dL); use with caution in other patients with renal impairment.

- Stress-related states: It may be necessary to discontinue acarbose and administer insulin if the patient is exposed to stress (ie, fever, trauma, infection, surgery).

Concurrent drug therapy issues:

- Sulfonylureas/insulin: In combination with a sulfonylurea or insulin will cause a further lowering of blood glucose and may increase the hypoglycemic potential of the sulfonylurea or insulin.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo specific trials in older adults have been conducted; mean age in clinical trials has been <60 years; monitor change in preprandial blood glucose concentrations to account for potential age-related changes in postprandial glucose. In clinical trials, elderly had serum concentrations 1.5 times those of younger adults. Patients with Cl_{cr} <25 mL/minute had serum concentrations 5 times those with normal renal clearance. No clinical significance can be attributed to this at this time. No adjustments in dose are recommended. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been reported in animal reproduction studies; therefore, acarbose is classified as pregnancy category B. Low amounts of acarbose are absorbed systemically which should limit fetal exposure. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Acarbose has been studied for its potential role in treating GDM; however, only limited information is available describing pregnancy outcomes. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if acarbose is found in breast milk; however, low amounts of acarbose are absorbed systemically in adults, which may limit the amount that could distribute into breast milk. Breast-feeding is not recommended by the manufacturer.

Pregnancy & Lactation, In-Depth

- Acarbose in Pregnancy & Lactation

Adverse Reactions

>10%:

Gastrointestinal: Diarrhea (31%) and abdominal pain (19%) tend to return to pretreatment levels over time; frequency and intensity of flatulence (74%) tend to abate with time

Hepatic: Transaminases increased (≤4%)

Postmarketing and/or case reports: Edema, erythema, exanthema, hepatitis, ileus/subileus, jaundice, liver damage, rash, urticaria

Drug Interactions

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Digoxin: Acarbose may decrease the serum concentration of Digoxin. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Limit ethanol.

Monitoring ParametersPostprandial glucose, glycosylated hemoglobin levels, serum transaminase levels should be checked every 3 months during the first year of treatment and periodically thereafter, renal function (serum creatinine); blood pressure

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response on a regular basis throughout therapy. Teach patient proper use (or refer patient to diabetic educator), possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report.

Monitoring: Lab TestsPostprandial glucose, glycosylated hemoglobin levels, and serum transaminase levels should be checked every 3 months during the first year of treatment and periodically thereafter, renal function (serum creatinine)

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take this medication exactly as directed, with the first bite of each main meal. Do not change dosage or discontinue this medicine without first consulting prescriber. Do not take other medications with or within 2 hours of this medication unless advised by prescriber. Avoid alcohol. It is important to follow dietary and lifestyle recommendations of prescriber. You will be instructed in signs of hypo- or hyperglycemia by prescriber or diabetic educator. If combining acarbose with other diabetic medication (eg, sulfonylureas, insulin), keep source of glucose in the form of dextrose (NOT table sugar, candy, or cookies) on hand in case hypoglycemia occurs. May cause mild side effects during first weeks of acarbose therapy (eg, bloating, flatulence, diarrhea, abdominal discomfort); these should diminish over time. Report severe or persistent side effects, fever, extended vomiting or flu, or change in color of urine or stool. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 25 mg, 50 mg, 100 mg

Precose®: 25 mg, 50 mg, 100 mg

Generic AvailableYes

ManufacturerBayer Corp (Biological and Pharmaceutical Division)

Pricing: U.S. (www.drugstore.com)

Tablets (Acarbose)

25 mg (100): $81.99

50 mg (100): $87.99

100 mg (100): $89.99

Tablets (Precose)

25 mg (90): $85.52

50 mg (90): $88.49

100 mg (90): $102.58

Mechanism of ActionCompetitive inhibitor of pancreatic α-amylase and intestinal brush border α-glucosidases, resulting in delayed hydrolysis of ingested complex carbohydrates and disaccharides and absorption of glucose; dose-dependent reduction in postprandial serum insulin and glucose peaks; inhibits the metabolism of sucrose to glucose and fructose

Pharmacodynamics/Kinetics

Absorption: <2% as active drug; ~35% as metabolites

Metabolism: Exclusively via GI tract, principally by intestinal bacteria and digestive enzymes; 13 metabolites identified (major metabolites are sulfate, methyl, and glucuronide conjugates)

Bioavailability: Low systemic bioavailability of parent compound; acts locally in GI tract

Half-life elimination: ~2 hours

Time to peak: Active drug: ~1 hour

Excretion: Urine (~34% as inactive metabolites, <2% parent drug and active metabolite); feces (~51% as unabsorbed drug)

Related Information

- Diabetes Mellitus Management, Adults

Dental Health: Effects on Dental TreatmentAlthough acarbose does not cause hypoglycemia, it is frequently used in combination and may complicate the management of hypoglecemic episodes caused by other medications. As part of its therapeutic effect, acarbose slows the absorption of complex sugars or disaccharides such as sucrose. This would delay effective treatment of hypoglycemia. Simple sugars, including glucose (dextrose), are not affected. If a patient experiences hypoglycemia, use of food items such as table sugar, candy, or cookies will NOT effectively increase blood glucose. Administration of oral glucose is required in mild-moderate hypoglycemia, and parenteral glucose is required for severe hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentAntipsychotics and tricyclic antidepressants may decrease the effects of acarbose. Monoamine oxidase inhibitors, SSRIs, and nefazodone may increase the effects of acarbose.

Cardiovascular ConsiderationsAcarbose produces a slight but statistically significant reduction in Hb A_{1c} (~1%) and fasting plasma glucose (~25 mg/dL). In general, acarbose may be used in combination with other agents (eg, sulfonylurea, metformin) or as monotherapy for patients with Type 2 diabetes. Therapy should be titrated slowly to minimize gastrointestinal side effects.

References

American Diabetes Association, “Standards of Medical Care in Diabetes -- 2008,” *Diabetes Care*, 2008, 31(Suppl 1):12-54. [PubMed 18165335]

Balfour JA and McTavish D, “Acarbose: A Reappraisal,” *Drugs*, 1993, 46(6):1025-54. [PubMed 7510610]

Bischoff H, “Pharmacology of α-Glucosidase Inhibition,” *Eur J Clin Invest*, 1994, 24(Suppl 3):3-10.

Scheen AJ, de Magalhaes AC, Salvatore T, et al, “Reduction of the Acute Bioavailability of Metformin by the α-Glucosidase Inhibitor Acarbose in Normal Man,” *Eur J Clin Invest*, 1994, 24(Suppl 3):50-4.

International Brand NamesDecarbay (TW); Deglu (TW); Dibose (MY); Glibose (TW); Glicobase (IT); Glucar (MY); Glucobay (AE, AR, AT, AU, BB, BD, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EG, ES, ET, FI, GB, GH, GM, GN, GT, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PK, PL, PT, PY, QA, SA, SC, SD, SE, SG, SL, SN, SR, SV, SY, TH, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Gluconase (PH); Glucor (FR); Glumida (ES); Incardel (MX); Prandase (IL); Precose (MY); Rebose (IN); Sincrosa (MX)

ACAV (J)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Wilms' Tumor

Regimen Use Wilms' tumor

Regimen

Dactinomycin: I.V.: 15 mcg/kg/day days 1 to 5 of weeks 0, 13, 26, 39, 52, and 65

[total dose/cycle = 450 mcg/kg]

Cyclophosphamide: I.V.: 10 mg/kg/day days 1, 2, and 3 of weeks 0, 6, 13, 19, 26, 32, 39, 45, 52, 58, and 65

[total dose/cycle = 330 mg/kg]

Doxorubicin: I.V.: 20 mg/m^2/day days 1, 2, and 3 of weeks 6, 19, 32, 45, and 58

[total dose/cycle = 300 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2 day 1 of weeks 0-10, 13, 14, 19, 20, 26, 27, 32, 33, 39, 40, 45, 52, 53, 56, 57, 65, and 66

[total dose/cycle = 42 mg/m^2]

References

D'Angio GJ, Breslow N, Beckwith JB, et al, âTreatment of Wilms' Tumor. Results of the Third National Wilms' Tumor Study,â *Cancer*, 1989, 64(2):349-60.[PubMed 2544249]

Acebutolol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Sectral® may be confused with Factrel®, Seconal®, Septra®

Pronunciation(a se BYOO toe lole)

U.S. Brand NamesSectral®

Canadian Brand NamesApo-Acebutolol®; Gen-Acebutolol; Monitan®; Novo-Acebutolol; Nu-Acebutolol; Rhotral; Rhoxal-acebutolol; Sandoz-Acebutolol; Sectral®

Pharmacologic CategoryAntiarrhythmic Agent, Class II; Beta Blocker With Intrinsic Sympathomimetic Activity

Use: Labeled IndicationsTreatment of hypertension; management of ventricular arrhythmias

Use: Unlabeled/InvestigationalTreatment of chronic stable angina

Dosing: Adults

Angina, ventricular arrhythmia: Oral: 400 mg/day in divided doses; maintenance: 600-1200 mg/day in divided doses; maximum: 1200 mg/day

Hypertension: Oral: 400-800 mg/day (larger doses may be divided); maximum: 1200 mg/day; usual dose range (JNC 7): 200-800 mg/day in 2 divided doses

Dosing: ElderlyOral: Initial: 200-400 mg/day; dose reduction due to age-related decrease in Cl_{cr} will be necessary; do not exceed 800 mg/day.

Dosing: Renal Impairment

Cl_{cr} 25-49 mL/minute: Reduce dose by 50%.

Cl_{cr} <25 mL/minute: Reduce dose by 75%.

Dosing: Hepatic ImpairmentUse with caution.

Calculations

- Creatinine Clearance: Adults

Administration: OralTo discontinue therapy, taper dose gradually over a period of 2 weeks. May be administered without regard to meals.

Dietary ConsiderationsMay be taken without regard to meals.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light and dispense in a light-resistant, tight container.

ContraindicationsOvert cardiac failure; cardiogenic shock; persistently-severe bradycardia or second- and third-degree heart block (except in patients with a functioning artificial pacemaker)

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Concerns related to adverse events:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; for patients with bronchospastic disease who do not respond to or cannot tolerate other therapies, initial low doses of acebutolol may be employed and used cautiously with close monitoring. Ensure patient has an inhaled $beta_2$-agonist immediately available.
- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.
- Heart failure (HF): Beta-blockers with intrinsic sympathomimetic activity (eg, acebutolol) are likely to worsen survival in patients with HF and should be avoided. Beta-blockers shown to improve survival in clinical trials should be used in these patients.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Mesenteric vascular disease: Can precipitate or aggravate symptoms of arterial insufficiency in patients with mesenteric vascular disease. Use with caution in these patients. Observe closely for progression of arterial obstruction.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis.

- Peripheral vascular disease (PVD): Can precipitate or aggravate symptoms of arterial insufficiency in patients with PVD. Use with caution in these patients. Observe closely for progression of arterial obstruction.

- Pheochromocytoma (untreated): Adequate alpha$_1$-receptor blockade is required prior to use of any beta-blocker.

- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

- Raynaud's disease: Use with caution in these patients with Raynaud's disease; may precipitate symptoms of Raynaud's.

- Renal impairment: Use with caution in patients with renal impairment, especially the elderly. Elimination of the metabolite, diacetolol, is reduced resulting in a two- to threefold increase in its half-life.

- Thyrotoxicosis: Beta-blockade may mask signs of hyperthyroidism (eg, tachycardia). Abrupt discontinuation may also induce a thyroid storm.

Special populations:

- Elderly: Use reduced doses in elderly patients; concentrations of acebutolol and diacetolol are significantly higher in the elderly. Dose should not exceed 800 mg/day.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.

Geriatric ConsiderationsSince bioavailability increased in elderly about twofold, geriatric patients may require lower maintenance doses, therefore, as serum and tissue concentrations increase beta$_1$ selectivity diminishes; due to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (ie, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20% to 50% in elderly populations. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults. Adjust dose for renal function.

Pregnancy Risk FactorB (manufacturer); D (2nd and 3rd trimesters - expert analysis)

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Acebutolol and its metabolite cross the human placenta. The neonatal half-life of acebutolol is 6-14 hours and diacetolol is 24-30 hours. Decreased birth weight, blood pressure, and heart rate have been observed in neonates following maternal use of acebutolol during pregnancy. Neonatal hypoglycemia has also been reported. Available evidence suggests beta-blockers are generally safe during pregnancy (JNC 7). Monitoring of the newborn is recommended.

LactationEnters breast milk/not recommended (AAP recommends “use with caution”)

Breast-Feeding ConsiderationsAcebutolol and its metabolites are found in human breast milk; the milk/plasma ratio is 7.1 for acebutolol and 12.2 for diacetolol. Hypotension, bradycardia, and tachypnea have been reported in nursing infants.

Adverse Reactions

>10%: Central nervous system: Fatigue (11%)

1% to 10%:

Cardiovascular: Chest pain (2%), edema (2%), bradycardia, hypotension, CHF

Central nervous system: Headache (6%), dizziness (6%), insomnia (3%), depression (2%), abnormal dreams (2%), anxiety, hyper-/hypoesthesia

Dermatologic: Rash (2%), pruritus

Gastrointestinal: Constipation (4%), diarrhea (4%), dyspepsia (4%), nausea (4%), flatulence (3%), abdominal pain, vomiting

Genitourinary: Micturition frequency (3%), dysuria, impotence, nocturia

Neuromuscular & skeletal: Myalgia (2%), back pain, joint pain

Ocular: Abnormal vision (2%), conjunctivitis, dry eyes, eye pain

Respiratory: Dyspnea (4%), rhinitis (2%), cough (1%), pharyngitis, wheezing

Postmarketing and/or case reports: Alkaline phosphatase increased, anorexia, AV block, bilirubin increased, cold extremities, drug-induced lupus-like syndrome, exacerbate pre-existing renal insufficiency, facial edema, hepatotoxic reaction, lichen planus, palpitation, pleurisy, pneumonitis, pulmonary granulomas, systemic lupus erythematosus, transaminases increased, urinary retention, ventricular arrhythmia, xerostomia

Potential adverse effects (based on experience with other beta-blocking agents) include agranulocytosis, allergic reactions, alopecia, catatonia, claudication, depression (reversible), disorientation, emotional lability, erythematous rash, ischemic colitis, laryngospasm, mesenteric artery thrombosis, Peyronie's disease, purpura, respiratory distress, short-term memory loss, slightly clouded sensorium, thrombocytopenia

Metabolism/Transport Effects**Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Theophylline Derivatives: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Peak serum acebutolol levels may be slightly decreased if taken with food.

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid yohimbe, ginseng (may worsen hypertension).

Test InteractionsIncreased AST, ALT, alkaline phosphatase, bilirubin, cholesterol, glucose, LDH, potassium, thyroxine, triglycerides, uric acid; decreased HDL

Monitoring ParametersBlood glucose; blood pressure, orthostatic hypotension, heart rate, CNS effects, ECG

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response on a regular basis during therapy. When discontinuing therapy, taper dosage over 2 weeks. Assess knowledge/teach patient appropriate use, possible side effects (including altered glucose tolerance for patients with diabetes)/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsBlood glucose

Patient EducationTake exactly as directed; do not increase, decrease, or adjust dosage without consulting prescriber. May be taken without regard to meals. Take pulse daily, prior to medication, and follow prescriber's instruction about holding medication. Do not take with antacids. Do not use OTC medications such as cold remedies without consulting prescriber. If you have diabetes, monitor serum sugar closely (drug may alter glucose tolerance or mask signs of hypoglycemia). May cause fatigue, dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when changing position from lying or sitting to standing or when climbing stairs); or alteration in sexual performance (reversible). Report chest pain or palpitations, unresolved swelling of extremities or unusual weight gain, respiratory difficulty or new cough, skin rash, unresolved fatigue, unresolved constipation or diarrhea, unusual muscle weakness, or CNS disturbances. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 200 mg, 400 mg

Sectral®: 200 mg, 400 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Acebutolol HCl)

200 mg (100): $54.98

400 mg (30): $21.99

Capsules (Sectral)

200 mg (60): $169.99

400 mg (30): $124.99

Mechanism of ActionCompetitively blocks beta$_1$-adrenergic receptors with little or no effect on beta$_2$-receptors except at high doses; exhibits membrane stabilizing and intrinsic sympathomimetic activity

Pharmacodynamics/Kinetics

Onset of action: 1-2 hours

Duration: 12-24 hours

Absorption: Oral: 40%

Protein binding: ~26%

Metabolism: Extensive first-pass effect to equipotent and cardioselective diacetolol metabolite

Half-life elimination: Parent drug: 3-4 hours; Metabolite: 8-13 hours

Time to peak: 2-4 hours

Excretion: Feces (50% to 60%); urine (30% to 40%); diacetolol eliminated primarily in the urine

Related Information

- Beta-Blockers

Dental Health: Effects on Dental TreatmentAcebutolol is a cardioselective beta-blocker. Local anesthetic with vasoconstrictor can be safely used in patients medicated with acebutolol. Nonselective beta-blockers (ie, propranolol, nadolol) enhance the pressor response to epinephrine, resulting in hypertension and bradycardia; this has not been reported for acebutolol. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions. Local anesthetic with vasoconstrictor can be safely used in patients medicated with acebutolol.

Mental Health: Effects on Mental StatusDrowsiness/fatigue is common; may cause insomnia, depression, abnormal dreams, and polyuria

Mental Health: Effects on Psychiatric TreatmentAdditive hypotensive and/or sedative effects may be seen with concurrent use of antipsychotics, antidepressants, or benzodiazepines

Cardiovascular ConsiderationsThis drug possesses intrinsic sympathomimetic activity (ISA). While beta-blockers with ISA induce fewer side effects, the cardiovascular benefits listed below are less clear than for beta-blockers without ISA.

Heart Failure: Beta-blockers with ISA (eg, acebutolol) are likely to worsen survival and should be avoided. Beta-blockers shown to improve survival in clinical trials should be used in these patients.

Hypertension: Beta-blocker therapy in the treatment of hypertension has been associated with improved cardiovascular outcomes. According to the 2003 JNC-VII guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Beta-blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for a beta-blocker include patients with heart failure, postmyocardial infarction, high coronary disease risk, or diabetes. In type 2 diabetic patients, a UK Prospective Diabetes Study Group (UKPDS) trial showed that beta-blocker therapy (atenolol) was as effective as an ACE inhibitor in reducing cardiovascular events and that the benefits of therapy were related more to the degree of antihypertensive efficacy rather than the class of drug used.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia and hypertension.

Index Terms Acebutolol Hydrochloride

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International Brand Names Abutol (PL); ACB (NZ); Acebutolol (PL); Acecor (PL); Acetanol (JP); Beloc (CN); Butobloc (ZA); Cetolol (PL); Diasectral (DK, FI); Flebutol (VE); Grifobutol (CN); Prent (CH, DE, IT, PT); Rhodiasectral (AR); Sectral (AE, AT, BB, BE, BG, BH, BM, BR, BS, BZ, CH, CY, CZ, EG, ES, FR, GB, GY, HK, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KW, LB, LU, LY, NL, OM, PL, QA, SA, SR, SY, TT, TW, YE, ZA); Sectral LP (FR); Wesfalin (AR)

Acenocoumarol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety IssuesInterferes with hepatic synthesis of vitamin K-dependent coagulation factors (II, VII, IX, X)

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(a see no KOOM a rol)

Canadian Brand NamesSintrom®

Pharmacologic CategoryAnticoagulant, Coumarin Derivative

Use: Labeled IndicationsProphylaxis and treatment of venous thrombosis, pulmonary embolism, and thromboembolic disorders; atrial fibrillation with risk of embolism; adjunct in the prophylaxis of coronary occlusion and transient ischemic attacks

Dosing: Adults**Note:** Dosage must be individualized. The following information is based on the manufacturer's labeling in Canada.

Oral: Initial: 8-12 mg on day 1, followed by 4-8 mg on day 2. Subsequent dosage should be based on PT/INR measurements. Usual range of maintenance doses: 1-10 mg/day. Tapering of dosage is recommended prior to discontinuation.

Dosing: ElderlyRefer to adult dosing.

Administration: OralAdminister at the same time each day.

Dietary ConsiderationsFoods high in vitamin K (eg, beef liver, pork liver, green tea, and leafy green vegetables) inhibit anticoagulant effect. Do not change dietary habits once stabilized on acenocoumarol therapy. A balanced diet with a consistent intake of vitamin K is essential. Avoid large amounts of alfalfa, asparagus, broccoli, Brussels sprouts, cabbage, cauliflower, green teas, kale, lettuce, spinach, turnip greens, watercress; these decrease efficacy of oral anticoagulants. It is recommended that the diet contain a CONSISTENT vitamin K content of 70-140 mcg/day. Check with healthcare provider before changing diet. Avoid using multivitamins that contain vitamin K.

Storage Store at 20°C to 25°C (68°F to 77°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to acenocoumarol or any component of the formulation; hemorrhagic tendencies; hemophilia; thrombocytopenia purpura; leukemia; recent or potential surgery of the eye or CNS; major regional lumbar block anesthesia or surgery resulting in large, open surfaces; bleeding from the GI, respiratory, or GU tract; threatened abortion; aneurysm; prolonged dietary insufficiencies (vitamin K deficiency); ascorbic acid deficiency; history of bleeding diathesis; prostatectomy; continuous tube drainage of the small intestine; polyarthritis; diverticulitis; emaciation; malnutrition; cerebrovascular hemorrhage; eclampsia/pre-eclampsia; blood dyscrasias; severe uncontrolled or malignant hypertension; severe hepatic disease; pericarditis or pericardial effusion; subacute bacterial endocarditis; visceral carcinoma; following spinal puncture and other diagnostic or therapeutic procedures with potential for significant bleeding; history of warfarin-induced necrosis; an unreliable, noncompliant patient; alcoholism; patient who has a history of falls or is a significant fall risk; pregnancy

Allergy Considerations

- Coumarin-Type Anticoagulant Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity: May cause hypersensitivity reactions, including anaphylaxis; use with caution in patients with anaphylactic disorders.
- Bleeding: May cause major or fatal bleeding. Risk factors for bleeding include high intensity anticoagulation (INR >4), age (>65 years), variable INRs, history of GI bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, severe diabetes, malignancy, trauma, renal insufficiency, polycythemia vera, vasculitis, open wound, history of PUD, indwelling catheters, menstruating and postpartum women, drug-drug interactions and long duration of therapy. Patient must be instructed to report bleeding, accidents, or falls as well as any new or discontinued medications, herbal or alternative products used, significant changes in smoking or dietary habits.
- Skin necrosis/gangrene: Necrosis or gangrene of the skin and other tissues can occur (rarely) due to early hypercoagulability; risk is increased in patients with protein C deficiency. "Purple toe” syndrome, due to cholesterol microembolization, has been described with coumarin-type anticoagulants.

Disease-related concerns:

- Infection: Use with caution in patients with acute infection or active TB; antibiotics and fever may alter response to acenocoumarol.
- Renal impairment: Use with caution in patients with renal impairment.
- Thyroid disease: Use with caution in patients with thyroid disease.

Special populations:

- Elderly: The elderly may be more sensitive to anticoagulant therapy.

- Ovulating women: May be at risk of developing ovarian hemorrhage at the time of ovulation.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Patient selection: Use care in the selection of patients appropriate for this treatment; ensure patient cooperation especially from the alcoholic, illicit drug user, demented, or psychotic patient.

Pregnancy ConsiderationsOral anticoagulants cross the placenta and produce fetal abnormalities. Fatal hemorrhage in the fetus has been reported even when the mother's acenocoumarol levels were in the therapeutic range. Acenocoumarol should not be used during pregnancy because of significant risks. Adjusted-dose heparin can be given safely throughout pregnancy in patients with venous thromboembolism. Women of childbearing potential are advised to use effective contraception during treatment.

LactationEnters breast milk/not recommended (per manufacturer)

Adverse ReactionsAs with all anticoagulants, bleeding is the major adverse effect of acenocoumarol. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the intensity of anticoagulation and patient susceptibility.

Frequency not defined.

Cardiovascular: Hemorrhagic shock

Central nervous system: Fever, headache, stroke (hemorrhagic)

Dermatologic: Rash, urticaria, skin necrosis

Skin necrosis/gangrene, due to paradoxical local thrombosis, is a known but rare risk of oral anticoagulant therapy. Its onset is usually within the first few days of therapy and is frequently localized to the limbs, breast, or penis. The risk of this effect is increased in patients with protein C or S deficiency.

Additional adverse reactions associated with warfarin, but likely to also occur with indanediones, include priapism and skin necrosis ("purple toe" syndrome or cutaneous gangrene).

Gastrointestinal: Gastrointestinal bleeding, melena

Genitourinary: Hematuria

Hematologic: Hemorrhage, retroperitoneal hematoma, unrecognized bleeding sites (eg, colon cancer) may be uncovered by anticoagulation. Other hematologic reactions reported with coumarin derivatives include agranulocytosis, red cell aplasia, anemia, thrombocytopenia, eosinophilia.

Hepatic: Hepatitis, hepatotoxicity, hematobilia

Ocular: Ocular hemorrhage

Respiratory: Epistaxis, hemoptysis, pulmonary hemorrhage

Miscellaneous: Hypersensitivity/allergic reactions

Metabolism/Transport Effects**Substrate** of CYP1A2 (major), 2C9 (major), 2C19 (minor)

Drug Interactions

Acetaminophen: May enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Allopurinol: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Aminoglutethimide: May increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Amiodarone: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Androgens: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Antineoplastic Agents: May enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. **Exceptions:** Alitretinoin; Altretamine; Aminoglutethimide; Anastrozole; Asparaginase; AzaCITIDine; Bleomycin; Capecitabine; CARBOplatin; Carmustine; Chlorambucil; CISplatin; Cladribine; Cytarabine; Cytarabine (Liposomal); Dacarbazine; DACTINomycin; DAUNOrubicin Citrate (Liposomal); DAUNOrubicin Hydrochloride; Denileukin Diftitox; Docetaxel; DOXOrubicin (Liposomal); Epirubicin; Estramustine; Etoposide Phosphate; Exemestane; Fludarabine; Goserelin; Hydroxyurea; IDArubicin; Irinotecan; Letrozole; Leuprolide; Lomustine; Mechlorethamine; Megestrol; Mitomycin; Mitoxantrone; Nilutamide; Paclitaxel; Pegaspargase; Pentostatin; Polyestradiol; Porfimer; RiTUXimab; Streptozocin; Tamoxifen; Temozolomide; Teniposide; Thioguanine; Thiotepa; Topotecan; Toremifene; Tretinoin (Oral); Valrubicin; VinBLAStine; Vinorelbine. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antithyroid Agents: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

AzaTHIOprine: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Vitamin K Antagonists. *Risk C: Monitor therapy*

Bosentan: May increase the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Capecitabine: May increase the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

CarBAMazepine: May decrease the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Cephalosporins: May enhance the anticoagulant effect of Vitamin K Antagonists. **Exceptions:** Cefaclor; Cefadroxil; Cefdinir; Cefepime; Cefixime; Cefonicid; Cefotaxime; Cefpodoxime; Cefprozil; Ceftazidime; Ceftibuten; Ceftizoxime; Ceftobiprole; Cefuroxime; Cephalexin; Cephradine [Off Market]. *Risk C: Monitor therapy*

Cimetidine: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Coenzyme Q-10: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Contraceptive (Progestins): May diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Dicloxacillin: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Disulfiram: May increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Drotrecogin Alfa: Vitamin K Antagonists may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Efavirenz: May increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Etoposide: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Fenugreek: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Fibric Acid Derivatives: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Fluconazole: May decrease the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Fluorouracil: May increase the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Gefitinib: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ginkgo Biloba: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Glucagon: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Glutethimide: May increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Griseofulvin: May increase the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: May enhance the anticoagulant effect of Vitamin K Antagonists. **Exceptions:** Atorvastatin. *Risk C: Monitor therapy*

Ifosfamide: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ivermectin: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Leflunomide: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Vitamin K Antagonists. **Exceptions:** Dirithromycin [Off Market]; Spiramycin. *Risk C: Monitor therapy*

Mercaptopurine: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

MetroNIDAZOLE: May decrease the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Nafcillin: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Phenytoin: May enhance the anticoagulant effect of Vitamin K Antagonists. Vitamin K Antagonists may increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Phytonadione: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Propafenone: May increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

QuiNIDine: May enhance the anticoagulant effect of Vitamin K Antagonists. Note that the prothrombin time might be unchanged in the face of increased bleeding. *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Sulfinpyrazone [Off Market]: May decrease the metabolism of Vitamin K Antagonists. Sulfinpyrazone [Off Market] may decrease the protein binding of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Tamoxifen: May increase the serum concentration of Vitamin K Antagonists. *Risk X: Avoid combination*

Tetracycline Derivatives: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thyroid Products: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Vitamin A: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Vitamin E: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Vorinostat: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zafirlukast: May decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol. Acute ethanol ingestion (binge drinking) decreases the metabolism of oral anticoagulants and increases PT/INR. Chronic daily ethanol use increases the metabolism of oral anticoagulants and decreases PT/INR.

Food: The anticoagulant effects of acenocoumarol may be decreased if taken with foods rich in vitamin K. Vitamin E may increase anticoagulant effect.

Herb/Nutraceutical: St John's wort may decrease oral anticoagulant levels. Alfalfa contains large amounts of vitamin K as do many enteral products. Coenzyme Q_{10} may decrease response to oral anticoagulants. Avoid cat's claw, dong quai, evening primrose, feverfew, red clover, horse chestnut, garlic, green tea, ginseng, and ginkgo (all have additional antiplatelet activity).

Monitoring ParametersPT/INR; hepatic function, CBC, urinalysis (for albuminuria/proteinuria)
Monitoring: Lab TestsPT/INR; hepatic function, CBC, urinalysis (for albuminuria/proteinuria)
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet:

Sintrom® [CAN]: 1 mg, 4 mg [not available in the U.S.]

Generic AvailableNo
ManufacturerPendopharm (Canada)
Mechanism of ActionInterferes with hepatic synthesis of vitamin K-dependent coagulation factors (II, VII, IX, X)
Pharmacodynamics/Kinetics

Onset of action: Peak anticoagulant effect: Oral: 36-48 hours

Absorption: Oral: 60%

Protein binding: 99%

Metabolism: Hepatic, via oxidation (possibly by CYP1A2, 2C9, and 2C19) to inactive metabolites

Half-life elimination: 8-11 hours

Time to peak, plasma: 1-3 hours

Excretion: Urine (60%) and feces (29%) as metabolites

Pharmacotherapy PearlsA variety of algorithms and computer-assisted dosing regimens have been reported. Sensitivity to the anticoagulant effect of acenocoumarol has been associated with genetic variations in CYP2C9.

Dental Health: Effects on Dental TreatmentSigns of acenocoumarol overdose may first appear as bleeding from gingival tissue; consultation with physician is advisable prior to surgery to determine temporary dose reduction or withdrawal of medication.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentCarbamazepine may decrease the effects of acenocoumarol; SSRIs may enhance the anticoagulant effects of acenocoumarol

Index TermsAcenocoumarin; Nicoumalone

International Brand NamesAcenocoumarol (PL); Acenocumarol (PL); Acenox (CN); Acitrom (IN); Neo-Sintrom (CN); Sinthrome (GB); Sintrom (AR, BE, BG, CH, FR, GR, IL, IT, MX, NL, PL, PY); Syncumar (PL)

Acetaminophen and Pamabrom

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation

(a seet a MIN oh fen & PAM a brom)

U.S. Brand NamesCramp Tabs [OTC]; Midol Teen Formula [OTC]; Tylenol® Women's Menstrual Relief [OTC]

Pharmacologic CategoryAnalgesic, Miscellaneous; Diuretic, Combination

Use: Labeled IndicationsTemporary relief of symptoms associated with premenstrual and menstrual symptoms (eg, cramps, bloating, water-weight gain, headache, backache, muscle aches)

Dosing: Adults**Menstrual symptoms:** Oral: Acetaminophen 650-1000 mg and pamabrom 50 mg every 4-6 hours as needed (maximum: 8 caplets/tablets/24 hours)

Dosing: PediatricChildren ≥12 years: Refer to adult dosing.

StorageStore at room temperature 15°C to 25°C (59°F to 77°F); avoid excessive heat.

Warnings/Precautions

Concerns related to adverse effects:

- Hepatotoxicity: Acetaminophen may cause hepatic toxicity with acute overdose; in addition chronic daily dosing has resulted in liver damage in some adults.

- Hypersensitivity: Discontinue use if hypersensitivity occurs.

Disease-related concerns:

- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.

Special populations:

- Pediatrics: Not for use in children <12 years of age.

Other warnings/precautions:

- Dosage limit: Limit acetaminophen dose to <4 g/day in adults.

- Self-medication (OTC use): Should not be used with other products containing acetaminophen. Patients should be instructed to contact healthcare provider if new symptoms occur, if redness or swelling occurs, or pain lasting >10 days.

Adverse ReactionsSee Acetaminophen monograph.

Drug Interactions

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Excessive intake of ethanol may increase the risk of acetaminophen-induced hepatotoxicity. Avoid ethanol or limit to <3 drinks/day.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet:

Midol Teen Formula: Acetaminophen 500 mg and pamabrom 25 mg

Tylenol® Women’s Menstrual Relief: Acetaminophen 500 mg and pamabrom 25 mg

Tablet:

Cramp Tabs: Acetaminophen 325 mg and pamabrom 25 mg

Generic AvailableYes

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentBarbiturates, carbamazepine, and phenytoin may increase the metabolism of acetaminophen diminishing its effect and increasing the risk of liver damage; monitor.

Index TermsPamabrom and Acetaminophen

Acetaminophen, Aspirin, and Caffeine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Excedrin® may be confused with Dexatrim®, Dexedrine®

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen, AS pir in, & KAF een)

U.S. Brand NamesExcedrin® Extra Strength [OTC]; Excedrin® Migraine [OTC]; Fem-Prin® [OTC]; Genaced™ [OTC]; Goody's® Extra Strength Headache Powder [OTC]; Goody's® Extra Strength Pain Relief [OTC]; Pain-Off [OTC]; Vanquish® Extra Strength Pain Reliever [OTC]

Pharmacologic CategoryAnalgesic, Miscellaneous

Use: Labeled IndicationsRelief of mild-to-moderate pain; mild-to-moderate pain associated with migraine headache

Dosing: Adults

Pain management:

Based on **acetaminophen** component:

Mild-to-moderate pain: Oral: 325-650 mg every 4-6 hours as needed; do **not** exceed 4 g/day

Mild-to-moderate pain associated with migraine headache: Oral: 500 mg/dose (in combination with 500 mg aspirin and 130 mg caffeine) every 6 hours while symptoms persist; do not use for longer than 48 hours

Based on **aspirin** component:

Mild-to-moderate pain: Oral: 325-650 mg every 4-6 hours as needed; do **not** exceed 4 g/day

Mild-to-moderate pain associated with migraine headache: Oral: 500 mg/dose (in combination with 500 mg acetaminophen and 130 mg caffeine) every 6 hours; do not use for longer than 48 hours

Product labeling:

Excedrin® Extra Strength, Excedrin® Migraine: Oral: 2 doses every 6 hours (maximum: 8 doses/24 hours)

Note: When used for migraine, do not use for longer than 48 hours

Goody's® Extra Strength Headache Powder: Oral: 1 powder, placed on tongue or dissolved in water, every 4-6 hours (maximum: 4 powders/24 hours)

Goody's® Extra Strength Pain Relief Tablets: Oral: 2 tablets every 4-6 hours (maximum: 8 tablets/24 hours)

Vanquish® Extra Strength Pain Reliever: Oral: 2 tablets every 4 hours (maximum: 12 tablets/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Product labeling:

Excedrin® Extra Strength, Excedrin® Migraine: Oral: Children >12 years: Refer to adult dosing

Goody's® Extra Strength Headache Powder: Oral: Children >12 years: Refer to adult dosing

Goody's® Extra Strength Pain Relief Tablets: Oral: Children >12 years: Refer to adult dosing

Vanquish® Extra Strength Pain Reliever: Oral: Children >12 years: Refer to adult dosing

Dosing: Hepatic ImpairmentUse with caution. Limited, low-dose therapy usually well tolerated in hepatic disease/cirrhosis. However, cases of hepatotoxicity at daily acetaminophen dosages <4 g/day have been reported. Avoid chronic use in hepatic impairment.

ContraindicationsHypersensitivity to acetaminophen, aspirin, salicylates, caffeine, or any component of the formulation; pregnancy

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity
- Salicylate Allergy/Sensitivity

Pregnancy Risk FactorD

Adverse ReactionsSee individual agents.

Metabolism/Transport Effects

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Aspirin: **Substrate** (minor) of CYP2C9

Caffeine: **Substrate** of CYP1A2 (major), 2C9 (minor), 2D6 (minor), 2E1 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 3A4 (moderate)

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: May decrease the metabolism of Caffeine. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Ofloxacin; Sparfloxacin; Trovafloxacin. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Regadenoson: Caffeine may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Excessive intake of ethanol may increase the risk of acetaminophen-induced hepatotoxicity. Avoid ethanol or limit to <3 drinks/day.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet:

Excedrin® Extra Strength, Excedrin® Migraine: Acetaminophen 250 mg, aspirin 250 mg, and caffeine 65 mg

Vanquish® Extra Strength Pain Reliever: Acetaminophen 194 mg, aspirin 227 mg, and caffeine 33 mg

Geltab (Excedrin® Extra Strength, Excedrin® Migraine): Acetaminophen 250 mg, aspirin 250 mg, and caffeine 65 mg

Powder (Goody's® Extra Strength Headache Powder): Acetaminophen 260 mg, aspirin 520 mg, and caffeine 32.5 mg [contains lactose]

Tablet:

Excedrin® Extra Strength, Excedrin® Migraine, Genaced™, Pain-Off: Acetaminophen 250 mg, aspirin 250 mg, and caffeine 65 mg

Fem-Prin®: Acetaminophen 194.4 mg, aspirin 226.8 mg, and caffeine 32.4 mg

Goody's® Extra Strength Pain Relief: Acetaminophen 130 mg, aspirin 260 mg, and caffeine 16.25 mg

Generic AvailableYes
Pharmacodynamics/KineticsSee individual agents.
Related Information

- Acetaminophen
- Aspirin
- Caffeine

Dental Health Professional ConsiderationsThere is no scientific evidence to warrant discontinuance of aspirin prior to dental surgery. Patients taking one aspirin tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with the physician before removal of the aspirin relative to prevention of postoperative bleeding.

The Food and Drug Administration (FDA), has issued a letter updating information and considerations regarding the use of ibuprofen (400 mg doses) in patients who are taking low dose aspirin (81 mg, immediate release; not enteric coated) for cardioprotection and stroke prevention. Ibuprofen, at these doses, may interfere with aspirin's antiplatelet effect depending upon when it is administered. Patients initiated on aspirin first (for ~1 week) then ibuprofen (400 mg 3 times/day for 10 days) seem to maintain aspirin's platelet effect (Cryer B, 2005). Ibuprofen has the greatest impact on aspirin if administered less than 8 hours before aspirin (Catella-Lawson F, 2001).

Patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. With occasional use of ibuprofen, a clinically-significant interaction with aspirin in unlikely. To avoid interference during chronic dosing, a single dose of ibuprofen should be taken 30-120 minutes after aspirin ingestion or at least 8 hours should elapse after ibuprofen dosing before giving aspirin (FDA, 2006; Catella-Lawson F, 2001).

The clinical implications of the interaction are unclear. There have not been any clinical endpoint studies conducted at this time. Avoidance of this interaction is potentially important because aspirin's vascular protection could be decreased or negated.

Other nonselective NSAIDs may have potential for a similar interaction with aspirin. Such has been described with naproxen (Capone ML, 2005). Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin. Other clinical scenarios (use of smaller ibuprofen doses, other aspirin products, other doses of aspirin) have not been evaluated.

Additional information is available at: http://www.fda.gov/cder/drug/infopage/aspirin/default.htm

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Aspirin: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity (see Dental Comment).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause anxiety, insomnia, and excitability
Mental Health: Effects on Psychiatric TreatmentEffects of CNS depressants may be lessened by caffeine component
Index TermsAspirin, Acetaminophen, and Caffeine; Aspirin, Caffeine and Acetaminophen; Caffeine, Acetaminophen, and Aspirin; Caffeine, Aspirin, and Acetaminophen
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Acetaminophen, Caffeine, and Dihydrocodeine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Panlor® DC may be confused with Pamelor®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen, KAF een, & dye hye droe KOE deen)
U.S. Brand NamesPanlor® DC; Panlor® SS; ZerLor™
Pharmacologic CategoryAnalgesic Combination (Opioid)
Use: Labeled IndicationsRelief of moderate to moderately-severe pain
Use: DentalRelief of moderate to moderately-severe dental pain
Dosing: AdultsRelief of pain: Oral:

Panlor® DC: 2 capsules every 4 hours as needed; adjust dose based on severity of pain (maximum dose: 10 capsules/24 hours)

Panlor® SS, ZerLor™: 1 tablet every 4 hours as needed; adjust dose based on severity of pain (maximum dose: 5 tablets/24 hours)

Dosing: ElderlyRefer to adult dosing.
StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from moisture.
RestrictionsC-III
ContraindicationsHypersensitivity to acetaminophen, caffeine, dihydrocodeine, codeine, or any component of the formulation; significant respiratory depression (in unmonitored settings); acute or severe bronchial asthma; hypercapnia; paralytic ileus
Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hepatotoxicity: Acetaminophen may cause severe hepatic toxicity on acute overdose; in addition, chronic daily dosing in adults has resulted in liver damage in some patients.
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene-derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.
- G6PD deficiency: Use with caution in patients with known G6PD deficiency.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Hypotension: Use with caution in patients with hypotension.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use with caution in patients with respiratory diseases including asthma, emphysema, and/or COPD.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- MAO inhibitors: Use with caution with concurrent use of MAO inhibitors.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Caffeine: May cause CNS and cardiovascular stimulation, as well as GI irritation in high doses. Use with caution in patients with a history of peptic ulcer or GERD; avoid in patients with symptomatic cardiac arrhythmias.

- Dosage limit: Limit total acetaminophen dose to <4 g/day.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsAcetaminophen and caffeine are both excreted in breast milk. Specific information for dihydrocodeine is not available; however, similar agents (eg, codeine, morphine) are excreted in breast milk.
Adverse ReactionsFrequency not defined. Most common reactions with this combination include:

Central nervous system: Dizziness, drowsiness, lightheadedness, sedation

Dermatologic: Pruritus, skin reactions

Gastrointestinal: Constipation, nausea, vomiting

Metabolism/Transport Effects

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Caffeine: **Substrate** of CYP1A2 (major), 2C9 (minor), 2D6 (minor), 2E1 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 3A4 (moderate)

Dihydrocodeine: **Substrate** of CYP2D6 (minor)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

QuiNIDine: May diminish the analgesic effect of Dihydrocodeine. *Risk D: Consider therapy modification*

Quinolone Antibiotics: May decrease the metabolism of Caffeine. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Ofloxacin; Sparfloxacin; Trovafloxacin. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Regadenoson: Caffeine may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Excessive intake of ethanol may increase the risk of acetaminophen-induced toxicity. Ethanol may also increase CNS depression.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Panlor® DC: Acetaminophen 356.4 mg, caffeine 30 mg, and dihydrocodeine bitartrate 16 mg

Tablet:

Panlor® SS, ZerLor™: Acetaminophen 712.8 mg, caffeine 60 mg, and dihydrocodeine bitartrate 32 mg

Generic Available

Yes: Tablet

Manufacturer

PamLab

Pricing: U.S. (www.drugstore.com)

Capsules (Panlor DC)

356.4-30-16 mg (30): $46.99

Tablets (Panlor SS)

712.8-60-32 mg (30): $58.99

Mechanism of Action

Acetaminophen inhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation; produces antipyresis from inhibition of hypothalamic heat-regulating center.

Caffeine is a CNS stimulant; use with acetaminophen and dihydrocodeine increases the level of analgesia provided by each agent.

Dihydrocodeine binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression.

Related Information

- Acetaminophen
- Caffeine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness

Mental Health: Effects on Psychiatric TreatmentMay cause nausea and vomiting; combined use with SSRIs, acetylcholinesterase inhibitors, aripiprazole, or ziprasidone may produce additive effects. The effects of benzodiazepines, mirtazapine, nefazodone, and venlafaxine may be enhanced by caffeine (CYP3A4 inhibitor). Use with chlorpromazine, fluoxetine, paroxetine, pergolide, or ropinirole may decrease the effects of dihydrocodeine. Fluvoxamine may increase the effects of caffeine. Reduce caffeine consumption by 50% or choose an alternative SSRI. Barbiturates, carbamazepine, and excessive intake of ethanol may decrease the effectiveness, as well as increase the hepatotoxic potential of acetaminophen. Combined use with psychotropics may produce additive sedative effects.

Index TermsCaffeine, Dihydrocodeine, and Acetaminophen; Dihydrocodeine Bitartrate, Acetaminophen, and Caffeine

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Acetaminophen, Chlorpheniramine, and Pseudoephedrine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Thera-Flu® may be confused with Tamiflu®, Thera-Flur-N®

Tylenol® may be confused with atenolol, timolol, Tuinal®, Tylox®

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen, klor fen IR a meen, & soo doe e FED rin)

U.S. Brand NamesActifed® Cold and Sinus [OTC]; Comtrex® Flu Therapy Nighttime [OTC]; Drinex [OTC]; Kolephrin® [OTC]; Sinutab® Sinus Allergy Maximum Strength [OTC]; Tylenol® Children’s Plus Cold Nighttime [OTC] [DSC]

Canadian Brand NamesSinutab® Sinus & Allergy; Tylenol® Allergy Sinus

Pharmacologic CategoryAlpha/Beta Agonist; Analgesic, Miscellaneous; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporary relief of sinus symptoms

Dosing: Adults

Pain (Analgesic): Oral: Based on acetaminophen component: 325-650 mg every 4-6 hours as needed; do **not** exceed 4 g/day

Rhinitis (Antihistamine): Oral: Based on chlorpheniramine maleate component: 4 mg every 4-6 hours (maximum: 24 mg/24 hours)

Nasal congestion (Decongestant): Oral: Based on pseudoephedrine component: 60 mg every 4 hours (maximum: 360 mg/24 hours)

Product labeling:

Sinutab® Sinus Allergy Maximum Strength: Oral: 2 tablets/caplets every 6 hours (maximum: 8 doses/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Analgesic: Oral: Based on acetaminophen component: 10-15 mg/kg/dose every 4-6 hours as needed; do **not** exceed 5 doses in 24 hours.

Antihistamine: Oral: Based on chlorpheniramine maleate component:

2-6 years: 1 mg every 4-6 hours (maximum: 6 mg/24 hours)

6-12 years: 2 mg every 4-6 hours (maximum: 12 mg/24 hours)

Children >12 years: Refer to adult dosing.

Decongestant: Oral: Based on pseudoephedrine component:

2-6 years: 15 mg every 4 hours (maximum: 90 mg/24 hours)

6-12 years: 30 mg every 4 hours (maximum: 180 mg/24 hours)

Children >12 years: Refer to adult dosing.

Product labeling:

Sinutab® Sinus Allergy Maximum Strength: Oral: Children >12 years: Refer to adult dosing.

Dosing: Hepatic ImpairmentUse with caution. Limited, low-dose therapy usually well tolerated in hepatic disease/cirrhosis; however, cases of hepatotoxicity at daily acetaminophen dosages <4 g/day have been reported. Avoid chronic use in hepatic impairment.

Dietary Considerations

Children's Tylenol® Plus Cold contains phenylalanine 6 mg/tablet.

Thera-Flu® Cold and Sore Throat Night Time contains phenylalanine 11 mg/packet.

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity

Pregnancy Risk FactorB

Adverse ReactionsSee individual agents.

Metabolism/Transport Effects

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Chlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Excessive intake of ethanol may increase the risk of acetaminophen-induced hepatotoxicity. Avoid ethanol or limit to <3 drinks/day.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet: Acetaminophen 325 mg, chlorpheniramine maleate 2 mg, and pseudoephedrine hydrochloride 30 mg

Actifed® Cold and Sinus, Sinutab® Sinus Allergy Maximum Strength: Acetaminophen 500 mg, chlorpheniramine maleate 2 mg, and pseudoephedrine hydrochloride 30 mg

Kolephrin®: Acetaminophen 325 mg, chlorpheniramine maleate 2 mg, and pseudoephedrine hydrochloride 30 mg

Liquid:

Comtrex® Flu Therapy Nighttime: Acetaminophen 100 mg, chlorpheniramine maleate 4 mg, and pseudoephedrine hydrochloride 60 mg per 30 mL (240 mL) [contains alcohol; cherry flavor]

Tylenol® Children's Plus Cold Nighttime: Acetaminophen 160 mg, chlorpheniramine maleate 1 mg, and pseudoephedrine hydrochloride 15 mg per 5 mL (120 mL) [contains sodium benzoate; grape flavor] [DSC]

Tablet:

Drinex: Acetaminophen 650 mg, chlorpheniramine maleate 4 mg, and pseudoephedrine hydrochloride 60 mg

Generic AvailableYes

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Acetaminophen
- Chlorpheniramine
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Chlorpheniramine: Significant xerostomia with prolonged use (normal salivary flow resumes upon discontinuation).

Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental Status Sedation with chlorpheniramine is countered by the excitability associated with pseudoephedrine; one effect may predominate in any particular patient

Mental Health: Effects on Psychiatric Treatment Usually none; sedative effect of chlorpheniramine may be potentiated by other CNS depressants and MAO inhibitors

Index Terms Acetaminophen, Pseudoephedrine, and Chlorpheniramine; Chlorpheniramine, Acetaminophen, and Pseudoephedrine; Chlorpheniramine, Pseudoephedrine, and Acetaminophen; Pseudoephedrine, Acetaminophen, and Chlorpheniramine; Pseudoephedrine, Chlorpheniramine, and Acetaminophen

References

Barker JD Jr, de Carle DJ, and Anuras S, "Chronic Excessive Acetaminophen Use in Liver Damage," *Ann Intern Med*, 1977, 87(3):299-301. [PubMed 900673]

Dionne RA, Campbell RA, Cooper SA, et al, "Suppression of Postoperative Pain by Preoperative Administration of Ibuprofen in Comparison to Placebo, Acetaminophen, and Acetaminophen Plus Codeine," *J Clin Pharmacol*, 1983, 23(1):37-43. [PubMed 6341415]

Licht H, Seeff LB, and Zimmerman HJ, "Apparent Potentiation of Acetaminophen Hepatotoxicity by Alcohol," *Ann Intern Med*, 1980, 92(4):511.

Mokhlesi B, Leikin JB, Murray P, et al, "Adult Toxicology in Critical Care: Part II: Specific Poisonings," *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand Names Coldrex Night (NZ); Panadol Allergy Sinus (AU); Sinumax Allergy Sinus (ZA)

Acetaminophen, Codeine, and Doxylamine

Lexi-Drugs Online

English

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen, KOE deen, & dox IL a meen)

Canadian Brand NamesMersyndol® With Codeine

Pharmacologic CategoryAnalgesic, Miscellaneous; Analgesic, Opioid; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsRelief of headache, cold symptoms, neuralgia, and muscular aches/pain

Dosing: AdultsOral: 1-2 tablets every 4 hours as needed; total dose should not exceed 12 tablets in a 24-hour period

Dosing: PediatricRefer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment required.

Dosing: Hepatic Impairment

Acetaminophen: Use with caution. Limited, low-dose therapy usually well tolerated in hepatic disease/cirrhosis. However, cases of hepatotoxicity at daily acetaminophen dosages <4 g/day have been reported. Avoid chronic use in hepatic impairment.

Codeine: Dosage adjustment of codeine is probably necessary in hepatic insufficiency; no specific guidelines available.

StorageStore at 20°C to 25°C (68°F to 77°F).

RestrictionsCDSA-1; Not available in U.S.

ContraindicationsHypersensitivity to acetaminophen, codeine, doxylamine, or any component of the formulation; significant respiratory depression (in unmonitored settings); acute or severe bronchial asthma; hypercapnia

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hepatotoxicity: Acetaminophen may cause severe hepatic toxicity on acute overdose; in addition, chronic daily dosing in adults has resulted in liver damage in some patients.
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene-derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension/hypotension and tachycardia).
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.
- G6PD deficiency: Use with caution in patients with known G6PD deficiency.
- Gastrointestinal motility disorders: Use with caution in patients with gastrointestinal motility disorders; avoid in paralytic ileus.
- Glaucoma: Use with caution in patients with angle-closure glaucoma and/or increased intraocular pressure.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

- Surgical patients: Use with caution in postoperative patients following thoracotomy or laparotomy due to suppression of cough.

Other warnings/precautions:

- Dosage limit: Limit total acetaminophen dose to <4 g/day.

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Should not be used in pregnancy unless the potential benefit to the mother justifies possible harm to the fetus. Refer to Codeine monograph.

LactationNo data available.

Breast-Feeding ConsiderationsDoxylamine may be excreted in breast milk, potentially resulting in sedative effects in nursing infants. Refer to Codeine monograph.

Adverse ReactionsSee individual agents.

Metabolism/Transport Effects

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Codeine: **Substrate** of CYP2D6 (major), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersRelief of pain, respiratory and mental status, blood pressure, bowel function

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet:

Mersyndol® With Codeine [CAN]: Acetaminophen 325 mg, codeine 8 mg, and doxylamine 5 mg [not available in the U.S.]

ManufacturerAventis Pharma Canada

Mechanism of ActionAcetaminophen inhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation; produces antipyresis from inhibition of hypothalamic heat-regulating center. Codeine binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; causes cough supression by direct central action in the medulla; produces generalized CNS depression. Doxylamine competes with histamine for H_1-receptor sites on effector cells; blocks chemoreceptor trigger zone, diminishes vestibular stimulation, and depresses labyrinthine function through its central anticholinergic activity.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Acetaminophen
- Codeine
- Doxylamine

Mental Health: Effects on Mental StatusDrowsiness is common; may cause dizziness, disorientation, euphoria, confusion, insomnia, hallucinations, or depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation and anticholinergic effects; conversely, the effects of cholinergic agonists will be ameliorated. Concurrent use with fluoxetine or paroxetine may result in loss of codeine's analgesic effects.

Index TermsCodeine, Doxylamine, and Acetaminophen; Doxylamine Succinate, Codeine Phosphate, and Acetaminophen

International Brand NamesMersyndol With Codeine (CA)

Acetaminophen and Codeine

Lexi-Drugs Online

English English

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Special Alerts

Tylenol® With Codeine: Health Canada Issues Warning Concerning Potentially Increased Morphine Levels In Milk of Nursing Mothers - October 9, 2008

Janssen-Ortho Inc, in conjunction with Health Canada, has issued a “Dear Healthcare Professional” letter concerning use of Tylenol® with Codeine (acetaminophen with codeine) products and the risk of elevated morphine levels in the serum and breast milk of nursing women who are ultra-rapid metabolizers of codeine. Consequently, infants of nursing mothers with a certain CYP2D6 (converts codeine to morphine) genotype, may be exposed to potentially dangerous serum levels of morphine as well.

Available data indicates the incidence of this CYP2D6 genotype in the general population varies and is estimated to occur in the following populations as follows: North African, Ethiopian, and Arab (16% to 28%); Chinese, Japanese, and Hispanic (0.5% to 1%); Caucasian (1% to 10%); African American (3%).

When using codeine in nursing women, healthcare providers are urged to prescribe and administer the lowest possible dose for the shortest time necessary to achieve adequate clinical effect. Nursing women should be advised of signs/symptoms of morphine toxicity for themselves (extreme sedation, confusion, shallow breathing) and for their infants (sedation, dyspnea, decreased tone, difficult breastfeeding). The manufacturer will be updating the product labeling to include these new warnings and precautions. A similar warning had previously been released in the U.S. in August 2007.

Additional information can be found at the following websites:

Canada: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/tylenol_codeine_hpc-cps-eng.php

U.S.: http://www.fda.gov/cder/drug/InfoSheets/HCP/codeineHCP.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Capital® may be confused with Capitrol®

Tylenol® may be confused with atenolol, timolol, Tuinal®, Tylox®

T3 is an error-prone abbreviation (mistaken as liothyronine)

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen & KOE deen)

U.S. Brand NamesCapital® and Codeine; Tylenol® With Codeine

Canadian Brand Namesratio-Emtec; ratio-Lenoltec; Triatec-30; Triatec-8; Triatec-8 Strong; Tylenol Elixir with Codeine; Tylenol No. 1; Tylenol No. 1 Forte; Tylenol No. 2 with Codeine; Tylenol No. 3 with Codeine; Tylenol No. 4 with Codeine

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled IndicationsRelief of mild-to-moderate pain

Use: DentalTreatment of postoperative pain

Dosing: AdultsDoses should be adjusted according to severity of pain and response of the patient. Adult doses ≥60 mg codeine fail to give commensurate relief of pain but merely prolong analgesia and are associated with an appreciably increased incidence of side effects.

Cough (Antitussive): Oral: Based on codeine (15-30 mg/dose) every 4-6 hours (maximum: 360 mg/24 hours based on codeine component)

Pain (Analgesic): Oral: Based on codeine (30-60 mg/dose) every 4-6 hours (maximum: 4000 mg/24 hours based on acetaminophen component)

1-2 tablets every 4 hours to a maximum of 12 tablets/24 hours

Dosing: ElderlyDoses should be titrated to appropriate analgesic effect.

1 Tylenol® [#3] or 2 Tylenol® [#2] tablets every 4 hours; do **not** exceed 4 g/day acetaminophen.

Dosing: Pediatric

Analgesic: Oral:

Codeine: 0.5-1 mg codeine/kg/dose every 4-6 hours

Acetaminophen: 10-15 mg/kg/dose every 4 hours up to a maximum of 2.6 g/24 hours for children <12 years

3-6 years: 5 mL 3-4 times/day as needed of elixir

7-12 years: 10 mL 3-4 times/day as needed of elixir

Children >12 years: 15 mL every 4 hours as needed of elixir

Dosing: Renal ImpairmentSee individual agents.

Dosing: Hepatic ImpairmentUse with caution. Limited, low-dose therapy is usually well tolerated in hepatic disease/cirrhosis; however, cases of hepatotoxicity at daily acetaminophen dosages <4 g/day have been reported. Avoid chronic use in hepatic impairment.

Dietary ConsiderationsMay be taken with food.

RestrictionsC-III; C-V

Note: In countries outside of the U.S., some formulations of Tylenol® with Codeine (eg, Tylenol® No. 3) include caffeine.

ContraindicationsHypersensitivity to acetaminophen, codeine, or any component of the formulation; significant respiratory depression (in unmonitored settings); acute or severe bronchial asthma; hypercapnia; paralytic ileus

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hepatotoxicity: May cause severe hepatic toxicity on acute overdose; in addition, chronic daily dosing in adults has resulted in liver damage in some patients.
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene-derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.
- G6PD deficiency: Use with caution in patients with known G6PD deficiency.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- CYP2D6 "ultra-rapid metabolizers": Use caution in patients with two or more copies of the variant CYP2D6*2 allele; may have extensive conversion to morphine and thus increased opioid-mediated effects.

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

Dosage form specific issues:

- Metabisulfite: Tablets contain metabisulfite which may cause allergic reactions.

- Non-U.S. formulations: Some non-U.S. formulations (including most Canadian formulations) may contain caffeine as an additional ingredient. Caffeine may cause CNS and cardiovascular stimulation, as well as GI irritation in high doses. Use with caution in patients with a history of peptic ulcer or GERD; avoid in patients with symptomatic cardiac arrhythmias.

Other warnings/precautions:

- Dosage limit: Limit total acetaminophen dose to <4 g/day.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Pregnancy Risk FactorC
Pregnancy ConsiderationsRefer to Codeine monograph.
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsRefer to Codeine monograph.
Adverse Reactions

>10%:

Central nervous system: Dizziness, lightheadedness, sedation

Gastrointestinal: Nausea, vomiting

Respiratory: Dyspnea

1% to 10%:

Central nervous system: Dysphonia, euphoria

Dermatologic: Pruritus

Gastrointestinal: Abdominal pain, constipation

Miscellaneous: Histamine release

<1%: Antidiuretic hormone release, biliary tract spasm, bradycardia, hypotension, intracranial pressure increased, miosis, palpitation, peripheral vasodilation, physical and psychological dependence, respiratory depression, urinary retention

Metabolism/Transport EffectsAcetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Excessive intake of ethanol may increase the risk of acetaminophen-induced hepatotoxicity. Avoid ethanol or limit to <3 drinks/day.

Monitoring ParametersRelief of pain, respiratory and mental status, blood pressure, bowel function

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product; [CAN] = Canadian brand name

Caplet:

ratio-Lenoltec No. 1 [CAN], Tylenol No. 1 [CAN]: Acetaminophen 300 mg, codeine phosphate 8 mg, and caffeine 15 mg [not available in the U.S.]

Tylenol No. 1 Forte [CAN]: Acetaminophen 500 mg, codeine phosphate 8 mg, and caffeine 15 mg [not available in the U.S.]

Elixir, oral [C-V]: Acetaminophen 120 mg and codeine phosphate 12 mg per 5 mL (5 mL, 10 mL, 12.5 mL, 15 mL, 120 mL, 480 mL) [contains alcohol 7%]

Tylenol® with Codeine [DSC]: Acetaminophen 120 mg and codeine phosphate 12 mg per 5 mL (480 mL) [contains alcohol 7%; cherry flavor]

Tylenol Elixir with Codeine [CAN]: Acetaminophen 160 mg and codeine phosphate 8 mg per 5 mL (500 mL) [contains alcohol 7%, sucrose 31%; cherry flavor; not available in the U.S.]

Suspension, oral [C-V] (Capital® and Codeine): Acetaminophen 120 mg and codeine phosphate 12 mg per 5 mL (480 mL) [alcohol free; fruit punch flavor]

Tablet [C-III]: Acetaminophen 300 mg and codeine phosphate 15 mg; acetaminophen 300 mg and codeine phosphate 30 mg; acetaminophen 300 mg and codeine phosphate 60 mg

ratio-Emtec [CAN], Triatec-30 [CAN]: Acetaminophen 300 mg and codeine phosphate 30 mg [not available in the U.S.]

ratio-Lenoltec No. 1 [CAN]: Acetaminophen 300 mg, codeine phosphate 8 mg, and caffeine 15 mg [not available in the U.S.]

ratio-Lenoltec No. 2 [CAN], Tylenol No. 2 with Codeine [CAN]: Acetaminophen 300 mg, codeine phosphate 15 mg, and caffeine 15 mg [not available in the U.S.]

ratio-Lenoltec No. 3 [CAN], Tylenol No. 3 with Codeine [CAN]: Acetaminophen 300 mg, codeine phosphate 30 mg, and caffeine 15 mg [not available in the U.S.]

ratio-Lenoltec No. 4 [CAN], Tylenol No. 4 with Codeine [CAN]: Acetaminophen 300 mg and codeine phosphate 60 mg [not available in the U.S.]

Triatec-8 [CAN]: Acetaminophen 325 mg, codeine phosphate 8 mg, and caffeine 30 mg [not available in the U.S.]

Triatec-8 Strong [CAN]: Acetaminophen 500 mg, codeine phosphate 8 mg, and caffeine 30 mg [not available in the U.S.]

Tylenol® with Codeine No. 3: Acetaminophen 300 mg and codeine phosphate 30 mg [contains sodium metabisulfite]

Tylenol® with Codeine No. 4: Acetaminophen 300 mg and codeine phosphate 60 mg [contains sodium metabisulfite]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Acetaminophen-Codeine)

120-12 mg/5 mL (118): $8.99

120-12 mg/5 mL (240): $13.99

Tablets (Acetaminophen-Codeine #2)

300-15 mg (30): $7.99

Tablets (Acetaminophen-Codeine #3)

300-30 mg (30): $11.99

Tablets (Acetaminophen-Codeine #4)

300-60 mg (30): $11.99

Tablets (Tylenol/Codeine #3)

300-30 mg (30): $27.99

Tablets (Tylenol/Codeine #4)

300-60 mg (30): $44.93

Mechanism of ActionInhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation; produces antipyresis from inhibition of hypothalamic heat-regulating center; binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; causes cough supression by direct central action in the medulla; produces generalized CNS depression. Caffeine (contained in some non-U.S. formulations) is a CNS stimulant; use with acetaminophen and codeine increases the level of analgesia provided by each agent.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Acetaminophen
- Codeine

Dental Health Professional ConsiderationsCodeine products, as with other narcotic analgesics, are recommended only for acute dosing (ie, 3 days or less). The most common adverse effect you will see in your dental patients from codeine is nausea, followed by sedation and constipation. Codeine has narcotic addiction liability, especially when given long-term. Because of the acetaminophen component, this product should be used with caution in patients with alcoholic liver disease.

A study by Hylek, et al, suggested that the combination of acetaminophen with warfarin (Coumadin®) may cause enhanced anticoagulation. The following recommendations have been made by Hylek, et al, and are supported by an editorial in *JAMA* by Bell.

Dose and duration of acetaminophen should be as low as possible, individualized, and monitored.

The study by Hylek reported that for patients who reported taking the equivalent of at least 4 regular strength (325 mg) tablets for longer than a week, the odds of having an INR >6.0 were increased 10-fold above those not taking acetaminophen. Risk decreased with lower intakes of acetaminophen reaching a background level of risk at a dose of 6 or fewer 325 mg tablets per week.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; less commonly, codeine may produce euphoria or dysphoria

Mental Health: Effects on Psychiatric TreatmentCodeine may produce physical and psychological dependence. Antipsychotics, TCAs, MAO inhibitors, barbiturates, benzodiazepines, and anticonvulsants may increase the toxicity of codeine. Barbiturates and carbamazepine may increase the hepatotoxic potential of acetaminophen. Diminution of pain relief may occur with the SSRIs.

Cardiovascular ConsiderationsCodeine may cause constipation which may be problematic in patients with unstable angina, and patients after myocardial infarction. Consider stool softener to reduce the potential for constipation. The hemodynamic responses to valsalva-like maneuvers due to straining may have adverse cardiovascular consequences in patients with critical coronary artery disease.

Index TermsCodeine and Acetaminophen

References

Dionne RA, “New Approaches to Preventing and Treating Postoperative Pain,” *J Am Dent Assoc*, 1992, 123(6):26-34.

Dionne RA, Campbell RA, Cooper SA, et al, “Suppression of Postoperative Pain by Preoperative Administration of Ibuprofen in Comparison to Placebo, Acetaminophen, and Acetaminophen Plus Codeine,” *J Clin Pharmacol*, 1983, 23(1):37-43. [PubMed 6341415]

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

Forbes JA, Butterworth GA, Burchfield WH, et al, “Evaluation of Ketorolac, Aspirin, and an Acetaminophen-Codeine Combination in Postoperative Oral Surgery Pain,” *Pharmacotherapy*, 1990, 10(6 Pt 2):77S-93S. [PubMed 2082317]

Gobetti JP, “Controlling Dental Pain,” *J Am Dent Assoc*, 1992, 123(6):47-52.

International Brand NamesAlgimide (CO); Algimide F (CO); Chemists Own Dolased Day Pain Relief (AU); Citodon (SE); Claradol Codeine (FR); Co-Cadamol (SG); Cod-Acamol Forte (IL); Codabrol (IL); Codalgin (AU); Codapane (AU, NZ); Codeidol (CO); Codeidol F (CO); Codeipar (CN); Codicet (TH); Codilprane Enfant (FR); Codipar (GB, IE); Coditam (ID); Codoliprane (FR); Codoliprane Enfant (FR); Codral Pain Relief (AU, NZ); Dafalgan Codeine (FR); Dolaforte (AU); Dolorol Forte (ZA); Dymadon Co (AU); Dymadon Forte (AU, NZ); Efferalgan Codeine (PY); Febricod (AU); Hexal Comfarol Plus (AU); Liquigesic Co (AU, NZ); Maxadol (ZA); Nasa w/codeine (TH); Paceco (MY, SG); Panadeine (AU, BB, BM, BS, BZ, CZ, GY, HK, HN, JM, MY, NL, SR, TT); Panadeine Co (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Panadeine Forte (AU, NZ); Panadiene (AU, BB, BM, BS, BZ, CZ, GY, HK, HN, JM, JP, MY, NL, NZ, SR, TT); Panado-Co Caplets (ZA); Panadol Duo (FI); Panadol Ultra (HK); Panamax (AU, NZ); Paracodol (ZA); Paradine (MY); Paramax (EE); Parcono (TH); Parcoten (HK); Perdolan codeine (BE); Prodeine Forte (AU); Prodeine-15 (AU); Rokamol Plus (IL); Solpadeine (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Solpadol (GB, IE); TWC 30 (IN); Tylex CD (CR, DO, GT, HN, MX, NI, PA, SV); Winadol Forte (CO); Zapain (GB, IE)

Acetaminophen, Dextromethorphan, and Phenylephrine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen, deks troe meth OR fan, & fen il EF rin)

U.S. Brand NamesAlka-Seltzer Plus® Day Cold [OTC]; Little Colds® Multi-Symptom Cold Formula [OTC] [DSC]; Mapap® Multi-Symptom Cold [OTC]; Tylenol® Cold Head Congestion Daytime [OTC]; Tylenol® Cold Multi-Symptom Daytime [OTC]; Tylenol® Plus Infants Cold & Cough [OTC] [DSC]; Vicks® DayQuil® Cold/Flu Multi-Symptom Relief [OTC]

Pharmacologic CategoryAnalgesic, Miscellaneous; Antitussive; Decongestant

Use: Labeled IndicationsTemporary relief of common cold and flu symptoms (eg, pain, fever, cough, congestion)

Dosing: Adults**Product labeling:** Relief of cold and flu symptoms: Oral:

Alka-Seltzer Plus® Day Cold: 2 capsules or 20 mL every 4 hours (maximum: 6 doses/24 hours)

Tylenol® Cold Head Congestion Daytime: 2 caplets every 4 hours (maximum: 6 doses/24 hours)

Tylenol® Cold Multi-Symptom Daytime: 2 caplets/gelcaps or 30 mL every 4 hours (maximum: 6 doses/24 hours)

Vicks® DayQuil® Cold/Flu Multi-Symptom Relief LiquiCaps: 2 capsules every 4 hours (maximum: 6 doses/24 hours)

Vicks® DayQuil® Cold/Flu Multi-Symptom Relief Liquid: 30 mL every 4 hours (maximum: 6 doses/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Product labeling:** Relief of cold and flu symptoms: Oral:

Vicks® DayQuil® Cold/Flu Multi-Symptom Relief Liquid:

Children 6-11 years: 15 mL every 4 hours, up to 5 doses/day (maximum: 75 mL/24 hours)

Children ≥12 years: Refer to adult dosing.

Alka-Seltzer Plus® Day Cold, Tylenol® Cold Head Congestion Daytime, Tylenol® Cold Multi-Symptom Daytime, Vicks® DayQuil® Cold/Flu Multi-Symptom Relief LiquiCaps: Children ≥12 years: Refer to adult dosing.

Administration: OralSolid dosage forms should be swallowed whole; do not crush, chew or dissolve. Administer liquid capsule formulations with water.

Dietary Considerations

Alka-Seltzer Plus® Day Cold liquid contains sodium 3 mg per 5 mL.

Tylenol® Cold Multi-Symptom Daytime liquid contains sodium 5 mg per 15 mL.

Vicks® DayQuil® Cold/Flu Multi-Symptom Relief liquid contains sodium 71 mg per 15 mL.

StorageStore at room temperature at 20°C to 25°C (68°F to 77°F). Protect from excessive heat and humidity.

ContraindicationsHypersensitivity to acetaminophen, dextromethorphan, phenylephrine, or any component of the formulation; use of MAO inhibitors within 14 days

Warnings/Precautions

Disease-related concerns:

- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.

- Hepatic impairment: Use caution in patients with hepatic impairment; acetaminophen may cause severe hepatic toxicity with acute overdose.

Special populations:

- Elderly: Use with caution in the elderly; more likely to experience adverse reactions to sympathomimetics.

- Pediatrics: Use with caution in children; do not exceed pediatric dosing recommendations. If no recommendations exist on OTC labeling for patient's age, the product should **not** be administered without the guidance of a physician.

Dosage form specific issues:

- Sodium: Some products may contain sodium; use with caution in sodium restricted patients.

Other warnings/precautions:

- OTC labeling: Patients with hypertension, hyperthyroidism, diabetes mellitus, glaucoma, cardiovascular disease, or prostatic hyperplasia should consult a physician prior to use. Patients with chronic cough (associated with COPD or smoking) and/or productive cough (eg, copious amounts of phlegm) should be evaluated by a healthcare provider prior to use. Products containing acetaminophen are not recommended in patients consuming ≥3 alcoholic beverages/day; consult a physician. If pain, nasal congestion, or cough increases in severity or persists >7 days in adults (or >5 days in children) during use, consult a physician. If redness, swelling, or rash occurs or if fever worsens or persists >3 days during therapy, consult a physician. Do not use in children <2 years of age.

Geriatric ConsiderationsAvoid multicomponent cold products in the elderly. See Warnings/Precautions for individual agents.

Adverse ReactionsSee individual agents.

Metabolism/Transport Effects

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Dextromethorphan: **Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Excessive intake of ethanol may increase the risk of acetaminophen-induced hepatotoxicity. Avoid ethanol or limit to <3 drinks/day.

Nursing: Physical Assessment/MonitoringSee individual agents for Acetaminophen and Phenylephrine.

Patient EducationSee individual agents for Acetaminophen and Phenylephrine.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet:

Mapap® Multi-Symptom Cold: Acetaminophen 325 mg, dextromethorphan hydrobromide 10 mg, and phenylephrine hydrochloride 5 mg

Tylenol® Cold Head Congestion Daytime: Acetaminophen 325 mg, dextromethorphan hydrobromide 10 mg, and phenylephrine hydrochloride 5 mg [Cool Burst™ flavor]

Tylenol® Cold Multi-Symptom Daytime: Acetaminophen 325 mg, dextromethorphan hydrobromide 10 mg, and phenylephrine hydrochloride 5 mg [Cool Burst™ flavor]

Capsule, liquid gel:

Alka-Seltzer Plus® Day Cold: Acetaminophen 325 mg, dextromethorphan hydrobromide 10 mg, and phenylephrine hydrochloride 5 mg

Capsule, liquicap:

Vicks® DayQuil® Cold/Flu Multi-Symptom Relief: Acetaminophen 325 mg, dextromethorphan hydrobromide 10 mg, and phenylephrine hydrochloride 5 mg

Gelcap:

Tylenol® Cold Multi-Symptom Daytime: Acetaminophen 325 mg, dextromethorphan hydrobromide 10 mg, and phenylephrine hydrochloride 5 mg

Liquid:

Alka-Seltzer Plus® Day Cold: Acetaminophen 162.5 mg, dextromethorphan hydrobromide 5 mg, and phenylephrine hydrochloride 2.5 mg per 5 mL (180 mL) [alcohol free; contains sodium 3 mg/5 mL, propylene glycol, and sodium benzoate; berry flavor]

Tylenol® Cold Multi-Symptom Daytime: Acetaminophen 325 mg, dextromethorphan hydrobromide 10 mg, and phenylephrine hydrochloride 5 mg per 15 mL (240 mL) [contains sodium 5 mg/15 mL, sodium benzoate, and propylene glycol; Citrus Burst™ flavor]

Vicks® DayQuil® Cold/Flu Multi-Symptom Relief: Acetaminophen 325 mg, dextromethorphan hydrobromide 10 mg, and phenylephrine hydrochloride 5 mg per 15 mL (180 mL, 300 mL) [contains sodium 71 mg/15 mL and propylene glycol]

Liquid [drops]:

Little Colds® Multi-Symptom Cold Formula: Acetaminophen 80 mg, dextromethorphan hydrobromide 2.5 mg, and phenylephrine hydrochloride 1.25 mg per 1 mL (15 mL) [alcohol free, dye free; contains propylene glycol and sodium benzoate; berry flavor] [DSC]

Tylenol® Plus Infants Cold & Cough: Acetaminophen 80 mg, dextromethorphan hydrobromide 2.5 mg, and phenylephrine hydrochloride 1.25 mg per 0.8 mL (15 mL) [contains sodium benzoate; cherry flavor] [DSC]

Generic AvailableYes: Caplet

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tachycardia, palpitations (use vasoconstrictor with caution), and xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response.

Mental Health: Effects on Mental StatusSedation with dextromethorphan may be countered by the excitability associated with phenylephrine; one effect may predominate in any particular patient

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment; avoid. Barbiturates and carbamazepine may increase the hepatotoxic potential of acetaminophen.

Index TermsDextromethorphan Hydrobromide, Acetaminophen, and Phenylephrine Hydrochloride; Phenylephrine, Acetaminophen, and Dextromethorphan; Phenylephrine, Dextromethorphan, and Acetaminophen

International Brand NamesTusedex (PH)

Acetaminophen, Dextromethorphan, and Pseudoephedrine

Lexi-Drugs Online

English English

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Sudafed® may be confused with Sufenta®

Thera-Flu® may be confused with Tamiflu®, Thera-Flur-N®

Tylenol® may be confused with atenolol, timolol, Tuinal®, Tylox®

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen, deks troe meth OR fan, & soo doe e FED rin)

U.S. Brand NamesTylenol® Cold Day Non-Drowsy [OTC]; Tylenol® Flu Non-Drowsy Maximum Strength [OTC]

Canadian Brand NamesContac® Complete; Contac® Cough, Cold and Flu Day & Night™; Sudafed® Cold & Cough Extra Strength; Tylenol® Cold Daytime

Pharmacologic CategoryAlpha/Beta Agonist; Analgesic, Miscellaneous; Antitussive

Use: Labeled IndicationsTreatment of mild-to-moderate pain and fever; symptomatic relief of cough and congestion

Dosing: Adults

Pain (Analgesic): Oral: Based on acetaminophen component: 325-650 mg every 4-7 hours as needed; do **not** exceed 4 g/day

Cough suppressant (Antitussive): Oral: Based on dextromethorphan component: 10-20 mg every 4-8 hours **or** 30 mg every 8 hours; do **not** exceed 120 mg/24 hours

Nasal congestion (Decongestant): Oral: Based on pseudoephedrine component: 60 mg every 4 hours (maximum: 360 mg/24 hours)

Product labeling:

Tylenol® Cold Non-Drowsy: Oral: 2 doses every 6 hours (maximum: 8 doses/24 hours)

Tylenol® Flu Non-Drowsy Maximum Strength: Oral: 2 doses every 6 hours (maximum: 8 doses/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Analgesic: Oral: Based on acetaminophen component: 10-15 mg/kg/dose every 4-6 hours as needed; do **not** exceed 5 doses/24 hours.

Cough suppressant: Oral: Based on dextromethorphan component:

Children 6-12 years: 15 mg every 6-8 hours; do **not** exceed 60 mg/24 hours

Children >12 years: Refer to adult dosing.

Decongestant: Oral: Based on pseudoephedrine component:

Children:

2-6 years: 15 mg every 4 hours (maximum: 90 mg/24 hours)

6-12 years: 30 mg every 4 hours (maximum: 180 mg/24 hours)

Children >12 years: Refer to adult dosing.

Product labeling:

Sudafed® Severe Cold, Thera-Flu® Non-Drowsy Maximum Strength (gelcap), Tylenol® Flu Non-Drowsy Maximum Strength: Oral: Children >12 years: Refer to adult dosing.

Tylenol® Cold Non-Drowsy: Oral:

Children 6-11 years: 1 dose every 6 hours (maximum: 4 doses/24 hours)

Children ≥12 years: Refer to adult dosing.

Thera-Flu® Non-Drowsy Maximum Strength: Oral: Children >12 years: Refer to adult dosing.

Dosing: Hepatic ImpairmentUse with caution. Limited, low-dose therapy usually well tolerated in hepatic disease/cirrhosis; however, cases of hepatotoxicity at daily acetaminophen dosages <4 g/day have been reported. Avoid chronic use in hepatic impairment.

ContraindicationsHypersensitivity to acetaminophen, dextromethorphan, pseudoephedrine, or any component of the formulation

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity

Adverse ReactionsSee individual agents.

Metabolism/Transport Effects

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Dextromethorphan: **Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Excessive intake of ethanol may increase the risk of acetaminophen-induced hepatotoxicity. Avoid ethanol or limit to <3 drinks/day.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet:

Tylenol® Cold Day Non-Drowsy: Acetaminophen 325 mg dextromethorphan hydrobromide 15 mg, and pseudoephedrine hydrochloride 30 mg

Gelcap:

Tylenol® Flu Non-Drowsy Maximum Strength: Acetaminophen 500 mg, dextromethorphan hydrobromide 15 mg, and pseudoephedrine hydrochloride 30 mg

Generic AvailableNo

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Acetaminophen
- Dextromethorphan
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusSedation with dextromethorphan tends to be countered by the excitability associated with pseudoephedrine; one effect may predominate in any particular patient

Mental Health: Effects on Psychiatric TreatmentIncreased toxicity and hypertensive crisis may be seen with concurrent use of MAO inhibitors and CNS depressants, effects of CNS depressants may be lessened

Index TermsDextromethorphan, Acetaminophen, and Pseudoephedrine; Pseudoephedrine, Acetaminophen, and Dextromethorphan; Pseudoephedrine, Dextromethorphan, and Acetaminophen

International Brand NamesLogicin Flu Strength Day & Night (HK); Panadol Cold & Flu (AU)

Acetaminophen, Diphenhydramine, and Phenylephrine

Lexi-Drugs Online

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Duplicate therapy issues: This product contains acetaminophen, which may be a component of combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen, dye fen HYE dra meen, & fen il EF rin)

U.S. Brand NamesBenadryl® Allergy and Cold [OTC]; Benadryl® Allergy and Sinus Headache [OTC]; Children’s Tylenol® Plus Cold and Allergy [OTC]; Sudafed PE® Nighttime Cold [OTC]; Sudafed PE® Severe Cold [OTC]; Tylenol® Allergy Multi-Symptom Nighttime [OTC]

Pharmacologic CategoryAnalgesic, Miscellaneous; Decongestant; Histamine H_1 Antagonist

Use: Labeled IndicationsTemporary relief of symptoms of hay fever and the common cold, including: sinus/nasal congestion and pain/pressure, headache, sneezing, runny nose, itchy/watery eyes, sore throat, cough, and minor aches and pains

Dosing: Adults**Hay fever/cold symptoms:** Oral: General dosing guidelines; refer to specific product labeling (Benadryl® Allergy and Cold, Benadryl® Allergy and Sinus Headache, Sudafed PE® Nighttime Cold, Sudafed PE® Severe Cold, Tylenol® Allergy Multi-Symptom Nighttime): Two caplets every 4 hours as needed; maximum: 12 caplets/24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Hay fever/cold symptoms:** Oral: General dosing guidelines; refer to specific product labeling:

Children 6-11 years (Benadryl® Allergy and Cold, Benadryl® Allergy and Sinus Headache, Sudafed PE® Severe Cold): One caplet every 4 hours as needed; maximum: 5 caplets/24 hours

Children 6-11 years; 48-95 lbs (Children's Tylenol® Plus Cold and Allergy): 10 mL every 4 hours as needed; maximum: 5 doses/24 hours

Children ≥12 years: Refer to adult dosing.

Administration: OralAdminister without regard to meals.

Liquid: Shake well before use. Only use enclosed dosing cup; do not use other devices.

Tylenol® Allergy Multi-Symptom Nighttime: Swallow whole; do not crush, chew, or dissolve.

StorageStore at room temperature. Protect from moisture.

ContraindicationsUse with or within 14 days of MAO inhibitor therapy; concurrent use with other products containing acetaminophen, diphenhydramine (including topical) or phenylephrine

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.

- Hepatic impairment: Use caution in patients with hepatic impairment; acetaminophen may cause severe hepatic toxicity with acute overdose.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Pediatrics: Use with caution in children; may cause excitability. Do not exceed pediatric dosing recommendations. If no recommendations exist on OTC labeling for patient's age, the product should **not** be administered without the guidance of a physician.

Other warnings/precautions:

- Dosage limit: Limit acetaminophen dose to <4 g/day (adults) or <2.6 g/day (children <12 years of age).

- Self-medication (OTC use): Patients with hypertension, thyroid disease, diabetes mellitus, glaucoma, cardiovascular disease, or prostatic hyperplasia should consult healthcare provider prior to use. Patients with chronic cough (associated with COPD or smoking) and/or productive cough (eg, copious amounts of phlegm) should be evaluated by a healthcare provider prior to use. Products containing acetaminophen are not recommended in patients consuming ≥3 alcoholic beverages/day; consult healthcare provider. If pain, nasal congestion, or cough increases in severity or persists >7 days in adults (or >5 days in children) during use, consult a physician. If redness, swelling, or rash occurs or if fever worsens or persists >3 days during therapy, consult healthcare provider. If sore throat is severe, accompanied by fever, nausea/vomiting, headache, swelling or rash, or last >2 days, discontinue use and consult healthcare provider.

Adverse ReactionsSee individual agents.

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet:

Benadryl® Allergy and Cold, Benadryl® Allergy and Sinus Headache, Sudafed PE® Severe Cold: Acetaminophen 325 mg, diphenhydramine hydrochloride 12.5 mg and phenylephrine hydrochloride 5 mg

Sudafed PE® Nighttime Cold: Acetaminophen 325 mg, diphenhydramine hydrochloride 25 mg and phenylephrine hydrochloride 5 mg

Tylenol® Allergy Multi-Symptom Nighttime: Acetaminophen 325 mg, diphenhydramine hydrochloride 25 mg and phenylephrine hydrochloride 5 mg [Cool Burst™ flavor]

Liquid:

Children's Tylenol® Plus Cold and Allergy: Acetaminophen 160 mg, Diphenhydramine 12.5 mg, and phenylephrine 2.5 mg per 5 mL (120 mL) [contains sodium benzoate; bubble gum flavor]

Generic AvailableNo

Mechanism of Action

Acetaminophen inhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation.

Diphenhydramine is an H_1-receptor antagonist.

Phenylephrine causes vasoconstriction of the arterioles of the nasal mucosa.

Pharmacodynamics/KineticsSee individual agents.

Mental Health: Effects on Mental StatusMay cause drowsiness, anxiety, or restlessness

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment. May cause CNS depression; concurrent use with psychotropics may produce additive effects. Barbiturates and carbamazepine may increase the hepatotoxic potential of acetaminophen. Individuals consuming ≥3 alcoholic drinks per day may increase the risk of liver damage.

Index TermsAcetaminophen, Phenylephrine, and Diphenhydramine; Diphenhydramine, Phenylephrine Hydrochloride, and Acetaminophen; Phenylephrine Hydrochloride, Acetaminophen, and Diphenhydramine

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Acetaminophen and Diphenhydramine

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Excedrin® may be confused with Dexatrim®, Dexedrine®

Percogesic® may be confused with paregoric, Percodan®

Tylenol® may be confused with atenolol, timolol, Tuinal®, Tylox®

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen & dye fen HYE dra meen)

U.S. Brand NamesExcedrin® P.M. [OTC]; Goody's PM® [OTC]; Legatrin PM® [OTC]; Percogesic® Extra Strength [OTC]; Tylenol® PM [OTC]; Tylenol® Severe Allergy [OTC]

Pharmacologic CategoryAnalgesic, Miscellaneous

Use: Labeled IndicationsAid in the relief of insomnia accompanied by minor pain

Dosing: AdultsInsomnia and pain: Oral: Adults: 50 mg of diphenhydramine HCl (76 mg diphenhydramine citrate) at bedtime or as directed by physician; do not exceed recommended dosage

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricNot for use in children <12 years of age.

Dosing: Hepatic ImpairmentUse with caution. Limited, low-dose therapy is usually well tolerated in hepatic disease/cirrhosis; however, cases of hepatotoxicity at daily acetaminophen dosages <4 g/day have been reported. Avoid chronic use in hepatic impairment.

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity

Adverse ReactionsSee individual agents.

Metabolism/Transport Effects

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Diphenhydramine: **Inhibits** CYP2D6 (moderate)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor*

therapy

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Excessive intake of ethanol may increase the risk of acetaminophen-induced hepatotoxicity. Avoid ethanol or limit to <3 drinks/day.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet: Acetaminophen 500 mg and diphenhydramine hydrochloride 25 mg

Excedrin® P.M.: Acetaminophen 500 mg and diphenhydramine citrate 38 mg

Legatrin PM®: Acetaminophen 500 mg and diphenhydramine hydrochloride 50 mg

Percogesic® Extra Strength: Acetaminophen 500 mg and diphenhydramine hydrochloride 25 mg

Tylenol® PM: Acetaminophen 500 mg and diphenhydramine hydrochloride 25 mg [also available in vanilla caplets]

Tylenol® Severe Allergy: Acetaminophen 500 mg and diphenhydramine hydrochloride 12.5 mg

Gelcap:

Tylenol® PM: Acetaminophen 500 mg and diphenhydramine hydrochloride 25 mg

Geltab: Acetaminophen 500 mg and diphenhydramine hydrochloride 25 mg

Excedrin® P.M.: Acetaminophen 500 mg and diphenhydramine citrate 38 mg

Tylenol® PM: Acetaminophen 500 mg and diphenhydramine hydrochloride 25 mg

Liquid:

Tylenol® PM: Acetaminophen 500 mg and diphenhydramine hydrochloride 25 mg per 15 mL (240 mL) [contains sodium benzoate; vanilla flavor]

Powder for oral solution:

Goody's PM®: Acetaminophen 500 mg and diphenhydramine citrate 38 mg [contains potassium 41.9 mg and sodium 3.15 mg per powder]

Tablet: Acetaminophen 500 mg and diphenhydramine hydrochloride 25 mg

Excedrin® P.M.: Acetaminophen 500 mg and diphenhydramine citrate 38 mg

Generic AvailableYes: Excludes gelcap, powder, and liquid

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Acetaminophen
- DiphenhydrAMINE

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common

Mental Health: Effects on Psychiatric TreatmentConcurrent use with CNS depressant may result in additive CNS depression. MAO inhibitor may cause additive anticholinergic effects.

Index TermsDiphenhydramine and Acetaminophen

References

Barker JD Jr, de Carle DJ, and Anuras S, “Chronic Excessive Acetaminophen Use in Liver Damage,” *Ann Intern Med*, 1977, 87(3):299-301. [PubMed 900673]

Dionne RA, Campbell RA, Cooper SA, et al, “Suppression of Postoperative Pain by Preoperative Administration of Ibuprofen in Comparison to Placebo, Acetaminophen, and Acetaminophen Plus Codeine,” *J Clin Pharmacol*, 1983, 23(1):37-43. [PubMed 6341415]

Licht H, Seeff LB, and Zimmerman HJ, “Apparent Potentiation of Acetaminophen Hepatotoxicity by Alcohol,” *Ann Intern Med*, 1980, 92(4):511.

Mokhlesi B, Leikin JB, Murray P, et al, "Adult Toxicology in Critical Care: Part II: Specific Poisonings," *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

Acetaminophen, Isometheptene, and Dichloralphenazone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Midrin® may be confused with Mydfrin®

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen, eye soe me THEP teen, & dye KLOR al FEN a zone)

U.S. Brand NamesAmidrine [DSC]; Duradrin® [DSC]; Midrin®; Migquin [DSC]; Migratine; Migrazone® [DSC]; Migrin-A [DSC]

Pharmacologic CategoryAnalgesic, Miscellaneous

Use: Labeled IndicationsRelief of migraine and tension headache

Dosing: Adults

Migraine headache: Oral: 2 capsules to start, followed by 1 capsule every hour until relief is obtained (maximum: 5 capsules/12 hours)

Tension headache: Oral: 1-2 capsules every 4 hours (maximum: 8 capsules/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic ImpairmentUse with caution. Limited, low-dose therapy usually well tolerated in hepatic disease/cirrhosis; however, cases of hepatotoxicity at daily acetaminophen dosages <4 g/day have been reported. Avoid chronic use in hepatic impairment.

RestrictionsC-IV

ContraindicationsHypersensitivity to acetaminophen, isometheptene, dichloralphenazone, or any component of the formulation; glaucoma; severe renal disease; hypertension; organic heart disease; hepatic disease; MAO inhibitor therapy

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsAcetaminophen and dichloralphenazone are excreted in breast milk; excretion of isometheptene is not known.

Adverse ReactionsFrequency not defined.

Central nervous system: Transient dizziness

Dermatological: Rash

Metabolism/Transport EffectsAcetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Beta-Blockers: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. *Risk D: Consider therapy modification*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Excessive intake of ethanol may increase the risk of acetaminophen-induced hepatotoxicity. Avoid ethanol or limit to <3 drinks/day.

Nursing: Physical Assessment/MonitoringSee individual agent for Acetaminophen.

Patient EducationSee individual agent for Acetaminophen.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule: Acetaminophen 325 mg, isometheptene mucate 65 mg, dichloralphenazone 100 mg [DSC]

Amidrine [DSC], Duradrin® [DSC], Midrin®, Migquin [DSC], Migrazone® [DSC], Migratine, Migrin-A [DSC]: Acetaminophen 325 mg, isometheptene mucate 65 mg, and dichloralphenazone 100 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Migratine)

325-65-100 mg (100): $37.57

Related Information

- Acetaminophen

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitor

Index TermsAcetaminophen, Dichloralphenazone, and Isometheptene; Dichloralphenazone, Acetaminophen, and Isometheptene; Dichloralphenazone, Isometheptene, and Acetaminophen; Isometheptene, Acetaminophen, and Dichloralphenazone; Isometheptene, Dichloralphenazone, and Acetaminophen

References

Barker JD Jr, de Carle DJ, and Anuras S, "Chronic Excessive Acetaminophen Use in Liver Damage," *Ann Intern Med*, 1977, 87(3):299-301. [PubMed 900673]

Dionne RA, Campbell RA, Cooper SA, et al, "Suppression of Postoperative Pain by Preoperative Administration of Ibuprofen in Comparison to Placebo, Acetaminophen, and Acetaminophen Plus Codeine," *J Clin Pharmacol*, 1983, 23(1):37-43. [PubMed 6341415]

Licht H, Seeff LB, and Zimmerman HJ, "Apparent Potentiation of Acetaminophen Hepatotoxicity by Alcohol," *Ann Intern Med*, 1980, 92(4):511.

Mokhlesi B, Leikin JB, Murray P, et al, "Adult Toxicology in Critical Care: Part II: Specific Poisonings," *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

Acetaminophen and Phenylephrine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Duplicate therapy issues: This product contains acetaminophen, which may be a component of combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen & fen il EF rin)

U.S. Brand NamesAlka-Seltzer Plus® Sinus Formula [OTC]; Contac® Cold + Flu Maximum Strength Non-Drowsy [OTC]; Mapap® Sinus Congestion and Pain Daytime [OTC]; Sinutab® Sinus [OTC]; Sudafed PE® Sinus Headache [OTC]; Tylenol® Sinus Congestion & Pain Daytime [OTC]

Pharmacologic CategoryAnalgesic, Miscellaneous; Decongestant

Use: Labeled IndicationsTemporary relief of sinus/nasal congestion and pressure, headache, and minor aches and pains

Dosing: AdultsSinus pain/pressure: Oral: General dosing guidelines, refer to specific product labeling: Acetaminophen 325 mg and phenylephrine 5 mg/caplet: Take 2 caplets every 4 hours as needed; maximum: 12 caplets/24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥12 years: Refer to adult dosing.

Administration: OralCaplets and gelcaps should be swallowed whole; do not crush, chew, or dissolve. Effervescent tablets should be dissolved in 4 ounces of water.

Dietary ConsiderationsAlka-Seltzer Plus® Sinus Formula contains sodium 477 mg/tablet and phenylalanine 4.2 mg/tablet

ContraindicationsHypersensitivity to acetaminophen, phenylephrine, or any component of the formulation; with or within 14 days of MAO inhibitor therapy

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Diabetes: Use with caution in patients with diabetes mellitus.
- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.
- Hepatic impairment: Use caution in patients with hepatic impairment; acetaminophen may cause severe hepatic toxicity with acute overdose.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- Elderly: Use with caution in the elderly; more likely to experience adverse reactions to sympathomimetics.
- Pediatrics: Use with caution in children; do not exceed pediatric dosing recommendations. Not for OTC use in children <12 years of age.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.
- Sodium: Some products may contain sodium; use with caution in sodium restricted patients.

Other warnings/precautions:

- Dosage limit: Limit acetaminophen dose to <4 g/day.
- Self-medication (OTC use): When used for self-medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever lasting >3 days. Discontinue and contact healthcare provider if nervousness, dizziness, or sleeplessness occur.

Geriatric ConsiderationsElderly are more predisposed to the adverse effects of sympathomimetics since they frequently have cardiovascular disease and diabetes mellitus, and are on multiple medications. Since oral and topical phenylephrine can be obtained OTC, elderly patients should be counseled about their proper use and in what disease states they should be avoided.

Adverse ReactionsSee individual agents.

Metabolism/Transport EffectsAcetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Drug Interactions

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet, oral:

Contac® Cold + Flu Maximum Strength Non Drowsy: Acetaminophen 500 mg and phenylephrine hydrochloride 5 mg

Mapap® Sinus Congestion and Pain Daytime, Sinutab® Sinus, Sudafed PE® Sinus Headache: Acetaminophen 325 mg and phenylephrine hydrochloride 5 mg

Tylenol® Sinus Congestion & Pain Daytime: Acetaminophen 325 mg and phenylephrine hydrochloride 5 mg [Cool Burst™ flavor]

Gelcap, oral:

Tylenol® Sinus Congestion & Pain Daytime: Acetaminophen 325 mg and phenylephrine hydrochloride 5 mg

Gelcap, rapid release, oral:

Tylenol® Sinus Congestion & Pain Datyime: Acetaminophen 325 mg and phenylephrine hydrochloride 5 mg

Tablet for solution, oral [effervescent]:

Alka-Seltzer Plus® Sinus Formula: Acetaminophen 250 mg and phenylephrine hydrochloride 5 mg [contains sodium 477 mg/tablet and phenylalanine 4.2 mg/tablet; lemon zest flavor]

Generic AvailableYes: Caplet

Mechanism of ActionAcetaminophen inhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation. Phenylephrine causes vasoconstriction of the arterioles of the nasal mucosa.

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tachycardia, palpitations (use vasoconstrictor with caution), and xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response.

Mental Health: Effects on Mental StatusMay cause anxiety and restlessness

Mental Health: Effects on Psychiatric TreatmentAvoid concurrent use with MAO inhibitors; may result in hypertensive crisis and is contraindicated. Barbiturates and carbamazepine may increase the hepatotoxic potential of acetaminophen. Individuals consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.

Index TermsPhenylephrine Hydrochloride and Acetaminophen

Acetaminophen and Phenyltoloxamine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Percogesic® may be confused with paregoric, Percodan®

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen & fen il to LOKS a meen)

U.S. Brand NamesAceta-Gesic [OTC]; Alpain; BeFlex; Dologesic®; Flextra 650; Flextra-DS; Genasec™ [OTC]; Hyflex-DS® [DSC]; Lagesic™; Percogesic® [OTC]; Phenagesic [OTC]; Phenylgesic [OTC]; RhinoFlex 650; RhinoFlex™; Staflex; Vistra 650; Zgesic

Pharmacologic CategoryAnalgesic, Miscellaneous

Use: Labeled IndicationsRelief of mild-to-moderate pain

Dosing: Adults

Pain (Analgesic): Oral: Based on acetaminophen component: 325-650 mg every 4-6 hours as needed (maximum: 4 g/day)

Product-specific labeling: Oral:

Dologesic®: 1-2 caplets/capsules **or** 15-30 mL every 4 hours (maximum: 8 caplets/24 hours **or** 120 mL/24 hours)

Flextra-650:$^1/_2$-1 tablet every 6 hours (maximum: 4 tablets/day)

Flextra-DS, RhinoFlex™, RhinoFlex™-650:$^1/_2$-1 tablet every 4 hours (maximum: 5 tablets/day)

Lagesic™, Zgesic: 1-2 caplets/tablets every 8-12 hours (maximum: 6 tablets/24 hours)

Percogesic®: 1-2 tablets every 4 hours (maximum: 8 tablets/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Analgesic: Oral:

Based on acetaminophen component: 10-15 mg/kg/dose every 4-6 hours as needed (maximum: 5 doses/24 hours)

Product-specific labeling: Oral:

Dologesic®:

Children <12 years: 1 caplet/capsule **or** 5 mL every 4 hours

Children ≥12 years: Refer to adult dosing

Flextra-650:

Children 6 to <12 years: $^1/_2$ tablet every 6 hours (maximum: 2 tablets/day)

Children ≥12 years: Refer to adults dosing.

Flextra-DS, RhinoFlex™, RhinoFlex™-650:

Children 6 to <12 years: $^1/_2$ tablet every 4 hours (maximum: 2.5 tablets/day)

Children ≥12 years: Refer to adult dosing.

Lagesic™:

Children 6-12 years: $^1/_2$ to 1 caplet every 12 hours (maximum: 2 caplets/day)

Children ≥12 years: Refer to adult dosing

Percogesic®: Children 6-12 years: 1 tablet every 4 hours (maximum: 4 tablets/24 hours)

Zgesic: Children >12 years: Refer to adult dosing

Dosing: Renal Impairment

Specific dosing adjustment not available. Monitor renal function with severe impairment.

Dosing: Hepatic Impairment Use with caution. Limited, low-dose therapy is usually well tolerated in hepatic disease/cirrhosis; however, cases of hepatotoxicity at daily acetaminophen dosages <4 g/day have been reported. Avoid chronic use in hepatic impairment.

Administration: Oral May be administered with food or milk.

Extended release caplet (Lagesic™): Caplet may be broken in half; do not chew or crush.

Prolonged release tablet (Zgesic): Swallow whole; do not chew or crush. May be taken with food or milk.

Dietary Considerations May be taken with food or milk.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Avoid excessive heat.

ContraindicationsHypersensitivity to acetaminophen, phenyltoloxamine, or any component of the formulation

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hepatotoxicity: May cause severe hepatic toxicity on acute overdose; in addition, chronic daily dosing in adults has resulted in liver damage in some patients.

Disease-related concerns:

- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.
- G6PD deficiency: Use with caution in patients with known G6PD deficiency.
- Glaucoma: Use with caution in patients with glaucoma.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Other warnings/precautions:

- Dosage limit: Limit acetaminophen dose to <4 g/day.
- Self-medication (OTC use): When used for self-medication, patients should be instructed to contact healthcare provider if used for fever lasting >3 days or for pain lasting >10 days in adults or >5 days in children.

Pregnancy Risk FactorC

Pregnancy Considerations Reproduction studies have not been conducted with this combination.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding Considerations Acetaminophen is excreted in breast milk. Excretion of phenyltoloxamine is not known.

Adverse Reactions Frequency not defined.

Central nervous system: Dizziness, drowsiness, lassitude

Dermatologic: Pruritus, rash

Gastrointestinal: Nausea

Ocular: Blurred vision

Miscellaneous: Diaphoresis

Metabolism/Transport EffectsAcetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Drug Interactions

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Excessive intake of ethanol may increase the risk of acetaminophen-induced hepatotoxicity. Avoid ethanol or limit to <3 drinks/day.

Food: Rate of absorption may be decreased when given with food.

Test InteractionsAcetaminophen may cause false-positive urinary 5-hydroxyindoleacetic acid

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet:

Alpain: Acetaminophen 500 mg and phenyltoloxamine citrate 60 mg

BeFlex: Acetaminophen 500 mg and phenyltoloxamine citrate 55 mg

Dologesic®: Acetaminophen 500 mg and phenyltoloxamine citrate 30 mg

Staflex: Acetaminophen 500 mg and phenyltoloxamine citrate 55 mg

Caplet, extended release [scored]:

Lagesic™: Acetaminophen 600 mg and phenyltoloxamine citrate 66 mg

Capsule:

Dologesic®: Acetaminophen 500 mg and phenyltoloxamine citrate 30 mg

Liquid:

Dologesic®: Acetaminophen 500 mg and phenyltoloxamine citrate 30 mg per 15 mL (180 mL)

Tablet: Acetaminophen 325 mg and phenyltoloxamine citrate 30 mg

Aceta-Gesic, Genasec™, Percogesic®, Phenagesic, Phenylgesic: Acetaminophen 325 mg and phenyltoloxamine citrate 30 mg

Flextra-650, Vistra 650: Acetaminophen 650 mg and phenyltoloxamine citrate 60 mg

Flextra-DS, Hyflex-DS® [DSC], RhinoFlex™: Acetaminophen 500 mg and phenyltoloxamine citrate 50 mg

RhinoFlex™-650: Acetaminophen 650 mg and phenyltoloxamine citrate 50 mg

Tablet, prolonged release, oral:

Zgesic: Acetaminophen 600 mg and phenyltoloxamine citrate 66 mg

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Tablets (Flextra DS)

50-500 mg (30): $26.99

Mechanism of ActionAcetaminophen inhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation; produces antipyresis from inhibition of hypothalamic heat-regulating center. Phenyltoloxamine is an antihistamine (H_1-blocking agent) which acts primarily to inhibit secretions in the nose, mouth, and pharynx, as well as causing CNS depression.

Related Information

- Acetaminophen

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may increase the hepatotoxic potential of acetaminophen
Index TermsPhenyltoloxamine Citrate and Acetaminophen
References

Barker JD Jr, de Carle DJ, and Anuras S, "Chronic Excessive Acetaminophen Use in Liver Damage," *Ann Intern Med*, 1977, 87(3):299-301. [PubMed 900673]

Dionne RA, Campbell RA, Cooper SA, et al, "Suppression of Postoperative Pain by Preoperative Administration of Ibuprofen in Comparison to Placebo, Acetaminophen, and Acetaminophen Plus Codeine," *J Clin Pharmacol*, 1983, 23(1):37-43. [PubMed 6341415]

Licht H, Seeff LB, and Zimmerman HJ, "Apparent Potentiation of Acetaminophen Hepatotoxicity by Alcohol," *Ann Intern Med*, 1980, 92(4):511.

Mokhlesi B, Leikin JB, Murray P, et al, "Adult Toxicology in Critical Care: Part II: Specific Poisonings," *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

Acetaminophen and Pseudoephedrine

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Ornex® may be confused with Orexin®, Orinase®

Sudafed® may be confused with Sufenta®

Tylenol® may be confused with atenolol, timolol, Tuinal®, Tylox®

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen & soo doe e FED rin)

U.S. Brand NamesAllerest® Allergy and Sinus Relief [OTC]; Genapap™ Sinus Maximum Strength [OTC] [DSC]; Mapap Sinus Maximum Strength

[OTC]; Medi-Synal [OTC]; Oranyl Plus [OTC]; Ornex® Maximum Strength [OTC]; Ornex® [OTC]; Sudafed® Multi-Symptom Sinus and Cold [OTC]; Tylenol® Cold Daytime, Children's [OTC]; Tylenol® Cold, Infants [OTC] [DSC]; Tylenol® Sinus Daytime [OTC]

Canadian Brand NamesContac® Cold and Sore Throat, Non Drowsy, Extra Strength; Dristan® N.D.; Dristan® N.D., Extra Strength; Sinutab® Non Drowsy; Sudafed® Head Cold and Sinus Extra Strength; Tylenol® Decongestant; Tylenol® Sinus

Pharmacologic CategoryAlpha/Beta Agonist; Analgesic, Miscellaneous

Use: Labeled IndicationsRelief of mild-to-moderate pain; relief of congestion

Dosing: Adults

Pain (Analgesic): Oral; Based on acetaminophen component: 325-650 mg every 4-6 hours as needed; do **not** exceed 4 g/day

Decongestant: Oral: Based on pseudoephedrine component: 60 mg every 4 hours; do **not** exceed 360 mg/day

Product labeling:

Sudafed® Multi-Symptom Sinus and Cold: 2 capsules every 4-6 hours (maximum: 8 capsules/24 hours)

Tylenol® Sinus Daytime: 2 caplets or gelcaps every 4-6 hours (maximum: 8 caplets or gelcaps/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Analgesic: Based on acetaminophen component: Oral:

Children: 10-15 mg/kg/dose every 4-6 hours as needed; do **not** exceed 5 doses in 24 hours

Decongestant: Based on pseudoephedrine component: Oral:

Children:

2-6 years: 15 mg every 4 hours; do **not** exceed 90 mg/day

6-12 years: 30 mg every 4 hours; do **not** exceed 180 mg/day

Children >12 years and Adults: Refer to adult dosing.

Product labeling:

Children's Tylenol® Cold Daytime: Children:

2-5 years (24-47 lb): 1 teaspoonful every 4-6 hours (maximum: 4 doses/24 hours)

6-11 years (48-95 lb): 2 teaspoonfuls every 4-6 hours (maximum: 4 doses/24 hours)

Sudafed® Multi-Symptom Sinus and Cold, Tylenol® Sinus Daytime: Children ≥12 years: Refer to adult dosing.

Dosing: Hepatic ImpairmentUse with caution. Limited, low-dose therapy usually well tolerated in hepatic disease/cirrhosis; however, cases of hepatotoxicity at daily acetaminophen dosages <4 g/day have been reported. Avoid chronic use in hepatic impairment.

Dietary Considerations

Sudafed® Multi-Symptom Sinus and Cold capsule contains acetaminophen 325 mg, pseudoephedrine hydrochloride 30 mg, and sodium 16 mg.

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity

Adverse ReactionsSee individual agents.

Metabolism/Transport EffectsAcetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor*

therapy

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Excessive intake of ethanol may increase the risk of acetaminophen-induced hepatotoxicity. Avoid ethanol or limit to <3 drinks/day.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet:

Allerest® Allergy and Sinus Relief, Ornex®: Acetaminophen 325 mg and pseudoephedrine hydrochloride 30 mg

Genapap™ Sinus Maximum Strength [DSC], Mapap Sinus Maximum Strength, Ornex® Maximum Strength, Tylenol® Sinus Daytime: Acetaminophen 500 mg and pseudoephedrine hydrochloride 30 mg

Capsule, liquid:

Sudafed® Multi-Symptom Sinus and Cold: Acetaminophen 325 mg and pseudoephedrine hydrochloride 30 mg [contains sodium 16 mg]

Gelcap:

Tylenol® Sinus Daytime: Acetaminophen 500 mg and pseudoephedrine hydrochloride 30 mg

Liquid:

Childrens Tylenol® Cold Daytime: Acetaminophen 160 mg and pseudoephedrine hydrochloride 15 mg per 5 mL (120 mL) [contains sodium benzoate; fruit flavor]

Liquid, oral [drops]:

Infants Tylenol® Cold: Acetaminophen 80 mg and pseudoephedrine 7.5 mg per 0.8 mL [contains sodium benzoate; bubble gum flavor] [DSC]

Tablet:

Medi-Synal: Acetaminophen 325 mg and pseudoephedrine hydrochloride 30 mg

Oranyl Plus: Acetaminophen 500 mg and pseudoephedrine hydrochloride 30 mg

Generic AvailableYes

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Acetaminophen
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusAnxiety, insomnia, excitability common; hallucination may be seen rarely

Mental Health: Effects on Psychiatric TreatmentHypertensive crisis may result with MAO inhibitor, effects of CNS depressants may be lessened

Cardiovascular ConsiderationsSympathomimetic or sympathomimetic-containing combination products may increase blood pressure. These preparations are relatively contraindicated in patients with significant hypertension, particularly in poorly controlled hypertension. In young, healthy patients presenting with new onset blood pressure elevations, it is important to exclude the recent use of sympathomimetics as a cause for the blood pressure elevation.

Index TermsPseudoephedrine and Acetaminophen

References

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand NamesPanadol Sinus (AU, HK); Sinumax Ped (ZA); Sinutab (BE)

Acetaminophen and Tramadol

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Medication Safety Issues

Sound-alike/look-alike issues:

Ultracet® may be confused with Ultane®, Ultram®

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen & TRA ma dole)

U.S. Brand NamesUltracet®

Canadian Brand NamesTramacet

Pharmacologic CategoryAnalgesic, Miscellaneous; Analgesic, Opioid

Use: Labeled IndicationsShort-term (≤5 days) management of acute pain

Use: DentalTreatment of postoperative pain (≤5 days)

Dosing: AdultsAcute pain: Oral: Two tablets every 4-6 hours as needed for pain relief (maximum: 8 tablets/day); treatment should not exceed 5 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute: Maximum of 2 tablets every 12 hours. Treatment should not exceed 5 days.

Dosing: Hepatic ImpairmentUse is not recommended.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsMay be taken with or without food. Avoid use of ethanol and ethanol-containing products.

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to acetaminophen, tramadol, opioids, or any component of the formulation; opioid-dependent patients; acute intoxication with ethanol, hypnotics, narcotics, centrally-acting analgesics, opioids, or psychotropic drugs; hepatic dysfunction

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Hepatotoxicity: May cause severe hepatic toxicity on acute overdose; in addition, chronic daily dosing in adults has resulted in liver damage in some patients.

- Seizures: Even when taken within the recommended dosage seizures may occur; risk is increased in patients receiving serotonin reuptake inhibitors (SSRIs or anorectics), tricyclic antidepressants, other cyclic compounds (including cyclobenzaprine, promethazine), neuroleptics, MAO inhibitors, or drugs which may lower seizure threshold. Patients with a history of seizures, or with a risk of seizures (head trauma, metabolic disorders, CNS infection, malignancy, or during alcohol/drug withdrawal) are also at increased risk.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists.

- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.

- G6PD deficiency: Use with caution in patients with known G6PD deficiency.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Renal impairment: Use tramadol with caution and reduce dosage in patients with renal impairment.

- Respiratory disease: Patients with chronic respiratory disorders may be at greater risk of adverse events.

Concurrent drug therapy issues:

- CNS depressants: Use with caution and reduce dosage when administering to patients receiving other CNS depressants.
- MAO inhibitors: Should be used only with extreme caution in patients receiving MAO inhibitors.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Dosage limit: Limit acetaminophen dose to <4 g/day.
- Withdrawal: Tolerance or drug dependence may result from extended use (withdrawal symptoms have been reported); abrupt discontinuation should be avoided. Tapering of dose at the time of discontinuation limits the risk of withdrawal symptoms.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTramadol has been shown to cross the placenta. Postmarketing reports following tramadol use during pregnancy include neonatal seizures, withdrawal syndrome, fetal death, and stillbirth. Not recommended for use during labor and delivery.

LactationTramadol: Enters breast milk/contraindicated

Breast-Feeding ConsiderationsNot recommended for postdelivery analgesia in nursing mothers.

Adverse Reactions

1% to 10%:

Central nervous system: Somnolence (6%), dizziness (3%), insomnia (2%), anxiety, confusion, euphoria, fatigue, headache, nervousness, tremor

Dermatologic: Pruritus (2%), rash

Endocrine & metabolic: Hot flashes

Gastrointestinal: Constipation (6%), anorexia (3%), diarrhea (3%), nausea (3%), dry mouth (2%), abdominal pain, dyspepsia, flatulence, vomiting

Genitourinary: Prostatic disorder (2%)

Neuromuscular & skeletal: Weakness

Miscellaneous: Diaphoresis increased (4%)

<1%: Abnormal thinking, abnormal vision, albuminuria, amnesia, anemia, arrhythmia, ataxia, chest pain, convulsions, depersonalization, drug abuse, dysphagia, dyspnea, emotional lability, hallucination, hyper-/hypotension, hypertonia, impotence, liver function abnormalities, melena, micturition disorder, migraine, muscle contractions (involuntary), oliguria, palpitation, paresthesia, paroniria, rigors, stupor, syncope, tachycardia, tinnitus, tongue edema, urinary retention, weight loss, vertigo

Postmarketing and/or case reports: Agitation, allergic reactions, anaphylactoid reactions, anaphylaxis, cognitive dysfunction, coma, depression, diaphoresis, difficulty concentrating, fever, gastrointestinal bleeding, hepatitis, hyper-reflexia, mental status change, myocardial ischemia, orthostatic hypotension, liver failure, pulmonary edema, seizure, serotonin syndrome, shivering, Stevens-Johnson syndrome, suicidal tendency, toxic epidermal necrolysis, urticaria, vasodilation

A withdrawal syndrome may occur with abrupt discontinuation; includes anxiety, diarrhea, hallucinations (rare), nausea, pain, piloerection, rigors, sweating, and tremor. Uncommon discontinuation symptoms may include severe anxiety, panic attacks, or paresthesia.

Metabolism/Transport Effects

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Tramadol: **Substrate** of CYP2D6 (major), 3A4 (major)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

MAO Inhibitors: TraMADol may enhance the neuroexcitatory and/or seizure-potentiating effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. TraMADol may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tricyclic Antidepressants: May enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (increased liver toxicity with concomitant use).

Food: May delay time to peak plasma levels, however, the extent of absorption is not affected.

Herb/Nutraceutical:

Acetaminophen: Avoid St John's wort (may decrease acetaminophen levels).

Tramadol: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersPain relief, respiratory rate, blood pressure, and pulse; signs of tolerance or abuse
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Acetaminophen 325 mg and tramadol hydrochloride 37.5 mg

Generic AvailableYes
ManufacturerOrtho-McNeil Pharmaceutical, Inc
Pricing: U.S. (www.drugstore.com)

Tablets (Tramadol-Acetaminophen)

37.5-325 mg (30): $27.99

Tablets (Ultracet)

37.5-325 mg (30): $49.42

Mechanism of Action

Based on **acetaminophen** component: Inhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation; produces antipyresis from inhibition of hypothalamic heat-regulating center

Based on **tramadol** component: Binds to μ-opiate receptors in the CNS causing inhibition of ascending pain pathways, altering the perception of and response to pain; also inhibits the reuptake of norepinephrine and serotonin, which also modifies the ascending pain pathway

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Acetaminophen

- TraMADol

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation, dizziness, insomnia, anxiety, confusion, or euphoria; monitor with concurrent psychotropic use

Mental Health: Effects on Psychiatric TreatmentContraindicated with acute intoxication of psychotropic drugs. Use with extreme caution with MAO inhibitors. Seizure risk is increased with SSRIs, TCAs, antipsychotics, and MAO inhibitors. Carbamazepine may decrease the half-life of tramadol (concurrent use is not recommended). Fluoxetine and paroxetine may increase tramadol serum concentrations.

Index TermsAPAP and Tramadol; Tramadol Hydrochloride and Acetaminophen

References

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand NamesCalmex (PY); Dolcet (PH); Ixprim (FR); Tramacet (DO, GB, IE, MX); Ultracet (BR, HK, KP, MY, SG, TH, TW, VE); Zaldiar (BE, CH, CN, CO, CR, CZ, DE, DO, EE, ES, FR, GT, HN, IL, MX, NI, NL, PA, PE, SV, VE); Zultracet (PK)

Acetaminophen

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Medication Safety Issues

Sound-alike/look-alike issues:

Acephen® may be confused with AcipHex®

FeverALL® may be confused with Fiberall®

Tylenol® may be confused with atenolol, timolol, Tuinal®, Tylox®

International issues:

Paralen® [Czech Republic] may be confused with Aralen® which is a brand name for chloroquine in the U.S.

Duorol® may be confused with Diuril® which is a brand name for chlorothiazide in the U.S.

Duplicate therapy issues: This product contains acetaminophen, which may be a component of combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(a seet a MIN oh fen)

U.S. Brand NamesAcephen™ [OTC]; Apra Children's [OTC]; Aspirin Free Anacin® Maximum Strength [OTC]; Cetafen Extra® [OTC]; Cetafen® [OTC]; Comtrex® Sore Throat Maximum Strength [OTC]; FeverALL® [OTC]; Genapap™ Children [OTC]; Genapap™ Extra Strength [OTC]; Genapap™ Infant [OTC]; Genapap™ [OTC]; Genebs Extra Strength [OTC]; Genebs [OTC]; Infantaire [OTC]; Little Fevers™ [OTC]; Mapap Children's [OTC]; Mapap Extra Strength [OTC]; Mapap Infants [OTC]; Mapap [OTC]; Nortemp Children's [OTC]; Pain Eze [OTC]; Silapap® Children's [OTC]; Silapap® Infants [OTC]; Tycolene Maximum Strength [OTC]; Tycolene [OTC]; Tylenol® 8 Hour [OTC]; Tylenol® Arthritis Pain [OTC]; Tylenol® Children's with Flavor Creator [OTC]; Tylenol® Children's [OTC]; Tylenol® Extra Strength [OTC]; Tylenol® Infants [OTC]; Tylenol® Junior [OTC]; Tylenol® [OTC]; Valorin Extra [OTC]; Valorin [OTC]

Canadian Brand NamesAbenol®; Apo-Acetaminophen®; Atasol®; Novo-Gesic; Pediatrix; Tempra®; Tylenol®

Pharmacologic Category[Analgesic, Miscellaneous]

Use: Labeled IndicationsTreatment of mild-to-moderate pain and fever (antipyretic/analgesic); does not have antirheumatic or anti-inflammatory effects

Use: DentalTreatment of postoperative pain

Dosing: AdultsPain or fever: Oral, rectal: 325-650 mg every 4-6 hours or 1000 mg 3-4 times/day; do **not** exceed 4 g/day.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricPain or fever: Oral, rectal: Children <12 years: 10-15 mg/kg/dose every 4-6 hours as needed; do **not** exceed 5 doses (2.6 g) in 24 hours; alternatively, the following doses may be used; see table.

Acetaminophen Dosing

Age	Dosage (mg)	Age	Dosage (mg)
0-3 mo	40	4-5 y	240
4-11 mo	80	6-8 y	320
1-2 y	120	9-10 y	400
2-3 y	160	11 y	480

Note: Higher rectal doses have been studied for use in preoperative pain control in children. However, specific guidelines are not available and dosing may be product dependent. The safety and efficacy of alternating acetaminophen and ibuprofen dosing has not been established.

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer every 6 hours.

Cl_{cr} <10 mL/minute: Administer every 8 hours (metabolites accumulate).

Moderately dialyzable (20% to 50%)

Dosing: Hepatic ImpairmentUse with caution. Limited, low-dose therapy is usually well tolerated in hepatic disease/cirrhosis. However, cases of hepatotoxicity at daily acetaminophen dosages <4 g/day have been reported. Avoid chronic use in hepatic impairment.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralShake suspension well before pouring dose.

Dietary ConsiderationsChewable tablets may contain phenylalanine (amount varies, ranges between 3-12 mg/tablet); consult individual product labeling.

StorageDo not freeze suppositories.

ContraindicationsHypersensitivity to acetaminophen or any component of the formulation

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Hepatotoxicity: May cause severe hepatic toxicity on acute overdose; in addition, chronic daily dosing in adults has resulted in liver damage in some patients.

Disease-related concerns:

- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.

- G6PD deficiency: Use with caution in patients with known G6PD deficiency.

Other warnings/precautions:

- Dosage limit: Limit dose to <4 g/day.

- Self-medication (OTC use): When used for self-medication, patients should be instructed to contact healthcare provider if used for fever lasting >3 days or for pain lasting >10 days in adults or >5 days in children.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAcetaminophen crosses the placenta. It is generally considered to be safe for use during pregnancy when used at therapeutic doses for short periods of time.

LactationEnters breast milk/compatible

Breast-Feeding Considerations

Acetaminophen is found in breast milk. The AAP considers acetaminophen to be “compatible” with breast-feeding.

Adverse ReactionsFrequency not defined.

Dermatologic: Rash

Endocrine & metabolic: May increase chloride, uric acid, glucose; may decrease sodium, bicarbonate, calcium

Hematologic: Anemia, blood dyscrasias (neutropenia, pancytopenia, leukopenia)

Hepatic: Bilirubin increased, alkaline phosphatase increased

Renal: Ammonia increased, nephrotoxicity with chronic overdose, analgesic nephropathy

Miscellaneous: Hypersensitivity reactions (rare)

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Drug Interactions

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Excessive intake of ethanol may increase the risk of acetaminophen-induced hepatotoxicity. Avoid ethanol or limit to <3 drinks/day.

Food: Rate of absorption may be decreased when given with food.

Herb/Nutraceutical: St John's wort may decrease acetaminophen levels.

Test InteractionsIncreased chloride, bilirubin, uric acid, glucose, ammonia (B), chloride (S), uric acid (S), alkaline phosphatase (S), chloride (S); decreased sodium, bicarbonate, calcium (S)

Monitoring ParametersRelief of pain or fever

Reference Range

Therapeutic concentration (analgesic/antipyretic): 10-30 mcg/mL

Toxic concentration (acute ingestion) with probable hepatotoxicity: >200 mcg/mL at 4 hours or 50 mcg/mL at 12 hours after ingestion

Nursing: Physical Assessment/Monitoring**Assess patient for history of liver disease or ethanol abuse** (acetaminophen and excessive ethanol may have adverse liver effects). Assess other medications patient may be taking for additive or adverse interactions. Assess knowledge/teach patient appropriate use. Teach patient to monitor for adverse reactions and appropriate interventions to reduce side effects.

Monitoring: Lab TestsSerum APAP levels with long-term use in patients with hepatic disease

Patient EducationTake exactly as directed; do not increase dose or frequency. Most adverse effects are related to excessive use. Take with food or milk. While using this medication, avoid or limit alcohol to <3 drinks/day and avoid other prescription or OTC medications that contain acetaminophen. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. This medication will not reduce inflammation; consult prescriber for anti-inflammatory, if needed. Report unusual bleeding (stool, mouth, urine) or bruising; unusual fatigue and weakness; change in elimination patterns; or change in color of urine or stool.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet: 500 mg

Cetafen Extra® Strength, Genapap™ Extra Strength, Genebs Extra Strength, Mapap Extra Strength, Tycolene Maximum Strength, Tylenol® Extra Strength: 500 mg

Caplet, extended release:

Tylenol® 8 Hour, Tylenol® Arthritis Pain: 650 mg

Capsule: 500 mg

Elixir: 160 mg/5 mL (120 mL, 480 mL, 3780 mL [DSC])

Apra Children’s: 160 mg/5 mL (120 mL, 480 mL, 3780 mL [DSC]) [alcohol free; contains benzoic acid; cherry and grape flavors]

Mapap Children's: 160 mg/5 mL (120 mL) [alcohol free; contains benzoic acid and sodium benzoate; cherry flavor]

Gelcap:

Mapap Extra Strength, Tylenol® Extra Strength: 500 mg

Geltab:

Tylenol® Extra Strength: 500 mg

Liquid, oral: 500 mg/15 mL (240 mL)

Comtrex® Sore Throat Maximum Strength: 500 mg/15 mL (240 mL) [contains sodium benzoate; honey lemon flavor]

Genapap™ Children: 160 mg/5 mL (120 mL) [contains sodium benzoate; cherry and grape flavors]

Silapap®: 160 mg/5 mL (120 mL, 240 mL, 480 mL) [sugar free; contains sodium benzoate; cherry flavor]

Tylenol® Extra Strength: 500 mg/15 mL (240 mL) [contains sodium benzoate; cherry flavor]

Solution, oral: 160 mg/5 mL (120 mL, 480 mL)

Solution, oral [drops]: 80 mg/0.8 mL (15 mL) [droppers are marked at 0.4 mL (40 mg) and at 0.8 mL (80 mg)]

Genapap™ Infant: 80 mg/0.8 mL (15 mL) [fruit flavor]

Infantaire: 80 mg/0.8mL (15 mL, 30 mL)

Little Fevers™: 80 mg/1 mL (30 mL) [alcohol free; contains propylene glycol, sodium benzoate; berry flavor; packaged with dropper and forehead thermometer]

Silapap® Infant's: 80 mg/0.8 mL (15 mL, 30 mL) [contains sodium benzoate; cherry flavor]

Suppository, rectal: 120 mg, 325 mg, 650 mg

Acephen™: 120 mg, 325 mg, 650 mg

FeverALL®: 80 mg, 120 mg, 325 mg, 650 mg

Mapap: 125 mg, 650 mg

Suspension, oral: 160 mg/5 mL (5 mL, 10 mL, 20 mL)

Mapap Children's: 160 mg/5 mL (120 mL) [contains sodium benzoate; cherry flavor]

Nortemp Children’s: 160 mg/5 mL (120 mL) [alcohol free; contains sodium benzoate; cotton candy flavor]

Tylenol® Children's: 160 mg/5 mL (120 mL, 240 mL) [contains sodium benzoate; bubble gum yum, cherry blast, dye free cherry, grape splash, and very berry strawberry flavors]

Tylenol® Children’s with Flavor Creator: 160 mg/5 mL (120 mL) [contains sodium 2 mg/5 mL and sodium benzoate; cherry blast flavor; packaged with apple (4), bubblegum (8), chocolate (4), & strawberry (4) sugar free flavor packets]

Suspension, oral [drops]:

Mapap Infants: 80 mg/0.8 mL (15 mL, 30 mL) [contains sodium benzoate; cherry flavor]

Tylenol® Infants: 80 mg/0.8 mL (15 mL, 30 mL) [contains sodium benzoate; cherry, dye free cherry, and grape flavors]

Tablet: 325 mg, 500 mg

Aspirin Free Anacin® Extra Strength, Genapap™ Extra Strength, Genebs Extra Strength, Mapap Extra Strength, Pain Eze, Tylenol® Extra Strength, Valorin Extra: 500 mg

Cetafen®, Genapap™, Genebs, Mapap, Tycolene, Tylenol®, Valorin: 325 mg

Tablet, chewable: 80 mg

Genapap™ Children: 80 mg [contains phenylalanine 6 mg/tablet; grape flavors] [DSC]

Mapap Children's: 80 mg [contains phenylalanine 3 mg/tablet; bubble gum, fruit, and grape flavors]

Mapap Junior Strength: 160 mg [contains phenylalanine 12 mg/tablet; grape flavor]

Tablet, orally disintegrating: 80 mg, 160 mg

Tylenol® Children’s Meltaways: 80 mg [bubble gum, grape, and watermelon flavors]

Tylenol® Junior Meltaways: 160 mg [bubble gum and grape flavors]

Generic AvailableYes: Excludes extended release products

Pricing: U.S. (www.drugstore.com)

Tablet, controlled release (Tylenol Arthritis Pain)

650 mg (100): $19.99

Tablets (Acetaminophen)

500 mg (700): $38.99

Tablets (Tylenol)

325 mg (100): $16.99

Mechanism of ActionInhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation; produces antipyresis from inhibition of hypothalamic heat-regulating center

Pharmacodynamics/Kinetics

Onset of action: <1 hour

Duration: 4-6 hours

Absorption: Incomplete; varies by dosage form

Protein binding: 8% to 43% at toxic doses

Metabolism: At normal therapeutic dosages, hepatic to sulfate and glucuronide metabolites, while a small amount is metabolized by CYP to a highly reactive intermediate (acetylimidoquinone) which is conjugated with glutathione and inactivated; at toxic doses (as little as 4 g daily) glutathione conjugation becomes insufficient to meet the metabolic demand causing an increase in acetylimidoquinone concentration, which may cause hepatic cell necrosis

Half-life elimination: Prolonged following toxic doses

Neonates: 2-5 hours

Adults: 1-3 hours (may be increased in elderly; however, this should not affect dosing)

Time to peak, serum: Oral: 10-60 minutes; may be delayed in acute overdoses

Excretion: Urine (2% to 5% unchanged; 55% as glucuronide metabolites; 30% as sulphate metabolites)

Dental Health Professional ConsiderationsHepatotoxicity caused by acetaminophen is potentiated by chronic ethanol consumption. People who consume ethanol at the same time that they use acetaminophen, even in therapeutic doses, are at risk of developing hepatotoxicity.

A study by Hylek, et al, suggested that the combination of acetaminophen with warfarin (Coumadin®) may cause enhanced anticoagulation. The following recommendations have been made by Hylek, et al, and supported by an editorial in *JAMA* by Bell.

Dose and duration of acetaminophen should be as low as possible, individualized, and monitored.

The study by Hylek reported that for patients who reported taking the equivalent of at least 4 regular strength (325 mg) tablets for longer than a week, the odds of having an INR >6.0 were increased 10-fold above those not taking acetaminophen. Risk decreased with lower intakes of acetaminophen reaching a background level of risk at a dose of 6 or fewer 325 mg tablets per week.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may increase the hepatotoxic potential of acetaminophen

Anesthesia and Critical Care Concerns/Other ConsiderationsAvoid excessive doses of acetaminophen particularly in patients with a significant alcohol history or poor nutritional habits. The 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) recommend prescribing <2 g/day for patients with a significant alcohol history or those with malnutrition. Other patients may be limited to <4 g/day. Susceptibility to acetaminophen hepatotoxicity may be due to induction of hepatic enzymes caused by chronic alcohol ingestion, depletion of glutathione, malnutrition, and impaired glucuronidation caused by fasting.

Index TermsAPAP; N-Acetyl-P-Aminophenol; Paracetamol

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International Brand NamesA-Mol (TH); Acamol (CN, IL); Acamol To-Go (IL); Acamoli Baby (IL); Acamoli Forte suppositories for Kids (IL); Acenol (PL); Acet (PH); ACET suppositories (SG); Acetalgin (CH); Acetamol (IT); Adinol (MX); Adorem (CO); Afebrin (HK, ID); Afebryl (LU); Alvedon (SE); Amol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Anadin (PL); Anadin dla dzieci (PL); Analgiser (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Analphen (MX); Antidol (PL, TW); APAP (PL); Arfen (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Atamel (PE); ben-u-ron (HU); Ben-U-Ron (PT); Benuron (JP, PL); Biogesic (ID, PH, TH); Biogesic Suspension (HK); Biopain (PH); Bodrex (ID); Calapol (ID); Calodol (PH); Calpol (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IE, IL, IN, IQ, IR, JM, JO, JP, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PL, PR, QA, SA, SC, SD, SL, SN, SR, SY, TH, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Causalon (AR); Cemol (TH); Children's S Tylenol (KP); Christamol (HK); Claradol (MA); Codipar (PL); Crocin (IN); Croix Blanche (LU); Curpol (LU); Dafalgan (BE, LU, PL); Dafalgan odis (LU); Daga (TH); Denamol (TH); Dirox (AR); Dismifen (MX); Dol-Stop (LU); Dolex (UY); Dolgesic (ES); Doliprane (FR, MA, PL); Dolitabs (FR); Dolofen (CO); Dolomol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Dolorol (ZA); Dolprone (LU); Doluvital (MX); Dolviran (MX); Dymadon (AU); Efferalgan (HU, LU, PL); Efferalgan 500 (CR, DO, EE, GT, HN, NI, PA, SV); Efferalganodis (FR); Enelfa (LU); Etoran (PL); Europain (HK); Expandol (FR); Febridol (AU); Fepril (MY); Fervex (BR); Filanc (MX); Gelocatil (ES); Geluprane 500 (FR); Grippostad (PL); Gunaceta (ID); Hedex (IE); Itamol (ID); Itamol Forte (ID); Kamolas (ID); Kyofen (CO); Lekadol (HR, PL); Lemgrip (BE, LU); Lexalgin (PH); Lonarid mono (LU); Lotemp (TH); Lupocet (HR); Maganol (ID); Malidens (IN); Mebinol (PE); Mejoralito Junior (MX); Mejoralito Pediátrico (MX); Metagesic (PH); Mexalen (AT, CZ, HN, HU); Minopan (KP); Momentum (LU); Mypara (TH); Nalgesik (ID); Napafen (EC); Napamol (ZA); Napran (PH); Naprex (ID); NEBS (JP); Nektol 500 (PH); Neuridon (LU); Nilapur (ID); Nordinet Infantil (MX); Novo-Gesic (PL); Pacimol (IN); Pamol (DK); Panadol (AE, AU, BE, BF, BG, BH, BJ, CH, CI, CL, CN, CY, EE, EG, ET, FI, FR, GB, GH, GM, GN, GR, HK, HU, ID, IE, IL, IQ, IR, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PK, PL, QA, SA, SC, SD, SL, SN, SY, TH, TN, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Panadol Actifast (MY, SG); Panadon (HR); Panamax (AU); Panodil (DK, NO, SE); Paracemol (PL); Paracenol (PL); Paracet (NO); Paracetamol (HR, PL); Paracetamol Pharmavit (HU); Paracetamol-ratiopharm (LU); Parageniol (PY); Paragin (TH); Parahexal (AU); Paramidol (PE); Paramol (IL, PL, TW); Parapaed (DE); Parapaed Junior (NZ); Parapaed Six Plus (NZ); Parcemol (HK); Parcemol Forte (HK); Parvid (PH); Paximol (SG); Pe-Tam (LU); Pedipan (KP); Penral-Night (KP); Perdolan Mono (LU); Perfalgan (PL); Pharmacen-M (MX); Pinex (NO); Plicet (HR, PL); Poro (MY, PH, SG); Puernol (IT); Raperon (KP); Rapidol (CN); Reliv (SE); Remedol (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Revanin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Rhinapen elixir (KP); Rubophen (HU); Salzone (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Saridon (CO); Sedalito (MX); Sensamol (IL); Serimol (HK); Sinedol (DO, MX); Supadol mono (LU); Suspen ER (KP); Tabcin (PL); Tamifen (EC); Tazamol (PL); Tempra (EC, GR, ID, JP, LU, MX, TH); Tempte (TW); Turpan (ID); Tylenol (AT, BR, CH, DE, FR, JP, KP, MX, PH, PT, TH, VE); Tylenol 8-hour (TH); Tylenol Acetaminophen Extended Relief (CL); Tylenol Extra Fuerte (PY); Tylenol Forte (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE); Tylex (CR, DO, GT, HN, MX, NI, PA, SV); Winadol (CO, VE); Xebramol (TH); XL-Dol Infantil (MX); Zydinol (PH)

AcetaZOLAMIDE

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Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - February 2008

The U.S. Food and Drug Administration (FDA) is informing healthcare professionals of an increased risk of suicidality (suicidal behavior or ideation) observed from analysis of clinical studies using various antiepileptic medications compared to placebo. The analysis was performed on 199 placebo-controlled studies involving 43,892 patients (27,863 treated patients versus 16,029 placebo patients) aged ≥5 years receiving one of the following 11 drugs: carbamazepine (Carbatrol®, Equetro™, Tegretol®, Tegretol® XR), felbamate (Felbatol®), gabapentin (Neurontin®), lamotrigine (Lamictal®), levetiracetam (Keppra®), oxcarbazepine (Trileptal®), pregabalin (Lyrica®), tiagabine (Gabitril®), topiramate (Topamax®), valproate (Depakote®, Depakote® ER, Depakene®, Depacon®), and zonisamide (Zonegran®). Studies examined medication efficacy in a variety of disorders, including epilepsy, psychiatric disorders (eg, depression, bipolar disorder), and other conditions (eg, migraine, neuropathic pain). According to the FDA, the results revealed a statistically significant increased risk of suicidality in 0.43% treated patients compared to 0.22% placebo patients, or an estimated 2.1 per 1000 (95% CI: 0.7, 4.2) more patients in the treated groups relative to placebo. This increased risk was reported anywhere from 1 week of therapy through 24 weeks. However, most trials were ≤24 weeks duration and the risk of suicide extending beyond 24 weeks is currently unknown. The relative risk of suicidal behavior or ideation in the treated patients was higher for patients with epilepsy (RR=3.6) compared to patients treated for psychiatric (RR=1.6) or other conditions (RR=2.3). Overall, the incidence of suicidal behavior or ideation occurred consistently across all demographic subgroups and with each of the drugs studied. Of note, four patients receiving an antiepileptic committed suicide relative to none in the placebo groups.

Forthcoming product labeling changes are likely to extend to all antiepileptic drugs and not limited to the drugs used in the studies, pending discussions scheduled for the upcoming advisory committee meeting. Healthcare professionals and family members/caregivers are encouraged to monitor patients receiving any antiepileptic medication for signs/symptoms of suicidality (eg, anxiety, depression, behavior changes). Patients should not stop taking their antiepileptic therapy unless advised by a healthcare professional.

Additional information can be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

AcetaZOLAMIDE may be confused with acetoHEXAMIDE

Diamox® Sequels® may be confused with Diabinese®, Dobutrex®, Trimox®

Pronunciation(a set a ZOLE a mide)

U.S. Brand NamesDiamox® Sequels®

Canadian Brand NamesApo-Acetazolamide®; Diamox®

Pharmacologic CategoryAnticonvulsant, Miscellaneous; Carbonic Anhydrase Inhibitor; Diuretic, Carbonic Anhydrase Inhibitor; Ophthalmic Agent, Antiglaucoma

Use: Labeled IndicationsTreatment of glaucoma (chronic simple open-angle, secondary glaucoma, preoperatively in acute angle-closure); drug-induced edema or edema due to congestive heart failure (adjunctive therapy); centrencephalic epilepsies (immediate release dosage form); prevention or amelioration of symptoms associated with acute mountain sickness

Use: Unlabeled/InvestigationalUrine alkalinization; respiratory stimulant in COPD; metabolic alkalosis

Dosing: Adults**Note:** I.M. administration is not recommended.

Glaucoma:

Chronic simple (open-angle): Oral: 250 mg 1-4 times/day or 500 mg extended release capsule twice daily

Secondary, acute (closed-angle): I.V.: 250-500 mg, may repeat in 2-4 hours to a maximum of 1 g/day

Edema: Oral, I.V.: 250-375 mg once daily

Epilepsy: Oral: 8-30 mg/kg/day in 1-4 divided doses, not to exceed 1 g/day. **Note:** Extended release capsule is not recommended for treatment of epilepsy.

Metabolic alkalosis (unlabeled use): I.V. 250 mg every 6 hours for 4 doses or 500 mg single dose; reassess need based upon acid-base status

Mountain sickness: Oral: 250 mg every 8-12 hours (or 500 mg extended release capsules every 12-24 hours). Therapy should begin 24-48 hours before and continue during ascent and for at least 48 hours after arrival at the high altitude.

Note: In situations of rapid ascent (such as rescue or military operations), 1000 mg/day is recommended.

Urine alkalinization (unlabeled use): Oral: 5 mg/kg/dose repeated 2-3 times over 24 hours

Respiratory stimulant in COPD (unlabeled use): Oral, I.V.: 250 mg twice daily

Dosing: ElderlyOral: Initial: 250 mg once or twice daily; use lowest effective dose possible.

Dosing: Pediatric**Note:** I.M. administration is not recommended.

Glaucoma:

Oral: 8-30 mg/kg/day or 300-900 mg/m^2/day divided every 8 hours

I.V.: 20-40 mg/kg/24 hours divided every 6 hours, not to exceed 1 g/day

Edema: Oral, I.V.: 5 mg/kg or 150 mg/m^2 once every day

Epilepsy: Oral: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer every 12 hours.

Cl_{cr} <10 mL/minute: Avoid use (ineffective).

Moderately dialyzable (20% to 50%)

Calculations

- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.

I.M. administration is painful because of the alkaline pH of the drug; use by this route is not recommended.

Administration: I.V. DetailpH: 9.2

Administration: OralOral: May cause an alteration in taste, especially carbonated beverages. Short-acting tablets may be crushed and suspended in cherry or chocolate syrup to disguise the bitter taste of the drug; do not use fruit juices. Alternatively, submerge tablet in 10 mL of hot water and add 10 mL honey or syrup.

Dietary ConsiderationsMay be taken with food to decrease GI upset. May have additive effects with other folic acid antagonists. Sodium content of 500 mg injection: 47.2 mg (2.05 mEq).

Storage

Capsules, tablets: Store at controlled room temperature.

Injection: Store vial for injection (prior to reconstitution) at controlled room temperature. Reconstituted solution may be refrigerated (2°C to 8°C) for 1 week, however, use within 12 hours is recommended. Stability of IVPB solution is 5 days at room temperature (25°C) and 44 days at refrigeration (5°C).

ReconstitutionInjection: Reconstitute with at least 5 mL sterile water to provide a solution containing not more than 100 mg/mL. Further dilute in D_5W or NS for I.V. infusion.

CompatibilityStable in dextran 6% in D_5W, dextran 6% in NS, D_5LR, D_5NS, $D_5{}^1/_2NS$, $D_5{}^1/_4NS$, D_5W, $D_{10}W$, LR, NS, $^1/_2NS$.

Y-site administration: Variable (consult detailed reference): Diltiazem, TPN.

Compatibility when admixed: Compatible: Cimetidine, ranitidine. **Incompatible:** Multivitamins.

Extemporaneously PreparedTablets may be crushed and suspended in cherry, chocolate, raspberry, or other highly-flavored carbohydrate syrup in concentrations of 25-100 mg/mL; simple suspensions are stable for 7 days. For solutions with longer stability, see references for Parastampuria and Alexander.

Alexander KS, Haribhakti RP, and Parker GA, "Stability of Acetazolamide in Suspension Compounded From Tablets," *Am J Hosp Pharm*, 1991, 48(6):1241-4.

McEvoy G, ed, AHFS Drug Information 96, Bethesda, MD: American Society of Health System Pharmacists, 1996.

Parastampuria J and Gupta VD, “Development of Oral Liquid Dosage Forms of Acetazolamide,” *J Pharm Sci*, 1990, 79:385-6.

ContraindicationsHypersensitivity to acetazolamide, sulfonamides, or any component of the formulation; hepatic disease or insufficiency; decreased sodium and/or potassium levels; adrenocortical insufficiency, cirrhosis; hyperchloremic acidosis, severe renal disease or dysfunction; severe pulmonary obstruction; long-term use in noncongestive angle-closure glaucoma

Allergy Considerations

- Carbonic Anhydrase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Impairment of mental alertness and/or physical coordination may occur.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonylurea allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Diabetes: Use with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Hepatic impairment: Use with caution in patients with hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Respiratory acidosis: Use with caution in patients with respiratory acidosis.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to side effects.

Other warnings/precautions:

- I.M. administration: Painful because of the alkaline pH of the drug; use by this route is not recommended.

Geriatric ConsiderationsMalaise and complaints of tiredness and myalgia are signs of excessive dosing and acidosis in older adults. Orthostatic hypotension may occur; assess blood pressure.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic in animal studies, however, there are no adequate and well-controlled studies in pregnant women.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Adverse ReactionsFrequency not defined.

Cardiovascular: Flushing

Central nervous system: Ataxia, confusion, convulsions, depression, dizziness, drowsiness, excitement, fatigue, fever, headache, malaise

Dermatologic: Allergic skin reactions, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Endocrine & metabolic: Electrolyte imbalance, growth retardation (children), hyperglycemia, hypoglycemia, hypokalemia, hyponatremia, metabolic acidosis

Gastrointestinal: Appetite decreased, diarrhea, melena, nausea, taste alteration, vomiting

Genitourinary: Crystalluria, glycosuria, hematuria, polyuria, renal failure

Hematologic: Agranulocytosis, aplastic anemia, leukopenia, thrombocytopenia, thrombocytopenic purpura

Hepatic: Cholestatic jaundice, fulminant hepatic necrosis, hepatic insufficiency, liver function tests abnormal

Local: Pain at injection site

Neuromuscular & skeletal: Flaccid paralysis, paresthesia

Ocular: Myopia

Otic: Hearing disturbance, tinnitus

Miscellaneous: Anaphylaxis

Metabolism/Transport Effects**Inhibits** CYP3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha-/Beta-Agonists: Carbonic Anhydrase Inhibitors may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amphetamines: Carbonic Anhydrase Inhibitors may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Barbiturate): Carbonic Anhydrase Inhibitors may enhance the adverse/toxic effect of Anticonvulsants (Barbiturate). Specifically, osteomalacia and rickets. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Carbonic Anhydrase Inhibitors may enhance the adverse/toxic effect of Anticonvulsants (Hydantoin). Specifically, osteomalacia and rickets. *Risk C: Monitor therapy*

CarBAMazepine: Carbonic Anhydrase Inhibitors may increase the serum concentration of CarBAMazepine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Flecainide: Carbonic Anhydrase Inhibitors may decrease the excretion of Flecainide. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Memantine: Carbonic Anhydrase Inhibitors may decrease the excretion of Memantine. *Risk C: Monitor therapy*

Methenamine: Carbonic Anhydrase Inhibitors may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Primidone: Carbonic Anhydrase Inhibitors may enhance the adverse/toxic effect of Primidone. Specifically, osteomalacia and rickets. Carbonic Anhydrase Inhibitors may decrease the serum concentration of Primidone. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: Carbonic Anhydrase Inhibitors may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Trientine: Carbonic Anhydrase Inhibitor Diuretics may decrease the serum concentration of Trientine. *Risk C: Monitor therapy*

Test InteractionsMay cause false-positive results for urinary protein with Albustix®, Labstix®, Albutest®, Bumintest®; interferes with HPLC theophylline assay and serum uric acid levels

Monitoring ParametersIntraocular pressure, potassium, serum bicarbonate; serum electrolytes, periodic CBC with differential; monitor growth in pediatric patients

Nursing: Physical Assessment/MonitoringAssess allergy history prior to beginning therapy. Assess effectiveness and interactions of other medications patient may be taking. Monitor for signs of excessive dosing and acidosis (especially in elderly). Measure intraocular pressure at the beginning of therapy and periodically while on this medication. Assess results of laboratory tests, therapeutic effectiveness, and adverse response. Monitor growth in pediatric patients. Monitor blood glucose levels closely if patients have diabetes. Assess knowledge/teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsIntraocular pressure, serum electrolytes, periodic CBC with differential

Patient EducationTake as directed; do not chew or crush long-acting capsule (contents may be sprinkled on soft food). May be administered with food to decrease GI upset. You will need periodic ophthalmic examinations while taking this medication. You may experience drowsiness, dizziness, or weakness (use caution when driving or engaging in tasks that require alertness until response to drug is known); or nausea, loss of appetite, or altered taste (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Monitor serum glucose closely (may cause altered blood glucose in some patients with diabetes, or unusual response to some forms of glucose testing). You may experience increased sensitivity to sunlight (use sunblock, protective clothing, and avoid exposure to direct sunlight). Report unusual and persistent tiredness; numbness, burning, or tingling of extremities or around mouth, lips, or anus; muscle weakness; black stool; or excessive depression. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release:

Diamox® Sequels®: 500 mg

Injection, powder for reconstitution: 500 mg

Tablet: 125 mg, 250 mg

Generic AvailableYes: Injection, tablet

Pricing: U.S. (www.drugstore.com)

Capsule, 12-hour (Diamox Sequels)

500 mg (60): $249.98

Tablets (AcetaZOLAMIDE)

125 mg (90): $15.00

250 mg (60): $29.99

Mechanism of ActionReversible inhibition of the enzyme carbonic anhydrase resulting in reduction of hydrogen ion secretion at renal tubule and an increased renal excretion of sodium, potassium, bicarbonate, and water to decrease production of aqueous humor; also inhibits carbonic anhydrase in central nervous system to retard abnormal and excessive discharge from CNS neurons

Pharmacodynamics/Kinetics

Onset of action: Capsule, extended release: 2 hours; I.V.: 2 minutes

Peak effect: Capsule, extended release: 8-12 hours; I.V.: 15 minutes; Tablet: 2-4 hours

Duration: Inhibition of aqueous humor secretion: Capsule, extended release: 18-24 hours; I.V.: 4-5 hours; Tablet: 8-12 hours

Distribution: Erythrocytes, kidneys; blood-brain barrier and placenta; distributes into milk (~30% of plasma concentrations)

Excretion: Urine (70% to 100% as unchanged drug)

Related Information

- Anticonvulsants by Seizure Type
- Glaucoma Drug Therapy
- Status Epilepticus
- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Metallic taste (resolves upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common, may produce depression less commonly

Mental Health: Effects on Psychiatric TreatmentCan rarely cause bone marrow suppression, therefore, use cautiously with clozapine and carbamazepine; may increase the excretion of lithium

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International Brand NamesAcetadiazol (MX); Acetak (PE); Albox (JP); Apo-Acetazolamide (MY); Azol (TW); Carbinib (PT); Cetamid (PH); Diamox (AE, AR, AT, AU, BD, BE, BG, BH, BR, CH, CL, CO, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, HK, HN, HR, ID, IE, IL, IN, IQ, IR, IT, JO, JP, KP, KW, LB, LU, LY, MY, NL, NO, OM, PH, PK, PT, QA, RU, SA, SE, SG, SY, TH, TR, TW, VE, YE, ZA); Diamox Sustets (CO); Diluran (CZ); Diural (UY); Diuramid (PL); Evamox (PK); Fonurit (HU); Glaupax (CH, DE, HR, JP, TH); Huma-Zolamide (HN, HU); Ledamox (JP); Lediamox (PT); Medene (TH); Optamide (PH); Renamid (HR); Stazol (PY); Synomax (IN); Uramox (IL); Zolmide (PH)

Acetic Acid, Propylene Glycol Diacetate, and Hydrocortisone

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Medication Safety Issues

Sound-alike/look-alike issues:

VoSol® may be confused with Vexol®

Pronunciation(a SEE tik AS id, PRO pa leen GLY kole dye AS e tate, & hye droe KOR ti sone)

U.S. Brand NamesAcetasol® HC; VoSol® HC

Pharmacologic CategoryOtic Agent, Anti-infective

Use: Labeled IndicationsTreatment of superficial infections of the external auditory canal caused by organisms susceptible to the action of the antimicrobial, complicated by swelling

Dosing: AdultsOtitis externa (superficial): Otic: Instill 3-5 drops in ear(s) every 4-6 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥3 years: Refer to adult dosing.

Administration: OtherAfter removing cerumen and debris, solution may be applied by inserting a cotton wick into the ear canal and saturating with the solution. Wick may remain in place for 24 hours and then removed; however, drops should continue to be instilled into ear canal as long as indicated.

ContraindicationsHypersensitivity to acetic acid, propylene glycol, hydrocortisone, or any component of the formulation; perforated tympanic membrane; herpes simplex; vaccinia, and varicella

Allergy Considerations

- Corticosteroid Allergy

Adverse ReactionsFrequency not defined: Otic: Transient burning or stinging may be noticed occasionally when the solution is first instilled into the acutely inflamed ear

Metabolism/Transport EffectsHydrocortisone: **Substrate** of CYP3A4 (minor); **Induces** CYP3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agent for Hydrocortisone.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, otic [drops]:

Acetasol® HC, VoSol® HC: Acetic acid 2%, propylene glycol diacetate 3%, and hydrocortisone 1% (10 mL)

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Solution (Acetasol HC)

2-1% (10): $21.99

Related Information

- Acetic Acid
- Hydrocortisone

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsAcetic Acid, Hydrocortisone, and Propylene Glycol Diacetate; Hydrocortisone, Acetic Acid, and Propylene Glycol Diacetate; Propylene Glycol Diacetate, Acetic Acid, and Hydrocortisone

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Acetic Acid

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

VoSol® may be confused with Vexol®

Pronunciation(a SEE tik AS id)

Pharmacologic CategoryOtic Agent, Anti-infective; Topical Skin Product

Use: Labeled IndicationsIrrigation of the bladder; treatment of superficial bacterial infections of the external auditory canal

Dosing: Adults

Irrigation (**Note:** Dosage of an irrigating solution depends on the capacity or surface area of the structure being irrigated):

For continuous irrigation of the urinary bladder with 0.25% acetic acid irrigation, the rate of administration will approximate the rate of urine flow; usually 500-1500 mL/24 hours

For periodic irrigation of an indwelling urinary catheter to maintain patency, about 50 mL of 0.25% acetic acid irrigation is required

Otitis externa: Otic: Insert saturated wick; keep moist 24 hours; remove wick and instill 5 drops 3-4 times/day

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to acetic acid or any component of the formulation; during transurethral procedures

Warnings/Precautions

Concerns related to adverse effects:

- Acidosis: Systemic acidosis may result from absorption.
- Bladder irritation: Use of irrigation in patients with mucosal lesions of urinary bladder may cause irritation.

Other warnings/precautions:

- Administration: Not for internal intake or I.V. infusion; topical use or irrigation use only.

Pregnancy Risk FactorC

Adverse Reactions<1%: Hematuria, systemic acidosis, urologic pain

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution for irrigation: 0.25% (250 mL, 500 mL, 1000 mL)

Solution, otic: 2% (15 mL)

Generic AvailableYes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsEthanoic Acid

References

Kawamata M, Fujita S, and Mayumi T, “Acetic Acid Intoxication by Rectal Administration,” *J Toxicol Clin Toxicol*, 1994, 32(3):333-6. [PubMed 8007044]

Penner GE, “Acid Ingestion: Toxicology and Treatment,” *Ann Emerg Med*, 1980, 9(7):374-9.[PubMed 7396252]

International Brand NamesAquaear (AU); Earcalm (GB, IE); Suym Otico (PE)

Acetohydroxamic Acid

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Lithostat® may be confused with Lithobid®

Pronunciation(a SEE toe hye droks am ik AS id)
U.S. Brand NamesLithostat®
Canadian Brand NamesLithostat®
Pharmacologic CategoryUrinary Tract Product
Use: Labeled IndicationsAdjunctive therapy in chronic urea-splitting urinary infection
Dosing: AdultsSusceptible infections: Oral: 250 mg 3-4 times/day for a total daily dose of 10-15 mg/kg/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricSusceptible infections: Oral: Initial: 10 mg/kg/day
Dosing: Renal ImpairmentNot recommended for use in significant renal impairment (Sr_{cr} >2.5 mg/dL).
Administration: OralShould be administered on an empty stomach.
Dietary ConsiderationsShould be taken on an empty stomach, 1 hour before or 2 hours after meals.
ContraindicationsHypersensitivity to acetohydroxamic acid or any component of the formulation; pregnancy
Warnings/Precautions

Concerns related to adverse effects:

- Bone marrow suppression: May suppress bone marrow function; use with caution in patients with prior bone marrow depression. Close monitoring of hematologic function is recommended.

- Hemolytic anemia: Has been associated with hemolytic anemia (Coombs' negative), which may be associated with gastrointestinal distress and systemic symptoms; use with caution in patients with anemia. Monitor hematologic parameters during extended therapy.

- Hepatotoxicity: May cause hepatic injury; close monitoring of hepatic function is recommended.

Disease-related concerns:

- Psychiatric disorders: Use with caution in patients with pre-existing psychiatric disorders; may be associated with nervousness, anxiety, and/or depression.

Pregnancy Risk FactorX
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Deep vein thrombosis (rare), embolism, palpitation, phlebitis

Central nervous system: Anorexia, anxiety, depression, headache, malaise, nervousness, tremor

Dermatologic: Flushing (with ethanol consumption), rash (nonpruritic, macular)

Gastrointestinal: Nausea, vomiting

Hematologic: Hemolytic anemia (15% with laboratory evidence; ~3% severe requiring discontinuation; may be accompanied by GI symptoms or systemic complaints of malaise and/or fatigue); hyperbilirubinemia

Respiratory: Pulmonary embolism (rare)

Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase incidence of rash and/or flushing).

Food: May decrease absorption of acetohydroxamic acid.

Monitoring ParametersIn patients receiving therapy >2 weeks, monitor CBC with reticulocytes at 3-month intervals during the duration of treatment.
Monitoring: Lab TestsIn patients receiving therapy >2 weeks, monitor CBC with reticulocytes at 3-month intervals during the duration of treatment.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Lithostate®: 250 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Lithostat)

250 mg (100): $143.99

Mechanism of ActionAcetohydroxamic acid inhibits bacterial urease enzymes, decreasing the formation of ammonia in the urine by urea-splitting organisms. A reduction in urinary ammonia may increase the antibacterial activity of some antibiotic agents.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAHA

International Brand NamesUronefrex (BE, ES, FR, LU)

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Acetylcholine may be confused with acetylcysteine

Pronunciation(a se teel KOE leen)
U.S. Brand NamesMiochol®-E
Canadian Brand NamesMiochol®-E
Pharmacologic CategoryCholinergic Agonist; Ophthalmic Agent, Miotic
Use: Labeled IndicationsProduces complete miosis in cataract surgery, keratoplasty, iridectomy, and other anterior segment surgery where rapid miosis is required
Dosing: AdultsTo produce miosis: Intraocular: 0.5-2 mL of 1% injection (5-20 mg) instilled into anterior chamber before or after securing one or more sutures
Dosing: ElderlyRefer to adult dosing.
Administration: OtherOpen under aseptic conditions only. Attach filter before irrigating eye.
StorageStore unopened vial at 4°C to 25°C (39°F to 77°F); prevent from freezing. Prepare solution immediately before use and discard unused portion. Acetylcholine solutions are unstable.
ReconstitutionReconstitute immediately before use.
ContraindicationsHypersensitivity to acetylcholine chloride or any component of the formulation; acute iritis and acute inflammatory disease of the anterior chamber
Warnings/Precautions

Disease-related concerns:

- Diseases affected by systemic effects: Systemic effects rarely occur but can cause problems for patients with asthma, GI spasm, acute heart failure, hyperthyroidism, Parkinson's disease, peptic ulcer disease, and or urinary tract obstruction.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Aseptic conditions: Open under aseptic conditions only.
- Cataract surgery: During cataract surgery, use only after lens is in place.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAcetylcholine is used primarily in the eye and there are no reports of its use in pregnancy. Because it is ionized at physiologic pH, transplacental passage would not be expected.
Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, flushing, hypotension

Central nervous system: Headache

Ocular: Clouding, corneal edema, decompensation

Respiratory: Dyspnea

Miscellaneous: Diaphoresis

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for solution, intraocular, as chloride:

Miochol®-E: 1:100 [20 mg; packaged with diluent (2 mL)]

Generic AvailableNo
Mechanism of ActionCauses contraction of the sphincter muscles of the iris, resulting in miosis and contraction of the ciliary muscle, leading to accommodation spasm
Pharmacodynamics/Kinetics

Onset of action: Rapid

Duration: ~10 minutes

Related Information

- Glaucoma Drug Therapy

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentIntraocular product; should not impact psychiatric drug treatment

Cardiovascular ConsiderationsSystemic effects are rare after intraocular administration, but can occur. Caution should be used in patients with cardiovascular disease.

Anesthesia and Critical Care Concerns/Other ConsiderationsSystemic effects are rare after intraocular administration, but can occur. Caution should be used in patients with cardiovascular disease.

Index TermsAcetylcholine Chloride

International Brand NamesAcetilcolina Colirio (AR); Acetilcolina Cusi (ES); Miochol (FI, GR, LU, NL, NZ); Miochol-E (AU, BE, CH, CN, DE, DK, FI, GB, HK, ID, IE, IL, IT, KP, NL, NO, SE, ZA); Miochole (FR); Miovisin (IT); OQ-Miot (CO)

Acetylcysteine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Acetylcysteine may be confused with acetylcholine

Mucomyst® may be confused with Mucinex®

Pronunciation(a se teel SIS teen)

U.S. Brand NamesAcetadote®

Canadian Brand NamesAcetylcysteine Solution; Mucomyst®; Parvolex®

Pharmacologic CategoryAntidote; Mucolytic Agent

Use: Labeled IndicationsAdjunctive mucolytic therapy in patients with abnormal or viscid mucous secretions in acute and chronic bronchopulmonary diseases; pulmonary complications of surgery and cystic fibrosis; diagnostic bronchial studies; antidote for acute acetaminophen toxicity

Use: Unlabeled/InvestigationalPrevention of radiocontrast-induced renal dysfunction (oral, I.V.); distal intestinal obstruction syndrome (DIOS, previously referred to as meconium ileus equivalent)

Dosing: Adults

Acetaminophen poisoning:

Oral: 140 mg/kg; followed by 17 doses of 70 mg/kg every 4 hours; repeat dose if emesis occurs within 1 hour of administration; therapy should continue until acetaminophen levels are undetectable and there is no evidence of hepatotoxicity.

I.V. (Acetadote®): Loading dose: 150 mg/kg over 60 minutes; **Note:** Extended infusion time recommended by manufacturer as of February, 2006. Loading dose is followed by 2 additional infusions: Initial maintenance dose of 50 mg/kg infused over 4 hours, followed by a second maintenance dose of 100 mg/kg infused over 16 hours. Total dosage: 300 mg/kg administered over 21 hours.

Patients <40 kg: Reduce fluid volume according to the following table.

Acetadote® Dosing / Fluid Volume Guidelines for Patients <40 kg

Body Weight (kg)	**Loading Dose 150 mg/kg over 1 h**		**Second Dose 50 mg/kg over 4 h**		**Third Dose 100 mg/kg over 16 h**	
	Acetadote® (mL)	**D_5W (mL)**	**Acetadote® (mL)**	**D_5W (mL)**	**Acetadote® (mL)**	**D_5W (mL)**
30	22.5	100	7.5	250	15	500
25	18.75	100	6.25	250	12.5	500
20	15	60	5	140	10	280
15	11.25	45	3.75	105	7.5	210
10	7.5	30	2.5	70	5	140

Note: If commercial I.V. form is unavailable, the following dose has been reported using solution for oral inhalation (unlabeled): Loading dose: 140 mg/kg, followed by 70 mg/kg every 4 hours, for a total of 13 doses (loading dose and 48 hours of treatment); infuse each dose over 1 hour through a 0.2 micron Millipore filter (in-line).

Shorter treatment courses have been proposed (Woo, 2000), however, only the full course of therapy is currently FDA approved

Adjuvant therapy in respiratory conditions:

Note: Patients should receive bronchodilator 15 minutes prior to dose.

Inhalation, nebulization (face mask, mouth piece, tracheostomy): Acetylcysteine 10% and 20% solution (dilute 20% solution with sodium chloride or sterile water for inhalation); 10% solution may be used undiluted: 3-5 mL of 20% solution or 6-10 mL of 10% solution until nebulized given 3-4 times/day; dosing range: 1-10 mL of 20% solution or 2-20 mL of 10% solution every 2-6 hours

Inhalation, nebulization (tent, croupette): Dose must be individualized; may require up to 300 mL solution/treatment

Direct instillation:

Into tracheostomy: 1-2 mL of 10% to 20% solution every 1-4 hours

Through percutaneous intratracheal catheter: 1-2 mL of 20% or 2-4 mL of 10% solution every 1-4 hours via syringe attached to catheter

Diagnostic bronchogram: Nebulization or intratracheal: 1-2 mL of 20% solution or 2-4 mL of 10% solution administered 2-3 times prior to procedure

Prevention of radiocontrast-induced renal dysfunction (unlabeled use): Oral: 600 mg twice daily for 2 days (beginning the day before the procedure); may be given as powder in capsules, some centers use solution (diluted in cola beverage or juice). Hydrate patient with saline concurrently.

Prevention of contrast-induced nephropathy (CIN) (unlabeled use): Oral: 600-1200 mg twice daily for 2 days (beginning the day before the procedure); may be given as powder in capsules (some centers use solution, diluted in cola beverage or juice)

Prevention of CIN in acute MI patients requiring emergent cardiac catheterization (unlabeled use):I.V.: 1200 mg over 5-10 minutes prior to cardiac catheterization, followed by 1200 mg **orally** twice daily for 48 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Acetaminophen poisoning: Refer to adult dosing.

Adjuvant therapy in respiratory conditions:

Note: Patients should receive an aerosolized bronchodilator 10-15 minutes prior to acetylcysteine

Inhalation, nebulization (face mask, mouth piece, tracheostomy): Acetylcysteine 10% and 20% solution (dilute 20% solution with sodium chloride or sterile water for inhalation); 10% solution may be used undiluted.

Infants: 1-2 mL of 20% solution or 2-4 mL 10% solution until nebulized given 3-4 times/day

Children: Refer to adult dosing.

Inhalation, nebulization (tent, croupette): Children: Refer to adult dosing.

Administration: I.V.Intravenous formulation (Acetadote®): Administer loading dose of 150 mg/kg over 60 minutes (see **"Note"**), followed by 2 separate maintenance infusions: 50 mg/kg over 4 hours followed by 100 mg/kg over 16 hours. If not using commercially available I.V. formulation, use a 0.2-µ millipore filter (in-line).

Note: Extended infusion time recommended by manufacturer as of February, 2006.

For use with CIN prevention for emergent cardiac catheterization (unlabeled use): Intravenous formulation (Acetadote®): Administer 1200 mg I.V. push over 5-10 minutes prior to contrast administration.

Administration: OralFor treatment of acetaminophen overdosage, administer orally as a 5% solution. Dilute the 20% solution 1:3 with a cola, orange juice, or other soft drink. Use within 1 hour of preparation. Unpleasant odor becomes less noticeable as treatment progresses. If patient vomits within 1 hour of dose, readminister.

Administration: InhalationAcetylcysteine is incompatible with tetracyclines, erythromycin, amphotericin B, iodized oil, chymotrypsin, trypsin, and hydrogen peroxide. Administer separately. Intermittent aerosol treatments are commonly given when patient arises, before meals, and just before retiring at bedtime.

Storage

Solution for injection (Acetadote®): Store vials at room temperature, 20°C to 25°C (68°F to 77°F). Following reconstitution with D_5W, solution is stable for 24 hours at room temperature. A color change may occur in opened vials (light purple) and does not affect the safety or efficacy.

Solution for inhalation (Mucomyst®): Store unopened vials at room temperature; once opened, store under refrigeration and use within 96 hours. A color change may occur in opened vials (light purple) and does not affect the safety or efficacy.

Reconstitution

Solution for injection (Acetadote®):

Loading dose: Dilute 150 mg/kg in D_5W 200 mL.

Initial maintenance dose: Dilute 50 mg/kg in D_5W 500 mL.

Second maintenance dose: Dilute 100 mg/kg in D_5W 1000 mL.

Note: To avoid fluid overload in patients <40 kg and those requiring fluid restriction, decrease volume of D_5W proportionally. Discard unused portion.

Solution for inhalation (Mucomyst®): The 20% solution may be diluted with sodium chloride or sterile water; the 10% solution may be used undiluted.

Intravenous administration of solution for inhalation (unlabeled route): Using D_5W, dilute acetylcysteine 20% oral solution to a 3% solution.

Compatibility

Inhalation: **Incompatible** with rubber and metals (particularly iron, copper, and nickel); do not mix with ampicillin, tetracycline, oxytetracycline, erythromycin.

Intravenous: **Compatible** with D_5W, $^{1}/_{2}$NS, SWFI. **Incompatible** with rubber and metals (particularly iron, copper, and nickel).

ContraindicationsHypersensitivity to acetylcysteine or any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Acetaminophen overdose: Appropriate use: The modified Rumack-Matthew nomogram allows for stratification of patients into risk categories based on the relationship between the serum acetaminophen level and time after ingestion. There are several situations where the nomogram is of limited use. Serum acetaminophen levels obtained prior to 4-hour postingestion are not interpretable; patients presenting late may have undetectable serum concentrations, but have received a lethal dose. The nomogram is less predictive in a chronic ingestion or in an overdose with an extended release product. Acetylcysteine should be administered for any signs of hepatotoxicity even if acetaminophen serum level is low or undetectable. The nomogram also does not take into account patients at higher risk of acetaminophen toxicity (eg, alcoholics, malnourished patients).

Dosage form specific issues:

- Inhalation: Since increased bronchial secretions may develop after inhalation, percussion, postural drainage, and suctioning should follow. If bronchospasm occurs, administer a bronchodilator; discontinue acetylcysteine if bronchospasm progresses.

- Intravenous: Acute flushing and erythema have been reported; usually occurs within 30-60 minutes and may resolve spontaneously. Serious anaphylactoid reactions have also been reported. Acetylcysteine infusion may be interrupted until treatment of allergic symptoms is initiated; the infusion can then be carefully restarted. Treatment for anaphylactic reactions should be immediately available. Use caution with asthma or history of bronchospasm.

Pregnancy Risk FactorB

Pregnancy ConsiderationsBased on limited reports using acetylcysteine to treat acetaminophen overdose in pregnant women, acetylcysteine has been shown to cross the placenta and may provide protective levels in the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

Inhalation: Frequency not defined.

Central nervous system: Drowsiness, chills, fever

Gastrointestinal: Vomiting, nausea, stomatitis

Local: Irritation, stickiness on face following nebulization

Respiratory: Bronchospasm, rhinorrhea, hemoptysis

Miscellaneous: Acquired sensitization (rare), clamminess, unpleasant odor during administration

Intravenous:

>10%: Miscellaneous: Anaphylactoid reaction (~17%; reported as severe in 1% or moderate in 10% of patients within 15 minutes of first infusion; severe in 1% or mild to moderate in 6% to 7% of patients after 60-minute infusion)

1% to 10%:

Cardiovascular: Angioedema (2% to 8%), vasodilation (1% to 6%), hypotension (1% to 4%), tachycardia (1% to 4%), syncope (1% to 3%), chest tightness (1%), flushing (1%)

Central nervous system: Dysphoria (<1% to 2%)

Dermatologic: Urticaria (2% to 7%), rash (1% to 5%), facial erythema (≤1%), palmar erythema (≤1%), pruritus (≤1% to 3%), pruritus with rash and vasodilation (2% to 9%)

Gastrointestinal: Vomiting (<1% to 10%), nausea (1% to 10%), dyspepsia (≤1%)

Neuromuscular & skeletal: Gait disturbance (<1% to 2%)

Ocular: Eye pain (<1% to 3%)

Otic: Ear pain (1%)

Respiratory: Bronchospasm (1% to 6%), cough (1% to 4%), dyspnea (<1% to 3%), pharyngitis (1%), rhinorrhea (1%), rhonchi (1%), throat tightness (1%)

Miscellaneous: Diaphoresis (≤1%)

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersAcetaminophen overdose: AST, ALT, bilirubin, PT, serum creatinine, BUN, serum glucose, and electrolytes. Acetaminophen levels at ~4 hours postingestion (every 4-6 hours if extended release acetaminophen; plot on the nomogram) and every 4-6 hours to assess serum levels, and LFTs for possible hepatotoxicity. Assess patient for nausea, vomiting, and skin rash following oral administration for treatment of acetaminophen poisoning. If administered I.V., monitor for anaphylaxis/anaphylactoid reactions.

Reference RangeDetermine acetaminophen level as soon as possible, but no sooner than 4 hours after ingestion (to ensure peak levels have been obtained); administer for acetaminophen level >150 mcg/mL at 4 hours following ingestion; toxic concentration with probable hepatotoxicity: >200 mcg/mL at 4 hours or 50 mcg at 12 hours

Nursing: Physical Assessment/MonitoringInstruct patient on appropriate use, adverse effects to report, and interventions to reduce side effects. Monitor pulmonary function and response to therapy. If giving I.V., monitor for possible anaphylactoid reactions and be prepared to treat appropriately if needed.

Monitoring: Lab TestsAcetaminophen overdose: AST, ALT, bilirubin, PT, serum creatinine, BUN, serum glucose, and electrolytes. Acetaminophen levels at ~4 hours postingestion (every 4-6 hours if extended release acetaminophen; plot on the nomogram) and every 4-6 hours to assess serum levels, and LFTs for possible hepatotoxicity.

Patient EducationPulmonary treatment: Prepare solution (may dilute with sterile water to reduce concentrate from impeding nebulizer) and use as directed. Clear airway by coughing deeply before using aerosol. Wash face and face mask after treatment to remove any residual. You may experience drowsiness (use caution when driving or engaging in tasks requiring alertness), nausea, or vomiting (small, frequent meals may help). Report persistent chills or fever, adverse change in respiratory status, palpitations, or extreme anxiety or nervousness. **Breast-feeding precaution:** Inform prescriber if you are breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Acetadote®: 20% (30 mL) [200 mg/mL; contains disodium edetate]

Solution, inhalation/oral: 10% (4 mL, 10 mL, 30 mL) [100 mg/mL]; 20% (4 mL, 10 mL, 30 mL) [200 mg/mL]

Generic AvailableYes: Solution for inhalation

Pricing: U.S. (www.drugstore.com)

Solution (Acetylcysteine)

10% (30): $17.99

10% (30): $25.99

20% (4): $7.99

20% (10): $22.99

20% (30): $17.99

Solution (Mucomyst)

20% (30): $18.99

Solution (Mucomyst-10)

10% (30): $18.99

Mechanism of ActionExerts mucolytic action through its free sulfhydryl group which opens up the disulfide bonds in the mucoproteins thus lowering mucous viscosity. The exact mechanism of action in acetaminophen toxicity is unknown; thought to act by providing substrate for conjugation with the toxic metabolite. The presumed mechanism in preventing contrast-induced nephropathy is its ability to scavenge oxygen-derived free radicals and improve endothelium-dependent vasodilation.

Pharmacodynamics/Kinetics

Onset of action: Inhalation: 5-10 minutes

Duration: Inhalation: >1 hour

Distribution: 0.47 L/kg

Protein binding, plasma: 83%

Half-life elimination:

Reduced acetylcysteine: 2 hours

Total acetylcysteine: Adults: 5.5 hours; Newborns: 11 hours

Time to peak, plasma: Oral: 1-2 hours

Excretion: Urine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, drowsiness, fever, vomiting, nausea, bronchospasm, rhinorrhea, hemoptysis, and dizziness

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentSedative effects may be potentiated by psychotropic agents

Cardiovascular Considerations

Contrast-Induced Nephropathy (CIN): Oral: Although study results vary, acetylcysteine may be beneficial in prevention of CIN in patients undergoing cardiac catheterization (Curhan, 2003). Tepel (2000) and his group originally randomized 83 patients with chronic renal insufficiency to oral acetylcysteine (600 mg twice daily) and intravenous saline 0.45% **or** placebo and intravenous saline 0.45%. All patients were having a CT scan with iopromide contrast. Patients receiving acetylcysteine had a significant reduction in serum creatinine 48 hours after the procedure. Conversely, patients in the placebo arm had significant increase in serum creatinine.

A recent randomized, placebo-controlled trial in 200 Chinese patients with stable mild-to-moderate renal insufficiency also evaluated acetylcysteine in prevention of CIN (Kay, 2003). Patients were undergoing elective coronary angiography and/or intervention, and had serum creatinine concentrations >1.2 mg/dL or Cl_{cr} <60 mL/minute (estimated and measured). A low-osmolality nonionic contrast agent was used. All patients received saline 0.9% I.V. at 1 mL/kg/hour for 12 hours before and for 6 hours after contrast exposure. Three doses of acetylcysteine (600 mg twice daily) or matching placebo were given before and one dose after dye exposure. Contrast nephropathy developed more frequently in the control group (12%) than in the acetylcysteine group (4%). The average length of hospitalization was 0.5 days shorter in the acetylcysteine group. No adverse events related to acetylcysteine were reported.

However, these results differed from those in another prospective, randomized trial (Allaqaband, 2002) that compared the efficacy of acetylcysteine (600 mg twice daily for 48 hours) plus saline 0.45% versus fenoldopam (0.1 mcg/kg/minute) plus saline 0.45% versus saline 0.45% alone (at 1 mL/kg/hour for 12 hours before procedure, during procedure, and 12 hours afterwards) in preventing CIN. Patients were high-risk (serum creatinine >1.6 mg/dL or Cl_{cr} <60 mL/minute) and undergoing cardiovascular procedures using low-osmolality nonionic contrast. Authors concluded that there was no benefit in either oral acetylcysteine or fenoldopam over saline in preventing CIN.

Marenzi, et al (2006) showed that acetylcysteine's effect may be dose dependent. Patients with acute MI requiring emergent cardiac catheterization for possible PCI received either high dose acetylcysteine (1200 mg I.V. bolus followed by 1200 mg administered orally twice daily for 48 hours), a low dose regimen (600 mg I.V. bolus followed by 600 mg administered orally twice daily for 48 hours) or placebo. The group that received the high dose regimen developed CIN (defined as an increase in serum creatinine concentration of ≥25% from baseline within 72 hour) less often than the low dose group ($p<0.001$). All patients received saline 0.9% NaCl at 1 mL/kg/hour (0.5 mL/kg/hour for cases of overt heart failure) for 12 hours.

Briguori, et al (2007) evaluated three prophylactic regimens (normal saline and acetylcysteine (NAC); sodium bicarbonate and NAC; normal saline, ascorbic acid and NAC) in 326 patients with chronic kidney disease (serum creatinine ≥2 mg/dL) undergoing coronary and/or peripheral procedures with iodixanol. Saline was given I.V. at 1 mL/kg/hour (0.5 ml/kg/hour for LVEF <40%) for 12 hours before and 12 hours after contrast administration. Sodium bicarbonate administration was similar to that in the Merten trial. The oral NAC dose was 1200 mg twice daily given the day before and the day of contrast administration (4 doses total). The ascorbic acid dose was given I.V. as 3 g 2 hours before the procedure followed by 2 g the night of and the morning after the procedure. The amount of contrast administered and the contrast nephropathy risk scores were similar in each group. Contrast induced nephropathy (CIN) occurred in 9.9% (11/111 of patients) of saline/NAC group, 2% (2/108 of patients) of bicarbonate/NAC group and 10.3 % (11/107 of patients) in saline/NAC/ascorbic acid group. The bicarbonate/NAC group had significantly fewer episodes of CIN when compared to saline/NAC group in this patient population.

Parameters used to define CIN varied among studies.

Contrast-Induced Nephropathy (CIN): I.V.: Several studies have evaluated intravenous acetylcysteine in the prevention of CIN. Three different dosing regimens were used. The initial study (Baker, 2003) randomized patients with stable renal function undergoing cardiac catheterization to intravenous acetylcysteine 150 mg/kg over 30 minutes followed by 50 mg/kg over 4 hours or placebo. The study was stopped when an interim analysis indicated borderline statistical significance ($p= 0.045$). Hydration volumes were different between the groups as well. The mean serum creatinine level in the active treatment group was lower after administration when compared to baseline. Acetylcysteine may have a direct affect on creatinine levels.

Another trial (Webb, 2004) studied 500 mg of intravenous acetylcysteine administered immediately before cardiac catheterization. No significant difference was seen between acetylcysteine and placebo.

Rashid (2004) randomized patients with peripheral vascular disease to 1 g acetylcysteine in 500 mL of normal saline 6-12 hours before and after the procedure. No significant differences were seen in renal function.

Marenzi, et al (2006) evaluated the use of an initial I.V. push dose (high and low dose) of acetylcysteine prior to cardiac catheterization in acute MI patients followed by an oral regimen (high and low dose) compared to placebo. This trial is described above.

Note: Itching, flushing, and rash, as well as more serious allergic reactions, may occur with intravenous acetylcysteine.

⬆ Anesthesia and Critical Care Concerns/Other ConsiderationsIntravenous acetylcysteine may be indicated over oral formulation in treatment of acetaminophen overdose for a restricted number of indications (oral cannot be tolerated; coingested toxin requires ongoing gastrointestinal decontamination; gastrointestinal tract nonfunctional; late presentation of acetaminophen overdose; neonatal toxicity from maternal overdose) (Yip, 1998). A commercially manufactured intravenous product is now available in the United States. If this formulation is unavailable, the product normally administered by inhalation can be administered intravenously. The inhalation preparation is sterile, but not labeled “pyrogen free.” In Yip's retrospective case series, adverse reactions occurred in 4 (~5%) cases. Flushing, pruritus, and phlebitis were reported; one was labeled as an “anaphylactic reaction.”

Bailey and McGuigan reviewed a retrospective case series of patients who received intravenous acetylcysteine and the literature to develop management guideline for anaphylactoid reactions (Bailey, 1998). Their recommendations for treatment of non-life-threatening allergic reactions include reassessing the need for intravenous acetylcysteine, and administering diphenhydramine (1 mg/kg I.V.; maximum dose: 50 mg). If the acetylcysteine infusion was stopped initially and symptoms resolved, consider restarting infusion 1 hour after diphenhydramine's administration. Anaphylactoid reactions have also been reported with the commercial I.V. formulation. Monitor closely for allergic reactions. Be prepared to handle anaphylactoid reaction if it occurs.

Index Terms *N*-Acetyl-L-cysteine; *N*-Acetylcysteine; Acetylcysteine Sodium; Mercapturic Acid; Mucomyst; NAC

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International Brand NamesACC (AR, HU, LU, MX, PL, ZA); ACC 200 (EE, HN); Acemuk (AR); Acet (TW); Acetain (KP); Acetylcystein NM Pharma (SE); Acetylcystein Tika (SE); Acypront (HK, PL); Alistine Forte (TH); Bromuc (BR); Broncoflem (PH); Drenaflen (EC); Ecomucyl (CH); Eloamin (CZ); Exomuc (FR, HK, LU); Fabrol (AT, GR); Flemex AC (TH); Fluimicil (CH, DE); Fluimiquil (LU); Fluimucil (AR, BG, BR, CL, CO, HK, HU, ID, IT, MA, NL, PE, PL, TH, TW); Fluimucil A (MY, PK); Fluimukan (HR); Flumil (ES); Flutafin (TW); Hidonac (ID, MY, PH, TH, TW); Libramucil (EC); Lubrisec (AR); Lysomucil (LU); Lysox (LU); Menaxol (CR, DO, GT, HN, NI, PA, SV); Mucofillin (JP); Mucolair (LU); Mucolator (LU, MY); Mucolitico (CN); Mucomiste (PT); Mucomyst (AT, AU, BE, DK, FI, FR, KP, LU, NO, SE); Mucoserin (KP); Mucosof (CL); Mucosten (KP); Mucosys (IN); Mucoza (TH); Mukolit (ID); Muteran (KP); Muxatil (PY); NAC-ratiopharm (LU); Parvolex (GB, IE, NZ, PH); Parvolex DBL (MY); Pectomucil (LU); Reolin (IL); Rumicil (LU); Simucin (TH); Siran 200 (IL); Solmucol (HU, LU); Spatam (SG); Sputopur (HU); Stecin (KP); Syntemucol (PL); Touxium Mucolyticum (LU); Tussicom (PL); Viskoferm (SE); Zifluvis (CO)

Acitretin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Soriatane® may be confused with Loxitane®

Pronunciation(a si TRE tin)

U.S. Brand NamesSoriatane® CK Convenience Kit™; Soriatane® [DSC]

Canadian Brand NamesSoriatane®

Pharmacologic CategoryRetinoid-Like Compound

Use: Labeled IndicationsTreatment of severe psoriasis

Dosing: Adults

Psoriasis: Oral: Individualization of dosage is required to achieve maximum therapeutic response while minimizing side effects

Initial therapy: Therapy should be initiated at 25-50 mg/day, given as a single dose with the main meal

Maintenance: Doses of 25-50 mg/day may be given after initial response to treatment; the maintenance dose should be based on clinical efficacy and tolerability

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsAdminister with food. Avoid ingestion of additional sources of exogenous vitamin A (in excess of RDA); use of ethanol and ethanol-containing products is contraindicated.

StorageStore between 15°C to 25°C (59°F to 77°F). Avoid high temperatures and humidity. Protect from light.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to acitretin, other retinoids, or any component of the formulation; patients who are pregnant or intend on becoming pregnant; ethanol ingestion; severe hepatic or renal dysfunction; chronically-elevated blood lipid levels; concomitant use with methotrexate or tetracyclines

Acitretin is contraindicated in females of childbearing potential unless all of the following conditions apply.

1) Patient has severe psoriasis unresponsive to other therapy or if clinical condition contraindicates other treatments.

2) Patient must have two negative urine or serum pregnancy tests prior to therapy.

3) Patient must have pregnancy test repeated monthly during therapy. After discontinuation of therapy, a pregnancy test must be repeated every 3 months for at least 3 years.

4) Patient must commit to using two effective forms of birth control starting 1 month prior to acitretin treatment and for 3 years after discontinuation. Prescriber must counsel patient about contraception every month during therapy and every 3 months following discontinuation for at least 3 years.

5) Patient is reliable in understanding and carrying out instructions.

6) Patient has received, and acknowledged, understanding of a careful oral and printed explanation of the hazards of fetal exposure to acitretin and the risk of possible contraception failure; this explanation may include showing a line drawing to the patient of an infant with the characteristic external deformities resulting from retinoid exposure during pregnancy. Patient must sign an agreement/informed consent document stating that she understands these risks and that she should not consume ethanol during therapy or for 2 months after discontinuation.

7) All patients (male and female) should not donate blood during and for 3 years following treatment with acitretin.

Warnings/Precautions

Boxed warnings:

- Blood donation: See “Other warnings/precautions” below.
- Ethanol use: See “Concurrent drug therapy issues” below.
- Hepatotoxicity: See “Concerns related to adverse effects” below.
- Medication guide: See “Other warnings/precautions” below.

- Pregnancy/Do Your P.A.R.T. program: See “Special populations” below.

Concerns related to adverse effects:

- Depression: Depression, including thoughts of self-harm have been reported; use with caution in patients with a history of mental illness.

- Hepatotoxicity: **[U.S. Boxed Warning]: Changes in transaminases occur in up to $^{1}/_{3}$ of patients.** Monitor for hepatotoxicity; discontinue if significant elevations of liver enzymes occur. Use with caution in patients at risk of hypertriglyceridemias.

- Hyperostosis: Patients receiving long-term treatment should be periodically examined for bony abnormalities; if occur risk vs. benefit of therapy should be considered.

- Lipid effects: Lipid changes including, increased triglycerides, increased cholesterol, and decreased HDL are common (up to 66%); increased triglycerides may lead to pancreatitis.

- Photosensitivity: May be photosensitizing; minimize sun or other UV exposure to treated areas.

- Pseudotumor cerebri: Rarely associated with pseudotumor cerebri.

- Visual disturbances: May cause a decrease in night vision or decreased tolerance to contact lenses; discontinue if visual changes occur.

Concurrent drug therapy issues:

- Ethanol use: **[U.S. Boxed Warning]: All patients (male and female) should abstain from ethanol or ethanol-containing products during therapy and for 2 months after discontinuation.**

- Tetracyclines: Pseudotumor cerebri (benign intracranial hypertension) has been reported with use of tetracyclines and acitretin independently; concomitant use is contraindicated.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children; growth potential may be affected.

- Pregnancy/Do Your P.A.R.T. program: **[U.S. Boxed Warning]: Not for use by women who are pregnant or want to become pregnant; patient should not get pregnant for at least 3 years after discontinuation.** The Do Your P.A.R.T. (Pregnancy Prevention Actively Required During and After Treatment) program explains teratogenic risks and requirements expected of females of childbearing potential to prevent pregnancies from occurring during use and 3 years following discontinuation; this should be used to educate patients and healthcare providers.

Other warnings/precautions:

- Blood donation: **[U.S. Boxed Warning]: All patients should be advised not to donate blood during therapy or for 3 years following completion of therapy.**

- Medication guide: **[U.S. Boxed Warning]: All patients must be provided with a medication guide each time acitretin is dispensed. Female patients must also sign an informed consent prior to therapy.**

Pregnancy Risk FactorX

Pregnancy ConsiderationsAcitretin is teratogenic in humans. Severe birth defects have been reported when conception occurred during treatment or after therapy was complete. **[U.S. Boxed Warning]: Not for use by women who want to become pregnant;** patient should not get pregnant for at least 3 years after discontinuation. In addition, because ethanol forms a teratogenic metabolite and would increase the duration of teratogenic potential, ethanol should not be consumed during treatment or for 2 months after discontinuation. Limited amounts of acitretin are found in seminal fluid; although it appears this poses little risk to a fetus, the actual risk of teratogenicity is not known. Any pregnancy which occurs during treatment, or within 3 years after treatment is discontinued, should be reported to the manufacturer at 1-888-500-3376 or to the FDA at 1-800-FDA-1088.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsAcitretin should not be given prior to or during nursing due to the potential for adverse effects in the nursing infant.

Adverse Reactions

>10%:

Central nervous system: Hyperesthesia (10% to 25%)

Dermatologic: Cheilitis (>75%), alopecia (50% to 75%), skin peeling (50% to 75%), dry skin (25% to 50%), nail disorder (25% to 50%), pruritus (25% to 50%), erythematous rash (10% to 25%), skin atrophy (10% to 25%), sticky skin (10% to 25%), paronychia (10% to 25%)

Endocrine & metabolic: Hypercholesterolemia (25% to 50%), hypertriglyceridemia (50% to 75%), HDL decreased (25% to 50%), phosphorus increased (10% to 25%), potassium increased (10% to 25%), sodium increased (10% to 25%), magnesium increased/decreased (10% to 25%), fasting blood sugar increased (25% to 50%), fasting blood sugar decreased (10% to 25%)

Gastrointestinal: Xerostomia (10% to 25%)

Hematologic: Reticulocytes increased (25% to 50%), hematocrit decreased (10% to 25%), hemoglobin decreased (10% to 25%), WBC increased/decreased (10% to 25%), haptoglobin increased (10% to 25%), neutrophils increased (10% to 25%)

Hepatic: Liver function tests increased (25% to 50%), alkaline phosphatase increased (10% to 25%), direct bilirubin increased (10% to 25%), GGTP increased (10% to 25%)

Neuromuscular & skeletal: Paresthesia (10% to 25%), arthralgia (10% to 25%), rigors (10% to 25%), CPK increased (25% to 50%), spinal hyperostosis progression (10% to 25%)

Ocular: Xerophthalmia (10% to 25%),

Renal: Uric acid increased (10% to 25%), acetonuria (10% to 25%), hematuria (10% to 25%), RBC in urine (10% to 25%)

Respiratory: Rhinitis (25% to 50%), epistaxis (10% to 25%)

1% to 10%:

Cardiovascular: Flushing, edema

Central nervous system: Headache, pain, depression, insomnia, somnolence, fatigue

Dermatologic: Skin odor, hair texture change, bullous eruption, dermatitis, diaphoresis increased, psoriasiform rash, purpura, pyogenic granuloma, rash, seborrhea, ulcers, fissures, sunburn

Endocrine & metabolic: Hot flashes, potassium decreased, phosphorus decreased, sodium decreased, calcium increased or decreased, chloride increased or decreased

Gastrointestinal: Gingival bleeding, gingivitis, saliva increased, stomatitis, thirst, ulcerative stomatitis, abdominal pain, diarrhea, nausea, taste disturbance, anorexia, appetite increased, tongue disorder

Hepatic: Total bilirubin increased

Neuromuscular & skeletal: Arthritis, back pain, hypertonia, myalgia, osteodynia, peripheral joint hyperostosis, Bell's palsy

Ocular: Blurred vision, blepharitis, conjunctivitis, night blindness, photophobia, corneal epithelial abnormality, eye pain, eyebrow or eyelash loss, diplopia, cataract

Otic: Earache, tinnitus

Renal: BUN increased, creatinine increased, glycosuria, proteinuria

Respiratory: Sinusitis

<1%: Abnormal gait, acne, anal disorder, anxiety, bleeding time increased, bone disorder, bursitis, chalazion, chest pain, cirrhosis, conjunctival hemorrhage, constipation, corneal ulceration, cough, cyanosis, deafness, diplopia, dizziness, dyspepsia, dysphonia, dysuria, ectropion, eczema, esophagitis, ethanol intolerance, fever, flu-like syndrome, fungal infection, furunculosis, gastritis, gastroenteritis, glossitis, gum hyperplasia, hair discoloration, healing impaired, hemorrhage, hemorrhoids, hepatic dysfunction, hepatitis, hyperkeratosis, hypertrichosis, hypoesthesia, intermittent claudication, itchy eyes, jaundice, lacrimation abnormal, leukorrhea, libido decreased, malaise, melena, migraine, moniliasis, muscle weakness, nervousness, neuritis, olecranon bursitis, papilledema, peripheral ischemia, pharyngitis, photosensitivity, pseudotumor cerebri, recurrent sties, scleroderma, skin hypertrophy, spinal hyperostosis (new lesion), taste loss, tendonitis, tenesmus, tongue ulceration, urticaria, vaginitis, weight gain

Postmarketing and/or case reports: Aggression, MI, myopathy with peripheral neuropathy, nail fragility, pancreatitis, skin fragility or thinning, stroke, suicidal thoughts, thromboembolism, vulvovaginitis

Drug Interactions

Alcohol (Ethyl): May enhance the teratogenic effect of Acitretin. *Risk X: Avoid combination*

Contraceptive (Progestins): Acitretin may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Methotrexate: Acitretin may enhance the hepatotoxic effect of Methotrexate. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Retinoic Acid Derivatives may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): Retinoic Acid Derivatives may diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. *Risk C: Monitor therapy*

Tetracycline Derivatives: May enhance the adverse/toxic effect of Retinoic Acid Derivatives. The development of pseudotumor cerebri is of particular concern. *Risk X: Avoid combination*

Vitamin A: May enhance the adverse/toxic effect of Retinoid-like Compounds. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Use leads to formation of etretinate, a teratogenic metabolite with a prolonged half-life; concomitant use of ethanol or ethanol-containing products is contraindicated.

Monitoring ParametersLipid profile (baseline and at 1- to 2-week intervals for 4-8 weeks); liver function tests (baseline, and at 1- to 2-week intervals until stable, then as clinically indicated); blood glucose in patients with diabetes; bone abnormalities (with long-term use)

Monitoring: Lab TestsLipid profile (baseline and at 1- to 2-week intervals for 4-8 weeks); liver function tests (baseline, and at 1- to 2-week intervals until stable, then as clinically indicated); blood glucose in patients with diabetes

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

Soriatane®: 10 mg [DSC], 25 mg [DSC]

Soriatane® CK Convenience Kit™: 10 mg, 25 mg [packaged with VersaFoam-EF™]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Soriatane)

25 mg (30): $607.90

Pharmacodynamics/KineticsEtretinate has been detected in serum for up to 3 years following therapy, possibly due to storage in adipose tissue.

Onset: May take 2-3 months for full effect; improvement may be seen within 8 weeks.

Absorption: Oral: ~72% absorbed when given with food

Protein binding: >99% bound, primarily to albumin

Metabolism: Metabolized to *cis*-acitretin; both compounds are further metabolized. Concomitant ethanol use leads to the formation of etretinate (active).

Half-life elimination: Acitretin: 49 hours (range: 33-96); *cis*-acitretin: 63 hours (range: 28-157); etretinate: 120 days (range: 84-168 days)

Excretion: Feces (34% to 54%); urine (16% to 53%)

Pharmacotherapy PearlsFemale patients are required to use two forms of birth control, at least one of which is a primary form, unless they have undergone a hysterectomy or are postmenopausal. Both forms of birth control must be used simultaneously for at least 1 month prior to therapy and for at least 3 years after discontinuation. Primary forms of birth control include tubal ligation, partner's vasectomy, IUD, or hormonal birth control products. Microdosed progestin products, referred to as “mini-pills,” have been shown to be less effective when used with acitretin, and are not recommended. Secondary forms of contraception include diaphragms, latex condoms and cervical caps, all if used with a spermicide.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesNeo-Tigason (TH); Neotigason (AR, AT, AU, BB, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CZ, DE, DK, EC, EE, EG, ET, FI, GB, GH, GM, GN, GR, GY, HN, IE, IL, IT, JM, KE, KP, LR, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, PE, PH, PL, PT, PY, SC, SD, SE, SL, SN, SR, TN, TT, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Soriatane (FR)

Acrivastine and Pseudoephedrine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(AK ri vas teen & soo doe e FED rin)

U.S. Brand NamesSemprex®-D

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation

Use: Labeled IndicationsTemporary relief of nasal congestion, decongest sinus openings, running nose, itching of nose or throat, and itchy, watery eyes due to hay fever or other upper respiratory allergies

Dosing: AdultsRhinitis, nasal congestion, allergic symptoms: Oral: 1 capsule 3-4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentDo not use.

ContraindicationsHypersensitivity to pseudoephedrine, acrivastine (or other alkylamine antihistamines), or any component of the formulation; MAO inhibitor therapy within 14 days of initiating therapy; severe hypertension, severe coronary artery disease; renal impairment (Cl_{cr} ≤48 mL/minute)

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Renal impairment: Use with caution in patients with renal impairment; contraindicated if Cl_{cr} ≤48 mL/minute.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Pregnancy Risk FactorB

LactationEnters breast milk/contraindicated

Adverse Reactions

>10%: Central nervous system: Drowsiness, headache

1% to 10%:

Cardiovascular: Tachycardia, palpitation

Central nervous system: Nervousness, dizziness, insomnia, vertigo, lightheadedness, fatigue

Gastrointestinal: Nausea, vomiting, xerostomia, diarrhea

Genitourinary: Dysuria

Neuromuscular & skeletal: Weakness

Respiratory: Pharyngitis, cough increased

Miscellaneous: Diaphoresis

<1%: Dysmenorrhea, dyspepsia

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase sedation)
Nursing: Physical Assessment/MonitoringSee individual agent for Pseudoephedrine.
Patient EducationSee individual agent for Pseudoephedrine.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Semprex®-D: Acrivastine 8 mg and pseudoephedrine hydrochloride 60 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Capsules (Semprex-D)

8-60 mg (30): $45.99

Mechanism of ActionRefer to Pseudoephedrine; acrivastine is an analogue of triprolidine and it is considered to be relatively less sedating than traditional antihistamines; believed to involve competitive blockade of H_1-receptor sites resulting in the inability of histamine to combine with its receptor sites and exert its usual effects on target cells

Pharmacodynamics/Kinetics

Pseudoephedrine: See Pseudoephedrine.

Acrivastine:

Metabolism: Minimally hepatic

Time to peak: ~1.1 hours

Excretion: Urine (84%); feces (13%)

Related Information

- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response
Mental Health: Effects on Mental StatusDrowsiness is common; may produce anxiety and insomnia
Mental Health: Effects on Psychiatric TreatmentHypertensive crisis may result with MAO inhibitor; effects of CNS depressants may be lessened

Index TermsPseudoephedrine Hydrochloride and Acrivastine

References

Brogden RN and McTavish D, “Acrivastine: A Review of Its Pharmacological Properties and Therapeutic Efficacy in Allergic Rhinitis, Urticaria, and Related Disorders,” *Drugs*, 1991, 41(6):927-40. [PubMed 1715267]

Levien TL and Baker DE, “Reviews of Acrivastine and Midotrine,” *Hosp Pharm*, 1995, 30(3):229-35.

International Brand NamesDuact (DK, FI)

Acyclovir

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Zovirax® may be confused with Zostrix®, Zyvox®

International issues:

Opthavir® [Mexico] may be confused with Optivar® which is a brand name for azelastine in the U.S.

Pronunciation(ay SYE kloe veer)

U.S. Brand NamesZovirax®

Canadian Brand NamesApo-Acyclovir®; Gen-Acyclovir; Nu-Acyclovir; ratio-Acyclovir; Zovirax®

Pharmacologic CategoryAntiviral Agent; Antiviral Agent, Topical

Use: Labeled IndicationsTreatment of genital herpes simplex virus (HSV), herpes labialis (cold sores), herpes zoster (shingles), HSV encephalitis, neonatal HSV, mucocutaneous HSV in immunocompromised patients, varicella-zoster (chickenpox)

Use: Unlabeled/InvestigationalPrevention of HSV reactivation in HIV-positive patients; prevention of HSV reactivation in hematopoietic stem-cell transplant (HSCT); prevention of HSV reactivation during periods of neutropenia in patients with acute leukemia

Use: DentalTreatment of initial and prophylaxis of recurrent mucosal and cutaneous herpes simplex (HSV-1 and HSV-2) infections in immunocompromised patients

Dosing: Adults**Note:** Obese patients should be dosed using ideal body weight

Genital HSV:

I.V.: Immunocompetent: Initial episode, severe: 5 mg/kg every 8 hours for 5-7 days

Oral:

Initial episode: 200 mg every 4 hours while awake (5 times/day) for 10 days (per manufacturer's labeling); 400 mg 3 times/day for 5-10 days has also been reported

Recurrence: 200 mg every 4 hours while awake (5 times/day) for 5 days (per manufacturer's labeling; begin at earliest signs of disease); 400 mg 3 times/day for 5 days has also been reported

Chronic suppression: 400 mg twice daily or 200 mg 3-5 times/day, for up to 12 months followed by re-evaluation (per manufacturer's labeling); 400-1200 mg/day in 2-3 divided doses has also been reported

Topical: Immunocompromised: Ointment: Initial episode: $^1/_2$" ribbon of ointment for a 4" square surface area every 3 hours (6 times/day) for 7 days

Herpes labialis (cold sores): Topical: Apply 5 times/day for 4 days

Herpes zoster (shingles):

Oral: Immunocompetent: 800 mg every 4 hours (5 times/day) for 7-10 days

I.V.: Immunocompromised: 10 mg/kg/dose or 500 mg/m^2/dose every 8 hours for 7 days

HSV encephalitis: I.V.: 10 mg/kg/dose every 8 hours for 10 days (per manufacturer's labeling); 10-15 mg/kg/dose every 8 hours for 14-21 days also reported

Mucocutaneous HSV:

I.V.: Immunocompromised: 5 mg/kg/dose every 8 hours for 7 days (per manufacturer's labeling); dosing for up to 14 days also reported

Oral: Immunocompromised (unlabeled use): 400 mg 5 times a day for 7-14 days

Topical: Ointment: Non-life-threatening, immunocompromised: $^1/_2$" ribbon of ointment for a 4" square surface area every 3 hours (6 times/day) for 7 days

Varicella-zoster (chickenpox): Begin treatment within the first 24 hours of rash onset:

Oral: >40 kg (immunocompetent): 800 mg/dose 4 times a day for 5 days

I.V.: Immunocompromised (unlabeled use): 1500 mg/m^2/day divided every 8 hours or 10 mg/kg/dose every 8 hours for 7-10 days

Prevention of HSV reactivation in HIV-positive patients, for use only when recurrences are frequent or severe (unlabeled use): Oral: 200 mg 3 times/day or

400 mg 2 times/day

Prevention of HSV reactivation in HSCT (unlabeled use): Note: Start at the beginning of conditioning therapy and continue until engraftment or until mucositis resolves (~30 days)

Oral: 200 mg 3 times/day

I.V.: 250 mg/m^2/dose every 12 hours

Bone marrow transplant recipients (unlabeled use): I.V.: Allogeneic patients who are HSV and CMV seropositive: 500 mg/m^2/dose (10 mg/kg) every 8 hours; for clinically-symptomatic CMV infection, consider replacing acyclovir with ganciclovir

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Obese patients should be dosed using ideal body weight

Genital HSV:

I.V.: Children ≥12 years: Refer to adult dosing.

Oral:

Initial episode (unlabeled use): 40-80 mg/kg/day divided into 3-4 doses for 5-10 days (maximum: 1 g/day)

Chronic suppression (unlabeled use; limited data): 80 mg/kg/day in 3 divided doses (maximum: 1 g/day), re-evaluate after 12 months of treatment

Herpes labialis (cold sores): Topical: Children ≥12 years: Refer to adult dosing.

Herpes zoster (shingles): I.V.:

Children <12 years (immunocompromised): 20 mg/kg/dose every 8 hours for 7 days

Children ≥12 years: Refer to adult dosing.

HSV encephalitis: I.V.:

Children 3 months to 12 years: 20 mg/kg/dose every 8 hours for 10 days (per manufacturer's labeling); dosing for 14-21 days also reported

Children ≥12 years: Refer to adult dosing.

Mucocutaneous HSV: I.V.:

Children <12 years (immunocompromised): 10 mg/kg/dose every 8 hours for 7 days

Children ≥12 years: Refer to adult dosing.

Neonatal HSV: I.V.: Neonate: Birth to 3 months: 10 mg/kg/dose every 8 hours for 10 days (manufacturer's labeling); 15 mg/kg/dose or 20 mg/kg/dose every 8 hours for 14-21 days has also been reported

Varicella-zoster (chickenpox): Begin treatment within the first 24 hours of rash onset:

Oral:

Children ≥2 years and ≤40 kg (immunocompetent): 20 mg/kg/dose (up to 800 mg/dose) 4 times/day for 5 days

Children >40 kg: Refer to adult dosing.

I.V.:

Children <1 year (immunocompromised, unlabeled use): 10 mg/kg/dose every 8 hours for 7-10 days

Children ≥1 year: Refer to adult dosing.

Prevention of HSV reactivation in HIV-positive patients, for use only when recurrences are frequent or severe (unlabeled use): Oral: 80 mg/kg/day in 3-4 divided doses

Prevention of HSV reactivation in HSCT (unlabeled use): Note: Start at the beginning of conditioning therapy and continue until engraftment or until mucositis resolves (~30 days): I.V.: 250 mg/m^2/dose every 8 hours or 125 mg/m^2/dose every 6 hours

Bone marrow transplant recipients (unlabeled use): I.V.: Refer to adult dosing.

Dosing: Renal Impairment

Oral:

Cl_{cr} 10-25 mL/minute/1.73 m^2: Normal dosing regimen 800 mg every 4 hours: Administer 800 mg every 8 hours

Cl_{cr} <10 mL/minute/1.73 m^2:

Normal dosing regimen 200 mg every 4 hours, 200 mg every 8 hours, or 400 mg every 12 hours: Administer 200 mg every 12 hours

Normal dosing regimen 800 mg every 4 hours: Administer 800 mg every 12 hours

I.V.:

Cl_{cr} 25-50 mL/minute/1.73 m^2: Administer recommended dose every 12 hours

Cl_{cr} 10-25 mL/minute/1.73 m^2: Administer recommended dose every 24 hours

Cl_{cr} <10 mL/minute/1.73 m^2: Administer 50% of recommended dose every 24 hours

Hemodialysis: Administer dose after dialysis

Continuous ambulatory peritoneal dialysis (CAPD): Administer 50% of normal dose once daily; no supplemental dose needed

Continuous renal replacement therapy (CRRT): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH or CVVHD/CVVHDF: 5-7.5 mg/kg every 24 hours

Note: The higher dose of 7.5 mg/kg is recommended for infections with CNS involvement (Trotman, 2005).

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Ideal Body Weight: Adults
- Ideal Body Weight: Pediatrics

Administration: I.V.For I.V. infusion only. Avoid rapid infusion. Infuse over 1 hour to prevent renal damage. Maintain adequate hydration of patient. Check for phlebitis and rotate infusion sites.

Administration: I.V. DetailpH: 10.5-11.6 (reconstituted solution)

Administration: OralMay be administered with or without food.

Administration: TopicalNot for use in the eye. Apply using a finger cot or rubber glove to avoid transmission to other parts of the body or to other persons.

Dietary ConsiderationsMay be taken with or without food. Acyclovir 500 mg injection contains sodium ~50 mg (~2 mEq).

Storage

Capsule, tablet: Store at controlled room temperature of 15°C to 25°C (59°F to 77°F); protect from moisture.

Cream, suspension: Store at controlled room temperature of 15°C to 25°C (59°F to 77°F).

Ointment: Store at controlled room temperature of 15°C to 25°C (59°F to 77°F) in a dry place.

Injection: Store powder at controlled room temperature of 15°C to 25°C (59°F to 77°F). Reconstituted solutions remain stable for 12 hours at room temperature. Do not refrigerate reconstituted solutions as they may precipitate. Once diluted for infusion, use within 24 hours.

ReconstitutionPowder for injection: Reconstitute acyclovir 500 mg with SWFI 10 mL; do not use bacteriostatic water containing benzyl alcohol or parabens. For intravenous infusion, dilute to a final concentration ≤7 mg/mL. Concentrations >10 mg/mL increase the risk of phlebitis.

CompatibilityStable in D_5W, D_5NS, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, LR, NS.

Incompatible with blood products and protein-containing solutions.

Y-site administration: Compatible: Allopurinol, amikacin, amphotericin B cholesteryl sulfate complex, ampicillin, cefamandole, cefazolin, cefoperazone, cefotaxime, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, chloramphenicol, cimetidine, clindamycin, co-trimoxazole, dexamethasone, dimenhydrinate, diphenhydramine, docetaxel, doxorubicin liposome, doxycycline, erythromycin lactobionate, etoposide, famotidine, filgrastim, fluconazole, gatifloxacin, gentamicin, granisetron, heparin, hydrocortisone sodium succinate, hydromorphone, imipenem/cilastatin, linezolid, lorazepam, magnesium sulfate, melphalan, methylprednisolone sodium succinate, metoclopramide, metronidazole, multivitamins, nafcillin, oxacillin, paclitaxel, penicillin G potassium, pentobarbital, perphenazine, piperacillin, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, tacrolimus, teniposide, theophylline, thiotepa, ticarcillin, tobramycin, vancomycin, zidovudine. **Incompatible:** Amifostine, amsacrine, aztreonam, cefepime, dobutamine, dopamine, fludarabine, foscarnet, gemcitabine, idarubicin, levofloxacin, ondansetron, piperacillin/tazobactam, sargramostim, vinorelbine. **Variable (consult detailed reference):** Cisatracurium, diltiazem, meperidine, meropenem, morphine, TPN.

Compatibility when admixed: Compatible: Fluconazole. **Incompatible:** Dobutamine, dopamine. **Variable (consult detailed reference):** Meropenem.

ContraindicationsHypersensitivity to acyclovir, valacyclovir, or any component of the formulation

Allergy Considerations

- Antiviral Acyclic Guanine Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Renal effects: Renal failure (sometimes fatal) has been reported. Dehydration, pre-existing renal disease and nephrotoxic drugs increase risk; infuse over at least 1 hour to reduce risk of renal tubular damage.

- Thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS): Has been reported.

Disease-related concerns:

- Varicella-zoster: Appropriate use: Treatment should begin within 24 hours of appearance of rash; oral route not recommended for routine use in otherwise healthy children with varicella, but may be effective in patients at increased risk of moderate to severe infection (>12 years of age, chronic cutaneous or pulmonary disorders, long-term salicylate therapy, corticosteroid therapy).

- Genital herpes: Appropriate use: Physical contact should be avoided when lesions are present; transmission may also occur in the absence of symptoms. Treatment should begin with the first signs or symptoms.

- Herpes labialis: Appropriate use: For external use only to the lips and face; do not apply to eye or inside the mouth or nose. Treatment should begin with the first signs or symptoms.

- Herpes zoster: Appropriate use: Therapy should be started within 72 hours of appearance of rash to be effective.

- Renal impairment: Use with caution in patients with pre-existing renal impairment; dosage adjustments recommended.

Concurrent drug therapy issues:

- Nephrotoxic drugs: Use with caution in patients receiving other nephrotoxic drugs.

Special populations:

- Elderly: Use with caution in the elderly; higher risk for CNS and renal adverse events.

- Immunocompromised patients: Use with caution in immunocompromised patients.

- Pediatrics: Safety and efficacy of oral formulations have not been established in children <2 years of age.

Dosage form specific issues:

- Injection: Use I.V. preparation with caution in patients with underlying neurologic abnormalities, serious hepatic or electrolyte abnormalities, or substantial hypoxia.

Other warnings/precautions:

- Adequate hydration: Maintain adequate hydration during oral or intravenous therapy.

Geriatric ConsiderationsFor herpes zoster, acyclovir should be started within 72 hours of the appearance of the rash to be effective. Dose adjustment may be necessary depending on creatinine clearance.
Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Acyclovir has been shown to cross the human placenta. There are no adequate and well-controlled studies in pregnant women. Results from a pregnancy registry, established in 1984 and closed in 1999, did not find an increase in the number of birth defects with exposure to acyclovir when compared to those expected in the general population. However, due to the small size of the registry and lack of long-term data, the manufacturer recommends using during pregnancy with caution and only when clearly needed. Data from the pregnancy registry may be obtained from GlaxoSmithKline.
LactationEnters breast milk/use with caution (AAP rates “compatible”)
Breast-Feeding ConsiderationsNursing mothers with herpetic lesions near or on the breast should avoid breast-feeding. Limited data suggest exposure to the nursing infant of ~0.3 mg/kg/day following oral administration of acyclovir to the mother.
Adverse Reactions

Systemic: Oral:

>10%: Central nervous system: Malaise (12%)

1% to 10%:

Central nervous system: Headache (2%)

Gastrointestinal: Nausea (2% to 5%), vomiting (3%), diarrhea (2% to 3%)

Systemic: Parenteral:

1% to 10%:

Dermatologic: Hives (2%), itching (2%), rash (2%)

Gastrointestinal: Nausea/vomiting (7%)

Hepatic: Liver function tests increased (1% to 2%)

Local: Inflammation at injection site or phlebitis (9%)

Renal: BUN increased (5% to 10%), creatinine increased (5% to 10%), acute renal failure

Topical:

>10%: Dermatologic: Mild pain, burning, or stinging (ointment 30%)

1% to 10%: Dermatologic: Pruritus (ointment 4%), itching

All forms: <1%, postmarketing, and/or case reports: Abdominal pain, aggression, agitation, alopecia, anaphylaxis, anemia, angioedema, anorexia, ataxia, coma, confusion, consciousness decreased, delirium, desquamation, diarrhea, disseminated intravascular coagulopathy (DIC), dizziness, dry lips, dysarthria, encephalopathy, erythema multiforme, fatigue, fever, gastrointestinal distress, hallucinations, hematuria, hemolysis, hepatitis, hyperbilirubinemia, hypotension, insomnia, jaundice, leukocytoclastic vasculitis, leukocytosis, leukopenia, local tissue necrosis (following extravasation), lymphadenopathy, mental depression, myalgia, neutrophilia, paresthesia, peripheral edema, photosensitization, pruritus, psychosis, renal failure, seizure, somnolence, sore throat, Stevens-Johnson syndrome, thrombocytopenia, thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), thrombocytosis, toxic epidermal necrolysis, tremor, urticaria, visual disturbances

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Mycophenolate: Acyclovir-Valacyclovir may increase the serum concentration of Mycophenolate. Mycophenolate may increase the serum concentration of Acyclovir-Valacyclovir. *Risk C: Monitor therapy*

Tenofovir: Acyclovir-Valacyclovir may decrease the excretion of Tenofovir. *Risk C: Monitor therapy*

Zidovudine: Acyclovir-Valacyclovir may enhance the CNS depressant effect of Zidovudine. *Risk C: Monitor therapy*

Zoster Vaccine: Acyclovir-Valacyclovir may diminish the therapeutic effect of Zoster Vaccine. Management: When possible, discontinue antiviral agents with anti-zoster activity (i.e., acyclovir, valacyclovir, famciclovir) for at least 24 hours prior to and 14 days after receiving a live attenuated zoster vaccine. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: Does not affect absorption of oral acyclovir.

Monitoring ParametersUrinalysis, BUN, serum creatinine, liver enzymes, CBC

Nursing: Physical Assessment/MonitoringAssess carefully for use cautions. Assess potential for interactions with other prescriptions, OTC, or herbal medications patient may be taking. Patient should be adequately hydrated during I.V. therapy and monitored closely during intravenous administration. Assess results of laboratory tests, therapeutic effects, and adverse responses according to purpose for use and formulation. Teach patient proper use (if self-administered), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsUrinalysis, BUN, serum creatinine, liver enzymes, CBC

Patient EducationDo not take any new medication during therapy (including creams, lotions, or ointments) unless approved by prescriber. This is not a cure for herpes (recurrences tend to continually reappear every 3-6 months after original infection), nor will this medication reduce the risk of transmission to others when lesions are present; avoid sexual intercourse when visible lesions are present. Use as directed for full course of therapy; do not discontinue even if feeling better. Oral doses may be taken with food. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); lightheadedness or dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known); or headache, fever, muscle pain (consult prescriber for approved analgesic). Report any change in urination (difficulty urinating, dark colored or concentrated urine); persistent lethargy; acute headache; severe nausea or vomiting; confusion or hallucinations; rash; or respiratory difficulty.

Topical: Apply as directed. Use gloves or finger cot when applying.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 200 mg

Zovirax®: 200 mg

Cream, topical:

Zovirax®: 5% (2 g, 5 g)

Injection, powder for reconstitution, as sodium: 500 mg, 1000 mg

Injection, solution, as sodium [preservative free]: 50 mg/mL (10 mL, 20 mL)

Ointment, topical:

Zovirax®: 5% (15 g)

Suspension, oral: 200 mg/5 mL (480 mL)

Zovirax®: 200 mg/5 mL (480 mL) [banana flavor]

Tablet: 400 mg, 800 mg

Zovirax®: 400 mg, 800 mg

Generic AvailableYes: Excludes cream, ointment

Pricing: U.S. (www.drugstore.com)

Capsules (Acyclovir)

200 mg (30): $12.99

Capsules (Zovirax)

200 mg (30): $79.65

Cream (Zovirax)

5% (2): $55.98

5% (5): $126.43

Ointment (Zovirax)

5% (15): $141.68

Suspension (Acyclovir)

200 mg/5 mL (473): $123.97

Suspension (Zovirax)

200 mg/5 mL (473): $219.95

Tablets (Acyclovir)

400 mg (60): $28.99

800 mg (30): $24.99

Tablets (Zovirax)

400 mg (60): $290.80

800 mg (30): $282.81

Mechanism of ActionAcyclovir is converted to acyclovir monophosphate by virus-specific thymidine kinase then further converted to acyclovir triphosphate by other cellular enzymes. Acyclovir triphosphate inhibits DNA synthesis and viral replication by competing with deoxyguanosine triphosphate for viral DNA polymerase and being incorporated into viral DNA.

Pharmacodynamics/Kinetics

Absorption: Oral: 15% to 30%

Distribution: V_d: 0.8 L/kg (63.6 L): Widely (eg, brain, kidney, lungs, liver, spleen, muscle, uterus, vagina, CSF)

Protein binding: 9% to 33%

Metabolism: Converted by viral enzymes to acyclovir monophosphate, and further converted to diphosphate then triphosphate (active form) by cellular enzymes

Bioavailability: Oral: 10% to 20% with normal renal function (bioavailability decreases with increased dose)

Half-life elimination: Terminal: Neonates: 4 hours; Children 1-12 years: 2-3 hours; Adults: 3 hours

Time to peak, serum: Oral: Within 1.5-2 hours

Excretion: Urine (62% to 90% as unchanged drug and metabolite)

Related Information

- Treatment of Sexually-Transmitted Infections
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Topical (Zovirax® cream): Dry/cracked lips and dry/flaky skin were reported in fewer than 1 in 100 patients in clinical studies.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay see lethargy, confusion, or agitation; rarely may see depression or insomnia

Mental Health: Effects on Psychiatric TreatmentUsually not a problem, may see additive sedation with sedating psychotropics

Index TermsAciclovir; ACV; Acycloguanosine

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Wood MJ, Johnson RW, McKendrick MW, et al, “A Randomized Trial of Acyclovir for 7 Days or 21 Days With and Without Prednisolone for Treatment of Acute Herpes Zoster,” *N Engl J Med*, 1994, 330(13):896-900.[PubMed 8114860]

International Brand NamesAbbovir (PL); ACERPES (DE); Acic Creme (DE); Aciclobeta (AU); Acicloftal (IT); Aciclor (VE); Aciclosina (PE); Aciclovir (PL); aciclovir von ct (LU); Aciclovir-BC IV (AU); Acifur (MX); Acihexal (AU); Acivir Cream (IL, IN, NZ); Acivir Eye (IN); Acix (PL); Aclova (KP); Aclovir (HR, TH, TW); Aclovirax (HK); ACS (KP); Activir (FR); Acyclo-V (AU, BH, NZ); Acyclostad (PL); Acyclovir (PL); Acyclovir Stada (PL); Acyhex (PH); Acyklowir (PL); Acylene (MY); Acyrova (KP); Acyvir (EC, HK, IT); Aias (KP); Antivir (PL); Apicol (CO); Apo-Acyclovir (PL); Avorax (HK, MY, SG); Avorax Cream (MY); Awirol (PL); Azovir (ID); Bearax (SG); Blistex Anitviral Cold Sore Cream (AU); Cicloferon (MX); Cicloviral (CO); Ciklovir (HU); Clinovir (ID, TH); Clirbest (MX); Clorixan (MX); Clovicin (TW); Clovir (BR); Cloviran (CN); Clyvorax (MX); Colsor (TH); Cusiviral (HK, MY, PL, SG); Cyclivex (ZA); Cyclomed (IL); Cyclorax (HK); Cyclostad (PH); Cyclovir (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Cyllanvir (PH); Danovir (SG); Deherp (TH, TW); Dravyr (SG); Duvimex (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ecuvir (EC); Entir (SG, TH); Erlvirax (SG); Euroclovir (HK); Eurovir (PY); Exavir (BR); Expit (UY); Geavir (DK, SE); Genovix (MX); Hascovir (PL); Helvevir (CH); Herax (ID); Hercivir (MX); Herpefug (DE); Herpesin (HU, PL); Herpex (BH, IN, PL); Herpizyg (TH); Herpoviric (DE); Herpoviric Rp Creme (DE); Heviran (PL); Ignis (MX); Inmerax (CN); Jersin (MX); Juviral (DE); Laciken (MX); Lermex (TH); Lisovyr (AR, CN); Lovir (AU, HK, MY, SG); Lovir Cold Sore Cream (AU); Lovire (ZA); Mapox (LU); Marvir (TH); Matrovir (ID); Maynor (ES); Medovir (AE, BF, BG, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, QA, SA, SC, SD, SG, SL, SN, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Molavir (ID); Nevirz (ID); Norum (TH); Oppvir (TH, TW); Opthavir (MX); Ozvir (AU); Poviral (EC); Proviral (AR); Qualiclovir (HK); Quavir (ID); Ranvir (TH); Ranviran (PL); Sophivir Ungena (MX); Supra-Vir (IL); Supraviran (DE, LU, PL); Supraviran Creme (AE, BH, CY, DE, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Syntovir (HK); Telviran (HU); Vacrax (MY); Vacrovir (KP); Vermis (TH); Vicorax (TH, TW); Victoclir (MX); Viracir (PL); Viralex-DS (PH); Viralis (ID); Virax (KP); Vircella (ID); Virest (MY, SG); Virestat (MX); Virex (CO); Virherpes (ES); Virless (CL, SG); Viroclear (HK); Virogon (TH); Virokill (HU); Virolan (TW); Virolex (HR, HU, PL); Viromed (TH); Virucid (HK); Virules (HK); Vivir (KP); Warviron (HK); Zeven Cream (MY); Zevin (TH); Zirconia (MX); Ziverone (MX); Zoral (HK, SG); Zoral Cream (MY); Zorax (SG); Zorel (ID); Zoter (ID); Zovir (DK); Zovirax (AE, AR, AT, AU, BB, BD, BE, BF, BG, BH, BJ, BM, BO, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PK, PR, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SV, SY, TH, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Zovirax [tabs./susp./ungt.] (PL); Zumasid (ID); Zyclir (AU); Zyclorax (ID); Zylovir (CL); Zyvir (KE)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Soft Tissue Sarcoma

Regimen UseSoft tissue sarcoma

Regimen

Doxorubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Dacarbazine: I.V.: 250 mg/m^2/day days 1 to 5

[total dose/cycle = 1250 mg/m^2]

Repeat cycle every 21 days

References

Borden EC, Amato DA, Rosenbaum C, et al, “Randomized Comparison of Three Adriamycin Regimens for Metastatic Soft Tissue Sarcomas,” *J Clin Oncol*, 1987, 5(6):840-50.[PubMed 3585441]

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Tumor Necrosis Factor: Alpha Blockers Associated with Unrecognized Invasive Fungal Infections - September 4, 2008

The U.S. Food and Drug Administration (FDA) is alerting healthcare professionals of an increased risk for opportunistic fungal infections in patients treated with antitumor necrosis factor (anti-TNF) agents adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), and infliximab (Remicade®). The FDA has received reports of pulmonary and disseminated cases of histoplasmosis, coccidioidomycosis, blastomycosis, and other fungal infections associated with use of these agents. In some cases, the symptoms of fungal infection (eg, fever, cough, malaise, dyspnea, fatigue) were unrecognized and precluded prompt antifungal treatment, resulting in 12 deaths. In response, the FDA is requiring manufacturers of these agents to strengthen the boxed warning statement in the labeling to further emphasize the risk of invasive fungal infection. Patients should be monitored closely for signs and symptoms suggestive of fungal infection, evidence of which should result in prompt discontinuation of the medication and appropriate diagnostic evaluation. Symptomatic patients should be questioned about their residence in or travel from areas of endemic mycoses, which should prompt consideration of empiric antifungal therapy.

Additional information can be found at: http://www.fda.gov/medwatch/safety/2008/safety08.htm#TNF2

Tumor Necrosis Factor (TNF) Blockers and Malignancy Risk - June 5, 2008

The U.S. Food and Drug Administration (FDA) issued an Early Communication to healthcare professionals regarding a possible association between TNF blocker (adalimumab, certolizumb pegol, etanercept, and infliximab) use and the development of malignancies in children and young adults. Over the last 10 years, the FDA has received ~30 reports of cancer in children or young adults who had been treated with TNF blockers prior to the age of 18 years. TNF blockers were given for the treatment of Juvenile Idiopathic Arthritis (JIA [formerly termed Juvenile Rheumatoid Arthritis]), Crohn’s disease, or other indications in combination with other immunosuppressive medications (eg, azathioprine, 6-mercaptopurine or methotrexate). Approximately half of the reported cancers were lymphomas (Hodgkin’s and non-Hodgkin’s), which are cancers involving the cells of the immune system.

TNF blockers work by suppressing the immune system. The prescribing information for each TNF blocker contains warnings regarding the possible association of malignancy development with use. Malignancies may not be detected in short-term studies; long-term studies are necessary to identify the impact of TNF blocker therapy on malignancy development. The manufacturers of the four TNF blockers available in the U.S. are being asked by the FDA to provide information regarding all cases of cancer reported in children taking TNF blockers. The FDA is expected to report its findings in approximately 6 months, after completing a safety review and evaluation.

Additional information is available at http://www.fda.gov/medwatch/safety/2008/safety08.htm#TNF

Medication Safety Issues

Sound-alike/look-alike issues:

Humira® may be confused with Humulin®, Humalog®

Humira® Pen may be confused with HumaPen® Memoir®

Pronunciation(a da LIM yoo mab)

U.S. Brand NamesHumira®

Canadian Brand NamesHumira®

Pharmacologic CategoryAntirheumatic, Disease Modifying; Gastrointestinal Agent, Miscellaneous; Monoclonal Antibody; Tumor Necrosis Factor (TNF) Blocking Agent

Use: Labeled Indications

Treatment of active rheumatoid arthritis (moderate-to-severe) and active psoriatic arthritis; may be used alone or in combination with disease-modifying antirheumatic drugs (DMARDs); treatment of ankylosing spondylitis

Treatment of moderately- to severely-active Crohn’s disease in patients with inadequate response to conventional treatment, or patients who have lost response to or are intolerant of infliximab

Treatment of moderate-to-severe plaque psoriasis

Treatment of moderately- to severely-active juvenile idiopathic arthritis

Dosing: Adults

Rheumatoid arthritis: SubQ: 40 mg every other week; may be administered with other DMARDs; patients not taking methotrexate may increase dose to 40 mg every week

Ankylosing spondylitis, psoriatic arthritis: SubQ: 40 mg every other week

Crohn's disease: SubQ: Initial: 160 mg given as 4 injections on day 1 or over 2 days, then 80 mg 2 weeks later (day 15); Maintenance: 40 mg every other week beginning day 29

Plaque psoriasis: SubQ: Initial: 80 mg as a single dose; maintenance: 40 mg every other week beginning 1 week after initial dose

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Juvenile idiopathic arthritis:** Children ≥4 years: SubQ:

15 kg to <30 kg: 20 mg every other week

≥30 kg: 40 mg every other week

Administration: OtherFor SubQ injection; rotate injection sites. Do not use if solution is discolored. Do not administer to skin which is red, tender, bruised, or hard; rotate injection sites. Needle cap of the prefilled syringe may contain latex.

StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsThere are no contraindications listed within the FDA-approved labeling.

Canada labeling: Additional contraindications (not in U.S. labeling): Hypersensitivity to adalimumab or any component of the formulation; severe infection (eg, sepsis, tuberculosis, opportunistic infection)

Warnings/Precautions

Boxed warnings:

- Fatal infections: See "Concerns related to adverse effects" below.
- Tuberculosis evaluation: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: May rarely cause hypersensitivity, anaphylaxis, anaphylactoid reactions, or angioedema; medications for the treatment of hypersensitivity reactions should be available for immediate use.
- Autoimmune disorder: Positive antinuclear antibody titers have been detected in patients (with negative baselines). Rare cases of autoimmune disorder, including lupus-like syndrome, have been reported; monitor and discontinue if symptoms develop.
- Fatal infections: **[U.S. Boxed Warning]: Serious and potentially fatal infections (including tuberculosis, invasive fungal and other opportunistic infections) have been reported in patients receiving TNF-blocking agents, including adalimumab.** Cases of unrecognized invasive fungal infections (eg, histoplasmosis, blastomycosis, coccidioidomycosis) have also been reported with anti-TNF agent use. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy. Other opportunistic infections included *Aspergillus* and *Nocardia*. Caution should be exercised when considering the use in patients with chronic infection, history of recurrent infection, or predisposition to infection (eg, diabetes or residence/travel from areas of endemic mycoses). Do not give to patients with an active chronic or localized infection. Patients who develop a new infection while undergoing treatment should be monitored closely. If a patient develops a serious infection, therapy should be discontinued.
- Hepatitis B: Rare reactivation of hepatitis B virus (HBV) has occurred in chronic virus carriers; evaluate prior to initiation, during, and for several months after treatment. Evaluate patients at risk for HBV infection prior to therapy to determine HBV status.
- Malignancy: Use may affect defenses against malignancies; impact on the development and course of malignancies is not fully defined. A higher incidence of nonmelanoma skin cancers was noted in adalimumab-treated patients (0.9/100 patient years), when compared to the control group (0.3/100 patient years). As compared to the general population, an increased risk of lymphoma has been noted in clinical trials; however, rheumatoid arthritis has been previously associated with an increased rate of lymphoma.
- Pancytopenia: Rare cases of pancytopenia (including aplastic anemia) have been reported with TNF-blocking agents; with significant hematologic abnormalities, consider discontinuing therapy.
- Tuberculosis evaluation: Tuberculosis (disseminated or extrapulmonary) has been reactivated while on adalimumab; most cases have been reported within the first 8 months of treatment. Doses higher than recommended are associated with an increased risk for tuberculosis reactivation. **[U.S. Boxed Warnings]: Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test prior to therapy.** Treatment of latent tuberculosis should be initiated before use. **Patients with initial negative tuberculin skin tests should receive continued monitoring for tuberculosis throughout treatment;** active tuberculosis has developed in this population during treatment. Use with caution in patients who have resided in regions where tuberculosis is endemic

Disease-related concerns:

- Demyelinating CNS disease: Use with caution in patients with pre-existing or recent onset CNS demyelinating disorders; rare cases of optic neuritis and demyelinating disease (new onset or exacerbation) have been reported.
- Heart failure (HF): Use with caution in patients with HF or decreased left ventricular function; worsening and new-onset HF has been

reported.

Dosage form specific issues:

- Latex: The packaging (needle cover of prefilled syringe) may contain latex.
- Polysorbate 80: Product may contain polysorbate 80.

Other warnings/precautions:

- Immunizations: Patients should be brought up to date with all immunizations before initiating therapy; live vaccines should not be given concurrently. There is no data available concerning the effects of therapy on vaccination or secondary transmission of live vaccines in patients receiving therapy.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies, however, there are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed. A pregnancy registry has been established to monitor outcomes of women exposed to adalimumab during pregnancy (877-311-8972).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known whether adalimumab is secreted in human milk. Because many immunoglobulins are secreted in milk and the potential for serious adverse reactions exists, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Adverse Reactions

>10%:

Central nervous system: Headache (12%)

Dermatologic: Rash (6% to 12%)

Local: Injection site reaction (12% to 20%; includes erythema, itching, hemorrhage, pain, swelling)

Neuromuscular & skeletal: CPK increased (15%)

Respiratory: Upper respiratory tract infection (17%), sinusitis (11%)

Miscellaneous: Antibodies to adalimumab (3% to 26%; significance unknown), positive ANA (12%)

5% to 10%:

Cardiovascular: Hypertension (5%)

Endocrine & metabolic: Hyperlipidemia (7%), hypercholesterolemia (6%)

Gastrointestinal: Nausea (9%), abdominal pain (7%)

Genitourinary: Urinary tract infection (8%)

Hepatic: Alkaline phosphatase increased (5%)

Local: Injection site reaction (8%; other than erythema, itching, hemorrhage, pain, swelling)

Neuromuscular & skeletal: Back pain (6%)

Renal: Hematuria (5%)

Miscellaneous: Accidental injury (10%), flu-like syndrome (7%)

<5%:

Cardiovascular: Arrhythmia, atrial fibrillation, chest pain, CHF, coronary artery disorder, heart arrest, MI, palpitation, pericardial effusion, pericarditis, peripheral edema, syncope, tachycardia, thrombosis (leg), vascular disorder

Central nervous system: Confusion, fever, hypertensive encephalopathy, multiple sclerosis, subdural hematoma

Dermatologic: Cellulitis, erysipelas

Endocrine & metabolic: Dehydration, menstrual disorder, parathyroid disorder

Gastrointestinal: Diverticulitis, esophagitis, gastroenteritis, gastrointestinal hemorrhage, vomiting

Genitourinary: Cystitis, pelvic pain

Hematologic: Agranulocytosis, granulocytopenia, leukopenia, pancytopenia, paraproteinemia, polycythemia

Hepatic: Cholecystitis, cholelithiasis, hepatic necrosis

Neuromuscular & skeletal: Arthralgia, arthritis, bone fracture, bone necrosis, joint disorder, muscle cramps, myasthenia, pain in extremity, paresthesia, pyogenic arthritis, synovitis, tendon disorder, tremor

Ocular: Cataract

Renal: Kidney calculus, pyelonephritis

Respiratory: Asthma, bronchospasm, dyspnea, lung function decreased, pleural effusion, pneumonia

Miscellaneous: Adenoma, allergic reactions (1%), carcinoma (including breast, gastrointestinal, skin, urogenital), healing abnormality, herpes zoster, ketosis, lupus erythematosus syndrome, lymphoma, melanoma, postsurgical infection, sepsis, tuberculosis (reactivation of latent infection; miliary, lymphatic, peritoneal and pulmonary)

Postmarketing and/or case reports: Anaphylactoid reaction, anaphylaxis, angioneurotic edema, aplastic anemia, cutaneous vasculitis, cytopenia, erythema multiforme, fixed drug eruption, Guillain-Barré syndrome, infections (bacterial, viral, fungal and protozoal), interstitial lung disease (eg, pulmonary fibrosis), intestinal perforation, septic arthritis, thrombocytopenia, transaminases increased, urticaria

Drug Interactions

Abatacept: Anti-TNF Agents may enhance the adverse/toxic effect of Abatacept. An increased risk of serious infection during concomitant use has been reported. *Risk D: Consider therapy modification*

Abciximab: May enhance the potential for allergic or hypersensitivity reactions to Monoclonal Antibodies. Also may cause thrombocytopenia or diminished therapeutic effects. *Risk C: Monitor therapy*

Anakinra: Anti-TNF Agents may enhance the adverse/toxic effect of Anakinra. An increased risk of serious infection during concomitant use has been reported. *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Rilonacept: Anti-TNF Agents may enhance the adverse/toxic effect of Rilonacept. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/nutraceutical: Echinacea may decrease the therapeutic effects of adalimumab; avoid concurrent use.

Monitoring ParametersPlace and read PPD before initiation. Monitor improvement of symptoms and physical function assessments; CBC; signs of infection, bleeding or bruising.

Nursing: Physical Assessment/MonitoringPerform tuberculin skin test prior to initiating therapy. Monitor for signs of tuberculosis throughout therapy. Do not initiate therapy if active infection (underlying chronic or localized infection) is occurring. Monitor for signs and symptoms of infection. Assess for liver dysfunction. Assess potential for interactions with other prescriptions, OTC medications, and herbal products patient may be taking. Assess results of laboratory tests (PDD), therapeutic effectiveness, and adverse response at regular intervals during treatment. Teach patient proper use if self-injected (appropriate injection technique and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report. Latex-sensitive patients: Needle cap of prefilled syringe contains latex.

Monitoring: Lab TestsCBC may be monitored during therapy for hematologic effects.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, allergies, history of tuberculosis, or any kind of infection you have. Do not take any new medication during therapy without consulting prescriber. If self-administered, follow directions for injection and needle/syringe disposal exactly. You may be more susceptible to infection. Do not have any vaccinations while using this medication without consulting prescriber first. May cause headache or dizziness (use caution when driving or engaged in potentially hazardous tasks); if persistent, consult prescriber for approved analgesic. Report persistent fever, increased bruising or bleeding, respiratory tract infection, unhealed or infected wounds, urinary tract infection, flu-like symptoms, unexplained weight loss, persistent cough, or unusual bump or sore that does not heal. Stop drug and report immediately persistent nausea, abdominal pain; numbness or tingling; problems with vision; weakness in legs; chest pains, respiratory difficulty; sudden weight gain of >3-5 pounds/week; swelling of extremeties; joint pain; skin rash; redness, swelling, or pain at injection site. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [pediatric; preservative free]:

Humira®: 20 mg/0.4 mL (0.4 mL) [contains polysorbate 80]

Injection, solution [preservative free]:

Humira®: 40 mg/0.8 mL (0.8 mL) [contains polysorbate 80]

Generic AvailableNo

ManufacturerAbbott Laboratories

Pricing: U.S. (www.drugstore.com)

Kit (Humira)

40 mg/0.8 mL (2): $1559.26

Kit (Humira Pen)

40 mg/0.8 mL (2): $1585.92

Mechanism of ActionAdalimumab is a recombinant monoclonal antibody that binds to human tumor necrosis factor alpha (TNF-alpha), thereby interfering with binding to TNFα receptor sites and subsequent cytokine-driven inflammatory processes. Elevated TNF levels in the synovial fluid are involved in the pathologic pain and joint destruction in immune-mediated arthritis. Adalimumab decreases signs and symptoms of psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis. It inhibits progression of structural damage of rheumatoid and psoriatic arthritis. Reduces signs and symptoms and maintains clinical remission in Crohn's disease; reduces epidermal thickness and inflammatory cell infiltration in plaque psoriasis.

Pharmacodynamics/Kinetics

Distribution: V_d: 4.7-6 L; Synovial fluid concentrations: 31% to 96% of serum

Bioavailability: Absolute: 64%

Half-life elimination: Terminal: ~2 weeks (range 10-20 days)

Time to peak, serum: SubQ: 131 ± 56 hours

Excretion: Clearance increased in the presence of antiadalimumab antibodies; decreased in patients 40 years and older

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause confusion; may exacerbate pre-existing or recent-onset demyelinating CNS disorder

Mental Health: Effects on Psychiatric TreatmentRare reports of pancytopenia, including aplastic anemia, have been reported with TNF-α-blocking agents. Medically-significant thrombocytopenia and leukopenia have been infrequently reported; use with caution in patients receiving clozapine, carbamazepine, valproic acid, and mirtazapine.

Index TermsAntitumor Necrosis Factor Apha (Human); D2E7; Human Antitumor Necrosis Factor Alpha

References

Gordon KB, Langley RG, Leonardi C, et al, "Clinical Response to Adalimumab Treatment in Patients With Moderate to Severe Psoriasis: Double-Blind, Randomized Controlled Trial and Open-Label Extension Study," *J Am Acad Dermatol*, 2006, 55(4):598-606.[PubMed 17010738]

Keystone EC, Kavanaugh AF, Sharp JYT, et al, "Radiographic, Clinical, and Functional Outcomes of Treatment With Adalimumab (A Human Anti-Tumor Necrosis Factor Monoclonal Antibody) in Patients With Active Rheumatoid Arthritis Receiving Concomitant Methotrexate Therapy: A Randomized, Placebo-Controlled, 52-Week Trial," *Arthritis Rheum*, 2004, 50(5):1400-11.[PubMed 15146409]

Sandborn WJ, Rutgeerts P, Enns R, et al, "Adalimumab Induction Therapy for Crohn Disease Previously Treated With Infliximab: A Randomized Trial.," *Ann Intern Med*, 2007, 146(12):829-38. [PubMed 17470824]

van der Heijde D, Kivitz A, Schiff MH, et al, "Efficacy and Safety of Adalimumab in Patients With Ankylosing Spondylitis: Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial," *Arthritis Rheum*, 2006, 54(7):2136-46. [PubMed 16802350]

International Brand NamesHumira (AE, AR, AT, AU, BE, BG, BH, CH, CN, CO, CY, CZ, DE, DK, EC, EG, FI, FR, GB, GR, HK, HN, IE, IL, IQ, IR, IT, JO, KW, LB, LY, MX, MY, NL, NO, OM, PT, PY, QA, RU, SA, SE, SG, SY, TR, TW, UY, VE, YE); Trudexa (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Adapalene and Benzoyl Peroxide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

U.S. Brand NamesEpiduoâ˘

Pharmacologic CategoryAcne Products; Topical Skin Product; Topical Skin Product, Acne

Use: Labeled IndicationsTopical treatment of acne vulgaris

Product AvailabilityEpiduoâ˘: FDA approved December 2008; availability anticipated in March 2009

Generic AvailableNo

ManufacturerGalderma Laboratories, L.P.

Index TermsBenzoyl Peroxide and Adapalene

Adapalene

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(a DAP a leen)
U.S. Brand NamesDifferin®
Canadian Brand NamesDifferin®; Differin® XP
Pharmacologic CategoryAcne Products; Topical Skin Product, Acne
Use: Labeled IndicationsTreatment of acne vulgaris
Dosing: AdultsAcne: Topical: Apply once daily before bedtime; results appear after 8-12 weeks of therapy.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren >12 years: Refer to adult dosing.
ContraindicationsHypersensitivity to adapalene or any component in the vehicle gel
Warnings/Precautions

Concerns related to adverse effects:

- Photosensitivity: Use is associated with increased susceptibility/sensitivity to UV light; avoid sunlamps or excessive sunlight exposure. Daily sunscreen use and other protective measures recommended.

- Skin irritation: Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning, or pruritus may occur during treatment; these are most likely to occur during the first 2-4 weeks and will usually lessen with continued use.

Disease-related concerns:

- Eczema: Use with caution in patients with eczema.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Appropriate use: For external use only; avoid contact with abraded skin, mucous membranes, eyes, mouth, angles of the nose.

Pregnancy Risk FactorC
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use only if benefit outweighs the potential risk to fetus.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%: Dermatologic: Erythema, scaling, dryness, pruritus, burning, pruritus or burning immediately after application

≤1%: Skin irritation, stinging, sunburn, acne flares, dermatitis, contact dermatitis, eyelid edema, conjunctivitis, skin discoloration, eczema, rash (topical cream)

Drug Interactions

Vitamin A: May enhance the adverse/toxic effect of Retinoid-like Compounds. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringAssess knowledge/teach patient appropriate use and adverse symptoms to report.
Patient EducationApply with gloves in thin film at night to thoroughly clean/dry skin; avoid area around eyes or mouth. Do not apply occlusive dressing. Results may take 8-12 weeks to appear. You may experience transient burning or stinging immediately after applying. Report worsening of condition or skin redness, dryness, peeling, or burning that persists between applications. Avoid excessive exposure to sunlight or sunlamps.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical:

Differin®: 0.1% (15 g, 45 g)

Gel, topical:

Differin®: 0.1% (15 g, 45 g) [alcohol free]; 0.3% (45 g) [alcohol free]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Cream (Differin)

0.1% (45): $159.47

Gel (Differin)

0.1% (45): $156.18

0.3% (45): $149.00

Mechanism of ActionRetinoid-like compound which is a modulator of cellular differentiation, keratinization, and inflammatory processes, all of which represent important features in the pathology of acne vulgaris

Pharmacodynamics/Kinetics

Absorption: Topical: Minimal

Excretion: Bile

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesAcure (TW); Adaferin (CR, DO, GT, HN, IN, MX, NI, PA, SV); Adaferin Gel (IL); Differin (AR, AU, BR, CL, CN, EE, FI, HK, HN, KP, MY, NO, PE, PH, PL, PY, SG, TH, TW, UY, VE, ZA); Differin Gel (AT, BE, CH, DE, GB, IE, IL, IT, SE); Differine (CZ, ES, FR); Evalen (ID); Klenzit (PH); Panalene (AR); Pindome (TW); Redap (DK)

Adefovir

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(a DEF o veer)

U.S. Brand NamesHepsera™

Canadian Brand NamesHepsera™

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)

Use: Labeled IndicationsTreatment of chronic hepatitis B with evidence of active viral replication (based on persistent elevation of ALT/AST or histologic evidence), including patients with lamivudine-resistant hepatitis B

Dosing: AdultsHepatitis B (chronic): Oral: 10 mg once daily. **Note:** Usual treatment duration is at least 1 year and varies with HBeAg status, consult current guidelines and literature.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricHepatitis B (chronic): Oral: Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentAdult recommendations only (no dosage adjustment recommendations available for patients <18 years with renal impairment):

Cl_{cr} ≥50 mL/minute: No dosage adjustment necessary

Cl_{cr} 30-49 mL/minute: 10 mg every 48 hours

Cl_{cr} 10-29 mL/minute: 10 mg every 72 hours

Hemodialysis: 10 mg every 7 days (following dialysis)

Dosing: Hepatic ImpairmentNo adjustment required.

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered without regard to food.

Dietary ConsiderationsMay be taken without regard to food.

StorageStore controlled room temperature of 25°C (77 °F).

ContraindicationsHypersensitivity to adefovir or any component of the formulation

Allergy Considerations

- Adefovir Allergy

Warnings/Precautions

Boxed warnings:

- Chronic hepatitis B: See “Disease-related concerns” below.
- Human immunodeficiency virus (HIV): See “Disease-related concerns” below.
- Lactic acidosis/hepatomegaly: See “Concerns related to adverse effects” below.
- Renal impairment: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).

Disease-related concerns:

- Chronic hepatitis B: **[U.S. Boxed Warning]: Severe, acute exacerbation of hepatitis B may occur upon discontinuation.** Exacerbations may occur in up to 25% of patients and usually within 12 weeks and may be self-limited or resolve upon resuming treatment; risk may be increased with advanced liver disease or cirrhosis. Monitor liver function several months after stopping treatment; reinitiation of antihepatitis B therapy may be required.

    Resistant hepatitis B virus (HBV): In patients with lamivudine-resistant HBV, switching to adefovir was associated with a higher risk of adefovir-resistance compared to adding adefovir to lamivudine therapy (Lok, 2007).

    Nonresponse to adefovir monotherapy (<2 log drop in HBV DNA after 6 months of treatment): Consider alternative treatment (Lok, 2007).

- HIV: **[U.S. Boxed Warning]:May cause the development of HIV resistance in chronic hepatitis B patients with unrecognized or untreated HIV infection.** Determine HIV status prior to initiating treatment with adefovir.

- Renal impairment: **[U.S. Boxed Warning]: Use with caution in patients with renal dysfunction or in patients at risk of renal toxicity (including concurrent nephrotoxic agents or NSAIDs).** Chronic administration may result in nephrotoxicity. Dosage adjustment is required in adult patients with renal dysfunction or in patients who develop renal dysfunction during therapy; no data available for use in children ≥12 years or adolescents with renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use in pregnancy only when clearly needed. Pregnant women exposed to adefovir should be registered with the pregnancy registry (800-258-4263).
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions
>10%:

Central nervous system: Headache (24% to 25%)

Gastrointestinal: Abdominal pain (15% to 18%), diarrhea (up to 13%)

Hepatic: Hepatitis exacerbation (up to 25% within 12 weeks of adefovir discontinuation)

Neuromuscular & skeletal: Weakness (13% to 25%)

Renal: Hematuria (grade ≥3: 11%)

1% to 10%:

Dermatologic: Rash, pruritus

Endocrine & metabolic: Hypophosphatemia (<2 mg/dL: 1% and 3% in pre-/post-liver transplant patients, respectively)

Gastrointestinal: Flatulence (up to 8%), dyspepsia (5% to 9%), nausea, vomiting

Renal: Serum creatinine increased (≥0.5 mg/dL: 2% to 3% in compensated liver disease; incidence may be higher in patients with decompensated cirrhosis or in liver transplant recipients), renal failure

Note: In liver transplant patients with baseline renal dysfunction, frequency of increased serum creatinine has been observed to be as high as 32% to 51% at 48 and 96 weeks post-transplantation, respectively; considering the concomitant use of other potentially nephrotoxic medications, baseline renal insufficiency, and predisposing comorbidities, the role of adefovir in these changes could not be established.

Respiratory: Cough (6% to 8%), rhinitis (up to 5%)

Postmarketing and/or case reports: Fanconi syndrome, hepatitis, myopathy, nephrotoxicity, osteomalacia

Drug Interactions

Ganciclovir-Valganciclovir: May enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. *Risk D: Consider therapy modification*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Tenofovir: Adefovir may diminish the therapeutic effect of Tenofovir. Specifically, adefovir-associated mutations in Hepatitis B viral reverse transcriptase may decrease viral susceptibility to tenofovir. Tenofovir may increase the serum concentration of Adefovir. Similarly, Adefovir may increase the concentration of Tenofovir. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Should be avoided in hepatitis B infection due to potential hepatic toxicity.

Food: Does not have a significant effect on adefovir absorption.

Monitoring ParametersHIV status (prior to initiation of therapy); serum creatinine (prior to initiation and during therapy; every 3 months in patients with medical conditions which predispose to renal insufficiency and in all patients treated for >1 year; more frequent monitoring required if preexisting real insufficiency detected [Lok, 2007]); viral load; LFTs for several months following discontinuation of adefovir
Nursing: Physical Assessment/MonitoringUse with caution in presence of renal dysfunction or risk of renal toxicity. Assess other pharmacological or herbal products patient may be taking for potential interactions or toxicity (especially any nephrotoxic agents). Assess results of laboratory tests, patient response (viral load), and adverse reactions (eg, lactic acidosis, altered hepatic status) on a regular basis throughout therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsHIV status (prior to initiation of therapy); serum creatinine (prior to initiation and during therapy; every 3 months in patients with medical conditions which predispose to renal insufficiency and in all patients treated for >1 year; more frequent monitoring required if preexisting real insufficiency detected [Lok, 2007]); viral load; LFTs for several months following discontinuation of adefovir
Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Use

appropriate precautions to prevent spread to other persons. Take as directed. Do not discontinue medication without consulting prescriber. You will require frequent blood tests; follow recommended schedule. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause headache or abdominal pain (consult prescriber for approved analgesia); or nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report unusual bleeding (blood in urine, tarry stools, or easy bruising); unresolved nausea or vomiting; signs of infection (eg, fever, chills, sore throat, burning urination, flu-like symptoms); persistent fatigue; muscle weakness; changes in urinary pattern; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as dipivoxil:

Hepsera®: 10 mg

Generic AvailableNo

ManufacturerGilead Sciences Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Hepsera)

10 mg (30): $753.68

Mechanism of ActionAcyclic nucleotide reverse transcriptase inhibitor (adenosine analog) which interferes with HBV viral RNA-dependent DNA polymerase resulting in inhibition of viral replication.

Pharmacodynamics/Kinetics

Distribution: 0.35-0.39 L/kg

Protein binding: ≤4%

Metabolism: Prodrug; rapidly converted to adefovir (active metabolite) in intestine

Bioavailability: 59%

Half-life elimination: 7.5 hours; prolonged in renal impairment

Time to peak: 1.75 hours

Excretion: Urine (45% as active metabolite within 24 hours)

Pharmacotherapy PearlsAdefovir dipivoxil is a prodrug, rapidly converted to the active component (adefovir). It was previously investigated as a treatment for HIV infections (at dosages substantially higher than the approved dose for hepatitis B). The NDA was withdrawn, and no further studies in the treatment of HIV are anticipated (per manufacturer).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentChronic administration may cause nephrotoxicity. In patients receiving lithium, gabapentin, or levetiracetam, a dosage adjustment may be needed; monitor.

Index TermsAdefovir Dipivoxil; Bis-POM PMEA

References

Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al, “Adefovir Dipivoxil for the Treatment of Hepatitis B e Antigen-Negative Chronic Hepatitis B,” *N Engl J Med*, 2003, 348(9):800-7.[PubMed 12606734]

Lok AS and McMahon BJ, “Chronic Hepatitis B,” *Hepatology*, 2007, 45(2):507-39.[PubMed 17256718]

Lok AS and McMahon BJ, “Corrections to AASLD Guidelines on Chronic Hepatitis B,” *Hepatology*, 2007, 45(6):1347.

Marcellin P, Chang T-T, Lim SG, et al, “Adefovir Dipivoxil for the Treatment of Hepatitis B e Antigen-Positive Chronic Hepatitis B,” *N Engl J Med*, 2003, 348(9):808-16.[PubMed 12606735]

International Brand NamesAdesera (IN); Hepsera (AR, AT, AU, BE, BG, CH, CL, CN, CR, CZ, DE, DK, DO, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IL, IT, KP, NI, NL, NO, PA, PE, PH, PK, PL, PT, RU, SE, SG, SV, TH, TR, TW, VE)

Adenosine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(a DEN oh seen)

U.S. Brand NamesAdenocard®; Adenoscan®

Canadian Brand NamesAdenocard®; Adenoscan®; Adenosine Injection, USP

Pharmacologic CategoryAntiarrhythmic Agent, Class IV; Diagnostic Agent

Use: Labeled Indications

Adenocard®: Treatment of paroxysmal supraventricular tachycardia (PSVT) including that associated with accessory bypass tracts (Wolff-Parkinson-White syndrome); when clinically advisable, appropriate vagal maneuvers should be attempted prior to adenosine administration; **not effective in atrial flutter, atrial fibrillation, or ventricular tachycardia**

Adenoscan®: Pharmacologic stress agent used in myocardial perfusion thallium-201 scintigraphy

Use: Unlabeled/InvestigationalAdenoscan®: Acute vasodilator testing in pulmonary artery hypertension

Dosing: Adults

Paroxysmal supraventricular tachycardia (Adenocard®): I.V. (rapid - over 1-2 seconds, via peripheral line): 6 mg; if not effective within 1-2 minutes, 12 mg may be given; may repeat 12 mg bolus if needed; maximum single dose: 12 mg.

Follow each I.V. bolus of adenosine with normal saline flush.

Note: Preliminary results in adults suggest adenosine may be administered via a central line at lower doses (ie, initial adult dose: 3 mg).

Pharmacologic stress agent (Adenoscan®): I.V.: Continuous I.V. infusion via peripheral line: 140 mcg/kg/minute for 6 minutes using syringe or columetric infusion pump; total dose: 0.84 mg/kg. Thallium-201 is injected at midpoint (3 minutes) of infusion.

Acute vasodilator testing (unlabeled use) (Adenoscan®): I.V.: Initial: 50 mcg/kg/minute increased by 50 mcg/kg/minute every 2 minutes to a maximum dose of 500 mcg/kg/minute; acutely assess vasodilator response

Dosing: ElderlyRefer to adult dosing. Elderly may be more sensitive to effects of adenosine.

Dosing: Pediatric

Paroxysmal supraventricular tachycardia (Adenocard®): Rapid I.V. push (over 1-2 seconds) via peripheral line: Infants and Children (manufacturer's recommendation):

Children <50 kg: 0.05-0.1 mg/kg. If conversion of PSVT does not occur within 1-2 minutes, may increase dose by 0.05-0.1 mg/kg. May repeat until sinus rhythm is established or to a maximum single dose of 0.3 mg/kg or 12 mg. Follow each dose with normal saline flush.

Children ≥50 kg: Refer to adult dosing.

Pediatric advanced life support (PALS): Treatment of SVT: I.V., I.O.: 0.1 mg/kg; if not effective, administer 0.2 mg/kg; maximum single dose: 12 mg. Follow each dose with normal saline flush.

Dosing: Renal Impairment

Hemodialysis: Significant drug removal is unlikely based on physiochemical characteristics.

Peritoneal dialysis: Significant drug removal is unlikely based on physiochemical characteristics.

Note: Higher doses may be needed for administration via peripheral versus central vein.

Administration: I.V.For rapid bolus I.V. use only. Administer I.V. push over 1-2 seconds at a peripheral I.V. site as proximal as possible to trunk (ie, not in lower arm, hand, lower leg, or foot). If administered into an I.V. line, administer as close to the patient's heart as possible (followed by saline flush).

Administration: I.V. DetailDo not mix with any other drugs in syringe or solution.

Dietary ConsiderationsAvoid dietary caffeine for 12-24 hours prior to pharmacologic stress testing.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Do **not** refrigerate; precipitation may occur (may dissolve by warming to room temperature).

CompatibilityStable in D_5LR, D_5W, LR, NS.

ContraindicationsHypersensitivity to adenosine or any component of the formulation; second- or third-degree AV block or sick sinus syndrome (except in patients with a functioning artificial pacemaker), atrial flutter, atrial fibrillation, and ventricular tachycardia (this drug is not effective in converting these arrhythmias to sinus rhythm). The manufacturer states that Adenoscan® should be avoided in patients with known or suspected bronchoconstrictive or bronchospastic lung disease.

Warnings/Precautions

Concerns related to adverse effects:

- Atrial fibrillation/flutter: There have been reports of atrial fibrillation/flutter in patients with paroxysmal supraventricular tachycardia (PSVT) associated with accessory conduction pathways after adenosine. Does not convert afib/flutter to normal sinus rhythm; risk of serious arrhythmias/hypotension. Not for use in patients with afib/flutter associated with Wolff-Parkinson-White Syndrome.

- Conduction disturbances: Adenosine decreases conduction through the AV node and may produce first-, second-, or third-degree heart block. Patients with pre-existing S-A nodal dysfunction may experience prolonged sinus pauses after adenosine; use caution in patients with first-degree AV block or bundle branch block; avoid use of adenosine for pharmacologic stress testing in patients with high-grade AV block or sinus node dysfunction (unless a functional pacemaker is in place). Rare, prolonged episodes of asystole have been reported, with fatal outcomes in some cases.

- Hypotension: May produce profound vasodilation with subsequent hypotension. When used as a bolus dose (PSVT), effects are generally self-limiting (due to the short half-life of adenosine). However, when used as a continuous infusion (pharmacologic stress testing), effects may be more pronounced and persistent, corresponding to continued exposure. Use infusions with caution in patients with autonomic dysfunction, carotid stenosis (with cerebrovascular insufficiency), uncorrected hypovolemia, pericarditis, pleural effusion and/or stenotic valvular heart disease.

- Proarrhythmic effects: Watch for proarrhythmic effects; monitor and adjust dose to prevent QT_c prolongation.

Disease-related concerns:

- Asthma: A limited number of patients with asthma have received adenosine and have not experienced exacerbation of their asthma. Adenosine may cause bronchoconstriction in patients with asthma; should be used cautiously in patients with obstructive lung disease not associated with bronchoconstriction (eg, emphysema, bronchitis).

- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.

Concurrent drug therapy issues:

- Caffeine: Pharmacologic stress testing: Withhold for five half-lives prior to adenosine use; avoid dietary caffeine for 12-24 hours prior to pharmacologic stress testing.

- Drugs which slow AV conduction: Use with caution in patients receiving other drugs which slow AV conduction (eg, digoxin, verapamil).

- Theophylline: Withhold for five half-lives prior to adenosine use whenever possible (eg, pharmacological stress testing).

Special populations:

- Elderly: Use with caution in the elderly; may be at increased risk of hemodynamic effects, bradycardia, and/or AV block.

Dosage form specific issues:

- Adenocard®: Transient AV block is expected. When used in PSVT, at the time of conversion to normal sinus rhythm, a variety of new rhythms may appear on the ECG. Administer as a rapid bolus, either directly into a vein or (if administered into an I.V. line), as close to the patient as possible (followed by saline flush).

Other warnings/precautions:

- CAST trial: In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, non-life-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide. An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. Antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Geriatric ConsiderationsElderly patients may be more sensitive to the effects of this medication.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReports of administration during pregnancy have indicated no adverse effects on fetus or newborn attributable to adenosine.

LactationExcretion in breast milk unknown

Adverse Reactions**Note:** Frequency varies based on use; higher frequency of infusion-related effects, such as flushing and lightheadedness, were reported with continuous infusion (Adenoscan®).

>10%:

Cardiovascular: Facial flushing (18% to 44%)

Central nervous system: Headache (2% to 18%), lightheadedness (2% to 12%)

Neuromuscular & skeletal: Discomfort of neck, throat, jaw (<1% to 15%)

Respiratory: Dyspnea (12% to 28%), chest pressure/discomfort (7% to 40%)

1% to 10%:

Cardiovascular: Hypotension (<1% to 2%), AV block (infusion 6%; third degree <1%), ST segment depression (3%), palpitation, chest pain

Central nervous system: Dizziness, nervousness (2%), apprehension

Gastrointestinal: Nausea (3%)

Neuromuscular & skeletal: Upper extremity discomfort (up to 4%), numbness (up to 2%), paresthesia (up to 2%)

Respiratory: Hyperventilation

Miscellaneous: Diaphoresis

<1% (Limited to important or life-threatening): Back discomfort, burning sensation, blurred vision, intracranial pressure increased, metallic taste, pressure in groin

Postmarketing and/or case reports: Asystole (prolonged), atrial fibrillation, bradycardia, bronchospasm, hypertension (transient), injection site reaction, respiratory arrest, seizure, torsade de pointes, ventricular fibrillation, ventricular tachycardia

Drug Interactions

Dipyridamole: May enhance the therapeutic effect of Adenosine. Dose reduction of adenosine may be needed. *Risk D: Consider therapy modification*

Nicotine: May enhance the AV-blocking effect of Adenosine. Nicotine may enhance the tachycardic effect of Adenosine. *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Adenosine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Avoid food or drugs with caffeine. Adenosine's therapeutic effect may be decreased if used concurrently with caffeine. Avoid dietary caffeine for 12-24 hours prior to pharmacologic stress testing.

Monitoring ParametersECG monitoring, heart rate, blood pressure

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Requires use of infusion pump and continuous cardiac and hemodynamic monitoring during infusion. Monitor for adverse reactions. Note that adenosine could produce bronchoconstriction in patients with asthma.

Patient EducationAdenosine is administered in emergencies; patient education should be appropriate to the situation. May cause facial flushing. Report chest pain or pressure, difficulty breathing immediately. **Pregnancy precautions:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 3 mg/mL (2 mL, 4 mL)

Adenocard®: 3 mg/mL (2 mL, 4 mL)

Adenoscan®: 3 mg/mL (20 mL, 30 mL)

Generic AvailableYes

ManufacturerFujisawa Healthcare, Inc

Mechanism of ActionSlows conduction time through the AV node, interrupting the re-entry pathways through the AV node, restoring normal sinus rhythm

Pharmacodynamics/Kinetics

Onset of action: Rapid

Duration: Very brief

Metabolism: Blood and tissue to inosine then to adenosine monophosphate (AMP) and hypoxanthine

Half-life elimination: <10 seconds

Related Information

- Antiarrhythmic Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness, anxiety, drowsiness, or emotional instability

Mental Health: Effects on Psychiatric TreatmentUse caution with carbamazepine and tricyclic antidepressants, may increase heart block. Postmarking experience reports seizures as a potential adverse reaction. Psychotropics have the potential to lower seizure threshold. Monitor for seizure activity.

Cardiovascular ConsiderationsAdenosine may be effective in interrupting re-entrant tachycardias, both AV-nodal re-entrant tachycardias and supraventricular tachycardias secondary to accessory pathways. Adenosine acts via interruption of AV-nodal conduction and, when used for this purpose, requires administration as rapid intravenous push in increasing doses. Because of more direct access when administered through a central line, lower doses of adenosine may be tried in these situations. It is not uncommon to see heart block and sinus pause soon after adenosine administration. Cardiac denervation after cardiac transplantation may cause patients to be hypersensitive to the effects of adenosine. Patients will often experience shortness of breath and/or chest pain having unknown etiology. While adenosine will not convert atrial fibrillation or atrial flutter, the consequent AV-nodal conduction slowing (reduced ventricular rate), in this setting, may aid in the identification of the arrhythmia by making the atrial fibrillation or flutter electrocardiographic morphology more apparent.

Pulmonary Artery Hypertension: Patients with pulmonary artery hypertension who respond acutely to vasodilators have improved survival with the long-term use of a calcium channel blocker.

Anesthesia and Critical Care Concerns/Other ConsiderationsShort action is an advantage; has prolonged effects in patients taking dipyridamole or carbamazepine and in denervated transplanted hearts; adjust doses or choose alternative agent accordingly.

Adenosine acts via interruption of AV-nodal conduction and, when used for this purpose, requires administration as rapid intravenous push in increasing doses. Because of more direct access when administered through a central line, lower doses of adenosine may be tried in these situations. It is not uncommon to see heart block and sinus pause soon after adenosine administration. May aid in the identification of the arrhythmia by making the atrial fibrillation or flutter electrocardiographic morphology more apparent.

Index Terms9-Beta-D-Ribofuranosyladenine

References

Ellenbogen KA, Thames MD, DiMarco JP, et al, “Electrophysiological Effects of Adenosine in the Transplanted Human Heart. Evidence of Supersensitivity,” *Circulation*, 1990, 81(3):821-8.[PubMed 2306833]

“Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, Part 6: Advanced Cardiovascular Life Support, The American Heart Association in Collaboration With the International Liaison Committee on Resuscitation,” *Circulation*, 2000, 102(8 Suppl):I86-171.

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Harrison JK, Greenfield RA, and Wharton JM, “Acute Termination of Supraventricular Tachycardia by Adenosine During Pregnancy,” *Am Heart J*, 1992, 123(5):1386-8. [PubMed 1575160]

McIntosh-Yellin NL, Drew BJ, and Scheinman MM, “Safety and Efficacy of Central Intravenous Bolus Administration of Adenosine for Termination of Supraventricular Tachycardia,” *J Am Coll Cardiol*, 1993, 22(3):741-5.[PubMed 8354807]

Schrader BJ, Inbar S, Kaufmann L, et al, “Comparison of the Effects of Adenosine and Nifedipine in Pulmonary Hypertension,” *J Am Coll Cardiol*, 1992, 19(5):1060-4.[PubMed 1552096]

International Brand NamesAdenocard (BR); Adenocor (AU, BE, BG, CZ, DK, EE, EG, ES, FI, GB, HN, HU, IE, IL, KP, LU, MY, NO, PE, PL, PT, SE, TH, TW, UY, VE, ZA); Adenocur (NL); Adenoject (IN); Adenoscan (ES, HK); Adenosin Ebewe (PL); Adenosina Biol (AR, PY); Adrekar (AT, DE); Cardiovert (PH); Fosfobion (PL); Krenosin (FR, IT, LU, MX); Krenosine (CH); Soladen (PL); Tricor (CN)

Agalsidase Alfa

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Agalsidase alfa may be confused with agalsidase beta, alglucerase, alglucosidase alfa

Pronunciation(aye GAL si days AL fa)

Canadian Brand NamesReplagal™

Pharmacologic CategoryEnzyme

Use: Labeled IndicationsReplacement therapy for Fabry disease

Dosing: Adults**Note:** Premedication with oral antihistamines and corticosteroids may alleviate infusion-related reactions associated with agalsidase alfa.

Fabry disease: I.V.: 0.2 mg/kg every 2 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Premedication with oral antihistamines and corticosteroids may alleviate infusion-related reactions associated with agalsidase alfa.

Fabry disease: Refer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment necessary.

Dosing: Hepatic ImpairmentNo data available.

Administration: I.V.Infuse over 40 minutes using a dedicated I.V. line with filter. Do not infuse other agents through same I.V. line. Interrupt infusion in the presence of infusion-related reactions (eg, chills, flushing, dyspnea, rigors, tachycardia, urticaria). Infusion may be restarted after 5-10 minutes if symptoms subside or after administration of analgesics, antipyretics, antihistamines, and/or corticosteroids.

StorageStore vials between 2°C to 8°C (36°F to 46°F). Product is preservative free. Administration within 3 hours after dilution is recommended, however, diluted solution is stable for 24 hours at 25°C (77°).

ReconstitutionTo make final infusion, add the desired amount of solution (based on patient weight) to 100 mL NS. Mix gently and avoid shaking. Discard unused product.

CompatibilityStable in NS. Do not mix or infuse with other products.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to agalsidase alfa or any component of the formulation; concomitant use with chloroquine, amiodarone, monobenzone, or gentamicin (these agents have the potential to inhibit intracellular agalsidase alfa activity)

Warnings/Precautions

Concerns related to adverse effects:

- Antibody formation: The presence IgG antibodies has been observed within 3 months from the onset of therapy in ~55% of treated patients. Approximately 60% of these patients are free of antibodies and >80% demonstrate immune tolerance, based on reduced titers of antibody within 12-18 months.

- Infusion reactions: Mild acute reactions (chills, facial flushing) are common and may occur during or within 1 hour after infusion. Severe reactions (nausea, pyrexia, rigors, tachycardia, urticaria, vomiting) are rare and usually occur within 2-4 months from the onset of therapy. Patients with a history of reactions may be premedicated with oral corticosteroids and antihistamines 1-3 hours prior to subsequent infusions.

Disease-related concerns:

- Fabry disease: Common symptoms observed in this patient population may be confused with adverse reactions related to treatment.

- Hepatic impairment: Safety and efficacy have not been established.

Pregnancy ConsiderationsAdverse events were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. The benefits versus risks should be considered carefully before initiating agalsidase alfa therapy in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**Note:** The most common and serious adverse reactions are infusion reactions (symptoms may include chills, dyspnea, facial flushing, fever, hypertension, nausea, rigors, tachycardia, urticaria, and vomiting).

>10%:

Cardiovascular: Flushing (24%)

Central nervous system: Fever (20%), headache (11%)

Neuromuscular & skeletal: Rigors (20%)

Miscellaneous: IgG antibody formation (55%), infusion-related reactions (13%)

1% to 10%:

Cardiovascular: Chest tightness (7%), hypertension (4%), tachycardia (4%), chest pain (2%), edema (2%), peripheral coldness (2%), peripheral edema (2%)

Central nervous system: Dizziness (9%), fatigue (9%), fatigue aggravated (7%), hypersomnia (2%), hypoesthesia (2%), panic attack (2%), pain/discomfort (7%), somnolence (2%), vertigo (2%)

Dermatologic: Acne (9%), erythema (7%), mottled skin(4%), pruritus (4%), dry skin (2%), eczema (2%), rash (2%)

Gastrointestinal: Nausea (9%), dysgeusia (6%), diarrhea (4%), vomiting (4%), abdominal pain (2%), dyspepsia (2%), gastrointestinal upset (2%), stomach cramps (2%), stomach discomfort (2%)

Neuromuscular & skeletal: Myalgia (6%), neuropathic pain (6%), tremor (4%), musculoskeletal discomfort (2%), back pain (2%), limb pain (2%), paraesthesia (2%), weakness (2%)

Ocular: Lacrimation increased (2%), periorbital edema (2%)

Respiratory: Hoarseness (6%), throat tightness (6%), cough (4%), dyspnea (4%), nasopharyngitis (4%), pharyngitis (4%), nasal congestion (2%), snoring (2%), throat irritation (2%)

Miscellaneous: Feeling hot (4%), influenza-like syndrome(2%), parosmia (2%)

<1%, postmarketing, and/or case reports: Chills, facial flushing, urticaria

Drug Interactions

Amiodarone: May inhibit the intracellular activity of agalsidase alfa; concomitant use is contraindicated.

Chloroquine: May inhibit the intracellular activity of agalsidase alfa; concomitant use is contraindicated.

Gentamicin: May inhibit the intracellular activity of agalsidase alfa; concomitant use is contraindicated.

Monobenzone: May inhibit the intracellular activity of agalsidase alfa; concomitant use is contraindicated.

Monitoring ParametersCreatinine clearance, ECG, echocardiography, Gb-3 levels (serum and urine)

Nursing: Physical Assessment/MonitoringAssess patient for previous experience with enzyme replacement therapy prior to beginning therapy. Assess risk potential for interactions with other prescriptions or herbal products patient may be taking. Note specific dosing information in product labeling. Premedication with antipyretics or corticosteroids for patients with previous infusion reactions is recommended. Patient should be monitored for infusion reactions during and following infusions. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Patient EducationThis medication can only be administered by infusion; you will be closely monitored during infusion. Report immediately unusual acute pain; difficulty breathing or chest tightness; vomiting; difficulty swallowing; itching or rash; or redness, swelling, or pain at infusion site. Between treatments, maintain adequate hydration (2-3 L/day of fluids, unless instructed to restrict fluid intake) and nutrition (small frequent meals). You may experience abdominal discomfort or vomiting (small, frequent meals and good mouth care may help); headache, fatigue, or dizziness (use caution when driving or engaging in tasks that require alertness until response to medication is known); limb, back, or muscle pain (consult prescriber for appropriate analgesia). Report chest discomfort, palpitations, rapid heart beat, or acute headache; signs of infection or rash; swelling of limbs or significant weight increase; difficulty breathing or chest tightness; persistent gastrointestinal discomfort or vomiting; tingling, pain, or numbness in extremities; or other unusual, persistent adverse reactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, solution [preservative free]:

Replagal™ [CAN]: 1 mg/1mL (3.5 mL) [not available in the U.S.]

Generic AvailableNo

ManufacturerShire Human Genetic Therapies Inc

Mechanism of ActionAgalsidase alfa is a recombinant form of the enzyme alpha-galactosidase-A, which catalyzes the hydrolysis of globotriaosylceramide (Gb-3) and other glycosphingolipids. These compounds may accumulate (over many years) within the tissues of patients with Fabry disease, leading to renal and cardiovascular complications. Agalsidase has been noted to reduce cellular levels of Gb-3 within the liver, heart, kidney, blood vessels, and in plasma.

Pharmacodynamics/Kinetics

Distribution: V_d: 17% of body weight

Metabolism: Plasma; via peptide hydrolysis

Half-life elimination: ~1.5-2 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, fatigue, hypersomnia, or panic attacks

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAgalsidase Alpha; Alpha-Galactosidase-A (Gene-Activated)

References

Lidove O, Joly D, Barbey F, et al, “Clinical Results of Enzyme Replacement Therapy in Fabry Disease: A Comprehensive Review of Literature”, *Int J*

Clin Pract, 2007, 61(2):293-302.[PubMed 17263716]

Ries M, Clarke JT, Whybra C, et al, “Enzyme-Replacement Therapy With Agalsidase Alfa in Children With Fabry Disease,” *Pediatrics*, 2006, 118(3):924-32.[PubMed 16950982]

International Brand Names Replagal (AU, BE, CH, CZ, DK, EE, ES, FI, IL, NO, NZ, SE, TW)

Agalsidase Beta

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Agalsidase beta may be confused with agalsidase alfa, alglucerase, alglucosidase alfa

International issues:

Agalsidase beta may be confused with agalsidase alfa, which is available in international markets

Pronunciation(aye GAL si days BAY ta)
U.S. Brand NamesFabrazyme®
Canadian Brand NamesFabrazyme®
Pharmacologic CategoryEnzyme
Use: Labeled IndicationsReplacement therapy for Fabry disease
Dosing: AdultsFabry disease: I.V.: 1 mg/kg every 2 weeks
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Fabry disease: Children ≥8 years: I.V.: 1 mg/kg every 2 weeks

Dosing: Renal ImpairmentNo dosage adjustment required.
Dosing: Adjustment for ToxicityPatient with IgE antibodies to agalsidase beta (rechallenge): 0.5 mg/kg every 2 weeks at an initial maximum infusion rate of 0.01 mg/minute; may gradually escalate dose (to maximum of 1 mg/kg every 2 weeks) and/or infusion rate (doubling the infusion rate every 30 minutes to a maximum rate of 0.25 mg/minute) as tolerated.
Administration: I.V.Antipyretics should be administered prior to infusion.
Administration: I.V. DetailInitial infusion rate should not exceed 0.25 mg/minute (15 mg/hour). Interrupt or decrease rate in the event of an infusion reaction; may be restarted after resolution of symptoms and/or after administration of antipyretics, antihistamines, and/or steroids. After patient tolerance to the infusion is established, rate may be increased in increments of 0.05-0.08 mg/minute (3-5 mg/hour) with each subsequent infusion. Maximum infusion rate: Patients <30 kg: 0.25 mg/minute; patients ≥30 kg: Infuse over at least 1.5 hours. An initial maximum infusion rate of 0.01 mg/minute should be used for rechallenge in patients with IgE antibodies; may increase infusion rate (doubling the infusion rate every 30 minutes) to a maximum rate of 0.25 mg/minute as tolerated. A 0.2 micron low protein-binding filter may be used during administration.
StorageStore intact vials between 2°C and 8°C (36°F and 46°F). Reconstituted vials and final infusion should be used immediately if possible, but may be stored for up to 24 hours between 2°C and 8°C (36°F and 46°F).
ReconstitutionEach 35 mg vial should be reconstituted with 7.2 mL SWFI; reconstitute 5 mg vials with 1.1 mL SWFI; inject down internal side wall of vial; roll and tilt gently. Resulting solution contains 5 mg/mL. Do not use filter needle to prepare. To make final infusion, add the desired amount of reconstituted solution to make a final volume based on patient weight. The minimum total volume will range from 50 mL in patients ≤35 kg to 500 mL in patients >100 kg. Avoid vigorous shaking or agitation.
CompatibilityStable in NS.

Compatibility when admixed: Do not mix with other products.

ContraindicationsHypersensitivity to agalsidase beta or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Antibody formation: Development of IgG antibodies is common, however some patients may also develop IgE antibodies; consider IgE testing in patients with allergic reaction. Rechallenge of patients with IgE-mediated reaction may be done with caution.

- Infusion reactions: Infusion-related reactions are common, and may be severe; pretreatment with antipyretics is advised. Medication for the treatment of reactions should be readily available.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; may have increased risk of complications from infusion reactions; monitor closely.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <8 years of age.

Other warnings/precautions:

- Registry: A registry has been created to monitor therapeutic responses and adverse effects during long-term treatment; patients should be encouraged to register (www.fabryregistry.com or 1-800-745-4447).

Pregnancy Risk FactorB

Pregnancy ConsiderationsAnimal reproduction studies have not demonstrated adverse effects. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential are encouraged to enroll in Fabry registry.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsNursing mothers are encouraged to enroll in Fabry registry.

Adverse Reactions**Note:** The most common and serious adverse reactions are infusion reactions (symptoms may include fever, tachycardia, hypertension, throat tightness, dyspnea, chills, abdominal pain, pruritus, urticaria, vomiting).

>10%:

Cardiovascular: Peripheral edema (21%)

Central nervous system: Chills (43%), headache (39%), fever (6% to 36%), fatigue (25%), dizziness (21%), pain (16%)

Gastrointestinal: Vomiting (24%)

Hematologic: Anemia (14%)

Neuromuscular & skeletal: Paresthesia (31%), limb pain (19%), back pain (16%)

Respiratory: Cough (33%), nasopharyngitis (28%), nasal congestion (19%), upper respiratory tract infection (19%), pharyngolaryngeal pain (16%), lower respiratory infection (11%)

Miscellaneous: IgG antibody formation (69% to 79%)

1% to 10%:

Cardiovascular: Hypertension (5% to 10%), chest discomfort (5%), tachycardia (5%), ventricular wall thickening (5%)

Central nervous system: Hypoesthesia (9%), insomnia (9%), anxiety (8%), depression (6%)

Dermatologic: Rash (10%), excoriation (9%), pruritus (8%), contact dermatitis (5%)

Endocrine & metabolic: Bicarbonate decreased (9%)

Gastrointestinal: Abdominal discomfort (6%), toothache (6%)

Neuromuscular & skeletal: Myalgia (8%), burning sensation (6%), muscle spasms (5%), neck pain (5%)

Otic: Tinnitus (8%), hearing impairment (5%)

Renal: Creatinine increased (9%), proteinuria (5%)

Respiratory: Sinusitis (9%), bronchitis (8%), congestion (8%), dyspnea (8%), pharyngitis (6%), wheezing (6%)

Miscellaneous: Feeling cold (10%), viral infection (5% to 6%), fungal infection (5%), infusion reactions (≥5%)

Other reported severe reactions (frequency not established): Abdominal pain, arrhythmia, ataxia, bradycardia, cardiac arrest, cardiac output decreased, chest pain, face edema, flushing, hypotension, nausea, nephrotic syndrome, pallor, stroke, throat tightness, urticaria, vertigo

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersDevelopment of IgG or IgE antibodies in patients with suspected allergic reactions (test available from manufacturer). Monitor for infusion-related reactions.

Nursing: Physical Assessment/MonitoringAssess patient for previous experience with enzyme replacement therapy prior to beginning therapy. Note specific administration details related to initial infusion rate and subsequent rates. Premedication with antipyretics is recommended. Patient must be monitored closely for infusion reactions (fever, chills, dyspnea, tachycardia, hypertension, pruritus, vomiting) during and following infusion; medication/equipment for treating reactions should be readily available. Encourage patients to enroll in Frabry registry (see product inset). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsDevelopment of IgG or IgE antibodies in patients with suspected allergic reactions (test available from manufacturer).

Patient EducationThis medication can only be administered by infusion; you will be closely monitored during infusion. Report immediately unusual acute pain; difficulty breathing or chest tightness; vomiting; difficulty swallowing; itching or rash; or redness, swelling, or pain at infusion site. Between treatments, maintain adequate hydration (2-3 L/day of fluids, unless instructed to restrict fluid intake) and nutrition (small frequent meals). You may experience abdominal discomfort or vomiting (small, frequent meals and good mouth care may help); headache, fatigue, or dizziness (use caution when driving or engaging in tasks that require alertness until response to medication is known); or limb, back, or muscle pain (consult prescriber for appropriate analgesia). Report chest discomfort, palpitations, rapid heart beat, or acute headache; signs of infection or rash; swelling of limbs or significant weight increase; difficulty breathing or chest tightness; persistent gastrointestinal discomfort or vomiting; tingling, pain, or numbness in extremities; or other unusual, persistent adverse reactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Fabrazyme®: 5 mg [contains mannitol 33 mg; derived from Chinese hamster cells]; 35 mg [contains mannitol 222 mg; derived from Chinese hamster cells]

Generic AvailableNo

ManufacturerGenzyme

Mechanism of ActionAgalsidase beta is a recombinant form of the enzyme alpha-galactosidase-A, which is required for the hydrolysis of GL-3 and other glycosphingolipids. The compounds may accumulate (over many years) within the tissues of patients with Fabry disease, leading to renal and cardiovascular complications. In clinical trials of limited duration, agalsidase been noted to reduce tissue inclusions of a key sphingolipid (GL-3). It is believed that long-term enzyme replacement may reduce clinical manifestations of renal failure, cardiomyopathy, and stroke. However, the relationship to a reduction in clinical manifestations has not been established.

Pharmacodynamics/Kinetics

Distribution: V_{dss}: Children: 247-1097 mL/kg; Adults: 112-570 mL/kg

Half-life elimination: Children: 86-151 minutes; Adults: 45-119 minutes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusAnxiety and dizziness are common; may cause depression
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsAlpha-Galactosidase-A (Recombinant); r-h α-GAL

References

Banikazemi M, Bultas J, Waldek S, et al, “Agalsidase-Beta Therapy for Advanced Fabry Disease: a Randomized Trial,” *Ann Intern Med*, 2007, 146(2):77-86.[PubMed 17179052]

Eng C, Guffton N, Wilcox WR, et al, “Safety and Efficacy of Recombinant Human Alpha-Galactosidase A Replacement Therapy in Fabry's Disease,” *N Engl J Med*, 2001, 345(1):9-16.[PubMed 11439963]

Lidove O, Joly D, Barbey, F, et al, “Clinical Results of Enzyme Replacement Therapy in Fabry Disease: A Comprehensive Review of Literature,” *Int J Clin Pract,* 2007, 61(2):293-302.[PubMed 17263716]

International Brand NamesFabrazyme (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, KP, NL, NO, NZ, PL, PT, RU, SE, TR)

Pharmacologic CategoryChemotherapy Regimen, Soft Tissue Sarcoma

Regimen UseSoft tissue sarcoma

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Doxorubicin: I.V.: 25 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Ifosfamide: I.V.: 2 g/m^2/day days 1 to 5

[total dose/cycle = 10 g/m^2]

Mesna: I.V.: 400 mg/m^2 day 1

followed by I.V.: 1200 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 6400 mg/m^2]

Repeat cycle every 3 weeks

Variation 2:

Doxorubicin: I.V.: 30 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 90 mg/m^2]

Ifosfamide: I.V.: 2.5 g/m^2 /day days 1 to 4

[total dose/cycle = 10 g/m^2]

Mesna: I.V.: 500 mg/m^2 day 1

followed by I.V.: 1500 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 6500 mg/m^2]

Filgrastim: SubQ: 5 mcg/kg/day days 5 through ANC recovery

Repeat cycle every 3 weeks

References

Patel SR, Vadhan-Raj S, Burgess MA, et al, âResults of Two Consecutive Trials of Dose-Intensive Chemotherapy With Doxorubicin and Ifosfamide in Patients With Sarcomas,â *Am J Clin Oncol*, 1998, 21(3):317-21. [PubMed 9626808]

Albendazole

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

International issues:

Albenza® may be confused with Avanza® which is a brand name for mirtazapine in Australia

Pronunciation(al BEN da zole)
U.S. Brand NamesAlbenza®
Pharmacologic CategoryAnthelmintic
Use: Labeled IndicationsTreatment of parenchymal neurocysticercosis caused by *Taenia solium* and cystic hydatid disease of the liver, lung, and peritoneum caused by *Echinococcus granulosus*
Use: Unlabeled/InvestigationalAlbendazole has activity against *Ascaris lumbricoides* (roundworm); *Ancylostoma caninum*; *Ancylostoma duodenale* and *Necator americanus* (hookworms); cutaneous larva migrans; *Enterobius vermicularis* (pinworm); *Gnathostoma spinigerum*; *Gongylonema* sp; *Mansonella perstans* (filariasis); *Opisthorchis sinensis* (liver fluke); visceral larva migrans (toxocariasis); activity has also been shown against the liver fluke *Clonorchis sinensis*, *Giardia lamblia*, *Cysticercus cellulosae*, and *Echinococcus multilocularis*. Albendazole has also been used for the treatment of intestinal microsporidiosis (*Encephalitozoon intestinalis*), disseminated microsporidiosis (*E. hellem*, *E. cuniculi*, *E. intestinalis*, *Pleistophora* sp, *Trachipleistophora* sp, *Brachiola vesicularum*), and ocular microsporidiosis (*E. hellem*, *E. cuniculi*, *Vittaforma corneae*).
Dosing: Adults
Neurocysticercosis: Oral:

<60 kg: 15 mg/kg/day in 2 divided doses (maximum: 800 mg/day) for 8-30 days

≥60 kg: 800 mg/day in 2 divided doses for 8-30 days

Note: Give concurrent anticonvulsant and steroid therapy during first week.

Hydatid: Oral:

<60 kg: 15 mg/kg/day in 2 divided doses (maximum: 800 mg/day)

≥60 kg: 800 mg/day in 2 divided doses

Note: Administer dose for three 28-day cycles with a 14-day drug-free interval in between. The manufacturer recommends a total of 3 cycles.

***Ancylostoma caninum*, *Ascaris lumbricoides*(roundworm), *Ancylostoma duodenale (hookworm)*, and *Necator americanus*(hookworm) (unlabeled use):** Oral: 400 mg as a single dose

***Clonorchis sinensis*(Chinese liver fluke) (unlabeled use):** Oral: 10 mg/kg for 7 days

Cutaneous larva migrans (unlabeled use): Oral: 400 mg once daily for 3 days

***Enterobius vermicularis*(pinworm) (unlabeled use):** Oral: 400 mg as a single dose; may repeat in 2 weeks

***Gnathostoma spinigerum* (unlabeled use):** Oral: 800 mg/day in 2 divided doses for 21 days

Gongylonemiasis (unlabeled use): Oral: 10 mg/kg/day for 3 days

***Mansonella perstans*(unlabeled use):** Oral: 800 mg/day in 2 divided doses for 10 days

Visceral larva migrans (toxocariasis) (unlabeled use): Oral: 800 mg/day in 2 divided doses for 5 days

***Cysticercus cellulosae*(unlabeled use):** Oral: 800 mg/day in 2 divided doses for 8-30 days; may be repeated as necessary

Disseminated microsporidiosis (unlabeled use): Oral: 800 mg/day in 2 divided doses

***Echinococcus granulosus*(tapeworm) (unlabeled use):** Oral: 800 mg/day in 2 divided doses for 1-6 months

Intestinal microsporidiosis (unlabeled use): Oral: 800 mg/day in 2 divided doses for 21 days

Ocular microsporidiosis (unlabeled use): Oral: 800 mg/day in 2 divided doses, in combination with fumagillin

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Neurocysticercosis: Oral: Refer to adult dosing.

Hydatid: Oral: Refer to adult dosing.

***Cysticercus cellulosae*(unlabeled use):** Oral: 15 mg/kg/day (maximum: 800 mg/day) in 2 divided doses for 8-30 days; may be repeated as necessary

***Echinococcus granulosus*(tapeworm) (unlabeled use):** Oral: 15 mg/kg/day (maximum: 800 mg) divided twice daily for 1-6 months

For the following unlabeled uses, refer to adult dosing:

Ancylostoma caninum, *Ascaris lumbricoides* (roundworm), *Ancylostoma duodenale* (hookworm), *Clonorchis sinensis*, (Chinese liver fluke), cutaneous larva migrans, *Enterobius vermicularis* (pinworm), *Gnathostoma spinigerum*, gongylonemiasis, *Mansonella perstans*, *Necator americanus* (hookworm), visceral larva migrans (toxocariasis)

Administration: OralShould be administered with a high-fat meal. Administer anticonvulsant and steroid therapy during first week of neurocysticercosis therapy. If patients have difficulty swallowing, tablets may be crushed or chewed, then swallowed with a drink of water.

Dietary ConsiderationsShould be taken with a high-fat meal.

StorageStore between 20°C and 25°C (68°F to 77°F)

ContraindicationsHypersensitivity to albendazole, benzimidazoles, or any component of the formulation

Allergy Considerations

- Benzimidazole Anthelmintics Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bone marrow suppression: Agranulocytosis, aplastic anemia, granulocytopenia, leukopenia, and pancytopenia have occurred leading to fatalities (rare); use with caution in patients with hepatic impairment (more susceptible to hematologic toxicity). Discontinue therapy in all patients who develop clinically significant decreases in blood cell counts.

- Transaminase elevations: Reversible elevations in hepatic enzymes have been reported. Patients with abnormal LFTs and hepatic echinococcosis are at an increased risk of hepatotoxicity. Discontinue therapy if LFT elevations are >2 times the upper limit of normal; may consider restarting treatment (with frequent monitoring of LFTs) when hepatic enzymes return to pretreatment values.

Disease-related concerns:

- Neurocysticercosis: Appropriate use: Corticosteroids should be administered before or upon initiation of albendazole therapy to minimize inflammatory reactions and prevent cerebral hypertension. Anticonvulsant therapy should be used concurrently during the first week of therapy to prevent seizures. If retinal lesions exist, weigh risk of further retinal damage due to albendazole-induced changes to the retinal lesion vs benefit of disease treatment.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAlbendazole has been shown to be teratogenic in laboratory animals and should not be used during pregnancy, if at all possible. Women should be advised to avoid pregnancy for at least 1 month following therapy. Discontinue if pregnancy occurs during treatment.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Central nervous system: Headache (11% neurocysticercosis; 1% hydatid)

Hepatic: LFTs increased (16% hydatid; <1% neurocysticercosis)

1% to 10%:

Central nervous system: Intracranial pressure increased (up to 2%), dizziness (≤1%), fever (≤1%), vertigo (≤1%), meningeal signs (1%)

Dermatologic: Alopecia (<1% to 2%)

Gastrointestinal: Abdominal pain (up to 6%), nausea/vomiting (4% to 6%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening symptoms): Acute liver failure, acute renal failure, aplastic anemia, agranulocytosis, erythema multiforme, granulocytopenia, hepatitis, hypersensitivity reaction, leukopenia, neutropenia, pancytopenia, rash, Stevens-Johnson syndrome, thrombocytopenia, urticaria

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 3A4; **Inhibits** CYP1A2 (weak)

Drug Interactions

Aminoquinolines (Antimalarial): May decrease the serum concentration of Anthelmintics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Albendazole serum levels may be increased if taken with a fatty meal (increases the oral bioavailability by up to 5 times).

Monitoring ParametersMonitor fecal specimens for ova and parasites for 3 weeks after treatment; if positive, retreat; LFTs and CBC with differential at start of each 28-day cycle and every 2 weeks during therapy (more frequent monitoring for patients with liver disease); pregnancy test

Nursing: Physical Assessment/MonitoringDosing based on identification of parasite. Note pretreatment suggestions. Assess laboratory results for therapeutic effectiveness (reduction or elimination of ova and parasites) and adverse reactions (eg, elevated LFTs, leukopenia). Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsMonitor fecal specimens for ova and parasites for 3 weeks after treatment; if positive, retreat; LFTs and CBC with differential at start of each 28-day cycle and every 2 weeks during therapy (more frequent monitoring for patients with liver disease); pregnancy test

Patient EducationYou may be prescribed other medications to take during first week of therapy. Do not take any other new medication during therapy unless approved by prescriber. Laboratory tests may be required; maintain recommended schedule. Take as directed, with a high-fat meal. Follow prescriber's suggestions to prevent reinfection. May cause loss of hair (reversible); nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or dizziness or headaches (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report unusual fever, persistent or unresolved abdominal pain, vomiting, yellowing of skin or eyes, darkening of urine, or light colored stools. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended. Becoming pregnant within 1 month following therapy is not advised.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Albenza®: 200 mg

Generic AvailableNo

ManufacturerSmithKline Beecham Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Albenza)

200 mg (12): $26.99

Mechanism of ActionActive metabolite, albendazole sulfoxide, causes selective degeneration of cytoplasmic microtubules in intestinal and tegmental cells of intestinal helminths and larvae; glycogen is depleted, glucose uptake and cholinesterase secretion are impaired, and desecratory substances accumulate intracellulary. ATP production decreases causing energy depletion, immobilization, and worm death.

Pharmacodynamics/Kinetics

Absorption: Poor; may increase up to 5 times when administered with a fatty meal

Distribution: Well inside hydatid cysts and CSF

Protein binding: 70%

Metabolism: Hepatic; extensive first-pass effect; pathways include rapid sulfoxidation to active metabolite (albendazole sulfoxide [major]), hydrolysis, and oxidation

Half-life elimination: 8-12 hours

Time to peak, serum: 2-5 hours

Excretion: Urine (<1% as active metabolite); feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay rarely cause bone marrow suppression; use caution with clozapine and carbamazepine. Carbamazepine may increase the metabolism of albendazole.

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Smego, RA, Bhatti S, Khaliq AA, et al, “Percutaneous Aspiration-Injection-Reaspiration Drainage Plus Albendazole or Mebendazole for Hepatic Cystic Echinococcosis: A Meta-Analysis,” *Clin Infect Dis*, 2003, 37(8):1073-83.[PubMed 14523772]

Wilson ME, Lorente CA, Allen JE, et al, “Gongylonema Infection of the Mouth in a Resident of Cambridge, Massachusetts,” *Clin Infect Dis*, 2001, 32(9):1378-80.[PubMed 11303277]

International Brand NamesABZ (IN); Acure (PK); Adazol (PH); Albatel (TH); Alben (BR); Albenzol (EC); Albex (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Albezole (IN); Alfuca (TH); Alminth (IN); Alzental (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SG, SY, YE); Alzol (TH); Bendex-400 (ZA); Benzol (PH); Bruzol (MX); Ceprazol (CN); Champs D-Worm 6 (MY); Ciclopar (CO); Dalben (HR); Digezanol (MX); Emanthal (IN); Eskasole (MX); Eskazole (AT, AU, DE, ES, GB, IL, JP, NL); Fintel (PE); Gascop (MX); Getzol (CO); Helmiben (UY); Helmidazole (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Labenda (TH); Lomsin (MX); Lurdex (MX); Mebenix (BR); Monodox (CO); Mycotel (TH); Nemozole (IN); Pantex (PY); Paranthil (ZA); Parhel (CR, DO, GT, HN, NI, PA, SV); Rotopar (EC); Sioban (IN); Valbazen Vet (NO); Vastus (AR); Vemizol (MY); Vermin Plus (MX); Xadem (CO); Zeben (TH); Zela (TH); Zentab (TH); Zentel (AE, AU, BB, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CY, CZ, DO, EG, ET, FR, GH, GM, GN, GR, GT, GY, HN, IL, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, OM, PA, PE, PH, PL, PR, PT, QA, SA, SC, SD, SL, SN, SR, SV, SY, TH, TN, TT, TZ, UG, VE, YE, ZA, ZM, ZW)

Albumin

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Medication Safety Issues

Sound-alike/look-alike issues:

Albutein® may be confused with albuterol

Buminate® may be confused with bumetanide

Pronunciation(al BYOO min)
U.S. Brand NamesAlbumarc®; Albuminar®; AlbuRx™; Albutein®; Buminate®; Flexbumin; Plasbumin®
Canadian Brand NamesPlasbumin®-25; Plasbumin®-5
Pharmacologic CategoryBlood Product Derivative; Plasma Volume Expander, Colloid
Use: Labeled IndicationsPlasma volume expansion and maintenance of cardiac output in the treatment of certain types of shock or impending shock; may be useful for burn patients, ARDS, and cardiopulmonary bypass; other uses considered by some investigators (but not proven) are retroperitoneal surgery, peritonitis, and ascites; unless the condition responsible for hypoproteinemia can be corrected, albumin can provide only symptomatic relief or supportive treatment
Use: Unlabeled/InvestigationalIn cirrhotics, administered with diuretics to help facilitate diuresis; large volume paracentesis; volume expansion in dehydrated, mildly-hypotensive cirrhotics
Dosing: Adults

Note: Use **5%** solution in hypovolemic patients or intravascularly-depleted patients. Use **25%** solution in patients in whom fluid and sodium intake is restricted.

Usual dose: 25 g; initial dose may be repeated in 15-30 minutes if response is inadequate; no more than 250 g should be administered within 48 hours.

Hypoproteinemia: I.V.: 0.5-1 g/kg/dose; repeat every 1-2 days as calculated to replace ongoing losses.

Hypovolemia: 5% albumin: 0.5-1 g/kg/dose; repeat as needed. **Note:** May be considered after inadequate response to crystalloid therapy and when nonprotein colloids are contraindicated. The volume administered and the speed of infusion should be adapted to individual response.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Note:5% should be used in hypovolemic patients or intravascularly-depleted patients. **25%** should be used in patients in whom fluid and sodium intake must be minimized.

Dose depends on condition of patient: Hypovolemia: I.V.: 0.5-1 g/kg/dose (10-20 mL/kg/dose of albumin 5%); maximum dose: 6 g/kg/day

Administration: I.V.For I.V. administration only. Use within 4 hours after opening vial; discard unused portion. In emergencies, may administer as rapidly as necessary to improve clinical condition. After initial volume replacement:

5%: Do not exceed 2-4 mL/minute in patients with normal plasma volume; 5-10 mL/minute in patients with hypoproteinemia

25%: Do not exceed 1 mL/minute in patients with normal plasma volume; 2-3 mL/minute in patients with hypoproteinemia

Administration: I.V. DetailDo not dilute 5% solution. Rapid infusion may cause vascular overload. Albumin 25% may be given undiluted or diluted in normal saline. May give in combination or through the same administration set as saline or carbohydrates. Do not use with ethanol or protein hydrolysates, precipitation may form.

pH: 6.4-7.4

Dietary Considerations

Albumarc®, Albuminar®, Albutein®, Buminate®, Flexbumin: 5% [50 mg/mL] and 25% [250 mg/mL] contain sodium 130-160 mEq/L

Plasbumin®: 5% [50 mg/mL] and 25% [250 mg/mL] contain sodium ~145 mEq/L

StorageStore at a temperature ≤30°C (86°F); do not freeze. Do not use solution if it is turbid or contains a deposit; use within 4 hours after opening vial; discard unused portion.
ReconstitutionIf 5% human albumin is unavailable, it may be prepared by diluting 25% human albumin with 0.9% sodium chloride or 5% dextrose in water. Do not use sterile water to dilute albumin solutions, as this has been associated with hypotonic-associated hemolysis.
CompatibilityStable in dextran 6% in D_5W, dextran 6% in NS, D_5LR, D_5NS, $D_5{}^1/_2NS$, $D_5{}^1/_4NS$, D_5W, $D_{10}W$, LR, NS, ${}^1/_2NS$; **incompatible** with sterile water.

Y-site administration: Compatible: Diltiazem, lorazepam. **Incompatible:** Midazolam, vancomycin, verapamil.

Compatibility when admixed: Compatible: TPN. **Incompatible:** Verapamil.

ContraindicationsHypersensitivity to albumin or any component of the formulation; patients with severe anemia or cardiac failure
Warnings/Precautions

Concerns related to adverse effects:

- Hypervolemia: All patients should be observed for signs of hypervolemia such as pulmonary edema; monitor closely with rapid infusions.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; protein load may exacerbate or precipitate encephalopathy.

- Renal impairment: Use with caution in patients with renal impairment; protein load may precipitate azotemia.

Special populations:

- Preterm infants: Avoid 25% concentration in preterm infants due to risk of intraventricular hemorrhage.

- Sodium restricted patients: Use with caution in those patients for whom sodium restriction is necessary.

Other warnings/precautions:

- Nutritional supplementation: Is not an appropriate indication for albumin.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/compatible
Adverse ReactionsFrequency not defined.

Cardiovascular: CHF precipitation, edema, hyper-/hypotension, hypervolemia, tachycardia

Central nervous system: Chills, fever, headache

Dermatologic: Pruritus, rash, urticaria

Gastrointestinal: Nausea, vomiting

Respiratory: Bronchospasm, pulmonary edema

Miscellaneous: Anaphylaxis

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersBlood pressure, pulmonary edema, hematocrit
Nursing: Physical Assessment/MonitoringAsses patient for hepatic or renal failure. Patient should be monitored closely for pulmonary edema and cardiac failure (vital signs, central venous pressure) during administration, with frequent assessment for hypovolemia or fluid overload. If adverse reactions (eg, fever, tachycardia, hypotension, or dyspnea) occur, infusion should be stopped and prescriber notified. Teach patient adverse symptoms to report.
Monitoring: Lab TestsHematocrit
Patient EducationEducation is provided as appropriate for patient condition. This medication can only be administered intravenously. You will be monitored closely during the infusion. Report immediately any pain or bruising at infusion site, acute headache, difficulty breathing, chills, chest pain or tightness, palpitations, or sudden pain. **Pregnancy precaution:** Inform prescriber if you are pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free; human]: 5% (250 mL, 500 mL); 25% (50 mL, 100 mL)

Albuminar®: 5% (50 mL, 250 mL, 500 mL) [50 mg/mL; contains sodium 130-160 mEq/L and potassium ≤1 mEq/L; packaging contains dry natural rubber]; 25% (20 mL, 50 mL, 100 mL) [250 mg/mL; contains sodium 130-160 mEq/L and potassium ≤1 mEq/L; packaging contains dry natural rubber]

AlbuRx™: 5% (250 mL, 500 mL) [50 mg/mL; contains sodium 130-160 mEq/L and potassium ≤2 mEq/L]; 25% (50 mL, 100 mL) [250 mg/mL; contains sodium 130-160 mEq/L and potassium ≤2 mEq/L]

Albutein®: 5% (250 mL, 500 mL) [50 mg/mL; contains sodium 130-160 mEq/L and potassium ≤2 mEq/L]

Buminate®: 5% (250 mL, 500 mL) [50 mg/mL; contains sodium 130-160 mEq/L and potassium ≤2 mEq/L; packaging contains dry natural rubber]; 25% (20 mL, 50 mL, 100 mL) [250 mg/mL; contains sodium 130-160 mEq/L and potassium ≤2 mEq/L; packaging contains dry natural rubber]

Flexbumin: 25% (50 mL, 100 mL) [250 mg/mL; contains sodium 130-160 mEq/L and potassium ≤2 mEq/L]

Human Albumin Grifols®: 25% (50 mL, 100 mL) [250 mg/mL; contains sodium 130-160 mEq/L and potassium ≤2 mEq/L]

Plasbumin®: 5% (50 mL, 250 mL) [50 mg/mL; contains sodium ~145 mEq/L and potassium ≤2 mEq/L]; 25% (20 mL, 50 mL, 100 mL) [250 mg/mL; contains sodium ~145 mEq/L and potassium ≤2 mEq/L]

Generic AvailableYes
Mechanism of ActionProvides increase in intravascular oncotic pressure and causes mobilization of fluids from interstitial into intravascular space

Pharmacotherapy Pearls Albumin 5% and 25% solutions contain 130-160 mEq/L sodium and are considered isotonic with plasma. Dilution of albumin 25% solution with sterile water produces a hypotonic solution; administration of such can cause hemolysis and/or renal failure. An albumin 5% solution is osmotically equivalent to an equal volume of plasma, whereas a 25% solution is osmotically equivalent to 5 times its volume of plasma. Albumin solutions are heated to 60°C for 10 hours, decreasing any possible risk of viral hepatitis transmission. To date, there have been no reports of viral transmission using these products.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Anesthesia and Critical Care Concerns/Other Considerations An Australian/New Zealand group recently published results from their evaluation of resuscitation fluid (4% albumin versus normal saline) in a heterogeneous intensive care population (Finfer, 2004). They conducted this multicenter, randomized, double-blind trial to compare the effects of resuscitation fluid on mortality from any cause during the 28-day period after randomization. Patients were eligible for inclusion if the treating clinician judged that fluid resuscitation was required for intravascular fluid depletion as supported by one of the following criteria:

Heart rate >90 bpm,

Systolic BP <100 mm Hg,

Mean arterial BP <75 mm Hg,

Decrease of 40 mm Hg in systolic or mean arterial BP (as compared with baseline),

CVP <10 mm Hg,

PCWP <12 mm Hg,

Respiratory variation in systolic or mean BP >5 mm Hg,

Capillary refill time >1 second, or

Urine output <0.5 mL/kg for 1 hour

Patients were excluded for a variety of reasons, including ICU transfer following cardiac or liver transplantation surgery, or burn treatment. Almost 7000 patients were randomized; 3497 to albumin and 3500 to saline. Baseline characteristics were similar between the groups, except CVP pressure was slightly higher in the albumin group (9.0 in albumin versus 8.6 in saline). There was no significant mortality difference between groups (726 deaths in albumin group; 729 deaths in saline group). There were no significant differences in secondary endpoints (length of stay in the ICU or hospital, days of mechanical ventilation, and days of renal replacement therapy). Similar outcomes resulted from use of either fluid for resuscitation in this patient population.

Index Terms Albumin (Human); Normal Human Serum Albumin; Normal Serum Albumin (Human); Salt Poor Albumin; SPA

References

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Centers for Disease Control and Prevention, “Hemolysis Associated With 25% Human Albumin Diluted With Sterile Water - United States, 1994-1998,” *MMWR*, March 5, 1999, 48(8):157-9. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/00056596.htm. Accessed February 26, 2004. [PubMed 10079061]

Finfer S, Bellomo R, Boyce N, et al, “A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. SAFE Study Investigators,” *N Engl J Med*, 2004, 350(22):2247-56.[PubMed 15163774]

International Brand Names Alba (IN); Albapure (ID, TW); Albotein (IT); Albuman (PE); Albumer (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, PH, SC, SD, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Albumex (AU); Albumin 5% (CH); Albumin 5% Human (DE); Albumin Human Salzarm 25% (DE); Albumina Humana (BR); Albuminar (BR, IL); Albuminate (ID); Albuminativ (NO); Alburaas (TH); Albutein 25% (BR, HK); Buminate 25% (HK); Flexbumin (SE); Human albumin (PL); Human Albumin (AT); Human Albumin 25% (DE); Human Albumin 5% (CZ, DE); Human Albumin ZLB (DK); Humanalbumin 5% (AT); Makroalbumina (PL); Octalbin (DK, FI, ID, MX); Plasbumin (ID); Seralbumin (CO, CR, DO, GT, HN, PA, SV); SRK (CH); Taninal (PL); Tanninum albuminatum (PL); Vialebex (FR); Volumin (IN)

Albuterol

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Special Alerts

FDA Advisory: Transition to HFA-Propelled Albuterol Inhalers - June 2008

The Food and Drug Administration (FDA) has issued a Public Health Advisory to announce a phase out of albuterol chlorofluorocarbon (CFC) propelled inhalers to hydrofluoralkane (HFA) propelled albuterol inhalers. The CFC propelled albuterol inhalers will not be available in the U.S. after December 31, 2008, and patients should be transitioned to a hydrofluoralkane (HFA) propelled albuterol inhaler now. To date, the three HFA-propelled albuterol inhalation aerosol inhalers on the market include ProAir™ HFA, Proventil® HFA, and Ventolin® HFA. In addition, levalbuterol, the (R) enantiomer of racemic albuterol, is also available as Xoponex HFA™ inhalation aerosol.

This national transition from CFC-propelled inhalers to HFA-propelled inhalers is ongoing and other medications using CFC-propelled inhalers will be phased out over the next several years.

Additional information may be found at http://www.fda.gov/cder/drug/advisory/albuterol_cfc.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Albuterol may be confused with Albutein®, atenolol

Proventil® may be confused with Bentyl®, Prilosec® Prinivil®

Salbutamol may be confused with salmeterol

Ventolin® may be confused with phentolamine, Benylin®, Vantin®

Volmax® may be confused with Flomax®

Pronunciation(al BYOO ter ole)

U.S. Brand NamesAccuNeb®; ProAir™ HFA; Proventil® HFA; Proventil® [DSC]; Ventolin® HFA; VoSpire ER®

Canadian Brand NamesAiromir; Alti-Salbutamol; Apo-Salvent®; Apo-Salvent® CFC Free; Apo-Salvent® Respirator Solution; Apo-Salvent® Sterules; Gen-Salbutamol; PMS-Salbutamol; ratio-Inspra-Sal; ratio-Salbutamol; Rhoxal-salbutamol; Salbu-2; Salbu-4; Ventolin®; Ventolin® Diskus; Ventolin® HFA; Ventolin® I.V. Infusion; Ventrodisk

Pharmacologic CategoryBeta$_2$ Agonist

Use: Labeled IndicationsBronchodilator in reversible airway obstruction due to asthma or COPD; prevention of exercise-induced bronchospasm

Use: Unlabeled/InvestigationalAs tocolytic agent (injectable form; not available in U.S.)

Dosing: Adults

Bronchospasm:

Metered-dose inhaler: 2 puffs every 4-6 hours as needed (NIH Guidelines, 2007):

Solution for nebulization: 1.25-5 mg every 4 to 8 hours as needed (NIH Guidelines, 2007)

Oral: 2-4 mg/dose 3-4 times/day; maximum dose not to exceed 32 mg/day (divided doses)

Extended release: 8 mg every 12 hours; maximum dose not to exceed 32 mg/day (divided doses). A 4 mg dose every 12 hours may be sufficient in some patients, such as adults of low body weight.

I.V. continuous infusion (Ventolin® I.V. solution [not available in U.S.]): Severe bronchospasm and status asthmaticus: Initial: 5 mcg/minute; may increase up to 10-20 mcg/minute at 15- to 30-minute intervals if needed

Exacerbation of asthma (acute, severe) (NIH Guidelines, 2007):

Metered-dose inhaler: 4-8 puffs every 20 minutes for up to 4 hours, then every 1-4 hours as needed

Solution for nebulization: 2.5-5 mg every 20 minutes for 3 doses, then 2.5-10 mg every 1-4 hours as needed, **or** 10-15 mg/hour by continuous nebulization

Exercise-induced bronchospasm (prevention):*Metered-dose inhaler:* 2 puffs 5-30 minutes prior to exercise

Dosing: Elderly

Inhalation: Refer to adult dosing.

Bronchospasm (treatment): Oral: 2 mg 3-4 times/day; maximum: 8 mg 4 times/day

Dosing: Pediatric

Bronchospasm:

Oral, regular release:

Children 2-6 years: 0.1-0.2 mg/kg/dose 3 times/day (maximum: 12 mg/day)

Children 6-12 years: 2 mg/dose 3-4 times/day (maximum 24 mg/day)

Children >12 years: 2-4 mg/dose 3-4 times/day (maximum: 32 mg/day)

Oral, extended release:

Children 6-12 years: 4 mg every 12 hours (maximum: 24 mg/day)

Children >12 years: 8 mg every 12 hours (maximum 32 mg/day)

Metered-dose inhaler (90 mcg/puff): NIH Guidelines, 2007: Quick relief:

Children ≤4 years: 1-2 puffs every 4-6 hours as needed

Children 5-11 years: 2 puffs every 4-6 hours as needed

Children ≥12 years: 2 puffs every 4-6 hours as needed

Solution for nebulization:

Manufacturer's recommendations:

Children 2-12 years (AccuNeb®): 0.63-1.25 mg every 4-6 hours as needed

Children ≥12 years: 2.5 mg every 4-8 hours as needed

NIH Guidelines, 2007: Quick relief:

Children ≤4 years: 0.63-2.5 mg every 4-6 hours as needed

Children ≥5 years: 1.25-5 mg every 4-8 hours as needed

I.V. (Ventolin® I.V. solution [not available in U.S.]): Dosage not established for children

Exacerbation of asthma (acute, severe) (NIH Guidelines, 2007):

Metered-dose inhaler (90 mcg/puff):

Children <12 years: 4-8 puffs every 20 minutes for 3 doses, then every 1-4 hours as needed

Children ≥12 years: 4-8 puffs every 20 minutes for up to 4 hours, then every 1-4 hours as needed

Solution for nebulization:

Children <12 years: 0.15 mg/kg (minimum: 2.5 mg) every 20 minutes for 3 doses, then 0.15-0.3 mg/kg (maximum: 10 mg) every 1-4 hours as needed, **or** 0.5 mg/kg/hour by continuous nebulization

Children ≥12 years: 2.5-5 mg every 20 minutes for 3 doses, then 2.5-10 mg every 1-4 hours as needed, **or** 10-15 mg/hour by continuous nebulization

Exercise-induced bronchospasm (prevention):*Metered-dose inhaler (90 mcg/puff):*

Children ≤4 years: 1-2 puffs 5 minutes prior to exercise (NIH Guidelines, 2007)

Children >4 years: 2 puffs 5-30 minutes prior to exercise

Dosing: Renal ImpairmentNot removed by hemodialysis

Administration: I.V.Infusion solution (Ventolin® I.V.): Do not inject undiluted. Reduce concentration by at least 50% before infusing. Administer as a continuous infusion via infusion pump. Discard unused portion of infusion within 24 hours of preparation.

Administration: OralDo not crush or chew extended release tablets.

Administration: Inhalation

Metered-dose inhaler: Shake well before use; prime prior to first use, and whenever inhaler has not been used for >2 weeks or when it has been dropped, by releasing 3-4 test sprays into the air (away from face). A spacer device or valved holding chamber is recommended for use with metered-dose inhalers.

Solution for nebulization: Concentrated solution should be diluted prior to use. Blow-by administration is not recommended, use a mask device if patient unable to hold mouthpiece in mouth for administration.

Dietary ConsiderationsOral forms should be administered with water 1 hour before or 2 hours after meals.

Storage

HFA aerosols: Store at 15°C to 25°C (59°F to 77°F).

Ventolin® HFA: Discard after using 200 actuations or 3 months after removal from protective pouch, whichever comes first. Store with mouthpiece down.

Infusion solution (not available in U.S.): Ventolin® I.V.: Store at 15°C to 30°C (59°F to 86°F). Protect from light. After dilution, discard after 24 hours.

Solution for nebulization (0.5%): Store at 2°C to 30°C (36°F to 86°F).

AccuNeb®: Store at 2°C to 25°C (36°F to 77°F). Do not use if solution changes color or becomes cloudy. Use within 1 week of opening foil pouch.

Syrup: Store at 2°C to 30°C (36°F to 86°F).

Tablet: Store at 2°C to 30°C (36°F to 86°F).

Tablet, extended release: Store at 20°C to 25°C (68°F to 77°F)

ReconstitutionSolution for nebulization: To prepare a 2.5 mg dose, dilute 0.5 mL of solution to a total of 3 mL with normal saline; also compatible with cromolyn or ipratropium nebulizer solutions.

Compatibility

Intravenous solution: Stable in water for injection, NS, D_5W, and D_5NS when mixed in PC bags or glass bottles. Avoid addition of other medications to infusion solution.

Solution for nebulization: **Compatible** with cromolyn sodium, budesonide inhalation suspension, ipratropium solution for nebulization

ContraindicationsHypersensitivity to albuterol, adrenergic amines, or any component of the formulation

Injection formulation (not available in U.S.): Patients with tachyarrhythmias; risk of abortion during first or second trimester

Warnings/Precautions

Concerns related to adverse effects:

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.

- Hypersensitivity reactions: Immediate hypersensitivity reactions (urticaria, angioedema, rash, bronchospasm) have been reported.

Disease-related concerns:

- Asthma: Appropriate use: Optimize anti-inflammatory treatment before initiating maintenance treatment with albuterol. Do not use as a component of chronic therapy without an anti-inflammatory agent. Only the mildest forms of asthma (Step 1 and/or exercise-induced) would not require concurrent use based upon asthma guidelines.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (arrhythmia or hypertension or HF); beta-agonists may cause elevation in blood pressure, heart rate and result in CNS stimulation/excitation. Beta$_2$-agonists may also increase risk of arrhythmias.

- Diabetes: Use with caution in patients with diabetes mellitus; beta$_2$-agonists may increase serum glucose.

- Glaucoma: Use with caution in patients with glaucoma; may elevate intraocular pressure.

- Hyperthyroidism: Use with caution in hyperthyroidism; may stimulate thyroid activity.

- Hypokalemia: Use with caution in patients with hypokalemia; beta$_2$-agonists may decrease serum potassium.

- Seizures: Use with caution in patients with seizure disorders; beta-agonists may result in CNS stimulation/excitation.

Special populations:

- Pediatrics: Face masks should be used in children <4 years of age.

Dosage form specific issues:

- Chlorofluorocarbons: Patient response may vary between inhalers that contain chlorofluorocarbons and those which are chlorofluorocarbon-free.

Other warnings/precautions:

- Appropriate use: Do not exceed recommended dose; serious adverse events, including fatalities, have been associated with excessive use of inhaled sympathomimetics.

- Patient information: Patients must be instructed to seek medical attention in cases where acute symptoms are not relieved or a previous level of response is diminished. The need to increase frequency of use may indicate deterioration of asthma, and treatment must not be delayed. A spacer device or valved holding chamber is recommended when using a metered-dose inhaler.

Geriatric ConsiderationsBecause of its minimal effect on beta$_1$-receptors and its relatively long duration of action, albuterol is a rational choice in elderly when a beta-agonist is indicated. Elderly patients may find it beneficial to utilize a spacer device when using a metered dose inhaler. Oral use should be avoided due to adverse effects.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAlbuterol crosses the placenta; tocolytic effects, fetal tachycardia, fetal hypoglycemia secondary to maternal hyperglycemia with oral or intravenous routes reported. Available evidence suggests safe use as an inhalation during pregnancy, and albuterol is the preferred short-acting beta agonist for use in asthma according to the NHLBI 2007 Guidelines for the Diagnosis and Management of Asthma.

Use of the parenteral formulation (not available in the U.S.) as a tocolytic agent has been associated with myocardial ischemia. Patients with a history of cardiac disease should be referred to a cardiologist for evaluation prior to initiating therapy in premature labor. If therapy is initiated, patients should be carefully monitored for ECG changes as well as for changes in fluid balance and cardiopulmonary function. Maternal pulse rate should not exceed 140 beats per minute during I.V. infusion of salbutamol. Consider discontinuing therapy with the development of signs of pulmonary edema or myocardial ischemia. Cautious use of parenteral salbutamol, as with other beta$_2$-agonists, is also warranted when used during labor and delivery for the relief of bronchospasm.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsIncidence of adverse effects is dependent upon age of patient, dose, and route of administration.

Cardiovascular: Angina, atrial fibrillation, arrhythmias, chest discomfort, chest pain, extrasystoles, flushing, hyper-/hypotension, palpitation, supraventricular tachycardia, tachycardia

Central nervous system: CNS stimulation, dizziness, drowsiness, headache, insomnia, irritability, lightheadedness, migraine, nervousness, nightmares, restlessness, seizure

Dermatologic: Angioedema, rash, urticaria

Endocrine & metabolic: Hyperglycemia, hypokalemia, lactic acidosis

Gastrointestinal: Diarrhea, dry mouth, dyspepsia, gastroenteritis, nausea, unusual taste, vomiting

Genitourinary: Micturition difficulty

Local: Injection: Pain, stinging

Neuromuscular & skeletal: Muscle cramps, musculoskeletal pain, tremor, weakness

Otic: Otitis media, vertigo

Respiratory: Asthma exacerbation, bronchospasm, cough, epistaxis, laryngitis, oropharyngeal drying/irritation, oropharyngeal edema, pharyngitis, rhinitis, upper respiratory inflammation, viral respiratory infection

Miscellaneous: Allergic reaction, anaphylaxis, diaphoresis, lymphadenopathy

Postmarketing and/or case reports: Anxiety, glossitis, hoarseness, myocardial ischemia, pulmonary edema, throat irritation, tongue ulceration

Drug Interactions

Alpha-/Beta-Blockers: May diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Atomoxetine: May enhance the tachycardic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Betahistine: May diminish the therapeutic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Avoid or limit caffeine (may cause CNS stimulation).

Herb/Nutraceutical: Avoid ephedra, yohimbe (may cause CNS stimulation). Avoid St John's wort (may decrease the levels/effects of albuterol).

Test InteractionsIncreased renin (S), increased aldosterone (S)

Monitoring ParametersFEV$_1$, peak flow, and/or other pulmonary function tests; blood pressure, heart rate; CNS stimulation; serum glucose, serum potassium; asthma symptoms; arterial or capillary blood gases (if patients condition warrants)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor vital signs, effectiveness of therapy, and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsArterial or capillary blood gases (if patients condition warrants); FEV_1, peak flow, and/or other pulmonary function tests; serum potassium, serum glucose (in selected patients)

Patient EducationUse exactly as directed; do not use more often than recommended. Take oral medicine with water 1 hour before or 2 hours after meals. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience nervousness, dizziness, or fatigue (use caution when driving or engaging in hazardous activities until response to drug is known); dry mouth, unpleasant taste, stomach upset (frequent, small meals, frequent mouth care, chewing gum, or sucking lozenges may help); or difficulty urinating (always void before treatment). Report unresolved GI upset, dizziness or fatigue, vision changes, chest pain or palpitations, persistent inability to void, nervousness or insomnia, muscle cramping or tremor, seizures, unusual swelling of extremities and weight gain, unusual respiratory difficulty, or unusual cough. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Self-administered inhalation: Do not freeze. Shake canister before using. Sit when using medication. Close eyes when administering albuterol to avoid spray getting into eyes. Exhale slowly and completely through nose; inhale deeply through mouth while administering aerosol. Hold breath for 5-10 seconds after inhalation. Wait at least 1 full minute between inhalations. Wash mouthpiece between use. If more than one inhalation medication is used, use albuterol first and wait 5 minutes between medications. Prime inhaler prior to first use, and whenever the inhaler has not been used for more than 2 weeks, by releasing 4 test sprays into the air (away from face). Discard inhaler after labeled number of doses are used, even if the canister does not feel empty. **Ventolin® HFA:** Discard canister after 200 actuations or 3 months after removal from foil pouch, whichever comes first. Store with mouthpiece down. Do not allow metal canister to become wet.

Self-administered nebulizer: Wash hands before and after treatment. Wash and dry nebulizer after each treatment. Twist open the top of one unit-dose vial and squeeze contents into nebulizer reservoir. Connect nebulizer reservoir to the mouthpiece or face mask. Connect nebulizer to compressor. Sit in comfortable, upright position. Place mouthpiece in your mouth or put on face mask and turn on compressor. If face mask is used, avoid leakage around the mask to avoid mist getting into eyes which may cause vision problems. Breathe calmly and deeply until no more mist is formed in nebulizer (about 5 minutes). At this point, treatment is finished.

Volmax®: Tablets should be swallowed whole; do not crush or chew. Outer coating of tablet is not absorbed and may be found eliminated in stool.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product; [CAN] = Canadian brand name

Aerosol, for oral inhalation: 90 mcg/metered inhalation (17 g) [200 metered inhalations; contains chlorofluorocarbons]

Proventil®: 90 mcg/metered inhalation (17 g) [200 metered inhalations; contains chlorofluorocarbons] [DSC]

Aerosol, for oral inhalation:

ProAir™ HFA: 90 mcg/metered inhalation (8.5 g) [200 metered inhalations; chlorofluorocarbon free]

Proventil® HFA: 90 mcg/metered inhalation (6.7 g) [200 metered inhalations; chlorofluorocarbon free]

Ventolin® HFA: 90 mcg/metered inhalation (8 g) [60 metered inhalation; chlorofluorocarbon free]; (18 g) [200 metered inhalations; chlorofluorocarbon free]

Injection, solution, as sulphate:

Ventolin® I.V. [CAN]: 1 mg/1mL (5 mL) [not available in U.S.]

Solution for nebulization: 0.042% (3 mL); 0.083% (3 mL); 0.5% (0.5 mL, 20 mL)

AccuNeb® [preservative free]: 0.63 mg/3 mL (3 mL) [0.021%]; 1.25 mg/3 mL (3 mL) [0.042%]

Proventil®: 0.083% (3 mL) [DSC] [preservative free]

Syrup, as sulfate: 2 mg/5 mL (480 mL)

Tablet: 2 mg, 4 mg

Tablet, extended release: 4 mg, 8 mg

VoSpire ER®: 4 mg, 8 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Aerosol solution (ProAir HFA)

108 (90 Base) mcg/ACT (8.5): $35.99

Aerosol solution (Proventil HFA)

108 (90 Base) mcg/ACT (6.7): $45.99

Aerosol solution (Ventolin HFA)

108 (90 Base) mcg/ACT (18): $37.99

Nebulization (AccuNeb)

0.63 mg/3 mL (75): $46.79

1.25 mg/3 mL (75): $48.99

Nebulization (Albuterol Sulfate)

0.63 mg/3 mL (3): $11.99

(2.5 MG/3ML) 0.083% (75): $18.99

(5 MG/ML) 0.5% (20): $15.99

Syrup (Albuterol Sulfate)

2 mg/5 mL (120): $12.99

Tablet, 12-hour (VoSpire ER)

4 mg (30): $49.95

8 mg (60): $183.86

Tablets (Albuterol Sulfate)

2 mg (90): $15.00

4 mg (100): $24.98

Mechanism of ActionRelaxes bronchial smooth muscle by action on beta$_2$-receptors with little effect on heart rate

Pharmacodynamics/Kinetics

Onset of action: Peak effect:

Nebulization/oral inhalation: 0.5-2 hours

CFC-propelled albuterol: 10 minutes

Ventolin® HFA: 25 minutes

Oral: 2-3 hours

Duration: Nebulization/oral inhalation: 3-4 hours; Oral: 4-6 hours

Metabolism: Hepatic to an inactive sulfate

Half-life elimination: Inhalation: 3.8 hours; Oral: 3.7-5 hours

Excretion: Urine (30% as unchanged drug)

Related Information

- Bronchodilators
- Inhalant Agents

Pharmacotherapy PearlsThe 2007 National Heart, Lung, and Blood Institute Guidelines for the Diagnosis and Management of Asthma do not recommend the use of oral systemic albuterol as a quick-relief medication and do not recommend regularly scheduled daily, chronic use of inhaled beta-agonists for long-term control of asthma.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay produce CNS stimulation resulting in anxiety, tremor, and insomnia

Mental Health: Effects on Psychiatric TreatmentEffect of propranolol may be reduced; cardiovascular effects (tachycardia, palpitations) may be increased with MAO inhibitors, TCAs, and amphetamines

Cardiovascular ConsiderationsBeta-agonists will induce increases in heart rate. This should be considered in patients with resting tachycardia. Because of the frequent coexistence of chronic obstructive lung disease and coronary artery disease, many patients are on simultaneous therapy with beta-agonists and beta-blockade. This combination should, for obvious reasons, be avoided. Frequent use of inhaled beta-agonists when used in patients with atrial fibrillation may counteract pharmacologic interventions directed at rate control. Inhaled beta-agonists may be used to treat acute hyperkalemia in patients with renal failure.

Anesthesia and Critical Care Concerns/Other ConsiderationsFrequent use of inhaled beta-agonists in patients with atrial fibrillation may counteract pharmacologic interventions directed at rate control. Inhaled beta-agonists may be used to treat acute hyperkalemia in patients with renal failure.

Index TermsAlbuterol Sulfate; Salbutamol; Salbutamol Sulphate

References

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International Brand NamesAero-Vent (PH); Aerolin (BR, CN, GR); Aeromol (TH); Airomir (AU, FR, HK, LU, MY, PL, SE, TH, UY); Almotex (PH); Antomol (TH); Asmacaire (PH); Asmadil (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Asmalin Pulmoneb (PH); Asmatol (AR); Asmidon (JP); Asmol CFC-Free (AU); Asmovent (MY); Assal (MX); Asthalin (IN); Asthalin HFA (HK); Asthavent (ZA); Asvimol (PH); Avedox-FC (MX); Azmacon (ID); Azmasol (SG); Bronchosol (TH); Broncovaleas (IT); Bronter (CO); Brusal (MX); Brytolin (PH); Butahale (SG); Butamol (AU); Buto-Asma (ES, SG, TH); Butotal (CN); Buventol (NO, SG, TW); Buventol Easyhaler (FR, ID, TH); Cybutol (ID); Easyhaler Salbutamol (GB, IE); Emplusal (PH); Epaq Inhaler (AU); Farcolin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Glisend (ID); Hivent DS (PH); Huma-Salmol (HU); Inbumed (MX); Libretin (PH); Medolin (SG); Mozal (TW); Provexel NS (PH); Pulmol-S (PE); Respax (NZ); Salamol (PL); Salbetol (IN); Salbron (ID); Salbulin (LU); Salbumed (PH); Salbutalan (MX); Salbutamol (HU, PL); Salbutamol-GW (HU); Salbutan (VE); Salbutin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Salbutol (KP, PE); Salbutron SR (KP); Salbuven (ID); Salbuvent (PL); Salda (TH); Salden (EC); Salmaplon (IN); Salmundin Retard (DE); Salomol (TW); Sedalin (PH); Solia (TH); Steri-Neb Salamol (PL); Sultanol (AT, DE, JP); Suprasma (ID); Teoden (BR); Tobybron (ID); Unibron (MX); Venalax (PH); Venderol (SG); Venetlin (JP); Venteze (ZA); Ventilan (CO, PT); Ventilastin Novolizer (DE, FR); Ventodisk (LU, PL); Ventol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ventolin (AE, AR, AU, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CL, CR, CY, CZ, EC, EE, EG, ET, GH, GM, GN, GT, GY, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, OM, PA, PE, PH, PK, PL, PY, QA, SA, SC, SD, SL, SN, SR, SV, SY, TH, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Ventolin CFC-Free (AU); Ventolin [tabs./sol./sir.] (PL); Ventoline (DK, FI, FR, NO, SE); Volmax (AE, BH, CY, EC, EG, HK, HU, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Zenmolin (AE, BH, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Zibil (MX)

Alclometasone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Aclovate® may be confused with Accolate®

Pronunciation(al kloe MET a sone)

U.S. Brand NamesAclovate®

Pharmacologic CategoryCorticosteroid, Topical

Use: Labeled IndicationsTreatment of inflammation of corticosteroid-responsive dermatosis (low to medium potency topical corticosteroid)

Use: DentalTreatment of inflammation of corticosteroid-responsive dermatosis (low to medium potency topical corticosteroid)

Dosing: AdultsSteroid-responsive dermatoses: Topical: Apply a thin film to the affected area 2-3 times/day. **Note:** Therapy should be discontinued when control is achieved; if no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricSteroid-responsive dermatoses: Topical: Children ≥1 year: Apply thin film to affected area 2-3 times/day. **Note:** Therapy should be discontinued when control is achieved; if no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. Do not use for >3 weeks.

Administration: TopicalFor external use only. Do not use on open wounds. Should not be used in the presence of open or weeping lesions. Apply sparingly to occlusive dressings.

StorageStore between 2°C and 30°C (36°F and 86°F).

ContraindicationsHypersensitivity to alclometasone or any component of the formulation; viral, fungal, or tubercular skin lesions

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <1 year of age. Chronic use of corticosteroids in children may interfere with growth and development. Not for the treatment of diaper dermatitis.

Geriatric ConsiderationsDue to age-related changes in skin, limit use of topical glucocorticosteroids.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects have been observed in animals administered topical corticosteroids.

Adverse ReactionsFrequency not defined.

Dermatologic: Acne, allergic dermatitis, hypopigmentation, maceration of the skin, perioral dermatitis, skin atrophy, striae, miliaria, telangiectasia

Endocrine & metabolic: HPA suppression, Cushing's syndrome, growth retardation

Local: Burning, erythema, itching, irritation, dryness, folliculitis, hypertrichosis, papular rash

Miscellaneous: Secondary infection

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Patient EducationBefore applying, gently wash area to reduce risk of infection. Apply a thin film to cleansed area and rub in gently and thoroughly until medication vanishes. Avoid exposure to sunlight; severe sunburn may occur.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, as dipropionate: 0.05% (15 g, 45 g, 60 g)

Aclovate®: 0.05% (15 g, 60 g)

Ointment, as dipropionate: 0.05% (15 g, 45 g, 60 g)

Aclovate®: 0.05% (15 g, 45 g, 60 g)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Cream (Aclovate)

0.05% (45): $73.99

Cream (Alclometasone Dipropionate)

0.05% (45): $38.99

0.05% (60): $52.99

Ointment (Aclovate)

0.05% (15): $44.99

Mechanism of ActionStimulates the synthesis of enzymes needed to decrease inflammation, suppress mitotic activity, and cause vasoconstriction

Pharmacodynamics/Kinetics

Absorption: Topical: ~3% absorbed systemically after 8 hours when applied to intact skin

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAlclometasone Dipropionate

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International Brand NamesAclosone (NL); Almeta (JP); Cloderm (ID); Delonal (DE); Demiderm (VE); Legederm (IT); Logoderm (NZ); Lomesone (GR); Miloderme (PT); Modraderm (BE); Modrasone (GB); Perderm (AE, BH, CY, EG, HK, HN, ID, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE)

Alcohol (Ethyl)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Ethanol may be confused with Ethyol®, Ethamolin®

Pronunciation(AL koe hol, ETH il)

U.S. Brand NamesEpiClenz™ [OTC]; Gel-Stat™ [OTC]; GelRite [OTC]; Isagel® [OTC] ; Lavacol® [OTC]; Prevacare® [OTC]; Protection Plus® [OTC]; Purell® 2 in 1 [OTC]; Purell® with Aloe [OTC]; Purell® [OTC]

Canadian Brand NamesBiobase-G™; Biobase™

Pharmacologic CategoryAntidote; Pharmaceutical Aid

Use: Labeled IndicationsTopical anti-infective; pharmaceutical aid; therapeutic neurolysis (nerve or ganglion block); replenishment of fluid and carbohydrate calories

Use: Unlabeled/InvestigationalAntidote for ethylene glycol overdose; antidote for methanol overdose; treatment of fat occlusion of central venous catheters

Dosing: Adults

Antiseptic:*Liquid denatured alcohol:* Topical: Apply 1-3 times/day as needed

Therapeutic neurolysis (nerve or ganglion block):*Dehydrated alcohol injection 98%:* Intraneural: Dosage variable depending upon the site of injection (eg, trigeminal neuralgia: 0.05-0.5 mL as a single injection per interspace vs subarachnoid injection: 0.5-1 mL as a single injection per interspace); single doses >1.5 mL are seldom required

Replenishment of fluid and carbohydrate calories:*Dehydrated alcohol infusion:* Alcohol 5% and dextrose 5%: 1-2 L/day by slow infusion

Treatment of methanol or ethylene glycol ingestion (unlabeled use):Note: I.V. administration is the preferred route; continue therapy until ethylene glycol and/or methanol is no longer detected or levels are <20 mg/dL **and** the patient is asymptomatic **and** metabolic acidosis has been corrected. If ethylene glycol and/or methanol levels are not available in a timely manner, continue therapy until the estimated time of clearance of ethylene glycol and/or methanol has elapsed **and** the patient is asymptomatic with a normal pH. If patient has coingested ethanol, measure the baseline serum ethanol concentration and adjust the ethyl alcohol loading dose based on results to achieve a serum ethanol level of ~100 mg/dL.

Absolute ethyl alcohol [98% (196 proof) = 77.4 g EtOH/dL]:

Oral: Solution must be diluted to a ≤20% concentration with water or juice and administered orally or via a nasogastric tube.

Initial: 600-700 mg/kg [equivalent to 0.78-0.9 mL/kg using a **98% solution**]

Maintenance: Goal of therapy is to maintain serum ethanol levels >100 mg/dL

Nondrinker: 66 mg/kg/hour [equivalent to 0.09 mL/kg/hour using a **98% solution**]

Chronic drinker: 154 mg/kg/hour [equivalent to 0.20 mL/kg/hour using a **98% solution**]

Dosage adjustment for hemodialysis: Maintenance dose:

Nondrinker: 169 mg/kg/hour [equivalent to 0.22 mL/kg/hour using a **98% solution**]

Chronic drinker: 257 mg/kg/hour [equivalent to 0.33 mL/kg/hour using a **98% solution**]

I.V.:

Initial: 600 mg/kg [equivalent to 7.6-8.9 mL/kg using a **10% solution**]

Maintenance: Goal of therapy is to maintain serum ethanol levels >100 mg/dL.

Nondrinker: 66 mg/kg/hour [equivalent to 0.83 mL/kg/hour using a **10% solution**]

Chronic drinker: 154 mg/kg/hour [equivalent to 1.96 mL/kg/hour using a **10% solution**]

Dosage adjustment for hemodialysis: Maintenance dose:

Nondrinker: 169 mg/kg/hour [equivalent to 2.13 mL/kg/hour using a **10% solution**]

Chronic drinker: 257 mg/kg/hour [equivalent to 3.26 mL/kg/hour using a **10% solution**]

Treatment of fat occlusion of central venous catheters (unlabeled use):*Dehydrated alcohol injection:* I.V. (see institutional-based protocol for catheter clearance assessment, the following assessment is a general methodology): Up to 3 mL of ethanol 70% (maximum: 0.55 mL/kg); the volume to instill is equal to the internal volume of the catheter

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Antiseptic:*Liquid denatured alcohol:* Refer to adult dosing.

Treatment of methanol or ethylene glycol ingestion (unlabeled use):*Absolute ethanol/ethyl alcohol:* Refer to adult dosing.

Treatment of fat occlusion of central venous catheters (unlabeled use):*Dehydrated alcohol injection:* Refer to adult dosing.

Dosing: Renal ImpairmentTreatment of methanol or ethylene glycol ingestion (unlabeled use): Absolute ethanol/ethyl alcohol: Dosage adjustment for hemodialysis: Maintenance dose:

Oral:

Nondrinker: 169 mg/kg/hour [equivalent to 0.22 mL/kg/hour using a **98% solution**]

Chronic drinker: 257 mg/kg/hour [equivalent to 0.33 mL/kg/hour using a **98% solution**]

I.V.:

Nondrinker: 169 mg/kg/hour [equivalent to 2.13 mL/kg/hour using a **10% solution**]

Chronic drinker: 257 mg/kg/hour [equivalent to 3.26 mL/kg/hour using a **10% solution**]

Administration: I.V.

Ethylene glycol or methanol poisoning: I.V. administration is the preferred route. Administer as a 10% solution in D$_5$W. Initial dose should be administered over 1 hour.

Treatment of occluded central venous catheter: Instill a 70% solution with a volume equal to the internal volume of the catheter. Assess patency at 30-60 minutes (or per institutional protocol).

Administration: OralEthylene glycol or methanol poisoning: Dilute ethyl alcohol to ≤20% solution with water or juice and administer hourly by mouth or via nasogastric tube. Out-of-hospital management with orally-administered ethanol is not recommended.

Administration: OtherIntraneural: Separate needles should be used for each of multiple injections or sites to prevent residual alcohol deposition at sites not intended for tissue destruction. Inject slowly after determining proper placement of needle. Since dehydrated alcohol is hypobaric when compared with spinal fluid, proper positioning of the patient is essential to control localization of injections into the subarachnoid space.

ContraindicationsHypersensitivity to ethyl alcohol or any component of the formulation; seizure disorder and diabetic coma; subarachnoid injection of dehydrated alcohol in patients receiving anticoagulants; pregnancy (prolonged use or high doses at term)

Warnings/Precautions

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; ethyl alcohol may decrease blood sugar.
- Gout: Use with caution in patients with gout.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Shock: Use with caution in patients with shock.

Special populations:

- Cranial surgery: Use with caution in patients following cranial surgery.
- Infants: Minimize dermal exposure of ethyl alcohol in infants as significant systemic absorption and toxicity can occur. Ethyl alcohol passes freely into breast milk at a level approximately equivalent to maternal serum level.
- Pregnancy: Use with caution in pregnant women with anticipated postpartum hemorrhage.

Other warnings/precautions:

- Administration: Proper positioning of the patient for neurolytic administration is essential to control localization of the injection of dehydrated alcohol (which is hypobaric) into the subarachnoid space; avoid extravasation. Not for SubQ administration. Do not administer simultaneously with blood due to the possibility of pseudoagglutination or hemolysis; may potentiate severe hypoprothrombic bleeding. Avoid extravasation during I.V. administration.
- Monitoring: Clinical evaluation and periodic lab determinations, including serum ethanol levels, are necessary to monitor effectiveness, changes in electrolyte concentrations, and acid-base balance (when used as an antidote). Monitor blood glucose closely, particularly in children as treatment of ingestions is associated with hypoglycemia.
- Proper storage: Flammable liquid and should be kept cool and away from any heat source.

Pregnancy Risk FactorC (D per expert opinion)/X (prolonged use or high doses at term)

Pregnancy ConsiderationsReproduction studies have not been conducted with alcohol injection. Ethanol crosses the placenta, enters the fetal circulation, and has teratogenic effects in humans. The following withdrawal symptoms have been noted in the neonate following maternal ethanol consumption during pregnancy: Crying, hyperactivity, irritability, poor suck, tremors, seizures, poor sleeping pattern, hyperphagia, and diaphoresis. Fetal alcohol syndrome (FAS) is a term referring to a combination of physical, behavioral, and cognitive abnormalities resulting from ethanol exposure during fetal development. Since a “safe” amount of ethanol consumption during pregnancy has not been determined, the AAP recommends those women who are pregnant or planning a pregnancy refrain from all ethanol intake. When used as an antidote during the second or third trimester, FAS is not likely to occur due to the short treatment period; use during the first trimester is controversial.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsEthanol is found in breast milk. Drowsiness, diaphoresis, deep sleep, weakness, decreased linear growth, and abnormal weight gain have been reported in infants following large amounts of ethanol ingestion by the mother. Ingestion >1 g/kg/day decreases milk ejection reflex. The actual clearance of ethanol from breast milk is dependent upon the mother's weight and amount of ethanol consumed.

Adverse ReactionsFrequency not defined.

Cardiovascular: Flushing, hypotension

Central nervous system: Disorientation, encephalopathy, sedation, seizure (rare), vertigo

Endocrine & metabolic: Hypoglycemia

Genitourinary: Urinary retention

Local: Nerve and tissue destruction

Miscellaneous: Intoxication

Drug Interactions

Acitretin: Alcohol (Ethyl) may enhance the teratogenic effect of Acitretin. *Risk X: Avoid combination*

Amprenavir: Alcohol (Ethyl) may enhance the adverse/toxic effect of Amprenavir. This is specifically related to the propylene glycol contained in amprenavir oral solution, not capsules. *Risk X: Avoid combination*

Cefamandole: May enhance the adverse/toxic effect of Alcohol (Ethyl). A disulfiram-like reaction may occur. *Risk C: Monitor therapy*

Cefotetan: May enhance the adverse/toxic effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the CNS depressant effect of Alcohol (Ethyl). **Exceptions:** Epinastine; Ketotifen; Levocabastine; Olopatadine. *Risk C: Monitor therapy*

Disulfiram: May enhance the adverse/toxic effect of Alcohol (Ethyl). A disulfiram-like reaction may occur. *Risk X: Avoid combination*

Furazolidone: May enhance the adverse/toxic effect of Alcohol (Ethyl). A disulfiram-like reaction may occur. *Risk C: Monitor therapy*

Griseofulvin: May enhance the adverse/toxic effect of Alcohol (Ethyl). A disulfiram-like reaction may occur. *Risk C: Monitor therapy*

MetroNIDAZOLE: May enhance the adverse/toxic effect of Alcohol (Ethyl). A disulfiram-like reaction may occur. *Risk C: Monitor therapy*

NIFEdipine: Alcohol (Ethyl) may increase the serum concentration of NIFEdipine. *Risk C: Monitor therapy*

Propranolol: Alcohol (Ethyl) may decrease the serum concentration of Propranolol. Alcohol (Ethyl) may increase the serum concentration of Propranolol. *Risk C: Monitor therapy*

Sulfonylureas: May enhance the adverse/toxic effect of Alcohol (Ethyl). A flushing reaction may occur. *Risk C: Monitor therapy*

Tacrolimus: May enhance the dermatologic adverse effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Verapamil: May increase the serum concentration of Alcohol (Ethyl). *Risk C: Monitor therapy*

Monitoring ParametersAntidotal therapy: Blood ethanol levels every 1-2 hours until steady state, then every 2-4 hours; blood glucose, electrolytes (including serum magnesium), arterial pH, blood gases, methanol or ethylene glycol blood levels; heart rate, blood pressure

Reference RangeAntidote for methanol/ethylene glycol: Blood ethanol level: Goal range: 100-150 mg/dL

Monitoring: Lab TestsAntidotal therapy: Blood ethanol levels every 1-2 hours until steady state, then every 2-4 hours; blood glucose, electrolytes (including serum magnesium), arterial pH, blood gases, methanol or ethylene glycol blood levels

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Foam, topical:

Epi-Clenz™: 62% (240 mL, 480 mL) [instant hand sanitizer; contains aloe vera and vitamin E]

Gel, topical:

Epi-Clenz™: 70% (45 mL, 120 mL, 480 mL) [instant hand sanitizer; contains aloe vera and vitamin E]

GelRite: 67% (120 mL, 480 mL, 800 mL) [instant hand sanitizer; contains vitamin E)

Gel-Stat™: 62% (120 mL, 480 mL) [instant hand sanitizer]

Isagel®: 60% (59 mL, 118 mL, 621 mL, 800 mL) [instant hand sanitizer]

Prevacare®: 60% (120 mL, 240 mL, 960 mL, 1200 mL, 1500 mL) [instant hand sanitizer]

Protection Plus®: 62% (800 mL) [instant hand sanitizer]

Purell®: 62% (15 mL, 30 mL, 59 mL, 120 mL, 236 mL, 250 mL, 360 mL, 500 mL, 800 mL, 1000 mL, 2000 mL) [instant hand sanitizer; contains moisturizers and vitamin E]

Purell® Moisture Therapy: 62% (75 mL) [instant hand sanitizer]

Purell® with Aloe: 62% (15 mL, 59 mL, 236 mL, 360 mL, 800 mL, 1000 mL, 2000 mL) [instant hand sanitizer; contains aloe and tartrazine]

Infusion [in D_5W, dehydrated]: Alcohol 5% (1000 mL) [DSC]

Injection, solution [dehydrated]: 98% (1 mL, 5 mL)

Liquid, topical [denatured]: 70% (3840 mL)

Lavacol®: 70% (473 mL)

Lotion, topical:

Purell® 2 in 1: 62% (60 mL, 360 mL, 1000 mL) [instant hand sanitizer]

Towelettes, topical:

Isagel®: 60% (50s, 300s) [instant hand sanitizer]

Purell®: 62% (35s, 175s) [instant hand sanitizer]

Generic AvailableYes

Mechanism of ActionWhen used to treat ethylene glycol or methanol toxicity, ethyl alcohol competitively inhibits alcohol dehydrogenase, an enzyme which catalyzes the metabolism of ethylene glycol and methanol to their toxic metabolites.

Pharmacodynamics/Kinetics

Absorption: Oral: Rapid

Distribution: V_d: 0.6-0.7 L/kg; decreased in women

Metabolism: Hepatic (90% to 98%) to acetaldehyde or acetate

Half-life elimination: Rate: 15-20 mg/dL/hour (range: 10-34 mg/dL/hour); increased in alcoholics

Excretion: Kidneys and lungs (~2% unchanged)

Pharmacotherapy Pearls

Neurolytic block: Pain will occur after initial injection for a short period of time and will subside when neurolysis occurs; agent will destroy nerve and should be administered when pain is from malignant origin only; administer carefully.

Replenishment of fluid and carbohydrate calories: If the daily fluid requirement is >3 L/day, use of alcohol 5% in dextrose 5% is not recommended.

Undiluted ethanol 196 proof = 98% solution = 77.4 g ethanol/dL

I.V. solution 10% = 7.9 g ethanol/dL

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause confusion, disorientation, encephalopathy, sedation, and dizziness

Mental Health: Effects on Psychiatric TreatmentAvoid use in patients receiving psychotropic agents. Concomitant use with psychotropic agents may produce additive sedation.

Anesthesia and Critical Care Concerns/Other Considerations

Neurolytic Block: Pain will occur after initial injection for a short period of time and will subside when neurolysis occurs. This agent will destroy nerve and should be administered when pain is from malignant origin only; administer carefully.

Methanol/ethylene Glycol Poisoning: Treatment involves inhibiting the formation of toxic metabolites by inhibiting alcohol dehydrogenase and/or urgent dialytic removal of these alcohols and their metabolites. Fomepizole and ethanol are both inhibitors of alcohol dehydrogenase and have been used to prevent toxicity. Currently, fomepizole is the drug of choice because of its ease of use and lack of CNS toxicity. When ethanol is used, a target serum level of 100-200 mg/dL (depending upon concurrent ethanol use) is maintained during treatment. Patients are treated until serum levels of the poison (ethylene glycol/methanol) are <20 mg/dL and patient is asymptomatic with normal pH or poison levels are undetectable.

Index TermsAlcohol, Absolute; Alcohol, Dehydrated; Ethanol; Ethyl Alcohol; EtOH

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International Brand NamesAogel (MX)

Aldesleukin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Aldesleukin may be confused with oprelvekin

Proleukin® may be confused with oprelvekin

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(al des LOO kin)

U.S. Brand NamesProleukin®

Canadian Brand NamesProleukin®

Pharmacologic CategoryAntineoplastic Agent, Miscellaneous; Biological Response Modulator

Use: Labeled IndicationsTreatment of metastatic renal cell cancer, metastatic melanoma

Use: Unlabeled/InvestigationalHIV infection, and AIDS; non-Hodgkin's lymphoma

Dosing: AdultsRefer to individual protocols.

Renal cell carcinoma: I.V.: 600,000 int. units/kg every 8 hours for a maximum of 14 doses; repeat after 9 days for a total of 28 doses per course. Retreat if needed 7 weeks after previous course.

Melanoma:

I.V.:

Single-agent use: 600,000 int. units/kg every 8 hours for a maximum of 14 doses; repeat after 9 days for a total of 28 doses per course. Retreat if needed 7 weeks after previous course.

In combination with cytotoxic agents (unlabeled use): 24 million int. units/m^2 days 12-16 and 19-23

SubQ (unlabeled route):

Single-agent doses: 3-18 million int. units/day for 5 days each week, up to 6 weeks

In combination with interferon:

5 million int. units/m^2 3 times/week

1.8 million int. units/m^2 twice daily 5 days/week for 6 weeks

Investigational regimen: SubQ: 11 million int. units (flat dose) daily for 4 days per week for 4 consecutive weeks; repeat every 6 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo specific recommendations by manufacturer. Use with caution.

Dosing: Combination Regimens

Melanoma:

Cisplatin-Dacarbazine-Interferon Alfa-2b-Aldesleukin

IL-2 + IFN

Renal cell cancer:

Interleukin 2 (Low Dose)-Interferon Alfa 2b

Interleukin 2-Interferon Alfa-2

Interleukin 2-Interferon Alfa-2-Fluorouracil

Calculations

- Body Surface Area: Adults

Administration: I.V.Infuse over 15 minutes. Do not administer with an inline filter. Flush before and after with D$_5$W, particularly if

maintenance I.V. line contains sodium chloride.
⇧ Administration: I.V. Detail

Management of symptoms related to vascular leak syndrome:

If actual body weight increases >10% above baseline, or rales or rhonchi are audible:

Administer furosemide at dosage determined by patient response.

Administer dopamine hydrochloride 1-5 mcg/kg/minute to maintain renal blood flow and urine output.

If patient has dyspnea at rest: Give supplemental oxygen by facemask.

If patient has severe respiratory distress: Intubate patient and provide mechanical ventilation. Administer ranitidine (as the hydrochloride salt) 50 mg I.V. every 8-12 hours as prophylaxis against stress ulcers.

⇧ Administration: OtherMay be administered by SubQ injection (unlabeled route).
⇧ StorageStore vials of lyophilized injection in a refrigerator at 2°C to 8°C (36°F to 46°F). Reconstituted vials and solutions diluted for infusion are stable for 48 hours at room temperature or refrigerated, per the manufacturer. Solution diluted with D_5W to a concentration of 220 mg/mL and repackaged into tuberculin syringes was reported to be stable for 14 days refrigerated.
⇧ Reconstitution Reconstitute vials with 1.2 mL SWFI to a concentration of 18 million units/1 mL (sterile water should be injected towards the side of the vial). Gently swirl; do not shake. Further dilute with 50 mL of D_5W. Smaller volumes of D_5W should be used for doses <1.5 mg; avoid concentrations <30 mcg/mL and >70 mcg/mL (an increased variability in drug delivery has been seen).

Note: Filtration will result in significant loss of bioactivity.

Final Dilution Concentration (mcg/mL)	**Final Dilution Concentration (10^6 int. units/mL)**	**Stability**
<30	<0.49	Albumin must be added to bag **prior to addition** of aldesleukin at a final concentration of 0.1% (1 mg/mL) albumin; stable at room temperature or at ≥32°C (89°F) for 6 days[1,2]
≥30 to ≤70	≥0.49 to ≤1.1	Stable at room temperature at 6 days without albumin added or at ≥32°C (89°F) for 6 days only if albumin is added (0.1%)[1,2]
70-100	1.2-1.6	Unstable; avoid use
>100-500	1.7-8.2	Stable at room temperature and at ≥32°C (89°F) for 6 days[1,2]

[1] These solutions do not contain a preservative; use for more than 24 hours may not be advisable.

[2] Continuous infusion via ambulatory infusion device raises aldesleukin to this temperature.

⇧ CompatibilityStable in D_5W.

Y-site administration: Compatible: Amikacin, amphotericin B, calcium gluconate, co-trimoxazole, diphenhydramine, dopamine, fat emulsion 10%, fluconazole, foscarnet, gentamicin, heparin, magnesium sulfate, metoclopramide, morphine, ondansetron, piperacillin, potassium chloride, ranitidine, thiethylperazine, ticarcillin, tobramycin. **Incompatible:** Ganciclovir, lorazepam, NS, pentamidine, prochlorperazine edisylate, promethazine.

Compatibility when admixed: Incompatible with NS.

⇧ ContraindicationsHypersensitivity to aldesleukin or any component of the formulation; patients with abnormal thallium stress or pulmonary function tests; patients who have had an organ allograft; retreatment in patients who have experienced sustained ventricular tachycardia (≥5 beats), refractory cardiac rhythm disturbances, recurrent chest pain with ECG changes consistent with angina or myocardial infarction, intubation ≥72 hours, pericardial tamponade, renal dialysis for ≥72 hours, coma or toxic psychosis lasting ≥48 hours, repetitive or refractory seizures, bowel ischemia/perforation, GI bleeding requiring surgery
⇧ Warnings/Precautions

Boxed warnings:

- Capillary leak syndrome (CLS): See “Concerns related to adverse effects” below.

- Experienced physician: See “Other warnings/precautions” below.
- Infection: See “Concerns related to adverse effects” below.
- Lethargy/somnolence: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Adverse effects: Are frequent and sometimes fatal.
- Capillary leak syndrome (CLS): **[U.S. Boxed Warning]: High-dose aldesleukin therapy has been associated with capillary leak syndrome (CLS) resulting in hypotension and reduced organ perfusion which may be severe and can result in death.** Therapy should be restricted to patients with normal cardiac and pulmonary functions as defined by thallium stress and formal pulmonary function testing. Extreme caution should be used in patients with a history of prior cardiac or pulmonary disease. Patients must have a serum creatinine ≤1.5 mg/dL prior to treatment.
- CNS effects: Mental status changes (irritability, confusion, depression) can occur and may indicate bacteremia, hypoperfusion, CNS malignancy, or CNS toxicity.
- Infection: **[U.S. Boxed Warning]: Impaired neutrophil function is associated with treatment; patients are at risk for sepsis, bacterial endocarditis, and central line-related gram-positive infections.** Antibiotic prophylaxis which has been associated with a reduced incidence of staphylococcal infections in aldesleukin studies includes the use of oxacillin, nafcillin, ciprofloxacin, or vancomycin.
- Lethargy/somnolence: **[U.S. Boxed Warning]: Withhold treatment for patients developing moderate-to-severe lethargy or somnolence; continued treatment may result in coma.**

Disease-related concerns:

- Autoimmune/inflammatory disorders: Use with caution in patients with autoimmune disease or inflammatory disorders; may exacerbate condition.
- CNS metastases: Patients should be evaluated and treated for CNS metastases and have a negative scan prior to treatment.

Concurrent drug therapy issues:

- Supportive care for high-dose treatment: Standard prophylactic supportive care during high-dose aldesleukin treatment includes acetaminophen to relieve constitutional symptoms and an H_2 antagonist to reduce the risk of GI ulceration and/or bleeding.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician in a facility with cardiopulmonary or intensive specialists and intensive care facilities available.**

Pregnancy Risk FactorC

Pregnancy ConsiderationsMaternal toxicity and embryocidal effects were noted in animal studies. There are no adequate and well-controlled studies in pregnant women; use during pregnancy only if benefits to the mother outweigh potential risk to the fetus. Contraception is recommended for fertile males or females using this medication.

LactationExcretion unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding should be discontinued during treatment.

Adverse Reactions

>10%:

Cardiovascular: Hypotension (71%; grade 4: 3%), peripheral edema (28%), tachycardia (23%), edema (15%), vasodilation (13%), cardiovascular disorder (11%; includes blood pressure changes, CHF and ECG changes)

Central nervous system: Chills (52%), confusion (34%), fever (29%; grade 4: 1%), malaise (27%), somnolence (22%), anxiety (12%), pain (12%), dizziness (11%)

Dermatologic: Rash (42%), pruritus (24%), exfoliative dermatitis (18%)

Endocrine & metabolic: Acidosis (12%), hypomagnesemia (12%), hypocalcemia (11%)

Gastrointestinal: Diarrhea (67%), vomiting (19% to 50%), nausea (19% to 35%), stomatitis (22%), anorexia (20%), weight gain (18%), abdominal pain (11%)

Hematologic: Thrombocytopenia (37%; grade 4: 1%), anemia (29%), leukopenia (16%)

Hepatic: Hyperbilirubinemia (40%), AST increased (23%)

Neuromuscular & skeletal: Weakness (23%)

Renal: Oliguria (63%; grade 4: 6%), creatinine increased (33%)

Respiratory: Dyspnea (43%), lung disorder (24%; includes pulmonary congestion, rales, and rhonchi), cough (11%), respiratory disorder (11%; includes acute respiratory distress syndrome, infiltrates and pulmonary changes)

Miscellaneous: Infection (13%; grade 4: 1%)

1% to 10%:

Cardiovascular: Arrhythmia (10%), cardiac arrest (grade 4: 1%), MI (grade 4: 1%), supraventricular tachycardia (grade 4: 1%), ventricular tachycardia (grade 4: 1%)

Gastrointestinal: Abdomen enlarged (10%)

Hematologic: Coagulation disorder (grade 4: 1%)

Hepatic: Alkaline phosphatase increased (10%)

Renal: Anuria (grade 4: 5%), acute renal failure (grade 4: 1%)

Respiratory: Rhinitis (10%), apnea (grade 4: 1%)

Miscellaneous: Sepsis (grade 4: 1%)

<1%, postmarketing, and/or case reports (limited to important or life threatenting): Acute tubular necrosis, allergic interstitial nephritis, allergic reactions, anaphylaxis, atrial arrhythmia, AV block, blindness (transient or permanent), bowel necrosis, bradycardia, bullous pemphigoid, BUN increased, cardiomyopathy, cellulitis, cerebral edema, cerebral lesions, cerebral vasculitis, CHF, cholecystitis, colitis, coma, crescentic IgA glomuleronephritis, Crohn’s disease exacerbation, depression (severe; leading to suicide), diabetes mellitus, duodenal ulcer, encephalitis, endocarditis, extrapyramidal syndrome, gastrointestinal hemorrhage, hematemesis, hemoptysis, hemorrhage, hepatic failure, hepatitis, hepatosplenomegaly, hypertension, hyperuricemia, hyperventilation, hypothermia, hyperthyroidism, hypoventilation, hypoxia, inflammatory arthritis, injection site necrosis, intestinal obstruction, intestinal perforation, leukocytosis, malignant hyperthermia, meningitis, myocardial ischemia, myocarditis, myopathy, myositis, neuritis, neuropathy, neutropenia, oculobulbar myasthenia gravis, optic neuritis, pancreatitis, pericardial effusion, pericarditis, peripheral gangrene, phlebitis, pneumonia, pneumothorax, pulmonary edema, pulmonary embolus, renal failure, respiratory acidosis, respiratory arrest, respiratory failure, retroperitoneal hemorrhage, rhabdomyolysis, scleroderma, seizure (including grand mal), shock, Stevens-Johnson syndrome, stroke, syncope, thrombosis, thyroiditis, tracheoesophageal fistula, transient ischemic attack, urticaria, ventricular extrasystoles

Oncology: VesicantNo

Oncology: Emetic PotentialModerate-to-high (30% to 90%)

Drug Interactions

Contrast Media (Non-ionic): May enhance the potential for allergic or hypersensitivity reactions to Aldesleukin. *Risk C: Monitor therapy*

Interferons (Alfa): May enhance the adverse/toxic effect of Aldesleukin. In particular, risks of myocardial and renal toxicity may be increased by this combination. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: May increase CNS adverse effects.

Monitoring Parameters

The following clinical evaluations are recommended for all patients prior to beginning treatment and then frequently during drug administration:

CBC with differential, blood chemistries including electrolytes, renal and hepatic function tests

Chest x-rays

Monitoring during therapy should include vital signs (temperature, pulse, blood pressure, and respiration rate) and weight; in a patient with a decreased blood pressure, especially <90 mm Hg, cardiac monitoring for rhythm should be conducted. If an abnormal complex or rhythm is seen, an ECG should be performed; vital signs in these hypotension patients should be taken hourly and central venous pressure (CVP) checked; monitor for change in mental status.

Pulmonary function (baseline and periodic) basis.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. See Administration I.V. specifics. Infusion site should be monitored for extravasation. Vital signs; cardiac, respiratory, and CNS status; fluid balance; signs of systemic sepsis, changes in mental status, and laboratory reports should be assessed daily prior to beginning infusion and for 2 hours following infusion. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential; blood chemistries including electrolytes, renal and hepatic function; chest x-rays

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Avoid alcohol. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will be susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause increased sensitivity to sunlight (use sunblock 15 SPF or greater, wear protective clothing, avoid direct sun exposure); or nausea, vomiting, stomatitis, anorexia (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help). This drug may result in many side effects; you will be monitored and assessed closely during therapy, however, it is important that you report any changes or problems for evaluation. Report any changes in urination, unusual bruising or bleeding, chest pain or palpitations, acute dizziness, respiratory difficulty, fever or chills, changes in cognition, rash, feelings of pain or numbness in extremities, severe or persistent GI upset or diarrhea, vaginal discharge or mouth sores, yellowing of eyes or skin, or changes in color of urine or stool. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Proleukin®: 22 x 10^6 int. units [18 million int. units/mL = 1.1 mg/mL when reconstituted]

Generic AvailableNo

ManufacturerChiron Therapeutics

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Proleukin)

22000000 unit (1): $855.71

Mechanism of ActionAldesleukin promotes proliferation, differentiation, and recruitment of T and B cells, natural killer (NK) cells, and thymocytes; causes cytolytic activity in a subset of lymphocytes and subsequent interactions between the immune system and malignant cells; can stimulate lymphokine-activated killer (LAK) cells and tumor-infiltrating lymphocytes (TIL) cells.

Pharmacodynamics/Kinetics

Distribution: V_d: 4-7 L; primarily in plasma and then in the lymphocytes

Half-life elimination: I.V.: Initial: 6-13 minutes; Terminal: 80-120 minutes

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy Pearls

1 Cetus unit = 6 int. units

1.1 mg = 18 x 10^6 int. units (or 3 x 10^6 Cetus units)

1 Roche unit (Teceleukin) = 3 int. units

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation, disorientation, delusions, and cognitive changes are common, reversible, and dose related

Mental Health: Effects on Psychiatric TreatmentPropranolol potentiates hypotensive effects. Interaction may occur with other psychotropic given aldesleukin's effect on mental status.

Index TermsEpidermal Thymocyte Activating Factor; IL-2; Interleukin-2; Lymphocyte Mitogenic Factor; NSC-373364; T-Cell Growth Factor; TCGF; Thymocyte Stimulating Factor

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International Brand NamesInterleukina 2 (PY); Interleukina II (CN); Proleukin (AR, AT, BE, BR, CH, CO, CZ, DE, DK, EC, EG, ES, FI, FR, GB, GR, HK, HN, HU, IE, IL, IT, KP, NL, NZ, PE, PL, PT, TW, UY)

Alefacept

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(a LE fa sept)
U.S. Brand NamesAmevive®
Canadian Brand NamesAmevive®
Pharmacologic Category[Monoclonal Antibody]
Use: Labeled IndicationsTreatment of moderate to severe chronic plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
Dosing: AdultsPsoriasis (moderate-to-severe chronic plaque psoriasis):

I.M.: 15 mg once weekly; usual duration of treatment: 12 weeks

Second course: A second course of treatment may be initiated at least 12 weeks after completion of the initial course of treatment, provided CD4$^+$ T-lymphocyte counts are within the normal range.

Note: CD4$^+$ T-lymphocyte counts should be monitored before initiation of treatment and every 2 weeks during therapy. Dosing should be withheld if CD4$^+$ counts are <250 cells/µL, and dosing should be permanently discontinued if CD4$^+$ lymphocyte counts remain at <250 cell/µL for longer than 1 month.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo dosage adjustment required.
Administration: I.M.I.M. injections should be administered at least 1 inch from previous administration sites.
StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F); protect from light. Following reconstitution, may be stored for up to 4 hours at 2°C to 8°C (36°F to 46°F). Discard any unused solution after 4 hours.
ReconstitutionReconstitute 15 mg vial for I.M. solution with 0.6 mL of SWFI (supplied); 0.5 mL of reconstituted solution contains 15 mg of alefacept. Gently swirl to avoid foaming. Do not filter reconstituted solutions. Do not mix with other medications or solutions.
CompatibilityDo not mix with other medications or solutions.
RestrictionsAlefacept will be distributed directly to physician offices or to a specialty pharmacy; injections are intended to be administered in the physician's office
ContraindicationsHypersensitivity to alefacept or any component of the formulation; history of severe malignancy; patients with HIV infection or other clinically-important infections
Warnings/Precautions

Concerns related to adverse effects:

- Hepatic injury: In post-marketing reports, significant transaminase elevations, as well as rare cases of hepatitis, fatty liver, decompensation of cirrhosis, and acute hepatic failure have occurred (causal relationship not established). Discontinue if signs and symptoms of hepatic injury occur.

- Hypersensitivity reactions: Has been associated with hypersensitivity reactions; rare anaphylaxis also reported. Discontinue use if severe reaction occurs.

- Immune suppression: May increase the risk of infection and may reactivate latent infection; monitor for new infections. Avoid use in patients receiving other immunosuppressant drugs or phototherapy.

- Infusion reactions: Acute infusion reactions may occur. Medication and equipment for management should be available for immediate use.

- Lymphopenia: Induces a decline in circulating T-lymphocytes (CD4$^+$ and CD8$^+$); CD4$^+$ lymphocyte counts should be monitored every 2 weeks throughout therapy. Do not initiate in pre-existing depression of CD4$^+$ lymphocytes and withhold treatment in any patient who develops a depressed CD4$^+$ lymphocyte count (<250 cells/µL) during treatment; permanently discontinue if CD4$^+$ lymphocyte counts remain <250 cells/µL for 1 month.

- Malignancy: May increase the risk of malignancies; use caution in patients at high risk for malignancy. Discontinue if malignancy develops during therapy.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Immunizations: Patients should be brought up to date with all immunizations before initiating therapy. Live vaccines should not be given concurrently; there is no data available concerning secondary transmission of live vaccines in patients receiving therapy.

Pregnancy Risk FactorB
Pregnancy ConsiderationsEffects in pregnancy are not known. Teratogenic effects have not been observed in animal studies. Patients who

become pregnant during therapy or within 8 weeks of treatment are advised to enroll in pregnancy registry (866-263-8483).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known whether alefacept is excreted in breast milk. Since alefacept is an immunosuppressant, and transfer of proteins into breast milk may occur, breast-feeding women are cautioned to discontinue breast-feeding or to discontinue use of the drug while breast-feeding (recommendations per manufacturer).

Adverse Reactions

≥10%:

Hematologic: Lymphopenia (up to 10% of patients required temporary discontinuation, up to 17% during a second course of therapy)

Local: Injection site reactions (up to 16% of patients; includes pain, inflammation, bleeding, edema, or other reaction)

1% to 10%:

Central nervous system: Chills (6%; primarily during intravenous administration), dizziness (≥2%)

Dermatologic: Pruritus (≥2%)

Gastrointestinal: Nausea (≥2%)

Neuromuscular & skeletal: Myalgia (≥2%)

Respiratory: Pharyngitis (≥2%), cough increased (≥2%)

Miscellaneous: Malignancies (1% vs 0.5% in placebo), antibodies to alefacept (3%; significance unknown), infection (1% requiring hospitalization)

<1%: Anaphylaxis, allergic reaction, angioedema, headache, hepatitis, hepatic failure, MI, transaminases increased (≥3 times ULN), urticaria

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase risk of liver toxicity).

Monitoring ParametersBaseline $CD4^+$ T-lymphocyte counts prior to initiation and every 2 weeks during treatment course; severity of psoriatic lesions; signs and symptoms of infection

Nursing: Physical Assessment/MonitoringMonitor closely for the development of malignancies or infections. Assess results of laboratory tests, therapeutic effectiveness, and adverse response. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsBaseline $CD4^+$ T-lymphocyte counts prior to initiation and every 2 weeks during treatment course

Patient EducationThis medication can only be administered by injection; report immediately any pain, redness, swelling at injection site, chills, rash, difficulty swallowing or breathing, or feelings of tightness in chest. Avoid alcohol. You will need weekly blood tests while receiving this medication. May cause nausea or muscle pain. Report unusual feelings of fatigue or weakness; signs of infection (eg, cough, runny nose, sore throat, unusual cough, swollen glands, mouth sores, vaginal itching or discharge, burning on urination, fever, chills, or unhealed sores); abdominal pain; jaundice; easy bruising; dark urine; or pale stools. Notify prescriber if pregnancy occurs during therapy or within 8 weeks of treatment. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Amevive®: 15 mg [for I.M. administration; contains sucrose 12.5 mg; supplied with SWFI]

Generic AvailableNo

ManufacturerBiogen

Mechanism of ActionBinds to CD2, a receptor on the surface of lymphocytes, inhibiting their interaction with leukocyte functional antigen 3 (LFA-3). Interaction between CD2 and LFA-3 is important for the activation of T lymphocytes in psoriasis. Activated T lymphocytes secrete a number of inflammatory mediators, including interferon gamma, which are involved in psoriasis. Since CD2 is primarily expressed on T lymphocytes, treatment results in a reduction in $CD4^+$ and $CD8^+$ T lymphocytes, with lesser effects on other cell populations (NK and B lymphocytes).

Pharmacodynamics/Kinetics

Distribution: V_d: 0.094 L/kg

Bioavailability: 63% (following I.M. administration)

Half-life: 270 hours (following I.V. administration)

Excretion: Clearance: 0.25 mL/hour/kg

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsB 9273; BG 9273; Human LFA-3/IgG(1) Fusion Protein; LFA-3/IgG(1) Fusion Protein, Human

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International Brand NamesAmevive (AR, CH, IL, NO)

Alemtuzumab

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Alemtuzumab: Reports of Infection-Related Fatalities - November 2008

Bayer HealthCare and Genzyme, in conjunction with Health Canada, have issued notice to Canadian hospitals concerning reports of infection-related fatalities in patients receiving consolidation therapy with MabCampath® (alemtuzumab). Preliminary safety data from the ongoing phase II U.S. clinical trial CALGB10101 has reported fatalities in 6 out of 51 patients with B-cell chronic lymphocytic leukemia (B-CLL) receiving fludarabine and rituximab induction therapy followed by alemtuzumab therapy for remission consolidation.

Fatal infections included viral meningitis, *Listeria* meningitis, *Legionella* pneumonia, cytomegalovirus (CMV), *Pneumocystis jiroveci* pneumonia (PCP), and Epstein-Barr virus (EBV) associated lymphoproliferative disorder.

The potential contributory role of any of the three chemotherapeutic agents is not clear based on available data. The infectious complications may have resulted from prolonged immunosuppression. An additional noninfection-related fatality, thought to be transfusion-associated graft-versus-host disease (TAGVHD), has also been reported.

Use of alemtuzumab as consolidation therapy is presently not approved in Canada. An updated product monograph including this new important safety information is forthcoming. Further information can be found at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/mabcampath_nth-aah-eng.php

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ay lem TU zoo mab)

U.S. Brand NamesCampath®

Canadian Brand NamesMabCampath®

Pharmacologic CategoryAntineoplastic Agent, Monoclonal Antibody

Use: Labeled IndicationsTreatment of B-cell chronic lymphocytic leukemia (B-CLL)

Use: Unlabeled/InvestigationalTreatment of refractory T-cell prolymphocytic leukemia (T-PLL); rheumatoid arthritis; graft-versus-host disease; multiple myeloma; preconditioning regimen for stem-cell transplantation and renal and liver transplantation; post-transplant rejection (renal); treatment of autoimmune cytopenias

Dosing: Adults

B-CLL: I.V. infusion, SubQ (unlabeled route):

Initial: 3 mg/day beginning on day 1; when tolerated (no grade 3 or 4 infusion reactions), increase to maintenance dose of 30 mg/dose 3 times/week on alternate days for a total duration of therapy of up to 12 weeks

Maximum dose/day: 30 mg; maximum cumulative dose/week: 90 mg

Note: Dose escalation is required; usually accomplished in 3-7 days. Do not exceed single doses >30 mg or cumulative doses >90 mg/week. Pretreatment (with acetaminophen and an oral antihistamine) is recommended prior to the first dose, with dose escalations, and as clinically indicated; I.V. hydrocortisone may be used for severe infusion-related reactions.

Dosing: ElderlyRefer to adult dosing.

Dosing: Adjustment for ToxicityHematologic toxicity (severe neutropenia or thrombocytopenia, not autoimmune): **Note:** If delay between dosing is ≥7 days, restart at 3 mg/day and escalate as tolerated.

First occurrence: ANC <250/µL and/or platelet count ≤25,000/µL: Hold therapy; resume at 30 mg/dose when ANC ≥500/µL and platelet count ≥50,000/µL

Second occurrence: ANC <250/µL and/or platelet count ≤25,000/µL: Hold therapy; resume at 10 mg/dose when ANC ≥500/µL and platelet count ≥50,000/µL

Third occurrence: ANC <250/µL and/or platelet count ≤25,000/µL: Permanently discontinue therapy

Patients with a baseline ANC ≤250/µL and/or a baseline platelet count ≤25,000/µL at initiation of therapy: If ANC and/or platelet counts decrease to ≤50% of the baseline value, hold therapy

First occurrence: When ANC and/or platelet count return to baseline, resume therapy at 30 mg/dose

Second occurrence: When ANC and/or platelet count return to baseline, resume therapy at 10 mg/dose

Third occurrence: Permanently discontinue therapy

Calculations

- ANC: Absolute Neutrophil Count

Administration: I.V.Administer by I.V. infusion over 2 hours. Consider premedicating with diphenhydramine 50 mg and acetaminophen 500-1000 mg 30 minutes before initiation of infusion. Hydrocortisone 200 mg has been effective in decreasing severe infusion-related events. Start anti-infective prophylaxis. Other drugs should not be added to or simultaneously infused through the same I.V. line. Do not give I.V. push.

Administration: I.V. DetailpH: 6.8-7.4

Administration: OtherSubQ (unlabeled route): A longer dose escalation time (1-2 weeks) may be needed due to injection site reactions. Premedication and anti-infective prophylaxis regimens should be given as are recommended with I.V. administration.

StoragePrior to dilution, store at 2°C to 8°C (36°F to 46°F); do not freeze (if accidentally frozen, thaw in refrigerator prior to administration). Do not shake; protect from light. Following dilution, store at room temperature or refrigerate; protect from light; use within 8 hours.

ReconstitutionDilute with 100 mL NS or D_5W. Gently invert the bag to mix the solution. Do not shake prior to use.

CompatibilityMedications should not be added to the solution or simultaneously infused through the same I.V. line.

ContraindicationsThere are no contraindications listed in the manufacturer's labeling

Warnings/Precautions

Boxed warnings:

- Hematologic toxicity: See “Concerns related to adverse effects” below.
- Infections: See “Concerns related to adverse effects” below.
- Infusion reactions: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Hematologic toxicity: **[U.S. Boxed Warning]: Severe, prolonged myelosuppression, autoimmune anemia, and autoimmune thrombocytopenia have occurred.** Single doses >30 mg and cumulative weekly doses >90 mg are associated with an increased incidence of pancytopenia and should not be administered. Hemolytic anemia, pure red cell aplasia, bone marrow aplasia, and hypoplasia have also been reported. Median duration of neutropenia is 21 days; median duration of thrombocytopenia is 21 days. Discontinue therapy during serious hematologic or other serious toxicity (except lymphopenia) until the event resolves. Permanently discontinue if autoimmune anemia or autoimmune thrombocytopenia occurs. Patients receiving blood products should only receive irradiated blood products due to the potential for GVHD during lymphopenia.
- Infections: **[U.S. Boxed Warning]: Serious infections (bacterial, viral, fungal, and protozoan) have been reported. Prophylactic therapy against PCP pneumonia and herpes viral infections is recommended upon initiation of therapy** and for at least 2 months following last dose or until $CD4^+$ counts are ≥200 cells/µL (whichever is later). $CD4^+$ and $CD8^+$ lymphocyte counts may not return to baseline levels for more than 1 year. Withhold treatment during serious infections; may be reinitiated upon resolution of infection.
- Infusion reactions: **[U.S. Boxed Warning]: Serious and potentially fatal infusion-related reactions (acute respiratory distress syndrome, bronchospasm, cardiac arrest, cardiac arrhythmias, chills, fever, hypotension, myocardial infarction, pulmonary infiltrates, rash, rigors, shortness of breath, syncope) may occur,** especially during the first week of treatment. Premedication with acetaminophen and an oral antihistamine is recommended. Withhold infusion for grade 3 or 4 infusion reaction. Use caution and carefully monitor blood pressure in patients with ischemic heart disease and patients on antihypertensive therapy. Gradual escalation to the recommended maintenance dose is required at initiation and after interruption of therapy for ≥7 days to minimize infusion-related reactions.

Special populations:

- Men of reproductive potential: Should use effective contraceptive methods during treatment and for a minimum of 6 months following therapy.
- Pediatrics: Safety and efficacy have not been established in children.
- Women of childbearing potential: Should use effective contraceptive methods during treatment and for a minimum of 6 months following therapy.

Other warnings/precautions:

- Immunizations: Patients should not be immunized with live, viral vaccines during or recently after treatment. The ability to respond to any vaccine following therapy is unknown.

Pregnancy Risk FactorC

Pregnancy ConsiderationsHuman IgG is known to cross the placental barrier; therefore, alemtuzumab may also cross the barrier and cause fetal B- and T-lymphocyte depletion. Well-controlled human trials have not been done. Use during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus. Effective contraception is recommended during and for 6 months after treatment for women of childbearing potential and men of reproductive potential.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsHuman IgG is excreted in breast milk; therefore, alemtuzumab may also be excreted in milk. Breast-feeding should be discontinued during treatment and for at least 3 months following the last dose.

Adverse Reactions

>10%:

- Cardiovascular: Hypotension (15% to 32%), peripheral edema (13%), hypertension (11% to 15%), dysrhythmia/tachycardia/SVT (10% to 14%)
- Central nervous system: Fever (69% to 85%), chills (53%), fatigue (22% to 34%), headache (13% to 24%), dysthesias (15%), dizziness (12%)
- Dermatologic: Rash (13% to 40%), urticaria (16% to 30%), pruritus (14% to 24%)
- Gastrointestinal: Nausea (47% to 54%), vomiting (33% to 41%), anorexia (20%), diarrhea (10% to 22%), stomatitis/mucositis (14%), abdominal pain (11%)
- Hematologic: Lymphopenia (grades 3/4: 97%), neutropenia (77% to 85%; grade 3/4: 42% to 70%; median duration: 28 days), anemia (76% to 80%; grade 3/4: 13% to 47%), thrombocytopenia (71% to 72%; grade 3/4: 13% to 52%; median duration: 21 days)
- Local: Injection site reaction (SubQ administration: 90%)
- Neuromuscular & skeletal: Rigors (86% to 89%), skeletal pain (24%), weakness (13%), myalgia (11%)
- Respiratory: Dyspnea (14% to 26%), cough (25%), bronchitis/pneumonitis (21%), pneumonia (16%), pharyngitis (12%)
- Miscellaneous: Infection (43% to 74%; grades 3/4: 21% to 37%; incidence is lower if prophylactic anti-infectives are utilized), CMV viremia (55%), infusion reactions (grades 3/4: 10% to 35%), diaphoresis (19%), CMV infection (16%), sepsis (15%), herpes viral infections (1% to 11%)

1% to 10%:

- Cardiovascular: Chest pain (10%)
- Central nervous system: Insomnia (10%), malaise (9%), anxiety (8%), depression (7%), temperature change sensation (5%), somnolence (5%)
- Dermatologic: Purpura (8%), erythema (4%)
- Gastrointestinal: Dyspepsia (10%), constipation (9%)
- Hematologic: Neutropenic fever (10%), pancytopenia/marrow hypoplasia (5% to 6%; grade 3/4: 3%), positive Coombs' test without hemolysis (2%), autoimmune thrombocytopenia (2%), autoimmune hemolytic anemia (1%)
- Neuromuscular & skeletal: Back pain (10%), tremor (3% to 7%)
- Respiratory: Bronchospasm (9%), epistaxis (7%), rhinitis (7%)
- Miscellaneous: Moniliasis (8%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Acidosis, acute renal failure, acute respiratory distress syndrome, agranulocytosis, alkaline phosphatase increased, allergic reactions, anaphylactoid reactions, angina pectoris, angioedema, anuria, aphasia, aplastic anemia, arrhythmia, ascites, asthma, atrial fibrillation, bacterial infection, biliary pain, bone marrow aplasia, bullous eruption, capillary fragility, cardiac arrest, cardiac failure, cardiac insufficiency, cardiomyopathy, cellulitis, cerebral hemorrhage, cerebrovascular disorder, chronic inflammatory demyelinating polyradiculoneuropathy, coagulation abnormality, colitis, coma, COPD, coronary artery disorder, cyanosis, deep vein thrombosis, dehydration, diabetes mellitus exacerbation, disseminated intravascular coagulation (DIC), duodenal ulcer, ejection fraction decreased, endophthalmitis, Epstein-Barr virus associated lymphoproliferative disorder, esophagitis, fluid overload, flu-like syndrome, gastrointestinal hemorrhage, Goodpasture’s syndrome, Graves' disease, Guillain-Barré syndrome, hallucinations, hematemesis, hematoma, hematuria, hemolysis, hemolytic anemia, hemoptysis, hepatic failure, hepatocellular damage, hyperbilirubinemia, hyper-/hypoglycemia, hyper-/hypokalemia, hyperthyroidism, hypoalbuminemia, hyponatremia, hypovolemia, hypoxia, idiopathic thrombocytopenic purpura (ITP), interstitial pneumonitis, intestinal obstruction, intestinal perforation, intracranial hemorrhage, *Legionella* pneumonia, *Listeria* meningitis, lymphadenopathy, marrow depression, melena, MI, mouth edema, myositis, optic neuropathy, osteomyelitis, pancreatitis, paralysis, paralytic ileus, paroxysmal nocturnal hemoglobinuria-like monocytes, peptic ulcer, pericarditis, peritonitis, plasma cell dyscrasia, phlebitis, pleural effusion, pleurisy, *Pneumocystis jiroveci* pneumonia, pneumothorax, polymyositis, progressive multifocal leukoencephalopathy, pseudomembranous colitis, pulmonary edema, pulmonary embolism, pulmonary fibrosis, pulmonary infiltration, pure red cell aplasia, purpuric rash, renal dysfunction, respiratory alkalosis, respiratory arrest, respiratory depression, respiratory insufficiency, seizure (grand mal), serum sickness, splenic infarction, splenomegaly, stridor, subarachnoid hemorrhage, syncope, toxic nephropathy, thrombocythemia, thrombophlebitis, throat tightness, tuberculosis, tumor lysis syndrome, ureteric obstruction, urinary retention, urinary tract infection, ventricular arrhythmia, ventricular tachycardia, viral meningitis

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

Abciximab: May enhance the potential for allergic or hypersensitivity reactions to Monoclonal Antibodies. Also may cause thrombocytopenia or diminished therapeutic effects. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Echinacea may diminish the therapeutic effect of alemtuzumab.
Test InteractionsMay interfere with diagnostic serum tests that utilize antibodies.
Monitoring ParametersVital signs; carefully monitor BP especially in patient with ischemic heart disease or on antihypertensive medications; CBC with differential and platelets (weekly); signs and symptoms of infection; CD4$^+$ lymphocyte counts (after treatment until recovery). Monitor closely for infusion reactions (including hypotension, rigors, fever, shortness of breath, bronchospasm, chills, and/or rash).
Nursing: Physical Assessment/MonitoringSee Warnings/Precautions and Contraindications for extensive use cautions. Note preinfusion medication instructions (see Administration). Monitor closely for alterations in blood pressure (especially in patients with heart disease or on antihypertensive medications) and/or infusion-related reactions during and for several hours following infusion. Assess knowledge/teach patient to monitor closely for postinfusion adverse reactions, appropriate interventions to reduce side effects, and symptoms to report (see Patient Education). **Pregnancy risk C** - benefits of use should outweigh possible risks. Breast-feeding is contraindicated.
Monitoring: Lab TestsCBC with differential and platelets; CD4$^+$ lymphocyte counts
Patient EducationThis medication can only be administered I.V. During infusion, you will be closely monitored. You will need frequent laboratory tests during course of therapy. Do not use any prescription or OTC medications unless approved by your prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition (small, frequent meals will help). You may experience abdominal pain, mouth sores, nausea, or vomiting (small, frequent meals, good mouth care with soft toothbrush or swabs, sucking lozenges or chewing gum, and avoidance of spicy or salty foods may help). Report unresolved GI problems, persistent fever, chills, muscle pain, skin rash, unusual bleeding or bruising, signs of infection (mouth sores, sore throat, white plaques in mouth or perianal area, burning on urination); swelling of extremities; respiratory difficulty; chest pain or palpitations; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Campath®: 30 mg/mL (1 mL) [contains polysorbate 80; disodium edetate]

Generic AvailableNo
ManufacturerBerlex Laboratories, Inc
Mechanism of ActionBinds to CD52, a nonmodulating antigen present on the surface of B and T lymphocytes, a majority of monocytes, macrophages, NK cells, and a subpopulation of granulocytes. After binding to CD52$^+$ cells, an antibody-dependent lysis of leukemic cells occurs.
Pharmacodynamics/Kinetics

Distribution: V_d: 0.1-0.4 L/kg

Metabolism: Clearance decreases with repeated dosing (due to loss of CD52 receptors in periphery), resulting in a sevenfold increase in AUC.

Half-life elimination: 11 hours (following first 30 mg dose; range: 2-32 hours); 6 days (following the last 30 mg dose; range: 1-14 days)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis and mucositis.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusFatigue is common; may cause dizziness, depression, insomnia
Mental Health: Effects on Psychiatric TreatmentHypotension is common; concurrent use with psychotropics may produce additive hypotensive effects; monitor. Nausea, vomiting, and diarrhea are common; may be additive when used with SSRIs; monitor. Neutropenia is common; use caution with clozapine and carbamazepine.
Index TermsC1H; Campath-1H; Humanized IgG1 Anti-CD52 Monoclonal Antibody; NSC-715969
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International Brand NamesCampath (AR, PE, UY); MabCampath (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, MY, NL, NO, PT, RU, SE, SG, TR, ZA); Mabcampath (PL)

Alendronate and Cholecalciferol

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Special Alerts

Bisphosphonates: Safety Update Regarding Possible Association With Atrial Fibrillation - November 2008

The Food and Drug Administration (FDA) has been reviewing placebo-controlled trials of the 7 bisphosphonates currently marketed in the US. This review is in response to study results associating an increased incidence of atrial fibrillation (AF) with alendronate or zoledronic acid use in women (65-89 years of age) with osteoporosis.

The FDA reviewed all the submitted data (19,687 bisphosphonate-treated patients and 18,358 placebo-treated patients) from these studies. Overall, the occurrence of AF was rare in each study with an absolute difference in event rates between each of the bisphosphonate and placebo arms of 0-3 per 1000. A zoledronic acid study showed a statistically significant increase in the rate of AF in the active treatment arm. However, no clear association between bisphosphonate use and AF could be established. In this study, AF events were diagnosed more than 30 days after receiving zoledronic acid in 47 of the 50 patients diagnosed with AF. According to the FDA, healthcare providers should not alter their prescribing patterns for bisphosphonates and patients should not stop taking their medication.

The FDA will continue monitoring the safety of bisphosphonates through postmarketing reports and is assessing the need for additional epidemiologic studies.

Further information is available at http://www.fda.gov/cder/drug/early_comm/bisphosphonates_update_200811.htm

Bisphosphonates: Possible Association with Severe Musculoskeletal Pain - January 2008

The Food and Drug Administration (FDA) is informing healthcare practitioners of the possible association between bisphosphonate use and the development of severe (possibly incapacitating) bone, muscle, and/or joint pain. The severe musculoskeletal pain may develop days, months, or years after initiating a bisphosphonate. This is a distinct event from the acute phase response (eg, fever, chills, bone pain, myalgia, arthralgia) that may occur following initial bisphosphonate administration which generally resolves within several days of continued use.

Frequency of and contributing risk factors between severe musculoskeletal pain and bisphosphonate use are currently unknown.

Further information is available at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Bisphosphonates

Pronunciation (a LEN droe nate & kole e kal SI fer ole)

U.S. Brand Names Fosamax Plus D™

Canadian Brand Names Fosavance

Pharmacologic Category Bisphosphonate Derivative; Vitamin D Analog

Use: Labeled Indications Treatment of osteoporosis in postmenopausal females; increase bone mass in males with osteoporosis

Dosing: Adults **Osteoporosis:** Oral: One tablet (alendronate 70 mg/cholecalciferol 2800 int. units **or** alendronate 70 mg/cholecalciferol 5600 int. units) once weekly. Appropriate dose in most osteoporotic women or men: Alendronate 70 mg/cholecalciferol 5600 int. units once weekly.

Dosing: Elderly Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 35-60 mL/minute: No adjustment needed.

Cl_{cr} <35 mL/minute: Not recommended.

Dosing: Hepatic Impairment Alendronate: None necessary. Cholecalciferol: May not be adequately absorbed in patients who have malabsorption due to inadequate bile production.

Calculations

- Creatinine Clearance: Adults

Administration: Oral Alendronate must be taken with plain water (6-8 oz) first thing in the morning and ≥30 minutes before the first food, beverage, or other medication of the day. Patient should be instructed to stay upright (not to lie down) for at least 30 minutes and until after first food of the day (to reduce esophageal irritation).

Dietary Considerations Ensure adequate calcium and vitamin D intake; supplemental calcium should be provided in patients whose dietary intake is inadequate. Recommended intake of vitamin D is 400-800 int. units daily. Certain patients may require additional vitamin D supplementation, particularly patients at risk for vitamin D deficiency (eg, malabsorption syndromes, chronically ill, >70 years of age).

Consider monitoring 25-hydroxy vitamin D in patients with malabsorption syndromes. Wait at least 30 minutes after taking alendronate with cholecalciferol before taking any supplement. Must be taken with at least 6-8 oz. plain water first thing in the morning and at least 30 minutes before the first food or beverage of the day. Administer with plain water only; do not administer with mineral-enriched water.

StorageStore at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture and light. Keep sealed in blister container or original bottle (with desiccant) until use.

ContraindicationsHypersensitivity to alendronate, other bisphosphonates, vitamin D derivatives, or any component of the formulation; hypocalcemia; abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia; inability to stand or sit upright for at least 30 minutes

Warnings/Precautions

Concerns related to adverse effects:

- Bone/joint/muscle pain: Severe (and occasionally debilitating) bone, joint, and/or muscle pain have been reported during bisphosphonate treatment. The onset of pain ranged from a single day to several months. Symptoms usually resolve upon discontinuation. Some patients experienced recurrence when rechallenged with same drug or another bisphosphonate; avoid use in patients with a history of these symptoms in association with bisphosphonate therapy. Discontinue use if severe symptoms occur.

- Gastrointestinal mucosa irritation: May cause irritation to upper gastrointestinal mucosa. Esophagitis, esophageal ulcers, esophageal erosions, and esophageal stricture (rare) have been reported with oral bisphosphonates; risk increases in patients unable to comply with dosing instructions. Use with caution in patients with dysphagia, esophageal disease, gastritis, duodenitis, or ulcers (may worsen underlying condition).

- Osteonecrosis of the jaw: Bisphosphonate therapy has been associated with osteonecrosis, primarily of the jaw; this has been observed mostly in cancer patients, but also in patients with postmenopausal osteoporosis and other diagnoses. Risk factors include a diagnosis of cancer, with concomitant chemotherapy, radiotherapy, or corticosteroids; anemia, coagulopathy, infection or pre-existing dental disease. Symptoms included nonhealing extraction socket or an exposed jawbone. There are no data addressing whether discontinuation of therapy reduces the risk of developing osteonecrosis. However, as a precautionary measure, dental exams and preventative dentistry should be performed prior to placing patients with risk factors on chronic bisphosphonate therapy. Invasive dental procedures should be avoided during treatment.

Disease-related concerns:

- Gastrointestinal malabsorption syndrome: Increased doses of vitamin D supplementation may be required in patients with GI malabsorption syndrome; consider monitoring 25-hydroxy vitamin D levels.

- Hypercalcemia: May exacerbate hypercalcemia and/or hypercalciuria in certain disease states (eg, leukemia, lymphoma, sarcoidosis); monitor serum and urine calcium levels.

- Hypocalcemia/vitamin D deficiency: Before therapy initiation hypocalcemia and/or vitamin D deficiency must be corrected; ensure adequate calcium and vitamin D intake. Do not use to treat vitamin D deficiency.

- Renal impairment: Use with caution in patients with renal impairment (not recommended for use in patients with Cl_{cr} <35 mL/minute).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have shown delays in delivery and fetal/neonatal death (secondary to hypocalcemia). Bisphosphonates are incorporated into the bone matrix and gradually released over time. Theoretically, there may be a risk of fetal harm when pregnancy follows the completion of therapy. No animal data are available for the use of cholecalciferol in pregnancy; however, high-dose ergocalciferol has demonstrated abortifacient properties and aortic abnormalities in rabbits. There are no adequate and well-controlled studies in pregnant women.

LactationCholecalciferol enters breast milk; excretion of alendronate in breast milk unknown/use caution

Adverse ReactionsSee individual agents.

Drug Interactions

Aminoglycosides: May enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Magaldrate; Sodium Bicarbonate. *Risk D: Consider therapy modification*

Aspirin: May enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Calcium Salts: May decrease the absorption of Bisphosphonate Derivatives. *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral iron salts are of concern. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Phosphate Supplements: Bisphosphonate Derivatives may enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsSee individual agents.

Test InteractionsBisphosphonates may interfere with diagnostic imaging agents such as technetium-99m-diphosphonate in bone scans.

Monitoring ParametersAlkaline phosphatase (measured periodically); urine and serum calcium, serum phosphorus, serum 25-hydroxy vitamin D; monitor pain and fracture rate; hormonal status (male and female) prior to therapy; bone mineral density (should be done prior to initiation of therapy and after 6-12 months of combined glucocorticoid and alendronate treatment)

Reference Range

Calcium (total): Adults: 9.0-11.0 mg/dL (2.05-2.54 mmol/L), may slightly decrease with aging

Phosphorus: 2.5-4.5 mg/dL (0.81-1.45 mmol/L)

25-hydroxyvitamin D: 10-80 ng/mL (higher during summer)

Nursing: Physical Assessment/MonitoringSee individual agent for Alendronate.

Monitoring: Lab TestsAlkaline phosphatase (measured periodically); urine and serum calcium, serum phosphorus, serum 25-hydroxy vitamin D

Patient EducationSee individual agent for Alendronate.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Fosamax Plus D™ 70/2800: Alendronate 70 mg and cholecalciferol 2800 int. units

Fosamax Plus D™ 70/5600: Alendronate 70 mg and cholecalciferol 5600 int. units

Generic AvailableNo

Manufacturer

Merck and Co, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Fosamax Plus D)

70-2800 mg-unit (4): $86.99

70-5600 mg-unit (4): $82.99

Mechanism of ActionSee individual agents.

Related Information

- Alendronate
- Cholecalciferol

Dental Health Professional ConsiderationsSee Alendronate monograph.

Dental Health: Effects on Dental TreatmentOsteonecrosis of the jaw (ONJ), generally associated with local infection and/or tooth extraction and often with delayed healing, has been reported in patients taking bisphosphonates. Symptoms included nonhealing extraction socket or an exposed jawbone. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates. However, some have occurred in patients with postmenopausal osteoporosis taking oral bisphosphonates. Dental surgery may exacerbate ONJ. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Patients who develop ONJ while on bisphosphonate therapy should receive care by an oral surgeon. See Dental Comment in Alendronate monograph.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause irritability or sedation; rarely associated with psychosis

Mental Health: Effects on Psychiatric TreatmentSymptoms of overdose are similar to those associated with lithium side effects/toxicity and psychogenic polydipsia.

Index TermsAlendronate Sodium and Cholecalciferol; Cholecalciferol and Alendronate; Vitamin D_3 and Alendronate

References

Ruggiero SL, Mehrotra B, Rosenberg TJ, et al, “Osteonecrosis of the Jaws Associated With the Use of Bisphosphonates: A Review of 63 Cases,” *J Oral Maxillofac Surg*, 2004, 62(5):527-34. [PubMed 15122554]

International Brand NamesFosamax Plus (AR, CN, EC, HK, ID, KP, MX, MY, NZ, SG, TW); Fosavance (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PH, PT, RU, SE, TR); Maximus (PE)

Alendronate

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Special Alerts

Bisphosphonates: Safety Update Regarding Possible Association With Atrial Fibrillation - November 2008

The Food and Drug Administration (FDA) has been reviewing placebo-controlled trials of the 7 bisphosphonates currently marketed in the US. This review is in response to study results associating an increased incidence of atrial fibrillation (AF) with alendronate or zoledronic acid use in women (65-89 years of age) with osteoporosis.

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The FDA will continue monitoring the safety of bisphosphonates through postmarketing reports and is assessing the need for additional epidemiologic studies.

Further information is available at http://www.fda.gov/cder/drug/early_comm/bisphosphonates_update_200811.htm

Bisphosphonates: Possible Association with Severe Musculoskeletal Pain - January 2008

The Food and Drug Administration (FDA) is informing healthcare practitioners of the possible association between bisphosphonate use and the development of severe (possibly incapacitating) bone, muscle, and/or joint pain. The severe musculoskeletal pain may develop days, months, or years after initiating a bisphosphonate. This is a distinct event from the acute phase response (eg, fever, chills, bone pain, myalgia, arthralgia) that may occur following initial bisphosphonate administration which generally resolves within several days of continued use.

Frequency of and contributing risk factors between severe musculoskeletal pain and bisphosphonate use are currently unknown.

Further information is available at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Bisphosphonates

Medication Safety Issues

Sound-alike/look-alike issues:

Fosamax® may be confused with Flomax®

International issues:

Fosamax® may be confused with Fisamox® which is a brand name for amoxicillin in Australia

Pronunciation(a LEN droe nate)

U.S. Brand NamesFosamax®

Canadian Brand NamesApo-Alendronate®; CO Alendronate; Dom-Alendronate; Fosamax®; Gen-Alendronate; Novo-Alendronate; PHL-Alendronate; PHL-Alendronate-FC; PMS-Alendronate; PMS-Alendronate-FC; ratio-Alendronate; Riva-Alendronate; Sandoz Alendronate

Pharmacologic CategoryBisphosphonate Derivative

Use: Labeled IndicationsTreatment and prevention of osteoporosis in postmenopausal females; treatment of osteoporosis in males; Paget's disease of the bone in patients who are symptomatic, at risk for future complications, or with alkaline phosphatase ≥2 times the upper limit of normal; treatment of glucocorticoid-induced osteoporosis in males and females with low bone mineral density who are receiving a daily dosage ≥7.5 mg of prednisone (or equivalent)

Dosing: Adults**Note:** Patients treated with glucocorticoids and those with Paget's disease should receive adequate amounts of calcium and vitamin D.

Osteoporosis in postmenopausal females: Oral:

Prophylaxis: 5 mg once daily **or** 35 mg once weekly

Treatment: 10 mg once daily **or** 70 mg once weekly

Osteoporosis in males: Oral: 10 mg once daily **or** 70 mg once weekly

Osteoporosis secondary to glucocorticoids in males and females: Oral: Treatment: 5 mg once daily; a dose of 10 mg once daily should be used in postmenopausal females who are not receiving estrogen.

Paget's disease of bone in males and females: Oral: 40 mg once daily for 6 months

Retreatment: Relapses during the 12 months following therapy occurred in 9% of patients who responded to treatment. Specific retreatment data are not available. Following a 6-month post-treatment evaluation period, treatment with alendronate may be considered in patients who have relapsed based on increases in serum alkaline phosphatase, which should be measured periodically. Retreatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 35-60 mL/minute: None necessary.

Cl_{cr} <35 mL/minute: Alendronate is not recommended due to lack of experience.

Dosing: Hepatic ImpairmentNo adjustment necessary.

Calculations

- Creatinine Clearance: Adults

Administration: OralAlendronate must be taken with plain water (tablets 6-8 oz; oral solution follow with 2 oz) first thing in the morning and ≥30 minutes before the first food, beverage, or other medication of the day. Do not take with mineral water or with other beverages. Patients should be instructed to stay upright (not to lie down) for at least 30 minutes **and** until after first food of the day (to reduce esophageal irritation). Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.

Dietary ConsiderationsEnsure adequate calcium and vitamin D intake; however, wait at least 30 minutes after taking alendronate before taking any supplement. Alendronate must be taken with plain water first thing in the morning and at least 30 minutes before the first food or beverage of the day.

StorageStore tablets and oral solution at room temperature of 15°C to 30°C (59°F to 86°F). Keep in well-closed container.

ContraindicationsHypersensitivity to alendronate, other bisphosphonates, or any component of the formulation; hypocalcemia; abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia; inability to stand or sit upright for at least 30 minutes; oral solution should not be used in patients at risk of aspiration

Allergy Considerations

- Bisphosphonate Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bone/joint/muscle pain: Severe (and occasionally debilitating) bone, joint, and/or muscle pain have been reported during bisphosphonate treatment. The onset of pain ranged from a single day to several months. Symptoms usually resolve upon discontinuation. Some patients experienced recurrence when rechallenged with same drug or another bisphosphonate; avoid use in patients with a history of these symptoms in association with bisphosphonate therapy. Discontinue use if severe symptoms occur.

- Gastrointestinal mucosa irritation: May cause irritation to upper gastrointestinal mucosa. Esophagitis, esophageal ulcers, esophageal erosions, and esophageal stricture (rare) have been reported with oral bisphosphonates; risk increases in patients unable to comply with dosing instructions. Use with caution in patients with dysphagia, esophageal disease, gastritis, duodenitis, or ulcers (may worsen underlying condition).

- Osteonecrosis of the jaw: Bisphosphonate therapy has been associated with osteonecrosis, primarily of the jaw; this has been observed mostly in cancer patients, but also in patients with postmenopausal osteoporosis and other diagnoses. Risk factors include a diagnosis of cancer, with concomitant chemotherapy, radiotherapy, or corticosteroids; anemia, coagulopathy, infection, or pre-existing dental disease. Symptoms included nonhealing extraction socket or an exposed jawbone. There are no data addressing whether discontinuation of therapy reduces the risk of developing osteonecrosis; however, as a precautionary measure, dental exams and preventative dentistry should be performed prior to placing patients with risk factors on chronic bisphosphonate therapy. Invasive dental procedures should be avoided during treatment.

Disease-related concerns:

- Hypocalcemia: Before therapy initiation hypocalcemia must be corrected; ensure adequate calcium and vitamin D intake.

- Renal impairment: Use with caution in patients with renal impairment (not recommended for use in patients with Cl_{cr} <35 mL/minute).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsSince many elderly patients receive diuretics, evaluation of electrolyte status (calcium, phosphate, magnesium, potassium) may need to be done periodically due to the drug class (bisphosphonate).

Pregnancy Risk FactorC

Pregnancy ConsiderationsSafety and efficacy have not been established in pregnant women. Animal studies have shown delays in delivery and fetal/neonatal death (secondary to hypocalcemia). Bisphosphonates are incorporated into the bone matrix and gradually released over time. Theoretically, there may be a risk of fetal harm when pregnancy follows the completion of therapy. Based on limited case reports with pamidronate, serum calcium levels in the newborn may be altered if administered during pregnancy.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**Note:** Incidence of adverse effects (mostly GI) increases significantly in patients treated for Paget's disease at 40 mg/day.

>10%: Endocrine & metabolic: Hypocalcemia (transient, mild, 18%); hypophosphatemia (transient, mild, 10%)

1% to 10%:

Cardiovascular: Atrial fibrillation (1% to 2%)

Central nervous system: Headache (up to 3%)

Gastrointestinal: Abdominal pain (1% to 7%), acid reflux (1% to 4%), dyspepsia (1% to 4%), nausea (1% to 4%), flatulence (up to 4%), diarrhea (1% to 3%), gastroesophageal reflux disease (1% to 3%), constipation (up to 3%), esophageal ulcer (up to 2%), abdominal distension (up to 1%), gastritis (up to 1%), vomiting (up to 1%), dysphagia (up to 1%), gastric ulcer (1%), melena (1%)

Neuromuscular & skeletal: Musculoskeletal pain (up to 6%), muscle cramps (up to 1%)

<1%, postmarketing, and/or case reports: Alopecia, anastomotic ulcer, angioedema; bone, muscle, or joint pain (occasionally severe, considered incapacitating in rare cases); dizziness, duodenal ulcer, episcleritis, erythema, esophageal erosions, esophageal perforation, esophageal stricture, esophagitis, fever, flu-like syndrome, hypersensitivity reactions, hypocalcemia (symptomatic), joint swelling, lymphocytopenia, malaise, myalgia, oropharyngeal ulceration, osteonecrosis (jaw), peripheral edema, photosensitivity (rare), pruritus, rash, scleritis (rare), Stevens-Johnson syndrome, taste perversion, toxic epidermal necrolysis, urticaria, uveitis (rare), vertigo, weakness

Drug Interactions

Aminoglycosides: May enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Magaldrate; Sodium Bicarbonate. *Risk D: Consider therapy modification*

Aspirin: May enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Calcium Salts: May decrease the absorption of Bisphosphonate Derivatives. *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral iron salts are of concern. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Phosphate Supplements: Bisphosphonate Derivatives may enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase risk of osteoporosis and gastric irritation).

Food: All food and beverages interfere with absorption. Coadministration with caffeine may reduce alendronate efficacy. Coadministration with dairy products may decrease alendronate absorption. Beverages (especially orange juice and coffee) and food may reduce the absorption of alendronate as much as 60%.

Test InteractionsBisphosphonates may interfere with diagnostic imaging agents such as technetium-99m-diphosphonate in bone scans.

Monitoring ParametersAlkaline phosphatase should be periodically measured; serum calcium and phosphorus; monitor pain and fracture rate; hormonal status (male and female) prior to therapy; bone mineral density (should be done prior to initiation of therapy and after 6-12 months of combined glucocorticoid and alendronate treatment)

Reference RangeCalcium (total): Adults: 9.0-11.0 mg/dL (2.05-2.54 mmol/L), may slightly decrease with aging; phosphorus: 2.5-4.5 mg/dL (0.81-1.45 mmol/L)

Nursing: Physical Assessment/MonitoringAssess history for any previous adverse response to bisphosphonates and ability to comply with administration instructions. Use caution with renal impairment. Correct any hypocalcemia prior to beginning treatment. Patients at risk for osteonecrosis (eg, chemotherapy, corticosteroids, poor oral hygiene) should have dental exams and necessary preventive dentistry should be done before beginning bisphosphonate therapy. Assess results of periodic laboratory tests, therapeutic effectiveness (eg, pain, fracture rate, bone density), and adverse reactions (eg, immediate or long-term musculoskeletal pain). Teach appropriate use and specific administration directions, lifestyle and dietary changes that will have a beneficial impact on Paget's disease or osteoporosis, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsAlkaline phosphatase should be periodically measured; serum calcium and phosphorus; hormonal status (male and female) prior to therapy; bone mineral density (should be done prior to initiation of therapy and after 6-12 months of combined glucocorticoid and alendronate treatment)

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, with a full glass of water first thing in the morning and at least 30 minutes before the first food or beverage of the day. Wait at least 30 minutes after taking Alendronate before taking anything else. Stay in sitting or standing position for 30 minutes following administration and until after the first food of the day to reduce potential for esophageal irritation. Consult prescriber to determine necessity of lifestyle changes (eg, decreased smoking, decreased alcohol intake, dietary supplements of calcium or vitamin D). May cause flatulence, bloating, nausea, or acid regurgitation; small, frequent meals may help. Bone, joint, and/or muscle pain have been reported, especially at the beginning of treatment; report persistent pain to prescriber. Report acute headache or gastric pain, unresolved GI upset, or acid stomach. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral:

Fosamax®: 70 mg/75 mL [contains parabens; raspberry flavor]

Tablet: 5 mg, 10 mg, 35 mg, 40 mg, 70 mg

Fosamax®: 5 mg, 10 mg, 35 mg, 40 mg, 70 mg

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Solution (Fosamax)

70 mg/75 mL (75): $30.99

Tablets (Alendronate Sodium)

5 mg (100): $255.98

10 mg (100): $234.99

35 mg (4): $49.99

70 mg (4): $32.99

Tablets (Fosamax)

5 mg (30): $85.99

10 mg (30): $88.99

35 mg (4): $81.99

70 mg (4): $83.99

Mechanism of ActionA bisphosphonate which inhibits bone resorption via actions on osteoclasts or on osteoclast precursors; decreases the rate of bone resorption, leading to an indirect increase in bone mineral density. In Paget's disease, characterized by disordered resorption and formation of bone, inhibition of resorption leads to an indirect decrease in bone formation; but the newly-formed bone has a more normal architecture.

Pharmacodynamics/Kinetics

Distribution: 28 L (exclusive of bone)

Protein binding: ~78%

Metabolism: None

Bioavailability: Fasting: 0.6%; reduced 60% with food or drink

Half-life elimination: Exceeds 10 years

Excretion: Urine; feces (as unabsorbed drug)

Dental Health Professional ConsiderationsA report by the Council of Scientific Affairs of the American Dental Association [(accessed at: http://www.ada.org/prof/resources/topics/osteonecrosis.asp)](http://www.ada.org/prof/resources/topics/osteonecrosis.asp) as of July 2006 gave an estimated incidence of 0.7 cases for every 100,000 person-years of exposure to alendronate (Fosamax®). This translates to one case for every 142,857 person-years exposure. This figure from the ADA report was based on information received from Merck & Co citing 170 worldwide cases for alendronate (Fosamax®). In addition, Procter & Gamble Pharmaceuticals has cited 20 cases for risedronate (Actonel®) and Roche Laboratories has cited one case for ibandronate (Boniva®).

Consumer Reports On Health stated that the risk of jaw bone osteoporosis due to alendronate (Fosamax®), risedronate (Actonel®), or ibandronate (Boniva®) taken to prevent osteoporosis is very low and is estimated to be one out of every 20,000 users. That report mentioned that tooth extraction or implants increase the risk of developing osteonecrosis in patients taking any of these drugs for osteoporosis. The report also recommended that patients should stop taking any of these oral drugs 1-2 months before and after such dental treatment. No evidence was presented to support this statement.

In terms of length of exposure to oral bisphosphonates prior to onset of ONJ, data from large population studies or controlled studies is lacking. A report by Marx et al, observed that of three cases of ONJ associated with Fosamax® exposure, one patient had been taking 10 mg/day by mouth for 6 years and the other two patients 10 mg/day by mouth for 3 and 2 years respectively. In contrast, they observed that in cancer patients receiving intravenous bisphosphonates, the time period between the first doses of the bisphosphonate to first recognition of exposed bone either by the patients or by the clinician, was 9.4 months for zoledronate (Zometa®), 14.3 months for pamidronate (Aredia®), and 12.1 months for pamidronate then to zoledronate.

Information on Fosamax® use in Australia and the incidence of ONJ has been reported. A survey form was sent to all of the Australian members of the Australian and New Zealand Association of Oral and Maxillofacial Surgeons requesting cases that they had identified as ONJ in 2004 and 2005. The definition of ONJ for the survey was an area of exposed bone in the jawbones that failed to heal within 6 weeks in patients taking bisphosphonates for bone disease. The frequency of ONJ in osteoporotic patients mainly on weekly oral alendronate was 1 in 8470 to 1 in 2260 (0.01% to 0.04%) patients. If extractions were carried out, the calculated frequency was 1 in 1130 to 1 in 296 (0.09% to 0.34%) patients. The minimum values in these cases were determined from the survey whereas the maximum values were obtained from the extrapolation to the entire Australia of the South Australian survey data. The median time to onset of ONJ in alendronate patients was 24 months.

A study from a Harvard group, shows that there may be a decrease in the incidence of ONJ in Fosamax® users compared to the normal population, and adds new data to the concerns about the Fosamax® user and the risk of developing ONJ. This new study used medical claims data from 714,217 people with osteoporosis or cancer to identify diagnostic codes or procedural codes for inflammatory conditions of the jaw, including osteonecrosis. Oral administration of bisphosphonates (BPs) decreased the risk of inflammatory conditions of the jaw. At the same time, intravenous administration significantly increased the risk of adverse jaw outcomes. While the data from the oral BPs counters previous reports, the intravenous BP data were consistent with reports showing the increased risk of ONJ after intravenous BP use in cancer patients.

The study, published in the Journal of the American Dental Association (Cartsos, 2008), collected data from the medical claims for inflammatory condition of the jaw (defined by the study authors as osteonecrosis of the jaw bone), from 2000-2006. There were 150 claims per 176,889 patients taking oral BPs, giving a ratio of 0.85 claims per 1000 individuals. Among patients with no BP association, there were more claims (339 claims per 263,352 patients) giving a ration of 1.3 claims per 1000 individuals. When statistics were used to calculate significance with a 95% confidence level, there was a definite decrease in the incidence of jaw bone adverse effects in the population taking oral BPs compared with those patients who did not take oral BPS.

Dental Health: Effects on Dental TreatmentOsteonecrosis of the jaw (ONJ), generally associated with local infection and/or tooth extraction and often with delayed healing, has been reported in patients taking bisphosphonates. Symptoms included nonhealing extraction socket or an exposed jawbone. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates. However, some have occurred in patients with postmenopausal osteoporosis taking oral bisphosphonates. Dental surgery may exacerbate ONJ. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Patients who develop ONJ while on bisphosphonate therapy should receive care by an oral surgeon. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause dizziness, weakness, and malaise

Mental Health: Effects on Psychiatric TreatmentMay produce GI side effects; concomitant use with SSRIs, carbamazepine, valproic acid, and lithium may produce additive effects

Index TermsAlendronate Sodium

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Mavrokokki T, Cheng A, Stein B, et al, “Nature and Frequency of Bisphosphonate-Associated Osteonecrosis of the Jaws in Australia,” *J Oral Maxillofac Surg*, 2007, 65(3):415-23.[PubMed 17307586]

Watts NB, “Treatment of Osteoporosis With Bisphosphonates,” *Rheum Dis Clin North Am*, 1994, 20(3):717-34.[PubMed 7984786]

International Brand NamesAldrox (CN); Alenato (AR); Alend (KP); Alendro (AU); Alenmax (KP); Alexonal (ID); Alnax (PY); Alond (KP); Alovell (ID); Arendal (PE); Armol (CO); Bifemelan (CO); Bifosa (IN); Bisbon (KP); Bonaid (KP); Bonapex (EG); Endronax (BR); Eucalen (CO); Fixopan (EC); Fosalan (IL); Fosamax (AR, AT, AU, BB, BE, BG, BM, BR, BS, BZ, CH, CL, CN, CR, CZ, DE, DK, EC, EE, EG, ES, FI, FR, GB, GR, GT, GY, HK, HN, ID, IE, IT, JM, KP, MX, MY, NI, NL, NO, PA, PE, PH, PK, SE, SG, SR, SV, TH, TT, TW, VE); Fosaqueen (KP); Fosmin (PE); Fosval (PY); Gendarin (SE); Marvil (PE, UY); MaxiBone (IL); MaxiBone 70 (IL); Neobon (CO); Nichospor (ID); Osdronat (CO); Oseotenk (AR); Osficar (CO); Osteofar (ID); Osteofos (HK, IN); Osteopor (UY); Osteosan (CN); Osteovan (CR); Osticalcin (CO); Porosal (VE); Tevanate (BG); Tibolene (CO); Voroste (ID)

Alfentanil

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Alfentanil may be confused with Anafranil®, fentanyl, remifentanil, sufentanil

Alfenta® may be confused with Sufenta®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(al FEN ta nil)

U.S. Brand NamesAlfenta®

Canadian Brand NamesAlfentanil Injection, USP; Alfenta®

Pharmacologic CategoryAnalgesic, Opioid; Anilidopiperidine Opioid

Use: Labeled IndicationsAnalgesic adjunct given by continuous infusion or in incremental doses in maintenance of anesthesia with barbiturate or N_2O or a primary anesthetic agent for the induction of anesthesia in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required

Dosing: AdultsDoses should be titrated to appropriate effects; wide range of doses is dependent upon desired degree of analgesia/anesthesia

Anesthesia: I.V.: Dose should be based on ideal body weight as follows (see table).

Alfentanil

Indication	**Approx Duration of Anesthesia (min)**	**Induction Period (Initial Dose) (mcg/kg)**	**Maintenance Period (Increments/ Infusion)**	**Total Dose (mcg/kg)**	**Effects**
Incremental injection	≤30	8-20	3-5 mcg/kg or 0.5-1 mcg/kg/min	8-40	Spontaneously breathing or assisted ventilation when required.
	30-60	20-50	5-15 mcg/kg	Up to 75	Assisted or controlled ventilation required. Attenuation of response to laryngoscopy and intubation.
Continuous infusion	>45	50-75	0.5-3 mcg/kg/min; average infusion rate 1-1.5 mcg/kg/min	Dependent on duration of procedure	Assisted or controlled ventilation required. Some attenuation of response to intubation and incision, with intraoperative stability.
Anesthetic induction	>45	130-245	0.5-1.5 mcg/kg/min or general anesthetic	Dependent on duration of procedure	Assisted or controlled ventilation required. Administer slowly (over 3 minutes). Concentration of inhalation agents reduced by 30% to 50% for initial hour.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Children <12 years: Dose has not been established.

Children ≥12 years: Refer to adult dosing.

Calculations

- Ideal Body Weight: Adults

Administration: I.V.Administer I.V. slowly over 3-5 minutes or by I.V. continuous infusion.
Administration: I.V. DetailpH: 4-6
StorageStore unopened ampuls at 20°C to 25°C (68°F to 77°F). Protect from light. For infusion, dilute in D$_5$W, NS, LR, or D$_5$NS to a concentration of 25-80 mcg/mL.
CompatibilityStable in D$_5$W, NS, LR, D$_5$NS.

Y-site administration: Compatible: Cisatracurium, etomidate, gatifloxacin, linezolid, propofol, remifentanil. **Incompatible:** Amphotericin B cholesteryl sulfate complex, thiopental.

Compatibility in syringe: Compatible: Atracurium, midazolam, ondansetron.

RestrictionsC-II
ContraindicationsHypersensitivity to alfentanil hydrochloride, to narcotics, or any component of the formulation; increased intracranial pressure, severe respiratory depression

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

- Opioid agonist toxicities: Shares the toxic potentials of opiate agonists, and precautions of opiate agonist therapy should be observed.

Disease-related concerns:

- Bradyarrhythmias: Use with caution when administering to patients with bradyarrhythmias.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Obesity: Use with caution in patients who are morbidly obese.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function.

Special populations:

- Neonates: Hypotension has occurred in neonates with respiratory distress syndrome.

- Pediatrics: Safety and efficacy have not been established in children <12 years old.

Other warnings/precautions:

- Rapid infusion: Inject slowly over 3-5 minutes; rapid I.V. infusion may result in skeletal muscle and chest wall rigidity, impaired ventilation, or respiratory distress/arrest; nondepolarizing skeletal muscle relaxant may be required.

- Trained individuals: Due to the high incidence of apnea, hypotension, tachycardia and muscle rigidity; it should be administered by individuals specifically trained in the use of anesthetic agents and should not be used in diagnostic or therapeutic procedures outside the monitored anesthesia setting; resuscitative and intubation equipment should be readily available.

Pregnancy Risk FactorC

Adverse Reactions

>10%:

Cardiovascular: Bradycardia, peripheral vasodilation

Central nervous system: Drowsiness, sedation, intracranial pressure increased

Gastrointestinal: Nausea, vomiting, constipation

Endocrine & metabolic: Antidiuretic hormone release

Ocular: Miosis

1% to 10%:

Cardiovascular: Cardiac arrhythmia, orthostatic hypotension

Central nervous system: Confusion, CNS depression

Ocular: Blurred vision

<1%: Convulsions, mental depression, paradoxical CNS excitation or delirium, dizziness, dysesthesia, rash, urticaria, itching, biliary tract spasm, urinary tract spasm, respiratory depression, bronchospasm, laryngospasm, physical and psychological dependence with prolonged use; cold, clammy skin

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Beta-Blockers: Anilidopiperidine Opioids may enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): Anilidopiperidine Opioids may enhance the bradycardic effect of Calcium Channel Blockers (Nondihydropyridine). Anilidopiperidine Opioids may enhance the hypotensive effect of Calcium Channel Blockers (Nondihydropyridine). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Alfentanil. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Diltiazem: May increase the serum concentration of Alfentanil. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Macrolide Antibiotics: May decrease the metabolism of Alfentanil. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

MAO Inhibitors: Anilidopiperidine Opioids may enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. *Risk D: Consider therapy modification*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Propofol: Alfentanil may enhance the adverse/toxic effect of Propofol. Specifically the development of opisthotonus and/or grand mal seizures. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Monitoring ParametersRespiratory rate, blood pressure, heart rate
Reference Range100-340 ng/mL (depending upon procedure)
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 500 mcg/mL (2 mL, 5 mL)

Alfenta®: 500 mcg/mL (2 mL, 5 mL, 10 mL, 20 mL)

Generic AvailableYes
Mechanism of ActionBinds with stereospecific receptors at many sites within the CNS, increases pain threshold, alters pain perception, inhibits ascending pain pathways; is an ultra short-acting narcotic

Pharmacodynamics/Kinetics

Onset of action: Rapid

Duration (dose dependent): 30-60 minutes

Distribution: V_d: Newborns, premature: 1 L/kg; Children: 0.163-0.48 L/kg; Adults: 0.46 L/kg

Half-life elimination: Newborns, premature: 5.33-8.75 hours; Children: 40-60 minutes; Adults: 83-97 minutes

Related Information

- Narcotic / Opioid Analgesics

Pharmacotherapy PearlsAlfentanil may produce more muscle rigidity compared to fentanyl, therefore, be sure to administer slowly.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension.

Erythromycin inhibits the liver metabolism of alfentanil resulting in increased sedation and prolonged respiratory depression. Clarithromycin may act similarly.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common, may see depression or confusion, rarely may cause seizures or delirium

Mental Health: Effects on Psychiatric TreatmentCNS depressant and beta-blockers may increase toxicity; phenothiazines may antagonize analgesic effect

Anesthesia and Critical Care Concerns/Other ConsiderationsAlfentanil may produce more muscle rigidity compared to fentanyl, therefore, be sure to administer slowly.

Index TermsAlfentanil Hydrochloride

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International Brand NamesAlfast (BR); Brevafen (AR); Fanaxal (ES); Fentalim (IT); Rapifen (AE, AT, AU, BE, BG, BH, BR, CH, CN, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, HK, HN, HR, HU, IE, IL, IQ, IR, IT, JO, KW, LB, LU, LY, NL, NO, OM, PL, PT, PY, QA, RU, SA, SE, SG, SY, TR, TW, UY, VE, YE, ZA)

Alfuzosin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(al FYOO zoe sin)
U.S. Brand NamesUroxatral®
Canadian Brand NamesXatral
Pharmacologic CategoryAlpha $_1$ Blocker
Use: Labeled IndicationsTreatment of the functional symptoms of benign prostatic hyperplasia (BPH)
Dosing: AdultsBenign prostatic hyperplasia (BPH): Oral: 10 mg once daily
Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentBioavailability and maximum serum concentrations are increased by ~50% with mild, moderate, or severe renal impairment.

Note: Safety has not been evaluated in patients with creatinine clearances <30 mL/minute.

Dosing: Hepatic Impairment

Mild hepatic impairment: Use has not been studied.

Moderate or severe hepatic impairment (Child-Pugh class B and C): Clearance is decreased $^1/_3$ to $^1/_4$ and serum concentration is increased three- to fourfold; use is contraindicated.

Calculations

- Creatinine Clearance: Adults

Administration: OralTablet should be swallowed whole; do not crush or chew. Administer once daily (with a meal); should be taken at the same time each day.
Dietary ConsiderationsTake following a meal at the same time each day.
StorageStore at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light and moisture.
ContraindicationsHypersensitivity to alfuzosin or any component of the formulation; moderate or severe hepatic insufficiency (Child-Pugh class B and C); concurrent use with potent CYP3A4 inhibitors (eg, itraconazole, ketoconazole, ritonavir)
Allergy Considerations

- Alpha-Blocker, Non-Quinazoline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Angina: Discontinue if symptoms of angina occur or worsen.
- Floppy iris syndrome: Intraoperative floppy iris syndrome has been observed in cataract surgery patients who were on or were previously treated with alpha$_1$-blockers; causality has not been established and there appears to be no benefit in discontinuing alpha-blocker therapy prior to surgery.
- Orthostatic hypotension/syncope: May cause significant orthostatic hypotension and syncope, especially with first dose; anticipate a similar effect if therapy is interrupted for a few days, if dosage is rapidly increased, or used with antihypertensives (particularly vasodilators), PDE-5 inhibitors, nitrates or other medications which may result in hypotension. Patients should be cautioned about performing hazardous tasks when starting new therapy or adjusting dosage upward.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with mild hepatic impairment; contraindicated in moderate to severe impairment.
- Prostate cancer: Rule out prostatic carcinoma before beginning therapy (many symptoms of BPH and prostate cancer are similar).
- QT prolongation: Alfuzosin has been shown to prolong the QT interval alone (minimal) and with other drugs with comparable effects on the QT interval (additive). Use with caution in patients with known QT prolongation (congenital or acquired).
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Pediatrics: Not indicated for use in children.

Other warning/precautions:

- Antihypertensive agent: Not intended for use as an antihypertensive drug.

Geriatric ConsiderationsAlfuzosin is a functionally uroselective alpha-blocker, therefore, having minimal effects on the cardiovascular system. Alfuzosin has been available in Europe for many years and appears to be well tolerated in elderly. In one study, orthostatic changes were minimal and not influenced by age.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; however, alfuzosin is not indicated for use in women.

LactationNot indicated for use in women

Adverse Reactions

1% to 10%:

Central nervous system: Dizziness (6%), fatigue (3%), headache (3%), pain (1% to 2%)

Gastrointestinal: Abdominal pain (1% to 2%), constipation (1% to 2%), dyspepsia (1% to 2%), nausea (1% to 2%)

Genitourinary: Impotence (1% to 2%)

Respiratory: Upper respiratory tract infection (3%), bronchitis (1% to 2%), pharyngitis (1% to 2%), sinusitis (1% to 2%)

<1%: Hypotension, postural hypotension, syncope

Postmarketing and/or case reports: Angina pectoris (pre-existing CAD), angioedema, chest pain, cholestatic liver injury, diarrhea, edema, flushing, intraoperative floppy iris syndrome (with cataract surgery), priapism, pruritus, rash, rhinitis, tachycardia, urticaria

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)

Drug Interactions

Alpha1-Blockers: May enhance the antihypertensive effect of Alfuzosin. Risk of orthostatic hypotension or syncope may be increased. Alfuzosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Alpha1-Blockers may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: May enhance the hypotensive effect of Alpha1-Blockers. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QTc-Prolonging Agents: Alfuzosin may enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tamsulosin: Alpha1-Blockers may enhance the antihypertensive effect of Tamsulosin. Risk of orthostatic hypotension or syncope may be increased. Tamsulosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Food increases the extent of absorption.

Herb/Nutraceutical: Avoid St John's wort (may decrease alfuzosin levels).

Monitoring ParametersUrine flow; blood pressure

Nursing: Physical Assessment/MonitoringProstatic carcinoma should be ruled out before beginning therapy. Assess for use cautions. Assess potential for interactions with other prescriptions, OTC medications, and herbal products patient may be taking. Monitor for patient response (eg, improved urine flow) and adverse reactions (hypotension) at beginning of therapy and on a regular basis with long-term therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take exactly as directed, with a meal at the same time each day. Swallow tablet whole; do not crush or chew. May cause drowsiness, dizziness, impaired judgment (use caution when driving or engaging in tasks that require alertness until response to drug is known), or postural hypotension (use caution when rising from sitting or lying position or when climbing stairs). Report unusual chest pain, respiratory difficulty, or any persistent adverse reactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, extended release, as hydrochloride:

Uroxatral®: 10 mg

Generic AvailableNo

ManufacturerSanofi-Synthelabo, Inc

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Uroxatral)

10 mg (30): $97.91

Mechanism of ActionAn antagonist of alpha$_1$-adrenoreceptors in the lower urinary tract. Smooth muscle tone is mediated by the sympathetic nervous stimulation of alpha$_1$-adrenoreceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenoreceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in BPH symptoms.

Pharmacodynamics/Kinetics

Absorption: Decreased 50% under fasting conditions

Distribution: V_d: 3.2 L/kg

Protein binding: 82% to 90%

Metabolism: Hepatic, primarily via CYP3A4; metabolism includes oxidation, O-demethylation, and N-dealkylation; forms metabolites (inactive)

Bioavailability: 49% following a meal

Half-life elimination: 10 hours

Time to peak, plasma: 8 hours following a meal

Excretion: Feces (69%); urine (24%; 11% as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentAlfuzosin may cause orthostasis. Concomitant use with psychotropics may produce additive effects on blood pressure. Use caution with thioridazine and ziprasidone; may prolong QT interval. Use caution with nefazodone; may increase levels of alfuzosin resulting in toxicity.

Index TermsAlfuzosin Hydrochloride

International Brand NamesAlfetim (HN); Alfusin (IN); Dalfaz (AR, ES, PL); Uroxatral (CN); Uroxatral OD (AR, UY); Uroxatral uno (CH, DE); Xatral (AT, BE, BF, BJ, CH, CI, CL, CZ, DK, ET, FI, FR, GB, GH, GM, GN, GR, IE, IL, IT, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, NO, SC, SD, SE, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Xatral LP (FR, HK); Xatral OD (BR, CO, CR, DO, EC, GT, HN, MX, NI, PA, PE, PH, PY, SE, SV, VE); Xatral SR (AT, BG, EE, EG, IL, PK, SG); Xatral XL (ID, IL, KP, SG, TH); Xatral XR 10 (SG)

Alglucerase

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Alglucerase may be confused with agalsidase alfa, agalsidase beta, alglucosidase alfa

Ceredase® may be confused with Cerezyme®

Pronunciation(al GLOO ser ase)
U.S. Brand NamesCeredase®
Pharmacologic CategoryEnzyme
Use: Labeled IndicationsReplacement therapy for Gaucher's disease (type 1)
Dosing: AdultsGaucher's disease: I.V.: Initial: 30-60 units/kg every 2 weeks; dosing is individualized based on disease severity; average dose: 60 units/kg every 2 weeks. Range: 2.5 units/kg 3 times/week to 60 units/kg once weekly to every 4 weeks. Once patient response is well established, dose may be reduced every 3-6 months to determine maintenance therapy.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Administration: I.V.Infuse I.V. over 1-2 hours; use of an in-line filter is recommended.
Administration: I.V. DetailEffective only via I.V. Filter during administration. Do not shake, shaking may render glycoprotein inactive. Dilute with NS only.
StorageRefrigerate (4°C), do not freeze. Contains no preservatives. Do not store opened vials for future use. Once diluted, 100 mL and 200 mL solutions for infusion are stable for 18 hours when stored at 2°C to 8°C.
ReconstitutionDilute with NS to a final volume ≤200 mL. Do not shake.
CompatibilityStable in NS; do not mix with any other additives.
ContraindicationsHypersensitivity to any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Patients who develop IgG antibodies may be at a higher risk for developing hypersensitivity. Use with caution in patients with prior allergies to hCG.

Disease-related concerns:

- Androgen-sensitive malignancies: Use with caution in patients with androgen-sensitive malignancies.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age (limited experience). May cause early virilization in males <10 years of age.

Dosage form specific issues:

- Placental tissue: Prepared from pooled human placental tissue that may contain the causative agents of some viral diseases.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies have not been conducted.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Peripheral edema

Central nervous system: Chills, fatigue, fever, headache, lightheadedness

Endocrine & metabolic: Hot flashes, menstrual abnormalities

Gastrointestinal: Abdominal discomfort, diarrhea, nausea, oral ulcerations, vomiting

Local: Injection site: Abscess, burning, discomfort, pruritus, swelling

Neuromuscular & skeletal: Backache, weakness

Miscellaneous: Dysosmia; hypersensitivity reactions (abdominal cramping, angioedema, chest discomfort, flushing, hypotension, nausea, pruritus, respiratory symptoms, urticaria); IgG antibody formation (~13%)

Drug InteractionsThere are no known significant interactions.
Test InteractionsFalse-positive pregnancy tests

Monitoring ParametersCBC, platelets, liver function tests, IgG antibody formation, acid phosphatase (AP); MRI or CT of liver and spleen, skeletal x-rays, physical exam every 6-12 months

Nursing: Physical Assessment/MonitoringUse caution with androgen-sensitive malignancies or prior allergies to hCG. Assess results of laboratory tests and therapeutic effectiveness (eg, energy level, change in bleeding tendency, reduced joint swelling, or bone pain). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC, platelets, acid phosphatase (AP), plasma glucocerebroside, IgG antibody formation

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. This medication will not cure Gaucher's disease, but rather, may help control it. Treatment is required for life. May cause abdominal discomfort, nausea, or vomiting (small, frequent meals, good mouth care, chewing gum, or sucking lozenges may help); these symptoms should go away with continued use. Inform prescriber if pain, swelling, or redness occurs at injection site or if GI symptoms persist. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Ceredase®: 80 units/mL (5 mL) [contains human albumin 1%]

Generic AvailableNo

Mechanism of ActionAlglucerase is a modified form of glucocerebrosidase; it is prepared from human placental tissue. Glucocerebrosidase is an enzyme deficient in Gaucher's disease. It is needed to catalyze the hydrolysis of glucocerebroside to glucose and ceramide.

Pharmacodynamics/KineticsHalf-life elimination: ~3-11 minutes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsGlucocerebrosidase

References

Barton NW, Brady RO, Dambrosia JM, et al, “Replacement Therapy for Inherited Enzyme Deficiency - Macrophage-Targeted Glucocerebrosidase for Gaucher's Disease,” *N Engl J Med*, 1991, 324(21):1464-70. [PubMed 2023606]

Charrow J, Andersson HC, Kaplan P, et al, “Enzyme Replacement Therapy and Monitoring for Children With Type 1 Gaucher Disease: Consensus Recommendations,” *J Pediatr*, 2004, 144(1):112-20. [PubMed 14722528]

Whittington R and Goa KL, “Alglucerase: A Review of Its Therapeutic Use in Gaucher's Disease,” *Drugs*, 1992, 44(1):72-93.[PubMed 1379912]

International Brand NamesCeredase (DE, ES, GB, NL)

Alglucosidase Alfa

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Alglucosidase alfa may be confused with agalsidase alfa, agalsidase beta, alglucerase

Pronunciation(al gloo KOSE i dase AL fa)

U.S. Brand NamesMyozyme®

Pharmacologic CategoryEnzyme

Use: Labeled IndicationsReplacement therapy for Pompe disease (infantile onset)

Dosing: PediatricReplacement therapy for Pompe disease (infantile onset): Children 1 month to 3.5 years (at first infusion): I.V.: 20 mg/kg over ~4 hours every 2 weeks

Administration: I.V.Infuse over ~4 hours; initiate at 1 mg/kg/hour. If tolerated, increase by 2 mg/kg/hour every 30 minutes to a maximum rate of 7 mg/kg/hour. Decrease rate or temporarily hold for infusion reactions. Infuse through a low protein-binding, 0.2 micron in-line filter.

StorageStore vials between 2°C and 8°C (36°F and 46°F); do not freeze. Protect from light. Allow vials to reach room temperature prior to reconstitution. Final solutions for infusion should be used immediately if possible, but may be stored for up to 24 hours between 2°C and 8°C (36°F and 46°F); do not freeze. Protect from light.

ReconstitutionReconstitute each vial with 10.3 mL SWFI. Inject slowly down internal side wall of vial (do not inject into powder; avoid foaming). Roll and tilt gently; do not invert, swirl, or shake. Resulting solution contains 5 mg/mL. To make final infusion, add the desired amount of reconstituted solution (based on patient weight) to 50-600 mL NS (do not use filter needle to prepare) to a final concentration of 0.5-4 mg/mL. Remove airspace from infusion bag prior to admixture to minimize particle formation due to sensitivity of drug to air-liquid interfaces. Do not shake.

CompatibilityStable in NS; do not infuse with other products.

ContraindicationsHypersensitivity to alglucosidase alfa or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Anaphylaxis/hypersensitivity reactions: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: **[U.S. Boxed Warning]: Severe hypersensitivity reactions, including anaphylactic reactions and anaphylactic shock have been reported during infusion. Immediate medical support should be readily available.**

- Infusion reactions: Infusion-related reactions are common; discontinue immediately for severe hypersensitivity or anaphylactic reaction; mild-to-moderate reactions may be managed by reducing the infusion rate and/or administering antihistamines and/or antipyretics. Appropriate medical support for the management of infusion reactions should be readily available. Use caution with subsequent infusions; infusion reactions have occurred despite premedication with antihistamines, antipyretics, and/or steroids. Patients with acute underlying illness are at greater risk for infusion reactions.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; may increase risk of infusion related reactions. Arrhythmias have been observed in patients with cardiac hypertrophy.

- Pompe disease: Safety and efficacy have not been established in juvenile-onset and adult-onset Pompe disease. Patients with Pompe disease are at increased risk for infusion-related cardiorespiratory failure (possibly due to fluid overload); monitor closely during infusion.

- Respiratory disease: Use with caution in patients with respiratory disease; may increase risk of infusion related reactions. Cardiorespiratory failure has been observed in patients with cardiac hypertrophy.

Other warnings/precautions:

- Registry: A registry has been created to monitor therapeutic responses and adverse effects during long-term treatment; patients should be encouraged to register (www.pompperegistry.com or 1-800-745-4447).

Pregnancy Risk FactorB

Pregnancy ConsiderationsAnimal studies have not demonstrated teratogenicity or fertility impairment. There are no adequate and well-controlled studies in pregnant women. A registry has been established for Pompe patients; women of childbearing potential are encouraged to enroll in the registry (www.pompperegistry.com or 1-800-745-4447).

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsA registry has been established for Pompe patients; women who are nursing are encouraged to enroll in the registry (www.pomperegistry.com or 1-800-745-4447)

Adverse Reactions

>20%:

Cardiovascular: Tachycardia (23%), bradycardia (21%), flushing (21%)

Central nervous system: Fever (92%), pain (postprocedural: 26%)

Dermatologic: Rash (54%), diaper dermatitis (36%), urticaria (21%)

Gastrointestinal: Diarrhea (62%), vomiting (49%), gastroenteritis (41%), oral candidiasis (31%), gastroesophageal reflux (26%), constipation (23%)

Hematologic: Anemia (31%)

Local: Catheter-related infections (28%)

Otic: Otitis media (33% to 44%)

Respiratory: Cough (46%), pneumonia (46%), upper respiratory tract infection (44%), oxygen saturation decreased (41%), pharyngitis (36%), respiratory distress (33%), respiratory failure (31%), rhinorrhea (28%), bronchiolitis (23%), nasopharyngitis (23%), tachypnea (23%)

Miscellaneous: Infusion reaction (51%)

≤20%, frequency not reported, and/or case reports: Abdominal pain, agitation, anaphylactic reactions, bronchospasm, cardiorespiratory failure, cyanosis, erythema, face edema, facial erythema, fluid overload, headache, hyperhidrosis, hypersensitivity, hyper-/hypotension, irritability, lacrimation increased, livedo reticularis, malaise, nausea, pallor, periorbital edema, pruritus, respiratory syncytial virus infection, restlessness, retching, rhinitis, rigors, tremor, wheezing

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersLiver enzymes (baseline and periodically; elevation may be due to disease process); vital signs during and following infusion; volume overload

Nursing: Physical Assessment/MonitoringPatient must be monitored closely during and following infusion for hypersensitivity reactions; life-threatening anaphylactic reactions (including anaphylactic shock) have been reported during infusion. Emergency response equipment should be readily available. Premedication with antihistamines and/or antipyretics may be ordered. Prescriber should be notified of any adverse reaction. Decrease rate or temporarily hold for infusion reaction. Teach patient/caregiver possible side effects and adverse symptoms to report. **Note:** A registry has been established for Pompe patients; women who are of childbearing potential or nursing should be encouraged to enroll in the registry.

Monitoring: Lab TestsLiver enzymes (baseline and periodically; elevation may be due to disease process)

Patient EducationThis medication can only be administered by intravenous infusion. Report immediately any redness, swelling, pain, or burning at infusion site, or any adverse response during infusion (eg, respiratory difficulty, facial edema, pain, restlessness, tremor, wheezing). Report rash, diarrhea or constipation; nausea or vomiting, change in appetite, mouth sores; respiratory distress, cough, respiratory tract infection or other adverse response that occurs between infusions. **Pregnancy/breast-feeding precautions:** Consult prescriber if you are or intend to be pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Myozyme®: 50 mg [contains mannitol 210 mg; polysorbate 80; derived from Chinese hamster ovary cells]

Generic AvailableNo

ManufacturerGenzyme Corporation

Mechanism of ActionAlglucosidase alfa is a recombinant form of the enzyme acid alpha-glucosidase (GAA), which is required for glycogen cleavage. Due to an inherited GAA deficiency, glycogen accumulates in the tissues of patients with Pompe disease, leading to progressive muscle weakness. In infantile-onset Pompe disease, glycogen accumulates in cardiac and skeletal muscles and hepatic tissue, leading to cardiomyopathy and respiratory failure. Juvenile- and adult-onset Pompe disease are limited to glycogen accumulation in skeletal muscle, leading to respiratory failure. Alglucosidase alfa binds to mannose-6-phosphate receptors on the cell surface, becomes internalized and transported to lysosomes resulting in increased enzymatic activity and glycogen cleavage.

Pharmacodynamics/Kinetics

Distribution: V_{ss}: 80-112 mL/kg

Half-life elimination: 2.3 hours

Pharmacotherapy PearlsPatients with sustained positive IgG antibody titers (≥12,800) to alglucosidase alfa may have poorer clinical response. Most patients (89%) develop antibodies within the first 3 months of therapy; concern is with patients with sustained high (≥12,800) antibody titers. Patients developing a decreased motor function should be tested for neutralization of enzyme uptake or activity. Infusion reactions are more common in antibody-positive patients. Patients with moderate-to-severe or recurrent reactions with suspected mast-cell activation may be tested for alglucosidase-alfa specific IgE antibodies.

Index TermsAlglucosidase; GAA; rhGAA

References

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Klinge L, Straub V, Neudorf U, et al, “Enzyme Replacement Therapy in Classical Infantile Pompe Disease: Results of a Ten-Month Follow-up Study,” *Neuropediatrics*, 2005, 36(1):6-11.[PubMed 15776317]

Klinge L, Straub V, Neudorf U, et al, “Safety and Efficacy of Recombinant Acid Alpha-Glucosidase (rhGAA) in Patients With Classical Infantile

Pompe Disease: Results of a Phase II Clinical Trial," *Neuromuscular Disorders*, 2005, 15(1):24-31.[PubMed 15639117]

International Brand Names Myozyme (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, NL, NO, PT, RU, SE, TR)

Aliskiren and Hydrochlorothiazide

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(a lis KYE ren & hye droe klor oh THYE a zide)

U.S. Brand NamesTekturna HCT®

Pharmacologic CategoryDiuretic, Thiazide; Renin Inhibitor

Use: Labeled IndicationsTreatment of hypertension (not recommended for initial treatment)

Dosing: AdultsHypertension: Oral: One tablet daily; dosage must be individualized (see below). May be substituted for previously titrated dosages of the individual components. Titrate at 2- to 4-week intervals as necessary.

Patients not controlled with single-agent therapy: Initiate by adding the lowest available dose of the alternative component (aliskiren 150 mg or hydrochlorothiazide 12.5 mg); titrate to effect (maximum daily aliskiren dose: 300 mg; maximum daily hydrochlorothiazide dose: 25 mg)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot recommended in patients with Cl_{cr} <30 mL/minute

Dosing: Hepatic ImpairmentDosage adjustment not required.

Calculations

- Creatinine Clearance: Adults

Administration: OralAdminister with or without meals.

Dietary ConsiderationsTake with or without meals; a high-fat meal reduces aliskiren absorption substantially.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to hydrochlorothiazide, thiazides, or sulfonamide-derived drugs; anuria

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: Since the effect of aliskiren on bradykinin levels is unknown, the risk of kinin-mediated etiologies of angioedema occurring is also unknown. Use caution in any patient with a history of angioedema (of any etiology) as angioedema has been observed (rarely) with aliskiren use. Discontinue immediately following any signs and symptoms of angioedema.

- Electrolyte disturbances: Hyperkalemia may occur with renin inhibitors; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Hypersensitivity reactions: Hypersensitivity reactions may occur with hydrochlorothiazide. Risk is increased in patients with a history of allergy or bronchial asthma.

- Hypotension: During the initiation of therapy, symptomatic hypotension may occur (rarely), particularly in volume- or salt-depleted patients.

- Photosensitivity: Due to the hydrochlorothiazide component photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure); deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use caution in patients with hepatic impairment. Avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.

- Renal artery stenosis: There has been no experience in treating patients with renal artery stenosis; use aliskiren with caution in patients with unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution in patients with renal impairment; not recommended in patients with severe renal impairment (Cl_{cr} <30 mL/minute). Avoid hydrochlorothiazide in severe renal disease (ineffective); may precipitate azotemia; discontinue or consider withholding if renal impairment occurs.

- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Concurrent drug therapy:

- High potential for interactions: use caution in patients taking strong inhibitors of P-glycoprotein (eg, cyclosporine); concomitant therapy with cyclosporine is not recommended.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Aliskiren should be discontinued as soon as possible once pregnancy is detected.**

Pregnancy Risk FactorD
Pregnancy ConsiderationsSee individual agents.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsFrequencies reported with combination product. See individual monographs for additional adverse effects reported with each agent.

>10%: Renal: BUN increased (12%)

1% to 10%:

Central nervous system: Dizziness (2%), vertigo (1%)

Endocrine & metabolic: Hypokalemia (2%), uric acid level increased (2%)

Gastrointestinal: Diarrhea (2%)

Hepatic: ALT increased (1%)

Neuromuscular & skeletal: Arthralgia (1%), weakness (1%)

Respiratory: Cough (1%)

Miscellaneous: Flu-like syndrome (2%)

<1% (Limited to important or life-threatening): Hematocrit decreased, hemoglobin decreased, hyperkalemia

Note: Angioedema and periorbital edema have been reported with aliskiren. Severe dermatologic reactions and pancreatitis have been reported with hydrochlorothiazide.

Metabolism/Transport EffectsSee individual agents.
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Atorvastatin: May increase the serum concentration of Aliskiren. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CycloSPORINE: May increase the serum concentration of Aliskiren. *Risk X: Avoid combination*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Furosemide: Aliskiren may decrease the serum concentration of Furosemide. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ketoconazole: May increase the serum concentration of Aliskiren. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Monitoring ParametersBlood pressure; serum electrolytes, BUN, serum creatinine; fluid status

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsSerum electrolytes, BUN, serum creatinine

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Tekturna HCT®:

150/12.5: Aliskiren 150 mg and hydrochlorothiazide 12.5 mg

150/25: Aliskiren 150 mg and hydrochlorothiazide 25 mg

300/12.5: Aliskiren 300 mg and hydrochlorothiazide 12.5 mg

300/25: Aliskiren 300 mg and hydrochlorothiazide 25 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Tekturna HCT)

300-25 mg (30): $91.78

Mechanism of ActionAliskiren is a direct renin inhibitor, resulting in blockade of the conversion of angiotensinogen to angiotensin I. Angiotensin I suppression decreases the formation of angiotensin II (Ang II), a potent blood pressure-elevating peptide (via direct vasoconstriction, aldosterone release, and sodium retention). Hydrochlorothiazide inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Aliskiren
- Hydrochlorothiazide

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentConcomitant use with psychotropics (especially those with significant alpha-adrenergic blocking properties) may produce additive hypotensive effects; monitor. Hydrochlorothiazide is used to treat lithium-induced diabetes insipidus; monitor for hypokalemia. May also decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels.

Index TermsAliskiren Hemifumarate and Hydrochlorothiazide; Hydrochlorothiazide and Aliskiren

References

Villamil A, Chrysant SG, Calhoun D, et al, “Renin Inhibition With Aliskiren Provides Additive Antihypertensive Efficacy When Used in Combination With Hydrochlorothiazide,” *J Hypertens*, 2007, 25(1):217-26.[PubMed 17143194]

Aliskiren

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

International issues:

Aliskiren may be confused with Aliseum which is a brand name for diazepam in Italy

Pronunciation(a lis KYE ren)

U.S. Brand NamesTekturna®

Canadian Brand NamesRasilez®

Pharmacologic CategoryRenin Inhibitor

Use: Labeled IndicationsTreatment of hypertension, alone or in combination with other antihypertensive agents

Use: Unlabeled/InvestigationalTreatment of persistent proteinuria in patients with type 2 diabetes mellitus, hypertension, and nephropathy despite administration of optimized recommended renoprotective therapy (eg, angiotensin II receptor blocker)

Dosing: AdultsHypertension: Initial: 150 mg once daily; may increase to 300 mg once daily (maximum: 300 mg/day). **Note:** Prior to initiation, correct hypovolemia and/or closely monitor volume status in patients on concurrent diuretics during treatment initiation.

Dosing: ElderlyRefer to adult dosing. No initial dosage adjustment required.

Dosing: PediatricChildren <18 years: Dosage not established.

Dosing: Renal Impairment

Mild-to-moderate impairment [GFR >30 mL/minute and/or S_{cr} <1.7 mg/dL (women); S_{cr} <2 mg/dL (men)]: No dose adjustment required

Severe impairment [GFR<30 mL/minute and/or S_{cr} >1.7 mg/dL (women); S_{cr} >2 mg/dL (men)]: Use caution; not studied in severe renal impairment

Dosing: Hepatic ImpairmentNo dosage adjustment required.

Administration: OralAdminister at the same time daily; may take with or without a meal, but consistent administration with regards to meals is recommended. Avoid taking with high-fat meals.

Dietary ConsiderationsMay be taken with or without food; however, a high-fat meal reduces absorption

StorageStore at 15°C to 30°C (59°F to 86°F). Protect from moisture.

Contraindications

U.S. labeling: There are no contraindications listed in manufacturer's labeling.

Canada labeling: Hypersensitivity to aliskiren or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: Since the effect of aliskiren on bradykinin levels is unknown, the risk of kinin-mediated etiologies of angioedema occurring is also unknown. Use caution in any patient with a history of angioedema (of any etiology) as angioedema has been observed (rarely) with aliskiren use. Discontinue immediately following any signs and symptoms of angioedema. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical.

- Hyperkalemia: May occur (rarely) during monotherapy; risk may increase in patients with predisposing factors (eg, renal dysfunction, diabetes mellitus or concomitant use with ACE inhibitors, potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts).

- Hypotension: During the initiation of therapy, symptomatic hypotension may occur (rarely), particularly in patients with an activated renin-angiotensin system (ie, volume or salt-depleted patients)

Disease-related concerns:

- Renal impairment: Use with caution in patients with severe renal impairment; not studied in patients with severe renal impairment [GFR <30 mL/minute and/or S_{cr} >1.7 mg/dL (women); S_{cr} >2 mg/dL (men)], history of dialysis, nephrotic syndrome, or renovascular hypertension. Use with caution or avoid in patients with deteriorating renal function or renal artery stenosis (bilateral or unilateral).

Concurrent drug therapy issues:

- High potential for interactions: Use caution in patients taking strong inhibitors of P-glycoprotein (eg, cyclosporine).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Aliskiren should be discontinued as soon as possible once pregnancy is detected.**

Geriatric ConsiderationsThe pharmacokinetic studies in elderly (≥65 years of age) demonstrated an increased AUC; however, adjustments in starting dose are not necessary. Blood pressure response and adverse effects were similar to younger adults in studies where 19% of patients were >65 years of age.

Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)

Pregnancy ConsiderationsMedications which act on the renin-angiotensin system are reported to have the following fetal/neonatal effects: Hypotension, neonatal skull hypoplasia, anuria, renal failure, and death; oligohydramnios is also reported. These effects are reported to occur with exposure during the second and third trimesters. There are no adequate and well-controlled studies in pregnant women. **[U.S. Boxed Warning]: Based on human data, drugs that act on the renin-angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Aliskiren should be discontinued as soon as possible once pregnancy is detected.**

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

1% to 10%:

Central nervous system: Dizziness (2%)

Dermatologic: Rash (1%)

Endocrine & metabolic: Hyperkalemia (monotherapy ≤1%; concurrent with ACE inhibitor in patients with diabetes 6%)

Gastrointestinal: Diarrhea (1% to 2%)

Hematologic: Creatine kinase increased (>300%: 1%)

Renal: BUN increased (≤7%), serum creatinine increased (≤7%)

Respiratory: Cough (1%)

<1%, postmarketing, and/or case reports: Abdominal pain, anemia, angina, angioedema, dyspepsia, gastroesophageal reflux, gout, hypotension (severe), myositis, renal stone formation, rhabdomyolysis, seizure, uric acid increased

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Atorvastatin: May increase the serum concentration of Aliskiren. *Risk C: Monitor therapy*

CycloSPORINE: May increase the serum concentration of Aliskiren. *Risk X: Avoid combination*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Furosemide: Aliskiren may decrease the serum concentration of Furosemide. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ketoconazole: May increase the serum concentration of Aliskiren. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: High-fat meals decrease absorption.

Monitoring ParametersBlood pressure; serum potassium, BUN, serum creatinine

Nursing: Physical Assessment/MonitoringEvaluate renal status prior to beginning therapy. Assess potential for adverse interactions with other pharmacological agents and herbal products patient may be taking (eg, increased risk for hyperkalemia). Assess results of laboratory tests (BUN, serum potassium, serum creatinine), therapeutic effectiveness (reduction in hypertension), and adverse response (eg, angioedema, hypotension) at beginning of therapy, when changing dose, and on a regular basis during long-term therapy. Teach patient proper use, possible side effects/interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum potassium, BUN, serum creatinine

Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. Take exactly as directed at same time each day; may be taken with meals. This drug does not eliminate the need for diet or exercise regimen as recommended by prescriber. May cause dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known) or hypotension (especially at beginning of therapy) (use caution when rising from lying or sitting position or climbing stairs). Report immediately any unusual swelling of eyes, face, lips, mouth, throat, or any difficulty swallowing of breathing; changes in urinary pattern; palpitations or irregular heartbeat; or any other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Breast-feeding not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Tekturna®: 150 mg, 300 mg

Generic AvailableNo

ManufacturerNovartis

Pricing: U.S. (www.drugstore.com)

Tablets (Tekturna)

150 mg (30): $75.67

300 mg (30): $95.13

Mechanism of ActionAliskerin is a direct renin inhibitor, resulting in blockade of the conversion of angiotensinogen to angiotensin I. Angiotensin I suppression decreases the formation of angiotensin II (Ang II), a potent blood pressure-elevating peptide (via direct vasoconstriction, aldosterone release, and sodium retention). Ang II also functions within the Renin-Angiotensin-Aldosterone System (RAAS) as a negative inhibitory feedback mediator within the renal parenchyma to suppress the further release of renin. Thus, reductions in Ang II levels suppress this feedback loop, leading to further increased plasma renin concentrations (PRC) and subsequent activity (PRA). This disinhibition effect can be potentially problematic for ACE inhibitor and ARB therapy, as increased PRA could partially overcome the pharmacologic inhibition of the RAAS. As aliskiren is a direct inhibitor of renin activity, blunting of PRA despite the increased PRC (from loss of the negative feedback) may be clinically advantageous. The effect of aliskiren on bradykinin levels is unknown.

Pharmacodynamics/Kinetics

Onset of action: Maximum antihypertensive effect: Within 2 weeks

Absorption: Poor; absorption decreased by high-fat meal. Aliskiren is a substrate of P-glycoprotein; concurrent use of P-glycoprotein inhibitors may increase absorption.

Metabolism: Extent of metabolism unknown; *in vitro* studies indicate metabolism via CYP3A4

Bioavailability: ~3%

Half-life elimination: ~24 hours (range: 16-32 hours)

Time to peak, plasma: 1-3 hours

Excretion: Urine (~25% of absorbed dose excreted unchanged in urine); feces (unchanged via biliary excretion)

Related Information

- Angiotensin Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications required

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentConcomitant use with psychotropics (especially those with significant alpha-adrenergic blocking properties) may produce additive hypotensive effects.

Index TermsAliskiren Hemifumarate; SPP100

References

Parving HH, Persson F, Lewis JB, et al, "Aliskiren Combined With Losartan in Type 2 Diabetes and Nephropathy," *N Engl J Med*, 2008, 358(23):2433-46.[PubMed 18525041]

Straessen JA, Li Y, and Richart T, "Oral Renin Inhibitors," *Lancet*, 2006, 368(9545):1449-56.[PubMed 17055947]

Vaidyanathan S, Warren V, Yeh C, et al, "Pharmacokinetics, Safety, and Tolerability of the Oral Renin Inhibitor Aliskiren in Patients With Hepatic Impairment," *J Clin Pharmacol*, 2007, 47(2):192-200.[PubMed 17244770]

International Brand NamesEnviage (EE); Rasilez (CH, CZ, EE, GB, IE, SE); Tekturna (EE)

Alitretinoin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Panretin® may be confused with pancreatin

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(a li TRET i noyn)

U.S. Brand NamesPanretin®

Canadian Brand NamesPanretin®

Pharmacologic CategoryAntineoplastic Agent, Miscellaneous; Retinoic Acid Derivative

Use: Labeled Indications**Orphan drug:** Topical treatment of cutaneous lesions in AIDS-related Kaposi's sarcoma

Use: Unlabeled/InvestigationalCutaneous T-cell lymphomas

Dosing: Adults

Kaposi's sarcoma: Topical: Apply gel twice daily to cutaneous lesions.

T-cell lymphomas (unlabeled use): Topical: Apply gel twice daily to cutaneous lesions.

Dosing: ElderlyRefer to adult dosing.

Administration: TopicalDo not use occlusive dressings.

StorageStore at room temperature.

ContraindicationsHypersensitivity to alitretinoin, other retinoids, or any component of the formulation; pregnancy

Allergy Considerations

- Retinoid Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Photosensitivity: May be photosensitizing (based on experience with other retinoids); minimize sun or other UV exposure of treated areas.

Concurrent drug therapy issues:

- Products containing DEET: Do not use concurrently with topical products containing DEET.

Special populations:

- Elderly: Safety has not been established in the elderly.
- Pediatrics: Safety has not been established in children.
- Pregnancy: May cause fetal harm if absorbed by a woman who is pregnant.

Pregnancy Risk FactorD

Pregnancy ConsiderationsPotentially teratogenic and/or embryotoxic; limb, craniofacial, or skeletal defects have been observed in animal models. If used during pregnancy or if the patient becomes pregnant while using alitretinoin, the woman should be advised of potential harm to the fetus. Women of childbearing potential should avoid becoming pregnant.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsExcretion in human breast milk is unknown; women are advised to discontinue breast-feeding prior to using this medication.

Adverse Reactions

>10%:

Central nervous system: Pain (0% to 34%)

Dermatologic: Rash (25% to 77%), pruritus (8% to 11%)

Neuromuscular & skeletal: Paresthesia (3% to 22%)

5% to 10%:

Cardiovascular: Edema (3% to 8%)

Dermatologic: Exfoliative dermatitis (3% to 9%), skin disorder (0% to 8%)

Oncology: Emetic PotentialVery low (<10%)

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringAssess effectiveness of therapy and adverse reactions at beginning and periodically during therapy. Teach patient appropriate use/application, need to avoid DEET-containing insect repellents, and adverse symptoms to report.

Patient EducationFor external use only. Use exactly as directed; do not overuse. Avoid use of any product such as insect repellents which contain DEET (check with your pharmacist). Wear protective clothing and/or avoid exposure to direct sun or sunlamps. Wash hands thoroughly before applying. Avoid applying skin products that contain alcohol or harsh chemicals during treatment. Do not apply occlusive dressings. Stop treatment and inform prescriber if rash, skin irritation, redness, scaling, or excessive dryness appears. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel:

Panretin®: 0.1% (60 g)

Generic AvailableNo

ManufacturerLigand Pharmaceuticals, Inc

Mechanism of ActionBinds to retinoid receptors to inhibit growth of Kaposi's sarcoma

Pharmacodynamics/KineticsAbsorption: Not extensive

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusPain is common

Mental Health: Effects on Psychiatric TreatmentMay be photosensitizing; caution with psychotropics

International Brand NamesPanretin (AR, AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Allopurinol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Allopurinol may be confused with Apresoline

Zyloprim® may be confused with Xylo-Pfan®, ZORprin®

Pronunciation(al oh PURE i nole)

U.S. Brand NamesAloprim™; Zyloprim®

Canadian Brand NamesAlloprin®; Apo-Allopurinol®; Novo-Purol; Zyloprim®

Pharmacologic CategoryXanthine Oxidase Inhibitor

Use: Labeled Indications

Oral: Prevention of attack of gouty arthritis and nephropathy; treatment of secondary hyperuricemia which may occur during treatment of tumors or leukemia; prevention of recurrent calcium oxalate calculi

I.V.: Treatment of elevated serum and urinary uric acid levels when oral therapy is not tolerated in patients with leukemia, lymphoma, and solid tumor malignancies who are receiving cancer chemotherapy

Dosing: AdultsDoses >300 mg should be given in divided doses.

Gout: Oral: Mild: 200-300 mg/day; Severe: 400-600 mg/day; to reduce the possibility of acute gouty attacks, initiate dose at 100 mg/day and increase weekly to recommended dosage. Maximum daily dose: 800 mg/day.

Secondary hyperuricemia associated with chemotherapy:

Oral: 600-800 mg/day in 2-3 divided doses for prevention of acute uric acid nephropathy for 2-3 days starting 1-2 days before chemotherapy

I.V.: 200-400 mg/m^2/day (maximum: 600 mg/day)

Note: Intravenous daily dose can be given as a single infusion or in equally divided doses at 6-, 8-, or 12-hour intervals. A fluid intake sufficient to yield a daily urinary output of at least 2 L in adults and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable.

Recurrent calcium oxalate stones: 200-300 mg/day in single or divided doses

Dosing: ElderlyOral: Initial: 100 mg/day; increase until desired uric acid level is obtained. Refer to adult dosing.

Dosing: Pediatric

Gout: Children >10 years: Refer to adult dosing.

Recurrent calcium oxalate stones: Children >10 years: Refer to adult dosing.

Secondary hyperuricemia associated with chemotherapy:

Oral: Children ≤10 years: 10 mg/kg/day in 2-3 divided doses **or** 200-300 mg/m^2/day in 2-4 divided doses, maximum: 800 mg/24 hours, for prevention of acute uric acid nephropathy (begin 1-2 days before chemotherapy)

Alternative (manufacturer labeling):

<6 years: 150 mg/day in 3 divided doses

6-10 years: 300 mg/day in 2-3 divided doses

>10 years: Refer to adult dosing.

I.V.:

Children ≤10 years: Starting dose: 200 mg/m^2/day

Note: Intravenous daily dose can be given as a single infusion or in equally divided doses at 6-, 8-, or 12-hour intervals. Adequate fluid intake and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable.

Children >10 years: Refer to adult dosing.

Dosing: Renal Impairment

Oral: Must be adjusted due to accumulation of allopurinol and metabolites; see table.

Adult Maintenance Doses of Allopurinol[1]

Creatinine Clearance (mL/min)	Maintenance Dose of Allopurinol (mg)
140	400 daily
120	350 daily
100	300 daily
80	250 daily
60	200 daily
40	150 daily
20	100 daily
10	100 every 2 days
0	100 every 3 days

[1] This table is based on a standard maintenance dose of 300 mg of allopurinol per day for a patient with a creatinine clearance of 100 mL/min.

I.V.:

Cl_{cr} 10-20 mL/minute: Administer 200 mg/day.

Cl_{cr} 3-10 mL/minute: Administer 100 mg/day.

Cl_{cr} <3 mL/minute: Administer 100 mg/day at extended intervals.

Hemodialysis: Administer dose after hemodialysis or administer 50% supplemental dose.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Infuse over 15-60 minutes. The rate of infusion depends on the volume of the infusion. Whenever possible, therapy should be initiated at 24-48 hours before the start of chemotherapy known to cause tumor lysis (including adrenocorticosteroids). I.V. daily dose can be administered as a single infusion or in equally divided doses at 6-, 8-, or 12-hour intervals.

Administration: OralShould be administered after meals with plenty of fluid.

Dietary ConsiderationsShould administer oral forms after meals with plenty of fluid. Fluid intake should be administered to yield neutral or slightly alkaline urine and an output of ~2 L (in adults).

Storage

Powder for injection: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F). Following reconstitution, intravenous solutions should be stored at 20°C to 25°C. Do not refrigerate reconstituted and/or diluted product. Must be administered within 10 hours of solution preparation.

Tablet: Store at controlled room temperature of 15°C to 25°C (59°F to 77°F).

ReconstitutionFurther dilution with NS or D_5W (50-100 mL) to ≤6 mg/mL is recommended.

CompatibilityStable in D_5W, NS, sterile water for injection.

Y-site administration: Compatible: Acyclovir, aminophylline, aztreonam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, cefazolin, cefoperazone, cefotetan, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cisplatin, co-trimoxazole, cyclophosphamide, dactinomycin, dexamethasone sodium phosphate, doxorubicin liposome, enalaprilat, etoposide, famotidine, fluconazole, fludarabine, fluorouracil, furosemide, ganciclovir, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, ifosfamide, lorazepam, mannitol, mesna, methotrexate, metronidazole, mitoxantrone, morphine, piperacillin, plicamycin, potassium chloride, ranitidine, thiotepa, ticarcillin, ticarcillin/clavulanate, vancomycin, vinblastine, vincristine, zidovudine. **Incompatible:** Amikacin, amphotericin B, carmustine, cefotaxime, chlorpromazine, cimetidine, clindamycin, cytarabine, dacarbazine, daunorubicin, diphenhydramine, doxorubicin, doxycycline, droperidol, floxuridine, gentamicin, haloperidol, hydroxyzine, idarubicin, imipenem/cilastatin, mechlorethamine, meperidine, methylprednisolone sodium succinate, metoclopramide, minocycline, nalbuphine, netilmicin, ondansetron, prochlorperazine edisylate, promethazine, sodium bicarbonate, streptozocin, tobramycin, vinorelbine.

Extemporaneously PreparedCrush tablets to make a 5 mg/mL suspension in simple syrup; stable 14 days under refrigeration

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, 1st ed, Harvey Whitney Books Co, 1990.

ContraindicationsHypersensitivity to allopurinol or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Allergic reaction: Has been associated with a number of hypersensitivity reactions, including severe reactions (vasculitis and Stevens-Johnson syndrome); discontinue at first sign of rash.
- Bone marrow suppression: Has been reported; use caution with other drugs causing myelosuppression.
- Hepatotoxicity: Reversible hepatotoxicity has been reported; use with caution in patients with pre-existing hepatic impairment.

Disease-related concerns:

- Asymptomatic hyperuricemia: Do not use to treat asymptomatic hyperuricemia.
- Renal impairment: Use with caution in patients with renal impairment; may be at increased risk for hypersensitivity reactions. Dosage adjustments needed.

Concurrent drug therapy issues:

- ACE inhibitors: The risk of hypersensitivity may be increased in patients receiving ACE inhibitors.
- Amoxicillin/ampicillin: Risk of skin rash may be increased in patients receiving amoxicillin or ampicillin.
- Azathioprine/mercaptopurine: Use with caution in patients taking mercaptopurine or azathioprine; dosage adjustment necessary.
- Diuretics: Use with caution in patients taking diuretics concurrently. The risk of hypersensitivity may be increased in patients receiving thiazides.

Geriatric ConsiderationsAdjust dose based on renal function.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are few reports describing the use of allopurinol during pregnancy; no adverse fetal outcomes attributable to allopurinol have been reported in humans; use only if potential benefit outweighs the potential risk to the fetus.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Adverse Reactions

>1%:

Dermatologic: Rash (increased with ampicillin or amoxicillin use, 1.5% per manufacturer, >10% in some reports)

Gastrointestinal: Nausea (1.3%), vomiting (1.2%)

Renal: Renal failure/impairment (1.2%)

<1%: Hypersensitivity syndrome, alkaline phosphatase or hepatic transaminases increased, granulomatous hepatitis, dyspepsia, pancreatitis, gynecomastia, agranulocytosis, aplastic anemia, acute tubular necrosis, interstitial nephritis, nephrolithiasis, vasculitis, toxic epidermal necrolysis, exfoliative dermatitis, Stevens-Johnson syndrome, granuloma annulare, toxic pustuloderma, peripheral neuropathy, neuritis, paresthesia, bronchospasm, cataracts, macular retinitis, angioedema, epistaxis

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

ACE Inhibitors: May enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Amoxicillin: Allopurinol may enhance the potential for allergic or hypersensitivity reactions to Amoxicillin. *Risk C: Monitor therapy*

Ampicillin: Allopurinol may enhance the potential for allergic or hypersensitivity reactions to Ampicillin. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Allopurinol. **Exceptions:** Sodium Bicarbonate. *Risk D: Consider therapy modification*

AzaTHIOprine: Allopurinol may decrease the metabolism of AzaTHIOprine. *Risk D: Consider therapy modification*

CarBAMazepine: Allopurinol may increase the serum concentration of CarBAMazepine. *Risk C: Monitor therapy*

ChlorproPAMIDE: Allopurinol may increase the serum concentration of ChlorproPAMIDE. *Risk C: Monitor therapy*

Cyclophosphamide: Allopurinol may enhance the adverse/toxic effect of Cyclophosphamide. Specifically, bone marrow suppression. *Risk C: Monitor therapy*

Didanosine: Allopurinol may decrease the metabolism of Didanosine. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the adverse/toxic effect of Allopurinol. Loop Diuretics may increase the serum concentration of Allopurinol. Specifically, Loop Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Mercaptopurine: Allopurinol may decrease the metabolism of Mercaptopurine. *Risk D: Consider therapy modification*

Pivampicillin: Allopurinol may enhance the potential for allergic or hypersensitivity reactions to Pivampicillin. *Risk C: Monitor therapy*

Theophylline Derivatives: Allopurinol may increase the serum concentration of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Allopurinol may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: May decrease effectiveness.

Iron supplements: Hepatic iron uptake may be increased.

Vitamin C: Large amounts of vitamin C may acidify urine and increase kidney stone formation.

Monitoring ParametersCBC, serum uric acid levels, I & O, hepatic and renal function, especially at start of therapy

Reference RangeUric acid, serum: An increase occurs during childhood

Adults:

Male: 3.4-7 mg/dL or slightly more

Female: 2.4-6 mg/dL or slightly more

Values >7 mg/dL are sometimes arbitrarily regarded as hyperuricemia, but there is no sharp line between normals on the one hand, and the serum uric acid of those with clinical gout. Normal ranges cannot be adjusted for purine ingestion, but high purine diet increases uric acid. Uric acid may be increased with body size, exercise, and stress.

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor laboratory values, effectiveness of therapy, and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. considerations.

Monitoring: Lab TestsCBC, serum uric acid levels, hepatic and renal function, especially at start of therapy

Patient EducationTake as directed. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. While using this medication, do not use alcohol, other prescriptions, OTC medications, or vitamins without consulting prescriber. You may experience drowsiness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or heartburn (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or hair loss (reversible). Report immediately skin rash or lesions; painful urination or blood in urine or stool; pain or irritation of the eyes; swelling of lips, mouth, or tongue. Also report unusual fatigue; easy bruising or bleeding; yellowing of skin or eyes; any change in color of urine or stool; unresolved nausea or vomiting; or numbness of extremities. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as sodium: 500 mg

Aloprim™: 500 mg

Tablet: 100 mg, 300 mg

Zyloprim®: 100 mg, 300 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Zyloprim)

100 mg (30): $23.99

300 mg (30): $44.98

Mechanism of ActionAllopurinol inhibits xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine to uric acid. Allopurinol is metabolized to oxypurinol which is also an inhibitor of xanthine oxidase; allopurinol acts on purine catabolism, reducing the production of uric acid without disrupting the biosynthesis of vital purines.

Pharmacodynamics/Kinetics

Onset of action: Peak effect: 1-2 weeks

Absorption: Oral: ~80%; Rectal: Poor and erratic

Distribution: V_d: ~1.6 L/kg; V_{ss}: 0.84-0.87 L/kg; enters breast milk

Protein binding: <1%

Metabolism: ~75% to active metabolites, chiefly oxypurinol

Bioavailability: 49% to 53%

Half-life elimination:

Normal renal function: Parent drug: 1-3 hours; Oxypurinol: 18-30 hours

End-stage renal disease: Prolonged

Time to peak, plasma: Oral: 30-120 minutes

Excretion: Urine (76% as oxypurinol, 12% as unchanged drug)

Allopurinol and oxypurinol are dialyzable

Related Information

- Antacid Drug Interactions

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness
Mental Health: Effects on Psychiatric TreatmentRarely may cause bone marrow suppression; use caution with clozapine and carbamazepine
Index TermsAllopurinol Sodium
References

Allen LV and Erickson MA 3d, “Stability of Acetazolamide, Allopurinol, Azathioprine, Clonazepam, and Flucytosine in Extemporaneously Compounded Oral Liquids,” *Am J Health Syst Pharm*, 1996, 53(16):1944-9. [PubMed 8862208]

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Emmerson BT, “The Management of Gout,” *N Engl J Med*, 1996, 334(7):445-51. [PubMed 8552148]

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Vinciullo C, “Allopurinol Hypersensitivity,” *Med J Aust*, 1984, 141(7):449-50.

International Brand NamesAdenock (JP); Alinol (TH); Allo (CO); Allo 300 (DE); Allo-Puren (DE); Allobeta (AU); Allohexal (AU); Allopin (TH); Allopur (CH, NO); Allopurinol (MY, PL); Allopurinol-ratiopharm (LU); Alloratio (PL); Alloril (IL); Allorin (NZ); Allosig (AU); Allozym (JP); Allpargin (LU); Allupol (PL); Allurase (PH); Allurit (IT); Alopron (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Alopurinol (HR); Alositol (JP); Alpurase (PH); Alpuric (LU); Alpurin (PH); Alunlan (PH, TW); Alurin (GT); Aluron (VE); Anoprolin (JP); Anzief (JP); Apo-Allopurinol (PL); Aprinol (JP); Apurin (FI, GR); Atisuril (MX); Benoxuric (ID); Bleminal (DE); Caplenal (GB); Capurate (TW); Cellidrin (DE); Clint (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Etindrax (MX); Foligan (DE); Genozyl (MX); Gichtex (AT); Hamarin (GB); Hexanurat (DK); Huma-Purol (HU); Hycemia (ID); Isoric (ID); Ketanrift (JP); Ketobun-A (JP); Licoric (ID); Litinol (VE); Llanol (ID, PH); Masaton (JP); Medoric (TH); Mephanol (AE, BF, BH, BJ, CH, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Milurit (BG, HK, HN, HU, PL); Miniplanor (JP); Neufan (JP); Nilapur (ID); Nipurol (VE); No-Uric (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Pritanol (ID); Progout (AU, HK, SG); Proxuric (ID); Puribel 300 (MX); Puricemia (ID); Puricos (ZA); Purinol (MY); Puristen (PH); Remid (DE); Riball (JP); Rinolic (ID); Salterprim (ZA); Sinoric (ID); Takanarumin (JP); Trianol (PH); Unizuric 300 (MX); Uric (JP); Uricad (TH); Uricnol (ID); Uriconorm (CH); Urinol (MY); Uripurinol (DE); Urogquad (AR); Uroquad (BB, BF, BJ, BM, BS, BZ, CI, ET, GH, GM, GN, GY, ID, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, PR, SC, SD, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Urosin (AT, DE, EC, LU); Xandase (TH); Xanturic (FR); Xanurace (PH); Xylonol (TW); Z300 (NZ); Zylapour (GR); Zylol (IL); Zyloprim (AU, BB, BM, BS, BZ, CR, DO, GT, GY, HN, JM, MX, NI, NL, PA, PH, PY, SR, SV, TT); Zyloric (AE, AT, BE, BF, BG, BH, BJ, BR, CH, CI, CN, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HN, ID, IE, IL, IN, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PE, PK, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SY, TH, TN, TR, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Zyroric (KP)

Almotriptan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Axert™ may be confused with Antivert®

Pronunciation(al moh TRIP tan)

U.S. Brand NamesAxert™

Canadian Brand NamesAxert™

Pharmacologic CategoryAntimigraine Agent; Serotonin 5-HT$_{1B, 1D}$ Receptor Agonist

Use: Labeled IndicationsAcute treatment of migraine with or without aura

Dosing: AdultsMigraine: Oral: Initial: 6.25-12.5 mg in a single dose; if the headache returns, repeat the dose after 2 hours; no more than 2 doses in 24-hour period

Note: If the first dose is ineffective, diagnosis needs to be re-evaluated. Safety of treating more than 4 migraines/month has not been established.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentInitial: 6.25 mg in a single dose; maximum daily dose: ≤12.5 mg

Dosing: Hepatic ImpairmentInitial: 6.25 mg in a single dose; maximum daily dose: ≤12.5 mg

Dietary ConsiderationsMay be taken without regard to meals

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to almotriptan or any component of the formulation; use as prophylactic therapy for migraine; hemiplegic or basilar migraine; cluster headache; known or suspected ischemic heart disease (angina pectoris, MI, documented silent ischemia, coronary artery vasospasm, Prinzmetal's variant angina); peripheral vascular syndromes (including ischemic bowel disease); uncontrolled hypertension; use within 24 hours of another 5-HT$_1$ agonist; use within 24 hours of ergotamine derivative; concurrent administration or within 2 weeks of discontinuing an MAO inhibitor (specifically MAO type A inhibitors)

Allergy Considerations

- Serotonin 5-HT$_{1B,1D}$ Receptor Agonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac events: Coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia/fibrillation, cardiac arrest, and death have been reported with 5-HT$_1$ agonist administration. Patients who experience sensations of chest pain/pressure/tightness or symptoms suggestive of angina following dosing should be evaluated for coronary artery disease or Prinzmetal's angina before receiving additional doses.
- Cerebrovascular events: Cerebral/subarachnoid hemorrhage and stroke have been reported with 5-HT$_1$ agonist administration.
- Elevated blood pressure: Significant elevation in blood pressure, including hypertensive crisis, has also been reported on rare occasions in patients with and without a history of hypertension.
- Vasospasm-related events: Peripheral vascular ischemia and colonic ischemia have been reported with 5-HT$_1$ agonist. administration.

Disease-related concerns:

- Coronary artery disease: Should not be given to patients who have risk factors for CAD (eg, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, menopause, male >40 years of age) without adequate cardiac evaluation. Patients with suspected CAD should have cardiovascular evaluation to rule out CAD before considering use; if cardiovascular evaluation “is satisfactory”, first dose should be given in the healthcare provider's office. Periodic evaluation of cardiovascular status should be done in all patients.
- Hepatic impairment: Use with caution in patients with hepatic impairment. Drug clearance may be reduced leading to increased plasma concentrations; dosage reduction is recommended.
- Renal impairment: Use with caution in patients with moderate to severe renal failure.

Concurrent drug therapy issues:

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce almotriptan's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

Other warnings/precautions:

- Appropriate use: Only indicated for treatment of acute migraine; if a patient does not respond to the first dose, the diagnosis of migraine should be reconsidered.

Geriatric ConsiderationsUse cautiously in elderly, particularly since many have cardiovascular disease, which would put them at risk for cardiovascular adverse effects. Safety and efficacy in elderly patients >65 years of age have not been established.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use in pregnancy should be limited to situations where benefit outweighs risk to fetus. In some (but not all) animal studies, administration was associated with embryolethality, fetal malformations, and decreased pup weight.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Central nervous system: Headache (>1%), dizziness (>1%), somnolence (>1%)

Gastrointestinal: Nausea (1% to 2%), xerostomia (1%)

Neuromuscular & skeletal: Paresthesia (1%)

<1%: Abdominal cramps, abdominal pain, abnormal coordination, anxiety, arthralgia, arthritis, back pain, bronchitis, chest pain, chills, colitis, conjunctivitis, coronary artery vasospasm, creatine phosphokinase increased, depressive symptoms, dermatitis, diaphoresis, diarrhea, diplopia, dream changes, dry eyes, dysmenorrhea, dyspepsia, dyspnea, ear pain, epistaxis, erythema, esophageal reflux, euphoria, eye irritation, eye pain, fatigue, fever, gastritis, gastroenteritis, GGTP increased, hyperacusis, hypercholesterolemia, hyperglycemia, hyperreflexia, hypertension, hypertonia, hyperventilation, hypoesthesia, impaired concentration, insomnia, laryngismus, laryngitis, muscular weakness, myalgia, myocardial ischemia, MI, myopathy, neck pain, nervousness, neuropathy, nightmares, nystagmus, otitis media, palpitation, parosmia, pharyngitis, photosensitivity reaction, pruritus, rash, restlessness, rhinitis, rigid neck, salivation increased, scotoma, shakiness, sinusitis, sneezing, stimulation, syncope, tachycardia, taste alterations, thirst, tinnitus, tremor, vasodilation, ventricular fibrillation, ventricular tachycardia, vertigo, vomiting, weakness

Metabolism/Transport Effects**Substrate** (minor) of CYP2D6, 3A4

Drug Interactions

Ergot Derivatives: May enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Ketoconazole: May increase the serum concentration of Almotriptan. *Risk C: Monitor therapy*

MAO Inhibitors: May decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Nursing: Physical Assessment/MonitoringClear diagnosis of migraines and cardiac status should be determined before beginning treatment. Assess for use cautions (eg, risk factors for coronary artery disease; liver or renal dysfunction). Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, ergot-containing drugs, SSRIs, MAO inhibitors). Assess effectiveness of therapy (relief of migraines) and adverse response (eg, hypertension or more serious cardiovascular symptoms). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationInform prescriber of all prescriptions (including oral contraceptives), OTC medications, or herbal products you are taking, and any allergies you have. This drug is to be used to reduce your migraine, not to prevent or reduce the number of attacks. Follow exact instructions for use. Do not use more than two doses in 24 hours and do not take within 24 hours of any other migraine medication without consulting prescriber. May cause dizziness, fatigue, or drowsiness (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Report immediately any chest pain, palpitations, or throbbing; feelings of tightness or pressure in jaw or throat; acute headache or dizziness; muscle cramping, pain, or tremors; skin rash; hallucinations, anxiety, panic; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as malate:

Axert™: 6.25 mg, 12.5 mg

Generic AvailableNo

ManufacturerPharmacia

Pricing: U.S. (www.drugstore.com)

Tablets (Axert)

6.25 mg (6): $125.20

12.5 mg (12): $229.97

Mechanism of ActionSelective agonist for serotonin (5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1F}$ receptors) in cranial arteries; causes vasoconstriction and reduce sterile inflammation associated with antidromic neuronal transmission correlating with relief of migraine

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: V_d: 180-200 L

Protein binding: ~35%

Metabolism: MAO type A oxidative deamination (~27% of dose); via CYP3A4 and 2D6 (~12% of dose) to inactive metabolites

Bioavailability: 70%

Half-life elimination: 3-4 hours

Time to peak: 1-3 hours

Excretion: Urine (40% as unchanged drug); feces (13% unchanged and metabolized)

Related Information

- Antimigraine Drugs: 5-HT1 Receptor Agonists

Dental Health: Effects on Dental TreatmentKey adverse effect(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Cardiovascular ConsiderationsCoronary vasospasm has been associated with 5-HT$_{1B/1D}$ agonists. These agents are contraindicated in patients with documented ischemic or vasospastic coronary artery disease. Patients with risk factors for CAD may receive these agents, provided a cardiovascular evaluation yields satisfactory evidence that the patient is free of cardiovascular disease. In patients with risk factors for CAD, administration of the initial dose in a medically staffed/equipped facility (ie, physician's office) is recommended. In addition, ECG monitoring after the initial dose should be considered. Patients who acquire risk factors for CAD, or long-term users of agents from this class of medications, should undergo periodic cardiovascular evaluation.

Anesthesia and Critical Care Concerns/Other ConsiderationsAlmotriptan should not be used in patients with a history of vasospastic disease, Prinzmetal's angina, or any critical vascular disease.

Index TermsAlmotriptan Malate

References

Boyer EW and Shannon M, “The Serotonin Syndrome,” *N Engl J Med*, 2005, 352:1112-20.[PubMed 15784664]

International Brand NamesAlmogran (BE, CH, DE, DK, ES, FI, FR, GB, IE, IS, IT, JP, NL, NO, PT, SE)

Alosetron

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Lotronex® may be confused with Lovenox®, Protonix®

International issues:

Lotronex® may be confused with Lotanax® which is a brand name for terfenadine in the Czech Republic

Pronunciation(a LOE se tron)

U.S. Brand NamesLotronex®

Pharmacologic CategorySelective 5-HT_3 Receptor Antagonist

Use: Labeled IndicationsTreatment of women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have failed to respond to conventional therapy

Dosing: AdultsIBS: Female: Oral: Initial: 0.5 mg twice daily for 4 weeks, with or without food; if tolerated, but response is inadequate, may be increased after 4 weeks to 1 mg twice daily. If response is inadequate after 4 weeks of 1 mg twice-daily dosing, discontinue treatment.

Note: Discontinue immediately if constipation or signs/symptoms of ischemic colitis occur. Do not reinitiate in patients who develop ischemic colitis.

Dosing: ElderlyRefer to adult dosing. Dosage adjustment is not required; however, postmarketing experience suggests that elderly patients may be at greater risk for complications of constipation.

Dosing: Renal ImpairmentThe need for dosage adjustment has not been defined (due to limited information on activity of metabolites).

Dosing: Hepatic ImpairmentIn mild-to-moderate dysfunction (Child-Pugh score ≤9), use caution. Contraindicated in severe hepatic dysfunction (Child-Pugh score ≥10).

Administration: OralMay be administered with or without food; however, when administered with food, absorption may be reduced by approximately 25%.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at controlled room temperature of 25°C (77°F).

RestrictionsOnly physicians enrolled in Prometheus' Prescribing Program for Lotronex® may prescribe this medication. Program stickers must be affixed to all prescriptions; no phone, fax, or computerized prescriptions are permitted with this program.

An FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsDo not start treatment in patients who are constipated. Hypersensitivity to alosetron or any component of the formulation; history of severe or chronic constipation or sequelae from constipation; history of ischemic colitis, intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation and/or adhesions; diverticulitis, current or history of Crohn's disease, or ulcerative colitis; severe hepatic impairment; history of impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; patients unable to understand or comply with "Patient-Physician" agreement; concomitant administration with fluvoxamine

Allergy Considerations

- Serotonin 5-HT_3 Antagonist Allergy

Warnings/Precautions

Boxed warnings:

- Appropriate use: See "Other warnings/precautions" below.
- Constipation: See "Concerns related to adverse effects" below.
- Ischemic colitis: See "Concerns related to adverse effects" below.
- Patient-Physician agreement: See "Other warnings/precautions" below.

Concerns related to adverse effects:

- Constipation: **[U.S. Boxed Warning]: Discontinue immediately in patients who develop constipation; serious complications of constipation have been infrequently reported (obstruction, ileus, perforation, impaction, toxic megacolon, secondary ischemia).** Constipation is a frequent, dose-related side effect; risk for complications from constipation may be increased in elderly, debilitated patients, or with concurrent use of other medications which decrease GI motility. Nonsevere constipation may be managed by temporarily interrupting therapy. Do not initiate in patients with constipation. Do not initiate in patients with constipation.

- Ischemic colitis: **[U.S. Boxed Warning]: Acute ischemic colitis has been reported during treatment.** Discontinue and evaluate immediately in patients who experience rectal bleeding or a sudden worsening of abdominal pain, and do not restart therapy if ischemic colitis is diagnosed.

Disease-related concerns:

- Hepatic impairment: Use caution in mild-to-moderate hepatic impairment (Child-Pugh score ≤9); contraindicated in severe impairment (Child-Pugh score ≥10).

Special populations:

- Elderly: Use with caution in the elderly due to increased risk of complications from constipation.

- Males: Safety and efficacy have not been established in males.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: **[U.S. Boxed Warning]: Only indicated for women with severe diarrhea-predominant irritable bowel syndrome with inadequate response to conventional therapy.**

- Patient-Physician agreement: **[U.S. Boxed Warning]: Should only be prescribed by physicians enrolled in the Prometheus' Prescribing Program for Lotronex®. Patients must read and sign a "Patient-Physician" agreement before receiving the initial prescription.**

Geriatric ConsiderationsPostmarketing experience suggests that elderly patients may be at greater risk for complications of constipation.
Pregnancy Risk FactorB
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Alosetron should be used in pregnant women only if clearly needed.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsAnimal studies indicate that alosetron and/or metabolites are excreted in breast milk. It is not known if alosetron in excreted in human milk. Caution should be used in administering alosetron to a nursing woman.
Adverse Reactions

>10%: Gastrointestinal: Constipation (dose related; 29%)

2% to 10%: Gastrointestinal: Abdominal discomfort and pain (7%), nausea (6%), gastrointestinal discomfort and pain (5%), abdominal distention (2%), hemorrhoids (2%), regurgitation and reflux (2%)

≤1% (Limited to important or life-threatening): Allergic skin reactions, alopecia, anxiety, arrhythmia, bilirubin level changes, bladder inflammation, bone pain, breathing disorder, cholecystitis, cognitive function disorders, confusion, cramps, colitis, depression, dermatitis, diaphoresis, diverticulitis, dyspepsia, extrasystoles, fatigue, fluid disturbances, gastroenteritis, GI intussusception, GI lesions, GI motility decreased, GI obstructions, GI spasms, hematoma, hemorrhage, hyperacidity, hyper-/hypoglycemia, hypertension, hypnagogic effects, hypoesthesia, hypothalamus/pituitary dysfunction, ileus, ischemic colitis, memory effects, muscle pain/stiffness, occult stools, pain, proctitis, RBC/hemoglobin defects, sedation, sexual dysfunction, skeletal pain, tachyarrhythmia, temperature regulation impairment, tremor, ulcerative colitis, urinary frequency, urticaria

Postmarketing and/or case reports: GI impaction, GI perforation, GI ulceration, headache, hepatitis, rash, small bowel mesenteric ischemia

Metabolism/Transport Effects**Substrate** of CYP1A2 (major), 2C9 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2E1 (weak)
Drug Interactions

Apomorphine: Antiemetics (5HT3 Antagonists) may enhance the hypotensive effect of Apomorphine. *Risk X: Avoid combination*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Fluvoxamine: May decrease the metabolism of Alosetron. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Antiemetics (5HT3 Antagonists). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: When administered with food, absorption may be reduced by ~25%.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Lotrenex®: 0.5 mg, 1 mg

Generic AvailableNo
ManufacturerPrometheus Laboratories
Pricing: U.S. (www.drugstore.com)

Tablets (Lotronex)

0.5 mg (30): $375.96

1 mg (30): $428.32

Mechanism of ActionAlosetron is a potent and selective antagonist of a subtype of the serotonin 5-HT$_3$ receptor. 5-HT$_3$ receptors are ligand-gated ion channels extensively distributed on enteric neurons in the human gastrointestinal tract, as well as other peripheral and central locations. Activation of these channels affect the regulation of visceral pain, colonic transit, and gastrointestinal secretions. In patients with irritable bowel syndrome, blockade of these channels may reduce pain, abdominal discomfort, urgency, and diarrhea.

Pharmacodynamics/Kinetics

Distribution: V$_d$: 65-95 L

Protein binding: 82%

Metabolism: Extensive hepatic metabolism. Alosetron is metabolized by CYP2C9, 3A4, and 1A2. Thirteen metabolites have been detected in the urine. Biological activity of these metabolites in unknown.

Bioavailability: Mean: 50% to 60% (range: 30% to >90%); decreased with food (25%)

Half-life elimination: 1.5 hours for alosetron

Time to peak: 1 hour after oral administration

Excretion: Urine (73%) and feces (24%); 7% as unchanged drug (1% feces, 6% urine)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression or sleep abnormalities; may rarely cause anxiety or sedation

Mental Health: Effects on Psychiatric TreatmentConstipation is common; use caution with concurrent psychotropics possessing anticholinergic activity (eg, benztropine, clozapine, TCAs); may cause nausea; concurrent use with SSRIs, lithium, or valproate may produce additive effects

References

Koch KM, Corrigan BW, Manzo J, et al, “Alosetron Repeat Dose Pharmacokinetics, Effects on Enzyme Activities, and Influence of Demographic Factors,” *Aliment Pharmacol Ther*, 2004, 20(2):223-30.[PubMed 15233703]

Alpha-Galactosidase

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Jump To Field (Select Field Name)

Pronunciation(AL fa ga lak TOE si days)
U.S. Brand Namesbeano® [OTC]
Pharmacologic CategoryEnzyme
Use: Labeled IndicationsPrevention of flatulence and bloating attributed to a variety of grains, cereals, nuts, and vegetables containing the sugars raffinose, stachyose, and/or verbascose
Dosing: AdultsFlatulence and bloating: Oral:

Drops: Take 5 drops per serving of problem food; adjust according to number of problem foods per meal; usual dose/meal: 10-15 drops

Tablet: One tablet per serving of problem food; adjust according to number of problem foods per meal; usual dose/meal: 2-3 tablets

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Flatulence and bloating: Children ≥12 years: Refer to adult dosing.

Administration: Oral

Drops: Take with meal; do not cook

Tablet: Swallow, chew, or crumble. Take with meal; do not cook.

Dietary ConsiderationsBeano® must be taken just before or during a meal to be effective. Drops contain 5 mg of sodium per 5 drops. Although made from safe, food-grade mold, there is no evidence that individuals with an allergy to penicillin or molds would have an allergy to Beano®. Beano® contains less than 0.00016% (point of detection) of gluten. Galactosemics should consult their healthcare provider.
StorageStore at or below room temperature. Avoid heat.
ContraindicationsHypersensitivity to any component of the formulation
Warnings/Precautions

Special populations:

- Galactosemic patients: Patients who are galactosemic should consult their healthcare provider prior to use.
- Pediatrics: Use is not recommended for children <12 years of age.
- Pregnancy: Patients who are pregnant or breast-feeding should consult a healthcare provider.

Other warnings/precautions:

- Approved use: Currently, there are no FDA-approved disease-prevention or therapeutic indications for this product.
- Heat exposure: Heat can inactivate; do not cook.

Nursing: Physical Assessment/MonitoringTeach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Patient EducationUse exactly as directed on package insert. Take at beginning of meal. Do not cook.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, oral [drops]:

beano®: 150 galactosidase units/5 drops [contains sodium 5 mg/5 drops]

Tablet, oral:

beano®: 150 galactosidase units/tablet

Generic AvailableNo
ManufacturerGlaxoSmithKline
Mechanism of ActionNatural food enzyme that breaks down complex sugars in gassy foods, making them more digestible and less gassy.
Index Terms*Aspergillus niger*

$_1$-Proteinase Inhibitor'; return;">

Alpha$_1$-Proteinase Inhibitor

Lexi-Drugs Online

English

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Special Alerts

Aralast NP Product Availability

The Food and Drug Administration (FDA) has approved Aralast NP (alpha$_1$-proteinase inhibitor) for the treatment of congenital alpha$_1$-antitrypsin deficiency. Aralast NP has the same formulation as Aralast; the name reflects a product which is completely processed by Baxter. A launch date has not yet been announced, but Aralast NP is expected to be available as supplies of Aralast are depleted.

Pronunciation(al fa won PRO tee in ase in HI bi tor)
U.S. Brand NamesAralast; Aralast NP; Prolastin®; Zemaira®
Canadian Brand NamesProlastin®
Pharmacologic CategoryAntitrypsin Deficiency Agent
Use: Labeled IndicationsReplacement therapy in congenital alpha$_1$-antitrypsin deficiency with clinical emphysema
Dosing: AdultsAlpha$_1$-antitrypsin deficiency: I.V.: 60 mg/kg once weekly
Dosing: ElderlyRefer to adult dosing.
Administration: I.V.For I.V. infusion only; reduce rate or temporarily discontinue infusion if adverse effects occur. Infuse at ~0.08 mL/kg/minute; actual rate may be increased or decreased based on patient response. Emergency equipment (including epinephrine) should be available during infusion. Do not mix with other agents or solutions.
Dietary ConsiderationsSodium content of 1 L after reconstitution:

Aralast, Aralast NP: ≤230 mEq/L

Prolastin®: 100-210 mEq/L

Zemaira®: 81 mEq/1000 mg

Storage

Aralast, Aralast NP: Store under refrigeration at 2°C to 8°C (35°F to 46°F). Do not freeze. May also be stored at room temperature 25°C (77°F) for up to 1 month.

Prolastin®: Store up to ≤25°C (≤77°F); avoid freezing.

Zemaira™: Store up to 25°C (77°F). Avoid freezing.

ReconstitutionReconstitute with SWFI. To mix, swirl; do not shake. Use within 3 hours of reconstitution.
ContraindicationsHypersensitivity to any component of the formulation or other A$_1$-PI products; selective IgA deficiency with known anti-IgA antibody
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1:1000) should be available. Severe anaphylaxis may occur in patients with anti-IgA antibody; use in patients with selective IgA deficiency with known anti-IgA antibody is contraindicated

Disease-related concerns:

- Fluid overload: Use with caution in patients at risk for fluid overload.

- Hepatitis B: May consider hepatitis B immunization.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%: Hepatic: ALT increased (11%; ~4 times ULN), AST increased (11%; ~4 times ULN)

1% to 10%:

Central nervous system: Headache (≤7%)

Neuromuscular & skeletal: Musculoskeletal discomfort (7%)

Respiratory: Pharyngitis (2%)

<1%, postmarketing, and/or case reports: Allergic reactions, asthma, back pain, bilateral pulmonary infiltrates, bloating, bronchitis, chest pain, chills, cough increased, dizziness, dyspnea, fever <102°F (delayed up to 12 hours after treatment), flu-like syndrome, hypotension, leukocytosis, lightheadedness, pain, peripheral edema, pruritus, rash, rhinitis, sinusitis, somnolence, tachycardia, vasodilation, viral infection, vision abnormal. Severe reactions (anaphylaxis) may occur in patients with anti-IgA antibody.

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersAlpha$_1$-PI serum levels; lung function; vital signs during infusion
Monitoring: Lab TestsAlpha$_1$-PI serum levels
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Aralast, Aralast NP: 500 mg, 1000 mg [contains sodium ≤230 MEq/L and polysorbate 80; packaged with diluent]

Prolastin®: 500 mg, 1000 mg [contains sodium 100-210 mEq/L and sucrose; packaged with diluent]

Zemaira®: 1000 mg [contains sodium 81 mEq/1000 mg; packaged with diluent]

Generic AvailableNo
Mechanism of ActionAlpha$_1$-antitrypsin (AAT) is the principle protease inhibitor in serum. Its major physiologic role is to render proteolytic enzymes (secreted during inflammation) inactive. A decrease in AAT, as seen in congenital AAT deficiency, leads to increased elastic damage in the lung, causing emphysema.
Pharmacodynamics/Kinetics

Distribution: V_d: ~3.5 L

Half-life elimination: Metabolic: 5.9 days (Aralast)

Time to peak, serum: ~1 hour; threshold levels achieved after 3 weeks

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pharyngitis
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsA$_1$-PI; Alpha$_1$-Antitrypsin; Alpha$_1$-PI; Alpha$_1$-Proteinase Inhibitor, Human; α_1-PI
References

Louie SG, Sclar DA, and Gill MA, "Aralast: A New Alpha1-Protease Inhibitor for Treatment of Alpha-Antitrypsin Deficiency, " *Ann Pharmacother*, 2005, 39(11):1861-9.

Stoller JK and Aboussouan LS, "Alpha1-Antitrypsin Deficiency," *Lancet*, 2005, 365(9478):2225-36.[PubMed 15978931]

International Brand NamesProlastin (CA)

ALPRAZolam

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

ALPRAZolam may be confused with alprostadil, LORazepam, triazolam

Xanax® may be confused with Lanoxin®, Tenex®, Tylox®, Xopenex®, Zantac®, Zyrtec®

Pronunciation(al PRAY zoe lam)

U.S. Brand NamesAlprazolam Intensol®; Niravam™; Xanax XR®; Xanax®

Canadian Brand NamesAlti-Alprazolam; Apo-Alpraz®; Apo-Alpraz® TS; Gen-Alprazolam; Novo-Alprazol; Nu-Alprax; Xanax TS™; Xanax®

Pharmacologic CategoryBenzodiazepine

Use: Labeled IndicationsTreatment of anxiety disorder (GAD); panic disorder, with or without agoraphobia; anxiety associated with depression

Use: Unlabeled/InvestigationalAnxiety in children

Use: DentalPreoperative sedation

Dosing: Adults**Note:** Treatment >4 months should be re-evaluated to determine the patient's continued need for the drug

Anxiety: Oral: *Immediate release:* Effective doses are 0.5-4 mg/day in divided doses; the manufacturer recommends starting at 0.25-0.5 mg 3 times/day; titrate dose upward; usual maximum: 4 mg/day. Patients requiring doses >4 mg/day should be increased cautiously. Periodic reassessment and consideration of dosage reduction is recommended.

Anxiety associated with depression: Oral: *Immediate release:* Average dose required: 2.5-3 mg/day in divided doses

Ethanol withdrawal (unlabeled use): Oral: *Immediate release:* Usual dose: 2-2.5 mg/day in divided doses

Panic disorder: Oral:

Immediate release: Initial: 0.5 mg 3 times/day; dose may be increased every 3-4 days in increments ≤1 mg/day. Mean effective dosage: 5-6 mg/day; many patients obtain relief at 2 mg/day, as much as 10 mg/day may be required

Extended release: 0.5-1 mg once daily; may increase dose every 3-4 days in increments ≤1 mg/day (range: 3-6 mg/day)

Switching from immediate release to extended release: Patients may be switched to extended release tablets by taking the total daily dose of the immediate release tablets and giving it once daily using the extended release preparation.

Preoperative sedation: Oral: 0.5 mg in evening at bedtime and 0.5 mg 1 hour before procedure

Dose reduction: Abrupt discontinuation should be avoided. Daily dose may be decreased by 0.5 mg every 3 days, however, some patients may require a slower reduction. If withdrawal symptoms occur, resume previous dose and discontinue on a less rapid schedule.

Dosing: ElderlyInitial: 0.125-0.25 mg twice daily; increase by 0.125 mg/day as needed. The smallest effective dose should be used.

Immediate release: Initial 0.25 mg 2-3 times/day

Extended release: Initial: 0.5 mg once daily

Dosing: Pediatric

Anxiety (unlabeled use): Oral: Immediate release: Initial: 0.005 mg/kg/dose or 0.125 mg/dose 3 times/day; increase in increments of 0.125-0.25 mg, up to a maximum of 0.02 mg/kg/dose or 0.06 mg/kg/day (0.375-3 mg/day). See "Dose Reduction" comment in adult dosing.

Note: Treatment >4 months should be re-evaluated to determine the patient's continued need for the drug.

Dosing: Renal ImpairmentNo guidelines for adjustment; use caution.

Dosing: Hepatic ImpairmentOral: Reduce dose by 50% to 60% or avoid in cirrhosis.

Administration: Oral

Immediate release preparations: Can be administered sublingually with comparable onset and completeness of absorption.

Extended release tablet: Should be taken once daily in the morning; do not crush, break, or chew.

Orally-disintegrating tablets: Using dry hands, place tablet on top of tongue. If using one-half of tablet, immediately discard remaining half (may not remain stable). Administration with water is not necessary.

StorageOrally-disintegrating tablet: Store at room temperature of 20°C to 25°C (68°F to 77°F). Protect from moisture. Seal bottle tightly and discard any cotton packaged inside bottle.

RestrictionsC-IV

ContraindicationsHypersensitivity to alprazolam or any component of the formulation (cross-sensitivity with other benzodiazepines may exist); narrow-angle glaucoma; concurrent use with ketoconazole or itraconazole; pregnancy

Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present; episodes of mania or hypomania have occurred in depressed patients treated with alprazolam.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use (generally >10 days).
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.
- Renal impairment: Use with caution in patients with renal impairment or predisposition to urate nephropathy; has weak uricosuric properties.
- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.
- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.
- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury.
- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.
- Obese patients: Use with caution in obese patients; may have prolonged action when discontinued.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.
- Breakthrough anxiety: At the end of dosing interval, breakthrough anxiety may occur.
- Withdrawal: Rebound or withdrawal symptoms, including seizures, may occur 18 hours to 3 days following abrupt discontinuation or large decreases in dose (more common in patients receiving >4 mg/day or prolonged treatment). Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsConsidered to be a benzodiazepine of choice in elderly due to the short duration of action.

Pregnancy Risk FactorD

Pregnancy ConsiderationsBenzodiazepines have the potential to cause harm to the fetus, particularly when administered during the first trimester. In addition, withdrawal symptoms may occur in the neonate following *in utero* exposure. Use during pregnancy should be avoided.

LactationEnters breast milk/not recommended (AAP rates “of concern”)

Breast-Feeding ConsiderationsSymptoms of withdrawal, lethargy, and loss of body weight have been reported in infants exposed to alprazolam and/or benzodiazepines while nursing. Breast-feeding is not recommended.

Adverse Reactions

>10%:

Central nervous system: Abnormal coordination, cognitive disorder, depression, drowsiness, fatigue, irritability, lightheadedness, memory impairment, sedation, somnolence

Gastrointestinal: Appetite increased/decreased, constipation, salivation decreased, weight gain/loss, xerostomia

Genitourinary: Micturition difficulty

Neuromuscular & skeletal: Dysarthria

1% to 10%:

Cardiovascular: Hypotension

Central nervous system: Agitation, attention disturbance, confusion, depersonalization, derealization, disorientation, disinhibition, dizziness, dream abnormalities, fear, hallucinations, hypersomnia, nightmares, seizure, talkativeness

Dermatologic: Dermatitis, pruritus, rash

Endocrine & metabolic: Libido decreased/increased, menstrual disorders

Gastrointestinal: Salivation increased

Genitourinary: Incontinence

Hepatic: Bilirubin increased, jaundice, liver enzymes increased

Neuromuscular & skeletal: Arthralgia, ataxia, myalgia, paresthesia

Ocular: Diplopia

Respiratory: Allergic rhinitis, dyspnea

<1% (Limited to important or life-threatening): Amnesia, falls

Postmarketing and/or case reports: Galactorrhea, gynecomastia, hepatic failure, hepatitis, hyperprolactinemia, Stevens-Johnson syndrome

Metabolism/Transport Effects **Substrate** of CYP3A4 (major)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Cigarette smoking: May decrease alprazolam concentrations up to 50%.

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Alprazolam serum concentration is unlikely to be increased by grapefruit juice because of alprazolam's high oral bioavailability. The C_{max} of the extended release formulation is increased by 25% when a high-fat meal is given 2 hours before dosing. T_{max} is decreased 30% when food is given immediately prior to dose. T_{max} is increased by 30% when food is given ≥1 hour after dose.

Herb/Nutraceutical: St John's wort may decrease alprazolam levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring Parameters Respiratory and cardiovascular status

Nursing: Physical Assessment/Monitoring Assess other medications patient may be taking for effectiveness and interactions. Assess for signs of CNS depression. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance; periodically evaluate need for continued use. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient Education Take exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. Avoid alcohol and do not take other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Do not stop medication or reduce dosage abruptly without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in hazardous tasks until response to drug is known); nausea, vomiting, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, and fiber may help); altered sexual drive or ability (reversible); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report persistent CNS effects (eg, confusion, depression, increased sedation, excitation, headache, agitation, insomnia or nightmares, dizziness, fatigue, impaired coordination, changes in personality, or changes in cognition); changes in urinary pattern; muscle cramping, weakness, tremors, or rigidity; ringing in ears or visual disturbances; chest pain, palpitations, or rapid heartbeat; excessive perspiration; excessive GI symptoms (eg, cramping, constipation, vomiting, anorexia); or worsening of condition. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures as recommended by your prescriber. Breast-feeding is not recommended.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral [concentrate]:

Alprazolam Intensol®: 1 mg/mL (30 mL) [alcohol free, dye free, sugar free; contains propylene glycol]

Tablet: 0.25 mg, 0.5 mg, 1 mg, 2 mg

Xanax®: 0.25 mg, 0.5 mg, 1 mg, 2 mg

Tablet, extended release: 0.5 mg, 1 mg, 2 mg, 3 mg

Xanax XR®: 0.5 mg, 1 mg, 2 mg, 3 mg

Tablet, orally disintegrating [scored]:

Niravam™: 0.25 mg, 0.5 mg, 1 mg, 2 mg [orange flavor]

Generic Available Yes: Extended release tablet, immediate release tablet

Pricing: U.S. (www.drugstore.com)

Concentrate (Alprazolam Intensol)

1 mg/mL (30): $65.08

Tablet, 24-hour (Alprazolam)

0.5 mg (30): $31.99

1 mg (30): $69.99

2 mg (30): $76.00

Tablet, 24-hour (Xanax XR)

0.5 mg (30): $77.69

1 mg (30): $99.11

2 mg (30): $128.72

3 mg (30): $193.07

Tablet, orally-disintegrating (Niravam)

0.25 mg (30): $39.30

0.5 mg (30): $48.38

1 mg (30): $59.51

2 mg (30): $100.79

Tablets (Alprazolam)

0.25 mg (30): $11.99

0.5 mg (30): $11.99

1 mg (30): $11.99

2 mg (30): $13.99

Tablets (Xanax)

0.25 mg (30): $44.09

0.5 mg (30): $51.44

1 mg (30): $65.09

2 mg (30): $105.99

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Onset of action: Immediate release and extended release formulations: 1 hour

Duration of action: Immediate release: 5.1 ± 1.7 hours; Extended release: 11.3 ± 4.2 hours

Absorption: Extended release: Slower relative to immediate release formulation resulting in a concentration that is maintained 5-11 hours after dosing

Distribution: V_d: 0.9-1.2 L/kg; enters breast milk

Protein binding: 80%; primarily to albumin

Metabolism: Hepatic via CYP3A4; forms two active metabolites (4-hydroxyalprazolam and α-hydroxyalprazolam)

Bioavailability: 90%

Half-life elimination:

Adults: 11.2 hours (immediate release range: 6.3-26.9; extended release range: 10.7-15.8)

Elderly: 16.3 hours (range: 9-26.9 hours)

Alcoholic liver disease: 19.7 hours (range: 5.8-65.3 hours)

Obesity: 21.8 hours (range: 9.9-40.4 hours)

Time to peak, serum: Immediate release: 1-2 hours; Extended release: ~9 hours; decreased by 1 hour following bedtime dosing compared to morning dosing

Excretion: Urine (as unchanged drug and metabolites)

Related Information

- Benzodiazepines
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsNot intended for management of anxieties and minor distresses associated with everyday life. Treatment longer than 4 months should be re-evaluated to determine the patient's need for the drug. Patients who become physically dependent on alprazolam tend to have a difficult time discontinuing it; withdrawal symptoms may be severe. To minimize withdrawal symptoms, taper dosage slowly; do not discontinue abruptly. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Child/Adolescent ConsiderationsChildren <18 years: Anxiety: Dose not established; investigationally, in children 7-16 years of age (n=13), initial doses of 0.005 mg/kg or 0.125 mg/dose were given 3 times/day for situational anxiety; increments of 0.125-0.25 mg were used to increase doses to maximum of 0.02 mg/kg/dose or 0.06 mg/kg/day; a range of 0.375-3 mg/day was needed.

Note: A more recent study in 17 children (8-17 years of age) with overanxious disorder or avoidant disorders used initial daily doses of 0.25 mg for children <40 kg and 0.5 mg for those >40 kg. The dose was titrated at 2-day intervals to a maximum of 0.04 mg/kg/day. Required doses ranged from 0.5-3.5 mg/day (mean: 1.6 mg/day). Based on clinical global ratings, alprazolam appeared to be better than placebo, however, this difference was **not** statistically significant; further studies are needed (Simeon, 1992).

Simeon JG, Ferguson HB, Knott V, et al, “Clinical, Cognitive, and Neurophysiological Effects of Alprazolam in Children and Adolescents With Overanxious and Avoidant Disorders,” *J Am Acad Child Adolesc Psychiatry*, 1992, 31(1):29-33.

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Alprazolam is a short half-life benzodiazepine. Duration of action after a single dose is determined by redistribution rather than metabolism. Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle-relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include personal or family history of substance abuse and personality disorder.

With the exception of a slower absorption rate, the extended release dosage form of alprazolam displays similar bioavailability and pharmacokinetics to the immediate release dosage form. The slower absorption rate results in a concentration that is maintained between 5-11 hours after dosing. The rate of absorption of benzodiazepines has been linked to abuse potential and side effect burden (sedation and cognitive impairment). The extended release dosage form may have less abuse potential and side effects relative to the immediate release dosage form.

Anesthesia and Critical Care Concerns/Other ConsiderationsChronic use of this agent may increase the perioperative benzodiazepine dose needed to achieve desired effect. Patients who become physically dependent on alprazolam tend to have a difficult time discontinuing it; withdrawal symptoms may be severe. To minimize withdrawal symptoms, taper dosage slowly; do not discontinue abruptly. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

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International Brand NamesAceprax (PY, UY); Afobam (PL); Alcelam (TH); Alganax (ID); Alnax (TH); Alpaz (PE); Alplax (AR); Alpralid (IL); Alpram (KP); Alpranax (MY); Alprax (AU, HK, IN, TH); Alpraz (LU); Alprazomerck (PL); Alprocontin (IN); Alprox (HU, IL, PL); Altrox (PH); Alviz (ID); Alzam (MX, ZA); Alzax (KP); Alzolam (IN); Anax (TH); Anpress (TH); Apo-Alpraz (SG); Apraz (BR); Aprazo (TW); Azor (ZA); Calmlet (ID); Cassadan (DE); Constan (JP); Daclor (DO); Dixin (CO); Farmapram (MX); Feprax (ID); Frontal (BR); Frontin (HU, PL); Helex (HR); Irizz. (MX); Kalma (AU); Kinax (TW); Marzolam (TH); Nalion (HK); Neupax (MX); Neurol (PL); Nirvan (CO); Pacyl (IN); Pharnax (TH); Prazol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Prinox (AR); Solanax (JP); Soxietas (ID); Tafil (CR, DE, DK, GT, HN, MX, NI, PA, SV, VE); Tafil D (MU); Tazun (MX); Tensivan (CO); Trankimazin Retard (ES); Tranquinal (BR, CR, DO, EC, GT, HN, NI, PA, PE, PY, SV, UY); Tricalma (CN); Valeans (IT); Xanacine (TH); Xanagis (IL); Xanax (AE, AR, AU, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CY, CZ, DE, EC, EE, EG, ET, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PE, PK, PL, PT, QA, SA, SC, SD, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Xanax SR (SG); Xanax XR (IL, TW); Xanor (AT, FI, NO, PH, SE, ZA); Xanor XR (PH); Zacetin (KP); Zamhexal (AU); Zanapam (AE, BH, CY, EG, IL, IQ, IR, JO, KP, KW, LB, LY, OM, QA, SA, SY, YE); Zolam (IN); Zolarem (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Zoldac (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Zomiren (PL); Zopax (ZA); Zotran (CN); Zypraz (ID)

Alprostadil

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English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Alprostadil may be confused with alPRAZolam

Pronunciation(al PROS ta dill)

U.S. Brand NamesCaverject Impulse®; Caverject®; Edex®; Muse®; Prostin VR Pediatric®

Canadian Brand NamesCaverject®; Muse® Pellet; Prostin® VR

Pharmacologic CategoryProstaglandin; Vasodilator

Use: Labeled Indications

Prostin VR Pediatric®: Temporary maintenance of patency of ductus arteriosus in neonates with ductal-dependent congenital heart disease until surgery can be performed. These defects include cyanotic (eg, pulmonary atresia, pulmonary stenosis, tricuspid atresia, Fallot's tetralogy, transposition of the great vessels) and acyanotic (eg, interruption of aortic arch, coarctation of aorta, hypoplastic left ventricle) heart disease.

Caverject®: Treatment of erectile dysfunction of vasculogenic, psychogenic, or neurogenic etiology; adjunct in the diagnosis of erectile dysfunction

Edex®, Muse®: Treatment of erectile dysfunction of vasculogenic, psychogenic, or neurogenic etiology

Use: Unlabeled/InvestigationalInvestigational: Treatment of pulmonary hypertension in infants and children with congenital heart defects with left-to-right shunts

Dosing: Adults

Erectile dysfunction:

Intracavernous (Caverject®, Edex®): Individualize dose by careful titration; doses >40 mcg (Edex®) or >60 mcg (Caverject®) are not recommended: Initial dose must be titrated in physician's office. Patient must stay in the physician's office until complete detumescence occurs; if there is no response, then the next higher dose may be given within 1 hour; if there is still no response, a 1-day interval before giving the next dose is recommended; increasing the dose or concentration in the treatment of impotence results in increasing pain and discomfort.

Vasculogenic, psychogenic, or mixed etiology: Initiate dosage titration at 2.5 mcg, increasing by 2.5 mcg to a dose of 5 mcg and then in increments of 5-10 mcg depending on the erectile response until the dose produces an erection suitable for intercourse, not lasting >1 hour; if there is absolutely no response to initial 2.5 mcg dose, the second dose may be increased to 7.5 mcg, followed by increments of 5-10 mcg

Neurogenic etiology (eg, spinal cord injury): Initiate dosage titration at 1.25 mcg, increasing to a dose of 2.5 mcg and then 5 mcg; increase further in increments 5 mcg until the dose is reached that produces an erection suitable for intercourse, not lasting >1 hour

Maintenance: Once appropriate dose has been determined, patient may self-administer injections at a frequency of no more than 3 times/week with at least 24 hours between doses

Intraurethral (Muse® Pellet):

Initial: 125-250 mcg

Maintenance: Administer as needed to achieve an erection; duration of action is about 30-60 minutes; use only two systems per 24-hour period

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Patent ductus arteriosus I.V.:

Prostin VR Pediatric®: I.V. continuous infusion into a large vein, or alternatively through an umbilical artery catheter placed at the ductal opening: 0.05-0.1 mcg/kg/minute with therapeutic response, rate is reduced to lowest effective dosage. With unsatisfactory response, rate is increased gradually; maintenance: 0.01-0.4 mcg/kg/minute.

Note: PGE_1 is usually given at an infusion rate of 0.1 mcg/kg/minute, but it is often possible to reduce the dosage to $^1/_2$ or even $^1/_{10}$ without losing the therapeutic effect. The mixing schedule is shown in the table.

Alprostadil

Add 1 Ampul (500 mcg) to:	Concentration (mcg/mL)	Infusion Rate	
		mL/min/kg Needed to Infuse 0.1 mcg/kg/min	mL/kg/24 h
250 mL	2	0.05	72
100 mL	5	0.02	28.8
50 mL	10	0.01	14.4
25 mL	20	0.005	7.2

Note: Therapeutic response is indicated by increased pH in those with acidosis or by an increase in oxygenation (PO_2) usually evident within 30 minutes.

Administration: OtherErectile dysfunction: Use a $^1/_2$ inch, 27- to 30-gauge needle. Inject into the dorsolateral aspect of the proximal third of the penis, avoiding visible veins; alternate side of the penis for injections.

Storage

Caverject® Impulse™: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F). Following reconstitution, use within 24 hours and discard any unused solution.

Caverject® powder: The 5 mcg, 10 mcg, and 20 mcg vials should be stored at or below 25°C (77°F); The 40 mcg vial should be stored at 2°C to 8°C until dispensed. After dispensing, stable for up to 3 months at or below 25°C. Following reconstitution, all strengths should be stored at or below 25°C (77°F); do not refrigerate or freeze; use within 24 hours.

Caverject® solution: Prior to dispensing, store frozen at -20°C to -10°C (-4°F to -14°F). Once dispensed, may be stored frozen for up to 3 months, or under refrigeration at 2°C to 8°C (36°F to 46°F) for up to 7 days. Do not refreeze. Once removed from foil wrap, solution may be allowed to warm to room temperature prior to use. If not used immediately, solution should be discarded. Shake well prior to use.

Edex®: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F); following reconstitution, use immediately and discard any unused solution.

Muse®: Refrigerate at 2°C to 8°C (36°F to 46°F); may be stored at room temperature for up to 14 days

Prostin VR Pediatric®: Refrigerate at 2°C to 8°C (36°F to 46°F). Prior to infusion, dilute with D_5W or NS; use within 24 hours.

Reconstitution

Caverject® Impulse™: Provided as a dual-chamber syringe with diluent in one chamber. To mix, hold syringe with needle pointing upward and turn plunger clockwise; turn upside down several times to mix. Device can be set to deliver specified dose, each device can be set at various increments.

Caverject® powder: Use only the supplied diluent for reconstitution (ie, bacteriostatic/sterile water with benzyl alcohol 0.945%).

Edex®: Reconstitute with NS.

ContraindicationsHypersensitivity to alprostadil or any component of the formulation; hyaline membrane disease or persistent fetal circulation and when a dominant left-to-right shunt is present; respiratory distress syndrome; conditions predisposing patients to priapism (sickle cell anemia, multiple myeloma, leukemia); patients with anatomical deformation of the penis, penile implants; use in men for whom sexual activity is inadvisable or contraindicated; pregnancy

Warnings/Precautions

Boxed warnings:

- Apnea: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Apnea: **[U.S. Boxed Warning]: Apnea may occur in 10% to 12% of neonates with congenital heart defects, especially in those weighing <2 kg at birth.** Apnea usually appears during the first hour of drug infusion.

Disease-related concerns:

- Erectile dysfunction: Appropriate use: When used in erectile dysfunction, priapism may occur; patient must be instructed to report to physician or seek immediate medical assistance if an erection persists for longer than 4 hours. Treat immediately to avoid penile tissue damage and permanent loss of potency; discontinue therapy if signs of penile fibrosis develop (penile angulation, cavernosal fibrosis, or Peyronie's disease).

- Patency of ductus arteriosus: Appropriate use: Infuse for the shortest time at the lowest dose consistent with good patient care. Use for

>120 hours has been associated with antral hyperplasia and gastric outlet obstruction.

Special populations:

- Neonates: Use with caution in neonates with bleeding tendencies.

Dosage form specific issues:

- Muse®: When used in erectile dysfunction, syncope occurring within 1 hour of administration has been reported. The potential for drug-drug interactions may occur when prescribed concomitantly with antihypertensives. Some lowering of blood pressure may occur without symptoms, and swelling of leg veins, leg pain, perineal pain, and rapid pulse have been reported in <2% of patients during in-clinic titration and home treatment.

Geriatric ConsiderationsElderly may have concomitant diseases which would contraindicate the use of alprostadil. Other forms of attaining penile tumescence are recommended.
Pregnancy Risk FactorX/C (Muse®)
Pregnancy ConsiderationsAlprostadil is embryotoxic in animal studies. It is not indicated for use in women. The manufacturer of Muse® recommends a condom barrier when being used during sexual intercourse with a pregnant women.
LactationNot indicated for use in women
Adverse Reactions

Intraurethral:

>10%: Genitourinary: Penile pain, urethral burning

2% to 10%:

Central nervous system: Headache, dizziness, pain

Genitourinary: Vaginal itching (female partner), testicular pain, urethral bleeding (minor)

<2%: Tachycardia, perineal pain, leg pain

Intracavernosal injection:

>10%: Genitourinary: Penile pain

1% to 10%:

Cardiovascular: Hypertension

Central nervous system: Headache, dizziness

Genitourinary: Prolonged erection (>4 hours, 4%), penile fibrosis, penis disorder, penile rash, penile edema

Local: Injection site hematoma and/or bruising

<1%: Balanitis, injection site hemorrhage, priapism (0.4%)

Intravenous:

>10%:

Cardiovascular: Flushing

Central nervous system: Fever

Respiratory: Apnea

1% to 10%:

Cardiovascular: Bradycardia, hyper-/hypotension, tachycardia, cardiac arrest, edema

Central nervous system: Seizure, headache, dizziness

Endocrine & metabolic: Hypokalemia

Gastrointestinal: Diarrhea

Hematologic: Disseminated intravascular coagulation

Neuromuscular & skeletal: Back pain

Respiratory: Upper respiratory infection, flu syndrome, sinusitis, nasal congestion, cough

Miscellaneous: Sepsis, localized pain in structures other than the injection site

<1%: Anemia, anuria, bleeding, bradypnea, bronchial wheezing, cerebral bleeding, CHF, gastric regurgitation, hematuria, hyperbilirubinemia, hyperemia, hyperextension of neck, hyperirritability, hyperkalemia, hypoglycemia, hypothermia, jitteriness, lethargy, peritonitis, second-degree heart block, shock, stiffness, supraventricular tachycardia, thrombocytopenia, ventricular fibrillation

Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb InteractionsEthanol: Avoid concurrent use (vasodilating effect).

Monitoring ParametersArterial pressure, respiratory rate, heart rate, temperature, degree of penile pain, length of erection, signs of infection

Nursing: Physical Assessment/Monitoring**Neonate:** Monitor closely; apnea has occurred during first hour after administration. **Erectile dysfunction:** After individual dose titration is determined by prescriber, the Caverject® injection (or Muse®) is generally self-administered. Teach patient proper use if self-administered (appropriate injection technique and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** See Pregnancy Issues.

Patient EducationUse only as directed, no more than 3 times/week, allowing 24 hours between injections. Avoid alcohol. Store in refrigerator and dilute with supplied diluent immediately before use. Use alternate sides of penis with each injection. Dispose of syringes and needle and single-dose vials in a safe manner (do not share medication, syringes, or needles). Note that the risk of transmitting blood-borne disease is increased with use of alprostadil injections since a small amount of bleeding at injection site is possible. Stop using and contact prescriber immediately if signs of priapism occur, erections last more than 4 hours, or you experience moderate to severe penile pain. Report penile problems (eg, nodules, new penile pain, rash, bruising, numbness, swelling, signs of infection, abnormal ejaculations); cardiac symptoms (hypo- or hypertension, chest pain, palpitations, irregular heartbeat); flushing, fever, flu-like symptoms; respiratory difficulty or wheezing; or other adverse reactions. Refer to prescriber every 3 months to ensure proper technique and for dosage evaluation. **Pregnancy precautions:** Consult prescriber about use of contraceptives. Do not give blood while taking this medication and for 1 month following discontinuance.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution:

Caverject®: 20 mcg, 40 mcg [contains lactose; diluent contains benzyl alcohol]

Caverject Impulse®: 10 mcg, 20 mcg [prefilled injection system; contains lactose; diluent contains benzyl alcohol]

Edex®: 10 mcg, 20 mcg, 40 mcg [contains lactose; packaged in kits containing diluent, syringe, and alcohol swab]

Injection, solution: 500 mcg/mL (1 mL)

Prostin VR Pediatric®: 500 mcg/mL (1 mL) [contains dehydrated alcohol]

Pellet, urethral:

Muse®: 125 mcg (6s) [DSC], 250 mcg (6s), 500 mcg (6s), 1000 mcg (6s)

Generic AvailableYes: Solution for injection

Pricing: U.S. (www.drugstore.com)

Kit (Caverject Impulse)

10 mcg (2): $66.14

20 mcg (2): $83.99

Kit (Edex)

10 mcg (1): $64.99

10 mcg (1): $170.99

20 mcg (1): $79.99

20 mcg (1): $216.99

40 mcg (1): $106.54

40 mcg (1): $295.63

Pellet (Muse)

125 mcg (6): $154.70

250 mcg (6): $161.07

500 mcg (6): $171.68

1000 mcg (6): $186.49

Solution (reconstituted) (Caverject)

40 mcg (6): $259.98

Mechanism of ActionCauses vasodilation by means of direct effect on vascular and ductus arteriosus smooth muscle; relaxes trabecular smooth muscle by dilation of cavernosal arteries when injected along the penile shaft, allowing blood flow to and entrapment in the lacunar spaces of the penis (ie, corporeal veno-occlusive mechanism)

Pharmacodynamics/Kinetics

Onset of action: Rapid

Duration: <1 hour

Distribution: Insignificant following penile injection

Protein binding, plasma: 81% to albumin

Metabolism: ~75% by oxidation in one pass via lungs

Half-life elimination: 5-10 minutes

Excretion: Urine (90% as metabolites) within 24 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness; rarely may produce irritability

Mental Health: Effects on Psychiatric TreatmentMay cause seizures; use caution with clozapine and bupropion

Index TermsPGE$_1$; Prostaglandin E$_1$

References

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International Brand NamesAlprostapint (BG, HU, PL); Befar (HK); Caverject (AE, AR, AT, BB, BH, BM, BO, BR, BS, BZ, CN, CO, CR, CY, DE, DO, EC, EE, EG, FR, GB, GT, GY, HN, HU, IE, IL, IQ, IR, JM, JO, KP, KW, LB, LU, LY, MX, MY, NI, NL, NO, NZ, OM, PA, PE, PL, PR, PT, PY, QA, SA, SE, SG, SR, SV, SY, TT, UY, VE, YE, ZA); Caverject Dual Chamber (FR, HK); Caverject Impulse (AU); Caverjet (IL); Edex (FR, PL); Eglandin (KP); Gaverject (PK); Liple (JP); Lyple (JP); Minprog (AT); Muse (AE, BH, CY, EG, GB, IE, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE, ZA); Palux (JP); Prink (KP); Promostan (TW); Prostandin (JP, KP); Prostavasin (AR, BR, CL, HK, HU, LU, PH, PL, UY); Prostin (CZ); Prostin Pediatrico (CN); Prostin VR (AE, AU, BE, BH, CH, CY, EG, GB, GR, HN, HU, IL, IN, IQ, IR, IT, JO, KW, LB, LY, NL, OM, PL, QA, SA, SY, TH, TW, YE, ZA); Prostin VR Paedeatric (MY); Prostine VR (FR); Prostivas (DK, FI, NO, SE); Sugiran (ES); Viridal (DE)

Alteplase

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Alteplase may be confused with Altace®

"tPA" abbreviation should not be used when writing orders for this medication; has been misread as TNKase (tenecteplase)

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V.) among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(AL te plase)

U.S. Brand NamesActivase®; Cathflo® Activase®

Canadian Brand NamesActivase® rt-PA; Cathflo® Activase®

Pharmacologic CategoryThrombolytic Agent

Use: Labeled IndicationsManagement of ST-elevation myocardial infarction (STEMI) for the lysis of thrombi in coronary arteries; management of acute ischemic stroke (AIS); management of acute pulmonary embolism

Recommended criteria for treatment:

STEMI: Chest pain ≥20 minutes duration, onset of chest pain within 12 hours of treatment (or within prior 12-24 hours in patients with continuing ischemic symptoms), and ST-segment elevation >0.1 mV in at least two contiguous precordial leads or two adjacent limb leads on ECG or new or presumably new left bundle branch block (LBBB)

AIS: Onset of stroke symptoms within 3 hours of treatment

Acute pulmonary embolism: Age ≤75 years: Documented massive pulmonary embolism by pulmonary angiography or echocardiography or high probability lung scan with clinical shock

Cathflo® Activase®: Restoration of central venous catheter function

Use: Unlabeled/InvestigationalAcute ischemic stroke with symptom onset within 3-4.5 hours of treatment; acute peripheral arterial occlusive disease

Dosing: Adults

ST-elevation myocardial infarction (STEMI): I.V. (Activase®): Front loading dose (weight-based):

Patients >67 kg: Total dose: 100 mg over 1.5 hours; infuse 15 mg over 1-2 minutes. Infuse 50 mg over 30 minutes. Infuse remaining 35 mg of alteplase over the next hour. See "Note."

Patients ≤67 kg: Infuse 15 mg I.V. bolus over 1-2 minutes, then infuse 0.75 mg/kg (not to exceed 50 mg) over next 30 minutes, followed by 0.5 mg/kg over next 60 minutes (not to exceed 35 mg). See "Note."

Note: All patients should receive 162-325 mg of chewable nonenteric coated aspirin as soon as possible and then daily. Administer concurrently with heparin 60 units/kg bolus (maximum: 4000 units) followed by continuous infusion of 12 units/kg/hour (maximum: 1000 units/hour) and adjust to aPTT target of 50-70 seconds (or 1.5-2 times the upper limit of control).

Acute pulmonary embolism: I.V. (Activase®): 100 mg over 2 hours.

Acute ischemic stroke: I.V. (Activase®): Doses should be given within the first 3 hours of the onset of symptoms; **Note:** Initiation of anticoagulants (eg, heparin) or antiplatelet agents (eg, aspirin) within 24 hours after starting alteplase is not recommended; however, initiation of aspirin between 24-48 hours after stroke onset is recommended (Adams, 2007).

Recommended total dose: 0.9 mg/kg (maximum total dose: 90 mg)

Patients ≤100 kg: Load with 0.09 mg/kg (10% of 0.9 mg/kg dose) as an I.V. bolus over 1 minute, followed by 0.81 mg/kg (90% of 0.9 mg/kg dose) as a continuous infusion over 60 minutes.

Patients >100 kg: Load with 9 mg (10% of 90 mg) as an I.V. bolus over 1 minute, followed by 81 mg (90% of 90 mg) as a continuous infusion over 60 minutes.

Unlabeled use: Administration of alteplase may be of benefit for select patients with acute ischemic stroke who present between 3 and 4.5 hours after onset of symptoms (Hacke, 2008)

Central venous catheter clearance: Intracatheter (Cathflo® Activase® 1 mg/mL):

Patients <30 kg: 110% of the internal lumen volume of the catheter, not to exceed 2 mg/2 mL; retain in catheter for 0.5-2 hours; may instill a second dose if catheter remains occluded

Patients ≥30 kg: 2 mg (2 mL); retain in catheter for 0.5-2 hours; may instill a second dose if catheter remains occluded

Acute peripheral arterial occlusive disease (unlabeled use): Intra-arterial: 0.02-0.1 mg/kg/hour for up to 36 hours

Advisory Panel to the Society for Cardiovascular and Interventional Radiology on Thrombolytic Therapy recommendation: ≤2 mg/hour and subtherapeutic heparin (aPTT <1.5 times baseline)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricCentral venous catheter clearance: Intracatheter: Patients <30 kg: 110% of the internal lumen volume of the catheter, not to exceed 2 mg/2 mL; retain in catheter for 0.5-2 hours; may instill a second dose if catheter remains occluded

Administration: I.V.

Activase®: ST-elevation MI: Accelerated infusion: Bolus dose may be prepared by one of three methods:

1) Removal of 15 mL reconstituted (1 mg/mL) solution from vial

2) Removal of 15 mL from a port on the infusion line after priming

3) Programming an infusion pump to deliver a 15 mL bolus at the initiation of infusion

Activase®: Acute ischemic stroke: Bolus dose (10% of total dose) may be prepared by one of three methods:

1) Removal of the appropriate volume from reconstituted solution (1 mg/mL)

2) Removal of the appropriate volume from a port on the infusion line after priming

3) Programming an infusion pump to deliver the appropriate volume at the initiation of infusion

Note: Remaining dose for STEMI, AIS, or total dose for acute pulmonary embolism may be administered as follows: Any quantity of drug not to be administered to the patient must be removed from vial(s) prior to administration of remaining dose.

50 mg vial: Either PVC bag or glass vial and infusion set

100 mg vial: Insert spike end of the infusion set through the same puncture site created by transfer device and infuse from vial

If further dilution is desired, may be diluted in equal volume of 0.9% sodium chloride or D$_5$W to yield a final concentration of 0.5 mg/mL.

Administration: I.V. DetailReconstituted solution should be clear or pale yellow and transparent. Avoid agitation during dilution.

pH: 5-7.3

Administration: OtherCathflo® Activase®: Intracatheter: Instill dose into occluded catheter. Do not force solution into catheter. After a 30-minute dwell time, assess catheter function by attempting to aspirate blood. If catheter is functional, aspirate 4-5 mL of blood in patients ≥10 kg or 3 mL in patients <10 kg to remove Cathflo® Activase® and residual clots. Gently irrigate the catheter with NS. If catheter remains nonfunctional, let Cathflo® Activase® dwell for another 90 minutes (total dwell time: 120 minutes) and reassess function. If catheter function is not restored, a second dose may be instilled.

Storage

Activase®: The lyophilized product may be stored at room temperature (not to exceed 30°C/86°F), or under refrigeration. Once reconstituted it should be used within 8 hours.

Cathflo® Activase®: Store lyophilized product in refrigerator. Once reconstituted, store at 2°C to 30°C (36°F to 86°F) and use within 8 hours.

Reconstitution

Activase®:

50 mg vial: Use accompanying diluent (50 mL sterile water for injection); do not shake. Final concentration: 1 mg/mL.

100 mg vial: Use transfer set with accompanying diluent (100 mL vial of sterile water for injection); no vacuum is present in 100 mg vial. Final concentration: 1 mg/mL.

Cathflo® Activase®: Add 2.2 mL SWFI to vial; do not shake. Final concentration: 1 mg/mL.

CompatibilityStable in NS, sterile water for injection; **incompatible** with bacteriostatic water; **variable stability (consult detailed reference)** in D$_5$W.

Y-site administration: Compatible: Lidocaine, metoprolol, propranolol. **Incompatible:** Dobutamine, dopamine, heparin, nitroglycerin.

Compatibility when admixed: Compatible: Lidocaine, morphine, nitroglycerin. **Incompatible:** Dobutamine, dopamine, heparin.

ContraindicationsHypersensitivity to alteplase or any component of the formulation

Treatment of STEMI or PE: Active internal bleeding; history of CVA; recent intracranial or intraspinal surgery or trauma; intracranial neoplasm; arteriovenous malformation or aneurysm; known bleeding diathesis; severe uncontrolled hypertension

Treatment of acute ischemic stroke: Evidence of intracranial hemorrhage or suspicion of subarachnoid hemorrhage on pretreatment evaluation; recent (within 3 months) intracranial or intraspinal surgery; prolonged external cardiac massage; suspected aortic dissection; serious head trauma or previous stroke; history of intracranial hemorrhage; uncontrolled hypertension at time of treatment (eg, >185 mm Hg systolic or >110 mm Hg diastolic); seizure at the onset of stroke; active internal bleeding; intracranial neoplasm; arteriovenous malformation or aneurysm; known bleeding diathesis including but not limited to: current use of anticoagulants or an INR >1.7, administration of heparin within 48 hours preceding the onset of stroke and an elevated aPTT at presentation, platelet count <100,000/mm^3.

Other exclusion criteria (NINDS recombinant tPA study): Stroke or serious head injury within 3 months, major surgery or serious trauma within 2 weeks, GI or urinary tract hemorrhage within 3 weeks, aggressive treatment required to lower blood pressure, glucose level <50 mg/dL or >400 mg/dL, arterial puncture at a noncompressible site or lumbar puncture within 1 week, clinical presentation suggesting post-MI pericarditis, pregnancy, breast-feeding.

Allergy Considerations

- Thrombolytic Agent, Fibrin-Specific Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Arrhythmias: Coronary thrombolysis may result in reperfusion arrhythmias.
- Bleeding: Doses >150 mg are associated with increased risk of intracranial hemorrhage; monitor all potential bleeding sites. If serious bleeding occurs, the infusion of alteplase and heparin should be stopped.

Disease-related concerns:

- Conditions that increase bleeding risk: For the following conditions, the risk of bleeding is higher with use of thrombolytics and should be weighed against the benefits of therapy: Recent (within 10 days) major surgery (eg, CABG, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels), cerebrovascular disease, recent gastrointestinal or genitourinary bleeding, recent trauma, hypertension (systolic BP >175 mm Hg and/or diastolic BP >110 mm Hg), high likelihood of left heart thrombus (eg, mitral stenosis with atrial fibrillation), acute pericarditis, subacute bacterial endocarditis, hemostatic defects including ones caused by severe renal or hepatic dysfunction, significant hepatic dysfunction, diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions, septic thrombophlebitis or occluded AV cannula at seriously infected site and/or any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of location.
- ST-elevation myocardial infarction (STEMI): Appropriate use: Follow standard management for STEMI while infusing alteplase.
- Stroke: Appropriate use: Treatment of patients with acute ischemic stroke more than 3 hours after symptom onset is not recommended. Treatment of patients with minor neurological deficit or with rapidly improving symptoms is not recommended.

Concurrent drug therapy issues:

- Anticoagulants: Use with caution in patients receiving oral anticoagulants; increased risk of bleeding.
- Heparin: Concurrent heparin anticoagulation may contribute to bleeding.

Special populations:

- Elderly: Use with caution in patients with advanced age (eg, >75 years); increased risk of bleeding.
- Pregnancy: Use with caution in pregnancy; increased risk of bleeding.

Dosage form specific issues:

- Cathflo® Activase®: When used to restore catheter function, use Cathflo® cautiously in those patients with known or suspected catheter infections. Evaluate catheter for other causes of dysfunction before use. Avoid excessive pressure when instilling into catheter.

Other warnings/precautions:

- Administration: Intramuscular injections and nonessential handling of the patient should be avoided. Venipunctures should be performed carefully and only when necessary. If arterial puncture is necessary, use an upper extremity vessel that can be manually compressed.

Geriatric ConsiderationsNo specific changes in use in elderly patients are necessary.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsAs with all drugs which may affect hemostasis, bleeding is the major adverse effect associated with alteplase. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the dosage administered, concurrent use of multiple agents which alter hemostasis, and patient predisposition. Rapid lysis of coronary artery thrombi by thrombolytic agents may be associated with reperfusion-related atrial and/or ventricular arrhythmia. **Note:** Lowest rate of bleeding complications expected with dose used to restore catheter function.

1% to 10%:

Cardiovascular: Hypotension

Central nervous system: Fever

Dermatologic: Bruising (1%)

Gastrointestinal: GI hemorrhage (5%), nausea, vomiting

Genitourinary: GU hemorrhage (4%)

Hematologic: Bleeding (0.5% major, 7% minor: GUSTO trial)

Local: Bleeding at catheter puncture site (15.3%, accelerated administration)

<1% (Limited to important or life-threatening): Intracranial hemorrhage (0.4% to 0.87% when dose is ≤100 mg), retroperitoneal hemorrhage, pericardial hemorrhage, gingival hemorrhage, epistaxis, allergic reactions: anaphylaxis, anaphylactoid reactions, laryngeal edema, rash, and urticaria (<0.02%).

Additional cardiovascular events associated **with use in STEMI:** AV block, cardiogenic shock, heart failure, cardiac arrest, recurrent ischemia/infarction, myocardial rupture, electromechanical dissociation, pericardial effusion, pericarditis, mitral regurgitation, cardiac tamponade, thromboembolism, pulmonary edema, asystole, ventricular tachycardia, bradycardia, ruptured intracranial AV malformation, seizure, hemorrhagic bursitis, cholesterol crystal embolization

Additional events associated **with use in pulmonary embolism:** Pulmonary re-embolization, pulmonary edema, pleural effusion, thromboembolism

Additional events associated **with use in stroke:** Cerebral edema, cerebral herniation, seizure, new ischemic stroke

Drug Interactions

Anticoagulants: Thrombolytic Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Aprotinin: May diminish the therapeutic effect of Thrombolytic Agents. *Risk D: Consider therapy modification*

Drotrecogin Alfa: Thrombolytic Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Thrombolytic Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Nitroglycerin: May decrease the serum concentration of Alteplase. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid cat's claw, dong quai, evening primrose, feverfew, red clover, horse chestnut, garlic, green tea, ginseng, ginkgo (all have additional antiplatelet activity).

Test InteractionsAltered results of coagulation and fibrinolytic agents

Monitoring Parameters

Acute ischemic stroke: In addition to monitoring for bleeding complications, the 2007 AHA/ASA Guidelines for the early management of acute ischemic stroke recommends the following:

Perform neurological assessments every 15 minutes during infusion and every 30 minutes thereafter for the next 6 hours, then hourly until 24 hours after treatment.

If severe headache, acute hypertension, nausea, or vomiting occurs, discontinue the infusion and obtain emergency CT scan.

Measure BP every 15 minutes for the first 2 hours then every 30 minutes for the next 6 hours, then hourly until 24 hours after initiation of alteplase. Increase frequency if a systolic BP is ≥180 mm Hg or if a diastolic BP is ≥105 mm Hg; administer antihypertensive medications to maintain BP at or below these levels.

Obtain a follow-up CT scan at 24 hours before starting anticoagulants or antiplatelet agents.

Central venous catheter clearance: Assess catheter function by attempting to aspirate blood.

ST-elevation MI: Assess for evidence of cardiac reperfusion through resolution of chest pain, resolution of baseline ECG changes, preserved left ventricular function, cardiac enzyme washout phenomenon, and/or the appearance of reperfusion arrhythmias; assess for bleeding potential through clinical evidence of GI bleeding, hematuria, gingival bleeding, fibrinogen levels, fibrinogen degradation products, prothrombin times, and partial thromboplastin times.

Reference Range

Not routinely measured; literature supports therapeutic levels of 0.52-1.8 mcg/mL

Fibrinogen: 200-400 mg/dL

Activated partial thromboplastin time (aPTT): 22.5-38.7 seconds

Prothrombin time (PT): 10.9-12.2 seconds

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (especially those medications that may affect coagulation or platelet function). Assess vital signs, results of laboratory tests, and ECG prior to, during, and after therapy. Arrhythmias may occur; antiarrhythmic drugs should be immediately available. Infusion site should be monitored and patient assessed for hemorrhage every 10 minutes (or according to institutional policy) during therapy and for 1 hour following therapy. Strict bedrest should be maintained and bleeding precautions should be instituted; avoid invasive procedures and activities that could cause trauma. Patient instructions determined by patient condition.

Monitoring: Lab TestsCBC, PTT

Patient EducationThis medication can only be administered by infusion; you will be monitored closely during and after treatment. You will have a tendency to bleed easily; use caution to prevent injury (use electric razor, soft toothbrush, and use caution with knives, needles, or anything sharp). Follow instructions for strict bedrest to reduce the risk of injury. If bleeding occurs, report immediately and apply pressure to bleeding spot until bleeding stops completely. Report unusual pain (acute headache, joint pain, chest pain); unusual bruising or bleeding; blood in urine, stool, or vomit; bleeding gums; vision changes; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, recombinant:

Activase®: 50 mg [29 million int. units; contains polysorbate 80; packaged with diluent]; 100 mg [58 million int. units; contains polysorbate 80; packaged with diluent and transfer device]

Cathflo® Activase®: 2 mg [contains polysorbate 80]

Generic AvailableNo

ManufacturerGenentech, Inc

Mechanism of ActionInitiates local fibrinolysis by binding to fibrin in a thrombus (clot) and converts entrapped plasminogen to plasmin

Pharmacodynamics/Kinetics

Duration: >50% present in plasma cleared ~5 minutes after infusion terminated, ~80% cleared within 10 minutes

Excretion: Clearance: Rapidly from circulating plasma (550-650 mL/minute), primarily hepatic; >50% present in plasma is cleared within 5 minutes after the infusion is terminated, ~80% cleared within 10 minutes

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: As with all drugs which may affect hemostasis, bleeding is the major adverse effect associated with alteplase. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables, including the dosage administered, concurrent use of multiple agents which alter hemostasis, and patient predisposition. Rapid lysis of coronary artery thrombi by thrombolytic agents may be associated with reperfusion-related atrial and/or ventricular arrhythmias.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular Considerations

ST-Elevation Myocardial Infarction: The 2004 ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction recommend prehospital thrombolysis in special circumstances (eg, transport time >30 minutes). Efforts to quickly identify and safely treat appropriate candidates for therapy continue. Reducing treatment delays is very important to improve mortality. Thrombolytic therapy is indicated in patients with ST-segment elevation >1 mm in two or more contiguous leads or at least two adjacent limb leads in patients with chest discomfort >30 minutes but ≤12 hours. Patients with chest discomfort suggestive of ischemia and new-onset left bundle branch block (LBBB) are also candidates for thrombolysis. Generally, there is only a small trend for benefit of therapy after a delay of more than 12-24 hours, but thrombolysis may be considered for selected patients with ongoing ischemic pain and extensive ST elevation. Additional absolute contraindications for fibrinolysis use in ST-elevation myocardial infarction from the 2004 ACC/AHA guidelines: Any prior intracranial hemorrhage, ischemic stroke within 3 months (except one within 3 hours), significant closed head or facial trauma within 3 months. Additional relative contraindications include history of chronic severe, poorly-controlled hypertension, severe uncontrolled hypertension on presentation (systolic BP >180 mm Hg or diastolic >110 mm Hg; could be an absolute contraindication in low-risk patients), history of prior ischemic stroke >3 months, dementia, or known intracranial pathology, traumatic or prolonged (>10 minutes) CPR or major surgery (<3 weeks), recent (within 2-4 weeks) internal bleeding, noncompressible vascular punctures, pregnancy, active peptic ulcer, current use of anticoagulants.

Thrombolytic and GP IIb/IIIa Inhibitor: In the GUSTO V trial, patients with STEMI were randomized to standard-dose reteplase or half-dose reteplase (two boluses of 5 units each, 30 minutes apart) and full dose abciximab. Thirty-day mortality (primary endpoint) was similar in both groups. The combination treatment group had fewer deaths or nonfatal reinfarctions, less need for urgent revascularization, and fewer major ischemic complications. More bleeding occurred in the combination treatment group, but intracranial hemorrhage and nonfatal disabling stroke were similar in both groups. All cause mortality at one year was similar in both groups. In TIMI 14, the combination of full-dose abciximab (0.25 mg/kg bolus followed by a 12-hour infusion of 0.125 mcg/kg/minute, maximum 10 mcg/minute) and half-dose alteplase (15 mg bolus followed by 35 mg infusion over 60 minutes) resulted in 74% of patients achieving TIMI grade 3 flow at 90 minutes. The 2004 ACC/AHA guidelines for the management of patients with STEMI suggests that abciximab and half-dose reteplase or tenecteplase may be considered for prevention of reinfarction in patients with an anterior MI, who are <75 years of age, and who have no risk factors for bleeding.

However, more recently, the 2008 American College of Chest Physicians guidelines recommends against the combination of half-dose reteplase or tenecteplase and standard-dose abciximab (with low dose unfractionated heparin) in any patient with STEMI due to the lack of mortality benefit and the risk of major bleeding (Goodman, 2008).

Anesthesia and Critical Care Concerns/Other Considerations

Acute Ischemic Stroke (AIS):

Presentation within 0-3 hours of stroke onset (FDA approved): Based on the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA stroke study, administration of alteplase within 0-3 hours after symptom onset is an established therapeutic modality in the treatment of AIS. The NINDS trial demonstrated significant neurological improvement at 24 hours and a greater number of patients experienced a favorable outcome (complete or nearly complete neurological recovery) at 90 days if they received alteplase compared to those receiving placebo. The decision to administer alteplase should be made after careful consideration of the patient's eligibility including level of neurological deficit, time of presentation, and existence of contraindications to alteplase (eg, intracranial hemorrhage). Since a powerful time-to-treatment effect exists with the administration of alteplase for AIS, any delay in treatment once a patient is identified to be a candidate for alteplase may compromise efficacy and possibly safety. With administration of alteplase for AIS, the clinician should be keenly aware of the potential serious side effect of bleeding especially intracranial hemorrhage (ICH) which occurs at a rate of approximately 6% in this population. Strict adherence to established protocols is necessary to prevent higher rates of ICH. Orolingual angioedema, a rare but serious complication, may also occur and compromise the airway.

Presentation within 3-4.5 hours of stroke onset (non-FDA approved): Administration of alteplase is currently recommended for patients with AIS who may be treated within 3 hours of symptom onset (2007 AHA/ASA guideline). However, more recently, the European Cooperative Acute Stroke Study III (ECASS III; Hacke, 2008), a double-blind, multicenter trial enrolled 821 patients with AIS presenting with onset of stroke symptoms between 3-4.5 hours. Patients were randomized to either placebo or standard-dose alteplase (total dose: 0.9 mg/kg over 60 minutes; maximum: 90 mg; with 10% of 0.9 mg/kg given as loading dose). Patients were excluded if they had evidence of brain hemorrhage or major infarction. Other notable exclusion criteria were age >80 years, severe stroke as assessed clinically (eg, NIH Stroke Scale >25) and/or by appropriate imaging techniques, and history of prior stroke and concomitant diabetes. The primary endpoint was disability at 90 days, dichotomized as a favorable or unfavorable outcome (score of 0-1 or 2-6 on the modified Rankin scale, respectively). The secondary endpoint was a global outcome analysis that combined the outcomes at day 90 of four neurologic and disability scores (modified Rankin scale, Barthel Index, NIH Stroke Scale, and Glasgow Outcome Scale). Median time to alteplase treatment was 239 minutes (3.9 hours) after onset of stroke symptoms. Compared to those who received placebo, patients receiving alteplase experienced less disability at 90 days (219 [52.4%] vs 182 [45.2%], p=0.04). A favorable global outcome was statistically more frequent with alteplase compared to placebo. More cases of intracranial hemorrhage (ICH) occurred in the alteplase group compared to placebo (any ICH, 113 [27%] vs 71 [17.6%], p=0.001; symptomatic ICH 10 [2.4%] vs 1 [0.2%], p=0.008), a rate similar to that of previous clinical trials when used within 0-3 hours. Although not a primary endpoint of the trial, there was no difference in mortality between the two groups (32 [7.7%] vs 34 [8.4%], p=0.68). ECASS III suggests the extension of the time window for treatment with alteplase. However, treatment should not be delayed for any appropriate candidate presenting with AIS.

Acute Pulmonary Embolism (PE): The American College of Chest Physicians (Kearon, 2008) recommends the following:

All patients with acute PE: All patients with diagnosed PE should undergo rapid risk stratification based on risk of death from PE and bleeding. In general, the majority of patients with PE will not require treatment with thrombolytics; however, treatment with anticoagulation (eg, enoxaparin, heparin) will be necessary unless contraindicated.

Patients with acute PE without hemodynamic compromise: In general, patients without hemodynamic compromise should not receive thrombolytic therapy. However, patients without hemodynamic compromise but with poor prognostic indicators (elevated troponin, right ventricular dysfunction on echocardiogram, etc) are at high risk of an adverse outcome and may derive benefit from receiving systemic thrombolysis. Therefore, the most recent recommendation is to administer thrombolysis in these selected high-risk patients who have a low risk of bleeding. The use of regimens with short infusion times (eg, 2-hour infusion) is recommended over longer infusion times (eg, 12-hour infusions). The most widely used thrombolytic for this indication is alteplase which is administered as an infusion of 100 mg over 2 hours. Urokinase may also be used; however, the administration time for urokinase is 12 hours.

Patients with acute PE with hemodynamic compromise: Since thrombolytic therapy has been shown to accelerate thrombolysis resulting in more rapid resolution of perfusion scan abnormalities, decrement angiographic thrombus, reduction in elevated pulmonary artery pressures, and normalization of right ventricular dysfunction in patients with PE and hemodynamic compromise (usually defined as SBP <90 mm Hg requiring vasopressor therapy), the use of thrombolytic therapy via a peripheral vein is recommended unless major contraindications exist. The use of regimens with short infusion times (eg, 2-hour infusion) is recommended over longer infusion times (eg, 12-hour infusions). The most widely used thrombolytic for this indication is alteplase which is administered as an infusion of 100 mg over 2 hours. Urokinase may also be used; however, the administration time for urokinase is 12 hours.

Patients with PE experiencing cardiac arrest: According to the 2005 ACLS guidelines, when PE is responsible for cardiac arrest and the patient is unresponsive to cardiopulmonary resuscitation (CPR), it is reasonable to administer bolus thrombolytic therapy, specifically alteplase (Böttiger, 2001); however, routine use in cardiac arrest or undifferentiated pulseless electrical activity (PEA) is not recommended. Of note, ongoing CPR is not a contraindication in this setting.

Intracerebral Hemorrhage (ICH) Due to Thrombolysis: Overall management of ICH is similar regardless of cause; however, iatrogenic spontaneous ICH may have specific treatments. According to the 2007 ACC/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage, fibrinolytic-related ICH should be treated with infusion of platelets (6-8 units) and cryoprecipitate which contains factor VIII (Class IIb recommendation).

Peripheral Arterial Occlusive Disease (PAOD) and Deep Venous Thrombosis (DVT): The Surgery Versus Thrombolysis for Ischemia of the Lower Extremity (STILE) trial (*Ann Surg*, 1994) compared surgery to intra-arterial thrombolytic therapy with either urokinase (250,000 units bolus, followed by 4000 units/minute for 4 hours, followed by 2000 units/minute for ≤36 hours) or alteplase (0.05 mg/kg/hour for ≤12 hours) in patients with acute (<14 days) or chronic peripheral arterial occlusive disease (PAOD). Patients with acute PAOD who received either fibrinolytic treatment had a shorter hospital stay and an improved amputation-free survival rate. There was no difference between alteplase or urokinase with regard to efficacy or bleeding events. A group from Stanford University recently did a retrospective comparison evaluating efficacy, safety, and cost of low-dose alteplase (<2 mg/hour) and subtherapeutic heparin to urokinase and therapeutic heparin for the treatment of PAOD or DVT (Sugimoto, 2003). Efficacy was similar for both groups. The average dose of alteplase was 0.86 mg/hour and the dose of urokinase was 2250 units/minute. Alteplase infusions were shorter and less expensive than urokinase.

Index TermsAlteplase, Recombinant; Alteplase, Tissue Plasminogen Activator, Recombinant; tPA

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International Brand Names Actilyse (AE, AR, AT, AU, BD, BE, BF, BG, BH, BJ, BR, CH, CI, CL, CN, CO, CY, CZ, DE, DK, EE, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, HU, ID, IE, IL, IN, IQ, IR, IT, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PH, PK, PL, PT, PY, QA, SA, SC, SD, SE, SG, SL, SN, SY, TH, TN, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Activacin (JP)

Altretamine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

International issues:

Hexalen®: Brand name for hexetidine in Greece

Pronunciation(al TRET a meen)

U.S. Brand NamesHexalen®

Canadian Brand NamesHexalen®

Pharmacologic CategoryAntineoplastic Agent, Miscellaneous

Use: Labeled IndicationsPalliative treatment of persistent or recurrent ovarian cancer

Dosing: AdultsRefer to individual protocols.

Ovarian cancer: Oral: 260 mg/m^2/day in 4 divided doses for 14 or 21 days of a 28-day cycle

Alternatively (unlabeled use): 4-12 mg/kg/day in 3-4 divided doses for 21-90 days

Alternatively (unlabeled use): 240-320 mg/m^2/day in 3-4 divided doses for 21 days, repeated every 6 weeks

Alternatively (unlabeled use): 150 mg/m^2/day in 3-4 divided doses for 14 days of a 28-day cycle

Dosing: ElderlyRefer to adult dosing.

Dosing: Adjustment for ToxicityTemporarily withhold for 14 days or longer, and resume dose at 200 mg/m^2/day for any of the following:

Platelet count <75,000/mm^3

White blood cell count <2000/mm^3 or granulocyte count <1000/mm^3

Progressive neurotoxicity

Gastrointestinal intolerance not responsive to antiemetic regimens

Calculations

- Body Surface Area: Adults

Administration: OralAdminister total daily dose as 3-4 divided doses after meals and at bedtime.

Dietary ConsiderationsShould be taken after meals at bedtime.

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to altretamine or any component of the formulation; pre-existing severe bone marrow suppression or severe neurologic toxicity; pregnancy

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.
- Neurotoxicity: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: Peripheral blood counts should be done routinely before and after drug therapy;** bone marrow suppression is common. Use with caution in patients previously treated with other myelosuppressive drugs.
- Neurotoxicity: **[U.S. Boxed Warning]: Neurologic examinations should be done routinely before and after drug therapy;** neurotoxicity is common. USe with caution in patients with pre-existing neurotoxicity.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenic effects were noted in animal studies. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should avoid becoming pregnant while on therapy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential toxicity in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

>10%:

Central nervous system: Peripheral sensory neuropathy (31%; moderate-to-severe 9%), neurotoxicity (21%; may be progressive and dose limiting)

Gastrointestinal: Nausea/vomiting (33% to 70%; severe 1%), diarrhea (48%)

Hematologic: Anemia (33%), leukopenia (5% to 15%; grade 4: 1%), neutropenia

1% to 10%:

Central nervous system: Fatigue (1%), seizure (1%)

Gastrointestinal: Stomach cramps, anorexia (1%)

Hematologic: Thrombocytopenia (9%)

Hepatic: Alkaline phosphatase increased (9%)

<1%: Alopecia, ataxia, depression, dizziness, hepatotoxicity, mood disorders, pruritus, rash, tremor, vertigo

Oncology: Emetic PotentialModerate-to-high (30% to 90%)

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

MAO Inhibitors: Altretamine may enhance the orthostatic effect of MAO Inhibitors. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Pyridoxine: May diminish the therapeutic effect of Altretamine. Specifically when altretamine is used in combination with Cisplatin the response duration may be diminished. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Altretamine may enhance the orthostatic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersCBC with differential, liver function tests; neurologic examination

Nursing: Physical Assessment/MonitoringAssess need for caution (eg, patients previously treated with other myelosuppressive drugs or with pre-existing neurotoxicity; renal or hepatic dysfunction). Monitor potential for drug/drug interactions. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, neuropathy, gastrointestinal upset, anemia). Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, liver function tests

Patient EducationDo not take any new medications (including aspirin or any aspirin-containing products) during treatment unless approved by prescriber. Take exactly as directed, preferably after meals. Avoid alcohol. May cause nausea or vomiting (small, frequent meals, good mouth care, chewing gum, or sucking lozenges may help). You will be more susceptible to infection (avoid crowds and exposure to infection). Report any numbness, tingling, or pain in extremities; unrelieved nausea or vomiting; tremors; yellowing of skin or eyes; fever; chills; easy bruising or unusual bleeding; extreme weakness; or increased fatigue. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate barrier contraceptive measures. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gelcap:

Hexalen®: 50 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Hexalen)

50 mg (100): $1120.62

Mechanism of ActionAlthough altretamine's clinical antitumor spectrum resembles that of alkylating agents, the drug has demonstrated activity in alkylator-resistant patients. The drug selectively inhibits the incorporation of radioactive thymidine and uridine into DNA and RNA, inhibiting DNA and RNA synthesis; reactive intermediates covalently bind to microsomal proteins and DNA; can spontaneously degrade to demethylated melamines and formaldehyde which are also cytotoxic.

Pharmacodynamics/Kinetics

Absorption: Well absorbed (75% to 89%)

Distribution: Highly concentrated hepatically and renally; low in other organs

Protein binding: 50% to 94%

Metabolism: Hepatic; rapid and extensive demethylation to active metabolites (pentamethylmelamine and tetramethylmelamine)

Half-life elimination: 13 hours

Time to peak, plasma: 0.5-3 hours

Excretion: Urine (90%, <1% as unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNeurotoxicity is common; rarely may produce depression

Mental Health: Effects on Psychiatric TreatmentBone marrow suppression may be seen; use caution with carbamazepine and clozapine; may produce seizures caution with bupropion and clozapine; may cause severe orthostatic hypotension when administered with MAO inhibitors

Index TermsHexamethylmelamine; HEXM; HMM; HXM; NSC-13875

References

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Sutton GP, “Secondary Therapy for Epithelial Ovarian Cancer - 1994,” *Semin Oncol*, 1994, 21(4 Suppl 7):32-6. [PubMed 8091239]

Thigpen JT, Vance RB, and Khansur T, “Second-Line Chemotherapy for Recurrent Carcinoma of the Ovary,” *Cancer*, 1993, 71(4 Suppl):1559-64.[PubMed 8094320]

International Brand NamesHexalen (AU, BG, GB, IL, JP, NO, NZ, SE, TH); Hexastat (AR, FR, IT, PT); Hexinawas (ES)

Aluminum Chloride Hexahydrate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Drysol™ may be confused with Drisdol®

Pronunciation(a LOO mi num KLOR ide heks a HYE drate)
U.S. Brand NamesCertain Dri® [OTC]; Drysol™; Hypercare™; Xerac AC™
Pharmacologic CategoryTopical Skin Product
Use: Labeled IndicationsAstringent in the management of hyperhidrosis
Dosing: AdultsHyperhidrosis: Topical: Apply once daily at bedtime; once excessive sweating has stopped, may decrease to once or twice weekly, or as needed. Wash treated area in the morning.
Dosing: ElderlyRefer to adult dosing.
Administration: TopicalApply to dry skin. Area may be covered with plastic wrap held in place with snug-fitting T-shirt; do not hold in place with tape.
StorageKeep container tightly closed.
ContraindicationsHypersensitivity to any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Skin irritation: Discontinue if skin irritation occurs.

Other warnings/precautions:

- Appropriate use: For external use only; avoid contact with eyes. Do not apply to broken or recently shaved skin. May be harmful to certain metals or fabrics.

Adverse ReactionsFrequency not defined.

Dermatologic: Skin irritation

Local: Burning sensation, prickling sensation, transient itching or stinging

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, topical:

Certain Dri®: 12% (36 mL)

Drysol™: 20% (35 mL, 37.5 mL, 60 mL) [contains ethanol 93%]

Hypercare™: 20% (35 mL, 37.5 mL, 60 mL) [contains ethanol 93%]

Xerac AC™: 6.25% (35 mL, 60 mL) [contains ethanol 96%]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Solution (Drysol)

20% (35): $17.99

20% (37.5): $16.99

20% (60): $18.99

Solution (Hypercare)

20% (35): $16.99

20% (37.5): $14.99

20% (60): $8.99

Solution (Xerac AC)

6.25% (35): $16.99

6.25% (60): $18.99

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesAnhydrol Forte (GB, IE, IL); Driclor (AU, GB, HK, IE, KP, PH, SG); Drysol (CN, MX)

Aluminum Chloride

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(a LOO mi num KLOR ide)

U.S. Brand Names Hemodent™

Pharmacologic Category Astringent; Hemostatic Agent

Use: Labeled Indications Hemostatic

Use: Dental Hemostatic; gingival retraction; to control bleeding created during a dental procedure

Dosing: Adults Control of bleeding: Apply retraction cord as directed

Dosing: Elderly Refer to adult dosing.

ContraindicationsNo data reported

Warnings/Precautions

Other warnings/precautions:

- Application: Since large amounts of astringents may cause tissue irritation and possible damage, only small amounts should be applied.

Adverse Reactions No data reported.

Drug Interactions There are no known significant interactions.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid:

Hemodent™: 21% (10 mL, 20 mL, 40 mL)

Retraction cord [impregnated with 21% solution]:

Hemodent™: Braided cord, thin (7 ft); braided cord medium thin (7 ft); twisted cord #3 (7 ft); twisted cord #9 (7ft)

Generic Available No

Mechanism of Action Precipitates tissue and blood proteins causing a mechanical obstruction to hemorrhage from injured blood vessels

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

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Aluminum Hydroxide and Magnesium Carbonate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(a LOO mi num hye DROKS ide & mag NEE zhum KAR bun nate)

U.S. Brand NamesAcid Gone Extra Strength [OTC]; Acid Gone [OTC]; Alenic Alka [OTC]; Gaviscon® Extra Strength [OTC]; Gaviscon® Liquid [OTC]; Genaton™ [OTC]

Pharmacologic CategoryAntacid

Use: Labeled IndicationsTemporary relief of symptoms associated with gastric acidity

Dosing: AdultsDyspepsia, gastric acidity: Oral:

Liquid:

Gaviscon® Regular Strength: 15-30 mL 4 times/day after meals and at bedtime

Gaviscon® Extra Strength: 15-30 mL 4 times/day after meals

Tablet (Gaviscon® Extra Strength): Chew 2-4 tablets 4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentAluminum and/or magnesium may accumulate in renal impairment.

Dietary ConsiderationsShould be taken 1-3 hours after meals with water, milk or juice. Some products contain sodium; Gaviscon® regular strength liquid: 0.57 mEq/5 mL, Gaviscon® Extra Strength liquid: 0.9 mEq/5 mL extra strength liquid, Gaviscon® Extra Strength tablet 19 mg [1.3 mEq], Alenic Alka liquid: 13 mg/5 mL

Geriatric ConsiderationsElderly, due to disease or drug therapy, may be predisposed to diarrhea or constipation. Diarrhea may result in electrolyte imbalance. Decreased renal function (Cl_{cr} <30 mL/minute) may result in toxicity of aluminum or magnesium. Drug interactions must be considered. If possible, administer antacid 1-2 hours apart from other drugs. When treating ulcers, consider buffer capacity (mEq/mL) to calculate dose of antacid.

Adverse Reactions1% to 10%:

Endocrine & metabolic: Hypermagnesemia, aluminum intoxication (prolonged use and concomitant renal failure), hypophosphatemia

Gastrointestinal: Constipation, diarrhea

Neuromuscular & skeletal: Osteomalacia

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Ascorbic Acid: May increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Antacids may decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Citric Acid Derivatives: May increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C:*

Monitor therapy

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Deferasirox: Aluminum Hydroxide may diminish the therapeutic effect of Deferasirox. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Ethambutol: Aluminum Hydroxide may decrease the absorption of Ethambutol. *Risk D: Consider therapy modification*

Fexofenadine: Antacids may decrease the serum concentration of Fexofenadine. Management: No specific recommendations concerning the time required between their administration are provided. Separate administration of each agent by as much time as possible to decrease the risk of an interaction. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid:

Acid Gone: Aluminum hydroxide 31.7 mg and magnesium carbonate 119.3 mg per 5 mL (360 mL)

Alenic Alka: Aluminum hydroxide 31.7 mg and magnesium carbonate 119.3 mg per 5 mL (355 mL) [contains magnesium 35 mg/5 mL, sodium 13 mg/5 mL, and benzyl alcohol; cool mint flavor]

Gaviscon®: Aluminum hydroxide 31.7 mg and magnesium carbonate 119.3 mg per 5 mL (355 mL) [contains sodium 0.57 mEq/5 mL and benzyl alcohol; cool mint flavor]

Gaviscon® Extra Strength: Aluminum hydroxide 84.6 mg and magnesium carbonate 79.1 mg per 5 mL (355 mL) [contains sodium 0.9 mEq/5 mL and benzyl alcohol; cool mint flavor]

Genaton™: Aluminum hydroxide 31.7 mg and magnesium carbonate 119.3 mg per 5 mL (360 mL)

Tablet, chewable:

Acid Gone Extra Strength: Aluminum hydroxide 160 mg and magnesium carbonate 105 mg

Gaviscon® Extra Strength: Aluminum hydroxide 160 mg and magnesium carbonate 105 mg [contains sodium 19 mg/tablet (1.3 mEq/tablet); cherry and original flavors]

Generic AvailableYes

Related Information

- Aluminum Hydroxide

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Chalky taste. Aluminum and magnesium ions prevent GI absorption of tetracycline by forming a large ionized chelated molecule with the tetracyclines in the stomach. Aluminum hydroxide prevents GI absorption of ketoconazole and itraconazole by increasing the pH in the GI tract. Any of these drugs should be administered at least 1 hour before aluminum hydroxide.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMagnesium Carbonate and Aluminum Hydroxide

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Maalox® may be confused with Maox®, Monodox®

Mylanta® may be confused with Mynatal®

Maalox® is a different formulation than Maalox® Total Stomach Relief®

Pronunciation(a LOO mi num hye DROKS ide, mag NEE zhum hye DROKS ide, & sye METH i kone)

U.S. Brand NamesAlamag Plus [OTC]; Aldroxicon I [OTC]; Aldroxicon II [OTC]; Almacone Double Strength® [OTC]; Almacone® [OTC]; Gelusil® [OTC]; Maalox® Max [OTC]; Maalox® [OTC]; Mi-Acid Maximum Strength [OTC]; Mi-Acid [OTC]; Mintox Extra Strength [OTC]; Mintox Plus [OTC]; Mylanta® Liquid [OTC]; Mylanta® Maximum Strength Liquid [OTC]

Canadian Brand NamesDiovol Plus®; Gelusil®; Mylanta® Double Strength; Mylanta® Extra Strength; Mylanta® Regular Strength

Pharmacologic CategoryAntacid; Antiflatulent

Use: Labeled IndicationsTemporary relief of hyperacidity associated with gas; may also be used for indications associated with other antacids

Dosing: AdultsDyspepsia, abdominal bloating: Oral: 10-20 mL or 2-4 tablets 4-6 times/day between meals and at bedtime; may be used every hour for severe symptoms

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentAluminum and/or magnesium may accumulate in renal impairment.

Dietary ConsiderationsShould be taken 1-3 hours after meals.

Pregnancy Risk FactorC

Adverse Reactions

>10%: Gastrointestinal: Chalky taste, stomach cramps, constipation, bowel motility decreased, fecal impaction, hemorrhoids

1% to 10%: Gastrointestinal: Nausea, vomiting, discoloration of feces (white speckles)

<1%: Hypophosphatemia, hypomagnesemia, dehydration or fluid restriction

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Ascorbic Acid: May increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Antacids may decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Citric Acid Derivatives: May increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Deferasirox: Aluminum Hydroxide may diminish the therapeutic effect of Deferasirox. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Ethambutol: Aluminum Hydroxide may decrease the absorption of Ethambutol. *Risk D: Consider therapy modification*

Fexofenadine: Antacids may decrease the serum concentration of Fexofenadine. Management: No specific recommendations concerning the time required between their administration are provided. Separate administration of each agent by as much time as possible to decrease the risk of an interaction. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid: Aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, and simethicone 20 mg per 5 mL (360 mL); aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, and simethicone 40 mg per 5 mL (360 mL)

Aldroxicon I: Aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, and simethicone 20 mg per 5 mL (30 mL)

Aldroxicon II: Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, and simethicone 40 mg per 5 mL (30 mL)

Almacone®: Aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, and simethicone 20 mg per 5 mL (360 mL)

Almacone Double Strength®: Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, and simethicone 40 mg per 5 mL (360 mL)

Maalox®: Aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, and simethicone 20 mg per 5 mL (360 mL, 770 mL) [lemon and mint flavors]

Maalox® Max: Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, and simethicone 40 mg per 5 mL (360 mL, 770 mL) [cherry, vanilla creme, and wild berry flavors]

Mi-Acid: Aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, and simethicone 20 mg per 5 mL (360 mL)

Mi-Acid Maximum Strength: Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, and simethicone 40 mg per 5 mL (360 mL)

Mintox Extra Strength: Aluminum hydroxide 500 mg, magnesium hydroxide 450 mg, and simethicone 40 mg per 5 mL (360 mL) [lemon creme flavor]

Mylanta®: Aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, and simethicone 20 mg per 5 mL (180 mL, 360 mL, 720 mL) [original, cherry, and mint flavors]

Mylanta® Maximum Strength: Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, and simethicone 40 mg per 5 mL (180 mL, 360 mL, 720 mL) [original, cherry, orange creme, and mint flavors]

Suspension (Alamag Plus): Aluminum hydroxide 225 mg, magnesium hydroxide 200 mg, and simethicone 25 mg per 5 mL (360 mL)

Tablet, chewable: Aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, and simethicone 25 mg

Alamag Plus: Aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, and simethicone 25 mg [cherry flavor]

Almacone®: Aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, and simethicone 20 mg [peppermint flavor]

Gelusil®: Aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, and simethicone 25 mg [peppermint flavor]

Mintox Plus: Aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, and simethicone 25 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Suspension (Mylanta)

200-200-20 mg/5 mL (355): $7.99

200-200-20 mg/5 mL (355): $8.99

200-200-20 mg/5 mL (710): $8.80

Suspension (Mylanta Double-Strength)

400-400-40 mg/5 mL (355): $7.99

400-400-40 mg/5 mL (710): $10.01

Related Information

- Aluminum Hydroxide
- Magnesium Hydroxide
- Simethicone

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Chalky taste. Aluminum and magnesium ions prevent GI absorption of tetracycline by forming a large ionized chelated molecule with the tetracyclines in the stomach. Aluminum hydroxide prevents GI absorption of ketoconazole and itraconazole by increasing the pH in the GI tract. Any of these drugs should be administered at least 1 hour before aluminum hydroxide.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentConstipation is common; use with low potency antipsychotics and TCAs will likely result in additive effects

Index TermsMagnesium Hydroxide, Aluminum Hydroxide, and Simethicone; Simethicone, Aluminum Hydroxide, and Magnesium Hydroxide

International Brand NamesDiovol Plus (CA); Gelusil (CA); Mylanta Double Strength (CA); Mylanta Extra Strength (CA); Mylanta Regular Strength (CA)

Aluminum Hydroxide and Magnesium Hydroxide

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

> Maalox® may be confused with Maox®, Monodox®

Pronunciation(a LOO mi num hye DROKS ide & mag NEE zhum hye DROK side)

U.S. Brand NamesAlamag [OTC]; Rulox No. 1 [DSC]; Rulox [OTC]

Canadian Brand NamesDiovol®; Diovol® Ex; Gelusil® Extra Strength; Mylanta™

Pharmacologic CategoryAntacid

Use: Labeled IndicationsAntacid, hyperphosphatemia in renal failure

Dosing: AdultsDyspepsia: Oral: 5-10 mL 4-6 times/day, between meals and at bedtime; may be used every hour for severe symptoms

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentAluminum and/or magnesium may accumulate in renal impairment.

Dietary ConsiderationsShould be taken 1-3 hours after meals.

Geriatric ConsiderationsElderly, due to disease or drug therapy, may be predisposed to diarrhea or constipation. Diarrhea may result in electrolyte imbalance. Decreased renal function (Cl_{cr} <30 mL/minute) may result in toxicity of aluminum or magnesium. Drug interactions must be considered. If possible, administer antacid 1-2 hours apart from other drugs. When treating ulcers, consider buffer capacity (mEq/mL) to calculate dose of antacid.

Pregnancy Risk FactorC

Adverse Reactions

>10%: Gastrointestinal: Constipation, chalky taste, stomach cramps, fecal impaction

1% to 10%: Gastrointestinal: Nausea, vomiting, discoloration of feces (white speckles)

<1%: Hypophosphatemia, hypomagnesemia

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Ascorbic Acid: May increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Antacids may decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Citric Acid Derivatives: May increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Deferasirox: Aluminum Hydroxide may diminish the therapeutic effect of Deferasirox. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Ethambutol: Aluminum Hydroxide may decrease the absorption of Ethambutol. *Risk D: Consider therapy modification*

Fexofenadine: Antacids may decrease the serum concentration of Fexofenadine. Management: No specific recommendations concerning the time required between their administration are provided. Separate administration of each agent by as much time as possible to decrease the risk of an interaction. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Suspension: Aluminum hydroxide 225 mg and magnesium hydroxide 200 mg per 5 mL (360 mL)

Alamag, Rulox: Aluminum hydroxide 225 mg and magnesium hydroxide 200 mg per 5 mL (360 mL)

Tablet, chewable:

Alamag: Aluminum hydroxide 300 mg and magnesium hydroxide 150 mg

Rulox No. 1: Aluminum hydroxide 200 mg and magnesium hydroxide 200 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Concentrate (Maalox TC)

600-300 mg/5 mL (355): $8.99

Related Information

- Aluminum Hydroxide
- Magnesium Hydroxide

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Chalky taste. Aluminum and magnesium ions prevent GI absorption of tetracycline by forming a large ionized chelated molecule with the tetracyclines in the stomach. Aluminum hydroxide prevents GI absorption of ketoconazole and itraconazole by increasing the pH in the GI tract. Any of these drugs should be administered at least 1 hour before aluminum hydroxide.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMagnesium Hydroxide and Aluminum Hydroxide

International Brand NamesDiovol (CA); Diovol Ex (CA); Gelusil Extra Strength (CA); Mylanta® (CA)

Aluminum Hydroxide and Magnesium Trisilicate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(a LOO mi num hye DROKS ide & mag NEE zhum trye SIL i kate)

U.S. Brand NamesAlenic Alka Tablet [OTC]; Gaviscon速 Tablet [OTC]; Genaton Tablet [OTC]

Pharmacologic CategoryAntacid

Use: Labeled IndicationsTemporary relief of hyperacidity

Dosing: AdultsDyspepsia, gastric acidity: Oral: Chew 2-4 tablets 4 times/day or as directed by healthcare provider

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentAluminum and/or magnesium may accumulate in renal impairment.

Administration: OralTablets should be chewed and not swallowed whole.

Dietary ConsiderationsShould be taken 1-3 hours after meals with water, milk, or juice. Gaviscon速 chewable tablet contains sodium 0.8 mEq/tablet.

Geriatric ConsiderationsElderly, due to disease or drug therapy, may be predisposed to diarrhea or constipation. Diarrhea may result in electrolyte imbalance. Decreased renal function (Cl_{cr} <30 mL/minute) may result in toxicity of aluminum or magnesium. Drug interactions must be considered. If possible, administer antacid 1-2 hours apart from other drugs. When treating ulcers, consider buffer capacity (mEq/mL) to calculate dose of antacid.

Pregnancy Risk FactorC

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Ascorbic Acid: May increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Antacids may decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Citric Acid Derivatives: May increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Deferasirox: Aluminum Hydroxide may diminish the therapeutic effect of Deferasirox. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Ethambutol: Aluminum Hydroxide may decrease the absorption of Ethambutol. *Risk D: Consider therapy modification*

Fexofenadine: Antacids may decrease the serum concentration of Fexofenadine. Management: No specific recommendations concerning the time required between their administration are provided. Separate administration of each agent by as much time as possible to decrease the risk of an interaction. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, chewable: Aluminum hydroxide 80 mg and magnesium trisilicate 20 mg

Alenic Alka: Aluminum hydroxide 80 mg and magnesium trisilicate 20 mg [butterscotch flavor]

Gaviscon速: Aluminum hydroxide 80 mg and magnesium trisilicate 20 mg [contains sodium 0.8 mEq/tablet; butterscotch flavor]

Genaton: Aluminum hydroxide 80 mg and magnesium trisilicate 20 mg

Generic AvailableYes

Related Information

- Aluminum Hydroxide

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Chalky taste. Aluminum and magnesium ions prevent GI absorption of tetracycline by forming a large ionized chelated molecule with the tetracyclines in the stomach. Aluminum hydroxide prevents GI absorption of ketoconazole and itraconazole by increasing the pH in the GI tract. Any of these drugs should be administered at least 1 hour before aluminum hydroxide.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMagnesium Trisilicate and Aluminum Hydroxide

Aluminum Hydroxide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(a LOO mi num hye DROKS ide)
U.S. Brand NamesALternaGel® [OTC]; Dermagran® [OTC]
Canadian Brand NamesAmphojel®; Basaljel®
Pharmacologic CategoryAntacid; Antidote; Protectant, Topical
Use: Labeled IndicationsTreatment of hyperacidity; hyperphosphatemia; temporary protection of minor cuts, scrapes, and burns
Dosing: Adults

Hyperphosphatemia: Oral: Initial: 300-600 mg 3 times/day with meals

Hyperacidity: Oral: 600-1200 mg between meals and at bedtime

Skin protectant: Topical: Apply to affected area as needed; reapply at least every 12 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric
Hyperphosphatemia: Oral: 50-150 mg/kg/24 hours in divided doses every 4-6 hours, titrate dosage to maintain serum phosphorus within normal range

Skin protectant: Topical: Refer to adult dosing.

Dosing: Renal ImpairmentAluminum may accumulate in renal impairment.
Administration: OralDose should be followed with water.
Administration: TopicalApply as needed to affected area; reapply at least every 12 hours.
Dietary ConsiderationsShould be taken 1-3 hours after meals when used as an antacid. When used to decrease phosphorus, should be taken within 20 minutes of a meal.
ContraindicationsHypersensitivity to aluminum salts or any component of the formulation
Warnings/Precautions

Dosage form specific issues:

- Oral: Hypophosphatemia may occur with prolonged administration or large doses; aluminum intoxication and osteomalacia may occur in patients with uremia. Use with caution in patients with HF, renal failure, edema, cirrhosis, and low sodium diets, and patients who have recently suffered gastrointestinal hemorrhage; uremic patients not receiving dialysis may develop osteomalacia and osteoporosis due to phosphate depletion. When used as an antacid in ulcer treatment, consider buffer capacity (mEq/mL) to calculate dose. Elderly may be predisposed to constipation and fecal impaction. Careful evaluation of possible drug interactions must be done.

- Topical: Not for application over deep wounds, puncture wounds, infected areas, or lacerations. When used for self medication (OTC use), consult with healthcare provider if needed for >7 days or for use in children <6 months of age.

Geriatric ConsiderationsElderly, due to disease and/or drug therapy, may be predisposed to constipation and fecal impaction. Careful evaluation of possible drug interactions must be done. When used as an antacid in ulcer treatment, consider buffer capacity (mEq/mL) to calculate dose. Consider renal insufficiency (<30 mL/minute) as predisposition to aluminum toxicity.
Pregnancy Risk FactorC
Pregnancy ConsiderationsNo data available on clinical effects on the fetus; available evidence suggests safe use during pregnancy and breast-feeding.
LactationExcretion in breast milk unknown
Adverse ReactionsFrequency not defined.

Gastrointestinal: Constipation, stomach cramps, fecal impaction, nausea, vomiting, discoloration of feces (white speckles)

Endocrine & metabolic: Hypophosphatemia, hypomagnesemia

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Ascorbic Acid: May increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Antacids may decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Citric Acid Derivatives: May increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Deferasirox: Aluminum Hydroxide may diminish the therapeutic effect of Deferasirox. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Ethambutol: Aluminum Hydroxide may decrease the absorption of Ethambutol. *Risk D: Consider therapy modification*

Fexofenadine: Antacids may decrease the serum concentration of Fexofenadine. Management: No specific recommendations concerning the time required between their administration are provided. Separate administration of each agent by as much time as possible to decrease the risk of an interaction. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Test InteractionsDecreased phosphorus, inorganic (S)

Monitoring ParametersMonitor phosphorus levels periodically when patient is on chronic therapy.

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests and therapeutic effectiveness. Assess for constipation and treat accordingly.

Monitoring: Lab TestsMonitor calcium and phosphate levels periodically when patient is on chronic therapy.

Patient EducationTake as directed, preferably 1-3 hours after meals (when used as an antacid) or with any other medications. When used to decrease phosphorus, take within 20 minutes of a meal. Do not increase sodium intake and maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience constipation (increased exercise, fluids, fruit, or fiber may help; if unresolved, contact prescriber). Report unresolved nausea, malaise, muscle weakness, blood in stool or black stool, or abdominal pain. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Ointment:

Dermagran®: 0.275% (120 g)

Suspension, oral: 320 mg/5 mL (473 mL)

ALternaGel®: 600 mg/5 mL (360 mL)

Generic AvailableYes: Suspension

Mechanism of ActionNeutralizes hydrochloride in stomach to form $Al(Cl)_3$ salt + H_2O

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Chalky taste. Aluminum and magnesium ions prevent GI absorption of tetracycline by forming a large ionized chelated molecule with the aluminum ion and tetracyclines in the stomach. Aluminum hydroxide prevents GI absorption of ketoconazole and itraconazole by increasing the pH in the GI tract. Any of these drugs should be administered at least 1 hour before $Al(OH)_3$.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentConstipation is common and may be additive when used with psychotropics; may decrease the absorption of benzodiazepines and phenothiazines

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Cumming RG and Klineberg RJ, “Aluminum in Antacids and Cooking Pots and the Risk of Hip Fractures in Elderly People,” *Age Ageing*, 1994, 23:468-72. [PubMed 9231940]

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Monteagudo FS, Cassidy MJ, and Folb PI, “Recent Developments in Aluminum Toxicity,” *Med Toxicol Adverse Drug Exp*, 1989, 4(1):1-16. [PubMed 2651849]

Robertson JA, Salusky IB, Goodman WG, et al, “Sucralfate, Intestinal Aluminum Absorption, and Aluminum Toxicity in a Patient on Dialysis,” *Ann Intern Med*, 1989, 111(2):179-81. [PubMed 2742249]

U.S. Department of Health and Human Services, “Toxicological Profile for Aluminum TP-91/01,” Agency for Toxic Substances and Diseases Registry, July 1992.

International Brand NamesAldrox (BE); Algeldraat (NL); Alu-Cap (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Alu-Tab (AU, HK, PH); Alucol (IT); Aludrox (DE); Alugel (DE, TW); Alumigel (JP); Alutab (MY); Alzinox (PH); Amphogel (KP); Amphojel (ZA); Pepsamar (BF, BJ, BR, CI, CN, CO, ES, ET, GH, GM, GN, GR, KE, LR, MA, ML, MR, MU, MW, NE, NG, PE, PT, SC, SD, SL, SN, TN, TZ, UG, VE, ZA, ZM, ZW); Rocgel (FR); Ulcerin-P (TW)

Aluminum Sulfate and Calcium Acetate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(a LOO mi num SUL fate & KAL see um AS e tate)

U.S. Brand NamesDomeboro® [OTC]; Gordon Boro-Packs [OTC]; Pedi-Boro® [OTC]

Pharmacologic CategoryTopical Skin Product

Use: Labeled IndicationsAstringent wet dressing for relief of inflammatory conditions of the skin; reduce weeping that may occur in dermatitis

Dosing: AdultsDermal inflammation, dermatitis: Topical: Soak affected area in the solution 2-4 times/day for 15-30 minutes or apply wet dressing soaked in the solution for more extended periods; rewet dressing with solution 2-4 times/day every 15-30 minutes

Dosing: ElderlyRefer to adult dosing.

StoragePrior to mixing, store powder or tablets at controlled room temperature, 15°C to 30°C (59°F to 86°F). Following reconstitution, unused solution may be covered and stored at room temperature for up to 7 days.

Reconstitution

Powder, for topical solution (Domeboro®, Pedi-Boro®): 1 packet/16 ounces of water = 1:40 dilution = Modified Burow's Solution

Tablet, effervescent, for topical solution (Domeboro®): 1 tablet/12 ounces of water = 1:40 dilution = Modified Burow's Solution

Warnings/Precautions

Other warnings/precautions:

- Appropriate use: For external use only; avoid contact with eyes. Discontinue use if irritation occurs.
- OTC duration of therapy: Not for OTC use >7 days.

Geriatric ConsiderationsNo special considerations necessary

Drug Interactions

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CefTRIAXone: Calcium Salts (Intravenous) may enhance the adverse/toxic effect of CefTRIAXone. Ceftriaxone binds to calcium forming an insoluble precipitate. *Risk X: Avoid combination*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Estramustine: Calcium Salts may decrease the absorption of Estramustine. *Risk D: Consider therapy modification*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Moxifloxacin. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder, for topical solution:

Domeboro®: Aluminum sulfate 1191 mg and calcium acetate 839 mg per packet (12s, 100s)

Gordon Boro-Packs: Aluminum sulfate 49% and calcium acetate 51% per packet (100s)

Pedi-Boro®: Aluminum sulfate 1191 mg and calcium acetate 839 mg per packet (12s, 100s)

Generic AvailableNo

Related Information

- Calcium Acetate

Pharmacotherapy PearlsAluminum sulfate and calcium acetate form aluminum acetate when mixed.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCalcium Acetate and Aluminum Sulfate

Alvimopan

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Alvimopan may be confused with almotriptan

Pronunciation(al vi MOE pan)

U.S. Brand NamesEntereg®

Pharmacologic CategoryGastrointestinal Agent, Miscellaneous; Opioid Antagonist, Peripherally-Acting

Use: Labeled IndicationsAccelerate the time to upper and lower GI recovery following partial large or small bowel resection surgery with primary anastomosis

Dosing: Adults**Note:** For hospital use only.

Management of postoperative ileus: Oral:

Initial: 12 mg administered 30 minutes to 5 hours prior to surgery

Maintenance: 12 mg twice daily beginning the day after surgery for a maximum of 7 days or until discharged from hospital (maximum total treatment doses: 15 doses)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Mild-to-severe impairment: No adjustment needed; use caution.

ESRD: Use not recommended.

Dosing: Hepatic Impairment

Mild-to-moderate impairment (Child-Pugh class A and B): No adjustment needed; use caution.

Severe impairment (Child-Pugh class C): Use not recommended.

Administration: OralPatient must be hospitalized. Initial dose should be administered 30 minutes to 5 hours prior to surgery.

Dietary ConsiderationsTake with or without food; high-fat meals may decrease the rate and extent of absorption

StorageStore at controlled room temperature of 25°C (77°F).

RestrictionsOnly hospitals enrolled in the ENTEREG Access Support and Education (E.A.S.E.™) Program may administer this medication. Hospital staff must be educated on need to limit to short-term (no more than 15 doses) and inpatient use. Hospitals may contact the E.A.S.E.™ program at 1-866-423-6567 (1-866-4ADOLOR).

ContraindicationsPatients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan

Warnings/Precautions

Boxed warnings:

- Appropriate use: See "Other warnings/precautions" below.

Concerns related to adverse effects:

- Cardiovascular effects: A trend towards an increased incidence of MI was observed in alvimopan (low dose) treated patients compared to placebo in a 12-month study in patients treated with opioids for chronic pain. MI was generally observed more frequently in the initial 1-4 months of treatment. Other studies have not observed this trend and a causal relationship has not been found.

Disease-related concerns:

- Complete bowel obstruction: Use not recommended in patients undergoing surgery for complete bowel obstruction.

- Hepatic impairment: Use with caution in patients with mild-to-moderate hepatic impairment (Child-Pugh classes A and B); use not recommended with severe impairment (Child-Pugh class C).

- Renal impairment: Use with caution in patients with renal impairment; use not recommended in patients with ESRD.

Concurrent drug therapy issues:

- Opioids: Use with caution in patients recently exposed to opioids; may be more sensitive to gastrointestinal adverse effects (eg, abdominal pain, diarrhea, nausea and vomiting). Contraindicated in patients who have received therapeutic opioids for >7 consecutive days immediately prior to use.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: **[U.S. Boxed Warning]: For short-term (≤15 doses) hospital use only. Only hospitals that have registered through the ENTEREG Access Support and Education (E.A.S.E.™) Program and met all requirements may use.** It will not be dispensed to patients who have been discharged from the hospital.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAnimal studies have not shown teratogenic effects to the fetus. However, there are no adequate and well-controlled studies in pregnant women; use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**Note:** Incidence reported limited to bowel resection patients only. 1% to 10%:

Endocrine & metabolic: Hypokalemia (10%)

Gastrointestinal: Dyspepsia (7%)

Genitourinary: Urinary retention (3%)

Hematologic: Anemia (5%)

Neuromuscular & skeletal: Back pain (3%)

Metabolism/Transport Effects**Substrate** of P-glycoprotein

Drug Interactions

Analgesics (Opioid): May enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: When administered with a high-fat meal, extent and rate of absorption may be reduced (C_{max} and AUC decreased by ~38% and 21%, respectively).

Nursing: Physical Assessment/MonitoringFor restricted in-hospital use only. See administration specifics. Teach patient possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis medication is used to improve bowel function after surgery. Report any gastrointestinal upset, difficulty passing urine, unusual back pain, or other adverse reactions. **Breast-feeding precautions:** Inform prescriber if you are or intend to breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Entereg®: 12 mg

Generic AvailableNo

ManufacturerAdolor Corporation

Mechanism of ActionAn opioid receptor antagonist which blocks opioid binding at the mu receptor; alvimopan has restricted ability to cross the blood-brain barrier at therapeutic doses. It selectively and competitively binds to the GI tract mu opioid receptors and antagonizes the peripheral effects of opioids on gastrointestinal motility and secretion. Does not affect opioid analgesic effects or induce opioid withdrawal symptoms.

Pharmacodynamics/Kinetics

Distribution: V_d: 20-40 L

Protein binding: Parent drug: 80%; metabolite: 94% (both primarily to albumin)

Metabolism: Hydrolyzed to an amide hydrolysis compound (active metabolite) by gut microflora; further metabolism of active metabolite to glucuronide conjugates and other minor metabolites.

Bioavailability: ~6% (range: 1% to 19%)

Half-life elimination: 10-18 hours

Time to peak, plasma: ~2 hours

Excretion: Urine (35% as unchanged drug and metabolites); feces (via biliary excretion)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentContraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to use.

Index TermsADL-2698; LY246736

References

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Taguchi A, Sharma N, Saleem RN, et al, "Selective Postoperative Inhibition of Gastrointestinal Opioid Receptors," *N Engl J Med*, 2001,

345(13):935-40.[PubMed 11575284]

Amantadine

Lexi-Drugs Online

English English

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Special Alerts

Amantadine ACIP 2008-2009 Influenza Guidelines (July 2008)

The Advisory Committee on Immunization Practices (ACIP), as part of their recommendations for the Prevention and Control of Influenza, do not recommend the use of amantadine or rimantadine for the treatment or chemoprophylaxis of influenza A infection. This recommendation is for the 2008-2009 season for residents of the United States and is based on current patterns of resistance to these medications. Oseltamivir or zanamivir are the recommended antiviral agents. In some areas, resistance is developing against oseltamivir. If resistance is suspected, amantadine or rimantadine may be used in combination with oseltamivir for the treatment or prophylaxis of influenza A infection when zanamivir therapy is not indicated (such as in children of certain ages).

For additional information, refer to the ACIP guidelines on the following CDC website: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e717a1.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Amantadine may be confused with ranitidine, rimantadine

Symmetrel® may be confused with Synthroid®

International issues:

Symmetrel® may be confused with Somatrel® which is a brand name for somatorelin in Denmark

Pronunciation(a MAN ta deen)
U.S. Brand NamesSymmetrel®
Canadian Brand NamesEndantadine®; PMS-Amantadine; Symmetrel®
Pharmacologic CategoryAnti-Parkinson's Agent, Dopamine Agonist; Antiviral Agent, Adamantane
Use: Labeled IndicationsProphylaxis and treatment of influenza A viral infection (per manufacturer labeling; also refer to current ACIP guidelines for recommendations during current flu season); treatment of parkinsonism; treatment of drug-induced extrapyramidal symptoms

Note: In certain circumstances, the ACIP recommends use of amantadine in combination with oseltamivir for the treatment or prophylaxis of influenza A infection when resistance to oseltamivir is suspected.

Dosing: Adults

Influenza A treatment: Oral: 100 mg twice daily; initiate within 24-48 hours after onset of symptoms; discontinue as soon as possible based on clinical response (generally within 3-5 days or within 24-48 hours after symptoms disappear).

Influenza A prophylaxis: Oral: 100 mg twice daily; continue treatment throughout the peak influenza activity in the community or throughout the entire influenza season in patients who cannot be vaccinated. Development of immunity following vaccination takes ~2 weeks; amantadine therapy should be considered for high-risk patients from the time of vaccination until immunity has developed.

Drug-induced extrapyramidal symptoms: Oral: 100 mg twice daily; may increase to 300-400 mg/day, if needed

Parkinson's disease or Creutzfeldt-Jakob disease (unlabeled use): Oral: 100 mg twice daily as sole therapy; may increase to 400 mg/day if needed with close monitoring; initial dose: 100 mg/day if with other serious illness or with high doses of other anti-Parkinson drugs

Dosing: ElderlyAdjust dose based on renal function; some patients tolerate the drug better when it is given in 2 divided daily doses (to avoid adverse neurologic reactions).
Influenza A prophylaxis or treatment: ≤100 mg/day in patients ≥65 years

Dosing: Pediatric

Influenza A treatment: Oral: **Note:** Initiate within 24-48 hours after onset of symptoms; discontinue as soon as possible based on clinical response (generally within 3-5 days or within 24-48 hours after symptoms disappear)

1-9 years: 5 mg/kg/day in 2 divided doses (manufacturers range: 4.4-8.8 mg/kg/day); maximum dose: 150 mg/day

≥10 years and <40 kg: 5 mg/kg/day; maximum dose: 150 mg/day

≥10 years and ≥40 kg: Refer to adult dosing.

Influenza A prophylaxis: Oral: Refer to “Influenza A treatment” dosing. Continue treatment throughout the peak influenza activity in the community or throughout the entire influenza season in patients who cannot be vaccinated. Development of immunity following vaccination takes ~2 weeks; amantadine therapy should be considered for high-risk patients from the time of vaccination until immunity has developed. For children <9 years receiving influenza vaccine for the first time, amantadine prophylaxis should continue for 6 weeks (4 weeks after the first dose and 2 weeks after the second dose)

Dosing: Renal Impairment

Cl_{cr} 30-50 mL/minute: Administer 200 mg on day 1, then 100 mg/day

Cl_{cr} 15-29 mL/minute: Administer 200 mg on day 1, then 100 mg on alternate days

Cl_{cr} <15 mL/minute: Administer 200 mg every 7 days

Hemodialysis: Administer 200 mg every 7 days

Peritoneal dialysis: No supplemental dose is needed

Continuous arteriovenous or venous-venous hemofiltration: No supplemental dose is needed

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

StorageStore at 25°C (77°F).

ContraindicationsHypersensitivity to amantadine, rimantadine, or any component of the formulation

Allergy Considerations

- Adamantane Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Impulsive control disorders: Dopamine agonists used for Parkinson’s disease or restless legs syndrome have been associated with compulsive behaviors and/or loss of impulse control, which has manifested as pathological gambling, libido increases (hypersexuality), and/or binge eating. Causality has not been established, and controversy exists as to whether this phenomenon is related to the underlying disease, prior behaviors/addictions and/or drug therapy. Dose reduction or discontinuation of therapy has been reported to reverse these behaviors in some, but not all cases.

- Neuroleptic malignant syndrome: Has been associated with neuroleptic malignant syndrome (associated with dose reduction or abrupt discontinuation).

- Suicidal ideation: There have been reports of suicidal ideation/attempt in patients with and without a history of psychiatric illness. May exacerbate mental problems in patients with a history of mental illness.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with heart failure, peripheral edema, or orthostatic hypotension.

- Eczema: Use with caution in patients with a history of recurrent and eczematoid dermatitis.

- Glaucoma: Avoid in untreated angle closure glaucoma.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Influenza A: Appropriate use: Consult current guidelines. Due to increased resistance, the ACIP has recommended that rimantadine and amantadine no longer be used for the treatment or prophylaxis of influenza A in the United States until susceptibility has been re-established.

- Parkinson's disease: Appropriate use: When treating Parkinson's disease, do not discontinue abruptly. In many patients, the therapeutic benefits of amantadine are limited to a few months.

- Psychosis: Use with caution in patients with uncontrolled psychosis or severe psychoneurosis.

- Renal impairment: Use with caution in patients with renal impairment; dosage reduction recommended.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Concurrent drug therapy issues:

- CNS stimulants: Use with caution in patients receiving CNS stimulant drugs.

Special populations:

- Elderly: Use with caution in the elderly; may be more susceptible to CNS effects (using 2 divided daily doses may minimize this effect).

- Pediatrics: Safety and efficacy have not been established in children <1 year of age.

Geriatric ConsiderationsElderly patients may be more susceptible to the CNS effects of amantadine; using 2 divided daily doses may minimize this effect. The syrup may be used to administer doses <100 mg; studies have demonstrated that young adults on 200 mg/day achieve a plasma concentration of 300 ng/mL. To achieve this concentration (for influenza prophylaxis) in elderly, studies have suggested a dose of 100 mg or 1.4 mg/kg/day.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were observed in animal studies; limited data in humans. Impaired fertility has also been reported during animal studies and during human *in vitro* fertilization.
LactationEnters breast milk/not recommended
Adverse Reactions

1% to 10%:

Cardiovascular: Orthostatic hypotension, peripheral edema

Central nervous system: Agitation, anxiety, ataxia, confusion, delirium, depression, dizziness, dream abnormality, fatigue, hallucinations, headache, insomnia, irritability, nervousness, somnolence

Dermatologic: Livedo reticularis

Gastrointestinal: Anorexia, constipation, diarrhea, nausea, xerostomia

Respiratory: Dry nose

<1%: Amnesia, CHF, dyspnea, eczematoid dermatitis, euphoria, hyperkinesis, hypertension, leukopenia, libido decreased, neutropenia, oculogyric episodes, photosensitivity, psychosis, rash, seizure, slurred speech, urinary retention, visual disturbances, vomiting, weakness; withdrawal reactions may include delirium, hallucinations, and psychosis

Postmarketing and/or case reports: Aggressive behavior, agranulocytosis, alkaline phosphatase increased, allergic reaction, ALT increased, AST increased, anaphylaxis, arrhythmia, bilirubin increased, BUN increased, cardiac arrest, coma, CPK increased, creatinine increased, delirium, delusions, diaphoresis, dysphagia, EEG changes, gait abnormal, GGT increased, hypertonia, hypokinesia, hypotension, keratitis, LDH increased, leukocytosis, mania, muscle contractions (involuntary), mydriasis, neuroleptic malignant syndrome (NMS; associated with dosage reduction or abrupt withdrawal of amantadine), paranoia, paresthesia, pruritus, pulmonary edema, respiratory failure (acute), stupor, suicidal ideation, suicide, tachycardia, tachypnea, tremor

Reported with dopamine agonists: Impulsive/compulsive behaviors (eg, pathological gambling, hypersexuality, binge eating)

Drug Interactions

Antipsychotics (Atypical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Antipsychotics (Typical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Influenza Virus Vaccine: Antiviral Agents (Influenza A and B) may diminish the therapeutic effect of Influenza Virus Vaccine. This only pertains to live, attentuated influenza virus vaccine. *Risk D: Consider therapy modification*

Metoclopramide: May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS adverse effects).
Monitoring ParametersRenal function, Parkinson's symptoms, mental status, influenza symptoms, blood pressure
Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor renal function, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically throughout therapy. Assess blood pressure; monitor for signs of fluid retention. When treating Parkinson's disease, taper slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Monitoring: Lab TestsRenal function
Patient EducationTake as directed; do not increase dosage, take more often than prescribed, or discontinue medication without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake and void before taking medication. Take last dose of day in the afternoon to reduce incidence of insomnia. Avoid getting up suddenly from a sitting or lying position; may cause dizziness or lightheadedness. Avoid alcohol, sedatives, or hypnotics unless consulting prescriber. You may experience decreased mental alertness or coordination (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); loss of impulse control (possibly manifested as pathological gambling, libido increases, and/or binge eating); or nausea or dry mouth (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report unusual swelling of extremities, respiratory difficulty or shortness of breath, change in vision, change in gait or increased tremors, suicide ideation, or changes in mentation (eg, depression, anxiety, irritability, hallucination, slurred speech). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 100 mg

Capsule, softgel, as hydrochloride: 100 mg

Solution, oral, as hydrochloride: 50 mg/5 mL (473 mL)

Syrup, oral, as hydrochloride: 50 mg/5 mL (10 mL, 480 mL)

Tablet, as hydrochloride: 100 mg

Symmetrel®: 100 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Amantadine HCl)

100 mg (30): $21.99

Syrup (Amantadine HCl)

50 mg/5 mL (120): $15.98

Syrup (Symmetrel)

50 mg/5 mL (120): $37.00

Tablets (Amantadine HCl)

100 mg (30): $33.99

Mechanism of ActionAs an antiviral, blocks the uncoating of influenza A virus preventing penetration of virus into host; antiparkinsonian activity may be due to its blocking the reuptake of dopamine into presynaptic neurons or by increasing dopamine release from presynaptic fibers

Pharmacodynamics/Kinetics

Onset of action: Antidyskinetic: Within 48 hours

Absorption: Well absorbed

Distribution: V_d: Normal: 1.5-6.1 L/kg; Renal failure: 5.1 ± 0.2 L/kg; in saliva, tear film, and nasal secretions; in animals, tissue (especially lung) concentrations higher than serum concentrations; crosses blood-brain barrier

Protein binding: Normal renal function: ~67%; Hemodialysis: ~59%

Metabolism: Not appreciable; small amounts of an acetyl metabolite identified

Bioavailability: 86% to 90%

Half-life elimination: Normal renal function: 16 ± 6 hours (9-31 hours); End-stage renal disease: 7-10 days

Excretion: Urine (80% to 90% unchanged) by glomerular filtration and tubular secretion

Total clearance: 2.5-10.5 L/hour

Related Information

- Antiparkinsonian Agents
- Community-Acquired Pneumonia in Adults
- Depression
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsPatients with intolerable CNS side effects often do better with rimantadine.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (prolonged use may cause significant xerostomia; normal salivary flow resumes upon discontinuation) and orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentThis agent should not be used for an acute dystonic reaction. No injectable dosage form is available. Amantadine is generally considered to be less effective than anticholinergic antiparkinsonian agents and beta-blockers for the management of akathisia. It is effective for pseudoparkinsonism, but long-term efficacy has not been established. Given its high cost relative to anticholinergics, it is usually reserved for second-line therapy. Tolerance has also been reported to occur with long-term use (Zubenko GS, 1984). However, it does not impair cognition by adding anticholinergic load. Amantadine should not be abruptly discontinued; doing so may precipitate a parkinsonian crisis. Additionally, agitation, delirium, delusions, hallucinations, paranoia, stupor, anxiety, depression, and slurred speech may be seen if it is abruptly stopped.

Zubenko GS, Barreira P, and Lipinski JF Jr, “Development of Tolerance to the Therapeutic Effect of Amantadine on Akathisia,” *J Clin Psychopharmacol*, 1984, 4(4):218-20.

Index TermsAdamantanamine Hydrochloride; Amantadine Hydrochloride

References

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Zubenko GS, Barreira P, and Lipinski JF Jr, "Development of Tolerance to the Therapeutic Effect of Amantadine on Akathisia," *J Clin Psychopharmacol*, 1984, 4(4):218-20.[PubMed 6470196]

International Brand Names a.m.t. (DE); Amanda (TW); Amandin (TW); Amandine (UY); Amantadin (EE); Amantadin-ratiopharm (PL); Amantadina Juventus (ES); Amantadina Llorente (ES); Amantan (BE, LU); Amantix (CO, PL); Amantrel (IN); Amazolon (JP); Atarin (CL, FI); Boidan (JP); Enzil (TW); Hofcomant (AT, FI); Infectoflu (DE); Influ-A (IL); Mantadan (IT); Mantadix (FR, LU); Mantidan (BR); Paritrel (IL); PK-Merz (MX); PK-Merz (AE, AT, BF, BG, BH, BJ, CH, CI, CN, CY, CZ, DE, EE, EG, ET, GH, GM, GN, HK, HN, HU, IL, IQ, IR, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, PK, PT, PY, QA, SA, SC, SD, SL, SN, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Prayanol (CN); Symmetrel (AE, AT, AU, BH, CH, CY, DE, EG, GB, GR, HR, IE, IL, IQ, IR, JO, KW, LB, LY, NL, NO, OM, QA, SA, SY, VE, YE); Tregor (DE); U.M.T. (DE); Viregyt-K (BG, HU, PL); Virofral (DK); Virosol (AR)

Ambenonium

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(am be NOE nee um)

U.S. Brand NamesMytelase®

Canadian Brand NamesMytelase®

Pharmacologic CategoryCholinergic Agonist

Use: Labeled IndicationsTreatment of myasthenia gravis

Dosing: AdultsMyasthenia gravis: Oral: 5-25 mg 3-4 times/day

Dosing: ElderlyRefer to adult dosing.

ContraindicationsRoutine administration of atropine or other belladonna alkaloids with ambenonium is contraindicated because they may suppress the muscarinic symptoms of excessive gastrointestinal stimulation, leaving only the more serious symptoms of muscle fasciculations and paralysis as signs of overdosage; should not be administered to patients receiving mecamylamine

Warnings/Precautions

Concerns related to adverse effects:

- Anticholinergic insensitivity: May develop for brief or prolonged periods; reduce or withhold dosages until the patient becomes sensitive again. May require respiratory support.

Disease-related concerns:

- Asthma: Use with caution in patients with asthma.
- Bradycardia: Use with caution in patients with bradycardia.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Parkinson's disease: Use with caution in patients with Parkinson's disease.
- Peptic ulcer disease: Use with caution in patients with peptic ulcer disease.
- Seizures: Use with caution in patients with a history of seizures.
- Urinary tract obstruction: Use with caution in patients with urinary obstruction.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Differentiation of cholinergic/myasthenia crisis is critical; use edrophonium and clinical judgment. Prolonged action after cholinergics; drug should be discontinued until the patient is stabilized.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias (especially bradycardia), hypotension, carbon monoxide decreased, tachycardia, AV block, nodal rhythm, ECG changes (nonspecific), cardiac arrest, syncope, flushing

Central nervous system: Convulsions, dysarthria, dysphonia, dizziness, loss of consciousness, drowsiness, headache

Dermatologic: Skin rash, thrombophlebitis (I.V.), urticaria

Gastrointestinal: Hyperperistalsis, nausea, vomiting, salivation, diarrhea, stomach cramps, dysphagia, flatulence

Genitourinary: Urinary urgency

Neuromuscular & skeletal: Weakness, fasciculations, muscle cramps, spasms, arthralgia

Ocular: Small pupils, lacrimation

Respiratory: Bronchial secretions increased, laryngospasm, bronchiolar constriction, respiratory muscle paralysis, dyspnea, respiratory depression, respiratory arrest, bronchospasm

Miscellaneous: Diaphoresis increased, anaphylaxis, allergic reactions

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringAssess bladder and sphincter adequacy prior to administering medication. Assess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness and adverse reactions (cholinergic crisis). Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationThis drug will not cure myasthenia gravis, but it may reduce the symptoms. Use as directed; do not increase dose or discontinue medication without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause dizziness, drowsiness, or postural hypotension (rise slowly from sitting or lying position and use caution when driving or climbing stairs); vomiting or loss of appetite (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (boiled milk, yogurt, or buttermilk may help). Report persistent abdominal discomfort; significantly increased salivation, sweating, tearing, or urination; flushed skin; chest pain or palpitations; acute headache; unresolved diarrhea; excessive fatigue, insomnia, dizziness, or depression; increased muscle, joint, or body pain; vision changes or blurred vision; or shortness of breath or wheezing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet, as chloride [scored]:

Mytelase®: 10 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Mytelase)

10 mg (100): $158.40

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay produce drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported; the cholinergic effects may counteract the anticholinergic effects of psychotropics

Index TermsAmbenonium Chloride

International Brand NamesMytelase (FI, HU, PL); Mytelase Chloride (BE, CZ, FR, HN, SE)

Ambrisentan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(am bri SEN tan)

U.S. Brand NamesLetairis™

Canadian Brand NamesVolibris™

Pharmacologic CategoryEndothelin Antagonist; Vasodilator

Use: Labeled IndicationsTreatment of pulmonary artery hypertension (PAH) World Health Organization (WHO) Group I in patients with WHO Class II or III symptoms to improve exercise capacity and decrease the rate of clinical deterioration

Dosing: AdultsPulmonary arterial hypertension: Oral: Initial: 5 mg once daily; if tolerated, may increase to maximum 10 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment is required in mild-to-moderate renal impairment. No data available for use in severe renal impairment.

Dosing: Hepatic ImpairmentAvoid use in patients with moderate-to-severe hepatic insufficiency. Dose reductions may be required in patients with mild hepatic insufficiency.

Dosing: Adjustment for ToxicityModifications based on transaminase elevation:

If any elevation, regardless of degree, is accompanied by clinical symptoms of hepatic injury (unusual fatigue, nausea, vomiting, abdominal pain, fever, or jaundice) or a serum bilirubin >2 times ULN, treatment should be stopped and not reintroduced.

AST/ALT >3 but ≤5 times ULN: Confirm with additional test; if confirmed, reduce dose or interrupt treatment. Monitor transaminase levels at least every 2 weeks until levels are <3 times ULN. Reinitiate treatment as appropriate with return to pretreatment values and with more frequent checks of transaminase levels.

AST/ALT >5 but ≤8 times ULN: Confirm with additional test; if confirmed, stop treatment. Monitor transaminase levels until they are <3 times ULN. May reintroduce treatment, as appropriate, at starting dose, following return to pretreatment values. More frequent checks of transaminase levels are required after resuming therapy.

AST/ALT >8 times ULN: Stop treatment and do not reintroduce.

Administration: OralSwallow tablet whole. Do not split, crush, or chew tablets. May be administered with or without food.

Dietary ConsiderationsMay be taken with or without food. Avoid grapefruit and grapefruit juice.

StorageStore at controlled room temperature of 25°C (77°F).

Restrictions

Ambrisentan (Letairis™) is only available through the limited distribution program (Letairis Education and Access Program [LEAP]). Only prescribers and pharmacies registered with LEAP may prescribe and dispense ambrisentan. Further information may be obtained from the manufacturer, Gilead Sciences, Inc (1-866-664-5327). FDA-approved medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsPregnancy

Canadian labeling: Additional contraindications (not in U.S. labeling): Hypersensitivity to ambrisentan or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Hepatic impairment: See “Disease-related concerns” below
- Pregnancy: See “Special populations” below

Concerns related to adverse effects:

- Fluid retention/peripheral edema: Development of peripheral edema due to treatment and/or disease state (pulmonary arterial hypertension) may occur; a higher incidence is seen in elderly patients. There have also been postmarketing reports of fluid retention requiring treatment (eg, diuretics, fluid management, hospitalization). Further evaluation may be necessary to determine cause and appropriate treatment or discontinuation of therapy.
- Hematologic changes: A reduction in hematocrit/hemoglobin may be observed within the first few weeks of therapy with subsequent stabilization of levels. Hemoglobin reductions >15% have been observed in some patients. Measure hemoglobin prior to initiating therapy, at 1 month, and periodically thereafter. Significant decreases in hemoglobin in the absence of other causes may warrant the discontinuation of therapy.

Disease-related concerns:

- Hepatic impairment: **[U.S. Boxed Warning]: Avoid use in moderate-to-severe hepatic impairment.** Has been associated with significant transaminase (ALT or AST) elevations (>3 times upper limit of normal [ULN]) in up to 3% of treated patients. Transaminase elevations are dose dependent. Avoid use in patients with elevated serum transaminases (>3 times ULN) at baseline. An increase in bilirubin may be observed as well. Monitor hepatic function closely (at least monthly) for the duration of treatment. Reduce dose or interrupt therapy if transaminases >3 times ULN and ≤5 times ULN and discontinue therapy with levels >5 times ULN and ≤8 times ULN. Treatment should be stopped in patients who develop elevated transaminases >8 times ULN, elevated transaminases accompanied by symptoms of hepatic injury (unusual fatigue, jaundice, nausea, vomiting, abdominal pain, and/or fever) or elevated serum bilirubin >2 times ULN. Safety of reintroduction is unknown. Use caution in mild hepatic impairment. Dose reduction may be necessary.

Concurrent drug therapy issues:

- High potential for interactions: Use caution in patients taking strong inhibitors or inducers of CYP3A4 or CYP2C19, inhibitors of P-glycoprotein (eg, cyclosporine), or agents which affect glucuronidation metabolism via uridine 5'-diphosphate glucuronosyltransferase (UGT) enzymes.

Special populations:

- Pediatrics: Safety and efficacy have not been established in patients <18 years of age.
- Pregnancy: **[U.S. Boxed Warning]: Use in pregnancy is contraindicated.** Exclude pregnancy prior to initiating therapy and monthly thereafter during therapy. Two reliable methods of contraception must be used during therapy except in patients with tubal ligation or an implanted IUD (Copper T 380A or LNg 20). No other contraceptive measures are required for these patients. A missed menses should be reported to healthcare provider and prompt immediate pregnancy testing.

Pregnancy Risk FactorX

Pregnancy Considerations**[U.S. Boxed Warning]: Use in pregnancy is contraindicated.** Based on animal studies, ambrisentan is likely to produce major birth defects if used by pregnant women. Pregnancy must be excluded prior to initiation of therapy and follow-up pregnancy tests should be obtained monthly. Two reliable methods of contraception must be used throughout treatment unless the patient has undergone a tubal ligation or the insertion of an intrauterine device (Copper T 380A or LNg 20). No other contraceptive measures are required for these patients.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Cardiovascular: Peripheral edema (17%)

Central nervous system: Headache (15%)

1% to 10%:

Cardiovascular: Palpitation (5%), flushing (4%)

Gastrointestinal: Constipation (4%), abdominal pain (3%)

Hematologic: Hemoglobin decreased (7% to 10%)

Hepatic: Liver enzymes increased (1% to 3%)

Respiratory: Nasal congestion (6%), dyspnea (4%), nasopharyngitis (3%), sinusitis (3%)

Postmarketing and/or case reports: Fluid retention

Metabolism/Transport Effects**Substrate** of CYP3A4 (major), 2C19 (major), P-glycoprotein

Drug Interactions

CycloSPORINE: May increase the serum concentration of Ambrisentan. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Grapefruit/grapefruit juice may increase levels/effects of ambrisentan.

Herb/Nutraceutical: Avoid St John’s wort (concurrent use may decrease levels/effects of ambrisentan).

Monitoring ParametersSerum transaminase (AST and ALT) and bilirubin should be determined prior to the initiation of therapy (baseline) and at monthly intervals thereafter. Monitor for clinical signs and symptoms of liver injury (eg, abdominal pain, fatigue, fever, jaundice, nausea, vomiting). Reduce dose or interrupt therapy if transaminases >3 times ULN and ≤5 times ULN and discontinue therapy with levels >5 times ULN and ≤8 times ULN. Monitor levels every 2 weeks until they are <3 times ULN. Therapy may be resumed with more frequent monitoring of levels. Discontinue therapy in patients with transaminases >8 times ULN, elevated transaminases with accompanying symptoms of hepatic injury, or bilirubin >2 times ULN. Monitor for significant peripheral edema and evaluate etiology if it occurs.

A woman of childbearing potential must have a negative pregnancy test prior to the initiation of therapy and monthly thereafter. Hemoglobin and hematocrit should be measured at baseline, at 1 month, and periodically thereafter (generally stabilizes after the first few weeks of treatment).

Nursing: Physical Assessment/MonitoringMonitor therapeutic response and adverse reactions at the beginning and periodically throughout therapy. Assess for symptoms of hepatic problems and fluid retention. Monitor laboratory tests. Assess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report. Pregnancy risk factor X; pregnancy must be excluded before starting medication.

Monitoring: Lab TestsSerum transaminase (AST and ALT) and bilirubin should be determined prior to the initiation of therapy (baseline) and at monthly intervals thereafter. Monitor for clinical signs and symptoms of liver injury (eg, abdominal pain, fatigue, fever, jaundice, nausea, vomiting). Reduce dose or interrupt therapy if transaminases >3 times ULN and ≤5 times ULN and discontinue therapy with levels >5 times ULN and ≤8 times ULN. Monitor levels every 2 weeks until they are <3 times ULN. Therapy may be resumed with more frequent monitoring of levels. Discontinue therapy in patients with transaminases >8 times ULN, elevated transaminases with accompanying symptoms of hepatic injury, or bilirubin >2 times ULN. Monitor for significant peripheral edema and evaluate etiology if it occurs.

A woman of childbearing potential must have a negative pregnancy test prior to the initiation of therapy and monthly thereafter. Hemoglobin and hematocrit should be measured at baseline, at 1 month, and periodically thereafter (generally stabilizes after the first few weeks of treatment).

Patient EducationInform prescriber of all prescription medications, OTC medications, or herbal products you are taking. Do not take any new medications without consulting prescriber. Pregnancy must be excluded prior to initiation and monthly thereafter. Two forms of contraception must be used during therapy (except in patients with tubal ligation or an implanted IUD). Avoid grapefruit or grapefruit juice. Maintain adequate hydration (2-3 L/day) unless instructed to restrict intake by prescriber. You may experience headache, nasal congestion, fatigue, or constipation (increasing exercise, fluids, fruit/fiber may help). Report signs of fluid retention (unusual weight gain >3-5 pounds/week, swelling of the extremities); shortness of breath; unusual bleeding or bruising; change in color of urine or stool; loss of appetite; abdominal pain; yellowing of skin or eyes; or unusual fatigue. **Pregnancy/breast-feeding precautions:** Do not get pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraception methods if necessary or if you suspect you might be pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Letairis™: 5 mg, 10 mg

Generic AvailableNo

ManufacturerGilead Sciences, Inc

Mechanism of ActionBlocks endothelin receptor subtypes ET_A and ET_B on vascular endothelium and smooth muscle. Stimulation of these receptors in smooth muscle cells is associated with vasoconstriction. Simulation of ET_B receptors in endothelial cells is associated with vasodilation and antiproliferative effects. Although ambrisentan blocks both ET_A and ET_B receptors, the affinity is greater for the A subtype. Improvement in symptoms of pulmonary artery hypertension and a decrease in the rate of clinical deterioration have been demonstrated in clinical trials.

Pharmacodynamics/Kinetics

Absorption: Rapid

Protein binding: 99%

Metabolism: Hepatic via CYP3A4, CYP2C19, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S, and 1A3S; *in vitro* studies also suggest it is a substrate of organic anion transport protein (OATP) and P-glycoprotein (P-gp)

Half-life elimination: 9 hours

Time to peak, plasma: 2 hours

Excretion: Primarily nonrenal

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Endothelin antagonists have caused bleeding gums; there have been no specific reports for ambrisentan

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusHeadache is common

Mental Health: Effects on Psychiatric TreatmentPeripheral edema is common; concomitant use with lithium may produce additive effects. High potential for drug-drug interactions. Carbamazepine, phenobarbital, phenytoin, secobarbital, and St John's wort may decrease the levels/effects of ambrisentan. Fluvoxamine and nefazodone may increase the levels/effects of ambrisentan.

Index TermsBSF208075

References

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Amcinonide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(am SIN oh nide)

Canadian Brand NamesAmcort®; Cyclocort®; ratio-Amcinonide; Taro-Amcinonide

Pharmacologic CategoryCorticosteroid, Topical

Use: Labeled IndicationsRelief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (high potency corticosteroid)

Dosing: AdultsSteroid-responsive dermatoses: Topical: Apply in a thin film 2-3 times/day. Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to amcinonide or any component of the formulation; use on the face, groin, or axilla

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.

- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Disease-related concerns:

- Infected/weeping lesions: Occlusive dressings should not be used in presence of infection or weeping lesions.

Special populations:

- Pediatrics: Chronic use of corticosteroids in children may interfere with growth and development.

Geriatric ConsiderationsDue to age-related changes in skin, limit use of topical glucocorticosteroids.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Dermatologic: Acne, hypopigmentation, allergic dermatitis, maceration of the skin, skin atrophy, striae, miliaria, telangiectasia

Endocrine & metabolic: Cushing's syndrome, growth retardation (long-term use), HPA suppression, hyperglycemia; these reactions occur more frequently with occlusive dressings

Local: Burning, itching, irritation, dryness, folliculitis, hypertrichosis

Miscellaneous: Secondary infection

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream: 0.1% (15 g, 30 g, 60 g) [contains benzyl alcohol]

Lotion: 0.1% (60 mL)

Ointment: 0.1% (30 g, 60 g) [contains benzyl alcohol]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Cream (Amcinonide)

0.1% (15): $20.99

0.1% (30): $26.99

0.1% (60): $45.99

Cream (Cyclocort)

0.1% (30): $32.99

0.1% (60): $53.99

Lotion (Cyclocort)

0.1% (60): $47.99

Ointment (Amcinonide)

0.1% (60): $43.99

Ointment (Cyclocort)

0.1% (15): $24.99

0.1% (30): $32.99

0.1% (60): $53.99

Mechanism of ActionStimulates the synthesis of enzymes needed to decrease inflammation, suppress mitotic activity, and cause vasoconstriction

Pharmacodynamics/Kinetics

Absorption: Adequate through intact skin; increases with skin inflammation or occlusion

Metabolism: Hepatic

Excretion: Urine and feces

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

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International Brand NamesAmciderm (DE, TH); Amcinil (IT); Amicla (BE, LU, NL); Cycloderm (BE); Penticort (FR, IT); Visderm (AR, JP)

Amifostine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Ethyol® may be confused with ethanol

Pronunciation(am i FOS teen)
U.S. Brand NamesEthyol®
Canadian Brand NamesEthyol®
Pharmacologic Category[Adjuvant, Chemoprotective Agent (Cytoprotective)](); [Antidote]()
Use: Labeled IndicationsReduce the incidence of moderate to severe xerostomia in patients undergoing postoperative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands; reduce the cumulative renal toxicity associated with repeated administration of cisplatin
Use: Unlabeled/InvestigationalPrevention of radiation proctitis in patients with rectal cancer
Dosing: Adults**Note:** Antiemetic medication, including dexamethasone 20 mg I.V. and a serotonin 5-HT_3 receptor antagonist, is recommended prior to and in conjunction with amifostine.
Cisplatin-induced renal toxicity, reduction: I.V.: 910 mg/m^2 once daily over 15 minutes 30 minutes prior to cytotoxic therapy

For 910 mg/m^2 doses, the manufacturer suggests the following blood pressure-based adjustment schedule:

The infusion of amifostine should be interrupted if the systolic blood pressure decreases significantly from baseline, as defined below:

Decrease of 20 mm Hg if baseline systolic blood pressure <100

Decrease of 25 mm Hg if baseline systolic blood pressure 100-119

Decrease of 30 mm Hg if baseline systolic blood pressure 120-139

Decrease of 40 mm Hg if baseline systolic blood pressure 140-179

Decrease of 50 mm Hg if baseline systolic blood pressure ≥180

If blood pressure returns to normal within 5 minutes (assisted by fluid administration and postural management) and the patient is asymptomatic, the infusion may be restarted so that the full dose of amifostine may be administered. If the full dose of amifostine cannot be administered, the dose of amifostine for subsequent cycles should be 740 mg/m^2.

Xerostomia from head and neck cancer, reduction:

I.V.: 200 mg/m^2 over 3 minutes once daily 15-30 minutes prior to radiation therapy **or**

SubQ (unlabeled route): 500 mg once daily prior to radiation therapy

Prevention of radiation proctitis in rectal cancer (unlabeled use): I.V.: 340 mg/m^2 once daily prior to radiation therapy (Keefe, 2007; Peterson, 2008)

Dosing: ElderlyRefer to adult dosing.
Calculations

- [Body Surface Area: Adults]()

Administration: I.V.Administer over 3 minutes (prior to radiation therapy) or 15 minutes (prior to cisplatin); administration as a longer infusion is associated with a higher incidence of side effects. Patients should be kept in supine position during infusion.
Administration: I.V. DetailpH: 7
Administration: OtherSubQ administration (unlabeled) has been used.
StorageStore intact vials of lyophilized powder at room temperature of 20°C to 25°C (68°F to 77°F). Reconstituted solutions (500 mg/10 mL) and solutions for infusion are chemically stable for up to 5 hours at room temperature (25°C) or up to 24 hours under refrigeration (2°C to 8°C).
ReconstitutionFor I.V. infusion, reconstitute intact vials with 9.7 mL 0.9% sodium chloride injection and dilute in 0.9% sodium chloride to a final concentration of 5-40 mg/mL. For SubQ administration, reconstitute with 2.5 mL NS or SWFI.
CompatibilityStable in NS.

Y-site administration: Compatible: Amikacin, aminophylline, ampicillin, ampicillin/sulbactam, aztreonam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, carmustine, cefazolin, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cimetidine, ciprofloxacin, clindamycin, co-trimoxazole, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin HCl, dexamethasone sodium phosphate, diphenhydramine, dobutamine, docetaxel, dopamine, doxorubicin HCl, doxycycline, droperidol, enalaprilat, etoposide, famotidine, floxuridine, fluconazole, fludarabine, fluorouracil, furosemide, gallium nitrate, gemcitabine, gentamicin, granisetron, haloperidol lactate, heparin, hydrocortisone sodium succinate, hydromorphone, idarubicin, ifosfamide, imipenem/cilastatin, leucovorin calcium, lorazepam, magnesium sulfate, mannitol, mechlorethamine, meperidine, mesna, methotrexate, methylprednisolone sodium succinate, metoclopramide, metronidazole, mitomycin, mitoxantrone, morphine, nalbuphine, ondansetron, pemetrexed, piperacillin, potassium chloride, promethazine, ranitidine, sodium bicarbonate, streptozocin, teniposide, thiotepa, ticarcillin/clavulanate, tobramycin, vancomycin, vinblastine, vincristine, zidovudine. **Incompatible:** Acyclovir, amphotericin B, chlorpromazine, cisplatin, ganciclovir, hydroxyzine HCl, prochlorperazine edisylate.

ContraindicationsHypersensitivity to aminothiol compounds or any component of the formulation

Allergy Considerations

- Mannitol Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cutaneous reactions: Serious cutaneous reactions, including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, toxoderma, and exfoliative dermatitis have been reported with amifostine. May be delayed, developing up to weeks after treatment initiation. Cutaneous reactions have been reported more frequently when used as a radioprotectant. Discontinue treatment for severe/serious cutaneous reaction, or with fever. Withhold treatment and obtain dermatologic consultation for rash involving lips or mucosa (of unknown etiology outside of radiation port) and for bullous, edematous or erythematous lesions on hands, feet or trunk; reinitiate only after careful evaluation.

- Hypersensitivity reactions: Rare hypersensitivity reactions, including anaphylaxis and allergic reaction, have been reported. Discontinue if allergic reaction occurs; do not rechallenge. Medications for the treatment of hypersensitivity reactions should be available.

- Hypocalcemia: Reports of clinically-relevant hypocalcemia are rare, but serum calcium levels should be monitored in patients at risk of hypocalcemia, such as those with nephrotic syndrome, or patients receiving multiple amifostine doses. May require calcium supplementation.

- Hypotension: Hypotension may occur during or shortly after infusion. Patients who are hypotensive or dehydrated should not receive amifostine. Adequately hydrate prior to treatment and keep in a supine position during the infusion. Monitor blood pressure every 5 minutes during the infusion. If hypotension requiring interruption of therapy occurs, patients should be placed in the Trendelenburg position and given an infusion of normal saline using a separate I.V. line; subsequent infusions may require a dose reduction. Infusions >15 minutes are associated with a higher incidence of adverse effects.

- Nausea/vomiting: The incidence of nausea and vomiting is higher in patients receiving amifostine, compared to chemotherapy alone. Antiemetic medications, including dexamethasone 20 mg I.V. and a serotonin 5-HT_3 receptor antagonist, should be administered prior to and in conjunction with amifostine. Use with caution in patients whom the adverse effects of nausea/vomiting may have serious adverse events.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease or whom the adverse effects of hypotension may have serious adverse events.

- Cerebrovascular disease: Use with caution in patients with cerebrovascular disease.

Concurrent drug therapy issues:

- Antihypertensive therapy: Interrupt antihypertensive therapy for 24 hours before treatment; patients who cannot safely stop their antihypertensives 24 hours before should not receive amifostine.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Should not be used (in patients receiving chemotherapy for malignancies other than ovarian cancer) where chemotherapy is expected to provide significant survival benefit or in patients receiving definitive radiotherapy, unless within the context of a clinical trial.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have demonstrated embryotoxicity. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for adverse reactions in the nursing infant, breast-feeding should be discontinued.

Adverse Reactions

>10%:

Cardiovascular: Hypotension (15% to 61%; grades 3/4: 3% to 8%; dose dependent)

Gastrointestinal: Nausea/vomiting (53% to 96%; grades 3/4: 8% to 30%; dose dependent)

1% to 10%: Endocrine & metabolic: Hypocalcemia (clinically significant: 1%)

<1%, postmarketing, and/or case reports: Apnea, anaphylactoid reactions, anaphylaxis, arrhythmia, atrial fibrillation, atrial flutter, back pain, bradycardia, cardiac arrest, chest pain, chest tightness, chills, cutaneous eruptions, dizziness, erythema multiforme, exfoliative dermatitis, extrasystoles, dyspnea, fever, flushing, hiccups, hypersensitivity reactions (fever, rash, hypoxia, dyspnea, laryngeal edema), hypertension (transient), hypoxia, malaise, MI, myocardial ischemia, pruritus, rash (mild), renal failure, respiratory arrest, rigors, seizure, sneezing, somnolence, Stevens-Johnson syndrome, supraventricular tachycardia, syncope, tachycardia, toxic epidermal necrolysis,

toxoderma, urticaria

Oncology: VesicantNo

Oncology: Emetic Potential

Higher doses: Moderate-to-high (30% to 90%)

Low-dose: Low (10% to 30%)

Drug Interactions

Antihypertensives: May enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Monitoring ParametersBlood pressure should be monitored every 5 minutes during the infusion and after administration if clinically indicated; serum calcium levels (in patients at risk for hypocalcemia). Evaluate for cutaneous reactions prior to each dose.

Nursing: Physical Assessment/MonitoringMonitor blood pressure closely during infusion (continuously or every 5-7 minutes; see Dosing). Can cause hypotension. Ensure adequate hydration prior to administration. Monitor nausea and treat with antiemetic as appropriate.

Monitoring: Lab TestsSerum calcium levels (in patients at risk for hypocalcemia)

Patient EducationThis I.V. medication is given to help reduce side effects of your chemotherapy and/or radiation therapy. Report immediately any nausea; you will be given medication. Report chills, severe dizziness, tremors or shaking, or sudden onset of hiccups. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 500 mg

Ethyol®: 500 mg

Generic AvailableYes

Mechanism of ActionProdrug that is dephosphorylated by alkaline phosphatase in tissues to a pharmacologically-active free thiol metabolite. The free thiol is available to bind to, and detoxify, reactive metabolites of cisplatin; and can also act as a scavenger of free radicals that may be generated (by cisplatin or radiation therapy) in tissues.

Pharmacodynamics/Kinetics

Distribution: V_d: 3.5 L

Metabolism: Hepatic dephosphorylation to two metabolites (active-free thiol and disulfide)

Half-life elimination: ~8-9 minutes

Excretion: Urine

Clearance, plasma: 2.17 L/minute

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy Pearls**Oncology Comment:** The American Society of Clinical Oncology (ASCO) guidelines for the use of protectants for chemotherapy and radiation (Hensley, 2008) recommend the use of amifostine for prevention of nephrotoxicity due to cisplatin-based chemotherapy and to decrease the incidence of acute and delayed radiation therapy-induced xerostomia. The ASCO guidelines do not recommend the use of amifostine to reduce the incidence of neutropenia or thrombocytopenia associated with chemotherapy or radiation therapy, neurotoxicity or ototoxicity associated with platinum-based chemotherapy, radiation therapy-induced mucositis associated with head and neck cancer, or esophagitis due to chemotherapy in patients with nonsmall cell lung cancer. Additionally, the guidelines do not support the use of amifostine in patients with head and neck cancer receiving concurrent platinum-based chemotherapy.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common

Mental Health: Effects on Psychiatric TreatmentHypotension is common and may be additive with psychotropics

Index TermsEthiofos; Gammaphos; WR-2721; YM-08310

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Bonner HS and Shaw LM, “New Dosing Regimens for Amifostine: A Pilot Study to Compare the Relative Bioavailability of Oral and Subcutaneous Administration With Intravenous Infusion,” *J Clin Pharmacol*, 2002, 42(2):166-74. [PubMed 11831539]

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Samuels MA, Chico IM, Hirsch RL, et al, "Ongoing Prospective Multicenter Safety Study of the Cytoprotectant Amifostine Given Subcutaneously: Overview of Trial Design," *Semin Oncol*, 2003, 30(6 Suppl 18):94-5.

Spencer CM and Goa KL, "Amifostine. A Review of Its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential as a Radioprotector and Cytotoxic Chemoprotector," *Drugs*, 1995, 50(6):1001-31. [PubMed 8612469]

Wasserman TH and Brizel DM, "The Role of Amifostine as a Radioprotector," *Oncology (Huntingt)*, 2001, 15(10):1349-54.

International Brand NamesAmiphos (IN); Cytofos (TH); Erifostine (AR); Ethyol (AR, AT, AU, BE, BG, BR, CH, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GT, HK, HN, IE, IL, IT, LU, MX, NI, NL, PA, PE, PH, PL, PT, SE, SV, TH, UY, VE)

Amikacin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Amikacin may be confused with Amicar®, anakinra

Amikin® may be confused with Amicar®

Pronunciation(am i KAY sin)

Canadian Brand NamesAmikacin Sulfate Injection, USP; Amikin®

Pharmacologic CategoryAntibiotic, Aminoglycoside

Use: Labeled IndicationsTreatment of serious infections (bone infections, respiratory tract infections, endocarditis, and septicemia) due to organisms resistant to gentamicin and tobramycin, including *Pseudomonas*, *Proteus*, *Serratia*, and other gram-negative bacilli; documented infection of mycobacterial organisms susceptible to amikacin

Use: Unlabeled/InvestigationalBacterial endophthalmitis

Dosing: AdultsIndividualization is critical because of the low therapeutic index

Note: Use of ideal body weight (IBW) for determining the mg/kg/dose appears to be more accurate than dosing on the basis of total body weight (TBW)

In morbid obesity, dosage requirement may best be estimated using a dosing weight of IBW + 0.4 (TBW - IBW)

Initial and periodic peak and trough plasma drug levels should be determined, particularly in critically-ill patients with serious infections or in disease states known to significantly alter aminoglycoside pharmacokinetics (eg, cystic fibrosis, burns, or major surgery)

Usual dosage range: I.M., I.V.: 5-7.5 mg/kg/dose every 8 hours

Note: Some clinicians suggest a daily dose of 15-20 mg/kg for all patients with normal renal function. This dose is at least as efficacious with similar, if not less, toxicity than conventional dosing.

Indication-specific dosing:

Endophthalmitis, bacterial (unlabeled use): Intravitreal: 0.4 mg/0.1 mL NS in combination with vancomycin

Hospital-acquired pneumonia (HAP): I.V.: 20 mg/kg/day with antipseudomonal beta-lactam or carbapenem (American Thoracic Society/ATS guidelines)

Meningitis*(Pseudomonas aeruginosa):* I.V.: 5 mg/kg every 8 hours (administered with another bacteriocidal drug)

Mycobacterium fortuitum, M. chelonae, or M. abscessus: I.V.: 10-15 mg/kg daily for at least 2 weeks with high dose cefoxitin

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric **Usual dosage range:** Infants and Children: I.M., I.V.: 5-7.5 mg/kg/dose every 8 hours

Note: Individualization is critical because of the low therapeutic index

Use of ideal body weight (IBW) for determining the mg/kg/dose appears to be more accurate than dosing on the basis of total body weight (TBW)

In morbid obesity, dosage requirement may best be estimated using a dosing weight of IBW + 0.4 (TBW - IBW)

Initial and periodic peak and trough plasma drug levels should be determined, particularly in critically-ill patients with serious infections or in disease states known to significantly alter aminoglycoside pharmacokinetics (eg, cystic fibrosis, burns, or major surgery)

Dosing: Renal ImpairmentIndividualization is critical because of the low therapeutic index. Some patients may require larger or more frequent doses if serum levels document the need (ie, cystic fibrosis or febrile granulocytopenic patients).

Cl_{cr} ≥60 mL/minute: Administer every 8 hours

Cl_{cr} 40-60 mL/minute: Administer every 12 hours

Cl_{cr} 20-40 mL/minute: Administer every 24 hours

Cl_{cr} <20 mL/minute: Loading dose, then monitor levels

Dialyzable (50% to 100%)

Administer dose postdialysis or administer $^{2}/_{3}$ normal dose as a supplemental dose postdialysis and follow levels.

Peritoneal dialysis effects: Dose as for Cl_{cr} <20 mL/minute: Follow levels.

Continuous arteriovenous or venovenous hemodiafiltration effects: Dose as for Cl_{cr} 10-40 mL/minute: Follow levels.

Calculations

- Adjusted Body Weight
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Ideal Body Weight: Adults
- Ideal Body Weight: Pediatrics

Administration: I.M.Administer I.M. injection in large muscle mass. Administer around-the-clock to promote less variation in peak and trough serum levels. Do not mix with other drugs, administer separately.

Administration: I.V.Infuse over 30-60 minutes.

Some penicillins (eg, carbenicillin, ticarcillin, and piperacillin) have been shown to inactivate *in vitro*. This has been observed to a greater extent with tobramycin and gentamicin, while amikacin has shown greater stability against inactivation. Concurrent use of these agents may pose a risk of reduced antibacterial efficacy *in vivo*, particularly in the setting of profound renal impairment. However, definitive clinical evidence is lacking. If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered.

Administration: I.V. DetailAdminister around-the-clock to promote less variation in peak and trough serum levels. Do not mix with other drugs, administer separately.

pH: 3.5-5.5

Dietary ConsiderationsSodium content of 1 g: 29.9 mg (1.3 mEq)

StorageStore at controlled room temperature. Following admixture at concentrations of 0.25-5 mg/mL, amikcain is stable for 24 hours at room temperature and 2 days at refrigeration when mixed in D_5W, NS, and LR.

CompatibilityStable in dextran 75 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_3NS$, $D_5{}^1/_2NS$, D_5NS, $D_{10}NS$, D_5W, $D_{10}W$, $D_{20}W$, mannitol 20%, $^1/_4NS$, $^1/_2NS$, NS; **variable stability (consult detailed reference)** in peritoneal dialysis solutions.

Y-site administration: Compatible: Acyclovir, alatrofloxacin, amifostine, amiodarone, amsacrine, aztreonam, cefpirome, cisatracurium, cyclophosphamide, dexamethasone sodium phosphate, diltiazem, docetaxel, enalaprilat, esmolol, etoposide, filgrastim, fluconazole, fludarabine, foscarnet, furosemide, gatifloxacin, gemcitabine, granisetron, idarubicin, IL-2, labetalol, levofloxacin, linezolid, lorazepam, magnesium sulfate, melphalan, midazolam, morphine, ondansetron, paclitaxel, perphenazine, remifentanil, sargramostim, teniposide, thiotepa, vinorelbine, warfarin, zidovudine. **Incompatible:** Allopurinol, amphotericin B cholesteryl sulfate complex, hetastarch, propofol.

Compatibility in syringe: Compatible: Clindamycin, doxapram. **Incompatible:** Heparin.

Compatibility when admixed: Compatible: Amobarbital, ascorbic acid injection, bleomycin, calcium chloride, calcium gluconate, cefepime, cefoxitin, chloramphenicol, chlorpheniramine, cimetidine, ciprofloxacin, clindamycin, colistimethate, dimenhydrinate, diphenhydramine, epinephrine, ergonovine, fluconazole, furosemide, hyaluronidase, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, lincomycin, metaraminol, metronidazole, metronidazole with sodium bicarbonate, norepinephrine, pentobarbital, phenobarbital, phytonadione, polymyxin B sulfate, prochlorperazine edisylate, promethazine, ranitidine, sodium bicarbonate, succinylcholine, vancomycin, verapamil. **Incompatible:** Amphotericin B, ampicillin, cefazolin, chlorothiazide, heparin, phenytoin, thiopental, vitamin B complex with C. **Variable (consult detailed reference):** Aminophylline, dexamethasone sodium phosphate, oxacillin, penicillin G potassium, potassium chloride.

ContraindicationsHypersensitivity to amikacin sulfate or any component of the formulation; cross-sensitivity may exist with other aminoglycosides

Warnings/Precautions

Boxed Warnings:

- Nephrotoxicity: See “Concerns related to adverse effects” below.
- Neuromuscular blockade and respiratory paralysis: See “Concerns related to adverse effects” below.
- Neurotoxicity: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Nephrotoxicity: **[U.S. Boxed Warning]: May cause nephrotoxicity;** usual risk factors include pre-existing renal impairment, concomitant nephrotoxic medications, advanced age and dehydration. Discontinue treatment if signs of nephrotoxicity occur; renal damage is usually reversible.
- Neuromuscular blockade and respiratory paralysis: **[U.S. Boxed Warning]: May cause neuromuscular blockade and respiratory paralysis;** especially when given soon after anesthesia or muscle relaxants.
- Neurotoxicity: **[U.S. Boxed Warning]: May cause neurotoxicity;** usual risk factors include pre-existing renal impairment, concomitant neuro-/nephrotoxic medications, advanced age and dehydration. Ototoxicity is proportional to the amount of drug given and the duration of treatment. Tinnitus or vertigo may be indications of vestibular injury and impending bilateral irreversible damage. Discontinue treatment if signs of ototoxicity occur.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hearing impairment: Use with caution in patients with pre-existing vertigo, tinnitus, or hearing loss.
- Hypocalcemia: Use with caution in patients with hypocalcemia.
- Neuromuscular disorders: Use with caution in patients with neuromuscular disorders, including myasthenia gravis.
- Renal impairment: Use with caution in patients with pre-existing renal insufficiency; dosage modification required.

Dosage form specific issues:

- Sulfite: Solution contains sodium metabisulfate; use caution in patients with sulfite allergy.

Geriatric ConsiderationsThe aminoglycosides are important therapeutic interventions for infections due to susceptible organisms and as empiric therapy in seriously ill patients. Their use is not without risk of toxicity, however, these risks can be minimized if initial dosing is adjusted for estimated renal function and appropriate monitoring performed. High dose, once daily aminoglycosides have been advocated as an alternative to traditional dosing regimens. Once daily or extended interval dosing is as effective and may be safer than traditional dosing. Interval must be adjusted for renal function.

Pregnancy Risk FactorD

Pregnancy Considerations

Amikacin crosses the placenta, produces detectable serum levels in the fetus, and concentrates in the fetal kidneys. Because of several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy, the manufacturer classifies amikacin as pregnancy risk factor D. Renal toxicity has been observed in animals, but fetal toxicity in humans has not been reported. No adequate and well-controlled studies have been conducted in pregnant women and it is not known whether amikacin can cause fetal harm. Although the manufacturer considers amikacin pregnancy risk factor D, amikacin-specific clinical data would suggest pregnancy risk factor C.

Due to pregnancy-induced physiologic changes, some pharmacokinetic parameters of amikacin may be altered. Pregnant women have an average-to-larger volume of distribution which may result in lower peak serum levels than for the same dose in nonpregnant women. Serum half-life is also shorter.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsAmikacin is excreted into breast milk in trace amounts; however, it is not absorbed when taken orally. This limited oral absorption may minimize exposure to the nursing infant. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Amikacin in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Central nervous system: Neurotoxicity

Otic: Ototoxicity (auditory), ototoxicity (vestibular)

Renal: Nephrotoxicity

<1%: Allergic reaction, arthralgia, drowsiness, drug fever, dyspnea, eosinophilia, headache, hypotension, nausea, paresthesia, rash, tremor, vomiting, weakness

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Test InteractionsSome penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*, leading to a potential underestimation of aminoglycoside serum concentration.

Monitoring ParametersUrinalysis, BUN, serum creatinine, appropriately timed peak and trough concentrations, vital signs, temperature, weight, I & O, hearing parameters

Some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*. This may be clinically-significant for certain penicillin (ticarcillin, piperacillin, carbenicillin) and aminoglycoside (gentamicin, tobramycin) combination therapy in patients with significant renal impairment. Close monitoring of aminoglycoside levels is warranted.

Reference Range

Sample size: 0.5-2 mL blood (red top tube) or 0.1-1 mL serum (separated)

Therapeutic levels:

Peak:

Life-threatening infections: 25-40 mcg/mL

Serious infections: 20-25 mcg/mL

Urinary tract infections: 15-20 mcg/mL

Trough: <8 mcg/mL

The American Thoracic Society (ATS) recommends trough levels of <4-5 mcg/mL for patients with hospital-acquired pneumonia.

Toxic concentration: Peak: >40 mcg/mL; Trough: >10 mcg/mL

Timing of serum samples: Draw peak 30 minutes after completion of 30-minute infusion or at 1 hour following initiation of infusion or I.M. injection; draw trough within 30 minutes prior to next dose

Nursing: Physical Assessment/MonitoringAssess allergy history prior to beginning therapy. Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response. Monitor for ototoxicity, nephrotoxicity, neurotoxicity. Hearing and renal status should be assessed before, during, and after therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity testing prior to initiating therapy. Urinalysis, BUN, serum creatinine, appropriately timed peak and trough concentrations. Initial and periodic peak and trough plasma drug levels should be determined, particularly in critically-ill patients with serious infections or in disease states known to significantly alter aminoglycoside pharmacokinetics (eg, cystic fibrosis, burns, or major surgery). Aminoglycoside levels measured from blood taken from Silastic® central catheters can sometimes give falsely high readings (draw levels from alternate lumen or peripheral stick, if possible). Some penicillin derivatives may accelerate the degradation of aminoglycosides.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug can only be administered by I.V. or I.M. injection. It is important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Report immediately any change in hearing acuity, ringing or roaring in ears, alteration in balance, vertigo, feeling of fullness in head; pain, tingling, or numbness of any body part; or change in urinary pattern or decrease in urine. Report signs of opportunistic infection (eg, white plaques in mouth, vaginal discharge, unhealed sores, sore throat, unusual fever, chills); persistent diarrhea; pain, redness, or swelling at injection site; or other adverse reactions. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sulfate: 50 mg/mL (2 mL); 250 mg/mL (2 mL, 4 mL)

Generic AvailableYes

Mechanism of ActionInhibits protein synthesis in susceptible bacteria by binding to 30S ribosomal subunits

Pharmacodynamics/Kinetics

Absorption:

I.M.: Rapid

Oral: Poorly absorbed

Distribution: Primarily into extracellular fluid (highly hydrophilic); penetrates blood-brain barrier when meninges inflamed

Relative diffusion of antimicrobial agents from blood into CSF: Good only with inflammation (exceeds usual MICs)

CSF:blood level ratio: Normal meninges: 10% to 20%; Inflamed meninges: 15% to 24%

Protein-binding: 0% to 11%

Half-life elimination (renal function and age dependent):

Infants: Low birth weight (1-3 days): 7-9 hours; Full-term >7 days: 4-5 hours

Children: 1.6-2.5 hours

Adults: Normal renal function: 1.4-2.3 hours; Anuria/end-stage renal disease: 28-86 hours

Time to peak, serum: I.M.: 45-120 minutes

Excretion: Urine (94% to 98%)

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults

Pharmacotherapy PearlsAminoglycoside levels measured from blood taken from Silastic® central catheters can sometimes give falsely high readings (draw levels from alternate lumen or peripheral stick, if possible).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness; case reports of delirium and psychosis

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAmikacin Sulfate

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International Brand NamesAgnicin (MX); Akacin (MX, TH); Akicin (TH); Alostil (ID); Amicasil (IT); Amicin (IN); Amikacin Fresenius (DE); Amikacina (CN); Amikacina Medical (ES); Amikacina Normon (ES, PT); Amikacine Aguettant (FR); Amikacine Dakota Pharm (FR); Amikacine Panpharma (FR); Amikafur (MX); Amikan (IT); Amikaxing (CL); Amikayect (MX); Amikin (AU, BF, BG, BJ, BR, CH, CI, CO, CZ, EE, ET, GB, GH, GM, GN, HK, HN, HU, ID, IE, KE, KP, LR, MA, ML, MR, MU, MW, MY, NE, NG, PE, PH, PK, PL, SC, SD, SG, SL, SN, TH, TN, TW, TZ, UG, ZA, ZM, ZW); Amikin. (MX); Amiklin (FR); Amikozit (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Amukin (BE, LU, NL); Biclin (ES, MX, PT); Biklin (AR, AT, DE, FI, PH, SE, VE); Biodacyna (PL); Biokacin (MX, PY); Briclin (UY); Briklin (GR); Chemacin (IT); Cidacid (PH); Cinmik (PH); Gamikal (MX); Glukamin (EC); Kacinth-A (ZA); Kamin (PH); Kamina (PT); Kanbine (ES); Karmikin (MX); Kormakin (PH); Lanomycin (GR); Likacin (AE, BH, CY, EG, HU, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Lisobac (MX); Lukadin (IT); Miacin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Mikasul (PH); Nica (PH); Novamin (BR); Oprad (MX); Orlobin (GR); Panmikin (PH); Riklinak (AR); Savox (TW); Selaxa (GR); Selemycin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Tybikin (TH); Yectamid (MX)

Amiloride and Hydrochlorothiazide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(a MIL oh ride & hye droe klor oh THYE a zide)

Canadian Brand NamesApo-Amilzide®; Gen-Amilazide; Moduret; Novamilor; Nu-Amilzide

Pharmacologic CategoryDiuretic, Combination

Use: Labeled IndicationsPotassium-sparing diuretic; antihypertensive

Dosing: AdultsHypertension, edema: Oral: Initial: 1 tablet/day; may be increased to 2 tablets/day if needed; usually given in a single dose

Dosing: ElderlyOral: Initial: $^1/_2$ to 1 tablet/day

Dosing: Renal ImpairmentSee individual agents.

Dietary ConsiderationsMay be taken with food.

Allergy Considerations

- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Hyperkalemia: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Electrolyte disturbances: Hypochloremic alkalosis and hyponatremia can occur.
- Hyperkalemia: **[U.S. Boxed Warning]: Hyperkalemia can occur; patients at risk include those with renal impairment, diabetes, the elderly, and the severely ill. Serum potassium levels must be monitored at frequent intervals especially when dosages are changed or with any illness that may cause renal dysfunction.**
- Photosensitivity: Photosensitization may occur with hydrochlorothiazide.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Diabetes: Use with extreme caution in patients with diabetes mellitus; may see a change in glucose control. Monitor closely; discontinue amiloride 3 days prior to glucose tolerance testing.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated with hydrochlorothiazide.
- Hepatic impairment: Use hydrochlorothiazide with caution in patients with severe hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use hydrochlorothiazide with caution in patients with moderate or high cholesterol concentrations.
- Metabolic/respiratory acidosis: Use with caution in patients who are at risk for metabolic or respiratory acidosis (eg, cardiopulmonary disease, uncontrolled diabetes).
- Renal impairment: Avoid use of hydrochlorothiazide in severe renal disease (ineffective).
- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Geriatric ConsiderationsPotassium excretion may be decreased in the elderly, increasing the risk of hyperkalemia with potassium-sparing diuretics such as amiloride.

Pregnancy Risk FactorB

Pregnancy ConsiderationsRefer to Hydrochlorothiazide.

LactationExcretion in breast milk unknown/contraindicated

Adverse ReactionsSee individual agents.

Drug Interactions

ACE Inhibitors: Potassium-Sparing Diuretics may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Ammonium Chloride: Potassium-Sparing Diuretics may enhance the adverse/toxic effect of Ammonium Chloride. Specifically the risk of systemic acidosis. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Cardiac Glycosides: Potassium-Sparing Diuretics may diminish the therapeutic effect of Cardiac Glycosides. Specifically, the inotropic effects. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Drospirenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Mitotane: Potassium-Sparing Diuretics may diminish the therapeutic effect of Mitotane. High dose diuretics (eg, Cushings syndrome) may present significantly higher risk than low doses (eg, CHF). *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: Potassium-Sparing Diuretics may diminish the therapeutic effect of QuiNIDine. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 5/50: Amiloride hydrochloride 5 mg and hydrochlorothiazide 50 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Amiloride-Hydrochlorothiazide)

5-50 mg (100): $27.99

Pharmacodynamics/KineticsSee individual agents.
Related Information

- AMILoride
- Hydrochlorothiazide

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness; rarely may cause insomnia and depression
Mental Health: Effects on Psychiatric TreatmentMay cause impotence and orthostatic hypotension which may be exacerbated by psychotropics; effective agent for the treatment of lithium-induced diabetes insipidus

Cardiovascular Considerations Amiloride may cause hyperkalemia, the ECG manifestations of which include peaked T waves, QRS prolongation, and cardiac conduction abnormalities. Thiazide diuretics are effective first-line therapeutic agents in the management of hypertension and have proven to be of benefit in terms of cardiovascular outcome. The combination of amiloride and hydrochlorothiazide may act together to lower blood pressure and limit diuretic-induced changes in plasma potassium. The benefits of thiazide diuretics in the treatment of hypertension is established and compares well with other first-line therapeutic agents.

Diuretics are standard therapy for the management of edema in patients with heart failure.

Index Terms Hydrochlorothiazide and Amiloride

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International Brand Names Adco-Retic (ZA); Add-Acten (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Ameride (ES); Amil-Co (GB); Amilco (DK); Amilco Mite (DK); Amilocomp beta (DE); Amiloretic (ZA); Amizide (AU, MY, TW); Amuretic (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Apo-Amilzide (MY); Biduret (IN); Bildiuretic (TH); Co-Amilozide (AU, GB); Hydrozide (NZ); Hyperetic (TH); Kaluril (IL); Lorinid (ID); Lorinid Mite (ID); Mengdaqing (CL); Moduretic (AU, BE, BF, BJ, BR, CH, CI, CO, CZ, DE, EE, ET, FI, GB, GH, GM, GN, GR, HK, IE, IT, KE, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, PE, PK, PT, PY, SC, SD, SE, SL, SN, TH, TN, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Moure-M (TH); Mourinate (TH); Sefaretic (HK); Sparkal (DK); Tiaden (TW); Uniretic (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Yostiretic (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE)

AMILoride

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English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

AMILoride may be confused with amiodarone, amLODIPine, amrinone

Pronunciation(a MIL oh ride)

Canadian Brand NamesApo-Amiloride®

Pharmacologic CategoryDiuretic, Potassium Sparing

Use: Labeled IndicationsCounteracts potassium loss induced by other diuretics in the treatment of hypertension or edematous conditions including CHF, hepatic cirrhosis, and hypoaldosteronism; usually used in conjunction with more potent diuretics such as thiazides or loop diuretics

Use: Unlabeled/InvestigationalInvestigational: Cystic fibrosis; reduction of lithium-induced polyuria; pediatric hypertension

Dosing: AdultsHypertension, edema (to limit potassium loss): Oral: Initial: 5-10 mg/day (up to 20 mg)

Hypertension (JNC 7): 5-10 mg/day in 1-2 divided doses

Dosing: ElderlyOral: Initial: 5 mg once daily or every other day

Dosing: PediatricHypertension (unlabeled use): Children 1-17 years: Oral: 0.4-0.625 mg/kg/day (maximum: 20 mg/day)

Dosing: Renal ImpairmentOral:

Cl_{cr} 10-50 mL/minute: Administer 50% of normal dose.

Cl_{cr} <10 mL/minute: Avoid use.

Calculations

- Creatinine Clearance: Adults

Administration: OralAdminister with food or meals to avoid GI upset.

Dietary ConsiderationsTake with food or meals to avoid GI upset. Do not use salt substitutes or low salt milk without checking with your healthcare provider; too much potassium can be as harmful as too little.

ContraindicationsHypersensitivity to amiloride or any component of the formulation; presence of elevated serum potassium levels (>5.5 mEq/L); if patient is receiving other potassium-conserving agents (eg, spironolactone, triamterene) or potassium supplementation (medicine, potassium-containing salt substitutes, potassium-rich diet); anuria; acute or chronic renal insufficiency; evidence of diabetic nephropathy. Patients with evidence of renal impairment or diabetes mellitus should not receive this medicine without close, frequent monitoring of serum electrolytes and renal function.

Warnings/Precautions

Boxed warnings:

- Hyperkalemia: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Fluid/electrolyte loss: Excess amounts can lead to profound diuresis with fluid and electrolyte loss; close medical supervision and dose evaluation are required. Watch for and correct electrolyte disturbances; adjust dose to avoid dehydration.

- Hyperkalemia: **[U.S. Boxed Warning]: Hyperkalemia can occur; patients at risk include those with renal impairment, diabetes, the elderly, and the severely ill. Serum potassium levels must be monitored at frequent intervals especially when dosages are changed or with any illness that may cause renal dysfunction.**

Disease-related concerns:

- Cirrhosis: In cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Diabetes: Use with extreme caution in patients with diabetes mellitus; monitor closely. Discontinue amiloride 3 days prior to glucose tolerance testing.

- Metabolic/respiratory acidosis: Use with caution in patients who are at risk for metabolic or respiratory acidosis (eg, cardiopulmonary disease, uncontrolled diabetes).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsUse lower initial dose, and adjust dose for renal impairment.
Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

1% to 10%:

Central nervous system: Headache, fatigue, dizziness

Endocrine & metabolic: Hyperkalemia (up to 10%; risk reduced in patients receiving kaliuretic diuretics), hyperchloremic metabolic acidosis, dehydration, hyponatremia, gynecomastia

Gastrointestinal: Nausea, diarrhea, vomiting, abdominal pain, gas pain, appetite changes, constipation

Genitourinary: Impotence

Neuromuscular & skeletal: Muscle cramps, weakness

Respiratory: Cough, dyspnea

<1% (Limited to important or life-threatening): Orthostatic hypotension, arrhythmia, palpitation, chest pain, alopecia, GI bleeding, polyuria, bladder spasms, dysuria, jaundice, intraocular pressure increased, dyspnea

Drug Interactions

ACE Inhibitors: Potassium-Sparing Diuretics may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Ammonium Chloride: Potassium-Sparing Diuretics may enhance the adverse/toxic effect of Ammonium Chloride. Specifically the risk of systemic acidosis. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Cardiac Glycosides: Potassium-Sparing Diuretics may diminish the therapeutic effect of Cardiac Glycosides. Specifically, the inotropic effects. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Drospirenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Mitotane: Potassium-Sparing Diuretics may diminish the therapeutic effect of Mitotane. High dose diuretics (eg, Cushings syndrome) may present significantly higher risk than low doses (eg, CHF). *Risk D: Consider therapy modification*

Potassium Salts: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: Potassium-Sparing Diuretics may diminish the therapeutic effect of QuiNIDine. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Hyperkalemia may result if amiloride is taken with potassium-containing foods.
Test InteractionsIncreased potassium (S)
Monitoring ParametersI & O, daily weights, blood pressure, serum electrolytes, renal function
Nursing: Physical Assessment/MonitoringAssess need for caution (eg, patients at risk for hyperkalemia). Monitor for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests (electrolytes), fluid status, therapeutic effectiveness, and adverse response (eg, dehydration, hyperkalemia, hyperchloremic metabolic acidosis, hyponatremia; see Adverse Reactions). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsSerum electrolytes, renal function
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, preferably early in day with food. Do not increase dietary intake of potassium unless instructed by prescriber (too much potassium can be as harmful as too little). May cause dizziness or fatigue (use caution when driving or engaging in tasks that require alertness until response to drug is known); constipation (increased exercise, fluids, fruit, and fiber may help); impotence (reversible); or loss of hair (rare). Report muscle cramping or weakness, unresolved nausea or vomiting, palpitations, or respiratory difficulty. **Breast-feeding precaution:** Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 5 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Amiloride HCl)

5 mg (30): $26.99

Tablets (Midamor)

5 mg (30): $25.99

Mechanism of ActionInhibits sodium reabsorption in the distal tubule, cortical collecting tubule, and collecting duct subsequently reducing both potassium and hydrogen excretion resulting in weak natriuretic, diuretic, and antihypertensive activity; increases sodium loss; increases potassium retention; decreases calcium excretion; decreases magnesium loss
Pharmacodynamics/Kinetics

Onset of action: 2 hours

Duration: 24 hours

Absorption: ~15% to 25%

Distribution: V_d: 350-380 L

Protein binding: 23%

Metabolism: No active metabolites

Half-life elimination: Normal renal function: 6-9 hours; End-stage renal disease: 8-144 hours

Time to peak, serum: 6-10 hours

Excretion: Urine and feces (equal amounts as unchanged drug)

Related Information

- Heart Failure (Systolic)

Pharmacotherapy PearlsMedication should be discontinued if potassium level exceeds 6.5 mEq/L. Combined with hydrochlorothiazide as Moduretic®. Amiloride is considered an alternative to triamterene or spironolactone.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness; rarely may cause insomnia and depression
Mental Health: Effects on Psychiatric TreatmentMay cause impotence and orthostatic hypotension which may be exacerbated by psychotropics; effective agent for the treatment of lithium-induced diabetes insipidus
Cardiovascular ConsiderationsAmiloride may cause hyperkalemia, the ECG manifestations of which include peaked T waves, QRS prolongation, and cardiac conduction abnormalities.
Anesthesia and Critical Care Concerns/Other ConsiderationsMedication should be discontinued if hyperkalemia develops. Amiloride may cause hyperkalemia. The ECG manifestations may include peaked T waves, QRS prolongation, and cardiac conduction abnormalities.
Index TermsAmiloride Hydrochloride
References

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Jaffey L and Martin A, “Malignant Hyperkalemia After Amiloride/Hydrochlorothiazide Treatment,” *Lancet*, 1981, 1(8232):1272.

Kleyman TR and Cragoe EJ Jr, “The Mechanism of Action of Amiloride,” *Semin Nephrol*, 1988, 8(3):242-8. [PubMed 2849182]

National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, “The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents,” *Pediatrics*, 2004, 114(2 Suppl):555-76.[PubMed 15286277]

Wang L, Sheldon RS, Mitchell LB, et al, “Amiloride-Quinidine Interaction: Adverse Outcomes,” *Clin Pharmacol Ther*, 1994, 56(6 Pt 1):659-67.[PubMed 7995008]

International Brand NamesAlverix (CY); Amiclaran (CZ); Amiduret Trom (DE); Amikal (DK); Amilamont (GB); Amilo 5 (KP); Amiloberag (DE); Amilorid NM Pharma (SE); Amilozid (HN); Amiride (IL); Berkamil (IE); Kaluril (AU, TW); Midamor (AT, CH, FI, GB, IE, NL, NO, NZ, SE); Modamide (FR); Moduretic (Combinado con hidroclorotiazida) (MX); Nirulid (DK); Pandiuren (AR); Puritrid (FI)

Amino Acid Injection

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Pronunciation(a MEE noe AS id in JEK shun)

U.S. Brand NamesAminosyn®; Branchamin®; Clinisol®; FreAmine®; HepatAmine®; Hepatasol®; NephrAmine®; Novamine®; Premasol™; Prosol; Renamin®; Travasol®; TrophAmine®

Canadian Brand NamesAminosyn; Aminosyn-PF; Aminosyn-RF; Primene®

Pharmacologic CategoryIntravenous Nutritional Therapy

Use: Labeled IndicationsAs part of parenteral nutrition to prevent nitrogen loss or treat negative nitrogen balance when alimentary tract cannot be used (eg, GI absorption is impaired, bowel rest is needed). Specialty amino acid formulas may be considered only in certain instances.

Dosing: AdultsProtein as amino acids: I.V. (as a component of parenteral nutrition):

Maintenance: 0.8-1 g/kg/day

Normal/mild stress level: 1-1.2 g/kg/day

Moderate stress level: 1.2-1.5 g/kg/day

Severe stress level: 1.5-2 g/kg/day

Burn patients (severe): Increase protein until significant wound healing achieved

Solid organ transplant: Perioperative: 1.5-2 g/kg/day

Renal failure:

Acute (severely malnourished or hypercatabolic): 1.5-1.8 g/kg/day

Chronic, with dialysis: 1.2-1.3 g/kg/day

Chronic, without dialysis: 0.6-0.8 g/kg/day

Continuous hemofiltration: ≥1 g/kg/day

Hepatic failure:

Acute management when other treatments have failed:

With encephalopathy: 0.6-1 g/kg/day

Without encephalopathy: 1-1.5 g/kg/day

Chronic encephalopathy: Use branch chain amino acid enriched diets only if unresponsive to pharmacotherapy

Pregnant women in second or third trimester: Add an additional 10-14 g/day

Dosing: PediatricProtein as amino acids: I.V. (as a component of parenteral nutrition):

Term: Initial: 2.5 g/kg/day; Goal: 3 g/kg/day

Extremely (<1000 g) and very (<1500 g) low-birth-weight (stable): Initial: 1-1.5 g/kg/day; Goal: 3.5-3.85 g/kg/day to promote utero growth rates

Sepsis, hypoxia: Initial: 1 g/kg/day; goal: 3-3.85 g/kg/day

Administration: I.V.Administered as a component of peripheral parenteral or total parenteral nutrition. Peripheral administration of nutrition is dependent upon osmolality of solution. Total parenteral nutrition must be administered via central venous access.

StorageStore at room temperature of 20°C to 25°C (68°F to 77°F); avoid excessive heat. Do not freeze. Protect from light.

ContraindicationsInborn errors of amino acid metabolism

Warnings/Precautions

Disease-related concerns:

- Heart failure: Use with caution in patients sensitive to volume overload (eg, heart failure, hepatic failure); consider concentrated total parenteral nutrition formula.
- Hepatic impairment: Use caution in protein delivery especially in patients with hepatic encephalopathy; dosage adjustments may be necessary. Consider volume status in patients with hepatic failure, may require concentrated total parenteral nutrition formula.
- Renal impairment: Use with caution in patients with severe renal impairment; dosage adjustments may be necessary depending upon renal replacement therapy options. It is essential to provide adequate calories in a minimal amount of fluid. Monitor fluid balance closely.

Dosage form specific issues:

- Aluminum: Solutions may contain aluminum; toxic levels may occur following prolonged administration in premature neonates or patients with renal impairment.

Other warning/precautions:

- Monitoring: Monitor fluid and electrolyte status.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Endocrine & metabolic: Fluid, electrolyte imbalance

Local: Erythema, phlebitis, thrombosis

Renal: Azotemia

Monitoring ParametersGeneral patient monitoring during I.V. nutritional therapy

Bone densitometry: Perform upon initiation of long-term therapy.

Efficacy: Nutrition and outcome parameters should be measured serially.

Electrolytes: Sodium, potassium, chloride, and bicarbonate should be monitored frequently upon initiation and until stable; phosphate should be monitored closely in patients with pulmonary disease.

Glucose: In patients with diabetes or patients with glucose intolerance risk factors, monitor closely. Monitor frequently upon initiation of therapy and with any changes in insulin dose or renal function.

Line site: Monitor for signs and symptoms of infection.

Liver function tests: Monitor periodically.

Neonates: Sodium, calcium, and phosphate should be monitored closely. Frequent (some advise

Refeeding syndrome: Patients at risk should have phosphorus, magnesium, potassium, and glucose levels monitored closely at initiation.

Triglycerides: Before initiation of lipid therapy and at least weekly during therapy.

Vitamin A status: Should be carefully monitored in patients with chronic renal failure.

Monitoring: Lab Tests

Efficacy: Nutrition and outcome parameters should be measured serially.

Electrolytes: Sodium, potassium, chloride, and bicarbonate should be monitored frequently upon initiation and until stable; phosphate should be monitored closely in patients with pulmonary disease.

Glucose: In patients with diabetes or patients with glucose intolerance risk factors, monitor closely. Monitor frequently upon initiation of therapy and with any changes in insulin dose or renal function.

Liver function tests: Monitor periodically.

Neonates: Sodium, calcium, and phosphate should be monitored closely. Frequent (some advise

Refeeding syndrome: Patients at risk should have phosphorus, magnesium, potassium, and glucose levels monitored closely at initiation.

Triglycerides: Before initiation of lipid therapy and at least weekly during therapy.

Vitamin A status: Should be carefully monitored in patients with chronic renal failure.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. Peripheral parenteral nutrition and total parenteral nutrition are usually compounded from optimal combinations of macronutrients (water, protein, dextrose, and lipids) and micronutrients (electrolytes, trace elements, and vitamins) to meet the specific nutritional requirements of a patient. Individual hospitals may have designated standard TPN formulas. There are a few commercially-available amino acids with electrolytes solutions; however, these products may not meet an individual's specific nutritional requirements. Consult with nutrition support service to determine adequate formula based upon patient specifics.

Amino acids, branched chain:

Aminosyn®-HBC: 7% (500 mL, 1000 mL)

Branchamin®: 4% (500 mL)

FreAmine® HBC: 6.9% (750 mL)

Amino acids, crystalline:

Aminosyn®: 3.5% (1000 mL); 5% (500 mL, 1000 mL); 7% (500 mL, 1000 mL); 8.5% (500 mL, 1000 mL), 10% (500 mL, 1000 mL)

Aminosyn® II: 7% (500 mL); 8.5% (500 mL, 1000 mL); 10% (500 mL, 1000 mL, 2000 mL); 15% (2000 mL)

Clinisol®: 15% (500 mL, 2000 mL)

FreAmine® III: 8.5% (500 mL, 1000 mL); 10% (500 mL, 1000 mL)

Premasol™: 6% (500 mL); 10% (500 mL, 1000 mL, 2000 mL)

Prosol: 20% (2000 mL)

Novamine®: 15% (500 mL)

Travasol®: 10% (500 mL, 1000 mL, 2000 mL)

Amino acids, hepatic:

Aminosyn®-HF: 8% (500 mL, 1000 mL)

HepatAmine®: 8% (500 mL)

Hepatasol®: 8% (500 mL)

Amino acids, renal:

Aminosyn®-RF: 5.2% (500 mL)

NephrAmine®: 5.4% (250 mL)

Renamin®: 6.5% (250 mL, 500 mL)

Amino acids, pediatric:

Aminosyn®-PF: 7% (500 mL)

TrophAmine®: 6% (500 mL); 10% (500 mL)

Related Information

- Dextrose
- Fat Emulsion
- Total Parenteral Nutrition

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Aminocamptothecin

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Pronunciation(a min o camp to THE sin)

Pharmacologic CategoryAntineoplastic Agent, DNA Binding Agent; Enzyme Inhibitor, Topoisomerase I Inhibitor

Use: Unlabeled/InvestigationalPhase II trials: Relapsed lymphoma, refractory breast cancer, nonsmall cell lung cancer, untreated colorectal carcinoma

Dosing: AdultsI.V.: 45-59 mcg/m^2/hour for 72 hours as a continuous infusion; repeat every 2 weeks **or** 35 mcg/m^2/hour as a 72-hour continuous infusion

Dosing: ElderlyRefer to adult dosing.

Calculations

- Body Surface Area: Adults

Administration: I.V.Continuous I.V. infusion

StorageStore ampuls at room temperature. Diluted solutions are stable for 28 hours at room temperature. Undiluted aminocamptothecin should not contact plastic items.

ReconstitutionContents of ampul are added to vial (supplied) containing 24.5 mL of special diluent. Resulting aminocamptothecin concentration is 100 mcg/mL. Further dilutions with special diluent for administration via syringe pump is acceptable. May further dilute with NS if resulting concentration is <1 mcg/mL.

RestrictionsNot available in U.S./Investigational

ContraindicationsHypersensitivity to aminocamptothecin or any component of the formulation

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Adverse ReactionsFrequency not defined.

Central nervous system: Fatigue

Dermatologic: Alopecia

Gastrointestinal: Nausea, vomiting, diarrhea, mucositis, anorexia

Hematologic: Neutropenia (may be dose limiting), thrombocytopenia (reversible, but may be dose limiting), anemia

Oncology: VesicantNo

Oncology: Emetic PotentialModerate (30% to 60%)

Drug Interactions

CarBAMazepine: May decrease the serum concentration of Aminocamptothecin. *Risk C: Monitor therapy*

PHENobarbital: May decrease the serum concentration of Aminocamptothecin. *Risk C: Monitor therapy*

Phenytoin: May decrease the serum concentration of Aminocamptothecin. *Risk C: Monitor therapy*

Valproic Acid: May decrease the serum concentration of Aminocamptothecin. *Risk C: Monitor therapy*

Monitoring ParametersWBC with differential, platelet count

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection: 5 mg ampul

Generic AvailableNo

Mechanism of ActionAminocamptothecin binds to topoisomerase I, stabilizing the cleavable DNA-topoisomerase I complex, resulting in arrest of the replication fork and inhibition of DNA synthesis.

Pharmacodynamics/KineticsRatio of lactone to total drug is 8.7% ± 4.7% because of instability of aminocamptothecin lactone in plasma.

Distribution: V_d: 46-92 L

Metabolism: None identified

Half-life elimination: Terminal: 8-17 hours for total aminocamptothecin

Excretion: Urine (32% of total drug delivered)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentMay cause GI side effects; concomitant use with SSRIs, lithium, or valproic acid may produce additive effects; monitor. May cause neutropenia and thrombocytopenia; monitor if using concomitantly with clozapine, valproic acid, and carbamazepine.

Index Terms9-AC; 9-Aminocamptothecin; NSC-603071

References

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Iyer L and Ratain MJ, "Clinical Pharmacology of Camptothecins," *Cancer Chemother Pharmacol*, 1998, 42(Suppl):31-43. [PubMed 9619755]

Potmesil M, Arbuck SG, Takimoto CH, et al, "9-Aminocamptothecin and Beyond. Preclinical and Clinical Studies," *Ann N Y Acad Sci*, 1996, 803:231-46. [PubMed 8993517]

Takimota CH, Wright J, and Arbuck SG, "Clinical Applications of the Camptothecins," *Biochim Biophys Acta*, 1998, 1400(1-3):107-19.[PubMed 9748525]

Aminocaproic Acid

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English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Amicar® may be confused with amikacin, Amikin®, Omacor®

Pronunciation(a mee noe ka PROE ik AS id)

U.S. Brand NamesAmicar®

Pharmacologic CategoryAntifibrinolytic Agent; Hemostatic Agent

Use: Labeled IndicationsTo enhance hemostasis when fibrinolysis contributes to bleeding (causes may include cardiac surgery, hematologic disorders, neoplastic disorders, abruption placentae, hepatic cirrhosis, and urinary fibrinolysis)

Use: Unlabeled/InvestigationalTreatment of traumatic hyphema; control bleeding in thrombocytopenia; control oral bleeding in congenital and acquired coagulation disorders; topical treatment (mouth rinse) of bleeding associated with dental procedures in patients on oral anticoagulant therapy; prevention of perioperative bleeding associated with cardiac surgery

Dosing: Adults

Acute bleeding syndrome: Oral, I.V.: Loading dose: 4-5 g during the first hour, followed by 1 g/hour for 8 hours or until bleeding controlled (maximum daily dose: 30 g)

Control of bleeding in thrombocytopenia (unlabeled use):

Initial: I.V.: 100 mg/kg over 30-60 minutes

Maintenance: Oral: 1-3 g every 6 hours

Control or oral bleeding in congenital and acquired coagulation disorder (unlabeled use): Oral: 50-60 mg/kg every 4 hours

Prevention of dental procedure bleeding in patients on oral anticoagulant therapy (unlabeled use): Oral rinse: Hold 4 g/10 mL in mouth for 2 minutes then spit out. Repeat every 6 hours for 2 days after procedure (Souto, 1996). Concentration and frequency may vary by institution and product availability.

Prevention of perioperative bleeding associated with cardiac surgery (unlabeled use): I.V.: 10 g over 20-30 minutes prior to skin incision, followed by 1-2.5 g/hour (usual dose 2 g/hour) until the end of operation (may continue infusion for 4 hours after protamine reversal of heparin). May add 10 g to cardiopulmonary bypass circuit priming solution.

or

10 g over 20-30 minutes prior to skin incision, followed by 10 g after heparin administration then 10 g at discontinuation of cardiopulmonary bypass prior to protamine reversal of heparin

Traumatic hyphema (unlabeled use): Oral: 100 mg/kg/dose every 4 hours (maximum daily dose: 30 g)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Acute bleeding syndrome (unlabeled use): Oral, I.V.: Loading dose: 100-200 mg/kg during the first hour, followed by continuous infusion at 33.3 mg/kg/hour (I.V.) or 100 mg/kg (oral or I.V.) every 6 hours

Prevention of perioperative bleeding associated with cardiac surgery (unlabeled use): I.V.: 100 mg/kg given over 20-30 minutes after induction and prior to incision, 100 mg/kg during cardiopulmonary bypass, and 100 mg/kg after protamine reversal of heparin

Traumatic hyphema (unlabeled use): Oral: Refer to adult dosing.

Dosing: Renal ImpairmentMay accumulate in patients with decreased renal function.

Administration: I.V.Rapid I.V. injection (IVP) of undiluted solution is not recommended due to possible hypotension, bradycardia, and arrhythmia.

I.V.: Acute bleeding syndrome: Administer loading dose over 1 hour, followed by a continuous infusion

I.V.: Prevention of perioperative bleeding associated with cardiac surgery (unlabeled use): Administer loading dose over 20-30 minutes prior to skin incision, followed by a continuous infusion until the end of operation **or** as 2 additional bolus doses (over 20-30 minutes) given after heparin administration and at discontinuation of cardiopulmonary bypass prior to protamine reversal of heparin.

Administration: I.V. DetailpH: 6.8 (adjusted); range: 6-7.6

StorageStore intact vials, tablets, and syrup at 15°C to 30°C (59°F to 86°F). Do not freeze injection or syrup. Solutions diluted for I.V. use in D_5W or NS to concentrations of 10-100 mg/mL are stable at 4°C (39°F) and 23°C (73°F) for 7 days (Zhang, 1997).

ReconstitutionDilute I.V. solution in D_5W, 0.9% sodium chloride, or Ringer's injection.

CompatibilityStable in D_5W, NS, Ringer's injection

ContraindicationsDisseminated intravascular coagulation (without heparin); evidence of an active intravascular clotting process

Warnings/Precautions

Concerns related to adverse effects:

- Intrarenal obstruction: May occur secondary to glomerular capillary thrombosis or clots in the renal pelvis and ureters; do not use in hematuria of upper urinary tract origin unless possible benefits outweigh risks.
- Skeletal muscle weakness: Ranging from mild myalgias and fatigue to severe myopathy with rhabdomyolysis and acute renal failure has been reported with prolonged use. Monitor CPK; discontinue treatment with a rise in CPK.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; may accumulate.

Concurrent drug therapy issues:

- Blood products: Do not administer with factor IX complex concentrates or anti-inhibitor coagulant complexes; may increase risk for thrombosis.

Dosage form specific issues:

- Benzyl alcohol: Injection contains benzyl alcohol which has been associated with "gasping syndrome" in neonates.

Other warnings/precautions:

- Appropriate use: Do not administer without a definite diagnosis of laboratory findings indicative of hyperfibrinolysis. Inhibition of fibrinolysis may promote clotting or thrombosis; more likely due to the presence of DIC.
- I.V. administration: Avoid rapid I.V. administration; may induce hypotension, bradycardia, or arrhythmia; rapid injection of undiluted solution is not recommended.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproductive studies have not been conducted.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, bradycardia, edema, hypotension, intracranial hypertension, peripheral ischemia, syncope, thrombosis

Central nervous system: Confusion, delirium, dizziness, fatigue, hallucinations, headache, malaise, seizure, stroke

Dermatologic: Rash, pruritus

Gastrointestinal: Abdominal pain, anorexia, cramps, diarrhea, GI irritation, nausea, vomiting

Genitourinary: Dry ejaculation

Hematologic: Agranulocytosis, bleeding time increased, leukopenia, thrombocytopenia

Local: Injection site necrosis, injection site pain, injectionsite reactions

Neuromuscular & skeletal: CPK increased, myalgia, myositis, myopathy, rhabdomyolysis (rare), weakness

Ophthalmic: Vision decreased, watery eyes

Otic: Tinnitus

Renal: BUN increased, intrarenal obstruction (glomerular capillary thrombosis), myoglobinuria (rare), renal failure (rare)

Respiratory: Dyspnea, nasal congestion, pulmonary embolism

Miscellaneous: Allergic reaction, anaphylactoid reaction, anaphylaxis

Postmarketing and/or case reports: Hepatic lesion, myocardial lesion

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Anti-inhibitor Coagulant Complex: Antifibrinolytic Agents may enhance the thrombogenic effect of Anti-inhibitor Coagulant Complex. *Risk D: Consider therapy modification*

Factor IX: Aminocaproic Acid may enhance the adverse/toxic effect of Factor IX. Specifically, use of this combination may increase the risk of thrombosis. *Risk X: Avoid combination*

Factor IX Complex (Human): Aminocaproic Acid may enhance the adverse/toxic effect of Factor IX Complex (Human). Specifically, use of this combination may increase the risk of thrombosis. *Risk X: Avoid combination*

Monitoring ParametersFibrinogen, fibrin split products, creatine phosphokinase (with long-term therapy), BUN, creatinine

Nursing: Physical Assessment/MonitoringMonitor laboratory results on a regular basis during therapy. Monitor (teach patient to monitor and report) signs of adverse reactions (eg, bleeding, clotting, thromboembolism, hypotension, or CNS changes).

Monitoring: Lab TestsFibrinogen, fibrin split products, creatine phosphokinase (with long-term therapy), BUN, creatinine

Patient EducationTake oral medication exactly as directed. This medication may cause dizziness and fatigue (use caution when driving or engaging in tasks that require alertness until response to drug is known); hypotension (use caution when rising from a lying or sitting position or climbing stairs); menstrual irregularities, increased body hair, or sexual dysfunction (should reverse when treatment is completed); or nausea or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report immediately any chest pain; dyspnea; swelling; nosebleed; warmth, swelling, pain, or redness in calves; skin rash; muscle pain or weakness; ringing in ears; or acute abdominal cramping. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 250 mg/mL (20 mL)

Amicar®: 250 mg/mL (20 mL) [contains benzyl alcohol]

Solution, oral: 1.25 g/5 mL (240 mL, 480 mL)

Syrup:

Amicar®: 1.25 g/5 mL (480 mL) [raspberry flavor]

Tablet [scored]: 500 mg

Amicar®: 500 mg, 1000 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Amicar)

500 mg (30): $91.34

Mechanism of ActionBinds competitively to plasminogen; blocking the binding of plasminogen to fibrin and the subsequent conversion to plasmin, resulting in inhibition of fibrin degradation (fibrinolysis).

Pharmacodynamics/Kinetics

Onset of action: ~1-72 hours

Distribution: Widely through intravascular and extravascular compartments

V_d: Oral: 23 L, I.V.: 30 L

Metabolism: Minimally hepatic

Half-life elimination: ~2 hours

Time to peak: Oral: Within 2 hours

Excretion: Urine (65% as unchanged drug, 11% as metabolite)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentMay cause hypotension which may be exacerbated by psychotropics; rarely may cause seizures; use caution with clozapine and bupropion

Index TermsEACA; Epsilon Aminocaproic Acid

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International Brand NamesAcepramin (HU); Acidum e-aminocapronicum (PL); Amicar (AU, ZA); Caproamin (ES); Caproamin Fides (ES); Caprolest (NL); Caprolisin (IT); EAC (DE); Epsamon (CH); Epsicaprom (PT); Epsilon (FI); Hemocaprol (ES); Hemocid (IN); Hexalense (FR); Ipsilon (AR, BR); Syrop acidi e-aminocapronici (PL)

Aminoglutethimide

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English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cytadren® may be confused with cytarabine

Pronunciation(a mee noe gloo TETH i mide)

U.S. Brand NamesCytadren®

Pharmacologic Category[Antineoplastic Agent, Aromatase Inhibitor](); [Enzyme Inhibitor](); [Hormonal Antagonist, Anti-Adrenal](); [Nonsteroidal Aromatase Inhibitor]()

Use: Labeled IndicationsSuppression of adrenal function in selected patients with Cushing's syndrome

Use: Unlabeled/InvestigationalTreatment of prostate cancer (androgen synthesis inhibitor)

Dosing: Adults **Note:** Glucocorticoid and mineralocorticoid replacement therapy may be necessary.

Adrenal suppression: Oral: 250 mg every 6 hours may be increased in increments of 250 mg/day at 1- to 2-week intervals to a total of 2 g/day

Prostate cancer (unlabeled use): Oral: 250 mg 3 times/day for 3 weeks, then increase to 4 times/day

Dosing: ElderlyRefer to adult dosing.

Administration: OralAdminister every 6 hours to reduce incidence of nausea and vomiting.

StorageStore at controlled room temperature not >30°C (86°F).

ContraindicationsHypersensitivity to aminoglutethimide, glutethimide, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal hypofunction: Adrenocortical hypofunction may occur, particularly under conditions of stress, including acute illness, surgery, and/or trauma. Monitor closely; may require glucocorticoid and mineralocorticoid supplementation. Dexamethasone clearance may be increased by aminoglutethimide and is not recommended for glucocorticoid replacement (hydrocortisone is preferred).
- CNS effects: May cause drowsiness; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hematologic abnormalities: Neutropenia, leukopenia, pancytopenia and agranulocytosis have been reported in patients with Cushing’s syndrome.
- Hypotension: May cause persistent hypotension or orthostatic hypotension due to suppression of aldosterone production.
- Hypothyroidism: Hypothyroidism may occur.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAdverse effects including reduced implantation, fetal deaths, and teratogenicity have been observed in animal studies. May cause fetal harm if administered to pregnant women. Suspected of causing virilization when given throughout pregnancy.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsMost adverse effects will diminish in incidence and severity after the first 2-6 weeks

>10%:

Central nervous system: Drowsiness (33%), lethargy

Dermatologic: Skin rash (17%)

Gastrointestinal: Anorexia (13%), nausea (13%),

1% to 10%:

Cardiovascular: Hypotension (3%; occasionally orthostatic), tachycardia (3%)

Central nervous system: Dizziness (5%), headache (5%)

Dermatologic: Pruritus (5%)

Endocrine & metabolic: Adrenocortical insufficiency (3%)

Gastrointestinal: Vomiting (3%)

Hematologic: Anemia (4%)

Neuromuscular & skeletal: Myalgia (3%)

<1%, postmarketing, and/or case reports: Adrenal suppression, agranulocytosis, aldosterone function suppression, alkaline phosphatase increased, allergic alveolitis, allergic reaction, bilirubin increased, cholestatic jaundice, fever, hematocrit decreased, hemoglobin decreased, hemolytic anemia (Coombs' negative), hepatotoxicity, hirsutism, hypercholesterolemia, hyperkalemia, hypersensitivity, hypothyroidism, goiter, interstitial alveolar infiltrates, leukopenia, masculinization of females, neutropenia, pancytopenia, precocious sexual development (in males), pulmonary hypersensitivity, thrombocytopenia, transaminases increased, urticaria

Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Induces** CYP1A2 (strong), 2C19 (strong), 3A4 (strong)
Drug Interactions

Bendamustine: CYP1A2 Inducers (Strong) may decrease the serum concentration of Bendamustine. Concentrations of active metabolites may be increased. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Aminoglutethimide may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inducers (Strong) may increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inducers (Strong) may increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Digitoxin: Aminoglutethimide may increase the metabolism of Digitoxin. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Progestins: Aminoglutethimide may increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Tamoxifen: Aminoglutethimide may increase the metabolism of Tamoxifen. *Risk D: Consider therapy modification*

Theophylline Derivatives: Aminoglutethimide may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Aminoglutethimide may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Test InteractionsIncreased alkaline phosphatase (S), AST, TSH; decreased plasma cortisol, thyroxine (S), and urinary aldosterone
Monitoring ParametersThyroid function, CBC, electrolytes, hepatic function; blood pressure

Follow adrenal cortical response by careful monitoring of plasma cortisol until the desired level of suppression is achieved. Mineralocorticoid (fludrocortisone) replacement therapy may be necessary in up to 50% of patients. If glucocorticoid replacement therapy is necessary, 20-30 mg hydrocortisone orally in the morning will replace endogenous secretion.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other medications patient may be taking. Evaluate results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, glucocorticoid deficiency [ataxia, hypotension, hypovolemia, somnolence, shock], nausea/vomiting, susceptibility to infection); glucocorticoid and mineralocorticoid replacement therapy may be necessary. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsThyroid function, CBC, electrolytes, hepatic function. Follow adrenal cortical response by careful monitoring of plasma cortisol until the desired level of suppression is achieved.
Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take exactly as directed; may be taken with food to reduce incidence of nausea. May cause drowsiness or dizziness (avoid driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when changing position from lying or sitting to standing or when climbing stairs); muscle or joint pain (consult prescriber for analgesic); nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report skin rash, persistent or unresolved lethargy, fatigue, nausea, vomiting, loss of appetite, easy bruising or bleeding, change in frequency or color of urine or stool, severe mood swings, palpitations, respiratory difficulty, or other adverse reactions. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate barrier contraceptive measures. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet [scored]:

Cytadren®: 250 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Cytadren)

250 mg (30): $47.99

Mechanism of Action Inhibits steroid synthesis by blocking the enzymatic conversion of cholesterol to delta-5-pregnenolone, thereby reducing the synthesis of adrenal glucocorticoids, mineralocorticoids, estrogens, aldosterone, and androgens. Aminoglutethimide is a first-generation aromatase inhibitor.

Pharmacodynamics/Kinetics

Onset of action: Adrenal suppression: 3-5 days

Duration: Adrenal gland synthesis returns within ~72 hours of discontinuation

Absorption: Rapid and complete

Protein binding, plasma: 20% to 25%

Metabolism: Major metabolite is N-acetylaminoglutethimide; induces its own metabolism

Half-life elimination: 11-14 hours; shorter following multiple doses

Time to peak, plasma: 1.5 hours

Excretion: Urine (34% to 54% as unchanged drug, 25% as metabolites)

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Nausea and orthostatic hypotension

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Drowsiness is common

Mental Health: Effects on Psychiatric Treatment May cause hypotension which may be exacerbated by psychotropics; may cause bone marrow suppression; use caution with clozapine and carbamazepine; propranolol may increase the risk of drowsiness

Index Terms BA-16038; Elipten

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International Brand Names Aminoglutetimid (PL); Cytadren (AU); Mamomit (HR); Orimeten (AR, AT, BE, BF, BJ, BR, CH, CI, CZ, DE, EG, ES, ET, FR, GB, GH, GM, GN, IT, KE, LR, LU, MA, ML, MR, MU, MW, NE, NG, NL, NO, PL, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Orimetene (HK, TW); Rodazol (CZ)

Aminolevulinic Acid

Lexi-Drugs Online

English

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Pronunciation(a MEE noh lev yoo lin ik AS id)

U.S. Brand NamesLevulan® Kerastick®

Canadian Brand NamesLevulan®

Pharmacologic CategoryPhotosensitizing Agent, Topical; Topical Skin Product

Use: Labeled IndicationsTreatment of minimally to moderately thick actinic keratoses (grade 1 or 2) of the face or scalp; to be used in conjunction with blue light illumination

Dosing: AdultsActinic keratoses: Topical: Apply to actinic keratoses (**not** perilesional skin) followed 14-18 hours later by blue light illumination. Application/treatment may be repeated at a treatment site after 8 weeks.

Dosing: ElderlyRefer to adult dosing.

Administration: TopicalDab lesion gently with wet applicator tip. Do not apply to periorbital area, ocular tissue, or mucosal surfaces. Allow to dry, then reapply to same lesion. Apply to either scalp or facial lesions, but not to both simultaneously. Follow application with blue light exposure in 14-18 hours.

StorageStore at 25°C (77°F). Once prepared, the topical solution should be used immediately and application must be completed within 2 hours of solution preparation.

ReconstitutionPrepare solution by holding applicator tube with cap pointing up. Apply finger pressure to “Position A” on cardboard sleeve to crush ampul containing solution vehicle. Apply finger pressure to “Position B” to crush ampul containing aminolevulinic acid powder. Shake gently for at least 3 minutes to dissolve; point applicator cap away from face while shaking tube. Remove cap; dab dry applicator tip on gauze pad until wet with solution.

ContraindicationsHypersensitivity to aminolevulinic acid or any component of the formulation; individuals with cutaneous photosensitivity at wavelengths of 400-450 nm; porphyria; allergy to porphyrins

Warnings/Precautions

Concerns related to adverse effects:

- Photosensitivity: Treatment site will become photosensitive following application. Patients should be instructed to avoid exposure to sunlight, bright indoor lights, or tanning beds during the period prior to blue light treatment.

Special populations:

- Patients with coagulation defects: Has not been tested in individuals with coagulation defects (acquired or inherited).

Other warnings/precautions:

- Appropriate use: For external use only. Do not apply to eyes or mucous membranes. Should be applied by a qualified health professional to avoid application to perilesional skin.

Geriatric ConsiderationsComplaints by elderly with skin lesions increase with age. Common skin lesions are actinic keratoses, squamous cell carcinoma, and basal cell carcinoma. Although other agents for treatment are commonly used for these diseases, this agent is an alternative agent.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted, and there are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsTransient stinging, burning, itching, erythema, and edema result from the photosensitizing properties of this agent. Symptoms subside between 1 minute and 24 hours after turning off the blue light illuminator. Severe stinging or burning was reported in at least 50% of patients from at least 1 lesional site treatment.

>10%: Dermatologic: Severe stinging or burning (50%), scaling of the skin/crusted skin (64% to 71%), hyper-/hypopigmentation (22% to 36%), itching (14% to 25%), erosion (2% to 14%)

1% to 10%:

Central nervous system: Dysesthesia (up to 2%)

Dermatologic: Skin ulceration (2% to 4%), vesiculation (4% to 5%), pustular drug eruption (up to 4%), skin disorder (5% to 12%)

Hematologic: Bleeding/hemorrhage (2% to 4%)

Local: Wheal/flare (2% to 7%), local pain (1%), tenderness (1% to 2%), edema (1%), scabbing (up to 2%), excoriation (1%)

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringSee Contraindications and Warnings/Precautions for safe use. Assess other medications patient may be taking for possible increase photosensitizing (see Drug Interactions). Monitor for therapeutic effect and adverse reactions (see Adverse Reactions and Overdose/Toxicology). Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse reactions to report (see Patient Education). **Pregnancy risk factor C** - benefits of use should outweigh possible risks. Note breast-feeding caution.

Patient EducationThis medication is for external use only; do not allow any solution to contact eyes, mouth, or nasal membranes. Follow exact directions for application (see below). You may experience stinging, burning, itching, swelling, or pain after turning off blue light illuminator. If these or any other adverse skin effects last longer than 24 hours, notify prescriber. Report immediately any indications of unusual bleeding or bruising. Solution should be used immediately following preparation of solution according to directions. Apply to clean, dry skin with applicator, directly to lesions. Blue light exposure should follow between 14-18 hours after the application. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for topical solution:

Levulan® Kerastick®: 20% (6s) [2-component system containing aminolevulinic acid hydrochloride 354 mg (powder) and diluent containing ethanol 48% (1.5 mL) packaged together in an applicator tube]

Generic AvailableNo

ManufacturerDUSA Pharmaceuticals, Inc

Mechanism of ActionAminolevulinic acid is a metabolic precursor of protoporphyrin IX (PpIX), which is a photosensitizer. Photosensitization following application of aminolevulinic acid topical solution occurs through the metabolic conversion to PpIX. When exposed to light of appropriate wavelength and energy, accumulated PpIX produces a photodynamic reaction.

Pharmacodynamics/Kinetics

PpIX:

Peak fluorescence intensity: 11 hours ± 1 hour

Half-life, mean clearance for lesions: 30 ± 10 hours

Pharmacotherapy PearlsUse in conjunction with the BLU-U™ Blue Light Photodynamic Therapy Illuminator.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Bleeding/hemorrhage (limited to application/treatment site).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAminolevulinic Acid Hydrochloride

International Brand NamesMetvix (AR, AU, BE, BR, CH, CN, CZ, DE, DK, FI, GB, IE, NO, NZ, SE)

Aminophylline

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Aminophylline may be confused with amitriptyline, ampicillin

Pronunciation(am in OFF i lin)

Canadian Brand NamesPhyllocontin®; Phyllocontin®-350

Pharmacologic CategoryTheophylline Derivative

Use: Labeled IndicationsBronchodilator in reversible airway obstruction due to asthma or COPD; increase diaphragmatic contractility

Use: Unlabeled/InvestigationalReversal of adenosine-, dipyridamole-, or regadenoson-induced adverse reactions (eg, angina, hypotension) during nuclear cardiac stress testing

Dosing: Adults

Treatment of acute bronchospasm: I.V.:

Loading dose (in patients not currently receiving aminophylline or theophylline): 6 mg/kg (based on aminophylline) administered I.V. over 20-30 minutes; administration rate should not exceed 25 mg/minute (aminophylline)

Approximate I.V. maintenance dosages: Based upon **continuous infusions**; bolus dosing may be determined by multiplying the hourly infusion rate by 24 hours and dividing by the desired number of doses/day

Smoker: 0.8 mg/kg/hour

Nonsmoker: 0.5 mg/kg/hour

Older patients and patients with cor pulmonale: 0.3 mg/kg/hour

Patients with congestive heart failure: 0.1-0.2 mg/kg/hour

Dosage should be adjusted according to serum level measurements during the first 12- to 24-hour period.

Reversal of adenosine-, dipyridamole-, or regadenoson-induced adverse reactions (eg, angina, hypotension) during nuclear cardiac stress testing (unlabeled use): I.V.: 50-250 mg administered over 30-60 seconds, repeat as necessary

Note: Since adenosine-induced side effects are short lived after discontinuation of the infusion, aminophylline administration is only very rarely required.

Bronchodilator: Oral: Initial: 380 mg/day (equivalent to theophylline 300 mg/day) in divided doses every 6-8 hours; may increase dose after 3 days; maximum dose: 928 mg/day (equivalent to theophylline 800 mg/day)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Treatment of acute bronchospasm: I.V.:

Loading dose: Patients not currently receiving aminophylline or theophylline: 6 mg/kg (based on aminophylline) administered I.V. over 20-30 minutes; administration rate should not exceed 25 mg/minute (aminophylline)

Approximate I.V. maintenance dosages: Based upon **continuous infusions**; bolus dosing (often used in children <6 months of age) may be determined by multiplying the hourly infusion rate by 24 hours and dividing by the desired number of doses/day

6 weeks to 6 months: 0.5 mg/kg/hour

6 months to 1 year: 0.6-0.7 mg/kg/hour

1-9 years: 1 mg/kg/hour

9-16 years: Refer to adult dosing.

Dosage should be adjusted according to serum level measurements during the first 12- to 24-hour period.

Bronchodilator: Oral: Children ≥45 kg: Refer to adult dosing.

Administration: I.M.Not recommended

Administration: I.V.Dilute with I.V. fluid to a concentration of 1 mg/mL and infuse over 20-30 minutes; maximum concentration: 25 mg/mL; maximum rate of infusion: 0.36 mg/kg/minute, and no greater than 25 mg/minute. I.M. administration is not recommended. Should be administered around-the-clock rather than 4 times/day, 3 times/day, etc (ie, 12-6-12-6, not 9-1-5-9) to promote less variation in peak and trough serum levels.

For reversal of adenosine-, dipyridamole-, or regadenoson-induced adverse events during nuclear cardiac stress testing, administer I.V. undiluted over 30-60 seconds, repeat as necessary. Since adenosine-induced side effects are short lived after discontinuation of the infusion, aminophylline administration is only very rarely required.

Administration: OralShould be administered around-the-clock rather than 4 times/day, 3 times/day, etc (ie, 12-6-12-6, not 9-1-5-9) to promote less variation in peak and trough serum levels.
StorageDo not use solutions if discolored or if crystals are present.
CompatibilityStable in dextran 6% in D_5W, dextran 6% in NS, D_5LR, D_5NS, $D_5{}^{1}/_{2}$NS, $D_5{}^{1}/_{4}$NS, D_5W, D_{10}W, D_{20}W, LR, ${}^{1}/_{2}$NS, NS; **variable stability (consult detailed reference)** in fat emulsion 10%.

Y-site administration: Compatible: Allopurinol, amifostine, amphotericin B cholesteryl sulfate complex, aztreonam, ceftazidime, cimetidine, cladribine, docetaxel, doxorubicin liposome, enalaprilat, esmolol, etoposide, famotidine, filgrastim, fluconazole, fludarabine, foscarnet, gatifloxacin, gemcitabine, granisetron, heparin with hydrocortisone sodium succinate, inamrinone, labetalol, levofloxacin, linezolid, melphalan, meropenem, morphine, paclitaxel, pancuronium, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, sargramostim, tacrolimus, teniposide, thiotepa, tolazoline, vecuronium, vitamin B complex with C. **Incompatible:** Amiodarone, ciprofloxacin, clarithromycin, dobutamine, hydralazine, ondansetron, vinorelbine, warfarin. **Variable (consult detailed reference):** Cisatracurium, diltiazem.

Compatibility in syringe: Compatible: Heparin, metoclopramide, pentobarbital, thiopental. **Incompatible:** Doxapram.

Compatibility when admixed: Compatible: Amobarbital, bretylium, calcium gluconate, chloramphenicol, cimetidine, dexamethasone, diphenhydramine, dopamine, erythromycin lactobionate, esmolol, floxacillin, flumazenil, furosemide, heparin, hydrocortisone sodium succinate, lidocaine, mephentermine, meropenem, methyldopate, metronidazole with sodium bicarbonate, nitroglycerin, pentobarbital, phenobarbital, potassium chloride, ranitidine, sodium bicarbonate, terbutaline. **Incompatible:** Atracurium, bleomycin, cefepime, ceftazidime, ceftriaxone, chlorpromazine, ciprofloxacin, clindamycin, dobutamine, doxorubicin, epinephrine, hydralazine, hydrocortisone sodium succinate with cephalothin sodium, hydroxyzine, insulin (regular), isoproterenol, levorphanol, meperidine, morphine, norepinephrine, papaverine with trimecaine, penicillin G potassium, pentazocine, prochlorperazine edisylate, prochlorperazine mesylate, promazine, promethazine, vitamin B complex with C. **Variable (consult detailed reference):** Amikacin, ascorbic acid, corticotropin, dimenhydrinate, methylprednisolone sodium succinate, nafcillin, procaine, vancomycin, verapamil, zinc.

ContraindicationsHypersensitivity to theophylline, ethylenediamine, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Theophylline toxicity: If a patient develops signs and symptoms of theophylline toxicity (eg, persistent, repetitive vomiting), a serum level should be measured and subsequent doses held.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with hypertension or cardiac arrhythmias (excluding bradyarrhythmias).

- Hyperthyroidism: Use with caution in patients with hyperthyroidism.

- Peptic ulcer disease: Use with caution in patient with peptic ulcer disease.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Other warnings/precautions:

- Dosage adjustments: Due to potential saturation of theophylline clearance at serum levels within (or in some patients less than) the therapeutic range, dosage adjustment should be made in small increments (maximum: 25% reduction).

- Monitoring: Due to wide interpatient variability, theophylline serum level measurements must be used to optimize therapy and prevent serious toxicity.

Geriatric ConsiderationsAlthough there is a great intersubject variability for half-lives of methylxanthines (2-10 hours), elderly, as a group, have slower hepatic clearance. Therefore, use lower initial doses and monitor closely for response and adverse reactions. Additionally, elderly patients are at greater risk for toxicity due to concomitant disease (eg, congestive heart failure, arrhythmias), and drug use (eg, cimetidine, ciprofloxacin, etc).
Pregnancy Risk FactorC
Pregnancy ConsiderationsTheophylline crosses the placenta; adverse effects may be seen in the newborn. Theophylline metabolism may change during pregnancy; monitor serum levels.
LactationEnters breast milk/compatible (AAP rates “compatible”)
Breast-Feeding ConsiderationsIrritability may be observed in the nursing infant.
Adverse Reactions

Uncommon at serum theophylline concentrations ≤15 mcg/mL

1% to 10%:

Cardiovascular: Tachycardia

Central nervous system: Nervousness, restlessness

Gastrointestinal: Nausea, vomiting

<1%: Insomnia, irritability, seizure, skin rash, gastric irritation, tremor, allergic reactions

Metabolism/Transport Effects**Substrate** of CYP1A2 (major), 2E1 (minor), 3A4 (minor)

Drug Interactions

Adenosine: Theophylline Derivatives may diminish the therapeutic effect of Adenosine. *Risk D: Consider therapy modification*

Allopurinol: May increase the serum concentration of Theophylline Derivatives. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Benzodiazepines: Theophylline Derivatives may diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Disulfiram: May increase the serum concentration of Theophylline Derivatives. *Risk C: Monitor therapy*

Fluvoxamine: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

Interferons: May decrease the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

Lithium: Theophylline Derivatives may increase the excretion of Lithium. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Theophylline Derivatives. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin; Telithromycin. *Risk D: Consider therapy modification*

Mexiletine: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

Moricizine: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Pentoxifylline: May increase the serum concentration of Theophylline Derivatives. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Theophylline Derivatives. Theophylline Derivatives may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the serum concentration of Theophylline Derivatives. **Exceptions:** Amprenavir; Fosamprenavir. *Risk C: Monitor therapy*

Quinolone Antibiotics: May decrease the metabolism of Theophylline Derivatives. Ciprofloxacin and enoxacin are of greatest concern. Theophylline/quinolone therapy might augment the seizure-producing potential of each of the individual agents. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Sparfloxacin; Trovafloxacin. *Risk D: Consider therapy modification*

Regadenoson: Aminophylline may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tacrine: May decrease the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Thiabendazole: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

Thyroid Products: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Ticlopidine: May decrease the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Zafirlukast: Theophylline Derivatives may decrease the serum concentration of Zafirlukast. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Food does not appreciably affect absorption. Avoid extremes of dietary protein and carbohydrate intake. Changes in diet may affect the elimination of theophylline; charcoal-broiled foods may increase elimination, reducing half-life by 50%.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as dihydrate: 25 mg/mL (10 mL, 20 mL)

Injection, solution, as dihydrate [preservative free]: 25 mg/mL (10 mL, 20 mL)

Tablet, as dihydrate: 100 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Aminophylline)

100 mg (30): $12.99

200 mg (90): $19.00

Mechanism of ActionCauses bronchodilatation, diuresis, CNS and cardiac stimulation, and gastric acid secretion by blocking phosphodiesterase which increases tissue concentrations of cyclic adenine monophosphate (cAMP) which in turn promote catecholamine stimulation of lipolysis, glycogenolysis, and gluconeogenesis and induce release of epinephrine from adrenal medulla cells

Pharmacodynamics/Kinetics

Theophylline:

Absorption: Oral: Dosage form dependent

Distribution: 0.45 L/kg based on ideal body weight

Protein binding: 40%, primarily to albumin

Metabolism: Children >1 year and Adults: Hepatic; involves CYP1A2, 2E1, and 3A4; forms active metabolites (caffeine and 3-methylxanthine)

Half-life elimination: Highly variable and dependent upon age, liver function, cardiac function, lung disease, and smoking history

Time to peak, serum:

Oral: Immediate release: 1-2 hours

I.V.: Within 30 minutes

Excretion: Children >3 months and Adults: Urine (10% as unchanged drug)

Related Information

- Asthma

Pharmacotherapy PearlsAminophylline is a 2:1 complex of theophylline and ethylenediamine.

Dental Health: Effects on Dental TreatmentPrescribe erythromycin products with caution to patients taking theophylline products. Erythromycin will delay the normal metabolic inactivation of theophyllines leading to increased blood levels; this has resulted in nausea, vomiting, and CNS restlessness.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness or restlessness

Mental Health: Effects on Psychiatric TreatmentCarbamazepine and barbiturates may decrease aminophylline levels; disulfiram and propranolol may increase aminophylline levels

Cardiovascular ConsiderationsTheophylline results in significant tachycardia and, at higher doses, may impair ventricular rate control in patients with atrial fibrillation. This is particularly a concern since patients with underlying chronic obstructive lung disease often have coexisting atrial fibrillation. Aminophylline can be used to treat patients who have adverse hemodynamic responses to adenosine, dipyridamole or regadenoson, when used during cardiovascular stress testing. Since adenosine-induced side effects are short lived after discontinuation of the infusion, aminophylline administration is only very rarely required.

Index TermsTheophylline Ethylenediamine

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Ludden TM, “Pharmacokinetic Interactions of the Macrolide Antibiotics,” *Clin Pharmacokinet*, 1985, 10(1):63-79.[PubMed 3882305]

Ranhosky A and Kempthorne-Rawson J, “The Safety of Intravenous Dipyridamole Thallium Myocardial Perfusion Imaging. Intravenous Dipyridamole Thallium Imaging Study Group,” *Circulation*, 1990, 81(4):1205-9.[PubMed 2107985]

International Brand NamesAminocont (FI); Aminofilina (EC, GT, PL); Aminomal (CH, CZ, IT); Aminophyllin (HR, NO); Aminophylline Renaudin (FR); Aminophyllinum (PL); Aminophyllinum Prolongatum (PL); Aminophyllinum Retard (HU, PL); Aminoslow (LU); Anephyllin (JP); Asiphylline (TW); Asthcontin (KP); Cardiomin (CN); Cardirenal (AR); Cardophyllin (AU); Carine (AU); Clonofillin SR (HU); Diaphyllin (HU); Escophyllin (CH); Eufilina (ES); Eufilina Mite (PT); Eufilina Venosa (ES); Euphyllin (AT, BE, BG, CH, CZ, DE, LU, NL); Euphyllin Retard (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Godafilin (ES); Kyophyllin (JP); Minophyl (IN); Neophyllin (SG); Pediatric Asthcontin for Children SR (KP); Peterphyllin (ZA); Pharmafil (MX); Phyllocontin (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GB, GH, GM, GN, GY, IE, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PK, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Phyllocontin Continus (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Phyllotemp (CH, DE, GR); Planphylline (FR); Retafilin (HR); Tefamin (IT); Teofylamin (DK); Teofyllamin Ipex (SE); Unifilin (BR)

Aminosalicylic Acid

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(a mee noe sal i SIL ik AS id)
U.S. Brand NamesPaser®
Pharmacologic CategorySalicylate
Use: Labeled IndicationsAdjunctive treatment of tuberculosis used in combination with other antitubercular agents
Use: Unlabeled/InvestigationalCrohn's disease
Dosing: Adults

Tuberculosis: Oral: 150 mg/kg/day in 2-3 equally divided doses

Crohn's disease (unlabeled use): 1.5 g/day

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricTuberculosis: Oral: 200-300 mg/kg/day in 3-4 equally divided doses
Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer 50% to 75% of dose.

Cl_{cr} <10 mL/minute: Administer 50% of dose.

Administer after hemodialysis: Administer 50% of dose.

Continuous arteriovenous hemofiltration: Dose for Cl_{cr} <10 mL/minute

Dosing: Hepatic ImpairmentUse with caution
Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralDo not use granules if packet is swollen or if granules are discolored (ie, brown or purple). Granules may be sprinkled on applesauce or yogurt (do not chew) or suspended in tomato or orange juice.
Dietary ConsiderationsMay be taken with food.
StoragePrior to dispensing, store granules below 15°C (59°F). Once dispensed, packets may be stored at room temperature for short periods of time. Do not use if packet is swollen or if granules are dark brown or purple.
ContraindicationsHypersensitivity to aminosalicylic acid or any component of the formulation
Allergy Considerations

- 5-Aminosalicylic Acid Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Salicylate sensitivity: Patients with sensitivity to tartrazine dyes, nasal polyps, and asthma may have an increased risk of salicylate sensitivity.

Disease-related concerns:

- Gastric ulcer: Use with caution in patients with gastric ulcer.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

Geriatric ConsiderationsElderly may require a lower recommended dose.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects have been reported in animals, however, adequate studies have not been done in humans. Use during pregnancy only if clearly needed.
LactationEnters breast milk/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Pericarditis, vasculitis

Central nervous system: Encephalopathy, fever

Dermatologic: Skin eruptions

Endocrine & metabolic: Goiter (with or without myxedema), hypoglycemia

Gastrointestinal: Abdominal pain, diarrhea, nausea, vomiting

Hematologic: Agranulocytosis, anemia (hemolytic), leukopenia, thrombocytopenia

Hepatic: Hepatitis, jaundice

Ocular: Optic neuritis

Respiratory: Eosinophilic pneumonia

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringMonitor for effectiveness of treatment and indications of adverse effects.

Patient EducationMay be taken with food; may sprinkle on applesauce or yogurt, or suspend in tomato or orange juice. Do not use granules if discolored (brown or purple) or if packet is swollen; see pharmacist for new prescription. Do not stop taking without consulting prescriber. Report persistent sore throat, fever, unusual bleeding or bruising, persistent nausea or vomiting, or abdominal pain. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Granules, delayed release:

Paser®: 4 g/packet (30s) [sugar free]

Generic AvailableNo

ManufacturerJacobus Pharmaceutical Co Inc

Mechanism of ActionAminosalicylic acid (PAS) is a highly-specific bacteriostatic agent active against *M. tuberculosis*. Structurally related to para-aminobenzoic acid (PABA) and its mechanism of action is thought to be similar to the sulfonamides, a competitive antagonism with PABA; disrupts plate biosynthesis in sensitive organisms.

Pharmacodynamics/Kinetics

Absorption: Readily, >90%

Protein binding: 50% to 60%

Metabolism: Hepatic (>50%) via acetylation

Half-life elimination: Reduced with renal impairment

Time to peak, serum: 6 hours

Excretion: Urine (>80% as unchanged drug and metabolites)

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause bone marrow suppression; use caution with clozapine and carbamazepine

Index Terms4-Aminosalicylic Acid; Aminosalicylate Sodium; Para-Aminosalicylate Sodium; PAS; Sodium PAS

References

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International Brand NamesApir Pas (ES); Ca-Oripas (FI); Entepas (IE); Eupasal Sodico (IT); Italpas Sodico (IT); Mesacol (IN); Paramisan Sodium (GB); Parispas (ES); Pas-Dexter (ES); Pas-Fatol N (DE); PAS-Infusion Bichsel (CH); Pasalba (AU); Quadrasa (FR, IT); Salf-Pas (IT); Sta-PAS (FR); Vacopas (IT)

Amiodarone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Simvastatin and Amiodarone Concurrent Therapy: Dose-Related Increased Risk of Rhabdomyolysis - August 2008

The U.S. Food and Drug Administration (FDA) has issued an alert to remind practitioners of a dose-related increased risk of rhabdomyolysis when amiodarone is used concurrently with simvastatin at doses >20 mg. If patients require simvastatin >20 mg, an alternative HMG-CoA reductase inhibitor (statin) should be used. This information has previously been incorporated into the Lexi-Comp monograph.

Additional information may be found at http://www.fda.gov/cder/drug/InfoSheets/HCP/simvastatin_amiodaroneHCP.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Amiodarone may be confused with aMILoride, amrinone

Cordarone® may be confused with Cardura®, Cordran®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(a MEE oh da rone)

U.S. Brand NamesCordarone®; Pacerone®

Canadian Brand NamesAlti-Amiodarone; Amiodarone Hydrochloride for Injection®; Apo-Amiodarone®; Cordarone®; Dom-Amiodarone; Gen-Amiodarone; Novo-Amiodarone; PHL-Amiodarone; PMS-Amiodarone; Ratio-Amiodarone; Ratio-Amiodarone I.V.; Sandoz-Amiodarone

Pharmacologic CategoryAntiarrhythmic Agent, Class III

Use: Labeled IndicationsManagement of life-threatening recurrent ventricular fibrillation (VF) or hemodynamically-unstable ventricular tachycardia (VT) refractory to other antiarrhythmic agents or in patients intolerant of other agents used for these conditions

Use: Unlabeled/Investigational

Cardiac arrest with persistent ventricular tachycardia (VT) or ventricular fibrillation (VF) if defibrillation, CPR, and vasopressor administration have failed (ACLS/PALS guidelines)

Control of hemodynamically-stable VT, polymorphic VT with a normal QT interval, or wide-complex tachycardia of uncertain origin (ACLS/PALS guidelines)

Control of rapid ventricular rate due to accessory pathway conduction in pre-excited atrial arrhythmias (ACLS guidelines)

Heart rate control in patients with atrial fibrillation and heart failure [no accessory pathway] (ACC/AHA/ESC Practice Guidelines)

Paroxysmal supraventricular tachycardia (SVT)

Prevention of postoperative atrial fibrillation during cardiothoracic surgery

Pharmacologic adjunct to ICD therapy to suppress symptomatic ventricular tachyarrhythmias in otherwise optimally-treated patients with heart failure (ACC/AHA/ESC Practice Guidelines)

Pharmacologic conversion of atrial fibrillation to normal sinus rhythm; maintenance of normal sinus rhythm

Dosing: Adults**Note:** Lower loading and maintenance doses are preferable in women and all patients with low body weight.

Ventricular arrhythmias: Oral: 800-1600 mg/day in 1-2 doses for 1-3 weeks, then 600-800 mg/day in 1-2 doses for 1 month; maintenance: 400 mg/day; lower doses are recommended for supraventricular arrhythmias.

Breakthrough VF or VT: I.V.: 150 mg supplemental doses in 100 mL D_5W over 10 minutes

Pulseless VF or VT: I.V. push: Initial: 300 mg in 20-30 mL NS or D_5W; if VF or VT recurs, supplemental dose of 150 mg followed by infusion of 1 mg/minute for 6 hours, then 0.5 mg/minute (maximum daily dose: 2.1 g)

I.V. to oral therapy conversion: Use the following as a guide:

<1 week I.V. infusion: 800-1600 mg/day

1- to 3-week I.V. infusion: 600-800 mg/day

>3 week I.V. infusion: 400 mg

Recommendations for conversion to intravenous amiodarone after oral administration: During long-term amiodarone therapy (ie, ≥4 months), the mean plasma-elimination half-life of the active metabolite of amiodarone is 61 days. Replacement therapy may not be necessary in such patients if oral therapy is discontinued for a period <2 weeks, since any changes in serum amiodarone concentrations during this period may **not** be clinically significant.

Unlabeled uses:

Atrial fibrillation prophylaxis following open heart surgery (unlabeled use):Note: A variety of regimens have been used in clinical trials, including oral and intravenous regimens:

Oral: Starting in postop recovery, 400 mg twice daily for up to 7 days. Alternative regimen of amiodarone: 600 mg/day for 7 days prior to surgery, followed by 200 mg/day until hospital discharge, has also been shown to decrease the risk of postoperative atrial fibrillation. **Note:** A variety of regimens have been used in clinical trials.

I.V.: Starting at postop recovery, 1000 mg infused over 24 hours for 2 days has been shown to reduce the risk of postoperative atrial fibrillation. **Note:** A variety of regimens have been used in clinical trials.

Atrial fibrillation pharmacologic cardioversion (ACC/AHA/ESC Practice Guidelines) (unlabeled use):

Oral: Inpatient: 1.2-1.8 g/day in divided doses until 10 g total, then 200-400 mg/day maintenance. **Note:** Other regimens have been described and may be used clinically (Roy, 2000):

400 mg 3 times/day for 5-7 days, then 400 mg/day for 1 month, then 200 mg/day

or

10 mg/kg/day for 14 days, followed by 300 mg/day for 4 weeks, followed by maintenance dosage of 100-200 mg/day

I.V.: 5-7 mg/kg over 30-60 minutes, then 1.2-1.8 g/day continuous infusion or in divided oral doses until 10 g total. Maintenance: See oral dosing.

Recurrent atrial fibrillation (unlabeled use): No standard regimen defined; examples of regimens include: Oral: Initial: 10 mg/kg/day for 14 days; followed by 300 mg/day for 4 weeks, followed by maintenance dosage of 100-200 mg/day (Roy D, 2000). Other regimens have been described and are used clinically (ie, 400 mg 3 times/day for 5-7 days, then 400 mg/day for 1 month, then 200 mg/day).

Stable VT or SVT (unlabeled use): I.V.: First 24 hours: 1050 mg according to following regimen

Step 1: 150 mg (100 mL) over first 10 minutes (mix 3 mL in 100 mL D_5W)

Step 2: 360 mg (200 mL) over next 6 hours (mix 18 mL in 500 mL D_5W): 1 mg/minute

Step 3: 540 mg (300 mL) over next 18 hours: 0.5 mg/minute

Note: After the first 24 hours: 0.5 mg/minute utilizing concentration of 1-6 mg/mL

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Arrhythmias (unlabeled use):

Loading dose: Oral: 10-20 mg/kg/day in 1-2 doses for 4-14 days or until adequate control of arrhythmia or prominent adverse effects occur; alternative loading dose in children <1 year: 600-800 mg/1.73 m^2/day in 1-2 divided doses/day.

Maintenance dose: Oral: Dose may be reduced to 5 mg/kg/day for several weeks (or 200-400 mg/1.73 m^2/day given once daily); if no recurrence of arrhythmia, dose may be further reduced to 2.5 mg/kg/day; maintenance doses may be given 5-7 days/week.

Arrhythmias (unlabeled use, dosing based on limited data):

Loading dose: I.V.: 5 mg/kg over 30 minutes; may repeat up to 3 times if no response.

Maintenance dose: I.V.: 2-20 mg/kg/day (5-15 mcg/kg/minute) by continuous infusion.

Note: I.V. administration at low flow rates (potentially associated with use in pediatrics) may result in leaching of plasticizers (DEHP) from intravenous tubing. DEHP may adversely affect male reproductive tract development. Alternative means of dosing and administration (1 mg/kg aliquots) may need to be considered.

Pulseless VF or VT (PALS dosing): I.V.: 5 mg/kg (maximum 300 mg/dose) rapid I.V. bolus or I.O.; repeat up to a maximum daily dose of 15 mg/kg. (**Note:** Maximum recommended daily dose in adolescents is 2.2 g.)

Perfusing tachycardias (PALS dosing): I.V.: Loading dose: 5 mg/kg (maximum 300 mg/dose) I.V. over 20-60 minutes or I.O.; may repeat up to maximum dose of 15 mg/kg/day. (**Note:** Maximum recommended daily dose in adolescents is 2.2 g.)

Dosing: Renal ImpairmentHemodialysis effects: Not removed by hemodialysis or peritoneal dialysis (0% to 5%); no supplemental doses required.

Dosing: Hepatic ImpairmentDosage adjustment is probably necessary in substantial hepatic impairment. No specific guidelines available. If hepatic enzymes exceed 3 times normal or double in a patient with an elevated baseline, consider decreasing the dose or discontinuing amiodarone.

Calculations

- Amiodarone

Administration: I.V.For infusions >1 hour, use concentrations ≤2 mg/mL unless a central venous catheter is used. Use only volumetric infusion pump; use of drop counting may lead to underdosing. Administer through I.V. line with in-line filter.

Adjust administration rate to urgency (give more slowly when perfusing arrhythmia present). Slow the infusion rate if hypotension or bradycardia develops. Infusions >2 hours must be administered in glass or polyolefin bottles. **Note:** I.V. administration at lower flow rates (potentially associated with use in pediatrics) and higher concentrations than recommended may result in leaching of plasticizers (DEHP) from intravenous tubing. DEHP may adversely affect male reproductive tract development. Alternative means of dosing and administration (1 mg/kg aliquots) may need to be considered.

Administration: I.V. Detail**Incompatible** with heparin. Flush with saline prior to and following infusion.

pH: 4.08

Administration: OralAdminister consistently with regard to meals. Take in divided doses with meals if high daily dose or if GI upset occurs. If GI intolerance occurs with single-dose therapy, use twice daily dosing.

Dietary ConsiderationsAdminister consistently with regard to meals. Amiodarone is a potential source of large amounts of inorganic iodine; ~3 mg of inorganic iodine per 100 mg of amiodarone is released into the systemic circulation. Recommended daily allowance for iodine in adults is 150 mcg.

Grapefruit juice is not recommended.

StorageStore at room temperature; protect from light. When admixed in D_5W to a final concentration of 1-6 mg/mL, the solution is stable at room temperature for 24 hours in polyolefin or glass, or for 2 hours in PVC. Infusions >2 hours must be administered in glass or polyolefin bottles. Do not use evacuated glass containers; buffer may cause precipitation.

Compatibility**Variable stability (consult detailed reference):** D_5W, NS.

Y-site administration:

Compatible: Amikacin, ceftizoxime, ceftriaxone, cefuroxime, clarithromycin, clindamycin, dobutamine, dopamine, doxycycline, erythromycin lactobionate, esmolol, gentamicin, insulin (regular), isoproterenol, labetalol, lidocaine, metaraminol, metronidazole, midazolam, morphine, nitroglycerin, norepinephrine, penicillin G potassium, phentolamine, phenylephrine, potassium chloride, procainamide, tobramycin, vancomycin. **Incompatible:** Aminophylline, cefamandole, heparin, sodium bicarbonate.

Variable (consult detailed reference): Cefazolin.

Visually Compatible (Chalmers, 2001): Amphotericin B, atracurium, atropine, calcium chloride, calcium gluconate, ciprofloxacin, epinephrine, eptifibatide, famotidine, fentanyl citrate, fluconazole, furosemide (1 mg/mL), lepirudin, lorazepam, magnesium sulfate (20 mg/mL), methylprednisolone sodium succinate, milrinone, sodium nitroprusside, tirofiban, vasopressin, vecuronium. **Visually Incompatible:** Ampicillin-sulbactam, ceftazidime, digoxin, furosemide (10 mg/mL), imipenem-cilastatin, magnesium sulfate (500 mg/mL), piperacillin, piperacillin-tazobactam, potassium phosphate, sodium phosphate.

Compatibility in syringe: Incompatible: Heparin.

Compatibility when admixed: Compatible: Dobutamine, lidocaine, potassium chloride, procainamide, propafenone, verapamil. **Variable (consult detailed reference):** Furosemide, quinidine.

Extemporaneously PreparedA 5 mg/mL oral suspension has been made from tablets and has an expected stability of 91 days under refrigeration; three 200 mg tablets are crushed in a mortar, 90 mL of methylcellulose 1%, and 10 mL of syrup (syrup NF (85% sucrose in water) or flavored syrup) are added in small amounts and triturated until uniform; purified water USP is used to make a quantity sufficient to 120 mL

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, 2nd ed, Cincinnati, OH: Harvey Whitney Books Co, 1992.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to amiodarone, iodine, or any component of the formulation; severe sinus-node dysfunction; second- and third-degree heart block (except in patients with a functioning artificial pacemaker); bradycardia causing syncope (except in patients with a functioning artificial pacemaker); cardiogenic shock; pregnancy

Warnings/Precautions

Boxed warnings:

- Arrhythmias: Appropriate use: See “Disease-related concerns” below.
- Hepatotoxicity: See “Concerns related to adverse effects” below.
- Proarrhythmic effect: See “Concerns related to adverse effects” below.
- Pulmonary toxicity: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Bradycardia/hypotension: May cause hypotension and bradycardia (infusion-rate related).
- Hepatotoxicity: **[U.S. Boxed Warning]: Liver toxicity is common, but usually mild with evidence of increased liver enzymes; severe liver toxicity can**

occur and has been fatal in a few cases.

- Optic neuritis/neuropathy: May cause optic neuropathy and/or optic neuritis, usually resulting in visual impairment. Corneal microdeposits occur in a majority of patients, and may cause visual disturbances in some patients (blurred vision, halos); these are not generally considered a reason to discontinue treatment. Corneal refractive laser surgery is generally contraindicated in amiodarone users (from manufacturers of surgical devices).

- Photosensitivity: Avoid excessive exposure to sunlight; may cause photosensitivity.

- Proarrhythmic effect: **[U.S. Boxed Warning]: Amiodarone can exacerbate arrhythmias, by making them more difficult to tolerate or reverse;** other types of arrhythmias have occurred, including significant heart block, sinus bradycardia new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and polymorphic ventricular tachycardia associated with QT$_c$ prolongation (torsade de pointes [TdP]). Risk may be increased with concomitant use of other antiarrhythmic agents or drugs that prolong the QT$_c$ interval. Proarrhythmic effects may be prolonged.

- Pulmonary toxicity: **[U.S. Boxed Warning]: Lung damage (abnormal diffusion capacity) may occur without symptoms;** monitor for pulmonary toxicity (eg, chronic interstitial pneumonitis, organizing pneumonia, acute respiratory distress syndrome, solitary pulmonary mass). Educate patients about monitoring for symptoms (eg, nonproductive cough, dyspnea, pleuritic pain, weight loss, fever, malaise). Evaluate new respiratory symptoms; pre-existing pulmonary disease does not increase risk of developing pulmonary toxicity, but if pulmonary toxicity develops then the prognosis is worse.

Disease-related concerns:

- Arrhythmias: Appropriate use: **[U.S. Boxed Warnings]: Only indicated for patients with life-threatening arrhythmias because of risk of toxicity. Alternative therapies should be tried first before using amiodarone. Patients should be hospitalized when amiodarone is initiated.** Currently, the 2005 ACLS guidelines recommend I.V. amiodarone as the preferred antiarrhythmic for the treatment of pulseless VT/VF, both life-threatening arrhythmias. In patients with non-life-threatening arrhythmias (eg, atrial fibrillation), amiodarone should be used only if the use of other antiarrhythmics has proven ineffective or are contraindicated.

- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Thyroid disease: Use very cautiously and with close monitoring in patients with thyroid disease; may cause hyper- or hypothyroidism. Hyperthyroidism may result in thyrotoxicosis and may aggravate or cause breakthrough arrhythmias. If any new signs of arrhythmia appear, hyperthyroidism should be considered. Thyroid function should be monitored prior to treatment and periodically thereafter, particularly in the elderly and in patients with underlying thyroid dysfunction.

Concurrent drug therapy issues:

- Drugs metabolized by CYP enzymes: Amiodarone is a potent inhibitor of CYP enzymes and transport proteins (including p-glycoprotein), which may lead to increased serum concentrations/toxicity of a number of medications.

- Drugs with QT prolongation potential: Particular caution must be used when a drug with QT$_c$-prolonging potential relies on metabolism via enzymes amiodarone inhibits, since the effect of elevated concentrations may be additive with the effect of amiodarone. Carefully assess risk:benefit of coadministration of other drugs which may prolong QT$_c$ interval.

Special populations:

- Elderly: Monitor thyroid function prior to treatment and periodically thereafter.

- Pediatrics: Safety and efficacy have not been fully established in children.

- Surgical patients: Caution in surgical patients; may enhance hemodynamic effect of anesthetics; associated with increased risk of adult respiratory distress syndrome (ARDS) postoperatively.

Dosage form specific issues:

- Benzyl alcohol: Injection contains benzyl alcohol which has been associated with “gasping syndrome” in neonates.

Other warnings/precautions:

- CAST trial: In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, nonlife-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide. An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. Use of amiodarone post-MI was not associated with an increase in mortality in two post-MI trials. Antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

- Discontinuation of therapy: Patients may still be at risk for amiodarone–related drug interactions after the drug has been discontinued. The pharmacokinetics are complex (due to prolonged duration of action and half-life) and difficult to predict.

Geriatric ConsiderationsInformation describing the clinical use and pharmacokinetics in elderly is lacking; however, elderly may be predisposed to toxicity. Half-life may be prolonged due to decreased clearance; monitor closely. It is recommended to start dosing at the lower end of dosing range.

Pregnancy Risk FactorD

Pregnancy ConsiderationsMay cause fetal harm when administered to a pregnant woman, leading to congenital goiter and hypo- or hyperthyroidism.

LactationEnters breast milk/not recommended (AAP rates “of concern”)

Breast-Feeding ConsiderationsHypothyroidism may occur in nursing infants. Both amiodarone and its active metabolite are excreted in human milk. Breast-feeding may lead to significant infant exposure and potential toxicity.

Adverse ReactionsIn a recent meta-analysis, patients taking lower doses of amiodarone (152-330 mg daily for at least 12 months) were more likely to develop thyroid, neurologic, skin, ocular, and bradycardic abnormalities than those taking placebo (Vorperian, 1997). Pulmonary toxicity was similar in both the low dose amiodarone group and in the placebo group but there was a trend towards increased toxicity in the amiodarone group. Gastrointestinal and hepatic events were seen to a similar extent in both the low dose amiodarone group and placebo group. As the frequency of adverse events varies considerably across studies as a function of route and dose, a consolidation of adverse event rates is provided by Goldschlager, 2000.

>10%:

Cardiovascular: Hypotension (I.V. 16%, refractory in rare cases)

Central nervous system (3% to 40%): Abnormal gait/ataxia, dizziness, fatigue, headache, malaise, impaired memory, involuntary movement, insomnia, poor coordination, peripheral neuropathy, sleep disturbances, tremor

Dermatologic: Photosensitivity (10% to 75%)

Endocrine & Metabolic: Hypothyroidism (1% to 22%)

Gastrointestinal: Nausea, vomiting, anorexia, and constipation (10% to 33%)

Hepatic: AST or ALT level >2x normal (15% to 50%)

Ocular: Corneal microdeposits (>90%; causes visual disturbance in <10%)

1% to 10%:

Cardiovascular: CHF (3%), bradycardia (3% to 5%), AV block (5%), conduction abnormalities, SA node dysfunction (1% to 3%), cardiac arrhythmia, flushing, edema. Additional effects associated with I.V. administration include asystole, cardiac arrest, electromechanical dissociation, ventricular tachycardia, and cardiogenic shock.

Dermatologic: Slate blue skin discoloration (<10%)

Endocrine & metabolic: Hyperthyroidism (3% to 10%; more common in iodine-deficient regions of the world), libido decreased

Gastrointestinal: Abdominal pain, abnormal salivation, abnormal taste (oral)

Hematologic: Coagulation abnormalities

Hepatic: Hepatitis and cirrhosis (<3%)

Local: Phlebitis (I.V., with concentrations >3 mg/mL)

Ocular: Visual disturbances (2% to 9%), halo vision (<5% occurring especially at night), optic neuritis (1%)

Respiratory: Pulmonary toxicity has been estimated to occur at a frequency between 2% and 7% of patients (some reports indicate a frequency as high as 17%). Toxicity may present as hypersensitivity pneumonitis; pulmonary fibrosis (cough, fever, malaise); pulmonary inflammation; interstitial pneumonitis; or alveolar pneumonitis. ARDS has been reported in up to 2% of patients receiving amiodarone, and postoperatively in patients receiving oral amiodarone.

Miscellaneous: Abnormal smell (oral)

<1% (Limited to important or life-threatening): Alopecia, cholestasis, delirium, diarrhea, dyskinesias, erectile dysfunction, encephalopathy, hyperglycemia, hypertriglyceridemia, hypotension (oral), impotence, jaw tremor, myoclonic jerks, optic neuropathy, parkinsonian symptoms, photophobia, proarrhythmia, pulmonary edema, QT interval increased, rash, spontaneous ecchymosis, Stevens-Johnson syndrome, torsade de pointes (rare), ventricular fibrillation

Postmarketing and/or case reports: Acute intracranial hypertension (I.V.), acute renal failure, agranulocytosis, anaphylactic shock, angioedema, aplastic anemia, bone marrow granuloma, bronchiolitis obliterans organizing pneumonia (BOOP), bronchospasm, confusion, disorientation, dyspnea, epididymitis (noninfectious), erythema multiforme, exfoliative dermatitis, gynecomastia, hallucination, hemolytic anemia, hemoptysis, hypoxia, injection site reactions, leukocytoclastic vasculitis, muscle weakness, myopathy, neutropenia, pancreatitis, pancytopenia, pleuritis, pruritus, pseudotumor cerebri, pulmonary alveolar hemorrhage, pulmonary mass, renal impairment, renal insufficiency, respiratory failure, rhabdomyolysis, SIADH, sinus arrest, thrombocytopenia, thyroid nodules, thyroid cancer, thyrotoxicosis, toxic epidermal necrolysis, vasculitis, wheezing

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2C8 (major at low concentration), 2C19 (minor), 2D6 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2A6 (moderate), 2B6 (weak), 2C9 (moderate), 2C19 (weak), 2D6 (moderate), 3A4 (moderate)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antiarrhythmic Agents (Class Ia): May enhance the QTc-prolonging effect of Amiodarone. Amiodarone may increase the metabolism of Antiarrhythmic Agents (Class Ia). *Risk D: Consider therapy modification*

Azithromycin: May enhance the QTc-prolonging effect of Amiodarone. *Risk D: Consider therapy modification*

Beta-Blockers: Amiodarone may enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the bioavailability of Amiodarone. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the bradycardic effect of Amiodarone. Sinus arrest has been reported. *Risk D:*

Consider therapy modification

Cardiac Glycosides: Amiodarone may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Amiodarone. Consider using an alternative H_2 antagonist. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CycloSPORINE: Amiodarone may decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2A6 Substrates: CYP2A6 Inhibitors (Moderate) may decrease the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2C8 Inducers (Highly Effective): May increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Moderate): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Strong): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: Amiodarone may increase the serum concentration of Dabigatran Etexilate. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Flecainide: Amiodarone may decrease the metabolism of Flecainide. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Grapefruit Juice: May diminish the therapeutic effect of Amiodarone. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Amiodarone may decrease the metabolism of HMG-CoA Reductase Inhibitors. Management: Dose of HMG-CoA reductase inhibitor may need to be reduced (e.g., simvastatin prescribing information recommends not exceeding 20 mg/day during concurrent therapy). **Exceptions:** Pravastatin. *Risk D: Consider therapy modification*

Lidocaine: Amiodarone may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Orlistat: May decrease the absorption of Amiodarone. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Amiodarone. Amiodarone may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Amiodarone. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Amiodarone. *Risk C: Monitor therapy*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Sodium Iodide I131: Amiodarone may diminish the therapeutic effect of Sodium Iodide I131. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Amiodarone may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Increases the rate and extent of absorption of amiodarone. Grapefruit juice increases bioavailability of oral amiodarone by 50% and decreases the conversion of amiodarone to N-DEA (active metabolite); altered effects are possible; use should be avoided during therapy.

Herb/Nutraceutical: St John's wort may decrease amiodarone levels or enhance photosensitization. Avoid ephedra (may worsen arrhythmia). Avoid dong quai.

Monitoring ParametersBlood pressure, heart rate (ECG) and rhythm throughout therapy; assess patient for signs of lethargy, edema of the hands or feet, weight loss, and pulmonary toxicity (baseline pulmonary function tests); liver function tests; monitor serum electrolytes, especially potassium and magnesium. Assess thyroid function tests before initiation of treatment and then periodically thereafter (some experts suggest every 3-6 months). If signs or symptoms of thyroid disease or arrhythmia breakthrough/exacerbation occur then immediate re-evaluation is necessary. Amiodarone partially inhibits the peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3); serum T_4 and reverse triiodothyronine (rT_3) concentrations may be increased and serum T_3 may be decreased; most patients remain clinically euthyroid, however, clinical hypothyroidism or hyperthyroidism may occur.

Perform regular ophthalmic exams.

Reference RangeTherapeutic: 0.5-2.5 mg/L (SI: 1-4 µmol/L) (parent); desethyl metabolite is active and is present in equal concentration to parent drug

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Eye examinations should be performed periodically. Monitor cardiac status closely and assess for CNS changes. Monitor for signs of pulmonary toxicity (eg, nonproductive cough, dyspnea, pleuritic pain, weight loss, fever, malaise). **I.V.:** Requires continuous cardiac/hemodynamic monitoring and observation for adverse reactions. **Oral:** Assess results of laboratory tests, therapeutic effectiveness, and symptoms of adverse effects at beginning of therapy and regularly during long-term therapy.

Monitoring: Lab TestsThyroid function before initiation of treatment and then periodically thereafter (some experts suggest every 3-6 months), pulmonary function, liver enzymes, serum electrolytes (potassium, magnesium)

Patient Education

I.V.: Emergency use: Patient condition will determine amount of patient education.

Oral: May be taken with food to reduce GI disturbance, but be consistent. Always take with food or always take without food. Avoid grapefruit juice. Do not change dosage or discontinue drug without consulting prescriber. Regular blood work, ophthalmic exams, and cardiac assessment will be necessary while taking this medication on a long-term basis. You may experience dizziness, weakness, or insomnia (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); hypotension (use caution when rising from sitting or lying position); nausea, vomiting, loss of appetite, stomach discomfort, or abnormal taste (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); or decreased libido (reversible). Report persistent dry cough or shortness of breath; chest pain, palpitations, irregular or slow heartbeat; unusual bruising or bleeding; blood in urine, feces (black stool), vomitus; warmth, swelling, pain in calves; heat or cold intolerance; weight loss or gain; restlessness; hair thinning; changes in menses; sweating; swelling in neck; muscle tremor, weakness, numbness, or changes in gait; fever; malaise; skin rash (bluish-gray color) or irritation; visual disturbances; or changes in urinary patterns. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride: 50 mg/mL (3 mL, 9 mL, 18 mL) [contains benzyl alcohol and polysorbate 80]

Tablet, as hydrochloride [scored]: 200 mg, 400 mg

Cordarone®: 200 mg

Pacerone®: 100 mg [not scored], 200 mg, 400 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Amiodarone HCl)

200 mg (30): $28.99

Tablets (Cordarone)

200 mg (60): $260.54

Tablets (Pacerone)

100 mg (30): $139.99

Mechanism of ActionClass III antiarrhythmic agent which inhibits adrenergic stimulation (alpha- and beta-blocking properties), affects sodium, potassium, and calcium channels, prolongs the action potential and refractory period in myocardial tissue; decreases AV conduction and sinus node function

Pharmacodynamics/Kinetics

Onset of action: Oral: 2 days to 3 weeks; I.V.: May be more rapid

Peak effect: 1 week to 5 months

Duration after discontinuing therapy: 7-50 days

Note: Mean onset of effect and duration after discontinuation may be shorter in children than adults

Distribution: V_d: 66 L/kg (range: 18-148 L/kg); crosses placenta; enters breast milk in concentrations higher than maternal plasma concentrations

Protein binding: 96%

Metabolism: Hepatic via CYP2C8 and 3A4 to active N-desethylamiodarone metabolite; possible enterohepatic recirculation

Bioavailability: Oral: ~50%

Half-life elimination: Terminal: 40-55 days (range: 26-107 days); shorter in children than adults

Excretion: Feces; urine (<1% as unchanged drug)

Related Information

- Antiarrhythmic Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral: Abnormal salivation and taste

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAmiodarone is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusInsomnia, nightmares, and fatigue are common; postmarketing reports of confusion, delirium, disorientation, and hallucinations

Mental Health: Effects on Psychiatric TreatmentContraindicated with ziprasidone. May cause hypotension which may be exacerbated by psychotropics; may cause hypothyroidism; use caution with lithium. Postmarketing reports of agranulocytosis; use caution with clozapine and carbamazepine.

Cardiovascular ConsiderationsAmiodarone is associated with less proarrhythmic effects compared to other antiarrhythmic drugs. Bradycardia often accompanies amiodarone use and should be anticipated, especially when combined with beta-blockers or nondihydropyridine calcium channel blockers. Clinical trials demonstrate that amiodarone is a safe and effective antiarrhythmic for the treatment of supraventricular and ventricular arrhythmias in patients with underlying cardiovascular disease (myocardial infarction, heart failure). In a recent study, early amiodarone administration prolonged survival to hospitalization in patients suffering out-of-hospital cardiac arrest. In the setting of acute myocardial infarction, beta-blocker therapy should still be initiated even though concomitant amiodarone therapy provides beta-blockade. To avoid potential side effects, chronic amiodarone therapy, when possible, should be maintained at the lowest effective dose (≤400 mg/day). The potential for drug interaction should be evaluated prior to amiodarone therapy (see Drug Interactions). Switching amiodarone formulations in some patients may lead to serious problems. Encourage patients to continue with initial product. If product is changed, monitoring for 1-3 months after change is necessary. Useful in treatment of atrial fibrillation in patients with heart failure (ACC/AHA/ESC Practice Guidelines).

Anesthesia and Critical Care Concerns/Other Considerations

Cardiac Arrest: The ARREST trial was a randomized, placebo-controlled trial evaluating amiodarone's efficacy in patients who had an out-of-hospital cardiac arrest with pulseless ventricular tachycardia or ventricular fibrillation. The primary endpoint was admission to the hospital with a spontaneous perfusing rhythm. Patients were randomized to receive 300 mg of intravenous amiodarone or placebo after being shocked >3 times, intubated, and receiving 1 mg of epinephrine. Ventricular fibrillation was the most common initial arrhythmia (88%). More patients in the amiodarone group were successfully resuscitated (44% amiodarone; 34% placebo; p=0.03) and admitted to the hospital, but mortality was similar in both groups (possibly due to sample size). More recently, the ALIVE trial compared amiodarone to lidocaine in out-of-hospital cardiac arrest victims whose ventricular fibrillation was resistant to 3 defibrillation attempts in addition to epinephrine and a fourth defibrillation attempt (Dorian, 2002). This was a randomized, double-blind comparison. Other inclusion criteria included ventricular fibrillation unrelated to trauma (or with other arrhythmias that converted to ventricular fibrillation) and recurrent ventricular fibrillation after successful initial defibrillation. The primary endpoint was the number of patients who were admitted to the hospital intensive care unit alive. Three hundred and forty-seven patients were enrolled. The initial amiodarone dose was 5 mg/kg and the lidocaine dose was 1.5 mg/kg. If ventricular fibrillation persisted after another shock, then the study drug could be administered again (amiodarone 2.5 mg/kg, lidocaine 1.5 mg/kg). Significantly more amiodarone patients (~23%) were admitted to the hospital alive than lidocaine patients (12%). The majority (>90%) of patients in the ALIVE trial had ventricular fibrillation as the initial arrhythmia. The authors concluded that intravenous amiodarone is superior to lidocaine in the treatment of shock-resistant, out-of-hospital ventricular fibrillation.

Arrhythmias: In patients with severe left ventricular dysfunction, amiodarone is preferable over other antiarrhythmics.

Index TermsAmiodarone Hydrochloride

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International Brand NamesAldarin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Aldarone (TH); Amdarone (TH); Amicordin (PL); Amiocar (AR); Amiodacore (IL); Amiodarex (DE); Amiodarona (CN); Amiohexal (DE); Amiokordin (PL); Ancaron (JP); Angiodarona (BR); Angoron (GR); Anoion (PH); Aratac (AU, MY, SG, TH, TW); Arycor (CO); Atlansil (AR, BR, CN, EC, PE, UY); Braxan (MX); Cardinorm (AU); Coedarone (MX); Corbionax (FR); Cordarex (DE); Cordarone (AE, BB, BE, BF, BG, BH, BJ, CH, CI, CL, CR, CY, CZ, DO, EC, EE, EG, ET, FI, FR, GH, GM, GN, GT, HK, HN, ID, IL, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PK, PL, PT, PY, QA, SA, SC, SD, SE, SL, SN, SV, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Cordarone X (AU, GB, IE, IN, ZA); Coronovo (AR); Diarona (UY); Escodaron (CH); Eurythmic (IN); Forken (MX); Hexarone (ZA); Kendaron (ID); Keritmon (MX); Miodar (DO); Opacorden (PL); Procor (IL); Rithmik (AU); Sedacoron (AT, HK, PL); Tachydaron (DE); Tiaryt (ID); Trangorex (ES, VE)

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(a mee TRIP ti leen & klor dye az e POKS ide)

U.S. Brand NamesLimbitrol®; Limbitrol® DS

Canadian Brand NamesLimbitrol®

Pharmacologic CategoryAntidepressant, Tricyclic (Tertiary Amine); Benzodiazepine

Use: Labeled IndicationsTreatment of moderate to severe anxiety and/or agitation and depression

Dosing: AdultsDepression and anxiety: Oral: Initial: 3-4 tablets in divided doses; this may be increased to 6 tablets/day as required. Some patients respond to smaller doses and can be maintained on 2 tablets.

Dosing: ElderlyRefer to adult dosing.

RestrictionsC-IV

An FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to benzodiazepines, tricyclic antidepressants, or any component of the formulation; depression of CNS; MAO inhibitors; acute recovery phase following MI; angle-closure glaucoma; pregnancy

Allergy Considerations

- Benzodiazepine Allergy
- Tricyclic Antidepressant and Related Compounds Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Amitriptyline and chlordiazepoxide combination is FDA approved for depression associated with anxiety in children ≥12 years of age.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **This combination is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. The degree of anticholinergic blockade produced by amitriptyline is very high relative to other antidepressants.

- Orthostatic hypotension: May cause orthostatic hypotension (risk is very high relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.

- Sedation: Both agents may cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is very high relative to other antidepressants.

- SIADH and hyponatremia: Has been associated with the development of SIADH and hyponatremia.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk conduction abnormalities with amitriptyline is high relative to other antidepressants.

- Depression: Use chlordiazepoxide with caution in patients with depression, particularly if suicidal risk may be present.

- Drug abuse: Use chlordiazepoxide with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Diabetes: Use amitriptyline with caution in patients with diabetes mellitus; may alter glucose regulation.

- Hepatic impairment: Use both agents with caution in patients with hepatic impairment.

- Impaired gag reflux: Use chlordiazepoxide with caution in patients with an impaired gag reflux.

- Porphyria: Use chlordiazepoxide with caution in patients with porphyria.

- Renal impairment: Use both agents with caution in patients with renal impairment.

- Respiratory disease: Use chlordiazepoxide with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

- Thyroid dysfunction: Use with caution in patients with hyperthyroidism or those receiving thyroid supplementation.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use chlordiazepoxide with caution in patients receiving other CNS depressants or psychoactive medication.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use chlordiazepoxide with caution in debilitated patients; active metabolites with extended half-lives may lead to delayed accumulation and adverse effects.

- Elderly: Use both agents with caution in the elderly. Benzodiazepines have been associated with falls and traumatic injury; active metabolites with extended half-lives may lead to delayed accumulation and adverse effects.

- Pediatrics: Use chlordiazepoxide with caution in children; active metabolites with extended half-lives may lead to delayed accumulation and adverse effects.

Dosage form specific issues:

- Chlordiazepoxide injection: Parenteral administration should be avoided in comatose patients or shock. Adequate resuscitative equipment/personnel should be available, and appropriate monitoring should be conducted at the time of injection and for several hours following administration. The parenteral formulation should be diluted for I.M. administration with the supplied diluent only. This diluent should not be used when preparing the drug for intravenous administration.

Other warnings/precautions:

- Appropriate use: Chlordiazepoxide does not have analgesic, antidepressant, or antipsychotic properties.

- Discontinuation of therapy: Amitriptyline therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods. Rebound or withdrawal symptoms may occur following abrupt discontinuation of chlordiazepoxide or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

Pregnancy Risk FactorD
LactationExcretion in breast milk unknown/contraindicated
Adverse ReactionsSee individual agents.
Metabolism/Transport Effects

Amitriptyline: **Substrate** of CYP1A2 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak)

Chlordiazepoxide: **Substrate** of CYP3A4 (major)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Tricyclic Antidepressants may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Agonists: Tricyclic Antidepressants may enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Alpha2-Agonists: Tricyclic Antidepressants may diminish the antihypertensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Altretamine: May enhance the orthostatic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Amphetamines: Tricyclic Antidepressants may enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Aspirin: Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Beta2-Agonists: Tricyclic Antidepressants may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cinacalcet: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Cisapride: Amitriptyline may enhance the arrhythmogenic effect of Cisapride. *Risk X: Avoid combination*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Tricyclic Antidepressants may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dexmethylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

DULoxetine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Iobenguane I 123: Tricyclic Antidepressants may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Lithium: May enhance the neurotoxic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

MAO Inhibitors: May enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

NSAID (COX-2 Inhibitor): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Protease Inhibitors: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Tricyclic Antidepressants may enhance the QTc-prolonging effect of QuiNIDine. QuiNIDine may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

St Johns Wort: May increase the metabolism of Tricyclic Antidepressants. The risk of serotonin syndrome may theoretically be increased. *Risk D: Consider therapy modification*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Sulfonylureas: Cyclic Antidepressants may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Terbinafine: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

TraMADol: Tricyclic Antidepressants may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. *Risk C: Monitor therapy*

Valproic Acid: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Tricyclic Antidepressants may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Monitoring ParametersSuicidal ideation (especially at the beginning of therapy or when doses are increased or decreased)

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 12.5/5: Amitriptyline hydrochloride 12.5 mg and chlordiazepoxide 5 mg; 25/10: Amitriptyline hydrochloride 25 mg and chlordiazepoxide 10 mg

Limbitrol®: 12.5/5: Amitriptyline hydrochloride 12.5 mg and chlordiazepoxide 5 mg

Limbitrol® DS: 25/10: Amitriptyline hydrochloride 25 mg and chlordiazepoxide 10 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Chlordiazepoxide-Amitriptyline)

5-12.5 mg (60): $44.99

10-25 mg (60): $65.99

Tablets (Limbitrol DS)

10-25 mg (60): $99.99

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Amitriptyline
- ChlordiazePOXIDE

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Amitriptyline: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), orthostatic hypotension, stomatitis, peculiar taste, and black tongue. Amitriptyline is the most anticholinergic and sedating of the antidepressants; has pronounced effects on the cardiovascular system. Long-term treatment with TCAs such as amitriptyline increases the risk of caries by reducing salivation and salivary buffer capacity. In a study by Rundergren, et al, pathological alterations were observed in the oral mucosa of 72% of 58 patients; 55% had new carious lesions after taking TCAs for a median of $5^1/_2$ years. Current research is investigating the use of the salivary stimulant pilocarpine (Salagen®) to overcome the xerostomia from amitriptyline.

Chlordiazepoxide: Over 10% of patients will experience xerostomia which disappears with cessation of drug therapy.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution; epinephrine and levonordefrin have been shown to have an increased pressor response in combination with TCAs

Mental Health CommentTricyclic antidepressants may be classified as tertiary (amitriptyline, doxepin, clomipramine, imipramine, trimipramine) or secondary amines (nortriptyline, desipramine, protriptyline). The tertiary amines are not recommended to treat depression in the elderly. If a TCA is used in the elderly, it should be a secondary amine. The tertiary amines are commonly used in low dosages for various conditions associated with pain. Toxicity is generally dose dependent. Relatively small overdoses (1-week supply) can be potentially fatal.

In 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

Risk factors for abuse include personal or family history of substance abuse and personality disorder.

Index TermsChlordiazepoxide and Amitriptyline Hydrochloride

References

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International Brand NamesLimbatril (DE); Limbatrilin (CN); Limbitrol (AE, AT, BE, BH, BR, CY, EG, FI, FR, GH, GR, ID, IL, IQ, IR, JO, KE, KW, LB, LY, NL, OM, QA, SA, SY, TW, TZ, UG, YE, ZM); Limbitryl (IT)

Amitriptyline and Perphenazine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(a mee TRIP ti leen & per FEN a zeen)

Canadian Brand NamesEtrafon®

Pharmacologic CategoryAntidepressant, Tricyclic (Tertiary Amine); Antipsychotic Agent, Typical, Phenothiazine

Use: Labeled IndicationsTreatment of patients with moderate to severe anxiety and depression

Use: Unlabeled/InvestigationalDepression with psychotic features

Dosing: AdultsDepression and anxiety: Oral: 1 tablet 2-4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic ImpairmentAvoid use in severe hepatic failure.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to amitriptyline, perphenazine, or any component of the formulation (cross-sensitivity with other phenothiazines may exist); angle-closure glaucoma; bone marrow depression; severe liver or cardiac disease; pregnancy

Allergy Considerations

- Phenothiazine Allergy
- Tricyclic Antidepressant and Related Compounds Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Amitriptyline is not FDA-approved for use in children <12 years of age; this combination is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **This combination is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics.

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to other neuroleptics, perphenazine has a low potency of cholinergic blockade and relative to other antidepressants amitriptyline has a high potential for cholinergic blockade.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).

- Extrapyramidal symptoms: May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is moderate-high relative to other neuroleptics).

- Neuroleptic malignant syndrome (NMS): Use of perphenazine may be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: Both agents may cause orthostatic hypotension (risk is very high relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Pigmentary retinopathy: Perphenazine use may be associated with pigmentary retinopathy.

- Sedation: Both agents may cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is high relative to other antidepressants.

- SIADH and hyponatremia: Has been associated with the development of SIADH and hyponatremia.

- Temperature regulation: Impaired core body temperature regulation may occur with perphenazine use; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use both agents with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk conduction abnormalities with this agent is high relative to other antidepressants.

- Diabetes: Use amitriptyline with caution in patients with diabetes mellitus; may alter glucose regulation.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use both agents with caution in patients with hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use perphenazine with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Prolactin-dependent tumors: Use perphenazine with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Renal impairment: Use both agents with caution in patients with renal impairment.

- Respiratory disease: Use perphenazine with caution in patients with respiratory disease.

- Seizure disorder: Use both agents with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

- Thyroid dysfunction: Use with caution in patients with hyperthyroidism or those receiving thyroid supplementation.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for developing tardive dyskinesia from perphenazine.

Other warnings/precautions:

- Discontinuation of therapy: Therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

Pregnancy Risk FactorD
LactationEnters breast milk/contraindicated
Adverse Reactions

Based on **amitriptyline** component: Anticholinergic effects may be pronounced; moderate to marked sedation can occur (tolerance to these effects usually occurs). Frequency not defined:

Cardiovascular: Orthostatic hypotension, tachycardia, ECG changes (nonspecific), AV conduction changes

Central nervous system: Restlessness, dizziness, insomnia, sedation, fatigue, anxiety, cognitive function impaired, seizure, extrapyramidal symptoms

Dermatologic: Allergic rash, urticaria, photosensitivity

Gastrointestinal: Weight gain, xerostomia, constipation

Genitourinary: Urinary retention

Ocular: Blurred vision, mydriasis

Miscellaneous: Diaphoresis

Based on **perphenazine** component: Frequency not defined:

Cardiovascular: Hyper-/hypotension, orthostatic hypotension, tachycardia, bradycardia, dizziness, cardiac arrest

Central nervous system: Extrapyramidal symptoms (pseudoparkinsonism, akathisia, dystonias, tardive dyskinesia), dizziness, cerebral edema, seizure, headache, drowsiness, paradoxical excitement, restlessness, hyperactivity, insomnia, neuroleptic malignant syndrome (NMS), impairment of temperature regulation

Dermatologic: Sun sensitivity increased, rash, discoloration of skin (blue-gray)

Endocrine & metabolic: Hypoglycemia, hyperglycemia, galactorrhea, lactation, breast enlargement, gynecomastia, menstrual irregularity, amenorrhea, SIADH, libido changes

Gastrointestinal: Constipation, weight gain, vomiting, stomach pain, nausea, xerostomia, salivation, diarrhea, anorexia, ileus

Genitourinary: Difficulty in urination, ejaculatory disturbances, incontinence, polyuria, ejaculating dysfunction, priapism

Hematologic: Agranulocytosis, leukopenia, eosinophilia, hemolytic anemia, thrombocytopenic purpura, pancytopenia

Hepatic: Cholestatic jaundice, hepatotoxicity

Neuromuscular & skeletal: Tremor

Ocular: Pigmentary retinopathy, blurred vision, cornea and lens changes

Respiratory: Nasal congestion

Miscellaneous: Diaphoresis

Metabolism/Transport Effects

Amitriptyline: **Substrate** of CYP1A2 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak)

Perphenazine: **Substrate** of CYP1A2 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Tricyclic Antidepressants may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Agonists: Tricyclic Antidepressants may enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Alpha2-Agonists: Tricyclic Antidepressants may diminish the antihypertensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Altretamine: May enhance the orthostatic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Amphetamines: Tricyclic Antidepressants may enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Analgesics (Opioid): Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antimalarial Agents: May increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Aspirin: Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Beta2-Agonists: Tricyclic Antidepressants may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Beta-Blockers: Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

BuPROPion: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cinacalcet: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Cisapride: Amitriptyline may enhance the arrhythmogenic effect of Cisapride. *Risk X: Avoid combination*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Desmopressin: Tricyclic Antidepressants may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dexmethylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

DULoxetine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Iobenguane I 123: Tricyclic Antidepressants may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May enhance the neurotoxic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

NSAID (COX-2 Inhibitor): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Tricyclic Antidepressants may enhance the QTc-prolonging effect of QuiNIDine. QuiNIDine may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

St Johns Wort: May increase the metabolism of Tricyclic Antidepressants. The risk of serotonin syndrome may theoretically be increased. *Risk D: Consider therapy modification*

Sulfonylureas: Cyclic Antidepressants may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Terbinafine: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

TraMADol: Tricyclic Antidepressants may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. *Risk C: Monitor therapy*

Valproic Acid: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Tricyclic Antidepressants may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased.

Risk X: Avoid combination

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to increased sedation).

Monitoring ParametersVital signs; lipid profile, fasting blood glucose/Hb A_{1c}; BMI, weight; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms (EPS), suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased)

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsLipid profile, fasting blood glucose/Hb A_{1c}; BMI

Patient EducationSee individual agents. Do not drink alcoholic beverages. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

2-10: Amitriptyline hydrochloride 10 mg and perphenazine 2 mg

2-25: Amitriptyline hydrochloride 25 mg and perphenazine 2 mg

4-10: Amitriptyline hydrochloride 10 mg and perphenazine 4 mg

4-25: Amitriptyline hydrochloride 25 mg and perphenazine 4 mg

4-50: Amitriptyline hydrochloride 50 mg and perphenazine 4 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Perphenazine-Amitriptyline)

2-10 mg (60): $16.99

2-25 mg (30): $13.99

4-25 mg (60): $19.99

4-50 mg (60): $27.99

Mechanism of Action

Amitriptyline increases the synaptic concentration of serotonin and/or norepinephrine in the central nervous system by inhibition of their reuptake by the presynaptic neuronal membrane.

Perphenazine is a piperazine phenothiazine antipsychotic which blocks postsynaptic mesolimbic dopaminergic receptors in the brain; exhibits alpha-adrenergic blocking effect and depresses the release of hypothalamic and hypophyseal hormones.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Amitriptyline
- Perphenazine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Amitriptyline: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), orthostatic hypotension, stomatitis, peculiar taste, and black tongue. Amitriptyline is the most anticholinergic and sedating of the antidepressants; has pronounced effects on the cardiovascular system. Long-term treatment with TCAs such as amitriptyline increases the risk of caries by reducing salivation and salivary buffer capacity. In a study by Rundergren, et al, pathological alterations were observed in the oral mucosa of 72% of 58 patients; 55% had new carious lesions after taking TCAs for a median of $5^1/_2$ years. Current research is investigating the use of the salivary stimulant pilocarpine (Salagen®) to overcome the xerostomia from amitriptyline.

Perphenazine: Extrapyramidal symptoms (pseudoparkinsonism, akathisia, dystonias, tardive dyskinesia), dizziness, seizures, headache, drowsiness, paradoxical excitement, restlessness, and hyperactivity.

Tardive dyskinesia: Prevalence rate may be 40% in elderly; development of the syndrome and the irreversible nature are proportional to duration and total cumulative dose over time. Extrapyramidal reactions are more common in elderly with up to 50% developing these reactions after 60 years of age. Drug-induced Parkinson's syndrome occurs often; akathisia is the most common extrapyramidal reaction in elderly.

Increased confusion, memory loss, psychotic behavior, and agitation frequently occur as a consequence of anticholinergic effects. Antipsychotic associated sedation in nonpsychotic patients is extremely unpleasant due to feelings of depersonalization, derealization, and dysphoria.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions

Amitriptyline: Use with caution; epinephrine and levonordefrin have been shown to have an increased pressor response in combination with TCAs

Perphenazine: No information available to require special precautions

Mental Health CommentTricyclic antidepressants may be classified as tertiary (amitriptyline, doxepin, clomipramine, imipramine, trimipramine) or secondary amines (nortriptyline, desipramine, protriptyline). The tertiary amines are not recommended to treat depression in the elderly. If a TCA is used in the elderly, it should be a secondary amine. The tertiary amines are commonly used in low dosages for various conditions associated with pain. Toxicity is generally dose dependent. Relatively small overdoses (1-week supply) can be potentially fatal.

Not commonly used; use of individual drugs allows for more flexibility in dosing and discontinuation of unneeded agent.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects. Long-term use of perphenazine, as is the case with any antipsychotic drug, may be associated with tardive dyskinesia (TD).

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Index Terms Perphenazine and Amitriptyline Hydrochloride

References

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International Brand Names Mutabon A (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Mutabon D (AE, AR, BH, CN, CY, EG, ID, IL, IQ, IR, JO, KW, LB, LY, OM, PY, QA, SA, SY, YE); Mutabon F (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Mutabon M (AE, BH, CY, EG, ID, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Mutabon-A (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Mutabon-D (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Mutabon-F (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Mutabon-M (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Neuragon-A (TH); Neuragon-B (TH); Polybon (TH); Triptafen (GB); Triptafen M (GB)

Amitriptyline

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Amitriptyline may be confused with aminophylline, imipramine, nortriptyline

Elavil® may be confused with Aldoril®, Eldepryl®, enalapril, Equanil®, Mellaril®, Oruvail®, Plavix®

Pronunciation(a mee TRIP ti leen)

Canadian Brand NamesApo-Amitriptyline®; Levate®; Novo-Triptyn; PMS-Amitriptyline

Pharmacologic CategoryAntidepressant, Tricyclic (Tertiary Amine)

Use: Labeled IndicationsRelief of symptoms of depression

Use: Unlabeled/InvestigationalAnalgesic for certain chronic and neuropathic pain; prophylaxis against migraine headaches; treatment of depressive disorders in children

Use: DentalManagement of chronic neuropathic pain in temporomandibular dysfunction (TMD)

Dosing: Adults

Depression: Oral: 50-150 mg/day single dose at bedtime or in divided doses; dose may be gradually increased up to 300 mg/day.

Chronic pain management (unlabeled use): Oral: Initial: 25 mg at bedtime; may increase as tolerated to 100 mg/day.

Migraine prophylaxis (unlabeled use): Oral: Initial: 10-25 mg at bedtime; usual dose: 150 mg; reported dosing ranges: 10-400 mg/day

Dosing: ElderlyDepression: Oral: Initial: 10-25 mg at bedtime; dose should be increased in 10-25 mg increments every week if tolerated; dose range: 25-150 mg/day. See Renal/Hepatic Impairment.

Dosing: Pediatric

Chronic pain management (unlabeled use): Oral: Initial: 0.1 mg/kg at bedtime, may advance as tolerated over 2-3 weeks to 0.5-2 mg/kg at bedtime

Depressive disorders:

Children (unlabeled use): Oral: Initial doses of 1 mg/kg/day given in 3 divided doses with increases to 1.5 mg/kg/day have been reported in a small number of children (n=9) 9-12 years of age; clinically, doses up to 3 mg/kg/day (5 mg/kg/day if monitored closely) have been proposed

Adolescents: Initial: 25-50 mg/day; may administer in divided doses; increase gradually to 100 mg/day in divided doses.

Migraine prophylaxis (unlabeled use): Oral: Initial: 0.25 mg/kg/day, given at bedtime; increase dose by 0.25 mg/kg/day to maximum 1 mg/kg/day. Reported dosing ranges: 0.1-2 mg/kg/day; maximum suggested dose: 10 mg.

Dosing: Renal ImpairmentNondialyzable

Dosing: Hepatic ImpairmentUse with caution and monitor plasma levels and patient response.

StorageProtect Elavil® 10 mg tablets from light.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to amitriptyline or any component of the formulation (cross-sensitivity with other tricyclics may occur); use of MAO inhibitors within past 14 days; acute recovery phase following myocardial infarction; concurrent use of cisapride

Allergy Considerations

- Tricyclic Antidepressant and Related Compounds Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Amitriptyline is not FDA-approved for use in children <12 years of age.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.
- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.
- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Amitriptyline is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. The degree of anticholinergic blockade produced by this agent is high relative to other antidepressants.
- Hematologic effects: TCAs may rarely cause bone marrow suppression; monitor for any signs of infection and obtain CBC if symptoms (eg, fever, sore throat) evident.
- Orthostatic hypotension: May cause orthostatic hypotension (risk is very high relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).
- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is very high relative to other antidepressants.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk of conduction abnormalities with this agent is high relative to other antidepressants.
- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose regulation.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.
- Thyroid dysfunction: Use with caution in patients with hyperthyroidism or those receiving thyroid supplementation due to concerns of pro-arrhythmogenesis.

Concurrent drug therapy issues:

- Anticholinergic and/or neuroleptic agents: Hyperpyrexia has been observed with TCAs in combination with anticholinergics and/or neuroleptics, particularly during hot weather.
- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Discontinuation of therapy: Recommended to discontinue prior to elective surgery requiring general anesthesia. Therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods.
- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

Geriatric ConsiderationsNot a drug of choice for elderly. The most anticholinergic and sedating of the antidepressants; pronounced effects on the cardiovascular system (hypotension), hence, many geropsychiatrists agree it is best to avoid in elderly.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects have been observed in animal studies. Amitriptyline crosses the human placenta; CNS effects, limb deformities and developmental delay have been noted in case reports.

LactationEnters breast milk/not recommended (AAP rates "of concern")

Breast-Feeding ConsiderationsGenerally, it is not recommended to breast-feed if taking antidepressants because of the long half-life, active metabolites, and the potential for side effects in the infant.

Adverse ReactionsAnticholinergic effects may be pronounced; moderate to marked sedation can occur (tolerance to these effects usually occurs).

Frequency not defined.

Cardiovascular: Orthostatic hypotension, tachycardia, ECG changes (nonspecific), AV conduction changes, cardiomyopathy (rare), MI, stroke, heart block, arrhythmia, syncope, hypertension, palpitation

Central nervous system: Restlessness, dizziness, insomnia, sedation, fatigue, anxiety, cognitive function impaired, seizure, extrapyramidal symptoms, coma, hallucinations, confusion, disorientation, coordination impaired, ataxia, headache, nightmares, hyperpyrexia

Dermatologic: Allergic rash, urticaria, photosensitivity, alopecia

Endocrine & metabolic: Syndrome of inappropriate ADH secretion

Gastrointestinal: Weight gain, xerostomia, constipation, paralytic ileus, nausea, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue

Genitourinary: Urinary retention

Hematologic: Bone marrow depression, purpura, eosinophilia

Neuromuscular & skeletal: Numbness, paresthesia, peripheral neuropathy, tremor, weakness

Ocular: Blurred vision, mydriasis, ocular pressure increased

Otic: Tinnitus

Miscellaneous: Diaphoresis, withdrawal reactions (nausea, headache, malaise)

Postmarketing and/or case reports: Neuroleptic malignant syndrome (rare), serotonin syndrome (rare)

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Tricyclic Antidepressants may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Agonists: Tricyclic Antidepressants may enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Alpha2-Agonists: Tricyclic Antidepressants may diminish the antihypertensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Altretamine: May enhance the orthostatic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Amphetamines: Tricyclic Antidepressants may enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Aspirin: Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Beta2-Agonists: Tricyclic Antidepressants may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cinacalcet: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Cisapride: Amitriptyline may enhance the arrhythmogenic effect of Cisapride. *Risk X: Avoid combination*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Desmopressin: Tricyclic Antidepressants may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dexmethylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

DULoxetine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Iobenguane I 123: Tricyclic Antidepressants may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May enhance the neurotoxic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

NSAID (COX-2 Inhibitor): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Tricyclic Antidepressants may enhance the QTc-prolonging effect of QuiNIDine. QuiNIDine may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

St Johns Wort: May increase the metabolism of Tricyclic Antidepressants. The risk of serotonin syndrome may theoretically be increased. *Risk D: Consider therapy modification*

Sulfonylureas: Cyclic Antidepressants may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Terbinafine: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

TraMADol: Tricyclic Antidepressants may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. *Risk C: Monitor therapy*

Valproic Acid: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Tricyclic Antidepressants may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Grapefruit juice may inhibit the metabolism of some TCAs and clinical toxicity may result.

Herb/Nutraceutical: St John's wort may decrease amitriptyline levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsMay cause false-positive reaction to EMIT immunoassay for imipramine

Monitoring ParametersMonitor blood pressure and pulse rate prior to and during initial therapy; evaluate mental status, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased); monitor weight; ECG in older adults and patients with cardiac disease

Reference RangeTherapeutic: Amitriptyline and nortriptyline 100-250 ng/mL (SI: 360-900 nmol/L); nortriptyline 50-150 ng/mL (SI: 190-570 nmol/L); Toxic: >0.5 mcg/mL; plasma levels do not always correlate with clinical effectiveness

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess for suicidal tendencies or unusual changes in behavior before beginning therapy and periodically thereafter. May cause physiological or psychological dependence, tolerance, or abuse; evaluate need for continued use periodically. Caution patients with diabetes; may alter serum glucose levels. Monitor therapeutic response and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed; do not increase dose or frequency. It may take several weeks to achieve desired results. Restrict use of alcohol and caffeine; avoid grapefruit juice. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, monitor glucose levels closely; this medication may alter glucose levels. May turn urine blue-green (normal). May cause drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); constipation (increased exercise, fluids, fruit, or fiber may help); urinary retention (void before taking medication); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); altered sexual drive or ability (reversible); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report persistent CNS effects (eg, nervousness, restlessness, insomnia, headache, agitation, impaired coordination, changes in cognition); suicidal ideation; muscle cramping, weakness, tremors, or rigidity; ringing in ears or visual disturbances; chest pain, palpitations, or irregular heartbeat; blurred vision; or worsening of condition. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Amitriptyline HCl)

25 mg (90): $11.99

50 mg (90): $12.99

75 mg (100): $14.44

100 mg (30): $13.99

150 mg (90): $21.98

Mechanism of ActionIncreases the synaptic concentration of serotonin and/or norepinephrine in the central nervous system by inhibition of their reuptake by the presynaptic neuronal membrane

Pharmacodynamics/Kinetics

Onset of action: Migraine prophylaxis: 6 weeks, higher dosage may be required in heavy smokers because of increased metabolism;
Depression: 4-6 weeks, reduce dosage to lowest effective level

Distribution: Crosses placenta; enters breast milk

Metabolism: Hepatic to nortriptyline (active), hydroxy and conjugated derivatives; may be impaired in the elderly

Half-life elimination: Adults: 9-27 hours (average: 15 hours)

Time to peak, serum: ~4 hours

Excretion: Urine (18% as unchanged drug); feces (small amounts)

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Dental Health Professional ConsiderationsAmitriptyline is known to prolong the QT interval. The QT interval is measured as the time and distance between the Q point of the QRS complex and the end of the T wave in the ECG tracing. After adjustment for heart rate, the QT interval is defined as prolonged if it is more than 450 msec in men and 460 msec in women. A long QT syndrome was first described in the 1950s and 60s as a congenital syndrome involving QT interval prolongation and syncope and sudden death. Some of the congenital long QT syndromes were characterized by a peculiar electrocardiographic appearance of the QRS complex involving a premature atria beat followed by a pause, then a subsequent sinus beat showing marked QT prolongation and deformity. This type of cardiac arrhythmia was originally termed “torsade de pointes” (translated from the French as “twisting of the points”).

Prolongation of the QT interval is thought to result from delayed ventricular repolarization. The repolarization process within the myocardial cell is due to the efflux of intracellular potassium. The channels associated with this current can be blocked by many drugs and predispose the electrical propagation cycle to torsade de pointes.

Amitriptyline is considered as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. It is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), orthostatic hypotension, stomatitis, peculiar taste, and black tongue. Amitriptyline is the most anticholinergic and sedating of the antidepressants; has pronounced effects on the cardiovascular system. Long-term treatment with TCAs such as amitriptyline increases the risk of caries by reducing salivation and salivary buffer capacity. In a study by Rundergren, et al, pathological alterations were observed in the oral mucosa of 72% of 58 patients; 55% had new carious lesions after taking TCAs for a median of $5^{1}/_{2}$ years. Current research is investigating the use of the salivary stimulant pilocarpine (Salagen®) to overcome the xerostomia from amitriptyline.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAmitriptyline is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution. See Dental Comment.

Mental Health CommentTricyclic antidepressants may be classified as tertiary (amitriptyline, doxepin, clomipramine, imipramine, trimipramine) or secondary amines (nortriptyline, desipramine, protriptyline). The tertiary amines are not recommended to treat depression in the elderly. If a TCA is used in the elderly, it should be a secondary amine. The tertiary amines are commonly used in low dosages for various conditions associated with pain. Toxicity is generally dose dependent. Relatively small overdoses (1-week supply) can be potentially fatal.

Cardiovascular ConsiderationsFrequently, low doses of tricyclics are used for the treatment of muscle cramps, neuralgia, etc. These low doses are not innocuous and may result in resting tachycardia and significant orthostatic hypotension. This is especially a problem in elderly patients on tricyclics and in patients who have coexisting diuretic therapy. Tricyclic antidepressants affect conduction and have anticholinergic effects and, therefore, should be used with caution in patients with underlying cardiovascular disease. Therapy is relatively contraindicated in patients with conduction abnormalities or in patients with symptomatic hypotension. Heart block may be precipitated in patients with pre-existing conduction system disease. Hemodynamics and cardiac conduction should be evaluated during therapy and before dose titration, particularly in patients with cardiovascular disease.

Anesthesia and Critical Care Concerns/Other ConsiderationsDesired therapeutic effect (for analgesia) may take as long as 1-3 weeks. When used for migraine headache prophylaxis, therapeutic effect may take as long as 6 weeks.

Tricyclic antidepressants affect conduction and have anticholinergic effects and, therefore, should be used with caution in patients with underlying cardiovascular disease. Therapy is relatively contraindicated in patients with conduction abnormalities or in patients with symptomatic hypotension. Heart block may be precipitated in patients with pre-existing conduction system disease.

Index TermsAmitriptyline Hydrochloride; Elavil

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International Brand Names Adepril (IT); Amilit (IT); Amineurin (DE); Amiprin (JP); Amitrip (NZ); Amitriptylinum (PL); Amytril (BR); Anapsique (MX); Antalin (CN); Conmitrip (TH); Domical (GB); Elatrol (IL); Elatrolet (IL); Elavil (FR); Endep (AU, NZ); Lantron (JP); Laroxyl (BF, BJ, CI, ET, FR, GH, GM, GN, IT, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Miketorin (JP); Neurotol (PY); Noriline (ZA); Novoprotect (DE); Pinsaun (TW); Protanol (BR); Psiquium (CO); Qualitriptine (HK); Redomex (BE); Saroten (BF, BJ, CI, CY, DE, DK, EE, ET, GH, GM, GN, GR, IR, KE, LR, MA, ML, MR, MU, MW, NE, NG, PT, SC, SD, SE, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Saroten Retard (CH, MY); Sarotena (IN); Sarotex (NL, NO, UY); Sarotex Retard (NO); Syneudon (DE); Teperin (HN, IQ, JO); Trepiline (ZA); Tridep (BG); Tripta (MY, TH); Triptanol (MX); Triptizol (IT); Trynol (TW); Tryptanol (AR, BR, JP, PE, TH); Tryptizol (AT, CH, EG, ES, GB, NL, PT, SE); Trytomer (IN); Uxen (AR)

Amlexanox

Lexi-Drugs Online

English

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Pronunciation(am LEKS an oks)
U.S. Brand NamesAphthasol®
Pharmacologic CategoryAnti-inflammatory, Locally Applied
Use: Labeled IndicationsTreatment of aphthous ulcers (ie, canker sores)
Use: Unlabeled/InvestigationalAllergic disorders
Use: DentalTreatment of aphthous ulcers (ie, canker sores)
Dosing: AdultsAphthous ulcers: Topical: Administer ~$^{1}/_{4}$ inch (0.5 cm) directly on ulcers 4 times/day following oral hygiene, after meals, and at bedtime.
Dosing: ElderlyRefer to adult dosing.
ContraindicationsHypersensitivity to amlexanox or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Mucositis: Discontinue therapy if contact mucositis develops.

- Rash: Discontinue therapy if rash develops.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorB
Pregnancy ConsiderationsDue to lack of data, avoid use in pregnancy, if possible.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

1% to 2%:

Dermatologic: Allergic contact dermatitis

Gastrointestinal: Oral irritation

<1%: Contact mucositis

Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringAssess knowledge/teach patient appropriate application and use, adverse effects to report, and interventions for side effects.
Patient EducationThis medication is only for treatment of mouth ulcers; do not apply to ulcers of the eye or any other part of the body. Use as directed. Apply after eating. Wash hands before and after use. Brush teeth and rinse mouth before applying directly to ulcers. Squeeze a small amount of paste on your clean finger tip and dab paste onto each ulcer in the mouth, using gentle pressure. Wash eyes immediately if any paste should come into contact with eyes. Notify prescriber or dentist if rash or irritation occurs, or if condition does not improve after 10 days use. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Paste, oral:

Aphthasol®: 5% (3 g) [contains benzyl alcohol]

Generic AvailableNo
ManufacturerBlock Drug Co, Inc
Pricing: U.S. (www.drugstore.com)

Paste (Aphthasol)

5% (5): $29.99

Mechanism of ActionAs a benzopyrano-bipyridine carboxylic acid derivative, amlexanox has anti-inflammatory and antiallergic properties; it inhibits chemical mediatory release of the slow-reacting substance of anaphylaxis (SRS-A) and may have antagonistic effects on interleukin-3
Pharmacodynamics/Kinetics

Absorption: Some from swallowed paste

Metabolism: Hydroxylated and conjugated metabolites

Half-life elimination: 3.5 hours

Time to peak, serum: 2 hours

Excretion: Urine (17% as unchanged drug)

Dental Health Professional Considerations Treatment of canker sores with amlexanox showed a 76% median reduction in ulcer size compared to a 40% reduction with placebo. Greer, et al, reported an overall mean reduction in ulcer size of 1.82 mm^2 for patients treated with 5% amlexanox versus an average reduction of 0.52 mm^2 for the control group. Recent studies in over thousands of patients have confirmed that amlexanox accelerates the resolution of pain and healing of aphthous ulcers more significantly than vehicle and no treatment.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Allergic contact dermatitis and oral irritation. Discontinue therapy if rash or contact mucositis develops (see Dental Comment).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

References

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International Brand Names Elics (JP); Solfa (JP)

Amlodipine and Atorvastatin

Lexi-Drugs Online

English

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Special Alerts

HMG-CoA Reductase Inhibitors: Evidence Does Not Suggest Increased Incidence of Amyotrophic Lateral Sclerosis (ALS) - Results of FDA Analysis - September 30, 2008

The U.S. Food and Drug Administration's (FDA) review of 41 long-term controlled clinical trials of HMG-CoA reductase inhibitors finds no evidence of an increased incidence of ALS (also known as Lou Gehrig's disease) related to these medications. This analysis occurred after the FDA had received notice of numerous adverse events of which 109 of these reports mentioned ALS, Lou Gehrig's disease, or motor neurone disease. The clinical trials included in the analysis had a median duration of treatment of 3.3 years (range of duration: 6 months to 5 years) and involved 120,964 patients. The analysis identified a total of 19 cases of ALS – 9 cases per 64,602 patients (0.014%) with statin therapy and 10 cases per 56,362 patients (0.017%) with placebo. The incidence rates, based on approximately 400,000 person-years, were 4.2 per 100,000 person-years in the statin-treated group and 5 per 100,000 person-years in the placebo-treated group.

The FDA recommends that health care providers continue to prescribe, and patients continue to use these products as described within their labeling.

For more information, healthcare professionals may refer to the following:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Statin

Colman E, Szarfman A, Wyeth J, et al, "An Evaluation of a Data Mining Signal for Amyotrophic Lateral Sclerosis and Statins Detected in FDA's Spontaneous Adverse Event Reporting System," *Pharmacoepidemiol Drug Saf*, 2008 (epub ahead of print)

Pronunciation(am LOW di peen & a TORE va sta tin)

U.S. Brand NamesCaduet®

Canadian Brand NamesCaduet®

Pharmacologic CategoryAntilipemic Agent, HMG-CoA Reductase Inhibitor; Calcium Channel Blocker

Use: Labeled IndicationsFor use when treatment with both amlodipine and atorvastatin is appropriate:

Amlodipine: Treatment of hypertension; treatment of symptomatic chronic stable angina, vasospastic (Prinzmetal's) angina (confirmed or suspected); prevention of hospitalization due to angina with documented CAD (limited to patients without heart failure or ejection fraction <40%)

Atorvastatin: Treatment of dyslipidemias or primary prevention of cardiovascular disease (atherosclerotic) as detailed here:

Primary prevention of cardiovascular disease (high-risk for CVD): To reduce the risk of MI or stroke in patients without evidence of heart disease who have multiple CVD risk factors or type 2 diabetes. Treatment reduces the risk for angina or revascularization procedures in patients with multiple risk factors.

Treatment of dyslipidemias: To reduce elevations in total cholesterol, LDL-C, apolipoprotein B, and triglycerides in patients with elevations of one or more components, and/or to increase HDL-C as present in heterozygous hypercholesterolemia (Fredrickson type IIa hyperlipidemias); treatment of primary dysbetalipoproteinemia (Fredrickson type III), elevated serum TG levels (Fredrickson type IV), and homozygous familial hypercholesterolemia

Treatment of heterozygous familial hypercholesterolemia (HeFH) in adolescent patients (10-17 years of age, females >1 year postmenarche) having LDL-C ≥190 mg/dL or LDL-C ≥160 mg/dL with positive family history of premature cardiovascular disease (CVD) or with two or more CVD risk factors.

Dosing: Adults

Amlodipine:

Hypertension: Oral: Initial dose: 5 mg once daily; maximum dose: 10 mg once daily; in general, titrate in 2.5 mg increments over 7-14 days. Usual dosage range (JNC 7): 2.5-10 mg once daily

Angina: Oral: Usual dose: 5-10 mg; lower dose suggested in elderly or hepatic impairment; most patients require 10 mg for adequate effect

Atorvastatin:

Hyperlipidemias: Oral: Initial: 10-20 mg once daily; patients requiring >45% reduction in LDL-C may be started at 40 mg once daily; range: 10-80 mg once daily

Primary prevention of CVD: Oral: 10 mg once daily

Dosing: ElderlyRefer to adult dosing.

Amlodipine: Dosing should start at the lower end of dosing range due to possible increased incidence of hepatic, renal, or cardiac impairment. Elderly patients also show decreased clearance of amlodipine.

Hypertension: 2.5 mg once daily

Angina: 5 mg once daily

Dosing: Pediatric

Hypertension:*Amlodipine:* Oral: Children >10 years: 2.5-5 mg once daily. **Note:** Use in ages >10 years because of atorvastatin content.

HeFH:*Atorvastatin:* Oral: Children 10-17 years (females >1 year postmenarche): 10 mg once daily (maximum: 20 mg/day)

Dosing: Renal ImpairmentNo dosage adjustment is necessary.

Dosing: Hepatic ImpairmentDo not use in active liver disease.

Administration: OralMay be administered without regard to meals.

Dietary ConsiderationsMay take with food if desired; may take without regard to time of day. Before initiation of therapy with atorvastatin, patients should be placed on a standard cholesterol-lowering diet for 3-6 months and the diet should be continued during drug therapy. Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.

StorageStore at controlled room temperature 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to amlodipine, atorvastatin, or any component of the formulation; active liver disease; unexplained persistent elevations of serum transaminases; pregnancy

Allergy Considerations

- Calcium Channel Blocker, Dihydropyridine Allergy
- HMG-CoA Reductase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Angina/MI: Increased angina and/or MI has occurred with initiation or dosage titration of calcium channel blockers.

- Myopathy/rhabdomyolysis: Patients receiving HMG-CoA reductase inhibitors have developed rhabdomyolysis with acute renal failure and/or myopathy; patients should be monitored closely. This risk is dose-related and is increased with concurrent use of other lipid lowering medications. Temporarily discontinue for elective major surgery, acute medical or surgical conditions, or in any patient experiencing an acute or serious condition predisposing to renal failure (eg, sepsis, hypotension, trauma, uncontrolled seizures). Based upon current evidence, HMG-CoA reductase inhibitor therapy should be continued in the perioperative period unless risk outweighs cardioprotective benefit. Use caution in patients with renal impairment, inadequately treated hypothyroidism, and those taking other drugs associated with myopathy (eg, colchicine); these patients are predisposed to myopathy. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine.

Disease-related concerns:

- Aortic stenosis: Use amlodipine with caution in patients with severe aortic stenosis.

- Hepatic impairment and/or ethanol use: Use atorvastatin with caution in patients who consume large amounts of ethanol or have a history of liver disease.

Concurrent drug therapy issues:

- High potential for interactions: Use atorvastatin with caution in patients taking strong CYP3A4 inhibitors (see drug interactions); consider alternative agents that avoid or lessen potential for CYP-mediated interactions.

Special populations:

- Elderly: Use atorvastatin with caution in patients with advanced age, these patients are predisposed to myopathy.

- Pediatrics: Safety and efficacy of the combination of amlodipine/atorvastatin have not been established in children. Safety and efficacy of amlodipine have not been established in patients <6 years of age. Safety and efficacy of atorvastatin have not been established in patients <10 years of age or in premenarcheal girls.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy with atorvastatin.

- Liver function tests: Must be monitored by periodic laboratory assessment while taking atorvastatin.

- Titration: Dosage titration of amlodipine should occur after 7-14 days on a given dose.

Pregnancy Risk FactorX

Pregnancy ConsiderationsSee individual agents.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsSee individual agents.

Adverse ReactionsSee individual agents.

Metabolism/Transport Effects

Amlodipine: **Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (moderate), 2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 2D6 (weak), 3A4 (weak)

Atorvastatin: **Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (weak)

Drug Interactions

Aliskiren: Atorvastatin may increase the serum concentration of Aliskiren. *Risk C: Monitor therapy*

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amiodarone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. Management: Dose of HMG-CoA reductase inhibitor may need to be reduced (e.g., simvastatin prescribing information recommends not exceeding 20 mg/day during concurrent therapy). *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Bosentan: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Clopidogrel: Atorvastatin may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Colchicine: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CycloSPORINE: May increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CycloSPORINE: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: Atorvastatin may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Danazol: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

DAPTOmycin: HMG-CoA Reductase Inhibitors may enhance the adverse/toxic effect of DAPTOmycin. Specifically, the risk of skeletal muscle toxicity may be increased. Management: Consider temporarily stopping HMG-CoA reductase inhibitor therapy prior to daptomycin. If used together, regular (i.e., at least weekly) monitoring of CPK concentrations is recommended. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Digoxin: Atorvastatin may increase the serum concentration of Digoxin. *Risk C: Monitor therapy*

Etravirine: May decrease the serum concentration of HMG-CoA Reductase Inhibitors. This applies to atorvastatin, lovastatin and simvastatin. Conversely, levels of fluvastatin may be increased. Management: Dose adjustment of the HMG-CoA reductase inhibitor may be warranted. No interaction is expected with rosuvastatin or pravastatin. *Risk C: Monitor therapy*

Fenofibrate: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Gemfibrozil: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Gemfibrozil may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Grapefruit Juice: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midazolam: Atorvastatin may increase the serum concentration of Midazolam. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Niacin: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Niacinamide: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Phenytoin: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk D: Consider therapy modification*

QuiNIDine: Calcium Channel Blockers (Dihydropyridine) may decrease the serum concentration of QuiNIDine. *Risk C: Monitor therapy*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Sildenafil: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

St Johns Wort: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

⬆ Ethanol/Nutrition/Herb InteractionsSee individual agents.
⬆ Monitoring ParametersBlood pressure; lipid levels after 2-4 weeks, CPK, liver function tests (LFTs); it is recommended that LFTs be performed prior to and at 12 weeks following both the initiation of therapy and any elevation in dose of atorvastatin, and periodically (eg,

semiannually) thereafter.

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsSee individual components listed in Related Information.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Caduet®

2.5/10: Amlodipine 2.5 mg and atorvastatin 10 mg

2.5/20: Amlodipine 2.5 mg and atorvastatin 20 mg

2.5/40: Amlodipine 2.5 mg and atorvastatin 40 mg

5/10: Amlodipine 5 mg and atorvastatin 10 mg

5/20: Amlodipine 5 mg and atorvastatin 20 mg

5/40: Amlodipine 5 mg and atorvastatin 40 mg

5/80: Amlodipine 5 mg and atorvastatin 80 mg

10/10: Amlodipine 10 mg and atorvastatin 10 mg

10/20: Amlodipine 10 mg and atorvastatin 20 mg

10/40: Amlodipine 10 mg and atorvastatin 40 mg

10/80: Amlodipine 10 mg and atorvastatin 80 mg

Generic AvailableNo

ManufacturerPfizer Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Caduet)

2.5-10 mg (30): $115.99

2.5-20 mg (30): $157.66

2.5-40 mg (30): $157.66

5-10 mg (30): $114.99

5-20 mg (30): $153.29

5-40 mg (30): $149.99

5-80 mg (30): $155.98

10-10 mg (30): $109.19

10-20 mg (30): $155.98

10-40 mg (30): $146.97

10-80 mg (30): $165.99

Mechanism of Action

Amlodipine: Inhibits calcium ion from entering the “slow channels” or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary vascular smooth muscle and coronary vasodilation; increases myocardial oxygen delivery in patients with vasospastic angina

Atorvastatin: Inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol synthesis (reduces the production of mevalonic acid from HMG-CoA); this then results in a compensatory increase in the expression of LDL receptors on hepatocyte membranes and a stimulation of LDL catabolism

Pharmacodynamics/KineticsSee individual agents.

Related Information

- AmLODIPine
- Atorvastatin

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Fewer reports of gingival hyperplasia with amlodipine than with other calcium channel blockers (usually resolves upon discontinuation); consultation with physician is suggested.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness; may rarely produce insomnia, nervousness, or euphoria

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular Considerations

Amlodipine:

Hypertension: Amlodipine therapy should be continued for 4-6 weeks before the dose is increased. Daily doses >10 mg are associated with an increase in side effects (eg, edema) without further reductions in blood pressure. The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ASCOT-BPLA trial evaluated two regimens (calcium channel blocker/ACE inhibitor vs beta-blocker/thiazide diuretic) to test their efficacy in the primary prevention of coronary disease (nonfatal MI and fatal coronary artery disease). Patients 40-79 years of age were recruited; their blood pressures were either >160 systolic or >100 diastolic (untreated) or >140 systolic or >90 diastolic (treated). Treatment with a calcium channel blocker/ACE inhibitor was more effective at reducing cardiovascular outcomes than the beta-blocker/diuretic regimen.

Coronary artery disease: The Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial compared a calcium channel blocker and ACE inhibitor in normotensive patients with coronary artery disease (Nissen, 2004). The primary outcome of CV events occurred in 151 (23.1%: placebo), 110 (16.6%: amlodipine), and 136 (20.2%: enalapril) of the patients. The only significant difference being a reduction in CV events with amlodipine compared with placebo, mainly representing a reduction in coronary revascularization and hospitalizations for angina with amlodipine. In the treatment of unstable angina/non-ST-segment elevation MI, oral long-acting calcium antagonists may also be considered in addition to beta-blockers and nitrates.

Heart failure: The ACC/AHA 2005 guidelines for management of heart failure state that calcium channel blockers are not indicated for the routine treatment of heart failure patients with current/prior symptoms of heart failure and reduced LVEF. Only amlodipine has been shown not to adversely affect survival, but most experience is not in patients on concurrent beta-blockers.

Atorvastatin:

HMG-CoA reductase inhibitors are effective in primary and secondary prevention of cardiovascular events in patients with hyperlipidemia. For primary prevention, a patient's major risk factors (cigarette smoking, hypertension or currently taking antihypertensives, low HDL-C, family history, age, gender) should be evaluated. Patients with multiple risk factors (≥2) require more intensive therapy guided by the calculation of a 10-year absolute CHD risk (eg, the percent probability of having a CHD event in next 10 years). An individual's 10-year absolute CHD risk can be calculated at www.med-decisions.com/cvtool/phys/phys.html. LDL cholesterol goals, therapeutic lifestyle changes, and drug therapy are determined based upon a patient's risk factor profile.

Primary prevention trials show that cholesterol-lowering drugs reduce the risk of major coronary events, coronary death, and cerebrovascular events even in the first 6-12 months of use. The WOSCOP trial suggested a trend towards enhanced survival using pravastatin in their patients (mean LDL-cholesterol of 192 mg/dL and no history of MI). In a recent trial (Sever PS, 2003), patients with HTN and at least three other risk factors were randomized to 10 mg daily of atorvastatin or placebo. These patients had a total nonfasting cholesterol <250 mg/dL before treatment. LDL-C levels were 132 mg/dL before treatment and fell to an average of 90 mg/dL in the atorvastatin-treated group. There was a significant reduction in stroke, cardiovascular events, and coronary events in the atorvastatin-treated group as compared to the placebo group. There was no difference in mortality between the groups.

Secondary prevention trials indicate that “statin” therapy reduces mortality, major coronary events, coronary artery procedures, and stroke. The Heart Protection Study proved that lowering serum cholesterol levels reduces the rate of major vascular events among high-risk individuals with documented vascular disease (CHD, cerebrovascular, peripheral vascular) or diabetes regardless of initial cholesterol concentrations. PROVE IT is a randomized, double-blind trial evaluating hospitalized patients with acute coronary syndrome to determine the effects of intense LDL-C lowering therapy. Four thousand patients with an LDL-C levels of 106 mg/dL were randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily. After 2 years, the combined cardiovascular endpoint (death, MI, unstable angina requiring hospitalization, revascularization and stroke) was ~26% in the pravastatin patients (median LDL-C 95 mg/dL) and ~22% in the atorvastatin treated patients (median LDL-C 62 mg/dL).

LaRosa and colleagues assessed the efficacy and safety of lowering LDL cholesterol <100 mg/dL in patients with stable coronary heart disease (LaRosa JC, 2005). Ten thousand and one patients with baseline LDL levels <130 mg/dL were randomized to atorvastatin 10 mg or 80 mg daily and followed for a median of 4.9 years. The primary endpoint was the occurrence of the first major cardiovascular event (death from CVD, MI, resuscitation after cardiac arrest, or stroke). A primary event occurred in 434 patients (8.7%) receiving 80 mg daily (mean LDL 77 mg/dL) and 548 patients (10.9%) receiving 10 mg dose (mean LDL 101 mg/dL) (95% CI, 0.69-0.89; p <0.001). There was no mortality difference between the two treatment groups.

HMG-CoA reductase inhibitors decrease levels of high-sensitivity C-reactive protein (hs-CRP). They also possess pleiotropic properties including improved endothelial function, reduced inflammation at the site of the coronary plaque, inhibition of platelet aggregation, and anticoagulant effects. These nonlipid effects may be beneficial when HMG-CoA reductase inhibitors are introduced early in the management of acute coronary syndromes (de Denus S, 2002).

Myopathy: Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years of age), women more frequently than men, small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, drug interactions (use with caution or avoid). The combination of a HMG-CoA reductase inhibitor plus nicotinic acid seems to carry a lower risk of myopathy than does a HMG-CoA reductase inhibitor plus a fibrate. Other medications, when used concurrently, may enhance the risk of myopathy associated with statins; these include drugs that inhibit CYP3A4 isoenzymes (lovastatin, simvastatin, atorvastatin) or CYP2C9 isoenzymes (fluvastatin). HMG-CoA reductase inhibitors may exacerbate exercise-induced skeletal muscle injury. Many experts favor getting a baseline creatine kinase (CK) measurement before initiating therapy (asymptomatic CK elevations are common). Obtain a CK measurement if patient complains of muscle soreness, tenderness, or pain.

Anesthesia and Critical Care Concerns/Other ConsiderationsBased on the atorvastatin component: **Myopathy:** Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years), gender (occurs in women more frequently than men), small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, and drug interactions (use with caution or avoid).

Based on current research, HMG-CoA reductase inhibitors should be continued in the perioperative period. Postoperative discontinuation of statin therapy is associated with an increased risk of cardiac morbidity and mortality.

Index Terms Atorvastatin Calcium and Amlodipine Besylate

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International Brand Names Caduet (AU, BG, CH, CN, CR, CZ, ES, FR, GT, HK, HN, IL, KP, MX, MY, NI, PA, SG, SV, TH, VE); Encavar (PH); Hipertensal Combi (AR); Liparten (PY); Norvator (PE)

Amlodipine and Benazepril

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(am LOE di peen & ben AY ze pril)

U.S. Brand NamesLotrel®

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Calcium Channel Blocker

Use: Labeled IndicationsTreatment of hypertension

Dosing: AdultsHypertension: Oral: 2.5-10 mg (amlodipine) and 10-40 mg (benazepril) once daily; maximum: Amlodipine: 10 mg/day; benazepril: 40 mg/day

Dosing: ElderlyInitial dose: 2.5 mg (based on amlodipine component). Refer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} ≤30 mL/minute: Use of combination product is not recommended.

Dosing: Hepatic ImpairmentInitial dose: 2.5 mg based on amlodipine component.

Calculations

- Creatinine Clearance: Adults

ContraindicationsHypersensitivity to amlodipine, benazepril, other ACE inhibitors, or any component of the formulation

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity
- Calcium Channel Blocker, Dihydropyridine Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angina/MI: With initiation or dosage titration of dihydropyridine calcium channel blockers; reflex tachycardia may occur resulting in angina and/or MI (rare) in patients with obstructive coronary disease (especially in the absence of concurrent beta-blockade).

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema or previous angioedema associated with ACE inhibitor therapy may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE Inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Peripheral edema: The most common side effect of amlodipine is peripheral edema (dose dependent); occurs within 2-3 weeks of starting therapy.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with extreme caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use benazepril with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.

- Hepatic impairment: Use amlodipine with caution in patients with hepatic impairment; may require lower starting dose.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use benazepril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use benazepril with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Patients with renal impairment may be at increased risk for hematologic toxicity. Avoid rapid dosage escalation which may lead to further renal impairment.

Special populations:

- Elderly: Initiate amlodipine at a lower dose in the elderly.

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Appropriate use: Used as a replacement for separate dosing of components or combination therapy when response to single agent is suboptimal; the fixed combination is not indicated for initial treatment of hypertension.

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsCombination products are not recommended as first-line treatment. Only use if doses of individual agents correspond to the combination available.
Pregnancy Risk FactorC/D (2nd and 3rd trimesters)
Pregnancy ConsiderationsSee individual agents.
Lactation

Amlodipine: Excretion in breast milk unknown

Benazepril: Enters breast milk

Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsAmlodipine: **Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (moderate), 2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 2D6 (weak), 3A4 (weak)
Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

CycloSPORINE: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk D: Consider therapy modification*

QuiNIDine: Calcium Channel Blockers (Dihydropyridine) may decrease the serum concentration of QuiNIDine. *Risk C: Monitor therapy*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Monitoring ParametersBUN, electrolytes, serum creatinine, and blood pressure. In patients with renal impairment and/or collagen vascular disease, monitor CBC with differential periodically.

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsBUN, electrolytes, and serum creatinine; in patients with renal impairment and/or collagen vascular disease, monitor CBC with differential periodically

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

2.5/10: Amlodipine 2.5 mg and benazepril hydrochloride 10 mg

5/10: Amlodipine 5 mg and benazepril hydrochloride 10 mg

5/20: Amlodipine 5 mg and benazepril hydrochloride 20 mg

10/20: Amlodipine 10 mg and benazepril hydrochloride 20 mg

Lotrel® 2.5/10: Amlodipine 2.5 mg and benazepril hydrochloride 10 mg

Lotrel® 5/10: Amlodipine 5 mg and benazepril hydrochloride 10 mg

Lotrel® 5/20: Amlodipine 5 mg and benazepril hydrochloride 20 mg

Lotrel® 5/40: Amlodipine 5 mg and benazepril hydrochloride 40 mg

Lotrel® 10/20: Amlodipine 10 mg and benazepril hydrochloride 20 mg

Lotrel® 10/40: Amlodipine 10 mg and benazepril hydrochloride 40 mg

Generic AvailableYes

ManufacturerNovartis Pharmaceuticals Corp

Pricing: U.S. (www.drugstore.com)

Capsules (Amlodipine Besy-Benazepril HCl)

2.5-10 mg (30): $69.99

5-10 mg (30): $74.99

5-20 mg (30): $69.99

10-20 mg (30): $89.99

Capsules (Lotrel)

2.5-10 mg (30): $89.99

5-10 mg (30): $89.97

5-20 mg (30): $92.99

5-40 mg (30): $96.99

10-20 mg (30): $109.99

10-40 mg (30): $115.99

Mechanism of ActionThe mechanism through which benazepril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system; benazepril has an antihypertensive effect even in patients with low-renin hypertension; amlodipine is a dihydropyridine calcium antagonist that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle; amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure

Pharmacodynamics/Kinetics See individual agents.

Related Information

- AmLODIPine
- Benazepril

Dental Health: Effects on Dental Treatment Fewer reports of gingival hyperplasia with amlodipine than with other CCBs (usually resolves upon discontinuation); consultation with physician is suggested.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause drowsiness; rarely may produce insomnia and nervousness

Mental Health: Effects on Psychiatric Treatment May decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Index Terms Benazepril Hydrochloride and Amlodipine Besylate

References

Hunt SA, Abraham WT, Chin MH , et al, "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure)," available at http://www.acc.org/qualityandscience/clinical/guidelines/failure/update/index.pdf.

Wynn RL, “An Update on Calcium Channel Blocker-Induced Gingival Hyperplasia,” *Gen Dent*, 1995, 43(3):218-22. [PubMed 8940577]

Wynn RL, “Calcium Channel Blockers and Gingival Hyperplasia,” *Gen Dent*, 1991, 39(4):240-3.[PubMed 1916193]

International Brand Names Ambix (UY); Amlibon B (VE); Ampliron Plus (PY); Pelmec Duo (AR); Terloc Duo (AR)

Amlodipine and Olmesartan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(am LOE di peen & olme SAR tan)

U.S. Brand NamesAzor™

Pharmacologic CategoryAngiotensin II Receptor Blocker; Calcium Channel Blocker

Use: Labeled IndicationsTreatment of hypertension

Dosing: AdultsHypertension: Oral: Amlodipine 5-10 mg and olmesartan 20-40 mg once daily; dose may be titrated after 2 weeks of therapy. Maximum recommended dose: Amlodipine 10 mg/day; olmesartan 40 mg/day.

Dosing: ElderlyRefer to adult dosing. Initiate at lower end of dosing range.

Dosing: Renal ImpairmentNo specific guidelines for dosage adjustment.

Dosing: Hepatic ImpairmentUse caution in hepatic impairment; amlodipine and olmesartan exposure increased in presence of hepatic impairment.

Administration: OralAdminister with or without food.

Dietary ConsiderationsAvoid salt substitutes which contain potassium. May be taken with or without food.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsThere are no contraindications listed in manufacturer's labeling.

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angina/MI: Increased angina and/or MI has occurred with initiation or dosage titration of calcium channel blockers. Use caution with severe obstructive CAD.
- Hyperkalemia: May occur with olmesartan use; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.
- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; use caution during initiation of therapy, particularly in patients with heart failure, severe aortic stenosis, post-MI patients, volume- or salt-depleted patients, or those undergoing surgery or dialysis.
- Peripheral edema: The most common side effect of amlodipine is peripheral edema; occurs within 2-3 weeks of starting therapy.
- Reflex tachycardia: May occur with amlodipine use.
- Renal function deterioration: Olmesartan may be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.
- Heart failure: Use caution when initiating in heart failure; may need to adjust dose, and/or concurrent diuretic therapy.
- Hepatic impairment: Use with caution in patients with hepatic impairment; amlodipine and olmesartan exposure increased in hepatic dysfunction.
- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.
- Renal artery stenosis: Use olmesartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.
- Renal impairment: Use with caution with pre-existing renal insufficiency and severe renal impairment.

Special populations:

- Elderly: Initiate at a lower dose in the elderly.
- Pediatrics: Safety and efficacy of this combination have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Appropriate use: Combination product is not indicated for initial therapy of hypertension.

- Titration: Dosage titration may occur after 2-4 weeks if blood pressure control inadequate. This may be done by increasing one component at a time or by increasing both components to achieve more rapid control of blood pressure.

Geriatric ConsiderationsSee individual agents.
Pregnancy Risk FactorC/D (2nd and 3rd trimesters)
Pregnancy ConsiderationsSee individual agents.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsReactions/percentages reported with combination product; also refer to individual agents

>10%: Cardiovascular: Peripheral edema (dose related: 18% to 26%)

Frequency not defined (limited to important or life-threatening): Hypotension, nocturia, orthostatic hypotension, palpitation, pruritus, rash, urinary frequency

Metabolism/Transport EffectsAmlodipine: **Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (moderate), 2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 2D6 (weak), 3A4 (weak)
Drug Interactions

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

CycloSPORINE: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk D: Consider therapy modification*

QuiNIDine: Calcium Channel Blockers (Dihydropyridine) may decrease the serum concentration of QuiNIDine. *Risk C: Monitor therapy*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may enhance antihypertensive effects).

Monitoring ParametersBaseline and periodic electrolyte panels, renal and liver function, urinalysis; BP, heart rate, peripheral edema; in CHF, serum potassium during dose escalation and periodically thereafter

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsBaseline and periodic electrolyte panels, renal and liver function, urinalysis

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Azor™:

5/20: Amlodipine besylate 5 mg and olmesartan medoxomil 20 mg

5/40: Amlodipine besylate 5 mg and olmesartan medoxomil 40 mg

10/20: Amlodipine besylate 10 mg and olmesartan medoxomil 20 mg

10/40: Amlodipine besylate 10 mg and olmesartan medoxomil 40 mg

Generic AvailableNo

ManufacturerDaiichi Sankyo Pharma GmbH

Pricing: U.S. (www.drugstore.com)

Tablets (Azor)

5-40 mg (30): $102.08

10-20 mg (30): $91.73

10-40 mg (90): $321.38

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- AmLODIPine
- Olmesartan

Dental Health: Effects on Dental TreatmentFewer reports of gingival hyperplasia with amlodipine than with other CCBs (usually resolves upon discontinuation); consultation with physician is suggested.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness; may rarely produce insomnia and nervousness

Mental Health: Effects on Psychiatric TreatmentMay cause hypotension, hyperglycemia, and hypertriglyceridemia; combined use with psychotropics (atypical antipsychotics and mirtazapine) may produce additive effects, May cause diarrhea, these effects may be additive with concurrent use of SSRIs, lithium, or valproate. May cause flu-like symptoms, take this into consideration if also concerned about SSRI discontinuation syndrome. Combined use with lithium may produce lithium toxicity; monitor lithium levels.

Index TermsAmlodipine Besylate and Olmesartan Medoxomil; Olmesartan and Amlodipine

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Amlodipine and Valsartan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(am LOE di peen & val SAR tan)

U.S. Brand NamesExforge®

Pharmacologic CategoryAngiotensin II Receptor Blocker; Calcium Channel Blocker

Use: Labeled IndicationsTreatment of hypertension

Dosing: Adults **Note:** Dose is individualized; combination product may be used as initial therapy or substituted for individual components in patients currently maintained on both agents separately or in patients not adequately controlled with monotherapy (using one of the agents or an agent within same antihypertensive class).

Hypertension: Oral:

Initial therapy: Amlodipine 5 mg and valsartan 160 mg once daily, dose may be titrated after 1-2 weeks of therapy. Maximum recommended doses: Amlodipine 10 mg/day; valsartan 320 mg/day

Add-on/replacement therapy: Amlodipine 5-10 mg and valsartan 160-320 mg once daily; dose may be titrated after 3-4 weeks of therapy. Maximum recommended doses: Amlodipine 10 mg/day; valsartan 320 mg/day

Dosing: ElderlyRefer to adult dosing. Initiate amlodipine at 2.5 mg/day; due to decreased clearance.

Dosing: Renal Impairment

Cl_{cr} >10 mL/minute: No dosage adjustment necessary.

Cl_{cr} ≤10 mL/minute: Use caution; titrate slowly.

Dosing: Hepatic ImpairmentMild-to-moderate hepatic impairment: No initial dosage adjustment required, titrate slowly. Amlodipine and valsartan exposure increased in presence of hepatic impairment.
Amlodipine: Use caution in severe hepatic impairment; lower initial doses may be required.

Valsartan: Mild-to-moderate hepatic impairment: No dosage adjustment required; however, patients with mild-to-moderate chronic disease have twice the exposure as healthy volunteers.

Administration: OralAdminister with or without food.

Dietary ConsiderationsAvoid salt substitutes which contain potassium. May be taken with or without food.

StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture.

ContraindicationsThere are no contraindications listed within the FDA-approved labeling.

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angina/MI: Increased angina and/or MI has occurred with initiation or dosage titration of calcium channel blockers.
- Hyperkalemia: May occur with valsartan use; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.
- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; use caution during initiation of therapy, particularly in patients with heart failure, severe aortic stenosis, or in post-MI patients or those undergoing surgery or dialysis.
- Peripheral edema: The most common side effect of amlodipine is peripheral edema; occurs within 2-3 weeks of starting therapy.
- Reflex tachycardia: May occur with amlodipine use.
- Renal function deterioration: Valsartan may be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.
- Heart failure: Use caution when initiating in heart failure; may need to adjust dose, and/or concurrent diuretic therapy.

- Hepatic impairment: Use with caution in patients with hepatic impairment; amlodipine and valsartan exposure increased in hepatic dysfunction.

- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.

- Renal artery stenosis: Use valsartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution with pre-existing renal insufficiency and severe renal impairment.

Special populations:

- Elderly: Initiate at a lower dose in the elderly.

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Titration: Dosage titration should occur after 3-4 weeks if blood pressure control inadequate.

Geriatric ConsiderationsSee individual agents.
Pregnancy Risk FactorD
Pregnancy ConsiderationsSee individual agents.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsReactions/percentages reported with combination product; also refer to individual agents

>10%: Central nervous system: Headache (11%)

1% to 10%:

Cardiovascular: Peripheral edema (5% to 8%)

Central nervous system: Anxiety (3%), somnolence (3%), dizziness (2%)

Endocrine & metabolic: Hyperkalemia (3% to 10%)

Gastrointestinal: Abdominal pain (upper; 3%), diarrhea (3%), nausea (3%)

Renal: BUN increased (6%)

Respiratory: Nasopharyngitis (4%), upper respiratory tract infection (3%), cough (2%)

Miscellaneous: Influenza (2%)

<1%, postmarketing, and/or case reports: Exanthema, hypersensitivity, hypotension, orthostatic hypotension, postural dizziness, syncope, tinnitus, visual disturbance

Frequency not defined, but occurred at ≥0.2% incidence (limited to important or life-threatening): Abdominal discomfort/distension, abdominal pain, arthralgia, cardiac murmur, chest pain, colitis, constipation, cystitis, depression, diabetes, dyspepsia, edema (including pitting), erectile dysfunction, erythema, fever, flatulence, flushing, gastritis, hematuria, hypercholesterolemia, infection, LFTs increased, lymphadenopathy, myalgia, nephrolithiasis, palpitation, paresthesia, pharyngitis, pneumonia, pruritus, rash, tachycardia, vomiting, weakness

Metabolism/Transport Effects

Amlodipine: **Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (moderate), 2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 2D6 (weak), 3A4 (weak)

Valsartan: **Inhibits** CYP2C9 (weak)

Drug Interactions

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

CycloSPORINE: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk D: Consider therapy modification*

QuiNIDine: Calcium Channel Blockers (Dihydropyridine) may decrease the serum concentration of QuiNIDine. *Risk C: Monitor therapy*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Decreases rate and extent of valsartan absorption by 50% and 40%, respectively.

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effects).

Monitoring ParametersBaseline and periodic electrolyte panels, renal and liver function, urinalysis; BP, heart rate, peripheral edema; in CHF, serum potassium during dose escalation and periodically thereafter

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsBaseline and periodic electrolyte panels, renal and liver function, urinalysis; in CHF, serum potassium during dose escalation and periodically thereafter

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Exforge®:

5/160: Amlodipine 5 mg and valsartan 160 mg

5/320 mg: Amlodipine 5 mg and valsartan 320 mg

10/160: Amlodipine 10 mg and valsartan 160 mg

10/320: Amlodipine 10 mg and valsartan 320 mg

Generic AvailableNo

ManufacturerNovartis Pharmaceuticals Corp

Pricing: U.S. (www.drugstore.com)

Tablets (Exforge)

5-160 mg (30): $81.59

5-320 mg (30): $103.78

10-160 mg (30): $92.97

10-320 mg (30): $111.17

Mechanism of Action

Amlodipine inhibits calcium ion from entering the “slow channels” or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary vascular smooth muscle and coronary vasodilation; increases myocardial oxygen delivery in patients with vasospastic angina.

Valsartan produces direct antagonism of the angiotensin II (AT2) receptors, unlike the ACE inhibitors. It displaces angiotensin II from the AT1 receptor and produces its blood pressure-lowering effects by antagonizing AT1-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic responses. This action results in more efficient blockade of the cardiovascular effects of angiotensin II and fewer side effects than the ACE inhibitors.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- AmLODIPine
- Valsartan

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Fewer reports of gingival hyperplasia with amlodipine than with other calcium channel blockers (usually resolves upon discontinuation); consultation with physician is suggested.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusHeadache is common; may cause anxiety, dizziness, or somnolence; may rarely cause insomnia and nervousness

Mental Health: Effects on Psychiatric TreatmentMay cause symptomatic hypotension; concomitant use with psychotropic agents may produce additive effects; monitor. Conversely, amphetamines may decrease the antihypertensive effects of valsartan. May increase the risk of lithium toxicity; monitor lithium levels.

Index TermsAmlodipine Besylate and Valsartan; Valsartan and Amlodipine

References

Poldermans D, Glazer R, Karagiannis S, et al, “Tolerability and Blood Pressure-Lowering Efficacy of the Combination of Amlodipine Plus Valsartan Compared With Lisinopril Plus Hydrochlorothiazide in Adult Patients with Stage 2 Hypertension,” *Clin Ther*, 2007, 20(2):279-89.

International Brand NamesCopalia (EE, SE); Diovan/Amlibon (VE); Exforge (BE, CH, CZ, DE, DK, EE, ES, GB, IE, NO, SE); Imprida (EE, SE)

AmLODIPine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

AmLODIPine may be confused with aMILoride

Norvasc® may be confused with Navane®, Norvir®, Vascor®

Pronunciation(am LOE di peen)

U.S. Brand NamesNorvasc®

Canadian Brand NamesNorvasc®

Pharmacologic CategoryCalcium Channel Blocker

Use: Labeled IndicationsTreatment of hypertension; treatment of symptomatic chronic stable angina, vasospastic (Prinzmetal's) angina (confirmed or suspected); prevention of hospitalization due to angina with documented CAD (limited to patients without heart failure or ejection fraction <40%)

Dosing: Adults

Hypertension: Oral: Initial dose: 5 mg once daily; maximum dose: 10 mg once daily. In general, titrate in 2.5 mg increments over 7-14 days. Usual dosage range (JNC 7): 2.5-10 mg once daily.

Angina: Oral: Usual dose: 5-10 mg; lower dose suggested in elderly or hepatic impairment; most patients require 10 mg for adequate effect.

Dosing: ElderlyDosing should start at the lower end of dosing range due to possible increased incidence of hepatic, renal, or cardiac impairment. Elderly patients also show decreased clearance of amlodipine.
Hypertension: Oral: 2.5 mg once daily

Angina: Oral: 5 mg once daily

Dosing: Pediatric**Hypertension:** Oral: Children 6-17 years: 2.5-5 mg once daily

Dosing: Hepatic Impairment

Hypertension: Administer 2.5 mg once daily

Angina: Administer 5 mg once daily

Administration: OralMay be administered without regard to meals.

Dietary ConsiderationsMay be taken without regard to meals.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).

Extemporaneously PreparedA 1 mg/mL suspension was stable for 91 days when refrigerated or 56 days when kept at room temperature when compounded as follows: Triturate fifty 5 mg tablets in a mortar, reduce to a fine powder. In a graduate, mix Ora-Sweet® 125 mL and Ora-Plus® 125 mL together. Add small amount of this mixture to the powder to make a paste. Add the remainder in small quantities while mixing. Shake well before using.

Nahata MC, Morosco RS, and Hipple TF, 4th ed, *Pediatric Drug Formulations*, Cincinnati, OH: Harvey Whitney Books Co, 2000.

ContraindicationsHypersensitivity to amlodipine or any component of the formulation

Allergy Considerations

- Calcium Channel Blocker, Dihydropyridine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Angina/MI: Increased angina and/or MI has occurred with initiation or dosage titration of calcium channel blockers.
- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition.
- Peripheral edema: The most common side effect is peripheral edema; occurs within 2-3 weeks of starting therapy.
- Reflex tachycardia: May occur with use.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis.
- Hepatic impairment: Use with caution in patients with hepatic impairment; may require lower starting dose.

- Idiopathic hypertrophic subaortic stenosis (IHSS): Use with caution in patients with IHSS.

Special populations:

- Elderly: Initiate at a lower dose in the elderly.
- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Other warnings/precautions:

- Titration: Dosage titration should occur after 7-14 days on a given dose.

Geriatric ConsiderationsElderly may experience a greater hypotensive response. Constipation may be more of a problem in elderly. Calcium channel blockers are no more effective in elderly than other therapies, however, they do not cause significant CNS effects which is an advantage over some antihypertensive agents.

Pregnancy Risk FactorC

Pregnancy ConsiderationsEmbryotoxic effects have been demonstrated in small animals. No well-controlled studies have been conducted in pregnant women. Use in pregnancy only when clearly needed and when the benefits outweigh the potential hazard to the fetus.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%: Cardiovascular: Peripheral edema (2% to 15% dose related)

1% to 10%:

Cardiovascular: Flushing (1% to 3%), palpitation (1% to 4%)

Central nervous system: Headache (7%; similar to placebo 8%), dizziness (1% to 3%), fatigue (4%), somnolence (1% to 2%)

Dermatologic: Rash (1% to 2%), pruritus (1% to 2%)

Endocrine & metabolic: Male sexual dysfunction (1% to 2%)

Gastrointestinal: Nausea (3%), abdominal pain (1% to 2%), dyspepsia (1% to 2%), gingival hyperplasia

Neuromuscular & skeletal: Muscle cramps (1% to 2%), weakness (1% to 2%)

Respiratory: Dyspnea (1% to 2%), pulmonary edema (15% from PRAISE trial, CHF population)

<1%: Abnormal dreams, abnormal vision, allergic reactions, angioedema, anorexia, anxiety, arrhythmia, arthrosis, back pain, bradycardia, chest pain, conjunctivitis, constipation, depersonalization, depression, diaphoresis increased, diarrhea, diplopia, dysphagia, epistaxis, erythema multiforme, eye pain, female sexual dysfunction, flatulence, hot flushes, hyperglycemia, hypoesthesia, hypotension, insomnia, joint stiffness, leukopenia, malaise, micturition disorder, micturition frequency, myalgia, nervousness, nocturia, pain, pancreatitis, paresthesia, peripheral ischemia, peripheral neuropathy, postural dizziness, postural hypotension, purpura, rash erythematous, rash maculopapular, rigors, syncope, tachycardia, thirst, thrombocytopenia, tinnitus, tremor, vasculitis, vertigo, vomiting, weight gain/loss, xerostomia

<0.1%: Abnormal visual accommodation, agitation, alopecia, amnesia, apathy, appetite increased, ataxia, cardiac failure, cold and clammy skin, cough, dermatitis, dysuria, extrasystoles, gastritis, hypertonia, loose stools, migraine, muscle weakness, parosmia, polyuria, pulse irregularity, rhinitis, skin discoloration, skin dryness, taste perversion, twitching, urticaria, xerophthalmia

Postmarketing and/or case reports: Cholestasis, dysosmia, EPS, erythema multiforme, exfoliative dermatitis, gynecomastia, hepatitis, jaundice, leukocytoclastic vasculitis, nonthrombocytopenic purpura, phototoxicity, Stevens-Johnson syndrome, transaminases increased

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (moderate), 2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 2D6 (weak), 3A4 (weak)

Drug Interactions

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

CycloSPORINE: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk D: Consider therapy modification*

QuiNIDine: Calcium Channel Blockers (Dihydropyridine) may decrease the serum concentration of QuiNIDine. *Risk C: Monitor therapy*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Grapefruit juice may modestly increase amlodipine levels.

Herb/Nutraceutical: St John's wort may decrease amlodipine levels. Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effects).

Monitoring ParametersHeart rate, blood pressure, peripheral edema

Nursing: Physical Assessment/MonitoringAssess potential for interactions with prescription, OTC medications, or herbal products patient may be taking (eg, nitrates or other drugs that effect blood pressure). Assess therapeutic effectiveness (blood pressure; cardiac rhythm; frequency and intensity of angina; I & O ratio; weight; edema, according to purpose for use) and signs of adverse reactions at beginning of therapy, when changing dose, and periodically during long-term therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed; do not alter dose or discontinue medication without consulting prescriber. May cause headache (if unrelieved, consult prescriber); nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum or sucking lozenges may help); constipation (increased dietary bulk and fluids may help); or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report unrelieved headache; vomiting, constipation; palpitations; peripheral or facial swelling; weight gain >5 lb/week; or respiratory changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 2.5 mg, 5 mg, 10 mg

Norvasc®: 2.5 mg, 5 mg, 10 mg

Generic AvailableYes

ManufacturerPfizer U.S. Pharmaceuticals Group

Pricing: U.S. (www.drugstore.com)

Tablets (Amlodipine Besylate)

2.5 mg (90): $15.99

10 mg (90): $18.00

Tablets (Norvasc)

2.5 mg (30): $61.99

5 mg (30): $64.99

10 mg (30): $81.99

Mechanism of ActionInhibits calcium ion from entering the “slow channels” or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary vascular smooth muscle and coronary vasodilation; increases myocardial oxygen delivery in patients with vasospastic angina

Pharmacodynamics/Kinetics

Onset of action: Antihypertensive: 30-50 minutes

Duration of antihypertensive effect: 24 hours

Absorption: Oral: Well absorbed

Distribution: V_d: 21 L/kg

Protein binding: 93% to 98%

Metabolism: Hepatic (>90%) to inactive metabolite

Bioavailability: 64% to 90%

Half-life elimination: 30-50 hours; increased with hepatic dysfunction

Time to peak, plasma: 6-12 hours

Excretion: Urine (10% as parent, 60% as metabolite)

Related Information

- Calcium Channel Blockers

Dental Health: Effects on Dental TreatmentFewer reports of gingival hyperplasia with amlodipine than with other CCBs (usually resolves upon discontinuation); consultation with physician is suggested.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness; rarely may produce insomnia and nervousness

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular Considerations

Hypertension: Amlodipine therapy should be continued for 4-6 weeks before the dose is increased. Daily doses >10 mg are associated with an increase in side effects (eg, edema) without further reductions in blood pressure. The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ASCOT-BPLA trial evaluated two regimens (calcium channel blocker/ACE inhibitor vs beta-blocker/thiazide diuretic) to test their efficacy in the primary prevention of coronary disease (nonfatal MI and fatal coronary artery disease). Patients 40-79 years of age were recruited; their blood pressures were either >160 systolic or >100 diastolic (untreated) or >140 systolic or >90 diastolic (treated). Treatment with a calcium channel blocker/ACE inhibitor was more effective at reducing cardiovascular outcomes than the beta-blocker/diuretic regimen.

Coronary Artery Disease: The Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial compared a calcium channel blocker and ACE inhibitor in normotensive patients with coronary artery disease (Nissen, 2004). The primary outcome of CV events occurred in 151 (23.1%: placebo), 110 (16.6%: amlodipine), and 136 (20.2%: enalapril) of the patients. The only significant difference being a reduction in CV events with amlodipine compared with placebo, mainly representing a reduction in coronary revascularization and hospitalizations for angina with amlodipine. In the treatment of unstable angina/non-ST-segment elevation MI, oral long-acting calcium antagonists may also be considered in addition to beta-blockers and nitrates.

Heart Failure: The ACC/AHA 2005 guidelines for management of heart failure state that calcium channel blockers are not indicated for the routine treatment of heart failure patients with current/prior symptoms of heart failure and reduced LVEF. Only amlodipine has been shown not to adversely affect survival but most experience is not in patients on concurrent beta-blockers.

Anesthesia and Critical Care Concerns/Other ConsiderationsAmlodipine may be used safely to treat hypertension and/or angina in patients with heart failure.

Index TermsAmlodipine Besylate

References

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, "Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)," *JAMA*, 2002, 288(23):2981-97.[PubMed 12479763]

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Joseffsson M, Zackrisson AL, and Ahlner J, “Effect of Grapefruit Juice on the Pharmacokinetics of Amlodipine in Healthy Volunteers,” *Eur J Clin Pharmacol*, 1996, 51(2):189-93. [PubMed 8911887]

Meredith PA and Elliott HL, "Clinical Pharmacokinetics of Amlodipine," *Clin Pharmacokinet* , 1992, 22(1):22-31.[PubMed 1532771]

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Vincent J, Harris SI, Foulds G, et al, “Lack of Effect of Grapefruit Juice on the Pharmacokinetics and Pharmacodynamics of Amlodipine,” *Br J Clin Pharmacol*, 2000, 50(5):455-63.[PubMed 11069440]

International Brand NamesAgen (EE); Aldan (PL); Alopine (TW); Amcard (IN); Amdepin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Amdipin (CO); Amdixal (ID); Amedin (HK); Amilo (TW); Amlate (ZA); Amloc (AR, CN); Amlocar (PE); Amlodin (JP); Amlodine (PH); Amlodipinum (PL); Amlopin (HR, KP, PL); Amlopine (TH); Amlopres (HK); Amlor (BE, FR, IL, LU); Amlostar (KP); Amlosyn (CO); Amlovas (CR, DO, GT, HN, NI, PA, SV); Amlovasc (CH); Amlozek (PL); Amodipin (KP); Ampliron (PY); Amze (AR); Anydipine (KP); Astudal (ES); Avistar (MX); Calchek (IN); Calvase (NZ); Cardilopin (PL); Cardinor (CO); Cordarene (BR); Covasc (MY); Deten (TH); Duactin 5 (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Eucoran (CO); Goritel (EC); Istin (GB, IE); Lama (IN); Lofral (MY); Lovas (TH); Nevadipin (KP); Nordipine (MY); Normodipine (HU, PL, SG); Norvas (CO, ES, MX); Norvasc (AT, AU, BB, BF, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CR, CZ, DE, DK, EC, EE, ET, FI, GH, GM, GN, GR, GT, GY, HK, HN, HU, IL, IT, JM, JP, KE, KP, LR, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, NO, PA, PE, PH, PK, PL, PT, SC, SD, SE, SG, SL, SN, SR, SV, TH, TN, TT, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Norvask (BG, ID); Novalopine (KP); Presilam (CN); Rustin (IE); Sinop (AR); Sistopress (MX); Skad (KP); Stamlo (SG); Tenox (PL); Tensivask (ID); Vasotop (EC); Vasten (CO)

Ammonia Spirit (Aromatic)

Lexi-Drugs Online

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Pronunciation(a MOE nee ah SPEAR it, air oh MAT ik)
Pharmacologic CategoryRespiratory Stimulant
Use: Labeled IndicationsRespiratory and circulatory stimulant; treatment of fainting
Use: DentalEmergency use in syncope
Dosing: AdultsFainting: Inhalation: Used as “smelling salts” to treat or prevent fainting
Dosing: ElderlyRefer to adult dosing.
StorageAromatic ammonia spirit should be protected from sunlight and stored at a temperature not exceeding 30°C.
ContraindicationsHypersensitivity to ammonia or any component of the formulation
Pregnancy Risk FactorC
Adverse Reactions1% to 10%:

Gastrointestinal: Nausea, vomiting

Respiratory: Irritation to nasal mucosa, cough

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, for inhalation: 1.7% to 2.1% (0.33 mL, 60 mL)

Generic AvailableYes
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsSmelling Salts

Ammonium Chloride

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(a MOE nee um KLOR ide)

Pharmacologic CategoryElectrolyte Supplement, Parenteral

Use: Labeled IndicationsTreatment of hypochloremic states or metabolic alkalosis

Dosing: AdultsMetabolic alkalosis: The following equations represent different methods of correction utilizing either the serum HCO_3^-, the serum chloride, or the base excess

Dosing of mEq NH_4Cl via the chloride-deficit method (hypochloremia):

> Dose of mEq NH_4Cl = [0.2 L/kg x body weight (kg)] x [103 - observed serum chloride]; administer 50% of dose over 12 hours, then re-evaluate
>
> **Note:** 0.2 L/kg is the estimated chloride volume of distribution and 103 is the average normal serum chloride concentration (mEq/L)

Dosing of mEq NH_4Cl via the bicarbonate-excess method (refractory hypochloremic metabolic alkalosis):

> Dose of NH_4Cl = [0.5 L/kg x body weight (kg)] x (observed serum HCO_3^- - 24); administer 50% of dose over 12 hours, then re-evaluate
>
> **Note:** 0.5 L/kg is the estimated bicarbonate volume of distribution and 24 is the average normal serum bicarbonate concentration (mEq/L)

These equations will yield different requirements of ammonium chloride

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricMetabolic alkalosis: Refer to adult dosing for weight-based equations.

Administration: I.V.Administer by slow intravenous infusion to avoid local irritation and adverse effects. Rate of infusion should not exceed 5 mL/minute in an adult.

StoragePrior to use, vials should be stored at controlled room temperature of 15°C to 30°C (59°F to 86°F). Solution may crystallize if exposed to low temperatures. If crystals are observed, warm vial to room temperature in a water bath prior to use.

ReconstitutionDilute prior to use; final concentration should not exceed 1% to 2% ammonium chloride. Suggested dilution: Mix contents of 1-2 vials (100-200 mEq) in 500-1000 mL NS.

CompatibilityStable in dextran 6% in D_5W, dextran 6% in NS, D_5LR, D_5NS, $D_5{}^1/_2NS$, $D_5{}^1/_4NS$, D_5W, $D_{10}W$, LR, $^1/_2NS$, NS.

Y-site administration: Variable (consult detailed reference): Warfarin.

Compatibility when admixed: Incompatible: Levorphanol. **Variable (consult detailed reference):** Dimenhydrinate, potassium chloride.

ContraindicationsSevere hepatic or renal dysfunction

Warnings/Precautions

Concerns related to adverse effects:

- Ammonia toxicity: Monitor closely for signs and symptoms of ammonia toxicity, including diaphoresis, altered breathing, bradycardia, arrhythmias, retching, twitching, and coma.

Disease-related concerns:

- Respiratory disease: Use with caution in patients with primary respiratory acidosis or pulmonary insufficiency.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo specific data available for elderly; monitor closely with hepatic disease for signs of toxicity.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

Adverse ReactionsFrequency not defined.

Central nervous system: Coma, drowsiness, EEG abnormalities, headache, mental confusion, seizure

Dermatologic: Rash

Endocrine & metabolic: Calcium-deficient tetany, hyperchloremia, hypokalemia, metabolic acidosis, potassium may be decreased, sodium may be decreased

Gastrointestinal: Abdominal pain, gastric irritation, nausea, vomiting

Hepatic: Ammonia may be increased

Local: Pain at site of injection

Neuromuscular & skeletal: Twitching

Respiratory: Hyperventilation

Drug Interactions

Amphetamines: Ammonium Chloride may decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

Analgesics (Opioid): Ammonium Chloride may increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the adverse/toxic effect of Ammonium Chloride. Specifically the risk of systemic acidosis. *Risk D: Consider therapy modification*

Monitoring ParametersSerum bicarbonate; signs and symptoms of ammonia toxicity

Monitoring: Lab TestsSerum bicarbonate

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: Ammonium 5 mEq/mL and chloride 5 mEq/mL (20 mL) [equivalent to ammonium chloride 267.5 mg/mL]

Generic AvailableYes

Mechanism of ActionIncreases acidity by increasing free hydrogen ion concentration

Pharmacodynamics/Kinetics

Metabolism: Hepatic; forms urea and hydrochloric acid

Excretion: Urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation and confusion

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Martin WJ and Matzke GR, “Treating Severe Metabolic Alkalosis,” *Clin Pharm*, 1982, 1(1):42-8. [PubMed 6764161]

Megarbane B, Bruneel F, Bedos JP, et al, “Ammonium Chloride Poisoning: A Misunderstood Cause of Metabolic Acidosis With Normal Anion Gap,” *Intensive Care Med*, 2000, 26(12):1869.[PubMed 11271099]

Amobarbital

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(am oh BAR bi tal)

U.S. Brand NamesAmytal®

Canadian Brand NamesAmytal®

Pharmacologic CategoryBarbiturate

Use: Labeled IndicationsHypnotic in short-term treatment of insomnia; reduce anxiety and provide sedation preoperatively

Use: Unlabeled/InvestigationalTherapeutic or diagnostic “Amytal® Interviewing”; Wada test

Dosing: Adults

Hypnotic: I.M., I.V.: 65-200 mg at bedtime (maximum single dose: 1000 mg)

Sedative: I.M., I.V.: 30-50 mg 2-3 times/day (maximum single dose: 1000 mg)

“Amytal® interview” (unlabeled use): I.V.: 50-100 mg/minute for total dose of 200-1000 mg or until patient experiences drowsiness, impaired attention, slurred speech, or nystagmus

Wada test (unlabeled use): Intra-arterial: 100 mg over 4-5 seconds via percutaneous transfemoral catheter

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Sedative: I.M., I.V.: 6-12 years: Manufacturer's dosing range: 65-500 mg

Hypnotic (unlabeled use): I.M.: 2-3 mg/kg (maximum: 500 mg)

Dosing: Renal ImpairmentDosing should be reduced; specific recommendations not available.

Dosing: Hepatic ImpairmentDosing should be reduced; specific recommendations not available.

Administration: I.M.Administer deeply into a large muscle. Do not use more than 5 mL at any single site (may cause tissue damage). I.M. dosages should not exceed 500 mg. Use 20% solution to facilitate larger doses.

Administration: I.V.Use only when I.M. administration is not feasible; administer by slow I.V. injection (maximum: 50 mg/minute in adults).

StoragePowder should be stored at 15°C to 30°C (59°F to 86°F). Following reconstitution, solution should be used within 30 minutes.

ReconstitutionReconstitute with SWFI to make a 10% I.V. solution; a 20% solution may be made for I.M. use. Rotate vial to dissolve, do not shake. Do not use unless a clear solution forms within 5 minutes.

CompatibilityStable in D_5LR, D_5NS, D_5W, $D_{10}W$, $D_{20}W$, LR, NS.

Compatibility when admixed: Compatible: Amikacin, aminophylline, sodium bicarbonate. **Incompatible:** Cefazolin, cimetidine, clindamycin, diphenhydramine, droperidol, hydroxyzine, insulin (regular), levorphanol, meperidine, morphine, norepinephrine, pancuronium, pentazocine, penicillin G potassium, procaine, streptomycin, vancomycin. **Variable (consult detailed reference):** Atracurium, dimenhydrinate, hydrocortisone sodium succinate, isoproterenol, metaraminol, methyldopate, norepinephrine, succinylcholine.

RestrictionsC-II

ContraindicationsHypersensitivity to barbiturates or any component of the formulation; marked hepatic impairment; dyspnea or airway obstruction; porphyria

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypersensitivity reactions: Postmarketing studies have indicated that the use of hypnotic/sedative agents for sleep has been associated with hypersensitivity reactions including anaphylaxis as well as angioedema.
- Paradoxical responses: May cause paradoxical responses, including agitation and hyperactivity, particularly in acute pain, chronic pain and pediatric patients.
- Sleep-related activities: An increased risk for hazardous sleep-related activities such as sleep-driving; cooking and eating food, and making phone calls while asleep has been noted with sedative-hypnotic medications. Discontinue treatment in patients who report a sleep-driving episode.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; may cause hypotension.

- Depression: Use with caution in patients with depression or suicidal tendencies.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Hepatic impairment: Use with caution in patients with hepatic impairment, decreased dosage may be needed; contraindicated in severe impairment.

- Insomnia: Appropriate use: When used as a hypnotic for the treatment of insomnia, effectiveness is limited to ≤2 weeks.

- Renal impairment: Use with caution in patients with renal impairment; decreased dosage may be needed.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; not recommended for use. Closely monitor elderly or debilitated patients for impaired cognitive or motor performance.

- Pediatrics: Safety and efficacy have not been established in children <6 years of age; use with caution in children ≥6 years of age.

Dosage form specific issues:

- Alkaline solution: Solution for injection is highly alkaline and extravasation may cause local tissue damage.

Other warnings/precautions:

- Rapid administration: Rapid I.V. administration may cause respiratory depression, apnea, and hypotension.

- Withdrawal: Gradual withdrawal is recommended if used over extended periods of time.

Pregnancy Risk FactorD

Pregnancy ConsiderationsBarbiturates cross the placenta and distribute in fetal tissue. Teratogenic effects have been reported with 1st trimester exposure. Exposure during the 3rd trimester may lead to symptoms of acute withdrawal following delivery; symptoms may be delayed up to 14 days.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsSmall amounts of barbiturates are excreted in breast milk; information specific for amobarbital is not available.

Adverse ReactionsFrequency not defined and is reported as barbiturate use (not specifically amobarbital).

Cardiovascular: Bradycardia, hypotension, syncope

Central nervous system: Agitation, anxiety, ataxia, confusion, CNS depression, dizziness, fever, hallucinations, headache, insomnia, nightmares, nervousness, psychiatric disturbances, somnolence, thinking abnormal

Gastrointestinal: Constipation, nausea, vomiting

Hematologic: Megaloblastic anemia (following chronic phenobarbital use)

Hepatic: Liver damage

Local: Injection site reaction

Neuromuscular & skeletal: Hyperkinesia

Respiratory: Apnea, atelectasis (postoperative), hypoventilation

Miscellaneous: Hypersensitivity reaction (including angioedema, rash, and exfoliative dermatitis)

Metabolism/Transport Effects**Induces** CYP2A6 (strong)

Drug Interactions

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2A6 Substrates: CYP2A6 Inducers (Strong) may increase the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

Griseofulvin: Barbiturates may decrease the absorption of Griseofulvin. *Risk D: Consider therapy modification*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Voriconazole: Barbiturates may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Monitoring ParametersVital signs should be monitored during injection and for several hours after administration.
Reference Range

Therapeutic: 1-5 mcg/mL (SI: 4-22 µmol/L)

Toxic: >10 mcg/mL (SI: >44 µmol/L)

Lethal: >50 mcg/mL

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as sodium:

Amytal®: 500 mg

Generic AvailableNo
Mechanism of ActionInterferes with transmission of impulses from the thalamus to the cortex of the brain resulting in an imbalance in central inhibitory and facilitatory mechanisms
Pharmacodynamics/Kinetics

Onset of action: I.V.: Within 5 minutes

Distribution: Readily crosses placenta; small amounts enter breast milk

Metabolism: Primarily hepatic via microsomal enzymes

Half-life elimination: 15-40 hours (mean: 25 hours)

Excretion: Urine, feces

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Index Terms Amobarbital Sodium; Amylobarbitone

References

Kavirajan H, “The Amobarbital Interview Revisited: A Review of the Literature Since 1966,” *Harv Rev Psychiatry*, 1999, 7(3):153-65.[PubMed 10483934]

International Brand Names Amycal (NO); Amytal Sodium (AU); Barbamyl (IL); Dorlotin (HU); Dorlotyn (HU); Eunoctal (FR); Isoamitil Sedante (ES); Isomytal (JP); Neur-Amyl (AU); Placidel (ES); Sodium Amytal (GB); Transital (ES)

Amonafide

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(a MON a fide)
Pharmacologic CategoryAntineoplastic Agent, DNA Binding Agent; Enzyme Inhibitor, Topoisomerase II Inhibitor
Use: Unlabeled/InvestigationalInvestigational: Breast, prostate, renal cell, ovarian, pancreatic, and nonsmall cell lung cancers
Dosing: AdultsRefer to individual protocols.

Breast cancer: 800 mg/m^2 over 3 hours every 28 days

Renal cell, ovarian, pancreatic cancer: Up to 450 mg/m^2 over 1 hour on days 1-5 every 21 days

Nonsmall cell lung cancer: 1600 mg/m^2 by continuous infusion over 24 hours every 21 days

Dosing: ElderlyRefer to adult dosing.
Dosing: Hepatic ImpairmentDosage adjustment may be required, but specific guidelines have not been established.
Calculations

- Body Surface Area: Adults

Administration: I.V.May be administered by short (1-3 hours) infusion or continuous (24-hour) infusion.
StorageStore intact vials under refrigeration at 2°C to 8°C (36°F to 46°F). Reconstituted vials and solutions for infusion are stable for up to 14 days at room temperature or under refrigeration.
ReconstitutionVials may be reconstituted with SWFI or 0.9% sodium chloride.
Compatibility**Incompatible** with dextrose solutions.
ContraindicationsHypersensitivity to amonafide or any component of the formulation; pregnancy
Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Toxicity: Amonafide toxicity, particularly hematologic, correlates with the patient's acetylator status. If possible, determination of acetylator type (fast vs slow) should be considered prior to beginning therapy.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with existing bone marrow suppression.

- Cardiovascular disease: Use with caution in patients with arrhythmias, conduction problems, and/or congestive heart failure.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Seizure disorder: Use with caution in patients with a history of seizure disorder or other neurological disorders.

Special populations:

- Bone marrow transplant recipients: Use with caution in bone marrow transplant patients.

Adverse Reactions

>10%:

Gastrointestinal: Nausea and vomiting (mild)

Hematologic: Granulocytopenia, possibly dose limiting; nadir occurs at days 12-15, recovery by day 21

1% to 10%:

Cardiovascular: Chest pain

Central nervous system: Dizziness, fatigue, headache

Dermatologic: Skin rash, exfoliative dermatitis, alopecia

Local: Inflammatory reactions

Otic: Tinnitus

Neuromuscular & skeletal: Myoclonic jerking, weakness

<1%: CHF, hypotension, taste alteration, thrombocytopenia

Oncology: VesicantNo
Oncology: Emetic PotentialModerate (30% to 60%)
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for injection, lyophilized: 500 mg

Generic AvailableNo
Mechanism of ActionAmonafide acts as a DNA intercalator, stabilizing DNA to thermal denaturation and producing single-strand DNA breaks.
Pharmacodynamics/Kinetics

Distribution: V_d: 370-530 L/m^2

Protein binding: High

Half-life:

Elimination: 3.5-11 hours

Terminal: 3-6 hours

Metabolism: Hepatic, primarily by oxidation and N-acetylation. N-acetylamonafide (active) and amonafide-N′-oxide are the major metabolites. Clearance depends on whether the patient is a fast or slow acetylator. Fast acetylators may experience greater toxicity from the drug.

Excretion: Urine (3% to 22% as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness and sedation
Mental Health: Effects on Psychiatric TreatmentGranulocytopenia is common; use caution with clozapine; monitor
Index TermsAmonafide Hydrochloride; Benzisoquinolinedione; BIDA; M-FA-142; Nafidimide; NSC-308847
References

Kornek G, Raderer M, Depisch D, et al, “Amonafide as First-Line Chemotherapy for Metastatic Breast Cancer,” *Eur J Cancer*, 1994, 30A(3):398-400.

Kreis W, Chan K, Budman DR, et al, “Clinical Pharmacokinetics of Amonafide (NSC-308847) in 62 Patients,” *Cancer Invest*, 1996, 14(4):320-7. [PubMed 8689426]

Leaf AN, Neuberg D, Schwartz EL, et al, “An ECOG Phase II Study of Amonafide in Unresectable or Recurrent Carcinoma of the Head and Neck (PB390). Eastern Cooperative Oncology Group,” *Invest New Drugs*, 1997, 15(2):165-72. [PubMed 9220297]

Marshall ME, Blumenstein B, Crawford ED, et al, “Phase II Trial of Amonafide for the Treatment of Advanced, Hormonally Refractory Carcinoma of the Prostate,” *Am J Clin Oncol*, 1994, 17(6):514-5. [PubMed 7977172]

Ratain MJ, Rosner G, Allen SL, et al, “Population Pharmacodynamic Study of Amonafide: A Cancer and Leukemia Group B Study,” *J Clin Oncol*, 1995, 13(3):741-7.[PubMed 7884434]

Amoxapine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Amoxapine may be confused with amoxicillin, Amoxil®

Asendin may be confused with aspirin

Pronunciation(a MOKS a peen)

Pharmacologic CategoryAntidepressant, Tricyclic (Secondary Amine)

Use: Labeled IndicationsTreatment of depression, psychotic depression, depression accompanied by anxiety or agitation

Dosing: AdultsOnce symptoms are controlled, decrease gradually to lowest effective dose. Maintenance dose is usually given at bedtime to reduce daytime sedation.

Depression: Oral: Initial: 25 mg 2-3 times/day. If tolerated, dosage may be increased to 100 mg 2-3 times/day. May be given in a single bedtime dose when dosage <300 mg/day.

Maximum daily dose: 600 mg (inpatients); 400 mg (outpatients)

Dosing: ElderlyOral: Initial: 25 mg at bedtime increased by 25 mg weekly for outpatients and every 3 days for inpatients if tolerated; usual dose: 50-150 mg/day, but doses up to 300 mg may be necessary. **Note:** Once symptoms are controlled, decrease gradually to lowest effective dose. See Geriatric Considerations.

Dosing: Pediatric

Depression: Oral:

Children: Not established in children <16 years of age.

Adolescents: Initial: 25-50 mg/day; increase gradually to 100 mg/day. May administer as divided doses or as a single dose at bedtime.

Note: Once symptoms are controlled, decrease gradually to lowest effective dose. Maintenance dose is usually given at bedtime to reduce daytime sedation.

Administration: OralMay be administered with food to decrease GI distress.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to amoxapine or any component of the formulation; use of MAO inhibitors within past 14 days; acute recovery phase following myocardial infarction

Allergy Considerations

- Tricyclic Antidepressant and Related Compounds Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Amoxapine is not FDA approved for use in patients <16 years of age.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Amoxapine is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. The degree of anticholinergic blockade produced by this agent is moderate relative to other antidepressants.

- Extrapyramidal symptoms: May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is low).

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: May cause orthostatic hypotension (risk is moderate relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is moderate relative to other antidepressants.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk conduction abnormalities with this agent is moderate relative to other antidepressants.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

- Thyroid dysfunction: Use with caution in patients with hyperthyroidism or those receiving thyroid supplementation.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Discontinuation of therapy: Therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

⇧ Geriatric ConsiderationsAmoxapine is not the drug of choice in the elderly. Significant anticholinergic and orthostatic effects can occur and there is a risk for tardive dyskinesia and neuroleptic malignant syndrome.
⇧ Pregnancy Risk FactorC
⇧ LactationEnters breast milk/contraindicated (AAP rates “of concern”)
⇧ Adverse Reactions

>10%:

Central nervous system: Drowsiness

Gastrointestinal: Xerostomia, constipation

1% to 10%:

Central nervous system: Anxiety, ataxia, confusion, dizziness, excitement, headache, insomnia, nervousness, restlessness

Dermatologic: Edema, skin rash

Endocrine: Prolactin levels increased

Gastrointestinal: Nausea

Neuromuscular & skeletal: Tremor, weakness

Ocular: Blurred vision

Miscellaneous: Diaphoresis

<1%: Abdominal pain, abnormal taste, agranulocytosis, allergic reactions, breast enlargement, diarrhea, epigastric distress, extrapyramidal symptoms, flatulence, galactorrhea, hyper-/hypotension, impotence, incoordination, intraocular pressure increased, lacrimation, leukopenia, libido decreased, libido increased, liver enzymes increased, menstrual irregularity, micturition delayed, mydriasis, nasal stuffiness, neuroleptic malignant syndrome, numbness, painful ejaculation, paresthesia, photosensitivity, seizure, SIADH, syncope, tachycardia, tardive dyskinesia, testicular edema, tinnitus, urinary retention, vomiting

Metabolism/Transport Effects **Substrate** of CYP2D6 (major)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Tricyclic Antidepressants may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Agonists: Tricyclic Antidepressants may enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Alpha2-Agonists: Tricyclic Antidepressants may diminish the antihypertensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Altretamine: May enhance the orthostatic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Amphetamines: Tricyclic Antidepressants may enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Beta2-Agonists: Tricyclic Antidepressants may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cinacalcet: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Desmopressin: Tricyclic Antidepressants may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dexmethylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

DULoxetine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Iobenguane I 123: Tricyclic Antidepressants may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May enhance the neurotoxic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Tricyclic Antidepressants may enhance the QTc-prolonging effect of QuiNIDine. QuiNIDine may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

St Johns Wort: May increase the metabolism of Tricyclic Antidepressants. The risk of serotonin syndrome may theoretically be increased. *Risk D: Consider therapy modification*

Sulfonylureas: Cyclic Antidepressants may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Terbinafine: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

TraMADol: Tricyclic Antidepressants may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. *Risk C: Monitor therapy*

Valproic Acid: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Tricyclic Antidepressants may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Grapefruit juice may inhibit the metabolism of some TCAs and clinical toxicity may result.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava.

Test InteractionsIncreased glucose, liver function tests; decreased WBC

Monitoring ParametersMonitor blood pressure and pulse rate prior to and during initial therapy evaluate mental status, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased); monitor weight; ECG in older adults

Reference RangeTherapeutic: Amoxapine: 20-100 ng/mL (SI: 64-319 nmol/L); 8-OH amoxapine: 150-400 ng/mL (SI: 478-1275 nmol/L); both: 200-500 ng/mL (SI: 637-1594 nmol/L)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions (eg, concomitant use with MAO inhibitors can be fatal). Monitor for unusual changes in behavior, clinical worsening, and suicidal ideation especially at time of initiation of therapy and during dosage adjustments. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance; periodically evaluate need for continued use. Caution patients with diabetes; may increase serum glucose levels. Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed; do not increase dose or frequency. It may take several weeks to achieve desired results. Restrict use of alcohol and caffeine; avoid grapefruit juice. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, monitor glucose levels closely; this medication may alter glucose levels. May cause drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, increased appetite, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); or altered sexual drive or ability (reversible). Report persistent CNS effects (eg, confusion, restlessness, anxiety, insomnia, excitation, headache, dizziness, fatigue, impaired coordination); muscle cramping, weakness, tremors, rigidity or alterations in ambulation; visual disturbances; excessive GI symptoms (eg, cramping, constipation, vomiting); or worsening of condition; and suicide ideation. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 25 mg, 50 mg, 100 mg, 150 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Amoxapine)

25 mg (60): $25.99

50 mg (60): $28.99

100 mg (30): $35.99

150 mg (30): $38.99

Mechanism of ActionReduces the reuptake of serotonin and norepinephrine. The metabolite, 7-OH-amoxapine has significant dopamine receptor blocking activity similar to haloperidol.

Pharmacodynamics/Kinetics

Onset of antidepressant effect: Usually occurs after 1-2 weeks, but may require 4-6 weeks

Absorption: Rapid and well absorbed

Distribution: V_d: 0.9-1.2 L/kg; enters breast milk

Protein binding: 80%

Metabolism: Primarily hepatic

Half-life elimination: Parent drug: 11-16 hours; Active metabolite (8-hydroxy): Adults: 30 hours

Time to peak, serum: 1-2 hours

Excretion: Urine (as unchanged drug and metabolites)

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsExtrapyramidal reactions and tardive dyskinesia may occur.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation). Long-term treatment with TCAs, such as amoxapine, increases the risk of caries by reducing salivation and salivary buffer capacity.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution; epinephrine and levonordefrin have been shown to have an increased pressor response in combination with TCAs. Amoxapine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health CommentAmoxapine's metabolite (7-OH-amoxapine) blocks dopamine receptors. Therefore, extrapyramidal side effects noted with antipsychotic agents may also be seen with this antidepressant. May be useful as a third-line agent to treat depression with psychotic features. Generally not recommended for elderly patients.

Index TermsAsendin [DSC]

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International Brand NamesAsendin (ID); Defanyl (FR); Demolox (DK, IN)

Amoxicillin and Clavulanate Potassium

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Augmentin® may be confused with Azulfidine®

Pronunciation(a moks i SIL in & klav yoo LAN ate poe TASS ee um)

U.S. Brand NamesAmoclan; Augmentin ES-600®; Augmentin XR®; Augmentin®

Canadian Brand NamesAlti-Amoxi-Clav; Apo-Amoxi-Clav®; Augmentin®; Clavulin®; Novo-Clavamoxin; ratio-Aclavulanate

Pharmacologic CategoryAntibiotic, Penicillin

Use: Labeled IndicationsTreatment of otitis media, sinusitis, and infections caused by susceptible organisms involving the lower respiratory tract, skin and skin structure, and urinary tract; spectrum same as amoxicillin with additional coverage of beta-lactamase producing *B. catarrhalis*, *H. influenzae*, *N. gonorrhoeae*, and *S. aureus* (not MRSA). The expanded coverage of this combination makes it a useful alternative when amoxicillin resistance is present and patients cannot tolerate alternative treatments.

Use: DentalTreatment of orofacial infections when beta-lactamase-producing staphylococci and beta-lactamase-producing *Bacteroides* are present

Dosing: Adults**Note:** Dose is based on the amoxicillin component; see "Augmentin® Product-Specific Considerations" table.

Susceptible infections: Children >40 kg and Adults: Oral: 250-500 mg every 8 hours or 875 mg every 12 hours

Augmentin® Product-Specific Considerations

Strength	**Form**	**Consideration**
125 mg	CT, S	q8h dosing
	S	For adults having difficulty swallowing tablets, 125 mg/5 mL suspension may be substituted for 500 mg tablet.
200 mg	CT, S	q12h dosing
	CT	Contains phenylalanine
	S	For adults having difficulty swallowing tablets, 200 mg/5 mL suspension may be substituted for 875 mg tablet.
250 mg	CT, S, T	q8h dosing
	CT	Contains phenylalanine
	T	Not for use in patients <40 kg
	CT, T	Tablet and chewable tablet are not interchangeable due to differences in clavulanic acid.
	S	For adults having difficulty swallowing tablets, 250 mg/5 mL suspension may be substituted for 500 mg tablet.
400 mg	CT, S	q12h dosing
	CT	Contains phenylalanine
	S	For adults having difficulty swallowing tablets, 400 mg/5 mL suspension may be substituted for 875 mg tablet.

500 mg	T	q8h or q12h dosing
600 mg	S	q12h dosing
		Contains phenylalanine
		Not for use in adults or children ≥40 kg
		600 mg/5 mL suspension is not equivalent to or interchangeable with 200 mg/5 mL or 400 mg/5 mL due to differences in clavulanic acid.
875 mg	T	q12h dosing; not for use in Cl_{cr} <30 mL/minute
1000 mg	XR	q12h dosing
		Not for use in children <16 years of age
		Not interchangeable with two 500 mg tablets
		Not for use if Cl_{cr} <30 mL/minute or hemodialysis
Legend: CT = chewable tablet, S = suspension, T = tablet, XR = extended release.		

Acute bacterial sinusitis: Oral: Extended release tablet: Two 1000 mg tablets every 12 hours for 10 days

Bite wounds (animal/human): Oral: 875 mg every 12 hours **or** 500 mg every 8 hours

Chronic obstructive pulmonary disease: Oral: 875 mg every 12 hours **or** 500 mg every 8 hours

Diabetic foot: Oral: Extended release tablet: Two 1000 mg tablets every 12 hours for 7-14 days

Diverticulitis, perirectal abscess: Oral: Extended release tablet: Two 1000 mg tablets every 12 hours for 7-10 days

Erysipelas: Oral: 875 mg every 12 hours **or** 500 mg every 8 hours

Febrile neutropenia: Oral: 875 mg every 12 hours

Pneumonia:

Aspiration: Oral: 875 mg every 12 hours

Community-acquired: Oral: Extended release tablet: Two 1000 mg tablets every 12 hours for 7-10 days

Pyelonephritis (acute, uncomplicated): Oral: 875 mg every 12 hours **or** 500 mg every 8 hours

Skin abscess: Oral: 875 mg every 12 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Dose is based on the amoxicillin component; see “Augmentin® Product-Specific Considerations” table.

Susceptible infections: Infants <3 months: Oral: 30 mg/kg/day divided every 12 hours using the 125 mg/5 mL suspension

Lower respiratory tract infections, severe infections, sinusitis: Children ≥3 months and <40 kg: Oral: 45 mg/kg/day divided every 12 hours **or** 40 mg/kg/day divided every 8 hours

Mild-to-moderate infections: Children ≥3 months and <40 kg: Oral: 25 mg/kg/day divided every 12 hours or 20 mg/kg/day divided every 8 hours

Otitis media (Augmentin® ES-600): Children ≥3 months and <40 kg: Oral: 90 mg/kg/day divided every 12 hours for 10 days in children with severe illness and when coverage for β-lactamase positive *H. influenzae* and *M. catarrhalis* is needed.

Children >40 kg: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} <30 mL/minute: Do not use 875 mg tablet or extended release tablets.

Cl_{cr} 10-30 mL/minute: 250-500 mg every 12 hours

Cl_{cr} <10 mL/minute: 250-500 every 24 hours

Hemodialysis: Moderately dialyzable (20% to 50%)

250-500 mg every 24 hours; administer dose during and after dialysis. Do not use extended release tablets.

Peritoneal dialysis: Moderately dialyzable (20% to 50%)

Amoxicillin: Administer 250 mg every 12 hours

Clavulanic acid: Dose for Cl_{cr} <10 mL/minute

Continuous arteriovenous or venovenous hemofiltration effects:

Amoxicillin: ~50 mg of amoxicillin/L of filtrate is removed

Clavulanic acid: Dose for Cl_{cr} <10 mL/minute

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels. Administer with food to decrease stomach upset; shake suspension well before use. Extended release tablets should be administered with food.

Some penicillins (eg, carbenicillin, ticarcillin, and piperacillin) have been shown to inactivate aminoglycosides *in vitro*. This has been observed to a greater extent with tobramycin and gentamicin, while amikacin has shown greater stability against inactivation. Concurrent use of these agents may pose a risk of reduced antibacterial efficacy *in vivo*, particularly in the setting of profound renal impairment. However, definitive clinical evidence is lacking. If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered.

Dietary ConsiderationsMay be taken with meals or on an empty stomach; take with meals to increase absorption and decrease GI intolerance; may mix with milk, formula, or juice. Extended release tablets should be taken with food. Some products contain phenylalanine. If you have phenylketonuria or PKU, avoid use. All dosage forms contain potassium.

Storage

Powder for oral suspension: Store dry powder at room temperature of 25°C (77°F).

Tablet: Store at room temperature of 25°C (77°F).

ReconstitutionReconstitute powder for oral suspension with appropriate amount of water as specified on the bottle. Shake vigorously until suspended. Reconstituted oral suspension should be kept in refrigerator. Discard unused suspension after 10 days. Unit-dose antibiotic oral syringes are stable for 48 hours.

ContraindicationsHypersensitivity to amoxicillin, clavulanic acid, penicillin, or any component of the formulation; history of cholestatic jaundice or hepatic dysfunction with amoxicillin/clavulanate potassium therapy; Augmentin XR™: severe renal impairment (Cl_{cr} <30 mL/minute) and hemodialysis patients

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients. Low incidence of cross-allergy with cephalosporins exists.

- Diarrhea: Incidence of diarrhea is higher than with amoxicillin alone.

- Hepatic effects: Although rare, hepatic dysfunction is more common in elderly and/or males, and occurs more frequently with prolonged treatment, and may occur after therapy is complete.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Infectious mononucleosis: A high percentage of patients with infectious mononucleosis have developed rash during therapy; ampicillin-class antibiotics not recommended in these patients.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Dosage form specific issues:

- Clavulanic acid content: Due to differing content of clavulanic acid, not all formulations are interchangeable.

- Phenylalanine: Some products contain phenylalanine.

Geriatric Considerations Expanded coverage of this combination makes it a useful alternative when amoxicillin resistance is present and patients cannot tolerate alternative treatments; consider renal function. Considered one of the drugs of choice in the outpatient treatment of community-acquired pneumonia in elderly.

Pregnancy Risk Factor B

Pregnancy Considerations Adverse events have not been observed in animal studies; therefore, amoxicillin/clavulanate is classified as pregnancy category B. Both amoxicillin and clavulanic acid cross the placenta. There is no documented increased risk of teratogenic affects caused by amoxicillin/clavulanate. A potential increased risk of necrotizing enterocolitis in the newborn has been noted after maternal use of amoxicillin/clavulanate for preterm labor or premature prolonged rupture of membranes. When used during pregnancy, pharmacokinetic changes have been observed with amoxicillin alone (refer to the Amoxicillin monograph for details).

Lactation Enters breast milk/use caution

Breast-Feeding Considerations Amoxicillin is found in breast milk. The manufacturer recommends that caution be used if administered to breast-feeding women. The use of amoxicillin/clavulanate may be safe while breast-feeding; however, the risk of adverse events in the infant may be increased when compared to the use of amoxicillin alone. The risk of adverse events may be related to maternal dose. Nondose-related effects could include modification of bowel flora and allergic sensitization of the infant.

Pregnancy & Lactation, In-Depth

- Amoxicillin and Clavulanate Potassium in Pregnancy & Lactation

Adverse Reactions

>10%: Gastrointestinal: Diarrhea (3% to 34% incidence varies upon dose and regimen used)

1% to 10%:

Dermatologic: Diaper rash, skin rash, urticaria

Gastrointestinal: Abdominal discomfort, loose stools, nausea, vomiting

Genitourinary: Vaginitis, vaginal mycosis

Miscellaneous: Moniliasis

<1%: Cholestatic jaundice, flatulence, headache, hepatic dysfunction, prothrombin time increased, thrombocytosis

Additional adverse reactions seen with **ampicillin-class antibiotics:** Agitation, agranulocytosis, alkaline phosphatase increased, anaphylaxis, anemia, angioedema, anxiety, behavioral changes, bilirubin increased, black “hairy” tongue, confusion, convulsions, crystalluria, dizziness, enterocolitis, eosinophilia, erythema multiforme, exanthematous pustulosis, exfoliative dermatitis, gastritis, glossitis, hematuria, hemolytic anemia, hemorrhagic colitis, indigestion, insomnia, hyperactivity, interstitial nephritis, leukopenia, mucocutaneous candidiasis, pruritus, pseudomembranous colitis, serum sickness-like reaction, Stevens-Johnson syndrome, stomatitis, transaminases increased, thrombocytopenia, thrombocytopenic purpura, tooth discoloration, toxic epidermal necrolysis

Drug Interactions

Allopurinol: May enhance the potential for allergic or hypersensitivity reactions to Amoxicillin. *Risk C: Monitor therapy*

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Test Interactions May interfere with urinary glucose tests using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution); may inactivate aminoglycosides *in vitro*.

Some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*, leading to a potential underestimation of aminoglycoside serum concentration.

Monitoring Parameters Assess patient at beginning and throughout therapy for infection; with prolonged therapy, monitor renal, hepatic, and hematologic function periodically; monitor for signs of anaphylaxis during first dose

Nursing: Physical Assessment/Monitoring See individual agent for Amoxicillin.

Monitoring: Lab Tests Renal, hepatic, and hematologic function periodically with prolonged therapy. Perform culture and sensitivity testing prior to initiating therapy.

Patient Education See individual agent for Amoxicillin.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Powder for oral suspension: 200: Amoxicillin 200 mg and clavulanate potassium 28.5 mg per 5 mL (50 mL, 75 mL, 100 mL) [contains phenylalanine]; 400: Amoxicillin 400 mg and clavulanate potassium 57 mg per 5 mL (50 mL, 75 mL, 100 mL) [contains phenylalanine]; 600: Amoxicillin 600 mg and clavulanate potassium 42.9 mg per 5 mL (75 mL, 125 mL, 200 mL) [contains phenylalanine]

Amoclan:

200: Amoxicillin 200 mg and clavulanate potassium 28.5 mg per 5 mL (50 mL, 75 mL, 100 mL) [contains phenylalanine 7 mg/5 mL and potassium 0.14 mEq/5 mL; fruit flavor]

400: Amoxicillin 400 mg and clavulanate potassium 57 mg per 5 mL (50 mL, 75 mL, 100 mL) [contains phenylalanine 7 mg/5 mL and potassium 0.29 mEq/5 mL; fruit flavor]

Augmentin®:

125: Amoxicillin 125 mg and clavulanate potassium 31.25 mg per 5 mL (75 mL, 100 mL, 150 mL) [contains potassium 0.16 mEq/5 mL; banana flavor]

200: Amoxicillin 200 mg and clavulanate potassium 28.5 mg per 5 mL (50 mL, 75 mL, 100 mL) [contains phenylalanine 7 mg/5 mL and potassium 0.14 mEq/5 mL; orange flavor] [DSC]

250: Amoxicillin 250 mg and clavulanate potassium 62.5 mg per 5 mL (75 mL, 100 mL, 150 mL) [contains potassium 0.32 mEq/5 mL; orange flavor]

400: Amoxicillin 400 mg and clavulanate potassium 57 mg per 5 mL (50 mL [DSC], 75 mL [DSC], 100 mL) [contains phenylalanine 7 mg/5 mL and potassium 0.29 mEq/5 mL; orange flavor]

Augmentin ES-600®: Amoxicillin 600 mg and clavulanate potassium 42.9 mg per 5 mL (75 mL, 125 mL, 200 mL) [contains phenylalanine 7 mg/5 mL and potassium 0.23 mEq/5 mL; strawberry cream flavor]

Tablet: 250: Amoxicillin 250 mg and clavulanate potassium 125 mg; 500: Amoxicillin 500 mg and clavulanate potassium 125 mg; 875: Amoxicillin 875 mg and clavulanate potassium 125 mg

Augmentin®:

250: Amoxicillin 250 mg and clavulanate potassium 125 mg [contains potassium 0.63 mEq/tablet]

500: Amoxicillin 500 mg and clavulanate potassium 125 mg [contains potassium 0.63 mEq/tablet]

875: Amoxicillin 875 mg and clavulanate potassium 125 mg [contains potassium 0.63 mEq/tablet]

Tablet, chewable: 200: Amoxicillin 200 mg and clavulanate potassium 28.5 mg [contains phenylalanine]; 400: Amoxicillin 400 mg and clavulanate potassium 57 mg [contains phenylalanine]

Augmentin®:

125: Amoxicillin 125 mg and clavulanate potassium 31.25 mg [contains potassium 0.16 mEq/tablet; lemon-lime flavor] [DSC]

200: Amoxicillin 200 mg and clavulanate potassium 28.5 mg [contains phenylalanine 2.1 mg/tablet and potassium 0.14 mEq/tablet; cherry-banana flavor] [DSC]

250: Amoxicillin 250 mg and clavulanate potassium 62.5 mg [contains potassium 0.32 mEq/tablet; lemon-lime flavor]

400: Amoxicillin 400 mg and clavulanate potassium 57 mg [contains phenylalanine 4.2 mg/tablet and potassium 0.29 mEq/tablet; cherry-banana flavor] [DSC]

Tablet, extended release:

Augmentin XR®: Amoxicillin 1000 mg and clavulanate acid 62.5 mg [contains potassium 12.6 mg (0.32 mEq) and sodium 29.3 mg (1.27 mEq) per tablet; packaged in either a 7-day or 10-day package]

Generic AvailableYes: Excludes extended release
ManufacturerGlaxoSmithKline
Pricing: U.S. (www.drugstore.com)

Chewable (Amoxicillin-Pot Clavulanate)

400-57 mg (20): $63.79

Suspension (reconstituted) (Amoxicillin-Pot Clavulanate)

600-42.9 mg/5 mL (75): $35.99

Tablet, 12-hour (Augmentin XR)

1000-62.5 mg (28): $111.14

Tablets (Amoxicillin-Pot Clavulanate)

250-125 mg (30): $116.54

500-125 mg (20): $45.99

875-125 mg (20): $95.97

Tablets (Augmentin)

250-125 mg (30): $118.99

500-125 mg (30): $166.71

875-125 mg (20): $145.99

Mechanism of ActionClavulanic acid binds and inhibits beta-lactamases that inactivate amoxicillin resulting in amoxicillin having an expanded spectrum of activity. Amoxicillin inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/KineticsAmoxicillin pharmacokinetics are not affected by clavulanic acid.

Amoxicillin: See Amoxicillin monograph.

Clavulanic acid:

Protein binding: ~25%

Metabolism: Hepatic

Half-life elimination: 1 hour

Time to peak: 1 hour

Excretion: Urine (30% to 40% as unchanged drug)

Related Information

- Amoxicillin
- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Neutropenic Fever Guidelines

Pharmacotherapy PearlsTwo 250 mg tablets are not equivalent to a 500 mg tablet (both tablet sizes contain equivalent clavulanate). Two 500 mg tablets are not equivalent to a single 1000 mg extended release tablet.

Dental Health Professional ConsiderationsIn maxillary sinus, anterior nasal cavity, and deep neck infections, beta-lactamase-producing staphylococci and beta-lactamase-producing *Bacteroides* usually are present. In these situations, antibiotics that resist the beta-lactamase enzyme are indicated. Amoxicillin and clavulanic acid is administered orally for moderate infections. Ampicillin sodium and sulbactam sodium (Unasyn®) is administered parenterally for more severe infections.

Dental Health: Effects on Dental TreatmentProlonged use of penicillins may lead to development of oral candidiasis (see Dental Comment)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusPenicillins have been reported to cause apprehension, illusions, agitation, insomnia, depersonalization, and encephalopathy

Mental Health: Effects on Psychiatric TreatmentDisulfiram may increase amoxicillin levels

Index TermsAmoxicillin and Clavulanic Acid; Clavulanic Acid and Amoxicillin

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International Brand Names Acarbixin (MX); Aclam (ID); Ambilan (PE); AMK (TH); Amobay Cl (MX); Amocla (KP); Amocla Duo (KP); Amoclan (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Amoclav (DE); Amoksiclav (TH); Amoksiklav (CL, PL); Amolanic (KP); Amolanic Duo (KP); Amoxi Plus (PY); Amoxiclav (MX); Amoxiclav-BID (MX); Amoxiclav-Teva (IL); Amoxsiklav Forte (TH); Amoxxlin (KP); Amoxyclav (IL); Auclatin Duo Dry Syrup (KP); Augamox (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); AugMaxcil (ZA); Augmentan (DE); Augmentin (AE, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CR, CY, CZ, DE, DK, DO, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PK, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SR, SV, SY, TH, TN, TR, TT, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Augmentine (ES); Augmex (PH); Augpen (TH); Augucillin Duo (KP); Augurcin (PH); Bactiv (PH); Bactoclav (PH); Bioclavid (AE, BH, CY, DE, DK, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PH, QA, SA, SE, SY, YE); Bioclavid Forte (PH); Cavumox (MY, TH); Cax (PH); Clacillin Duo Dry Syrup (KP); Clamax (KP); Clamentin (ZA); Clamohexal (AU); Clamohexal Duo (AU); Clamonex (SG); Clamovid (HK, MY, SG); Clamoxin (MX); Clamoxyl (AU); Clamoxyl Duo 400 (AU); Clamoxyl DuoForte (AU); Clavamox (DE, ID, IN); Clavant (MX); Clavar (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Claventin (IL); Clavinex (CN, EC); Clavipen (MX); Clavodar (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Clavoxil (BR); Clavoxine (EC); Clavucyd (MX); Clavulin (BF, BJ, CI, CO, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MX, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Clavulin Duo Forte (AU); Clavulox Duo (AR, PY); Clavumox (DE, PE, ZA); Clavuser (MX); Cramon Duo (KP); Curam (AU, CO, CR, DO, GT, HK, MY, NI, PA, PE, PL, SG, SV, TH, TW); Danoclav (ID); Darzitil Plus (AR); E-Moxclav (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Enhancin (SG); Exten (PH); Fleming (HK); Forcid (PL); Fugentin (SG); Fullicilina Plus (AR); Gimaclav (MX); Hibiotic (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Klamonex (KP); Klavic (PH); Klavocin (PL); Kmoxilin (KP); Lactamox (KP); Lansiclav (ID); Moxiclav (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SG, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Moxicle (KP, TH); Moxlin (MX); Natravox (PH); Novamox (BR); Nufaclav (ID); Quali-Mentin (HK); Ramoclav (PL); Ranclav (TH, ZA); Riclasip (MX); Servamox (MX); Sinufin (MX); Spektramox (SE); Sullivan (PH); Suplentin (PH); Synermox (NZ); Taromentin (PL); Velamox CL (PE); Vestaclav (MY); Viaclav (ID); Vulamox (CO, ID)

Amoxicillin

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Amoxicillin may be confused with amoxapine, Amoxil®, Atarax®

Amoxil® may be confused with amoxapine, amoxicillin

International issues:

Fisamox® [Australia] may be confused with Fosamax® which is a brand name for alendronate in the U.S.

Fisamox® [Australia] may be confused with Vigamox™ which is a brand name for moxifloxacin in the U.S.

Pronunciation(a moks i SIL in)

U.S. Brand NamesAmoxil®

Canadian Brand NamesApo-Amoxi®; Gen-Amoxicillin; Lin-Amox; Novamoxin®; Nu-Amoxi; PHL-Amoxicillin; PMS-Amoxicillin

Pharmacologic CategoryAntibiotic, Penicillin

Use: Labeled IndicationsTreatment of otitis media, sinusitis, and infections caused by susceptible organisms involving the respiratory tract, skin, and urinary tract; prophylaxis of infective endocarditis in patients undergoing surgical or dental procedures; as part of a multidrug regimen for *H. pylori* eradication

Use: Unlabeled/InvestigationalPostexposure prophylaxis for anthrax exposure with documented susceptible organisms

Use: DentalAntibiotic for standard prophylactic regimen for dental patients who are at risk for infective endocarditis; prophylaxis in total joint replacement patients undergoing dental procedures which produce bacteremia; antibiotic used to treat orofacial infections

Dosing: Adults

Usual dosage range: Oral: 250-500 mg every 8 hours or 500-875 mg twice daily

Anthrax exposure (CDC guidelines): Oral: **Note:** Postexposure prophylaxis in pregnant or nursing women only with documented susceptible organisms: 500 mg every 8 hours

Ear, nose, throat, genitourinary tract, or skin/skin structure infections:

Mild to moderate: Oral: 500 mg every 12 hours **or** 250 mg every 8 hours

Severe: Oral: 875 mg every 12 hours **or** 500 mg every 8 hours

***Helicobacter pylori*eradication:** Oral: 1000 mg twice daily; requires combination therapy with at least one other antibiotic and an acid-suppressing agent (proton pump inhibitor or H_2 blocker)

Lower respiratory tract infections: Oral: 875 mg every 12 hours **or** 500 mg every 8 hours

Lyme disease: Oral: 500 mg every 6-8 hours (depending on size of patient) for 21-30 days

Prophylaxis against infective endocarditis: Oral: 2 g 30-60 minutes before procedure. **Note:** American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur. As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Prophylaxis in total joint replacement patients undergoing dental procedures which produce bacteremia: 2 g 1 hour prior to procedure

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Usual dosage range:

Children ≤3 months: Oral: 20-30 mg/kg/day divided every 12 hours

Children >3 months and <40 kg: Oral: 20-50 mg/kg/day in divided doses every 8-12 hours

Acute otitis media: Children >3 months and <40 kg: Oral: 80-90 mg/kg/day divided every 12 hours

Anthrax exposure (CDC guidelines): Children >3 months and <40 kg: Oral: **Note:** Postexposure prophylaxis only with documented susceptible organisms: 80 mg/kg/day in divided doses every 8 hours (maximum: 500 mg/dose)

Community-acquired pneumonia:

4 months to <5 years: 80-100 mg/kg/day divided every 8 hours

5-15 years: 100 mg/kg/day divided every 8 hours; **Note:** Treatment with a macrolide or doxycycline (if age >8 years) is preferred due to higher prevalence of atypical pathogens in this age group

Ear, nose, throat, genitourinary tract, or skin/skin structure infections: Children >3 months and <40 kg: Oral:

Mild to moderate: 25 mg/kg/day in divided doses every 12 hours **or** 20 mg/kg/day in divided doses every 8 hours

Severe: 45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours

Lower respiratory tract infections: Children >3 months and <40 kg: Oral: 45 mg/kg/day in divided doses every 12 hours **or** 40 mg/kg/day in divided doses every 8 hours

Lyme disease: Children >3 months and <40 kg: Oral: 25-50 mg/kg/day divided every 8 hours (maximum: 500 mg)

Prophylaxis against infective endocarditis: Children >3 months and <40 kg: Oral: 50 mg/kg 1 hour before procedure. **Note:** American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur. As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Dosing: Renal Impairment

The 875 mg tablet should not be used in patients with Cl_{cr} <30 mL/minute.

Cl_{cr} 10-30 mL/minute: 250-500 mg every 12 hours

Cl_{cr} <10 mL/minute: 250-500 mg every 24 hours

Moderately dialyzable (20% to 50%) by hemodialysis or peritoneal dialysis; approximately 50 mg of amoxicillin per liter of filtrate is removed by continuous arteriovenous or venovenous hemofiltration. Dose as per Cl_{cr} <10 mL/minute guidelines.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: Oral Administer around-the-clock to promote less variation in peak and trough serum levels. The appropriate amount of suspension may be mixed with formula, milk, fruit juice, water, ginger ale, or cold drinks; administer dose immediately after mixing.

Some penicillins (eg, carbenicillin, ticarcillin, and piperacillin) have been shown to inactivate aminoglycosides *in vitro*. This has been observed to a greater extent with tobramycin and gentamicin, while amikacin has shown greater stability against inactivation. Concurrent use of these agents may pose a risk of reduced antibacterial efficacy *in vivo*, particularly in the setting of profound renal impairment. However, definitive clinical evidence is lacking. If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered.

Dietary Considerations May be taken with food. Amoxil® chewable contains phenylalanine 1.82 mg per 200 mg tablet, phenylalanine 3.64 mg per 400 mg tablet.

Storage Amoxil®: Oral suspension remains stable for 14 days at room temperature or if refrigerated (refrigeration preferred). Unit-dose antibiotic oral syringes are stable for 48 hours.

Contraindications Hypersensitivity to amoxicillin, penicillin, or any component of the formulation

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Infectious mononucleosis: A high percentage of patients with infectious mononucleosis have developed rash during therapy; ampicillin-class antibiotics not recommended in these patients.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Dosage form specific issues:

- Phenylalanine: Chewable tablets contain phenylalanine.

Geriatric Considerations Resistance to amoxicillin has been a problem in patients on frequent antibiotics or in nursing homes. Alternative antibiotics may be necessary in these populations. Consider renal function.

Pregnancy Risk Factor B

Pregnancy Considerations Adverse events have not been observed in animal studies; therefore, amoxicillin is classified as pregnancy category B. There is no documented increased risk of adverse pregnancy outcome or teratogenic affects caused by amoxicillin. It is the drug of choice for the treatment of chlamydial infections in pregnancy and for anthrax prophylaxis when penicillin susceptibility is documented.

Due to pregnancy-induced physiologic changes, amoxicillin clearance is increased during pregnancy resulting in lower concentrations and smaller AUCs. Oral ampicillin-class antibiotics are poorly-absorbed during labor.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsVery small amounts of amoxicillin are excreted in breast milk. The manufacturer recommends that caution be exercised when administering amoxicillin to nursing women. The AAP considers amoxicillin to be “usually compatible with breastfeeding." Nondose-related effects could include modification of bowel flora and allergic sensitization of the infant.

Pregnancy & Lactation, In-Depth

- Amoxicillin in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Hyperactivity, agitation, anxiety, insomnia, confusion, convulsions, behavioral changes, dizziness

Dermatologic: Acute exanthematous pustulosis, erythematous maculopapular rash, erythema multiforme, mucocutaneous candidiasis, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, hypersensitivity vasculitis, urticaria

Gastrointestinal: Black hairy tongue, nausea, diarrhea, hemorrhagic colitis, pseudomembranous colitis, tooth discoloration (brown, yellow, or gray; rare), vomiting

Hematologic: Anemia, hemolytic anemia, thrombocytopenia, thrombocytopenia purpura, eosinophilia, leukopenia, agranulocytosis

Hepatic: AST and ALT increased, cholestatic jaundice, hepatic cholestasis, acute cytolytic hepatitis

Renal: Crystalluria

Drug Interactions

Allopurinol: May enhance the potential for allergic or hypersensitivity reactions to Amoxicillin. *Risk C: Monitor therapy*

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Test InteractionsMay interfere with urinary glucose tests using cupric sulfate (Benedict's solution, Clinitest®)

Some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*, leading to a potential underestimation of aminoglycoside serum concentration.

Monitoring ParametersWith prolonged therapy, monitor renal, hepatic, and hematologic function periodically; assess patient at beginning and throughout therapy for infection; monitor for signs of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringAssess culture and sensitivity report and patient allergy history prior to starting therapy. Assess potential for interactions with other medications patient may be taking. Caution patients with diabetes about altered response to Clinitest®. Assess for therapeutic effectiveness and adverse reactions (eg, opportunistic infection [fever, chills, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge, fatigue] - see Adverse Reactions and Overdose/Toxicology). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity testing prior to initiating therapy.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take entire prescription, even if you are feeling better. Take at equal intervals around-the-clock. May be taken with milk, juice, or food. If you have diabetes, drug may cause false test results with Clinitest® urine glucose monitoring; use of another type of glucose monitoring is preferable. May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report rash; unusual or persistent diarrhea; vaginal itching, burning, or pain; unresolved vomiting or constipation; fever or chills; abdominal pain; jaundice; unusual bruising or bleeding; opportunistic infection [fever, chills, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge, fatigue]; or if condition being treated worsens or does not improve by the time prescription is completed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule: 250 mg, 500 mg

Amoxil®: 500 mg

Powder for oral suspension: 125 mg/5 mL (80 mL, 100 mL, 150 mL); 200 mg/5 mL (50 mL, 75 mL, 100 mL); 250 mg/5 mL (80 mL, 100 mL, 150 mL); 400 mg/5 mL (50 mL, 75 mL, 100 mL)

Amoxil®: 200 mg/5 mL (50 mL, 75 mL, 100 mL) [contains sodium benzoate; bubble gum flavor] [DSC]; 250 mg/5 mL (100 mL, 150 mL) [contains sodium benzoate; bubble gum flavor]; 400 mg/5 mL (5 mL [DSC], 50 mL [DSC], 75 mL [DSC], 100 mL) [contains sodium benzoate; bubble gum flavor]

Powder for oral suspension [drops]:

Amoxil®: 50 mg/mL (30 mL) [contains sodium benzoate; bubble gum flavor]

Tablet: 500 mg, 875 mg

Amoxil®: 500 mg, 875 mg [DSC]

Tablet, chewable: 125 mg, 200 mg, 250 mg, 400 mg

Amoxil®: 200 mg [contains phenylalanine 1.82 mg/tablet; cherry banana peppermint flavor] [DSC]; 400 mg [contains phenylalanine 3.64 mg/tablet; cherry banana peppermint flavor] [DSC]

Generic AvailableYes: Excludes drops
Pricing: U.S. (www.drugstore.com)

Capsules (Amoxicillin)

250 mg (90): $15.00

500 mg (30): $12.99

Capsules (Amoxil)

500 mg (30): $15.99

Chewable (Amoxicillin)

125 mg (21): $11.99

250 mg (30): $13.99

400 mg (20): $10.91

Chewable (Amoxil)

400 mg (20): $13.99

Suspension (reconstituted) (Amoxicillin)

250 mg/5 mL (150): $12.99

Suspension (reconstituted) (Amoxil)

50 mg/mL (30): $8.99

200 mg/5 mL (100): $11.99

250 mg/5 mL (100): $8.99

250 mg/5 mL (150): $8.99

400 mg/5 mL (50): $8.99

400 mg/5 mL (75): $9.99

400 mg/5 mL (100): $11.99

Suspension (reconstituted) (Trimox)

125 mg/5 mL (100): $11.99

250 mg/5 mL (80): $11.99

Tablets (Amoxicillin)

500 mg (100): $49.99

875 mg (30): $24.99

Tablets (Amoxil)

500 mg (21): $12.99

875 mg (21): $21.99

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.
Pharmacodynamics/Kinetics

Absorption: Oral: Rapid and nearly complete; food does not interfere

Distribution: Widely to most body fluids and bone; poor penetration into cells, eyes, and across normal meninges

Pleural fluids, lungs, and peritoneal fluid; high urine concentrations are attained; also into synovial fluid, liver, prostate, muscle, and gallbladder; penetrates into middle ear effusions, maxillary sinus secretions, tonsils, sputum, and bronchial secretions

CSF:blood level ratio: Normal meninges: <1%; Inflamed meninges: 8% to 90%

Protein binding: 17% to 20%

Metabolism: Partially hepatic

Half-life elimination:

Neonates, full-term: 3.7 hours

Infants and Children: 1-2 hours

Adults: Normal renal function: 0.7-1.4 hours

Cl_{cr} <10 mL/minute: 7-21 hours

Time to peak: Capsule: 2 hours; Suspension: 1 hour

Excretion: Urine (80% as unchanged drug); lower in neonates

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Prevention of Infective Endocarditis
- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentProlonged use of penicillins may lead to development of oral candidiasis

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusRarely large doses may produce confusion, hallucinations, and depression; penicillins have been reported to cause apprehension, illusions, agitation, insomnia, depersonalization, and encephalopathy

Mental Health: Effects on Psychiatric TreatmentDisulfiram may increase amoxicillin levels

Cardiovascular ConsiderationsFor the prevention of bacterial endocarditis, amoxicillin 2 g orally can be given 1 hour before, in the absence of a contraindication, for a dental, oral, respiratory tract, or esophageal procedure.

Index Terms*p*-Hydroxyampicillin; Amoxicillin Trihydrate; Amoxycillin

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International Brand NamesAbdimox (ID); Acilina (PY); Acimox (MX); Adbiotin (CO); Alfamox (IT); Almodan (GB); Almorsan (AR); Alphamox (AU); Amagesen Solutab (DE); Amelox (PH); Amicil (MX); Amimox (SE); Amobay (MX); Amoclave (ES); Amoclen (CZ); Amodex (FR); Amoflux (BR); Amohexal (AU); Amolin (JP); Amoling (CL); Amonex (KP); Amosine (ID); Amotaks (PL); Amox (AE, BH, CY, EG, IL, IQ, IR, IT, JO, KW, LB, LY, OM, QA, SA, SY, YE); Amoxa (HK); Amoxal (CO, VE); Amoxapen (BB, BM, BS, BZ, GY, HK, JM, NL, SG, SR, TT); Amoxcil (CL); Amoxcillin (TH); Amoxi (IL); Amoxi TO (TH); Amoxi-basan (DE); Amoxicap (PK); Amoxicilina (CO, EC); Amoxicilline (PL); Amoxiclin (PE); Amoxidal (AR, UY); Amoxidin (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Amoxifur (MX); Amoxihexal (DE); Amoxil (AE, AU, BB, BF, BH, BJ, BM, BR, BS, BZ, CI, CY, EG, ET, GB, GH, GM, GN, GR, GY, ID, IE, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NZ, OM, PE, PL, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Amoxil Duo (AU); Amoxillin (IL, IT); Amoxin (FI); Amoxinova (MX); Amoxipen (IT); Amoxipenil (CN); Amoxisol (MX); Amoxivan (IN); Amoxivet (MX); Amoxsan (ID); Amoxsan Forte (ID); Amoxy-diolan (DE); Amoxycillin (PL); Amoxypen (DE, PE); Apo-Amoxi (MY, PL); Aroxin (SG); Azillin (CH); Bacihexal (PH); Bactamox (VE); Bactox (EE); Bactox Ge (FR); Beamoxy (MY); Bimox (CO); Bimxan (MX); Bintamox (ID); Biotamoxal (AR); Bioxyllin (ID); Bristamox (EC, FR); Cilamox (AU, PH); Clamoxyl (AT, AU, BB, BE, BM, BS, BZ, CH, FR, GY, JM, JP, NL, PE, PT, SR, TT); Dimopen (MX); Duomox (BG, HN, PL); Edamox (HK); Efpinex (JP); Ethimox (ID); Farconcil (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Fisamox (AU); Flemoxin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Flemoxine Ge (FR); Flubiotic (ES); Foxolin (KP); Fullcilina (AR); Gexcil (PH); Gimalxina (MX); Gomcillin (KP); Grinsul (AR); Grunamox (EC, PL); Hamoxillin (HK); Hiconcil (BE, FR, ID, NL, PL); Hidramox (MX); Hipen (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Ibiamox (AE, AU, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, TH, YE); Ikamoxil (ID); Imacillin (DK, NO, SE); Imadrax (DK); Imaxilin (CO); Intermox (PH); Isimoxin (IT); Izoltil (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Jutamox (DE); Kamoxin (TH); Ladoxillin (PH); Lamoxy (IN); Magnimox (PE); Maxamox (AU, NZ); Maxcil (ZA); Medimox (ID); Meixil (TH); Mopen (IT); Mox (IN); Moxacin (AU, NZ); Moxarin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Moxilen (BF, BJ, CI, ET, GH, GM, GN, HK, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SG, SL, SN, TN, TW, TZ, UG, ZA, ZM, ZW); Moxitab (TH); Moxlin (NZ); Moxtid (ID); Moxylin (EC); Moxypen (IL, ZA); Moxyvit (IL); Neogram (CO); Novabritine (BE); Novamox (PH, PL); Novoxil (BR); Ospamox (AE, AT, BG, BH, CY, DE, EG, HK, ID, IL, IQ, IR, JO, KW, LB, LY, MY, NZ, OM, PE, PL, PT, QA, SA, SY, UY, YE); Pamocil (IT); Pamoxin (KP); Pasetocin (JP); Penamox (MX, NZ, PE); Penbiosyn (PH); Piramox (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Polymox (MX); Pondnoxcill (TH); Promox (PH); Rancil (TH); Ranmoxy (ZA); Ranoxil (TH); Ranoxyl (MY); Robamox (ID); Sawacillin (JP); Sawamezin (JP); Servamox (TW); Setmoxil (HK); Shamoxil (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Sia-mox (TH); Simoxil (IT); Solciclina (MX); Solpenox (ID); Sterimox (PH);

Teramoxyl (PH); Trifamox (AR, PY); Trimox (TH); Vastamox (PH); Velamox (PE); Vistrep (PH); Widecillin (ID); Winpen (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Xalyn-Or (MX); Xazexy (PH); Xiltrop (ID); Zamox (CO); Zamoxil (MY); Zerrsox (PH); Zimox (IT)

Amphotericin B (Conventional)

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Medication Safety Issues

Safety issues:

Conventional amphotericin formulations (Amphocin®, Fungizone®) may be confused with lipid-based formulations (AmBisome®, Abelcet®, Amphotec®).

Large overdoses have occurred when conventional formulations were dispensed inadvertently for lipid-based products. Single daily doses of conventional amphotericin formulation never exceed 1.5 mg/kg.

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (intrathecal administration) among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(am foe TER i sin bee con VEN sha nal)

U.S. Brand NamesAmphocin® [DSC]

Canadian Brand NamesFungizone®

Pharmacologic CategoryAntifungal Agent, Parenteral

Use: Labeled IndicationsTreatment of severe systemic and central nervous system infections caused by susceptible fungi such as *Candida* species, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Aspergillus* species, *Blastomyces dermatitidis*, *Torulopsis glabrata*, and *Coccidioides immitis*; fungal peritonitis; irrigant for bladder fungal infections; used in fungal infection in patients with bone marrow transplantation, amebic meningoencephalitis, ocular aspergillosis (intraocular injection), candidal cystitis (bladder irrigation), chemoprophylaxis (low-dose I.V.), immunocompromised patients at risk of aspergillosis (intranasal/nebulized), refractory meningitis (intrathecal), coccidioidal arthritis (intra-articular/I.M.).

Low-dose amphotericin B has been administered after bone marrow transplantation to reduce the risk of invasive fungal disease.

Dosing: Adults

Note: Premedication: For patients who experience infusion-related immediate reactions, premedicate with the following drugs 30-60 minutes prior to drug administration: NSAID (with or without diphenhydramine) **or** acetaminophen with diphenhydramine **or** hydrocortisone 50-100 mg. If the patient experiences rigors during the infusion, meperidine may be administered.

Test dose: I.V.: 1 mg infused over 20-30 minutes. Many clinicians believe a test dose is unnecessary.

Aspergillosis, disseminated: I.V.: 0.6-0.7 mg/kg/day for 3-6 months

Bone marrow transplantation (prophylaxis): I.V.: Low-dose amphotericin B 0.1-0.25 mg/kg/day has been administered after bone marrow transplantation to reduce the risk of invasive fungal disease.

Candidemia (neutropenic or non-neutropenic): I.V.: 0.6-1 mg/kg/day until 14 days after last positive blood culture and resolution of signs and symptoms

Candidiasis, chronic, disseminated: I.V.: 0.6-0.7 mg/kg/day for 3-6 months and resolution of radiologic lesions

Cystitis (Candidal): Bladder irrigation: Irrigate with 50 mcg/mL solution instilled periodically or continuously for 5-10 days or until cultures are clear.

Dematiaceous fungi: I.V.: 0.7 mg/kg/day in combination with an azole

Endocarditis: I.V.: 0.6-1 mg/kg/day (with or without flucytosine) for 1 week, then 0.8 mg/kg/day every other day for 6-8 weeks postoperatively

Endophthalmitis, fungal:

Intravitreal (unlabeled): 10 mcg in 0.1 mL (in conjunction with systemic therapy)

I.V.: 0.7-1 mg/kg/day (with or without flucytosine) for at least 4 weeks

Esophagitis: I.V.: 0.3-0.7 mg/kg/day for 14-21 after clinical improvement

Histoplasmosis: Chronic, severe pulmonary or disseminated: I.V.: 0.5-1 mg/kg/day for 7 days, then 0.8 mg/kg every other day (or 3 times/week) until total dose of 10-15 mg/kg; may continue itraconazole as suppressive therapy (lifelong for immunocompromised patients)

Meningitis:

Candidal: I.V.: 0.7-1 mg/kg/day (with or without flucytosine) for at least 4 weeks

Cryptococcal or Coccidioides: I.T.: Initial: 25-300 mcg every 48-72 hours; increase to 500 mcg to 1 mg as tolerated; maximum total dose: 15 mg has been suggested

Histoplasma: I.V.: 0.5-1 mg/kg/day for 7 days, then 0.8 mg/kg every other day (or 3 times/week) for 3 months total duration; follow with fluconazole suppressive therapy for up to 12 months

Meningoencephalitis, cryptococcal: I.V.:

HIV positive: 0.7-1 mg/kg/day (plus flucytosine 100 mg/kg/day) for 2 weeks, then change to oral fluconazole for at least 10 weeks; alternatively, amphotericin and flucytosine may be continued uninterrupted for 6-10 weeks

HIV negative: 0.5-0.7 mg/kg/day (plus flucytosine) for 2 weeks

Osteomyelitis: Candidal: I.V.: 0.5-1 mg/kg/day for 6-10 weeks

Penicillium marneffei: I.V.: 0.6 mg/kg/day for 2 weeks

Pneumonia: Cryptococcal (mild to moderate): I.V.:

HIV positive: 0.5-1 mg/kg/day

HIV negative: 0.5-0.7 mg/kg/day (plus flucytosine) for 2 weeks

Sporotrichosis: Pulmonary, meningeal, osteoarticular or disseminated: I.V.: Total dose of 1-2 g, then change to oral itraconazole or fluconazole for suppressive therapy

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Note: Premedication: For patients who experience infusion-related immediate reactions, premedicate with the following drugs 30-60 minutes prior to drug administration: NSAID (with or without diphenhydramine) **or** acetaminophen with diphenhydramine **or** hydrocortisone 50-100 mg. If the patient experiences rigors during the infusion, meperidine may be administered.

Test dose: I.V.: Infants and Children: 0.1 mg/kg/dose to a maximum of 1 mg; infuse over 30-60 minutes. Many clinicians believe a test dose is unnecessary.

Susceptible fungal infections: I.V.: Infants and Children: Maintenance dose: 0.25-1 mg/kg/day given once daily; infuse over 2-6 hours. Once therapy has been established, amphotericin B can be administered on an every-other-day basis at 1-1.5 mg/kg/dose; cumulative dose: 1.5-2 g over 6-10 weeks

Note: Duration of therapy varies with nature of infection: Usual duration is 4-12 weeks or cumulative dose of 1-4 g.

Meningitis, coccidioidal or cryptococcal: I.T.: Children: 25-100 mcg every 48-72 hours; increase to 500 mcg as tolerated

Dosing: Renal Impairment

If renal dysfunction is due to the drug, the daily total can be decreased by 50% or the dose can be given every other day. I.V. therapy may take several months.

Poorly dialyzed; no supplemental dose is necessary when using hemo- or peritoneal dialysis or continuous renal replacement therapy (CRRT).

Administration in dialysate: 1-2 mg/L of peritoneal dialysis fluid either with or without low-dose I.V. amphotericin B (a total dose of 2-10 mg/kg given over 7-14 days).

Administration: I.V.May be infused over 4-6 hours. For a patient who experiences chills, fever, hypotension, nausea, or other nonanaphylactic infusion-related reactions, premedicate with the following drugs 30-60 minutes prior to drug administration: A nonsteroidal (eg, ibuprofen, choline magnesium trisalicylate) with or without diphenhydramine **or** acetaminophen with diphenhydramine **or** hydrocortisone 50-100 mg. If the patient experiences rigors during the infusion, meperidine may be administered. Bolus infusion of normal saline immediately preceding, or immediately preceding and following amphotericin B may reduce drug-induced nephrotoxicity. Risk of nephrotoxicity increases with amphotericin B doses >1 mg/kg/day. Infusion of admixtures more concentrated than 0.25 mg/mL should be limited to patients absolutely requiring volume contraction.

Administration: I.V. DetailPrecipitate may form in ionic dialysate solutions.

pH: 5.7 (100 mg/L in D_5W)

StorageStore intact vials under refrigeration; protect from light. Reconstituted vials are stable, protected from light, for 24 hours at room temperature and 1 week when refrigerated. Parenteral admixtures are stable, protected from light, for 24 hours at room temperature and 2 days under refrigeration. Short-term exposure (<24 hours) to light during I.V. infusion does **not** appreciably affect potency.

ReconstitutionAdd 10 mL of SWFI (without a bacteriostatic agent) to each vial of amphotericin B. Further dilute with 250-500 mL D_5W; final concentration should not exceed 0.1 mg/mL (peripheral infusion) or 0.25 mg/mL (central infusion).

Compatibility

Solution compatibility:

Compatible: Heparin sodium, hydrocortisone, sodium bicarbonate.

Incompatible: Ampicillin, calcium gluconate, carbenicillin, cimetidine, dopamine, gentamicin, lidocaine, potassium chloride, sodium chloride, tetracycline, verapamil.

ContraindicationsHypersensitivity to amphotericin or any component of the formulation

Allergy Considerations

- Amphotericin Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis: Has been reported with amphotericin B-containing drugs; facilities for cardiopulmonary resuscitation should be available during administration due to the possibility of anaphylactic reaction. If severe respiratory distress occurs, the infusion should be immediately discontinued; during the initial dosing, the drug should be administered under close clinical observation.

- Infusion reactions: Acute reactions (including fever and chills) may occur 1-3 hours after starting an intravenous infusion. These reactions are usually more common with the first few doses and generally diminish with subsequent doses.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Nephrotoxic drugs: Avoid use with other nephrotoxic drugs; drug-induced renal toxicity usually improves with interrupting therapy, decreasing dosage, or increasing dosing interval.

Special populations:

- Neutropenic patients: Pulmonary reactions may occur in neutropenic patients receiving leukocyte transfusions; separation of the infusions as much as possible is advised.

Geriatric ConsiderationsThe pharmacokinetics and dosing of amphotericin have not been studied in elderly. It appears that use is similar to young adults; caution should be exercised and renal function and desired effect monitored closely.

Pregnancy Risk FactorB

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions

Systemic:

>10%:

Cardiovascular: Hypotension, tachypnea

Central nervous system: Fever, chills, headache (less frequent with I.T.), malaise

Endocrine & metabolic: Hypokalemia, hypomagnesemia

Gastrointestinal: Anorexia, nausea (less frequent with I.T.), vomiting (less frequent with I.T.), diarrhea, heartburn, cramping epigastric pain

Hematologic: Normochromic-normocytic anemia

Local: Pain at injection site with or without phlebitis or thrombophlebitis (incidence may increase with peripheral infusion of admixtures)

Neuromuscular & skeletal: Generalized pain, including muscle and joint pains (less frequent with I.T.)

Renal: Decreased renal function and renal function abnormalities including azotemia, renal tubular acidosis, nephrocalcinosis (>0.1 mg/mL)

1% to 10%:

Cardiovascular: Hypertension, flushing

Central nervous system: Delirium, arachnoiditis, pain along lumbar nerves (especially I.T. therapy)

Genitourinary: Urinary retention

Hematologic: Leukocytosis

Neuromuscular & skeletal: Paresthesia (especially with I.T. therapy)

<1% (Limited to important or life-threatening): Acute liver failure, agranulocytosis, anuria, bone marrow suppression, cardiac arrest, coagulation defects, convulsions, dyspnea, hearing loss, leukopenia, maculopapular rash, renal failure, renal tubular acidosis, thrombocytopenia, vision changes

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Aminoglycosides: Amphotericin B may enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Amphotericin B may enhance the nephrotoxic effect of Colistimethate. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

CycloSPORINE: Amphotericin B may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Amphotericin B may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Test InteractionsIncreased BUN (S), serum creatinine, alkaline phosphate, bilirubin; decreased magnesium, potassium (S)

Monitoring ParametersRenal function (monitor frequently during therapy), electrolytes (especially potassium and magnesium), liver function tests, temperature, PT/PTT, CBC; monitor input and output; monitor for signs of hypokalemia (muscle weakness, cramping, drowsiness, ECG changes, etc)

Reference RangeTherapeutic: 1-2 mcg/mL (SI: 1-2.2 µmol/L)

Nursing: Physical Assessment/MonitoringAssess culture and sensitivity report and patient's previous exposure to amphotericin B prior to starting therapy. Assess potential for interactions with other medications patient may be taking (eg, other nephrotoxic drugs). See Administration for specific infusion directions and premedication recommendations prior to administering first dose. Patient should be monitored closely for infusion-related reactions (eg, anaphylaxis, chills, fever, nausea, vomiting, rigors, hypotension, acute respiratory distress) and cardiopulmonary resuscitation should be available. If acute respiratory distress occurs, infusion should be stopped and prescriber notified. Assess results of laboratory tests, therapeutic effectiveness, and adverse response frequently during therapy. Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsBUN and serum creatinine levels should be determined every other day when therapy is increased and at least weekly thereafter. Monitor serum electrolytes (especially potassium and magnesium), liver function, and CBC. Perform culture and sensitivity testing prior to initiating therapy.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. I.V.: You will be monitored closely during and after infusion; report immediately any pain or swelling at infusion site, chills, nausea, chest pain, swelling of face or mouth, difficulty breathing, muscle cramping, acute anxiety, or other infusion reactions. Take entire prescription, even if you are feeling better. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause nausea, vomiting, or anorexia (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); generalized muscle or joint pain (consult prescriber for approved analgesic); or hypotension (use caution when rising from sitting or lying position or when climbing stairs). Report severe muscle cramping or weakness; chest pain or palpitations; CNS disturbances; skin rash; change in urinary patterns or difficulty voiding; black stool; unusual bruising or bleeding; or pain, redness, or swelling at infusion site. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution, as desoxycholate: 50 mg

Amphocin®: 50 mg [DSC]

Generic AvailableYes

Mechanism of ActionBinds to ergosterol altering cell membrane permeability in susceptible fungi and causing leakage of cell components with subsequent cell death. Proposed mechanism suggests that amphotericin causes an oxidation-dependent stimulation of macrophages (Lyman, 1992).

Pharmacodynamics/Kinetics

Distribution: Minimal amounts enter the aqueous humor, bile, CSF (inflamed or noninflamed meninges), amniotic fluid, pericardial fluid, pleural fluid, and synovial fluid

Protein binding, plasma: 90%

Half-life elimination: Biphasic: Initial: 15-48 hours; Terminal: 15 days

Time to peak: Within 1 hour following a 4- to 6-hour dose

Excretion: Urine (2% to 5% as biologically active form); ~40% eliminated over a 7-day period and may be detected in urine for at least 7 weeks after discontinued use

Related Information

- Antifungal Agents
- Desensitization Protocols
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsPremedication with diphenhydramine and acetaminophen may reduce the severity of acute infusion-related reactions. Meperidine reduces the duration of amphotericin B-induced rigors and chilling. Hydrocortisone may be used in patients with severe or refractory infusion-related reactions. Bolus infusion of normal saline immediately preceding, or immediately preceding and following amphotericin B may reduce drug-induced nephrotoxicity. Risk of nephrotoxicity increases with amphotericin B doses >1 mg/kg/day. Infusion of admixtures more concentrated than 0.25 mg/mL should be limited to patients absolutely requiring volume restriction. Amphotericin B does not have a bacteriostatic constituent, subsequently admixture expiration is determined by sterility more than chemical stability.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause delirium

Mental Health: Effects on Psychiatric TreatmentMay cause bone marrow suppression; use caution with clozapine and carbamazepine

Anesthesia and Critical Care Concerns/Other ConsiderationsPatients may be premedicated with acetaminophen and diphenhydramine 30 minutes prior to the amphotericin infusion. Meperidine (Demerol®) may help to reduce rigors. Avoid rapid injection (usually 4- to 6-hour infusion required). Dosage adjustments are not necessary with renal impairment. If decreased renal function is due to amphotericin, the daily dose can be decreased by 50% or the dose can be given every other day.

Hydrocortisone may be used in patients with severe or refractory infusion-related reactions. Bolus infusion of normal saline immediately preceding, or immediately preceding and following amphotericin B may reduce drug-induced nephrotoxicity. Risk of nephrotoxicity increases with amphotericin B doses >1 mg/kg/day. Infusion of admixtures more concentrated than 0.25 mg/mL should be limited to patients absolutely requiring volume restriction. Amphotericin B does not have a bacteriostatic constituent, subsequently admixture expiration is determined by sterility more than chemical stability.

Index Terms Amphotericin B Desoxycholate

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International Brand Names Amphocil (MX); Fungizone (PL); Terix (MX)

Amphotericin B (Lipid Complex)

Lexi-Drugs Online

English English

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Medication Safety Issues

Safety issues:

Lipid-based amphotericin formulations (Abelcet®) may be confused with conventional formulations (Amphocin®, Fungizone®)

Large overdoses have occurred when conventional formulations were dispensed inadvertently for lipid-based products. Single daily doses of conventional amphotericin formulation never exceed 1.5 mg/kg.

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(am foe TER i sin bee LIP id KOM pleks)

U.S. Brand NamesAbelcet®

Canadian Brand NamesAbelcet®; Amphotec®

Pharmacologic CategoryAntifungal Agent, Parenteral

Use: Labeled IndicationsTreatment of aspergillosis or any type of progressive fungal infection in patients who are refractory to or intolerant of conventional amphotericin B therapy

Use: Unlabeled/InvestigationalEffective in patients with serious *Candida* species infections

Dosing: Adults

Note: Premedication: For patients who experience infusion-related immediate reactions, premedicate with the following drugs 30-60 minutes prior to drug administration: A nonsteroidal anti-inflammatory agent ± diphenhydramine **or** acetaminophen with diphenhydramine **or** hydrocortisone 50-100 mg. If the patient experiences rigors during the infusion, meperidine may be administered.

Usual dosage: I.V.: 2.5-5 mg/kg/day as a single infusion

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Dosing: Renal ImpairmentThe effects of renal impairment on drug pharmacokinetics or pharmacodynamics are currently unknown. The dose of amphotericin B lipid complex may be adjusted or drug administration may have to be interrupted in patients with acute kidney dysfunction to reduce the magnitude of renal impairment.

Hemodialysis: Supplemental dose is not necessary.

Peritoneal dialysis: Supplemental dose is not necessary.

Continuous renal replacement therapy (CRRT): No supplemental dosage necessary

Administration: I.V.For patients who experience nonanaphylactic infusion-related reactions, premedicate 30-60 minutes prior to drug administration with a nonsteroidal anti-inflammatory agent ± diphenhydramine **or** acetaminophen with diphenhydramine **or** hydrocortisone 50-100 mg. If the patient experiences rigors during the infusion, meperidine may be administered.

Invert infusion container several times prior to administration and every 2 hours during infusion.

Administration: I.V. DetailDo not use an in-line filter. Flush line with dextrose; normal saline may cause precipitate.

StorageIntact vials should be stored at 2°C to 8°C (35°F to 46°F) and protected from exposure to light; do not freeze intact vials. Solutions for infusion are stable for 48 hours under refrigeration and 6 hours at room temperature. Protect from light. Following reconstitution, protect from light.

ReconstitutionShake vial gently to disperse yellow sediment at bottom of container. Dilute with D_5W to 1-2 mg/mL.

Compatibility

Incompatible with any blood products, intravenous drugs, or intravenous fluids other than D_5W when admixed or as Y-site administration.

ContraindicationsHypersensitivity to amphotericin or any component of the formulation

Allergy Considerations

- Amphotericin Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis: Has been reported with amphotericin B-containing drugs; facilities for cardiopulmonary resuscitation should be available during administration due to the possibility of anaphylactic reaction. If severe respiratory distress occurs, the infusion should be immediately discontinued; during the initial dosing, the drug should be administered under close clinical observation.

- Infusion reactions: Acute reactions (including fever and chills) may occur 1-3 hours after starting an intravenous infusion. These reactions are usually more common with the first few doses and generally diminish with subsequent doses.

Special populations:

- Neutropenic patients: Pulmonary reactions may occur in neutropenic patients receiving leukocyte transfusions; separation of the infusions as much as possible is advised.

Geriatric ConsiderationsThe pharmacokinetics and dosing of amphotericin have not been studied in elderly. It appears that use is similar to young adults; caution should be exercised and renal function and desired effect monitored closely.
Pregnancy Risk FactorB
LactationEnters breast milk/contraindicated
Breast-Feeding ConsiderationsDue to limited data, consider discontinuing nursing during therapy.
Adverse ReactionsNephrotoxicity and infusion-related hyperpyrexia, rigor, and chilling are reduced relative to amphotericin deoxycholate.

>10%:

Central nervous system: Chills, fever

Renal: Serum creatinine increased

Miscellaneous: Multiple organ failure

1% to 10%:

Cardiovascular: Hypotension, cardiac arrest

Central nervous system: Headache, pain

Dermatologic: Rash

Endocrine & metabolic: Bilirubinemia, hypokalemia, acidosis

Gastrointestinal: Nausea, vomiting, diarrhea, gastrointestinal hemorrhage, abdominal pain

Renal: Renal failure

Respiratory: Respiratory failure, dyspnea, pneumonia

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

Aminoglycosides: Amphotericin B may enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Amphotericin B may enhance the nephrotoxic effect of Colistimethate. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

CycloSPORINE: Amphotericin B may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Amphotericin B may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Test InteractionsIncreased BUN (S), serum creatinine, alkaline phosphate, bilirubin; decreased magnesium, potassium (S)
Monitoring ParametersRenal function (monitor frequently during therapy), electrolytes (especially potassium and magnesium), liver function tests, temperature, PT/PTT, CBC; monitor input and output; monitor for signs of hypokalemia (muscle weakness, cramping, drowsiness, ECG changes, etc)
Nursing: Physical Assessment/MonitoringAssess culture and sensitivity report and patient's previous exposure to amphotericin B prior to starting therapy. Assess potential for interactions with other medications patient may be taking (eg, other nephrotoxic drugs). See Administration for specific infusion directions and premedication recommendations prior to administering first dose. Patient should be monitored closely for infusion related reactions (eg, anaphylaxis, chills, fever, nausea, vomiting, rigors, hypotension, acute respiratory distress) and cardiopulmonary resuscitation should be available. If acute respiratory distress occurs, infusion should be stopped and prescriber notified. Assess results of laboratory tests, therapeutic effectiveness, and adverse response frequently during therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.
Monitoring: Lab TestsBUN and serum creatinine levels should be determined every other day while therapy is increased and at least weekly thereafter. Monitor serum electrolytes (especially potassium and magnesium), liver function, and CBC. Perform culture and sensitivity testing prior to initiating therapy.
Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by infusion and therapy may last several weeks. Maintain good personal hygiene to reduce spread and recurrence of lesions. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause postural hypotension (use caution when changing from lying or sitting position to standing or when climbing stairs); or nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report chest pain or palpitations; CNS disturbances; skin rash; chills or fever; persistent nausea, vomiting, or abdominal pain; sore throat; excessive fatigue; swelling of extremities or unusual weight gain; respiratory difficulty; pain at

infusion site; muscle cramping or weakness; or other adverse reactions. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension [preservative free]:

Abelcet®: 5 mg/mL (20 mL)

Generic AvailableNo

Mechanism of ActionBinds to ergosterol altering cell membrane permeability in susceptible fungi and causing leakage of cell components with subsequent cell death. Proposed mechanism suggests that amphotericin causes an oxidation-dependent stimulation of macrophages.

Pharmacodynamics/Kinetics

Distribution: V_d: Increases with higher doses; reflects increased uptake by tissues (131 L/kg with 5 mg/kg/day)

Half-life elimination: ~24 hours

Excretion: Clearance: Increases with higher doses (5 mg/kg/day): 400 mL/hour/kg

Related Information

- Amphotericin B (Conventional)

Pharmacotherapy PearlsAs a modification of dimyristoyl phosphatidylcholine:dimyristoyl phosphatidylglycerol 7:3 (DMPC:DMPG) liposome, amphotericin B lipid-complex has a higher drug to lipid ratio and the concentration of amphotericin B is 33 M. ABLC is a ribbon-like structure, not a liposome.

Controlled trials which compare the original formulation of amphotericin B to the newer liposomal formulations (ie, Abelcet®) are lacking. Thus, comparative data discussing differences among the formulations should be interpreted cautiously. Although the risk of nephrotoxicity and infusion-related adverse effects may be less with Abelcet®, the efficacy profiles of Abelcet® and the original amphotericin formulation are comparable. Consequently, Abelcet® should be restricted to those patients who cannot tolerate or fail a standard amphotericin B formulation.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause delirium

Mental Health: Effects on Psychiatric TreatmentMay cause bone marrow suppression; use caution with clozapine and carbamazepine

Anesthesia and Critical Care Concerns/Other ConsiderationsThis product is significantly more expensive than conventional amphotericin B. The incidence of nephrotoxicity with ABLC appears to be less when compared to conventional amphotericin B. The incidence of infusion-related reactions does not appear to be decreased with ABLC, but tolerance usually develops. Premedication may be considered to prevent/attenuate infusion-related adverse events. To prevent aggregation of the lipid products, it is important to shake the bag before hanging and once every 2 hours. *In vitro* experiments confirm that liposomal amphotericin B is at least as active as amphotericin B against clinical isolates of *Candida*, *Cryptococcus*, *Blastomyces*, and *Aspergillus*. Their activities also have appeared to be equal against *Fusarium*. Abelcet® may be restricted to patients who cannot tolerate or fail a standard amphotericin B formulation.

Index TermsABLC

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International Brand Names Abelcet (AR, AT, BE, BR, CZ, DK, FI, FR, GB, GR, HN, IE, NL, NO, NZ, SE); Ambisome (AU, FR, HK, IL, KP); Ampholip (IN)

Amphotericin B (Liposomal)

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English English

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Medication Safety Issues

Safety issues:

Lipid-based amphotericin formulations (AmBisome®) may be confused with conventional formulations (Amphocin®, Fungizone®)

Large overdoses have occurred when conventional formulations were dispensed inadvertently for lipid-based products. Single daily doses of conventional amphotericin formulation never exceed 1.5 mg/kg.

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(am foe TER i sin bee lye po SO mal)
U.S. Brand NamesAmBisome®
Canadian Brand NamesAmBisome®
Pharmacologic Category[Antifungal Agent, Parenteral]()
Use: Labeled IndicationsEmpirical therapy for presumed fungal infection in febrile, neutropenic patients; treatment of patients with *Aspergillus* species, *Candida* species, and/or *Cryptococcus* species infections refractory to amphotericin B desoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B desoxycholate; treatment of cryptococcal meningitis in HIV-infected patients; treatment of visceral leishmaniasis
Use: Unlabeled/InvestigationalEffective in patients with serious *Candida* species infections
Dosing: Adults**Note:Premedication:** For patients who experience nonanaphylactic infusion-related immediate reactions, premedicate with the following drugs 30-60 minutes prior to drug administration: A nonsteroidal anti-inflammatory agent ± diphenhydramine; **or** acetaminophen with diphenhydramine; **or** hydrocortisone 50-100 mg. If the patient experiences rigors during the infusion, meperidine may be administered.

Candidal infection:

Endocarditis: 3-6 mg/kg/day with flucytosine 25-37.5 mg/kg 4 times daily

Meningitis: 5 mg/kg/day with flucytosine 100 mg/kg/day

Cryptococcal meningitis (HIV-positive): 6 mg/kg/day

Note: IDSA guidelines (April, 2000) report doses of 3-6 mg/kg/day, noting that 4 mg/kg/day was effective in a small, open-label trial. The manufacturer's labeled dose of 6 mg/kg/day was approved in June, 2000.

Empiric therapy: 3 mg/kg/day

Fungal sinusitis: 5-7.5 mg/kg/day

Note: Use azole antifungal if causative organism is *Pseudallescheria boydii* (*Scedosporium* sp).

Systemic fungal infections *(Aspergillus, Candida, Cryptococcus)*: 3-5 mg/kg/day

Visceral leishmaniasis:

Immunocompetent: 3 mg/kg/day on days 1-5, and 3 mg/kg/day on days 14 and 21; a repeat course may be given in patients who do not achieve parasitic clearance

Note: Alternate regimen of 2 mg/kg/day for 5 days has been reportedly effective.

Immunocompromised: 4 mg/kg/day on days 1-5, and 4 mg/kg/day on days 10, 17, 24, 31, and 38

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Note:Premedication:** For patients who experience nonanaphylactic infusion-related immediate reactions, premedicate with the following drugs 30-60 minutes prior to drug administration: A nonsteroidal anti-inflammatory agent ± diphenhydramine; **or** acetaminophen with diphenhydramine; **or** hydrocortisone 50-100 mg. If the patient experiences rigors during the infusion, meperidine may be administered.

Candidal infection: Children ≥1 month: I.V.: Refer to adult dosing.

Cryptococcal meningitis (HIV-positive): Children ≥1 month: I.V.: Refer to adult dosing.

Empiric therapy: Children ≥1 month: I.V.: Refer to adult dosing.

Systemic fungal infections *(Aspergillus, Candida, Cryptococcus)*: Children ≥1 month: I.V.: Refer to adult dosing.

Visceral leishmaniasis: Children ≥1 month: I.V.: Refer to adult dosing.

Dosing: Renal Impairment None necessary; effects of renal impairment are not currently known.

Hemodialysis: Supplemental dose is not necessary.

Peritoneal dialysis effects: Supplemental dose is not necessary.

Continuous renal replacement therapy (CRRT): No supplemental dosage necessary

Administration: I.V.Intravenous infusion, over a period of approximately 2 hours. Infusion time may be reduced to approximately 1 hour in patients in whom the treatment is well-tolerated. If the patient experiences discomfort during infusion, the duration of infusion may be increased. Discontinue if severe respiratory distress occurs.

For a patient who experiences chills, fever, hypotension, nausea, or other nonanaphylactic infusion-related reactions, premedicate with the following drugs, 30-60 minutes prior to drug administration: A nonsteroidal (eg, ibuprofen, choline magnesium trisalicylate) with or without diphenhydramine **or** acetaminophen with diphenhydramine **or** hydrocortisone 50-100 mg. If the patient experiences rigors during the infusion, meperidine may be administered.

Administration: I.V. DetailExisting intravenous line should be flushed with D$_5$W prior to infusion (if not feasible, administer through a separate line). An in-line membrane filter (not less than 1 micron) may be used.

StorageUnopened vials should be refrigerated at 2°C to 8°C (36°F to 46°F). Vials reconstituted with SWFI are stable for 24 hours under refrigeration. Infusion should begin within 6 hours of dilution with D5W.

ReconstitutionAdd 12 mL SWFI to vial. The use of any solution other than those recommended, or the presence of a bacteriostatic agent in the solution, may cause precipitation. **Shake the vial vigorously** for 30 seconds.

Filtration and dilution: The 5-micron filter should be on the syringe used to remove the reconstituted AmBisome®. Dilute to a final concentration of 1-2 mg/mL (0.2-0.5 mg/mL for infants and small children).

CompatibilityStable in D$_5$W; **incompatible** with NS, $^1/_2$NS, other saline-containing solutions, or preservatives.

ContraindicationsHypersensitivity to amphotericin B or any component of the formulation

Allergy Considerations

- Amphotericin Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis: Has been reported with amphotericin B-containing drugs; facilities for cardiopulmonary resuscitation should be available during administration due to the possibility of anaphylactic reaction. If severe respiratory distress occurs, the infusion should be immediately discontinued; during the initial dosing, the drug should be administered under close clinical observation.

- Infusion reactions: Acute reactions (including fever and chills) may occur 1-3 hours after starting infusions; reactions are more common with the first few doses and generally diminish with subsequent doses. Immediately discontinue infusion if severe respiratory distress occurs; the patient should not receive further infusions.

Special populations:

- Pediatrics: Safety and efficacy have not been established in patients <1 month of age.

Pregnancy Risk FactorB

LactationExcretion in breast milk unknown/contraindicated

Adverse ReactionsPercentage of adverse reactions is dependent upon population studied and may vary with respect to premedications and underlying illness. Incidence of decreased renal function and infusion-related events are lower than rates observed with amphotericin B deoxycholate.

>10%:

Cardiovascular: Peripheral edema (15%), edema (12% to 14%), tachycardia (9% to 18%), hypotension (7% to 14%), hypertension (8% to 20%), chest pain (8% to 12%), hypervolemia (8% to 12%)

Central nervous system: Chills (29% to 48%), insomnia (17% to 22%), headache (9% to 20%), anxiety (7% to 14%), pain (14%), confusion (9% to 13%)

Dermatologic: Rash (5% to 25%), pruritus (11%)

Endocrine & metabolic: Hypokalemia (31% to 51%), hypomagnesemia (15% to 50%), hyperglycemia (8% to 23%), hypocalcemia (5% to 18%), hyponatremia (8% to 12%)

Gastrointestinal: Nausea (16% to 40%), vomiting (10% to 32%), diarrhea (11% to 30%), abdominal pain (7% to 20%), constipation (15%), anorexia (10% to 14%)

Hematologic: Anemia (27% to 48%), blood transfusion reaction (9% to 18%), leukopenia (15% to 17%), thrombocytopenia (6% to 13%)

Hepatic: Alkaline phosphatase increased (7% to 22%), BUN increased (7% to 21%), bilirubinemia (9% to 18%), ALT (15%) increased, AST increased (13%), liver function tests abnormal (not specified) (4% to 13%)

Local: Phlebitis (9% to 11%)

Neuromuscular & skeletal: Weakness (6% to 13%), back pain (12%)

Renal: Creatinine increased (18% to 40%), hematuria (14%)

Respiratory: Dyspnea (18% to 23%), lung disorder (14% to 18%), cough increased (2% to 18%), epistaxis (8% to 15%), pleural effusion (12%), rhinitis (11%)

Miscellaneous: Sepsis (7% to 14%), infection (11% to 12%)

2% to 10%:

Cardiovascular: Arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, cardiomegaly, facial swelling, flushing, postural hypotension, valvular heart disease, vascular disorder

Central nervous system: Agitation, abnormal thinking, coma, convulsion, depression, dysesthesia, dizziness (7% to 8%), hallucinations, malaise, nervousness, somnolence

Dermatologic: Alopecia, bruising, cellulitis, dry skin, maculopapular rash, petechia, purpura, skin discoloration, skin disorder, skin ulcer, urticaria, vesiculobullous rash

Endocrine & metabolic: Acidosis, fluid overload, hypernatremia (4%), hyperchloremia, hyperkalemia, hypermagnesemia, hyperphosphatemia, hypophosphatemia, hypoproteinemia, lactate dehydrogenase increased, nonprotein nitrogen increased

Gastrointestinal: Constipation, dry mouth, dyspepsia, abdomen enlarged, amylase increased, eructation, fecal incontinence, flatulence, gastrointestinal hemorrhage (10%), hematemesis, hemorrhoids, gum/oral hemorrhage, ileus, mucositis, rectal disorder, stomatitis, ulcerative stomatitis

Genitourinary: Vaginal hemorrhage

Hematologic: Coagulation disorder, hemorrhage, prothrombin decreased, thrombocytopenia

Hepatic: Hepatocellular damage, hepatomegaly, veno-occlusive liver disease

Local: Injection site inflammation

Neuromuscular & skeletal: Arthralgia, bone pain, dystonia, myalgia, neck pain, paresthesia, rigors, tremor

Ocular: Conjunctivitis, dry eyes, eye hemorrhage

Renal: Abnormal renal function, acute kidney failure, dysuria, kidney failure, toxic nephropathy, urinary incontinence

Respiratory: Asthma, atelectasis, cough, dry nose, hemoptysis, hyperventilation, lung edema, pharyngitis, pneumonia, respiratory alkalosis, respiratory insufficiency, respiratory failure, sinusitis, hypoxia (6% to 8%)

Miscellaneous: Allergic reaction, cell-mediated immunological reaction, flu-like syndrome, graft-versus-host disease, herpes simplex, hiccup, procedural complication (8% to 10%), diaphoresis (7%)

Postmarketing and/or case reports: Angioedema, erythema, urticaria, cyanosis/hypoventilation, pulmonary edema, agranulocytosis, hemorrhagic cystitis

Drug Interactions

Aminoglycosides: Amphotericin B may enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Amphotericin B may enhance the nephrotoxic effect of Colistimethate. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

CycloSPORINE: Amphotericin B may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Amphotericin B may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Monitoring ParametersRenal function (monitor frequently during therapy), electrolytes (especially potassium and magnesium), liver function tests, temperature, PT/PTT, CBC; monitor input and output; monitor for signs of hypokalemia (muscle weakness, cramping, drowsiness, ECG changes, etc)

Nursing: Physical Assessment/MonitoringAssess culture and sensitivity report and patient's previous exposure to amphotericin B prior to starting therapy. Assess potential for interactions with other medications patient may be taking (eg, other nephrotoxic drugs). See Administration for specific infusion directions and premedication recommendations prior to administering first dose. Patient should be monitored closely for infusion related reactions (eg, anaphylaxis, chills, fever, nausea, vomiting, rigors, hypotension, acute respiratory distress) and cardiopulmonary resuscitation should be available. If acute respiratory distress occurs, infusion should be stopped and prescriber notified. Assess results of laboratory tests, therapeutic effectiveness, and adverse response frequently during therapy. Teach patient possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsBUN and serum creatinine levels should be determined every other day while therapy is increased and at least weekly thereafter. Serum potassium and magnesium should be monitored closely. Monitor electrolytes, liver function, hematocrit, and CBC regularly.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by infusion and therapy may last several weeks. You will be monitored closely during and after infusion; report immediately any pain or swelling at infusion site, chills, nausea, chest pain, swelling of face or mouth, difficulty breathing, muscle cramping, acute anxiety, or other infusion reactions. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause postural hypotension (use caution when changing from lying or sitting position to standing or when climbing stairs); or nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report chest pain or palpitations, CNS disturbances, skin rash, unusual chills or fever, persistent nausea, vomiting, abdominal pain, sore throat, excessive fatigue, swelling of extremities, unusual weight gain, difficulty breathing, pain at infusion site, muscle cramping or weakness, or other adverse reactions. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

AmBisome®: 50 mg [contains soy and sucrose]

Generic AvailableNo

Mechanism of ActionBinds to ergosterol altering cell membrane permeability in susceptible fungi and causing leakage of cell components with subsequent cell death. Proposed mechanism suggests that amphotericin causes an oxidation-dependent stimulation of macrophages (Lyman, 1992).

Pharmacodynamics/Kinetics

Distribution: V_d: 131 L/kg

Half-life elimination: Terminal: 174 hours

Pharmacotherapy PearlsAmphotericin B (liposomal) is a true single bilayer liposomal drug delivery system. Liposomes are closed, spherical vesicles created by mixing specific proportions of amphophilic substances such as phospholipids and cholesterol so that they arrange themselves into multiple concentric bilayer membranes when hydrated in aqueous solutions. Single bilayer liposomes are then formed by microemulsification of multilamellar vesicles using a homogenizer. Amphotericin B (liposomal) consists of these unilamellar bilayer liposomes with amphotericin B intercalated within the membrane. Due to the nature and quantity of amphophilic substances used, and the lipophilic moiety in the amphotericin B molecule, the drug is an integral part of the overall structure of the amphotericin B liposomal liposomes. Amphotericin B (liposomal) contains true liposomes that are <100 nm in diameter.

Dental Health Professional ConsiderationsAmphotericin B, liposomal is a true single bilayer liposomal drug delivery system. Liposomes are closed, spherical vesicles created by mixing specific proportions of amphophilic substances such as phospholipids and cholesterol so that they arrange themselves into multiple concentric bilayer membranes when hydrated in aqueous solutions. Single bilayer liposomes are then formed by microemulsification of multilamellar vesicles using a homogenizer. Amphotericin B, liposomal consists of these unilamellar bilayer liposomes with amphotericin B intercalated within the membrane. Due to the nature and quantity of amphophilic substances used, and the lipophilic moiety in the amphotericin B molecule, the drug is an integral part of the overall structure of the amphotericin B liposomes. Amphotericin B, liposomal contains true liposomes that are <100 nm in diameter.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Facial swelling, postural hypotension, mucositis, stomatitis, and ulcerative stomatitis (see Dental Comment)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause delirium

Mental Health: Effects on Psychiatric TreatmentMay cause bone marrow suppression; use caution with clozapine and carbamazepine

Anesthesia and Critical Care Concerns/Other ConsiderationsThis product is significantly more expensive than conventional amphotericin B; Infectious Disease consult is recommended. AmBisome® is a true single bilayer liposomal drug delivery system. Liposomes are closed, spherical vesicles created by mixing specific proportions of amphophilic substances such as phospholipids and cholesterol so that they arrange themselves into multiple concentric bilayer membranes when hydrated in aqueous solutions. Single bilayer liposomes are then formed by microemulsification of multilamellar vesicles using a homogenizer. AmBisome® consists of these unilamellar bilayer liposomes with amphotericin B intercalated within the membrane. Due to the nature and quantity of amphophilic substances used, and the lipophilic moiety in the amphotericin B molecule, the drug is an integral part of the overall structure of the AmBisome® liposomes. AmBisome® contains true liposomes that are <100 nm in diameter.

Index TermsL-AmB

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International Brand Names AmBisome (AR, AT, AU, BE, CH, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, NL, NO, PY, SE, SG, TH, TW); Ambisome (PL); Fengkesong (CL)

Amphotericin B Cholesteryl Sulfate Complex

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Safety issues:

Lipid-based amphotericin formulations (Amphotec®) may be confused with conventional formulations (Amphocin®, Fungizone®)

Large overdoses have occurred when conventional formulations were dispensed inadvertently for lipid-based products. Single daily doses of conventional amphotericin formulation never exceed 1.5 mg/kg.

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(am foe TER i sin bee kole LES te ril SUL fate KOM plecks)

U.S. Brand NamesAmphotec®

Canadian Brand NamesAmphotec®

Pharmacologic CategoryAntifungal Agent, Parenteral

Use: Labeled IndicationsTreatment of invasive aspergillosis in patients who have failed amphotericin B deoxycholate treatment, or who have renal impairment or experience unacceptable toxicity which precludes treatment with amphotericin B deoxycholate in effective doses.

Use: Unlabeled/InvestigationalEffective in patients with serious *Candida* species infections

Dosing: Adults

Note: Premedication: For patients who experience chills, fever, hypotension, nausea, or other nonanaphylactic infusion-related immediate reactions, premedicate with the following drugs 30-60 minutes prior to drug administration: A nonsteroidal (eg, ibuprofen, choline magnesium trisalicylate) with or without diphenhydramine **or** acetaminophen with diphenhydramine **or** hydrocortisone 50-100 mg. If the patient experiences rigors during the infusion, meperidine may be administered.

Usual dosage: I.V.: 3-4 mg/kg/day (infusion of 1 mg/kg/hour); maximum: 7.5 mg/kg/day

A regimen of 6 mg/kg/day has been used for treatment of life-threatening invasive mold infections in immunocompromised patients; maximum: 7.5 mg/kg/day.

Initially infuse at 1 mg/kg/hour. Rate of infusion may be increased with subsequent doses to 3 mg/kg/hour as patient tolerance allows. Treatment should continue as patient tolerance allows, until complete resolution of microbiologic and clinical evidence of fungal disease.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: I.V.For a patient who experiences chills, fever, hypotension, nausea, or other nonanaphylactic infusion-related reactions, premedicate with the following drugs 30-60 minutes prior to drug administration: A nonsteroidal (eg, ibuprofen, choline magnesium trisalicylate) with or without diphenhydramine **or** acetaminophen with diphenhydramine **or** hydrocortisone 50-100 mg. If the patient experiences rigors during the infusion, meperidine may be administered. If severe respiratory distress occurs, the infusion should be immediately discontinued.

Administration: I.V. DetailAvoid injection faster than 1 mg/kg/hour.

StorageStore intact vials under refrigeration. After reconstitution, the solution should be refrigerated at 2°C to 8°C (36°F to 46°F) and used within 24 hours. Concentrations of 0.1-2 mg/mL in dextrose 5% in water are stable for 14 days at 4°C and 23°C if protected from light, however, due to the occasional formation of subvisual particles, solutions should be used within 48 hours.

ReconstitutionReconstitute 50 mg and 100 mg vials with 10 mL and 20 mL of SWI, respectively. The reconstituted vials contain 5 mg/mL of amphotericin B. Shake the vial gently by hand until all solid particles have dissolved. Further dilute amphotericin B colloidal dispersion with dextrose 5% in water.

CompatibilityStable in D_5W; **incompatible** with NS.

Y-site administration: Compatible: Acyclovir, aminophylline, cefoxitin, ceftizoxime, clindamycin, dexamethasone sodium phosphate, fentanyl, furosemide, ganciclovir, granisetron, hydrocortisone sodium succinate, ifosfamide, lorazepam, mannitol, methotrexate, methylprednisolone sodium succinate, nitroglycerin, sufentanil, trimethoprim/sulfamethoxazole, vinblastine, vincristine, zidovudine. **Incompatible:** Alfentanil, amikacin, ampicillin, ampicillin/sulbactam, atenolol, aztreonam, bretylium, buprenorphine, butorphanol, calcium chloride, calcium gluconate, carboplatin, cefazolin, cefepime, cefoperazone, ceftazidime, ceftriaxone, chlorpromazine, cimetidine, cisatracurium, cisplatin, cyclophosphamide, cyclosporine, cytarabine, diazepam, digoxin, diphenhydramine, dobutamine, dopamine, doxorubicin, doxorubicin liposome, droperidol, enalaprilat, esmolol, famotidine, fluconazole, fluorouracil, gatifloxacin, gentamicin, haloperidol, heparin, hydromorphone, hydroxyzine, imipenem/cilastatin, labetalol, leucovorin, lidocaine, magnesium sulfate, meperidine, mesna, metoclopramide, metoprolol, metronidazole, midazolam, mitoxantrone, morphine, nalbuphine, naloxone, ofloxacin, ondansetron, paclitaxel, pentobarbital, phenobarbital, phenytoin, piperacillin, piperacillin/tazobactam, potassium chloride, prochlorperazine, promethazine, propranolol, ranitidine, remifentanil, sodium bicarbonate, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, vecuronium, verapamil, vinorelbine.

ContraindicationsHypersensitivity to amphotericin B or any component of the formulation

Allergy Considerations

- Amphotericin Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis: Has been reported with amphotericin B-containing drugs; facilities for cardiopulmonary resuscitation should be available during administration due to the possibility of anaphylactic reaction. If severe respiratory distress occurs, the infusion should be immediately discontinued. During the initial dosing, the drug should be administered under close clinical observation.

- Infusion reactions: Sometimes severe, usually subside with continued therapy - manage with decreased rate of infusion and pretreatment with antihistamines/corticosteroids.

Special populations:

- Neutropenic patients: Pulmonary reactions may occur in neutropenic patients receiving leukocyte transfusions; separation of the infusions as much as possible is advised.

Geriatric ConsiderationsThe pharmacokinetics and dosing of amphotericin have not been studied in the elderly. It appears that use is similar to young adults. Caution should be exercised and renal function and desired effect monitored closely.

Pregnancy Risk FactorB

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsDue to limited data, consider discontinuing nursing during therapy.

Adverse Reactions

>10%: Central nervous system: Chills, fever

1% to 10%:

Cardiovascular: Hypotension, tachycardia

Central nervous system: Headache

Dermatologic: Rash

Endocrine & metabolic: Hypokalemia, hypomagnesemia

Gastrointestinal: Nausea, diarrhea, abdominal pain

Hematologic: Thrombocytopenia

Hepatic: LFT change

Neuromuscular & skeletal: Rigors

Renal: Creatinine increased

Respiratory: Dyspnea

Note: Amphotericin B colloidal dispersion has an improved therapeutic index compared to conventional amphotericin B, and has been used safely in patients with amphotericin B-related nephrotoxicity; however, continued decline of renal function has occurred in some patients.

Drug Interactions

Aminoglycosides: Amphotericin B may enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Amphotericin B may enhance the nephrotoxic effect of Colistimethate. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

CycloSPORINE: Amphotericin B may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Amphotericin B may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Monitoring ParametersLiver function tests, electrolytes, BUN, Cr, temperature, CBC, I/O, signs of hypokalemia (muscle weakness, cramping, drowsiness, ECG changes)

Nursing: Physical Assessment/MonitoringAssess culture and sensitivity report and patient's previous exposure to amphotericin B prior to starting therapy. Assess potential for interactions with other medications patient may be taking (eg, other nephrotoxic drugs). See Administration for specific infusion directions and premedication recommendations prior to administering first dose. Patient should be monitored closely for infusion related reactions (eg, anaphylaxis, chills, fever, nausea, vomiting, rigors, hypotension, acute respiratory distress) and cardiopulmonary resuscitation should be available. If acute respiratory distress occurs, infusion should be stopped and prescriber notified. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (see Adverse Reactions) frequently during therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsMonitor serum electrolytes (especially potassium and magnesium), liver function, and CBC. Perform culture and sensitivity testing prior to initiating therapy.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by infusion and therapy may last several weeks. You will be monitored closely during and after infusion; report immediately any pain or swelling at infusion site, chills, nausea, chest pain, swelling of face or mouth, difficulty breathing, muscle cramping, acute anxiety, or other infusion reactions. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause postural hypotension (use caution when changing from lying or sitting position to standing or when climbing stairs); or nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report chest pain or palpitations; CNS disturbances; skin rash; unusual chills or fever; persistent nausea, vomiting, or abdominal pain; sore throat; excessive fatigue; swelling of extremities or unusual weight gain; difficulty breathing; pain at infusion site; muscle cramping or weakness; or other adverse reactions. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Amphotec®: 50 mg, 100 mg

Generic AvailableNo

Mechanism of ActionBinds to ergosterol altering cell membrane permeability in susceptible fungi and causing leakage of cell components with subsequent cell death. Proposed mechanism suggests that amphotericin causes an oxidation-dependent stimulation of macrophages (Lyman, 1992).

Pharmacodynamics/Kinetics

Distribution: V_d: Total volume increases with higher doses, reflects increasing uptake by tissues (with 4 mg/kg/day = 4 L/kg); predominantly distributed in the liver; concentrations in kidneys and other tissues are lower than observed with conventional amphotericin B

Half-life elimination: 28-29 hours; prolonged with higher doses

Pharmacotherapy PearlsControlled trials which compare the original formulation of amphotericin B to the newer liposomal formulations (ie, Amphotec®) are lacking. Thus, comparative data discussing differences among the formulations should be interpreted cautiously. Although the risk of nephrotoxicity and infusion-related adverse effects may be less with Amphotec®, the efficacy profiles of Amphotec® and the original amphotericin formulation are comparable. Consequently, Amphotec® should be restricted to those patients who cannot tolerate or fail a standard amphotericin B formulation.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause bone marrow suppression; use caution with clozapine and carbamazepine

Anesthesia and Critical Care Concerns/Other ConsiderationsPatients may be premedicated with acetaminophen and diphenhydramine 30 minutes prior to infusion. Meperidine (Demerol®) may help reduce rigors.

Controlled trials which compare the original formulation of amphotericin B to the newer liposomal formulations (ie, Amphotec®) are lacking. Thus, comparative data discussing differences among the formulations should be interpreted cautiously. Although the risk of nephrotoxicity and infusion-related adverse effects may be less with Amphotec®, the efficacy profiles of Amphotec® and the original amphotericin formulation are comparable. Consequently, Amphotec® should be restricted to those patients who cannot tolerate or who fail a standard amphotericin B formulation. This product is significantly more expensive than conventional amphotericin B; Infectious Disease consult is recommended.

Index TermsABCD; Amphotericin B Colloidal Dispersion

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International Brand NamesAmphocil (AT, AU, BR, CZ, DK, FI, GB, HK, HN, IL, IT, MX, MY, NL, SE, TH)

Ampicillin and Sulbactam

Lexi-Drugs Online

English English

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Pronunciation(am pi SIL in & SUL bak tam)

U.S. Brand NamesUnasyn®

Canadian Brand NamesUnasyn®

Pharmacologic CategoryAntibiotic, Penicillin

Use: Labeled IndicationsTreatment of susceptible bacterial infections involved with skin and skin structure, intra-abdominal infections, gynecological infections; spectrum is that of ampicillin plus organisms producing beta-lactamases such as *S. aureus*, *H. influenzae*, *E. coli*, *Klebsiella*, *Acinetobacter*, *Enterobacter*, and anaerobes

Use: DentalParenteral beta-lactamase-resistant antibiotic combination to treat more severe orofacial infections where beta-lactamase-producing staphylococci and beta-lactamase-producing *Bacteroides* are present

Dosing: AdultsDoses expressed as ampicillin/sulbactam combination.

Susceptible infections: I.M., I.V.: 1.5-3 g every 6 hours (maximum: Unasyn® 12 g)

Amnionitis, cholangitis, diverticulitis, endometritis, endophthalmitis, epididymitis/orchitis, liver abscess, osteomyelitis (diabetic foot), peritonitis: I.V.: 3 g every 6 hours

Endocarditis: I.V.: 3 g every 6 hours with gentamicin or vancomycin for 4-6 weeks

Orbital cellulitis: I.V.: 1.5 g every 6 hours

Parapharyngeal space infections: I.V.: 3 g every 6 hours

***Pasteurella multocida*(human, canine/feline bites):** I.V.: 1.5-3 g every 6 hours

Pelvic inflammatory disease: I.V.: 3 g every 6 hours with doxycycline

Peritonitis (CAPD): Intraperitoneal:

Anuric, intermittent: 3 g every 12 hours

Anuric, continuous: Loading dose: 1.5 g; maintenance dose: 150 mg

Pneumonia:

Aspiration, community-acquired: I.V.: 1.5-3 g every 6 hours

Hospital-acquired: I.V.: 3 g every 6 hours

Urinary tract infections, pyelonephritis: I.V.: 3 g every 6 hours for 14 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Epiglottitis: Children ≥1 year: I.V.: 100-200 mg ampicillin/kg/day divided in 4 doses

Mild-to-moderate infections: Children ≥1 year: I.V.: 100-200 mg ampicillin/kg/day (150-300 mg Unasyn®) divided every 6 hours (maximum: 8 g ampicillin/day, 12 g Unasyn®)

Peritonsillar and retropharyngeal abscess: Children ≥1 year: I.V.: 50 mg ampicillin/kg/dose every 6 hours

Severe infections: Children ≥1 year: I.M., I.V.: 200-400 mg ampicillin/kg/day divided every 6 hours (maximum: 8 g ampicillin/day, 12 g Unasyn®)

Note: The American Academy of Pediatrics recommends a dose of up to 300 mg/kg/day for severe infection in infants >1 month of age.

Dosing: Renal Impairment

Cl_{cr} 15-29 mL/minute: Administer every 12 hours

Cl_{cr} 5-14 mL/minute: Administer every 24 hours

Continuous ambulatory peritoneal dialysis (CAPD): 3 g every 24 hours

Continuous renal replacement therapy (CRRT): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH: 3 g every 12 hours

CVVHD/CVVHDF: 3 g every 8 hours

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Administer around-the-clock to promote less variation in peak and trough serum levels. Administer by slow injection over 10-15 minutes or I.V. over 15-30 minutes. Ampicillin and gentamicin should not be mixed in the same I.V. tubing.

Some penicillins (eg, carbenicillin, ticarcillin, and piperacillin) have been shown to inactivate aminoglycosides *in vitro*. This has been observed to a greater extent with tobramycin and gentamicin, while amikacin has shown greater stability against inactivation. Concurrent use of these agents may pose a risk of reduced antibacterial efficacy *in vivo*, particularly in the setting of profound renal impairment. However, definitive clinical evidence is lacking. If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered.

Administration: I.V. DetailpH: 8-10

Dietary ConsiderationsSodium content of 1.5 g injection: 115 mg (5 mEq)

StoragePrior to reconstitution, store at ≤30°C (86°F). Solutions made in NS are stable up to 72 hours when refrigerated whereas dextrose solutions (same concentration) are stable for only 4 hours.

ReconstitutionI.M. and direct I.V. administration: Use within 1 hour after preparation. Reconstitute with sterile water for injection or 0.5% or 2% lidocaine hydrochloride injection (I.M.). Sodium chloride 0.9% (NS) is the diluent of choice for I.V. piggyback use.

CompatibilityStable in NS; **variable stability (consult detailed reference)** in $D_5{}^1/_2NS$, D_5W, LR.

Y-site administration: Compatible: Amifostine, aztreonam, cefepime, docetaxel, enalaprilat, etoposide, famotidine, filgrastim, fluconazole, fludarabine, gatifloxacin, gemcitabine, granisetron, heparin, insulin (regular), linezolid, meperidine, morphine, paclitaxel, remifentanil, tacrolimus, teniposide, theophylline, thiotepa. **Incompatible:** Aminoglycosides (gentamicin, tobramycin), amphotericin B cholesteryl sulfate complex, ciprofloxacin, idarubicin, ondansetron, sargramostim. **Variable (consult detailed reference):** Cisatracurium, diltiazem, vancomycin.

Compatibility when admixed: Compatible: Aztreonam. **Incompatible:** Aminoglycosides.

ContraindicationsHypersensitivity to ampicillin, sulbactam, penicillins, or any component of the formulations

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- Rash: Appearance of a rash should be carefully evaluated to differentiate a nonallergic ampicillin rash from a hypersensitivity reaction; rash occurs in 5% to 10% of children and is a generalized dull red, maculopapular rash, generally appearing 3-14 days after the start of therapy. It normally begins on the trunk and spreads over most of the body. It may be most intense at pressure areas, elbows, and knees.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Infectious mononucleosis: A high percentage of patients with infectious mononucleosis have developed rash during therapy; ampicillin-class antibiotics not recommended in these patients.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <1 year of age.

Geriatric ConsiderationsAdjust dose for renal function.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, ampicillin/sulbactam is classified as pregnancy category B. Both ampicillin and sulbactam cross the placenta. When used during pregnancy, pharmacokinetic changes have been observed with ampicillin alone (refer to the Ampicillin monograph for details).

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsAmpicillin and sulbactam are both excreted into breast milk in low concentrations. The manufacturer recommends that caution be used if administering to lactating women. Nondose-related effects could include modification of bowel flora and allergic sensitization of the infant. The maternal dose of sulbactam does not need altered in the postpartum period. Also refer to the Ampicillin monograph.

Pregnancy & Lactation, In-Depth

- Ampicillin and Sulbactam in Pregnancy & Lactation

Adverse ReactionsAlso see Ampicillin.

>10%: Local: Pain at injection site (I.M.)

1% to 10%:

Dermatologic: Rash

Gastrointestinal: Diarrhea

Local: Pain at injection site (I.V.), thrombophlebitis

Miscellaneous: Allergic reaction (may include serum sickness, urticaria, bronchospasm, hypotension, etc)

<1%: Abdominal distension, candidiasis, chest pain, chills, dysuria, edema, epistaxis, erythema, facial swelling, fatigue, flatulence, glossitis, hairy tongue, headache, interstitial nephritis, itching, liver enzymes increased, malaise, mucosal bleeding, nausea, pseudomembranous colitis, seizure, substernal pain, throat tightness, thrombocytopenia, urine retention, vomiting

Drug Interactions

Allopurinol: May enhance the potential for allergic or hypersensitivity reactions to Ampicillin. *Risk C: Monitor therapy*

Atenolol: Ampicillin may decrease the bioavailability of Atenolol. *Risk C: Monitor therapy*

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Test InteractionsMay interfere with urinary glucose tests using cupric sulfate (Benedict's solution, Clinitest®).

Some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*, leading to a potential underestimation of aminoglycoside serum concentration.

Monitoring ParametersWith prolonged therapy, monitor hematologic, renal, and hepatic function; monitor for signs of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringSee individual agent for Ampicillin.

Monitoring: Lab TestsHematologic, renal, and hepatic function with prolonged therapy. Perform culture and sensitivity testing prior to initiating therapy.

Patient EducationSee individual agent for Ampicillin.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 1.5 g: Ampicillin 1 g and sulbactam 0.5 g [contains sodium 115 mg (5 mEq)/1.5 g)]; 3 g: Ampicillin 2 g and sulbactam 1 g [contains sodium 115 mg (5 mEq)/1.5 g)]; 15 g: Ampicillin 10 g and sulbactam 5 g [bulk package; contains sodium 115 mg (5 mEq)/1.5 g]

Unasyn®:

1.5 g: Ampicillin 1 g and sulbactam 0.5 g [contains sodium 115 mg (5 mEq)/1.5 g)]

3 g: Ampicillin 2 g and sulbactam 1 g [contains sodium 115 mg (5 mEq)/1.5 g)]

15 g: Ampicillin 10 g and sulbactam 5 g [bulk package; contains sodium 115 mg (5 mEq)/1.5 g)]

Generic AvailableYes

ManufacturerPfizer U.S. Pharmaceuticals Group

Mechanism of ActionThe addition of sulbactam, a beta-lactamase inhibitor, to ampicillin extends the spectrum of ampicillin to include some beta-lactamase-producing organisms; inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Ampicillin: See Ampicillin.

Sulbactam:

Distribution: Bile, blister, and tissue fluids

Protein binding: 38%

Half-life elimination: Normal renal function: 1-1.3 hours

Excretion: Urine (~75% to 85% as unchanged drug) within 8 hours

Related Information

- Ampicillin
- Antimicrobial Drugs of Choice
- Treatment of Sexually-Transmitted Infections

Dental Health Professional ConsiderationsIn maxillary sinus, anterior nasal cavity, and deep neck infections, beta-lactamase-producing staphylococci and beta-lactamase-producing *Bacteroides* usually are present. In these situations, antibiotics that resist the beta-lactamase enzyme should be administered. Amoxicillin and clavulanic acid is administered orally for moderate infections. Ampicillin sodium and sulbactam sodium (Unasyn®) is administered parenterally for more severe infections.

Dental Health: Effects on Dental TreatmentProlonged use of penicillins may lead to development of oral candidiasis (see Dental Comment)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusLarge I.V. doses may rarely produce encephalopathy; penicillins have been reported to cause apprehension, illusions, agitation, insomnia, depersonalization, and encephalopathy

Mental Health: Effects on Psychiatric TreatmentRarely may cause bone marrow suppression; use caution with clozapine and carbamazepine

Index TermsSulbactam and Ampicillin

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International Brand NamesAmpibactan (VE); Amplisul (EC); Ansulina (TW); Bactacin (KP); Bactesyn (ID); Easyn (MY); Picyn (ID); Prixin (PY); Rukasyn (KP); Sulbaccin (TH); Sulbacin (IN, KP); Sultamicilina (AR); Ubacillin (KP); Ubactam (KP); Unacid (DE); Unacim (FR); Unasyn (AE, AT, BF, BH, BJ, BR, CI, CL, CN, CO, CR, CY, CZ, EC, EE, EG, ET, GH, GM, GN, GT, HK, HN, ID, IL, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NI, OM, PA, PE, PH, QA, SA, SC, SD, SL, SN, SV, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Unasyna (AR, UY)

Ampicillin

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English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Ampicillin may be confused with aminophylline

Pronunciation(am pi SIL in)
Canadian Brand NamesApo-Ampi®; Novo-Ampicillin; Nu-Ampi
Pharmacologic CategoryAntibiotic, Penicillin
Use: Labeled IndicationsTreatment of susceptible bacterial infections (nonbeta-lactamase-producing organisms); treatment or prophylaxis of infective endocarditis; susceptible bacterial infections caused by streptococci, pneumococci, nonpenicillinase-producing staphylococci, *Listeria*, meningococci; some strains of *H. influenzae*, *Salmonella*, *Shigella*, *E. coli*, *Enterobacter*, and *Klebsiella*
Use: DentalI.V. or I.M. administration for the prevention of infective endocarditis in patients not allergic to penicillin and unable to take oral amoxicillin; I.V. or I.M. administration for prophylaxis in total joint replacement patients not allergic to penicillin and unable to take oral medications undergoing dental procedures which produce bacteremia
Dosing: Adults

Usual dosage range:

Oral: 250-500 mg every 6 hours

I.M., I.V.: 250-500 mg every 6 hours

Actinomycosis: I.V.: 50 mg/kg/day for 4-6 weeks then oral amoxicillin

Cholangitis (acute): I.V.: 2 g every 4 hours with gentamicin

Diverticulitis: I.M., I.V.: 2 g every 6 hours with metronidazole

Endocarditis:

Infective: I.V.: 12 g/day via continuous infusion or divided every 4 hours

Prophylaxis: Dental, oral, or respiratory tract procedures: I.M., I.V.: 2 g within 30-60 minutes prior to procedure in patients not allergic to penicillin and unable to take oral amoxicillin. Intramuscular injections should be avoided in patients who are receiving anticoagulant therapy. In these circumstances, orally administered regimens should be given whenever possible. Intravenously administered antibiotics should be used for patients who are unable to tolerate or absorb oral medications. **Note:** American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur.

Prophylaxis in total joint replacement patient: I.M., I.V.: 2 g 1 hour prior to the procedure

Genitourinary and gastrointestinal tract procedures: I.M., I.V.:

High-risk patients: 2 g within 30 minutes prior to procedure, followed by ampicillin 1 g (or amoxicillin 1g orally) 6 hours later; must be used in combination with gentamicin. **Note:** As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Moderate-risk patients: 2 g within 30 minutes prior to procedure

Group B strep prophylaxis (intrapartum): I.V.: 2 g initial dose, then 1 g every 4 hours until delivery

***Listeria*infections:** I.V.: 200 mg/kg/day divided every 6 hours

Sepsis/meningitis: I.M., I.V.: 150-250 mg/kg/day divided every 3-4 hours (range: 6-12 g/day)

Urinary tract infections (enterococcus suspected): I.V.: 1-2 g every 6 hours with gentamicin

Dosing: ElderlyAdminister usual adult dose unless renal function is markedly reduced.
Dosing: Pediatric

Endocarditis prophylaxis: Infants and Children: I.M., I.V.:

Dental, oral, or respiratory tract procedures: 50 mg/kg within 30-60 minutes prior to procedure in patients not allergic to penicillin and unable to take oral amoxicillin. Intramuscular injections should be avoided in patients who are receiving anticoagulant therapy. In these circumstances, orally administered regimens should be given whenever possible. Intravenously administered antibiotics should be used for patients who are unable to tolerate or absorb oral medications.

Note: American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur.

Genitourinary and gastrointestinal tract procedures:

High-risk patients: 50 mg/kg (maximum: 2 g) within 30 minutes prior to procedure, followed by ampicillin 25 mg/kg (or amoxicillin 25 mg/kg orally) 6 hours later; must be used in combination with gentamicin. **Note:** As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Moderate-risk patients: 50 mg/kg within 30 minutes prior to procedure.

Mild-to-moderate infections: Infants and Children:

Oral: 50-100 mg/kg/day in doses divided every 6 hours (maximum: 2-4 g/day)

I.M., I.V.: 100-150 mg/kg/day in divided doses every 6 hours (maximum: 2-4 g/day)

Severe infections/meningitis: Infants and Children: I.M., I.V.: 200-400 mg/kg/day in divided doses every 6 hours (maximum: 6-12 g/day)

Dosing: Renal Impairment

Cl_{cr} >50 mL/minute: Administer every 6 hours

Cl_{cr} 10-50 mL/minute: Administer every 6-12 hours

Cl_{cr} <10 mL/minute: Administer every 12-24 hours

Hemodialysis: Moderately dialyzable (20% to 50%); administer dose after dialysis

Peritoneal dialysis: Moderately dialyzable (20% to 50%)

Administer 250 mg every 12 hours

Continuous arteriovenous or venovenous hemofiltration effects: Dose as for Cl_{cr} 10-50 mL/minute; ~50 mg of ampicillin per liter of filtrate is removed

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Administer around-the-clock to promote less variation in peak and trough serum levels. Administer over 3-5 minutes (125-500 mg) or over 10-15 minutes (1-2 g). More rapid infusion may cause seizures. Ampicillin and gentamicin should not be mixed in the same I.V. tubing.

Some penicillins (eg, carbenicillin, ticarcillin, and piperacillin) have been shown to inactivate aminoglycosides *in vitro*. This has been observed to a greater extent with tobramycin and gentamicin, while amikacin has shown greater stability against inactivation. Concurrent use of these agents may pose a risk of reduced antibacterial efficacy *in vivo*, particularly in the setting of profound renal impairment. However, definitive clinical evidence is lacking. If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered.

Administration: I.V. DetailpH: 8-10 (reconstituted solution)

Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels. Administer on an empty stomach (ie, 1 hour prior to, or 2 hours after meals) to increase total absorption.

Dietary ConsiderationsTake on an empty stomach 1 hour before or 2 hours after meals.

Sodium content of 5 mL suspension (250 mg/5 mL): 10 mg (0.4 mEq)

Sodium content of 1 g: 66.7 mg (3 mEq)

Storage

Oral: Oral suspension is stable for 7 days at room temperature or for 14 days under refrigeration.

I.V.:

Solutions for I.M. or direct I.V. should be used within 1 hour. Solutions for I.V. infusion will be inactivated by dextrose at room temperature. If dextrose-containing solutions are to be used, the resultant solution will only be stable for 2 hours versus 8 hours in the 0.9% sodium chloride injection. D_5W has limited stability.

Stability of parenteral admixture in NS at room temperature (25°C) is 8 hours.

Stability of parenteral admixture in NS at refrigeration temperature (4°C) is 2 days.

ReconstitutionI.V.: Minimum volume: Concentration should not exceed 30 mg/mL due to concentration-dependent stability restrictions. Standard diluent: 500 mg/50 mL NS; 1 g/50 mL NS; 2 g/100 mL NS.

Compatibility**Incompatible** in D_5W, D_5NS, $D_{10}W$, fat emulsion 10%, hetastarch 6%, LR; **variable stability (consult detailed reference)** in NS.

Y-site administration: Compatible: Acyclovir, amifostine, aztreonam, clarithromycin, cyclophosphamide, docetaxel, doxorubicin liposome, enalaprilat, esmolol, etoposide, famotidine, filgrastim, fludarabine, foscarnet, gatifloxacin, gemcitabine, granisetron, heparin, heparin with hydrocortisone sodium succinate, insulin (regular), labetalol, levofloxacin, linezolid, magnesium sulfate, melphalan, meperidine, morphine, multivitamins, ofloxacin, perphenazine, phytonadione, potassium chloride, propofol, remifentanil, tacrolimus, teniposide, theophylline, thiotepa, tolazoline, vitamin B complex with C. **Incompatible:** Amphotericin B cholesteryl sulfate complex, epinephrine, fluconazole, hydralazine, midazolam, ondansetron, sargramostim, verapamil, vinorelbine. **Variable (consult detailed reference):** Calcium gluconate, cisatracurium, diltiazem, hetastarch, hydromorphone, vancomycin.

Compatibility in syringe: Compatible: Chloramphenicol, colistimethate, diatrizoate meglumine 52%, diatrizoate sodium 8%, diatrizoate sodium 60%, heparin, iohexol, iopamidol, iothalamate meglumine 60%, ioxaglate meglumine 39.3%, ioxaglate 19.6%, procaine. **Incompatible:** Erythromycin lactobionate, gentamicin, hydromorphone, kanamycin, lincomycin, metoclopramide. **Variable (consult detailed reference):** Lidocaine, polymyxin B sulfate, streptomycin.

Compatibility when admixed: Compatible: Clindamycin, erythromycin lactobionate, floxacillin, furosemide. **Incompatible:** Amikacin, chlorpromazine, dopamine, gentamicin, hydralazine, prochlorperazine. **Variable (consult detailed reference):** Aztreonam, cefepime, cimetidine, heparin, hydrocortisone sodium succinate, metronidazole, metronidazole with sodium bicarbonate, ranitidine, sodium bicarbonate, verapamil.

ContraindicationsHypersensitivity to ampicillin, any component of the formulation, or other penicillins

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- Rash: Appearance of a rash should be carefully evaluated to differentiate a nonallergic ampicillin rash from a hypersensitivity reaction; rash occurs in 5% to 10% of children and is a generalized dull red, maculopapular rash, generally appearing 3-14 days after the start of therapy. It normally begins on the trunk and spreads over most of the body. It may be most intense at pressure areas, elbows, and knees.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Infectious mononucleosis: A high percentage of patients with infectious mononucleosis have developed rash during therapy; ampicillin-class antibiotics not recommended in these patients.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Geriatric ConsiderationsAdjust dose for renal function.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, ampicillin is classified as pregnancy category B. Ampicillin crosses the human placenta, providing detectable concentrations in the cord serum and amniotic fluid. Most studies have not identified a teratogenic potential for ampicillin use during pregnancy. Two possible associations (congenital heart disease and cleft palate) have been noted; each of these was observed in a single study, was not substantiated by other studies, and may have been chance associations. Ampicillin is recommended for use in pregnant women for the management of premature rupture of membranes. Ampicillin is considered an acceptable alternative to penicillin for the prevention of early-onset Group B Streptococcal (GBS) disease in newborns.

The volume of distribution of ampicillin is increased during pregnancy and the half-life is decreased. As a result, serum concentrations in pregnant patients are approximately 50% of those in nonpregnant patients receiving the same dose. Higher doses may be needed during pregnancy. Although oral absorption is not altered during pregnancy, oral ampicillin is poorly-absorbed during labor.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsAmpicillin is excreted in breast milk. The manufacturer recommends that caution be exercised when administering ampicillin to nursing women. Due to the low concentrations in human milk, minimal toxicity would be expected in the nursing infant. Nondose-related effects could include modification of bowel flora and allergic sensitization.

Pregnancy & Lactation, In-Depth

- Ampicillin in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Fever, penicillin encephalopathy, seizure

Dermatologic: Erythema multiforme, exfoliative dermatitis, rash, urticaria

Note: Appearance of a rash should be carefully evaluated to differentiate (if possible) nonallergic ampicillin rash from hypersensitivity reaction. Incidence is higher in patients with viral infection, *Salmonella* infection, lymphocytic leukemia, or patients that have hyperuricemia.

Gastrointestinal: Black hairy tongue, diarrhea, enterocolitis, glossitis, nausea, oral candidiasis, pseudomembranous colitis, sore mouth or tongue, stomatitis, vomiting

Hematologic: Agranulocytosis, anemia, hemolytic anemia, eosinophilia, leukopenia, thrombocytopenia purpura

Hepatic: AST increased

Renal: Interstitial nephritis (rare)

Respiratory: Laryngeal stridor

Miscellaneous: Anaphylaxis, serum sickness-like reaction

Drug Interactions

Allopurinol: May enhance the potential for allergic or hypersensitivity reactions to Ampicillin. *Risk C: Monitor therapy*

Atenolol: Ampicillin may decrease the bioavailability of Atenolol. *Risk C: Monitor therapy*

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Food decreases ampicillin absorption rate; may decrease ampicillin serum concentration.
Test InteractionsMay interfere with urinary glucose tests using cupric sulfate (Benedict's solution, Clinitest®)

Some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*, leading to a potential underestimation of aminoglycoside serum concentration.

Monitoring ParametersWith prolonged therapy, monitor renal, hepatic, and hematologic function periodically; observe signs and symptoms of anaphylaxis during first dose
Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's allergy history prior to starting therapy. Assess potential for interactions with other medications patient may be taking. Caution patients with diabetes about altered response to Clinitest®. Assess therapeutic effectiveness and adverse reactions (eg, opportunistic infection [fever, chills, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge, fatigue]). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsPerform culture and sensitivity testing prior to initiating therapy.
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take entire prescription, even if you are feeling better. Take at equal intervals around-the-clock; preferably on an empty stomach with a full glass of water (1 hour before or 2 hours after meals). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, drug may cause false test results with Clinitest® urine glucose monitoring; use of another type of glucose monitoring is preferable. May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report immediately any rash; persistent diarrhea; swelling of face, tongue, mouth, or throat; or chest tightness. Report if condition being treated worsens or does not improve by the time prescription is completed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 250 mg, 500 mg

Injection, powder for reconstitution, as sodium: 125 mg, 250 mg, 500 mg, 1 g, 2 g, 10 g

Powder for oral suspension: 125 mg/5 mL (100 mL, 200 mL); 250 mg/5 mL (100 mL, 200 mL)

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsules (Ampicillin)

250 mg (30): $12.99

250 mg (90): $31.95

500 mg (100): $49.99

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: Oral: 50%

Distribution: Bile, blister, and tissue fluids; penetration into CSF occurs with inflamed meninges only, good only with inflammation (exceeds usual MICs)

Normal meninges: Nil; Inflamed meninges: 5% to 10%

Protein binding: 15% to 25%

Half-life elimination:

Children and Adults: 1-1.8 hours

Anuria/end-stage renal disease: 7-20 hours

Time to peak: Oral: Within 1-2 hours

Excretion: Urine (~90% as unchanged drug) within 24 hours

Related Information

- Antibiotic Treatment of Adults With Infective Endocarditis
- Antimicrobial Drugs of Choice
- Desensitization Protocols
- Prevention of Infective Endocarditis
- Skin Tests

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral candidiasis, black hairy tongue, glossitis, sore mouth or tongue, and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusLarge I.V. doses may rarely produce encephalopathy; penicillins have been reported to cause apprehension, illusions, agitation, insomnia, depersonalization, and encephalopathy

Mental Health: Effects on Psychiatric TreatmentRarely may cause bone marrow suppression; use caution with clozapine and carbamazepine

Index TermsAminobenzylpenicillin; Ampicillin Sodium; Ampicillin Trihydrate

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International Brand Names Aldribid (PH); Alphacin (AU, NZ); Alphapen (MX); Ambiopi (ID); Amcillin (ID); Amcopen (PK); Amfipen (AE, BH, CY, EG, GB, IE, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Amipenix (JP); Ampecu (EC); Ampen (VE); Ampenolet (GR); Ampiblan (CO); Ampicher (EC); Ampicil (BR); Ampicilina (EC); Ampicillin (PL); Ampicin (PH); Ampiclox (BB, BM, BS, BZ, GY, JM, NL, SG, SR, TT); Ampidar (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ampifen (NL); Ampiflex (PE); Ampiger (BR); Ampilag (BB, BF, BJ, BM, BS, BZ, CI, ET, GH, GM, GN, GY, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, SC, SD, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Ampilin (IN); Ampillin (MY); Ampimedin (PY); Ampipen (IN, ZA); Ampitenk (AR); Ampivral (CO); Ampliblan (CO); Ampolin (TW); Amsapen (MX); Arcocillin (ID); Binotal (AT, BR, CO, EC, MX, UY); Biocil (MY); Bridopen (PH); Brupen (MX); Camicil (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Cilisod (TW); Citicil (IT); Clovillin (PH); Dhacillin (HK, MY); Dibacilina (MX); Doktacillin (SE); Duacillin (MY); Eracillin (TH); Eurocin (PH); Excillin (PH); Extrapen (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Flamicina (MX); Gramcil (PH); H-Ambiotico (CO); Ibimycin (AU); Intramed (ZA); Iwacillin (JP); Julphapen (PE); Magnapen (PE); Marovilina (MX); Maxipen (CO); Omnipen (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, MX, OM, PE, QA, SA, SY, YE); Oracipen (ID); Pamecil (BF, BJ, CI, ET, GH, GM, GN, HK, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SG, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Panacta (PH); Penbiotic (ID); Penbritin (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, HK, ID, IE, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Penibrin (IL); Penodil (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Pentrexyl (BE, BF, BJ, CI, DK, ET, GB, GH, GM, GN, GR, IT, KE, LR, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, PE, SC, SD, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Petercillin (ZA); Picylin (CO); Polypen (PH); Primapen (ID); Promecilina (MX); Radiocillina (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Rimacillin (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Roscillin (IN); Sanpicillin (ID); Semicillin (HN); Shacillin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Sintelin (PE); Standacillin (AE, BG, BH, CY, EE, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Standcillin (MY); Synthocilin (IN); Totapen (FR); Tricil (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Trifalicina (AR); Trilaxin (PH); Vacillin (TH); Viccillin (ID); Vidopen (GB, IE); Virucil (CO)

Amprenavir

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(am PREN a veer)

U.S. Brand NamesAgenerase® [DSC]

Canadian Brand NamesAgenerase®

Pharmacologic CategoryAntiretroviral Agent, Protease Inhibitor

Use: Labeled IndicationsTreatment of HIV infections in combination with at least two other antiretroviral agents; oral solution should only be used when capsules or other protease inhibitors are not therapeutic options

Dosing: Adults**Note:** Capsule and oral solution are **not** interchangeable on a mg-per-mg basis.

HIV infection: Oral:

Capsule:

<50 kg: 20 mg/kg twice daily (maximum: 2400 mg/day)

≥50 kg: 1200 mg twice daily

Dosage adjustments for amprenavir when administered in combination therapy:

Efavirenz: Adjustments necessary for both agents:

Amprenavir 1200 mg 3 times/day (single protease inhibitor) **or**

Amprenavir 1200 mg twice daily plus ritonavir 200 mg twice daily

Ritonavir: Adjustments necessary for both agents:

Amprenavir 1200 mg plus ritonavir 200 mg once daily **or**

Amprenavir 600 mg plus ritonavir 100 mg twice daily

Note: Oral solution of ritonavir and amprenavir should not be coadministered.

Solution:

<50 kg: 22.5 mg/kg (maximum: 2800 mg/day)

≥50 kg: 1400 mg twice daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Capsule and oral solution are **not** interchangeable on a mg-per-mg basis.

HIV infection: Oral:

Capsule:

Children 4-12 years **or** 13-16 years (<50 kg): 20 mg/kg twice daily or 15 mg/kg 3 times daily; maximum: 2400 mg/day

Children >13 years (≥50 kg): 1200 mg twice daily

Solution:

Children 4-12 years **or** 13-16 years (<50 kg): 22.5 mg/kg twice daily or 17 mg/kg 3 times daily; maximum: 2800 mg/day

Children >13 years (≥50 kg): 1400 mg twice daily

Dosing: Renal ImpairmentOral solution is contraindicated in renal failure.

Dosing: Hepatic Impairment

Child-Pugh score between 5-8:

Capsule: 450 mg twice daily

Solution: 513 mg twice daily; contraindicated in hepatic failure.

Child-Pugh score between 9-12:

Capsule: 300 mg twice daily

Solution: 342 mg twice daily; contraindicated in hepatic failure.

Dietary ConsiderationsMay be taken with or without food; do not take with high-fat meal. The 50 mg capsules contain 36.3 int. units of vitamin E per capsule; oral solution contains 46 int. units of vitamin E per mL; avoid additional vitamin E-containing supplements.

ContraindicationsHypersensitivity to amprenavir or any component of the formulation; concurrent therapy with cisapride, ergot derivatives, midazolam, pimozide, and triazolam; severe previous allergic reaction to sulfonamides; oral solution is contraindicated in infants or children <4 years of age, pregnant women, patients with renal or hepatic failure, and patients receiving concurrent metronidazole or disulfiram

Allergy Considerations

- Amprenavir Allergy

Warnings/Precautions

Boxed warnings:

- Ethnic populations: See “Special populations” below.

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Hypersensitivity reactions: Protease inhibitors have been associated with a variety of hypersensitivity events (some severe), including rash, anaphylaxis (rare), angioedema, bronchospasm, erythema multiforme, and/or Stevens-Johnson syndrome (rare). It is generally recommended to discontinue treatment if severe rash or moderate symptoms accompanied by other systemic symptoms occur.
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Sulfonamide allergy: Use with caution in patients with sulfonamide allergy.

Disease-related concerns:

- Diabetes: Changes in glucose tolerance, hyperglycemia, exacerbation of diabetes, DKA, and new-onset diabetes mellitus have been reported in patients receiving protease inhibitors.
- Hemophilia A or B: Use with caution in patients with hemophilia A or B; increased bleeding during protease inhibitor therapy has been reported.
- Hepatic impairment: May cause hepatitis and/or exacerbate pre-existing hepatic dysfunction; use with caution in patients with underlying hepatic disease, such as hepatitis B or C or cirrhosis.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.
- Vitamin E: Formulations contain vitamin E; additional vitamin E supplements should be avoided.

Special Populations:

- Ethnic populations: **[U.S. Boxed Warning]: Certain ethnic populations (Asians, Eskimos, Native Americans) may be at increased risk of propylene glycol-associated adverse effects; use of the oral solution of amprenavir should be avoided.**
- Pediatrics: Safety and efficacy in children <4 years of age have not been established.

Dosage form specific issues:

- Oral solution: Use oral solution only when capsules or other protease inhibitors are not options; due to increased risk of propylene glycol-associated adverse effects.

Pregnancy Risk FactorC

Pregnancy ConsiderationsIt is not known if amprenavir crosses the human placenta and there are no clinical studies currently underway to evaluate its use in pregnant women. Use of oral solution is contraindicated during pregnancy. Pregnancy and protease inhibitors are both associated with an increased risk of hyperglycemia. Glucose levels should be closely monitored. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse Reactions

>10%:

Central nervous system: Depression/mood disorder (9% to 16%), paresthesia (peripheral 10% to 14%)

Dermatologic: Rash (20% to 27%)

Endocrine & metabolic: Hyperglycemia (>160 mg/dL: 37% to 41%), hypertriglyceridemia (>399 mg/dL: 36% to 47%; >750 mg/dL: 8% to 13%)

Gastrointestinal: Nausea (43% to 74%), vomiting (24% to 34%), diarrhea (39% to 60%), abdominal symptoms

Miscellaneous: Perioral tingling/numbness (26% to 31%)

1% to 10%:

Central nervous system: Headache, fatigue

Dermatologic: Stevens-Johnson syndrome (1% of total, 4% of patients who develop a rash)

Endocrine & metabolic: Hypercholesterolemia (>260 mg/dL: 4% to 9%), hyperglycemia (>251 mg/dL: 2% to 3%), fat redistribution

Gastrointestinal: Taste disorders (2% to 10%), amylase increased (3% to 4%)

Hepatic: AST increased (3% to 5%), ALT increased (4%)

<1%: New-onset diabetes

Metabolism/Transport Effects **Substrate** of CYP2C9 (minor), 3A4 (major); **Inhibits** CYP2C19 (weak), 3A4 (strong)
Drug Interactions

Abacavir: Protease Inhibitors may decrease the serum concentration of Abacavir. *Risk C: Monitor therapy*

Alcohol (Ethyl): May enhance the adverse/toxic effect of Amprenavir. This is specifically related to the propylene glycol contained in amprenavir oral solution, not capsules. *Risk X: Avoid combination*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amiodarone: Protease Inhibitors may decrease the metabolism of Amiodarone. *Risk X: Avoid combination*

Antacids: May decrease the absorption of Protease Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Protease Inhibitors may decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Dihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Protease Inhibitors. Protease Inhibitors may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cisapride: Protease Inhibitors may decrease the metabolism of Cisapride. The resultant increase in serum cisapride concentrations may result in QTc prolongation and malignant cardiac arrhythmias. *Risk X: Avoid combination*

Clarithromycin: Protease Inhibitors may diminish the therapeutic effect of Clarithromycin. Specifically, certain protease inhibitors may decrease formation of the active 14-hydroxy-clarithromycin metabolite, which may negatively impact clarithromycin effectiveness vs. H. influenzae and other non-MAC infections. Protease Inhibitors may increase the serum concentration of Clarithromycin. Clarithromycin dose adjustment in renally impaired patients may be needed. Clarithromycin may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): Protease Inhibitors may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk D: Consider therapy modification*

CycloSPORINE: Protease Inhibitors may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Delavirdine: Amprenavir may decrease the serum concentration of Delavirdine. Delavirdine may increase the serum concentration of Amprenavir. *Risk X: Avoid combination*

Digoxin: Protease Inhibitors may increase the serum concentration of Digoxin. Increased serum concentrations of digoxin may increase risk of

AV nodal blockade. *Risk C: Monitor therapy*

Disulfiram: May enhance the adverse/toxic effect of Amprenavir. This is specifically related to the propylene glycol contained in amprenavir oral solution, not capsules. Management: Specifically, concurrent amprenavir oral solution and disulfiram is contraindicated due to the large amount of propylene glycol in the oral solution. *Risk X: Avoid combination*

Efavirenz: May increase the metabolism of Protease Inhibitors. This specifically includes amprenavir, indinavir, and saquinavir. Efavirenz may increase the serum concentration of Protease Inhibitors. This specifically includes nelfinavir and ritonavir. *Risk D: Consider therapy modification*

Enfuvirtide: Protease Inhibitors may increase the serum concentration of Enfuvirtide. Enfuvirtide may increase the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

Eplerenone: Protease Inhibitors may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Protease Inhibitors may decrease the metabolism of Ergot Derivatives. **Exceptions:** Cabergoline. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

FentaNYL: Protease Inhibitors may decrease the metabolism of FentaNYL. *Risk C: Monitor therapy*

Fusidic Acid: Protease Inhibitors may decrease the metabolism of Fusidic Acid. Fusidic Acid may decrease the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Garlic: May decrease the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Protease Inhibitors may increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. **Exceptions:** Fluvastatin. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Meperidine: Protease Inhibitors may enhance the adverse/toxic effect of Meperidine. Protease Inhibitors may decrease the serum concentration of Meperidine. Concentrations of the toxic Normeperidine metabolite may be increased. *Risk D: Consider therapy modification*

Methadone: Protease Inhibitors may decrease the metabolism of Methadone. *Risk C: Monitor therapy*

MetroNIDAZOLE: May enhance the adverse/toxic effect of Amprenavir. This is specifically related to the propylene glycol contained in amprenavir oral solution, not capsules. *Risk X: Avoid combination*

Nefazodone: Protease Inhibitors may decrease the metabolism of Nefazodone. *Risk C: Monitor therapy*

Nevirapine: May increase the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): May diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

PARoxetine: Amprenavir may decrease the serum concentration of PARoxetine. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the serum concentration of Amprenavir. Amprenavir may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: Protease Inhibitors may decrease the metabolism of Phosphodiesterase 5 Inhibitors. Management: Dose restrictions for tadalafil, and/or sildenafil and vardenafil are recommended in combination with ritonavir, atazanavir, indinavir, darunavir and saquinavir. Consult specific prescribing information for detailed recommendations. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Protease Inhibitors may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Protease Inhibitors: May increase the serum concentration of other Protease Inhibitors. Management: Atazanavir--indinavir combination contraindicated. Amprenavir oral solution not recommended with ritonavir oral solution; tipranavir/ritonavir or atazanavir/ritonavir not recommended with other protease inhibitors. Other combos may require dose changes. *Risk D: Consider therapy modification*

QuiNIDine: Protease Inhibitors may decrease the metabolism of QuiNIDine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: Protease Inhibitors may decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Sirolimus: Protease Inhibitors may increase the serum concentration of Sirolimus. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Protease Inhibitors. *Risk X: Avoid combination*

Tacrolimus: Protease Inhibitors may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Temsirolimus: Protease Inhibitors may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tenofovir: May decrease the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Tenofovir. *Risk C: Monitor therapy*

TraZODone: Protease Inhibitors may increase the serum concentration of TraZODone. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Protease Inhibitors may increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Valproic Acid: Protease Inhibitors may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Zidovudine: Protease Inhibitors may decrease the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol with amprenavir oral solution.

Food: Levels increased sixfold with high-fat meals.

Herb/Nutraceutical: Amprenavir serum concentration may be decreased by St John's wort; avoid concurrent use. Formulations contain vitamin E; avoid additional supplements.

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions or toxicity (multiple liver enzyme interactions may increase or decrease levels/effects of drugs and increase potential for severe toxicity or loss of effectiveness); dosing adjustments may be necessary. A list of medications that should not be used is available in each bottle and patients should be provided with this information. Assess therapeutic response (CD4 count, hepatic function) and adverse reactions (eg, gastrointestinal disturbance, nausea, vomiting, diarrhea that can lead to dehydration and weight loss; hyperlipidemia and redistribution of body fat; rash; CNS effects, malaise, insomnia, abnormal thinking; electrolyte imbalance) at regular intervals during therapy. Caution patients to monitor glucose levels closely; protease inhibitors may cause hyperglycemia or new-onset diabetes. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions (eg, glucose testing; use of barrier contraceptives, protease inhibitors may decrease effectiveness of oral contraceptives), and adverse symptoms to report.

Monitoring: Lab TestsViral load

Patient EducationYou will be provided with a list of specific medications that should not be used during therapy; do not take any new prescriptions, over-the-counter medications, or herbal products (even if they are not on the list) without consulting prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. This drug is prescribed as one part of a multidrug combination; take exactly as directed for full course of therapy. May take with light meal (eg, dry toast, skim milk, corn flakes) to reduce GI upset. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. Do not take antacids within one hour of this medication. You may be susceptible to infection; avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber. Frequent blood tests may be required with prolonged therapy. You may be advised to check your glucose levels; medication can cause hyperglycemia. May cause body changes due to redistribution of body fat, facial atrophy, or breast enlargement (normal effects of drug); nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); muscle weakness or flank pain (consult prescriber for approved analgesic); headache or insomnia (consult prescriber for medication); or diarrhea (boiled milk, buttermilk, or yogurt may help). Inform prescriber if you experience muscle numbness or tingling; unresolved persistent vomiting, diarrhea, or abdominal pain; respiratory difficulty or chest pain; unusual skin rash; unusual depression; change in color of stool or urine; or any persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug decreases the effect of oral contraceptives; use of alternative (nonhormonal) forms of contraception is recommended; consult prescriber for use of appropriate barrier contraceptives. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

Agenerase®: 50 mg [contains vitamin E 36.3 int. units (as TPGS)] [DSC]

Solution, oral:

Agenerase®: 15 mg/mL (240 mL) [contains propylene glycol 550 mg/mL and vitamin E 46 int. units/mL; grape-bubble gum-peppermint flavor] [DSC]

Generic AvailableNo

ManufacturerGlaxoSmithKline
Pricing: U.S. (www.drugstore.com)

Capsules (Agenerase)

50 mg (480): $269.04

Solution (Agenerase)

15 mg/mL (240): $49.99

Mechanism of ActionBinds to the protease activity site and inhibits the activity of the enzyme. HIV protease is required for the cleavage of viral polyprotein precursors into individual functional proteins found in infectious HIV. Inhibition prevents cleavage of these polyproteins, resulting in the formation of immature, noninfectious viral particles.

Pharmacodynamics/Kinetics

Absorption: 63%

Distribution: 430 L

Protein binding: 90%

Metabolism: Hepatic via CYP (primarily CYP3A4)

Bioavailability: Not established; increased sixfold with high-fat meal; oral solution: 86% relative to capsule formulation (14% less bioavailable than capsule)

Half-life elimination: 7.1-10.6 hours

Time to peak: 1-2 hours

Excretion: Feces (75%, ~68% as metabolites); urine (14% as metabolites)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV

Pharmacotherapy PearlsPropylene glycol is included in the oral solution; a dose of 22.5 mg/kg twice daily corresponds to an intake of 1650 mg/kg of propylene glycol. Capsule and oral solution are not interchangeable on a mg-per-mg basis.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Perioral tingling/numbness and taste disorder

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDepression is common; may cause headache and fatigue

Mental Health: Effects on Psychiatric TreatmentContraindicated with midazolam and triazolam. Concurrent use with vitamin E and sildenafil should be avoided. May increase concentrations of alprazolam, clorazepate, diazepam, flurazepam, sildenafil, carbamazepine, and pimozide. May increase adverse effects of TCAs (monitor serum levels). Concomitant use of amprenavir and St John's wort is not recommended. Coadministration of protease inhibitors (amprenavir) with St John's wort is expected to substantially decrease protease inhibitor serum concentrations leading to a loss of virologic response and possible resistance to amprenavir or to the class of protease inhibitors.

Anesthesia and Critical Care Concerns/Other ConsiderationsPropylene glycol is included in the oral solution; a dose of 22.5 mg/kg twice daily corresponds to an intake of 1650 mg/kg of propylene glycol. Capsule and oral solution are not interchangeable on a mg-per-mg basis.

References

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Kaul DR, Cinti SK, Carver PL, et al, “HIV Protease Inhibitors: Advances in Therapy and Adverse Reactions, Including Metabolic Complications,” *Pharmacotherapy*, 1999, 19(3):281-98. [PubMed 10221367]

“Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States,” October 12, 2006. Available at: http://www.aidsinfo.nih.gov.

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” February 28, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesAgenerase (AR, AT, AU, BE, BG, BR, CH, CN, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, MX, NL, NO, PL, PT, RU, SE, TR, UY, VE)

Amsacrine

English

Jump To Field (Select Field Name)

Pronunciation(AM sah kreen)

Canadian Brand NamesAMSA PD

Pharmacologic CategoryAntineoplastic Agent

Use: Labeled IndicationsCanada: Refractory acute leukemia

Use: Unlabeled/InvestigationalAcute myeloid leukemia (AML)

Dosing: AdultsDetails concerning dosing in combination regimens should also be consulted.

Acute leukemia: I.V.:

Induction: 75-125 mg/m^2/day for 5 days every 3-4 weeks (125 mg/m^2/day is preferred; two courses may be necessary to achieve induction; increase dose by 20% in second and subsequent cycles if marrow hypoplasia not achieved and in absence of significant toxicity in previous course.)

Maintenance: Once remission has been achieved, maintenance dose should be ~50% of induction dose, administered every 4-8 weeks, depending on blood counts and marrow recovery

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Dosage reduction recommended; specific guidelines from the manufacturer are not available; the following guidelines have been used by some clinicians:

Hall, 1983:

Serum creatinine 1.2-1.8 mg/dL: No adjustment recommended

Serum creatinine 2-3 mg/dL, oliguric patients: Administer 60% to 70% of dose; may increase subsequent dose based on toxicity.

Hornedo, 1985: BUN >20 mg/dL or serum creatinine >1.5 mg/dL: Administer 75% of dose

Dosing: Hepatic ImpairmentBilirubin >2 mg/dL: Dosage reduction recommended; specific guidelines from the manufacturer are not available; the following guidelines have been used by some clinicians:

Hall, 1983: Bilirubin >2 mg/dL: Administer 60% to 70% of dose; may increase subsequent dose based on toxicity.

Hornedo, 1985: Bilirubin >2 mg/dL: Administer 75% of dose

Koren, 1992: Severe hepatic dysfunction: Administer ≤50% of dose

Dosing: Adjustment for ToxicityConsider decreasing dose by 20% if life-threatening infection or hemorrhage occurred in previous cycle; delay second and subsequent cycles until recovery from myelosuppression or evidence of leukemic infiltrate is evident.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Infuse over 60-90 minutes; avoid extravasation.

StorageStore intact ampuls and diluent vials at controlled room temperature of 15°C to 25°C (59°F to 77°F). Concentrated amsacrine should not be stored in plastic syringes for >15 minutes. Reconstituted vials may be stored at room temperature for up to 24 hours, under ambient light conditions. Solutions diluted for administration are stable for up to 7 days in glass or plastic containers, however, the manufacturer recommends use with in 24 hours when stored at room temperature and 72 hours if refrigerated.

ReconstitutionUse appropriate precautions for handling and disposal. Reconstitute by adding 1.5 mL amsacrine to diluent vial (containing 13.5 mL L-lactic acid), resulting in a 5 mg/mL reconstituted solution. Glass syringes should be used, however if using plastic syringes, do not allow concentrated amsacrine to remain in plastic syringe for >15 minutes. Further dilute appropriate dose in 500 mL D_5W (the solution may be mixed in plastic bags when diluted for infusion).

CompatibilityStable in D_5W; **incompatible** with BNS, D_5NS, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5LR, $D_{10}NS$, NSS, LR, chloride ion. Amsacrine forms an immediate precipitate in the presence of chloride ion; do not mix with drugs that are chloride or hydrochloride salts.

Y-site administration: Compatible: Amikacin, chlorpromazine, clindamycin, cytarabine, dexamethasone, diphenhydramine, famotidine, fludarabine, gentamicin, granisetron, haloperidol, hydrocortisone sodium succinate, hydromorphone, lorazepam, morphine, prochlorperazine, promethazine, ranitidine, sodium bicarbonate, tobramycin, vancomycin. **Incompatible:** Acyclovir, amphotericin, aztreonam, calcium chloride, ceftazidime, ceftriaxone, cephalothin, cimetidine, cisplatin, filgrastim, furosemide, ganciclovir, heparin, methylprednisolone, metoclopramide, ondansetron, potassium chloride, sargramostim.

Compatibility when admixed: Compatible: Sodium bicarbonate, bleomycin

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to amsacrine, acridine derivatives, or any component of the formulation; pre-existing bone marrow suppression due to chemotherapy or radiation therapy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Myelosuppression, including transient leukopenia, is a common toxicity; prolonged marrow aplasia may occur. May require dose reduction, therapy interruption or treatment delay.
- Cardiovascular effects: Acute cardiotoxicity, including arrhythmia, ECG changes, and rarely, cardiomyopathy and CHF, have been reported with use, although generally not considered to be a cumulative dose effect. Risk factors for cardiotoxicity may include hypokalemia and a history of anthracycline therapy. Correct fluid and electrolyte imbalance prior to treatment initiation. Use with caution in patients with underlying cardiovascular disease.
- Tumor lysis syndrome: Tumor lysis syndrome may occur; adequate hydration and prophylactic uric acid reduction should be considered prior to or during treatment; monitor closely.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with significant hepatic impairment (bilirubin >2 mg/dL); toxicity may be increased. Hepatic metabolism and biliary excretion are major routes of elimination. Dosage reductions may be recommended. Evaluate hepatic function prior to and during treatment.
- Hypokalemia: Serum potassium should be >4 mEq/L prior to administration (Arlin, 1988). The risk for arrhythmia is decreased by ensuring normal potassium levels.
- Renal impairment: Use with caution in patients with significant renal impairment (BUN >20 mg/dL; serum creatinine >1.2 mg/dL); toxicity may be increased. Dosage reductions may be recommended. Evaluate renal function prior to and during treatment.

Concurrent drug therapy issues:

- Anthracyclines: Use with caution in patients who have received high cumulative doses of anthracyclines (may increase the risk for cardiotoxicity).
- Vaccinations: Avoid vaccination with live virus vaccines during treatment.

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Women of childbearing potential should avoid becoming pregnant while receiving treatment.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsBreast-feeding should be discontinued prior to treatment.

Adverse Reactions

>10%:

Gastrointestinal: Nausea (>10%), vomiting (>10%), stomatitis (>10%), diarrhea (>10%), perirectal abscess (>10%), abdominal pain (>10%)

Hematologic: Myelosuppression, leukopenia (nadir: 11-13 days; recovery: days 17-25)

Frequency not defined:

Cardiovascular: Atrial tachyarrhythmia, atrial tachycardia, atrial fibrillation, bradycardia, cardiomyopathy (rare), cardiopulmonary arrest, CHF (rare); ECG changes (QT prolongation, nonspecific ST segment or T wave changes); ejection fraction decreased, hypotension, sinus tachycardia, tachycardia, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular tachyarrhythmia

Central nervous system: Confusion, dizziness, emotional lability, fever, headache, hypoesthesia, lethargy, seizure

Dermatologic: Alopecia, cutaneous inflammatory reaction, dermatologic reaction, purpura, rash (purpuric or maculopapular), urticaria

Gastrointestinal: Anorexia, dysphagia, gingivitis, gum hemorrhage, hematemesis, weight changes

Genitourinary: Orange-red discoloration of the urine

Hematologic: Anemia, granulocytopenia, hemorrhage, pancytopenia, thrombocytopenia

Hepatic: Alkaline phosphatase increased, AST increased, bilirubin increased, hepatic insufficiency, hepatitis, hepatotoxicity, jaundice, progressive liver failure

Local: Injection site inflammation, phlebitis

Neuromuscular & skeletal: Musculoskeletal pain, paresthesia, weakness

Renal: BUN increased, creatinine increased, hematuria, proteinuria, renal failure

Respiratory: Dyspnea

Miscellaneous: Allergic reaction, infection

Oncology: VesicantYes; see Management of Drug Extravasations.
Oncology: Emetic PotentialModerate (30% to 60%)
Drug Interactions

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Monitoring Parameters

CBC with differential, bone marrow studies, serum potassium, hepatic function, renal function; ECG (during and after infusion)

Monitoring: Lab Tests

CBC with differential, bone marrow studies, serum potassium, hepatic function, renal function

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, solution [preservative free]:

AMSA PD [CAN]: 50 mg/mL (1.5 mL) [supplied with L-lactic acid 0.0353 M 13.5 mL] [not available in the U.S.]

Generic AvailableNo
Mechanism of ActionAmsacrine has been shown to inhibit DNA synthesis by binding to, and intercalating with, DNA; inhibits topoisomerase II activity.
Pharmacodynamics/Kinetics

Distribution: V_d: 1.67 L/kg; minimal CNS penetration

Protein binding: 96% to 98%

Metabolism: Hepatic, to inactive metabolites (major metabolite is 5′ glutathione conjugate)

Half-life elimination: 1.4-5 hours; Terminal: 8-9 hours

Excretion: Bile; urine (35%; 20% as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral ulcerations and stomatitis
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness or confusion
Mental Health: Effects on Psychiatric TreatmentECG changes are common; avoid concomitant use with ziprasidone. GI side effects are common; concomitant use with SSRIs, lithium, or valproic acid may produce additive effects. Hematologic adverse effects are common; use caution with clozapine and valproic acid.
Index Terms4-(9-Acridinylamino) Methanesulfon-m-Anisidide; Acridinyl Anisidide; AMSA; m-AMSA; NSC-249992
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International Brand NamesAmekrin (DK, SE); Amsidine (BE, NL); Amsidyl (AU)

Amyl Nitrite

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(AM il NYE trite)

Pharmacologic CategoryAntidote; Vasodilator

Use: Labeled IndicationsCoronary vasodilator in angina pectoris; adjunct in treatment of cyanide poisoning; produce changes in the intensity of heart murmurs

Dosing: Adults

Angina: Inhalation: 1-6 inhalations from 1 crushed ampul; may repeat in 3-5 minutes

Cyanide poisoning: Inhalation: Inhale the vapor from a 0.3 mL crushed ampul every minute for 15-30 seconds until I.V. sodium nitrite infusion is available

Dosing: ElderlyRefer to adult dosing.

Administration: OralAdminister nasally. Keep patient lying down during administration. Crush ampul in woven covering between fingers and then hold under patient's nostrils for 15-30 seconds.

StorageStore in cool place and protect from light.

ContraindicationsHypersensitivity to nitrates; severe anemia; head injury; angle-closure glaucoma; postural hypotension; head trauma or cerebral hemorrhage; pregnancy

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease and patients with hypotension.
- Increased intracranial pressure: Use with caution in patients with increased intracranial pressure.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Postural hypotension, cutaneous flushing of head, neck, and clavicular area, palpitations, tachycardia, sinus tachycardia, vasodilation

Central nervous system: Headache, incoherent speech, restlessness

Dermatologic: Contact dermatitis

Gastrointestinal: Nausea, colitis, vomiting

Genitourinary: Penile erection enhanced, retarded ejaculation

Hematologic: Heinz body hemolysis/hemolytic anemia

Ocular: Increased intraocular pressure, blurred vision

Respiratory: Tracheobronchitis

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Monitoring ParametersMonitor blood pressure during therapy

Nursing: Physical Assessment/MonitoringMonitor blood pressure and heart rate closely during and following therapy. **Pregnancy risk factor X.** Breast-feeding is not recommended.

Patient EducationWhen this drug is used in emergency situations, patient education should be appropriate to situation (ie, do not change positions or make any sudden moves without asking for assistance). If patient administered, lie down during administration, crush ampul in woven covering between fingers, and then hold under nose and inhale. May repeat in 3-5 minutes if necessary. If no relief after three doses, contact emergency services for immediate transport to the hospital. Vapors are highly flammable; do not use where vapors may ignite. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant, may cause severe fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Vapor for inhalation [crushable covered glass capsules]: Amyl nitrite USP (0.3 mL)

Generic AvailableYes

Mechanism of ActionRelaxes vascular smooth muscle; decreased venous ratios and arterial blood pressure; reduces left ventricular work; decreases myocardial O_2 consumption; in cyanide poisoning, amyl nitrite converts hemoglobin to methemoglobin that binds with cyanide to form cyanate hemoglobin

Pharmacodynamics/Kinetics

Onset of action: Angina: Within 30 seconds

Duration: 3-15 minutes

Pharmacotherapy PearlsAmyl nitrite may be used during echocardiographic evaluation to elicit a gradient across the cardiovascular outflow tract in patients with underlying hypertrophic obstructive cardiomyopathy. Amyl nitrite is also used as a recreational drug during intercourse. However, when used in combination with sildenafil (Viagra®), significant and profound hypotension may result.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Postural hypotension

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause headache

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsAmyl nitrite may be used during echocardiographic evaluation to elicit a gradient across the cardiovascular outflow tract in patients with underlying hypertrophic obstructive cardiomyopathy. Amyl nitrite is also used as a recreational drug during intercourse. However, when used in combination with sildenafil (Viagra®), significant and profound hypotension may result.

Anesthesia and Critical Care Concerns/Other ConsiderationsHighly flammable - do not use where it might be ignited. Amyl nitrate is also used as a recreational drug during intercourse. However, when used in combination with phosphodiesterase-5 enzyme inhibitors, significant and profound hypotension may result.

Index TermsIsoamyl Nitrite

References

Dudley MJ and Solomon T, “A Case of Methaemoglobinaemia,” *Arch Emerg Med*, 1993, 10(2):117-9. [PubMed 8329079]

Laaban JP, Bodenan P, and Rochemaure J, “Amyl Nitrite Poppers and Methemoglobinemia,” *Ann Intern Med*, 1985, 103(5):804-5.

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

Osterloh J and Olson K, “Toxicities of Alkyl Nitrites,” *Ann Intern Med*, 1986, 104(5):727.

Schwartz RH, “When to Suspect Inhalant Abuse,” *Patient Care*, 1989, 23:39-64.

International Brand NamesAmyl Nitrite (NZ)

Anagrelide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(an AG gre lide)
U.S. Brand NamesAgrylin®
Canadian Brand NamesAgrylin®; Dom-Anagrelide; Gen-Anagrelide; PHL-Anagrelide; PMS-Anagrelide; Sandoz-Anagrelide
Pharmacologic CategoryPhospholipase A_2 Inhibitor
Use: Labeled IndicationsTreatment of thrombocythemia associated with myeloproliferative disorders
Use: Unlabeled/InvestigationalTreatment of essential thrombocythemia (ET)
Dosing: AdultsThrombocythemia: Oral: 0.5 mg 4 times/day or 1 mg twice daily (most patients will experience adequate response at dose ranges of 1.5-3 mg/day)

Note: Maintain for ≥1 week, then adjust to the lowest effective dose to reduce and maintain platelet count <600,000/µL ideally to the normal range; the dose must not be increased by >0.5 mg/day in any 1 week; maximum dose: 10 mg/day or 2.5 mg/dose

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricThrombocythemia: Oral: Initial: 0.5 mg/day (range: 0.5 mg 1-4 times/day); see "**Note**" in adult dosing.
Dosing: Hepatic Impairment

Moderate impairment: Initial: 0.5 mg once daily; maintain for at least 1 week with careful monitoring of cardiovascular status; the dose must not be increased by >0.5 mg/day in any 1 week.

Severe impairment: Contraindicated

Administration: OralAdminister 2-4 times/day. May be taken without regard to food.
Dietary ConsiderationsMay be taken without regard to food.
StorageStore at 27°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.
ContraindicationsSevere hepatic impairment
Allergy Considerations

- Anagrelide Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Pulmonary disorders: Interstitial lung disease (including allergic alveolitis, eosinophilic pneumonia, and interstitial pneumonitis) has been associated with use. Onset is from 1 week to several years, with most cases presenting with progressive dyspnea with lung infiltrations; symptoms usually improve after discontinuation.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with known or suspected heart disease; tachycardia, orthostatic hypotension, and heart failure have been reported. Pretreatment cardiovascular evaluation and careful monitoring during treatment is recommended.

- Hepatic impairment: Use with caution in patients with mild-to-moderate hepatic impairment (measures of liver function >1.5 times ULN); dosage reduction and careful cardiovascular monitoring is required for moderate impairment; use is contraindicated in severe hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment (serum creatinine ≥2 mg/dL); monitor closely.

Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; however, decreased pup survival was noted. Use of anagrelide during pregnancy is limited. The manufacturer recommends effective contraception in women of childbearing potential. Use during pregnancy only if potential benefit to mother outweighs possible risk to the fetus.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%:

Cardiovascular: Palpitation (26%), edema (21%)

Central nervous system: Headache (44%), dizziness (15%), pain (15%)

Gastrointestinal: Diarrhea (26%), nausea (17%), abdominal pain (16%)

Neuromuscular & skeletal: Weakness (23%)

Respiratory: Dyspnea (12%)

1% to 10%:

Cardiovascular: Peripheral edema (9%), chest pain (8%), tachycardia (8%), angina, arrhythmia, cardiovascular disease, CHF, hypertension, postural hypotension, syncope, thrombosis, vasodilatation

Central nervous system: Fever (9%), malaise (6%), amnesia, chills, confusion, depression, insomnia, migraine, nervousness, somnolence

Dermatologic: Rash (8%), pruritus (6%), alopecia, bruising, photosensitivity, urticaria

Endocrine & skeletal: Dehydration

Gastrointestinal: Flatulence (10%), vomiting (10%), anorexia (8%), dyspepsia (5%), aphthous stomatitis, constipation, eructation, gastritis, GI distress, GI hemorrhage, melena

Hematologic: Thrombocytopenia (9%; grades 3/4: 5%), anemia, hemorrhage

Hepatic: Liver enzymes increased

Neuromuscular & skeletal: Back pain (6%), paresthesia (6%), arthralgia, leg cramps, myalgia

Ocular: Amblyopia, diplopia, visual field abnormality

Otic: Tinnitus

Renal: Dysuria, hematuria

Respiratory: Pharyngitis (7%), cough (6%), asthma, bronchitis, epistaxis, pneumonia, rhinitis, sinusitis

Miscellaneous: Flu-like syndrome, lymphadenopathy

Frequency not defined: Atrial fibrillation, cardiomegaly, cardiomyopathy, cerebrovascular accident, complete heart block, deep vein thrombosis, gastric/duodenal ulceration; interstitial lung disease (allergic alveolitis, eosinophilic pneumonia, interstitial pneumonitis); leukocyte count increased, MI, myelofibrosis, pancreatitis, pericarditis, pericardial effusion, pleural effusion, polycythemia, pulmonary fibrosis, pulmonary hypertension, pulmonary infiltrates, renal abnormalities, renal failure, seizure, stroke, transient ischemic attack

Oncology: Emetic PotentialLow (10% to 30%)

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor)

Drug Interactions

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: May increase CNS adverse effects.

Food: No clinically significant effect on absorption.

Herb/Nutraceutical: Avoid herbs with anticoagulant/antiplatelet properties (alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose oil, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng [American], ginseng [Panax], ginseng [Siberian], grape seed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe [S-adenosylmethionine], sweet clover, turmeric, white willow); may enhance the adverse effect of antiplatelets agents.

Monitoring ParametersPlatelet count (every 2 days during the first week of treatment and at least weekly until the maintenance dose is reached); CBC with differential, ALT, AST, BUN, and serum creatinine (monitor closely during first weeks of treatment); blood pressure; cardiovascular exam (pretreatment; monitor during therapy). Monitor for thrombosis or bleeding.

Monitoring: Lab TestsPlatelet count (every 2 days during the first week of treatment and at least weekly until the maintenance dose is reached); CBC with differential, ALT, AST, BUN, and serum creatinine (monitor closely during first weeks of treatment); blood pressure; cardiovascular exam (pretreatment; monitor during therapy).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 0.5 mg, 1 mg

Agrylin®: 0.5 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Agrylin)

0.5 mg (50): $270.99

1 mg (50): $546.00

Capsules (Anagrelide HCl)

0.5 mg (30): $79.55

1 mg (50): $99.99

Mechanism of ActionAnagrelide appears to inhibit cyclic nucleotide phosphodiesterase and the release of arachidonic acid from phospholipase, possibly by inhibiting phospholipase A_2. It also causes a dose-related reduction in platelet production, which results from decreased megakaryocyte hypermaturation (disrupts the postmitotic phase of maturation).

Pharmacodynamics/Kinetics

Onset: Initial: Within 7-14 days; complete response (platelets $\leq$600,000/mm^3): 4-12 weeks

Duration: 6-24 hours; upon discontinuation, platelet count begins to rise within 4 days

Metabolism: Hepatic; to RL603 and 3-hydroxy anagrelide

Half-life elimination, plasma: 1.3 hours

Time to peak, serum: 1 hour

Excretion: Urine (<1% as unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay impair ability to concentrate and produce bad dreams

Mental Health: Effects on Psychiatric TreatmentMay cause hypotension which may be exacerbated by psychotropics; may cause heart block; use caution with TCAs

Index TermsAnagrelide Hydrochloride; BL4162A; NSC-724577

References

Anagrelide Study Group, “Anagrelide, a Therapy for Thrombocythemic States: Experience in 577 Patients,” *Am J Med*, 1992, 92:69-76. [PubMed 1731512]

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Pescatore SL and Lindley C, “Anagrelide: A Novel Agent for the Treatment of Myeloproliferative Disorders,” *Expert Opin Pharmacother*, 2000, 1(3):537-46. [PubMed 11249536]

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Spencer CM and Brogden RN, “Anagrelide. A Review of Its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential in the Treatment of Thrombocythaemia,” *Drugs*, 1994, 47(5):809-22.[PubMed 7520859]

Steurer M, Gastl G, Jedrzejczak WW, et al, Anagrelide for Thrombocytosis in Myeloproliferative Disorders: A Prospective Study to Assess Efficacy and Adverse Event Profile," Cancer, 2004, 101(10):2239-46.[PubMed 15476273]

International Brand NamesAgrelid (AR); Agrylin (AU, HK, ID, IL, KP, PH, TW); Thromboreductin (HK, ID, MY); Xagrid (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Anakinra

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Anakinra may be confused with amikacin

Pronunciation(an a KIN ra)

U.S. Brand NamesKineret®

Canadian Brand NamesKineret®

Pharmacologic CategoryAntirheumatic, Disease Modifying; Interleukin-1 Receptor Antagonist

Use: Labeled IndicationsTreatment of moderately- to severely-active rheumatoid arthritis in adult patients who have failed one or more disease-modifying antirheumatic drugs (DMARDs); may be used alone or in combination with DMARDs (other than tumor necrosis factor-blocking agents)

Dosing: AdultsRheumatoid arthritis: SubQ: 100 mg once daily (administer at approximately the same time each day)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute and/or end-stage renal disease: 100 mg every other day

Administration: OtherSubQ: Rotate injection sites (thigh, abdomen, upper arm); injection should be given at least 1 inch away from previous injection site. Do not shake. Provided in single-use, preservative free syringes with 27-gauge needles; discard any unused portion.

StorageStore in refrigerator at 2°C to 8°C (36°F to 46°F); do not freeze. Do not shake. Protect from light.

ContraindicationsHypersensitivity to *E. coli*-derived proteins, anakinra, or any component of the formulation; patients with active infections (including chronic or local infection)

Allergy Considerations

- Anakinra Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: May cause hypersensitivity, anaphylaxis, or anaphylactoid reactions; medications for the treatment of hypersensitivity reactions should be available for immediate use.

- Infections: Caution should be exercised when considering the use in patients with a history of new/recurrent infections, with conditions that predispose them to infections, or with chronic, latent, or localized infections. Patients who develop a new infection while undergoing treatment should be monitored closely. If a patient develops a serious infection, therapy should be discontinued.

- Malignancy: Use may affect defenses against malignancies; impact on the development and course of malignancies is not fully defined. As compared to the general population, an increased risk of lymphoma has been noted in clinical trials; however, rheumatoid arthritis has been previously associated with an increased rate of lymphoma.

Disease-related concerns:

- Asthma: Use with caution in patients with asthma; may have increased risk of serious infection.

- Hematologic disorders: Use with caution in patients with a history of significant hematologic abnormalities; therapy has been associated with uncommon, but significant decreases in hematologic parameters (particularly neutrophil counts). Patients must be advised to seek medical attention if they develop signs and symptoms suggestive of blood dyscrasias; discontinue if significant hematologic abnormalities are confirmed.

- Renal impairment: Use caution in patients with renal impairment; consider increased dosing intervals for severe renal dysfunction (Cl_{cr} <30 mL/minute).

Concurrent drug therapy issues:

- TNF-blocking agents: Should not be used in combination with tumor necrosis factor antagonists, unless no satisfactory alternatives exist, and then only with extreme caution.

Special populations:

- Elderly: Use caution due to the potential higher risk for infections.

- Pediatrics: Efficacy has not been established in children; use is not recommended.

Dosage form specific issues:

- Latex: The packaging (needle cover) contains latex.

Other warnings/precautions:

- Immunizations: Patients should be brought up to date with all immunizations before initiating therapy; live vaccines should not be given concurrently. There is no data available concerning the effects of therapy on vaccination or secondary transmission of live vaccines in patients receiving therapy.

Geriatric ConsiderationsClinical trials with older adults (65% to 75%) demonstrated no clinical differences between elderly patients and younger adults in safety and efficacy. Since elderly may be more liable to infections in general, use with caution. Also, since many elderly patients may have Cl_{cr} <30 mL/minute, close monitoring should be followed with calculation of creatinine clearance prior to initiating therapy with anakinra.

Pregnancy Risk FactorB

Pregnancy ConsiderationsNo evidence of impaired fertility or harm to fetus in animal models; however, there are no controlled trials in pregnant women. Women exposed to anakinra during pregnancy may contact the Organization of Teratology Information Services (OTIS), Rheumatoid Arthritis and Pregnancy Study at 1-877-311-8972.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsEndogenous interleukin-1 receptor antagonist can be found in breast milk; specific excretion of anakinra is not known.

Adverse Reactions

>10%:

Central nervous system: Headache (12%)

Local: Injection site reaction (majority mild, typically lasting 14-28 days, characterized by erythema, ecchymosis, inflammation, and pain; up to 71%)

Miscellaneous: Infection (39% versus 37% in placebo; serious infection 2% to 3%)

1% to 10%:

Gastrointestinal: Nausea (8%), diarrhea (7%), abdominal pain (5%)

Hematologic: Neutropenia (8%; grades 3/4: 0.4%)

Respiratory: Sinusitis (7%)

Miscellaneous: Flu-like syndrome (6%)

<1%: Cellulitis, leukopenia, opportunistic infection, malignancies (including lymphoma, melanoma), thrombocytopenia

Drug Interactions

Anti-TNF Agents: May enhance the adverse/toxic effect of Anakinra. An increased risk of serious infection during concomitant use has been reported. *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersCBC with differential (baseline, then monthly for 3 months, then every 3 months); serum creatinine

Nursing: Physical Assessment/MonitoringSee Contraindications and Warnings/Precautions for use cautions. Monitor effectiveness of therapy (eg, pain, range of motion, mobility, ADL function, inflammation). Teach patient proper use if self-administered (appropriate injection technique and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report (see Patient Education). Note breast-feeding caution.

Monitoring: Lab TestsCBC with differential (baseline, then monthly for 3 months, then every 3 months); serum creatinine

Patient EducationIf self-injecting, follow instructions for injection and disposal of needles exactly. If redness, swelling, or irritation appears at the injection site, contact prescriber. Do not have any vaccinations while using this medication without consulting prescriber first. You may experience headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known). If stomach pain or cramping, unusual bleeding or bruising, persistent fever, or paleness occurs, stop medication and contact prescriber **immediately**. Also, immediately report skin rash, unusual muscle or bone weakness, or signs of respiratory flu or other infection (eg, chills, fever, sore throat, easy bruising or bleeding, mouth sores, unhealed sores). **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Kineret®: 100 mg/0.67 mL (1 mL) [prefilled syringe; needle cover contains latex]

Generic AvailableNo

ManufacturerAmgen Inc

Pricing: U.S. (www.drugstore.com)

Solution (Kineret)

100 mg/0.67 mL (4.69): $349.99

Mechanism of ActionAntagonist of the interleukin-1 (IL-1) receptor. Endogenous IL-1 is induced by inflammatory stimuli and mediates a variety of immunological responses, including degradation of cartilage (loss of proteoglycans) and stimulation of bone resorption.

Pharmacodynamics/Kinetics

Bioavailability: SubQ: 95%

Half-life elimination: Terminal: 4-6 hours

Time to peak: SubQ: 3-7 hours

Pharmacotherapy PearlsAnakinra is produced by recombinant DNA/*E. coli* technology.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia and rarely neutropenia; use caution with clozapine and carbamazepine. May cause nausea and diarrhea; monitor with concurrent SSRI, lithium, or valproic acid use.

Index TermsIL-1Ra; Interleukin-1 Receptor Antagonist

References

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Fleischmann RM, Tesser J, Schiff MH, et al, Safety of Extended Treatment With Anakinra in Patients With Rheumatoid Arthritis, *Ann Rheum Dis*, 2006,65(8):1006-12.[PubMed 16396977]

Genovese MC, Cohen S, Moreland L, et al, “Combination Therapy With Etanercept and Anakinra in the Treatment of Patients With Rheumatoid Arthritis Who Have Been Treated Unsuccessfully With Methotrexate,” *Arthritis Rheum*, 2004, 50(5):1412-9.[PubMed 15146410]

International Brand NamesKineret (AU, CZ, DE, DK, EE, FI, GB, IE, IT, NL, NO, SE)

Anastrozole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Anastrozole may be confused with letrozole

Pronunciation(an AS troe zole)
U.S. Brand NamesArimidex®
Canadian Brand NamesArimidex®
Pharmacologic CategoryAntineoplastic Agent, Aromatase Inhibitor
Use: Labeled IndicationsTreatment of locally-advanced or metastatic breast cancer (ER-positive or hormone receptor unknown) in postmenopausal women; treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy; adjuvant treatment of early ER-positive breast cancer in postmenopausal women
Dosing: AdultsBreast cancer: Oral (refer to individual protocols): 1 mg once daily
Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentDosage adjustment is not necessary.
Dosing: Hepatic ImpairmentMild-to-moderate impairment: Plasma concentrations in subjects with stable hepatic cirrhosis were within the range concentrations in normal subjects across all clinical trials; therefore, no dosage adjustment required; however, patients should be monitored for side effects. Safety and efficacy in severe hepatic impairment have not been established.
StorageStore at 20°C to 25°C (68°F to 77°F).
ContraindicationsHypersensitivity to anastrozole or any component of the formulation; pregnancy
Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Decreased bone mineral density: May cause decreases in bone mineral density.
- Hyperlipidemia: Total cholesterol and LDL-cholesterol increase in patients receiving anastrozole; use with caution in patients with hyperlipidemias.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: Exclude pregnancy before initiating.
- Premenopausal women: Safety and efficacy have not been established in premenopausal women.

Geriatric ConsiderationsNo age-related changes in pharmacokinetics were noted in clinical trials.
Pregnancy Risk FactorD
Pregnancy ConsiderationsFetotoxicity was observed in animal studies. Safety and efficacy have not been established in premenopausal women; exclude pregnancy prior to treatment.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%:

Cardiovascular: Vasodilatation (25% to 36%), hypertension (2% to 13%)

Central nervous system: Mood disturbance (19%), fatigue (19%), pain (11% to 17%), headache (9% to 13%), depression (5% to 13%)

Dermatologic: Rash (6% to 11%)

Endocrine & metabolic: Hot flashes (12% to 36%)

Gastrointestinal: Nausea (11% to 19%), vomiting (8% to 13%)

Neuromuscular & skeletal: Weakness (16% to 19%), arthritis (17%), arthralgia (2% to 15%), back pain (10% to 12%), bone pain (6% to 11%), osteoporosis (11%)

Respiratory: Pharyngitis (6% to 14%), cough increased (8% to 11%)

1% to 10%:

Cardiovascular: Peripheral edema (5% to 10%), chest pain (5% to 7%), ischemic cardiovascular disease (4%), venous thromboembolic events (3% to 4%), ischemic cerebrovascular events (2%), angina (2%)

Central nervous system: Insomnia (2% to 10%), dizziness (6% to 8%), anxiety (2% to 6%), fever (2% to 5%), malaise (2% to 5%), confusion (2% to 5%), nervousness (2% to 5%), somnolence (2% to 5%), lethargy (1%)

Dermatologic: Alopecia (2% to 5%), pruritus (2% to 5%)

Endocrine & metabolic: Hypercholesterolemia (9%), breast pain (2% to 8%)

Gastrointestinal: Constipation (7% to 9%), abdominal pain (7% to 9%), diarrhea (8% to 9%), anorexia (5% to 7%), xerostomia (6%), dyspepsia (7%), weight gain (2% to 9%), weight loss (2% to 5%)

Genitourinary: Urinary tract infection (2% to 8%), vulvovaginitis (6%), pelvic pain (5%), vaginal bleeding (1% to 5%), vaginitis (4%), vaginal discharge (4%), vaginal hemorrhage (2% to 4%), leukorrhea (2% to 3%), vaginal dryness (2%)

Hematologic: Anemia (2% to 5%), leukopenia (2% to 5%)

Hepatic: Liver function tests increased (2% to 5%), alkaline phosphatase increased (2% to 5%), gamma GT increased (2% to 5%)

Local: Thrombophlebitis (2% to 5%)

Neuromuscular & skeletal: Fracture (2% to 10%), arthrosis (7%), paresthesia (5% to 7%), joint disorder (6%), myalgia (2% to 6%), neck pain (2% to 5%), hypertonia (3%)

Ocular: Cataracts (6%)

Respiratory: Dyspnea (8% to 10%), sinusitis (2% to 6%), bronchitis (2% to 5%), rhinitis (2% to 5%)

Miscellaneous: Lymph edema (10%), infection (2% to 9%), flu-like syndrome (2% to 7%), diaphoresis (2% to 5%), cyst (5%), tumor flare (3%)

<1%, postmarketing, and/or case reports: Anaphylaxis, angioedema, CVA, cerebral ischemia, cerebral infarct, endometrial cancer, erythema multiforme, joint pain, joint stiffness, MI, myocardial ischemia, pulmonary embolus, retinal vein thrombosis, Stevens-Johnson syndrome, urticaria

Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Inhibits** CYP1A2 (weak), 2C8 (weak), 2C9 (weak), 3A4 (weak)
Drug Interactions

Tamoxifen: May decrease the serum concentration of Anastrozole. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid black cohosh, hops, licorice, red clover, thyme, and dong quai.
Test InteractionsLab test abnormalities: GGT, AST, ALT, alkaline phosphatase, total cholesterol, and LDL increased; threefold elevations of mean serum GGT levels have been observed among patients with liver metastases. These changes were likely related to the progression of liver metastases in these patients, although other contributing factors could not be ruled out. Mean serum total cholesterol levels increased by 0.5 mmol/L among patients.
Monitoring ParametersBone mineral density; total cholesterol and LDL
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, tamoxifen and estrogens). Assess results of laboratory tests; may decrease bone mineral density and elevate serum cholesterol. Therapeutic effectiveness and adverse reactions (eg, hyperlipidemia, hypotension, CNS changes, thrombophlebitis, bone pain or fracture) should be assessed periodically during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsBone mineral density; total cholesterol and LDL
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause headache (consult prescriber for approved analgesic); drowsiness, dizziness, anxiety (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or increased pelvic, bone or tumor pain (may lessen with continued use; if not, consult prescriber for approved analgesic), or hot flashes (cool cloths may help). Report unresolved nausea or vomiting; pain or burning on urination; severe mood swings, confusion, anxiety; palpitations; swelling of extremities; unusual chest pain; flu-like symptoms; persistent bone or joint pain; respiratory difficulty; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Arimidex®: 1 mg

Generic AvailableNo
ManufacturerAstraZeneca Pharmaceuticals LP
Pricing: U.S. (www.drugstore.com)

Tablets (Arimidex)

1 mg (30): $316.53

Mechanism of ActionPotent and selective nonsteroidal aromatase inhibitor. By inhibiting aromatase, the conversion of androstenedione to estrone, and testosterone to estradiol, is prevented. Anastrozole causes an 85% decrease in estrone sulfate levels.
Pharmacodynamics/Kinetics

Onset of estradiol reduction: 70% reduction after 24 hours; 80% after 2 weeks therapy

Duration of estradiol reduction: 6 days

Absorption: Well absorbed; not affected by food

Protein binding, plasma: 40%

Metabolism: Extensively hepatic (~85%) via N-dealkylation, hydroxylation, and glucuronidation; primary metabolite inactive

Half-life elimination: ~50 hours

Excretion: Urine (10% as unchanged drug; 60% as metabolites)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness, confusion, insomnia, and anxiety are common

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsICI-D1033; NSC-719344; ZD1033

References

Boeddinghaus IM and Dowsett M, “Comparative Clinical Pharmacology and Pharmacokinetic Interactions of Aromatase Inhibitors,” *J Steroid Biochem Mol Biol*, 2001, 79(1-5):85-91. [PubMed 11850211]

Buzdar AU, Robertson JF, Eiermann W, et al, “An Overview of the Pharmacology and Pharmacokinetics of the Newer Generation Aromatase Inhibitors Anastrozole, Letrozole, and Exemestane,” *Cancer*, 2002, 95(9):2006-16. [PubMed 12404296]

Higa GM and AlKhouri N, “Anastrozole: A Selective Aromatase Inhibitor for the Treatment of Breast Cancer,” *Am J Health Syst Pharm*, 1998, 55(5):445-52. [PubMed 9522927]

Kendall A, Dowsett M, Folkerd E, et al, “Caution: Vaginal Estradiol Appears to be Contraindicated in Postmenopausal Women on Adjuvant Aromatase Inhibitors,” *Ann Oncol*, 2006, 17(4):584-7.[PubMed 16443612]

Koberle D and Thurlimann B, “Anastrozole: Pharmacological and Clinical Profile in Postmenopausal Women With Breast Cancer,” *Expert Rev Anticancer Ther*, 2001, 1(2):169-76. [PubMed 12113022]

Lonning PE, Geisler J, and Dowsett M, “Pharmacological and Clinical Profile of Anastrozole,” *Breast Cancer Res Treat*, 1998, 49(Suppl 1):53-7.

Njar VC and Brodie AM, “Comprehensive Pharmacology and Clinical Efficacy of Aromatase Inhibitors,” *Drugs*, 1999, 58(2):233-55.[PubMed 10473018]

International Brand NamesAltraz (IN); Anazol (TW); Arimidex (AR, AT, AU, BB, BD, BE, BF, BG, BJ, BM, BO, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CZ, DE, DK, DO, EC, EE, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HU, ID, IE, IL, IN, IT, JM, JP, KE, KP, LR, LU, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, PA, PE, PH, PK, PL, PR, PT, PY, SC, SD, SE, SG, SL, SN, SR, SV, TH, TN, TT, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Trozolet (CN, CO, EC, PE, PY, UY, VE); Trozolite (AR)

Anidulafungin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(ay nid yoo la FUN jin)

U.S. Brand NamesEraxis™

Canadian Brand NamesEraxis™

Pharmacologic CategoryAntifungal Agent, Parenteral; Echinocandin

Use: Labeled IndicationsTreatment of candidemia and other forms of *Candida* infections (including those of intra-abdominal, peritoneal, and esophageal locus)

Use: Unlabeled/InvestigationalTreatment of infections due to *Aspergillus* spp.

Dosing: Adults

Candidemia, intra-abdominal or peritoneal candidiasis: I.V.: 200 mg loading dose on day 1, followed by 100 mg daily for at least 14 days after last positive culture

Esophageal candidiasis: I.V.: 100 mg loading dose on day 1, followed by 50 mg daily for at least 14 days and for at least 7 days after symptom resolution

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment necessary, including dialysis patients.

Dosing: Hepatic ImpairmentNo adjustment necessary.

Administration: I.V.For intravenous use only; infusion rate should not exceed 1.1 mg/minute

StorageStore between 15°C to 30°C (59°F to 86°F). Reconstituted and diluted solutions are stable for 24 hours at room temperature. Do not refrigerate or freeze.

ReconstitutionAseptically add 15 mL (50 mg vial) or 30 mL (100 mg vial) of companion diluent (20% w/w dehydrated alcohol in water for injection) to each vial. Swirl to dissolve; do not shake. Further dilute 50 mg, 100 mg, or 200 mg in 100 mL, 250 mL, or 500 mL, respectively, of D_5W or NS.

CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Acyclovir, amikacin, aminophylline, ampicillin-sulbactam, carboplatin, cefazolin, cefepime, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cimetidine, ciprofloxacin, cisplatin, clindamycin, cyclophosphamide, cyclosporine, cytarabine, daunorubicin, dexamethasone, digoxin, dobutamine, docetaxel, dopamine, doxorubicin, epinephrine, erythromycin, etoposide, famotidine, fentanyl, fluconazole, fluorouracil, furosemide, ganciclovir, gatifloxacin, gemcitabine, gentamicin, heparin, hydrocortisone, hydromorphone, ifosfamide, imipenem–cilastatin, leucovorin, levofloxacin, linezolid, meperidine, meropenem, methylprednisolone, metronidazole, midazolam, morphine, mycophenolate mofetil, norepinephrine, paclitaxel, pantoprazole, phenylephrine, piperacillin-tazobactam, potassium chloride, quinupristin–dalfopristin, ranitidine, sulfamethoxazole-trimethoprim, tacrolimus, ticarcillin, tobramycin, vancomycin, vincristine, voriconazole, zidovudine. **Incompatible:** Amphotericin B, ertapenem, sodium bicarbonate.

ContraindicationsHypersensitivity to anidulafungin, other echinocandins, or any component of the formulation

Allergy Considerations

- Echinocandin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hepatic effects: Elevated liver function tests, hepatitis, and worsening hepatic failure have been reported; monitor for progressive hepatic impairment if increased transaminase enzymes noted.
- Histamine-mediated reactions: Histamine-mediated reactions (eg, urticaria, flushing, hypotension) have been observed; these may be related to infusion rate.

Disease-related concerns:

- Candidal infections: Safety and efficacy have not been established in other *Candida* infections (eg, endocarditis, osteomyelitis, meningitis).

Special populations:

- Neutropenic patients: Safety and efficacy have not been established in neutropenic patients.
- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsSkeletal teratogenic effects were noted in animal studies. There are no adequate and well-controlled studies in pregnant women. Use only if benefit outweighs risk.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

2% to 10%:

Endocrine & metabolic: Hypokalemia (3%)

Gastrointestinal: Diarrhea (3%)

Hepatic: Transaminase increased (<1% to 2%)

<2%: Abdominal pain, alkaline phosphatase increased, amylase increased, angioneurotic edema, atrial fibrillation, back pain, bilirubin increased, bundle branch block (right), candidiasis, cholestasis, clostridial infection, coagulopathy, constipation, cough, CPK increased, creatinine increased, diaphoresis, diarrhea, dizziness, DVT, dyspepsia, ECG abnormality (including QT prolongation), erythema, eye pain, fecal incontinence, flushing, fungemia, GGT increased, headache, hepatic necrosis, hepatitis, hepatic dysfunction, hot flushes, hypercalcemia, hyperglycemia, hyperkalemia, hypernatremia, hyper-/hypotension, hypomagnesemia, infusion-related reaction, leukopenia (0.7%), lipase increased, nausea, neutropenia (1%), peripheral edema, phlebitis, platelet count increased, prothrombin time prolonged, pruritus, pyrexia, rash, rigors, seizure, sinus arrhythmia, thrombocytopenia, thrombophlebitis, urea increased, urticaria, ventricular extrasystoles, vision blurred, visual disturbance, vomiting

Drug Interactions

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Monitoring ParametersLiver function tests

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests (liver function), therapeutic effectiveness, and adverse reactions on a regular basis during therapy. See Administration for I.V. specifics. Teach patient possible adverse symptoms to report.

Monitoring: Lab TestsLiver function tests

Patient EducationThis medication can only be administered by infusion. Report immediately any pain, burning, or swelling at infusion site, or any signs of allergic reaction (eg, respiratory difficulty or swallowing, back pain, chest tightness, rash, hives, or swelling of lips or mouth). Report diarrhea, nausea, vomiting, or abdominal pain. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Eraxis™: 50 mg [contains polysorbate 80; packaged with dehydrated alcohol as diluent]; 100 mg [contains polysorbate 80; packaged with dehydrated alcohol as diluent]

Generic AvailableNo

Mechanism of ActionNoncompetitive inhibitor of 1,3-beta-D-glucan synthase resulting in reduced formation of 1,3-beta-D-glucan, an essential polysaccharide comprising 30% to 60% of *Candida* cell walls (absent in mammalian cells); decreased glucan content leads to osmotic instability and cellular lysis

Pharmacodynamics/Kinetics

Distribution: 30-50 L

Protein binding: 84%

Metabolism: No hepatic metabolism observed; undergoes slow chemical hydrolysis to open-ring peptide-lacking antifungal activity

Half-life elimination: 27 hours

Excretion: Feces (30%, 10% as unchanged drug); urine (<1%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsLY303366

References

Trissel LA and Ogundele AB, "Compatibility of Anidulafungin With Other Drugs During Simulated Y-Site Administration," *Am J Health-Sys Pharm*, 2005, 62:834-7.

Vazquez JA, "Anidulafungin: A New Echinocandin With a Novel Profile," *Clin Ther*, 2005, 27(6):657-73.[PubMed 16117974]

Walsh TJ, Anaissie EJ, Denning DW, et al, "Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America," *Clin Infect Dis*, 2008, 46(3):327-60.[PubMed 18177225]

International Brand NamesECALTA (IE, SE)

Anthralin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(AN thra lin)
U.S. Brand NamesDritho-Scalp®; Psoriatec™
Canadian Brand NamesAnthraforte®; Anthranol®; Anthrascalp®; Micanol®
Pharmacologic CategoryAntipsoriatic Agent; Keratolytic Agent
Use: Labeled IndicationsTreatment of psoriasis (quiescent or chronic psoriasis)
Dosing: Adults

Psoriasis: Topical: Generally, apply once a day or as directed. The irritant potential of anthralin is directly related to the strength being used and each patient's individual tolerance. Always commence treatment using a short, daily contact time (5-10 minutes) for at least 1 week using the lowest strength possible. Contact time may be gradually increased (to 20-30 minutes) as tolerated.

Skin application: Apply sparingly only to psoriatic lesions and rub gently and carefully into the skin until absorbed. Avoid applying an excessive quantity which may cause unnecessary soiling and staining of the clothing or bed linen.

Scalp application: Comb hair to remove scalar debris, wet hair and, after suitably parting, rub cream well into the lesions, taking care to prevent the cream from spreading onto the forehead.

Note: Remove by washing or showering; optimal period of contact will vary according to the strength used and the patient's response to treatment. Continue treatment until the skin is entirely clear (ie, when there is nothing to feel with the fingers and the texture is normal).

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricUnlabeled use: Refer to adult dosing.
Administration: TopicalMay apply using latex gloves to prevent staining of fingers. Apply directly to plaques; rub in gently but thoroughly; avoid application to unaffected skin. When applying to scalp, part hair in one-inch segments to reach plaques. Remove by washing after conclusion of prescribed contact period. When rinsing, take care to avoid contact with eyes. Immediately clean tub or shower to prevent staining. Dry off using old towel (stains on fabric may be permanent). Petroleum jelly may be used around the edges of plaques, in body folds, or skin creases to prevent irritation of unaffected skin.
StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Avoid excessive heat.
ContraindicationsHypersensitivity to anthralin or any component of the formulation; acute psoriasis (acutely or actively inflamed psoriatic eruptions)
Warnings/Precautions

Concerns related to adverse effects:

- Redness: If redness is observed, reduce frequency of dosage or discontinue application.
- Staining: May stain skin, hair, fingernails (temporary), or fabrics (may be permanent).

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal disease.

Special populations:

Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate application: Avoid eye contact; should generally not be applied to opposing skin surfaces that may rub or touch (eg, skin folds of the groin, axilla, and breasts) and high strengths should not be used on these sites; do not apply to genitalia.
- Prolonged/extensive use: Use with caution in patients extensive and prolonged applications.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined: Dermatologic: Transient primary irritation of uninvolved skin; temporary discoloration of skin, hair, and fingernails; contact allergic reactions; erythema
Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringWhen applied to large areas of skin or for extensive periods of time, monitor for adverse skin or systemic reactions. Assess knowledge/teach patient appropriate application and use and adverse symptoms to report.
Patient EducationFor external use only. Use exactly as directed; do not overuse. Before using, wash and dry area gently. Wear gloves to apply a thin film to affected area and rub in gently. Remove by washing; may discolor fabric, skin, or hair. Use a porous dressing if necessary. For lesions on scalp, comb hair to remove scalar debris, part hair, and rub cream into lesions. Do not allow cream to spread to forehead or onto neck. Remove by washing hair. Avoid contact with eyes. Avoid exposing treated areas to direct sunlight; sunburn can occur. Optimal period of contact will vary according to strength used and response to treatment. Report increased swelling, redness, rash, itching, signs of infection, worsening of condition, or lack of healing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant.

Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream:

Dritho-Scalp®: 0.5% (50 g)

Psoriatec™: 1% (50 g)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Cream (Dritho-Scalp)

0.5% (50): $95.99

Cream (Psoriatec)

1% (50): $105.99

Mechanism of ActionReduction of the mitotic rate and proliferation of epidermal cells in psoriasis by inhibiting synthesis of nucleic protein from inhibition of DNA synthesis to affected areas

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDithranol

References

Farber EM and Nall L, “Childhood Psoriasis,” *Cutis*, 1999, 64(5):309-14. [PubMed 10582153]

Silverman A, Menter A, and Hairston JL, “Tars and Anthralins,” *Dermatol Clin*, 1995, 13(4):817-33.[PubMed 8785886]

International Brand NamesAnthraderm (AT); Anthramed (ID); Anthranol (AE, BH, CY, EG, ES, FR, IL, IQ, IR, JO, KW, LB, LY, OM, PH, QA, SA, SY, YE, ZA); Anthrin (KP); Antranol (BR); Desmoline (PT); Dithrasis (FR); Dithrocream (AU, GB, IE, IL); Ditranol FNA (NL); Filorose (GR); Micanol (AT, BE, DE, DK, IL, NO, SE); Psoradexan (BG); Psoriderm (IT); Psorinol (IN); Timicolid (IT)

Anthrax Vaccine Adsorbed

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(AN thraks vak SEEN ad SORBED)

U.S. Brand NamesBioThrax™

Pharmacologic CategoryVaccine

Use: Labeled IndicationsImmunization against *Bacillus anthracis*. Recommended for individuals who may come in contact with animal products which come from anthrax endemic areas and may be contaminated with *Bacillus anthracis* spores; recommended for high-risk persons such as veterinarians and other handling potentially infected animals. Routine immunization for the general population is not recommended.

The Department of Defense is implementing an anthrax vaccination program against the biological warfare agent anthrax, which will be administered to all active duty and reserve personnel.

Use: Unlabeled/InvestigationalPostexposure prophylaxis in combination with antibiotics

Dosing: Adults

Primary immunization: SubQ: Three injections of 0.5 mL each given 2 weeks apart, followed by three additional injections given at 6-, 12-, and 18 months; it is not necessary to restart the series if a dose is not given on time; resume as soon as practical

Subsequent booster injections: SubQ: 0.5 mL at 1-year intervals are recommended for immunity to be maintained

Dosing: ElderlySafety and efficacy have not been established.

Dosing: PediatricRefer to adult dosing.

Administration: OtherAdminister SubQ; shake well before use. Do not use if discolored or contains particulate matter. Do not use the same site for more than one injection. Do not mix with other injections. After administration, massage injection site to disperse the vaccine. Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze.

RestrictionsNot commercially available in the U.S.; presently, all anthrax vaccine lots are owned by the U.S. Department of Defense. The Centers for Disease Control (CDC) does not currently recommend routine vaccination of the general public.

ContraindicationsHypersensitivity to anthrax vaccine or any component of the formulation; severe anaphylactic reaction to a previous dose of anthrax vaccine; history of anthrax; history of Guillain-Barré syndrome; pregnancy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.
- Fever/chills: Discontinue immunization in patients with chills or fever associated with administration.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).
- Guillain-Barré syndrome: Patients with a history of Guillain-Barré syndrome should not be given the vaccine unless there is a clear benefit that outweighs the potential risk of recurrence.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination.
- Elderly: Safety and efficacy have not been established in adults >65 years of age.
- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Latex: Packaging may contain natural latex rubber.

Pregnancy Risk FactorD

Pregnancy ConsiderationsReproduction studies have not been conducted. Use during pregnancy only if clearly needed. Unpublished data from the Department of Defense suggest the vaccine may be linked with an increased number of birth defects when given during pregnancy.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsThere are no adequate and well-controlled studies using this vaccine in breast-feeding women; however, the administration of nonlive vaccines during breast-feeding is generally not medically contraindicated.

Adverse Reactions(Includes pre- and postlicensure data; systemic reactions reported more often in women than in men)

>10%:

Central nervous system: Malaise (4% to 11%)

Local: Tenderness (58% to 71%), erythema (12% to 43%), subcutaneous nodule (4% to 39%), induration (8% to 21%), warmth (11% to 19%), local pruritus (7% to 19%)

Neuromuscular & skeletal: Arm motion limitation (7% to 12%)

1% to 10%:

Central nervous system: Headache (4% to 7%), fever (<1% to 7%)

Gastrointestinal: Anorexia (4%), vomiting (4%), nausea (<1% to 4%)

Local: Mild local reactions (edema/induration <30 mm) (9%), edema (8%)

Neuromuscular & skeletal: Myalgia (4% to 7%)

Respiratory: Respiratory difficulty (4%)

<1%: Chills, body aches, delayed hypersensitivity reaction (started approximately day 17), moderate local reactions (edema/induration >30 mm and <120 mm), severe local reactions (edema/induration >120 mm in diameter or accompanied by marked limitation of arm motion or marked axillary node tenderness)

Postmarketing and/or case reports: Anaphylaxis, angioedema, aplastic anemia, arthralgia, aseptic meningitis, asthma, atrial fibrillation, cardiomyopathy, cellulitis, cerebrovascular accident, CNS lymphoma, cysts, collagen vascular disease, dizziness, encephalitis, endocarditis, facial palsy, fatigue, glomerulonephritis, Guillain-Barré syndrome, hearing disorder, idiopathic thrombocytopenia purpura, immune deficiency, inflammatory arthritis, injection site pain/tenderness, leukemia, liver abscess, lymphoma, mental status change, multiple sclerosis, myocarditis, neutropenia, pemphigus vulgaris, peripheral swelling, polyarteritis nodosa, psychiatric disorders, renal failure, seizure, sepsis, spontaneous abortion, sudden cardiac arrest, suicide, syncope, transverse myelitis, tremor, systemic lupus erythematosus, visual disorder

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Monitoring ParametersMonitor for local reactions, chills, fever, anaphylaxis

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension:

BioThrax™: *Bacillus anthracis* proteins (5 mL) [contains aluminum, natural rubber/natural latex in packaging]

Generic AvailableNo

ManufacturerBioport Corporation

Mechanism of ActionActive immunization against *Bacillus anthracis*. The vaccine is prepared from a cell-free filtrate of *B. anthracis*, but no dead or live bacteria.

Pharmacodynamics/KineticsDuration: Unknown; may be 1-2 years following two inoculations based on animal data

Pharmacotherapy PearlsNot commercially available in the U.S.

Local reactions increase in severity by the fifth dose. Moderate local reactions (>5 cm) may be pruritic and may occur if given to a patient with a previous history of anthrax infection. Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely produce malaise or fatigue

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAVA

References

Advisory Committee on Immunization Practices, “Use of Anthrax Vaccine in the United States,” *MMWR Recomm Rep*, 2000, 49(RR-15):1-20.

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 1994, 43(RR-1):23.

Anti-inhibitor Coagulant Complex

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(an tee-in HI bi tor coe AG yoo lant KOM pleks)
U.S. Brand NamesAutoplex® T [DSC]; Feiba VH
Canadian Brand NamesFeiba VH Immuno
Pharmacologic CategoryActivated Prothrombin Complex Concentrate (aPCC); Antihemophilic Agent; Blood Product Derivative
Use: Labeled IndicationsHemophilia A & B patients with factor VIII inhibitors who are to undergo surgery or those who are bleeding
Dosing: AdultsControl of bleeding: I.V.:

Autoplex® T: Dosage range: 25-100 factor VIII correctional units per kg depending on the severity of hemorrhage; may repeat in ~6 hours if needed. Adjust dose based on patient response.

Feiba VH: General dosing guidelines: 50-100 units/kg (maximum 200 units/kg)

Joint hemorrhage: 50 units/kg every 12 hours; may increase to 100 units/kg; continue until signs of clinical improvement occur

Mucous membrane bleeding: 50 units/kg every 6 hours; may increase to 100 units/kg (maximum: 2 administrations/day or 200 units/kg/day

Soft tissue hemorrhage: 100 units/kg every 12 hours (maximum: 200 units/kg/day)

Other severe hemorrhage: 100 units/kg every 12 hours; may be used every 6 hours if needed; continue until clinical improvement

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Administration: I.V.

Autoplex® T: Initial rate of infusion: 2 mL/minute; may gradually increase to 10 mL/minute as tolerated. Infusion should be completed within 1 hour of reconstitution.

Feiba VH: Maximum infusion rate: 2 units/kg/minute. Following reconstitution, complete infusion within 3 hours.

Dietary ConsiderationsAutoplex® T contains sodium 162-192 mEq/L; Feiba VH contains sodium 8 mg/mL
StorageStore at 2°C to 8°C (36°F to 46°F); avoid freezing. Feiba VH may be stored at room temperature of 25˚C (77˚F) for up to 6 months prior to reconstitution; do not re-refrigerate.
ReconstitutionPrior to reconstitution, bring to room temperature. Reconstitute with provided SWI. Swirl to gently dissolve powder; do not shake vigorously. Do **not** refrigerate after reconstitution.
ContraindicationsHypersensitivity to any component of the formulation; disseminated intravascular coagulation (DIC); fibrinolysis; patients with normal coagulation mechanism
Warnings/Precautions

Concerns related to adverse effects:

- Thrombotic events: High doses of Feiba VH have been associated with thrombotic complications; single doses should not exceed 100 units/kg and daily doses should not exceed 200 units/kg. Use with caution in patients at risk for thrombotic events.

Disease-related concerns:

- Hepatic impairment: Use with extreme caution in patients with hepatic impairment.

Dosage form specific issues:

- Factor VIII: Products may contain minute amounts of factor VIII which may cause an anamnestic response.
- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.
- Latex: Products may contain natural rubber latex.

Other warnings/precautions:

- Appropriate use: Identification of the clotting deficiency as caused by factor VIII inhibitors is essential prior to starting therapy. Tests used to control improvement, such as aPTT, WBCT, and TEG, do not correlate with clinical efficacy. Dosing to normalize these values may result in DIC.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Blood pressure changes, flushing, MI, pulse rate changes

Central nervous system: Headache, lethargy

Dermatologic: Rash, urticaria

Gastrointestinal: Nausea

Hematologic: DIC

Miscellaneous: Allergic reaction, anamnestic response, infusion-related reactions (fever, chills)

Drug Interactions

Antifibrinolytic Agents: May enhance the thrombogenic effect of Anti-inhibitor Coagulant Complex. *Risk D: Consider therapy modification*

Test InteractionsIncreased/decreased PT, increased/decreased PTT, decreased WBCT, decreased fibrin, decreased platelets, increased fibrin split products

Monitoring ParametersMonitor for control of bleeding; signs and symptoms of DIC (blood pressure changes, pulse rate changes, chest pain/cough, fibrinogen decreased, platelet count decreased, fibrin-fibrinogen degradation products, significantly-prolonged thrombin time, PT, or partial thromboplastin time); hypotension; have epinephrine ready to treat hypersensitivity reactions. **Note:** Tests used to control efficacy such as aPTT, WBCT, and TEG do not correlate with clinical improvement. Dosing to normalize these values may result in DIC.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking that may affect coagulation or platelet function. Patient should be monitored closely during and after infusion for any change in vital signs, cardiac and CNS status, or hypersensitivity reactions (chills, fever, chest pain, respiratory difficulty). **Caution:** See Laboratory Monitoring. If hypotension develops, the rate of infusion should be slowed and prescriber notified. Provide patient education according to patient condition.

Monitoring: Lab TestsMonitor for control of bleeding; signs and symptoms of DIC (blood pressure changes, pulse rate changes, chest pain/cough, fibrinogen decreased, platelet count decreased, fibrin-fibrinogen degradation products, significantly-prolonged thrombin time, PT, or partial thromboplastin time); hypotension; have epinephrine ready to treat hypersensitivity reactions. **Note:** Tests used to control efficacy such as aPTT, WBCT, and TEG do not correlate with clinical improvement. Dosing to normalize these values may result in DIC.

Patient EducationThis medication can only be administered by infusion; you will be monitored during and after infusion. Report immediately any sudden onset headache, rash, chest or back pain, wheezing or respiratory difficulties, hives, itching, low-grade fever, stomach pain, or nausea/vomiting to prescriber. Wear identification indicating that you have a hemophilic condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Autoplex® T: Each bottle is labeled with correctional units of factor VIII [contains heparin 2 units/mL and sodium 162-192 mEq/L; packaging contains natural rubber latex] [DSC]

Feiba VH: Each bottle is labeled with Immuno units of factor VIII [heparin free; contains sodium 8 mg/mL; packaging contains natural rubber latex]

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAICC; Coagulant Complex Inhibitor

References

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Monahan PE and Aledort LM, “Factors Affecting Choice of Hemostatic Agent for the Hemophilia Patient With an Inhibitor Antibody,” *Am J Hematol*, 2004, 77(4):346-50.[PubMed 15558804]

Antihemophilic Factor (Human)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(an tee hee moe FIL ik FAK tor HYU man)
U.S. Brand NamesHemofil M; Koāte®-DVI; Monarc-M™; Monoclate-P®
Canadian Brand NamesHemofil M
Pharmacologic Category[Antihemophilic Agent](); [Blood Product Derivative]()
Use: Labeled IndicationsPrevention and treatment of hemorrhagic episodes in patients with hemophilia A (classic hemophilia); perioperative management of hemophilia A; can be of significant therapeutic value in patients with acquired factor VIII inhibitors not exceeding 10 Bethesda units/mL
Dosing: Adults**Hemophilia:** I.V.: Individualize dosage based on coagulation studies performed prior to treatment and at regular intervals during treatment. In general, administration of factor VIII 1 int. unit/kg will increase circulating factor VIII levels by ~2 int. units/dL. (General guidelines presented; consult individual product labeling for specific dosing recommendations.)

Dosage based on desired factor VIII increase (%):

To calculate dosage needed based on desired factor VIII increase (%):

Body weight (kg) x 0.5 int. units/kg x desired factor VIII increase (%) = int. units factor VIII required

For example:

50 kg x 0.5 int. units/kg x 30 (% increase) = 750 int. units factor VIII

Dosage based on expected factor VIII increase (%):

It is also possible to calculate the **expected** % factor VIII increase:

(# int. units administered x 2%/int. units/kg) divided by body weight (kg) = expected % factor VIII increase

For example:

(1400 int. units x 2%/int. units/kg) divided by 70 kg = 40%

General guidelines:

Minor hemorrhage: 10-20 int. units/kg as a single dose to achieve FVIII plasma level ~20% to 40% of normal. Mild superficial or early hemorrhages may respond to a single dose; may repeat dose every 12-24 hours for 1-3 days until bleeding is resolved or healing achieved.

Moderate hemorrhage/minor surgery: 15-25 int. units/kg to achieve FVIII plasma level 30% to 50% of normal. If needed, may continue with a maintenance dose of 10-15 int. units/kg every 8-12 hours.

Major to life-threatening hemorrhage: Initial dose 40-50 int. units/kg, followed by a maintenance dose of 20-25 int. units/kg every 8-12 hours until threat is resolved, to achieve FVIII plasma level 80% to 100% of normal.

Major surgery: 50 int. units/kg given preoperatively to raise factor VIII level to 100% before surgery begins. May repeat as necessary after 6-12 hours initially and for a total of 10-14 days until healing is complete. Intensity of therapy may depend on type of surgery and postoperative regimen.

Bleeding prophylaxis: May be administered on a regular basis for bleeding prophylaxis. Doses of 24-40 int. units/kg 3 times/week have been reported in patients with severe hemophilia to prevent joint bleeding.

If bleeding is not controlled with adequate dose, test for presence of inhibitor. It may not be possible or practical to control bleeding if inhibitor titers are >10 Bethesda units/mL.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Administration: I.V.Over 5-10 minutes (maximum: 10 mL/minute). Infuse Monoclate-P® at 2 mL/minute.
StorageStore under refrigeration, 2°C to 8°C (36°F to 46°F); avoid freezing. Use within 3 hours of reconstitution. Do not refrigerate after reconstitution, precipitation may occur.

Hemofil M, Monarc-M™: May also be stored at room temperature not to exceed 30°C (86°F).

Koāte®-DVI; Monoclate-P®: May also be stored at room temperature of 25°C (77°F) for ≤6 months.

ReconstitutionIf refrigerated, the dried concentrate and diluent should be warmed to room temperature before reconstitution. Gently swirl or rotate vial after adding diluent; do not shake vigorously.
ContraindicationsHypersensitivity to any component of the formulation
Warnings/Precautions

Special populations:

- Blood types A, B, and AB: Contains trace amounts of blood groups A and B isohemagglutinins and when large or frequently repeated doses are given to individuals with blood groups A, B, and AB, the patient should be monitored for signs of progressive anemia and the possibility of intravascular hemolysis should be considered.

Dosage form specific issues:

- Albumin: Products vary by preparation method; final formulations contain human albumin.

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer. Hepatitis B vaccination is recommended for all patients. Hepatitis A vaccination is also recommended for seronegative patients.

- Latex: Natural rubber latex is a component of Hemofil M and Monarc-M™ packaging.

- Mouse protein: Hemofil M, Monoclate-P®, and Monarc-M™ contain trace amounts of mouse protein.

- von Willebrand factor: Products contain naturally-occurring von Willebrand factor for stabilization, however efficacy has not been established for the treatment of von Willebrand disease.

Other warnings/precautions:

- Dose requirements: The dosage requirement will vary in patients with factor VIII inhibitors; optimal treatment should be determined by clinical response.

Geriatric ConsiderationsResponse in the elderly is not expected to differ from that of younger patients; dosage should be individualized.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted. Safety and efficacy in pregnant women have not been established. Use during pregnancy only if clearly needed. Parvovirus B19 or hepatitis A, which may be present in plasma-derived products, may affect a pregnant woman more seriously than nonpregnant women.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions<1%: Acute hemolytic anemia, AHF inhibitor development, allergic reactions (rare), anaphylaxis (rare), bleeding tendency increased, blurred vision, chest tightness, chills, fever, headache, hyperfibrinogenemia, jittery feeling, lethargy, nausea, somnolence, stinging at the infusion site, stomach discomfort, tingling, urticaria, vasomotor reactions with rapid infusion, vomiting
Drug InteractionsThere are no known significant interactions.
Monitoring ParametersHeart rate and blood pressure (before and during I.V. administration); AHF levels prior to and during treatment; in patients with circulating inhibitors, the inhibitor level should be monitored; hematocrit; monitor for signs and symptoms of intravascular hemolysis; bleeding
Reference RangeClassification of hemophilia; normal is defined as 1 int. unit/mL of factor VIII

Severe: Factor level <1% of normal

Moderate: Factor level 1% to 5% of normal

Mild: Factor level >5% to <40% of normal

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking that may affect coagulation or platelet function. Patient should be monitored closely during and after infusion for any change in vital signs, cardiac and CNS status, or hypersensitivity reactions (eg, chills, fever, chest pain, respiratory difficulty). Assess response (eg, results of laboratory tests [hematocrit and coagulation studies]), therapeutic effectiveness (bleeding and coagulation status), and adverse reactions (eg, bleeding or anemia). Provide patient education according to patient condition.
Monitoring: Lab TestsIn patients with circulating inhibitors, the inhibitor level should be monitored; hematocrit
Patient EducationThis medication can only be given intravenously. Report immediately any sudden-onset headache, rash, chest or back pain, wheezing or respiratory difficulties, hives, itching, low-grade fever, stomach pain, or nausea/vomiting to prescriber. Wear identification indicating that you have a hemophilic condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Hemofil M: Vial labeled with international units [contains albumin; derived from mouse proteins; packaging may contain natural rubber latex]

Koate®-DVI: ~250 int. units, ~500 int. units, ~1000 int. units [contains albumin]

Monarc-M™: Vial labeled with international units [contains albumin; derived from mouse proteins; packaging may contain natural rubber latex]

Monoclate-P®: ~250 int. units, ~500 int. units, ~1000 int. units, ~1500 int. units [contains albumin; derived from mouse proteins]

Generic AvailableYes
Mechanism of ActionProtein (factor VIII) in normal plasma which is necessary for clot formation and maintenance of hemostasis; activates factor X in conjunction with activated factor IX; activated factor X converts prothrombin to thrombin, which converts fibrinogen to fibrin, and with factor XIII forms a stable clot
Pharmacodynamics/KineticsHalf-life elimination: Mean: 8-27 hours
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAHF (Human); Factor VIII (Human)

References

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Manucci PM, “Impact of Recombinant Factor VIII on Hemophilia Care,” *Vox Sang*, 1994, 67(Suppl 3):49-52. [PubMed 7975511]

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Peterson CW, “Treating Hemophilia,” *Am Pharm*, 1994, NS34(8):57-67.

White GC, Rosendaal F, Aledort LM, et al, “Definitions in Hemophilia. Recommendation of the Scientific Subcommittee on Factor VIII and Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis,” *Thromb Haemost*, 2001, 85(3):560.[PubMed 11307831]

International Brand NamesAntihemophilic Factor (Recombinant) (IL); Benefix (KP); Factane (FR); Haemate P (GB, IE); Haemoctin SDH (IL); Hemofil M (FR); Kogenate (FR, NZ, TW); Kogenate FS (AU, IL); Monoclate P (GB, IE); Octanate (MX); Optivate (GB, IE); Recombinate (AR, AT, AU, BE, BR, CH, DE, DK, EE, FI, FR, HN, IT, NL, SE); Replenate (GB, IE)

Antihemophilic Factor (Recombinant)

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Special Alerts

ReFacto®: Product Availability - September 2008

ReFacto® will no longer be available after May 31, 2009. Wyeth has replaced it with Xyntha™ which is available as of September 2008.

Medication Safety IssuesConfusion may occur due to the omitting of "Factor VIII" from some product labeling. Review product contents carefully prior to dispensing any antihemophilic factor.

Pronunciation(an tee hee moe FIL ik FAK tor ree KOM be nant)

U.S. Brand NamesAdvate; Helixate® FS; Kogenate® FS; Recombinate; ReFacto®; Xyntha™

Canadian Brand NamesHelixate® FS; Kogenate®; Kogenate® FS; Recombinate; ReFacto®

Pharmacologic CategoryAntihemophilic Agent

Use: Labeled IndicationsPrevention and treatment of hemorrhagic episodes in patients with hemophilia A (classic hemophilia or congenital factor VIII deficiency); perioperative management of hemophilia A; can be of significant therapeutic value in patients with acquired factor VIII inhibitors ≤10 Bethesda units/mL; prophylaxis of joint bleeding and to reduce risk of joint damage in children with hemophilia A with no preexisting joint damage

Dosing: Adults**Hemophilia:** I.V.: Individualize dosage based on coagulation studies performed prior to treatment and at regular intervals during treatment. In general, administration of factor VIII 1 int. unit/kg will increase circulating factor VIII levels by ~2 int. units/dL. (General guidelines presented; consult individual product labeling for specific dosing recommendations.)

Dosage based on desired factor VIII increase (%):

To calculate dosage needed based on desired factor VIII increase (%):

[Body weight (kg) x desired factor VIII increase (%)] divided by 2%/int. units/kg = int. units factor VIII required

For example:

50 kg x 30 (% increase) divided by 2%/int. units/kg = 750 int. units factor VIII

Dosage based on expected factor VIII increase (%):

It is also possible to calculate the **expected** % factor VIII increase:

(# int. units administered x 2%/int. units/kg) divided by body weight (kg) = expected % factor VIII increase

For example:

(1400 int. units x 2%/int. units/kg) divided by 70 kg = 40%

General guidelines:

Minor hemorrhage: 10-20 int. units/kg as a single dose to achieve FVIII plasma level ~20% to 40% of normal. Mild superficial or early hemorrhages may respond to a single dose; may repeat dose every 12-24 hours for 1-3 days until bleeding is resolved or healing achieved.

Moderate hemorrhage/minor surgery: 15-30 int. units/kg to achieve FVIII plasma level 30% to 60% of normal. May repeat 1 dose at 12-24 hours if needed. Some products suggest continuing for ≥3 days until pain and disability are resolved

Major to life-threatening hemorrhage: Initial dose 40-50 int. units/kg followed by a maintenance dose of 20-25 int. units/kg every 8-24 hours until threat is resolved, to achieve FVIII plasma level 60% to 100% of normal.

Major surgery: 50 int. units/kg given preoperatively to raise factor VIII level to 100% before surgery begins. May repeat as necessary after 6-12 hours initially and for a total of 10-14 days until healing is complete. Intensity of therapy may depend on type of surgery and postoperative regimen.

Bleeding prophylaxis: May be administered on a regular basis for bleeding prophylaxis. Doses of 24-40 int. units/kg 3 times/week have been reported in patients with severe hemophilia to prevent joint bleeding.

If bleeding is not controlled with adequate dose, test for presence of inhibitor. It may not be possible or practical to control bleeding if inhibitor titers >10 Bethesda units/mL.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Hemophilia: Refer to adult dosing.

Joint bleeding prophylaxis (Kogenate® FS): 25 int. units/kg every other day

Administration: I.V.Infuse over 5-10 minutes (maximum: 10 mL/minute).

Advate: Infuse over ≤5 minutes (maximum: 10 mL/minute).

Kogenate® FS: Infuse over 1-15 minutes; based on patient tolerability

Xyntha™: Infuse over several minutes; adjust based on patient comfort. Do not admix or administer in same tubing as other medications.

Dietary ConsiderationsAdvate contains sodium 108 mEq/L; Helixate® FS and Kogenate® FS contain sodium 27-36 mEq/L; Recombinate contains sodium 180 mEq/L

StorageStore under refrigeration, 2°C to 8°C (36°F to 46°F); avoid freezing. Use within 3 hours of reconstitution. Do not refrigerate after reconstitution, a precipitation may occur.

Advate: May also be stored at room temperature for up to 6 months.

Helixate® FS, Kogenate® FS, ReFacto®, Xyntha™: May also be stored at room temperature (not to exceed 25°C [36°F]) up to 3 months; avoid prolonged exposure to light during storage.

Recombinate: May also be stored at room temperature, not to exceed 30˚C (86˚F).

ReconstitutionIf refrigerated, the dried concentrate and diluent should be warmed to room temperature before reconstitution. Gently agitate or rotate vial after adding diluent, do not shake vigorously.

ContraindicationsHypersensitivity to any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Antibody formation: The development of factor VIII antibodies has been reported with antihemophilic factors; monitor for signs of formation of antibodies to factor VIII; may occur at anytime but more common in young children with severe hemophilia.

- Hypersensitivity reactions: Allergic hypersensitivity reactions (including anaphylaxis) may occur; monitor.

Dosage form specific issues:

- Albumin: Recombinate is stabilized using human albumin.

- Bovine: Recombinate may contain bovine protein.

- Mouse/hamster protein: Advate, Helixate® FS, Kogenate® FS, Recombinate, ReFacto®, and Xyntha™ may contain trace amounts of mouse or hamster protein.

- Sucrose: Helixate® FS and Kogenate® FS are stabilized with sucrose.

- von Willebrand factor: Products contain naturally-occurring von Willebrand factor for stabilization, however efficacy has not been established for the treatment of von Willebrand disease.

Other warnings/precautions:

- Dose requirements: The dosage requirement will vary in patients with factor VIII inhibitors; optimal treatment should be determined by clinical response.

Geriatric ConsiderationsResponse in the elderly is not expected to differ from that of younger patients; dosage should be individualized.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Safety and efficacy in pregnant women has not been established. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsActual frequency may vary by product.

>1%:

Central nervous system: Chills, dizziness, fever, headache, pain

Dermatologic: Pruritus, rash, urticaria

Gastrointestinal: Diarrhea, nausea, taste perversion, vomiting

Hematologic: Hemorrhage

Local: Injection site pain, injection site inflammation, infusion site reaction

Neuromuscular & skeletal: Arthralgia, weakness

Respiratory: Cough, dyspnea, nasopharyngitis, pharyngolaryngeal pain

Miscellaneous: Catheter thrombosis, factor VIII inhibitor formation

≤1%, postmarketing, and/or case reports: Abdominal pain, adenopathy, allergic reactions, anaphylaxis, anemia, anorexia, arthralgia, AST increased, chest discomfort, chest pain, constipation, depersonalization, diaphoresis, edema, epistaxis, facial edema, facial flushing, factor VIII decreased, fatigue, fever, GI hemorrhage, hives, hot flashes, hypersensitivity reaction, hyper-/hypotension (slight), infection, joint swelling, lethargy, otitis media, pallor, paresthesia, restlessness, rhinitis, rigors, shortness of breath, somnolence, tachycardia, urinary tract infection, vasodilation, venous catheter access complications

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersHeart rate and blood pressure (before and during I.V. administration); plasma factor VIII activity prior to and during treatment; development of factor VIII inhibitors; signs of bleeding

Reference RangeClassification of hemophilia; normal is defined as 1 int. unit/mL of factor VIII

Severe: Factor level <1% of normal

Moderate: Factor level 1% to 5% of normal

Mild: Factor level >5% to <40% of normal

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking that may affect coagulation or platelet function. Patient should be monitored closely during and after infusion for any change in vital signs, cardiac and CNS status, or hypersensitivity reactions (eg, chills, fever, chest pain, respiratory difficulty). Assess response (eg, results of laboratory tests [hematocrit and coagulation studies]), therapeutic effectiveness (bleeding and coagulation status), and adverse reactions (eg, bleeding or anemia). Provide patient education according to patient condition.

Monitoring: Lab TestsPlasma factor VIII activity; development of factor VIII inhibitors; hemoglobin, hematocrit

Patient EducationThis medication can only be given intravenously. Report immediately any sudden-onset headache, rash, chest or back pain, wheezing or respiratory difficulties, hives, itching, low-grade fever, stomach pain, or nausea/vomiting to prescriber. Wear identification indicating that you have a hemophilic condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, recombinant [preservative free]:

Advate: 250 int. units, 500 int. units, 1000 int. units, 1500 int. units, 2000 int. units, 3000 int. units [plasma/albumin free; contains sodium 108 mEq/L, mannitol; derived from hamster or mouse proteins]

Helixate® FS: 250 int. units, 500 int. units, 1000 int. units [albumin free; contains sucrose 28 mg/vial, sodium 27-36 mEq/L, polysorbate 80; derived from hamster or mouse protein]

Kogenate® FS: 250 int. units, 500 int. units, 1000 int. units, 2000 int. units [albumin free; contains sucrose 28-56 mg/vial, sodium 27-36 mEq/L; derived from hamster or mouse protein]

Recombinate: 250 int. units, 500 int. units, 1000 int. units [contains human albumin, sodium 180 mEq/L; derived from bovine, hamster or mouse proteins; packaging contains natural rubber latex]

ReFacto®: 250 int. units, 500 int. units, 1000 int. units, 2000 int. units [contains sucrose; derived from hamster or mouse proteins]

Xyntha™: 250 int. units, 500 int. units, 1000 int. units, 2000 int. units [albumin free; contains sucrose, polysorbate 80; derived from hamster proteins]

Generic AvailableNo

Mechanism of ActionFactor VIII replacement, necessary for clot formation and maintenance of hemostasis. It activates factor X in conjunction with activated factor IX; activated factor X converts prothrombin to thrombin, which converts fibrinogen to fibrin, and with factor XIII forms a stable clot.

Pharmacodynamics/Kinetics

Distribution: V_{ss}: 0.36-0.57 dL/kg

Half-life elimination: Mean: 8-19 hours

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAHF (Recombinant); Factor VIII (Recombinant); rAHF

References

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Peterson CW, “Treating Hemophilia,” *Am Pharm*, 1994, NS34(8):57-67.

White GC, Rosendaal F, Aledort LM, et al, “Definitions in Hemophilia. Recommendation of the Scientific Subcommittee on Factor VIII and

Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis," *Thromb Haemost*, 2001, 85(3):560.[PubMed 11307831]

International Brand NamesKoate DVI (MX); Novo Nordsk (MX); Novoseven (MX)

Antihemophilic Factor/von Willebrand Factor Complex (Human)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(an tee hee moe FIL ik FAK tor von WILL le brand FAK tor KOM plex HYU man)

U.S. Brand NamesAlphanate® *[new formulation]*; Humate-P®

Canadian Brand NamesHumate-P®

Pharmacologic CategoryAntihemophilic Agent; Blood Product Derivative

Use: Labeled Indications

Prevention and treatment of hemorrhagic episodes in patients with hemophilia A (classical hemophilia) (Alphanate®, Humate-P®) or acquired factor VIII deficiency (Alphanate®)

Prophylaxis with surgical and/or invasive procedures in patients with von Willebrand disease (vWD) when desmopressin is either ineffective or contraindicated (Alphanate®)

Treatment of spontaneous or trauma-induced bleeding, as well as prevention of excessive bleeding during and after surgery, in patients with vWD (mild, moderate, or severe) where use of desmopressin is known or suspected to be inadequate (Humate-P®)

Dosing: Adults

Hemophilia A: I.V.: Individualize dosage based on coagulation studies performed prior to treatment and at regular intervals during treatment; in general, administration of factor VIII 1 int. unit/kg will increase circulating factor VIII levels by ~2 int. units/dL.

Minor hemorrhage: Loading dose: FVIII:C 15 int. units/kg to achieve FVIII:C plasma level ~30% of normal. If second infusion is needed, half the loading dose may be given once or twice daily for 1-2 days.

Moderate hemorrhage: Loading dose: FVIII:C 25 int. units/kg to achieve FVIII:C plasma level ~50% of normal; Maintenance: FVIII:C 15 int. units/kg every 8-12 hours for 1-2 days in order to maintain FVIII:C plasma levels at 30% of normal. Repeat the same dose once or twice daily for up to 7 days or until adequate wound healing.

Life-threatening hemorrhage/major surgery: Loading dose: FVIII:C 40-50 int. units/kg; Maintenance: FVIII:C 20-25 int. units/kg every 8 hours to maintain FVIII:C plasma levels at 80% to 100% of normal for 7 days. Continue same dose once or twice daily for another 7 days in order to maintain FVIII:C levels at 30% to 50% of normal.

von Willebrand disease (vWD): Treatment (Humate-P®): I.V.: Individualize dosage based on coagulation studies performed prior to treatment and at regular intervals during treatment; in general, administration of factor VIII1 int. unit/kg would be expected to raise circulating vWF:RCof ~5 int. units/dL

Type 1, mild (if desmopressin is not appropriate): Major hemorrhage:

Loading dose: vWF:RCof 40-60 int. units/kg

Maintenance dose: vWF:RCof 40-50 int. units/kg every 8-12 hours for 3 days, keeping vWF:RCof nadir >50%; follow with 40-50 int. units/kg daily for up to 7 days

Type 1, moderate or severe:

Minor hemorrhage: vWF:RCof 40-50 int. units/kg for 1-2 doses

Major hemorrhage:

Loading dose: vWF:RCof 50-75 int. units/kg

Maintenance dose: vWF:RCof 40-60 int. units/kg every 8-12 hours for 3 days to keep the vWF:RCof nadir >50%, then 40-60 int. units/kg daily for a total of up to 7 days

Types 2 and 3:

Minor hemorrhage: vWF:RCof 40-50 int. units/kg for 1-2 doses

Major hemorrhage:

Loading dose: vWF:RCof 60-80 int. units/kg

Maintenance dose: vWF:RCof 40-60 int. units/kg every 8-12 hours for 3 days, keeping the vWF:RCof nadir >50%; follow with 40-60 int. units/kg daily for a total of up to 7 days

von Willebrand disease (vWD): Surgery/procedure prophylaxis (except patients with type 3 undergoing major surgery) (Alphanate®): I.V.:

Preoperative dose: vWF:RCof 60 int. units /kg 1 hour prior to surgery

Maintenance dose: vWF:RCof 40-60 int. units/kg every 8-12 hours as clinically needed. May reduce dose after third postoperative day;

continue treatment until healing is complete. For minor procedures, maintain vWF of 40% to 50% during postoperative days 1-3; for major procedures maintain vWF of 40% to 50% for ≥3-7 days.

von Willebrand disease (vWD): Surgery/procedure prevention of bleeding (Humate-P®): I.V.:

Emergency surgery: Administer vWF:RCof 50-60 int units/kg; monitor trough coagulation factor levels for subsequent doses

Surgical management (nonemergency):

Loading dose calculation based on baseline target vWF:RCof: (Target peak vWF:RCof - Baseline vWF:RCof) x weight (in kg) / IVR = int. units vWF:RCof required. Administer loading dose 1-2 hours prior to surgery. **Note:** If IVR not available, assume 2 int. units/dL per int. units/kg of VWF:RCof product administered.

Target concentrations for vWF:RCof following loading dose:

Major surgery: 100 int. units/dL

Minor surgery: 50-60 int. units/dL

Maintenance dose: Initial: $^{1}/_{2}$ loading dose followed by dosing determined by target tough concentrations, generally every 8-12 hours. Patients with shorter half lives may require dosing every 6 hours.

Target maintenance trough vWF:RCof concentrations:

Major surgery: >50 int. units/dL for up to 3 days, followed by >30 int. units/dL for a minimum total treatment of 72 hours

Minor surgery: ≥30 int. units/dL for a minimum duration of 48 hours

Oral surgery: ≥30 int. units/dL for a minimum duration of 8-12 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Hemophilia A and vWD treatment: Refer to adult dosing.

von Willebrand disease (vWD) surgery/procedure prophylaxis (except patients with type 3 undergoing major surgery) (Alphanate®): I.V.:

Preoperative dose: vWF:RCof 75 int. units /kg 1 hour prior to surgery

Maintenance dose: vWF:RCof 50-75 int. units/kg every 8-12 hours as clinically needed. May reduce dose after third postoperative day; continue treatment until healing is complete.

Administration: I.V.

Alphanate®: Infuse slowly (maximum rate 10 mL/minute)

Humate-P®: Infuse slowly (maximum rate 4 mL/minute)

Storage

Alphanate®: Store under refrigeration, 2°C to 8°C (36°F to 46°F); avoid freezing. May also be stored at room temperature (not to exceed 30˚C/86˚F) for ≤2 months. Use as soon as possible after reconstitution.

Humate-P®: Store unopened vials at ≤25°C (≤77°F) until expiration date on label; avoid freezing. Use within 3 hours of reconstitution. Do not refrigerate after reconstitution, precipitation may occur.

ReconstitutionIf refrigerated, the dried concentrate and diluent should be warmed to room temperature before reconstitution. Gently swirl or rotate vial after adding diluent; do not shake vigorously. Use provided filter spike to withdraw solution from vial; remove filter spike prior to administration.

ContraindicationsHistory of anaphylactic or severe systemic response to antihemophilic factor or von Willebrand factor formulations; hypersensitivity to any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Antibody formation: The development of factor VIII antibodies has been reported with antihemophilic factor preparations; the risk of developing alloantibodies to von Willebrand factor is not known.
- Thrombotic events: Risk of thromboembolic events may be increased; use with caution when treating vWD in patients with risk factors for thrombosis. Incidence of thrombosis may be increased in females.

Special populations:

- Blood types A, B, and AB: Contains trace amounts of blood groups A and B isohemagglutinins and when large or frequently repeated doses are given to individuals with blood groups A, B, and AB, the patient should be monitored for signs of progressive anemia and the possibility of intravascular hemolysis should be considered.

Dosage form specific issues:

- Alphanate®: Not approved for use in patients with type 3 vWD (severe) undergoing major surgery.
- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors,

as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer. Strongly consider hepatitis A and B vaccination.

Other warnings/precautions:

- Dose requirements: The dosage requirement will vary in patients with factor VIII inhibitors; optimal treatment should be determined by clinical response.

Geriatric ConsiderationsResponse in the elderly is not expected to differ from that of younger patients; dosage should be individualized.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted. Safety and efficacy in pregnant women have not been established. Use during pregnancy only if clearly needed. Parvovirus B19 or hepatitis A, which may be present in plasma-derived products, may affect a pregnant woman more seriously than nonpregnant women.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiorespiratory arrest, chest tightness, edema, femoral venous thrombosis, flushing, hypervolemia, orthostatic hypotension, shock, thromboembolic events, vasodilation

Central nervous system: Chills, dizziness, fever, headache, lethargy, pain, seizure, somnolence

Dermatologic: Itching, pruritus, rash, urticaria

Endocrine & metabolic: Parotid gland swelling

Gastrointestinal: Nausea, vomiting

Hematologic: Hematocrit decreased (moderate), hemorrhage, hemolysis, pseudothrombocytopenia (severe)

Hepatic: ALT increased

Local: Injection site stinging, phlebitis

Neuromuscular & skeletal: Extremity pain, joint pain, paresthesia, rigors

Respiratory: Dyspnea, pharyngitis, pulmonary embolus (large doses)

Miscellaneous: Allergic reactions, anaphylactic reactions, factor VIII inhibitor formation

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersHeart rate and blood pressure (before and during I.V. administration); AHF levels prior to and during treatment; in patients with circulating inhibitors, the inhibitor level should be monitored; hematocrit; monitor for signs and symptoms of intravascular hemolysis; bleeding; vWF activity [circulating levels of functional vWF are measured as ristocetin cofactor activity (vWF:RCof)]. In surgical patients, monitor vWF:RCof at baseline and after surgery, trough vWF:RCof and FVIII:C at least daily.
Reference Range

Classification of hemophilia; normal is defined as 1 int. unit/mL of factor VIII:C

Severe: Factor level <1% of normal

Moderate: Factor level 1% to 5% of normal

Mild: Factor level >5% to <40% of normal

Classification of von Willebrand disease

Severe forms: vWF:RCof <10 units/dL and factor VIII:C <20 units/dL

Moderate forms: vWF:RCof 10-30 units/dL and factor VIII:C 20-40 units/dL

Mild forms: vWF:RCof 30-50 units/dL and factor VIII:C 40-60 units/dL

Note: Circulating levels of functional VWF are measured as ristocetin cofactor activity (vWF:RCof)]

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking that may affect coagulation or platelet function. Patient should be monitored closely during and after infusion for any change in vital signs, cardiac and CNS status, or hypersensitivity reactions (eg, chills, fever, chest pain, respiratory difficulty). Assess response (eg, results of laboratory tests [hematocrit and coagulation studies]), therapeutic effectiveness (bleeding and coagulation status), and adverse reactions (eg, bleeding or anemia). Provide patient education according to patient condition.
Monitoring: Lab TestsAHF levels prior to and during treatment; in patients with circulating inhibitors, the inhibitor level should be monitored; hematocrit; monitor for signs and symptoms of intravascular hemolysis; bleeding; vWF activity [circulating levels of functional vWF are measured as ristocetin cofactor activity (vWF:RCof)]. In surgical patients, monitor vWF:RCof at baseline and after surgery, trough vWF:RCof and FVIII:C at least daily.
Patient EducationThis medication can only be given intravenously. Report immediately any sudden-onset headache, rash, chest or back pain, wheezing or respiratory difficulties, hives, itching, low-grade fever, stomach pain, or nausea/vomiting to prescriber. Wear identification indicating that you have a hemophilic condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [human derived]:

Alphanate®:

- 250 int. units [Factor VIII and vWF:RCof ratio varies by lot; contains sodium ≥10 mEq/vial, albumin and polysorbate 80; packaged with diluent]
- 500 int. units [Factor VIII and vWF:RCof ratio varies by lot; contains sodium ≥10 mEq/vial, albumin and polysorbate 80; packaged with diluent]
- 1000 int. units [Factor VIII and vWF: RCof ratio varies by lot; contains sodium ≥10 mEq/vial, albumin and polysorbate 80; packaged with diluent]
- 1500 int. units [Factor VIII and vWF:RCof ratio varies by lot; contains sodium ≥10 mEq/vial, albumin and polysorbate 80; packaged with diluent]

Humate-P®:

- FVIII 250 int. units and vWF:RCof 600 int. units [contains albumin; packaged with diluent]
- FVIII 500 int. units and vWF:RCof 1200 int. units [contains albumin; packaged with diluent]
- FVIII 1000 int. units and vWF:RCof 2400 int. units [contains albumin; packaged with diluent]

Generic Available No

Mechanism of Action Factor VIII and von Willebrand factor (vWF), obtained from pooled human plasma, are used to replace endogenous factor VIII and vWF in patients with hemophilia or vWD. Factor VIII in conjunction with activated factor IX, activates factor X which converts prothrombin to thrombin and fibrinogen to fibrin. vWF promotes platelet aggregation and adhesion to damaged vascular endothelium and acts as a stabilizing carrier protein for factor VIII. [Circulating levels of functional vWF are measured as ristocetin cofactor activity (vWF:RCof)]

Pharmacodynamics/Kinetics

Duration: vWD: Shortening of bleeding time sustained 22-26 hours postinfusion

Distribution: V_d: vWF:RCof: 53-59 mL/kg

Half-life elimination:

- Factor VIII coagulant activity (FVIII:C): 8-28 hours in patients with hemophilia A
- vWF:RCof: 3-34 hours in patients with vWD

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Index TermsAHF (Human); Factor VIII (Human); FVIII/vWF; vWF:RCof

References

Berntorp E, “Plasma Product Treatment in Various Types of von Willebrand Disease,” *Haemostasis*, 1994, 24(5):289-97. [PubMed 7843640]

Federici AB, “Clinical Diagnosis of von Willebrand's Disease,” *Haemophilia*, 2004, 10(Suppl 4):169-76.

Kreuz W, Mentzer D, Becker S, et al, “Haemate P in Children With von Willebrand's Disease,” *Haemostasis*, 1994, 24(5):304-10. [PubMed 7843642]

Peterson CW, “Treating Hemophilia,” *Am Pharm*, 1994, NS34(8):57-67.

Scharrer I, Vigh T, and Aygoren-Purun E, “Experience With Haemate P in von Willebrand's Disease in Adults,” *Haemostasis*, 1994, 24(5):298-303.[PubMed 7843641]

White GC, Rosendaal F, Aledort LM, et al, “Definitions in Hemophilia. Recommendation of the Scientific Subcommittee on Factor VIII and Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis,” *Thromb Haemost*, 2001, 85(3):560.[PubMed 11307831]

Antipyrine and Benzocaine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(an tee PYE reen & BEN zoe kane)

U.S. Brand NamesA/B Otic; Allergen®; Aurodex

Canadian Brand NamesAuralgan®

Pharmacologic CategoryOtic Agent, Analgesic; Otic Agent, Cerumenolytic

Use: Labeled IndicationsTemporary relief of pain and reduction of swelling associated with acute congestive and serous otitis media, swimmer's ear, otitis externa; facilitates ear wax removal

Dosing: Adults

Pain and swelling associated with otitis media, swimmer's ear, otitis externa: Otic: Fill ear canal with solution; moisten cotton pledget with solution, place in external ear, repeat every 1-2 hours until pain and congestion are relieved

Ear wax removal: Otic: Instill drops 3-4 times/day for 2-3 days

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: OtherOtic: Otitis media: Fill ear canal with solution. Moisten cotton pledget with solution and place in external ear. Avoid touching ear with dropper. Do not rinse dropper after use.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from light and heat. Do not use if brown or contains a precipitate. Discard 6 months after placing dropper into solution.

ContraindicationsHypersensitivity to antipyrine, benzocaine, or any component of the formulation; perforated tympanic membrane

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue if sensitization or irritation occur.

Other warnings/precautions:

- Appropriate use: For otic use only, do not apply to eyes.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsPostmarketing and/or case reports: Methemoglobinemia (rare with topical benzocaine)

Drug InteractionsThere are no known significant interactions.

Patient EducationFor the ear. Discard bottle 6 months after opening.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, otic [drops]: Antipyrine 5.4% and benzocaine 1.4% (10 mL)

A/B Otic, Allergen®, Aurodex: Antipyrine 5.4% and benzocaine 1.4% (15 mL)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (A/B Otic)

1.4-5.4% (15): $11.99

Solution (Antipyrine-Benzocaine)

5.4-1.4% (10): $12.99

Mechanism of ActionAntipyrine has analgesic properties; benzocaine is a local anesthetic; the glycerin base provides decreased middle ear pressure by osmosis.

Pharmacodynamics/KineticsOnset: Pain relief: ~30 minutes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBenzocaine and Antipyrine

References

Hoberman A, Paradise JL, Reynolds EA, et al, "Efficacy of Auralgan for Treating Ear Pain in Children With Acute Otitis Media," *Arch Pediatr Adolesc Med*, 1997, 151(7):675-8.[PubMed 9232040]

Rodriguez LF, Smolik LM, and Zbehlik AJ, “Benzocaine-Induced Methemoglobinemia: Report of a Severe Reaction and Review of the Literature,” *Ann Pharmacother*, 1994, 28(5):643-9.[PubMed 8069004]

International Brand Names Auralgan (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Auralgan (non-prescription) (AU); Oidisan (CO); Otogesic (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE)

Antithrombin III

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English

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Pronunciation(an tee THROM bin three)
U.S. Brand NamesThrombate III®
Canadian Brand NamesThrombate III®
Pharmacologic CategoryAnticoagulant; Blood Product Derivative
Use: Labeled IndicationsTreatment of hereditary antithrombin III deficiency in connection with surgical procedures, obstetrical procedures, or thromboembolism
Use: Unlabeled/InvestigationalAcquired antithrombin III deficiencies related to disseminated intravascular coagulation (DIC)
Dosing: Adults**Antithrombin III deficiency:**

Initial dose: Dosing is individualized based on pretherapy AT-III levels. The initial dose should raise antithrombin III levels (AT-III) to 120% and may be calculated based on the following formula:

[desired AT-III level % - baseline AT-III level %] x body weight (kg)

divided by 1.4%/int. units/kg

For example, if a 70 kg adult patient had a baseline AT-III level of 57%, the initial dose would be

[(120% - 57%) x 70] divided by 1.4 = 3150 int. units

Maintenance dose: Subsequent dosing should be targeted to keep levels between 80% to 120% which may be achieved by administering 60% of the initial dose every 24 hours. Adjustments may be made by adjusting dose or interval. Maintain level within normal range for 2-8 days depending on type of procedure.

Dosing: ElderlyRefer to adult dosing.
Administration: I.V.Infuse over 10-20 minutes.
Administration: I.V. DetailpH: 6-7.5
Dietary ConsiderationsContains sodium 110-210 mEq/L
StorageStore vials under refrigeration at 2°C to 8°C (36°F to 46°F); avoid freezing. Bring drug and diluent to room temperature prior to reconstitution. Administer within 3 hours of mixing.
ReconstitutionReconstitute with sterile water for injection. Do not shake; swirl to mix to avoid foaming. Filter through sterile filter needle provided prior to administration.
ContraindicationsHypersensitivity to any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Infections: Product of human plasma; may potentially contain infectious agents which could transmit disease; screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces this risk. Infections thought to be transmitted by this product should be reported to Talecris Biotherapeutics at 1-800-520-2807.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Although FDA indicated for obstetrical procedures, there are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

1% to 10%: Central nervous system: Dizziness (2%)

<1%: Bowel fullness, chest pain, chest tightness, chills, cramps, dyspnea, fever, film over eye, foul taste, hematoma, hives, lightheadedness, nausea

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Drotrecogin Alfa: Antithrombin III may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Recent use/intake of herbs with anticoagulant or antiplatelet activity (including cat's claw, dong quai, evening primrose, garlic, ginkgo and ginseng) may increase the risk of bleeding.

Monitoring ParametersMonitor antithrombin III peak and trough levels (preinfusion and 20 minutes postinfusion) for each dose and monitor levels 12 hours after initial loading dose; liver function tests; monitor antithrombin III levels in neonates of parents with hereditary antithrombin III deficiency immediately after birth

Reference RangeMaintain antithrombin III level in plasma >80%; plasma AT-III levels are ~60% lower near term infants than levels observed in adults; premature infants may have levels lower than other neonates.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (especially drugs affecting coagulation and platelet activity). Vital signs, cardiac status, and CNS status should be monitored during and after therapy. If tachycardia develops, infusion should be discontinued and prescriber notified.

Monitoring: Lab TestsMonitor antithrombin III peak and trough levels (preinfusion and 20 minutes postinfusion) for each dose and monitor levels 12 hours after initial loading dose; liver function tests; monitor antithrombin III levels in neonates of parents with hereditary antithrombin III deficiency immediately after birth

Patient EducationThis medication can only be given intravenously. Report immediately any sudden onset headache; rash, itching, or hives; chest or back pain; dizziness (use caution when rising from sitting or lying position, climbing stairs, driving, or engaging in tasks requiring alertness until response to drug is known); or wheezing or respiratory difficulties. Wear identification indicating that you have an antithrombin III deficiency. **Breast-feeding precautions:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Thrombate III®: 500 int. units, 1000 int. units [contains heparin, sodium chloride 110-210 mEq/L; packaged with diluent]

Generic AvailableNo

Mechanism of ActionAntithrombin III is the primary physiologic inhibitor of *in vivo* coagulation. It is an alpha$_2$-globulin. Its principal actions are the inactivation of thrombin, plasmin, and other active serine proteases of coagulation, including factors IXa, Xa, XIa, and XIIa. The inactivation of proteases is a major step in the normal clotting process. The strong activation of clotting enzymes at the site of every bleeding injury facilitates fibrin formation and maintains normal hemostasis. Thrombosis in the circulation would be caused by active serine proteases if they were not inhibited by antithrombin III after the localized clotting process.

Pharmacodynamics/KineticsHalf-life elimination: Biologic: 2.5 days (immunologic assay); 3.8 days (functional AT-III assay). Half-life may be decreased following surgery, with hemorrhage, acute thrombosis, and/or during heparin administration.

Pharmacotherapy PearlsThromboembolism has been reported in children of women with hereditary antithrombin III (AT-III) deficiency; AT-III levels in neonates of parents with hereditary AT-III deficiency should be measured immediately after birth. Plasma AT-III levels are typically lower in neonates and infants than in adults. Low plasma AT-III levels in neonates may not be indicative of deficiency; consultation with a coagulation expert is recommended.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAT-III; Heparin Cofactor I

References

Schwartz RS, Bauer KA, Rosenberg RD, et al, “Clinical Experience With Antithrombin III Concentrate in Treatment of Congenital and Acquired Deficiency of Antithrombin. The Antithrombin III Study Group,” *Am J Med*, 1989, 87(3B):53S-60S.

International Brand NamesAnbin (ES); Anbinex (IL); Anthrobin P (JP); Antithrombin III (HK); Antithrombin III Baxter (PL); Antithrombin III Grifols (PL); Antithrombin III Immuno (HR, HU); Atenativ (DE, DK, FI, IT, NL, NO, SE); Atenativ (ES, HU); Atenativ 500 (AT, CH, HN); Atend (MX); Athimbin HS 500 (AT); Atryn (EE); Kybernin (CZ, ES, HR, HU); Kybernin P (AR, BR, ES, ID, PL); Neuart (JP); Thrombate III (PL); Thrombotrol-VF (AU)

Antithymocyte Globulin (Equine)

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Atgam® may be confused with Ativan®

Pronunciation(an te THY moe site GLOB yu lin, E kwine)

U.S. Brand NamesAtgam®

Canadian Brand NamesAtgam®

Pharmacologic Category[Immune Globulin](); [Immunosuppressant Agent]()

Use: Labeled IndicationsPrevention and treatment of acute renal allograft rejection; treatment of moderate to severe aplastic anemia in patients not considered suitable candidates for bone marrow transplantation

Use: Unlabeled/InvestigationalPrevention and treatment of other solid organ allograft rejection; prevention of graft-versus-host disease following bone marrow transplantation

Dosing: Adults**Note:** An intradermal skin test is recommended prior to administration of the initial dose of ATG; use 0.1 mL of a 1:1000 dilution of ATG in normal saline. A positive skin reaction consists of a wheal ≥10 mm in diameter. If a positive skin test occurs, the first infusion should be administered in a controlled environment with intensive life support immediately available. A systemic reaction precludes further administration of the drug. The absence of a reaction does **not** preclude the possibility of an immediate sensitivity reaction.

Note: Premedication with diphenhydramine, hydrocortisone, and is recommended prior to first dose.

Aplastic anemia protocol: I.V.: 10-20 mg/kg/day for 8-14 days, then give every other day for 7 more doses for a total of 21 doses in 28 days.

Renal allograft rejection, prevention: I.V.: 15 mg/kg/day for 14 days, then give every other day for 7 more doses for a total of 21 doses in 28 days; initial dose should be administered within 24 hours before or after transplantation.

Renal allograft rejection, treatment: I.V.: 10-15 mg/kg/day for 14 days, then give every other day for 7 more doses.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** See adult dosing for notes on intradermal skin testing and premedication.

Aplastic anemia protocol: I.V.: 10-20 mg/kg/day for 8-14 days; then administer every other day for 7 more doses; addition doses may be given every other day for 21 total doses in 28 days.

Renal allograft: I.V.: 5-25 mg/kg/day

Administration: I.V.Infuse dose over at least 4 hours. Any severe systemic reaction to the skin test, such as generalized rash, tachycardia, dyspnea, hypotension, or anaphylaxis, should preclude further therapy. Epinephrine and resuscitative equipment should be nearby. Patient may need to be pretreated with an antipyretic, antihistamine, and/or corticosteroid. Mild itching and erythema can be treated with antihistamines. Infuse into a vascular shunt, arterial venous fistula, or high-flow central vein through a 0.2-1 micron in-line filter.

First dose: Premedicate with diphenhydramine orally 30 minutes prior to and hydrocortisone I.V. 15 minutes prior to infusion and acetaminophen 2 hours after start of infusion.

StorageAmpuls must be refrigerated; do not freeze. Diluted solution is stable for 24 hours (including infusion time) at refrigeration.

ReconstitutionDilute into inverted bottle of sterile vehicle to ensure that undiluted lymphocyte immune globulin does not contact air. Gently rotate or swirl to mix. Final concentration should be 4 mg/mL. May be diluted in NS, $D_5$1/4NS, $D_5$1/2NS.

ContraindicationsHypersensitivity to lymphocytic immune globulin, any component of the formulation, or other equine gamma globulins

Warnings/Precautions

Boxed warnings:

- Experienced physician: See "Other warnings/precautions" below.

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1:1000) should be available. Rash, dyspnea, hypotension, or anaphylaxis precludes further administration of the drug.

- Leukopenia: Discontinue if severe and unremitting leukopenia occurs.

- Thrombocytopenia: Discontinue if severe and unremitting thrombocytopenia occurs.

Other warnings/precautions:

- Administration: Must be administered via central line due to chemical phlebitis. Dose must be administered over at least 4 hours; patient may need to be pretreated with an antipyretic, antihistamine, and/or corticosteroid.

- Experienced physician: **[U.S. Boxed Warning]: Should only be used by physicians experienced in immunosuppressive therapy or management of solid organ or bone marrow transplant patients. Adequate laboratory and supportive medical resources must be readily available in the facility for patient management.**

- Skin testing: Intradermal skin testing is recommended prior to first-dose administration.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted; use during pregnancy is not recommended. Women exposed to Atgam® during pregnancy may be enrolled in the National Transplantation Pregnancy Registry (877-955-6877).

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Fever, chills

Dermatologic: Pruritus, rash, urticaria

Hematologic: Leukopenia, thrombocytopenia

1% to 10%:

Cardiovascular: Bradycardia, chest pain, CHF, edema, encephalitis, hyper-/hypotension, myocarditis, tachycardia

Central nervous system: Agitation, headache, lethargy, lightheadedness, listlessness, seizure

Gastrointestinal: Diarrhea, nausea, stomatitis, vomiting

Hepatic: Hepatosplenomegaly, liver function tests abnormal

Local: Pain at injection site, phlebitis, thrombophlebitis, burning soles/palms

Neuromuscular & skeletal: Myalgia, back pain, arthralgia

Ocular: Periorbital edema

Renal: Abnormal renal function tests

Respiratory: Dyspnea, respiratory distress

Miscellaneous: Anaphylaxis, serum sickness, viral infection, night sweats, diaphoresis, lymphadenopathy

<1%: Dizziness, epigastric pain, faintness, herpes simplex reactivation, hiccups, hyperglycemia, iliac vein obstruction, infection, laryngospasm, malaise, paresthesia, pulmonary edema, renal artery thrombosis, serum sickness, toxic epidermal necrosis, weakness, wound dehiscence

Postmarketing and/or case reports: Acute renal failure, anemia, aplasia, confusion, cough, deep vein thrombosis, disorientation, GI bleeding, granulocytopenia, hemolysis, kidney enlarged, neutropenia, nosebleed, pancytopenia, vasculitis

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Vaccines (Live): Immune Globulins may diminish the therapeutic effect of Vaccines (Live). **Exceptions:** Influenza Virus Vaccine; Yellow Fever Vaccine. *Risk D: Consider therapy modification*

Monitoring ParametersLymphocyte profile, CBC with differential and platelet count, vital signs during administration

Nursing: Physical Assessment/MonitoringAssess for history of previous allergic reactions. Monitor vital signs during infusion and observe for adverse or allergic reactions. Teach patient adverse symptoms to report.

Monitoring: Lab TestsLymphocyte profile, CBC with differential, platelet count

Patient EducationThis medication can only be administered by infusion. You will be closely monitored during the infusion. Do not get up alone; ask for assistance if you must get up or change position. Do not have any vaccinations for the next 3 months without consulting prescriber. Immediately report chills; persistent dizziness or nausea; itching or stinging; acute back pain; chest pain, tightness, or rapid heartbeat; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Atgam®: 50 mg/mL (5 mL)

Generic AvailableNo

Mechanism of ActionMay involve elimination of antigen-reactive T lymphocytes (killer cells) in peripheral blood or alteration of T-cell function

Pharmacodynamics/Kinetics

Distribution: Poorly into lymphoid tissues; binds to circulating lymphocytes, granulocytes, platelets, bone marrow cells

Half-life elimination, plasma: 1.5-12 days

Excretion: Urine (~1%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause malaise

Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; use caution with clozapine and carbamazepine

Index TermsAntithymocyte Immunoglobulin; ATG; Horse Antihuman Thymocyte Gamma Globulin; Lymphocyte Immune Globulin

References

Rosenfeld SJ, Kimball J, Vining D, et al, “Intensive Immunosuppression With Antithymocyte Globulin and Cyclosporine as Treatment for Severe Acquired Aplastic Anemia,” *Blood*, 1995, 85(11):3058-65. [PubMed 7756640]

Whitehead B, James I, Helms P, et al, “Intensive Care Management of Children Following Heart and Heart-Lung Transplantation,” *Intensive Care Med*, 1990, 16(7):426-30.[PubMed 2269710]

International Brand NamesAtgam (BG, IN, MY, NZ, SG); Lymphoglobuline (TW)

Antithymocyte Globulin (Rabbit)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(an te THY moe site GLOB yu lin RAB bit)

U.S. Brand NamesThymoglobulin®

Pharmacologic CategoryImmune Globulin; Immunosuppressant Agent

Use: Labeled IndicationsTreatment of acute rejection of renal transplant; used in conjunction with concomitant immunosuppression

Use: Unlabeled/InvestigationalInduction therapy in renal transplant

Dosing: AdultsTreatment of acute rejection: I.V.: 1.5 mg/kg/day for 7-14 days

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Dosing: Adjustment for Toxicity

WBC count 2000-3000 cells/mm^3 or platelet count 50,000-75,000 cells/mm^3: Reduce dose by 50%

WBC count <2000 cells/mm^3 or platelet count <50,000 cells/mm^3: Consider discontinuing treatment

Administration: I.V.The first dose should be infused over at least 6 hours through a high-flow vein. Subsequent doses should be administered over at least 4 hours. Administer through an in-line 0.22 micron filter. Premedication with corticosteroids, acetaminophen, and/or an antihistamine may reduce infusion-related reactions.

StorageStore powder under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Use immediately following reconstitution.

ReconstitutionAllow vials to reach room temperature, then reconstitute each vial with SWFI 5 mL. Rotate vial gently until dissolved. Prior to administration, further dilute one vial in 50 mL saline or dextrose (total volume is usually 50-500 mL depending on total number of vials needed per dose). Mix by gently inverting infusion bag once or twice.

ContraindicationsHypersensitivity to antithymocyte globulin, rabbit proteins, or any component of the formulation; acute viral illness

Warnings/Precautions

Boxed warnings:

- Experienced physician: See "Other warnings/precautions" below.

Concerns related to adverse effects:

- Anaphylaxis: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1:1000) should be available.
- Infection: Severe infections may develop following concomitant use of immunosuppressants and prolonged use or overdose of antithymocyte globulin. Appropriate antiviral, antibacterial, antiprotozoal, and/or antifungal prophylaxis is recommended.
- Malignancy: An increased incidence of lymphoma, post-transplant lymphoproliferative disease (PTLD) or other malignancies may develop following concomitant use of immunosuppressants and prolonged use or overdose of antithymocyte globulin.
- Hematologic toxicity: Reversible neutropenia and thrombocytopenia may result from the development of cross-reactive antibodies. Dose adjustment may be necessary.

Other warnings/precautions:

- Administration: Initial dose must be administered over at least 6 hours into a high flow vein; may pretreat with an antipyretic, antihistamine, and/or corticosteroid.
- Experienced physician: **[U.S. Boxed Warning]: Should only be used by physicians experienced in immunosuppressive therapy for the treatment of renal transplant patients.** Medical surveillance is required during the infusion.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Cardiovascular: Hypertension, peripheral edema, tachycardia

Central nervous system: Chills, fever, headache, pain, malaise

Endocrine & metabolic: Hyperkalemia

Gastrointestinal: Abdominal pain, diarrhea, nausea

Genitourinary: Urinary tract infection

Hematologic: Leukopenia, thrombocytopenia

Neuromuscular & skeletal: Weakness

Respiratory: Dyspnea

Miscellaneous: Antirabbit antibody development, sepsis, systemic infection

1% to 10%:

Central nervous system: Dizziness

Gastrointestinal: Gastritis, gastrointestinal moniliasis

Miscellaneous: Herpes simplex infection, moniliasis

Postmarketing and/or case reports: Anaphylaxis, cytokine release syndrome, PTLD, neutropenia, serum sickness (delayed)

Oncology: Vesicant No

Oncology: Emetic Potential Very low (<10%)

Drug Interactions There are no known significant interactions.

Monitoring Parameters Lymphocyte profile, CBC with differential and platelet count; vital signs during administration; signs and symptoms of infection

Monitoring: Lab Tests Lymphocyte profile, CBC with differential and platelet count

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Thymoglobulin®: 25 mg

Generic Available No

Mechanism of Action Polyclonal antibody which appears to cause immunosuppression by acting on T-cell surface antigens and depleting CD4 lymphocytes

Pharmacodynamics/Kinetics

Duration of action: Lymphopenia may persist ≥1 year

Half-life elimination, plasma: 2-3 days

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment Leukopenia and thrombocytopenia are common; use caution with clozapine, carbamazepine, and valproic acid

Index Terms Antithymocyte Immunoglobulin; rATG

References

Hardinger KL, “Rabbit Antithymocyte Globulin Induction Therapy in Adult Renal Transplantation,” *Pharmacotherapy*, 2006, 26(12):1771-83.[PubMed 17125438]

International Brand Names ATG-Fresinius (EE, SE); Thymoblobuline (BG, DK, FI, GR, NO)

Latrodectus mactans)'; return;">

Antivenin (*Latrodectus mactans*)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(an tee VEN in lak tro DUK tus MAK tans)

Pharmacologic CategoryAntivenin

Use: Labeled IndicationsTreatment of patients with symptoms of black widow spider bites

Dosing: Adults

Skin test: Intradermal: 0.02 mL of a 1:10 dilution in NS (also use a control solution of NS); evaluate in 10 minutes. Positive reaction is urticarial wheal surrounded by zone of erythema.

Conjunctival test: Ophthalmic: Instill 1 drop of a 1:10 dilution into the conjunctival sac

Note: Itching of the eye and/or reddening of conjunctiva indicates a positive reaction, usually occurring within 10 minutes.

Desensitization: Note: In separate vials or syringes, prepare 1:10 and 1:100 dilutions of antivenin in NS.

SubQ: Inject 0.1, 0.2, and 0.5 mL of the 1:100 dilution at 15- to 30- minute intervals. Proceed with the next dose only if no reaction has occurred following the previous. Repeat procedure using the 1:10 dilution and then undiluted antivenin.

If a reaction occurs, apply tourniquet proximal to the injection site and administer epinephrine 1:1000. Wait at least 30 minutes, then administer another antivenin injection at the last dose which did not evoke a reaction.

If no reaction has occurred following 0.5 mL of undiluted antivenin, continue the dose at 15-minute intervals until entire dose has been administered.

Treatment of symptoms due to black widow spider bite: Administer only following the skin test or conjunctival test: I.M., I.V..: 2.5 mL

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Skin test: Intradermal: Refer to adult dosing.

Conjunctival test: Ophthalmic: Instill 1 drop of a 1:100 dilution into the conjunctival sac

Note: Itching of the eye and/or reddening of conjunctiva indicates a positive reaction, usually occurring within 10 minutes.

Desensitization: Refer to adult dosing.

Treatment of symptoms due to black widow spider bite: Administer only following the skin test or conjunctival test:

Children <12 years: I.V.: 2.5 mL

Children >12 years: Refer to adult dosing.

Administration: I.M.Administer in the anterolateral thigh; apply tourniquet if systemic reaction occurs.

Administration: I.V.Administer over 15 minutes; I.V. administration is preferred in severe cases, with shock, or in children <12 years of age.

StorageStore between 2°C to 8°C (36°F to 46°F). Do not freeze.

ReconstitutionReconstitute with 2.5 mL of the provided diluent. With needle still in rubber stopper, shake well to dissolve. Excessive agitation or shaking of the reconstituted vial may cause foaming, which may lead to denaturation of the antivenin. Prior to I.V. infusion, further dilute in 10-50 mL NS.

Warnings/Precautions

Concerns related to adverse effects:

- Delayed serum sickness: Delayed serum sickness may occur 1-3 weeks from administration (especially when large doses used) even with a negative allergic history and absence of reaction to skin test.
- Horse serum hypersensitivity: Carefully review allergies and history of exposure to products containing horse serum. History of atopic sensitivity to horses may increase risk of immediate sensitivity reactions. Use with caution in patients with asthma, hay fever, or urticaria.

Dosage form specific issues:

- Thimerosal: Some products may contain thimerosal.

Other warnings/precautions:

- Desensitization: A desensitization protocol is available if sensitivity tests are mildly or questionably positive to reduce risk of immediate severe hypersensitivity reaction. Desensitization should be performed only when antivenin administration would be lifesaving. In otherwise healthy adults (16-60 years), use of antivenin may be deferred and other treatments may be considered. Epinephrine 1:1000 should be readily available.

- Skin/conjunctival test: A skin or conjunctival test should be performed prior to use in all patients. The absence of a skin hypersensitivity reaction does not exclude anaphylaxis or hypersensitivity following antivenin administration. False-negative rate for skin testing is 10% with similar agents. Conversely, hypersensitivity is not an absolute contraindication in a significantly envenomated patient.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsMiscellaneous: Allergic reactions (75%), anaphylaxis, serum sickness
Drug InteractionsThere are no known significant interactions.
Monitoring ParametersSerum sickness reaction (for 8-12 days following administration); allergic reaction (for 7-14 days following administration)
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 6000 antivenin units [equine origin; contains thimerosal; packaged with diluent and normal horse serum for sensitivity testing]

Generic AvailableNo
Mechanism of ActionNeutralizes the venom of black widow spiders (*Latrodectus mactans*)
Pharmacotherapy PearlsEarly treatment is emphasized for prompt relief of symptoms; however, successful treatment has been seen following administration 90 hours after bite.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index Terms*Latrodectus mactans* Antivenin; Black Widow Spider Species Antivenin
References

O'Malley GF, Dart RC, and Kuffner EF, “Successful Treatment of Latrodectism With Antivenin After 90 hours,” *N Engl J Med*, 1999, 340(8):657. [PubMed 10049091]

Saucier JR, “Arachnid Envenomation,” *Emerg Med Clin North Am*, 2004, 22(2):405-22.[PubMed 15163574]

Micrurus fulvius)'; return;">
Antivenin (*Micrurus fulvius*)

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English

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Special Alerts

North American Coral Snake Antivenin Expiration Date Extended - November 20, 2008

Wyeth Pharmaceuticals no longer manufactures this antivenin; the last available lot (4030026) expired on October 31, 2008. There is no alternative antidote to treat coral snake envenomations. As a result, the FDA has extended the expiration on this lot until October 31, 2009. Lot 4030026 continues to be available and Wyeth will supply product to their direct customers.

Additional information available at the following FDA website: http://www.fda.gov/cber/safety/wyecor102808.htm

Pronunciation(an tee VEN in mye KRU rus FUL vee us)
Pharmacologic CategoryAntivenin
Use: Labeled IndicationsNeutralization of venoms of Eastern coral snake and Texas coral snake
Dosing: AdultsNeutralize Eastern and Texas coral snake venom (does not neutralize venom of Arizona or Sonoran coral snake): I.V.: 3-5 vials by slow injection (dependent on severity of signs/symptoms; some patients may need more than 10 vials)

Note: Each vial of antivenom neutralizes ~2 mg of venom.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Administration: I.V.Have ready access to drugs and equipment for resuscitation. Perform skin test prior to administration. An intravenous infusion of NS 250-500 mL should be started, and doses of antivenin delivered by slow injection or via reservoir bottle. Inject the first 1-2 mL of antivenin over 3-5 minutes. Rate of infusion will be regulated by tolerance of antivenin and severity of envenomation.
StoragePrior to reconstitution, store at 2°C to 8°C (36°F to 46°F). Do not freeze.
ReconstitutionDilute each vial with SWFI 10 mL. Vial contains a vacuum which will pull the diluent in; point diluent stream at the center of the lyophilized pellet. If diluent runs down side of vial, the pellet will float and adhere to vial stopper. Swirl gently for 1 minute; do not shake. Repeat every 5 minutes. Reconstitution takes ~30 minutes/vial. Color of final solution may vary from clear to slight yellow or green.
ContraindicationsConcomitant use with opioid analgesics or other respiratory depressants; history of anaphylaxis to equine-derived serum is a relative contraindication
Warnings/Precautions

Concerns related to adverse effects:

- Delayed serum sickness: Delayed serum sickness may occur 1-3 weeks from administration (especially when large doses used) even with a negative allergic history and absence of reaction to skin test.
- Horse serum hypersensitivity: Carefully review allergies and history of exposure to products containing horse serum. History of atopic sensitivity to horses may increase risk of immediate sensitivity reactions. Use with caution in patients with asthma, hay fever, or urticaria.

Other warnings/precautions:

- Resuscitation precautions: When administering this agent, have ready access to drugs and equipment for resuscitation.
- Skin test: Perform skin test prior to administration. The absence of a skin hypersensitivity reaction does not exclude anaphylaxis or hypersensitivity following antivenin administration. False-negative rate for skin testing is 10% with similar agents. Conversely, hypersensitivity is not an absolute contraindication in a significantly envenomated patient.
- Does not neutralize venom of Arizona or Sonoran coral snake

Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined.

Central nervous system: Meningismus, pain

Neuromuscular & skeletal: Muscle weakness, peripheral neuritis

Miscellaneous:

Immediate systemic reactions (allergic, anaphylaxis, shock): May occur within 30 minutes and may start before needle is withdrawn; symptoms include apprehension, cough, collapse, cyanosis, dyspnea, edema (face, throat, tongue), flushing, itching, urticaria, vomiting

Delayed systemic reactions (serum sickness): Usually occur 5-24 days following administration; symptoms include arthralgia, edema, fever, lymphadenopathy, malaise, urticaria, nausea, vomiting

Drug Interactions There are no known significant interactions.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: Derived from *Micrurus fulvius* venom [equine origin; contains phenol and thimerosal; packaged with diluent] [DSC]

Generic Available No

Mechanism of Action Neutralizes the venom of the Eastern coral snake and Texas coral snake with specific antibodies.

Pharmacotherapy Pearls Refer to manufacturer's labeling for skin test instructions and desensitization protocol.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment Combined use with a beta-blocker may increase the severity of anaphylaxis. Contraindicated with opioids. Use caution with psychotropic agents; may produce additive respiratory-depressant effects.

Index Terms *Micrurus fulvius* Antivenin; North American Coral Snake Antivenin

References

de Roodt AR, Paniagua-Solis JF, Dolab JA, et al, “Effectiveness of Two Common Antivenoms for North, Central, and South American *Micrurus* Envenomations,” *J Toxicol Clin Toxicol*, 2004, 42(2):171-8. [PubMed 15214622]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Endometrial Cancer

Regimen UseEndometrial cancer

Regimen

Doxorubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Cisplatin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 21-28 days

References

Barrett RJ, Blessing JA, Homesley HD, et al, âCircadian-Timed Combination Doxorubicin-Cisplatin Chemotherapy for Advanced Endometrial Carcinoma. A Phase II Study of the Gynecologic Oncology Group,â *Am J Clin Oncol*, 1993, 16(6):494-6.[PubMed 8256764]

Apomorphine

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English

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Pronunciation(a poe MOR feen)

U.S. Brand NamesApokyn®

Pharmacologic CategoryAnti-Parkinson's Agent, Dopamine Agonist

Use: Labeled IndicationsTreatment of hypomobility, “off” episodes with Parkinson's disease

Use: Unlabeled/InvestigationalTreatment of erectile dysfunction

Dosing: AdultsBegin antiemetic therapy 3 days prior to initiation and continue for 2 months before reassessing need.

Parkinson's disease, “off” episode: SubQ: Initial test dose 2 mg, **medical supervision required; see “Note”**. Subsequent dosing is based on both tolerance and response to initial test dose.

If patient tolerates test dose and responds: Starting dose: 2 mg as needed; may increase dose in 1 mg increments every few days; maximum dose: 6 mg

If patient tolerates but does not respond to 2 mg test dose: Second test dose: 4 mg

If patient tolerates and responds to 4 mg test dose: Starting dose: 3 mg, as needed for “off” episodes; may increase dose in 1 mg increments every few days; maximum dose 6 mg

If patient does not tolerate 4 mg test dose: Third test dose: 3 mg

If patient tolerates 3 mg test dose: Starting dose: 2 mg as needed for “off” episodes; may increase dose in 1 mg increments to a maximum of 3 mg

If therapy is interrupted for >1 week, restart at 2 mg and gradually titrate dose.

Note: Medical supervision is required for all test doses with standing and supine blood pressure monitoring predose and 20-, 40-, and 60 minutes postdose. If subsequent test doses are required, wait >2 hours before another test dose is given; next test dose should be timed with another “off” episode. If a single dose is ineffective for a particular “off” episode, then a second dose should not be given. The average dosing frequency was 3 times/day in the development program with limited experience in dosing >5 times/day and with total daily doses >20 mg. Apomorphine is intended to treat the “off” episodes associated with levodopa therapy of Parkinson's disease and has not been studied in levodopa-naive Parkinson's patients.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Mild-to-moderate impairment: Reduce test dose and starting dose: 1 mg

Severe impairment: Has not been studied

Dosing: Hepatic Impairment

Mild-to-moderate impairment: Use caution

Severe impairment: Has not been studied

Administration: I.V.Not for I.V. administration.

Administration: OtherSubQ: Initiate antiemetic 3 days before test dose of apomorphine and continue for 2 months (if patient to be treated) before reassessment. Administer in abdomen, upper arm, or upper leg; change site with each injection. 3 mL cartridges are used with a manual, reusable, multidose injector pen. Injector pen can deliver doses up to 1 mL in 0.02 mL increments. Do not give intravenously; thrombus formation or pulmonary embolism may occur.

Dietary ConsiderationsAvoid ethanol consumption.

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to apomorphine or any component of the formulation; **concomitant use with $5HT_3$antagonists**; intravenous administration

Warnings/Precautions

Concerns related to adverse effects:

- Hallucinations: May cause hallucinations.
- Impulsive control disorders: Dopamine agonists used for Parkinson’s disease or restless legs syndrome have been associated with compulsive behaviors and/or loss of impulse control, which has manifested as pathological gambling, libido increases (hypersexuality), and/or binge eating. Causality has not been established, and controversy exists as to whether this phenomenon is related to the underlying disease, prior behaviors/addictions and/or drug therapy. Dose reduction or discontinuation of therapy has been reported to reverse these behaviors in some, but not all cases.
- Orthostatic hypotension: May cause orthostatic hypotension; Parkinson's disease patients appear to have an impaired capacity to

respond to a postural challenge. Use with caution in patients at risk of hypotension (such as those receiving antihypertensive drugs) or where transient hypotensive episodes would be poorly tolerated (cardiovascular disease or cerebrovascular disease). Parkinson's patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation, and should be informed of this risk. Orthostasis peaks 20 minutes after dosing and lasts at least 90 minutes. If patient develops clinically-significant orthostatic hypotension with test dose, then apomorphine should not be used.

- Pleural/retroperitoneal fibrosis: Ergot-derived dopamine agonists have also been associated with fibrotic complications (eg, retroperitoneal fibrosis, pleural thickening, and pulmonary infiltrates); monitor closely for signs and symptoms of fibrosis.
- Retinal changes: Pathologic degenerative changes were observed in the retinas of albino rats during studies with this agent, but were not observed in the retinas of albino mice or in other species. The significance of these data for humans remains uncertain.
- Somnolence: Patients have reported falling asleep while engaging in activities of daily living; this has been reported to occur without significant warning signs. Monitor for daytime somnolence or pre-existing sleep disorder; caution with concomitant sedating medication; discontinue if significant daytime sleepiness or episodes of falling asleep occur. Patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). Use with caution in patients receiving other CNS depressants or psychoactive agents. Effects with other sedative drugs or ethanol may be potentiated.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; hypotension may cause coronary ischemia.
- Cerebrovascular disease: Use with caution in patients with cerebrovascular disease; hypotension may cause cerebral ischemia.
- Dyskinesias: Use with caution in patients with pre-existing dyskinesias; may be exacerbated.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Patients at risk for torsade de pointes: Use with caution in patients with risk factors for torsade de pointes (hypokalemia, hypomagnesemia, bradycardia, concurrent use of drugs that prolong QT_c, or genetic predisposition).
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Antiemetic pretreatment: **Pretreatment with antiemetic is necessary;** avoid pretreatment with antidopaminergic and antiserotonin antiemetic agents (antiemetic experience is greatest with trimethobenzamide).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Metabisulfite: Contains metabisulfite which may cause allergic reactions in some individuals.

Other warnings/precautions:

- Abuse: Rare cases of abuse have been reported.
- Discontinuation of therapy: Dopaminergic agents have been associated with a syndrome resembling neuroleptic malignant syndrome on abrupt withdrawal or significant dosage reduction after long-term use.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted; use only if clearly needed.
LactationExcretion in breast milk unknown/contraindicated
Adverse Reactions

>10%:

Cardiovascular: Chest pain/pressure or angina (15%)

Central nervous system: Drowsiness or somnolence (35%), dizziness or orthostatic hypotension (20%)

Gastrointestinal: Nausea and/or vomiting (30%)

Neuromuscular & skeletal: Falls (30%), dyskinesias (24% to 35%)

Respiratory: Yawning (40%), rhinorrhea (20%)

1% to 10%:

Cardiovascular: Edema (10%), vasodilation (3%), hypotension (2%), syncope (2%), CHF

Central nervous system: Hallucinations or confusion (10%), anxiety, depression, fatigue, headache, insomnia, pain

Dermatologic: Bruising

Endocrine & metabolic: Dehydration

Gastrointestinal: Constipation, diarrhea

Local: Injection site reactions

Neuromuscular & skeletal: Arthralgias, weakness

Miscellaneous: Diaphoresis increased

<1%: Angina, cardiac arrest, focal panniculitis, libido increased, MI, priapism, psychosexual stimulation, skin nodules, sudden death

Postmarketing and/or case reports: Reported with dopamine agonists: Impulsive/compulsive behaviors (eg, pathological gambling, hypersexuality, binge eating)

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 3A4, 2C19; **Inhibits** CYP1A2 (weak), 3A (weak), 2C19 (weak)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antiemetics (5HT3 Antagonists): May enhance the hypotensive effect of Apomorphine. *Risk X: Avoid combination*

Antipsychotics (Atypical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Antipsychotics (Typical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

COMT Inhibitors: May decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Metoclopramide: May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Caution with ethanol consumption; may increase risk of hypotension.

Monitoring ParametersEach test dose: Supine and standing blood pressure predose and 20, 40, and 60 minutes postdose; drowsiness

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. See Dosing and Administration for specifics about "test" doses and necessity of premedication with antiemetic prior to each dose. Patient must be monitored closely for minimum of 90 minutes following each test dose (eg, orthostatic hypotension). Assess therapeutic effectiveness and adverse response (eg, orthostatic hypotension, nausea, vomiting, dyskinesias, excessive sedation or somnolence) at beginning of therapy, with each change in dose, and at regular intervals during therapy. Teach patient (or caregiver) proper use (injection pen or syringe, needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medications during therapy without consulting prescriber. Follow specific directions for administration with injection pen or syringe and needle disposal. Avoid alcohol while taking Apokyn™. An antiemetic may be prescribed to reduce nausea or vomiting; take as directed. May cause headache, drowsiness, or dizziness (use caution when climbing stairs, driving, or engaged in potentially hazardous tasks until response to drug is known); loss of impulse control (possibly manifested as pathological gambling, libido increases, and/or binge eating); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); or nausea or vomiting (if antiemetic medication does not relieve this, contact prescriber). Report immediately any irregular or rapid heartbeat, chest pain, palpitations, difficulty breathing, shortness of breath; unusual or sudden sleepiness; unusual muscle or skeletal movements or weakness, tremors, or altered gait; CNS changes (hallucinations, confusion, insomnia, anxiety, or depression); suicide ideation; redness, swelling, or irritation at injection site; or other persistent side effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is contraindicated.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride:

Apokyn®: 10 mg/mL (2 mL) [ampul; contains sodium metabisulfite]; (3 mL) [multidose cartridge; contains sodium metabisulfite and benzyl alcohol]

Generic AvailableNo

ManufacturerMylan Bertek Pharmaceuticals

Mechanism of ActionStimulates postsynaptic D2-type receptors within the caudate putamen in the brain.

Pharmacodynamics/Kinetics

Onset: SubQ: Rapid

Distribution: V_d: Mean: 218 L

Metabolism: Not established; potential routes of metabolism include sulfation, N-demethylation, glucuronidation, and oxidation; catechol-O methyltransferase and nonenzymatic oxidation. CYP isoenzymes do not appear to play a significant role.

Half-life elimination: Terminal: 40 minutes

Time to peak, plasma: Improved motor scores: 20 minutes

Excretion: Urine 93% (as metabolites); feces 16%

Related Information

- Antiparkinsonian Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension has been reported in significant numbers of patients.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsApomorphine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Index TermsApomorphine Hydrochloride; Apomorphine Hydrochloride Hemihydrate

References

Factor SA, “Current Status of Symptomatic Medical Therapy in Parkinson’s Disease,” *Neurotherapeutics*, 2008, 5(2):164-80. [PubMed 18394561]

Molina JA, Sàinz-Artiga MJ, Fraile A, et al, “Pathologic Gambling in Parkinson's Disease: A Behavioral Manifestation of Pharmacologic Treatment,” *Mov Disord*, 2000, 15(5):869-72.[PubMed 11009192]

Weintraub D, Siderowf AD, Potenza MN, et al, “Association of Dopamine Agonist Use With Impulse Control Disorders in Parkinson Disease,” *Arch Neurol*, 2006, 63(7):969-73.[PubMed 16831966]

International Brand NamesApo (NL); Apo-Go (CZ, DE, DK, ES, HN, IL, NO, SE, TW); APO-go (PL); Apomine (NZ); Britaject (PL); Ixense (SE); NOC (CN); Stillman (PY); Taluvian (FR); Uprima (AE, BH, BR, CY, EE, EG, IL, IQ, IR, IT, JO, KP, KW, LB, LY, OM, PL, QA, SA, SE, SY, YE); Uprima SL (NZ)

Apraclonidine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Iopidine® may be confused with indapamide, iodine, Lodine®

Pronunciation(a pra KLOE ni deen)

U.S. Brand NamesIopidine®

Canadian Brand NamesIopidine®

Pharmacologic CategoryAlpha$_2$ Agonist, Ophthalmic

Use: Labeled IndicationsPrevention and treatment of postsurgical intraocular pressure (IOP) elevation; short-term, adjunctive therapy in patients who require additional reduction of IOP

Dosing: AdultsPostsurgical intraocular pressure elevation (prevention/treatment): Ophthalmic:

0.5%: Instill 1-2 drops in the affected eye(s) 3 times/day

1%: Instill 1 drop in operative eye 1 hour prior to anterior segment laser surgery, second drop in eye immediately upon completion of procedure

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentAlthough the topical use of apraclonidine has not been studied in renal failure patients, structurally-related clonidine undergoes a significant increase in half-life in patients with severe renal impairment. Close monitoring of cardiovascular parameters in patients with impaired renal function is advised.

Dosing: Hepatic ImpairmentClose monitoring of cardiovascular parameters in patients with impaired liver function is advised because the systemic dosage form of clonidine is partially metabolized in the liver.

Administration: OtherWait 5 minutes between instillation of other ophthalmic agents to avoid washout of previous dose. After topical instillation, finger pressure should be applied to lacrimal sac to decrease drainage into the nose and throat and minimize possible systemic absorption.

StorageStore between 2°C to 27°C (36°F to 80°F). Protect from freezing and light.

ContraindicationsHypersensitivity to apraclonidine, clonidine, or any component of the formulation; use with or within 14 days of MAO inhibitors

Allergy Considerations

- Apraclonidine Allergy

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease, coronary insufficiency, or recent myocardial infarction.
- Vasovagal reactions: Use with caution in patients with history of vasovagal reactions.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Monitoring efficacy: The IOP-lowering efficacy observed during the first month of therapy may not always reflect the long-term level of IOP reduction; routinely monitor IOP.

Geriatric ConsiderationsDetermine that the patient or caregiver can adequately administer ophthalmic medication dosage form.

Pregnancy Risk FactorC

Pregnancy ConsiderationsEmbryocidal effects were observed in some animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

Ocular:

5% to 15%: Discomfort, hyperemia, pruritus

1% to 5%: Blanching, blurred vision, conjunctivitis, discharge, dry eye, foreign body sensation, lid edema, tearing

<1%: Abnormal vision, blepharitis, blepharoconjunctivitis, conjunctival edema, conjunctival follicles, corneal erosion, corneal infiltrate,

corneal staining, edema, irritation, keratitis, keratopathy, lid disorder, lid erythema, lid margin crusting, lid retraction, lid scales, pain, photophobia

Other body systems:

1% to 10%: Gastrointestinal: Dry mouth (10%)

<3%:

Cardiovascular: Arrhythmia, chest pain, facial edema, peripheral edema

Central nervous system: Depression, dizziness, headache, insomnia, malaise, nervousness, somnolence

Dermatologic: Contact dermatitis, dermatitis

Gastrointestinal: Constipation, nausea, taste perversion

Neuromuscular & skeletal: Abnormal coordination, myalgia, paresthesia, weakness

Respiratory: Asthma, dry nose, dyspnea, parosmia, pharyngitis, rhinitis

Postmarketing and/or case reports: Allergic reactions, bradycardia

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Alpha2-Agonists (Ophthalmic). *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Monitoring ParametersClosely monitor patients who develop exaggerated reductions in intraocular pressure

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking. Monitor therapeutic response (intraocular pressure) and adverse effects (ocular and other systems). Teach patient proper use, side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationFor use in eyes only. May sting on instillation, do not touch dropper to eye. Visual acuity may be decreased after administration. Night vision may be decreased. Distance vision may be altered. Read package instructions for insertion. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnancy. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic:

Iopidine®: 0.5% (5 mL, 10 mL); 1% (0.1 mL) [contains benzalkonium chloride]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Iopidine)

0.5% (5): $85.99

0.5% (10): $160.52

1% (24): $299.97

Mechanism of ActionApraclonidine is a potent alpha-adrenergic agent similar to clonidine; relatively selective for alpha$_2$-receptors but does retain some binding to alpha$_1$-receptors; appears to result in reduction of aqueous humor formation; its penetration through the blood-brain barrier is more polar than clonidine which reduces its penetration through the blood-brain barrier and suggests that its pharmacological profile is characterized by peripheral rather than central effects.

Pharmacodynamics/Kinetics

Onset of action: 1 hour

Peak effect: Decreased intraocular pressure: 3-5 hours

Absorption: Ocular: Systemically absorbed

Half-life elimination, systemic: 8 hours

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes

upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentDry mouth may be exacerbated by concurrent use of psychotropics

Index TermsAplonidine; Apraclonidine Hydrochloride; p-Aminoclonidine

International Brand NamesAlfadrops (IN); Iopidine (AR, AT, AU, BE, BF, BG, BJ, BR, CH, CI, CN, DE, DK, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, IE, IL, IT, KE, KP, LR, LU, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, PE, PL, PT, PY, SC, SD, SE, SG, SL, SN, TN, TZ, UG, VE, ZA, ZM, ZW); Iopimax (ES)

Aprepitant

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Aprepitant may be confused with fosaprepitant

Emend® (aprepitant) oral capsule formulation may be confused with Emend® for injection (fosaprepitant).

Pronunciation(ap RE pi tant)
U.S. Brand NamesEmend®
Canadian Brand NamesEmend®
Pharmacologic CategoryAntiemetic; Substance P/Neurokinin 1 Receptor antagonist
Use: Labeled IndicationsPrevention of acute and delayed nausea and vomiting associated with moderately- and highly-emetogenic chemotherapy (in combination with other antiemetics); prevention of postoperative nausea and vomiting (PONV)
Dosing: Adults

Prevention of chemotherapy induced nausea/vomiting: Oral: 125 mg on day 1, followed by 80 mg on days 2 and 3 in combination with other antiemetics

Prevention of PONV: Oral: 40 mg within 3 hours prior to induction

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo dose adjustment necessary in patients with renal disease or end-stage renal disease maintained on hemodialysis.
Dosing: Hepatic Impairment

Mild-to-moderate impairment (Child-Pugh Class A and B): No adjustment necessary.

Severe impairment (Child-Pugh Class C): No data available.

Administration: OralAdminister with or without food.

Chemotherapy induced nausea/vomiting: First dose should be given 1 hour prior to antineoplastic therapy; subsequent doses should be given in the morning.

PONV: Administer within 3 hours of induction

Dietary ConsiderationsMay be taken with or without food.
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).
ContraindicationsHypersensitivity to aprepitant or any component of the formulation; use with cisapride or pimozide
Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

- Nausea/vomiting: Appropriate use: Not intended for treatment of existing nausea and vomiting or for chronic continuous therapy.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions. The effect on orally administered CYP3A4 substrates is greater than those administered intravenously.

Geriatric ConsiderationsIn two studies by the manufacturer, with a total of 544 patients, 31% were >65 years of age, while 5% were >75 years. No differences in safety and efficacy were noted between elderly subjects and younger adults. No dosing adjustment is necessary.
Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women; use only if clearly needed.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions**Note:** Adverse reactions reported as part of a combination chemotherapy regimen or with general anesthesia.

>10%:

Central nervous system: Fatigue (18% to 22%)

Gastrointestinal: Nausea (7% to 13%), constipation (9% to 12%)

Neuromuscular & skeletal: Weakness (3% to 18%)

Miscellaneous: Hiccups (11%)

1% to 10%:

Cardiovascular: Hypotension (≤6%), bradycardia (4%)

Central nervous system: Dizziness (≤7%)

Endocrine & metabolic: Dehydration (6%), hot flushing (3%)

Gastrointestinal: Diarrhea (6% to 10%), dyspepsia (8%), abdominal pain (5%), stomatitis (5%), epigastric discomfort (4%), gastritis (4%), throat pain (3%), vomiting (3%)

Hematologic: Neutropenia (3% to 9%), leukopenia (9%), hemoglobin decreased (2% to 5%)

Hepatic: ALT increased (1% to 6%), AST increased (3%)

Renal: BUN increased (5%), proteinuria (7%), serum creatinine increased (4%)

>0.5%: Acid reflux, acne, albumin decreased, alkaline phosphatase increased, anemia, anxiety, appetite decreased, arthralgia, back pain, bilirubin increased, candidiasis, confusion, conjunctivitis, cough, deglutition disorder, depression, diabetes mellitus, diaphoresis, dry mouth, DVT, dysgeusia, dysphagia, dyspnea, dysuria, edema, eructation, erythrocyturia, febrile neutropenia, flatulence, flushing, herpes simplex, hyperglycemia, hypertension, hypokalemia, hyponatremia, hypovolemia, hypoxia, glucosuria, leukocytes increased, leukocyturia, malaise, MI, muscular weakness, musculoskeletal pain, myalgia, nasal secretion, obstipation, palpitation, pelvic pain, peripheral neuropathy, pharyngitis, pneumonitis, pulmonary embolism, rash, renal insufficiency, respiratory infection, respiratory insufficiency, rigors, salivation increased, sensory neuropathy, septic shock, syncope, tachycardia, taste disturbance, thrombocytopenia, tremor, urinary tract infection, vocal disturbance, weight loss

Postmarketing and/or case reports: Angioedema, disorientation, duodenal ulcer (perforating), dysarthria, enterocolitis, hypoesthesia, neutropenic sepsis, pneumonia, sensory disturbance, sinus tachycardia, Stevens-Johnson syndrome, urticaria, visual acuity decreased, wheezing

Metabolism/Transport Effects **Substrate** of CYP1A2 (minor), 2C19 (minor), 3A4 (major); **Inhibits** CYP2C9 (weak), 2C19 (weak), 3A4 (moderate); **Induces** CYP2C9 (weak), 3A4 (weak)

Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Aprepitant. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Aprepitant may increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cisapride: Aprepitant may increase the serum concentration of Cisapride. *Risk X: Avoid combination*

Contraceptive (Progestins): Aprepitant may decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Aprepitant may increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diltiazem: Aprepitant may increase the serum concentration of Diltiazem. Diltiazem may increase the serum concentration of Aprepitant. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Aprepitant may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Aprepitant may increase the serum concentration of Pimozide. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Aprepitant. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Warfarin: Aprepitant may decrease the serum concentration of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Aprepitant serum concentration may be increased when taken with grapefruit juice; avoid concurrent use.

Herb/Nutraceutical: Avoid St John's wort (may decrease aprepitant levels).

Nursing: Physical Assessment/MonitoringShould be used in combination with other medications (corticosteroid and 5-HT$_3$ receptor antagonist). Assess potential for interactions with other pharmacological agents and herbal products patient may be taking. Assess for therapeutic effectiveness (decreased nausea/vomiting) and adverse reactions (fatigue, weakness, gastrointestinal disturbance, dehydration). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis medication may be prescribed in combination with other medications; follow directions and timing exactly. May take with or without food depending on reason for use; avoid grapefruit juice and St John's wort while taking this medication. Report unusual fatigue, weakness, dizziness, disorientation, abdominal discomfort, chest pain, respiratory distress, or other persistent side effects to prescriber. **Breast-feeding precautions:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Emend®: 40 mg, 80 mg, 125 mg

Combination package [each package contains]:

Emend®:

Capsule: 80 mg (2s)

Capsule: 125 mg (1s)

Generic AvailableNo

ManufacturerMerck and Co, Inc

Pricing: U.S. (www.drugstore.com)

Capsules (Emend)

40 mg (1): $52.99

40 mg (5): $239.99

80 mg (2): $190.99

80 mg (5): $499.95

80 mg (6): $579.97

125 mg (6): $819.99

Misc (Emend Tri-fold)

80 & 125 mg (3): $322.30

Mechanism of ActionPrevents acute and delayed vomiting by inhibiting the substance P/neurokinin 1 (NK$_1$) receptor; augments the antiemetic activity of the 5-HT$_3$ receptor antagonist and corticosteroid activity and inhibits both acute and delayed phases of chemotherapy-induced emesis.

Pharmacodynamics/Kinetics

Distribution: V$_d$: ~70 L; crosses the blood brain barrier

Protein binding: >95%

Metabolism: Extensively hepatic via CYP3A4 (major); CYP1A2 and CYP2C19 (minor); forms 7 metabolites (weakly active)

Bioavailability: 60% to 65%

Half-life elimination: Terminal: ~9-13 hours

Time to peak, plasma: ~3-4 hours

Pharmacotherapy Pearls**Oncology Comment:** Aprepitant is recommended in the American Society of Clinical Oncology (ASCO) oncology antiemetic guidelines for use in combination with a serotonin receptor antagonist and dexamethasone for chemotherapy with high emetic risk and for chemotherapy regimens of moderate emetic risk which contain an anthracycline and cyclophosphamide (Kris, 2006). The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Antiemesis recommend the same use of aprepitant as is in the ASCO recommendation. The NCCN guidelines however, also suggest that aprepitant may be used for select moderately emetogenic regimens (carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, and methotrexate).

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Hiccups, stomatitis, and mucous membrane disorder.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusFatigue and weakness are common; may cause dizziness

Mental Health: Effects on Psychiatric TreatmentContraindicated with pimozide. Nausea is common; may be additive when used with SSRIs; monitor. Nefazodone may inhibit aprepitant's metabolism, while carbamazepine may increase its metabolism. Plasma levels of alprazolam, midazolam, and triazolam may be increased when combined with aprepitant. Plasma levels of paroxetine may be decreased with combined use; monitor.

Index TermsL 754030; MK 869

References

Kris MG, Hesketh PJ, Somerfield MR, et al, “American Society of Clinical Oncology Guideline for Antiemetics in Oncology: Update 2006,” *J Clin Oncol*, 2006, 24(18):2932-47.[PubMed 16717289]

National Comprehensive Cancer Network (NCCN), “Clinical Practice Guidelines in Oncology™: Antiemesis,” Version 1, 2008. Available at http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf.

International Brand NamesEmend (AR, AT, AU, BE, BG, BR, CH, CR, CZ, DE, DK, DO, ES, FI, FR, GB, GR, GT, HK, HN, IE, IL, IT, MX, MY, NI, NL, NO, PA, PE, PT, RU, SE, SG, SV, TH, TR, TW, VE)

Aprotinin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.
Special Alerts

Aprotinin (Trasylol®) Removed From U.S. Market - May 2008

Following publication of the "Blood Conservation Using Antifibrinolytics: A Randomized Trial in a Cardiac Surgery Population (BART)" study in the May 14, 2008 issue of *The New England Journal of Medicine*, Bayer Pharmaceuticals Inc has notified the U.S. Food and Drug Administration (FDA) of their intent to remove all remaining supplies of aprotinin from U.S. hospital pharmacies and warehouses. The BART study revealed that although aprotinin was associated with a reduction in massive postoperative bleeding, aprotinin was associated with a higher rate of mortality from any cause.

Access to aprotinin is now limited to investigational use only. A specific treatment protocol outlines use in patients who are at increased risk of blood loss and transfusions during coronary artery bypass graft surgery with no acceptable therapeutic alternative. Healthcare providers using aprotinin for this situation must also ensure that the benefits outweigh the risks for their patient.

Further information can be found at the following website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01834.html

Pronunciation(a proe TYE nin)
U.S. Brand NamesTrasylol®
Canadian Brand NamesTrasylol®
Pharmacologic CategoryBlood Product Derivative; Hemostatic Agent
Use: Labeled IndicationsPrevention of perioperative blood loss in patients who are at increased risk for blood loss and blood transfusions in association with cardiopulmonary bypass in coronary artery bypass graft surgery
Dosing: AdultsTest dose: **All** patients should receive a 1 mL (1.4 mg) I.V. test dose at least 10 minutes prior to the loading dose to assess the potential for allergic reactions.

Notes:

The loading dose should be given after induction of anesthesia but prior to sternotomy. In patients with previous exposure to aprotinin, administer loading dose just prior to cannulation. A constant infusion is continued until surgery is complete.

To avoid physical incompatibility with heparin when adding to pump-prime solution, each agent should be added during recirculation to assure adequate dilution.

Regimen A (standard dose):

2 million KIU (280 mg; 200 mL) loading dose I.V. over 20-30 minutes

2 million KIU (280 mg; 200 mL) into pump prime volume

500,000 KIU/hour (70 mg/hour; 50 mL/hour) I.V. during operation

Regimen B (low dose):

1 million KIU (140 mg; 100 mL) loading dose I.V. over 20-30 minutes

1 million KIU (140 mg; 100 mL) into pump prime volume

250,000 KIU/hour (35 mg/hour; 25 mL/hour) I.V. during operation

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo adjustment required, but increased risk of worsening renal dysfunction with use; monitor closely
Dosing: Hepatic ImpairmentNo information available.
Administration: I.V.Administer through a central line. Infuse loading dose over 20-30 minutes, then continuous infusion at 50 mL/hour (regimen A) or 25 mL/hour (regimen B). Rapid infusion (<20 minutes) can cause transient blood pressure decrease; to avoid incompatibility with heparin, add while recirculating the prime fluid of the cardiac bypass circuit.
Administration: I.V. DetailDo not infuse any other drug through the same line.

pH: 4.5-6.5

StorageStore at 2°C to 25°C (36°F to 77°F). Protect from freezing.
Compatibility**Incompatible** with corticosteroids, heparin, tetracyclines, amino acid solutions, and fat emulsion.
RestrictionsAvailable in U.S. under an investigational new drug (IND) process. The program will provide aprotinin for the treatment of adult

patients undergoing coronary artery bypass graft (CABG) surgery requiring cardiopulmonary bypass (CPB) who are at increased risk of bleeding and transfusion during CABG surgery with no acceptable therapeutic alternative. Healthcare providers using aprotinin for this situation must also ensure that the benefits outweigh the risks for their patient. U.S. healthcare providers with patients who may qualify can access information and forms for enrollment at http://www.trasylol.com/main.htm or contact Bayer Medical Communications at (888) 842-2937.

ContraindicationsHypersensitivity to aprotinin or any component of the formulation; known or suspected exposure (including through fibrin sealant products that contain aprotinin) within the past 12 months

Warnings/Precautions

Boxed warnings:

- Anaphylaxis/hypersensitivity reactions: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: **[U.S. Boxed Warning]: Anaphylactic reactions are possible.** Hypersensitivity reactions are more common with repeated use; the risk of fatal reactions appears to be greater upon re-exposure within 12 months of previous use. Patients with a history of allergic reactions may also be more likely to develop a reaction. All patients should receive a test dose at least 10 minutes before the loading dose, although the test dose does not fully predict a patient’s risk. Fatal hypersensitivity reactions have occurred in patients who tolerated the test dose. Epinephrine, steroids, and facilities for cardiopulmonary resuscitation should be available in case such a reaction occurs. In order to administer in a more controlled setting, patients should be in the OR, intubated and ready for rapid cannulation and initiation of cardiopulmonary bypass before the test dose is administered. Delay adding aprotinin to the pump prime solution until after the loading dose has been safely administered. Hypotension is the most frequently reported sign of the hypersensitivity reaction.

- Death: Has been linked to an increased risk of death in observational studies.

- Heart failure: Has been linked to an increased heart failure in observational studies.

- Renal dysfunction: Has been linked to serious kidney damage in observational studies. Renal dysfunction (elevations of >0.5 mg/dL over baseline serum creatinine) may occur with use and may increase the need for dialysis in the perioperative period. Patients at greatest risk are those with pre-existing renal dysfunction (Cl_{cr} <60 mL/minute) or those receiving potential nephrotoxins (eg, aminoglycosides). Monitor renal function closely following administration.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Fever (15%)

Gastrointestinal: Nausea (11%)

1% to 10%:

Cardiovascular: Atrial flutter (6%), ventricular extrasystoles (6%), ventricular tachycardia (1% to 5%), heart failure (1% to 5%), arrhythmia (4%), supraventricular tachycardia (4%), bradycardia (1% to 2%), thrombosis (1% to 2%), bundle branch block (1% to 2%), cardiac arrest (1% to 2%), heart block (1% to 2%), hemorrhage (1% to 2%), myocardial ischemia (1% to 2%), pericardial effusion (1% to 2%), ventricular fibrillation (1% to 2%), shock (<1% to 2%)

Central nervous system: Agitation (1% to 2%), anxiety (1% to 2%), dizziness (1% to 2%), seizure (1% to 2%)

Endocrine & metabolic: Creatinine phosphokinase increase (2%), acidosis (1% to 2%), hyperglycemia (1% to 2%), hypervolemia (1% to 2%), hypokalemia

Gastrointestinal: Diarrhea (3%), dyspepsia (1% to 2%), gastrointestinal hemorrhage (1% to 2%)

Hematologic: Disseminated intravascular coagulation (DIC), leukocytosis (1% to 2%), prothrombin decreased (1% to 2%), thrombocytopenia (1% to 2%)

Hepatic: Jaundice (1% to 2%), hepatic failure (1% to 2%)

Neuromuscular & skeletal: Arthralgia (1% to 2%)

Renal: Serum creatinine increase of >0.5 mg/dL above baseline (high dose: 9%), oliguria (1% to 2%), tubular necrosis (1% to 2%), kidney failure (1%)

Respiratory: Hypoxia (2%), pulmonary hypertension (1% to 2%), pneumonia (1% to 2%), apnea (1% to 2%), cough increased (1% to 2%)

Miscellaneous: Sepsis (1% to 2%), multisystem organ failure (1% to 2%)

<1%: Anaphylactic reaction/hypersensitivity (no prior exposure: <0.1%; re-exposure within 6 months 5%; re-exposure >6 months <1%)

Postmarketing and/or case reports: Hemoperitoneum, skin discoloration

Drug Interactions

ACE Inhibitors: Aprotinin may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thrombolytic Agents: Aprotinin may diminish the therapeutic effect of Thrombolytic Agents. *Risk D: Consider therapy modification*

Test InteractionsAprotinin significantly increases aPTT and celite Activated Clotting Time (ACT) which may not reflect the actual degree of anticoagulation by heparin. Kaolin-based ACTs are not affected by aprotinin to the same degree as celite ACTs.

Monitoring ParametersBleeding times, prothrombin time, activated clotting time, platelet count, red blood cell counts, hematocrit, hemoglobin and fibrinogen degradation products; for toxicity also include renal function tests and blood pressure

Because aPTT and ACT are difficult to interpret with aprotinin use, the manufacturer recommends two different ways to administer heparin:

1). Fixed heparin dosing where a standard loading dose of heparin plus the quantity of heparin added to the prime volume of the CPB circuit should total at least 350 units/kg. Additional heparin should be administered based on patient's weight and duration of CPB.

2). Heparin dosing based upon a protamine titration method. A heparin dose response, assessed by protamine titration, should be performed prior to administration of aprotinin to determine the heparin loading dose.

Reference RangeAntiplasmin effects occur when plasma aprotinin concentrations are 125 KIU/mL and antikallikrein effects occur when plasma levels are 250-500 KIU/mL; it remains unknown if these plasma concentrations are required for clinical benefits to occur during cardiopulmonary bypass; **Note:** KIU = Kallikrein inhibitor unit

While institutional protocols may vary, a minimal celite ACT of 750 seconds or kaolin-ACT of 480 seconds is recommended in the presence of aprotinin. Consult the manufacturer’s information on specific ACT test interpretation in the presence of aprotinin.

Nursing: Physical Assessment/Monitoring**Monitor infusion site carefully.** Systemic hemodynamic monitoring is generally in effect when patients receive this drug. Continuous blood pressure monitoring is required. Sudden drops in blood pressure may occur. Observe for adequate fluid balance and adequate respiratory function.

Monitoring: Lab TestsBleeding times, prothrombin time, activated clotting time, platelet count, red blood cell counts, hematocrit, hemoglobin, and fibrinogen degradation products; for toxicity also include renal function.

Patient EducationYou will be unaware of the effects of this drug, however, you will be closely monitored at all times. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Trasylol®: 1.4 mg/mL [10,000 KIU/mL] (100 mL, 200 mL) [bovine derived]

Generic AvailableNo

ManufacturerBayer Corp (Biological and Pharmaceutical Division)

Mechanism of ActionBleeding from CABG surgery is thought to result from a systemic inflammatory response induced by the procedure. Contact of blood cells with the cardiopulmonary bypass (CPB) equipment leads to deregulated activation of the coagulation and fibrinolysis systems, with concurrent upregulation of proinflammatory cytokines. Aprotinin is a broad spectrum serine protease inhibitor that attenuates the coagulation, fibrinolytic and inflammatory pathways by interfering with the chemical mediators (thrombin, plasmin, kallikrein). Additionally, it protects platelet-expressed glycoproteins from mechanical shear forces. This preserves normal hemostatic activity through protease receptor-independent mechanisms (eg, via ADP, IIb/IIIa), while blocking CPB-induced thrombin-mediated aggregation.

Pharmacodynamics/Kinetics

Distribution: Extracellular space; renal phagolysosomes

Metabolism: Aprotinin is slowly degraded by lysosomal enzymes.

Half-life elimination: 2.5 hours (plasma); terminal: 10 hours

Excretion: Urine (25% to 40%; <10% as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause confusion

Mental Health: Effects on Psychiatric TreatmentMay cause renal dysfunction; use caution with lithium and gabapentin; may rarely cause seizures; use caution with clozapine

Anesthesia and Critical Care Concerns/Other ConsiderationsBayer Pharmaceuticals Inc is suspending the marketing of aprotinin (Trasylol®) in the U.S. and Canada at the request of both the U.S. Food and Drug Administration (FDA) and Health Canada. Preliminary data from the now suspended, *Blood Conservation Using Antifibrinolytics: A Randomized Trial in a Cardiac Surgery Population (BART)* study in Canada, suggests an increased risk of death associated with aprotinin use when compared with other antifibrinolytic agents. In the study, hemorrhage-related deaths were observed more often in the aprotinin study population.

Aprotinin was associated with an increased risk of long-term mortality (5 years of evaluation after CABG surgery) following use during surgery (Mangano, 2007).

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International Brand NamesAntagosan (DE, HR); Antikrein (JP); Aprotimbin (HR, KP); Contrycal (EE); Contrykal (DE); Fase (IT); Gordox (HU); Haemoprot (IN); Hetailin (CL); Iniprol (BE, FR, IT, LU); Onquinin (JP); Pantinol (AT); Protosol (IL); Repulson (JP); Rivilina (AR, PE); Traskolan (PL); Trasylol (PL); Trasylol (AE, AT, AU, BE, BG, BH, BR, CH, CN, CO, CY, CZ, DE, DK, EG, FI, FR, GB, GR, HK, HN, HR, ID, IE, IL, IQ, IR, IT, JO, KW, LB, LU, LY, MX, MY, NL, NO, OM, PE, QA, SA, SE, SY, TW, UY, VE, YE, ZA); Trazinine (JP)

Arformoterol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ar for MOE ter ol)

U.S. Brand NamesBrovana®

Pharmacologic Category Beta$_2$ Agonist

Use: Labeled IndicationsLong-term maintenance treatment of bronchoconstriction in chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema

Dosing: Adults **COPD:** Nebulization: 15 mcg twice daily; maximum: 30 mcg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment required.

Dosing: Hepatic ImpairmentNo dosage adjustment required, but use caution; systemic drug exposure prolonged (1.3- to 2.4-fold).

Administration: InhalationNebulization: Remove each vial from individually sealed foil pouch immediately before use. Use with standard jet nebulizer connected to an air compressor, administer with mouthpiece or face mask. Administer vial undiluted and do not mix with other medications in nebulizer.

StoragePrior to dispensing, store in protective foil pouch under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light and excessive heat. After dispensing, unopened foil pouches may be stored at room temperature at 20°C to 25°C (68°F to 77°F) for up to 6 weeks. Only remove vial from foil pouch immediately before use.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to arformoterol, racemic formoterol, or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Asthma-related deaths: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Asthma-related deaths: **[U.S. Boxed Warning]: Long-acting beta$_2$-agonists may increase the risk of asthma-related deaths.** In a large, randomized clinical trial (SMART, 2006), salmeterol was associated with a small, but statistically significant increase in asthma-related deaths (when added to usual asthma therapy); risk may be greater in African-American patients versus Caucasians. Data is not available to determine whether rate of death is increased with long-acting beta$_2$-agonists in COPD setting.

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.

- Hypersensitivity reactions: Immediate hypersensitivity reactions (urticaria, angioedema, rash, bronchospasm) have been reported.

- Serious effects/fatalities: Do not exceed recommended dose; serious adverse events, including fatalities, have been associated with excessive use of inhaled sympathomimetics.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (eg, arrhythmia, hypertension, HF); beta-agonists may cause elevation in blood pressure, heart rate and result in CNS stimulation/excitation. Beta$_2$-agonists may also increase risk of arrhythmias and prolong QT_c interval.

- COPD: Appropriate use: Arformoterol should only be used for long-term maintenance treatment and should not be used as rescue therapy in treatment of acute episodes. It should not be initiated in patients with acutely deteriorating COPD or combined with other long-acting beta$_2$-agonists.

- Diabetes: Use with caution in patients with diabetes mellitus; beta$_2$-agonists may increase serum glucose.

- Hepatic impairment: Use with caution in patients with hepatic impairment; systemic clearance prolonged in hepatic dysfunction.

- Hyperthyroidism: Use with caution in patients with hyperthyroidism; may stimulate thyroid activity.

- Hypokalemia: Use with caution in patients with hypokalemia; beta$_2$-agonists may decrease serum potassium.

- Seizure disorders: Use with caution in patients with seizure disorders; beta$_2$-agonists may result in CNS stimulation/excitation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Patient information: Patients using inhaled, short-acting beta$_2$-agonists should be instructed to discontinue routine use of these medications prior to beginning treatment; short-acting agents should be reserved for symptomatic relief of acute symptoms. Patients must be instructed to seek medical attention in cases where acute symptoms are not relieved or a previous level of response is diminished. The need to increase frequency of use may indicate deterioration of COPD, and treatment must not be delayed.

- Tolerance/Tachyphylaxis: Tolerance to the bronchodilator effect, measured by FEV$_1$, has been observed in studies.

Geriatric ConsiderationsIn clinical trials, no significant difference was seen in the AUC and C$_{max}$ between younger and older subjects. In addition, no significant difference in clinical response was noted.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects, decreased fetal weight and increased fetal loss were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Beta-agonists may interfere with uterine contractility if administered during labor. Use in pregnancy and/or during labor should be limited to situations where benefit outweighs risk to fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

2% to 10%:

Cardiovascular: Chest pain (7%), peripheral edema (3%)

Central nervous system: Pain (8%)

Dermatologic: Rash (4%)

Gastrointestinal: Diarrhea (6%)

Neuromuscular & skeletal: Back pain (6%), leg cramps (4%)

Respiratory: Dyspnea (4%), sinusitis (5%), congestive conditions (2%)

Miscellaneous: Flu-like syndrome (3%)

<2%: Abscess, agitation, allergic reaction, arteriosclerosis, arthralgia, arthritis, atrial flutter, AV block, bone disorder, calcium crystalluria, cystitis, cerebral infarct, CHF, circumoral paresthesia, constipation, dehydration, dry skin, ECG changes, edema, fever, gastritis, glaucoma, glucose tolerance decreased, glycosuria, gout, heart block, hematuria, hyper-/hypoglycemia, hyperlipemia, hypokalemia, hypokinesia, inverted T-wave, kidney calculus, lung carcinoma, melena, MI, neck rigidity, neoplasm, nocturia, oral moniliasis, paradoxical bronchospasm, paralysis, pelvic pain, periodontal abscess, PSA increased, pyuria, QT interval increased, rectal hemorrhage, retroperitoneal hemorrhage, rheumatoid arthritis, skin discoloration, skin hypertrophy, somnolence, supraventricular tachycardia, tendinous contracture, tremor, urinary tract disorder, urine abnormality, viral infection, vision abnormalities, voice alteration

Metabolism/Transport Effects**Substrate** of CY2D6 (minor) and CYP2C19 (minor)

Drug Interactions

Alpha-/Beta-Blockers: May diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Atomoxetine: May enhance the tachycardic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Betahistine: May diminish the therapeutic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Monitoring ParametersFEV$_1$, peak flow, and/or other pulmonary function tests; blood pressure, heart rate; CNS stimulation; serum glucose, serum potassium. Monitor for increased use of short-acting beta$_2$-agonist inhalers; may be marker of a deteriorating COPD condition.

Nursing: Physical Assessment/MonitoringMonitor therapeutic response and adverse reactions at the beginning and periodically throughout therapy. Assess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use and care of nebulizer, side effects, and symptoms to report.

Monitoring: Lab TestsFEV$_1$, peak flow, and/or other pulmonary function tests; serum glucose, serum potassium

Patient EducationThis drug is intended for chronic COPD use, not sudden onset of COPD symptoms. Inform prescriber of all prescription medications, OTC medications, or herbal products you are taking or before stopping this medication. Do not take any new medications without consulting prescriber. Use as directed. Do not use more frequently than ordered. Do not mix with other medications in your nebulizer. If you have diabetes, monitor your blood glucose levels carefully; can cause hyperglycemia. Maintain adequate hydration (2-3 L/day) unless instructed to restrict intake by prescriber. You may experience nervousness, tremor, headache, muscle cramps, trouble sleeping, dizziness, or tiredness. Use caution when driving or engaging in tasks requiring alertness until response to drug is known. Report rapid heart rate, chest pain, or palpitations; swelling of extremities or sudden weight gain of 3-5 pounds/week; back or leg pain; increased shortness of breath; or difficulty breathing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution for nebulization:

Brovana®: 15 mcg/2 mL (30s, 60s)

Generic AvailableNo

ManufacturerSepracor, Inc

Mechanism of ActionArformoterol, the (R,R)-enantiomer of the racemic formoterol, is a long-acting beta$_2$-agonist that relaxes bronchial smooth muscle by selective action on beta$_2$-receptors with little effect on cardiovascular system.

Pharmacodynamics/Kinetics

Onset of action: 7-20 minutes

Peak effect: 1-3 hours

Absorption: A portion of inhaled dose is absorbed into systemic circulation

Protein binding: 52% to 65%

Metabolism: Hepatic via direct glucuronidation and secondarily via O-demethylation; CYP2D6 and CYP2C19 (to a lesser extent) involved in O-demethylation

Half-life elimination: 26 hours

Time to peak: 0.5-3 hours

Related Information

- Bronchodilators
- Inhalant Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness, restlessness, or anxiety with excessive use

Mental Health: Effects on Psychiatric TreatmentConcurrent use with atomoxetine may enhance tachycardia

Index Terms(R,R)-Formoterol L-Tartrate; Arformoterol Tartrate

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Argatroban

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Argatroban may be confused with Aggrastat®, Orgaran®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ar GA troh ban)

Pharmacologic CategoryAnticoagulant, Thrombin Inhibitor

Use: Labeled IndicationsProphylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT); adjunct to percutaneous coronary intervention (PCI) in patients who have or are at risk of thrombosis associated with HIT

Use: Unlabeled/InvestigationalTo maintain extracorporeal circuit patency (prefilter administration) of continuous renal replacement therapy (CRRT) in critically-ill patients with HIT

Dosing: Adults

Prophylaxis of thrombosis (heparin-induced thrombocytopenia): I.V.:

Initial dose: 2 mcg/kg/minute

Maintenance dose: Patient may not be at steady-state but measure aPTT after 2 hours; adjust dose until the steady-state aPTT is 1.5-3.0 times the initial baseline value, not exceeding 100 seconds; dosage should not exceed 10 mcg/kg/minute

Note: Critically-ill patients with normal hepatic function became excessively anticoagulated with FDA-approved or lower starting doses of argatroban. Doses between 0.15-1.3 mcg/kg/minute were required to maintain aPTTs in the target range (Reichert, 2003). In a prospective observational study of critically-ill patients with MODS and suspected or proven HIT, an initial infusion dose of 0.2 mcg/kg/minute was found to be sufficient and safe in this population (Beiderlinden, 2007). Consider reducing starting dose to 0.2 mcg/kg/minute in critically-ill patients with multiple organ dysfunction (MODS) defined as a minimum number of two organ failures. Another report of a cardiac patient with anasarca secondary to acute renal failure had a reduction in argatroban clearance similar to patients with hepatic dysfunction. Reduced clearance may have been due to reduced liver perfusion (de Denus, 2003). The American College of Chest Physicians has recommended an initial infusion rate of 0.5-1.2 mcg/kg/minute for patients with heart failure, MODS, severe anasarca, or postcardiac surgery (Hirsch, 2008).

Conversion to oral anticoagulant: Because there may be a combined effect on the INR when argatroban is combined with warfarin, loading doses of warfarin should not be used. Warfarin therapy should be started at the expected daily dose.

Patients receiving ≤2 mcg/kg/minute of argatroban: Argatroban therapy can be stopped when the combined INR on warfarin and argatroban is >4; repeat INR measurement in 4-6 hours; if INR is below therapeutic level, argatroban therapy may be restarted. Repeat procedure daily until desired INR on warfarin alone is obtained.

Patients receiving >2 mcg/kg/minute of argatroban: In order to predict the INR on warfarin alone, reduce dose of argatroban to 2 mcg/kg/minute; measure INR for argatroban and warfarin 4-6 hours after dose reduction; argatroban therapy can be stopped when the combined INR on warfarin and argatroban is >4. Repeat INR measurement in 4-6 hours; if INR is below therapeutic level, argatroban therapy may be restarted. Repeat procedure daily until desired INR on warfarin alone is obtained.

Note: The American College of Chest Physicians recommends monitoring chromogenic factor X assay when transitioning from argatroban to warfarin (Hirsh, 2008). Factor X levels <45% have been associated with INR values >2 after the effects of argatroban have been eliminated (Arpino, 2005).

Prefilter administration for continuous renal replacement therapy (CRRT) in critically-ill patients with HIT (unlabeled use; Link, 2008): 0.1 – 1.5 mcg/kg/min Note: Loading dose of 100 mcg/kg was administered during clinical trial; however, this may be unnecessary.

Percutaneous coronary intervention (PCI): I.V.:

Initial: Begin infusion of 25 mcg/kg/minute and administer bolus dose of 350 mcg/kg (over 3-5 minutes). ACT should be checked 5-10 minutes after bolus infusion; proceed with procedure if ACT >300 seconds. Following initial bolus:

ACT <300 seconds: Give an additional 150 mcg/kg bolus, and increase infusion rate to 30 mcg/kg/minute (recheck ACT in 5-10 minutes)

ACT >450 seconds: Decrease infusion rate to 15 mcg/kg/minute (recheck ACT in 5-10 minutes)

Once a therapeutic ACT (300-450 seconds) is achieved, infusion should be continued at this dose for the duration of the procedure.

If dissection, impending abrupt closure, thrombus formation during PCI, or inability to achieve ACT >300 seconds: An additional bolus of 150 mcg/kg, followed by an increase in infusion rate to 40 mcg/kg/minute may be administered.

Note: Post-PCI anticoagulation, if required, may be achieved by continuing infusion at a reduced dose of 2-10 mcg/kg/minute, with close monitoring of aPTT.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Heparin-induced thrombocytopenia** (dosing based on limited data from critically-ill patients): I.V.:

Initial dose: 0.75 mcg/kg/minute

Maintenance dose: Patient may not be at steady-state but measure aPTT after 2 hours; adjust dose until the steady-state aPTT is 1.5-3.0 times the initial baseline value, not exceeding 100 seconds; dosage may be adjusted in increments of 0.1-0.25 mcg/kg/minute. **Note:** Frequent dosage adjustments may be required to maintain desired anticoagulant activity.

Dosing: Renal ImpairmentRemoval during hemodialysis and continuous venovenous hemofiltration is clinically insignificant. No dosage adjustment required.

Dosing: Hepatic ImpairmentDecreased clearance and increased elimination half-life are seen with hepatic impairment; dose should be reduced.

Children: Initial dose: 0.2 mcg/kg/minute; adjust dose in increments of ≤0.05 mcg/kg/minute

Adults: Initial dose for moderate hepatic impairment is 0.5 mcg/kg/minute. **Note:** During PCI, avoid use in patients with elevations of ALT/AST (>3 times ULN); the use of argatroban in these patients has not been evaluated.

Administration: I.V.Solution **must be diluted to 1 mg/mL** prior to administration.

StoragePrior to use, store at 15°C to 30°C (59°F to 86°F). Protect from light. The prepared solution is stable for 24 hours at 15°C to 30°C (59°F to 86°F) in ambient indoor light. Do not expose to direct sunlight. Prepared solutions that are protected from light and kept at controlled room temperature of 20°C to 25°C (68°F to 77°F) or under refrigeration at 2°C to 8°C (36°F to 46°F) are stable for up to 96 hours.

ReconstitutionMay be mixed with 0.9% sodium chloride injection, 5% dextrose injection, or lactated Ringer's injection. Do not mix with other medications. To prepare solution for I.V. administration, dilute each 250 mg vial with 250 mL of diluent. Mix by repeated inversion for one minute. Once mixed, final concentration should be 1 mg/mL. A slight but brief haziness may occur prior to mixing.

CompatibilityStable in 0.9% NS, D_5W, LR.

Y-site administration: Incompatible with other medications.

Compatibility when admixed: Incompatible with other medications.

ContraindicationsHypersensitivity to argatroban or any component of the formulation; overt major bleeding

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: The most common complication is bleeding. Certain patients are at increased risk of bleeding; risk factors include bacterial endocarditis; congenital or acquired bleeding disorders; recent puncture of large vessels or organ biopsy; recent CVA, stroke, intracerebral surgery, or other neuraxial procedure; severe uncontrolled hypertension; renal impairment; recent major surgery; recent major bleeding (intracranial, GI, intraocular, or pulmonary). Monitor for signs and symptoms of bleeding.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; may require >4 hours to achieve full reversal of argatroban's anticoagulant effect following treatment. Avoid use during PCI in patients with elevations of ALT/AST (>3 times ULN); use in these patients has not been evaluated.

Concurrent drug therapy issues:

- Parenteral anticoagulants: Discontinue all parenteral anticoagulants prior to starting therapy; allow reversal of heparin's effects before initiation.

- Thrombolytic agents: Safety and efficacy for use with thrombolytic agents has not been established.

- Warfarin: Argatroban prolongs the PT/INR. Concomitant use with warfarin will cause increased prolongation of the PT and INR greater than that of warfarin alone. If warfarin is intiated concurrently with argatroban, initial PT/INR goals while on argatroban may require modification; alternative guidelines for monitoring therapy should be followed.

Special populations:

- Critically-ill patients: Use with caution in critically-ill patients; reduced clearance may require dosage reduction.

- Pediatrics: Limited pharmacokinetic and dosing information is available following use in critically-ill children with heparin-induced thrombocytopenia.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Argatroban should be used in pregnant women only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if argatroban is excreted in human milk. Because of the serious potential of adverse effects to the nursing infant, a decision to discontinue nursing or discontinue argatroban should be considered.

Adverse ReactionsAs with all anticoagulants, bleeding is the major adverse effect of argatroban. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the intensity of anticoagulation and patient susceptibility.

>10%:

Cardiovascular: Chest pain (PCI related: <1% to 15%), hypotension (7% to 11%)

Gastrointestinal: Gastrointestinal bleed (major: <1% to 3%; minor: 3% to 14%)

Genitourinary: Genitourinary bleed and hematuria (major: <1%; minor: 2% to 12%)

1% to 10%:

Cardiovascular: Vasodilation (1% to 10%), cardiac arrest (6%), ventricular tachycardia (5%), bradycardia (5%), myocardial infarction (PCI: 4%), atrial fibrillation (3%), angina (2%), CABG-related bleeding (minor, 2%), myocardial ischemia (2%), cerebrovascular disorder (<1% to 2%), thrombosis (<1% to 2%)

Central nervous system: Fever (<1% to 7%), headache (5%), pain (5%), intracranial bleeding (1% to 4%)

Dermatologic: Skin reactions (bullous eruption, rash; 1% to <10%)

Gastrointestinal: Nausea (5% to 7%), diarrhea (6%), vomiting (4% to 6%), abdominal pain (3% to 4%)

Genitourinary: Urinary tract infection (5%)

Hematologic: Hemoglobin decreased (<2 g/dL), hematocrit decreased (minor: 2% to 10%; major: <1%)

Local: Bleeding at injection or access site (minor: 2% to 5%)

Neuromuscular & skeletal: Back pain (PCI related: 8%)

Renal: Abnormal renal function (3%)

Respiratory: Dyspnea (8% to 10%), cough (3% to 10%), hemoptysis (minor: <1% to 3%), pneumonia (3%)

Miscellaneous: Sepsis (6%), infection (4%)

<1% (Limited to important or life-threatening): Allergic reactions, GERD, limb and below-the-knee stump bleed, multisystem hemorrhage and DIC, pulmonary edema, retroperitoneal bleeding

Metabolism/Transport Effects **Substrate** of CYP3A4 (minor)

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Test Interactions PT/INR levels may become elevated in the absence of warfarin. If warfarin is started, initial PT/INR goals while on argatroban may require modification.

Monitoring Parameters Obtain baseline aPTT prior to start of therapy. Patient may not be at steady-state but check aPTT 2 hours after start of therapy to adjust dose, keeping the steady-state aPTT 1.5-3 times the initial baseline value (not exceeding 100 seconds). Monitor hemoglobin, hematocrit, signs and symptoms of bleeding.

PCI: Monitor ACT before dosing, 5-10 minutes after bolus dosing, and after any change in infusion rate and at the end of the procedure. Additional ACT assessments should be made every 20-30 minutes during extended PCI procedures.

Nursing: Physical Assessment/Monitoring Assess patient for use cautions. Assess potential for interactions with other pharmacological agents patient may be taking (especially drugs which affect platelet function or coagulation). Assess for therapeutic effectiveness according to purpose for use and adverse reactions (abnormal bleeding, GI pain, epistaxis, hematuria, irritation at infusion site) frequently during therapy. Observe bleeding precautions and teach patient interventions to reduce side effects and adverse reactions to report.

Monitoring: Lab Tests Hemoglobin, hematocrit; baseline aPTT prior to start of therapy. Patient may not be at steady-state but check aPTT 2 hours after start of therapy to adjust dose, keeping the steady-state aPTT 1.5-3 times the initial baseline value (not exceeding 100 seconds).

Patient Education This medication can only be administered by intravenous infusion and you will be monitored with blood tests during therapy. You may have a tendency to bleed easily; use electric razor, brush teeth with soft brush, floss with waxed floss, avoid all scissors or sharp instruments (knives, needles, etc), and avoid injury or bruising. Report stomach cramping or pain; dark or bloody stools; blood in urine; acute headache or confusion; respiratory difficulty; nosebleed; or bleeding from gums. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 100 mg/mL (2.5 mL) [contains dehydrated alcohol 1000 mg/mL]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Argatroban)

100 mg/mL (2.5): $1254.41

Mechanism of ActionA direct, highly-selective thrombin inhibitor. Reversibly binds to the active thrombin site of free and clot-associated thrombin. Inhibits fibrin formation; activation of coagulation factors V, VIII, and XIII; activation of protein C; and platelet aggregation.

Pharmacodynamics/Kinetics

Onset of action: Immediate

Distribution: 174 mL/kg

Protein binding: Albumin: 20%; α_1-acid glycoprotein: 35%

Metabolism: Hepatic via hydroxylation and aromatization. Metabolism via CYP3A4/5 to four known metabolites plays a minor role. Unchanged argatroban is the major plasma component. Plasma concentration of metabolite M1 is 0% to 20% of the parent drug and is three- to fivefold weaker.

Half-life elimination: 39-51 minutes; Hepatic impairment: ≤181 minutes

Time to peak: Steady-state: 1-3 hours

Excretion: Feces (65%); urine (22%); low quantities of metabolites M2-4 in urine

Clearance is decreased in critically-ill pediatric patients

Pharmacotherapy PearlsPlatelet counts recovered by day 3 in 53% of patients with heparin-induced thrombocytopenia and in 58% of patients with heparin-induced thrombocytopenia with thrombosis syndrome.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: As with all anticoagulants, bleeding is a potential adverse effect of argatroban during dental surgery; risk is dependent on multiple variables, including the intensity of anticoagulation and patient susceptibility. Medical consult is suggested. It is unlikely that ambulatory patients presenting for dental treatment will be taking intravenous anticoagulant therapy.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsArgatroban achieves steady state rapidly (4-5 hours after initiating therapy) when administered I.V., with a predictable dose-response effect. PTTs generally remain stable at a given dose. Argatroban does not induce formation of antibodies that can alter its clearance, as is seen with lepirudin. Patients with a reduced cardiac output and/or fluid overload may require a reduced dose. Reduced clearance may be attributed to hepatic congestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsArgatroban achieves steady state rapidly (4-5 hours after initiating therapy) when administered I.V., with a predictable dose-response effect. PTTs generally remain stable at a given dose. Argatroban does not induce formation of antibodies that can alter its clearance, as is seen with lepirudin. Reduce dose in critically-ill patients, particularly those who may have multiple organ dysfunction (especially hepatic dysfunction).

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International Brand NamesArgatra (DE); Novastan (CL, DK, JP, KP, NO, SE)

Arginine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(AR ji neen)

U.S. Brand NamesR-Gene®

Pharmacologic CategoryDiagnostic Agent

Use: Labeled IndicationsPituitary function test (growth hormone)

Use: Unlabeled/InvestigationalManagement of severe, uncompensated, metabolic alkalosis (pH ≥7.55) **after** optimizing therapy with sodium and potassium supplements

Dosing: AdultsPituitary function test: I.V.: 30 g (300 mL) administered over 30 minutes

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricPituitary function test: I.V.: 500 mg/kg/dose administered over 30 minutes

Dietary ConsiderationsContains chloride 0.475 mEq/mL.

StorageStore at room temperature of 25°C (77°F). Do not use if frozen.

ContraindicationsHypersensitivity to arginine or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Electrolyte imbalance: Arginine infusion has been associated with acute electrolyte disturbances, including hyperkalemia, hyponatremia (following overdose), hypophosphatemia, and acidosis; risk is increased in patients with hepatic impairment, renal dysfunction, or diabetes mellitus.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; use may lead to life-threatening hyperkalemia.
- Electrolyte imbalance: Use with caution in patients with electrolyte imbalance.
- Hepatic impairment: Use with caution in patients with hepatic impairment; use may lead to life-threatening hyperkalemia.
- Myocardial infarction: Avoid use in myocardial infarction.
- Renal impairment: Use with caution in patients with renal impairment; use may lead to life-threatening hyperkalemia.

Special populations:

- Pediatrics: Use with caution in children.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; however, the manufacturer does not recommend use of arginine during pregnancy.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsAmino acids are excreted in breast milk, the amount following arginine administration is not known.

Adverse Reactions

1% to 10%:

Cardiovascular: Rapid I.V. infusion may produce flushing

Central nervous system: Headache

Gastrointestinal: Nausea, vomiting

Local: Venous irritation

Neuromuscular & skeletal: Numbness

<1%: Allergic reaction

Postmarketing and/or case reports: Hyperkalemia

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersMonitor acid-base status (arterial or capillary blood gases), serum electrolytes (sodium, potassium, chloride, HCO_3^-), BUN, glucose

Monitoring: Lab TestsMonitor acid-base status (arterial or capillary blood gases), serum electrolytes (sodium, potassium, chloride, HCO_3^{--}), BUN, glucose

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride:

R-Gene®: 10% (300 mL) [100 mg/mL = 950 mOsm/L; contains chloride 0.475 mEq/mL]

Generic AvailableNo

Mechanism of ActionStimulates pituitary release of growth hormone and prolactin through origins in the hypothalamus; patients with impaired pituitary function have lower or no increase in plasma concentrations of growth hormone after administration of arginine. Arginine hydrochloride has been used for severe metabolic alkalosis due to its high chloride content.

Arginine hydrochloride has been used investigationally to treat metabolic alkalosis. Arginine contains 475 mEq of hydrogen ions and 475 mEq of chloride ions/L. Arginine is metabolized by the liver to produce hydrogen ions. It may be used in patients with relative hepatic insufficiency because arginine combines with ammonia in the body to produce urea.

Pharmacodynamics/Kinetics

Absorption: Oral: Well absorbed

Time to peak, serum: Oral: ~2 hours; I.V.: 20-30 minutes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsRecently, the use of **L-arginine** to improve endothelial function has been the focus of many research protocols. L-arginine acts as a substrate for nitric oxide production, resulting in vasodilation effects.

A recent single-center, randomized, double-blind study (VINTAGE MI) determined whether the addition of L-arginine to standard post-MI therapy improved ejection fraction over 6 months (Schulman, 2006). One hundred and fifty-three patients were enrolled after STEMI. Patients were randomized to oral L-arginine (titrated to 3 g three times/day for 6 months) or placebo. Baseline characteristics, vascular stiffness measurements, and left ventricular function were similar in both groups at time of enrollment and 6 months after treatment. Mortality was significantly higher in the L-arginine group. The authors concluded that arginine should not be recommended following acute MI.

Index TermsArginine Hydrochloride

References

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International Brand NamesArginina (PL); Rocmaline (FR)

Aripiprazole

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

Gill SS, Bronskill SE, Normand SL, et al, “Antipsychotic Drug Use and Mortality in Older Adults With Dementia,” *Ann Intern Med*, 2007, 146(11):775-86.[PubMed 17548409]

Schneeweiss S, Setoguchi S, Brookhart A, et al, “Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients,” *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Medication Safety Issues

Sound-alike/look-alike issues:

Aripiprazole may be confused with proton pump inhibitors (eg, rabeprazole)

Pronunciation(ay ri PIP ray zole)

U.S. Brand NamesAbilify®; Abilify® Discmelt™

Pharmacologic CategoryAntipsychotic Agent, Atypical

Use: Labeled Indications

Oral: Acute and maintenance treatment of schizophrenia; stabilization, maintenance, and adjunctive therapy (to lithium or valproate) of bipolar disorder (with acute manic or mixed episodes); adjunctive treatment of major depressive disorder

Injection: Agitation associated with schizophrenia or bipolar mania

Use: Unlabeled/InvestigationalDepression with psychotic features; aggression (children); conduct disorder (children); Tourette syndrome (children); psychosis/agitation related to Alzheimer's dementia

Dosing: Adults**Note:** Oral solution may be substituted for the oral tablet on a mg-per-mg basis, up to 25 mg. Patients receiving 30 mg tablets should be given 25 mg oral solution. Orally disintegrating tablets (Abilify® Discmelt™) are bioequivalent to the immediate release tablets

(Abilify®).

Acute agitation (schizophrenia/bipolar mania): I.M.: 9.75 mg as a single dose (range: 5.25-15 mg); repeated doses may be given at ≥2-hour intervals to a maximum of 30 mg/day. **Note:** If ongoing therapy with aripiprazole is necessary, transition to oral therapy as soon as possible.

Bipolar disorder (acute manic or mixed episodes):

Stabilization: Oral: Initial: 15 mg once daily as monotherapy or adjunctive to lithium or valproic acid. May increase to 30 mg once daily if clinically indicated; safety of doses >30 mg/day has not been evaluated

Maintenance: Continue stabilization dose for up to 6 weeks; efficacy of continued treatment >6 weeks has not been established.

Depression (adjunctive with antidepressants): Oral: Initial: 2-5 mg/day (range: 2-15 mg/day); dose adjustments of up to 5 mg/day may be made in intervals of ≥1 week. **Note:** Dosing based on patients already receiving antidepressant therapy.

Schizophrenia: Oral: 10-15 mg once daily; may be increased to a maximum of 30 mg once daily (efficacy at dosages above 10-15 mg has not been shown to be increased). Dosage titration should not be more frequent than every 2 weeks.

Dosage adjustment with concurrent CYP450 inducer or inhibitor therapy: Oral:

CYP3A4 inducers (eg, carbamazepine): Aripiprazole dose should be doubled (20-30 mg/day); dose should be subsequently reduced (10-15 mg/day) if concurrent inducer agent discontinued.

CYP3A4 inhibitors (eg, ketoconazole): Aripiprazole dose should be reduced to $^{1}/_{2}$ of the usual dose, and proportionally increased upon discontinuation of the inhibitor agent.

CYP2D6 inhibitors (eg, fluoxetine, paroxetine): Aripiprazole dose should be reduced to $^{1}/_{2}$ of the usual dose, and proportionally increased upon discontinuation of the inhibitor agent.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Aggression, conduct disorder, Tourette syndrome (unlabeled uses): Oral: 5-20 mg/day

Bipolar I disorder (acute manic or mixed episodes): Children ≥10 years: Oral: Initial: 2 mg daily for 2 days, followed by 5 mg daily for 2 days with a further increase to target dose of 10 mg daily as monotherapy or adjunctive therapy; subsequent dose increases may be made in 5 mg increments, up to a maximum of 30 mg/day.

Schizophrenia: Adolescents ≥13 years: Oral: Initial: 2 mg daily for 2 days, followed by 5 mg daily for 2 days with a further increase to target dose of 10 mg daily; subsequent dose increases may be made in 5 mg increments up to a maximum of 30 mg/day (30 mg/day not shown to be more efficacious than 10 mg/day).

Dosing: Renal ImpairmentNo dosage adjustment required.
Dosing: Hepatic ImpairmentNo dosage adjustment required.
Administration: I.M.For I.M. use only; do not administer SubQ or I.V.; inject slowly into deep muscle mass
Administration: OralMay be administered with or without food. Tablet and oral solution may be interchanged on a mg-per-mg basis, up to 25 mg. Doses using 30 mg tablets should be exchanged for 25 mg oral solution. Orally disintegrating tablets (Abilify® Discmelt™) are bioequivalent to the immediate release tablets (Abilify®).

Orally-disintegrating tablet: Remove from foil blister by peeling back (do not push tablet through the foil). Place tablet in mouth immediately upon removal. Tablet dissolves rapidly in saliva and may be swallowed without liquid. If needed, can be taken with liquid. Do not split tablet.

Dietary ConsiderationsMay be taken with or without food. Oral solution contains sucrose 400 mg/mL and fructose 200 mg/mL. Orally disintegrating tablet contains phenylalanine; avoid use in phenylketonuria.
Storage

Injection solution: Store at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.

Oral solution: Store at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Use within 6 months after opening.

Tablet: Store at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.
ContraindicationsHypersensitivity to aripiprazole or any component of the formulation
Warnings/Precautions

Boxed warnings:

- Dementia: See “Disease-related concerns” below.
- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Aripiprazole is not FDA approved for adjunctive treatment of depression in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy. Patients should be screened for bipolar disorder prior to initiation of treatment of major depression.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

Concerns related to adverse reactions:

- Altered cardiac conduction: May alter cardiac conduction; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (eg, Alzheimer's disease).

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is generally much lower relative to typical/conventional antipsychotics; frequencies reported are similar to placebo). Risk of dystonia (and probably other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Hyperglycemia: Atypical antipsychotics have been associated with development of hyperglycemia; in some cases, may be extreme and associated with ketoacidosis, hyperosmolar coma, or death. Use with caution in patients with diabetes or other disorders of glucose regulation; monitor for worsening of glucose control. Reports of hyperglycemia with aripiprazole therapy have been few and specific risk associated with this agent is not known.

- Neuroleptic malignant syndrome (NMS): Use may be associated with neuroleptic malignant syndrome (NMS); monitor for mental status changes, fever, muscle rigidity and/or autonomic instability.

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

- Weight gain: Significant weight gain has been observed with antipsychotic therapy; incidence varies with product. Monitor waist circumference and BMI.

Disease-related concerns:

- Cardiac disease: Use with caution in patients with cardiac disease, cerebrovascular disease, or conditions which predispose to hypotension.

- Dementia: **[U.S. Boxed Warning]: Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo.** An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Aripiprazole is not approved for this indication.

- Parkinson's disease: Use with caution in patients with Parkinson's disease.

- Seizures: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold. Elderly patients may be at increased risk of seizures due to an increased prevalence of predisposing factors.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <10 years of age.

Dosage form specific issues:

- Phenylalanine: Abilify® Discmelt™ contains phenylalanine.

Geriatric ConsiderationsElderly patients have an increased risk of adverse response to side effects or adverse reactions to antipsychotics. Aripiprazole has been studied in elderly patients with psychosis associated with Alzheimer's disease. The package insert does not provide the outcomes of this study other than somnolence was more frequent with aripiprazole (8%) than placebo (1%). Clinical data have shown an increased incidence of serious cerebrovascular events in the elderly, some fatal. In light of significant risks and adverse effects in the elderly population (compared with limited data demonstrating efficacy in the treatment of dementia-related psychosis, aggression, and agitation), an extensive risk:benefit analysis should be performed prior to use. Aripiprazole's delayed onset of action and long half-life may limit its role in treating older persons with psychosis. Not approved for the treatment of patients with dementia-related psychosis.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAripiprazole demonstrated developmental toxicity and teratogenic effects in animal models. There are no adequate and well-controlled trials in pregnant women. Should be used in pregnancy only when potential benefit to mother outweighs possible risk to the fetus. Healthcare providers are encouraged to enroll women 18-45 years of age exposed to aripiprazole during pregnancy in the Atypical Antipsychotics Pregnancy Registry (1-866-961-2388).

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsUnless otherwise noted, frequency of adverse reactions is shown as reported for adult patients receiving oral administration. Spectrum and incidence of adverse effects similar in children; exceptions noted when incidence much higher in children.

>10%:

Central nervous system: Headache (27%; children 16%; injection 12%), agitation (19%), insomnia (18%), anxiety (17%), akathisia (10% to 13%; injection 2%), lightheadedness (11%)

Gastrointestinal: Weight gain (8% to 30%; highest frequency in patients with BMI <23; children 3%), nausea (15%; injection 9%), dyspepsia (9% to 15%; injection 1%), constipation (11% to 13%), vomiting (11%; injection 3%)

1% to 10%:

Cardiovascular: Orthostatic hypotension (1% to 5%), tachycardia (injection 2%), chest pain, hypertension, peripheral edema

Central nervous system: Dizziness (10%; children 5%; injection 8%), sedation (dose-related 5% to 8%; children 20% to 23%; injection: 7%), EPS (5% to 6%; children 19% to 20%), restlessness (5% to 6%), fatigue (6%; children 7% to 11%), pain (3%), dystonia (children 2%), irritability, suicidal ideation

Dermatologic: Rash

Gastrointestinal: Salivation increased (children 4% to 8%), xerostomia (5%; children 2%; injection 1%), toothache (4%), abdominal discomfort (3%), diarrhea (children 3%), weight loss

Neuromuscular & skeletal: Tremor (5% to 9%), weakness (8%), arthralgia (5%; children 2%), extremity pain (4%), stiffness (4%), myalgia (2% to 4%), spasm (2%)

Ocular: Blurred vision (3%; children 5% to 8%)

Respiratory: Pharyngolaryngeal pain (3%), cough (3%), nasal congestion

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Aggression, agitation, agranulocytosis, alopecia, akinesia, amenorrhea, anaphylactic reaction, anger, angina pectoris, angioedema, anorexia, anorgasmia, asphyxia, aspiration pneumonia, atrial fibrillation, atrial flutter, atrioventricular block, bilirubin increased, bradycardia, bradykinesia, breast pain, bundle branch block, cardiopulmonary failure, cardiorespiratory arrest, catatonia, cerebrovascular accident, cholelithiasis, choreoathetosis, cogwheel rigidity, complete atrioventricular block, creatine phosphokinase increased, creatinine increased, deep vein thrombosis, delirium, diplopia, diabetes mellitus, DKA, dysphagia, dyspnea, edema (facial), erectile dysfunction, esophagitis, extrasystoles, galactorrhea, gastrointestinal hemorrhage, GGT increased, glycosylated hemoglobin increased, gynecomastia, heat stroke, hepatic enzyme increased, hepatitis, homicidal ideation, hostility, hyper-/hypoglycemia, hyperlipidemia, hypersensitivity, hyper-/hypotonia, hypotension, hypokalemia, hypokinesia, hyponatremia, hypothermia cholecystitis, idiopathic thrombocytopenic purpura, intentional self injury, jaundice, lactate dehydrogenase increased, leukopenia, libido changes, memory impairment, menstrual irregularities, MI, muscle rigidity, muscle spasms, myocardial ischemia, myoclonus, neutropenia, nocturia, oropharyngeal spasm, palpitation, pancreatitis, parkinsonism, phlebitis, photophobia, polydypsia, polyuria, priapism, prolactin increased, pruritus, psychomotor agitation, pulmonary embolism, QT_c prolonged, respiratory distress, rhabdomyolysis, seizure (grand mal), shock, speech disorder, suicide, suicide attempt, supraventricular tachycardia, swollen tongue, tardive dyskinesia, thrombocytopenia, thrombophlebitis, tic, ulcer, urea increased, urinary retention, urticaria, ventricular tachycardia

Metabolism/Transport Effects**Substrate** (major) of CYP2D6, 3A4

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Atypical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

CarBAMazepine: May decrease the serum concentration of Aripiprazole. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Ingestion with a high-fat meal delays time to peak plasma level.

Herb/Nutraceutical: St John's wort may decrease aripiprazole levels. Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Monitoring ParametersVital signs; fasting lipid profile and fasting blood glucose/Hb A_{1c} (prior to treatment, at 3 months, then annually); BMI, personal/family history of diabetes, waist circumference, blood pressure, mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms (EPS). Weight should be assessed prior to treatment, at 4 weeks, 8 weeks, 12 weeks, and then at quarterly intervals. Consider titrating to a different antipsychotic agent for a weight gain ≥5% of the initial weight.

Nursing: Physical Assessment/MonitoringAssess personal/family history of diabetes vital signs, blood pressure; mental status, thoughts of suicide ideation, abnormal involuntary movement scale (AIMS), and extrapyramidal symptoms (EPS). Weight and waist circumference should be assessed prior to treatment, at 4 weeks, 8 weeks, 12 weeks, and then at quarterly intervals. Consider titrating to a different antipsychotic agent for a weight gain ≥5% of the initial weight. This drug may alter glucose regulation and control. Monitor closely. Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests (eg, ophthalmic, hematological, cardiovascular) prior to and periodically during therapy. Assess therapeutic effectiveness and adverse response (eg, extrapyramidal symptoms, neuroleptic malignant syndrome) at beginning of and at regular intervals during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsFasting lipid profile and fasting blood glucose/Hb A_{1c} (prior to treatment, at 3 months, then annually); BMI

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take exactly as directed at the same time of day, without regard to meals. Do not alter dose; it may take some time to achieve desired results. Avoid alcohol. If you have diabetes, monitor blood glucose levels closely at beginning of therapy and periodically thereafter. May cause hyperglycemia. You may be more vulnerable to overheating and dehydration while taking this medication. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. May cause headache, dizziness, lightheadedness, problems sleeping, anxiety (use caution when driving or engaged in potentially hazardous tasks until response to drug is known), nausea or vomiting (small frequent meals and frequent mouth care may help), constipation (increased fluids, fiber, fruit, and exercise may help) or orthostatic hypotension (use caution when changing position from lying or sitting to standing and when climbing stairs). Report chest pain or palpitations; persistent gastrointestinal effects; muscle or skeletal pain, weakness, cramping, or tremors; involuntary movements, altered gait; change in vision; change in mental status (especially suicide ideation); weight gain or loss; or respiratory changes or flu-like symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Abilify®: 7.5 mg/mL (1.3 mL)

Solution, oral:

Abilify®: 1 mg/mL (150 mL) [contains propylene glycol, sucrose 400 mg/mL, and fructose 200 mg/mL; orange cream flavor]

Tablet:

Abilify®: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg

Tablet, orally disintegrating:

Abilify® Discmelt™: 10 mg [contains phenylalanine 1.12 mg; creme de vanilla flavor]; 15 mg [contains phenylalanine 1.68 mg; creme de vanilla flavor]

Generic AvailableNo

ManufacturerBristol-Myers Squibb Co

Pricing: U.S. (www.drugstore.com)

Tablet, orally-disintegrating (Abilify Discmelt)

10 mg (30): $449.97

Tablets (Abilify)

2 mg (30): $373.06

5 mg (30): $374.11

10 mg (30): $369.87

15 mg (30): $375.98

20 mg (30): $508.82

30 mg (30): $508.82

Mechanism of ActionAripiprazole is a quinolinone antipsychotic which exhibits high affinity for D_2, D_3, 5-HT_{1A}, and 5-HT_{2A} receptors; moderate affinity for D_4, 5-HT_{2C}, 5-HT_7, alpha_1 adrenergic, and H_1 receptors. It also possesses moderate affinity for the serotonin reuptake transporter; has no affinity for muscarinic (cholinergic) receptors. Aripiprazole functions as a partial agonist at the D_2 and 5-HT_{1A} receptors, and as an antagonist at the 5-HT_{2A} receptor.

Pharmacodynamics/Kinetics

Onset: Initial: 1-3 weeks

Absorption: Well absorbed

Distribution: V_d: 4.9 L/kg

Protein binding: ≥99%, primarily to albumin

Metabolism: Hepatic, via CYP2D6, CYP3A4 (dehydro-aripiprazole metabolite has affinity for D_2 receptors similar to the parent drug and represents 40% of the parent drug exposure in plasma)

Bioavailability: I.M.: 100%; Tablet: 87%

Half-life elimination: Aripiprazole: 75 hours; dehydro-aripiprazole: 94 hours

CYP2D6 poor metabolizers: Aripiprazole: 146 hours

Time to peak, plasma: I.M.: 1-3 hours; Tablet: 3-5 hours

With high-fat meal: Aripiprazole: Delayed by 3 hours; dehydro-aripiprazole: Delayed by 12 hours

Excretion: Feces (55%, ~18% unchanged drug); urine (25%, <1% unchanged drug)

Related Information

- Agents Approved for Bipolar Disorder
- Antipsychotic Agents
- Antipsychotic Receptor Profile
- Atypical Antipsychotics
- CMS: Long-Term Care Facility Thresholds
- Teratogenic Risks of Psychotropic Medications

Dental Health Professional ConsiderationsAripiprazole works differently from the classic antipsychotics, such as chlorpromazine, in that it does not appear to block central dopaminergic receptors, but rather seems to be a stabilizer of dopamine-serotonin central systems. The risk of extrapyramidal reactions such as pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia are low and the frequencies reported are similar to placebo. Aripiprazole may be associated with neuroleptic malignant syndrome (NMS).

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Extrapyramidal symptoms (similar to placebo) (see Dental Comment); xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentAripiprazole is an antipsychotic agent of a class often referred to as atypical. Some have referred to this agent as a new generation agent since its pharmacology differs (partial dopamine agonist) from the other atypical agents. It should be noted that the definition of the term “atypical” is not universally agreed upon. Some prefer to describe antipsychotics based on their pharmacological properties. A common feature of all definitions used to describe “atypical” antipsychotics is the lack of significant acute or subacute EPS, at dosages generally associated with antipsychotic actions. Other experts have included definitions of atypicality that include a) failure to increase serum prolactin levels; b) superior efficacy for positive, negative, and cognitive symptoms; and c) lack of evidence of tardive dyskinesia or dystonia following chronic administration. Clinically, if a patient with schizophrenia is not doing well on a particular dose, it is not clear whether the dose should be increased or decreased (15 mg/day dose did not differ from 30 mg/day dose in schizophrenia clinical trials). It is helpful, however, for patients with significant GI side effects to lower the dose and wait for tolerance to develop before going to a higher dose. While the dose for individuals with bipolar is similar to those with schizophrenia (15-30 mg/day) when used as an adjunctive agent for the management of depression the dose is 2-15 mg/day.

The short-acting I.M. formulation appears to be as efficacious as other available agents for the management of acute agitation; however, comparative trials have not been conducted.

Tardive dyskinesia (TD) secondary to **typical** antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. The incidence of TD associated with the atypical antipsychotics is estimated to be 0.5% to 1%. It is not clear if this estimate represents a risk associated with mental illness or to what extent drug therapy can be implicated. Atypical antipsychotics appear less likely to cause tardive dyskinesia than typical antipsychotics (fluphenazine, haloperidol).

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Index Terms BMS 337039; OPC-14597

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International Brand Names Abilify (AT, AU, BE, BG, BR, CH, CN, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, ID, IE, IT, KP, MX, MY, NL, NO, PE, PH, PT, RU, SE, SG, TH, TR, TW, VE); Arizol (UY); Arlemide (AR); Brisking (CL); Ilimit (UY); Irazem (AR); Real One (IN)

Armodafinil

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(ar moe DAF i nil)

U.S. Brand NamesNuvigil™

Pharmacologic CategoryStimulant

Use: Labeled IndicationsImprove wakefulness in patients with excessive daytime sleepiness associated with narcolepsy and shift work sleep disorder (SWSD); adjunctive therapy for obstructive sleep apnea/hypopnea syndrome (OSAHS)

Dosing: Adults

Narcolepsy: Oral: 150-250 mg once daily in the morning

Obstructive sleep apnea/hypopnea syndrome (OSAHS): Oral: 150-250 mg once daily in the morning; 250 mg was not shown to have any increased benefit over 150 mg

Shift work sleep disorder (SWSD): Oral: 150 mg given once daily ~1 hour prior to work shift

Dosing: ElderlyRefer to adult dosing. Consider lower initial dosage. Concentrations were almost doubled in clinical trials (based on modafinil).

Dosing: PediatricNot approved for use in children.

Dosing: Renal ImpairmentInadequate data to determine safety and efficacy in severe renal impairment.

Dosing: Hepatic ImpairmentSevere hepatic impairment (Child-Pugh classes B and C): Based on modafinil, dose should be reduced by half.

Administration: OralMay be administered without regard to food.

Dietary ConsiderationsTake with or without meals.

StorageStore at 20°C to 25°C (68°F to 77°F).

RestrictionsC-IV

ContraindicationsHypersensitivity to armodafinil, modafinil, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Dermatologic effects (severe): Serious and life-threatening rashes including Stevens-Johnson Syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms have been reported with modafinil, the racemate of armodafinil. In clinical trials of modafinil, these rashes were more likely to occur in children; however, in the postmarketing period, serious reactions have occurred in both adults and children. Most cases have been reported within the first 5 weeks of initiating therapy; however, rare cases have occurred after prolonged therapy. No risk factors have been identified to predict occurrence or severity of these reactions. Patients should be advised to discontinue drug at first sign of rash.

- Hypersensitivity reactions: Rare cases of multiorgan hypersensitivity reactions in association with modafinil and cases of angioedema and anaphylactoid reactions have been reported with the use of armodafinil. Signs and symptoms of multiorgan hypersensitivity reactions are diverse. Patients typically present with fever and rash associated with other organ system involvement. Patients should be advised to discontinue therapy and promptly report any signs or symptoms related to these adverse effects.

Disease-related concerns:

- Cardiovascular disease: Use is not recommended in patients with a history of left ventricular hypertrophy or patients with mitral valve prolapse who have developed mitral valve prolapse syndrome with previous CNS stimulant use. Patients with these conditions may also experience chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on ECG. Due to limited experience use caution in patients with history of myocardial infarction (MI), angina, or hypertension. Blood pressure monitoring may be required in patients on armodafinil. New or additional antihypertensive therapy may be needed.

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage reduction is recommended with severe dysfunction.

- Psychiatric disorders: Use caution in patients with a history of psychosis, depression, or mania. Modafinil has been shown to worsen the symptoms of these diseases (eg, mania, hallucinations, suicidal thoughts).

- Renal impairment: Safety and efficacy have not been established with severe renal impairment.

- Sleep disorders: Appropriate use: For use following complete evaluation of sleepiness and in conjunction with other standard treatments (eg, CPAP). The degree of sleepiness should be reassessed frequently; some patients may not return to a normal level of wakefulness. Patients with excessive sleepiness should be advised to avoid driving or any other potentially dangerous activity.

- Tourette's syndrome: Use with caution in patients with Tourette's syndrome; stimulants may unmask tics.

Special populations:

- Elderly: Use reduced doses in elderly patients; concentrations of armodafinil are significantly higher in patients >65 years of age.

- Pediatrics: Safety and efficacy have not been established in children <17 years of age.

Other warnings/precautions:

- Abuse potential: Use with caution in patients with a history of drug abuse; potential for drug dependency exists.

Geriatric ConsiderationsThere are no specific pharmacokinetic data for armodafinil, but the clearance of modafinil may be reduced in the elderly. Safety and effectiveness in persons >65 years of age have not been established.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no well-controlled studies of armodafinil in pregnant women. There have been reports of intrauterine growth retardation and spontaneous abortions in women using the both armodafinil and modafinil, but relationship to the drug is unknown.

Adverse events have been observed in animal studies. Armodafinil and modafinil have been studied in both rats and rabbits. Developmental toxicity (including visceral and skeletal abnormalities and decreased fetal weight) in rats (armodafinil and modafinil) and rabbits (modafinil) has been observed at doses correlating to those used clinically. Efficacy of steroidal contraceptives may be decreased; alternate means of contraception should be considered during therapy and for 1 month after modafinil is discontinued.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Central nervous system: Headache (14% to 23%; dose related)

1% to 10%:

Cardiovascular: Palpitation (2%), increased heart rate (1%)

Central nervous system: Dizziness (5%), insomnia (4% to 6%; dose related), anxiety (4%), depression (1% to 3%; dose related), fatigue (2%), agitation (1%), attention disturbance (1%), depressed mood (1%), migraine (1%), nervousness (1%), pain (1%), pyrexia (1%), tremor (1%)

Dermatologic: Rash (1% to 4%; dose related), contact dermatitis (1%), hyperhidrosis (1%)

Gastrointestinal: Nausea (6% to 9%; dose related), xerostomia (2% to 7%; dose related), diarrhea (4%), abdominal pain (2%), dyspepsia (2%), anorexia (1%), appetite decreased (1%), constipation (1%), loose stools (1%), vomiting (1%)

Genitourinary: Polyuria (1%)

Hepatic: GGT increased (1%)

Neuromuscular & skeletal: Paresthesia (1%)

Respiratory: Dyspnea (1%)

Miscellaneous: Flu-like syndrome (1%), thirst (1%)

Postmarketing and/or case reports: Anaphylactoid reaction, angioedema, hypersensitivity, liver enzymes increased, pancytopenia, systolic blood pressure increased

Metabolism/Transport Effects

Substrate of CYP3A4 (major); **Inhibits** CYP2C19 (moderate); **Induces** CYP1A2 (weak), 3A4 (moderate)

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Armodafinil may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol.

Food: Delays absorption, but minimal effects on bioavailability. Food may affect the onset and time course of armodafinil.

Monitoring ParametersSigns of hypersensitivity, rash, psychiatric symptoms, levels of sleepiness, blood pressure, and drug abuse

Nursing: Physical Assessment/MonitoringMonitor therapeutic response, adverse reactions, and blood pressure at the beginning and periodically throughout therapy. Assess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking. Do not take any new medications without consulting prescriber. Avoid or limit alcohol. May cause headache, dizziness (use caution when driving or engaging in activities requiring alertness until response to drug is known); dry mouth (sucking on lozenges or hard candy may help), or nausea (small, frequent meals, frequent oral care, sucking lozenges, or chewing gum may help). Report mental disturbances, persistent insomnia or headaches, rash, or heart disturbances including chest pain. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Nuvigil™: 50 mg, 150 mg, 250 mg

Generic AvailableNo

ManufacturerCephalon, Inc

Mechanism of ActionThe exact mechanism of action of armodafinil is unknown. It is the R-enantiomer of modafinil. Armodafinil binds to the dopamine transporter and inhibits dopamine reuptake, which may result in increased extracellular dopamine levels in the brain. However, it does not appear to be a dopamine receptor agonist and also does not appear to bind to or inhibit the most common receptors or enzymes that are relevant for sleep/wake regulation.

Pharmacodynamics/Kinetics

Absorption: Readily absorbed

Distribution: V_d: 42 L

Protein binding: ~60% (based on modafinil; primarily albumin)

Metabolism: Hepatic, multiple pathways, including CYP3A4/5; metabolites include R-modafinil acid and modafinil sulfone

Clearance: 33 mL/minute, mainly via hepatic metabolism

Half-life elimination: 15 hours; Steady state: ~7 days

Time to peak, plasma: 2 hours (fasted)

Excretion: Urine (80% predominantly as metabolites; <10% as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse vasoconstrictor with caution. Patients may experience heart palpitations and increased heart rate when taking armodafinil.

Mental Health CommentArmodafinil is a stimulant and has been shown to worsen symptoms of psychosis (hallucinations), depression (suicidal thoughts), and mania in some vulnerable patients. Patients with bipolar disorder should not receive stimulant medication in the absence of treatment with a concomitant mood-stabilizing medication. Stimulants may also unmask tics in patients with Tourette's syndrome. Armodafinil has the potential to be abused and for individuals to become dependent. Assess patients' history of drug abuse. Monitor for life-threatening rashes including Stevens-Johnson syndrome. Armodafinil uses CYP3A4 as a major metabolic pathway. Evaluate medication regimen for potential drug-drug interactions.

Index TermsR-modafinil

References

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Arsenic Trioxide

Lexi-Drugs Online

English

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(AR se nik tri OKS id)

U.S. Brand NamesTrisenox®

Pharmacologic CategoryAntineoplastic Agent, Miscellaneous

Use: Labeled IndicationsInduction of remission and consolidation in patients with relapsed or refractory acute promyelocytic leukemia (APL) which is specifically characterized by t(15;17) translocation or PML/RAR-alpha gene expression

Use: Unlabeled/InvestigationalTreatment of myelodysplastic syndrome (MDS), multiple myeloma

Dosing: Adults**APL:** I.V.:

Induction: 0.15 mg/kg/day; administer daily until bone marrow remission; maximum induction: 60 doses

Consolidation: 0.15 mg/kg/day starting 3-6 weeks after completion of induction therapy; maximum consolidation: 25 doses over 5 weeks

MDS, multiple myeloma (unlabeled uses): I.V.: 0.25 mg/kg/day 5 consecutive days/week for 2 weeks, followed by a 2-week rest period

Dosing: ElderlySafety and efficacy have not been established. Clinical trials included patients ≤72 years of age. Use with caution due to the increased risk of renal impairment in the elderly.

Dosing: Pediatric**APL:** Children ≥5 years: Refer to adult dosing.

Dosing: Renal ImpairmentSafety and efficacy have not been established; use with caution due to renal elimination.

Dosing: Hepatic ImpairmentSafety and efficacy have not been established.

Administration: I.V.I.V. infusion over 1-2 hours. If acute vasomotor reactions occur, infuse over a maximum of 4 hours. Does not require administration via a central venous catheter.

Administration: I.V. DetailpH: 7.5-8.5

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F); do not freeze. Following dilution, stable for 24 hours at room temperature or 48 hours when refrigerated.

ReconstitutionDilute in 100-250 mL D_5W or 0.9% NaCl. Discard unused portion.

ContraindicationsHypersensitivity to arsenic or any component of the formulation

Warnings/Precautions

Boxed warnings:

- APL differentiation syndrome: See “Concerns related to adverse effects” below.
- Baseline tests: See “Other warnings/precautions” below.
- Experienced physician: See “Other warnings/precautions” below.
- QT prolongation: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- APL differentiation syndrome: **[U.S. Boxed Warning]: May cause retinoic-acid-acute promyelocytic leukemia (RA-APL) syndrome or APL differentiation syndrome** (dyspnea, fever, weight gain, pulmonary infiltrates, and pleural or pericardial effusions) in patients with APL. High-dose steroids have been used for treatment.
- Hyperleukocytosis: May lead to the development of hyperleukocytosis (leukocytes ≥10,000/mm^3).
- QT prolongation: **[U.S. Boxed Warning]: May prolong the QT interval. May lead to torsade de pointes or complete AV block.** Risk factors for torsade de pointes include HF, a history of torsade de pointes, pre-existing QT interval prolongation, patients taking potassium-wasting diuretics, and conditions which cause hypokalemia or hypomagnesemia. If possible, discontinue all medications known to prolong the QT interval. Correct QT_c >500 msec prior to treatment. Discontinue therapy and hospitalize patient if QT_c >500 msec, syncope, or irregular heartbeats develop during therapy; do not reinitiate until QT_c <460 msec.

Disease-related concerns:

- Electrolyte imbalances: Correct electrolyte abnormalities prior to treatment and monitor potassium and magnesium levels during therapy (potassium should stay >4 mEq/dL and magnesium >1.8 mg/dL).

- Renal impairment: Use with caution in patients with renal impairment; arsenic is eliminated renally.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <5 years of age; limited experience with children 5-16 years of age.

Other warnings/precautions:

- Baseline tests: **[U.S. Boxed Warning]: A baseline 12-lead ECG, serum electrolytes (potassium, calcium, magnesium), and creatinine should be obtained prior to treatment.**

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsIncreased resorptions, neural-tube defects, and ophthalmic abnormalities have been observed in animal studies. Arsenic crosses the human placenta. In studies of women exposed to high levels of arsenic from drinking water, cord blood levels were similar to maternal serum levels. Dimethylarsinic acid (DMA) was the form of arsenic found in the fetus. An increased risk of low birth weight and still births were observed in women who ingested high levels of dietary arsenic. There are no studies of arsenic trioxide therapy in pregnant women. Women of childbearing potential should avoid pregnancy.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsArsenic is naturally found in breast milk; concentrations range from 0.2-6 mcg/kg. In studies of women exposed to high levels of arsenic from drinking water, breast milk concentrations were low (~3.1 mcg/kg) and did not correlate with maternal serum levels. The possible effect of maternal arsenic trioxide therapy on breast milk concentrations is not known. Due to the potential for serious adverse reactions in a nursing infant, breast-feeding during therapy is not recommended.

Adverse Reactions

>10%:

Cardiovascular: Tachycardia (55%), edema (40%), QT interval >500 msec (40%), chest pain (25%; grades 3/4: 5%), hypotension (25%; grades 3/4: 5%)

Central nervous system: Fatigue (63%), fever (63%), headache (60%), insomnia (43%), anxiety (30%), dizziness (23%), depression (20%), pain (15%)

Dermatologic: Dermatitis (43%), pruritus (33%), bruising (20%), dry skin (13%)

Endocrine & metabolic: Hypokalemia (50%; grades 3/4: 13%), hyperglycemia (45%; grades 3/4: 13%), hypomagnesemia (45%; grades 3/4: 13%), hyperkalemia (18%; grades 3/4: 5%)

Gastrointestinal: Nausea (75%), abdominal pain (58%), vomiting (58%), diarrhea (53%), sore throat (35% to 40%), constipation (28%), anorexia (23%), appetite decreased (15%), weight gain (13%)

Genitourinary: Vaginal hemorrhage (13%)

Hematologic: Leukocytosis (50%; grades 3/4: 3%), APL differentiation syndrome (23%), anemia (20%; grades 3/4: 5%), thrombocytopenia (18%; grades 3/4: 13%), febrile neutropenia (13%; grades 3/4: 8%)

Hepatic: ALT increased (20%; grades 3/4: 5%), AST increased (13%; grades 3/4: 3%)

Local: Injection site: Pain (20%), erythema (13%)

Neuromuscular & skeletal: Neuropathy (43%), rigors (38%), arthralgia (33%), paresthesia (33%), myalgia (25%), bone pain (23%), back pain (18%), limb pain (13%), neck pain (13%), tremor (13%)

Respiratory: Cough (65%), dyspnea (38% to 53%; grades 3/4: 10%), epistaxis (25%), hypoxia (23%), pleural effusion (20%), sinusitis (20%), postnasal drip (13%), upper respiratory tract infection (13%), wheezing (13%)

Miscellaneous: Herpes simplex (13%)

1% to 10%:

Cardiovascular: Hypertension (10%), flushing (10%), pallor (10%), palpitation (10%), facial edema (8%), abnormal ECG (not QT prolongation) (7%)

Central nervous system: Convulsion (8%; grades 3/4: 5%), somnolence (8%), agitation (5%), coma (5%), confusion (5%)

Dermatologic: Erythema (10%), hyperpigmentation (8%), petechia (8%), skin lesions (8%), urticaria (8%), local exfoliation (5%)

Endocrine & metabolic: Hypocalcemia (10%), hypoglycemia (8%), acidosis (5%)

Gastrointestinal: Dyspepsia (10%), loose stools (10%), abdominal distension (8%), abdominal tenderness (8%), xerostomia (8%), fecal incontinence (8%), gastrointestinal hemorrhage (8%), hemorrhagic diarrhea (8%), oral blistering (8%), weight loss (8%), oral candidiasis (5%)

Genitourinary: Intermenstrual bleeding (8%), incontinence (5%)

Hematologic: Neutropenia (10%; grades 3/4: 10%), DIC (8%), hemorrhage (8%), lymphadenopathy (8%)

Local: Injection site edema (10%)

Neuromuscular & skeletal: Weakness (10%)

Ocular: Blurred vision (10%), eye irritation (10%), dry eye (8%), eyelid edema (5%), painful eye (5%)

Otic: Earache (8%), tinnitus (5%)

Renal: Renal failure (8%; grades 3/4: 3%), renal impairment (8%), oliguria (5%)

Respiratory: Crepitations (10%), breath sounds decreased (10%), rales (10%), hemoptysis (8%), rhonchi (8%), tachypnea (8%), nasopharyngitis (5%)

Miscellaneous: Diaphoresis increased (10%), APL differentiation syndrome (8%), bacterial infection (8%), herpes zoster (8%), night sweats (8%), hypersensitivity (5%), sepsis (5%; grades 3/4: 5%)

Postmarketing and/or case reports: Atrial dysrhythmia, AV block, torsade de pointes

Oncology: VesicantNo

Oncology: Emetic PotentialModerate-to-high (30% to 90%)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid homeopathic products (arsenic is present in some homeopathic medications). Avoid hypoglycemic herbs, including alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng, gymnema, marshmallow, and stinging nettle (may enhance the hypoglycemic effect of arsenic trioxide).

Monitoring ParametersBaseline then weekly 12-lead ECG, baseline then twice weekly serum electrolytes, hematologic and coagulation profiles at least twice weekly during induction and at least weekly during consolidation; more frequent monitoring may be necessary in unstable patients

Nursing: Physical Assessment/MonitoringTo be used only by physicians experienced with the treatment of acute leukemia. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (especially anything that may cause hypokalemia or hypomagnesemia, or antiarrhythmic agents). Assess results of laboratory tests and patient response at beginning and periodically during therapy (especially cardiac and electrolyte status). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsBaseline then weekly 12-lead ECG, baseline then twice weekly serum electrolytes, hematologic and coagulation profiles at least twice weekly during induction and at least weekly during consolidation; more frequent monitoring may be necessary in unstable patients .

Patient EducationDo not take any new medication during therapy unless approved by physician. This medication can only be administered by intravenous infusion. Report immediately any redness, swelling, pain, or burning at infusion site. May cause dizziness, fatigue, blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea, vomiting, diarrhea, or decreased appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report immediately unexplained fever; respiratory difficulty; chest pain or palpitations; confusion, lightheadedness, or fainting; unusual joint, back, or muscle pain, tingling or loss of feeling; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform physician if you are pregnant. Do not get pregnant while take this medication. Consult physician for appropriate contraceptive methods. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Trisenox®: 1 mg/mL (10 mL)

Generic AvailableNo

Mechanism of ActionNot fully understood; causes *in vitro* morphological changes and DNA fragmentation to NB4 human promyelocytic leukemia cells; also damages or degrades the fusion protein PML-RAR alpha

Pharmacodynamics/Kinetics

Distribution: V_d: ~4 L

Metabolism: Hepatic; pentavalent arsenic is reduced to trivalent arsenic (active) by arsenate reductase; trivalent arsenic is methylated to monomethylarsinic acid, which is then converted to dimethylarsinic acid via methyltransferases

Half-life elimination: Initial: 0.6-1.2 hours; Elimination: 9-15 hours

Excretion: Urine (as methylated metabolite)

Pharmacotherapy PearlsArsenic is stored in liver, kidney, heart, lung, hair, and nails. Arsenic trioxide is a human carcinogen.

Oncology Comment: Arsenic trioxide is listed within National Comprehensive Cancer Network (NCCN) guidelines for the treatment of acute myeloid leukemia as the recommended salvage therapy for relapsed or persistent APL. For patients with APL in their second complete response, who are not candidates for stem cell transplant, in the absence of an appropriate clinical trial, maintenance therapy with arsenic trioxide is an option.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsArsenic trioxide is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusFatigue, insomnia, anxiety, dizziness, and depression are common; may cause agitation and confusion

Mental Health: Effects on Psychiatric TreatmentContraindicated with ziprasidone. Gastrointestinal side effects are common; may produce additive GI side effects when used in combination with SSRIs. Hypotension is common and combined use with psychotropics may produce additive hypotension. May cause thrombocytopenia and neutropenia. Use caution with clozapine, carbamazepine, and valproic acid. Concurrent use with thioridazine may increase the risk of potentially fatal arrhythmias.

Cardiovascular ConsiderationsArsenic trioxide may prolong the QT interval and cause torsade de pointes or complete AV block and, therefore, should be administered in a controlled setting with careful monitoring of blood pressure and electrocardiogram. Hypokalemia and hypomagnesemia should be corrected, if present, prior to initiation of therapy. Patients with concomitant congestive heart failure, history of torsade de pointes, long QT syndrome, and/or on other medications that prolong the QT interval may be at a greater risk for torsade de pointes.

Index TermsAs$_2$O$_3$; NSC-706363

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International Brand NamesAsadin (TW); Trisenox (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Articaine and Epinephrine

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Pronunciation(AR ti kane & ep i NEF rin)

U.S. Brand NamesSeptocaine® with epinephrine 1:100,000; Septocaine® with epinephrine 1:200,000; Zorcaine™

Canadian Brand NamesAstracaine® with epinephrine 1:200,000; Astracaine® with epinephrine forte 1:100,000; Septanest® N; Septanest® SP; Ultracaine® D-S; Ultracaine® D-S Forte; Zorcaine™

Pharmacologic CategoryLocal Anesthetic

Use: DentalLocal, infiltrative, or conductive anesthesia in both simple and complex dental and periodontal procedures

Dosing: AdultsSummary of recommended volumes and concentrations for various types of anesthetic procedures; dosages (administered by submucosal injection and/or nerve block) apply to normal healthy adults:

Infiltration: Injection volume of 4% solution: 0.5-2.5 mL; total dose: 20-100 mg

Nerve block: Injection volume of 4% solution: 0.5-3.4 mL; total dose: 20-136 mg

Oral surgery: Injection volume of 4% solution: 1-5.1 mL; total dose: 40-204 mg

Note: These dosages are guides only; other dosages may be used; however, do not exceed maximum recommended dose

Special populations: The clinician is reminded that these doses serve only as a guide to the amount of anesthetic required for most routine procedures. The actual volumes to be used depend upon a number of factors, such as type and extent of surgical procedure, depth of anesthesia, degree of muscular relaxation, and condition of the patient. In all cases, the smallest dose that will produce the desired result should be given. Dosages should be reduced for pediatric patients, elderly patients, and patients with cardiac and/or liver disease.

Maximum recommended dosages:

Adults (normal, healthy): Submucosal infiltration and/or nerve block: Not to exceed 7 mg/kg (0.175 mL/kg) **or** 3.2 mg/lb (0.0795 mL/lb) of body weight

The following numbers of dental cartridges (1.7 mL) provide the indicated amounts of articaine hydrochloride 4% and epinephrine 1:100,000:

1 cartridge provides 68 mg articaine HCl (4%) and 0.017 mg vasoconstrictor (epinephrine 1:100,000)

2 cartridges provides 136 mg articaine HCl (4%) and 0.034 mg vasoconstrictor (epinephrine 1:100,000)

3 cartridges provides 204 mg articaine HCl (4%) and 0.051 mg vasoconstrictor (epinephrine 1:100,000)

4 cartridges provides 272 mg articaine HCl (4%) and 0.068 mg vasoconstrictor (epinephrine 1:100,000)

5 cartridges provides 340 mg articaine HCl (4%) and 0.085 mg vasoconstrictor (epinephrine 1:100,000)

6 cartridges provides 408 mg articaine HCl (4%) and 0.102 mg vasoconstrictor (epinephrine 1:100,000)

7 cartridges provides 476 mg articaine HCl (4%) and 0.119 mg vasoconstrictor (epinephrine 1:100,000)

8 cartridges provides 544 mg articaine HCl (4%) and 0.136 mg vasoconstrictor (epinephrine 1:100,000)

The following numbers of dental cartridges (1.7 mL) provide the indicated amounts of articaine hydrochloride 4% and epinephrine 1:200,000:

1 cartridge provides 68 mg articaine HCl (4%) and 0.0085 mg vasoconstrictor (epinephrine 1:200,000)

2 cartridges provides 136 mg articaine HCl (4%) and 0.017 mg vasoconstrictor (epinephrine 1:200,000)

3 cartridges provides 204 mg articaine HCl (4%) and 0.026 mg vasoconstrictor (epinephrine 1:200,000)

4 cartridges provides 272 mg articaine HCl (4%) and 0.034 mg vasoconstrictor (epinephrine 1:200,000)

5 cartridges provides 340 mg articaine HCl (4%) and 0.043 mg vasoconstrictor (epinephrine 1:200,000)

6 cartridges provides 408 mg articaine HCl (4%) and 0.051 mg vasoconstrictor (epinephrine 1:200,000)

7 cartridges provides 476 mg articaine HCl (4%) and 0.060 mg vasoconstrictor (epinephrine 1:200,000)

8 cartridges provides 544 mg articaine HCl (4%) and 0.068 mg vasoconstrictor (epinephrine 1:200,000)

Dosing: ElderlyAdminister smallest dose to produce desired result.

Geriatric patients (dosages in a clinical trial):

65-75 years

Simple procedures: 0.43-4.76 mg/kg (0.9-11.9 mL) was administered safely to 35 patients.

Complex procedures: 1.05-4.27 mg/kg (1.3-6.8 mL) was administered safely to 19 patients.

≥75 years:

Simple procedures: 0.78-4.76 mg/kg (1.3-11.9 mL) was administered safely to 7 patients.

Complex procedures: 1.12-2.17 mg/kg (1.3-5.1 mL) was administered safely to 4 patients.

Note: Approximately 6% of the patients 65-75 years of age (none of the patients ≥75 years of age) required additional injections for complete anesthesia, compared to 11% of the patients 17-65 years of age who required additional injections.

Dosing: Pediatric**Note:** Give smallest dose that will produce desired result

Children <4 years: Safety and efficacy have not been established

Children 4-16 years (dosages in a clinical trial of 61 patients):

Simple procedures: 0.76-5.65 mg/kg (0.9-5.1 mL) was administered safely to 51 patients

Complex procedures: 0.37-7.48 mg/kg (0.7-3.9 mL) was administered safely to 10 patients

Note: Approximately 13% of the pediatric patients required additional injections for complete anesthesia

Maximum recommended dosages: Children (use in pediatric patients <4 years is not recommended): Not to exceed 7 mg/kg (0.175 mL/kg) **or** 3.2 mg/lb (0.0795 mL/lb) of body weight

ContraindicationsHypersensitivity to local anesthetics of the amide type or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Cardiovascular effects: Systemic absorption of local anesthetics may produce cardiovascular effects. Changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal at blood concentrations produced by therapeutic doses. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to AV block, ventricular arrhythmias, and cardiac arrest (sometimes resulting in death). In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs should be done following each local anesthetic injection.

- CNS toxicity: Careful and constant monitoring of the patient's state of consciousness should be done following each local anesthetic injection; at such times, restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of CNS toxicity. Treatment is primarily symptomatic and supportive.

- Methemoglobinemia: Has been reported with articaine; may be treated with methylene blue, 1-2 mg/kg I.V. infused over several minutes.

- Respiratory arrest: Local anesthetics have been associated with rare occurrences of sudden respiratory arrest.

- Seizures: Convulsions due to systemic toxicity leading to cardiac arrest have also been reported, presumably following unintentional intravascular injection.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with impaired cardiovascular function, since they may be less able to compensate for function changes associated with prolonged AV conduction produced by these drugs. Use with caution in patients with heart block.

- Hepatic impairment: Use with caution in patients with severe hepatic disease; *in vitro* studies show that ~5% to 10% of articaine is metabolized by the human liver microsomal P450 isoenzyme system; however, no studies have been performed in patient with liver dysfunction.

- Vascular disease: Local anesthetic solutions containing a vasoconstrictor should be used cautiously. Patients with peripheral vascular disease or hypertensive vascular disease may exhibit exaggerated vasoconstrictor response, possibly resulting in ischemic injury or necrosis.

Concurrent drug therapy issues:

- Epinephrine: Contains epinephrine, which can cause local tissue necrosis or systemic toxicity, usual precautions for epinephrine administration should be observed. Administration of articaine HCl with epinephrine results in a three- to fivefold increase in plasma epinephrine concentrations compared to baseline; however, in healthy adults, it does not appear to be associated with marked increases in blood pressure or heart rate, except in the case of accidental intravascular injection.

- General anesthetics: Use with caution in patients during or following the administration of a potent general anesthetic agent, since cardiac arrhythmias may occur under these conditions.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <4 years of age.

Dosage form specific issues:

- Sodium metabisulfite: Products may contain sodium metabisulfite, which may cause allergic-type reactions (including anaphylactic symptoms, and life-threatening or less severe asthmatic episodes) in certain susceptible patients. The overall prevalence of the sulfite sensitivity in the general population is unknown, and is seen more frequently in asthmatic than in nonasthmatic persons.

Other warnings/precautions:

- Administration: Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

- Appropriate dosing: To avoid serious adverse effects and high plasma levels, the lowest dosage resulting in effective anesthesia should be administered. Repeated doses may cause significant increases in blood levels with each repeated dose due to the possibility of accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with patient status. Reduced dosages, commensurate with age and physical condition, should be given to debilitated patients, elderly patients, acutely-ill patients, and pediatric patients.

- Dental blocks: Small doses of local anesthetics injected into dental blocks may produce adverse reactions similar to systemic toxicity seen in unintentional intravascular injections at larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving such blocks should be observed constantly with resuscitative equipment and personnel trained in treatment of adverse reactions immediately available. Dosage recommendations should not be exceeded.

- Trained personnel: Dental practitioners and/or clinicians using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known whether articaine is excreted in human milk.

Adverse ReactionsAdverse reactions to Septocaine™ are characteristic of those associated with other amide-type local anesthetics; adverse reactions to this group of drugs may also result from excessive plasma levels which may be due to overdosage, unintentional intravascular injection, or slow metabolic degradation.

≥1% (in controlled trial of 882 patients):

Central nervous system: Headache (4%), paresthesia (1%)

Gastrointestinal: Gingivitis (1%)

Miscellaneous: Pain (body as a whole 13%), facial edema (1%)

<1% (adverse and intercurrent events recorded in 1 or more patients in controlled trials, occurring at an overall rate of <1%, and considered clinically significant): Abdominal pain, accidental injury, arthralgia, asthenia, back pain, constipation, diarrhea, dizziness, dry mouth, dysmenorrhea, dyspepsia, ear pain, ecchymosis, edema, facial paralysis, glossitis, gum hemorrhage, hemorrhage, hyperesthesia, lymphadenopathy, malaise, methemoglobinemia, migraine, mouth ulceration, myalgia, nausea, neck pain, nervousness, neuropathy, osteomyelitis, pharyngitis, pruritus, rhinitis, salivation increased, skin disorder, somnolence, stomatitis, syncope, tachycardia, taste perversion, thirst, tongue edema, tooth disorder, vomiting

Additional adverse reactions reported with articaine and epinephrine: Arrhythmia, myocardial depression, asthma, convulsions, allergic reactions, injection site reactions, tissue necrosis

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. *Risk D: Consider therapy modification*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

COMT Inhibitors: May decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

Inhalational Anesthetics: May enhance the arrhythmogenic effect of EPINEPHrine. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). *Risk D: Consider therapy modification*

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, solution:

Astracaine® with epinephrine 1:200,000 [CAN]: Articaine 4% and epinephrine 1:200,000 (1.8 mL) [not available in the U.S.]

Astracaine® Forte with epinephrine forte 1:100,000 [CAN]: Articaine 4% and epinephrine 1:100,000 (1.8 mL) [not available in the U.S.]

Septanest® N [CAN]: Articaine 4% and epinephrine 1:200,000 (1.7 mL) [not available in the U.S.]

Septanest® SP [CAN]: Articaine 4% and epinephrine 1:100,000 (1.7 mL) [not available in the U.S.]

Septocaine® with epinephrine 1:100,000: Articaine hydrochloride 4% and epinephrine bitartrate 1:100,000 (1.7 mL) [contains sodium metabisulfite]

Septocaine® with epinephrine 1:200,000: Articaine hydrochloride 4% and epinephrine bitartrate 1:200,000 (1.7 mL) [contains sodium metabisulfite]

Ultracaine DS® [CAN]: Articaine hydrochloride 4% and epinephrine 1:200,000 (1.7 mL) [contains sodium metabisulfite; not available in the U.S.]

Ultracaine DS Forte® [CAN]: Articaine hydrochloride 4% and epinephrine 1:100,000 (1.7 mL) [contains sodium metabisulfite; not available in the U.S.]

Zorcaine™: Articaine hydrochloride 4% and epinephrine bitartrate 1:100,000 (1.7 mL) [contains sodium metabisulfite]

Generic Available

No

Mechanism of Action

Local anesthetics block the generation and conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of the affected nerve fibers. Clinically, the order of loss of nerve function is as follows: 1) pain, 2) temperature, 3) touch, 4) proprioception, and 5) skeletal muscle tone.

Pharmacodynamics/Kinetics

Onset of action: 1-6 minutes

Duration: Complete anesthesia: ~1 hour

Metabolism: Hepatic via plasma carboxyesterase to articainic acid (inactive)

Half-life elimination: Articaine: 1.8 hours; Articainic acid: 1.5 hours

Excretion: Urine (primarily as metabolites)

Pharmacotherapy Pearls

Septocaine™ (articaine hydrochloride 4% and epinephrine 1:100,000) is the first FDA approval in 30 years of a new local dental anesthetic providing complete pulpal anesthesia for approximately 1 hour. Chemically, articaine contains both an amide linkage and an ester linkage, making it chemically unique in the class of local anesthetics.

Dental Health Professional Considerations

Septocaine™ (articaine hydrochloride 4% and epinephrine 1:100,000) is the first FDA approval in 30 years of a new local dental anesthetic providing complete pulpal anesthesia for approximately 1 hour. Chemically, articaine contains both an amide linkage and an ester linkage, making it chemically unique in the class of local anesthetics. Since it contains the ester linkage, articaine HCl is rapidly metabolized by plasma carboxyesterase to its primary metabolite, articainic acid, which is an inactive product of this metabolism. According to the manufacturer, *in vitro* studies show that the human liver microsomal P450 isoenzyme system metabolizes approximately 5% to 10% of available articaine with nearly quantitative conversion to articainic acid. The elimination half-life of articaine is about 1.8 hours, and that of articainic acid is about 1.5 hours. Articaine is excreted primarily through urine with 53% to 57% of the administered dose eliminated in the first 24 hours following submucosal administration. Articainic acid is the primary metabolite in urine. A minor metabolite, articainic acid glucuronide, is also excreted in the urine. Articaine constitutes only 2% of the total dose excreted in urine.

The anesthetic efficacy of the articaine 4% with 1:200,000 epinephrine (A/200) was compared to that of articaine 4% with 1:100,000 (A/100) using electric pulp tester to assess anesthesia using 63 subjects after either maxillary infiltration (Moore, 2006) or inferior alveolar block (Hersh, 2006).

After maxillary infiltration of 1 mL of each formula, the onset times to anesthesia were 3.1 ± 2.3 minutes for articaine 4% and 1:200,000 epinephrine (A/200), 3 ± 2.1 minutes for articaine 4% and 1:100,000 epinephrine (A/100), 3 ± 2 minutes for articaine 4% with no epinephrine (A/no). These three mean times of onset were not statistically different. Durations of anesthesia were 41.6 ± 21.1 minutes A/200, 45 ± 23.6 minutes A/100, 13.3 ± 6.8 minutes for A/no. There was no statistically significant difference between the durations elicited by the A/200 and A/100 formulations (Moore, 2006). In the second trial of the study, also using 63 subjects, the investigators administered an inferior alveolar nerve block injection of one cartridge (1.7 mL) using a standard intra-oral injection technique for inferior alveolar block anesthesia. Pulpal anesthesia was measured again using the pulp tester.

The onset times to anesthesia were 4.7 ± 2.6 minutes A/200, 4.2 ± 2.8 minutes A/100, and 4.3 ± 2.5 minutes for A/no. There were no statistically significant differences in these times to onset. Durations of anesthesia were 51.2 ± 55.9 minutes A/200, 61.8 ± 59 minutes A/100, and 49.7 ± 44.6 minutes for A/no. There were no statistically significant differences in the duration between A/200, A/100, and A/no formulations (Hersh, 2006).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions (see Dental Comment)

Mental Health: Effects on Mental StatusMay cause depression, nervousness, sedation, or dizziness

Mental Health: Effects on Psychiatric TreatmentLocal anesthetics pose several drug-drug interactions with psychotropic agents (refer to Drug Interactions). Best to avoid use with ziprasidone since local anesthetics have the potential to produce adverse cardiovascular effects.

Index TermsEpinephrine and Articaine Hydrochloride

References

Hersh EV, Giannakopoulos H, Levin LM, et al, "The Pharmacokinetics and Cardiovascular Effects of High-Dose Articaine With 1:100,000 and 1:200,000 Epinephrine," *J Am Dent Assoc*, 2006, 137(11):1562-71.[PubMed 17082283]

Moore PA, Boynes SG, Hersh EV, et al, "The Anesthetic Efficacy of 4 Percent Articaine 1:200,000 Epinephrine: Two Controlled Clinical Trials," *J Am Dent Assoc*, 2006, 137(11):1572-81.[PubMed 17082284]

International Brand NamesBucanest (AU); Deltazine (AU); Septanest (AU, CH, DK, IT, NZ); Septanest N (IL); Septocaine (DK, NO, SE); Ubestesin Adrenalinee (FR); Ubistesin (EE, FI, HK, HN, IL, SE); Ubistesin Forte (HK, IL); Ultracain Epinefrina (ES)

Artificial Tears

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Isopto® Tears may be confused with Isoptin®

Murocel® may be confused with Murocoll-2®

Pronunciation(ar ti FISH il tears)

U.S. Brand NamesAkwa Tears® [OTC]; AquaSite® [OTC]; Bion® Tears [OTC]; HypoTears PF [OTC]; HypoTears [OTC]; Liquifilm® Tears [OTC]; Moisture® Eyes PM [OTC]; Moisture® Eyes [OTC]; Murine® Tears [OTC]; Murocel® [OTC]; Nature's Tears® [OTC]; Nu-Tears® II [OTC]; Nu-Tears® [OTC]; OcuCoat® PF [OTC]; OcuCoat® [OTC]; Puralube® Tears [OTC]; Refresh Plus® [OTC]; Refresh Tears® [OTC]; Refresh® [OTC]; Soothe® [OTC]; Systane® Free [OTC]; Systane® [OTC]; Teargen® II [OTC]; Teargen® [OTC]; Tearisol® [OTC]; Tears Again® [OTC]; Tears Naturale® Free [OTC]; Tears Naturale® II [OTC]; Tears Naturale® [OTC]; Tears Plus® [OTC]; Tears Renewed® [OTC]; Ultra Tears® [OTC]; Viva-Drops® [OTC]

Canadian Brand NamesTeardrops®

Pharmacologic CategoryOphthalmic Agent, Miscellaneous

Use: Labeled IndicationsOphthalmic lubricant; for relief of dry eyes and eye irritation

Dosing: AdultsOcular dryness/irritation: Ophthalmic: Use as needed to relieve symptoms, 1-2 drops into eye(s) 3-4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Warnings/Precautions

Dosage form specific issues:

- Active ingredient: Individual product formulations may include (as an active ingredient) benzalkonium chloride, polyvinyl alcohol, carboxymethylcellulose, hydroxymethylcellulose, hydroxypropyl methylcellulose, propylene glycol, dextran 70, or polysorbate 80. Refer to product labeling for specific ingredients.

Geriatric ConsiderationsAssure the patient or caregiver can adequately administer ophthalmic medication.

Pregnancy Risk FactorC

Adverse Reactions1% to 10%: Ocular: May cause mild stinging or temporary blurred vision

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic: 15 mL and 30 mL dropper bottles

Generic AvailableYes

Pharmacotherapy PearlsNot for use with soft contact lenses

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsHydroxyethylcellulose; Polyvinyl Alcohol

International Brand NamesTeardrops (CA)

Ascorbic Acid

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

International issues:

Rubex® [Ireland] may be confused with Revex® which is a brand name for nalmefene in the U.S.

Rubex® [Ireland]: Brand name for doxurbicin in the U.S.

Pronunciation(a SKOR bik AS id)

U.S. Brand NamesAcerola [OTC]; Asco-Caps [OTC]; Asco-Tabs [OTC]; Ascocid® [OTC]; Ascor L 500®; Ascor L NC®; C-Gel [OTC]; C-Gram [OTC]; C-Time [OTC]; Cecon® [OTC]; Cemill [OTC]; Cenolate®; Chew-C [OTC]; Dull-C® [OTC]; Mild-C® [OTC]; One Gram C [OTC]; Time-C [OTC]; Time-C-Bio [OTC]; Vicks® Vitamin C [OTC]; Vita-C® [OTC]

Canadian Brand NamesProflavanol C™; Revitalose C-1000®

Pharmacologic CategoryVitamin, Water Soluble

Use: Labeled IndicationsPrevention and treatment of scurvy; acidify the urine

Use: Unlabeled/InvestigationalInvestigational: In large doses, to decrease the severity of “colds”; dietary supplementation; a 20-year study was recently completed involving 730 individuals which indicates a possible decreased risk of death by stroke when ascorbic acid at doses ≥45 mg/day was administered

Dosing: Adults

Recommended daily allowance (RDA): Upper limit of intake should not exceed 2000 mg/day

- Male: 90 mg
- Female: 75 mg
  - Pregnant female:
    - ≤18 years: 80 mg; upper limit of intake should not exceed 1800 mg/day
    - 19-50 years: 85 mg; upper limit of intake should not exceed 2000 mg/day
  - Lactating female:
    - ≤18 years: 15 mg; upper limit of intake should not exceed 1800 mg/day
    - 19-50 years: 20 mg; upper limit of intake should not exceed 2000 mg/day
- Adult smoker: Add an additional 35 mg/day

Scurvy: Oral, I.M., I.V., SubQ: 100-250 mg 1-2 times/day for at least 2 weeks

Urinary acidification: Oral, I.V.: 4-12 g/day in 3-4 divided doses

Prevention and treatment of colds: Oral: 1-3 g/day

Dietary supplement: Oral: 50-200 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Recommended daily allowance (RDA):

- <6 months: 30 mg
- 6 months to 1 year: 35 mg
- 1-3 years: 40 mg
- 4-10 years: 45 mg
- 11-14 years: 50 mg
- >14 years: 60 mg

Scurvy: Oral, I.M., I.V., SubQ: Children: 100-300 mg/day in divided doses for at least 2 weeks

Urinary acidification: Oral, I.V.: Children: 500 mg every 6-8 hours

Dietary supplement: Oral: Children: 35-100 mg/day

Administration: I.V.Avoid rapid I.V. injection.
Administration: I.V. DetailpH: 5.5-7
Dietary ConsiderationsMild-C®: 3600 mg/teaspoonful contains calcium 400 mg/teaspoonful. Vicks® Vitamin C: 25 mg contains sodium 5 mg
StorageInjectable form should be stored under refrigeration (2°C to 8°C). Protect oral dosage forms from light. Rapidly oxidized when in solution in air and alkaline media.
CompatibilityStable in dextran 6% in D_5W, dextran 6% in NS, D_5LR, D_5NS, $D_5{}^1/_2NS$, $D_5{}^1/_4NS$, D_5W, $D_{10}W$, LR, $^1/_2NS$, NS; **variable stability (consult detailed reference)** in fat emulsion 10%

Y-site administration: Compatible: Warfarin. **Incompatible:** Etomidate, thiopental. **Variable (consult detailed reference):** Propofol, TPN.

Compatibility in syringe: Compatible: Metoclopramide. **Incompatible:** Cefazolin, doxapram.

Compatibility when admixed: Compatible: Amikacin, calcium chloride, calcium gluconate, chloramphenicol, chlorpromazine, colistimethate, cyanocobalamin, diphenhydramine, heparin, hydrocortisone sodium succinate, kanamycin, methyldopate, penicillin G potassium, polymyxin B sulfate, procaine, prochlorperazine, promethazine, verapamil. **Incompatible:** Bleomycin, chlorothiazide, nafcillin, sodium bicarbonate, theophylline. **Variable (consult detailed reference):** Aminophylline, erythromycin lactobionate.

Warnings/Precautions

Disease-related concerns:

- Diabetes: Patients with diabetes mellitus should not take excessive doses for extended periods of time.

- Renal calculi: Patients prone to recurrent renal calculi (eg, dialysis patients) should not take excessive doses for extended periods of time.

Dosage form specific issues:

- Aluminum: Some parenteral products contain aluminum; use caution in patients with impaired renal function and neonates.

Geriatric ConsiderationsMinimum RDA for elderly is not established. Vitamin C is provided mainly in citrus fruits and tomatoes. The elderly, however, avoid citrus fruits due to cost and difficulty preparing (peeling). Daily replacement through a single multiple vitamin is recommended. Use of natural vitamin C or rose hips offers no advantages. Acidity may produce GI complaints.
Pregnancy Risk FactorA/C (dose exceeding RDA recommendation)
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted.
LactationEnters breast milk/compatible
Adverse Reactions

1% to 10%: Renal: Hyperoxaluria with large doses

<1%: Flushing, faintness, dizziness, headache, fatigue, nausea, vomiting, heartburn, diarrhea, flank pain

Drug Interactions

Aluminum Hydroxide: Ascorbic Acid may increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Amphetamines: Gastrointestinal Acidifying Agents may decrease the serum concentration of Amphetamines. *Risk C: Monitor therapy*

Deferoxamine: Ascorbic Acid may enhance the adverse/toxic effect of Deferoxamine. Left ventricular dysfunction is of particular concern. *Risk D: Consider therapy modification*

Test InteractionsFalse-positive urinary glucose with cupric sulfate reagent, false-negative urinary glucose with glucose oxidase method; false-negative stool occult blood 48-72 hours after ascorbic acid ingestion
Monitoring ParametersMonitor pH of urine when using as an acidifying agent
Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Instruct patients with diabetes accordingly. Assess knowledge/teach patient appropriate administration according to formulation of drug and purpose for ascorbic acid therapy and adverse symptoms to report.
Monitoring: Lab TestspH of urine when used as an acidifying agent
Patient EducationTake exactly as directed; do not take more than the recommended dose. Do not chew or crush extended release tablets. Take oral doses with 8 oz of water. If you have diabetes, use serum glucose monitoring method. Report pain on urination, faintness, or flank pain. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet: 1000 mg

Caplet, timed release: 500 mg, 1000 mg

Capsule:

Mild-C®: 500 mg

Capsule, softgel:

C-Gel: 1000 mg

Capsule, sustained release:

C-Time: 500 mg

Capsule, timed release: 500 mg

Asco-Caps: 500 mg, 1000 mg [sugar free]

Time-C®: 500 mg

Crystals for solution, oral: 4 g/teaspoonful (170 g, 1000 g)

Mild-C®: 3600 mg/teaspoonful [contains calcium 400 mg/teaspoonful]

Vita-C®: 4 g/teaspoonful (100 g, 454 g)

Injection, solution: 500 mg/mL (50 mL)

Cenolate®: 500 mg/mL (1 mL, 2 mL) [contains aluminum, sodium hydrosulfite]

Injection, solution [preservative free]:

Ascor L 500®: 500 mg/mL (50 mL) [contains edetate disodium]

Ascor L NC®: 500 mg/mL (50 mL) [contains edetate disodium]

Liquid, oral: 500 mg/5 mL

Lozenge:

Vicks® Vitamin C: 25 mg [contains sodium 5 mg; orange flavor]

Powder, for solution, oral:

Ascocid®: 4000 mg/5 mL (227 g); 4300 mg/5 mL (227 g, 454 g); 5000 mg/5 mL (227 g, 454 g)

Dull-C®: 4 g/teaspoonful

Solution, oral:

Cecon®: 90 mg/mL

Tablet: 100 mg, 250 mg, 500 mg, 1000 mg

Asco-Tabs: 1000 mg [sugar free]

Ascocid®: 500 mg [sugar free]

C-Gram, One Gram C: 1000 mg

Tablet, chewable: 250 mg, 500 mg

Acerola: 500 mg [cherry flavor]

Chew-C: 500 mg [orange flavor]

Mild-C®: 250 mg

Tablet, timed release: 500 mg, 1000 mg

Cemill: 500 mg, 1000 mg

Mild-C®: 1000 mg

Time-C-Bio: 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Vitamin C)

500 mg (100): $12.99

Mechanism of ActionNot fully understood; necessary for collagen formation and tissue repair; involved in some oxidation-reduction reactions as well as other metabolic pathways, such as synthesis of carnitine, steroids, and catecholamines and conversion of folic acid to folinic acid

Pharmacodynamics/Kinetics

Absorption: Oral: Readily absorbed; an active process thought to be dose dependent

Distribution: Large

Metabolism: Hepatic via oxidation and sulfation

Excretion: Urine (with high blood levels)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental Status Rare reports of drowsiness; usually well tolerated

Mental Health: Effects on Psychiatric Treatment May decrease fluphenazine levels; clinical significance unknown but likely not problematic

Cardiovascular Considerations The majority of studies show that supplemental vitamin C (ascorbic acid) has no beneficial effect on reducing cardiovascular risk; routine use in this setting is not recommended. The 2004 ACC/AHA STEMI guidelines do not recommend it.

Index Terms Vitamin C

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Asparaginase

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Asparaginase may be confused with pegaspargase

Elspar® may be confused with Elaprase™

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of classes of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(a SPEAR a ji nase)
U.S. Brand NamesElspar®
Canadian Brand NamesElspar®; Kidrolase®
Pharmacologic Category[Antineoplastic Agent, Miscellaneous]
Use: Labeled IndicationsTreatment of acute lymphocytic leukemia (ALL)
Use: Unlabeled/InvestigationalTreatment of lymphoma
Dosing: AdultsRefer to individual protocols. **Note:** Dose, frequency, number of doses, and start date may vary by protocol and treatment phase.

ALL:

I.V.:

6000 units/m^2/dose 3 times/week for ~6-9 doses **or**

1000 units/kg/day for 10 days **or**

High-dose therapy (unlabeled dose): 10,000 units/m^2/day for ~3-12 doses

Single-agent therapy (rare): 200 units/kg/day for 28 days

I.M.:

6000 units/m^2/dose 3 times/week for ~6-9 doses **or** 6000 units/m^2/dose every ~3 days for ~6-9 doses

High-dose therapy (unlabeled dose): 10,000 units/m^2/day for ~3-12 doses

Test dose: A test dose is often recommended prior to the first dose of asparaginase, or prior to restarting therapy after a hiatus of several days. Most commonly, 0.1 mL of a 20 units/mL (2 units) asparaginase dilution is injected intradermally, and the patient observed for at least 1 hour. False-negative rates of up to 80% to test doses of 2-50 units are reported.

Some practitioners recommend an asparaginase desensitization regimen for patients who react to a test dose, or are being retreated following a break in therapy. Doses are doubled and given every 10 minutes until the total daily dose for that day has been administered. One schedule begins with a total of 1 unit given I.V. and doubles the dose every 10 minutes until the total amount given is the planned dose for that day. For example, if a patient was to receive a total dose of 4000 units, he/she would receive injections 1 through 12 during the desensitization. See table.

Asparaginase Desensitization

Injection No.	Elspar Dose (int. units)	Accumulated Total Dose
1	1	1
2	2	3
3	4	7
4	8	15

5	16	31
6	32	63
7	64	127
8	128	255
9	256	511
10	512	1023
11	1024	2047
12	2048	4095
13	4096	8191
14	8192	16,383
15	16,384	32,767
16	32,768	65,535
17	65,536	131,071
18	131,072	262,143

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols. **Note:** Dose, frequency, number of doses, and start date may vary by protocol and treatment phase.

ALL:

I.V.:

6000 units/m^2/dose 3 times/week for ~6-9 doses **or**

1000 units/kg/day for 10 days **or**

High-dose therapy (unlabeled dose): 10,000 units/m^2/dose every ~3 days for ~4-8 doses

I.M.:

6000 units/m^2/dose 3 times/week **or** 6000 units/m^2/dose every ~3 days for ~6-9 doses

High-dose therapy (unlabeled dose): 10,000 units/m^2/dose every ~3 days for ~4-8 doses **or** 25,000 units/m^2/dose weekly for ~9 doses (generally used in high-risk continuation therapy)

Test dose: Refer to adult dosing.

Dosing: Combination Regimens

Leukemia, acute lymphocytic:

Hyper-CVAD (Leukemia, Acute Lymphocytic)

Larson Regimen

Linker Protocol

PVA (POG 8602)

PVDA

Leukemia, acute myeloid: CA

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.M.Doses should be given as a deep intramuscular injection into a large muscle; volumes >2 mL should be divided and administered in 2 separate sites

Administration: I.V.

Note: I.V. administration greatly increases the risk of allergic reactions and should be avoided if possible.

The following precautions should be taken when administering. Administer in 50-250 mL of D_5W over at least 30-60 minutes. The manufacturer recommends a test dose (0.1 mL of a dilute 20 unit/mL solution) prior to initial administration and when given after an interval of 7 days or more. Institutional policies vary. The skin test site should be observed for at least 1 hour for a wheal or erythema. Note that a negative skin test does not preclude the possibility of an allergic reaction. Desensitization may be performed in patients who have been found to be hypersensitive by the intradermal skin test or who have received previous courses of therapy with the drug. Have epinephrine, diphenhydramine, and hydrocortisone at the bedside. Have a running I.V. in place. A physician should be readily accessible.

Administration: I.V. DetailThe intradermal skin test is commonly given prior to the initial injection, using a dose of 0.1 mL of 20 units/mL solution (~2 units). The skin test site should be observed for at least 1 hour for a wheal or erythema. Do not infuse through filter.

Gelatinous fiber-like particles may develop on standing. Filtration through a 5-micron filter during administration will remove the particles with no loss of potency.

pH: 7.4; 6.5-8 (active enzyme)

Administration: OtherHas been administered SubQ in specific protocols

StorageIntact vials of powder should be refrigerated at 2°C to 8°C (36°F to 48°F). Reconstituted solutions are stable 1 week refrigerated at 8°C (Stecher, 1999), although the manufacturer recommends use within 8 hours. Solutions for I.V. infusion are stable for 8 hours at room temperature or under refrigeration.

ReconstitutionLyophilized powder should be reconstituted with 1-5 mL sterile water for injection or NS for I.V. administration; NS for I.M. use. Shake well, but not too vigorously. A 5 micron filter may be used to remove fiber-like particles in the solution (do not use a 0.2 micron filter; has been associated with loss of potency).

Standard I.M. dilution: 2000, 5000, or 10,000 int. units/mL

Standard I.V. dilution: Dilute in 50-250 mL NS or D_5W

Test dose preparation: Reconstitute a 10,000 unit vial with 5 mL NS or SWFI (concentration = 2000 units/mL); withdraw 0.1 mL and add to 9.9 mL NS (concentration = 20 units/mL); test dose is 0.1 mL (2 units)

CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Methotrexate, sodium bicarbonate

ContraindicationsHistory of serious allergic reaction to asparaginase or any *E. coli*-derived asparaginase; history of serious thrombosis with prior asparaginase treatment; history of pancreatitis with prior asparaginase treatment; serious hemorrhagic events with prior asparaginase treatment

Allergy Considerations

- Asparaginase Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Allergic reactions: Severe allergic reactions may occur; monitor; immediate treatment for hypersensitivity reactions should be available during administration. Risk factors for allergic reactions include: I.V. administration, doses >6000-12,000 units/m^2, patients who have received previous cycles of asparaginase, and intervals of even a few days between doses. Up to 33% of patients who have an allergic reaction to *E. coli* asparaginase will also react to the *Erwinia* form or pegaspargase. A test dose may be administered prior to the first dose of asparaginase, or prior to restarting therapy after a hiatus of several days. **False-negative rates of up to 80% to test doses of 2-50 units are reported.** Desensitization may be performed in patients found to be hypersensitive by the intradermal test dose or who have received previous courses of therapy with the drug.

- Coagulopathy: Increased prothrombin time, partial thromboplastin time, and hypofibrinogenemia may occur; cerebrovascular hemorrhage has been reported; monitor coagulation parameters. Use with caution in patients with an underlying coagulopathy.

- Hyperglycemia: May cause hyperglycemia/glucose intolerance (may be irreversible); monitor blood glucose.

- Pancreatitis: May cause serious and possibly fatal pancreatitis; promptly evaluate patients with abdominal pain; discontinue permanently if pancreatitis develops.

- Thrombotic events: Serious thrombosis, including sagittal sinus thrombosis may occur; discontinue with serious thrombotic events.

- Tumor lysis syndrome: Appropriate measures must be taken to prevent tumor lysis syndrome and subsequent hyperuricemia and uric acid nephropathy; monitor, consider allopurinol, hydration and urinary alkalization.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with pre-existing hepatic impairment; may alter function.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDecreased weight gain, resorptions, gross abnormalities, and skeletal abnormalities were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions**Note:** Immediate effects: Fever, chills, nausea, and vomiting occur in 50% to 60% of patients.

>10%:

Central nervous system: Fatigue, fever, chills, depression, agitation, seizure (10% to 60%), somnolence, stupor, confusion, coma (25%)

Endocrine & metabolic: Hyperglycemia/glucose intolerance (10%)

Gastrointestinal: Nausea, vomiting (50% to 60%), anorexia, abdominal cramps (70%), acute pancreatitis (15%, may be severe in some patients)

Hematologic: Hypofibrinogenemia and depression of clotting factors V and VIII, variable decrease in factors VII and IX, severe protein C deficiency and decrease in antithrombin III (may be dose limiting or fatal)

Hepatic: Transaminases, bilirubin, and alkaline phosphatase increased (transient)

Hypersensitivity: Acute allergic reactions (fever, rash, urticaria, arthralgia, hypotension, angioedema, bronchospasm, respiratory distress, anaphylaxis (15% to 35%); may be dose limiting in some patients, may be fatal)

Renal: Azotemia (66%)

1% to 10%:

Endocrine & metabolic: Hyperuricemia

Gastrointestinal: Stomatitis

Miscellaneous: Allergic reaction (including anaphylaxis), antibody formation/immunogenicity (~25%)

<1%, postmarketing case reports, and/or frequency not defined: Acute renal failure, albumin decreased, cerebrovascular hemorrhage, cerebrovascular thrombosis, cough, disorientation, drowsiness, fatty liver, fibrinogen decreased, glucosuria, hallucinations, headache, hemorrhagic pancreatitis, hyper-/hypolipidemia, hyperthermia, hypocholesterolemia, hypotension, insulin-dependent diabetes, intracranial hemorrhage, irritability, ketoacidosis, laryngospasm, malabsorption syndrome, pancreatic pseudocyst, Parkinsonian symptoms (including tremor and increased muscle tone), partial thromboplastin time increased, peripheral edema, polyuria, proteinuria, prothrombin time increased, pruritus, rash, renal insufficiency, serum ammonia increased, serum cholesterol decreased, sagittal sinus thrombosis, thrombosis, urticaria, venous thrombosis, weight loss; mild-to-moderate myelosuppression, leukopenia, anemia, thrombocytopenia (onset: 7 days, nadir: 14 days, recovery: 21 days)

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Test InteractionsDecreased thyroxine and thyroxine-binding globulin

Monitoring ParametersVital signs during administration; CBC with differential, urinalysis, amylase, liver enzymes, coagulation parameters (baseline and periodic), renal function tests, urine dipstick for glucose, blood glucose, uric acid. Monitor for allergic reaction, be prepared to treat anaphylaxis at each administration; monitor for onset of abdominal pain and mental status changes.

Nursing: Physical Assessment/MonitoringSee information related to skin tests and desensitization. Assess potential for interactions with other pharmacological agents patient may be taking. Assess results of skin tests and regular laboratory tests prior to and frequently during therapy. With each dose, patient should be monitored closely for adverse reactions; acute hypersensitivity reactions (may occur in 10% to 40% of patients and can be fatal), hyperglycemia, CNS changes, or nausea or vomiting. In event of hypersensitivity or hyperglycemia, infusion should be stopped and prescriber notified immediately. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, serum amylase, blood glucose, uric acid, liver function prior to and frequently during therapy

Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. This medication can only be given I.M. or I.V. Report immediately any pain or burning at infusion/injection site, rash, chest pain, respiratory difficulty or chest tightness, difficulty swallowing, or sharp back pain. It is vital to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and good nutritional status (small, frequent meals may help). May cause acute nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help - or consult prescriber for approved antiemetic). Report unusual fever or chills; changes in mentation (confusion, agitation, depression, stupor, seizures); yellowing of skin or eyes; unusual bleeding or bruising; unhealed sores; or vaginal discharge. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Elspar®: 10,000 units

Generic AvailableNo

ManufacturerOvation Pharmaceuticals, Inc

Mechanism of ActionAsparaginase inhibits protein synthesis by hydrolyzing asparagine to aspartic acid and ammonia. Leukemia cells, especially lymphoblasts, require exogenous asparagine; normal cells can synthesize asparagine. Asparaginase is cycle-specific for the G_1 phase.

Pharmacodynamics/Kinetics

Absorption: I.M.: Produces peak blood levels 50% lower than those from I.V. administration

Distribution: V_d: 4-5 L/kg; 70% to 80% of plasma volume; <1% CSF penetration

Metabolism: Systemically degraded

Half-life elimination: I.M.: 39-49 hours; I.V.: 8-30 hours

Time to peak, plasma: I.M.: 14-24 hours

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsSome institutions recommended the following precautions for asparaginase administration: Parenteral epinephrine, diphenhydramine, and hydrocortisone available at bedside; freely running I.V. in place; physician readily accessible; monitor the patient closely for 30-60 minutes; avoid administering at night.

The *E. coli* and the *Erwinia* strains of asparaginase differ slightly in their gene sequencing, and have slight differences in their enzyme characteristics. Both are highly specific for asparagine and have <10% activity for the D-isomer. The *E. coli* form is more commonly used. The *Erwinia* variety is no longer commercially available in the U.S., although may be obtained through clinical trials or on a compassionate use basis.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusRare reports of depression, disorientation, and hallucinations

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine

Index Terms*E. coli* Asparaginase; *Erwinia* Asparaginase; L-asparaginase; NSC-106977 (*Erwinia*); NSC-109229 (*E. coli*)

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International Brand NamesAsparaginase medac (PL); Crasnitin (AT, CH, HN, PT); Elspar (BR, MX); Erwinase (DE, DK, FI, GB, NL, NO, NZ, SE); Kidrolase (AR, BG, CZ, EG, FR, IL, PE, PL, UY); Laspar (ZA); Leunase (AU, BD, CL, HK, ID, IN, JP, KP, MY, PH, PK, SG, TH, TW); Oncaspar (DE); Paronal (BE)

Aspirin and Diphenhydramine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation

(AS pir in & dye fen HYE dra meen)

U.S. Brand NamesAlka-Seltzer® P.M. [OTC]; Bayer® PM [OTC]
Pharmacologic CategoryAnalgesic, Miscellaneous
Use: Labeled IndicationsAid in the relief of insomnia accompanied by minor pain or headache
Dosing: Adults

Pain-associated insomnia: Oral: Two tablets (650 mg aspirin/76 mg diphenhydramine citrate) **or** 2 caplets (1000 mg aspirin/76 mg diphenhydramine citrate) at bedtime or as directed by physician; do not exceed recommended dosage

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Children ≥12 years: Refer to adult dosing.

Administration: Oral

Alka-Seltzer® PM: Dissolve tablets in 4 ounces of water before taking.

Bayer® PM: Administer each dose with a full glass of water.

Dietary ConsiderationsAlka-Seltzer® PM contains phenylalanine 4 mg per tablet and sodium 504 mg per tablet.
Contraindications

Hypersensitivity to aspirin, other pain relievers or fever reducers; other products containing diphenhydramine (including topical); use in children <12 years of age; pregnancy (third trimester)

Warnings/Precautions

Concerns related to adverse effects:

- Salicylate sensitivity: Patients with nasal polyps, asthma, and sensitivity to tartrazine dyes may have an increased risk of salicylate sensitivity.

Special populations:

- Pediatrics: When used for self-medication (OTC labeling): Children and teenagers who have or are recovering from chickenpox or flu-like symptoms should not use this product. Changes in behavior (along with nausea and vomiting) may be an early sign of Reye's syndrome; patients should be instructed to contact their healthcare provider if these occur.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Other warnings/precautions:

- Self-medication (OTC use): Prior to self-medication, patients should contact healthcare provider if they have had recurring stomach pain or upset, ulcers, bleeding problems, asthma, emphysema, chronic bronchitis, glaucoma, enlarged prostate, other serious medical problems, on a sodium-restricted diet, are currently taking an anticoagulant or sedative, or medicine for arthritis, diabetes, or gout. Recommended dosages should not be exceeded, due to an increased risk of GI bleeding. Stop use and consult a healthcare provider if symptoms get worse; if an allergic reaction occurs; if ringing in the ears or hearing loss occurs; if sleeplessness lasts for >2 weeks or if pain lasts >10 days. Consuming ≥3 alcoholic beverages/day or taking longer than recommended may increase the risk of GI bleeding.

Pregnancy ConsiderationsSee individual agents.
LactationSee individual agents.
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsSee individual agents.
Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central).

Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol Avoid ethanol (may enhance gastric mucosal damage).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet:

Bayer® PM: Aspirin 500 mg and diphenhydramine citrate 38.3 mg

Tablet, effervescent:

Alka-Seltzer® PM: Aspirin 325 mg and diphenhydramine citrate 38 mg [contains phenylalanine 4 mg/tablet and sodium 504 mg/tablet]

Generic AvailableNo

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Aspirin
- DiphenhydrAMINE

Pharmacotherapy PearlsDiphenhydramine hydrochloride 50 mg = Diphenhydramine citrate 76 mg

Mental Health: Effects on Mental StatusMay cause confusion, dizziness, drowsiness, euphoria, excitation, fatigue, insomnia, irritability, nervousness, paradoxical excitement, and restlessness

Mental Health: Effects on Psychiatric TreatmentMay cause drowsiness and anticholinergic effects; concomitant use with psychotropic agents may produce additive effects. The anticholinergic effects of diphenhydramine may mitigate beneficial effects of acetylcholinesterase inhibitors. May cause leukopenia; use caution with clozapine and carbamazepine. Aspirin may displace valproic acid from binding sites resulting in an increase of unbound drug; monitor for toxicity. Diphenhydramine may diminish the therapeutic effect of tramadol via inhibition of CYP2D6 preventing the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects.

Index TermsASA and Diphenhydramine; Aspirin and Diphenhydramine Citrate; Diphenhydramine and ASA; Diphenhydramine and Aspirin; Diphenhydramine Citrate and Aspirin

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Aspirin and Dipyridamole

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Aggrenox® may be confused with Aggrastat®

Pronunciation(AS pir in & dye peer ID a mole)

U.S. Brand NamesAggrenox®

Canadian Brand NamesAggrenox®

Pharmacologic CategoryAntiplatelet Agent

Use: Labeled IndicationsReduction in the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis

Dosing: AdultsStroke prevention: Oral: 1 capsule (200 mg dipyridamole, 25 mg aspirin) twice daily

Alternative regimen for patients with intolerable headache: 1 capsule at bedtime and low-dose aspirin in the morning. Return to usual dose (1 capsule twice daily) as soon as tolerance to headache develops (usually within a week).

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentAvoid use in patients with severe renal dysfunction (Cl_{cr} <10 mL/minute).

Dosing: Hepatic ImpairmentAvoid use in patients with severe hepatic impairment.

Calculations

- Creatinine Clearance: Adults

Administration: OralCapsule should be swallowed whole; do not crush or chew. May be given with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from excessive moisture.

ContraindicationsHypersensitivity to dipyridamole, aspirin, or any component of the formulation; allergy to NSAIDs; patients with asthma, rhinitis, and nasal polyps; bleeding disorders (factor VII or IX deficiencies); children <16 years of age with viral infections; pregnancy (aspirin)

Allergy Considerations

- Salicylate Allergy/Sensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: Watch for signs and symptoms of GI ulcers and bleeding.
- Salicylate sensitivity: Patients with sensitivity to tartrazine dyes, nasal polyps, and asthma may have an increased risk of salicylate sensitivity.
- Tinnitus: Discontinue use if tinnitus or impaired hearing occurs.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with hypotension, unstable angina, and/or recent MI.
- Bleeding disorders: Use with caution in patients with platelet and bleeding disorders.
- Gastrointestinal disease: Use with caution in patients with erosive gastritis or peptic ulcer disease.
- Ethanol use: Heavy ethanol use (>3 drinks/day) can increase bleeding risks.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Myocardial prophylaxis use: Dose of aspirin in this combination is inadequate to prevent MI.
- Renal impairment: Use with caution in patients with renal impairment; avoid use in severe impairment.

Special populations:

- Elderly: Use with caution in the elderly who are at high risk for adverse events.
- Pediatrics: Safety and efficacy have not been established in children.
- Surgical patients: ASA should be avoided (if possible) in surgical patients for 1-2 weeks prior to surgery, to reduce the risk of excessive bleeding.

Geriatric ConsiderationsPlasma concentrations were 40% higher, but specific dosage adjustments have not been recommended. Some evidence suggests that the doses of dipyridamole commonly used are ineffective for prevention of platelet aggregation, however, the addition of aspirin will add substantial efficacy. The dose of aspirin is effective for platelet inhibition, but low enough to offer a low adverse drug reaction rate.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal reproduction studies have shown an increase in aspirin-related fetal toxicity with this combination. Use during pregnancy is not recommended; should not be used in the 3rd trimester of pregnancy. Maternal aspirin use during later pregnancy may result in low infant birth weight, stillbirth, neonatal death, and an increased incidence of intracranial hemorrhage in premature infants.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsBoth aspirin and dipyridamole are excreted in breast milk.

Adverse Reactions

>10%:

Central nervous system: Headache (38%; tolerance usually develops)

Gastrointestinal: Dyspepsia, abdominal pain (18%), nausea (16%), diarrhea (13%)

1% to 10%:

Cardiovascular: Cardiac failure (2%), syncope (1%)

Central nervous system: Fatigue (6%), pain (6%), amnesia (2%), malaise (2%), seizure (2%), confusion (1%), somnolence (1%)

Dermatologic: Purpura (1%)

Gastrointestinal: Vomiting (8%), bleeding (4%), rectal bleeding (2%), hemorrhoids (1%), hemorrhage (1%), anorexia (1%)

Hematologic: Anemia (2%)

Neuromuscular & skeletal: Arthralgia (6%), back pain (5%), weakness (2%), arthritis (2%), arthrosis (1%), myalgia (1%)

Respiratory: Cough (2%), epistaxis (2%) , upper respiratory tract infection (1%)

<1% (Limited to important or life-threatening): Agitation, allergic reaction, allergic vasculitis, alopecia, anaphylaxis, anemia (aplastic), angina pectoris, angioedema, antepartum and postpartum bleeding, arrhythmia, asthma, bronchospasm, bruising, cerebral edema, cerebral hemorrhage, chest pain, cholelithiasis, coagulopathy, coma, deafness, dehydration, disseminated intravascular coagulation (DIC), dizziness, dyspnea, ecchymosis, fever, flushing, gastritis, gingival bleeding, hearing impairment, hematemesis, hematoma, hematuria, hemoptysis, hepatic function abnormality, hepatic failure, hepatitis, hyper-/hypoglycemia, hyperpnea, hypotension, hypothermia, interstitial nephritis, intracranial hemorrhage (0.6%), jaundice, laryngeal edema, lower weight infants, palpitation, pancreatitis, pancytopenia, papillary necrosis, paresthesia, perforation, pregnancy and labor prolonged, PT time prolonged, proteinuria, pruritus, pulmonary edema, rash, renal insufficiency and failure, Reye's syndrome, rhabdomyolysis, Stevens-Johnson syndrome, stillbirths, subarachnoid hemorrhage, supraventricular tachycardia, tachycardia, tachypnea, taste loss, thirst, thrombocytopenia, thrombocytosis, tinnitus, ulceration, urticaria, uterine hemorrhage

Metabolism/Transport EffectsAspirin: **Substrate** of CYP2C9 (minor)

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Adenosine: Dipyridamole may enhance the therapeutic effect of Adenosine. Dose reduction of adenosine may be needed. *Risk D: Consider therapy modification*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Beta-Blockers: Dipyridamole may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Regadenoson: Dipyridamole may enhance the therapeutic effect of Regadenoson. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Topotecan: BCRP/ABCG2 Inhibitors may increase the serum concentration of Topotecan. *Risk D: Consider therapy modification*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy*

modification

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to GI irritation).
Monitoring ParametersHemoglobin, hematocrit, signs or symptoms of bleeding, signs or symptoms of stroke or transient ischemic attack
Nursing: Physical Assessment/MonitoringSee individual agents.
Monitoring: Lab TestsHemoglobin, hematocrit
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, variable release:

Aggrenox®: Aspirin 25 mg (immediate release) and dipyridamole 200 mg (extended release)

Generic AvailableNo
ManufacturerBoehringer Ingelheim, Corp
Pricing: U.S. (www.drugstore.com)

Capsule, 12-hour (Aggrenox)

25-200 mg (60): $161.99

Mechanism of ActionThe antithrombotic action results from additive antiplatelet effects. Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells, and erythrocytes. Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclooxygenase and thus inhibits the generation of thromboxane A_2.
Pharmacodynamics/KineticsSee individual agents.
Related Information

- Aspirin
- Dipyridamole

Dental Health Professional ConsiderationsThere is no scientific evidence to warrant discontinuance of aspirin prior to dental surgery. Patients taking one aspirin tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with the physician before removal of the aspirin relative to prevention of postoperative bleeding.

The Food and Drug Administration (FDA), has issued a letter updating information and considerations regarding the use of ibuprofen (400 mg doses) in patients who are taking low dose aspirin (81 mg, immediate release; not enteric coated) for cardioprotection and stroke prevention. Ibuprofen, at these doses, may interfere with aspirin's antiplatelet effect depending upon when it is administered. Patients initiated on aspirin first (for ~1 week) then ibuprofen (400 mg 3 times/day for 10 days) seem to maintain aspirin's platelet effect (Cryer B, 2005). Ibuprofen has the greatest impact on aspirin if administered less than 8 hours before aspirin (Catella-Lawson F, 2001).

Patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. With occasional use of ibuprofen, a clinically-significant interaction with aspirin in unlikely. To avoid interference during chronic dosing, a single dose of ibuprofen should be taken 30-120 minutes after aspirin ingestion or at least 8 hours should elapse after ibuprofen dosing before giving aspirin (FDA, 2006; Catella-Lawson F, 2001).

The clinical implications of the interaction are unclear. There have not been any clinical endpoint studies conducted at this time. Avoidance of this interaction is potentially important because aspirin's vascular protection could be decreased or negated.

Other nonselective NSAIDs may have potential for a similar interaction with aspirin. Such has been described with naproxen (Capone ML, 2005). Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin. Other clinical scenarios (use of smaller ibuprofen doses, other aspirin products, other doses of aspirin) have not been evaluated.

Additional information is available at: http://www.fda.gov/cder/drug/infopage/aspirin/default.htm

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity (see Dental Comment).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause amnesia, fatigue, and confusion
Mental Health: Effects on Psychiatric TreatmentEffect of antidepressants may be blunted due to sedation and fatigue; rare reports of pancytopenia; use caution with clozapine and carbamazepine
Index TermsAspirin and Extended-Release Dipyridamole; Dipyridamole and Aspirin
References

Capone ML, Sciulli MG, Tacconelli S, et al, "Pharmacodynamic Interaction of Naproxen With Low-Dose Aspirin in Healthy Subjects," *J Am Coll Cardiol*, 2005, 45(8):1295-1301.[PubMed 15837265]

Catella-Lawson F, Reilly MP, Kapoor SC, et al, "Cyclooxygenase Inhibitors and the Antiplatelet Effects of Aspirin," *N Engl J Med*, 2001, 345(25):1809-17.[PubMed 11752357]

Cryer B, Verlin RG, Cooper SA, et al, "Double-Blind, Randomized, Parallel, Placebo-Controlled Study of Ibuprofen Effects on Thromboxane B2 Concentrations in Aspirin-Treated Healthy Adult Volunteers," *Clin Ther*, 2005, 27(2):185-191.[PubMed 15811481]

International Brand NamesAggrenox (BE, HK, ID, PH, TH, TW); Asasantin (DE); Asasantin Retard (CH, DK, FI, GB, IE, NO, SE); Asasantin SR (AU); Asasantine LP (FR)

Aspirin and Pravastatin

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English

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Special Alerts

HMG-CoA Reductase Inhibitors: Evidence Does Not Suggest Increased Incidence of Amyotrophic Lateral Sclerosis (ALS) - Results of FDA Analysis - September 30, 2008

The U.S. Food and Drug Administration’s (FDA) review of 41 long-term controlled clinical trials of HMG-CoA reductase inhibitors finds no evidence of an increased incidence of ALS (also known as Lou Gehrig’s disease) related to these medications. This analysis occurred after the FDA had received notice of numerous adverse events of which 109 of these reports mentioned ALS, Lou Gehrig’s disease, or motor neurone disease. The clinical trials included in the analysis had a median duration of treatment of 3.3 years (range of duration: 6 months to 5 years) and involved 120,964 patients. The analysis identified a total of 19 cases of ALS – 9 cases per 64,602 patients (0.014%) with statin therapy and 10 cases per 56,362 patients (0.017%) with placebo. The incidence rates, based on approximately 400,000 person-years, were 4.2 per 100,000 person-years in the statin-treated group and 5 per 100,000 person-years in the placebo-treated group.

The FDA recommends that health care providers continue to prescribe, and patients continue to use these products as described within their labeling.

For more information, healthcare professionals may refer to the following:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Statin

Colman E, Szarfman A, Wyeth J, et al, “An Evaluation of a Data Mining Signal for Amyotrophic Lateral Sclerosis and Statins Detected in FDA’s Spontaneous Adverse Event Reporting System,” *Pharmacoepidemiol Drug Saf*, 2008 (epub ahead of print)

Pronunciation(AS pir in & PRA va stat in)

U.S. Brand NamesPravigard™ PAC [DSC]

Canadian Brand NamesPravASA

Pharmacologic CategoryAntilipemic Agent, HMG-CoA Reductase Inhibitor; Salicylate

Use: Labeled IndicationsCombination therapy in patients who need treatment with aspirin and pravastatin to reduce the incidence of cardiovascular events, including myocardial infarction, stroke, and death

Dosing: Adults

Reduction in cardiac events: Initial: Oral: Pravastatin 40 mg with aspirin (either 81 mg or 325 mg); both medications taken once daily. If pravastatin 40 mg does not achieve the desired cholesterol result, dosage may be increased to 80 mg once daily with aspirin (either 81 mg or 325 mg) once daily. Some patients may achieve/maintain goal cholesterol levels at a pravastatin dosage of 20 mg.

See Pravastatin for dosing in renal or hepatic impairment, as well as, dosing with concurrent cyclosporine therapy.

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsMay be taken with or without food. Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.

StorageStore at 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to pravastatin, aspirin, salicylates, or other NSAIDs, or any component of the formulation; syndrome of asthma, rhinitis, and nasal polyps; inherited or acquired bleeding disorders (including factor VII and factor IX deficiency); active liver disease; unexplained persistent elevations of serum transaminases; pregnancy; breast-feeding

Allergy Considerations

- HMG-CoA Reductase Inhibitor Allergy
- Salicylate Allergy/Sensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Myopathy/rhabdomyolysis: Patients receiving HMG-CoA reductase inhibitors have developed rhabdomyolysis with acute renal failure and/or myopathy; patients should be monitored closely. This risk is dose-related and is increased with concurrent use of other lipid lowering medications. Temporarily discontinue for elective major surgery, acute medical or surgical conditions, or in any patient experiencing an acute or serious condition predisposing to renal failure (eg, sepsis, hypotension, trauma, uncontrolled seizures). Based upon current evidence, HMG-CoA reductase inhibitor therapy should be continued in the perioperative period unless risk outweighs cardioprotective benefit. Use caution in patients with renal impairment, inadequately treated hypothyroidism, and those taking other drugs associated with myopathy (eg, colchicine); these patients are predisposed to myopathy. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine.

- Salicylate sensitivity: Patients with sensitivity to tartrazine dyes, nasal polyps, and asthma may have an increased risk of salicylate sensitivity.

- Tinnitus: Discontinue use if tinnitus or impaired hearing occurs.

Disease-related concerns:

- Bleeding disorders: Use aspirin with caution in patients with platelet and bleeding disorders.
- Dehydration: Use aspirin with caution in patients with dehydration.
- Gastrointestinal disease: Use aspirin with caution in patients with erosive gastritis or peptic ulcer disease.
- Hepatic impairment and/or ethanol use: Use with caution in patients who consume large amounts of ethanol or have a history of liver disease.
- Renal impairment: Use aspirin with caution in patients with mild-to-moderate renal impairment (only at high dosages); avoid in severe impairment.

Special populations:

- Pediatrics: Combination product is not appropriate for use in children.
- Surgical patients: Should avoid ASA if possible in surgical patients, for 1-2 weeks prior to surgery, to reduce the risk of excessive bleeding.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.
- Liver function tests: Must be monitored by periodic laboratory assessment.

Pregnancy Risk FactorX
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/contraindicated
Adverse ReactionsClinical studies of this combination product have not been conducted. See individual agents.
Metabolism/Transport Effects

Aspirin: **Substrate** of CYP2C9 (minor)

Pravastatin: **Substrate** of CYP3A4 (minor); **Inhibits** CYP2C9 (weak), 2D6 (weak), 3A4 (weak)

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Colchicine: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

CycloSPORINE: May increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

DAPTOmycin: HMG-CoA Reductase Inhibitors may enhance the adverse/toxic effect of DAPTOmycin. Specifically, the risk of skeletal muscle toxicity may be increased. Management: Consider temporarily stopping HMG-CoA reductase inhibitor therapy prior to daptomycin. If used together, regular (i.e., at least weekly) monitoring of CPK concentrations is recommended. *Risk D: Consider therapy modification*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Fenofibrate: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Gemfibrozil: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Gemfibrozil may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Niacin: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Niacinamide: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): HMG-CoA Reductase Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsSee individual agents.

Monitoring ParametersPravastatin: Obtain baseline LFTs and total cholesterol profile; creatine phosphokinase. Repeat LFTs prior to elevation of dose. May be measured when clinically indicated and/or periodically thereafter.

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsPravastatin: Obtain baseline LFTs and total cholesterol profile; creatine phosphokinase. Repeat LFTs prior to elevation of dose. May be measured when clinically indicated and/or periodically thereafter.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Combination package (Pravigard™ PAC) [each administration card contains] [DSC]:

81/20:

Tablet: Aspirin, buffered 81 mg (5/card) [contains calcium carbonate, and magnesium oxide, and magnesium carbonate]

Tablet (Pravachol®): Pravastatin sodium 20 mg (5/card) [contains lactose]

81/40:

Tablet: Aspirin, buffered 81 mg (5/card) [contains calcium carbonate, and magnesium oxide, and magnesium carbonate]

Tablet (Pravachol®): Pravastatin sodium 40 mg (5/card) [contains lactose]

81/80:

Tablet: Aspirin, buffered 81 mg (5/card) [contains calcium carbonate, and magnesium oxide, and magnesium carbonate]

Tablet (Pravachol®): Pravastatin sodium 80 mg (5/card) [contains lactose]

325/20:

Tablet: Aspirin, buffered 325 mg (5/card) [contains calcium carbonate, and magnesium oxide, and magnesium carbonate]

Tablet (Pravachol®): Pravastatin sodium 20 mg (5/card) [contains lactose]

325/40:

Tablet: Aspirin, buffered 325 mg (5/card) [contains calcium carbonate, and magnesium oxide, and magnesium carbonate]

Tablet (Pravachol®): Pravastatin sodium 40 mg (5/card) [contains lactose]

325/80:

Tablet: Aspirin, buffered 325 mg (5/card) [contains calcium carbonate, and magnesium oxide, and magnesium carbonate]

Tablet (Pravachol®): Pravastatin sodium 80 mg (5/card) [contains lactose]

Generic AvailableNo

ManufacturerBristol-Myers Squibb

Pricing: U.S. (www.drugstore.com)

Misc (Pravigard Pac)

81-40 mg (30): $146.16

Mechanism of Action

Aspirin: Inhibits prostaglandin synthesis, acts on the hypothalamus heat-regulating center to reduce fever, blocks prostaglandin synthetase action which prevents formation of the platelet-aggregating substance thromboxane A_2

Pravastatin: Competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the rate-limiting enzyme involved in *de novo* cholesterol synthesis.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Aspirin
- Pravastatin

Dental Health Professional ConsiderationsThere is no scientific evidence to warrant discontinuance of aspirin prior to dental surgery. Patients taking one aspirin tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with the physician before removal of the aspirin relative to prevention of postoperative bleeding.

The Food and Drug Administration (FDA), has issued a letter updating information and considerations regarding the use of ibuprofen (400 mg doses) in patients who are taking low dose aspirin (81 mg, immediate release; not enteric coated) for cardioprotection and stroke prevention. Ibuprofen, at these doses, may interfere with aspirin's antiplatelet effect depending upon when it is administered. Patients initiated on aspirin first (for ~1 week) then ibuprofen (400 mg 3 times/day for 10 days) seem to maintain aspirin's platelet effect (Cryer B, 2005). Ibuprofen has the greatest impact on aspirin if administered less than 8 hours before aspirin (Catella-Lawson F, 2001).

Patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. With occasional use of ibuprofen, a clinically-significant interaction with aspirin in unlikely. To avoid interference during chronic dosing, a single dose of ibuprofen should be taken 30-120 minutes after aspirin ingestion or at least 8 hours should elapse after ibuprofen dosing before giving aspirin (FDA, 2006; Catella-Lawson F, 2001).

The clinical implications of the interaction are unclear. There have not been any clinical endpoint studies conducted at this time. Avoidance of this interaction is potentially important because aspirin's vascular protection could be decreased or negated.

Other nonselective NSAIDs may have potential for a similar interaction with aspirin. Such has been described with naproxen (Capone ML, 2005). Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin. Other clinical scenarios (use of smaller ibuprofen doses, other aspirin products, other doses of aspirin) have not been evaluated.

Additional information is available at: http://www.fda.gov/cder/drug/infopage/aspirin/default.htm

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Aspirin: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity (see Dental Comment).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness

Mental Health: Effects on Psychiatric TreatmentAspirin may cause leukopenia; use caution with clozapine and carbamazepine; may also displace valproic acid from binding sites resulting in an increase of unbound drug; monitor for toxicity.

Cardiovascular ConsiderationsHMG-CoA reductase inhibitors are effective in primary and secondary prevention of cardiovascular events in patients with hyperlipidemia. For primary prevention, a patient's major risk factors (cigarette smoking, hypertension or currently taking antihypertensives, low HDL-C, family history, age, gender) should be evaluated. Patients with multiple risk factors (≥2) require more intensive therapy guided by the calculation of a 10-year absolute CHD risk (eg, the percent probability of having a CHD event in next 10 years). An individual's 10-year absolute CHD risk can be calculated at www.med-decisions.com/cvtool/phys/phys.html. LDL cholesterol goals, therapeutic lifestyle changes, and drug therapy are determined based upon a patient's risk factor profile.

Primary prevention trials show that cholesterol-lowering drugs reduce the risk of major coronary events, coronary death, and cerebrovascular events even in the first 6-12 months of use. The WOSCOP trial suggested a trend towards enhanced survival using pravastatin in their patients (mean LDL-cholesterol of 192 mg/dL and no history of MI). In a recent trial (Sever, 2003), patients with HTN and at least three other risk factors were randomized to 10 mg daily of atorvastatin or placebo. These patients had a total nonfasting cholesterol <250 mg/dL before treatment. LDL-C levels were 132 mg/dL before treatment and fell to an average of 90 mg/dL in the atorvastatin-treated group. There was a significant reduction in stroke, cardiovascular events, and coronary events in the atorvastatin-treated group as compared to the placebo group. There was no difference in mortality between the groups.

Secondary prevention trials indicate that "statin" therapy reduces mortality, major coronary events, coronary artery procedures, and stroke. The Heart Protection Study proved that lowering serum cholesterol levels reduces the rate of major vascular events among high-risk individuals with documented vascular disease (CHD, cerebrovascular, peripheral vascular) or diabetes regardless of initial cholesterol concentrations. PROVE IT is a randomized, double-blind trial evaluating hospitalized patients with acute coronary syndrome to determine the effects of intense LDL-C lowering therapy. Four thousand patients with an LDL-C levels of 106 mg/dL were randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily. After 2 years, the combined cardiovascular endpoint (death, MI, unstable angina requiring hospitalization, revascularization and stroke) was ~26% in the pravastatin patients (median LDL-C 95 mg/dL) and ~22% in the atorvastatin treated patients (median LDL-C 62 mg/dL).

LaRosa and colleagues assessed the efficacy and safety of lowering LDL cholesterol <100 mg/dL in patients with stable coronary heart disease (LaRosa, 2005). Ten thousand and one patients with baseline LDL levels <130 mg/dL were randomized to atorvastatin 10 mg or 80 mg daily and followed for a median of 4.9 years. The primary endpoint was the occurrence of the first major cardiovascular event (death from CVD, MI, resuscitation after cardiac arrest, or stroke). A primary event occurred in 434 patients (8.7%) receiving 80 mg daily (mean LDL 77 mg/dL) and 548 patients (10.9%) receiving 10 mg dose (mean LDL 101 mg/dL) (95% CI, 0.69-0.89; p <0.001). There was no mortality difference between the two treatment groups.

HMG-CoA reductase inhibitors decrease levels of high-sensitivity C-reactive protein (hs-CRP). They also possess pleiotropic properties including improved endothelial function, reduced inflammation at the site of the coronary plaque, inhibition of platelet aggregation, and anticoagulant effects. These nonlipid effects may be beneficial when HMG-CoA reductase inhibitors are introduced early in the management of acute coronary syndromes (de Denus, 2002).

Myopathy: Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years of age), women more frequently than men, small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, drug interactions (use with caution or avoid). The combination of a HMG-CoA reductase inhibitor plus nicotinic acid seems to carry a lower risk of myopathy than does a HMG-CoA reductase inhibitor plus a fibrate. Other medications, when used concurrently, may enhance the risk of myopathy associated with statins; these include drugs that inhibit CYP3A4 isoenzymes (lovastatin, simvastatin, atorvastatin) or CYP2C9 isoenzymes (fluvastatin). HMG-CoA reductase inhibitors may exacerbate exercise-induced skeletal muscle injury. Many experts favor getting a baseline creatine kinase (CK) measurement before initiating therapy (asymptomatic CK elevations are common). Obtain a CK measurement if patient complains of muscle soreness, tenderness, or pain.

Anesthesia and Critical Care Concerns/Other ConsiderationsBased on the pravastatin component: **Myopathy:** Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years), gender (occurs in women more frequently than men), small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, and drug interactions (use with caution or avoid).

Based on current research, HMG-CoA reductase inhibitors should be continued in the perioperative period. Postoperative discontinuation of statin therapy is associated with an increased risk of cardiac morbidity and mortality.

Index Terms Buffered Aspirin and Pravastatin Sodium; Pravastatin and Aspirin

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International Brand Names PravASA (CA)

Aspirin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Aspirin may be confused with Afrin®, Asendin®

Ascriptin® may be confused with Aricept®

Ecotrin® may be confused with Akineton®, Edecrin®, Epogen®

Halfprin® may be confused with Halfan®, Haltran®

ZORprin® may be confused with Zyloprim®

International issues:

Cartia® [multiple international markets] may be confused with Cartia XT™ which is a brand name for diltiazem in the U.S.

Pronunciation(AS pir in)

U.S. Brand NamesAscriptin® Maximum Strength [OTC]; Ascriptin® [OTC]; Aspercin [OTC]; Aspergum® [OTC]; Aspirtab [OTC]; Bayer® Aspirin Extra Strength [OTC]; Bayer® Aspirin Regimen Adult Low Dose [OTC]; Bayer® Aspirin Regimen Children's [OTC]; Bayer® Aspirin Regimen Regular Strength [OTC]; Bayer® Genuine Aspirin [OTC]; Bayer® Plus Extra Strength [OTC]; Bayer® with Heart Advantage [OTC]; Bayer® Women's Aspirin Plus Calcium [OTC]; Buffasal [OTC]; Bufferin® Extra Strength [OTC]; Bufferin® [OTC]; Buffinol [OTC]; Easprin®; Ecotrin® Low Strength [OTC]; Ecotrin® Maximum Strength [OTC]; Ecotrin® [OTC]; Genacote™ [OTC]; Halfprin® [OTC]; St. Joseph® Adult Aspirin [OTC]; ZORprin®

Canadian Brand NamesAsaphen; Asaphen E.C.; Entrophen®; Novasen

Pharmacologic CategorySalicylate

Use: Labeled IndicationsTreatment of mild-to-moderate pain, inflammation, and fever; may be used as prophylaxis of myocardial infarction; prophylaxis of stroke and/or transient ischemic episodes; management of rheumatoid arthritis, rheumatic fever, osteoarthritis, and gout (high dose); adjunctive therapy in revascularization procedures (coronary artery bypass graft [CABG], percutaneous transluminal coronary angioplasty [PTCA], carotid endarterectomy), stent implantation

Use: Unlabeled/InvestigationalLow doses have been used in the prevention of pre-eclampsia, complications associated with autoimmune disorders such as lupus or antiphospholipid syndrome

Use: DentalTreatment of postoperative pain

Dosing: Adults

Acute ischemic stroke: Oral: 150-325 mg once daily, initiated within 48 hours (in patients who are not candidates for alteplase and not receiving systemic anticoagulation)

Analgesic and antipyretic:

Oral: 325-650 mg every 4-6 hours up to 4 g/day

Rectal: 300-600 mg every 4-6 hours up to 4 g/day

Anti-inflammatory: Oral: Initial: 2.4-3.6 g/day in divided doses; usual maintenance: 3.6-5.4 g/day; monitor serum concentrations

Atrial fibrillation (in patients not candidates for warfarin or at low risk of ischemic stroke): Oral: 75-325 mg once daily

Bioprosthetic aortic valve: Oral: 50-100 mg once daily; usual dose: 81 mg once daily

Bioprosthetic mitral valve (following 3 months of anticoagulation): Oral: 50-100 mg once daily; usual dose: 81 mg once daily

CABG: Oral: 75-100 mg once daily (usual dose: 81 mg) initiated 6 hours following surgery; if bleeding prevents administration at 6 hours after CABG, initiate as soon as possible

CABG (internal mammary bypass graft): Oral: 75-162 mg once daily

Carotid artery stenting: Oral: 81-325 mg once daily beginning at least 24 hours (preferably 4 days) prior to procedure with concomitant clopidogrel

Carotid endarterectomy: Oral: 50-100 mg once daily preoperatively and daily thereafter; usual dose: 81 mg once daily

Infrainguinal arterial reconstruction/bypass: Oral: 75-100 mg once daily (begin preoperatively); usual dose: 81 mg once daily

Mechanical heart valve (with additional risk factors for thromboembolism): Oral: 50-100 mg once daily (in addition to warfarin); usual dose: 81 mg once daily

Mitral annular calcification (with documented stroke, TIA, or systemic embolism): Oral: 50-100 mg once daily; usual dose: 81 mg once daily

Mitral valve prolapse (with documented stroke or TIA): Oral: 50-100 mg once daily; usual dose: 81 mg once daily

Myocardial infarction (primary prevention): Oral: 75-162 mg once daily (Antman, 2004) **or** 75-100 mg (usual dose: 81 mg) once daily (Hirsh, 2008)

Non-ST-segment elevation myocardial infarction (NSTEMI): Oral: Initial: 162-325 mg; Maintenance: 75-100 mg once daily indefinitely; usual maintenance dose: 81 mg once daily

PCI: Oral: Initial: 75-325 mg (300-325 mg in aspirin native patients) starting at least 2 hours (preferably 24 hours) before procedure; post procedure: 162-325 mg once daily (dose and duration varies with type of stent implanted); **Note:** Dose may be reduced to 75-162 mg once daily after appropriate duration based on stent-type is complete

Pericarditis associated with myocardial infarction: Oral: 162-325 mg once daily; doses as high as 650 mg every 4-6 hours may be required

Peripheral arterial disease: 75-100 mg once daily; usual dose: 81 mg once daily

Pre-eclampsia prevention (unlabeled use): 60-81 mg once daily (usual dose: 81 mg) during gestational weeks 13-26 (patient selection criteria not established)

Prosthetic valve thromboprophylaxis in pregnancy: 75-100 mg once daily; usual dose: 81 mg once daily

ST-segment elevation myocardial infarction (STEMI): Initial: 162-325 mg given on presentation (patient should chew nonenteric-coated aspirin especially if not taking before presentation); for patients unable to take oral, may use rectal suppository (300 mg). Maintenance (secondary prevention): 75-162 mg once daily indefinitely

Stroke (cardioembolic; anticoagulation contraindicated): Oral: 75-325 mg once daily

Stroke/TIA (noncardioembolic; secondary prevention): Oral: 50-325 mg once daily (Adams, 2008) **or** 50-100 mg once daily; usual dose: 81 mg once daily (Hirsh, 2008)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Analgesic and antipyretic: Oral, rectal: 10-15 mg/kg/dose every 4-6 hours, up to a total of 4 g/day

Anti-inflammatory: Oral: Initial: 60-90 mg/kg/day in divided doses; usual maintenance: 80-100 mg/kg/day divided every 6-8 hours; monitor serum concentrations

Antiplatelet effects: Oral: Adequate pediatric studies have not been performed; pediatric dosage is derived from adult studies and clinical experience and is not well established; suggested doses have ranged from 3-5 mg/kg/day to 5-10 mg/kg/day given as a single daily dose. Doses are rounded to a convenient amount (eg, $^{1}/_{2}$ of 81 mg tablet).

Mechanical prosthetic heart valves: Oral: 6-20 mg/kg/day given as a single daily dose (used in combination with an oral anticoagulant in children who have systemic embolism despite adequate oral anticoagulation therapy (INR 2.5-3.5) and used in combination with low-dose anticoagulation (INR 2-3) and dipyridamole when full-dose oral anticoagulation is contraindicated)

Blalock-Taussig shunts: Oral: 3-5 mg/kg/day given as a single daily dose

Kawasaki disease: Oral: 80-100 mg/kg/day divided every 6 hours; monitor serum concentrations; after fever resolves: 3-5 mg/kg/day once daily; in patients without coronary artery abnormalities, give lower dose for at least 6-8 weeks or until ESR and platelet count are normal; in patients with coronary artery abnormalities, low-dose aspirin should be continued indefinitely

Antirheumatic: Oral: 60-100 mg/kg/day in divided doses every 4 hours

Dosing: Renal Impairment

Cl_{cr} <10 mL/minute: Avoid use.

Dialyzable (50% to 100%)

Dosing: Hepatic ImpairmentAvoid use in severe liver disease.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralDo not crush sustained release or enteric coated tablet. Administer with food or a full glass of water to minimize GI distress. For acute myocardial infarction, have patient chew tablet.

Dietary ConsiderationsTake with food or large volume of water or milk to minimize GI upset.

StorageKeep suppositories in refrigerator; do not freeze. Hydrolysis of aspirin occurs upon exposure to water or moist air, resulting in salicylate and acetate, which possess a vinegar-like odor. Do not use if a strong odor is present.

ContraindicationsHypersensitivity to salicylates, other NSAIDs, or any component of the formulation; asthma; rhinitis; nasal polyps; inherited or acquired bleeding disorders (including factor VII and factor IX deficiency); do not use in children (<16 years of age) for viral infections (chickenpox or flu symptoms), with or without fever, due to a potential association with Reye's syndrome; pregnancy (3rd trimester especially)

Allergy Considerations

- Salicylate Allergy/Sensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Salicylate sensitivity: Patients with sensitivity to tartrazine dyes, nasal polyps, and asthma may have an increased risk of salicylate sensitivity.

- Tinnitus: Discontinue use if tinnitus or impaired hearing occurs.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with platelet and bleeding disorders.

- Dehydration: Use with caution in patients with dehydration.

- Ethanol use: Heavy ethanol use (>3 drinks/day) can increase bleeding risks.

- Gastrointestinal disease: Use with caution in patients with erosive gastritis or peptic ulcer disease.

- Hepatic impairment: Avoid use in severe severe hepatic failure.

- Renal impairment: Use with caution in patients with mild-to-moderate renal impairment (only at high dosages); avoid in severe impairment.

Concurrent drug therapy issues:

- Alteplase: In the treatment of acute ischemic stroke, avoid aspirin for 24 hours following administration of alteplase; administration within 24 hours increases the risk of hemorrhagic transformation.

Special populations:

- Pediatrics: When used for self-medication (OTC labeling): Children and teenagers who have or are recovering from chickenpox or flu-like symptoms should not use this product. Changes in behavior (along with nausea and vomiting) may be an early sign of Reye's syndrome; patients should be instructed to contact their healthcare provider if these occur.

- Surgical patients: ASA should be avoided (if possible) in surgical patients for 1-2 weeks prior to surgery, to reduce the risk of excessive bleeding (except in patients with cardiac stents that have not completed their full course of dual antiplatelet therapy [aspirin, clopidogrel]; patient specific situations need to be discussed with cardiologist; AHA/ACC/SCAI/ACS/ADA Science Advisory provides recommendations).

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from nonsteroidal anti-inflammatory agents. As much as 60% of elderly with GI complications to NSAIDs can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only prophylactic agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (full-dose aspirin in 3rd trimester - expert analysis)

Pregnancy ConsiderationsSalicylates have been noted to cross the placenta and enter fetal circulation. Adverse effects reported in the fetus include mortality, intrauterine growth retardation, salicylate intoxication, bleeding abnormalities, and neonatal acidosis. Use of aspirin close to delivery may cause premature closure of the ductus arteriosus. Adverse effects reported in the mother include anemia, hemorrhage, prolonged gestation, and prolonged labor. Aspirin has been used for the prevention of pre-eclampsia; however, the ACOG currently recommends that it not be used in low-risk women. Low-dose aspirin is used to treat complications resulting from antiphospholipid syndrome in pregnancy (either primary or secondary to SLE). In general, low doses during pregnancy needed for the treatment of certain medical conditions have not been shown to cause fetal harm, however, discontinuing therapy prior to delivery is recommended. Use of safer agents for routine management of pain or headache should be considered.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsLow amounts of aspirin can be found in breast milk. Milk/plasma ratios ranging from 0.03-0.3 have been reported. Peak levels in breast milk are reported to be at ~9 hours after a dose. Metabolic acidosis was reported in one infant following an aspirin dose of 3.9 g/day in the mother. The AAP states that aspirin should be used with caution while breast-feeding. The WHO considers occasional doses of aspirin to be compatible with breast-feeding, but to avoid long-term therapy and consider monitoring the infant for adverse effects. Other sources suggest avoiding aspirin while breast-feeding due to the theoretical risk of Reye's syndrome.

Adverse ReactionsAs with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity. Accurate estimation of frequencies is not possible. The reactions listed below have been reported for aspirin.

Cardiovascular: Dysrhythmias, edema, hypotension, tachycardia

Central nervous system: Agitation, cerebral edema, coma, confusion, dizziness, fatigue, headache, hyperthermia, insomnia, lethargy, nervousness

Dermatologic: Angioedema, rash, urticaria

Endocrine & metabolic: Acidosis, dehydration, hyperglycemia, hypoglycemia (children), hyperkalemia, hypernatremia (buffered forms)

Gastrointestinal: Duodenal ulcers, dyspepsia, epigastric discomfort, gastric erosions, gastric erythema, gastrointestinal ulceration (6% to 31%), heartburn, nausea, stomach pain, vomiting

Hematologic: Anemia, bleeeding, coagulopathy, disseminated intravascular coagulation (DIC), hemolytic anemia, iron-deficiency anemia, prothrombin times prolonged, thrombocytopenia, Hepatic: Hepatitis (reversible), hepatotoxicity, transaminases increased

Neuromuscular & skeletal: Rhabdomyolysis, weakness, acetabular bone destruction (OA)

Otic: Hearing loss, tinnitus

Renal: BUN increased, interstitial nephritis, papillary necrosis, proteinuria, renal impairment, renal failure (including cases caused by rhabdomyolysis), serum creatinine increased

Respiratory: Asthma, bronchospasm, dyspnea, hyperpnea, laryngeal edema, noncardiogenic pulmonary edema, respiratory alkalosis, tachypnea

Miscellaneous: Anaphylaxis, low birth weight, peripartum bleeding, prolonged pregnancy and labor, Reye's syndrome, stillbirths

Postmarketing and/or case reports: Cholestatic jaundice, colitis, colonic ulceration, conduction defect and atrial fibrillation (toxicity), coronary artery spasm, delirium, esophageal stricture, esophageal hematoma, esophagitis with esophageal ulcer, ischemic brain infarction, oral mucosal ulcers (aspirin-containing chewing gum), periorbital edema, rectal stenosis (suppository), rhinosinusitis

Metabolism/Transport Effects **Substrate** of CYP2C9 (minor)

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal damage).

Food: Food may decrease the rate but not the extent of oral absorption.

Folic acid: Hyperexcretion of folate; folic acid deficiency may result, leading to macrocytic anemia.

Iron: With chronic aspirin use and at doses of 3-4 g/day, iron-deficiency anemia may result.

Sodium: Hypernatremia resulting from buffered aspirin solutions or sodium salicylate containing high sodium content. Avoid or use with caution in CHF or any condition where hypernatremia would be detrimental.

Benedictine liqueur, prunes, raisins, tea, and gherkins: Potential salicylate accumulation.

Fresh fruits containing vitamin C: Displace drug from binding sites, resulting in increased urinary excretion of aspirin.

Herb/Nutraceutical: Avoid cat's claw, dong quai, evening primrose, feverfew, garlic, ginger, ginkgo, red clover, horse chestnut, green tea, ginseng (all have additional antiplatelet activity). Limit curry powder, paprika, licorice; may cause salicylate accumulation. These foods contain 6 mg salicylate/100 g. An ordinarily American diet contains 10-200 mg/day of salicylate.

Test InteractionsFalse-negative results for glucose oxidase urinary glucose tests (Clinistix®); false-positives using the cupric sulfate method (Clinitest®); also, interferes with Gerhardt test, VMA determination; 5-HIAA, xylose tolerance test and T_3 and T_4

Reference RangeTiming of serum samples: Peak levels usually occur 2 hours after ingestion. Salicylate serum concentrations correlate with the pharmacological actions and adverse effects observed. The serum salicylate concentration (mcg/mL) and the corresponding clinical correlations are as follows: See table.

Serum Salicylate: Clinical Correlations

Serum Salicylate Concentration (mcg/mL)	**Desired Effects**	**Adverse Effects / Intoxication**
~100	Antiplatelet Antipyresis Analgesia	GI intolerance and bleeding, hypersensitivity, hemostatic defects
150-300	Anti-inflammatory	Mild salicylism
250-400	Treatment of rheumatic fever	Nausea/vomiting, hyperventilation, salicylism, flushing, sweating, thirst, headache, diarrhea, and tachycardia
>400-500		Respiratory alkalosis, hemorrhage, excitement, confusion, asterixis, pulmonary edema, convulsions, tetany, metabolic acidosis, fever, coma, cardiovascular collapse, renal and respiratory failure

Nursing: Physical Assessment/Monitoring**Do not use for persons with allergic reaction to salicylate or other NSAIDs.** Assess other medications patient may be taking for additive or adverse interactions. Monitor therapeutic effectiveness and for signs of adverse reactions or overdose at beginning of therapy and periodically with long-term therapy. Assess knowledge/teach patient appropriate use. Teach patient to monitor for adverse reactions, adverse reactions to report, and appropriate interventions to reduce side effects.

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Adverse reactions can occur with overuse. Take with food or milk. Do not use aspirin with strong vinegar-like odor. Do not crush or chew extended release products. While using this medication, avoid alcohol, excessive amounts of vitamin C, or salicylate-containing foods (eg, curry powder, prunes, raisins, tea, or licorice), other prescription or OTC medications containing aspirin or salicylate, or other NSAIDs without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience nausea, vomiting, gastric discomfort (frequent mouth care, small frequent meals, sucking lozenges, or chewing gum may help); GI bleeding, ulceration, or perforation (can occur with or without pain); or discoloration of stool (pink/red). Stop taking aspirin and report ringing in ears; persistent stomach pain; unresolved nausea or vomiting; respiratory difficulty or shortness of breath; unusual bruising or bleeding (mouth, urine, stool); or skin rash. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet:

Bayer® Aspirin Extra Strength: 500 mg

Bayer® Aspirin Regimen Regular Strength: 325 mg

Bayer® Genuine Aspirin: 325 mg

Bayer® Plus Extra Strength: 500 mg [contains calcium carbonate]

Bayer® with Heart Advantage: 81 mg [contains phytosterols, tartrazine]

Bayer® Women's Aspirin Plus Calcium: 81 mg [contains elemental calcium 300 mg]

Caplet, buffered:

Ascriptin® Maximum Strength: 500 mg [contains aluminum hydroxide, calcium carbonate, and magnesium hydroxide]

Gum:

Aspergum®: 227 mg [cherry or orange flavor]

Suppository, rectal: 300 mg, 600 mg

Tablet: 325 mg

Aspercin, Aspirtab: 325 mg

Bayer® Genuine Aspirin: 325 mg

Tablet, buffered: 325 mg

Ascriptin®: 325 mg [contains aluminum hydroxide, calcium carbonate, and magnesium hydroxide]

Buffasal: 325 mg [contains magnesium oxide]

Bufferin®: 325 mg [contains calcium carbonate, magnesium oxide, and magnesium carbonate; contains calcium 65 mg/tablet, magnesium 50 mg/tablet]

Bufferin® Extra Strength: 500 mg [contains calcium carbonate, magnesium oxide, and magnesium carbonate; contains calcium 90 mg/tablet, magnesium 70 mg/tablet]

Buffinol: 325 mg [contains magnesium oxide]

Tablet, chewable: 81 mg

Bayer® Aspirin Regimen Children's: 81 mg [cherry or orange flavor]

St. Joseph® Adult Aspirin: 81 mg [orange flavor]

Tablet, controlled release:

ZORprin®: 800 mg

Tablet, delayed release, enteric coated:

Easprin®: 975 mg

Tablet, enteric coated: 81 mg, 325 mg, 500 mg, 650 mg, 975 mg [DSC]

Bayer® Aspirin Regimen Adult Low Dose, Ecotrin® Low Strength, St. Joseph Adult Aspirin: 81 mg

Ecotrin®, Genacote™: 325 mg

Ecotrin® Maximum Strength: 500 mg

Halfprin®: 81 mg, 162 mg

Generic AvailableYes: Excludes gum

Pricing: U.S. (www.drugstore.com)

Tablet, controlled release (Zorprin)

800 mg (100): $125.53

Tablet, EC (Aspirin)

975 mg (90): $11.25

Tablets (Aspirin)

325 mg (100): $11.99

Mechanism of ActionIrreversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antiplatelet, antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Duration: 4-6 hours

Absorption: Rapid

Distribution: V_d: 10 L; readily into most body fluids and tissues

Metabolism: Hydrolyzed to salicylate (active) by esterases in GI mucosa, red blood cells, synovial fluid, and blood; metabolism of salicylate occurs primarily by hepatic conjugation; metabolic pathways are saturable

Bioavailability: 50% to 75% reaches systemic circulation

Half-life elimination: Parent drug: 15-20 minutes; Salicylates (dose dependent): 3 hours at lower doses (300-600 mg), 5-6 hours (after 1 g), 10 hours with higher doses

Time to peak, serum: ~1-2 hours

Excretion: Urine (75% as salicyluric acid, 10% as salicylic acid)

Dental Health Professional ConsiderationsThere is no scientific evidence to warrant discontinuance of aspirin prior to dental surgery. Patients taking one aspirin tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with the physician before removal of the aspirin relative to prevention of postoperative bleeding.

The Food and Drug Administration (FDA), has issued a letter updating information and considerations regarding the use of ibuprofen (400 mg doses) in patients who are taking low dose aspirin (81 mg, immediate release; not enteric coated) for cardioprotection and stroke prevention. Ibuprofen, at these doses, may interfere with aspirin's antiplatelet effect depending upon when it is administered. Patients initiated on aspirin first (for ~1 week) then ibuprofen (400 mg 3 times/day for 10 days) seem to maintain aspirin's platelet effect (Cryer B, 2005). Ibuprofen has the greatest impact on aspirin if administered less than 8 hours before aspirin (Catella-Lawson F, 2001).

Patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. With occasional use of ibuprofen, a clinically-significant interaction with aspirin in unlikely. To avoid interference during chronic dosing, a single dose of ibuprofen should be taken 30-120 minutes after aspirin ingestion or at least 8 hours should elapse after ibuprofen dosing before giving aspirin (FDA, 2006; Catella-Lawson F, 2001).

The clinical implications of the interaction are unclear. There have not been any clinical endpoint studies conducted at this time. Avoidance of this interaction is potentially important because aspirin's vascular protection could be decreased or negated.

Other nonselective NSAIDs may have potential for a similar interaction with aspirin. Such has been described with naproxen (Capone ML, 2005). Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin. Other clinical scenarios (use of smaller ibuprofen doses, other aspirin products, other doses of aspirin) have not been evaluated.

Additional information is available at: http://www.fda.gov/cder/drug/infopage/aspirin/default.htm

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity (see Dental Comment).

Aspirin and clopidogrel (Plavix®) in combination is the primary prevention strategy against stent thrombosis after placement of drug-eluting metal stents in coronary patients. Premature discontinuation of this combination antiplatelet therapy strongly increases the risk of a catastrophic event of stent thrombosis leading to myocardial infarction and/or death, so says a science advisory issued in January 2007 from the American Heart Association in collaboration with the American Dental Association and other professional healthcare organizations. The advisory stresses a 12-month therapy of aspirin and Plavix® combination after placement of a drug-eluting stent in order to prevent thrombosis at the stent site. Any elective surgery should be postponed for 1 year after stent implantation, and if surgery must be performed, consideration should be given to continuing the antiplatelet therapy during the perioperative period in high-risk patients with drug-eluting stents.

This advisory was issued from a science panel made up of representatives from the American Heart Association (AHA), the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American College of Surgeons, the American Dental Association (ADA), and the American College of Physicians (Grines, 2007).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; may displace valproic acid from binding sites resulting in an increase of unbound drug; monitor for toxicity

Cardiovascular Considerations

Primary Prevention: The U.S. Preventive Services Task Force strongly recommends that clinicians discuss aspirin therapy for primary prevention of heart disease with adults who are at increased risk. The balance of benefits and harm is most favorable in patients at high risk for coronary heart disease (those with a 5-year risk ≥3%). Risk can be calculated at www.med-decisions.com. Adequate blood pressure control is necessary in hypertensive patients who are candidates for aspirin.

Secondary Prevention: In unstable angina, aspirin reduces the rate of refractory angina, nonfatal MI, and death. Aspirin reduces the rate of recurrent ischemia and infarction, stroke, and death following MI. In patients who have acute coronary syndrome (ACS) but are not already receiving aspirin, the first dose may be chewed to rapidly establish a high blood level.

Resistance: The definition of biochemical aspirin resistance is measurable, persistent platelet activation that occurs in patients prescribed a therapeutic dose of aspirin. Clinical aspirin resistance is considered aspirin treatment failure; the recurrence of some vascular event despite a regular therapeutic dose of aspirin. Proposed mechanisms of aspirin resistance include poor adherence with therapy, poor absorption, inadequate dosage, drug interactions, increased isoprostane activity, platelet hypersensitivity to agonists, increased COX-2 activity, COX-1 polymorphism, and platelet alloantigen 2 polymorphism of platelet glycoprotein IIIa. Aspirin resistance has been evaluated clinically. A stable group of 326 cardiovascular patients taking 325 mg of aspirin a day for >7 days was prospectively evaluated (Gum PA, 2003). Platelet aggregation was evaluated by optical platelet aggregation using ADP and AA. The primary outcome was defined as a composite of death, MI, or CVA. Seventeen (~5%) patients had biochemical aspirin resistance. Patients who were aspirin-resistant were more likely to have a CV event than those who were aspirin-sensitive (24% vs 10%, CI 1.1-8.9, p = 0.03). There have been other studies evaluating biochemical and clinical aspirin resistance; different methods have been used to determine aspirin resistance. Patient adherence has not been evaluated. Aspirin resistance is likely dose related, may be influenced by dynamic factors yet to be identified and further research is required.

Coronary Artery Stents: The AHA/ACC/SCAI/ACS/ADA Science Advisory (2007) published recommendations (*Circulation*, February 13, 2007) to prevent premature discontinuation of dual antiplatelet therapy (clopidogrel, aspirin) in patients with coronary artery stents. This advisory panel agreed with the 2004 ACC/AHA guidelines stressing the importance of 12 months of dual antiplatelet therapy after placement of a drug-eluting stent (DES) in patients who are not at high risk of bleeding. The advisory panel included these recommendations. Minor surgery, teeth cleaning, and tooth extraction can usually be performed without increased bleeding on the dual antiplatelet regimen. If increased bleeding is anticipated, then the procedure should be delayed until the antiplatelet regimen is completed. Elective procedures with a significant risk of bleeding should be postponed until the antiplatelet regimen is completed. The Advisory panel recommends healthcare providers who perform invasive or surgical procedures contact the patient's cardiologist before discontinuing antiplatelet therapy. For patients with drug-eluting stents who must undergo a procedure that requires discontinuation of thienopyridine therapy, aspirin should be continued if possible and the thienopyridine restarted as soon as possible after the procedure. "Bridging" stent patients with warfarin, other antithrombins, or glycoprotein IIb/IIIa agents is not supported by the Advisory Committee.

For the complete review and additional recommendations available at: http://www.acc.org/qualityandscience/clinical/pdfs/Final_Dual_Antiplatelet_Statement_010507.pdf. Last accessed January 19, 2007.

Drug Interactions: The question frequently arises as to whether or not concurrent NSAID use interferes with the antiplatelet effects of aspirin. It is known that if taken within 2 hours following an aspirin dose or if taken regularly in a patient on cardioprotective doses of aspirin, ibuprofen will interfere with the antiplatelet effects of aspirin. Less is known about the other NSAIDs, but some data are available. In a pharmacodynamic trial, diclofenac did not interfere with aspirin's antiplatelet effects after six straight days of combined use. In a retrospective analysis, diclofenac did not impact cardiovascular and all-cause morality when taken regularly in patients receiving daily aspirin. A subgroup analysis of the Physician's Health Study (a primary prevention trial) identified that the use of NSAIDs (specific agents were not identified) at <60 days/year did not diminish aspirin's ability to prevent an initial MI in contrast to taking NSAIDs more frequently. It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain first access to the active site. In either case, aspirin inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible).

Index TermsAcetylsalicylic Acid; ASA

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International Brand NamesAAS (AR, BR, ES); Acard (PL); Aceprin (MY); Acesal (IT); Acesan (PL); Acetard (FI); Aceticil (BR); Adiro (MX); Adiro (VE); Albyl-E (NO); Alka-Seltzer (AU, PL); Ampiryna (PL); Anopyrin (PL); Ansin (TW); Antacsal-E (MX); Anthrom (PH); Aptor (ID); ASA (PL); Asapor (FI); Asawin (CO, EC); Ascardia (ID); Asopiryna (PL); Aspa (TW); Aspec-EC (PH); Aspegic (PL); Aspent (TH); Aspex (IL); Aspi (PL); Aspilets (ID); Aspirem (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Aspirin (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, HK, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PL, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Aspirin Bayer (HK); Aspirin Protect (PL); Aspirina (CN, CO, EC); Aspirina efervescente (MX); Aspirina Junior (MX); Aspirisucre (FR); Aspisal (BG); Aspotabs (PL); Aspro (AT, AU, CH, CZ, GB, HN, IT, MY, NL); Asprovit (EE); Asrina (TH); ASS (DE); Asta (PY); Astrix (PH); Bamyl (SE); Bayaspirina (AR); Bayer Aspirin Cardio (ZA); Bestpirin (PL); Bufferin (IT, UY); Callous (PL); Caprin (GB); Cardioaspirina (CO, PE); Cardiopirin (PL); Cardioprin 100 (IL); Carnyl (DK); Cartia (AU, PT); Caspirin (MY); Claragine (FR); Colfarit (AT, CZ, HN); Comoprin (TH); Cortal (PH); Dispril (AE, BE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, NO, OM, QA, SA, SY, YE); Disprin (AU, BB, BF, BJ, BM, BS, BZ, CI, ET, GB, GH, GM, GN, GY, HK, IE, IN, JM, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, NL, PK, PR, SC, SD, SG, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Ecasil (BR); Ecotrin (AR, AU, CN, MX, TW); Ecotrin 650 (HK); Encine EM (TW); Encopirin (PL); Enteroprin (PH); Eskotrin (VE); Galocard (PL); Globentyl (DK); Godamed (IL); Idotyl (DK); Keypo (TW); Laspal (PL); Magnecyl (SE); Melabon (DE); Miraspryn (PL); Naspro (ID); Nipas (PL); Novasen (PL); Novaspryn (PL); Nu-Seals (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Plewin (CN); Polocard (PL); Polopiryna (PL); Proficar (PL); Proprin (GB); Rhonal (NL, PE, VE); Salisalido (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Salpirin (PL); Salvequick (PL); Seal and Heal (PL); Sedergine (BE); Solprin (AU); Tevapirin (IL); Thrombo ASS (PL); Thrombo-Aspilets (ID); Thrombo-ASS (EE); Togal ASS (PL); Tromcor (PH); Upsarin (PL); V-AS (TH)

AT

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Breast Cancer]

Regimen UseBreast cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 3 weeks

Variation 2:

Doxorubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Docetaxel: I.V.: 60 mg/m^2

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 3 weeks

Variation 3:

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 14 days

Variation 4:

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Docetaxel: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 3 weeks

Variation 5:

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Docetaxel: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 3-4 weeks

Variation 6:

Doxorubicin: I.V.: 56 mg/m^2 day 1

[total dose/cycle = 56 mg/m^2]

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 3 weeks

Variation 7:

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Docetaxel: I.V.: 75 mg/m^2 day 2

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 4 weeks

References

Variation 1:

von Minckwitz G, Costa SD, Eiermann W, et al, “Maximized Reduction of Primary Breast Tumor Size Using Preoperative Chemotherapy With Doxorubicin and Docetaxel,” *J Clin Oncol*, 1999, 17(7):1999-2005. [PubMed 10561250]

Variation 2:

Dieras V, “Docetaxel in Combination With Doxorubicin: A Phase I Dose-Finding Study,” *Oncology (Williston Park)*, 1997, 11(6 Suppl 6):17-20. [PubMed 9213322]

Variation 3:

von Minckwitz G, Costa SD, Raab G, et al, “Dose-Dense Doxorubicin, Docetaxel, and Granulocyte Colony-Stimulating Factor Support With or Without Tamoxifen as Preoperative Therapy in Patients With Operable Carcinoma of the Breast: A Randomized, Controlled, Open Phase IIB Study,” *J Clin Oncol*, 2001, 19(15):3506-15.[PubMed 11481357]

Variation 4:

Muthalib A, Darwis I, Prayogo N, et al, “Preliminary Results of Multicenter Phase II Trial of Docetaxel (Taxotere) in Combination With Doxorubicin as First-Line Chemotherapy in Indonesian Patients With Advanced or Metastatic Breast Cancer,” *Gan To Kagaku Ryoho*, 2000, 27(Suppl 2):498-504.[PubMed 10895201]

Variation 5:

Aihara T, Takatsuka Y, Itoh K, et al, “Phase II Study of Concurrent Administration of Doxorubicin and Docetaxel as First-Line Chemotherapy for Metastatic Breast Cancer,” *Oncology*, 2003, 64(2):124-30. [PubMed 12566909]

Variation 6:

Miller KD, McCaskill-Stevens W, Sisk J, et al, “Combination Versus Sequential Doxorubicin and Docetaxel as Primary Chemotherapy for Breast Cancer: A Randomized Pilot Trial of the Hoosier Oncology Group,” *J Clin Oncol*, 1999, 17(10):3033-7.[PubMed 10506597]

Variation 7:

Palmeri S, Leonardi V, Tamburo De Bella M, et al, “Doxorubicin-Docetaxel Sequential Schedule: Results of Front-Line Treatment in Advanced Breast Cancer,” *Oncology*, 2002, 63(3):205-12. [PubMed 12381898]

Atazanavir

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English English

Jump To Field (Select Field Name)

Pronunciation(at a za NA veer)
U.S. Brand NamesReyataz®
Canadian Brand NamesReyataz®
Pharmacologic CategoryAntiretroviral Agent, Protease Inhibitor
Use: Labeled IndicationsTreatment of HIV-1 infections in combination with at least two other antiretroviral agents

Note: In patients with prior virologic failure, coadministration with ritonavir is recommended.

Dosing: Adults

Treatment of HIV-1 infection: Oral:

Antiretroviral-naive patients: Atazanavir 300 mg once daily **plus** ritonavir 100 mg once daily **or** 400 mg once daily in patients unable to tolerate ritonavir

Antiretroviral-experienced patients: Atazanavir 300 mg once daily **plus** ritonavir 100 mg once daily. **Note:** Atazanavir without ritonavir is not recommended in antiretroviral-experienced patients with prior virologic failure.

Dosage adjustments for concomitant therapy: Oral:

Coadministration with efavirenz:

Antiretroviral-naive patients: Atazanavir 400 mg plus ritonavir 100 mg given with efavirenz 600 mg (all as a single daily dose)

Antiretroviral-experienced patients: Concurrent use not recommended due to decreased atazanavir exposure.

Coadministration with didanosine buffered or enteric-coated formulations: Administer atazanavir 2 hours before or 1 hour after didanosine buffered formulations

Coadministration with H_2 antagonists:

Antiretroviral-naive patients: Atazanavir 300 mg plus ritonavir 100 mg given simultaneously with, or at least 10 hours after an H_2 antagonist equivalent dose of ≤80 mg famotidine/day

Patients unable to tolerate ritonavir: Atazanavir 400 mg once daily given at least 2 hours before or at least 10 hours after an H_2 antagonist equivalent daily dose of ≤40 mg famotidine (single dose ≤20 mg)

Antiretroviral-experienced patients: Atazanavir 300 mg plus ritonavir 100 mg given simultaneously with, or at least 10 hours after an H_2 antagonist equivalent dose of ≤40 mg famotidine/day

With tenofovir: Increase atazanavir to 400 mg (plus ritonavir 100 mg) once daily

Coadministration with proton pump inhibitors:

Antiretroviral-naive patients: Atazanavir 300 mg plus ritonavir 100 mg given 12 hours after a proton pump inhibitor equivalent dose of ≤20 mg omeprazole/day

Antiretroviral-experienced patients: Concurrent use not recommended.

Antiretroviral-experienced patients: Concurrent use not recommended.

Coadministration with tenofovir: Atazanavir 300 mg plus ritonavir 100 mg given with tenofovir 300 mg (all as a single daily dose); if H_2 antagonist coadministered, increase atazanavir to 400 mg (plus ritonavir 100 mg) once daily

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Treatment of HIV-1 infection: Oral: Children ≥6 years and Adolescents:

Antiretroviral-naive patients:

15-24 kg: Atazanavir 150 mg once daily **plus** ritonavir 80 mg once daily

25-31 kg: Atazanavir 200 mg once daily **plus** ritonavir 100 mg once daily

32-38 kg: Atazanavir 250 mg once daily **plus** ritonavir 100 mg once daily

≥39 kg: Atazanavir 300 mg once daily **plus** 100 mg ritonavir once daily. **Note:** Treatment-naive patients ≥39 kg and ≥13 years of age who are unable to tolerate ritonavir, refer to adult dosing.

or

15-19 kg: Atazanavir 8.5 mg/kg/dose once daily (rounded to available capsule strengths) **plus** ritonavir 4 mg/kg once daily

≥20 kg: Atazanavir 7 mg/kg/dose once daily (round to available capsule strengths) (maximum 300 mg) **plus** ritonavir 4 mg/kg once daily

Antiretroviral-experienced patients: **Note:** Atazanavir without ritonavir is not recommended in antiretroviral-experienced patients with prior virologic failure:

25-31 kg: Atazanavir 200 mg once daily **plus** ritonavir 100 mg once daily

32-38 kg: Atazanavir 250 mg once daily **plus** ritonavir 100 mg once daily

≥39 kg: Atazanavir 300 mg once daily **plus** 100 mg ritonavir once daily

Dosage adjustments for concomitant therapy: Oral: Adolescents >13 years: Refer to adult dosing.

Dosing: Renal Impairment

Not on hemodialysis: No adjustment necessary

Hemodialysis:

Antiretroviral-naive patients: Use boosted therapy of atazanavir 300 mg with ritonavir 100 mg once daily

Antiretroviral-experienced patients: Not recommended.

Dosing: Hepatic Impairment

Mild-to-moderate hepatic insufficiency: Use with caution; if moderate insufficiency (Child-Pugh class B) and no prior virologic failure, reduce dose to 300 mg once daily.

Severe hepatic insufficiency (Child-Pugh class C): Not recommended.

Note: Patients with underlying hepatitis B or C may be at increased risk of hepatic decompensation. Combination therapy (with ritonavir) in patients with hepatic impairment not recommended.

Administration: Oral

Administer with food.

Dietary ConsiderationsShould be taken with food to enhance absorption.

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to atazanavir or any component of the formulation; concurrent therapy with cisapride, ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine), indinavir, irinotecan, lovastatin, midazolam (oral), pimozide, rifampin, simvastatin, St John’s wort, or triazolam

Warnings/Precautions

Concerns related to adverse effects:

- Elevated bilirubin: Asymptomatic elevations in bilirubin (unconjugated) occur commonly during therapy; consider alternative therapy if bilirubin is >5 times ULN. Evaluate alternative etiologies if transaminase elevations also occur.

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).

- Hypersensitivity reactions: Protease inhibitors have been associated with a variety of hypersensitivity events (some severe), including rash, anaphylaxis (rare), angioedema, bronchospasm, erythema multiforme, and/or Stevens-Johnson syndrome (rare). It is generally recommended to discontinue treatment if severe rash or moderate symptoms accompanied by other systemic symptoms occur.

- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.

- Nephrolithiasis: Cases have been reported in postmarketing surveillance; temporary or permanent discontinuation of therapy should be considered if symptoms develop.

Disease-related concerns:

- Conduction abnormalities: May prolong PR interval, use with caution in patients with pre-existing conduction abnormalities or with medications which prolong AV conduction (dosage adjustment required with some agents); rare cases of second-degree AV block have been reported.

- Diabetes: Changes in glucose tolerance, hyperglycemia, exacerbation of diabetes, DKA, and new-onset diabetes mellitus have been reported in patients receiving protease inhibitors.

- Hemophilia A or B: Use with caution in patients with hemophilia A or B; increased bleeding during protease inhibitor therapy has been reported.

- Hepatic impairment: Protease inhibitors may cause hepatitis and/or exacerbate pre-existing hepatic dysfunction; use with caution in patients with underlying hepatic disease, such as hepatitis B or C or cirrhosis; monitor closely.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers, and major CYP2C8 substrates; consider alternative agents that avoid or lessen the potential for CYP- or glucuronidation-mediated interactions. Contraindicated with drugs that are major CYP3A4 or UGT1A1 substrates (see Drug Interactions).

Special populations:

- Pediatrics: Optimal dosing in pediatric patients <6 years of age has not been established; do not use in children <3 months of age due to potential for kernicterus.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects not observed in animal studies. Pregnancy and protease inhibitors are both associated with an increased risk of hyperglycemia. Glucose levels should be closely monitored. Atazanavir crosses the human placenta in low/variable amounts; it is not known if atazanavir will exacerbate hyperbilirubinemia in neonates. Based on limited studies, normal dosing achieves adequate serum concentrations in pregnant women. Atazanavir is currently not recommended for use during pregnancy. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse ReactionsIncludes data from both treatment-naive and treatment-experienced patients. Percentages listed for adults unless otherwise specified.

>10%:

Dermatologic: Rash (5% to 21%; median onset 8 weeks)

Endocrine & metabolic: Cholesterol increased (≥240 mg/dL: 6% to 25%)

Gastrointestinal: Nausea (3% to 14%), amylase increased (14%)

Hepatic: Bilirubin increased (≥2.6 times ULN: 34% to 49%)

Neuromuscular & skeletal: CPK increased (5% to 11%)

Respiratory: Cough (children 21%)

2% to 10%:

Cardiovascular: AV block (first degree: 6%; second degree [children] 2%)

Central nervous system: Headache (1% to 6%; children 7%), peripheral neuropathy (<1% to 4%), insomnia (<1% to 3%), depression (2%), fever (2%; children 19%), dizziness (<1% to 2%)

Endocrine & metabolic: Triglycerides increased (<1% to 8%), hyperglycemia (≥251 mg/dL: 5%)

Gastrointestinal: Lipase increased (<1% to 5%), abdominal pain (4%), vomiting (3% to 4%; children 8%), diarrhea (1% to 3%; children 8%)

Hematologic: Neutropenia (3% to 7%), hemoglobin decreased (<1% to 5%), thrombocytopenia (up to 2%)

Hepatic: ALT increased (>5 times ULN: 4% to 9%; 15% to 25% in patients seropositive for hepatitis B and/or C), AST increased (>5 times ULN: 2% to 7%; 9% to 10% in patients seropositive for hepatitis B and/or C), jaundice (4% to 9%; children 13%)

Neuromuscular & skeletal: Myalgia (4%)

Respiratory: Rhinorrhea (children 6%)

<2%, postmarketing and/or case reports: Alopecia, arthralgia, AV block (second- and third-degree, rare), cholecystitis, cholelithiasis, cholestasis, diabetes mellitus, edema, erythema multiforme, immune reconstitution syndrome, left bundle branch block, macropapular rash, nephrolithiasis, pancreatitis, pruritus, QT_c prolongation, Stevens-Johnson syndrome

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (weak), 2C8 (strong), 2C9 (weak), 3A4 (strong), UGT1A1 (strong)

Drug Interactions

Abacavir: Protease Inhibitors may decrease the serum concentration of Abacavir. *Risk C: Monitor therapy*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amiodarone: Protease Inhibitors may decrease the metabolism of Amiodarone. *Risk X: Avoid combination*

Antacids: May decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Protease Inhibitors may decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Buprenorphine: Atazanavir may increase the serum concentration of Buprenorphine. *Risk C: Monitor therapy*

Calcium Channel Blockers (Dihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Protease Inhibitors. Protease Inhibitors may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cisapride: Protease Inhibitors may decrease the metabolism of Cisapride. The resultant increase in serum cisapride concentrations may result in QTc prolongation and malignant cardiac arrhythmias. *Risk X: Avoid combination*

Clarithromycin: Protease Inhibitors may diminish the therapeutic effect of Clarithromycin. Specifically, certain protease inhibitors may decrease formation of the active 14-hydroxy-clarithromycin metabolite, which may negatively impact clarithromycin effectiveness vs. H. influenzae and other non-MAC infections. Protease Inhibitors may increase the serum concentration of Clarithromycin. Clarithromycin dose adjustment in renally impaired patients may be needed. Clarithromycin may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): Protease Inhibitors may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk D: Consider therapy modification*

CycloSPORINE: Protease Inhibitors may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Strong) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Delavirdine: Protease Inhibitors may decrease the serum concentration of Delavirdine. Delavirdine may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Didanosine: May decrease the absorption of Atazanavir. Only the buffered formulations of didanosine are of concern. Atazanavir may decrease the serum concentration of Didanosine. Reported with enteric coated didanosine capsules. *Risk D: Consider therapy modification*

Digoxin: Protease Inhibitors may increase the serum concentration of Digoxin. Increased serum concentrations of digoxin may increase risk of AV nodal blockade. *Risk C: Monitor therapy*

Efavirenz: May decrease the serum concentration of Atazanavir. *Risk D: Consider therapy modification*

Enfuvirtide: Protease Inhibitors may increase the serum concentration of Enfuvirtide. Enfuvirtide may increase the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

Eplerenone: Protease Inhibitors may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Protease Inhibitors may decrease the metabolism of Ergot Derivatives. **Exceptions:** Cabergoline. *Risk X: Avoid combination*

Etravirine: Atazanavir may increase the serum concentration of Etravirine. Etravirine may decrease the serum concentration of Atazanavir. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

FentaNYL: Protease Inhibitors may decrease the metabolism of FentaNYL. *Risk C: Monitor therapy*

Fusidic Acid: Protease Inhibitors may decrease the metabolism of Fusidic Acid. Fusidic Acid may decrease the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Garlic: May decrease the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

H2-Antagonists: May decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: Protease Inhibitors may increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. **Exceptions:** Fluvastatin. *Risk D: Consider therapy modification*

Irinotecan: Atazanavir may increase the serum concentration of Irinotecan. The metabolism (via glucuronidation) of the active SN-38 metabolite may be primarily impacted by this interaction. *Risk X: Avoid combination*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Meperidine: Protease Inhibitors may enhance the adverse/toxic effect of Meperidine. Protease Inhibitors may decrease the serum concentration of Meperidine. Concentrations of the toxic Normeperidine metabolite may be increased. *Risk D: Consider therapy modification*

Nefazodone: Protease Inhibitors may decrease the metabolism of Nefazodone. *Risk C: Monitor therapy*

Nevirapine: May increase the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): May diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Phosphodiesterase 5 Inhibitors: Protease Inhibitors may decrease the metabolism of Phosphodiesterase 5 Inhibitors. Management: Dose restrictions for tadalafil, and/or sildenafil and vardenafil are recommended in combination with ritonavir, atazanavir, indinavir, darunavir and saquinavir. Consult specific prescribing information for detailed recommendations. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Protease Inhibitors may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Protease Inhibitors: May increase the serum concentration of other Protease Inhibitors. Management: Atazanavir--indinavir combination contraindicated. Amprenavir oral solution not recommended with ritonavir oral solution; tipranavir/ritonavir or atazanavir/ritonavir not recommended with other protease inhibitors. Other combos may require dose changes. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

QuiNIDine: Protease Inhibitors may decrease the metabolism of QuiNIDine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifampin: May decrease the serum concentration of Atazanavir. *Risk X: Avoid combination*

Rifamycin Derivatives: Protease Inhibitors may decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Sirolimus: Protease Inhibitors may increase the serum concentration of Sirolimus. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Protease Inhibitors. *Risk X: Avoid combination*

Tacrolimus: Protease Inhibitors may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Temsirolimus: Protease Inhibitors may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tenofovir: May decrease the serum concentration of Atazanavir. Atazanavir may increase the serum concentration of Tenofovir. Management: When combined use required, tenofovir 300mg and atazanavir 300mg should be used together with ritonavir 100mg, all given as a single daily dose with food. Atazanavir without ritonavir should not be used with tenofovir. *Risk D: Consider therapy modification*

Theophylline Derivatives: Protease Inhibitors may decrease the serum concentration of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

TraZODone: Protease Inhibitors may increase the serum concentration of TraZODone. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Protease Inhibitors may increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Valproic Acid: Protease Inhibitors may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Warfarin: Atazanavir may increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

Zidovudine: Protease Inhibitors may decrease the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Bioavailability of atazanavir increased when taken with food.

Herb/Nutraceutical: St John's wort (*Hypericum perforatum*) decreases serum concentrations of protease inhibitors and may lead to treatment failures; concurrent use is contraindicated.

Monitoring ParametersViral load, CD4, serum glucose; liver function tests, bilirubin, drug levels (with certain concomitant medications), ECG monitoring in patients with prolonged PR interval or with concurrent AV nodal blocking drugs

Nursing: Physical Assessment/MonitoringUse with caution in presence of hepatic dysfunction or hemophilia. Assess all other pharmacologic or herbal products patient may be taking for potential interactions or toxicity; dosing adjustments or alternative agents may be necessary (multiple liver enzyme interactions may increase or decrease levels/effects of drugs and increase potential for severe toxicity or loss of effectiveness). A list of medications that should not be used is available in each bottle and patients should be provided with this information. Assess therapeutic response (CD4 count, hepatic function) and adverse reactions at regular intervals during therapy (eg, hypersensitivity reaction [can be severe], gastrointestinal disturbance [nausea, vomiting, diarrhea] that can lead to dehydration and weight loss, hyperlipidemia and redistribution of body fat, rash, CNS effects [malaise, insomnia, abnormal thinking], electrolyte imbalance) at regular intervals during therapy. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions (eg, glucose testing [protease inhibitors may cause hyperglycemia or new-onset diabetes], use of barrier contraceptives [protease inhibitors may decrease effectiveness of oral contraceptives]), and adverse symptoms to report.

Monitoring: Lab TestsViral load, CD4, serum glucose; liver function tests, bilirubin, drug levels (with certain concomitant medications)

Patient EducationYou will be provided with a list of specific medications that should not be used during therapy; do not take any new prescriptions, over-the-counter medications, or herbal products (even if they are not on the list) without consulting prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. This drug is prescribed as one part of a multidrug combination; take exactly as directed for full course of therapy. May take with light meal (eg, dry toast, skim milk, corn flakes) to reduce GI upset. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. You may be susceptible to infection; avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber. You may be advised to check your glucose levels; medication can cause hyperglycemia. Frequent blood tests may be required with prolonged therapy. May cause body changes due to redistribution of body fat, facial atrophy, or breast enlargement (normal effects of drug); nausea, vomiting, or flatulence (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); muscle weakness or flank pain (consult prescriber for approved analgesic); headache or insomnia (consult prescriber for medication); or diarrhea (boiled milk, buttermilk, or yogurt may help). Inform prescriber immediately if you experience hypersensitivity (skin rash; swelling of face, mouth, or tongue; difficulty swallowing or breathing) or chest pain or palpitations. Report muscle numbness or tingling; unresolved persistent vomiting, diarrhea, or abdominal pain; change in color of stool or urine; or any persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug decreases the effect of oral contraceptives; use of alternative (nonhormonal) forms of contraception is recommended; consult prescriber for appropriate contraceptives. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as sulfate:

Reyataz®: 100 mg, 150 mg, 200 mg, 300 mg

Generic AvailableNo

ManufacturerBristol-Myers Squibb

Pricing: U.S. (www.drugstore.com)

Capsules (Reyataz)

150 mg (30): $489.90

200 mg (60): $919.94

300 mg (30): $918.91

Mechanism of ActionInhibits the HIV-1 protease; inhibition of the viral protease prevents cleavage of the gag-pol polyprotein resulting in the production of immature, noninfectious virus

Pharmacodynamics/Kinetics

Absorption: Rapid; enhanced with food

Protein binding: 86%

Metabolism: Hepatic, via multiple pathways including CYP3A4; forms two metabolites (inactive)

Half-life elimination: Unboosted therapy: 7-8 hours; Boosted therapy (with ritonavir): 9-18 hours

Time to peak, plasma: 2-3 hours

Excretion: Feces (79%, 20% as unchanged drug); urine (13%, 7% as unchanged drug)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV

Pharmacotherapy PearlsA listing of medications that should not be used concurrently is available with each bottle and patients should be provided with this information.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression, insomnia, dizziness, and fatigue

Mental Health: Effects on Psychiatric TreatmentContraindicated with midazolam, pimozide, St John's wort, triazolam, and ergot derivatives.

Carbamazepine may decrease serum levels of atazanavir. TCA and sildenafil serum concentrations may be increased by atazanavir; monitor. Nausea, dizziness, hypotension, and syncope have been reported with concomitant use of trazodone and ritonavir.

Index Terms Atazanavir Sulfate; BMS-232632

References

“Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, Panel on Clinical Practices for Treatment of HIV Infection,” January 29, 2008. Available at http://www.aidsinfo.nih.gov.

“Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,” July 8, 2008. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” July 29, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand Names Reyataz (AR, AT, AU, BE, BG, CH, CL, CN, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, ID, IE, IT, KP, MX, NL, NO, PE, PT, RU, SE, SG, TR, TW)

Atenolol and Chlorthalidone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(a TEN oh lole & klor THAL i done)

U.S. Brand NamesTenoretic®

Canadian Brand NamesApo-Atenidone®; Novo-Atenolthalidone; Tenoretic®

Pharmacologic CategoryBeta Blocker, Beta$_1$ Selective; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension with a cardioselective beta-blocker and a diuretic

Dosing: AdultsHypertension: Oral: Initial: 1 (50) tablet once daily, then individualize dose until optimal dose is achieved

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl$_{cr}$ 15-35 mL/minute: Administer 50 mg/day.

Cl$_{cr}$ <15 mL/minute: Administer 50 mg every other day.

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered without regard to meals.

Dietary ConsiderationsMay be taken without regard to meals.

ContraindicationsHypersensitivity to atenolol, chlorthalidone, or any component of the formulation; pregnancy

Allergy Considerations

- Beta-Blocker Allergy
- Thiazide/Thiazide-Related Diuretic Allergy

Pregnancy Risk FactorD

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsSee individual agents.

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Ampicillin: May decrease the bioavailability of Atenolol. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Theophylline Derivatives: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

50: Atenolol 50 mg and chlorthalidone 25 mg

100: Atenolol 100 mg and chlorthalidone 25 mg

Tenoretic®:

50: Atenolol 50 mg and chlorthalidone 25 mg

100: Atenolol 100 mg and chlorthalidone 25 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Atenolol-Chlorthalidone)

50-25 mg (30): $13.99

100-25 mg (90): $31.00

Tablets (Tenoretic 100)

100-25 mg (30): $83.19

Tablets (Tenoretic 50)

50-25 mg (30): $62.39

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Atenolol
- Chlorthalidone

Dental Health: Effects on Dental TreatmentAtenolol is a cardioselective beta-blocker. Local anesthetic with vasoconstrictor can be safely used in patients medicated with atenolol. Nonselective beta-blockers (ie, propranolol, nadolol) enhance the pressor response to epinephrine, resulting in hypertension and bradycardia; this has not been reported for atenolol. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue, insomnia, and confusion which can clinically look like depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with other psychotropics may produce an additive hypotensive response (especially low-potency antipsychotics and TCAs)

Cardiovascular ConsiderationsSee individual components.

Index TermsChlorthalidone and Atenolol

References

Foster CA and Aston SJ, “Propranolol-Epinephrine Interaction: A Potential Disaster,” *Plast Reconstr Surg*, 1983, 72(1):74-8. [PubMed 6867180]

Wong DG, Spence JD, Lamki L, et al, “Effect of Nonsteroidal Anti-inflammatory Drugs on Control of Hypertension of Beta-Blockers and Diuretics,” *Lancet*, 1986, 1(8488):997-1001.

Wynn RL, “Dental Nonsteroidal Anti-inflammatory Drugs and Prostaglandin-Based Drug Interactions - Part Two,” *Gen Dent*, 1992, 40(2):104, 106, 108. [PubMed 1354194]

Wynn RL, “Epinephrine Interactions With Beta-Blockers,” *Gen Dent*, 1994, 42(1):16, 18.[PubMed 7911769]

International Brand NamesAblok Plus (BR); Apo-Atenidone (MY); Atecard-D (IN); Ateclor (DO, GT, NI, SV); Atel (DE); Atemine (KP); Atenigron (IT); Atenogamma (DE); Atenoric (BR); Atensil-D (PY); Blokium-Diu (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Blokiuret (VE); Prenoretic (PY); Pretenol C (MY); Shpyuja (TW); Target (SG, TW); Tenchlor (ZA); Teneretic (DE); Tenolone (IT); Tenoret (AE, BF, BH, BJ, CI, CY, EG, ET, GB, GH, GM, GN, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Tenoret 50 (HK, ID, MY, TH); Tenoretic (AE, AT, BB, BE, BF, BH, BJ, BM, BR, BS, BZ, CH, CI, CN, CY, CZ, DE, DK, EG, ES, ET, GB, GH, GM, GN, GR, GY, HK, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, OM, PE, PH, PT, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, UY, YE, ZA, ZM, ZW); Tenoric (IN); Tractocile (FR, HU, SE)

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Atenolol may be confused with albuterol, Altenol®, timolol, Tylenol®

Tenormin® may be confused with Imuran®, Norpramin®, thiamine, Trovan®

International issues:

Betanol® [Bangladesh] may be confused with Patanol® which is a brand name for olopatadine in the U.S.

Pronunciation(a TEN oh lole)

U.S. Brand NamesTenormin®

Canadian Brand NamesApo-Atenol®; Gen-Atenolol; Novo-Atenol; Nu-Atenol; PMS-Atenolol; RAN™-Atenolol; Rhoxal-atenolol; Riva-Atenolol; Sandoz-Atenolol; Tenolin; Tenormin®

Pharmacologic CategoryBeta Blocker, Beta$_1$ Selective

Use: Labeled IndicationsTreatment of hypertension, alone or in combination with other agents; management of angina pectoris, postmyocardial infarction patients

Use: Unlabeled/InvestigationalAcute ethanol withdrawal, supraventricular and ventricular arrhythmias, and migraine headache prophylaxis

Dosing: Adults

Hypertension:

Oral: 25-50 mg once daily, may increase to 100 mg/day. Doses >100 mg are unlikely to produce any further benefit.

I.V.: Dosages of 1.25-5 mg every 6-12 hours have been used in short-term management of patients unable to take oral enteral beta-blockers

Angina pectoris: Oral: 50 mg once daily; may increase to 100 mg/day. Some patients may require 200 mg/day.

Postmyocardial infarction:

I.V.: Early treatment: 5 mg slow I.V. over 5 minutes; may repeat in 10 minutes. If both doses are tolerated, may start oral atenolol 50 mg every 12 hours or 100 mg/day for 6-9 days postmyocardial infarction.

Oral: Follow I.V. dose with 100 mg/day or 50 mg twice daily for 6-9 days postmyocardial infarction.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Hypertension: Oral: Children: 0.5-1 mg/kg/dose given daily; range of 0.5-1.5 mg/kg/day; maximum dose: 2 mg/kg/day up to 100 mg/day

Dosing: Renal Impairment

Cl_{cr} 15-35 mL/minute: Administer 50 mg/day maximum.

Cl_{cr} <15 mL/minute: Administer 50 mg every other day maximum.

Hemodialysis effects: Moderately dialyzable (20% to 50%) via hemodialysis. Administer dose postdialysis or administer 25-50 mg supplemental dose. Elimination is not enhanced with peritoneal dialysis. Supplemental dose is not necessary.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.When administered acutely for cardiac treatment, monitor ECG and blood pressure. The injection can be administered undiluted or diluted with a compatible I.V. solution. May administer by rapid infusion (I.V. push) at a rate of 1 mg/minute or by slow infusion over ~30 minutes. Necessary monitoring for surgical patients who are unable to take oral beta-blockers (prolonged ileus) has not been defined. Some institutions require monitoring of baseline and postinfusion heart rate and blood pressure when a patient's response to beta-blockade has not been characterized (ie, the patient's initial dose or following a change in dose). Consult individual institutional policies and procedures.

Administration: I.V. DetailpH: 5.5-6.5
Dietary ConsiderationsMay be taken without regard to meals.
StorageProtect from light.
CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Meperidine, meropenem, morphine. **Incompatible:** Amphotericin B cholesteryl sulfate complex.

Extemporaneously PreparedA 2 mg/mL atenolol oral liquid compounded from tablets and a commercially available oral diluent was found to be stable for up to 40 days when stored at 5°C or 25°C.

> Garner SS, Wiest DB, and Reynolds ER, “Stability of Atenolol in an Extemporaneously Compounded Oral Liquid,” *Am J Hosp Pharm*, 1994, 51(4):508-11.

ContraindicationsHypersensitivity to atenolol or any component of the formulation; sinus bradycardia; sinus node dysfunction; heart block greater than first-degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; uncompensated cardiac failure; pulmonary edema; pregnancy
Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Boxed warnings:

- Abrupt withdrawal: See “Other warnings/precautions” below

Concerns related to adverse events:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; however, atenolol, with B_1 selectivity, has been used cautiously with close monitoring.

- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.

- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.

- Heart failure (HF): Use with caution in patients with compensated heart failure and monitor for a worsening of the condition (efficacy of atenolol in HF has not been demonstrated).

- Myasthenia gravis: Use with caution in patients with myasthenia gravis.

- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).

- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.

- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents which decrease myocardial function.

- Calcium channel blockers: Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur. Avoid concurrent I.V. use of both agents.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: **[U.S. Boxed Warning]: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.**

Geriatric ConsiderationsDue to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (ie, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20% to 50% in the elderly. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults. Since many elderly have Cl_{cr} <35 mL/minute, creatinine clearance should be estimated or measured such that appropriate dose adjustment can be made.
Pregnancy Risk FactorD
Pregnancy ConsiderationsAtenolol crosses the placenta; beta-blockers have been associated with persistent bradycardia, hypotension, and IUGR; IUGR is probably related to maternal hypertension. Available evidence suggests beta-blockers are generally safe during pregnancy (JNC 7). Cases of neonatal hypoglycemia have been reported following maternal use of beta-blockers at parturition or during breast-feeding. Monitor breast-fed infant for symptoms of beta-blockade.

LactationEnters breast milk/use caution

Breast-Feeding Considerations Symptoms of beta-blockade including cyanosis, hypothermia, and bradycardia have been reported in nursing infants.

Adverse Reactions

1% to 10%:

Cardiovascular: Persistent bradycardia, hypotension, chest pain, edema, heart failure, second- or third-degree AV block, Raynaud's phenomenon

Central nervous system: Dizziness, fatigue, insomnia, lethargy, confusion, mental impairment, depression, headache, nightmares

Gastrointestinal: Constipation, diarrhea, nausea

Genitourinary: Impotence

Miscellaneous: Cold extremities

<1% (Limited to important or life-threatening): Alopecia, dyspnea (especially with large doses), hallucinations, impotence, liver enzymes increased, lupus syndrome, Peyronie's disease, positive ANA, psoriasiform rash, psychosis, thrombocytopenia, wheezing

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Ampicillin: May decrease the bioavailability of Atenolol. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Theophylline Derivatives: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Atenolol serum concentrations may be decreased if taken with food.

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Test InteractionsIncreased glucose; decreased HDL

Monitoring ParametersAcute cardiac treatment: Monitor ECG and blood pressure with I.V. administration; heart rate and blood pressure with oral administration

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. **I.V.:** Requires cardiac and hemodynamic monitoring and hypotensive precautions. **Oral:** Assess blood pressure and heart rate prior to and following first dose and any change in dosage. Assess therapeutic effectiveness and adverse effects (eg, CHF, edema, new cough, dyspnea, unresolved fatigue). Advise patients with diabetes to monitor glucose levels closely (beta-blockers may alter glucose tolerance). Do not discontinue abruptly; taper dose gradually. Teach patient appropriate use, possible side effects/interventions (hypotension precautions), and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed; with or without regard to meals; do not take with antacids. Do not adjust dosage or discontinue medication without consulting prescriber. Take pulse daily (prior to medication) and follow prescriber's instruction about holding medication. If you have diabetes, monitor serum sugar closely (drug may alter glucose tolerance or mask signs of hypoglycemia). May cause fatigue, dizziness, or postural hypotension (use caution when changing position from lying or sitting to standing, when driving, or climbing stairs until response to medication is known). Alteration in sexual performance (reversible); or constipation (increased dietary bulk and fluids and exercise may help). Report unresolved swelling of extremities, respiratory difficulty or new cough, unresolved fatigue, unusual weight gain, unresolved constipation, or unusual muscle weakness. **Pregnancy/breast-feeding precautions:** Do not get pregnant or cause a pregnancy (males) while using this medication. Consult prescriber for appropriate contraceptive measures. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution:

Tenormin®: 0.5 mg/mL (10 mL) [DSC]

Tablet: 25 mg, 50 mg, 100 mg

Tenormin®: 25 mg, 50 mg, 100 mg

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Tablets (Atenolol)

25 mg (90): $11.99

50 mg (90): $17.99

100 mg (90): $15.89

Tablets (Tenormin)

25 mg (30): $58.24

50 mg (30): $58.23

100 mg (30): $79.03

Mechanism of ActionCompetitively blocks response to beta-adrenergic stimulation, selectively blocks beta$_1$-receptors with little or no effect on beta$_2$-receptors except at high doses

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Oral: 2-4 hours

Duration: Normal renal function: 12-24 hours

Absorption: Incomplete

Distribution: Low lipophilicity; does not cross blood-brain barrier

Protein binding: 3% to 15%

Metabolism: Limited hepatic

Half-life elimination: Beta:

Neonates: ≤35 hours; Mean: 16 hours

Children: 4.6 hours; children >10 years may have longer half-life (>5 hours) compared to children 5-10 years (<5 hours)

Adults: Normal renal function: 6-9 hours, prolonged with renal impairment; End-stage renal disease: 15-35 hours

Excretion: Feces (50%); urine (40% as unchanged drug)

Related Information

- Beta-Blockers

Dental Health: Effects on Dental TreatmentAtenolol is a cardioselective beta-blocker. Local anesthetic with vasoconstrictor can be safely used in patients medicated with atenolol. Nonselective beta-blockers (ie, propranolol, nadolol) enhance the pressor response to epinephrine, resulting in hypertension and bradycardia; this has not been reported for atenolol. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue, insomnia, and confusion which can clinically look like depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with other psychotropics may produce an additive hypotensive response (especially low-potency antipsychotics and TCAs)

Cardiovascular Considerations

Atrial Fibrillation: Beta-blocker therapy provides effective rate control in patients with atrial fibrillation.

Chronic Stable Angina: Beta-blockers are effective in the treatment of chronic stable angina as monotherapy or when combined with nitrates and/or calcium channel blockers. In patients with severe intractable angina requiring negative cardiac chronotropic medications, pacemaker placement has been carried out to maintain heart rate in the setting of large doses of beta-blockers and/or calcium channel blockers. Beta-blockers are ineffective in the treatment of pure vasospastic (Prinzmetal) angina.

Hypertension: Beta-blocker therapy in the treatment of hypertension has been associated with improved cardiovascular outcomes. According to the 2003 JNC-VII guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Beta-blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for a beta-blocker include patients with heart failure, postmyocardial infarction, high coronary disease risk, or diabetes. In type 2 diabetic patients, a UK Prospective Diabetes Study Group (UKPDS) trial showed that beta-blocker therapy (atenolol) was as effective as an ACE inhibitor in reducing cardiovascular events and that the benefits of therapy were related more to the degree of antihypertensive efficacy rather than the class of drug used.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

ST-Segment Elevation Myocardial Infarction (STEMI): Beta-blockers, without intrinsic sympathomimetic activity (ISA), have been shown to decrease morbidity and mortality when initiated in the acute treatment of STEMI and continued long-term. Oral beta-blockade should be initiated promptly in patients without contraindications (eg, signs of heart failure, evidence of a low output state, risk of cardiogenic shock, or other beta-blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade may be considered and given promptly if the patient is experiencing concomitant hypertension or a tachyarrhythmia (Class IIa recommendation).

Unstable Angina/Non-ST-Segment Elevation MI (UA/NSTEMI): In the treatment of UA/NSTEMI, oral beta-blockade should be initiated within the first 24 hours in patients without contraindications (eg, signs of heart failure, evidence of a low output state, risk of cardiogenic shock, or other beta-blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade should only be considered if the patient is experiencing concomitant hypertension upon presentation (Class IIa recommendation).

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia and hypertension.

Anesthesia and Critical Care Concerns/Other Considerations**Surgery:** Based on available evidence, beta-blockers should be started days to weeks before elective surgery in selected patients when possible and titrated to a heart rate <65 beats per minute. Additional data suggest that long acting beta-blockers may be superior to short acting ones (Redelmeier, 2005). The ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery recommend beta-blockers be continued in patients undergoing surgery who are receiving beta-blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA Class I guideline indications (Class I recommendation). The guidelines also recommend that beta-blockers be given to patients undergoing vascular surgery who have myocardial ischemia demonstrated during preoperative testing (Class I recommendation).

The guidelines also state that beta-blockers are probably recommended in patients undergoing intermediate risk (eg, carotid endarterectomy, prostate surgery) or vascular surgery in whom preoperative assessment identifies coronary heart disease or high cardiac risk (Class IIa recommendation). High cardiac risk is defined as having >1 of the following clinical risk factors: History of ischemic heart disease, compensated or prior heart failure, cerebrovascular disease, diabetes mellitus, or renal insufficiency. The use of beta-blockers is uncertain in patients undergoing intermediate risk or vascular surgery with ≤1 clinical risk factor (Class IIb recommendation).

The majority of published trials suggest a benefit of perioperative beta-blocker use during noncardiac surgery especially in high-risk patients; however, more recent clinical trials have not shown a benefit to perioperative beta-blockade for noncardiac surgery (Juul, 2006; Yang, 2006).

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International Brand NamesAblok (BR); Aloten (PH); Altol (IN); Amolin (IE); Anolene (KP); Anolpin (KP); Anselol (NZ); Antipressan (GB, IE); Apo-Atenol (PL); Arandin (KP); Atarox (PY); Atcard (TH); Atecard (IN); AteHexal (AU, DE); Atehexal (LU, PL); Atelol (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Atendol (DE, PL); Atenet (DK); Ateni (IL); Atenil (CH); Ateno (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Atenobene (HU); Atenodeks (EE); Atenogamma (DE); Atenol (IT); Atenolol (PL); Atenolol Pharmavit (HU); Atenolol von ct (LU); Atenolol-B (HU); Atereal (DE); Atestad (PH); Atoken (MX); B-Vasc (ZA); Betablok (ID); Betacar (CN); Betacard (IN); Betatop Ge (FR); Beten (MY); Betenol (KP); Biofilen (MX); Bloket (PY); Blokium (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, GR, HU, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, VE, YE, ZA, ZM, ZW); Blotex (MX); Cardioten (PH); Catenol (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Coratol (MY); Corotenol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Durabeta (PH); Emtenol (KP); Enolol (TH); Farnormin (ID); Felo-Bits (AR); Hypernol (SG); Hypoten (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Internol (MX); Internolol (ID); Lo-ten (HK, NZ); Loten (MY); Lotenal (KP); Martenol (HK); Myocord (AR); Neotenol (BR); Nolol (DO, TH); Normalol (IL); Normaten (HK); Normiten (IL); Normocard (PL); Nortelol (HK, TH); Noten (AU, MY, SG); Notenol (AU); Oraday (IN, MY, TH); Ormidol (HR); Paesumex (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Plenacor (BR, CO, EC); Preloc (TH); Prenolol (SG, TH); Prenormine (AR); Ranlol (MY); Serten (PH); Tenblok (ID); Tenidon (DK); Tenoblock (FI); Tenocor (TH); Tenol (TH); Tenolol (BF, BJ, CI, ET, GH, GM, GN, KE, LR, LU, MA, ML, MR, MU, MW, NE, NG, SC, SD, SG, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Tenopress (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Tenoprin (FI); Tenormin (AE, AT, AU, BB, BD, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CL, CN, CR, CY, CZ, DE, DK, DO, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PK, PL, PT, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SV, SY, TH, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW);

Tenormin ICN (HU); Tenormine (FR); Tenostat (PH); Tensig (AU); Ternolol (HK); Trebanol (MX); Tredol (AE, BG, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Urosin (MY); Vascoten (HK, MY, SG, TH); Velorin (PH); Vericordin (AR)

Atomoxetine

Lexi-Drugs Online

English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) issued a statement in April 2008 recommending that all children diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the statement due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: Methylphenidate, amphetamine, dextroamphetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children’s Healthcare Quality.

For more information, refer to:

- http://americanheart.mediaroom.com/index.php?s=43&item=422
- http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1
- http://americanheart.mediaroom.com/index.php?s=43&item=398
- http://www.fda.gov/medwatch/safety/2007/safety07.htm
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Pronunciation(AT oh mox e teen)
U.S. Brand NamesStrattera®
Canadian Brand NamesStrattera®
Pharmacologic CategoryNorepinephrine Reuptake Inhibitor, Selective
Use: Labeled IndicationsTreatment of attention deficit/hyperactivity disorder (ADHD)
Dosing: Adults

Treatment of ADHD: Oral: Initial: 40 mg/day, increased after minimum of 3 days to ~80 mg/day; may administer as either a single daily dose or 2 evenly divided doses in morning and late afternoon/early evening. May increase to 100 mg/day in 2-4 additional weeks to achieve optimal response.

Dosage adjustment in patients receiving strong CYP2D6 inhibitors (eg, paroxetine, fluoxetine, quinidine) or patients known to be CYP2D6 poor metabolizers: Do not exceed 80 mg/day; dose adjustments should occur only after 4 weeks.

Note: Atomoxetine may be discontinued without the need for tapering dose.

Dosing: ElderlyUse has not been evaluated in the elderly.
Dosing: Pediatric**Treatment of ADHD:**

Children ≥6 years and ≤70 kg: Oral: Initial: 0.5 mg/kg/day, increase after minimum of 3 days to ~1.2 mg/kg/day; may administer as either a single daily dose or 2 evenly divided doses in morning and late afternoon/early evening. Maximum daily dose: 1.4 mg/kg or 100 mg, whichever is less.

Dosage adjustment in patients receiving strong CYP2D6 inhibitors (eg, paroxetine, fluoxetine, quinidine) or patients known to be CYP2D6 poor metabolizers: Do not exceed 1.2 mg/kg/day; dose adjustments should occur only after 4 weeks.

Children ≥6 years and >70 kg: Refer to adult dosing.

Note: Atomoxetine may be discontinued without the need for tapering dose.

Dosing: Renal ImpairmentNo adjustment needed.
Dosing: Hepatic Impairment

Moderate hepatic insufficiency (Child-Pugh class B): All doses should be reduced to 50% of normal.

Severe hepatic insufficiency (Child-Pugh class C): All doses should be reduced to 25% of normal.

Administration: OralMay be administered with or without food. Swallow capsules whole; do not open capsules. Powder in capsules is an ocular irritant.
Dietary ConsiderationsMay be taken with or without food.
StorageStore at room temperature of 25°C (77°F).
RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) for this medication. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to all patients or parents or guardians of children and teenagers receiving this medication.
ContraindicationsHypersensitivity to atomoxetine or any component of the formulation; use with or within 14 days of MAO inhibitors; narrow-angle glaucoma
Allergy Considerations

- Atomoxetine Allergy

Warnings/Precautions

Boxed warnings:

- Pediatrics: See “Special populations” below.

Concerns related to adverse effects:

- Aggressive behavior: New or worsening symptoms of hostility or aggressive behaviors have been associated with atomoxetine, particularly with the initiation of therapy.

- Allergic reactions: Angioneurotic edema, urticaria, and rash may occur (rare).

- Cardiovascular events: CNS stimulant use has been associated with serious cardiovascular events including sudden death in patients with pre-existing structural cardiac abnormalities or other serious heart problems (sudden death in children and adolescents; sudden death, stroke, and MI in adults). These products should be avoided in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that could increase the risk of sudden death that these conditions alone carry. Patients should be carefully evaluated for cardiac disease prior to initiation of therapy.

- Hepatotoxicity: Use may be associated with rare but severe hepatotoxicity; discontinue and do not restart if signs or symptoms of hepatotoxic reaction (eg, jaundice, pruritus, flu-like symptoms) are noted. Use with caution in patients with hepatic impairment; dosage adjustments may be necessary. Use with caution in patients who are poor metabolizers of CYP2D6 metabolized drugs ("poor metabolizers"); bioavailability increases.

- Priapism: Priapism has been associated with use (rarely).

Disease-related concerns:

- ADHD and comorbidities: Randomized, controlled trials have demonstrated that atomoxetine does not worsen anxiety in patients with existing anxiety disorders or tics related to Tourette's disorder.

- Hypertension: Use with caution in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases in blood pressure or heart rate.

- Psychiatric disorders: Use caution in patients with a history of psychotic illness or bipolar disorder; therapy may induce mixed/manic disorder or psychotic symptoms. Atomoxetine is not approved for major depressive disorder; patients presenting with depressive symptoms should be screened for bipolar disorder.

- Urinary retention: Use with caution in patients with a history of urinary retention or bladder outlet obstruction; may cause urinary retention/hesitancy.

Special populations:

- Pediatrics: **[U.S. Boxed Warning]: Use with caution in pediatric patients; may be an increased risk of suicidal ideation.** Closely monitor for clinical worsening, suicidality, or unusual changes in behavior; especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. The family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. Growth should be monitored during treatment. Height and weight gain may be reduced during the first 9-12 months of treatment, but should recover by 3 years of therapy. Safety and efficacy have not been evaluated in pediatric patients <6 years of age.

Other warnings/precautions:

- ADHD treatment: Appropriate use: Recommended to be used as part of a comprehensive treatment program for attention deficit disorders.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDecreased pup weight and survival were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use only if potential benefit to the mother outweighs possible risk to fetus.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsPercentages as reported in children and adults; some adverse reactions may be increased in "poor metabolizers" (CYP2D6).

>10%:

Central nervous system: Headache (2% to 19%), insomnia (2% to 15%), somnolence (4% to 11%)

Gastrointestinal: Xerostomia (21%), nausea (7% to 21%), abdominal pain (7% to 18%), appetite decreased (11% to 16%), vomiting (3% to 11%)

1% to 10%:

Cardiovascular: Systolic blood pressure increased (4% to 5%), diastolic pressure increased (≤4%), palpitation (3%), flushing (≥2%), tachycardia (≤2%), orthostatic hypotension (<2%)

Central nervous system: Fatigue/lethargy (6% to 9%), dizziness (5% to 6%), irritability (≤6%), chills (3%), sleep disturbance (3%), mood swings (1% to 2%)

Dermatologic: Hyperhidrosis (4%), rash (2%)

Endocrine & metabolic: Hot flashes (8%), dysmenorrhea (6%), libido decreased (4%), menstruation disturbance (2%), orgasm abnormal (2%)

Gastrointestinal: Constipation (1% to 9%), dyspepsia (4%), anorexia (<3%), weight loss (2% to 3%)

Genitourinary: Erectile disturbance (9%), urinary hesitation/retention (7%), dysuria (3%), ejaculatory disturbance (3%), prostatitis (2%)

Neuromuscular & skeletal: Tremor (2%)

Ocular: Mydriasis (≥2%)

Respiratory: Sinus headache (3%)

Miscellaneous: Jittery feeling (2%)

Postmarketing and/or case reports: Allergic reactions, aggressiveness, agitation, akathisia, allergy, angioedema, anxiety, delusional thinking, growth suppression (children), hallucinations, hepatotoxicity, hostility, hypomania, impulsiveness, jaundice, mania, MI, panic attacks, pelvic pain, peripheral vascular instability, priapism, pruritus, QT prolongation, Raynaud's phenomenon, seizure (including patients with no prior history or known risk factors for seizure), stroke, suicidal ideation, syncope, urticaria

Metabolism/Transport Effects**Substrate** of CYP2C19 (minor), 2D6 (major)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Beta2-Agonists: Atomoxetine may enhance the tachycardic effect of Beta2-Agonists. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Antidepressants (Selective Norepinephrine Reuptake Inhibitor) may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the neurotoxic (central) effect of Atomoxetine. *Risk X: Avoid combination*

PARoxetine: May decrease the metabolism of Atomoxetine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersPatient growth (weight/height gain in children); attention, hyperactivity, anxiety, worsening of aggressive behavior or hostility; blood pressure and pulse (baseline and following dose increases and periodically during treatment)

Family members and caregivers need to monitor patient daily for emergence of irritability, agitation, unusual changes in behavior, and suicidal ideation. Pediatric patients should be monitored closely for suicidality, clinical worsening, or unusual changes in behavior, especially during the initial for months of therapy or at times of dose changes. Appearance of symptoms needs to be immediately reported to healthcare provider. Weekly office visits from patient or caregiver are necessary for the first 4 weeks, then every other week for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact may be required between office visits.

When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure, and consider obtaining ECG prior to initiation (Vetter, 2008)

Nursing: Physical Assessment/MonitoringEvaluate need for cautious use (eg, presence of hepatic impairment, renal impairment, hypertension, cardiovascular disease, history of urinary retention, bladder outlet obstruction, psychotic illness, or bipolar disorder). Assess other pharmacological agents or biologicals that patient may be taking for potential interactions (dose adjustments may be necessary). Assess therapeutic effectiveness and adverse response at regular intervals during therapy. Pediatric patients should be screened/monitored for cardiovascular conditions prior to and during use; observed closely during first few months of therapy and when dose is increased or decreased (may be at increased risk of suicidal ideation); growth (height and weight) should also be monitored regularly. Teach patient/caregiver proper use, possible side effects/appropriate interventions, and adverse symptoms to report. Instruct patient/caregiver to read the medication guide that is dispensed with each prescription.

Patient EducationDo not take any new prescription or over-the-counter medications, or herbal products during therapy without consulting prescriber. Take exactly as directed at the same time of day, without regard for meals. Do not discontinue or alter dose without consulting prescriber. Avoid alcohol (may increase CNS depression). You may experience CNS changes; fatigue/lethargy, irritability, sleep disturbances (use caution when driving or engaged in potentially hazardous tasks until response to drug is known); nausea, vomiting, or decreased appetite (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea or constipation (if persistent consult prescriber); menstrual disturbances, abnormal orgasm, erectile or ejaculatory disturbance, impotence; muscle, bone, or joint pain. Report immediately any chest pain, palpitations, rapid heartbeat; suicidal ideation; or persistent CNS changes (especially any increase in aggression or hostility). Inform prescriber of persistent gastrointestinal effects (pain, vomiting, decreased appetite); muscle or skeletal pain or weakness; dark urine, jaundice, right upper-quadrant pain, unexplained flu-like symptoms, or other persistent adverse effects.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Strattera®: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg

Generic AvailableNo

ManufacturerEli Lilly and Company

Pricing: U.S. (www.drugstore.com)

Capsules (Strattera)

10 mg (30): $141.69

18 mg (30): $150.94

25 mg (30): $142.08

40 mg (30): $149.48

60 mg (30): $149.48

80 mg (30): $163.24

100 mg (30): $165.37

Mechanism of ActionSelectively inhibits the reuptake of norepinephrine (Ki 4.5nM) with little to no activity at the other neuronal reuptake pumps or receptor sites.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: V_d: I.V.: 0.85 L/kg

Protein binding: 98%, primarily albumin

Metabolism: Hepatic, via CYP2D6 and CYP2C19; forms metabolites (4-hydroxyatomoxetine, active, equipotent to atomoxetine; N-desmethylatomoxetine in poor metabolizers, limited activity)

Bioavailability: 63% in extensive metabolizers; 94% in poor metabolizers

Half-life elimination: Atomoxetine: 5 hours (up to 24 hours in poor metabolizers); Active metabolites: 4-hydroxyatomoxetine: 6-8 hours; N-desmethylatomoxetine: 6-8 hours (34-40 hours in poor metabolizers)

Time to peak, plasma: 1-2 hours

Excretion: Urine (80%, as conjugated 4-hydroxy metabolite); feces (17%)

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Use vasoconstrictor with caution. Atomoxetine may increase heart rate or blood pressure in the presence of pressor agents. Pressor agents include the vasoconstrictors epinephrine and levonordefrin (Neo-Cobefrin®)

Index Terms Atomoxetine Hydrochloride; LY139603; Methylphenoxy-Benzene Propanamine; Tomoxetine

References

Vetter VL, Elia J, Erickson CH, et al, “Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing,” *Circulation*, 2008, 117:2407-23.[PubMed 18427125]

International Brand Names Attentrol (IN); Passiva (PE); Recit (AR); Strattera (AR, AU, BE, CN, CO, CR, CZ, DE, DK, DO, EE, GB, GT, HK, HN, IE, MX, MY, NI, NL, NO, PA, PE, PH, SE, SG, SV, TH)

Atorvastatin

Lexi-Drugs Online

English

English

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Special Alerts

HMG-CoA Reductase Inhibitors: Evidence Does Not Suggest Increased Incidence of Amyotrophic Lateral Sclerosis (ALS) - Results of FDA Analysis - September 30, 2008

The U.S. Food and Drug Administration's (FDA) review of 41 long-term controlled clinical trials of HMG-CoA reductase inhibitors finds no evidence of an increased incidence of ALS (also known as Lou Gehrig's disease) related to these medications. This analysis occurred after the FDA had received notice of numerous adverse events of which 109 of these reports mentioned ALS, Lou Gehrig's disease, or motor neurone disease. The clinical trials included in the analysis had a median duration of treatment of 3.3 years (range of duration: 6 months to 5 years) and involved 120,964 patients. The analysis identified a total of 19 cases of ALS – 9 cases per 64,602 patients (0.014%) with statin therapy and 10 cases per 56,362 patients (0.017%) with placebo. The incidence rates, based on approximately 400,000 person-years, were 4.2 per 100,000 person-years in the statin-treated group and 5 per 100,000 person-years in the placebo-treated group.

The FDA recommends that health care providers continue to prescribe, and patients continue to use these products as described within their labeling.

For more information, healthcare professionals may refer to the following:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Statin

Colman E, Szarfman A, Wyeth J, et al, "An Evaluation of a Data Mining Signal for Amyotrophic Lateral Sclerosis and Statins Detected in FDA's Spontaneous Adverse Event Reporting System," *Pharmacoepidemiol Drug Saf*, 2008 (epub ahead of print)

Medication Safety Issues

Sound-alike/look-alike issues:

Lipitor® may be confused with Levatol®

Pronunciation(a TORE va sta tin)

U.S. Brand NamesLipitor®

Canadian Brand NamesLipitor®

Pharmacologic CategoryAntilipemic Agent, HMG-CoA Reductase Inhibitor

Use: Labeled IndicationsTreatment of dyslipidemias or primary prevention of cardiovascular disease (atherosclerotic) as detailed below:

Primary prevention of cardiovascular disease (high-risk for CVD): To reduce the risk of MI or stroke in patients without evidence of heart disease who have multiple CVD risk factors or type 2 diabetes. Treatment reduces the risk for angina or revascularization procedures in patients with multiple risk factors.

Secondary prevention of cardiovascular disease: To reduce the risk of MI, stroke, revascularization procedures, and angina in patients with evidence of heart disease. To reduce the risk of hospitalization for heart failure.

Treatment of dyslipidemias: To reduce elevations in total cholesterol, LDL-C, apolipoprotein B, and triglycerides in patients with elevations of one or more components, and/or to increase HDL-C as present in Fredrickson type IIa, IIb, III, and IV hyperlipidemias; treatment of primary dysbetalipoproteinemia, homozygous familial hypercholesterolemia

Treatment of heterozygous familial hypercholesterolemia (HeFH) in adolescent patients (10-17 years of age, females >1 year postmenarche) having LDL-C ≥190 mg/dL or LDL-C ≥160 mg/dL with positive family history of premature cardiovascular disease (CVD) or with two or more CVD risk factors.

Dosing: Adults

Hypercholesterolemia (heterozygous familial and nonfamilial) and mixed hyperlipidemia (Fredrickson types IIa and IIb): Oral: Initial: 10-20 mg once daily; patients requiring >45% reduction in LDL-C may be started at 40 mg once daily; range: 10-80 mg once daily

Homozygous familial hypercholesterolemia: Oral: 10-80 mg once daily

Note: Doses should be individualized according to the baseline LDL-cholesterol levels, the recommended goal of therapy, and patient response; adjustments should be made at intervals of 2-4 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

HeFH: Children 10-17 years (females >1 year postmenarche): Oral: 10 mg once daily (maximum: 20 mg/day)

Note: Doses should be individualized according to the baseline LDL-cholesterol levels, the recommended goal of therapy, and patient response; adjustments should be made at intervals of 2-4 weeks

Dosing: Renal ImpairmentNo adjustment is necessary.
Dosing: Hepatic ImpairmentDecrease dosage with severe disease (eg, chronic alcoholic liver disease).
Administration: OralMay be administered with food if desired; may take without regard to time of day.
Dietary ConsiderationsMay take with food if desired; may take without regard to time of day. Before initiation of therapy, patients should be placed on a standard cholesterol-lowering diet for 3-6 months and the diet should be continued during drug therapy. Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.
ContraindicationsHypersensitivity to atorvastatin or any component of the formulation; active liver disease; unexplained persistent elevations of serum transaminases; pregnancy
Allergy Considerations

- HMG-CoA Reductase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Myopathy/rhabdomyolysis: Patients receiving HMG-CoA reductase inhibitors have developed rhabdomyolysis with acute renal failure and/or myopathy; patients should be monitored closely. This risk is dose-related and is increased with concurrent use of CYP3A4 inhibitors (eg, CSA, clarithromycin, protease inhibitors), fibric acid derivatives (eg, gemfibrozil), or niacin (doses ≥1 g/day) (see Drug Interactions). If concurrent use of clarithromycin or combination protease inhibitors (eg, lopinavir/ritonavir or ritonavir/saquinavir) is warranted consider dose adjustment of atorvastatin. Ensure patient is on the lowest effective atorvastatin dose in all circumstances. Temporarily discontinue for elective major surgery, acute medical or surgical conditions, or in any patient experiencing an acute or serious condition predisposing to renal failure (eg, sepsis, hypotension, trauma, uncontrolled seizures). Based upon current evidence, HMG-CoA reductase inhibitor therapy should be continued in the perioperative period unless risk outweighs cardioprotective benefit. Use caution in patients with renal impairment, inadequately treated hypothyroidism, and those taking other drugs associated with myopathy (eg, colchicine); these patients are predisposed to myopathy. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine.

Disease-related concerns:

- Hemorrhagic stroke: Patients with a history of hemorrhagic stroke may be at increased risk for another with use.

- Hepatic impairment and/or ethanol use: Use with caution in patients who consume large amounts of ethanol or have a history of liver disease.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors (see Drug Interactions); consider alternative agents that avoid or lessen potential for CYP-mediated interactions.

Special populations:

- Elderly: Use with caution in patients with advanced age, these patients are predisposed to myopathy.

- Pediatrics: Safety and efficacy have not been established in patients <10 years or in premenarcheal girls.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

Geriatric ConsiderationsEffective and well tolerated in elderly. The definition of and, therefore, when to treat hyperlipidemia in the elderly is a controversial issue. The National Cholesterol Education Program recommends that all adults maintain a plasma cholesterol <160 mg/dL. Elderly patients with one additional risk factor, goal LDL would be <130 mg/dL. It is the authors' belief that pharmacologic treatment be reserved for those who are unable to obtain a desirable plasma cholesterol concentration by diet alone and for whom the benefits of treatment are believed to outweigh the potential adverse effects, drug interactions, and cost of treatment.
Pregnancy Risk FactorX
Pregnancy ConsiderationsCholesterol biosynthesis may be important in fetal development. Contraindicated in pregnancy. Administer to women of childbearing potential only when conception is highly unlikely and patients have been informed of potential hazards.
LactationEnters breast milk/contraindicated
Adverse Reactions

>10%: Central nervous system: Headache (3% to 17%)

2% to 10%:

Cardiovascular: Chest pain, peripheral edema

Central nervous system: Insomnia, dizziness

Dermatologic: Rash (1% to 4%)

Gastrointestinal: Abdominal pain (up to 4%), constipation (up to 3%), diarrhea (up to 4%), dyspepsia (1% to 3%), flatulence (1% to 3%), nausea

Genitourinary: Urinary tract infection

Hepatic: Transaminases increased (2% to 3% with 80 mg/day dosing)

Neuromuscular & skeletal: Arthralgia (up to 5%), arthritis, back pain (up to 4%), myalgia (up to 6%), weakness (up to 4%)

Respiratory: Sinusitis (up to 6%), pharyngitis (up to 3%), bronchitis, rhinitis

Miscellaneous: Infection (3% to 10%), flu-like syndrome (up to 3%), allergic reaction (up to 3%)

<2% (Limited to important or life-threatening): Abnormal dreams, acne, alopecia, amblyopia, anemia, angina, anorexia, appetite increased, arrhythmia, biliary pain, bursitis, cheilitis, cholestatic jaundice, colitis, cystitis, deafness, depression, dry skin, dry eyes, duodenal ulcer, dysphagia, dyspnea, dysuria, ecchymosis, eczema, edema, emotional lability, enteritis, epididymitis, epistaxis, eructation, esophagitis, eye hemorrhage, facial edema, facial paralysis, fever, fibrocystic breast disease, gastritis, gastroenteritis, gingival hemorrhage, glaucoma, glossitis, gout, hematuria, hepatitis, hyper-/hypoglycemia, hyperkinesia, hypertension, hypertonia, hypoesthesia, impotence, incoordination, kidney calculus, leg cramps, libido decreased, lymphadenopathy, malaise, melena, metrorrhagia, migraine, mouth ulcer, myasthenia, myopathy, myositis, neck rigidity, nephritis, nocturia, palpitation, pancreatitis, paresthesia, parosmia, peripheral neuropathy, petechiae, pharyngitis, phlebitis, photosensitivity, pneumonia, postural hypotension, pruritus, rectal hemorrhage, seborrhea, skin ulcer, somnolence, stomatitis, syncope, taste loss, taste perversion, tendinous contracture, tenesmus, thrombocytopenia, tinnitus, torticollis, urticaria, vaginal hemorrhage, vasodilation, vomiting, weight gain, xerostomia

Postmarketing reports: Anaphylaxis, angioneurotic edema, bullous rash, erythema multiforme, fatigue, rhabdomyolysis, Stevens-Johnson syndrome, tendon rupture, toxic epidermal necrolysis

Additional class-related events or case reports (not necessarily reported with atorvastatin therapy): Alkaline phosphatase increased, cataracts, cirrhosis, CPK increased (>10x normal), dermatomyositis, eosinophilia, erectile dysfunction, extraocular muscle movement impaired, fulminant hepatic necrosis, gynecomastia, hemolytic anemia, memory loss, ophthalmoplegia, peripheral nerve palsy, polymyalgia rheumatica, positive ANA, renal failure (secondary to rhabdomyolysis), systemic lupus erythematosus-like syndrome, thyroid dysfunction, tremor, vasculitis, vertigo

Metabolism/Transport Effects **Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (weak)

Drug Interactions

Aliskiren: Atorvastatin may increase the serum concentration of Aliskiren. *Risk C: Monitor therapy*

Amiodarone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. Management: Dose of HMG-CoA reductase inhibitor may need to be reduced (e.g., simvastatin prescribing information recommends not exceeding 20 mg/day during concurrent therapy). *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Bosentan: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Clopidogrel: Atorvastatin may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Colchicine: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CycloSPORINE: May increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: Atorvastatin may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Danazol: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

DAPTOmycin: HMG-CoA Reductase Inhibitors may enhance the adverse/toxic effect of DAPTOmycin. Specifically, the risk of skeletal muscle toxicity may be increased. Management: Consider temporarily stopping HMG-CoA reductase inhibitor therapy prior to daptomycin. If used together, regular (i.e., at least weekly) monitoring of CPK concentrations is recommended. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Digoxin: Atorvastatin may increase the serum concentration of Digoxin. *Risk C: Monitor therapy*

Etravirine: May decrease the serum concentration of HMG-CoA Reductase Inhibitors. This applies to atorvastatin, lovastatin and simvastatin. Conversely, levels of fluvastatin may be increased. Management: Dose adjustment of the HMG-CoA reductase inhibitor may be warranted. No interaction is expected with rosuvastatin or pravastatin. *Risk C: Monitor therapy*

Fenofibrate: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Gemfibrozil: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Gemfibrozil may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Grapefruit Juice: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Macrolide Antibiotics: May decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Midazolam: Atorvastatin may increase the serum concentration of Midazolam. *Risk C: Monitor therapy*

Nefazodone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Niacin: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Niacinamide: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Protease Inhibitors: May increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Sildenafil: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

St Johns Wort: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid excessive ethanol consumption (due to potential hepatic effects).

Food: Atorvastatin serum concentrations may be increased by grapefruit juice; avoid concurrent intake of large quantities (>1 quart/day). Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.

Herb/Nutraceutical: St John's wort may decrease atorvastatin levels.

Monitoring ParametersLipid levels after 2-4 weeks; LFTs, CPK

It is recommended that liver function tests (LFTs) be performed prior to and at 12 weeks following both the initiation of therapy and any elevation in dose, and periodically (eg, semiannually) thereafter.

Nursing: Physical Assessment/MonitoringEvaluate patient prior to use for history/existence of liver disease, large alcohol intake, or previous hemorrhagic stroke. Assess risk potential for interactions with other prescriptions or herbal products patient may be taking (especially those that may increase risk of rhabdomyolysis). Assess results of laboratory tests prior to initiation and at regular intervals (eg, liver function tests, lipid levels, CPK). Assess for therapeutic response (decreased lipid levels) and adverse effects at regular intervals during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Instruct patients of childbearing age about appropriate contraceptive measures.

Monitoring: Lab TestsMonitor lipid levels after 2-4 weeks; LFTs prior to initiation and 12 weeks after initiation or first dose or dose elevation, and periodically (semiannually) thereafter; CPK

Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. May take without regard to food (avoid large intake of grapefruit juice). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will need periodic laboratory evaluation during therapy. This drug does not eliminate the need for diet or exercise regimen as recommended by prescriber. May cause headache (consult prescriber for approved analgesic); insomnia or dizziness (use caution when driving or engaging in tasks that require alertness until response to medication is known); diarrhea (buttermilk, boiled milk, or yogurt may help), or constipation (increased dietary fluid and fiber may help). Report chest pain or unusual swelling of extremities; unresolved diarrhea or constipation; itching or burning on urination; unusual muscle cramping or weakness; yellowing of skin or eyes; easy bruising or bleeding, or unusual fatigue. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during therapy. Consult prescriber for instructions on appropriate contraceptive measures. This drug can cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Lipitor®: 10 mg, 20 mg, 40 mg, 80 mg

Generic AvailableNo

ManufacturerPfizer
Pricing: U.S. (www.drugstore.com)

Tablets (Lipitor)

10 mg (30): $85.99

20 mg (30): $119.99

40 mg (30): $119.99

80 mg (30): $119.99

Mechanism of ActionInhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis (reduces the production of mevalonic acid from HMG-CoA); this then results in a compensatory increase in the expression of LDL receptors on hepatocyte membranes and a stimulation of LDL catabolism
Pharmacodynamics/Kinetics

Onset of action: Initial changes: 3-5 days; Maximal reduction in plasma cholesterol and triglycerides: 2 weeks

Absorption: Rapid

Distribution: V_d: 318 L

Protein binding: ≥98%

Metabolism: Hepatic; forms active ortho- and parahydroxylated derivates and an inactive beta-oxidation product

Bioavailability: ~14% (parent drug); ~30% (parent drug and equipotent metabolites)

Half-life elimination: Parent drug: 14 hours; Equipotent metabolites: 20-30 hours

Time to peak, serum: 1-2 hours

Excretion: Bile; urine (2% as unchanged drug)

Related Information

- Antacid Drug Interactions
- Hyperlipidemia Management
- Lipid-Lowering Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause fatigue; rare reports of euphoria
Mental Health: Effects on Psychiatric TreatmentNone reported
Cardiovascular ConsiderationsHMG-CoA reductase inhibitors are effective in primary and secondary prevention of cardiovascular events in patients with hyperlipidemia. For primary prevention, a patient's major risk factors (cigarette smoking, hypertension or currently taking antihypertensives, low HDL-C, family history, age, gender) should be evaluated. Patients with multiple risk factors (≥2) require more intensive therapy guided by the calculation of a 10-year absolute CHD risk (eg, the percent probability of having a CHD event in next 10 years). An individual's 10-year absolute CHD risk can be calculated at www.med-decisions.com/cvtool/phys/phys.html. LDL cholesterol goals, therapeutic lifestyle changes, and drug therapy are determined based upon a patient's risk factor profile.

Primary prevention trials show that cholesterol-lowering drugs reduce the risk of major coronary events, coronary death, and cerebrovascular events even in the first 6-12 months of use. The WOSCOP trial suggested a trend towards enhanced survival using pravastatin in their patients (mean LDL-cholesterol of 192 mg/dL and no history of MI). In a recent trial (Sever PS, 2003), patients with HTN and at least three other risk factors were randomized to 10 mg daily of atorvastatin or placebo. These patients had a total nonfasting cholesterol <250 mg/dL before treatment. LDL-C levels were 132 mg/dL before treatment and fell to an average of 90 mg/dL in the atorvastatin-treated group. There was a significant reduction in stroke, cardiovascular events, and coronary events in the atorvastatin-treated group as compared to the placebo group. There was no difference in mortality between the groups.

Secondary prevention trials indicate that “statin” therapy reduces mortality, major coronary events, coronary artery procedures, and stroke. The Heart Protection Study proved that lowering serum cholesterol levels reduces the rate of major vascular events among high-risk individuals with documented vascular disease (CHD, cerebrovascular, peripheral vascular) or diabetes regardless of initial cholesterol concentrations. PROVE IT is a randomized, double-blind trial evaluating hospitalized patients with acute coronary syndrome to determine the effects of intense LDL-C lowering therapy. Four thousand patients with an LDL-C levels of 106 mg/dL were randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily. After 2 years, the combined cardiovascular endpoint (death, MI, unstable angina requiring hospitalization, revascularization and stroke) was ~26% in the pravastatin patients (median LDL-C 95 mg/dL) and ~22% in the atorvastatin treated patients (median LDL-C 62 mg/dL).

LaRosa and colleagues assessed the efficacy and safety of lowering LDL cholesterol <100 mg/dL in patients with stable coronary heart disease (LaRosa JC, 2005). Ten thousand and one patients with baseline LDL levels <130 mg/dL were randomized to atorvastatin 10 mg or 80 mg daily and followed for a median of 4.9 years. The primary endpoint was the occurrence of the first major cardiovascular event (death from CVD, MI, resuscitation after cardiac arrest, or stroke). A primary event occurred in 434 patients (8.7%) receiving 80 mg daily (mean LDL 77 mg/dL) and 548 patients (10.9%) receiving 10 mg dose (mean LDL 101 mg/dL) (95% CI, 0.69-0.89; p <0.001). There was no mortality difference between the two treatment groups.

HMG-CoA reductase inhibitors decrease levels of high-sensitivity C-reactive protein (hs-CRP). They also possess pleiotropic properties including improved endothelial function, reduced inflammation at the site of the coronary plaque, inhibition of platelet aggregation, and anticoagulant effects. These nonlipid effects may be beneficial when HMG-CoA reductase inhibitors are introduced early in the management of acute coronary syndromes (de Denus S, 2002).

Myopathy: Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years of age), women more frequently than men, small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, drug interactions (use with caution or avoid). The combination of a HMG-CoA reductase inhibitor plus nicotinic acid seems to carry a lower risk of myopathy than does a HMG-CoA reductase inhibitor plus a fibrate. Other medications, when used concurrently, may enhance the risk of myopathy associated with statins; these include drugs that inhibit CYP3A4 isoenzymes (lovastatin, simvastatin, atorvastatin) or CYP2C9 isoenzymes (fluvastatin). HMG-CoA reductase inhibitors may exacerbate exercise-induced skeletal muscle injury. Many experts favor getting a baseline creatine kinase (CK) measurement before initiating therapy (asymptomatic CK elevations are common). Obtain a CK measurement if patient complains of muscle soreness, tenderness, or pain.

Anesthesia and Critical Care Concerns/Other Considerations **Myopathy:** Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years), gender (occurs in women more frequently than men), small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, and drug interactions (use with caution or avoid).

Based on current research, HMG-CoA reductase inhibitors should be continued in the perioperative period. Postoperative discontinuation of statin therapy is associated with an increased risk of cardiac morbidity and mortality.

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International Brand NamesAtarva (AR); Atopitar (PH); Ator (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Atoris (BE, PL); Atorlip (CO); Atorsan (ID); Atovarol (CO); Cardyl (ES); Citalor (BR); Glustar (CO); Hipolixan (CN); Lipitor (AE, AR, AU, BD, BE, BF, BH, BJ, BO, BR, CI, CL, CN, CO, CR, CY, DO, EC, EE, EG, ET, FI, GB, GH, GM, GN, GR, GT, HK, HN, ID, IE, IL, IN, IQ, IR, IT, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PK, PR, PY, QA, SA, SC, SD, SE, SG, SL, SN, SV, SY, TH, TN, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Lipodar (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Lipomax (PY); Lowlipen (CO); Sortis (AT, BG, CH, CZ, DE, HN, PL, SE); Storvas (IN, MY); Tahor (FR, MU); Tulip (PL); Zarator (AR, CN, DK, ES, PT)

Atovaquone and Proguanil

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Pronunciation(a TOE va kwone & pro GWA nil)

U.S. Brand NamesMalarone®

Canadian Brand NamesMalarone®; Malarone® Pediatric

Pharmacologic CategoryAntimalarial Agent

Use: Labeled IndicationsPrevention or treatment of acute, uncomplicated *P. falciparum* malaria

Dosing: AdultsDoses given in mg of atovaquone and proguanil:

Prevention of malaria: Oral: Atovaquone/proguanil 250 mg/100 mg once daily; start 1-2 days prior to entering a malaria-endemic area, continue throughout the stay and for 7 days after returning.

Treatment of acute malaria: Oral: Atovaquone/proguanil 1 g/400 mg as a single dose, once daily for 3 consecutive days

Dosing: ElderlyRefer to adult dosing. Use with caution due to possible decrease in renal and hepatic function, as well as possible decreases in cardiac function, concomitant diseases, or other drug therapy.

Dosing: PediatricDoses given in mg of atovaquone and proguanil (dosage based on body weight):

Prevention of malaria: Oral: Start 1-2 days prior to entering a malaria-endemic area, continue throughout the stay and for 7 days after returning. Take as a single dose, once daily.

11-20 kg: Atovaquone/proguanil 62.5 mg/25 mg

21-30 kg: Atovaquone/proguanil 125 mg/50 mg

31-40 kg: Atovaquone/proguanil 187.5 mg/75 mg

>40 kg: Atovaquone/proguanil 250 mg/100 mg

Treatment of acute malaria: Oral: Take as a single dose, once daily for 3 consecutive days.

5-8 kg: Atovaquone/proguanil 125 mg/50 mg

9-10 kg: Atovaquone/proguanil 187.5 mg/75 mg

11-20 kg: Atovaquone/proguanil 250 mg/100 mg

21-30 kg: Atovaquone/proguanil 500 mg/200 mg

31-40 kg: Atovaquone/proguanil 750 mg/300 mg

>40 kg: Atovaquone/proguanil 1 g/400 mg

Dosing: Renal ImpairmentNo dosage adjustment required in mild-to-moderate renal impairment. Contraindicated as prophylaxis in severe renal impairment (Cl_{cr} <30 mL/minute). May use for 3-day treatment in patients with severe renal impairment if benefit outweighs risk.

Dosing: Hepatic ImpairmentNo dosage adjustment required in mild-to-moderate hepatic impairment. No data available for use in severe hepatic impairment.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister with food or milk-based drink at the same time each day. If patient vomits within 1 hour of administration, repeat the dose. For children who have difficulty swallowing tablets, tablets may be crushed and mixed with condensed milk just prior to administration.

Dietary ConsiderationsMust be taken with food or a milky drink.

StorageStore tablets at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to atovaquone, proguanil, or any component of the formulation; prophylactic use in severe renal impairment (Cl_{cr} <30 mL/minute)

Warnings/Precautions

Concerns related to adverse events:

- Hepatic effects: Increased transaminase levels and hepatitis (rare) have been reported with prophylactic use; single case report of hepatic failure requiring transplantation documented. Monitor closely and use caution in patients with existing hepatic impairment. Data from clinical trials indicates that elevations in AST/ALT may persist for up to 4 weeks following treatment.

Disease-related concerns:

- Diarrhea/vomiting: Absorption of atovaquone may be decreased in patients who have diarrhea or vomiting; monitor closely and consider use of an antiemetic. If severe, consider use of an alternative antimalarial.

- Malaria: Appropriate use: Not indicated for severe or complicated malaria. Delayed cases of *P. falciparum* malaria may occur after stopping prophylaxis; travelers returning from endemic areas who develop febrile illnesses should be evaluated for malaria. Recrudescent infections or infections following prophylaxis with this agent should be treated with alternative agent(s).

- Renal impairment: Use with caution in patients with pre-existing renal disease. May use with caution for treatment of malaria in patients with severe renal impairment (Cl_{cr} <30 mL/minute) if benefit outweighs risk. Contraindicated for prophylactic use in severe renal impairment.

Special populations:

- Pediatrics: Not for use in patients <5 kg (treatment) or <11 kg (prophylaxis).

Pregnancy Risk FactorC

Pregnancy ConsiderationsUse in pregnant women only if the potential benefit outweighs the possible risk to the fetus. There are no adequate and well-controlled studies of atovaquone and/or proguanil in pregnant women. Because *P. falciparum* malaria can cause maternal death and fetal loss, pregnant women traveling to malaria-endemic areas must use personal protection against mosquito bites.

Lactation

Atovaquone: Excretion in breast milk unknown/use caution

Proguanil: Enters breast milk (small amounts)/use caution

Adverse ReactionsThe following adverse reactions were reported in patients being treated for malaria. When used for prophylaxis, reactions are similar to those seen with placebo.

>10%:

Gastrointestinal: Abdominal pain (17%), nausea (12%), vomiting (children 10% to 13%, adults 12%)

Hepatic: Transaminase increases (ALT 27%, AST 17%; increased LFT values typically normalized after ~4 weeks)

1% to 10%:

Central nervous system: Headache (10%), dizziness (5%)

Dermatologic: Pruritus (children 6%)

Gastrointestinal: Diarrhea (children 6%, adults 8%), anorexia (5%)

Neuromuscular & skeletal: Weakness (8%)

Postmarketing and/or case reports: Anaphylaxis, anemia (rare), angioedema, erythema multiforme, hallucinations, hepatitis, hepatic failure (case report), neutropenia, pancytopenia (with severe renal impairment), photosensitivity, psychotic episodes, rash, seizure, Stevens-Johnson syndrome, urticaria

Metabolism/Transport EffectsProguanil: **Substrate** (minor) of 1A2, 2C19, 3A4

Drug Interactions

Antipsychotic Agents (Phenothiazines): Antimalarial Agents may increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Indinavir: Atovaquone may decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Atovaquone. *Risk D: Consider therapy modification*

Ritonavir: May decrease the serum concentration of Atovaquone. *Risk C: Monitor therapy*

Tetracycline: May decrease the serum concentration of Atovaquone. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Atovaquone taken with dietary fat increases the rate and extent of absorption.

Herb/Nutraceutical: Herbs with hypoglycemic properties may enhance the hypoglycemic effect of atovaquone. This includes alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, stinging nettle.

Nursing: Physical Assessment/MonitoringSee individual agent for Atovaquone.

Patient EducationSee individual agent for Atovaquone.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, oral:

Malarone®: Atovaquone 250 mg and proguanil hydrochloride 100 mg

Tablet, oral [pediatric]:

Malarone®: Atovaquone 62.5 mg and proguanil hydrochloride 25 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Malarone)

62.5-25 mg (7): $26.99

250-100 mg (7): $48.95

Mechanism of Action

Atovaquone: Selectively inhibits parasite mitochondrial electron transport.

Proguanil: The metabolite cycloguanil inhibits dihydrofolate reductase, disrupting deoxythymidylate synthesis. Together, atovaquone/cycloguanil affect the erythrocytic and exoerythrocytic stages of development.

Pharmacodynamics/Kinetics

Atovaquone: See Atovaquone.

Proguanil:

Absorption: Extensive

Distribution: 42 L/kg

Protein binding: 75%

Metabolism: Hepatic to active metabolites, cycloguanil (via CYP2C19) and 4-chlorophenylbiguanide

Half-life elimination: 12-21 hours

Excretion: Urine (40% to 60%)

Related Information

- Atovaquone
- Malaria Treatment

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay produce abnormal dreams; may rarely cause seizures and hallucinations

Mental Health: Effects on Psychiatric TreatmentSignificant adverse GI effects; use caution with SSRIs

Index TermsAtovaquone and Proguanil Hydrochloride; Proguanil and Atovaquone; Proguanil Hydrochloride and Atovaquone

International Brand NamesMalalone (KP); Malarone (AU, BE, CH, CZ, DE, DK, EE, ES, FI, FR, GB, HK, IE, IL, IT, MY, NO, PE, PT, SE, SG)

Atovaquone

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English English

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Pronunciation(a TOE va kwone)
U.S. Brand NamesMepron®
Canadian Brand NamesMepron®
Pharmacologic CategoryAntiprotozoal
Use: Labeled IndicationsAcute oral treatment of mild-to-moderate *Pneumocystis jirovecii* pneumonia (PCP) in patients who are intolerant to co-trimoxazole; prophylaxis of PCP in patients who are intolerant to co-trimoxazole
Use: Unlabeled/InvestigationalTreatment of babesiosis; treatment/suppression of *Toxoplasma gondii* encephalitis; primary prophylaxis of HIV-infected persons at high risk for developing *Toxoplasma gondii* encephalitis
Dosing: Adults

Prevention of PCP: Oral: 1500 mg once daily with food

Treatment of mild-to-moderate PCP: Oral: 750 mg twice daily with food for 21 days

Babesiosis (unlabeled use): 750 mg twice daily with azithromycin for 7-10 days

***Toxoplasma gondii*encephalitis (unlabeled use; AIDSinfo guidelines):** Oral:

Prophylaxis: 1500 mg once daily with food

Treatment: 750 mg 4 times daily or 1500 mg twice daily with food for at least 6 weeks after resolution of signs and symptoms

Suppression after treatment: 750 mg 2-4 times/day with food

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Children <13 years (unlabeled uses, AIDSinfo guidelines):

Prevention of PCP: Oral:

1-3 months: 30 mg/kg once daily with food

4-24 months: 45 mg/kg once daily with food

>24 months: 30 mg/kg once daily with food

Treatment of mild-to-moderate PCP: Oral:

Birth to 3 months: 30-40 mg/kg/day in 2 divided doses with food (maximum: 1500 mg/day)

3-24 months: 45 mg/kg/day in 2 divided doses with food

≥24 months: 30-40 mg/kg/day in 2 divided doses with food (maximum: 1500 mg/day)

Babesiosis: Oral: 20 mg/kg/day in 2 divided doses with food for 7-10 days

Toxoplasma gondii*prophylaxis:* Oral:

1-3 months: 30 mg/kg once daily with food

4-24 months: 45 mg/kg once daily with food

>24 months: 30 mg/kg once daily with food

Adolescents 13-16 years: Refer to adult dosing.
Administration: OralMust be taken administered meals. Shake suspension gently before use. Once opened, the foil pouch can be emptied on a dosing spoon, in a cup, or directly into the mouth.
Dietary ConsiderationsMust be taken with meals.
StorageStore at 15°C to 25°C (59°F to 77°F). Do not freeze.
ContraindicationsLife-threatening allergic reaction to atovaquone or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Diarrhea/vomiting: Absorption may be decreased in patients who have diarrhea or vomiting; monitor closely and consider use of an antiemetic. If severe, consider use of an alternative antimalarial.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with severe hepatic impairment; rare cases of hepatitis, elevated liver function tests, and liver failure have been reported.

- *Pneumocystis jirovecii* pneumonia (PCP): Appropriate use: When used for treatment, has only been indicated in mild-to-moderate PCP; not studied for use in severe PCP.

Special populations:

- Elderly: Use with caution in elderly patients due to potentially impaired renal, hepatic, and cardiac function.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies of atovaquone in pregnant women. Use in pregnant women only if the potential benefit outweighs the possible risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**Note:** Adverse reaction statistics have been compiled from studies including patients with advanced HIV disease. Consequently, it is difficult to distinguish reactions attributed to atovaquone from those caused by the underlying disease or a combination thereof.

>10%:

Central nervous system: Fever (14% to 40%), headache (16% to 31%), insomnia (10% to 19%), depression, pain

Dermatologic: Rash (22% to 46%), pruritus (5% to ≥10%)

Gastrointestinal: Diarrhea (19% to 42%), nausea (21% to 32%), vomiting (14% to 22%), abdominal pain (4% to 21%)

Neuromuscular & skeletal: Weakness (8% to 31%), myalgia

Respiratory: Cough (14% to 25%), rhinitis (5% to 24%), dyspnea (15% to 21%), sinusitis (7% to ≥10%)

Miscellaneous: Infection (18% to 22%), diaphoresis, flu-like syndrome

1% to 10%:

Cardiovascular: Hypotension (≤1%)

Central nervous system: Dizziness (3% to 8%), anxiety (≤7%)

Endocrine & metabolic: Hyponatremia (7% to 10%), hyperglycemia (≤9%), hypoglycemia (≤1%)

Gastrointestinal: Amylase increased (7% to 8%), anorexia (≤7%), dyspepsia (≤5%), constipation (≤3%), taste perversion (≤3%)

Hematologic: Anemia (4% to 6%), neutropenia (3% to 5%)

Hepatic: Liver enzymes increased (4% to 8%)

Renal: BUN increased (≤1%), creatinine increased (≤1%)

Respiratory: Bronchospasm (2% to 4%)

Miscellaneous: Oral moniliasis (5% to 10%)

Postmarketing and/or case reports: Acute renal failure, allergic reaction, angioedema, erythema multiforme, hepatitis (rare), hypersensitivity reactions, liver failure (rare), methemoglobinemia, pancreatitis, skin desquamation, Stevens-Johnson syndrome, throat tightness, thrombocytopenia, urticaria, vortex keratopathy

Drug Interactions

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Indinavir: Atovaquone may decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Atovaquone. *Risk D: Consider therapy modification*

Ritonavir: May decrease the serum concentration of Atovaquone. *Risk C: Monitor therapy*

Tetracycline: May decrease the serum concentration of Atovaquone. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Ingestion with a fatty meal increases absorption.

Herb/Nutraceutical: Herbs with hypoglycemic properties may enhance the hypoglycemic effect of atovaquone. This includes alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, stinging nettle.

Nursing: Physical Assessment/MonitoringMonitor for CNS and respiratory changes and patient's knowledge of adverse reactions. Assess for interactions with other prescription or OTC medications.

Patient EducationTake as directed. Take with high-fat meals. You may experience dizziness or lightheadedness; use caution when driving or engaging in tasks that require alertness until response to drug is known. Small meals may help reduce nausea. Report unresolved diarrhea, fever, mouth sores (use good mouth care), unresolved headache, or vomiting. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, oral:

Mepron®: 750 mg/5 mL (5 mL, 210 mL) [contains benzyl alcohol; citrus flavor]

Generic AvailableNo
ManufacturerGlaxoSmithKline
Mechanism of ActionInhibits electron transport in mitochondria resulting in the inhibition of key metabolic enzymes responsible for the synthesis of nucleic acids and ATP
Pharmacodynamics/Kinetics

Absorption: Significantly increased with a high-fat meal

Distribution: V_{dss}: 0.6 ± 17 L/kg

Protein binding: >99%

Metabolism: Undergoes enterohepatic recirculation

Bioavailability: 32% to 62%

Half-life elimination: 1.5-4 days

Excretion: Feces (>94% as unchanged drug); urine (<1%)

Related Information

- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral moniliasis
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause anxiety
Mental Health: Effects on Psychiatric TreatmentMay cause anemia and neutropenia; use caution with clozapine and carbamazepine
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International Brand NamesMepron (BB, BM, BS, BZ, GY, JM, NL, PL, SR, TT); Wellvone (AT, AU, CH, DE, DK, ES, FR, GB, IE, IT, NL, SE)

Atracurium

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English

English

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(a tra KYOO ree um)

Canadian Brand NamesAtracurium Besylate Injection

Pharmacologic CategoryNeuromuscular Blocker Agent, Nondepolarizing

Use: Labeled IndicationsAdjunct to general anesthesia to facilitate endotracheal intubation and to relax skeletal muscles during surgery; to facilitate mechanical ventilation in ICU patients; does not relieve pain or produce sedation

Dosing: AdultsFor I.V. administration only (not to be used I.M.): Dose to effect; doses must be individualized due to interpatient variability; use ideal body weight for obese patients.

Adjunct to surgical anesthesia (neuromuscular blockade):

I.V. (bolus): 0.4-0.5 mg/kg, then 0.08-0.1 mg/kg 20-45 minutes after initial dose to maintain neuromuscular block, followed by repeat doses of 0.08-0.1 mg/kg at 15- to 25-minute intervals

Initial dose after succinylcholine for intubation (balanced anesthesia): 0.2-0.4 mg/kg

Pretreatment/priming: I.V.: 10% of intubating dose given 3-5 minutes before initial dose

I.V. continuous infusion: Initial: 9-10 mcg/kg/minute at initial signs of recovery from bolus dose; block is usually maintained by a rate of 5-9 mcg/kg/minute under balanced anesthesia.

ICU neuromuscular blockade: I.V.: Initial (bolus) 0.4-0.5 mg/kg, followed by I.V. continuous infusion at an initial rate of 5-10 mcg/kg/minute; block is usually maintained by rate of 11-13 mcg/kg/minute (rates for pediatric patients may be higher).

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Adjunct to surgical anesthesia:** I.V. (not to be used I.M.): Dose to effect; doses must be individualized due to interpatient variability; use ideal body weight for obese patients

Children 1 month to 2 years: Initial: 0.3-0.4 mg/kg followed by maintenance doses as needed to maintain neuromuscular blockade

Children >2 years: Refer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentNo adjustment is necessary.

Calculations

- Atracurium

Administration: I.M.Not for I.M. injection due to tissue irritation.

Administration: I.V.May be given undiluted as a bolus injection. Administration via infusion requires the use of an infusion pump. Use infusion solutions within 24 hours of preparation.

Administration: I.V. DetailpH: 3.25-3.65 (adjusted)

StorageRefrigerate intact vials at 2°C to 8°C (36°F to 46°F). Protect from freezing. Use vials within 14 days upon removal from the refrigerator to room temperature of 25°C (77°F). Dilutions of 0.2 mg/mL or 0.5 mg/mL in 0.9% sodium chloride, dextrose 5% in water, or 5% dextrose in sodium chloride 0.9% are stable for up to 24 hours at room temperature or under refrigeration.

ReconstitutionAtracurium should not be mixed with alkaline solutions.

CompatibilityStable in D_5W, NS, D_5NS; **incompatible** with LR.

Y-site administration: Compatible: Cefazolin, cefuroxime, cimetidine, clarithromycin, dobutamine, dopamine, epinephrine, esmolol, etomidate, fentanyl, gentamicin, heparin, hydrocortisone sodium succinate, isoproterenol, lorazepam, midazolam, milrinone, morphine, nitroglycerin, ranitidine, sodium nitroprusside, trimethoprim/sulfamethoxazole, vancomycin. **Incompatible:** Diazepam, propofol, thiopental.

Compatibility in syringe: Compatible: Alfentanil, fentanyl, midazolam, sufentanil.

Compatibility when admixed: Compatible: Bretylium, cimetidine, dobutamine, dopamine, esmolol, gentamicin, isoproterenol, lidocaine, morphine, potassium chloride, procainamide, vancomycin. **Incompatible:** Aminophylline, cefazolin, heparin, quinidine gluconate, ranitidine, sodium nitroprusside.

ContraindicationsHypersensitivity to atracurium besylate or any component of the formulation

Allergy Considerations

- Neuromuscular-Blocking Agent Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bradycardia: May be more common with atracurium than with other neuromuscular-blocking agents since it has no clinically-significant effects on heart rate to counteract the bradycardia produced by anesthetics.
- Neuromuscular cross-sensitivity: Cross-sensitivity with other neuromuscular-blocking agents may occur; use extreme caution in patients with previous anaphylactic reactions.

Disease-related concerns:

- Burn injury: Resistance may occur in burn patients (>30% of body) for period of 5-70 days postinjury.
- Conditions which may antagonize neuromuscular blockade: Alkalosis, hypercalcemia, demyelinating lesions, peripheral neuropathies, denervation, infection, muscle trauma, and diabetes mellitus may result in antagonism of neuromuscular blockade.
- Conditions which may potentiate neuromuscular blockade: Electrolyte abnormalities, severe hyponatremia, severe hypocalcemia, severe hypokalemia, hypermagnesemia, neuromuscular diseases, acidosis, acute intermittent porphyria, Eaton-Lambert syndrome, myasthenia gravis, renal failure, and hepatic failure may result in potentiation of neuromuscular blockade.

Special populations:

- Elderly: Use with caution in the elderly, effects and duration are more variable.
- Immobilized patients: Resistance may occur in patients who are immobilized.

Other warnings/precautions:

- Appropriate use: Maintenance of an adequate airway and respiratory support is critical. Resistance may develop with chronic treatment.
- Experienced personnel: Should be administered by adequately trained individuals familiar with its use.
- Histamine release: Reduce initial dosage and inject slowly (over 1-2 minutes) in patients in whom substantial histamine release would be potentially hazardous (eg, patients with clinically-important cardiovascular disease).

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsMild, rare, and generally suggestive of histamine release

1% to 10%: Cardiovascular: Flushing

<1%: Bronchial secretions, erythema, hives, itching, wheezing

Postmarketing and/or case reports: Allergic reaction, bradycardia, bronchospasm, dyspnea, hypotension, injection site reaction, seizure, acute quadriplegic myopathy syndrome (prolonged use), laryngospasm, myositis ossificans (prolonged use), tachycardia, urticaria

Causes of prolonged neuromuscular blockade: Excessive drug administration; cumulative drug effect, metabolism/excretion decreased (hepatic and/or renal impairment); accumulation of active metabolites; electrolyte imbalance (hypokalemia, hypocalcemia, hypermagnesemia, hypernatremia); hypothermia

Drug Interactions

Acetylcholinesterase Inhibitors: May diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). Acetylcholinesterase Inhibitors may decrease the metabolism of Neuromuscular-Blocking Agents (Nondepolarizing). This is only true for mivacurium in which case the neuromuscular blocking effects might be prolonged. *Risk C: Monitor therapy*

Aminoglycosides: May enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Neuromuscular-Blocking Agents may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Neuromuscular-Blocking Agents may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Calcium Channel Blockers: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Cardiac Glycosides: Neuromuscular-Blocking Agents may enhance the arrhythmogenic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Colistimethate: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Neuromuscular-Blocking Agents (Nondepolarizing) may enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

Inhalational Anesthetics: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Neuromuscular-Blocking Agents (Nondepolarizing). Specifically, episodes of apnea have been reported in patients using this combination. *Risk C: Monitor therapy*

Lincosamide Antibiotics: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Lithium: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Loop Diuretics: May diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Loop Diuretics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Magnesium Salts: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Polymyxin B: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Procainamide: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

QuiNIDine: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Tetracycline Derivatives: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Vancomycin: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Monitoring ParametersVital signs (heart rate, blood pressure, respiratory rate); degree of muscle relaxation (via peripheral nerve stimulator and presence of spontaneous movement); renal function (serum creatinine, BUN) and liver function when in ICU

In the ICU setting, prolonged paralysis and generalized myopathy, following discontinuation of agent, may be minimized by appropriately monitoring degree of blockade.

Nursing: Physical Assessment/MonitoringOnly clinicians experienced in the use of neuromuscular-blocking drugs should administer and/or manage the use of atracurium. Dosage and rate of administration should be individualized and titrated to the desired effect, according to relevant clinical factors, premedication, concomitant medications, age, and general condition of the patient. Ventilatory support must be instituted and maintained until adequate respiratory muscle function and/or airway protection are assured. Assess other medications for effectiveness and safety. Other drugs that affect neuromuscular activity may increase/decrease neuromuscular block induced by atracurium. This drug does not cause anesthesia or analgesia; pain must be treated with appropriate analgesic agents. Continuous monitoring of vital signs, cardiac status, respiratory status, and degree of neuromuscular block (objective assessment with peripheral external nerve stimulator) is mandatory during infusion and until full muscle tone has returned. Muscle tone returns in a predictable pattern, starting with diaphragm, abdomen, chest, limbs, and finally muscles of the neck, face, and eyes. Safety precautions must be maintained until full muscle tone has returned. **Note:** It may take longer for return of muscle tone in obese or elderly patients or patients with renal or hepatic disease, myasthenia gravis, myopathy, other neuromuscular disease, dehydration, electrolyte imbalance, or severe acid/base imbalance. Provide appropriate patient teaching/support prior to and following administration.

Long-term use: Monitor fluid levels (intake and output) during and following infusion. Reposition patient and provide appropriate skin care, mouth care, and care of patient's eyes every 2-3 hours while sedated. Provide appropriate emotional and sensory support (auditory and environmental).

Monitoring: Lab TestsRenal function (serum creatinine, BUN) and liver function when in ICU

Patient EducationPatient will usually be unconscious prior to administration. Patient education should be appropriate to individual situation. Reassurance of constant monitoring and emotional support to reduce fear and anxiety should precede and follow administration. Following return of muscle tone, do not attempt to change position or rise from bed without assistance. Report immediately any skin rash or hives, pounding heartbeat, respiratory difficulty, or muscle tremors. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, as besylate: 10 mg/mL (10 mL) [contains benzyl alcohol]

Injection, as besylate [preservative free]: 10 mg/mL (5 mL)

Generic AvailableYes

Mechanism of ActionBlocks neural transmission at the myoneural junction by binding with cholinergic receptor sites

Pharmacodynamics/Kinetics

Onset of action (dose dependent): 2-3 minutes

Duration: Recovery begins in 20-35 minutes following initial dose of 0.4-0.5 mg/kg under balanced anesthesia; recovery to 95% of control takes 60-70 minutes

Metabolism: Undergoes ester hydrolysis and Hofmann elimination (nonbiologic process independent of renal, hepatic, or enzymatic function); metabolites have no neuromuscular blocking properties; laudanosine, a product of Hofmann elimination, is a CNS stimulant and can accumulate with prolonged use. Laudanosine is hepatically metabolized.

Half-life elimination: Biphasic: Adults: Initial (distribution): 2 minutes; Terminal: 20 minutes

Excretion: Urine (<5%)

Related Information

- Neuromuscular-Blocking Agents

Pharmacotherapy PearlsAtracurium is classified as an intermediate-duration neuromuscular-blocking agent. It does not appear to have a cumulative effect on the duration of blockade. It does not relieve pain or produce sedation.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other ConsiderationsAtracurium is classified as an intermediate duration neuromuscular-blocking agent; does not appear to have a cumulative effect on the duration of blockade.

Critically-Ill Adult Patients:

The 2008 Surviving Sepsis Campaign guidelines recommend avoiding use of neuromuscular blockers if at all possible in the septic patient due to the risk of prolonged neuromuscular blockade following discontinuation. If one is required, monitor the depth of blockade (Grade 1B).

The 2002 ACCM/SCCM/ASHP clinical practice guidelines for sustained neuromuscular blockade in the adult critically-ill patient recommend:

Optimize sedatives and analgesics prior to initiation, and monitor and adjust accordingly during course. Neuromuscular blockers do not relieve pain or produce sedation.

Protect patient's eyes from development of keratitis and corneal abrasion by administering ophthalmic ointment and taping eyelids closed or using eye patches. Reposition patient routinely to protect pressure points from breakdown. Address DVT prophylaxis.

Concurrent use of a neuromuscular blocker and corticosteroids appear to increase the risk of certain ICU myopathies; avoid or administer the corticosteroid at the lowest dose possible. Reassess need for neuromuscular blocker daily.

Using daily drug holidays (stopping neuromuscular-blocking agent until patient requires it again) may decrease the incidence of acute quadriplegic myopathy syndrome.

Tachyphylaxis can develop; switch to another neuromuscular blocker (taking into consideration the patient's organ function) if paralysis is still necessary.

Acidosis and severe hypothermia may delay the elimination of atracurium and cisatracurium.

Atracurium or cisatracurium is recommended for patients with significant hepatic or renal disease due to organ-independent Hofmann elimination.

Monitor patients clinically and via “Train of Four” (TOF) testing with a goal of adjusting the degree of blockade to 1-2 twitches or based upon the patient's clinical condition.

Index TermsAtracurium Besylate

References

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International Brand NamesAbbocurium (PL); Aculex (KP); Atra (TH); Genso (TW); Nimbex (PL); Notrixum (ID); Relatrac (CO, MX, PE); Tracrium (AE, AR, AT, AU, BB, BD, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CL, CN, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PH, PK, PL, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Tracur (BR); Tracurix (AR); Tramus (ID)

Atropine and Pralidoxime

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English

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Pronunciation(A troe peen & pra li DOKS eem)

U.S. Brand NamesATNAA; Duodote™

Pharmacologic CategoryAnticholinergic Agent; Antidote

Use: Labeled Indications

ATNAA: Treatment of poisoning by susceptible organophosphorous nerve agents having anticholinesterase activity for self or buddy-administration by military personnel

Duodote™: Treatment of poisoning by organophosphorous nerve agents (eg, tabun, sarin, soman) or organophosphorous insecticide for use by trained emergency medical services personnel

Dosing: AdultsOrganophosphorous poisoning: I.M.: **Note:** If suspected, antidotal therapy should be given immediately as soon as symptoms appear (critical to administer immediately in case of soman exposure). Definitive medical care should be sought after any injection given. One injection only may be given as self-aid. If repeat injections needed, administration must be done by another trained individual. Emergency medical personnel who have self-administered a dose must determine capacity to continue to provide care.

ATNAA:

Mild symptoms (some or all mild symptoms): Self-Aid or Buddy-Aid: 1 injection (wait 10-15 minutes for effect); if patient is able to ambulate, and knows who and where they are, then no more injections are needed. If symptoms still present: Buddy-Aid: May repeat 1-2 more injections

Severe symptoms (if most or all): Buddy-Aid: If no self-aid given, 3 injections in rapid succession; if 1 self-aid injection given, 2 injections in rapid succession

Maximum cumulative dose: 3 injections

Symptoms provided by manufacturer in ATNAA product labeling to guide therapy:

Mild symptoms: Breathing difficulties, chest tightness, coughing, difficulty in seeing, drooling, headache, localized sweating and muscular twitching, miosis, nausea (with or without vomiting), runny nose, stomach cramps, tachycardia (followed by bradycardia), wheezing

Severe symptoms: Bradycardia, confused/strange behavior, convulsions, increased wheezing and breathing difficulties, involuntary urination/defecation, miosis (severe), muscular twitching/generalized weakness (severe), red/teary eyes, respiratory failure, unconsciousness, vomiting

Duodote™:

Mild symptoms (≥2 mild symptoms): 1 injection (wait 10-15 minutes for effect); if after 10-15 minutes no severe symptoms emerge, no further injections are indicated; if any severe symptoms emerge at any point following initial injection, repeat dose by giving 2 additional injections in rapid succession. Transport to medical care facility.

Severe symptoms (≥1 severe symptom): 3 injections in rapid succession. Transport to medical care facility.

Maximum cumulative dose: 3 injections unless medical care support (eg, hospital, respiratory support) is available

Symptoms provided by manufacturer in Duodote™ product labeling to guide therapy:

Mild symptoms: Airway secretions increased, blurred vision, bradycardia, breathing difficulties, chest tightness, drooling miosis, nausea, vomiting, runny nose, salivation, stomach cramps (acute onset), tachycardia, teary eyes, tremors/muscular twitching, wheezing/coughing

Severe symptoms: Breathing difficulties (severe), confused/strange behavior, convulsions, copious secretions from lung or airway, involuntary urination/defecation, muscular twitching/generalized weakness (severe)

Dosing: ElderlyRefer to adult dosing. No dosing adjustment recommended.

Dosing: Renal ImpairmentUse caution in renal impairment; pralidoxime is renally eliminated.

Administration: I.M.Self-administration: Hold device firmly at center with green tip (needle end) pointing down; remove gray safety release with other hand; do not touch green tip at any time. The device is ready for administration into the mid-outer thigh; removal of clothing is not necessary, but pockets should be empty. Swing at a 90° angle to allow the green tip to push against the mid-outer thigh. Hold firmly in place until auto-injector triggers and an additional 10 seconds after device has triggered. After administration, needle will be visible; if needle is not visible, repeat above steps. After use, bend needle against a hard surface (needle does not retract) to avoid accidental injury.

ATNAA: May be administered in lateral thigh muscle or buttocks

StorageStore at 15°C to 30°C (59°F to 86°F); avoid freezing. Protect from light.

Restrictions

ATNAA (**A**ntidote **T**reatment-**N**erve **A**gent **A**uto-Injector) is only available for use by U.S. Armed Forces military personnel. Information on distribution is available at Defense Services Supply Center-Philadelphia at https://dmmonline.dscp.dla.mil/pharm/nerve.asp

Duodote™ is only available for use by trained emergency medical services personnel to treat civilians. Distribution is limited to directly from manufacturer (Meridian Medical Technologies, Inc.) to emergency medical service organizations or their suppliers.

ContraindicationsHypersensitivity to atropine, pralidoxime, or any component of the formulation; no contraindications exist in the treatment of life-threatening organophosphorous poisoning

Warnings/Precautions

Concerns related to adverse effects:

- Atropinization: Signs of atropinization (eg, flushing, mydriasis, tachycardia, dryness of mouth or nose) may occur earlier than expected with use of combination product compared to atropine alone. Monitor effects closely when administering subsequent injections as necessary.

- Hyperthermia: Atropine may inhibit sweating and possibly lead to heat injury or hyperthermia in patients exposed to warm environments or exercise.

Disease-related concerns: The following diseases are precautions only when symptoms of poisoning are **not** severe:

- Cardiovascular disease: Use with caution in patients with heart disease, arrhythmias (eg, atrial flutter), severe CAD, or history of recent MI; treatment-related blood pressure increases and tachycardia may lead to ischemia, precipitate an MI, or increase arrhythmogenic potential.

- Chronic lung disease: Use with caution in patients with chronic lung disease patients; may cause inspiration of bronchial secretions and formation of dangerous viscid plugs.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; may precipitate myasthenic crisis.

- Narrow-angle glaucoma: Use with caution in patients with severe narrow-angle glaucoma; may precipitate acute glaucoma.

- Prostatic hyperplasia: Use with caution in patients with prostatic hyperplasia; may cause urinary retention.

- Pyloric stenosis: Use with caution in patients with pyloric stenosis; may cause complete pyloric obstruction.

- Renal impairment: Use with caution in renal impairment; pralidoxime is excreted renally.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to the anticholinergic effects of atropine.

- Pediatrics: Safety and efficacy have not been established in children. Children may be more sensitive to the anticholinergic effects of atropine.

Other warnings/precautions:

- Appropriate use: Clinical symptoms consistent with highly-suspected organophosphorous poisoning should be treated with antidote immediately; administration should not be delayed for confirmatory laboratory tests. Treatment should always include proper evacuation and decontamination procedures; medical personnel should protect themselves from inadvertent contamination. Antidotal administration is intended only for initial management; definitive and more extensive medical care is required following administration. Individuals should not rely solely on antidote for treatment, as other supportive measures (eg, artificial respiration) may still be required.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Also refer to individual agents.

Lactation

Atropine: Enters breast milk (trace amounts)/use caution (AAP rates “compatible”)

Pralidoxime: Excretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsSee individual agents.

Adverse ReactionsAlso see individual agents.

Reactions reported with Duodote™. Frequency not defined:

Cardiovascular: Blood pressure increased (transient; usually occurring 15 minutes after administration and returning to baseline 4 hours postdose)

Local: Injection site muscle tightness and pain (mild-to-moderate)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Monitoring ParametersRespiratory status, ABGs, pulse oximeter; body temperature (especially in warm climates); blood pressure (peak effect occurs ~15 minutes after administration); symptoms of poisoning

Reference RangeDirect measurement of RBC acetylcholinesterase activity provides a measure of degree of toxicity, although symptoms may not correlate with degree of inactivation unless activity reduced to <50%. Sequential measurement (if rapidly available) may help determine the effectiveness of oxime therapy. Plasma (or pseudo) cholinesterase activity is more easily performed, but does not correlate well with severity and should not be used to guide therapy.

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationThis medication will only be administered in an emergency situation. Primary protection against exposure to chemical nerve agents and insecticide poisoning is the wearing of protective garments and mask. Evacuation and decontamination should be done as soon as possible.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

ATNAA, Duodote™: Atropine 2.1 mg/0.7 mL and pralidoxime chloride 600 mg/2 mL [contains benzyl alcohol; prefilled autoinjector]

Generic AvailableNo

ManufacturerMeridian Medical Technologies™, Inc

Mechanism of Action

Atropine: Functions as a competitive antagonist of acetylcholine at muscarinic receptors in the peripheral and central nervous system, thus reducing the symptoms of parasympathetic overstimulation resulting from excess acetylcholine caused by organophosphorous poisoning. Parasympatholytic action of atropine decreases oral and respiratory secretions, relieves airway constriction, and attenuates the bradycardia induced by organophosphates. Antagonizes acetylcholine accumulation at respiratory center and may reduce centrally-mediated respiratory paralysis.

Pralidoxime: An oxime which functions by way of nucleophilic attack on the ester site of the acetylcholinesterase enzyme deactivated by phosphorylation. Displacement of the phosphoryl group allows reactivation of acetylcholinesterase's hydrolytic activity, thus permitting renewed catalysis of accumulated acetylcholine. Destruction of accumulated acetylcholine allows for restoration of normal functioning at neuromuscular junctions and relief of respiratory muscle paralysis.

Pharmacodynamics/KineticsSee individual agents.

Pharmacotherapy PearlsEvacuation and decontamination procedures should be undertaken as soon as possible. Medical personnel need to protect themselves from accidental exposure. Primary prophylaxis against organophosphorous nerve agents should always consist of appropriate protective garments and masks. Organophosphate agents are well absorbed through skin, lungs, and GI tract. They are usually described as having a petroleum or garlic like odor. Once absorbed, organophosphate agents bind to acetylcholinesterase (also known as RBC acetylcholinesterases) and inactivate the enzyme. Acetylcholinesterases catalyze the hydrolysis of acetylcholine to choline and acetic acid; therefore, once inactivated excess acetylcholine accumulates.

Clinical symptoms of toxicity are associated with cholinergic excess and involve the autonomic nervous system, CNS, and neuromuscular junction. Clinical features of acute cholinergic toxicity include bradycardia, miosis, lacrimation, salivation, bronchorrhea, bronchospasm, emesis and diarrhea. At times, mydriasis and tachycardia may be observed. 100% oxygen and fluid resuscitation are important initial steps in management. Onset and duration of clinical features consistent with poisoning vary depending on agent and route of exposure; therefore, every effort should be made to identify poisoning agent. In addition, time interval to "aging" process (irreversible binding between organophosphates and acetylcholinesterase) vary depending on nerve agent. Once "aging" has occurred, oxime therapy (eg, pralidoxime) is ineffective, thus making timing of antidote administration critical, particularly in the case of soman exposure where "aging" process occurs within minutes of exposure.

Mental Health: Effects on Mental StatusMay cause ataxia, hallucinations, dizziness, drowsiness, amnesia, difficulty concentrating, agitation, delirium, paranoia, anxiety, and mania

Mental Health: Effects on Psychiatric TreatmentAtropine and pralidoxime may decrease the effects of acetylcholinesterase inhibitors. Concurrent use with psychotropics may result in additive anticholinergic side effects (eg, dry mouth, blurred vision, or constipation); avoid use with phenothiazines; effects of barbiturates may be increased by atropine and pralidoxime

Index TermsAtropine and Pralidoxime Chloride; Mark 1™; NAAK; Nerve Agent Antidote Kit; Pralidoxime and Atropine

References

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Atropine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues
International issues:

Genatropine® [France] may be confused with Genotropin®

Pronunciation(A troe peen)

U.S. Brand NamesAtroPen®; Atropine-Care®; Isopto® Atropine; Sal-Tropine™

Canadian Brand NamesDioptic's Atropine Solution; Isopto® Atropine

Pharmacologic CategoryAnticholinergic Agent; Anticholinergic Agent, Ophthalmic; Antidote; Antispasmodic Agent, Gastrointestinal; Ophthalmic Agent, Mydriatic

Use: Labeled Indications

Injection: Preoperative medication to inhibit salivation and secretions; treatment of symptomatic sinus bradycardia; AV block (nodal level); ventricular asystole; antidote for anticholinesterase inhibitor poisoning (carbamate insecticides, nerve agents, organophosphate insecticides)

Ophthalmic: Produce mydriasis and cycloplegia for examination of the retina and optic disc and accurate measurement of refractive errors; uveitis

Oral: Inhibit salivation and secretions

Use: Unlabeled/InvestigationalPulseless electric activity, asystole, neuromuscular blockade reversal

Use: DentalReduction of salivation and bronchial secretions

Dosing: AdultsDoses <0.5 mg have been associated with paradoxical bradycardia.

Asystole:

I.V.: 1 mg; repeat in 3-5 minutes if asystole persists; total dose of 0.04 mg/kg.

Intratracheal: Administer 2-2.5 times the recommended I.V. dose; dilute in 10 mL NS or distilled water. **Note:** Absorption is greater with distilled water, but causes more adverse effects on PaO_2.

Inhibit salivation and secretions (preanesthesia):

I.M., I.V., SubQ: 0.4-0.6 mg 30-60 minutes preop and repeat every 4-6 hours as needed.

Oral: 0.4 mg; may repeat in 4 hours if necessary; 0.4 mg initial dose may be exceeded in certain cases and may repeat in 4 hours if necessary

Bradycardia:*I.V.:* 0.5-1 mg every 5 minutes, not to exceed a total of 3 mg or 0.04 mg/kg; may give intratracheal in 1 mg/10 mL dilution only, intratracheal dose should be 2-2.5 times the I.V. dose.

Neuromuscular blockade reversal:*I.V.:* 25-30 mcg/kg 30-60 seconds before neostigmine or 7-10 mcg/kg 30-60 seconds before edrophonium

Organophosphate or carbamate poisoning:Note: The dose of atropine required varies considerably with the severity of poisoning. Total amount of atropine used in carbamate poisoning is usually less. Severely poisoned patients may exhibit significant tolerance to atropine; ≥2 times the suggested doses may be needed. Titrate to pulmonary status (decreased bronchial secretions). Once patient is stable for a period of time, the dose/dosing frequency may be decreased. If atropinization occurs after 1-2 mg of atropine then re-evaluate working diagnosis.

I.V.: Initial: 1-5 mg; doses should be doubled every 5 minutes until signs of muscarinic excess abate (clearing of bronchial secretions, bronchospasm, and adequate oxygenation). Overly aggressive dosing may cause anticholinergic toxicity (eg, delirium, hyperthermia, and muscle twitching).

I.V. Infusion: 0.5-1 mg/hour or 10% to 20% of loading dose/hour

I.M.: AtroPen®: Mild symptoms: Administer 2 mg as soon as exposure is known or suspected. If severe symptoms develop after first dose, 2 additional doses should be repeated in 10 minutes; do not administer more than 3 doses. Severe symptoms: Immediately administer three 2 mg doses.

Nerve agent toxicity management: *I.M.:* See **Note**. Prehospital (“in the field”) or hospital/emergency department: Mild-to-moderate symptoms: 2-4 mg; severe symptoms: 6 mg

Note: Pralidoxime is a component of the management of nerve agent toxicity; consult Pralidoxime for specific route and dose.

Prehospital (“in the field”) management: Repeat atropine I.M. (2 mg) at 5-10 minute intervals until secretions have diminished and breathing is comfortable or airway resistance has returned to near normal.

Hospital management: Repeat atropine I.M. (2 mg) at 5-10 minute intervals until secretions have diminished and breathing is comfortable or airway resistance has returned to near normal.

Mydriasis, cycloplegia (preprocedure): *Ophthalmic* (1% solution): Instill 1-2 drops 1 hour before the procedure.

Uveitis: *Ophthalmic:*

1% solution: Instill 1-2 drops 4 times/day.

Ointment: Apply a small amount in the conjunctival sac up to 3 times/day. Compress the lacrimal sac by digital pressure for 1-3 minutes after instillation.

Dosing: ElderlyRefer to adult dosing.

Nerve agent toxicity management: See **Note**. I.M.: Elderly and frail patients:

Prehospital ("in the field"): Mild-to-moderate symptoms: 1 mg; severe symptoms: 2-4 mg

Hospital/emergency department: Mild-to-moderate symptoms: 1 mg; severe symptoms: 2 mg

Note: Pralidoxime is a component of the management of nerve agent toxicity; consult Pralidoxime for specific route and dose.

Prehospital ("in the field") management: Repeat atropine I.M. (2 mg) at 5-10 minute intervals until secretions have diminished and breathing is comfortable or airway resistance has returned to near normal.

Hospital management: Repeat atropine I.M. (2 mg) at 5-10 minute intervals until secretions have diminished and breathing is comfortable or airway resistance has returned to near normal.

Dosing: Pediatric**Note:** Doses <0.1 mg have been associated with paradoxical bradycardia.

Inhibit salivation and secretions (preanesthesia): Oral, I.M., I.V., SubQ: Neonates, Infants, and Children:

Children <5 kg: 0.02 mg/kg/dose 30-60 minutes preop then every 4-6 hours as needed. Use of a minimum dosage of 0.1 mg in neonates <5 kg will result in dosages >0.02 mg/kg. There is no documented minimum dosage in this age group.

Children >5 kg: 0.01-0.02 mg/kg/dose to a maximum 0.4 mg/dose 30-60 minutes preop; minimum dose: 0.1 mg

Alternate dosing:

3-7 kg (7-16 lb): 0.1 mg

8-11 kg (17-24 lb): 0.15 mg

11-18 kg (24-40 lb): 0.2 mg

18-29 kg (40-65 lb): 0.3 mg

>30 kg (>65 lb): 0.4 mg

Bradycardia: I.V., intratracheal: Neonates, Infants, and Children:

0.02 mg/kg, minimum dose 0.1 mg, maximum single dose: 0.5 mg in children and 1 mg in adolescents; may repeat in 5-minute intervals to a maximum total dose of 1 mg in children or 2 mg in adolescents. (**Note:** For intratracheal administration, the dosage must be diluted with normal saline to a total volume of 1-5 mL). When treating bradycardia in neonates, reserve use for those patients unresponsive to improved oxygenation and epinephrine.

Organophosphate or carbamate poisoning:

I.V.: Children: 0.03-0.05 mg/kg every 10-20 minutes until atropine effect, then every 1-4 hours for at least 24 hours

I.M. (AtroPen®): Children: Mild symptoms: Administer dose listed below as soon as exposure is known or suspected. If severe symptoms develop after first dose, 2 additional doses should be repeated in 10 minutes; do not administer more than 3 doses. Severe symptoms: Immediately administer 3 doses as follows:

<6.8 kg (15 lb): Use of **AtroPen® formulation not recommended**; administer atropine 0.05 mg/kg

6.8-18 kg (15-40 lb): 0.5 mg/dose

18-41 kg (40-90 lb): 1 mg/dose

>41 kg (>90 lb): 2 mg/dose

Nerve agent toxicity management: I.M.: Infants and Children: See following **Note**.

Prehospital ("in the field"):

Birth to <2 years: Mild-to-moderate symptoms: 0.05 mg/kg; severe symptoms: 0.1 mg/kg

2-10 years: Mild-to-moderate symptoms: 1 mg; severe symptoms: 2 mg

>10 years: Mild-to-moderate symptoms: 2 mg; severe symptoms: 4 mg

Hospital/emergency department:

Birth to <2 years: Mild-to-moderate symptoms: 0.05 mg/kg I.M. **or** 0.02 mg/kg I.V.; severe symptoms: 0.1 mg/kg I.M. **or** 0.02 mg/kg I.V.

2-10 years: Mild-to-moderate symptoms: 1 mg; severe symptoms: 2 mg

>10 years: Mild-to-moderate symptoms: 2 mg; severe symptoms: 4 mg

Note: Pralidoxime is a component of the management of nerve agent toxicity; consult Pralidoxime for specific route and dose.

Prehospital ("in the field") management: Repeat atropine I.M. (0.05-0.1 mg/kg) at 5-10 minute intervals until secretions have diminished and breathing is comfortable or airway resistance has returned to near normal.

Hospital management: Repeat atropine I.M. (infants: 1 mg; all others: 2 mg) at 5-10 minute intervals until secretions have diminished and breathing is comfortable or airway resistance has returned to near normal.

Administration: I.M.AtroPen®: Administer to outer thigh. May be given through clothing as long as pockets at the injection site are empty. Hold autoinjector in place for 10 seconds following injection; massage the injection site.

Administration: I.V.Administer undiluted by rapid I.V. injection; slow injection may result in paradoxical bradycardia.

Administration: I.V. DetailpH: 3-6.5; AtroPen®: pH: 4-5

Administration: OtherIntratracheal: Dilute in NS or distilled water. Absorption is greater with distilled water, but causes more adverse effects on PaO_2. Pass catheter beyond tip of tracheal tube, stop compressions, spray drug quickly down tube. Follow immediately with several quick insufflations and continue chest compressions.

StorageStore injection at controlled room temperature of 15°C to 30°C (59°F to 86°F); avoid freezing. In addition, AtroPen® should be protected from light.

Compatibility

Y-site administration: Compatible: Etomidate, famotidine, heparin, hydrocortisone sodium succinate, inamrinone, meropenem, nafcillin, potassium chloride, propofol, sufentanil, vitamin B complex with C. **Incompatible:** Thiopental.

Compatibility in syringe: Compatible: Butorphanol, chlorpromazine, cimetidine, dimenhydrinate, diphenhydramine, droperidol, fentanyl, glycopyrrolate, heparin, hydromorphone, hydroxyzine, hydroxyzine with meperidine, meperidine, meperidine with promethazine, metoclopramide, midazolam, milrinone, morphine, nalbuphine, ondansetron, pentazocine, perphenazine, prochlorperazine, promazine, promethazine, propiomazine, ranitidine, scopolamine, sufentanil. **Incompatible:** Cimetidine with pentobarbital. **Variable (consult detailed reference):** Pentobarbital.

Compatibility when admixed: Compatible: Dobutamine, furosemide, meropenem, sodium bicarbonate, verapamil. **Incompatible:** Floxacillin, metaraminol, methohexital, norepinephrine.

RestrictionsThe AtroPen® formulation is available for use primarily by the Department of Defense.

ContraindicationsHypersensitivity to atropine or any component of the formulation; narrow-angle glaucoma; adhesions between the iris and lens; tachycardia; obstructive GI disease; paralytic ileus; intestinal atony of the elderly or debilitated patient; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; hepatic disease; obstructive uropathy; renal disease; myasthenia gravis (unless used to treat side effects of acetylcholinesterase inhibitor); asthma; thyrotoxicosis; Mobitz type II block

Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hyperthermia: In the presence of a high environmental temperature, heat prostration can occur.
- Psychosis: Can occur in sensitive individuals.

Disease-related concerns:

- Autonomic neuropathy: Use with caution in patients with autonomic neuropathy.
- Benign prostatic hyperplasia (BPH): Use with caution in patients with BPH.
- Cardiovascular disease: Use with caution in patients with myocardial ischemia, HF, tachyarrhythmias, and/or hypertension.
- Hiatal hernia: Use with caution in patients with hiatal hernia associated with reflux esophagitis.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.

Special populations:

- Elderly: Use with caution in the elderly; may be sensitive to side effects.
- Pediatrics: Use with caution in children with spastic paralysis.

Dosage form specific issues:

- AtroPen®: There are no absolute contraindications for the use of atropine in severe organophosphate poisonings, however in mild poisonings, use caution in those patients where the use of atropine would be otherwise contraindicated. Formulation for use by trained personnel only.

Geriatric ConsiderationsAnticholinergic agents are generally not well tolerated in the elderly and their use should be avoided when possible. In elderly, anticholinergic agents should not be used as prophylaxis against extrapyramidal symptoms.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Atropine has been found to cross the human placenta.

LactationEnters breast milk (trace amounts)/use caution (AAP rates "compatible")

Breast-Feeding ConsiderationsAnticholinergic agents may suppress lactation.

Adverse ReactionsSeverity and frequency of adverse reactions are dose related and vary greatly; listed reactions are limited to significant and/or life-threatening.

Cardiovascular: Arrhythmia, flushing, hypotension, palpitation, tachycardia

Central nervous system: Ataxia, coma, delirium, disorientation, dizziness, drowsiness, excitement, fever, hallucinations, headache, insomnia, nervousness

Dermatologic: Anhidrosis, urticaria, rash, scarlatiniform rash

Gastrointestinal: Bloating, constipation, delayed gastric emptying, loss of taste, nausea, paralytic ileus, vomiting, xerostomia, dry throat, nasal dryness

Genitourinary: Urinary hesitancy, urinary retention

Neuromuscular & skeletal: Weakness

Ocular: Angle-closure glaucoma, blurred vision, cycloplegia, dry eyes, mydriasis, ocular tension increased

Respiratory: Dyspnea, laryngospasm, pulmonary edema

Miscellaneous: Anaphylaxis

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Monitoring ParametersHeart rate, blood pressure, pulse, mental status; intravenous administration requires a cardiac monitor

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor for tachycardia, hypotension especially if cardiac problems are present. Be alert to the potential of heat prostration in the presence of high temperatures. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake oral forms exactly as directed, 30 minutes before meals. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Void before taking medication. You may experience dizziness, blurred vision, sensitivity to light (use caution when driving or engaging in tasks requiring alertness until response to drug is known); dry mouth, nausea, or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); orthostatic hypotension (use caution when climbing stairs and when rising from lying or sitting position); constipation (increased exercise, fluids, fruit, or fiber may help; if not effective, consult prescriber); increased sensitivity to heat and decreased perspiration (avoid extremes of heat, reduce exercise in hot weather); or decreased milk if breast-feeding. Report hot, dry, flushed skin; blurred vision or vision changes; difficulty swallowing; chest pain, palpitations, or rapid heartbeat; painful or difficult urination; increased confusion, depression, or loss of memory; rapid or difficult respirations; muscle weakness or tremors; or eye pain.

Ophthalmic: Instill as often as recommended. Wash hands before using. Sit or lie down, open eye, look at ceiling, and instill prescribed amount of solution. Do not blink for 30 seconds, close eye and roll eye in all directions, and apply gentle pressure to inner corner of eye for 1-2 minutes. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Temporary stinging or blurred vision may occur.

Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sulfate: 0.05 mg/mL (5 mL); 0.1 mg/mL (5 mL, 10 mL); 0.4 mg/0.5 mL (0.5 mL); 0.4 mg/mL (0.5 mL, 1 mL, 20 mL); 1 mg/mL (1 mL)

AtroPen®: 0.25 mg/0.3 mL (0.3 mL); 0.5 mg/0.7 mL (0.7 mL); 1 mg/0.7 mL (0.7 mL); 2 mg/0.7 mL (0.7 mL) [prefilled autoinjector]

Ointment, ophthalmic, as sulfate: 1% (3.5 g)

Solution, ophthalmic, as sulfate: 1% (2 mL, 5 mL, 15 mL)

Atropine-Care®: 1% (2 mL) [contains benzalkonium chloride]

Isopto® Atropine: 1% (5 mL, 15 mL) [contains benzalkonium chloride]

Tablet, as sulfate:

Sal-Tropine™: 0.4 mg

Generic AvailableYes: Excludes tablet

Pricing: U.S. (www.drugstore.com)

Ointment (Atropine Sulfate)

1% (3.5): $8.99

Solution (Atropine Sulfate)

0.4 mg/mL (200): $23.14

1% (5): $8.99

1% (15): $12.99

Solution (Atropine-Care)

1% (2): $7.99

Solution (Isopto Atropine)

1% (5): $24.13

1% (15): $31.45

Tablets (Sal-Tropine)

0.4 mg (30): $19.99

Mechanism of ActionBlocks the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands, and the CNS; increases cardiac output, dries secretions. Atropine reverses the muscarinic effects of cholinergic poisoning. The primary goal in cholinergic poisonings is reversal of bronchorrhea and bronchoconstriction. Atropine has no effect on the nicotinic receptors responsible for muscle weakness, fasciculations, and paralysis.

Pharmacodynamics/Kinetics

Onset of action: I.V.: Rapid

Absorption: Complete

Distribution: Widely throughout the body; crosses placenta; trace amounts enter breast milk; crosses blood-brain barrier

Metabolism: Hepatic

Half-life elimination: 2-3 hours

Excretion: Urine (30% to 50% as unchanged drug and metabolites)

Related Information

- Cycloplegic Mydriatics
- Pralidoxime

Dental Health Professional ConsiderationsThe possibility of the need for an initial dose in excess of 0.4 mg has been confirmed by the American Dental Association in its recommendation on the use of this medication to reduce salivation during dental procedures.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), dry throat, and nasal dryness

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusUse of injectable dosage form may cause ataxia, hallucinations, dizziness, amnesia, difficulty concentrating, agitation, delirium, paranoia, anxiety, and mania

Mental Health: Effects on Psychiatric TreatmentMay decrease the effects of phenothiazines; concurrent use with psychotropics may result in additive anticholinergic side effects (dry mouth, blurred vision, constipation)

Cardiovascular ConsiderationsAtropine, at usual recommended cardiovascular doses, causes blockade of muscarinic receptors at the cardiac SA-node and is parasympatholytic (ie, blocks vagal activity increasing heart rate). A dose 0.5-1 mg is recommended for the treatment of bradyarrhythmias. In administering atropine, it is important to recognize that lower doses (<0.5 mg) may have vagalmimetic effects (ie, increase vagal tone causing paradoxical bradycardia). It is likely that the vagal tonic effects of atropine are mediated by blockade of muscarinic receptors at the level of the brain. Thus, it is important that the recommended dose of atropine be administered by rapid intravenous injection. Slow injection may result in paradoxical bradycardia. Atropine is also recommended as part of the ACLS protocol. In this situation, in the absence of vascular access, atropine can be administered intratracheally. For intratracheal administration, the dosage must be diluted with normal saline to a total volume of 10 mL.

Atropine causes mydriasis which makes the pupils unable to be evaluated in a neurologic examination.

Anesthesia and Critical Care Concerns/Other ConsiderationsAtropine, at usual recommended cardiovascular doses, causes blockade of muscarinic receptors at the cardiac SA-node and is parasympatholytic (ie, blocks vagal activity increasing heart rate). A dose 0.5-1 mg is recommended for the treatment of bradyarrhythmias. In administering atropine, it is important to recognize that lower doses (<0.5 mg) may have vagalmimetic effects (ie, increase vagal tone causing paradoxical bradycardia). A total dose of 3 mg (0.04 mg/kg) results in full vagal blockade in humans. In the absence of vascular access, atropine can be administered intratracheally.

Index TermsAtropine Sulfate

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International Brand NamesAtropin "Dak" (DK); Atropin (DE, FI, HR, SE); Atropin Dispersa (LU); Atropin Minims (NO); Atropina (IT); Atropina Braun (ES); Atropina Llorens (ES); Atropina Sulfato Serra (ES); Atropine (GR); Atropine Dispersa (HK); Atropine Martinet (FR); Atropine Sulfate (IL); Atropine Sulfate Tablets (GB); Atropini sulfas (HR); Atropinsulfat Braun (LU); Atropinsulfat Lannacher (AT); Atropinsulfatloesung Fresenius (LU); Atropinum Sulfuricum (HU, PL); Atropinum Sulfuricum Nycomed (AT); Atropocil (PT); Atropt (AU); Atrospan (IL); Bellafit N (CH); Bellapan (PL); Bellpino-Artin (IN); Ciba Vision Atropine (TH); Colircusi Atropina (ES); Colirio Ocul Atropina (ES); Isopto (GB); Isopto Atropin (SE); Isopto Atropina (AR); Isopto Atropine (AE, BE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, PH, PK, QA, SA, SC, SD, SL, SN, SY, TH, TN, TZ, UG, YE, ZA, ZM, ZW); Minims Atropine (AT); Minims Atropine Sulfaat (NL); Minims Atropine Sulfate (AE, BH, CY, EG, GB, HK, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Minims Atropine Sulphate (FI); Minims-Atropine (IE); Minims-Atropinsulfat (AT); Oft Cusi Atropina (ES); Oftan Atropin (FI); Redotex (MX); Stellatropine (LU); Sulfate d'Atropine-Chauvin (LU)

Attapulgite

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Note: Attapulgite preparations have been discontinued in the U.S.; refer to Bismuth monograph for newly-reformulated Kaopectate® products.

Sound-alike/look-alike issues:

Kaopectate® may be confused with Kayexalate®

Pronunciation(at a PULL gite)

Canadian Brand NamesKaopectate® Children’s [OTC]; Kaopectate® Extra Strength [OTC]; Kaopectate® [OTC]

Pharmacologic CategoryAntidiarrheal

Use: Labeled IndicationsSymptomatic treatment of diarrhea and cramps

Dosing: Adults**Diarrhea:** Oral (give after each bowel movement): 1200-1500 mg/dose; maximum dose: 8400 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Diarrhea:** Oral (give after each bowel movement):

Children:

3-6 years: 300 mg/dose; maximum dose: 2100 mg/day

6-12 years: 600-750 mg/dose; maximum dose: 4500 mg/day

Children >12 years: Refer to adult dosing.

Administration: OralShake liquid well before administering. Do not administer within 2-3 hours of other medications.

RestrictionsNot available in the U.S.

ContraindicationsHypersensitivity to attapulgite or any component of the formulation

Warnings/PrecautionsConsult healthcare provider before initiating therapy if high fever or bloody stools are present. Do not use for >2 days. If diarrhea persists, consult healthcare provider. Dosage not established in children <3 years of age.

Geriatric ConsiderationsElderly often present bowel impaction with diarrhea. The use of adsorbents in the face of fecal impaction could aggravate this serious condition. Also, diarrhea causes fluid/electrolyte loss which elderly do not tolerate well. Use of adsorbents can cause further loss of fluid/electrolytes.

Drug InteractionsThere are no known significant interactions.

Monitoring Parameters

Signs of fluid and electrolyte loss

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Suspension, oral:

Kaopectate® [CAN]: 600 mg/15 mL (250 mL, 350 mL) [vanilla flavor] [not available in the U.S.]

Kaopectate® Children’s [CAN]: 600 mg/15 mL (180 mL) [cherry flavor] [not available in the U.S.]

Kaopectate® Extra Strength [CAN]: 750 mg/15 mL (250 mL, 350 mL) [peppermint flavor] [not available in the U.S.]

Mechanism of ActionNonselectively absorbs excess intestinal fluid, thereby reducing stool liquidity. May interfere with absorption of nutrients and other drugs as well.

Pharmacodynamics/KineticsAbsorption: Not absorbed

Related Information

- Bismuth

Pharmacotherapy PearlsAttapulgite has been removed from the U.S. market. The U.S. Food and Drug Administration (FDA) found controlled studies documenting the efficacy of attapulgite to be inadequate.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive GI effects (constipation)

References

Engle JP, “Antidiarrheal Products,” *American Druggist*, August 1994:48, 50.

Ericsson CD, “Nonantimicrobial Agents in the Prevention and Treatment of Traveler’s Diarrhea,” *Clin Infect Dis*, 2005, 41(Suppl 8):557-63.[PubMed 16267719]

Forrester A, “Diarrhea,” *Patient Self-Care (PSC)*, Canadian Pharmacists Association, 2002: 238-51.

Horne JS and Swanson LN, “Diarrhea,” *U.S. Pharm*, May 1997. http://www.uspharmacist.com/oldformat.asp?url=newlook/files/feat/acf2ef8.htm

Kim-Jung L, Holquist C, and Phillips J, “Kaopectate Reformulation and Upcoming Labeling Changes,” *Drug Topics*, 2004, April 19:58-60.

International Brand NamesActapulgite (CH, FR); Kaopectate (PL)

Auranofin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Ridaura® may be confused with Cardura®

Pronunciation(au RANE oh fin)

U.S. Brand NamesRidaura®

Canadian Brand NamesRidaura®

Pharmacologic CategoryGold Compound

Use: Labeled IndicationsManagement of active stage of classic or definite rheumatoid arthritis in patients who do not respond to or tolerate other agents; psoriatic arthritis; adjunctive or alternative therapy for pemphigus

Dosing: AdultsRheumatoid arthritis, psoriatic arthritis, pemphigus: Oral: Initial: 6 mg/day in 1-2 divided doses; after 3 months may be increased to 9 mg/day in 3 divided doses; if still no response after 3 months at 9 mg/day, discontinue drug

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRheumatoid arthritis: Oral: Initial: 0.1 mg/kg/day divided daily; usual maintenance: 0.15 mg/kg/day in 1-2 divided doses; maximum: 0.2 mg/kg/day in 1-2 divided doses

Dosing: Renal Impairment

Cl_{cr} 50-80 mL/minute: Administer 50% of dose.

Cl_{cr} <50 mL/minute: Avoid use.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

StorageStore in tight, light-resistant containers at 15°C to 30°C.

ContraindicationsHypersensitivity to auranofin or any component of the formulation; renal disease, history of blood dyscrasias, congestive heart failure, exfoliative dermatitis, necrotizing enterocolitis, history of anaphylactic reactions

Allergy Considerations

- Gold Salt Allergy

Warnings/Precautions

Boxed warnings:

- Gold toxicity: **[U.S. Boxed Warning]: May be associated with significant toxicity involving dermatologic, gastrointestinal, hematologic, pulmonary, renal, and hepatic systems (see below); patient eduction is required.**

Concerns related to adverse effects:

- Dermatologic reactions: Dermatitis and lesions of the mucous membranes are common and may be serious; pruritus may precede the early development of a skin reaction. Consider alternative therapy in patients with dermatitis (urticaria or eczema; relative contraindication); may increase risk and/or symptoms of gold toxicity may be more difficult to detect.

- Gastrointestinal effects: Signs of toxicity include persistent diarrhea, stomatitis, and enterocolitis; avoid use in patients with prior inflammatory bowel disease.

- Hematologic effects: Signs of toxicity include hematologic depression (depressed hemoglobin, leukocytes, granulocytes, or platelets). Avoid use in patients with a history of blood dyscrasias (anemia, agranulocytosis), hemorrhagic diathesis, or drug induced granulocytopenia. Symptoms of gold toxicity may be difficult to detect in patients with prior abnormalities; consider alternative therapy. Therapy should be discontinued if platelet count falls to <100,000/mm^3, WBC <4000, granulocytes <1500/mm^3.

- Hepatic effects: May be associated with the development of cholestatic jaundice. Consider alternative therapy in patients with hepatic impairment (relative contraindication); may increase risk and/or symptoms of gold toxicity may be more difficult to detect.

- Pulmonary toxicity: May be associated with interstitial fibrosis; monitor closely.

- Renal effects: Renal toxicity ranges from mild proteinuria to nephrotic syndrome. Consider alternative therapy in patients with renal impairment; may increase risk and/or symptoms of gold toxicity may be more difficult to detect.

Concurrent drug therapy issues:

- ACE inhibitors: Concurrent use with ACE inhibitors may increase the risk of nitritoid reactions.

Other warnings/precautions:

- Monitoring: Laboratory monitoring should be completed prior to each new prescription. Frequent monitoring of patients for signs and symptoms of toxicity will prevent serious adverse reactions.

Geriatric ConsiderationsTolerance to gold decreases with advanced age; use cautiously only after traditional therapy and other disease modifying antirheumatic drugs (DMARDs) have been attempted.

Pregnancy Risk FactorC

LactationEnters breast milk/contraindicated

Adverse Reactions

>10%:

Dermatologic: Rash (24%), pruritus (17%)

Gastrointestinal: Diarrhea/loose stools (47%), abdominal pain (14%), stomatitis (13%)

Ocular: Conjunctivitis

Renal: Proteinuria

1% to 10%:

Dermatologic: Alopecia, urticaria

Gastrointestinal: Anorexia, constipation, dyspepsia, dysgeusia, flatulence, glossitis

Hematologic: Anemia, eosinophilia, leukopenia, thrombocytopenia

Hepatic: Transaminases increased

Renal: Hematuria, proteinuria

<1%: Agranulocytosis, angioedema, corneal deposits, dysphagia, enterocolitis (ulcerative), GI hemorrhage, gingivitis, gold bronchitis, hepatotoxicity, interstitial pneumonitis, jaundice, metallic taste, melena, neutropenia, pancytopenia, peripheral neuropathy, red cell aplasia. **Note:** Exfoliative dermatitis has been reported with other gold compounds.

Drug InteractionsThere are no known significant interactions.

Test InteractionsMay enhance the response to a tuberculin skin test

Monitoring ParametersPatients should have a CBC with differential, platelet count, hemoglobin determination and urinalysis for protein, white cells, red cells and casts; at baseline and periodically during therapy (at least monthly). Skin and oral mucosa should be inspected for skin rash, bruising or oral ulceration/stomatitis. Specific questioning for symptoms such as pruritus, rash, stomatitis or metallic taste should be included. Dosing should be withheld in patients with significant gastrointestinal, renal, dermatologic, or hematologic effects (platelet count falls to <100,000/mm^3, WBC <4000, granulocytes <1500/mm^3

Reference RangeGold: Normal: 0-0.1 mcg/mL (SI: 0-0.0064 µmol/L); Therapeutic: 1-3 mcg/mL (SI: 0.06-0.18 µmol/L); Urine: <0.1 mcg/24 hours

Monitoring: Lab TestsPatients should have a CBC with differential, platelet count, hemoglobin determination and urinalysis for protein, white cells, red cells and casts; at baseline and periodically during therapy (at least monthly). Dosing should be withheld in patients with significant gastrointestinal, renal, dermatologic, or hematologic effects (platelet count falls to <100,000/mm^3, WBC <4000, granulocytes <1500/mm^3

Monitor urine for protein, CBC and platelets; may monitor auranofin serum levels

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Ridaura®: 3 mg [29% gold]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Ridaura)

3 mg (60): $279.29

Mechanism of ActionThe exact mechanism of action of gold is unknown; gold is taken up by macrophages which results in inhibition of phagocytosis and lysosomal membrane stabilization; other actions observed are decreased serum rheumatoid factor and alterations in immunoglobulins. Additionally, complement activation is decreased, prostaglandin synthesis is inhibited, and lysosomal enzyme activity is decreased.

Pharmacodynamics/Kinetics

Onset of action: Delayed; therapeutic response may require as long as 3-4 months

Duration: Prolonged

Absorption: Oral: ~20% gold in dose is absorbed

Protein binding: 60%

Half-life elimination (single or multiple dose dependent): 21-31 days

Time to peak, serum: ~2 hours

Excretion: Urine (60% of absorbed gold); remainder in feces

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Glossitis and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay rarely produce agranulocytosis; use caution with clozapine and carbamazepine

References

Bell RA and Dale IM, “Gold Secretion in Maternal Milk,” *Arthritis Rheum*, 1976, 19(6):1374. [PubMed 826260]

Bunch TW, “Gold Overdose Treated With BAL,” *Arthritis Rheum*, 1974, 19(1):123-5.

Cook NJ, Owen ET, and Donlon JB, “A Further Possible Cause of Diarrhoea Caused by Oral Gold,” *Br J Rheumatol*, 1995, 34(4):395-6. [PubMed 7788162]

Davis CM, “D-Penicillamine for the Treatment of Gold Dermatitis,” *Am J Med*, 1969, 46(3):472-6. [PubMed 4238369]

Fernandez-Herlihy L, “Requiem for Gold?” *Ann Intern Med*, 1991, 114(11):993-4.

Godfrey NF, Peter A, Simon TM, et al, “I.V. N-acetylcysteine Treatment of Hematologic Reactions to Chrysotherapy,” *J Rheumatol*, 1982, 9(4):519-26. [PubMed 6813467]

Kozloff M, Votaw M, and Penner JA, “Gold-Induced Thrombocytopenia Responsive to Cyclophosphamide,” *South Med J*, 1979, 72(11):1490-2. [PubMed 388652]

Parez MC, Gomez C, Mataix R, et al, “Bone Marrow Splasia and Gold Salts. Report of Two Cases and Review of the Literature,” *Rev Clin Esp*, 1995, 194:540-2. [PubMed 7938822]

Ulmeanu V, Toma M, Eugah B, et al, “Severe Thrombocytopenia Following Treatment With Gold Salts,” *Clin Exp Rheumatol*, 12(Suppl 11):112.

International Brand NamesAktil (TH); Auropan (HN, HR, HU); Crytion (UY); Goldar (IN); Ridaura (AE, AR, AT, AU, BE, BF, BG, BH, BJ, BR, CH, CI, CL, CY, CZ, DE, DK, EE, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HN, IE, IL, IQ, IR, IT, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, NO, OM, PT, QA, RU, SA, SC, SD, SE, SL, SN, SY, TN, TR, TW, TZ, UG, YE, ZA, ZM, ZW); Ridaura Tiltab (AE, BH, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, MY, OM, QA, SA, SY, YE); Ridauran (FR)

AV (EE)

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Wilms' Tumor
Regimen UseWilms' tumor
Regimen

Dactinomycin: I.V.: 15 mcg/kg/day days 1 to 5 of weeks 0, 5, 13, and 26

[total dose/cycle = 300 mcg/kg]

Vincristine: I.V.: 1.5 mg/m^2/dose day 1 of weeks 1 to 10, and days 1 and 5 of weeks 13 and 26

[total dose/cycle = 21 mg/m^2]

References

D'Angio GJ, Breslow N, Beckwith JB, et al, âTreatment of Wilms' Tumor. Results of the Third National Wilms' Tumor Study,â *Cancer*, 1989, 64(2):349-60.[PubMed 2544249]

AV (K)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Wilms' Tumor

Regimen Use Wilms' tumor

Regimen

Dactinomycin: I.V.: 15 mcg/kg/day days 1 to 5 of weeks 0, 5, 13, 22, 31, 40, 49, and 58

[total dose/cycle = 600 mcg/kg]

Vincristine: I.V.: 1.5 mg/m^2/dose day 1 of weeks 0-10, 15-20, 24-29, 33-38, 42-47, 51-56, and 60-65

[total dose/cycle = 70.5 mg/m^2]

References

D'Angio GJ, Breslow N, Beckwith JB, et al, âTreatment of Wilms' Tumor. Results of the Third National Wilms' Tumor Study,â *Cancer*, 1989, 64(2):349-60.[PubMed 2544249]

AV (L)

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Wilms' Tumor]
Regimen UseWilms' tumor
Regimen

Dactinomycin: I.V.: 15 mcg/kg/day days 1 to 5 of weeks 0 and 5

[total dose/cycle = 150 mcg/kg]

Vincristine: I.V.: 1.5 mg/m^2 day 1 of weeks 0-10

[total dose/cycle = 16.5 mg/m^2]

References

D'Angio GJ, Breslow N, Beckwith JB, et al, âTreatment of Wilms' Tumor. Results of the Third National Wilms' Tumor Study,â *Cancer*, 1989, 64(2):349-60.[PubMed 2544249]

AV (Wilms' Tumor)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Wilms' Tumor]

Regimen Use Wilms' tumor

Regimen

Dactinomycin: I.V.: 15 mcg/kg/day days 1 to 5 of weeks 0, 13, 26, 39, 52, and 65

[total dose/cycle = 450 mcg/kg]

Vincristine: I.V.: 1.5 mg/m^2/dose day 1 of weeks 1 to 8, 13, 14, 26, 27, 39, 40, 52, 53, 65, and 66

[total dose/cycle = 27 mg/m^2]

References

Green DM, Breslow NE, Evans I, et al, âTreatment of Children With Stage IV Favorable Histology Wilms' Tumor: A Report From the National Wilms Tumor Study Group,â *Med Pediatr Oncol*, 1996, 26(3):147-52.[PubMed 8544795]

AVD

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Wilms' Tumor

Regimen UseWilms' tumor

Regimen

Dactinomycin: I.V.: 15 mcg/kg/day days 1 to 5 of weeks 0, 13, 26, 39, 52, and 65

[total dose/cycle = 450 mcg/kg]

Doxorubicin: I.V.: 60 mg/m^2 day 1 of weeks 6, 19, 32, 45, and 58

[total dose/cycle = 300 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2 day 1 of weeks 1 to 8, 13, 14, 26, 27, 39, 40, 52, 53, 65, and 66

[total dose/cycle = 27 mg/m^2]

References

Green DM, Breslow NE, Evans I, et al, âTreatment of Children With Stage IV Favorable Histology Wilms Tumor: A Report From the National Wilms' Tumor Study Group,â *Med Pediatr Oncol*, 1996, 26(3):147-52.[PubMed 8544795]

AzaCITIDine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

AzaCITIDine may be confused with azaTHIOprine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ay za SYE ti deen)

U.S. Brand NamesVidaza®

Pharmacologic CategoryAntineoplastic Agent, DNA Methylation Inhibitor

Use: Labeled IndicationsTreatment of myelodysplastic syndrome (MDS)

Use: Unlabeled/InvestigationalTreatment of acute myelogenous leukemia (AML)

Dosing: Adults

MDS: I.V., SubQ: 75 mg/m^2/day for 7 days repeated every 4 weeks. Dose may be increased to 100 mg/m^2/day if no benefit is observed after 2 cycles and no toxicity other than nausea and vomiting have occurred. Treatment is recommended for at least 4 cycles; treatment may be continued as long as patient continues to benefit.

AML (unlabeled use): SubQ: 75 mg/m2/day for 7 days repeated every 4 weeks (Sudan, 2006)

Dosage adjustment based on hematology: Adults: I.V., SubQ: MDS:

For baseline WBC ≥3.0 x 10^9/L, ANC ≥1.5 x 10^9/L, and platelets ≥75 x 10^9/L:

Nadir count: ANC <0.5 x 10^9/L or platelets <25 x 10^9/L: Administer 50% of dose during next treatment course

Nadir count: ANC 0.5-1.5 x 10^9/L or platelets 25-50 x 10^9/L: Administer 67% of dose during next treatment course

Nadir count: ANC >1.5 x 10^9/L or platelets >50 x 10^9/L: Administer 100% of dose during next treatment course

For baseline WBC <3 x 10^9/L, ANC <1.5 x 10^9/L, or platelets <75 x 10^9/L: Adjust dose as follows based on nadir counts and bone marrow biopsy cellularity at the time of nadir, unless clear improvement in differentiation at the time of the next cycle:

WBC or platelet nadir decreased 50% to 75% from baseline and bone marrow biopsy cellularity at time of nadir 30% to 60%: Administer 100% of dose during next treatment course

WBC or platelet nadir decreased 50% to 75% from baseline and bone marrow biopsy cellularity at time of nadir 15% to 30%: Administer 50% of dose during next treatment course

WBC or platelet nadir decreased 50% to 75% from baseline and bone marrow biopsy cellularity at time of nadir <15%: Administer 33% of dose during next treatment course

WBC or platelet nadir decreased >75% from baseline and bone marrow biopsy cellularity at time of nadir 30% to 60%: Administer 75% of dose during next treatment course

WBC or platelet nadir decreased >75% from baseline and bone marrow biopsy cellularity at time of nadir 15% to 30%: Administer 50% of dose during next treatment course

WBC or platelet nadir decreased >75% from baseline and bone marrow biopsy cellularity at time of nadir <15%: Administer 33% of dose during next treatment course

Note: If a nadir defined above occurs, administer the next treatment course 28 days after the start of the preceding course as long as WBC and platelet counts are >25% above the nadir and rising. If a >25% increase above the nadir is not seen by day 28, reassess counts every 7 days. If a 25% increase is not seen by day 42, administer 50% of the scheduled dose.

Dosage adjustment based on serum electrolytes: The manufacturer recommends that if serum bicarbonate falls to <20 mEq/L (unexplained decrease): Reduce dose by 50% for next treatment course

Dosing: ElderlyRefer to adult dosing. Due to the potential for decreased renal function in the elderly, select dose carefully and closely monitor renal function.

Dosing: Pediatric

Pediatric AML and ANLL (unlabeled uses): I.V.: 250 mg/m^2 days 4 and 5 every 4 weeks

Pediatric AML induction (unlabeled use): I.V.: 300 mg/m^2 days 5 and 6

Dosing: Renal ImpairmentNot studied in patients with renal impairment; select dose carefully (excretion is primarily renal; consider dose reduction); monitor closely for toxicity.

Dosing: Hepatic ImpairmentNot studied in patients with hepatic impairment; use caution. Contraindicated in patients with advanced malignant hepatic tumors.

Dosing: Adjustment for Toxicity**Renal toxicity:** If increases in BUN or serum creatinine (unexplained) occur, delay next cycle until values reach baseline or normal, then reduce dose by 50% for next treatment course.

Calculations

- ANC: Absolute Neutrophil Count
- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Premedication for nausea and vomiting is recommended. Infuse over 10-40 minutes; infusion must be completed within 1 hour of (vial) reconstitution.

Administration: OtherSubQ: Premedication for nausea and vomiting is recommended. The manufacturer recommends equally dividing volumes >4 mL into 2 syringes and injecting into 2 separate sites; however, policies for maximum SubQ administration volume may vary by institution; interpatient variations may also apply. Administer subsequent injections at least 1 inch from previous injection sites. Allow refrigerated suspensions to come to room temperature (up to 30 minutes) prior to administration. Resuspend by inverting the syringe 2-3 times and then rolling the syringe between the palms for 30 seconds. If azacitidine suspension comes in contact with the skin, immediately wash with soap and water.

StoragePrior to reconstitution, store powder at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

SubQ: Following reconstitution, suspension may be stored at room temperature for up to 1 hour, or immediately refrigerated at 2°C to 8°C (36°F to 46°F) and stored for up to 8 hours.

I.V.: **Solutions for I.V. administration have very limited stability and must be prepared immediately prior to each dose.** Administration must be completed within 1 hour of (vial) reconstitution.

ReconstitutionUse appropriate precautions for handling and disposal.

SubQ: To prepare a 25 mg/mL suspension, slowly add 4 mL SWFI to each vial. Vigorously shake or roll vial until a suspension is formed (suspension will be cloudy).

I.V.: Reconstitute vial with 10 mL SWFI to form a 10 mg/mL solution; vigorously shake until solution is dissolved and clear. Mix in 50-100 mL of NS or lactated Ringer's injection for infusion.

CompatibilityStable in LR, NS

Compatibility when admixed: Incompatible with D_5W, hetastarch, or solutions containing bicarbonate

ContraindicationsHypersensitivity to azacitidine, mannitol, or any component of the formulation; advanced malignant hepatic tumors

Allergy Considerations

- Mannitol Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Neutropenia, thrombocytopenia, and anemia are common; may cause therapy delays and/or dosage reductions.

- Hepatotoxicity: May be hepatotoxic, progressive hepatic coma leading to death has been reported (rare) in patients with extensive tumor burden, especially those with a baseline albumin <30 g/L.

- Renal toxicities: Serum creatinine elevations, renal tubular acidosis, and renal failure have been reported with combination chemotherapy; decrease or withhold dose for unexplained elevations in BUN or serum creatinine, or reductions in serum bicarbonate to <20 mEq/L.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment. Patients with hepatic impairment were excluded from clinical studies. Use is contraindicated in patients with advanced malignant hepatic tumors.

- Renal impairment: Use with caution in patients with renal impairment; dose adjustment may be required. Patients with renal impairment were excluded from clinical studies.

Special populations:

- Pediatrics: Not FDA approved for use in children.

Pregnancy Risk FactorD

Pregnancy ConsiderationsEmbryotoxicity, fetal death, and fetal abnormalities were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid pregnancy during treatment. In addition, males should be advised to avoid fathering a child while on azacitidine therapy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

>10%:

Cardiovascular: Peripheral edema (7% to 19%), chest pain (16%), pallor (16%), pitting edema (15%)

Central nervous system: Fever (30% to 52%), fatigue (13% to 36%), headache (22%), dizziness (19%), anxiety (5% to 13%), depression (12%), insomnia (9% to 11%), malaise (11%), pain (11%)

Dermatologic: Bruising (19% to 31%), petechiae (11% to 24%), erythema (7% to 17%), skin lesion (15%), rash (10% to 14%), pruritus (12%)

Endocrine & metabolic: Hypokalemia (6% to 13%)

Gastrointestinal: Nausea (48% to 71%), vomiting (27% to 54%), diarrhea (36%), constipation (34% to 50%), anorexia (13% to 21%), weight loss (16%), abdominal pain (11% to 16%), abdominal tenderness (12%)

Hematologic: Thrombocytopenia (66% to 70%; grades 3/4: 58%), anemia (51% to 70%; grades 3/4: 14%), neutropenia (32% to 66%; grades 3/4: 61%), leukopenia (18% to 48%; grades 3/4: 15%), febrile neutropenia (14% to 16%; grades 3/4: 13%), myelosuppression (nadir: days 10-17; recovery: days 28-31)

Local: Injection site reactions (14% to 29%): Erythema (35% to 43%; more common with I.V. administration), pain (19% to 23%; more common with I.V. administration), bruising (5% to 14%)

Neuromuscular & skeletal: Weakness (29%), rigors (26%), arthralgia (22%), limb pain (20%), back pain (19%), myalgia (16%)

Respiratory: Cough (11% to 30%), dyspnea (5% to 29%), pharyngitis (20%), epistaxis (16%), nasopharyngitis (15%), upper respiratory tract infection (9% to 13%), pneumonia (11%), crackles (11%)

Miscellaneous: Diaphoresis (11%)

5% to 10%:

Cardiovascular: Cardiac murmur (10%), hypertension (≤9%), tachycardia (9%), hypotension (7%), syncope (6%), chest wall pain (5%)

Central nervous system: Lethargy (7% to 8%), hypoesthesia (5%), postprocedural pain (5%)

Dermatologic: Cellulitis (8%), urticaria (6%), dry skin (5%), skin nodule (5%)

Gastrointestinal: Gingival bleeding (10%), oral mucosal petechiae (8%), stomatitis (8%), weight loss (≤8%), dyspepsia (6% to 7%), hemorrhoids (7%), abdominal distension (6%), loose stools (6%), dysphagia (5%), oral hemorrhage (5%), tongue ulceration (5%)

Genitourinary: Dysuria (8%), urinary tract infection (8% to 9%)

Hematologic: Hematoma (9%), postprocedural hemorrhage (6%)

Local: Injection site reactions: Pruritus (7%), hematoma (6%), rash (6%), granuloma (5%), induration (5%), pigmentation change (5%), swelling (5%)

Neuromuscular & skeletal: Muscle cramps (6%)

Renal: Hematuria (≤6%)

Respiratory: Rhinorrhea (10%), rales (9%), wheezing (9%), breath sounds decreased (8%), pharyngolaryngeal pain (6%), pleural effusion (6%), postnasal drip (6%), rhinitis (6%), rhonchi (6%), nasal congestion (6%), atelectasis (5%), sinusitis (5%)

Miscellaneous: Lymphadenopathy (10%), herpes simplex (9%), night sweats (9%), transfusion reaction (7%), mouth hemorrhage (5%)

<5%, postmarketing, and/or case reports (limited to important or life-threatening): Abscess (limb), agranulocytosis, anaphylactic shock, atrial fibrillation, azotemia, blastomycosis, bone marrow depression/failure, bone pain aggravated, cardiac failure, cardiorespiratory arrest, catheter site hemorrhage, cellulitis, cerebral hemorrhage, CHF, cholecystectomy, cholecystitis, congestive cardiomyopathy, dehydration, diverticulitis, eye hemorrhage, fibrosis (interstitial and alveolar), gastrointestinal hemorrhage, glycosuria, hemoptysis, hepatic coma, hypersensitivity reaction, hypophosphatemia, infection (bacterial), injection site infection, intracranial hemorrhage, leukemia cutis, lung infiltration, melena, neutropenic sepsis, orthostatic hypotension, pancytopenia, pneumonitis, polyuria, pyoderma gangrenosum, renal failure, renal tubular acidosis, seizure, respiratory distress, sepsis, septic shock, serum bicarbonate levels decreased, serum creatinine increased, splenomegaly, systemic inflammatory response syndrome, toxoplasmosis

Oncology: VesicantNo. Subcutaneous injection of undissolved crystals may cause localized reactions.

Oncology: Emetic PotentialModerate (30% to 60%)

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop.

Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersLiver function tests, electrolytes, CBC with differential and platelets, renal function tests (BUN and serum creatinine) should be obtained prior to initiation of therapy. Electrolytes, renal function (BUN and creatinine), CBC should be monitored prior to each cycle and periodically as needed to monitor response and toxicity.

Nursing: Physical Assessment/MonitoringUse with caution in presence of hepatic or renal impairment (dose adjustment may be required). Pretreatment with antiemetic is recommended to reduce nausea and vomiting. Note specific administration, reconstitution, and storage instructions (I.V. and SubQ stability differs). Assess results of laboratory tests prior to beginning therapy and prior to each cycle. Patient should be monitored closely for adverse effects (eg, edema, chest pain, hypotension, CNS changes, gastrointestinal disturbances, hematologic, hepatic effects). Teach patient (or caregiver) possible side effects/appropriate intervention and adverse symptoms to report.

Monitoring: Lab TestsLiver function tests, electrolytes, CBC with differential and platelets, renal function tests (BUN and serum creatinine) should be obtained prior to initiation of therapy. Electrolytes, renal function (BUN and creatinine), CBC should be monitored prior to each cycle and periodically as needed to monitor response and toxicity.

Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. This medication can only be administered by injection or I.V.; report immediately any pain, burning, or swelling at injection/infusion site. Limit oral intake for 4-6 hours before therapy to reduce potential for nausea/vomiting. It is important that you maintain adequate nutrition between treatments (small, frequent meals may help) and adequate hydration (2-3 L/day of fluids), unless advised by prescriber to restrict fluids. You may be susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea, vomiting, abdominal tenderness, or anorexia (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help - if nausea/vomiting are severe, request antiemetic); mouth sores (use soft toothbrush or cotton swabs for mouth care); or loss of hair (reversible). Report chest pain or palpitations; sore throat, fever, chills, unusual weakness or fatigue; unusual bruising/bleeding; change in color or frequency of urine or stool; itching or burning on urination; difficulty breathing; change in visual acuity; pain, redness, or swelling at injection site; or any other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant or cause a pregnancy (males) during therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for suspension [preservative free]:

Vidaza®: 100 mg [contains mannitol 100 mg]

Generic AvailableNo

Mechanism of ActionAntineoplastic effects may be a result of azacitidine's ability to promote hypomethylation of DNA leading to direct toxicity of abnormal hematopoietic cells in the bone marrow.

Pharmacodynamics/Kinetics

Absorption: SubQ: Rapid and complete

Distribution: V_d: I.V.: 76 ± 26 L; does not cross blood-brain barrier

Metabolism: Hepatic; hydrolysis to several metabolites

Bioavailability: SubQ: ~89%

Half-life elimination: I.V., SubQ: ~4 hours

Time to peak, plasma: SubQ: 30 minutes

Excretion: Urine (50% to 85%); feces (minor)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis, gingival bleeding, oral mucosal petechiae, stomatitis, oral hemorrhage, and tongue ulceration.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusHigh doses may produce coma

Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; use caution with clozapine and carbamazepine

Index Terms5-Azacytidine; 5-AZC; AZA-CR; Azacytidine; Ladakamycin; NSC-102816

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AzaTHIOprine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

AzaTHIOprine may be confused with azaCITIDine, azatadine, azidothymidine, azithromycin, Azulfidine®

Imuran® may be confused with Elmiron®, Enduron®, Imdur®, Inderal®, Tenormin®

Azathioprine is metabolized to mercaptopurine; concurrent use of these commercially-available products has resulted in profound myelosuppression.

Pronunciation(ay za THYE oh preen)

U.S. Brand NamesAzasan®; Imuran®

Canadian Brand NamesAlti-Azathioprine; Apo-Azathioprine®; Gen-Azathioprine; Imuran®; Novo-Azathioprine

Pharmacologic CategoryImmunosuppressant Agent

Use: Labeled IndicationsAdjunctive therapy in prevention of rejection of kidney transplants; management of active rheumatoid arthritis (RA)

Use: Unlabeled/InvestigationalAdjunct in prevention of rejection of solid organ (nonrenal) transplants; steroid-sparing agent for corticosteroid-dependent Crohn's disease (CD) and ulcerative colitis (UC); maintenance of remission in CD; fistulizing Crohn's disease

Use: DentalAdjunct with prednisone for managing severe erosive lichen planus, major aphthous stomatitis, erythema multiforme, and benign mucous membrane pemphigoid

Dosing: Adults**Note:** Patients with intermediate TPMT activity may be at risk for increased myelosuppression; those with low or absent TPMT activity receiving conventional azathioprine doses are at risk for developing severe, life-threatening myelotoxicity. Dosage reductions are recommended for patients with reduced TPMT activity.

I.V. dose is equivalent to oral dose (dosing should be transitioned from I.V. to oral as soon as tolerated):

Renal transplantation (treatment usually started the day of transplant, however, has been initiated [rarely] 1-3 days prior to transplant): Oral, I.V.: Initial: 3-5 mg/kg/day usually given as a single daily dose, then 1-3 mg/kg/day maintenance

Rheumatoid arthritis: Oral:

Initial: 1 mg/kg/day given once daily or divided twice daily, for 6-8 weeks; increase by 0.5 mg/kg every 4 weeks until response or up to 2.5 mg/kg/day; an adequate trial should be a minimum of 12 weeks

Maintenance dose: Reduce dose by 0.5 mg/kg every 4 weeks until lowest effective dose is reached; optimum duration of therapy not specified; may be discontinued abruptly

Adjunctive management of severe recurrent aphthous stomatitis (unlabeled use): Oral: 50 mg once daily in conjunction with prednisone

Reduction of steroid use in CD or UC, maintenance of remission in CD or fistulizing disease (unlabeled uses): Oral: Initial: 50 mg once daily; may increase by 25 mg/day every 1-2 weeks as tolerated to target dose of 2-3 mg/kg/day

Dosage adjustment for concomitant use with allopurinol: Reduce azathioprine dose to one-third or one-fourth the usual dose when used concurrently with allopurinol. Patients with low or absent TPMT activity may require further dose reductions or discontinuation.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Patients with intermediate TPMT activity may be at risk for increased myelosuppression; those with low or absent TPMT activity receiving conventional azathioprine doses are at risk for developing severe, life-threatening myelotoxicity. Dosage reductions are recommended for patients with reduced TPMT activity.

Renal transplantation, rheumatoid arthritis (unlabeled uses): Refer to adult dosing.

Dosing: Renal ImpairmentAlthough dosage reductions are recommended, specific guidelines are not available in the FDA-approved labeling; the following guidelines have been used by some clinicians (Aronoff, 2007):

Cl_{cr} >50 mL/minute: No adjustment recommended.

Cl_{cr} 10-50 mL/minute: Administer 75% of normal dose.

Cl_{cr} <10 mL/minute: Administer 50% of normal dose.

Hemodialysis (dialyzable; ~45% removed in 8 hours): Children: Administer 50% of normal dose; Adults: Supplement: 0.25 mg/kg

CAPD: Children: Administer 50% of normal dose; Adults: Unknown

CRRT: Children and Adults: Administer 75% of normal dose

Dosing: Adjustment for Toxicity

Rapid WBC count decrease, persistently low WBC count, or serious infection: Reduce dose or temporarily withhold treatment.

Severe toxicity in renal transplantation: May require discontinuation.

Hepatic veno-occlusive disease: Permanently discontinue.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Ideal Body Weight: Adults
- Ideal Body Weight: Pediatrics

Administration: I.V.Can be administered IVP over 5 minutes at a concentration not to exceed 10 mg/mL **or** azathioprine can be further diluted with normal saline or D_5W and administered by intermittent infusion usually over 30-60 minutes; may be extended up to 8 hours.

Administration: I.V. DetailpH: 9.6

Administration: OralAdministering tablets after meals or in divided doses may decrease adverse GI events.

Dietary ConsiderationsMay be taken with food.

Storage

Tablet: Store at room temperature of 15°C to 25°C (59°F to 77°F); protect from light.

Powder for injection: Store intact vials at room temperature of 15°C to 25°C (59°F to 77°F). Protect from light. Reconstituted solution is stable for up to 2 weeks at room temperature or up to 4 days refrigerated; solutions diluted in D_5W, $^1/_2$NS, or NS for infusion are stable at room temperature or refrigerated for up to 16 days; however, the manufacturer recommends use within 24 hours of reconstitution.

ReconstitutionPowder for injection: Reconstitute each vial with 10 mL sterile water for injection; may further dilute for infusion (in D_5W, $^1/_2$NS, or NS). Use appropriate precautions for handling and disposal.

CompatibilityStable in D_5W, $^1/_2$NS, NS. Stable in neutral or acid solutions, but is hydrolyzed to mercaptopurine in alkaline solutions.

Extemporaneously PreparedA 50 mg/mL oral suspension can be prepared by crushing one hundred twenty (120) 50 mg tablets in a mortar (reducing to a fine powder), and then mixing in a small amount of vehicle (a 1:1 combination of Ora-Sweet® or Ora-Sweet® SF and Ora-Plus®) to create a uniform paste. Continue to add vehicle in geometric amounts (while mixing) until near-final volume is achieved. Transfer to a graduate and add sufficient quantity to make 120 mL. Label "shake well" and "refrigerate." Refrigerated stability is 60 days.

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ContraindicationsHypersensitivity to azathioprine or any component of the formulation; pregnancy (in patients with rheumatoid arthritis); patients with rheumatoid arthritis and a history of treatment with alkylating agents (eg, cyclophosphamide, chlorambucil, melphalan) may have a prohibitive risk of neoplasia with azathioprine treatment

Allergy Considerations

- AzaTHIOprine Allergy

Warnings/Precautions

Boxed warnings:

- Experienced physician: See "Other warnings/precautions" below.
- Neoplasia: See "Concerns related to adverse effects" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Gastrointestinal toxicity: Within the first several weeks of therapy gastrointestinal toxicity (reversible) may occur; symptoms may include severe nausea, vomiting, diarrhea, rash, fever, malaise, myalgia, hypotension, and liver enzyme abnormalities.
- Hematologic toxicity: Dose-related, delayed hematologic toxicities (leukopenia, thrombocytopenia, macrocytic anemia, pancytopenia) may occur; may be more severe with renal transplants undergoing rejection and patients with thiopurine methyltransferase (TPMT) deficiency; monitor hematologic function closely. May require dosage modification.
- Hepatotoxicity: Hepatotoxicity (transaminase, bilirubin, and alkaline phosphatase elevations) may occur, usually in renal transplant patients. Usually occurs within 6 months of transplant and is normally reversible with discontinuation. Monitor liver function periodically. Rarely, hepatic veno-occlusive disease (VOD) has been reported; discontinue if hepatic VOD is suspected.
- Infections: Chronic immunosuppression increases the risk of serious infections.
- Neoplasia: **[U.S. Boxed Warning]: Chronic immunosuppression increases the risk of neoplasia;** azathioprine has mutagenic potential to both men and women.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment; dosage reductions may be necessary.
- TPMT deficiency: Patients with genetic deficiency of TPMT may be sensitive to myelosuppressive effects. Patients with intermediate TPMT activity may be at risk for increased myelosuppression; those with low or absent TPMT activity are at risk for developing severe and life-threatening hematologic toxicity. TPMT genotyping or phenotyping may assist in identifying patients at risk for developing toxicity. TPMT testing does not substitute for CBC monitoring.

Concurrent drug therapy issues:

- Mercaptopurine: Azathioprine is metabolized to mercaptopurine; concomitant use may result in profound myelosuppression and should be avoided.
- TPMT or xanthine oxidase inhibitors: Patients on concurrent therapy with drugs which may inhibit TPMT (eg, olsalazine) or xanthine oxidase (eg, allopurinol) may be sensitive to myelosuppressive effects. Dose adjustment of azathioprine may be recommended when used concurrently with allopurinol; patients with low or absent TPMT activity may require further dose reductions or discontinuation.
- Vaccines: Immune response to vaccines may be diminished.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be prescribed by physicians familiar with the risks, including hematologic toxicities and mutagenic potential.**

Geriatric ConsiderationsToxicity to immunosuppressives is increased in elderly. Start with lowest recommended adult doses. Signs of infection, such as fever and WBC rise, may not occur. Lethargy and confusion may be more prominent signs of infection. In the elderly, adjust dose to creatinine clearance.
Pregnancy Risk FactorD
Pregnancy ConsiderationsAzathioprine was found to be teratogenic in animal studies; temporary depression in spermatogenesis and reduction in sperm viability and sperm count were also reported in mice. Azathioprine crosses the placenta in humans; congenital anomalies, immunosuppression, hematologic toxicities (lymphopenia, pancytopenia), and intrauterine growth retardation have been reported. There are no adequate and well-controlled studies in pregnant women. Azathioprine should not be used to treat arthritis during pregnancy. The potential benefit to the mother versus possible risk to the fetus should be considered when treating other disease states.

The National Transplantation Pregnancy Registry (NTPR, Temple University) is a registry for pregnant women taking immunosuppressants following any solid organ transplant. The NTPR encourages reporting of all immunosuppressant exposures during pregnancy in transplant recipients at 877-955-6877.

LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsDue to risk of immunosuppression and serious adverse effects in the nursing infant, breast-feeding is not recommended.
Adverse ReactionsFrequency not always defined; dependent upon dose, duration, indication, and concomitant therapy. Central nervous system: Fever, malaiseGastrointestinal: Nausea/vomiting (RA: 12%), diarrheaHematologic: Leukopenia (renal transplant: >50%; RA: 28%), thrombocytopeniaHepatic: Alkaline phosphatase increased, bilirubin increased, hepatotoxicity, transaminases increasedNeuromuscular & skeletal: MyalgiaMiscellaneous: Infection (renal transplant: 20%; RA: <1%; includes bacterial, fungal, protozoal, viral), neoplasia (other than lymphoma: 3%)<1%, postmarketing, and/or case reports: Abdominal pain, alopecia, arthralgia, bleeding, bone marrow suppression, fever, hepatic veno-occlusive disease, hepatosplenic T-cell lymphoma, hypersensitivity, hypotension, interstitial pneumonitis, lymphoma, macrocytic anemia, negative nitrogen balance, pancreatitis, pancytopenia, rash, steatorrhea
Drug Interactions

5-ASA Derivatives: May decrease the metabolism of Thiopurine Analogs. *Risk C: Monitor therapy*

ACE Inhibitors: May enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Allopurinol: May decrease the metabolism of AzaTHIOprine. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Mercaptopurine: AzaTHIOprine may enhance the myelosuppressive effect of Mercaptopurine. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Sulfamethoxazole: May enhance the myelosuppressive effect of AzaTHIOprine. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Trimethoprim: May enhance the myelosuppressive effect of AzaTHIOprine. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): AzaTHIOprine may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid cat's claw, echinacea (have immunostimulant properties).

Test InteractionsTPMT phenotyping results will not be accurate following recent blood transfusions.

Monitoring ParametersCBC with differential and platelets (weekly during first month, twice monthly for months 2 and 3, then monthly; monitor more frequently with dosage modifications), total bilirubin, liver function tests, TPMT genotyping or phenotyping

For use as immunomodulatory therapy in CD or UC, monitor CBC with differential weekly for 1 month, then biweekly for 1 month, followed by monitoring every 1-2 months throughout the course of therapy. LFTs should be assessed every 3 months.

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess results of laboratory tests, therapeutic effectiveness (according to purpose for use) and adverse reactions at beginning of therapy and periodically throughout therapy, especially opportunistic infection. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelets (weekly during first month, twice monthly for months 2 and 3, then monthly; monitor more frequently with dosage modifications), total bilirubin, liver function tests, TPMT genotyping or phenotyping

For use as immunomodulatory therapy in CD or UC, monitor CBC with differential weekly for 1 month, then biweekly for 1 month, followed by monitoring every 1-2 months throughout the course of therapy. LFT's should be assessed every 3 months.

Patient EducationTake as prescribed (may take in divided doses or with food if GI upset occurs). You will be susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations unless approved by prescriber). You may experience nausea, vomiting, loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report abdominal pain and unresolved GI upset (eg, persistent vomiting or diarrhea); unusual fever or chills; bleeding or bruising; sore throat, unhealed sores, or signs of infection; yellowing of skin or eyes; or change in color of urine or stool.

Rheumatoid arthritis: Response may not occur for up to 3 months; do not discontinue medication without consulting prescriber.

Organ transplant: Azathioprine will usually be prescribed with other antirejection medications.

Pregnancy/breast-feeding precautions: Do not get pregnant while taking this medication; use appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 100 mg

Tablet [scored]: 50 mg

Azasan®: 75 mg, 100 mg

Imuran®: 50 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Azasan)

75 mg (30): $87.27

100 mg (30): $106.45

Tablets (Azathioprine)

50 mg (30): $27.99

Tablets (Imuran)

50 mg (30): $101.49

Mechanism of ActionAzathioprine is an imidazolyl derivative of mercaptopurine; antagonizes purine metabolism and may inhibit synthesis of DNA, RNA, and proteins; may also interfere with cellular metabolism and inhibit mitosis. The 6-thioguanine nucleotides appear to mediate the majority of azathioprine's immunosuppressive and toxic effects.

Pharmacodynamics/Kinetics

Absorption: Oral: Well absorbed

Distribution: Crosses placenta

Protein binding: ~30%

Metabolism: Hepatic, to 6-mercaptopurine (6-MP), possibly by glutathione S-transferase (GST). Further metabolism of 6-MP (in the liver and GI tract), via three major pathways: Hypoxanthine guanine phosphoribosyltransferase (to 6-thioguanine-nucleotides, or 6-TGN), xanthine oxidase (to 6-thiouric acid), and thiopurine methyltransferase (TPMT), which forms 6-methylmercapotpurine (6-MMP).

Half-life elimination: Parent drug: 12 minutes; mercaptopurine: 0.7-3 hours; End-stage renal disease: Slightly prolonged

Time to peak, plasma: 1-2 hours (including metabolites)

Excretion: Urine (primarily as metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay produce pancytopenia; use caution with clozapine and carbamazepine

Index TermsAzathioprine Sodium

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International Brand NamesAza-Q (DE); Azafalk (DE); Azahexal (AU); Azamun (NZ, PL); Azamune (GB); Azanin (JP); Azapin (AU); Azapress (ZA); Azaprine (KP); Azarekhexal (EE); Azarex (DE); Azathiodura (DE); Azathioprine (PL); Azatioprina Wellcome (IT); Azatrilem (MX); Azopi (IL); Azoran (IN); Colinsan (DE); Immuthera (KP); Imunen (BR); Imuprin (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, FI, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PR, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Imuran (AE, AR, AU, BB, BD, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CI, CL, CN, CO, CY, CZ, EE, EG, ET, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, OM, PH, PK, PL, PT, PY, QA, SA, SC, SD, SG, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Imurek (AT, CH, DE); Imurel (DK, ES, FI, FR, NO, SE); Thioprine (AU); Transimune (IN); Zaprine (ZA); Zytrim (DE)

Azelaic Acid

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(a zeh LAY ik AS id)
U.S. Brand NamesAzelex®; Finacea®
Canadian Brand NamesFinacea®
Pharmacologic CategoryTopical Skin Product, Acne
Use: Labeled IndicationsTopical treatment of inflammatory papules and pustules of mild-to-moderate rosacea; mild-to-moderate inflammatory acne vulgaris

Finacea®: Not FDA-approved for the treatment of acne

Dosing: Adults

Acne vulgaris: Topical: Cream 20%: After skin is thoroughly washed and patted dry, gently but thoroughly massage a thin film of azelaic acid cream into the affected areas twice daily, in the morning and evening. The duration of use can vary and depends on the severity of the acne. In the majority of patients with inflammatory lesions, improvement of the condition occurs within 4 weeks.

Rosacea: Topical: Gel 15%: Massage gently into affected areas of the face twice daily; use beyond 12 weeks has not been studied

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricAcne vulgaris: Adolescents ≥12 years: Refer to adult dosing.
Administration: TopicalApply to clean, dry skin; wash hands following application. Avoid the use of occlusive dressings or wrappings. For gel formulation, cosmetics may be applied after the gel has dried. Not to be used orally, intravaginally, or for the eyes.
Dietary Considerations

Gel: Foods and beverages that might provoke erythema, flushing, and blushing, such as spicy food, alcoholic beverages, and thermally hot drinks (including hot coffee and tea), should be avoided.

StorageStore between 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to azelaic acid or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Hypopigmentation: There have been isolated reports of hypopigmentation after use.

- Skin irritation: If sensitivity or severe irritation develops, discontinue treatment and institute appropriate therapy.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Dosage form specific issues:

- Gel: Use of gel beyond 12 weeks has not been studied.

Other warnings/precautions:

- Appropriate use: For external use only; not for ophthalmic or vaginal use. Use of occlusive dressings or wrappings should be avoided.

Pregnancy Risk FactorB
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsSince <4% of a topically applied dose is systemically absorbed, the uptake of azelaic acid into breast milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. However, exercise caution when administering to a nursing mother.
Adverse Reactions

>5%: Dermatologic: Pruritus (1% to 6%), burning/stinging/itching (1% to 6%)

1% to 5%:

Dermatologic: Acne (<1% to 1%), edema, erythema, rash, peeling, dermatitis, contact dermatitis, irritation, scaling/dry skin/xerosis

Neuromuscular & skeletal: Paresthesia

Postmarketing and/or case reports: Asthma exacerbation, herpes labialis exacerbation, hypertrichosis, reddening, small depigmented spots, vitiligo depigmentation

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringAssess therapeutic effectiveness and adverse response (sensitivity, severe irritation, or hypopigmentation in dark skinned patients) at regular intervals during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis medication is for application to affected skin areas only; as per directions of prescriber. Use for full prescribed treatment period. Do not apply any other skin products without consulting prescriber; especially avoid alcoholic cleansers, tinctures, and astringents; abrasives and peeling agents. Temporary skin irritation (eg pruritus, burning, stinging) may occur when applied to broken or inflamed skin, usually at start of treatment. If irritation continues, apply only once a day or stop treatment until these effects have subsided. If irritation reoccurs with further use, discontinue and consult prescriber. If you have dark skin, report immediately any complexion changes or loss of color. **Breast-feeding precaution:** Consult prescriber if you are breast-feeding.

Application: Apply with gloves and wash hands following application. Do not allow medication to come into contact with eyes, mouth, or mucous membranes (if it does come into contact with eyes, wash with large amount of water and consult prescriber if eye irritation persists). Apply nonirritating cosmetics after gel has dried.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream:

Azelex®: 20% (30 g, 50 g) [contains benzoic acid and propylene glycol]

Gel:

Finacea®: 15% (50 g) [contains benzoic acid and propylene glycol]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Cream (Azelex)

20% (30): $107.64

20% (50): $139.89

Gel (Finacea)

15% (50): $126.21

Mechanism of ActionAzelaic acid is a dietary constituent normally found in whole grain cereals; can be formed endogenously. Exact mechanism is not known. *In vitro*, azelaic acid possesses antimicrobial activity against *Propionibacterium acnes* and *Staphylococcus epidermidis*. May decrease microcomedo formation.

Pharmacodynamics/Kinetics

Absorption: Cream: ~3% to 5% penetrates stratum corneum; up to 10% found in epidermis and dermis; 4% systemic

Half-life elimination: Topical: Healthy subjects: 12 hours

Excretion: Urine (as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesAcne-Derm (PL); Acnederm Medicated Lotion (MY, SG); Aza 20 (ID); Azel (TW); Azelan (BR); Aziderm (IN); Cutacelan (AR, CO, PE, VE); Finacea (AU, FR, GB, IE, MX, SE); Hascoderm (PL); Qualicren (HK); Qualilaic (HK); Skinoderm (IL); Skinorem (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Skinoren (AT, BE, BG, CH, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HK, HN, ID, IE, MY, NO, NZ, PH, PK, PL, PT, SE, TH, TW, ZA); ZA (TW); Zelface (ID); Zeliris (ID)

Azelastine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Optivar® may be confused with Optiray®, Optive™

International issues:

Optivar® may be confused with Opthavir® which is a brand name for acyclovir in Mexico

Pronunciation(a ZEL as teen)

U.S. Brand NamesAstelin®; Optivar®

Canadian Brand NamesAstelin®

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation

Use: Labeled Indications

Nasal spray: Treatment of the symptoms of seasonal allergic rhinitis such as rhinorrhea, sneezing, and nasal pruritus in children ≥5 years of age and adults; treatment of the symptoms of vasomotor rhinitis in children ≥12 years of age and adults

Ophthalmic: Treatment of itching of the eye associated with seasonal allergic conjunctivitis in children ≥3 years of age and adults

Dosing: Adults

Seasonal allergic rhinitis: Intranasal: 1-2 sprays each nostril twice daily

Vasomotor rhinitis: Intranasal: 2 sprays each nostril twice daily.

Seasonal allergic conjunctivitis: Ophthalmic: Instill 1 drop into affected eye(s) twice daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Seasonal allergic rhinitis: Intranasal:

5-11 years: 1 spray each nostril twice daily

≥12 years: Refer to adult dosing.

Vasomotor rhinitis: Intranasal: Children ≥12 years: Refer to adult dosing.

Seasonal allergic conjunctivitis: Ophthalmic: Children ≥3 years: Refer to adult dosing.

Administration: InhalationBefore initial use of the nasal spray, the delivery system should be primed with 4 sprays or until a fine mist appears. If 3 or more days have elapsed since last use, the delivery system should be reprimed with 2 sprays or until a fine mist appears. Blow nose to clear nostrils. Keep head tilted downward when spraying. Insert applicator into nostril, keeping bottle upright, and close off the other nostril. Breathe in through nose. While inhaling, press pump to release spray. Alternate sprays between nostrils. After each use, wipe the spray tip with a clean tissue or cloth.

Storage

Nasal spray: Store upright at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from freezing.

Ophthalmic solution: Store upright at controlled room temperature of 2°C to 25°C (36°F to 77°F).

ContraindicationsHypersensitivity to azelastine or any component of the formulation

Warnings/Precautions

Dosage form specific issues:

- Nasal spray: May cause drowsiness in some patients; instruct patient to use caution when driving or operating machinery. Effects may be additive with CNS depressants and/or ethanol. Safety and efficacy have not been established in children <5 years of age.
- Ophthalmic: Solution contains benzalkonium chloride; remove lens prior to administration and wait at least 10 minutes before reinserting. Do not use contact lenses if eyes are red. Safety and efficacy have not been established in children <3 years of age.

Geriatric ConsiderationsOnly a small number of older subjects were included in premarketing trials. In those patients, side effects were no different than in younger patients.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Animal reproduction studies have shown toxic effects to the fetus at maternally toxic doses. Use during pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

Nasal spray:

>10%:

Central nervous system: Headache (8% to 15%), somnolence (<1% to 12%)

Gastrointestinal: Bitter taste (8% to 20%)

Respiratory: Cold symptoms/rhinitis (2% to 17%), cough (11%)

2% to 10%:

Central nervous system: Dysesthesia (8%), dizziness (2%), fatigue (2%)

Gastrointestinal: Nausea (3%), weight gain (2%), xerostomia (3%)

Neuromuscular & skeletal: Myalgia (≤2%)

Ocular: Conjunctivitis (<2% to 5%)

Respiratory: Asthma (5%), nasal burning (4%), pharyngitis (4%), paroxysmal sneezing (3%), sinusitis (3%), epistaxis (2% to 3%)

<2%:

Cardiovascular: Flushing, hypertension, tachycardia

Central nervous system: Abnormal thinking, anxiety, depersonalization, depression, drowsiness, fever, hypoesthesia, malaise, nervousness, sleep disorder, vertigo

Dermatologic: Contact dermatitis, eczema, furunculosis, hair and follicle infection, skin laceration

Endocrine & metabolic: Amenorrhea, breast pain

Gastrointestinal: Abdominal pain, aphthous stomatitis, appetite increased, constipation, diarrhea, gastroenteritis, glossitis, loss of taste, ulcerative stomatitis, toothache, vomiting

Genitourinary: Albuminuria, hematuria, polyuria

Hepatic: ALT increased

Neuromuscular & skeletal: Back pain, extremity pain, hyperkinesia, rheumatoid arthritis, temporomandibular dislocation

Ocular: Eye pain, watery eyes

Respiratory: Bronchitis, bronchospasm, laryngitis, nasal congestion, nocturnal dyspnea, postnasal drip, sinus hypersecretion, throat burning

Miscellaneous: Allergic reactions, viral infection

<1%, postmarketing, and/or case reports: Anaphylactoid reaction, atrial fibrillation, chest pain, confusion, dyspnea, facial edema, involuntary muscle contractions, loss of smell, palpitation, paresthesia, parosmia, pruritus, rash, skin irritation, tolerance, transaminases increased, urinary retention, visual abnormalities, xerophthalmia

Ophthalmic:

>10%:

Central nervous system: Headache (15%)

Ocular: Transient burning/stinging (30%)

1% to 10%:

Central nervous system: Fatigue

Dermatologic: Pruritus

Gastrointestinal: Bitter taste (10%)

Ocular: Conjunctivitis, eye pain, blurred vision (temporary)

Respiratory: Asthma, dyspnea, pharyngitis, rhinitis

Miscellaneous: Flu-like syndrome

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 2C19, 2D6, 3A4; **Inhibits** CYP2B6 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may cause increased somnolence or fatigue).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, intranasal, as hydrochloride [spray]:

Astelin®: 1 mg/mL (30 mL) [contains benzalkonium chloride; 137 mcg/spray; 200 metered sprays]

Solution, ophthalmic, as hydrochloride:

Optivar®: 0.05% (6 mL) [contains benzalkonium chloride]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Astelin)

137 mcg/spray (30): $95.00

Solution (Optivar)

0.05% (6): $94.49

Mechanism of ActionCompetes with histamine for H$_1$-receptor sites on effector cells and inhibits the release of histamine and other mediators involved in the allergic response; when used intranasally, reduces hyper-reactivity of the airways; increases the motility of bronchial epithelial cilia, improving mucociliary transport

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Nasal spray: 3 hours; Ophthalmic solution: 3 minutes

Duration: Nasal spray: 12 hours; Ophthalmic solution: 8 hours

Distribution: V$_d$: 14.5 L/kg

Protein binding: Azelastine: 88%; Desmethylazelastine: 97%

Metabolism: Hepatic via CYP; active metabolite, desmethylazelastine

Bioavailability: Intranasal: 40%

Half-life elimination: 22 hours

Time to peak, serum: 2-3 hours

Excretion: Feces (75 %, <10% as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Bitter taste, xerostomia (normal salivary flow resumes upon discontinuation), aphthous stomatitis, glossitis, and burning sensation in throat. Chronic use of antihistamines will inhibit salivary flow, particularly in elderly patients. May contribute to periodontal disease and oral discomfort.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; rare reports of anxiety and nervousness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation

Index TermsAzelastine Hydrochloride

References

Dykewicz MS, Fineman S, Nicklas R, et al, “Diagnosis and Management of Rhinitis: Complete Guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. American Academy of Allergy, Asthma, and Immunology,” *Ann Allergy Asthma Immunol*, 1998, 81(5 Pt 2):478-518.[PubMed 9860027]

International Brand NamesAlastine (KP); Alerdual (FR); Allergodil (AR, AT, BE, BG, CH, CN, CZ, DE, DK, EE, FR, HN, HU, IT, LU, NL, PL, PT, RU); Amsler (MX); Astelin (MX, PK); Az Ofteno (MX); Azel (CO); Azelagen (KP); Azelone (PH); Azep (CL, IN); Azep Hayfever Nasal Spray (AU); Azeptin (JP, KP); Brixia (AR, PY, UY, VE); Corifina Colirio (ES); Eyezep Eye Drops (NZ); Lastin (FI, NO, SE); Opthazel (PE); Optilast (IL); Prorhinite (FR); Rhinolast (GB, IE, IL); Rinalin (CR, DO, GT, HN, NI, PA, SV); Rino-Lastin (BR); Xanaes (AR)

Azithromycin

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English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Azithromycin may be confused with azathioprine, erythromycin

Zithromax® may be confused with Zinacef®

Pronunciation(az ith roe MYE sin)

U.S. Brand NamesAzaSite™; Zithromax®; Zmax™

Canadian Brand NamesApo-Azithromycin®; CO Azithromycin; Dom-Azithromycin; GMD-Azithromycin; Novo-Azithromycin; PHL-Azithromycin; PMS-Azithromycin; ratio-Azithromycin; Sandoz-Azithromycin; Zithromax®

Pharmacologic CategoryAntibiotic, Macrolide; Antibiotic, Ophthalmic

Use: Labeled Indications

Oral, I.V.: Treatment of acute otitis media due to *H. influenzae*, *M. catarrhalis*, or *S. pneumoniae*; pharyngitis/tonsillitis due to *S. pyogenes*; treatment of mild-to-moderate upper and lower respiratory tract infections, infections of the skin and skin structure, community-acquired pneumonia, pelvic inflammatory disease (PID), sexually-transmitted diseases (urethritis/cervicitis), pharyngitis/tonsillitis (alternative to first-line therapy), and genital ulcer disease (chancroid) due to susceptible strains of *C. trachomatis*, *M. catarrhalis*, *H. influenzae*, *S. aureus*, *S. pneumoniae*, *Mycoplasma pneumoniae*, and *C. psittaci*; acute bacterial exacerbations of chronic obstructive pulmonary disease (COPD) due to *H. influenzae*, *M. catarrhalis,* or *S. pneumoniae*; acute bacterial sinusitis

Ophthalmic: Bacterial conjunctivitis

Use: Unlabeled/InvestigationalPrevention of (or to delay onset of) or treatment of MAC in patients with advanced HIV infection; prophylaxis of infective endocarditis in patients who are allergic to penicillin and undergoing surgical or dental procedures; pertussis

Use: DentalAlternate oral antibiotic for prevention of infective endocarditis in individuals allergic to penicillins or ampicillin, when amoxicillin cannot be used; alternate antibiotic in the treatment of common orofacial infections caused by aerobic gram-positive cocci and susceptible anaerobes

Dosing: Adults**Note: Extended release suspension (Zmax™) is not interchangeable with immediate release formulations.** Use should be limited to approved indications. All doses are expressed as immediate release azithromycin unless otherwise specified.

Bacterial conjunctivitis: Instill 1 drop into affected eye(s) twice daily (8-12 hours apart) for 2 days, then 1 drop once daily for 5 days

Bacterial sinusitis: Oral: 500 mg/day for a total of 3 days

Extended release suspension (Zmax™): 2 g as a single dose

Cat scratch disease (unlabeled use): Oral: >45.5 kg: 500 mg as a single dose, then 250 mg once daily for 4 days

Chancroid due to*H. ducreyi:* Oral: 1 g as a single dose

Community-acquired pneumonia:

Oral (Zmax™): 2 g as a single dose

I.V.: 500 mg as a single dose for at least 2 days, follow I.V. therapy by the oral route with a single daily dose of 500 mg to complete a 7- to 10-day course of therapy.

Disseminated*M. avium*complex disease in patient with advanced HIV infection (unlabeled use): Oral:

Prophylaxis: 1200 mg once weekly (may be combined with rifabutin)

Treatment: 600 mg daily in combination with ethambutol 15 mg/kg

Prophylaxis against infective endocarditis (unlabeled use): Oral: 500 mg 30-60 minutes prior to the procedure. **Note:** American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur. As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Mild-to-moderate respiratory tract, skin, and soft tissue infections: Oral: 500 mg in a single loading dose on day 1 followed by 250 mg/day as a single dose on days 2-5

Alternative regimen: Bacterial exacerbation of COPD: 500 mg/day for a total of 3 days

Pelvic inflammatory disease (PID): I.V.: 500 mg as a single dose for 1-2 days, follow I.V. therapy by the oral route with a single daily dose of 250 mg to complete a 7-day course of therapy.

Pertussis (CDC guidelines): Oral: 500 mg on day 1 followed by 250 mg/day on days 2-5 (maximum: 500 mg/day)

Urethritis/cervicitis: Oral:

Due to *C. trachomatis*: 1 g as a single dose

Due to *N. gonorrhoeae*: 2 g as a single dose

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Note:** Adolescents ≥16 years: Refer to adult dosing.

Bacterial conjunctivitis: Children ≥1 year: Ophthalmic: Refer to adult dosing.

Bacterial sinusitis: Children ≥6 months: Oral: 10 mg/kg once daily for 3 days (maximum: 500 mg/day)

Cat scratch disease (unlabeled use): Oral: <45.5 kg: 10 mg/kg as a single dose, then 5 mg/kg once daily for 4 days

Community-acquired pneumonia: Children ≥6 months: Oral: 10 mg/kg on day 1 (maximum: 500 mg/day) followed by 5 mg/kg/day once daily on days 2-5 (maximum: 250 mg/day)

Disseminated*M. avium*(unlabeled use):

HIV-infected patients: Oral: 5 mg/kg/day once daily (maximum: 250 mg/day) or 20 mg/kg (maximum: 1200 mg) once weekly given alone or in combination with rifabutin

Treatment and secondary prevention in HIV-negative patients: 5 mg/kg/day once daily (maximum: 250 mg/day) in combination with ethambutol, with or without rifabutin

Prophylaxis against infective endocarditis (unlabeled use): Oral: 15 mg/kg 30-60 minutes before procedure. **Note:** American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur. As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Otitis media: Children ≥6 months: Oral:

1-day regimen: 30 mg/kg as a single dose (maximum dose: 1500 mg)

3-day regimen: 10 mg/kg once daily for 3 days (maximum: 500 mg/day)

5-day regimen: 10 mg/kg on day 1 (maximum: 500 mg/day) followed by 5 mg/kg/day once daily on days 2-5 (maximum: 250 mg/day)

Pharyngitis, tonsillitis: Children ≥2 years: Oral: 12 mg/kg/day once daily for 5 days (maximum: 500 mg/day)

Pertussis (CDC guidelines):

Children <6 months: 10 mg/kg/day for 5 day

Children ≥6 months: 10 mg/kg on day 1 (maximum: 500 mg/day) followed by 5 mg/kg/day once daily on days 2-5 (maximum: 250 mg/day)

Uncomplicated chlamydial urethritis or cervicitis (unlabeled use): Children ≥45 kg: 1 g as a single dose

Dosing: Renal ImpairmentUse caution in patients with Cl_{cr} <10 mL/minute
Dosing: Hepatic ImpairmentUse with caution due to potential for hepatotoxicity (rare). Specific guidelines for dosing in hepatic impairment have not been established.
Administration: I.V.Other medications should not be infused simultaneously through the same I.V. line.
Administration: I.V. DetailInfusate concentration and rate of infusion for azithromycin for injection should be either 1 mg/mL over 3 hours or 2 mg/mL over 1 hour.
Administration: OralImmediate release suspension and tablet may be taken without regard to food; extended release suspension should be taken on an empty stomach (at least 1 hour before or 2 hours following a meal), within 12 hours of reconstitution.
Administration: OtherOphthalmic: Shake bottle once prior to each administration. Wash hands before and after instillation.
Dietary Considerations

Oral suspension, immediate release, may be administered with or without food.

Oral suspension, extended release, should be taken on an empty stomach (at least 1 hour before or 2 hours following a meal).

Tablet may be administered with food to decrease GI effects.

Sodium content:

Injection: 114 mg (4.96 mEq) per vial

Oral suspension, immediate release: 3.7 mg per 100 mg/5 mL of constituted suspension; 7.4 mg per 200 mg/5 mL of constituted suspension; 37 mg per 1 g single-dose packet

Oral suspension, extended release: 148 mg per 2 g constituted suspension

Tablet: 0.9 mg/250 mg tablet; 1.8 mg/500 mg tablet; 2.1 mg/600 mg tablet

Storage

Injection (Zithromax®): Store intact vials of injection at room temperature. Reconstituted solution is stable for 24 hours when stored below

30°C/86°F.

Ophthalmic solution: Prior to use, store unopened under refrigeration at 2°C to 8°C (36°F to 46°F). After opening, store at 2°C to 25°C (36°F to 77°F) for ≤14 days; discard any remaining solution after 14 days.

Suspension, immediate release (Zithromax®): Store dry powder below 30°C (86°F). Following reconstitution, store at 5°C to 30°C (41°F to 86°F).

Suspension, extended release (Zmax™): Store dry powder below 30°C (86°F). Following reconstitution, store at 15°C to 30°C (59°F to 86°F); do not freeze. Should be consumed within 12 hours following reconstitution.

Tablet (Zithromax®): Store between 15°C to 30°C (59°F to 86°F).

ReconstitutionInjection (Zithromax®): Prepare initiation solution by adding 4.8 mL of sterile water for injection to the 500 mg vial (resulting concentration: 100 mg/mL). Use of a standard syringe is recommended due to the vacuum in the vial (which may draw additional solution through an automated syringe).

The initial solution should be further diluted to a concentration of 1 mg/mL (500 mL) to 2 mg/mL (250 mL) in 0.9% sodium chloride, 5% dextrose in water, or lactated Ringer's. The diluted solution is stable for 24 hours at or below room temperature (30°C or 86°F) and for 7 days if stored under refrigeration (5°C or 41°F).

CompatibilityOther medications should not be infused simultaneously through the same I.V. line.

ContraindicationsHypersensitivity to azithromycin, other macrolide antibiotics, or any component of the formulation

Allergy Considerations

- Macrolide Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: Macrolides have been associated with rare QT_c prolongation and ventricular arrhythmias, including torsade de pointes; use with caution in patients at risk of prolonged cardiac repolarization.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Gonorrhea/syphilis: May mask or delay symptoms of incubating gonorrhea or syphilis, so appropriate culture and susceptibility tests should be performed prior to initiating azithromycin.
- Hepatic impairment: Use with caution in patients with pre-existing liver disease; hepatic impairment, including hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been observed. Discontinue if symptoms of malaise, nausea, vomiting, abdominal colic, and fever.
- Renal impairment: Use with caution in patients with severe renal impairment (Cl_{cr} <10 mL/minute).

Special populations:

- Contact lens wearers: Ophthalmic solution contains benzalkonium chloride which may be absorbed by contact lenses; contact lens should not be worn during treatment of ophthalmic infections.
- Pediatrics: Safety and efficacy of systemically-administered azithromycin (oral, intravenous) have not been established in children <6 months of age with acute otitis media, acute bacterial sinusitis, or community-acquired pneumonia, or in children <2 years of age with pharyngitis/tonsillitis. Safety and efficacy for ophthalmic use have not been established in children <1 year of age.

Dosage form specific issues:

- Oral suspensions: Immediate release and extended release suspensions are not interchangeable.
- Ophthalmic solution: Eye drops should not be injected subconjunctivally or introduced directly into the anterior chamber of the eye.

Geriatric ConsiderationsDosage adjustment does not appear to be necessary in the elderly. Considered to be one of the drugs of choice in the outpatient treatment of community-acquired pneumonia in elderly. Evaluate the patient's ability to self-administer the ophthalmic product.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events were not observed in animal studies; therefore, azithromycin is classified as pregnancy category B. Low levels of azithromycin have been shown to cross the placenta. Azithromycin may be used for the treatment of some infections during pregnancy. The CDC and IDSA provide recommendations for the treatment of chlamydial infections and MAC in pregnant patients. Since serum concentrations determine fetal exposure and azithromycin has much higher concentrations in tissue than serum, treatment results in the mother may be obtained with lower exposure to the fetus. Although no adverse reports in human or animal fetuses have been documented, information in pregnant women is limited.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsAzithromycin is excreted in low amounts into breast milk. Compared to erythromycin, azithromycin achieves higher tissue concentrations when compared to serum concentrations. Since serum concentrations determine infant exposure, azithromycin may achieve treatment results in the mother with less exposure to the breast-feeding infant. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Azithromycin in Pregnancy & Lactation

Adverse Reactions

>10%: Gastrointestinal: Diarrhea (4% to 9%; high single-dose regimens 14%), nausea (≤7%; high single-dose regimens 18%)

2% to 10%:

Dermatologic: Pruritus, rash

Gastrointestinal: Abdominal pain, anorexia, cramping, vomiting (especially with high single-dose regimens)

Genitourinary: Vaginitis

Local: (with I.V. administration): Injection site pain, inflammation

Ocular (with ophthalmic solution use): Eye irritation (1% to 2%)

≤1%: Systemic therapy: Agitation, allergic reaction, anemia, angioedema, bronchospasm, candidiasis, chest pain, cholestatic jaundice, conjunctivitis, constipation, cough increased, dermatitis (fungal), diaphoresis, dizziness, dyspepsia, eczema, enteritis, facial edema, fatigue, fever, flatulence, fungal infection, gastritis, headache, hyperkinesia, insomnia, jaundice, leukopenia, malaise, melena, mucositis, nephritis, nervousness, oral moniliasis, pain, palpitation, pharyngitis, photosensitivity, pleural effusion, rhinitis, somnolence, taste perversion, urticaria, vertigo, vesiculobullous rash

1%: Ophthalmic solution: Contact dermatitis, corneal erosion, dysgeusia, nasal congestion, ocular discharge, ocular dryness; ocular stinging, burning, and irritation upon instillation; punctate keratitis, sinusitis

Postmarketing and/or case reports (all formulations): Acute renal failure, aggressive behavior, anaphylaxis, anxiety, arrhythmia (including ventricular tachycardia), arthralgia, deafness, dehydration, edema, erythema multiforme (rare), hearing disturbance, hearing loss, hepatic failure (rare), hepatic necrosis (rare), hepatitis, hyperactivity, hypertrophic pyloric stenosis, hypotension, interstitial nephritis, loss of smell, loss of taste, LFTs increased, neutropenia (mild), oral candidiasis, pancreatitis, paresthesia, pseudomembranous colitis, QT_c prolongation (rare), seizure, smell perversion, somnolence, Stevens-Johnson syndrome (rare), syncope, thrombocytopenia, tinnitus, tongue discoloration (rare), torsade de pointes (rare), toxic epidermal necrolysis (rare), weakness

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor); **Inhibits** CYP3A4 (weak)
Drug Interactions

Amiodarone: Azithromycin may enhance the QTc-prolonging effect of Amiodarone. *Risk D: Consider therapy modification*

Cardiac Glycosides: Macrolide Antibiotics may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

CycloSPORINE: Macrolide Antibiotics may decrease the metabolism of CycloSPORINE. *Risk C: Monitor therapy*

Nelfinavir: May decrease the excretion of Azithromycin. *Risk C: Monitor therapy*

Tacrolimus: Macrolide Antibiotics may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Macrolide Antibiotics may decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Rate and extent of GI absorption may be altered depending upon the formulation. Azithromycin suspension, not tablet form, has significantly increased absorption (46%) with food.
Monitoring ParametersLiver function tests, CBC with differential
Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's allergy history prior to beginning therapy. Assess potential for interactions with other pharmacological agents patient may be taking. I.V.: See administration specifics. Evaluate results of laboratory tests (LFTs, CBC with diff), therapeutic effectiveness, and adverse effects. Instruct patients being treated for STDs about preventing transmission. Teach patient appropriate use (according to formulation and purpose for use), possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsLiver function, CBC with differential. Perform culture and sensitivity testing prior to initiating therapy.
Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. If administered by infusion; report immediately any redness, swelling, or pain at infusion site. If self-administered, take exactly as directed according to formulation. Take all of prescribed medication and do not discontinue without consulting prescriber until prescription is completed. Oral: Take extended release suspension 1 hour before or 2 hours after meals; immediate release suspension and tablets may be taken with or without food; tablet form may be taken with meals to decrease GI effects. Do not take with antacids that contain aluminum or magnesium. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If taken to treat a sexually-transmitted disease, follow advice of prescriber related to sexual intercourse and preventing transmission. May cause transient abdominal distress, diarrhea, and headache. Report signs of additional infections (eg, sores in mouth or vagina, vaginal discharge, unresolved fever, severe vomiting, or loose or foul-smelling stools). **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Ophthalmic: Store under refrigeration. Shake bottle once prior to each administration. Wash hands before and after installation. Tilt head back, invert bottle, and gently squeeze bottle to instill prescribed amount into the affected eye(s). Contact lenses should not be worn during treatment of ophthalmic infection. You may experience mild eye irritation (if persistent, contact prescriber).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: Strength expressed as base

Injection, powder for reconstitution, as dihydrate: 500 mg

Zithromax®: 500 mg [contains sodium 114 mg (4.96 mEq) per vial]

Injection, powder for reconstitution, as hydrogencitrate: 500 mg

Injection, powder for reconstitution, as monohydrate: 500 mg

Microspheres for oral suspension, extended release, as dihydrate:

Zmax™: 2 g [single-dose bottle; contains sodium 148 mg per bottle; cherry and banana flavor]

Powder for oral suspension, as monohydrate: 100 mg/5 mL (15 mL); 200 mg/5 mL (15 mL, 22.5 mL, 30 mL)

Powder for oral suspension, immediate release, as dihydrate:

Zithromax®: 100 mg/5 mL (15 mL) [contains sodium 3.7 mg/ 5 mL; cherry creme de vanilla and banana flavor]; 200 mg/5 mL (15 mL, 22.5 mL, 30 mL) [contains sodium 7.4 mg/5 mL; cherry creme de vanilla and banana flavor]; 1 g/packet (3s, 10s) [single-dose packet; contains sodium 37 mg per packet; cherry creme de vanilla and banana flavor]

Solution, ophthalmic:

AzaSite™: 1% (2.5 mL) [contains benzalkonium chloride]

Tablet, as dihydrate:

Zithromax®: 250 mg [contains sodium 0.9 mg per tablet]; 500 mg [contains sodium 1.8 mg per tablet]; 600 mg [contains sodium 2.1 mg per tablet]

Zithromax® TRI-PAK™ [unit-dose pack]: 500 mg (3s) [contains sodium 1.8 mg per tablet]

Zithromax® Z-PAK® [unit-dose pack]: 250 mg (6s) [contains sodium 0.9 mg per tablet]

Tablet, as monohydrate: 250 mg, 500 mg, 600 mg

Generic AvailableYes: Injection, powder for oral suspension, tablet
ManufacturerPfizer U.S. Pharmaceuticals Group
Pricing: U.S. (www.drugstore.com)

Pack (Zithromax)

1 g (3): $103.39

Solution (AzaSite)

1% (2.5): $64.99

Suspension (reconstituted) (Azithromycin)

200 mg/5 mL (15): $32.27

Suspension (reconstituted) (Zithromax)

100 mg/5 mL (15): $47.24

200 mg/5 mL (15): $46.19

200 mg/5 mL (22.5): $46.99

200 mg/5 mL (30): $46.19

Tablets (Azithromycin)

250 mg (6): $25.99

250 mg (30): $98.99

500 mg (3): $44.32

500 mg (30): $438.00

600 mg (30): $399.94

Tablets (Zithromax)

250 mg (30): $297.66

500 mg (30): $559.88

600 mg (30): $660.48

Tablets (Zithromax Tri-Pak)

500 mg (3): $62.99

Tablets (Zithromax Z-Pak)

250 mg (6): $62.24

Mechanism of Action Inhibits RNA-dependent protein synthesis at the chain elongation step; binds to the 50S ribosomal subunit resulting in blockage of transpeptidation

Pharmacodynamics/Kinetics

Absorption: Oral: Rapid; Ophthalmic: Negligible

Distribution: Extensive tissue; distributes well into skin, lungs, sputum, tonsils, and cervix; penetration into CSF is poor; I.V.: 33.3 L/kg; Oral: 31.1 L/kg

Protein binding (concentration dependent): Oral, I.V.: 7% to 51%

Metabolism: Hepatic

Bioavailability: Oral: 38%, decreased by 17% with extended release suspension; variable effect with food (increased with immediate or delayed release oral suspension, unchanged with tablet)

Half-life elimination: Oral, I.V.: Terminal: Immediate release: 68-72 hours; Extended release: 59 hours

Time to peak, serum: Oral: Immediate release: 2-3 hours; Extended release: 5 hours

Excretion: Oral, I.V.: Biliary (major route); urine (6%)

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Prevention of Infective Endocarditis
- Treatment of Sexually-Transmitted Infections
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy Pearls Zithromax® tablets and immediate release suspension may be interchanged (eg, two Zithromax® 250 mg tablets may be substituted for one Zithromax® 500 mg tablet or the tablets may be substituted with the immediate release suspension); however, the extended release suspension (Zmax™) is not bioequivalent with Zithromax® and therefore should not be interchanged.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Macrolides have been reported to cause nightmares, confusion, anxiety, and mood lability; may rarely cause dizziness, agitation, nervousness, and insomnia

Mental Health: Effects on Psychiatric Treatment Contraindicated with pimozide; may increase concentration of bromocriptine, carbamazepine, and triazolam

Cardiovascular Considerations The clinical implications of the association between infection (*Chlamydia* and cytomegalovirus) and coronary artery disease (CAD) is unknown. A recent trial showed no difference in clinical events in azithromycin-treated patients who had CAD and positive *C. pneumoniae* antibodies.

Index Terms Azithromycin Dihydrate; Azithromycin Hydrogencitrate; Azithromycin Monohydrate; Zithromax® TRI-PAK™; Zithromax® Z-PAK®

References

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International Brand NamesAtizor (CN); Azadose (FR); Azenil (IL); Azithral (IN); Azitrocin (IT, MX); Azitrohexal (MX); Azitromax (NO, SE); Aziwok (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Azo-Max (MX); Azro (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Aztrin (ID); Binozyt (ID, TH); Clindal AZ (BR); Cronopen (AR); Forcin (CN); Imbys (CR, DO, GT, HN, NI, PA, SV); Inedol (PE); Koptin (MX); Kromicin (CO); Macrozit (MX, PE); Mezatrin (ID); Oranex (PL); Sumamed (BG, CZ, EE, HN, PL); Sumir (AR); Tromix (CO); Ultreon (DE); Xithrone (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Zaret (CO); Zeto (IL); Zibramax (ID); Zifin (ID); Zistic (ID); Zithran (MX); Zithromax (AE, AT, AU, BB, BD, BF, BH, BJ, BM, BS, BZ, CH, CI, CL, CN, CR, CY, DE, DO, EG, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, ID, IE, IL, IN, IQ, IR, JM, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, OM, PA, PH, PK, QA, SA, SC, SD, SG, SL, SN, SR, SV, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Zithromax IV (MY, SG); Zithrox (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Zitrim (CO); Zitromax (AR, BE, BR, DK, EC, ES, IT, PE, UY, VE); Zmax One Dose (PH); Zomax (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE)

Aztreonam

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Aztreonam may be confused with azidothymidine

Pronunciation(AZ tree oh nam)

U.S. Brand NamesAzactam®

Canadian Brand NamesAzactam®

Pharmacologic CategoryAntibiotic, Miscellaneous

Use: Labeled IndicationsTreatment of patients with urinary tract infections, lower respiratory tract infections, septicemia, skin/skin structure infections, intra-abdominal infections, and gynecological infections caused by susceptible gram-negative bacilli

Dosing: Adults

Urinary tract infection: I.M., I.V.: 500 mg to 1 g every 8-12 hours

Moderately severe systemic infections:

I.M.: 1 g every 8-12 hours

I.V.: 1-2 g every 8-12 hours

Severe systemic or life-threatening infections (especially caused by*Pseudomonas aeruginosa*): I.V.: 2 g every 6-8 hours; maximum: 8 g/day

Meningitis (gram-negative): I.V.: 2 g every 6-8 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Susceptible infections: I.M., I.V.: Children >1 month:

Mild-to-moderate infections: 30 mg/kg every 8 hours

Moderate-to-severe infections: 30 mg/kg every 6-8 hours; maximum: 120 mg/kg/day (8 g/day)

Infection in children with cystic fibrosis: I.V.: Children >1 month: 50 mg/kg/dose every 6-8 hours (ie, up to 200 mg/kg/day); maximum: 8 g/day

Dosing: Renal ImpairmentAdults: Following initial dose, maintenance doses should be given as follows:

Cl_{cr} 10-30 mL/minute: 50% of usual dose at the usual interval

Cl_{cr} <10 mL/minute: 25% of usual dosage at the usual interval

Hemodialysis: Moderately dialyzable (20% to 50%); Loading dose of 500 mg, 1 g, or 2 g, followed by 25% of initial dose at usual interval; for serious/life-threatening infections, administer $^1/_8$ of initial dose after each hemodialysis session (given in addition to the maintenance doses)

Continuous ambulatory peritoneal dialysis (CAPD): Administer as for Cl_{cr} <10 mL/minute

Continuous renal replacement therapy (CRRT): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH: 1-2 g every 12 hours

CVVHD/CVVHDF: 2 g every 12 hours

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Administer by deep injection into large muscle mass, such as upper outer quadrant of gluteus maximus or the lateral part of the thigh. Doses >1 g should be administered I.V.

Administration: I.V.I.V. route is preferred for doses >1 g or in patients with severe life-threatening infections. Administer by slow I.V. push over 3-5 minutes or by intermittent infusion over 20-60 minutes.

Administration: I.V. DetailMonitor infusion/injection sites carefully. Administer around-the-clock to promote less variation in peak and trough serum levels.

pH: 4.5-7.5 (aqueous solution)

StoragePrior to reconstitution, store at room temperature; avoid excessive heat. Reconstituted solutions are colorless to light yellow straw and may turn pink upon standing without affecting potency. Use reconstituted solutions and I.V. solutions (in NS and D_5W) within 48 hours if kept at room temperature (25°C) or 7 days under refrigeration (4°C).

Infusion: Solution for infusion may be frozen at less than -2°C (less than -4°F) for up to 3 months. Thawed solution should be used within 24 hours if thawed at room temperature or within 72 hours if thawed under refrigeration. **Do not refreeze.**

Reconstitution

I.M.: Reconstitute with at least 3 mL SWFI, sterile bacteriostatic water for injection, NS, or bacteriostatic sodium chloride.

I.V.:

Bolus injection: Reconstitute with 6-10 mL SWFI.

Infusion: Reconstitute to a final concentration ≤2%; the final concentration should not exceed 20 mg/mL.

CompatibilitySolution for infusion: Stable in D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, mannitol 5%, mannitol 10%, LR, NS; **variable stability (consult detailed reference)** in peritoneal dialysis solution.

Y-site administration: Compatible: Allopurinol, amifostine, amikacin, aminophylline, ampicillin, ampicillin/sulbactam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, carmustine, cefazolin, cefepime, cefoperazone, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cimetidine, ciprofloxacin, cisatracurium, cisplatin, clindamycin, co-trimoxazole, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dexamethasone sodium phosphate, diltiazem, diphenhydramine, dobutamine, docetaxel, dopamine, doxorubicin, doxorubicin liposome, doxycycline, droperidol, enalaprilat, etoposide, etoposide phosphate, famotidine, filgrastim, floxuridine, fluconazole, fludarabine, fluorouracil, foscarnet, furosemide, gatifloxacin, gemcitabine, gentamicin, granisetron, haloperidol, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, idarubicin, ifosfamide, imipenem/cilastatin, insulin (regular), leucovorin, linezolid, magnesium sulfate, mannitol, mechlorethamine, melphalan, meperidine, mesna, methotrexate, methylprednisolone sodium succinate, metoclopramide, minocycline, morphine, nalbuphine, netilmicin, ondansetron, piperacillin, piperacillin/tazobactam, plicamycin, potassium chloride, promethazine, propofol, ranitidine, remifentanil, sargramostim, sodium bicarbonate, teniposide, theophylline, thiotepa, ticarcillin, ticarcillin/clavulanate, tobramycin, vinblastine, vincristine, vinorelbine, zidovudine. **Incompatible:** Acyclovir, alatrofloxacin, amphotericin B, amphotericin B cholesteryl sulfate complex, amsacrine, chlorpromazine, daunorubicin, ganciclovir, lorazepam, metronidazole, mitomycin, mitoxantrone, prochlorperazine edisylate, streptozocin. **Variable (consult detailed reference):** Vancomycin.

Compatibility in syringe: Compatible: Clindamycin.

Compatibility when admixed: Compatible: Ampicillin/sulbactam, cefazolin, ciprofloxacin, clindamycin, gentamicin, linezolid, tobramycin. **Incompatible:** Metronidazole, nafcillin. **Variable (consult detailed reference):** Ampicillin, cefoxitin, vancomycin.

ContraindicationsHypersensitivity to aztreonam or any component of the formulation

Allergy Considerations

- Monobactam Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cephalosporin/penicillin allergy: Rare cross-allergenicity to penicillins and cephalosporins has been reported.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment..

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosing adjustment required.

Geriatric ConsiderationsAdjust dose relative to renal function.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal reproduction studies; therefore, the manufacturer classifies aztreonam as pregnancy category B. Aztreonam crosses the placenta and enters cord blood during middle and late pregnancy. Distribution to the fetus is minimal in early pregnancy. Aztreonam is used therapeutically in newborns.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsVery small amounts of aztreonam are excreted in breast milk. The poor oral absorption of aztreonam (<1%) may limit adverse effects to the infant. Although the manufacturer recommends considering temporary discontinuation of nursing during therapy, the AAP considers aztreonam to be "usually compatible with breast-feeding." Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Aztreonam in Pregnancy & Lactation

Adverse ReactionsAs reported in adults:

1% to 10%:

Dermatologic: Rash

Gastrointestinal: Diarrhea, nausea, vomiting

Local: Thrombophlebitis, pain at injection site

<1%: Abdominal cramps, abnormal taste, anaphylaxis, anemia, angioedema, aphthous ulcer, breast tenderness, bronchospasm, *C. difficile*-associated diarrhea, chest pain, confusion, diaphoresis, diplopia, dizziness, dyspnea, eosinophilia, erythema multiforme, exfoliative dermatitis, fever, flushing, halitosis, headache, hepatitis, hypotension, insomnia, jaundice, leukopenia, liver enzymes increased, muscular aches myalgia, neutropenia, numb tongue, pancytopenia, paresthesia, petechiae, pruritus, pseudomembranous colitis, purpura, seizure, sneezing, thrombocytopenia, tinnitus, toxic epidermal necrolysis, urticaria, vaginitis, vertigo, weakness, wheezing

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Test InteractionsMay interfere with urine glucose tests containing cupric sulfate (Benedict's solution, Clinitest®); positive Coombs' test

Monitoring ParametersPeriodic liver function test; monitor for signs of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's allergy history before initiating therapy. I.V.: Infusion site should be monitored closely. Assess therapeutic effectiveness and adverse response. Caution patients with diabetes about altered response to Clinitest®. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsObtain specimens for culture and sensitivity before the first dose.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by injection or infusion. Report immediately any burning, pain, swelling, or redness at infusion/injection site. May cause nausea or GI distress (frequent mouth care, frequent small meals, sucking lozenges, or chewing gum may help relieve these symptoms). If you have diabetes, drug may cause false tests with Clinitest® urine glucose monitoring; use of another type of glucose monitoring is preferable. Report any persistent and unrelieved diarrhea or vomiting, pain at injection site, unresolved fever, unhealed or new sores in mouth or vagina, vaginal discharge, or acute onset of respiratory difficulty. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Infusion premixed iso-osmotic solution:

Azactam®: 1 g (50 mL); 2 g (50 mL)

Injection, powder for reconstitution:

Azactam®: 500 mg [DSC], 1 g, 2 g

Generic AvailableNo

ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested. Monobactam structure makes cross-allergenicity with beta-lactams unlikely.

Pharmacodynamics/Kinetics

Absorption: I.M.: Well absorbed; I.M. and I.V. doses produce comparable serum concentrations; Oral: <1%

Distribution: Widely to most body fluids and tissues

V_d: Children: 0.2-0.29 L/kg; Adults: 0.2 L/kg

Relative diffusion of antimicrobial agents from blood into CSF: Good only with inflammation (exceeds usual MICs)

CSF:blood level ratio: Meninges: Inflamed: 8% to 40%; Normal: ~1%

Protein binding: 56%

Metabolism: Hepatic (minor %)

Half-life elimination:

Children 2 months to 12 years: 1.7 hours

Adults: Normal renal function: 1.7-2.9 hours

End-stage renal disease: 6-8 hours

Time to peak: I.M., I.V. push: Within 60 minutes; I.V. infusion: 1.5 hours

Excretion: Urine (60% to 70% as unchanged drug); feces (~13% to 15%)

Related Information

- Antimicrobial Drugs of Choice

- Community-Acquired Pneumonia in Adults

Pharmacotherapy PearlsAlthough marketed as an agent similar to aminoglycosides, aztreonam is a monobactam antimicrobial with almost pure gram-negative aerobic activity. It cannot be used for gram-positive infections. Aminoglycosides are often used for synergy in gram-positive infections.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely produce confusion

Mental Health: Effects on Psychiatric TreatmentRarely produces leukopenia and neutropenia; use caution with clozapine and carbamazepine

Anesthesia and Critical Care Concerns/Other ConsiderationsAlthough marketed as an agent similar to aminoglycosides, aztreonam is a monobactam antimicrobial with almost pure gram-negative aerobic activity. It cannot be used for gram-positive infections, whereas aminoglycosides are often used for synergy in gram-positive infections.

Index TermsAzthreonam

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Tunkel AR, Hartman BJ, Kaplan SL, et al, “Practice Guidelines for the Management of Bacterial Meningitis,” *Clin Infect Dis*, 2004, 39(9):1267-84.[PubMed 15494903]

International Brand NamesAzactam (AR, AT, AU, BB, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HN, IE, IT, JM, JP, KE, KP, LR, MA, ML, MR, MU, MW, NE, NG, NL, NO, PE, PH, PK, PL, PT, RU, SC, SD, SE, SG, SL, SN, SR, TN, TR, TT, TW, TZ, UG, VE, ZA, ZM, ZW); Azenam (IN); Squibb-Azactam (CO)

Bacitracin, Neomycin, Polymyxin B, and Hydrocortisone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(bas i TRAY sin, nee oh MYE sin, pol i MIKS in bee, & hye droe KOR ti sone)
U.S. Brand NamesCortisporin® Ointment
Canadian Brand NamesCortisporin® Topical Ointment
Pharmacologic CategoryAntibiotic, Ophthalmic; Antibiotic, Topical; Corticosteroid, Ophthalmic; Corticosteroid, Topical
Use: Labeled IndicationsPrevention and treatment of susceptible inflammatory conditions where bacterial infection (or risk of infection) is present
Dosing: Adults

Ophthalmic infection: Ophthalmic ointment: Instill $^{1}/_{2}$ inch ribbon to inside of lower lid every 3-4 hours until improvement occurs.

Superficial dermal infection: Topical: Apply sparingly 2-4 times/day.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
StorageStore at controlled room temperature of 15°C to 25°C (59°F to 77°F).
ContraindicationsHypersensitivity to bacitracin, neomycin, polymyxin B, hydrocortisone, or any component of the formulation; not for use in viral infections, fungal diseases, mycobacterial infections
Allergy Considerations

- Bacitracin Allergy
- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Neomycin sensitization: Symptoms of neomycin sensitization include itching, reddening, edema, and failure to heal. Discontinuation of product and avoidance of similar products should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, and fluid and electrolyte changes.

Dosage form specific issues:

- Ophthalmic ointment: Should never be directly introduced into the anterior chamber. May retard corneal healing. Prolonged use may result in ocular hypertension/glaucoma, corneal and scleral thinning, potentially resulting in perforation. Use with caution in glaucoma. Avoid use following ocular cataract surgery. Inadvertent contamination of multiple-dose ophthalmic solutions, has caused bacterial keratitis.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined. For additional information, see individual agents.

Ophthalmic ointment:

Dermatologic: Delayed wound healing, rash

Ocular: Cataracts, corneal thinning, glaucoma, irritation, keratitis (bacterial), intraocular pressure increase, optic nerve damage, scleral thinning

Miscellaneous: Hypersensitivity (including anaphylaxis), secondary infection, sensitization to kanamycin, paromomycin, streptomycin, and gentamicin

Topical ointment:

Dermatologic: Acneiform eruptions, allergic contact dermatitis, burning skin, dryness, folliculitis, hypertrichosis, hypopigmentation, irritation, maceration of skin, miliaria, ocular hypertension, perioral dermatitis, pruritus, skin atrophy, striae

Otic: Ototoxicity

Renal: Nephrotoxicity

Miscellaneous: Hypersensitivity (including anaphylaxis), secondary infection, sensitization to karamycin, paromycin, streptomycin, and gentamicin

Metabolism/Transport EffectsHydrocortisone: **Substrate** of CYP3A4 (minor); **Induces** CYP3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Polymyxin B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

Cardiac Glycosides: Aminoglycosides may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

Colistimethate: Polymyxin B may enhance the neuromuscular-blocking effect of Colistimethate. *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents: Polymyxin B may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Monitoring ParametersIf ophthalmic ointment is used >10 days or in patients with glaucoma, monitor intraocular pressure (IOP).

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Ointment, ophthalmic: Bacitracin 400 units, neomycin 3.5 mg, polymyxin B 10,000 units, and hydrocortisone 10 mg per g (3.5 g)

Ointment, topical:

Cortisporin®: Bacitracin 400 units, neomycin 3.5 mg, polymyxin B 5000 units, and hydrocortisone 10 mg per g (15 g)

Generic AvailableYes: Ophthalmic ointment

Pricing: U.S. (www.drugstore.com)

Ointment (Bacitra-Neomycin-Polymyxin-HC)

1% (3.5): $7.99

Ointment (Cortisporin)

1% (15): $70.84

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Bacitracin
- Hydrocortisone
- Neomycin
- Polymyxin B

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsHydrocortisone, Bacitracin, Neomycin, and Polymyxin B; Neomycin, Bacitracin, Polymyxin B, and Hydrocortisone; Polymyxin B, Bacitracin, Neomycin, and Hydrocortisone

References

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

International Brand NamesCortisporin Topical Ointment (CA); Polybamycin (SG)

Bacitracin, Neomycin, Polymyxin B, and Pramoxine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(bas i TRAY sin, nee oh MYE sin, pol i MIKS in bee, & pra MOKS een)

U.S. Brand NamesNeosporin® + Pain Relief Ointment [OTC]; Spectrocin Plus™ [OTC] [DSC]; Tri Biozene [OTC]

Pharmacologic CategoryAntibiotic, Topical

Use: Labeled IndicationsPrevention and treatment of susceptible superficial topical infections and provide temporary relief of pain or discomfort

Dosing: AdultsTopical: Apply 1-3 times/day to infected areas; cover with sterile bandage if needed

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricTopical: Children ≥2 years: Refer to adult dosing.

ContraindicationsHypersensitivity to bacitracin, neomycin, polymyxin B, pramoxine, or any component of the formulation

Allergy Considerations

- Bacitracin Allergy

Warnings/Precautions

Other warnings/precautions:

• Appropriate use: For external use only; avoid in eyes. Not for use over large areas of the body or for longer than 1 week.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Ointment, topical: Bacitracin 500 units, neomycin 3.5 mg, polymyxin B 10,000 units, and pramoxine hydrochloride 10 mg (15 g, 30 g)

Neosporin® + Pain Relief Ointment: Bacitracin 500 units, neomycin 3.5 mg, polymyxin B 10,000 units, and pramoxine hydrochloride 10 mg per g (15 g, 30 g)

Spectrocin Plus™: Bacitracin 500 units, neomycin 3.5 mg, polymyxin B 10,000 units, and pramoxine hydrochloride 10 mg per g (30 g) [DSC]

Tri Biozene: Bacitracin 500 units, neomycin 3.5 mg, polymyxin B 10,000 units, and pramoxine hydrochloride 10 mg per g (15 g)

Generic AvailableYes

Related Information

- Bacitracin
- Neomycin
- Polymyxin B
- Pramoxine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsNeomycin, Bacitracin, Polymyxin B, and Pramoxine; Polymyxin B, Neomycin, Bacitracin, and Pramoxine; Pramoxine, Neomycin, Bacitracin, and Polymyxin B

Bacitracin, Neomycin, and Polymyxin B

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(bas i TRAY sin, nee oh MYE sin, & pol i MIKS in bee)
U.S. Brand NamesNeosporin® Neo To Go® [OTC]; Neosporin® Ophthalmic Ointment [DSC]; Neosporin® Topical [OTC]
Canadian Brand NamesNeosporin® Ophthalmic Ointment
Pharmacologic CategoryAntibiotic, Ophthalmic; Antibiotic, Topical
Use: Labeled IndicationsHelps prevent infection in minor cuts, scrapes, and burns; short-term treatment of superficial external ocular infections caused by susceptible organisms
Dosing: Adults

Ophthalmic infection: Ophthalmic ointment: Instill $^{1}/_{2}$” into the conjunctival sac every 3-4 hours for 7-10 days for acute infections

Superficial dermal infection: Topical: Apply 1-3 times/day to infected area; may cover with sterile bandage if necessary.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
ContraindicationsHypersensitivity to neomycin, polymyxin B, zinc bacitracin, or any component of the formulation; epithelial herpes simplex keratitis; mycobacterial or fungal infections; topical ointments for external use only
Allergy Considerations

- Bacitracin Allergy

Warnings/Precautions

Ophthalmic ointment: Bacterial keratitis has been reported with the use of topical ophthalmic products in multiple-dose containers. Care should be taken to not contaminate the container.

Topical ointment: When used for self-medication (OTC use), patients should notify healthcare provider if needed for >1 week. Should not be used for self-medication on deep or puncture wounds, animal bites, or serious burns. Not for application to large areas of the body.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Dermatologic: Reddening, allergic contact dermatitis

Local: Itching, failure to heal, swelling, irritation

Ophthalmic: Conjunctival edema

Miscellaneous: Anaphylaxis

Drug Interactions

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Polymyxin B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

Cardiac Glycosides: Aminoglycosides may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

Colistimethate: Polymyxin B may enhance the neuromuscular-blocking effect of Colistimethate. *Risk C: Monitor therapy*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Polymyxin B may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Ointment, ophthalmic (Neosporin® [DSC]): Bacitracin 400 units, neomycin 3.5 mg, and polymyxin B 10,000 units per g (3.5 g)

Ointment, topical: Bacitracin 400 units, neomycin 3.5 mg, and polymyxin B 5000 units per g (0.9 g, 15 g, 30 g, 454 g)

Neosporin®: Bacitracin 400 units, neomycin 3.5 mg, and polymyxin B 5000 units per g (15 g, 30 g)

Neosporin® Neo To Go®: Bacitracin 400 units, neomycin 3.5 mg, and polymyxin B 5000 units per g (0.9 g)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Ointment (Neomycin-Bacitracin Zn-Polymyx)

5-400-10000 (3.5): $7.99

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Bacitracin
- Neomycin
- Polymyxin B

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsNeomycin, Bacitracin, and Polymyxin B; Polymyxin B, Bacitracin, and Neomycin; Triple Antibiotic

International Brand NamesBamyxin (IL); Dactrol (ID); Multimycin (PE); My-B (TH); Neo-Polybacin (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Neosporin Dermico (MX); Neosporin Ophthalmic Ointment (AU, IN); Novosporina (PY); Polixin Ungena (MX); Polysporin (BR); Terramycin Plus (PH); Tribiot (MX); Yentuogin (TW)

Bacitracin and Polymyxin B

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Betadine® may be confused with Betagan®, betaine

Pronunciation(bas i TRAY sin & pol i MIKS in bee)

U.S. Brand NamesAK-Poly-Bac™; Betadine® First Aid Antibiotics + Moisturizer [OTC] [DSC]; Polysporin® [OTC]

Canadian Brand NamesLID-Pack®; Optimyxin®

Pharmacologic CategoryAntibiotic, Ophthalmic; Antibiotic, Topical

Use: Labeled IndicationsTreatment of superficial infections caused by susceptible organisms

Dosing: Adults

Ophthalmic infection: Ophthalmic (ointment): Instill $^1/_2$" ribbon in the affected eye(s) every 3-4 hours for acute infections or 2-3 times/day for mild-to-moderate infections for 7-10 days.

Superficial dermal infection: Topical ointment/powder: Apply to affected area 1-4 times/day; may cover with sterile bandage if needed.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

ContraindicationsHypersensitivity to bacitracin, polymyxin B, or any component of the formulation

Allergy Considerations

- Bacitracin Allergy

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/use caution

Adverse Reactions1% to 10%: Local: Rash, itching, burning, anaphylactoid reactions, swelling, conjunctival erythema

Drug Interactions

Capreomycin: May enhance the neuromuscular-blocking effect of Polymyxin B. *Risk C: Monitor therapy*

Colistimethate: Polymyxin B may enhance the neuromuscular-blocking effect of Colistimethate. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Polymyxin B may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Ointment, ophthalmic: Bacitracin 500 units and polymyxin B 10,000 units per g (3.5 g)

AK-Poly-Bac™: Bacitracin 500 units and polymyxin 10,000 units per g (3.5 g)

Ointment, topical: Bacitracin 500 units and polymyxin B 10,000 units per g in white petrolatum (15 g, 30 g)

Betadine® First Aid Antibiotics + Moisturizer: Bacitracin 500 units and polymyxin B 10,000 units per g (14 g) [DSC]

Polysporin®: Bacitracin 500 units and polymyxin B 10,000 units per g (0.9 g, 15 g, 30 g)

Powder, topical:

Polysporin®: Bacitracin 500 units and polymyxin B 10,000 units per g (10 g)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Ointment (Bacitracin-Polymyxin B)

500-10000 units/g (3.5): $17.99

Ointment (Polysporin)

500-10000 units/g (3.5): $34.99

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Bacitracin
- Polymyxin B

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPolymyxin B and Bacitracin

International Brand NamesGlubacida (MX); Miratracina (CO); Nebacetina (MX); Neobacitracine (BE); Neosporín Dérmico (MX); Polisulfade (PT); Polixin Ungena (MX); Polyfax (MY); Polysporin Ophthalmic (ZA); Tribiot (MX)

Bacitracin

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English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Bacitracin may be confused with Bactrim®, Bactroban®

Pronunciation(bas i TRAY sin)

U.S. Brand NamesBaci-Rx; Baciguent® [OTC]; BaciiM®

Canadian Brand NamesBaciguent®; Baciject®

Pharmacologic CategoryAntibiotic, Miscellaneous; Antibiotic, Ophthalmic; Antibiotic, Topical

Use: Labeled IndicationsTreatment of susceptible bacterial infections mainly; has activity against gram-positive bacilli; due to toxicity risks, systemic and irrigant uses of bacitracin should be limited to situations where less toxic alternatives would not be effective

Use: Unlabeled/InvestigationalOral administration: Successful in antibiotic-associated colitis; has been used for enteric eradication of vancomycin-resistant enterococci (VRE)

Dosing: AdultsDo not administer I.V.:

Antibiotic-associated colitis: Oral: 25,000 units 4 times/day for 7-10 days

VRE eradication (unlabeled use): Oral: 25,000 units 4 times/day for 7-10 days

Superficial dermal infection: Topical: Apply 1-5 times/day.

Ophthalmic infection: Ophthalmic (ointment): Instill $^{1}/_{4}$" to $^{1}/_{2}$" ribbon every 3-4 hours into conjunctival sac for acute infections, or 2-3 times/day for mild-to-moderate infections for 7-10 days.

Local irrigation: Solution: 50-100 units/mL in normal saline, lactated Ringer's, or sterile water for irrigation; soak sponges in solution for topical compresses 1-5 times/day or as needed during surgical procedures.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDo not administer I.V.

Treatment of infection:

Infants: I.M.:

≤2.5 kg: 900 units/kg/day in 2-3 divided doses

>2.5 kg: 1000 units/kg/day in 2-3 divided doses

Children: I.M.: 800-1200 units/kg/day divided every 8 hours

Superficial dermal infection: Topical: Refer to adult dosing.

Ophthalmic infection: Ophthalmic (ointment): Refer to adult dosing.

Local irrigation: Solution: Refer to adult dosing.

Administration: I.M.For I.M. administration only. pH of urine should be kept >6 by using sodium bicarbonate. Bacitracin sterile powder should be dissolved in 0.9% sodium chloride injection containing 2% procaine hydrochloride. Do not use diluents containing parabens.

Administration: I.V.Not for I.V. administration.

Administration: OralThe injection formulation is extemporaneously prepared and flavored to improve palatability.

ReconstitutionFor I.M. use only. Bacitracin sterile powder should be dissolved in 0.9% sodium chloride injection containing 2% procaine hydrochloride. Once reconstituted, bacitracin is stable for 1 week under refrigeration (2°C to 8°C). Sterile powder should be stored in the refrigerator. Do not use diluents containing parabens.

Extemporaneously PreparedIn some institutions, oral formulations have been prepared either by preparation of capsules from powder or oral administration of I.V. solution.

ContraindicationsHypersensitivity to bacitracin or any component of the formulation; I.M. use is contraindicated in patients with renal impairment

Allergy Considerations

- Bacitracin Allergy

Warnings/Precautions

Boxed warnings:

- Renal failure: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Renal failure: **[U.S. Boxed Warning]: I.M. use may cause renal failure due to tubular and glomerular necrosis; monitor renal function daily.** Avoid concurrent use with other nephrotoxic drugs; discontinue use if toxicity occurs.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment..

Other warnings/precautions:

- Appropriate administration: Do not administer intravenously because severe thrombophlebitis occurs.

Pregnancy ConsiderationsIt is unknown if bacitracin crosses the placenta. The minimal absorption after topical use should limit the amount of medication available for transfer to the fetus.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is unknown if bacitracin is distributed in human milk. The minimal absorption after topical use should limit the amount of medication available for transfer.

Pregnancy & Lactation, In-Depth

- Bacitracin in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Cardiovascular: Hypotension, edema of the face/lips, chest tightness

Central nervous system: Pain

Dermatologic: Rash, itching

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, rectal itching

Hematologic: Blood dyscrasias

Miscellaneous: Diaphoresis

<1%: Rare cases of anaphylaxis have been reported in association with topical and intraoperative exposures.

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersI.M.: Urinalysis, renal function tests

Nursing: Physical Assessment/MonitoringDo not administer I.V. Assess potential for interactions with other pharmacological agents patient may be taking (eg, nephrotoxic drugs, neuromuscular blocking agents, and anesthetics). Assess laboratory results (urinalysis and renal function with I.M.), effectiveness of therapy, and adverse reactions. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsI.M.: Urinalysis, renal function

Patient Education

Oral/I.M.: Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Report rash, redness, or itching; change in urinary pattern; acute dizziness; swelling of face or lips; chest pain or tightness; acute nausea or vomiting; or loss of appetite (small, frequent meals or frequent mouth care may help).

Ophthalmic: Instill as many times per day as directed. Wash hands before using. Gently pull lower eyelid forward, instill prescribed amount of ointment into lower eyelid. Close eye and roll eyeball in all directions. May cause blurred vision; use caution when driving or engaging in tasks that require clear vision. Report any adverse reactions such as rash or itching, swelling of face or lips, burning or pain in eye, worsening of condition, or if condition does not improve.

Topical: Apply a thin film as many times a day as prescribed to the affected area. May cover with porous sterile bandage (avoid occlusive dressings). Do not use longer than 1 week unless advised by prescriber. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 50,000 units

BaciiM®: 50,000 units

Ointment, ophthalmic: 500 units/g (3.5 g)

Ointment, topical: 500 units/g (0.9 g, 15 g, 30 g, 120 g, 454 g)

Baciguent®: 500 units/g (15 g, 30 g)

Powder, for prescription compounding [micronized]:

Baci-Rx: 5 million units

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Ointment (Bacitracin)

500 units/g (3.5): $8.99

500 units/g (28.4): $12.99

Mechanism of ActionInhibits bacterial cell wall synthesis by preventing transfer of mucopeptides into the growing cell wall

Pharmacodynamics/Kinetics

Duration: 6-8 hours

Absorption: Poor from mucous membranes and intact or denuded skin; rapidly following I.M. administration; not absorbed by bladder irrigation, but absorption can occur from peritoneal or mediastinal lavage

Distribution: CSF: Nil even with inflammation

Protein binding, plasma: Minimal

Time to peak, serum: I.M.: 1-2 hours

Excretion: Urine (10% to 40%) within 24 hours

Related Information

- Antimicrobial Drugs of Choice

Pharmacotherapy Pearls1 unit is equivalent to 0.026 mg

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

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Kelly CP, Pothoulakis C, and LaMont JT, “*Clostridium difficile* Colitis,” *N Engl J Med*, 1994, 330(4):257-62. [PubMed 8043060]

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O'Donovan CA, Fan-Havard P, Tecson-Tumang FT, et al, “Enteric Eradication of Vancomycin-Resistant *Enterococcus faecium* With Oral Bacitracin,” *Diagn Microbiol Infect Dis*, 1994, 18(2):105-9. [PubMed 8062527]

Vale MA, Connolly A, Epstein AM, et al, “Bacitracin-Induced Anaphylaxis,” *Arch Dermatol*, 1978, 114(5):800.

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Young GP, Ward PB, Bayley N, et al, “Antibiotic-Associated Colitis Due to *Clostridium difficile*: Double-Blind Comparison of Vancomycin With Bacitracin,” *Gastroenterology*, 1985, 89(5):1038-45.[PubMed 4043661]

International Brand NamesGlubacida (MX); Nebacetina (MX); Neosporin Dérmico (MX); Polixin Ungena (MX); Tribiot (MX)

Baclofen

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Baclofen may be confused with Bactroban®

Lioresal® may be confused with lisinopril, Lotensin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (intrathecal administration) among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(BAK loe fen)

U.S. Brand NamesLioresal®

Canadian Brand NamesApo-Baclofen®; Gen-Baclofen; Lioresal®; Liotec; Nu-Baclo; PMS-Baclofen

Pharmacologic CategorySkeletal Muscle Relaxant

Use: Labeled IndicationsTreatment of reversible spasticity associated with multiple sclerosis or spinal cord lesions

Orphan drug: Intrathecal: Treatment of intractable spasticity caused by spinal cord injury, multiple sclerosis, and other spinal disease (spinal ischemia or tumor, transverse myelitis, cervical spondylosis, degenerative myelopathy)

Use: Unlabeled/InvestigationalIntractable hiccups, intractable pain relief, bladder spasticity, trigeminal neuralgia, cerebral palsy, Huntington's chorea

Dosing: Adults

Spasticity:

Oral: 5 mg 3 times/day, may increase 5 mg/dose every 3 days to a maximum of 80 mg/day

Intrathecal:

Test dose: 50-100 mcg, doses >50 mcg should be given in 25 mcg increments, separated by 24 hours. A screening dose of 25 mcg may be considered in very small patients. Patients not responding to screening dose of 100 mcg should not be considered for chronic infusion/implanted pump.

Maintenance: After positive response to test dose, a maintenance intrathecal infusion can be administered via an implanted intrathecal pump. Initial dose via pump: Infusion at a 24-hourly rate dosed at twice the test dose. Avoid abrupt discontinuation.

Hiccups (unlabeled use): Oral: 10-20 mg 2-3 times/day

Dosing: ElderlyOral (the lowest effective dose is recommended): Initial: 5 mg 2-3 times/day, increasing gradually as needed; if benefits are not seen withdraw the drug slowly.

Dosing: Pediatric**Spasticity:**

Oral (avoid abrupt withdrawal of drug) (unlabeled use): Caution: Pediatric dosing expressed as a daily amount, and NOT in mg/kg. Limited published data in children; the following is a compilation of small prospective studies (Albright, 1996; Milla, 1977; Scheinberg, 2006) and one large retrospective study (Lubsch, 2006):

<2 years: 10-20 mg daily divided every 8 hours; titrate dose every 3 days in increments of 5-15mg/day to a maximum of 40 mg daily

2-7 years: Initial: 20-30 mg daily divided every 8 hours; titrate dose every 3 days in increments of 5-15 mg/day to a maximum of 60 mg daily

≥8 years: 30-40 mg daily divided every 8 hours; titrate dose every 3 days in increments of 5-15 mg/day to a maximum of 120 mg daily

Note: Baclofen dose may need to be increased over time. One retrospective analysis (Lubsch, 2006) suggested that increased doses were needed as the time increased from spasticity onset, as age increased, and as the number of concomitant antispasticity medications increased. A small number of patients required daily doses exceeding 200 mg.

Intrathecal: Refer to adult dosing.

Dosing: Renal ImpairmentMay be necessary to reduce dosage; no specific guidelines have been established

Administration: I.V. DetailpH: 5-7

Administration: OtherIntrathecal: For screening dosages, dilute with preservative-free sodium chloride to a final concentration of 50 mcg/mL for bolus injection into the subarachnoid space. For maintenance infusions, concentrations of 500-2000 mcg/mL may be used.

CompatibilityStable in sterile, preservative free NS.

Compatibility when admixed: Compatible: Morphine.

Extemporaneously PreparedMake a 5 mg/mL suspension by crushing fifteen 20 mg tablets; wet with glycerin, gradually add 45 mL simple syrup in 3 x 5 mL aliquots to make a total volume of 60 mL; refrigerate; stable 35 days

> Johnson CE and Hart SM, “Stability of an Extemporaneously Compounded Baclofen Oral Liquid,” *Am J Hosp Pharm*, 1993, 50:2353-5.

ContraindicationsHypersensitivity to baclofen or any component of the formulation

Allergy Considerations

- Baclofen Allergy

Warnings/Precautions

Boxed warnings:

- Abrupt withdrawal: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment.

- Seizure disorder. Use with caution in patients with a history of seizure disorder.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse CNS effects, especially at higher doses.

Other warnings/precautions:

- Abrupt withdrawal: **[U.S. Boxed Warning]: Avoid abrupt withdrawal of the drug; abrupt withdrawal of intrathecal baclofen has resulted in severe sequelae (hyperpyrexia, obtundation, rebound/exaggerated spasticity, muscle rigidity, and rhabdomyolysis), leading to organ failure and some fatalities.** Risk may be higher in patients with injuries at T-6 or above, history of baclofen withdrawal, or limited ability to communicate.

Geriatric ConsiderationsThe elderly are more sensitive to the effects of baclofen and are more likely to experience adverse CNS effects at higher doses. Two cases of encephalopathy were reported after inadvertent high doses (50 mg/day and 90 mg/day) were given to elderly patients.

Pregnancy Risk FactorC

LactationEnters breast milk (small amounts)/compatible

Adverse Reactions

>10%:

> Central nervous system: Drowsiness, vertigo, psychiatric disturbances, insomnia, slurred speech, ataxia, hypotonia
>
> Neuromuscular & skeletal: Weakness

1% to 10%:

> Cardiovascular: Hypotension
>
> Central nervous system: Fatigue, confusion, headache
>
> Dermatologic: Rash
>
> Gastrointestinal: Nausea, constipation
>
> Genitourinary: Polyuria

<1%: Palpitation, chest pain, syncope, euphoria, excitement, depression, hallucinations, xerostomia, anorexia, abnormal taste, abdominal pain, vomiting, diarrhea, enuresis, urinary retention, dysuria, impotence, inability to ejaculate, nocturia, paresthesia, hematuria, dyspnea

Withdrawal reactions have occurred with abrupt discontinuation (particularly severe with intrathecal use).

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola.

Test InteractionsIncreased alkaline phosphatase, AST, glucose, ammonia (B); decreased bilirubin (S)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake this drug as prescribed. Do not discontinue this medicine without consulting prescriber (abrupt discontinuation may cause hallucinations). Do not take any prescription or OTC sleep-inducing drugs, sedatives, or antispasmodics without consulting prescriber. Avoid alcohol use. You may experience transient drowsiness, lethargy, or dizziness; use caution when driving or engaging in tasks requiring alertness until response to drug is known. Frequent small meals or lozenges may reduce GI upset.

Intrathecal use: Keep scheduled pump refill visits; abrupt interruption can cause serious withdrawal symptoms. Report increased spasticity, itching, numbness, unresolved insomnia, painful urination, change in urinary patterns, constipation, high fever, or persistent confusion.

Pregnancy precaution: Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, intrathecal [preservative free]:

Lioresal®: 50 mcg/mL (1 mL); 500 mcg/mL (20 mL); 2000 mcg/mL (5 mL, 20 mL)

Tablet: 10 mg, 20 mg

Generic AvailableYes: Tablets only

Pricing: U.S. (www.drugstore.com)

Tablets (Baclofen)

10 mg (30): $9.99

20 mg (30): $15.99

Mechanism of ActionInhibits the transmission of both monosynaptic and polysynaptic reflexes at the spinal cord level, possibly by hyperpolarization of primary afferent fiber terminals, with resultant relief of muscle spasticity

Pharmacodynamics/Kinetics

Onset of action: 3-4 days

Peak effect: 5-10 days

Absorption (dose dependent): Oral: Rapid

Protein binding: 30%

Metabolism: Hepatic (15% of dose)

Half-life elimination: 3.5 hours

Time to peak, serum: Oral: Within 2-3 hours

Excretion: Urine and feces (85% as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and insomnia are common; rare reports of depression, euphoria, and hallucinations

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation; concurrent use with MAO inhibitors may potentiate their hypotensive effects

Anesthesia and Critical Care Concerns/Other ConsiderationsAvoid abrupt withdrawal of the drug; abrupt withdrawal of intrathecal baclofen has resulted in severe sequelae (hyperpyrexia, obtundation, rebound/exaggerated spasticity, muscle rigidity, and rhabdomyolysis), leading to organ failure and some fatalities. Risk may be higher in patients with injuries at T-6 or above, history of baclofen withdrawal, or limited ability to communicate. Elderly are more sensitive to the effects of baclofen and are more likely to experience adverse CNS effects at higher doses.

References

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Tan AK and Tan CB, “The Syndrome of Painful Legs and Moving Toes - A Case Report,” *Singapore Med J*, 1996, 37(4):446-7.[PubMed 8993154]

International Brand NamesAlpha-Baclofen (NZ); Alpha-Clofen (AU); Baclan (KP); Baclo (AU); Baclofen (PL); Baclofen-ratiopharm (LU); Baclofene (FR); Baclon (FI, TW); Baclopar (IE); Baclosal (IL, TH); Bacofen (KP); Bafen (TH); Baklofen (DK, NO); Clofen (AU, MY); Curofen (KP); Diafen (UY); Espast (PE); Liobac (TH); Lioresal (AE, AR, AT, AU, BB, BD, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PH, PK, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Lioresyl (CN); Lyflex (GB, IE); Onelaxant-R (PH); Pacifen (NZ, TW); Solofen (TW); Spinax (TW); Stelax (AU, HK)

Balanced Salt Solution

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(BAL anced salt soe LOO shun)
U.S. Brand NamesAquaLase™; BSS Plus®; BSS®
Canadian Brand NamesBSS Plus®; BSS®; Eye-Stream®
Pharmacologic CategoryIrrigating Solution; Ophthalmic Agent, Miscellaneous
Use: Labeled Indications

Irrigation solution for ophthalmic surgery:

AquaLase™, BSS®: Intraocular or extraocular irrigating solution

BSS® Plus: Intraocular irrigating solution

Irrigation solution for eyes, ears, nose, or throat

Dosing: AdultsIrrigation: Based on standard for each surgical procedure
Dosing: ElderlyRefer to adult dosing.
StorageStore between 2°C to 25°C (36°F to 77°F); do not freeze.
ReconstitutionBSS Plus®: Prior to administration, add contents of the “Part II” vial to the contents of the “Part I” bottle. Mix gently and use within 6 hours.
ContraindicationsHypersensitivity to any component of the formulation; injection or I.V. infusion; use during electrosurgical procedures
Warnings/Precautions

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; intraoperative lens changes have been observed when undergoing vitrectomy procedure.

Other warnings/precautions:

- Appropriate use: For use during surgical procedures with an expected duration ≤60 minutes.

Adverse ReactionsFrequency not defined.

Ocular: Bullous keratopathy, corneal clouding, corneal decompensation, corneal edema, corneal swelling, inflammatory reactions, lens changes

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, irrigation [preservative free]: Sodium chloride 0.64%, potassium chloride 0.075%, calcium chloride 0.048%, magnesium chloride 0.03%, sodium acetate 0.39%, sodium citrate 0.17% (500 mL)

Solution, ophthalmic [irrigation; preservative free]: Sodium chloride 0.64%, potassium chloride 0.075%, calcium chloride 0.048%, magnesium chloride 0.03%, sodium acetate 0.39%, sodium citrate 0.17% (18 mL, 500 mL)

AquaLase™: Sodium chloride 0.64%, potassium chloride 0.075%, calcium chloride 0.048%, magnesium chloride 0.03%, sodium acetate 0.39%, sodium citrate 0.17% (90 mL)

BSS®: Sodium chloride 0.64%, potassium chloride 0.075%, calcium chloride 0.048%, magnesium chloride 0.03%, sodium acetate 0.39%, sodium citrate 0.17% (15 mL, 30 mL, 250 mL, 500 mL)

BSS Plus®: Sodium chloride 0.71%, potassium chloride 0.038%, calcium chloride 0.015%, magnesium chloride 0.02%, sodium phosphate 0.042%, sodium bicarbonate 0.21%, dextrose 0.092%, glutathione 0.018% (250 mL, 500 mL)

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Solution (Akorn Balanced Salt)

(18): $15.99

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand Names Balanced Salt Solution (NZ); Balanced Salt Solution (DK, FI, GB, NZ)

Balsalazide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Colazal® may be confused with Clozaril®

Pronunciation(bal SAL a zide)

U.S. Brand NamesColazal®

Pharmacologic Category[5-Aminosalicylic Acid Derivative](); [Anti-inflammatory Agent]()

Use: Labeled IndicationsTreatment of mild-to-moderate active ulcerative colitis

Dosing: Adults**Ulcerative colitis:** Oral: 2.25 g (three 750 mg capsules) 3 times/day for 8-12 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Ulcerative colitis:** Oral: Children 5-17 years: 750 mg 3 times/day for up to 8 weeks **or** 2.25 g (three 750 mg capsules) 3 times/day for 8 weeks

Dosing: Renal ImpairmentRenal toxicity has been observed with other 5-aminosalicylic acid products; use with caution.

Dosing: Hepatic ImpairmentNo specific dosage adjustment available.

Administration: OralCapsules should be swallowed whole or may be opened and sprinkled on applesauce. Applesauce mixture may be chewed; swallow immediately, do not store mixture for later use. When sprinkled on food, may cause staining of teeth or tongue.

Dietary ConsiderationsColazal® 750 mg capsule contains sodium ~86 mg.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to balsalazide, metabolites to balsalazide, salicylates, or any component of the formulation

Allergy Considerations

- [5-Aminosalicylic Acid Derivative Allergy]()

Warnings/Precautions

Concerns related to adverse effects:

- Colitis: May exacerbate symptoms of ulcerative colitis.

Disease-related concerns:

- Pyloric stenosis: Use with caution in patients with pyloric stenosis; prolonged gastric retention of capsules may occur, delaying release of drug in the colon.
- Renal impairment: Use with caution in patients with renal impairment; renal toxicity has been observed with other mesalamine (5-aminosalicylic acid) products.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <5 years of age.

Other warnings/precautions:

- Duration of therapy: Safety and efficacy of use beyond 12 weeks in adults or 8 weeks in children have not been established.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies have been done in pregnant women. Balsalazide should be used in pregnant women only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Headache (children 15%; adults 8%)

Gastrointestinal: Abdominal pain (children 12% to 13%; adults 6%)

1% to 10%:

Central nervous system: Insomnia (adults 2%), fatigue (children 4%; adults 2%), fever (children 6%; adults 2%)

Endocrine & metabolic: Dysmenorrhea (children 3%)

Gastrointestinal: Diarrhea (children 9%; adults 5%), ulcerative colitis exacerbation (children 6%; adults 1%), nausea (children 4%; adults 5%), vomiting (children 10%; adults 4%), hematochezia (children 4%), stomatitis (children 3%), anorexia (adults 2%), dyspepsia (adults

2%), flatulence (adults 2%), cramps (adults 1%), constipation (adults 1%), xerostomia (adults 1%)

Genitourinary: Urinary tract infection (adults 1%)

Neuromuscular & skeletal: Arthralgia (adults 4%), back pain (adults 2%), myalgia (adults 1%)

Respiratory: Respiratory infection (adults 4%), cough (children 3%; adults 2%), pharyngitis (children 6%; adults 2%), pharyngolaryngeal pain (children 3%), rhinitis (adults 2%)

Miscellaneous: Flu-like syndrome (children 4%; adults 1%)

Postmarketing and/or case reports: Alopecia, cholestatic jaundice, cirrhosis, hepatocellular damage, hepatotoxicity, jaundice, hypersensitivity pericarditis, Kawasaki-like syndrome, liver failure, liver necrosis, liver function tests increased, myocarditis

Drug Interactions

Cardiac Glycosides: 5-ASA Derivatives may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

Thiopurine Analogs: 5-ASA Derivatives may decrease the metabolism of Thiopurine Analogs. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: 5-ASA Derivatives may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. The primary concern is the potential development of Reye's Syndrome, a condition that has been associated with the use of salicylates in children with varicella infections. *Risk D: Consider therapy modification*

Monitoring ParametersImprovement or worsening of symptoms

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as disodium: 750 mg

Colazal®: 750 mg [contains sodium ~86 mg/capsule]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Balsalazide Disodium)

750 mg (280): $319.98

Capsules (Colazal)

750 mg (280): $449.96

Mechanism of ActionBalsalazide is a prodrug, converted by bacterial azoreduction to 5-aminosalicylic acid (mesalamine, active), 4-aminobenzoyl-β-alanine (inert), and their metabolites. 5-aminosalicylic acid may decrease inflammation by blocking the production of arachidonic acid metabolites topically in the colon mucosa.

Pharmacodynamics/Kinetics

Onset of action: Delayed; may require several days to weeks

Absorption: Very low and variable

Protein binding: Balsalazide: ≥99%

Metabolism: Azoreduced in the colon to 5-aminosalicylic acid (active), 4-aminobenzoyl-β-alanine (inert), and N-acetylated metabolites

Half-life elimination: Primary effect is topical (colonic mucosa); systemic half-life not determined

Time to peak: Balsalazide: 1-2 hours

Excretion: Feces (65% as 5-aminosalicylic acid, 4-aminobenzoyl-β-alanine, and N-acetylated metabolites); urine (25% as N-acetylated metabolites); Parent drug: Urine or feces (<1%)

Pharmacotherapy PearlsBalsalazide 750 mg is equivalent to mesalamine 267 mg

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia, fatigue, and dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBalsalazide Disodium

References

Adhiyaman V, Vaishnavi A, and Froese A, “Drug Points: Hypersensitivity Reaction to Balsalazide,” *BMJ*, 2001, 323(7311):489.[PubMed 11532843]

Kornbluth A and Sachar DB, “Practice Parameters Committee of the American College of Gastroenterology. Ulcerative Colitis Practice Guidelines in Adults (update): American College of Gastroenterology, Practice Parameters Committee,” *Am J Gastroenterol*, 2004, 99(7):1371-85.[PubMed 15233681]

Lennard L, “Clinical Implications of Thiopurine Methyltransferase - Optimization of Drug Dosage and Potential Drug Interactions,” *Ther Drug Monit*, 1998, 20(5):527-31.[PubMed 9780130]

Robertson E, Austin D, Jamieson N, et al, “Balsalazide-Induced Myocarditis,” *Int J Cardiol*, 2007 [epub ahead of print]. [PubMed 17889383]

International Brand Names Balzide (IT); Basazyde (TW); Benoquin (AR); Calazide (AU); Colazal (KP); Colazid (NO, SE); Colazide (AT, GB); Garian (UY); Premid (DK)

Barium

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(BA ree um)

U.S. Brand NamesAnatrast; Bar-Test; Baricon™; Baro-Cat®; Barobag®; Barosperse®; CheeTah®; E-Z-Cat®; E-Z-Cat® Dry; E-Z-Disk™; Enhancer; Entero Vu™; Entrobar®; EntroEase®; Esopho-Cat®; HD 200® Plus; Intropaste; Liqui-Coat HD®; Liquid Barosperse®; Medebar® Plus; Prepcat; Readi-Cat®; Readi-Cat® 2; Tomocat®; Tomocat® 1000; Tonojug; Tonopaque; Varibar® Honey; Varibar® Nectar; Varibar® Pudding; Varibar® Thin Honey; Varibar® Thin Liquid; VoLumen™

Pharmacologic CategoryRadiopaque Agents

Use: Labeled IndicationsDiagnostic aid for computed tomography or x-ray examinations of the GI tract

ContraindicationsHypersensitivity to barium or any component of the formulation; known or suspected obstruction of the colon, known or suspected GI tract perforation, suspected tracheoesophageal fistula, obstructing lesions of small intestine, pyloric stenosis

Specific agents may also be contraindicated with inflammation or neoplastic lesions of the rectum, recent rectal biopsy; use in infants with swallowing disorders; newborns with complete duodenal or jejunal obstruction with suspected distal small bowel or colon obstruction; very small preterm infants and young babies requiring small volumes of contrast media; infants and young children with possible leakage from GI tract (eg, necrotizing enterocolitis, unexplained pneumoperitoneum, gasless abdomen, bowel or esophageal perforation, postoperative anastomosea)

Pregnancy ConsiderationsSafety and efficacy for use during pregnancy have not been established. In general, elective radiography of the abdomen is avoided during pregnancy unless essential for diagnosis.

Breast-Feeding ConsiderationsBarium sulfate is not systemically absorbed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, oral, as sulfate:

Esopho-Cat®: 3% w/w (30 g) [contains sodium benzoate; vanilla flavor]

Paste, oral, as sulfate:

Varibar® Pudding: 40% w/v (230 mL) [target viscosity 5000 CPS; contains sodium benzoate; vanilla flavor]

Powder for suspension, oral, as sulfate:

Baricon™: 98% w/w (340 g) [lemon-vanilla flavor]

Enhancer: 98% w/w (312 g) [lemon-vanilla flavor]

E-Z-Cat® Dry: 2% w/w (23 g) [provides 450 mL 2% w/w suspension after mixing; orange vanilla flavor]

HD 200® Plus: 98% w/w (312 g) [strawberry flavor]

Tonopaque: 95% w/w (180 g) [cherry flavor]

Varibar® Thin Liquid: 40% w/v (148 g) [provides 40% w/v suspension after mixing; target viscosity 4 CPS; apple flavor]

Powder for suspension, oral/rectal, as sulfate:

Barosperse®: 95% w/w (225 g, 900 g) [vanilla flavor]

Tonojug: 95% w/w (1200 g) [cherry flavor]

Powder for suspension, rectal, as sulfate:

Barobag®: 97% w/w (340 g, 454 g) [packaged as an enema kit]

Suspension, oral, as sulfate:

Entero Vu™: 24% w/v (600 mL) [contains sodium benzoate; blueberry flavor]

EntroEase®: 13% w/v (600 mL) [contains sodium benzoate; marshmallow flavor]

E-Z-Cat®: 4.9% w/v (255 mL) [orange flavor]

Liqui-Coat HD®: 210% w/v (150 mL) [contains sodium benzoate; vanilla-raspberry flavor]

Readi-Cat® 2: 2.1% w/v (250 mL) [contains benzoic acid and sodium benzoate; banana smoothie flavor]; (450 mL) [contains benzoic acid and sodium benzoate; apple smoothie, banana smoothie, and berry smoothie flavors]

Varibar® Honey: 40% w/v (250 mL) [target viscosity 3000 CPS; contains sodium benzoate; apple flavor]

Varibar® Nectar: 40% w/v (240 mL) [target viscosity 300 CPS; contains sodium benzoate; apple flavor]

Varibar® Thin Honey: 40% w/v (250 mL) [target viscosity 1500 CPS; contains sodium benzoate; apple flavor]

VoLumen™: 0.1% w/v (450 mL) [contains benzoic acid, sodium benzoate; blueberry flavor]

Suspension, oral/rectal, as sulfate:

Baro-Cat®: 1.5% w/v (300 mL, 900 mL) [banana-pineapple flavor]

CheeTah®: 2.2% w/w (450 mL, 900 mL) [contains sodium benzoate; butterscotch vanilla flavor]

Liquid Barosperse®: 60% w/v (355 mL) [vanilla flavor]

Prepcat: 1.5% w/v (450 mL) [strawberry flavor]

Readi-Cat®: 1.3% w/v (450 mL, 900 mL, 1900 mL) [contains sodium benzoate; orange vanilla flavor; also supplied as a Cat-Pak with enema tubing]

Readi-Cat® 2: 2.1% w/v (450 mL, 900 mL, 1900 mL) [contains sodium benzoate; orange vanilla flavor]

Tomocat®: 5% w/v (145 mL) [concentrate to make a 1.5% solution; strawberry flavor]

Tomocat® 1000: 5% w/v (225 mL) [concentrate; strawberry flavor]

Suspension paste, rectal:

Anatrast: 100% w/v (500 g) [suspension paste; packaged with enema tips]

Intropaste: 70% w/v (454 g) [raspberry flavor]

Suspension, rectal, as sulfate:

Entrobar®: 50% w/v (500 mL) [packaged in administration kit]

Medebar® Plus: 100% w/v (1900 mL)

Tablet, oral, as sulfate:

Bar-Test, E-Z-Disk™: 648 mg

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBarium Sulfate

References

ACOG Committee on Obstetric Practice, "ACOG Committee Opinion. Guidelines for Diagnostic Imaging During Pregnancy," *Obstet Gynecol*, 2004, 104(3):647-51.[PubMed 15339791]

International Brand NamesBarium Sulfuricum (PL); Falibaryt (PL); Micropaque (PL); Microtrast (PL); Prontobario (PL)

Basiliximab

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ba si LIK si mab)

U.S. Brand NamesSimulect®

Canadian Brand NamesSimulect®

Pharmacologic CategoryMonoclonal Antibody

Use: Labeled IndicationsProphylaxis of acute organ rejection in renal transplantation

Dosing: Adults**Note:** Patients previously administered basiliximab should only be re-exposed to a subsequent course of therapy with extreme caution.

Renal transplantation: I.V.: 20 mg within 2 hours prior to transplant surgery, followed by a second 20 mg dose 4 days after transplantation. The second dose should be withheld if complications occur (including severe hypersensitivity reactions or graft loss).

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Patients previously administered basiliximab should only be re-exposed to a subsequent course of therapy with extreme caution.

Renal transplantation: I.V.:

Children <35 kg: 10 mg within 2 hours prior to transplant surgery, followed by a second 10 mg dose 4 days after transplantation; the second dose should be withheld if complications occur (including severe hypersensitivity reactions or graft loss)

Children ≥35 kg: Refer to adult dosing

Dosing: Renal ImpairmentNo specific dosing adjustment is recommended.

Dosing: Hepatic ImpairmentNo specific dosing adjustment is recommended.

Administration: I.V.For intravenous administration only. Infuse as a bolus or I.V. infusion over 20-30 minutes. (Bolus dosing is associated with nausea, vomiting and local pain at the injection site.)

StorageStore intact vials under refrigeration 2°C to 8°C (36°F to 46°F). It is recommended that after reconstitution, the solution should be used immediately. If not used immediately, it can be stored at 2°C to 8°C for up to 24 hours or at room temperature for up to 4 hours. Discard the reconstituted solution within 24 hours.

ReconstitutionReconstitute vials with sterile water for injection, USP. Shake the vial gently to dissolve. Further dilute reconstituted solution with 25-50 mL 0.9% sodium chloride or dextrose 5% in water. When mixing the solution, gently invert the bag to avoid foaming. Do not shake.

ContraindicationsHypersensitivity to basiliximab, murine proteins, or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Severe hypersensitivity reactions, occurring within 24 hours, have been reported. Reactions, including anaphylaxis, have occurred both with the initial exposure and/or following re-exposure after several months; use caution during re-exposure to a subsequent course of therapy in a patient who has previously received basiliximab. Discontinue the drug permanently if a reaction occurs. Medications for the treatment of hypersensitivity reactions should be available for immediate use.

- Human antimurine antibodies (HAMA): Treatment may result in the development of HAMA; however, limited evidence suggesting the use of muromonab-CD3 or other murine products is not precluded.

- Lymphoproliferative disorders: The incidence of lymphoproliferative disorders may be increased by immunosuppressive therapy.

- Opportunistic infections: The incidence opportunistic infections may be increased by immunosuppressive therapy.

Other warnings/precautions:

- Appropriate use: To be used as a component of immunosuppressive regimen which includes cyclosporine and corticosteroids.

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of a physician experienced in immunosuppression therapy.**

Pregnancy Risk FactorB (manufacturer)

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. IL-2 receptors play an important role in the development of the immune system. Use in pregnant women only when benefit exceeds potential risk to the fetus. Women of childbearing potential should use effective contraceptive measures before beginning treatment and for 4 months after completion of therapy with this agent.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding Considerations It is not known whether basiliximab is excreted in human milk. Because many immunoglobulins are secreted in milk and the potential for serious adverse reactions exists, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Adverse Reactions Administration of basiliximab did not appear to increase the incidence or severity of adverse effects in clinical trials. Adverse events were reported in 96% of both the placebo and basiliximab groups.

>10%:

- Cardiovascular: Hypertension, peripheral edema
- Central nervous system: Fever, headache, insomnia, pain
- Dermatologic: Acne, wound complications
- Endocrine & metabolic: Hypercholesterolemia, hyperglycemia, hyper-/hypokalemia, hyperuricemia, hypophosphatemia
- Gastrointestinal: Abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting
- Genitourinary: Urinary tract infection
- Hematologic: Anemia
- Neuromuscular & skeletal: Tremor
- Respiratory: Dyspnea, infection (upper respiratory)
- Miscellaneous: Viral infection

3% to 10%:

- Cardiovascular: Abnormal heart sounds, angina pectoris, arrhythmia, atrial fibrillation, cardiac failure, chest pain, generalized edema, hypotension, tachycardia
- Central nervous system: Agitation, anxiety, depression, dizziness, fatigue, hypoesthesia, malaise, neuropathy, rigors
- Dermatologic: Cyst, hypertrichosis, pruritus, rash, skin disorder, skin ulceration
- Endocrine & metabolic: Acidosis, dehydration, diabetes mellitus, fluid overload, hyper-/hypocalcemia, hyperlipidemia, hypertriglyceridemia, hypoglycemia, hypomagnesemia, hyponatremia
- Gastrointestinal: Abdomen enlarged, esophagitis, flatulence, gastroenteritis, GI hemorrhage, gingival hyperplasia, melena, moniliasis, stomatitis (including ulcerative), weight gain
- Genitourinary: Albuminuria, bladder disorder, dysuria, genital edema, hematuria, impotence, oliguria, renal function abnormal, renal tubular necrosis, ureteral disorder, urinary frequency, urinary retention
- Hematologic: Hematoma, hemorrhage, leukopenia, polycythemia, purpura, thrombocytopenia, thrombosis
- Neuromuscular & skeletal: Arthralgia, arthropathy, back pain, cramps, fracture, hernia, leg pain, myalgia, paresthesia, weakness
- Ocular: Abnormal vision, cataract, conjunctivitis
- Respiratory: Bronchitis, bronchospasm, cough, pharyngitis, pneumonia, pulmonary edema, sinusitis, rhinitis
- Miscellaneous: Accidental trauma, facial edema, glucocorticoids increased, herpes infection, sepsis

Postmarketing and/or case reports: Capillary leak syndrome, cytokine release syndrome; severe hypersensitivity reactions, including anaphylaxis, have been reported (symptoms may include hypotension, tachycardia, cardiac failure, dyspnea, bronchospasm, pulmonary edema, urticaria, rash, pruritus, sneezing, and respiratory failure)

Oncology: Vesicant No

Oncology: Emetic Potential Very low (<10%)

Drug Interactions

Abciximab: May enhance the potential for allergic or hypersensitivity reactions to Monoclonal Antibodies. Also may cause thrombocytopenia or diminished therapeutic effects. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions Herb/Nutraceutical: Echinacea may diminish the therapeutic effect of basiliximab. Avoid hypoglycemic herbs, including alfalfa, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng, gymnema, marshmallow, and stinging nettle (may enhance the hypoglycemic effect of basiliximab).

Monitoring ParametersSigns and symptoms of acute rejection

Nursing: Physical Assessment/MonitoringMonitor cardiorespiratory function, renal function, and adverse reactions during infusion and periodically following infusion. Be alert to opportunistic infections. Assess knowledge/teach patient possible side effects/interventions and adverse symptoms to report as inpatient or following discharge.

Patient EducationThis medication, which may help to reduce transplant rejection, can only be given by infusion. You will be monitored and assessed closely during infusion and thereafter. It is important that you report any changes or problems for evaluation. You will be susceptible to infection (avoid crowds and exposure to infection). Frequent mouth care and small frequent meals may help counteract any GI effects you may experience and will help maintain adequate nutrition and fluid intake. You may experience trouble sleeping or headaches. Report any changes in urination; unusual bruising or bleeding; chest pain or palpitations; acute dizziness; respiratory difficulty; fever or chills; changes in cognition; rash; feelings of pain or numbness in extremities; swelling of extremities; severe GI upset or diarrhea; unusual back or leg pain or muscle tremors; vision changes; or any sign of infection (eg, chills, fever, sore throat, easy bruising or bleeding, mouth sores, unhealed sores, vaginal discharge). **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Simulect®: 10 mg, 20 mg

Generic AvailableNo

ManufacturerNovartis Pharmaceuticals Corp

Mechanism of ActionChimeric (murine/human) monoclonal antibody which blocks the alpha-chain of the interleukin-2 (IL-2) receptor complex; this receptor is expressed on activated T lymphocytes and is a critical pathway for activating cell-mediated allograft rejection

Pharmacodynamics/Kinetics

Duration: Mean: 36 days (determined by IL-2R alpha saturation)

Distribution: Mean: V_d: Children 1-11 years: 4.8 ± 2.1 L; Adolescents 12-16 years: 7.8 ± 5.1 L; Adults: 8.6 ± 4.1 L

Half-life elimination: Children 1-11 years: 9.5 days; Adolescents 12-16 years: 9.1 days; Adults: Mean: 7.2 days

Excretion: Clearance: Children 1-11 years: 17 mL/hour; Adolescents 12-16 years: 31 mL/hour; Adults: Mean: 41 mL/hour

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Facial edema and ulcerative stomatitis. Causes gingival hypertrophy (GH) similar to that caused by cyclosporine; early reports indicate that frequency/incidence of basiliximab-induced GH not as high as cyclosporine-induced GH.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness, headache, and insomnia are common. May cause agitation, anxiety, depression, malaise, or fatigue.

Mental Health: Effects on Psychiatric TreatmentSide effects mimic depressive symptoms; effects of benzodiazepines and antidepressants may be altered

International Brand NamesSimulect (AR, AT, AU, BE, BG, BR, CH, CL, CN, CO, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, MX, MY, NL, NO, PE, PH, PK, PL, PT, PY, RU, SE, SG, TH, TR, TW, UY, VE)

BCG Vaccine

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(bee see jee vak SEEN)

U.S. Brand NamesTheraCys®; TICE® BCG

Canadian Brand NamesImmuCyst®; Oncotice™; Pacis™

Pharmacologic CategoryBiological Response Modulator; Vaccine

Use: Labeled IndicationsImmunization against tuberculosis and immunotherapy for cancer; treatment and prophylaxis of carcinoma *in situ* of the bladder; prophylaxis of primary or recurrent superficial papillary tumors following transurethral resection

Dosing: Adults

Immunization against tuberculosis: Percutaneous: 0.2-0.3 mL (full strength dilution); conduct postvaccinal tuberculin test (5 TU of PPD) in 2-3 months; if test is negative, repeat vaccination. **Note:** Initial lesion usually appears after 10-14 days consisting of small, red papule at injection site and reaches maximum diameter of 3 mm in 4-6 weeks.

Immunotherapy for bladder cancer: Intravesicular:

TheraCys®: One dose instilled into bladder (for 2 hours) once weekly for 6 weeks followed by one treatment at 3, 6, 12, 18, and 24 months after initial treatment.

TICE® BCG: One dose instilled into the bladder (for 2 hours) once weekly for 6 weeks followed by once monthly for 6-12 months.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Immunization against tuberculosis: Percutaneous:

Children <1 month: 0.2-0.3 mL (half-strength dilution). Administer tuberculin test (5 TU) after 2-3 months; repeat vaccination after 1 year of age for negative tuberculin test if indications persist. **Note:** Initial lesion usually appears after 10-14 days consisting of small, red papule at injection site and reaches maximum diameter of 3 mm in 4-6 weeks.

Children >1 month: Refer to adult dosing.

Administration: OtherShould only be given intravesicularly (bladder irrigation) or percutaneously; **do not administer I.V., SubQ, or intradermally**.

Intravesicular: Empty or drain bladder. Instill BCG vaccine; retain for up to 2 hours. Patient should lie prone, rotating positions every 15 minutes to maximize bladder surface exposure.

Percutaneous: Apply vaccine with syringe and needle by dropping onto 1-2 inch area of horizontally positioned surface of cleansed, dry site (deltoid region of arm preferred); pulling skin tight, puncture skin with multiple puncture device centered over the vaccine; apply pressure for 5 seconds; spread vaccine evenly over puncture area. Apply loose covering and keep dry for 24 hours.

StorageStore vials under refrigeration at 2°C to 8°C (36°F to 46°F); protect from light. Use within 2 hours of mixing.

Reconstitution

TheraCys®: Reconstitute with 3 mL of diluent provided and shake gently. Withdraw contents and add 50 mL of 0.9% NaCl (preservative free).

TICE® BCG: Reconstitute with 1 mL 0.9% NaCl (preservative free) using a 3 mL syringe. Mix by drawing and expelling solution into ampul three times. Add to a catheter tip syringe containing 49 mL of 0.9% NaCl (preservative free).

BCG Vaccine U.S.P.: Reconstitute with 1 mL of SWFI; swirl gently, do not vigorously shake. For children <1 month, reconstitute with 2 mL SWFI.

ContraindicationsHypersensitivity to BCG vaccine or any component of the formulation; immunocompromised state, HIV-infected, and burn patients; active tuberculosis; intravesicular BCG is contraindicated in febrile illness, urinary tract infection, gross hematuria and recent (<7-14 days) biopsy, transurethral resection (TUR), or traumatic catheterization

Warnings/Precautions

Boxed warnings:

- Hazardous agent: See “Special handling” below.
- Systemic reactions: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: **[U.S. Boxed Warning]: Use appropriate precautions for handling and disposal. BCG is a biohazardous agent; proper technique and disposal of all equipment in contact with BCG vaccine as a biohazardous material is recommended.** BCG infections have been reported in healthcare workers due to accidental exposure (needlestick, skin laceration); nosocomial infections have been reported in patients receiving parenteral medications prepared in areas where BCG vaccine was prepared. To avoid cross contamination, do not prepare parenteral medications in an area where BCG vaccine has been prepared.

Concerns related to adverse effects:

- Systemic reactions: **[U.S. Boxed Warning]: Systemic reactions have been reported in patients treated as immunotherapy for bladder cancer.**

Disease-related concerns:

- HIV: Should be administered with caution to persons in groups at high risk for HIV; although limited data suggest that the vaccine may be safe for use in asymptomatic children infected with HIV, BCG vaccination is not recommended for HIV-infected adults. HIV-infected persons thought to be infected with *Mycobacterium tuberculosis* should be strongly recommended for tuberculosis preventive therapy.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination.

- Pediatrics: Safety and efficacy of intravesicular BCG have not been established in children.

- Positive PPD reaction: BCG vaccination is not recommended for persons with a positive PPD reaction. Until further research can clearly define the risks and benefits of BCG vaccination for this population, vaccination should be restricted to persons at exceptionally high risk for tuberculosis infection.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have not been conducted. There are no adequate and well-controlled studies in pregnant women. Both intravesicular and percutaneous BCG vaccines are not recommended for use in pregnant women. Women of childbearing potential should be advised to avoid pregnancy while on therapy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions, breast-feeding is not recommended.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Adverse reactions associated with **intravesicular administration**:

>10%:

Central nervous system: Malaise (7% to 40%), fever (20% to 38%), chills (34%)

Gastrointestinal: Nausea/vomiting (3% to 16%), anorexia/weight loss (2% to 11%)

Genitourinary: Dysuria (52% to 60%), bladder irritation (50% to 60%), polyuria (40% to 42%), hematuria (26% to 39%), cystitis (6% to 29%), urinary urgency (6% to 18%), urinary tract infection (2% to 18%)

Hematological: Anemia (<1% to 21%)

Miscellaneous: Flu-like syndrome (33%)

1% to 10%:

Central nervous system: Fatigue (7%), headache/dizziness (2%)

Dermatologic: Rash (2%)

Gastrointestinal: Diarrhea (6%), abdominal pain (2% to 3%)

Genitourinary: Genital pain (10%), bladder cramps/pain (6%), urinary incontinence (2% to 6%), bladder spasm (5%), nocturia (5%), urinary debris (2%), genital inflammation/abscess (2%)

Hematological: Leukopenia (5%), coagulopathy (3%)

Neuromuscular & skeletal: Arthralgia/myalgia (3% to 7%), cramps/pain (4% to 6%), rigors (3%)

Renal: Renal toxicity (10%)

Respiratory: Pulmonary infection (3%)

Miscellaneous: Infection (3%), allergy (2%)

<1%: Abscesses, conjunctivitis, constipation, disseminated sepsis, epididymitis, granulomatous chorioretinitis, hepatitis, hepatic granuloma, keratitis, *M. bovis* infection (lung, liver, bone, bone marrow, kidney, lymph nodes, prostate), orchitis, pneumonitis, prostatitis, skin ulceration, thrombocytopenia, urethritis, urinary obstruction, uveitis

Adverse reactions associated with **BCG vaccination**: Axillary lymphadenopathy, cervical lymphadenopathy, disseminated BCG infection (BCG osteomyelitis), local reactions (induration, itching, lesions, lymphadenitis, pustule, tenderness, ulceration). Local reactions may persist for up to 3 months; more severe manifestations may occur up to 5 months after vaccination and persist for several weeks.

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

Immune Globulins: May diminish the therapeutic effect of Vaccines (Live). *Risk D: Consider therapy modification*

Immunosuppressants: May enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Tuberculin Tests: Vaccines (Live) may diminish the diagnostic effect of Tuberculin Tests. *Risk D: Consider therapy modification*

Test InteractionsPPD intradermal test; BCG vaccination results in reactive tuberculin skin test; rule out active tuberculosis prior to initiating intravesicular BCG treatment

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, intravesical [preservative free]:

TheraCys®: 81 mg [contains natural rubber/natural latex in packaging, polysorbate 80 (in diluent)]

TICE® BCG: 50 mg

Injection, powder for reconstitution, percutaneous [preservative free]:

BCG Vaccine: 50 mg

Generic AvailableNo

Mechanism of ActionBCG live is an attenuated strain of bacillus Calmette-Guérin (*Mycobacterium bovis*) used as a biological response modifier. BCG live, when used intravesicularly for treatment of bladder carcinoma *in situ*, is thought to cause a local, chronic inflammatory response involving macrophage and leukocyte infiltration of the bladder. By a mechanism not fully understood, this local inflammatory response leads to destruction of superficial tumor cells of the urothelium. BCG is active immunotherapy which stimulates the host's immune mechanism to reject the tumor. Evidence of systemic immune response is also commonly seen, manifested by a positive PPD tuberculin skin test reaction, however, its relationship to clinical efficacy is not well-established.

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsWhen used for immunization against tuberculosis, Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record. Multiple puncture device for vaccination available from Organon Tenika (1-800-662-6842).

BCG vaccination is not recommended by the CDC for general use in the U.S. for prevention of tuberculosis (TB).

BCG vaccination is recommended for infants and children with negative tuberculin skin tests who:

- are at high risk of intimate and prolonged exposure to persistently untreated or ineffectively treated patients with infectious pulmonary tuberculosis

- cannot be removed from the source of exposure

- cannot be placed on long-term preventive therapy

- are continuously exposed with tuberculosis who have bacilli resistant to isoniazid and rifampin

BCG vaccination is recommended for healthcare workers (HCW) in high-risk settings where:

- a high percentage of TB patients are infected with *M. tuberculosis* strains resistant to both isoniazid and rifampin

- transmission of drug-resistant *M. tuberculosis* strains and subsequent infection are likely

- comprehensive TB infection control precautions have been implemented yet have not been successful

BCG vaccination in not recommended for HCWs in low-risk settings.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBacillus Calmette-Guérin (BCG) Live; BCG Vaccine U.S.P. *(percutaneous use product)*; BCG, Live

References

Alexandroff AB, Jackson AM, O'Donnell MA, et al, “BCG Immunotherapy of Bladder Cancer: 20 Years On,” *Lancet*, 1999, 353(9165):1689-94. [PubMed 10335805]

Badalament RA and Farah RN, “Treatment of Superficial Bladder Cancer With Intravesicle Chemotherapy,” *Semin Surg Oncol*, 1997, 13(5):335-41. [PubMed 9259089]

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Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 2002, 51(RR-2):1-36.

Centers for Disease Control and Prevention,“TB Elimination: BCG Vaccine,” Document 250120, January, 2005; available at http://www.cdc.gov/nchstp/tb/pubs/tbfactsheets/250120.pdf

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Martinez-Pineiro JA and Martinez-Pineiro L, “BCG Update: Intravesical Therapy,” *Eur Urol*, 1997, 31(Suppl 1):31-41. [PubMed 9076484]

Meyer JP, Persad R, and Gillatt DA, “Use of Bacille Calmette-Guerin in Superficial Bladder Cancer,” *Postgrad Med J*, 2002, 78(922):449-54. [PubMed 12185215]

Nathanson L, “Use of BCG in the Treatment of Human Neoplasms: A Review,” *Semin Oncol*, 1974, 1(4):337-50. [PubMed 4620439]

Nseyo UO and Lamm DL, “Immunotherapy of Bladder Cancer,” *Semin Surg Oncol*, 1997, 13(5):342-9. [PubMed 9259090]

Rischmann P, Desgrandchamps F, Malavaud B, et al, “BCG Intravesical Instillations: Recommendations for Side-Effects Management,” *Eur Urol*, 2000, 37(Suppl 1):33-6.[PubMed 10575271]

International Brand NamesBcg-medac (PL); Immucyst (AT, AU, BE, BG, CN, CO, CZ, DE, EE, GB, HK, HN, IL, IT, MY, PE, PY, SG, TW); Immucyst bcg immunostymulant (PL); Oncotice (DK, FI, GR, IN, NL); OncoTICE (MX, SE); OncoTice (VE); Onko bcg (PL)

BEACOPP

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Lymphoma, Hodgkin's Disease]

Regimen UseLymphoma, Hodgkin's disease

Regimen

Bleomycin: I.V.: 10 units/m^2 day 8

[total dose/cycle = 10 units/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1, 2 and 3

[total dose/cycle = 300 mg/m^2]

Doxorubicin: I.V.: 25 mg/m^2 day 1

[total dose/cycle = 25 mg/m^2]

Cyclophosphamide: I.V.: 650 mg/m^2 day 1

[total dose/cycle = 650 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 (maximum 2 mg) day 8

[total dose/cycle = 1.4 mg/m^2; maximum 2 mg]

Procarbazine: Oral: 100 mg/m^2/day days 1 to 7

[total dose/cycle = 700 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14

[total dose/cycle = 560 mg/m^2]

Repeat cycle every 21 days

References

Diehl V, Franklin J, Hasenclever D, et al, âBEACOPP, a New Dose-Escalated and Accelerated Regimen, Is at Least as Effective as COPP/ABVD in Patients With Advanced-Stage Hodgkin's Lymphoma: Interim Report From a Trial of the German Hodgkin's Lymphoma Study Group,â *J Clin Oncol*, 1998, 16(12):3810-21.[PubMed 9850026]

Becaplermin

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Becaplermin (Regranex®) Gel: New Boxed Warning (Associated With Increased Risk of Mortality From Cancer in Diabetic Patients) - June 2008

The Food and Drug Administration (FDA) has issued a follow-up Dear Healthcare professional letter regarding an earlier safety review of becaplermin, a recombinant human platelet-derived growth factor. In March, 2008 the FDA announced that it had received information from a retrospective study and was investigating the possibility of an increased risk of cancer and/or mortality from cancer in patients with diabetes who used becaplermin, compared to patients who did not use becaplermin. The FDA has completed its review of this study, suggesting an increased risk of mortality from cancer in patients who used ≥3 tubes of becaplermin gel. As a result, the becaplermin prescribing information has been updated to include a new boxed warning regarding this finding. It is important to note that while the study showed an increase in mortality from cancer, the number of mortalities were small, there was no overall increase in the incidence of cancer, and the observed malignancies were remote from the ulcer treatment site. The FDA recommends the use of becaplermin only when the potential benefits outweigh the risks.

For more information, see http://www.fda.gov/medwatch/safety/2008/safety08.htm#Regranex

Medication Safety Issues

Sound-alike/look-alike issues:

Regranex® may be confused with Granulex®, Repronex®

Pronunciation(be KAP ler min)

U.S. Brand NamesRegranex®

Canadian Brand NamesRegranex®

Pharmacologic CategoryGrowth Factor, Platelet-derived; Topical Skin Product

Use: Labeled IndicationsAdjunctive treatment of diabetic neuropathic ulcers occurring on the lower limbs and feet that extend into subcutaneous tissue (or beyond) and have adequate blood supply

Dosing: Adults**Diabetic ulcers (lower extremity):** Topical: Apply appropriate amount of gel once daily with a cotton swab or similar tool, as a coating over the ulcer. The amount of becaplermin to be applied will vary depending on the size of the ulcer area.

Note: If the ulcer does not decrease in size by ~30% after 10 weeks of treatment or complete healing has not occurred in 20 weeks, continued treatment with becaplermin gel should be reassessed.

Estimation of gel requirement: To calculate the length of gel applied to the ulcer, measure the greatest length of the ulcer by the greatest width of the ulcer. Tube size and unit of measure will determine the formula used in the calculation. Recalculate amount of gel needed every 1-2 weeks, depending on the rate of change in ulcer area.

Centimeters:

15 g tube: [ulcer length (cm) x width (cm)] divided by 4 = length of gel (cm)

2 g tube: [ulcer length (cm) x width (cm)] divided by 2 = length of gel (cm)

Inches:

15 g tube: [length (in) x width (in)] x 0.6 = length of gel (in)

2 g tube: [length (in) x width (in)] x 1.3 = length of gel (in)

Dosing: ElderlyRefer to adult dosing.

Administration: TopicalFor external use only. Squeeze appropriate amount of gel onto clean measuring surface (eg, wax paper), spread onto entire ulcer area in a thin, continuous layer ~$^{1}/_{16}$ inch thick. Cover with saline moistened dressing; leave dressing in place ~12 hours. After 12 hours, remove dressing, rinse with saline or water to remove residual becaplermin gel and cover with saline moistened dressing (without becaplermin gel) for remainder of the day. Continue use once daily until ulcer is completely healed.

StorageRefrigerate at 2°C to 8°C (36°F to 46°F); do not freeze.

ContraindicationsHypersensitivity to becaplermin or any component of the formulation; known neoplasm(s) at the site(s) of application

Warnings/Precautions

Boxed warnings:

- Malignancy: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Malignancy: **[U.S. Boxed Warning]: An increase in mortality secondary to systemic malignancies has been observed in a retrospective study of patients treated with ≥3 tubes of becaplermin.** Malignancies of varying types have been reported; all were remote from the becaplermin treatment site. Use with caution in patients with known malignancy.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <16 years of age.

Other warnings/precautions:

- Appropriate use: For external use only; do not use in wounds that close by primary intention. Use with caution in ulcer wounds related to arterial or venous insufficiency and when there are thermal, electrical, or radiation burns at wound site. Effects on exposed joints, tendons, ligaments and bone have not been established.

Geriatric ConsiderationsNo specific information for use in elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Use in pregnancy only if clearly needed.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

1% to 10%: Dermatologic: Erythematous rash (2%)

<1%: Erythema with purulent discharge, ulcer infection, tunneling of ulcer, exuberant granulation tissue, local pain, skin ulceration

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersUlcer volume (pressure ulcers); wound area; evidence of closure; drainage (diabetic ulcers); signs/symptoms of toxicity (erythema, local infections)
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel, topical:

Regranex®: 0.01% (2 g, 15 g)

Generic AvailableNo
ManufacturerOrtho-McNeil Pharmaceutical, Inc
Pricing: U.S. (www.drugstore.com)

Gel (Regranex)

0.01% (15): $642.55

Mechanism of ActionRecombinant B-isoform homodimer of human platelet-derived growth factor (rPDGF-BB) which enhances formation of new granulation tissue, induces fibroblast proliferation and differentiation to promote wound healing; also promotes angiogenesis.
Pharmacodynamics/Kinetics

Onset of action: Complete healing: 15% of patients within 8 weeks, 25% at 10 weeks

Absorption: Minimal

Distribution: Binds to PDGF beta-receptors in normal skin and granulation tissue

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsRecombinant Human Platelet-Derived Growth Factor B; rPDGF-BB
References

Seeger JD, Fife D, Ziyadeh N, et al, "A Cohort Study of the Risk of Cancer in Regranex (Becaplermin) Users and Matched Comparators," *Pharmacoepidemiol Drug Saf*, 2007, 16(S2):167-8:353 [abstract of the 23rd ICPE]

International Brand NamesRegranex (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, KP, MX, NL, NO, PL, PT, RU, SE, TR)

Beclomethasone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Vanceril® may be confused with Vancenase®

Pronunciation(be kloe METH a sone)

U.S. Brand NamesBeconase® AQ; QVAR®

Canadian Brand NamesApo-Beclomethasone®; Gen-Beclo; Nu-Beclomethasone; Propaderm®; QVAR®; Rivanase AQ; Vanceril® AEM

Pharmacologic CategoryCorticosteroid, Inhalant (Oral); Corticosteroid, Nasal

Use: Labeled Indications

Oral inhalation: Maintenance and prophylactic treatment of asthma; includes those who require corticosteroids and those who may benefit from a dose reduction/elimination of systemically-administered corticosteroids. Not for relief of acute bronchospasm.

Nasal aerosol: Symptomatic treatment of seasonal or perennial rhinitis; prevent recurrence of nasal polyps following surgery.

Dosing: AdultsNasal inhalation and oral inhalation dosage forms are not to be used interchangeably.

Rhinitis, nasal polyps: Inhalation, nasal (Beconase® AQ): 1-2 inhalations each nostril twice daily; total dose 168-336 mcg/day

Asthma: Inhalation, oral (doses should be titrated to the lowest effective dose once asthma is controlled) (QVAR®):

Patients previously on bronchodilators only: Initial dose 40-80 mcg twice daily; maximum dose 320 mcg twice day

Patients previously on inhaled corticosteroids: Initial dose 40-160 mcg twice daily; maximum dose 320 mcg twice daily

NIH Asthma Guidelines (NIH, 2007): HFA formulation (eg, QVAR®): Administer in divided doses:

"Low" dose: 80-240 mcg/day

"Medium" dose: >240-480 mcg/day

"High" dose: >480 mcg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricNasal inhalation and oral inhalation dosage forms are not to be used interchangeably.

Rhinitis, nasal polyps: Inhalation, nasal (Beconase® AQ): Children ≥6 years: Refer to adult dosing

Asthma: Inhalation, oral (doses should be titrated to the lowest effective dose once asthma is controlled) (QVAR®):

Children 5-11 years: Initial: 40 mcg twice daily; maximum dose: 80 mcg twice daily

Children ≥12 years: Refer to adult dosing

NIH Asthma Guidelines (NIH, 2007): HFA formulation (eg, QVAR®): Administer in divided doses:

Children 5-11 years:

"Low" dose: 80-160 mcg/day

"Medium" dose: >160-320 mcg/day

"High" dose: >320 mcg/day

Children ≥12 years: Refer to adult dosing.

Administration: Inhalation

Beconase AQ®: Shake well before use. Nasal applicator and dust cap may be washed in warm water and dry thoroughly.

QVAR®: Rinse mouth and throat after use to prevent *Candida* infection. Do not wash or put inhaler in water; mouth piece may be cleaned with a dry tissue or cloth. Prime canister before using.

StorageDo not store near heat or open flame. Do not puncture canisters. Store at room temperature. Rest QVAR® on concave end of canister with actuator on top.

ContraindicationsHypersensitivity to beclomethasone or any component of the formulation; status asthmaticus

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections.

- Bronchospasm: May occur with wheezing after inhalation; if this occurs stop steroid and treat with a fast-acting bronchodilator.

- Delayed wound healing: Avoid nasal corticosteroid use in patients with recent nasal septal ulcers, nasal surgery or nasal trauma until healing has occurred.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox should be avoided; corticosteroids should not be used to treat ocular herpes simplex. Corticosteroids should not be used for cerebral malaria. Close observation is required in patients with latent tuberculosis and/or TB reactivity; restrict use in active TB (only in conjunction with antituberculosis treatment).

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

Disease-related concerns:

- Asthma: Supplemental steroids (oral or parenteral) may be needed during stress or severe asthma attacks. Not to be used in status asthmaticus or for the relief of acute bronchospasm.

- Cardiovascular disease: Use with caution in patients with HF; long-term use has been associated with fluid retention and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.

- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids.

- Myocardial infarct (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Pediatrics: Orally-inhaled and intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients (~1 centimeter per year [range 0.3-1.8 cm per year] and related to dose and duration of exposure). To minimize the systemic effects of orally-inhaled and intranasal corticosteroids, each patient should be titrated to the lowest effective dose. Growth should be routinely monitored in pediatric patients. Safety and efficacy have not been established in children <5 years of age.

Other warnings/precautions:

- Discontinuation of therapy: Withdraw systemic therapy with gradual tapering of dose. There have been reports of systemic corticosteroid withdrawal symptoms (eg, joint/muscle pain, lassitude, depression) when withdrawing oral inhalation therapy.

Geriatric ConsiderationsElderly patients may have difficulty with oral metered dose inhalers and may benefit from the use of a spacer or chamber device.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were observed in animal studies. No human data on beclomethasone crossing the placenta or effects on the fetus. A decrease in fetal growth has not been observed with inhaled corticosteroid use during pregnancy. Inhaled corticosteroids are recommended for the treatment of asthma (most information available using budesonide) and allergic rhinitis during pregnancy.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsOther corticosteroids have been found in breast milk; however, information for beclomethasone is not available. Inhaled corticosteroids are recommended for the treatment of asthma (most information available using budesonide) while breast-feeding.

Adverse ReactionsFrequency not defined.

Central nervous system: Agitation, depression, dizziness, dysphonia, headache, lightheadedness, mental disturbances

Dermatologic: Acneiform lesions, angioedema, atrophy, bruising, pruritus, purpura, striae, rash, urticaria

Endocrine & metabolic: Cushingoid features, growth velocity reduction in children and adolescents, HPA function suppression, weight gain

Gastrointestinal: Dry/irritated nose, throat and mouth, hoarseness, localized *Candida* or *Aspergillus* infection, loss of smell, loss of taste, nausea, unpleasant smell, unpleasant taste, vomiting

Local: Nasal spray: Burning, epistaxis, localized *Candida* infection, nasal septum perforation (rare), nasal stuffiness, nosebleeds, rhinorrhea, sneezing, transient irritation, ulceration of nasal mucosa (rare)

Ocular: Cataracts, glaucoma, intraocular pressure increased

Respiratory: Cough, paradoxical bronchospasm, pharyngitis, sinusitis, wheezing

Miscellaneous: Anaphylactic/anaphylactoid reactions, death (due to adrenal insufficiency, reported during and after transfer from systemic corticosteroids to aerosol in asthmatic patients), immediate and delayed hypersensitivity reactions

Drug Interactions

Amphotericin B: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antidiabetic Agents: Corticosteroids (Orally Inhaled) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringNot to be used to treat status asthmaticus or fungal infections of nasal passages. Monitor therapeutic effectiveness and adverse reactions. When changing from systemic steroids to inhalational steroids, taper reduction of systemic medication slowly. Growth should be routinely monitored in pediatric patients. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationUse as directed; do not increase dosage or discontinue abruptly without consulting prescriber. It may take 1-4 weeks for you to realize full effects of treatment. Review use of inhaler or spray with prescriber or follow package insert for directions. Keep oral inhaler clean and unobstructed. Always rinse mouth and throat after use of inhaler to prevent infection. If you are also using an inhaled bronchodilator, wait 10 minutes before using this steroid aerosol. Report adverse effects such as skin redness, rash, or irritation; pain or burning of nasal mucosa; white plaques in mouth or fuzzy tongue; unresolved headache; or worsening of condition or lack of improvement. Discard after date calculated by prescriber; the amount of medication in canister cannot be guaranteed after using the labeled number of actuations (sprays) even though it may not feel empty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Inhalation: Sit when using. Take deep breaths for 3-5 minutes, and clear nasal passages before administration (use decongestant as needed). Hold breath for 5-10 seconds after use, and wait 1-3 minutes between inhalations. Follow package insert instructions for use. Do not exceed maximum dosage. If also using inhaled bronchodilator, use before beclomethasone. Rinse mouth and throat after use to reduce aftertaste and prevent candidiasis.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol for oral inhalation, as dipropionate:

QVAR®: 40 mcg/inhalation [100 metered actuations] (7.3 g); 80 mcg/inhalation [100 metered actuations] (7.3 g)

Suspension, intranasal, as dipropionate [aqueous spray]:

Beconase® AQ: 42 mcg/inhalation [180 metered sprays (25 g)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Aerosol solution (Qvar)

40 mcg/ACT (7.3): $75.59

80 mcg/ACT (7.3): $92.87

Suspension (Beconase AQ)

42 mcg/spray (25): $149.32

Mechanism of Action Controls the rate of protein synthesis; depresses the migration of polymorphonuclear leukocytes, fibroblasts; reverses capillary permeability and lysosomal stabilization at the cellular level to prevent or control inflammation

Pharmacodynamics/Kinetics

Onset of action: Therapeutic effect: 1-4 weeks

Absorption: Readily; quickly hydrolyzed by pulmonary esterases prior to absorption

Distribution: Beclomethasone: 20 L; active metabolite: 424 L

Protein binding: 87%

Metabolism: Hepatic via CYP3A4 to active metabolites

Bioavailability: Of active metabolite, 44% following nasal inhalation (43% from swallowed portion)

Half-life elimination: Initial: 3 hours

Excretion: Feces (60%); urine (12%)

Related Information

- Asthma
- Inhalant Agents
- Status Epilepticus

Pharmacotherapy Pearls Effects of inhaled/intranasal steroids on growth have been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally-inhaled and intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Oral candidiasis, xerostomia (normal salivary flow resumes upon discontinuation), nasal dryness, and dry throat. Localized infections with *Candida albicans* or *Aspergillus niger* occur frequently in the mouth and pharynx with repetitive use of an oral inhaler; may require treatment with appropriate antifungal therapy or discontinuance of inhaler use.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause agitation, depression, dizziness, euphoria, insomnia, mood swings, and personality changes; may cause exacerbation of pre-existing psychiatric conditions

Mental Health: Effects on Psychiatric Treatment None reported

Anesthesia and Critical Care Concerns/Other Considerations

Surgery: For patients who have received oral systemic corticosteroids during the past 6 months and for selected patients on long-term, high-dose, inhaled corticosteroid (ICS), give stress doses of hydrocortisone intravenously during the surgical period and reduce the dose rapidly within 24 hours after surgery (Expert Panel Report 3, 2007). Clinically important adrenal suppression has been reported in patients receiving high doses of an ICS, particularly children.

Index Terms Beclomethasone Dipropionate

References

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Wyatt R, Waschek J, Weinberger M, et al, "Effects of Inhaled Beclomethasone Dipropionate and Alternate-Day Prednisone on Pituitary-Adrenal Function in Children With Chronic Asthma," *N Engl J Med*, 1978, 299(25):1387-92.[PubMed 362207]

International Brand NamesAerobec (SE); Afifon (IL); Alanase (NZ); Aldecin (AU, BG, MY); Atomase (MY, NZ); Beclate (IN, ZA); Beclazone (MX, MY, NZ); Beclo-Asma (HK); Beclo-Asma CFC Free (SG); Becloforte (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Beclomet (CH, MY, SE, TW); Beclomet Easyhaler (ID, TH); Beclomet Nasal Aqua (ID); Beclometasone (FR); Beclone (FR); Beclosol Aquoso (BR); Beclospin (FR); Beconase (AE, BB, BF, BH, BJ, BM, BS, BZ, CH, CI, CL, CO, CR, CY, DO, EE, EG, ET, FI, FR, GB, GH, GM, GN, GT, GY, HN, ID, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, OM, PA, PE, PK, QA, SA, SC, SD, SL, SN, SR, SV, SY, TH, TN, TT, TZ, UG, VE, YE, ZA, ZM, ZW); Becotide (AE, AT, BB, BD, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CL, CR, CY, CZ, DE, DK, DO, EE, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PK, PT, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SV, SY, TH, TN, TR, TT, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Belax (TW); Bemase (TH); Bemedrex Easyhaler (FR); Bronconox (CO); Bronconox Forte (CO); Clenil (AE, AR, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, TW, YE); Clenil Forte (ID); Clenil HFA Modulate (MY); Clenil Modulite (GB); Clipper (BE, GB); Decomit (SG); Dobipro (MX); Easyhaler Beclomethasone (GB, IE); Ecobec (FR); Filair (CN); Miflasone (FR); Nasair (VE); Nasobec Aqueous (HK, KP); Nexxair (FR); Oxiplus (PY, UY); Propavent (AR); Q Var (CR, GT, HN, MY, NZ, PA, PH, SV, TH); Qvar (MX); Qvar Autohaler (AU, FR); Qvar Inhaler (AU); Respocort (MY, NZ, PH); Rhino Clenil (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Rino-Clenil (TH); Viarex (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Viarox (ZA)

Belladonna and Opium

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English

Jump To Field (Select Field Name)

Pronunciation(bel a DON a & OH pee um)

U.S. Brand NamesB&O Supprettes® [DSC]

Pharmacologic CategoryAnalgesic Combination (Opioid); Antispasmodic Agent, Urinary

Use: Labeled IndicationsRelief of moderate-to-severe pain associated with ureteral spasms not responsive to nonopioid analgesics and to space intervals between injections of opiates

Dosing: AdultsPain: Rectal: 1 suppository 1-2 times/day, up to 4 doses/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricPain: Children >12 years: Refer to adult dosing.

Administration: OtherPrior to rectal insertion, the finger and suppository should be moistened. Assist with ambulation.

StorageStore at 15°C to 30°C. Do not refrigerate.

RestrictionsC-II

ContraindicationsHypersensitivity to belladonna, opium, or any component of the formulation; glaucoma; severe renal or hepatic disease; bronchial asthma; respiratory depression; convulsive disorders; acute alcoholism; premature labor

Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Atropine idiosyncrasy: Use with caution in patients with known idiosyncrasy to atropine or atropine-like compounds.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene-derivative opioid agonists (codeine, hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Drug abuse: Use with caution in patients with a history of opiate drug abuse or acute alcoholism; potential for drug dependency exists.
- Increased intracranial pressure: Use with caution in patients with increased intracranial pressure; exaggerated elevation of ICP may occur.
- Prostatic hyperplasia: Use with caution in patients with prostatic hyperplasia; may cause urinary retention.
- Psychosis: Use with caution in patients with toxic psychosis; may exacerbate condition.
- Thyroid dysfunction: Use with caution in patients with myxedema; may exacerbate condition.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Not recommended for use in children ≤12 years of age.

Other warnings/precautions:

- Appropriate use: Usual precautions of opiate agonist therapy should be observed.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this product. Refer to Atropine and Morphine Sulfate monographs for additional information.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if/how much morphine or atropine may be found in breast milk following rectal administration of this product. Refer to Atropine and Morphine Sulfate monographs for additional information.

Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation

Central nervous system: Dizziness, drowsiness

Dermatologic: Pruritus, urticaria

Gastrointestinal: Constipation, nausea, vomiting, xerostomia

Genitourinary: Urinary retention

Ocular: Blurred vision, photophobia

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase sedation).

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for additive or adverse interactions. Monitor therapeutic effectiveness, signs of overdose, and adverse effects at beginning of therapy and at regular intervals with long-term use. May cause physical and/or psychological dependence. For inpatients, implement safety measures. Assess knowledge/teach patient appropriate use if self-administered. Teach patient to monitor for adverse reactions, adverse reactions to report, and appropriate interventions to reduce side effects.

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause hypotension, dizziness, or drowsiness; use caution when driving, climbing stairs, or changing position (rising from sitting or lying to standing) or when engaging in tasks requiring alertness (until response to drug is known); dry mouth or throat (frequent mouth care, frequent sips of fluids, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help; if unresolved, consult prescriber about use of stool softeners); photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); or decreased perspiration (avoid extremes in temperature or excessive activity in hot environments). Report chest pain or palpitations; persistent dizziness; changes in mentation; changes in gait; blurred vision; shortness of breath or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Suppository: Belladonna extract 16.2 mg and opium 30 mg; belladonna extract 16.2 mg and opium 60 mg

B&O Supprettes® #15 A: Belladonna extract 16.2 mg and opium 30 mg [DSC]

B&O Supprettes® #16 A: Belladonna extract 16.2 mg and opium 60 mg [DSC]

Generic AvailableYes

Mechanism of ActionThe pharmacologically active agents present in the belladonna component are atropine and scopolamine. Atropine blocks the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands, and the CNS causing a relaxation of smooth muscle and drying of secretions. The principle agent in opium is morphine. Morphine binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain.

Pharmacodynamics/Kinetics Absorption: Rectal absorption is dependent upon body hydration, not temperature

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), and dry throat and nose.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment Constipation and dry mouth are common; use with low potency antipsychotics and TCAs will likely result in additive effects

Index Terms Opium and Belladonna

References

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

Belladonna, Phenobarbital, and Ergotamine

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English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(bel a DON a, fee noe BAR bi tal, & er GOT a meen)

U.S. Brand NamesBellamine S [DSC]; Eperbel-S [DSC]; Spastrin® [DSC]

Canadian Brand NamesBellergal® Spacetabs®

Pharmacologic CategoryErgot Derivative

Use: Labeled IndicationsManagement and treatment of menopausal disorders, GI disorders, and recurrent throbbing headache

Dosing: AdultsMenopausal disorders, GI disorders, and recurrent throbbing headache: Oral: 1 tablet each morning and evening

Dosing: ElderlyRefer to adult dosing and dosing in individual monographs.

ContraindicationsHypersensitivity to belladonna alkaloids, phenobarbital, ergotamine, or any component of the formulation; dopamine therapy; ergot alkaloids are contraindicated with potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics); hypertension; glaucoma; coronary heart disease and peripheral vascular disease; impaired hepatic or renal function; sepsis; history of manifest or latent porphyria; pregnancy

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity
- Belladonna Alkaloid Allergy
- Ergot Alkaloid Allergy

Warnings/Precautions

Boxed warnings:

- CYP3A4 inhibitors: See “Concurrent drug therapy issues” below.

Concerns related to adverse effects:

- Cardiac valvular fibrosis: Ergot alkaloids have been associated with fibrotic valve thickening (eg, aortic, mitral, tricuspid); usually associated with long-term, chronic use.
- Cardiovascular effects: Vasospasm or vasoconstriction can occur, possibly resulting in decreased cerebral blood flow, ECG changes, and hypertension; sustained vasoconstriction may also lead to ischemic colitis, intermittent claudication, aggravation of angina, or precipitation of MI. Do not use is any patient at risk or predisposed to vascular effects of ergot alkaloids.
- Ergotism: Ergot alkaloid use may result in ergotism (intense vasoconstriction) resulting in peripheral vascular ischemia and possible gangrene. Ergotism is usually associated with overdosage or prolonged chronic use; do not exceed dosing guidelines and avoid prolonged administration.
- Habit-forming: May be habit-forming.
- Pleural/retroperitoneal fibrosis: Rare cases of pleural and/or retroperitoneal fibrosis have been reported with prolonged daily use.

Disease-related concerns:

- Asthma: Use with caution in patients with bronchial asthma.
- Uropathy: Use with caution in patients with obstructive uropathy.

Concurrent drug therapy issues:

- CYP3A4 inhibitors: **[U.S. Boxed Warning]: Ergot alkaloids are contraindicated with potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics); concomitant use associated with acute ergot toxicity (ergotism).**

Special populations:

- Elderly: Use with extreme caution or avoid use in the elderly; due to vasoconstrictive properties and cardiovascular adverse effects associated with ergot alkaloids.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Weekly dosage: Total weekly dosage of ergotamine should not exceed 10 mg.
- Withdrawal: Discontinuation after extended use may result in withdrawal symptoms (eg, rebound headache).

Pregnancy Risk FactorX

Pregnancy ConsiderationsPotential uterotonic effects

LactationEnters breast milk (ergotamine)/contraindicated

Adverse Reactions

>10%:

Cardiovascular: Peripheral vascular effects (numbness and tingling of fingers and toes)

Central nervous system: Drowsiness, dizziness

Dermatologic: Dry skin

Gastrointestinal: Constipation, dry mouth and throat, diarrhea, nausea, vomiting

Respiratory: Dry nose

Miscellaneous: Diaphoresis decreased

1% to 10%:

Cardiovascular: Precordial distress and pain, transient tachycardia or bradycardia

Dermatologic: Photosensitivity

Endocrine & metabolic: Breast milk flow decreased

Gastrointestinal: Swallowing difficulty

Neuromuscular & skeletal: Muscle pain in extremities, weakness in legs

<1% (Limited to important or life-threatening): Orthostatic hypotension, ventricular fibrillation, tachycardia, palpitation, confusion, headache, memory loss, drowsiness, skin rash, intraocular pain increased, blurred vision

Metabolism/Transport Effects

Phenobarbital: **Substrate** of CYP2C8/9 (minor), 2C19 (major), 2E1 (minor); **Induces** CYP1A2 (strong), 2A6 (strong), 2B6 (strong), 2C8/9 (strong), 3A4 (strong)

Ergotamine: **Substrate** of CYP3A4 (major); Inhibits 3A4 (weak)

Drug Interactions

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Aminocamptothecin: PHENobarbital may decrease the serum concentration of Aminocamptothecin. *Risk C: Monitor therapy*

Amphetamines: May decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inducers (Strong) may decrease the serum concentration of Bendamustine. Concentrations of active metabolites may be increased. *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May enhance the adverse/toxic effect of Anticonvulsants (Barbiturate). Specifically, osteomalacia and rickets. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inducers (Strong) may increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2A6 Substrates: CYP2A6 Inducers (Strong) may increase the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inducers (Strong) may increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inducers (Highly Effective) may increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inducers (Highly Effective) may increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Darunavir: PHENobarbital may decrease the serum concentration of Darunavir. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Efavirenz: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically, the risk for peripheral vasospasm and ischemia may be increased. *Risk X: Avoid combination*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Etravirine: PHENobarbital may decrease the serum concentration of Etravirine. Management: The manufacturer of etravirine states these drugs should not be used in combination *Risk X: Avoid combination*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

Folic Acid: May decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Griseofulvin: Barbiturates may decrease the absorption of Griseofulvin. *Risk D: Consider therapy modification*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Lacosamide: PHENobarbital may decrease the serum concentration of Lacosamide. *Risk C: Monitor therapy*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Leucovorin-Levoleucovorin: May decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Macrolide Antibiotics: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Methylfolate: May decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

OXcarbazepine: PHENobarbital may decrease the serum concentration of OXcarbazepine. *Risk C: Monitor therapy*

Posaconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Ergot Derivatives. *Risk X: Avoid combination*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Rufinamide: May increase the serum concentration of PHENobarbital. PHENobarbital may decrease the serum concentration of Rufinamide. *Risk C: Monitor therapy*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Serotonin 5-HT1D Receptor Agonists: Ergot Derivatives may enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Ergot Derivatives. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tipranavir: PHENobarbital may decrease the serum concentration of Tipranavir. Tipranavir may decrease the serum concentration of PHENobarbital. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Voriconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Voriconazole: Barbiturates may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, warfarin). This combination drug interacts with many commonly prescribed drugs to potentiate adverse/toxic reactions or to reduce the effectiveness of other drugs. Use caution with prolonged use; may be habit-forming. Abrupt discontinuation after long-term use may result in withdrawal symptoms (eg, rebound headache). Assess therapeutic effect and adverse reactions at regular intervals during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to females of childbearing age unless they are capable of complying with contraceptive use. Instruct patient about appropriate contraceptives.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed; do not take more than recommended dose. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake and nutrition. May cause drowsiness or dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known); dry throat or mouth (frequent mouth care or sucking on lozenges may help); dry nose (use humidifier); photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); nausea or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); dry skin (mild skin lotion may help); or orthostatic hypotension (use caution when rising from sitting or lying position or climbing stairs). Report any signs of numbness in extremities (fingers and toes); unusual leg pain or cyanosis of extremities; difficulty swallowing; persistent muscle pain or weakness; pain in eye or vision changes; or chest pain, rapid heartbeat, or palpitations. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant and do not get pregnant during therapy. Consult prescriber for instruction on appropriate contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet:

Bellamie S [DSC], Eperbel-S [DSC], Spastrin® [DSC]: Belladonna alkaloids 0.2 mg, phenobarbital 40 mg, and ergotamine 0.6 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Bellamine S)

0.6-40-0.2 mg (60): $15.99

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Ergotamine
- PHENobarbital

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), dry throat, nasal dryness, and difficulty swallowing.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDrowsiness and dizziness are common
Mental Health: Effects on Psychiatric TreatmentCombined use with TCAs and antipsychotics may potentiate the depressant actions
Index TermsErgotamine Tartrate, Belladonna, and Phenobarbital; Phenobarbital, Belladonna, and Ergotamine Tartrate
International Brand NamesBellergal Retard (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TZ, UG, ZM, ZW); Bellergal Spacetabs (CA)

Benazepril and Hydrochlorothiazide

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ben AY ze pril & hye droe klor oh THYE a zide)

U.S. Brand NamesLotensin® HCT

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension

Dosing: AdultsHypertension: Oral: Dose is individualized (range: benazepril: 5-20 mg; hydrochlorothiazide: 6.25-25 mg/day)

Dosing: ElderlyDose is individualized.

Dosing: Renal ImpairmentCl$_{cr}$ <30 mL/minute: Not recommended; loop diuretics are preferred.

Calculations

- Creatinine Clearance: Adults

ContraindicationsHypersensitivity to benazepril, any other ACE inhibitor, hydrochlorothiazide, sulfonamide-derived drugs, or any component of the formulation; anuria

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema or previous angioedema associated with ACE inhibitor therapy may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Electrolyte disturbances: Hyperkalemia may occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE Inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.
- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.
- Collagen vascular disease: Use benazepril with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity. Hydrochlorothiazide can cause systemic lupus erythematosus (SLE) exacerbation or activation.
- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control. Use benazepril with caution in patients with diabetes receiving insulin or oral antidiabetic agents; may be at increased risk for episodes of hypoglycemia.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.
- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.
- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.
- Porphyria: Use with caution in patients with porphyria; acute porphyritic attacks have occurred with hydrochlorothiazide.
- Renal artery stenosis: Use benazepril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.
- Renal impairment: Use ACE inhibitors with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment. Avoid hydrochlorothiazide in severe renal disease (ineffective). Contraindicated in anuric patients.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsIn clinical studies, of the total number of patients who received Lotensin® HCT in U.S., 19% were ≥65 years of age, while ~1.5% were ≥75 years. Overall differences in effectiveness or safety were not observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
Pregnancy Risk FactorC/D (2nd and 3rd trimesters)
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/compatible
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsSee individual agents.
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure; BUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsBUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 5/6.25: Benazepril hydrochloride 5 mg and hydrochlorothiazide 6.25 mg; 10/12.5: Benazepril hydrochloride 10 mg and hydrochlorothiazide 12.5 mg; 20/12.5: Benazepril hydrochloride 20 mg and hydrochlorothiazide 12.5 mg; 20/25: Benazepril hydrochloride 20 mg and hydrochlorothiazide 25 mg

Lotensin® HCT 5/6.25: Benazepril hydrochloride 5 mg and hydrochlorothiazide 6.25 mg

Lotensin® HCT 10/12.5: Benazepril hydrochloride 10 mg and hydrochlorothiazide 12.5 mg

Lotensin® HCT 20/12.5: Benazepril hydrochloride 20 mg and hydrochlorothiazide 12.5 mg

Lotensin® HCT 20/25: Benazepril hydrochloride 20 mg and hydrochlorothiazide 25 mg

Generic AvailableYes
ManufacturerCiba-Geigy Pharmaceuticals
Pricing: U.S. (www.drugstore.com)

Tablets (Benazepril-Hydrochlorothiazide)

5-6.25 mg (30): $25.91

10-12.5 mg (30): $22.99

20-12.5 mg (30): $26.99

20-25 mg (30): $26.99

Tablets (Lotensin HCT)

5-6.25 mg (30): $39.20

10-12.5 mg (30): $48.34

20-12.5 mg (30): $48.99

20-25 mg (30): $48.30

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Benazepril
- Hydrochlorothiazide

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness
Mental Health: Effects on Psychiatric TreatmentMay decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels
Index TermsHydrochlorothiazide and Benazepril
International Brand NamesCibacen HCT (PT); Cibadrex (AE, AT, BB, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CY, DE, EG, ET, FR, GH, GM, GN, GR, GY, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PR, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Lotensin H (BR); Lotenssin HCT (HN)

Benazepril

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Benazepril may be confused with Benadryl®

Lotensin® may be confused with Lioresal®, lovastatin

International issues:

Lotensin® may be confused with Latensin® which is a brand name for bacillus cereus in Germany

Pronunciation(ben AY ze pril)

U.S. Brand NamesLotensin®

Canadian Brand NamesApo-Benazepril®; Lotensin®

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor

Use: Labeled IndicationsTreatment of hypertension, either alone or in combination with other antihypertensive agents

Dosing: AdultsHypertension: Oral: Initial: 10 mg/day in patients not receiving a diuretic; 20-80 mg/day as a single dose or 2 divided doses; the need for twice-daily dosing should be assessed by monitoring peak (2-6 hours after dosing) and trough responses.

Note: Patients taking diuretics should have them discontinued 2-3 days prior to starting benazepril. If they cannot be discontinued, then initial dose should be 5 mg; restart after blood pressure is stabilized if needed.

Dosing: ElderlyOral: Initial: 5-10 mg/day in single or divided doses; usual range: 20-40 mg/day; adjust for renal function. Also see “Note” in adult dosing.

Dosing: PediatricHypertension: Children ≥6 years: Oral: Initial: 0.2 mg/kg/day (up to 10 mg/day) as monotherapy; dosing range: 0.1-0.6 mg/kg/day (maximum dose: 40 mg/day)

Dosing: Renal Impairment

Cl_{cr} <30 mL/minute:

Children: Use is not recommended.

Adults: Administer 5 mg/day initially; maximum daily dose: 40 mg.

Hemodialysis: Moderately dialyzable (20% to 50%); administer dose postdialysis or administer 25% to 35% supplemental dose.

Peritoneal dialysis: Supplemental dose is not necessary.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Extemporaneously PreparedTo prepare a 2 mg/mL suspension, mix 15 benazepril 20 mg tablets in a bottle with Ora-Plus® 75 mL. Shake for 2 minutes, allow suspension to stand for ≥1 hour, then shake again for at least 1 additional minute. Add Ora-Sweet® 75 mL to suspension and shake to disperse. Will make 150 mL of a 2 mg/mL suspension. Store under refrigeration at 2°C to 8°C (36°F to 46°F) for up to 30 days. Shake prior to each use.

ContraindicationsHypersensitivity to benazepril or any component of the formulation; angioedema or serious hypersensitivity related to previous treatment with an ACE inhibitor

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE Inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.

- Diabetes: Use with caution in patients with diabetes receiving insulin or oral antidiabetic agents; may be at increased risk for episodes of hypoglycemia.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss, or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsDue to frequent decreases in glomerular filtration (also Cl_{cr}) with aging, elderly patients may have exaggerated responses to ACE inhibitors; differences in clinical response due to hepatic changes are not observed. ACE inhibitors may be preferred agents in elderly patients with congestive heart failure and diabetes mellitus. Diabetic proteinuria is reduced and insulin sensitivity is enhanced. In general, the side effect profile is favorable in elderly and causes little or no CNS confusion; use lowest dose recommendations initially. Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.

Benazepril and benazeprilat are substantially excreted by the kidney. Because elderly are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Pregnancy Risk FactorD

Pregnancy ConsiderationsDue to adverse events observed in humans, benazepril is considered pregnancy category D. Benazepril crosses the placenta. First trimester exposure to ACE inhibitors may cause major congenital malformations. An increased risk of cardiovascular and/or central nervous system malformations was observed in one study; however, an increased risk of teratogenic events was not observed in other studies. Second and third trimester use of an ACE inhibitor is associated with oligohydramnios. Oligohydramnios due to decreased fetal renal function may lead to fetal limb contractures, craniofacial deformation, and hypoplastic lung development. The use of ACE inhibitors during the second and third trimesters is also associated with anuria, hypotension, renal failure (reversible or irreversible), skull hypoplasia, and death in the fetus/neonate. Chronic maternal hypertension itself is also associated with adverse events in the fetus/infant. ACE inhibitors are not recommended during pregnancy to treat maternal hypertension or heart failure. Those who are planning a pregnancy should be considered for other medication options if an ACE inhibitor is currently prescribed or the ACE inhibitor should be discontinued as soon as possible once pregnancy is detected. The exposed fetus should be monitored for fetal growth, amniotic fluid volume, and organ formation. Infants exposed to an ACE inhibitor *in utero*, especially during the second and third trimester, should be monitored for hyperkalemia, hypotension, and oliguria.

[U.S. Boxed Warning]: Based on human data, ACE inhibitors can cause injury and death to the developing fetus. ACE inhibitors should be discontinued as soon as possible once pregnancy is detected.

LactationEnters breast milk

Breast-Feeding ConsiderationsSmall amounts of benazepril and benazeprilat are found in breast milk.

Pregnancy & Lactation, In-Depth

- Benazepril in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Cardiovascular: Postural dizziness (2%)

Central nervous system: Headache (6%), dizziness (4%), fatigue (2%), somnolence (2%)

Gastrointestinal: Nausea (1%)

Renal: Serum creatinine increased (2%), worsening of renal function may occur in patients with bilateral renal artery stenosis or hypovolemia

Respiratory: Cough (1% to 10%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Agranulocytosis, alopecia, anaphylactoid reaction, angina, angioedema (includes head, neck and intestinal angioedema), arthralgia, arthritis, asthma, BUN increased (transient), dermatitis, dyspnea, ECG changes, eosinophilia, flushing, gastritis, hemolytic anemia, hyperbilirubinemia, hyperglycemia, hyperkalemia, hypersensitivity, hypertonia, hyponatremia, hypotension, impotence, insomnia, leukopenia, myalgia, neutropenia, palpitations, pancreatitis, paresthesia, pemphigus, peripheral edema, photosensitivity, postural hypotension, proteinuria, pruritis, rash, shock, Stevens-Johnson syndrome, syncope, thrombocytopenia, transaminases increased, uric acid increased, vomiting

Eosinophilic pneumonitis, anaphylaxis, renal insufficiency, and renal failure have been reported with other ACE inhibitors. In addition, a syndrome including fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash, eosinophilia, and elevated ESR has been reported to be associated with ACE inhibitors.

Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure; serum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions. Assess results of laboratory tests, therapeutic effectiveness (blood pressure should be monitored after first doses and periodically during therapy), and adverse response on a regular basis during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take exactly as directed; do not alter dose or discontinue drug without consulting prescriber. Take first dose at bedtime. Do not take potassium supplements or salt substitutes containing potassium without consulting prescriber. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); nausea, vomiting, abdominal pain, dry mouth, or transient loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); report if these side effects persist. Report mouth sores; fever or chills; swelling of extremities, face, mouth, or tongue; respiratory difficulty or unusual cough; or other persistent adverse reactions. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 5 mg, 10 mg, 20 mg, 40 mg

Lotensin®: 5 mg, 10 mg, 20 mg, 40 mg

Generic AvailableYes

ManufacturerNovartis Pharmaceuticals Corp

Pricing: U.S. (www.drugstore.com)

Tablets (Benazepril HCl)

5 mg (90): $64.97

10 mg (30): $23.99

20 mg (30): $23.99

40 mg (30): $23.99

Tablets (Lotensin)

5 mg (30): $51.99

10 mg (30): $51.99

20 mg (30): $51.99

40 mg (30): $51.99

Mechanism of ActionCompetitive inhibition of angiotensin I being converted to angiotensin II, a potent vasoconstrictor, through the angiotensin I-converting enzyme (ACE) activity, with resultant lower levels of angiotensin II which causes an increase in plasma renin activity and a reduction in aldosterone secretion

Pharmacodynamics/Kinetics

Reduction in plasma angiotensin-converting enzyme (ACE) activity:

Onset of action: Peak effect: 1-2 hours after 2-20 mg dose

Duration: >90% inhibition for 24 hours after 5-20 mg dose

Reduction in blood pressure:

Peak effect: Single dose: 2-4 hours; Continuous therapy: 2 weeks

Absorption: Rapid (37%); food does not alter significantly; metabolite (benazeprilat) itself unsuitable for oral administration due to poor absorption

Distribution: V_d: ~8.7 L

Protein binding:

Benazepril: ~97%

Benazeprilat: ~95%

Metabolism: Rapidly and extensively hepatic to its active metabolite, benazeprilat, via enzymatic hydrolysis; extensive first-pass effect

Half-life elimination: Benazeprilat: Effective: 10-11 hours; Terminal: Children: 5 hours, Adults: 22 hours

Time to peak: Parent drug: 0.5-1 hour

Excretion:

Urine (trace amounts as benazepril; 20% as benazeprilat; 12% as other metabolites)

Clearance: Nonrenal clearance (ie, biliary, metabolic) appears to contribute to the elimination of benazeprilat (11% to 12%), particularly patients with severe renal impairment; hepatic clearance is the main elimination route of unchanged benazepril

Dialysis: ~6% of metabolite removed within 4 hours of dialysis following 10 mg of benazepril administered 2 hours prior to procedure; parent compound not found in dialysate

Related Information

- Angiotensin Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentMay decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Congestive Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines recommend that ACE inhibitors be used in patients with a reduced EF (with or without heart failure symptoms) unless contraindicated. ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. In this situation, they decrease hospitalizations for, and retard progression to, congestive heart failure. When used in patients with heart failure, the target dose should be achieved, if possible. Lower daily doses of ACE inhibitors have demonstrated the same mortality effects as high doses, but have not decreased hospitalizations to the extent that high-dose ACE inhibitors have, as demonstrated in the ATLAS study (Packer M, 1999).

Hypertension: The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, and chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) can be beneficial in patients with hypertension and LVH without symptoms of heart failure. JNC 7 suggests that patients can benefit from treatment with an ACE inhibitor if they have hypertension **and** heart failure, acute myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, or history of stroke.

Vascular Disease: The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors can be useful in preventing heart failure in patients who have a history of atherosclerotic vascular disease, diabetes, or hypertension with associated cardiovascular risk factors. The HOPE trial (Heart Outcomes Prevention Evaluation Study Investigators, 2000) investigated the value of an ACE inhibitor (ramipril 5-10 mg daily) versus placebo in patients who had evidence of vascular disease or diabetes (one other cardiovascular risk factor) and were at least 55 years of age. Patients were excluded if they had a low ejection fraction, heart failure, or were on an ACE inhibitor. The primary outcome was a composite of death from cardiovascular cause, myocardial infarction, or stroke; 9297 patients were enrolled and randomized. Ramipril significantly reduced the risk of death from CV causes, MI, or stroke over placebo. New cases of diabetes were also reduced in the ramipril group. In the EUROPA trial, patients with stable coronary artery disease (at low-risk for cardiovascular events) received perindopril or placebo and were evaluated for incidence of cardiovascular events after 4 years of treatment. In this randomized, placebo-controlled, prospective study, 12,218 patients received either perindopril (8 mg/day, n=6110) or placebo (n=6108) and were assessed for the primary endpoint of a cardiovascular event, defined as cardiovascular death, myocardial infarction, or cardiac arrest. The study population was well balanced with respect to baseline demographics and concomitant medication use (including beta-blockers, platelet inhibitors, antihyperlipidemics, calcium channel blockers, nitrates, and diuretics). Intent-to-treat analysis revealed that 603 (10%) of placebo patients experienced the primary endpoint of a cardiovascular event compared to 488 (8%) of perindopril-receiving patients, for a 20% relative risk reduction (p=0.0003). This result was not influenced by presence of other comorbidities (eg, diabetes, hypertension) or concomitant beta-blocker, calcium channel blocker, or lipid-lowering therapies. Withdrawal from the study (postrandomization) due to adverse reactions was similar between treatment groups. The number needed to treat analysis suggests that treatment of 50 patients over a 4-year period will prevent one major cardiovascular event.

Acute Coronary Syndromes: In the treatment of unstable angina/non-ST-segment elevation MI, ACE inhibitors are recommended when hypertension persists despite treatment with nitroglycerin and a beta-blocker in patients with LV systolic dysfunction or CHF and in ischemic patients with diabetes (Class I). ACE inhibitors are also recommended for all post-ACS individuals (Class IIa). According to 2004 ACC/AHA STEMI guidelines, an ACE inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF <0.4, in the absence of hypotension or known contraindications to this class of medicines. In the emergency management of complicated STEMI, a short-acting ACEI (eg, captopril 1-6.25 mg) may be added once the patient's systolic blood pressure is >100 mm Hg and not <30 mm Hg below baseline. The VALIANT trial evaluated the effects of valsartan (target dose: 160 mg twice daily), captopril (target dose: 50 mg twice daily), and the combination (target doses: valsartan 80 mg twice daily and captopril 150 mg once daily) in a randomized, double-blind trial of patients with acute MI (0.5-10 days post-MI) complicated by left ventricular systolic dysfunction, heart failure, or both. Enrollment in the study numbered 14,703 patients and followed for a median of 24.7 months. There was no difference in the primary endpoint (all cause mortality) among the three groups. There was no difference in incidence of CV death, recurrent MI, or hospitalization for heart failure either. Hypotension and renal dysfunction occurred significantly more often in the valsartan group than with captopril alone. Cough, rash, and taste disturbances occurred more often in the captopril group. The authors (Pfeffer MA, 2003) concluded that valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after MI. Combining valsartan with captopril increased the rate of adverse events without improving survival.

Potential Adverse Events: ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. In those patients experiencing cough on an ACE inhibitor, the ACE inhibitor may be discontinued and, if necessary, ARB therapy instituted. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Drug Interactions: Concomitant indomethacin therapy may blunt the reduction in sitting and 24-hour ambulatory diastolic blood pressure. Use of NSAIDs should be avoided or limited, with monitoring of blood pressure control in this setting. In patients with heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

Anesthesia and Critical Care Concerns/Other ConsiderationsAging patients with a decrease in glomerular filtration (also creatinine clearance), severe congestive heart failure, and renal failure may experience an exaggerated response with administration of ACE inhibitors. Diabetic proteinuria is reduced and insulin sensitivity is enhanced. In general, the side effect profile is favorable in elderly and causes little or no CNS confusion.

ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. In this situation, they decrease hospitalizations for, and retard progression to, congestive heart failure. ACE inhibitors are also indicated in patients postmyocardial infarction in whom left ventricular ejection fraction is <40%. When used in patients with heart failure, the target dose or maximum tolerated dose, should be achieved, if possible. Lower daily doses of ACE inhibitors have not demonstrated the same cardioprotective effects. ACE inhibitors have renal protective effects in patients with proteinuria and possibly cardioprotective effects in high-risk patients.

ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. In those patients experiencing cough on an ACE inhibitor, the ACE inhibitor may be discontinued and, if necessary, angiotensin-receptor blocker therapy instituted. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Index TermsBenazepril Hydrochloride

References

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International Brand Names Benace (IN); Boncordin (AR); Cibacen (AE, AT, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CY, DE, DK, EG, ES, ET, GH, GM, GN, GR, GY, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PH, PT, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Cibacen Cor (DE); Cibacene (FR); Labopal (ES); Lotensin (BR, CL, HN, HU, MX, PE, PL, UY, VE); Zaprace (CL)

Bendamustine-Rituximab

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's (Mantle cell or low-grade NHL)

Index TermsRituximab-Bendamustine

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Pretreatment:

Rituximab: I.V.: 375 mg/m^2 1 week before the start of cycle 1

[total dose/pretreatment = 375 mg/m^2]

Cycles:

Rituximab: I.V.: 375 mg/m^2 day 1

[total dose/cycle = 375 mg/m^2]

Bendamustine: I.V.: 90 mg/m^2 days 2 and 3

[total dose/cycle = 180 mg/m^2]

Repeat cycle every 4 weeks for up to 4 cycles

Post-Treatment:

Rituximab: I.V.: 375 mg/m^2 4 weeks after the last cycle

[total dose/post-treatment = 375 mg/m^2]

Variation 2:

Pretreatment:

Rituximab: I.V.: 375 mg/m^2 1 week before the start of cycle 1

[total dose/pretreatment = 375 mg/m^2]

Cycles:

Rituximab: I.V.: 375 mg/m^2 day 1

[total dose/cycle = 375 mg/m^2]

Bendamustine: I.V.: 90 mg/m^2 days 2 and 3

[total dose/cycle = 180 mg/m^2]

Repeat cycle every 4 weeks for 4-6 cycles

Post-Treatment:

Rituximab: I.V.: 375 mg/m^2 4 weeks after the last cycle

[total dose/post-treatment = 375 mg/m^2]

References

Variation 1:

Rummel MJ, Al-Batran SE, Kim SZ, et al, "Bendamustine Plus Rituximab Is Effective and Has a Favorable Toxicity Profile in the Treatment of Mantle Cell and Low-Grade Non-Hodgkin's Lymphoma," *J Clin Oncol*, 2005, 23(15):3383-9.[PubMed 15908650]

Variation 2:

Robinson KS, Williams ME, van der Jagt RH, et al, "Phase II Multicenter Study of Bendamustine Plus Rituximab in Patients With Relapsed Indolent B-Cell and Mantle Cell Non-Hodgkin's Lymphoma," *J Clin Oncol*, 2008, 26(27):4473-9.[PubMed 18626004]

Bendamustine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Bendamustine may be confused with carmustine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ben da MUS teen)
U.S. Brand NamesTreanda®
Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent
Use: Labeled IndicationsTreatment of chronic lymphocytic leukemia (CLL); treatment of progressed indolent B-cell non-Hodgkin's lymphoma (NHL)
Use: Unlabeled/InvestigationalTreatment of mantle cell lymphoma; salvage therapy for relapsed multiple myeloma
Dosing: Adults

CLL: I.V.: 100 mg/m^2 on days 1 and 2 of a 28-day treatment cycle (for up to 6 cycles)

NHL: I.V.: 120 mg/m^2 on days 1 and 2 of a 21-day treatment cycle for up to 8 cycles

Mantle cell lymphoma (unlabeled use): I.V.: 90 mg/m^2 days 2 and 3 of a 28-day treatment cycle for up to 4 cycles (Rummel, 2005)

Multiple myeloma (unlabeled use): I.V.: 90-100 mg/m^2 on days 1 and 2 of a 28-day treatment cycle for at least 2 cycles (Knop, 2005)

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal Impairment
Mild-to-moderate renal impairment: Use with caution.

Cl_{cr} <40 mL/minute: Use is not recommended.

Dosing: Hepatic Impairment

Mild hepatic impairment: Use with caution.

Moderate hepatic impairment (AST or ALT 2.5-10 times ULN and total bilirubin 1.5-3 times ULN): Use is not recommended.

Severe hepatic impairment (total bilirubin >3 times ULN): Use is not recommended.

Dosing: Adjustment for Toxicity
Treatment delay:

Hematologic toxicity ≥grade 4: Delay treatment until resolves (ANC ≥1000/mm^3, platelets ≥75,000/mm^3)

Nonhematologic toxicity ≥grade 2 (clinically significant): Delay treatment until resolves to ≤grade 1

Dose modification CLL:

Hematologic toxicity ≥grade 3: Reduce dose to 50 mg/m^2 on days 1 and 2 of each treatment cycle. For recurrent hematologic toxicity (≥grade 3), further reduce dose to 25 mg/m^2 on days 1 and 2 of the treatment cycle. May cautiously re-escalate dose in subsequent cycles.

Nonhematologic toxicity ≥grade 3 (clinically significant): Reduce dose to 50 mg/m^2 on days 1 and 2 of the treatment cycle with discretion. May cautiously re-escalate dose in subsequent cycles.

Dose modification in NHL:

Hematologic toxicity grade 4: Reduce dose to 90 mg/m^2 on days 1 and 2 of each treatment cycle. For recurrent hematologic toxicity (grade 4), further reduce dose to 60 mg/m^2 on days 1 and 2 of each treatment cycle.

Nonhematologic toxicity ≥grade 3: Reduce dose to 90 mg/m^2 on days 1 and 2 of the treatment cycle with discretion. For recurrent toxicity ≥grade 3, further reduce dose to 60 mg/m^2 on days 1 and 2 of each treatment cycle.

Dosing: Combination Regimens

Lymphoma, non-Hodgkin's: Bendamustine-Rituximab

Lymphoma, non-Hodgkin's: (Mantle Cell): Bendamustine-Rituximab

Calculations

- Body Surface Area: Adults
- Creatinine Clearance: Adults

Administration: I.V.Infuse over 30 minutes for the treatment of CLL and over 60 minutes for NHL. Prophylactic treatment with allopurinol may be needed in patients at risk for tumor lysis syndrome. Consider premedication with antihistamines, antipyretics, and/or corticosteroids for patients with a previous grade 1 or 2 infusion reaction to bendamustine.

Administration: I.V. DetailpH: 2.5-3.5

Dietary ConsiderationsPatients should maintain adequate hydration.

StoragePrior to reconstitution, store intact vials at 25°C (77°F); excursions permitted up to 30°C (86°F). Protect from light. The solution in the vial (reconstituted with SWFI) is stable for 30 minutes (transfer to 500 mL infusion bag within that 30 minutes). The solution diluted in 500 mL for infusion is stable for 24 hours refrigerated or 3 hours at room temperature and room light. Infusion must be completed within these time frames.

ReconstitutionUse appropriate precautions for handling and disposal. Reconstitute 100 mg vial with 20 mL of sterile water for injection to a concentration of 5 mg/mL; powder usually dissolves within 5 minutes. Prior to administration, dilute appropriate dose in 500 mL NS (or $D_{2.5}{}^{1}/_{2}NS$) to a final concentration of 0.2-0.6 mg/mL; mix thoroughly.

CompatibilityStable in NS, $D_{2.5}{}^{1}/_{2}NS$

ContraindicationsHypersensitivity to bendamustine, mannitol, or any component of the formulation

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Myelosuppression (neutropenia, thrombocytopenia and anemia) is a common toxicity; may require therapy delay and/or dose reduction; monitor. Complications due to febrile neutropenia and severe thrombocytopenia have been reported. ANC should recover to ≥1000/mm^3 and platelets to ≥75,000/mm^3 prior to therapy/cycle initiation.

- Dermatologic toxicity: Rash, toxic skin reactions and bullous exanthema have been reported with monotherapy and in combination with other antineoplastics; may be progressive or worsen with continued treatment. Toxic epidermal necrolysis has been reported when used in combination with rituximab. Discontinue bendamustine treatment for severe or progressive skin reaction.

- Hypersensitivity/infusion reaction: Infusion reactions, which may include chills, fever, pruritus, and rash, are common. Rarely, anaphylactic and anaphylactoid reactions have occurred, particularly with the second or subsequent cycle(s). In general, patients who experienced grade 3 or 4 allergic reactions were not rechallenged in CLL clinical trials. Consider premedication with antihistamines, antipyretics and/or corticosteroids for patients with a history of grade 1 or 2 infusion reaction. Discontinue for severe allergic reaction; consider discontinuation with grade 3 or 4 infusion reaction.

- Infection: Infections, including pneumonia and sepsis have been reported with use; may require hospitalization; septic shock and fatalities have occurred. Patients with myelosuppression are more susceptible to infection; monitor closely.

- Malignancy: Malignancies (including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial cancer) have been reported in patients who have received bendamustine.

- Tumor lysis syndrome: Tumor lysis syndrome may occur as a consequence of leukemia treatment, including treatment with bendamustine, usually occurring in the first treatment cycle. May lead to life threatening acute renal failure; adequate hydration and prophylactic allopurinol should be instituted prior to treatment in high risk patients; monitor closely.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with mild hepatic impairment. Use is not recommended in patients with moderate (AST or ALT 2.5-10 times ULN and total bilirubin 1.5-3 times ULN) or severe (total bilirubin >3 times ULN) hepatic impairment.

- Renal impairment: Use with caution in patients with mild-to-moderate renal impairment. Use is not recommended in patient with Cl_{cr} <40 mL/minute.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenic and nonteratogenic events were observed in animal studies following intraperitoneal dosing. There are no adequate and well-controlled studies in pregnant women. May cause fetal harm if administered during pregnancy. Effective contraception is recommended during and for 3 months after treatment for women and men of reproductive potential.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

>10%:

Cardiovascular: Peripheral edema (≤13%)

Central nervous system: Fatigue (9% to 57%), fever (24% to 34%), headache (≤21%), chills (6% to 14%), dizziness (≤14%), insomnia (≤13%)

Dermatologic: Rash (8% to 16%; grades 3/4: ≤3%)

Endocrine & metabolic: Dehydration (≤14%)

Gastrointestinal: Nausea (20% to 75%), vomiting (16% to 40%), diarrhea (9% to 37%), constipation (≤29%), anorexia (≤23%), weight loss (7% to 18%), stomatitis (≤15%), abdominal pain (5% to 13%), appetite loss (≤13%), dyspepsia (≤11%)

Hematologic: Myelosuppression (nadir: in week 3), lymphopenia (68% to 99%; grades 3/4: 47% to 94%), leukopenia (61% to 94%; grades 3/4: 28% to 56%), anemia (88% to 89%; grades 3/4: 11% to 13%), thrombocytopenia (77% to 86%; grades 3/4: 11% to 25%), neutropenia (75% to 86%; grades 3/4: 43% to 60%)

Hepatic: Bilirubin increased (≤34%; grades 3/4: 3%)

Neuromuscular & skeletal: Back pain (≤14%), weakness (8% to 11%)

Respiratory: Cough (4% to 22%), dyspnea (≤16%)

1% to 10%:

Cardiovascular: Tachycardia (≤7%), hypotension (≤6%), chest pain (≤6%), hypertension aggravated (≤3%)

Central nervous system: Anxiety (≤8%), depression (≤6%), pain (≤6%)

Dermatologic: Pruritus (5% to 6%), dry skin (≤5%)

Endocrine & metabolic: Hypokalemia (≤9%), hyperuricemia (≤7%; grades 3/4: 2%), hyperglycemia (grades 3/4: ≤3%), hypocalcemia (grades 3/4: ≤2%), hyponatremia (grades 3/4: ≤2%)

Gastrointestinal: Gastroesophageal reflux disease (≤10%), xerostomia (9%), taste alteration (≤7%), oral candidiasis (≤6%), abdominal distention (≤5%)

Genitourinary: Urinary tract infection (≤10%)

Hematologic: Febrile neutropenia (3% to 6%)

Hepatic: ALT increased (grades 3/4: ≤3%), AST increased (grades 3/4: ≤1%)

Local: Infusion site pain (≤6%), catheter site pain (≤5%)

Neuromuscular & skeletal: Arthralgia (≤6%), bone pain (≤5%), limb pain (≤5%)

Renal: Creatinine increased (grades 3/4: ≤2%)

Respiratory: Upper respiratory infection (10%), sinusitis (≤9%), pharnygolaryngeal pain (≤8%), pneumonia (≤8%), nasopharyngitis (6% to 7%), wheezing (≤5%), nasal congestion (≤5%)

Miscellaneous: Herpes infection (3% to 10%), infection (≤6%; grades 3/4: 2%), hypersensitivity (≤5%; grades 3/4: 1%), diaphoresis (≤5%), night sweats (≤5%)

<1%, postmarketing, and/or case reports: Acute renal failure, alopecia, anaphylaxis, bullous exanthema, cardiac failure, dermatitis, erythema, hemolysis, infusion reaction, injection/infusion site reaction (irritation, pruritus, swelling), malaise, mucosal inflammation, myelodysplastic syndrome, pulmonary fibrosis, sepsis, septic shock, skin necrosis, somnolence, toxic epidermal necrolysis, toxic skin reactions, tumor lysis syndrome

Oncology: Emetic PotentialLow (10% to 30%)

Metabolism/Transport Effects**Substrate** of CYP1A2; P-glycoprotein (ABCB1); BCRP (ABCG2)

Drug Interactions

CYP1A2 Inducers (Strong): May decrease the serum concentration of Bendamustine. Concentrations of active metabolites may be increased. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. *Risk C: Monitor therapy*

Monitoring ParametersCBC with differential (in clinical trials, WBC with differential and hemoglobin were monitored weekly; platelets were monitored with each cycle); serum creatinine (pretreatment); ALT, AST, and total bilirubin (pretreatment); monitor potassium and uric acid levels in patients at risk for tumor lysis syndrome

Nursing: Physical Assessment/MonitoringUse with caution in presence of hepatic or renal impairment. Assess all other pharmacological or herbal products patient may be taking for potential interactions or toxicity. See specific instructions for reconstitution and administration. Assess results of laboratory tests at baseline and periodically during therapy (myelosuppression may require therapy delay or dose reduction). Monitor therapeutic response and adverse effects regularly during therapy (infusion reactions, including toxic skin reactions, can occur with first or subsequent cycles and may require premedication or discontinuation). Teach patient or caregiver possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential (in clinical trials, WBC with differential and hemoglobin were monitored weekly; platelets were monitored with each cycle); serum creatinine (pretreatment); ALT, AST, and total bilirubin (pretreatment); monitor potassium and uric acid levels in patients at risk for tumor lysis syndrome

Patient EducationDo not take any new prescription or over-the-counter medications, or herbal products during therapy without consulting prescriber. This medication can only be administered by I.V. Report immediately any pain, burning, swelling at infusion site; sudden onset chest pain, respiratory difficulty, difficulty swallowing. It is important that you maintain adequate nutrition between treatments (small, frequent meals may help) and adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will be susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea, vomiting, or weight loss (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea (boiled milk, buttermilk, or yogurt may help). Report immediately chills, fever, skin rash, persistent unusual fatigue; unusual bruising/bleeding; signs of infection, or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Treanda®: 100 mg [contains mannitol 170 mg]

Generic AvailableNo

ManufacturerCephalon, Inc

Mechanism of ActionBendamustine is an alkylating agent (nitrogen mustard derivative) with a benzimidazole ring (purine analog) which demonstrates only partial cross-resistance (in vitro) with other alkylating agents. It leads to cell death via single and double strand DNA cross-linking. Bendamustine is active against quiescent and dividing cells. The primary cytotoxic activity is due to bendamustine (as compared to metabolites).

Pharmacodynamics/Kinetics

Distribution: V_{ss}: ~25 L

Protein binding: 94% to 96%

Metabolism: Hepatic, via CYP1A2 to active (minor) metabolites gamma-hydroxy bendamustine (M3) and N-desmethyl-bendamustine (M4)

Half-life elimination: Bendamustine: ~40 minutes; M3: ~3 hours; M4: ~30 minutes

Time to peak, serum: At end of infusion

Excretion: Feces (~90%); urine (1% to 10%)

Related Information

- Common Toxicity Criteria
- Management of Nausea and Vomiting
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue

Mental Health: Effects on Psychiatric TreatmentBone marrow suppression is common; use caution with clozapine, carbamazepine, and valproic acid. GI side effects are common; concomitant use with lithium, valproic acid, carbamazepine, and SSRIs may produce additive effects. Carbamazepine and phenobarbital may decease the levels/effects of bendamustine. Fluvoxamine may increase the levels/effects of bendamustine.

Index TermsBendamustine Hydrochloride; Cytostasan; SDX-105

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15845750]

Benserazide and Levodopa

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(ben SER a zide & lee voe DOE pa)

Canadian Brand NamesProlopa®

Pharmacologic CategoryAnti-Parkinson's Agent, Dopamine Agonist

Use: Labeled IndicationsTreatment of Parkinson's disease (except drug-induced Parkinsonism)

Dosing: Adults

Parkinson's disease: Oral: **Note:** Dosage expressed as levodopa/benserazide:

Initial: 100/25 mg 1-2 times/day, increase every 3-4 days until therapeutic effect; optimal dosage: 400/100 mg to 800/200 mg/day divided into 4-6 doses

Note: 200/50 mg used only when maintenance therapy is reached and not to exceed levodopa 1000-1200 mg/benserazide 250-300 mg per day

Patients previously on levodopa: Allow 12 hours or more to lapse between last dose of levodopa; start at 15% of previous levodopa dosage

Note: Dosages should be introduced gradually, individualized, and continued for 3-6 weeks before assessing benefit. Decrease dosage in patients with dystonia.

Dosing: ElderlyRefer to adult dosing.

Administration: OralCapsules should be swallowed whole; do not crush, chew, open, or dissolve in liquid.

Dietary ConsiderationsHigh-protein diets may decrease effect of levodopa. Food impairs or reduces the rate and extent of levodopa absorption (15% to 30%). Pyridoxine may inhibit levodopa's antiparkinsonian effects (monitor for reduced effect).

StorageStore at 15°C to 30°C (59°F to 86°F) in tightly closed, light-resistant container.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to benserazide, levodopa, sympathomimetics, or any component of the formulation; use of MAO inhibitors within prior 14 days; patients with clinical laboratory evidence of uncompensated cardiovascular, endocrine, renal, hepatic, hematologic, or pulmonary disease; patients with decompensated endocrine, renal, hepatic, cardiac disorders, psychiatric disorders, narrow-angle glaucoma, or closed-angle glaucoma; patients <25 years of age (due to possibility of skeletal abnormalities from benserazide); pregnancy or use in women of childbearing potential without adequate contraception

Warnings/Precautions

Concerns related to adverse effects:

- Increased growth hormone levels: May increase human growth hormone levels.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (MI, atrial, nodal, or ventricular arrhythmias); initiate in a monitored setting.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Glaucoma: Use with caution in patients with glaucoma; monitor IOP carefully in patients with wide-angle glaucoma.
- Melanoma: Use with caution in patients with melanoma or suspicious undiagnosed skin lesions.
- Peptic ulcer disease: Use with caution in patients with peptic ulcer disease.
- Psychotic disorders: Use with extreme caution in patients with psychotic disorders; observe patients closely for development of depression with concomitant suicidal tendencies.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Concurrent drug therapy issues:

- Current levodopa therapy: If patient is already receiving levodopa, discontinue levodopa at least 12 hours before starting benserazide/levodopa and begin at 15% of previous amount of levodopa.
- Phenothiazines: Use with caution in patients receiving phenothiazines.
- Reserpine: Use with caution in patients receiving reserpine.
- Tricyclic antidepressants (TCAs): Use with caution in patients receiving TCAs.

Other warnings/precautions:

- Abrupt withdrawal: Do not withdraw abruptly (may cause neuroleptic malignant syndrome).

- Appropriate use: Not indicated in management of intention tremor, Huntington's chorea, or drug-induced extrapyramidal symptoms. Administer in careful increments and observe closely for development of abnormal involuntary movements.

- Patient information: Patient must be instructed to resume normal activities gradually (rapid mobilization may increase risk of injury).

Pregnancy Risk FactorX (based on similar agents)

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Levodopa has caused visceral and skeletal malformations in animals and is therefore contraindicated in pregnant women and women of childbearing age without proper contraception.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsIt is not known if benserazide passes into breast milk, but breast-feeding is not recommended since occurrence of skeletal malformations in infants cannot be excluded.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, chest pain, edema, ECG changes (nonspecific), flushing, hypertension, orthostatic hypotension, phlebitis

Central nervous system: Agitation, ataxia, bruxism, confusion, convulsions, delusions, dementia, depression, euphoria, faintness, fatigue, fever, gait abnormalities, hallucinations, headache, insomnia, lethargy, malaise, nightmares, oculogyric crisis, paranoid ideation, psychotic episodes, sedation, suicidal tendencies/behavior, temporal disorientation, anxiety, trismus

Dermatological: Alopecia, pruritus, rash

Endocrine & metabolic: Libido increased, protein-bound iodine increased, uric acid increased, weight gain/loss

Gastrointestinal: Abdominal distress or pain, anorexia, constipation, diarrhea, duodenal ulcer, dyspepsia, epigastric pain, eructation, flatulence, GI bleeding, nausea, sialorrhea, taste alterations, vomiting

Genitourinary: Discoloration of urine, hematuria, nocturia, urinary frequency, urinary retention or incontinence

Hematologic: Positive Coombs' test

Hepatic: Alkaline phosphatase increased, bilirubin increased, LDH increased, transaminases increased

Neuromuscular & skeletal: Akinesia paradoxica, choreiform and involuntary movements, dystonia, end-of-dose akinesia, hand tremor, low back pain, muscle spasm and twitching, musculoskeletal pain, numbness, torticollis, weakness

Ocular: Activation of latent Horner's syndrome, blepharospasm, blurred vision, diplopia, diluted pupils

Renal: BUN increased

Respiratory: Bizarre breathing pattern, cough, hoarseness, postnasal drip

Miscellaneous: Discoloration of sweat; hiccups; lip, mouth, tongue tightness

Drug Interactions

Antipsychotics (Atypical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Antipsychotics (Typical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Levodopa. Only applies to oral iron preparations. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

MAO Inhibitors: Levodopa may enhance the adverse/toxic effect of MAO Inhibitors. Of particular concern is the development of hypertensive reactions when levodopa is used with nonselective MAOI. *Risk D: Consider therapy modification*

Methionine: May diminish the therapeutic effect of Levodopa. Probably only with large doses of methionine. Data was generated using 4.5gm daily. *Risk D: Consider therapy modification*

Metoclopramide: May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk C: Monitor therapy*

Phenytoin: May diminish the therapeutic effect of Levodopa. *Risk C: Monitor therapy*

Pyridoxine: May diminish the therapeutic effect of Levodopa. *Risk D: Consider therapy modification*

Sapropterin: May enhance the adverse/toxic effect of Levodopa. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: High-protein diets may decrease effect of levodopa; food impairs or reduces the rate and extent of levodopa absorption (15% to 30%). Iron salts (ferrous sulfate) may decrease the absorption of levodopa.

Test InteractionsCatecholamines, creatinine, uric acid, and glucose

Monitoring ParametersRegular assessment of cardiovascular, hepatic, hematopoietic, and renal function. If you have diabetes, monitor blood glucose.

Monitoring: Lab TestsRegular assessment of cardiovascular, hepatic, hematopoietic, and renal function. If you have diabetes, monitor blood glucose.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Capsule:

Prolopa® [CAN]:

50-12.5: Levodopa 50 mg and benserazide 12.5 mg [not available in the U.S.]

100-25: Levodopa 100 mg and benserazide 25 mg [not available in the U.S.]

200-50: Levodopa 200 mg and benserazide 50 mg [not available in the U.S.]

Generic AvailableNo

Mechanism of ActionLevodopa appears to correct the akinesia of Parkinson's disease by formation of dopamine at nigrostriatal dopaminergic sites that remain functional. Benserazide inhibits peripheral decarboxylation of levodopa without significantly affecting its metabolism in brain.

Pharmacodynamics/Kinetics

Absorption: 66% to 74% from GI tract

Distribution: 57 L

Half-life elimination: 1.5 hours

Time to peak serum concentration: 1.5 hours

Excretion: 53% to 64% in urine

Pharmacotherapy PearlsNot available in U.S.
“On-off” (a clinical syndrome characterized by sudden periods of drug activity/inactivity) can be managed by giving smaller, more frequent doses or adding a dopamine agonist or selegiline. Protein in the diet should be distributed throughout the day to avoid fluctuations in levodopa absorption.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSevere psychiatric adverse effects (including depression, suicidal ideation, and suicide attempt) may occur. May also cause agitation, ataxia, confusion, convulsions, delusions, dementia, euphoria, fatigue, hallucinations, insomnia, nightmares, paranoid ideation, psychotic episodes, or sedation.

Mental Health: Effects on Psychiatric TreatmentContraindicated in patients with a psychiatric disorder as well as with or within 14 days of MAO inhibitor therapy. Benserazide and levodopa is not approved for tremor, Huntington's chorea, or drug-induced extrapyramidal symptoms. Use with caution in patients receiving a phenothiazine or a TCA. Do not stop abruptly; may lead to neuroleptic malignant syndrome.

Index TermsLevodopa and Benserazide

References

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International Brand NamesLevazide (ID); Levopar (DE, ID); Levopar Plus (IL); Madopar (AR, AU, CH, CL, CO, CZ, DE, DK, EE, ES, FI, GB, GR, HK, HN, ID, IE, IN, KP, MX, NL, NO, PE, PH, PK, PT, TH, TW, VE); Madopark (SE); Modopar (FR); Prolopa (BE, BR, CN, PY, UY); Seler (PY); Tonotil (UY); Vopar (TH)

Pronunciation(BEN toe kwa tam)
U.S. Brand NamesIvyBlock® [OTC]
Pharmacologic CategoryTopical Skin Product
Use: Labeled IndicationsSkin protectant for the prevention of allergic contact dermatitis to poison oak, ivy, and sumac
Dosing: AdultsPrevention of contact dermatitis: Topical: Apply to skin 15 minutes prior to potential exposure to poison ivy, poison oak, or poison sumac, and reapply every 4 hours
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren >6 years: Refer to adult dosing.
ContraindicationsHypersensitivity to bentoquatam or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Allergic-type responses: Use with caution in patients with history of allergic-type responses to medications (especially topical formulations).

Disease-related concerns:

- Cutaneous conditions: Use with caution in patients with open wounds, psoriatic lesions, or other cutaneous conditions.
- Poison oak/ivy/sumac: Use with caution in patients who are postexposure to poison oak, ivy, or sumac (lack of efficacy).

Adverse Reactions<1%: Erythema
Drug InteractionsThere are no known significant interactions.
Monitoring ParametersSigns and symptoms of exposure to poison oak, ivy, or sumac (rash, swelling, blisters)
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Lotion:

IvyBlock®: 5% (120 mL) [contains alcohol 25% and benzyl alcohol]

Generic AvailableNo
Mechanism of ActionAn organoclay substance which is capable of absorbing or binding to urushiol, the active principle in poison oak, ivy, and sumac. Bentoquatam serves as a barrier, blocking urushiol skin contact/absorption.
Pharmacodynamics/KineticsAbsorption: Has not been studied
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsQuaternium-18 Bentonite

Benzalkonium Chloride and Isopropyl Alcohol

Jump To Field (Select Field Name)

Pronunciation(benz al KOE nee um KLOR ide & eye so PRO pil AL koe hol)
U.S. Brand NamesViroxyn® [OTC]
Pharmacologic CategoryAntiseptic, Topical
Use: DentalTopical: Germicidal for the treatment of cold sores/fever blisters
Dosing: AdultsTopical: One single application treatment to affected area. Secondary events (new viral load in the initial lesion, which may occur 12-72 hours after initial symptoms) or additional sore presentations will require additional treatment with a new vial. See Administration information for application instructions.

Manufacturer states medication should not be used >3 times/day; however, instructions indicate that a single application is generally effective if instructions are followed.

Dosing: ElderlyRefer to adult dosing.
Administration: OtherUse this product according to the following directions from the manufacturer:

1) Prior to treatment, clean area to be treated of all other preparations (ointments, treatments, lipstick). Do not use soap or other cleansers. A dry wipe may be sufficient, or you may use water or alcohol if necessary.

2) Remove cap from vial and replace on the other end over the clear plastic tube. Hold vial between thumb and index finger, applicator end up. Pinch vial in the center at top of cap until the inner ampul of medication breaks.

3) Hold white applicator down and allow medication to saturate the swab. If necessary, pinch vial gently until a drop of medication just appears.

4) Place the applicator against the area of skin to be treated so that the tip of the applicator is held flat against the skin. The key is to massage medication into the sore and the surrounding area by rubbing. Do not rub so hard that you cause damage to the skin. For best results, the patient should massage drug into the sore by rubbing. The rubbing should proceed for about 10 minutes or until all the drug has been massaged into the sore. The application may sting. This is normal and should subside quickly. For best results, medication must penetrate the subepidermal layers of the skin to site of infection. The ingredients facilitate penetration, but mechanical action is critical. Simply dabbing the drug onto the sore is not likely to give best results.

5) If treating at prodrome (tingling sensation before lesion erupts), a more vigorous rubbing is easily tolerated and gives best results. If the lesion has progressed to vesicle or ulcerated lesion, the patient may prefer to rub less vigorously but for a longer time period.

6) Keep applicator saturated at all times. If necessary, pause and hold vial so as to allow medication to flow into applicator. When finished recap vial. Dispose of immediately. Do not disassemble. Store at room temperature. Flammable; do not expose to high heat or flame. Keep out of reach of children.

Dietary ConsiderationsAvoid citric acid-containing beverages (eg, lemonade or orange juice) for at least 1 hour following application.
StorageStore at room temperature. Flammable; do not expose to high heat or flame.
ContraindicationsHypersensitivity to benzalkonium chloride, isopropyl alcohol, or any component of the formulation
Warnings/Precautions

Special populations:

- Pediatrics: Avoid use in children <2 years of age.

- Pregnancy: Avoid use in pregnant or lactating women.

Other warnings/precautions:

- Appropriate use: For topical use only; ingestion may lead to gastric irritation or distress. Avoid contact with eyes; flush with eye bath if inadvertent contact occurs. Avoid use of anionic cleansers or acidic products for at least 1 hour following application (active ingredient will be neutralized). Avoid the use of soap, toothpaste, cleansers, or drinks containing citric acid (including lemonade and orange juice). Should not be used >3 times/day.

- Flammable: Formulation in isopropyl alcohol is flammable; avoid use near sparks, flames, or high temperatures.

Adverse ReactionsFrequency not defined

Ocular: Irritation (following inadvertent contact)

Respiratory: Vapors may cause cough, dyspnea

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, topical: Benzalkonium 0.13% in isopropyl alcohol [kit includes 3 single-dose applicators]

Generic AvailableNo

Mechanism of ActionGermicidal due to disruption of the viral capsid coat by the quaternary ammonium benzalkonium chloride ingredient.

Dental Health Professional ConsiderationsUse this product according to the following directions from the manufacturer. 1) Prior to treatment, clean area to be treated of all other preparations (ointments, treatments, lipstick). Do not use soap or other cleansers. A dry wipe may be sufficient, or you may use water or alcohol if necessary. 2) Remove cap from vial and replace on the other end over the clear plastic tube. Hold vial between thumb and index finger, applicator end up. Pinch vial in the center at top of cap until the inner ampul of medication breaks. 3) Hold white applicator down and allow medication to saturate the swab. If necessary, pinch vial gently until a drop of medication just appears. 4) Place the applicator against the area of skin to be treated so that the tip of the applicator is held flat against the skin. The key is to massage medication into the sore and the surrounding area by rubbing. Do not rub so hard that you cause damage to the skin. For best results, the patient should massage drug into the sore by rubbing. The rubbing should proceed for about 10 minutes or until all the drug has been massaged into the sore. The application may sting. This is normal and should subside quickly. For best results, medication must penetrate the subepidermal layers of the skin to site of infection. The ingredients facilitate penetration, but mechanical action is critical. Simply dabbing the drug onto the sore is not likely to give best results. 5) If treating at prodrome (tingling sensation before lesion erupts), a more vigorous rubbing is easily tolerated and gives best results. If the lesion has progressed to vesicle or ulcerated lesion, the patient may prefer to rub less vigorously but for a longer time period. 6) Keep applicator saturated at all times. If necessary, pause and hold vial so as to allow medication to flow into applicator. When finished recap vial. Dispose of immediately. Do not disassemble. Store at room temperature. Flammable; do not expose to high heat or flame. Keep out of reach of children.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsIsopropyl Alcohol Tincture of Benzylkonium Chloride

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Benzalkonium Chloride

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Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Benza® may be confused with Benzac®

Pronunciation(benz al KOE nee um KLOR ide)

U.S. Brand Names3M™ Cavilon™ Skin Cleanser [OTC] [DSC]; HandClens® [OTC]; Pedi-Pro®; Pronto® Plus Lice Egg Remover Kit [OTC]; Zephiran® [OTC]

Pharmacologic CategoryAntibiotic, Topical

Use: Labeled IndicationsSurface antiseptic and germicidal preservative

Use: DentalSurface antiseptic and germicidal preservative

Dosing: AdultsAntiseptic: Topical: Thoroughly rinse anionic detergents and soaps from the skin or other areas prior to use of solutions because they reduce the antibacterial activity of BAC. To protect metal instruments stored in BAC solution, add crushed Anti-Rust Tablets, 4 tablets/quart, to antiseptic solution, change solution at least once weekly. Not to be used for storage of aluminum or zinc instruments, instruments with lenses fastened by cement, lacquered catheters, or some synthetic rubber goods.

Dosing: ElderlyRefer to adult dosing.

Compatibility**Incompatible** with BAC solutions: Iodine, silver nitrate, fluorescein, nitrates, peroxide, lanolin, potassium permanganate, aluminum, caramel, kaolin, pine oil, zinc sulfate, zinc oxide, and yellow mercuric oxide.

ContraindicationsHypersensitivity to benzalkonium or any component of the formulation

Pregnancy Risk FactorC

Adverse Reactions1% to 10%: Hypersensitivity

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Lotion, topical [foam]:

HandClens®: 0.13% (50 mL, 240 mL, 1800 mL)

Lotion, topical [spray]:

HandClens®: 0.13% (15 mL)

Powder, topical:

Pedi-Pro®: 1% (60 g)

Solution, topical:

Pronto® Plus Lice Egg Remover Kit: 0.1% (60 mL)

Zephiran®: 1:750 (240 mL, 3840 mL) [aqueous]

Solution, topical [spray]:

3M™ Cavilon™ Skin Cleanser: 0.11% (240 mL) [DSC]

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBAC

International Brand NamesAgena (IT); Ajatin (CZ); Alfa C (IT); Armil (ES); Armil Concentrado (ES); Asepsol (HR); Baktonium (DE); Benzalc (ES); Benzalconio Cloruro (IT); Benzalcream (AR); Benzaltex (CH); Bradosol (GB); Callusolve (GB); Capitol (GB); Cedium (BE, LU); Citrosil (IT); Colli (IT); Collirium Geymonat (IT); Contusil (IT); Crema Contracepti Lanzas (ES); Dimill (IT); Disintyl (IT); Display (IT); Disteril (IT); Flexoygne (FR); Geyderm (IT); Hamamilla (IT); Herbe (IT); Inhivirus (AR); Ionax (GB, IE); Ionax Scrub (GB); Iridina Light (IT); Lacribase (IT); Laudamonium (DE); Lozione Vittoria Ottolenghi (IT); Lysoform Killavon (DE); Mini Ovulo Lanzas (ES); Nasimild (AT); Neo-Desogen (IT); Neomedil (IT); Novamina (ES); Oftan (FI); Otazul Collirio (IT); Pharmatex (AR, BE, FR, LU, PT); Pupilla Light (IT); Rashfree (IN); Rheila Stringiet N (DE, LU); Roccal (GB, IE); Sagrotan Med (DE); Sangen (IT); Saquat (IT); Sguardi (IT); Sirigen (IT); Sparaplaie (FR); Steramina (IT); Steramina G (IT); Sterilix (IT); Stilla Delicato (IT); Video-light (IT)

Benzocaine, Butamben, and Tetracaine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(BEN zoe kane, byoo TAM ben, & TET ra kane)
U.S. Brand NamesCetacaine®; Exactacain™
Pharmacologic CategoryLocal Anesthetic
Use: Labeled IndicationsTopical anesthetic to control pain in surgical or endoscopic procedures; anesthetic for accessible mucous membranes except for the eyes
Use: DentalTopical anesthetic for accessible mucous membranes
Dosing: AdultsAnesthesia: Topical:

Cetacaine®:

Aerosol: Apply for ≤1 second; use of sprays >2 seconds is contraindicated

Gel: Apply ~1/2 inch (13 mm) x 3/16 inch (5 mm); application of >1 inch (26 cm) x 3/16 inch (5 mm) is contraindicated

Liquid: Apply 6-7 drops (0.2 mL); application of >12-14 drops (0.4 mL) is contraindicated

Exactacain™: 3 metered sprays (use of >6 metered sprays is contraindicated)

Dosing: ElderlyDose reduction is suggested; refer to adult dosing.
Dosing: PediatricDose has not been established; dose reduction is suggested
Administration: TopicalAvoid application to large areas of broken skin, especially in children. When possible, apply to clean, dry area, however, tissue need not be dried prior to application. When administering a spray formulation, the number of sprays administered and the length of each spray should be monitored and recorded.

Aerosol (Exactacain™): Insert disposable applicator into the spray nozzle on can. Apply directly to the site where pain or gag control is desired for procedure (ear, nose, mouth, pharynx, larynx, trachea, bronchi, esophagus, vagina, or rectum). Discard applicator after each use.

Gel (Cetacaine®): Spread thinly and evenly over application area.

Liquid (Cetacaine®): Apply with cotton applicator or directly onto tissue; do not hold applicator in position for prolonged periods of time.

StorageExactacain™: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Do not store near (or expose to) heat, open flame, or temperatures >120°F. Do not puncture container.
ContraindicationsHypersensitivity to benzocaine, butamben, tetracaine, or any component of the formulation; ophthalmic use; cholinesterase deficiencies; large areas of denuded or inflamed tissue; administration in excess of product labeling
Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Methemoglobinemia: Has been reported following topical benzocaine use (rare), particularly with higher concentration (14% to 20%) spray formulations applied to the mouth or mucous membranes. The classical clinical finding of methemoglobinemia is chocolate brown-colored arterial blood. However, suspected cases should be confirmed by co-oximetry, which yields a direct and accurate measure of methemoglobin levels. Standard pulse oximetry readings or arterial blood gas values are not reliable. Clinically-significant methemoglobinemia requires immediate treatment. Use caution with breathing problems (asthma, bronchitis, emphysema, in smokers), inflamed/damaged mucosa, heart disease, children <6 months of age, and hemoglobin or enzyme abnormalities (glucose-6-phosphate dehydrogenase deficiency, hemoglobin-M disease, NADH-methemoglobin reductase deficiency, pyruvate-kinase deficiency). Alternatives to benzocaine sprays, such as topical lidocaine preparations, should be considered for patients at higher risk of this reaction.

Special populations:

- Acutely ill patients: Use with caution in acutely ill patients; dose adjustment is suggested.

- Debilitated patients: Use with caution in debilitated patients; dose adjustment is suggested.

- Elderly: Use with caution in the elderly; dose adjustment is suggested.

- Pediatrics: Use with caution in very young patients; dose adjustment is suggested.

Other warnings/precautions:

- Administration: For topical use only. Do not use under dentures or cotton rolls; retention of active ingredients may cause escharotic effect.

Pregnancy ConsiderationsSafety has not been established; use is not recommended during early pregnancy unless the potential benefits outweigh the risks.
Adverse ReactionsFrequency not defined. Also see individual monographs for Benzocaine and Tetracaine.

Dermatologic: Contact dermatitis (eg, erythema, pruritus, vesiculation, oozing); dehydration of the epithelium; escharotic effect

Miscellaneous: Hypersensitivity/anaphylaxis reaction (rare)

Drug InteractionsThere are no known significant interactions.
Monitoring Parameters

Monitor patients for signs and symptoms of methemoglobinemia such as pallor, cyanosis, nausea, muscle weakness, dizziness, confusion, agitation, dyspnea and tachycardia. The classical clinical finding of methemoglobinemia is chocolate brown-colored arterial blood. However, suspected cases should be confirmed by co-oximetry, which yields a direct and accurate measure of methemoglobin levels. Standard pulse oximetry readings or arterial blood gas values are not reliable. Clinically significant methemoglobinemia requires immediate treatment.

Nursing: Physical Assessment/MonitoringSee individual agents for Benzocaine and Tetracaine.
Monitoring: Lab TestsThe classical clinical finding of methemoglobinemia is chocolate brown-colored arterial blood. However, suspected cases should be confirmed by co-oximetry, which yields a direct and accurate measure of methemoglobin levels. Standard pulse oximetry readings or arterial blood gas values are not reliable. Clinically significant methemoglobinemia requires immediate treatment.
Patient EducationSee individual agents for Benzocaine and Tetracaine.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol, topical [spray]:

> Cetacaine®: Benzocaine 14%, butamben 2%, and tetracaine hydrochloride 2% (56 g) [delivers benzocaine 28 mg, butamben 4 mg, and tetracaine hydrochloride 4 mg per second; contains benzalkonium chloride and CFCs; packaged with cannula]
>
> Exactacain™: Benzocaine 14%, butamben 2%, and tetracaine hydrochloride 2% (60 g) [delivers benzocaine 9.3 mg, butamben 1.3 mg, and tetracaine 1.3 mg per metered spray; contains benzalkonium chloride; cherry flavor; packaged with 100 disposable applicators]

Gel, topical:

> Cetacaine®: Benzocaine 14%, butamben 2%, and tetracaine hydrochloride 2% (29 g) [provides benzocaine 28 mg, butamben 4 mg and tetracaine hydrochloride 4 mg per 0.5 inch (13 mm) x 3/16 inch (5 mm) application; contains benzalkonium chloride]

Liquid, topical:

> Cetacaine®: Benzocaine 14%, butamben 2%, and tetracaine hydrochloride 2% (56 g) [provides benzocaine 28 mg, butamben 4 mg, and tetracaine hydrochloride 4 mg per 6-7 drops (0.2 mL); contains benzalkonium chloride]

Generic AvailableNo
Mechanism of ActionReversible blockage of initiation and conduction of nerve impulses by deceasing the neuronal membrane's permeability to sodium ions
Pharmacodynamics/KineticsAlso see individual monographs for Benzocaine and Tetracaine.

Onset of action: ~30 seconds

Duration: 30-60 minutes

Metabolism: Plasma via hydrolysis by cholinesterase to inactive metabolites

Excretion: Urine (as inactive metabolites)

Related Information

- Benzocaine
- Tetracaine

Dental Health Professional ConsiderationsManufacturer indication for use is suppression of gag reflex for gastroenterological procedures.

Health Canada has issued a reminder to healthcare professionals that benzocaine sprays must be used judiciously to minimize the risk of methemoglobinemia. Almost all reported cases have been associated with higher concentration (14% to 20% benzocaine) spray products used in the mouth and on other mucous membranes. Alternatives to benzocaine sprays, such as topical lidocaine preparations, should be considered for patients at higher risk of this reaction.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: A patient history of allergy to ester-type local anesthetics contraindicates the use of this product (see Dental Comment).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsBenzocaine, Butamben, and Tetracaine Hydrochloride; Benzocaine, Butyl Aminobenzoate, and Tetracaine; Butamben, Tetracaine, and Benzocaine; Tetracaine, Benzocaine, and Butamben

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Benzocaine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Orabase®-B may be confused with Orinase®

Pronunciation(BEN zoe kane)

U.S. Brand NamesAmericaine® Hemorrhoidal [OTC]; Anbesol® Baby [OTC]; Anbesol® Cold Sore Therapy [OTC]; Anbesol® Jr. [OTC]; Anbesol® Maximum Strength [OTC]; Anbesol® [OTC]; Benzodent® [OTC]; Bi-Zets; Boil-Ease® Pain Relieving; Cepacol® Sore Throat [OTC]; Chiggerex® Plus; Chiggerex® [OTC]; Chiggertox® [OTC]; Cylex® [OTC]; Dent's Extra Strength Toothache [OTC]; Dentapaine [OTC]; Dermoplast® Antibacterial [OTC]; Dermoplast® Pain Relieving [OTC]; Detane® [OTC]; Foille® [OTC]; HDA® Toothache [OTC]; Hurricaine® [OTC]; Ivy-Rid® [OTC]; Kank-A® Soft Brush™ [OTC]; Lanacane® Maximum Strength [OTC]; Lanacane® [OTC]; Little Teethers® [OTC]; Mycinettes® [OTC]; Orabase® with Benzocaine [OTC]; Orajel PM® Maximum Strength [OTC]; Orajel® Baby Daytime and Nighttime [OTC]; Orajel® Baby Teething Nighttime [OTC]; Orajel® Baby Teething [OTC]; Orajel® Denture Plus [OTC]; Orajel® Maximum Strength [OTC]; Orajel® Medicated Toothache [OTC]; Orajel® Mouth Sore [OTC]; Orajel® Multi-Action Cold Sore [OTC]; Orajel® Ultra Mouth Sore [OTC]; Outgro® [OTC]; Red Cross™ Canker Sore [OTC]; Rid-A-Pain Dental [OTC]; Sepasoothe®; Skeeter Stik [OTC]; Sting-Kill [OTC]; Tanac® [OTC]; Thorets [OTC]; Trocaine® [OTC]; Zilactin Toothache and Gum Pain® [OTC]; Zilactin®-B [OTC]

Canadian Brand NamesAnbesol® Baby; Zilactin Baby®; Zilactin-B®

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsTemporary relief of pain associated with pruritic dermatosis, pruritus, minor burns, acute congestive, bee stings, and insect bites; mouth and gum irritations (toothache, minor sore throat pain, canker sores, dentures, orthodontia, teething, mucositis, stomatitis); sunburn; hemorrhoids; anesthetic lubricant for passage of catheters and endoscopic tubes

Use: DentalEster-type topical local anesthetic for temporary relief of pain associated with toothache, minor sore throat pain, and canker sore

Dosing: Adults**Note:** These are general dosing guidelines; Refer to specific product labeling for dosing instructions.

Bee stings, insect bites, minor burns, sunburn: Topical 5% to 20%: Apply to affected area 3-4 times a day as needed. In cases of bee stings, remove stinger before treatment.

Lubricant for passage of catheters and instruments: Topical 20%: Apply evenly to exterior of instrument prior to use.

Mouth and gum irritation: Topical (oral) 10% to 20%: Apply thin layer to affected area up to 4 times daily

Sore throat: Oral: Allow 1 lozenge (10-15 mg) to dissolve slowly in mouth; may repeat every 2 hours as needed

Hemorrhoids: Rectal 5% to 20%: Apply externally to affected area up to 6 times daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** These are general dosing guidelines; refer to specific product labeling for dosing instructions.

Teething pain: Children ≥4 months: Topical (oral): 7.5% to 10%: Apply to affected gum area up to 4 times daily

Bee stings, insect bites, minor burns, sunburn: Topical: Children ≥2 years: Refer to adult dosing.

Lubricant for passage of catheters and instruments: Topical: Children ≥2 years: Refer to adult dosing.

Mouth and gum irritation: Topical (oral) 10% to 20%: Children ≥2 years: Refer to adult dosing.

Sore throat: Oral: Children ≥5 years: Refer to adult dosing.

Hemorrhoids: Rectal 5% to 20%: Children ≥12 years: Refer to adult dosing.

Administration: TopicalAvoid application to large areas of broken skin, especially in children. When possible, apply to clean, dry area. When administering a spray formulation, the number of sprays administered and the length of each spray should be monitored and recorded.

ContraindicationsHypersensitivity to benzocaine, other ester-type local anesthetics, or any component of the formulation; secondary bacterial infection of area; ophthalmic use

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Methemoglobinemia: Has been reported following topical use (rare), particularly with higher concentration (14% to 20%) spray formulations applied to the mouth or mucous membranes. When applied as a spray to the mouth or throat, multiple sprays (or sprays of longer than indicated duration) are not recommended. Use caution with breathing problems (asthma, bronchitis, emphysema, in smokers), inflamed/damaged mucosa, heart disease, children <6 months of age, and hemoglobin or enzyme abnormalities (glucose-6-phosphate dehydrogenase deficiency, hemoglobin-M disease, NADH-methemoglobin reductase deficiency, pyruvate-kinase deficiency). Alternatives to benzocaine sprays, such as topical lidocaine preparations, should be considered for patients at higher risk of this reaction. The classical clinical finding of methemoglobinemia is chocolate brown-colored arterial blood. However, suspected cases should be confirmed by co-oximetry, which yields a direct and accurate measure of methemoglobin levels. Standard pulse oximetry readings or arterial blood gas values are not reliable. Clinically significant methemoglobinemia requires immediate treatment.

Other warnings/precautions:

- Self-medication (OTC use): When used for self-medication, notify healthcare provider if condition worsens or does not improve within 7 days, or if swelling, rash, or fever develops. Do not use on open wounds. Avoid contact with the eyes.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Hematologic: Methemoglobinemia

Local: Burning, contact dermatitis, edema, erythema, pruritus, rash, stinging, tenderness, urticaria

Miscellaneous: Hypersensitivity

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersMonitor patients for signs and symptoms of methemoglobinemia such as pallor, cyanosis, nausea, muscle weakness, dizziness, confusion, agitation, dyspnea and tachycardia. The classical clinical finding of methemoglobinemia is chocolate brown-colored arterial blood. However, suspected cases should be confirmed by co-oximetry, which yields a direct and accurate measure of methemoglobin levels. Standard pulse oximetry readings or arterial blood gas values are not reliable. Clinically significant methemoglobinemia requires immediate treatment.
Nursing: Physical Assessment/MonitoringMonitor for effectiveness of application and adverse reactions. Monitor for cyanosis, dyspnea, weakness, or tachycardia. This could indicate a life-threatening situation. **Oral:** Use caution to prevent gagging or choking and avoid food or drink for 1 hour. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.
Monitoring: Lab TestsThe classical clinical finding of methemoglobinemia is chocolate brown-colored arterial blood. However, suspected cases should be confirmed by co-oximetry, which yields a direct and accurate measure of methemoglobin levels. Standard pulse oximetry readings or arterial blood gas values are not reliable. Clinically significant methemoglobinemia requires immediate treatment.
Patient EducationUse as directed; do not overuse. Use least amount possible to obtain desired effect. Do not apply when infections are present and do not apply to large areas of broken skin. Do not eat or drink for 1 hour following oral application. Discontinue application and report if swelling of mouth, lips, tongue, or throat occurs; or if skin irritation occurs at application site. When using as a self-medication (OTC), notify prescriber if condition worsens or does not improve within 7 days or if swelling, rash, or fever develops. Report cyanosis (turning blue in color), weakness, problems breathing, or rapid heartbeat immediately. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol, oral spray:

Hurricaine®: 20% (60 mL) [dye free; cherry flavor]

Aerosol, topical spray:

Dermoplast® Antibacterial: 20% (83 mL) [contains aloe vera, benzethonium chloride, menthol]

Dermoplast® Pain Relieving: 20% (60 mL, 83 mL) [contains menthol]

Foille®: 5% (92 g) [contains chloroxylenol 0.63% and corn oil]

Ivy-Rid®: 2% (83 mL)

Lanacane® Maximum Strength: 20% (120 mL) [contains ethanol 36%]

Combination package (Orajel® Baby Daytime and Nighttime):

Gel, oral [Daytime Regular Formula]: 7.5% (5.3 g)

Gel, oral [Nighttime Formula]: 10% (5.3 g)

Cream, oral:

Benzodent®: 20% (7.5 g, 30 g)

Orajel PM® Maximum Strength: 20% (5.3 g, 7 g) [contains menthol]

Cream, topical:

Lanacane®: 6% (30 g, 60 g)

Lanacane® Maximum Strength: 20% (30 g)

Gel, oral:

Anbesol®: 10% (7.5 g) [contains benzyl alcohol; cool mint flavor]

Anbesol® Baby: 7.5% (7.5 g) [contains benzoic acid; grape flavor]

Anbesol® Jr.: 10% (7 g) [contains benzyl alcohol; bubble gum flavor]

Anbesol® Maximum Strength: 20% (7.5 g, 10 g) [contains benzyl alcohol]

Dentapaine: 20% (11 g) [contains clove oil]

HDA® Toothache: 6.5% (15 mL) [contains benzyl alcohol]

Hurricaine®: 20% (5 g) [dye free; wild cherry flavor]; (30 g) [dye free; mint, pina colada, watermelon, and wild cherry flavors]

Kank-A® Soft Brush™: 20% (2 mL) [packaged in applicator with brush tip]

Little Teethers®: 7.5% (9.4 g) [cherry flavor]

Orabase® with Benzocaine®: 20% (7 g) [contains ethanol 48%; mild mint flavor]

Orajel®: 10% (5.3 g, 7 g, 9.4 g)

Orajel® Baby Teething: 7.5% (9.4 g, 11.9 g) [cherry flavor]

Orajel® Baby Teething Nighttime: 10% (5.3 g)

Orajel® Denture Plus: 15% (9 g) [contains menthol 2%, ethanol 66.7%]

Orajel® Maximum Strength: 20% (5.3 g, 7 g, 9.4 g, 11.9 g)

Orajel® Mouth Sore: 20% (5.3 g, 9.4 g, 11.9 g) [contains allantoin, benzalkonium chloride 0.02%, zinc chloride 0.1%]

Orajel® Multi-Action Cold Sore: 20% (9.4 g) [contains allantoin 0.5%, camphor 3%, dimethicone 2%]

Orajel® Ultra Mouth Sore: 15% (9.4 g) [contains ethanol 66.7%, menthol 2%]

Zilactin®-B: 10% (7.5 g)

Gel, topical:

Detane®: 7.5% (15 g)

Liquid, oral:

Anbesol®: 10% (9 mL) [cool mint flavor; contains benzyl alcohol]

Anbesol® Maximum Strength: 20% (9 mL) [contains benzyl alcohol]

Hurricaine®: 20% (30 mL) [pina colada and wild cherry flavors; dye free]

Orajel® Baby Teething: 7.5% (13 mL) [very berry flavor]

Orajel® Maximum Strength: 20% (13 mL) [contains ethanol 44%, tartrazine]

Tanac®: 10% (13 mL) [contains benzalkonium chloride]

Liquid, oral [drops]:

Rid-A-Pain Dental: 6.3% (30 mL) [contains ethanol 70%]

Liquid, topical:

Chiggertox®: 2% (30 mL)

Outgro®: 20% (9 mL)

Skeeter Stik: 5% (14 mL) [contains menthol]

Lozenge: 6 mg (18s) [contains menthol]; 15 mg (10s)

Bi-Zets: 15 mg (10s)

Cepacol® Sore Throat: 15 mg (18s) [contains cetylpyridinium, menthol; cherry, citrus, and honey lemon flavors]

Cepacol® Sore Throat: 15 mg (16s) [sugar free; contains cetylpyridinium, menthol; cherry and menthol flavors]

Cylex®: 15 mg (12s) [sugar free; contains cetylpyridinium chloride 5 mg; cherry flavor]

Mycinettes®: 15 mg (12s) [sugar free; contains sodium 9 mg; cherry or regular flavor]

Sepasoothe®: 10 mg (6s, 24s, 100s, 250s, 500s) [sugar free; contains cetylpyridium 0.5 mg/lozenge; wild cherry flavor]

Thorets: 18 mg (300s) [sugar free]

Trocaine®: 10 mg (50s, 300s)

Ointment, oral:

Anbesol® Cold Sore Therapy: 20% (7.1 g) [contains benzyl alcohol, allantoin, aloe, camphor, menthol, vitamin E]

Red Cross™ Canker Sore: 20% (7.5 g) [contains coconut oil]

Ointment, rectal:

Americaine® Hemorrhoidal: 20% (30 g)

Ointment, topical:

Boil-Ease® Pain Relieving: 20% (30 g)

Chiggerex®: 2% (50 g) [contains aloe vera] [DSC]

Chiggerex® Plus: 6% (50 g) [contains aloe]

Foille®: 5% (3.5 g, 14 g, 28 g) [contains chloroxylenol 0.1%, benzyl alcohol; corn oil base]

Pads, topical:

Sting-Kill: 20% (8s) [contains menthol and tartrazine]

Paste, oral:

Orabase® with Benzocaine: 20% (6 g)

Swabs, oral:

Hurricaine®: 20% (6s, 100s) [dye free; wild cherry flavor]

Orajel® Baby Teething: 7.5% (12s) [berry flavor]

Orajel® Medicated Mouth Sore, Orajel® Medicated Toothache: 20% (8s, 12s) [contains tartrazine]

Zilactin® Toothache and Gum Pain: 20% (8s) [grape flavor]

Swabs, topical:

Boil-Ease® Pain Relieving: 20% (12s) [contains tartrazine]

Sting-Kill: 20% (5s) [contains menthol and tartrazine]

Wax, oral:

Dent's Extra Strength Toothache Gum: 20% (1 g)

Generic AvailableYes: Lozenge

Pricing: U.S. (www.drugstore.com)

Gel (Americaine Anesthetic)

20% (28): $22.99

Solution (Oticaine Otic)

20% (15): $18.99

Mechanism of ActionEster local anesthetic blocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction

Pharmacodynamics/Kinetics

Absorption: Topical: Poor to intact skin; well absorbed from mucous membranes and traumatized skin

Metabolism: Hepatic (to a lesser extent) and plasma via hydrolysis by cholinesterase

Excretion: Urine (as metabolites)

Dental Health Professional ConsiderationsHealth Canada has issued a reminder to healthcare professionals that benzocaine sprays must be used judiciously to minimize the risk of methemoglobinemia. Almost all reported cases have been associated with higher concentration (14% to 20% benzocaine) spray products used in the mouth and on other mucous membranes. Alternatives to benzocaine sprays, such as topical lidocaine preparations, should be considered for patients at higher risk of this reaction.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsEthyl Aminobenzoate

References

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Guertler AT and Pearce WA, “A Prospective Evaluation of Benzocaine-Associated Methemoglobinemia in Human Beings,” *Ann Emerg Med*, 1994, 24(4):628-30.

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Rynn KO, Jahns BE, and Sabbun R, “Acute Myocardial Infarction (AMI) Secondary to Benzocaine-Induced Methemoglobinemia,” *Clin Toxicol*, 1995, 33(5):495.

Shua-Haim JR and Gross JS, “Methemoglobinemia Toxicity From Topical Benzocaine Spray,” *J Am Geriatr Soc*, 1995, 43(5):590.

Stein JM and Warfield CA, “Local Anesthetics: Principles of Safe Use,” *Hosp Pract (Off Ed)*, 1983, 18(5):73-8.

International Brand NamesAAA Spray (GB); Anaestherit (AT); Anaesthesin (DE); Auralyt (MX); Baby Orajel (PL); Babydent (CZ); Claudemor (PT); Dentispray (ES, PL); Dermopur (PL); Dolodent (DK); Etylu Aminobenzoesan (PL); Gartricin (ES); Gengivarium (IT); Graneodin-B (MX); Hurricaine (ES, LU); Lanacane (ES); Lodoc (AR); Nani Pre Dental (ES); Octicaina (CO); Orajel (CH, PL); Oramed Gel (IL); Otisyn (FI); Topicaine (AU)

Benzoin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(BEN zoin)
U.S. Brand NamesBenz-Protect Swabs™ [OTC]; Sprayzoin™ [OTC]
Pharmacologic CategoryAntibiotic, Topical; Topical Skin Product
Use: Labeled IndicationsProtective application for irritations of the skin; sometimes used in boiling water as steam inhalants for its expectorant and soothing action
Dosing: AdultsSkin protectant: Topical: Apply 1-2 times/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tincture: Benzoin USP (60 mL); Benzoin Compound USP (30 mL, 60 mL, 120 mL, 480 mL)

Tincture [swab]:

Benz-Protect Swabs™: Benzoin Compound USP (50s)

Tincture [spray]: Benzoin USP (120 mL)

Sprayzoin™: Benzoin Compound USP (120 mL)

Generic AvailableYes
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsGum Benjamin

Benzonatate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(ben ZOE na tate)
U.S. Brand NamesTessalon®
Canadian Brand NamesTessalon®
Pharmacologic CategoryAntitussive
Use: Labeled IndicationsSymptomatic relief of nonproductive cough
Dosing: AdultsCough: Oral: 100 mg 3 times/day or every 4 hours up to 600 mg/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren >10 years: Refer to adult dosing.
Administration: OralSwallow capsule whole (do not break or chew).
ContraindicationsHypersensitivity to benzonatate, related compounds (such as tetracaine), or any component of the formulation
Geriatric ConsiderationsNo specific geriatric information is available about benzonatate. Avoid use in patients with impaired gag reflex or who cannot swallow the capsule whole.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse Reactions1% to 10%:

Central nervous system: Sedation, headache, dizziness

Dermatologic: Rash

Gastrointestinal: GI upset

Neuromuscular & skeletal: Chest numbness

Ocular: Burning sensation in eyes

Respiratory: Nasal congestion

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersMonitor patient's chest sounds and respiratory pattern
Nursing: Physical Assessment/MonitoringAssess patient response, effectiveness of therapy (relief of cough, lung sounds, and respiratory pattern), and adverse reactions (eg, CNS changes) at beginning of therapy and periodically with long-term use. Teach patient appropriate use, possible side effects/interventions, and adverse symptoms to report.
Patient EducationDo not take any new medications (especially depressants or sleep-inducing agents) without consulting prescriber. Take only as prescribed; do not exceed prescribed dose or frequency. Do not break or chew capsule. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, impaired coordination, blurred vision, or increased anxiety (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or upset stomach or nausea (small, frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help). Report persistent CNS changes (dizziness, sedation, tremor, or agitation); numbness in chest or feeling of chill; visual changes or burning in eyes; numbness of mouth or difficulty swallowing; or lack of improvement or worsening or condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, softgel: 100 mg, 200 mg

Tessalon®: 100 mg, 200 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsules (Benzonatate)

100 mg (30): $17.99

200 mg (30): $33.99

Capsules (Tessalon Perles)

100 mg (30): $45.75

Mechanism of ActionTetracaine congener with antitussive properties; suppresses cough by topical anesthetic action on the respiratory stretch receptors
Pharmacodynamics/Kinetics

Onset of action: Therapeutic: 15-20 minutes

Duration: 3-8 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness
Mental Health: Effects on Psychiatric TreatmentMay potentiate sedative effects of sedating psychotropics
References

Mongan PD and Culling Rd, “Rapid Oral Anesthesia for Awake Intubation,” *J Clin Anesth*, 1992, 4(2):101-5.[PubMed 1562332]

International Brand NamesTusitato (MX)

Benzoyl Peroxide and Hydrocortisone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(BEN zoe il peer OKS ide & hye droe KOR ti sone)

U.S. Brand NamesVanoxide-HC速

Canadian Brand NamesVanoxide-HC速

Pharmacologic CategoryAcne Products; Topical Skin Product; Topical Skin Product, Acne

Use: Labeled IndicationsTreatment of acne vulgaris and oily skin

Dosing: AdultsAcne vulgaris: Topical: Shake well; apply thin film 1-3 times/day; gently massage into skin

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAdolescents: Refer to adult dosing.

Allergy Considerations

- Corticosteroid Allergy

Pregnancy Risk FactorC

LactationFor topical use

Adverse ReactionsSee individual agents.

Metabolism/Transport EffectsHydrocortisone: **Substrate** of CYP3A4 (minor); **Induces** CYP3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be

increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agent for Hydrocortisone.
Patient EducationSee individual agent for Hydrocortisone.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Lotion: Benzoyl peroxide 5% and hydrocortisone acetate 0.5% (25 mL)

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Lotion (Vanoxide-HC)

5-0.5% (25): $55.99

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Benzoyl Peroxide
- Hydrocortisone

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsHydrocortisone and Benzoyl Peroxide
International Brand NamesVanoxide-HC (CA)

Benzoyl Peroxide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Benzoyl Peroxide 10% Acne Products: Recall Prompted by Bacteria Contamination - November 2008

Certain products of benzoyl peroxide have been recalled because samples of the products were found to contain *Burkholderia cepacia* (formerly known as *Pseudomonas cepacia*) which may increase the risk of infection in patients with compromised skin conditions or immunosuppressed patients.

For additional information on products affected, please refer to the FDA MedWatch alert: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Benzoyl

Medication Safety Issues

Sound-alike/look-alike issues:

Benoxyl® may be confused with Brevoxyl®, Peroxyl®

Benzac® may be confused with Benza®

Brevoxyl® may be confused with Benoxyl®

Fostex® may be confused with pHisoHex®

Pronunciation(BEN zoe il peer OKS ide)

U.S. Brand NamesBenzac® AC; Benzac® AC Wash; Benzac® W Wash; Benzagel®; BenzaShave®; Benziq™; Benziq™ LS; Brevoxyl®; Brevoxyl® Cleansing; Brevoxyl® Wash [DSC]; breze™; Clearplex [OTC]; Clinac™ BPO; Del Aqua®; Desquam-E™ [DSC]; Desquam-X®; Exact® Acne Medication [OTC]; Fostex® 10% BPO [OTC]; Inova™; NeoBenz® Micro; NeoBenz® Micro SD; Neutrogena® Acne Mask [OTC]; Neutrogena® On The Spot® Acne Treatment [OTC]; Oxy 10® Balance Spot Treatment [OTC]; Oxy 10® Balanced Medicated Face Wash [OTC]; Palmer's® Skin Success Acne [OTC]; PanOxyl®; PanOxyl® Aqua Gel; PanOxyl® Bar [OTC]; PanOxyl®-AQ; Seba-Gel™; Triaz®; Triaz® Cleanser; Zapzyt® [OTC]; Zoderm®; Zoderm® Hydrating Wash™

Canadian Brand NamesAcetoxyl®; Benoxyl®; Benzac AC®; Benzac W® Gel; Benzac W® Wash; Desquam-X®; Oxyderm™; PanOxyl®; Solugel®

Pharmacologic CategoryAcne Products; Topical Skin Product; Topical Skin Product, Acne

Use: Labeled IndicationsAdjunctive treatment of mild-to-moderate acne vulgaris and acne rosacea

Dosing: AdultsAcne: Topical:

Cleansers: Wash once or twice daily; control amount of drying or peeling by modifying dose frequency or concentration

Lotion: Apply sparingly once daily; gradually increase to 2-3 times/day if needed. If excessive dryness or peeling occurs, reduce dose frequency or concentration. If excessive stinging or burning occurs, remove with mild soap and water; resume use the next day.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAdolescents: Refer to adult dosing.

Pregnancy Risk FactorC

Adverse Reactions1% to 10%: Dermatologic: Irritation, contact dermatitis, dryness, erythema, peeling, stinging

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, topical:

BenzaShave®: 5% (120 g); 10% (120 g) [contains sodium coconut sulfate and coconut acid]

Exact® Acne Medication: 5% (18 g)

NeoBenz® Micro: 3.5% (45 g); 5.5% (45 g); 8.5% (45 g)

NeoBenz® Micro SD: 3.5% (0.5 g); 5.5% (0.5 g); 8.5% (0.5 g)

Neutrogena® Acne Mask: 5% (60 g)

Neutrogena® On The Spot® Acne Treatment: 2.5% (22.5 g)

Zoderm®: 4.5% (125 mL) [contains urea 10%]; 6.5% (125 mL) [contains urea 10%]; 8.5% (125 mL) [contains urea 10%]

Emulsion, topical [cleanser]:

Zoderm®: 4.5% (400 mL) [contains urea 10%]; 6.5% (400 mL) [contains urea 10%]; 8.5% (400 mL) [contains urea 10%]

Gel, topical: 2.5% (60 g); 5% (45 g, 60 g, 90 g); 10% (45 g, 60 g, 90 g)

Benzac® AC [water based]: 5% (60 g); 10% (60 g)

Benzagel®: 5% (45 g); 10% (45 g)

Benziq™: 5.25% (50 g)

Benziq™ LS: 2.75% (50 g)

Brevoxyl®: 4% (43 g, 90 g); 8% (43 g, 90 g)

Clearplex: 5% (45 g); 10% (45 g)

Clinac™ BPO: 7% (45 g)

Desquam-E™ [water based]: 2.5% (42.5 g) [DSC]; 5% (42.5 g) [emollient gel] [DSC]

Desquam-X®: 5% (42.5 g, 90 g) [DSC]; 10% (42.5 g, 90 g)

Fostex® 10% BPO: 10% (45 g)

Oxy 10® Balance Spot Treatment: 5% (30 g); 10% (30 g)

PanOxyl® [alcohol based]: 5% (57 g, 113 g); 10% (57 g, 113 g)

PanOxyl® AQ [water based]: 2.5% (57 g, 113 g); 5% (57 g, 113 g); 10% (57 g, 113 g)

PanOxyl® Aqua Gel [water based]: 10% (42.5 g)

Seba-Gel™: 5% (90 g); 10% (90 g)

Triaz® Cleanser: 3% (170 g, 340 g); 6% (170 g, 340 g); 10% (170 g, 340 g)

Zapzyt®: 10% (30 g)

Zoderm®: 4.5% (125 mL) [contains urea 10%]; 6.5% (125 mL) [contains urea 10%]; 8.5% (125 mL) [contains urea 10%]

Liquid, topical: 2.5% (240 mL); 5% (120 mL, 150 mL, 240 mL); 10% (150 mL, 240 mL)

Benzac® AC Wash [water based]: 5% (240 mL); 10% (240 mL)

Benzac® W Wash [water based]: 5% (240 mL)

Benziq™ [wash]: 5.25% (175 g)

Del-Aqua®: 5% (45 mL); 10% (45 mL)

Desquam-X®: 5% (150 mL)

Oxy-10® Balance Medicated Face Wash: 10% (240 mL)

Liquid, topical [wash]:

Zoderm® Hydrating Wash™: 5.75% (473 mL) [contains urea 10%]

Lotion, topical: 5% (30 mL); 5% (227 g) [lathering base]; 10% (30 mL); 10% (227 g) [lathering base]

Brevoxyl® Cleansing: 4% (297 g); 8% (297 g) [in a lathering vehicle]

Brevoxyl® Wash: 4% (170 g); 8% (170 g) [in a lathering vehicle] [DSC]

Fostex® 10% BPO: 10% (150 mL)

Palmer's® Skin Success Acne: 10% (30 mL) [contains vitamin E and aloe]

Pad, topical:

breze™: 4.75% (30s); 7.75% (30s)

Inova™: 4% (30s); 8% (30s)

Triaz®: 3% (30s, 60s); 6% (30s, 60s); 9% (30s)

Zoderm®: 4.5% (30s); 6.5% (30s); 8.5% (30s)

Soap, topical [bar]:

Fostex® 10% BPO: 10% (113 g)

PanOxyl® Bar: 5% (113 g); 10% (113 g)

Generic AvailableYes: Excludes cream, pads, and soap

Pricing: U.S. (www.drugstore.com)

Cream (Benzashave)

5% (113.4): $60.49

10% (113.4): $63.79

Cream (NeoBenz Micro)

3.5% (45): $117.99

5.5% (45): $117.99

8.5% (45): $120.99

Cream (NeoBenz Micro SD)

3.5% (30): $169.99

5.5% (30): $169.99

Cream (Zoderm)

4.5-10% (125): $155.58

Gel (Benzac AC)

2.5% (60): $21.99

5% (60): $59.99

10% (60): $63.82

Gel (Benzac W)

2.5% (60): $20.99

5% (60): $21.99

10% (60): $21.99

Gel (Benzagel Wash)

10% (60): $26.03

Gel (Benziq)

5.25% (50): $81.57

Gel (Benziq LS)

2.75% (50): $77.72

Gel (Benzoyl Peroxide)

2.5% (60): $23.99

5% (45): $12.99

5% (60): $24.99

5% (90): $21.99

10% (45): $13.99

10% (60): $26.99

10% (90): $28.99

Gel (Brevoxyl)

4% (42.5): $89.87

4% (90): $71.42

8% (42.5): $89.96

Gel (Clinac BPO)

7% (45): $43.99

Gel (Desquam-E)

2.5% (42.5): $21.99

5% (42.5): $22.99

10% (42.5): $16.99

Gel (Panoxyl Aqua)

10% (42.5): $8.99

Gel (Seba-Gel)

10% (60): $21.99

10% (90): $26.40

Gel (Zoderm)

4.5-10% (125): $155.95

Kit (Benzoyl Peroxide Creamy Wash)

4% (1): $59.99

8% (1): $69.99

Kit (Brevoxyl-4 Acne Wash)

4% (1): $79.79

Kit (Brevoxyl-8 Acne Wash)

8% (1): $79.79

Liquid (Benzac AC Wash)

2.5% (240): $30.98

5% (226): $86.22

10% (226): $93.11

Liquid (Benzac W Wash)

5% (226): $83.91

10% (226): $96.01

Liquid (Benziq Wash)

5.25% (175): $74.25

Liquid (Benzoyl Peroxide Creamy Wash)

4% (170.1): $34.99

Liquid (Benzoyl Peroxide Wash)

5% (142): $21.99

10% (142): $21.99

Liquid (Zoderm Cleanser)

4.5-10% (400): $103.36

6.5-10% (400): $106.24

8.5-10% (400): $112.20

Lotion (Triaz Cleanser)

3% (170.3): $69.67

3% (340.2): $121.45

6% (170.3): $70.73

6% (340.2): $125.16

9% (170.3): $78.75

9% (340.2): $129.92

Pads (Triaz)

3% (30): $125.19

3% (60): $236.20

6% (30): $125.19

6% (60): $236.20

9% (30): $125.19

Pads (Zoderm)

4.5-10% (30): $121.51

6.5-10% (30): $117.11

Mechanism of ActionReleases free-radical oxygen which oxidizes bacterial proteins in the sebaceous follicles decreasing the number of anaerobic bacteria and decreasing irritating-type free fatty acids

Pharmacodynamics/Kinetics

Absorption: ~5% via skin; gel more penetrating than cream

Metabolism: Converted to benzoic acid in skin

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesAcne Derm (IL); Acnecide (IE); Acnetick-10 (CO); Acnexyl (TH); Acnie (TW); Aczee (TH); Aknefug (EE); Aknefug-oxid (PL); Akneroxid (AT, BE, CH, CZ, DE, HN, HU, LU, MY, NL, PL); Ambix (PL); Antopar (HR, PL); Basiron (CZ, DK, FI, NO); Basiron AC (SE); Benoxid (IT); Benoxyl (AE, BB, BF, BH, BJ, BM, BR, BS, BZ, CI, CY, EG, ET, GB, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PH, PR, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, VE, YE, ZA, ZM, ZW); Benoxyl AQ AL (MX); Benzac (AU, IL, IT, LU, PT); Benzac AC (AU, CR, DO, GT, HK, HN, MX, MY, NI, NZ, PA, PE, SG, SV, TW, VE); Benzac W (AU, BB, BM, BS, BZ, CN, GR, GY, JM, MX, NL, PR, SR, TT); Benzacne (PL); Benzapur (PL); Benzihex (AR, CL); Benzihex AC (PY, UY); Benzoile Perossido (IT); Benzomix (IT); Benzoylperoxide-Galderma (LU); Benzperox (BG); Bexid (SE); Brevoxyl (AU, CH, DE, FI, FR, PK, PL, SE, SG, TW); Clearasil Ultra (IT, PL); Eclaran (FR, LU); Ecuaderm (VE); Effacne (FR, LU); Enzoxid (TH); Lubexyl (PL); Medigel (PL); Oxiderma (ES); Oxy (BR, HU, PL, SE); Oxy Preps. (AU); Pangel (BE); Panoxyl (AE, AT, BB, BH, BM, BR, BS, BZ, CO, CY, DE, EG, FR, GB, GY, HK, IE, IL, IQ, IR, IT, JM, JO, KW, LB, LU, LY, MY, NL, NO, OM, PH, QA, SA, SR, SY, TH, TT, TW, YE, ZA); PanOxyl (AU); Panoxyl AQ (CR, DO, GT, HK, HN, NI, PA, SV, TH, TW); Pansulfox (CN); Pernox Gel (IN); Peroxiben (PT); Persol Gel (IN); Pimplex (ID); Reloxyl (IT); Scherogel (AT, IT, LU); Stioxyl (SE); Tinagel (LU); Ultra Clearasil (PH); Vixiderm (AR)

Benzphetamine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

International issues:

Didrex® may be confused with Nitrex® which is a brand name for isosorbide mononitrate in Italy

Pronunciation(benz FET a meen)
U.S. Brand NamesDidrex®
Canadian Brand NamesDidrex®
Pharmacologic CategoryAnorexiant; Sympathomimetic
Use: Labeled IndicationsShort-term (few weeks) adjunct in exogenous obesity
Dosing: AdultsObesity (short-term adjunct): Oral: Dose should be individualized based on patient response: Initial: 25-50 mg once daily; titrate to 25-50 mg 1-3 times/day; once-daily dosing should be administered midmorning or midafternoon; maximum dose: 50 mg 3 times/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricObesity (short-term adjunct): Children ≥12 years: Refer to adult dosing.
Calculations

- Body Mass Index

Dietary ConsiderationsMost effective when combined with a low calorie diet and behavior modification counseling.
StorageStore at room temperature of 20°C to 25°C (68°F to 77°F).
RestrictionsC-III

Pharmacotherapy for weight loss is recommended only for obese patients with a body mass index ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of other risk factors such as hypertension, diabetes, and/or dyslipidemia or a high waist circumference; therapy should be used in conjunction with a comprehensive weight management program. Rule out organic causes of obesity (eg, untreated hypothyroidism) prior to use.

Note: Benzphetamine is not approved for long-term use. The limited usefulness of medications in this class should be weighed against possible risks associated with their use. Consult weight loss guidelines for current pharmacotherapy recommendations.

ContraindicationsHypersensitivity or idiosyncrasy to benzphetamine or other sympathomimetic amines; advanced arteriosclerosis, symptomatic cardiovascular disease, moderate-to-severe hypertension; pulmonary hypertension; hyperthyroidism; glaucoma; agitated states, history of drug abuse; during or within 14 days following MAO inhibitor therapy, concurrent use with other CNS stimulants; pregnancy
Allergy Considerations

- Amphetamine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Amphetamines may impair the ability to engage in potentially hazardous activities.
- Primary pulmonary hypertension (PPH): A rare, frequently fatal disease of the lungs, PPH has been found to occur with increased frequency in patients receiving some anorexigens.
- Valvular heart disease: The use of some anorexigens has been associated with the development of valvular heart disease. Avoid stimulants in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that could increase the risk of sudden death that these conditions alone carry.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; antidiabetic agent requirements may be altered with anorexigens and concomitant dietary restrictions.
- Hypertension: Use with caution in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases in blood pressure or heart rate.
- Seizure disorders: Use with caution in patients with a history of seizure disorders.
- Tourette's syndrome: Use with caution in patients with Tourette's syndrome; stimulants may unmask tics.

Concurrent drug therapy issues:

- Anorexigens: Safety and efficacy have not been established for use with other weight loss medications, including over-the-counter or herbal products. Not recommended for use in patients who have used other anorectic agents within the past year.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Abuse potential: Benzphetamine is pharmacologically related to the amphetamines, which have a high abuse potential; prolonged use may lead to dependency. Prescriptions should be written for the smallest quantity consistent with good patient care to minimize possibility of overdose.

- Discontinuation of therapy: Discontinue if satisfactory weight loss has not occurred within the first 4 weeks of treatment, or if tolerance develops.

Pregnancy Risk FactorX
Pregnancy ConsiderationsReproduction studies have not been conducted with benzphetamine. Amphetamines are teratogenic and embryotoxic in animal studies.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsAmphetamines are excreted in breast milk.
Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiomyopathy (with chronic amphetamine use), hypertension, palpitation, tachycardia

Central nervous system: Depression (with withdrawal), dizziness, headache, insomnia, nervousness, psychosis, restlessness

Dermatologic: Urticaria

Endocrine & metabolic: Libido changes

Gastrointestinal: Diarrhea, nausea, unpleasant taste, xerostomia

Neuromuscular & skeletal: Tremor

Ocular: Mydriasis

Miscellaneous: Diaphoresis, tachyphylaxis

Metabolism/Transport Effects**Substrate** of CYP2B6 (minor), 3A4 (major)
Drug Interactions

Alkalinizing Agents: May decrease the excretion of Amphetamines. *Risk D: Consider therapy modification*

Ammonium Chloride: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

Analgesics (Opioid): Amphetamines may enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Antihistamines: Amphetamines may diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antipsychotics: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Amphetamines. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ethosuximide: Amphetamines may diminish the therapeutic effect of Ethosuximide. Amphetamines may decrease the serum concentration of Ethosuximide. *Risk C: Monitor therapy*

Gastrointestinal Acidifying Agents: May decrease the serum concentration of Amphetamines. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Methenamine: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

PHENobarbital: Amphetamines may decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Phenytoin: Amphetamines may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions Herb/Nutraceutical: St John's wort may decrease benzphetamine levels.

Monitoring Parameters Weight, waist circumference, blood pressure

Reference Range

Adult classification of weight by BMI (kg/m^2):

Underweight: <18.5

Normal: 18.5-24.9

Overweight: 25-29.9

Obese, class I: 30-34.9

Obese, class II: 35-39.9

Extreme obesity (class III): ≥40

Waist circumference: In adults with a BMI of 25-34.9 kg/m^2, high-risk waist circumference is defined as:

Men >102 cm (>40 in)

Women >88 cm (>35 in)

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 50 mg

Didrex®: 50 mg

Generic Available Yes

Pricing: U.S. (www.drugstore.com)

Tablets (Didrex)

50 mg (90): $137.98

Mechanism of Action Benzphetamine is a sympathomimetic amine with pharmacologic properties similar to the amphetamines. The mechanism of action in reducing appetite appears to be secondary to CNS effects, including stimulation of the hypothalamus to release norepinephrine.

Related Information

- Obesity Treatment Guidelines for Adults

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and metallic taste.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Use with caution since amphetamines have actions similar to epinephrine and norepinephrine

Index Terms Benzphetamine Hydrochloride

References

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"U.S. Preventative Services Task Force. Screening for Obesity in Adults: Recommendations and Rationale," *Ann Intern Med*, 2003, 139(11):933-49[PubMed 14644896]

International Brand Names Didrex (CA)

Benztropine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Benztropine may be confused with bromocriptine

Pronunciation(BENZ troe peen)
U.S. Brand NamesCogentin®
Canadian Brand NamesApo-Benztropine®
Pharmacologic CategoryAnti-Parkinson's Agent, Anticholinergic; Anticholinergic Agent
Use: Labeled IndicationsAdjunctive treatment of Parkinson's disease; treatment of drug-induced extrapyramidal symptoms (except tardive dyskinesia)
Dosing: Adults

Drug-induced extrapyramidal symptom: Oral, I.M., I.V.: 1-4 mg/dose 1-2 times/day

Acute dystonia: I.M., I.V.: 1-2 mg

Parkinsonism: Oral: 0.5-6 mg/day in 1-2 divided doses; if one dose is greater, give at bedtime. Titrate dose in 0.5 mg increments at 5- to 6-day intervals.

Dosing: ElderlyOral: Initial: 0.5 mg once or twice daily; titrate dose in 0.5 mg increments at every 5-6 days; maximum: 4 mg/day.
Dosing: Pediatric**Note:** Use in children ≤3 years of age should be reserved for life-threatening emergencies.

Drug-induced extrapyramidal symptoms: Oral, I.M., I.V.: Children >3 years: 0.02-0.05 mg/kg/dose 1-2 times/day

Administration: I.V. DetailpH: 5-8
Compatibility

Y-site administration: Compatible: Fluconazole, tacrolimus.

Compatibility in syringe: Compatible: Chlorpromazine, fluphenazine, metoclopramide, perphenazine. **Variable (consult detailed reference):** Haloperidol.

ContraindicationsHypersensitivity to benztropine or any component of the formulation; pyloric or duodenal obstruction, stenosing peptic ulcers; bladder neck obstructions; achalasia; myasthenia gravis; children <3 years of age
Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anhidrosis/hyperthermia: May cause anhidrosis and hyperthermia, which may be severe; use with caution in hot weather or during exercise. The risk is increased in hot environments, particularly in the elderly, alcoholics, patients with CNS disease, and those with prolonged outdoor exposure.
- CNS effects: May be associated with confusion or hallucinations (generally at higher dosages); intensification of symptoms or toxic psychosis may occur in patients with mental disorders. May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Weakness: When given in large doses or to susceptible patients, may cause weakness and inability to move particular muscle groups.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with tachycardia, cardiac arrhythmias, hypertension, or hypotension.
- GI obstruction: Use with caution in patients with obstructive disease of the GI.
- Glaucoma: Use with caution in patients with glaucoma.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture or retention.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Elderly: Frequently develop increased sensitivity and require strict dosage regulation; side effects may be more severe in elderly patients with atherosclerotic changes.

- Pediatrics: Use with caution in older children; dose has not been established.

Other warnings/precautions:

- Tardive dyskinesia: Does not relieve symptoms of tardive dyskinesia.

Geriatric ConsiderationsAnticholinergic agents are generally not well tolerated in the elderly (often results in bowel, bladder, and CNS adverse effects) and their use should be avoided when possible. In the elderly, anticholinergic agents should not be used as prophylaxis against extrapyramidal symptoms.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Tachycardia

Central nervous system: Confusion, disorientation, memory impairment, toxic psychosis, visual hallucinations

Dermatologic: Rash

Endocrine & metabolic: Heat stroke, hyperthermia

Gastrointestinal: Constipation, dry throat, ileus, nasal dryness, nausea, vomiting, xerostomia

Genitourinary: Urinary retention, dysuria

Ocular: Blurred vision, mydriasis

Miscellaneous: Fever

Metabolism/Transport Effects**Substrate** of CYP2D6 (minor)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Monitoring ParametersSymptoms of EPS or Parkinson's, pulse, anticholinergic effects
Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and at regular intervals throughout therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Patient EducationTake exactly as directed; do not increase, decrease, or discontinue this medicine without consulting prescriber. Take at the same time each day. Do not use alcohol and any prescription or OTC sedatives or CNS depressants without consulting prescriber. You may experience drowsiness, dizziness, confusion, and blurred vision (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); increased susceptibility to heat stroke, decreased perspiration (use caution in hot weather, maintain adequate fluids and reduce exercise activity); or constipation (increased exercise, fluids, fruit, or fiber may help). Report unresolved nausea, vomiting, or gastric disturbances; rapid or pounding heartbeat, chest pain, or palpitation; respiratory difficulty; CNS changes (hallucination, loss of memory, nervousness, etc); eye pain; prolonged fever; painful or difficult urination; unresolved constipation; increased muscle spasticity or rigidity; skin rash; or significant worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as mesylate (Cogentin®): 1 mg/mL (2 mL)

Tablet, as mesylate: 0.5 mg, 1 mg, 2 mg

Generic AvailableYes: Tablet
Pricing: U.S. (www.drugstore.com)

Tablets (Benztropine Mesylate)

0.5 mg (60): $15.99

1 mg (60): $15.99

2 mg (90): $22.99

Mechanism of Action Possesses both anticholinergic and antihistaminic effects. *In vitro* anticholinergic activity approximates that of atropine; *in vivo* it is only about half as active as atropine. Animal data suggest its antihistaminic activity and duration of action approach that of pyrilamine maleate. May also inhibit the reuptake and storage of dopamine, thereby prolonging the action of dopamine.

Pharmacodynamics/Kinetics

Onset of action: Oral: Within 1 hour; Parenteral: Within 15 minutes

Duration: 6-48 hours

Metabolism: Hepatic (N-oxidation, N-dealkylation, and ring hydroxylation)

Bioavailability: 29%

Related Information

- Antiparkinsonian Agents
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy Pearls No significant difference in onset of I.M. or I.V. injection, therefore, there is usually no need to use the I.V. route. Improvement is sometimes noticeable a few minutes after injection.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), dry throat, and nasal dryness (very prevalent).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health Comment Along with diphenhydramine, benztropine is considered the drug of choice for patients with acute dystonic reactions. The usual adult dosage is I.M. 2 mg. In an emergency situation (laryngeal spasm), it should be given intravenously. Benztropine has a long duration of action and may be given once daily, preferable at bedtime due to possible sedation when used to treat pseudoparkinsonism and akathisia.

Index Terms Benztropine Mesylate

References

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International Brand Names Bentrop (AU); Cogentin (AU, GB, HK, IE, MY, PT, SE)

Benzydamine

Lexi-Drugs Online

English

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Pronunciation(ben ZID a meen)

Canadian Brand NamesApo-Benzydamine®; Dom-Benzydamine; Novo-Benzydamine; PMS-Benzydamine; ratio-Benzydamine; Sun-Benz®; Tantum®

Pharmacologic CategoryLocal Anesthetic, Oral

Use: Labeled IndicationsSymptomatic treatment of pain associated with acute pharyngitis; treatment of pain associated with radiation-induced oropharyngeal mucositis

Use: DentalSymptomatic treatment of pain associated with acute pharyngitis; treatment of pain associated with radiation-induced oropharyngeal mucositis

Dosing: Adults

Acute pharyngitis: Oral rinse: Gargle with 15 mL of undiluted solution every $1^{1}/_{2}$-3 hours until symptoms resolve. Patient should expel solution from mouth following use; solution should not be swallowed.

Mucositis: Oral rinse: 15 mL of undiluted solution as a gargle or rinse 3-4 times/day; contact should be maintained for at least 30 seconds, followed by expulsion from the mouth. Clinical studies maintained contact for ~2 minutes, up to 8 times/day. Patient should not swallow the liquid. Begin treatment 1 day prior to initiation of radiation therapy and continue daily during treatment. Continue oral rinse treatments after the completion of radiation therapy until desired result/healing is achieved.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment required.

StorageStore at 15°C to 30°C. Protect from freezing.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to benzydamine or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Irritation/burning: May cause local irritation and/or burning sensation in patients with altered mucosal integrity; dilution (1:1 in warm water) may attenuate this effect.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children ≤5 years of age.

Pregnancy ConsiderationsSafety has not been established in pregnant women. Use only when potential benefit outweighs possible risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

Central nervous system: Drowsiness, headache

Gastrointestinal: Nausea and/or vomiting (2%), dry mouth

Local: Numbness (10%), burning/stinging sensation (8%)

Respiratory: Pharyngeal irritation, cough

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 2C19, 2D6, 3A4

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Oral rinse: 0.15% (100 mL, 250 mL) [not available in the U.S.]

Generic AvailableYes

Mechanism of ActionLocal anesthetic and anti-inflammatory, reduces local pain and inflammation. Does not interfere with arachidonic acid metabolism.

Pharmacodynamics/Kinetics

Absorption: Oral rinse may be absorbed, at least in part, through the oral mucosa

Excretion: Urine (primarily as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Numbness, burning/stinging sensation, and xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBenzydamine Hydrochloride

References

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International Brand NamesAndolex (NO, SE); Benalgin (PL); Bendamina (PE); Benzirin (CO); Bevidam (VE); Bucodrin (PE); Difflam (AU, HK, IE, MY, PH, SG, TH, TW); Easy Gel (IL); Hascosept (PL); Opalgyne (FR); Tantum (AT, BG, DE, GR, HN, ID, IN, IT, PL, PT, VE); Tantum Rosa (PL); Tantum Verde (PL); Vantal (CR, DO, GT, HN, NI, PA, SV)

Benzylpenicilloyl-polylysine

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Pronunciation(BEN zil pen i SIL oyl pol i LIE seen)

U.S. Brand NamesPre-Pen® [DSC]

Pharmacologic CategoryDiagnostic Agent

Use: Labeled IndicationsAdjunct in assessing the risk of administering penicillin (penicillin or benzylpenicillin) in adults with a history of clinical penicillin hypersensitivity

Dosing: AdultsDiagnostic aid for penicillin allergy: PPL is administered by a scratch technique or by intradermal injection. For initial testing, PPL should always be applied via the scratch technique. **Do not administer intradermally to patients who have positive reactions to a scratch test.** PPL test alone does not identify those patients who react to a minor antigenic determinant and does not appear to predict reliably the occurrence of late reactions.

Scratch test: Use scratch technique with a 20-gauge needle to make 3-5 mm nonbleeding scratch on epidermis, apply a small drop of solution to scratch, rub in gently with applicator or toothpick. A positive reaction consists of a pale wheal surrounding the scratch site which develops within 10 minutes and ranges from 5-15 mm or more in diameter.

Intradermal test: Use intradermal test with a tuberculin syringe with a 26- to 30-gauge short bevel needle; a dose of 0.01-0.02 mL is injected intradermally. A control of 0.9% sodium chloride should be injected at least 1.5" from the PPL test site. Most skin responses to the intradermal test will develop within 5-15 minutes.

Interpretation:

(-) Negative: No reaction

(±) Ambiguous: Wheal only slightly larger than original bleb with or without erythematous flare and larger than control site

(+) Positive: Itching and marked increase in size of original bleb

Control site should be reactionless

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: OtherPPL is administered by a scratch technique or by intradermal injection. For initial testing, PPL should always be applied via the scratch technique. Do not give intradermally to patients who have positive reactions to a scratch test. Have epinephrine 1:1000 immediately available.

StorageRefrigerate; discard if left at room temperature for longer than 1 day.

ContraindicationsKnown hypersensitivity to penicillin or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Allergic reactions: PPL test alone does not identify those patients who react to a minor antigenic determinant and does not appear to predict reliably the occurrence of late reactions. A negative skin test is associated with an incidence of allergic reactions <5% after penicillin administration and a positive skin test is associated with a >20% incidence of allergic reaction after penicillin administration; have epinephrine 1:1000 available.

Pregnancy Risk FactorC

Pregnancy ConsiderationsSafety for use during pregnancy has not been established.

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension

Dermatologic: Angioneurotic edema, pruritus, erythema, urticaria

Local: Intense local inflammatory response at skin test site, wheal (locally)

Respiratory: Dyspnea

Miscellaneous: Systemic allergic reactions occur rarely

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution: 6 x 10^{-5} M (0.25 mL) [DSC]

Generic AvailableNo

Mechanism of ActionElicits IgE antibodies which produce type I accelerate urticarial reactions to penicillins

Related Information

- Skin Tests

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsPenicilloyl-polylysine; PPL
References

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Sullivan TJ, Wedner HJ, Schatz GS, et al, “Skin Testing to Detect Penicillin Allergy,” *J Allergy Clin Immunol*, 1981, 68:171-80.

Weiss ME and Adkinson NF, “β-lactam Allergy” in *Principles & Practice of Infectious Diseases*, 3rd ed, Mandell GL, Douglas RG, Bennett, JE, 1990, Churchill Livingstone, 264-9.

Wendel GD Jr, Stark BJ, Jamison RB, et al, “Penicillin Allergy and Desensitization in Serious Infections During Pregnancy,” *N Engl J Med*, 1985, 312(19):1229-32.

BEP (Ovarian Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Ovarian Cancer

Regimen Use Ovarian cancer

Regimen

Bleomycin: I.V.: 20 units/m^2 (maximum 30 units) day 1

[total dose/cycle = 20 units/m^2]

Etoposide: I.V.: 75 mg/m^2/day days 1 to 5

[total dose/cycle = 375 mg/m^2]

or 75 mg/m^2/day days 1 to 4 (if received prior radiation therapy)

[total dose/cycle = 300 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 3 weeks for 4 cycles

References

Homesley HD, Bundy BN, Hurteau JA, et al, âBleomycin, Etoposide, and Cisplatin Combination Therapy of Ovarian Granulosa Cell Tumors and Other Stromal Malignancies: A Gynecologic Oncology Group Study,â *Gynecol Oncol*, 1999, 72(2):131-7.[PubMed 10021290]

Pharmacologic CategoryChemotherapy Regimen, Ovarian Cancer; Chemotherapy Regimen, Testicular Cancer

Regimen UseOvarian cancer; Testicular cancer

Regimen

Bleomycin: I.V.: 30 units/day days 2, 9, and 16

[total dose/cycle = 90 units]

Etoposide: I.V.: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

or 120 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 360 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21 days

References

Horwich A, Sleijfer DT, Fossa SD, et al, “Randomized Trial of Bleomycin, Etoposide, and Cisplatin Compared With Bleomycin, Etoposide, and Carboplatin in Good-Prognosis Metastatic Nonseminomatous Germ Cell Cancer: A Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial,” *J Clin Oncol*, 1997, 15(5):1844-52. [PubMed 9164194]

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Williams S, Blessing JA, Liao SY, et al, “Adjuvant Therapy of Ovarian Germ Cell Tumors With Cisplatin, Etoposide, and Bleomycin: A Trial of the Gynecologic Oncology Group,” *J Clin Oncol*, 1994, 12(4):701-6.[PubMed 7512129]

BEP (Testicular Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Testicular Cancer

Regimen UseTesticular cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Bleomycin: I.V.: 30 units/day days 2, 9, and 16

[total dose/cycle = 90 units]

Etoposide: I.V.: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Bleomycin: I.V.: 30 units once weekly

[total dose/cycle = 90 units]

Etoposide: I.V.: 120 mg/m^2/day days 1, 3, and 5

[total dose/cycle = 360 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21 days

Variation 3:

Bleomycin: I.V.: 30 units/day days 1, 8, and 15

[total dose/cycle = 90 units]

Etoposide: I.V.: 165 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 495 mg/m^2]

Cisplatin: I.V.: 50 mg/m^2/day days 1 and 2

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21 days

References

Variation 1:

Williams SD, Birch R, Einhorn LH, et al, “Treatment of Disseminated Germ-Cell Tumors With Cisplatin, Bleomycin, and Either Vinblastine or Etoposide,” *N Engl J Med*, 1987, 316(23):1435-40. [PubMed 2437455]

Variation 2:

de Wit R, Stoter G, Sleijfer DT, et al, “Four Cycles of BEP vs Four Cycles of VIP in Patients With Intermediate-Prognosis Metastatic Testicular Nonseminoma: A Randomized Study of the EORTC Genitourinary Tract Cancer Cooperative Group. European Organization for Research and Treatment of Cancer,” *Br J Cancer*, 1998, 78(6):828-32. [PubMed 9743309]

Variation 3:

de Wit R, Roberts JT, Wilkinson PM, et al, “Equivalence of Three or Four Cycles of Bleomycin, Etoposide, and Cisplatin Chemotherapy and of a 3- or 5-Day Schedule in Good-Prognosis Germ Cell Cancer: A Randomized Study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council,” *J Clin Oncol*, 2001, 19(6):1629-40.[PubMed 11250991]

Beractant

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Survanta® may be confused with Sufenta®

Pronunciation(ber AKT ant)

U.S. Brand NamesSurvanta®

Canadian Brand NamesSurvanta®

Pharmacologic CategoryLung Surfactant

Use: Labeled IndicationsPrevention and treatment of respiratory distress syndrome (RDS) in premature infants

Prophylactic therapy: Body weight <1250 g in infants at risk for developing, or with evidence of, surfactant deficiency (administer within 15 minutes of birth)

Rescue therapy: Treatment of infants with RDS confirmed by x-ray and requiring mechanical ventilation (administer as soon as possible - within 8 hours of age)

Dosing: Pediatric

Respiratory distress treatment:

Prophylactic treatment: Intratracheal: Administer 100 mg phospholipids (4 mL/kg) as soon as possible; as many as 4 doses may be administered during the first 48 hours of life, no more frequently than 6 hours apart. The need for additional doses is determined by evidence of continuing respiratory distress; if the infant is still intubated and requiring at least 30% inspired oxygen to maintain a PaO_2 ≤80 torr.

Rescue treatment: Intratracheal: Administer 100 mg phospholipids (4 mL/kg) as soon as the diagnosis of RDS is made; may repeat if needed, no more frequently than every 6 hours to a maximum of 4 doses

Administration: Other

For intratracheal administration only

Suction infant prior to administration. Inspect solution to verify complete mixing of the suspension.

Administer intratracheally by instillation through a 5-French end-hole catheter inserted into the infant's endotracheal tube.

Administer the dose in four 1 mL/kg aliquots. Each quarter-dose is instilled over 2-3 seconds; each quarter-dose is administered with the infant in a different position. Slightly downward inclination with head turned to the right, then repeat with head turned to the left; then slightly upward inclination with head turned to the right, then repeat with head turned to the left.

Storage**Refrigerate**; protect from light. Prior to administration, warm by standing at room temperature for 20 minutes or held in hand for 8 minutes. **Artificial warming methods should not be used.** Unused, unopened vials warmed to room temperature may be returned to the refrigerator within 8 hours of warming only once.

Warnings/Precautions

Concerns related to adverse effects:

- Transient adverse effects: Transient episodes of bradycardia and decreased oxygen saturation occur. Discontinue dosing procedure and initiate measures to alleviate the condition; may reinstitute after the patient is stable.

Other warnings/precautions:

- Administration: For intratracheal administration only.

- Monitoring: Produces rapid improvements in lung oxygenation and compliance that may require frequent adjustments to oxygen delivery and ventilator settings.

- Trained personnel: Rapidly affects oxygenation and lung compliance; restrict use to a highly-supervised clinical setting with immediate availability of clinicians experienced in intubation and ventilatory management of premature infants.

Adverse ReactionsDuring the dosing procedure:

>10%: Cardiovascular: Transient bradycardia

1% to 10%: Respiratory: Oxygen desaturation

<1%: Apnea, endotracheal tube blockage, hypercarbia, hypertension, hypocarbia, hypotension, pallor, pulmonary air leaks, pulmonary interstitial emphysema, post-treatment nosocomial sepsis probability increased, vasoconstriction

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersContinuous ECG and transcutaneous O_2 saturation should be monitored during administration; frequent arterial blood gases are necessary to prevent postdosing hyperoxia and hypocarbia

Monitoring: Lab TestsContinuous ECG and transcutaneous O_2 saturation should be monitored during administration; frequent arterial blood gases are necessary to prevent postdosing hyperoxia and hypocarbia

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, intratracheal [preservative free; bovine derived]:

Survanta®: 25 mg/mL (4 mL, 8 mL)

Generic AvailableNo

ManufacturerRoss Laboratories

Mechanism of ActionReplaces deficient or ineffective endogenous lung surfactant in neonates with respiratory distress syndrome (RDS) or in neonates at risk of developing RDS. Surfactant prevents the alveoli from collapsing during expiration by lowering surface tension between air and alveolar surfaces.

Pharmacodynamics/KineticsExcretion: Clearance: Alveolar clearance is rapid

Pharmacotherapy PearlsEach mL contains 25 mg phospholipids suspended in 0.9% sodium chloride solution. Contents of 1 mL: 0.5-1.75 mg triglycerides, 1.4-3.5 mg free fatty acids, and <1 mg protein.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBovine Lung Surfactant; Natural Lung Surfactant

International Brand NamesSurfacten (JP); Survanta (AE, AR, AT, AU, BB, BE, BG, BH, BM, BR, BS, BZ, CH, CO, CR, CY, CZ, DE, DO, EC, EG, ES, FR, GB, GR, GT, GY, HK, HN, HU, IE, IL, IQ, IR, JM, JO, KW, LB, LU, LY, MX, MY, NI, NL, NO, OM, PA, PE, PH, PL, QA, SA, SG, SR, SV, SY, TH, TT, TW, YE, ZA); Survanta-Vent (SE)

Beta-Carotene

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(BAY ta KARE oh teen)
U.S. Brand NamesA-Caro-25; B-Caro-T™; Lumitene™
Pharmacologic CategoryVitamin, Fat Soluble
Use: Unlabeled/InvestigationalProphylaxis and treatment of polymorphous light eruption; prophylaxis against photosensitivity reactions in erythropoietic protoporphyria
Dosing: Adults(Non-FDA-approved uses) Prophylaxis and treatment of polymorphous light eruption; prophylaxis against photosensitivity reactions in erythropoietic protoporphyria: Oral: 30-300 mg/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricOral: <14 years: 30-150 mg/day
Dietary ConsiderationsMay be taken with meals.
ContraindicationsHypersensitivity to beta-carotene or any component of the formulation
Allergy Considerations

- Retinoid Allergy

Warnings/Precautions

Disease-related concerns:

• Hepatic impairment: Use with caution in patients with hepatic impairment.

• Renal impairment: Use with caution in patients with renal impairment.

Other warnings/precautions:

• Sunscreen use: Not proven effective as a sunscreen.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%: Dermatologic: Carotenodermia (yellowing of palms, hands, or soles of feet, and to a lesser extent the face)

<1%: Dizziness, bruising, diarrhea, arthralgia

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersHepatic and renal function
Nursing: Physical Assessment/MonitoringMonitor hepatic and renal function with long-term use. Assess knowledge/teach patient appropriate use, possible side effects, and adverse symptoms to report.
Monitoring: Lab TestsHepatic and renal function
Patient EducationTake exactly as directed; do not take more than the recommended dose. Take with meals. Do not take additional vitamins without consulting prescriber. Skin may appear slightly yellow-orange. Not a proven sunblock. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, softgel: 10,000 int. units (6 mg); 25,000 int. units (15 mg)

A-Caro-25: 25,000 int. units (15 mg) [contains soy]

B-Caro-T™: 25,000 int. units (15 mg) [contains soybean lecithin and soybean oil]

Capsule:

Lumitene™: 50,000 int. units (30 mg)

Tablet: 10,000 int. units

Generic AvailableYes
Mechanism of ActionThe exact mechanism of action in erythropoietic protoporphyria has not as yet been elucidated; although patient must become carotenemic before effects are observed, there appears to be more than a simple internal light screen responsible for the drug's action. A protective effect was achieved when beta-carotene was added to blood samples. The concentrations of solutions used were similar to those achieved in treated patients. Topically applied beta-carotene is considerably less effective than systemic therapy.
Pharmacodynamics/Kinetics

Metabolism: Prior to absorption, converted to vitamin A in the wall of the small intestine, then oxidized to retinoic acid and retinol in the presence of fat and bile acids; small amounts are then stored in the liver; retinol (active) is conjugated with glucuronic acid

Excretion: Urine and feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsThere is no compelling evidence that supplemental antioxidant therapy has a role in the primary prevention of cardiovascular disease. The role of antioxidant therapy in secondary prevention has also not been established, in part, because of a lack of concordance between studies, reports of increased risk with specific antioxidants (eg, beta-carotene), not fully understanding the underlying pathophysiologic mechanisms, and the use of different doses or combinations of antioxidants. In general, secondary prevention trials evaluating vitamin E have shown the most promise. However, a recent trial (HOPE) demonstrated no cardiovascular benefit from the use of vitamin E in patients with or at risk for coronary artery disease. Until further outcome trials establish the role of vitamin E and possible other antioxidants for the secondary prevention of cardiovascular disease, patients should be encouraged to follow a balanced diet that is rich in antioxidants (eg, citrus fruits, vegetables, whole grains).

International Brand NamesB-Tene (AU); Carotaben (CH, DE, NO); Natural Betacarotene (AU); Solvin (EC)

Betahistine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(bay ta HISS teen)
Canadian Brand NamesSerc®
Pharmacologic CategoryHistamine H_1 Agonist
Use: Labeled IndicationsTreatment of Ménière's disease (to decrease episodes of vertigo)
Dosing: AdultsMénière's disease: Oral: 8-16 mg 3 times/day. Administration with meals is recommended.
Dosing: ElderlyRefer to adult dosing.
Administration: OralAdministration with meals is recommended.
Dietary ConsiderationsShould be taken with food.
StorageStore at 15°C to 30°C.
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to betahistine or any component of the formulation; peptic ulcer disease; pheochromocytoma
Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Respiratory disease: Use with caution in patients with respiratory diseases, including asthma and COPD with bronchospastic component.

Concurrent drug therapy issues:

- Antihistamines: Avoid concurrent use with antihistamines.

Special populations:

- Pediatrics: Not recommended for use in children.

Pregnancy Risk FactorNot available
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Should be used only when potential benefit to the woman outweighs possible risk to fetus.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Central nervous system: Headache, somnolence (case reports)

Cardiovascular: Ventricular extrasystoles (case reports)

Dermatologic; Rash, pruritus, urticaria

Gastrointestinal: Dyspepsia, nausea, peptic ulcer disease (including exacerbation of previous disease)

Drug Interactions

Antihistamines: May diminish the therapeutic effect of Betahistine. **Exceptions:** Epinastine; Ketotifen; Levocabastine; Olopatadine. *Risk C: Monitor therapy*

Beta2-Agonists: Betahistine may diminish the therapeutic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet:

Serc® [CAN]: 16 mg, 24 mg [not available in the U.S.]

Generic AvailableNo
ManufacturerSolvay (Canada)
Pharmacodynamics/Kinetics

Absorption: Rapid, complete

Metabolism: Hepatic

Half-life elimination: 3.4 hours

Excretion: Urine (as inactive metabolites)

Pharmacotherapy PearlsNot available in U.S.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBetahistine Dihydrochloride

International Brand NamesAequamen (DE); Agiserc (IL); Alfinor (MY); Betahistine-Eurogenerics (LU); Betaserc (AT, BE, BG, BR, CH, CO, CZ, DK, EC, EE, FI, GR, HK, HN, HR, HU, ID, LU, NL, NO, PE, PL, PT); Betistin (UY); Fidium (ES); Histimerck (PL); Lectil (FR); Lobione (LU); Meniace (JP); Merislon (CL, CR, DO, GT, HK, ID, JP, MY, PH, SG, SV, TH, TW); Mertigo (ID); Meslon (TW); Microser (AR, CN, EC, IT, PE, PK, PL, VE); Serc (AU, GB, IE, MX, PK, ZA); Suzutolon (JP); Urutal (HR); Vasomotal (DE, PY); Vasotal (UY); Verdiz (PH); Vergo (NZ); Vertin (IN); Vertiserc (IT); Verum (CO)

Betaine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

> Betaine may be confused with Betadine®
>
> Cystadane® may be confused with cysteamine, cysteine

Pronunciation(BAY ta een)
U.S. Brand NamesCystadane®
Canadian Brand NamesCystadane®
Pharmacologic CategoryHomocystinuria, Treatment Agent
Use: Labeled IndicationsTreatment of homocystinuria (eg, deficiencies or defects in cystathionine beta-synthase [CBS], 5,10-methylene tetrahydrofolate reductase [MTHFR], and cobalamin cofactor metabolism [CBL])
Dosing: AdultsTreatment of homocystinuria: Oral: 6 g/day administered in divided doses of 3 g twice daily. Dosages of up to 20 g/day have been necessary to control homocysteine levels in some patients.

Note: Dosage in all patients can be gradually increased until plasma total homocysteine is undetectable or present only in small amounts

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Treatment of homocystinuria: Oral:

> *Children <3 years:* Dosage may be started at 100 mg/kg/day and then increased weekly by 50 mg/kg increments.
>
> *Children ≥3 years:* Refer to adult dosing.
>
> **Note:** Dosage in all patients can be gradually increased until plasma total homocysteine is undetectable or present only in small amounts. One study in six patients with CBS deficiency, ranging from 6-17 years of age, showed minimal benefit from exceeding a twice daily dosing schedule and a 150 mg/kg/day dosage.

Administration: OralMeasure prescribed amount with provided measuring scoop and dissolve in 120-180 mL of water for immediate ingestion.
Dietary ConsiderationsBetaine is a metabolite of choline and is present in small amounts in foods such as beets, spinach, cereals, and seafood.
StorageStore at 15°C to 30°C (59°F to 86°F). Protect from moisture
ContraindicationsHypersensitivity to betaine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Cerebral edema: May be associated with hypermethioninemia.

Special populations:

- Cystathionine beta-synthase (CBS) deficiency: Use caution in patients with CBS deficiency; treatment with betaine may cause large increases of plasma methionine concentrations.

Other warnings/precautions:

- Experienced personnel: Use of betaine should be limited to healthcare providers knowledgable in treating patients with homocystinuria.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with betaine. It is not known whether betaine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Betaine should be given to a pregnant woman only if needed.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsBetaine is found naturally in human breast milk. The influence from betaine therapy is unknown.
Adverse Reactions

Frequency not defined: Gastrointestinal: Diarrhea, GI distress, nausea

Postmarketing and/or case reports: Cerebral edema (associated with hypermethioninemia)

Drug InteractionsThere are no known significant interactions.

Monitoring Parameters

Total plasma homocysteine levels to determine therapeutic response. In patients with elevated plasma methionine (eg, CBS deficiency), monitor plasma methionine (maintain <1000 micromol/L).

Monitoring: Lab TestsTotal plasma homocysteine levels to determine therapeutic response. In patients with elevated plasma methionine (eg, CBS deficiency), monitor plasma methionine (maintain <1000 micromol/L).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for oral solution, anhydrous:

Cystadane®: 1 g/scoop (180 g) [1 scoop = 1.7 mL]

Generic AvailableNo

Mechanism of ActionBetaine acts as a methyl group donor in the remethylation of homocysteine to methionine. Homocystinuria is an inborn error of metabolism in which elevated plasma homocysteine levels can lead to mental retardation, ocular abnormalities, osteoporosis, premature atherosclerosis and thromboembolic disease. Remethylation is one of the two divergent pathways in the metabolism of homocysteine. The second pathway involves transsulfuration of homocysteine to produce cysteine. A number of enzymes and cofactors are also involved in these pathways.

Pharmacotherapy PearlsBetaine has been used in conjunction with vitamin B_6 (pyridoxine), vitamin B_{12} (cobalamin), and folate in the management of homocystinuria.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBetaine Anhydrous

References

Burns SP, Iles RA, Ryalls M, et al "Methylgenesis From Betaine in Cystathionine-Beta-Synthase Deficiency," *Biochem Soc Trans*, 1993, 21:455S. [PubMed 7510653]

Devlin AM, Hajipour L, Gholkar A, "Cerebral Edema Associated With Betaine Treatment in Classical Homocystinuria," *J Pediatr*, 2001,144(4):545-8.[PubMed 15069409]

Kishi T, Kawamura I, Harada Y, et al, "Effect of Betaine on S-Adenosylmethionine Levels in the Cerebrospinal Fluid in a Patient With Methylenetetrahydrofolate Reductase Deficiency and Peripheral Neuropathy," *J Inherit Metab Dis*, 1994, 17:560-5. [PubMed 7837762]

Lawson-Yuen A and Levy, HL, "The Use of Betaine in the Treatment of Elevated Homocysteine," *Mol Genet Metab*, 2006, 88(3):201-7.[PubMed 16545978]

Matthews A, Johnson TN, Rostami-Hodjegan A, et al, "An Indirect Response Model of Homocysteine Suppression by Betaine: Optimising the Dosage Regimen of Betaine in Homocystinuria," *Br J Clin Pharmacol*, 2002, 54(2):140-6. [PubMed 12207633]

Smolin LA, Benevenga NJ, and Berlow S, "The Use of Betaine for the Treatment of Homocystinuria," *J Pediatr*, 1981, 99:467-72.[PubMed 7264811]

International Brand NamesCystadan (AU, IL)

Betamethasone and Clotrimazole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Clotrimazole may be confused with co-trimoxazole

Lotrisone® may be confused with Lotrimin®

Pronunciation(bay ta METH a sone & kloe TRIM a zole)

U.S. Brand NamesLotrisone®

Canadian Brand NamesLotriderm®

Pharmacologic CategoryAntifungal Agent, Topical; Corticosteroid, Topical

Use: Labeled IndicationsTopical treatment of various dermal fungal infections (including tinea pedis, cruris, and corpora in patients ≥17 years of age)

Use: DentalTreatment of a variety of oral diseases of allergic, inflammatory, or autoimmune origin

Dosing: Adults

Allergic or inflammatory diseases: Topical: Apply to affected area twice daily, morning and evening

Tinea corporis, tinea cruris: Topical: Massage into affected area twice daily, morning and evening. Do not use for longer than 2 weeks; re-evaluate after 1 week if no clinical improvement. Do not exceed 45 g cream/week or 45 mL lotion/week.

Tinea pedis: Topical: Massage into affected area twice daily, morning and evening. Do not use for longer than 4 weeks; re-evaluate after 2 weeks if no clinical improvement. Do not exceed 45 g cream/week or 45 mL lotion/week.

Dosing: ElderlyRefer to adult dosing. Use with caution. Skin atrophy and skin ulceration (rare) have been reported in patients with thinning skin. Do not use for diaper dermatitis or under occlusive dressings.

Dosing: Pediatric

Children <17 years: Do not use.

Children ≥17 years: Refer to adult dosing.

Administration: TopicalFor external use only. Do not use on open wounds. Do not cover with occlusive dressings. Shake lotion well prior to use

Storage

Cream: Store at controlled room temperature of 25°C (77°F).

Lotion: Store upright at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to betamethasone, clotrimazole, other corticosteroids or imidazoles, or any component of the formulation

Allergy Considerations

- Azole Antifungal Allergy
- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Disease-related concerns:

- Diaper dermatitis: Do not use for diaper dermatitis; adverse reactions associated with corticosteroids have occurred.

Special populations:

- Elderly: Use topical corticosteroids with caution in the elderly; skin atrophy and, rarely, skin ulcerations have been reported.

- Pediatrics: Safety and efficacy have not been established in children <17 years of age; striae and growth suppression have been reported with use in infants and children.

Other warnings/precautions:

- Appropriate use: For topical use only; do not use intravaginally. Avoid contact with eyes or mouth. Do not use occlusive dressings; discontinue use if irritation occurs.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies using topical betamethasone during pregnancy. However, intrauterine growth retardation has been reported with another topical steroid. Avoid use in large amounts for long periods of time during pregnancy. Clotrimazole is poorly absorbed when used topically.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsBetamethasone: Systemic corticosteroids are excreted in human milk. The extent of topical absorption is variable. Use with caution while breast-feeding; do not apply to nipples.

Adverse ReactionsAlso see individual agents.

1% to 10%:

Dermatologic: Dry skin (2%)

Local: Burning (2%)

Neuromuscular & skeletal: Paresthesia (2%)

<1%: Edema, rash, secondary infection, stinging. Cushing's syndrome (HPA axis suppression), growth suppression, intracranial hypertension (benign), and skin atrophy have also been reported with use in children.

Postmarketing and/or case reports: Skin ulceration (rare)

Metabolism/Transport Effects

Betamethasone: **Inhibits** CYP3A4 (weak)

Clotrimazole: **Inhibits** CYP1A2 (weak), 2A6 (weak), 2B6 (weak), 2C8/9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak), 3A4 (moderate)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Monitoring ParametersUrinary free cortisol test, morning plasma cortisol test, and ACTH stimulation test may be used to evaluate HPA axis suppression; signs of infection

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsUrinary free cortisol test, morning plasma cortisol test, and ACTH stimulation test may be used to evaluate HPA axis suppression

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream: Betamethasone dipropionate 0.05% (base) and clotrimazole 1% (15 g, 45 g) [contains benzyl alcohol]

Lotrisone®: Betamethasone dipropionate 0.05% (base) and clotrimazole 1% (15 g, 45 g) [contains benzyl alcohol]

Lotion: Betamethasone dipropionate 0.05% (base) and clotrimazole 1% (30 mL) [contains benzyl alcohol]

Lotrisone®: Betamethasone dipropionate 0.05% (base) and clotrimazole 1% (30 mL) [contains benzyl alcohol]

Generic AvailableYes

ManufacturerSchering/Key

Pricing: U.S. (www.drugstore.com)

Cream (Clotrimazole-Betamethasone)

1-0.05% (15): $14.99

1-0.05% (45): $35.99

Lotion (Clotrimazole-Betamethasone)

1-0.05% (30): $39.99

Lotion (Lotrisone)

1-0.05% (30): $76.99

Mechanism of ActionBetamethasone dipropionate is a corticosteroid which controls the rate of protein synthesis; depresses the migration of polymorphonuclear leukocytes, fibroblasts; reverses capillary permeability and lysosomal stabilization at the cellular level to prevent or control inflammation. Clotrimazole is an antifungal agent that binds to phospholipids in the fungal cell membrane altering cell wall permeability resulting in loss of essential intracellular elements.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Betamethasone
- Clotrimazole

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsClotrimazole and Betamethasone

References

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

Reed, BD, “Dermatologic Drugs, Pregnancy, and Lactation. A Conservative Guide,” *Arch Dermatol*, 1997, 133: 894-8.

International Brand NamesBetamethasone Clo (MY); Clotrason (DK); Clotrasone (CL); Clotrisone (IL); Dermal C (MY); Derzid-C (TH); Flotiran (PT); Heltiskin (ID); Lotricomb (AR, DE, NZ); Lotriderm (AE, BE, BH, CH, CO, CR, CY, DO, EC, EG, GB, GT, HN, IL, IQ, IR, JO, KW, LB, LY, MX, NI, OM, PA, QA, SA, SV, SY, YE, ZA); Novadrel (CN)

Betamethasone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Luxiq® may be confused with Lasix®

International issues:

Beta-Val® may be confused with Betanol® which is a brand name for metipranolol in Monaco

Pronunciation(bay ta METH a sone)

U.S. Brand NamesBeta-Val®; Celestone®; Celestone® Soluspan®; Diprolene®; Diprolene® AF; Luxiq®

Canadian Brand NamesBetaderm; Betaject™; Betnesol®; Betnovate®; Celestone® Soluspan®; Diprolene® Glycol; Diprosone®; Ectosone; Prevex® B; Taro-Sone®; Topilene®; Topisone®; Valisone® Scalp Lotion

Pharmacologic CategoryCorticosteroid, Systemic; Corticosteroid, Topical

Use: Labeled IndicationsInflammatory dermatoses such as seborrheic or atopic dermatitis, neurodermatitis, anogenital pruritus, psoriasis, inflammatory phase of xerosis

Use: Unlabeled/InvestigationalAccelerate fetal lung maturation in patients with preterm labor

Use: DentalTreatment of a variety of oral diseases of allergic, inflammatory, or autoimmune origin

Dosing: AdultsBase dosage on severity of disease and patient response

Inflammatory conditions:

Oral: 2.4-4.8 mg/day in 2-4 doses; range: 0.6-7.2 mg/day

I.M.: Betamethasone sodium phosphate and betamethasone acetate: 0.6-9 mg/day (generally, $^{1}/_{3}$ to $^{1}/_{2}$ of oral dose) divided every 12-24 hours

Psoriasis (scalp): Topical (foam): Apply to the scalp twice daily, once in the morning and once at night.

Rheumatoid arthritis/osteoarthritis:

Intrabursal, intra-articular, intradermal: 0.25-2 mL

Intralesional:

Very large joints: 1-2 mL

Large joints: 1 mL

Medium joints: 0.5-1 mL

Small joints: 0.25-0.5 mL

Steroid-responsive dermatoses: Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.

Gel, augmented formulation: Apply once or twice daily; rub in gently. **Note:** Do not exceed 2 weeks of treatment or 50 g/week.

Lotion: Apply a few drops twice daily

Augmented formulation: Apply a few drops once or twice daily; rub in gently. **Note:** Do not exceed 2 weeks of treatment or 50 mL/week.

Cream/ointment: Apply once or twice daily

Augmented formulation: Apply once or twice daily. **Note:** Do not exceed 2 weeks of treatment or 45 g/week.

Dosing: ElderlyRefer to adult dosing. Use the lowest effective dose.

Dosing: PediatricBase dosage on severity of disease and patient response.

Inflammatory conditions:Note: Use lowest dose listed as initial dose for adrenocortical insufficiency (physiologic replacement).

I.M.:

Children ≤12 years: 0.0175-0.125 mg base/kg/day divided every 6-12 hours **or** 0.5-7.5 mg base/m^2/day divided every 6-12 hours

Children >13 years: Refer to adult dosing.

Oral:

Children ≤12 years: 0.0175-0.25 mg/kg/day divided every 6-8 hours **or** 0.5-7.5 mg/m^2/day divided every 6-8 hours

Children >13 years: Refer to adult dosing.

Topical: Children ≥13 years (use in children ≤12 years is not recommended): Use minimal amount for shortest period of time to avoid HPA axis suppression

Steroid-responsive dermatoses: Topical: Refer to adult dosing

Dosing: Hepatic ImpairmentAdjustments may be necessary in patients with liver failure because betamethasone is extensively metabolized in the liver

Calculations

- Body Surface Area: Pediatrics
- Corticosteroid Conversion

Administration: I.M.Do **not** give injectable sodium phosphate/acetate suspension I.V.

Administration: OralNot for alternate day therapy; once daily doses should be given in the morning.

Administration: TopicalApply topical sparingly to areas. Not for use on broken skin or in areas of infection. Do not apply to wet skin unless directed; do not cover with occlusive dressing. Do not apply very high potency agents to face, groin, axillae, or diaper area.

Foam: Invert can and dispense a small amount onto a saucer or other cool surface. Do not dispense directly into hands. Pick up small amounts of foam and gently massage into affected areas until foam disappears. Repeat until entire affected scalp area is treated.

Dietary ConsiderationsMay be taken with food to decrease GI distress.

Compatibility

Y-site administration: Compatible: Heparin, hydrocortisone sodium succinate, potassium chloride, vitamin B complex with C.

ContraindicationsHypersensitivity to betamethasone, other corticosteroids, or any component of the formulation; systemic fungal infections; I.M. administration contraindicated in idiopathic thrombocytopenia purpura

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections. In stressful situations, HPA axis-suppressed patients should receive adequate supplementation with natural glucocorticoids (hydrocortisone or cortisone) rather than betamethasone (due to lack of mineralocorticoid activity).

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox should be avoided; corticosteroids should not be used to treat ocular herpes simplex. Corticosteroids should not be used for cerebral malaria or viral hepatitis. Close observation is required in patients with latent tuberculosis and/or TB reactivity; restrict use in active TB (only in conjunction with antituberculosis treatment).

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Myopathy: Acute myopathy has been reported with high dose corticosteroids, usually in patients with neuromuscular transmission disorders; may involve ocular and/or respiratory muscles; monitor creatine kinase; recovery may be delayed.

- Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

- Skin reactions: Discontinue if skin irritation or contact dermatitis should occur; do not use in patients with decreased skin circulation.

Disease-related issues:

- Cardiovascular disease: Use with caution in patients with HF; long-term use has been associated with fluid retention and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.

- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.

- Head injury: Increased mortality was observed in patients receiving high-dose I.V. methylprednisolone; high-dose corticosteroids should not be used for the management of head injury.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids.

- Myocardial infarction (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Consider routine eye exams in chronic users.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Elderly: Because of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly in the smallest possible effective dose for the shortest duration.

- Pediatrics: May affect growth velocity; growth should be routinely monitored in pediatric patients. Topical use in patients ≤12 years of age is not recommended.

Dosage form specific issues:

- Topical: Do not use occlusive dressings on weeping or exudative lesions and general caution with occlusive dressings should be observed; adverse effects may be increased.

- Very high potency topical products: Not for treatment of rosacea, perioral dermatitis; not for use on face, groin, or axillae; not for use in a diapered area. Avoid concurrent use of other corticosteroids.

Other warnings/precautions:

- Discontinuation of therapy: Withdraw therapy with gradual tapering of dose.

Geriatric ConsiderationsBecause of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly, in the smallest possible dose, and for the shortest possible time.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed with corticosteroids in animal reproduction studies. Betamethasone crosses the placenta; approximately 25% is metabolized by placental enzymes to an inactive metabolite. Due to its positive effect on stimulating fetal lung maturation, the injection is often used in patients with premature labor (24-34 weeks gestation). Topical products are not recommended for extensive use, in large quantities, or for long periods of time in pregnant women. Some studies have shown an association between first trimester systemic corticosteroid use and oral clefts; adverse events in the fetus/neonate have been noted in case reports following large doses of systemic corticosteroids during pregnancy. Women exposed to betamethasone during pregnancy for the treatment of an autoimmune disease may contact the OTIS Autoimmune Diseases Study at 877-311-8972.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsCorticosteroids are excreted in human milk. The onset of milk secretion after birth may be delayed and the volume of milk produced may be decreased by antenatal betamethasone therapy; this affect was seen when delivery occurred 3-9 days after the betamethasone dose in women between 28 and 34 weeks gestation. Antenatal betamethasone therapy did not affect milk production when birth occurred <3 days or >10 days of treatment. It is not known if systemic absorption following topical administration results in detectable quantities in human milk. Use with caution while breast-feeding; do not apply to nipples.

Adverse Reactions

Systemic:

Cardiovascular: Congestive heart failure, edema, hyper-/hypotension

Central nervous system: Dizziness, headache, insomnia, intracranial pressure increased, lightheadedness, nervousness, pseudotumor cerebri, seizure, vertigo

Dermatologic: Ecchymoses, facial erythema, fragile skin, hirsutism, hyper-/hypopigmentation, perioral dermatitis (oral), petechiae, striae, wound healing impaired

Endocrine & metabolic: Amenorrhea, Cushing's syndrome, diabetes mellitus, growth suppression, hyperglycemia, hypokalemia, menstrual irregularities, pituitary-adrenal axis suppression, protein catabolism, sodium retention, water retention

Gastrointestinal: Abdominal distention, appetite increased, hiccups, indigestion, peptic ulcer, pancreatitis, ulcerative esophagitis

Local: Injection site reactions (intra-articular use), sterile abscess

Neuromuscular & skeletal: Arthralgia, muscle atrophy, fractures, muscle weakness, myopathy, osteoporosis, necrosis (femoral and humeral heads)

Ocular: Cataracts, glaucoma, intraocular pressure increased

Miscellaneous: Anaphylactoid reaction, diaphoresis, hypersensitivity, secondary infection

Topical:

Dermatologic: Acneiform eruptions, allergic dermatitis, burning, dry skin, erythema, folliculitis, hypertrichosis, irritation, miliaria, pruritus, skin atrophy, striae, vesiculation

Endocrine and metabolic effects have occasionally been reported with topical use.

Metabolism/Transport Effects **Inhibits** CYP3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Betamethasone interferes with calcium absorption.

Herb/Nutraceutical: Avoid cat's claw, echinacea (have immunostimulant properties).

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic response and adverse effects according to indications for therapy, dose, route (systemic or topical), and duration of therapy. When used for long-term therapy (>10-14 days), do not discontinue abruptly; decrease dosage incrementally. Growth should be routinely monitored in pediatric patients. With systemic administration, caution patients with diabetes to monitor glucose levels closely (corticosteroids may alter glucose levels). Teach patient proper use (according to formulation), side effects/appropriate interventions, and symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed; do not increase dose or discontinue this medicine abruptly without consulting prescriber. Take oral medication with or after meals. Avoid alcohol and limit intake of caffeine or stimulants. Prescriber may recommend increased dietary vitamins, minerals, or iron. If you have diabetes, monitor glucose levels closely (antidiabetic medication may need to be adjusted). Inform prescriber if you are experiencing greater-than-normal levels of stress (medication may need adjustment). You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccination without consulting prescriber). Some forms of this medication may cause GI upset (small frequent meals and frequent mouth care may help or oral medication may be taken with meals to reduce GI upset). Report promptly excessive nervousness or sleep disturbances; signs of infection (eg, sore throat, unhealed injuries); excessive growth of body hair or loss of skin color; vision changes; excessive or sudden weight gain (>5 lb/week); swelling of face or extremities; respiratory difficulty; muscle weakness; change in color of stools (tarry) or persistent abdominal pain; or worsening of condition or failure to improve.

Topical: For external use only. Do not use for eyes, mucous membranes, or open wounds. Use exactly as directed. Before using, wash and dry area gently. Apply in a thin layer (may rub in lightly). Apply light dressing (if necessary) to area being treated. Do not use occlusive dressing unless so advised by prescriber. Avoid prolonged or excessive use around sensitive tissues, genital, or rectal areas. Avoid exposing treated area to direct sunlight. Inform prescriber if condition worsens (redness, swelling, irritation, signs of infection, or open sores) or fails to improve.

Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: Potency expressed as betamethasone base.

Aerosol, topical, as valerate [foam]:

Luxiq®: 0.12% (50 g, 100 g, 150 g) [strength expressed as salt; contains ethanol 60.4%]

Cream, topical, as dipropionate: 0.05% (15 g, 45 g)

Cream, topical, as dipropionate augmented: 0.05% (15 g, 50 g)

Diprolene® AF: 0.05% (15 g, 50 g)

Cream, topical, as valerate (Beta-Val®): 0.1% (15 g, 45 g)

Beta-Val®: 0.1% (15 g, 45 g)

Gel, topical, as dipropionate augmented: 0.05% (15 g, 50 g)

Injection, suspension:

Celestone® Soluspan®: Betamethasone sodium phosphate 3 mg and betamethasone acetate 3 mg per 1 mL (5 mL) [6 mg/mL]

Lotion, topical, as dipropionate: 0.05% (60 mL)

Lotion, topical, as dipropionate augmented:

Diprolene®: 0.05% (30 mL, 60 mL)

Lotion, topical, as valerate: 0.1% (60 mL)

Beta-Val®: 0.1% (60 mL)

Ointment, topical, as dipropionate: 0.05% (15 g, 45 g)

Ointment, topical, as dipropionate augmented: 0.05% (15 g, 50 g)

Diprolene®: 0.05% (15 g, 50 g)

Ointment, topical, as valerate: 0.1% (15 g, 45 g)

Solution, as base:

Celestone®: 0.6 mg/5 mL (118 mL) [contains alcohol and sodium benzoate; cherry-orange flavor]

Generic AvailableYes: Excludes aerosol, injection, solution

ManufacturerSchering-Plough Corp

Pricing: U.S. (www.drugstore.com)

Cream (Aug Betamethasone Dipropionate)

0.05% (15): $31.99

0.05% (50): $59.99

Cream (Beta-Val)

0.1% (15): $11.99

0.1% (45): $12.99

Cream (Betamethasone Dipropionate)

0.05% (15): $12.99

0.05% (45): $11.99

Cream (Diprolene AF)

0.05% (15): $64.00

0.05% (50): $135.62

Foam (Luxiq)

0.12% (50): $131.23

0.12% (100): $233.04

Gel (AlphaTrex)

0.05% (15): $48.39

Gel (Aug Betamethasone Dipropionate)

0.05% (15): $34.15

0.05% (50): $55.99

Gel (Diprolene)

0.05% (15): $49.99

0.05% (50): $103.99

Lotion (Aug Betamethasone Dipropionate)

0.05% (60): $89.99

Lotion (Beta-Val)

0.1% (60): $14.99

Lotion (Betamethasone Dipropionate)

0.05% (60): $21.99

Lotion (Diprolene)

0.05% (30): $72.69

0.05% (60): $136.70

Ointment (Aug Betamethasone Dipropionate)

0.05% (15): $28.99

0.05% (45): $53.99

Ointment (Betamethasone Dipropionate)

0.05% (15): $12.99

0.05% (45): $11.99

Ointment (Betamethasone Valerate)

0.1% (15): $11.99

0.1% (45): $15.87

Ointment (Diprolene)

0.05% (15): $64.00

0.05% (50): $135.99

Mechanism of ActionControls the rate of protein synthesis; depresses the migration of polymorphonuclear leukocytes, fibroblasts; reverses capillary permeability and lysosomal stabilization at the cellular level to prevent or control inflammation

Pharmacodynamics/Kinetics

Protein binding: 64%

Metabolism: Hepatic

Half-life elimination: 6.5 hours

Time to peak, serum: I.V.: 10-36 minutes

Excretion: Urine (<5% as unchanged drug)

Related Information

- Corticosteroids

Pharmacotherapy Pearls

Very high potency: Augmented betamethasone dipropionate ointment, lotion

High potency: Augmented betamethasone dipropionate cream, betamethasone dipropionate cream and ointment

Intermediate potency: Betamethasone dipropionate lotion, betamethasone valerate cream

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, insomnia, or nervousness

Mental Health: Effects on Psychiatric TreatmentEnzyme inducers (barbiturates) may decrease the effects of corticosteroids

Cardiovascular ConsiderationsLong-term steroid therapy is associated with fluid retention and hypertension. Glucocorticoid agents have some mineralocorticoid activity with consequent hemodynamic effects. Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. In discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that the steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia.

Oral and intravenous steroid therapy in patients with heart failure should be administered cautiously with special attention given to signs and symptoms of fluid retention.

Anesthesia and Critical Care Concerns/Other Considerations

Neuromuscular Effects: ICU-acquired paresis was recently studied in five ICUs (three medical and two surgical) at four French hospitals. All ICU patients without pre-existing neuromuscular disease admitted from March 1999 through June 2000 were evaluated (de Jonghe, 2002). Each patient had to be mechanically ventilated for ≥7 days and was screened daily for awakening. The first day the patient was considered awake was Study Day 1. Patients with severe muscle weakness on Study Day 7 were considered to have ICU-acquired paresis. Among the 95 patients who were evaluable, about 25% developed ICU-acquired paresis. Independent predictors included female gender, the number of days with two or more organ dysfunctions, and administration of corticosteroids. Further studies may be required to verify and characterize the association between the development of ICU-acquired paresis and use of corticosteroids. Concurrent use of a corticosteroid and muscle relaxant appear to increase the risk of certain ICU myopathies; avoid or administer the corticosteroid at the lowest dose possible.

Adrenal Insufficiency: Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. When discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that the steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia. Patients on long-term steroid supplementation will require higher corticosteroid doses, with hydrocortisone or cortisone, when subject to stress (ie, trauma, surgery, severe infection). Guidelines for glucocorticoid replacement during various surgical procedures has been published (Coursin, 2002; Salem, 1994).

Septic Shock: A recent randomized, double-blind, placebo-controlled trial assessed whether low-dose corticosteroid administration could improve 28-day survival in patients with septic shock and relative adrenal insufficiency. Relative adrenal insufficiency was defined as an inappropriate response to corticotropin administration (increase of serum cortisol ≤9 mcg/dL from baseline). Cortisol levels were drawn immediately before corticotropin administration and 30-60 minutes afterwards. Three hundred adult septic shock patients requiring mechanical ventilation and vasopressor support were randomized to either hydrocortisone (50 mg IVP every 6 hours) and fludrocortisone (50 mcg tablet daily via nasogastric tube) or matching placebos for 7 days. In patients who did not appropriately respond to corticotropin (nonresponders), there were significantly fewer deaths in the active treatment group. Vasopressor therapy was withdrawn more frequently in this subset of the active treatment group. Adverse events were similar in both groups. Patients who lack adrenal reserve and thus have relative adrenal insufficiency during the stress of septic shock may benefit from physiologic steroid replacement. However, there was a trend for increased mortality in patients who responded to the corticotropin test (increase of serum cortisol >9 mcg/dL from baseline). These patients may not benefit from physiologic steroid replacement. Further study is required to better characterize the patient populations who may benefit.

Head Injury: The use of high-dose corticosteroids in acute head injury has been investigated in an international, double-blind, placebo-controlled trial. The purpose of this trial was to evaluate the effect of early administration of a 48-hour infusion of methylprednisolone on the risk of death and disability after a head injury. Adults (≥16 years of age) were randomized within 8 hours of a head injury if they had a Glasgow coma score of 14 or less and had no clear indication or contraindication for corticosteroid use. Ten thousand and eight patients were randomized to either placebo or 2 g of methylprednisolone infused over 1 hour, followed by a continuous infusion of 0.4 g per hour for 48 hours. Primary outcome measures were death from any cause within 2 weeks of injury and the composite of death or disability after 6 months. Patients that received methylprednisolone had a higher relative risk of death at 2 weeks and at 6 months. The risk of death or disability at 6 months was higher in the methylprednisolone group, but this result was not statistically significant. There were also no subsets of patients (time since injury, severity of injury) that benefited from corticosteroid treatment. The investigators concluded that corticosteroids should not be routinely used in the treatment of acute head injury (CRASH Trial Collaborators; Roberts, 2004; Edwards, 2005).

Index TermsBetamethasone Dipropionate; Betamethasone Dipropionate, Augmented; Betamethasone Sodium Phosphate; Betamethasone Valerate; Flubenisolone

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International Brand NamesAntroquoril (AU); Beavate (MY); Becasone (TH, TW); Beloderm (PL); Benoson (500 mcg) (ID); Besone (MY); Beta cream (NZ); Beta ointment (NZ); Beta Scalp (NZ); Betacorten (SG); Betamamallet (JP); Betanoid (ZA); Betapred (NO); Betason (500 mcg) (ID); Betnelan (500 mcg) (AE, BH, CY, EG, IL, IN, IQ, IR, JO, KW, LB, LY, NL, OM, PH, QA, SA, SY, YE); Betnelan (GB, PK); Betnesol (BG, GR, IL, LU, PL); Betnosone (MY); Betnovate (AU, CZ, EE, ES, MX, MY, PL); Buccobet (FR); Celestamine (DE); Celestan (AT); Celestene (FR); Celestoderm (FI); Celestoderm V (ES); Celestoderm-V (MY); Celeston (DK, SE); Celestone (500 mcg) (AE, AR, BB, BF, BH, BJ, BM, BO, BR, BS, BZ, CI, CN, CO, CR, CY, DO, EC, EG, ET, GH, GM, GN, GT, GY, HN, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NI, NL, OM, PA, PE, PH, PR, PY, QA, SA, SC, SD, SL, SN, SR, SV, SY, TN, TT, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Celestone (AR, BE, CH, GR, HU, IT, LU, MX, PL, PT); Celestone-M (AU); Corteroid (AR); Cortival (AU); Cortixyl (PE); Cronolevel (MX); Dendri (KP); Dermasole (MY); Diprofast (MX); Diprolene (PL); Dipronova (MX); Diprosone (IE, MX, PL); Diprospan (MX); Erispan (MX); Flosteron solubile (PL); Hormezone (JP); Sanbetason (JP); Synmethasone (HK); Walacort (IN)

Betaxolol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

> Betaxolol may be confused with bethanechol, labetalol
>
> Betoptic® S may be confused with Betagan®, Timoptic®

Pronunciation(be TAKS oh lol)

U.S. Brand NamesBetoptic® S; Kerlone®

Canadian Brand NamesBetoptic® S; Sandoz-Betaxolol

Pharmacologic CategoryBeta Blocker, Beta$_1$ Selective; Ophthalmic Agent, Antiglaucoma

Use: Labeled Indications

Ophthalmic: Treatment of chronic open-angle glaucoma or ocular hypertension

Oral: Management of hypertension

Dosing: Adults

Glaucoma: Ophthalmic:

> Solution: Instill 1-2 drops into affected eye(s) twice daily.
>
> Suspension (Betoptic® S): Instill 1 drop into affected eye(s) twice daily.

Hypertension, angina: Oral: 5-10 mg/day; may increase dose to 20 mg/day after 7-14 days if desired response is not achieved

Dosing: Elderly

Ophthalmic: Refer to adult dosing.

Hypertension: Oral: Initial: 5 mg/day

Dosing: Pediatric**Elevated intraocular pressure:** Ophthalmic suspension (Betoptic® S): Instill 1 drop into affected eye(s) twice daily.

Dosing: Renal Impairment
Severe impairment: Initial dose: 5 mg/day; may increase every 2 weeks up to a maximum of 20 mg/day.

Hemodialysis: Initial dose: 5 mg/day; may increase every 2 weeks up to a maximum of 20 mg/day. Supplemental dose not required.

Calculations

- Creatinine Clearance: Adults

Administration: OralAbsorption is not affected by food.

Administration: OtherOphthalmic: Shake suspension well before using. Tilt head back and instill in eye. Keep eye open and do not blink for 30 seconds. Apply gentle pressure to lacrimal sac for 1 minute. Wipe away excess from skin. Do not touch applicator to eye and do not contaminate tip of applicator.

StorageAvoid freezing. Store tablets at room temperature of 15°C to 25°C (59°F to 77°F). Store ophthalmic suspension upright at 2°C to 25°C (36°F to 77°F). Store ophthalmic solution at room temperature.

ContraindicationsHypersensitivity to betaxolol or any component of the formulation; sinus bradycardia; heart block greater than first-degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; uncompensated cardiac failure

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Concerns related to adverse events:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; however, betaxolol, with B$_1$

selectivity, may be used cautiously with the lowest possible dose (eg, 5-10 mg/day), availability of a bronchodilator, and close monitoring; if a dosage increase is indicated, administer in divided doses.

- Cerebrovascular insufficiency: Use with caution in patients with cerebrovascular insufficiency; hypotension and decreased heart rate may reduce cerebral blood flow.
- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating therapy.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate and/or mask signs and symptoms of hypoglycemia.
- Heart failure (HF): Use with caution in patients with compensated heart failure and monitor for a worsening of the condition. Discontinue ophthalmic preparations with signs of cardiac failure.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; may potentiate myasthenia-related muscle weakness, including diplopia and ptosis.
- Peripheral vascular disease (PVD) and Raynaud's disease: May precipitate or aggravate symptoms of arterial insufficiency in patients with PVD and Raynaud's disease. Use with caution and monitor for progression of arterial obstruction.
- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.
- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required in severe impairment and in patients on dialysis.
- Thyroid disease: May mask signs of hyperthyroidism (eg, tachycardia). If hyperthyroidism is suspected, carefully manage and monitor; abrupt withdrawal may precipitate thyroid storm.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents which decrease myocardial function.
- Calcium channel blockers: Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur.
- Cardiac glycosides: Use with caution in patients receiving digoxin; bradycardia or heart block can occur.

Special populations:

- Contact lens wearers: Ophthalmic suspension contains benzalkonium chloride which may be absorbed by contact lenses; remove contact lens prior to administration and wait 15 minutes before reinserting.
- Elderly: Bradycardia may be observed more frequently in elderly patients (>65 years of age); dosage reductions may be necessary.
- Pediatrics: Safety and efficacy of the oral formulation have not been established in children.

Dosage form specific issues:

- Ophthalmic: Inadvertent contamination of multiple-dose ophthalmic solutions has caused bacterial keratitis. Should not be used alone in angle-closure glaucoma (has no effect on pupillary constriction). Choroidal detachment has been reported with aqueous suppressant therapy after filtration procedures.

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, ischemia, and/or angina exacerbation.

Geriatric ConsiderationsDue to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (ie, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20% to 50% in elderly populations. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; however, there was drug-related postimplantation loss in rats and rabbits. There are no adequate and well-controlled studies in pregnant women.

LactationOral: Enters breast milk/use caution

Adverse Reactions

Ophthalmic:

>10%: Ocular: Short-term discomfort (≤25%)

<1%: Alopecia, asthma, bradycardia, bronchial secretions thickened, bronchospasm, depression, dizziness, dyspnea, glossitis, heart block, heart failure, headache, hives, insomnia, lethargy, myasthenia gravis exacerbation, respiratory failure, smell/taste perversion, toxic epidermal necrolysis, vertigo

Frequency not defined: Ocular: Allergic reaction, anisocoria, blurred vision, choroidal detachment, corneal punctate keratitis, corneal punctate staining (with or without dendritic formations), corneal sensitivity decreased, corneal staining, crusty lashes, discharge, dry eyes, edema, erythema, foreign body sensation, inflammation, itching sensation, keratitis, ocular pain, photophobia, tearing, visual acuity decreased

Systemic:

2% to 10%:

Cardiovascular: Bradycardia (6% to 8%; symptomatic bradycardia: <1% to 2%; dose-dependent), chest pain (2% to 7%), palpitation (2%), edema (≤2%; similar to placebo)

Central nervous system: Fatigue (3% to 10%), insomnia (1% to 5%), lethargy (3%)

Gastrointestinal: Nausea (2% to 6%), dyspepsia (4% to 5%), diarrhea (2%)

Neuromuscular & Skeletal: Arthralgia (3% to 5%), paresthesia (2%)

Respiratory: Dyspnea (2%), pharyngitis (2%)

Miscellaneous: Antinuclear antibody positive (5%), cold extremities (2%)

<2%, postmarketing, and/or case reports (limited to important or life-threatening): Acidosis, allergy, alopecia, ALT increased, AST increased, amnesia, anemia, angina, anorexia, arrhythmia, arthropathy, ataxia, atrioventricular block, blepharitis, breast fibroadenosis, bronchitis, bronchospasm, cataract, cerebrovascular disorder, conjunctivitis, constipation, cough, cystitis, deafness, depression (<1%), diabetes, diaphoresis, dreams abnormal (1%), dysphagia, dysuria, emotional lability, epistaxis, erythematous rash, fever, flu, flushing, hallucinations, heart failure, hyper-/hypotension, hypercholesterolemia, hyperglycemia, hypo/hyperkalemia, hyperlipemia, hypertrichosis, hyperuricemia, impotence (1%), intermittent claudication, iritis, labyrinth disorder, LDH increased, leukocytosis, libido decreased, lymphadenopathy, malaise, menstrual disorder, MI, muscle cramps, nervousness (1%), neuralgia, neuropathy, numbness, ocular hemorrhage, oliguria, peripheral ischemia, Peyronie's disease, pneumonia, prostatitis, proteinuria, pruritus, purpura, rash (1%), renal function abnormal, rhinitis (1%), rigors, scotoma, sinusitis, stupor, syncope, taste abnormal, tendonitis, thinking abnormal, thrombophlebitis, thrombosis, tinnitus, tremor, twitching, thrombocytopenia, vision abnormal, vomiting, weight gain/loss, xerostomia

Metabolism/Transport Effects **Substrate** (major) of CYP1A2, 2D6; **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid bayberry; blue cohosh, cayenne, ephedra, ginger, ginseng (American), gotu kola, and licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effects).

Test InteractionsOral betaxolol may interfere with glaucoma screening tests.

Monitoring ParametersOphthalmic: Intraocular pressure. Systemic: Blood pressure, pulse; baseline renal function

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (especially products that affects cardiac function or blood pressure). Assess therapeutic response and adverse effects. Patients with diabetes should be cautioned that beta-blockers may mask prominent hypoglycemic symptoms. Teach patient proper use (according to formulation), side effects/appropriate interventions, and symptoms to report. Systemic absorption from ophthalmic instillation is minimal. Intraocular pressure should be measured periodically.

Monitoring: Lab TestsOphthalmic: Intraocular pressure. Systemic: Baseline renal function.

Patient EducationDo not take any new medication during therapy unless approved by prescriber.

Oral: Use as directed and do not discontinue this medicine without consulting prescriber. May cause dizziness or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). If you have diabetes, may mask prominent hypoglycemic symptoms. Monitor blood glucose levels closely. Report chest pain, palpitations or irregular heartbeat; persistent GI upset (eg, nausea, vomiting, diarrhea, or constipation); unusual cough; respiratory difficulty; swelling or coolness of extremities; or unusual mental depression. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Ophthalmic: Shake suspension well before using. Tilt head back and instill in eye. Keep eye open; do not blink for 30 seconds. Apply gentle pressure to corner of eye for 1 minute. Wipe away excess from skin. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Report if condition does not improve or if you experience eye pain, vision changes, or other adverse eye response. Remove contact lens prior to administration and wait 15 minutes before reinserting. If other ophthalmic medicines are being used, administer at least 10 minutes prior to instilling this medicine.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, ophthalmic: 0.5% (5 mL, 10 mL, 15 mL) [contains benzalkonium chloride]

Suspension, ophthalmic:

Betoptic® S: 0.25% (5 mL [DSC], 10 mL, 15 mL) [contains benzalkonium chloride]

Tablet, as hydrochloride: 10 mg, 20 mg

Kerlone®: 10 mg, 20 mg

Generic AvailableYes: Solution, tablet

Pricing: U.S. (www.drugstore.com)

Solution (Betaxolol HCl)

0.5% (15): $79.69

Suspension (Betoptic-S)

0.25% (5): $51.99

0.25% (10): $95.99

0.25% (15): $142.76

Tablets (Betaxolol HCl)

10 mg (30): $36.99

Tablets (Kerlone)

10 mg (30): $50.99

Mechanism of ActionCompetitively blocks beta$_1$-receptors, with little or no effect on beta$_2$-receptors; with ophthalmic use, reduces intraocular pressure by reducing the production of aqueous humor

Pharmacodynamics/Kinetics

Onset of action: Ophthalmic: 30 minutes; Oral: 1-1.5 hours

Duration: Ophthalmic: ≥12 hours

Absorption: Ophthalmic: Some systemic; Oral: ~100%

Metabolism: Hepatic to multiple metabolites

Protein binding: Oral: ~50%

Bioavailability: Oral: 89%

Half-life elimination: Oral: 14-22 hours; prolonged in hepatic disease and/or chronic renal failure

Time to peak: Ophthalmic: ~2 hours; Oral: 1.5-6 hours

Excretion: Urine (>80%; as unchanged drug [15%] and inactive metabolites)

Related Information

- Beta-Blockers
- Glaucoma Drug Therapy

Dental Health: Effects on Dental TreatmentBetaxolol is a cardioselective beta-blocker. Local anesthetic with vasoconstrictor can be safely used in patients medicated with betaxolol. Nonselective beta-blockers (ie, propranolol, nadolol) enhance the pressor response to epinephrine, resulting in hypertension and bradycardia; this has not been reported for betaxolol. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness; rare reports of depression and hallucinations

Mental Health: Effects on Psychiatric TreatmentHas been used to treat akathisia; propranolol preferred

Cardiovascular Considerations

Hypertension: Beta-blocker therapy in the treatment of hypertension has been associated with improved cardiovascular outcomes. This class of drug is beneficial for elderly patients with hypertension. A recent UKPDS study showed that beta-blocker therapy (atenolol) was as effective as an ACE inhibitor in reducing cardiovascular events and that the benefits of therapy were related more to the degree of antihypertensive efficacy rather than the class of drug used.

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia and hypertension.

Anesthesia and Critical Care Concerns/Other Considerations**Surgery:** Based on available evidence, beta-blockers should be started days to weeks before elective surgery in selected patients when possible and titrated to a heart rate <65 beats per minute. Additional data suggest that long acting beta-blockers may be superior to short acting ones (Redelmeier, 2005). The ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery recommend beta-blockers be continued in patients undergoing surgery who are receiving beta-blockers to treat angina, symptomatic arrhythmias, hypertension, and other ACC/AHA Class I guideline indications (Class I recommendation). The guidelines also recommend that beta-blockers be given to patients undergoing vascular surgery who have myocardial ischemia demonstrated during preoperative testing (Class I recommendation). Since the publication of these guidelines, there have been two large trials published regarding this issue.

The guidelines also state that beta-blockers are probably recommended in patients undergoing intermediate risk (eg, carotid endarterectomy, prostate surgery) or vascular surgery in whom preoperative assessment identifies coronary heart disease or high cardiac risk (Class IIa recommendation). High cardiac risk is defined as having >1 of the following clinical risk factors: History of ischemic heart disease, compensated or prior heart failure, cerebrovascular disease, diabetes mellitus, or renal insufficiency. The use of beta-blockers is uncertain in patients undergoing intermediate risk or vascular surgery with ≤1 clinical risk factor (Class IIb recommendation).

The majority of published trials suggest a benefit of perioperative beta-blocker use during noncardiac surgery especially in high-risk patients; however, more recent clinical trials have not shown a benefit to perioperative beta-blockade for noncardiac surgery (Juul, 2006; Yang, 2006).

Index TermsBetaxolol Hydrochloride

References

Antman EM, Anbe SC, Alpert JS, et al, “ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction - Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction),” *Circulation*, 2004, 110(5):588-636. Available at: http://www.circulationaha.org/cgi/content/full/110/5/588. Last accessed October 26, 2004. [PubMed 15289388]

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Chobanian AV, Bakris GL, Black HR, et al, “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report,” *JAMA*, 2003, 289(19):2560-71. [PubMed 12748199]

“Consensus Recommendations for the Management of Chronic Heart Failure. On Behalf of the Membership of the Advisory Council to Improve Outcomes Nationwide in Heart Failure,” *Am J Cardiol*, 1999, 83(2A):1A-38A. [PubMed 10072251]

Gibbons RJ, Abrams J, Chatterjee K, et al, “ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina - Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina),” *J Am Coll Cardiol*, 2003, 41(1):159-68. [PubMed 12570960]

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Redelmeier D, Scales D, and Kopp A, "Beta Blockers for Elective Surgery in Elderly Patients: Population Based, Retrospective Cohort Study," *BMJ*, 2005, 331(7522):932.[PubMed 16210252]

Wong DG, Spence JD, Lamki L, et al, “Effect of Nonsteroidal Anti-inflammatory Drugs on Control of Hypertension of Beta-Blockers and Diuretics,” *Lancet*, 1986, 1(8488):997-1001.

Yang H, Raymer K, Butler R, et al, “The Effects of Perioperative Beta-Blockade: Results of the Metoprolol After Vascular Surgery (MaVS) Study, a Randomized Controlled Trial,” *Am Hear J*, 2006, 152(5):983-90.[PubMed 17070177]

International Brand NamesAlcon Betoptic (PH); Betabion (PL); Betac (MY, SG, TW); Betarun (TW); Betasel (AR); Betaxa (BG); Betoptic (AE, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CN, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HN, HR, HU, IE, IL, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PE, PK, PL, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Betoptic S (AU, BG, BR, CL, CN, CO, CR, CZ, EE, GR, GT, HK, HN, IL, KP, MX, NI, NO, PA, PH, PL, SE, SG, SV, TH, TW, VE, ZA); Betoptima (DE, ID); Betoquin (AU); Daberot (KP); Kerlon (CH, FI, IT, NL); Kerlone (BE, DE, FR, GR, KP, LU, MY, PH, PT, PY, TW); Kerlong (JP); Lokren (HN, HU, PL); Optibet (ID); Optibetol (PL); Optipress (IN); Tonobexol (AR)

Bethanechol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Bethanechol may be confused with betaxolol

Pronunciation(be THAN e kole)
U.S. Brand NamesUrecholine®
Canadian Brand NamesDuvoid®; PMS-Bethanechol
Pharmacologic CategoryCholinergic Agonist
Use: Labeled IndicationsTreatment of acute postoperative and postpartum nonobstructive (functional) urinary retention; treatment of neurogenic atony of the urinary bladder with retention
Use: Unlabeled/InvestigationalGastroesophageal reflux
Dosing: Adults

Urinary retention, neurogenic bladder: Oral: Initial: 10-50 mg 3-4 times/day (some patients may require dosages of 50-100 mg 4 times/day). To determine effective dose, may initiate at a dose of 5-10 mg, with additional doses of 5-10 mg hourly until an effective cumulative dose is reached. Cholinergic effects at higher oral dosages may be cumulative.

Gastroesophageal reflux (unlabeled): Oral: 25 mg 4 times/day

Dosing: ElderlyRefer to adult dosing. Use the lowest effective dose.
Dosing: Pediatric

Urinary retention (unlabeled use): Oral: 0.3-0.6 mg/kg/day in 3-4 divided doses

Gastroesophageal reflux (unlabeled use): Oral: 0.3-0.6 mg/kg/day in 3-4 divided doses

Dietary ConsiderationsShould be taken 1 hour before meals or 2 hours after meals.
StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to bethanechol or any component of the formulation; mechanical obstruction of the GI or GU tract or when the strength or integrity of the GI or bladder wall is in question; hyperthyroidism, peptic ulcer disease, epilepsy, asthma, bradycardia, vasomotor instability, coronary artery disease, hypotension, or parkinsonism
Allergy Considerations

- Bethanechol Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Reflux infection: Potential for reflux infection if the sphincter fails to relax as bethanechol contracts the bladder.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsUrinary incontinence in elderly patients should be investigated. Bethanechol may be used for overflow incontinence (ie, dribbling) caused by an atonic or hypotonic bladder, but clinical efficacy is variable.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension, tachycardia, flushed skin

Central nervous system: Headache, malaise, seizure

Gastrointestinal: Abdominal cramps, belching, borborygmi, colicky pain, diarrhea, nausea, vomiting, salivation

Genitourinary: Urinary urgency

Ocular: Lacrimation, miosis

Respiratory: Asthmatic attacks, bronchial constriction

Miscellaneous: Diaphoresis

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Test InteractionsIncreased lipase, amylase (S), bilirubin, aminotransferase [ALT/AST] (S)

Monitoring ParametersObserve closely for side effects.

Nursing: Physical Assessment/MonitoringAssess bladder and sphincter adequacy prior to administering medication. Assess other medications patient may be taking for effectiveness and interactions. Assess therapeutic effectiveness and adverse reactions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake as directed, on an empty stomach to avoid nausea or vomiting. Do not discontinue this medicine without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause dizziness or hypotension (rise slowly from sitting or lying position and use caution when driving or climbing stairs); or vomiting or loss of appetite (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report persistent abdominal discomfort; significantly increased salivation, sweating, tearing, or urination; flushed skin; chest pain or palpitations; acute headache; unresolved diarrhea; excessive fatigue, insomnia, dizziness, or depression; increased muscle, joint, or body pain; vision changes or blurred vision; or respiratory difficulty or wheezing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet, as chloride: 5 mg, 10 mg, 25 mg, 50 mg

Duvoid® [CAN]: 10 mg, 25 mg, 50 mg [not available in U.S.]

Urecholine®: 5 mg, 10 mg, 25 mg, 50 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Bethanechol Chloride)

5 mg (90): $59.99

10 mg (90): $89.98

25 mg (90): $128.99

50 mg (90): $179.99

Tablets (Urecholine)

5 mg (90): $78.48

10 mg (90): $117.59

25 mg (90): $239.80

50 mg (90): $243.59

Mechanism of ActionDue to stimulation of the parasympathetic nervous system, bethanechol increases bladder muscle tone causing contractions which initiate urination. Bethanechol also stimulates gastric motility, increases gastric tone and may restore peristalsis.

Pharmacodynamics/Kinetics

Onset of action: 30-90 minutes

Duration: Up to 6 hours

Absorption: Variable

Dental Health: Effects on Dental TreatmentThis is a cholinergic agent similar to pilocarpine; expect to see salivation and sweating in patients.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentContraindicated in Parkinson's disease

Index TermsBethanechol Chloride

References

Andersson KE, “Current Concepts in the Treatment of Disorders of Micturition,” *Drugs*, 1988, 35(4):477-94. [PubMed 3292211]

Borzyskowski M and Mundy AR, “The Management of the Neuropathic Bladder in Childhood,” *Pediatr Nephrol*, 1988, 2(1):56-66[PubMed 2908664]

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Holloway RH, McCallum RW. “A Practical Approach to Gastroesophageal Reflux,” *Drug Ther*, 1983, 13(3):151-60.

Guerra MF and Ives TJ, “Bethanechol and Hypothermia,” *Ann Intern Med*, 1983, 99(2):279-80.

Romanowski GL, Shimp LA, Balson AB, et al, “Urinary Incontinence in the Elderly: Etiology and Treatment,” *Drug Intell Clin Pharm*, 1988, 22(7-8):525-33.[PubMed 3046886]

Sher PP, “Drug Interferences With Clinical Laboratory Tests,” *Drugs*, 1982, 24(1):24-63.[PubMed 6179732]

Sondheimer JM, Mintz, HL, and Michaels M. "Bethanechol Treatment of Gastroesophageal Reflux in Infants: Effect on Continuous Esophageal pH Records.," *J Pediatr*, 1984, 104(1):128-31.[PubMed 6690657]

International Brand NamesHinecol (KP); Liberon (BR); Miotonoachol (AR); Muscaran (BE, LU); Myo Hermes (ES); Myocholine Glenwood (CH); Myocholine-Glenwood (AT, DE, IT); Myotonine Chloride (GB, UY); Ucholine (TH); Urecholine (FI); Uriflow (PH); Urocarb (AU); Urotone (IN); Wecoli (TW)

Bevacizumab-Capecitabine

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Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer

Regimen Use Breast cancer

Index Terms Capecitabine-Bevacizumab

Regimen

Capecitabine: Oral: 1250 mg/m^2 twice daily days 1 to 14

[total dose/cycle = 35,000 mg/m^2]

Bevacizumab: I.V.: 15 mg/kg day 1

[total dose/cycle = 15 mg/kg]

Repeat cycle every 21 days for up to 35 cycles

References

Miller KD, Chap LI, Holmes FA, et al, "Randomized Phase III Trial of Capecitabine Compared With Bevacizumab Plus Capecitabine in Patients With Previously Treated Metastatic Breast Cancer," *J Clin Oncol*, 2005, 23(4):792-9.[PubMed 15681523]

Bevacizumab-Cisplatin-Gemcitabine (NSCLC)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Nonsmall Cell)

Regimen UseLung cancer, nonsmall cell

Index TermsCisplatin-Gemcitabine-Bevacizumab (NSCLC)

Regimen

Bevacizumab: I.V.: 7.5 or 15 mg/kg/dose day 1

[total dose/cycle = 7.5 or 15 mg/kg]

Cisplatin: I.V.: 80 mg/m^2/dose day 1

[total dose/cycle = 80 mg/m^2]

Gemcitabine: I.V.: 1250 mg/m^2/dose days 1 and 8

[total dose/cycle = 2500 mg/m^2]

Repeat cycle every 21 days for up to 6 cycles (bevacizumab monotherapy may be continued thereafter until disease progression)

References

Manegold C, von Pawel J, Zatloukal P, et al, “Randomised, Double-Blind Multicentre Phase III Study of Bevacizumab in Combination With Cisplatin and Gemcitabine in Chemotherapy-Naïve Patients With Advanced or Recurrent Non-Squamous Non-Small Cell Lung Cancer (NSCLC): BO17704,” *J Clin Oncol*, 2007, 25(18S) [abstract LBA7514 from 2007 ASCO Annual Meeting].

Bevacizumab-Fluorouracil-Leucovorin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Colorectal Cancer

Regimen Use Colorectal cancer

Index Terms Fluorouracil-Leucovorin-Bevacizumab

Regimen

Bevacizumab: I.V.: 5 mg/kg/day days 1, 15, 29, and 43

[total dose/cycle = 20 mg/kg]

Leucovorin: I.V.: 500 mg/m^2/day days 1, 8, 15, 22, 29, and 36

[total dose/cycle = 3000 mg/m^2]

Fluorouracil: I.V.: 500 mg/m^2/day days 1, 8, 15, 22, 29, and 36

[total dose/cycle = 3000 mg/m^2]

Repeat cycle every 56 days

References

Kabbinavar FF, Schulz J, McCleod M, et al, "Addition of Bevacizumab to Bolus Fluorouracil and Leucovorin in First-Line Metastatic Colorectal Cancer: Results of a Randomized Phase II Trial," *J Clin Oncol*, 2005, 23(16):3697-705.[PubMed 15738537]

Bevacizumab-Interferon Alfa-2a

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Renal Cell Cancer
Regimen UseRenal cell cancer
Index TermsInterferon Alfa 2a-Bevacizumab

Regimen

Interferon Alfa-2a: SubQ: 9 million units 3 times/week

[total dose/cycle = 54 million units]

Bevacizumab: I.V.: 10 mg/kg day 1

[total dose/cycle = 10 mg/kg]

Repeat cycle every 14 days for up to 1 year or until disease progression

References

Escudier B, Koralewski P, Pluzanska A, et al, "A Randomized, Controlled, Double-Blind Phase III Study (AVOREN) of Bevacizumab/Interferon-Îą2a vs Placebo/Interferon-Îą2a as First-Line Therapy in Metastatic Renal Cell Carcinoma," *J Clin Oncol*, 2007, 25(18S):3 [abstract from 2007 ASCO Annual Meeting Proceedings, Part I]

Escudier B, Pluzanska A, Koralewski P, et al, "Bevacizumab Plus Interferon Alfa-2a for Treatment of Metastatic Renal Cell Carcinoma: A Randomised, Double-Blind Phase III Trial," *Lancet*, 2007, 370(9605):2103-11.[PubMed 18156031]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Brain Tumors

Regimen UseBrain tumors

Index TermsIrinotecan-Bevacizumab (Glioblastoma)

Regimen**Note:** Patients receiving concurrent antiepileptic enzyme-inducing drugs received an increased dose of irinotecan (340 mg/m^2/dose).

Bevacizumab: I.V.: 10 mg/kg day 1

[total dose/cycle = 10 mg/kg]

Irinotecan: I.V.: 125 mg/m^2 day 1

[total dose/cycle = 125 mg/m^2]

Repeat cycle every 14 days

References

Vredenburgh JJ, Desjardins A, Herndon JE 2nd, et al, "Bevacizumab Plus Irinotecan in Recurrent Glioblastoma Multiforme," *J Clin Oncol*, 2007, 25(30):4722-9.[PubMed 17947719]

Bevacizumab-Irinotecan-Fluorouracil-Leucovorin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Colorectal Cancer

Regimen UseColorectal cancer

Index TermsIrinotecan-Fluorouracil-Leucovorin-Bevacizumab

Regimen

Bevacizumab: I.V.: 5 mg/kg/day days 1, 15, and 29

[total dose/cycle = 15 mg/kg]

Irinotecan: I.V.: 125 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 500 mg/m^2]

Fluorouracil: I.V.: 500 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 2000 mg/m^2]

Leucovorin: I.V.: 20 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 80 mg/m^2]

Repeat cycle every 42 days

References

Hurwitz H, Fehrenbacher L, Novotny W, et al, "Bevacizumab Plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer," *N Engl J Med*, 2004, 350(23):2335-42.[PubMed 15175435]

Bevacizumab-Oxaliplatin-Fluorouracil-Leucovorin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Colorectal Cancer

Regimen Use Colorectal cancer

Index Terms Bevacizumab-Oxaliplatin-Leucovorin-Fluorouracil; Oxaliplatin-Fluorouracil-Leucovorin-Bevacizumab

Regimen

Bevacizumab: I.V.: 10 mg/kg day 1

[total dose/cycle = 10 mg/kg]

Oxaliplatin: I.V.: 85 mg/m^2 day 1

[total dose/cycle = 85 mg/m^2]

Leucovorin: I.V.: 200 mg/m^2/day days 1 and 2

[total dose/cycle = 400 mg/m^2]

Fluorouracil: I.V. bolus: 400 mg/m^2/day days 1 and 2

followed by I.V.: 600 mg/m^2 continuous infusion over 22 hours days 1 and 2

[total dose/cycle = 2000 mg/m^2]

Repeat cycle every 14 days

References

Giantonio BJ, Catalano PJ, Meropol NJ, et al, "Bevacizumab in Combination With Oxaliplatin, Fluorouracil, and Leucovorin (FOLFOX4) for Previously Treated Metastatic Colorectal Cancer: Results From the Eastern Cooperative Oncology Group Study E3200," *J Clin Oncol*, 2007, 25(12):1539-44.[PubMed 17442997]

Bevacizumab

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Bevacizumab: Reports of Toxic Anterior Segment Syndrome (TASS), Endophthalmitis, and Eye Inflammation with Intravitreal Use - December 2008

Hoffman-La Roche Limited (Roche), in conjunction with Health Canada, has issued a “Dear Healthcare Professional” letter concerning intravitreal (off-label) use of bevacizumab (Avastin®) and reports of endophthalmitis, eye inflammation, blurred vision, floaters, and Toxic Anterior Segment Syndrome (TASS). TASS, a sterile postoperative inflammatory reaction that leads to intraocular tissue toxicity, is due to the introduction of a non-infectious substance into the anterior segment of the eye.

As of November 2008, all cases reported in Canada (n=25), have been associated with intravitreal use of a specific lot of bevacizumab (B3002B028). In Canada, bevacizumab is approved for intravenous administration in the treatment of metastatic colon or rectal carcinoma and **is not** authorized for use in the ophthalmology setting.

Further information can be found at:

Canada: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/avastin_4_hpc-cps-eng.php

Bevacizumab: Reports of Microangiopathic Hemolytic Anemia (MAHA) in Association With Concomitant Sunitinib Therapy - July 2008

Genentech Inc (in conjunction with the U.S. Food and Drug Administration [FDA]) and Hoffmann-La Roche Limited (in conjunction with Health Canada) have issued warnings to their respective healthcare professionals regarding the risk for MAHA in association with the concomitant use of bevacizumab (Avastin®) and sunitinib (Sutent®). Upcoming changes to the Canadian labeling for bevacizumab are based on observations made in 2 recent investigational U.S. studies involving combination therapy with a fixed dose of bevacizumab (10 mg/kg every 2 weeks) and variable doses of sunitinib (25 mg, 37.5 mg, or 50 mg/day) in patients with metastatic renal cell carcinoma (mRCC).

Although not reported in patients receiving bevacizumab with sunitinib at lower doses, laboratory findings (schistocytes on microscopy, LDH increased, serum haptoglobin decreased) consistent with MAHA were observed in 37% (n=19) of patients receiving bevacizumab and sunitinib 50 mg/day. Symptoms of MAHA include darkened urine, jaundice, confusion, fever, and splenomegaly or hepatomegaly. Grades 3 or 4 hypertension and reversible posterior leukoencephalopathy syndrome (RPLS), were observed in some patients who developed MAHA. Resolution of these adverse findings was observed within 3 weeks of discontinuing both bevacizumab and sunitinib. In the U.S. and in Canada bevacizumab is **not** approved for use in combination with sunitinib or in the treatment of mRCC. Additionally in Canada, bevacizumab is **not** approved for use at doses above 5 mg/kg every 2 weeks.

Further information may be found at:

U.S.: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Avastin

Canada:

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/avastin_nth-aah-eng.ph

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2008/avastin_pc-cp-eng.php

Medication Safety Issues

Sound-alike/look-alike issues:

Bevacizumab may be confused with cetuximab

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(be vuh SIZ uh mab)

U.S. Brand NamesAvastin®

Canadian Brand NamesAvastin®

Pharmacologic CategoryAntineoplastic Agent, Monoclonal Antibody; Vascular Endothelial Growth Factor (VEGF) Inhibitor

Use: Labeled IndicationsTreatment of metastatic colorectal cancer; treatment of nonsquamous, nonsmall cell lung cancer; treatment of breast cancer (metastatic, HER-2 negative)

Use: Unlabeled/InvestigationalTreatment of ovarian cancer (early stage), renal cell cancer, age-related macular degeneration (AMD)

Dosing: AdultsDetails concerning dosing in combination regimens should also be consulted.

Breast cancer: I.V.: 10 mg/kg every 2 weeks (in combination with paclitaxel)

Colorectal cancer: I.V.: 5 or 10 mg/kg every 2 weeks (in combination with fluorouracil-based chemotherapy)

Lung cancer, nonsquamous cell nonsmall cell: I.V.: 15 mg/kg every 3 weeks (in combination with carboplatin and paclitaxel)

AMD (unlabeled use): Intravitreal: 1.25 mg (0.05 mL) monthly until improvement/resolution, usually ~1-3 injections (Avery, 2006) or 2.5 mg (0.1 mL) every 4 weeks for 3 doses (Bashshur, 2006)

Renal cell cancer (unlabeled use): I.V.: 10 mg/kg every 2 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Adjustment for ToxicityI.V. administration (systemic): Temporary suspension is recommended in moderate-to-severe proteinuria (in most studies, treatment was withheld for ≥2 g proteinuria/24 hours) or in patients with severe hypertension which is not controlled with medical management. Permanent discontinuation is recommended (by the manufacturer) in patients who develop wound dehiscence requiring intervention, fistula (gastrointestinal and nongastrointestinal), gastrointestinal perforation, hypertensive crisis, hypertensive encephalopathy, intra-abdominal abscess, serious bleeding, severe arterial thrombotic event, nephrotic syndrome, or RPLS.

Dosing: Combination Regimens

Brain tumors: Bevacizumab-Irinotecan (Glioblastoma)

Breast cancer:

Bevacizumab-Capecitabine

Docetaxel-Bevacizumab

Paclitaxel-Bevacizumab

Colorectal cancer:

Bevacizumab-Fluorouracil-Leucovorin

Bevacizumab-Irinotecan-Fluorouracil-Leucovorin

Bevacizumab-Oxaliplatin-Fluorouracil-Leucovorin

Lung cancer (nonsmall cell):

Bevacizumab-Cisplatin-Gemcitabine

Paclitaxel-Carboplatin-Bevacizumab

Renal cell cancer: Bevacizumab-Interferon Alfa-2a

Administration: I.V.

I.V. infusion, usually after the other antineoplastic agents. Infuse the initial dose over 90 minutes. Infusion may be shortened to 60 minutes if the initial infusion is well tolerated. The third and subsequent infusions may be shortened to 30 minutes if the 60-minute infusion is well tolerated. Some institutions use a 10-minute infusion (0.5 mg/kg/minute) for bevacizumab dosed at 5 mg/kg (Reidy, 2007).

Intravitreal injection (unlabeled use): Adequate anesthesia and a broad-spectrum antimicrobial agent should be administered prior to the procedure; administer topical antibiotics for 3 days after procedure.

Administration: I.V. DetailMonitor closely during the infusion for signs/symptoms of an infusion reaction.

pH: 6.2

StorageStore vials at 2°C to 8°C (36°F to 46°F). Protect from light; do not freeze or shake. Diluted solutions are stable for up to 8 hours under refrigeration.

ReconstitutionPrior to infusion, dilute prescribed dose of bevacizumab in 100 mL NS. Do not mix with dextrose-containing solutions.

ContraindicationsThere are no contraindications listed in the manufacturer's labeling.

Allergy Considerations

- Bevacizumab Allergy

Warnings/Precautions

Boxed warnings:

- Bleeding: See "Concerns related to adverse effects" below.
- Gastrointestinal perforation: See "Concerns related to adverse effects" below.
- Wound dehiscence: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Bleeding: **[U.S. Boxed Warning]: Avoid use in patients with recent hemoptysis (>2.5 mL blood); significant pulmonary bleeding has been reported in patients receiving bevacizumab (primarily in patients with nonsmall cell lung cancer with squamous cell histology [not an FDA-approved indication]).** Other serious bleeding events may occur, but with a lower frequency; discontinuation of treatment is recommended in all patients with serious hemorrhage.

- Gastrointestinal perforation: **[U.S. Boxed Warning]: Gastrointestinal perforation, fistula (including gastrointestinal, enterocutaneous, esophageal, duodenal, and rectal fistulas), and intra-abdominal abscess have been reported in patients (not related to treatment duration);** monitor patients for signs/symptoms (eg, abdominal pain with constipation and/or vomiting). Permanently discontinue in patients who develop these complications.

- Hypertension: May cause and/or worsen hypertension significantly; use caution in patients with pre-existing hypertension and monitor BP closely in all patients. Permanent discontinuation is recommended in patients who experience a hypertensive crisis or encephalopathy. Temporarily discontinue in patients who develop uncontrolled hypertension.

- Infusion reactions: Infusion reactions (eg, hypertension, hypertensive crisis, wheezing, hypersensitivity, chest pain, headache, diaphoresis) may occur with the first infusion (uncommon). Interrupt therapy in patients experiencing severe infusion reactions; there are no data to address reinstitution of therapy in patients who experience severe infusion reactions.

- Nephrotic syndrome/proteinuria: Proteinuria and/or nephrotic syndrome has been associated with use; discontinue in patients with nephrotic syndrome.

- Nongastrointestinal fistula formation: Nongastrointestinal fistula formation (including tracheoesophageal, bronchopleural, biliary, vaginal, and bladder fistulas) has been observed, most commonly within the first 6 months of treatment. Permanently discontinue in patients who develop internal organ fistulas.

- Reversible posterior leukoencephalopathy syndrome (RPLS): Cases of reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Symptoms (which include headache, seizure, confusion, lethargy, blindness and/or other vision, or neurologic disturbances) may occur from 16 hours to 1 year after treatment initiation. RPLS may be associated with hypertension; discontinue therapy and begin management of hypertension, if present.

- Thromboembolism: An increased risk for arterial thromboembolic events (eg, stroke, MI, TIA, angina) is associated with use in combination with chemotherapy. History of arterial thromboembolism or ≥65 years of age may present an even greater risk; permanently discontinue if serious arterial thromboembolic events occur. Although patients with cancer are at risk for venous thromboembolism, a meta-analysis of 15 controlled trials has demonstrated an increased risk for venous thromboembolism in patients who received bevacizumab (Nalluri, 2008).

- Wound dehiscence: **[U.S. Boxed Warning]: Wound dehiscence/wound healing complications have been reported in patients (not related to treatment duration);** monitor patients for signs/symptoms of improper wound healing. Permanently discontinue in patients who develop these complications. The appropriate intervals between administration of bevacizumab and surgical procedures to avoid impairment in wound healing has not been established. Therapy should not be initiated within 28 days of major surgery and only following complete healing of the incision. Bevacizumab should be discontinued prior to elective surgery and the estimated half-life (20 days) should be considered.

Disease-related concerns:

- Cardiovascular disease: The risk for heart failure, including left ventricular dysfunction, is higher in patients receiving bevacizumab plus chemotherapy when compared to chemotherapy alone. Use with caution in patients with cardiovascular disease; patients with significant recent cardiovascular disease were excluded from clinical trials. The safety of therapy resumption or continuation in patients with cardiac dysfunction has not been studied.

- CNS metastases: Avoid use in patients with CNS metastases; patients with CNS metastases were excluded from clinical trials due to concerns for bleeding.

Concurrent drug therapy issues:

- Anthracyclines: May potentiate cardiotoxic effects of anthracyclines. HF is more common with prior anthracycline exposure and/or left chest wall irradiation.

- Myelosuppressive chemotherapy: When used in combination with myelosuppressive chemotherapy, increased rates of severe or febrile neutropenia and neutropenic infection were reported.

- Sunitinib: Microangiopathic hemolytic anemia (MAHA) has been reported when bevacizumab has been used in combination with sunitinib.

Special populations:

- Elderly: Use with caution in patients >65 years old; greater risk for adverse events, including arterial thrombotic events and proteinuria.

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsElderly patients ≥65 years of age had an increased incidence of arterial thromboembolic events; an increased risk for proteinuria; other serious adverse events occurring often include weakness, sepsis, hyper-/hypotension, CHF, constipation, anorexia, anemia, hyper-/hypokalemia, and diarrhea.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate or well-controlled studies in pregnant women, however, bevacizumab is teratogenic in animal models. Angiogenesis is of critical importance to fetal development, and bevacizumab is likely to have adverse consequences in terms of fetal development. Adequate contraception during therapy is recommended. The risk and benefit of treatment should be evaluated in pregnant women. Patients should also be counseled regarding prolonged exposure following discontinuation of therapy due to the long half-life of bevacizumab.

Based on animal studies, bevacizumab may disrupt normal menstrual cycles and impair fertility by several effects, including reduced endometrial proliferation and follicular developmental arrest. Some parameters do not recover completely, or recover very slowly following discontinuation.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsImmunoglobulins are excreted in breast milk, and it is assumed that bevacizumab may appear in breast milk. Due to concerns for effects on the infant, breast-feeding is not recommended. The half-life of bevacizumab is up to 50 days (average 20 days), and this should be considered when decisions are made concerning breast-feeding resumption.

Adverse ReactionsPercentages reported as monotherapy and as part of combination chemotherapy regimens. Some studies only reported hematologic toxicities grades ≥4 and nonhematologic toxicities grades ≥3.

>10%:

Cardiovascular: Hypertension (23% to 67%; grades 3/4: 8% to 18%), thromboembolic event (grades 3/4: 15%), hypotension (7% to 15%)

Central nervous system: Pain (61% to 62%), headache (26%; grades 3/4: 2% to 4%), dizziness (19% to 26%), fatigue (grades 3/4: 5% to 19%), sensory neuropathy (grades 3/4: 1% to 17%; in combination with paclitaxel: 24%)

Dermatologic: Alopecia (6% to 32%), dry skin (7% to 20%), exfoliative dermatitis (3% to 19%), skin discoloration (2% to 16%)

Endocrine & metabolic: Hypokalemia (12% to 16%)

Gastrointestinal: Abdominal pain (50% to 61%; grades 3/4: 8%), vomiting (47% to 52%; grades 3/4: 6% to 11%), anorexia (35% to 43%), constipation (29% to 40%), diarrhea (grades 3/4: 2% to 34%), stomatitis (30% to 32%), gastrointestinal hemorrhage (19% to 24%), dyspepsia (17% to 24%), taste disorder (14% to 21%), flatulence (11% to 19%), weight loss (15% to 16%), nausea (grades 3/4: 4% to 12%)

Hematologic: Leukopenia (grades 3/4: 37%), neutropenia (grade 4: 6% to 27%)

Neuromuscular & skeletal: Weakness (73% to 74%), myalgia (8% to 15%)

Ocular: Tearing increased (6% to 18%)

Renal: Proteinuria (36%; grades 3/4: 3%)

Respiratory: Upper respiratory infection (40% to 47%), epistaxis (32% to 35%), dyspnea (25% to 26%)

Miscellaneous: Infection (serious: 9% to 14%; pneumonia, catheter, or wound infections)

1% to 10%:

Cardiovascular: DVT (6% to 9%; grades 3/4: 9%), venous thrombus/embolus (grades 3/4: 5%), arterial thrombosis (3% to 4%), syncope (grades 3/4: 3%), intra-abdominal venous thrombosis (grades 3/4: 3%), cardio-/cerebrovascular arterial thrombotic event (2% to 4%), CHF (2%)

Central nervous system: Confusion (1% to 6%), abnormal gait (1% to 5%)

Dermatologic: Nail disorder (2% to 8%), rash desquamation (grades 3/4: 3%), wound dehiscence (1%)

Endocrine & metabolic: Dehydration (grades 3/4: 3% to 10%), hyponatremia (grades 3/4: 4%)

Gastrointestinal: Xerostomia (4% to 7%), colitis (1% to 6%), ileus (grades 3/4: 4% to 5%), gingival bleeding (2%), fistula (1%), gastrointestinal perforation (≤4%), intra-abdominal abscess (1%)

Genitourinary: Polyuria/urgency (3% to 6%), vaginal hemorrhage (4%)

Hematologic: Neutropenic fever/infection (5%; grades 3 and/or 4: 4% to 5%), thrombocytopenia (5%), hemorrhage (grades 3/4: 4% to 5%)

Hepatic: Bilirubinemia (1% to 6%)

Neuromuscular & skeletal: Bone pain (grades 3/4: 4%)

Respiratory: Voice alteration (6% to 9%), pneumonitis/pulmonary infiltrates (grades 3/4: 5%), hemoptysis (nonsquamous histology 2%)

Miscellaneous: Infusion reactions (<3%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Anastomotic ulceration, angina, cerebral infarction; fistula (biliary, bladder, bronchopleural, duodenal, enterocutaneous, esophageal, gastrointestinal, rectal, tracheoesophageal [TE] and vaginal); hemorrhagic stroke, hypertensive crises, hypertensive encephalopathy, intestinal necrosis, intestinal obstruction, mesenteric venous occlusion, microangiopathic hemolytic anemia (when used in combination with sunitinib), MI, nasal septum perforation, nephrotic syndrome, pancytopenia, polyserositis, pulmonary embolism, pulmonary hemorrhage, pulmonary hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), subarachnoid hemorrhage, transient ischemic attack, ureteral stricture, wound healing complications

Oncology: VesicantNo

Oncology: Emetic PotentialVery low <10%

Drug Interactions

Antineoplastic Agents (Anthracycline): Bevacizumab may enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk C: Monitor therapy*

Irinotecan: Bevacizumab may enhance the adverse/toxic effect of Irinotecan. *Risk C: Monitor therapy*

Sunitinib: May enhance the adverse/toxic effect of Bevacizumab. Specifically, the risk of a specific form of anemia, microangiopathic hemolytic anemia (MAHA), may be increased. *Risk X: Avoid combination*

Monitoring ParametersMonitor closely during the infusion for signs/symptoms of an infusion reaction. Monitor CBC with differential; signs/symptoms of gastrointestinal perforation, fistula, or abscess (including abdominal pain, constipation, vomiting, and fever); signs/symptoms of bleeding, including hemoptysis, gastrointestinal, and/or CNS bleeding, and/or epistaxis. Monitor blood pressure every 2-3 weeks; more frequently if hypertension develops during therapy. Continue to monitor blood pressure after discontinuing due to bevacizumab-induced hypertension. Monitor for proteinuria/nephrotic syndrome.

AMD: Monitor intraocular pressure and retinal artery perfusion

Nursing: Physical Assessment/MonitoringAssess patient prior to beginning treatment (eg, recent abdominal surgery, cardiovascular disease, hemoptysis). Assess other pharmacologic or herbal products patient may be taking for potential adverse interactions (anthracycline, irinotecan). Evaluate results of laboratory tests and adverse response (gastrointestinal perforation [abdominal pain, constipation, vomiting], serious bleeding, arterial thrombotic event, nephrotic syndrome, encephalopathy, CHF) at each infusion and throughout therapy; discontinuation may be necessary. Teach patient possible side effects/appropriate interventions, and adverse symptoms to report.

I.V.: Note specific directions for administration. Patient must be monitored closely during each infusion for infusion reaction (eg, hypertensive crisis, chest pain, wheezing, diaphoresis).

Monitoring: Lab TestsCBC with differential; urinalysis

Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. This medication can only be administered by infusion: You will be closely monitored during infusion; report immediately unusual back or abdominal pain, acute headache, difficulty breathing or chest tightness, difficulty swallowing, itching or rash, redness, swelling, or pain at infusion site. Between treatments, maintain adequate hydration (2-3 L/day of fluids, u unless instructed to restrict fluid intake) and nutrition (small frequent meals). You may experience loss of appetite, nausea, dry mouth, or taste changes (frequent oral care, sucking lozenges, or chewing gum may help); loss of hair (will grow back when therapy is completed); or muscle or skeletal pain (consult prescriber for appropriate analgesia). Report immediately any unusual bleeding (blood in urine or stool, nose bleeds, vaginal bleeding, bleeding from wound); abdominal pain, constipation, and vomiting; acute headache, dizziness, or confusion; seizure, visions changes, or unusual lethargy; changes in urinary pattern; pain, redness, swelling, or loss of sensation in extremities; unusual bleeding (blood in urine or stool, nose bleeds, vaginal bleeding); skin rash; unusual infection (respiratory or urinary tract); or any other adverse reactions. **Pregnancy precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Avastin®: 25 mg/mL (4 mL, 16 mL)

Generic AvailableNo

ManufacturerGenentech

Pricing: U.S. (www.drugstore.com)

Solution (Avastin)

100 mg/4 mL (4): $645.98

400 mg/16 mL (16): $2499.75

Mechanism of ActionBevacizumab is a recombinant, humanized monoclonal antibody which binds to, and neutralizes, vascular endothelial growth factor (VEGF), preventing its association with endothelial receptors, Flt-1 and KDR. VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels). The inhibition of microvascular growth is believed to retard the growth of all tissues (including metastatic tissue).

Pharmacodynamics/Kinetics

Distribution: V_d: 46 mL/kg

Half-life elimination: ~20 days (range: 11-50 days)

Excretion: Clearance: 2.75-5 mL/kg/day

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), stomatitis, taste disorder, and gingival bleeding.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause confusion

Mental Health: Effects on Psychiatric TreatmentGastrointestinal side effects are common; these effects may be additive with concurrent use of SSRIs, acetylcholinesterase inhibitors, aripiprazole, or ziprasidone. Hematologic adverse effects are common; use caution with clozapine, carbamazepine, valproate, mirtazapine. May cause hypokalemia; use caution with ziprasidone.

Index TermsAnti-VEGF Monoclonal Antibody; NSC-704865; rhuMAb-VEGF

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International Brand NamesAvastin (AR, AT, AU, BE, BG, BR, CH, CN, CO, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IT, KP, MX, NL, NO, PE, PH, PL, PT, RU, SE, SG, TH, TR, TW, UY)

Bexarotene

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(beks AIR oh teen)

U.S. Brand NamesTargretin®

Canadian Brand NamesTargretin®

Pharmacologic CategoryAntineoplastic Agent, Miscellaneous

Use: Labeled Indications

Oral: Treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy

Topical: Treatment of cutaneous lesions in patients with refractory cutaneous T-cell lymphoma (stage 1A and 1B) or who have not tolerated other therapies

Dosing: Adults

Cutaneous T-cell lymphoma: Oral: 300-400 mg/m^2/day taken as a single daily dose.

Cutaneous lesions of T-cell lymphoma: Topical: Apply to lesions once every other day for first week, then increase on a weekly basis to once daily, 2 times/day, 3 times/day, and finally 4 times/day, according to tolerance.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo studies have been conducted; however, renal insufficiency may result in significant protein binding changes and alter pharmacokinetics of bexarotene.

Dosing: Hepatic ImpairmentNo studies have been conducted; however, hepatic impairment would be expected to result in decreased clearance of bexarotene due to the extensive hepatic contribution to elimination.

Calculations

- Body Surface Area: Adults

Administration: OralAdminister capsule following a fat-containing meal.

Administration: TopicalAllow gel to dry before covering with clothing. Avoid application to normal skin. Use of occlusive dressings is not recommended.

Dietary ConsiderationsIt is preferable to take the oral capsule following a fat-containing meal.

StorageStore at 2°C to 25°C (36°F to 77°F). Protect from light.

ContraindicationsHypersensitivity to bexarotene or any component of the formulation; pregnancy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Hypothyroidism: In about a third of patients, hypothyroidism occurs; monitor.
- Leukopenia: Leukopenia and neutropenia may occur (may be delayed); monitor for signs and symptoms of infection about 4-8 weeks after initiation.
- Lipid effects: Induces significant lipid abnormalities in a majority of patients (triglyceride, total cholesterol, and HDL); reversible on discontinuation. Use extreme caution in patients with underlying hypertriglyceridemia.
- Liver function test abnormalities: Monitor for liver function test abnormalities and discontinue drug if tests are three times the upper limit of normal values for AST, ALT, or bilirubin.
- Pancreatitis: Pancreatitis secondary to hypertriglyceridemia has been reported. Patients with risk factors for pancreatitis (eg, prior pancreatitis, uncontrolled hyperlipidemia, excess ethanol consumption, uncontrolled diabetes, biliary tract disease) should generally not receive bexarotene (oral).

- Photosensitivity: May cause photosensitization.
- Visual disturbances: Any new visual abnormalities experienced by the patient should be evaluated by an ophthalmologist (cataracts can form, or worsen, especially in the geriatric population).

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus.
- Hepatic impairment: Use only with extreme caution in patients with hepatic impairment.

Concurrent drug therapy issues:

- Vitamin A: Limit additional vitamin A intake to <15,000 int. units/day.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: **[U.S. Boxed Warning]: Bexarotene is a retinoid, a drug class associated with birth defects in humans; do not administer during pregnancy.** Pregnancy test needed 1 week before initiation and every month thereafter. Effective contraception must be in place 1 month before initiation, during therapy, and for at least 1 month after discontinuation. Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant, must use condoms during sexual intercourse during treatment and for 1 month after last dose.

Pregnancy Risk FactorX

Pregnancy Considerations**[U.S. Boxed Warning]: Bexarotene is a retinoid, a drug class associated with birth defects in humans; do not administer during pregnancy.** Bexarotene caused birth defects when administered orally to pregnant rats. It must not be given to a pregnant woman or a woman who intends to become pregnant. If a woman becomes pregnant while taking the drug, it must be stopped immediately and appropriate counseling be given. Women of childbearing potential should use two forms of reliable contraception, one should be nonhormonal.

LactationExcretion in breast milk unknown/contraindicated

Adverse ReactionsFirst percentage is at a dose of 300 mg/m^2/day; the second percentage is at a dose >300 mg/m^2/day.

Oral:

>10%:

Cardiovascular: Peripheral edema (13% to 11%)

Central nervous system: Headache (30% to 42%), chills (10% to 13%)

Dermatologic: Rash (17% to 23%), exfoliative dermatitis (10% to 28%)

Endocrine & metabolic: Hyperlipidemia (about 79% in both dosing ranges), hypercholesteremia (32% to 62%), hypothyroidism (29% to 53%)

Hematologic: Leukopenia (17% to 47%)

Neuromuscular & skeletal: Weakness (20% to 45%)

Miscellaneous: Infection (13% to 23%)

<10%:

Cardiovascular: Hemorrhage, hypertension, angina pectoris, right heart failure, tachycardia, cerebrovascular accident, syncope

Central nervous system: Fever (5% to 17%), insomnia (5% to 11%), subdural hematoma, depression, agitation, ataxia, confusion, dizziness, hyperesthesia

Dermatologic: Dry skin (about 10% for both dosing ranges), alopecia (4% to 11%), skin ulceration, acne, skin nodule, maculopapular rash, serous drainage, vesicular bullous rash, cheilitis

Endocrine & metabolic: Hypoproteinemia, hyperglycemia, weight loss/gain, breast pain

Gastrointestinal: Abdominal pain (11% to 4%), nausea (16% to 8%), diarrhea (7% to 42%), vomiting (4% to 13%), anorexia (2% to 23%), constipation, xerostomia, flatulence, colitis, dyspepsia, gastroenteritis, gingivitis, melena, pancreatitis, serum amylase increased

Genitourinary: Albuminuria, hematuria, urinary incontinence, urinary tract infection, urinary urgency, dysuria, kidney function abnormality

Hematologic: Hypochromic anemia (4% to 13%), anemia (6% to 25%), eosinophilia, thrombocythemia, coagulation time increased, lymphocytosis, thrombocytopenia

Hepatic: LDH increased (7% to 13%), hepatic failure

Neuromuscular & skeletal: Back pain (2% to 11%), arthralgia, myalgia, bone pain, myasthenia, arthrosis, neuropathy

Ocular: Dry eyes, conjunctivitis, blepharitis, corneal lesion, visual field defects, keratitis

Otic: Ear pain, otitis externa

Renal: Creatinine increased

Respiratory: Pharyngitis, rhinitis, dyspnea, pleural effusion, bronchitis, cough increased, lung edema, hemoptysis, hypoxia

Miscellaneous: Flu-like syndrome (4% to 13%), bacterial infection (1% to 13%)

Topical:

Cardiovascular: Edema (10%)

Central nervous system: Headache (14%), weakness (6%), pain (30%)

Dermatologic: Rash (14% to 72%), pruritus (6% to 40%), contact dermatitis (14%), exfoliative dermatitis (6%)

Hematologic: Leukopenia (6%), lymphadenopathy (6%)

Neuromuscular & skeletal: Paresthesia (6%)

Respiratory: Cough (6%), pharyngitis (6%)

Miscellaneous: Diaphoresis (6%), infection (18%)

Oncology: Emetic PotentialLow (10% to 30%)
Metabolism/Transport Effects**Substrate** of CYP3A4 (minor); **Induces** CYP3A4 (weak)
Drug Interactions

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Retinoic Acid Derivatives may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): Retinoic Acid Derivatives may diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. *Risk C: Monitor therapy*

Tetracycline Derivatives: May enhance the adverse/toxic effect of Retinoic Acid Derivatives. The development of pseudotumor cerebri is of particular concern. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Take with a fat-containing meal. Bexarotene serum levels may be increased by grapefruit juice; avoid concurrent use.

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization). St John's wort may decrease bexarotene levels. Additional vitamin A supplements may lead to vitamin A toxicity (dry skin, irritation, arthralgias, myalgias, abdominal pain, hepatic changes).

Monitoring ParametersIf female, pregnancy test 1 week before initiation then monthly while on bexarotene; lipid panel before initiation, then weekly until lipid response established and then at 8-week intervals thereafter; baseline LFTs, repeat at 1, 2, and 4 weeks after initiation then at 8-week intervals thereafter if stable; baseline and periodic thyroid function tests; baseline CBC with periodic monitoring
Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions. Assess results of laboratory tests (pregnancy, lipid panel, LFTs, thyroid function, CBC) prior to and during therapy. Assess therapeutic response (reduction of cutaneous lesions), and adverse reactions (eg, CNS or cardiovascular effects, opportunistic infection, visual abnormalities, hypoglycemia). Teach patient proper use according to formulation, side effects/appropriate interventions, and symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Instruct female patients of childbearing age and males who may have intercourse with females of childbearing age about appropriate use of barrier contraceptives 1 month prior to, during, and 1 month following treatment.
Monitoring: Lab TestsIf female, pregnancy test 1 week before initiation then monthly while on bexarotene; lipid panel before initiation, then weekly until lipid response established and then at 8-week intervals thereafter; baseline LFTs, repeat at 1, 2, and 4 weeks after initiation then at 8-week intervals thereafter if stable; baseline and periodic thyroid function tests; baseline CBC with periodic monitoring
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Use exactly as directed; it is preferable to take capsules after a fat-containing meal. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid grapefruit juice, St John's wort, or additional vitamin A supplements while using this medication. You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea, vomiting, anorexia, flatulence (frequent, small meals, good mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluid, fruit, or fiber may help); diarrhea (buttermilk, boiled milk, or yogurt may help); headache, back or muscle pain (consult prescriber for mild analgesic); or photosensitivity (avoid direct sunlight, wear protective clothing and hat, use sunblock, and protective eyewear). Report chest pain, rapid heartbeat; unresolved GI effects; headache, back or muscle pain; skin dryness, skin rash or peeling; mucous membrane lesions; altered urinary patterns; flu syndrome or opportunistic infection (eg, weakness, fatigue, white plaques or sores in mouth, vaginal discharge, chills, fever); CNS disturbances (insomnia, dizziness, agitation, confusion, depression); vision or hearing changes; or any other adverse effects. **Pregnancy/breast-feeding precautions:** Pregnancy test is needed 1 week before initiation of therapy and every month during therapy. Consult prescriber for appropriate barrier contraceptives if necessary or if you suspect you might be pregnant. Effective contraception must be in place 1 month before initiation, during therapy, and for at least 1 month after discontinuation. Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant, must use condoms when having sexual intercourse while using this medication and for 1 month after last dose. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Do not breast-feed.

Oral: Take exactly as directed, at the same time each day with a fat-containing meal. If you miss a dose, take as soon as possible. If it is almost time for next dose, skip the missed dose and continue on regular schedule. Do not double doses.

Topical: Apply as directed. Allow gel to dry before covering. Avoid applying to normal skin or mucous membranes. Do not use occlusive dressings.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Targretin®: 75 mg

Gel: 1% (60 g)

Targretin®: 1% (60 g) [contains dehydrated alcohol]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Targretin)

75 mg (30): $686.79

Mechanism of ActionThe exact mechanism is unknown. Binds and activates retinoid X receptor subtypes. Once activated, these receptors function as transcription factors that regulate the expression of genes which control cellular differentiation and proliferation. Bexarotene inhibits the growth *in vitro* of some tumor cell lines of hematopoietic and squamous cell origin.

Pharmacodynamics/Kinetics

Absorption: Significantly improved by a fat-containing meal

Protein binding: >99%

Metabolism: Hepatic via CYP3A4 isoenzyme; four metabolites identified; further metabolized by glucuronidation

Half-life elimination: 7 hours

Time to peak: 2 hours

Excretion: Primarily feces; urine (<1% as unchanged drug and metabolites)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and gingivitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia, agitation, confusion, and depression

Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; use caution with clozapine and carbamazepine; effects of psychotropics may be altered secondary to the insomnia, confusion, agitation, and depression seen with bexarotene

References

Duvic M, “Bexarotene and DAB(389)IL-2 (Denileukin Diftitox, ONTAK) in Treatment of Cutaneous T-Cell Lymphomas: Algorithms,” *Clin Lymphoma*, 2000, 1(Suppl 1):51-5.

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Hurst RE, "Bexarotene Ligand Pharmaceuticals," *Curr Opin Investig Drugs*, 2000, 1(4):514-23.[PubMed 11249708]

Lowe MN and Plosker GL, "Bexarotene," *Am J Clin Dermatol*, 1(4):245-50.

Martin AG, "Bexarotene Gel: A New Skin-Directed Treatment Option for Cutaneous T-Cell Lymphomas," *J Drugs Dermatol*, 2003, 2(2):155-67.[PubMed 12852367]

International Brand NamesTargretin (AR, AT, BE, BG, CH, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Bezafibrate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(be za FYE brate)

Canadian Brand NamesBezalip®; PMS-Bezafibrate

Pharmacologic CategoryAntilipemic Agent, Fibric Acid

Use: Labeled IndicationsAdjunct to diet and other therapeutic measures for treatment of type IIa and IIb mixed hyperlipidemia, to regulate lipid and apoprotein levels (reduce serum TG, LDL-cholesterol, and apolipoprotein B, increase HDL-cholesterol and apolipoprotein A); treatment of adult patients with high to very high triglyceride levels (Fredrickson classification type IV and V hyperlipidemias) who are at high risk of sequelae and complications from their dyslipidemia

Dosing: Adults

Dyslipidemia: Oral:

> *Immediate release:* 200 mg 2-3 times/day; may reduce to 200 mg twice daily in patients with good response
>
> *Sustained release:* 400 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} >60 mL/minute: 200 mg 3 times/day

Cl_{cr} 60-40 mL/minute: 200 mg 2 times/day

Cl_{cr} 40-15 mL/minute: 200 mg every 1-2 days

Cl_{cr} <15 mL/minute: 200 mg every 3 days

Hemodialysis: 200 mg every 3 days

Calculations

- Creatinine Clearance: Adults

Administration: Oral

Immediate release: Swallow tablet without chewing and with sufficient fluid, with or after meals.

Sustained release: Swallow tablet without chewing and with sufficient fluid; Take in morning or evening with or after meals.

Dietary ConsiderationsShould be taken with or after meals. Before initiation of therapy, patients should be placed on a standard lipid-lowering diet for 6 weeks and the diet should be continued during drug therapy.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from high humidity.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to bezafibrate, fibrates, or any component of the formulation; hepatic or renal dysfunction; primary biliary cirrhosis; pre-existing gallbladder disease; concurrent use of MAO inhibitors; pregnancy or breast-feeding; not indicated for the treatment of type I hyperlipoproteinemia

Allergy Considerations

- Fibric Acid Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hepatic effects: Has been shown to be hepatotoxic; discontinue if response is not obtained in 3 months. Use with caution in patients with history of jaundice or hepatic disorder; abnormal liver function tests have been observed (reversible when discontinued).
- Myopathy/rhabdomyolysis: Has been associated with rare myositis or rhabdomyolysis; patients should be monitored closely. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine.
- Tumorigenic: Has been shown to be possibly tumorigenic (animal models); discontinue if response is not obtained in 3 months.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment, hypoalbuminemia, or nephrotic syndrome; dosage reduction required.

Concurrent drug therapy issues:

- HMG-CoA reductase inhibitors: Use caution with HMG-CoA reductase inhibitors; may lead to myopathy, rhabdomyolysis.
- Warfarin: Use with caution in patient taking warfarin; adjustments in warfarin therapy may be required.

Special populations:

- Pediatrics: Limited experience is available in children; therefore, caution should be used when treating children.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

Pregnancy Risk FactorNot available; not recommended (per manufacturer)

Pregnancy ConsiderationsEmbryotoxicity has occurred in animals at toxic doses. Women planning pregnancy should discontinue bezafibrate several months before conception; strict birth control procedures must be exercised.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsDo not use during lactation due to absence of data concerning the presence of bezafibrate in human breast milk.

Adverse Reactions

1% to 10%

Central nervous system: Dizziness (2%), insomnia (1%), migraine (1%), pain (1%)

Dermatologic: Pruritus (3%), eczema (1%), rash

Gastrointestinal: Gastritis (6%), flatulence (5%), dyspepsia (3%), nausea, diarrhea, constipation

Hematologic: Anemia (1%)

Hepatic: Transaminases increased

Miscellaneous: Allergic reaction (1%)

Neuromuscular & skeletal: CPK increased

Renal: Creatinine increased

<1%: Alkaline phosphatase increased, alopecia, asthenia, cholelithiasis, epigastric distress, erythema, headache, impotence, muscle pain, muscle cramps, myopathy, rhabdomyolysis, urticaria

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)

Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Fibric Acid Derivatives. **Exceptions:** Colesevelam. *Risk D: Consider therapy modification*

Ezetimibe: Fibric Acid Derivatives may increase the serum concentration of Ezetimibe. *Risk C: Monitor therapy*

Sulfonylureas: Fibric Acid Derivatives may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Fibric Acid Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Test InteractionsGlucose, creatinine, ALT, TG, and CPK

Monitoring ParametersPeriodic evaluation of serum lipids, cholesterol, and triglycerides (especially in the first few months of therapy). LFTs after 3-6 months; then annually. CBC (periodically during the first 12 months). Fasting glucose, creatinine, and CPK periodically.

Monitoring: Lab TestsPeriodic evaluation of serum lipids, cholesterol, and triglycerides (especially in the first few months of therapy). LFTs after 3-6 months; then annually. CBC (periodically during the first 12 months). Fasting glucose, creatinine, and CPK periodically.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet, immediate release: 200 mg [not available in the U.S.]

PMA-Bezafibrate [CAN]: 200 mg [not available in the U.S.]

Tablet, sustained release:

Bezalip® [CAN]: 400 mg [not available in the U.S.]

Generic AvailableYes: 200 mg immediate release only

Mechanism of ActionMechanism not definitely established; may increase VLDL catabolism by increasing lipoprotein and hepatic triglyceride lipase activities; attenuation of triglyceride biosynthesis by inhibition of acetyl-CoA carboxylase; decreased cholesterol biosynthesis by inhibition of 3-hydroxy-3-methyglutaryl-coenzyme A reductase

Pharmacodynamics/Kinetics

Absorption: Immediate release: Almost completely; Sustained release: 70%

Distribution: 17 L

Protein binding: 94% to 96%

Half-life elimination: 1-2 hours

Time to peak, serum: Immediate release: 1-2 hours; Sustained release: 3-4 hours

Excretion: Urine (95%); feces (3%)

Pharmacotherapy PearlsNot available in U.S.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or insomnia

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors

References

Bezalip® product monograph, Hoffman-La Roche Ltd/Ltee, Ontario, January 2002.

Ericsson CG, Nilsson J, Grip L, et al, “Effect of Bezafibrate Treatment Over Five Years on Coronary Plaques Causing 20% to 50% Diameter Narrowing (The Bezafibrate Coronary Atherosclerosis Intervention Trial [BECAIT]),” *Am J Cardiol*, 1997, 80(9):1125-9. [PubMed 9359536]

“Secondary Prevention by Raising HDL Cholesterol and Reducing Triglycerides in Patients With Coronary Artery Disease: The Bezafibrate Infarction Prevention (BIP) Study. The BIP Study Group,” *Circulation*, 2000, 102(1):21-7[PubMed 10880410]

International Brand NamesBefizal (FR); Befizal LP (FR); Bezacur (LU); Bezafibrat (DK); Bezafibrat Genericon (AT); Bezafibrat Lannacher (AT); Bezafibrat Merck (AT); Bezalip (AR, AT, CZ, FI, GB, GR, HK, HN, HU, IE, IN, IT, KP, MX, NL, NO, NZ, PE, PK, PL, PT, SE, TH, TW, VE, ZA); Bezalip Retard (HK, IN, KP, MX, NZ, PL, PT, TH, TW, UY); Bezamidin (CZ, HR, HU, PL); Bezastad (AT, PH); Bezatol SR (JP); Cedur (BE, BR, DE, LU); Cedur Retard (CH); Clofibral (PY); Etifibrat (SV); Eulitop (ES); Evicta (TH); Fibalip (NZ); Lacromid (CY); Lipocin (MX); Lipocor (PK); Lipox (DE); Nimus (CN, EC); Norlip (IL); Oralipin (CN); Oralipin Retard (PY); Zafibral (SG)

Bicalutamide + LHRH-A

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer

Regimen UseProstate cancer

Index TermsBI; BZ

Regimen

Bicalutamide: Oral: 50 mg/day

[total dose/cycle = 50 mg]

with

Goserelin acetate: SubQ: 3.6 mg day 1

[total dose/cycle = 3.6 mg]

or

Leuprolide depot: I.M.: 7.5 mg day 1

[total dose/cycle = 7.5 mg]

Repeat cycle every 28 days

References

Schellhammer PF, Scharifi R, Block NL, et al, âA Controlled Trial of Bicalutamide Versus Flutamide, Each in Combination With Luteinizing Hormone-Releasing Hormone Analogue Therapy, in Patients With Advanced Prostate Cancer. Casodex Combination Study Group.â *Urology*, 1995, 45(5):745-52.[PubMed 7538237]

Bicalutamide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(bye ka LOO ta mide)

U.S. Brand NamesCasodex®

Canadian Brand NamesCasodex®; CO Bicalutamide; Gen-Bicalutamide; Novo-Bicalutamide; PHL-Bicalutamide; PMS-Bicalutamide; Pro-Bicalutamide; ratio-Bicalutamide; Sandoz-Bicalutamide

Pharmacologic CategoryAntineoplastic Agent, Antiandrogen

Use: Labeled IndicationsIn combination therapy with LHRH agonist analogues in treatment of metastatic prostate cancer

Use: Unlabeled/InvestigationalMonotherapy for locally-advanced prostate cancer

Dosing: Adults

Metastatic prostate cancer: Oral: 50 mg once daily (in combination with an LHRH analogue)

Locally-advanced prostate cancer (unlabeled use): Oral: 150 mg once daily (as monotherapy)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment required

Dosing: Hepatic ImpairmentNo adjustment required for mild, moderate, or severe hepatic impairment; use caution with moderate-to-severe impairment. Discontinue if ALT >2 times ULN or patient develops jaundice.

Dosing: Combination Regimens

Prostate cancer: Bicalutamide + LHRH-A

Administration: OralDose should be taken at the same time each day with or without food. Treatment should be started concomitantly with an LHRH analogue.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to bicalutamide or any component of the formulation; female patients; pregnancy

Allergy Considerations

- Bicalutamide Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Gynecomastia: May cause gynecomastia or breast pain.
- Hepatitis: Rare cases of death or hospitalization due to hepatitis have been reported postmarketing; hepatotoxicity generally occurs within the first 3-4 months of use. Use with caution in moderate-to-severe hepatic dysfunction. Patients should be monitored for signs and symptoms of liver dysfunction; discontinue if patients have jaundice or ALT is >2 times the upper limit of normal.
- Spermatogenesis: May lead to spermatogenesis inhibition.

Geriatric ConsiderationsRenal impairment has no clinically-significant changes in elimination of the parent compound or active metabolite; therefore, no dosage adjustment is needed in the elderly. In dosage studies, no difference was found between young adults and elderly with regard to steady-state serum concentrations for bicalutamide and its active R-enantiomer metabolite.

Pregnancy Risk FactorX

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenicity. Bicalutamide is not indicated for women.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsBicalutamide is not indicated for use in women.

Adverse ReactionsAdverse reaction percentages reported as part of combination regimen with an LHRH analogue.

>10%:

Cardiovascular: Peripheral edema (13%)

Central nervous system: Pain (35%)

Endocrine & metabolic: Hot flashes (53%)

Gastrointestinal: Constipation (22%), nausea (15%), diarrhea (12%), abdominal pain (11%)

Genitourinary: Pelvic pain (21%), nocturia (12%), hematuria (12%)

Hematologic: Anemia (11%)

Neuromuscular & skeletal: Back pain (25%), weakness (22%)

Respiratory: Dyspnea (13%)

Miscellaneous: Infection (18%)

≥2% to 10%:

Cardiovascular: Chest pain (8%), hypertension (8%), angina pectoris (2% to <5%), CHF (2% to <5%), edema (2% to <5%), MI (2% to <5%), coronary artery disorder (2% to <5%), syncope (2% to <5%)

Central nervous system: Dizziness (10%), headache (7%), insomnia (7%), anxiety (5%), depression (4%), chills (2% to <5%), confusion (2% to <5%), fever (2% to <5%), nervousness (2% to <5%), somnolence (2% to <5%)

Dermatologic: Rash (9%), alopecia (2% to <5%), dry skin (2% to <5%), pruritus (2% to <5%), skin carcinoma (2% to <5%)

Endocrine & metabolic: Gynecomastia (9%), breast pain (6%; up to 39% as monotherapy), hyperglycemia (6%), dehydration (2% to <5%), gout (2% to <5%), hypercholesterolemia (2% to <5%), libido decreased (2% to <5%)

Gastrointestinal: Dyspepsia (7%), weight loss (7%), anorexia (6%), flatulence (6%), vomiting (6%), weight gain (5%), dysphagia (2% to <5%), gastrointestinal carcinoma (2% to <5%), melena (2% to <5%), periodontal abscess (2% to <5%), rectal hemorrhage (2% to <5%), xerostomia (2% to <5%)

Genitourinary: Urinary tract infection (9%), impotence (7%), polyuria (6%), urinary retention (5%), urinary impairment (5%), urinary incontinence (4%), dysuria (2% to <5%), urinary urgency (2% to <5%)

Hepatic: LFTs increased (7%), alkaline phosphatase increased (5%)

Neuromuscular & skeletal: Bone pain (9%), paresthesia (8%), myasthenia (7%), arthritis (5%), pathological fracture (4%), hypertonia (2% to <5%), leg cramps (2% to <5%), myalgia (2% to <5%), neck pain (2% to <5%), neuropathy (2% to <5%)

Ocular: Cataract (2% to <5%)

Renal: BUN increased, creatinine increased, hydronephrosis

Respiratory: Cough (8%), pharyngitis (8%), bronchitis (6%), pneumonia (4%), rhinitis (4%), asthma (2% to <5%), epistaxis (2% to <5%), sinusitis (2% to <5%)

Miscellaneous: Flu syndrome (7%), diaphoresis (6%), cyst (2% to <5%), hernia (2% to <5%), herpes zoster (2% to <5%), sepsis (2% to <5%)

Postmarketing and/or case reports: Bilirubin increased, hemoglobin decreased, hepatitis, hypersensitivity reactions (including angioneurotic edema and urticaria), interstitial pneumonitis, pulmonary fibrosis, WBC decreased

Oncology: Emetic PotentialVery low (<10%)

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersPeriodically monitor CBC, ECG, echocardiograms, serum testosterone, luteinizing hormone, and prostate specific antigen. Liver function tests should be obtained at baseline and repeated regularly during the first 4 months of treatment, and periodically thereafter; monitor for signs and symptoms of liver dysfunction (discontinue if jaundice is noted or ALT is >2 times the upper limit of normal).

Nursing: Physical Assessment/MonitoringUse caution in presence of hepatic impairment. Monitor prothrombin time closely in patients taking coumarin-derivative anticoagulants concomitantly. Assess results of laboratory tests (LFTs) at baseline and periodically during therapy. Assess therapeutic effectiveness (eg, slowed disease progression) and adverse effects regularly. Advise patients with diabetes to monitor glucose levels closely (may induce hyperglycemia). Teach patient appropriate use (including absolute need for barrier contraceptives), possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Instruct patient on absolute need for barrier contraceptives.

Monitoring: Lab TestsLiver function tests should be obtained at baseline and repeated regularly during the first 4 months of treatment, and periodically thereafter (in addition to monitoring signs/symptoms of liver dysfunction). Discontinue if jaundice is noted or ALT is >2 times the upper limit of normal. Periodically monitor CBC, ECG, echocardiograms, serum testosterone, luteinizing hormone, and prostate specific antigen.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, at the same time each day, with or without food. Do not alter dose or discontinue this medicine without consulting prescriber. If you have diabetes, monitor serum glucose closely and notify prescriber of changes (this medication may alter glucose levels). May cause dizziness, confusion, or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); constipation (increased exercise, fluids, fruit, or fiber may help); hair loss; or impotence. Report easy bruising or bleeding; yellowing of skin or eyes; change in color of urine or stool; unresolved CNS changes (eg, nervousness, chills, insomnia, somnolence); skin rash, redness, or irritation; chest pain or palpitations; respiratory difficulty; urinary retention or inability to void; muscle weakness, tremors, or pain; persistent nausea, vomiting, diarrhea, constipation; or other unusual signs or adverse reactions. **Pregnancy/breast-feeding precautions:** This drug will cause fetal abnormalities - consult prescriber for effective contraceptives.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 50 mg

Generic AvailableNo

ManufacturerAstraZeneca Pharmaceuticals LP

Pricing: U.S. (www.drugstore.com)

Tablets (Casodex)

50 mg (30): $478.36

Mechanism of ActionPure nonsteroidal antiandrogen that binds to androgen receptors; specifically a competitive inhibitor for the binding of dihydrotestosterone and testosterone; prevents testosterone stimulation of cell growth in prostate cancer

Pharmacodynamics/Kinetics

Absorption: Rapid and complete

Protein binding: 96%

Metabolism: Extensively hepatic; glucuronidation and oxidation of the R (active) enantiomer to inactive metabolites

Half-life elimination: Active enantiomer ~6 days, ~10 days in severe liver disease

Time to peak, plasma: 31 hours

Excretion: Urine (36%, as inactive metabolites); feces (42%, as unchanged drug and inactive metabolites)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay produce anxiety, depression, and confusion

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCDX; ICI-176334; NC-722665

References

Blackledge GR, Cockshott ID, and Furr BJ, “Casodex (Bicalutamide): Overview of a New Antiandrogen Developed for the Treatment of Prostate Cancer,” *Eur Urol*, 1997, 31(Suppl 2):30-9.

Cockshott ID, “Bicalutamide: Clinical Pharmacokinetics and Metabolism,” *Clin Pharmacokinet*, 2004, 43(13):855-78.[PubMed 15509184]

Goa KL and Spencer CM, “Bicalutamide in Advanced Prostate Cancer. A Review,” *Drugs Aging*, 1998, 12(5):401-22 [PubMed 9606617]

Iversen P, “Bicalutamide Monotherapy for Early Stage Prostate Cancer: An Update,” *J Urol*, 2003, 170(6 Pt 2 Suppl):48-52.[PubMed 12796642]

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International Brand NamesBicalan (EE); Bidrostat (AR); Biprosta (IN); Calutide-50 (IN); Casodex (AR, AT, BB, BD, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CZ, DE, DK, DO, EC, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HU, ID, IE, IL, IN, IT, JM, JP, KE, KP, LR, LU, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, PA, PE, PH, PK, PL, PT, RU, SC, SD, SE, SG, SL, SN, SR, SV, TH, TN, TR, TT, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Cosudex (AU); Lutamidal (CN, CO, PE, PY)

Bimatoprost

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(bi MAT oh prost)

U.S. Brand NamesLumigan®

Canadian Brand NamesLumigan®

Pharmacologic CategoryOphthalmic Agent, Antiglaucoma; Prostaglandin, Ophthalmic

Use: Labeled IndicationsReduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Dosing: AdultsOpen-angle glaucoma or ocular hypertension: Ophthalmic: Instill 1 drop into affected eye(s) once daily in the evening; do not exceed once-daily dosing (may decrease IOP-lowering effect). If used with other topical ophthalmic agents, separate administration by at least 5 minutes.

Dosing: ElderlyRefer to adult dosing.

Administration: OtherMay be used with other eye drops to lower intraocular pressure. If using more than one ophthalmic product, wait at least 5 minutes in between application of each medication. Remove contact lenses prior to administration and wait 15 minutes before reinserting.

StorageStore between 2°C to 25°C (36°F to 77°F).

ContraindicationsHypersensitivity to bimatoprost or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Bacterial keratitis: Inadvertent contamination of multiple-dose ophthalmic solutions, has caused bacterial keratitis.
- Ocular effects: May permanently change/increase brown pigmentation of the iris, the eyelid skin, and eyelashes. In addition, may increase the length and/or number of eyelashes (may vary between eyes); changes occur slowly and may not be noticeable for months or years. Long-term consequences and potential injury to eye are not known.

Disease-related concerns:

- Ocular disease: Use with caution in patients with intraocular inflammation, aphakic patients, pseudophakic patients with a torn posterior lens capsule, or patients with risk factors for macular edema. Safety and efficacy have not been determined for use in patients with angle-closure-, inflammatory-, or neovascular glaucoma.

Special populations:

- Contact lens wearers: Contains benzalkonium chloride which may be adsorbed by contact lenses; remove contacts prior to administration and wait 15 minutes before reinserting.
- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsEvaluate patient's ability to self-administer eye drops

Pregnancy Risk FactorC

Pregnancy ConsiderationsDecreased gestation, decreased body weight, increased late resorptions, and increased mortality were observed in animal studies with oral doses achieving serum levels >33 times human exposure. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Ocular (15% to 45%): Conjunctival hyperemia, growth of eyelashes, ocular pruritus

1% to 10%:

- Central nervous system: Headache (1% to 5%)
- Dermatologic: Hirsutism (1% to 5%)
- Hepatic: Liver function tests abnormal (1% to 5%)
- Neuromuscular & skeletal: Weakness (1% to 5%)
- Ocular:
    - 3% to 10%: Blepharitis, burning, cataract, dryness, eyelid redness, eyelash darkening, foreign body sensation, irritation, pain, pigmentation of periocular skin, superficial punctate keratitis, visual disturbance
    - 1% to 3%: Allergic conjunctivitis, asthenopia, conjunctival edema, discharge, iris pigmentation increased, photophobia, tearing
- Respiratory: Upper respiratory tract infection (10%)

<1%: Iritis

Postmarketing and/or case reports: Bacterial keratitis (caused by inadvertent contamination of multiple-dose ophthalmic solutions), macular edema

Drug Interactions

Latanoprost: The concomitant use of Latanoprost and Bimatoprost may result in increased intraocular pressure. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic response and adverse effects. Teach patient proper use, side effects/appropriate interventions, and symptoms to report.

Patient EducationFor use in eyes only. Wash hands before instilling. Sit or lie down to instill. Open eye, look at ceiling, and instill prescribed amount of solution. Apply gentle pressure to inner corner of eye. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Contact prescriber concerning continued use of drops if eye infection develops, trauma occurs to the eye, and prior to eye surgery. This product contains benzalkonium chloride which may be adsorbed by contact lenses; remove contacts prior to administration and wait 15 minutes before reinserting. May cause permanent changes in eye color (increases the amount of brown pigment in the iris), eyelid, and eyelashes. May also increase the length and/or number of eyelashes. Changes may occur slowly (months to years). May be used with other eye drops to lower intraocular pressure. If using more than one eye drop medicine, wait at least 5 minutes in between application of each medication. Notify prescriber if conjunctivitis or eyelid reactions occur with use of this product. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant or breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic:

Lumigan®: 0.03% (2.5 mL, 5 mL, 7.5 mL) [contains benzalkonium chloride]

Generic AvailableNo

ManufacturerAllergan, Inc

Pricing: U.S. (www.drugstore.com)

Solution (Lumigan)

0.03% (2.5): $74.89

0.03% (5): $145.51

0.03% (7.5): $221.47

Mechanism of ActionAs a synthetic analog of prostaglandin with ocular hypotensive activity, bimatoprost decreases intraocular pressure by increasing the outflow of aqueous humor.

Pharmacodynamics/Kinetics

Onset of action: Reduction of IOP: ~4 hours

Peak effect: Maximum reduction of IOP: ~8-12 hours

Distribution: 0.67 L/kg

Protein binding: ~88%

Metabolism: Undergoes oxidation, N-demethylation, and glucuronidation after reaching systemic circulation; forms metabolites

Half-life elimination: I.V.: 45 minutes

Time to peak: 10 minutes

Excretion: Urine (67%); feces (25%)

Related Information

- Glaucoma Drug Therapy

Pharmacotherapy PearlsThe IOP-lowering effect was shown to be 7-8 mm Hg in clinical studies.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesLumigan (AR, AT, AU, BE, BG, BR, CH, CN, CO, CR, CZ, DE, DK, EC, ES, FI, FR, GB, GR, GT, HK, HN, IE, IL, IN, IT, KP, MX, MY, NL, NO, PA, PE, PT, RU, SE, SG, SV, TH, TR, TW, UY, VE, ZA)

BIP

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Pharmacologic Category[Chemotherapy Regimen, Cervical Cancer]

Regimen UseCervical cancer

Regimen

Bleomycin: I.V.: 30 units continuous infusion day 1

[total dose/cycle = 30 units]

Cisplatin: I.V.: 50 mg/m^2 day 2

[total dose/cycle = 50 mg/m^2]

Ifosfamide: I.V.: 5 g/m^2 continuous infusion day 2

[total dose/cycle = 5 g/m^2]

Mesna: I.V.: 6 g/m^2 continuous infusion over 36 hours day 2 (start with ifosfamide)

[total dose/cycle = 6 g/m^2]

Repeat cycle every 21 days

References

Buxton EJ, Meanwell CA, Hilton C, et al, âCombination Bleomycin, Ifosfamide, and Cisplatin Chemotherapy in Cervical Cancer,â *J Natl Cancer Inst*, 1989, 81(5):359-61.[PubMed 2464699]

Bisacodyl

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Doxidan® may be confused with doxepin

Modane® may be confused with Matulane®, Moban®

Pronunciation(bis a KOE dil)

U.S. Brand NamesAlophen® [OTC]; Bisac-Evac™ [OTC]; Bisacodyl Uniserts® [OTC] [DSC]; Biscolax™ [OTC]; Correctol® Tablets [OTC]; Dacodyl™ [OTC]; Doxidan® [OTC]; Dulcolax® [OTC]; ex-lax® Ultra [OTC]; Fematrol [OTC]; Femilax™ [OTC]; Fleet® Bisacodyl [OTC]; Fleet® Stimulant Laxative [OTC]; Veracolate [OTC]

Canadian Brand NamesApo-Bisacodyl®; Carter's Little Pills®; Dulcolax®; Gentlax®

Pharmacologic CategoryLaxative, Stimulant

Use: Labeled IndicationsTreatment of constipation; colonic evacuation prior to procedures or examination

Dosing: Adults

Relief of constipation:

Oral: 5-15 mg as single dose (up to 30 mg when complete evacuation of bowel is required)

Rectal: Suppository: 10 mg as single dose

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Relief of constipation:

Oral: Children >6 years: 5-10 mg (0.3 mg/kg) at bedtime or before breakfast

Rectal (suppository): Children:

<2 years: 5 mg as a single dose

>2 years: 10 mg

Administration: OralAdminister with a glass of water on an empty stomach for rapid effect. Do not administer within 1 hour of milk, any dairy products, or taking an antacid, to protect the coating.

Dietary ConsiderationsShould not be administered within 1 hour of milk, any dairy products, or taking an antacid, to protect the coating. Should be administered with a glass of water on an empty stomach for rapid effect.

ContraindicationsHypersensitivity to bisacodyl or any component of the formulation; abdominal pain or obstruction, nausea, or vomiting

Geriatric ConsiderationsThe chronic use of stimulant cathartics is inappropriate and should be avoided; although constipation is a common complaint from elderly, such complaints require evaluation; elderly are often predisposed to constipation due to disease, drugs, immobility, and a decreased fluid intake, partially because they have a blunted “thirst reflex” with aging; short-term use of stimulants is best; if prophylaxis is desired, this can be accomplished with bulk agents (psyllium), stool softeners, and hyperosmotic agents (sorbitol 70%); stool softeners are unnecessary if stools are well hydrated, soft, or “mushy”.

Pregnancy Risk FactorC

Adverse Reactions<1%:

Central nervous system: Vertigo

Endocrine & metabolic: Electrolyte and fluid imbalance (metabolic acidosis or alkalosis, hypocalcemia)

Gastrointestinal: Mild abdominal cramps, nausea, vomiting, rectal burning

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Antacids: May diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Milk or dairy products may disrupt enteric coating, increasing stomach irritation.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, rectal [enema]:

Fleet® Bisacodyl: 10 mg/30 mL (37 mL)

Suppository, rectal: 10 mg

Bisac-Evac™, Bisacodyl Uniserts® [DSC], Biscolax™, Dulcolax®: 10 mg

Tablet [enteric coated]: 5 mg

Alophen®, Bisac-Evac™, Correctol®, Dacodyl™, Dulcolax®, ex-lax® Ultra, Fematrol, Femilax™, Veracolate: 5 mg

Tablet, delayed release: 5 mg

Doxidan®, Fleet® Stimulant Laxative: 5 mg

Generic AvailableYes: Excludes enema

Pricing: U.S. (www.drugstore.com)

Suppository (Bisacodyl)

10 mg (100): $18.99

Mechanism of ActionStimulates peristalsis by directly irritating the smooth muscle of the intestine, possibly the colonic intramural plexus; alters water and electrolyte secretion producing net intestinal fluid accumulation and laxation

Pharmacodynamics/Kinetics

Onset of action: Oral: 6-10 hours; Rectal: 0.25-1 hour

Absorption: Oral, rectal: Systemic, <5%

Related Information

- Laxatives, Classification and Properties

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesAlaxa (IT); Alsylax (CN); Anan (JP); Anulax (EC); Atzirut X (IL); Bekunis B (LU); Bicolax (ID); Bioyl (TW); Bisacod (TH); Bisacodyl (PL); Bisakodils (EE); Bisalax (AU, BG); Contalax (FR); Correctol (HK); Dissilax (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Dulco Laxo (ES); Dulco-lax perles (GB); Dulcolan (VE); Dulcolax (AE, AR, AT, BB, BE, BF, BH, BJ, BM, BR, BS, BZ, CH, CI, CO, CY, DE, DK, EG, ET, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, ID, IL, IN, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PH, PK, PT, PY, QA, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Extralax (CZ); Fenolax (CZ); Gencolax (TH); Johnlax (TW); Kadolax (TH); Lax-Tab (AU); Laxacod (ID); Laxadin (IL); Laxadyl (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Laxamex (ID); Laxans-ratiopharm (LU); Laxcodyl (TH); Laxitab 5 (TH); Marcholax (HK); Medesup (ES); Moderlax (PT); Perilax (DK, ZA); Purgo-Pil (LU); Pyrilax (CZ, PL); Satolax-10 (JP); Tirgon N (LU); Toilax (DK, FI, IE, NL, NO, SE); Vacolax (TH)

Bismuth, Metronidazole, and Tetracycline

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(BIZ muth, me troe NI da zole, & tet ra SYE kleen)

U.S. Brand NamesHelidac®; Pylera™

Pharmacologic CategoryAntibiotic, Miscellaneous; Antibiotic, Tetracycline Derivative; Antidiarrheal

Use: Labeled IndicationsAs part of a multidrug regimen for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence in combination with an H_2 agonist (Helidac®) or omeprazole (Pylera™)

Dosing: AdultsDuodenal ulcer associated with *H. pylori* infection: Oral:

Helidac®: Two bismuth subsalicylate 262.4 mg tablets, 1 metronidazole 250 mg tablet, and 1 tetracycline 500 mg capsule 4 times/day at meals and bedtime, plus an H_2 antagonist (at the appropriate dose) for 14 days; follow with 8 oz of water; the H_2 antagonist should be continued for a total of 28 days

Pylera™: Three capsules 4 times/day after meals and at bedtime, plus omeprazole 20 mg twice daily for 10 days; follow each dose with 8 oz of water (each capsule contains bismuth subcitrate potassium 140 mg, metronidazole 125 mg, and tetracycline 125 mg)

Dosing: ElderlyRefer to adult dosing.

Administration: Oral

Helidac®: Chew bismuth tablets; swallow **(do not chew)** metronidazole and tetracycline. Take with a full glass (8 oz) of water. Administer an H_2 antagonist at appropriate dose.

Pylera™: Swallow capsules whole with full glass of water. Administer omeprazole after morning meal and evening meal.

StorageStore at 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to bismuth, metronidazole, tetracycline, or any component of the formulation; children; significant renal/hepatic impairment; pregnancy

Helidac® is also contraindicated in patients with hypersensitivity to salicylates

Warnings/PrecautionsSee individual agents.

Pregnancy Risk FactorD

Pregnancy ConsiderationsSee individual agents.

LactationEnters breast milk/contraindicated

Adverse ReactionsAlso see individual agents.

Helidac® (includes studies with/without concomitant acid-suppression therapy):

>10%: Gastrointestinal: Nausea (12%)

1% to 10%:

Central nervous system: Dizziness (2%), headache (2%), insomnia (1%), pain (1%)

Gastrointestinal: Abdominal pain (7%), diarrhea (7%), melena (3%), anorexia (2%), constipation (2%), dyspepsia (2%), tongue discoloration (2%), vomiting (2%), abnormal stools (1%), anal discomfort (1%), duodenal ulcer (1%), flatulence (1%), GI hemorrhage (1%), taste perversion (1%)

Neuromuscular & skeletal: Weakness (2%), paresthesia (1%)

Respiratory: Upper respiratory infection (2%), sinusitis (1%)

<1%: Acne, ALT increased, AST increased, arthritis, bruising, cerebral ischemia, chest pain, conjunctivitis, dysphagia, eructation, flu-like syndrome, gastrointestinal moniliasis, glossitis, hypertension, infection, intestinal obstruction, malaise, MI, neoplasm, nervousness, photosensitivity reaction, pruritus, rash, rectal hemorrhage, rheumatoid arthritis, rhinitis, somnolence, stomatitis, syncope, tendonitis, tooth disorder, urinary tract infection, xerostomia

Pylera™ (with concomitant omeprazole):

>10%: Gastrointestinal: Abnormal stools (16%)

1% to 10%:

Cardiovascular: Chest pain (1%), palpitation (1%)

Central nervous system: Headache (8%), dizziness (3%), pain (2%), anxiety (1%)

Dermatologic: Maculopapular rash (1%)

Gastrointestional: Abdominal pain (9%), diarrhea (9%), dyspepsia (9%), nausea (8%), taste perversion (5%), gastritis (1%), gastroenteritis (1%), vomiting (1%), xerostomia (1%)

Genitourinary: Vaginitis (4%), urine abnormality (2%)

Hepatic: ALT increased (2%), AST increased (1%)

Neuromuscular & skeletal: Weakness (4%), back pain (2%)

Respiratory: Pharyngitis (2%), rhinitis (1%)

Miscellaneous: Flu-like syndrome (5%), infection (1% to 2%)

<1%: Cough, flatulence, rash, sinusitis

Metabolism/Transport Effects

Metronidazole: **Inhibits** CYP2C8/9 (weak), 3A4 (moderate)

Tetracycline: **Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (moderate)

Drug Interactions

Alcohol (Ethyl): MetroNIDAZOLE may enhance the adverse/toxic effect of Alcohol (Ethyl). A disulfiram-like reaction may occur. *Risk C: Monitor therapy*

Amprenavir: MetroNIDAZOLE may enhance the adverse/toxic effect of Amprenavir. This is specifically related to the propylene glycol contained in amprenavir oral solution, not capsules. *Risk X: Avoid combination*

Antacids: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Atovaquone: Tetracycline may decrease the serum concentration of Atovaquone. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Bismuth: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Bismuth Subsalicylate: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Busulfan: MetroNIDAZOLE may increase the serum concentration of Busulfan. *Risk D: Consider therapy modification*

Calcineurin Inhibitors: MetroNIDAZOLE may decrease the metabolism of Calcineurin Inhibitors. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May enhance the adverse/toxic effect of MetroNIDAZOLE. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Tetracycline Derivatives. Only a concern with orally administered products. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mebendazole: May enhance the adverse/toxic effect of MetroNIDAZOLE. Particularly the risk for Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis may be increased. *Risk D: Consider therapy modification*

Mycophenolate: MetroNIDAZOLE may decrease the serum concentration of Mycophenolate. Specifically, metronidazole may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Tetracycline Derivatives may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Penicillins: Tetracycline Derivatives may diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Quinapril: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: Tetracycline Derivatives may enhance the adverse/toxic effect of Retinoic Acid Derivatives. The development of pseudotumor cerebri is of particular concern. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Tetracycline Derivatives: Bismuth may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tipranavir: MetroNIDAZOLE may enhance the adverse/toxic effect of Tipranavir. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): MetroNIDAZOLE may decrease the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Tetracycline Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zinc Salts: May decrease the absorption of Tetracycline Derivatives. Only a concern when both products are administered orally. **Exceptions:** Zinc Chloride. *Risk D: Consider therapy modification*

Monitoring ParametersSee individual agents.

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Pylera™: Bismuth subcitrate potassium 140 mg, metronidazole 125 mg, and tetracycline hydrochloride 125 mg

Combination package:

Helidac® [each package contains 14 blister cards (2-week supply); each card contains the following]:

Capsule: Tetracycline hydrochloride: 500 mg (4)

Tablet, chewable: Bismuth subsalicylate: 262.4 mg (8)

Tablet: Metronidazole: 250 mg (4)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Misc (Helidac)

(56): $304.69

Mechanism of ActionBismuth, metronidazole, and tetracycline individually have demonstrated *in vitro* activity against most susceptible strains of *H. pylori* isolated from patients with duodenal ulcers. Resistance to metronidazole is increasing in the U.S.; an alternative regimen, not containing metronidazole, if *H. pylori* is not eradicated follow therapy.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Bismuth
- MetroNIDAZOLE
- Tetracycline

Dental Health: Effects on Dental TreatmentTetracyclines are not recommended for use during pregnancy since they can cause enamel hypoplasia and permanent teeth discoloration; long-term use associated with oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness common; metronidazole has been reported to cause depression, insomnia, confusion, panic, delusions, hallucinations, and exacerbation of schizophrenia; tetracycline has been reported to produce memory disturbances as well as mood stabilizing and antidepressant effects

Mental Health: Effects on Psychiatric TreatmentMetronidazole and tetracycline may increase serum lithium levels and produce lithium toxicity; monitor serum lithium levels

Index TermsBismuth Subcitrate Potassium, Tetracycline, and Metronidazole; Bismuth Subsalicylate, Tetracycline, and Metronidazole; Metronidazole, Bismuth Subcitrate Potassium, and Tetracycline; Metronidazole, Bismuth Subsalicylate, and Tetracycline; Tetracycline, Metronidazole, and Bismuth Subcitrate Potassium; Tetracycline, Metronidazole, and Bismuth Subsalicylate

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Bismuth

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English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Kaopectate® may be confused with Kayexalate®

Maalox® Total Stomach Relief® is a different formulation than Maalox®

Note: Canadian formulation of Kaopectate® does not contain bismuth; the active ingredient in the Canadian formulation is attapulgite.

Pronunciation(BIZ muth)

U.S. Brand NamesBismatrol Maximum Strength [OTC]; Bismatrol [OTC]; Diotame® [OTC]; Kao-Tin [OTC]; Kaopectate® Extra Strength [OTC]; Kaopectate® [OTC]; Kapectolin [OTC]; Maalox® Total Stomach Relief® [OTC]; Peptic Relief [OTC]; Pepto Relief [OTC]; Pepto-Bismol® Maximum Strength [OTC]; Pepto-Bismol® [OTC]

Pharmacologic CategoryAntidiarrheal

Use: Labeled IndicationsSubsalicylate formulation: Symptomatic treatment of mild, nonspecific diarrhea; control of traveler's diarrhea (enterotoxigenic *Escherichia coli*); as part of a multidrug regimen for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence

Dosing: Adults

Treatment of nonspecific diarrhea, control/relieve traveler's diarrhea: Oral: Subsalicylate (doses based on 262 mg/15 mL liquid or 262 mg tablets): 2 tablets or 30 mL every 30 minutes to 1 hour as needed up to 8 doses/24 hours

***Helicobacter pylori*eradication:** Oral: Subsalicylate: 524 mg 4 times/day with meals and at bedtime; requires combination therapy

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Nonspecific diarrhea, control/relieve traveler's diarrhea: Subsalicylate (doses based on 262 mg/5 mL liquid or 262 mg tablet): Oral:

Children: Up to 8 doses/24 hours:

3-6 years: $^1/_3$ tablet or 5 mL every 30 minutes to 1 hour as needed

6-9 years: $^2/_3$ tablet or 10 mL every 30 minutes to 1 hour as needed

9-12 years: 1 tablet or 15 mL every 30 minutes to 1 hour as needed

>12 years: Refer to adult dosing

Dosing: Renal ImpairmentShould probably be avoided in patients with renal impairment.

Administration: OralLiquids must be shaken prior to use. Chewable tablets should be chewed thoroughly. Nonchewable caplets should be swallowed whole with a full glass of water.

Dietary ConsiderationsDrink plenty of fluids to help prevent dehydration caused by diarrhea. Different dosage forms contain variable amounts of sodium; consult individual product labeling.

ContraindicationsHypersensitivity to bismuth or any component of the formulation

Subsalicylate formulation: Do not use subsalicylate in patients with influenza or chickenpox because of risk of Reye's syndrome; hypersensitivity to salicylates or any component of the formulation; history of severe GI bleeding; history of coagulopathy; pregnancy (3rd trimester)

Warnings/Precautions

Concerns related to adverse effects:

- Neurotoxicity: Bismuth products may be neurotoxic with very large doses.

Concurrent drug therapy issues:

- Aspirin: Bismuth subsalicylate should be used with caution if patient is taking aspirin.

Special populations:

- Pediatrics: Use with caution in children, especially those <3 years of age and those with viral illness.

Other warnings/precautions:

- Self-medication (OTC use): Children and teenagers who have or are recovering from chickenpox or flu-like symptoms should not use subsalicylate. Changes in behavior (along with nausea and vomiting) may be an early sign of Reye's syndrome; patients should be instructed to contact their healthcare provider if these occur. Patients should be instructed to contact healthcare provider for diarrhea lasting >2 days, hearing loss, or ringing in the ears. Not labeled for OTC use in children <12 years of age.

Geriatric ConsiderationsTinnitus and CNS side effects (confusion, dizziness, high tone deafness, delirium, psychosis) may be difficult to assess in some elderly patients. Limit use of this agent in elderly.

Pregnancy Risk FactorC/D (3rd trimester)

LactationExcretion in breast milk unknown (salicylates enter breast milk)/use caution

Adverse ReactionsFrequency not defined; subsalicylate formulation:

Central nervous system: Anxiety, confusion, headache, mental depression, slurred speech

Gastrointestinal: Discoloration of the tongue (darkening), grayish black stools, impaction may occur in infants and debilitated patients

Neuromuscular & skeletal: Muscle spasms, weakness

Ocular: Hearing loss, tinnitus

Drug Interactions

Tetracycline Derivatives: Bismuth may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Test InteractionsIncreased uric acid, increased AST; bismuth absorbs x-rays and may interfere with diagnostic procedures of GI tract

Nursing: Physical Assessment/MonitoringAssess patient allergy history prior to beginning treatment (contains ASA). Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, aspirin products). Assess therapeutic effectiveness (reduction in diarrhea) and adverse response (eg, CNS changes, impactions, tinnitus). Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Chew tablet well or shake suspension well before using. Maintain adequate fluid intake to prevent dehydration: 2-3 L/day of fluids (unless instructed to restrict fluid intake). May darken stools and turn tongue black. If diarrhea persists for more than 2 days, consult healthcare provider. If tinnitus (ringing in the ears) occurs this may indicate toxicity; discontinue use and notify healthcare provider. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to be pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet, as subsalicylate:

Kaopectate®: 262 mg

Pepto-Bismol®: 262 mg [sugar free; contains sodium 2 mg/caplet]

Liquid, as subsalicylate: 262 mg/15 mL (240 mL)

Bismatrol: 262 mg/15 mL (240 mL)

Bismatrol Maximum Strength: 525 mg/15 mL (240 mL)

Diotame®: 262 mg/15 mL (30 mL) [sugar free]

Kaopectate®: 262 mg/15 mL (240 mL, 360 mL) [contains potassium 5 mg/15 mL, sodium 10 mg/15 mL; regular and peppermint flavors]

Kaopectate®: 262 mg/15 mL (180 mL) [contains sodium 10 mg/15 mL; cherry flavor]

Kaopectate® Extra Strength: 525 mg/15 mL (240 mL) [contains potassium 5 mg/15 mL, sodium 10 mg/15 mL; peppermint flavor]

Kao-Tin: 262 mg/15 mL (240 mL, 480 mL) [contains sodium benzoate]

Maalox® Total Stomach Relief®: 525 mg/15 mL (360 mL) [contains sodium 3.3 mg/15mL; strawberry and peppermint flavor]

Peptic Relief: 262 mg/15 mL (240 mL) [sugar free; mint flavor]

Pepto-Bismol®: 262 mg/15 mL (120 mL, 240 mL, 360 mL, 480 mL) [sugar free; contains sodium 6 mg/15 mL and benzoic acid; cherry and wintergreen flavors]

Pepto-Bismol® Maximum Strength: 525 mg/15 mL (120 mL, 240 mL, 360 mL) [sugar free; contains sodium 6 mg/15 mL and benzoic acid; wintergreen flavor]

Suspension, as subsalicylate:

Kapectolin: 262 mg/15 mL (480 mL) [mint flavor]

Tablet, chewable, as subsalicylate: 262 mg

Bismatrol: 262 mg

Diotame®: 262 mg [sugar free]

Peptic Relief, Pepto Relief: 262 mg

Pepto-Bismol®: 262 mg [sugar free; contains sodium <1 mg; cherry and wintergreen flavors]

Generic AvailableYes

Mechanism of Action

Bismuth subsalicylate exhibits both antisecretory and antimicrobial action. This agent may provide some anti-inflammatory action as well. The salicylate moiety provides antisecretory effect and the bismuth exhibits antimicrobial directly against bacterial and viral gastrointestinal pathogens.

Pharmacodynamics/Kinetics

Absorption: Bismuth: <1%; Subsalicylate: >90%

Metabolism: Bismuth subsalicylate is converted to salicylic acid and insoluble bismuth salts in the GI tract.

Half-life elimination: Terminal: Bismuth: Highly variable

Excretion: Bismuth: Urine and feces; Salicylate: Urine

Related Information

- Antimicrobial Drugs of Choice

Pharmacotherapy Pearls

Bismuth subcitrate potassium is bismuth salt that is only available in the combination product Pylera™, approved for use as part of a multidrug regimen for *H. pylori* eradication. It is not available as a single-agent product.

Dental Health: Effects on Dental Treatment

Key adverse event(s) related to dental treatment: Darkening of tongue.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions

No information available to require special precautions

Mental Health: Effects on Mental Status

May rarely cause anxiety, confusion, or depression

Mental Health: Effects on Psychiatric Treatment

None reported

Index Terms

Bismatrol; Bismuth Subsalicylate; Pink Bismuth

References

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Department of Health and Human Services, Food and Drug Administration, “Labeling for Oral and Rectal Over-the-Counter Drug Products Containing Aspirin and Nonaspirin Salicylates; Reye's Syndrome Warning; Final Rule (29 CFR Part 201),” *Fed Regist*, April 17, 2003, 18861-9. [PubMed 10177739]

Drumm B, Sherman P, Karmali M, et al, “Treatment of *Campylobacter pylori*-Associated Antral Gastritis in Children With Bismuth Subsalicylate and Ampicillin,” *J Pediatr*, 1988, 113(5):908-12. [PubMed 3183851]

Graham DY, Lew GM, Evans DG, et al, “Effect of Triple Therapy (Antibiotics Plus Bismuth) on Duodenal Ulcer Healing,” *Ann Intern Med*, 1991, 115(4):266-9. [PubMed 1854110]

Graham DY, Lew GM, Klein PD, et al, “Effect of Treatment of *Helicobacter pylori* Infection on the Long-Term Recurrence of Gastric or Duodenal Ulcer,” *Ann Intern Med*, 1992, 116(9):705-8. [PubMed 1558340]

Ormand JE and Talley NJ, “*Helicobacter pylori*: Controversies and an Approach to Management,” *Mayo Clin Proc*, 1990, 65(3):414-26. [PubMed 2179647]

Soriano-Brucher HE, Avendano P, O'Ryan M, et al, “Use of Bismuth Subsalicylate in Acute Diarrhea in Children,” *Rev Infect Dis*, 1990, 12(Suppl 1):51-5.

International Brand Names

A-Migdobis (MX); Assure (TW); Bisbacter (CO); Bismucar (PE); Bismuthum subgallicum (PL); Bismutol (EC); Bismutsubsalicylat-Steigerwald (DE); Cytribin (PL); De-nol (PL); Dermatol (DE, PL); Facidmol (MX); Gastro-Bismol (TH); Jatrox (DE); Kalbeten (IL); Pylorid (PL); Subsalicilato de Bismuto (MX); Trigastronol (ES); Ulcolind Wismut (DE); Ventrisol (PL)

Bisoprolol and Hydrochlorothiazide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Ziac® may be confused with Tiazac®, Zerit®

Pronunciation(bis OH proe lol & hye droe klor oh THYE a zide)
U.S. Brand NamesZiac®
Canadian Brand NamesZiac®
Pharmacologic CategoryBeta Blocker, Beta$_1$ Selective; Diuretic, Thiazide
Use: Labeled IndicationsTreatment of hypertension
Use: Unlabeled/InvestigationalPediatric hypertension
Dosing: AdultsHypertension: Oral: Dose is individualized, given once daily.
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Hypertension (unlabeled use): Oral: Initial: Bisoprolol 2.5 mg/hydrochlorothiazide 6.25 mg once daily; up to a maximum of bisoprolol 10 mg/hydrochlorothiazide 6.25 mg daily

Dosing: Hepatic ImpairmentCaution should be used in dosing/titrating patients.
ContraindicationsHypersensitivity to bisoprolol, hydrochlorothiazide, or any component of the formulation; pregnancy 2nd and 3rd trimesters
Allergy Considerations

- Beta-Blocker Allergy
- Thiazide/Thiazide-Related Diuretic Allergy

Pregnancy Risk FactorC/D (2nd and 3rd trimesters)
LactationEnters breast milk/use caution
Adverse Reactions

>10%: Central nervous system: Fatigue

1% to 10%:

Cardiovascular: Chest pain, edema, bradycardia, hypotension

Central nervous system: Headache, dizziness, depression, abnormal dreams, insomnia

Dermatologic: Rash, photosensitivity

Endocrine & metabolic: Hypokalemia, fluid and electrolyte imbalances (hypocalcemia, hypomagnesemia, hyponatremia), hyperglycemia

Gastrointestinal: Constipation, diarrhea, dyspepsia, nausea, flatulence

Genitourinary: Micturition (frequency)

Hematologic: Blood dyscrasias (rare)

Neuromuscular & skeletal: Arthralgia, myalgia

Ocular: Abnormal vision

Renal: Prerenal azotemia

Respiratory: Rhinitis, cough, dyspnea

<1% (Limited to important or life-threatening): Angioedema, bronchospasm, CNS depression (sedation), exfoliative dermatitis, gout, hypercalcemia, orthostasis, pancreatitis, paresthesia, Peyronie's disease, syncope, vasculitis

Metabolism/Transport EffectsBisoprolol: **Substrate** of CYP2D6 (minor), 3A4 (major)
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

2.5/6.25: Bisoprolol fumarate 2.5 mg and hydrochlorothiazide 6.25 mg

5/6.25: Bisoprolol fumarate 5 mg and hydrochlorothiazide 6.25 mg

10/6.25: Bisoprolol fumarate 10 mg and hydrochlorothiazide 6.25 mg

Generic AvailableYes
ManufacturerLederle Laboratories
Pricing: U.S. (www.drugstore.com)

Tablets (Bisoprolol-Hydrochlorothiazide)

2.5-6.25 mg (90): $59.99

5-6.25 mg (90): $19.96

10-6.25 mg (30): $22.99

Tablets (Ziac)

2.5-6.25 mg (30): $91.16

5-6.25 mg (30): $91.13

10-6.25 mg (30): $91.16

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Bisoprolol
- Hydrochlorothiazide

Dental Health: Effects on Dental TreatmentBisoprolol is a cardioselective beta-blocker. Local anesthetic with vasoconstrictor can be safely used in patients medicated with bisoprolol. Nonselective beta-blockers (ie, propranolol, nadolol) enhance the pressor response to epinephrine, resulting in hypertension and bradycardia; this has not been reported for bisoprolol. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusFatigue is common; may cause insomnia, confusion, depression, dizziness, headache, sleep disturbance, vivid dreams, anxiety, restlessness, and decreased concentration
Mental Health: Effects on Psychiatric TreatmentBarbiturates may decrease the effects of beta-blockers; may decrease lithium clearance, resulting in elevated serum lithium levels and potential lithium toxicity; monitor serum lithium levels
Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for bisoprolol and hydrochlorothiazide combination therapy may include improved compliance and synergistic reductions in blood pressure with an accomplished reduction in side effects. Beta-blockers and thiazide diuretics are first-line therapies for the treatment of hypertension. See Cardiovascular Considerations for individual agents.
Index TermsHydrochlorothiazide and Bisoprolol

References

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Kaplan NM and Sever PS, “Combination Therapy: A Key to Comprehensive Patient Care,” *Am J Hypertens*, 1997, 10(7 Pt 2):127S. [PubMed 9231887]

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International Brand NamesBiconcor (BR, MX); Biol Comp (CH); Cobis (KP); Concor Plus (AT, CH, PT); Concor Plus Forte (AT); Corentel D (PY, UY); Lodoz (BE, BG, CL, CZ, EE, FI, HK, ID, IN, NO, SG, TH); Wytens (FR); Ziac (AR, CN, CO, CR, DO, EC, GT, HN, NI, PA, PE, SV, VE); Ziak (ZA)

Bisoprolol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Zebeta® may be confused with DiaBeta®, Zetia®

Pronunciation(bis OH proe lol)

U.S. Brand NamesZebeta®

Canadian Brand NamesApo-Bisoprolol®; Monocor®; Novo-Bisoprolol; PMS-Bisoprolol; Sandoz-Bisoprolol; Zebeta®

Pharmacologic CategoryBeta Blocker, Beta$_1$ Selective

Use: Labeled IndicationsTreatment of hypertension, alone or in combination with other agents

Use: Unlabeled/InvestigationalChronic stable angina, supraventricular arrhythmias, PVCs, heart failure (HF)

Dosing: Adults

Hypertension: Oral: 2.5-5 mg once daily; may be increased to 10 mg and then up to 20 mg once daily, if necessary; usual dose range (JNC 7): 2.5-10 mg once daily

HF (unlabeled use): Initial: 1.25 mg once daily; maximum recommended dose: 10 mg once daily. **Note:** Increase dose gradually and monitor for signs and symptoms of CHF.

Dosing: ElderlyOral: Initial: 2.5 mg/day; may be increased by 2.5-5 mg/day; maximum recommended dose: 20 mg/day

Dosing: Renal Impairment

Cl$_{cr}$ <40 mL/minute: Oral: Initial: 2.5 mg/day; increase cautiously

Not dialyzable

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsMay be taken without regard to meals.

ContraindicationsCardiogenic shock; overt cardiac failure; marked sinus bradycardia; heart block greater than first-degree (except in patients with a functioning artificial pacemaker)

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Concerns related to adverse events:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; for patients with bronchospastic disease who do not respond to or cannot tolerate other therapies, initial low doses of beta$_1$-selective bisoprolol may be employed and used cautiously with close monitoring. Ensure patient has an inhaled beta$_2$-agonist immediately available. At doses ≥20 mg/day, slight asymptomatic increases in airway resistance and decreases in forced expiratory volume (FEV$_1$) has been observed.

- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.

- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.

- Heart failure (HF): Use with caution in patients with compensated heart failure and monitor for a worsening of the condition. Patients should be stabilized on heart failure regimen prior to initiation of beta-blocker. Beta-blocker therapy should be initiated at very low doses with gradual and very careful titration. Adjustment of other medications (ACE inhibitors and/or diuretics) may be required

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment required with severe impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis.

- Peripheral vascular disease (PVD) and Raynaud's disease: Can precipitate or aggravate symptoms of arterial insufficiency in patients with PVD and Raynaud's disease. Use with caution and monitor for progression of arterial obstruction.

- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.
- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required with Cl_{cr} <40 mL/minute.
- Thyrotoxicosis: Beta-blockade may mask signs of hyperthyroidism (eg, tachycardia). Abrupt discontinuation of beta-blockade may exacerbate symptoms of hyperthyroidism and may also induce thyroid storm.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents which decrease myocardial function (eg, ether, cyclopropane, and trichloroethylene).
- Calcium channel blockers: Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block may occur.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.

Geriatric ConsiderationsDue to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (ie, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20% to 50% in elderly populations. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults.

Pregnancy Risk FactorC (manufacturer); D (2nd and 3rd trimesters - expert analysis)

Pregnancy ConsiderationsNo data available on whether bisoprolol crosses the placenta. Beta-blockers have been associated with persistent bradycardia, hypotension, and IUGR; IUGR is probably related to maternal hypertension. Available evidence suggests beta-blockers are generally safe during pregnancy (JNC 7). Cases of neonatal hypoglycemia have been reported following maternal use of beta-blockers at parturition or during breast-feeding. Monitor breast-fed infant for symptoms of beta-blockade.

LactationEnters breast milk/use caution

Adverse Reactions

1% to 10%:

Cardiovascular: Chest pain (1% to 2%)

Central nervous system: Fatigue (dose related; 6% to 8%), insomnia (2% to 3%), hypoesthesia (1% to 2%)

Gastrointestinal: Diarrhea (dose related; 3% to 4%), nausea (2%), vomiting (1% to 2%)

Neuromuscular & skeletal: Arthralgia, asthenia (dose related; ≤2%)

Respiratory: Upper respiratory infection (5%), rhinitis (3% to 4%), sinusitis (dose related; 2%), dyspnea (1% to 2%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Abdominal pain, acne, alopecia, angioedema, anxiety, arrhythmia, asthma, back/neck pain, bradycardia (dose related), bronchitis, bronchospasm, BUN/creatinine increased, claudication, cold extremities, confusion (especially in the elderly), congestive heart failure, constipation, coughing, cutaneous vasculitis, cystitis, depression, dermatitis, dizziness, dyspepsia, dyspnea on exertion, eczema, edema, flushing, gastritis, gout, hallucinations, headache, hearing decreased, hyper-/hypoesthesia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypertriglyceridemia, hypotension, impotence, lacrimation (abnormal), leukopenia, libido decreased, malaise, memory loss, muscle cramps, muscle/joint pain, nervousness, ocular pain/pressure, orthostatic hypotension, palpitations, paresthesia, peptic ulcer, Peyronie's disease, pharyngitis, polyuria, positive ANA titers, pruritus, psoriasis, psoriasiform eruption, purpura, rash, renal colic, restlessness, rhythm disturbances, sleep disturbances, somnolence, syncope, taste abnormality, thrombocytopenia, tinnitus, transaminases increased, tremor, twitching, uric acid increased, vasculitis, vertigo, visual disturbances, weight gain, xerostomia

Metabolism/Transport Effects**Substrate** of CYP2D6 (minor), 3A4 (major)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure, ECG, neurologic status

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Blood pressure and heart rate should be assessed prior to and following first dose and with any change in dosage. Assess for therapeutic effectiveness and adverse effects. Instruct patients with diabetes to monitor glucose levels closely (beta-blockers may alter glucose tolerance). Teach patient proper use, possible side effects/appropriate interventions (hypotension precautions), and adverse symptoms to report.

Monitoring: Lab TestsSerum glucose regularly (if you have diabetes)

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed, with or without regard to meals. Do not take with antacids. Do not adjust dosage or discontinue medication without consulting prescriber. Take pulse daily (prior to medication) and follow prescriber's instruction about holding medication. If you have diabetes, monitor serum sugar closely (drug may alter glucose tolerance or mask signs of hypoglycemia). May cause fatigue, dizziness, or postural hypotension (use caution when changing position from lying or sitting to standing, when driving, or climbing stairs until response to medication is known); alteration in sexual performance (reversible); or constipation (increased dietary bulk and fluids and exercise may help). Report unresolved swelling of extremities, respiratory difficulty or new cough, unresolved fatigue, unusual weight gain, unresolved constipation, or unusual muscle weakness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as fumarate: 5 mg, 10 mg

Generic AvailableYes

ManufacturerLederle Laboratories

Pricing: U.S. (www.drugstore.com)

Tablets (Bisoprolol Fumarate)

5 mg (30):	$32.99
10 mg (30):	$35.13

Tablets (Zebeta)

5 mg (30):	$91.26
10 mg (30):	$91.26

Mechanism of ActionSelective inhibitor of beta$_1$-adrenergic receptors; competitively blocks beta$_1$-receptors, with little or no effect on beta$_2$-receptors at doses ≤20 mg

Pharmacodynamics/Kinetics

Onset of action: 1-2 hours

Absorption: Rapid and almost complete

Distribution: Widely; highest concentrations in heart, liver, lungs, and saliva; crosses blood-brain barrier; enters breast milk

Protein binding: ~30%

Metabolism: Extensively hepatic; significant first-pass effect (~20%)

Bioavailability: ~80%

Half-life elimination: Normal renal function: 9-12 hours; Cl$_{cr}$ <40 mL/minute: 27-36 hours; Hepatic cirrhosis: 8-22 hours

Time to peak: 2-4 hours

Excretion: Urine (50% as unchanged drug, remainder as inactive metabolites); feces (<2%)

Related Information

- Beta-Blockers

Dental Health: Effects on Dental TreatmentBisoprolol is a cardioselective beta-blocker. Local anesthetic with vasoconstrictor can be safely used in patients medicated with bisoprolol. Nonselective beta-blockers (ie, propranolol, nadolol) enhance the pressor response to epinephrine, resulting in hypertension and bradycardia; this has not been reported for bisoprolol. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusFatigue is common; may cause insomnia, confusion, depression, dizziness, headache, sleep disturbance, vivid dreams, anxiety, restlessness, and decreased concentration

Mental Health: Effects on Psychiatric TreatmentBarbiturates may decrease the effects of beta-blockers

Cardiovascular Considerations

Atrial Fibrillation: Beta-blocker therapy provides effective rate control in patients with atrial fibrillation.

Chronic Stable Angina: Beta-blockers are effective in the treatment of angina as monotherapy or when combined with nitrates and/or calcium channel blockers. In patients with severe intractable angina requiring negative cardiac chronotropic medications, pacemaker placement has been carried out to maintain heart rate in the setting of large doses of beta-blockers and/or calcium channel blockers. Beta-blockers are ineffective in the treatment of pure vasospastic (Prinzmetal) angina.

Heart Failure: Strong evidence supports that beta-blocker therapy, without intrinsic sympathomimetic activity (ISA), should be initiated in select patients with stable congestive heart failure (NYHA Class II-III). To date, carvedilol, sustained release metoprolol, and bisoprolol have demonstrated a beneficial effect on morbidity and mortality. It is important that beta-blocker therapy be instituted initially at very low doses with gradual and very careful titration. In the CIBIS-II trial, bisoprolol (beta-1 selective beta-blocker) improved morbidity and mortality in patients with moderate heart failure (NYHA Class III-IV).

Hypertension: Beta-blocker therapy in the treatment of hypertension has been associated with improved cardiovascular outcomes. According to the 2003 JNC-VII guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Beta-blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for a beta-blocker include patients with heart failure, post myocardial infarction, high coronary disease risk, or diabetes. In type-2 diabetic patients, a UK Prospective Diabetes Study Group (UKPDS) trial showed that beta-blocker therapy (atenolol) was as effective as an ACE inhibitor in reducing cardiovascular events and that the benefits of therapy were related more to the degree of antihypertensive efficacy rather than the class of drug used.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

ST-segment Elevation Myocardial Infarction (STEMI): Beta-blockers, without intrinsic sympathomimetic activity (ISA), have been shown to decrease morbidity and mortality when initiated in the acute treatment of STEMI and continued long-term. Oral beta-blockade should be initiated promptly in patients without contraindications (eg, signs of heart failure, evidence of a low-output state, risk of cardiogenic shock, or other beta-blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade may be considered and given promptly if the patient is experiencing concomitant hypertension or a tachyarrhythmia (Class IIa recommendation).

Unstable Angina/Non-ST-Segment Elevation MI (UA/NSTEMI): In the treatment of UA/NSTEMI, oral beta-blockade should be initiated within the first 24 hours in patients without contraindications (eg, signs of heart failure, evidence of a low-output state, risk of cardiogenic shock, or other beta blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade should only be considered if the patient is experiencing concomitant hypertension upon presentation (Class IIa recommendation).

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia and hypertension.

Anesthesia and Critical Care Concerns/Other Considerations**Surgery:** Based on available evidence, beta-blockers should be started days to weeks before elective surgery in selected patients when possible and titrated to a heart rate <65 beats per minute. Additional data suggest that long acting beta-blockers may be superior to short acting ones (Redelmeier, 2005). The ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery recommend beta-blockers be continued in patients undergoing surgery who are receiving beta-blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA Class I guideline indications (Class I recommendation). The guidelines also recommend that beta-blockers be given to patients undergoing vascular surgery who have myocardial ischemia demonstrated during preoperative testing (Class I recommendation).

The guidelines also state that beta-blockers are probably recommended in patients undergoing intermediate risk (eg, carotid endarterectomy, prostate surgery) or vascular surgery in whom preoperative assessment identifies coronary heart disease or high cardiac risk (Class IIa recommendation). High cardiac risk is defined as having >1 of the following clinical risk factors: History of ischemic heart disease, compensated or prior heart failure, cerebrovascular disease, diabetes mellitus, or renal insufficiency. The use of beta-blockers is uncertain in patients undergoing intermediate risk or vascular surgery with ≤1 clinical risk factor (Class IIb recommendation).

The majority of published trials suggest a benefit of perioperative beta-blocker use during noncardiac surgery especially in high-risk patients; however, more recent clinical trials have not shown a benefit to perioperative beta-blockade for noncardiac surgery (Juul, 2006; Yang, 2006).

Index TermsBisoprolol Fumarate

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International Brand NamesB-Beta (ID); Beta-One (KP); Betaprol (KP); Bicor (AU); Biol (CH); Biso 5 (TW); Bisobloc (NL); Bisocard (PL); Bisohexal (PL); Bisolol (IL); Bisomerck (DE); Bisoprolol (PL); Bisopromerck (PL); Bisoratio (PL); Bispro (AU); Cardensiel (FR); Cardicor (DK, IE); Cardiloc (IL); Concor (AR, AT, BG, BR, CH, CL, CN, CO, CR, CZ, DE, DO, EC, EE, EG, GT, HK, HN, HR, HU, ID, IN, IT, KP, LU, MX, MY, NI, PA, PK, PL, PT, SV, TH, TW, VE, ZA); Concor COR (DE); Concor Cor (PL); Concore (PH); Corbis (AR); Corentel (PE, PY, UY); Detensiel (FR); Emconcor (BE, DK, ES, FI, NO, SE); Emcor (GB, NL); Euradal (ES); Hapsen (ID); Hemiprol (KP); Isoten (BE); Jutabis (DE); Maintate (ID, JP); Pactens (GR); Soprol (IE)

Bivalirudin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(bye VAL i roo din)
U.S. Brand NamesAngiomax®
Canadian Brand NamesAngiomax®
Pharmacologic CategoryAnticoagulant, Thrombin Inhibitor
Use: Labeled IndicationsAnticoagulant used in conjunction with aspirin for patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA) or percutaneous coronary intervention (PCI) with provisional glycoprotein IIb/IIIa inhibitor; anticoagulant used in patients undergoing PCI with (or at risk of) heparin-induced thrombocytopenia (HIT) / thrombosis syndrome (HITTS)
Use: Unlabeled/InvestigationalHeparin-induced thrombocytopenia (HIT)
Dosing: Adults
Acute coronary syndromes (moderate-high risk) undergoing invasive strategy (unlabeled dose): Initial dose: 0.1 mg/kg bolus, followed by 0.25 mg/kg/hour. Prior to PCI, give an additional bolus of 0.5 mg/kg and increase infusion rate to 1.75 mg/kg/hour.

Anticoagulant in patients undergoing PTCA/PCI or PCI with HITS/HITTS (treatment should be started just prior to procedure): I.V.: Initial: Bolus: 0.75 mg/kg, followed by continuous infusion: 1.75 mg/kg/hour for the duration of procedure and up to 4 hours postprocedure if needed; determine ACT 5 minutes after bolus dose; may administer additional bolus of 0.3 mg/kg if necessary.

A glycoprotein IIb/IIIa inhibitor may be administered concomitantly during the procedure.

If needed, infusion may be continued beyond initial 4 hours at 0.2 mg/kg/hour for up to 20 hours.

Cardiac surgery (unlabeled; Warkentin, 2008):

Off-pump: Initial bolus: 0.75 mg/kg, followed by continuous infusion 1.75 mg/kg/hour to maintain ACT >300 seconds

On-pump: Initial bolus: 1 mg/kg, followed by continuous infusion 2.5 mg/kg/hour; 50 mg bolus added to priming solution of cardiopulmonary bypass (CPB) circuit

Additional boluses of 0.1-0.5 mg may be given to maintain ACT >2.5 times baseline ACT. **Note:** Special maneuvers needed to prevent stasis and consequent clotting within CPB circuit during or after surgery.

HIT (unlabeled use; Warkentin, 2008): Normal renal function: Initial dose: ~0.15 mg/kg/hour; adjust to aPTT 1.5-2.5 times baseline value

Dosing: ElderlyRefer to adult dosing. No dosage adjustment is needed in elderly patients with normal renal function. Puncture site hemorrhage and catheterization site hemorrhage were seen in more patients ≥65 years of age than in patients <65 years of age.
Dosing: Renal ImpairmentInfusion dose should be reduced based on degree of renal impairment. Initial bolus dose remains unchanged. Monitor activated coagulation time (ACT) or aPTT depending on indication.

For use in PCI:

Cl_{cr} ≥30 mL/minute: No adjustment required

Cl_{cr} 10-29 mL/minute: Decrease infusion rate to 1 mg/kg/hour

Dialysis-dependent patients (off dialysis): Decrease infusion rate to 0.25 mg/kg/hour

Clearance of bivalirudin remains 1.8-fold greater than the glomerular filtration rate, regardless of the degree in renal impairment.

Hemodialysis: Approximately 25% removed during hemodialysis

Dosing: Hepatic ImpairmentNo adjustment necessary.
Calculations

- Creatinine Clearance: Adults

Administration: I.V.For I.V. administration only.
StorageStore unopened vials at 15°C to 30°C. Following reconstitution, vials should be stored at 2°C to 8°C. Do not freeze. Final dilutions of 0.5 mg/mL or 5 mg/mL are stable at room temperature for up to 24 hours.
ReconstitutionReconstitute each 250 mg with 5 mL SWFI. Gently swirl to dissolve. Further dilution in D_5W or NS (50 mL to make 5 mg/mL solution **or** 500 mL to make 0.5 mg/mL solution) is required prior to infusion. Do not administer in same line with other medications.
CompatibilityStable in D_5W, NS, or sterile water for injection; do not administer in same line with other medications.

Y-site administration: Compatible: Dobutamine (concentration up to 4 mg/mL). **Incompatible:** Alteplase, amiodarone, amphotericin B, chlorpromazine, diazepam, dobutamine (concentration of 12.5 mg/mL), prochlorperazine, reteplase, streptokinase, vancomycin.

Contraindications Hypersensitivity to bivalirudin or any component of the formulation; active major bleeding

Allergy Considerations

- Hirudin Derivatives Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: The most common complication is bleeding. Certain patients are at increased risk of bleeding; risk factors include bacterial endocarditis; congenital or acquired bleeding disorders; recent puncture of large vessels or organ biopsy; recent CVA, stroke, intracerebral surgery, or other neuraxial procedure; severe uncontrolled hypertension; renal impairment; recent major surgery; recent major bleeding (intracranial, GI, intraocular, or pulmonary). Monitor for signs and symptoms of bleeding.
- Thrombus formation: Increased risk of thrombus formation (some fatal) has been reported with use in gamma brachytherapy.

Disease-related concerns:

- Angina/ACS: Safety and efficacy have not been established in patients with unstable angina or acute coronary syndromes who are not undergoing PTCA or PCI.
- Renal impairment: Use with caution in patients with renal impairment; dosage reduction required.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Intramuscular administration: Not for intramuscular (I.M.) use.

Pregnancy Risk Factor B

Pregnancy Considerations Although animal studies have not shown harm to the fetus, safety and efficacy for use in pregnant women have not been established. Bivalirudin is used in conjunction with aspirin, which may lead to maternal or fetal adverse effects, especially during the third trimester. Use during pregnancy only if clearly needed.

Lactation Excretion in breast milk unknown/use caution

Adverse Reactions As with all anticoagulants, bleeding is the major adverse effect of bivalirudin. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the intensity of anticoagulation and patient susceptibility. Additional adverse effects are often related to idiosyncratic reactions, and the frequency is difficult to estimate. Adverse reactions reported were generally less than those seen with heparin.

>10%:

Cardiovascular: Hypotension (3% to 12%)

Central nervous system: Pain (15%), headache (3% to 12%)

Gastrointestinal: Nausea (3% to 15%)

Neuromuscular & skeletal: Back pain (9% to 42%)

1% to 10%:

Cardiovascular: Hypertension (6%), bradycardia (5%), angina (up to 5%)

Central nervous system: Insomnia (7%), anxiety (6%), fever (5%), nervousness (5%)

Gastrointestinal: Vomiting (6%), dyspepsia (5%), abdominal pain (5%)

Genitourinary: Urinary retention (4%)

Hematologic: Major hemorrhage (2% to 4%, compared to 4% to 9% with heparin); transfusion required (1% to 2%, compared to 2% to 6% with heparin), thrombocytopenia (<1% to 4%)

Local: Injection site pain (3% to 8%)

Neuromuscular & skeletal: Pelvic pain (6%)

<1%: Cerebral ischemia, confusion, facial paralysis, fever, infection, intracranial bleeding, kidney failure, lung edema, oliguria, retroperitoneal bleeding, sepsis, syncope, vascular anomaly, ventricular fibrillation

Postmarketing and/or case reports: Fatal bleeding, allergic reaction (including anaphylaxis), thrombus formation (during PCI, including intracoronary brachytherapy)

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Test InteractionsPT/INR levels may become elevated in the absence of warfarin. If warfarin is initiated, initial PT/INR goals while on bivalirudin may require modification.
Monitoring ParametersDepends upon indication for use of bivalirudin: ACT or aPTT
Monitoring: Lab TestsDepends upon indication for use of bivalirudin: ACT or aPTT
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 250 mg

Generic AvailableNo
Mechanism of ActionBivalirudin acts as a specific and reversible direct thrombin inhibitor; it binds to the catalytic and anionic exosite of both circulating and clot-bound thrombin. Catalytic binding site occupation functionally inhibits coagulant effects by preventing thrombin-mediated cleavage of fibrinogen to fibrin monomers, and activation of factors V, VIII, and XIII. Shows linear dose- and concentration-dependent prolongation of ACT, aPTT, PT, and TT.
Pharmacodynamics/Kinetics

Onset of action: Immediate

Duration: Coagulation times return to baseline ~1 hour following discontinuation of infusion

Distribution: 0.2 L/kg

Protein binding, plasma: Does not bind other than thrombin

Metabolism: Blood proteases

Half-life elimination: Normal renal function: 25 minutes; Cl_{cr} 10-29 mL/minute: 57 minutes; Dialysis-dependent patients (off dialysis): 3.5 hours

Excretion: Urine (20%), proteolytic cleavage

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: As with all anticoagulants, bleeding is the major adverse effect of bivalirudin. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the intensity of anticoagulation and patient susceptibility. Additional adverse effects are often related to idiosyncratic reactions, and the frequency is difficult to estimate. Adverse reactions reported were generally less than those seen with heparin.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause insomnia, anxiety, or nervousness
Mental Health: Effects on Psychiatric TreatmentNausea is common; this effect may be additive with concurrent use of SSRIs, lithium, or valproate. Do not administer bivalirudin in the same intravenous line with chlorpromazine, diazepam, or prochlorperazine; this results in haze formation, microparticulate formation, or gross precipitation.
Cardiovascular Considerations

Acute Coronary Syndromes (ACS): In the ACUITY trial, patients with moderate- or high-risk ACS undergoing an early invasive strategy with GP IIb/IIIa inhibition, developed similar rates of ischemia and bleeding when receiving bivalirudin as compared to heparin (Stone, 2005). Use of bivalirudin alone was associated with similar rates of ischemia with less bleeding as compared to either heparin (or bivalirudin) plus GP IIb/IIIa inhibition. ACUITY was an open-label, randomized, multicenter, noninferiority trial in which 13,819 patients were randomized to either bivalirudin plus GPIIb/IIIa inhibition, heparin plus GP IIb/IIIa inhibition, or bivalirudin alone. Patients were excluded if they had STEMI or shock, bleeding diathesis, major bleeding episode within 2 weeks prior, thrombocytopenia, or a Cl_{cr} <30 mL/minute. Patients who received bivalirudin received an initial bolus dose of 0.1 mg/kg followed by a continuous infusion of 0.25 mg/kg/hour prior to angiography. If the patient required PCI, the patient received an additional 0.5 mg/kg IV bolus with an increase in the infusion rate to 1.75 mg/kg/hour. Ninety-nine percent of all patients underwent angiography within 19.6 hours after admission. PCI was performed in 56%, CABG was performed in 11%, and 33% received medical therapy.

Cardiac Surgery: Bivalirudin has been used as an anticoagulant in CABG surgery as documented by case reports, case series (Koster, 2003; 2004), and more recently larger clinical trials. Bivalirudin binds to both exosite 1 and the active site of thrombin, producing only transient inhibition of thrombin. This is because thrombin cleaves bivalirudin and allows the active site to function again. This may be problematic in cases where there is not continuous blood flow through catheters, autotransfusion machines (eg, cell-saver devices), or intravenous lines (eg, CABG).

A number of clinical trials have demonstrated effectiveness in cardiac surgery for patients **without** HIT/HITTS (Merry, 2004; Smedira, 2006; Dyke, 2006). However, higher rates of bleeding with the use of bivalirudin as an alternative to heparin/protamine during cardiac surgery preclude its routine use in this setting.

Two prospective, open-label, multicenter trials demonstrated the safety and efficacy of bivalirudin as an alternative to heparin in patients **with** HIT/HITTS requiring on pump (Koster, 2007) and off pump (Dyke, 2007) cardiac surgery.

On-Pump Trial (CHOOSE-ON): Forty-nine patients with HIT/HITTS requiring cardiac surgery (redo-CABG, single valve surgery, or CABG + single-valve surgery) were treated with bivalirudin during CPB. Patients were excluded if Cl_{cr} <30 mL/minute, dependent on dialysis, had an EF <30%, or required surgery on >1 heart valve. A bivalirudin bolus of 50 mg was added to the priming solution of the CPB circuit. The patient was administered a bivalirudin bolus of 1 mg/kg I.V., followed by a continuous infusion of 2.5 mg/kg/hour until ~15 minutes before end of CPB. Patients were considered adequately anticoagulated if the ACT was ≥2.5 times the baseline. The primary endpoint of the study was in-hospital acute procedural success (defined as absence of death, Q-wave MI, repeat coronary revascularization, or stroke). Mean ACT achieved was not reported. Twenty percent of the patients had a Cl_{cr} 30-60 mL/minute. Procedural success in hospital or at 7 days occurred in 46 (94%) of patients. Mean intraoperative and 24-hour blood loss was 575 ± 524 mL and 998 ± 595 mL, respectively. No differences in outcome were noted between patients overall versus patients with moderate renal impairment.

Off-Pump Trial (CHOOSE-OFF): Thirty-five patients with HIT/HITTS requiring off-pump coronary artery bypass (OPCAB) were treated with bivalirudin. Patients were excluded if Cl_{cr} <30 mL/minute, EF <30%, or recent stroke (within prior 6 months). A bivalirudin bolus of 0.75 mg/kg was administered to the patient upon the surgeon's request with a continuous infusion of 1.75 mg/kg/hour. The target ACT was >300 seconds. Additional boluses or infusion titration was discouraged. Mean maximum ACT post-baseline was 388.2 ± 53.2 seconds. Procedural success at 7 days/discharge occurred in 47 (92%) patients. Chest tube output within 24 hours after surgery was 936 ± 525 mL. Two patients required reexploration for persistent postoperative hemorrhage.

Hemofiltration during CPB can be used to reduce concentrations of bivalirudin at the end of the procedure if needed.

Heparin-Induced Thrombocytopenia (HIT): Because bivalirudin has no structural similarity to heparin, it may be safely administered to patients with HIT or heparin-induced thrombotic thrombocytopenia syndrome (HITTS) or a history of HIT or HITTS. The 2004 ACC/AHA guidelines for the management of patients with acute MI recommend use of bivalirudin in HIT patients. The ACC/AHA/SCAI 2005 PCI guidelines recommend bivalirudin or argatroban as a heparin alternative in patients with HIT.

Percutaneous Coronary Intervention (PCI): Compared with heparin, bivalirudin reduced the composite endpoint of death, myocardial infarction, or revascularization in patients undergoing PCI (Bittl, 2001). Bleeding complications were significantly decreased as well. REPLACE-2 is a randomized, double-blind, heparin/GP IIb/IIIa inhibitor-controlled, international trial in patients undergoing PCI. Patients requiring reperfusion for acute MI were excluded. Patients were randomized to receive I.V. bivalirudin (0.75 mg/kg bolus plus 1.75 mg/kg/hour infusion for the duration of PCI) with provisional GP IIb/IIIa inhibitor (abciximab or eptifibatide, using FDA-approved dosing) or heparin bolus (65 units/kg) and planned GP IIb/IIIa inhibitor. More than 85% of all patients received aspirin and a thienopyridine. The study composite endpoint was 30-day incidence of death, MI, refractory ischemia, or in-hospital major bleeding. The results showed that bivalirudin with provisional GP IIb/IIIa inhibitor (used in 7.2% of patients) was not inferior to heparin plus planned GP IIb/IIIa inhibitor. There were more non-Q-wave MIs, but fewer in-hospital major bleeding events in the bivalirudin group. Long-term (1 year) follow-up with bivalirudin and provisional GP IIb/IIIa blockade is comparable to that of heparin and planned GP IIb/IIIa blockade (Lincolf, 2004). The ACC/AHA/SCAI 2005 guidelines state that bivalirudin is a reasonable alternative to UFH and GPIIb/IIIa antagonists in low-risk patients undergoing elective PCI.

Anesthesia and Critical Care Concerns/Other Considerations

Heparin-induced thrombocytopenia (HIT): Because bivalirudin has no structural similarity to heparin, it may be safely administered to patients with HIT or heparin-induced thrombotic thrombocytopenia syndrome (HITTS), or a history of HIT or HITTS.

Index TermsHirulog

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International Brand NamesAngiomax (AR, AU, CN, IL); Angiox (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Bleomycin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Bleomycin may be confused with Cleocin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(blee oh MYE sin)

U.S. Brand NamesBlenoxane® [DSC]

Canadian Brand NamesBlenoxane®; Bleomycin Injection, USP

Pharmacologic CategoryAntineoplastic Agent, Antibiotic

Use: Labeled IndicationsTreatment of squamous cell carcinomas, melanomas, sarcomas, testicular carcinoma, Hodgkin's lymphoma, and non-Hodgkin's lymphoma; sclerosing agent for malignant pleural effusion

Dosing: AdultsMaximum cumulative lifetime dose: 400 units; refer to individual protocols; 1 unit = 1 mg; may be administered I.M., I.V., SubQ, or intracavitary.

Test dose for lymphoma patient: I.M., I.V., SubQ: Because of the possibility of an anaphylactoid reaction, administer 1-2 units of bleomycin before the first 1-2 doses; monitor vital signs every 15 minutes; wait a minimum of 1 hour before administering remainder of dose; if no acute reaction occurs, then the regular dosage schedule may be followed. **Note:** Test doses may produce false-negative results.

Single agent therapy:

I.M./I.V./SubQ: Squamous cell carcinoma, lymphosarcoma, reticulum cell sarcoma, testicular carcinoma: 0.25-0.5 units/kg (10-20 units/m^2) 1-2 times/week

Continuous intravenous infusion: 15 units/m^2 over 24 hours/day for 4 days

Pleural sclerosing: Intrapleural: 60 units as a single instillation (some recommend limiting the dose in the elderly to 40 units/m^2; usual maximum: 60 units). Dose may be repeated at intervals of several days if fluid continues to accumulate (mix in 50-100 mL of NS); may add lidocaine 100-200 mg to reduce local discomfort.

Dosing: ElderlyRefer to adult dosing. Some recommend limiting the dose in the elderly to 40 units/m^2; usual maximum: 60 units.

Dosing: PediatricRefer to adult dosing.

Dosing: Renal Impairment

The FDA-approved labeling recommends the following adjustments:

Cl_{cr} 40-50 mL/minute: Administer 70% of normal dose

Cl_{cr} 30-40 mL/minute: Administer 60% of normal dose

Cl_{cr} 20-30 mL/minute: Administer 55% of normal dose

Cl_{cr} 10-20 mL/minute: Administer 45% of normal dose

Cl_{cr} 5-10 mL/minute: Administer 40% of normal dose

The following guidelines have been used by some clinicians:

Arnoff, 2007: Adults: Continuous renal replacement therapy (CRRT): Administer 75% of dose

Kintzel, 1995:

Cl_{cr} 46-60 mL/minute: Administer 70% of dose

Cl_{cr} 31-45 mL/minute: Administer 60% of dose

Cl_{cr} <30 mL/minute: Consider use of alternative drug

Dosing: Hepatic ImpairmentNot studied in patients with hepatic impairment; adjustment for hepatic impairment may be needed.

Dosing: Combination Regimens

Cervical cancer: BIP

Head and neck cancer: CABO

Lymphoma, Hodgkin's:

- ABVD
- BEACOPP
- CAD/MOPP/ABV
- MOPP/ABV Hybrid
- MOPP/ABVD
- Stanford V Regimen

Lymphoma, non-Hodgkin's:

- CEPP(B)
- COP-BLAM
- MACOP-B
- m-BACOD
- Pro-MACE-CytaBOM

Melanoma:

- BOLD
- BOLD + Interferon
- BOLD (Melanoma)

Osteosarcoma: POG-8651

Ovarian cancer:

- BEP (Ovarian Cancer)
- BEP (Ovarian Cancer, Testicular Cancer)

Testicular cancer:

- BEP (Ovarian Cancer, Testicular Cancer)
- BEP (Testicular Cancer)
- PVB
- VBP

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.May cause pain at injection site.

Administration: I.V.I.V. doses should be administered slowly (over 10-60 minutes).

Administration: I.V. DetailpH: 4-6 (reconstituted solution, varies depending on diluent)

Administration: Other

Intrapleural: 60 units in 50-100 mL NS; use of topical anesthetics or narcotic analgesia is usually not necessary

SubQ: May cause pain at injection site.

StorageRefrigerate intact vials of powder. Intact vials are stable for up to 1 month at 45°C. Solutions for infusion are stable for 96 hours at room temperature and 14 days under refrigeration.

ReconstitutionReconstitute powder with 1-5 mL BWFI or BNS which is stable at room temperature or under refrigeration for 28 days.

Standard I.V. dilution: Dose/50-1000 mL NS.

CompatibilityStable in NS; **variable stability (consult detailed reference)** in D_5W.

Y-site administration: Compatible: Allopurinol, amifostine, aztreonam, cefepime, cisplatin, cyclophosphamide, doxorubicin, doxorubicin liposome, droperidol, etoposide phosphate, filgrastim, fludarabine, fluorouracil, gemcitabine, granisetron, heparin, leucovorin, melphalan, methotrexate, metoclopramide, mitomycin, ondansetron, paclitaxel, piperacillin/tazobactam, sargramostim, teniposide, thiotepa, vinblastine, vincristine, vinorelbine.

Compatibility in syringe: Compatible: Cisplatin, cyclophosphamide, doxorubicin, droperidol, fluorouracil, furosemide, heparin, leucovorin, methotrexate, metoclopramide, mitomycin, vinblastine, vincristine.

Compatibility when admixed: Compatible: Amikacin, dexamethasone sodium phosphate, diphenhydramine, fluorouracil, gentamicin, heparin, hydrocortisone sodium phosphate, phenytoin, streptomycin, tobramycin, vinblastine, vincristine. **Incompatible:** Aminophylline, ascorbic acid injection, cefazolin, diazepam, hydrocortisone sodium succinate, methotrexate, mitomycin, nafcillin, penicillin G sodium, terbutaline.

ContraindicationsHypersensitivity to bleomycin or any component of the formulation; severe pulmonary disease; pregnancy
Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.
- Idiosyncratic reaction: See “Concerns related to adverse effects” below.
- Pulmonary fibrosis: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Hepatotoxicity: May cause hepatic toxicity.
- Idiosyncratic reaction: **[U.S. Boxed Warning]: A severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing (similar to anaphylaxis) has been reported in 1% of lymphoma patients treated with bleomycin.** Since these reactions usually occur after the first or second dose, careful monitoring is essential after these doses.
- Pulmonary fibrosis: **[U.S. Boxed Warning]: Occurrence of pulmonary fibrosis (commonly presenting as pneumonitis) is higher in elderly patients, patients receiving >400 units total lifetime dose or single doses >30 units, smokers, and patients with prior radiation therapy or receiving concurrent oxygen.**
- Renal toxicity: May cause renal toxicity.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment, may require dose adjustment.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**
- O_2 during surgery: Use caution when administering O_2 during surgery to patients who have received bleomycin.

Geriatric ConsiderationsPulmonary toxicity has been reported more frequently in geriatric patients (>70 years of age).
Pregnancy Risk FactorD
Pregnancy ConsiderationsAnimal studies have demonstrated teratogenic and abortifacient effects. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should avoid becoming pregnant during treatment.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.
Adverse Reactions

>10%:

Dermatologic: Pain at the tumor site, phlebitis. About 50% of patients develop erythema, rash, striae, induration, hyperkeratosis, vesiculation, and peeling of the skin, particularly on the palmar and plantar surfaces of the hands and feet. Hyperpigmentation (50%), alopecia, nailbed changes may also occur. These effects appear dose related and reversible with discontinuation.

Gastrointestinal: Stomatitis and mucositis (30%), anorexia, weight loss

Respiratory: Tachypnea, rales, acute or chronic interstitial pneumonitis, and pulmonary fibrosis (5% to 10%); hypoxia and death (1%). Symptoms include cough, dyspnea, and bilateral pulmonary infiltrates. The pathogenesis is not certain, but may be due to damage of pulmonary, vascular, or connective tissue. Response to steroid therapy is variable and somewhat controversial.

Miscellaneous: Acute febrile reactions (25% to 50%)

1% to 10%:

Dermatologic: Skin thickening, diffuse scleroderma, onycholysis, pruritus

Miscellaneous: Anaphylactoid-like reactions (characterized by hypotension, confusion, fever, chills, and wheezing; onset may be immediate or delayed for several hours); idiosyncratic reactions (1% in lymphoma patients)

<1%: Angioedema, cerebrovascular accident, cerebral arteritis, hepatotoxicity, malaise, MI, nausea, Raynaud’s phenomenon, renal toxicity, scleroderma-like skin changes, thrombotic microangiopathy, vomiting; Myelosuppression (rare); Onset: 7 days, Nadir: 14 days, Recovery: 21

days

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Gemcitabine: May enhance the adverse/toxic effect of Bleomycin. The risk of pulmonary toxicity may be increased. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersPulmonary function tests (total lung volume, forced vital capacity, carbon monoxide diffusion), renal function, liver function, chest x-ray, temperature initially; check body weight at regular intervals

Nursing: Physical Assessment/MonitoringAssess pulmonary and pregnancy status prior to beginning therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions. Pulmonary status should be evaluated for fine rales prior to each treatment (may be the first symptom of pulmonary toxicity) and physician notified of any changes. Lymphoma patients should be closely monitored for 1 hour following test dose before remainder of dose is administered. Infusion or injection site must be monitored closely to avoid extravasation. Assess results of laboratory tests (pulmonary, renal, and hepatic function), therapeutic effectiveness, and adverse reactions regularly during therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsPulmonary function (total lung volume, forced vital capacity, carbon monoxide diffusion), renal function, chest x-ray, liver function

Patient EducationDo not take any new medications during treatment unless approved by physician. This medication can only be administered by injection or infusion; report immediately any redness, burning, pain, or swelling at injection/infusion site. May cause loss of appetite, nausea, or vomiting (small, frequent meals, sucking lozenges, or chewing gum may help); mouth sores (frequent mouth care with soft swabs and mouth rinses may help); fever or chills (will usually resolve); redness, peeling, or increased color of skin; or loss of hair (reversible after cessation of therapy). Report any change in respiratory status; respiratory difficulty; wheezing; air hunger; increased secretions; difficulty expectorating secretions; confusion; unresolved fever or chills; sores in mouth; vaginal itching, burning, or discharge; sudden onset of dizziness; acute headache; or burning, stinging, redness, or swelling at injection site. **Pregnancy/breast-feeding precautions:** Inform physician if you are pregnant. Do not get pregnant during or for 1 month following therapy. Consult physician for instruction on appropriate contraceptives. This drug may cause severe fetal defects. Breast-feeding is not recommended

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution, as sulfate: 15 units, 30 units

Blenoxane®: 15 units [DSC], 30 units [DSC]

Generic AvailableYes

Mechanism of ActionInhibits synthesis of DNA; binds to DNA leading to single- and double-strand breaks

Pharmacodynamics/Kinetics

Absorption: I.M. and intrapleural administration: 30% to 50% of I.V. serum concentrations; intraperitoneal and SubQ routes produce serum concentrations equal to those of I.V.

Distribution: V_d: 22 L/m^2; highest concentrations in skin, kidney, lung, heart tissues; lowest in testes and GI tract; does not cross blood-brain barrier

Protein binding: 1%

Metabolism: Via several tissues including hepatic, GI tract, skin, pulmonary, renal, and serum

Half-life elimination: Biphasic (renal function dependent):

Normal renal function: Initial: 1.3 hours; Terminal: 9 hours

End-stage renal disease: Initial: 2 hours; Terminal: 30 hours

Time to peak, serum: I.M.: Within 30 minutes

Excretion: Urine (50% to 70% as active drug)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis and mucositis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment May rarely produce myelosuppression; use caution with clozapine and carbamazepine

Anesthesia and Critical Care Concerns/Other Considerations The use of oxygen concentrations (>30%) in animals previously treated with bleomycin has been reported to promote pulmonary toxicity. Although this is still controversial, supplemental oxygen should be used judiciously in patients who have received bleomycin.

Index Terms Bleo; Bleomycin Sulfate; BLM; NSC-125066

References

Aronoff GR, Bennett WM, Berns JS, et al, *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*, 5th ed. Philadelphia, PA: American College of Physicians; 2007, p 97.

Kintzel PE and Dorr RT, "Anticancer Drug Renal Toxicity and Elimination: Dosing Guidelines for Altered Renal Function," *Cancer Treat Rev*, 1995, 21(1):33-64.[PubMed 7859226]

Lamey PJ and Lewis MAO, “Oral Medicine in Practice: White Patches,” *Br Dent J*, 1990, 168(4):147-52. [PubMed 2310634]

Lazo JS and Sebti SM, “Bleomycin,” *Cancer Chemother Biol Response Modif*, 1994, 15:44-50. [PubMed 7540032]

Lazo JS, Sebti SM, and Schellens JH, “Bleomycin,” *Cancer Chemother Biol Response Modif*, 1996, 16:39-47. [PubMed 8639392]

Mir LM, Tounekti O, and Orlowski S, “Bleomycin: Revival of an Old Drug,” *Gen Pharmacol*, 1996, 27(5):745-8.[PubMed 8842674]

International Brand Names Bileco (AR); Blenamax (AU, MY, TW); Blenoxane (AU, BR, EC, EG, PH, ZA); Bleo (HK, JP); Bleo S (JP); Bleocin (BG, CZ, EE, EG, GR, HK, HN, HU, ID, IN, JP, MY, PL, PT, SG, TH, TW); Bleocin-S (MY); Bleocina (UY); Bleocris (PY); Bleolem (MX, TH); Bleomax (MX); Bleomicina (ES, IT, PE); Bleomycin (AT, CH, DK, FI, GB, NL, NO, SE); Bleomycin PFI (IL); Bleomycine (BE, FR, LU); Bleomycinum (DE); Blexit (CN); Bloicin-S (PH)

BOLD (Melanoma)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Melanoma]

Regimen UseMelanoma

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Bleomycin: SubQ: 7.5 units/day days 1 and 4 (cycle 1 only)

followed by SubQ: 15 units/day days 1 and 4 (subsequent cycles)

[total dose/cycle = 45 units; maximum total dose (all cycles) = 400 units]

Vincristine: I.V.: 1 mg/m^2/day days 1 and 5

[total dose/cycle = 2 mg/m^2]

Lomustine: Oral: 80 mg/m^2 (maximum 150 mg/dose) day 1

[total dose/cycle = 80 mg/m^2]

Dacarbazine: I.V.: 200 mg/m^2/day (maximum 400 mg/dose) days 1 to 5

[total dose/cycle = 1000 mg/m^2; maximum 2000 mg]

Repeat cycle every 4-6 weeks

Variation 2:

Bleomycin: I.V.: 15 units/day days 1 and 4

[total dose/cycle = 30 units]

Vincristine: I.V.: 1 mg/m^2/day days 1 and 5

[total dose/cycle = 2 mg/m^2]

Lomustine: Oral: 80 mg/m^2 (maximum 150 mg/dose) day 1

[total dose/cycle = 80 mg/m^2]

Dacarbazine: I.V.: 200 mg/m^2/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

Repeat cycle every 4 weeks

Variation 3:

Bleomycin: I.V.: 15 units/day days 1 and 4

[total dose/cycle = 30 units]

Vincristine: I.V.: 1 mg/m^2 day 1

[total dose/cycle = 1 mg/m^2]

Lomustine: Oral: 80 mg/m^2 day 3 (odd numbered cycles)

[total dose/cycle = 80 mg/m^2; every other cycle]

Dacarbazine: I.V.: 200 mg/m^2/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

Repeat cycle every 4 weeks

References

Variation 1:

Seigler HF, Lucas VS, Pickett NJ, et al, “DTIC, CCNU, Bleomycin and Vincristine (BOLD) in Metastatic Melanoma,” *Cancer*, 1980, 46(11):2346-8.[PubMed 6159960]

Variation 2:

York RM and Foltz AT, “Bleomycin, Vincristine, Lomustine, and DTIC Chemotherapy for Metastatic Melanoma,” *Cancer*, 1988, 61(11):2183-6.[PubMed 2452681]

Variation 3:

Lakhani S, Selby P, Bliss JM, et al, “Chemotherapy for Malignant Melanoma: Combinations and High Doses Produce More Responses Without Survival Benefit,” *Br J Cancer*, 1990, 61(2):330-4. [PubMed 1690022]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Melanoma

Regimen UseMelanoma

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Bleomycin: I.V.: 15 units/day days 2 and 5

[total dose/cycle = 30 units]

Vincristine: I.V.: 1 mg/m^2/day days 1 and 4

[total dose/cycle = 2 mg/m^2]

Lomustine: Oral: 80 mg day 1

[total dose/cycle = 80 mg]

Dacarbazine: I.V.: 200 mg/m^2/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

Interferon Alfa-2b: SubQ: 3 million units/day days 8 to 49 (cycles 1 and 2)

[total dose through day 49 = 126 million units]

followed by SubQ: 6 million units 3 times/week (beginning day 50 and subsequent cycles)

[total dose/cycle = 72 million units]

Repeat cycle every 4 weeks

Variation 2:

Bleomycin: I.V.: 30 units day 1

[total dose/cycle = 30 units]

Vincristine: I.V.: 2 mg day 1

[total dose/cycle = 2 mg]

Lomustine: Oral: 80 mg day 1

[total dose/cycle = 80 mg]

Dacarbazine: I.V.: 700 mg/m^2 day 1

[total dose/cycle = 700 mg/m^2]

Interferon Alfa-2b: SubQ: 3 million units 3 times/week

[total dose/cycle = 36 million units]

Repeat cycle every 4 weeks

Variation 3:

Bleomycin: I.V.: 15 units/day days 2 and 5

[total dose/cycle = 30 units]

Vincristine: I.V.: 1-2 mg/day days 1 and 4

[total dose/cycle = 2-4 mg]

Lomustine: Oral: 80 mg day 1

[total dose/cycle = 80 mg]

Dacarbazine: I.V.: 200 mg/m^2/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

Interferon Alfa-2b: SubQ: 6 million units 3 times/week, for 6 doses, starting day 8

[total dose/cycle = 36 million units]

Repeat cycle every 4 weeks

Variation 4:

Bleomycin: I.V.: 15 units/day days 2 and 5

[total dose/cycle = 30 units]

Vincristine: I.V.: 1 mg/m^2/day (maximum 2 mg/dose) days 1 and 4

[total dose/cycle = 2 mg/m^2]

Lomustine: Oral: 80 mg day 1

[total dose/cycle = 80 mg]

Dacarbazine: I.V.: 200 mg/m^2/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

Interferon Alfa-2b: SubQ: 3 million units/day days 8, 10, 12, 15, 17, and 19

[total dose/cycle = 18 million units]

Repeat cycle every 4 weeks

References

Variation 1:

Pyrhonen S, Hahka-Kemppinen M, and Muhonen T, “A Promising Interferon Plus Four-Drug Chemotherapy Regimen for Metastatic Melanoma,” *J Clin Oncol*, 1992, 10(12):1919-26.[PubMed 1280673]

Variation 2:

Vuoristo MS, Grohn P, Kumpulainen E, et al, “Treatment of Patients With Metastatic Melanoma With a One Day Regimen of Dacarbazine, Vincristine, Bleomycin, and Lomustine Plus Interferon Alfa,” *Eur J Cancer*, 1994, 30A(3):420.[PubMed 7515632]

Variation 3:

Vuoristo M, Grohn P, Kellokumpu-Lehtinen P, et al, “Intermittent Interferon and Polychemotherapy in Metastatic Melanoma,” *J Cancer Res Clin Oncol*, 1995, 121(3):175-80.[PubMed 7536196]

Variation 4:

Nathan FE, Berd D, Sato T, et al, “BOLD + Interferon in the Treatment of Metastatic Uveal Melanoma: First Report of Active Systemic Therapy,” *J Exp Clin Cancer Res*, 1997, 16(2):201-8.[PubMed 9261748]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Melanoma

Regimen UseMelanoma

Regimen

Dacarbazine: I.V.: 200 mg/m^2/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

Vincristine: I.V.: 1 mg/m^2/day days 1 and 4

[total dose/cycle = 2 mg/m^2]

Bleomycin: I.V.: 15 units/day days 2 and 5

[total dose/cycle = 30 units]

Lomustine: Oral: 80 mg day 1

[total dose/cycle = 80 mg]

Repeat cycle every 4 weeks

References

Nathan FE, Berd D, Sato T, et al, “BOLD + Interferon in the Treatment of Metastatic Uveal Melanoma: First Report of Active Systemic Therapy,” *J Exp Clin Cancer Res*, 1997, 16(2):201-8. [PubMed 9261748]

Punt CJ, van Herpen CM, Janasen RL, et al, “Chemoimmunotherapy With Bleomycin, Vincristine, Lomustine, Dacarbazine (BOLD) Plus Interferon Alpha for Metastatic Melanoma: A Multicentre Phase II Study,” *Br J Cancer*, 1997, 76(2):266-9.[PubMed 9231931]

Bortezomib-Dexamethasone

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Multiple Myeloma

Regimen Use Multiple myeloma

Index Terms Dexamethasone-Bortezomib

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Cycles 1 and 2:

Bortezomib: I.V.: 1.3 mg/m^2/day days 1, 4, 8, and 11

[total dose/cycle = 5.2 mg/m^2]

Dexamethasone: Oral: 40 mg/day days 1 to 4 and days 9 to 12

[total dose/cycle = 320 mg]

Treatment cycle is 21 days

Cycles 3 and 4:

Bortezomib: I.V.: 1.3 mg/m^2/day days 1, 4, 8, and 11

[total dose/cycle = 5.2 mg/m^2]

Dexamethasone: Oral: 40 mg/day days 1 to 4

[total dose/cycle = 160 mg]

Treatment cycle is 21 days

Variation 2:

Cycles 1 and 2:

Bortezomib: I.V.: 1.3 mg/m^2/day days 1, 4, 8, and 11

[total dose/cycle = 5.2 mg/m^2]

Treatment cycle is 21 days

Cycles 3 through 6 (begin dexamethasone after cycle 2 if partial response not achieved or after cycle 4 if complete response not achieved):

Bortezomib: I.V.: 1.3 mg/m^2/day days 1, 4, 8, and 11

[total dose/cycle = 5.2 mg/m^2]

Dexamethasone: Oral: 40 mg/day days 1 and 2

[total dose/cycle = 80 mg]

Treatment cycle is 21 days (for up to a total of 6 cycles)

References

Variation 1:

Harousseau JL, Attal M, Leleu X, et al, "Bortezomib Plus Dexamethasone as Induction Treatment Prior to Autologous Stem Cell Transplantation in Patients With Newly Diagnosed Multiple Myeloma: Results of an IFM Phase II Study," *Haematologica*, 2006, 91(11):1498-505.[PubMed 17043025]

Harousseau JL, Mathiot C, Attal M, et al, "VELCADE/Dexamethasone (Vel/D) Versus VAD as Induction Treatment Prior to Autologous Stem Cell Transplantation (ASCT) in Newly Diagnosed Multiple Myeloma (MM): Updated Results of the IFM 2005/01 Trial," *Blood*, 2007, 110(11): 450, ASH 2007 Annual Meeting Abstract 450.

Variation 2:

Jagannath S, Durie BG, Wolf J, et al, "Bortezomib Therapy Alone and in Combination With Dexamethasone for Previously Untreated Symptomatic Multiple Myeloma," *Br J Haematol*, 2005, 129(6):776-83.[PubMed 15953004]

Bortezomib-Doxorubicin (Liposomal)-Dexamethasone

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Multiple Myeloma]

Regimen UseMultiple myeloma

Index TermsDexamethasone-Bortezomib-Doxorubicin (Liposomal); Doxorubicin (Liposomal)-Dexamethasone-Bortezomib

Regimen

Bortezomib: I.V.: 1.3 mg/m^2/day days 1, 4, 8, and 11

> [total dose/cycle = 5.2 mg/m^2]

Doxorubicin (Liposomal): I.V.: 30 mg/m^2 day 1

> [total dose/cycle = 30 mg/m^2]

Dexamethasone: Oral: 40 mg/day days 1 to 4

> [total dose/cycle = 160 mg]

Repeat cycle every 28 days for up to 6 cycles

References

Palumbo A, Gay F, Bringhen S, et al, "Bortezomib, Doxorubicin and Dexamethasone in Advanced Multiple Myeloma," *Ann Oncol*, 2008, 19(6):1160-5.[PubMed 18326520]

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Multiple Myeloma

Regimen Use Multiple myeloma

Index Terms Doxorubicin (Liposomal)-Bortezomib

Regimen

Bortezomib: I.V.: 1.3 mg/m^2/day days 1, 4, 8, and 11

[total dose/cycle = 5.2 mg/m^2]

Doxorubicin (liposomal): I.V.: 30 mg/m^2 day 4

[total dose/cycle = 30 mg/m^2]

Repeat cycle every 21 days for up to 8 cycles

References

Biehn SE, Moore DT, Voorhees PM, et al, "Extended Follow-Up of Outcome Measures in Multiple Myeloma Patients Treated on a Phase I Study With Bortezomib and Pegylated Liposomal Doxorubicin," *Ann Hematol*, 2007, 86(3):211-6.[PubMed 17146676]

Orlowski RZ, Nagler A, Sonneveld P, et al, "Randomized Phase III Study of Pegylated Liposomal Doxorubicin Plus Bortezomib Compared With Bortezomib Alone in Relapsed or Refractory Multiple Myeloma: Combination Therapy Improves Time to Progression," *J Clin Oncol*, 2007, 25(25):3892-901.[PubMed 17679727]

Orlowski RZ, Voorhees PM, Garcia RA, et al, "Phase 1 Trial of the Proteasome Inhibitor Bortezomib and Pegylated Liposomal Doxorubicin in Patients With Advanced Hematologic Malignancies," *Blood*, 2005, 105(8):3058-65.[PubMed 15626743]

Bortezomib-Doxorubicin-Dexamethasone

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Multiple Myeloma

Regimen UseMultiple myeloma

Index TermsDexamethasone-Bortezomib-Doxorubicin; Doxorubicin-Dexamethasone-Bortezomib; PAD

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cycle 1:

Bortezomib: I.V.: 1.3 mg/m^2/day days 1, 4, 8, and 11

[total dose/cycle = 5.2 mg/m^2]

Dexamethasone: Oral: 40 mg/day days 1 to 4, 8 to 11, and 15 to 18

[total dose/cycle = 480 mg]

Doxorubicin: I.V.: 4.5 or 9 mg/m^2/day days 1 to 4

[total dose/cycle = 18-36 mg/m^2]

Treatment cycle is 21 days

Cycles 2-4:

Bortezomib: I.V.: 1.3 mg/m^2/day days 1, 4, 8, and 11

[total dose/cycle = 5.2 mg/m^2]

Dexamethasone: Oral: 40 mg/day days 1 to 4

[total dose/cycle = 160 mg]

Doxorubicin: I.V.: 4.5 or 9 mg/m^2/day days 1 to 4

[total dose/cycle = 18-36 mg/m^2]

Treatment cycle is 21 days

Variation 2:

Cycle 1:

Bortezomib: I.V.: 1 mg/m^2/day days 1, 4, 8, and 11

[total dose/cycle = 4 mg/m^2]

Dexamethasone: Oral: 40 mg/day days 1 to 4, 8 to 11, and 15 to 18

[total dose/cycle = 480 mg]

Doxorubicin: I.V.: 9 mg/m^2/day days 1 to 4

[total dose/cycle = 36 mg/m^2]

Treatment cycle is 21 days

Cycles 2-4:

Bortezomib: I.V.: 1 mg/m^2/day days 1, 4, 8, and 11

[total dose/cycle = 4 mg/m^2]

Dexamethasone: Oral: 40 mg/day days 1 to 4

[total dose/cycle = 160 mg]

Doxorubicin: I.V.: 9 mg/m^2/day days 1 to 4

[total dose/cycle = 36 mg/m^2]

Treatment cycle is 21 days

Variation 3:

Bortezomib: I.V.: 1.3 mg/m^2/day days 1, 4, 8, and 11

[total dose/cycle = 5.2 mg/m^2]

Dexamethasone: Oral: 40 mg/day days 1 to 4

[total dose/cycle = 160 mg]

Doxorubicin: I.V.: 20 mg/m^2/day days 1 and 4

[total dose/cycle = 40 mg/m^2]

Repeat cycle every 28 days for up to 6 cycles

References

Variation 1:

Oakervee HE, Popat R, Curry N, et al, "PAD Combination Therapy (PS-341/Bortezomib, Doxorubicin and Dexamethasone) for Previously Untreated Patients With Multiple Myeloma," *Br J Haematol*, 2005, 129(6):755-62.[PubMed 15953001]

Popat R, Oakervee HE, Hallam S, et al, "Bortezomib, Doxorubicin and Dexamethasone (PAD) Front-Line Treatment of Multiple Myeloma: Updated Results After Long-Term Follow-Up," *Br J Haematol*, 2008, 41(4):512-6.[PubMed 18371113]

Variation 2:

Popat R, Oakervee HE, Hallam S, et al, "Bortezomib, Doxorubicin and Dexamethasone (PAD) Front-Line Treatment of Multiple Myeloma: Updated Results After Long-Term Follow-Up," *Br J Haematol*, 2008, 41(4):512-6.[PubMed 18371113]

Variation 3:

Palumbo A, Gay F, Bringhen S, et al, "Bortezomib, Doxorubicin and Dexamethasone in Advanced Multiple Myeloma," *Ann Oncol*, 2008, 19(6):1160-5.[PubMed 18326520]

Bortezomib-Melphalan-Prednisone-Thalidomide

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category [Chemotherapy Regimen, Multiple Myeloma]

Regimen Use Multiple myeloma

Index Terms Melphalan-Prednisone-Bortezomib-Thalidomide; VMPT

Regimen

Bortezomib: I.V.: 1-1.3 mg/m^2/day days 1, 4, 15, and 22

[total dose/cycle = 4-5.2 mg/m^2]

Melphalan: Oral: 6 mg/m^2/day days 1 to 5

[total dose/cycle = 30 mg/m^2]

Prednisone: Oral: 60 mg/m^2/day days 1 to 5

[total dose/cycle = 300 mg/m^2]

Thalidomide: Oral: 50 mg/day days 1 to 35

[total dose/cycle = 1750 mg]

Repeat cycle every 35 days for 6 cycles

References

Palumbo A, Ambrosini MT, Benevolo G, et al, "Bortezomib, Melphalan, Prednisone, and Thalidomide for Relapsed Multiple Myeloma," *Blood*, 2007, 109(7):2767-72. [PubMed 17148584]

Bortezomib-Melphalan-Prednisone

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Multiple Myeloma]

Regimen Use Multiple myeloma

Index Terms Melphalan-Prednisone-Bortezomib; VMP

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Bortezomib: I.V.: 1.3 mg/m^2/day days 1, 4, 8, 11, 22, 25, 29, and 32

[total dose/cycle = 10.4 mg/m^2]

Melphalan: Oral: 9 mg/m^2/day days 1 to 4

[total dose/cycle = 36 mg/m^2]

Prednisone: Oral: 60 mg/m^2/day days 1 to 4

[total dose/cycle = 240 mg/m^2]

Repeat cycle every 42 days for 4 cycles

followed by

Bortezomib: I.V.: 1.3 mg/m^2/day days 1, 8, 22, and 29

[total dose/cycle = 5.2 mg/m^2]

Melphalan: Oral: 9 mg/m^2/day days 1 to 4

[total dose/cycle = 36 mg/m^2]

Prednisone: Oral: 60 mg/m^2/day days 1 to 4

[total dose/cycle = 240 mg/m^2]

Repeat cycle every 42 days for 5 cycles

Variation 2:

Bortezomib: I.V.: 1-1.3 mg/m^2/day days 1, 4, 8, 11, 22, 25, 29, and 32

[total dose/cycle = 8-10.4 mg/m^2]

Melphalan: Oral: 9 mg/m^2/day days 1 to 4

[total dose/cycle = 36 mg/m^2]

Prednisone: Oral: 60 mg/m^2/day days 1 to 4

[total dose/cycle = 240 mg/m^2]

Repeat cycle every 42 days for 4 cycles

followed by

Bortezomib: I.V.: 1-1.3 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 4-5.2 mg/m^2]

Melphalan: Oral: 9 mg/m^2/day days 1 to 4

[total dose/cycle = 36 mg/m^2]

Prednisone: Oral: 60 mg/m^2/day days 1 to 4

[total dose/cycle = 240 mg/m^2]

Repeat cycle every 35 days for 5 cycles

References

Variation 1:

San Miguel JF, Schlag R, Khuageva NK, et al, "Bortezomib Plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma," *N Engl J Med*, 2008, 359(9):906-17.[PubMed 18753647]

Variation 2:

Mateos MV, Hernรกndez JM, Hernรกndez MT, et al, "Bortezomib Plus Melphalan and Prednisone in Elderly Untreated Patients With Multiple Myeloma: Results of a Multicenter Phase 1/2 Study," *Blood*, 2006, 108(7):2165-72.[PubMed 16772605]

Mateos MV, Hernรกndez JM, Hernรกndez MT, et al, "Bortezomib Plus Melphalan and Prednisone in Elderly Untreated Patients With Multiple Myeloma: Updated Time-to-Events Results and Prognostic Factors for Time to Progression," *Haematologica*, 2008, 93(4):560-5.[PubMed 18322252]

Bortezomib

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(bore TEZ oh mib)

U.S. Brand NamesVelcade®

Canadian Brand NamesVelcade®

Pharmacologic CategoryAntineoplastic Agent; Proteasome Inhibitor

Use: Labeled IndicationsTreatment of multiple myeloma; treatment of relapsed or refractory mantle cell lymphoma

Use: Unlabeled/InvestigationalTreatment of non-Hodgkin’s lymphomas (other than mantle cell lymphoma)

Dosing: AdultsDetails concerning dosing in combination regimens should also be consulted.

Multiple myeloma (first-line therapy; in combination with melphalan and prednisone): I.V.: 1.3 mg/m^2 days 1, 4, 8, 11, 22, 25, 29, and 32 of a 42-day treatment cycle for 4 cycles, followed by 1.3 mg/m^2 days 1, 8, 22 and 29 of a 42-day treatment cycle for 5 cycles.

Relapsed multiple myeloma and mantle cell lymphoma: I.V.: 1.3 mg/m^2 twice weekly for 2 weeks on days 1, 4, 8, and 11 of a 21-day treatment cycle. Consecutive doses should be separated by at least 72 hours. Therapy extending beyond 8 cycles may be given once weekly for 4 weeks (days 1, 8, 15, and 22), followed by a 13-day rest (days 23 through 35).

Non-Hodgkin’s lymphoma, other than mantle cell (unlabeled use): I.V.: 1.3-1.5 mg/m^2 twice weekly for 2 weeks on days 1, 4, 8, and 11 of a 21-day treatment cycle.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment necessary. **Note:** Dialysis may reduce bortezomib concentrations; administer postdialysis.

Dosing: Hepatic ImpairmentSpecific guidelines are not available; clearance may be decreased; monitor closely for toxicity.

Dosing: Adjustment for Toxicity

Myeloma (first-line therapy):

Platelets should be ≥70,000/mm^3, ANC should be ≥1000/mm^3, and nonhematologic toxicities should resolve to grade 1 or baseline prior to therapy initiation.

Platelets ≤30,000/mm^3 or ANC <750/mm^3 on bortezomib day(s): Withhold bortezomib; if several consecutive bortezomib doses are withheld, reduce dose 1 level (1.3 mg/m^2/dose reduced to 1 mg/m^2/dose; 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose)

Grade ≥3 nonhematological toxicity (other than neuropathy): Withhold bortezomib until toxicity resolves to grade 1 or baseline. May reinitiate bortezomib at 1 dose level reduction (1.3 mg/m^2/dose reduced to 1 mg/m^2/dose; 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose).

Neuropathic pain and/or peripheral sensory neuropathy: See "Neuropathic pain and/or peripheral sensory neuropathy" toxicity adjustment guidelines below.

Relapsed multiple myeloma and mantle cell lymphoma:

Grade 3 nonhematological (excluding neuropathy) or Grade 4 hematological toxicity: Withhold until toxicity resolved; may reinitiate with a 25% dose reduction (1.3 mg/m^2/dose reduced to 1 mg/m^2/dose; 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose)

Neuropathic pain and/or peripheral sensory neuropathy:

Grade 1 without pain or loss of function: No action needed

Grade 1 with pain or Grade 2 interfering with function but not activities of daily living: Reduce dose to 1 mg/m^2

Grade 2 with pain or Grade 3 interfering with activities of daily living: Withhold until toxicity resolved, may reinitiate at 0.7 mg/m^2 once weekly

Grade 4: Discontinue therapy

Dosing: Combination Regimens

Multiple myeloma:

Bortezomib-Dexamethasone

Bortezomib-Doxorubicin-Dexamethasone

Bortezomib-Doxorubicin (Liposomal)

Bortezomib-Doxorubicin (Liposomal)-Dexamethasone

Bortezomib-Melphalan-Prednisone

Bortezomib-Melphalan-Prednisone-Thalidomide

Calculations

- Body Surface Area: Adults

Administration: I.V.Administer via rapid I.V. push (3-5 seconds).
Administration: I.V. DetailpH: 2-6.5
StoragePrior to reconstitution, store at room temperature of 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Protect from light. Once reconstituted, although the manufacturer recommends use within 8 hours, solution may be stored at room temperature for up to 3 days, or under refrigeration for up to 5 days, in vial or syringe (Andre, 2005). Protect from light.
ReconstitutionDilute each 3.5 mg vial with 3.5 mL NS to a final concentration of 1 mg/mL. Use appropriate precautions for handling and disposal.
ContraindicationsHypersensitivity to bortezomib, boron, mannitol, or any component of the formulation
Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Hematologic toxicity, including neutropenia and severe thrombocytopenia may occur; risk is increased in patients with pretreatment platelet counts <75,000/µL; frequent monitoring is required throughout treatment; may require dosage adjustments; withhold treatment for platelets <25,000/µL. Hemorrhage (gastrointestinal and intracerebral) due to low platelet count has been observed.

- Cardiovascular effects: May cause hypotension (including postural and orthostatic); use caution with dehydration, history of syncope, or medications associated with hypotension. Has been associated with the development or exacerbation of congestive heart failure and decreased left ventricular ejection fraction; use caution in patients with risk factors or existing heart disease. Has also been associated with QT_c prolongation.

- Hepatotoxicity: Acute liver failure has been reported (rarely) in patients receiving multiple concomitant medications; hepatitis, transaminase increases, and hyperbilirubinemia have also been reported. Use caution in patients with hepatic dysfunction; toxicities may be increased.

- Herpes reactivation: Herpes (zoster and simplex) reactivation has been reported with bortezomib; consider antiviral prophylaxis during therapy.

- Peripheral neuropathy: May cause peripheral neuropathy (usually sensory but may be mixed sensorimotor); risk may be increased with previous use of neurotoxic agents or pre-existing peripheral neuropathy; adjustment of dose and schedule may be required.

- Pulmonary toxicity: Pulmonary disorders including pneumonitis, interstitial pneumonia, lung infiltrates, and acute respiratory distress syndrome (ARDS) have been reported. Pulmonary hypertension (without left heart failure or significant pulmonary disease) has been reported rarely.

- Reversible posterior leukoencephalopathy syndrome (RPLS): Has been reported (rarely). Symptoms of RPLS include confusion, headache, hypertension, lethargy, seizure, blindness and/or other vision, or neurologic disturbances; discontinue if RPLS occurs. The safety of reinitiating bortezomib in patients previously experiencing RPLS is unknown.

- Tumor lysis syndrome: May cause tumor lysis syndrome; risk is increased in patients with high tumor burden prior to treatment

Disease-related concerns:

- Diabetes: Hyper-and hypoglycemia may occur in diabetic patients receiving oral hypoglycemics; monitor; may require adjustment of diabetes medications.

- Hepatic impairment: Use with caution in patients with hepatic impairment; clearance may be reduced; monitor for toxicity.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorD
Pregnancy ConsiderationsAdverse effects (fetal loss and decreased fetal weight) were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Effective contraception is recommended for women of childbearing potential.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.
Adverse Reactions

>10%:

Cardiovascular: Edema (11% to 28%), hypotension (12% to 15%; grades 3/4: 3%)

Central nervous system: Fever (19% to 37%), psychiatric disturbance (35%), headache (17% to 26%), dysesthesia (9% to 27%), insomnia (18%

to 21%), dizziness (14% to 23%; excludes vertigo), anxiety (5% to 11%)

Dermatologic: Rash (17% to 28%), pruritus (11%)

Endocrine & metabolic: Dehydration (7% to 11%)

Gastrointestinal: Diarrhea (47% to 57%), nausea (44% to 57%), constipation (40% to 50%), anorexia (34% to 39%), vomiting (27% to 35%), abdominal pain (14% to 16%), abnormal taste (13%), dyspepsia (13%)

Hematologic: Thrombocytopenia (21% to 38%; grade 4: 4% to 5%; nadir: day 11; recovery: by day 21), anemia (17% to 30%; grade 4: <1%), neutropenia (6% to 19%; grade 4: 2% to 3%; nadir: day 11; recovery: by day 21)

Neuromuscular & skeletal: Weakness (61% to 72%; grades 3/4: 12% to 19%), peripheral neuropathy (36% to 55%; grade 3: 7% to 11%; grade 4: <1%), paresthesia (9% to 27%), arthralgia (13% to 18%), limb pain (5% to 17%), bone pain (2% to 16%), back pain (<1 % to 15%), myalgia (10% to 12%), muscle cramps (5% to 12%), rigors (11%)

Ocular: Blurred vision (11%)

Respiratory: Dyspnea (20% to 23%), cough (19% to 21%), lower respiratory infection (15%), upper respiratory tract infection (11% to 15%), nasopharyngitis (8% to 14%), pneumonia (9% to 12%)

Miscellaneous: Herpesvirus infections (7% to 13%)

1% to 10%:

Cardiovascular: Syncope (2%)

Endocrine & metabolic: Hypercalcemia (grade 4: 2%)

Frequency not defined (including postmarketing and/or case reports; limited to important or life-threatening): Acute diffuse infiltrative pulmonary disease, acute respiratory distress syndrome, alkaline phosphatase increased, allergic reaction, amyloidosis, anaphylaxis, angina, angioedema, ascites, aspergillosis, atelectasis, atrial fibrillation, atrial flutter, AV block, bacteremia, bradycardia, cardiac amyloidosis, cardiac arrest, cardiac tamponade, cardiogenic shock, cardiopulmonary arrest, cerebral hemorrhage, cerebrovascular accident, CHF, cholestasis, coma, complete heart block, confusion, cranial palsy, deafness, deep venous thrombosis, diplopia, disseminated intravascular coagulation (DIC), duodenitis (hemorrhagic), dysautonomia, dysphagia, edema (facial), encephalopathy, embolism, epistaxis, fecal impaction, fracture, gastritis (hemorrhagic), gastroenteritis, GGT increased, glomerular nephritis, hematemesis, hematuria, hemoptysis, hemorrhagic cystitis, hepatic failure, hepatic hemorrhage, hepatitis, hepatocellular damage, herpes meningoencephalitis, hyperbilirubinemia, hyper-/hypoglycemia, hyper-/hypokalemia, hyper-/hyponatremia, hypersensitivity, hyperuricemia, hypocalcemia, hypoxia, immune complex hypersensitivity, injection site reaction, intestinal obstruction, intestinal perforation, intracerebral hemorrhage, ischemic colitis, ischemic stroke, laryngeal edema, leukocytoclastic vasculitis, leukopenia, listeriosis, lymphopenia, melena, mental status change, MI, myocardial ischemia, neuralgia, neutropenic fever, ophthalmic herpes, oral candidiasis, pancreatitis, paralytic ileus, paraplegia, pericardial effusion, pericarditis, peritonitis, pleural effusion, pneumonia, pneumonitis, portal vein thrombosis, proliferative glomerular nephritis, psychosis, pulmonary alveolar hemorrhage, pulmonary edema, pulmonary embolism, pulmonary hypertension, psychosis, QT_c prolongation, renal calculus, renal failure, respiratory failure, respiratory insufficiency, reversible posterior leukoencephalopathy syndrome (RPLS), seizure, septic shock, sepsis, sinus arrest, spinal cord compression, stomatitis, stroke (hemorrhagic), stroke, subarachnoid hemorrhage, subdural hematoma, suicidal ideation, tachycardia, torsade de pointes, toxic epidermal necrolysis, toxoplasmosis, transaminases increased, transient ischemic attack, tumor lysis syndrome, urinary incontinence, urinary retention, urinary tract infection, urticaria, ventricular tachycardia

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2C9 (minor), 2C19 (major), 2D6 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2C19 (moderate), 2D6 (weak), 3A4 (weak)

Drug Interactions

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid St John's wort (may decrease bortezomib levels).

Monitoring ParametersSigns/symptoms of peripheral neuropathy, dehydration, or hypotension; CBC with differential and platelets (monitor frequently throughout therapy); renal function, pulmonary function (with new or worsening pulmonary symptoms), liver function tests (in patients with existing hepatic impairment)

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, effectiveness of therapy, and adverse reactions on regular basis during therapy (eg, peripheral neuropathy, postural hypotension, dehydration, congestive heart failure, infections). Monitor for psychiatric disturbances. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelets (monitor frequently throughout therapy); liver function tests (in patients with existing hepatic impairment)

Patient EducationDo not take any new medication during therapy without consulting prescriber. This medication can only be administered intravenously; you will be monitored during and following infusion. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause headache, dizziness (use caution when changing positions), anxiety, sleep disturbances, fever, or fatigue (use caution when driving or engaging in hazardous tasks until response to drug is known); nausea, vomiting, loss of appetite, or abnormal taste (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation; or diarrhea (boiled milk, yogurt, or buttermilk may help). You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). Report immediately any chest pain, respiratory difficulty, itching, rash, acute headache, throat tightness, pain, redness, or swelling at infusion site. Report swelling in extremities, recent weight gain (>3-5 pounds/week), persistent headache; muscle, bone, or back pain; abdominal pain; cramping or loss of sensation or tingling of extremities; unusual bleeding; changes in vision; psychiatric disturbances; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant or cause a pregnancy (males) during therapy or for 1 month following therapy. Consult prescriber for instructions on appropriate nonhormonal contraceptive measures. This drug may cause fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Velcade®: 3.5 mg [contains mannitol 35 mg]

Generic AvailableNo

ManufacturerMillennium (Takeda Oncology Co)

Mechanism of ActionBortezomib inhibits proteasomes, enzyme complexes which regulate protein homeostasis within the cell. Specifically, it reversibly inhibits chymotrypsin-like activity at the 26S proteasome, leading to activation of signaling cascades, cell-cycle arrest, and apoptosis.

Pharmacodynamics/Kinetics

Distribution: 498-1884 L/m^2

Protein binding: ~83%

Metabolism: Hepatic primarily via CYP2C19 and 3A4 and to a lesser extent CYP1A2; forms metabolites (inactive) via deboronization followed by hydroxylation

Half-life elimination: Single dose: 9-15 hours; multiple dosing: 1 mg/m^2: 40-193 hours; 1.3 mg/m^2: 76-108 hours

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Abnormal taste and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia, dizziness, and anxiety are common; may cause agitation, confusion, psychosis, and suicidal ideation

Mental Health: Effects on Psychiatric TreatmentGastrointestinal side effects are common; use caution with SSRIs. May cause neutropenia and thrombocytopenia; use caution with clozapine, carbamazepine, and valproic acid. Fluoxetine, fluvoxamine, and nefazodone may increase bortezomib serum levels, while carbamazepine and barbiturates may decrease its serum levels.

Index TermsLDP-341; MLN341; NSC-681239; PS-341

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International Brand NamesVelcade (AR, AT, AU, BE, BG, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, EE, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IL, IT, MX, MY, NL, NO, PA, PH, PT, PY, RU, SE, TH, TR, TW, VE)

Bosentan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Tracleer® may be confused with TriCor©

Pronunciation(boe SEN tan)

U.S. Brand NamesTracleer®

Canadian Brand NamesTracleer®

Pharmacologic CategoryEndothelin Antagonist; Vasodilator

Use: Labeled IndicationsTreatment of pulmonary artery hypertension (PAH) (WHO Group I) in patients with World Health Organization (WHO) Class III or IV symptoms to improve exercise capacity and decrease the rate of clinical deterioration

Dosing: AdultsPulmonary artery hypertension: Oral: Initial: 62.5 mg twice daily for 4 weeks; increase to maintenance dose of 125 mg twice daily; adults <40 kg should be maintained at 62.5 mg twice daily. Doses >125 mg twice daily do not appear to confer additional clinical benefit but may increase risk of liver toxicity.

Note: When discontinuing treatment, consider a reduction in dosage to 62.5 mg twice daily for 3-7 days (to avoid clinical deterioration).

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricPulmonary artery hypertension:

Children ≤12 years (unlabeled use):

10-20 kg: Initial: 31.25 mg once daily for 4 weeks; increase to maintenance dose of 31.25 mg twice daily

>20-40 kg: Initial: 31.25 mg twice daily for 4 weeks; increase to maintenance dose of 62.5 mg twice daily

>40 kg: Initial: 62.5 mg twice daily for 4 weeks; increase to maintenance dose of 125 mg twice daily

Adolescents >12 years and ≥40 kg: Refer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment required.

Dosing: Hepatic ImpairmentAvoid use in patients with **pretreatment** moderate to severe hepatic insufficiency.

Modification based on transaminase elevation:

If any elevation, regardless of degree, is accompanied by clinical symptoms of hepatic injury (unusual fatigue, nausea, vomiting, abdominal pain, fever, or jaundice) or a serum bilirubin ≥2 times the upper limit of normal, treatment should be stopped.

AST/ALT >3 times but ≤5 times upper limit of normal: Confirm with additional test; if confirmed, reduce dose or interrupt treatment. Monitor transaminase levels at least every 2 weeks. May continue or reintroduce treatment, as appropriate, following return to pretreatment values. Begin with initial dose (above) and recheck transaminases within 3 days

AST/ALT >5 times but ≤8 times upper limit of normal: Confirm with additional test; if confirmed, stop treatment. Monitor transaminase levels at least every 2 weeks. May reintroduce treatment, as appropriate, at starting dose, following return to pretreatment values. Recheck within 3 days and thereafter following reinitiation.

AST/ALT >8 times upper limit of normal: Stop treatment and do not reintroduce.

Administration: OralMay be administered with or without food, once in the morning and once in the evening. Women of childbearing potential should avoid excessive handling broken tablets.

Dietary ConsiderationsMay be taken with or without food. Avoid grapefruit and grapefruit juice.

StorageStore at 15°C to 30°C (59°F to 86°F).

Extemporaneously PreparedUse a commercial pill cutter to prepare a 31.25 mg dose from the 62.5 mg tablet. Half-cut 62.5 mg tablets are stable for up to 4 weeks, when stored at room temperature in the high-density polyethylene plastic bottle provided by the manufacturer of the drug.

Women of childbearing potential should avoid exposure to dust generated from broken or split tablets, especially if repeated exposure is expected.

Suspension preparation: Dissolve the 62.5 mg tablet in 10-20 mL water. Tablets will disintegrate rapidly without crushing (within ~5 minutes); stirring will accelerate disintegration. Bosentan should not be mixed or dissolved in liquids with an acidic pH (eg, fruit juices) due to poor solubility; the drug is most soluble in solutions with a pH >8.5. Bosentan is soluble in water, and sediment will form quickly when left to rest. Homogeneity of suspension cannot be assured; therefore, the manufacturer emphasizes that division of the dose by volume of suspension may not be particularly accurate.

Restrictions Bosentan (Tracleer®) is available only through a limited distribution program directly from the manufacturer (Actelion Pharmaceuticals 1-866-228-3546). It will not be available through wholesalers or individual pharmacies. An FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

Contraindications Hypersensitivity to bosentan or any component of the formulation; concurrent use of cyclosporine or glyburide; pregnancy

Warnings/Precautions

Boxed Warnings:

- Hepatic effects: See “Concerns related to adverse effects” below.
- Pregnancy: See “Special populations” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Fluid retention: May cause fluid retention evidenced by signs and symptoms of peripheral edema, weight gain, and heart failure.
- Hepatic effects: **[U.S. Boxed Warning]:Has been associated with a high incidence (12%) of significant transaminase elevations, and rare cases of unexplained hepatic cirrhosis have occurred, including after long-term therapy.** Transaminase elevations are dose dependent, generally asymptomatic, occur both early and late in therapy, progress slowly, and are usually reversible after treatment interruption or discontinuation. Avoid use in moderate-to-severe hepatic impairment or patients with elevated serum transaminases (>3 times upper limit of normal) at baseline. Monitor hepatic function closely (at least monthly) for the duration of treatment. Treatment should be stopped in patients who develop elevated transaminases (ALT or AST) in combination with symptoms of hepatic injury (unusual fatigue, jaundice, nausea, vomiting, abdominal pain, and/or fever) or elevated serum bilirubin ≥2 times upper limit of normal. Safety of reintroduction is unknown.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with ischemic cardiovascular disease.
- Low hemoglobin: Use with caution in patients with low hemoglobin levels; may cause dose-related decreases in hemoglobin and hematocrit (monitoring of hemoglobin is recommended).
- Pulmonary veno-occlusive disease (PVOD): Discontinue in any patient with pulmonary edema suggestive of pulmonary veno-occlusive disease (PVOD).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children ≤12 years of age.
- Pregnancy: **[U.S. Boxed Warning]: Use in pregnancy is contraindicated;** exclude pregnancy prior to initiation of therapy and shipment of each monthly refill. Efficacy of hormonal contraceptive may be decreased, and should not be the sole contraceptive method in patients receiving bosentan. A missed menses should be reported to healthcare provider and prompt immediate pregnancy testing. Women of childbearing potential should avoid excessive handling of broken tablets.

Pregnancy Risk Factor X

Pregnancy Considerations **[U.S. Boxed Warning]: Use in pregnancy is contraindicated.** Based on animal studies, bosentan is likely to produce major birth defects if used by pregnant women. Pregnancy must be excluded prior to initiation of therapy and follow-up pregnancy tests should be obtained monthly. Effective contraception must be maintained throughout treatment. Hormonal contraception is not recommended as the sole contraceptive therapy due to a potential lack of efficacy in patients receiving bosentan. Women of childbearing potential should avoid exposure to dust generated from broken or split tablets, especially if repeated exposure is expected (tablet splitting is currently outside of product labeling). Irreversible testicular atrophy and decreased fertility in males was observed in animal studies with long-term exposure.

Lactation Excretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Central nervous system: Headache (16% to 22%)

Hematologic: Hemoglobin decreased (≥1 g/dL in up to 57%; <11 g/dL: 3% to 6%; typically in first 6 weeks of therapy)

Hepatic: Transaminases increased (>3 times upper limit of normal; up to 12%; dose-related)

Respiratory: Nasopharyngitis (11%)

1% to 10%:

Cardiovascular: Flushing (7% to 9%), edema (lower limb, 5% to 8%; generalized 4%), hypotension (7%), palpitation (5%)

Central nervous system: Fatigue (4%)

Dermatologic: Pruritus (4%)

Gastrointestinal: Dyspepsia (4%)

Hematologic: Anemia (3%)

Hepatic: Abnormal hepatic function (6% to 8%)

<1%, postmarketing, and/or case reports: Angioneurotic edema, heart failure (exacerbation), cirrhosis (prolonged therapy), hyperbilirubinemia, hypersensitivity, leukocytoclastic vasculitis, liver failure (rare), peripheral edema, rash, thrombocytopenia, weight gain

Metabolism/Transport Effects**Substrate** (major) of CYP2C9, 3A4; **Induces** CYP2C9 (strong), 3A4 (strong)

Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Bosentan. *Risk C: Monitor therapy*

CycloSPORINE: May increase the serum concentration of Bosentan. Bosentan may decrease the serum concentration of CycloSPORINE. *Risk X: Avoid combination*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inducers (Highly Effective) may increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

GlyBURIDE: May enhance the hepatotoxic effect of Bosentan. GlyBURIDE may increase the metabolism of Bosentan. Bosentan may increase the metabolism of GlyBURIDE. *Risk X: Avoid combination*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Bosentan may increase the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Pravastatin; Rosuvastatin. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Sildenafil: Bosentan may increase the metabolism of Sildenafil. Sildenafil may increase the serum concentration of Bosentan. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Bosentan may increase the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Bioavailability of bosentan is not affected by food.

Herb/Nutraceutical: Avoid St John's wort (may decrease serum concentrations of bosentan).

Monitoring ParametersSerum transaminase (AST and ALT) and bilirubin should be determined prior to the initiation of therapy and at monthly intervals thereafter. Monitor for clinical signs and symptoms of liver injury (eg, abdominal pain, fatigue, fever, jaundice, nausea, vomiting).

A woman of childbearing potential must have a negative pregnancy test prior to the initiation of therapy and monthly thereafter (prior to shipment of monthly refill). Hemoglobin and hematocrit should be measured at baseline, at 1 month and 3 months of treatment, and every 3 months thereafter (generally stabilizes after 4-12 weeks of treatment).

Monitor for clinical signs and symptoms of liver injury.

Nursing: Physical Assessment/MonitoringAssess interactions with other prescription, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions on a regular basis during therapy. Assess for fluid retention. Instruct patient on appropriate use, side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that female patient is not pregnant prior to beginning therapy and monthly during therapy. Do not give to a female patient of childbearing age unless patient is capable of adhering to specific contraceptive measures during therapy. Instruct patient in appropriate contraceptive measures.

Monitoring: Lab TestsSerum transaminase (AST and ALT) and bilirubin should be determined prior to the initiation of therapy and at monthly intervals thereafter. A woman of childbearing potential must have a negative pregnancy test prior to the initiation of therapy and monthly thereafter (prior to shipment of each refill). Hemoglobin and hematocrit should be measured at baseline, at 1 month and 3 months of treatment, and every 3 months thereafter (generally stabilizes after 4-12 weeks of treatment).

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, with or without food. You will need frequent laboratory tests to determine effectiveness of this medication. You may experience headache (consult prescriber for approved analgesic); or GI upset (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report persistent headache or GI problems, swelling of extremities, or unusual weight gain (>5 lb/week); runny nose or persistent signs of a cold, increased shortness of breath; chest pain or palpitations; unusual fatigue or weakness; yellowing of skin or eyes; change in color of stool or urine; or other persistent reactions. **Pregnancy/breast-feeding precautions:** Female patients must have a negative pregnancy test prior to beginning therapy. This drug may cause severe fetal abnormalities. Any delay of menses or other suspicion of pregnancy should be reported to prescriber immediately. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Tracleer®: 62.5 mg, 125 mg

Generic AvailableNo

ManufacturerActelion

Mechanism of ActionBlocks endothelin receptors on vascular endothelium and smooth muscle. Stimulation of these receptors is associated with vasoconstriction. Although bosentan blocks both ET_A and ET_B receptors, the affinity is higher for the A subtype. Improvement in symptoms of pulmonary artery hypertension and a decrease in the rate of clinical deterioration have been demonstrated in clinical trials.

Pharmacodynamics/Kinetics

Distribution: V_d: 18 L

Protein binding, plasma: >98% primarily to albumin

Metabolism: Hepatic via CYP2C9 and 3A4 to three primary metabolites (one contributing ~10% to 20% pharmacologic activity)

Bioavailability: 50%

Half-life elimination: 5 hours; prolonged with heart failure, possibly in PAH

Time to peak, plasma: 3-5 hours

Excretion: Feces (as metabolites); urine (<3% as unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Endothelin antagonists have caused bleeding gums; there have been no specific reports for bosentan

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentCarbamazepine, other anticonvulsants, and St John's wort may decrease the effects of bosentan. Conversely, nefazodone may increase the effects of bosentan.

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International Brand NamesTracleer (AU, BE, BR, CH, CZ, DE, DK, EE, ES, GB, HK, IE, IL, IT, KP, MY, NL, NO, NZ, SE, TH, TW)

Jump To Field (Select Field Name)

Pronunciation(BOT yoo lin num pen ta VAY lent [aye, bee, cee, dee, ee] TOKS oyd)
Pharmacologic CategoryToxoid
Use: Unlabeled/InvestigationalInvestigational: Prophylaxis for *C. botulinum* exposure (high-risk research laboratory personnel actively working with, or expect to work with, known cultures and purified botulinum toxin)
Dosing: AdultsDo not inject intracutaneously or into superficial structures.

Initial vaccination series: 0.5 mL deep SubQ at 0-, 2-, and 12 weeks

First booster: 0.5 mL deep SubQ 12 months after first injection of the initial series

Subsequent boosters: 0.5 mL deep SubQ at 2-year intervals based on antitoxin titers as checked by CDC

Dosing: ElderlyRefer to adult dosing.
Adverse ReactionsModerate-to-severe effects (initial series 5.6%, booster 12.3%, systemic 4.5% initial & booster)

Central nervous system: Fever, headache

Dermatologic: Rash

Local: Pain/soreness at injection site

Neuromuscular & skeletal: Muscle pain

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.
Pharmacotherapy PearlsEach vial contains 0.022% formaldehyde and 1:10,000 thimerosal as a preservative; manufactured by Michigan Biologic Products Institute, Lansing, Michigan, 48909.

For advice on vaccine administration and contraindications, contact the Division of Immunization, CDC, Atlanta, GA 30333 (404-639-3670, FAX 404-639-3717).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsBotulinum Toxoid, Pentavalent Vaccine (Against Types A / B / C / D / E Strains of *C. botulinum*)

Botulinum Toxin Type A

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Botulinum Types A and B: Reports of Serious Adverse Events Including Fatalities - Updated March 2008

The U.S. Food and Drug Administration (FDA) and Health Canada have issued respective early communications to healthcare professionals alerting them of serious adverse events (including fatalities) in association with the use of botulinum types A (Botox®, Botox® Cosmetic) and type B (Myobloc®). Events reported are suggestive of botulism, indicating systemic spread of the botulinum toxin beyond the site of injection. Reactions were observed in both adult and pediatric patients treated for a variety of conditions with varying doses. However, the most serious outcomes, including respiratory failure and death, were associated with the use in children for cerebral palsy limb spasticity. In the U.S., the use of botulinum toxins for the treatment of limb spasticity or the use in children <12 years of age (for any condition) is **not** approved by the FDA. In Canada, botulinum toxin type A **is** approved for the treatment of limb spasticity in adults and pediatric patients who are ≥2 years of age. Botulinum toxin type B at this time is not marketed in Canada.

Presently, the warnings sections of botulinum toxins types A and B product labeling indicate that severe dysphagia and dyspnea have occurred after local injection of typical doses of botulinum toxin in patients afflicted with neuromuscular diseases. The FDA has evaluated postmarketing cases and now reports that systemic and potentially fatal toxicity may result from local injection of the botulinum toxins in the treatment of other underlying conditions such as cerebral palsy associated with limb spasticity. There have been no reports of systemic toxin spread in Canada.

The FDA and Health Canada continue to evaluate safety data regarding these reports. In the interim, healthcare professionals are reminded to be aware of the potency differences between the botulinum products; use for approved indications only; monitor patients closely for signs/symptoms of systemic toxic effects (possibly occurring 1 day to several weeks after treatment); and instruct patients to seek immediate medical attention with worsening symptoms or dysphagia, dyspnea, muscle weakness, or difficulty speaking.

Additional information can be found at:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#botox

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_32_e.html

Pronunciation(BOT yoo lin num TOKS in type aye)

U.S. Brand NamesBotox®; Botox® Cosmetic

Canadian Brand NamesBotox®; Botox® Cosmetic

Pharmacologic CategoryNeuromuscular Blocker Agent, Toxin; Ophthalmic Agent, Toxin

Use: Labeled IndicationsTreatment of strabismus and blepharospasm associated with dystonia (including benign essential blepharospasm or VII nerve disorders) in patients ≥12 years of age; cervical dystonia (spasmodic torticollis) in patients ≥16 years of age; temporary improvement in the appearance of lines/wrinkles of the face (moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity) in adult patients ≤65 years of age; treatment of severe primary axillary hyperhidrosis in adults not adequately controlled with topical treatments

Canadian labeling: Additional use (not in U.S. labeling): Focal spasticity, including treatment of stroke related upper limb spasticity; dynamic equines foot deformity in pediatric cerebral palsy patients

Use: Unlabeled/InvestigationalTreatment of oromandibular dystonia, spasmodic dysphonia (laryngeal dystonia) and other dystonias (ie, writer's cramp, focal task-specific dystonias); migraine treatment and prophylaxis; treatment of dynamic muscle contracture in pediatric cerebral palsy patients

Dosing: Adults

Cervical dystonia: I.M.: For dosing guidance, the mean dose is 236 units (25th to 75th percentile range 198-300 units) divided among the affected muscles in patients previously treated with botulinum toxin. Initial dose in previously untreated patients should be lower. Sequential dosing should be based on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and previous adverse reactions. The total dose injected into the sternocleidomastoid muscles should be ≤100 units to decrease the occurrence of dysphagia.

Canadian labeling (not in U.S. labeling): Effective range of 200-360 units has been used in clinical practice; maximum dose: 6 units/kg every 2 months

Blepharospasm: I.M.: Initial dose: 1.25-2.5 units injected into the medial and lateral pretarsal orbicularis oculi of the upper lid and lateral pretarsal orbicularis oculi of lower lid; dose may be increased up to twice the previous dose if the response from the initial dose lasted ≤2 months; maximum dose per site: 5 units. Tolerance may occur if treatments are given more often than every 3 months, but the effect is not usually permanent. Cumulative dose:

U.S. labeling: ≤200 units in 30-day period

Canadian labeling (not in U.S. labeling): ≤200 units in 60-day period

Spasticity (focal):*Canadian labeling (not approved in U.S. labeling):* I.M.: Individualize dose based on patient size, extent, and location of muscle involvement, degree of spasticity, local muscle weakness, and response to prior treatment. In clinical trials total doses up to 360 units were administered as separate injections typically divided among flexor muscles of the elbow, wrist, and fingers; may repeat therapy at 3-4 months with appropriate dosage based upon the clinical condition of patient at time of retreatment.

Suggested guidelines for the treatment of stroke-related upper limb spasticity: **Note:** Dose listed is total dose administered as individual or separate intramuscular injection(s):

Biceps brachii: 100-200 units (up to 4 sites)

Flexor digitorum profundus: 15-50 units (1-2 sites)

Flexor digitorum sublimes: 15-50 units (1-2 sites)

Flexor carpi radialis: 15-60 units (1-2 sites)

Flexor carpi ulnaris: 10-50 units (1-2 sites)

Adductor pollicis: 20 units (1-2 sites)

Flexor pollicis longus: 20 units (1-2 sites)

Strabismus: I.M.: **Note:** Several minutes prior to injection, administration of local anesthetic and ocular decongestant drops are recommended.

Initial dose:

Vertical muscles and for horizontal strabismus <20 prism diopters: 1.25-2.5 units in any one muscle

Horizontal strabismus of 20-50 prism diopters: 2.5-5 units in any one muscle

Persistent VI nerve palsy ≥1 month: 1.25-2.5 units in the medial rectus muscle

Re-examine patients 7-14 days after each injection to assess the effect of that dose. Subsequent doses for patients experiencing incomplete paralysis of the target may be increased up to twice the previous administered dose. The maximum recommended dose as a single injection for any one muscle is 25 units. Do not administer subsequent injections until the effects of the previous dose are gone.

Primary axillary hyperhidrosis: Intradermal: 50 units/axilla. Injection area should be defined by standard staining techniques. Injections should be evenly distributed into multiple sites (10-15), administered in 0.1-0.2 mL aliquots, ~1-2 cm apart. May repeat when clinical effect diminishes.

Reduction of glabellar lines: Adults ≤65 years: I.M.: An effective dose is determined by gross observation of the patient's ability to activate the superficial muscles injected. The location, size and use of muscles may vary markedly among individuals. Inject 0.1 mL (4 units) dose into each of five sites, two in each corrugator muscle and one in the procerus muscle for a total dose 0.5 mL (20 units) administered no more frequently than every 3-4 months.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Blepharospasm/strabismus: Children ≥12 years: Refer to adult dosing.

Cervical dystonia: Children ≥16 years: Refer to adult dosing.

Spasticity (cerebral palsy related):*Canadian labeling (not approved in U.S. labeling):* Children ≥2 years: I.M.: 4 units/kg (total dose) divided into two injections into medial and lateral heads of the gastrocnemius of affected limb; if clinically indicated, may repeat every 2 months (maximum dose: 200 units)

Dosing: Renal ImpairmentNo adjustment is recommended.

Dosing: Hepatic ImpairmentNo adjustment necessary.

Administration: I.M.

Cervical dystonia: Use 25-, 27-, or 30-gauge needle for superficial muscles and a longer 22-gauge needle for deeper musculature; electromyography may help localize the involved muscles.

Blepharospasm: Use a 27- or 30-gauge needle without electromyography guidance. Avoid injecting near the levator palpebrae superioris (may decrease ptosis); avoid medial lower lid injections (may decrease diplopia). Apply pressure at the injection site to prevent ecchymosis in the soft eyelid tissues.

Spasticity (cerebral palsy related; Canadian labeling [not in U.S. labeling]): Use a 23 to 26-gauge needle for administration into the medial and lateral heads of the gastrocnemius muscle of the affected limb.

Spasticity (focal; Canadian labeling [not in U.S. labeling]): Use a 25, 27, or 30-gauge needle for superficial muscles and a longer 22-gauge needle for deeper musculature; electromyography or nerve stimulation may help localize the involved muscles.

Strabismus injections: Must use surgical exposure or electromyographic guidance; use the electrical activity recorded from the tip of the injections needle as a guide to placement within the target muscle. Local anesthetic and ocular decongestant should be given before injection. The volume of injection should be 0.05-0.15 mL per muscle. Many patients will require additional doses because of inadequate response to initial dose.

Reduction of glabellar lines (Botox® Cosmetic): Use a 30-gauge needle. Ensure injected volume/dose is accurate and where feasible keep to a minimum. Avoid injection near the levator palpebrae superioris. Medial corrugator injections should be at least 1 cm above the bony supraorbital ridge. Do not inject toxin closer than 1 cm above the central eyebrow.

Administration: OtherPrimary axillary hyperhidrosis: Inject each dose intradermally to a depth of ~2 mm and at a 45° angle. Do not inject directly into areas marked in ink (to avoid permanent tattoo effect). Prior to administration, injection area should be defined by standard staining techniques such as Minor's Iodine-Starch Test.

Instructions for Minor's Iodine-Starch Test: Patient should shave underarms and refrain from using deodorants or antiperspirants for 24 hours prior to test. At 30 minutes prior to test, patient should be at rest, no exercise, and not consume hot beverages. Underarm area should be dried and immediately painted with iodine solution. After area dries, lightly sprinkle with starch powder. Gently blow off excess powder. A deep blue-black color will develop over the hyperhidrotic area in ~10 minutes.

StorageStore undiluted vials under refrigeration at 2°C to 8°C for up to 24 months (Botox® Cosmetic) or up to 36 months (Botox®). After reconstitution, store in refrigerator (2°C to 8°C) and use within 4 hours (does not contain preservative).

ReconstitutionReconstitute with sterile, preservative free 0.9% sodium chloride.

Botox®: Reconstitute vials with 1 mL of diluent to obtain concentration of 10 units per 0.1 mL; 2 mL of diluent to obtain concentration of 5 units per 0.1 mL; 4 mL of diluent to obtain concentration of 2.5 units per 0.1 mL; 8 mL of diluent to obtain concentration of 1.25 units per 0.1 mL.

Botox® Cosmetic: Reconstitute vials with 2.5 mL of diluent to obtain concentration of 4 units per 0.1 mL (20 units per 0.5 mL).

ContraindicationsHypersensitivity to albumin, botulinum toxin, or any component of the formulation; infection at the proposed injection site(s)

Canadian labeling: Additional contraindications (not in U.S. labeling): Myasthenia gravis or Eaton-Lambert syndrome

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions may occur rarely; immediate treatment (including epinephrine 1:1000) should be available.
- Antibody formation: Higher doses or more frequent administration may result in neutralizing antibody formation and loss of efficacy.
- Cardiovascular events: Rarely, arrhythmia and myocardial infarction have been reported, sometimes in patients with preexisting cardiovascular disease.
- Dysphagia: Common when used for cervical dystonia and may persist anywhere from 2 weeks up to 5 months after administration. Risk of upper respiratory infection may be increased and, in severe cases, patients may require alternative feeding methods. Risk factors include smaller neck muscle mass, bilateral injections into the sternocleidomastoid muscle, or injections into the levator scapulae.

Disease-related concerns:

- Neuromuscular disease: Use with caution in patients with neuromuscular diseases such as myasthenia gravis or Eaton-Lambert syndrome (contraindicated in Canadian labeling) and neuropathic disorders (such as amyotrophic lateral sclerosis).
- Ocular diseases: Reduced blinking from injection of the orbicularis muscle can lead to corneal exposure and ulceration when treating blepharospasm. Retrobulbar hemorrhages may occur from needle penetration into orbit when treating strabismus; spatial disorientation, double vision, or past pointing may occur if one or more extraocular muscles are paralyzed. Covering the affected eye may help. Careful testing of corneal sensation, avoidance of lower lid injections, and treatment of epithelial defects are necessary. Use caution in patients with angle closure glaucoma.

Concurrent drug therapy issues:

- Neuromuscular transmission: Use with extreme caution in patients receiving other agents that may interfere with neuromuscular transmission (eg, aminoglycosides, neuromuscular-blocking agents)

Dosage form specific issues:

- Albumin: Product contains albumin and may carry a remote risk of virus transmission.

Other warnings/precautions:

- Chronic therapy: Long-term effects of chronic therapy unknown.
- Injection site: Use with caution if there is excessive weakness or atrophy at the proposed injection site(s); use is contraindicated if infection is present.
- Primary axillary hyperhidrosis: Appropriate use: Evaluate for secondary causes prior to treatment (eg, hyperthyroidism). Safety and efficacy for treatment of hyperhidrosis in other areas of the body have not been established.
- Temporary reduction in glabellar lines: Appropriate use: Do not use more frequently than every 3 months. Patients with marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or the inability to substantially lessen glabellar lines by physically spreading them apart were excluded from clinical trials. Reduced blinking from injection of the orbicularis muscle can lead to corneal exposure and ulceration. Spatial disorientation, double vision, or past pointing may occur if one or more extraocular muscles are paralyzed.

Geriatric ConsiderationsNo specific dosing adjustment recommended.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDecreased fetal body weight, delayed ossification, maternal toxicity, abortions, and fetal malformations were observed in animal studies. Human reproduction studies have not been conducted. Avoid use in pregnancy. Based on limited case reports, adverse fetal effects have not been observed with inadvertent administration during pregnancy. It is currently recommended to ensure adequate contraception in women of childbearing potential.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsAdverse effects usually occur in 1 week and may last up to several months

>10%:

Cervical dystonia:

Central nervous system: Pain (32%), headache (up to 11%)

Gastrointestinal: Dysphagia (19%)

Neuromuscular & skeletal: Focal weakness (17%), neck pain (11%)

Respiratory: Upper respiratory infection (12%)

Other indications (blepharospasm, primary axillary hyperhidrosis, strabismus):

Neuromuscular & skeletal: Primary axillary hyperhidrosis (3% to 10%)

Ocular: Ptosis (blepharospasm 21%; strabismus 1% to 38%), vertical deviation (strabismus 17%)

2% to 10%:

Cervical dystonia:

Central nervous system: Dizziness, drowsiness, fever, malaise, speech disorder

Gastrointestinal: Nausea, xerostomia

Local: Injection site reaction: Soreness

Neuromuscular & skeletal: Back pain, hypertonia, weakness, stiffness

Respiratory: Cough, rhinitis

Miscellaneous: Flu-like syndrome

Cerebral palsy spasticity:

Central nervous system: Pain (1% to 2%), fever (1%), lethargy (1%)

Neuromuscular & skeletal: Falling, weakness

Focal spasticity:

Central nervous system: Arm pain (1% to 3%)

Dermatologic: Bruising (1% to 3%)

Local: Injection site reactions: burning, pain (1% to 3%)

Neuromuscular & skeletal: Hypertonia (1% to 3%), weakness (1% to 3%)

Other indications (blepharospasm, primary axillary hyperhidrosis, reduction of glabellar lines, strabismus):

Central nervous system: Anxiety, dizziness

Dermatologic: Pruritus

Gastrointestinal: Nausea

Local: Injection site reaction: Soreness

Neuromuscular & skeletal: Back pain, facial pain, weakness

Ocular: Irritation/tearing (includes dry eye, lagophthalmos, photophobia); ptosis, superficial punctate keratitis

Respiratory: Pharyngitis

Miscellaneous: Flu-like syndrome, infection, nonaxillary sweating

<2%, postmarketing, and/or case reports:*Any indication:* Abdominal pain, acute angle closure glaucoma, allergic reactions, anaphylaxis, ankle pain, anterior segment eye ischemia, appetite decreased, arrhythmia, arthralgia, aspiration pneumonia, blurred vision, brachial plexopathy, bruising, ciliary ganglion damage, corneal perforation, dermatitis, diaphoresis, diarrhea, diplopia, dyspepsia, dysphonia, dyspnea, ectropion, entropion, erythema multiforme, eyelid edema, facial weakness, focal facial paralysis, glaucoma, hearing loss, hypoesthesia, hypertension, knee pain, leg cramps, lethargy, malaise, MI, myalgia, myasthenia gravis exacerbation, neutralizing antibody formation, numbness, pneumonia, pruritus, psoriasiform eruption, ptosis, rash, reduced blinking leading to corneal ulceration, retinal vein occlusion, retrobulbar hemorrhage, seizure, skin tightness, syncope, tooth disorder, urticaria, vertigo with nystagmus, vitreous hemorrhage, vomiting

Drug Interactions

Aminoglycosides: May enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Botulinum Toxin Type A may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: May enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringUse with caution in presence of disease that affects neuromuscular transmission or coagulation. Prior to administration, assess potential for interactions with other medications patient may be taking (eg, anything that may affect neuromuscular transmission). See specific Dosing and Administration instructions according to purpose for use. Assess therapeutic effects and adverse response following each treatment (systemic toxic effects may occur 1 day to several weeks after treatment). Teach patient about necessary aftercare, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis medication is administered by injection. Follow aftercare instructions exactly. When used to improve appearance of lines/wrinkles in face: May cause headache; dry, painful, watery, or bloodshot eyes; a feeling of something in the eye; increased sensitivity to light; or slightly blurred vision. Other uses: May cause headache, dizziness, drowsiness (use caution when driving or engaged in tasks that require alertness until response to drug is known), gastrointestinal upset, neck pain, upper respiratory infection, sore throat, or rhinitis. Report immediately difficulty swallowing, breathing, or speaking; muscle weakness; worsening symptoms; or other persistent or acute adverse symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]: *Clostridium botulinum* toxin type A 100 units [contains human albumin]

Generic AvailableNo

ManufacturerAllergan, Inc

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Botox)

100 unit (1): $609.98

Mechanism of ActionBotulinum A toxin is a neurotoxin produced by *Clostridium botulinum*, spore-forming anaerobic bacillus, which appears to affect only the presynaptic membrane of the neuromuscular junction in humans, where it prevents calcium-dependent release of acetylcholine and produces a state of denervation. Muscle inactivation persists until new fibrils grow from the nerve and form junction plates on new areas of the muscle-cell walls. Intradermal injection results in temporary sweat gland denervation, reducing local sweating.

Pharmacodynamics/Kinetics

Onset of action (improvement):

Blepharospasm: ~3 days

Cervical dystonia: ~2 weeks

Reduction of glabellar lines (Botox® Cosmetic): 1-2 days, increasing in intensity during first week

Spasticity (focal and cerebral palsy related): <2 weeks

Strabismus: ~1-2 days

Duration:

Blepharospasm: ~3 months

Cervical dystonia: <3 months

Primary axillary hyperhidrosis: 201 days (mean)

Reduction of glabellar lines (Botox® Cosmetic): ~3-4 months

Spasticity (cerebral palsy related): ~3-3.5 months

Strabismus: ~2-6 weeks

Absorption: Not expected to be present in peripheral blood at recommended doses following intramuscular (I.M.) injection

Time to peak:

Blepharospasm: 1-2 weeks

Cervical dystonia: ~6 weeks

Spasticity (focal): 4-6 weeks

Strabismus: Within first week

Pharmacotherapy PearlsUnits of biological activity of Botox® cannot be compared with units of any other botulinum toxin.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes

upon discontinuation), facial pain, and facial weakness. Affects occur in ~1 week and may last up to several months.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBTX-A

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International Brand NamesBotox (AR, AU, BE, CH, CZ, DE, DK, ES, FI, FR, GB, HR, IE, IT, LU, NL, NO, PL, SE); Dysport (BE, CH, DE, DK, ES, FR, GB, IE, IT, NL, PL, SE)

Botulinum Toxin Type B

Lexi-Drugs Online

English

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Special Alerts

Botulinum Types A and B: Reports of Serious Adverse Events Including Fatalities - Updated March 2008

The U.S. Food and Drug Administration (FDA) and Health Canada have issued respective early communications to healthcare professionals alerting them of serious adverse events (including fatalities) in association with the use of botulinum types A (Botox®, Botox® Cosmetic) and type B (Myobloc®). Events reported are suggestive of botulism, indicating systemic spread of the botulinum toxin beyond the site of injection. Reactions were observed in both adult and pediatric patients treated for a variety of conditions with varying doses. However, the most serious outcomes, including respiratory failure and death, were associated with the use in children for cerebral palsy limb spasticity. In the U.S., the use of botulinum toxins for the treatment of limb spasticity or the use in children <12 years of age (for any condition) is **not** approved by the FDA. In Canada, botulinum toxin type A **is** approved for the treatment of limb spasticity in adults and pediatric patients who are ≥2 years of age. Botulinum toxin type B at this time is not marketed in Canada.

Presently, the warnings sections of botulinum toxins types A and B product labeling indicate that severe dysphagia and dyspnea have occurred after local injection of typical doses of botulinum toxin in patients afflicted with neuromuscular diseases. The FDA has evaluated postmarketing cases and now reports that systemic and potentially fatal toxicity may result from local injection of the botulinum toxins in the treatment of other underlying conditions such as cerebral palsy associated with limb spasticity. There have been no reports of systemic toxin spread in Canada.

The FDA and Health Canada continue to evaluate safety data regarding these reports. In the interim, healthcare professionals are reminded to be aware of the potency differences between the botulinum products; use for approved indications only; monitor patients closely for signs/symptoms of systemic toxic effects (possibly occurring 1 day to several weeks after treatment); and instruct patients to seek immediate medical attention with worsening symptoms or dysphagia, dyspnea, muscle weakness, or difficulty speaking.

Additional information can be found at:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#botox

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_32_e.html

Pronunciation(BOT yoo lin num TOKS in type bee)

U.S. Brand NamesMyobloc®

Pharmacologic CategoryNeuromuscular Blocker Agent, Toxin

Use: Labeled IndicationsTreatment of cervical dystonia (spasmodic torticollis)

Use: Unlabeled/InvestigationalTreatment of cervical dystonia in patients who have developed resistance to botulinum toxin type A

Dosing: AdultsCervical dystonia: I.M.: Initial: 2500-5000 units divided among the affected muscles in patients **previously treated** with botulinum toxin; initial dose in **previously untreated** patients should be lower. Subsequent dosing should be optimized according to patient's response.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricNot established in pediatric patients

Dosing: Renal ImpairmentNo adjustment is recommended.

Dosing: Hepatic ImpairmentNo adjustment necessary.

StorageStore vials under refrigeration at 2°C to 8°C (36°F to 46°F) for up to 21 months. Once diluted, use within 4 hours. Does not contain preservative. Single use vial. Do not freeze.

ReconstitutionMay be diluted with normal saline. Do not shake.

CompatibilityDo not mix with any other medicines.

ContraindicationsHypersensitivity to albumin, botulinum toxin, or any component of the formulation; infection at the injection site(s). Relative contraindications include diseases of neuromuscular transmission; coagulopathy, including therapeutic anticoagulation; inability of patient to cooperate.

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions may occur; immediate treatment (including epinephrine 1:1000) should be available.
- Antibody formation: Higher doses or more frequent administration may result in neutralizing antibody formation and loss of efficacy.
- Dysphagia: Common when used for cervical dystonia. It may be severe requiring alternative feeding methods. Risk factors include smaller neck muscle mass, bilateral injections into the sternocleidomastoid muscle, or injections into the levator scapulae.

Dysphasia may be associated with increased risk of upper respiratory infection.

Disease-related concerns:

- Neuromuscular disease: Use with caution in patients with neuromuscular diseases (such as myasthenia gravis), neuropathic disorders (such as amyotrophic lateral sclerosis), or patients taking aminoglycosides or other drugs that interfere with neuromuscular transmission.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Albumin: Product contains albumin and may carry a remote risk of virus transmission.

Other warnings/precautions:

- Appropriate use: Concurrent use of botulinum toxin type A or within <4 months of type B is not recommended.
- Chronic therapy: Long-term effects of chronic therapy unknown.
- Injection site: Use with caution if there is inflammation, excessive weakness, or atrophy at the proposed injection site(s).

Geriatric ConsiderationsNo dosage adjustments required, but limited experience in patients ≥75 years of age.

Pregnancy Risk FactorC (manufacturer)

Pregnancy ConsiderationsReproduction studies have not been conducted. Based on limited case reports using botulinum toxin A, adverse fetal effects have not been observed with inadvertent administration during pregnancy. It is currently recommended to ensure adequate contraception in women of childbearing years.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Headache (10% to 16%), pain (6% to 13%; placebo 10%)

Gastrointestinal: Dysphagia (10% to 25%), xerostomia (3% to 34%)

Local: Injection site pain (12% to 16%)

Neuromuscular & skeletal: Neck pain (up to 17%; placebo: 16%)

Miscellaneous: Infection (13% to 19%; placebo: 15%)

1% to 10%:

Cardiovascular: Chest pain, vasodilation, peripheral edema

Central nervous system: Dizziness (3% to 6%), fever, malaise, migraine, anxiety, tremor, hyperesthesia, somnolence, confusion, vertigo

Dermatologic: Pruritus, bruising

Gastrointestinal: Nausea (3% to 10%; placebo: 5%), dyspepsia (up to 10%; placebo: 5%), vomiting, stomatitis, taste perversion

Genitourinary: Urinary tract infection, cystitis, vaginal moniliasis

Hematologic: Serum neutralizing activity

Neuromuscular & skeletal: Torticollis (up to 8%; placebo: 7%), arthralgia (up to 7%; placebo: 5%), back pain (3% to 7%; placebo: 3%), myasthenia (3% to 6%; placebo: 3%), weakness (up to 6%; placebo: 4%), arthritis

Ocular: Amblyopia, abnormal vision

Otic: Otitis media, tinnitus

Respiratory: Cough (3% to 7%; placebo: 3%), rhinitis (1% to 5%; placebo: 6%), dyspnea, pneumonia

Miscellaneous: Flu-syndrome (6% to 9%), allergic reaction, viral infection, abscess, cyst

Drug Interactions

Aminoglycosides: May enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Botulinum Toxin Type A: May enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: May enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringUse with caution in presence of disease that affects neuromuscular transmission or coagulation. Prior to administration, assess potential for interactions with other medications patient may be taking (eg, anything that may affect neuromuscular transmission). See specific Dosing and Administration instructions according to purpose for use. Assess therapeutic effects and adverse response following each treatment (systemic toxic effects may occur 1 day to several weeks after treatment). Teach patient about necessary aftercare, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis medication is administered by injection. Follow aftercare instructions exactly. When used to improve appearance of lines/wrinkles in face: May cause headache; dry, painful, watery, or bloodshot eyes; a feeling of something in the eye; increased sensitivity to light; or slightly blurred vision. Other uses: May cause headache, dizziness, drowsiness (use caution when driving or engaged in tasks that require alertness until response to drug is known), gastrointestinal upset, neck pain, upper respiratory infection, sore throat, or rhinitis. Report immediately difficulty swallowing, breathing, or speaking; muscle weakness; worsening symptoms; or other persistent or acute adverse symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Myobloc®: 5000 units/mL (0.5 mL, 1 mL, 2 mL) [contains albumin 0.05%]

Generic AvailableNo

ManufacturerElan Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Solution (Myobloc)

10000 units/2 mL (2): $1003.30

Mechanism of ActionBotulinum B toxin is a neurotoxin produced by *Clostridium botulinum*, spore-forming anaerobic bacillus. It cleaves synaptic Vesicle Association Membrane Protein (VAMP; synaptobrevin) which is a component of the protein complex responsible for docking and fusion of the synaptic vesicle to the presynaptic membrane. By blocking neurotransmitter release, botulinum B toxin paralyzes the muscle.

Pharmacodynamics/Kinetics

Duration: 12-16 weeks

Absorption: Not expected to be present in peripheral blood at recommended doses

Pharmacotherapy PearlsUnits of biological activity of Myobloc® cannot be compared with units of any other botulinum toxin.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), stomatitis, and abnormal taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, dizziness, sedation, or confusion

Mental Health: Effects on Psychiatric TreatmentMay cause torticollis, use atypical antipsychotics with caution; may cause flu-like syndrome (take this into consideration if also concerned about SSRI discontinuation syndrome)

Anesthesia and Critical Care Concerns/Other ConsiderationsUnits of biological activity of Myobloc® cannot be compared with units of any other botulinum toxin.

References

Brashear A, Lew MF, Dykstra DD, et al, “Safety and Efficacy of NeuroBloc (Botulinum Toxin Type B) in Type A-Responsive Cervical Dystonia,” *Neurology*, 1999, 53(7):1439-46. [PubMed 10534248]

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Botulism Immune Globulin (Intravenous-Human)

Lexi-Drugs Online

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Medication Safety Issues

Sound-alike/look-alike issues:

BabyBIG® may be confused with HBIG

Pronunciation(BOT yoo lism i MYUN GLOB you lin, in tra VEE nus, YU man)
U.S. Brand NamesBabyBIG®
Pharmacologic CategoryImmune Globulin
Use: Labeled IndicationsTreatment of infant botulism caused by toxin type A or B
Dosing: PediatricInfant botulism: Children <1 year: I.V.: 1 mL/kg (50 mg/kg) as a single dose; infuse at 0.5 mL/kg/hour (25 mg/kg/hour) for the first 15 minutes. If well tolerated, may increase to 1 mL/kg/hour (50 mg/kg/hour).
Administration: I.V.For I.V. infusion only. Do not administer if solution is turbid. Epinephrine should be available for the treatment of acute allergic reaction. Administer using low volume tubing and infusion pump with an in-line or syringe tip 18 µm filter. Infuse at 0.5 mL/kg/hour (25 mg/kg/hour) for the first 15 minutes; if well tolerated, may increase to 1 mL/kg/hour (50 mg/kg/hour). Infusion should take ~67.5 minutes. Infusion should be slowed or temporarily interrupted for minor side effects; discontinue in case of hypotension or anaphylaxis.
StoragePrior to reconstitution, store between 2°C to 8°C (35.6°F to 46.4°F). Infusion should begin within 2 hours of reconstitution and be completed within 4 hours of reconstitution.
ReconstitutionReconstitute with SWFI 2 mL. Swirl gently to wet powder; do not shake. Powder should dissolve in ~30 minutes.
CompatibilityAdministration with other medications is not recommended. If necessary, may be piggybacked into an existing I.V. line containing NS or the following dextrose solutions with or without sodium chloride: $D_{2.5}W$, D_5W, $D_{20}W$; do not dilute more than 1:2.
RestrictionsAvailable from the California Department of Health
ContraindicationsHypersensitivity to human immune globulin preparations or any component of the formulation; selective immunoglobulin A deficiency
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1:1000) should be available.
- Aseptic meningitis: Aseptic meningitis syndrome (AMS) has been reported with intravenous immune globulin administration (rare); may occur with high doses (≥2 g/kg).
- Renal impairment: Acute renal dysfunction (increased serum creatinine, oliguria, acute renal failure) can rarely occur; usually within 7 days of use (more likely with products stabilized with sucrose). Use with caution in the elderly, patients with renal disease, diabetes mellitus, volume depletion, sepsis, paraproteinemia, and nephrotoxic medications due to risk of renal dysfunction. In patients at risk of renal dysfunction, the rate of infusion and concentration of solution should be minimized. discontinue if renal function deteriorates.

Disease-related concerns:

- Hypovolemia: Patients should not be volume depleted prior to therapy.

Special populations:

- Adults: Not indicated for use in adults.
- Pediatrics: Safety and efficacy established for infants <1 year of age; not indicated for children ≥ 1 year of age.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

Other warnings/precautions:

- Administration: For I.V. infusion only; do not exceed recommended rate of administration.

Pregnancy ConsiderationsReproduction studies have not been conducted.
Adverse ReactionsPercentages reported in open-label study except where otherwise noted; may reflect pathophysiology of infant botulism.

>10%:

Cardiovascular: Blood pressure increased (transient, 75%), pallor (28%), edema (18%), blood pressure decreased (transient, 16%); cardiac murmur (15%)

Central nervous system: Irritability (41%), pyrexia (17%), body temperature decreased (16%)

Dermatologic: Contact dermatitis (24%), erythematous rash (22%, reported as 14% vs 8% in placebo-controlled study)

Gastrointestinal: Dysphagia (65%), loose stools (25%), vomiting (20%), abdominal distension (11%)

Otic: Otitis media (11%, reported in placebo-controlled study)

Respiratory: Atelectasis (39%), rhonchi (34%), nasal congestion (18%), oxygen saturation decreased (17%), cough (13%), rales (13%)

1% to 10%:

Cardiovascular: Tachycardia (7%), peripheral coldness (7%)

Central nervous system: Agitation (10%)

Endocrine & metabolic: Dehydration (10%), hyponatremia (6%), metabolic acidosis (5%)

Hematologic: Hemoglobin decreased (9%), anemia (5%)

Local: Injection site reaction (7%), injection site erythema (5%)

Renal: Neurogenic bladder

Respiratory: Breath sounds decreased (10%), stridor (9%), lower respiratory tract infection (8%), dyspnea (6%), tachypnea (5%)

Miscellaneous: Oral candidiasis (8%), intubation (5%), infusion rate reactions (<5%, includes chills, back pain, fever, muscle cramps, nausea, vomiting, wheezing)

Drug Interactions

Vaccines (Live): Immune Globulins may diminish the therapeutic effect of Vaccines (Live). **Exceptions:** Influenza Virus Vaccine; Yellow Fever Vaccine. *Risk D: Consider therapy modification*

Monitoring ParametersRenal function (BUN, serum creatinine, urinary output); vital signs (continuously during infusion); aseptic meningitis syndrome (may occur hours to days following IGIV therapy); signs of relapse (may occur up to 1 month following recovery)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

BabyBIG®: ~100 mg [contains albumin and sucrose; packaged with SWFI]

Generic AvailableNo

Mechanism of ActionBIG-IV is purified immunoglobulin derived from the plasma of adults immunized with botulinum toxoid types A and B. BIG-IV provides antibodies to neutralize circulating toxins.

Pharmacodynamics/Kinetics

Duration: Protective neutralizing antibody levels: 6 months

Half-life elimination: 28 days

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusIrritability is common; may cause agitation

Mental Health: Effects on Psychiatric TreatmentRash is common; be mindful if patient is also receiving lamotrigine. GI side effects are common; concomitant use with SSRIs, lithium, or valproic acid may produce additive effects.

Index TermsBIG-IV

Brimonidine and Timolol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

International issues:

Combigan® may be confused with Combivent® which is a brand name for ipratropium/albuterol in the U.S.; may be confused with Comtan® which is a brand name for entacapone in the U.S.

Pronunciation(bri MOE ni deen & TIM oh lol)

U.S. Brand NamesCombigan™

Canadian Brand NamesCombigan®

Pharmacologic CategoryAlpha$_2$ Agonist, Ophthalmic; Beta Blocker, Nonselective; Ophthalmic Agent, Antiglaucoma

Use: Labeled IndicationsReduction of intraocular pressure (IOP) in patients with glaucoma or ocular hypertension

Dosing: AdultsGlaucoma, ocular hypertension: Ophthalmic: Instill 1 drop into affected eye(s) twice daily

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricGlaucoma, ocular hypertension: Children ≥2 years: Ophthalmic: Instill 1 drop into affected eye(s) twice daily

Note: In the Canadian labeling, use in children (at any age) is not recommended

Administration: OtherAdminister approximately every 12 hours. Remove contact lenses prior to administration; wait 15 minutes before reinserting if using products containing benzalkonium chloride. Separate administration of other ophthalmic agents by 5-10 minutes.

StorageStore at 15°C to 25°C (59°F to 77°F). Protect from light.

Contraindications

Hypersensitivity to brimonidine, timolol, or any other component of the formulation; current or history of bronchial asthma, severe chronic obstructive pulmonary disease (COPD); sinus bradycardia, second- or third-degree atrioventricular block, overt cardiac failure, cardiogenic shock. Also see individual agents.

Canadian labeling: Additional contraindications (not in U.S. labeling): Monoamine oxidase (MAO) inhibitor therapy (concurrent or within 14 days)

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to a variety of allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.
- Bacterial keratitis: Inadvertent contamination of multiple-dose ophthalmic solutions has the potential to cause bacterial keratitis.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Ocular effects: Use of agents that reduce/suppress aqueous humor production has been associated with choroidal detachment after filtration procedures. Discontinue use in patients with chronic or recurrent choroidal detachment.
- Orthostatic hypotension: Use with caution. Signs and symptoms of hypotension may be enhanced.

Disease-related concerns:

- Angle-closure glaucoma: Appropriate use: Not for use alone to treat acute angle-closure glaucoma (has no effect on papillary constriction).
- Bronchospastic disease: In general, patients with bronchospastic disease (eg, asthma, COPD) should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.
- Conduction abnormalities: Consider pre-existing conditions such as sick sinus syndrome before initiating.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.
- Heart failure: Use with caution in patients with compensated heart failure and monitor for a worsening of the condition.
- Hepatic impairment: Use with caution in patients with hepatic impairment; not studied.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; may worsen myasthenia-related muscle weakness.
- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

- Renal Impairment: Use with caution in patients with renal impairment; not studied.
- Thyrotoxicosis: Signs of hyperthyroidism (eg, tachycardia) may be masked by beta-blockers. Avoid abrupt withdrawal if thyrotoxicosis is suspected (may precipitate thyroid storm).
- Vascular disease: Use with caution in patients with cerebral/coronary insufficiency as well as peripheral vascular disease (including Raynaud's, thromboangiitis obliterans).

Special populations:

- Contact lens wearers: Product contains benzalkonium chloride which may be absorbed by soft contact lenses; remove lens prior to administration and wait 15 minutes before reinserting.
- Pediatrics: Safety and efficacy have not been established in children <2 years of age; use in children <2 years of age is not recommended. **Note:** In the Canadian labeling, use in children (at any age) is not recommended. Serious adverse reactions (eg, bradycardia, hypotension, apnea, dyspnea, cyanosis) resulting in hospitalization have been reported in association with brimonidine administration in infants ages 28 days to 3 months.

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.
- Absorption: Systemic absorption and adverse effects may occur with ophthalmic use, including bradycardia and/or hypotension.
- General anesthesia: Use with caution in patients undergoing general anesthesia; severe hypotension, difficulty in restarting/maintaining heartbeat and/or impaired ability of the heart to respond to stimuli may occur; withdrawal of beta-blockade prior to elective surgery may be advised.

Also see individual agents.

Pregnancy Risk FactorC

Pregnancy Considerations There are no adequate and well-controlled studies in pregnant women with the combination product. Use only if benefit outweighs risk. Also see individual agents.

LactationEnters breast milk (timolol)/not recommended

Breast-Feeding ConsiderationsTimolol has been detected in human breast milk following ophthalmic administration. It is not known if brimonidine is excreted in human milk.

Adverse ReactionsPercentages as reported with combination product. Also see individual agents.

>10%: Ocular: Conjunctival hyperemia (15%), burning sensation (11%)

1% to 10%:

Cardiovascular: Hypertension

Central nervous system: Somnolence (2%; children 25% to 83%), headache (1%), depression

Gastrointestinal: Xerostomia (2%)

Neuromuscular & skeletal: Weakness (2%)

Ocular: Stinging (6%), pruritus (6%), allergic conjunctivitis (5%), conjunctival folliculosis (5%), blurred vision (4%), blepharitis (3%), corneal erosion (3%), dry eyes (3%), epiphora (3%), eye discharge (3%), eyelid edema (3%), eyelid erythema (3%), superficial punctuate keratitis (3%), eye pain (2%), foreign body sensation (1%), eye irritation, eyelid pruritus

<1%: Conjunctival edema, follicular conjunctivitis

Metabolism/Transport EffectsTimolol: **Substrate** of CYP2D6 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Alpha2-Agonists (Ophthalmic). *Risk X: Avoid combination*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Monitoring ParametersIntraocular pressure; monitor for systemic effect of beta-blockade with ophthalmic administration; blood pressure
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian availability

Solution, ophthalmic [drops]:

Combigan™: Brimonidine tartrate 0.2% and timolol maleate 0.5% (5 mL,10 mL) [contains benzalkonium chloride]

Combigan® [CAN]: Brimonidine tartrate 0.2% and timolol maleate 0.5% (2.5 mL, 5 mL,10 mL) [contains benzalkonium chloride]

Generic AvailableNo
ManufacturerAllergan, Inc
Pricing: U.S. (www.drugstore.com)

Solution (Combigan)

0.2-0.5% (5): $67.99

Mechanism of Action

Brimonidine: Selective agonism for alpha$_2$-receptors; causes reduction of aqueous humor formation and increased uveoscleral outflow

Timolol: Blocks both beta$_1$- and beta$_2$-adrenergic receptors, reduces intraocular pressure by reducing aqueous humor production or possibly outflow; reduces blood pressure by blocking adrenergic receptors and decreasing sympathetic outflow, produces a negative chronotropic and inotropic activity by blocking beta$_1$-adrenergic receptors

Pharmacodynamics/KineticsSee individual agents.

Index TermsBrimonidine Tartrate and Timolol Maleate; Timolol and Brimonidine

References

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Lang DM, “Anaphylactoid and Anaphylactic Reactions. Hazards of Beta-Blockers,” *Drug Saf*, 1995, 12(5):299-304.[PubMed 7669259]

Larsson LI, “Aqueous Humor Flow in Normal Human Eyes Treated With Brimonidine and Timolol, Alone and in Combination,” *Arch Ophthalmol*, 2001, 119(4):492-5.[PubMed 11296014]

Sherwood MB, Craven ER, Chou C, et al, “Twice-Daily 0.2% Brimonidine-0.5% Timolol Fixed-Combination Therapy vs Monotherapy With Timolol or Brimonidine in Patients With Glaucoma or Ocular Hypertension: A 12-Month Randomized Trial,” *Arch Ophthalmol*, 2006, 124(9):1230-8.[PubMed 16966616]

Stewart WC, Stewart JA, and Jackson AL, “Cardiovascular Effects of Timolol Maleate, Brimonidine, or Brimonidine/Timolol Maleate in Concomitant Therapy,” *Acta Ophthalmol Scand*, 2002, 80(3):277-81.[PubMed 12059866]

International Brand NamesCombigan® (CA)

Brimonidine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Brimonidine may be confused with bromocriptine

Pronunciation(bri MOE ni deen)
U.S. Brand NamesAlphagan® P
Canadian Brand NamesAlphagan®; Apo-Brimonidine®; PMS-Brimonidine Tartrate; ratio-Brimonidine; Sandoz-Brimonidine
Pharmacologic CategoryAlpha$_2$ Agonist, Ophthalmic; Ophthalmic Agent, Antiglaucoma
Use: Labeled IndicationsLowering of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
Dosing: AdultsGlaucoma: Ophthalmic: Instill 1 drop in affected eye(s) 3 times/day (approximately every 8 hours)
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren ≥2 years of age: Refer to adult dosing.
Administration: OtherRemove contact lenses prior to administration; wait 15 minutes before reinserting if using products containing benzalkonium chloride. Separate administration of other ophthalmic agents by 5 minutes.
StorageStore between 15°C to 25°C (59°F to 77°F).
ContraindicationsHypersensitivity to brimonidine tartrate or any component of the formulation; during or within 14 days of MAO inhibitor therapy
Allergy Considerations

- Brimonidine Allergy

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.
- Cerebrovascular insufficiency: Use with caution in patients with cerebral insufficiency.
- Depression: Use with caution in patients with depression.
- Orthostatic hypotension: Use with caution in patients with orthostatic hypotension.
- Raynaud's phenomenon: Use with caution in patients with Raynaud's phenomenon.
- Thromboangiitis obliterans: Use with caution in patients with thromboangiitis obliterans.

Special populations:

- Contact lens wearers: Contains benzalkonium chloride which may be adsorbed by contact lenses; remove contacts prior to administration and wait 15 minutes before reinserting.
- Pediatrics: Safety and efficacy have not been established in children <2 years of age. Systemic absorption has been reported; children are at higher risk of systemic adverse events.

Other warnings/precautions:

- Monitoring efficacy: The IOP-lowering efficacy observed during the first month of therapy may not always reflect the long-term level of IOP reduction; routinely monitor IOP.

Geriatric ConsiderationsAssess patient's ability to self-administer eye drops.
Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsActual frequency of adverse reactions may be formulation dependent; percentages reported with Alphagan® P:

>10%:

Central nervous system: Somnolence (adults 1% to 4%; children 25% to 83%)

Ocular: Allergic conjunctivitis, conjunctival hyperemia, eye pruritus

1% to 10% (unless otherwise noted 1% to 4%):

Cardiovascular: Hypertension (5% to 9%), hypotension

Central nervous system: Alertness decreased (children), dizziness, fatigue, headache, insomnia

Dermatologic: Rash

Endocrine & metabolic: Hypercholesterolemia

Gastrointestinal: Xerostomia (5% to 9%), dyspepsia

Neuromuscular & skeletal: Weakness

Ocular: Burning sensation (5% to 9%), conjunctival folliculosis (5% to 9%), ocular allergic reaction (5% to 9%), visual disturbance (5% to 9%), blepharitis, blepharoconjunctivitis, blurred vision, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, dry eye, epiphora, eye discharge, eyelid disorder, eyelid edema, eyelid erythema, follicular conjunctivitis, foreign body sensation, irritation, keratitis, pain, photophobia, stinging, superficial punctate keratopathy, visual acuity worsened, visual field defect, vitreous detachment, vitreous floaters, watery eyes

Respiratory: Bronchitis, cough, dyspnea, pharyngitis, rhinitis, sinus infection, sinusitis

Miscellaneous: Allergic reaction, flu-like syndrome, infection

<1%: Corneal erosion, hordeolum, nasal dryness, taste perversion

Postmarketing and/or case reports: Anterior uveitis, bradycardia, depression, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (erythema, eyelid pruritus, vasodilation), tachycardia; apnea, bradycardia, hypothermia, and hypotonia have been reported in infants

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Alpha2-Agonists (Ophthalmic). *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid herbs with **hypertensive** properties (bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng, gotu kola, licorice); may diminish antihypertensive effect. Avoid herbs with **hypotensive** properties (black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse); may enhance hypotensive effect.

Monitoring ParametersClosely monitor patients who develop fatigue or drowsiness; IOP

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Monitor intraocular pressure periodically. Assess therapeutic response and adverse effects. Teach patient proper use, side effects/appropriate interventions, and symptoms to report.

Patient EducationFor use in eyes only. Wash hands before instilling. Remove contacts prior to administration and wait 15 minutes before reinserting. Sit or lie down to instill. Open eye, look at ceiling, and instill prescribed amount of solution. Apply gentle pressure to inner corner of eye. Do not let tip of applicator touch eyes; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Brimonidine tartrate may cause fatigue or drowsiness in some patients. Avoid engaging in hazardous activities due to potential for decreased mental alertness. Wait at least 15 minutes after instilling brimonidine tartrate before reinserting soft contact lenses. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic, as tartrate: 0.2% (5 mL, 10 mL, 15 mL) [may contain benzalkonium chloride]

Alphagan® P: 0.1% (5 mL, 10 mL, 15 mL) [contains Purite® as preservative]; 0.15% (5 mL, 10 mL, 15 mL) [contains Purite® as preservative]

Generic AvailableYes

ManufacturerAllergan, Inc

Pricing: U.S. (www.drugstore.com)

Solution (Alphagan P)

0.1% (15): $175.47

0.15% (5): $63.12

0.15% (10): $115.55

0.15% (15): $167.98

Solution (Brimonidine Tartrate)

0.2% (5): $31.99

0.2% (10): $51.99

0.2% (15): $93.02

Mechanism of Action Selective agonism for alpha$_2$-receptors; causes reduction of aqueous humor formation and increased uveoscleral outflow

Pharmacodynamics/Kinetics

Onset of action: Peak effect: 2 hours

Metabolism: Hepatic

Half-life elimination: 2-3 hours

Time to peak, plasma: 0.5-2.5 hours

Excretion: Urine (74%)

Related Information

- Glaucoma Drug Therapy

Pharmacotherapy Pearls The use of Purite® as a preservative in Alphagan® P has lead to a reduced incidence of certain adverse effects associated with products using benzalkonium chloride as a preservative. The 0.1% and 0.15% solutions are comparable to the 0.2% solution in lowering intraocular pressure.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Drowsiness is common

Mental Health: Effects on Psychiatric Treatment Contraindicated with MAO inhibitors; concurrent use with psychotropics may produce additive sedation

Index Terms Brimonidine Tartrate

References

Byles DB, Frith P, and Salmon JF, “Anterior Uveitis as a Side Effect of Topical Brimonidine,” *Am J Ophthalmol*, 2000, 130(3):287-91.[PubMed 11020406]

Levy Y and Zadok D, “Systemic Side Effects of Ophthalmic Drops,” *Clin Pediatr* (Phila), 2004, 43(1):99-101.

International Brand Names Agglad Ofteno (MX); Alphagan (AT, AU, BE, BR, CH, CN, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IN, IT, MX, NL, NO, PE, PL, PT, SE, UY, VE, ZA); Alphagan-P (AR, BR, CR, EC, GT, HK, IL, KP, MY, PA, SG, SV, TH); Brimopress (PY, UY); Enidin (AU); Iobrim (IN); Nor-Tenz (MX)

Brinzolamide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(brin ZOH la mide)
U.S. Brand NamesAzopt®
Canadian Brand NamesAzopt®
Pharmacologic CategoryCarbonic Anhydrase Inhibitor; Ophthalmic Agent, Antiglaucoma
Use: Labeled IndicationsLowers intraocular pressure in patients with ocular hypertension or open-angle glaucoma
Dosing: AdultsGlaucoma: Ophthalmic: Instill 1 drop in affected eye(s) 3 times/day
Dosing: ElderlyRefer to adult dosing.
Administration: OtherMay be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, administer drugs at least 10 minutes apart.
StorageStore at 4°C to 30°C (39°F to 86°F). Shake well before use.
ContraindicationsHypersensitivity to brinzolamide, sulfonamides, or any component of the formulation
Allergy Considerations

- Carbonic Anhydrase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Systemic absorption may cause serious hypersensitivity reactions to recur.
- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.
- Systemic effects: Systemic absorption and adverse effects (similar to sulfonamides) including, blood dyscrasias, Stevens-Johnson syndrome, toxic epidermal necrolysis, and fulminant hepatic necrosis may occur with ophthalmic use.

Disease-related concerns:

- Acute angle-closure glaucoma: Has not been studied in acute angle-closure glaucoma.
- Hepatic impairment: Safety and efficacy have not been established with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment; parent and metabolite may accumulate.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Prolonged use: Effects of prolonged use on corneal epithelial cells have not been evaluated.

Geriatric ConsiderationsThe oral carbonic anhydrase inhibitors are useful for patients who have difficulty administering ophthalmic drugs, who do not achieve sufficient lowering of intraocular pressure, or who cannot tolerate other agents. Brinzolamide is a useful agent apart from those who need a carbonic anhydrase inhibitor and can administer ophthalmic drops.
Pregnancy Risk FactorC
Pregnancy ConsiderationsDevelopmental toxicities have been observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

1% to 10%:

Dermatologic: Dermatitis (1% to 5%)

Gastrointestinal: Taste disturbances (5% to 10%)

Ocular: Blurred vision (5% to 10%), blepharitis (1% to 5%), dry eye (1% to 5%), foreign body sensation (1% to 5%), eye discharge (1% to 5%), eye pain (1% to 5%), itching of eye (1% to 5%)

Respiratory: Rhinitis (1% to 5%)

<1%: Allergic reactions alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dyspnea, eye fatigue, headache, lid crusting, nausea, pharyngitis, urticaria, xerostomia

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)
Drug Interactions

Memantine: Carbonic Anhydrase Inhibitors may decrease the excretion of Memantine. *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Monitoring ParametersIntraocular pressure
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic response and adverse effects. Measure intraocular pressure periodically. Teach patient proper use, side effects/appropriate interventions, and symptoms to report
Patient EducationFor use in eyes only. Tilt head back, place medication in conjunctival sac, and close eyes. Apply finger pressure at corner of eye for 1 minute following application. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). If using other ophthalmic preparations, administer 10 minutes apart. Avoid excessive use of aspirin or aspirin-containing medications (may cause toxicity). May cause taste changes; runny nose; or vision changes (blurred vision, dry eye, foreign body sensation, eye discharge, temporary sensitivity to bright light, blurring or stinging, altered distance perception, reduced night vision acuity). Report persistent dizziness or headache, skin rash, loss of hair, unresolved GI disturbance, difficulty breathing, or persistent sore throat. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Suspension, ophthalmic:

Azopt®: 1% (5 mL [DSC], 10 mL, 15 mL) [contains benzalkonium chloride]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Suspension (Azopt)

1% (10): $85.99

1% (15): $119.99

Mechanism of ActionBrinzolamide inhibits carbonic anhydrase, leading to decreased aqueous humor secretion. This results in a reduction of intraocular pressure.
Pharmacodynamics/Kinetics

Onset of action: Peak effect: 2 hours

Duration: 8-12 hours

Absorption: Topical: Into systemic circulation

Distribution: Accumulates in red blood cells, binding to carbonic anhydrase (brinzolamide and metabolite)

Metabolism: To N-desmethyl brinzolamide

Excretion: Urine (as unchanged drug and metabolites)

Related Information

- Glaucoma Drug Therapy

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste disturbances.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay rarely cause dizziness
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesAzopt (AR, AT, AU, BE, BG, BR, CH, CL, CN, CO, CR, CZ, DE, DK, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IL, IT, KP, MX, MY, NI, NL, NO, PA, PE, PH, PL, PT, PY, RU, SE, SG, SV, TH, TR, TW, UY, VE); Azoptic (ZA); BrinzoQuin (AU)

Bromazepam

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

International issues:

Lexotan® [multiple international markets] may be confused with Cefotan® which is a brand name for cefotetan in the U.S.

Lexotan® [multiple international markets] may be confused with Cefiton® which is a brand name for cefixime in Portugal

Lexotan® [multiple international markets] may be confused with Loxitane® which is a brand name for loxapine in the U.S.

Pronunciation(broe MA ze pam)

Canadian Brand NamesApo-Bromazepam®; Gen-Bromazepam; Lectopam®; Novo-Bromazepam; Nu-Bromazepam; Pro Doc Limitee Bromazepam

Pharmacologic CategoryBenzodiazepine

Use: Labeled IndicationsShort-term, symptomatic treatment of anxiety

Dosing: AdultsAnxiety: Oral: Initial: 6-18 mg/day in equally divided doses. Initial course of treatment should not last longer than 1 week. Optimal dosage range: 6-30 mg/day.

Debilitated patients: Initial dose: 3 mg/day in divided doses

Dosing: ElderlyInitial dose: 3 mg/day in divided doses

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at 20°C to 25°C (68°F to 77°F).

RestrictionsCDSA IV; Not available in U.S.

ContraindicationsHypersensitivity to bromazepam or any component of the formulation (cross-sensitivity with other benzodiazepines may exist); myasthenia gravis; narrow-angle glaucoma; severe hepatic or respiratory disease; sleep apnea; pregnancy

Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.
- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury.

- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.

- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Pregnancy Risk FactorD (based on other benzodiazepines)
Pregnancy ConsiderationsCrosses the placenta. Oral clefts reported, however, more recent data does not support an association between drug and oral clefts; inguinal hernia, cardiac defects, spina bifida, dysmorphic facial features, skeletal defects, multiple other malformations reported; hypotonia and withdrawal symptoms reported following use near time of delivery.
LactationEnters breast milk/contraindicated (AAP rates other benzodiazepines “of concern”)
Breast-Feeding ConsiderationsCrosses into breast milk. Clinical effects on the infant: Sedation; AAP reports benzodiazepine use MAY BE OF CONCERN.
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension, palpitation, tachycardia

Central nervous system: Drowsiness, ataxia, dizziness, confusion, depression, euphoria, lethargy, slurred speech, stupor, headache, seizure, anterograde amnesia. In addition, paradoxical reactions (including excitation, agitation, hallucinations, and psychosis) are known to occur with benzodiazepines.

Dermatologic: Rash, pruritus

Endocrine & metabolic: Hyperglycemia, hypoglycemia

Gastrointestinal: Xerostomia, nausea, vomiting

Genitourinary: Incontinence, libido decreased

Hematologic: Hemoglobin decreased, hematocrit decreased, WBCs increased/decreased

Hepatic: Transaminases increased, alkaline phosphatase increased, bilirubin increased

Neuromuscular & skeletal: Weakness, muscle spasm

Ocular: Blurred vision, depth perception decreased

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP2E1 (weak)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Serum concentration may be increased by grapefruit juice.

Herb/Nutraceutical: St John's wort may decrease bromazepam serum concentrations. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Nursing: Physical Assessment/MonitoringFor inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions (see Adverse Reactions) at beginning of therapy and periodically with long-term use.

Patient EducationTake exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, loss of appetite, or dry mouth (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help). Report CNS changes (eg, confusion, depression, increased sedation, excitation, headache, agitation, insomnia or nightmares, dizziness, fatigue, or impaired coordination) or changes in cognition; respiratory difficulty or shortness of breath; changes in urinary pattern; changes in sexual activity; muscle cramping, weakness, tremors, or rigidity; ringing in ears or visual disturbances, excessive perspiration, or excessive GI symptoms (eg, cramping, constipation, vomiting, anorexia). **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet: 1.5 mg, 3 mg, 6 mg [not available in the U.S.]

Generic AvailableYes

ManufacturerHoffman-La Roche Ltd

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Protein binding: 70%

Metabolism: Hepatic

Bioavailability: 60%

Half-life elimination: 20 hours

Excretion: Urine (69%), as metabolites

Related Information

- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsNot available in U.S.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

Risk factors for abuse include personal or family history of substance abuse and personality disorder.

References

Lectopam® product monograph, Hoffman-La Roche Ltd, Ontario, January 2001.

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand NamesAkamon (HK, MY, TW); Ansiosel (CO); Anxyrex (FR); Benedorm (AR); Brazepam (ZA); Bromazanil (LU); Bromaze (ZA); Bromazepam Genericon (AT); Bromazepam Lannacher (AT); Bromazepam MSD (AT); Bromazepam-Eurogenerics (LU); Bromidem (LU); Durazanil (DE); Gityl (DE); Lekotam (BG, HR); Lenitin (IL); Lexatin (ES); Lexaurin (CZ, HR); Lexilium (CY, HR); Lexomil (FR); Lexostad (DE); Lexotan (AU, BE, BR, CO, DK, EC, HK, ID, IE, IT, LU, MX, PE, PH, PL, PT, PY, SG, TH, TW, UY); Lexotanil (AR, AT, CH, CN, CZ, DE, GR, NL, NO, PK, VE); Lexotanol (EE); Nervan (VE); Octanyl (CR, EC, GT, HN, NI, SV, UY); Otedram (MX); Relaxil (BR); Sedam (PL); Sedamax (PE); Seniran (JP); Totasedan (CN); Tredum (PY)

Bromfenac

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English

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Pronunciation(BROME fen ak)
U.S. Brand NamesXibrom™
Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Ophthalmic
Use: Labeled IndicationsTreatment of postoperative inflammation and reduction in ocular pain following cataract removal
Dosing: AdultsOphthalmic: Instill 1 drop into affected eye(s) twice daily beginning 24 hours after surgery and continuing for 2 weeks postoperatively
Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo adjustment required.
StorageStore at 15°C to 25°C (59°F to 77°F).
Warnings/Precautions

Concerns related to adverse effects:

- Aspirin/NSAID sensitivity: Use with caution in patients with previous sensitivity to acetylsalicylic acid and phenylacetic acid derivatives, including patients who experience bronchospasm, asthma, rhinitis, or urticaria following NSAID or aspirin.

- Keratitis: May cause keratitis; continued use in a patient with keratitis may cause severe corneal adverse reactions, potentially resulting in loss of vision. Immediately discontinue use in patients with evidence of corneal epithelial damage.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with a predisposition to bleeding (bleeding tendencies or medications which interfere with coagulation).

- Diabetes: Use with caution in patients with diabetes mellitus; may be at risk of corneal adverse events, potentially resulting in loss of vision.

- Ocular disease: Use with caution in patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, ocular surface disease, or repeat ocular surgeries (within a short timeframe); may be at risk of corneal adverse events, potentially resulting in loss of vision.

- Rheumatoid arthritis: Use with caution in patients with rheumatoid arthritis; may be at risk of corneal adverse events, potentially resulting in loss of vision.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Surgery patients: May slow/delay healing or prolong bleeding time following surgery.

Dosage form specific issues:

- Sulfites: Contains sulfites, which may cause allergic reactions.

Other warnings/precautions:

- Duration of therapy: Use for more than 1 day prior to surgery or for 14 days beyond surgery may increase risk and severity of corneal adverse events.

- Soft contact lenses: Patients using ophthalmic drops should not wear soft contact lenses.

Geriatric ConsiderationsNo differences in safety and efficacy noted between elderly and younger adults. No dosage adjustment necessary. Elderly may be taking other medications that will increase bleeding.
Pregnancy Risk FactorC/D (3rd trimester)
Pregnancy ConsiderationsSafety and efficacy in pregnant women have not been established. In animal studies, at exposures much higher than those which would result from ophthalmic use, embryo-fetal lethality and increased postimplantation loss occurred. Exposure to nonsteroidal anti-inflammatory drugs late in pregnancy may lead to premature closure of the ductus arteriosus and may inhibit uterine contractions.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

2% to 7%:

Central nervous system: Headache

Ocular: Abnormal vision, abnormal sensation, conjunctival hyperemia, eye pain, iritis, pruritus

Postmarketing and/or case reports: Corneal erosion, corneal thinning, corneal perforation, epithelial breakdown

Drug Interactions

Latanoprost: NSAID (Ophthalmic) may diminish the therapeutic effect of Latanoprost. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringAssess for intraocular bleeding. Evaluate allergy history with aspirin or other NSAIDs. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationDo not wear contact lenses while using this medication. Report any abnormal sensation in eye, redness, severe headache, or pain.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic:

Xibrom™: 0.09% (2.5 mL, 5 mL) [contains benzalkonium chloride and sodium sulfite]

Generic AvailableNo

ManufacturerISTA Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Solution (Xibrom)

0.09% (2.5): $104.70

0.09% (5): $194.44

Mechanism of ActionInhibits prostaglandin synthesis by decreasing the activity of the enzyme, cyclooxygenase, which results in decreased formation of prostaglandin precursors.

Pharmacodynamics/Kinetics

Absorption: Theoretically, systemic absorption may occur following ophthalmic use (not characterized); anticipated levels are below the limits of assay detection

Metabolism: Hepatic

Half-life elimination: 0.5-4 hours (following oral administration)

Pharmacotherapy PearlsAn oral formulation of bromfenac was previously available and was withdrawn from the market following reports of idiosyncratic hepatotoxicity.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBromfenac Sodium

References

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Kashiwagi K and Tsukahara S, “Effect of Nonsteroidal Anti-inflammatory Ophthalmic Solution on Intraocular Pressure Reduction by Latanoprost,” *Br J Ophthalmol*, 2003, 87(3):297-301.[PubMed 12598441]

Miyake-Kashima M, Takano Y, Tanaka M, et al, “Comparison of 0.1% Bromfenac Sodium and 0.1% Pemirolast Potassium for the Treatment of Allergic Conjunctivitis,” *Jpn J Ophthalmol*, 2004, 48(6):587-90.[PubMed 15592786]

Rabkin JM, Smith MJ, Orloff SL, et al, “Fatal Fulminant Hepatitis Associated With Bromfenac Use,” *Ann Pharmacother*, 1999, 33(9):945-7.[PubMed 10492497]

Skjodt NM and Davies NM, “Clinical Pharmacokinetics and Pharmacodynamics of Bromfenac,” *Clin Pharmacokinet*, 1999, 36(6):399-408.[PubMed 10427465]

International Brand NamesNatax (AR)

Bromocriptine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Bromocriptine may be confused with benztropine, brimonidine

Parlodel® may be confused with pindolol, Provera®

Pronunciation(broe moe KRIP teen)

U.S. Brand NamesParlodel®; Parlodel® SnapTabs®

Canadian Brand NamesApo-Bromocriptine®; Parlodel®; PMS-Bromocriptine

Pharmacologic CategoryAnti-Parkinson's Agent, Dopamine Agonist; Ergot Derivative

Use: Labeled IndicationsTreatment of hyperprolactinemia associated with amenorrhea with or without galactorrhea, infertility, or hypogonadism; treatment of prolactin-secreting adenomas; treatment of acromegaly; treatment of Parkinson's disease

Use: Unlabeled/InvestigationalNeuroleptic malignant syndrome

Dosing: Adults

Parkinsonism: Oral: 1.25 mg twice daily, increased by 2.5 mg/day in 2- to 4-week intervals (usual dose range is 30-90 mg/day in 3 divided doses; maximum: 100 mg/day), though elderly patients can usually be managed on lower doses.

Neuroleptic malignant syndrome (unlabeled use): Oral: 2.5-5 mg 3 times/day

Acromegaly: Oral: Initial: 1.25-2.5 mg daily increasing by 1.25-2.5 mg daily as necessary every 3-7 days; usual dose: 20-30 mg/day (maximum: 100 mg/day)

Hyperprolactinemia: Oral: Initial: 1.25-2.5 mg/day; may be increased by 2.5 mg/day as tolerated every 2-7 days until optimal response (range: 2.5-15 mg/day)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Hyperprolactinemia: Oral:

Children 11-15 years (based on limited information): Initial: 1.25-2.5 mg daily. Dosage may be increased as tolerated to achieve a therapeutic response (range 2.5-10 mg daily).

Children ≥16 years: Refer to adult dosing.

Dosing: Hepatic ImpairmentNo guidelines are available, however, adjustment may be necessary.

Dietary ConsiderationsMay be taken with food to decrease GI distress.

ContraindicationsHypersensitivity to bromocriptine, ergot alkaloids, or any component of the formulation; ergot alkaloids are contraindicated with potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics); uncontrolled hypertension; severe ischemic heart disease or peripheral vascular disorders; pregnancy (risk to benefit evaluation must be performed in women who become pregnant during treatment for acromegaly, prolactinoma, or Parkinson's disease - hypertension during treatment should generally result in efforts to withdraw)

Allergy Considerations

- Ergot Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac valvular fibrosis: Ergot alkaloids and derivatives have been associated with fibrotic valve thickening (eg, aortic, mitral, tricuspid); usually associated with long-term, chronic use.
- Cardiovascular effects: Symptomatic hypotension may occur in a significant number of patients. In addition, hypertension, seizures, MI, and stroke have been rarely associated with therapy. Severe headache or visual changes may precede events. The onset of reactions may be immediate or delayed (often may occur in the second week of therapy).
- Impulsive control disorders: Dopamine agonists used for Parkinson’s disease or restless legs syndrome have been associated with compulsive behaviors and/or loss of impulse control, which has manifested as pathological gambling, libido increases (hypersexuality), and/or binge eating. Causality has not been established, and controversy exists as to whether this phenomenon is related to the underlying disease, prior behaviors/addictions and/or drug therapy. Dose reduction or discontinuation of therapy has been reported to reverse these behaviors in some, but not all cases.
- Pleural/retroperitoneal fibrosis: Rare cases of pleural and/or retroperitoneal fibrosis have been reported with prolonged daily use.

- Sedation: Sudden sleep onset and somnolence have been reported with use, primarily in patients with Parkinson's disease. Patients must be cautioned about performing tasks which require mental alertness.

Disease-related concerns:

- Acromegaly: Appropriate use: In the treatment of acromegaly, discontinuation is recommended if tumor expansion occurs during therapy. Digital vasospasm (cold sensitive) may occur in some patients with acromegaly; may require dosage reduction.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (myocardial infarction, arrhythmia). Should not be used postpartum in women with coronary artery disease or other cardiovascular disease; use to control or prevent lactation or in patients with uncontrolled hypertension is not recommended.
- Dementia: Use with caution in patients with dementia.
- Hepatic impairment: Safety and efficacy have not been established in patients with hepatic impairment.
- Macroadenomas: Discontinuation of therapy in patients with macroadenomas has been associated with rapid regrowth of tumor and increased prolactin serum levels.
- Parkinson's disease: Safety has not been established for use >2 years in patients with Parkinson's disease.
- Peptic ulcer disease: Use with caution in patients with peptic ulcer disease.
- Psychosis: Use with caution in patients with psychosis.
- Renal disease: Safety and efficacy have not been established in patients with renal impairment.

Concurrent drug therapy issues:

- Antihypertensives: Concurrent antihypertensives or drugs which may alter blood pressure should be used with caution.
- Levodopa: Concurrent use with levodopa has been associated with an increased risk of hallucinations; consider dosage reduction and/or discontinuation in patients with hallucinations. Hallucinations may require weeks to months before resolution.

Special populations:

- Pediatrics: Safety and effectiveness have not been established in children <11 years of age for pituitary adenoma.
- Pregnancy: Patients who receive during and immediately following pregnancy as a continuation of previous therapy (eg, acromegaly) should be closely monitored for cardiovascular effects.

Other warnings/precautions:

- Pituitary function evaluation: Complete evaluation of pituitary function should be completed prior to initiation of treatment.
- Visual monitoring: Monitoring and careful evaluation of visual changes during the treatment of hyperprolactinemia is recommended to differentiate between tumor shrinkage and traction on the optic chiasm; rapidly progressing visual field loss requires neurosurgical consultation.

Geriatric ConsiderationsNo special considerations are recommended since drug is dosed to response; however, elderly may have concomitant diseases or drug therapy which may complicate therapy.

Pregnancy Risk FactorB

Pregnancy ConsiderationsNo evidence of teratogenicity or fetal toxicity in animal studies. Bromocriptine is used for ovulation induction in women with hyperprolactinemia. In general, therapy should be discontinued if pregnancy is confirmed unless needed for treatment of macroprolactinoma. Data collected from women taking bromocriptine during pregnancy suggest the incidence of birth defects is not increased with use. However, the majority of women discontinued use within 8 weeks of pregnancy. Women not seeking pregnancy should be advised to use appropriate contraception.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsA previous indication for prevention of postpartum lactation was withdrawn voluntarily by the manufacturer following reports of serious adverse reactions, including stroke, MI, seizures, and severe hypertension. Based on the risk/benefit assessment, other treatments should be considered for lactation suppression.

Adverse Reactions**Note:** Frequency of adverse effects may vary by dose and/or indication.

>10%:

Central nervous system: Dizziness, headache

Gastrointestinal: Constipation, nausea

1% to 10%:

Cardiovascular: Hypotension (including postural/orthostatic), Raynaud's syndrome exacerbation, syncope

Central nervous system: Drowsiness, fatigue, lightheadedness

Gastrointestinal: Abdominal cramps, anorexia, diarrhea, dyspepsia, GI bleeding, vomiting, xerostomia

Neuromuscular & skeletal: Digital vasospasm

Respiratory: Nasal congestion

Frequency not defined, postmarketing, and/or case reports: Abdominal discomfort, alcohol potentiation, alopecia, anxiety, arrhythmia, ataxia, blepharospasm, blurred vision, bradycardia, cerebrospinal fluid rhinorrhea, cold tolerance decreased, confusion, constrictive pericarditis, delusional psychosis, depression, dyskinesia, dysphagia, dyspnea, ear tingling, epileptiform seizure, ergotism, erythromelalgia, facial pallor, faintness, hallucinations, heavy headedness, insomnia, involuntary movements, lassitude, lethargy, lightheadedness, mottling of skin, muscle cramps, nervousness, nightmares, “on-off” phenomenon, paranoia, paresthesia, pericardial effusion, peripheral edema, pleural effusion, pleural/pulmonary fibrosis, psychomotor agitation/excitation, rash, sleep requirement decreased, sluggishness, urinary frequency, urinary retention, vasovagal attack, ventricular tachycardia, vertigo, visual disturbance, weakness

Withdrawal reactions: Abrupt discontinuation has resulted in rare cases of a withdrawal reaction with symptoms similar to neuroleptic malignant syndrome.

Postmarketing and/or case reports: Reported with dopamine agonists: Impulsive/compulsive behaviors (eg, pathological gambling, hypersexuality, binge eating)

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (weak), 3A4 (weak)

Drug Interactions

Alpha-/Beta-Agonists: May enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Antipsychotics (Atypical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Antipsychotics (Typical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

CycloSPORINE: Bromocriptine may increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Efavirenz: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically, the risk for peripheral vasospasm and ischemia may be increased. *Risk X: Avoid combination*

Macrolide Antibiotics: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Metoclopramide: May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk C: Monitor therapy*

Posaconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Protease Inhibitors: May decrease the metabolism of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: Ergot Derivatives may enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Ergot Derivatives. This may cause serotonin syndrome. *Risk X: Avoid combination*

Voriconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase GI side effects or ethanol intolerance).

Herb/Nutraceutical: St John's wort may decrease bromocriptine levels.

Monitoring ParametersMonitor blood pressure closely as well as hepatic, hematopoietic, and cardiovascular function; visual field monitoring is recommended (prolactinoma); pregnancy test during amenorrheic period; growth hormone and prolactin levels.

Nursing: Physical Assessment/MonitoringMonitor blood pressure at beginning of therapy and periodically during course of treatment. Assess therapeutic effectiveness (eg, mental status, involuntary movements) and adverse reactions at beginning of therapy and periodically throughout therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsPregnancy test during amenorrheic period; growth hormone and prolactin levels

Patient EducationTake exactly as directed (may be prescribed in conjunction with levodopa/carbidopa); do not change dosage or discontinue this medicine without consulting prescriber. Therapeutic effects may take several weeks or months to achieve and you may need frequent monitoring during first weeks of therapy. Take with meals if GI upset occurs, before meals if dry mouth occurs, or after eating if drooling or if nausea occurs. Take at the same time each day. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake; void before taking medication. Do not use alcohol, prescription or OTC sedatives, or CNS depressants without consulting prescriber. Urine or perspiration may appear darker. You may experience drowsiness (can be sudden onset), dizziness, confusion, or vision changes (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); loss of impulse control (possibly manifested as pathological gambling, libido increases, and/or binge eating); orthostatic hypotension (use caution when rising from sitting or lying position); constipation (increased exercise, fluids, fruit, or fiber may help); nasal congestion (consult prescriber for appropriate relief); or nausea, vomiting, loss of appetite, or stomach discomfort (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report unresolved constipation or vomiting; chest pain or irregular heartbeat; acute headache or dizziness; CNS changes (eg, hallucination, loss of memory, seizures, acute headache, nervousness); suicide ideation; painful or difficult urination; increased muscle spasticity, rigidity, or involuntary movements; skin rash; or significant worsening of condition. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as mesylate: 5 mg

Parlodel®: 5 mg

Tablet, as mesylate: 2.5 mg

Parlodel® SnapTabs®: 2.5 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Parlodel)

5 mg (30): $213.65

Tablets (Bromocriptine Mesylate)

2.5 mg (30): $61.99

Tablets (Parlodel)

2.5 mg (30): $135.37

Mechanism of ActionSemisynthetic ergot alkaloid derivative and a dopamine receptor agonist which activates postsynaptic dopamine receptors in the tuberoinfundibular (inhibiting pituitary prolactin secretion) and nigrostriatal pathways (enhancing coordinated motor control).

Pharmacodynamics/Kinetics

Onset of action: Prolactin decreasing effect: 1-2 hours

Protein binding: 90% to 96%

Metabolism: Primarily hepatic via CYP3A; extensive first-pass biotransformation

Bioavailability: 28%

Half-life elimination: Biphasic: Terminal: 15 hours (range 8-20 hours)

Time to peak, serum: 1-3 hours

Excretion: Feces; urine (2% to 6% as unchanged drug and metabolites)

Related Information

- Antiparkinsonian Agents
- Discontinuation of Psychotropic Drugs

Pharmacotherapy PearlsUsually used with levodopa or levodopa/carbidopa to treat Parkinson's disease. When adding bromocriptine, the dose of levodopa/carbidopa can usually be decreased.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause hallucinations

Mental Health: Effects on Psychiatric TreatmentUsed to treat neuroleptic malignant syndrome and cocaine abuse; fluvoxamine and nefazodone may increase bromocriptine concentrations; monitor for hypotension, headache, nausea

Index TermsBromocriptine Mesylate

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Weintraub D, Siderowf AD, Potenza MN, et al, “Association of Dopamine Agonist Use With Impulse Control Disorders in Parkinson Disease,” *Arch Neurol*, 2006, 63(7):969-73.[PubMed 16831966]

International Brand NamesApo-Bromocriptine (NZ); Aspen Bromocriptine (ZA); Bagren (BR); Barlolin (TW); Brameston (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Brocaden (TH); Bromed (AT); Bromergon (HR, PL); Bromidine (KP); Bromo-Kin (FR); Bromocorn (PL); Bromocriptin-Richter (HU); Bromohexal (AU); Bromokin (FI); Demil (TW); Deprolac (TW); Ergolaktyna (PL); Kripton (AU); Medocriptine (HK); Parilac (IL); Parlodel (AE, AR, AT, AU, BD, BE, BF, BG, BH, BJ, BR, CH, CI, CL, CO, CY, CZ, DE, DK, EE, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PH, PK, PL, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SY, TH, TN, TR, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Pravidel (SE); Provasyn (PH); Ronalin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Serocryptin (AE, BH, CY, EG, GR, HU, IL, IN, IQ, IR, IT, JO, KW, LB, LY, MY, OM, PE, QA, SA, SY, YE); Suplac (TH); Syntocriptine (HK); Umprel (AT)

Brompheniramine, Pseudoephedrine, and Dextromethorphan

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(brome fen IR a meen, soo doe e FED rin, & deks troe meth OR fan)

U.S. Brand NamesAccuHist® PDX Drops; AllanHist PDX; Anaplex® DM; Anaplex® DMX; Andehist DM NR; Bromaline® DM [OTC]; Bromatane DX; Brometane DX [DSC]; Bromhist DM; Bromhist PDX; Bromphenex DM; Bromplex DX; Brotapp-DM; Carbofed DM; EndaCof-DM; EndaCof-PD; Histacol™ BD; Myphetane DX; PediaHist DM

Pharmacologic CategoryAlpha/Beta Agonist; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsRelief of cough and upper respiratory symptoms (including nasal congestion) associated with allergy or the common cold

Dosing: Adults

Cough and upper respiratory symptoms associated with common cold: Oral:

Anaplex® DM: 5 mL every 4-6 hours (maximum: 4 doses/24 hours)

Anaplex® DMX: 5 mL every 12 hours (maximum: 10 mL/24 hours)

Bromaline® DM: 20 mL every 4-6 hours (maximum: 4 doses/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Cough and upper respiratory symptoms: Oral:

1-3 months (AccuHist® PDX, EndaCof-PD): 0.25 mL 4 times/day

3-6 months (AccuHist® PDX, EndaCof-PD): 0.5 mL 4 times/day

6-12 months (AccuHist® PDX, EndaCof-PD): 0.75 mL 4 times/day

12-24 months (AccuHist® PDX, EndaCof-PD): 1 mL 4 times/day

2-6 years:

Anaplex® DM, EndaCof-DM: 1.25 mL every 4-6 hours (maximum: 4 doses/24 hours)

Anaplex® DMX: 1.25 mL every 12 hours (maximum: 2.5 mL/24 hours)

6-12 years:

Anaplex® DM, EndaCof-DM: 2.5 mL every 4-6 hours (maximum: 4 doses/24 hours)

Anaplex® DMX: 2.5 mL every 12 hours (maximum: 5 mL/24 hours)

Bromaline® DM: 10 mL every 4-6 hours (maximum: 4 doses/24 hours)

≥12 years: Refer to adult dosing.

Administration: OralAnaplex® DMX: Shake well prior to use.

StorageStore between 8°C to 30°C (46°F to 86°F). Avoid exposure to heat; keep tightly closed.

ContraindicationsHypersensitivity to brompheniramine, pseudoephedrine, dextromethorphan or any component of the formulation; severe hypertension or coronary artery disease; MAO inhibitor therapy; GI or GU obstruction; peptic ulcer disease; narrow-angle glaucoma; acute asthma attack

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Asthma: Use with caution in patients with a history of asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in sedated, debilitated patients confined to supine position.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children. Use with caution in atopic children.

Pregnancy Risk FactorC

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsSmall amounts of antihistamines and pseudoephedrine are excreted in breast milk. Premature infants and newborns have a higher risk of intolerance to antihistamines. Antihistamines may inhibit lactation.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, flushing, hypertension, pallor, palpitation, tachycardia

Central nervous system: Convulsions, CNS stimulation, dizziness, drowsiness, excitability (children; rare), giddiness, hallucinations, headache, insomnia, irritability, lassitude, nervousness, sedation

Dermatologic: Photosensitivity, pruritus, rash, urticaria

Gastrointestinal: Anorexia, constipation, diarrhea, dyspepsia, GI upset, nausea, vomiting, xerostomia

Hematologic: Agranulocytosis, hemolytic anemia, thrombocytopenia

Neuromuscular skeletal: Tremors, weakness

Ocular: Diplopia

Renal: Dysuria, polyuria, urinary retention (with BPH)

Respiratory: Respiratory difficulty

Metabolism/Transport EffectsDextromethorphan: **Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Elixir:

Bromaline® DM: Brompheniramine maleate 1 mg, pseudoephedrine hydrochloride 15 mg, and dextromethorphan hydrobromide 5 mg per 5 mL (120 mL, 480 mL) [alcohol free; contains sodium benzoate; grape flavor]

Liquid:

Bromplex DM: Brompheniramine maleate 4 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free]

Brotapp-DM: Brompheniramine maleate 1 mg, pseudoephedrine hydrochloride 15 mg, and dextromethorphan hydrobromide 5 mg per 5 mL (120 mL, 240 mL) [grape flavor]

Solution, oral [drops]:

AccuHist® PDX, AllanHist PDX: Brompheniramine maleate 1 mg, pseudoephedrine hydrochloride 12.5 mg, and dextromethorphan hydrobromide 3 mg per 1 mL (30 mL) [alcohol free, sugar free; contains sodium benzoate; grape flavor]

Bromhist DM, PediaHist DM: Brompheniramine maleate 1 mg, pseudoephedrine hydrochloride 15 mg, and dextromethorphan hydrobromide 4 mg per 1 mL (30 mL) [grape flavor]

Bromhist PDX, EndaCof-PD: Brompheniramine maleate 1 mg, pseudoephedrine hydrochloride 12.5 mg, and dextromethorphan hydrobromide 3 mg per 1 mL (30 mL) [grape flavor]

Histacol™ BD: Brompheniramine maleate 1 mg, pseudoephedrine hydrochloride 12.5 mg, and dextromethorphan hydrobromide 3 mg per 1 mL (30 mL) [contains sodium benzoate; grape flavor]

Suspension: Brompheniramine tannate 8 mg, pseudoephedrine tannate 90 mg, and dextromethorphan tannate 60 mg per 5 mL (480 mL)

Anaplex® DMX: Brompheniramine tannate 8 mg, pseudoephedrine tannate 90 mg, and dextromethorphan tannate 60 mg per 5 mL (480 mL) [alcohol free, sugar free; grape flavor]

Syrup: Brompheniramine maleate 4 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg per 5 mL (480 mL)

Anaplex® DM: Brompheniramine maleate 4 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; fruit flavor]

Andehist DM NR: Brompheniramine maleate 4 mg, pseudoephedrine hydrochloride 45 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [grape flavor]

Bromatane DX, Brometane DX [DSC]: Brompheniramine maleate 2 mg, pseudoephedrine hydrochloride 30 mg, and dextromethorphan hydrobromide 10 mg per 5 mL (480 mL)

Bromphenex DM: Brompheniramine maleate 4 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; fruit flavor]

Carbofed DM: Brompheniramine maleate 4 mg, pseudoephedrine hydrochloride 45 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [alcohol free, sugar free; grape flavor]

EndaCof-DM: Brompheniramine maleate 4 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; fruit flavor]

Myphetane DX: Brompheniramine maleate 2 mg, pseudoephedrine hydrochloride 30 mg, and dextromethorphan hydrobromide 10 mg per 5 mL (480 mL) [contains alcohol <1%; butterscotch flavor]

Sildec-DM: Brompheniramine maleate 4 mg, pseudoephedrine hydrochloride 45 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [grape flavor]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Syrup (Bromaxefed DM RF)

45-4-15 mg/5 mL (118): $18.00

Syrup (Rondec DM)

45-4-15 mg/5 mL (480): $103.10

Mechanism of ActionBrompheniramine maleate is an antihistamine with H_1-receptor activity; pseudoephedrine, a sympathomimetic amine and isomer of ephedrine, acts as a decongestant in respiratory tract mucous membranes with less vasoconstrictor action than ephedrine in normotensive individuals; dextromethorphan, a non-narcotic antitussive, increases cough threshold by its activity on the medulla oblongata.

Related Information

- Dextromethorphan
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause CNS stimulation, insomnia, dizziness, hallucinations, irritability, nervousness, and drowsiness

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors

Index TermsDextromethorphan Hydrobromide, Brompheniramine Maleate, and Pseudoephedrine Hydrochloride; Pseudoephedrine Tannate, Dextromethorphan Tannate, and Brompheniramine Tannate

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Brompheniramine and Pseudoephedrine

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state "Do not use in children under four years of age." In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, "Infant Deaths Associated with Cough and Cold Medications - Two States, 2005," *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Bromfed® may be confused with Bromphen®

Pronunciation(brome fen IR a meen & soo doe e FED rin)

U.S. Brand NamesAccuHist®; Andehist NR Syrup; Bromaline® [OTC]; Bromfenex® PD [DSC]; Bromfenex® [DSC]; Bromhist Pediatric; Bromhist-NR; Brotapp; Brovex SR; Dimaphen [OTC]; Histex® SR; Lodrane® 12D; Lodrane® 24D; Lodrane® D; Lodrane® [DSC]; LoHist 12D; LoHist LQ; LoHist PD; Respahist®; Sildec Syrup; Touro® Allergy

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporary relief of symptoms of seasonal and perennial allergic rhinitis, and vasomotor rhinitis, including nasal obstruction

Dosing: AdultsRhinitis and nasal congestion: Oral:

Capsule, long acting:

Based on 60 mg pseudoephedrine: 1-2 capsules every 12 hours

Based on 120 mg pseudoephedrine: 1 capsule every 12 hours

Liquid:

Based on brompheniramine 1 mg/pseudoephedrine 15 mg per 5 mL: 20 mL every 4 hours (maximum: 4 doses/24 hours)

Based on brompheniramine 4 mg/pseudoephedrine 30 mg: 5 mL 3 times/day

Brompheniramine 4 mg/pseudoephedrine 45 mg per 5 mL: 5 mL 4 times/day

Tablet, extended release: Based on pseudoephedrine 45 mg: 1-2 tablets every 12 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRhinitis/nasal congestion: Oral:

Capsule, long acting:

Based on 60 mg pseudoephedrine:

Children 6-12 years: 1 capsule every 12 hours

Children ≥12 years: Refer to adult dosing.

Based on 120 mg pseudoephedrine: Children ≥12 years: Refer to adult dosing.

Liquid:

Based on brompheniramine 1 mg/pseudoephedrine 15 mg per 1 mL: Children:

1-3 months: 0.25 mL 4 times/day

3-6 months: 0.5 mL 4 times/day

6-12 months: 0.75 mL 4 times/day

12-24 months: 1 mL 4 times/day

Based on brompheniramine 1 mg/pseudoephedrine 15 mg per 5 mL: Children:

6-11 months (6-8 kg): 2.5 mL every 6-8 hours (maximum: 4 doses/24 hours)

12-23 months (8-10 kg): 3.75 mL every 6-8 hours (maximum: 4 doses/24 hours)

2-6 years: 5 mL every 6-8 hours (maximum: 4 doses/24 hours)

6-12 years: 10 mL every 6-8 hours (maximum: 4 doses/24 hours)

>12 years: Refer to adult dosing.

Based on brompheniramine 4 mg/pseudoephedrine 30 mg:

Children 2-6 years: 2.5 mL 3 times/day

Children >6 years: Refer to adult dosing.

Brompheniramine 4 mg/pseudoephedrine 45 mg per 5 mL:

Children 2-6 years: 2.5 mL 4 times/day

Children >6 years: Refer to adult dosing.

Tablet, extended release: Based on pseudoephedrine 45 mg:

Children 6-12 years: 1 tablet every 12 hours

Children ≥12 years: Refer to adult dosing.

Administration: OralDo not crush, break, or chew sustained-release dosage forms.
StorageStore at room temperature.
ContraindicationsHypersensitivity or idiosyncrasy to brompheniramine, pseudoephedrine, or any component of the formulation; severe hypertension, severe coronary artery disease; MAO inhibitor therapy; GI or GU obstruction; peptic ulcer disease; narrow-angle glaucoma; acute asthmatic attack
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Asthma: Use with caution in patients with a history of asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children. Not labeled for OTC use in children <6 years of age.

Other warnings/precautions:

- Self-medication (OTC use): When used for self-medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever. Discontinue and contact healthcare provider if nervousness, dizziness, or sleeplessness occur.

Pregnancy Risk FactorC
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsSmall amounts of antihistamines and pseudoephedrine are excreted in breast milk. Premature infants and newborns have a higher risk of intolerance to antihistamines. Antihistamines may inhibit lactation.
Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, flushing, hypertension, pallor, palpitation, tachycardia

Central nervous system: Convulsions, CNS stimulation, dizziness, excitability (children; rare), giddiness, hallucinations, headache, insomnia, irritability, lassitude, nervousness, sedation

Gastrointestinal: Anorexia, diarrhea, dyspepsia, nausea, vomiting, xerostomia

Neuromuscular skeletal: Tremors, weakness

Ocular: Diplopia

Renal: Dysuria, polyuria, urinary retention (with BPH)

Respiratory: Respiratory difficulty

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet, extended release:

Histex® SR: Brompheniramine maleate 10 mg and pseudoephedrine hydrochloride 120 mg

Capsule, extended release:

Bromfenex®: Brompheniramine maleate 12 mg and pseudoephedrine hydrochloride 120 mg [DSC]

Bromfenex® PD: Brompheniramine maleate 6 mg and pseudoephedrine hydrochloride 60 mg [DSC]

Lodrane® 24D: Brompheniramine maleate 12 mg and pseudoephedrine hydrochloride 90 mg

Capsule, sustained release:

Brovex SR: Brompheniramine maleate 9 mg and pseudoephedrine hydrochloride 90 mg

Respahist®: Brompheniramine maleate 6 mg and pseudoephedrine hydrochloride 60 mg

Touro® Allergy: Brompheniramine maleate 5.75 mg and pseudoephedrine hydrochloride 60 mg [DSC]

Elixir:

Dimaphen: Brompheniramine maleate 1 mg and pseudoephedrine hydrochloride 15 mg per 5 mL (120 mL, 480 mL)

Liquid: Brompheniramine maleate 4 mg and pseudoephedrine hydrochloride 60 mg per 5 mL (480 mL)

Brotapp: Brompheniramine maleate 1 mg and pseudoephedrine hydrochloride 15 mg per 5 mL (120 mL, 240 mL, 480 mL) [grape flavor]

Lodrane®: Brompheniramine maleate 4 mg and pseudoephedrine hydrochloride 60 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; cherry flavor] [DSC]

LoHist LQ: Brompheniramine maleate 4 mg and pseudoephedrine hydrochloride 60 mg per 5 mL (480 mL) [cherry flavor]

Liquid, oral [drops]:

AccuHist®: Brompheniramine maleate 1 mg and pseudoephedrine hydrochloride 12.5 mg per 1 mL (30 mL) [sugar free; cherry flavor]

Bromhist NR: Brompheniramine maleate 1 mg and pseudoephedrine hydrochloride 12.5 mg per 1 mL (30 mL) [cherry flavor]

Bromhist Pediatric: Brompheniramine maleate 1 mg and pseudoephedrine hydrochloride 15 mg per 1 mL (30 mL) [cherry flavor]

LoHist PD: Brompheniramine maleate 1 mg and pseudoephedrine hydrochloride 12.5 mg per 1 mL (30 mL) [cherry flavor]

Solution:

Bromaline®: Brompheniramine maleate 1 mg and pseudoephedrine hydrochloride 15 mg per 5 mL (120 mL, 480 mL) [alcohol free; contains sodium benzoate; grape flavor]

Suspension:

Lodrane® D: Brompheniramine tannate 8 mg and pseudoephedrine tannate 90 mg per 5 mL (480 mL) [alcohol free, sugar free; strawberry flavor]

Syrup:

Andehist NR: Brompheniramine maleate 4 mg and pseudoephedrine sulfate 45 mg per 5 mL (473 mL) [raspberry flavor]

Sildec: Brompheniramine maleate 4 mg and pseudoephedrine hydrochloride 45 mg per 5 mL (480 mL) [raspberry flavor]

Tablet, extended release:

Lodrane® 12D: Brompheniramine maleate 6 mg and pseudoephedrine hydrochloride 45 mg [dye free]

LoHist 12D: Brompheniramine maleate 6 mg and pseudoephedrine hydrochloride 45 mg

Tablet, prolonged release:

Touro® Allergy: Brompheniramine maleate 6 mg and pseudoephedrine hydrochloride 45 mg

Tablet, sustained release: Brompheniramine maleate 6 mg and pseudoephedrine hydrochloride 45 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Syrup (Bromaxefed RF)

4-45 mg/5 mL (473): $39.97

Tablet, 12-hour (Lodrane 12D)

6-45 mg (30): $12.81

Mechanism of ActionBrompheniramine maleate is an antihistamine with H_1-receptor activity; pseudoephedrine, a sympathomimetic amine and isomer of ephedrine, acts as a decongestant in respiratory tract mucous membranes with less vasoconstrictor action than ephedrine in normotensive individuals.

Pharmacodynamics/Kinetics

See Pseudoephedrine.

Brompheniramine:

Metabolism: Hepatic

Time to peak: Syrup: 5 hours

Excretion: Urine

Related Information

- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Brompheniramine: Prolonged use may decrease salivary flow.

Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDrowsiness, nervousness, insomnia, and slight stimulation are common; may cause fatigue or dizziness; may rarely cause depression or hallucinations

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics and other CNS depressants may produce additive adverse effects; tachycardia is common; use caution with clozapine and TCAs

Index TermsBrompheniramine Maleate and Pseudoephedrine Hydrochloride; Brompheniramine Maleate and Pseudoephedrine Sulfate; Pseudoephedrine and Brompheniramine

International Brand NamesDimetapp (MX)

English English

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state "Do not use in children under four years of age." In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, "Infant Deaths Associated with Cough and Cold Medications - Two States, 2005," *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(brome fen IR a meen)

U.S. Brand NamesB-Vex; Bidhist; BroveX™; BroveX™ CT ; Lodrane® 12 Hour ; Lodrane® 24; Lodrane® XR ; LoHist-12; TanaCof-XR

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of perennial and seasonal allergic rhinitis, vasomotor rhinitis, and other respiratory allergies

Dosing: AdultsAllergic rhinitis, allergic symptoms, vasomotor rhinitis: Oral:

B-Vex, BroveX™: 5-10 mL every 12 hours (maximum: 20 mL/day)

BroveX™ CT: 1-2 tablets every 12 hours (maximum: 4 tablets/day)

Lodrane® 12 Hour, LoHist: 1-2 tablets every 12 hours (maximum: 4 tablets/day)

Lodrane® 24: 1-2 capsules once daily

Lodrane® XR, TanaCof-XR: 5 mL every 12 hours (maximum: 10 mL/day)

Dosing: Elderly

Initial (also refer to adult dosing):

- B-Vex, BroveX™: 5 mL every 12 hours
- BroveX™ CT, Lodrane® 12 Hour, LoHist: 1 tablet every 12 hours
- Lodrane® 24: 1 capsule/24 hours
- Lodrane® XR, TanaCof-XR: 2.5 mL every 12 hours

Dosing: PediatricAllergic rhinitis, allergic symptoms, vasomotor rhinitis: Oral: Children:

1-2 years (B-Vex, BroveX™): 1.25 mL every 12 hours (maximum: 2.5 mL/day)

2-6 years:

- B-Vex, BroveX™: 2.5 mL every 12 hours (maximum: 5 mL/day)
- BroveX™ CT: $^1/_2$ tablet every 12 hours (maximum: 1 tablet/day)
- Lodrane® XR, TanaCof-XR: 1.25 mL every 12 hours (maximum: 2.5 mL/day)

6-12 years:

- B-Vex, BroveX™: 5 mL every 12 hours (maximum: 10 mL/day)
- BroveX™ CT: $^1/_2$ to 1 tablet every 12 hours (maximum: 2 tablets/day)
- Lodrane® 12 Hour, LoHist-12: One tablet every 12 hours (maximum: 2 tablets/day)
- Lodrane® 24: One capsule once daily
- Lodrane® XR, TanaCof-XR: 2.5 mL every 12 hours (maximum: 5 mL/day)

>12 years (B-Vex, BroveX™, BroveX™ CT, Lodrane® 12 Hour, Lodrane® 24, Lodrane® XR, LoHist-12, TanaCof-XR): Refer to adult dosing.

Administration: OralExtended release tablets are to be swallowed whole; do not crush or chew.

Dietary ConsiderationsMay be taken with food, water, or milk. TanaCof-XR contains phenylalanine.

StorageStore between 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to brompheniramine or any component of the formulation; use with or within 14 days of MAO inhibitor therapy; narrow-angle glaucoma; urinary retention; peptic ulcer disease; during acute asthmatic attacks

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Asthma: Use with caution in patients with a history of asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.
- Tartrazine: Some products may contain tartrazine.

Geriatric ConsiderationsAnticholinergic action may cause significant confusional symptoms, constipation, or problems voiding urine. If an antihistamine is indicated, a second generation nonsedating antihistamine would be a more appropriate choice.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use in pregnancy only when clearly needed. May cause severe reactions (convulsions) in newborns and premature infants; avoid use in 3rd trimester.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsSome antihistamines are excreted in breast milk. Premature infants and newborns have a higher risk of intolerance to antihistamines. Use while breast-feeding is contraindicated by the manufacturer.

Adverse ReactionsFrequency not defined.

Cardiovascular: Angina, blood pressure increased, circulatory collapse, extrasystoles, hypotension, palpitation, tachycardia

Central nervous system: Anxiety, chills, confusion, coordination impaired, dizziness, drowsiness, euphoria, excitation, fatigue, headache, hysteria, insomnia, irritability, nervousness, neuritis, restlessness, sedation, seizure, sleepiness, stimulation, tension, vertigo

Dermatologic: Photosensitivity, rash, urticaria

Endocrine & metabolic: Early menses

Gastrointestinal: Abdominal cramps, anorexia, constipation, diarrhea, dry throat, epigastric distress, nausea, vomiting, xerostomia

Genitourinary: Dysuria, polyuria, urinary retention

Hematologic: Agranulocytosis, hemolytic anemia, hypoplastic anemia, thrombocytopenia

Neuromuscular & skeletal: Paresthesia, tremor, weakness

Ocular: Blurred vision, diplopia, mydriasis

Otic: Labyrinthitis (acute), tinnitus

Respiratory: Dry nose, nasal congestion, thickening of bronchial secretions, wheezing

Miscellaneous: Anaphylactic shock, diaphoresis

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Test InteractionsMay interfere with skin tests using allergen extracts.

Nursing: Physical Assessment/MonitoringMonitor therapeutic response and adverse reactions. Assess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Patient EducationInform prescriber of all prescription medications, OTC medications, or herbal products you are taking. Avoid alcohol, depressants, and sleep inducing medication unless approved by prescriber. You may experience drowsiness or dizziness (use caution when driving or engaging in activities requiring alertness until response to drug is known). Report persistent sedation, confusion, or agitation; changes in urinary pattern, blurred vision, chest pain, rapid heart beat, or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release:

Lodrane® 24: 12 mg [dye free]

Suspension, as tannate:

B-Vex, BroveX™: 12 mg/5 mL (120 mL) [contains sodium benzoate and tartrazine; banana flavor]

Lodrane® XR: 8 mg/5 mL (480 mL) [alcohol free, sugar free; strawberry flavor]

TanaCof-XR: 8 mg/5 mL (480 mL) [alcohol free, sugar free; contains phenylalanine; strawberry creme flavor]

Tablet, chewable, as tannate: 12 mg

BroveX™ CT: 12 mg [banana flavor]

Tablet, extended release, as maleate:

Bidhist: 6 mg

Tablet, extended release, as maleate [scored]:

Lodrane® 12 Hour, LoHist-12: 6 mg [dye free]

Tablet, timed release, as maleate: 6 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Lodrane 24)

12 mg (60): $59.99

Chewable (Brovex CT)

12 mg (60): $79.99

Tablet, 12-hour (Lodrane 12 Hour)

6 mg (100): $47.22

Mechanism of ActionCompetes with histamine for H_1-receptor sites on effector cells

Pharmacodynamics/Kinetics

Metabolism: Hepatic

Excretion: Urine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Chronic use of antihistamines will inhibit salivary flow, particularly in elderly patients; this may contribute to periodontal disease and oral discomfort.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause agitation, confusion, dizziness, drowsiness, or fatigue. May cause paradoxical excitation in pediatric patients; may cause hallucinations in overdose.

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive anticholinergic and/or sedative effects; monitor

Index TermsBrompheniramine Maleate; Brompheniramine Tannate

Budesonide and Formoterol

Lexi-Drugs Online

English

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(byoo DES oh nide & for MOH te rol)

U.S. Brand NamesSymbicort®

Canadian Brand NamesSymbicort®

Pharmacologic CategoryBeta$_2$ Agonist; Beta$_2$ Agonist, Long-Acting; Corticosteroid, Inhalant (Oral)

Use: Labeled IndicationsTreatment of asthma in patients ≥12 years of age where combination therapy is indicated

Use: Unlabeled/InvestigationalTreatment of asthma in children 5-11 years of age where combination therapy is indicated

Dosing: Adults**Asthma:** Oral inhalation:

U.S. labeling: Symbicort® 80/4.5, Symbicort® 160/4.5: 2 inhalations twice daily. Patients currently receiving a low-to-medium dose inhaled corticosteroid may be started on the lower strength combination; those receiving a medium-to-high dose inhaled corticosteroid may be started on the higher strength combination. Consider the higher dose combination for patients not adequately controlled on the lower combination following 1-2 weeks of therapy. Do not use more than 2 inhalations twice daily of either strength.

Canadian labeling:

Symbicort® 100 Turbuhaler® [CAN; not available in U.S.], Symbicort® 200 Turbuhaler® [CAN; not available in U.S.]:

Initial: 1-2 inhalations twice daily until symptom control, then titrate to lowest effective dosage to maintain control

Maintenance: 1-2 inhalations once or twice daily (maximum: 8 inhalations/day as temporary treatment in periods of worsening asthma)

Symbicort® Maintenance and Reliever Therapy (Symbicort® SMART): **Note:** Not approved in the U.S.:

Maintenance: Symbicort® 100 Turbuhaler® [CAN] **or** Symbicort® 200 Turbuhaler® [CAN]: 1-2 inhalations twice daily **or** 2 inhalations once daily

Reliever therapy: Symbicort® 100 Turbuhaler [CAN] **or** Symbicort® 200 Turbuhaler® [CAN.]: 1 additional inhalation as needed, may repeat if no relief for up to 6 inhalations total (maximum: 8 inhalations/day)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Asthma:**Oral inhalation:

Children 5-11 years (NIH Guidelines): Symbicort® 80/4.5: 2 inhalations twice daily. Do not exceed 4 inhalations per day.

Children ≥12 years: Refer to adult dosing.

Administration: Inhalation

Symbicort® 80/4.5, Symbicort® 160/4.5: Prior to first use, inhaler must be primed by releasing 2 test sprays into the air; shake well for 5 seconds before each spray. Inhaler must be reprimed if not used for >7 days or if it has been dropped. Shake well for 5 seconds before each use. Discard inhaler after the labeled number of inhalations have been used or within 3 months after removal from foil pouch (do not use the “float test” to determine amount remaining in canister).

Symbicort® Turbuhaler® [CAN; not available in U.S.]:

To “load” inhaler: Turn grip on inhaler as far as it will move in one direction, then turn in opposite direction as far as it will go (inhaler is “loaded” with a dose, indicated by a “click”). Prior to first use, this procedure should be done twice, it does not need to be repeated with subsequent uses even when not used regularly.

Delivery of dose: Instruct patient to place mouthpiece gently between teeth, closing lips around inhaler. Instruct patient to inhale deeply and hold breath held for 5-10 seconds. The amount of drug delivered is small, and the individual will not sense the medication as it is inhaled. Remove mouthpiece prior to exhalation. Patient should not breathe out through the mouthpiece. After use of the inhaler, patient should rinse mouth/oropharynx with water and spit out rinse solution.

Storage

Symbicort® 80/4.5, Symbicort® 160/4.5: Store at room temperature of 20°C to 25°C (68°F to 77°F) with mouthpiece down. Discard inhaler after the labeled number of inhalations have been used or within 3 months after removal from foil pouch.

Symbicort® Turbuhaler®: Store at room temperature of 15°C to 30°C. Protect from heat and moisture.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to adrenergic amines, formoterol, budesonide, or any component of the formulation; need for acute bronchodilation (including status asthmaticus)

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Boxed warnings:

- Asthma-related deaths: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections. Do not use this product to transfer patients from oral corticosteroid therapy.

- Asthma-related deaths: **[U.S. Boxed Warning]: Long-acting beta$_2$-agonists may increase the risk of asthma-related deaths.** In a large, randomized clinical trial (SMART, 2006), salmeterol was associated with a small, but statistically significant increase in asthma-related deaths (when added to usual asthma therapy); risk may be greater in African-American patients versus Caucasians.

- Bone density: Long-term use may affect bone mineral density in adults.

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.

- Hypersensitivity reactions: Immediate hypersensitivity reactions (urticaria, angioedema, rash, bronchospasm) have been reported.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox should be avoided; corticosteroids should not be used to treat ocular herpes simplex. Corticosteroids should not be used for cerebral malaria. Close observation is required in patients with latent tuberculosis and/or TB reactivity. Restrict use in active TB (only in conjunction with antituberculosis treatment).

- Oral candidiasis: Infections with *Candida albicans* in the mouth and throat (thrush) have been reported with use.

- Serious effects/fatalities: Do not exceed recommended dose; serious adverse events, including fatalities, have been associated with excessive use of inhaled sympathomimetics.

Disease-related concerns:

- Asthma: Appropriate use: Should only be used as adjuvant therapy in patients not adequately controlled on other asthma-controller medications. Formoterol is generally not meant to relieve acute asthmatic symptoms or to relieve rapidly-deteriorating symptoms. Acute episodes should be treated with short-acting beta$_2$ agonist.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (arrhythmia or hypertension or HF); beta agonists may cause elevation in blood pressure, heart rate and result in CNS stimulation/excitation. Beta$_2$ agonists may also increase risk of arrhythmias.

- Diabetes: Use with caution in patients with diabetes mellitus; beta$_2$ agonists may increase serum glucose.

- Hypokalemia: Use with caution in patients with hypokalemia; beta$_2$ agonists may decrease serum potassium.

- Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Consider routine eye exams in chronic users.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Seizure disorders: Use with caution in patients with seizure disorders; beta agonists may result in CNS stimulation/excitation.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Pediatrics: Orally-inhaled and intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients (~1 centimeter per year [range 0.3-1.8 cm per year] and related to dose and duration of exposure). To minimize the systemic effects of orally-inhaled and intranasal corticosteroids, each patient should be titrated to the lowest effective dose. Growth should be routinely monitored in pediatric patients.

Dosage form specific issues:

- Lactose: Some products (available in Canada) contain lactose; very rare anaphylactic reactions have been reported in patients with severe milk protein allergy.

Other warnings/precautions:

- Discontinuation of therapy: Withdraw systemic therapy with gradual tapering of dose. There have been reports of systemic corticosteroid withdrawal symptoms (eg, joint/muscle pain, lassitude, depression) when withdrawing oral inhalation therapy.

- Patient information: Patients must be instructed to seek medical attention in cases where acute symptoms are not relieved by short-acting beta-agonist (not formoterol) or a previous level of response is diminished. Treatment must not be delayed. Patients using inhaled, short acting beta$_2$ agonists should be instructed to discontinue routine use of these medications prior to beginning treatment with Symbicort®; short acting agents should be reserved for symptomatic relief of acute symptoms. Patients should not use additional long-acting beta$_2$-adrenergic agonists.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic and embryocidal effects were observed in animal studies when administered by inhalation at doses less than the maximum equivalent human dose. Also see individual agents.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**Note:** Percentage of adverse events may be dose related; causation not established. Also see individual agents.

>10%:

Central nervous system: Headache (7% to 11%)

Respiratory: Nasopharyngitis (10% to 11%), upper respiratory tract infections (8% to 11%)

3% to 10%:

Gastrointestinal: Stomach discomfort (1% to 7%), oral candidiasis (1% to 3%), vomiting (1% to 3%)

Neuromuscular & skeletal: Back pain (2% to 3%)

Respiratory: Pharyngolaryngeal pain (6% to 9%), sinusitis (5% to 6%), bronchitis (<4%), cough (<4%), nasal congestion (3%), influenza (2% to 3%)

≥1% to <3%: Abdominal pain (upper), allergic rhinitis, arthralgia, asthma, bronchitis, diarrhea, dizziness, dyspepsia, dysphonia, gastroenteritis (viral), lower respiratory tract infection, migraine, muscle spasms, myalgia, nausea, pain (extremity), palpitation, pharyngitis, post procedural pain, pyrexia, rhinitis, sinus congestion, sinus headache, tension headache, tremor, urinary tract infection

<1%, postmarketing, and/or case reports: Agitation, anaphylaxis, anxiety, atrial arrhythmia, bronchospasm, bruising, cataract, coronary ischemia, depression, glaucoma, hyper-/hypocorticism symptoms, hyper-/hypotension, hyperglycemia, hypersensitivity reactions, hypertensive crisis, hypokalemia, irritability, nervousness, psychiatric symptoms (eg, aggression, behavioral disturbances, psychosis), restlessness, tachycardia, taste disturbance, ventricular arrhythmia

Metabolism/Transport Effects

Budesonide: **Substrate** (minor) of CYP3A4

Formoterol: **Substrate** (minor) of CYP2A6, 2C9, 2C19, 2D6

Drug Interactions

Alpha-/Beta-Blockers: May diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Amphotericin B: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Orally Inhaled) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Orally Inhaled). *Risk C: Monitor therapy*

Atomoxetine: May enhance the tachycardic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Betahistine: May diminish the therapeutic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Loop Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Corticosteroids (Orally Inhaled). *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Monitoring ParametersPeak flow meter and/or other pulmonary function tests; monitor growth in pediatric patients, symptom relief, monitor for increased use if short-acting beta$_2$-adrenergic agonists (may be a sign of asthma deterioration)

Monitoring: Lab TestsPeak flow meter; growth (in pediatric patients)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian product

Aerosol for oral inhalation:

Symbicort® 80/4.5: Budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg per actuation (6.9 g) [60 metered inhalations]; budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg per actuation (10.2 g) [120 metered inhalations]

Symbicort® 160/4.5: Budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg per actuation (6 g) [60 metered inhalations]; budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg per actuation (10.2 g) [120 metered inhalations]

Powder for oral inhalation:

Symbicort® 100 Turbuhaler® [CAN]: Budesonide 100 mcg and formoterol dihydrate 6 mcg per inhalation (available in 60 or 120 metered doses) [delivers ~80 mcg budesonide and 4.5 mcg formoterol per inhalation; contains lactose] [not available in the U.S]

Symbicort® 200 Turbuhaler® [CAN]: Budesonide 200 mcg and formoterol dihydrate 6 mcg per inhalation (available in 60 or 120 metered doses) [delivers ~160 mcg budesonide and 4.5 mcg formoterol per inhalation; contains lactose] [not available in the U.S]

Pricing: U.S. (www.drugstore.com)

Aerosol (Symbicort)

80-4.5 mcg/ACT (6.9): $114.09

80-4.5 mcg/ACT (10.2): $163.79

160-4.5 mcg/ACT (10.2): $192.73

Mechanism of ActionFormoterol relaxes bronchial smooth muscle by selective action on beta$_2$ receptors with little effect on heart rate. Formoterol has a long-acting effect. Budesonide is a corticosteroid which controls the rate of protein synthesis, depresses the migration of polymorphonuclear leukocytes/fibroblasts, reverses capillary permeability and lysosomal stabilization at the cellular level to prevent or control inflammation.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Budesonide
- Formoterol

Pharmacotherapy PearlsEffects of inhaled/intranasal steroids on growth have been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally-inhaled and intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Formoterol: Xerostomia (normal salivary flow resumes upon discontinuation). Localized infections with *Candida albicans* or *Aspergillus niger* have occurred frequently in the mouth and pharynx with repetitive use of oral inhaler of corticosteroids. These infections may require treatment with appropriate antifungal therapy or discontinuance of treatment with corticosteroid inhaler.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness, dizziness, or insomnia

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment. Concurrent use with TCAs, pimozide, thioridazine, or mesoridazine may potentiate cardiovascular effects.

Index TermsBudesonide and Eformoterol; Eformoterol and Budesonide; Formoterol Fumarate Dihydrate and Budesonide

References

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Pohunek P, Kuna P, Jorup C, et al, “Budesonide/Formoterol Improved Lung Function Compared With Budesonide Alone in Children With Asthma,” *Pediatr Allergy Immunol*, 2006, 17(6):458-65.[PubMed 16925692]

International Brand NamesSymbicort Turbohaler (BE, DE, GB, IE); Symbicort Turbuhaler (AR, AU, BG, BR, CH, CL, CN, CO, CR, CZ, DK, DO, EE, FI, FR, GT, HK, HN, ID, IL, IT, KP, MY, NI, PA, PE, PH, PT, PY, SE, SG, SV, TH, TW, UY, VE); Symbiocort Turbuhaler (ES, MX); Vent FB Inhaler (IN)

Budesonide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(byoo DES oh nide)

U.S. Brand NamesEntocort® EC; Pulmicort Flexhaler™; Pulmicort Respules®; Rhinocort® Aqua®

Canadian Brand NamesEntocort®; Gen-Budesonide AQ; Pulmicort®; Rhinocort® Aqua™; Rhinocort® Turbuhaler®

Pharmacologic CategoryCorticosteroid, Inhalant (Oral); Corticosteroid, Nasal; Corticosteroid, Systemic

Use: Labeled Indications

Intranasal: Management of symptoms of seasonal or perennial rhinitis

Canadian labeling: Additional use (not in U.S. labeling): Prevention and treatment of nasal polyps

Nebulization: Maintenance and prophylactic treatment of asthma

Oral capsule: Treatment of active Crohn's disease (mild-to-moderate) involving the ileum and/or ascending colon; maintenance of remission (for up to 3 months) of Crohn's disease (mild-to-moderate) involving the ileum and/or ascending colon

Oral inhalation: Maintenance and prophylactic treatment of asthma; includes patients who require oral corticosteroids and those who may benefit from systemic dose reduction/elimination

Dosing: Adults

Asthma:*Oral inhalation:*

Pulmicort Flexhaler™: Initial: 360 mcg twice daily (selected patients may be initiated at 180 mcg twice daily); maximum 720 mcg twice daily

NIH Asthma Guidelines (NIH, 2007) (administer in divided doses twice daily):

"Low" dose: 180-600 mcg/day

"Medium" dose: >600-1200 mcg/day

"High" dose: >1200 mcg/day

Pulmicort® Turbuhaler®: [CAN, not available in the U.S.]: Initial (during periods of severe asthma or when switching from oral corticosteroid therapy): 400-2400 mcg daily in 2-4 divided doses; Maintenance: 200-400 mcg twice daily (higher doses may be needed for short periods of time). **Note:** Patients taking 400 mcg/day may take as a single daily dose

Crohn's disease (active):*Oral:* 9 mg once daily in the morning for up to 8 weeks; recurring episodes may be treated with a repeat 8-week course of treatment. **Note:** Patients receiving CYP3A4 inhibitors should be monitored closely for signs and symptoms of hypercorticism; dosage reduction may be required. If switching from oral prednisolone, prednisolone dosage should be tapered while budesonide (Entocort™ EC) treatment is initiated.

Maintenance of remission: Following treatment of active disease (control of symptoms with CDAI <150), treatment may be continued at a dosage of 6 mg once daily for up to 3 months. If symptom control is maintained for 3 months, tapering of the dosage to complete cessation is recommended. Continued dosing beyond 3 months has not been demonstrated to result in substantial benefit.

Nasal polyps:*Nasal inhalation:*

Canadian labeling:

Rhinocort® Aqua®: 256 mcg/day administered as a single 64 mcg spray in each nostril twice daily; maximum dose: 256 mcg/day

Rhinocort® Turbuhaler®: 100 mcg into each nostril twice daily; maximum: 400 mcg/day

Rhinitis:*Nasal inhalation:*

U.S. labeling (Rhinocort® Aqua®): 64 mcg/day as a single 32 mcg spray in each nostril. Some patients who do not achieve adequate control may benefit from increased dosage. A reduced dosage may be effective after initial control is achieved

Maximum dose: Children <12 years: 128 mcg/day; Adults: 256 mcg/day)

Canadian labeling:

Rhinocort® Aqua®: Initial: 256 mcg/day administered as two 64 mcg sprays in each nostril once daily or a single 64 mcg spray in each nostril twice daily; Maintenance: Individualize, lowest effective dose (maximum dose: 256 mcg/day)

Rhinocort® Turbuhaler®: Initial: 200 mcg into each nostril once daily; Maintenance: Individualize, lowest effective dose (maximum: 400 mcg/day)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Asthma:

Oral inhalation:

Pulmicort Flexhaler™: ≥6 years: Initial: 180 mcg twice daily (some patients may be initiated at 360 mcg twice daily); maximum 360 mcg twice daily

NIH Asthma Guidelines (NIH, 2007) (administer in divided doses twice daily):

Children 5-11 years:

“Low” dose: 180-400 mcg/day

“Medium” dose: >400-800 mcg/day

“High” dose: >800 mcg/day

Children ≥12 years: Refer to adult dosing.

Pulmicort® Turbuhaler®: [CAN, not available in the U.S.]: Initial (during periods of severe asthma or when switching from oral corticosteroid therapy): 200-400 mcg daily in 2 divided doses; Maintenance: Individualized, lowest effective dose.

Nebulization: Children 12 months to 8 years: Pulmicort Respules®: Titrate to lowest effective dose once patient is stable; start at 0.25 mg/day or use as follows:

Previous therapy of bronchodilators alone: 0.5 mg/day administered as a single dose or divided twice daily (maximum daily dose: 0.5 mg)

Previous therapy of inhaled corticosteroids: 0.5 mg/day administered as a single dose or divided twice daily (maximum daily dose: 1 mg)

Previous therapy of oral corticosteroids: 1 mg/day administered as a single dose or divided twice daily (maximum daily dose: 1 mg)

NIH Asthma Guidelines (NIH, 2007):

Children 0-4 years:

“Low” dose: 0.25-0.5 mg/day

“Medium” dose: >0.5-1 mg/day

“High” dose: >1 mg/day

Children 5-11 years:

“Low” dose: 0.5 mg/day

“Medium” dose: 1 mg/day

“High” dose: 2 mg/day

Nasal polyps:*Nasal inhalation:*

Canadian labeling: Children ≥6 years: Refer to adult dosing.

Rhinitis:*Nasal inhalation:*

U.S. labeling (Rhinocort® Aqua®): Children ≥6 years: Refer to adult dosing.

Canadian labeling (Rhinocort® Aqua®, Rhinocort® Turbuhaler®): Children ≥6 years: Refer to adult dosing.

Dosing: Hepatic ImpairmentMonitor closely for signs and symptoms of hypercorticism; dosage reduction may be required.

Administration: OralOral capsule: Capsule should be swallowed whole; do not crush or chew.

Administration: Inhalation

Powder for inhalation:

Pulmicort Flexhaler™: Hold inhaler in upright position (mouthpiece up) to load dose. Do not shake prior to use. Unit should be primed prior to first use only. It will not need primed again, even if not used for a long time. Place mouthpiece between lips and inhale forcefully and deeply. Do not exhale through inhaler; do not use a spacer. Dose indicator does not move with every dose, usually only after 5 doses. Discard when dose indicator reads “0”. Rinse mouth with water after each use to reduce incidence of candidiasis.

Pulmicort Turbuhaler® [CAN, not available in the U.S.]: Hold inhaler in upright position (mouthpiece up) to load dose. Do not shake inhaler after dose is loaded. Unit should be primed prior to first use. Place mouthpiece between lips and inhale forcefully and deeply; mouthpiece should face up. Do not exhale through inhaler; do not use a spacer. When a red mark appears in the dose indicator window, 20 doses are left. When the red mark reaches the bottom of the window, the inhaler should be discarded. Rinse mouth with water after use to reduce incidence of candidiasis.

Rhinocort® Turbuhaler® [CAN, not available in the U.S.]: Hold inhaler in upright position and turn grey grip as far as it will go in one direction and then back to original position. Clicking sound means inhaler is loaded with dose and ready for use. Place nasal adapter into nostril and ensure firm fit. Cover opposite nostril with finger and inhale (sniff) quickly and forcefully. Do not exhale through inhaler. When a red mark appears in the dose indicator window, 20 doses are left. When the red mark reaches the bottom of the window, the inhaler should be discarded

Suspension for nebulization: Shake well before using. Use Pulmicort Respules® with jet nebulizer connected to an air compressor; administer with mouthpiece or facemask. Do not use ultrasonic nebulizer. Do not mix with other medications in nebulizer. Rinse mouth following treatments to decrease risk of oral candidiasis (wash face if using face mask).

Suspension for nasal inhalation: Shake gently before use. Prime before first use; discard after 120 sprays.

Dietary Considerations Avoid grapefruit juice when using oral capsules.

Storage

Suspension for nebulization: Store upright at 20°C to 25°C (68°F to 77°F). Protect from light. Do not refrigerate or freeze. Once aluminum package is opened, solution should be used within 2 weeks. Continue to protect from light.

Nasal inhaler: Store with valve up at 15°C to 30°C (59°F to 86°F). Protect from high humidity.

Nasal spray: Store with valve up at 20°C to 25°C (68°F to 77°F); do not freeze. Protect from light.

Oral inhaler (Pulmicort Flexhaler™): Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from moisture.

Contraindications Hypersensitivity to budesonide or any component of the formulation

Inhalation: Contraindicated in primary treatment of status asthmaticus, acute episodes of asthma; not for relief of acute bronchospasm

Canadian labeling: Additional contraindications (not in U.S. labeling): Moderate-to-severe bronchiectasis, pulmonary tuberculosis (active or quiescent), untreated respiratory infection (bacterial, fungal, or viral); use of Rhinocort® Aqua™ and Rhinocort® Turbuhaler® in patients <6 years of age

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections. Do not use this product to transfer patients directly from oral corticosteroid therapy.

- Bronchospasm: May occur with wheezing after inhalation; if this occurs stop steroid and treat with a fast-acting bronchodilator (eg, albuterol).

- Delayed wound healing: Avoid nasal corticosteroid use in patients with recent nasal septal ulcers, nasal surgery or nasal trauma until healing has occurred.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox should be avoided; corticosteroids should not be used to treat ocular herpes simplex. Corticosteroids should not be used for cerebral malaria or viral hepatitis. Close observation is required in patients with latent tuberculosis and/or TB reactivity restrict use in active TB (only in conjunction with antituberculosis treatment).

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Local oral infections: *Candida albicans* infections may occur in the mouth and pharynx; rinsing (and spitting) with water after inhaler use may decrease risk.

- Myopathy: Acute myopathy has been reported with high-dose corticosteroids, usually in patients with neuromuscular transmission disorders; may involve ocular and/or respiratory muscles; monitor creatine kinase; recovery may be delayed.

- Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

Disease-related concerns:

- Asthma: Supplemental steroids (oral or parenteral) may be needed during stress or severe asthma attacks. Not to be used in status asthmaticus or for the relief of acute bronchospasm.

- Cardiovascular disease: Use with caution in patients with HF or hypertension; long-term use has been associated with fluid retention and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.

- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids.

- Myocardial infarct (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Consider routine eye exams in chronic users.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Elderly: Because of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly in the smallest possible effective dose for the shortest duration.

- Pediatrics: Orally-inhaled and intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients (~1 centimeter per year [range 0.3-1.8 cm per year] and related to dose and duration of exposure). To minimize the systemic effects of orally-inhaled and intranasal corticosteroids, each patient should be titrated to the lowest effective dose. Growth should be routinely monitored in pediatric patients.

Dosage form specific issues:

- Lactose: Pulmicort Flexhaler™ contains lactose; very rare anaphylactic reactions have been reported in patients with severe milk protein allergy.

Other warnings/precautions:

- Discontinuation of therapy: Withdraw systemic therapy with gradual tapering of dose. There have been reports of systemic corticosteroid withdrawal symptoms (eg, joint/muscle pain, lassitude, depression) when withdrawing oral inhalation therapy.

Geriatric ConsiderationsEnsure that patients can correctly use nasal inhaler.
Pregnancy Risk FactorC (capsule)/B (inhalation)
Pregnancy ConsiderationsAdverse events have been observed with corticosteroids in animal reproduction studies. Studies of pregnant women using inhaled budesonide have not demonstrated an increased risk of abnormalities. Some studies have shown an association between first trimester systemic corticosteroid use and oral clefts; adverse events in the fetus/neonate have been noted in case reports following large doses of systemic corticosteroids during pregnancy. Budesonide is the preferred inhaled corticosteroid for the treatment of asthma in pregnant women.
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsFollowing use of the powder for oral inhalation, ~0.3% to 1% of the maternal dose was found in breast milk. The maximum concentration appeared within 45 minutes of dosing. Plasma budesonide levels obtained from infants ~90 minutes after breast-feeding (~140 minutes after maternal dose) were below the limit of quantification.
Adverse ReactionsReaction severity varies by dose and duration; not all adverse reactions have been reported with each dosage form.
>10%:

Central nervous system: Headache (≤21%)

Gastrointestinal: Nausea (≤11%)

Respiratory: Respiratory infection, rhinitis

Miscellaneous: Symptoms of HPA axis suppression and/or hypercorticism may occur in >10% of patients following administration of dosage forms which result in higher systemic exposure (ie, oral capsule), but may be less frequent than rates observed with comparator drugs (prednisolone). These symptoms may be rare (<1%) following administration via methods which result in lower exposures (topical).

1% to 10%:

Cardiovascular: Chest pain, edema, flushing, hypertension, palpitation, syncope, tachycardia

Central nervous system: Dizziness, dysphonia, emotional lability, fatigue, fever, insomnia, migraine, nervousness, pain, vertigo

Dermatologic: Acne, alopecia, bruising, contact dermatitis, eczema, hirsutism, pruritus, pustular rash, rash, striae

Endocrine & metabolic: Adrenal insufficiency, hypokalemia, menstrual disorder

Gastrointestinal: Abdominal pain, anorexia, diarrhea, dyspepsia, flatulence, gastroenteritis (including viral), oral candidiasis, taste perversion, vomiting, weight gain, xerostomia

Genitourinary: Dysuria, hematuria, nocturia, pyuria

Hematologic: Cervical lymphadenopathy, leukocytosis, purpura

Hepatic: Alkaline phosphatase increased

Neuromuscular & skeletal: Arthralgia, back pain, fracture, hyperkinesis, hypertonia, myalgia, neck pain, paresthesia, weakness

Ocular: Conjunctivitis, eye infection

Otic: Earache, ear infection, external ear infection

Respiratory: Bronchitis, bronchospasm, cough, epistaxis, hoarseness, nasal congestion, nasal irritation, pharyngitis, sinusitis, stridor, throat irritation

Miscellaneous: Abscess, allergic reaction, C-reactive protein increased, erythrocyte sedimentation rate increased, fat distribution (moon face, buffalo hump); flu-like syndrome, herpes simplex, infection, moniliasis, viral infection, voice alteration

<1%, postmarketing, and/or case reports: Aggressive reactions, alopecia, angioedema, anxiety, avascular necrosis of the femoral head, benign intracranial hypertension, bone mineral density decreased, cataracts, depression, dyspnea, glaucoma, growth suppression, hypersensitivity reactions (immediate and delayed [includes rash, contact dermatitis, angioedema, bronchospasm]), hypocorticism, intermenstrual bleeding, irritability, nasal septum perforation, osteoporosis, psychosis, somnolence, urticaria, wheezing (patients with severe milk allergy)

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)
Drug Interactions

Amphotericin B: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Orally Inhaled) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Orally Inhaled). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Corticosteroids (Orally Inhaled). *Risk D: Consider therapy modification*

Thiazide Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Grapefruit juice may double systemic exposure of orally-administered budesonide. Administration of capsules with a high-fat meal delays peak concentration, but does not alter the extent of absorption.
Monitoring ParametersMonitor growth in pediatric patients; blood pressure, serum glucose, weight with high-dose or long-term oral use

Asthma: FEV_1, peak flow, and/or other pulmonary function tests

Nursing: Physical Assessment/MonitoringMonitor therapeutic effectiveness and adverse reactions. When changing from systemic steroids to inhalational steroids, taper reduction of systemic medication slowly (may take several months). Growth should be routinely monitored in pediatric patients. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Patient EducationUse as directed; do not increase dosage or discontinue abruptly without consulting prescriber. May take 1-2 weeks or longer before full effects are seen. Avoid grapefruit juice while taking this medication. May be more susceptible to infection; avoid exposure to chickenpox and measles unless immunity has been established. If exposure to measles or chickenpox occurs, notify your prescriber immediately. Report acute nervousness or inability to sleep; severe sneezing or nosebleed; respiratory difficulty, sore throat, hoarseness, bronchitis, or bronchospasms; disturbed menstrual pattern; vision changes; loss of taste or smell perception; or worsening of condition or lack of improvement. Regular eye exams should be considered with long-term use (risk of cataracts or glaucoma). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Oral capsule: Swallow whole; do not crush or chew capsule.

Inhalation/nebulization: This is not a bronchodilator and will not relieve acute asthma attacks. It may take several days for you to realize full effects of treatment. If you are also using an inhaled bronchodilator, wait 10 minutes before using this steroid aerosol. Take 5-10 deep breaths. Use inhaler on inspiration. Hold breath for 5-10 seconds after inhalation. Allow 1 full minute between inhalations. You may experience dizziness, anxiety, or blurred vision (rise slowly from sitting or lying position and use caution when driving or engaging in tasks requiring alertness until response to drug is known); or taste disturbance or aftertaste (frequent mouth care and mouth rinses may help). Rinse mouth with water following oral treatments to decrease risk of oral candidiasis (wash face if using a face mask).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name; [DSC] = Discontinued product

Capsule, enteric coated:

Entocort® EC: 3 mg

Powder for nasal inhalation:

Rhinocort® Turbuhaler® [CAN]: 100 mcg/inhalation [delivers 200 metered actuations] [not available in the U.S.]

Powder for oral inhalation:

Pulmicort Flexhaler™: 90 mcg/inhalation (165 mg) [contains lactose; delivers ~80 mcg/inhalation; 60 actuations]

Pulmicort Flexhaler™: 180 mcg/inhalation (225 mg) [contains lactose; delivers ~160 mcg/inhalation; 120 actuations]

Pulmicort Turbuhaler® [CAN]: 100 mcg/inhalation [delivers 200 metered actuations]; 200 mcg/inhalation [delivers 200 metered actuations]; 400 mcg/inhalation [delivers 200 metered actuations] [not available in the U.S.]

Suspension, intranasal [spray]:

Rhinocort® Aqua®: 32 mcg/inhalation (8.6 g) [120 metered actuations]

Rhinocort® Aqua® [CAN]: 64 mcg/inhalation [120 metered actuations] [not available in the U.S.]

Suspension for nebulization:

Pulmicort Respules®: 0.25 mg/2 mL (2 mL); 0.5 mg/2 mL (2 mL); 1 mg/2 mL (2 mL)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Entocort EC)

3 mg (30): $190.73

Inhalation (Pulmicort Flexhaler)

90 mcg/ACT (1): $99.84

180 mcg/ACT (1): $132.35

Suspension (Pulmicort)

0.25 mg/2 mL (60): $176.96

0.5 mg/2 mL (60): $208.12

Suspension (Rhinocort Aqua)

32 mcg/ACT (8.6): $101.55

Mechanism of ActionControls the rate of protein synthesis; depresses the migration of polymorphonuclear leukocytes, fibroblasts; reverses capillary permeability and lysosomal stabilization at the cellular level to prevent or control inflammation. Has potent glucocorticoid activity and weak mineralocorticoid activity.

Pharmacodynamics/Kinetics

Onset of action: Pulmicort Respules®: 2-8 days; Rhinocort® Aqua®: ~10 hours; Inhalation: 24 hours

Peak effect: Pulmicort Respules®: 4-6 weeks; Rhinocort® Aqua®: ~2 weeks; Inhalation: 1-2 weeks

Distribution: 2.2-3.9 L/kg

Protein binding: 85% to 90%

Metabolism: Hepatic via CYP3A4 to two metabolites: 16 alpha-hydroxyprednisolone and 6 beta-hydroxybudesonide; minor activity

Bioavailability: Limited by high first-pass effect; Capsule: 9% to 21%; Pulmicort Respules®: 6%; Inhalation: 6% to 13%; Nasal: 34%

Half-life elimination: 2-3.6 hours

Time to peak: Capsule: 0.5-10 hours (variable in Crohn's disease); Pulmicort Respules®: 10-30 minutes; Inhalation: 1-2 hours; Nasal: 1 hour

Excretion: Urine (60%) and feces as metabolites

Related Information

- Asthma
- Inhalant Agents
- Status Epilepticus

Pharmacotherapy PearlsEffects of inhaled/intranasal steroids on growth have been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally-inhaled and intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), dry throat, abnormal taste, and herpes simplex. Localized infections with *Candida albicans* or *Aspergillus niger* have occurred frequently in the mouth and pharynx with repetitive use of oral inhaler of corticosteroids. These infections may require treatment with appropriate antifungal therapy or discontinuance of treatment with corticosteroid inhaler.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness and insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other Considerations

Surgery: For patients who have received oral systemic corticosteroids during the past 6 months and for selected patients on long-term, high-dose, inhaled corticosteroid (ICS), give stress doses of hydrocortisone intravenously during the surgical period and reduce the dose rapidly within 24 hours after surgery (Expert Panel Report 3, 2007). Clinically important adrenal suppression has been reported in patients receiving high doses of an ICS, particularly children.

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Todd GR, Acerini CL, Ross-Russell R, et al, "Survey of Adrenal Crisis Associated With Inhaled Corticosteroids in the United Kingdom," *Arch Dis Child*, 2002, 87(6):457-61.[PubMed 12456538]

International Brand NamesAeronide (TH); Aerosial (MX); Allercort (TW); Apulein (HU); Aquacort (DE); Asmavent (PH); B Cort (CO); Bidien (IT); Bronex (PH); Budecort (KP); Budecort CFC Free (TH); Budecort Nasal (PH); Budeflam (ZA); Budenase AQ (HK); Budenofalk (DE, HK, KP, MY, PH, PL, SG); Buderhin (PL); Budeson (AR); Budesonid (PL); Budesonid-Polfa (HU); Budiair (TH); Budicort Respules (IL); Budo-san (AT); Bunase (TH); Butacort (NZ); Butacort Aqueous (MY); Clebudan (CN, CO); Cycortide (HK); Duasma (TW); Eltair (MY, NZ, SG); Entocort (AE, AT, BH, BR, CY, EG, HU, IL, IQ, IR, JO, KW, LB, LY, MX, OM, PL, QA, SA, SY, YE); Entocort Enema (LU); Esonide (SG); Giona Easyhaler (MY, SG, TH); Horacort (PL); Inflammide (CO, MY, PE, SG); Miflonide (DE, IL, MX, PL); Neo-Rinactive (TW); Neumocort (PY); Novopulmon (AE, BH, CY, DE, EG, FR, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Numark (MX); Predermid (AT); Preferid (IT, LU); Pulmaxan (IT); Pulmicon Susp for Nebulizer (KP); Pulmicort (AT, BB, BE, BG, BM, BR, BS, BZ, CH, CN, CO, CR, CZ, DE, DK, DO, EE, ES, FI, FR, GB, GR, GY, HN, HU, IN, JM, LU, MX, NI, NL, PA, PK, PL, PT, SE, SR, TT, TW, UY, VE); Pulmicort Nasal (TW); Pulmicort Nasal Turbohaler (CL, KE, MU, NG); Pulmicort Turbuhaler (KE, MU, NG, PL); Rafton (FR); Rhinocort (AE, AT, AU, BE, BH, CH, CL, CY, EG, ES, FI, FR, GB, HK, HN, HU, ID, IE, IL, IQ, IR, JO, KP, KW, LB, LU, LY, MX, MY, NL, NO, OM, PE, PL, QA, SA, SE, SY, TH, YE); Rhinocort Aqua (BB, BM, BS, BZ, GY, HU, JM, NL, SR, TT); Rhinocort Aqueous (AU); Rhinocort Hayfever (AU); Rhinoside (GR); Tafen (PL)

Bumetanide

Lexi-Drugs Online

English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Bumetanide may be confused with Buminate®

Bumex® may be confused with Brevibloc®, Buprenex®, Permax®

Pronunciation(byoo MET a nide)

U.S. Brand NamesBumex®

Canadian Brand NamesBumex®; Burinex®

Pharmacologic CategoryDiuretic, Loop

Use: Labeled IndicationsManagement of edema secondary to congestive heart failure or hepatic or renal disease including nephrotic syndrome; may be used alone or in combination with antihypertensives in the treatment of hypertension; can be used in furosemide-allergic patients

Dosing: Adults

Edema:

Oral: 0.5-2 mg/dose (maximum dose: 10 mg/day) 1-2 times/day

I.M., I.V.: 0.5-1 mg/dose; may repeat in 2-3 hours for up to 2 doses if needed (maximum dose: 10 mg/day)

Continuous I.V. infusion: Initial: 1 mg load then 0.5-2 mg/hour (ACC/AHA 2005 practice guidelines for chronic heart failure)

Hypertension: Oral: 0.5 mg daily (maximum dose: 5 mg/day)

Usual dosage range (JNC 7): 0.5-2 mg/day in 2 divided doses

Dosing: ElderlyInitial: Oral: 0.5 mg once daily, increase as necessary.

Dosing: PediatricEdema (diuresis): Oral, I.M., I.V.:

Neonates (see Warnings/Precautions): 0.01-0.05 mg/kg/dose every 24-48 hours

Infants and Children: 0.015-0.1 mg/kg/dose every 6-24 hours (maximum dose: 10 mg/day)

Administration: I.V.Administer I.V. slowly, over 1-2 minutes. An alternate-day schedule or a 3-4 daily dosing regimen with rest periods of 1-2 days in between may be the most tolerable and effective regimen for the continued control of edema. Reserve I.V. administration for those unable to take oral medications.

Administration: I.V. DetailpH: 6.8-7.8 (adjusted)

Dietary ConsiderationsMay require increased intake of potassium-rich foods.

Storage

I.V.: Store vials at 15°C to 30°C (59°F to 86°F). Infusion solutions should be used within 24 hours after preparation. Light sensitive; discoloration may occur when exposed to light.

Tablet: Store at 15°C to 30°C (59°F to 86°F).

CompatibilityStable in D_5W, NS, LR.

Y-site administration: Compatible: Allopurinol, amifostine, aztreonam, cefepime, cisatracurium, cladribine, clarithromycin, diltiazem, docetaxel, etoposide, filgrastim, gemcitabine, granisetron, lorazepam, melphalan, meperidine, milrinone, morphine, piperacillin/tazobactam, propofol, remifentanil, teniposide, thiotepa, vinorelbine. **Incompatible:** Midazolam.

Compatibility in syringe: Compatible: Doxapram.

Compatibility when admixed: Compatible: Floxacillin, furosemide. **Incompatible:** Dobutamine, milrinone.

ContraindicationsHypersensitivity to bumetanide, any component of the formulation, or sulfonylureas; anuria; patients with hepatic coma or in states of severe electrolyte depletion until the condition improves or is corrected; pregnancy (based on expert analysis)

Allergy Considerations

- Loop Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Fluid/electrolyte loss: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Fluid/electrolyte loss: **[U.S. Boxed Warning]: Loop diuretics are potent diuretics; excess amounts can lead to profound diuresis with fluid and electrolyte loss; close medical supervision and dose evaluation are required.** Watch for and correct electrolyte disturbances; adjust dose to avoid dehydration.

- Hyperuricemia: Asymptomatic hyperuricemia has been reported with use.

- Nephrotoxicity: Monitor fluid status and renal function in an attempt to prevent oliguria, azotemia, and reversible increases in BUN and creatinine; close medical supervision of aggressive diuresis required.

- Ototoxicity: Rapid I.V. administration, renal impairment, excessive doses, and concurrent use of other ototoxins is associated with ototoxicity.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonylurea allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Cirrhosis: In cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

Concurrent drug therapy issues:

- Antihypertensives: Coadministration of antihypertensives may increase the risk of hypotension.

Special populations:

- Neonates: *In vitro* studies using pooled sera from critically-ill neonates have shown bumetanide to be a potent displacer of bilirubin; avoid use in neonates at risk for kernicterus.

Geriatric ConsiderationsLoop diuretics are potent diuretics; excess amounts can lead to profound diuresis with fluid and electrolyte loss; close medical supervision and dose evaluation is required, particularly in the elderly. Severe loss of sodium and/or increases in BUN can cause confusion; for any change in mental status in patients on bumetanide, monitor electrolytes and renal function.

Pregnancy Risk FactorC (manufacturer); D (expert analysis)

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Endocrine & metabolic: Hyperuricemia (18%), hypochloremia (15%), hypokalemia (15%)

Renal: Azotemia (11%)

1% to 10%:

Central nervous system: Dizziness (1%)

Endocrine & metabolic: Hyponatremia (9%); hyperglycemia (7%); variations in phosphorus (5%), CO_2 content (4%), bicarbonate (3%), and calcium (2%)

Neuromuscular & skeletal: Muscle cramps (1%)

Otic: Ototoxicity (1%)

Renal: Serum creatinine increased (7%)

<1% (Limited to important or life-threatening): Hypotension, orthostatic hypotension, headache, nausea, encephalopathy (in patients with pre-existing liver disease), hearing impaired, pruritus, weakness, hives, abdominal pain, arthritic pain, musculoskeletal pain, rash, vomiting, vertigo, chest pain, ear discomfort, fatigue, dehydration, diaphoresis, hyperventilation, dry mouth, upset stomach, renal failure, asterixis, itching, nipple tenderness, diarrhea, premature ejaculation, hypernatremia

Drug Interactions

ACE Inhibitors: Loop Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Loop Diuretics may enhance the adverse/toxic effect of Allopurinol. Loop Diuretics may increase the serum concentration of Allopurinol. Specifically, Loop Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoglycosides: Loop Diuretics may enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Loop Diuretics. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dofetilide: Loop Diuretics may enhance the QTc-prolonging effect of Dofetilide. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Loop Diuretics may diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Loop Diuretics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Phenytoin: May diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid dong quai if using for hypertension (has estrogenic activity). Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure, serum electrolytes, renal function

Nursing: Physical Assessment/MonitoringAssess history of allergies, renal, electrolyte, hepatic, and pregnancy status prior to beginning treatment. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, increased risk of hyperglycemia, hypotension, arrhythmias, ototoxicity). Blood pressure, weight, and fluid status should be monitored at beginning of therapy and periodically during therapy. Glucose levels for patients with diabetes should be monitored closely (glucose tolerance may be decreased by loop diuretics, requiring adjustment of hypoglycemic agents). Assess results of laboratory tests (electrolytes and renal function), therapeutic effectiveness (reduced edema and cardiopulmonary symptoms), and adverse effects (hypotension, electrolyte imbalance, ototoxicity). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum electrolytes, renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. May be taken with food to reduce GI effects. If taking one dose daily, take single dose early in day; if taking twice daily, take last dose early in afternoon to prevent sleep interruptions. Include orange juice or bananas (or other sources of potassium-rich foods) in your daily diet, but do not take supplemental potassium without consulting prescriber. If you have diabetes, monitor glucose levels closely (glucose tolerance may be decreased by loop diuretics), and notify prescriber of noted changes (hypoglycemic agent may need to be adjusted). May cause dizziness, hypotension, lightheadedness, or weakness (use caution when changing position from sitting or lying position, when driving, exercising, climbing stairs, or performing hazardous tasks until response to drug is known). Report palpitations or chest pain; swelling of ankles or feet; weight increase or decrease (>3 lb in any one day); increased fatigue, muscle cramps, or trembling; and any changes in hearing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant; contraceptives may be recommended. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution: 0.25 mg/mL (2 mL, 4 mL, 10 mL)

Tablet: 0.5 mg, 1 mg, 2 mg

Bumex®: 0.5 mg [DSC]; 1 mg; 2 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Bumetanide)

2 mg (100): $82.39

Mechanism of ActionInhibits reabsorption of sodium and chloride in the ascending loop of Henle and proximal renal tubule, interfering with the chloride-binding cotransport system, thus causing increased excretion of water, sodium, chloride, magnesium, phosphate, and calcium; it does not appear to act on the distal tubule

Pharmacodynamics/Kinetics

Onset of action: Oral, I.M.: 0.5-1 hour; I.V.: 2-3 minutes

Duration: 4-6 hours

Distribution: V_d: 13-25 L/kg

Protein binding: 95%

Metabolism: Partially hepatic

Half-life elimination: Neonates: ~6 hours; Infants (1 month): ~2.4 hours; Adults: 1-1.5 hours

Excretion: Primarily urine (as unchanged drug and metabolites)

Related Information

- Heart Failure (Systolic)
- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness
Mental Health: Effects on Psychiatric TreatmentLithium excretion may be decreased; monitor serum lithium levels
Cardiovascular ConsiderationsIt is important that patients be closely followed for hypokalemia, hypomagnesemia, and volume depletion because of significant diuresis.
Anesthesia and Critical Care Concerns/Other ConsiderationsIf given the morning of surgery, it may render the patient volume depleted and blood pressure may be labile during general anesthesia.

Patients with impaired hepatic function must be monitored carefully, often requiring reduced doses. Larger doses may be necessary in patients with impaired renal function to obtain the same therapeutic response.

It is important that patients be closely followed for hypokalemia, hypomagnesemia, and volume depletion because of significant diuresis.

References

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Hunt SA, Abraham WT, Chin MH , et al, "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure)," available at http://www.acc.org/qualityandscience/clinical/guidelines/failure/update/index.pdf.

Montgomery PA and Christen C, “Policy to Restrict Use of I.V. Bumetanide,” *Am J Health Syst Pharm*, 1995, 52(16):1802-4. [PubMed 8528838]

Ward A and Heel RC, “Bumetanide: A Review of Its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Use,” *Drugs*, 1984, 28(5):426-64. [PubMed 6391889]

Wells TG, “The Pharmacology and Therapeutics of Diuretics in the Pediatric Patient,” *Pediatr Clin North Am*, 1990, 37(2):463-504.[PubMed 2184406]

International Brand NamesAneiromox (ES); Aquazone (ES); Budema (TW); Bumelex (VE); Bumet (DO, GT, HN, IN, PA, SV); Bumetanid (CY); Burinax (BR); Burinex (AT, AU, BB, BE, BF, BJ, BM, BS, BZ, CH, CI, CR, DE, DK, DO, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, IE, JM, KE, LR, LU, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, PA, PH, PK, PR, SC, SD, SE, SL, SN, SR, SV, TH, TN, TT, TZ, UG, ZA, ZM, ZW); Butinat (AR); Drenural (MX); Farmadiuril (ES); Fontego (IT); Fordiuran (ES); Huiyuan (CL); Lunetoron (JP); Miccil (MX, PE)

Bupivacaine and Epinephrine

Lexi-Drugs Online

English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (epidural administration) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(byoo PIV a kane & ep i NEF rin)

U.S. Brand NamesMarcaine® with Epinephrine; Sensorcaine® with Epinephrine; Sensorcaine®-MPF with Epinephrine; Vivacaine™

Canadian Brand NamesSensorcaine® with Epinephrine

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsLocal anesthetic (injectable) for peripheral nerve block, infiltration, sympathetic block, caudal or epidural block, retrobulbar block

Use: DentalLocal anesthesia

Dosing: AdultsDose varies with procedure, depth of anesthesia, vascularity of tissues, duration of anesthesia, and condition of patient. Do not use solutions containing preservatives for caudal or epidural block.

Caudal block (preservative free): 15-30 mL of 0.25% or 0.5%

Epidural block (other than caudal block, preservative free): 10-20 mL of 0.25% or 0.5%. Administer in 3-5 mL increments, allowing sufficient time to detect toxic manifestations of inadvertent I.V. or I.T. administration.

Surgical procedures requiring a high degree of muscle relaxation and prolonged effects only: 10-20 mL of 0.75% (**Note:** Not to be used in obstetrical cases)

Local anesthesia: Infiltration: 0.25% infiltrated locally (maximum: 175 mg of bupivacaine)

Peripheral nerve block: 5 mL of 0.25 or 0.5% (maximum: 400 mg/day of bupivacaine)

Retrobulbar anesthesia: 2-4 mL of 0.75%

Sympathetic nerve block: 20-50 mL of 0.25%

Infiltration and nerve block in maxillary and mandibular area: 9 mg (1.8 mL) of bupivacaine as a 0.5% solution with epinephrine 1:200,000 per injection site. A second dose may be administered if necessary to produce adequate anesthesia after allowing up to 10 minutes for onset. Up to a maximum of 90 mg of bupivacaine hydrochloride per dental appointment. The effective anesthetic dose varies with procedure, intensity of anesthesia needed, duration of anesthesia required, and physical condition of the patient; always use the lowest effective dose along with careful aspiration.

The following numbers of dental carpules (1.8 mL) provide the indicated amounts of bupivacaine hydrochloride 0.5% and vasoconstrictor (epinephrine 1:200,000). See table.

# of Cartridges (1.8 mL)	Mg Bupivacaine (0.5%)	Mg Vasoconstrictor (Epinephrine 1:200,000)
1	9	0.009
2	18	0.018
3	27	0.027
4	36	0.036
5	45	0.045
6	54	0.054
7	63	0.063

8	72	0.072
9	81	0.081
10	90	0.090

Note: Adult and children doses of bupivacaine hydrochloride with epinephrine cited from USP Dispensing Information (USP DI), 17th ed, The United States Pharmacopeial Convention, Inc, Rockville, MD, 1997, 134.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Children >12 years: Refer to adult dosing.

Administration: I.V. DetailpH: 3:3-5.5
StorageStore at controlled room temperature of 15°C to 30°C (59° to 86°F) and protect from light. Do not autoclave.
ContraindicationsHypersensitivity to bupivacaine, epinephrine, amide-type local anesthetics, or any component of the formulation
Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Boxed warnings:

- Obstetrical anesthesia: See “Dosage form specific issues” below.

Concerns related to adverse effects:

- Respiratory arrest: Local anesthetics have been associated with rare occurrences of sudden respiratory arrest, especially when administered near the head or neck.
- Seizures: Convulsions due to systemic toxicity leading to cardiac arrest have also been reported, presumably following unintentional intravascular injection or administration near the head or neck.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease or compromised blood supply.
- Hepatic impairment: Use with caution in patients with hepatic impairment.

Special populations:

- Acutely ill patients: Use with caution in acutely ill patients; dose reduction may be required.
- Debilitated patients: Use with caution in debilitated patients; dose reduction may be required.
- Elderly: Use with caution in the elderly; dose reduction may be required.
- Pediatrics: Not recommended for use in children <12 years of age.

Dosage form specific issues:

- Obstetrical anesthesia: **[U.S. Boxed Warning]: The 0.75% is not recommended for obstetrical anesthesia.**
- Preservative-containing solutions: Do not use solutions containing preservatives for caudal or epidural block.
- Sodium metabisulfite: Some commercially available formulations contain sodium metabisulfite, which may cause allergic-type reactions.

Other warnings/precautions:

- Administration: Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided.
- Test dose: A test dose is recommended prior to epidural administration (prior to initial dose) and all reinforcing doses with continuous catheter technique.
- Trained personnel: Dental practitioners and/or clinicians using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorC
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/not recommended
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsBupivacaine: **Substrate** (minor) of CYP1A2, 2C19, 2D6, 3A4

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. *Risk D: Consider therapy modification*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

COMT Inhibitors: May decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

Inhalational Anesthetics: May enhance the arrhythmogenic effect of EPINEPHrine. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). *Risk D: Consider therapy modification*

Monitoring Parameters

Vital signs, state of consciousness; signs of CNS toxicity; fetal heart rate during paracervical anesthesia

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: Bupivacaine hydrochloride 0.25% and epinephrine bitartrate 1:200,000 (10 mL, 30 mL); bupivacaine hydrochloride 0.5% and epinephrine bitartrate 1:200,000 (1.8 mL, 10 mL, 30 mL)

> Marcaine® with Epinephrine: Bupivacaine hydrochloride 0.25% and epinephrine bitartrate 1:200,000 (10 mL, 30 mL) [contains edetate calcium disodium and sodium metabisulfite]; bupivacaine hydrochloride 0.5% and epinephrine bitartrate 1:200,000 (1.8 mL, 3 mL, 10 mL, 30 mL) [contains edetate calcium disodium and sodium metabisulfite]; bupivacaine hydrochloride 0.75% and epinephrine bitartrate 1:200,000 (30 mL) [contains edetate calcium disodiam and sodium metabisulfite]
>
> Sensorcaine® MPF with Epinephrine: Bupivacaine hydrochloride 0.25% and epinephrine bitartrate 1:200,000 (10 mL, 30 mL) [contains sodium metabisulfite]; bupivacaine hydrochloride 0.5% and epinephrine bitartrate 1:200,000 (10 mL, 30 mL) [contains sodium metabisulfite]
>
> Vivacaine™: Bupivacaine hydrochloride 0.5% and epinephrine bitartrate 1:200,000 (1.8 mL) [contains edetate calcium disodium, sodium metabisulfite]

Injection, solution: Bupivacaine hydrochloride 0.25% and epinephrine bitartrate 1:200,000 (50 mL); bupivacaine hydrochloride 0.5% and epinephrine bitartrate 1:200,000 (50 mL)

> Marcaine® with Epinephrine: Bupivacaine hydrochloride 0.25% and epinephrine bitartrate 1:200,000 (50 mL) [contains methylparaben, edetate calcium disodium, and sodium metabisulfite]; bupivacaine hydrochloride 0.5% and epinephrine bitartrate 1:200,000 (50 mL) [contains methylparaben, edetate calcium disodium, and sodium metabisulfite]
>
> Sensorcaine® with Epinephrine: Bupivacaine hydrochloride 0.25% and epinephrine bitartrate 1:200,000 (50 mL) [contains methylparaben and sodium metabisulfite]; bupivacaine hydrochloride 0.5% and epinephrine bitartrate 1:200,000 (50 mL) [contains methylparaben and sodium metabisulfite]

Generic Available

Yes

Mechanism of Action

Local anesthetics bind selectively to the intracellular surface of sodium channels to block influx of sodium into the axon. As a result, depolarization necessary for action potential propagation and subsequent nerve function is prevented. The block at the sodium channel is reversible. When drug diffuses away from the axon, sodium channel function is restored and nerve propagation returns.

Epinephrine prolongs the duration of the anesthetic actions of bupivacaine by causing vasoconstriction (alpha-adrenergic receptor agonist) of the vasculature surrounding the nerve axons. This prevents the diffusion of bupivacaine away from the nerves resulting in a longer retention in the axon

Pharmacodynamics/Kinetics

Refer to Bupivacaine; epinephrine reduces the rate of absorption and peak plasma concentration of bupivacaine

Related Information

- Bupivacaine
- EPINEPHrine

Dental Health: Effects on Dental Treatment

It is common to misinterpret psychogenic responses to local anesthetic injection as an allergic reaction. Intraoral injections are perceived by many patients as a stressful procedure in dentistry. Common symptoms to this stress are diaphoresis, palpitations, and hyperventilation. Patients may exhibit hypersensitivity to bisulfites contained in local anesthetic solution to prevent oxidation of epinephrine. In general, patients reacting to bisulfites have a history of asthma and their airways are hyper-reactive to asthmatic syndrome.

Degree of adverse effects in the CNS and cardiovascular system is directly related to the blood levels of bupivacaine: Bradycardia, hypersensitivity reactions (rare; may be manifest as dermatologic reactions and edema at injection site), asthmatic syndromes.

High blood levels: Anxiety, restlessness, disorientation, confusion, dizziness, tremors, seizures, CNS depression (resulting in somnolence, unconsciousness and possible respiratory arrest), nausea, and vomiting.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, restlessness, confusion, dizziness, and sedation

Mental Health: Effects on Psychiatric TreatmentUse with caution in patients receiving phenothiazines, MAO inhibitors, or TCAs; severe hypertension or hypotension may result

Index TermsEpinephrine Bitartrate and Bupivacaine Hydrochloride

References

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Jastak JT and Yagiela JA, “Vasoconstrictors and Local Anesthesia: A Review and Rationale for Use,” *J Am Dent Assoc*, 1983, 107(4):623-30. [PubMed 6355236]

MacKenzie TA and Young ER, “Local Anesthetic Update,” *Anesth Prog*, 1993, 40(2):29-34. [PubMed 8185087]

Wynn RL, “Epinephrine Interactions With Beta-Blockers,” *Gen Dent*, 1994, 42(1):16, 18. [PubMed 7911769]

Yagiela JA, “Local Anesthetics,” *Anesth Prog*, 1991, 38(4-5):128-41.[PubMed 1819966]

International Brand NamesBarcaine (KR); Carbostesin mit Adrenalin (DE); Carbostesin mit Epinephrin (AT, CH); Duracaine (PY); Kamacaine adrenaline (IL); Macaine with Adrenaline (ZA); Marcain + Adrenalin (HU); Marcain Adrenalin (FI, IT, SE); Marcain with Adrenaline (AU, NZ); Marcain with Adrenaline Dental (AU); Marcain-Adrenalin (DK); Marcaine Adrenaline (HK, TW); Marcaine met Adrenaline (BE); Marcaine with Adrenaline (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TH, TZ, UG, ZM, ZW); Marcaine+Adrenaline (NL); Marcaine-Adrenaline (CZ, EE, GR, IL); Neocaina (PE); Sensorcaine with Epinephrine (CA)

Bupivacaine

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English

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Bupivacaine may be confused with mepivacaine, ropivacaine

Marcaine® may be confused with Narcan®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (epidural administration) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(byoo PIV a kane)

U.S. Brand NamesMarcaine®; Marcaine® Spinal; Sensorcaine®; Sensorcaine®-MPF; Sensorcaine®-MPF Spinal

Canadian Brand NamesMarcaine®; Sensorcaine®

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsLocal anesthetic (injectable) for peripheral nerve block, infiltration, sympathetic block, caudal or epidural block, retrobulbar block

Use: DentalNone; not to be confused with bupivacaine and epinephrine dental anesthetic. Refer to Bupivacaine and Epinephrine.

Dosing: Adults**Note:** Dose varies with procedure, depth of anesthesia, vascularity of tissues, duration of anesthesia, and condition of patient. Do not use solutions containing preservatives for caudal or epidural block.

Local anesthesia: Infiltration: 0.25% infiltrated locally; maximum: 175 mg

Caudal block) (preservative free: 15-30 mL of 0.25% or 0.5%

Epidural block (other than caudal block; preservative free): Administer in 3-5 mL increments, allowing sufficient time to detect toxic manifestations of inadvertent I.V. or I.T. administration: 10-20 mL of 0.25% or 0.5%

Surgical procedures requiring a high degree of muscle relaxation and prolonged effects **only**: 10-20 mL of 0.75% (**Note:** Not to be used in obstetrical cases)

Peripheral nerve block: 5 mL of 0.25 or 0.5%; maximum: 400 mg/day

Sympathetic nerve block: 20-50 mL of 0.25%

Retrobulbar anesthesia: 2-4 mL of 0.75%

Spinal anesthesia: Preservative free solution of 0.75% bupivacaine in 8.25% dextrose:

Lower extremity and perineal procedures: 1 mL

Lower abdominal procedures: 1.6 mL

Normal vaginal delivery: 0.8 mL (higher doses may be required in some patients)

Cesarean section: 1-1.4 mL

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Dose varies with procedure, depth of anesthesia, vascularity of tissues, duration of anesthesia, and condition of patient. Do not use solutions containing preservatives for caudal or epidural block.

Caudal block, epidural block, local anesthesia: Children >12 years: Refer to adult dosing.

Peripheral or sympathetic nerve block: Children >12 years: Refer to adult dosing.

Retrobulbar anesthesia: Children >12 years: Refer to adult dosing.

Administration: I.V. DetailpH: 4.0-6.5

Administration: OtherSolutions containing preservatives should not be used for epidural or caudal blocks.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86˚F).

CompatibilityStable in NS.

Compatibility in syringe: Compatible: Clonidine with morphine, diamorphine, fentanyl with ketamine, hydromorphone, iohexol, morphine. **Variable (consult detailed reference):** Sodium bicarbonate.

Compatibility when admixed: Compatible: Buprenorphine, diamorphine, epinephrine, fentanyl, hydromorphone, morphine, sufentanil.

ContraindicationsHypersensitivity to bupivacaine hydrochloride, amide-type local anesthetics, or any component of the formulation; obstetrical paracervical block anesthesia

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Boxed warnings:

- Obstetrical anesthesia: See “Dosage form specific issues” below.

Concerns related to adverse effects:

- Respiratory arrest: Local anesthetics have been associated with rare occurrences of sudden respiratory arrest, especially when administered near the head or neck.
- Seizures: Convulsions due to systemic toxicity leading to cardiac arrest have also been reported, presumably following unintentional intravascular injection or administration near the head or neck.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Hepatic impairment: Use with caution in patients with hepatic impairment.

Special populations:

- Acutely ill patients: Use with caution in acutely ill patients; dose reduction may be required.
- Debilitated patients: Use with caution in debilitated patients; dose reduction may be required.
- Elderly: Use with caution in the elderly; dose reduction may be required.
- Pediatrics: Not recommended for use in children <12 years of age. The solution for spinal anesthesia should not be used in children <18 years of age.

Dosage form specific issues:

- Obstetrical anesthesia: **[U.S. Boxed Warning]: The 0.75% is not recommended for obstetrical anesthesia.**
- Preservative-containing solutions: **Do not use solutions containing preservatives for caudal or epidural block**.

Other warnings/precautions:

- Administration: Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided.
- Test dose: A test dose is recommended prior to epidural administration (prior to initial dose) and all reinforcing doses with continuous catheter technique.
- Trained personnel: Clinicians using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDecreased pup survival and embryocidal effects were observed in animal studies. Bupivacaine is approved for use at term in obstetrical anesthesia or analgesia. **[U.S. Boxed Warning]: The 0.75% is not recommended for obstetrical anesthesia.** Bupivacaine 0.75% solutions have been associated with cardiac arrest following epidural anesthesia in obstetrical patients and use of this concentration is not recommended for this purpose. Use in obstetrical paracervical block anesthesia is contraindicated.

LactationEnters breast milk/not recommended

Adverse Reactions**Note:** Incidence of adverse reactions is difficult to define. Most effects are dose related, and are often due to accelerated absorption from the injection site, unintentional intravascular injection, or slow metabolic degradation. The development of any central nervous system symptoms may be an early indication of more significant toxicity (seizure).

Cardiovascular: Hypotension, bradycardia, palpitation, heart block, ventricular arrhythmia, cardiac arrest

Central nervous system: Restlessness, anxiety, dizziness, seizure (0.1%); rare symptoms (usually associated with unintentional subarachnoid injection during high spinal anesthesia) include persistent anesthesia, paresthesia, paralysis, headache, septic meningitis, and cranial nerve palsies

Gastrointestinal: Nausea, vomiting; rare symptoms (usually associated with unintentional subarachnoid injection during high spinal anesthesia) include fecal incontinence and loss of sphincter control

Genitourinary: Rare symptoms (usually associated with unintentional subarachnoid injection during high spinal anesthesia) include urinary incontinence, loss of perineal sensation, and loss of sexual function

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision, pupillary constriction

Otic: Tinnitus

Respiratory: Apnea, hypoventilation (usually associated with unintentional subarachnoid injection during high spinal anesthesia)

Miscellaneous: Allergic reactions (urticaria, pruritus, angioedema), anaphylactoid reactions

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 2C19, 2D6, 3A4

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersVital signs, state of consciousness; signs of CNS toxicity; fetal heart rate during paracervical anesthesia

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for additive or adverse interactions. Monitor for effectiveness of anesthesia and adverse reactions. Monitor for return of sensation. Teach patient adverse reactions to report; use and teach appropriate interventions to promote safety.

Patient EducationThis medication is given to reduce sensation in the injected area. You will experience decreased sensation to pain, heat, or cold in the area and/or decreased muscle strength (depending on area of application) until the effects wear off; use necessary caution to reduce incidence of possible injury until full sensation returns. If used in mouth, do not eat or drink until full sensation returns. Immediately report chest pain or palpitations; increased restlessness, anxiety, or dizziness; skeletal or muscle weakness; respiratory difficulty; ringing in ears; or vision changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride [preservative free]: 0.25% (10 mL, 20 mL, 30 mL, 50 mL); 0.5% (10 mL, 20 mL, 30 mL); 0.75% (10 mL, 20 mL, 30 mL)

> Marcaine®: 0.25% (10 mL, 30 mL); 0.5% (10 mL, 30 mL); 0.75% (10 mL, 30 mL)
>
> Sensorcaine®-MPF: 0.25% (10 mL, 30 mL); 0.5% (10 mL, 30 mL); 0.75% (10 mL, 30 mL)

Injection, solution, as hydrochloride [preservative free]: 0.75% (2 mL) [in dextrose 8.25%]

> Marcaine® Spinal: 0.75% (2 mL) [in dextrose 8.25%]
>
> Sensorcaine®-MPF Spinal: 0.75% (2 mL) [in dextrose 8.25%]

Injection, solution, as hydrochloride:

> Marcaine®, Sensorcaine®: 0.25% (50 mL); 0.5% (50 mL) [contains methylparaben]

Generic AvailableYes

Mechanism of ActionBlocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction

Pharmacodynamics/Kinetics

Onset of action: Anesthesia (route and dose dependent): 1-17 minutes

Duration (route and dose dependent): 2-9 hours

Protein binding: ~95%

Metabolism: Hepatic; forms metabolite (PPX)

Half-life elimination (age dependent): Neonates: 8.1 hours; Adults: 1.5-5.5 hours

Excretion: Urine (~6% unchanged)

Related Information

- Bupivacaine and Epinephrine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety and restlessness

Mental Health: Effects on Psychiatric TreatmentUse with caution in patients receiving phenothiazines, MAO inhibitors, or TCAs; severe hypertension or hypotension may result

Anesthesia and Critical Care Concerns/Other Considerations

Local anesthetic toxicity: Cardiac arrest: Lipid infusion has been used in animal studies and several human cases (Bupivacaine: Rosenblatt, 2006; Levobupivacaine: Foxall, 2007; Ropivacaine: Litz, 2006) where cardiovascular toxicity, unresponsive to conventional resuscitation, resulted. Additional information is available at http://www.lipidrescue.org. The protocol from the website is: **20% Fat Emulsion:** 1.5 mL/kg administered over 1 minute, followed immediately by an infusion of 0.25 mL/kg/minute. Continue chest compressions (lipid must circulate). Repeat bolus every 3-5 minutes up to 3 mL/kg total dose until circulation restored. Continue infusion until hemodynamic stability is restored. Increase the infusion rate to 0.5 mL/kg/minute if BP declines. A maximum total dose of 8 mL/kg is recommended.

Index TermsBupivacaine Hydrochloride

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Foxall G, McCahon R, Lamb J, et al, "Levobupivacaine-Induced Seizures and Cardiovascular Collapse Treated With Intralipid," *Anaesthesia*, 2007, 62(5):516-8.[PubMed 17448066]

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Scott DB, Lee A, Fagan D, et al, "Acute Toxicity of Ropivacaine Compared With That of Bupivacaine," *Anesth Analg*, 1989, 69(5):563-9. [PubMed 2679230]

Sun KO, "Convulsion Following Spinal Anaesthesia," *Anaesth Intensive Care*, 1995, 23(4):520-1. [PubMed 7485961]

Tuominen MK, Pere P, and Rosenberg PH, "Unintentional Arterial Catheterization and Bupivacaine Toxicity Associated With Continuous Interscalene Brachial Plexus Block," *Anesthesiology*, 1991, 75(2):356-8.[PubMed 1859023]

International Brand NamesAnekain (HR); Bicain (FI); Bloqueina (AR); Bucain (DE, HU); Bupicaina (AR); Bupiforan (IT); Bupinex (AR); Bupivacain INFOsint (CH); Bupivacain Jenapharm (DE); Bupivacain-HCl Sintetica (CH); Bupivacain-RPR (DE); Bupivacain-RPR CO!2 (DE); Bupivacaina Angelini (IT); Bupivacaine Aguettant (FR); Bupivacaine B. Braun (FR); Bupivacaine Bioren (CH); Bupivacaine Hydrochloride Injection BP (AU); Bupivacainum hydrochloricum (PL); Bupivakain (NO); Caina-G (AR); Carbostesin (AT, CH, DE); Chirocaine (PL); Chlorhydrate de Bupivacaine Dakota (FR); Dolanaest (DE); Duracain (CH); Marcain (AU, DK, FI, HU, IN, JP, NO, PT, SE); Marcaina (IT); Marcaine (BE, CZ, FR, LU, NL, PL); Marcaine Spinal (PL); Sensorcaine (IN); Svedocain (ES)

Buprenorphine and Naloxone

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(byoo pre NOR feen & nal OKS one)
U.S. Brand NamesSuboxone®
Pharmacologic CategoryAnalgesic, Opioid
Use: Labeled IndicationsTreatment of opioid dependence
Dosing: AdultsOpioid dependence: Sublingual: **Note:** This combination product is not recommended for use during the induction period; initial treatment should begin using buprenorphine oral tablets. Patients should be switched to the combination product for maintenance and unsupervised therapy.

Maintenance: Target dose (based on buprenorphine content): 16 mg/day; range: 4-24 mg/day

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricOpioid dependence: Children ≥16 years: Refer to adult dosing.
Administration: OralSublingual: Tablet should be placed under the tongue until dissolved; should not be swallowed. If two or more tablets are needed per dose, all may be placed under the tongue at once, or two at a time. To ensure consistent bioavailability, subsequent doses should always be taken the same way.
Dietary Considerations

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

StorageStore at room temperature of 25°C (77°F).
RestrictionsC-III; Prescribing of tablets for opioid dependence is limited to physicians who have met the qualification criteria and have received a DEA number specific to prescribing this product. Tablets will be available through pharmacies and wholesalers which normally provide controlled substances.
ContraindicationsHypersensitivity to buprenorphine, naloxone, or any component of the formulation
Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- Bowel obstruction: Use with caution in patients with a history of ileus or bowel obstruction.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Ethanol abuse: Use with caution in patients with alcoholism or delirium tremens.
- Glaucoma: Use with caution in patients with glaucoma.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Obesity: Use with caution in patients who are morbidly obese.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Psychosis: Use with caution in patients with toxic psychosis.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Safety and efficacy have not been established in children <16 years of age.

Other warnings/precautions:

- Appropriate use: Combination product is indicated for maintenance therapy and should not be used for induction. Oral buprenorphine is not approved for management of pain.

- Withdrawal: Partial antagonist activity of buprenorphine may precipitate acute narcotic withdrawal in opioid-dependent individuals upon rapid discontinuation. Naloxone may precipitate intense withdrawal symptoms in patients addicted to opiates when administered before the opioid effects have subsided, or misused parenterally in opioid-dependent individuals.

Pregnancy Risk FactorC

Pregnancy ConsiderationsWithdrawal has been reported in infants of women receiving buprenorphine during pregnancy. Onset of symptoms ranged from day 1 to day 8 of life, most occurring on day 1.

LactationBuprenorphine: Enters breast milk/not recommended

Adverse ReactionsAlso see individual agents.

>10%:

Central nervous system: Headache (36%), pain (22%)

Gastrointestinal: Nausea (15%), constipation (12%), abdominal pain (11%)

Miscellaneous: Withdrawal syndrome (25%; placebo 37%), diaphoresis (14%)

1% to 10%:

Cardiovascular: Vasodilation (9%)

Gastrointestinal: Vomiting (7%)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Atazanavir: May increase the serum concentration of Buprenorphine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Monitoring ParametersRespiratory and mental status, CNS depression; symptoms of withdrawal
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, sublingual: Buprenorphine 2 mg and naloxone 0.5 mg; buprenorphine 8 mg and naloxone 2 mg [lemon-lime flavor]

Generic AvailableNo
ManufacturerReckitt Benckiser
Pricing: U.S. (www.drugstore.com)

Sublingual (Suboxone)

8-2 mg (30): $172.33

Mechanism of ActionSee individual agents.
Pharmacodynamics/KineticsSee individual agents.

Absorption: Absorption of the combination product is variable among patients following sublingual use, but variability within each individual patient is low.

Related Information

- Addiction Treatments
- Buprenorphine
- Naloxone

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Index TermsBuprenorphine Hydrochloride and Naloxone Hydrochloride Dihydrate; Naloxone and Buprenorphine; Naloxone Hydrochloride Dihydrate and Buprenorphine Hydrochloride
References

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand NamesSuboxone (AT, AU, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, MY, NL, NO, NZ, PT, RU, SE, TR)

Buprenorphine

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Buprenex® may be confused with Brevibloc®, Bumex®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(byoo pre NOR feen)
U.S. Brand NamesBuprenex®; Subutex®
Canadian Brand NamesBuprenex®; Subutex®
Pharmacologic CategoryAnalgesic, Opioid
Use: Labeled Indications

Injection: Management of moderate to severe pain

Tablet: Treatment of opioid dependence

Use: Unlabeled/InvestigationalInjection: Heroin and opioid withdrawal
Dosing: Adults**Long-term use is not recommended**

Note: These are guidelines and do not represent the maximum doses that may be required in all patients. Doses should be titrated to pain relief/prevention. In high-risk patients (eg, elderly, debilitated, presence of respiratory disease) and/or concurrent CNS depressant use, reduce dose by one-half. Buprenorphine has an analgesic ceiling.

Acute pain (moderate to severe):

I.M.: Initial: Opiate-naive: 0.3 mg every 6-8 hours as needed; initial dose (up to 0.3 mg) may be repeated once in 30-60 minutes after the initial dose if needed; usual dosage range: 0.15-0.6 mg every 4-8 hours as needed

Slow I.V.: Initial: Opiate-naive: 0.3 mg every 6-8 hours as needed; initial dose (up to 0.3 mg) may be repeated once in 30-60 minutes after the initial dose if needed

Heroin or opiate withdrawal (unlabeled use): I.M., slow I.V.: Variable; 0.1-0.4 mg every 6 hours

Opioid dependence: Sublingual:

Induction: Range: 12-16 mg/day (doses during an induction study used 8 mg on day 1, followed by 16 mg on day 2; induction continued over 3-4 days). Treatment should begin at least 4 hours after last use of heroin or short-acting opioid, preferably when first signs of withdrawal appear. Titrating dose to clinical effectiveness should be done as rapidly as possible to prevent undue withdrawal symptoms and patient drop-out during the induction period.

Maintenance: Target dose: 16 mg/day; range: 4-24 mg/day; patients should be switched to the buprenorphine/naloxone combination product for maintenance and unsupervised therapy

Dosing: ElderlyModerate to severe pain: I.M., slow I.V.: 0.15 mg every 6 hours; elderly patients are more likely to suffer from confusion and drowsiness compared to younger patients. **Long-term use is not recommended.**
Dosing: Pediatric

Acute pain (moderate to severe):

Children 2-12 years: I.M., slow I.V.: 2-6 mcg/kg every 4-6 hours

Children ≥13 years: Refer to adult dosing.

Opioid dependence: Children ≥16 years: Refer to adult dosing.

Calculations

- Opioid Agonist Conversion

Administration: I.V.Administer slowly, over at least 2 minutes.
Administration: I.V. DetailpH: 3.5-5.5
Administration: OralSublingual: Tablet should be placed under the tongue until dissolved; should not be swallowed. If two or more tablets are needed per dose, all may be placed under the tongue at once, or two at a time. To ensure consistent bioavailability, subsequent doses should always be taken the same way.

Storage

Injection: Protect from excessive heat >40°C (>104°F) and light.

Tablet: Store at room temperature of 25°C (77°F).

CompatibilityInjection:

Y-site administration: Compatible: Allopurinol, amifostine, aztreonam, cefepime, cisatracurium, cladribine, docetaxel, etoposide, filgrastim, gatifloxacin, gemcitabine, granisetron, linezolid, melphalan, piperacillin/tazobactam, propofol, remifentanil, teniposide, thiotepa, vinorelbine. **Incompatible:** Amphotericin B cholesteryl sulfate complex, doxorubicin liposome.

Compatibility in syringe: Compatible: Midazolam.

Compatibility when admixed: Compatible: Atropine, bupivacaine, diphenhydramine, droperidol, glycopyrrolate, haloperidol, hydroxyzine, promethazine, scopolamine. **Incompatible:** Diazepam, floxacillin, furosemide, lorazepam.

RestrictionsInjection: C-V/C-III; Tablet: C-III

Prescribing of tablets for opioid dependence is limited to physicians who have met the qualification criteria and have received a DEA number specific to prescribing this product. Tablets will be available through pharmacies and wholesalers which normally provide controlled substances.

ContraindicationsHypersensitivity to buprenorphine or any component of the formulation

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.

- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.

- Bowel obstruction: Use with caution in patients with a history of ileus or bowel obstruction.

- CNS depression/coma: Use with caution in patients with CNS depression or coma.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Obesity: Use with caution in patients who are morbidly obese.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Psychosis: Use with caution in patients with toxic psychosis.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Safety and efficacy of the tablet formulation have not been established in children <16 years of age; safety and efficacy of the injection formulation have not been established in children <2 years of age.

Other warnings/precautions:

- Optimal regimen: An opioid-containing analgesic regimen should be tailored to each patient's needs and based upon the type of pain being treated (acute versus chronic), the route of administration, degree of tolerance for opioids (naive versus chronic user), age, weight, and medical condition. The optimal analgesic dose varies widely among patients; doses should be titrated to pain relief/prevention.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms. Tablets, which are used for induction treatment of opioid dependence, should not be started until effects of withdrawal are evident.

Geriatric ConsiderationsOne postmarketing study found that elderly patients were more likely to suffer from confusion and drowsiness after buprenorphine as compared to younger patients.

Pregnancy Risk FactorC

Pregnancy ConsiderationsWithdrawal has been reported in infants of women receiving buprenorphine during pregnancy. Onset of symptoms ranged from day 1 to day 8 of life, most occurring on day 1.

LactationEnters breast milk/not recommended

Adverse Reactions

Injection:

>10%: Central nervous system: Sedation

1% to 10%:

Cardiovascular: Hypotension

Central nervous system: Respiratory depression, dizziness, headache

Gastrointestinal: Vomiting, nausea

Ocular: Miosis

Otic: Vertigo

Miscellaneous: Diaphoresis

<1%: Agitation, allergic reaction, apnea, appetite decreased, blurred vision, bradycardia, confusion, constipation, convulsion, coma, cyanosis, depersonalization, depression, diplopia, dyspnea, dysphoria, euphoria, fatigue, flatulence, flushing, hallucinations, hypertension, injection site reaction, malaise, nervousness, pallor, paresthesia, pruritus, psychosis, rash, slurred speech, tachycardia, tinnitus, tremor, urinary retention, urticaria, weakness, Wenckebach block, xerostomia

Tablet:

>10%:

Central nervous system: Headache (30%), pain (24%), insomnia (21% to 25%), anxiety (12%), depression (11%)

Gastrointestinal: Nausea (10% to 14%), abdominal pain (12%), constipation (8% to 11%)

Neuromuscular & skeletal: Back pain (14%), weakness (14%)

Respiratory: Rhinitis (11%)

Miscellaneous: Withdrawal syndrome (19%; placebo 37%), infection (12% to 20%), diaphoresis (12% to 13%)

1% to 10%:

Central nervous system: Chills (6%), nervousness (6%), somnolence (5%), dizziness (4%), fever (3%)

Gastrointestinal: Vomiting (5% to 8%), diarrhea (5%), dyspepsia (3%)

Ocular: Lacrimation (5%)

Respiratory: Cough (4%), pharyngitis (4%)

Miscellaneous: Flu-like syndrome (6%)

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (weak), 2A6 (weak), 2C19 (weak), 2D6 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Atazanavir: May increase the serum concentration of Buprenorphine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersPain relief, respiratory and mental status, CNS depression, blood pressure; LFTs

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for possible additive or adverse interactions. Monitor for effectiveness of pain relief and adverse reactions or overdose (can cause respiratory depression) at beginning of therapy and at regular intervals with long-term use. For inpatients, implement safety measures. Assess knowledge/teach patient appropriate use (if self-administered). Teach patient to monitor and report adverse reactions and appropriate interventions to reduce side effects.

Monitoring: Lab TestsLFTs

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. May cause dizziness, drowsiness, confusion, or blurred vision (use caution when driving, climbing stairs, rising from sitting or lying position, or engaging in tasks requiring alertness until response to drug is known). You may experience nausea or vomiting (frequent mouth care, small frequent meals, sucking lozenges, or chewing gum may help); or constipation (increased exercise, fluids, or dietary fruit and fiber may help). If constipation is unresolved, consult prescriber about use of stool softeners and/or laxatives. Report unresolved nausea or vomiting; respiratory difficulty or shortness of breath; excessive sedation or unusual weakness; or rapid heartbeat or palpitations. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 0.3 mg/mL (1 mL) [C-III]

Buprenex®: 0.3 mg/mL (1 mL) [C-V]

Tablet, sublingual:

Subutex®: 2 mg, 8 mg

Generic AvailableYes: Injection

Pricing: U.S. (www.drugstore.com)

Solution (Buprenex)

0.3 mg/mL (5): $26.25

Mechanism of ActionBuprenorphine exerts its analgesic effect via high affinity binding to μ opiate receptors in the CNS; displays both agonist and antagonist activity

Pharmacodynamics/Kinetics

Onset of action: Analgesic: 10-30 minutes

Duration: 6-8 hours

Absorption: I.M., SubQ: 30% to 40%

Distribution: V_d: 97-187 L/kg

Protein binding: High

Metabolism: Primarily hepatic; extensive first-pass effect

Half-life elimination: 2.2-3 hours

Excretion: Feces (70%); urine (20% as unchanged drug)

Related Information

- Addiction Treatments
- Narcotic / Opioid Analgesics

Pharmacotherapy PearlsSubutex® (buprenorphine) should be limited to supervised use whenever possible; patients should be switched to Suboxone® (buprenorphine/naloxone) for maintenance and unsupervised therapy

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; rare reports of euphoria

Mental Health: Effects on Psychiatric TreatmentConcurrent use with benzodiazepines or barbiturates may result in CNS or respiratory depression

Anesthesia and Critical Care Concerns/Other ConsiderationsBuprenorphine has a longer duration of action than either morphine or meperidine. It may precipitate withdrawal in narcotic-dependent patients. Buprenorphine is not readily reversed by naloxone. Avoid in labor.

Index TermsBuprenorphine Hydrochloride

References

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International Brand NamesBrospina (MX); Bunondol (PL); Buprex (PE, PT); Buprine (TH); Butrans (GB, IE); Nopan (IL); Norphin (IN); Norspan Patch (AU, KP); Pentorel (IN); Shumeifen (CL); Subutex (AU, BE, CH, CZ, DE, DK, EE, FI, FR, HK, IE, IL, MY, NO, PT, SE); Temgesic (AE, AR, AT, BE, BF, BG, BH, BJ, BR, CH, CI, CY, CZ, DE, DK, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, NZ, OM, PK, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SY, TN, TR, TW, TZ, UG, YE, ZA, ZM, ZW); Tidigesic (IN); Transtec (CN, DE, ES, GB, HN, IE, MX, PL)

BuPROPion

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) has issued a statement in April 2008 recommending that all children diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the recommendations due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: Methylphenidate, amphetamine, dextroamphetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children’s Healthcare Quality.

For more information, refer to:

- http://americanheart.mediaroom.com/index.php?s=43&item=422
- http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1
- http://americanheart.mediaroom.com/index.php?s=43&item=398
- http://www.fda.gov/medwatch/safety/2007/safety07.htm
- http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html

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“Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder,” *J Am Acad*

Child Adolesc Psychiatry, 2007, 46(7):894-921.

Vetter VL, Elia J, Erickson CH, et al, “Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing,” *Circulation*, 2008, 117:2407-23.

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Medication Safety Issues

Sound-alike/look-alike issues:

BuPROPion may be confused with busPIRone

Wellbutrin SR® may be confused with Wellbutrin XL™

Wellbutrin XL™ may be confused with Wellbutrin SR®

Zyban® may be confused with Zagam®, Diovan®

Pronunciation(byoo PROE pee on)
U.S. Brand NamesBudeprion XL®; Budeprion™ SR; Buproban™; Wellbutrin SR®; Wellbutrin XL™; Wellbutrin®; Zyban®
Canadian Brand NamesNovo-Bupropion SR; Wellbutrin XL™; Wellbutrin®; Zyban®
Pharmacologic CategoryAntidepressant, Dopamine-Reuptake Inhibitor; Smoking Cessation Aid
Use: Labeled IndicationsTreatment of major depressive disorder, including seasonal affective disorder (SAD); adjunct in smoking cessation
Use: Unlabeled/InvestigationalAttention-deficit/hyperactivity disorder (ADHD); depression associated with bipolar disorder
Dosing: Adults

Depression: Oral:

Immediate release: 100 mg 3 times/day; begin at 100 mg twice daily; may increase to a maximum dose of 450 mg/day.

Sustained release: Initial: 150 mg/day in the morning; may increase to 150 mg twice daily by day 4 if tolerated; target dose: 300 mg/day given as 150 mg twice daily; maximum dose: 400 mg/day given as 200 mg twice daily.

Extended release: Initial: 150 mg/day in the morning; may increase as early as day 4 of dosing to 300 mg/day; maximum dose: 450 mg/day

SAD (Wellbutrin XL™): Oral: Initial: 150 mg/day in the morning; if tolerated, may increase after 1 week to 300 mg/day

Note: Prophylactic treatment should be reserved for those patients with frequent depressive episodes and/or significant impairment. Initiate treatment in the Autumn prior to symptom onset, and discontinue in early Spring with dose tapering to 150 mg/day for 2 weeks

Smoking cessation (Zyban®): Oral: Initiate with 150 mg once daily for 3 days; increase to 150 mg twice daily; treatment should continue for 7-12 weeks.

Dosing conversion between immediate, sustained, and extended release products: Convert using same total daily dose (up to the maximum recommended dose for a given dosage form), but adjust frequency as indicated for sustained (twice daily) or extended (once daily) release products.

Dosing: Elderly

Depression: Oral: Initial: 37.5 mg of immediate release tablets twice daily or 100 mg/day of sustained release tablets; increase by 37.5-100 mg every 3-4 days as tolerated. There is evidence that the elderly respond at 150 mg/day in divided doses, but some may require a higher dose. **Note:** Patients with Alzheimer’s dementia-related depression may require a lower starting dosage of 37.5 mg once or twice daily (100 mg/day sustained release), increased as needed up to 300 mg/day in divided doses (300 mg/day for sustained release)

Smoking cessation: Refer to adult dosing.

Dosing: PediatricADHD (unlabeled use): Oral: Children and Adolescents: 1.4-6 mg/kg/day
Dosing: Renal ImpairmentPer the manufacturer, the elimination of hydroxybupropion and threohydrobupropion are reduced in patients with end stage renal failure. Other research has noted a reduction in bupropion clearance (Turpeinen, 2007). Consider a reduction in frequency and/or dosage in this patient population.
Dosing: Hepatic Impairment

Mild-to-moderate hepatic impairment: Use with caution and/or reduced dose/frequency

Severe hepatic cirrhosis: Use with extreme caution; maximum dose:

Wellbutrin®: 75 mg/day;

Wellbutrin SR®: 100 mg/day or 150 mg every other day

Wellbutrin XL™: 150 mg every other day

Zyban®: 150 mg every other day

Note: The mean AUC increased by ~1.5-fold for hydroxybupropion and ~2.5-fold for erythro/threohydrobupropion; median T_{max} was observed 19 hours later for hydroxybupropion, 31 hours later for erythro/threohydrobupropion; mean half-life for hydroxybupropion increased fivefold, and increased twofold for erythro/threohydrobupropion in patients with severe hepatic cirrhosis compared to healthy volunteers.

Administration: Oral May be taken without regard to meals. Zyban® and extended release tablets should be swallowed whole; do not crush, chew, or divide. The insoluble shell of the extended-release tablet may remain intact during GI transit and is eliminated in the feces. Data from the manufacturer states that dividing Wellbutrin® SR tablets resulted in an increased rate of release at 15 minutes: “However, the divided tablet retained its sustained-release characteristics with similar increases of released bupropion at each sampling point beyond 15 minutes when compared to the intact Wellbutrin® SR tablet...” Bupropion is hydroscopic and therefore should be stored in a dry place. Splitting of large quantities in advance of administration is not advised since loss of potency may result. If necessary, splitting should be done cleanly without crushing.

Storage

Store at controlled room temperature of 20°C to 25°C (68°F to 77°F).

Wellbutrin XL™: Store at 15°C to 30°C (59°F to 86°F).

Restrictions An FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

Contraindications Hypersensitivity to bupropion or any component of the formulation; seizure disorder; anorexia/bulimia; use of MAO inhibitors within 14 days; patients undergoing abrupt discontinuation of ethanol or sedatives (including benzodiazepines); patients receiving other dosage forms of bupropion

Allergy Considerations

- BuPROPion Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Bupropion is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Bupropion is not FDA approved for bipolar depression.**

Concerns related to adverse effects:

- CNS stimulation: May cause CNS stimulation (restlessness, anxiety, insomnia) or anorexia.

- Cognitive impairment: May cause motor or cognitive impairment in some patients, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Delayed hypersensitivity reactions: Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity resembling serum sickness have been reported.

- Seizures: The risk of seizures is dose-dependent and increased in patients with a history of seizures, anorexia/bulimia, head trauma, CNS tumor, severe hepatic cirrhosis, abrupt discontinuation of sedative-hypnotics or ethanol, medications which lower seizure threshold (antipsychotics, antidepressants, theophyllines, systemic steroids), stimulants, or hypoglycemic agents. Discontinue and do not restart in patients experiencing a seizure.

- Sexual dysfunction: The incidence of sexual dysfunction with bupropion is generally lower than with SSRIs.

- Weight loss: May cause weight loss; use caution in patients where weight loss is not desirable.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease, history of hypertension, or coronary artery disease; treatment-emergent hypertension (including some severe cases) has been reported, both with bupropion alone and in combination with nicotine transdermal systems.

- Hepatic impairment: Use with caution in patients with hepatic impairment; reduced dose recommended.
- Renal impairment: Use with caution in patients with renal impairment; reduced dose recommended.

Special populations:

- Elderly: Use with caution in the elderly; may be at greater risk of accumulation during chronic dosing. Reduced dose recommended.

Dosage form specific issues:

- Extended release tablet: Insoluble tablet shell may remain intact and be visible in the stool.

Other warnings/precautions:

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

Geriatric ConsiderationsLimited data available about the use of bupropion in the elderly; two studies have found it equally effective when compared to imipramine. Its side effect profile (minimal anticholinergic and blood pressure effects) may make it useful in persons who do not tolerate traditional cyclic antidepressants. A single and multiple dose pharmacokinetic study suggested that accumulation of bupropion and its metabolites may occur in the elderly.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDue to adverse events observed in some animal studies, bupropion is classified as pregnancy category C. A significant increase in major teratogenic effects has not been observed following exposure to bupropion during pregnancy; however, the risk of spontaneous abortions may be increased (additional studies are needed to confirm). The long-term effects on development and behavior have not been studied.

Pregnancy itself does not provide protection against depression. The ACOG recommends that therapy with antidepressants during pregnancy be individualized and should incorporate the clinical expertise of the mental health clinician, obstetrician, primary care provider, and pediatrician. If treatment is needed, consider gradually stopping antidepressants 10-14 days before the expected date of delivery to prevent potential withdrawal symptoms in the infant. If this is done and the woman is considered to be at risk of relapse from her major depressive disorder, the medication can be restarted following delivery, although the dose should be readjusted to that required before pregnancy. Bupropion has also been evaluated for smoking cessation during pregnancy; current recommendations suggest that pharmacologic treatments be considered only after other therapies have failed. A registry has been established for women exposed to bupropion during pregnancy (800-336-2176).

LactationEnters breast milk/not recommended (AAP rates “of concern”)

Breast-Feeding ConsiderationsBupropion and its metabolites are excreted into breast milk, although neither bupropion nor its metabolites have been detected in the plasma of breast-fed infants. Adverse events have not been reported in older breast-fed infants; however, a seizure was noted in one 6-month old infant (a causal effect could not be confirmed). Breast-feeding is not recommended by the manufacturer. The AAP considers bupropion to be a “drug for which the effect on the nursing infant is unknown, but may be of concern.”

Pregnancy & Lactation, In-Depth

- BuPROPion in Pregnancy & Lactation

Adverse ReactionsFrequencies, when reported, reflect highest incidence reported with sustained release product.

>10%:

Cardiovascular: Tachycardia (11%)

Central nervous system: Headache (25% to 34%), insomnia (11% to 20%), dizziness (6% to 11%)

Gastrointestinal: Xerostomia (17% to 26%), weight loss (14% to 23%), nausea (1% to 18%)

Respiratory: Pharyngitis (3% to 13%)

1% to 10%:

Cardiovascular: Palpitation (2% to 6%), arrhythmias (5%), chest pain (3% to 4%), hypertension (2% to 4%, may be severe), flushing (1% to 4%), hypotension (3%)

Central nervous system: Agitation (2% to 9%), confusion (8%), anxiety (5% to 7%), hostility (6%), nervousness (3% to 5%), sleep disturbance (4%), sensory disturbance (4%), migraine (1% to 4%), abnormal dreams (3%), irritability (2% to 3%), somnolence (2% to 3%), pain (2% to 3%), memory decreased (up to 3%), fever (1% to 2%), CNS stimulation (1% to 2%), depression

Dermatologic: Rash (1% to 5%), pruritus (2% to 4%), urticaria (1% to 2%)

Endocrine & metabolic: Menstrual complaints (2% to 5%), hot flashes (1% to 3%), libido decreased (3%)

Gastrointestinal: Constipation (5% to 10%), abdominal pain (2% to 9%), diarrhea (5% to 7%), flatulence (6%), anorexia (3% to 5%), appetite increased (4%), taste perversion (2% to 4%), vomiting (2% to 4%), dyspepsia (3%), dysphagia (up to 2%)

Genitourinary: Urinary frequency (2% to 5%), urinary urgency (up to 2%), vaginal hemorrhage (up to 2%), UTI (up to 1%)

Neuromuscular & skeletal: Tremor (3% to 6%), myalgia (2% to 6%), weakness (2% to 4%), arthralgia (1% to 4%), arthritis (2%), akathisia (2%), paresthesia (1% to 2%), twitching (1% to 2%), neck pain

Ocular: Amblyopia (2%), blurred vision (2% to 3%)

Otic: Tinnitus (3% to 6%), auditory disturbance (5%)

Respiratory: Upper respiratory infection (9%), cough increased (1% to 4%), sinusitis (1% to 5%)

Miscellaneous: Infection (8% to 9%), diaphoresis increased (5% to 6%), allergic reaction (including anaphylaxis, pruritus, urticaria)

Postmarketing and/or case reports: Accommodation abnormality, aggression, akinesia, alopecia, amnesia, anemia, angioedema, aphasia, ataxia, atrioventricular block, bronchospasm, bruxism, chills, colitis, coma, coordination abnormal, cystitis, deafness, delirium, delusions, depersonalization, derealization, diplopia, dry eye, dysarthria, dyskinesia, dyspareunia, dysphoria, dystonia, ecchymosis, EEG abnormality, ejaculation abnormality, emotional lability, esophagitis, euphoria, exfoliative dermatitis, extrapyramidal syndrome, extrasystoles, facial edema, fever with rash (and other symptoms suggestive of delayed hypersensitivity resembling serum sickness), gastric reflux, gastrointestinal hemorrhage, gingivitis, glossitis, glycosuria, gum hemorrhage, gynecomastia, hallucinations, hepatic damage, hepatitis, hirsutism, hostility, hyper-/hypoglycemia, hyper-/hypokinesia, hypertonia, hypoesthesia, hypomania, impotence, intestinal perforation, intraocular pressure increased, jaundice, leg cramps, leukocytosis, leukopenia, libido increased, liver function abnormal, lymphadenopathy, maculopapular rash, malaise, manic reaction, menopause, MI, mouth ulcers, muscle rigidity, muscle weakness, musculoskeletal chest pain, mydriasis, myoclonus, neuralgia, neuropathy, painful erection, pancreatitis, pancytopenia, paranoia, paranoid reaction, phlebitis, pneumonia, photosensitivity, postural hypotension, prostate disorder, pulmonary embolism, restlessness, rhabdomyolysis, salivation increased, salpingitis, sciatica, seizure, SIADH, stomach ulcer, stomatitis, stroke, suicidal ideation, syncope, tardive dyskinesia, thirst, thrombocytopenia, tongue edema, urinary incontinence, urinary retention, vaginitis, vasodilation, vertigo

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2A6 (minor), 2B6 (major), 2C9 (minor), 2D6 (minor), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2D6 (weak)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2B6 Inducers (Strong): May increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Strong): May decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

Lopinavir: May decrease the serum concentration of BuPROPion. Concentrations of the active metabolite, hydroxybupropion, may also be decreased. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the neurotoxic (central) effect of BuPROPion. *Risk X: Avoid combination*

Ritonavir: May decrease the serum concentration of BuPROPion. *Risk C: Monitor therapy*

Tricyclic Antidepressants: BuPROPion may decrease the metabolism of Tricyclic Antidepressants. **Exceptions:** Amoxapine; Protriptyline. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, gotu kola, kava kava (may increase CNS depression).

Monitoring ParametersBody weight; mental status for depression, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased), anxiety, social functioning, mania, panic attacks

When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure, and consider obtaining ECG prior to initiation (Vetter, 2008).

Reference RangeTherapeutic levels (trough, 12 hours after last dose): 50-100 ng/mL
Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Perform careful cardiovascular assessment prior to initiating therapy. Monitor blood pressure at beginning of therapy and periodically with long-term use. Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Monitor for clinical worsening and suicidality, especially at the beginning of therapy or when dose changes occur. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Patient EducationBe aware that bupropion is marketed under different names and should not be taken together; Zyban® is for smoking cessation and Wellbutrin® is for treatment of depression. **Note:** Excessive use or abrupt discontinuation of alcohol or sedatives may alter seizure threshold.

Depression: Take as directed, in equally divided doses; do not take in larger dose or more often than recommended. Do not discontinue this medicine without consulting prescriber. Do not use alcohol or OTC medications not approved by prescriber. May cause drowsiness, clouded sensorium, headache, restlessness, or agitation (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or dry mouth (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); weight loss; constipation (increased exercise, fluids, fruit, or fiber may help); or impotence (reversible). Report persistent CNS effects (eg, agitation, confusion, anxiety, restlessness, insomnia, psychosis, hallucinations, seizures); suicidal ideation; muscle weakness or tremor; skin rash or irritation; chest pain or palpitations, abdominal pain or blood in stools; yellowing of skin or eyes; or respiratory difficulty, bronchitis, or unusual cough.

Smoking cessation: Use as directed; do not take extra doses. Do not combine nicotine patches with use of Zyban® unless approved by prescriber. May cause dry mouth and insomnia (these may resolve with continued use). Report any respiratory difficulty, unusual cough, dizziness, or muscle tremors.

Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 75 mg [generic for Wellbutrin®], 100 mg [generic for Wellbutrin®]

Wellbutrin®: 75 mg, 100 mg

Tablet, extended release, as hydrochloride: 100 mg [generic for Wellbutrin® SR], 150 mg [generic for Wellbutrin® SR], 150 mg [generic for Zyban®], 200 mg [generic for Wellbutrin® SR], 300 mg [generic for Wellbutrin XL™]

Budeprion™ SR: 100 mg [generic for Wellbutrin® SR; contains tartrazine], 150 mg [generic for Wellbutrin® SR]

Budeprion XL®: 150 mg [generic for Wellbutrin® XL], 300 mg [contains tartrazine; generic for Wellbutrin® XL]

Buproban™: 150 mg [generic for Zyban®]

Wellbutrin XL™: 150 mg, 300 mg

Tablet, sustained release, as hydrochloride: 100 mg [generic for Wellbutrin® SR], 150 mg [generic for Wellbutrin® SR], 150 mg [generic for Zyban®], 200 mg [generic for Wellbutrin® SR]

Wellbutrin® SR: 100 mg, 150 mg, 200 mg

Zyban®: 150 mg

Generic AvailableYes
ManufacturerGlaxoSmithKline
Pricing: U.S. (www.drugstore.com)

Tablet, 12-hour (Budeprion SR)

100 mg (60): $69.99

150 mg (30): $34.99

Tablet, 12-hour (BuPROPion HCl)

150 mg (60): $69.98

200 mg (60): $124.99

Tablet, 12-hour (BuPROPion HCl (Smoking Deter))

150 mg (60): $69.98

Tablet, 12-hour (Wellbutrin SR)

100 mg (60): $196.83

150 mg (60): $194.45

200 mg (60): $368.47

Tablet, 12-hour (Zyban)

150 mg (60): $198.72

Tablet, 24-hour (Budeprion XL)

150 mg (30): $125.99

300 mg (30): $129.98

Tablet, 24-hour (BuPROPion HCl)

300 mg (30): $132.98

Tablet, 24-hour (Wellbutrin XL)

150 mg (30): $152.19

300 mg (30): $201.40

Tablets (BuPROPion HCl)

75 mg (90): $61.99

100 mg (90): $79.99

Tablets (Wellbutrin)

75 mg (90): $181.93

100 mg (90): $240.31

Mechanism of ActionAminoketone antidepressant structurally different from all other marketed antidepressants; like other antidepressants the mechanism of bupropion's activity is not fully understood. Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine, and does not inhibit monoamine oxidase or the reuptake of serotonin. Metabolite inhibits the reuptake of norepinephrine. The primary mechanism of action is thought to be dopaminergic and/or noradrenergic.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: V_d: 19-21 L/kg

Protein binding: 82% to 88%

Metabolism: Extensively hepatic via CYP2B6 to hydroxybupropion; non-CYP-mediated metabolism to erythrohydrobupropion and threohydrobupropion. Metabolite activity ranges from 20% to 50% potency of bupropion.

Bioavailability: 5% to 20% in animals

Half-life:

Distribution: 3-4 hours

Elimination: 21 ± 9 hours; Metabolites: Hydroxybupropion: 20 ± 5 hours; Erythrohydrobupropion: 33 ± 10 hours; Threohydrobupropion: 37 ± 13 hours (metabolite accumulation has been noted in ESRD).

Time to peak, serum: Bupropion: ~3 hours; bupropion extended release: ~5 hours

Metabolites: Hydroxybupropion, erythrohydrobupropion, threohydrobupropion: 6 hours

Excretion: Urine (87%); feces (10%)

Related Information

- Addiction Treatments
- Antidepressant Agents
- Antidepressant Receptor Profile

Pharmacotherapy PearlsRisk of seizures: When using immediate release tablets, seizure risk is increased at total daily dosage >450 mg, individual dosages >150 mg, or by sudden, large increments in dose. Data for the immediate-release formulation of bupropion revealed a seizure incidence of 0.4% in patients treated at doses in the 300-450 mg/day range. The estimated seizure incidence increases almost 10-fold between 450 mg and 600 mg per day. Data for the sustained release dosage form revealed a seizure incidence of 0.1% in patients treated at a dosage range of 100-300 mg/day, and increases to ~0.4% at the maximum recommended dose of 400 mg/day.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Abnormal taste, significant xerostomia (normal salivary flow resumes with discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsPart of the mechanism of bupropion is to block reuptake of norepinephrine along with dopamine. Because of the potential for norepinephrine elevation within CNS synapses, it is suggested that vasoconstrictor be administered with caution and to monitor vital signs in dental patients taking antidepressants that affect norepinephrine in this way.

Mental Health: Child/Adolescent ConsiderationsAttention-deficit/hyperactivity disorder (ADHD): 1.4-5.7 mg/kg/day (mean: 3.3 mg/kg/day) was utilized in 15 ADHD subjects 7-17 years of age (Barrickman, 1995); 72 children with ADHD (6-12 years of age) received 3-6 mg/kg/day (Conners, 1996); adolescents with conduct disorder and substance use disorder were titrated to a maximum fixed daily dose of 300 mg (Riggs, 1998). The immediate-release dosage form was studied in clinical trials for indications other than depression in 104 pediatric patients. This limited exposure does not allow for assessment of the safety of bupropion in pediatric patients. Bupropion 100–350 mg/day (mean: 3.5 ± 0.8 mg/kg/day) was given to 57 children and adolescents 9–18 years of age with ADHD in a randomized controlled trial to assess whether it prevented smoking in nonsmokers for ≤6.5 years (mean: 12 months). Bupropion was not found to be superior to placebo for smoking prevention in youth with ADHD. Adverse effects were similar in bupropion and placebo groups (Monuteaux, 2007).

A pharmacokinetic study of bupropion SR, showed the mean half-life and threohydrobupropion metabolite of bupropion were significantly shorter in children 11-17 years of age compared to adults. The AUC were 19% and 80% higher for bupropion and its metabolite (respectively). This indicates it may be preferable to dose bupropion SR twice daily in children (Daviss, 2005).

Barrickman LL, Petty PJ, Allen AJ, et al, “Bupropion Versus Methylphenidate in the Treatment of Attention-Deficit Hyperactivity Disorder,” *J Am Acad Child Adolesc Psychiatry*, 1995, 34(5):649-57.

Conners CK, Casat CD, Gualtieri CT, et al, “Bupropion Hydrochloride in Attention Deficit Disorder With Hyperactivity,” *J Am Acad Child Adolesc Psychiatry*, 1996, 35(10):1314-21.

Daviss WB, Perel JM, Birmaher B, et al, “Steady-State Clinical Pharmacokinetics of Bupropion Extended-Release in Youths,” *J Am Acad Child Adolesc Psychiatry*, 2006, 45(12):1503-9.

Monuteaux MC, Spencer TJ, Faraone SV, et al, “A Randomized, Placebo-Controlled Clinical Trial of Bupropion for the Prevention of Smoking in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder,” *J Clin Psychiatry*, 2007, 68(7):1094-101.

Riggs PD, Leon SL, Mikulich SK, et al, “An Open Trial of Bupropion for ADHD in Adolescents With Substance Use Disorders and Conduct Disorder,” *J Am Acad Child Adolesc Psychiatry*, 1998, 37(12):1271-8.

Mental Health Comment Bupropion is an activating antidepressant that may be particularly useful for individuals whose depression is associated with fatigue and poor concentration. It is also used as an adjunct in smoking cessation and may benefit those with ADHD. While some evidence suggests that it is less likely to induce mania when used in individuals with bipolar disorder, the trials suggesting this are flawed. It is not associated with withdrawal symptoms so it can be stopped abruptly. Sexual dysfunction, seen commonly with the SSRI, is less problematic with bupropion.

Cardiovascular Considerations There are relatively few cardiovascular side effects compared to tricyclic antidepressants. However, several case reports include cardiovascular complications, including hypotension, hypertension, and MI. Use with caution in patients with recent MI or unstable angina. Recent information suggests that hypertension, in some cases severe and requiring acute treatment, has been reported in patients receiving bupropion alone, and especially when bupropion is used in conjunction with nicotine replacement therapy. These events have been observed in both patients with and without evidence of pre-existing hypertension. Data from a comparative study of sustained-release bupropion, nicotine transdermal system (NTS), the combination of sustained-release bupropion and NTS, and placebo suggest a higher incidence of treatment-emergent hypertension (>6%) in patients treated with the combination of sustained-release bupropion and NTS. The majority of these patients had evidence of pre-existing hypertension. Monitoring of blood pressure is recommended in patients receiving the combination of bupropion and nicotine replacement, particularly in those with hypertension and/or significant coronary artery disease. Possible potential problems need to be balanced against the very substantial benefits of smoking cessation.

Anesthesia and Critical Care Concerns/Other Considerations There are relatively few cardiovascular side effects compared to tricyclic antidepressants. However, several case reports include cardiovascular complications, including hypotension and MI. Use with caution in patients with recent MI or unstable angina. Recent information suggests that hypertension, in some cases severe and requiring acute treatment, has been reported in patients receiving bupropion alone, and especially when bupropion is used in conjunction with nicotine replacement therapy. Monitoring of blood pressure is recommended in patients receiving the combination of bupropion and nicotine replacement, particularly in those with hypertension and/or significant coronary artery disease.

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Barrickman LL, Petty PJ, Allen AJ, et al, “Bupropion Versus Methylphenidate in the Treatment of Attention-Deficit Hyperactivity Disorder,” *J Am Acad Child Adolesc Psychiatry*, 1995, 34(5):649-57. [PubMed 7775360]

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International Brand Names Bupep SR (IN); Buxon (CN); Clorprax (AU); Elontril (EE); Odranal (AR, CO); Prolev SR (HN); Quomen (TH); Wellbutrin (BB, BM, BS, BZ, CR, DO, GT, GY, HN, JM, MX, NI, NL, PA, PE, PY, SR, SV, TT, TW, VE); Wellbutrin SR (AR, CN, CO, HK, KP, PE, SG, UY); Zyban (BB, BE, BG, BM, BR, BS, BZ, CH, CZ, DE, DK, FI, FR, GB, GY, HK, IE, IL, IT, JM, MY, NL, NO, NZ, PL, PT, SE, SG, SR, TT, TW); Zyban LP (FR); Zyban SR (SG); Zyban Sustained Release (AU); Zyntabac (ES)

Buserelin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Suprefact® may be confused with Suprane®

Pronunciation(BYOO se rel in)

Canadian Brand NamesSuprefact®; Suprefact® Depot

Pharmacologic CategoryGonadotropin Releasing Hormone Agonist

Use: Labeled IndicationsPalliative treatment in patients with hormone-dependent advanced prostate cancer (stage D); treatment of endometriosis in women who do not require surgical intervention as first-line therapy (length of therapy is usually 6 months, but no longer than 9 months)

Use: Unlabeled/InvestigationalDiagnostic test for hypogonadotropic hypogonadism in males with delayed puberty

Dosing: Adults

Prostate cancer:Note: Administration of an antiandrogen agent beginning 7 days prior to initiation of buserelin therapy and continuing for ~5 weeks with buserelin therapy is recommended in patients with prostate cancer.

Sub Q:

Suprefact®: Initial: 500 mcg every 8 hours for 7 days. Maintenance: 200 mcg once daily

Suprefact Depot®

2-month: 6.3 mg implant injected into lateral abdominal wall every 8 weeks

3-month: 9.45 mg injected into lateral abdominal wall every 12 weeks

Intranasal (Suprefact®): Maintenance: 400 mcg (200 mcg into each nostril) 3 times/day

Endometriosis: Intranasal (Suprefact®): 400 mcg (200 mcg into each nostril) 3 times/day for 6-9 months

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Delayed puberty diagnostic test (unlabeled use):** Male: SubQ: 100 mcg once

Dosing: Renal ImpairmentNo adjustment necessary.

Dosing: Hepatic ImpairmentNo adjustment necessary.

Administration: InhalationAdminister at equal time intervals; before first application pump bottle several times in upright position until a uniform mist is released; priming may need to be repeated between uses

Administration: OtherSubQ: Rotate injection sites; administer at equal time intervals; a local anesthetic may be administered to injection site prior to implantation of depot

Storage

Injection: Store at room temperature of 15°C to 30°C (59°F to 86°F); do not freeze. Protect from light.

Depot: Store at room temperature of 15°C to 30°C (59°F to 86°F); protect from excessive heat.

Nasal solution: Store at room temperature of 15°C to 30°C (59°F to 86°F); do not freeze. Protect from light. Store in upright position.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to buserelin or any component of the formulation; patients with nonhormone-dependent prostate cancer; patients who have undergone orchiectomy; patients with undiagnosed abnormal vaginal bleeding; pregnancy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid reactions: Reactions including allergic asthma with dyspnea as well as rare anaphylactic/anaphylactoid shock have been observed in buserelin treated patients.
- Exacerbation of disease: A transient (usual duration <10 days) exacerbation of the signs and symptoms of the disease process may be observed with the initiation of therapy. Adjunctive antiandrogen therapy is recommended for patients with prostate cancer to minimize exacerbations.
- Pituitary adenoma: The development of pituitary adenomas may rarely be seen with long-term therapy.

Disease related concerns:

- Depression: Monitor patients with a history of depression and treat appropriately where indicated.

- Diabetes: Reduced glucose tolerance has been noted in rare cases. Use caution in patients with diabetes.

- Endometriosis: A transient exacerbation of the signs/symptoms may be associated with the initiation of therapy. Oral contraceptives should be discontinued prior to starting therapy; use of a nonhormonal contraceptive is recommended.

- Hypertension: Increases in blood pressure (including hypertensive crisis) may occur in patients being treated for hypertension. Monitor blood pressure regularly.

- Osteoporosis: Treatment inducing a hypoestrogenic state may lead to changes in bone density. The benefits and risks of potential buserelin therapy should be considered before treatment is initiated. Patients at risk for reduced bone density include those with chronic alcohol and/or tobacco use, family history of osteoporosis, and chronic treatment with anticonvulsants or corticosteroids. Use of buserelin for >6 months or in association with other risk factors may contribute to additional bone loss.

- Prostate cancer: Initiation of therapy without a concomitant antiandrogen agent may lead to a transient worsening of symptoms including bone pain, weakness of leg muscles, impaired micturition, hydronephrosis, lymphostasis, or thrombosis with pulmonary embolus. Caution and close monitoring should be used in patients with vertebral metastases who are at risk for lesion exacerbation with possible spinal cord compression; initiate antiandrogen therapy 7 days prior to beginning buserelin therapy and continue for 5 weeks with buserelin therapy. Reversal of hypogonadism induced by therapy has not been established in this patient population.

- Urinary obstruction: In patients with prostatic disease, a transient increase in patient symptoms may occur early in therapy. Monitor for signs of obstruction, urinary retention.

Other warnings and precautions:

- Pediatrics: Safety and efficacy have not been established in patients <18 years of age.

Pregnancy ConsiderationsBuserelin is contraindicated in pregnant women. Patients should employ a nonhormonal method of contraception during therapy. Ovulation may occur with a missed dose; in the event a patient conceives, therapy should be discontinued.

LactationEnters breast milk/not recommended

Adverse Reactions**Note:** Adverse reaction profile differs based on population/medication and route of administration.

Depot:

>10%:

Endocrine & metabolic: Hot flushes (14% to 23%)

Genitourinary: Impotence (2% to 23%)

Neuromuscular & skeletal: Weakness (<1% to 14%)

1% to 10%:

Cardiovascular: Hypertension (2% to 9%), palpitation (5%), edema (1%)

Central nervous system: Dizziness (5%), insomnia (<1% to 5%), depression (2%), pain (2%)

Endocrine & metabolic: Libido decreased (2% to 5%)

Gastrointestinal: Appetite increased (5%), nausea (5%)

Local: Injection site reaction (1% to 5%)

Neuromuscular & skeletal: Arthralgia (5%), myalgia (5%)

SubQ or intranasal:

>10%:

Central nervous system: Headache (20% to 29%)

Endocrine & metabolic: Libido decreased (12% to 85%), hot flushes (66% to 72%), vaginal dryness (29%), menorrhagia (24%)

Genitourinary: Impotence (75% to 80%)

Local: Injection site reaction (8% to 12%)

1% to 10%:

Cardiovascular: Edema (1% to 5%), palpitation (1% to 5%)

Central nervous system: Dizziness (9%), depression (8%), emotional lability (7%), anxiety (1% to 5%), hostility (1% to 5%), insomnia (1% to 5%), migraine (1% to 5%), nervousness (1% to 5%), pain (1% to 5%), malaise, sleep disorder

Dermatologic: Acne (5%), dry skin (1% to 5%), purpura (1% to 5%), skin disorder (1% to 5%), flare reaction (1% to 2%), pruritus

Endocrine & metabolic: Breast pain (1% to 5%), hirsutism (1% to 5%), menstrual disorder (1% to 5%), gynecomastia (1% to 2%), premenstrual syndrome

Gastrointestinal: Nausea (5% to 7%), constipation (1% to 5%), diarrhea (1% to 5%), gastrointestinal fullness (1% to 5%), taste perversion (1% to 5%), weight loss/gain (1% to 5%), xerostomia (1% to 2%), flatulence, sore throat, vomiting

Genitourinary: Dyspareunia (1% to 5%), vaginitis (1% to 5%), leukorrhea, pelvic pain, vaginal discharge, vaginal discomfort

Neuromuscular & skeletal: Weakness (7%), arthralgia (1% to 5%), myalgia (1% to 5%), neck rigidity (1% to 5%), paresthesia (1% to 5%), back pain

Respiratory: Upper respiratory infection (1% to 5%), rhinitis (1% to 5%), dry nose (1% to 2%)

Miscellaneous: Diaphoresis (1% to 2%), infection

All formulations: <1%, postmarketing, and/or case reports: Abnormal ejaculation, abnormal thinking, allergic reaction, amnesia, anorexia, arthritis, bilirubin increased, blurred vision, breast atrophy, chronic intestinal pseudo-obstruction, constipation, diabetes mellitus, drowsiness, dry eye, dyspnea, ear pain, epistaxis, exacerbation, fatigue, feminization (males), gastrointestinal pain, heart failure, hyperalgesia, hypercholesterolemia, hyperglycemia, hyperlipidemia, injection site hemorrhage, male genital pain, leukopenia, myeloid metaplasia, myopathy, ovarian cysts, pharyngitis, photosensitivity, pituitary adenoma, polydipsia, pyrexia, rash, suicide attempt, syncope, tachycardia, temporary blindness, thrombopenia, thrombophlebitis, thrombosis, tinnitus, transaminases increased, urinary retention, vaginal hemorrhage, vasodilation, vertigo

Drug Interactions

Antidiabetic Agents: Luteinizing Hormone-Releasing Hormone Analogs may diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Monitoring ParametersSerum testosterone levels (4-6 weeks after initiation of therapy and every 3 months thereafter), serum estradiol levels, prostate specific antigen (PSA), prostatic acid phosphatase (PAP), blood glucose levels(in patients with diabetes); bone scan, CT scan, ultrasound; digital rectal exam; blood pressure; mood changes

Hypogonadotropic hypogonadism testing (unlabeled use): Serum LH and FSH 4 hours after administration

Monitoring: Lab TestsSerum testosterone levels (4-6 weeks after initiation of therapy and every 3 months thereafter), serum estradiol levels, prostate specific antigen (PSA), prostatic acid phosphatase (PAP), blood glucose levels(in patients with diabetes)

Hypogonadotropic hypogonadism testing (unlabeled use): Serum LH and FSH 4 hours after administration

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, solution:

Suprefact® [CAN]: 1 mg/mL (5.5 mL, 10 mL) [contains benzyl alcohol] [not available in U.S.]

Solution, intranasal:

Suprefact® [CAN]: 1mg/1mL (10 mL) [contains benzalkonium chloride] [not available in U.S.]

Implant, subcutaneous:

Suprefact® [CAN] Depot: 6.3 mg [released over 2 months]; 9.45 mg [released over 3 months] [not available in U.S.]

ManufacturerSanofi-Aventis

Mechanism of ActionSynthetic peptide analog of Gonadotropin hormone releasing hormone (GnRH) with substitutions at positions 6 and 10; altered peptide structure results in a significantly magnified GnRH agonist effect with an extended duration of activity. Following an initial rise in the pituitary gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), chronic administration of buserelin results in a sustained suppression of LH and FSH and an interference with the production of ovarian and testicular steroids. Eventually, a decline in gonadal steroids to castration levels is observed.

Pharmacodynamics/Kinetics

Protein binding: 15%

Metabolism: Plasma; inactive metabolites

Half-life elimination: 70-80 minutes; Depot implants: 20-30 Days

Time to peak, plasma: Depot: <1 day

Excretion: Urine (67% as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsBuserelin may cause hypertension and palpitations. Monitor blood pressure prior to dental procedures if using local anesthesia with vasoconstrictor. There have been no reports of any direct interaction with buserelin and vasoconstrictor.

Mental Health: Effects on Mental StatusMay cause dizziness, insomnia, depression, emotional lability, anxiety, hostility, or nervousness

Mental Health: Effects on Psychiatric TreatmentSexual dysfunction is common; concurrent use with psychotropics may produce additive effects

Index TermsBuserelin Acetate

References

Ohlsson B, Veress B, Janciauskiene S, et al, “Chronic Intestinal Pseudo-Obstruction Due to Buserelin-Induced Formation of Anti-GnRH Antibodies,” *Gastroenterology*, 2007, 132(1):45-51.[PubMed 17241858]

Wilson DA, Hofman PL, Miles HL, et al, “Evaluation of the Buserelin Stimulation Test in Diagnosing Gonadotropin Deficiency in Males With

Delayed Puberty," *J Pediatr*, 2006, 148(1):89-94.[PubMed 17241858]

International Brand NamesSuprefact® Depot [CA]; Suprefact® [CA]

BusPIRone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

BusPIRone may be confused with buPROPion

Pronunciation(byoo SPYE rone)

U.S. Brand NamesBuSpar®

Canadian Brand NamesApo-Buspirone®; BuSpar®; Buspirex; Bustab®; CO Buspirone; Dom-Buspirone; Gen-Buspirone; Lin-Buspirone; Novo-Buspirone; Nu-Buspirone; PMS-Buspirone; ratio-Buspirone; Riva-Buspirone

Pharmacologic CategoryAntianxiety Agent, Miscellaneous

Use: Labeled IndicationsManagement of generalized anxiety disorder (GAD)

Use: Unlabeled/InvestigationalManagement of aggression in mental retardation and secondary mental disorders; major depression; potential augmenting agent for antidepressants; premenstrual syndrome

Dosing: AdultsAnxiety disorders (GAD): Oral: 15 mg/day (7.5 mg twice daily); may increase in increments of 5 mg/day every 2-3 days to a maximum of 60 mg/day. Target dose for most people is 20-30 mg/day (10-15 mg twice daily).

Dosing: ElderlyOral: Initial: 5 mg twice daily, increase by 5 mg/day every 2-3 days as needed up to 20-30 mg/day; maximum daily dose: 60 mg/day (see Geriatric Considerations).

Dosing: PediatricGeneralized anxiety disorder (GAD): Children ≥6 years and Adolescents: Oral: Initial: 5 mg daily; increase in increments of 5 mg/day at weekly intervals as needed, to a maximum dose of 60 mg/day divided into 2-3 doses

Dosing: Renal ImpairmentPatients with impaired renal function demonstrated increased plasma levels and a prolonged half-life of buspirone. Use in patients with severe renal impairment not recommended.

Dosing: Hepatic ImpairmentPatients with impaired hepatic function demonstrated increased plasma levels and a prolonged half-life of buspirone. Use in patients with severe hepatic impairment not recommended.

StorageStore at USP controlled room temperature of 25°C (77°F). Protect from light.

ContraindicationsHypersensitivity to buspirone or any component of the formulation

Allergy Considerations

- BusPIRone Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cognitive/motor impairment: Low potential for cognitive or motor impairment; until effects on patient known, patients should be warned to use caution when performing tasks which require mental alertness (eg, operating machinery or driving).
- Restlessness syndrome: Has been reported in small number of patients; may be attributable to buspirone’s antagonism of central dopamine receptors. Monitor for signs of any dopamine-related movement disorders (eg, dystonia, akathisia, pseudo-parkinsonism)

Disease-related concerns:

- Hepatic impairment: Use in patients with severe hepatic impairment is not recommended.
- Renal impairment: Use in patients with severe renal impairment is not recommended.

Concurrent drug therapy issues:

- MAO inhibitors: Use with MAO inhibitors may result in hypertensive reactions; concurrent use is not recommended.

Special populations:

- Pediatrics: Safety and efficacy of buspirone have not been established in children <6 years of age. No long-term safety/efficacy data available in children.

Other warnings/precautions:

- Sedative/hypnotic withdrawal: Buspirone does not exhibit cross-tolerance with benzodiazepines or other sedative/hypnotic agents. If substituting buspirone for any of these agents, gradually withdraw the drug(s) prior to initiating buspirone.

Geriatric ConsiderationsBecause buspirone is less sedating than other anxiolytics, it may be a useful agent in geriatric patients when an anxiolytic is indicated.

Pregnancy Risk FactorB

Pregnancy ConsiderationsNo impairment of fertility or fetotoxic effects were noted in animal studies with doses 30 times maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%: Central nervous system: Dizziness (12%)

1% to 10%:

Cardiovascular: Chest pain (>1%)

Central nervous system: Drowsiness (10%), headache (6%), nervousness (5%), lightheadedness (3%), anger/hostility (2%), confusion (2%), excitement (2%), dream disturbance (≥1%)

Dermatologic: Rash (1%)

Gastrointestinal: Nausea (8%), diarrhea (2%)

Neuromuscular & skeletal: Numbness (2%), weakness (2%), musculoskeletal pain (1%), paresthesia (1%), incoordination (1%), tremor (1%)

Ocular: Blurred vision (2%)

Otic: Tinnitus (≥1%)

Respiratory: Nasal congestion (≥1%), sore throat (≥1%)

Miscellaneous: Diaphoresis (1%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Akathisia, allergic reaction, angioedema, anorexia, bradycardia, bruising, cardiomyopathy, cogwheel rigidity, conjunctivitis, CVA, dyskinesia, dyspnea, dystonia, edema, enuresis, eosinophilia, epistaxis, EPS, galactorrhea, hallucination, heart failure, hyper-/hypotension, hyperventilation, irritable colon, leukopenia, menstrual irregularity, MI, muscle spasms, parkinsonism, personality disorders, PID, psychosis, rectal bleeding, restless leg syndrome, seizure, serotonin syndrome, suicidal ideation, syncope, thrombocytopenia, thyroid abnormality, transaminase increases, visual disturbances (tunnel vision)

Metabolism/Transport Effects

Substrate of CYP2D6 (minor), 3A4 (major)

Drug Interactions

Antidepressants (Serotonin Reuptake Inhibitor/Antagonist): BusPIRone may enhance the serotonergic effect of Antidepressants (Serotonin Reuptake Inhibitor/Antagonist). This may cause serotonin syndrome. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of BusPIRone. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

MAO Inhibitors: BusPIRone may enhance the adverse/toxic effect of MAO Inhibitors. Elevated blood pressure has been reported. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: BusPIRone may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. Selective Serotonin Reuptake Inhibitors may decrease the metabolism of BusPIRone. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Ethanol (may increase CNS depression).

Food: Food may decrease the absorption of buspirone, but it may also decrease the first-pass metabolism, thereby increasing the bioavailability of buspirone. Grapefruit juice may cause increased buspirone concentrations; avoid intake of large quantities of grapefruit juice.

Herb/Nutraceutical: St John's wort may decrease buspirone levels or increase CNS depression. Avoid valerian, gotu kola, kava kava (may increase CNS depression).

Monitoring ParametersMental status, symptoms of anxiety

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake only as directed; do not increase dose or take more often than prescribed. May take 2-3 weeks to see full effect; do not discontinue this medicine without consulting prescriber. Avoid large quantities of grapefruit juice. Do not use alcohol or other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or upset stomach, nausea (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report persistent vomiting; chest pain or rapid heartbeat; persistent CNS effects (eg, confusion, restlessness, anxiety, insomnia, excitation, headache, dizziness, fatigue, impaired coordination); or worsening of condition. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 5 mg, 7.5 mg, 10 mg, 15 mg, 30 mg

BuSpar®: 5 mg, 10 mg, 15 mg, 30 mg

Generic AvailableYes

ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)

Pricing: U.S. (www.drugstore.com)

Tablets (BuSpar)

5 mg (60): $67.99

10 mg (60): $109.99

15 mg (60): $169.97

30 mg (30): $147.73

Tablets (BusPIRone HCl)

5 mg (30): $14.00

7.5 mg (60): $45.99

10 mg (90): $19.00

15 mg (90): $69.31

30 mg (30): $50.99

Mechanism of ActionThe mechanism of action of buspirone is unknown. Buspirone has a high affinity for serotonin 5-HT$_{1A}$ and 5-HT$_2$ receptors, without affecting benzodiazepine-GABA receptors. Buspirone has moderate affinity for dopamine D$_2$ receptors.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: V$_d$: 5.3 L/kg

Protein binding: 86% to 95%

Metabolism: Hepatic oxidation, primarily via CYP3A4; extensive first-pass effect

Bioavailability: ~4%

Half-life elimination: 2-3 hours

Time to peak, serum: 40-90 minutes

Excretion: Urine: 29% to 63% (<0.1% dose excreted unchanged); feces: 18% to 38%

Related Information

- Nonbenzodiazepine Anxiolytics and Hypnotics
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsHas shown little potential for abuse; needs continuous use. Because of slow onset, not appropriate for “as needed” (prn) use or for brief, situational anxiety. Ineffective for treatment of benzodiazepine or ethanol withdrawal.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Child/Adolescent ConsiderationsAnxiety disorders: One pilot study of 15 children, 6-14 years of age (mean: 10 years), with mixed anxiety disorders, used initial doses of 5 mg/day; doses were individualized with increases in increments of 5 mg/day weekly as needed, to a maximum dose of 20 mg/day divided into 2 doses (mean dose required: 18.6 mg/day). Some authors (Carrey, 1996 and Kutcher, 1992), based on their clinical experience, recommend higher doses. Open-label study in 25 prepubertal inpatients (mean age: 8 years) with anxiety symptoms and moderately-aggressive behavior utilized a mean optimal dose of 28 mg/day (Pfeffer, 1997). Dosages ranging from 15-45 mg/day were utilized in children 6-17 years of age with pervasive developmental disorders (Buitelaar, 1998). The safety and efficacy of buspirone were evaluated in two placebo-controlled 6-week trials involving a total of 559 pediatric patients (6-17 years of age) with generalized anxiety disorder (GAD). Doses studied were 7.5-30 mg twice daily (15-60 mg/day). There were no significant differences between buspirone and placebo with regard to the symptoms of GAD following doses recommended for the treatment of GAD in adults (Bristol-Myers Squibb, BuSpar® package labeling, July 2001).

An open-label pharmacokinetic study was conducted in children (n=13), adolescents (n=12) with anxiety disorders, and healthy adults (n=14) to measure blood levels and adverse effects over 3 weeks. Children had the highest blood levels, significantly higher than adults on all doses studied. The most frequently reported adverse events in children and adolescents were lightheadedness (68%), headache (48%), and dyspepsia (20%); two children withdrew from the study at the higher doses (15 mg and 30 mg twice daily) due to adverse effects (Salazar, 2001).

Buitelaar JK, van der Gaag RJ, and van der Hoeven J, “Buspirone in the Management of Anxiety and Irritability in Children With Pervasive Developmental Disorders: Results of an Open-Label Study,” *J Clin Psychiatry*, 1998, 59(2):56-9.

Carrey NJ, Wiggins DM, and Milin RP, “Pharmacological Treatment of Psychiatric Disorders in Children and Adolescents,” *Drugs*, 1996, 51(5):750-9.

Kutcher SP, Reiter S, Gardner DM, et al, “The Pharmacotherapy of Anxiety Disorders in Children and Adolescents,” *Psychiatr Clin North Am*, 1992, 15(1):41-67.

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Salazar DE, Frackiewicz EJ, Dockens R, et al, "Pharmacokinetics and Tolerability of Buspirone During Oral Administration to Children and Adolescents With Anxiety Disorder and Normal Healthy Adults," *J Clin Pharmacol*, 2001, 41(12):1351-8.

Mental Health CommentBuspirone is an azaspirodecanedione (nonbenzodiazepine) anxiolytic and is not GABA-ergic. It is extensively metabolized primarily by oxidation producing several hydroxylated derivatives and a pharmacologically-active metabolite, 1-pyrimidinyl piperazine (1-PP). 1-PP has about 20% the activity of buspirone. Buspirone decreases anxiety without causing sedation or having anticonvulsant or muscle relaxant properties. Initial therapeutic effect is usually seen as a decrease in irritability and worry. Buspirone may be as effective as the benzodiazepines in relieving anxiety, but has a slow onset of action. It is important to wait 3-4 weeks before assessing the response to buspirone.

The advantages of buspirone include a low abuse potential (no reinforcing value in substance abusers and tended to cause dysphoria at doses >40 mg/day), causes no impairment of psychomotor activity, is not associated with dependence and can be abruptly discontinued, produces minimal sedation, and does not potentiate the effects of alcohol. May be useful for those who become disinhibited on benzodiazepines, those with a history of benzodiazepines/substance abuse, and those with a medical history in whom the use of a benzodiazepines may be risky.

The disadvantages of buspirone include a lag time for onset of anxiolytic effect similar to antidepressants, the requirement for multiple daily dosing, an inability to use as a PRN medication, a lack of cross tolerance with benzodiazepines, an inability to prevent withdrawal from benzodiazepines or alcohol, the requirement for adherent patients, and the potential for patients with previous exposure to benzodiazepines to be less likely to respond. For these reasons, buspirone is uncommonly utilized as an anxiolytic in most clinical settings.

Anesthesia and Critical Care Concerns/Other ConsiderationsTakes 2-3 weeks for full effect. Because of slow onset, not appropriate for “as needed” (prn) use or for brief, situational anxiety; not effective for severe anxiety; does not show cross-tolerance with benzodiazepines or other sedatives; less sedating than other anxiolytics; has shown little potential for abuse; needs continuous use; ineffective for benzodiazepine or ethanol withdrawal

Index TermsBuspirone Hydrochloride

References

Buitelaar JK, van der Gaag RJ, and van der Hoeven J, “Buspirone in the Management of Anxiety and Irritability in Children With Pervasive Developmental Disorders: Results of an Open-Label Study,” *J Clin Psychiatry*, 1998, 59(2):56-9.

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International Brand NamesActium (PY); Ansial (AR); Ansitec (BR); Anxinil (TW); Anxiolan (TH); Anxiron (AE, BH, CY, EG, HN, HU, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Anxut (DE); Bespar (DE, GR); Biron (NZ); Busiral (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Buspar (AT, AU, BE, BG, BR, CH, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, IE, IT, KP, LU, MX, NL, NO, PK, PT, RU, SE, TR, TW, ZA); Busparium (UY); Buspin (IN); Buspirone (GR, PL); Buxal (PL); Dalpas (VE); Kallmiren (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Mabuson (PL); Normaton (CO); Pasrin (ZA); Paxon (CN); Qibite (CL); Relac (TW); Seron (KP); Sorbon (IL); Spamilan (PL); Spitomin (BG, HU); Tran-Q (ID); Travin (HR); Xiety (ID)

Busulfan

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Busulfan may be confused with Butalan®

Myleran® may be confused with Alkeran®, Leukeran®, melphalan, Mylicon®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(byoo SUL fan)

U.S. Brand NamesBusulfex®; Myleran®

Canadian Brand NamesBusulfex®; Myleran®

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent

Use: Labeled Indications

Oral: Chronic myelogenous leukemia (CML); conditioning regimens for bone marrow transplantation

I.V.: Combination therapy with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia

Use: Unlabeled/InvestigationalOral: Bone marrow disorders, such as polycythemia vera and myeloid metaplasia; thrombocytosis

Dosing: Adults**Note:** Premedicate with prophylactic anticonvulsant therapy (eg, phenytoin) prior to high-dose busulfan treatment.

CML remission induction: Oral: 60 mcg/kg/day or 1.8 mg/m^2/day; usual range: 4-8 mg/day (may be as high as 12 mg/day); Maintenance doses: 1-4 mg/day to 2 mg/week to maintain WBC 10,000-20,000 cells/mm^3

BMT marrow-ablative conditioning regimen:

Oral: 1 mg/kg/dose (ideal body weight) every 6 hours for 16 doses

I.V.: 0.8 mg/kg (ideal body weight or actual body weight, whichever is lower); for obese or severely-obese patients adjusted ideal body weight is recommended) every 6 hours for 4 days (a total of 16 doses)

Polycythemia vera (unlabeled use): Oral: 2-6 mg/day

Thrombocytosis (unlabeled use): Oral: 4-6 mg/day

Dosing: ElderlyOral (refer to individual protocols): Start with lowest recommended doses for adults.

Dosing: Pediatric**Note:** Premedicate with prophylactic anticonvulsant therapy (eg, phenytoin) prior to high-dose busulfan treatment.

CML remission: Oral: Induction: 0.06-0.12 mg/kg/day **or** 1.8-4.6 mg/m^2/day; titrate dosage to maintain leukocyte count above 40,000/mm^3; reduce dosage by 50% if the leukocyte count reaches 30,000-40,000/mm^3; discontinue drug if counts fall to ≤20,000/mm^3.

BMT marrow-ablative conditioning regimen:

Oral: 1 mg/kg/dose (ideal body weight) every 6 hours for 16 doses

I.V.:

≤12 kg: 1.1 mg/kg/dose (ideal body weight) every 6 hours for 16 doses

>12 kg: 0.8 mg/kg/dose (ideal body weight) every 6 hours for 16 doses

Adjust dose to desired AUC [1125 µmol(min)] using the following formula:

Adjusted dose (mg) = Actual dose (mg) x [target AUC µmol(min) / actual AUC µmol(min)]

Dosing: Renal ImpairmentI.V.: Has not been studied in patients with renal impairment per the FDA-approved labeling. Some clinicians suggest adjustment is not necessary (Aronoff, 2007).

Dosing: Hepatic Impairment I.V.: Has not been administered in clinical studies in patients with hepatic impairment per the FDA-approved labeling. Busulfan has extensive hepatic metabolism and risk of hepatic veno-occlusive disease with high doses; dosage adjustment may be needed.

Oncology: Bone Marrow - High Dose**Note:** Generally combined with other high-dose chemotherapeutic drugs or total body irradiation.

Oral:

0.875-1 mg/kg/dose every 6 hours for 16 doses; total dose: 12-16 mg/kg

37.5 mg/m^2 every 6 hours for 16 doses; total dose: 600 mg/m^2 (studied primarily in pediatric patients)

150 mg/m^2 daily for 4 days; total dose: 600 mg/m^2 (studied primarily in pediatric patients)

I.V.: 0.8 mg/kg every 6 hours for 16 doses (4 days)

Calculations

- Body Surface Area: Pediatrics
- Ideal Body Weight: Adults
- Ideal Body Weight: Pediatrics

Administration: I.V.Intravenous busulfan should be administered as a 2-hour via central line.
Administration: Oral**BMT only:** To facilitate ingestion of high oral doses, insert multiple tablets into gelatin capsules.
Storage

Injection: Store unopened ampuls and vials under refrigeration (2°C to 8°C). Final solution is stable for up to 8 hours at room temperature (25°C); the infusion must be completed within that 8-hour timeframe. Dilution of busulfan injection in 0.9% sodium chloride is stable for up to 12 hours at refrigeration (2°C to 8°C); the infusion must be completed within that 12-hour timeframe.

Tablet: Store at room temperature at 15°C to 30°C (59°F to 86°F).

ReconstitutionInjection: Dilute (using manufacturer provided 5-micron filters for ampuls) in 0.9% sodium chloride injection or dextrose 5% in water. The dilution volume of busulfan injection, ensuring that the final concentration of busulfan is 0.5 mg/mL.
Compatibility**Variable stability (consult detailed reference)** in D_5W, NS.
ContraindicationsHypersensitivity to busulfan or any component of the formulation; oral busulfan is contraindicated in patients without a definitive diagnosis of CML
Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See "Concerns related to adverse effects" below.

- Experienced physician: See "Other warnings/precautions" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: Severe bone marrow suppression is common, resulting in possibly prolonged pancytopenia.** May result in severe neutropenia, thrombocytopenia, and/or anemia.

- Cardiovascular: Cardiac tamponade has been reported in children with thalassemia treated with high dose oral busulfan in combination with cyclophosphamide,

- Hepatic veno-occlusive disease: High busulfan area under the concentration versus time curve (AUC) values (>1500 µM/minute) are associated with increased risk of hepatic veno-occlusive disease (VOD) during conditioning for allogenic BMT. Patients with a history of radiation therapy, prior chemotherapy (≥3 cycles) and prior stem cell transplantation are also at increased risk of hepatic VOD at recommended doses regimens. Oral busulfan doses above 16 mg/kg (based on IBW) and concurrent use with alkylating agents may also increase the risk for hepatic VOD.

- Ovarian failure: Use has been associated with ovarian failure (including failure to achieve puberty) and amenorrhea.

- Pulmonary toxicity: May cause delayed pulmonary toxicity (known as "busulfan lung" − bronchopulmonary dysplasia with pulmonary fibrosis); may occur between 4 months and 10 years after treatment (the average onset is 4 years).

- Secondary malignancies: Tumors and acute leukemias have been reported following use.

- Seizures: Have been reported with use; initiate prophylactic anticonvulsant therapy (eg, phenytoin) prior to treatment.

Disease-related concerns:

- Seizures: Use with caution in patients predisposed to seizures, with a history of seizures or head trauma; initiate prophylactic anticonvulsant therapy (eg, phenytoin) prior to treatment.

Dosage form specific issues:

- Dimethylacetamide (DMA): The solvent in I.V. busulfan, DMA, may impair fertility. DMA may also be associated with hepatotoxicity, hallucinations, somnolence, lethargy, and confusion.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Geriatric ConsiderationsToxicity to immunosuppressives is increased in the elderly. Start with lowest recommended adult doses. Signs of infection, such as fever and rise in WBCs, may not occur. Lethargy and confusion may be more prominent signs of infection.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenic effects. May cause fetal harm if administered during pregnancy. The solvent in I.V. busulfan, DMA, is associated with teratogenic effects and may impair fertility. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should avoid pregnancy while receiving treatment.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the tumorigenicity potential and the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

I.V.:

>10%:

Cardiovascular: Tachycardia (44%), hypertension (36%; grades 3/4: 7%), edema (28% to 79%), thrombosis (33%), chest pain (26%), vasodilation (25%), hypotension (11%; grades 3/4: 3%)

Central nervous system: Insomnia (84%), fever (80%), anxiety (72% to 75%), headache (69%), chills (46%), pain (44%), dizziness (30%), depression (23%), confusion (11%)

Dermatologic: Rash (57%), pruritus (28%), alopecia (2% to 15%)

Endocrine & metabolic: Hypomagnesemia (77%), hyperglycemia (66%; grades 3/4: 15%), hypokalemia (64%), hypocalcemia (49%), hypophosphatemia (17%)

Gastrointestinal: Nausea (98%), mucositis/stomatitis (97%; grades 3/4: 26%), vomiting (43% to 95%), anorexia (85%), diarrhea (84%; grades 3/4: 5%), abdominal pain (72%), dyspepsia (44%), constipation (38%), xerostomia (26%), rectal disorder (25%), abdominal fullness (23%)

Hematologic: Myelosuppression (≤100%), neutropenia (100%; median recovery: 13 days), thrombocytopenia (98%; median onset: 5-6 days), lymphopenia (children: 79%), anemia (69%)

Hepatic: Hyperbilirubinemia (49%; grades 3/4: 30%), ALT increased (31%; grades 3/4: 7%), veno-occlusive disease (adults: 8% to 12%; children: 21%), jaundice (12%)

Local: Injection site inflammation (25%), injection site pain (15%)

Neuromuscular & skeletal: Weakness (51%), back pain (23%), myalgia (16%), arthralgia (13%)

Renal: Creatinine increased (21%), oliguria (15%)

Respiratory: Rhinitis (44%), lung disorder (34%), cough (28%), epistaxis (25%), dyspnea (25%), pneumonia (children: 21%), hiccup (18%), pharyngitis (18%)

Miscellaneous: Infection (51%), allergic reaction (26%)

1% to 10%:

Cardiovascular: Arrhythmia (5%), cardiomegaly (5%), atrial fibrillation (2%), ECG abnormal (2%), heart block (2%), heart failure (grade 3/4: 2%), pericardial effusion (2%), tamponade (children with thalassemia: 2%), ventricular extrasystoles (2%), hypervolemia

Central nervous system: Lethargy (7%), hallucination (5%), agitation (2%), delirium (2%), encephalopathy (2%), seizure (2%), somnolence (2%), cerebral hemorrhage (1%)

Dermatologic: Vesicular rash (10%), vesiculobullous rash (10%), skin discoloration (8%), maculopapular rash (8%), acne (7%), exfoliative dermatitis (5%), erythema nodosum (2%)

Endocrine & metabolic: Hyponatremia (2%)

Gastrointestinal: Ileus (8%), weight gain (8%), hematemesis (2%), pancreatitis (2%)

Hematologic: Prothrombin time increased (2%)

Hepatic: Hepatomegaly (6%)

Renal: Hematuria (8%), dysuria (7%), hemorrhagic cystitis (grade 3/4: 7%), BUN increased (3%)

Respiratory: Asthma (8%), alveolar hemorrhage (5%), hyperventilation (5%), hemoptysis (3%), pleural effusion (3%), sinusitis (3%), atelectasis (2%), hypoxia (2%)

Oral: Frequency not defined:

Central nervous system: Seizure

Dermatologic: Hyperpigmentation of skin (busulfan tan 5% to 10%), alopecia, rash, urticaria

Endocrine & metabolic: Amenorrhea, ovarian suppression

Hematologic: Myelosuppression (anemia, leukopenia, thrombocytopenia), pancytopenia

I.V. and/or Oral: Infrequent, postmarketing, and/or case reports: Acute leukemias, adrenal suppression, alopecia (permanent), aplastic anemia (may be irreversible), azoospermia, blurred vision, cataracts, cheilosis, cholestatic jaundice, corneal thinning, dry skin, endocardial fibrosis, erythema multiforme, erythema nodosum, esophageal varices, gynecomastia, hemorrhagic cystitis, hepatic dysfunction, hepatocellular atrophy, hyperuricemia, hyperuricosuria, interstitial pulmonary fibrosis (busulfan lung; manifested by a diffuse interstitial pulmonary fibrosis and persistent cough, fever, rales, and dyspnea; may be relieved by corticosteroids); malignant tumors, myasthenia gravis, ocular (lens) changes, ovarian failure, porphyria cutanea tarda, radiation myelopathy, radiation recall (skin rash), sepsis, sterility, testicular atrophy

Oncology: VesicantNo
Oncology: Emetic Potential

Low-dose: Very low (<10%)

High-dose: Moderate-to-high (30% to 90%)

Oncology: Bone Marrow - Unique Toxicity

Central nervous system: Generalized or myoclonic seizures and loss of consciousness, abnormal electroencephalographic findings

Gastrointestinal: Mucositis, anorexia, moderately emetogenic

Hepatic: Veno-occlusive disease (VOD), hyperbilirubinemia

Respiratory: Idiopathic pneumonia syndrome

Miscellaneous: Transient pain at tumor sites, transient autoimmune disorders

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)
Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Busulfan. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

MetroNIDAZOLE: May increase the serum concentration of Busulfan. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol due to GI irritation.

Food: No clear or firm data on the effect of food on busulfan bioavailability.

Herb/Nutraceutical: Avoid St John's wort (may decrease busulfan levels).

Monitoring ParametersCBC with differential and platelet count, liver function tests (evaluate transaminases, alkaline phosphatase, and bilirubin daily for at least 28 days post transplant)
Nursing: Physical Assessment/MonitoringIdentify any history of seizures, recent myelosuppressive therapy or radiation treatment, and pregnancy status prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, anything that may increase or decrease levels/effects of busulfan). Dosing should be based on adjusted ideal body weight (refer to individual protocols). BMT: Phenytoin or clonazepam may be ordered prophylactically during and for at least 48 hours following completion of busulfan to reduce risk of seizures if patient is predisposed to seizures. Assess results of laboratory tests (CBC with differential, platelet count, LFTs) and adverse pulmonary (pulmonary fibrosis or toxicity; may be delayed 4 months to 10 years) or hematologic effects (pancytopenia, leukopenia, thrombocytopenia, anemia, and bone marrow suppression) during therapy and for several months following therapy. Teach patient proper use (oral), possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsCBC with differential and platelet count, liver function (evaluate transaminases, alkaline phosphatase, and bilirubin daily for at least 28 days post transplant)
Patient EducationDo not take any new prescription, OTC medications, or herbal products during therapy unless approved by prescriber. Take

oral medication as directed. Maintain adequate nutrition (small, frequent meals) and hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid excess alcohol and acidic or spicy foods (may increase gastrointestinal irritation). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations unless approved by prescriber). May cause dizziness, insomnia, or confusion (use caution when driving or engaging in hazardous tasks until response to drug is known); mouth sores (brush teeth with soft toothbrush or cotton swab); loss of hair or darkening of skin color (reversible when medication is discontinued); nausea, vomiting, or loss of appetite (small, frequent meals, chewing gum, or sucking hard candy may help); constipation (increased exercise, fruit, fluids, or fiber may help); diarrhea (consult prescriber if severe or persistent); amenorrhea; sterility; or skin rash. Report palpitations or chest pain, excessive weight gain of >5 pounds; CNS changes (anxiety, confusion, depression); unusual cough or difficulty breathing; numbness or tingling of extremities; unusual bruising or bleeding; pain or changes in urination; or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Consult physician for instruction on appropriate barrier contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Busulfex®: 6 mg/mL (10 mL) [contains N,N-dimethylacetamide (DMA)]

Tablet:

Myleran®: 2 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Myleran)

2 mg (60): $173.76

Mechanism of ActionBusulfan is an alkylating agent which reacts with the N-7 position of guanosine and interferes with DNA replication and transcription of RNA. Busulfan has a more marked effect on myeloid cells than on lymphoid cells and is also very toxic to hematopoietic stem cells. Busulfan exhibits little immunosuppressive activity. Interferes with the normal function of DNA by alkylation and cross-linking the strands of DNA.

Pharmacodynamics/Kinetics

Duration: 28 days

Absorption: Rapid and complete

Distribution: V_d: ~1 L/kg; into CSF and saliva with levels similar to plasma

Protein binding: 32% to plasma proteins and 47% to red blood cells

Metabolism: Extensively hepatic (may increase with multiple doses); glutathione conjugation followed by oxidation

Half-life elimination: After first dose: 3.4 hours; After last dose: 2.3 hours

Time to peak, serum: Oral: Within 4 hours; I.V.: Within 5 minutes

Excretion: Urine (10% to 50% as metabolites) within 24 hours (<2% as unchanged drug)

Related Information

- Hematopoietic Stem Cell Transplantation
- Management of Nausea and Vomiting
- Safe Handling of Hazardous Drugs

Pharmacotherapy Pearls**Oncology Comment:** Low-dose monotherapy with oral busulfan for the palliative treatment of CML is no longer common. Treatment with imatinib or hematopoietic stem cell transplant (HSCT) are considered the primary treatments for CML (NCCN v1.2008).

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), mucositis/stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause severe pancytopenia; use caution with clozapine and carbamazepine

Oncology: Bone Marrow CommentsPhenytoin or clonazepam should be administered prophylactically during and for at least 48 hours following completion of busulfan. Risk of seizures is increased in patients with sickle cell disease. Increased risk of VOD when busulfan AUC >3000 µmol(min)/L (mean AUC, 2012 µmol(min)/L). Increased risk of failure to engraft for allogeneic BMT patients when AUC is <900 µmol (min)/L. To facilitate ingestion of high doses, multiple tablets may be inserted into gelatin capsules. Ursodiol 9-12 mg/kg/day may reduce the risk of hepatotoxicity.

Index TermsNSC-750

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International Brand Names Busilvex (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Busulfex (HK, IL, KP, MY, SG, TH); Mielucin (ES); Myleran (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CN, CY, CZ, DE, DK, EC, EG, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PL, PT, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, UY, YE, ZA, ZM, ZW)

Butabarbital

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Butabarbital may be confused with butalbital

Pronunciation(byoo ta BAR bi tal)

U.S. Brand NamesButisol Sodium®

Pharmacologic CategoryBarbiturate

Use: Labeled IndicationsSedative; hypnotic

Dosing: Adults

Anxiety (sedative): Oral: 15-30 mg 3-4 times/day

Insomnia (hypnotic): Oral: 50-100 mg at bedtime. When used for insomnia, treatment should be limited since barbiturates lose effectiveness for sleep induction and maintenance after 2 weeks.

Preoperative sedation: Oral: 50-100 mg 1-$1^{1}/_{2}$ hours before surgery

Dosing: ElderlyRefer to adult dosing. Use with caution; reduce dose if use is needed.

Dosing: PediatricPreoperative sedation: Oral: 2-6 mg/kg/dose; maximum: 100 mg

Dosing: Renal ImpairmentReduce dose if use is needed.

Dosing: Hepatic ImpairmentReduce dose if use is needed.

RestrictionsC-III

ContraindicationsHypersensitivity to barbiturates or any component of the formulation; porphyria

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypersensitivity reactions: Postmarketing studies have indicated that the use of hypnotic/sedative agents for sleep has been associated with hypersensitivity reactions including anaphylaxis as well as angioedema.
- Paradoxical responses: May cause paradoxical responses, including agitation and hyperactivity, particularly with pain, and in pediatric patients.
- Sleep-related activities: An increased risk for hazardous sleep-related activities such as sleep-driving; cooking and eating food, and making phone calls while asleep have also been noted. Discontinue treatment in patients who report a sleep-driving episode.

Disease-related concerns:

- Depression: Use with caution in patients with depression or suicidal tendencies.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease; may cause respiratory depression.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly. Closely monitor elderly or debilitated patients for impaired cognitive or motor performance.
- Pediatrics: Use with caution in children.

Dosage form specific issues:

- Tartrazine: Some products may contain tartrazine.

Other warnings/precautions:

- Appropriate use: Symptomatic treatment of insomnia should be initiated only after careful evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric and/or medical illness. A worsening of insomnia or the emergence of new abnormalities of thought or behavior may represent unrecognized psychiatric or medical illness and requires immediate and careful evaluation.

- Withdrawal: Abrupt cessation may precipitate withdrawal, including status epilepticus in epileptic patients.

Geriatric ConsiderationsElderly may react to barbiturates with marked excitement, depression, and confusion.
Pregnancy Risk FactorD
Pregnancy ConsiderationsBarbiturates cross the placenta and can be found in fetal tissues. Acute withdrawal symptoms may occur in the neonate following *in utero* exposure near term. Withdrawal symptoms may include seizures and hyperirritabilility and may be delayed for up to 14 days after birth.
LactationEnters breast milk/use with caution
Adverse Reactions

1% to 3%: Central nervous system: Somnolence

<1%: Abnormal thinking, agitation, anxiety, apnea, ataxia, bradycardia, confusion, constipation, depression, dizziness, hallucination, hyperkinesias, hypotension, hypoventilation, insomnia, nausea, nervousness, nightmares, psychiatric disturbance, syncope, vomiting

Frequency not defined, postmarketing, and/or case reports: Agranulocytosis, anaphylaxis, angioedema, complex sleep-related activities, dependence, exfoliative dermatitis, fever, headache, hypersensitivity reactions, liver damage, megaloblastic anemia, rash, respiratory depression, Stevens-Johnson syndrome, thrombocytopenia, thrombophlebitis

Drug Interactions

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

Griseofulvin: Barbiturates may decrease the absorption of Griseofulvin. *Risk D: Consider therapy modification*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Voriconazole: Barbiturates may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Rate of absorption is increased if given as solution on an empty stomach.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersCBC, renal and hepatic function with prolonged therapy

Reference RangeSerum plasma: Habitual/therapeutic: 1-15 mg/L; toxic: 10-20 mg/L; lethal 30 mg/L

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance. Evaluate periodically for need for continued use. Be alert to possibility of anaphylaxis any time during therapy. After long-term use, taper dosage slowly when discontinuing. For inpatient use, institute safety measures, monitor effectiveness and adverse reactions. For outpatient use, monitor effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC, renal and hepatic function with prolonged therapy

Patient EducationUse exactly as directed; do not increase dose or frequency or discontinue this medicine without consulting prescriber. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol or other prescription or OTC medications (especially, pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution driving or engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help). Report skin rash or irritation; CNS changes (confusion, depression, increased sedation, excitation, headache, insomnia, or nightmares); respiratory difficulty or shortness of breath; unusual swelling, especially on face and neck; difficulty swallowing or feeling of tightness in throat; unusual weakness or unusual bleeding in mouth, urine, or stool; or other unanticipated adverse effects. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Elixir, as sodium:

Butisol Sodium®: 30 mg/5 mL (480 mL) [contains alcohol 7%, propylene glycol, sodium benzoate, and tartrazine]

Tablet, as sodium:

Butisol Sodium®: 30 mg [contains tartrazine], 50 mg [contains tartrazine]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Elixir (Butisol Sodium)

30 mg/5 mL (140): $71.68

Tablets (Butisol Sodium)

30 mg (30): $52.42

50 mg (30): $68.68

Mechanism of ActionInterferes with transmission of impulses from the thalamus to the cortex of the brain resulting in an imbalance in central inhibitory and facilitatory mechanisms

Pharmacodynamics/Kinetics

Onset of action: 45-60 minutes

Duration: 6-8 hours

Absorption: Rapid

Metabolism: Hepatic

Half-life elimination: ~100 hours

Excretion: Urine (as metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common

Mental Health: Effects on Psychiatric TreatmentRare reports of agranulocytosis; use caution with clozapine and carbamazepine; enzyme induction effects of barbiturates may decrease effects of psychotropics; CNS depressant effects of psychotropics may be enhanced by barbiturates

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep. Barbiturates are generally not utilized as first-line agents to manage anxiety or insomnia due to abuse potential and potential for drug interactions and adverse effects.

References

Repetto MR and Repett M, “Habitual, Toxic and Lethal Concentrations of 103 Drugs of Abuse in Humans,” *J Toxicol Clin Toxicol*, 1997, 35(1):1-9.[PubMed 9022645]

International Brand NamesBrevinarcon (PL); Soneryl (GB)

Butalbital, Acetaminophen, Caffeine, and Codeine

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Medication Safety Issues

Sound-alike/look-alike issues:

Fioricet® may be confused with Fiorinal®, Florinef®, Lorcet®, Percocet®

Phrenilin® may be confused with Phenergan®, Trinalin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(byoo TAL bi tal, a seet a MIN oh fen, KAF een, & KOE deen)
U.S. Brand NamesFioricet® with Codeine; Phrenilin® with Caffeine and Codeine
Pharmacologic CategoryAnalgesic Combination (Opioid); Barbiturate
Use: Labeled IndicationsRelief of symptoms of complex tension (muscle contraction) headache
Dosing: AdultsOral: Adults: 1-2 capsules every 4 hours. Total daily dosage should not exceed 6 capsules.
Dosing: ElderlyRefer to adult dosing.
Dosing: Hepatic ImpairmentUse with caution. Limited, low-dose therapy usually well tolerated in hepatic disease/cirrhosis. However, cases of hepatotoxicity at daily acetaminophen dosages <4 g/day have been reported. Avoid chronic use in hepatic impairment.
StorageStore below 30°C (86°F).
RestrictionsC-III
ContraindicationsHypersensitivity to butalbital, codeine, caffeine, acetaminophen, or any component of the formulation; porphyria
Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity
- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hepatotoxicity: May cause severe hepatic toxicity on acute overdose; in addition, chronic daily dosing in adults has resulted in liver damage in some patients.
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene-derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.
- G6PD deficiency: Use with caution in patients with known G6PD deficiency.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

- CYP2D6 “ultra-rapid metabolizers”: Use caution in patients with two or more copies of the variant CYP2D6*2 allele; may have extensive conversion from codeine to morphine and thus increased opioid-mediated effects.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Caffeine: May cause CNS and cardiovascular stimulation, as well as GI irritation in high doses. Use with caution in patients with a history of peptic ulcer or GERD; avoid in patients with symptomatic cardiac arrhythmias.

- Dosage limit: Limit acetaminophen to <4 g/day.

Geriatric ConsiderationsElderly may react to barbiturates with marked excitement, depression, and confusion.

Pregnancy Risk FactorC (per manufacturer)

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Refer to the acetaminophen, caffeine, and codeine monographs for additional information. Butalbital crosses the placenta; may cause withdrawal seizures when taken during pregnancy.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsRefer to individual agents. Information specific to butalbital is not available. Discontinuation of breast-feeding or discontinuation of the drug should be considered.

Adverse ReactionsFrequency not defined.

Cardiovascular: Syncope, tachycardia

Central nervous system: Agitation, depression, dizziness, drowsiness, euphoria, excitement, fatigue, fever, headache, high energy, intoxicated feeling, lightheadedness, mental confusion, sedation, seizure, sluggishness

Dermatologic: Hyperhidrosis, pruritus

Endocrine & metabolic: Hot flashes

Gastrointestinal: Abdominal pain, constipation, dysphagia, flatulence, heartburn, nausea, vomiting, xerostomia

Neuromuscular & skeletal: Leg pain, muscle fatigue, numbness, paresthesia, shaky feeling

Ocular: Heavy eyelids

Otic: Earache, tinnitus

Renal: Diuresis

Respiratory: Dyspnea, nasal congestion

Miscellaneous: Allergic reaction

Note: Potential reactions associated with components of Fioricet® with Codeine include agranulocytosis, cardiac stimulation, dependence, erythema multiforme, hyperglycemia, irritability, nephrotoxicity, rash, thrombocytopenia, toxic epidermal necrolysis, tremor

Metabolism/Transport Effects

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Caffeine: **Substrate** of CYP1A2 (major), 2C9 (minor), 2D6 (minor), 2E1 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 3A4 (moderate)

Codeine: **Substrate** of CYP2D6 (major), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic

doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Griseofulvin: Barbiturates may decrease the absorption of Griseofulvin. *Risk D: Consider therapy modification*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Quinolone Antibiotics: May decrease the metabolism of Caffeine. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Ofloxacin; Sparfloxacin; Trovafloxacin. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Regadenoson: Caffeine may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Voriconazole: Barbiturates may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Test InteractionsAcetaminophen may produce false-positive tests for urinary 5-hydroxyindoleacetic acid; codeine may increase serum amylase levels
Monitoring ParametersHepatic and renal function tests (in patients with impairment)
Nursing: Physical Assessment/MonitoringSee individual agents for Acetaminophen, Caffeine, and Codeine.
Monitoring: Lab TestsHepatic and renal function tests (in patients with impairment)
Patient EducationSee individual agents for Acetaminophen, Caffeine, and Codeine.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: Butalbital 50 mg, acetaminophen 325 mg, caffeine 40 mg, and codeine phosphate 30 mg

Fioricet® with Codeine: Butalbital 50 mg, acetaminophen 325 mg, caffeine 40 mg, and codeine phosphate 30 mg

Phrenilin® with Caffeine and Codeine: Butalbital 50 mg, acetaminophen 325 mg, caffeine 40 mg, and codeine phosphate 30 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsules (Butalbital-APAP-Caff-Cod)

50-325-40-30 mg (30): $44.99

Capsules (Fioricet/Codeine)

50-325-40-30 mg (30): $94.58

Mechanism of ActionCombination product for the treatment of tension headache. Contains codeine (narcotic analgesic), butalbital (barbiturate), caffeine (CNS stimulant), and acetaminophen (nonopiate, nonsalicylate analgesic).

Related Information

- Acetaminophen
- Caffeine
- Codeine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause confusion, disorientation, nervousness, hallucinations, euphoria, agitation, irritability, depression, or drowsiness

Mental Health: Effects on Psychiatric TreatmentMay cause severe hepatic toxicity in overdose, use caution in patients with alcoholic liver disease. May cause agranulocytosis, use caution with clozapine and carbamazepine. May cause thrombocytopenia, use caution with valproate.

Index TermsAcetaminophen, Caffeine, Codeine, and Butalbital; Caffeine, Acetaminophen, Butalbital, and Codeine; Codeine, Acetaminophen, Butalbital, and Caffeine

References

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

Butalbital, Acetaminophen, and Caffeine

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Fioricet® may be confused with Fiorinal®, Lorcet®

Repan® may be confused with Riopan®

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(byoo TAL bi tal, a seet a MIN oh fen, & KAF een)

U.S. Brand NamesAnolor 300; Dolgic® LQ; Dolgic® Plus; Esgic-Plus™; Esgic®; Fioricet®; Medigesic®; Repan®; Zebutal™

Pharmacologic CategoryBarbiturate

Use: Labeled IndicationsRelief of the symptomatic complex of tension or muscle contraction headache

Dosing: AdultsTension or muscle contraction headache: Oral: 1-2 tablets or capsules (or 15-30 mL solution) every 4 hours; not to exceed 6 tablets or capsules (or 180 mL solution) daily

Dosing: ElderlyNot recommended for use in the elderly.

Dosing: Renal ImpairmentDosage should be reduced.

Dosing: Hepatic ImpairmentDosage should be reduced.

StorageStore at room temperature below 30°C (86°F). Protect from moisture.

ContraindicationsHypersensitivity to butalbital, acetaminophen, caffeine, or any component of the formulation; porphyria

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity
- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Hepatotoxicity: May cause severe hepatic toxicity on acute overdose; in addition, chronic daily dosing in adults has resulted in liver damage in some patients.

Disease-related concerns:

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.

- G6PD deficiency: Use with caution in patients with known G6PD deficiency.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Caffeine: May cause CNS and cardiovascular stimulation, as well as GI irritation in high doses. Use with caution in patients with a history of peptic ulcer or GERD; avoid in patients with symptomatic cardiac arrhythmias.

- Dosage limit: Limit acetaminophen to <4 g/day.

Geriatric ConsiderationsElderly may react to barbiturates with marked excitement, depression, and confusion.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. The FDA pregnancy classification for most other barbiturates is Category D. Withdrawal seizures were reported in an infant 2 days after birth following maternal use of a butalbital product during the last 2 months of pregnancy; butalbital levels were measured in the infants serum. In general, barbiturates cross the placenta and distribute in fetal tissue. Teratogenic effects have been reported with 1st trimester exposure. Exposure during the third trimester may lead to symptoms of acute withdrawal following delivery; symptoms may be delayed up to 14 days. Refer to individual agents for specific information related to acetaminophen and caffeine.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsSpecific data is not available for butalbital. Barbiturates, caffeine, and acetaminophen are excreted in breast milk. The manufacturer recommends discontinuing this medication or discontinuing nursing.

Adverse Reactions**Note:** Specific percentages not reported.

Frequently observed:

Central nervous system: Dizziness, drowsiness, lightheadedness, sedation

Gastrointestinal: Abdominal pain, nausea, vomiting

Respiratory: Dyspnea

Miscellaneous: Intoxicated feeling

Infrequently observed:

Cardiovascular: Tachycardia

Central nervous system: Agitation, confusion, depression, euphoria, excitement, faintness, fever, headache, seizure

Dermatologic: Hyperhidrosis, pruritus

Endocrine & metabolic: Hot spells

Gastrointestinal: Constipation, dysphagia, heartburn, flatulence, xerostomia

Neuromuscular & skeletal: Leg pain, muscle fatigue, numbness, paresthesia

Ocular: Heavy eyelids

Otic: Earache, tinnitus

Renal: Diuresis

Respiratory: Nasal congestion

Miscellaneous: Allergic reaction, high energy, shaky feeling, sluggishness

Metabolism/Transport Effects

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Caffeine: **Substrate** of CYP1A2 (major), 2C9 (minor), 2D6 (minor), 2E1 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 3A4 (moderate)

Drug Interactions

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Griseofulvin: Barbiturates may decrease the absorption of Griseofulvin. *Risk D: Consider therapy modification*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Quinolone Antibiotics: May decrease the metabolism of Caffeine. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Ofloxacin; Sparfloxacin; Trovafloxacin. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Regadenoson: Caffeine may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Voriconazole: Barbiturates may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Test InteractionsAcetaminophen may produce false-positive tests for urinary 5-hydroxyindoleacetic acid.
Nursing: Physical Assessment/MonitoringSee individual agents for Acetaminophen and Caffeine.
Patient EducationSee individual agents for Acetaminophen and Caffeine.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Anolor 300, Esgic®, Medigesic®: Butalbital 50 mg, acetaminophen 325 mg, and caffeine 40 mg

Dolgic® Plus: Butalbital 50 mg, acetaminophen 750 mg, and caffeine 40 mg

Esgic-Plus™, Zebutal™: Butalbital 50 mg, acetaminophen 500 mg, and caffeine 40 mg

Solution:

Dolgic® LQ: Butalbital 50 mg, acetaminophen 325 mg, and caffeine 40 mg per 15 mL (480 mL) [contains alcohol 7%; tropical fruit punch flavor]

Tablet: Butalbital 50 mg, acetaminophen 325 mg, and caffeine 40 mg; butalbital 50 mg, acetaminophen 500 mg, and caffeine 40 mg

Esgic®, Fioricet®, Repan®: Butalbital 50 mg, acetaminophen 325 mg, and caffeine 40 mg

Esgic-Plus™: Butalbital 50 mg, acetaminophen 500 mg, and caffeine 40 mg

Generic AvailableYes: Excludes solution
Pricing: U.S. (www.drugstore.com)

Capsules (Butalbital-APAP-Caffeine)

50-325-40 mg (100): $39.99

Capsules (Zebutal)

50-500-40 mg (30): $46.27

Tablets (Butalbital-APAP-Caffeine)

50-500-40 mg (30): $18.99

Tablets (Dolgic Plus)

50-750-40 mg (100): $139.99

Tablets (Esgic)

50-325-40 mg (30): $70.71

Tablets (Esgic-Plus)

50-500-40 mg (30): $58.23

Tablets (Fioricet)

50-325-40 mg (30): $49.44

Tablets (Repan)

50-325-40 mg (30): $36.59

Mechanism of Action

Butalbital is a short- to intermediate-acting barbiturate. Barbiturates depress the sensory cortex, decrease motor activity, alter cerebellar function, and produce drowsiness, sedation, hypnosis, and dose-dependent respiratory depression.

Acetaminophen inhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation; produces antipyresis from inhibition of hypothalamic heat-regulating center

Caffeine increases levels of 3'5' cyclic AMP by inhibiting phosphodiesterase; CNS stimulant which increases medullary respiratory center sensitivity to carbon dioxide, stimulates central inspiratory drive, and improves skeletal muscle contraction (diaphragmatic contractility)

Pharmacodynamics/KineticsAlso see Acetaminophen and Caffeine.

Absorption: Butalbital: Well absorbed

Protein binding: Butalbital: 45%

Half-life elimination: Butalbital: 35 hours

Excretion: Butalbital: Urine (59% to 88% as unchanged drug and metabolites)

Related Information

- Acetaminophen
- Caffeine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause depression, nervousness, insomnia, and nightmares; rare reports of hallucinations

Mental Health: Effects on Psychiatric TreatmentRare reports of agranulocytosis; use caution with clozapine and carbamazepine; CNS depressant effects of psychotropics may be enhance by barbiturates; enzyme induction effects of barbiturates may decrease effects of psychotropics

Index TermsAcetaminophen, Butalbital, and Caffeine

Butalbital and Acetaminophen

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Medication Safety Issues

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(byoo TAL bi tal & a seet a MIN oh fen)

U.S. Brand NamesBupap; Cephadyn; Phrenilin®; Phrenilin® Forte; Promacet; Sedapap®

Pharmacologic CategoryAnalgesic, Miscellaneous; Barbiturate

Use: Labeled IndicationsRelief of the symptomatic complex of tension or muscle contraction headache

Dosing: Adults**Tension or muscle contraction headache:** Oral: One tablet/capsule every 4 hours as needed (maximum dose: 6 tablets/day)

Phrenilin®: 1-2 tablets every 4 hours as needed (maximum 6 tablets in 24 hours)

Dosing: ElderlyRefer to adult dosing. Use with caution.

Dosing: Renal ImpairmentMild-to-moderate: Should decrease dose; in severe impairment, use with caution.

Dosing: Hepatic ImpairmentMild-to-moderate: Should decrease dose; in severe impairment, use with caution.

StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light.

ContraindicationsHypersensitivity to butalbital, acetaminophen, or any component of the formulation; porphyria

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hepatotoxicity: May cause severe hepatic toxicity on acute overdose; in addition, chronic daily dosing in adults has resulted in liver damage in some patients.

Disease-related concerns:

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.
- G6PD deficiency: Use with caution in patients with known G6PD deficiency.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Renal impairment: Use with caution in patients with severe renal impairment.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.
- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Dosage limit: Limit acetaminophen to <4 g/day.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. The FDA pregnancy classification for most other barbiturates is Category D. Withdrawal seizures were reported in an infant 2 days after birth following maternal use of a butalbital product during the last 2 months of pregnancy; butalbital levels were measured in the infant's serum. In general, barbiturates cross the placenta and distribute in fetal tissue. Teratogenic effects have been reported with first trimester exposure. Exposure during the third trimester may lead to symptoms of acute withdrawal following delivery; symptoms may be delayed up to 14 days. Refer to Acetaminophen monograph for information specific to acetaminophen.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsSpecific data is not available for butalbital. Barbiturates and acetaminophen are excreted in breast milk. The manufacturer recommends discontinuing this medication or discontinue nursing.

Adverse Reactions

Frequently observed:

Central nervous system: Dizziness, drowsiness, lightheadedness, sedation

Gastrointestinal: Abdominal pain, nausea, vomiting

Respiratory: Dyspnea

Miscellaneous: Intoxicated feeling

Infrequently observed:

Cardiovascular: Tachycardia

Central nervous system: Agitation, confusion, depression, euphoria, excitement, faintness, fever, headache, seizure

Dermatologic: Hyperhidrosis, pruritus

Endocrine & metabolic: Hot spells

Gastrointestinal: Constipation, dysphagia, heartburn, flatulence, xerostomia

Neuromuscular & skeletal: Leg pain, muscle fatigue, numbness, paresthesia

Ocular: Heavy eyelids

Otic: Earache, tinnitus

Renal: Diuresis

Respiratory: Nasal congestion

Miscellaneous: Allergic reaction, high energy, shaky feeling, sluggishness

Postmarketing and/or case reports (limited to important or life-threatening): Toxic epidermal necrolysis, erythema multiforme

Metabolism/Transport Effects

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Butalbital: See Phenobarbital monograph

Drug Interactions

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

Griseofulvin: Barbiturates may decrease the absorption of Griseofulvin. *Risk D: Consider therapy modification*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Voriconazole: Barbiturates may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Test InteractionsAcetaminophen may produce false-positive tests for urinary 5-hydroxyindoleacetic acid.
Nursing: Physical Assessment/MonitoringSee individual agent for Acetaminophen.
Patient EducationSee individual agent for Acetaminophen.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Phrenilin®: Butalbital 50 mg and acetaminophen 325 mg

Bupap, Cephadyn, Promacet, Sedapap®: Butalbital 50 mg and acetaminophen 650 mg

Capsule:

Phrenilin® Forte: Butalbital 50 mg and acetaminophen 650 mg [may contain benzyl alcohol]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Repan-CF)

50-650 mg (30): $16.47

Tablets (Sedapap)

50-650 mg (100): $87.48

Mechanism of Action

Butalbital is a short- to intermediate-acting barbiturate. Barbiturates depress the sensory cortex, decrease motor activity, alter cerebellar function, and produce drowsiness, sedation, hypnosis, and dose-dependent respiratory depression.

Acetaminophen inhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation; produces antipyresis from inhibition of hypothalamic heat-regulating center.

Pharmacodynamics/KineticsAlso see Acetaminophen monograph.

Absorption: Butalbital: Well absorbed

Protein binding: Butalbital: 45%

Half-life elimination: Butalbital: 35 hours

Excretion: Butalbital: Urine (59% to 88% as unchanged drug or metabolites)

Related Information

- Acetaminophen
- PHENobarbital

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness, drowsiness, and sedation are common; may cause agitation, confusion, euphoria, or excitement

Mental Health: Effects on Psychiatric TreatmentSedation is common; concomitant use with psychotropics may produce additive CNS depressant effects

Index TermsAcetaminophen and Butalbital

Butalbital, Aspirin, Caffeine, and Codeine

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Medication Safety Issues

Sound-alike/look-alike issues:

Fiorinal® may be confused with Fioricet®, Florical®, Florinef®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(byoo TAL bi tal, AS pir in, KAF een, & KOE deen)

U.S. Brand NamesAscomp® with Codeine; Fiorinal® with Codeine

Canadian Brand NamesFiorinal®-C 1/2; Fiorinal®-C 1/4; Tecnal C 1/2; Tecnal C 1/4

Pharmacologic CategoryAnalgesic Combination (Opioid); Barbiturate

Use: Labeled IndicationsRelief of symptoms of complex tension (muscle contraction) headache

Dosing: AdultsTension headache: Oral: 1-2 capsules every 4 hours as needed (maximum: 6 capsules/day)

Dosing: ElderlyUse with caution; however, barbiturates (butalbital) are generally not recommended in the elderly.

StorageStore below 25°C (77°F). Protect from moisture.

RestrictionsC-III

ContraindicationsHypersensitivity to butalbital, codeine, aspirin, caffeine, or any component of the formulation; opium derivatives; hemorrhagic diathesis (eg, hemophilia, hypoprothrombinemia, von Willebrand disease, the thrombocytopenias, thrombasthenia, and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency, and severe liver damage); nasal polyp syndrome, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs; peptic ulcer or other serious GI lesions; porphyria

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity
- Salicylate Allergy/Sensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene-derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).
- Salicylate sensitivity: Patients with sensitivity to tartrazine dyes, nasal polyps, and asthma may have an increased risk of salicylate sensitivity.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Bleeding disorders: Use with caution in patients with platelet and bleeding disorders.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Gastrointestinal disease: Use with caution in patients with erosive gastritis or peptic ulcer disease.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Renal impairment: Use with caution in patients with severe renal impairment.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Anticoagulant therapy: Use with caution in patients on anticoagulant therapy.
- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- CYP2D6 "ultra-rapid metabolizers": Use caution in patients with two or more copies of the variant CYP2D6*2 allele; may have extensive conversion from codeine to morphine and thus increased opioid-mediated effects.
- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.
- Pediatrics: Children and teenagers who have or are recovering from chickenpox or flu-like symptoms should not use this product. Changes in behavior (along with nausea and vomiting) may be an early sign of Reye's syndrome; patients should be instructed to contact their healthcare provider if these occur.

Other warnings/precautions:

- Caffeine: May cause CNS and cardiovascular stimulation, as well as GI irritation in high doses. Use with caution in patients with a history of peptic ulcer or GERD; avoid in patients with symptomatic cardiac arrhythmias.

Geriatric ConsiderationsElderly may react to barbiturates with marked excitement, depression, and confusion.

Pregnancy Risk FactorC (per manufacturer)

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Refer to the individual monographs for Aspirin, Caffeine, and Codeine for additional information. Butalbital crosses the placenta; may cause withdrawal seizures when taken during pregnancy.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsRefer to individual agents. Information specific to butalbital is not available. Discontinuation of breast-feeding or discontinuation of the drug should be considered.

Adverse Reactions

1% to 10%:

Central nervous system: Dizziness/lightheadedness (3%), drowsiness (2%), intoxicated feeling (1%)

Gastrointestinal: Abdominal pain/nausea (4%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Agitation, allergic reaction, anaphylactic shock, anorexia, chest pain, cholangiocarcinoma, depression, disorientation, diuresis, dysphagia, dysuria, edema, epistaxis, erythema multiforme, esophagitis, exfoliative dermatitis, fainting, gastroenteritis, GI spasm, hallucinations, hives, hypotension, nervousness, neuropathy, numbness, palpitations, psychosis, pyloric ulcer, rash, renal impairment, slurred speech, syncope, tachycardia, tinnitus, toxic epidermal necrolysis, unconsciousness, vertigo, vomiting

Note: Potential reactions associated with components of Fiorinal® with Codeine include acute airway obstruction, anemia, bleeding time prolonged, cardiac stimulation, dependence, hemolytic anemia, hepatitis, hyperglycemia, irritability, nephrotoxicity, occult blood loss, peptic ulcer, pruritus, renal toxicity (high doses, prolonged therapy) thrombocytopenia, tremor, urate excretion impaired

Metabolism/Transport Effects

Aspirin: **Substrate** of CYP2C9 (minor)

Caffeine: **Substrate** of CYP1A2 (major), 2C9 (minor), 2D6 (minor), 2E1 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 3A4 (moderate)

Codeine: **Substrate** of CYP2D6 (major), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Griseofulvin: Barbiturates may decrease the absorption of Griseofulvin. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Quinolone Antibiotics: May decrease the metabolism of Caffeine. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Ofloxacin; Sparfloxacin; Trovafloxacin. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Regadenoson: Caffeine may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131

Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Voriconazole: Barbiturates may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Test InteractionsAspirin may interfere with amylase (S), fasting blood glucose (S), cholesterol (S), protein (S), glutamic-oxaloacetic transaminases (SGOT) (S), uric acid (S, U), prothrombin time (S), bleeding time (S), glucose, 5-hydroxy-indoleacetic acid (U), Gerhardt ketone (U), vanillylmandelic acid (U), diacetic acid (U), and spectrophotometric detection of barbiturates; codeine may increase amylase levels (S)

Monitoring ParametersSerial hepatic and renal function tests (in patients with impairment)

Nursing: Physical Assessment/MonitoringSee individual agents for Aspirin, Caffeine, and Codeine.

Monitoring: Lab TestsSerial hepatic and renal function tests (in patients with impairment)

Patient EducationSee individual agents for Aspirin, Caffeine, and Codeine.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: Butalbital 50 mg, aspirin 325 mg, caffeine 40 mg, and codeine phosphate 30 mg

Ascomp® with Codeine, Fiorinal® with Codeine: Butalbital 50 mg, aspirin 325 mg, caffeine 40 mg, and codeine phosphate 30 mg [may contain benzyl alcohol]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Butalbital-ASA-Caff-Codeine)

50-325-40-30 mg (30): $45.99

Capsules (Fiorinal/Codeine #3)

50-325-40-30 mg (30): $101.03

Mechanism of ActionButalbital is a short-to-intermediate acting barbiturate; aspirin inhibits prostaglandin synthesis and has analgesic, antipyretic and anti-inflammatory actions; caffeine is a CNS stimulant; codeine is a narcotic analgesic and antitussive which produced generalized CNS depression. The combination product is for the treatment of tension headache, however, the role of each component in the relief of symptoms is not completely understood.

Pharmacodynamics/KineticsSee individual agents. Bioavailability of the combination is identical to their bioavailability when codeine is administered separately from butalbital, aspirin, and caffeine.

Related Information

- Aspirin
- Caffeine
- Codeine

Dental Health Professional ConsiderationsThere is no scientific evidence to warrant discontinuance of aspirin prior to dental surgery. Patients taking one aspirin tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with the physician before removal of the aspirin relative to prevention of postoperative bleeding.

The Food and Drug Administration (FDA), has issued a letter updating information and considerations regarding the use of ibuprofen (400 mg doses) in patients who are taking low dose aspirin (81 mg, immediate release; not enteric coated) for cardioprotection and stroke prevention. Ibuprofen, at these doses, may interfere with aspirin’s antiplatelet effect depending upon when it is administered. Patients initiated on aspirin first (for ~1 week) then ibuprofen (400 mg 3 times/day for 10 days) seem to maintain aspirin’s platelet effect (Cryer B, 2005). Ibuprofen has the greatest impact on aspirin if administered less than 8 hours before aspirin (Catella-Lawson F, 2001).

Patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. With occasional use of ibuprofen, a clinically-significant interaction with aspirin in unlikely. To avoid interference during chronic dosing, a single dose of ibuprofen should be taken 30-120 minutes after aspirin ingestion or at least 8 hours should elapse after ibuprofen dosing before giving aspirin (FDA, 2006; Catella-Lawson F, 2001).

The clinical implications of the interaction are unclear. There have not been any clinical endpoint studies conducted at this time. Avoidance of this interaction is potentially important because aspirin’s vascular protection could be decreased or negated.

Other nonselective NSAIDs may have potential for a similar interaction with aspirin. Such has been described with naproxen (Capone ML, 2005). Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin. Other clinical scenarios (use of smaller ibuprofen doses, other aspirin products, other doses of aspirin) have not been evaluated.

Additional information is available at: http://www.fda.gov/cder/drug/infopage/aspirin/default.htm

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Aspirin: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity (see Dental Comment).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause depression, nervousness, insomnia, and nightmares; rare reports of hallucinations

Mental Health: Effects on Psychiatric TreatmentRare reports of agranulocytosis; use caution with clozapine and carbamazepine; CNS depressant effects of psychotropics may be enhance by barbiturates; enzyme induction effects of barbiturates may decrease effects of psychotropics

Index TermsAspirin, Caffeine, Codeine, and Butalbital; Butalbital Compound and Codeine; Codeine and Butalbital Compound; Codeine, Butalbital, Aspirin, and Caffeine

References

Capone ML, Sciulli MG, Tacconelli S, et al, “Pharmacodynamic Interaction of Naproxen With Low-Dose Aspirin in Healthy Subjects,” *J Am Coll Cardiol*, 2005, 45(8):1295-1301.[PubMed 15837265]

Catella-Lawson F, Reilly MP, Kapoor SC, et al, “Cyclooxygenase Inhibitors and the Antiplatelet Effects of Aspirin,” *N Engl J Med*, 2001, 345(25):1809-17.[PubMed 11752357]

Cryer B, Verlin RG, Cooper SA, et al, “Double-Blind, Randomized, Parallel, Placebo-Controlled Study of Ibuprofen Effects on Thromboxane B2 Concentrations in Aspirin-Treated Healthy Adult Volunteers,” *Clin Ther*, 2005, 27(2):185-191.[PubMed 15811481]

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand NamesFiorinal-C 1/2 (CA); Fiorinal-C 1/4 (CA); Tecnal C 1/2 (CA); Tecnal C 1/4 (CA)

Butalbital, Aspirin, and Caffeine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Fiorinal® may be confused with Fioricet®, Florical®, Florinef®

Pronunciation(byoo TAL bi tal, AS pir in, & KAF een)

U.S. Brand NamesFiorinal®

Canadian Brand NamesFiorinal®

Pharmacologic CategoryBarbiturate

Use: Labeled IndicationsRelief of the symptomatic complex of tension or muscle contraction headache

Dosing: AdultsTension or muscle contraction headache: Oral: 1-2 tablets or capsules every 4 hours; not to exceed 6 tablets or capsules/day

Dosing: ElderlyNot recommended for use in the elderly.

Dosing: Renal ImpairmentDosage should be reduced.

Dosing: Hepatic ImpairmentDosage should be reduced.

StorageStore below 25°C (77°F).

RestrictionsC-III

ContraindicationsHypersensitivity to butalbital or any component of the formulation; porphyria; pregnancy (prolonged use or high doses at term)

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity
- Salicylate Allergy/Sensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Salicylate sensitivity: Patients with sensitivity to tartrazine dyes, nasal polyps, and asthma may have an increased risk of salicylate sensitivity.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with platelet and bleeding disorders.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Gastrointestinal disease: Use with caution in patients with erosive gastritis or peptic ulcer disease.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

Concurrent drug therapy issues:

- Anticoagulant therapy: Use with caution in patients on anticoagulant therapy.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Children and teenagers who have or are recovering from chickenpox or flu-like symptoms should not use this product. Changes in behavior (along with nausea and vomiting) may be an early sign of Reye's syndrome; patients should be instructed to contact their healthcare provider if these occur.

Other warnings/precautions:

- Caffeine: May cause CNS and cardiovascular stimulation, as well as GI irritation in high doses. Use with caution in patients with a history of peptic ulcer or GERD; avoid in patients with symptomatic cardiac arrhythmias.

Geriatric ConsiderationsElderly may react to barbiturates with marked excitement, depression, and confusion.
Pregnancy Risk FactorC/D (prolonged use or high doses at term)
LactationEnters breast milk/use caution due to aspirin content
Adverse Reactions

>10%:

Central nervous system: Dizziness, lightheadedness, drowsiness, “hangover” effect

Gastrointestinal: Heartburn, stomach pain, dyspepsia, epigastric discomfort, nausea

1% to 10%:

Central nervous system: Confusion, mental depression, unusual excitement, nervousness, faint feeling, headache, insomnia, nightmares, fatigue

Dermatologic: Skin rash

Gastrointestinal: Constipation, vomiting, gastrointestinal ulceration

Hematologic: Hemolytic anemia

Neuromuscular & skeletal: Weakness

Respiratory: Troubled breathing

Miscellaneous: Anaphylactic shock

Metabolism/Transport Effects

Aspirin: **Substrate** of CYP2C9 (minor)

Caffeine: **Substrate** of CYP1A2 (major), 2C9 (minor), 2D6 (minor), 2E1 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 3A4 (moderate)

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Griseofulvin: Barbiturates may decrease the absorption of Griseofulvin. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Quinolone Antibiotics: May decrease the metabolism of Caffeine. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Ofloxacin; Sparfloxacin; Trovafloxacin. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Regadenoson: Caffeine may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Voriconazole: Barbiturates may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Nursing: Physical Assessment/MonitoringSee individual agents for Aspirin and Caffeine.
Patient EducationSee individual agents for Aspirin and Caffeine.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: Butalbital 50 mg, aspirin 325 mg, and caffeine 40 mg

Fiorinal®: Butalbital 50 mg, aspirin 325 mg, and caffeine 40 mg

Tablet: Butalbital 50 mg, aspirin 325 mg, and caffeine 40 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsules (Butalbital-ASA-Caffeine)

50-325-40 mg (30): $25.99

Capsules (Fiorinal)

50-325-40 mg (100): $149.99

Tablets (Butalbital-Aspirin-Caffeine)

50-325-40 mg (30): $19.99

Tablets (Fortabs)

50-325-40 mg (100): $39.99

Related Information

- Aspirin
- Caffeine

Dental Health Professional Considerations There is no scientific evidence to warrant discontinuance of aspirin prior to dental surgery. Patients taking one aspirin tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with the physician before removal of the aspirin relative to prevention of postoperative bleeding.

The Food and Drug Administration (FDA), has issued a letter updating information and considerations regarding the use of ibuprofen (400 mg doses) in patients who are taking low dose aspirin (81 mg, immediate release; not enteric coated) for cardioprotection and stroke prevention. Ibuprofen, at these doses, may interfere with aspirin's antiplatelet effect depending upon when it is administered. Patients initiated on aspirin first (for ~1 week) then ibuprofen (400 mg 3 times/day for 10 days) seem to maintain aspirin's platelet effect (Cryer B, 2005). Ibuprofen has the greatest impact on aspirin if administered less than 8 hours before aspirin (Catella-Lawson F, 2001).

Patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. With occasional use of ibuprofen, a clinically-significant interaction with aspirin in unlikely. To avoid interference during chronic dosing, a single dose of ibuprofen should be taken 30-120 minutes after aspirin ingestion or at least 8 hours should elapse after ibuprofen dosing before giving aspirin (FDA, 2006; Catella-Lawson F, 2001).

The clinical implications of the interaction are unclear. There have not been any clinical endpoint studies conducted at this time. Avoidance of this interaction is potentially important because aspirin's vascular protection could be decreased or negated.

Other nonselective NSAIDs may have potential for a similar interaction with aspirin. Such has been described with naproxen (Capone ML, 2005). Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin. Other clinical scenarios (use of smaller ibuprofen doses, other aspirin products, other doses of aspirin) have not been evaluated.

Additional information is available at: http://www.fda.gov/cder/drug/infopage/aspirin/default.htm

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Aspirin: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity (see Dental Comment).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Drowsiness is common; may cause depression, nervousness, insomnia, and nightmares; rare reports of hallucinations

Mental Health: Effects on Psychiatric Treatment Rare reports of agranulocytosis; use caution with clozapine and carbamazepine; CNS depressant effects of psychotropics may be enhance by barbiturates; enzyme induction effects of barbiturates may decrease effects of psychotropics

Index Terms Aspirin, Caffeine, and Butalbital; Butalbital Compound

References

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International Brand Names Fiorinal (CA)

Butenafine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Lotrimin may be confused with Lotrisone®, Otrivin®

Pronunciation(byoo TEN a feen)

U.S. Brand NamesLotrimin® Ultra™ [OTC]; Mentax®

Pharmacologic CategoryAntifungal Agent, Topical

Use: Labeled IndicationsTopical treatment of tinea pedis (athlete's foot), tinea cruris (jock itch), tinea corporis (ringworm), and tinea versicolor

Dosing: Adults

Tinea corporis, tinea cruris (Lotrimin® Ultra™): Apply once daily for 2 weeks to affected area and surrounding skin

Tinea versicolor (Mentax®): Apply once daily for 2 weeks to affected area and surrounding skin

Tinea pedis (Lotrimin® Ultra™): Apply to affected skin between and around the toes, twice daily for 1 week, or once daily for 4 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren >12 years: Refer to adult dosing.

Administration: TopicalApply to clean, dry skin. Avoid occlusive dressings.

StorageStore at 5°C to 30°C (41°F to 86°F).

ContraindicationsHypersensitivity to butenafine or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Allylamine antifungal hypersensitivity: Use caution in patients sensitive to allylamine antifungals (eg naftifine, terbinafine); cross sensitivity to butenafine may exist.
- Irritation: Discontinue if sensitivity or irritation occurs

Special populations:

- Immunocompromised patients: Has not been studied in immunocompromised patients.
- Pediatrics: Safety and efficacy have not been established in children <12 years of age

Other warnings/precautions:

- Appropriate use: For topical use only; avoid contact with eyes, mouth, nose, or other mucous membranes.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions>1%: Dermatologic: Burning, contact dermatitis, erythema, irritation, pruritus, stinging

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersCulture and KOH exam, clinical signs of tinea pedis

Monitoring: Lab TestsCulture and KOH exam

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, as hydrochloride:

Lotrimin® Ultra™: 1% (12 g, 24 g) [contains benzyl alcohol and sodium benzoate]

Mentax®: 1% (15 g, 30 g) [contains benzyl alcohol and sodium benzoate]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Cream (Mentax)

1% (15): $45.99

Mechanism of ActionButenafine exerts fungicidal activity against dermatophytes (eg trichophyton, epidermophyton) by blocking squalene epoxidation, resulting in inhibition of ergosterol synthesis and subsequent weakening of fungal cell membranes.

Pharmacodynamics/Kinetics

Absorption: Minimal systemic

Metabolism: Hepatic via hydroxylation

Half-life elimination: Biphasic: Alpha: 35 hours; Beta: >150 hours

Time to peak, serum: 6-15 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsButenafine Hydrochloride

References

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McNeely W and Spencer CM, “Butenafine,” *Drugs*, 1998, 55(3):405-12. [PubMed 9530545]

Reyes BA, Beutner KR, Cullen SI, et al, “Butenafine, a Fungicidal Benzylamine Derivative, Used Once Daily for the Treatment of Interdigital Tinea Pedis,” *Int J Dermatol*, 1998, 37(6):450-3. [PubMed 9646136]

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“Topical Butenafine for Tinea Pedis,” *Med Lett Drugs Ther*, 1997, 39(1004):63-4. [PubMed 9217695]

Tschen E, Elewski B, Gorsulowsky DC, et al, “Treatment of Interdigital Tinea Pedis With a 4-Week Once-Daily Regimen of Butenafine Hydrochloride 1% Cream,” *J Am Acad Dermatol*, 1997, 36(2 Pt 1):S9-14.[PubMed 9039199]

International Brand NamesButop (IN); Dermacom (CN); Funcid (PH); Mentax (EE, IL, JP, KP)

Butoconazole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(byoo toe KOE na zole)
U.S. Brand NamesGynazole-1®
Canadian Brand NamesFemstat® One; Gynazole-1®
Pharmacologic CategoryAntifungal Agent, Vaginal
Use: Labeled IndicationsLocal treatment of vulvovaginal candidiasis
Dosing: AdultsVulvovaginal candidiasis: Intravaginal: *Gynazole-1®:* Insert 1 applicatorful (~5 g) intravaginally as a single dose; treatment may need to be extended for up to 6 days in pregnant women (use in pregnancy during 2nd or 3rd trimester only)
Dosing: ElderlyRefer to adult dosing.
StorageStore at 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to butoconazole or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Irritation: If irritation or sensitization occurs, discontinue use.

Special populations:

- Pediatrics: Safety and efficacy have not been established in females <12 years of age.

Dosage form specific issues:

- Petrolatum-based: Contains mineral oil which may weaken latex or rubber products (condoms, vaginal contraceptive diaphragms); do not use these products within 72 hours of treatment.

- OTC product: Not for use in women with a first-time vaginal yeast infection.

Other warnings/precautions:

- HIV infection consideration: HIV infection should be considered in sexually-active women with difficult to eradicate recurrent vaginal yeast infections.

Pregnancy Risk FactorC (use only in 2nd or 3rd trimester)
Pregnancy ConsiderationsNo adequate and well-controlled studies have been conducted in pregnant women. However, butoconazole has been used during pregnancy. Use should be limited to the 2nd or 3rd trimesters only.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Gastrointestinal: Abdominal pain or cramping

Genitourinary: Pelvic pain; vulvar/vaginal burning, itching, soreness, and swelling

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, vaginal, as nitrate:

Gynazole-1®: 2% (5 g) [prefilled applicator]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Cream (Gynazole-1)

2% (5.8): $68.94

Mechanism of ActionIncreases cell membrane permeability in susceptible fungi (*Candida*)
Pharmacodynamics/Kinetics

Absorption: 2%

Metabolism: Not reported

Time to peak: 12-24 hours

Related Information

- Treatment of Sexually-Transmitted Infections

Pharmacotherapy PearlsGynazole-1®: This product is delivered in a base allowing the active ingredient to remain vaginally for 4 days. It is associated with less leakage and can therefore be applied at any time during the day or night (per product information, Gynazole-1®).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsButoconazole Nitrate

International Brand NamesFemstat One (CA); Gynazole-1 (CA)

Butorphanol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Stadol® may be confused with Haldol®, sotalol

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(byoo TOR fa nole)

U.S. Brand NamesStadol® [DSC]

Canadian Brand NamesApo-Butorphanol®; PMS-Butorphanol

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled Indications

Parenteral: Management of moderate-to-severe pain; preoperative medication; supplement to balanced anesthesia; management of pain during labor

Nasal spray: Management of moderate-to-severe pain, including migraine headache pain

Dosing: Adults **Note:** These are guidelines and do not represent the maximum doses that may be required in all patients. Doses should be titrated to pain relief/prevention. Butorphanol has an analgesic ceiling.

Acute pain (moderate to severe):

I.M.: Initial: 2 mg, may repeat every 3-4 hours as needed; usual range: 1-4 mg every 3-4 hours as needed

I.V.: Initial: 1 mg, may repeat every 3-4 hours as needed; usual range: 0.5-2 mg every 3-4 hours as needed

Intranasal (spray) (includes use for migraine headache pain): Initial: 1 spray (~1 mg per spray) in 1 nostril; if adequate pain relief is not achieved within 60-90 minutes, an additional 1 spray in 1 nostril may be given; may repeat initial dose sequence in 3-4 hours after the last dose as needed

Alternatively, an initial dose of 2 mg (1 spray in each nostril) may be used in patients who will be able to remain recumbent (in the event drowsiness or dizziness occurs); additional 2 mg doses should not be given for 3-4 hours

Note: In some clinical trials, an initial dose of 2 mg (as 2 doses 1 hour apart or 2 mg initially - 1 spray in each nostril) has been used, followed by 1 mg in 1 hour; side effects were greater at these dosages

Migraine: *Nasal spray:* Refer to “moderate to severe pain” indication

Preoperative medication: *I.M.:* 2 mg 60-90 minutes before surgery

Supplement to balanced anesthesia: *I.V.:* 2 mg shortly before induction and/or an incremental dose of 0.5-1 mg (up to 0.06 mg/kg), depending on previously administered sedative, analgesic, and hypnotic medications

Pain during labor (fetus >37 weeks gestation and no signs of fetal distress):

I.M., I.V.: 1-2 mg; may repeat in 4 hours

Note: Alternative analgesia should be used for pain associated with delivery or if delivery is anticipated within 4 hours

Dosing: Elderly

I.M., I.V.: Initial dosage should generally be $^{1}/_{2}$ of the recommended dose; repeated dosing must be based on initial response rather than fixed intervals, but generally should be at least 6 hours apart

Nasal spray: Initial dose should not exceed 1 mg; a second dose may be given after 90-120 minutes

Dosing: Renal Impairment

I.M., I.V.: Initial dosage should generally be $^{1}/_{2}$ of the recommended dose; repeated dosing must be based on initial response rather than fixed intervals, but generally should be at least 6 hours apart

Nasal spray: Initial dose should not exceed 1 mg; a second dose may be given after 90-120 minutes

Dosing: Hepatic Impairment

I.M., I.V.: Initial dosage should generally be $^1/_2$ of the recommended dose; repeated dosing must be based on initial response rather than fixed intervals, but generally should be at least 6 hours apart

Nasal spray: Initial dose should not exceed 1 mg; a second dose may be given after 90-120 minutes

Calculations

- Opioid Agonist Conversion

Administration: I.V. DetailpH: 3.0-5.5
Administration: InhalationSee Dosing.
Administration: OtherIntranasal: Consider avoiding simultaneous intranasal migraine sprays; may want to separate by at least 30 minutes
StorageStore at room temperature; protect from freezing.
Compatibility

Y-site administration: Compatible: Allopurinol, amifostine, aztreonam, cefepime, cisatracurium, cladribine, docetaxel, doxorubicin liposome, enalaprilat, esmolol, etoposide, filgrastim, fludarabine, gatifloxacin, gemcitabine, granisetron, labetalol, linezolid, melphalan, paclitaxel, piperacillin/tazobactam, propofol, remifentanil, sargramostim, teniposide, thiotepa, vinorelbine. **Incompatible:** Amphotericin B cholesteryl sulfate complex, midazolam.

Compatibility in syringe: Compatible: Atropine, chlorpromazine, cimetidine, diphenhydramine, droperidol, fentanyl, hydroxyzine, meperidine, methotrimeprazine, metoclopramide, midazolam, morphine, pentazocine, perphenazine, prochlorperazine, promethazine, scopolamine, thiethylperazine. **Incompatible:** Dimenhydrinate, pentobarbital.

RestrictionsC-IV
ContraindicationsHypersensitivity to butorphanol or any component of the formulation; avoid use in opiate-dependent patients who have not been detoxified, may precipitate opiate withdrawal; pregnancy (prolonged use or high doses at term)
Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.

- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.

- CNS depression/coma: Use with caution in patients with CNS depression or coma.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Obesity: Use with caution in patients who are morbidly obese.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

- Sumatriptan nasal spray: Concurrent use of sumatriptan nasal spray and butorphanol nasal spray may increase risk of transient high blood pressure.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precaution:

- Abuse/misuse/diversion: Healthcare provider should be alert to problems of abuse, misuse, and diversion.

- Optimal regimen: An opioid-containing analgesic regimen should be tailored to each patient's needs and based upon the type of pain being treated (acute versus chronic), the route of administration, degree of tolerance for opioids (naive versus chronic user), age, weight, and medical condition. The optimal analgesic dose varies widely among patients; doses should be titrated to pain relief/prevention.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsAdjust dose for renal function in the elderly.
Pregnancy Risk FactorC/D (prolonged use or high doses at term)
LactationEnters breast milk/use caution (AAP rates “compatible”)
Adverse Reactions

>10%:

Central nervous system: Drowsiness (43%), dizziness (19%), insomnia (Stadol® NS)

Gastrointestinal: Nausea/vomiting (13%)

Respiratory: Nasal congestion (Stadol® NS)

1% to 10%:

Cardiovascular: Vasodilation, palpitation

Central nervous system: Lightheadedness, headache, lethargy, anxiety, confusion, euphoria, somnolence

Dermatologic: Pruritus

Gastrointestinal: Anorexia, constipation, xerostomia, stomach pain, unpleasant aftertaste

Neuromuscular & skeletal: Tremor, paresthesia, weakness

Ocular: Blurred vision

Otic: Ear pain, tinnitus

Respiratory: Bronchitis, cough, dyspnea, epistaxis, nasal irritation, pharyngitis, rhinitis, sinus congestion, sinusitis, upper respiratory infection

Miscellaneous: Diaphoresis increased

<1%: Bradycardia or tachycardia, hypertension, paradoxical CNS stimulation, hallucinations, mental depression, malaise, restlessness, nightmares, CNS depression, urination decreased, rash, stomach cramps, painful urination, blurred vision, tinnitus, weakness, dyspnea, respiratory depression, dependence with prolonged use, difficulty speaking (transient), hypotension, syncope, agitation, dysphoria, hostility, vertigo, withdrawal symptoms, hives.

<1% (Stadol® NS): Edema, chest pain, hypertension, tachycardia, convulsions, delusions, depressions, apnea, shallow breathing

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol (may increase CNS depression). Watch for sedation.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersPain relief, respiratory and mental status, blood pressure
Reference Range0.7-1.5 ng/mL
Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for possible additive or adverse interactions. Monitor for effectiveness of pain relief, signs of overdose, vital signs, and adverse effects at beginning of therapy and at regular intervals with long-term use. For inpatients, implement safety measures. May cause physical and/or psychological dependence. Assess knowledge/teach patient appropriate use (if self-administered), adverse reactions to report, and appropriate interventions to reduce side effects.
Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. May cause dizziness, drowsiness, confusion, or blurred vision (use caution when driving, climbing stairs, or changing position - rising from sitting or lying to standing, or when engaging in tasks requiring alertness until response to drug is known); nausea or vomiting, or loss of appetite (frequent mouth care, small frequent meals, sucking lozenges, or chewing gum may help). Report unresolved nausea or vomiting; respiratory difficulty or shortness of breath; restlessness, insomnia, euphoria, or nightmares; excessive sedation or unusual weakness; facial flushing, rapid heartbeat, or palpitations; urinary difficulty; or vision changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. If you are breast-feeding, take dose immediately after breast-feeding or 3-4 hours prior to next feeding.

Nasal administration: Do not use more frequently than prescribed. Blow nose prior to administering. Follow directions on package insert. Insert nozzle of applicator gently into one nostril and exhale. With next breath, squeeze applicator once firmly and quickly once as you breath in. If adequate relief from headache is not achieved within 60-90 minutes, an additional 1 spray may be given. May be repeated in 3-4 hours following last dose, as needed. **Alternatively:** Two sprays may be given - one spray in each nostril, if you are able to remain lying down (in the event of drowsiness or dizziness). Additional doses should not be taken for 3-4 hours. Avoid using simultaneously with intranasal migraine sprays. Separate by at least 30 minutes.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as tartrate [preservative free]: 1 mg/mL (1 mL); 2 mg/mL (1 mL, 2 mL)

Injection, solution, as tartrate [with preservative]: 2 mg/mL (10 mL)

Solution, intranasal, as tartrate [spray]: 10 mg/mL (2.5 mL) [14-15 doses]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Solution (Butorphanol Tartrate)

10 mg/mL (2.5): $56.99

Mechanism of ActionMixed narcotic agonist-antagonist with central analgesic actions; binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression
Pharmacodynamics/Kinetics

Onset of action: I.M.: 5-10 minutes; I.V.: <10 minutes; Nasal: Within 15 minutes

Peak effect: I.M.: 0.5-1 hour; I.V.: 4-5 minutes

Duration: I.M., I.V.: 3-4 hours; Nasal: 4-5 hours

Absorption: Rapid and well absorbed

Protein binding: 80%

Metabolism: Hepatic

Bioavailability: Nasal: 60% to 70%

Half-life elimination: 2.5-4 hours

Excretion: Primarily urine

Related Information

- Narcotic / Opioid Analgesics

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and unpleasant aftertaste.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDrowsiness is common; may rarely produce CNS stimulation or depression, hallucinations, and confusion
Mental Health: Effects on Psychiatric TreatmentContraindicated in opiate dependent patients; may precipitate opiate withdrawal; concurrent use with psychotropic may produce additive sedation

Anesthesia and Critical Care Concerns/Other Considerations Butorphanol is a mixed agonist-antagonist opiate; may precipitate withdrawal in narcotic-dependent patients. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms. This agent can potentially cause hallucinations.

Index Terms Butorphanol Tartrate

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Srinivas NR, Shyu WC, Upmalis D, et al, “Lack of Pharmacokinetic Interaction Between Butorphanol Tartrate Nasal Spray and Sumatriptan Succinate,” *J Clin Pharmacol*, 1995, 35(4):432-7. [PubMed 7650235]

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Vachharajani NN, Shyu WC, Greene DS, et al, “The Pharmacokinetics of Butorphanol and Its Metabolites at Steady State Following Nasal Administration in Humans,” *Biopharm Drug Dispos*, 1997, 18(3):191-202.[PubMed 9113342]

International Brand Names Beforal (CZ, PL); Bunol (KP); Busphen (KP); Butaro (TW); Butrum (IN); Moradol (PL); Stadol (JP, PH, PL); Verstadol (ES)

C1 Inhibitor (Human)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation

(cee won in HIB i ter HYU man)

U.S. Brand NamesCinryze™

Pharmacologic Category[Blood Product Derivative]()

Use: Labeled IndicationsRoutine prophylaxis against angioedema attacks in patients with hereditary angioedema (HAE) or inherited C1 inhibitor deficiency

Use: Unlabeled/InvestigationalTreatment of acute or severe angioedema attacks (eg, laryngeal swelling) in patients with HAE

Dosing: Adults**Routine prophylaxis against HAE attacks:** I.V.: 1000 units every 3-4 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Children: Dosage not established.

Adolescents: Refer to adult dosing.

Administration: I.V.Administer at 1 mL/minute (over 10 minutes). Allow to warm to room temperature prior to administration and use within 3 hours of reconstitution.

StorageStore under refrigeration at 2°C to 25°C (36°F to 77°F); do not freeze. **Protect from light** prior to reconstitution.

ReconstitutionProduct should come to room temperature before combining with diluent (sterile water for injection). Reconstitute each vial with 5 mL of sterile water for injection using the double-ended transfer needle; do not use product if there is no vacuum in the vial. Use 2 reconstituted vials to make single 1000 unit dose. After combining with diluent, gently swirl vial to completely dissolve powder. Reconstituted product should be clear and colorless or slightly blue; do not use if turbid or discolored. The provided filter needle should be used to withdraw the reconstituted product. Remove filter needle and attach reconstituted solution to infusion set or appropriate needle for infusion and use within 3 hours of reconstitution.

ContraindicationsHistory of anaphylactic or life-threatening hypersensitivity reactions to human C1 inhibitor or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity: Severe hypersensitivity reactions (eg, urticaria, hives, wheezing, hypotension, anaphylaxis) may occur rarely during or after administration. Signs/symptoms of hypersensitivity reactions may be similar to the attacks associated with hereditary angioedema, therefore, consideration should be given to treatment methods. In the event of acute hypersensitivity reactions to C1 inhibitor therapy, treatment should be discontinued and epinephrine should be available.

- Thrombotic events: Consider potential risk of thrombosis with use; thrombotic events have been reported when used off-label at doses higher than recommended in product labeling.

Special Populations:

- Pediatrics: Safety and efficacy have been established in adolescents and adults. Only a small number of children were included in clinical trials.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

Geriatric ConsiderationsInsufficient geriatric patients have been studied to determine any difference in response from younger patients.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. There are no adequate and well-controlled studies in pregnant women. Information related to use during pregnancy is limited. Pregnancy may increase the incidence of attacks in patients with HAE.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsReactions reported below were observed in a study involving 24 patients.

≥5%:

Central nervous system: Headache

Dermatologic: Pruritus, rash

Neuromuscular & skeletal: Back pain, extremity pain

Respiratory: Bronchitis, sinusitis, upper respiratory tract infection

Miscellaneous: Limb injury

Drug InteractionsThere are no known significant interactions.

Dosage Forms

Injection, powder for reconstitution:

Cinryze™: 500 units [contains sucrose 21 mg/mL]

Generic AvailableNo

Mechanism of ActionC1 inhibitor, one of the serine proteinase inhibitors found in human blood, plays a role in regulating the complement and intrinsic coagulation (contact system) pathway, and is also involved in the fibrinolytic and kinin pathways. C1 inhibitor therapy in patients with C1 inhibitor deficiency, such as HAE, is believed to suppress contact system activation via inactivation of plasma kallikrein and factor XIIa, thus preventing bradykinin production. Unregulated bradykinin production is thought to contribute to the increased vascular permeability and angioedema observed in HAE.

Pharmacodynamics/Kinetics

Onset of action: Increased plasma C1 inhibitor levels observed ~1 hour or less

Half-life elimination: 56 hours (range: 11-108 hours)

Time to peak: ~4 hours

Pharmacotherapy Pearls1 unit of Cinryze™ corresponds to C1 inhibitor present in 1 mL of normal fresh plasma

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsC1 Esterase Inhibitor; C1-INH; C1-Inhibitor; C1INHRP; Human C1 Inhibitor

References

Cicardi M and Zingale L, “How Do We Treat Patients With Hereditary Angioedema,” *Transfus Apher Sci*, 2003, 29(3):221-7.[PubMed 14572813]

Farkas H, Jakab L, Temesszentandrasi G, et al, “Hereditary Angioedema: A Decade of Human C1-inhibitor Concentrate Therapy,” *J Allergy Clin Immunol*, 2007, 120(4):941-7.[PubMed 17761272]

Frank MM and Jiang H, “New Therapies for Hereditary Angioedema: Disease Outlook Changes Dramatically,” *J Allergy Clin Immunol*, 2008, 121(1):272-80.[PubMed 18206518]

Hermans C, “Successful Management With C1-Inhibitor Concentrate of Hereditary Angioedema Attacks During Two Successive Pregnancies: A Case Report,” *Arch Gynecol Obstet*, 2007, 276(3):271-6.[PubMed 17653743]

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Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid
Regimen UseLeukemia, acute myeloid
Regimen

Cytarabine: I.V.: 3000 mg/m^2 every 12 hours days 1 and 2 (4 doses)

[total dose/cycle = 12,000 mg/m^2]

Asparaginase: I.M.: 6000 units/m^2 at hour 42

[total dose/cycle = 6000 units/m^2]

Repeat cycle every 7 days for 2 or 3 cycles

References

Capizzi RL, Davis R, Powell B, et al, âSynergy Between High-Dose Cytarabine and Asparaginase in the Treatment of Adults With Refractory and Relapsed Acute Myelogenous Leukemia: A Cancer and Leukemia Group B Study,â *J Clin Oncol*, 1988, 6(3):499-508.[PubMed 3162515]

Cabergoline

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(ca BER goe leen)
U.S. Brand NamesDostinex® [DSC]
Canadian Brand NamesCO Cabergoline; Dostinex®
Pharmacologic CategoryErgot Derivative
Use: Labeled IndicationsTreatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas
Dosing: AdultsHyperprolactinemic disorders: Oral: Initial dose: 0.25 mg twice weekly; the dose may be increased by 0.25 mg twice weekly up to a maximum of 1 mg twice weekly according to the patient's serum prolactin level. Dosage increases should not occur more rapidly than every 4 weeks. Once a normal serum prolactin level is maintained for 6 months, the dose may be discontinued and prolactin levels monitored to determine if cabergoline is still required. The durability of efficacy beyond 24 months of therapy has not been established.
Dosing: ElderlyRefer to adult dosing. No dosage recommendations suggested; however, start at the low end of the dosage range.
Dosing: Renal ImpairmentNo adjustment required.
Dosing: Hepatic Impairment

Mild-to-moderate dysfunction (Child-Pugh Class B): No adjustment required

Severe dysfunction (Child-Pugh Class C): Use caution; significant increase in AUC

StorageStore at 20°C to 25°C (68°F to 77°F).
ContraindicationsHypersensitivity to ergot derivatives; uncontrolled hypertension; history of pulmonary, pericardial, cardiac valvular or retroperitoneal fibrotic disorders
Allergy Considerations

- Ergot Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac valvular fibrosis: Cardiac valvular disease (mitral, aortic, tricuspid regurgitation) has been associated with cabergoline (a potent 5-HT_{2B} agonist). Incidence may be higher for daily doses >2 mg and for duration of use ≥6 months. Following diagnosis of fibrosis/valvulopathy, discontinuation of cabergoline may result in improvement in condition.

- Orthostatic hypotension: Initial doses >1 mg may cause orthostatic hypotension. Concurrent use with antihypertensives may increase risk.

- Pleural/retroperitoneal fibrosis: Rare cases of pleural effusion, pulmonary/retroperitoneal fibrosis have been reported with prolonged daily use.

- Psychiatric disorders: Pathological gambling, increased libido, and hypersexuality have been reported with use; generally reversible with dose reduction or discontinuation of treatment.

Disease-related concerns:

- Hepatic impairment: Use with caution and carefully monitor patients with hepatic impairment; extensively metabolized by the liver.

- Pregnancy-induced hypertension: Should not be used in patients with pregnancy-induced hypertension unless benefit outweighs potential risk.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Not indicated for the inhibition or suppression of physiologic lactation; other dopamine agonists are associated with cases of hypertension, stroke, and seizures.

- Monitoring: In all patients, prolactin concentrations should be monitored monthly until normalized.

Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in most animal studies when administered in maternally nontoxic doses. Treatment of hyperprolactinemia may restore fertility in a previously infertile woman. Because information concerning the use of cabergoline in pregnancy is limited, bromocriptine is generally recommended to treat hyperprolactinemia in women who wish to conceive. Based on preliminary data, cabergoline has not been shown to increase the risk of congenital malformations or miscarriages when used early in pregnancy (treatment was generally stopped once pregnancy was diagnosed). Not recommended for use in patients with pregnancy-induced hypertension unless benefit outweighs potential risk.
LactationExcretion in breast milk unknown/not recommended

Breast-Feeding Considerations Interferes with lactation and should not be given to women postpartum who are breast-feeding or who are planning to breast-feed. Not indicated for the suppression of physiologic lactation.

Adverse Reactions

>10%:

- Central nervous system: Headache (26%), dizziness (15% to 17%)
- Gastrointestinal: Nausea (27% to 29%)

1% to 10%:

- Cardiovascular: Postural hypotension (4%), hypotension (1%), dependent edema (1%), edema (peripheral 1%), palpitation (1%), syncope (1%)
- Central nervous system: Fatigue (5% to 7%), vertigo (1% to 4%), depression (3%), somnolence (2% to 5%), nervousness (1% to 2%), anxiety (1%), insomnia (1%), concentration impaired (1%), malaise (1%)
- Dermatologic: Acne (1%), pruritus (1%)
- Endocrine: Hot flashes (1% to 3%), breast pain (1% to 2%), dysmenorrhea (1%)
- Gastrointestinal: Constipation (7% to 10%), abdominal pain (5%), dyspepsia (2% to 5%), vomiting (2% to 4%), xerostomia (2%), diarrhea (2%), flatulence (2%), anorexia (1%), throat irritation (1%), toothache (1%)
- Neuromuscular & skeletal: Weakness (6% to 9%), pain (2%), paresthesia (1% to 2%), arthralgia (1%)
- Ocular: Abnormal vision (1%), periorbital edema (1%)
- Respiratory: Rhinitis (1%)
- Miscellaneous: Flu-like syndrome (1%)

<1%: Confusion (in patients with Parkinson's disease [PD]), constrictive pericarditis (in PD patients), duodenal ulcer (in PD patients), dyskinesia (in PD patients), epistaxis, facial edema, gastric ulcer (in PD patients), hallucinations (in PD patients), heart failure (in PD patients), libido increased, pleural effusion (in PD patients), pulmonary fibrosis (in PD patients), weight gain/loss

Postmarketing and/or case reports: Aggression, alopecia, cardiac fibrosis, hypersexuality, pathological gambling, psychosis, valvulopathy

Drug Interactions

Efavirenz: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically, the risk for peripheral vasospasm and ischemia may be increased. *Risk X: Avoid combination*

Posaconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: Ergot Derivatives may enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Ergot Derivatives. This may cause serotonin syndrome. *Risk X: Avoid combination*

Voriconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions Herb/Nutraceutical: Avoid products that enhance serotonin activity (includes SAMe [S-adenosylmethionine] and St John's wort); may increase the risk of serotonin syndrome.

Monitoring Parameters Blood pressure (both sitting/supine and standing); serum prolactin level, echocardiogram with long-term use (>6 months)

Monitoring: Lab Tests Serum prolactin level

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: 0.5 mg

- Dostinex®: 0.5 mg [DSC]

Generic Available Yes

Pricing: U.S. (www.drugstore.com)

Tablets (Cabergoline)

- 0.5 mg (8): $265.97

Mechanism of Action Cabergoline is a long acting dopamine receptor agonist with a high affinity for D_2 receptors; prolactin secretion by the anterior pituitary is predominantly under hypothalamic inhibitory control exerted through the release of dopamine. It is a potent 5-HT_{2B}-receptor agonist, which may contribute to observed fibrotic/valvulopathic events.

Pharmacodynamics/Kinetics

Distribution: Extensive, particularly to the pituitary

Protein binding: 40% to 42%

Metabolism: Extensively hepatic via hydrolysis; minimal CYP mediated metabolism

Half-life elimination: 63-69 hours

Time to peak: 2-3 hours

Excretion: Primarily feces (~60%); urine (~22%, <4% as unchanged drug)

Related Information

- Antiparkinsonian Agents

Pharmacotherapy Pearls Bromocriptine and cabergoline are the only drugs indicated for the treatment of hyperprolactinemia. In the largest comparative clinical trial, prolactin levels normalized in 77% of patients treated with cabergoline compared to 59% of patients treated with bromocriptine. In that trial, 3% of patients discontinued treatment due to adverse effects in the cabergoline group versus 12% of patients in the bromocriptine group. In addition to the improved safety and efficacy profile, cabergoline (administered twice weekly) is more convenient than bromocriptine (administered 1-3 times/day) for patients to take.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), throat irritation, and toothache.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Dizziness is common; may cause depression

Mental Health: Effects on Psychiatric Treatment Antipsychotics may decrease the therapeutic effects of cabergoline; avoid combination

Cardiovascular Considerations Valvular damage may be mediated through the serotonin receptor subtype 5-HT$_{2B}$ as proliferation of fibroblasts occurs within valve tissue when stimulated. Some experts recommend avoiding prescribing medications that are potent 5-HT$_{2B}$-receptor agonists.

References

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European Multicentre Study Group for Cabergoline in Lactation Inhibition, “Single Dose Cabergoline Versus Bromocriptine in Inhibition of Puerperal Lactation: Randomised, Double-Blind, Multicentre Study,” *Br Med J*, 1991, 302:1367-71.

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Giusti M, Porcella E, Carraro A, et al, “A Cross-Over Study With the Two Novel Dopaminergic Drugs Cabergoline and Quinagolide in Hyperprolactinemic Patients,” *J Endocrinol Invest*, 1994, 17:51-7. [PubMed 7911813]

Rains CP, Bryson HM, and Fitton A, “Cabergoline: A Review of Its Pharmacological Properties and Therapeutic Potential in the Treatment of Hyperprolactinemia and Inhibition of Lactation,” *Drugs*, 1995, 49:255-79. [PubMed 7729332]

Ricci E, Parazzini F, Motta T, et al, “Pregnancy Outcome After Cabergoline Treatment in Early Weeks of Gestation,” *Reprod Toxicol*, 2002, 16(6):791-3.[PubMed 12401507]

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Webster J, Piscitelli G, Polli A, et al, “A Comparison of Cabergoline and Bromocriptine in the Treatment of Hyperprolactinemic Amenorrhea,” *N Engl J Med*, 1994, 331:904-9. [PubMed 7915824]

Webster J, Piscitelli G, Polli A, et al, “Dose-Dependent Suppression of Serum Prolactin by Cabergoline in Hyperprolactinaemia: A Placebo Controlled, Double Blind, Multicentre Study,” *Clin Endocrinol (Oxf)*, 1992, 68:1201-6.

Webster J, Piscitelli G, Polli A, et al, “The Efficacy and Tolerability of Long-Term Cabergoline Therapy in Hyperprolactinaemic Disorders: An Open, Uncontrolled, Multicentre Study,” *Clin Endocrinol (Oxf)*, 1993, 39:323-9.

Zanettini R, Antonini A, Gatto G, et al, “Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson’s Disease,” *N Engl J Med*2007, 356(1):39-46.[PubMed 17202454]

International Brand Names Cabaser (AR, AU, CH, DK, GB, IE, IL, PL, SE); Cabergoline-Pharmacia (LU); Cabotrim (IL); Dostinex (AE, AT, AU, BE, BG, BH, BR, CH, CN, CR, CY, CZ, DE, DK, EC, EG, ES, FI, FR, GB, GR, GT, HK, HN, IE, IL, IQ, IR, IT, JO, KW, LB, LU, LY, MX, MY, NI, NL, NO, OM, PA, PE, PL, PT, QA, RU, SA, SE, SG, SV, SY, TR, UY, VE, YE, ZA); Prolastat (CO)

CABO

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Head and Neck Cancer
Regimen UseHead and neck cancer
Regimen

Cisplatin: I.V.: 50 mg/m^2 day 4

[total dose/cycle = 50 mg/m^2]

Methotrexate: I.V.: 40 mg/m^2/day days 1 and 15

[total dose/cycle = 80 mg/m^2]

Bleomycin: I.V.: 10 units/day days 1, 8, and 15

[total dose/cycle = 30 units]

Vincristine: I.V.: 2 mg/day days 1, 8, and 15

[total dose/cycle = 6 mg]

Repeat cycle every 21 days

References

Clavel M, Vermorken JB, Cognetti F, et al, âRandomized Comparison of Cisplatin, Methotrexate, Bleomycin, and Vincristine (CABO) Versus Cisplatin and 5-Fluorouracil (CF) Versus Cisplatin in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck. A Phase III Study of the EORTC Head and Neck Cancer Cooperative Group,â *Ann Oncol*, 1994, 5(6):521-6.[PubMed 7522527]

CAD/MOPP/ABV

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, Hodgkin's Disease

Regimen UseLymphoma, Hodgkin's disease

Regimen

CAD:

Lomustine: Oral: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Melphalan: Oral: 6 mg/m^2/day days 1 to 4

[total dose/cycle = 24 mg/m^2]

Vindesine: I.V.: 3 mg/m^2/day days 1 and 8

[total dose/cycle = 6 mg/m^2]

MOPP:

Mechlorethamine: I.V.: 6 mg/m^2/day days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Procarbazine: Oral: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14

[total dose/cycle = 560 mg/m^2]

ABV:

Doxorubicin: I.V.: 25 mg/m^2/day days 1 and 14

[total dose/cycle = 50 mg/m^2]

Bleomycin: SubQ: 6 units/m^2/day days 1 and 14

[total dose/cycle = 12 units/m^2]

Vinblastine: I.V.: 2 mg/m^2 continuous infusion days 4 to 12 and 18 to 26

[total dose/cycle = 36 mg/m^2]

CAD is administered first, then MOPP begins on day 29 or day 37 following CAD. ABV is administered on day 29 following MOPP; CAD recycles on day 29 following ABV.

References

Straus DJ, Myers J, Koziner B, et al, âCombination Chemotherapy for the Treatment of Hodgkin's Disease in Relapse. Results With Lomustine (CCNU), Melphalan (Alkeran), and Vindesine (DVA) Alone (CAD) and in Alternation With MOPP and Doxorubicin (Adriamycin), Bleomycin, and Vinblastine (ABV),â *Cancer Chemother Pharmacol*, 1983, 11(2):80-5.[PubMed 6194913]

CAF

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cyclophosphamide: Oral: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2/day days 1 and 8

[total dose/cycle = 60 mg/m^2]

Fluorouracil: I.V.: 500 mg/m^2/day days 1 and 8

[total dose/cycle = 1000 mg/m^2]

Repeat cycle every 28 days

Variation 2:

Cyclophosphamide: Oral: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Doxorubicin: I.V.: 25 mg/m^2/day days 1 and 8

[total dose/cycle = 50 mg/m^2]

Fluorouracil: I.V.: 500 mg/m^2/day days 1 and 8

[total dose/cycle = 1000 mg/m^2]

Repeat cycle every 28 days

References

Variation 1:

Bull JM, Tormey DC, Li SH, et al, “A Randomized Comparative Trial of Adriamycin® Versus Methotrexate in Combination Drug Therapy,” *Cancer*, 1978, 41(5):1649-57. [PubMed 348293]

Variation 2:

Aisner J, Weinberg V, Perloff M, et al, “Chemotherapy Versus Chemoimmunotherapy (CAF v CAFVP v CMF each +/- MER) for Metastatic Carcinoma of the Breast,” *J Clin Oncol*, 1987, 5(10):1523-33.[PubMed 3655855]

Caffeine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(KAF een)
U.S. Brand NamesCafcit®; Enerjets [OTC]; No Doz® Maximum Strength [OTC]; Vivarin® [OTC]
Pharmacologic CategoryStimulant
Use: Labeled Indications

Caffeine citrate: Treatment of idiopathic apnea of prematurity

Caffeine and sodium benzoate: Treatment of acute respiratory depression (not a preferred agent)

Caffeine [OTC labeling]: Restore mental alertness or wakefulness when experiencing fatigue

Use: Unlabeled/InvestigationalCaffeine and sodium benzoate: Treatment of spinal puncture headache; CNS stimulant; diuretic; augmentation of seizure induction during electroconvulsive therapy (ECT)
Dosing: Adults

Note: Caffeine citrate should not be interchanged with the caffeine sodium benzoate formulation.

Caffeine and sodium benzoate:

Electroconvulsive therapy: I.V.: 300-2000 mg

Respiratory depression: I.M., I.V.: 250 mg as a single dose; may repeat as needed. Maximum single dose should be limited to 500 mg; maximum amount in any 24-hour period should generally be limited to 2500 mg.

Spinal puncture headache (unlabeled use):

I.V.: 500 mg in 1000 mL NS infused over 1 hour, followed by 1000 mL NS infused over 1 hour; a second course of caffeine can be given for unrelieved headache pain in 4 hours.

Oral: 300 mg as a single dose

Stimulant/diuretic (unlabeled use): I.M., I.V.: 500 mg, maximum single dose: 1 g

OTC labeling (stimulant): Oral: 100-200 mg every 3-4 hours as needed

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Note: Caffeine citrate should not be interchanged with the caffeine sodium benzoate formulation.

Caffeine citrate: Apnea of prematurity: Neonates: Oral, I.V.:

Loading dose: 10-20 mg/kg as caffeine citrate (5-10 mg/kg as caffeine base). If theophylline has been administered to the patient within the previous 3 days, a full or modified loading dose (50% to 75% of a loading dose) may be given.

Maintenance dose: 5 mg/kg/day as caffeine citrate (2.5 mg/kg/day as caffeine base) once daily starting 24 hours after the loading dose. Maintenance dose is adjusted based on patient's response and serum caffeine concentrations.

Caffeine and sodium benzoate: Stimulant:

I.M., I.V., SubQ: 8 mg/kg every 4 hours as needed

Oral: OTC labeling: Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment required.
Administration: I.M.Parenteral: **Caffeine and sodium benzoate:** May administer I.M. undiluted
Administration: I.V.Parenteral:

Caffeine citrate: Infuse loading dose over at least 30 minutes; maintenance dose may be infused over at least 10 minutes. May administer without dilution or diluted with D_5W to 10 mg caffeine citrate/mL.

Caffeine and sodium benzoate: I.V. as slow direct injection. For spinal headaches, dilute in 1000 mL NS and infuse over 1 hour. Follow with 1000 mL NS; infuse over 1 hour. May administer I.M. undiluted.

Administration: OralMay be administered without regard to feedings or meals. May administer injectable formulation (caffeine citrate) orally.
StorageStore at 20°C to 25°C (68°F to 77°F).

Caffeine citrate: Injection and oral solution contain no preservatives; injection is chemically stable for at least 24 hours at room temperature when diluted to 10 mg/mL (as caffeine citrate) with D$_5$W, D$_{50}$W, Intralipid® 20%, and Aminosyn® 8.5%; also compatible with dopamine (600 mcg/mL), calcium gluconate 10%, heparin (1 unit/mL), and fentanyl (10 mcg/mL) at room temperature for 24 hours.

CompatibilityCaffeine citrate: Stable in D$_5$W, D$_{50}$W, Intralipid® 20%, Aminosyn® 8.5%.

Compatible: Calcium gluconate 10%, dopamine (600 mcg/mL), fentanyl (10 mcg/mL), heparin (1 unit/mL).

ContraindicationsHypersensitivity to caffeine or any component of the formulation; sodium benzoate is not for use in neonates
Warnings/Precautions

Disease-related concerns:

- Anxiety: Avoid use in patients with anxiety, agitation, or tremor.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease; avoid use in patients with symptomatic cardiac arrhythmias.
- Gastrointestinal disease: Use with caution in patients with a history of peptic ulcer and/or gastroesophageal reflux.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Seizure disorder: Use with caution in patients with a history of seizure disorder; may lower seizure threshold leading to new onset or breakthrough seizure activity.

Special populations:

- Neonates: Caffeine citrate should be closely monitored for the development of necrotizing enterocolitis in the neonate; caffeine serum levels should be closely monitored to optimize therapy and prevent serious toxicity. Avoid use of products containing sodium benzoate in neonates; has been associated with a potentially fatal toxicity (“gasping syndrome”) in neonates, including metabolic acidosis, respiratory distress, gasping respirations, seizures, intracranial hemorrhage, hypotension, and cardiovascular collapse. *In vitro* and animal studies have shown that benzoate also displaces bilirubin from protein-binding sites.

Dosage form specific issues:

- OTC products: Over-the-counter [OTC] products contain an amount of caffeine similar to one cup of coffee; limit the use of other caffeine-containing beverages or foods.
- Product interchangeability: **Caffeine citrate should not be interchanged with caffeine and sodium benzoate.**

Pregnancy Risk FactorC
Pregnancy ConsiderationsCaffeine crosses the placenta; serum levels in the fetus are similar to those in the mother. When large bolus doses are administered to animals, teratogenic effects have been reported. Similar doses are not probable following normal caffeine consumption and moderate consumption is not associated with congenital malformations, spontaneous abortions, preterm birth or low birth weight. According to one source, pregnant women who do not smoke or drink alcohol could consume ≤5 mg/kg of caffeine over the course of a day without reproductive risk. Another source recommends limiting caffeine intake to <150 mg/day. The half-life of caffeine is prolonged during the second and third trimesters of pregnancy.
LactationEnters breast milk/use caution (AAP rates “compatible”)
Breast-Feeding ConsiderationsIrritability and poor sleeping patterns have been reported following maternal consumption of large amounts of caffeine. Moderate intake (2-3 cups/day) is considered to be compatible with breast-feeding.
Adverse ReactionsFrequency not specified; primarily serum-concentration related.
Cardiovascular: Angina, arrhythmia (ventricular), chest pain, flushing, palpitation, sinus tachycardia, tachycardia (supraventricular), vasodilation

Central nervous system: Agitation, delirium, dizziness, hallucinations, headache, insomnia, irritability, psychosis, restlessness

Dermatologic: Urticaria

Gastrointestinal: Esophageal sphincter tone decreased, gastritis

Neuromuscular & skeletal: Fasciculations

Ocular: Intraocular pressure increased (>180 mg caffeine), miosis

Renal: Diuresis

Metabolism/Transport Effects**Substrate** of CYP1A2 (major), 2C9 (minor), 2D6 (minor), 2E1 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 3A4 (moderate)
Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Quinolone Antibiotics: May decrease the metabolism of Caffeine. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Ofloxacin; Sparfloxacin; Trovafloxacin. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Regadenoson: Caffeine may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Reference Range

Therapeutic: Apnea of prematurity: 8-20 mcg/mL

Potentially toxic: >20 mcg/mL

Toxic: >50 mcg/mL

Nursing: Physical Assessment/MonitoringAssess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Patient EducationTake as directed. Do not exceed recommended dosage. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake by prescriber. You may experience CNS stimulation, excitability, sensorium changes, flushing, dizziness, insomnia, or agitation. Report excessive excitability or nervousness, rapid heartbeat or palpitations, chest pain, or respiratory difficulty. **Pregnancy/breast-feeding precaution:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet:

NoDoz® Maximum Strength, Vivarin®: 200 mg

Injection, solution, as citrate [preservative free]: 20 mg/mL (3 mL) [equivalent to 10 mg/mL caffeine base]

Cafcit®: 20 mg/mL (3 mL) [equivalent to 10 mg/mL caffeine base]

Injection, solution [with sodium benzoate]: Caffeine 125 mg/mL and sodium benzoate 125 mg/mL (2 mL); caffeine 121 mg/mL and sodium benzoate 129 mg/mL (2 mL) [DSC]

Lozenge:

Enerjets®: 75 mg [classic coffee, hazelnut cream, or mochamint flavor]

Solution, oral, as citrate [preservative free]: 20 mg/mL (3 mL) [equivalent to 10 mg/mL caffeine base]

Cafcit®: 20 mg/mL (3 mL) [equivalent to 10 mg/mL caffeine base]

Tablet: 200 mg

Vivarin®: 200 mg

Generic AvailableYes: Tablet, caffeine and sodium benzoate injection, injection, oral solution

Mechanism of ActionIncreases levels of 3'5' cyclic AMP by inhibiting phosphodiesterase; CNS stimulant which increases medullary respiratory center sensitivity to carbon dioxide, stimulates central inspiratory drive, and improves skeletal muscle contraction (diaphragmatic contractility); prevention of apnea may occur by competitive inhibition of adenosine

Pharmacodynamics/Kinetics

Distribution: V_d:

Neonates: 0.8-0.9 L/kg

Children >9 months to Adults: 0.6 L/kg

Protein binding: 17% (children) to 36% (adults)

Metabolism: Hepatic, via demethylation by CYP1A2. **Note:** In neonates, interconversion between caffeine and theophylline has been reported (caffeine levels are ~25% of measured theophylline after theophylline administration and ~3% to 8% of caffeine would be expected to be converted to theophylline)

Half-life elimination:

Neonates: 72-96 hours (range: 40-230 hours)

Children >9 months and Adults: 5 hours

Time to peak, serum: Oral: Within 30 minutes to 2 hours

Excretion:

Neonates ≤1 month: 86% excreted unchanged in urine

Infants >1 month and Adults: In urine, as metabolites

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia, nervousness, anxiety, and delirium.

Mental Health: Effects on Psychiatric TreatmentMay counteract sedative/hypnotics; may also lower seizure threshold and increase risk for epilepsy/convulsions

Anesthesia and Critical Care Concerns/Other ConsiderationsCaffeine has 40% of the bronchodilatory activity of theophylline. Lithium blood levels may increase during caffeine withdrawal. Analgesia from transcutaneous electrical nerve stimulation may be lessened with concomitant caffeine use.

Index TermsCaffeine and Sodium Benzoate; Caffeine Citrate; Sodium Benzoate and Caffeine

References

American Academy of Pediatrics Committee on Drugs, “The Transfer of Drugs and Other Chemicals Into Human Milk,” *Pediatrics*, 2001, 108(3):776-89. [PubMed 11533352]

Choi A, Laurito CE, and Cunningham FE, “Pharmacologic Management of Postdural Puncture Headache,” *Ann Pharmacother*, 1996, 30(7-8):831-9. [PubMed 8826568]

Christian MS and Brent RL, “Teratogen Update: Evaluation of the Reproductive and Developmental Risks of Caffeine,” *Teratology*, 2001, 64(1):51-78. [PubMed 11410911]

Koren G, “Caffeine During Pregnancy? In Moderation,” *Can Fam Physician*, 2000, 46(4):801-3. [PubMed 10790810]

Yucel A, Ozyalcin S, Talu GK, et al, “Intravenous Administration of Caffeine Sodium Benzoate for Postdural Puncture Headache,” *Reg Anesth Pain Med*, 1999, 24(1):51-4.[PubMed 9952095]

International Brand NamesCoffeinum Natrium Benzoicum (PL); Kofex (PL)

Calcipotriene and Betamethasone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(kal si POE try een & bay ta METH a sone)
U.S. Brand NamesTaclonex Scalp®; Taclonex®
Canadian Brand NamesDovobet®
Pharmacologic CategoryCorticosteroid, Topical; Vitamin D Analog
Use: Labeled IndicationsTreatment of psoriasis vulgaris
Use: Unlabeled/InvestigationalTreatment of corticosteroid-responsive dermatoses
Dosing: Adults

Psoriasis vulgaris: Topical:

Cream/ointment: Apply to affected area once daily for up to 4 weeks (maximum recommended dose: 100 g/week). Application to >30% of body surface area is not recommended.

Suspension: Apply to affected area of the scalp once daily for 2 weeks or until clear; may continue for up to 8 weeks (maximum recommended dose: 100 g/week)

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentSafety and efficacy have not been established with severe renal impairment.
Dosing: Hepatic ImpairmentSafety and efficacy have not been established with severe hepatic impairment.
Administration: TopicalWash hands before and after use.

Cream/ointment: Rub into affected area gently and completely. Do not apply to face, axillae, or groin.

Suspension: Shake well before use. Do not apply within 12 hours of chemical hair treatment. Do not wash hair directly after use.

StorageStore at controlled room temperature of 20°C to 2°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Do not refrigerate. Discard suspension 3 months from date opened. Keep suspension bottle in outer carton when not in use.
Contraindications

Cream, ointment: Hypersensitivity to calcipotriene, betamethasone, or any component of the formulation; disorders of calcium metabolism; erythrodermic, exfolliative, and pustular psoriasis; viral, fungal, or bacterial infection of the skin; evidence of vitamin D toxicity

Suspension: There are no contraindications listed within the FDA-approved labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.

- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.

- Hypercalcemia/hypercalciuria: May cause transient increases in serum and urinary calcium (reversible); if hypercalcemia or hypercalciuria occurs, discontinue treatment until levels return to normal.

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children; may be at higher risk of systemic side effects.

Other warnings/precautions:

- Application site: Do not use on the face, axillae, groin, or in the presence of pre-existing skin atrophy at the treatment site. Avoid exposure of suspension to the eyes; irritation may occur. Avoid excessive exposure of treated skin to sunlight (natural or artificial).

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this topical combination. There are no adequate and well-controlled studies in pregnant women. See individual agents.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsSee individual agents.

Adverse Reactions

1% to 10%: Dermatologic: Pruritus (4%), erythema (2%), irritation (1%), scaly rash (1%), folliculitis (≤1%)

<1%: Acne, eye irritation, HPA axis suppression, hypercalcemia, hypercalciuria, papular rash, psoriasis exacerbation, pustular psoriasis, pustular rash, skin atrophy, skin hyper-/hypopigmentation, telangiectasia

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop.

Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Cream, topical:

Dovobet® [CAN]: Calcipotriol 50 mcg and betamethasone 0.5 mg per gram (3 g, 30 g, 60 g, 100 g, 120 g) [not available in the U.S.]

Ointment, topical:

Taclonex®: Calcipotriene 0.005% and betamethasone dipropionate 0.064% (60 g, 100 g)

Suspension, topical:

Taclonex Scalp®: Calcipotriene 0.005% and betamethasone dipropionate 0.064% (15 g, 30 g, 60 g, 2 x 60 g)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Ointment (Taclonex)

0.005-0.064% (60): $454.42

0.005-0.064% (100): $729.01

Mechanism of ActionCalcipotriene is a vitamin D derivative and betamethasone dipropionate ointment is a high-potency corticosteroid.

Related Information

- Betamethasone
- Calcipotriene

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBetamethasone Dipropionate and Calcipotriene Hydrate; Calcipotriol and Betamethasone Dipropionate

References

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

International Brand NamesDovobet (CA)

Calcipotriene

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(kal si POE try een)
U.S. Brand NamesDovonex®
Canadian Brand NamesDovonex®
Pharmacologic CategoryTopical Skin Product; Vitamin D Analog
Use: Labeled IndicationsTreatment of plaque psoriasis; chronic, moderate-to-severe psoriasis of the scalp
Use: Unlabeled/InvestigationalVitiligo
Dosing: AdultsPsoriasis: Topical:

Cream: Apply a thin film to the affected skin twice daily and rub in gently and completely, for up to 8 weeks

Solution: Apply to the affected scalp twice daily and rub in gently and completely, for up to 8 weeks

Dosing: ElderlyRefer to adult dosing.
Administration: TopicalFor external use only.
Cream: Apply to affected skin; rub in gently and completely. Wash hands thoroughly before and after use.

Solution: Prior to using scalp solution, comb hair to remove debris; apply only to lesions. Rub in gently and completely. Avoid solution spreading or dripping onto forehead. Avoid contact with eyes. Wash hands thoroughly before and after use.

StorageStore at controlled room temperature of 15° to 25°C (59° to 77°F). Do not freeze. Solution should be kept away from open flame; avoid sunlight.
ContraindicationsHypersensitivity to calcipotriene or any component of the formulation; patients with demonstrated hypercalcemia or evidence of vitamin D toxicity; use on the face; patients with acute psoriatic eruptions (scalp solution)
Warnings/Precautions

Concerns related to adverse effects:

- Hypercalcemia: May cause transient increases in serum calcium (reversible); if hypercalcemia occurs, discontinue treatment until levels return to normal.
- Irritation: Discontinue use if irritation occurs.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: For external use only; not for ophthalmic, oral, or intravaginal use. Avoid or limit excessive exposure to natural or artificial sunlight, or phototherapy.

Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects have been observed in animal studies. There are no adequate or well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency may vary with site of application.

>10%: Dermatologic: Burning, itching, rash, skin irritation, stinging, tingling

1% to 10%: Dermatologic: Dermatitis, dry skin, erythema, peeling, pruritus, worsening of psoriasis

Note: Skin atrophy, hyperpigmentation, folliculitis, and hypercalcemia are potential adverse effects of calcipotriene.

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersSerum calcium
Nursing: Physical Assessment/MonitoringWhen applied to large areas of skin or for extensive periods of time, monitor for adverse skin or systemic reactions. Assess knowledge/teach patient appropriate application and use and adverse symptoms to report.
Monitoring: Lab TestsSerum calcium
Patient EducationFor external use only. Use exactly as directed; do not overuse. Before using, wash and dry area gently. Wear gloves to apply a thin film to affected area and rub in gently. If dressing is necessary, use a porous dressing. Avoid contact with eyes. Avoid exposing treated area to direct sunlight; sunburn can occur. Report increased swelling, redness, rash, itching, signs of infection, worsening of condition, or lack of healing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream:

Dovonex®: 0.005% (60 g, 120 g)

Ointment:

Dovonex®: 0.005% (60 g, 120 g) [DSC]

Solution, topical: 0.005% (60 mL)

Dovonex®: 0.005% (60 mL)

Generic AvailableYes: Excludes cream, ointment

ManufacturerWarner Chilcott

Pricing: U.S. (www.drugstore.com)

Cream (Dovonex)

0.005% (60): $237.55

0.005% (120): $449.34

Ointment (Dovonex)

0.005% (120): $413.27

Solution (Calcipotriene)

0.005% (60): $159.98

Solution (Dovonex)

0.005% (60): $236.48

Mechanism of ActionSynthetic vitamin D_3 analog which regulates skin cell production and proliferation

Pharmacodynamics/Kinetics

Onset of action: Improvement begins after 2 weeks; marked improvement seen after 8 weeks

Absorption: When applied to psoriasis plaques: Cream, ointment: ~6%; Solution: <1%

Metabolism: Converted in the skin to inactive metabolites

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

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Ameen M, Exarchou V, and Chu AC, "Topical Calcipotriol as Monotherapy and in Combination With Psoralen Plus Ultraviolet A in the Treatment of Vitiligo," *Br J Dermatol*, 2001, 145(3):476-9.[PubMed 11531840]

Gargoom AM, Duweb GA, Elzorghany AH, et al, "Calcipotriol in the Treatment of Childhood Vitiligo," *Int J Clin Pharmacol Res*, 2004, 24(1):11-4.[PubMed 15575172]

Grimes PE, "New Insights and New Therapies in Vitiligo," *JAMA*, 2005, 293(6):730-5.[PubMed 15701915]

Yalcin B, Sahin S, Bukulmez G, et al, "Experience With Calcipotriol as Adjunctive Treatment for Vitiligo in Patients Who Do Not Respond to PUVA Alone: A Preliminary Study," *J Am Acad Dermatol*, 2001, 44(4):634-7.[PubMed 11260538]

International Brand NamesDaivonex (AR, AU, BB, BE, BG, BM, BR, BS, BZ, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, EE, FI, FR, GT, GY, HK, HN, ID, IL, IN, IT, JM, MX, MY, NL, NO, PA, PH, PK, PR, PT, SE, SR, SV, TH, TT, TW, UY, VE); Dovonex (EG, GB, GR, IE, JP, ZA); Psorcutan (AT, DE); Psotriol (IN)

Calcitonin

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Medication Safety Issues

Sound-alike/look-alike issues:

Calcitonin may be confused with calcitriol

Miacalcin® may be confused with Micatin®

Calcitonin nasal spray is administered as a single spray into **one** nostril daily, using alternate nostrils each day.

Pronunciation(kal si TOE nin)

U.S. Brand NamesFortical®; Miacalcin®

Canadian Brand NamesApo-Calcitonin®; Calcimar®; Caltine®; Miacalcin® NS; Pro-Calcitonin

Pharmacologic CategoryAntidote; Hormone

Use: Labeled IndicationsCalcitonin (salmon): Treatment of Paget's disease of bone (osteitis deformans); adjunctive therapy for hypercalcemia; treatment of osteoporosis in women >5 years postmenopause

Dosing: Adults

Paget's disease*(Miacalcin®)*: I.M., SubQ: Initial: 100 units/day; maintenance: 50 units/day or 50-100 units every 1-3 days

Hypercalcemia*(Miacalcin®)*: Initial: I.M., SubQ: 4 units/kg every 12 hours; may increase up to 8 units/kg every 12 hours to a maximum of every 6 hours

Postmenopausal osteoporosis:

Miacalcin®: I.M., SubQ: 100 units/every other day

Fortical®, Miacalcin®: Intranasal: 200 units (1 spray) in one nostril daily

Dosing: ElderlyRefer to adult dosing.

Administration: I.M.Administer injection solution I.M. or SubQ; intramuscular route is recommended over the subcutaneous route when the volume of calcitonin to be injected exceeds 2 mL.

Administration: InhalationNasal spray: Before first use, allow bottle to reach room temperature, then prime pump by releasing at least 5 sprays until full spray is produced. To administer, place nozzle into nostril with head in upright position. Alternate nostrils daily. Do not prime pump before each daily use. Discard after 30 doses.

Dietary ConsiderationsAdequate vitamin D and calcium intake is essential for preventing/treating osteoporosis. Patients with Paget's disease and hypercalcemia should follow a low calcium diet as prescribed.

Storage

Injection: Store under refrigeration at 2°C to 8°C (36°F to 46°F); protect from freezing.

Nasal: Store unopened bottle under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze.

Fortical®: After opening, store for up to 30 days at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Store in upright position.

Miacalcin®: After opening, store for up to 35 days at room temperature of 15°C to 30°C (59°F to 86°F). Store in upright position.

ReconstitutionInjection: NS has been recommended for the dilution to prepare a skin test in patients with suspected sensitivity.

ContraindicationsHypersensitivity to calcitonin salmon or any component of the formulation

Allergy Considerations

- Calcitonin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Salmon-derived products: Have epinephrine immediately available for a possible hypersensitivity reaction. A skin test should be performed prior to initiating therapy of calcitonin salmon in patients with suspected sensitivity; a detailed skin testing protocol is available from the manufacturer.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Nasal spray: Temporarily withdraw use of nasal spray if ulceration of nasal mucosa occurs. Patients >65 years of age may experience a higher incidence of nasal adverse events with calcitonin nasal spray.

Geriatric ConsiderationsStudies have shown calcitonin's effects on bone density and fracture rates are beneficial, particularly in women unable to tolerate estrogens. Calcium and vitamin D supplements should also be given. Calcitonin may also be effective in steroid-induced osteoporosis and other states associated with high bone turnover. Nasal spray may provide faster onset of analgesic effects than I.M.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDecreased birth weight was observed in animal studies. Calcitonin does not cross the placental barrier. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsHas been shown to decrease milk production in animals.

Adverse ReactionsUnless otherwise noted, frequencies reported are with nasal spray.

>10%: Respiratory: Rhinitis (12%)

1% to 10%:

Cardiovascular: Flushing (nasal spray: <1%; injection: 2% to 5%), angina (1% to 3%), hypertension (1% to 3%)

Central nervous system: Depression (1% to 3%), dizziness (1% to 3%), fatigue (1% to 3%)

Dermatologic: Erythematous rash (1% to 3%)

Gastrointestinal: Abdominal pain (1% to 3%), constipation (1% to 3%), diarrhea (1% to 3%), dyspepsia (1% to 3%), nausea (injection: 10%; nasal spray: 1% to 3%)

Genitourinary: Cystitis (1% to 3%)

Local: Injection site reactions (injection: 10%)

Neuromuscular & skeletal: Back pain (5%), arthrosis (1% to 3%), myalgia (1% to 3%), paresthesia (1% to 3%)

Ocular: Conjunctivitis (1% to 3%), lacrimation abnormality (1% to 3%)

Respiratory: Bronchospasm (1% to 3%), sinusitis (1% to 3%), upper respiratory tract infection (1% to 3%)

Miscellaneous: Flu-like syndrome (1% to 3%), infection (1% to 3%), lymphadenopathy (1% to 3%)

<1%: Agitation, allergic reactions, alopecia, anaphylaxis, anemia, anorexia, anxiety, appetite increased, arthritis, blurred vision, bronchitis, bundle branch block, cerebrovascular accident, cholelithiasis, cough, diaphoresis, dyspnea, earache, eczema, fever, flatulence, gastritis, goiter, hearing loss, hematuria, hepatitis, hyperthyroidism, insomnia, migraine, myocardial infarction, neuralgia, nocturia, palpitation, parosmia, periorbital edema, pharyngitis, pneumonia, polymyalgia rheumatica, pruritus, pyelonephritis, rash, renal calculus, skin ulceration, stiffness, tachycardia, taste perversion, thirst, thrombophlebitis, tinnitus, vertigo, vitreous floater, vomiting, weight gain, xerostomia

Oncology: VesicantNo

Oncology: Emetic PotentialModerate (30% to 60%); nausea and vomiting are generally mild

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase risk of osteoporosis).

Monitoring ParametersSerum electrolytes and calcium; alkaline phosphatase and 24-hour urine collection for hydroxyproline excretion (Paget's disease), urinalysis (urine sediment); bone mineral density

Nasal formulation: Visualization of nasal mucosa, turbinate, septum, and mucosal blood vessels)

Reference RangeTherapeutic: <19 pg/mL (SI: 19 ng/L) basal, depending on the assay

Nursing: Physical Assessment/MonitoringSkin test should be administered before initiating therapy (increased erythema or skin wheal indicates positive reaction and allergy). Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests and patient response (eg, hypocalcemic tetany, hypercalcemia) at regular intervals during therapy. Teach appropriate administration (eg, subcutaneous or I.M. injections or nasal spray), dietary requirements (low calcium diet if used for hypercalcemia), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum electrolytes and calcium, alkaline phosphatase and 24-hour urine collection for hydroxyproline excretion (Paget's disease), urinalysis (urine sediment); bone mineral density

Patient EducationDo not take any new medication during therapy unless approved by prescriber. If administered by injection, you or a significant other will be instructed on how to give the injections and dispose of syringes/needles (follow directions exactly). Keep drug vials in refrigerator; do not freeze. May cause increased warmth and flushing (this should only last about 1 hour after administration; taking drug in evening may minimize these discomforts). Report significant nasal irritation if using nasal spray. Immediately report twitching, muscle spasm, dark-colored urine, hives, significant skin rash, palpitations, or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [calcitonin-salmon]:

Miacalcin®: 200 int. units/mL (2 mL)

Solution, intranasal [spray, calcitonin-salmon]:

Fortical®: 200 int. units/0.09 mL (3.7 mL) [rDNA origin; contains benzyl alcohol; delivers 30 doses, 200 units/actuation]

Miacalcin®: 200 int. units/0.09 mL (3.7 mL) [contains benzalkonium chloride; delivers 30 doses, 200 units/actuation]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Miacalcin)

200 units/ACT (3.7): $123.32

200 units/mL (2): $55.92

Mechanism of ActionPeptide sequence similar to human calcitonin; functionally antagonizes the effects of parathyroid hormone. Directly inhibits osteoclastic bone resorption; promotes the renal excretion of calcium, phosphate, sodium, magnesium, and potassium by decreasing tubular reabsorption; increases the jejunal secretion of water, sodium, potassium, and chloride

Pharmacodynamics/Kinetics

Hypercalcemia: I.M. or SubQ:

Onset of action: ~2 hours

Duration: 6-8 hours

Absorption: Nasal: ~3% of I.M. level (range: 0.3% to 31%)

Distribution: Does not cross placenta

Half-life elimination: SubQ: 1.2 hours; Nasal: 43 minutes

Time to peak: Nasal: ~30-40 minutes

Excretion: Urine (as inactive metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression, dizziness, or fatigue. Rarely associated with agitation, anxiety, and insomnia.

Mental Health: Effects on Psychiatric TreatmentMay cause GI side effects; concomitant use with SSRIs, carbamazepine, valproic acid, and lithium may produce additive effects.

Index TermsCalcitonin (Salmon)

References

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International Brand NamesCadens (FR); Calcihexal [salmon] (PL); Calcinin (TW); Calcitonin [salmon] (PL); Calcitoran (JP); Calco (TH); Calco [salmon] (HU); Calsynar (BR, TW); Calsynar [salmon] (AU, HU, LU, PL); Cibacalcin (AE, AT, BH, CY, EG, GR, IL, IQ, IR, IT, JO, KW, LB, LY, MY, NL, OM, QA, SA, SY, YE); Cibacalcin [human] (AU); Cibacalcine (BE, FR); Cibacalcine [human] (LU); Citonina (AR); Forcaltonin (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, NL, NO, PT, RU, SE, TR); Karil (LU); Karil [salmon] (LU); Menocal (KP); Miacalcic (AE, AT, BE, BG, BH, BR, CH, CL, CN, CO, CY, CZ, DE, DK, EC, EG, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IN, IQ, IR, IT, JO, KW, LB, LY, MX, MY, NL, NO, NZ, OM, PE, PH, PT, QA, RU, SA, SE, SG, SY, TH, TR, TW, YE); Miacalcic [salmon] (AU, HR, HU, PL); Oseum (MX); Ostostabil [salmon] (PL); Salmocalcin (AR); Tonocalcin (ID, MY); Tonocalcin [salmon] (PL); Ucecal [salmon] (LU); Zycalcit (IN)

Calcitriol

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Calcitriol may be confused with calcifediol, Calciferol®, calcitonin

Dosage is expressed in mcg (micrograms), **not** mg (milligrams); rare cases of acute overdose have been reported

Pronunciation(kal si TRYE ole)

U.S. Brand NamesCalcijex®; Rocaltrol®

Canadian Brand NamesCalcijex®; Rocaltrol®

Pharmacologic CategoryVitamin D Analog

Use: Labeled IndicationsManagement of hypocalcemia in patients on chronic renal dialysis; management of secondary hyperparathyroidism in patients with chronic kidney disease (CKD); management of hypocalcemia in hypoparathyroidism and pseudohypoparathyroidism

Use: Unlabeled/InvestigationalDecrease severity of psoriatic lesions in psoriatic vulgaris; vitamin D-dependent rickets

Dosing: Adults

Hypocalcemia in patients on chronic renal dialysis (manufacturer labeling):

Oral: 0.25 mcg/day or every other day (may require 0.5-1 mcg/day); increases should be made at 4- to 8-week intervals

I.V.: Initial: 1-2 mcg 3 times/week (0.02 mcg/kg) approximately every other day. Adjust dose at 2-4 week intervals; dosing range: 0.5-4 mcg 3 times/week

Hypocalcemia in hypoparathyroidism/pseudohypoparathyroidism (manufacturers labeling): Oral (evaluate dosage at 2- to 4-week intervals): Initial: 0.25 mcg/day, range: 0.5-2 mcg once daily

Secondary hyperparathyroidism associated with moderate-to-severe CKD in patients not on dialysis (manufacturer labeling): Oral: 0.25 mcg/day; may increase to 0.5 mcg/day

K/DOQI guidelines for vitamin D therapy in CKD:

CKD stage 3: Oral: 0.25 mcg/day. Treatment should only be started with serum 25(OH) D >30 ng/mL, serum iPTH >70 pg/mL, serum calcium <9.5 mg/dL and serum phosphorus <4.6 mg/dL

CKD stage 4: Oral: 0.25 mcg/day. Treatment should only be started with serum 25(OH) D >30 ng/mL, serum iPTH >110 pg/mL, serum calcium <9.5 mg/dL and serum phosphorus <4.6 mg/dL

CKD stage 5:

Peritoneal dialysis: Oral: Initial: 0.5-1 mcg 2-3 times/week or 0.25 mcg/day

Hemodialysis: **Note:** The following initial doses are based on plasma PTH and serum calcium levels for patients with serum phosphorus <5.5 mg/dL and Ca-P product <55. Adjust dose based on serum phosphate, calcium, and PTH levels. Intermittent I.V. administration may be more effective than daily oral dosing.

Plasma PTH 300-600 pg/mL and serum Ca <9.5 mg/dL: Oral, I.V.: 0.5-1.5 mcg

Plasma PTH 600-1000 pg/mL and serum Ca <9.5 mg/dL:

Oral: 1-4 mcg

I.V.: 1-3 mcg

Plasma PTH >1000 pg/mL and serum Ca <10 mg/dL:

Oral: 3-7 mcg

I.V.: 3-5 mcg

Vitamin D-dependent rickets (unlabeled use): Oral: 1 mcg once daily

Dosing: ElderlyRefer to adult dosing. No dosage recommendations, but start at the lower end of the dosage range.

Dosing: Pediatric

Hypocalcemia in hypoparathyroidism/pseudohypoparathyroidism (manufacturers labeling): Oral (evaluate dosage at 2- to 4-week intervals):

Children <1 year (unlabeled use): 0.04-0.08 mcg/kg once daily

Children 1-5 years: 0.25-0.75 mcg once daily

Children ≥6 years: Refer to adults dosing.

Secondary hyperparathyroidism associated with moderate-to-severe CKD in patients not on dialysis (manufacturer labeling): Oral:

Children <3 years: Initial dose: 0.01-0.015 mcg/kg/day

Children ≥3 years: Refer to adults dosing.

K/DOQI guidelines for vitamin D therapy in CKD:

CKD stage 2, 3: Oral:

<10 kg: 0.05 mcg every other day

10-20 kg: 0.1-0.15 mcg/day

>20 kg: 0.25 mcg/day

Note: Treatment should only be started with serum 25(OH) D >30 ng/mL, serum iPTH >70 pg/mL, serum calcium <10 mg/dL and serum phosphorus less than or equal to the age appropriate level.

CKD stage 4: Oral:

<10 kg: 0.05 mcg every other day

10-20 kg: 0.1-0.15 mcg/day

>20 kg: 0.25 mcg/day

Note: Treatment should only be started with serum 25(OH) D >30 ng/mL, serum iPTH >110 pg/mL, serum calcium <10 mg/dL and serum phosphorus less than or equal to the age appropriate level.

CKD stage 5: Oral, I.V.: **Note:** The following initial doses are based on plasma PTH and serum calcium levels for patients with serum phosphorus <5.5 mg/dL in adolescents or <6.5 in infants and children, and Ca-P product <55 in adolescents or <65 in infants and children <12 years. Adjust dose based on serum phosphate, calcium and PTH levels. Administer dose with each dialysis session (3 times/week). Intermittent I.V./oral administration is more effective than daily oral dosing.

Plasma PTH 300-500 pg/mL and serum Ca <10 mg/dL: 0.0075 mcg/kg (maximum: 0.25 mcg/day)

Plasma PTH >500-1000 pg/mL and serum Ca <10 mg/dL: 0.015 mcg/kg (maximum: 0.5 mcg/day)

Plasma PTH >1000 pg/mL and serum Ca <10.5 mg/dL: 0.025 mcg/kg (maximum: 1 mcg/day)

Vitamin D-dependent rickets (unlabeled use): Refer to adults dosing.

Dosing: Adjustment for ToxicityK/DOQI guidelines: Children and Adults: CKD stage 3 and 4:

iPTH below target: Hold calcitriol until levels rise then resume treatment at half the previous dose. If the lowest dose was being used, switch to alternate day therapy.

Corrected total calcium >9.5 mg/dL (adults) or 10.2 mg/dL (children): Hold calcitriol until serum calcium returns to <9.5 mg/dL (adults) or <9.8 mg/dL (children) then resume treatment at half the previous dose. If the lowest dose was being used, switch to alternate day therapy.

Serum phosphorus >4.6 mg/dL (adults) or greater than the age appropriate limits in children: Hold calcitriol (or add/increase dose of phosphate binder) until levels of phosphorous decrease, then resume at half the prior dose.

Dosing: Combination Regimens

Prostate cancer: Estramustine + Docetaxel + Calcitriol

Administration: I.V.May be administered as a bolus dose I.V. through the catheter at the end of hemodialysis.

Administration: I.V. DetailpH: 5.9-7.0

Administration: OralMay be administered without regard to food. Give with meals to reduce GI problems.

Dietary ConsiderationsMay be taken without regard to food. Give with meals to reduce GI problems. Adequate calcium intake should be maintained during therapy; dietary phosphorous may need to be restricted. Rocaltrol® capsules contain coconut oil; Rocaltrol® solution contains palm seed oil.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

CompatibilityStable in D_5W, NS, sterile water for injection.

ContraindicationsHypersensitivity to calcitriol or any component of the formulation; hypercalcemia, vitamin D toxicity

Warnings/Precautions

Concerns related to adverse effects:

- Excessive vitamin D: Excessive vitamin D administration may lead to over suppression of PTH, progressive or acute hypercalcemia, hypercalciuria, hyperphosphatemia and adynamic bone disease.

Disease-related concerns:

- Malabsorption syndrome: Use with caution in patients with malabsorption syndromes; efficacy may be limited and/or response may be unpredictable.

- Renal impairment: Use of calcitriol for the treatment of secondary hyperparathyroidism associated with CKD is not recommended in patients with rapidly worsening kidney function or in noncompliant patients. Increased serum phosphate levels in patients with renal failure may lead to ectopic calcification; the use of an aluminum-containing phosphate binder is recommended along with a low phosphate diet in these patients.

Concurrent drug therapy issues:

- Calcium: Adequate dietary (supplemental) calcium is necessary for clinical response to vitamin D.

- Cardiac glycosides: Use with caution in patients taking cardiac glycosides; digitalis toxicity is potentiated by hypocalcemia.

Dosage form specific issues:

- Coconut oil: Products may contain coconut oil (capsule).

- Palm seed oil: Products may contain palm seed oil (oral solution).

- Tartrazine: Some products may contain tartrazine.

Other warnings/precautions:

- Calcium-phosphate product: Serum calcium times phosphorus must not exceed 70 mg^2/dL^2.

Geriatric ConsiderationsRecommended daily allowances (RDA) have not been developed for persons >65 years of age; vitamin D, folate, and B_{12} (cyanocobalamin) have decreased absorption with age, but the clinical significance is yet unknown. Calorie requirements decrease with age and therefore, nutrient density must be increased to ensure adequate nutrient intake, including vitamins and minerals. Therefore, the use of a daily supplement with a multiple vitamin with minerals is recommended. Elderly consume less vitamin D, absorption may be decreased, and many elderly have decreased sun exposure; therefore, elderly should receive supplementation with 800 units of vitamin D (20 mcg)/day. This is a recommendation of particular need to those with high risk for osteoporosis.

Pregnancy Risk FactorC (manufacturer); A/D (dose exceeding RDA recommendation) (expert analysis)

Pregnancy ConsiderationsTeratogenic effects have been observed in animal studies. Mild hypercalcemia has been reported in a newborn following maternal use of calcitriol during pregnancy. If calcitriol is used for the management of hypoparathyroidism in pregnancy, dose adjustments may be needed as pregnancy progresses and again following delivery. Vitamin D and calcium levels should be monitored closely and kept in the lower normal range.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsLow levels are found in breast milk (~2 pg/mL)

Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiac arrhythmia, hypertension

Central nervous system: Apathy, headache, hypothermia, psychosis, sensory disturbances, somnolence

Dermatologic: Erythema multiforme, pruritus

Endocrine & metabolic: Dehydration, growth suppression, hypercalcemia, hypercholesterolemia, hypermagnesemia, hyperphosphatemia, libido decreased, polydipsia

Gastrointestinal: Abdominal pain, anorexia, constipation, metallic taste, nausea, pancreatitis, stomach ache, vomiting, weight loss, xerostomia

Genitourinary: Nocturia, urinary tract infection

Hepatic: ALT increased, AST increased

Local: Injection site pain (mild)

Neuromuscular & skeletal: Bone pain, myalgia, dystrophy, soft tissue calcification, weakness

Ocular: Conjunctivitis, photophobia

Renal: Albuminuria, BUN increased, creatinine increased, hypercalciurianephrocalcinosis, polyuria

Respiratory: Rhinorrhea

Miscellaneous: Allergic reaction

Metabolism/Transport Effects**Induces** CYP3A4 (weak)

Drug Interactions

Bile Acid Sequestrants: May decrease the serum concentration of Calcitriol. *Risk C: Monitor therapy*

Cardiac Glycosides: Calcitriol may enhance the arrhythmogenic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Magnesium Salts: Calcitriol may increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Thiazide Diuretics: May enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Monitoring ParametersSigns and symptoms of vitamin D intoxication; alkaline phosphatase, serum creatinine

Serum calcium and phosphorus:

CKD stage 2-4: Every month for the first 3 months, then every 3 months

CKD stage 5: Every 2 weeks for 1 month, then monthly

Serum or plasma intact PTH (iPTH):

CKD stage 3 and 4: Every 3 months for 6 months, then every 3 months

CKD stage 5: Monthly for 3 months, then every 3 months

Reference Range

CKD K/DOQI guidelines definition of stages; chronic disease is kidney damage or GFR <60 mL/minute/1.73 m^2 for ≥3 months:

Stage 2: GFR 60-89 mL/minute/1.73 m^2 (kidney damage with mild decrease GFR)

Stage 3: GFR 30-59 mL/minute/1.73 m^2 (moderate decrease GFR)

Stage 4: GFR 15-29 mL/minute/1.73 m^2 (severe decrease GFR)

Stage 5: GFR <15 mL/minute/1.73 m^2 or dialysis (kidney failure)

Target range for iPTH:

Stage 2 CKD: 35-70 pg/mL (children)

Stage 3 CKD: 35-70 pg/mL (children and adults)

Stage 4 CKD: 70-110 pg/mL (children and adults)

Stage 5 CKD: 150-300 pg/mL (adults); 200-300 pg/mL (children)

Serum phosphorus:

Stage 3 and 4 CKD: ≥2.7 to <4.6 mg/dL (adults); within age appropriate limits (children)

Stage 5 CKD: 3.5-5.5 mg/dL (children >12 years and adults); 4-6 mg/dL (children 1-12 years)

Serum calcium-phosphorus product:

Stage 3-5 CKD: <55 mg^2/dL^2 (children >12 years and adults); <65 mg^2/dL^2 (children ≤12 years)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse effects at beginning of therapy and regularly with long-term use. Assess knowledge/teach patient appropriate use, appropriate nutritional counseling, possible side effects/interventions, and adverse symptoms to report.

Monitoring: Lab TestsAlkaline phosphatase, serum creatinine

Serum calcium and phosphorus:

CKD stage 2-4: Every month for the first 3 months, then every 3 months

CKD stage 5: Every 2 weeks for 1 month, then monthly

Serum or plasma intact PTH (iPTH):

CKD stage 3 and 4: Every 3 months for 6 months, then every 3 months

CKD stage 5: Monthly for 3 months, then every 3 months

Patient EducationTake exact dose as prescribed; do not increase dose. Maintain recommended diet and calcium supplementation. Avoid taking magnesium-containing antacids. You may experience nausea, vomiting, loss of appetite, or metallic taste (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report chest pain or palpitations; acute headache; skin rash; change in vision or eye irritation; CNS changes; unusual weakness or fatigue; persistent nausea, vomiting, cramps, or diarrhea; or muscle or bone pain. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, softgel: 0.25 mcg, 0.5 mcg

Rocaltrol®: 0.25 mcg [contains coconut oil]; 0.5 mcg [contains coconut oil]

Injection, solution: 1 mcg/mL (1 mL)

Calcijex®: 1 mcg/mL (1 mL) [contains aluminum]

Solution, oral: 1 mcg/mL (15 mL)

Rocaltrol®: 1 mcg/mL (15 mL) [contains palm seed oil]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Calcitriol)

0.25 mcg (30): $34.99

0.5 mcg (30): $55.99

Capsules (Rocaltrol)

0.25 mcg (30): $44.99

0.5 mcg (30): $63.99

Mechanism of ActionCalcitriol is a potent active metabolite of vitamin D. Vitamin D promotes absorption of calcium in the intestines and retention at the kidneys thereby increasing calcium levels in the serum; decreases excessive serum phosphatase levels, parathyroid hormone levels, and decreases bone resorption; increases renal tubule phosphate resorption

Pharmacodynamics/Kinetics

Onset of action: ~2-6 hours

Duration: 3-5 days

Absorption: Oral: Rapid

Protein binding: 99.9%

Metabolism: Primarily to 1,24,25-trihydroxycholecalciferol and 1,24,25-trihydroxy ergocalciferol

Half-life elimination: Children ~27 hours; Normal adults: 5-8 hours; Hemodialysis: 16-22 hours

Time to peak, serum: Oral: 3-6 hours; Hemodialysis: 8-12 hours

Excretion: Primarily feces; urine

Related Information

- Antacid Drug Interactions

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Metallic taste and xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation or irritability

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms1,25 Dihydroxycholecalciferol

References

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“K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Guideline 8B. Vitamin D Therapy in Patients on Dialysis (CKD Stage 5),” *Am J Kidney Dis*, 2003, 42(4 Suppl 3):92-98.

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Myrianthopoulos M, “Dietary Treatment of Hyperlipidemia in the Elderly,” *Clin Geriatr Med*, 1987, 3(2):343-59.[PubMed 3581018]

International Brand Names Altrol (MX); Bocatriol (DE); Bonky (KP); Calcijex (AU, GB, HU, ID, LU, MY, PL, TW); Calcit (ID); Calcit SG (TH); Calcitriol (CO, GR); Calsolid (EC); Citrihexal (AU); Decostriol (DE, TH); Ecatrol (ID); Ecatrol F (ID); Gyneamsa (MX); Hitrol (ID); Kalcytriol (PL); Kolkatriol (ID); Kosteo (AU); Lemytriol (MX); Macolol (TW); Meditrol (TH); Nafartol (MX); Neobon (KP); Osteo D (TH); Osteocap (MY); Osteofem (ID); Osteomeg (PH); Osteotriol (DE); Poscal (KP); Raquitriol (AR); Renatriol (DE); Rocaltriol (DK); Rocaltrol (AE, AT, AU, BB, BE, BG, BH, BM, BR, BS, BZ, CH, CL, CN, CO, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GH, GR, GY, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JM, JO, JP, KE, KW, LB, LU, LY, MX, NL, NO, OM, PE, PL, PT, QA, RU, SA, SE, SR, SY, TH, TR, TT, TW, TZ, UG, UY, VE, YE, ZM); Roical (MY, SG); Rolsical (IN); Sical (AU); Silkis (ES, FR, GB, HK, IE, MX, NO, PL, SG, TW); Sitriol (AU); Tariol (KP); Tirocal (MX); Triocalcit (PE)

Calcium Acetate

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Medication Safety Issues

Sound-alike/look-alike issues:

PhosLo® may be confused with Phos-Flur®, ProSom™

Pronunciation(KAL see um AS e tate)
U.S. Brand NamesPhosLo®
Canadian Brand NamesPhosLo®
Pharmacologic CategoryAntidote; Calcium Salt; Phosphate Binder
Use: Labeled IndicationsControl of hyperphosphatemia in end-stage renal failure; does not promote aluminum absorption
Dosing: Adults

Dietary Reference Intake:

Adults, Male/Female:

19-50 years: 1000 mg/day

≥51 years: 1200 mg/day

Female: Pregnancy/Lactating: Same as for Adults, Male/Female

Control of hyperphosphatemia (ESRD, on dialysis): Oral: Initial: 1334 mg with each meal, can be increased gradually to bring the serum phosphate value <6 mg/dL as long as hypercalcemia does not develop (usual dose: 2001-2868 mg calcium acetate with each meal); do not give additional calcium supplements

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Dietary Reference Intake:

0-6 months: 210 mg/day

7-12 months: 270 mg/day

1-3 years: 500 mg/day

4-8 years: 800 mg/day

9-18 years: 1300 mg/day

Dosing: Renal ImpairmentRefer to adult dosing.
Administration: OralAdminister with meals.
Dietary ConsiderationsOral dosage forms must be administered with meals to be effective.
Compatibility

Compatibility when admixed: Incompatible: Carbonates, phosphates, sulfates, tartrates.

ContraindicationsHypersensitivity to any component of the formulation; hypercalcemia, renal calculi
Warnings/Precautions

Concerns related to adverse effects:

- Gastrointestinal effects: Constipation, bloating, and gas are common with calcium supplements (especially carbonate salt).

Disease-related concerns:

- Arrhythmias: Use with caution in patients who may be at risk of cardiac arrhythmias.

- Hypoparathyroid disease: Hypercalcemia and hypercalciuria are most likely to occur in hypoparathyroid patients receiving high doses of vitamin D.

Concurrent drug therapy issues:

- Digitalis: Use with caution in digitalized patients; hypercalcemia may precipitate cardiac arrhythmias.

- Minerals/other oral drugs: Calcium administration interferes with absorption of some minerals and drugs; use with caution.

Geriatric ConsiderationsConstipation and gas can be significant in the elderly, but are usually mild.

Dietary Reference Intake: Adults, ≥51 years: 1200 mg/day

Pregnancy Risk FactorC

Adverse Reactions

Mild hypercalcemia (calcium: >10.5 mg/dL to ≤12 mg/dL) may be asymptomatic or manifest itself as constipation, anorexia, nausea, and vomiting

More severe hypercalcemia (calcium: >12 mg/dL) is associated with confusion, delirium, stupor, and coma

Postmarketing and/or case reports: Pruritus, allergic reaction

Drug Interactions

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CefTRIAXone: Calcium Salts (Intravenous) may enhance the adverse/toxic effect of CefTRIAXone. Ceftriaxone binds to calcium forming an insoluble precipitate. *Risk X: Avoid combination*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Estramustine: Calcium Salts may decrease the absorption of Estramustine. *Risk D: Consider therapy modification*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Moxifloxacin. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Monitoring ParametersSerum calcium, serum phosphate; for control of hypophosphatemia, serum calcium times phosphate should not exceed 66

Reference Range

Serum calcium: 8.4-10.2 mg/dL

Due to a poor correlation between the serum ionized calcium (free) and total serum calcium, particularly in states of low albumin or acid/base imbalances, direct measurement of ionized calcium is recommended.

In low albumin states, the corrected **total** serum calcium may be estimated by the following equation (assuming a normal albumin of 4 g/dL).

Corrected total calcium = total serum calcium + 0.8 (4.0 - measured serum albumin)

or

Corrected calcium = measured calcium - measured albumin + 4.0

Monitoring: Lab TestsSerum calcium, serum phosphate; for control of hypophosphatemia, serum calcium times phosphate should not exceed 66

Patient EducationInform prescriber of any other medications or dietary supplements you are taking. Do not take any new medication during therapy without consulting prescriber. Follow exact instructions for dosing. Take with meals. Avoid alcohol, other antacids, caffeine, or other calcium supplements unless approved by prescriber. May cause constipation (increased exercise, fluids, fiber, or fruits may help) or dry mouth (frequent mouth care, chewing gum, or sucking lozenges may help). Report severe, unresolved GI disturbances and unusual emotional lability (mood swings). **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gelcap: 667 mg

PhosLo®: 667 mg [equivalent to elemental calcium 169 mg (8.45 mEq)]

Generic AvailableYes

ManufacturerBraintree Laboratories, Inc

Pricing: U.S. (www.drugstore.com)

Capsules (PhosLo)

667 mg (200): $198.00

Mechanism of ActionCombines with dietary phosphate to form insoluble calcium phosphate which is excreted in feces

Pharmacodynamics/Kinetics

Absorption: Requires vitamin D; minimal unless chronic, high doses are given; calcium is absorbed in soluble, ionized form; solubility of calcium is increased in an acid environment

Distribution: Crosses placenta; enters breast milk

Excretion: Primarily feces (as unabsorbed calcium); urine (20%)

Pharmacotherapy Pearls Calcium acetate binds to phosphorus in the GI tract better than other calcium salts due to its lower solubility and subsequent reduced absorption and increased formation of calcium phosphate.

12.7 mEq calcium/g; 250 mg/g elemental calcium (25% elemental calcium)

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause confusion and delirium (as a consequence of hypercalcemia)

Mental Health: Effects on Psychiatric Treatment None reported

Cardiovascular Considerations Hypercalcemia is evident on ECG by shortening of the QT interval and possibly lengthening of the PR interval. Hypocalcemia causes prolongation of the QT interval. This prolongation is due to lengthening of the ST segment; the T waves remain unchanged. However, in severe hypocalcemia, T waves may be inverted. Note that only hypocalcemia and hypothermia lengthen the ST segment without altering T-wave duration. Hypocalcemia may also present clinically with skeletal muscle spasm.

References

Kaiser W, Biesenbach G, Kramar R, et al, “Calcium Free Hemodialysis: An Effective Therapy in Hypercalcemic Crisis - Report of Four Cases,” *Intensive Care Med*, 1989, 15(7):471-4. [PubMed 2600293]

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

Texier D, Chevallier P, Perrotin D, et al, “Hypercalcemia Associated With Resorbable Haemostatic Compresses,” *Lancet*, 1982, 1(8273):688-9.

International Brand Names Acid Mantle (MX); Caphos (TW); Hypophos (IN); Nephracet 600 (DE); Phos-Ex (DE); Phosex (GB); Phosphosorb (DE); Phostat (IN); Proca (TW); Procal (TW); Renacet (DE); Royen (UY)

Calcium Carbonate and Magnesium Hydroxide

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Mylanta® may be confused with Mynatal®

Pronunciation(KAL see um KAR bun ate & mag NEE zhum hye DROKS ide)

U.S. Brand NamesMi-Acid™ Double Strength [OTC]; Mylanta® Gelcaps® [OTC]; Mylanta® Supreme [OTC]; Mylanta® Ultra [OTC]; Rolaids® Extra Strength [OTC]; Rolaids® [OTC]

Pharmacologic CategoryAntacid

Use: Labeled IndicationsHyperacidity

Dosing: AdultsHyperacidity: Oral: 2-4 tablets between meals, at bedtime, or as directed by healthcare provider

Dosing: ElderlyRefer to adult dosing.

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Antacids may decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Estramustine: Calcium Salts may decrease the absorption of Estramustine. *Risk D: Consider therapy modification*

Fexofenadine: Antacids may decrease the serum concentration of Fexofenadine. Management: No specific recommendations concerning the time required between their administration are provided. Separate administration of each agent by as much time as possible to decrease the risk of an interaction. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Moxifloxacin. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gelcap (Mylanta® Gelcaps®): Calcium carbonate 550 mg and magnesium hydroxide 125 mg

Liquid (Mylanta® Supreme): Calcium carbonate 400 mg and magnesium hydroxide 135 mg per 5 mL (360 mL, 720 mL) [cherry flavor]

Tablet, chewable:

Mi-Acid™ Double Strength: Calcium carbonate 700 mg and magnesium hydroxide 300 mg

Mylanta® Ultra: Calcium carbonate 700 mg and magnesium hydroxide 300 mg [cherry créme and cool mint flavors]

Rolaids®: Calcium carbonate 550 mg and magnesium hydroxide 110 mg [sodium free; contains elemental calcium 220 mg and elemental magnesium 45 mg; original (peppermint), cherry, and spearmint flavors]

Rolaids® Extra Strength: Calcium carbonate 675 mg and magnesium hydroxide 135 mg [sodium free; contains elemental calcium 271 mg and elemental magnesium 56 mg, fruit flavor contains tartrazine; cool strawberry, fresh mint, fruit, and tropical fruit punch flavors]

Generic AvailableYes: Chewable tablet

Pricing: U.S. (www.drugstore.com)

Chewable (Mylanta Ultra)

700-300 mg (35): $8.99

700-300 mg (70): $8.99

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Calcium Carbonate
- Magnesium Hydroxide

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentAntacids may decrease the excretion of amphetamines; monitor. Antacids may decrease the absorption of antipsychotics; monitor.

Index TermsMagnesium Hydroxide and Calcium Carbonate

Calcium Carbonate and Simethicone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(KAL see um KAR bun ate & sye METH i kone)

U.S. Brand NamesGas Ban™ [OTC]; Titralac® Plus [OTC]

Pharmacologic CategoryAntacid; Antiflatulent

Use: Labeled IndicationsRelief of acid indigestion, heartburn

Dosing: AdultsHyperacidity, gas: Oral (OTC labeling): Two tablets every 2-3 hours as needed (maximum: 19 tablets/24 hours)

Dosing: ElderlyRefer to adult dosing.

Administration: OralTablets may be chewed, swallowed whole, or allowed to melt in the mouth.

Pregnancy Risk FactorC

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Antacids may decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Estramustine: Calcium Salts may decrease the absorption of Estramustine. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Moxifloxacin. *Risk D: Consider therapy modification*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, chewable:

Gas Ban™: Calcium carbonate 300 mg and simethicone 40 mg

Titralac® Plus: Calcium carbonate 420 mg and simethicone 21 mg [equivalent to elemental calcium 168 mg; sugar free; spearmint flavor]

Generic AvailableNo
Pharmacodynamics/KineticsSee individual agents.
Related Information

- Calcium Carbonate
- Simethicone

Pharmacotherapy Pearls40% of calcium carbonate is elemental calcium
Dental Health: Effects on Dental TreatmentDo not give tetracyclines concomitantly.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsSimethicone and Calcium Carbonate

Calcium Carbonate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Florical® may be confused with Fiorinal®

Mylanta® may be confused with Mynatal®

Nephro-Calci® may be confused with Nephrocaps®

Os-Cal® may be confused with Asacol®

International issues:

Remegel® [Great Britain, Ireland, Italy] may be confused with Renagel® which is a brand name for sevelamer in the U.S.

Pronunciation(KAL see um KAR bun ate)

U.S. Brand NamesAlcalak [OTC]; Alka-Mints® [OTC]; Cal-Gest [OTC]; Cal-Mint [OTC]; Calcarb 600 [OTC]; Calci-Chew® [OTC]; Calci-Mix® [OTC]; Caltrate® 600 [OTC]; Children's Pepto [OTC]; Chooz® [OTC]; Florical® [OTC]; Maalox® Regular Chewable [OTC]; Mylanta® Children's [OTC]; Nephro-Calci® [OTC]; Nutralox® [OTC]; Os-Cal® 500 [OTC] [DSC]; Oysco 500 [OTC]; Oyst-Cal 500 [OTC]; Rolaids® Softchews [OTC]; Titralac™ [OTC]; Tums® E-X [OTC]; Tums® Extra Strength Sugar Free [OTC]; Tums® Smoothies™ [OTC]; Tums® Ultra [OTC]; Tums® [OTC]

Canadian Brand NamesApo-Cal®; Calcite-500; Caltrate®; Caltrate® Select; Os-Cal®

Pharmacologic CategoryAntacid; Antidote; Calcium Salt; Electrolyte Supplement, Oral

Use: Labeled IndicationsAs an antacid; treatment and prevention of calcium deficiency or hyperphosphatemia (eg, osteoporosis, osteomalacia, mild/moderate renal insufficiency, hypoparathyroidism, postmenopausal osteoporosis, rickets); has been used to bind phosphate

Dosing: AdultsDosage is in terms of elemental calcium:

Dietary Reference Intake: Oral:

Adults, Male/Female:

19-50 years: 1000 mg/day

≥51 years: 1200 mg/day

Female: Pregnancy/Lactating: Same as for Adults, Male/Female

Hypocalcemia (dose depends on clinical condition and serum calcium level): Oral: Dose expressed in mg of **elemental calcium**: 1-2 g or more/day in 3-4 divided doses

Dietary supplementation: Oral: 500 mg to 2 g divided 2-4 times/day

Antacid: Oral: Dosage based on acid-neutralizing capacity of specific product; generally, 1-2 tablets or 5-10 mL every 2 hours; maximum: 7000 mg calcium carbonate per 24 hours; specific product labeling should be consulted

Osteoporosis: Oral: Adults >51 years: 1200 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDosage is in terms of elemental calcium:

Dietary Reference Intake: Oral:

0-6 months: 210 mg/day

7-12 months: 270 mg/day

1-3 years: 500 mg/day

4-8 years: 800 mg/day

9-19 years: 1300 mg/day

Hypocalcemia (dose depends on clinical condition and serum calcium level): Oral: Dose expressed in mg of **elemental calcium**

Neonates: 50-150 mg/kg/day in 4-6 divided doses; not to exceed 1 g/day

Children: 45-65 mg/kg/day in 4 divided doses

Antacid: Oral:

Children 2-5 years (24-47 lb): Elemental calcium 161 mg as needed; maximum 483 mg per 24 hours

Children 6-11 years (48-95 lb): Elemental calcium 322 mg as needed; maximum: 966 mg per 24 hours

Dosing: Renal ImpairmentCl_{cr} <25 mL/minute: Dosage adjustments may be necessary depending on the serum calcium levels.

Calculations

- Calcium Correction

Dietary ConsiderationsAs a dietary supplement, should be given with meals to increase absorption. May decrease iron absorption, so should be administered 1-2 hours before or after iron supplementation. Limit intake of bran, foods high in oxalates, or whole grain cereals which may decrease calcium absorption.

Maalox® Quick Dissolve 600 mg tablet contains phenylalanine 0.5 mg/tablet.

Tums® Extra Strength Sugar Free 750 mg tablet contains phenylalanine <1 mg/tablet.

Titralac™ 420 mg tablet and Titralac™ Extra Strength 750 mg tablet each contain sodium 1.1 mg/tablet.

Compatibility

Compatibility when admixed: Incompatible: Carbonates, phosphates, sulfates, tartrates.

ContraindicationsHypercalcemia, renal calculi, hypophosphatemia; patients with suspected digoxin toxicity

Warnings/Precautions

Concerns related to adverse effects:

- Gastrointestinal effects: Constipation, bloating, and gas are common with calcium supplements (especially carbonate salt).

Disease-related concerns:

- Achlorhydria: Calcium absorption is impaired in achlorhydria; administration is followed by increased gastric acid secretion within 2 hours of administration especially with high doses. Common in the elderly, use an alternate salt (eg, citrate) and administer with food.

- Hypoparathyroid disease: Hypercalcemia and hypercalciuria are most likely to occur in hypoparathyroid patients receiving high doses of vitamin D.

- Kidney stones (calcium-containing): Use caution when administering calcium supplements to patients with a history of kidney stones.

Concurrent drug therapy issues:

- Minerals/other oral drugs: Calcium administration interferes with absorption of some minerals and drugs; use with caution.

- Vitamin D: It is recommended to concomitantly administer vitamin D for optimal calcium absorption.

Other warnings/precautions:

- Absorption: Taking calcium (≤500 mg) with food improves absorption.

Pregnancy ConsiderationsAvailable evidence suggests safe use during pregnancy and breast-feeding.

Adverse ReactionsWell tolerated

1% to 10%:

Central nervous system: Headache

Endocrine & metabolic: Hypophosphatemia, hypercalcemia

Gastrointestinal: Constipation, laxative effect, acid rebound, nausea, vomiting, anorexia, abdominal pain, xerostomia, flatulence

Miscellaneous: Milk-alkali syndrome with very high, chronic dosing and/or renal failure (headache, nausea, irritability, and weakness or alkalosis, hypercalcemia, renal impairment)

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Antacids may decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Estramustine: Calcium Salts may decrease the absorption of Estramustine. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Moxifloxacin. *Risk D: Consider therapy modification*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase risk of osteoporosis).

Food: Food may increase calcium absorption. Calcium may decrease iron absorption. Bran, foods high in oxalates, or whole grain cereals may decrease calcium absorption.

Test InteractionsIncreased calcium (S); decreased magnesium

Reference Range

Serum calcium: 8.4-10.2 mg/dL: Monitor plasma calcium levels if using calcium salts as electrolyte supplements for deficiency

Due to a poor correlation between the serum ionized calcium (free) and total serum calcium, particularly in states of low albumin or acid/base imbalances, direct measurement of ionized calcium is recommended

In low albumin states, the corrected **total** serum calcium may be estimated by:

Corrected total calcium = total serum calcium + 0.8 (4.0 - measured serum albumin)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effectiveness, and adverse/toxic effects. Assess knowledge/teach patient proper use, appropriate interventions to reduce side effects, and adverse symptoms to report.

Patient EducationFollow instructions for dosing. Take with a full glass of water or juice 1-2 hours before any iron supplements and 1-3 hours after meals or other medications. Avoid alcohol, other antacids, caffeine, or other calcium supplements, unless approved by prescriber. You may experience constipation (increased exercise, fluids, fiber, or fruit may help) or dry mouth (sucking lozenges or hard candy may help). Report severe, unresolved GI disturbances and unusual emotional liability (mood swings). **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

Calci-Mix®: 1250 mg [equivalent to elemental calcium 500 mg]

Florical®: 364 mg [equivalent to elemental calcium 145.6 mg; contains sodium fluoride 3.75 mg]

Gum, chewing: 250 mg (30s)

Chooz®: 500 mg [equivalent to elemental calcium 200 mg; mint flavor]

Powder: 4000 mg/teaspoonful (480 g) [equivalent to 1600 mg elemental calcium/teaspoonful]

Suspension, oral: 1250 mg/5 mL (5 mL, 500 mL) [equivalent to elemental calcium 500 mg/5 mL; mint flavor]

Tablet: 1250 mg [equivalent to elemental calcium 500 mg]; 1500 mg [equivalent to elemental calcium 600 mg]

Calcarb 600, Caltrate® 600, Nephro-Calci®: 1500 mg [equivalent to elemental calcium 600 mg]

Florical®: 364 mg [equivalent to elemental calcium 145.6 mg; contains sodium fluoride 8.3 mg]

Os-Cal® 500: 1250 mg [equivalent to elemental calcium 500 mg; contains tartrazine] [DSC]

Oysco 500, Oyst-Cal 500: 1250 mg [equivalent to elemental calcium 500 mg]

Tablet, chewable: 500 mg [equivalent to elemental calcium 200 mg]; 650 mg [equivalent to elemental calcium 260 mg]; 750 mg [equivalent to elemental calcium 300 mg]

Alcalak: 420 mg [equivalent to elemental calcium 168 mg; mint flavor]

Alka-Mints®: 850 mg [equivalent to elemental calcium 340 mg; spearmint flavor]

Cal-Gest: 500 mg [equivalent to elemental calcium 200 mg; assorted flavors]

Calci-Chew®: 1250 mg [equivalent to elemental calcium 500 mg; cherry, lemon, and orange flavors]

Cal-Mint: 650 mg [equivalent to elemental calcium 260 mg; mint flavor]

Children's Pepto: 400 mg [equivalent to elemental calcium 161 mg; bubble gum or watermelon flavors]

Maalox® Regular: 600 mg [equivalent to elemental calcium 222 mg; contains phenylalanine 0.5 mg/tablet; lemon flavor]

Mylanta® Children's: 400 mg [equivalent to elemental calcium 160 mg; bubble gum flavor]

Nutralox®: 420 mg [equivalent to elemental calcium 168 mg; sugar free; mint flavor]

Os-Cal® 500: 1250 mg [equivalent to elemental calcium 500 mg; Bavarian cream flavor] [DSC]

Titralac™: 420 mg [equivalent to elemental calcium 168 mg; sugar free; contains sodium 1.1 mg/tablet; spearmint flavor]

Tums®: 500 mg [equivalent to elemental calcium 200 mg; contains tartrazine; assorted fruit and peppermint flavors]

Tums® E-X: 750 mg [equivalent to elemental calcium 300 mg; contains tartrazine; assorted fruit, cool relief mint, fresh blend, tropical assorted fruit, wintergreen, and assorted berry flavors]

Tums® Extra Strength Sugar Free: 750 mg [equivalent to elemental calcium 300 mg; sugar free; contains phenylalanine <1 mg/tablet; orange cream flavor]

Tums® Smoothies™: 750 mg [equivalent to elemental calcium 300 mg; contains tartrazine; assorted fruit, assorted tropical fruit, peppermint flavors]

Tums® Ultra®: 1000 mg [equivalent to elemental calcium 400 mg; contains tartrazine; assorted berry, assorted fruit, assorted tropical fruit, peppermint, and spearmint flavors]

Tablet, softchew:

Rolaids®: 1177 mg [equivalent to elemental calcium 471 mg; contains coconut oil and soy lecithin; vanilla creme and wild cherry flavors]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Chewable (Childrens Mylanta)

400 mg (24): $8.99

Suspension (Calcium Carbonate)

1250 mg/5 mL (500): $11.00

Tablets (Calcium Carbonate)

648 mg (100): $0.75

Tablets (Caltrate 600)

1500 mg (60): $14.99

Tablets (Oyst-Cal)

500 mg (120): $8.99

Mechanism of ActionAs dietary supplement, used to prevent or treat negative calcium balance; in osteoporosis, it helps to prevent or decrease the rate of bone loss. The calcium in calcium salts moderates nerve and muscle performance and allows normal cardiac function. Also used to treat hyperphosphatemia in patients with advanced renal insufficiency by combining with dietary phosphate to form insoluble calcium phosphate, which is excreted in feces. Calcium salts as antacids neutralize gastric acidity resulting in increased gastric and duodenal bulb pH; they additionally inhibit proteolytic activity of peptic if the pH is increased >4 and increase lower esophageal sphincter tone.

Pharmacodynamics/Kinetics

Absorption: Requires vitamin D; minimal unless chronic, high doses are given; calcium is absorbed in soluble, ionized form; solubility of calcium is increased in an acid environment

Distribution: Crosses placenta; enters breast milk

Excretion: Primarily feces (as unabsorbed calcium); urine (20%)

Pharmacotherapy Pearls20 mEq calcium/g; 400 mg elemental calcium/g calcium carbonate (40% elemental calcium)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely produce irritability

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsHypercalcemia is evident on ECG by shortening of the QT interval and possibly lengthening of the PR interval. Hypocalcemia causes prolongation of the QT interval. This prolongation is due to lengthening of the ST segment; the T waves remain unchanged. However, in severe hypocalcemia, T waves may be inverted. Note that only hypocalcemia and hypothermia lengthen the ST segment without altering T-wave duration. Hypocalcemia may also present clinically with skeletal muscle spasm.

Calcium salts may enhance the arrhythmogenic effects of digoxin. Part of the inotropic action of digoxin appears to be associated with increased intracellular calcium availability. Chronotropic effects are also calcium mediated. The administration of exogenous calcium (especially by parenteral routes) can lead to cardiac arrhythmias.

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International Brand NamesAdditiva Calcium (PL); Andrews TUMS Antacid (AU); Apo-Cal (HK, MY); Bica (AR); Biolectra (AT); Bo-Ne-Ca (TH); Cacit (GB, IE); Cal-Sup (AU); Calcanate (TH); Calcefor (PE); Calci Aid (PH); Calcichew (FI, GB, IE, LU); Calcidrink (GB); Calcifar (PL); Calcigamma (DE); Calcigran Sine (EE); Calcilos (DE); Calcimax (PY); Calcioral (PT); Calcit (BE, FR, IT, NL); Calcium (BG, PL); Calcium 20 Madariaga (ES); Calcium

Carbonate (FR); Calcium Dago (DE); Calcium effervescens (PL); Calcium Genericon (AT); Calcium Klopfer (AT); Calcium Pharmavit (HN); Calcium-500 (GB); Calcium-Carbonat Salmon Pharma (CH); Calcium-Phosphatbinder Bichsel (CH); Calcium-Sandoz Forte (BG); Calciumcarbonat Fresenius (CH); Calciumcarbonat-Dial (AT); Calcuren (FI); Caldoral (CO); Calmate 500 (PH); Calnat (ID); Calperos (CH, PL); Calsan (CH, MX, PE, PH); Calsuba (ZA); Caltab (TH); Caltess (PL); Caltrate (AE, AU, BB, BH, BM, BS, BZ, CO, CY, EG, GY, IL, IQ, IR, JM, JO, KW, LB, LY, MX, MY, NL, OM, PL, PR, QA, SA, SR, SY, TT, YE); Caltrate 600 (CO, EC, PE, VE); Caltrón (MX); Cantacid (KP); Caosina (ES); Carbocal (ES); CC-Nefro 500 (DE); Chooz Antacid Gum 500 (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Cimascal (ES); Citrical (GB); Densical (ES); Dreisacarb (AT); Fixateur phospho-calcique Bichsel (CH); Fixical (FR); Fortical (ES); FructiCal (PL); Iroviton Calcium (AT); Kalcidon (SE); Kalcij-karbonat (HR); Kalcijev karbonat (HR); Kalcitena (SE); Kalzonorm (AT); Mastical (ES); Maxi-calc (CH); Maxi-Kalz (CZ); Mubonet (MX); Natecal (ES); Noacid (UY); Orocal (FR); Osteocal 500 (FR); Osteomin (MX); Pluscal (AR); Plusssz balance calcium (PL); Sandocal (IN); Tetesept Calcium (AT); Titralac (NO); Tums (IL, MX); Tums EX Sugar Free (IL); Tums Ultra Assorted Berries (IL); Tums Ultra Spearmint (IL); Tzarevet X (IL); Vicalvit (PL); Vitacalcin (PL); Weifa-Kalsium (NO)

Calcium Chloride

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Dosing issues:

Calcium chloride may be confused with calcium gluconate

Confusion with the different intravenous salt forms of calcium has occurred. There is a threefold difference in the primary cation concentration between calcium chloride (in which 1g = 13.6 mEq [270 mg] of elemental Ca++) and calcium gluconate (in which 1g = 4.65 mEq [90 mg] of elemental Ca++).

Prescribers should specify which salt form is desired. Dosages should be expressed either as mEq, mg, or grams of the salt form.

Pronunciation(KAL see um KLOR ide)

Pharmacologic CategoryCalcium Salt; Electrolyte Supplement, Parenteral

Use: Labeled IndicationsTreatment of acute symptomatic hypocalcemia; cardiac disturbances of hyperkalemia or hypocalcemia; emergent treatment of hypocalcemic tetany; treatment of severe hypermagnesemia

Use: Unlabeled/InvestigationalCalcium channel blocker overdose; severe hyperkalemia (K+ >7 mEq/L with toxic ECG changes) [ACLS guidelines]; malignant arrhythmias associated with hypermagnesemia [ACLS guidelines]

Dosing: Adults**Note:** One gram of calcium chloride is equal to 270 mg of elemental calcium.

Dosages are expressed in terms of the calcium chloride salt based on a solution concentration of 100 mg/mL (10%) containing 1.4 mEq (27.3 mg)/mL elemental calcium.

Acute, symptomatic ionized hypocalcemia, hyperkalemia, or magnesium toxicity:Note: Routine use in cardiac arrest is not recommended due to the lack of improved survival [ACLS 2005 Guidelines]: I.V.: 500-1000 mg, may repeat as necessary

Calcium channel blocker overdose (unlabeled use):

I.V.: 1000 mg every 10-20 minutes (total of 4 doses) **or** 1000 mg every 2-3 minutes until clinical effect is achieved; if favorable response obtained, consider I.V. infusion

I.V. infusion: 20-50 mg/kg/hour

Hypocalcemia secondary to citrated blood transfusion: I.V.: 200-500 mg per 500 mL of citrated blood (infused into another vein)

Note: Routine administration of calcium, in the absence of signs/symptoms of hypocalcemia, is generally not recommended. A number of recommendations have been published seeking to address potential hypocalcemia during massive transfusion of citrated blood; however, many practitioners recommend replacement only as guided by clinical evidence of hypocalcemia and/or serial monitoring of ionized calcium. In adults, clinically-significant hypocalcemia usually dose not occur until >5 units of packed red blood cells have been administered.

Hypocalcemic tetany: I.V.: 1000 mg over 10-30 minutes; may repeat after 6 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** One gram of calcium chloride is equal to 270 mg of elemental calcium.

Dosages are expressed in terms of the calcium chloride salt based on a solution concentration of 100 mg/mL (10%) containing 1.4 mEq (27.3 mg)/mL elemental calcium.

Acute, symptomatic ionized hypocalcemia, hyperkalemia, or magnesium toxicity:Note: Routine use in cardiac arrest is not recommended due to the lack of improved survival [PALS 2005 Guidelines]: I.V.:

Neonates: 20 mg/kg; may repeat as necessary

Infants and Children: 20 mg/kg; may repeat as necessary [PALS 2005 Guidelines]

Calcium channel blocker overdose (unlabeled use): Neonates, Infants, and Children [PALS 2005 Guidelines]:

I.V., I.O.: 20 mg/kg (maximum: 1000 mg/dose) over 5-10 minutes; if favorable response obtained, consider I.V. infusion

I.V. infusion: 20-50 mg/kg/hour

Hypocalcemic tetany: I.V.:

Neonates: 40-60 mg/kg/dose repeated every 6-8 hours

Infants and Children: 10 mg/kg over 5-10 minutes; may repeat after 6-8 hours or follow with an infusion with a maximum dose of 200 mg/kg/day; alternatively, higher doses of 35-50 mg/kg/dose repeated every 6-8 hours have been used

Hypocalcemia secondary to citrated blood transfusion: I.V.: Neonates, Infants, and Children: Give 32 mg (0.45 mEq elemental calcium) for each 100 mL citrated blood infused

Note: Routine administration of calcium, in the absence of signs/symptoms of hypocalcemia, is generally not recommended. A number of recommendations have been published seeking to address potential hypocalcemia during massive transfusion of citrated blood; however, many practitioners recommend replacement only as guided by clinical evidence of hypocalcemia and/or serial monitoring of ionized calcium.

Dosing: Renal ImpairmentCl_{cr} <25 mL/minute: Dosage adjustments may be necessary depending on the serum calcium levels.

Calculations

- Calcium Correction

Administration: I.V.For I.V. administration only; avoid extravasation. Avoid rapid administration (do not exceed 100 mg/minute). May be given over 2-5 minutes if rapid increase in serum calcium concentration is required. For I.V. infusion, dilute to a maximum concentration of 20 mg/mL and infuse over 1 hour or no greater than 45-90 mg/kg/hour (0.6-1.2 mEq/kg/hour); administration via a central or deep vein is preferred; do not use scalp, small hand or foot veins for I.V. administration since severe necrosis and sloughing may occur. Monitor ECG if calcium is infused faster than 2.5 mEq/minute; **stop the infusion if the patient complains of pain or discomfort.** Warm to body temperature. **Do not infuse calcium chloride in the same I.V. line as phosphate-containing solutions**.

StorageDo not refrigerate solutions; IVPB solutions/I.V. infusion solutions are stable for 24 hours at room temperature.

Although calcium chloride is not routinely used in the preparation of parenteral nutrition, it is important to note that phosphate salts may precipitate when mixed with calcium salts. Solubility is improved in amino acid parenteral nutrition solutions. Check with a pharmacist to determine compatibility.

CompatibilityStable in most common intravenous infusion solutions; **variable stability (consult detailed reference)** in fat emulsion 10%.

Y-site administration: Compatible: Amiodarone, dobutamine, epinephrine, esmolol, gatifloxacin, inamrinone, milrinone, morphine, paclitaxel, sodium nitroprusside. **Incompatible:** Amphotericin B cholesteryl sulfate complex, ceftriaxone, propofol, sodium bicarbonate.

Compatibility in syringe: Compatible: Milrinone. **Incompatible:** Pantoprazole.

Compatibility when admixed: Compatible: Amikacin, ascorbic acid injection, chloramphenicol, dopamine, hydrocortisone sodium succinate, isoproterenol, lidocaine, norepinephrine, penicillin G potassium, penicillin G sodium, pentobarbital, phenobarbital, sodium bicarbonate, verapamil, vitamin B complex with C. **Incompatible:** Amphotericin B, chlorpheniramine, pantoprazole. **Variable (consult detailed reference):** Dobutamine, potassium phosphate.

ContraindicationsHypercalcemia, known or suspected digoxin toxicity; not recommended as routine treatment in cardiac arrest (includes asystole, ventricular fibrillation, pulseless ventricular tachycardia, or pulseless electrical activity)

Warnings/Precautions

Disease-related concerns:

- Acidosis: Use with caution in patients with respiratory acidosis, renal impairment, or respiratory failure; acidifying effect of calcium chloride may potentiate acidosis.

- Hyperphosphatemia: Use with caution in patients with severe hyperphosphatemia as elevated levels of phosphorus and calcium may result in soft tissue and pulmonary arterial calcium-phosphate precipitation.

- Hypokalemia: Use with caution in patients with severe hypokalemia as acute rises in serum calcium levels may result in life-threatening cardiac arrhythmias.

- Renal impairment: Use with caution in patients with chronic renal failure to avoid hypercalcemia; frequent monitoring of serum calcium and phosphorus is necessary.

Concurrent drug therapy issues:

- Digoxin: Use with caution in digitalized patients; hypercalcemia may precipitate cardiac arrhythmias.

Dosage form specific issues:

- Aluminum: Solutions may contain aluminum; toxic levels may occur following prolonged administration in premature neonates or patients with renal impairment.

Other warnings/precautions:

- Duration of use: Avoid metabolic acidosis (ie, administer only 2-3 days then change to another calcium salt).

- I.V. administration: For I.V. use only; do not inject SubQ or I.M. Avoid rapid I.V. administration (do not exceed 100 mg/minute). May be given over 2-5 minutes if rapid increase in serum calcium concentrations are required. Avoid extravasation.

Geriatric ConsiderationsWhen using in the elderly, check albumin status and make appropriate decisions concerning reference serum concentrations. Elderly, especially the ill, often have low albumin due to malnutrition.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined. I.V.:

Cardiovascular: Arrhythmia, bradycardia, cardiac arrest, hypotension, syncope, vasodilation

Endocrine & metabolic: Hypercalcemia

Gastrointestinal: Irritation, chalky taste

Hepatic: Elevated serum amylase

Neuromuscular & skeletal: Tingling sensation

Renal: Renal calculi

Miscellaneous: Hot flashes

Postmarketing and/or case reports: Calcinosis cutis

Drug Interactions

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CefTRIAXone: Calcium Salts (Intravenous) may enhance the adverse/toxic effect of CefTRIAXone. Ceftriaxone binds to calcium forming an insoluble precipitate. *Risk X: Avoid combination*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Test Interactions Increased calcium

Monitoring Parameters Monitor infusion site, ECG when appropriate; serum calcium and ionized calcium (normal: 8.5-10.2 mg/dL [total]; 4.5-5.0 mg/dL [ionized]), albumin, serum phosphate

Reference Range

Serum calcium: 8.4-10.2 mg/dL

Due to a poor correlation between the serum ionized calcium (free) and total serum calcium, particularly in states of low albumin or acid/base imbalances, direct measurement of ionized calcium is recommended.

In low albumin states, the corrected **total** serum calcium may be estimated by the following equation (assuming a normal albumin of 4 g/dL).

Corrected total calcium = total serum calcium + 0.8 (4.0 - measured serum albumin)

or

Corrected calcium = measured calcium - measured albumin + 4.0

Serum/plasma chloride: 95-108 mEq/L

Nursing: Physical Assessment/Monitoring Assess other medications or herbal/natural products the patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effect, and adverse/toxic effects. Infusion site should be monitored closely to prevent extravasation (see Administration).

Monitoring: Lab Tests Serum calcium and ionized calcium (normal: 8.5-10.2 mg/dL [total]; 4.5-5.0 mg/dL [ionized]), albumin, serum phosphate

Patient Education This medication can only be given intravenously. Do not make rapid postural changes while calcium is infusing. Report any feelings of excitation, chest pain, irregular or pounding heartbeat, vomiting, acute headache, or dizziness.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 10% (10 mL) [present as calcium chloride 100 mg (1.36 mEq)/mL; provides elemental calcium 27.2 mg/mL (1.36 mEq)/mL]

Injection, solution: 10% (10 mL) [present as calcium chloride 100 mg (1.36 mEq)/mL; provides elemental calcium 27.2 mg (1.36 mEq)/mL]

Generic Available Yes

Mechanism of Action Moderates nerve and muscle performance via action potential excitation threshold regulation

Pharmacodynamics/Kinetics

Distribution: Crosses placenta; enters breast milk

Excretion: Primarily feces (80% as insoluble calcium); urine (20%)

Pharmacotherapy Pearls 14 mEq calcium/g (10 mL); 270 mg elemental calcium/g calcium chloride (27% elemental calcium)

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause drowsiness; rare reports of mania

Mental Health: Effects on Psychiatric Treatment None reported

Cardiovascular Considerations Hypercalcemia is evident on ECG by shortening of the QT interval and possibly lengthening of the PR interval. Hypocalcemia causes prolongation of the QT interval. This prolongation is due to lengthening of the ST segment; the T waves remain unchanged. However, in severe hypocalcemia, T waves may be inverted. Note that only hypocalcemia and hypothermia lengthen the ST segment without altering T-wave duration. Hypocalcemia may also present clinically with skeletal muscle spasm.

Calcium salts may enhance the arrhythmogenic effects of digoxin. Part of the inotropic action of digoxin appears to be associated with increased intracellular calcium availability. Chronotropic effects are also calcium mediated. The administration of exogenous calcium (especially by parenteral routes) can lead to cardiac arrhythmias.

Cardiac Arrest: According to the 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, routine use in cardiac arrest is not recommended due to lack of improved survival. However, in patients with acute, symptomatic hypocalcemia (total serum calcium concentration <8.5 mg/dL [or ionized calcium <4.2 mg/dL; <1 mmol/L], hyperkalemia with associated ECG changes, or magnesium toxicity, the use of intravenous calcium chloride may be helpful and is recommended.

Anesthesia and Critical Care Concerns/Other Considerations

Hypocalcemia in the Critically-Ill Patient: Treatment of patients with asymptomatic hypocalcemia, defined as a total serum calcium concentration <8.5 mg/dL (or ionized calcium <4.2 mg/dL; <1 mmol/L) with intravenous calcium salts is generally not recommended. Symptoms usually occur when ionized calcium levels fall to <2.5 mg/dL. Symptoms include paresthesias of the extremities and face, muscle cramps, carpopedal spasm, stridor, tetany, and seizures. However, if the patient is experiencing hemodynamic compromise or life-threatening arrhythmias with any degree of hypocalcemia, treatment with intravenous calcium is warranted. Use of calcium chloride is preferred due to the higher bioavailability as compared with calcium gluconate. If the patient has concomitant hypomagnesemia, replacement with calcium may be ineffective. It is recommended that serum magnesium levels be corrected prior to administration of calcium.

Calcium Channel Blocker (CCB) Overdose: Effects of CCB overdose vary depending on the type ingested. Dihydropyridine CCBs (eg, nifedipine) exhibit peripheral vasodilation primarily although if large amounts are ingested, effects on the AV node may be seen. Nondihydropyridine CCBs (eg, verapamil) exhibit negative inotropic, chronotropic, and dromotropic actions although if large amounts are ingested, peripheral vasodilation effects may be present.

Calcium chloride may be an effective treatment for the CCB overdose. In addition to the use of calcium chloride, other successful treatments include high-dose insulin with supplemental dextrose and potassium (HDIDK therapy), beta$_1$/alpha$_1$-agonists (eg, dopamine), and glucagon may be used.

References

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International Brand Names Calcium chloratum (PL); Solural (MX)

Calcium Citrate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Citracal® may be confused with Citrucel®

Pronunciation(KAL see um SIT rate)
U.S. Brand NamesCal-C-Caps [OTC]; Cal-Cee [OTC]; Cal-Citrate-225; Cal-Citrate® 250 [OTC] [DSC]; Citracal® Kosher [OTC]
Canadian Brand NamesOsteocit®
Pharmacologic CategoryCalcium Salt
Use: Labeled IndicationsAntacid; treatment and prevention of calcium deficiency or hyperphosphatemia (eg, osteoporosis, osteomalacia, mild/moderate renal insufficiency, hypoparathyroidism, postmenopausal osteoporosis, rickets)
Dosing: AdultsOral: Dosage is in terms of elemental calcium

Dietary Reference Intake:

Adults, Male/Female:

19-50 years: 1000 mg/day

≥51 years: 1200 mg/day

Female: Pregnancy/Lactating: Same as for Adults, Male/Female

Dietary supplement: Oral: Usual dose: 500 mg to 2 g 2-4 times/day

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricOral: Dosage is in terms of elemental calcium

Dietary Reference Intake:

0-6 months: 210 mg/day

7-12 months: 270 mg/day

1-3 years: 500 mg/day

4-8 years: 800 mg/day

9-18 years: 1300 mg/day

ContraindicationsHypersensitivity to any component of the formulation; hypercalcemia, renal calculi, ventricular fibrillation
Warnings/Precautions

Concerns related to adverse effects:

- Gastrointestinal effects: Constipation, bloating, and gas are common with calcium supplements (especially carbonate salt).

Disease-related concerns:

- Achlorhydria: Calcium absorption is impaired in achlorhydria; common in elderly. Citrate may be preferred because better absorbed.

- Hypoparathyroid disease: Hypercalcemia and hypercalciuria are most likely to occur in hypoparathyroid patients receiving high doses of vitamin D.

- Kidney stones (calcium-containing): Use caution when administering calcium supplements to patients with a history of kidney stones.

- Renal impairment: Use with caution in patients with renal failure to avoid hypercalcemia; frequent monitoring of serum calcium and phosphorus is necessary.

Concurrent drug therapy issues:

- Minerals/other oral drugs: Calcium administration interferes with absorption of some minerals and drugs; use with caution.

- Vitamin D: It is recommended to concomitantly administer vitamin D for optimal calcium absorption.

Other warnings/precautions:

- Absorption: Taking calcium (≤500 mg) with food improves absorption.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined:

Mild hypercalcemia (calcium: >10.5 mg/dL) may be asymptomatic or manifest itself as constipation, anorexia, nausea, and vomiting

More severe hypercalcemia (calcium: >12 mg/dL) is associated with confusion, delirium, stupor, and coma

Central nervous system: Headache

Endocrine & metabolic: Hypophosphatemia, hypercalcemia

Gastrointestinal: Nausea, anorexia, vomiting, abdominal pain, constipation

Miscellaneous: Thirst

Drug Interactions

Aluminum Hydroxide: Citric Acid Derivatives may increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Estramustine: Calcium Salts may decrease the absorption of Estramustine. *Risk D: Consider therapy modification*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Moxifloxacin. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase risk of osteoporosis).

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess therapeutic effect and adverse/toxic effects. Assess knowledge/teach patient proper use, appropriate interventions to reduce side effects, and adverse symptoms to report.

Patient EducationInform prescriber of any other medications or dietary supplements you are taking. Do not take any new medication during therapy without consulting prescriber. Follow exact instructions for dosing. Take with a full glass of water or juice, 1-3 hours after other medications, and 1-2 hours before any approved iron supplements. Avoid alcohol, other antacids, caffeine, or other calcium supplements unless approved by prescriber. May cause constipation (increased exercise, fluids, fiber, or fruits may help) or dry mouth (frequent mouth care, chewing gum, or sucking lozenges may help). Report severe, unresolved GI disturbances and unusual emotional lability (mood swings). **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

Cal-C-Caps: Elemental calcium 180 mg

Cal-Citrate-225: Elemental calcium 225 mg

Granules: Elemental calcium 760 mg/teaspoonful (480 g)

Tablet: Elemental calcium 200 mg, 250 mg

Cal-Citrate®: Elemental calcium 250 mg [DSC]

Cal-Cee: Elemental calcium 250 mg

Citracal® Kosher: Elemental calcium 200 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Citracal)

950 mg (200): $15.00

Mechanism of ActionModerates nerve and muscle performance via action potential excitation threshold regulation

Pharmacodynamics/KineticsAbsorption: Requires vitamin D

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause confusion and delirium (as a consequence of hypercalcemia)

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular Considerations Hypercalcemia is evident on ECG by shortening of the QT interval and possibly lengthening of the PR interval. Hypocalcemia causes prolongation of the QT interval. This prolongation is due to lengthening of the ST segment; the T waves remain unchanged. However, in severe hypocalcemia, T waves may be inverted. Note that only hypocalcemia and hypothermia lengthen the ST segment without altering T-wave duration. Hypocalcemia may also present clinically with skeletal muscle spasm.

References

"Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine," National Academy of Sciences, Washington, DC: National Academy Press, 1997. Available at: http://www.nap.edu.

International Brand Names Calbo (TW); Calcite (KP); Calcival (MX); Citrokalcium (HN); Jia-Cal (TW); Mei-Cal (TW)

Calcium Glubionate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Calcium glubionate may be confused with calcium gluconate

Pronunciation(KAL see um gloo BYE oh nate)

U.S. Brand NamesCalcionate [OTC]

Pharmacologic CategoryCalcium Salt

Use: Labeled IndicationsDietary supplement

Dosing: AdultsDosage is in terms of **elemental** calcium

Dietary Reference Intake:

Adults, Male/Female:

19-50 years: 1000 mg/day

≥51 years: 1200 mg/day

Female: Pregnancy/Lactating: Same as for Adults, Male/Female

Dietary supplement: Oral: 1 tablespoonful 3 times a day

Pregnant or lactating women: 1 tablespoonful 4 times a day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDosage is in terms of **elemental** calcium

Dietary Reference Intake:

0-6 months: 210 mg/day

7-12 months: 270 mg/day

1-3 years: 500 mg/day

4-8 years: 800 mg/day

9-18 years: 1300 mg/day

Dietary supplement: Oral:

Infants <12 months: 1 teaspoonful 5 times a day; may mix with juice or formula

Children <4 years: 2 teaspoonsful 3 times a day

Children ≥4 years: Refer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <25 mL/minute: Dosage adjustments may be necessary depending on the serum calcium levels.

Administration: OralTake with a full glass of water or juice, 1-3 hours after meals and other medications, and 1-2 hours before any approved iron supplements.

Dietary ConsiderationsShould be taken before meals to enhance absorption. May decrease iron absorption so should be administered 1-2 hours before or after iron supplementation. Limit intake of bran, foods high in oxalates, or whole grain cereals which may decrease calcium absorption.

ContraindicationsHypersensitivity to any component of the formulation; renal calculi

Warnings/Precautions

Concerns related to adverse effects:

- Gastrointestinal effects: Constipation, bloating, and gas are common with calcium supplements (especially carbonate salt).

Disease-related concerns:

- Achlorhydria: Calcium absorption is impaired in achlorhydria; common in elderly, use an alternate salt (eg, citrate) and administer with food.
- Hypoparathyroid disease: Hypercalcemia and hypercalciuria are most likely to occur in hypoparathyroid patients receiving high doses of

vitamin D.

- Kidney stones (calcium-containing): Use caution when administering calcium supplements to patients with a history of kidney stones.

Concurrent drug therapy issues:

- Minerals/other oral drugs: Calcium administration interferes with absorption of some minerals and drugs; use with caution.

- Vitamin D: It is recommended to concomitantly administer vitamin D for optimal calcium absorption.

Other warnings/precautions:

- Absorption: Taking calcium (≤500 mg) with food improves absorption.

Adverse Reactions

Frequency not defined; symptoms reported with hypercalcemia:

Gastrointestinal: Abdominal pain, anorexia, constipation, nausea, thirst, vomiting, xerostomia

Genitourinary: Polyuria

Drug Interactions

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Estramustine: Calcium Salts may decrease the absorption of Estramustine. *Risk D: Consider therapy modification*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Moxifloxacin. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase risk of osteoporosis).

Food: Food may increase calcium absorption. Calcium may decrease iron absorption. Bran, foods high in oxalates, or whole grain cereals may decrease calcium absorption.

Test Interactions

Decreased magnesium

Reference Range

Serum calcium: 8.4-10.2 mg/dL: Monitor plasma calcium levels if using calcium salts as electrolyte supplements for deficiency.

Due to a poor correlation between the serum ionized calcium (free) and total serum calcium, particularly in states of low albumin or acid/base imbalances, direct measurement of ionized calcium is recommended.

In low albumin states, the corrected **total** serum calcium may be estimated by:

Corrected total calcium = total serum calcium + 0.8 (4.0 - measured serum albumin)

Patient Education

Do not take any new medication during therapy without consulting prescriber. Follow exact instructions for dosing. Take with a full glass of water or juice, 1-3 hours after meals and other medications, and 1-2 hours before any approved iron supplements. Avoid alcohol, other antacids, caffeine, or other calcium supplements unless approved by prescriber. May cause constipation (increased exercise, fluids, fiber, or fruits may help) or dry mouth (frequent mouth care, chewing gum, or sucking lozenges may help). Report severe, unresolved GI disturbances and unusual emotional lability (mood swings). **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Syrup:

Calcionate: 1.8 g/5 mL (480 mL) [equivalent to elemental calcium 115 mg/5 mL; contains benzoic acid; caramel and orange flavor]

Generic Available

Yes

Mechanism of Action

As dietary supplement, used to prevent or treat negative calcium balance. The calcium in calcium salts moderates nerve and muscle performance and allows normal cardiac function.

Pharmacodynamics/Kinetics

Absorption: Requires vitamin D; calcium is absorbed in soluble, ionized form; solubility of calcium is increased in an acid environment

Distribution: Crosses placenta; enters breast milk

Excretion: Primarily feces (as unabsorbed calcium); urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause confusion and delirium (as a consequence of hypercalcemia)
Mental Health: Effects on Psychiatric TreatmentNone reported
Cardiovascular ConsiderationsHypercalcemia is evident on ECG by shortening of the QT interval and possibly lengthening of the PR interval. Hypocalcemia causes prolongation of the QT interval. This prolongation is due to lengthening of the ST segment; the T waves remain unchanged. However, in severe hypocalcemia, T waves may be inverted. Note that only hypocalcemia and hypothermia lengthen the ST segment without altering T-wave duration. Hypocalcemia may also present clinically with skeletal muscle spasm.
References

“Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine,” National Academy of Sciences, Washington, DC: National Academy Press, 1997. Available at: http://www.nap.edu.

International Brand NamesCalcium (BE, NO); Calcium Pliva (PL); Calcium Polfa (PL); Calcium Sandoz (AT, ES, FI, HR, NL); Calcium-Sandoz (CH, DK, FR, IN, SE, ZA); Sandocal (PT); Satural (PL)

Calcium Gluconate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Calcium gluconate may be confused with calcium glubionate

Pronunciation(KAL see um GLOO koe nate)

U.S. Brand NamesCal-G [OTC]; Cal-GLU™

Pharmacologic CategoryCalcium Salt; Electrolyte Supplement, Oral; Electrolyte Supplement, Parenteral

Use: Labeled IndicationsTreatment and prevention of hypocalcemia; treatment of tetany, cardiac disturbances of hyperkalemia, cardiac resuscitation when epinephrine fails to improve myocardial contractions, hypocalcemia; calcium supplementation; hydrofluoric acid (HF) burns

Use: Unlabeled/InvestigationalCalcium channel blocker overdose

Dosing: Adults

Adequate Intake (as elemental calcium):

Adults, Male/Female:

19-50 years: 1000 mg/day

≥51 years: 1200 mg/day

Female: Pregnancy/Lactating: Same as for Adults, Male/Female

Dosage note: Calcium chloride has 3 times more elemental calcium than calcium gluconate. Calcium chloride is 27% elemental calcium; calcium gluconate is 9% elemental calcium. One gram of calcium chloride is equal to 270 mg of elemental calcium; 1 gram of calcium gluconate is equal to 90 mg of elemental calcium. The following dosages are expressed in terms of the calcium gluconate salt based on a solution concentration of 100 mg/mL (10%) containing 0.465 mEq (9.3 mg)/mL elemental calcium:

Hypocalcemia:

I.V.: 2-15 g/24 hours as a continuous infusion or in divided doses

Oral: 500 mg to 2 g 2-4 times/day

Hypocalcemia secondary to citrated blood infusion: I.V.: 500 mg to 1 g per 500 mL of citrated blood (infused into another vein). Single doses up to 2 g have also been recommended.

Note: Routine administration of calcium, in the absence of signs/symptoms of hypocalcemia, is generally not recommended. A number of recommendations have been published seeking to address potential hypocalcemia during massive transfusion of citrated blood; however, many practitioners recommend replacement only as guided by clinical evidence of hypocalcemia and/or serial monitoring of ionized calcium.

Hypocalcemic tetany: I.V.: 1-3 g/dose may be administered until therapeutic response occurs

Magnesium intoxication or cardiac arrest in the presence of hyperkalemia or hypocalcemia: I.V.: 500-800 mg/dose (maximum: 3 g/dose)

Maintenance electrolyte requirements for TPN: I.V.: Daily requirements: 1.7-3.4 g/1000 kcal/24 hours

Calcium channel blocker overdose (unlabeled use): I.V. infusion: 10% solution: 0.6-1.2 mL/kg/hour or I.V. 0.2-0.5 ml/kg every 15-20 minutes for 4 doses (maximum: 2-3 g/dose). In life-threatening situations, 1 g has been given every 1-10 minutes until clinical effect is achieved (case reports of resistant hypotension reported use of 12-18 g total).

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Adequate Intake (as elemental calcium):

0-6 months: 210 mg/day

7-12 months: 270 mg/day

1-3 years: 500 mg/day

4-8 years: 800 mg/day

9-18 years: 1300 mg/day

Dosage note: Calcium chloride has 3 times more elemental calcium than calcium gluconate. Calcium chloride is 27% elemental calcium; calcium gluconate is (9% elemental calcium). One gram of calcium chloride is equal to 270 mg of elemental calcium; 1 gram of calcium gluconate is equal to 90 mg of elemental calcium. The following dosages are expressed in terms of the calcium gluconate salt based on a solution concentration of 100 mg/mL (10%) containing 0.465 mEq (9.3 mg)/mL elemental calcium:

Hypocalcemia:

I.V.:

Neonates: 200-800 mg/kg/day as a continuous infusion or in 4 divided doses (maximum: 1 g/dose)

Infants and Children: 200-500 mg/kg/day as a continuous infusion or in 4 divided doses (maximum: 2-3 g/dose)

Oral: Children: 200-500 mg/kg/day divided every 6 hours

Hypocalcemia secondary to citrated blood infusion: I.V.: Neonates, Infants, and Children: Give 98 mg (0.45 mEq **elemental** calcium) for each 100 mL citrated blood infused.

Note: Routine administration of calcium, in the absence of signs/symptoms of hypocalcemia, is generally not recommended. A number of recommendations have been published seeking to address potential hypocalcemia during massive transfusion of citrated blood; however, many practitioners recommend replacement only as guided by clinical evidence of hypocalcemia and/or serial monitoring of ionized calcium.

Hypocalcemic tetany: I.V.: Infants and Children: 100-200 mg/kg/dose over 5-10 minutes; may repeat every 6-8 hours **or** follow with an infusion of 500 mg/kg/day

Magnesium intoxication or cardiac arrest in the presence of hyperkalemia or hypocalcemia: I.V.: Infants and Children: 60-100 mg/kg/dose (maximum: 3 g/dose)

Dosing: Renal ImpairmentCl_{cr} <25 mL/minute: Dosage adjustments may be necessary depending on the serum calcium levels.

Calculations

- Calcium Correction

Administration: I.M.Not for I.M. or SubQ administration

Administration: I.V.For I.V. administration only; administer slowly (~1.5 mL calcium gluconate 10% per minute) through a small needle into a large vein in order to avoid too rapid increased in serum calcium and extravasation

Administration: OtherNot for SubQ administration.

Storage

Do not refrigerate solutions. IVPB solutions/I.V. infusion solutions are stable for 24 hours at room temperature.

Standard diluent: 1 g/100 mL D_5W or NS; 2 g/100 mL D_5W or NS.

Maximum concentration in parenteral nutrition solutions is variable depending upon concentration and solubility (consult detailed reference).

CompatibilityStable in D_5LR, D_5NS, D_5W, $D_{10}W$, $D_{20}W$, LR, NS; **incompatible** in fat emulsion 10%.

Y-site administration: Compatible: Aldesleukin, allopurinol, amifostine, aztreonam, cefazolin, cefepime, ciprofloxacin, cisatracurium, cladribine, dobutamine, docetaxel, doxorubicin liposome, enalaprilat, epinephrine, etoposide, famotidine, filgrastim, gatifloxacin, gemcitabine, granisetron, heparin with hydrocortisone sodium succinate, labetalol, linezolid, melphalan, midazolam, milrinone, piperacillin/tazobactam, potassium chloride, prochlorperazine edisylate, propofol, remifentanil, sargramostim, tacrolimus, teniposide, thiotepa, tolazoline, vinorelbine, vitamin B complex with C. **Incompatible:** Amphotericin B cholesteryl sulfate complex, fluconazole, indomethacin. **Variable (consult detailed reference):** Ampicillin, meropenem.

Compatibility in syringe: Incompatible: Metoclopramide.

Compatibility when admixed: Compatible: Amikacin, aminophylline, ascorbic acid injection, bretylium, chloramphenicol, corticotropin, dimenhydrinate, furosemide, heparin, hydrocortisone sodium succinate, lidocaine, magnesium sulfate, norepinephrine, penicillin G potassium, penicillin G sodium, phenobarbital, potassium chloride, tobramycin, vancomycin, verapamil, vitamin B complex with C. **Incompatible:** Amphotericin B, cefamandole, cefazolin, clindamycin, dobutamine, floxacillin, methylprednisolone sodium succinate. **Variable (consult detailed reference):** Folic acid, potassium phosphate, prochlorperazine edisylate, sodium bicarbonate; maximum concentration in parenteral nutrition solutions is variable depending upon concentration and solubility.

Extemporaneously PreparedTo make calcium gluconate gel, 3.5 g of calcium gluconate can be added to 5 oz tube of a surgical lubricant (water soluble such as K-Y® Jelly).

ContraindicationsHypersensitivity to calcium gluconate or any component of the formulation; ventricular fibrillation during cardiac resuscitation; digitalis toxicity or suspected digoxin toxicity; hypercalcemia

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac arrest: May produce cardiac arrest.

- Gastrointestinal effects: Constipation, bloating, and gas are common with oral calcium supplements (especially carbonate salt).

Disease-related concerns:

- Acidosis: Use with caution in patients with respiratory acidosis, renal impairment, or respiratory failure; acidifying effect of calcium chloride may potentiate acidosis.

- Hyperphosphatemia: Use with caution in patients with severe hyperphosphatemia.

- Kidney stones (calcium-containing): Use caution when administering calcium supplements to patients with a history of kidney stones.

- Renal impairment: Use with caution in patients with renal failure to avoid hypercalcemia; frequent monitoring of serum calcium and phosphorus is necessary.

Concurrent drug therapy issues:

- Digitalis: Use with caution in digitalized patients; hypercalcemia may precipitate cardiac arrhythmias.

- Minerals/other oral drugs: Calcium administration interferes with absorption of some minerals and drugs; use with caution.

- Vitamin D: It is recommended to concomitantly administer vitamin D for optimal calcium absorption.

Dosage form specific issues:

- Absorption: Taking oral calcium (≤500 mg) with food improves absorption.

- Aluminum: Solutions may contain aluminum; toxic levels may occur following prolonged administration in premature neonates or patients with renal impairment.

- I.V. administration: For I.V. use only; do not inject SubQ or I.M. Avoid too rapid I.V. administration and avoid extravasation.

Geriatric ConsiderationsConstipation and gas can be significant in elderly, but are usually mild.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been completed.
LactationEnters breast milk
Breast-Feeding ConsiderationsEndogenous calcium is excreted in breast milk.
Adverse ReactionsFrequency not defined.

I.V.:

Cardiovascular: Arrhythmia, bradycardia, cardiac arrest, hypotension, vasodilation, and syncope may occur following rapid I.V. injection

Central nervous system: Sense of oppression

Gastrointestinal: Chalky taste

Local: Abscess and necrosis following I.M. administration

Neuromuscular & skeletal: Tingling sensation

Miscellaneous: Heat waves

Postmarketing and/or case reports: Calcinosis cutis

Oral: Gastrointestinal: Constipation

Drug Interactions

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CefTRIAXone: Calcium Salts (Intravenous) may enhance the adverse/toxic effect of CefTRIAXone. Ceftriaxone binds to calcium forming an insoluble precipitate. *Risk X: Avoid combination*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Estramustine: Calcium Salts may decrease the absorption of Estramustine. *Risk D: Consider therapy modification*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Moxifloxacin. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Test InteractionsIncreased calcium (S); decreased magnesium
Reference Range

Serum calcium: 8.4-10.2 mg/dL: Monitor plasma calcium levels if using calcium salts as electrolyte supplements for deficiency

Due to a poor correlation between the serum ionized calcium (free) and total serum calcium, particularly in states of low albumin or acid/base imbalances, direct measurement of ionized calcium is recommended

In low albumin states, the corrected **total** serum calcium may be estimated by: Corrected total calcium = total serum calcium + 0.8 (4.0 - measured serum albumin)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effect, and adverse/toxic effects. Assess knowledge/teach patient proper use, appropriate interventions to reduce side effects, and adverse symptoms to report. If administered I.V., monitor ECG, vital signs, and CNS. Observe infusion site closely. Avoid extravasation.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Follow exact instructions for dosing. Oral: Take with a full glass of water or juice, 1-3 hours after other medications, and 1-2 hours before any approved iron supplements. Avoid alcohol, other antacids, caffeine, or other calcium supplements unless approved by prescriber. May cause constipation (increased exercise, fluids, fiber, or fruits may help) or dry mouth (frequent mouth care, chewing gum, or sucking lozenges may help). Report severe, unresolved GI disturbances and unusual emotional lability (mood swings). **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, oral:

Cal-G: 700 mg [gluten free, wheat free; equivalent to elemental calcium 65 mg]

Capsule, oral [preservative free]:

Cal-GLU™: 515 mg [dye free, sugar free; equivalent to elemental calcium 50 mg]

Injection, solution [preservative free]: 10% (10 mL, 50 mL, 100 mL, 200 mL) [100 mg/mL; equivalent to elemental calcium 9 mg/mL; calcium 0.46 mEq/mL]

Powder: 347 mg/tablespoonful (480 g)

Tablet: 500 mg [equivalent to elemental calcium 45 mg]; 650 mg [equivalent to elemental calcium 58.5 mg]; 975 mg [equivalent to elemental calcium 87.75 mg]

Generic AvailableYes

Mechanism of ActionAs dietary supplement, used to prevent or treat negative calcium balance; in osteoporosis, it helps to prevent or decrease the rate of bone loss. The calcium in calcium salts moderates nerve and muscle performance and allows normal cardiac function.

Pharmacodynamics/Kinetics

Absorption: Requires vitamin D; calcium is absorbed in soluble, ionized form; solubility of calcium is increased in an acid environment

Distribution: Primarily in bones and teeth; crosses placenta; enters breast milk

Protein binding: Primarily albumin

Excretion: Primarily feces (as unabsorbed calcium); urine (20%)

Pharmacotherapy PearlsA topical 2.5% to 5% calcium gel for the treatment of hydrofluoric acid (HF) burns can be prepared by adding calcium gluconate to a surgical lubricant (water soluble such as K-Y® Jelly). Calcium chloride should not be used for this purpose. Use of injectable calcium gluconate (I.V., SubQ) has also been reported in the literature for the treatment of HF burns not amenable to topical treatment.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness; may cause confusion and delirium (as a consequence of hypercalcemia)

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsHypercalcemia is evident on ECG by shortening of the QT interval and possibly lengthening of the PR interval. Hypocalcemia causes prolongation of the QT interval. This prolongation is due to lengthening of the ST segment; the T waves remain unchanged. However, in severe hypocalcemia, T waves may be inverted. Note that only hypocalcemia and hypothermia lengthen the ST segment without altering T-wave duration. Hypocalcemia may also present clinically with skeletal muscle spasm.

Calcium salts may enhance the arrhythmogenic effects of digoxin. Part of the inotropic action of digoxin appears to be associated with increased intracellular calcium availability. Chronotropic effects are also calcium mediated. The administration of exogenous calcium (especially by parenteral routes) can lead to cardiac arrhythmias.

Anesthesia and Critical Care Concerns/Other Considerations

Hypocalcemia in the Critically-Ill Patient: Treatment of patients with asymptomatic hypocalcemia, defined as a total serum calcium concentration <8.5 mg/dL (or ionized calcium <4.2 mg/dL; <1 mmol/L) with intravenous calcium salts is generally not recommended. Symptoms usually occur when ionized calcium levels fall to <2.5 mg/dL. Symptoms include paresthesias of the extremities and face, muscle cramps, carpopedal spasm, stridor, tetany, and seizures. However, if the patient is experiencing hemodynamic compromise or life-threatening arrhythmias with any degree of hypocalcemia, treatment with intravenous calcium is warranted. Use of calcium chloride is preferred due to the higher bioavailability as compared with calcium gluconate. If the patient has concomitant hypomagnesemia, replacement with calcium may be ineffective. It is recommended that serum magnesium levels be corrected prior to administration of calcium.

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[PubMed 2664428]

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International Brand NamesBiogam Ca (BE); Calcedon (DE); Calcii Gluconas (FI); Calcimusc (HU); Calcio Gluconato (AR, IT); Calcium Braun (DE); Calcium Gluconicum (PL); Calcium Gluconicum Granulatum (PL); Calcium Pliva (PL); Calcium Polfa (PL); Gluconate de Calcium Lavoisier (FR); Gluconato Calc Fresenius (ES); Gluconato Calcico (ES); Novacalc (NO); VIta-Valu Calcium Gluconate (AU)

Calcium Lactate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(KAL see um LAK tate)

Pharmacologic Category[Calcium Salt]

Use: Labeled IndicationsAdjunct in prevention of postmenopausal osteoporosis; treatment and prevention of calcium depletion

Dosing: AdultsDosage in terms of calcium lactate

Dietary Reference Intake (in terms of elemental calcium):

Adults, Male/Female:

19-50 years: 1000 mg/day

≥51 years: 1200 mg/day

Female: Pregnancy/Lactating: Same as Adults, Male/Female

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricOral (in terms of calcium lactate):

Dietary Reference Intake (in terms of elemental calcium):

0-6 months: 210 mg/day

7-12 months: 270 mg/day

1-3 years: 500 mg/day

4-8 years: 800 mg/day

9-18 years: 1300 mg/day

Dosing: Renal ImpairmentCl_{cr} <25 mL/minute: Dosage adjustments may be necessary depending on the serum calcium levels.

Warnings/Precautions

Concerns related to adverse effects:

- Gastrointestinal effects: Constipation, bloating, and gas are common with calcium supplements (especially carbonate salt).

Disease-related concerns:

- Achlorhydria: Calcium absorption is impaired in achlorhydria; common in elderly, use an alternate salt (eg, citrate) and administer with food.
- Hypoparathyroid disease: Hypercalcemia and hypercalciuria are most likely to occur in hypoparathyroid patients receiving high doses of vitamin D.
- Kidney stones (calcium-containing): Use caution when administering calcium supplements to patients with a history of kidney stones.
- Renal impairment: Use with caution in patients with renal failure to avoid hypercalcemia; frequent monitoring of serum calcium and phosphorus is necessary.

Concurrent drug therapy issues:

- Minerals/other oral drugs: Calcium administration interferes with absorption of some minerals and drugs; use with caution.
- Vitamin D: It is recommended to concomitantly administer vitamin D for optimal calcium absorption.

Other warnings/precautions:

- Absorption: Taking calcium (≤500 mg) with food improves absorption.

Pregnancy Risk FactorC

Adverse Reactions<1%: Constipation, dizziness, dry mouth, headache, hypercalcemia, hypercalciuria, hypomagnesemia, hypophosphatemia, mental confusion, milk-alkali syndrome, nausea, vomiting

Drug Interactions

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Estramustine: Calcium Salts may decrease the absorption of Estramustine. *Risk D: Consider therapy modification*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Moxifloxacin. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase risk of osteoporosis).

Patient EducationDo not take any new medication during therapy without consulting prescriber. Follow exact instructions for dosing. Take with a full glass of water or juice, 1-3 hours after other medications, and 1-2 hours before any approved iron supplements. Avoid alcohol, other antacids, caffeine, or other calcium supplements unless approved by prescriber. May cause constipation (increased exercise, fluids, fiber, or fruits may help) or dry mouth (frequent mouth care, chewing gum, or sucking lozenges may help). Report severe, unresolved GI disturbances and unusual emotional lability (mood swings). **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 650 mg [equivalent to elemental calcium 84.5 mg]

Generic AvailableYes

Mechanism of ActionAs dietary supplement, used to prevent or treat negative calcium balance; in osteoporosis, it helps to prevent or decrease the rate of bone loss. The calcium in calcium salts moderates nerve and muscle performance and allows normal cardiac function.

Pharmacodynamics/KineticsAbsorption: Requires vitamin D

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause confusion or dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsHypercalcemia is evident on ECG by shortening of the QT interval and possibly lengthening of the PR interval. Hypocalcemia causes prolongation of the QT interval. This prolongation is due to lengthening of the ST segment; the T waves remain unchanged. However, in severe hypocalcemia, T waves may be inverted. Note that only hypocalcemia and hypothermia lengthen the ST segment without altering T-wave duration. Hypocalcemia may also present clinically with skeletal muscle spasm.

References

"Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine," National Academy of Sciences, Washington, DC: National Academy Press, 1997. Available at: http://www.nap.edu.

International Brand NamesBiocalcium (PL); Calcium natural (PL)

Calcium Phosphate (Tribasic)

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(KAL see um FOS fate tri BAY sik)

U.S. Brand NamesPosture® [OTC]

Pharmacologic CategoryCalcium Salt

Use: Labeled IndicationsDietary supplement

Dosing: Adults

Adequate Intake (as elemental calcium): Oral:

Male/Female:

19-50 years: 1000 mg/day

≥51 years: 1200 mg/day

Female: Pregnancy/Lactating: Same as for Adults, Male/Female

Dietary supplement: Oral: 2 tablets daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Adequate Intake (as elemental calcium):** Oral:

0-6 months: 210 mg/day

7-12 months: 270 mg/day

1-3 years: 500 mg/day

4-8 years: 800 mg/day

9-18 years: 1300 mg/day

Dosing: Renal ImpairmentCl_{cr} <25 mL/minute: Dosage adjustments may be necessary depending on the serum calcium levels.

Warnings/Precautions

Concerns related to adverse effects:

- Gastrointestinal effects: Constipation, bloating, and gas are common with calcium supplements (especially carbonate salt).

Disease-related concerns:

- Achlorhydria: Calcium absorption is impaired in achlorhydria; common in elderly, use an alternate salt (eg, citrate) and administer with food.
- Hypoparathyroid disease: Hypercalcemia and hypercalciuria are most likely to occur in hypoparathyroid patients receiving high doses of vitamin D.
- Kidney stones (calcium-containing): Use caution when administering calcium supplements to patients with a history of kidney stones.
- Renal impairment: Use with caution in patients with renal failure to avoid hypercalcemia; frequent monitoring of serum calcium and phosphorus is necessary.

Concurrent drug therapy issues:

- Minerals/other oral drugs: Calcium administration interferes with absorption of some minerals and drugs; use with caution.
- Vitamin D: It is recommended to concomitantly administer vitamin D for optimal calcium absorption.

Other warnings/precautions:

- Absorption: Taking calcium (≤500 mg) with food improves absorption.

Adverse Reactions<1%: Constipation, dry mouth, hypercalcemia, hypophosphatemia, milk-alkali syndrome, nausea

Drug Interactions

Antacids: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: May enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Calcium Salts: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Estramustine: Calcium Salts may decrease the absorption of Estramustine. *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Moxifloxacin. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase risk of osteoporosis).

Patient EducationDo not take any new medication during therapy without consulting prescriber. Follow exact instructions for dosing. Take with a full glass of water or juice, 1-3 hours after meals and other medications, and 1-2 hours before any approved iron supplements. Avoid alcohol, other antacids, caffeine, or other calcium supplements unless approved by prescriber. May cause constipation (increased exercise, fluids, fiber, or fruits may help) or dry mouth (frequent mouth care, chewing gum, or sucking lozenges may help). Report severe, unresolved GI disturbances and unusual emotional lability (mood swings). **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet:

Posture®: Calcium 600 mg and phosphorus 280 mg [as tricalcium phosphate]

Generic AvailableNo

Mechanism of ActionAs dietary supplement, used to prevent or treat negative calcium balance; in osteoporosis, it helps to prevent or decrease the rate of bone loss. The calcium in calcium salts moderates nerve and muscle performance and allows normal cardiac function.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsTricalcium Phosphate

References

"Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine," National Academy of Sciences, Washington, DC: National Academy Press, 1997. Available at: http://www.nap.edu.

Calcium and Vitamin D

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(KAL see um & VYE ta min dee)

U.S. Brand NamesCal-CYUM [OTC]; Caltrate® 600+ Soy™ [OTC]; Caltrate® 600+D [OTC]; Caltrate® ColonHealth™ [OTC]; Chew-Cal [OTC]; Liqua-Cal [OTC]; Os-Cal® 500+D [OTC]; Oysco 500+D [OTC]; Oysco D [OTC]; Oyst-Cal-D 500 [OTC]; Oyst-Cal-D [OTC]

Pharmacologic CategoryCalcium Salt; Electrolyte Supplement, Oral; Vitamin, Fat Soluble

Use: Labeled IndicationsDietary supplement, antacid

Dosing: AdultsCalcium supplement, hyperphosphatemia: Oral: Refer to individual monographs for dietary reference intake.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentUse caution in severe renal impairment.

Administration: OralAdminister, preferably with food, 2 hours before or after other medications.

Dietary ConsiderationsTake with food to minimize GI upset. Some products may contain phenylalanine (avoid use in phenylketonurics), tartrazine, gluten, and/or soy.

ContraindicationsHypersensitivity to any component of the formulation; hypophosphatemia, hypercalcemia, evidence of vitamin D toxicity; history of kidney stones

Warnings/Precautions

Concerns related to adverse effects:

- Gastrointestinal effects: Constipation, bloating, and gas are common with calcium supplements (especially carbonate salt).

Disease-related concerns:

- Achlorhydria: Calcium absorption is impaired in achlorhydria; common in elderly, use an alternate salt (eg, citrate) and administer with food.
- Hypoparathyroid disease: Hypercalcemia and hypercalciuria are most likely to occur in hypoparathyroid patients receiving high doses of vitamin D.
- Kidney stones (calcium-containing): Use caution when administering calcium supplements to patients with a history of kidney stones.
- Renal impairment: Use with caution in patients with renal failure to avoid hypercalcemia; frequent monitoring of serum calcium and phosphorus is necessary.

Concurrent drug therapy issues:

- Minerals/other oral drugs: Calcium administration interferes with absorption of some minerals and drugs; use with caution.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.
- Shellfish: Some products may be derived from shellfish.
- Soy: Some products may contain soy.
- Tartrazine: Some products may contain tartrazine.

Other warnings/precautions:

- Absorption: Taking calcium (≤500 mg) with food improves absorption.

Pregnancy ConsiderationsAvailable evidence suggests safe use during pregnancy.

Breast-Feeding ConsiderationsAvailable evidence suggests safe use during lactation.

Adverse ReactionsFrequency not defined; also see individual agents

Central nervous system: Headache

Endocrine & metabolic: Hypercalcemia, hypercalciuria

Gastrointestinal: Gastrointestinal discomfort

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Antacids may decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Estramustine: Calcium Salts may decrease the absorption of Estramustine. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Moxifloxacin. *Risk D: Consider therapy modification*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase risk of osteoporosis).

Food: Food may increase calcium absorption. Calcium may decrease iron absorption. Bran, foods high in oxalates, or whole grain cereals may decrease calcium absorption.

Monitoring ParametersMonitor serum calcium (particularly if used in patients with severe renal impairment)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effectiveness, and adverse/toxic effects. Assess knowledge/teach patient proper use, appropriate interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsMonitor serum calcium (particularly if used in patients with severe renal impairment)

Patient EducationFollow instructions for dosing. Take with a full glass of water or juice 1-2 hours before any iron supplements and 1-3 hours after meals or other medications. Avoid alcohol, other antacids, caffeine, or other calcium supplements, unless approved by prescriber. You may experience constipation (increased exercise, fluids, fiber, or fruit may help) or dry mouth (sucking lozenges or hard candy may help). Report severe, unresolved GI disturbances and unusual emotional liability (mood swings). **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, softgel: Calcium 500 mg and vitamin D 500 int. units; calcium 600 mg and vitamin D 100 int. units; calcium 600 mg and vitamin D 200 int. units

Liqua-Cal: Calcium 600 mg and vitamin D 200 int. units [contains beeswax, lecithin, and soybean oil]

Tablet: Calcium 250 mg and vitamin D 125 int. units; calcium 500 mg and vitamin D 125 int. units; calcium 500 mg and vitamin D 200 int. units; calcium 600 mg and vitamin D 125 int. units; calcium 600 mg and vitamin D 200 int. units

Caltrate® 600+D: Calcium 600 mg and vitamin D 200 int. units [contains soybean oil]

Caltrate® 600+ Soy™: Calcium 600 mg and vitamin D 200 int. units [contains soy isoflavones 25 mg]

Caltrate® ColonHealth™: Calcium 600 mg and vitamin D 200 int. units [contains soybean oil]

Oysco D: Calcium 250 mg and vitamin D 125 int. units

Oysco 500+D: Calcium 500 mg and vitamin D 200 int. units [contains tartrazine]

Oyst-Cal-D: Calcium 250 mg and vitamin D 125 int. units [sodium free, sugar free; contains tartrazine]

Oyst-Cal-D 500: Calcium 500 mg and vitamin D 200 int. units [sodium free, sugar free; contains tartrazine]

Tablet, chewable: Calcium 500 mg and vitamin D 100 int. units; Calcium 600 mg and vitamin D 400 int. units

Os-Cal® 500+D: Calcium 500 mg and vitamin D 400 int. units [sugar free; contains phenylalanine; light lemon flavor]

Wafer, chewable:

Cal-CYUM: Calcium 519 mg and vitamin D 150 int. units (50s) [dye free; vanilla flavor]

Chew-Cal: Calcium 333 mg and vitamin D 40 int. units (100s, 250s)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Calcium Carbonate-Vitamin D)

600-400 mg-unit (150): $14.00

Tablets (Caltrate 600+D)

600-400 mg-unit (120): $19.99

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsVitamin D and Calcium Carbonate

Calfactant

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(kaf AKT ant)
U.S. Brand NamesInfasurf®
Pharmacologic CategoryLung Surfactant
Use: Labeled IndicationsPrevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS and for the treatment ("rescue") of premature infants who develop RDS

Prophylaxis: Therapy at birth with calfactant is indicated for premature infants <29 weeks of gestational age at significant risk for RDS. Should be administered as soon as possible, preferably within 30 minutes after birth.

Treatment: For infants ≤72 hours of age with RDS (confirmed by clinical and radiologic findings) and requiring endotracheal intubation.

Dosing: PediatricPrevention or treatment of RDS in premature infants: Intratracheal administration **only**: Each dose is 3 mL/kg body weight at birth; should be administered every 12 hours for a total of up to 3 doses
Administration: OtherShould be administered intratracheally through an endotracheal tube. Dose is drawn into a syringe from the single-use vial using a 20-gauge or larger needle with care taken to avoid excessive foaming. Should be administered in two aliquots of 1.5 mL/kg each. After each aliquot is instilled, the infant should be positioned with either the right or the left side dependent. Administration is made while ventilation is continued over 20-30 breaths for each aliquot, with small bursts timed only during the inspiratory cycles. A pause followed by evaluation of the respiratory status and repositioning should separate the two aliquots.
StorageGently swirling or agitation of the vial of suspension is often necessary for redispersion. **Do not shake.** Visible flecks of the suspension and foaming under the surface are normal. Calfactant should be stored at refrigeration (2°C to 8°C/36°F to 46°F). Warming before administration is not necessary. Unopened and unused vials of calfactant that have been warmed to room temperature can be returned to the refrigeration storage within 24 hours for future use. Repeated warming to room temperature should be avoided. Each single-use vial should be entered only once and the vial with any unused material should be discarded after the initial entry.
Warnings/Precautions

Concerns related to adverse effects:

- Transient adverse effects: Transient episodes of bradycardia, decreased oxygen saturation, endotracheal tube blockage or reflux of calfactant into endotracheal tube may occur. Discontinue dosing procedure and initiate measures to alleviate the condition; may reinstitute after the patient is stable.

Other warnings/precautions:

- Administration: For intratracheal administration only.

- Monitoring: Produces rapid improvements in lung oxygenation and compliance that may require frequent adjustments to oxygen delivery and ventilator settings.

- Trained personnel: Rapidly affects oxygenation and lung compliance; restrict use to a highly-supervised clinical setting with immediate availability of clinicians experienced in intubation and ventilatory management of premature infants.

Adverse Reactions

Cardiovascular: Bradycardia (34%), cyanosis (65%)

Respiratory: Airway obstruction (39%), reflux (21%), requirement for manual ventilation (16%), reintubation (1% to 10%)

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersFollowing administration, patients should be carefully monitored so that oxygen therapy and ventilatory support can be modified in response to changes in respiratory status.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, intratracheal [preservative free; calf lung derived]:

Infasurf®: 35 mg/mL (3 mL, 6 mL)

Generic AvailableNo
Mechanism of ActionEndogenous lung surfactant is essential for effective ventilation because it modifies alveolar surface tension, thereby stabilizing the alveoli. Lung surfactant deficiency is the cause of respiratory distress syndrome (RDS) in premature infants and lung surfactant restores surface activity to the lungs of these infants.
Pharmacodynamics/KineticsNo human studies of absorption, biotransformation, or excretion have been performed
Pharmacotherapy PearlsEach mL = 35 mg total phospholipids (including 26 mg phosphatidylcholine, of which 16 mg is desaturated phosphatidylcholine) and 0.65 protein (including 0.26 mg SP-B)
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Bloom BT, Kattwinkel J, Hall RT, et al, “Comparison of Infasurf® (Calf Lung Surfactant Extract) to Survanta® (Beractant) in the Treatment and Prevention of Respiratory Distress Syndrome,” *Pediatrics*, 1997, 100(1):31-8. [PubMed 9200357]

Hudak ML, Martin DJ, Egan EA, et al, “A Multicenter Randomized Masked Comparison Trail of Synthetic Surfactant Versus Calf Lung Surfactant Extract in the Prevention of Neonatal Respiratory Distress Syndrome,” *Pediatrics*, 1997, 100(1):39-50.[PubMed 9200358]

Camphor and Menthol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(KAM for & MEN thol)
U.S. Brand NamesMen-Phor [OTC]; Mentholatum® [OTC]; Sarna® [OTC]; Soltice Quick-Rub® [OTC]
Pharmacologic CategoryTopical Skin Product
Use: Labeled IndicationsRelief of dry, itching skin
Dosing: AdultsDry skin: Topical: Apply as needed
Dosing: ElderlyRefer to adult dosing.
Pregnancy Risk FactorC
Adverse Reactions1% to 10%: Dermatologic: Burning sensation, especially on broken skin
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical:

Soltice Quick-Rub®: Camphor 5.1% and menthol 5.1% (40 g, 90 g)

Lotion, topical:

Men-Phor: Camphor 0.5% and menthol 0.5% (222 mL, 225 mL)

Sarna®: Camphor 0.5% and menthol 0.5% (222 mL)

Ointment, topical:

Mentholatum®: Camphor 9% and menthol 1.3% (30 g, 90 g)

Generic AvailableNo
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsMenthol and Camphor

Camphor and Phenol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(KAM for & FEE nole)

U.S. Brand NamesCampho-Phenique® [OTC]

Pharmacologic CategoryTopical Skin Product

Use: Labeled IndicationsRelief of pain and itching associated with minor burns, sunburn, minor cuts, insect bites, minor skin irritation; temporary relief of pain from cold sores

Dosing: AdultsRelief of pain/itching: Apply 1-3 times/day

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to camphor, phenol, or any component of the formulation

Warnings/Precautions

Other warnings/precautions:

- Appropriate use: For external use only; do not cover affected area with bandage.
- Self-medication (OTC use): When used for self-medication (OTC use), do not use on deep puncture wounds, animal bites, serious burns, or for >7 days.

Pregnancy Risk FactorC

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel, topical:

Campho-Phenique®: Camphor 10.8% and phenol 4.7% (7 g, 14 g)

Liquid, topical: Camphor 10.8% and phenol 4.7% (45 mL)

Campho-Phenique®: Camphor 10.8% and phenol 4.7% (22.5 mL, 45 mL)

Generic AvailableYes: Liquid

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPhenol and Camphor

Candesartan and Hydrochlorothiazide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(kan de SAR tan & hye droe klor oh THYE a zide)

U.S. Brand NamesAtacand HCT®

Canadian Brand NamesAtacand® Plus

Pharmacologic CategoryAngiotensin II Receptor Blocker; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension; combination product should not be used for initial therapy

Dosing: AdultsHypertension, replacement therapy: Oral: Combination product can be substituted for individual agents; maximum therapeutic effect would be expected within 4 weeks

Usual dosage range:

Candesartan: 16-32 mg/day, given once daily or twice daily in divided doses

Hydrochlorothiazide: 12.5-25 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentSerum levels of candesartan are increased and the half-life of hydrochlorothiazide is prolonged in patients with renal impairment. Contraindicated with severe renal impairment (Cl_{cr} <30 mL/minute).

Dosing: Hepatic ImpairmentUse with caution with moderate hepatic impairment. Contraindicated with severe hepatic impairment and/or cholestasis.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsMay be given with or without food.

StorageStore at 25°C (77°F). Store in tightly closed container.

ContraindicationsHypersensitivity to candesartan, hydrochlorothiazide, or any component of the formulation; hypersensitivity to sulfonamide-derived drugs; severe renal impairment (Cl_{cr} <30 mL/minute); severe hepatic impairment and/or cholestasis; refractory hypokalemia; refractory hypercalcemia; gout; pregnancy; breast-feeding

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Electrolyte disturbances: Hyperkalemia may occur with angiotensin II receptor antagonists; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use caution in patients with moderate hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy. Contraindicated with severe hepatic impairment and/or cholestasis.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.

- Renal artery stenosis: Use candesartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use candesartan with caution with pre-existing renal insufficiency. May precipitate azotemia; discontinue or consider withholding if renal impairment occurs. Contraindicated in severe renal disease (Cl_{cr} <30 mL/minute).

- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Concurrent drug therapy issues:

- ACE inhibitors: Although some properties may be shared between these agents, concurrent therapy with ACE inhibitor may be rational in selected patients.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Anesthesia/surgery: Hypotension may occur during major surgery and anesthesia; use cautiously before, during, and immediately after such interventions.

Geriatric ConsiderationsNo initial dosage adjustment is recommended in patients with normal renal and hepatic function; some patients may have increased sensitivity.

Pregnancy Risk FactorC/D (2nd and 3rd trimesters)

Pregnancy Considerations

Candesartan: C/D (2nd and 3rd trimesters): Discontinue as soon as possible when pregnancy is detected. Drugs that act directly on renin-angiotensin can cause fetal and neonatal morbidity and death. Adverse effects to the fetus appear to be limited to the 2nd and 3rd trimesters.

Hydrochlorothiazide: B (per manufacturer), D (based on expert analysis): Although there are no adequate and well-controlled studies using hydrochlorothiazide in pregnancy, thiazide diuretics may cause an increased risk of congenital defects. Hypoglycemia, hypokalemia, hyponatremia, jaundice, and thrombocytopenia are also reported as possible complications to the fetus or newborn.

LactationEnters breast milk/contraindicated

Breast-Feeding Considerations

Candesartan: Avoid use in the nursing mother, if possible, since candesartan may be excreted in breast milk.

Hydrochlorothiazide: Thiazides are excreted in human breast milk. Benefits to the mother should be weighed against possible risk to the newborn if used in a nursing woman.

Adverse ReactionsReactions which follow have been reported with the combination product; see individual drug agents for additional adverse reactions that may be expected from each agent.

1% to 10%:

Central nervous system: Dizziness (3%), headache (3%, placebo 5%)

Neuromuscular & skeletal: Back pain (3%)

Respiratory: Upper respiratory tract infection (4%)

Miscellaneous: Flu-like syndrome (2%)

<1%: Abdominal pain, abnormal ECG, abnormal hepatic function, agranulocytosis, angina pectoris, angioedema (<0.5%), anxiety, arthralgia, arthritis, arthrosis, asthenia, bradycardia, bronchitis, BUN increased, chest pain, conjunctivitis, cough, CPK increased, cystitis, depression, dermatitis, diaphoresis increased, diarrhea, dyspepsia, dyspnea, eczema, epistaxis, extrasystoles, fatigue, gastritis, gastroenteritis, hematuria, hepatitis, hyperglycemia, hyperuricemia, hypoesthesia, hypokalemia, infection, insomnia, leg cramps, leukopenia, myalgia, MI (<0.5%), nausea, neutropenia, pain, palpitation, paresthesia, peripheral edema, pharyngitis, pruritus, rash, rhinitis, sciatica, sinusitis, tachycardia, tinnitus, transaminases increased, urinary tract infection, urticaria, vertigo, viral infection, vomiting; rhabdomyolysis has been reported (rarely) with angiotensin-receptor antagonists

Metabolism/Transport EffectsCandesartan: **Substrate** of CYP2C9 (minor); **Inhibits** CYP2C8 (weak), 2C9 (weak)

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may potentiate orthostatic hypotension).

Monitoring ParametersAssess weight, I & O reports daily to determine fluid loss; blood pressure, symptomatic hypotension, and tachycardia; serum electrolytes, BUN, creatinine

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsSerum electrolytes, BUN, creatinine

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Atacand HCT®:

16/12.5: Candesartan cilexetil 16 mg and hydrochlorothiazide 12.5 mg

32/12.5: Candesartan cilexetil 32 mg and hydrochlorothiazide 12.5 mg

32/25: Candesartan cilexetil 32 mg and hydrochlorothiazide 25 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Atacand HCT)

16-12.5 mg (30): $83.19

32-12.5 mg (30): $85.27

Mechanism of Action

Candesartan: Candesartan is an angiotensin receptor antagonist. Angiotensin II acts as a vasoconstrictor. In addition to causing direct vasoconstriction, angiotensin II also stimulates the release of aldosterone. Once aldosterone is released, sodium as well as water are reabsorbed. The end result is an elevation in blood pressure. Candesartan binds to the AT1 angiotensin II receptor. This binding prevents angiotensin II from binding to the receptor, thereby blocking the vasoconstriction and the aldosterone-secreting effects of angiotensin II.

Hydrochlorothiazide: Inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Candesartan
- Hydrochlorothiazide

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause decreased renal lithium clearance; monitor serum lithium levels

Cardiovascular Considerations

Congestive Heart Failure: Currently, the use of angiotensin II receptor blockers (ARBs) should not supersede angiotensin converting enzyme inhibitors (ACEIs) in the treatment of congestive heart failure. One may be considered, however, when an ACEI cannot be tolerated. Because they are angiotensin II blockers rather than inhibitors of ACE, ARBs do not cause increases in bradykinin levels. *ELITE II* (Pitt, 2000) compared losartan (50 mg/day) with captopril (150 mg/day) in a heart failure population (mean EF 31%). There were 280 deaths in the losartan group and 250 in the captopril group. Mortality was insignificantly higher for losartan (17.7% vs 16% for captopril). The secondary endpoint (sudden cardiac death or resuscitated cardiac arrest) favored captopril, but the improvement did not achieve statistical significance. The discontinuation rate for adverse events was significantly lower for losartan. In the doses used, losartan appears to be less effective or as effective as captopril.

CHARM-Alternative is a prospective, randomized trial (Granger, 2003) in ACE inhibitor-intolerant patients with CHF. Patients were randomized to candesartan (target dose: 32 mg/day; mean dose at 6 months: 23 mg/day) or placebo. Baseline characteristics included NYHA Class II or III (97% of patients), and mean LVEF 30%. Therapy included beta-blocker (55%), diuretic (86%), spironolactone (24%), and digitalis (46%). During a 33-month follow-up, the combined primary endpoint (CV death or heart failure hospitalizations) was significantly reduced in the candesartan group mainly because of reduced hospitalization. Death due to cardiovascular disease was not significantly different. There were significantly more MIs (75) in the candesartan group than in the placebo group (48). Candesartan was discontinued because of hypotension, renal dysfunction, and hyperkalemia.

Congestive Heart Failure: Concomitant ACE-I Therapy: The *Val-HeFT study* (Cohn, 2001) randomized CHF patients maintained on standard therapy to valsartan (320 mg/day; mean dose 254 mg/day) or placebo. The primary outcome was mortality and a combined endpoint of morbidity and mortality (cardiac arrest, hospitalization for CHF, need for intravenous inotrope or vasodilator). Patients (5010 in number) with predominately NYHA class II or III heart failure (85% on diuretic, 67% on digoxin, 35% on beta-blocker, ~93% on ACEI, 5% on spironolactone) were randomized to valsartan or placebo. The mean duration of follow-up was 23 months. Overall mortality was similar in both groups. The incidence of combined endpoints was lower with valsartan than placebo (p=.009) primarily because of decreased heart failure hospitalizations in the valsartan group. In a posthoc analysis of the endpoints in subgroups defined by baseline treatments (ACEI or beta-blockers), valsartan had a positive effect on patients receiving neither or one of these drugs. A higher incidence of mortality was seen in patients receiving valsartan in combination with an ACEI and a beta-blocker.

CHARM-Added trial is a prospective, randomized trial (McMurray, 2003) evaluating the addition of candesartan therapy (target dose: 32 mg/day; mean dose at 6 months: 24 mg/day) to CHF patients maintained on an ACEI. Baseline characteristics: NYHA class II (24%), class III (73%), and mean LVEF 28%. Baseline therapy was similar to CHARM-Alternative except all patients were maintained on an ACEI and ~55% were on a beta-blocker. The median duration of follow-up was 41 months. The combined primary endpoint (CV death or heart failure hospitalizations) was significantly reduced in the candesartan group.

Hypertension: According to the 2003 JNC7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Myocardial Infarction: The 2004 ACC/AHA STEMI guidelines suggest an angiotensin receptor blocker should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF <0.4. The *OPTIMAAL trial* evaluated whether losartan (50 mg/day) would be superior or noninferior to captopril (150 mg/day) in post-MI patients. They were randomized to one of two treatments and followed up for 2.7 years. There was no difference between the two treatment groups (499 deaths in losartan group; 447 deaths in the captopril-treated group). The VALIANT trial compared the effects of valsartan, captopril, and the combination in patients who had suffered a recent MI (0.5 to 10 days prior) complicated by left ventricular systolic dysfunction (Pfeffer, 2003). The primary endpoint was mortality from any cause. Mortality in the valsartan group and the valsartan-captopril group was similar to the captopril group alone. Valsartan was found to be noninferior to captopril in this patient population. Combining valsartan with captopril increased the rate of adverse events without improving survival. Hypotension and renal dysfunction were more common in the valsartan group. Cough, rash, and taste disturbances were more common in the captopril group.

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Index TermsCandesartan Cilexetil and Hydrochlorothiazide

References

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International Brand NamesAtacand D (AR); Atacand HCT (BR); Atacand Plus (AU, BE, BF, BJ, CH, CI, CO, CR, CZ, DK, DO, EE, ES, ET, FI, GH, GM, GN, GT, HN, IE, IL, KE, KP, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NO, PA, SC, SD, SE, SG, SL, SN, SV, TN, TZ, UG, ZA, ZM, ZW); Blopresid (IT); Blopress Comp (SE); Blopress Plus (CH, EC, HK, PH, TH, UY); Blopress-D (CN); Blox-D (CN); Candesar-H (IN); Cokenzen (FR); Hytacand (FR, PT); Tiadyl Plus (AR)

Candesartan

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English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(kan de SAR tan)

U.S. Brand NamesAtacand®

Canadian Brand NamesAtacand®

Pharmacologic CategoryAngiotensin II Receptor Blocker

Use: Labeled IndicationsAlone or in combination with other antihypertensive agents in treating essential hypertension; treatment of heart failure (NYHA class II-IV)

Dosing: Adults

Hypertension: Oral: 4-32 mg once daily. Dosage must be individualized. Blood pressure response is dose related over the range of 2-32 mg. The usual recommended starting dose is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. It can be administered once or twice daily with total daily doses ranging from 8-32 mg; larger doses do not appear to have a greater effect and there is relatively little experience with such doses.

Congestive heart failure: Oral: Initial: 4 mg once daily; double the dose at 2-week intervals, as tolerated; target dose: 32 mg

Note: In selected cases, concurrent therapy with an ACE inhibitor may provide additional benefit.

Dosing: ElderlyRefer to adult dosing. No initial dosage adjustment is necessary for elderly patients (although higher concentrations (C_{max}) and AUC were observed in these populations), for patients with mildly impaired renal function, or for patients with mildly impaired hepatic function.

Dosing: Hepatic Impairment

Mild hepatic impairment: No initial dosage adjustment required.

Moderate hepatic impairment: Consider initiation at lower dosages (AUC increased by 145%).

Severe hepatic impairment and/or cholestasis: Contraindicated

ContraindicationsHypersensitivity to candesartan or any component of the formulation; severe hepatic impairment and/or cholestasis; pregnancy; breast-feeding

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Hyperkalemia: May occur; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic/mitral stenosis: Use caution in patients with significant aortic/mitral stenosis.

- Heart failure: Use caution when initiating in heart failure; may need to adjust dose, and/or concurrent diuretic therapy, because of candesartan-induced hypotension.

- Hepatic impairment: Use caution in patients with moderate hepatic impairment. Contraindicated in severe hepatic impairment and/or cholestasis.

- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.

- Renal artery stenosis: Use candesartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution with pre-existing renal insufficiency and severe renal impairment.

Concurrent drug therapy issues:

- ACE inhibitors: Although some properties may be shared between these agents, concurrent therapy with ACE inhibitor may be rational in selected patients.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Anesthesia/surgery: Hypotension may occur during major surgery and anesthesia; use cautiously before, during, and immediately after such interventions.

Geriatric Considerations High concentrations occur in the elderly compared to younger subjects. AUC may be doubled in patients with renal impairment. No initial dose adjustment necessary since repeated dose did not demonstrate accumulation of drug or metabolites in elderly.

Pregnancy Risk Factor C (1st trimester); D (2nd and 3rd trimesters)

Pregnancy Considerations Medications which act on the renin-angiotensin system are reported to have the following fetal/neonatal effects: Hypotension, neonatal skull hypoplasia, anuria, renal failure, and death; oligohydramnios is also reported. These effects are reported to occur with exposure during the second and third trimesters. There are no adequate and well-controlled studies in pregnant women. **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Lactation Enters breast milk/contraindicated

Adverse Reactions

Cardiovascular: Angina, hypotension (CHF 19%), MI, palpitation, tachycardia

Central nervous system: Dizziness, lightheadedness, drowsiness, headache, vertigo, anxiety, depression, somnolence, fever

Dermatologic: Angioedema, rash

Endocrine & metabolic: Hyperglycemia, hyperkalemia (CHF <1% to 6%), hypertriglyceridemia, hyperuricemia

Gastrointestinal: Dyspepsia, gastroenteritis

Genitourinary: Hematuria

Neuromuscular & skeletal: Back pain, CPK increased, myalgia, paresthesia, weakness

Renal: Serum creatinine increased (up to 13% in patients with CHF with drug discontinuation required in 6%)

Respiratory: Dyspnea, epistaxis, pharyngitis, rhinitis, upper respiratory tract infection

Miscellaneous: Diaphoresis increased

<1%, postmarketing, and/or case reports: Abnormal hepatic function, agranulocytosis, anemia, hepatitis, hyponatremia, leukopenia, neutropenia, pruritus, renal failure, renal impairment, rhinitis, sinusitis, thrombocytopenia, urticaria; rhabdomyolysis has been reported (rarely) with angiotensin-receptor antagonists

Metabolism/Transport Effects **Substrate** of CYP2C9 (minor); **Inhibits** CYP2C8 (weak), 2C9 (weak)

Drug Interactions

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Food reduces the time to maximal concentration and increases the C_{max}.

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersSupine blood pressure, electrolytes, serum creatinine, BUN, urinalysis, symptomatic hypotension, and tachycardia; in CHF, serum potassium during dose escalation and periodically thereafter

Nursing: Physical Assessment/MonitoringEvaluate renal status and history prior to beginning treatment. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, increased risk for hypotension, hyperkalemia). Assess results of laboratory tests (electrolytes, serum creatinine, BUN, urinalysis), effectiveness of therapy (reduced hypertension), and adverse response (eg, tachycardia, CNS changes, hyperglycemia, hypotension) at beginning of therapy, when changing dose, and on a regular basis during long-term therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsElectrolytes, serum creatinine, BUN, urinalysis; in CHF, serum potassium during dose escalation and periodically thereafter

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed and do not discontinue medication without consulting prescriber. Preferable to take on an empty stomach, 1 hour before or 2 hours after meals. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea (boiled milk, buttermilk, or yogurt may help). Report chest pain or palpitations; unusual weight gain or swelling of ankles and hands; persistent fatigue; unusual flu or cold symptoms or dry cough; respiratory difficulty; swelling of eyes, face, or lips; skin rash; muscle pain or weakness; unusual bleeding (blood in urine or stool, or from gums); or excessive sweating. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as cilexetil:

Atacand®: 4 mg, 8 mg, 16 mg, 32 mg

Generic AvailableNo

ManufacturerAstraZeneca Pharmaceuticals LP

Pricing: U.S. (www.drugstore.com)

Tablets (Atacand)

4 mg (30): $62.39

8 mg (30): $64.47

16 mg (30): $61.99

32 mg (30): $84.23

Mechanism of ActionCandesartan is an angiotensin receptor antagonist. Angiotensin II acts as a vasoconstrictor. In addition to causing direct vasoconstriction, angiotensin II also stimulates the release of aldosterone. Once aldosterone is released, sodium as well as water are reabsorbed. The end result is an elevation in blood pressure. Candesartan binds to the AT1 angiotensin II receptor. This binding prevents angiotensin II from binding to the receptor thereby blocking the vasoconstriction and the aldosterone secreting effects of angiotensin II.

Pharmacodynamics/Kinetics

Onset of action: 2-3 hours

Peak effect: 6-8 hours

Duration: >24 hours

Distribution: V_d: 0.13 L/kg

Protein binding: 99%

Metabolism: To candesartan by the intestinal wall cells

Bioavailability: 15%

Half-life elimination (dose dependent): 5-9 hours

Time to peak: 3-4 hours

Excretion: Urine (26%)

Clearance: Total body: 0.37 mL/kg/minute; Renal: 0.19 mL/kg/minute

Related Information

- Angiotensin Agents

Pharmacotherapy PearlsMay have an advantage over losartan due to minimal metabolism requirements and consequent use in mild-to-moderate hepatic impairment
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness; may rarely cause anxiety or depression
Mental Health: Effects on Psychiatric TreatmentNone reported
Cardiovascular Considerations

Congestive Heart Failure: Currently, the use of angiotensin II receptor blockers (ARBs) should not supersede angiotensin converting enzyme inhibitors (ACEIs) in the treatment of congestive heart failure. One may be considered, however, when an ACEI cannot be tolerated. Because they are angiotensin II blockers rather than inhibitors of ACE, ARBs do not cause increases in bradykinin levels. *ELITE II* (Pitt, 2000) compared losartan (50 mg/day) with captopril (150 mg/day) in a heart failure population (mean EF 31%). There were 280 deaths in the losartan group and 250 in the captopril group. Mortality was insignificantly higher for losartan (17.7% vs 16% for captopril). The secondary endpoint (sudden cardiac death or resuscitated cardiac arrest) favored captopril, but the improvement did not achieve statistical significance. The discontinuation rate for adverse events was significantly lower for losartan. In the doses used, losartan appears to be less effective or as effective as captopril.

CHARM-Alternative is a prospective, randomized trial (Granger, 2003) in ACE inhibitor-intolerant patients with CHF. Patients were randomized to candesartan (target dose: 32 mg/day; mean dose at 6 months: 23 mg/day) or placebo. Baseline characteristics included NYHA Class II or III (97% of patients), and mean LVEF 30%. Therapy included beta-blocker (55%), diuretic (86%), spironolactone (24%), and digitalis (46%). During a 33-month follow-up, the combined primary endpoint (CV death or heart failure hospitalizations) was significantly reduced in the candesartan group mainly because of reduced hospitalization. Death due to cardiovascular disease was not significantly different. There were significantly more MIs (75) in the candesartan group than in the placebo group (48). Candesartan was discontinued because of hypotension, renal dysfunction, and hyperkalemia.

Congestive Heart Failure: Concomitant ACE-I Therapy: The *Val-HeFT study* (Cohn, 2001) randomized CHF patients maintained on standard therapy to valsartan (320 mg/day; mean dose 254 mg/day) or placebo. The primary outcome was mortality and a combined endpoint of morbidity and mortality (cardiac arrest, hospitalization for CHF, need for intravenous inotrope or vasodilator). Patients (5010 in number) with predominately NYHA class II or III heart failure (85% on diuretic; 67% on digoxin; 35% on beta-blocker; ~93% on ACEI; 5% on spironolactone) were randomized to valsartan or placebo. The mean duration of follow-up was 23 months. Overall mortality was similar in both groups. The incidence of combined endpoints was lower with valsartan than placebo (p=.009) primarily because of decreased heart failure hospitalizations in the valsartan group. In a posthoc analysis of the endpoints in subgroups defined by baseline treatments (ACEI or beta-blockers), valsartan had a positive effect on patients receiving neither or one of these drugs. A higher incidence of mortality was seen in patients receiving valsartan in combination with an ACEI and a beta-blocker.

CHARM-Added trial is a prospective, randomized trial (McMurray, 2003) evaluating the addition of candesartan therapy (target dose: 32 mg/day; mean dose at 6 months: 24 mg/day) to CHF patients maintained on an ACEI. Baseline characteristics: NYHA class II (24%), class III (73%), and mean LVEF 28%. Baseline therapy was similar to CHARM-Alternative except all patients were maintained on an ACEI and ~55% were on a beta-blocker. The median duration of follow-up was 41 months. The combined primary endpoint (CV death or heart failure hospitalizations) was significantly reduced in the candesartan group.

Hypertension: According to the 2003 JNC 7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Myocardial Infarction: The 2004 ACC/AHA STEMI guidelines suggest an angiotensin receptor blocker should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF <0.4. The *OPTIMAAL trial* evaluated whether losartan (50 mg/day) would be superior or noninferior to captopril (150 mg/day) in post-MI patients. They were randomized to one of two treatments and followed up for 2.7 years. There was no difference between the two treatment groups (499 deaths in losartan group; 447 deaths in the captopril-treated group). The VALIANT trial compared the effects of valsartan, captopril, and the combination in patients who had suffered a recent MI (0.5 to 10 days prior) complicated by left ventricular systolic dysfunction (Pfeffer, 2003). The primary endpoint was mortality from any cause. Mortality in the valsartan group and the valsartan-captopril group was similar to the captopril group alone. Valsartan was found to be noninferior to captopril in this patient population. Combining valsartan with captopril increased the rate of adverse events without improving survival. Hypotension and renal dysfunction were more common in the valsartan group. Cough, rash, and taste disturbances were more common in the captopril group.

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Anesthesia and Critical Care Concerns/Other Considerations The angiotensin II receptor antagonists appear to have similar indications as the ACE inhibitors. In heart failure, the angiotensin II antagonists are especially useful in providing an alternative therapy in those patients who have intractable cough in response to ACE inhibitor therapy. Candesartan has been studied as an alternative therapy in chronic heart failure patients who cannot tolerate an ACE-I (CHARM-Alternative) and as an added therapy in heart failure patients who are maintained on an ACE-I (CHARM-Added). In both studies, the combined endpoint of cardiovascular death or heart failure hospitalizations was significantly improved over the placebo-treated group. Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control.

Index Terms Candesartan Cilexetil

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International Brand Names Amias (GB, IE); Atacand (AR, AT, AU, BB, BE, BF, BJ, BM, BR, BS, BZ, CH, CI, CN, CO, CR, CZ, DE, DK, DO, EE, ES, ET, FI, FR, GH, GM, GN, GR, GT, GY, HN, IE, IL, JM, KE, KP, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, PA, PL, PT, SC, SD, SE, SG, SL, SN, SR, SV, TN, TT, TZ, UG, UY, ZA, ZM, ZW); Bilaten (CN); Blopress (AE, AT, BH, BR, CH, CL, CO, CY, DE, EC, EG, HK, ID, IL, IQ, IR, IT, JO, JP, KW, LB, LY, MX, MY, OM, PE, PH, PK, PL, QA, SA, SY, TH, VE, YE); Blox (CN); Candesar (IN); Kenzen (FR); Tiadyl (AR, PY)

Candida albicans (*Monilia*)'; return;">

Candida albicans (*Monilia*)

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Jump To Field (Select Field Name)

Pronunciation(KAN dee da AL bi kans mo NIL ya)

U.S. Brand NamesCandinÂŽ

Pharmacologic CategoryDiagnostic Agent

Use: Labeled IndicationsScreen for detection of nonresponsiveness to antigens in immunocompromised individuals

Dosing: AdultsScreening for anergy: Intradermal: 0.1 mL, examine reaction site in 24-48 hours; induration âĽ5 mm in diameter is a positive reaction

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

StorageRefrigerate.

Pregnancy Risk FactorC

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 0.1 mL/dose (1 mL)

Generic AvailableNo

Related Information

- Skin Tests

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms*Monilia* Skin Test

Cantharidin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(kan THAR e din)
Canadian Brand NamesCanthacur速; Cantharone速
Pharmacologic CategoryKeratolytic Agent
Use: Labeled IndicationsRemoval of ordinary and periungual warts
Dosing: AdultsWarts: Topical: Apply directly to lesion, cover with nonporous tape, remove tape in 24 hours, reapply if necessary
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
ContraindicationsHypersensitivity to cantharidin or any component of the formulation
Pregnancy Risk FactorC
Adverse Reactions1% to 10%:

Cardiovascular: Syncope

Central nervous system: Delirium, ataxia

Dermatologic: Dermal irritation, dermal burns, acantholysis

Gastrointestinal: GI hemorrhage, rectal bleeding, dysphagia

Genitourinary: Priapism

Hepatic: Fatty degeneration

Neuromuscular & skeletal: Hyper-reflexia

Ocular: Conjunctivitis, iritis, keratitis

Renal: Proteinuria, hematuria

Respiratory: Burning of oropharynx

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.
Generic AvailableNo
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause delirium
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesCanthacur (CA); Cantharone (CA)

CAP

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Bladder Cancer]

Regimen UseBladder cancer

Regimen

Cyclophosphamide: I.V.: 400 mg/m^2 day 1

[total dose = 400 mg/m^2]

Doxorubicin: I.V.: 40 mg/m^2 day 1

[total dose = 40 mg/m^2]

Cisplatin: I.V.: 60 mg/m^2 day 1

[total dose = 60 mg/m^2]

Repeat cycle every 21 days

References

Eagan RT, Frytak S, Creagan ET, et al, âPhase II Study of Cyclophosphamide, Adriamycin, and Cis-Dichlorodiammineplatinum (II) by Infusion in Patients With Adenocarcinoma and Large Cell Carcinoma of the Lung,â *Cancer Treat Rep*, 1979, 63(9-10):1589-91.[PubMed 227597]

Capecitabine + Docetaxel (Breast Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Breast Cancer]

Regimen UseBreast cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Capecitabine: Oral: 1250 mg/m^2 twice daily days 1 to 14

[total dose/cycle = 35,000 mg/m^2]

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 3 weeks

Variation 2:

Capecitabine: Oral: 1000 mg/m^2 twice daily days 2 to 15

[total dose/cycle = 28,000 mg/m^2]

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 3 weeks

Variation 3:

Capecitabine: Oral: 937.5 mg/m^2 twice daily days 2 to 15

[total dose/cycle = 26,250 mg/m^2]

Docetaxel: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 3 weeks

References

Variation 1:

O'Shaughnessy J, Miles D, Vukelja S, et al, “Superior Survival With Capecitabine Plus Docetaxel Combination Therapy in Anthracycline-Pretreated Patients With Advanced Breast Cancer: Phase III Trial Results,” *J Clin Oncol*, 2002, 20(12):2812-23.[PubMed 12065558]

Variation 2:

Lebowitz PF, Eng-Wong J, Swain SM, et al, “A Phase II Trial of Neoadjuvant Docetaxel and Capecitabine for Locally Advanced Breast Cancer,” *Clin Cancer Res*, 2004, 10(20):6764-9.[PubMed 15501952]

Variation 3:

Lebowitz PF, Eng-Wong J, Swain SM, et al, “A Phase II Trial of Neoadjuvant Docetaxel and Capecitabine for Locally Advanced Breast Cancer,” *Clin Cancer Res*, 2004, 10(20):6764-9.[PubMed 15501952]

Capecitabine + Docetaxel (Gastric Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Gastric Cancer

Regimen Use Gastric cancer

Regimen NOTE: Multiple variations are listed below

Variation 1:

Capecitabine: Oral: 1000 mg/m^2 twice daily days 1 to 14

[total dose/cycle = 28,000 mg/m^2]

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 3 weeks

Variation 2:

Capecitabine: Oral: 1000 mg/m^2 twice daily days 1 to 14

[total dose/cycle = 28,000 mg/m^2]

Docetaxel: I.V.: 36 mg/m^2 days 1 and 8

[total dose/cycle = 72 mg/m^2]

Repeat cycle every 3 weeks

References

Variation 1:

Kim JG, Sohn SK, Kim DH, et al, “Phase II Study of Docetaxel and Capecitabine in Patients With Metastatic or Recurrent Gastric Cancer,” *Oncology*, 2005, 68(2-3):190-5. [PubMed 16006756]

Variation 2:

Chun JH, Kim HK, Lee JS, et al, “Weekly Docetaxel in Combination With Capecitabine in Patients With Metastatic Gastric Cancer,” *Am J Clin Oncol*, 2005, 28(2):188-94.[PubMed 15803015]

Capecitabine-Docetaxel (NSCLC)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lung Cancer (Nonsmall Cell)

Regimen Use Lung cancer, nonsmall cell

Regimen NOTE: Multiple variations are listed below

Variation 1:

Capecitabine: Oral: 1000 mg/m^2 twice daily days 1 to 14

[total dose/cycle = 28,000 mg/m^2]

Docetaxel: I.V.: 36 mg/m^2 days 1 and 8

[total dose/cycle = 72 mg/m^2]

Repeat cycle every 3 weeks

Variation 2:

Capecitabine: Oral: 625 mg/m^2 twice daily days 5 to 18

[total dose/cycle = 17,500 mg/m^2]

Docetaxel: I.V.: 36 mg/m^2 days 1, 8, and 15

[total dose/cycle = 108 mg/m^2]

Repeat cycle every 4 weeks

References

Variation 1:

Han JY, Lee DH, Kim HY, et al, “A Phase II Study of Weekly Docetaxel Plus Capecitabine for Patients With Advanced Nonsmall Cell Lung Carcinoma,” *Cancer*, 2003, 98(9):1918-24. [PubMed 14584075]

Variation 2:

Kindwall-Keller T, Otterson GA, Young D, et al, “Phase II Evaluation of Docetaxel-Modulated Capecitabine in Previously Treated Patients With Non-Small Cell Lung Cancer,” *Clin Cancer Res*, 2005, 11(5):1870-6.[PubMed 15756012]

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer
Regimen Use Breast cancer
Index Terms Lapatinib-Capecitabine
Regimen

Capecitabine: Oral: 1000 mg/m^2 twice daily days 1 to 14

[total dose/cycle = 28,000 mg/m^2]

Lapatinib: Oral: 1250 mg/day days 1 to 21

[total dose/cycle = 26,250 mg]

Repeat cycle every 3 weeks

References

Geyer CE, Forster J, Lindquist D, et al, "Lapatinib Plus Capecitabine for HER2-Positive Advanced Breast Cancer," *N Engl J Med*, 2006, 355(26):2733-43.[PubMed 17192538]

Capecitabine-Trastuzumab

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Breast Cancer](#)

Regimen UseBreast cancer

Index TermsTrastuzumab-Capecitabine

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cycle 1:

Capecitabine: Oral: 1250 mg/m^2 twice daily days 1 to 14

[total dose/cycle 1 = 35,000 mg/m^2]

Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1 cycle 1

followed by I.V.: 2 mg/kg/day days 8 and 15 cycle 1

[total dose/cycle 1 = 8 mg/kg]

Treatment cycle is 21 days

Subsequent cycles:

Capecitabine: Oral: 1250 mg/m^2 twice daily days 1 to 14

[total dose/cycle = 35,000 mg/m^2]

Trastuzumab: I.V.: 2 mg/kg/day days 1, 8, and 15

[total dose/cycle = 6 mg/kg]

Repeat cycle every 21 days

Variation 2:

Cycle 1:

Capecitabine: Oral: 1250 mg/m^2 twice daily days 1 to 14

[total dose/cycle 1 = 35,000 mg/m^2]

Trastuzumab: I.V.: 8 mg/kg (loading dose) day 1 cycle 1

[total dose/cycle 1 = 8 mg/kg]

Treatment cycle is 21 days

Subsequent cycles:

Capecitabine: Oral: 1250 mg/m^2 twice daily days 1 to 14

[total dose/cycle = 35,000 mg/m^2]

Trastuzumab: I.V.: 6 mg/kg day 1

[total dose/cycle = 6 mg/kg]

Repeat cycle every 21 days

References

Variation 1:

Schaller G, Fuchs I, Gonsch T, et al, "Phase II Study of Capecitabine Plus Trastuzumab in Human Epidermal Growth Factor Receptor 2 Overexpressing Metastatic Breast Cancer Pretreated With Anthracyclines or Taxanes," *J Clin Oncol*, 2007, 25(22):3246-50.[PubMed 17577021]

Variation 2:

Bartsch R, Wenzel C, Altorjai G, et al, "Capecitabine and Trastuzumab in Heavily Pretreated Metastatic Breast Cancer," *J Clin Oncol*, 2007, 25(25):3853-8.[PubMed 17679724]

Capecitabine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Xeloda® may be confused with Xenical®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ka pe SITE a been)

U.S. Brand NamesXeloda®

Canadian Brand NamesXeloda®

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite; Antineoplastic Agent, Antimetabolite (Pyrimidine Analog)

Use: Labeled IndicationsTreatment of metastatic colorectal cancer; adjuvant therapy of Dukes' C colon cancer; treatment of metastatic breast cancer

Use: Unlabeled/InvestigationalTreatment of gastric cancer, pancreatic cancer, esophageal cancer, ovarian cancer, metastatic renal cell cancer, neuroendocrine tumors, metastatic CNS lesions

Dosing: Adults**Note:** Details concerning dosing in combination regimens should also be consulted. Capecitabine toxicities, particularly hand-foot syndrome, may be higher in North American populations (for the treatment of colorectal cancer); therapy initiation at doses of 1000 mg/m^2 twice daily (for 2 weeks every 21 days) may be considered (Haller, 2006; NCCN Colon Cancer Guidelines)

Metastatic breast cancer, metastatic colorectal cancer: Oral: 1250 mg/m^2 twice daily (morning and evening) for 2 weeks, every 21 days

Adjuvant therapy of Dukes' C colon cancer: Recommended for a total of 24 weeks (8 cycles of 2 weeks of drug administration and 1 week rest period.

Pancreatic cancer (unlabeled use): 1000-1250 mg/m^2 twice daily (morning and evening) for 2 weeks, every 21 days

Dosing: ElderlyThe elderly may be more sensitive to the toxic effects of fluorouracil. Insufficient data are available to provide dosage modifications.

Dosing: Renal Impairment

Cl$_{cr}$ 51-80 mL/minute: No adjustment of initial dose.

Cl$_{cr}$ 30-50 mL/minute: Administer 75% of normal dose.

Cl$_{cr}$ <30 mL/minute: Use is contraindicated.

Dosing: Hepatic Impairment

Mild-to-moderate impairment: No starting dose adjustment is necessary; however, carefully monitor patients.

Severe hepatic impairment: Patients have not been studied.

Dosing: Adjustment for Toxicity

Dosage modification guidelines: See table.

Refer to package labeling for modifications when administered in combination with docetaxel.

Recommended Dose Modifications

Toxicity NCI Grades	During a Course of Therapy (Monotherapy)	Dose Adjustment for Next Cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to grade 0-1	100%

2nd appearance	Interrupt until resolved to grade 0-1	75%
3rd appearance	Interrupt until resolved to grade 0-1	50%
4th appearance	Discontinue treatment permanently	
Grade 3		
1st appearance	Interrupt until resolved to grade 0-1	75%
2nd appearance	Interrupt until resolved to grade 0-1	50%
3rd appearance	Discontinue treatment permanently	
Grade 4		
1st appearance	Discontinue permanently	
	or	
	If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%

Dosage adjustments for hematologic toxicity in combination therapy with ixabepilone:

Neutrophils $<500/\text{mm}^3$ for ≥7 days or neutropenic fever: Hold for concurrent diarrhea or stomatitis until neutrophils recover to $>1000/\text{mm}^3$, then continue at same dose

Platelets $<25{,}000/\text{mm}^3$ (or $<50{,}000/\text{mm}^3$ with bleeding): Hold for concurrent diarrhea or stomatitis until platelets recover to $>50{,}000/\text{mm}^3$, then continue at same dose

Dosing: Combination Regimens

Biliary adenocarcinoma: Gemcitabine-Capecitabine

Breast cancer:

- Bevacizumab-Capecitabine
- Capecitabine + Docetaxcel (Breast Cancer)
- Capecitabine + Lapatinib
- Capecitabine-Trastuzumab
- Ixabepilone-Capecitabine
- TEX (Capecitabine + Docetaxel + Epirubicin)

Colorectal cancer: XelOx

Esophageal cancer: Epirubicin-Oxaliplatin-Capecitabine

Gastric cancer:

- Capecitabine + Docetaxel (Gastric Cancer)
- Epirubicin-Oxaliplatin-Capecitabine

Lung cancer (nonsmall cell): Capecitabine + Docetaxel (NSCLC)

Pancreatic cancer: Gemcitabine-Capecitabine

Calculations

- Body Surface Area: Adults
- Creatinine Clearance: Adults

Administration: OralUsually administered in 2 divided doses taken 12 hours apart. Doses should be taken with water within 30 minutes after a meal.

Dietary ConsiderationsBecause current safety and efficacy data are based upon administration with food, it is recommended that capecitabine be administered with food. In all clinical trials, patients were instructed to take with water within 30 minutes after a meal.

StorageStore at room temperature of 25°C (77°F); excursions between 15°C and 30°C (59°F and 86°F) permitted.

Extemporaneously PreparedCapecitabine oral solution: A solution of capecitabine in water may be prepared by adding 2000 mg capecitabine (powder) to 200 mL water. Capecitabine tablets are water soluble (data on file from Roche). Administer immediately after preparation, 30 minutes after a meal. Use appropriate precautions for handling and disposal.

> Judson IR, Beale PJ, Trigo JM, et al, "A Human Capecitabine Excretion Balance and Pharmacokinetic Study After Administration of a Single Oral Dose of ^{14}C-Labelled Drug," *Invest New Drugs*, 1999, 17(1):49-56.

ContraindicationsHypersensitivity to capecitabine, fluorouracil, or any component of the formulation; known deficiency of dihydropyrimidine dehydrogenase (DPD); severe renal impairment (Cl_{cr} <30 mL/minute)

Warnings/Precautions

Boxed warnings:

- Warfarin: See "Concurrent drug therapy issues" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Cardiotoxicity: There has been cardiotoxicity associated with fluorinated pyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death, ECG changes, and cardiomyopathy. These adverse events may be more common in patients with a history of coronary artery disease.
- Diarrhea: Can cause severe diarrhea; median time to first occurrence is 34 days; subsequent doses should be reduced after grade 3 or 4 diarrhea or recurrence of grade 2 diarrhea.
- Hand-and-foot syndrome: May cause hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) is characterized by numbness, dysesthesia/paresthesia, tingling, painless or painful swelling, erythema, desquamation, blistering, and severe pain. If grade 2 or 3 hand-and-foot syndrome occurs, interrupt administration of capecitabine until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-and-foot syndrome, decrease subsequent doses of therapy.
- Necrotizing enterocolitis (typhlitis): Has been reported.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with bone marrow suppression.
- Dihydropyrimidine dehydrogenase (DPD) deficiency: Rare and unexpected severe toxicity (stomatitis, diarrhea, neutropenia, neurotoxicity) may be attributed to dihydropyrimidine dehydrogenase (DPD) deficiency.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment; reduce dose with moderate impairment and carefully monitor and reduce subsequent dose (with any grade 2 or higher adverse effect) with mild-to-moderate impairment.

Concurrent drug therapy issues:

- Alkylating therapy: Use with caution in patients who have received alkylating therapy.
- Fluorouracil/leucovorin (FU/LV): In patients with colorectal cancer, treatment with capecitabine immediately following 6 weeks of FU/LV therapy has been associated with an increased incidence of grade ≥3 toxicity, when compared to patients receiving the reverse sequence, capecitabine (two 3-week courses) followed by FU/LV (Hennig, 2008).
- Warfarin: **[U.S. Boxed Warning]: Capecitabine may increase the anticoagulant effects of warfarin; monitor closely.**

Special populations:

- Elderly: Use with caution in patients ≥80 years of age.
- Pediatrics: Safety and efficacy have not been established in children.
- Pelvic radiation therapy recipients: Use with caution in patients who have received extensive pelvic radiation.

Geriatric ConsiderationsPatients ≥80 years of age may experience a greater incidence of grade 3 or 4 adverse events (diarrhea, hand-and-foot syndrome, nausea/vomiting).

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenicity and fetal loss. There are no adequate and well-controlled studies in pregnant women; however, fetal harm may occur. Women of childbearing potential should avoid pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if the drug is excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving capecitabine therapy.

Adverse ReactionsFrequency listed derived from monotherapy trials.

>10%:

Cardiovascular: Edema (9% to 15%)

Central nervous system: Fatigue (16% to 42%), fever (7% to 18%), pain (12%)

Dermatologic: Palmar-plantar erythrodysesthesia (hand-and-foot syndrome) (54% to 60%; grade 3: 11% to 17%; may be dose limiting), dermatitis (27% to 37%)

Gastrointestinal: Diarrhea (47% to 57%; may be dose limiting; grade 3: 12% to 13%; grade 4: 2% to 3%), nausea (34% to 53%), vomiting (15% to 37%), abdominal pain (7% to 35%), stomatitis (22% to 25%), appetite decreased (26%), anorexia (9% to 23%), constipation (9% to 15%)

Hematologic: Lymphopenia (94%; grade 4: 14%), anemia (72% to 80%; grade 4: <1% to 1%), neutropenia (2% to 26%; grade 4: 2%), thrombocytopenia (24%; grade 4: 1%)

Hepatic: Bilirubin increased (22% to 48%; grades 3/4: 11% to 23%)

Neuromuscular & skeletal: Paresthesia (21%)

Ocular: Eye irritation (13% to 15%)

Respiratory: Dyspnea (14%)

5% to 10%:

Cardiovascular: Venous thrombosis (8%), chest pain (6%)

Central nervous system: Headache (5% to 10%), lethargy (10%), dizziness (6% to 8%), insomnia (7% to 8%), mood alteration (5%), depression (5%)

Dermatologic: Nail disorder (7%), rash (7%), skin discoloration (7%), alopecia (6%), erythema (6%)

Endocrine & metabolic: Dehydration (7%)

Gastrointestinal: Motility disorder (10%), oral discomfort (10%), dyspepsia (6% to 8%), upper GI inflammatory disorders (colorectal cancer: 8%), hemorrhage (6%), ileus (6%), taste perversion (colorectal cancer: 6%)

Neuromuscular & skeletal: Back pain (10%), weakness (10%), neuropathy (10%), myalgia (9%), arthralgia (8%), limb pain (6%)

Ocular: Abnormal vision (colorectal cancer: 5%), conjunctivitis (5%)

Respiratory: Cough (7%)

Miscellaneous: Viral infection (colorectal cancer: 5%)

<5%: Abdominal distension, angina, appetite increased, arthritis, ascites, asthma, ataxia, atrial fibrillation, bone pain, bradycardia, bronchitis, bronchopneumonia, bronchospasm, cachexia, cardiac arrest, cardiac failure, cardiomyopathy, cerebral vascular accident, cholestasis, coagulation disorder, colitis, confusion, deep vein thrombosis, diaphoresis, duodenitis, dysarthria, dysphagia, dysrhythmia, ecchymoses, ECG changes, encephalopathy, epistaxis, esophagitis, fibrosis, fungal infection, gastric ulcer, gastritis, gastroenteritis, hematemesis, hemoptysis, hepatic fibrosis, hepatitis, hoarseness, hot flushes, hypokalemia, hypomagnesemia, hyper-/hypotension, hypersensitivity, hypertriglyceridemia, idiopathic thrombocytopenia purpura, ileus, impaired balance, infection, influenza-like illness, intestinal obstruction (~1%), irritability, joint stiffness, keratoconjunctivitis, laryngitis, leukopenia, loss of consciousness, lymphedema, MI, myocardial ischemia, myocarditis, necrotizing enterocolitis (typhlitis), nocturia, oral candidiasis, pericardial effusion, thrombocytopenic purpura, pancytopenia, photosensitivity reaction, pneumonia, proctalgia, pruritus, pulmonary embolism, radiation recall syndrome, renal impairment, respiratory distress, sedation, sepsis, skin ulceration, sore throat, tachycardia, thirst, thrombophlebitis, toxic megacolon, tremor, ventricular extrasystoles, vertigo, weight gain

Postmarketing and/or case reports: Hepatic failure, lacrimal duct stenosis, multifocal leukoencephalopathy

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Phenytoin: Capecitabine may increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Capecitabine may increase the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Food reduced the rate and extent of absorption of capecitabine.

Monitoring ParametersRenal function should be estimated at baseline to determine initial dose. During therapy, CBC with differential, hepatic function, and renal function should be monitored.

Nursing: Physical Assessment/MonitoringMonitor coagulation parameters regularly for patients receiving an oral coumarin-derivative anticoagulant. Assess results of laboratory tests (renal and hepatic function, CBC with differential) at baseline and during therapy. Monitor therapeutic response and adverse reactions (eg, gastrointestinal disturbance [nausea, vomiting, pain, dehydration, or severe diarrhea that can occur at any time during therapy], hematologic [lymphopenia, anemia, thrombocytopenia], cardiovascular [edema, chest pain], and paresthesia) periodically during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsRenal function should be estimated at baseline to determine initial dose. During therapy, CBC with differential, hepatic function, and renal function should be monitored.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take with water within 30 minutes after meal. Avoid use of antacids within 2 hours of taking this medication. Do not crush, chew, or dissolve tablets. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause lethargy, dizziness, visual changes, confusion, anxiety (avoid driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, loss of appetite, or dry mouth (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); loss of hair (will grow back when treatment is discontinued); photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); or dry, itchy, skin, and dry or irritated eyes (avoid contact lenses). Report persistent diarrhea or abdominal pain; skin rash, pain, tenderness, or peeling (especially hands and feet); chills or fever, confusion, persistent or violent vomiting; respiratory difficulty; chest pain or palpitations; unusual bleeding or bruising; bone pain; muscle spasms/tremors; or vision changes immediately. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Xeloda®: 150 mg, 500 mg

Generic AvailableNo

ManufacturerRoche Laboratories Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Xeloda)

150 mg (60): $371.93

500 mg (120): $2408.11

Mechanism of ActionCapecitabine is a prodrug of fluorouracil. It undergoes hydrolysis in the liver and tissues to form fluorouracil which is the active moiety. Fluorouracil is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G_1 and S phases of the cell cycle.

Pharmacodynamics/Kinetics

Absorption: Rapid and extensive

Protein binding: <60%; ~35% to albumin

Metabolism:

Hepatic: Inactive metabolites: 5′-deoxy-5-fluorocytidine, 5′-deoxy-5-fluorouridine

Tissue: Active metabolite: Fluorouracil

Half-life elimination: 0.5-1 hour

Time to peak: 1.5 hours; Fluorouracil: 2 hours

Excretion: Urine (96%, 57% as α-fluoro-β-alanine); feces (<3%)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, abnormal taste, and taste disturbance.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause dizziness or insomnia

Mental Health: Effects on Psychiatric TreatmentNeutropenia is common; use caution with clozapine and carbamazepine

Index TermsNSC-712807

References

Cartwright TH, Cohn A, Varkey JA, et al, “Phase II Study of Oral Capecitabine in Patients With Advanced or Metastatic Pancreatic Cancer,” J Clin Oncol, 2002, 20(1):160-4. [PubMed 11773165]

Cassidy J, Tabernero J, Twelves C, et al, "XELOX (Capecitabine Plus Oxaliplatin): Active First-Line Therapy for Patients With Metastatic Colorectal Cancer," *J Clin Oncol*, 2004, 22(11):2084-91.[PubMed 15169795]

Haller DG, Cassidy J, Clarke S, et al, “Tolerability of Fluoropyrimidines Appears to Differ by Region,” *J Clin Oncol*, 2006, 24(18S):3514 [abstract from 2006 ASCO Annual Meeting Proceedings]

Hennig IM, Naik JD, Brrown S, et al, “Severe Sequence-Specific Toxicity When Capecitabine is Given After Fluorouracil and Leucovorin,” *J Clin Oncol*, 2008, 26(20):3411-7.[PubMed 18612156]

Hoff PM, Ansari R, Batist G, et al, “Comparison of Oral Capecitabine Versus Intravenous Fluorouracil Plus Leucovorin as First-Line Treatment in 605 Patients With Metastatic Colorectal Cancer: Results of a Randomized Phase III Study,” *J Clin Oncol*, 2001, 19(8):2282-92. [PubMed 11304782]

Ishitsuka H, “Capecitabine: Preclinical Pharmacology Studies,” *Invest New Drugs*, 2000, 18(4):343-54. [PubMed 11081570]

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International Brand NamesApecitab (AR); Xeloda (AR, AT, AU, BB, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CZ, DE, DK, EC, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, ID, IE, IL, IN, IS, IT, JM, KE, KP, LR, LU, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, PE, PH, PK, PL, PT, PY, RU, SC, SD, SE, SG, SL, SN, SR, TH, TN, TR, TT, TZ, UG, UY, VE, ZA, ZM, ZW)

Capreomycin

Lexi-Drugs Online

English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Capastat® may be confused with Cepastat®

Pronunciation(kap ree oh MYE sin)

U.S. Brand NamesCapastat® Sulfate

Pharmacologic CategoryAntibiotic, Miscellaneous; Antitubercular Agent

Use: Labeled IndicationsTreatment of tuberculosis in conjunction with at least one other antituberculosis agent

Dosing: AdultsTuberculosis: I.M., I.V.: 1 g/day (maximum: 20 mg/kg/day) for 60-120 days, followed by 1 g 2-3 times/week **or** 15 mg/kg/day (maximum: 1 g/dose) for 2-4 months, followed by 15 mg/kg (maximum: 1 g/dose) 2-3 times/week (*MMWR*, 2003)

Dosing: ElderlyRefer to adult dosing. Use with caution due to the increased potential for pre-existing renal dysfunction or impaired hearing. The manufacturer recommends initiating at lower end of dosing range. Adults >59 years of age: 10 mg/kg (maximum: 750 mg/dose) for 5-7 days per week for 2-4 months, followed by 10 mg/kg (maximum: 750 mg/dose) 2-3 times/week (*MMWR*, 2003).

Dosing: PediatricTuberculosis: I.M., I.V.:

Infants and Children <15 years and ≤40 kg (unlabeled use): 15-30 mg/kg/day (maximum: 1 g/day) for 2-4 months, followed by 15-30 mg/kg (maximum: 1 g/day) twice weekly (*MMWR*, 2003)

Children ≥15 years or >40 kg (unlabeled use): 15 mg/kg/day (maximum: 1 g/dose) for 2-4 months followed by 15 mg/kg (maximum: 1 g/dose) 2-3 times/week (*MMWR*, 2003)

Dosing: Renal ImpairmentAdults:

The FDA-approved labeling contains the following renal dosing adjustment guidelines (maximum: 1 g/dose):

Cl_{cr} 110 mL/minute: Administer 13.9 mg/kg every 24 hours

Cl_{cr} 100 mL/minute: Administer 12.7 mg/kg every 24 hours

Cl_{cr} 80 mL/minute: Administer 10.4 mg/kg every 24 hours

Cl_{cr} 60 mL/minute: Administer 8.2 mg/kg every 24 hours

Cl_{cr} 50 mL/minute: Administer 7 mg/kg every 24 hours **or** 14 mg/kg every 48 hours

Cl_{cr} 40 mL/minute: Administer 5.9 mg/kg every 24 hours **or** 11.7 mg/kg every 48 hours

Cl_{cr} 30 mL/minute: Administer 4.7 mg/kg every 24 hours **or** 9.5 mg/kg every 48 hours **or** 14.2 mg/kg every 72 hours

Cl_{cr} 20 mL/minute: Administer 3.6 mg/kg every 24 hours **or** 7.2 mg/kg every 48 hours **or** 10.7 mg/kg every 72 hours

Cl_{cr} 10 mL/minute: Administer 2.4 mg/kg every 24 hours **or** 4.9 mg/kg every 48 hours **or** 7.3 mg/kg every 72 hours

Cl_{cr} 0 mL/minute: Administer 1.3 mg/kg every 24 hours **or** 2.6 mg/kg every 48 hours **or** 3.9 mg/kg every 72 hours

The following (unlabeled) guidelines may also be used:

MMWR, 2003:

Cl_{cr} ≥30 mL/minute: No adjustment required

Cl_{cr} <30 mL/minute and hemodialysis: 12-15 mg/kg (maximum: 1 g/dose) 2-3 days per week (**NOT** daily)

Aronoff, 2007:

Cl_{cr} ≥10 mL/minute: 1 g every 24 hours

Cl_{cr} <10 mL/minute: 1 g every 48 hours

Hemodialysis: Administer dose after hemodialysis only

Continuous renal replacement therapy (CRRT): 5 mg/kg every 24 hours

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Administer by deep I.M. injection into a large muscle mass.
Administration: I.V.Administer over 60 minutes.
StoragePowder for injection should be stored at room temperature of 15°C to 30°C (59°F to 86°F). Following reconstitution, may store under refrigeration for up to 24 hours.
ReconstitutionDissolve powder with 2 mL of NS or SWFI; allow 2-3 minutes for dissolution.

For I.V. administration: Further dilute in NS 100 mL.

For I.M. administration:

1 g dose: Administer contents of reconstituted vial

<1 g dose: See table:

Capreomycin Dilution for Doses <1 g (I.M. Administration)

Diluent Volume (mL)	**Capreomycin Solution Volume (mL)**	**Final Concentration (approximate)**
2.15	2.85	370 mg/mL
2.63	3.33	315 mg/mL
3.3	4	260 mg/mL
4.3	5	210 mg/mL

ContraindicationsHypersensitivity to capreomycin or any component of the formulation
Warnings/Precautions

Boxed warnings:

- Auditory impairment: See "Disease-related concerns and Concurrent drug therapy issues" below.
- Pediatrics: See "Special populations" below.
- Pregnancy: See "Special populations" below.
- Renal impairment: See "Disease-related concerns and Concurrent drug therapy issues" below.

Concerns related to adverse effects:

- Electrolyte imbalance: Hypocalcemia, hypokalemia, and hypomagnesemia have been reported with use.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Auditory impairment: **[U.S. Boxed Warning]: Use in patients with pre-existing auditory impairment must be undertaken with great caution, and the risk of additional eighth nerve impairment should be weighed against the benefits to be derived from therapy.**
- Renal impairment: **[U.S. Boxed Warning]: Use in patients with renal impairment must be undertaken with great caution, and the risk of additional renal injury should be weighed against the benefits to be derived from therapy.** Dosage reductions are recommended for known or suspected renal impairment.

Concurrent drug therapy issues:

- Drugs with ototoxic or nephrotoxic potential: **[U.S. Boxed Warning]: Use with nonantituberculous drugs (ie, aminoglycoside antibiotics) having ototoxic or nephrotoxic potential should be undertaken only with great caution.**
- Parenteral antituberculous agents: **[U.S. Boxed Warning]: Since other parenteral antituberculous agents (eg, streptomycin) also have similar and sometimes irreversible toxic effects, particularly on eighth cranial nerve and renal function, simultaneous administration of these agents with capreomycin is not recommended.**

Special populations;

- Elderly: Use with caution in the elderly.
- Pediatrics: **[U.S. Boxed Warning]: Safety has not been established in children.**

- Pregnancy: **[U.S. Boxed Warning]: Safety has not been established in pregnant women.**

Geriatric ConsiderationsHas not been studied in the elderly. I.M. administration may limit use due to painful injection or lack of sites in patients with decreased muscle mass. Use with caution in patients with pre-existing hearing impairment due to potential ototoxicity.

Pregnancy Risk FactorC

Pregnancy ConsiderationsCapreomycin has been shown to be teratogenic in animal studies. **[U.S. Boxed Warning]: Safety has not been established in pregnant women**; use during pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Otic: Ototoxicity (subclinical hearing loss: 11%; clinical loss: 3%)

Renal: Nephrotoxicity (36%, increased BUN)

1% to 10%: Hematologic: Eosinophilia (dose related, mild)

<1%, postmarketing, and/or case reports: Acute tubular necrosis, Bartter's syndrome, creatinine increased, hypersensitivity (maculopapular rash, urticaria and/or fever), hypocalcemia, hypokalemia, hypomagnesemia, injection site reactions (abscess, bleeding, induration and pain), leukocytosis, leukopenia, liver function decreased (BSP excretion decreased), renal injury, thrombocytopenia (rare), tinnitus, toxic nephritis, urinary sediment abnormal, vertigo

Drug Interactions

Aminoglycosides: Capreomycin may enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Capreomycin may enhance the neuromuscular-blocking effect of Colistimethate. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Capreomycin may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Polymyxin B: Capreomycin may enhance the neuromuscular-blocking effect of Polymyxin B. *Risk C: Monitor therapy*

Monitoring ParametersAudiometric measurements and vestibular function at baseline and during therapy; renal function at baseline and weekly during therapy; frequent assessment of serum electrolytes (including calcium, magnesium, and potassium), liver function tests

Reference RangeRecommended concentration for susceptibility testing: 10 mcg/mL

Monitoring: Lab TestsAudiometric measurements and vestibular function at baseline and during therapy; renal function at baseline and weekly during therapy; frequent assessment of serum electrolytes (including calcium, magnesium, and potassium), liver function tests

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as sulfate:

Capastat® Sulfate: 1 g

Generic AvailableNo

Mechanism of ActionCapreomycin is a cyclic polypeptide antimicrobial. It is administered as a mixture of capreomycin IA and capreomycin IB. The mechanism of action of capreomycin is not well understood. Mycobacterial species that have become resistant to other agents are usually still sensitive to the action of capreomycin. However, significant cross-resistance with viomycin, kanamycin, and neomycin occurs.

Pharmacodynamics/Kinetics

Half-life elimination: Normal renal function: 4-6 hours; Cl_{cr} 100-110 mL/minute: 5-6 hours; Cl_{cr} 50-80 mL/minute: 7-10 hours; Cl_{cr} 20-40 mL/minute: 12-20 hours; Cl_{cr} 10 mL/minute: 29 hours; Cl_{cr} 0 mL/minute: 55 hours

Time to peak, serum: I.M.: 1-2 hours

Excretion: Urine (52% within 12 hours)

Related Information

- Antimicrobial Drugs of Choice
- Tuberculosis

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCapreomycin Sulfate

References

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Lehmann CR, Garrett LE, Winn RE, et al, “Capreomycin Kinetics in Renal Impairment and Clearance by Hemodialysis,” *Am Rev Respir Dis*, 1988, 138(5):1312-3.[PubMed 2462388]

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International Brand NamesCapacin (KP); Capastat (AT, AU, CZ, ES, GB, GR, IE, PL); Kapocin (IN)

Capsaicin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Zostrix® may be confused with Zestril®, Zovirax®

Pronunciation(kap SAY sin)

U.S. Brand NamesCapzasin-HP® [OTC]; Capzasin-P® [OTC]; DiabetAid Pain and Tingling Relief [OTC]; Zostrix® Neuropathy [OTC]; Zostrix® [OTC]; Zostrix®-HP [OTC]

Canadian Brand NamesZostrix®; Zostrix® H.P.

Pharmacologic CategoryAnalgesic, Topical; Topical Skin Product

Use: Labeled IndicationsTopical treatment of pain associated with postherpetic neuralgia, rheumatoid arthritis, osteoarthritis, diabetic neuropathy; postsurgical pain

Use: Unlabeled/InvestigationalTreatment of pain associated with psoriasis, chronic neuralgias unresponsive to other forms of therapy, and intractable pruritus

Use: DentalPotential use as topical agent in burning mouth syndrome and oral mucositis

Dosing: AdultsTreatment of pain: Topical: Apply to affected area at least 3-4 times/day; application frequency less than 3-4 times/day prevents the total depletion, inhibition of synthesis, and transport of substance P resulting in decreased clinical efficacy and increased local discomfort

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren >10 years: Refer to adult dosing.

Administration: TopicalWear gloves to apply; wash hands with soap and water after applying to avoid spreading to eyes or other sensitive areas of the body.

ContraindicationsHypersensitivity to capsaicin or any component of the formulation

Warnings/Precautions

Other warnings/precautions:

- Appropriate use: For external use only; avoid contact with eyes. Should not be applied to broken or irritated skin. Affected area should not be tightly bandaged.

Geriatric ConsiderationsCapsaicin products are available over-the-counter. Counsel patients about the appropriate use of these products. The American College of Rheumatology recommends capsaicin for the symptomatic treatment of osteoarthritis of the knee.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Dermatologic: Itching, stinging sensation, erythema

Local: Transient burning on application which usually diminishes with repeated use

Respiratory: Cough

Metabolism/Transport Effects**Substrate** of CYP2E1 (minor)

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, topical: 0.025% (60 g); 0.075% (60 g)

Capzasin-P®: 0.025% (45 g)

Capzasin-HP®: 0.075% (45 g)

Zostrix®: 0.025% (60 g)

Zostrix®-HP: 0.075% (60 g)

Zostrix® Neuropathy: 0.25% (60 g) [in Lidocare™ vehicle]

Lotion, topical:

DiabetAid Pain and Tingling Relief: 0.025% (120 mL)

Generic AvailableYes: Cream

Pricing: U.S. (www.drugstore.com)

Cream (Zostrix-HP)

0.075% (56.6): $16.71

Mechanism of ActionInduces release of substance P, the principal chemomediator of pain impulses from the periphery to the CNS, from peripheral sensory neurons; after repeated application, capsaicin depletes the neuron of substance P and prevents reaccumulation

Pharmacodynamics/Kinetics

Onset of action: 14-28 days

Peak effect: 4-6 weeks of continuous therapy

Duration: Several hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

"Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee: 2000 Update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines," *Arthritis Rheum*, 2000, 43(9):1905-15.[PubMed 11014340]

International Brand NamesAntidol Forte (UY); Axsain (GB, IE); Capsain-P (IN); Capsidol (ES, MX); Capsina (NO, SE); Casacin (TW); Casacine (CO); Diaxen Cream (KP); Dipental Cream (KP); Dolpyc (BE, IT); Gelcen (ES); Hercap (BR); Katrum (ES); Moment (BR); Neodor (PT); Presyc (CN); Presyc Forte (CN); Priltam (ES); Redol (AR); Zostrix Cream (AU, IL, KP); Zostrix-HP (AU, IL)

Captopril and Hydrochlorothiazide

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(KAP toe pril & hye droe klor oh THYE a zide)

U.S. Brand NamesCapozide®

Canadian Brand NamesCapozide®

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Diuretic, Thiazide

Use: Labeled IndicationsManagement of hypertension

Dosing: AdultsHypertension, CHF: May be substituted for previously titrated dosages of the individual components; alternatively, may initiate as follows: Oral:

Initial: Single tablet (captopril 25 mg/hydrochlorothiazide 15 mg) taken once daily; daily dose of captopril should not exceed 150 mg; daily dose of hydrochlorothiazide should not exceed 50 mg

Dosing: ElderlyRefer to dosing in individual monographs.

Dosing: Renal ImpairmentMay respond to smaller or less frequent doses.

ContraindicationsHypersensitivity to captopril, any other ACE inhibitor, hydrochlorothiazide, sulfonamide-derived drugs, or any component of the formulation; angioedema or serious hypersensitivity related to previous treatment with an ACE inhibitor; anuria

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required, especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use is contraindicated with previous angioedema associated with ACE inhibitor therapy.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Electrolyte disturbances: Hyperkalemia may occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Captopril has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Closely monitor CBC with differential for the first 3 months of therapy and periodically thereafter in these patients. Onset of neutropenia is usually within 3 months of captopril initiation. Neutrophil count generally returns to baseline within 2 weeks of discontinuation.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity. Hydrochlorothiazide can cause systemic lupus erythematosus (SLE) exacerbation or activation.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use captopril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use ACE inhibitors with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment. Patients with renal impairment may be at increased risk for hematologic toxicity. Avoid hydrochlorothiazide in severe renal disease (ineffective). Contraindicated in anuric patients.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsCombination products are not recommended for first-line treatment and divided doses of diuretics may increase the incidence of nocturia in the elderly.
Pregnancy Risk FactorC/D (2nd and 3rd trimesters)
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/compatible
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsCaptopril: **Substrate** of CYP2D6 (major)
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure; BUN, serum creatinine, and electrolytes; in patients with renal impairment and/or collagen vascular disease, closely monitor CBC with differential for the first 3 months of therapy and periodically thereafter.

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsBUN, serum creatinine, and electrolytes; in patients with renal impairment and/or collagen vascular disease, closely monitor CBC with differential for the first 3 months of therapy and periodically thereafter.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

25/15: Captopril 25 mg and hydrochlorothiazide 15 mg

25/25: Captopril 25 mg and hydrochlorothiazide 25 mg

50/15: Captopril 50 mg and hydrochlorothiazide 15 mg

50/25: Captopril 50 mg and hydrochlorothiazide 25 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Capozide)

50-25 mg (30): $95.55

Tablets (Captopril-Hydrochlorothiazide)

25-15 mg (90): $44.99

25-25 mg (90): $44.99

50-15 mg (60): $53.99

50-25 mg (60): $53.99

Mechanism of ActionCaptopril is a competitive inhibitor of angiotensin-converting enzyme (ACE); prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. This results in lower levels of angiotensin II which causes an increase in plasma renin activity and a reduction in aldosterone secretion. Hydrochlorothiazide inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Captopril
- Hydrochlorothiazide

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or insomnia

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for captopril and hydrochlorothiazide combination therapy may include improved compliance and synergistic reductions in blood pressure with an accomplished reduction in side effects. See Cardiovascular Considerations for individual agents.

Index TermsHydrochlorothiazide and Captopril

References

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Moser M and Black HR, “The Role of Combination Therapy in the Treatment of Hypertension,” *Am J Hypertens*, 1998, 11(6 Pt 2):73S-8S, 95S-100S.[PubMed 9655566]

International Brand NamesAcediur (IT); Acenorm (DE); Aceplus (IT, NL); Acezide (GB); Adcomp (DE); Capozid (DK); Capozide (BB, BM, BS, BZ, CH, DE, GB, GY, ID, IE, JM, MX, NL, NZ, PE, PH, PK, SR, TT, VE, ZA); Capozide Forte (AT); Capozit (KP); Caprizide (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Captea (FR); Captopress (GR); Captoprilan-D (DO); Ecazide (CN, FR); Jutacor Comp (AE, BH, CY, DE, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Lopiretic (PT); Lopril-D (BR); Zapto-Co (ZA)

Captopril

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Captopril may be confused with Capitrol®, carvedilol

International issues:

Acepril® [Great Britain] may be confused with Accupril® which is a brand name for quinapril in the U.S.

Acepril®: Brand name for enalapril in Hungary and Switzerland; brand name for lisinopril in Denmark

Pronunciation(KAP toe pril)

U.S. Brand NamesCapoten®

Canadian Brand NamesAlti-Captopril; Apo-Capto®; Capoten™; Gen-Captopril; Novo-Captopril; Nu-Capto; PMS-Captopril

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor

Use: Labeled IndicationsManagement of hypertension; treatment of heart failure, left ventricular dysfunction after myocardial infarction, diabetic nephropathy

Use: Unlabeled/InvestigationalTo delay the progression of nephropathy and reduce risks of cardiovascular events in hypertensive patients with type 1 or 2 diabetes mellitus; treatment of hypertensive crisis, rheumatoid arthritis; diagnosis of anatomic renal artery stenosis, hypertension secondary to scleroderma renal crisis; diagnosis of aldosteronism, idiopathic edema, Bartter's syndrome, postmyocardial infarction for prevention of ventricular failure; increase circulation in Raynaud's phenomenon, hypertension secondary to Takayasu's disease

Dosing: Adults**Note:** Titrate dose according to patient's response.

Acute hypertension (urgency/emergency): Oral: 12.5-25 mg, may repeat as needed (may be given sublingually, but no therapeutic advantage demonstrated)

Hypertension: Oral: Initial: 12.5-25 mg 2-3 times/day; may increase by 12.5-25 mg/dose at 1- to 2-week intervals up to 50 mg 3 times/day. Maximum: 150 mg 3 times/day. Add diuretic before further dosage increases.

Usual dose range (JNC 7): 25-100 mg/day in 2 divided doses

Congestive heart failure: Oral:

Initial: 6.25-12.5 mg 3 times/day in conjunction with cardiac glycoside and diuretic therapy. Initial dose depends upon patient's fluid/electrolyte status.

Target: 50 mg 3 times/day

Prevention of LV dysfunction following MI: Oral: Initial: 6.25 mg; followed by 12.5 mg 3 times/day; increase to 25 mg 3 times/day over the next few days; following by gradual increase to a goal of 50 mg 3 times/day (Some dosage schedules increase the dosage more aggressively to achieve goal dosage within the first few days of initiation).

Diabetic nephropathy: Oral:

25 mg 3 times/day. May be taken with other antihypertensive therapy if required to further lower blood pressure.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Titrate dose according to patient's response.

Hypertension: Oral:

Infants: Initial: 0.15-0.3 mg/kg/dose; titrate dose upward to maximum of 6 mg/kg/day in 1-4 divided doses; usual required dose: 2.5-6 mg/kg/day

Children: Initial: 0.5 mg/kg/dose; titrate upward to maximum of 6 mg/kg/day in 2-4 divided doses.

Older Children: Initial: 6.25-12.5 mg/dose every 12-24 hours; titrate upward to maximum of 6 mg/kg/day.

Adolescents: Initial: 12.5-25 mg/dose given every 8-12 hours; increase by 25 mg/dose to maximum of 450 mg/day.

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer 75% of normal dose.

Cl_{cr} <10 mL/minute: Administer 50% of normal dose.

Note: Smaller dosages given every 8-12 hours are indicated in patients with renal dysfunction. Renal function and leukocyte count should be carefully monitored during therapy.

Hemodialysis effects: Moderately dialyzable (20% to 50%); administer dose postdialysis or administer 25% to 35% supplemental dose.

Peritoneal dialysis: Supplemental dose is not necessary.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralUnstable in aqueous solutions; to prepare solution for oral administration, mix prior to administration and use within 10 minutes.

Dietary ConsiderationsShould be taken at least 1 hour before or 2 hours after eating.

Extemporaneously PreparedCaptopril has limited stability in aqueous preparations. The addition of an antioxidant (sodium ascorbate) has been shown to increase the stability of captopril in solution; captopril (1 mg/mL) in syrup with methylcellulose is stable for 7 days stored either at 4°C or 22°C; captopril (1 mg/mL) in distilled water (no additives) is stable for 14 days if stored at 4°C and 7 days if stored at 22°C; captopril (1 mg/mL) with sodium ascorbate (5 mg/mL) in distilled water is stable for 56 days at 4°C and 14 days at 22°C.

Captopril (0.75 mg/mL) in cherry syrup is stable for only 2 days in amber clear plastic containers stored at room temperature or under refrigeration; captopril (0.75 mg/mL) in either a 1:1 mixture of Ora-Sweet® and Ora-Plus® or a 1:1 mixture of Ora-Sweet® SF and Ora-Plus® is stable for 10 days or less depending on the storage temperature (see Allen, 1996).

Powder papers can also be made; powder papers are stable for 12 weeks when stored at room temperature

Allen LV and Erickson III MA, “Stability of Baclofen, Captopril, Diltiazem Hydrochloride, Dipyridamole, and Flecainide Acetate in Extemporaneously Compounded Oral Liquids,” *Am J Health Syst Pharm*, 1996, 53:2179-84.

Nahata MC, Morosco RS, and Hipple TF, “Stability of Captopril in Three Liquid Dosage Forms,” *Am J Hosp Pharm*, 1994, 51(1):95-6.

Taketomo CK, Chu SA, Cheng MH, et al, “Stability of Captopril in Powder Papers Under Three Storage Conditions,” *Am J Hosp Pharm*, 1990, 47(8):1799-1801.

ContraindicationsHypersensitivity to captopril, any other ACE inhibitor, or any component of the formulation; angioedema related to previous treatment with an ACE inhibitor

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Captopril has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Closely monitor CBC with differential for the first 3 months of therapy and periodically thereafter in these patients. Onset of neutropenia is usually within 3 months of captopril initiation. Neutrophil count generally returns to baseline within 2 weeks of discontinuation.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment.

Special populations:

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric Considerations Due to frequent decreases in glomerular filtration (also Cl_{cr}) with aging, elderly patients may have exaggerated responses to ACE inhibitors; differences in clinical response due to hepatic changes are not observed. ACE inhibitors may be preferred agents in elderly patients with congestive heart failure and diabetes mellitus. Diabetic proteinuria is reduced and insulin sensitivity is enhanced. In general, the side effect profile is favorable in the elderly and causes little or no CNS confusion; use lowest dose recommendations initially. Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.

Pregnancy Risk Factor C (1st trimester); D (2nd and 3rd trimesters)

Pregnancy Considerations Due to adverse events observed in some animal studies, captopril is considered pregnancy category C during the first trimester. Based on human data, captopril is considered pregnancy category D if used during the second and third trimesters (per the manufacturer; however, one study suggests that fetal injury may occur at anytime during pregnancy). Captopril crosses the placenta and may affect ACE activity in the fetus. First trimester exposure to ACE inhibitors may cause major congenital malformations. An increased risk of cardiovascular and/or central nervous system malformations was observed in one study; however, an increased risk of teratogenic events was not observed in other studies. Second and third trimester use of an ACE inhibitor is associated with oligohydramnios. Oligohydramnios due to decreased fetal renal function may lead to fetal limb contractures, craniofacial deformation, and hypoplastic lung development. The use of ACE inhibitors during the second and third trimesters is also associated with anuria, hypotension, renal failure (reversible or irreversible), skull hypoplasia, and death in the fetus/neonate. Chronic maternal hypertension itself is also associated with adverse events in the fetus/infant. ACE inhibitors are not recommended during pregnancy to treat maternal hypertension or heart failure. Those who are planning a pregnancy should be considered for other medication options if an ACE inhibitor is currently prescribed or the ACE inhibitor should be discontinued as soon as possible once pregnancy is detected. The exposed fetus should be monitored for fetal growth, amniotic fluid volume, and organ formation. Infants exposed to an ACE inhibitor *in utero*, especially during the second and third trimester, should be monitored for hyperkalemia, hypotension, and oliguria.

[U.S. Boxed Warning]: Based on human data, ACE inhibitors can cause injury and death to the developing fetus when used in the second and third trimesters. ACE inhibitors should be discontinued as soon as possible once pregnancy is detected.

Lactation Enters breast milk/not recommended (AAP rates "compatible")

Breast-Feeding Considerations Captopril is excreted in breast milk. Breast-feeding is not recommended by the manufacturer. The American Academy of Pediatrics considers captopril to be "usually compatible with breast-feeding."

Pregnancy & Lactation, In-Depth

- Captopril in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Cardiovascular: Hypotension (1% to 3%), tachycardia (1%), chest pain (1%), palpitation (1%)

Dermatologic: Rash (maculopapular or urticarial) (4% to 7%), pruritus (2%); in patients with rash, a positive ANA and/or eosinophilia has been noted in 7% to 10%.

Endocrine & metabolic: Hyperkalemia (1% to 11%)

Hematologic: Neutropenia may occur in up to 4% of patients with renal insufficiency or collagen-vascular disease.

Renal: Proteinuria (1%), serum creatinine increased, worsening of renal function (may occur in patients with bilateral renal artery stenosis or hypovolemia)

Respiratory: Cough (<1% to 2%)

Miscellaneous: Hypersensitivity reactions (rash, pruritus, fever, arthralgia, and eosinophilia) have occurred in 4% to 7% of patients (depending on dose and renal function); dysgeusia - loss of taste or diminished perception (2% to 4%)

Frequency not defined:

Cardiovascular: Angioedema, cardiac arrest, cerebrovascular insufficiency, rhythm disturbances, orthostatic hypotension, syncope, flushing, pallor, angina, MI, Raynaud's syndrome, CHF

Central nervous system: Ataxia, confusion, depression, nervousness, somnolence

Dermatologic: Bullous pemphigus, erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis

Endocrine & metabolic: Alkaline phosphatase increased, bilirubin increased, gynecomastia

Gastrointestinal: Pancreatitis, glossitis, dyspepsia

Genitourinary: Urinary frequency, impotence

Hematologic: Anemia, thrombocytopenia, pancytopenia, agranulocytosis, anemia

Hepatic: Jaundice, hepatitis, hepatic necrosis (rare), cholestasis, hyponatremia (symptomatic), transaminases increased

Neuromuscular & skeletal: Asthenia, myalgia, myasthenia

Ocular: Blurred vision

Renal: Renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria

Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis

Miscellaneous: Anaphylactoid reactions

<1% (Limited to important or life-threatening; frequency ≤ to placebo): Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, xerostomia, dyspnea, alopecia, paresthesia, angina, glomerulonephritis, cholestatic jaundice, psoriasis, hyperthermia, myalgia, arthralgia

Postmarketing and/or case reports: Aplastic anemia, hemolytic anemia, bronchospasm, alopecia, systemic lupus erythematosus, Kaposi's sarcoma, pericarditis, exacerbations of Huntington's disease, Guillain-Barré syndrome, seizure (in premature infants). A syndrome which may include fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash, eosinophilia, and elevated ESR has been reported for captopril and other ACE inhibitors.

Metabolism/Transport Effects **Substrate** of CYP2D6 (major)
Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Captopril serum concentrations may be decreased if taken with food. Long-term use of captopril may result in a zinc deficiency which can result in a decrease in taste perception.

Herb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, california poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Test InteractionsPositive Coombs' [direct]; may cause false-positive results in urine acetone determinations using sodium nitroprusside reagent

Monitoring ParametersBUN, electrolytes, serum creatinine; blood pressure. In patients with renal impairment and/or collagen vascular disease, closely monitor CBC with differential for the first 3 months of therapy and periodically thereafter.

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions (especially anything that may impact renal function). Patient should be closely monitored when beginning therapy (anaphylactic reaction or severe angioedema can occur). Assess results of laboratory tests (renal function), therapeutic effectiveness (blood pressure), and adverse response (eg, hypovolemia, angioedema, postural hypotension) when beginning therapy, adjusting dosage, and on a regular basis during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsBUN, electrolytes, serum creatinine; in patients with renal impairment and/or collagen vascular disease, closely monitor CBC with differential for the first 3 months of therapy and periodically thereafter

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Do not use potassium supplement or salt substitutes without consulting prescriber. Take exactly as directed; do not discontinue this medication without consulting prescriber. Take first dose at bedtime. Take all doses on an empty stomach, 1 hour before or 2 hours after meals. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); or nausea, vomiting, abdominal pain, dry mouth, or transient loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report immediately swelling or numbness of face, mouth, or throat; unusual chest pain or palpitations; decreased urinary output; fever or chills; swelling of extremities; skin rash; numbness, tingling, or pain in muscles; respiratory difficulty or unusual cough; and other persistent adverse reactions. **Pregnancy precautions** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 12.5 mg, 25 mg, 50 mg, 100 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Capoten)

100 mg (60): $240.90

Tablets (Captopril)

12.5 mg (100): $11.99

25 mg (90): $13.99

50 mg (100): $15.67

100 mg (90): $19.99

Mechanism of ActionCompetitive inhibitor of angiotensin-converting enzyme (ACE); prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor; results in lower levels of angiotensin II which causes an increase in plasma renin activity and a reduction in aldosterone secretion

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Blood pressure reduction: 1-1.5 hours after dose

Duration: Dose related, may require several weeks of therapy before full hypotensive effect

Absorption: 60% to 75%; reduced 30% to 40% by food

Protein binding: 25% to 30%

Metabolism: 50%

Half-life elimination (renal and cardiac function dependent):

Adults, healthy volunteers: 1.9 hours; Heart failure: 2.06 hours; Anuria: 20-40 hours

Time to peak: 1 hour

Excretion: Urine (>95%) within 24 hours (40% to 50% as unchanged drug)

Related Information

- Angiotensin Agents
- Antacid Drug Interactions
- Heart Failure (Systolic)
- Hypertension

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Loss or diminished perception of taste and orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or insomnia

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Congestive Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines recommend that ACE inhibitors be used in patients with a reduced EF (with or without heart failure symptoms) unless contraindicated. ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. In this situation, they decrease hospitalizations for, and retard progression to, congestive heart failure. When used in patients with heart failure, the target dose should be achieved, if possible. Lower daily doses of ACE inhibitors have demonstrated the same mortality effects as high doses, but have not decreased hospitalizations to the extent that high-dose ACE inhibitors have, as demonstrated in the ATLAS study (Packer M, 1999).

Hypertension: The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) can be beneficial in patients with hypertension and LVH without symptoms of heart failure. JNC 7 suggests that patients can benefit from treatment with an ACE inhibitor if they have hypertension **and** heart failure, acute myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, history of stroke.

Vascular Disease: The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors can be useful in preventing heart failure in patients who have a history of atherosclerotic vascular disease, diabetes, or hypertension with associated cardiovascular risk factors. The HOPE trial (Heart Outcomes Prevention Evaluation Study Investigators, 2000) investigated the value of an ACE inhibitor (ramipril 5-10 mg daily) versus placebo in patients who had evidence of vascular disease or diabetes (one other cardiovascular risk factor) and were at least 55 years of age. Patients were excluded if they had a low ejection fraction, heart failure, or were on an ACE inhibitor. The primary outcome was a composite of death from cardiovascular cause, myocardial infarction, or stroke; 9297 patients were enrolled and randomized. Ramipril significantly reduced the risk of death from CV causes, MI, or stroke over placebo. New cases of diabetes were also reduced in the ramipril group. In the EUROPA trial, patients with stable coronary artery disease (at low risk for cardiovascular events) received perindopril or placebo and were evaluated for incidence of cardiovascular events after 4 years of treatment. In this randomized, placebo-controlled, prospective study, 12,218 patients received either perindopril (8 mg/day, n=6110) or placebo (n=6108) and were assessed for the primary endpoint of a cardiovascular event, defined as cardiovascular death, myocardial infarction, or cardiac arrest. The study population was well balanced with respect to baseline demographics and concomitant medication use (including beta-blockers, platelet inhibitors, antihyperlipidemics, calcium channel blockers, nitrates, and diuretics). Intent-to-treat analysis revealed that 603 (10%) of placebo patients experienced the primary endpoint of a cardiovascular event compared to 488 (8%) of perindopril-receiving patients, for a 20% relative risk reduction (p=0.0003). This result was not influenced by presence of other comorbidities (eg, diabetes, hypertension) or concomitant beta-blocker, calcium channel blocker, or lipid-lowering therapies. Withdrawal from the study (postrandomization) due to adverse reactions was similar between treatment groups. Number needed to treat analysis suggests that treatment of 50 patients over a 4-year period will prevent one major cardiovascular event.

Acute Coronary Syndromes: In the treatment of unstable angina/non-ST-segment elevation MI, ACE inhibitors are recommended when hypertension persists despite treatment with nitroglycerin and a beta-blocker in patients with LV systolic dysfunction or CHF and in ischemic patients with diabetes (Class I). ACE inhibitors are also recommended for all post-ACS individuals (Class IIa). According to 2004 ACC/AHA STEMI guidelines, an ACE inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF <0.4, in the absence of hypotension or known contraindications to this class of medicines. In the emergency management of complicated STEMI, a short-acting ACEI (eg, captopril 1-6.25 mg) may be added once the patient's systolic blood pressure is >100 mm Hg and not <30 mm Hg below baseline. The VALIANT trial evaluated the effects of valsartan (target dose: 160 mg twice daily), captopril (target dose: 50 mg twice daily), and the combination (target doses: valsartan 80 mg twice daily and captopril 150 mg once daily) in a randomized, double-blind trial of patients with acute MI (0.5-10 days post-MI) complicated by left ventricular systolic dysfunction, heart failure, or both. Enrollment in the study numbered 14,703 patients and followed for a median of 24.7 months. There was no difference in the primary endpoint (all cause mortality) among the 3 groups. There was no difference in incidence of CV death, recurrent MI, or hospitalization for heart failure either. Hypotension and renal dysfunction occurred significantly more often in the valsartan group than captopril alone. Cough, rash, and taste disturbances occurred more often in the captopril group. The authors (Pfeffer MA, 2003) concluded that valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after MI. Combining valsartan with captopril increased the rate of adverse events without improving survival.

Potential Adverse Events: ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. In those patients experiencing cough on an ACE inhibitor, the ACE inhibitor may be discontinued and, if necessary, ARB therapy instituted. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Drug Interactions: Concomitant indomethacin therapy may blunt the reduction in sitting and 24-hour ambulatory diastolic blood pressure. Use of NSAIDs should be avoided or limited, with monitoring of blood pressure control in this setting. In patients with heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

Anesthesia and Critical Care Concerns/Other ConsiderationsSevere hypotension may occur in patients who are sodium and/or volume depleted.

ACE inhibitors are indicated in patients postmyocardial infarction in whom left ventricular ejection fraction is <40%. When used in patients with heart failure, the target dose of 50 mg 3 times/day should be achieved, if possible. Lower daily doses of ACE inhibitors have not demonstrated the same cardioprotective effects.

ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Index TermsACE

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International Brand Names Ace-Bloc (TW); Acenorm (AU); Acepress (ID, IT); Acepril (GB); Aceril (IL); Aceten (IN); Adocor (DE); Altran (CO); Antasten (AR); Apuzin (MY); Asisten (UY); Capace (ZA); Capomed (PH); Caposan (PE); Capoten (AU, BB, BE, BM, BR, BS, BZ, CL, CN, CO, CZ, DK, ES, ET, FI, GB, GR, GY, HK, ID, IE, IT, JM, KE, LU, MY, NG, NL, NO, PH, PK, PT, SE, SR, TH, TT, TZ, UG, VE, ZA, ZM); Capotena (MX); Capotril (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Capril (KP, TW); Captace (PH); Captensin (ID); Captodoc (DE); Captoflux (DE); Captohexal (AU, EE, LU, PL); Captolane (FR); Captopren (AE, BH, CO, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Captopril (DO, PL); Captopril Pharmavit (HU); Captoprilan (DO); Captotec (BR); Captral (MX); Cardiagen (DE); Catoplin (SG); Cesplon (ES); Debax (AT); Dexacap (ID); Ecapres (DO); Ecaten (MX); Epsitron (HK, TH); Farcopril (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Farmoten (ID); Forten (ID); Hartylox (PH); Hiperil (PT); Huma-Captopril (HU); Hypopress (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Hypotensor (GR); Katopril (AU); Locap (ID); Lopirin (AT, CH, DE); Lopril (FI, FR); Lotensin (ID); Midrat (MX); Minitent (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Nolectin (PE); Otoryl (ID); Praten (ID); Prelat (PH); Primace (PH); Properil (CN); Retensin (PH); Rilcapton (HK, SG); Ropril (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Tenofax (ID); Tensicap (ID); Tensiomen (BG, HN); Tensiomin (HU); Tensobon (DE); Tensoril (PH); Topace (AU); Unihype (PH); Vasosta (PH); Zapto (ZA)

Carbachol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Isopto® Carbachol may be confused with Isopto® Carpine

Pronunciation(KAR ba kole)

U.S. Brand NamesIsopto® Carbachol; Miostat®

Canadian Brand NamesIsopto® Carbachol; Miostat®

Pharmacologic CategoryCholinergic Agonist; Ophthalmic Agent, Antiglaucoma; Ophthalmic Agent, Miotic

Use: Labeled IndicationsLowers intraocular pressure in the treatment of glaucoma; cause miosis during surgery

Dosing: Adults

Glaucoma: Ophthalmic: Instill 1-2 drops up to 3 times/day

Ophthalmic surgery (miosis): Intraocular: 0.5 mL instilled into anterior chamber before or after securing sutures

Dosing: ElderlyRefer to adult dosing.

Administration: Other

Ophthalmic: Finger pressure should be applied on the lacrimal sac for 1-2 minutes following topical instillation; remove excess around the eye with a tissue.

Intraocular: Instillation for miosis prior to eye surgery should be gentle and parallel to the iris face and tangential to the pupil border; discard unused portion. Do not inject >0.5 mL into the anterior chamber. Instillation may occur before or after securing sutures. Sterile technique must be used.

Storage

Intraocular: Store at room temperature of 15°C to 30°C (59°F to 86°F).

Topical: Store at 8°C to 27°C (46°F to 80°F).

ContraindicationsHypersensitivity to carbachol or any component of the formulation; acute iritis, acute inflammatory disease of the anterior chamber

Warnings/Precautions

Disease-related concerns:

- Asthma: Use with caution in patients with asthma.
- Corneal abrasion: Use with caution in the presence of corneal abrasion.
- Gastrointestinal disease: Use with caution in patients with peptic ulcer disease or gastrointestinal spasm.
- Heart failure: Use with caution in patients with acute heart failure.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Parkinson's disease: Use with caution in patients with Parkinson's disease.
- Urinary tract obstruction: Use with caution in patients with urinary tract obstruction.

Concurrent drug therapy issues:

- General anesthesia: Use with caution in patients undergoing general anesthesia.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsAssess patient's ability to self-administer.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, flushing, hypotension, syncope

Central nervous system: Headache

Gastrointestinal: Abdominal cramps, diarrhea, epigastric distress, salivation, vomiting

Genitourinary: Urinary bladder tightness

Ocular: Bullous keratopathy, burning (transient), ciliary spasm, conjunctival injection, corneal clouding, irritation, postoperative iritis (following cataract extraction), retinal detachment, stinging (transient)

Respiratory: Asthma

Miscellaneous: Diaphoresis

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Patient EducationMay sting on instillation. May cause headache, altered distance vision, and decreased night vision. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, intraocular:

Miostat®): 0.01% (1.5 mL)

Solution, ophthalmic:

Isopto® Carbachol: 1.5% (15 mL); 3% (15 mL) [contains benzalkonium chloride]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Isopto Carbachol)

1.5% (15): $44.08

3% (15): $55.99

Mechanism of ActionSynthetic direct-acting cholinergic agent that causes miosis by stimulating muscarinic receptors in the eye

Pharmacodynamics/Kinetics

Ophthalmic instillation:

Onset of action: Miosis: 10-20 minutes

Duration: Reduction in intraocular pressure: 4-8 hours

Intraocular administration:

Onset of action: Miosis: 2-5 minutes

Duration: 24 hours

Related Information

- Glaucoma Drug Therapy

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Increased salivation.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCarbacholine; Carbamylcholine Chloride

International Brand NamesCarbachol (PL); Doryl (CH, FI); Isopto Carbachol (AE, AU, BF, BH, BJ, CH, CI, CY, CZ, DE, EG, ET, GB, GH, GM, GN, HR, IL, IQ, IR, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PL, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Isopto Karbakolin (SE); Isopto-Carbachol (FI, IE); Karbakolin Isopto (DK); Miostat (AR, BE, BR, CH, FR, HN, IL, LU, PK, PL); Mioticol (IT); Spersacarbachol (CH)

CarBAMazepine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Carbamazepine Genetic Testing for Susceptibility to Serious Skin Reactions - December 2007; Health Canada Update - March 2008

The U.S. Food and Drug Administration (FDA) and Health Canada have alerted their respective healthcare professionals of changes to the prescribing information, including a new boxed warning, for carbamazepine products (Tegretol®, Carbatrol®, Equetro®) regarding the potential for serious, and potentially fatal, skin reactions in susceptible patients. Individuals who possess a genetic susceptibility marker known as the *HLA-B*1502* allele have an increased risk of developing Stevens-Johnson syndrome (SJS) and/or toxic epidermal necrolysis (TEN) (usually manifests within first few months of treatment) compared to persons without this genotype. The presence of this genetic variant exists in up to 15% of people of Asian descent, varying from <1% in Japanese and Koreans, to 2% to 4% of South Asians and Indians, to 10% to 15% of populations from China, Taiwan, Malaysia, and the Philippines. This variant is virtually absent in those of Caucasian, African-American, Hispanic, or European ancestry. Risk assessments have suggested that incidence of SJS/TEN in Asians could be ~60 cases/10,000 new users depending on the country of origin (a nearly 10-fold higher incidence than in predominantly Caucasian populations). Presence of the *HLA-B*1502* allele may signify greater risk of developing SJS/TEN with other antiepileptic agents for which this degree of dermatologic reactions has been documented.

The manufacturers of these products now recommend genetic testing prior to initiation of therapy in most patients of Asian ancestry for the presence of this genetic marker. A positive result should preclude use of carbamazepine, unless the benefit exceeds risk. Patients with negative results are much less likely to develop a serious skin reaction, though careful monitoring is prudent. Patients (including those previously determined to harbor the *HLA-B*1502* allele) currently tolerating carbamazepine for several months are likely at a very low risk of developing these reactions.

Additional information, including a copy of the revised prescribing information can be found at:

http://www.fda.gov/cder/drug/infopage/carbamazepine/default.htm

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2008/tegretol_hpc-cps_e.html

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - February 2008

The U.S. Food and Drug Administration (FDA) is informing healthcare professionals of an increased risk of suicidality (suicidal behavior or ideation) observed from analysis of clinical studies using various antiepileptic medications compared to placebo. The analysis was performed on 199 placebo-controlled studies involving 43,892 patients (27,863 treated patients versus 16,029 placebo patients) aged ≥5 years receiving one of the following 11 drugs: carbamazepine (Carbatrol®, Equetro®, Tegretol®, Tegretol® XR), felbamate (Felbatol®), gabapentin (Neurontin®), lamotrigine (Lamictal®), levetiracetam (Keppra®), oxcarbazepine (Trileptal®), pregabalin (Lyrica®), tiagabine (Gabitril®), topiramate (Topamax®), valproate (Depakote®, Depakote® ER, Depakene®, Depacon®), and zonisamide (Zonegran®). Studies examined medication efficacy in a variety of disorders, including epilepsy, psychiatric disorders (eg, depression, bipolar disorder), and other conditions (eg, migraine, neuropathic pain). According to the FDA, the results revealed a statistically significant increased risk of suicidality in 0.43% treated patients compared to 0.22% placebo patients, or an estimated 2.1 per 1000 (95% CI: 0.7, 4.2) more patients in the treated groups relative to placebo. This increased risk was reported anywhere from 1 week of therapy through 24 weeks. However, most trials were ≤24 weeks duration and the risk of suicide extending beyond 24 weeks is currently unknown. The relative risk of suicidal behavior or ideation in the treated patients was higher for patients with epilepsy (RR=3.6) compared to patients treated for psychiatric (RR=1.6) or other conditions

(RR=2.3). Overall, the incidence of suicidal behavior or ideation occurred consistently across all demographic subgroups and with each of the drugs studied. Of note, four patients receiving an antiepileptic committed suicide relative to none in the placebo groups.

Forthcoming product labeling changes are likely to extend to all antiepileptic drugs and not limited to the drugs used in the studies, pending discussions scheduled for the upcoming advisory committee meeting. Healthcare professionals and family members/caregivers are encouraged to monitor patients receiving any antiepileptic medication for signs/symptoms of suicidality (eg, anxiety, depression, behavior changes). Patients should not stop taking their antiepileptic therapy unless advised by a healthcare professional.

Additional information can be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

CarBAMazepine may be confused with OXcarbazepine

Carbatrol® may be confused with Cartrol®

Epitol® may be confused with Epinal®

Tegretol®, Tegretol®-XR may be confused with Mebaral®, Tegrin®, Toprol-XL®, Toradol®, Trental®

Pronunciation(kar ba MAZ e peen)

U.S. Brand NamesCarbatrol®; Epitol®; Equetro®; Tegretol®; Tegretol®-XR

Canadian Brand NamesApo-Carbamazepine®; Bio-Carbamazepine; Carbamazepine; Dom-Carbamazepine; Gen-Carbamazepine CR; Mapezine®; Novo-Carbamaz; Nu-Carbamazepine; PHL-Carbamazepine; PMS-Carbamazepine; Sandoz-Carbamazepine; Taro-Carbamazepine Chewable; Tegretol®

Pharmacologic CategoryAnticonvulsant, Miscellaneous

Use: Labeled Indications

Carbatrol®, Tegretol®, Tegretol®-XR: Partial seizures with complex symptomatology (psychomotor, temporal lobe), generalized tonic-clonic seizures (grand mal), mixed seizure patterns, trigeminal neuralgia

Equetro®: Acute manic and mixed episodes associated with bipolar 1 disorder

Use: Unlabeled/InvestigationalTreatment of resistant schizophrenia, ethanol withdrawal, restless leg syndrome, post-traumatic stress disorders

Use: DentalPain relief of trigeminal or glossopharyngeal neuralgia

Dosing: AdultsDosage must be adjusted according to patient's response and serum concentrations. Administer tablets (chewable or conventional) in 2-3 divided doses daily and suspension in 4 divided doses daily. Oral:

Epilepsy: Initial: 400 mg/day in 2 divided doses (tablets or extended release tablets) or 4 divided doses (oral suspension); increase by up to 200 mg/day at weekly intervals using a twice daily regimen of extended release tablets or capsules, or a 3-4 times/day regimen of other formulations until optimal response and therapeutic levels are achieved; usual dose: 800-1200 mg/day

Maximum recommended dose: 1600 mg/day; however, some patients have required up to 1.6-2.4 g/day

Trigeminal or glossopharyngeal neuralgia: Initial: 200 mg/day in 2 divided doses (tablets, extended release tablets, or extended release capsules) or 4 divided doses (oral suspension) with food, gradually increasing in increments of 200 mg/day as needed.

Maintenance: Usual: 400-800 mg daily in 2 divided doses (tablets, extended release tablets, or extended release capsules) or 4 divided doses (oral suspension); maximum dose: 1200 mg/day

Bipolar disorder: Initial: 400 mg/day in 2 divided doses (tablets, extended release tablets, or extended release capsules) or 4 divided doses (oral suspension), may adjust by 200 mg/day increments; maximum dose: 1600 mg/day.

Note: Equetro® is the only formulation specifically approved by the FDA for the management of bipolar disorder.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDosage must be adjusted according to patient's response and serum concentrations. Administer tablets (chewable or conventional) in 2-3 divided doses daily and suspension in 4 divided doses daily.

Epilepsy: Oral:

Children <6 years: Initial: 10-20 mg/kg/day divided twice or 3 times daily as tablets or 4 times/day as suspension; increase dose every week until optimal response and therapeutic levels are achieved

Maintenance dose: Divide into 3-4 doses daily (tablets or suspension); maximum recommended dose: 35 mg/kg/day

Children 6-12 years: Initial: 200 mg/day in 2 divided doses (tablets or extended release tablets) or 4 divided doses (oral suspension); increase by up to 100 mg/day at weekly intervals using a twice daily regimen of extended release tablets or 3-4 times daily regimen of other formulations until optimal response and therapeutic levels are achieved

Maintenance: Usual: 400-800 mg/day; maximum recommended dose: 1000 mg/day

Note: Children <12 years who receive ≥400 mg/day of carbamazepine may be converted to extended release capsules (Carbatrol®) using the same total daily dosage divided twice daily

Children >12 years: Refer to adult dosing.

Maximum recommended doses:

Children 12-15 years: 1000 mg/day

Children >15 years: 1200 mg/day

Administration: Oral

Suspension: Must be given on a 3-4 times/day schedule versus tablets which can be given 2-4 times/day. Since a given dose of suspension will produce higher peak and lower trough levels than the same dose given as the tablet form, patients given the suspension should be started on lower doses given more frequently (same total daily dose) and increased slowly to avoid unwanted side effects. When carbamazepine suspension has been combined with chlorpromazine or thioridazine solutions, a precipitate forms which may result in loss of effect. Therefore, it is recommended that the carbamazepine suspension dosage form not be administered at the same time with other liquid medicinal agents or diluents. Should be administered with meals.

Extended release capsule (Carbatrol®, Equetro®): Consists of three different types of beads: Immediate release, extended-release, and enteric release. The bead types are combined in a ratio to allow twice daily dosing. May be opened and contents sprinkled over food such as a teaspoon of applesauce; may be administered with or without food; do not crush or chew.

Extended release tablet: Should be inspected for damage. Damaged extended release tablets (without release portal) should not be administered. Should be administered with meals; swallow whole, do not crush or chew.

Dietary ConsiderationsDrug may cause GI upset, take with large amount of water or food to decrease GI upset. May need to split doses to avoid GI upset.

ContraindicationsHypersensitivity to carbamazepine, tricyclic antidepressants, or any component of the formulation; bone marrow depression; with or within 14 days of MAO inhibitor use; concurrent use of nefazodone

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Blood dyscrasias: See “Concerns related to adverse effects” below.
- Dermatologic reactions: See “Special populations” below.

Concerns related to adverse effects:

- Blood dyscrasias: **[U.S. Boxed Warning]: Potentially fatal blood cell abnormalities have been reported following treatment.** A spectrum of hematologic effects has been reported with use (eg, agranulocytosis, aplastic anemia, neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias); patients with a previous history of adverse hematologic reaction to any drug may be at increased risk. Early detection of hematologic change is important; advise patients of early signs and symptoms including fever, sore throat, mouth ulcers, infections, easy bruising, petechial or purpuric hemorrhage.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Dermatologic reactions: Severe reactions, including toxic epidermal necrolysis and Stevens-Johnson syndromes, although rarely reported, have resulted in fatalities; use caution and screen for genetic susceptibility in Asian patients (see "Special populations" below); drug should be discontinued if there are any signs of hypersensitivity.
- Multiorgan hypersensitivity reactions: Potentially serious, sometimes fatal multiorgan hypersensitivity reactions have been reported with some antiepileptic drugs; monitor for signs and symptoms of possible disparate manifestations associated with lymphatic, hepatic, renal, and/or hematologic organ systems; gradual discontinuation and conversion to alternate therapy may be required.
- Psychiatric effects: May activate latent psychosis and/or cause confusion or agitation; elderly patients may be at an increased risk for psychiatric effects.

Disease-related concerns:

- Anticholinergic sensitivity: Has mild anticholinergic activity; use with caution in patients with sensitivity to anticholinergic effects (urinary retention, increased intraocular pressure, constipation).
- Cardiovascular disease: May cause conduction abnormalities; use caution in patients with underlying EKG abnormalities, pre-existing cardiac damage, or patients who are at risk for conduction abnormalities.
- Hepatic impartment: Use with caution in patients with hepatic impairment or history of hepatic porphyria; rare cases of hepatic failure have been reported.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 induces or inhibitors. Carbamazepine may significantly induce many CYP450 enzymes, including 1A2, 2B6, 2C9, 2C19, and 3A4; use with caution with medications significantly metabolized through these pathways.
- Nefazodone: Coadministration yields insufficient plasma levels of nefazodone to achieve a therapeutic effect; concurrent use is

contraindicated.

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Asian ancestry: **[U.S. Boxed Warning]: Patients of Asian descent should be screened for the variant _HLA-B*1502_** allele prior to initiating therapy. This genetic variant has been associated with a significantly increased risk of developing Stevens-Johnson syndrome and/or toxic epidermal necrolysis. Patients with a positive result should not be started on carbamazepine.

- Elderly: There may be an increased risk of SIADH-like syndrome in the elderly; may activate latent psychosis, confusion, or agitation.

- Pediatrics: Exacerbation of certain seizure types have been seen after initiation of therapy in children with mixed seizure disorders.

Dosage form specific issues:

- Suspension: Administration of the suspension will yield higher peak and lower trough serum levels than an equal dose of the tablet form; consider a lower starting dose given more frequently (same total daily dose) when using the suspension.

Other warnings/precautions:

- Appropriate use: Not effective in absence, myoclonic, or akinetic seizures; carbamazepine administration may increase the frequency of seizures in patients with these types of seizures

- Bipolar disorder use: The smallest effective dose is suggested for use in bipolar disorder to reduce the risk for overdose/suicide; high-risk patients should be monitored for suicidal ideations. Prescription should be written for the smallest quantity consistent with good patient care. Actuation of latent psychosis is possible.

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsElderly may have increased risk of SIADH-like syndrome. Elderly are more susceptible to carbamazepine-induced confusion and agitation, AV block, and bradycardia.

Pregnancy Risk FactorD

Pregnancy ConsiderationsCrosses the placenta. Dysmorphic facial features, cranial defects, cardiac defects, spina bifida, IUGR, and multiple other malformations reported. Epilepsy itself, number of medications, genetic factors, or a combination of these probably influences the teratogenicity of anticonvulsant therapy. Benefit:risk ratio usually favors continued use during pregnancy and breast-feeding. Contraceptives may be rendered less effective by the coadministration of carbamazepine; alternative methods of contraception should be considered.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsCarbamazepine and its metabolites are found in breast milk. The manufacturer does not recommend use while breast-feeding. However, AAP rates this medication "compatible" in breast-feeding.

Adverse ReactionsFrequency not defined, unless otherwise specified.

Cardiovascular: Arrhythmias, AV block, bradycardia, chest pain (bipolar use), CHF, edema, hyper-/hypotension, lymphadenopathy, syncope, thromboembolism, thrombophlebitis

Central nervous system: Amnesia (bipolar use), anxiety (bipolar use), aseptic meningitis (case report), ataxia (bipolar use 15%), confusion, depression (bipolar use), dizziness (bipolar use 44%), fatigue, headache (bipolar use 22%), sedation, slurred speech, somnolence (bipolar use 32%)

Dermatologic: Alopecia, alterations in skin pigmentation, erythema multiforme, exfoliative dermatitis, photosensitivity reaction, pruritus (bipolar use 8%), purpura, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Endocrine & metabolic: Chills, fever, hyponatremia, syndrome of inappropriate ADH secretion (SIADH)

Gastrointestinal: Abdominal pain, anorexia, constipation, diarrhea, dyspepsia (bipolar use), gastric distress, nausea (bipolar use 29%), pancreatitis, vomiting (bipolar use 18%), xerostomia (bipolar use)

Genitourinary: Azotemia, impotence, renal failure, urinary frequency, urinary retention

Hematologic: Acute intermittent porphyria, agranulocytosis, aplastic anemia, bone marrow suppression, eosinophilia, leukocytosis, leukopenia, pancytopenia, thrombocytopenia

Hepatic: Abnormal liver function tests, hepatic failure, hepatitis, jaundice

Neuromuscular & skeletal: Back pain, pain (bipolar use 12%), peripheral neuritis, weakness

Ocular: Blurred vision, conjunctivitis, lens opacities, nystagmus

Otic: Hyperacusis, tinnitus

Miscellaneous: Diaphoresis, hypersensitivity (including multiorgan reactions, may include disorders mimicking lymphoma, eosinophilia, hepatosplenomegaly, vasculitis); infection (bipolar use 12%)

Postmarketing and/or case reports: Suicidal ideation

Metabolism/Transport Effects**Substrate** of CYP2C8 (minor), 3A4 (major); **Induces** CYP1A2 (strong), 2B6 (strong), 2C8 (strong), 2C9 (strong), 2C19 (strong), 3A4 (strong)

Drug Interactions

Acetaminophen: CarBAMazepine may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Allopurinol: May increase the serum concentration of CarBAMazepine. *Risk C: Monitor therapy*

Aminocamptothecin: CarBAMazepine may decrease the serum concentration of Aminocamptothecin. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of CarBAMazepine. *Risk C: Monitor therapy*

Aripiprazole: CarBAMazepine may decrease the serum concentration of Aripiprazole. *Risk D: Consider therapy modification*

Bendamustine: CYP1A2 Inducers (Strong) may decrease the serum concentration of Bendamustine. Concentrations of active metabolites may be increased. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): CarBAMazepine may increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Dihydropyridine): CarBAMazepine may increase the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of CarBAMazepine. CarBAMazepine may increase the metabolism of Calcium Channel Blockers (Nondihydropyridine). *Risk D: Consider therapy modification*

Carbonic Anhydrase Inhibitors: May increase the serum concentration of CarBAMazepine. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Caspofungin: Inducers of Drug Clearance may decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) when coadministered with known inducers of drug clearance. *Risk D: Consider therapy modification*

Cimetidine: May increase the serum concentration of CarBAMazepine. The serum carbamazepine concentration might return to normal within one week of starting cimetidine. *Risk C: Monitor therapy*

ClomiPRAMINE: CarBAMazepine may increase the serum concentration of ClomiPRAMINE. *Risk C: Monitor therapy*

Clozapine: CarBAMazepine may increase the metabolism of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): CarBAMazepine may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CycloSPORINE: CarBAMazepine may decrease the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inducers (Strong) may increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inducers (Strong) may increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inducers (Strong) may increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inducers (Highly Effective) may increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inducers (Highly Effective) may increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Danazol: May decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Darunavir: CarBAMazepine may decrease the serum concentration of Darunavir. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: CarBAMazepine may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Doxycycline: CarBAMazepine may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Etravirine: CarBAMazepine may decrease the serum concentration of Etravirine. Management: The manufacturer of etravirine states these drugs should not be used in combination. *Risk X: Avoid combination*

Fluconazole: May decrease the metabolism of CarBAMazepine. *Risk C: Monitor therapy*

Flunarizine: CarBAMazepine may decrease the serum concentration of Flunarizine. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of CarBAMazepine. *Risk C: Monitor therapy*

Haloperidol: CarBAMazepine may increase the metabolism of Haloperidol. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Isoniazid: May decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Lacosamide: CarBAMazepine may decrease the serum concentration of Lacosamide. *Risk C: Monitor therapy*

LamoTRIgine: May enhance the adverse/toxic effect of CarBAMazepine. CarBAMazepine may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Lithium: CarBAMazepine may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of CarBAMazepine. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mebendazole: CarBAMazepine may decrease the serum concentration of Mebendazole. *Risk D: Consider therapy modification*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Methadone: CarBAMazepine may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Methylfolate: May decrease the serum concentration of CarBAMazepine. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): CarBAMazepine may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Paliperidone: CarBAMazepine may decrease the serum concentration of Paliperidone. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: CarBAMazepine may increase the metabolism of Phenytoin. Phenytoin may increase the metabolism of CarBAMazepine. CarBAMazepine may decrease the metabolism of Phenytoin. Possibly by competitive inhibition at sites of metabolism. *Risk D: Consider therapy modification*

Propoxyphene: May decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Protease Inhibitors: CarBAMazepine may increase the metabolism of Protease Inhibitors. Protease Inhibitors may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Risperidone: CarBAMazepine may decrease the serum concentration of Risperidone. *Risk C: Monitor therapy*

Rufinamide: May decrease the serum concentration of CarBAMazepine. CarBAMazepine may decrease the serum concentration of Rufinamide. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of CarBAMazepine. Specifically those SSRIs that inhibit CYP3A4 isoenzymes. CarBAMazepine may increase the metabolism of Selective Serotonin Reuptake Inhibitors. Specifically those agents metabolized via CYP1A2, 2C, and/or 3A4 isoenzymes. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Temsirolimus: CarBAMazepine may decrease the serum concentration of Temsirolimus. Concentrations of the active metabolite, sirolimus, are also likely to be decreased (and maybe to an even greater degree). Management: Temsirolimus prescribing information recommends against coadministration with strong CYP3A4 inducers such as carbamazepine; however, if concurrent therapy is necessary, an increase in temsirolimus dose to 50 mg/week should be considered. *Risk D: Consider therapy modification*

Theophylline Derivatives: CarBAMazepine may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Thyroid Products: CarBAMazepine may decrease the serum concentration of Thyroid Products. *Risk C: Monitor therapy*

Topiramate: CarBAMazepine may decrease the serum concentration of Topiramate. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: CarBAMazepine may increase the metabolism of Tricyclic Antidepressants. **Exceptions:** ClomiPRAMINE. *Risk C: Monitor therapy*

Valproic Acid: CarBAMazepine may increase the metabolism of Valproic Acid. Valproic Acid may decrease the serum concentration of CarBAMazepine. Carbamazepine-Epoxide concentrations might increase, offsetting the decreases in the parent compound. *Risk C: Monitor therapy*

Vecuronium: CarBAMazepine may decrease the serum concentration of Vecuronium. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): CarBAMazepine may decrease the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Voriconazole: CarBAMazepine may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Ziprasidone: CarBAMazepine may increase the metabolism of Ziprasidone. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Carbamazepine serum levels may be increased if taken with food. Carbamazepine serum concentration may be increased if taken with grapefruit juice; avoid concurrent use.

Herb/Nutraceutical: Avoid evening primrose (seizure threshold decreased). Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsMay interact with some pregnancy tests; increased BUN, AST, ALT, bilirubin, alkaline phosphatase (S); decreased calcium, T_3, T_4, sodium (S)

Monitoring ParametersCBC with platelet count, reticulocytes, serum iron, lipid panel, liver function tests, urinalysis, BUN, serum carbamazepine levels, thyroid function tests, serum sodium; pregnancy test; ophthalmic exams (pupillary reflexes); observe patient for excessive sedation, especially when instituting or increasing therapy; signs of rash; *HLA-B*1502* genotype screening prior to therapy initiation in patients of Asian descent.

Reference Range

Timing of serum samples: Absorption is slow, peak levels occur 6-8 hours after ingestion of the first dose; the half-life ranges from 8-60 hours, therefore, steady-state is achieved in 2-5 days

Therapeutic levels: 4-12 mcg/mL (SI: 17-51 µmol/L)

Toxic concentration: >15 mcg/mL; patients who require higher levels of 8-12 mcg/mL (SI: 34-51 µmol/L) should be watched closely. Side effects including CNS effects occur commonly at higher dosage levels. If other anticonvulsants are given therapeutic range is 4-8 mcg/mL.

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness, laboratory values, and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Observe and teach seizure/safety precautions. Monitor for mental and CNS changes, excessive sedation (especially when initiating or increasing therapy), suicide ideation. Baseline and periodic eye exams (slit lamp, funduscopy, and tonometry) are recommended. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC with platelet count, reticulocytes, serum iron, liver function tests, urinalysis, BUN, serum carbamazepine levels, thyroid function tests, serum sodium; pregnancy test; signs of rash; *HLA-B*1502* genotype screening prior to therapy initiation in patients of Asian descent.

Patient EducationTake exactly as directed; do not increase dose or frequency or discontinue this medication without consulting prescriber. Do not use extended release tablets which have been damaged or crushed. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Avoid grapefruit juice. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea, vomiting, loss of appetite, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Wear identification of epileptic status and medications. Report CNS changes, suicide ideation, mentation changes, suicidal ideation, depression, or changes in cognition; muscle cramping, weakness, tremors, sore throat, mouth ulcers, swollen glands, fever, jaundice, changes in gait; persistent GI symptoms (cramping, constipation, vomiting, anorexia); rash or skin irritations; unusual bruising or bleeding (mouth, urine, stool); or worsening of seizure activity, or loss of seizure control. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release:

Carbatrol®, Equetro®: 100 mg, 200 mg, 300 mg

Suspension, oral: 100 mg/5 mL (5 mL, 10 mL, 450 mL)

Tegretol®: 100 mg/5 mL (450 mL) [contains propylene glycol; citrus vanilla flavor]

Tablet: 200 mg

Epitol®, Tegretol®: 200 mg

Tablet, chewable: 100 mg

Tegretol®: 100 mg

Tablet, extended release:

Tegretol®-XR: 100 mg, 200 mg, 400 mg

Generic AvailableYes: Excludes capsule (extended release), tablet (extended release)

Pricing: U.S. (www.drugstore.com)

Capsule, 12-hour (Carbatrol)

100 mg (30): $45.99

200 mg (60): $86.66

300 mg (60): $82.00

Capsule, 12-hour (Equetro)

100 mg (60): $78.61

200 mg (60): $97.19

300 mg (60): $120.05

Chewable (Carbamazepine)

100 mg (60): $12.99

Chewable (Tegretol)

100 mg (60): $35.99

Suspension (Carbamazepine)

100 mg/5 mL (450): $28.26

Suspension (Tegretol)

100 mg/5 mL (450): $58.28

Tablet, 12-hour (Tegretol XR)

100 mg (30): $23.99

200 mg (30): $35.99

400 mg (30): $57.14

Tablets (Carbamazepine)

200 mg (90): $13.99

Tablets (Tegretol)

200 mg (60): $56.99

Mechanism of ActionIn addition to anticonvulsant effects, carbamazepine has anticholinergic, antineuralgic, antidiuretic, muscle relaxant, antimanic, antidepressive, and antiarrhythmic properties; may depress activity in the nucleus ventralis of the thalamus or decrease synaptic transmission or decrease summation of temporal stimulation leading to neural discharge by limiting influx of sodium ions across cell membrane or other unknown mechanisms; stimulates the release of ADH and potentiates its action in promoting reabsorption of water; chemically related to tricyclic antidepressants

Pharmacodynamics/Kinetics

Absorption: Slow

Distribution: V_d: Neonates: 1.5 L/kg; Children: 1.9 L/kg; Adults: 0.59-2 L/kg

Protein binding: Carbamazepine: 75% to 90%, may be decreased in newborns; Epoxide metabolite: 50%

Metabolism: Hepatic via CYP3A4 to active epoxide metabolite; induces hepatic enzymes to increase metabolism

Bioavailability: 85%

Half-life elimination: **Note:** Half-life is variable because of autoinduction which is usually complete 3-5 weeks after initiation of a fixed carbamazepine regimen.

Carbamazepine: Initial: 25-65 hours; Extended release: 35-40 hours; Multiple doses: Children: 8-14 hours; Adults: 12-17 hours

Epoxide metabolite: Initial: 25-43 hours

Time to peak, serum: Unpredictable:

Immediate release: Suspension: 1.5 hour; tablet: 4-5 hours

Extended release: Carbatrol®, Equetro®: 12-26 hours (single dose), 4-8 hours (multiple doses); Tegretol®-XR: 3-12 hours

Excretion: Urine 72% (1% to 3% as unchanged drug); feces (28%)

Related Information

- Adverse Effects of Approved Mood Stabilizers / Anticonvulsants
- Agents Approved for Bipolar Disorder
- Anticonvulsants by Seizure Type
- Depression
- Liquid Compatibility
- Status Epilepticus
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentThe extended-release capsule (Equetro®) is approved for acute manic and mixed episodes associated with bipolar I disorder. Like valproic acid and lithium, carbamazepine is considered a first-line agent. However, it is a significant inducer of hepatic enzymes. It is a heteroinducer and therefore, induces its own metabolism as well as metabolism of other drugs. Single-dose studies of carbamazepine show half-life ranges of 30-40 hours. After 3 weeks of continuous administration, the half-life decreases to ~20 hours. This reduction is caused by an increase in clearance resulting from autoinduction in metabolism. It is prudent to recheck serum carbamazepine levels after the first month of maintenance therapy. During chronic monotherapy, the half-life is ~12 hours and during polytherapy (with enzyme inducers; eg, phenytoin, phenobarbital), it is reduced to 8 hours. Maximal hepatic activation occurs within 2-4 weeks. Because of this, one has to be vigilant for drug-drug interactions. Studies have failed to document a correlation between plasma levels of carbamazepine and clinical response. However, correlation between CSF levels of carbamazepine's principle metabolite, the 10,11-epoxide, and clinical response in mania and depression have been observed. Therefore, this agent is best dosed clinically. Serum levels >12 mcg/mL do, however, correlate with toxicity. Carbamazepine is also used for a variety of other disorders such as aggressive behavior/episodic dyscontrol, eating disorders, alcohol withdrawal, anxiety disorders, behavioral disturbances in the developmentally disabled, and as an adjunctive agent to antipsychotic for the treatment of psychosis.

Anesthesia and Critical Care Concerns/Other ConsiderationsSimultaneous administration of carbamazepine suspension with other liquids can precipitate the drug.

Index TermsCBZ; SPD417

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International Brand NamesActebral (EC); Actebral Retard (EC); Actinerval (AR, EC, PY); Amizepin (PL); Apo-Carbamazepine (MY); Azepal (HU); Bamgetol (ID); Basitrol (PE); Brucarcer (MX); C.P.Carba (HK); Camapine (TH, TW); Carazepin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Carbabeta (AU); Carbadac (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Carbalex (EE); Carbamazepin-B (HU); Carbatol (IN); Carbatol CR (SG); Carbazene (TH); Carbazep (MX); Carbazina (MX); Carmapine (TH, TW); Carmaz (IN); Carmian (CN); Carmine (KP); Carpin (MX); Carzepin (HK, MY); Carzepine (TH); Cetiril (CO); Clostedal (MX); Degranol (ZA); Elpenor (DE); Epazin (PH); Epazin CR (PH); Epikor (PH); Epileptol (KP); Epileptol CR (KP); Eposal Retard (CO); Espa-lepsin (DE); Finlepsin (BG, HU, PL); Gericarb SR (IE); Hermolepsin (SE); Karbamazepin (DK, NO); Neugeron (MX); Neurolep (MX); Neurotol (FI); Neurotop (AT, HN, HU, PL); Neurotop Retard (SG); Panitol (TH); Sepibest (MX); Sirtal (DE); Stazepine (HU); Taver (MY, TH); Tegol (TW); Tegral (PK); Tegretal (CN, DE); Tegretol (AE, AR, AU, BB, BD, BE, BF, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CO, CY, CZ, DK, EC, EE, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PH, PK, PL, PT, PY, QA, SA, SC, SD, SE, SG, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Tegretol CR (AU, CZ, EE, IL, KP, NZ); Tegretol Retard (FI); Temporol (HU, ZA); Teril (AU, HK, ID, IL, TW); Teril-CR (IL); Timonil (DE, HU, PL); Timonil Retard (CH, DE, IL); Trepina (MX); Vulsivan (CO); Zeptol CR (TH)

Carbamide Peroxide

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English

English

Jump To Field (Select Field Name)

Pronunciation(KAR ba mide per OKS ide)

U.S. Brand NamesAuraphene® B [OTC]; Auro® [OTC]; Cankaid® [OTC]; Debrox® [OTC]; Dent's Ear Wax [OTC] [DSC]; E•R•O [OTC]; Gly-Oxide® [OTC]; Murine® Ear Wax Removal System [OTC]; Orajel® Perioseptic® Spot Treatment [OTC]; Otix® [OTC]

Pharmacologic CategoryAnti-inflammatory, Locally Applied; Otic Agent, Cerumenolytic

Use: Labeled IndicationsRelief of minor inflammation of gums, oral mucosal surfaces, and lips including canker sores and dental irritation; emulsify and disperse ear wax

Use: DentalRelief of minor inflammation of gums, oral mucosal surfaces, and lips (including canker sores and dental irritation)

Dosing: Adults

Minor inflammation of gums, oral mucosal surfaces, and lips: Topical: Oral solution (should not be used for >7 days): Apply several drops undiluted on affected area 4 times/day after meals and at bedtime; expectorate after 2-3 minutes **or** place 10 drops onto tongue, mix with saliva, swish for several minutes, expectorate

Ear wax removal: Otic: Tilt head sideways and instill 5-10 drops twice daily up to 4 days, tip of applicator should not enter ear canal; keep drops in ear for several minutes by keeping head tilted and placing cotton in ear

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Relief of minor inflammation of gums, oral mucosal surfaces, and lips: Topical: Children ≥2 years: Refer to adult dosing.

Ear wax removal: Otic:

Children <12 years: Tilt head sideways and individualize the dose according to patient size; 3 drops (range: 1-5 drops) twice daily for up to 4 days, tip of applicator should not enter ear canal. Keep drops in ear for several minutes by keeping head tilted and placing cotton in ear.

Children ≥12 years: Refer to adult dosing.

StorageProtect from excessive heat and direct sunlight.

ContraindicationsHypersensitivity to carbamide peroxide or any component of the formulation; otic preparation should not be used in patients with a perforated tympanic membrane; ear drainage, ear pain, or rash in the ear

Warnings/Precautions

Dosage form specific issues:

- Oral: With prolonged use of oral carbamide peroxide, there is a potential for overgrowth of opportunistic organisms, damage to periodontal tissues, and delayed wound healing; should not be used for longer than 7 days. Not for OTC use in children <2 years of age.
- Otic: Do not use if ear drainage or discharge, ear pain, irritation, or rash in ear. Should not be used for longer than 4 days. Not for OTC use in children <12 years of age.

Geriatric ConsiderationsAvoid contact with hearing aids.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Dermatologic: Rash

Local: Irritation, redness

Miscellaneous: Superinfection

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Liquid, oral: 10% (60 mL)

Cankaid®: 10% (22 mL)

Gly-Oxide®: 10% (15 mL, 60 mL)

Solution, otic [drops]: 6.5% (15 mL)

Auraphene® B, Otix®: 6.5% (15 mL)

Auro®: 6.5% (22.2 mL)

Debrox®: 6.5% (15 mL, 30 mL)

Dent's Ear Wax: 6.5% (3.7 mL) [DSC]

E•R•O: 6.5% (15 mL) [alcohol free]

Murine® Ear Wax Removal System: 6.5% (15 mL) [contains alcohol 6.3%]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Gly-Oxide)

10% (60): $8.99

Mechanism of ActionCarbamide peroxide releases hydrogen peroxide which serves as a source of nascent oxygen upon contact with catalase; deodorant action is probably due to inhibition of odor-causing bacteria; softens impacted cerumen due to its foaming action

Pharmacodynamics/KineticsOnset of action: ~24 hours

Pharmacotherapy PearlsOtic preparation should not be used for >4 days. Oral preparation should not be used for longer than 7 days.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsUrea Peroxide

International Brand NamesBlanc-Dient (AR); Ear Clear for Ear Wax Removal (NZ); Earclear (NZ)

Carbenicillin

Lexi-Drugs Online

English English

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Pronunciation(kar ben i SIL in)

U.S. Brand NamesGeocillin® [DSC]

Pharmacologic CategoryAntibiotic, Penicillin

Use: Labeled IndicationsTreatment of serious urinary tract infections and prostatitis caused by susceptible gram-negative aerobic bacilli

Dosing: Adults

Prostatitis: Oral: 2 tablets every 6 hours

Urinary tract infections: Oral: 1-2 tablets every 6 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricSusceptible infections: Oral: 30-50 mg/kg/day divided every 6 hours (maximum dose: 2-3 g/day)

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer every 12-24 hours.

Cl_{cr} <10 mL/minute: Not recommended.

Moderately dialyzable (20% to 50%)

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels.

Some penicillins (eg, carbenicillin, ticarcillin and piperacillin) have been shown to inactivate aminoglycosides *in vitro*. This has been observed to a greater extent with tobramycin and gentamicin, while amikacin has shown greater stability against inactivation. Concurrent use of these agents may pose a risk of reduced antibacterial efficacy *in vivo*, particularly in the setting of profound renal impairment. However, definitive clinical evidence is lacking. If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered.

Dietary ConsiderationsShould be taken with water on empty stomach. Sodium content of 382 mg tablet: 23 mg (1 mEq).

Compatibility Solution:

Compatible: Ampicillin, cimetidine, clindamycin, dopamine, hydrocortisone, lidocaine, potassium chloride, verapamil.

Incompatible: Aminophylline, amphotericin B, epinephrine, erythromycin, gentamicin, levarterenol, tetracycline, vitamin B and C complex.

ContraindicationsHypersensitivity to carbenicillin, penicillins, or any component of the formulation

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment recommended.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended. Avoid use in severe impairment (Cl_{cr} <10 mL/minute).

Geriatric ConsiderationsHas not been studied in the elderly. Adjust dose for renal function in the elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, carbenicillin is classified as pregnancy category B. Penicillins cross the placenta; adequate and well-controlled studies with carbenicillin have not been completed in pregnant women.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsVery small amounts of carbenicillin are excreted in breast milk. The manufacturer recommends that caution be exercised when administering carbenicillin to nursing women. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Carbenicillin in Pregnancy & Lactation

Adverse Reactions

>10%: Gastrointestinal: Diarrhea

1% to 10%: Gastrointestinal: Nausea, bad taste, vomiting, flatulence, glossitis

<1%: Anemia, AST increased (mild), eosinophilia, epigastric distress, furry tongue, headache, hematuria, hypersensitivity reactions, hyperthermia, hypokalemia, leukopenia, LFTs increased, neutropenia, rash, thrombocytopenia, urticaria

Drug Interactions

Aminoglycosides: Penicillins may decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. *Risk D: Consider therapy modification*

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Test InteractionsMay interfere with urinary glucose tests using cupric sulfate (Benedict's solution, Clinitest®); false-positive urine or serum proteins.

Some penicillin derivatives may accelerate the degradation of aminoglycosides. *In vitro*, leading to a potential underestimation of aminoglycoside serum concentration.

Monitoring ParametersRenal, hepatic, and hematologic function tests

Reference RangeTherapeutic: Not established; Toxic: >250 mcg/mL (SI: >660 µmol/L)

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to beginning treatment. Use caution in presence of renal or hepatic impairment. Assess other pharmacological or herbal products patient may be taking for potential interactions. Assess results of laboratory tests, therapeutic effectiveness, and adverse response. Advise patients with diabetes about use of Clinitest®. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsRenal and hepatic function, CBC, serum potassium, bleeding times. Perform culture and sensitivity testing prior to initiating therapy.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as prescribed, at equal intervals around-the-clock, with a full glass of water, and preferably on an empty stomach, 1 hour before or 2 hours after meals. Do not skip doses and take full course of treatment even if feeling better. If you have diabetes, drug may cause false test results with Clinitest® urine glucose monitoring; use of another form of glucose monitoring is preferable. May cause diarrhea (boiled milk, buttermilk, or yogurt may help - if diarrhea persists for more than 2 days, contact prescriber for approved antidiarrhea medication); or dry mouth and bitter aftertaste (frequent mouth care may help). Report respiratory difficulty; easy bruising or bleeding; rash, itching, hives; or signs of opportunistic infection (eg, sore throat, fever, chills, fatigue, thrush, vaginal discharge, diarrhea). **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet:

Geocillin®: 382 mg [contains sodium 23 mg/tablet] [DSC]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Geocillin)

382 mg (28): $88.00

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: 30% to 40%

Distribution: Distributes into bile; low concentrations attained in CSF

Protein binding: ~50%

Half-life elimination: Children: 0.8-1.8 hours; Adults: 1-1.5 hours, prolonged to 10-20 hours with renal insufficiency

Time to peak, serum: Normal renal function: 0.5-2 hours; concentrations are inadequate for treatment of systemic infections

Excretion: Urine (~80% to 99% as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Unpleasant taste and glossitis. Prolonged use of penicillins may lead to development of oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusPenicillins have been reported to cause apprehension, illusions, agitation, insomnia, depersonalization, and encephalopathy

Mental Health: Effects on Psychiatric TreatmentRare reports of leukopenia and neutropenia; use caution with clozapine and carbamazepine

Index TermsCarbenicillin Indanyl Sodium; Carindacillin

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International Brand NamesCarbenicillin (PL)

Carbetapentane and Chlorpheniramine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(kar bay ta PEN tane & klor fen IR a meen)

U.S. Brand NamesC-Tanna 12; Tannate 12 S; Tannic-12 S; Tannic-12 [DSC]; Tannihist-12 RF [DSC]; Trionate® [DSC]; Tussi-12 S™; Tussi-12®; Tussizone-12 RF™; Tustan 12S™

Pharmacologic CategoryAntitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of cough associated with upper respiratory tract conditions, such as the common cold, bronchitis, bronchial asthma

Dosing: AdultsCough and upper respiratory symptoms: Oral (based on carbetapentane 60 mg and chlorpheniramine 5 mg per tablet): 1-2 tablets every 12 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricCough and upper respiratory symptoms: Oral (based on carbetapentane 30 mg and chlorpheniramine 4 mg per 5 mL suspension):

2-6 years: 2.5-5 mL every 12 hours

>6 years: 5-10 mL every 12 hours

Dietary ConsiderationsTussi-12 S™ contains tartrazine.
StorageStore at controlled room temperature.
ContraindicationsHypersensitivity to carbetapentane, chlorpheniramine, or any component of the formulation; use with or within 14 days of MAO inhibitors; newborns; breast-feeding
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Antihistamines may cause excitation in young children. Safety and efficacy have not been established in children <2 years of age.

Dosage form specific issues:

- Tartrazine: Some products may contain tartrazine.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been performed; use during pregnancy only if clearly needed.
LactationExcretion in breast milk unknown/contraindicated
Adverse ReactionsFrequency not defined.

Central nervous system: Drowsiness, excitation (children), sedation

Gastrointestinal: GI motility decreased, dry mucous membranes

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Suspension:

C-Tanna 12: Carbetapentane tannate 30 mg and chlorpheniramine tannate 4 mg per 5 mL (480 mL) [contains benzoic acid and tartrazine; strawberry currant flavor]

Tannate 12 S: Carbetapentane tannate 30 mg and chlorpheniramine tannate 4 mg per 5 mL (120 mL, 480 mL) [contains benzoic acid]

Tannic-12 S: Carbetapentane tannate 30 mg and chlorpheniramine tannate 4 mg per 5 mL (120 mL) [contains benzoic acid; strawberry flavor]

Tannihist-12 RF: Carbetapentane tannate 30 mg and chlorpheniramine tannate 4 mg per 5 mL (120 mL, 480 mL) [strawberry-black currant flavor] [DSC]

Tussi-12 S™: Carbetapentane tannate 30 mg and chlorpheniramine tannate 4 mg per 5 mL (120 mL) [contains benzoic acid and tartrazine; strawberry-currant flavor]

Tussizone-12 RF™: Carbetapentane tannate 30 mg and chlorpheniramine tannate 4 mg per 5 mL (120 mL, 480 mL) [contains benzoic acid and tartrazine; strawberry-black currant flavor] [DSC]

Tustan 12S™: Carbetapentane tannate 30 mg and chlorpheniramine tannate 4 mg per 5 mL (120 mL, 480 mL) [contains sodium benzoate; grape flavor]

Tablet:

Tannic-12 [DSC], Trionate® [DSC], Tussi-12®, Tussizone-12 RF™: Carbetapentane tannate 60 mg and chlorpheniramine tannate 5 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Suspension (Tannihist-12 RF)

4-30 mg/5 mL (90): $20.99

Tablets (Tussi-12)

5-60 mg (30): $91.35

Tablets (Tussizone-12 RF)

5-60 mg (30): $37.99

Mechanism of ActionCarbetapentane is a nonopioid cough suppressant; chlorpheniramine is an H_1-receptor antagonist

Pharmacodynamics/Kinetics

Carbetapentane: Data not available

Chlorpheniramine: See individual agents

Related Information

- Chlorpheniramine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dry mucous membranes. Chronic use of antihistamines will inhibit salivary flow, particularly in elderly patients; this may contribute to periodontal disease and oral discomfort.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; combined use with psychotropics may produce additive sedation; monitor

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors. Anticholinergic effects may be potentiated with combined psychotropic use.

Index TermsCarbetapentane Tannate and Chlorpheniramine Tannate; Chlorpheniramine and Carbetapentane

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Carbetapentane, Guaifenesin, and Phenylephrine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(kar bay ta PEN tane, gwye FEN e sin, & fen il EF rin)
U.S. Brand NamesCarbetaplex; Extendryl® GCP; Gentex LQ; Levall™; Phencarb GG
Pharmacologic Category[Antitussive](); [Expectorant](); [Expectorant/Decongestant/Antitussive](); [Sympathomimetic]()
Use: Labeled IndicationsRelief of nonproductive cough accompanying respiratory tract congestion associated with the common cold, influenza, sinusitis, and bronchitis
Dosing: AdultsRelief of cough: Oral:

Gentex LQ: 5-10 mL every 4-6 hours

Levall™: 5 mL every 4-6 hours; maximum dose of phenylephrine: 60 mg/24 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRelief of cough: Oral:

Children <2 years: Dosage not established

Children 2-6 years:

Gentex LQ: 2.5 mL every 4-6 hours

Levall™: 1.25 mL every 4-6 hours; maximum dose of phenylephrine: 15 mg/24 hours

Children 6-12 years:

Gentex LQ: 5 mL every 4-6 hours

Levall™: 2.5 mL every 4-6 hours; maximum dose of phenylephrine: 30 mg/24 hours

Children ≥12 years: Refer to adult dosing.

StorageStore between 15°C and 30°C (59°F and 86°F).
ContraindicationsHypersensitivity to carbetapentane, guaifenesin, phenylephrine, or any component of the formulation; use with or within 14 days of MAO inhibitors; severe hypertension or coronary artery disease; hyperthyroidism; newborns or infants; breast-feeding
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.

- Diabetes: Use with caution in patients with diabetes mellitus.

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination; the manufacturer does not recommend use in pregnant women.
LactationExcretion in milk unknown/not recommended
Adverse ReactionsFrequency not defined. Also see individual agents.

Central nervous system: Dizziness, drowsiness, excitability, headache, insomnia, nervousness, mild stimulation, restlessness, weakness

Gastrointestinal: Nausea, vomiting

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Test InteractionsPossible color interference with determination of 5-HIAA and VMA; discontinue for 48 hours prior to test
Nursing: Physical Assessment/MonitoringSee individual agents for Guaifenesin and Phenylephrine.
Patient EducationSee individual agents for Guaifenesin and Phenylephrine.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid:

Carbetaplex: Carbetapentane citrate 20 mg, guaifenesin 100 mg, and phenylephrine hydrochloride 15 mg per 5 mL (480 mL) [alcohol free, sugar free, dye free; strawberry flavor]

Gentex LQ: Carbetapentane citrate 20 mg, guaifenesin 100 mg, and phenylephrine hydrochloride 10 mg per 5 mL [contains edetate disodium and benzoic acid; spearmint flavor]

Levall™: Carbetapentane citrate 15 mg, guaifenesin 100 mg, and phenylephrine hydrochloride 5 mg per 5 mL (480 mL) [alcohol free; strawberry flavor]

Phencarb GG: Carbetapentane citrate 20 mg, guaifenesin 100 mg, and phenylephrine hydrochloride 10 mg per 5 mL (480 mL) [spearmint flavor]

Solution, oral:

Extendryl® GCP: Carbetapentane citrate 15 mg, guaifenesin 100 mg, and phenylephrine hydrochloride 5 mg per 5 mL (473 mL) [alcohol free; contains propylene glycol; strawberry flavor]

Generic AvailableYes
Mechanism of Action

Carbetapentane is a centrally-acting nonopioid cough suppressant.

Guaifenesin is an expectorant.

Phenylephrine hydrochloride is a sympathomimetic agent (primarily alpha), decongestant.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Guaifenesin: No significant effects or complications reported

Phenylephrine: Tachycardia, palpitations (use vasoconstrictor with caution)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response
Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, excitability, insomnia, nervousness, CNS stimulation, or restlessness
Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors or within 14 days of MAO inhibitor
Index TermsGuaifenesin, Carbetapentane Citrate, and Phenylephrine Hydrochloride; Phenylephrine Hydrochloride, Carbetapentane Citrate, and Guaifenesin

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Carbetapentane, Phenylephrine, and Chlorpheniramine

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Pronunciation(kar bay ta PEN tane, fen il EF rin, & klor fen IR a meen)

U.S. Brand NamesCarbaphen 12 Ped®; Carbaphen 12®; XiraTuss™ [DSC]

Pharmacologic CategoryAlpha/Beta Agonist; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of cough, nasal congestion, and discharge associated with the common cold, bronchial asthma, acute and chronic bronchitis, and other respiratory tract conditions

Dosing: AdultsRelief of cough, congestion: Oral:

Carbaphen 12®: 5-10 mL every 12 hours

XiraTuss tablet: 1-2 tablets every 12 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRelief of cough, congestion: Oral:

Children 2-6 years:

Carbaphen 12 Ped®: 1-2 mL every 12 hours

XiraTuss suspension: 2.5-5 mL every 12 hours

Children 6-12 years:

Carbaphen 12 Ped®: 2-4 mL every 12 hours

XiraTuss suspension: 5-10 mL every 12 hours

Children >12 years: Refer to adult dosing.

Dietary Considerations

Carbaphen 12® contains phenylalanine 1 mg/5 mL.

Carbaphen 12 Ped® contains phenylalanine 1.6 mg/mL.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to carbetapentane, phenylephrine, chlorpheniramine, or any component of the formulation; use with or within 14 days of MAO inhibitors; newborns; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination.

LactationExcretion in breast milk unknown/contraindicated

Adverse ReactionsAlso refer to individual agents. Frequency not defined.

Cardiovascular: Hypotension

Central nervous system: Dizziness, drowsiness, sedation

Gastrointestinal: Xerostomia

Metabolism/Transport EffectsChlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Nursing: Physical Assessment/MonitoringSee individual agent for Phenylephrine.

Patient EducationSee individual agent for Phenylephrine.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Suspension:

Carbaphen 12®: Carbetapentane tannate 60 mg, phenylephrine tannate 20 mg, and chlorpheniramine tannate 8 mg per 5 mL (480 mL) [contains benzoic acid, phenylalanine 1 mg/5 mL; alcohol free, sugar free; blueberry-banana flavor]

Carbaphen 12 Ped®: Carbetapentane tannate 15 mg, phenylephrine tannate 2.5 mg, and chlorpheniramine tannate 2 mg per 1 mL (60 mL) [contains benzoic acid, phenylalanine 1.6 mg/mL; alcohol free, sugar free; blueberry-banana flavor]

XiraTuss™: Carbetapentane tannate 30 mg, phenylephrine tannate 12.5 mg, and chlorpheniramine tannate 4 mg per 5 mL (120 mL) [strawberry flavor] [DSC]

Tablet:

XiraTuss™: Carbetapentane tannate 60 mg, phenylephrine tannate 10 mg, and chlorpheniramine tannate 5 mg [DSC]

Generic AvailableYes; Suspension

Mechanism of Action

Carbetapentane is a nonopioid cough suppressant.

Phenylephrine hydrochloride is a sympathomimetic agent (primarily alpha), decongestant.

Chlorpheniramine is a histamine H_1 antagonist.

Related Information

- Chlorpheniramine
- Phenylephrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Also refer to individual agents.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusSedation is common; concurrent use with psychotropic agents may produce additive sedative effects; monitor

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors. Concurrent use with psychotropic agents may produce additive anticholinergic effects; monitor.

Index TermsChlorpheniramine, Carbetapentane, and Phenylephrine; Phenylephrine, Chlorpheniramine, and Carbetapentane

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Carbetapentane, Phenylephrine, and Pyrilamine

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Pronunciation(kar bay ta PEN tane, fen il EF rin, & peer II a meen)
U.S. Brand NamesC-Tanna 12D; Tannihist-12 D [DSC]; Tussi-12® D; Tussi-12® DS
Pharmacologic CategoryAlpha/Beta Agonist; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation
Use: Labeled IndicationsSymptomatic relief of cough associated with respiratory tract conditions such as the common cold, bronchial asthma, acute and chronic bronchitis
Dosing: AdultsRelief of cough (Tussi-12® D): Oral: 1-2 tablets every 12 hours
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRelief of cough: Oral:

2-6 years (Tussi-12® DS): 2.5-5 mL every 12 hours

6-11 years:

Tussi-12® D: $^1/_2$ to 1 tablet every 12 hours

Tussi-12® DS: 5-10 mL every 12 hours

≥12 years: Refer to adult dosing.

Dietary ConsiderationsTussi-12® DS (suspension) contains tartrazine which may cause allergic-type reactions in patients sensitive to this dye.
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).
ContraindicationsHypersensitivity to carbetapentane, pyrilamine, phenylephrine, or any component of the formulation; use with or within 14 days of MAO inhibitors; breast-feeding; newborns
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children.

Dosage form specific issues:

- Tartrazine: Some products may contain tartrazine.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination.
LactationExcretion unknown/contraindicated
Breast-Feeding ConsiderationsSpecific information is not available; however, infants may be more sensitive to the effects of antihistamines.
Adverse ReactionsFrequency not defined.

Central nervous system: Drowsiness, sedation

Gastrointestinal: Xerostomia

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Suspension:

C-Tanna 12D: Carbetapentane tannate 30 mg, pyrilamine tannate 30 mg, and phenylephrine tannate 5 mg per 5 mL (120 mL) [contains benzoic acid and tartrazine; strawberry currant flavor]

Tannihist-12 D: Carbetapentane tannate 30 mg, pyrilamine tannate 30 mg, and phenylephrine tannate 5 mg per 5 mL (120 mL) [alcohol free; contains sugar 15% and tartrazine; strawberry black currant flavor] [DSC]

Tussi-12® DS: Carbetapentane tannate 30 mg, pyrilamine tannate 30 mg, and phenylephrine tannate 5 mg per 5 mL (120 mL) [contains benzoic acid and tartrazine; strawberry currant flavor; packaged with oral syringe]

Tablet:

C-Tanna 12D, Tussi-12® D: Carbetapentane tannate 60 mg, pyrilamine tannate 40 mg, and phenylephrine tannate 10 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Tussi-12D)

10-40-60 mg (100): $240.84

Mechanism of Action

Carbetapentane is a nonopioid cough suppressant

Phenylephrine hydrochloride is a sympathomimetic agent (primarily alpha), decongestant.

Pyrilamine is an H_1-receptor antagonist.

Related Information

- Phenylephrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tachycardia, palpitations (use vasoconstrictor with caution), and xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusSedation is common; may cause paradoxical excitation in pediatric patients

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment. Concurrent use with psychotropics may produce additive sedation and anticholinergic side effects; monitor.

Index TermsPhenylephrine Tannate, Carbetapentane Tannate, and Pyrilamine Tannate; Pyrilamine, Phenylephrine, and Carbetapentane

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Carbetapentane and Phenylephrine

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state "Do not use in children under four years of age." In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, "Infant Deaths Associated with Cough and Cold Medications - Two States, 2005," *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(kar bay ta PEN tane & fen il EF rin)

U.S. Brand NamesL-All 12

Pharmacologic CategoryAntitussive; Antitussive/Decongestant; Sympathomimetic

Use: Labeled IndicationsSymptomatic relief of upper respiratory tract conditions such as the common cold, bronchial asthma, and bronchitis (acute and chronic)

Dosing: Adults**Upper respiratory symptoms:** Oral: 5-10 mL every 12 hours, not to exceed 20 mL/24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricUpper respiratory symptoms: Oral:

Children:

2-6 years: 2.5 mL every 12 hours, not to exceed 5 mL/24 hours

6-12 years: 5 mL every 12 hours, not to exceed 10 mL/24 hours

Children >12 years: Refer to adult dosing.

Dietary ConsiderationsL-All 12 contains phenylalanine.
StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to carbetapentane, and phenylephrine, or any component of the formulation; use with or within 14 days of MAO inhibitor; newborns; breast-feeding
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).

- Diabetes: Use with caution in patients with diabetes mellitus.

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination.
LactationExcretion in breast milk unknown/contraindicated
Adverse ReactionsAlso see Phenylephrine monograph. Frequency not defined.

Central nervous system: Drowsiness, sedation

Gastrointestinal: Xerostomia

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Nursing: Physical Assessment/MonitoringAssess effectiveness and adverse reactions (CNS depression, gastrointestinal upset), also see Phenylephrine monograph. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Patient EducationUse exactly as directed; do not exceed recommended dosage. You may experience dizziness, anxiety, or drowsiness (use caution when driving or engaged in tasks that require alertness until response to drug is known); headache (consult prescriber for analgesic). Report changes in urinary pattern, palpitations of changes in heartbeat; persistent CNS effects (restlessness, tremors, excitability) or other adverse reactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension:

L-All 12: Carbetapentane tannate 30 mg and phenylephrine tannate 30 mg per 5 mL (120 mL) [contains sodium benzoate and phenylalanine; strawberry flavor]

Generic AvailableNo
ManufacturerMidlothian Laboratories
Mechanism of ActionCarbetapentane is a nonopioid cough suppressant; phenylephrine is a sympathomimetic agent (primarily alpha), decongestant
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Phenylephrine: Tachycardia, palpitations (use vasoconstrictor with caution), and xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause anxiety, restlessness, or sedation

Mental Health: Effects on Psychiatric TreatmentConcurrent use with MAO inhibitors is contraindicated. May cause sedation and xerostomia; concomitant use with psychotropics may produce additive effects.

Index TermsPhenylephrine Tannate and Carbetapentane Tannate

Carbetapentane and Pseudoephedrine

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(kar bay ta PEN tane & soo doe e FED rin)

U.S. Brand NamesPseudacarb™; Respi-Tann™

Pharmacologic CategoryAntitussive/Decongestant

Use: Labeled IndicationsRelief of cough and congestion due to the common cold, influenza, sinusitis, or bronchitis

Dosing: AdultsRelief of cough and congestion: Oral: 2 tablets or 10 mL suspension every 12 hours (maximum: 4 doses/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRelief of cough and congestion: Oral:

2-6 years: $^1/_2$ tablet or 2.5 mL suspension every 12 hours (maximum: 4 doses/24 hours)

6-12 years: 1 tablet or 5 mL suspension every 12 hours (maximum: 4 doses/24 hours)

>12 years: Refer to adult dosing.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to carbetapentane, pseudoephedrine, or any component of the formulation; use with or within 14 days of MAO inhibitors; severe hypertension or cardiovascular disease; neonates, infants; breast-feeding

Warnings/Precautions

Disease-related concerns:

- Asthma: Use with caution in patients with a history of asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination product.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsPseudoephedrine is excreted in breast milk. The manufacturer of this product contraindicates its use; the AAP considers it to be “compatible” with breast-feeding. Information is not available for carbetapentane.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, cardiovascular collapse with hypotension, pallor, palpitation, tachycardia

Central nervous system: Anxiety, CNS depression, convulsions, dizziness, fear, hallucinations, headache, insomnia, restlessness, tenseness

Gastrointestinal: Nausea

Genitourinary: Dysuria

Neuromuscular & skeletal: Tremor, weakness

Respiratory: Respiratory difficulty

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension: Carbetapentane tannate 25 mg and pseudoephedrine tannate 75 mg per 5 mL (480 mL)

Respi-Tann™: Carbetapentane tannate 25 mg and pseudoephedrine tannate 75 mg per 5 mL (480 mL) [dye free; contains sodium benzoate; cherry flavor]

Tablet, chewable:

Respi-Tann™: Carbetapentane tannate 25 mg and pseudoephedrine tannate 75 mg [dye free; cherry flavor]

Pseudacarb™: Carbetapentane tannate 25 mg and pseudoephedrine tannate 75 mg [dye free; grape flavor]

Generic AvailableYes: Suspension

ManufacturerKiel Laboratories; marketed by Teamm Pharmaceuticals

Mechanism of Action

Carbetapentane is a non-narcotic antitussive.

Pseudoephedrine is a sympathomimetic amine and isomer of ephedrine; acts as a decongestant in respiratory tract mucous membranes with less vasoconstrictor action than ephedrine in normotensive individuals.

Related Information

- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause anxiety, dizziness, insomnia, restlessness, hallucinations, or depression

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment; may cause tremor which may be mistaken for EPS; may cause tachycardia; tachycardia is also common with clozapine; monitor vital signs

Index TermsCarbetapentane Tannate and Pseudoephedrine Tannate; Pseudoephedrine and Carbetapentane

References

American Academy of Pediatrics Committee on Drugs, “The Transfer of Drugs and Other Chemicals Into Human Milk,” *Pediatrics*, 2001, 108(3):776-89.[PubMed 11533352]

Carbidopa and Levodopa

Lexi-Drugs Online

English

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Pronunciation(kar bi DOE pa & lee voe DOE pa)
U.S. Brand NamesParcopa™; Sinemet®; Sinemet® CR
Canadian Brand NamesApo-Levocarb®; Apo-Levocarb® CR; Endo®-Levodopa/Carbidopa; Novo-Levocarbidopa; Nu-Levocarb; Pro-Levocarb; Sinemet®; Sinemet® CR
Pharmacologic CategoryAnti-Parkinson's Agent, Dopamine Agonist
Use: Labeled IndicationsIdiopathic Parkinson's disease; postencephalitic parkinsonism; symptomatic parkinsonism
Use: Unlabeled/InvestigationalRestless leg syndrome
Dosing: Adults

Parkinson's disease: Oral: Initial:

Immediate release tablet:

Initial: Carbidopa 25 mg/levodopa 100 mg 3 times/day

Dosage adjustment: Alternate tablet strengths may be substituted according to individual carbidopa/levodopa requirements. Increase by 1 tablet every other day as necessary, except when using the carbidopa 25 mg/levodopa 250 mg tablets where increases should be made using $^1/_2$-1 tablet every 1-2 days. Use of more than 1 dosage strength or dosing 4 times/day may be required (maximum: 8 tablets of any strength/day or 200 mg of carbidopa and 2000 mg of levodopa)

Sustained release tablet:

Initial: Carbidopa 50 mg/levodopa 200 mg 2 times/day, at intervals not <6 hours

Dosage adjustment: May adjust every 3 days; intervals should be between 4-8 hours during the waking day (maximum: 8 tablets/day)

Restless leg syndrome (unlabeled use): Oral: Carbidopa 25 mg/levodopa 100 mg given 30-60 minutes before bedtime; may repeat dose once

Dosing: ElderlyInitial dose: 25/100 twice daily, increase as necessary. Sinemet® CR may be used as initial therapy.
Administration: OralSpace doses evenly over the waking hours. Give with meals to decrease GI upset. Sustained release product should not be crushed. Orally-disintegrating tablets do not require water; the tablet should disintegrate on the tongue's surface before swallowing.
Dietary ConsiderationsLevodopa peak serum concentrations may be decreased if taken with food. High protein diets (>2 g/kg) may decrease the efficacy of levodopa via competition with amino acids in crossing the blood-brain barrier.

Parcopa™: Contains phenylalanine 3.4 mg per 10/100 mg and 25/100 mg strengths; phenylalanine 8.4 mg in 25/250 mg strength

StorageStore at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Protect from light and moisture.
ContraindicationsHypersensitivity to levodopa, carbidopa, or any component of the formulation; narrow-angle glaucoma; use of MAO inhibitors within prior 14 days (however, may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B); history of melanoma or undiagnosed skin lesions
Allergy Considerations

- Levodopa Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Dyskinesias: May cause or exacerbate dyskinesias.
- Impulsive control disorders: Dopamine agonists used for Parkinson’s disease or restless legs syndrome have been associated with compulsive behaviors and/or loss of impulse control, which has manifested as pathological gambling, libido increases (hypersexuality), and/or binge eating. Causality has not been established, and controversy exists as to whether this phenomenon is related to the underlying disease, prior behaviors/addictions and/or drug therapy. Dose reduction or discontinuation of therapy has been reported to reverse these behaviors in some, but not all cases.
- Orthostatic hypotension: May cause orthostatic hypotension; Parkinson's disease patients appear to have an impaired capacity to respond to a postural challenge. Use with caution in patients at risk of hypotension (such as those receiving antihypertensive drugs) or where transient hypotensive episodes would be poorly tolerated (cardiovascular disease or cerebrovascular disease). Parkinson's patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation, and should be informed of this risk.
- Somnolence: Patients have reported falling asleep while engaging in activities of daily living; this has been reported to occur without significant warning signs. Monitor for daytime somnolence or pre-existing sleep disorder; caution with concomitant sedating medication; discontinue if significant daytime sleepiness or episodes of falling asleep occur. Patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). Use with caution in patients receiving other CNS depressants or psychoactive agents. Effects with other sedative drugs or ethanol may be potentiated.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease, including a history of myocardial infarction and arrhythmias.
- Endocrine disease: Use with caution when interpreting plasma/urine catecholamine levels; falsely-diagnosed pheochromocytoma has been rarely reported.
- Glaucoma: Use with caution in patients with glaucoma; monitor IOP carefully in patients with wide-angle glaucoma.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Peptic ulcer disease: Use with caution in patients with peptic ulcer disease.
- Psychotic disorders: Use with extreme caution in patients with psychotic disorders; observe patients closely for development of depression with concomitant suicidal tendencies.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to CNS effects of levodopa.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Dietary protein: Distribute dietary protein throughout the day to avoid fluctuations in levodopa absorption.
- Discontinuation of therapy: Dopaminergic agents have been associated with a syndrome resembling neuroleptic malignant syndrome on abrupt withdrawal or significant dosage reduction after long-term use.

Geriatric ConsiderationsThe elderly may be more sensitive to the CNS effects of levodopa.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were observed with levodopa and carbidopa in animal studies. There are case reports of levodopa crossing the placenta in humans.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Orthostatic hypotension, arrhythmia, chest pain, hypertension, syncope, palpitation, phlebitis

Central nervous system: Dizziness, anxiety, confusion, nightmares, headache, hallucinations, on-off phenomenon, decreased mental acuity, memory impairment, disorientation, delusions, euphoria, agitation, somnolence, insomnia, gait abnormalities, nervousness, ataxia, EPS, falling, psychosis, peripheral neuropathy, seizure (causal relationship not established)

Dermatologic: Rash, alopecia, malignant melanoma, hypersensitivity (angioedema, urticaria, pruritus, bullous lesions, Henoch-Schönlein purpura)

Endocrine & metabolic: Increased libido

Gastrointestinal: Anorexia, nausea, vomiting, constipation, GI bleeding, duodenal ulcer, diarrhea, dyspepsia, taste alterations, sialorrhea, heartburn

Genitourinary: Discoloration of urine, urinary frequency

Hematologic: Hemolytic anemia, agranulocytosis, thrombocytopenia, leukopenia; decreased hemoglobin and hematocrit; abnormalities in AST and ALT, LDH, bilirubin, BUN, Coombs' test

Neuromuscular & skeletal: Choreiform and involuntary movements, paresthesia, bone pain, shoulder pain, muscle cramps, weakness

Ocular: Blepharospasm, oculogyric crises (may be associated with acute dystonic reactions)

Renal: Difficult urination

Respiratory: Dyspnea, cough

Miscellaneous: Hiccups, discoloration of sweat, diaphoresis (increased)

Postmarketing and/or case reports: Reported with dopamine agonists: Impulsive/compulsive behaviors (eg, pathological gambling, hypersexuality, binge eating)

Drug Interactions

Antipsychotics (Atypical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Antipsychotics (Typical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Levodopa. Only applies to oral iron preparations. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

MAO Inhibitors: Levodopa may enhance the adverse/toxic effect of MAO Inhibitors. Of particular concern is the development of hypertensive reactions when levodopa is used with nonselective MAOI. *Risk D: Consider therapy modification*

Methionine: May diminish the therapeutic effect of Levodopa. Probably only with large doses of methionine. Data was generated using 4.5gm daily. *Risk D: Consider therapy modification*

Metoclopramide: May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk C: Monitor therapy*

Phenytoin: May diminish the therapeutic effect of Levodopa. *Risk C: Monitor therapy*

Pyridoxine: May diminish the therapeutic effect of Levodopa. *Risk D: Consider therapy modification*

Sapropterin: May enhance the adverse/toxic effect of Levodopa. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (due to CNS depression).

Food: Avoid high protein diets and high intakes of vitamin B_6.

Herb/Nutraceutical: Avoid kava kava (may decrease effects). Pyridoxine in doses >10-25 mg (for levodopa alone) or higher doses >200 mg/day (for levodopa/carbidopa) may decrease efficacy.

Test InteractionsFalse-positive reaction for urinary glucose with Clinitest®; false-negative reaction using Clinistix®; false-positive urine ketones with Acetest®, Ketostix®, Labstix®

Monitoring ParametersBlood pressure, standing and sitting/supine; symptoms of parkinsonism, dyskinesias, mental status

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness and adverse reactions (including levodopa toxicity) at beginning of therapy and periodically throughout therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed; do not change dosage or discontinue without consulting prescriber. Do not crush sustained release form. Therapeutic effects may take several weeks or months to achieve and you may need frequent monitoring during first weeks of therapy. Take with meals if GI upset occurs, before meals if dry mouth occurs, after eating if drooling or if nausea occurs. Take at the same time each day. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake; void before taking medication. Do not use alcohol and prescription or OTC sedatives or CNS depressants without consulting prescriber. Urine or perspiration may appear darker. You may experience drowsiness, dizziness, confusion, or vision changes (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); loss of impulse control (possibly manifested as pathological gambling, libido increases, and/or binge eating); orthostatic hypotension (use caution when changing position - rising to standing from sitting or lying); increased susceptibility to heat stroke, decreased perspiration (use caution in hot weather - maintain adequate fluids and reduce exercise activity); constipation (increased exercise, fluids, fruit, or fiber may help); dry skin or nasal passages (consult prescriber for appropriate relief); or nausea, vomiting, loss of appetite, or stomach discomfort (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report unresolved constipation or vomiting; chest pain or irregular heartbeat; respiratory difficulty; acute headache or dizziness; CNS changes (hallucination, loss of memory, nervousness, etc); suicide ideation; painful or difficult urination; abdominal pain or blood in stool; increased muscle spasticity or rigidity; skin rash; or significant worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 10/100: Carbidopa 10 mg and levodopa 100 mg; 25/100: Carbidopa 25 mg and levodopa 100 mg; 25/250: Carbidopa 25 mg and levodopa 250 mg

Sinemet®:

10/100: Carbidopa 10 mg and levodopa 100 mg

25/100: Carbidopa 25 mg and levodopa 100 mg

25/250: Carbidopa 25 mg and levodopa 250 mg

Tablet, extended release: 25/100: Carbidopa 25 mg and levodopa 100 mg; 50/200: Carbidopa 50 mg and levodopa 200 mg

Tablet, orally disintegrating: 10/100: Carbidopa 10 mg and levodopa 100 mg; 25/100: Carbidopa 25 mg and levodopa 100 mg; 25/250: Carbidopa 25 mg and levodopa 250 mg

Parcopa™:

10/100: Carbidopa 10 mg and levodopa 100 mg [contains phenylalanine 3.4 mg/tablet; mint flavor]

25/100: Carbidopa 25 mg and levodopa 100 mg [contains phenylalanine 3.4 mg/tablet; mint flavor]

25/250: Carbidopa 25 mg and levodopa 250 mg [contains phenylalanine 8.4 mg/tablet; mint flavor]

Tablet, sustained release: 25/100: Carbidopa 25 mg and levodopa 100 mg; 50/200: Carbidopa 50 mg and levodopa 200 mg

Sinemet® CR:

25/100: Carbidopa 25 mg and levodopa 100 mg

50/200: Carbidopa 50 mg and levodopa 200 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, controlled release (Carbidopa-Levodopa CR)

25-100 mg (60): $40.99

50-200 mg (60): $80.99

Tablet, controlled release (Sinemet CR)

25-100 mg (60): $72.53

50-200 mg (60): $131.86

Tablet, orally-disintegrating (Parcopa)

10-100 mg (30): $29.66

25-100 mg (30): $39.02

25-250 mg (30): $47.03

Tablets (Carbidopa-Levodopa)

10-100 mg (90): $34.99

25-100 mg (90): $39.99

25-250 mg (60): $33.99

Tablets (Sinemet)

10-100 mg (90): $85.19

25-100 mg (90): $105.98

25-250 mg (60): $82.77

Mechanism of ActionParkinson's symptoms are due to a lack of striatal dopamine; levodopa circulates in the plasma to the blood-brain-barrier (BBB), where it crosses, to be converted by striatal enzymes to dopamine; carbidopa inhibits the peripheral plasma breakdown of levodopa by inhibiting its decarboxylation, and thereby increases available levodopa at the BBB

Pharmacodynamics/Kinetics

Duration: Variable, 6-12 hours; longer with sustained release forms

See individual agents.

Related Information

- Antiparkinsonian Agents

Pharmacotherapy Pearls50-100 mg/day of carbidopa is needed to block the peripheral conversion of levodopa to dopamine. “On-off” (a clinical syndrome characterized by sudden periods of drug activity/inactivity), can be managed by giving smaller, more frequent doses of Sinemet® or adding a dopamine agonist or selegiline; when adding a new agent, doses of Sinemet® can usually be decreased. Protein in the diet should be distributed throughout the day to avoid fluctuations in levodopa absorption. Levodopa is the drug of choice when rigidity is the predominant presenting symptom.

Conversion from levodopa to carbidopa/levodopa: **Note:** Levodopa must be discontinued at least 12 hours prior to initiation of levodopa/carbidopa:

Initial dose: Levodopa portion of carbidopa/levodopa should be at least 25% of previous levodopa therapy.

Levodopa <1500 mg/day: Sinemet® or Parcopa™ (levodopa 25 mg/carbidopa 100 mg) 3-4 times/day

Levodopa ≥1500 mg/day: Sinemet® or Parcopa™ (levodopa 25 mg/carbidopa 250 mg) 3-4 times/day

Conversion from immediate release carbidopa/levodopa (Sinemet® or Parcopa™) to Sinemet® CR (50/200):

Sinemet® or Parcopa™ [total daily dose of levodopa]/Sinemet® CR:

Sinemet® or Parcopa™ (levodopa 300-400 mg/day): Sinemet® CR (50/200) 1 tablet twice daily

Sinemet® or Parcopa™ (levodopa 500-600 mg/day): Sinemet® CR (50/200) 1 1/2 tablets twice daily or 1 tablet 3 times/day

Sinemet® or Parcopa™ (levodopa 700-800 mg/day): Sinemet® CR (50/200) 4 tablets in 3 or more divided doses

Sinemet® or Parcopa™ (levodopa 900-1000 mg/day): Sinemet® CR (50/200) 5 tablets in 3 or more divided doses

Intervals between doses of Sinemet® CR should be 4-8 hours while awake; when divided doses are not equal, smaller doses should be given toward the end of the day,

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and taste alterations. Dopaminergic therapy in Parkinson's disease (ie, treatment with levodopa and carbidopa combination) is associated with orthostatic hypotension. Patients medicated with this drug combination should be carefully assisted from the chair and observed for signs of orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Anesthesia and Critical Care Concerns/Other ConsiderationsConsider use of alternative therapies before attempting to use levodopa containing products.

50-100 mg/day of carbidopa is needed to block the peripheral conversion of levodopa to dopamine. “On-off” (a clinical syndrome characterized by sudden periods of drug activity/inactivity), can be managed by giving smaller, more frequent doses of Sinemet® or adding a dopamine agonist or selegiline; when adding a new agent, doses of Sinemet® can usually be decreased. Protein in the diet should be distributed throughout the day to avoid fluctuations in levodopa absorption. Levodopa is the drug of choice when rigidity is the predominant presenting symptom.

Index TermsLevodopa and Carbidopa

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International Brand NamesApo-Levotard (MY); Carbilev (ZA); Cardopar (SG); Carlevod (AR); Cinetol (PE); Cronomet (BR); Dopadura (DE); Dopicar (IL); DuoDopa (BE, GB, IE); Grifoparkin (CN, PE); Kinson (AU); Lebocar (AR); Levohexal (AU); Levomed (HK, MY); Levomet (HK, SG, TH); Nakom (EE); Parken (CO); Parkin (KP); Parkomet (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Racovel (MX); Saniter (CN); Sindopa (NZ); Sinedopa (HK); Sinemet (AT, AU, BE, BG, BR, CH, CZ, DE, DK, EG, ES, FI, FR, GB, GR, HK, HN, IE, IT, KP, MX, MY, NL, NO, PK, PT, PY, RU, SE, TH, TR, TW, UY, VE); Sinemet 25 100 (HK, MY, PH); Sinemet CR (AU, BE, BG, CH, CL, CZ, GB, GR, HK, HN, IL, IT, MY, NL, PE, PH, PT, RU); Sinemet Retard (ES); Sulconar (PE); Syndopa (IN); Tidomet (PH); Tidomet Forte (IN, SG); Tidomet L.S. (IN); Tidomet Plus (IN)

English

Jump To Field (Select Field Name)

Medication Safety Issues

International issues:

Lodosyn® may be confused with Lidosen® which is a brand name for lidocaine in Italy

Pronunciation(kar bi DOE pa)
U.S. Brand NamesLodosyn®
Pharmacologic CategoryAnti-Parkinson's Agent, Dopamine Agonist
Use: Labeled IndicationsGiven with levodopa in the treatment of parkinsonism to enable a lower dosage of levodopa to be used and a more rapid response to be obtained and to decrease side effects; for details of administration and dosage, see Levodopa; has no effect without levodopa
Dosing: AdultsParkinson's disease (adjunct to levodopa): Oral: 70-100 mg/day; maximum daily dose: 200 mg
Dosing: ElderlyRefer to adult dosing.
Dietary ConsiderationsMay be taken with meals to decrease GI upset.
ContraindicationsHypersensitivity to carbidopa or levodopa, or any component of the formulation; use of nonselective MAO antagonists; narrow-angle glaucoma; history of melanoma or undiagnosed skin lesions
Warnings/Precautions

Concerns related to adverse effects:

- Dyskinesias: May occur at lower levodopa dosages than with monotherapy (levodopa dosage may need to be reduced).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease, including a history of myocardial infarction and arrhythmias.
- Endocrine disease: Use with caution in patients with endocrine disease.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Peptic ulcer disease: Use with caution in patients with peptic ulcer disease.
- Psychotic disorders: Use with extreme caution in patients with psychotic disorders; observe patients closely for development of depression with concomitant suicidal tendencies.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Other warnings/precautions:

- Antiparkinsonian activity: Has no antiparkinsonian activity when administered alone.
- Discontinuation of therapy: Dopaminergic agents have been associated with a syndrome resembling neuroleptic malignant syndrome on abrupt withdrawal or significant dosage reduction after long-term use.

Pregnancy Risk FactorC
Adverse ReactionsAdverse reactions are associated with concomitant administration with levodopa

>10%: Central nervous system: Anxiety, confusion, nervousness, mental depression

1% to 10%:

Cardiovascular: Orthostatic hypotension, palpitation, cardiac arrhythmia

Central nervous system: Memory loss, insomnia, fatigue, hallucinations, ataxia, dystonic movements

Gastrointestinal: Nausea, vomiting, GI bleeding

Ocular: Blurred vision

<1%: Hypertension, duodenal ulcer, hemolytic anemia

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 25 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Lodosyn)

25 mg (30): $30.76

Mechanism of ActionCarbidopa is a peripheral decarboxylase inhibitor with little or no pharmacological activity when given alone in usual doses. It inhibits the peripheral decarboxylation of levodopa to dopamine; and as it does not cross the blood-brain barrier, unlike levodopa, effective brain concentrations of dopamine are produced with lower doses of levodopa. At the same time, reduced peripheral formation of dopamine reduces peripheral side-effects, notably nausea and vomiting, and cardiac arrhythmias, although the dyskinesias and adverse mental effects associated with levodopa therapy tend to develop earlier.
Pharmacodynamics/Kinetics

Absorption: 40% to 70%

Distribution: Does not cross the blood-brain barrier; in rats, reported to cross placenta and be excreted in milk

Protein binding: 36%

Half-life elimination: 1-2 hours

Excretion: Urine (as unchanged drug and metabolites)

Related Information

- Carbidopa and Levodopa

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension. Dopaminergic therapy in Parkinson's disease includes the use of carbidopa in combination with levodopa. Carbidopa/levodopa combination is associated with orthostatic hypotension. Patients medicated with this drug combination should be carefully assisted from the chair and observed for signs of orthostatic hypotension.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
International Brand NamesDuellin [+ Levodopa] (PL); Nakom [+ Levodopa] (PL); Pardopa [+ Levidopa] (PL); Poldomet [+ Levidopa] (PL); Sinemet [+ Levodopa] (PL)

Carbinoxamine and Pseudoephedrine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(kar bi NOKS a meen & soo doe e FED rin)

U.S. Brand NamesAndehist NR Drops [DSC]; Carbaxefed RF [DSC]; Carboxine-PSE [DSC]; Cordron-D NR [DSC]; Hydro-Tussin™-CBX [DSC]; Palgic®-D [DSC]; Palgic®-DS [DSC]; Pediatex™-D [DSC]; Sildec [DSC]

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSeasonal and perennial allergic rhinitis; vasomotor rhinitis

Dosing: AdultsNasal congestion, allergic symptoms: Oral:

Liquid (Pediatex™-D): 10 mL 4 times/day

Syrup (Hydro-Tussin™-CBX, Palgic®-DS): 10 mL 4 times/day

Tablet, timed release (Palgic®-D): 1 tablet every 12 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricNasal congestion, allergic symptoms: Oral:

Children:

Drops (Andehist NR, Carbaxefed RF, Sildec):

1-3 months: 0.25 mL 4 times/day

3-6 months: 0.5 mL 4 times/day

6-12 months: 0.75 mL 4 times/day

12-24 months: 1 mL 4 times/day

Liquid (Pediatex™-D):

1-3 months: 1.25 mL up to 4 times/day

3-6 months: 2.5 mL up to 4 times/day

6-9 months: 3.75 mL up to 4 times/day

9-18 months: 3.75-5 mL up to 4 times/day

18 months to 6 years: 5 mL 3-4 times/day

>6 years: Refer to adult dosing.

Syrup (Hydro-Tussin™-CBX, Palgic®-DS):

1-3 months: 1.25 mL up to 4 times/day

3-6 months: 2.5 mL up to 4 times/day

6-9 months: 3.75 mL up to 4 times/day

9-18 months: 3.75-5 mL up to 4 times/day

18 months to 6 years: 5 mL 3-4 times/day

>6 years: Refer to adult dosing.

Tablet, timed release:

6-12 years (Palgic®-D): One-half tablet every 12 hours

≥12 years (Palgic®-D): Refer to adult dosing.

Administration: OralPalgic®-D: Tablets may be broken in half; do not crush or chew.
StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to carbinoxamine, pseudoephedrine, or any component of the formulation; severe hypertension or coronary artery disease; MAO inhibitor therapy; GI or GU obstruction; peptic ulcer disease; narrow-angle glaucoma; avoid use in premature or term infants due to a possible association with SIDS; acute asthma attack
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Asthma: Use with caution in patients with a history of asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children. Safety and efficacy have not been established in children <1 month of age. Use with caution in atopic children.

Geriatric ConsiderationsElderly are more predisposed to adverse effects of sympathomimetics since they frequently have cardiovascular diseases and diabetes mellitus, and may be on multidrug therapy. It may be advisable to treat with a short-acting immediate-release formulation before initiating sustained-release long-acting formulations. Carbinoxamine exhibits anticholinergic action which may cause constipation, urinary retention, and mental confusion in the elderly.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsSmall amounts of antihistamines and pseudoephedrine are excreted in breast milk. Premature infants and newborns have a higher risk of intolerance to antihistamines. Antihistamines may inhibit lactation.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, cardiovascular collapse, hypertension, pallor, tachycardia

Central nervous system: Anxiety, convulsions, CNS stimulation, dizziness, excitability (children; rare), fear, hallucinations, headache, insomnia, nervousness, restlessness, sedation

Gastrointestinal: Anorexia, diarrhea, dyspepsia, nausea, vomiting, xerostomia

Neuromuscular skeletal: Tremors, weakness

Ocular: Diplopia

Renal: Dysuria, polyuria, urinary retention (with BPH)

Respiratory: Respiratory difficulty

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Nursing: Physical Assessment/MonitoringSee individual agent for Pseudoephedrine.

Patient EducationSee individual agent for Pseudoephedrine.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Liquid:

Cordron-D NR: Carbinoxamine maleate 2 mg and pseudoephedrine hydrochloride 12.5 mg per 5 mL (480 mL) [cotton candy flavor] [DSC]

Pediatex™-D: Carbinoxamine maleate 2 mg and pseudoephedrine hydrochloride 20 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; cotton candy flavor] [DSC]

Solution: Carbinoxamine maleate 2 mg and pseudoephedrine hydrochloride 25 mg per 5 mL (480 mL) [DSC]

Carboxine-PSE: Carbinoxamine maleate 2 mg and pseudoephedrine hydrochloride 20 mg per 5 mL (480 mL) [peach flavor] [DSC]

Solution, oral drops:

Andehist NR: Carbinoxamine maleate 1 mg and pseudoephedrine hydrochloride 15 mg per mL (30 mL) [alcohol and sugar free; raspberry flavor] [DSC]

Carbaxefed RF: Carbinoxamine maleate 1 mg and pseudoephedrine hydrochloride 15 mg per mL (30 mL) [alcohol free; contains sodium benzoate; cherry flavor] [DSC]

Sildec: Carbinoxamine maleate 1 mg and pseudoephedrine hydrochloride 15 mg per mL (30 mL) [raspberry flavor] [DSC]

Syrup: Carbinoxamine maleate 2 mg and pseudoephedrine hydrochloride 25 mg per 5 mL (480 mL)

Hydro-Tussin™-CBX [DSC], Palgic®-DS [DSC]: Carbinoxamine maleate 2 mg and pseudoephedrine hydrochloride 25 mg per 5 mL (480 mL) [alcohol, dye, and sugar free; strawberry/pineapple flavor]

Tablet, timed release:

Palgic®-D: Carbinoxamine maleate 8 mg and pseudoephedrine hydrochloride 80 mg [dye free] [DSC]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablet, 12-hour (Rondec-TR)

8-120 mg (30): $42.99

Mechanism of ActionCarbinoxamine competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract; pseudoephedrine, a sympathomimetic amine and isomer of ephedrine, acts as a decongestant in respiratory tract mucous membranes with less vasoconstrictor action than ephedrine in normotensive individuals
Related Information

- Carbinoxamine
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response
Mental Health: Effects on Mental StatusDrowsiness is common; may cause fatigue, nervousness, or dizziness; may rarely produce depression
Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors; concurrent use with sedating psychotropics or CNS depressants may produce additive adverse effects
Index TermsPseudoephedrine and Carbinoxamine
International Brand NamesPrindex Pediátrico (MX)

Carbinoxamine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state "Do not use in children under four years of age." In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, "Infant Deaths Associated with Cough and Cold Medications - Two States, 2005," *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(kar bi NOKS a meen)

U.S. Brand NamesPalgic®

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSeasonal and perennial allergic rhinitis; vasomotor rhinitis; urticaria; decrease severity of other allergic reactions

Dosing: Adults

Allergic rhinitis/urticaria: Oral (Palgic®): 4-8 mg 3-4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Allergic rhinitis/urticaria:** Oral (Palgic®): Children:

>3-6 years: 2-5 mg 3-4 times/day

>6 years: 4-6 mg 3-4 times/day

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to carbinoxamine or any component of the formulation; use with or within 14 days of MAO inhibitor therapy; children <2 years of age; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Asthma: Use with caution in patients with a history of asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children. Safety and efficacy have not been established in children <2 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsIt is not known if carbinoxamine is found in breast milk; prolonged or large doses may cause drowsiness in breast-feeding infants. Use while breast-feeding is contraindicated by the manufacturer.

Adverse ReactionsFrequency not defined.

Cardiovascular: Extrasystoles, hypotension, palpitation, tachycardia

Central nervous system: Chills, confusion, coordination impaired (most frequent), dizziness (most frequent), euphoria, excitability (children), fatigue, headache, insomnia, irritability, nervousness, neuritis, restlessness, sedation (most frequent), seizure, sleepiness (most frequent), vertigo

Dermatologic: Photosensitivity, rash, urticaria

Endocrine & metabolic: Early menses

Gastrointestinal: Anorexia, constipation, diarrhea, epigastric distress (most frequent), heartburn, nausea, vomiting, xerostomia

Genitourinary: Difficult urination, urinary frequency, urinary retention

Hematologic: Agranulocytosis, hemolytic anemia, thrombocytopenia

Neuromuscular & skeletal: Paresthesia, tremor, weakness

Ocular: Blurred vision, diplopia

Otic: Labyrinthitis, tinnitus

Renal: Polyuria

Respiratory: Bronchial secretions thickening (most frequent), chest tightness, nasal congestion, nasopharyngeal dryness, wheezing

Miscellaneous: Hypersensitivity reactions (including anaphylactic shock), diaphoresis

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, as maleate:

Palgic®: 4 mg/5 mL (480 mL) [bubble gum flavor]

Tablet, as maleate [scored]:

Palgic®: 4 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Palgic)

4 mg (60): $57.76

Mechanism of ActionCarbinoxamine competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract.

Pharmacodynamics/KineticsHalf-life elimination: 10-20 hours

Pharmacotherapy PearlsCarbinoxamine maleate is ~71% carbinoxamine.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, nervousness, or sedation; may cause excitability in children

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment; concurrent use with psychotropics may produce additive sedation

Index TermsCarbinoxamine Maleate

International Brand NamesAllergefon (FR); Histin (TH); Prindex (MX); Upvena (TW)

Carbo-Tax (Adenocarcinoma)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Adenocarcinoma (Unknown Primary)
Use: Labeled Indications Adenocarcinoma, unknown primary
Regimen Use Adenocarcinoma, unknown primary
Index Terms Paclitaxel-Carboplatin (Adenocarcinoma)
Regimen

Paclitaxel: I.V.: 135 mg/m^2 infused over 24 hours day 1,

[total dose = 135 mg/m^2]

followed by

Carboplatin: I.V.: Target AUC 7.5

[total dose = AUC = 7.5]

Repeat cycle every 21 days

References

Sulkes A, Uziely B, Isacson R, et al, “Combination Chemotherapy in Metastatic Tumors of Unknown Origin. 5-Fluorouracil, Adriamycin®, and Mitomycin C for Adenocarcinomas and Adriamycin®, Vinblastine and Mitomycin C for Anaplastic Carcinomas,” *Isr J Med Sci*, 1988, 24(9-10):604-10.[PubMed 3204009]

Carbo-Tax (NSCLC)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lung Cancer (Nonsmall Cell)

Regimen Use Lung cancer, nonsmall cell

Index Terms Paclitaxel-Carboplatin (Nonsmall Cell Lung Cancer)

Regimen

Paclitaxel: I.V.: 135-215 mg/m^2 infused over 24 hours day 1

[total dose/cycle = 135-215 mg/m^2]

or I.V.: 175 mg/m^2 infused over 3 hours day 1

[total dose/cycle = 175 mg/m^2]

followed by

Carboplatin: I.V.: Target AUC 7.5

[total dose/cycle = AUC = 7.5]

Repeat cycle every 21 days

References

Langer CJ, Leighton JC, Comis RL, et al, âPaclitaxel By 24- or 1-hour Infusion in Combination With Carboplatin in Advanced Nonsmall-Cell Lung Cancer: The Fox Chase Cancer Center Experience,â *Semin Oncol*, 1995, 22(4 Suppl 9):18-29.[PubMed 7544025]

Carbo-Tax (Ovarian Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category [Chemotherapy Regimen, Ovarian Cancer]

Regimen Use Ovarian cancer

Index Terms Paclitaxel-Carboplatin (Ovarian Cancer)

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Paclitaxel: I.V.: 135 mg/m^2 infused over 24 hours day 1

[total dose/cycle = 135 mg/m^2]

or I.V.: 175 mg/m^2 infused over 3 hours day 1

[total dose/cycle = 175 mg/m^2]

followed by

Carboplatin: I.V.: Target AUC 5

[total dose/cycle = AUC = 5]

Repeat cycle every 21 days

Variation 2:

Paclitaxel: I.V.: 175 mg/m^2 day 1

[total dose/cycle = 175 mg/m^2]

Carboplatin: I.V.: AUC 7.5 day 1

[total dose/cycle = AUC = 7.5]

Repeat cycle every 21 days

Variation 3:

Paclitaxel: I.V.: 185 mg/m^2 day 1

[total dose/cycle = 185 mg/m^2]

Carboplatin: I.V.: AUC 6 day 1

[total dose/cycle = AUC = 6]

Repeat cycle every 21 days

References

Variation 1:

Ozols RF, “Carboplatin and Paclitaxel in Ovarian Cancer,” *Semin Oncol*, 1995, 22(3 Suppl 6):78-83. [PubMed 7541158]

Ozols RF, “Update of the NCCN Ovarian Cancer Practice Guidelines,” *Oncology (Huntingt)*, 1997, 11(11A):95-105. [PubMed 9430180]

Variation 2:

Ozols RF, “Combination Regimens of Paclitaxel and the Platinum Drugs as First-Line Regimens for Ovarian Cancer,” *Semin Oncol*, 1995, 22(6 Suppl 15):1-6. [PubMed 8643963]

Variation 3:

Meerpohl HG, du Bois A, Kuhnle H, et al, “Paclitaxel Combined With Carboplatin in the First-Line Treatment of Advanced Ovarian Cancer,” *Semin Oncol*, 1995, 22(6 Suppl 15):7-12.[PubMed 8643973]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Head and Neck Cancer

Regimen UseHead and neck cancer

Index TermsCetuximab-Carboplatin

Regimen

Cycle 1:

Cetuximab: I.V.: 400 mg/m^2 (loading dose) day 1 (week 1, cycle 1 only)

[total loading dose = 400 mg/m^2]

followed by I.V.: 250 mg/m^2/day days 8 and 15

[total dose/cycle 1 = 900 mg/m^2]

Carboplatin: I.V.: AUC 5 day 1

[total dose/cycle = AUC = 5]

Treatment cycle is 3 weeks

Subsequent cycles:

Cetuximab: I.V.: 250 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 750 mg/m^2]

Carboplatin: I.V.: AUC 5 day 1

[total dose/cycle = AUC = 5]

Repeat cycle every 3 weeks

References

Chan AT, Hsu MM, Goh BC, et al, "Multicenter, Phase II Study of Cetuximab in Combination With Carboplatin in Patients With Recurrent or Metastatic Nasopharyngeal Carcinoma," *J Clin Oncol*, 2005, 23(15):3568-76.[PubMed 15809453]

CARBOplatin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

CARBOplatin may be confused with CISplatin, oxaliplatin

Paraplatin® may be confused with Platinol®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(KAR boe pla tin)

Canadian Brand NamesParaplatin-AQ

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent; Antineoplastic Agent, Platinum Analog

Use: Labeled IndicationsTreatment of ovarian cancer

Use: Unlabeled/InvestigationalLung cancer, head and neck cancer, endometrial cancer, esophageal cancer, bladder cancer, breast cancer, cervical cancer, CNS tumors, germ cell tumors, osteogenic sarcoma, and high-dose therapy with stem cell/bone marrow support

Dosing: AdultsRefer to individual protocols: **Note:** Doses are usually determined by the AUC using the Calvert formula.

IVPB, I.V. infusion:

Ovarian cancer: 300-360 mg/m^2 every 4 weeks

Autologous BMT (unlabeled use): 1600 mg/m^2 (total dose) divided over 4 days

In adults, dosing is commonly calculated using the Calvert formula:

Total dose (mg) = Target AUC x (GFR + 25)

Usual target AUCs:

Previously untreated patients: 6-8

Previously treated patients: 4-6

Intraperitoneal (unlabeled use): 200-650 mg/m^2 in 2 L of dialysis fluid have been administered into the peritoneum of ovarian cancer patients or target AUC: 5-7

Dosing: ElderlyThe Calvert formula should be used to calculate dosing for elderly patients.

Dosing: PediatricRefer to individual protocols:

IVPB, I.V. infusion:

Solid tumor (unlabeled use): 300-600 mg/m^2 once every 4 weeks

Brain tumor (unlabeled use): 175 mg/m^2 weekly for 4 weeks every 6 weeks, with a 2-week recovery period between courses

Dosing: Renal Impairment**Note:** Dose determination with Calvert formula uses GFR and, therefore, inherently adjusts for renal dysfunction.

The FDA-approved labeling recommends the following dosage adjustment guidelines:

Baseline Cl_{cr} 41-59 mL/minute: Initiate at 250 mg/m^2 and adjust subsequent doses based on bone marrow toxicity

Baseline Cl_{cr} 16-40 mL/minute: Initiate at 200 mg/m^2 and adjust subsequent doses based on bone marrow toxicity

Baseline Cl_{cr} ≤15 mL/minute: No guidelines are available.

The following dosage adjustments have been used by some clinicians (Aronoff, 2007): Adults (for dosing based on mg/m^2):

Hemodialysis: Administer 50% of dose

Continuous ambulatory peritoneal dialysis (CAPD): Administer 25% of dose

Continuous renal replacement therapy (CRRT): 200 mg/m^2

Dosing: Hepatic ImpairmentMinimal hepatic metabolism; dosage adjustment may not be needed. No specific dosage adjustment guidelines are available.

Dosing: Adjustment for ToxicityPlatelets <50,000 cells/mm^3 or ANC <500 cells/mm^3: Administer 75% of dose

Dosing: Combination Regimens

Adenocarcinoma, unknown primary:

- Carbo-Tax (Adenocarcinoma)
- Paclitaxel-Carboplatin-Etoposide
- PCE

Bladder cancer:

- Gemcitabine-Carboplatin (Bladder Cancer)
- Paclitaxel-Carboplatin (Bladder Cancer)
- Paclitaxel-Carboplatin-Gemcitabine

Breast cancer:

- Docetaxel-Trastuzumab-Carboplatin
- ICE-T
- Trastuzumab-Paclitaxel-Carboplatin

Cervical cancer: Paclitaxel-Carboplatin (Cervical Cancer)

Head and neck cancer:

- Carboplatin-Cetuximab
- Cetuximab-Carboplatin-Fluorouracil
- Fluorouracil + Carboplatin

Lung cancer (nonsmall cell):

- Carbo-Tax (NSCLC)
- CaT (NSCLC)
- EC (NSCLC)
- Gemcitabine-Carboplatin (NSCLC)
- Paclitaxel-Carboplatin-Bevacizumab
- PC (NSCLC)

Lung cancer (small cell): EC (Small Cell Lung Cancer)

Lymphoma, non-Hodgkin's:

- ICE (Lymphoma, non-Hodgkin's)
- RICE

Malignant pleural mesothelioma: Pemetrexed-Carboplatin

Neuroblastoma:

- CE (Neuroblastoma)
- CE-CAdO
- CI (Neuroblastoma)

Osteosarcoma: ICE (Sarcoma)

Ovarian cancer:

- Carbo-Tax (Ovarian Cancer)
- CaT (Ovarian Cancer)
- CC
- Gemcitabine-Carboplatin (Ovarian Cancer)

Prostate cancer:

Estramustine + Docetaxel + Carboplatin

Paclitaxel + Estramustine + Carboplatin

Retinoblastoma: CE (Retinoblastoma)

Rhabdomyosarcoma: CEV

Sarcoma, soft tissue:

ICE (Sarcoma)

ICE-T

Oncology: Bone Marrow - High DoseI.V.: 1.2-2.4 g/m^2 administered as 3-4 divided doses every 24-48 hours; generally infused over at least 60 minutes; 400 mg/m^2 has been infused over 15-30 minutes; generally combined with other high-dose chemotherapeutic drugs.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Calvert Formula

Administration: I.V.Infuse over 15 minutes to 24 hours. May also be administered intraperitoneally. When administered as sequential infusions, taxane derivatives (docetaxel, paclitaxel) should be administered before platinum derivatives to limit myelosuppression and to enhance efficacy.

Administration: I.V. DetailObserve serum creatinine. Carboplatin is nephrotoxic and drug accumulation occurs with decreased creatinine clearance.

pH: 5-7

StorageStore intact vials at room temperature of 15°C to 30°C (59°F to 86°F); protect from light. Further dilution to a concentration as low as 0.5 mg/mL is stable at room temperature (25°C) for 8 hours in NS; stable at room temperature or under refrigeration for at least 9 days in D_5W, although the manufacturer states to use within 8 hours due to lack of preservative.

Powder for reconstitution: Reconstituted to a final concentration of 10 mg/mL is stable for 5 days at room temperature (25°C).

Solution for injection: Multidose vials are stable for up to 14 days after opening when stored at room temperature.

ReconstitutionReconstitute powder to yield a final concentration of 10 mg/mL. Reconstituted carboplatin 10 mg/mL should be further diluted to a final concentration of 0.5-2 mg/mL with D_5W or NS for administration.

CompatibilityStable in $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, NS.

Y-site administration: Compatible: Allopurinol, amifostine, aztreonam, cefepime, cladribine, doxorubicin liposome, etoposide phosphate, filgrastim, fludarabine, gatifloxacin, gemcitabine, granisetron, linezolid, melphalan, ondansetron, paclitaxel, piperacillin/tazobactam, propofol, sargramostim, teniposide, thiotepa, topotecan, vinorelbine. **Incompatible:** Amphotericin B cholesteryl sulfate complex.

Compatibility when admixed: Compatible: Cisplatin, etoposide, floxuridine, ifosfamide, ifosfamide with etoposide, paclitaxel. **Incompatible:** Fluorouracil, mesna.

ContraindicationsHistory of severe allergic reaction to cisplatin, carboplatin, other platinum-containing formulations, or any component of the formulation; pregnancy; breast-feeding

Allergy Considerations

- Platinum Derivative Allergy

Warnings/Precautions

Boxed warnings:

- Allergic reactions: See “Concerns related to adverse effects” below.
- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.
- Vomiting: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Allergic reactions: **[U.S. Boxed Warning]: Increased risk of allergic reactions**in patients previously exposed to platinum therapy.
- Bone marrow suppression: **[U.S. Boxed Warning]: Bone marrow suppression, which may be severe, is dose related;** reduce dosage in patients with bone marrow suppression and impaired renal function. Anemia is cumulative.
- Liver function abnormalities: High doses have resulted in severe abnormalities of liver function tests.

- Vision loss: Loss of vision (reversible) has been reported with higher than recommended doses.
- Vomiting: **[U.S. Boxed Warning]: May occur and is dose related.**

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Cisplatin: There is an increased incidence of peripheral neuropathy in patients who have previously received cisplatin.
- Taxane derivatives: When administered as sequential infusions, taxane derivatives (docetaxel, paclitaxel) should be administered before the platinum derivatives (carboplatin, cisplatin) to limit myelosuppression and to enhance efficacy.

Special populations:

- Elderly: There is an increased incidence of peripheral neuropathy in patients >65 years of age.
- Pediatrics: Clinically significant hearing loss has been reported to occur in pediatric patients when therapy was administered at higher than recommended doses in combination with other ototoxic agents.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Geriatric ConsiderationsPeripheral neuropathy is more frequent in patients >65 years of age.
Pregnancy Risk FactorD
LactationExcretion in breast milk unknown/contraindicated
Breast-Feeding ConsiderationsDue to the potential for toxicity in nursing infants, breast-feeding is contraindicated.
Adverse ReactionsPercentages reported with single-agent therapy.

>10%:

Central nervous system: Pain (23%)

Endocrine & metabolic: Hyponatremia (29% to 47%), hypomagnesemia (29% to 43%), hypocalcemia(22% to 31%), hypokalemia (20% to 28%)

Gastrointestinal: Vomiting (65% to 81%), abdominal pain (17%), nausea (10% to 15%)

Hematologic: Myelosuppression (dose related and dose limiting; nadir at ~21 days; recovery by ~28 days), leukopenia (85%; grades 3/4: 15% to 26%), anemia (71% to 90%; grades 3/4: 21%), neutropenia (67%; grades 3/4: 16% to 21%), thrombocytopenia (62%; grades 3/4: 25% to 35%)

Hepatic: Alkaline phosphatase increased (24% to 37%), AST increased (15% to 19%)

Neuromuscular & skeletal: Weakness (11%)

Renal: Creatinine clearance decreased (27%), BUN increased (14% to 22%)

1% to 10%:

Central nervous system: Neurotoxicity (5%)

Dermatologic: Alopecia (2% to 3%)

Gastrointestinal: Constipation (5%), diarrhea (6%), stomatitis/mucositis (1%), taste dysgeusia (1%)

Hematologic: Hemorrhagic complications (5%)

Hepatic: Bilirubin increased (5%)

Local: Pain at injection site

Neuromuscular & skeletal: Peripheral neuropathy (4% to 6%; up to 10% in older and/or previously-treated patients)

Ocular: Visual disturbance (1%)

Otic: Ototoxicity (1%)

Renal: Creatinine increased (6% to 10%)

Miscellaneous: Infection (5%), hypersensitivity (2%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Anaphylaxis, anorexia, bronchospasm, cardiac failure, cerebrovascular accident, embolism, erythema, fever, hemolytic uremic syndrome (HUS), hyper-/hypotension, malaise, necrosis (associated with extravasation), nephrotoxicity, neurotoxicity, pruritus, rash, secondary malignancies, urticaria, vision loss

Oncology: VesicantNo
Oncology: Emetic PotentialModerate (30% to 60%)
Oncology: Bone Marrow - Unique Toxicity

Dermatologic: Alopecia

Endocrine & metabolic: Hypokalemia, hypomagnesemia

Gastrointestinal: Nausea, vomiting, mucositis

Hepatic: Liver function tests elevated

Renal: Nephrotoxicity

Drug Interactions

Aminoglycosides: May enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Taxane Derivatives: Platinum Derivatives may enhance the myelosuppressive effect of Taxane Derivatives. Administer Taxane derivative before Platinum derivative when given as sequential infusions to limit toxicity. *Risk D: Consider therapy modification*

Topotecan: Platinum Derivatives may enhance the adverse/toxic effect of Topotecan. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid black cohosh, dong quai in estrogen-dependent tumors.

Monitoring ParametersCBC (with differential and platelet count), serum electrolytes, creatinine clearance, liver function tests, BUN, creatinine

Nursing: Physical Assessment/MonitoringAssess patient allergy history prior to therapy and note specific use cautions (eg, bone marrow suppression and renal function). Assess other pharmacological or herbal products patient may be taking for potential interactions (especially products that may be ototoxic or nephrotoxic and need for sequencing with taxane derivatives). Assess results of laboratory tests (hematology, electrolytes, renal and hepatic function), prior to treatment and on a regular basis during therapy. Monitor patient response (eg, nausea and vomiting; pretreatment with antiemetic may be required), ototoxicity (audiometry may be advisable), bone marrow depression, anemia, bleeding, peripheral neuropathy frequently throughout therapy. Teach patient (or caregiver) possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelet count, serum electrolytes, creatinine clearance, liver function, BUN, creatinine

Patient EducationDo not take any new medication during therapy unless approved by healthcare provider. This medicine can only be administered intravenously. Report immediately any redness, burning, pain, or swelling at infusion site. It is important that you maintain adequate nutrition (small, frequent meals may help) and adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will be susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea and vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help - if unresolved, consult prescriber for antiemetic); mouth sores (use soft toothbrush or cotton swabs for mouth care); or loss of hair (reversible). Report chest pain or palpitations; sore throat, fever, chills, unusual fatigue; unusual bruising/bleeding; respiratory difficulty; numbness, pain, or tingling in extremities; muscle cramps or twitching; change in hearing acuity; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Male: Do not cause a female to become pregnant. Male/female: Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution: 50 mg, 150 mg, 450 mg

Injection, solution: 10 mg/mL (5 mL, 15 mL, 45 mL, 60 mL)

Injection, solution [preservative free]: 10 mg/mL (5 mL, 15 mL, 45 mL)

Generic AvailableYes

Mechanism of ActionCarboplatin is an alkylating agent which covalently binds to DNA; possible cross-linking and interference with the function of DNA

Pharmacodynamics/Kinetics

Distribution: V_d: 16 L/kg; into liver, kidney, skin, and tumor tissue

Protein binding: 0%; platinum is 30% irreversibly bound

Metabolism: Minimally hepatic to aquated and hydroxylated compounds

Half-life elimination: Terminal: 22-40 hours; Cl_{cr} >60 mL/minute: 2.5-5.9 hours

Excretion: Urine (~60% to 90%) within 24 hours

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, mucositis, and taste dysgeusia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine

Oncology: Bone Marrow CommentsObserve serum creatinine. Carboplatin is nephrotoxic and drug accumulation occurs with decreased creatinine clearance.

Index TermsCBDCA; NSC-241240

References

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Zeltzer PM, Epport K, Nelson MD Jr, et al, “Prolonged Response to Carboplatin in an Infant With Brain Stem Glioma,” *Cancer*, 1991, 67(1):43-7.[PubMed 1985722]

International Brand NamesBagotanilo (MX); Biovinate (PH); Biplatinex (VE); Blastocarb (CN); Blastocarb RU (MX, TH); Carboplat (AR, DE, MX); Carboplatin (AU, DK, IL, NO, PL); Carboplatin a (PT); Carboplatin Abic (TH); Carboplatin dbl (GR, PT); Carboplatin DBL (MY); Carboplatin “Delta West” (HR); Carboplatin-David Bull (LU); Carboplatin-Ebewe (PL); Carboplatin-Medac (LU); Carboplatin-Teva (HU); Carboplatino (EC, PE); Carboplatinum Cytosafe-Delta West (LU); Carbosin (BE, GR, MY, NO); Carbosin Lundbeck (FI); Carbotec (MX); Carbotinol (PH); Carplan (KP); Cycloplatin (CZ, HU, PL); Delta West Carboplatin (ID, PH); Karboplatyna-knoll (PL); Kemocarb (PH, TH); Neoplatin (KP); Neoplatine (BR); Omilipis (AR, PY); Oncocarbin (IN); P&U Carboplatin (ZA); Paraplatin (AT, BE, BG, BR, CH, CL, EC, EE, EG, ES, FI, FR, GB, GR, HK, HN, HR, HU, ID, IE, IT, LU, MY, NL, NO, NZ, PH, PL, PT, SE, SG, TH, TW, UY); Pharmaplatin (PK)

Carboprost Tromethamine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(KAR boe prost tro METH a meen)

U.S. Brand NamesHemabate®

Canadian Brand NamesHemabate®

Pharmacologic CategoryAbortifacient; Prostaglandin

Use: Labeled IndicationsTermination of pregnancy; treatment of refractory postpartum uterine bleeding

Use: Unlabeled/InvestigationalInvestigational: Hemorrhagic cystitis

Dosing: Adults

Abortion: I.M.: 250 mcg, then 250 mcg at 1.5- to 3.5-hour intervals, depending on uterine response; a 500 mcg dose may be given if uterine response is not adequate after several 250 mcg doses; do not exceed 12 mg total dose or continuous administration for >2 days

Refractory postpartum uterine bleeding: I.M.: Initial: 250 mcg; if needed, may repeat at 15- to 90-minute intervals; maximum total dose: 2 mg (8 doses)

Hemorrhagic cystitis (unlabeled use): Bladder irrigation: [0.1-1.0 mg/dL as solution] 50 mL instilled into bladder 4 times/day for 1 hour

Dosing: ElderlyRefer to adult dosing.

Administration: I.M.Give deep I.M.; rotate site if repeat injections are required.

Administration: I.V.Do not inject I.V.; may result in bronchospasm, hypertension, vomiting, or anaphylaxis.

StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F).

Bladder irrigation: Dilute immediately prior to administration in NS; stability unknown.

ReconstitutionBladder irrigation: Dilute immediately prior to administration in NS; stability unknown.

ContraindicationsHypersensitivity to carboprost tromethamine or any component of the formulation; acute pelvic inflammatory disease; active cardiac, pulmonary, renal, or hepatic dysfunction

Warnings/Precautions

Boxed warnings:

- Potent oxytocic agent: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Hypertension: Increased blood pressure may be observed with treatment.
- Pyrexia: Transient pyrexia may be observed with treatment.

Disease-related concerns:

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency.
- Anemia: Use with caution in patients with anemia.
- Asthma: Use with caution in patients with a history of asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease, especially hypotension or hypertension.
- Compromised uteri: Use with caution in patients with compromised (scarred) uterus.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Hepatic impairment: Use with caution in patients with hepatic impairment, especially jaundice.
- Renal impairment: Use with caution in patients with renal impairment.
- Seizures: Use with caution in patients with a history of seizure disorder.

Concurrent drug therapy issues:

- Antiemetic/antidiarrheals: Concomitant use of antiemetic and antidiarrheal agents is recommended to decrease incidence of GI side effects.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Potent oxytocic agent: **[U.S. Boxed Warning] Potent oxytocic agent; use with strict adherence to recommended dosing. Immediate intensive care and acute surgical facilities must be available.**

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Carboprost tromethamine is not considered feticidal, but is used to terminate pregnancy due to its ability to stimulate uterine contractions. Use is not indicated if the fetus has reached a stage of viability *in utero*. Complete abortion may not be induced in ~20% of cases.

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined. Effects due to increased smooth muscle contractility are most common.

Cardiovascular: Chest pain, flushing, hypertension, syncope, palpitation, tachycardia, tightness of chest

Central nervous system: Anxiety, chills/shivering, dizziness, drowsiness, dystonia, faintness, headache, lethargy, lightheadedness, nervousness, sleep disturbance, temperature elevation (may be drug induced or due to postabortion endometritis), vasovagal syndrome, vertigo

Dermatologic: Rash

Endocrine & metabolic: Breast tenderness, dysmenorrhea-like pain, endometritis, hot flashes, thyroid storm

Gastrointestinal: Choking sensation, diarrhea (~$^{2}/_{3}$ patients), dry throat, epigastric pain, gagging/retching, hematemesis, nausea (~$^{1}/_{3}$ patients), taste alteration, thirst, throat fullness, vomiting (~$^{2}/_{3}$ patients), xerostomia

Genitourinary: Perforated uterus, posterior cervical perforation, urinary tract infection, uterine bleeding (excessive), uterine rupture, uterine sacculation

Local: Injection site pain

Neuromuscular & skeletal: Backache, leg cramps, muscular pain, paresthesia, torticollis, weakness

Ocular: Blurred vision, eye pain, eyelid twitching

Otic: Tinnitus

Respiratory: Asthma, cough, bronchospasm, dyspnea, epistaxis, hyperventilation, pulmonary edema, respiratory distress, upper respiratory tract infection, wheezing

Miscellaneous: Diaphoresis, hiccups, retained placental fragment, septic shock

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringPremedication with an antiemetic should be considered. Monitor blood pressure, therapeutic effectiveness, and adverse reactions. Assess for complete expulsion of uterine contents (fetal tissue). Assess knowledge/instruct patient on adverse symptoms to report.

Patient EducationThis medication is used to stimulate expulsion of uterine contents (fetal tissue) or stimulate uterine contractions to reduce uterine bleeding. Report increased blood loss, acute abdominal cramping, foul-smelling vaginal discharge, or persistent elevation of temperature. Increased temperature (elevated temperature) may occur 1-16 hours after therapy and last for several hours. **Pregnancy/breast-feeding precautions:** If being treated for hemorrhagic cystitis, inform prescriber if you are pregnant. Inform prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Hemabate®: Carboprost 250 mcg and tromethamine 83 mcg per mL (1 mL) [contains benzyl alcohol]

Generic AvailableNo

Mechanism of ActionCarboprost tromethamine is a prostaglandin similar to prostaglandin F_2 alpha (dinoprost) except for the addition of a methyl group at the C-15 position. This substitution produces longer duration of activity than dinoprost; carboprost stimulates uterine contractility which usually results in expulsion of the products of conception and is used to induce abortion between 13-20 weeks of pregnancy. Hemostasis at the placentation site is achieved through the myometrial contractions produced by carboprost.

Pharmacodynamics/KineticsExcretion: Urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or nervousness; rare reports of dystonia

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCarboprost; Prostaglandin F_2

References

Ippoliti C, Przepiorka D, Mehra R, et al, “Intravesicular Carboprost for the Treatment of Hemorrhagic Cystitis After Marrow Transplantation,” *Urology*, 1995, 46(6):811-5.[PubMed 7502421]

Levine LA and Jarrard DF, “Treatment of Cyclophosphamide-Induced Hemorrhagic Cystitis With Intravesical Carboprost Tromethamine,” *J Urol*, 1993, 149(4):719-23.[PubMed 8455230]

West NJ, “Prevention and Treatment of Hemorrhagic Cystitis,” *Pharmacotherapy*, 1997, 17(4):696-706.[PubMed 9250547]

International Brand NamesHemabate (CL, GB, TW); Prostin 15m (BE, BG, CZ, HN, NL, NZ); Prostin/15M (HR, LU); Prostinfenem (DK, NO, SE); Prostodin (IN)

Carboxymethylcellulose

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Optive™ may be confused with Optivar®

Pronunciation(kar boks ee meth il SEL yoo lose)

U.S. Brand NamesOptive™ [OTC]; Refresh Liquigel® [OTC]; Refresh Plus® [OTC]; Refresh Tears® [OTC]; Tears Again® Gel Drops™ [OTC]; Tears Again® Night and Day™ [OTC]; Theratears®

Canadian Brand NamesCelluvisc™; Refresh Plus®; Refresh Tears®

Pharmacologic CategoryOphthalmic Agent, Miscellaneous

Use: Labeled IndicationsArtificial tear substitute

Dosing: AdultsDry eyes: Ophthalmic: Instill 1-2 drops into eye(s) 3-4 times/day

Dosing: ElderlyRefer to adult dosing.

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel, ophthalmic, as sodium:

Tears Again® Night and Day™: 1.5% (3.5 g)

Solution ophthalmic, as sodium [drops]:

Optive™: 0.5% (15 mL, 30 mL) [contains glycerin 0.9%]

Refresh Liquigel®: 1% (15 mL) [liquid gel formulation]

Refresh Tears®: 0.5% (15 mL)

Tears Again® Gel Drops™: 0.7% (15 mL)

Theratears®: 0.25% (15 mL)

Solution, ophthalmic, as sodium [drops; preservative free]:

Refresh Plus®: 0.5% (0.4 mL) [available in packages of 30 or 50]

Theratears®: 0.25% (0.6 mL)

Generic AvailableYes: Excludes gel

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCarbose D; Carboxymethylcellulose Sodium

International Brand NamesCellufresh (AU, PH, TH); Cellufresh MD (PH, TH); Celluvisc (AU, CH, DE, DK, FI, FR, GB, GR, IE, IL, IN, IT, PH, PT, SE, TH, ZA); Celluvisc MD (TH); Refresh Celluvisc (CO, EC, KP, PE, TW); Refresh Liquigel (CO, EC, GT, HK, MX, PA, PE, SV, TW); Refresh Plus (AU, KP, TW); Refresh Plus/Celluvisc (HK); Refresh Tears (CO, CR, EC, GT, HK, IL, MX, PA, PE, SG, SV, TW)

Carisoprodol, Aspirin, and Codeine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(kar eye soe PROE dole, AS pir in, and KOE deen)

U.S. Brand NamesSoma® Compound w/Codeine [DSC]

Pharmacologic CategorySkeletal Muscle Relaxant

Use: Labeled IndicationsSkeletal muscle relaxant

Use: DentalTreatment of muscle spasms and pain associated with acute temporomandibular joint pain (TMJ)

Dosing: AdultsSkeletal muscle relaxant, analgesic: Oral: 1 or 2 tablets 4 times/day (maximum: 8 tablets/day); treatment should be temporary (2-3 weeks)

Dosing: ElderlyAvoid or use with caution in the elderly (>65 years of age); adverse effects (eg, orthostatic hypotension and CNS depression) may be potentiated.

StorageStore at controlled room temperature 15°C to 30°C (59°F to 86°F). Protect from light and moisture.

RestrictionsC-III

ContraindicationsHypersensitivity to a carbamate (eg, meprobamate); serious gastrointestinal complications (eg, bleeding, perforations, obstruction) due to aspirin use; aspirin-induced asthma; acute intermittent porphyria

Allergy Considerations

- Salicylate Allergy/Sensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Gastrointestinal effects: Serious GI effects (eg, bleeding, perforation, and intestinal obstruction) may occur (possibly fatal) with aspirin use. Use with caution in patients with a history of GI bleeding from ulcers; history of poor baseline health; geriatric patients; patients taking high doses of aspirin; patients taking concurrent anticoagulants, NSAIDs, or large amounts of ethanol.
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene-derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).
- Salicylate sensitivity: Patients with sensitivity to tartrazine dyes, nasal polyps, and asthma may have an increased risk of salicylate sensitivity.
- Seizures: Carisoprodol has been associated (rarely) with seizures in patients with and without seizure history.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment; not studied.
- Renal impairment: Use with caution in patients with renal impairment; not studied.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- CYP2D6 “ultra-rapid metabolizers”: Use caution in patients with two or more copies of the variant CYP2D6*2 allele; may have extensive conversion from codeine to morphine and thus increased opioid-mediated effects.

- Elderly: Avoid or use with caution in the elderly (>65 years of age); may be more sensitive to adverse effects.
- Pediatrics: Safety and efficacy have not been established in children <16 years of age.
- Surgical patients: Aspirin should be avoided (if possible) in surgical patients for 1-2 weeks prior to surgery, to reduce the risk of excessive bleeding.

Other warnings/precautions:

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms

Pregnancy Risk FactorD
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsRefer to Codeine monograph.
Adverse ReactionsSee individual agents.
Metabolism/Transport Effects

Carisoprodol: **Substrate** of CYP2C19 (major)

Aspirin: **Substrate** of CYP2C9 (minor)

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: St John's wort may decrease codeine levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression). Avoid cat's claw, dong quai, evening primrose, feverfew, garlic, ginger, ginkgo, red clover, horse chestnut, green tea, ginseng (all have additional antiplatelet activity). Limit curry powder, paprika, licorice; may cause salicylate accumulation (these foods contain 6 mg salicylate/100 g; an ordinary American diet contains 10-200 mg/day of salicylate).

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: Carisoprodol 200 mg, aspirin 325 mg, and codeine phosphate 16 mg

Soma® Compound w/Codeine: Carisoprodol 200 mg, aspirin 325 mg, and codeine phosphate 16 mg [DSC]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Carisoprodol-Aspirin-Codeine)

200-325-16 mg (30): $69.53

Mechanism of ActionSee individual agents.
Pharmacodynamics/KineticsSee individual agents.
Related Information

- Aspirin
- Carisoprodol
- Codeine

Dental Health Professional ConsiderationsThere is no scientific evidence to warrant discontinuance of aspirin prior to dental surgery. Patients taking one aspirin tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with the physician before removal of the aspirin relative to prevention of postoperative bleeding.

The Food and Drug Administration (FDA), has issued a letter updating information and considerations regarding the use of ibuprofen (400 mg doses) in patients who are taking low dose aspirin (81 mg, immediate release; not enteric coated) for cardioprotection and stroke prevention. Ibuprofen, at these doses, may interfere with aspirin's antiplatelet effect depending upon when it is administered. Patients initiated on aspirin first (for ~1 week) then ibuprofen (400 mg 3 times/day for 10 days) seem to maintain aspirin's platelet effect (Cryer B, 2005). Ibuprofen has the greatest impact on aspirin if administered less than 8 hours before aspirin (Catella-Lawson F, 2001).

Patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. With occasional use of ibuprofen, a clinically-significant interaction with aspirin in unlikely. To avoid interference during chronic dosing, a single dose of ibuprofen should be taken 30-120 minutes after aspirin ingestion or at least 8 hours should elapse after ibuprofen dosing before giving aspirin (FDA, 2006; Catella-Lawson F, 2001).

The clinical implications of the interaction are unclear. There have not been any clinical endpoint studies conducted at this time. Avoidance of this interaction is potentially important because aspirin's vascular protection could be decreased or negated.

Other nonselective NSAIDs may have potential for a similar interaction with aspirin. Such has been described with naproxen (Capone ML, 2005). Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin. Other clinical scenarios (use of smaller ibuprofen doses, other aspirin products, other doses of aspirin) have not been evaluated.

Additional information is available at: http://www.fda.gov/cder/drug/infopage/aspirin/default.htm

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Aspirin: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity (see Dental Comment).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDrowsiness is common; may produce depression or paradoxical CNS stimulation
Mental Health: Effects on Psychiatric TreatmentRarely may cause leukopenia or aplastic anemia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation
Index TermsAspirin, Carisoprodol, and Codeine; Codeine, Aspirin, and Carisoprodol

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Carisoprodol and Aspirin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(kar eye soe PROE dole & AS pir in)

U.S. Brand NamesSoma® Compound

Pharmacologic CategorySkeletal Muscle Relaxant

Use: Labeled IndicationsSkeletal muscle relaxant

Use: DentalTreatment of muscle spasms and pain associated with acute temporomandibular joint pain (TMJ)

Dosing: AdultsSkeletal muscle relaxant (including TMJ pain/spasm): Oral: 1 or 2 tablets 4 times/day

Dosing: ElderlyAvoid use in the elderly due to risk of orthostatic hypotension and CNS depression.

Allergy Considerations

- Salicylate Allergy/Sensitivity

Pregnancy Risk FactorC/D (full-dose aspirin in 3rd trimester)

LactationEnters breast milk/contraindicated

Metabolism/Transport Effects

Carisoprodol: **Substrate** of CYP2C19 (major)

Aspirin: **Substrate** of CYP2C9 (minor)

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Carisoprodol 200 mg and aspirin 325 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Carisoprodol-Aspirin)

200-325 mg (30): $15.99

Tablets (Soma Compound)

200-325 mg (30): $137.54

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Aspirin
- Carisoprodol

Dental Health Professional ConsiderationsThere is no scientific evidence to warrant discontinuance of aspirin prior to dental surgery. Patients taking one aspirin tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with the physician before removal of the aspirin relative to prevention of postoperative bleeding.

The Food and Drug Administration (FDA), has issued a letter updating information and considerations regarding the use of ibuprofen (400 mg doses) in patients who are taking low dose aspirin (81 mg, immediate release; not enteric coated) for cardioprotection and stroke prevention. Ibuprofen, at these doses, may interfere with aspirin's antiplatelet effect depending upon when it is administered. Patients initiated on aspirin first (for ~1 week) then ibuprofen (400 mg 3 times/day for 10 days) seem to maintain aspirin's platelet effect (Cryer B, 2005). Ibuprofen has the greatest impact on aspirin if administered less than 8 hours before aspirin (Catella-Lawson F, 2001).

Patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. With occasional use of ibuprofen, a clinically-significant interaction with aspirin in unlikely. To avoid interference during chronic dosing, a single dose of ibuprofen should be taken 30-120 minutes after aspirin ingestion or at least 8 hours should elapse after ibuprofen dosing before giving aspirin (FDA, 2006; Catella-Lawson F, 2001).

The clinical implications of the interaction are unclear. There have not been any clinical endpoint studies conducted at this time. Avoidance of this interaction is potentially important because aspirin's vascular protection could be decreased or negated.

Other nonselective NSAIDs may have potential for a similar interaction with aspirin. Such has been described with naproxen (Capone ML, 2005). Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin. Other clinical scenarios (use of smaller ibuprofen doses, other aspirin products, other doses of aspirin) have not been evaluated.

Additional information is available at: http://www.fda.gov/cder/drug/infopage/aspirin/default.htm

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Aspirin: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity (see Dental Comment).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may produce depression or paradoxical CNS stimulation

Mental Health: Effects on Psychiatric TreatmentRarely may cause leukopenia or aplastic anemia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation

Index TermsAspirin and Carisoprodol

References

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Catella-Lawson F, Reilly MP, Kapoor SC, et al, "Cyclooxygenase Inhibitors and the Antiplatelet Effects of Aspirin," *N Engl J Med*, 2001, 345(25):1809-17.[PubMed 11752357]

Cryer B, Verlin RG, Cooper SA, et al, "Double-Blind, Randomized, Parallel, Placebo-Controlled Study of Ibuprofen Effects on Thromboxane B2 Concentrations in Aspirin-Treated Healthy Adult Volunteers," *Clin Ther*, 2005, 27(2):185-191.[PubMed 15811481]

Carisoprodol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(kar eye soe PROE dole)
U.S. Brand NamesSoma®
Canadian Brand NamesSoma®
Pharmacologic CategorySkeletal Muscle Relaxant
Use: Labeled IndicationsShort-term (2-3 weeks) relief of skeletal muscle pain
Use: DentalTreatment of muscle spasms and pain associated with acute temporomandibular joint (TMJ) pain
Dosing: Adults**Note:** Carisoprodol should only be used for short periods (2-3 weeks) due to lack of evidence of effectiveness with prolonged use.

Treatment of muscle spasms and pain associated with acute TMJ pain: Oral: 250-350 mg 3 times/day and at bedtime

Dosing: ElderlyNot recommended for use in the elderly (see Geriatric Considerations).
Dosing: Pediatric

Children ≥16 years: Refer to adult dosing.

Administration: OralAdminister with or without food.
Dietary ConsiderationsMay give with or without food.
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).
ContraindicationsHypersensitivity to carisoprodol, meprobamate, or any component of the formulation; acute intermittent porphyria
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Idiosyncratic reactions: May occur following the initial dose and may include severe weakness, transient quadriplegia, euphoria, or vision loss (temporary).

- Seizures: Has been associated (rarely) with seizures in patients with and without seizure history.

Disease-related concerns:

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use. Limit use to 2-3 weeks. Withdrawal symptoms have been reported after abrupt cessation of prolonged use.

- Hepatic impairment: Safety has not been established in patients with hepatic impairment; use caution.

- Renal impairment: Safety has not been established in patients with renal impairment; use caution.

Concurrent drug therapy issues:

- Poor metabolizers: Carisoprodol should be used with caution in patients with reduced functional alleles of CYP2C19; poor metabolizers have been shown to have a fourfold increase in exposure to carisoprodol and a 50% reduced exposure to the metabolite meprobamate compared to normal metabolizers.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <16 years of age.

Geriatric ConsiderationsAvoid or use with caution in the elderly; not considered a drug of choice because of the risk of orthostatic hypotension and CNS depression; no data available on the use of skeletal muscle relaxants in the geriatric population.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal data suggests that carisoprodol crosses placenta and adverse events have been observed in animal studies. Limited postmarketing data with meprobamate (the active metabolite) demonstrate a possible risk for congenital malformations. Use only if benefit outweighs the risk.
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsCarisoprodol levels in breast milk may be 2-4 times that of maternal plasma levels. The estimated dose to the infant was reported as 6.9% of the weight adjusted maternal dose in one case report and ~4% of the weight-adjusted maternal dose in another. In both cases, breast milk production was decreased requiring supplemental formula or cessation of breast-feeding. Other than slight sedation reported in one infant, no symptoms of withdrawal or other adverse events were noted in these 2 cases. Effects on long-term development are not known.

Adverse Reactions

>10%: Central nervous system: Drowsiness (13% to 17%)

1% to 10%: Central nervous system: Dizziness (7% to 8%), headache (3% to 5%)

Postmarketing and/or case reports: Agitation, anaphylaxis, angioedema, asthma exacerbation, ataxia, burning eyes, depression, dermatitis (allergic), dyspnea, epigastric pain, eosinophilia, erythema multiforme, fixed drug eruption, flushing of face, headache, hiccups, hypersensitivity reactions, hypotension (postural), idiosyncratic reaction (symptoms may include agitation, ataxia, confusion, diplopia, disorientation, dysarthria, euphoria, extreme weakness, mydriasis, temporary vision loss, and/or transient quadriplegia); insomnia, irritability, leukopenia, nausea, pancytopenia, paradoxical CNS stimulation, pruritus, rash, seizure, syncope, tachycardia, tremor, urticaria, vertigo, vomiting, weakness, withdrawal syndrome (abdominal cramps, headache, insomnia, nausea, seizure)

Metabolism/Transport Effects

Substrate of CYP2C19 (major)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Monitoring Parameters

Look for relief of pain and/or muscle spasm and avoid excessive drowsiness; signs of drug abuse in addiction-prone individuals

Nursing: Physical Assessment/Monitoring

Assess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy (according to rationale for therapy) and adverse reactions. Monitor for excessive drowsiness at beginning of therapy and periodically with long-term use. Do not discontinue abruptly; taper dosage slowly (withdrawal symptoms may occur). Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient Education

Take exactly as directed. Do not increase dose or discontinue this medication without consulting prescriber. Do not use alcohol, prescriptive or OTC antidepressants, sedatives, or pain medications without consulting prescriber. You may experience drowsiness, dizziness, lightheadedness (avoid driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or cramping (small frequent meals, frequent mouth care, or sucking hard candy may help); headache; or postural hypotension (change position slowly when rising from sitting or lying or when climbing stairs). Report excessive drowsiness or mental agitation; palpitations, rapid heartbeat, chest pain; skin rash; muscle cramping or tremors; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 350 mg

Soma®: 250 mg, 350 mg

Generic Available

Yes

Pricing: U.S. (www.drugstore.com)

Tablets (Carisoprodol)

350 mg (30): $13.99

Tablets (Soma)

250 mg (100): $268.78

350 mg (30): $159.59

Mechanism of Action

Precise mechanism is not yet clear, but many effects have been ascribed to its central depressant actions. In animals, carisoprodol blocks interneuronal activity and depresses polysynaptic neuron transmission in the spinal cord and reticular formation of the brain. It is also metabolized to meprobamate, which has anxiolytic and sedative effects.

Pharmacodynamics/Kinetics

Onset of action: ~30 minutes

Duration: 4-6 hours

Metabolism: Hepatic, via CYP2C19 to active metabolite (meprobamate)

Half-life elimination: 2.4 hours; Meprobamate: 10 hours

Time to peak, plasma: 1.5-2 hours

Excretion: Urine, as metabolite

Dental Health: Effects on Dental Treatment

No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions

No information available to require special precautions

Mental Health: Effects on Mental Status

Drowsiness is common; may produce depression or paradoxical CNS stimulation

Mental Health: Effects on Psychiatric Treatment

Rarely may cause leukopenia or aplastic anemia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation

Index Terms

Carisoprodate; Isobamate

References

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Briggs GG, Ambrose PJ, Nageotte MP, et al, “High-Dose Carisoprodol During Pregnancy and Lactation,” *Ann Pharmacother*, 2008, 42(6):898-901.[PubMed 18460586]

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Luehr JG, Meyerle KA, and Larson EW, “Mail-Order (Veterinary) Drug Dependence,” *JAMA*, 1990, 263(5):657.

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International Brand NamesArtifar (GR); Carisoma (GB, IN); Carisoprodol Sintesina (AR); Listaflex (AR); Meprodat (FI); Mio Relax (ES); Sanoma (DE); Scutamil C (CZ); Soma (GR); Somadril (DK, NO, SE)

Carmustine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Carmustine may be confused with bendamustine, lomustine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(kar MUS teen)

U.S. Brand NamesBiCNU®; Gliadel®

Canadian Brand NamesBiCNU®; Gliadel Wafer®

Pharmacologic CategoryAntineoplastic Agent; Antineoplastic Agent, Alkylating Agent (Nitrosourea); Antineoplastic Agent, DNA Adduct-Forming Agent; Antineoplastic Agent, DNA Binding Agent

Use: Labeled Indications

Injection: Treatment of brain tumors (glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors), multiple myeloma, Hodgkin's disease (relapsed or refractory), non-Hodgkin's lymphomas (relapsed or refractory)

Wafer (implant): Adjunct to surgery in patients with recurrent glioblastoma multiforme; adjunct to surgery and radiation in patients with high-grade malignant glioma

Use: Unlabeled/InvestigationalMelanoma

Dosing: AdultsRefer to individual protocols.

Usual dosage (per manufacturer labeling): I.V.: 150-200 mg/m^2 every 6 weeks **or** 75-100 mg/m^2/day for 2 days every 6 weeks

Alternative regimens (unlabeled):

75-120 mg/m^2 days 1 and 2 every 6-8 weeks **or**

50-80 mg/m^2 days 1,2,3 every 6-8 weeks

Primary brain cancer: I.V.:

150-200 mg/m^2 every 6-8 weeks as a single dose **or**

75-120 mg/m^2 days 1 and 2 every 6-8 weeks **or**

20-65 mg/m^2 every 4-6 weeks **or**

0.5-1 mg/kg every 4-6 weeks **or**

40-80 mg/m^2/day for 3 days every 6-8 weeks

Autologous BMT: I.V.: ALL OF THE FOLLOWING DOSES ARE FATAL WITHOUT BMT

Combination therapy: Up to 300-900 mg/m^2

Single-agent therapy: Up to 1200 mg/m^2 (fatal necrosis is associated with doses >2 g/m^2)

Glioblastoma multiforme (recurrent), malignant glioma: Implantation (wafer): Up to 8 wafers may be placed in the resection cavity (total dose 62.6 mg); should the size and shape not accommodate 8 wafers, the maximum number of wafers allowed should be placed

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols: Children (unlabeled use): I.V.: 200-250 mg/m^2 every 4-6 weeks as a single dose

Dosing: Renal ImpairmentI.V.: The FDA-approved labeling does not contain renal dosing adjustment guidelines. The following dosage adjustments have been used by some clinicians (Kintzel, 1995):

Cl_{cr} 46-60 mL/minute: Administer 80% of dose

Cl_{cr} 31-45 mL/minute: Administer 75% of dose

Cl_{cr} ≤30 mL/minute: Consider use of alternative drug.

Dosing: Hepatic ImpairmentDosage adjustment may be necessary; however, no specific guidelines are available.
Dosing: Combination Regimens

Lymphoma, Hodgkin's disease: mini-BEAM

Melanoma:

Cisplatin-Dacarbazine-Carmustine (Melanoma)

Dartmouth Regimen

Multiple myeloma:

M-2

VBAP

VBMCP

Oncology: Bone Marrow - High DoseI.V.: 300-800 mg/m^2 infused over at least 2 hours; may be divided into two doses administered every 12 hours; generally combined with other high-dose chemotherapeutic drugs. **(High-dose carmustine is fatal if not followed by bone marrow or peripheral stem cell infusions.)**
Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Irritant (alcohol-based diluent). Injection: Significant absorption to PVC containers - should be administered in either glass or polyolefin containers. I.V. infusion over 1-2 hours is recommended; infusion through a free-flowing saline or dextrose infusion, or administration through a central catheter can alleviate venous pain/irritation.

High-dose carmustine: Maximum rate of infusion of ≤3 mg/m^2/minute to avoid excessive flushing, agitation, and hypotension; infusions should run over at least 2 hours; some investigational protocols dictate shorter infusions. **(High-dose carmustine is fatal if not followed by bone marrow or peripheral stem cell infusions.)**

Administration: I.V. Detail
Extravasation management: Elevate extremity. Inject long-acting dexamethasone (Decadron® LA) or by hyaluronidase throughout tissue with a 25- to 37-gauge needle. Apply warm, moist compresses.

BMT only: Vital signs must be monitored frequently during the infusion of high-dose carmustine.

BMT only: Patients receiving high-dose carmustine must be supine and may require the Trendelenburg position, fluid support, and vasopressor support.

Infusion-related cardiovascular effects are primarily due to concomitant ethanol and acetaldehyde. Use with great caution in patients with aldehyde dehydrogenase-2 deficiency or history of “alcohol flushing syndrome”. Acute lung injury tends to occur 1-3 months following carmustine infusion. Patients must be counseled to contact their BMT physician for dyspnea, cough, or fever following carmustine. Acute lung injury is managed with a course of corticosteroids.

pH: 5.6-6.0

Administration: Other

Implant: Use appropriate precautions for handling and disposal; double glove before handling; outer gloves should be discarded as chemotherapy waste after handling wafers. Any wafer or remnant that is removed upon repeat surgery should be discarded as chemotherapy waste. The outer surface of the external foil pouch is not sterile. Open pouch gently; avoid pressure on the wafers to prevent breakage. Wafer that are broken in half may be used, however, wafers broken into more than 2 pieces should be discarded. Oxidized regenerated cellulose (Surgicel®) may be placed over the wafer to secure; irrigate cavity prior to closure.

Storage

Injection: Store intact vials under refrigeration at 2°C to 8°C (36°F to 46°F); vials are stable for 36 days at room temperature. Reconstituted solutions are stable for 8 hours at room temperature (25°C) and 24 hours under refrigeration (2°C to 8°C) and protected from light. Further dilution in D_5W or NS is stable for 8 hours at room temperature (25°C) and 48 hours under refrigeration (4°C) in glass or polyolefin containers and protected from light.

Wafer: Store at or below -20°C (-4°F). Unopened foil pouches may be kept at room temperature for up to 6 hours.

ReconstitutionInjection: Initially, dilute with 3 mL of absolute alcohol. Further dilute with SWFI (27 mL) to a concentration of 3.3 mg/mL; protect from light; may further dilute with D_5W or NS, using a non-PVC container.
CompatibilityCompatible with D_5W, NS, SWFI, dacarbazine.

Y-site administration: Compatible: Amifostine, aztreonam, cefepime, filgrastim, fludarabine, gemcitabine, granisetron, ondansetron, piperacillin/tazobactam, sargramostim, teniposide, thiotepa, vinorelbine. **Incompatible:** Allopurinol, sodium bicarbonate.

Compatibility when admixed: Incompatible with sodium bicarbonate.

ContraindicationsHypersensitivity to carmustine or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.
- Pulmonary toxicity: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: Bone marrow suppression (thrombocytopenia, leukopenia) is the major toxicity and may be delayed;** monitor blood counts weekly for at least 6 weeks after administration. Myelosuppression is cumulative; consider nadir blood counts from prior dose for dosage adjustment. May cause bleeding (due to thrombocytopenia) or infections (due to neutropenia); monitor closely. Administer with caution to patients with depressed platelet, leukocyte, or erythrocyte counts; renal or hepatic impairment.
- Pulmonary toxicity: **[U.S. Boxed Warnings]: Dose-related pulmonary toxicity may occur; patients receiving cumulative doses >1400 mg/m^2 are at higher risk. Delayed onset of pulmonary fibrosis has occurred up to 17 years after treatment in children (1-16 years) who received carmustine in cumulative doses ranging from 770-1800 mg/m^2 combined with cranial radiotherapy for intracranial tumors.** Baseline pulmonary function tests are recommended.
- Secondary malignancies: Long-term use may be associated with the development of secondary malignancies.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Injection: Diluent contains significant amounts of ethanol; use caution with aldehyde dehydrogenase-2 deficiency or history of “alcohol-flushing syndrome.”

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenicity and embryotoxicity have been demonstrated in animal studies. Carmustine can cause fetal harm if administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should avoid becoming pregnant while on treatment.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding should be discontinued.

Adverse Reactions

>10%:

Cardiovascular: Hypotension (with high-dose I.V. therapy, due to the alcohol content of the diluent)

Central nervous system: Ataxia, dizziness

Postoperatively: Seizure (wafer 5% to 54%), brain edema (wafer 4% to 23%)

Dermatologic: Burning (with skin contact), hyperpigmentation of skin (with skin contact)

Gastrointestinal: Severe nausea and vomiting, usually begins within 2-4 hours of drug administration and lasts for 4-6 hours; dose related. Patients should receive a prophylactic antiemetic regimen.

Hematologic: Myelosuppression (cumulative, dose related, delayed, and dose limiting), thrombocytopenia (onset: 28 days; recovery: 35-42 days), leukopenia (onset: 35-42 days; recovery: 42-56 days)

Hepatic: Reversible increases in bilirubin, alkaline phosphatase, and AST occur in 20% to 25% of patients

Local: Pain and burning at injection site, phlebitis

Neuromuscular & skeletal: Weakness (wafer 22%)

Ocular: Ocular toxicities (transient conjunctival flushing and blurred vision), retinal hemorrhages

Respiratory: Interstitial fibrosis occurs in up to 50% of patients receiving a cumulative dose >1400 mg/m^2, or bone marrow transplantation doses; may be delayed up to 3 years; rare in patients receiving lower doses. A history of lung disease or concomitant bleomycin therapy may increase the risk of this reaction. Patients with forced vital capacity (FVC) or carbon monoxide diffusing capacity of the lungs (DLCO) <70% of predicted are at higher risk.

Miscellaneous: Disease progression/performance deterioration (wafer 82%)

1% to 10%:

Cardiovascular: Chest pain, deep thrombophlebitis (wafer), facial edema (wafer), peripheral edema (wafer)

Central nervous system: Wafer: Amnesia, anxiety, aphasia, ataxia, brain abscess, confusion, convulsion, CSF leaks, depression, diplopia, dizziness, facial paralysis, headache, hemiplegia, hydrocephalus, hypoesthesia, insomnia, intracranial hypertension, meningitis, somnolence, speech disorder, stupor

Dermatologic: Facial flushing, probably due to the alcohol diluent; alopecia, rash (wafer), wound healing abnormal (wafer)

Gastrointestinal: Abdominal pain, anorexia, constipation, diarrhea, stomatitis

Hematologic: Anemia, hemorrhage (wafer)

Local: Abscess (wafer)

Neuromuscular & skeletal: Back pain

<1%: Allergic reaction, azotemia (progressive), cerebral hemorrhage infarction (wafer), cyst formation (wafer), dermatitis, hepatic coma, hyperpigmentation, hypotension, kidney size decreased, neuroretinitis, painless jaundice, renal failure, subacute hepatitis, tachycardia, thrombosis

Oncology: VesicantNo; the alcohol-based diluent may be an irritant, especially with high doses.
Oncology: Emetic PotentialVery high (>90%)
Oncology: Bone Marrow - Unique Toxicity

Cardiovascular: Hypotension (infusion related), arrhythmias (infusion related)

Central nervous system: Encephalopathy, ethanol intoxication, seizures, fever

Endocrine & metabolic: Hyperprolactinemia and hypothyroidism in patients with brain tumors treated with radiation

Gastrointestinal: Severe nausea and vomiting

Hepatic Hepatitis, hepatic veno-occlusive disease

Pulmonary: Dyspnea

Drug Interactions

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Carmustine. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Diluent for infusion contains ethanol; avoid concurrent use of medications that inhibit aldehyde dehydrogenase-2 or cause disulfiram-like reactions.
Monitoring ParametersCBC with differential and platelet count, pulmonary function, liver function, and renal function tests; monitor blood pressure during administration

Wafer: Complications of craniotomy (seizures, intracranial infection, brain edema)

Nursing: Physical Assessment/MonitoringShould only be administered under the supervision of an experienced cancer chemotherapy physician. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, medications that inhibit aldehyde dehydrogenase-2 or cause disulfiram-like reactions). Administer antiemetic prior to therapy. Infusion site should be monitored closely to prevent extravasation (see Extravasation Management). For BMT high-dose infusion: Patient must be monitored closely during and following infusion; supine, (Trandelenburg position may be necessary), fluid support, and vasopressor support should be available. Assess results of laboratory tests (eg, hematology, pulmonary, hepatic, and renal function) at baseline and periodically during therapy. Evaluate therapeutic response and adverse effects regularly during and for some time following therapy. Pulmonary function should be assessed for extended periods following high dose or BMT doses; acute lung injury can occur 1-3 months after treatment and pulmonary fibrosis may be delayed up to 3 years. Teach patient or caregiver possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsCBC with differential, platelet count, pulmonary function, liver and renal function
Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. This medication is usually administered by I.V. Report immediately any pain, burning, or swelling at infusion site; sudden onset chest pain; or difficulty breathing or swallowing. Limit oral intake for 4-6 hours before therapy to reduce potential for nausea/vomiting. It is important that you maintain adequate nutrition between treatments (small, frequent meals may help) and adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will be susceptible to infection (avoid crowds and exposure to infection and do not have

any vaccinations without consulting prescriber). May cause nausea, vomiting, or anorexia (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help - if nausea/vomiting are severe, request antiemetic); mouth sores (use soft toothbrush or cotton swabs for mouth care); hyperpigmentation of skin and loss of hair (reversible). Report immediately any dyspnea, cough, or fever; chest pain or palpitations; sore throat, chills, persistent or unusual fatigue; unusual bruising/bleeding; change in color of urine or stool; change in urinary pattern; change in visual acuity; seizure activity; or CNS changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant or cause a pregnancy (males) during therapy or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Implant:

Gliadel®: 7.7 mg (8s)

Injection, powder for reconstitution:

BiCNU®: 100 mg [packaged with 3 mL of absolute alcohol as diluent]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Wafer (Gliadel Wafer)

7.7 mg (8): $20998.04

Mechanism of ActionInterferes with the normal function of DNA and RNA by alkylation and cross-linking the strands of DNA and RNA, and by possible protein modification; may also inhibit enzyme processes by carbamylation of amino acids in protein

Pharmacodynamics/Kinetics

Distribution: 3.3 L/kg; readily crosses blood-brain barrier producing CSF levels equal to >50% of blood plasma levels; highly lipid soluble

Metabolism: Rapidly hepatic; forms active metabolites

Half-life elimination: Biphasic: Initial: 1.4 minutes; Secondary: 20 minutes (active metabolites: plasma half-life of 67 hours)

Excretion: Urine (~60% to 70%) within 96 hours; lungs (6% to 10% as CO_2)

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsAccidental skin contact may cause transient burning and brown discoloration of the skin. Delayed onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in patients who received cumulative doses >1400 mg/m^2.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine

Oncology: Bone Marrow CommentsDue to risk of hypotension, patients receiving high-dose carmustine must be supine and may require the Trendelenburg position, fluid support, and vasopressor support. Vital signs must be monitored frequently during the infusion of high-dose carmustine.

Infusion-related cardiovascular effects are primarily due to concomitant ethanol and acetaldehyde. Use with great caution in patients with aldehyde dehydrogenase-2 deficiency or history of “alcohol flushing syndrome”. Avoid concurrent use of medications that inhibit aldehyde dehydrogenase-2 or cause disulfiram-like reactions. Acute lung injury tends to occur 1-3 months following carmustine infusion. Patients must be counseled to contact their BMT physician for dyspnea, cough, or fever following carmustine. Acute lung injury is managed with a course of corticosteroids.

Index TermsBCNU; bis-chloronitrosourea; Carmustinum; NSC-409962; WR-139021

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Weiss RB and Issell BF, “The Nitrosoureas: Carmustine (BCNU) and Lomustine (CCNU),” *Cancer Treat Rev*, 1982, 9(4):313-30.[PubMed 6762924]

International Brand NamesBcnu (BG, HN, TW); Becenun (BR, FI, NO); BiCNU (AR, AU, CN, CZ, FR, GB, GR, IE, MX, MY, NL, PH, PT, UY, ZA); Bicnu (CL, HU); Carmubris (AT, DE); Gliadel (IL, TH); Gliadel Implant (AU, ES); Nitrumon (BE, IT, LU)

Carteolol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Carteolol may be confused with carvedilol

Pronunciation(KAR tee oh lole)

Canadian Brand NamesOcupress® Ophthalmic

Pharmacologic CategoryOphthalmic Agent, Antiglaucoma

Use: Labeled IndicationsTreatment of chronic open-angle glaucoma and intraocular hypertension

Dosing: AdultsGlaucoma or intraocular hypertension: Ophthalmic: Instill 1 drop in affected eye(s) twice daily

Dosing: ElderlyRefer to adult dosing.

Administration: OtherOphthalmic: Intended for twice daily dosing. Keep eye open and do not blink for 30 seconds after instillation. Wear sunglasses to avoid photophobic discomfort. Apply gentle pressure to lacrimal sac during and immediately following instillation (1 minute).

ContraindicationsHypersensitivity to carteolol or any component of the formulation; sinus bradycardia; heart block greater than first-degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; bronchial asthma, bronchospasm, or COPD; uncompensated cardiac failure; pulmonary edema

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.
- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.
- Heart failure (HF): Use with caution in patients with compensated heart failure and monitor for a worsening of the condition.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis.
- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).
- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Ophthalmic: Systemic absorption and adverse effects may occur, including bradycardia and/or hypotension. Should not be used alone in angle-closure glaucoma (has no effect on pupillary constriction).

Geriatric ConsiderationsDue to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (ie, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20% to 50% in elderly populations. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults; adjust dose for renal function in the elderly.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Ocular: Conjunctival hyperemia

1% to 10%: Ocular: Anisocoria, corneal punctate keratitis, corneal staining, corneal sensitivity decreased, eye pain, vision disturbances

Metabolism/Transport Effects**Substrate** of CYP2D6 (minor)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Monitoring ParametersOphthalmic: Intraocular pressure

Nursing: Physical Assessment/MonitoringAssess effects and interactions with other medications patient may be taking. Instruct patient on appropriate instillation.

Patient EducationWash hands before instilling. Sit or lie down to instill. Open eye, look at ceiling, and instill prescribed amount of medication. Keep eye open and do not blink for 30 seconds after instillation. Apply gentle pressure to inner corner of eye during and immediately following installation (1 minute). Do not touch tip of applicator or let tip of applicator touch eye. Temporary stinging or burning may occur. Wear sunglasses to avoid sun sensitivity or eye discomfort. Report persistent pain, burning, vision changes, swelling, itching, or worsening of condition.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic, as hydrochloride: 1% (5 mL, 10 mL, 15 mL) [contains benzalkonium chloride]

Generic AvailableYes

ManufacturerAbbott Laboratories (Pharmaceutical Product Division)

Pricing: U.S. (www.drugstore.com)

Solution (Carteolol HCl)

1% (5): $17.99

1% (10): $31.99

1% (15): $46.99

Tablets (Cartrol)

2.5 mg (30): $41.24

5 mg (30): $41.24

Mechanism of ActionBlocks both beta$_1$- and beta$_2$-receptors and has mild intrinsic sympathomimetic activity; reduces intraocular pressure by decreasing aqueous humor production

Related Information

- Glaucoma Drug Therapy

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue, insomnia, confusion, and nightmares and clinically look like a major depression

Mental Health: Effects on Psychiatric TreatmentAntipsychotics and MAO inhibitors may increase the effects of beta-blockers; conversely beta-blockers may increase the effects of antipsychotics and benzodiazepines

Index TermsCarteolol Hydrochloride

References

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International Brand NamesArteoptic (BE, CH, CZ, DE, DK, ES, FI, HK, HN, PL, PT, SE, TH, TW); Calte (KP); Carteabak (FR); Carteol (BE, FR, IT, LU); Carteol LP (FR); Catol (TW); Elebloc (AR, TW); Endak (AT, DE); Glauteolol (AR); Karol (KP); Karteol (TW); Mikelan (BD, CL, ES, FR, HK, ID, IN, JP, KP, MY, PH, PK, SG, TH, TW, ZA); Stobol (BG); Teoptic (GB, IE, NL)

Carvedilol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Carvedilol may be confused with atenolol, captopril, carbidopa, carteolol

Coreg® may be confused with Corgard®, Cortef®, Cozaar®

International issues:

Talliton® [Hungary] may be confused with Talacen® which is a brand name for pentazocine/acetaminophen combination in the U.S.

Pronunciation(KAR ve dil ole)

U.S. Brand NamesCoreg CR®; Coreg®

Canadian Brand NamesApo-Carvedilol®; Coreg®; Novo-Carvedilol; PMS-Carvedilol; RAN™-Carvedilol; ratio-Carvedilol

Pharmacologic CategoryBeta Blocker With Alpha-Blocking Activity

Use: Labeled IndicationsMild-to-severe heart failure of ischemic or cardiomyopathic origin (usually in addition to standard therapy); left ventricular dysfunction following myocardial infarction (MI) (clinically stable with LVEF ≤40%); management of hypertension

Use: Unlabeled/InvestigationalAngina pectoris

Dosing: AdultsReduce dosage if heart rate drops to <55 beats/minute.

Hypertension: Oral:

Immediate release: 6.25 mg twice daily; if tolerated, dose should be maintained for 1-2 weeks, then increased to 12.5 mg twice daily. If necessary, dosage may be increased to a maximum of 25 mg twice daily after 1-2 weeks.

Extended release: Initial: 20 mg once daily, if tolerated, dose should be maintained for 1-2 weeks then increased to 40 mg once daily if necessary; maximum dose: 80 mg once daily

Heart failure: Oral:

Immediate release: 3.125 mg twice daily for 2 weeks; if this dose is tolerated, may increase to 6.25 mg twice daily. Double the dose every 2 weeks to the highest dose tolerated by patient. (Prior to initiating therapy, other heart failure medications should be stabilized and fluid retention minimized.)

Maximum recommended dose:

Mild-to-moderate heart failure:

<85 kg: 25 mg twice daily

>85 kg: 50 mg twice daily

Severe heart failure: 25 mg twice daily

Extended release: Initial: 10 mg once daily for 2 weeks; if the dose is tolerated, increase dose to 20 mg, 40 mg, and 80 mg over successive intervals of at least 2 weeks. Maintain on lower dose if higher dose is not tolerated.

Left ventricular dysfunction following MI: Oral: **Note:** Should be initiated only after patient is hemodynamically stable and fluid retention has been minimized.

Immediate release: Initial 3.125-6.25 mg twice daily; increase dosage incrementally (ie, from 6.25-12.5 mg twice daily) at intervals of 3-10 days, based on tolerance, to a target dose of 25 mg twice daily.

Extended release: Initial: Extended release: Initial: 10-20 mg once daily; increase dosage incrementally at intervals of 3-10 days, based on tolerance, to a target dose of 80 mg once daily.

Angina pectoris (unlabeled use): Oral: *Immediate release:* 25-50 mg twice daily

Conversion from immediate release to extended release (Coreg CR®):

Current dose immediate release tablets 3.125 mg twice daily: Convert to extended release capsules 10 mg once daily

Current dose immediate release tablets 6.25 mg twice daily: Convert to extended release capsules 20 mg once daily

Current dose immediate release tablets 12.5 mg twice daily: Convert to extended release capsules 40 mg once daily

Current dose immediate release tablets 25 mg twice daily: Convert to extended release capsules 80 mg once daily

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNone necessary
Dosing: Hepatic ImpairmentUse is contraindicated in severe liver dysfunction.
Administration: OralAdminister with food. Extended release capsules should not be crushed or chewed. Capsules may be opened and sprinkled on applesauce for immediate use.
Dietary ConsiderationsShould be taken with food to minimize the risk of orthostatic hypotension.
Storage

Coreg®: Store at <30°C (<86°F). Protect from moisture.

Coreg CR®: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsSerious hypersensitivity to carvedilol or any component of the formulation; decompensated cardiac failure requiring intravenous inotropic therapy; bronchial asthma or related bronchospastic conditions; second- or third-degree AV block, sick sinus syndrome, and severe bradycardia (except in patients with a functioning artificial pacemaker); cardiogenic shock; severe hepatic impairment
Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

- Hypotension/syncope: Symptomatic hypotension with or without syncope may occur with carvedilol (usually within the first 30 days of therapy); close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Initiation with a low dose, gradual up-titration, and administration with food may help to decrease the occurrence of hypotension or syncope. Patients should be advised to avoid driving or other hazardous tasks during initiation of therapy due to the risk of syncope.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.

- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.

- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms (eg, sweating, anxiety, tachycardia).

- Heart failure (HF): Heart failure patients may experience a worsening of renal function (rare); risk factors include ischemic heart disease, diffuse vascular disease, underlying renal dysfunction, and systolic BP <100 mm Hg. In the severe chronic heart failure trials, patients were excluded if they had a baseline serum creatinine >2.8 mg/dL or increasing serum creatinine. Initiate cautiously and monitor for possible deterioration in patient status (eg, symptoms of HF). Worsening heart failure or fluid retention may occur during upward titration; dose reduction or temporary discontinuation may be necessary. Adjustment of other medications (ACE inhibitors and/or diuretics) may also be required.

- Hepatic impairment: Use with caution in patients with mild-to-moderate hepatic impairment; use is contraindicated in patients with severe hepatic impairment. Manufacturer recommends discontinuation of therapy if liver injury occurs (confirmed by laboratory testing).

- Myasthenia gravis: Use with caution in patients with myasthenia gravis.

- Peripheral vascular disease (PVD): May precipitate or aggravate symptoms of arterial insufficiency in patients with PVD and Raynaud’s disease; use with caution and monitor for progression of arterial obstruction.

- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.

- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

- Thyroid disease: May mask signs of hyperthyroidism (eg, tachycardia). If hyperthyroidism is suspected, carefully manage and monitor; abrupt withdrawal may exacerbate symptoms of hyperthyroidism or precipitate thyroid storm.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents which decrease myocardial function.

- Calcium channel blockers: Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.

Geriatric Considerations Due to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults. In U.S. trials conducted by the manufacturer, hypertension patients who were elderly (>65%) had a higher incidence of dizziness (8.8% vs 6%) than seen in younger patients. No other differences noted between young and old in these trials.

Pregnancy Risk Factor C (manufacturer); D (2nd and 3rd trimesters - expert analysis)

Pregnancy Considerations Postimplantation losses were observed in animal studies. No data available on whether carvedilol crosses the placenta. Beta-blockers have been associated with persistent bradycardia, hypotension, and IUGR; IUGR probably related to maternal hypertension. Cases of neonatal hypoglycemia have been reported following maternal use of beta-blockers at parturition or during breast-feeding.

Lactation Excretion in breast milk unknown/not recommended

Adverse Reactions **Note:** Frequency ranges include data from hypertension and heart failure trials. Higher rates of adverse reactions have generally been noted in patients with heart failure. However, the frequency of adverse effects associated with placebo is also increased in this population.

>10%:

Cardiovascular: Hypotension (9% to 20%)

Central nervous system: Dizziness (2% to 32%), fatigue (4% to 24%)

Endocrine & metabolic: Hyperglycemia (5% to 12%)

Gastrointestinal: Weight gain (10% to 12%), diarrhea (1% to 12%)

Neuromuscular & skeletal: Weakness (7% to 11%)

1% to 10%:

Cardiovascular: Bradycardia (2% to 10%), syncope (3% to 8%), peripheral edema (1% to 7%), generalized edema (5% to 6%), angina (1% to 6%), dependent edema (≤4%), AV block, cerebrovascular accident, hypertension, hyper-/hypovolemia, postural hypotension, palpitation

Central nervous system: Headache (5% to 8%), depression, fever, hypoesthesia, hypotonia, insomnia, malaise, somnolence, vertigo

Endocrine & metabolic: Hypercholesterolemia (1% to 4%), hypertriglyceridemia (1%), diabetes mellitus, gout, hyperkalemia, hyperuricemia, hypoglycemia, hyponatremia

Gastrointestinal: Nausea (2% to 9%), vomiting (1% to 6%), abdominal pain, melena, periodontitis, weight loss

Genitourinary: Impotence

Hematologic: Anemia, prothrombin decreased, purpura, thrombocytopenia

Hepatic: Alkaline phosphatase increased (1% to 3%), GGT increased, transaminases increased

Neuromuscular & skeletal: Back pain (2% to 7%), arthralgia (1% to 6%), arthritis, muscle cramps, paresthesia

Ocular: Blurred vision (1% to 5%)

Renal: BUN increased (≤6%), nonprotein nitrogen increased (6%), albuminuria, creatinine increased, glycosuria, hematuria, renal insufficiency

Respiratory: Cough (5% to 8%), nasopharyngitis (4%), rales (4%), dyspnea (>3%), pulmonary edema (>3%), rhinitis (2%), nasal congestion (1%), sinus congestion (1%)

Miscellaneous: Injury (3% to 6%), allergy, flu-like syndrome, sudden death

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Anaphylactoid reaction, alopecia, aplastic anemia (rare, all events occurred in patients receiving other medications capable of causing this effect), amnesia, asthma, bronchospasm, bundle branch block, cholestatic jaundice, concentration decreased, diaphoresis, erythema multiforme, exfoliative dermatitis, GI hemorrhage, HDL decreased, hearing decreased, hyperbilirubinemia, hypokalemia, hypokinesia, interstitial pneumonitis, leukopenia, libido decreased, migraine, myocardial ischemia, nervousness, neuralgia, nightmares, pancytopenia, paresis, peripheral ischemia, photosensitivity, pruritus, rash (erythematous, maculopapular, and psoriaform), respiratory alkalosis, seizure, Stevens-Johnson syndrome, tachycardia, tinnitus, toxic epidermal necrolysis, urinary incontinence, xerostomia

Metabolism/Transport Effects **Substrate** of CYP1A2 (minor), 2C9 (major), 2D6 (major), 2E1 (minor), 3A4 (minor)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Beta2-Agonists: Alpha-/Beta-Blockers may diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Carvedilol. *Risk C: Monitor therapy*

CycloSPORINE: Carvedilol may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Digoxin: Carvedilol may increase the serum concentration of Digoxin. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Alpha-/Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Food decreases rate but not extent of absorption. Administration with food minimizes risks of orthostatic hypotension.

Herb/Nutraceutical: Avoid herbs with hypertensive properties (bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng [American], kola, licorice); may diminish the antihypertensive effect of carvedilol. Avoid herbs with hypotensive properties (black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse); may enhance the hypotensive effect of carvedilol.

Monitoring ParametersHeart rate, blood pressure (base need for dosage increase on trough blood pressure measurements and for tolerance on standing systolic pressure 1 hour after dosing); renal studies, BUN, liver function; in patient with increase risk for developing renal dysfunction, monitor during dosage titration.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (especially anything that will effect blood pressure). Blood pressure and heart rate should be assessed prior to and following first doses and any change in dose. Caution patients with diabetes to monitor glucose levels closely (beta-blockers may alter glucose tolerance). Assess results of laboratory tests, therapeutic effectiveness (eg, reduction of hypertension or angina), and adverse response (eg, CHF). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsRenal studies, BUN, liver function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed. Do not alter dose or discontinue this medication without consulting prescriber. Take pulse daily, prior to taking medication; follow prescriber's instruction about holding medication. If you have diabetes, monitor serum glucose closely (drug may alter glucose tolerance or mask signs of hypoglycemia). You may experience fatigue, dizziness, or postural hypotension (use caution when changing position from lying or sitting to standing, driving, or climbing stairs until response to medication is known); decrease in tear production; alteration in sexual performance (reversible); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report unresolved swelling of extremities; respiratory difficulty or new cough; unresolved fatigue; unusual weight gain (>5 lb/week); unresolved constipation or diarrhea; or unusual muscle weakness.

Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Do not get pregnant while taking this medications. Consult prescriber for appropriate contraceptive use. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release; as phosphate:

Coreg CR®: 10 mg, 20 mg, 40 mg, 80 mg

Tablet: 3.125 mg, 6.25 mg, 12.5 mg, 25 mg

Coreg®: 3.125 mg, 6.25 mg, 12.5 mg, 25 mg

Generic AvailableYes: Tablet

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Coreg CR)

10 mg (30): $122.71

20 mg (30): $122.71

40 mg (30): $122.71

80 mg (30): $122.71

Tablets (Carvedilol)

3.125 mg (30): $25.99

6.25 mg (30): $14.99

12.5 mg (30): $14.99

25 mg (30): $15.99

Tablets (Coreg)

3.125 mg (60): $131.99

6.25 mg (30): $70.99

12.5 mg (60): $136.00

25 mg (60): $136.00

Mechanism of ActionAs a racemic mixture, carvedilol has nonselective beta-adrenoreceptor and alpha-adrenergic blocking activity. No intrinsic sympathomimetic activity has been documented. Associated effects in hypertensive patients include reduction of cardiac output, exercise- or beta-agonist-induced tachycardia, reduction of reflex orthostatic tachycardia, vasodilation, decreased peripheral vascular resistance (especially in standing position), decreased renal vascular resistance, reduced plasma renin activity, and increased levels of atrial natriuretic peptide. In CHF, associated effects include decreased pulmonary capillary wedge pressure, decreased pulmonary artery pressure, decreased heart rate, decreased systemic vascular resistance, increased stroke volume index, and decreased right arterial pressure (RAP).

Pharmacodynamics/Kinetics

Onset of action: 1-2 hours

Peak antihypertensive effect: ~1-2 hours

Absorption: Rapid and extensive

Distribution: V_d: 115 L

Protein binding: >98%, primarily to albumin

Metabolism: Extensively hepatic, via CYP2C9, 2D6, 3A4, and 2C19 (2% excreted unchanged); three active metabolites (4-hydroxyphenyl metabolite is 13 times more potent than parent drug for beta-blockade); first-pass effect; plasma concentrations in the elderly and those with cirrhotic liver disease are 50% and 4-7 times higher, respectively

Bioavailability: Immediate release: 25% to 35% (due to significant first-pass metabolism); Extended release: 85% of immediate release

Half-life elimination: 7-10 hours

Time to peak, plasma: Extended release: 5 hours

Excretion: Primarily feces

Related Information

- Beta-Blockers

Pharmacotherapy PearlsFluid retention during therapy should be treated with an increase in diuretic dosage.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Postural hypotension. Periodontitis has been reported in product labeling for carvedilol; no other reports have confirmed this effect; any possible mechanism for this effect is unknown. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue, insomnia, confusion, and nightmare and clinically look like a major depression

Mental Health: Effects on Psychiatric TreatmentFluoxetine and paroxetine may increase carvedilol's (a CYP2D6 substrate) serum levels

Cardiovascular Considerations

Atrial Fibrillation: Beta-blocker therapy provides effective rate control in patients with atrial fibrillation.

Chronic Stable Angina: Beta-blockers are effective in the treatment of chronic stable angina as monotherapy or when combined with nitrates and/or calcium channel blockers. In patients with severe intractable angina requiring negative cardiac chronotropic medications, pacemaker placement has been carried out to maintain heart rate in the setting of large doses of beta-blockers and/or calcium channel blockers. Beta-blockers are ineffective in the treatment of pure vasospastic (Prinzmetal) angina.

Heart Failure: Strong evidence supports that beta-blocker therapy, without intrinsic sympathomimetic activity (ISA), should be initiated in select patients with **stable** congestive heart failure (NYHA Class II-III). Carvedilol is a nonselective beta-blocker with alpha-blocking and antioxidant properties. To date, carvedilol, sustained release metoprolol, and bisoprolol have demonstrated a beneficial effect on morbidity and mortality. It is important that beta-blocker therapy be instituted initially at very low doses with gradual and very careful titration. Because carvedilol has alpha-adrenergic blocking effects, it may lower blood pressure to a greater extent. The definitive clinical benefits of the antioxidant property are not known at this time.

Hypertension: Beta-blocker therapy in the treatment of hypertension has been associated with improved cardiovascular outcomes. According to the 2003 JNC-VII guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists that requires the use of other drugs, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Beta-blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for a beta-blocker include patients with heart failure, postmyocardial infarction, high coronary disease risk, or diabetes. In type 2 diabetic patients, a UK Prospective Diabetes Study Group (UKPDS) trial showed that beta-blocker therapy (atenolol) was as effective as an ACE inhibitor in reducing cardiovascular events and that the benefits of therapy were related more to the degree of antihypertensive efficacy rather than the class of drug used.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

ST-Segment Elevation Myocardial Infarction (STEMI): Beta-blockers, without intrinsic sympathomimetic activity (ISA), have been shown to decrease morbidity and mortality when initiated in the acute treatment of STEMI and continued long-term. Oral beta-blockade should be initiated promptly in patients without contraindications (eg, signs of heart failure, evidence of a low output state, risk of cardiogenic shock, or other beta-blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade may be considered and given promptly if the patient is experiencing concomitant hypertension or a tachyarrhythmia (Class IIa recommendation).

Unstable Angina/Non-ST-Segment Elevation MI (UA/NSTEMI): In the treatment of UA/NSTEMI, oral beta-blockade should be initiated within the first 24 hours in patients without contraindications (eg, signs of heart failure, evidence of a low output state, risk of cardiogenic shock, or other beta-blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade should only be considered if the patient is experiencing concomitant hypertension upon presentation (Class IIa recommendation).

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia and hypertension.

Anesthesia and Critical Care Concerns/Other Considerations

Surgery: Based on available evidence, beta-blockers should be started days to weeks before elective surgery in selected patients when possible and titrated to a heart rate <65 beats per minute. Additional data suggest that long acting beta-blockers may be superior to short acting ones (Redelmeier, 2005). The ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery recommend beta-blockers be continued in patients undergoing surgery who are receiving beta-blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA Class I guideline indications (Class I recommendation). The guidelines also recommend that beta-blockers be given to patients undergoing vascular surgery who have myocardial ischemia demonstrated during preoperative testing (Class I recommendation).

The guidelines also state that beta-blockers are probably recommended in patients undergoing intermediate risk (eg, carotid endarterectomy, prostate surgery) or vascular surgery in whom preoperative assessment identifies coronary heart disease or high cardiac risk (Class IIa recommendation). High cardiac risk is defined as having >1 of the following clinical risk factors: History of ischemic heart disease, compensated or prior heart failure, cerebrovascular disease, diabetes mellitus, or renal insufficiency. The use of beta-blockers is uncertain in patients undergoing intermediate risk or vascular surgery with ≤1 clinical risk factor (Class IIb recommendation).

The majority of published trials suggest a benefit of perioperative beta-blocker use during noncardiac surgery especially in high-risk patients; however, more recent clinical trials have not shown a benefit to perioperative beta-blockade for noncardiac surgery (Juul. 2006; Yang, 2006).

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International Brand NamesBetaplex (CN); Carbloxal (ID); Cardiol (FI); Cardivas (IN); Carloc (ZA); Carlov (PK); Carvedexxon (IL); Carvedil (EC); Carvedilol (PL); Carvedlol (KP); Carvelol (KP); Carvenal (KP); Carveta (KP); Carvo (TW); Carvol (HN); Caslot (MY); Cavedia (KP); Cavel (MY); Coreg (BB, BM, BR, BS, BZ, GY, JM, NL, SR, TT); Coritensil (AR); Coryol (CR, GT, HN, NI, PA, PL, SV); Dilatrend (AR, AT, AU, BF, BG, BJ, BR, CH, CI, CL, CN, CO, CZ, DE, EC, EE, EG, ET, GH, GM, GN, HK, HN, HU, IT, KE, KP, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NO, PE, PH, PL, PY, SC, SD, SL, SN, TH, TN, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Dilbloc (ID, PT); Dilol (AU); Dimitone (DK); Dirant (KP); Duvelol (KP); Eucardic (GB, IE, NL); Karter (KP); Karvil (PH); Kredex (AU, BE, ES, FR, LU, NO, PL, SE); Longcardio (TW); Querto (DE); Syntrend (TW); Talliton (BB, BM, BS, BZ, GY, JM, NL, SR, TT); V-Bloc (ID); Vasodilren (KP); Vasolexin (PH); Vivacor (PL); Wonvelol (KP)

Caspofungin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(kas poe FUN jin)

U.S. Brand NamesCancidas®

Canadian Brand NamesCancidas®

Pharmacologic CategoryAntifungal Agent, Parenteral; Echinocandin

Use: Labeled IndicationsTreatment of invasive *Aspergillus* infections in patients who are refractory or intolerant of other therapy; treatment of candidemia and other *Candida* infections (intra-abdominal abscesses, esophageal, peritonitis, pleural space); empirical treatment for presumed fungal infections in febrile neutropenic patient

Use: DentalManagement of angular cheilitis

Dosing: Adults**Note:** Duration of caspofungin treatment should be determined by patient status and clinical response. Empiric therapy should be given until neutropenia resolves. In patients with positive cultures, treatment should continue until 14 days after last positive culture. In neutropenic patients, treatment should be given at least 7 days after both signs and symptoms of infection **and** neutropenia resolve.

Aspergillosis, invasive: Initial dose: 70 mg on day 1; subsequent dosing: 50 mg/day. If clinical response inadequate, may increase up to 70 mg/day if tolerated, but increased efficacy not demonstrated. **Note:** Duration of therapy should be a minimum of 6-12 weeks or throughout period of immunosuppression.

Candidiasis: Initial dose: 70 mg on day 1; subsequent dosing: 50 mg/day

Esophageal: 50 mg/day; **Note:** The majority of patients studied for this indication also had oropharyngeal involvement.

Empiric therapy: Initial dose: 70 mg on day 1; subsequent dosing: 50 mg/day; if clinical response inadequate, may increase up to 70 mg/day if tolerated, but increased efficacy not demonstrated

Dosage adjustment with concomitant use of an enzyme inducer:

Patients receiving rifampin: 70 mg caspofungin daily

Patients receiving carbamazepine, dexamethasone, efavirenz, nevirapine, or phenytoin (and possibly other enzyme inducers) may require an increased daily dose of caspofungin (70 mg/day).

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Aspergillosis, candidiasis, empiric therapy: Children >3 months to 17 years: I.V.: Initial dose: 70 mg/m^2 on day 1, subsequent dosing: 50 mg/m^2 once daily, may increase to 70 mg/m^2 once daily if clinical response inadequate (maximum dose: 70 mg)

Dosage adjustment with concomitant use of an enzyme inducer: Patients receiving carbamazepine, dexamethasone, efavirenz, nevirapine, phenytoin, or rifampin (and possibly other enzyme inducers): Consider 70 mg/m^2 once daily (maximum: 70 mg/day)

Dosing: Renal ImpairmentNo specific dosage adjustment is required; supplemental dose is not required following dialysis.

Dosing: Hepatic Impairment

Children: Mild-to-severe hepatic insufficiency: No clinical experience

Adults:

Mild hepatic insufficiency (Child-Pugh score 5-6): No adjustment necessary

Moderate hepatic insufficiency (Child-Pugh score 7-9): 35 mg/day; initial 70 mg loading dose should still be administered in treatment of invasive infections

Severe hepatic insufficiency (Child-Pugh score >9): No clinical experience

Calculations

- Body Surface Area: Pediatrics

Administration: I.V.Infuse slowly, over 1 hour.

Administration: I.V. DetailMonitor during infusion. Isolated cases of possible histamine-related reactions have occurred during clinical trials (rash, flushing, pruritus, facial edema).

StorageStore vials at 2°C to 8°C (36°F to 46°F). Reconstituted solution may be stored at ≤25°C (≤77°F) for 1 hour prior to preparation of infusion solution. Infusion solutions may be stored at ≤25°C (≤77°F) and should be used within 24 hours; up to 48 hours if stored at 2°C to 8°C (36°F to 46°F).

ReconstitutionBring refrigerated vial to room temperature. Reconstitute vials using 0.9% sodium chloride for injection, SWFI, or bacteriostatic water for injection. Mix gently until clear solution is formed; do not use if cloudy or contains particles. Solution should be further diluted with 0.9%, 0.45%, or 0.225% sodium chloride or LR (do not exceed final concentration of 0.5 mg/mL).

CompatibilityStable in NS, $^{1}/_{2}$NS, $^{1}/_{4}$NS, LR. Do not mix with dextrose-containing solutions. Do not coadminister with other medications.

ContraindicationsHypersensitivity to caspofungin or any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; increased transaminases and rare cases of liver impairment have been reported. Dosage reduction required in moderate impairment.

Concurrent drug therapy issues:

- Cyclosporine: Concurrent use of cyclosporine should be limited to patients for whom benefit outweighs risk, due to a high frequency of hepatic transaminase elevations observed during concurrent use.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <3 months of age.

Other warnings/precautions:

- Duration of therapy: Limited data are available concerning treatment durations longer than 4 weeks; however, treatment appears to be well tolerated.

Geriatric ConsiderationsThe number of patients >65 years of age in clinical studies was not sufficient to establish whether a difference in response may be anticipated.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Cardiovascular: Hypotension (6% to 20%), peripheral edema (6% to 11%), tachycardia (4% to 11%)

Central nervous system: Fever (13% to 30%), chills (8% to 23%), headache (5% to 15%)

Dermatologic: Rash (4% to 23%)

Endocrine & metabolic: Hypokalemia (5% to 23%)

Gastrointestinal: Diarrhea (7% to 27%), vomiting (7% to 17%), nausea (4% to 15%)

Hematologic: Hemoglobin decreased (5% to 21%), hematocrit decreased (13% to 18%), WBC decreased (12%), anemia (2% to 11%)

Hepatic: Serum alkaline phosphatase increased (13% to 22%), transaminases increased (2% to 18%), bilirubin increased (5% to 13%)

Local: Phlebitis/thrombophlebitis (18%)

Renal: Serum creatinine increased (3% to 11%), urinary RBCs increased (10%)

Respiratory: Respiratory failure (11% to 20%), cough (6% to 11%), pneumonia (4% to 11%)

Miscellaneous: Infusion reactions (20% to 35%), septic shock (11%)

1% to 10%:

Cardiovascular: Hypertension (children 9% to 10%), edema (3% to 4%)

Dermatologic: Erythema (4% to 9%), pruritus (5% to 7%)

Endocrine & metabolic: Hypomagnesemia (7%), hyperglycemia (6%), hyperkalemia (3%)

Gastrointestinal: Mucosal inflammation (4% to 10%), abdominal pain (4% to 9%)

Hepatic: Albumin decreased (7%)

Local: Infection (1% to 9%, central line)

Neuromuscular & skeletal: Back pain (children up to 4%)

Renal: Nephrotoxicity (13%), blood urea nitrogen increased (4% to 9%)

> **Note:** Nephrotoxicity defined as serum creatinine ≥2x baseline value or ≥1 mg/dL in patients with serum creatinine above ULN range (patients with Cl_{cr} <30 mL/minute were excluded)

Respiratory: Dyspnea (9%), pleural effusion (9%), respiratory distress (children up to 8%), rales (7%), tachypnea (1%)

<1%, postmarketing. and/or case reports: Abdominal distention, anaphylaxis, anorexia, anxiety, appetite decrease, arrhythmia, arthralgia, atrial fibrillation, bradycardia, coagulopathy, confusion, constipation, depression, dizziness, dyspepsia, dystonia, epistaxis, erythema multiforme, fatigue, febrile neutropenia, fluid overload, flushing, hematuria, hepatic necrosis, hepatomegaly, hepatotoxicity,

hypercalcemia, hypoxia, infusion site reactions (pain/pruritus/swelling), insomnia, jaundice, liver failure, MI, pain (extremities), pancreatitis, petechiae, pulmonary edema, renal failure/insufficiency, seizure, skin exfoliation, skin lesion, somnolence, stridor, Stevens-Johnson syndrome, tachypnea, thrombocytopenia, tremor, urinary tract infection, urticaria, weakness; histamine-mediated reactions (including facial swelling, bronchospasm, sensation of warmth) have been reported

Drug Interactions

CycloSPORINE: May enhance the adverse/toxic effect of Caspofungin. Significant increases in alanine transaminase have been reported. *Risk D: Consider therapy modification*

Inducers of Drug Clearance: May decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) when coadministered with known inducers of drug clearance. *Risk D: Consider therapy modification*

Rifampin: May decrease the serum concentration of Caspofungin. Management: Caspofungin prescribing information recommends using a dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) who are also receiving rifampin. *Risk D: Consider therapy modification*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Tacrolimus: Caspofungin may decrease the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Monitoring ParametersLiver function

Nursing: Physical Assessment/MonitoringUse caution in presence of hepatic impairment. Assess therapeutic effectiveness (according to purpose for use) and monitor closely for adverse reactions. See Administration for I.V. specifics. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsLiver function

Patient EducationThis medication can only be administered by infusion. Report immediately any pain, burning, or swelling at infusion site or any signs of allergic reaction (eg, respiratory difficulty or swallowing, back pain, chest tightness, rash, hives, swelling of lips or mouth). Report gastrointestinal upset (nausea, vomiting, abdominal pain, diarrhea); swelling of extremities; chest pain or palpations; unusual cough; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as acetate:

Cancidas®: 50 mg [contains sucrose 39 mg], 70 mg [contains sucrose 54 mg]

Generic AvailableNo

ManufacturerMerck

Mechanism of ActionInhibits synthesis of β(1,3)-D-glucan, an essential component of the cell wall of susceptible fungi. Highest activity in regions of active cell growth. Mammalian cells do not require β(1,3)-D-glucan, limiting potential toxicity.

Pharmacodynamics/Kinetics

Protein binding: ~97% to albumin

Metabolism: Slowly, via hydrolysis and *N*-acetylation as well as by spontaneous degradation, with subsequent metabolism to component amino acids. Overall metabolism is extensive.

Half-life elimination: Beta (distribution): 9-11 hours; Terminal: 40-50 hours

Excretion: Urine (41% as metabolites, 1% to 9% unchanged) and feces (35% as metabolites)

Related Information

- Antifungal Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness and insomnia

Mental Health: Effects on Psychiatric TreatmentCarbamazepine may decrease serum concentration of caspofungin

Index TermsCaspofungin Acetate

References

Mora-Duarte J, Betts R, Rotstein C, et al, "Comparison of Caspofungin and Amphotericin B for Invasive Candidiasis," *N Engl J Med*, 2002, 347(25):2020-9. [PubMed 12490683]

Pappas PG, Rex JH, Sobel JD, et al, "Guidelines for Treatment of Candidiasis," *Clin Infect Dis*, 2004, 38:161-89. [PubMed 14699449]

Stone EA, Fung HB, and Kirschenbaum HL, "Caspofungin: An Echinocandin Antifungal Agent," *Clin Ther*, 2002, 24(3):351-77.[PubMed 11952021]

Walsh TJ, Anaissie EJ, Denning DW, et al, "Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America," *Clin Infect Dis*, 2008, 46(3):327-60.[PubMed 18177225]

International Brand NamesCancidas (AR, AT, BE, BG, BR, CH, CL, CN, CO, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, MX, MY, NL, NO, NZ, PE, PT, RU, SE, SG, TH, TR, TW, UY, VE)

Castor Oil

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(KAS tor oyl)

Pharmacologic CategoryLaxative, Miscellaneous

Use: Labeled IndicationsPreparation for rectal or bowel examination or surgery; rarely used to relieve constipation; also applied to skin as emollient and protectant

Dosing: Adults**Bowel evacuation, constipation:** Oil: Oral: 15-60 mL as a single dose

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Bowel evacuation, constipation:** Oil: Oral:

Children 2-11 years: 5-15 mL as a single dose

Children ≥12 years: Refer to adult dosing.

Dietary ConsiderationsShould be taken on an empty stomach with juice or carbonated beverages.

StorageProtect from heat.

Geriatric ConsiderationsElderly are often predisposed to constipation due to disease, immobility, drugs, low residue diets, and a decreased fluid intake usually due to a decreased “thirst reflex” with age. Avoid stimulant cathartic use on a chronic basis if possible. Use osmotic, lubricant, stool softeners, and bulk agents as prophylaxis. Patients should be instructed for proper dietary fiber and fluid intake as well as regular exercise. Monitor closely for fluid/electrolyte imbalance, CNS signs of fluid/electrolyte loss, and hypotension. Strong and chronic purging may cause severe fluid and electrolyte loss which may affect mental function (CNS). Not a drug of first choice for constipation in the elderly.

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension

Central nervous system: Dizziness

Endocrine & metabolic: Electrolyte disturbance

Gastrointestinal: Abdominal cramps, diarrhea, nausea

Genitourinary: Pelvic congestion

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Oil, oral: 100% (60 mL, 120 mL, 180 mL, 480 mL, 3840 mL)

Generic AvailableYes: Oil

Mechanism of ActionActs primarily in the small intestine; hydrolyzed to ricinoleic acid which reduces net absorption of fluid and electrolytes and stimulates peristalsis

Pharmacodynamics/KineticsOnset of action: 2-6 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsOleum Ricini

International Brand NamesOleum Ricini (BG, EE)

CaT (NSCLC)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lung Cancer (Nonsmall Cell)

Regimen Use Lung cancer, nonsmall cell

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Paclitaxel: I.V.: 175 mg/m^2 day 1

[total dose/cycle = 175 mg/m^2]

or 135 mg/m^2 continuous infusion day 1

[total dose/cycle = 135 mg/m^2]

Carboplatin: I.V.: AUC 7.5 day 1 or 2

[total dose/cycle = AUC = 7.5]

Repeat cycle every 21 days

Variation 2:

Paclitaxel: I.V.: 225 mg/m^2 day 1

[total dose/cycle = 225 mg/m^2]

Carboplatin: I.V.: AUC 6 day 1

[total dose/cycle = AUC = 6]

Repeat cycle every 21 days

References

Variation 1:

Langer CJ, Leighton JC, Comis RL, et al, “Paclitaxel by 24- or 1-Hour Infusion in Combination With Carboplatin in Advanced Nonsmall-Cell Lung Cancer: The Fox Chase Cancer Center Experience,” *Semin Oncol*, 1995, 22(4 Suppl 9):18-29. [PubMed 7544025]

Variation 2:

Schiller JH, Harrington D, Belani CP, et al, “Comparison of Four Chemotherapy Regimens for Advanced Nonsmall-Cell Lung Cancer,” *N Engl J Med*, 2002, 346(2):92-8.[PubMed 11784875]

CaT (Ovarian Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Ovarian Cancer

Regimen Use Ovarian cancer

Regimen

Paclitaxel: I.V.: 175 mg/m^2 day 1

[total dose/cycle = 175 mg/m^2]

or 135 mg/m^2 continuous infusion day 1

[total dose/cycle = 135 mg/m^2]

Carboplatin: I.V.: AUC 7.5 day 1 or 2

[total dose/cycle = AUC = 7.5]

Repeat cycle every 21 days

References

Bookman MA, McGuire WP 3rd, Kilpatrick D, et al, âCarboplatin and Paclitaxel in Ovarian Carcinoma: A Phase I Study of the Gynecologic Oncology Group,â *J Clin Oncol*, 1996, 14(6):1895-902.[PubMed 8656258]

CAV-P/VP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Neuroblastoma

Regimen Use Neuroblastoma

Regimen

Course 1, 2, 4, and 6:

Cyclophosphamide: I.V.: 70 mg/kg/day days 1 and 2

[total dose/cycle = 140 mg/kg]

Doxorubicin: I.V.: 25 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Vincristine: I.V.: 0.033 mg/kg/day continuous infusion days 1, 2, and 3

[total dose/cycle = 0.099 mg/kg]

Vincristine: I.V.: 1.5 mg/m^2 day 9

[total dose/cycle = 1.5 mg/m^2]

Course 3, 5, and 7:

Etoposide: I.V.: 200 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 600 mg/m^2]

Cisplatin: I.V.: 50 mg/m^2/day days 1 to 4

[total dose/cycle = 200 mg/m^2]

References

Kushner BH, LaQuaglia MP, Bonilla MA, et al, âHighly Effective Induction Therapy for Stage 4 Neuroblastoma in Children Over 1 Year of Age,â *J Clin Oncol*, 1994, 12(12):2607-13.[PubMed 7527454]

CAVE

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Lung Cancer (Small Cell)]

Regimen UseLung cancer, small cell

Regimen

Cyclophosphamide: I.V.: 750 mg/m^2 day 1

[total dose/cycle = 750 mg/m^2]

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 (maximum 2 mg) day 1

[total dose/cycle = 1.4 mg/m^2]

Etoposide: I.V.: 60-100 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 180-300 mg/m^2]

Repeat cycle every 21 days

References

Jett JR, Everson L, Therneau TM, et al, “Treatment of Limited-Stage Small-Cell Lung Cancer With Cyclophosphamide, Doxorubicin, and Vincristine With Or Without Etoposide: A Randomized Trial of the North Central Cancer Treatment Group,” *J Clin Oncol*, 1990, 8(1):33-8. [PubMed 2153193]

Sufarlan AW and Zainudin BM, “Combination Chemotherapy for Small Cell Lung Cancer,” *Med J Malaysia*, 1993, 48(2):166-70.[PubMed 8394502]

CC

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Ovarian Cancer

Regimen Use Ovarian cancer

Regimen

Carboplatin: I.V.: Target AUC 5-7.5 day 1

[total dose/cycle = AUC = 5-7.5]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 28 days

References

Alberts DS, Green S, Hannigan EV, et al, “Improved Therapeutic Index of Carboplatin Plus Cyclophosphamide Versus Cisplatin Plus Cyclophosphamide: Final Report by the Southwest Oncology Group of a Phase III Randomized Trial in Stages III and IV Ovarian Cancer,” *J Clin Oncol*, 1992, 10(5):706-17. [PubMed 1569443]

Swenerton K, Jeffrey J, Stuart G, et al, “Cisplatin-Cyclophosphamide Versus Carboplatin-Cyclophosphamide in Advanced Ovarian Cancer: A Randomized Phase III Study of the National Cancer Institute of Canada Clinical Trials Group,” *J Clin Oncol*, 1992, 10(5):718-26.[PubMed 1569444]

CCCDE (Retinoblastoma)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Retinoblastoma]

Regimen Use Retinoblastoma

Regimen

Cyclophosphamide: I.V.: 150 mg/m^2/day days 1 to 7

[total dose/cycle = 1050 mg/m^2]

Cyclophosphamide: Oral: 150 mg/m^2/day days 22 to 28 and 43 to 49

[total dose/cycle = 2100 mg/m^2]

Doxorubicin: I.V.: 35 mg/m^2/day days 10 and 52

[total dose/cycle = 70 mg/m^2]

Cisplatin: I.V.: 90 mg/m^2/day days 8, 50, and 71

[total dose/cycle = 270 mg/m^2]

Etoposide: I.V.: 150 mg/m^2/day continuous infusion days 29 to 31 and 73 to 75

[total dose/cycle = 900 mg/m^2]

References

Advani SH, Rao SR, Iyer RS, et al, âPilot Study of Sequential Combination Chemotherapy in Advanced and Recurrent Retinoblastoma,â *Med Pediatr Oncol*, 1994, 22(2):125-8.[PubMed 8259098]

CCDDT (Neuroblastoma)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Neuroblastoma

Regimen UseNeuroblastoma

Regimen

Cyclophosphamide: I.V.: 40 mg/kg/day days 1 and 2

[total dose/cycle = 80 mg/kg]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Teniposide: I.V.: 100 mg/m^2 day 7

[total dose/cycle = 100 mg/m^2]

Doxorubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Dacarbazine: I.V.: 250 mg/m^2/day days 1 to 5

[total dose/cycle = 1250 mg/m^2]

Repeat cycle every 21-28 days

References

Ikeda K, Nakagawara A, Yano H, et al, âImproved Survival Rates in Children Over 1 Year of Age With Stage III or IV Neuroblastoma Following an Intensive Chemotherapeutic Regimen,â *J Pediatr Surg*, 1989, 24(2):189-93.[PubMed 2724012]

CCDT (Melanoma)

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Melanoma]

Regimen UseMelanoma

Regimen

Dacarbazine: I.V.: 220 mg/m^2/day days 1, 2, and 3, every 21 to 28 days

[total dose/cycle = 660 mg/m^2]

Carmustine: I.V.: 150 mg/m^2 day 1, every 42 to 56 days

[total dose/cycle = 150 mg/m^2]

Cisplatin: I.V.: 25 mg/m^2/day days 1, 2, and 3, every 21 to 28 days

[total dose/cycle = 75 mg/m^2]

Tamoxifen: Oral: 20 mg/day (use of tamoxifen is optional)

References

Del Prete SA, Maurer LH, O'Donnell J, et al, “Combination Chemotherapy With Cisplatin, Carmustine, Dacarbazine, and Tamoxifen in Metastatic Melanoma,” *Cancer Treat Rep*, 1984, 68(11):1403-5. [PubMed 6541973]

Rusthoven JJ, Quirt IC, Iscoe NA, et al, “Randomized, Double-Blind, Placebo-Controlled Trial Comparing the Response Rates of Carmustine, Dacarbazine, and Cisplatin With and Without Tamoxifen in Patients With Metastatic Melanoma. National Cancer Institute of Canada Clinical Trials Group,” *J Clin Oncol*, 1996, 14(7):2083-90.[PubMed 8683240]

CCT (Neuroblastoma)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Neuroblastoma

Regimen UseNeuroblastoma

Regimen

Cyclophosphamide: I.V.: 40 mg/kg/day days 1 and 2

[total dose/cycle = 80 mg/kg]

Cisplatin: I.V.: 20 mg/m^2/day days 22 to 26

[total dose/cycle = 100 mg/m^2]

Teniposide: I.V.: 100 mg/m^2 day 28

[total dose/cycle = 100 mg/m^2]

Repeat every 42 days for 3 cycles

References

Ikeda K, Nakagawara A, Yano H, et al, âImproved Survival Rates in Children Over 1 Year of Age With Stage III or IV Neuroblastoma Following an Intensive Chemotherapeutic Regimen,â *J Pediatr Surg*, 1989, 24(2):189-93.[PubMed 2724012]

CDDP/VP-16

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Brain Tumors]

Regimen UseBrain tumors

Regimen

Cisplatin: I.V.: 90 mg/m^2 day 1

[total dose/cycle = 90 mg/m^2]

Etoposide: I.V.: 150 mg/m^2/day days 3 and 4

[total dose/cycle = 300 mg/m^2]

Repeat cycle every 21 days

References

Kovnar EH, Kellie SJ, Horowitz ME, et al, âPreirradiation Cisplatin and Etoposide in the Treatment of High-Risk Medulloblastoma and Other Malignant Embryonal Tumors of the Central Nervous System: A Phase II Study,â *J Clin Oncol*, 1990, 8(2):330-6.[PubMed 2153766]

CE (Neuroblastoma)

Jump To Field (Select Field Name)

↑ Pharmacologic CategoryChemotherapy Regimen, Neuroblastoma

↑ Regimen UseNeuroblastoma

↑ Regimen

Carboplatin: I.V.: 500 mg/m^2/day days 1 and 2

[total dose/cycle = 1000 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 300 mg/m^2]

Repeat cycle every 21-28 days

↑ References

Alvarado CS, Kretschmar C, Joshi VV, et al, âChemotherapy for Patients With Recurrent or Refractory Neuroblastoma: A POG Phase II Study,â *J Pediatr Hematol Oncol*, 1997, 19(1):62-7.[PubMed 9065721]

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Retinoblastoma

Regimen Use Retinoblastoma

Regimen

Etoposide: I.V.: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Carboplatin: I.V.: 160 mg/m^2/day days 1 to 5

[total dose/cycle = 800 mg/m^2]

Repeat cycle every 21 days

References

Doz F, Neuenschwander S, Plantaz D, et al, âEtoposide and Carboplatin in Extraocular Retinoblastoma: A Study by the Societe Francaise d'Oncologie Pediatrique,â *J Clin Oncol*, 1995, 13(4):902-9.[PubMed 7707117]

CE-CAdO

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Neuroblastoma]

Regimen UseNeuroblastoma

Regimen

Carboplatin: I.V.: 160 mg/m^2/day days 1 to 5

[total dose/cycle = 800 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

or

Carboplatin: I.V.: 200 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 600 mg/m^2]

Etoposide: I.V.: 150 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 450 mg/m^2]

and

Cyclophosphamide: I.V.: 300 mg/m^2/day days 1 to 5

[total dose/cycle = 1500 mg/m^2]

Doxorubicin: I.V.: 60 mg/m^2 day 5

[total dose/cycle = 60 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2/day days 1 and 5

[total dose/cycle = 3 mg/m^2]

Repeat cycle every 21 days

References

Rubie H, Michon J, Plantaz D, et al, âUnresectable Localized Neuroblastoma: Improved Survival After Primary Chemotherapy Including Carboplatin-Etoposide. Neuroblastoma Study Group of the Societe Francaise d'Oncologie Pediatrique (SFOP),â *Br J Cancer*, 1998, 77(12):2310-7.[PubMed 9649151]

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

Regimen

Cyclophosphamide: Oral: 75 mg/m^2/day days 1 to 14

[total dose/cycle = 1050 mg/m^2]

Epirubicin: I.V.: 60 mg/m^2/day days 1 and 8

[total dose/cycle = 120 mg/m^2]

Fluorouracil: I.V.: 500 mg/m^2/day days 1 and 8

[total dose/cycle = 1000 mg/m^2]

Repeat cycle every 28 days

References

Levine MN, Bramwell VH, Pritchard KI, et al, âRandomized Trial of Intensive Cyclophosphamide, Epirubicin, and Fluorouracil Chemotherapy Compared With Cyclophosphamide, Methotrexate, and Fluorouracil in Premenopausal Women With Node-Positive Breast Cancer, National Cancer Institute of Canada Clinical Trials Group,â *J Clin Oncol*, 1998, 16(8):2651-8.[PubMed 9704715]

Cefaclor

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cefaclor may be confused with cephalexin

Pronunciation(SEF a klor)
U.S. Brand NamesRaniclor™
Canadian Brand NamesApo-Cefaclor®; Ceclor®; Novo-Cefaclor; Nu-Cefaclor; PMS-Cefaclor
Pharmacologic CategoryAntibiotic, Cephalosporin (Second Generation)
Use: Labeled IndicationsTreatment of susceptible bacterial infections including otitis media, lower respiratory tract infections, acute exacerbations of chronic bronchitis, pharyngitis and tonsillitis, urinary tract infections, skin and skin structure infections
Use: DentalAlternative antibiotic for treatment of orofacial infections in patients allergic to penicillins; susceptible bacteria including aerobic gram-positive bacteria and anaerobes
Dosing: AdultsTreatment of infections: Oral: Dosing range: 250-500 mg every 8 hours
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Treatment of infections: Oral: Children >1 month: Dosing range: 20-40 mg/kg/day divided every 8-12 hours; maximum dose: 1 g/day

Otitis media: Oral: 40 mg/kg/day divided every 12 hours

Pharyngitis: Oral: 20 mg/kg/day divided every 12 hours

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer 50% to 100% of dose

Cl_{cr} <10 mL/minute: Administer 50% of dose

Hemodialysis: Moderately dialyzable (20% to 50%)

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels.

Chewable tablet: Should be chewed before swallowing; should not be swallowed whole.

Oral suspension: Shake well before using.

Dietary ConsiderationsCapsule, chewable tablet, and suspension may be taken with or without food. Raniclor™ contains phenylalanine 2.8 mg/cefaclor 125 mg.
StorageStore at controlled room temperature. Refrigerate suspension after reconstitution. Discard after 14 days. Do not freeze.
ContraindicationsHypersensitivity to cefaclor, any component of the formulation, or other cephalosporins
Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- *H. influenzae* infections: Beta-lactamase-negative, ampicillin-resistant (BLNAR) strains of *H. influenzae* should be considered resistant to cefaclor.
- Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.

Special populations:

- Pediatrics: Extended release tablets are not approved for use in children <16 years of age.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Geriatric ConsiderationsHas not been studied in the elderly. Adjust dose for renal function in elderly. Considered to be one of the drugs of choice in the outpatient treatment of community-acquired pneumonia in elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events were not observed in animal reproduction studies; therefore, cefaclor is classified as pregnancy category B. It is not known if cefaclor crosses the placenta; other cephalosporins cross the placenta and are considered safe for use during pregnancy. An increased risk of teratogenic effects has not been observed following maternal use of cefaclor.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsSmall amounts of cefaclor are excreted in breast milk. The manufacturer recommends that caution be exercised when administering cefaclor to nursing women. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Cefaclor in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Dermatologic: Rash (maculopapular, erythematous, or morbilliform) (1% to 2%)

Gastrointestinal: Diarrhea (3%)

Genitourinary: Vaginitis (2%)

Hematologic: Eosinophilia (2%)

Hepatic: Transaminases increased (3%)

Miscellaneous: Moniliasis (2%)

<1%: Agitation, agranulocytosis, anaphylaxis, angioedema, aplastic anemia, arthralgia, cholestatic jaundice, CNS irritability, confusion, dizziness, hallucinations, hemolytic anemia, hepatitis, hyperactivity, insomnia, interstitial nephritis, nausea, nervousness, neutropenia, paresthesia, pruritus, pseudomembranous colitis, PT prolonged, seizure, serum-sickness, somnolence, Stevens-Johnson syndrome, urticaria, thrombocytopenia, toxic epidermal necrolysis, vomiting

Reactions reported with other cephalosporins: Fever, abdominal pain, superinfection, renal dysfunction, toxic nephropathy, hemorrhage, cholestasis

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Cefaclor serum levels may be decreased slightly if taken with food. The bioavailability of cefaclor extended release tablets is decreased 23% and the maximum concentration is decreased 67% when taken on an empty stomach.

Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction

Monitoring ParametersAssess patient at beginning and throughout therapy for infection; monitor for signs of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, nephrotoxicity). Assess results of laboratory tests, therapeutic effectiveness, and adverse effects (hypersensitivity can occur days after therapy is started) regularly during therapy. Advise patients with diabetes about use of Clinitest®. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, hypersensitivity, opportunistic infection).

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy; renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, at regular intervals around-the-clock (with or without food). Chilling oral suspension improves flavor (do not freeze). Do not chew or crush extended release tablets. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Complete full course of medication, even if you feel better. May cause false test results with Clinitest®; use of another type of testing is preferable. May cause diarrhea (yogurt, boiled milk, or buttermilk may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage; sores in mouth; blood in stool or urine, vaginal itching or drainage, unusual fever or chills); or CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 250 mg, 500 mg

Powder for oral suspension: 125 mg/5 mL (75 mL, 150 mL); 250 mg/5 mL (75 mL, 150 mL); 375 mg/5 mL (50 mL, 100 mL)

Tablet, chewable:

Raniclor™: 250 mg [contains phenylalanine 5.6 mg/tablet and tartrazine; fruity flavor]; 375 mg [contains phenylalanine 8.4 mg/tablet and tartrazine; fruity flavor]

Tablet, extended release: 500 mg

Generic AvailableYes: Excludes chewable tablet
Pricing: U.S. (www.drugstore.com)

Capsules (Ceclor)

250 mg (30): $75.99

500 mg (30): $139.99

Capsules (Cefaclor)

250 mg (30): $37.99

500 mg (30): $41.99

Suspension (reconstituted) (Cefaclor)

125 mg/5 mL (75): $11.99

125 mg/5 mL (150): $18.99

187 mg/5 mL (50): $11.99

187 mg/5 mL (100): $18.99

250 mg/5 mL (75): $16.99

250 mg/5 mL (150): $29.99

375 mg/5 mL (50): $22.99

375 mg/5 mL (100): $29.99

Tablet, 12-hour (Cefaclor CR)

500 mg (20): $75.86

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.
Pharmacodynamics/Kinetics

Absorption: Well absorbed, acid stable

Distribution: Widely throughout the body and reaches therapeutic concentration in most tissues and body fluids, including synovial, pericardial, pleural, peritoneal fluids; bile, sputum, and urine; bone, myocardium, gallbladder, skin and soft tissue

Protein binding: 25%

Metabolism: Partially hepatic

Half-life elimination: 0.5-1 hour; prolonged with renal impairment

Time to peak: Capsule: 60 minutes; Suspension: 45 minutes

Excretion: Urine (80% as unchanged drug)

Related Information

- Antimicrobial Drugs of Choice
- Cephalosporins by Generation

Dental Health Professional ConsiderationsPatients allergic to penicillins can use a cephalosporin; the incidence of cross-reactivity between penicillins and cephalosporins is 1% when the allergic reaction to penicillin is delayed. Cefaclor is effective against anaerobic bacteria, but the sensitivity of alpha-hemolytic *Streptococcus* varies; approximately 10% of strains are resistant. Nearly 70% are intermediately sensitive. If the patient has a history of immediate reaction to penicillin, the incidence of cross-reactivity is 20%; cephalosporins are contraindicated in these patients.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins
Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine
References

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Smith GH, "Oral Cephalosporins in Perspective," *DICP*, 1990, 24(1):45-51. [PubMed 2405586]

Wright AJ, "The Penicillins," *Mayo Clin Proc*, 1999, 74(3):290-307.[PubMed 10090000]

International Brand Names Aclor (AU); Alfacet (PL); Alfatil (FR); Alfatil LP (FR); Apo-Cefaclor (PL); Capabiotic (ID); Cec (MX); CEC (ZA); CEC 500 (DE); Ceclobid (PH); Ceclor (AT, AU, BB, BE, BF, BJ, BM, BR, BS, BZ, CH, CI, CL, CZ, EC, ES, ET, GH, GM, GN, GR, GY, HK, HN, ID, JM, KE, KP, LR, MA, ML, MR, MU, MW, MX, NE, NG, NL, PE, PH, PK, PL, PT, SC, SD, SL, SN, SR, TN, TT, TZ, UG, VE, ZA, ZM, ZW); Ceclor AF (PE); Ceclor CD (AU, PH); Ceclor MR (BF, BJ, CI, ET, GH, GM, GN, HK, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Ceclor Retard (CH, CO, ES); Cecrocin (KP); Cecrun (KP); Cefabac (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ceflacid (MX); Cefor (PL); Cefral (AR); CEK (PL); Celco (TH); Cephlor (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ceracl (KP); Cero (TW); Cleancef (KP, SG); Clex (KP); Cloracef (ID); Cloracef MR (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Clorcef (PH); Clorotir (NZ, PH, TH); Distaclor (GB, IE, TH); Especlor (ID); Faclor (BR); Fasiclor (MX); Forbatec (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Forifek (ID); Haxifal (FR); Karlor (AU); Karlor CD (AU); Kefaclor (TZ); Keflor (AU, CL, CN, IN); Kefolor (FI); Kemocin (KP); Kloracef (PL); Kwicap (AR); Lorcef (PH); Mediconcef (ID); Medoclor (BG, HK); Miclor (KP); Panacef (IT, PE); Panacef RM (PE); Panclor (PL); Panoral (DE); Panoral Forte (DE); Pharmaclor (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Qualiceclor (HK); Qualiphor (HK); Ranclor (MX); Serviclor (MX, PL); Sifaclor (TH); Soficlor (HK, MY, SG); Taracef (PL); U-Clor (TW); Vefarol (PH); Vercef (BF, BJ, CI, ET, GH, GM, GN, HK, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, PL, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Vercef MR (PL); Verzat ER (PH); Xelent (PH)

Cefadroxil

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English

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Pronunciation(sef a DROKS il)

U.S. Brand NamesDuricef® [DSC]

Canadian Brand NamesApo-Cefadroxil®; Duricef®; Novo-Cefadroxil; Pro-Cefadroxil

Pharmacologic CategoryAntibiotic, Cephalosporin (First Generation)

Use: Labeled IndicationsTreatment of susceptible bacterial infections, including those caused by group A beta-hemolytic *Streptococcus*

Use: DentalAlternative antibiotic for treatment of orofacial infections in patients allergic to penicillins; susceptible bacteria including aerobic gram-positive bacteria and anaerobes

Dosing: Adults

Susceptible infections: Oral: 1-2 g/day in 2 divided doses

Orofacial infections: Oral: 250-500 mg every 8 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Susceptible infections:** Oral: 30 mg/kg/day divided twice daily up to a maximum of 2 g/day

Dosing: Renal Impairment

Cl_{cr} 10-25 mL/minute: Administer every 24 hours.

Cl_{cr} <10 mL/minute: Administer every 36 hours.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels.

ReconstitutionRefrigerate suspension after reconstitution. Discard after 14 days.

ContraindicationsHypersensitivity to cefadroxil, any component of the formulation, or other cephalosporins

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.

Geriatric ConsiderationsAdjust dose for renal function in the elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events were not observed in animal reproduction studies; therefore, cefadroxil is classified as pregnancy category B. Cefadroxil crosses the placenta. Limited data is available concerning the use of cefadroxil in pregnancy; however, adverse fetal effects were not noted in a small clinical trial. Adequate and well-controlled studies have been not completed in pregnant women.

LactationEnters breast milk (small amounts)/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsVery small amounts of cefadroxil are excreted in breast milk. The manufacturer recommends that caution be exercised when administering cefadroxil to nursing women. The American Academy of Pediatrics considers cefadroxil to be “usually compatible with breastfeeding”. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Cefadroxil in Pregnancy & Lactation

Adverse Reactions

1% to 10%: Gastrointestinal: Diarrhea

<1%: Anaphylaxis, rash (maculopapular and erythematous), erythema multiforme, Stevens-Johnson syndrome, serum sickness, arthralgia, urticaria, pruritus, angioedema, pseudomembranous colitis, abdominal pain, dyspepsia, nausea, vomiting, cholestasis, vaginitis,

neutropenia, agranulocytosis, thrombocytopenia, transaminases increased, fever

Reactions reported with other cephalosporins: Toxic epidermal necrolysis, abdominal pain, superinfection, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, prothrombin time prolonged, BUN increased, creatinine increased, eosinophilia, pancytopenia, seizure

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Concomitant administration with food, infant formula, or cow's milk does **not** significantly affect absorption.

Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction

Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose.

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, anticoagulants). Assess results of laboratory tests, therapeutic response, and adverse effects (eg, hypersensitivity can occur several days after therapy is started) regularly during therapy. Advise patients with diabetes about use of Clinitest®. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, hypersensitivity, opportunistic infection, renal dysfunction, anemia).

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy; renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, at regular intervals around-the-clock (with or without food). Chilling oral suspension improves flavor (do not freeze). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Complete full course of medication, even if you feel better. May cause false test results with Clinitest®; use of another type of glucose testing is preferable. May cause diarrhea (yogurt, boiled milk, or buttermilk may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage; sores in mouth; blood in urine or stool; unusual fever or chills); or CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Note: Strength is expressed as base

Capsule, as hemihydrate: 500 mg

Capsule, as monohydrate: 500 mg

Powder for oral suspension, as monohydrate: 250 mg/5 mL (100 mL); 500 mg/5 mL (75 mL, 100 mL)

Duricef®: 250 mg/5 mL (50 mL, 100 mL) [DSC]; 500 mg/5 mL (75 mL, 100 mL) [contains sodium benzoate; orange-pineapple flavor] [DSC]

Tablet, as hemihydrate: 1 g

Tablet, as monohydrate: 1 g

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Cefadroxil)

500 mg (30): $34.99

Tablets (Cefadroxil)

1 g (30): $139.99

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: Rapid and well absorbed

Distribution: Widely throughout the body and reaches therapeutic concentrations in most tissues and body fluids, including synovial, pericardial, pleural, and peritoneal fluids; bile, sputum, and urine; bone, myocardium, gallbladder, skin, and soft tissue

Protein binding: 20%

Half-life elimination: 1-2 hours; Renal failure: 20-24 hours

Time to peak, serum: 70-90 minutes

Excretion: Urine (>90% as unchanged drug)

Related Information

- Cephalosporins by Generation

- Prevention of Infective Endocarditis

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins

Mental Health: Effects on Psychiatric Treatment May rarely cause neutropenia; use caution with clozapine and carbamazepine

Index Terms Cefadroxil Monohydrate

References

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Marshall WF and Blair JE, “The Cephalosporins,” *Mayo Clin Proc*, 1999, 74(2):187-95. [PubMed 10069359]

Smith GH, “Oral Cephalosporins in Perspective,” *DICP*, 1990, 24(1):45-51.[PubMed 2405586]

International Brand Names Adroxef (CN); Amben (HK); Ancefa (ID); Baxan (GB); Bidicef (ID); Biodroxil (AE, BH, CO, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE); Biodroxyl (VE); Biofaxil (PT); Camex (KP); Cedrox (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Cefacar (AR); Cefadril (IT); Cefadrol (IN); Cefalom (GR); Cefamox (BR, SE, UY); Cefaroxil (KP); Cefat (ID); Ceforal (PT); Cefra-Om (PT); Cephos (IT); Curisafe (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Cyclomycin-K (GR); Dacef (ZA); Doxef (ID); Drocef (BR, KP); Drolex (PH); Droxef (PL); Droxicef (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Droxil (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Droxilon (EC); Droxyl (IN); Drozid (PH); Duracef (AT, BE, BF, BG, BJ, CI, CO, CZ, EE, ES, ET, FI, GH, GM, GN, HK, HN, KE, LR, MA, ML, MR, MU, MW, MX, NE, NG, PE, PH, PL, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Duricef (KP, PK, SG); Erphadrox (ID); Ethicef (ID); Evacef (KP); Fadrox (CO); Gruncef (DE); Hanacef (KP); Justum (PY); Kefloxcin (MY); Kelfex (ID); Kleotrat (GR); Lapicef (ID); Lesporina (CO); Likodin (TW); Lydroxil (IN); Medicefa (KP); Moxacef (GR, NL); Nefalox (GR); Nor-Dacef (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Odoxil (IN); Oracefal (FR); Oradroxil (IT); QCef (ID); Qualidrox (HK); Rafemox (CN); Sofidrox (MY, SG); Tadroxil (PL); Ucefa (TW); Ultracef (IE); Vepan (IN); Versatic (AR); Vidcef (KP); Xianfengjiu (CL)

CeFAZolin

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Medication Safety Issues

Sound-alike/look-alike issues:

CeFAZolin may be confused with cefprozil, cefTRIAXone, cephalexin, cephalothin

Kefzol® may be confused with Cefzil®

Pronunciation(sef A zoe lin)

Pharmacologic CategoryAntibiotic, Cephalosporin (First Generation)

Use: Labeled IndicationsTreatment of respiratory tract, skin and skin structure, genital, urinary tract, biliary tract, bone and joint infections, and septicemia due to susceptible gram-positive cocci (except enterococcus); some gram-negative bacilli including *E. coli*, *Proteus*, and *Klebsiella* may be susceptible; perioperative prophylaxis

Use: Unlabeled/InvestigationalProphylaxis against infective endocarditis

Use: DentalAlternative antibiotic for prevention of infective endocarditis when parenteral administration is needed. Individuals allergic to amoxicillin (penicillins) may receive cefazolin provided they have not had an immediate, local, or systemic IgE-mediated anaphylactic allergic reaction to penicillin. Alternate antibiotic for premedication in patients not allergic to penicillin who may be at potential increased risk of hematogenous total joint infection when parenteral administration is needed.

Dosing: Adults

Usual dosage range: I.M., I.V.: 1-2 g every 8 hours, depending on severity of infection; maximum: 12 g/day

Mild-to-moderate infections: 500 mg to 1 g every 6-8 hours

Mild infection with gram-positive cocci: 250-500 mg every 8 hours

Perioperative prophylaxis: 1 g given 30 minutes prior to surgery (repeat with 500 mg to 1 g during prolonged surgery); followed by 500 mg to 1 g every 6-9 hours for 24 hours postop

Pneumococcal pneumonia: 500 mg every 12 hours

Severe infection: 1-2 g every 6 hours

Prophylaxis against infective endocarditis (unlabeled use): 1 g 30-60 minutes before procedure. **Note:** Intramuscular injections should be avoided in patients who are receiving anticoagulant therapy. In these circumstances, orally administered regimens should be given whenever possible. Intravenously administered antibiotics should be used for patients who are unable to tolerate or absorb oral medications.

> **Note:** American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur. As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Prophylaxis in total joint replacement patient: I.M., I.V.: 1 g 1 hour prior to the procedure

UTI (uncomplicated): 1 g every 12 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Usual dosage range: I.M., I.V.: Children >1 month: 25-100 mg/kg/day divided every 6-8 hours; maximum: 6 g/day

Prophylaxis against infective endocarditis (unlabeled use): Infants and Children: 50 mg/kg 30-60 minutes before procedure; maximum dose: 1 g. Intramuscular injections should be avoided in patients who are receiving anticoagulant therapy. In these circumstances, orally administered regimens should be given whenever possible. Intravenously administered antibiotics should be used for patients who are unable to tolerate or absorb oral medications.

> **Note:** American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur. As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Dosing: Renal Impairment

Cl_{cr} 35-54 mL/minute: Administer full dose in intervals of ≥8 hours

Cl_{cr} 11-34 mL/minute: Administer 1/2 usual dose every 12 hours

Cl_{cr} ≤10 mL/minute: Administer 1/2 usual dose every 18-24 hours

Hemodialysis: Moderately dialyzable (20% to 50%); administer dose postdialysis or administer supplemental dose of 0.5-1 g after dialysis

Continuous ambulatory peritoneal dialysis (CAPD): Administer 0.5 g every 12 hours

Continuous renal replacement therapy (CRRT): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH: 1-2 g every 12 hours

CVVHD/CVVHDF: 2 g every 12 hours

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Inject deep I.M. into large muscle mass.
Administration: I.V.Inject direct I.V. over 5 minutes. Infuse intermittent infusion over 30-60 minutes.

Some penicillins (eg, carbenicillin, ticarcillin, and piperacillin) have been shown to inactivate aminoglycosides *in vitro*. This has been observed to a greater extent with tobramycin and gentamicin, while amikacin has shown greater stability against inactivation. Concurrent use of these agents may pose a risk of reduced antibacterial efficacy *in vivo*, particularly in the setting of profound renal impairment. However, definitive clinical evidence is lacking. If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered. Refer to Compatibility.

Administration: I.V. DetailpH: 4.5-6.0
Dietary ConsiderationsSodium content of 1 g: 48 mg (2 mEq)
StorageStore intact vials at room temperature and protect from temperatures exceeding 40°C. Reconstituted solutions of cefazolin are light yellow to yellow. Protection from light is recommended for the powder and for the reconstituted solutions. Reconstituted solutions are stable for 24 hours at room temperature and for 10 days under refrigeration. Stability of parenteral admixture at room temperature (25°C) is 48 hours. Stability of parenteral admixture at refrigeration temperature (4°C) is 14 days.

DUPLEX™: Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) prior to activation. Following activation, stable for 24 hours at room temperature and for 7 days under refrigeration.

ReconstitutionDilute large vial with 2.5 mL SWFI; 10 g vial may be diluted with 45 mL to yield 1 g/5 mL or 96 mL to yield 1 g/10 mL. May be injected or further dilution for I.V. administration in 50-100 mL compatible solution. Standard diluent is 1 g/50 mL D_5W or 2 g/50 mL D_5W.
CompatibilityStable in D_5W, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, $D_{10}W$,LR, NS; **variable stability (consult detailed reference)** in peritoneal dialysis solutions.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, atracurium, aztreonam, calcium gluconate, cefpirome, cyclophosphamide, diltiazem, docetaxel, doxorubicin liposome, enalaprilat, esmolol, etoposide, famotidine, filgrastim, fluconazole, fludarabine, foscarnet, gatifloxacin, gemcitabine, granisetron, heparin, insulin (regular), labetalol, lidocaine, linezolid, magnesium sulfate, melphalan, meperidine, midazolam, morphine, multivitamins, ondansetron, pancuronium, perphenazine, propofol, ranitidine, remifentanil, sargramostim, tacrolimus, teniposide, theophylline, thiotepa, vecuronium, vitamin B complex with C, warfarin. **Incompatible:** Amphotericin B cholesteryl sulfate complex, idarubicin, pentamidine, vinorelbine. **Variable (consult detailed reference):** Amiodarone, cisatracurium, hetastarch, hydromorphone, promethazine, vancomycin.

Compatibility in syringe: Compatible: Heparin, vitamin B complex. **Incompatible:** Ascorbic acid injection, cimetidine, lidocaine. **Variable (consult detailed reference):** Hydromorphone, vitamin B complex with C.

Compatibility when admixed: Compatible: Aztreonam, clindamycin, famotidine, fluconazole, linezolid, meperidine, metronidazole, metronidazole with sodium bicarbonate, verapamil. **Incompatible:** Amikacin, amobarbital, atracurium, bleomycin, calcium gluconate, clindamycin with gentamicin, colistimethate, kanamycin, pentobarbital, polymyxin B sulfate, ranitidine. **Variable (consult detailed reference):** Cimetidine.

ContraindicationsHypersensitivity to cefazolin sodium, any component of the formulation, or other cephalosporins
Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Elevated INR: May be associated with increased INR, especially in nutritionally-deficient patients, prolonged treatment, hepatic or renal disease.

- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures.

Geriatric ConsiderationsAdjust dose for renal function.
Pregnancy Risk FactorB
Pregnancy ConsiderationsAdverse effects were not observed in animal reproduction studies; therefore, cefazolin is classified as pregnancy category B. Cefazolin crosses the placenta. Adverse events have not been reported in the fetus following administration of cefazolin prior to caesarean section. Cefazolin is recommended for group B streptococcus prophylaxis in pregnant patients with a nonanaphylactic penicillin allergy.

Due to pregnancy-induced physiologic changes, the pharmacokinetics of cefazolin are altered. The half-life is shorter and the AUC is smaller. The volume of distribution is unchanged.

LactationEnters breast milk (small amounts)/use caution (AAP rates “compatible”)
Breast-Feeding ConsiderationsSmall amounts of cefazolin are excreted in breast milk. The manufacturer recommends that caution be exercised when administering cefazolin to nursing women. The American Academy of Pediatrics considers cefazolin to be "usually compatible with breast-feeding." Nondose-related effects could include modification of bowel flora.
Pregnancy & Lactation, In-Depth

- CeFAZolin in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Fever, seizure

Dermatologic: Rash, pruritus, Stevens-Johnson syndrome

Gastrointestinal: Diarrhea, nausea, vomiting, abdominal cramps, anorexia, pseudomembranous colitis, oral candidiasis

Genitourinary: Vaginitis

Hepatic: Transaminases increased, hepatitis

Hematologic: Eosinophilia, neutropenia, leukopenia, thrombocytopenia, thrombocytosis

Local: Pain at injection site, phlebitis

Renal: BUN increased, serum creatinine increased, renal failure

Miscellaneous: Anaphylaxis

Reactions reported with other cephalosporins: Toxic epidermal necrolysis, abdominal pain, cholestasis, superinfection, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, prothrombin time prolonged, pancytopenia

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Cephalosporins may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction.

Some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*, leading to a potential underestimation of aminoglycoside serum concentration.

Monitoring ParametersRenal function periodically when used in combination with other nephrotoxic drugs, hepatic function tests, CBC; monitor for signs of anaphylaxis during first dose
Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, anticoagulants). Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, hypersensitivity can occur several days after therapy is started) regularly during therapy. Advise patients with diabetes about use of Clinitest®. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, hypersensitivity, opportunistic infection, renal dysfunction, anemia).
Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy; renal function
Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is administered by injection or infusion. Report immediately any redness, swelling, burning, or pain at injection/infusion site; rash or hives; or respiratory difficulty, chest pain, or difficulty swallowing. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, drug may cause false test results with Clinitest® urine glucose monitoring; use of another type of glucose monitoring is preferable. May cause diarrhea (yogurt, boiled milk, or buttermilk may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage, sores in mouth, blood in stool or urine, unusual fever or chills); or CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precautions:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [iso-osmotic dextrose solution]: 1 g (50 mL)

Injection, powder for reconstitution: 500 mg, 1 g, 10 g, 20 g

Generic AvailableYes

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Distribution: Widely into most body tissues and fluids including gallbladder, liver, kidneys, bone, sputum, bile, pleural, and synovial; CSF penetration is poor

Protein binding: 74% to 86%

Metabolism: Minimally hepatic

Half-life elimination: 90-150 minutes; prolonged with renal impairment

Time to peak, serum: I.M.: 0.5-2 hours

Excretion: Urine (80% to 100% as unchanged drug)

Related Information

- Antibiotic Treatment of Adults With Infective Endocarditis
- Cephalosporins by Generation
- Community-Acquired Pneumonia in Adults
- Prevention of Infective Endocarditis

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine

Index TermsAncef; Cefazolin Sodium

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International Brand NamesAohe Xintalin (CL); Azolin (IN); Basocef (DE); Biofazolin (PL); Biozolin (ID); Cefacidal (BE, EC, LU, PE, ZA); Cefamezin (AR, HR, IL, JP, KP, PL, PT, TH); Cefarad (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Cefazin (TW); Cefazol (ID, TH); Cefazolin Biochemie (PL); Cefazoline Panpharma (FR); Cefzolin (TH); Celmetin (NO); Cezolin (BR); Cizo (PH); Cloviz (PH); Fazol (PH); Fazolin (TH); Fonvicol (PH); Gramaxin (AT); Ilozef (PH); Izacef (ZA); Karidina (ES); Kefarin (GR); Kefazin (IL); Kefzol (AT, AU, BF, BJ, CH, CI, CN, CZ, ET, GB, GH, GM, GN, HN, HR, HU, IE, KE, LR, LU, MA, ML, MR, MU, MW, NE, NG, NL, PK, PL, SC, SD, SL, SN, TN, TW, TZ, UG, VE, ZA, ZM, ZW); Kelin (TW); Kofatol (TW); Maxcep (PH); Megacef (PH); Oricef (TW); Orizolin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Oryant (PH); Reflin (IN); Samarial (PH); Stancef (PH); Tarfazolin (PL); Totacef (EE, HN, HU, IT); Zalulin (PH); Zepilen (BG, NZ); Zolecef (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Zolicef (AT, TH); Zolidina (PY, UY); Zolimed (TH); Zolival (PH)

Cefdinir

Lexi-Drugs Online

English English

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Pronunciation(SEF di ner)
U.S. Brand NamesOmnicef®
Canadian Brand NamesOmnicef®
Pharmacologic CategoryAntibiotic, Cephalosporin (Third Generation)
Use: Labeled IndicationsTreatment of community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute bacterial otitis media, acute maxillary sinusitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections.
Dosing: Adults

Acute exacerbations of chronic bronchitis, pharyngitis/tonsillitis: Oral: 300 mg twice daily for 5-10 days **or** 600 mg once daily for 10 days

Acute maxillary sinusitis: Oral: 300 mg twice daily **or** 600 mg once daily for 10 days

Community-acquired pneumonia, uncomplicated skin and skin structure infections: Oral: 300 mg twice daily for 10 days

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Children 6 months to 12 years:

Acute bacterial otitis media, pharyngitis/tonsillitis: Oral: 7 mg/kg/dose twice daily for 5-10 days **or** 14 mg/kg/dose once daily for 10 days (maximum: 600 mg/day)

Acute maxillary sinusitis: Oral: 7 mg/kg/dose twice daily **or** 14 mg/kg/dose once daily for 10 days (maximum: 600 mg/day)

Uncomplicated skin and skin structure infections: Oral: 7 mg/kg/dose twice daily for 10 days (maximum: 600 mg/day)

Children >12 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} <30 mL/minute:

Children: 7 mg/kg once daily (maximum: 300 mg/day)

Adults: 300 mg once daily

Hemodialysis removes cefdinir; recommended initial dose: 300 mg (or 7 mg/kg/dose) every other day. At the conclusion of each hemodialysis session, 300 mg (or 7 mg/kg/dose) should be given. Subsequent doses (300 mg or 7 mg/kg/dose) should be administered every other day.

Dosing: Hepatic ImpairmentNo adjustment necessary.
Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralTwice daily doses should be given every 12 hours. May be taken with or without food. Manufacturer recommends administering at least 2 hours before or after antacids or iron supplements. Shake suspension well before use.
Dietary ConsiderationsSuspension contains sucrose 2.86 g/5 mL
StorageCapsules and unmixed powder should be stored at room temperature of 15°C to 30°C (59°F to 86°F). After mixing, the suspension can be stored at room temperature of 25°C (77°F) for 10 days.
ReconstitutionOral suspension should be mixed with 38 mL water for the 60 mL bottle and 63 mL of water for the 100 mL bottle.
ContraindicationsHypersensitivity to cefdinir, any component of the formulation, other cephalosporins, or related antibiotics
Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment may be required.

Special populations:

- Pediatrics: Safety and efficacy in infants <6 months of age have not been established.

Geriatric ConsiderationsCefdinir has not been studied exclusively in the elderly. Patients ≥65 years of age have been included in clinical. No information is available on their response or tolerance.
Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic events have not been observed in animal studies; therefore, cefdinir is classified as pregnancy category B. It is not known if cefdinir crosses the human placenta.
LactationExcretion in breast milk unknown
Breast-Feeding ConsiderationsCefdinir is not detectable in breast milk following a single cefdinir 600 mg dose. It is not known if it would be detectable after multiple doses. If present in breast milk, nondose-related effects could include modification of bowel flora.
Pregnancy & Lactation, In-Depth

- Cefdinir in Pregnancy & Lactation

Adverse Reactions

>10%: Gastrointestinal: Diarrhea (8% to 15%)

1% to 10%:

Central nervous system: Headache (2%)

Dermatologic: Rash (≤3%)

Gastrointestinal: Nausea (≤3%), abdominal pain (≤1%), vomiting (≤1%)

Genitourinary: Vaginal moniliasis (≤4%), urine leukocytes increased (2%), urine protein increased (1% to 2%), vaginitis (≤1%)

Hematologic: Eosinophils increased (1%)

Hepatic: Alkaline phosphatase increased (≤1%), platelets increased (1%)

Renal: Microhematuria (1%)

Miscellaneous: Lymphocytes increased (≤2%), GGT increased (1%), lactate dehydrogenase increased (≤1%), bicarbonate decreased (≤1%), lymphocytes decreased (≤1%), PMN changes (≤1%)

<1% (Limited to important or life-threatening): Anorexia, constipation, cutaneous moniliasis, dizziness, dyspepsia, flatulence, hyperkinesia, insomnia, leukopenia, leukorrhea, maculopapular rash, moniliasis, pruritus, somnolence, stools abnormal, weakness, xerostomia

Postmarketing and/or case reports: Allergic vasculitis, amylase increased, anaphylaxis, bleeding tendency, bloody diarrhea, cardiac failure, chest pain, cholestasis, coagulation disorder, conjunctivitis, disseminated intravascular coagulation (DIC), enterocolitis (acute), eosinophilic pneumonia, erythema multiforme, erythema nodosum, exfoliative dermatitis, facial edema, fever, fulminant hepatitis, granulocytopenia, hemolytic anemia, hemorrhagic colitis, hepatic failure, hepatitis (acute), hypertension, idiopathic thrombocytopenia purpura, ileus, interstitial pneumonia (idiopathic), involuntary movement, jaundice, laryngeal edema, loss of consciousness, melena, myocardial infarction, nephropathy, pancytopenia, peptic ulcer, pneumonia (drug-induced), pseudomembranous colitis, renal failure (acute), respiratory failure (acute), rhabdomyolysis, serum sickness, shock, Stevens-Johnson syndrome, stomatitis, thrombocytopenia, toxic epidermal necrolysis, upper GI bleed

Reactions reported with other cephalosporins: Dizziness, fever, encephalopathy, asterixis, neuromuscular excitability, seizure, aplastic anemia, interstitial nephritis, toxic nephropathy, angioedema, hemorrhage, PT prolonged, and superinfection

Drug Interactions

Iron Salts: May decrease the serum concentration of Cefdinir. Red-appearing, non-bloody stools may also develop due to the formation of an insoluble iron-cefdinir complex. Management: Avoid concurrent cefdinir and iron when possible. Separating doses by several hours may minimize interaction. Iron-containing infant formulas do not appear to interact with cefdinir. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Test InteractionsFalse-positive reaction for urinary ketones may occur with nitroprusside- but not nitroferricyanide-based tests. False-positive urine glucose results may occur when using Clinitest®, Benedict's solution, or Fehling's solution; glucose-oxidase-based reaction systems (eg, Clinistix®, Tes-Tape®) are recommended. May cause positive direct Coombs' test.
Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose.
Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions. Assess therapeutic response and adverse effects during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, opportunistic infection, hypersensitivity).
Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy; renal function.
Patient EducationTake as directed, at regular intervals around-the-clock (with or without food). Avoid taking for 2 hours before or after antacids or iron supplements. Chilling oral suspension improves flavor (do not freeze). Complete full course of medication, even if you feel

better. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause diarrhea (yogurt, boiled milk, or buttermilk may help); or nausea, vomiting, flatulence (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage; sores in mouth; blood in stool or urine, unusual fever or chills); CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 300 mg

Omnicef®: 300 mg

Powder for oral suspension: 125 mg/5 mL (60 mL, 100 mL); 250 mg/5 mL (60 mL, 100 mL)

Omnicef®: 125 mg/5 mL (60 mL, 100 mL) [contains sodium benzoate and sucrose 2.86 g/5 mL; strawberry flavor]; 250 mg/5 mL (60 mL, 100 mL) [contains sodium benzoate and sucrose 2.86 g/5 mL; strawberry flavor]

Generic AvailableYes

ManufacturerCEPH International for Abbott Laboratories

Pricing: U.S. (www.drugstore.com)

Capsules (Cefdinir)

300 mg (20): $35.99

Capsules (Omnicef)

300 mg (20): $110.14

Suspension (reconstituted) (Omnicef)

125 mg/5 mL (100): $88.31

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Distribution: V_d:

Children 6 months to 12 years: 0.29-1.05 L/kg

Adults: 0.06-0.64 L/kg

Protein binding: 60% to 70%

Metabolism: Minimally hepatic

Bioavailability: Capsule: 16% to 21%; suspension 25%

Half-life elimination: 100 minutes

Time to peak, plasma: 3 hours

Excretion: Primarily urine

Related Information

- Cephalosporins by Generation

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine

Index TermsCFDN

References

Marshall WF and Blair JE, “The Cephalosporins,” *Mayo Clin Proc*, 1999, 74(2):187-95.[PubMed 10069359]

International Brand NamesCefzon (JP); Omnicef R (MX)

Cefditoren

Lexi-Drugs Online

English English

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Medication Safety Issues

International issues:

> Spectracef® may be confused with Spectrocef® which is a brand name for cefotaxime in Italy

Pronunciation(sef de TOR en)
U.S. Brand NamesSpectracef®
Pharmacologic CategoryAntibiotic, Cephalosporin (Third Generation)
Use: Labeled IndicationsTreatment of acute bacterial exacerbation of chronic bronchitis or community-acquired pneumonia (due to susceptible organisms including *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Streptococcus pneumoniae*-penicillin susceptible only, *Moraxella catarrhalis*); pharyngitis or tonsillitis (*Streptococcus pyogenes*); and uncomplicated skin and skin-structure infections (*Staphylococcus aureus* - not MRSA, *Streptococcus pyogenes*)
Use: DentalBactericidal antibiotic for infections due to susceptible organisms
Dosing: Adults

Acute bacterial exacerbation of chronic bronchitis: Oral: 400 mg twice daily for 10 days

Community-acquired pneumonia: Oral: 400 mg twice daily for 14 days

Dental infections (unlabeled use): Oral: 400 mg twice daily for 10 days

Pharyngitis, tonsillitis, uncomplicated skin and skin structure infections: Oral: 200 mg twice daily for 10 days

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren ≥12 years: Refer to adult dosing.
Dosing: Renal Impairment

Cl_{cr} 30-49 mL/minute/1.73 m^2: Maximum dose: 200 mg twice daily

Cl_{cr} <30 mL/minute/1.73 m^2: Maximum dose: 200 mg once daily

End-stage renal disease: Appropriate dosing not established

Dosing: Hepatic Impairment

Mild-to-moderate impairment: Adjustment not required

Severe impairment (Child-Pugh class C): Specific guidelines not available

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralShould be taken with meals.
Dietary ConsiderationsCefditoren should be taken with meals. Plasma carnitine levels are decreased during therapy (39% with 200 mg dosing, 63% with 400 mg dosing); normal concentrations return within 7-10 days after treatment is discontinued.
StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from light and moisture.
ContraindicationsHypersensitivity to cefditoren, any component of the formulation, other cephalosporins, or milk protein; carnitine deficiency
Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Elevated INR: May be associated with increased INR, especially in nutritionally-deficient patients, prolonged treatment, hepatic or renal disease.

- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Carnitine deficiency: Do not use in patients with carnitine deficiency; causes renal excretion of carnitine.
- Hepatic impairment: Use with caution in patients with hepatic impairment
- Renal impairment: Use with caution in patients with renal impairment; modify dosage in moderate to severe impairment.
- Seizure disorders: Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Dosage form specific issues:

- Sodium caseinate: Tablets contain sodium caseinate, which may cause hypersensitivity reactions in patients with milk protein hypersensitivity; this does not affect patients with lactose intolerance.

Other warnings/precautions:

- Duration of therapy: Not for long-term therapy due to the possible development of carnitine deficiency over time.

Geriatric ConsiderationsNo dose adjustment is necessary for patients with normal age-adjusted renal function.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal reproduction studies; therefore, the manufacturer classifies cefditoren as pregnancy category B. Other cephalosporins cross the placenta and are considered safe in pregnancy.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known whether cefditoren is excreted in human milk. The manufacturer recommends caution when using cefditoren during breast-feeding. Other cephalosporins are considered safe during breast-feeding. If cefditoren reaches the breast milk, the limited oral absorption may minimize the effect on the nursing infant. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Cefditoren in Pregnancy & Lactation

Adverse Reactions

>10%: Gastrointestinal: Diarrhea (11% to 15%)

1% to 10%:

Central nervous system: Headache (2% to 3%)

Endocrine & metabolic: Glucose increased (1% to 2%)

Gastrointestinal: Nausea (4% to 6%), abdominal pain (2%), dyspepsia (1% to 2%), vomiting (1%)

Genitourinary: Vaginal moniliasis (3% to 6%)

Hematologic: Hematocrit decreased (2%)

Renal: Hematuria (3%), urinary white blood cells increased (2%)

<1%, postmarketing, and/or case reports: Abnormal dreams, acute renal failure, albumin decreased, allergic reaction, ALT increased, AST increased, anorexia, appetite increased, arthralgia, asthma, BUN increased, calcium decreased, chloride decreased, cholesterol increased, coagulation time increased, constipation, diaphoresis, dizziness, dry mouth, eosinophilic pneumonia, eosinophils increased, eructation, erythema multiforme, facial edema, fever, flatulence, fungal infection, gastritis, gastrointestinal disorder, hemoglobin decreased, hyperglycemia, inorganic phosphorus decreased, insomnia, interstitial pneumonia, leukopenia, leukorrhea, lymphocytes increased, mouth ulceration, myalgia, nervousness, neutrophils decreased, oral moniliasis, pain, peripheral edema, pharyngitis, positive direct Coombs' test, potassium increased, pseudomembranous colitis, proteinuria, pruritus, rash, rhinitis, sinusitis, sodium decreased, somnolence, Stevens-Johnson syndrome, stomatitis, taste perversion, thirst, thrombocythemia, thrombocytopenia, toxic epidermal necrolysis, urinary frequency, urticaria, vaginitis, weakness, weight loss, white blood cell increase/decrease

Reactions reported with other cephalosporins: Anaphylaxis, aplastic anemia, cholestasis, hemorrhage, hemolytic anemia, renal dysfunction, reversible hyperactivity, serum sickness-like reaction, toxic nephropathy

Drug Interactions

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Cephalosporins may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Moderate- to high-fat meals increase bioavailability and maximum plasma concentration.

Test InteractionsMay induce a positive direct Coomb's test. May cause a false-negative ferricyanide test. Glucose oxidase or hexokinase methods recommended for blood/plasma glucose determinations. False-positive urine glucose test when using copper reduction based assays (eg, Clinitest®).

Monitoring ParametersAssess patient at beginning and throughout therapy for infection; monitor for signs of anaphylaxis during first dose.

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions. Assess therapeutic response and adverse effects during therapy. Advise patients with diabetes about use of Clinitest®. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, hypersensitivity, opportunistic infection, gastrointestinal upset, diarrhea).

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy; renal function

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take as directed, at regular intervals around-the-clock, with food. Maintain adequate hydration (2-3 L/day of fluids unless instructed to restrict fluid intake). Complete full course of medication, even if you feel better. If you have diabetes, monitor glucose levels closely; may cause false test results with Clinitest® urine glucose monitoring; use of another type of glucose monitoring is preferable. May cause diarrhea (yogurt, buttermilk, or boiled milk may help); or nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; opportunistic infection (eg, vaginal itching or drainage, sores in mouth, blood in stool or urine, or unusual fever or chills); or CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Spectracef®: 200 mg [contains sodium caseinate]

Generic AvailableNo

ManufacturerTAP Pharmaceuticals Inc

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Distribution: 9.3 ± 1.6 L

Protein binding: 88% (*in vitro*), primarily to albumin

Metabolism: Cefditoren pivoxil is hydrolyzed to cefditoren (active) and pivalate

Bioavailability: ~14% to 16%, increased by moderate to high-fat meal

Half-life elimination: 1.6 ± 0.4 hours

Time to peak: 1.5-3 hours

Excretion: Urine (as cefditoren and pivaloylcarnitine)

Related Information

- Cephalosporins by Generation

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause abnormal dreams, insomnia, and dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCefditoren Pivoxil

References

Darkes MJ and Plosker GL, "Cefditoren Pivoxil," *Drugs*, 2002, 62(2):319-36.[PubMed 11817976]

International Brand NamesMeiact (CL, ES, JP, TH)

Cefepime

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Cefepime: Safety Review Ongoing - May 2008

The Food and Drug Administration (FDA) announced that it is continuing to review safety data concerning cefepime. The safety review was initiated in November 2007 following a published meta-analysis (Yahav, 2007) which raised concerns of increased mortality in cefepime treated patients. The FDA will release its conclusions at the completion of the safety review.

Additional information may be found at http://www.fda.gov/medwatch/safety/2007/safety07.htm#Cefepime

Pronunciation(SEF e pim)

U.S. Brand NamesMaxipime®

Canadian Brand NamesMaxipime®

Pharmacologic CategoryAntibiotic, Cephalosporin (Fourth Generation)

Use: Labeled IndicationsTreatment of uncomplicated and complicated urinary tract infections, including pyelonephritis caused by typical urinary tract pathogens; monotherapy for febrile neutropenia; uncomplicated skin and skin structure infections caused by *Streptococcus pyogenes*; moderate-to-severe pneumonia caused by pneumococcus, *Pseudomonas aeruginosa*, and other gram-negative organisms; complicated intra-abdominal infections (in combination with metronidazole). Also active against methicillin-susceptible staphylococci, *Enterobacter* sp, and many other gram-negative bacilli.

Children 2 months to 16 years: Empiric therapy of febrile neutropenia patients, uncomplicated skin/soft tissue infections, pneumonia, and uncomplicated/complicated urinary tract infections.

Dosing: Adults

Brain abscess, postneurosurgical prevention (unlabeled use): I.V.: 2 g every 8 hours with vancomycin

Febrile neutropenia, monotherapy: I.V: 2 g every 8 hours for 7 days or until the neutropenia resolves

Intra-abdominal infections, complicated: I.V.: 2 g every 12 hours for 7-10 days with metronidazole

Otitis externa, malignant (unlabeled use): I.V.: 2 g every 12 hours

Pneumonia: I.V.:

Nosocomial (HAP/VAP): 1-2 g every 8-12 hours; **Note:** Duration of therapy may vary considerably (7-21 days); usually longer courses are required if *Pseudomonas*. In absence of *Pseudomonas*, and if appropriate empiric treatment used and patient responsive, it may be clinically appropriate to reduce duration of therapy to 7-10 days (American Thoracic Society Guidelines, 2005).

Community-acquired (including pseudomonal): 1-2 g every 12 hours for 10 days

Septic lateral/cavernous sinus thrombosis (unlabeled use): I.V.: 2 g every 8-12 hours; with metronidazole for lateral

Skin and skin structure, uncomplicated: I.V.: 2 g every 12 hours for 10 days

Urinary tract infections, complicated and uncomplicated:

Mild-to-moderate: I.M., I.V.: 500-1000 mg every 12 hours for 7-10 days

Severe: I.V.: 2 g every 12 hours for 10 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Febrile neutropenia: I.V.: 50 mg/kg every 8 hours for 7 days or until neutropenia resolves

Skin and skin structure infections (uncomplicated) and pneumonia: I.V.: 50 mg/kg every 12 hours for 10 days

Urinary tract infections, complicated and uncomplicated: I.V., I.M.: 50 mg/kg every 12 hours for 7-10 days; **Note:** I.M. may be considered for mild-to-moderate infection only.

Dosing: Renal Impairment

Adjustment of recommended maintenance schedule is required:

Normal dosing schedule: 500 mg every 12 hours

Cl_{cr} 30-60 mL/minute: 500 mg every 24 hours

Cl_{cr} 11-29 mL/minute: 500 mg every 24 hours

Cl_{cr} <11 mL/minute: 250 mg every 24 hours

Normal dosing schedule: 1 g every 12 hours

Cl_{cr} 30-60 mL/minute: 1 g every 24 hours

Cl_{cr} 11-29 mL/minute: 500 mg every 24 hours

Cl_{cr} <11 mL/minute: 250 mg every 24 hours

Normal dosing schedule: 2 g every 12 hours

Cl_{cr} 30-60 mL/minute: 2 g every 24 hours

Cl_{cr} 11-29 mL/minute: 1 g every 24 hours

Cl_{cr} <11 mL/minute: 500 mg every 24 hours

Normal dosing schedule: 2 g every 8 hours

Cl_{cr} 30-60 mL/minute: 2 g every 12 hours

Cl_{cr} 11-29 mL/minute: 2 g every 24 hours

Cl_{cr} <11 mL/minute: 1 g every 24 hours

Hemodialysis: Initial: 1 g (single dose) on day 1. Maintenance: 500 mg once daily (1 g once daily in febrile neutropenic patients). Dosage should be administered after dialysis on dialysis days.

Continuous ambulatory peritoneal dialysis (CAPD): Removed to a lesser extent than hemodialysis; administer normal recommended dose every 48 hours

Continuous renal replacement therapy (CRRT) (Trotman, 2005): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH: 1-2 g every 12 hours

CVVHDF: 2 g every 12 hours

Note: Consider higher dosage of 4 g/day if treating *Pseudomonas* or life-threatening infections in order to maximize time above MIC.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Inject deep I.M. into large muscle mass.

Administration: I.V.Inject direct I.V. over 5 minutes. Infuse intermittent infusion over 30 minutes.

Administration: I.V. DetailpH: 4-6

StorageStable with normal saline, D_5W, and a variety of other solutions for 24 hours at room temperature and 7 days refrigerated.

CompatibilityStable in D_5LR, D_5NS, D_5W, $D_{10}W$, NS, bacteriostatic water, sterile water for injection; **variable stability (consult detailed reference)** in peritoneal dialysis solutions.

Y-site administration: Compatible: Ampicillin/sulbactam, aztreonam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, carmustine, co-trimoxazole, cyclophosphamide, cytarabine, dactinomycin, dexamethasone sodium phosphate, docetaxel, doxorubicin liposome, fluconazole, fludarabine, fluorouracil, furosemide, granisetron, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, imipenem/cilastatin, leucovorin, lorazepam, melphalan, mesna, methotrexate, methylprednisolone sodium succinate, metronidazole, paclitaxel, piperacillin/tazobactam, ranitidine, sargramostim, sodium bicarbonate, thiotepa, ticarcillin/clavulanate, zidovudine. **Incompatible:** Acyclovir, amphotericin B, amphotericin B cholesteryl sulfate complex, chlordiazepoxide, chlorpromazine, cimetidine, ciprofloxacin, cisplatin, dacarbazine, daunorubicin, diazepam, diphenhydramine, dobutamine, dopamine, doxorubicin, droperidol, enalaprilat, etoposide, etoposide phosphate, famotidine, filgrastim, floxuridine, ganciclovir, haloperidol, hydroxyzine, idarubicin, ifosfamide, magnesium sulfate, mannitol, mechlorethamine, meperidine, metoclopramide, mitomycin, mitoxantrone, morphine, nalbuphine, ofloxacin, ondansetron, plicamycin, prochlorperazine edisylate, promethazine, streptozocin, vancomycin, vinblastine, vincristine.

Compatibility when admixed: Compatible: Amikacin, clindamycin, heparin, potassium chloride, theophylline, vancomycin. **Incompatible:** Aminophylline, gentamicin, netilmicin, tobramycin. **Variable (consult detailed reference):** Ampicillin, metronidazole.

ContraindicationsHypersensitivity to cefepime, any component of the formulation, or other cephalosporins

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Elevated INR: May be associated with increased INR, especially in nutritionally-deficient patients, prolonged treatment, hepatic or renal disease.
- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.
- Seizure disorders: Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures.

Geriatric Considerations Adjust dose for changes in renal function.

Pregnancy Risk Factor B

Pregnancy Considerations Teratogenic effects were not observed in animal studies; therefore, cefepime is classified as pregnancy category B. It is not known if cefepime crosses the human placenta.

Lactation Enters breast milk/use caution

Breast-Feeding Considerations Small amounts of cefepime are excreted in breast milk. The manufacturer recommends that caution be exercised when administering cefepime to nursing women. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Cefepime in Pregnancy & Lactation

Adverse Reactions

>10%: Hematologic: Positive Coombs' test without hemolysis

1% to 10%:

Central nervous system: Fever (1%), headache (1%)

Dermatologic: Rash, pruritus

Gastrointestinal: Diarrhea, nausea, vomiting

Local: Pain, erythema at injection site

<1%, postmarketing, and/or case reports: Agranulocytosis, anaphylactic shock, anaphylaxis, coma, encephalopathy, hallucinations, leukopenia, myoclonus, neuromuscular excitability, neutropenia, seizure, status epilepticus (nonconvulsive), thrombocytopenia

Reactions reported with other cephalosporins: Aplastic anemia, erythema multiforme, hemolytic anemia, hemorrhage, pancytopenia, PT prolonged, renal dysfunction, Stevens-Johnson syndrome, superinfection, toxic epidermal necrolysis, toxic nephropathy, vaginitis

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Test Interactions Positive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction, false-positive urinary proteins and steroids

Monitoring Parameters Obtain specimen for culture and sensitivity prior to the first dose. Monitor for signs of anaphylaxis during first dose.

Nursing: Physical Assessment/Monitoring Assess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions. Note I.V. or I.M. administration specifics prior to starting treatment. Assess results of laboratory tests (prothrombin time), therapeutic response, and adverse effects during therapy. Advise patients with diabetes about use of Clinitest®. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, hypersensitivity, nephrotoxicity, opportunistic infection).

Monitoring: Lab Tests Perform culture and sensitivity studies prior to initiating drug therapy; renal function

Patient Education Do not take any new medication during therapy unless approved by prescriber. This medication is administered by infusion or injection. Report immediately any redness, swelling, burning, or pain at injection/infusion site; itching or hives; chest pain; or difficulty swallowing or breathing. Maintain adequate hydration (2-3 L/day of fluids unless instructed to restrict fluid intake). May cause false test results with Clinitest®; use of another type of glucose testing is preferable. May cause diarrhea (yogurt, boiled milk, or buttermilk may help); nausea and vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage, sores in mouth, blood in stool or urine, unusual fever or chills); CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as hydrochloride: 500 mg, 1 g, 2 g

Maxipime®: 500 mg, 1 g, 2 g

Generic AvailableYes

ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysis and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: I.M.: Rapid and complete

Distribution: V_d: Adults: 14-20 L; penetrates into inflammatory fluid at concentrations ~80% of serum levels and into bronchial mucosa at levels ~60% of those reached in the plasma; crosses blood-brain barrier

Protein binding, plasma: 16% to 19%

Metabolism: Minimally hepatic

Half-life elimination: 2 hours

Time to peak: 0.5-1.5 hours

Excretion: Urine (85% as unchanged drug)

Related Information

- Antimicrobial Drugs of Choice
- Cephalosporins by Generation
- Community-Acquired Pneumonia in Adults
- Neutropenic Fever Guidelines

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins; has rarely been associated with encephalopathy (confusion, hallucinations, stupor, and coma); most cases occurred in patients with renal impairment who received doses that exceeded recommendations

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine

Anesthesia and Critical Care Concerns/Other ConsiderationsThe Food and Drug Administration (FDA) informed practitioners (November, 2007) of a review of new safety data and a request for additional data for cefepime after a recently published meta-analysis (Yahav, 2007) raised concerns of an increased risk of death in patients treated with cefepime. The authors of the meta-analysis reviewed the results from 57 randomized controlled trials comparing cefepime to other beta-lactams in a variety of infections. The primary outcome of the analysis was 30-day all-cause mortality; however, all-cause mortality data was only available in 41 of the trials. In addition, distribution of specific pathogens to infections in relation to all-cause mortality was not available, including patients with documented gram-negative and *Pseudomonas* infections. The authors reported an increase in all-cause mortality in the cefepime group relative to the comparator group (relative risk 1.26 [95% CI 1.08 to 1.40]; p=0.005). Only two subsets showed a significant difference in all cause mortality and include the group comparing cefepime to piperacillin-tazobactam (relative risk 2.14 [95% CI 1.17 to 3.89]; p=0.01) and the subset of patients with febrile neutropenia (relative risk 1.42 [95% CI 1.09 to 1.84]; p=0.009).

The FDA is currently evaluating the data, and in the interim, is reminding practitioners to consider the risks and benefits of cefepime prior to use. The FDA will provide additional communication and any recommendations, if necessary, following the conclusion of the evaluation, which is expected to take ~4 months (March, 2008).

Additional information may be found at http://www.fda.gov/medwatch/safety/2007/safety07.htm#Cefepime.

Index TermsCefepime Hydrochloride

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Yahav D, Paul M, Fraser A, et al, “Efficacy and Safety of Cefepime: A Systematic Review and Meta-Analysis,” *Lancet Infect Dis*, 2007, 7(5):338-48.[PubMed 17448937]

International Brand Names Axepim (FR); Cefepim (AT); Cefepitax (BR); Ceficad (IN); Cepimax (PH); Exepime (ID); Forzyn Beta (PY); Maxcef (AR, UY); Maxef (MX); Maxfrom (AR); Maxicef (ID); Maxipime (AT, AU, BE, BG, CH, CL, CN, CO, CZ, DE, DK, EC, EE, ES, FI, GR, HK, HN, HU, ID, IT, JP, KP, LU, MX, MY, NL, PE, PK, PL, PT, SE, SG, TH, TW, VE, ZA); Procepim (ID); Sandocef (ID)

Cefixime

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Suprax® may be confused with Sporanox®, Surbex®

International issues:

Cefiton® [Portugal] may be confused with Cefotan® which is a brand name for cefotetan in the U.S.

Cefiton® [Portugal] may be confused with Ceftim® which is a brand name for ceftazidime in Italy

Cefiton® [Portugal] may be confused with Ceftin® which is a brand name for cefuroxime in the U.S.

Cefiton® [Portugal] may be confused with Lexotan® which is a brand name for bromazepam in multiple international markets

Pronunciation(sef IKS eem)

U.S. Brand NamesSuprax®

Canadian Brand NamesSuprax®

Pharmacologic CategoryAntibiotic, Cephalosporin (Third Generation)

Use: Labeled IndicationsTreatment of urinary tract infections, otitis media, respiratory infections due to susceptible organisms including *S. pneumoniae* and *S. pyogenes*, *H. influenzae*, and many Enterobacteriaceae; uncomplicated cervical/urethral gonorrhea due to *N. gonorrhoeae*

Dosing: Adults

Susceptible infections: Oral: 400 mg/day divided every 12-24 hours

***S. pyogenes* infections:** Treat for 10 days

Typhoid fever: Oral: 20-30 mg/kg/day in 2 divided doses for 7-14 days after I.V. therapy

Uncomplicated cervical/urethral gonorrhea due to *N. gonorrhoeae*: Oral: 400 mg as a single dose

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Susceptible infections: Oral:

Children ≥6 months: 8 mg/kg/day divided every 12-24 hours

Children >50 kg or >12 years: Refer to adult dosing.

***S. pyogenes* infections:** Treat for 10 days

Typhoid fever: Oral: 20 mg/kg/day for 10-14 days; maximum 400 mg

Dosing: Renal Impairment

Cl_{cr} 21-60 mL/minute: Administer 75% of the standard dose.

Cl_{cr} <20 mL/minute: Administer 50% of the standard dose.

10% removed by hemodialysis

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralMay be administered with or without food. Administer with food to decrease GI distress. Shake oral suspension well before use.

Dietary ConsiderationsMay be taken with food.

StorageAfter reconstitution, suspension may be stored for 14 days at room temperature or under refrigeration.

ContraindicationsHypersensitivity to cefixime, any component of the formulation, or other cephalosporins

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; modify dosage.

Geriatric Considerations

Adjust dose for renal impairment.

Pregnancy Risk Factor

B

Pregnancy Considerations

Teratogenic effects were not observed in animal studies; therefore cefixime is classified as pregnancy category B. It is not known if cefixime crosses the human placenta; other cephalosporins cross the placenta and are considered safe in pregnancy. Congenital anomalies have not been associated with cefixime use during pregnancy (limited data). Cefixime is recommended for use in pregnant women for the treatment of gonococcal infections.

Lactation

Excretion in breast milk unknown

Breast-Feeding Considerations

It is not known if cefixime is excreted in breast milk. The manufacturer recommends that consideration be given to discontinuing nursing temporarily during treatment. Other cephalosporins are considered safe during breast-feeding. If present in breast milk, nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Cefixime in Pregnancy & Lactation

Adverse Reactions

>10%: Gastrointestinal: Diarrhea (16%)

2% to 10%: Gastrointestinal: Abdominal pain, nausea, dyspepsia, flatulence, loose stools

<2%: Acute renal failure, anaphylactic/anaphylactoid reactions, angioedema, BUN increased, candidiasis, creatinine increased, dizziness, drug fever, eosinophilia, erythema multiforme, facial edema, fever, headache, hepatitis, hyperbilirubinemia, jaundice, leukopenia, neutropenia, pruritus, pseudomembranous colitis, PT prolonged, rash, seizure, serum sickness-like reaction, Stevens-Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis, transaminases increased, urticaria, vaginitis, vomiting

Reactions reported with other cephalosporins: Interstitial nephritis, aplastic anemia, hemolytic anemia, hemorrhage, pancytopenia, agranulocytosis, colitis, superinfection

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Delays cefixime absorption.

Test Interactions

Positive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction

Monitoring Parameters

With prolonged therapy, monitor renal and hepatic function periodically. Observe for signs and symptoms of anaphylaxis during first dose.

Nursing: Physical Assessment/Monitoring

Assess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions. Assess results of laboratory tests (prothrombin time), therapeutic response, and adverse effects (eg, anemia, hemorrhage, pancytopenia, agranulocytosis, colitis) during therapy. Advise patients with diabetes about use of Clinitest®. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, hypersensitivity, opportunistic infection).

Monitoring: Lab Tests

Perform culture and sensitivity studies prior to initiating drug therapy; renal function

Patient Education

Do not take any new medication during therapy unless approved by prescriber. Take as directed, at regular intervals around-the-clock (with or without food). Chilling oral suspension improves flavor (do not freeze); shake suspension thoroughly before using. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Complete full course of medication, even if you feel better. May cause false test results with Clinitest®; use of another type of glucose testing is preferable. May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (yogurt, boiled milk, or buttermilk may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage; sores in mouth; blood in stool or urine; unusual fever or chills); CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Powder for oral suspension, as trihydrate:

Suprax®: 100 mg/5 mL (50 mL, 75 mL [DSC], 100 mL) [contains sodium benzoate; strawberry flavor]; 200 mg/5 mL (50 mL, 75 mL) [contains sodium benzoate; strawberry flavor]

Tablet, oral, as trihydrate:

Suprax®: 400 mg

Generic AvailableNo

ManufacturerLederle Laboratories

Pricing: U.S. (www.drugstore.com)

Suspension (reconstituted) (Suprax)

100 mg/5 mL (100): $173.99

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs); which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: 40% to 50%

Distribution: Widely throughout the body and reaches therapeutic concentration in most tissues and body fluids, including synovial, pericardial, pleural, peritoneal; bile, sputum, and urine; bone, myocardium, gallbladder, and skin and soft tissue

Protein binding: 65%

Half-life elimination: Normal renal function: 3-4 hours; Renal failure: Up to 11.5 hours

Time to peak, serum: 2-6 hours; delayed with food

Excretion: Urine (50% of absorbed dose as active drug); feces (10%)

Related Information

- Antimicrobial Drugs of Choice
- Cephalosporins by Generation
- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine

Index TermsCefixime Trihydrate

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International Brand NamesAerocef (AT); Axetef (PH); Cefirax (KP); Cefix (AE, BH, BR, CY, EG, IL, IQ, IR, JO, KP, KW, LB, LY, OM, QA, SA, SY, YE); Cefspan (CL, CN, ID, JP, PK, TH, TW); Cephoral (CH, DE, PL); Cexima (PY); Denvar (CR, DO, ES, GT, HN, MX, NI, PA, PE, SV); Devoxim (CO); Fixcef (PH); Fixef (ID); Fixim (NL); Fixime (ZA); Fixiphar (ID); Fixx (IN); Lanfix (ID); Longacef (VE); Maxpro (ID); Minixime (MY); Necopen (ES); Novacef (AR); Opixime (ID); Oralcef (UY); Oroken (FR); Pancef (BG); Pocef (KP); Sofix (ID); Spancef (ID); Spaxim (ID); Starcef (ID); Supracef (FI); Supran (IL); Suprax (CZ, DE, GB, HN, HU, IE, IT, PL); Tergecef (PH); Tocef (ID); Tricef (CN, PT, SE); Ultraxime (PH); Zefral (PH)

Cefotaxime

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cefotaxime may be confused with cefoxitin, ceftizoxime, cefuroxime

International issues:

Spectrocef® [Italy] may be confused with Spectracef® which is a brand name for cefditoren in the U.S.

Pronunciation(sef oh TAKS eem)
U.S. Brand NamesClaforan®
Canadian Brand NamesClaforan®
Pharmacologic CategoryAntibiotic, Cephalosporin (Third Generation)
Use: Labeled IndicationsTreatment of susceptible infection in respiratory tract, skin and skin structure, bone and joint, urinary tract, gynecologic as well as septicemia, and documented or suspected meningitis. Active against most gram-negative bacilli (not *Pseudomonas*) and gram-positive cocci (not enterococcus). Active against many penicillin-resistant pneumococci.
Dosing: Adults

Arthritis (septic): I.V.: 1 g every 8 hours

Brain abscess and meningitis: I.V.: 2 g every 4-6 hours

C-section: 1 g as soon as the umbilical cord is clamped, then 1 g I.M., I.V. at 6- and 12-hours intervals

Epiglottitis: I.V.: 2 g every 4-8 hours

Gonorrhea: I.M.: 1 g as a single dose; disseminated 1 g every 8 hours

Life-threatening infections: I.V.: 2 g every 4 hours

Liver abscess: I.V.: 1-2 g every 6 hours

Lyme disease:

Cardiac manifestations: I.V.: 2 g every 4 hours

CNS manifestations: I.V.: 2 g every 8 hours for 14-28 days

Moderate/severe infections: I.M., I.V.: 1-2 g every 8 hours

Orbital cellulitis: I.V.: 2 g every 4 hours

Peritonitis (spontaneous): I.V.: 2 g every 8 hours, unless life-threatening then 2 g every 4 hours

Septicemia: I.V.: 2 g every 6-8 hours

Skin and soft tissue:

Mixed, necrotizing: I.V.: 2 g every 6 hours, with metronidazole or clindamycin

Bite wounds (animal): I.V.: 2 g every 6 hours

Surgical prophylaxis: I.M., I.V.: 1 g 30-90 minutes before surgery

Uncomplicated infections: I.M., I.V.: 1 g every 12 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Infants and Children 1 month to 12 years:

Susceptible infections: I.M., I.V.: Infants and Children 1 month to 12 years: <50 kg: 50-200 mg/kg/day in divided doses every 6-8 hours

Epiglottitis: I.M., I.V.: 150-200 mg/kg/day in 4 divided doses with clindamycin for 7-10 days

Meningitis: I.M., I.V.: 200 mg/kg/day in divided doses every 6 hours

Pneumonia: I.V.: 200 mg/kg/day divided every 8 hours

Sepsis: I.V.: 150 mg/kg/day divided every 8 hours

Typhoid fever: I.M., I.V.: 150-200 mg/kg/day in 3-4 divided doses (maximum: 12 g/day); fluoroquinolone resistant: 80 mg/kg/day in 3-4 divided doses (maximum: 12 g/day)

Children >12 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer every 8-12 hours.

Cl_{cr} <10 mL/minute: Administer every 24 hours.

Moderately dialyzable (20% to 50%)

Continuous ambulatory peritoneal dialysis (CAPD): Administer 0.5-1 g every 24 hours

Continuous renal replacement therapy (CRRT): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH: 1-2 g every 12 hours

CVVHD/CVVHDF: 2 g every 12 hours

Dosing: Hepatic ImpairmentModerate dosage reduction is recommended in severe liver disease.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Inject deep I.M. into large muscle mass.

Administration: I.V.Inject direct I.V. over 3-5 minutes. Infuse intermittent infusion over 30 minutes.

Administration: I.V. DetailpH: 5.0-7.5 (injectable solution)

Dietary ConsiderationsSodium content of 1 g: 50.5 mg (2.2 mEq)

ReconstitutionReconstituted solution is stable for 12-24 hours at room temperature and 7-10 days when refrigerated and for 13 weeks when frozen. For I.V. infusion in NS or D_5W, solution is stable for 24 hours at room temperature, 5 days when refrigerated, or 13 weeks when frozen in Viaflex® plastic containers. Thawed solutions previously of frozen premixed bags are stable for 24 hours at room temperature or 10 days when refrigerated.

CompatibilityStable in $D_5{}^{1}/_{4}NS$, $D_5{}^{1}/_{2}NS$, D_5NS, D_5W, $D_{10}W$, LR, NS; **variable stability (consult detailed reference)** in peritoneal dialysis solutions

Y-site administration: Compatible: Acyclovir, amifostine, aztreonam, cyclophosphamide, diltiazem, docetaxel, etoposide, famotidine, fludarabine, granisetron, hydromorphone, levofloxacin, lorazepam, magnesium sulfate, melphalan, meperidine, midazolam, morphine, ondansetron, perphenazine, propofol, remifentanil, sargramostim, teniposide, thiotepa, tolazoline, vinorelbine. **Incompatible:** Allopurinol, filgrastim, fluconazole, gemcitabine, hetastarch, pentamidine. **Variable (consult detailed reference):** Cisatracurium, vancomycin.

Compatibility in syringe: Compatible: Heparin, ofloxacin. **Incompatible:** Doxapram.

Compatibility when admixed: Compatible: Clindamycin, metronidazole, verapamil. **Incompatible:** Aminoglycosides, aminophylline, sodium bicarbonate.

ContraindicationsHypersensitivity to cefotaxime, any component of the formulation, or other cephalosporins

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Arrhythmia: A potentially life-threatening arrhythmia has been reported in patients who received a rapid bolus injection via central line.
- Granulocytopenia: Granulocytopenia and more rarely agranulocytosis may develop during prolonged treatment (>10 days).
- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.
- Tissue inflammation: Minimize tissue inflammation by changing infusion sites when needed.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.

Geriatric ConsiderationsAdjust dose for renal impairment.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; therefore, cefotaxime is classified as pregnancy category

B. Cefotaxime crosses the placenta and can be found in fetal tissue. An increased risk of teratogenic effects has not been observed following maternal use. During pregnancy, peak cefotaxime serum concentrations are decreased and the serum half-life is shorter.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsVery small amounts of cefotaxime are excreted in breast milk. The manufacturer recommends that caution be exercised when administering cefotaxime to nursing women. The American Academy of Pediatrics considers cefotaxime to be "usually compatible with breast-feeding." Nondose-related effects could include modification of bowel flora. The pregnancy-related changes in cefotaxime pharmacokinetics continue into the early postpartum period.

Pregnancy & Lactation, In-Depth

- Cefotaxime in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Dermatologic: Rash, pruritus

Gastrointestinal: Diarrhea, nausea, vomiting, colitis

Local: Pain at injection site

<1%: Anaphylaxis, arrhythmia (after rapid I.V. injection via candidiasis, central catheter), BUN increased, creatinine increased, eosinophilia, erythema multiforme, fever, headache, interstitial nephritis, neutropenia, phlebitis, pseudomembranous colitis, Stevens-Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis, transaminases increased, urticaria, vaginitis

Reactions reported with other cephalosporins: Agranulocytosis, aplastic anemia, cholestasis, hemolytic anemia, hemorrhage, pancytopenia, renal dysfunction, seizure, superinfection, toxic nephropathy.

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction

Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose; CBC with differential (especially with long courses)

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, nephrotoxicity). Evaluate results of laboratory tests (prothrombin time, CBC with differential), therapeutic response, and adverse effects (diarrhea, nausea/vomiting, nephrotoxicity) regularly during therapy. Advise patients with diabetes about use of Clinitest®. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, hypersensitivity, opportunistic infection).

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy; CBC with differential (especially with long courses); renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is administered by injection or infusion. Report immediately any redness, swelling, burning, or pain at injection/infusion site; chest pain, palpitations, respiratory difficulty or swallowing; or itching or hives. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause false test results with Clinitest®; use of another type of glucose testing is preferable. May cause diarrhea (yogurt, boiled milk, or buttermilk may help); GI distress or nausea (small, frequent meals, frequent oral care, chewing gum, or sucking lozenges may help). Report unresolved or persistent diarrhea; opportunistic infection (vaginal itching or drainage, sores in mouth, blood in stool or urine, easy bleeding or bruising, unusual fever or chills); or respiratory difficulty. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed iso-osmotic solution]:

Claforan®: 1 g (50 mL); 2 g (50 mL) [contains sodium 50.5 mg (2.2 mEq) per cefotaxime 1 g]

Injection, powder for reconstitution: 500 mg, 1 g, 2 g, 10 g, 20 g

Claforan®: 500 mg, 1 g, 2 g, 10 g [contains sodium 50.5 mg (2.2 mEq) per cefotaxime 1 g]

Generic AvailableYes: Powder

ManufacturerHoechst-Marion Roussel

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Distribution: Widely to body tissues and fluids including aqueous humor, ascitic and prostatic fluids, bone; penetrates CSF best when meninges are inflamed

Metabolism: Partially hepatic to active metabolite, desacetylcefotaxime

Half-life elimination:

Cefotaxime: Premature neonates <1 week: 5-6 hours; Full-term neonates <1 week: 2-3.4 hours; Adults: 1-1.5 hours; prolonged with renal and/or hepatic impairment

Desacetylcefotaxime: 1.5-1.9 hours; prolonged with renal impairment

Time to peak, serum: I.M.: Within 30 minutes

Excretion: Urine (as unchanged drug and metabolites)

Related Information

- Antibiotic Treatment of Adults With Infective Endocarditis
- Antimicrobial Drugs of Choice
- Cephalosporins by Generation
- Community-Acquired Pneumonia in Adults

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins
Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine
Index TermsCefotaxime Sodium
References

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Tunkel AR, Hartman BJ, Kaplan SL, et al, “Practice Guidelines for the Management of Bacterial Meningitis,” *Clin Infect Dis*, 2004, 39(9):1267-84.[PubMed 15494903]

International Brand NamesBaxima (ID); Benaxima (MX); Biocef (ID); Biosint (MX); Biotaksym (PL); Biotax (IN); Cefacolin (AR); Cefalekol (HU); Cefirad (KP); Cefocam (PY); Cefotaksim (HR); Cefotax (AE, BH, CY, EG, IL, IQ, IR, JO, JP, KW, LB, LY, OM, QA, SA, SY, TH, YE); Cefotaxim (DE, NO); Cefoxim (KP); Cefpiran (KP); Ceptax (PH); Cetax (TW); Clacef (ID, SG); Cladex (PH); Clafetam (PH); Claforan (AE, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CR, CY, CZ, DE, DK, DO, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, NO, NZ, OM, PA, PE, PH, PK, PL, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SV, SY, TH, TN, TR, TT, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Claraxim (MY, TH); Clatax (ID); Clavocef (PH); Clavox (TW); Efotax (ID); Fot-Amsa (MX); Fotax (TH); Fotexina (CO, MX); Goforon (ID); Grifotaxima (CN, PE); Kalfoxim (ID); Lancef (ID); Lapixime (ID); Lyforan (IN); Makrocef (HR); Molelant (GR); Motaxim (TH); Naspor (PE); Newtaxime (KP); Omnatax (IN); Oritaxim (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Pantaxin (PH); Policef (BR); Procefa (ID); Ralopar (PT); Rantaksym (PL); Raxim (CL); Reftax (ZA); Sefotak (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Soclaf (ID); Spirosine (GR); Stoparen (GR); Taporin (MX); Tarcefoksym (PL); Taximax (ID); Taxime (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Tebruxim (MX); Tirdicef (ID); Tirotax (MX, PL); Ultracef (UY); Valoran (EE); Viken (MX); Xedin (MX); Zariviz (IT); Zefocent (PH)

Cefotetan

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cefotetan may be confused with cefoxitin, Ceftin®

Cefotan® may be confused with Ceftin®

International issues:

Cefotan® may be confused with Lexotan® which is a brand name for bromazepam in multiple international markets

Cefotan® may be confused with Cefiton® which is a brand name for cefixime in Portugal

Pronunciation(SEF oh tee tan)

Pharmacologic CategoryAntibiotic, Cephalosporin (Second Generation)

Use: Labeled IndicationsSurgical prophylaxis; intra-abdominal infections and other mixed infections; respiratory tract, skin and skin structure, bone and joint, urinary tract and gynecologic as well as septicemia; active against gram-negative enteric bacilli including *E. coli*, *Klebsiella*, and *Proteus*; less active against staphylococci and streptococci than first generation cephalosporins, but active against anaerobes including *Bacteroides fragilis*

Dosing: Adults

Susceptible infections: I.M., I.V.: 1-6 g/day in divided doses every 12 hours; usual dose: 1-2 g every 12 hours for 5-10 days; 1-2 g may be given every 24 hours for urinary tract infection

Orbital cellulitis, odontogenic infections: I.V.: 2 g every 12 hours

Pelvic inflammatory disease: I.V.: 2 g every 12 hours; used in combination with doxycycline

Preoperative prophylaxis: I.M., I.V.: 1-2 g 30-60 minutes prior to surgery; when used for cesarean section, dose should be given as soon as umbilical cord is clamped

Urinary tract infection: I.M., I.V.: 1-2 g may be given every 24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Severe infections (unlabeled use): I.M., I.V.: 20-40 mg/kg/dose every 12 hours (maximum: 6 g/day)

Preoperative prophylaxis (unlabeled use): I.M., I.V.: 40 mg/kg 30-60 minutes prior to surgery

Pelvic inflammatory disease: Adolescents: I.V.: Refer to adult dosing.

Dosing: Renal ImpairmentI.M., I.V.:

Cl_{cr} 10-30 mL/minute: Administer every 24 hours

Cl_{cr} <10 mL/minute: Administer every 48 hours

Hemodialysis: Dialyzable (5% to 20%); administer $^1/_4$ the usual dose every 24 hours on days between dialysis; administer $^1/_2$ the usual dose on the day of dialysis.

Continuous arteriovenous or venovenous hemodiafiltration effects: Administer 750 mg every 12 hours

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Inject deep I.M. into large muscle mass.

Administration: I.V.Inject direct I.V. over 3-5 minutes. Infuse intermittent infusion over 30 minutes.

Administration: I.V. DetailpH: 4.5-6.5 (reconstituted solution)

Dietary ConsiderationsContains sodium of 80 mg (3.5 mEq) per cefotetan 1 g

ReconstitutionReconstituted solution is stable for 24 hours at room temperature and 96 hours when refrigerated. For I.V. infusion in NS or D_5W solution and after freezing, thawed solution is stable for 24 hours at room temperature or 96 hours when refrigerated. Frozen solution is stable for 12 weeks.

Compatibility Stable in D_5W, NS.

Y-site administration: Compatible: Allopurinol, amifostine, aztreonam, diltiazem, docetaxel, etoposide, famotidine, filgrastim, fluconazole, fludarabine, gatifloxacin, gemcitabine, granisetron, heparin, insulin (regular), linezolid, melphalan, meperidine, morphine, paclitaxel, propofol, remifentanil, sargramostim, tacrolimus, teniposide, theophylline, thiotepa. **Incompatible:** Promethazine, vinorelbine. **Variable (consult detailed reference):** Cisatracurium, vancomycin.

Compatibility in syringe: Incompatible: Doxapram, promethazine.

Compatibility when admixed: Compatible: Amikacin, aminophylline, ampicillin, atropine, azlocillin, cimetidine, digoxin, dopamine, doxycycline, epinephrine, erythromycin lactobionate, furosemide, kanamycin, multivitamins, oxytocin, penicillin G potassium, piperacillin, ticarcillin, tobramycin, vitamin B complex with C. **Incompatible:** Gentamicin, heparin, tetracyclines.

Contraindications Hypersensitivity to cefotetan, any component of the formulation, or other cephalosporins; previous cephalosporin-associated hemolytic anemia

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

• Bleeding: Although it contains the methyltetrazolethiol side chain, bleeding has not been a significant problem.

• Elevated INR: May be associated with increased INR, especially in nutritionally-deficient patients, prolonged treatment, hepatic or renal disease.

• Hemolytic anemia: Has been associated with a higher risk of hemolytic anemia relative to other cephalosporins (approximately threefold); monitor carefully during use and consider cephalosporin-associated immune anemia in patients who have received cefotetan within 2-3 weeks (either as treatment or prophylaxis).

• Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).

• Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

• Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.

Geriatric Considerations Cefotetan has not been studied in the elderly. Adjust dose for renal function in the elderly.

Pregnancy Risk Factor B

Pregnancy Considerations Adverse events have not been observed in animal reproduction studies; therefore, the manufacturer classifies cefotetan as pregnancy category B. Cefotetan crosses the placenta and produces therapeutic concentrations in the amniotic fluid and cord serum.

Lactation Enters breast milk (small amounts)/use caution

Breast-Feeding Considerations Very small amounts of cefotetan are excreted in human milk. The manufacturer recommends caution when giving cefotetan to a breast-feeding mother. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Cefotetan in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Gastrointestinal: Diarrhea (1%)

Hepatic: Transaminases increased (1%)

Miscellaneous: Hypersensitivity reactions (1%)

<1%: Anaphylaxis, urticaria, rash, pruritus, pseudomembranous colitis, nausea, vomiting, eosinophilia, thrombocytosis, agranulocytosis, hemolytic anemia, leukopenia, thrombocytopenia, prolonged PT, bleeding, BUN increased, creatinine increased, nephrotoxicity, phlebitis, fever

Reactions reported with other cephalosporins: Seizure, Stevens-Johnson syndrome, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, pancytopenia, agranulocytosis, colitis, superinfection

Drug Interactions

Alcohol (Ethyl): Cefotetan may enhance the adverse/toxic effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Cephalosporins may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may cause a disulfiram-like reaction).
Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction
Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose; monitor for signs and symptoms of hemolytic anemia, including hematologic parameters where appropriate.
Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions. Assess results of laboratory tests (prothrombin time), therapeutic response, and adverse effects (eg, hemolytic anemia, hypoprothrombinemia, and bleeding) regularly during therapy. Advise patients with diabetes about use of Clinitest® (may cause false-positive test). Teach patient possible side effects/appropriate interventions and adverse symptoms to report (eg, nephrotoxicity, opportunistic infection, hypersensitivity reaction).
Monitoring: Lab TestsProthrombin time; perform culture and sensitivity studies prior to initiating drug therapy; renal function
Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is administered by injection or infusion. Report immediately any redness, swelling, burning, or pain at injection/infusion site, or immediately report any itching, hives, difficulty swallowing, or respiratory difficulty. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid alcohol during therapy and for 72 hours after last dose (may cause severe disulfiram-like reactions). May cause false test results with Clinitest®; use of another type of glucose testing is preferable. May cause diarrhea (yogurt, boiled milk, or buttermilk may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage; sores in mouth; blood in stool or urine; unusual fever or chills); CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 1 g, 2 g [contains sodium 80 mg/g (3.5 mEq/g)]

Generic AvailableYes
ManufacturerAstraZeneca Pharmaceuticals LP
Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.
Pharmacodynamics/Kinetics

Distribution: Widely to body tissues and fluids including bile, sputum, prostatic, peritoneal; low concentrations enter CSF

Protein binding: 76% to 90%

Half-life elimination: 3-5 hours

Time to peak, serum: I.M.: 1.5-3 hours

Excretion: Primarily urine (as unchanged drug); feces (20%)

Related Information

- Antimicrobial Drugs of Choice
- Cephalosporins by Generation
- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins
Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine
Index TermsCefotetan Disodium
References

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International Brand NamesApacef (BE, FR, LU); Apatef (AU, DE, IT, PT); Ceftenon (AT); Darvilen (DE); Tetan (KP); Yamatetan (JP, KP)

Cefoxitin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cefoxitin may be confused with cefotaxime, cefotetan, Cytoxan®

Mefoxin® may be confused with Lanoxin®

Pronunciation(se FOKS i tin)

Canadian Brand NamesApo-Cefoxitin®

Pharmacologic CategoryAntibiotic, Cephalosporin (Second Generation)

Use: Labeled IndicationsLess active against staphylococci and streptococci than first generation cephalosporins, but active against anaerobes including *Bacteroides fragilis*; active against gram-negative enteric bacilli including *E. coli*, *Klebsiella*, and *Proteus*; used predominantly for respiratory tract, skin and skin structure, bone and joint, urinary tract and gynecologic as well as septicemia; surgical prophylaxis; intra-abdominal infections and other mixed infections; indicated for bacterial *Eikenella corrodens* infections

Dosing: Adults

Susceptible infections: I.M., I.V.: 1-2 g every 6-8 hours (I.M. injection is painful); up to 12 g/day

Amnionitis and endomyometritis: I.M., I.V.: 2 g every 6-8 hours

Aspiration pneumonia, empyema, orbital cellulitis, parapharyngeal space, and human bites: I.M., I.V.: 2 g every 8 hours

Liver abscess: I.V.: 1 g every 4 hours

Mycobacterium species, not MTB or MAI: I.V.: 12 g/day with amikacin

Pelvic inflammatory disease:

Inpatients: I.V.: 2 g every 6 hours **plus** doxycycline 100 mg I.V. or 100 mg orally every 12 hours until improved, followed by doxycycline 100 mg orally twice daily to complete 14 days

Outpatients: I.M.: 2 g **plus** probenecid 1 g orally as a single dose, followed by doxycycline 100 mg orally twice daily for 14 days

Perioperative prophylaxis: I.M., I.V.: 1-2 g 30-60 minutes prior to surgery followed by 1-2 g every 6-8 hours for no more than 24 hours after surgery depending on the procedure

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Perioperative prophylaxis: I.V.:

Infants >3 months and Children: 30-40 mg/kg 30-60 minutes prior to surgery followed by 30-40 mg/kg/dose every 6 hours for no more than 24 hours after surgery depending on the procedure

Adolescents: Refer to adult dosing.

Mild-to-moderate infection: I.M., I.V.: Infants >3 months and Children: 80-100 mg/kg/day in divided doses every 4-6 hours

Severe infection: I.M., I.V.: Infants >3 months and Children: 100-160 mg/kg/day in divided doses every 4-6 hours

Maximum dose: 12 g/day

Dosing: Renal ImpairmentI.M., I.V.:

Cl_{cr} 30-50 mL/minute: Administer 1-2 g every 8-12 hours

Cl_{cr} 10-29 mL/minute: Administer 1-2 g every 12-24 hours

Cl_{cr} 5-9 mL/minute: Administer 0.5-1 g every 12-24 hours

Cl_{cr} <5 mL/minute: Administer 0.5-1 g every 24-48 hours

Hemodialysis: Moderately dialyzable (20% to 50%); administer a loading dose of 1-2 g after each hemodialysis; maintenance dose as noted above based on Cl_{cr}

Continuous arteriovenous or venovenous hemodiafiltration effects: Dose as for Cl_{cr} 10-50 mL/minute

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Inject deep I.M. into large muscle mass.

Administration: I.V.Can be administered IVP over 3-5 minutes at a maximum concentration of 100 mg/mL or I.V. intermittent infusion over 10-60 minutes at a final concentration for I.V. administration not to exceed 40 mg/mL

Administration: I.V. DetailpH: 4.2-7.0 (reconstituted solution); 6.5 (frozen premixed solution)

Dietary ConsiderationsSodium content of 1 g: 53 mg (2.3 mEq)

StorageReconstituted solution is stable for 6 hours at room temperature or 7 days when refrigerated; I.V. infusion in NS or D_5W solution is stable for 18 hours at room temperature or 48 hours when refrigerated. Premixed frozen solution, when thawed, is stable for 24 hours at room temperature or 21 days when refrigerated.

ReconstitutionReconstitute vials with SWFI, bacteriostatic water for injection, NS, or D_5W. For I.V. infusion, solutions may be further diluted in NS, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, D_5LR, mannitol 10%, or sodium bicarbonate 5%.

CompatibilityStable in D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, NS, mannitol 10%, sodium bicarbonate 5%; **variable stability (consult detailed reference)** in peritoneal dialysis solution.

Y-site administration: Compatible: Acyclovir, amifostine, amphotericin B cholesteryl sulfate complex, aztreonam, cyclophosphamide, diltiazem, docetaxel, doxorubicin liposome, etoposide, famotidine, fluconazole, foscarnet, gemcitabine, granisetron, hydromorphone, linezolid, magnesium sulfate, meperidine, morphine, ondansetron, perphenazine, propofol, ranitidine, remifentanil, teniposide, thiotepa. **Incompatible:** Filgrastim, gatifloxacin, hetastarch, pentamidine. **Variable (consult detailed reference):** Cisatracurium, vancomycin.

Compatibility in syringe: Compatible: Heparin.

Compatibility when admixed: Compatible: Amikacin, cimetidine, clindamycin, gentamicin, kanamycin, metronidazole, metronidazole with sodium bicarbonate, multivitamins, sodium bicarbonate, tobramycin, verapamil, vitamin B complex with C. **Incompatible:** Ranitidine. **Variable (consult detailed reference):** Aztreonam.

ContraindicationsHypersensitivity to cefoxitin, any component of the formulation, or other cephalosporins

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.

Geriatric ConsiderationsAdjust dose for renal function in the elderly.

Pregnancy Risk FactorB

Pregnancy Considerations

Adverse events have not been observed in animal reproduction studies; therefore, cefoxitin is classified as pregnancy category B. Cefoxitin crosses the placenta and reaches the cord serum and amniotic fluid. Adequate well-controlled studies are not available in pregnant women.

Peak serum concentrations of cefoxitin during pregnancy may be similar to or decreased compared to nonpregnant values. Maternal half-life may be shorter at term. Pregnancy-induced hypertension increases trough concentrations in the immediate postpartum period.

LactationEnters breast milk (small amounts)/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsVery small amounts of cefoxitin are excreted in breast milk. The manufacturer recommends that caution be exercised when administering cefoxitin to nursing women. The American Academy of Pediatrics considers cefoxitin to be "usually compatible with breast-feeding." Nondose-related effects could include modification of bowel flora. Cefoxitin pharmacokinetics may be altered immediately postpartum.

Pregnancy & Lactation, In-Depth

- Cefoxitin in Pregnancy & Lactation

Adverse Reactions

1% to 10%: Gastrointestinal: Diarrhea

<1%: Anaphylaxis, angioedema, bone marrow suppression, BUN increased, creatinine increased, dyspnea, eosinophilia, exacerbation of myasthenia gravis, exfoliative dermatitis, fever, hemolytic anemia, hypotension, interstitial nephritis, jaundice, leukopenia, nausea, nephrotoxicity increased (with aminoglycosides), phlebitis, prolonged PT, pruritus, pseudomembranous colitis, rash, thrombocytopenia, thrombophlebitis, toxic epidermal necrolysis, transaminases increased, urticaria, vomiting

Reactions reported with other cephalosporins: Agranulocytosis, aplastic anemia, cholestasis, colitis, erythema multiforme, hemolytic anemia, hemorrhage, pancytopenia, renal dysfunction, serum-sickness reactions, seizure, Stevens-Johnson syndrome, superinfection, toxic nephropathy, vaginitis

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Cephalosporins may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction

Monitoring ParametersMonitor renal function periodically when used in combination with other nephrotoxic drugs; observe for signs and symptoms of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, nephrotoxicity). Evaluate results of laboratory tests (prothrombin time, CBC with differential), therapeutic response, and adverse effects (diarrhea, nausea/vomiting, nephrotoxicity) on a regular basis during therapy. Advise patients with diabetes about use of Clinitest®. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, hypersensitivity, opportunistic infection).

Monitoring: Lab TestsProthrombin times; perform culture and sensitivity studies prior to initiating drug therapy; renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is administered by injection or infusion. Report immediately any redness, swelling, burning, or pain at injection/infusion site; chest pain, palpitations, respiratory difficulty or swallowing; itching or hives. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause false test results with Clinitest®; use of another type of glucose testing is preferable. May cause diarrhea (yogurt, boiled milk, or buttermilk may help); GI distress or nausea (small, frequent meals, frequent oral care, chewing gum, or sucking lozenges may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage, sores in mouth, blood in stool or urine, unusual fever or chills); CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 1 g, 2 g, 10 g [contains sodium 53.8 mg/g (2.3 mEq/g)]

Powder for prescription compounding: 100 g

Generic AvailableYes

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Distribution: Widely to body tissues and fluids including pleural, synovial, ascitic, bile; poorly penetrates into CSF even with inflammation of the meninges

Protein binding: 65% to 79%

Half-life elimination: 45-60 minutes; significantly prolonged with renal impairment

Time to peak, serum: I.M.: 20-30 minutes

Excretion: Urine (85% as unchanged drug)

Related Information

- Antimicrobial Drugs of Choice
- Cephalosporins by Generation
- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine

Index TermsCefoxitin Sodium

References

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Regazzi MB, Chirico G, Cristiani D, et al, “Cefoxitin in Newborn Infants. A Clinical and Pharmacokinetic Study,” *Eur J Clin Pharmacol*, 1983, 25(4):507-9.[PubMed 6653646]

International Brand NamesCefaxicina (ES); Cefmore (TW); Cefoxin (TH); Cefoxitin Sodium (AU); Cefoxitine Panpharma (FR); Cefoxona (AR); Cefxitin (TH); Cenomycin (JP); Gamacef (BR); Jeitin (KP); Lofatin (TW); Mefoxil (GR); Mefoxin (AE, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CI, CY, CZ, EG, ET, FI, FR, GB, GH, GM, GN, GY, HN, HU, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, NZ, OM, PH, PT, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Mefoxitin (AT, CH, DE, DK, ES, NO, SE, VE); Merxin (JP); Monowel (PH); Panafox (PH); Sephros (MY); Voxitin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Zefin (TH); Zepax (PH)

Cefpodoxime

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Vantin® may be confused with Ventolin®

Pronunciation(sef pode OKS eem)

U.S. Brand NamesVantin®

Canadian Brand NamesVantin®

Pharmacologic CategoryAntibiotic, Cephalosporin (Third Generation)

Use: Labeled IndicationsTreatment of susceptible acute, community-acquired pneumonia caused by *S. pneumoniae* or nonbeta-lactamase producing *H. influenzae*; acute uncomplicated gonorrhea caused by *N. gonorrhoeae*; uncomplicated skin and skin structure infections caused by *S. aureus* or *S. pyogenes*; acute otitis media caused by *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*; pharyngitis or tonsillitis; and uncomplicated urinary tract infections caused by *E. coli*, *Klebsiella*, and *Proteus*

Dosing: Adults

Acute community-acquired pneumonia and bacterial exacerbations of chronic bronchitis: Oral: 200 mg every 12 hours for 14 days and 10 days, respectively

Acute maxillary sinusitis: Oral: 200 mg every 12 hours for 10 days

Pharyngitis/tonsillitis: Oral: 100 mg every 12 hours for 5-10 days

Skin and skin structure: Oral: 400 mg every 12 hours for 7-14 days

Uncomplicated gonorrhea (male and female) and rectal gonococcal infections (female): Oral: 200 mg as a single dose

Uncomplicated urinary tract infection: Oral: 100 mg every 12 hours for 7 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Acute maxillary sinusitis: Oral: Children: 2 months to 12 years: 10 mg/kg/day divided every 12 hours for 10 days (maximum: 200 mg/dose)

Acute otitis media: Oral: Children:

≥12 years: 2 months to 12 years: 10 mg/kg/day divided every 12 hours (400 mg/day) for 5 days (maximum: 200 mg/dose)

≥12 years: Refer to adult dosing.

Pharyngitis/tonsillitis: Oral: Children:

2 months to 12 years: 10 mg/kg/day in 2 divided doses for 5-10 days (maximum: 100 mg/dose)

≥12 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} <30 mL/minute: Administer every 24 hours.

Hemodialysis: Dose 3 times/week following dialysis.

Dosing: Hepatic ImpairmentDose adjustment is not necessary in patients with cirrhosis.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels.

Dietary ConsiderationsMay be taken with food.

ReconstitutionShake well before using. After mixing, keep suspension in refrigerator. Discard unused portion after 14 days.

ContraindicationsHypersensitivity to cefpodoxime, any component of the formulation, or other cephalosporins

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.

Geriatric ConsiderationsConsidered one of the drugs of choice for outpatient treatment of community-acquired pneumonia in the elderly. Adjust dosage with renal impairment.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic events were not observed in animal studies; therefore, cefpodoxime is classified as pregnancy category B. It is not known if cefpodoxime crosses the human placenta. Other cephalosporins cross the placenta and are considered safe in pregnancy.

LactationEnters breast milk (small amounts)/not recommended

Breast-Feeding ConsiderationsVery small amounts of cefpodoxime are excreted in breast milk. Breast-feeding is not recommended by the manufacturer. Other cephalosporins are considered safe during breast-feeding. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Cefpodoxime in Pregnancy & Lactation

Adverse Reactions

>10%:

Dermatologic: Diaper rash (12%)

Gastrointestinal: Diarrhea in infants and toddlers (15%)

1% to 10%:

Central nervous system: Headache (1%)

Dermatologic: Rash (1%)

Gastrointestinal: Diarrhea (7%), nausea (4%), abdominal pain (2%), vomiting (1% to 2%)

Genitourinary: Vaginal infection (3%)

<1%: Anaphylaxis, chest pain, hypotension, fungal skin infection, pseudomembranous colitis, vaginal candidiasis, pruritus, flatulence, decreased salivation, malaise, fever, decreased appetite, cough, epistaxis, dizziness, fatigue, anxiety, insomnia, flushing, weakness, nightmares, taste alteration, eye itching, tinnitus, purpuric nephritis

Reactions reported with other cephalosporins: Seizure, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, urticaria, serum-sickness reactions, renal dysfunction, interstitial nephritis toxic nephropathy, cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, pancytopenia, agranulocytosis, colitis, vaginitis, superinfection

Drug Interactions

Antacids: May decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

H2-Antagonists: May decrease the absorption of Cefpodoxime. Separate oral doses by at least 2 hours. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Food delays absorption; cefpodoxime serum levels may be increased if taken with food.

Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction

Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions. Assess results of laboratory tests (prothrombin time), therapeutic response, and adverse effects (eg, hemolytic anemia, hypoprothrombinemia, and bleeding) regularly during therapy. Advise patients with diabetes about use of Clinitest® (may cause false-positive test). Teach patient possible side effects/appropriate interventions and adverse symptoms to report (eg, nephrotoxicity, opportunistic infection, hypersensitivity reaction).

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy; renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, at regular intervals around-the-clock (with or without food). Chilling oral suspension improves flavor (do not freeze); shake well before using. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Complete full course of medication, even if you feel better. May cause false test results with Clinitest®; use of another type of glucose testing is preferable. May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (yogurt, boiled milk, or buttermilk may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage, sores in mouth, blood in stool or urine, unusual fever or chills); CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Granules for oral suspension: 50 mg/5 mL (50 mL, 75 mL, 100 mL); 100 mg/5 mL (50 mL, 75 mL, 100 mL)

Vantin®: 50 mg/5 mL (100 mL) [contains sodium benzoate; lemon creme flavor] [DSC]; 100 mg/5 mL (100 mL) [contains sodium benzoate; lemon creme flavor] [DSC]

Tablet: 100 mg, 200 mg

Vantin®: 100 mg, 200 mg

Generic Available Yes

Manufacturer Pharmacia & Upjohn

Pricing: U.S. (www.drugstore.com)

Suspension (reconstituted) (Vantin)

50 mg/5 mL (50): $33.99

50 mg/5 mL (100): $61.99

100 mg/5 mL (50): $56.99

100 mg/5 mL (100): $113.99

Tablets (Cefpodoxime Proxetil)

200 mg (20): $114.03

Tablets (Vantin)

100 mg (20): $127.59

200 mg (20): $168.29

Mechanism of Action Inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: Rapid and well absorbed (50%), acid stable; enhanced in the presence of food or low gastric pH

Distribution: Good tissue penetration, including lung and tonsils; penetrates into pleural fluid

Protein binding: 18% to 23%

Metabolism: De-esterified in GI tract to active metabolite, cefpodoxime

Half-life elimination: 2.2 hours; prolonged with renal impairment

Time to peak: Within 1 hour

Excretion: Urine (80% as unchanged drug) in 24 hours

Related Information

- Antimicrobial Drugs of Choice
- Cephalosporins by Generation
- Community-Acquired Pneumonia in Adults
- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins

Mental Health: Effects on Psychiatric Treatment May rarely cause neutropenia; use caution with clozapine and carbamazepine

Index Terms Cefpodoxime Proxetil

References

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International Brand NamesBanan (CL, HK, ID, JP, KP, TH); Banan Dry Syrup (KP); Biocef (AT); Cefodox (AE, BH, CY, EG, IE, IL, IQ, IR, IT, JO, KW, LB, LU, LY, OM, QA, SA, SY, YE); Cefpobact (SE); Cepodem (IN, PL, ZA); Orelox (BB, BM, BS, BZ, CH, CZ, DE, FI, FR, GB, GY, IT, JM, LU, MX, NL, NO, PK, PL, PT, SE, SR, TT); Otreon (AT, ES, IT); Podomexef (CH, DE); Podox (KP); Zudem (PH)

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cefprozil may be confused with ceFAZolin, cefuroxime

Cefzil® may be confused with Cefol®, Ceftin®, Kefzol®

Pronunciation(sef PROE zil)
Canadian Brand NamesApo-Cefprozil®; Cefzil®; Ran-Cefprozil; Sandoz-Cefprozil
Pharmacologic CategoryAntibiotic, Cephalosporin (Second Generation)
Use: Labeled IndicationsTreatment of otitis media and infections involving the respiratory tract and skin and skin structure; active against methicillin-sensitive staphylococci, many streptococci, and various gram-negative bacilli including *E. coli*, some *Klebsiella*, *P. mirabilis*, *H. influenzae*, and *Moraxella*.
Dosing: Adults

Pharyngitis/tonsillitis: Oral: 500 mg every 24 hours for 10 days

Secondary bacterial infection of acute bronchitis or acute bacterial exacerbation of chronic bronchitis: Oral: 500 mg every 12 hours for 10 days

Uncomplicated skin and skin structure infections: Oral: 250 mg every 12 hours, or 500 mg every 12-24 hours for 10 days

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Otitis media: Oral: Children >6 months to 12 years: 15 mg/kg every 12 hours for 10 days

Pharyngitis/tonsillitis: Oral: Children:

2-12 years: 7.5-15 mg/kg/day divided every 12 hours for 10 days (administer for >10 days if due to *S. pyogenes*); maximum: 1 g/day

≥13 years: Refer to adult dosing.

Uncomplicated skin and skin structure infections: Oral:

2-12 years: 20 mg/kg every 24 hours for 10 days; maximum: 1 g/day

≥13 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} <30 mL/minute: Reduce dose by 50%.

Hemodialysis effects: 55% is removed by hemodialysis.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels. Chilling the reconstituted oral suspension improves flavor (do not freeze).
Dietary ConsiderationsMay be taken with food. Oral suspension contains phenylalanine 28 mg/5 mL.
ContraindicationsHypersensitivity to cefprozil, any component of the formulation, or other cephalosporins
Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Geriatric ConsiderationsHas not been studied exclusively in the elderly. Adjust dose for estimated renal function.
Pregnancy Risk FactorB
Pregnancy ConsiderationsAdverse events were not observed in animal reproduction studies; therefore, cefprozil is classified as pregnancy category B. It is not known if cefprozil crosses the human placenta. Other cephalosporins cross the placenta and are considered safe for use during pregnancy.
LactationEnters breast milk/use caution (AAP rates “compatible”)
Breast-Feeding Considerations

Small amounts of cefprozil are excreted in breast milk. The manufacturer recommends that caution be exercised when administering cefprozil to nursing women. The American Academy of Pediatrics considers cefprozil to be “usually compatible with breastfeeding.” Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Cefprozil in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Central nervous system: Dizziness (1%)

Dermatologic: Diaper rash (2%)

Gastrointestinal: Diarrhea (3%), nausea (4%), vomiting (1%), abdominal pain (1%)

Genitourinary: Vaginitis, genital pruritus (2%)

Hepatic: Transaminases increased (2%)

Miscellaneous: Superinfection

<1%: Anaphylaxis, angioedema, pseudomembranous colitis, rash, urticaria, erythema multiforme, serum sickness, Stevens-Johnson syndrome, hyperactivity, headache, insomnia, confusion, somnolence, leukopenia, eosinophilia, thrombocytopenia, BUN increased, creatinine increased, arthralgia, cholestatic jaundice, fever

Reactions reported with other cephalosporins: Seizure, toxic epidermal necrolysis, renal dysfunction, interstitial nephritis, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, pancytopenia, agranulocytosis, colitis, vaginitis, superinfection

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Food delays cefprozil absorption.
Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction
Monitoring ParametersAssess patient at beginning and throughout therapy for infection; monitor for signs of anaphylaxis during first dose
Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, interstitial nephritis, hemolytic anemia, hemorrhage). Advise patients with diabetes about use of Clinitest® (may cause false-positive test). Teach patient possible side effects/appropriate interventions and adverse symptoms to report (eg, opportunistic infection, hypersensitivity reactions).
Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy; renal function
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, at regular intervals around-the-clock (with or without food). Chilling oral suspension improves flavor (do not freeze). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Complete full course of medication, even if you feel better. May cause false test results with Clinitest®; use of another type of glucose testing is preferable. May cause dizziness (use caution when driving or engaging in potentially hazardous tasks until response to drug is known); nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (yogurt, boiled milk, or buttermilk may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage, sores in mouth, blood in stool or urine, unusual fever or chills); CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for oral suspension, as anhydrous: 125 mg/5 mL (50 mL, 75 mL, 100 mL); 250 mg/5 mL (50 mL, 75 mL, 100 mL)

Tablet, as anhydrous: 250 mg, 500 mg

Generic AvailableYes
ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)

Pricing: U.S. (www.drugstore.com)

Suspension (reconstituted) (Cefprozil)

250 mg/5 mL (100): $59.99

Suspension (reconstituted) (Cefzil)

125 mg/5 mL (50): $21.99

125 mg/5 mL (75): $32.99

125 mg/5 mL (100): $42.99

250 mg/5 mL (50): $39.99

250 mg/5 mL (75): $57.99

250 mg/5 mL (100): $73.99

Tablets (Cefzil)

250 mg (20): $81.79

500 mg (20): $165.99

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: Well absorbed (94%)

Protein binding: 35% to 45%

Half-life elimination: Normal renal function: 1.3 hours

Time to peak, serum: Fasting: 1.5 hours

Excretion: Urine (61% as unchanged drug)

Related Information

- Cephalosporins by Generation
- Community-Acquired Pneumonia in Adults

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine

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International Brand NamesArzimol (ES); Brisoral (ES); Ceforzil (KP); Cefzil (BB, BG, BM, BR, BS, BZ, CL, EE, EG, GB, GY, HN, ID, JM, KP, NL, PL, SR, TT); Lizor (ID); Procef (AR, AT, CH, CN, CO, EC, HK, IT, MX, MY, PH, TH, VE); Prozef (ZA); Rozicef (KP); Zilpro (PK)

Ceftazidime

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Ceftazidime may be confused with ceftizoxime

Ceptaz® may be confused with Septra®

Tazicef® may be confused with Tazidime®

Tazidime® may be confused with Tazicef®

International issues:

Ceftim® [Italy] may be confused with Ceftin® which is a brand name for cefuroxime in the U.S.

Ceftim® [Italy] may be confused with Cefiton® which is a brand name for cefixime in Portugal

Ceftim® [Italy] may be confused with Ceftina® which is a brand name for cefalotin in Mexico

Pronunciation(SEF tay zi deem)

U.S. Brand NamesFortaz®; Tazicef®

Canadian Brand NamesFortaz®

Pharmacologic CategoryAntibiotic, Cephalosporin (Third Generation)

Use: Labeled IndicationsTreatment of documented susceptible *Pseudomonas aeruginosa* infection and infections due to other susceptible aerobic gram-negative organisms; empiric therapy of a febrile, granulocytopenic patient

Use: Unlabeled/InvestigationalBacterial endophthalmitis

Dosing: Adults

Bacterial arthritis (gram negative bacilli): I.V.: 1-2 g every 8 hours

Bone and joint infections: I.V.: 2 g every 12 hours

Cystic fibrosis, lung infection caused by *Pseudomonas*spp: I.V.: 30-50 mg/kg every 8 hours (maximum: 6 g/day)

Endophthalmitis, bacterial (unlabeled use): Intravitreal: 2.25 mg/0.1 mL NS in combination with vancomycin

Melioidosis: I.V.: 40 mg/kg every 8 hours for 10 days, followed by oral therapy with doxycycline or TMP/SMX

Otitis externa: I.V.: 2 g every 8 hours

Peritonitis (CAPD):

Anuric, intermittent: 1000-1500 mg/day

Anuric, continuous (per liter exchange): Loading dose: 250 mg; maintenance dose: 125 mg

Pneumonia: I.V.:

Uncomplicated: 500 mg to 1 g every 8 hours

Complicated or severe: 2 g every 8 hours

Skin and soft tissue infections: I.V., I.M.: 500 mg to 1 g every 8 hours

Severe infections, including meningitis, complicated pneumonia, endophthalmitis, CNS infection, osteomyelitis, intra-abdominal and gynecological, skin and soft tissue: I.V.: 2 g every 8 hours

Urinary tract infections: I.V., I.M.:

Uncomplicated: 250 mg every 12 hours

Complicated: 500 mg every 8-12 hours

Dosing: ElderlyI.M., I.V.: Dosage should be based on renal function with a dosing interval not more frequent then every 12 hours.

Dosing: PediatricSusceptible infections: I.V.:

Children 1 month to 12 years: 30-50 mg/kg/dose every 8 hours; maximum dose: 6 g/day (higher doses reserved for immunocompromised patients, cystic fibrosis, or meningitis)

Children ≥12 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 30-50 mL/minute: Administer every 12 hours

Cl_{cr} 10-30 mL/minute: Administer every 24 hours

Cl_{cr} <10 mL/minute: Administer every 48-72 hours

Hemodialysis: Dialyzable (50% to 100%)

Continuous renal replacement therapy (CRRT): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH: 1-2 g every 12 hours

CVVHD/CVVHDF: 2 g every 12 hours

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Inject deep I.M. into large mass muscle.

Administration: I.V.Ceftazidime can be administered IVP over 3-5 minutes or I.V. intermittent infusion over 15-30 minutes.

Administration: I.V. DetailAny carbon dioxide bubbles that may be present in the withdrawn solution should be expelled prior to injection. Administer around-the-clock to promote less variation in peak and trough serum levels.

pH: 5-8 (Fortaz®); 5.0-7.5 (Ceptaz®)

Dietary ConsiderationsSodium content of 1 g: 2.3 mEq

Storage

Vials: Reconstituted solution and solution further diluted for I.V. infusion are stable for 12 hours at room temperature, for 3 days when refrigerated, or for 12 weeks when frozen at -20°C (-4°F). After freezing, thawed solution in SWFI for I.M. administration is stable for 3 hours at room temperature or for 3 days when refrigerated, thawed solution in NS in a Viaflex® small volume container for I.V. administration is stable for 12 hours at room temperature or for 3 days when refrigerated, and thawed solution in SWFI in the original container is stable for 8 hours at room temperature or for 3 days when refrigerated.

Premixed frozen solution: Store frozen at -20°C (-4°F). Thawed solution is stable for 8 hours at room temperature or for 3 days under refrigeration; do not refreeze.

CompatibilityStable in D_5NS, D_5W, NS, sterile water for injection; **variable stability (consult detailed reference)** in peritoneal dialysis solutions.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, aminophylline, aztreonam, ciprofloxacin, diltiazem, docetaxel, enalaprilat, esmolol, etoposide phosphate, famotidine, filgrastim, fludarabine, foscarnet, gatifloxacin, gemcitabine, granisetron, heparin, hydromorphone, labetalol, linezolid, melphalan, meperidine, morphine, ondansetron, paclitaxel, propofol, ranitidine, remifentanil, tacrolimus, teniposide, theophylline, thiotepa, vinorelbine, zidovudine. **Incompatible:** Alatrofloxacin, amphotericin B cholesteryl sulfate complex, amsacrine, doxorubicin liposome, fluconazole, idarubicin, midazolam, pentamidine, warfarin. **Variable (consult detailed reference):** Cisatracurium, sargramostim, vancomycin.

Compatibility in syringe: Compatible: Hydromorphone.

Compatibility when admixed: Compatible: Ciprofloxacin, clindamycin, fluconazole, linezolid, metronidazole, ofloxacin. **Incompatible:** Aminoglycosides (in same bottle/bag), aminophylline, ranitidine. **Variable (consult detailed reference):** Vancomycin.

ContraindicationsHypersensitivity to ceftazidime, any component of the formulation, or other cephalosporins

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Elevated INR: May be associated with increased INR, especially in nutritionally-deficient patients, prolonged treatment, hepatic or renal disease.
- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.
- Seizure disorders: Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures.

Geriatric ConsiderationsChanges in renal function associated with aging and corresponding alterations in pharmacokinetics result in every 12-hour dosing being an adequate dosing interval. Adjust dose based on renal function.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; therefore, ceftazidime is classified as pregnancy category B. Ceftazidime crosses the placenta and reaches the cord serum and amniotic fluid. Maternal peak serum concentration is unchanged in the first trimester. After the first trimester, serum concentrations decrease by approximately 50% of those in nonpregnant patients. Renal clearance is increased during pregnancy.

LactationEnters breast milk (small amounts)/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsVery small amounts of ceftazidime are excreted in breast milk. The manufacturer recommends that caution be exercised when administering ceftazidime to nursing women. The American Academy of Pediatrics considers ceftazidime to be "usually compatible with breast-feeding." Ceftazidime in not absorbed when given orally; therefore, any medication that is distributed to human milk should not result in systemic concentrations in the nursing infant. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Ceftazidime in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Gastrointestinal: Diarrhea (1%)

Local: Pain at injection site (1%)

Miscellaneous: Hypersensitivity reactions (2%)

<1%: Anaphylaxis, angioedema, asterixis, BUN increased, candidiasis, creatinine increased, dizziness, encephalopathy, eosinophilia, erythema multiforme, fever, headache, hemolytic anemia, hyperbilirubinemia, jaundice, leukopenia, myoclonus, nausea, neuromuscular excitability, paresthesia, phlebitis, pruritus, pseudomembranous colitis, rash, Stevens-Johnson syndrome, thrombocytosis, toxic epidermal necrolysis, transaminases increased, vaginitis, vomiting

Reactions reported with other cephalosporins: Seizure, urticaria, serum-sickness reactions, renal dysfunction, interstitial nephritis, toxic nephropathy, elevated BUN, elevated creatinine, cholestasis, aplastic anemia, hemolytic anemia, pancytopenia, agranulocytosis, colitis, prolonged PT, hemorrhage, superinfection

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction

Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy (eg, nephrotoxicity). Assess results of laboratory tests (prothrombin time), therapeutic response, and adverse effects (eg, hemolytic anemia, hypoprothrombinemia, and bleeding) during therapy. Advise patients with diabetes about use of Clinitest® (may cause false-positive test). Teach patient possible side effects/appropriate interventions and adverse symptoms to report (eg, opportunistic infection, hypersensitivity reaction).

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy; renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is administered by infusion or injection. Report immediately any redness, swelling, burning, or pain at injection/infusion site. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause false test results with Clinitest®; use of another type of glucose testing is preferable. May cause diarrhea (yogurt, boiled milk, or buttermilk may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage, sores in mouth, blood in stool or urine, unusual fever or chills); CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed iso-osmotic solution, frozen]:

Fortaz®: 1 g (50 mL) [contains sodium carbonate, sodium ~54 mg (2.3 mEq)/g]; 2 g (50 mL) [contains sodium ~54 mg (2.3 mEq)/g]

Injection, powder for reconstitution: 1 g, 2 g, 6 g

Fortaz®: 500 mg, 1 g, 2 g, 6 g [contains sodium ~54 mg (2.3 mEq)/g]

Tazicef®: 1 g, 2 g, 6 g [contains sodium ~54 mg (2.3 mEq)/g]

Generic AvailableYes: Injection

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Distribution: Widely throughout the body including bone, bile, skin, CSF (higher concentrations achieved when meninges are inflamed), endometrium, heart, pleural and lymphatic fluids

Protein binding: 17%

Half-life elimination: 1-2 hours, prolonged with renal impairment; Neonates <23 days: 2.2-4.7 hours

Time to peak, serum: I.M.: ~1 hour

Excretion: Urine (80% to 90% as unchanged drug)

Related Information

- Antimicrobial Drugs of Choice
- Cephalosporins by Generation
- Neutropenic Fever Guidelines

Pharmacotherapy PearlsWith some organisms, resistance may develop during treatment (including *Enterobacter* spp and *Serratia* spp). Consider combination therapy or periodic susceptibility testing for organisms with inducible resistance.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine

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International Brand NamesBaxidyme (PH); Biotum (PL); Caltum (ID); Cef-Dime (TH); Cef-H (MY); Cefazime (SG); Ceffotan (CO); Cefortam (PT);

Cefpiran (PE); Ceftidin (IN); Ceftim (IT, PT); Ceftum (ID); Cetazine (TW); Cetazum (ID); Dimase (TH); Dimcef (PH); Extimon (ID); Fortam (CH, ES, UY); Fortaz (BR); Fortum (AE, AR, AT, AU, BB, BF, BG, BH, BJ, BM, BS, BZ, CI, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EE, EG, ET, FR, GB, GH, GM, GN, GT, GY, HK, HN, HU, ID, IE, IL, IN, IQ, IR, JM, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PL, PR, PY, QA, SA, SC, SD, SE, SL, SN, SR, SV, SY, TH, TN, TT, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Fortum Pro (HN); Fortumset (FR); Forzid (PH, TH); Ftazidime (GR); Glazidim (BE, FI, IT, LU); Izadima (EC); Kefadim (BF, BJ, BR, CI, CZ, ET, GH, GM, GN, KE, LR, LU, MA, ML, MR, MU, MW, NE, NG, PK, PL, SC, SD, SL, SN, TN, TW, TZ, UG, ZA, ZM, ZW); Kefazim (AT); Kefzim (CN); Lacedim (ID); Mirocef (HR, PL); Pharodime (ID); Septax (IL); Solvetan (GR); Spectrum (IT); Starcef (IT); Tagal (MX); Tazicef (PH); Tazid (TH); Tazidan (PH); Tazidem (PH); Tazime (KP); Thidim (ID); Tinacef (AR); Uniranz (PH); Zadim (PH); Zadolina (MX); Zedim (TH); Zeptrigen (PH); Zibac (ID); Zytaz (IN)

Ceftibuten

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

International issues:

Cedax® may be confused with Codex which is a brand name for *Saccharomyces boulardii* in Italy

Pronunciation(sef TYE byoo ten)

U.S. Brand NamesCedax®

Pharmacologic CategoryAntibiotic, Cephalosporin (Third Generation)

Use: Labeled IndicationsOral cephalosporin for treatment of bronchitis, otitis media, and pharyngitis/tonsillitis due to *H. influenzae* and *M. catarrhalis*, both beta-lactamase-producing and nonproducing strains, as well as *S. pneumoniae* (weak) and *S. pyogenes*

Dosing: AdultsSusceptible infections: Oral: 400 mg once daily for 10 days; maximum: 400 mg

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricSusceptible infections: Oral:

<12 years: 9 mg/kg/day for 10 days; maximum daily dose: 400 mg

≥12 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 30-49 mL//minute: Administer 4.5 mg/kg or 200 mg every 24 hours.

Cl_{cr} 5-29 mL/minute: Administer 2.25 mg/kg or 100 mg every 24 hours.

Hemodialysis: Administer 400 mg or 9 mg/kg (maximum: 400 mg) after hemodialysis

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister at the same time each day to maintain adequate blood levels. Shake suspension well before use.

Dietary Considerations

Capsule: Take without regard to food.

Suspension: Take 2 hours before or 1 hour after meals; contains 1 g of sucrose per 5 mL

StorageReconstituted suspension is stable for 14 days when refrigerated.

ContraindicationsHypersensitivity to ceftibuten, any component of the formulation, or other cephalosporins

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.

Geriatric ConsiderationsHas not been studied specifically in the elderly. Adjust dose for renal function.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; therefore, ceftibuten is classified as pregnancy category B. It is not know if ceftibuten crosses the placenta; other cephalosporins cross the placenta and are considered safe for use during pregnancy. Adequate and well-controlled studies have been completed in pregnant women.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsCeftibuten was not detectable in milk after a single 200 mg dose (limit of detection 1 mcg/mL). It is not known if it would be detectable after a 400 mg dose or multiple doses. The manufacturer recommends that caution be exercised when administering ceftibuten to nursing women. If ceftibuten does reach the human milk, nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Ceftibuten in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Central nervous system: Headache (3%), dizziness (1%)

Gastrointestinal: Nausea (4%), diarrhea (3%), dyspepsia (2%), vomiting (1%), abdominal pain (1%)

Hematologic: Eosinophils increased (3%), hemoglobin decreased (2%), thrombocytosis

Hepatic: ALT increased (1%), bilirubin increased (1%)

Renal: BUN increased (4%)

<1%: Anorexia, agitation, constipation, creatinine increased, diaper rash, dry mouth, dyspnea, dysuria, fatigue, candidiasis, rash, urticaria, irritability, paresthesia, nasal congestion, insomnia, rigors, transaminases increased, leukopenia

Reactions reported with other cephalosporins: Anaphylaxis, fever, paresthesia, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, angioedema, pseudomembranous colitis, hemolytic anemia, candidiasis, vaginitis, encephalopathy, asterixis, neuromuscular excitability, seizure, serum-sickness reactions, renal dysfunction, interstitial nephritis, toxic nephropathy, cholestasis, aplastic anemia, hemolytic anemia, pancytopenia, agranulocytosis, colitis, prolonged PT, hemorrhage, superinfection

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction

Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose; with prolonged therapy, monitor renal, hepatic, and hematologic function periodically

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, nephrotoxicity). Assess results of laboratory tests, therapeutic response, and adverse effects (eg, hemolytic anemia, hypoprothrombinemia, and bleeding) regularly during therapy. Advise patients with diabetes about use of Clinitest® (may cause false-positive test). Teach patient possible side effects/appropriate interventions and adverse symptoms to report (eg, opportunistic infection, hypersensitivity reaction).

Monitoring: Lab TestsRenal, hepatic, and hematologic function periodically with prolonged therapy; perform culture and sensitivity studies prior to initiating drug therapy

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, at regular intervals around-the-clock (take capsules with or without food; take suspension 2 hours before or 1 hour after meals). Chilling oral suspension improves flavor (do not freeze). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Complete full course of medication, even if you feel better. May cause false test results with Clinitest®; use of another type of testing is preferable. May cause headache or dizziness (use caution when driving or engaging in potentially hazardous tasks until response to drug is known); nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (yogurt, boiled milk, or buttermilk may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage, sores in mouth, blood in stool or urine, unusual fever or chills); CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Cedax®: 400 mg

Powder for oral suspension:

Cedax®: 90 mg/5 mL (30 mL, 60 mL, 90 mL, 120 mL) [contains sucrose 1g/5 mL and sodium benzoate; cherry flavor]

Generic AvailableNo

ManufacturerSchering-Plough Corp

Pricing: U.S. (www.drugstore.com)

Capsules (Cedax)

400 mg (20): $286.85

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: Rapid; food decreases peak concentrations, delays T_{max}, and lowers AUC

Distribution: V_d: Children: 0.5 L/kg; Adults: 0.21 L/kg

Protein binding: 65%

Half-life elimination: 2 hours

Time to peak: 2-3 hours

Excretion: Urine (52%); feces (39%)

Related Information

- Cephalosporins by Generation

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine

References

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International Brand NamesBiocef (ES); Caedax (AT, PT); Cedax (AR, BB, BG, BM, BS, BZ, CH, CZ, EC, FI, GB, GY, HK, HN, HU, ID, IE, IT, JM, MX, MY, NL, PL, SE, SR, TH, TT, VE); Keimax (DE); Seftem (JP, TW); Sepex (AR)

Ceftizoxime

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Ceftizoxime may be confused with cefotaxime, ceftazidime, cefuroxime

Pronunciation(sef ti ZOKS eem)

U.S. Brand NamesCefizox®

Canadian Brand NamesCefizox®

Pharmacologic CategoryAntibiotic, Cephalosporin (Third Generation)

Use: Labeled IndicationsTreatment of susceptible bacterial infections, mainly respiratory tract, skin and skin structure, bone and joint, urinary tract and gynecologic, as well as septicemia; active against many gram-negative bacilli (not *Pseudomonas*), some gram-positive cocci (not *Enterococcus*), and some anaerobes

Dosing: Adults**Usual dosage:** I.M., I.V.: 1-2 g every 8-12 hours, up to 2 g every 4 hours or 4 g every 8 hours for life-threatening infections

Gonococcal:

Disseminated infection: I.M., I.V.: 1 g every 8 hours

Uncomplicated: I.M.: 1 g as single dose

Life-threatening infections: I.V.: 2 g every 4 hours or 4 g every 8 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricUsual dosage: I.M., I.V.: Children ≥6 months: 150-200 mg/kg/day divided every 6-8 hours (maximum: 12 g/24 hours)

Dosing: Renal Impairment

Cl_{cr} 50-79 mL/minute: Administer 500-1500 mg every 8 hours.

Cl_{cr} 5-49 mL/minute: Administer 250-1000 mg every 12 hours.

Cl_{cr} 0-4 mL/minute: Administer 500-1000 mg every 48 hours or 250-500 mg every 24 hours.

Moderately dialyzable (20% to 50%)

Continuous arteriovenous hemofiltration: Dose as for Cl_{cr} 10-50 mL/minute.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Inject deep I.M. into large muscle mass.

Administration: I.V.Inject direct I.V. over 3-5 minutes. Infuse intermittent infusion over 30 minutes.

Administration: I.V. DetailpH: 6-8 (reconstituted solution); 5.5-8.0 (frozen premixed infusion solution)

Dietary ConsiderationsSodium content of 1 g: 60 mg (2.6 mEq)

StorageReconstituted solution is stable for 24 hours at room temperature and 96 hours when refrigerated. For I.V. infusion in NS or D_5W, solution is stable for 24 hours at room temperature, 96 hours when refrigerated, or 12 weeks when frozen. After freezing, thawed solution is stable for 24 hours at room temperature or 10 days when refrigerated.

CompatibilityStable in $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, NS, sodium bicarbonate 5%.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, amphotericin B cholesteryl sulfate complex, aztreonam, docetaxel, doxorubicin liposome, enalaprilat, esmolol, etoposide, famotidine, fludarabine, foscarnet, gatifloxacin, gemcitabine, granisetron, hydromorphone, labetalol, linezolid, melphalan, meperidine, morphine, ondansetron, propofol, ranitidine, remifentanil, sargramostim, teniposide, thiotepa, vinorelbine. **Incompatible:** Filgrastim. **Variable (consult detailed reference):** Cisatracurium, promethazine, vancomycin.

Compatibility when admixed: Compatible: Clindamycin, metronidazole.

ContraindicationsHypersensitivity to ceftizoxime, any component of the formulation, or other cephalosporins

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.

Geriatric ConsiderationsAdjust dose for renal function in the elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects have not been observed in animal studies; therefore, ceftizoxime is classified as pregnancy category B. Ceftizoxime crosses the placenta and is found in the cord blood and amniotic fluid in amounts that are higher than the maternal serum. The maternal peak concentrations at term are similar to those in nonpregnant volunteers.

LactationEnters breast milk (small amounts)/use caution

Breast-Feeding ConsiderationsVery small amounts of ceftizoxime are excreted in breast milk. The manufacturer recommends that caution be exercised when administering ceftizoxime to nursing women. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Ceftizoxime in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Central nervous system: Fever

Dermatologic: Rash, pruritus

Hematologic: Eosinophilia, thrombocytosis

Hepatic: Alkaline phosphatase increased, transaminases increased

Local: Pain, burning at injection site

<1%: Anaphylaxis, diarrhea, nausea, vomiting, injection site reactions, phlebitis, paresthesia, numbness, bilirubin increased, BUN increased, creatinine increased, anemia, leukopenia, neutropenia, thrombocytopenia, vaginitis

Reactions reported with other cephalosporins: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, pseudomembranous colitis, angioedema, hemolytic anemia, candidiasis, encephalopathy, asterixis, neuromuscular excitability, seizure, serum-sickness reactions, renal dysfunction, interstitial nephritis, toxic nephropathy, cholestasis, aplastic anemia, hemolytic anemia, pancytopenia, agranulocytosis, colitis, prolonged PT, hemorrhage, superinfection

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction

Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions. Assess results of laboratory tests (prothrombin times), therapeutic response, and adverse effects (eg, hemolytic anemia, hypoprothrombinemia, and bleeding) regularly during therapy. Advise patients with diabetes about use of Clinitest® (may cause false-positive test). Teach patient possible side effects/appropriate interventions and adverse symptoms to report (eg, opportunistic infection, hypersensitivity reactions).

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy; renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is administered by infusion or injection. Report immediately any redness, swelling, burning, or pain at injection/infusion site; itching or hives; or difficulty swallowing or breathing. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause false test results with Clinitest®; use of another type of glucose testing is preferable. Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage, sores in mouth, blood in stool or urine, unusual fever or chills); CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed iso-osmotic solution]:

Cefizox®: 1 g (50 mL); 2 g (50 mL)

Injection, powder for reconstitution:

Cefizox®: 1 g, 2 g, 10 g [DSC]

Generic AvailableNo

ManufacturerFujisawa Healthcare, Inc

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Distribution: V_d: 0.35-0.5 L/kg; widely into most body tissues and fluids including gallbladder, liver, kidneys, bone, sputum, bile, pleural and synovial fluids; has good CSF penetration

Protein binding: 30%

Half-life elimination: 1.6 hours; Cl_{cr} <10 mL/minute: 25 hours

Time to peak, serum: I.M.: 0.5-1 hour

Excretion: Urine (as unchanged drug)

Related Information

- Antimicrobial Drugs of Choice
- Cephalosporins by Generation
- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine

Index TermsCeftizoxime Sodium

References

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Donowitz GR and Mandell GL, “Beta-Lactam Antibiotics,” *N Engl J Med*, 1988, 318(7):419-26, 318(8):490-500. [PubMed 3277054]

Klein NC and Cunha BA, “Third-Generation Cephalosporins,” *Med Clin North Am*, 1995, 79(4):705-19. [PubMed 7791418]

Marshall WF and Blair JE, “The Cephalosporins,” *Mayo Clin Proc*, 1999, 74(2):187-95.[PubMed 10069359]

International Brand NamesCefizox (AE, AT, BH, CY, CZ, EG, ES, FR, GB, ID, IE, IL, IN, IQ, IR, JO, KW, LB, LY, NL, OM, PK, PT, QA, SA, SY, YE); Ceftix (AR, DE); Ceftizon (AR); Epocelin (ES, FI, HU, JP, PL); Eposerin (IT); Kidoxone (TW); Tizos (ID); Unizox (PH); Zhuobisha (CL)

Ceftobiprole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(sef toe BYE prole)

Canadian Brand NamesZeftera™

Pharmacologic CategoryAntibiotic, Cephalosporin

Use: Labeled IndicationsTreatment of complicated skin and skin structure infections, including diabetic foot infections without concurrent osteomyelitis, caused by *Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Staphylococcus aureus* (including methicillin resistant staphylococcus aureus [MRSA]) and *Streptococcus pyogenes*

Dosing: Adults

Usual dosage range: I.V.: 500 mg every 8-12 hours

Indication specific dosing:

Complicated skin and skin structure infections (not including diabetic foot infections): I.V.:

Gram positive: 500 mg every 12 hours for 7-14 days

Gram negative or mixed infection: 500 mg every 8 hours for 7-14 days

Complicated skin and skin structure infections including diabetic foot infections (nonlimb-threatening and without concurrent osteomyelitis): I.V.: *Gram positive, gram negative, and mixed infection:* 500 mg every 8 hours for 7-14 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Mild impairment (Cl_{cr} 50-80 mL/minute): No adjustment necessary.

Moderate renal impairment (Cl_{cr} 30 to <50 mL/minute): 500 mg every 12 hours

Severe renal impairment:

Cl_{cr} <30 mL/minute: 250 mg every 12 hours

Cl_{cr} <10 mL/minute: Use has not been studied.

Dosing: Hepatic ImpairmentNo dosage adjustment is necessary.

Calculations

- Creatinine Clearance: Adults

Administration: I.V.Administer by I.V. infusion over 1 hour for gram-positive infections (without diabetic foot infections). Administer over 2 hours for gram-positive infections (with diabetic foot infections) and gram-negative/mixed (gram-positive and gram-negative) infections (with or without diabetic foot infections). Infuse over 2 hours in moderate-to-severe renal impairment, regardless of indication. Parenteral admixture does not need protected from light during infusion.

Administration: I.V. DetailpH: 4.52

StorageStore vials at 2°C to 8°C (36°F to 46°F); protect from light. After reconstitution with 10 mL diluent SWFI or D_5W, resulting solution is stable for 1 hour at 25°C (77°F) or 24 hours at 2°C to 8°C. Do not freeze vials (before or after reconstitution) or admixtures.

Admixture stability:

25°C (77°F): NS or LR: 24 hours if protected from light and 12 hours if not protected from light; D_5W: 8 hours irrespective of light exposure

2°C to 8°C (36°F to 46°F): NS or D_5W: 4 days if protected from light; LR: Do not refrigerate

Reconstitution

Reconstitute vial with 10 mL of diluent (SWFI or D_5W) to obtain a concentration of 50 mg/mL. Shake vial vigorously until total dissolution of powder. After reconstitution of powder, further dilution into 250 mL (125 mL if severe renal impairment) of NS, LR, or D_5W is required.

CompatibilityStable in D_5W, NS, LR, SWFI

Y-site administration: Compatible: Aminophylline, azithromycin, bumetanide, clindamycin, cyclosporine, dexamethasone, digoxin, doripenem, drotrecogin alfa, enalaprilat, fentanyl, fluconazole, furosemide, granisetron, heparin, hydrocortisone sodium succinate, lorazepam, mannitol, methylprednisolone sodium succinate, metoprolol, metronidazole, multivitamins, norepinephrine, potassium chloride, propofol, ranitidine, sodium bicarbonate, sulfamethoxazole-trimethoprim, vasopressin, voriconazole. **Incompatible:** Amikacin, amiodarone, amphotericin B (colloidal), calcium gluconate, caspofungin, ciprofloxacin, cisatracurium, diazepam, diltiazem, diphenhydramine, dobutamine, dopamine, famotidine, filgrastim, gentamicin, haloperidol, hydromorphone, hydroxyzine, insulin (regular), labetalol, levofloxacin, lidocaine, magnesium sulfate, meperidine, metoclopramide, midazolam, morphine, moxifloxacin, ondansetron, potassium phosphate, promethazine, tobramycin. **Variable (consult detailed reference):** Acyclovir, esomeprazole, insulin (lispro), milrinone, pantoprazole, remifentanil, sodium phosphate.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to ceftobiprole, any component of the formulation, or other cephalosporins; demonstrated anaphylaxis to beta-lactams

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hyponatremia: Hyponatremia has been observed in clinical trials; use with caution in patients at risk for hyponatremia (eg, primary adrenal insufficiency, syndrome of inappropriate antidiuretic hormone [SIADH]); monitor sodium levels during therapy.

- Hypersensitivity: Anaphylaxis has been reported with use; individuals with prior hypersensitivity reactions to other cephalosporins, beta-lactams, or multiple allergens are more likely to be at risk; discontinue use immediately with onset of signs/symptoms of allergic reaction.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment is required in moderate-to-severe impairment (Cl_{cr} 10 to <50 mL/minute). Use in end-stage renal disease (ESRD) (Cl_{cr} <10 mL/minute) has not been studied.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizure activity associated with use has most commonly been observed in this patient population; high levels of ceftobiprole, particularly in the presence of renal impairment, may increase risk of seizures.

Special populations:

- Pediatrics: Safety and efficacy have not been established in patients <18 years of age.

Other warnings/precautions:

- Appropriate use: Use in immunosuppressed patients or patients with necrotizing fasciitis, gas gangrene, eczema, neutropenia, or neoplasia has not been evaluated and is not recommended. The 12-hour dosing interval in the treatment of diabetic foot infections has not been evaluated and is not recommended

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Use has not been studied in pregnant women.

LactationExcretion into breast milk unknown/not recommended

Adverse Reactions

1% to 10%:

Central nervous system: Headache (5%), dizziness (3%), chills (≤1%), fatigue (≤1%), fever (≤1%)

Dermatologic: Rash (3%), pruritus (2%)

Endocrine & metabolic: Hyponatremia (1%)

Gastrointestinal: Nausea (9%), taste disturbance (6%), diarrhea (5%), vomiting (5%), constipation (1%), dyspepsia (≤1%)

Hepatic: ALT increased (≤2%), AST increased (≤1%)

Local: Phlebitis (2%)

<1%, postmarketing, and/or case reports: Abdominal pain, agitation, allergic dermatitis, anaphylactic shock, anaphylaxis, anemia, anxiety, back pain, basophilia, catheter site phlebitis, CDAD, creatinine increased, creatinine clearance decreased, dyspnea, eosinophilia, erythema, extremity pain, fungal infection, GGT increased, hot flush, hyperglycemia, hyperhidrosis, hypersensitivity, hypertension, triglycerides increased, infusion site reactions (pain, phlebitis), insomnia, LDH increased, maculopapular rash, muscle spasms, peripheral edema, pharyngeal pain, pollakiuria, seizures, somnolence, stomach discomfort, thrombocytosis, thrombophlebitis, urine odor abnormal, urticaria, vulvovaginal fungal infection, weakness, xerostomia

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Monitoring ParametersSigns/symptoms of anaphylaxis/allergic or hypersensitivity reactions; BUN, creatinine, CBC, basic metabolic panel (BMP), culture and sensitivity

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests, patient's allergy history, and appropriateness for therapy prior to treatment. Use with caution in presence of renal impairment (dosage adjustment may be necessary). Note specific directions for reconstitution, compatibility, and administration. Patient should be monitored closely for hypersensitivity reactions. Evaluate results of laboratory tests, therapeutic response (according to indication for use), and adverse effects regularly during therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsBUN, creatinine, CBC, basic metabolic panel (BMP), culture and sensitivity

Patient EducationThis medication can only be administered by infusion. Report immediately any pain, burning, or swelling at infusion site or any signs of allergic reaction (eg, respiratory difficulty or swallowing, back pain, chest tightness, rash, hives, swelling of lips or mouth). Report unusual headache, dizziness, chills, fever, gastrointestinal upset (nausea, vomiting, abdominal pain, or diarrhea), or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage Forms[CAN] = Canadian product

Injection, powder for reconstitution:

Zeftera™ [CAN]: 500 mg [not available in U.S.]

Generic AvailableNo

ManufacturerJanssen-Ortho, Inc

Mechanism of ActionProdrug converted in vivo to active drug with bactericidal activity; Inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs), including PBP2a on methicillin resistant staphylococcus, which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Distribution: V_{dss}: 18 L

Protein binding: ~16% (concentration independent); primarily to albumin and alpha-1 acid glycoprotein

Metabolism: Ceftobiprole medocaril (prodrug) rapidly metabolized by plasma esterases to ceftobiprole (active drug) which undergoes minimal metabolism to an inactive metabolite

Half-life elimination: ~3 hours; increased with renal impairment

Excretion: Urine (83% as active drug, 5% as inactive metabolite, <1% as unchanged prodrug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste disturbances have been reported; xerostomia and changes in salivation have been reported in <1% of individuals (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index TermsBAL5788; BAL9141; Ceftobiprole Medocaril

References

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Chan P, Bishop A, Kupiec TC, et al, “Compatibility of Ceftobiprole Medocaril With Selected Drugs During Simulated Y-site Administration,” *Am J Health Syst Pharm*, 2008, 65(16):1545-51.[PubMed 18693210]

Murthy B and Schmitt-Hoffmann A, “Pharmacokinetics and Pharmacodynamics of Ceftobiprole, an Anti-MRSA Cephalosporin With Broad-Spectrum Activity,” *Clin Pharmacokinet*, 2008, 47(1):21-33.[PubMed 18076216]

Noel GJ, Strauss RS, Amsler K, et al, “Results of a Double-Blind, Randomized Trial of Ceftobiprole Treatment of Complicated Skin and Skin Structure Infections Caused by Gram-Positive Bacteria,” *Antimicrobial Agents Chemother*, 2008, 52(1):37-44.[PubMed 17954698]

CefTRIAXone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Ceftriaxone: Health Canada Issues Warning Concerning Precipitation Risks Associated With Calcium-Containing Products - August, 2008

Health Canada has issued a warning to Canadian hospitals alerting them of the potential risk of precipitation between ceftriaxone and calcium-containing products when infused together intravenously. A similar warning was previously issued by the U.S. Food and Drug Administration (FDA) in 2007.

Additional information may be found at:

Canada: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/ceftriaxone_nth-aah-eng

U.S.: http://www.fda.gov/medwatch/safety/2007/safety07.htm#Rocephin

Medication Safety Issues

Sound-alike/look-alike issues:

Rocephin® may be confused with Roferon®

Pronunciation(sef trye AKS one)

U.S. Brand NamesRocephin®

Canadian Brand NamesRocephin®

Pharmacologic CategoryAntibiotic, Cephalosporin (Third Generation)

Use: Labeled IndicationsTreatment of lower respiratory tract infections, acute bacterial otitis media, skin and skin structure infections, bone and joint infections, intra-abdominal and urinary tract infections, pelvic inflammatory disease (PID), uncomplicated gonorrhea, bacterial septicemia, and meningitis; used in surgical prophylaxis

Use: Unlabeled/InvestigationalTreatment of chancroid, epididymitis, complicated gonococcal infections; sexually-transmitted diseases (STD); periorbital or buccal cellulitis; salmonellosis or shigellosis; atypical community-acquired pneumonia; epiglottitis, Lyme disease; used in chemoprophylaxis for high-risk contacts and persons with invasive meningococcal disease; sexual assault; typhoid fever, Whipple's disease

Use: DentalAlternative antibiotic for prevention of infective endocarditis when parenteral administration is needed. Individuals allergic to amoxicillin (penicillins) may receive ceftriaxone provided they have not had an immediate, local, or systemic IgE-mediated anaphylactic allergic reaction to penicillin.

Dosing: Adults

Dosage range: Usual dose: 1-2 g every 12-24 hours, depending on the type and severity of infection

Arthritis, septic (unlabeled use): I.V.: 1-2 g once daily

Brain abscess (unlabeled use): I.V.: 2 g every 12 hours with metronidazole

Cavernous sinus thrombosis (unlabeled use): I.V.: 2 g once daily with vancomycin or linezolid

Chancroid (unlabeled use): I.M.: 250 mg as single dose

Chemoprophylaxis for high-risk contacts and persons with invasive meningococcal disease (unlabeled use): I.M.: 250 mg in a single dose

Gonococcal infections:

Conjunctivitis, complicated (unlabeled use): I.M., I.V.: 1 g in a single dose

Disseminated (unlabeled use): I.M., I.V.: 1 g once daily for 7 days

Endocarditis (unlabeled use): I.M., I.V.: 1-2 g every 24 hours for at least 28 days

Epididymitis, acute (unlabeled use): I.M.: 250 mg in a single dose with doxycycline

Prostatitis (unlabeled use): I.M.: 125-250 mg in a single dose with doxycycline

Uncomplicated: I.M.: 125-250 mg in a single dose

Infective endocarditis: I.M., I.V.:

Native valve: 2 g once daily for 2-4 weeks; **Note:** If using 2-week regimen, concurrent gentamicin is recommended

Prosthetic valve: I.M., I.V.: 2 g once daily for 6 weeks (with or without 2 weeks of gentamicin [dependent on penicillin MIC]); **Note:** For HACEK organisms, duration of therapy is 4 weeks

Enterococcus faecalis (resistant to penicillin, aminoglycoside, and vancomycin), native or prosthetic valve: 2 g twice daily for ≥8 weeks administered concurrently with ampicillin

Prophylaxis: I.M., I.V.: 1 g 30-60 minutes before procedure. Intramuscular injections should be avoided in patients who are receiving anticoagulant therapy. In these circumstances, orally administered regimens should be given whenever possible. Intravenously administered antibiotics should be used for patients who are unable to tolerate or absorb oral medications.

Note: American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur. As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Lyme disease (unlabeled use): I.V.: 2 g once daily for 14-28 days

Mastoiditis (hospitalized; unlabeled use): I.V.: 2 g once daily; >60 years old: 1 g once daily

Meningitis: I.V.: 2 g every 12 hours for 7-14 days (longer courses may be necessary for selected organisms

Orbital cellulitis (unlabeled use) and endophthalmitis: I.V.: 2 g once daily

PID: I.M.: 250 mg in a single dose

Pneumonia, community-acquired: I.V.: 1 g once daily, usually in combination with a macrolide; consider 2 g/day for patients at risk for more severe infection and/or resistant organisms (ICU status, age >65 years, disseminated infection)

Septic/toxic shock/necrotizing fasciitis (unlabeled use): I.V.: 2 g once daily; with clindamycin for toxic shock

STD prophylaxis in sexual assault victims: I.M.: 125 mg as a single dose

Surgical prophylaxis: I.V.: 1 g 30 minutes to 2 hours before surgery

Syphilis (unlabeled use): I.M., I.V.: 1 g once daily for 8-10 days

Typhoid fever (unlabeled use): I.V.: 2 g once daily for 14 days

Whipple's disease (unlabeled use): Initial: 2 g once daily for 10-14 days, then oral therapy for ~ 1 year.

⇧ Dosing: ElderlyRefer to adult dosing.
⇧ Dosing: Pediatric

Dosage range: Infants and Children: Usual dose: I.M., I.V.:

Mild-to-moderate infections: 50-75 mg/kg/day in 1-2 divided doses every 12-24 hours (maximum: 2 g/day); continue until at least 2 days after signs and symptoms of infection have resolved

Serious infections: 80-100 mg/kg/day in 1-2 divided doses (maximum: 4 g/day)

Epiglottis (unlabeled use): I.M., I.V.: 50-100 mg/kg once daily; reported duration of treatment ranged from 2-14 days

Gonococcal infections:

Conjunctivitis, complicated (unlabeled use): I.M.:

<45 kg: 50 mg/kg in a single dose (maximum: 1 g)

≥45 kg: 1 g in a single dose

Disseminated (unlabeled use): I.M., I.V.:

<45 kg: 25-50 mg/kg once daily (maximum: 1 g)

≥45 kg: 1 g once daily for 7 days

Endocarditis (unlabeled use):

<45 kg: I.M., I.V.: 50 mg/kg/day every 12 hours (maximum: 2 g/day) for at least 28 days

≥45 kg: I.V.: 1-2 g every 12 hours, for at least 28 days

Prophylaxis (due to maternal gonococcal infection): I.M., I.V.: 25-50 mg/kg as a single dose (maximum: 125 mg)

Uncomplicated: I.M.: 125 mg in a single dose

Infective endocarditis: I.M., I.V.:

Native valve: 100 mg/kg once daily for 2-4 weeks; **Note:** If using 2-week regimen, concurrent gentamicin is recommended

Prosthetic valve: 100 mg/kg once daily for 6 weeks (with or without 2 weeks of gentamicin [dependent on penicillin MIC]); **Note:** For HACEK organisms, duration of therapy is 4 weeks

Enterococcus faecalis (resistant to penicillin, aminoglycoside, and vancomycin), native or prosthetic valve: 100 mg/kg once daily for ≥8 weeks administered concurrently with ampicillin

Prophylaxis: 50 mg/kg 30-60 minutes before procedure; maximum dose: 1 g. Intramuscular injections should be avoided in patients who are receiving anticoagulant therapy. In these circumstances, orally administered regimens should be given whenever possible. Intravenously administered antibiotics should be used for patients who are unable to tolerate or absorb oral medications.

Note: American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur. As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Lyme disease, persistent arthritis (unlabeled use): I.M., I.V.: 75-100 mg/kg (maximum: 2 g) for 2-4 weeks

Meningitis: I.M., I.V.:

Uncomplicated: Loading dose of 100 mg/kg (maximum: 4 g), followed by 100 mg/kg/day divided every 12-24 hours (maximum: 4 g/day); usual duration of treatment is 7-14 days

Gonococcal, complicated:

<45 kg: 50 mg/kg/day given every 12 hours (maximum: 2 g/day); usual duration of treatment is 10-14 days

>45 kg: I.V.: 1-2 g every 12 hours; usual duration of treatment is 10-14 days

Otitis media: I.M.:

Acute: 50 mg/kg in a single dose (maximum: 1 g)

Persistent or relapsing (unlabeled use): 50 mg/kg once daily for 3 days

Pneumonia: I.V.: 50-75 mg/kg once daily

Skin/skin structure infections: I.M., I.V.: 50-75 mg/kg/day in 1-2 divided doses (maximum: 2 g/day)

STD, sexual assault (unlabeled uses): 125 mg in a single dose

Typhoid fever (unlabeled use): I.V.: 75-80 mg/kg once daily for 5-14 days

Chemoprophylaxis for high-risk contacts and persons with invasive meningococcal disease (unlabeled use):

Children ≤15 years: I.M.: 125 mg in a single dose

Children >15 years: Refer to adult dosing.

Epididymitis, acute: Children >8 years (≥45 kg) and Adolescents (unlabeled use): I.M.: 125 mg in a single dose

Dosing: Renal Impairment

No adjustment is generally necessary; if severe impairment, particularly with concurrent hepatic dysfunction, do not exceed 2 g/day without serum concentration monitoring.

Not dialyzable (0% to 5%)

Administer dose postdialysis.

Continuous ambulatory peritoneal dialysis (CAPD): Administer 1 g every 12 hours

Continuous renal replacement therapy (CRRT): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH or CVVHD/CVVHDF: 2 g every 12-24 hours

Dosing: Hepatic ImpairmentNo adjustment necessary.

Administration: I.M.Inject deep I.M. into large muscle mass; a concentration of 250 mg/mL or 350 mg/mL is recommended for all vial sizes except the 250 mg size (250 mg/mL is suggested); can be diluted with 1:1 water and 1% lidocaine for I.M. administration.

Administration: I.V.Refer to Compatibility. Do not reconstitute or coadminister with calcium-containing solutions. Infuse intermittent infusion over 30 minutes.

Administration: I.V. DetailpH: 6.6 (premixed infusion solution); 6.7 (1% aqueous solution)

Dietary ConsiderationsSodium contents: ~83 mg (3.6 mEq) per ceftriaxone 1 g

Storage

Powder for injection: Prior to reconstitution, store at room temperature ≤25°C (≤77°F). Protect from light.

Premixed solution (manufacturer premixed): Store at -20°C; once thawed, solutions are stable for 3 days at room temperature of 25°C (77°F) or for 21 days refrigerated at 5°C (41°F). Do not refreeze.

Stability of reconstituted solutions:

10-40 mg/mL: Reconstituted in D_5W, $D_{10}W$, NS, or SWFI: Stable for 2 days at room temperature of 25°C (77°F) or for 10 days when refrigerated at 4°C (39°F). Stable for 26 weeks when frozen at -20°C when reconstituted with D_5W or NS. Once thawed (at room temperature), solutions are stable for 2 days at room temperature of 25°C (77°F) or for 10 days when refrigerated at 4°C (39°F); does not apply to manufacturer's premixed bags. Do not refreeze.

100 mg/mL:

Reconstituted in D$_5$W, SWFI, or NS: Stable for 2 days at room temperature of 25°C (77°F) or for 10 days when refrigerated at 4°C (39°F).

Reconstituted in lidocaine 1% solution or bacteriostatic water: Stable for 24 hours at room temperature of 25°C (77°F) or for 10 days when refrigerated at 4°C (39°F).

250-350 mg/mL: Reconstituted in D$_5$W, NS, lidocaine 1% solution, bacteriostatic water, or SWFI: Stable for 24 hours at room temperature of 25°C (77°F) or for 3 days when refrigerated at 4°C (39°F).

Reconstitution

I.M. injection: Vials should be reconstituted with appropriate volume of diluent (including D$_5$W, NS, SWFI, bacteriostatic water, or 1% lidocaine) to make a final concentration of 250 mg/mL or 350 mg/mL.

Volume to add to create a **250 mg/mL** solution:

250 mg vial: 0.9 mL

500 mg vial: 1.8 mL

1 g vial: 3.6 mL

2 g vial: 7.2 mL

Volume to add to create a **350 mg/mL** solution:

500 mg vial: 1.0 mL

1 g vial: 2.1 mL

2 g vial: 4.2 mL

I.V. infusion: Infusion is prepared in two stages: Initial reconstitution of powder, followed by dilution to final infusion solution.

Vials: Reconstitute powder with appropriate I.V. diluent (including SWFI, D$_5$W, D$_{10}$W, NS) to create an initial solution of ~100 mg/mL. Recommended volume to add:

250 mg vial: 2.4 mL

500 mg vial: 4.8 mL

1 g vial: 9.6 mL

2 g vial: 19.2 mL

Note: After reconstitution of powder, further dilution into a volume of compatible solution (eg, 50-100 mL of D$_5$W or NS) is recommended.

Piggyback bottle: Reconstitute powder with appropriate I.V. diluent (D$_5$W or NS) to create a resulting solution of ~100 mg/mL. Recommended initial volume to add:

1 g bottle:10 mL

2 g bottle: 20 mL

Note: After reconstitution, to prepare the final infusion solution, further dilution to 50 mL or 100 mL volumes with the appropriate I.V. diluent (including D$_5$W or NS) is recommended.

CompatibilityStable in D$_5$W with KCl 10 mEq, D$_5{}^1/_4$NS with KCl 20 mEq, D$_5{}^1/_2$ NS, D$_5$W, D$_{10}$W, NS, mannitol 5%, mannitol 10%, sodium bicarbonate 5%, bacteriostatic water, sterile water for injection. **Incompatible** with calcium-containing solutions (eg, LR, Hartmann's solution, parenteral nutrition solutions). **Variable stability (consult detailed reference)** in peritoneal dialysis solutions.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, amiodarone, anidulafungin, aztreonam, bivalirudin, cisatracurium, daptomycin, dexmedetomidine, diltiazem, docetaxel, doxorubicin liposome, drotrecogin alfa, etoposide phosphate, famotidine, fenoldopam, fludarabine, foscarnet, gallium nitrate, gatifloxacin, gemcitabine, granisetron, heparin, lansoprazole, linezolid, melphalan, meperidine, methotrexate, morphine, paclitaxel, pantoprazole, pemetrexed, propofol, remifentanil, sargramostim, sodium bicarbonate, tacrolimus, teniposide, theophylline, thiotepa, warfarin, zidovudine. **Incompatible:** Alatrofloxacin, amphotericin B cholesteryl sulfate complex, amsacrine, azithromycin, calcium, filgrastim, fluconazole, Hartmann's solution, labetalol, LR, pentamidine, parenteral nutrition solutions (containing calcium), vinorelbine. **Variable (consult detailed reference):** Anakinra, vancomycin.

Compatibility in syringe: Variable (consult detailed reference): Lidocaine.

Compatibility when admixed: Compatible: Amikacin, metronidazole. **Incompatible:** Aminophylline, amsacrine, calcium, clindamycin, fluconazole, linezolid, theophylline. **Variable (consult detailed reference):** Gentamicin, metronidazole hydrochloride, vancomycin.

ContraindicationsHypersensitivity to ceftriaxone sodium, any component of the formulation, or other cephalosporins; **do not use in hyperbilirubinemic neonates**, particularly those who are premature since ceftriaxone is reported to displace bilirubin from albumin binding sites; concomitant use with intravenous calcium-containing solutions/products in neonates (≤28 days)

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Elevated INR: May be associated with increased INR (rarely), especially in nutritionally-deficient patients, prolonged treatment, hepatic or renal disease.
- Pancreatitis: Secondary to biliary obstruction, pancreatitis has been reported rarely.
- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Gallbladder disease: Abnormal gallbladder sonograms have been reported, possibly due to ceftriaxone-calcium precipitates; discontinue in patients with signs and symptoms of gallbladder disease.
- Gastrointestinal disease: Use with caution in patients with a history of GI disease, especially colitis.
- Renal impairment: No adjustment is generally necessary in patients with renal impairment; if severe renal impairment, particularly with concurrent hepatic dysfunction, do not exceed 2 g/day without serum concentration monitoring.

Special populations:

- Neonates: Use extreme caution in neonates due to risk of hyperbilirubinemia, particularly in premature infants (contraindicated in hyperbilirubinemic neonates). Fatal precipitation reactions in neonates due to coadministration of calcium-containing solutions have been reported; concurrent use in neonates is contraindicated.

Other warnings/precautions:

- Precipitation: Ceftriaxone may complex with calcium causing precipitation. Fatal lung and kidney damage associated with calcium-ceftriaxone precipitates has been observed in premature and term neonates. Due to reports of precipitation reaction in neonates, do not reconstitute, admix, or coadminister with calcium-containing solutions (eg, LR, Hartmann's solution, parenteral nutrition), even via separate infusion lines/sites or at different times in any patient, regardless of age (contraindicated in neonates). Recommendations further state to avoid administration of intravenous calcium-containing solutions and ceftriaxone within 48 hours of each other in all patients. However, extending these recommendations to all patients is based solely on theoretical data, as there have been no reports of precipitant-induced adverse effects in non-neonatal patients.

Geriatric ConsiderationsNo adjustment for changes in renal function necessary.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects have not been observed in animal studies; therefore, ceftriaxone is classified as pregnancy category B. The pharmacokinetics of ceftriaxone in the third trimester are similar to those of nonpregnant patients, with the possible exception of lower peak concentrations during labor. Ceftriaxone crosses the placenta and distributes to amniotic fluid. Ceftriaxone is recommended for use in pregnant women for the treatment of gonococcal infections.

LactationEnters breast milk/use caution (AAP rates "compatible")

Breast-Feeding ConsiderationsSmall amounts of ceftriaxone are excreted in breast milk. The manufacturer recommends that caution be exercised when administering ceftriaxone to nursing women. The American Academy of Pediatrics considers ceftriaxone to be "usually compatible with breast-feeding." Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- CefTRIAXone in Pregnancy & Lactation

Adverse Reactions

>10%: Local: Induration (I.M. 5% to 17%), warmth (I.M.), tightness (I.M.)

1% to 10%:

Dermatologic: Rash (2%)

Gastrointestinal: Diarrhea (3%)

Hematologic: Eosinophilia (6%), thrombocytosis (5%), leukopenia (2%)

Hepatic: Transaminases increased (3%)

Local: Tenderness at injection site (I.V. 1%), pain

Renal: BUN increased (1%)

<1%: Abdominal pain, agranulocytosis, alkaline phosphatase increased, allergic pneumonitis, anaphylaxis, anemia, basophilia, biliary lithiasis, bilirubin increased, bronchospasm, chills, colitis, creatinine increased, diaphoresis, dizziness, dysgeusia, dyspepsia, epistaxis, fever, flatulence, flushing, gallbladder sludge, gallstones, glycosuria, headache, hematuria, hemolytic anemia, jaundice, leukocytosis, lymphocytosis, lymphopenia, monocytosis, moniliasis, nausea, nephrolithiasis, neutropenia, palpitation, pancreatitis, phlebitis, prolonged or decreased PT, pruritus, pseudomembranous colitis, seizure, serum sickness, thrombocytopenia, urinary casts, vaginitis, vomiting

Postmarketing and/or case reports: Allergic dermatitis, edema, erythema multiforme, exanthema, glossitis, Lyell's syndrome, oliguria, renal and pulmonary ceftriaxone-calcium precipitations (neonates; including some fatalities), Stevens-Johnson syndrome, stomatitis, toxic epidermal necrolysis, urticaria

Reactions reported with other cephalosporins: Angioedema, allergic reaction, aplastic anemia, asterixis, cholestasis, encephalopathy, hemorrhage, hepatic dysfunction, hyperactivity (reversible), hypertonia, interstitial nephritis, LDH increased, neuromuscular excitability, pancytopenia, paresthesia, renal dysfunction, superinfection, toxic nephropathy

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Calcium Salts (Intravenous): May enhance the adverse/toxic effect of CefTRIAXone. Ceftriaxone binds to calcium forming an insoluble precipitate. *Risk X: Avoid combination*

Ringer's Injection (Lactated): May enhance the adverse/toxic effect of CefTRIAXone. Ceftriaxone binds to calcium in the Lactated Ringer's forming an insoluble precipitate. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Cephalosporins may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction

Monitoring ParametersObserve for signs and symptoms of anaphylaxis

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions or toxicity (eg, coumarin derivatives, calcium-containing products). I.V.: Note specific directions for reconstitution, compatibility, and administration. Assess results of laboratory tests (prothrombin times), therapeutic response, and adverse effects regularly during therapy. Advise patients with diabetes about use of Clinitest® (may cause false-positive test). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsProthrombin times; perform culture and sensitivity studies prior to initiating drug therapy.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. This medication can only be administered by injection or infusion. Report immediately any swelling, pain, burning, or redness at infusion/injection site; back pain; difficulty breathing or swallowing; rapid heartbeat; or chills. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause false test results with Clinitest®; use of another type of glucose testing is preferable. Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage, sores in mouth, blood in stool or urine, vaginal itching or drainage, unusual fever or chills); or CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Infusion [premixed in dextrose]: 1 g (50 mL); 2 g (50 mL)

Injection, powder for reconstitution: 250 mg, 500 mg, 1 g, 2 g, 10 g

Rocephin®: 250 mg [DSC], 500 mg, 1 g, 2 g [DSC], 10 g [contains sodium ~83 mg (3.6 mEq) per ceftriaxone 1 g] [DSC]

Generic AvailableYes

ManufacturerRoche Laboratories Inc

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: I.M.: Well absorbed

Distribution: V_d: 6-14 L; widely throughout the body including gallbladder, lungs, bone, bile, CSF (higher concentrations achieved when meninges are inflamed)

Protein binding: 85% to 95%

Half-life elimination: Normal renal and hepatic function: 5-9 hours; Renal impairment (mild-to-severe): 12-16 hours

Time to peak, serum: I.M.: 2-3 hours

Excretion: Urine (33% to 67% as unchanged drug); feces (as inactive drug)

Related Information

- Antibiotic Treatment of Adults With Infective Endocarditis
- Antimicrobial Drugs of Choice
- Cephalosporins by Generation
- Community-Acquired Pneumonia in Adults
- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins

Mental Health: Effects on Psychiatric Treatment May rarely cause neutropenia; use caution with clozapine and carbamazepine

Index Terms Ceftriaxone Sodium

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International Brand Names Acantex (AR, CN, PY); Amcef (MX); Aurofox (MX); Axone (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Axtar (CO, MX); Benaxona (MX); Biotrakson (PL); Biotriax (ID); Bioxon (ID); Broadced (ID); Brospec (ID); Cefaflox (ID); Cefalogen (PE); Cefaxona (MX); Cefaxone (KP, MY, SG); Cefin (CL); Cefraden (MX); Cefriex (ID); Ceftrex (MX, TH); Ceftrian (EC); Ceftrianol (MX); Ceftriaxon Torrex (PL); Ceftrilem (MX); Cefxon (ID); Cerixon (KP); Chef (TW); Cikedrix (PH); Cryaxon (PH); Ecotrixon (ID); Eftriax (MY); Elpicef (ID); Exempla (AR); Ferfacef (ID); Forgram (PH); Glicocef (BR); Gomcephin (KP); Grifotriaxona (PE); Keftriaxone (IL); Keptrix (PH); Lendacin (HR, HU, PL); Longacef (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Longaceph (PL); Lyceft (IN); Medoxonum (HK); Megion (CR, DO, GT, MX, NI, PA, PH, PL, SV); Mesporin (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EE, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Mesporin IM (BB, BM, BS, BZ, GY, HK, JM, NL, SR, TT); Mesporin IV (BB, BM, BS, BZ, GY, HK, JM, NL, SR, TT); Monocef (IN); Nakaxone (TW); Newcef (KP); Novocef (PH); Novosef (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Oframax (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, PL, SC, SD, SG, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Pantrixon (PH); Retrokor (PH); Rocefalin (ES); Rocefin (BR, CO, IT); Rocephalin (DK, FI, NO, SE); Rocephin "Biochemie" (AT); Rocephin "Roche" (AT, CZ); Rocephin (AE, AU, BB, BH, BM, BS, BZ, CH, CL, CY, DE, EC, EG, GB, GH, GR, GY, HK, HN, HR, HU, ID, IE, IL, IQ, IR, JM, JO, JP, KE, KP, KW, LB, LY, MX, MY, NL, OM, PE, PH, PK, PL, PT, QA, SA, SG, SR, SY, TH, TT, TW, TZ, UG, UY, VE, YE, ZM); Rocephin Roche (CZ); Rocephine " Roche" (BG); Rocephine (BE, FR, IL, LU); Rocidar (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Roxcef (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Roxon (PH); Samixon (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Sintrex (TW); Socef (ID); Sunflow (TW); Tacex (MX); Tartriakson (PL); Terbac (MX); Trexofin (SG); Triacef (TH); Triaken (MX); Triax (IL); Tricef (TW); Tricefin (SG); Tricephin (TH); Trijec (ID); Triox (MX); Xtenda (PH); Zefaxone (TH); Zefone 250 (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW)

Cefuroxime

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cefuroxime may be confused with cefotaxime, cefprozil, ceftizoxime, deferoxamine

Ceftin® may be confused with Cefzil®, Cipro®

Zinacef® may be confused with Zithromax®

International issues:

Ceftin® may be confused with Cefiton® which is a brand name for cefixime in Portugal

Ceftin® may be confused with Ceftina® which is a brand name for cefalotin in Mexico

Ceftin® may be confused with Ceftim® which is a brand name for ceftazidime in Italy

Pronunciation(se fyoor OKS eem)

U.S. Brand NamesCeftin®; Zinacef®

Canadian Brand NamesApo-Cefuroxime®; Ceftin®; Cefuroxime For Injection; Pro-Cefuroxime; Ratio-Cefuroxime; Zinacef®

Pharmacologic CategoryAntibiotic, Cephalosporin (Second Generation)

Use: Labeled IndicationsTreatment of infections caused by staphylococci, group B streptococci, *H. influenzae* (type A and B), *E. coli*, *Enterobacter*, *Salmonella*, and *Klebsiella*; treatment of susceptible infections of the upper and lower respiratory tract, otitis media, urinary tract, uncomplicated skin and soft tissue, bone and joint, sepsis, uncomplicated gonorrhea, and early Lyme disease; preoperative prophylaxis of susceptible infections

Dosing: Adults**Note:** Cefuroxime axetil film-coated tablets and oral suspension are not bioequivalent and are not substitutable on a mg/mg basis. All oral doses listed are for tablet formulation:

Acute bacterial maxillary sinusitis: Oral: 250 mg twice daily for 10 days

Bronchitis, acute (and exacerbations of chronic bronchitis):

Oral: 250-500 mg every 12 hours for 10 days

I.V.: 500-750 mg every 8 hours (complete therapy with oral dosing)

Cellulitis, orbital: I.V.: 1.5 g every 8 hours

Gonorrhea:

Disseminated: I.M., I.V.: 750 mg every 8 hours

Uncomplicated:

Oral: 1 g as a single dose

I.M.: 1.5 g as single dose (administer in two different sites with probenecid)

Lyme disease (early): Oral: 500 mg twice daily for 20 days

Pharyngitis/tonsillitis and sinusitis: Oral: 250 mg twice daily for 10 days

Skin/skin structure infection, uncomplicated:

Oral: 250-500 mg every 12 hours for 10 days

I.M., I.V.: 750 mg every 8 hours

Pneumonia, uncomplicated: I.M., I.V.: 750 mg every 8 hours

Severe or complicated infections: I.M., I.V.: 1.5 g every 8 hours (up to 1.5 g every 6 hours in life-threatening infections)

Surgical prophylaxis:

I.V.: 1.5 g 30 minutes to 1 hour prior to procedure (if procedure is prolonged can give 750 mg every 8 hours I.M.)

Open heart: I.V.: 1.5 g every 12 hours to a total of 6 g

Urinary tract infection, uncomplicated:

Oral: 125-250 mg twice daily for 7-10 days

I.V., I.M.: 750 mg every 8 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Note:** Cefuroxime axetil film-coated tablets and oral suspension are not bioequivalent and are not substitutable on a mg/mg basis.

Children 3 months to 12 years:

Epiglottitis: 150 mg/kg/day in 3 divided doses for 7-10 days

Acute otitis media, impetigo:

Oral:

Suspension: 30 mg/kg/day (maximum: 1 g/day) in 2 divided doses

Tablet: 250 mg every 12 hours

I.M., I.V.: 75-150 mg/kg/day divided every 8 hours (maximum dose: 6 g/day)

Acute bacterial maxillary sinusitis: Oral:

Suspension: 30 mg/kg/day in 2 divided doses for 10 days (maximum dose: 1 g/day)

Tablet: 250 mg twice daily for 10 days

Meningitis: NOT recommended (doses of 200-240 mg/kg/day divided every 6-8 hours have been used) (maximum dose: 9 g/day)

Pharyngitis, tonsillitis:

Oral:

Suspension: 20 mg/kg/day (maximum: 500 mg/day) in 2 divided doses for 10 days

Tablet: 125 mg every 12 hours for 10 days

I.M., I.V.: 75-150 mg/kg/day divided every 8 hours; maximum dose: 6 g/day

Children ≥13 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 10-20 mL/minute: Administer every 12 hours.

Cl_{cr} <10 mL/minute: Administer every 24 hours.

Hemodialysis: Dialyzable (25%)

Peritoneal dialysis: Dose every 24 hours

Continuous renal replacement therapy (CRRT): 1 g every 12 hours

Note: Cefuroxime axetil film-coated tablets and oral suspension are not bioequivalent and are not substitutable on a mg/mg basis.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Inject deep I.M. into large muscle mass.
Administration: I.V.Inject direct I.V. over 3-5 minutes. Infuse intermittent infusion over 15-30 minutes.
Administration: I.V. DetailpH: 6.0-8.5 (vials); 5.0-7.5 (frozen premixed solution)
Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels. Oral suspension: Administer with food. Shake well before use.
Dietary ConsiderationsMay be taken with food.

Zinacef®: Sodium content: 1.8 mEq (41 mg) per 750 mg

Ceftin®: Powder for oral suspension 125 mg/5 mL contains phenylalanine 11.8 mg/5 mL; 250 mg/5 mL contains phenylalanine 25.2 mg/5 mL.

Storage

Injection: Reconstituted solution is stable for 24 hours at room temperature and 48 hours when refrigerated. I.V. infusion in NS or D_5W solution is stable for 24 hours at room temperature, 7 days when refrigerated, or 26 weeks when frozen. After freezing, thawed solution is stable for 24 hours at room temperature or 21 days when refrigerated.

Oral suspension: Prior to reconstitution, store at 2°C to 30°C (36°F to 86°F). Reconstituted suspension is stable for 10 days at 2°C to 8°C (36°F to

46°F).

Tablet: Store at 15°C to 30°C (59°F to 86°F).

CompatibilityStable in $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, NS.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, atracurium, aztreonam, cyclophosphamide, diltiazem, docetaxel, etoposide, famotidine, fludarabine, foscarnet, gemcitabine, granisetron, hydromorphone, linezolid, melphalan, meperidine, morphine, ondansetron, pancuronium, perphenazine, propofol, remifentanil, sargramostim, tacrolimus, teniposide, thiotepa, vecuronium. **Incompatible:** Clarithromycin, filgrastim, fluconazole, midazolam, vinorelbine. **Variable (consult detailed reference):** Cisatracurium, vancomycin.

Compatibility in syringe: Incompatible: Doxapram.

Compatibility when admixed: Compatible: Clindamycin, floxacillin, furosemide, heparin, metronidazole, potassium chloride. **Incompatible:** Aminoglycosides, sodium bicarbonate. **Variable (consult detailed reference):** Gentamicin, ranitidine.

ContraindicationsHypersensitivity to cefuroxime, any component of the formulation, or other cephalosporins

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Elevated INR: May be associated with increased INR, especially in nutritionally-deficient patients, prolonged treatment, hepatic or renal disease.
- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.
- Suspension/tablet bioequivalence: Tablets and oral suspension are not bioequivalent; do not substitute on a mg-per-mg basis.

Geriatric ConsiderationsAdjust dose for renal function in the elderly. Considered one of the drugs of choice for outpatient treatment of community-acquired pneumonia in the elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events were not observed in animal studies; therefore, cefuroxime is classified as pregnancy category B. Cefuroxime crosses the placenta and reaches the cord serum and amniotic fluid. Placental transfer is decreased in the presence of oligohydraminios. Several studies have failed to identify a teratogenic risk to the fetus from maternal cefuroxime use.

During pregnancy, mean plasma concentrations of cefuroxime are 50% lower, the AUC is 25% lower, and the plasma half-life is shorter than nonpregnant values. At term, plasma half-life is similar to nonpregnant values and peak maternal concentrations after I.M. administration are slightly decreased. Pregnancy does not alter the volume of distribution.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsCefuroxime is excreted in breast milk. Manufacturer recommendations vary; caution is recommended if cefuroxime I.V. is given to a nursing woman and it is recommended to consider discontinuing nursing temporarily during treatment following oral cefuroxime. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Cefuroxime in Pregnancy & Lactation

Adverse Reactions

>10%: Gastrointestinal: Diarrhea (4% to 11%, duration-dependent)

1% to 10%:

Dermatologic: Diaper rash (3%)

Endocrine & metabolic: Alkaline phosphatase increased (2%), lactate dehydrogenase increased (1%)

Gastrointestinal: Nausea/vomiting (3% to 7%)

Genitourinary: Vaginitis (≤5%)

Hematologic: Eosinophilia (7%), hemoglobin and hematocrit decreased (10%)

Hepatic: Transaminases increased (2% to 4%)

Local: Thrombophlebitis (2%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Anaphylaxis, angioedema, BUN increased, chest pain, cholestasis, colitis, creatinine increased, dyspnea, erythema multiforme, fever, GI bleeding, hemolytic anemia, hepatitis, hives, hyperbilirubinemia, hypersensitivity, interstitial nephritis, jaundice, leukopenia, neutropenia, pain at injection site, pancytopenia, positive Coombs test, prolonged PT/INR, pseudomembranous colitis, rash, renal dysfunction, seizure, Stevens-Johnson syndrome, stomach cramps, tachycardia, thrombocytopenia (rare), tongue swelling, toxic epidermal necrolysis, urticaria

Reactions reported with other cephalosporins: Agranulocytosis, aplastic anemia, asterixis, encephalopathy, hemorrhage, neuromuscular excitability, serum-sickness reactions, superinfection, toxic nephropathy

Drug Interactions

Antacids: May decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

H2-Antagonists: May decrease the absorption of Cefuroxime. Separate oral doses by at least 2 hours. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Bioavailability is increased with food; cefuroxime serum levels may be increased if taken with food or dairy products.

Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution); false-negative may occur with ferricyanide test. Glucose oxidase or hexokinase-based methods should be used.

Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose; with prolonged therapy, monitor renal, hepatic, and hematologic function periodically; monitor prothrombin time in patients at risk of prolongation during cephalosporin therapy (nutritionally-deficient, prolonged treatment, renal or hepatic disease)

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, nephrotoxicity). Assess results of laboratory tests (prothrombin times), therapeutic response, and adverse reactions (eg, hemolytic anemia, hypoprothrombinemia, and bleeding) regularly during therapy. Advise patients with diabetes about use of Clinitest® (may cause false-positive test). Teach patient possible side effects/appropriate interventions and adverse symptoms to report (eg, opportunistic infection, hypersensitivity reaction).

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating therapy; renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. If administered by injection or infusion, report immediately any swelling, redness, or pain at injection/infusion site; respiratory difficulty or swallowing; chest pain; or rash. Oral tablets or suspension should be taken as directed, at regular intervals around-the-clock (with or without food). Chilling oral suspension improves flavor (do not freeze); shake well before using. Complete full course of medication, even if you feel better. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause false test results with Clinitest®; use of another type of glucose testing is preferable. Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage, sores in mouth, blood in stool or urine, unusual fever or chills); CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: Strength expressed as base

Infusion, as sodium [premixed]: 750 mg (50 mL); 1.5 g (50 mL)

Zinacef®: 750 mg (50 mL); 1.5 g (50 mL) [contains sodium 4.8 mEq (111 mg) per 750 mg]

Injection, powder for reconstitution, as sodium: 750 mg, 1.5 g, 7.5 g, 75 g, 225 g

Zinacef®: 750 mg, 1.5 g, 7.5 g [contains sodium 1.8 mEq (41 mg) per 750 mg]

Powder for suspension, oral, as axetil: 125 mg/5 mL (100 mL); 250 mg/5 mL (50 mL, 100 mL)

Ceftin®: 125 mg/5 mL (100 mL) [contains phenylalanine 11.8 mg/5 mL; tutti-frutti flavor]; 250 mg/5 mL (50 mL, 100 mL) [contains phenylalanine 25.2 mg/5 mL; tutti-frutti flavor]

Tablet, as axetil: 250 mg, 500 mg

Ceftin®: 250 mg, 500 mg

Generic AvailableYes

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Suspension (reconstituted) (Cefuroxime Axetil)

250 mg/5 mL (100): $89.99

Tablets (Ceftin)

250 mg (20): $177.24

500 mg (20): $308.62

Tablets (Cefuroxime Axetil)

250 mg (20): $70.99

500 mg (20): $73.98

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: Oral (cefuroxime axetil): Increases with food

Distribution: Widely to body tissues and fluids; crosses blood-brain barrier; therapeutic concentrations achieved in CSF even when meninges are not inflamed

Protein binding: 33% to 50%

Bioavailability: Tablet: Fasting: 37%; Following food: 52%

Half-life elimination: Children 1-2 hours; Adults: 1-2 hours; prolonged with renal impairment

Time to peak, serum: I.M.: ~15-60 minutes; I.V.: 2-3 minutes; Oral: Children: 3-4 hours; Adults: 2-3 hours

Excretion: Urine (66% to 100% as unchanged drug)

Related Information

- Antimicrobial Drugs of Choice
- Cephalosporins by Generation
- Community-Acquired Pneumonia in Adults

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine

Index TermsCefuroxime Axetil; Cefuroxime Sodium

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International Brand NamesAltacef (PH); Anbacim (ID); Axetine (HK); Axurocef (TH); Bacticef (IN); Bearcef (ID, KP); Biofuroksym (PL); Bioracef (PL); Cefabiot (MX); Ceflour (HK); Ceftil (ID, KP); Cefudura (DE); Cefuhexal (DE); Cefuracet (MX); Cefurax (DE); Cefuro-Puren (DE); Cefurox-wolff (DE); Cefutil (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Celocid (ID); Ceroxim (IL, PL, ZA); Cervin (PH); Cethixim (ID); Cetoxil (MX); Cexim (HU); Curocef (AT, CN); Curoxime (PT); Deltrox (AR); Efurox (MY); Elobact (DE); Eroxmit (PH); Farmacef (TH); Froxime (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Furacam (EC); Furobioxin (MX); Furoxime (TH); Jectocef (PH); Kalcef (ID); Kefezy (PH); Kefurox (LU); Ketocef (HR); Laxinat (PH); Magnaspor (TH); Neuroxime (KP); Novador (MX); Novocef (HR); Oraxim (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Plixym (PL); Sharox-500 (ID); Tarsime (PL); Unoximed (PH); Vekfazolin (GR); Xorim (PL); Xorimax (PH); Xorufec (MX); Zegen (PH); Zinacef (AT, BE, BG, CH, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HN, HU, IE, IT, LU, NL, NO, NZ, PH, PL, PT, RU, SE, TR); Zinat (CH); Zinnat (AE, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CN, CR, CY, CZ, DE, DK, DO, EE, EG, ES, ET, FI, FR, GB, GH, GM, GN, GT, GY, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, OM, PA, PE, PH, PK, PL, PY, QA, SA, SC, SD, SL, SN, SR, SV, SY, TH, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Zocef (MY); Zonef (TH); Zoref (PT)

Celecoxib

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Celebrex® may be confused with Celexa®, cerebra, Cerebyx®

Pronunciation(se le KOKS ib)

U.S. Brand NamesCelebrex®

Canadian Brand NamesCelebrex®; GD-Celecoxib

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), COX-2 Selective

Use: Labeled IndicationsRelief of the signs and symptoms of osteoarthritis, ankylosing spondylitis, juvenile rheumatoid arthritis (JRA), and rheumatoid arthritis; management of acute pain; treatment of primary dysmenorrhea; to reduce the number of intestinal polyps in familial adenomatous polyposis (FAP)

Canadian note: Celecoxib is only indicated for relief of symptoms of rheumatoid arthritis, osteoarthritis, and relief of acute pain in adults

Use: DentalManagement of acute dental pain

Dosing: Adults**Note:** Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals.

Osteoarthritis: Oral: 200 mg/day as a single dose or in divided dose twice daily

Ankylosing spondylitis: Oral: 200 mg/day as a single dose or in divided doses twice daily; if no effect after 6 weeks, may increase to 400 mg/day. If no response following 6 weeks of treatment with 400 mg/day, consider discontinuation and alternative treatment.

Rheumatoid arthritis: Oral: 100-200 mg twice daily

Familial adenomatous polyposis: Oral: 400 mg twice daily

Acute pain or primary dysmenorrhea: Oral: Initial dose: 400 mg, followed by an additional 200 mg if needed on day 1; maintenance dose: 200 mg twice daily as needed

Dosing: ElderlyRefer to adult dosing. No specific adjustment based on age is recommended. However, the AUC in elderly patients may be increased by 50% as compared to younger subjects. Initiate at the lowest recommended dose in patients weighing <50 kg.

Dosing: Pediatric**Note:** Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals.

JRA: Oral: Children ≥2 years:

≥10 kg to ≤25 kg: 50 mg twice daily

>25 kg: 100 mg twice daily

Dosing: Renal ImpairmentNo specific dosage adjustment is recommended. Not recommended in patients with severe renal dysfunction.

Dosing: Hepatic ImpairmentReduced dosage is recommended (AUC may be increased by 40% to 180%). Decrease dose by 50% in patients with moderate hepatic impairment (Child-Pugh class B). Not recommended for use with severe impairment.

Administration: OralLower doses (200 mg twice daily) may be taken without regard to meals. Larger doses should be taken with food to improve absorption. Capsules may be swallowed whole or the entire contents emptied onto a teaspoon of cool or room temperature applesauce. The contents of the capsules sprinkled onto applesauce may be stored under refrigeration for up to 6 hours.

Dietary ConsiderationsLower doses (200 mg twice daily) may be taken without regard to meals. Larger doses should be taken with food to improve absorption.

StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to celecoxib, sulfonamides, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass surgery (CABG); pregnancy (3rd trimester)

Canadian labeling: Additional contraindications (not in U.S. labeling): Pregnancy (3rd trimester); women who are breast-feeding; severe, uncontrolled heart failure; active gastrointestinal ulcer (gastric, duodenal, peptic) or bleeding; inflammatory bowel disease; cerebrovascular bleeding; severe liver impairment or active hepatic disease; severe renal impairment (Cl_{cr} <30 mL/minute) or deteriorating renal disease; known hyperkalemia; use in children

Allergy Considerations

- Celecoxib Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure, anaphylactic reactions and angioedema may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. May cause sodium and fluid retention, use with caution in patients with heart failure, edema or hypertension. Long-term cardiovascular risk in children has not been evaluated. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular; alternate therapies should be considered for patients at high risk.
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.
- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of rash.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.
- Coronary artery bypass surgery: **[U.S. Boxed Warning]: Celecoxib is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass surgery (CABG).** Risk of MI and stroke may be increased with use following CABG surgery.
- Cytochrome P450 isoenzyme 2C9 deficiency: Use with caution in patients with known or suspected deficiency of cytochrome P450 isoenzyme 2C9; poor metabolizers may have higher plasma levels due to reduced metabolism.
- Familial adenomatous polyposis (FAP): When used for the treatment of FAP, routine monitoring and care should be continued.
- Hepatic impairment: Use with caution in patients with moderate hepatic impairment; dosage adjustment recommended. Not recommended for patients with severe hepatic impairment. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, hepatic necrosis, jaundice, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.
- Renal impairment: NSAID use may compromise existing renal function. Dose-dependent decreases in prostaglandin synthesis may result from NSAID use, causing a reduction in renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics and ACEI, and the elderly are at greater risk for renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Pediatrics: When used for JRA, celecoxib is not FDA-approved in children <2 years of age or in children <10 kg. Use caution with systemic-onset JRA (may be at risk for disseminated intravascular coagulation). Safety and efficacy have not been established for use in children for indications other than JRA.

Geriatric ConsiderationsThe elderly are at increased risk for adverse effects from NSAIDs. As many as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically; however, elderly patients may demonstrate these adverse effects at lower doses than younger adults. The elderly are also at increased risk of renal toxicity. Although celecoxib is associated with a decreased incidence of GI side effects, use the lowest recommended dose in patients weighing <50 kg.

Pregnancy Risk FactorC/D (3rd trimester)

Pregnancy ConsiderationsTeratogenic effects were observed in animal studies. Avoid use in the 3rd trimester of pregnancy, this drug may cause premature closure of the ductus arteriosus.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsBased on limited data, celecoxib has been found to be excreted in milk; a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Adverse Reactions

>10%:

Cardiovascular: Hypertension (≤13%)

Central nervous system: Headache (10% to 16%)

Gastrointestinal: Diarrhea (4% to 11%)

2% to 10%:

Cardiovascular: Peripheral edema (2%)

Central nervous system: Fever (≤9%), insomnia (2%), dizziness (1% to 2%)

Dermatologic: Skin rash (2%)

Gastrointestinal: Dyspepsia (9%), nausea (4% to 7%), gastroesophageal reflux (≤5%), abdominal pain (4% to 8%), vomiting (≤6%), flatulence (2%)

Neuromuscular & skeletal: Arthralgia (≤7%), back pain (3%)

Respiratory: Upper respiratory tract infection (8%), cough (≤7%), nasopharyngitis (≤6%), sinusitis (5%), dyspnea (≤3%), pharyngitis (2%), rhinitis (2%)

Miscellaneous: Accidental injury (3%)

0.1% to 2%:

Cardiovascular: Angina, aortic valve incompetence, chest pain, coronary artery disorder, DVT, edema, facial edema, hypertension (aggravated), MI, palpitation, sinus bradycardia, tachycardia, ventricular hypertrophy

Central nervous system: Anxiety, cerebral infarction, depression, fatigue, hypoesthesia, migraine, nervousness, pain, somnolence, vertigo

Dermatologic: Alopecia, bruising, cellulitis, dermatitis, dry skin, nail disorder, photosensitivity, pruritus, rash (erythematous), rash (maculopapular), urticaria

Endocrine & metabolic: Breast fibroadenosis, breast neoplasm, breast pain, diabetes mellitus, dysmenorrhea, hot flashes, hypercholesterolemia, hyperglycemia, hyper-/hypokalemia, hypernatremia, menstrual disturbances, ovarian cyst, testosterone decreased

Gastrointestinal: Anorexia, appetite increased, constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, hemorrhoids, hiatal hernia, melena, stomatitis, taste disturbance, tenesmus, tooth disorder, weight gain, xerostomia

Genitourinary: Cystitis, dysuria, incontinence, monilial vaginitis, prostate disorder, urinary frequency, urinary tract infection, vaginal bleeding, vaginitis

Hematologic: Anemia, thrombocytopenia

Hepatic: Alkaline phosphatase increased, transaminases increased

Neuromuscular & skeletal: Arthrosis, bone disorder, CPK increased, fracture, leg cramps, myalgia, neck stiffness, neuralgia, neuropathy, paresthesia, hypertonia, synovitis, tendon rupture, tendonitis, weakness

Ocular: Blurred vision, cataract, conjunctival hemorrhage, conjunctivitis, eye pain, glaucoma, vitreous floaters

Otic: Deafness, earache, labyrinthitis, otitis media, tinnitus

Renal: Albuminuria, BUN increased, creatinine increased, hematuria, nonprotein nitrogen increased, renal calculi

Respiratory: Bronchitis, bronchospasm, epistaxis, laryngitis, pneumonia

Miscellaneous: Allergic reactions, allergy aggravated, diaphoresis, flu-like syndrome, herpes infection, infection (bacterial, fungal, viral), moniliasis

<0.1% (Limited to important or life-threatening): Acute renal failure, ataxia, cerebrovascular accident, CHF, cholelithiasis, colitis, esophageal perforation, gangrene, gastrointestinal bleeding, ileus, intestinal obstruction, intestinal perforation, pancreatitis, pulmonary embolism, sepsis, sudden death, suicide, syncope, thrombophlebitis, ventricular fibrillation

Postmarketing and/or case reports: Agranulocytosis, anaphylactoid reactions, angioedema, aplastic anemia, aseptic meningitis, erythema multiforme, exfoliative dermatitis, hepatic failure, hepatic necrosis, hepatitis (including fulminant), hypoglycemia, hyponatremia, interstitial nephritis, intracranial hemorrhage, jaundice, leukopenia, pancytopenia, renal papillary necrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis

Metabolism/Transport Effects **Substrate** of CYP2C9 (major), 3A4 (minor); **Inhibits** CYP2C8 (moderate), 2D6 (weak)

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk D: Consider therapy modification*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (COX-2 Inhibitor) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (increased GI irritation).

Food: Peak concentrations are delayed and AUC is increased by 10% to 20% when taken with a high-fat meal.

Herb/Nutraceutical: Avoid concomitant use with herbs possessing anticoagulation/antiplatelet properties, including alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnuts, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow.

Monitoring ParametersCBC; blood chemistry profile; occult blood loss and periodic liver function tests; monitor renal function (urine output, serum BUN and creatinine; monitor response (pain, range of motion, grip strength, mobility, ADL function), inflammation; observe for weight gain, edema; observe for bleeding, bruising; evaluate gastrointestinal effects (abdominal pain, bleeding, dyspepsia); blood pressure

FAP: Continue routine endoscopic exams

JRA: Monitor for development of abnormal coagulation tests with systemic onset JRA

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess effectiveness and interactions of other medications patient may be taking (ie, monitor patients taking lithium closely). Assess allergy history (aspirin, NSAIDs, salicylates). Monitor blood pressure at the beginning of therapy and periodically during use. Monitor effectiveness of therapy. Assess knowledge/teach patient appropriate use, possible side effects/interventions, and adverse symptoms to report.
Monitoring: Lab TestsCBC, blood chemistry profile, periodic liver function tests; renal function (urine output, serum BUN and creatinine)

FAP: Continue routine endoscopic exams

JRA: Monitor for development of abnormal coagulation tests with systemic onset JRA

Patient EducationDo not take more than recommended dose. May be taken with food to reduce GI upset. Do not take with antacids. Avoid alcohol, aspirin, and OTC medication unless approved by prescriber. You may experience dizziness, confusion, or blurred vision (avoid driving or engaging in tasks requiring alertness until response to drug is known); anorexia, nausea, vomiting, taste disturbance, gastric distress (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). GI bleeding, ulceration, or perforation can occur with or without pain. It is unclear whether celecoxib has rates of these events which are similar to nonselective NSAIDs. Stop taking medication and report immediately stomach pain or cramping; unusual bleeding or bruising (blood in vomitus, stool, or urine); chest pain; shortness of breath; weakness of extremities; or slurring of speech. Report persistent insomnia; skin rash; unusual fatigue or flu-like symptoms; jaundice; muscle pain, tremors, or weakness; sudden weight gain or edema; changes in hearing (ringing in ears) or vision; changes in urination pattern; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform your prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Celebrex®: 50 mg, 100 mg, 200 mg, 400 mg

Generic AvailableNo
ManufacturerPfizer, Inc
Pricing: U.S. (www.drugstore.com)

Capsules (Celebrex)

100 mg (30): $75.99

200 mg (30): $120.91

400 mg (30): $176.00

Mechanism of Action Inhibits prostaglandin synthesis by decreasing the activity of the enzyme, cyclooxygenase-2 (COX-2), which results in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties
Pharmacodynamics/Kinetics

Distribution: V_d (apparent): ~400 L

Protein binding: ~97% primarily to albumin

Metabolism: Hepatic via CYP2C9; forms inactive metabolites

Bioavailability: Absolute: Unknown

Half-life elimination: ~11 hours (fasted)

Time to peak: ~3 hours

Excretion: Feces (57% as metabolites, <3% as unchanged drug); urine (27% as metabolites, <3% as unchanged drug)

Related Information

- Nonsteroidal Anti-inflammatory Agents

Pharmacotherapy PearlsCelecoxib does not inhibit cyclooxygenase-1 (COX-1) at therapeutic concentrations. Celecoxib does not affect platelet aggregation.
Dental Health Professional ConsiderationsThe Food and Drug Administration (FDA) has announced product labeling changes for all NSAIDs, including COX-2 selective and over-the-counter (OTC) medications. These changes are the result of the Arthritis and Drug Safety and Risk Management Advisory Committee meeting held in February, 2005.

The FDA has asked that all labels be revised to include information related to the potential for increased risk of cardiovascular (CV) events and gastrointestinal (GI) bleeding associated with their use. In addition, prescription nonselective NSAIDs are being asked to add a contraindication for use in patients who have recently undergone coronary artery bypass graft (CABG) surgery and a boxed warning concerning the CV and GI events. Medication guides will be required for all prescription products. Manufacturers of OTC products are being asked to include a warning about potential skin reactions, which is already included in prescription labeling. The FDA will be working with manufacturers to conduct long-term clinical trials to assess the safety of these agents.

Pfizer, Inc, the manufacturer of celecoxib (Celebrex®) has reported an increased risk of cardiovascular events in one clinical trial during an interim analysis. The increased risk was observed in a trial evaluating celecoxib in patients at risk of colon cancer, prompting the National

Cancer Institute to end the study. Other similar clinical studies (which were subjected to analysis by data monitoring committees) are continuing, since an interim analysis of these trials did not reveal an increased risk of cardiovascular events. Further analysis of risk factors related to cardiovascular risk appear warranted. A notice posted by the Food and Drug Administration (FDA) states that the agency "will obtain all available data on these and other ongoing Celebrex® trials as soon as possible and will determine the appropriate regulatory action."

The FDA further notes that these new findings for celecoxib are similar to results with other drugs in this class. Increased cardiovascular risk noted in a study of rofecoxib (Vioxx®) led to a voluntary withdrawal of the product by Merck. In addition, another drug in this class, valdecoxib (Bextra®) demonstrated an increased risk for cardiovascular events in patients following cardiovascular surgery. Valdecoxib (Bextra®) was withdrawn from the market in May 2005.

In their statement, the FDA encourages physicians to consider this developing information in risk-to-benefit evaluations as they consider the use of celecoxib in individual patients. In addition, the FDA advises an evaluation of alternative therapy. If physicians determine that continued use is appropriate for individual patients, the lowest effective dose of celecoxib should be prescribed. Pfizer has not announced a decision to withdraw celecoxib from the market as of December 20, 2004.

The association between selective COX-2 inhibitors and increased cardiovascular risk has been noted previously and prompted by publication of a meta-analysis entitled "Risk of Cardiovascular Events Associated With Selective COX-2 Inhibitors" in the August 22, 2001, edition of the *Journal of the American Medical Association (JAMA)*. The researchers reanalyzed four previously published trials, assessing cardiovascular events in patients receiving either celecoxib or rofecoxib. They found an association between the use of COX-2 inhibitors and cardiovascular events (including MI and ischemic stroke). The annualized MI rate was found to be significantly higher in patients receiving celecoxib or rofecoxib than in the control (placebo) group from a recent meta-analysis of primary prevention trials. Although cause and effect cannot be established (these trials were originally designed to assess GI effects, not cardiovascular ones), the authors believe the available data raise a cautionary flag concerning the risk of cardiovascular events with the use of COX-2 inhibitors. The manufacturers of these agents, as well as other healthcare professionals, dispute the methods and validity of the study's conclusions. To date, the FDA has not required any change in the labeling of these agents. Further study is required before any potential risk may be defined.

Cross-reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in aspirin-sensitive patients. The manufacturer suggests that celecoxib should not be administered to patients with this type of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

The manufacturer studied the effect of celecoxib on the anticoagulant effect of warfarin and found no alteration of anticoagulant effect, as determined by prothrombin time, in patients taking 2 mg to 5 mg daily. However, the manufacturer has issued a caution when using celecoxib with warfarin since those patients are at increased risk of bleeding complications.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, abnormal taste, xerostomia (normal salivary flow resumes upon discontinuation), and tooth disorder. Nonselective NSAIDs are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. According to the manufacturer, celecoxib, at single doses up to 800 mg and multiple doses of 600 mg twice daily, had no effect on platelet aggregation or bleeding time. Comparative NSAIDs (naproxen 500 mg twice daily, ibuprofen 800 mg three times daily, or diclofenac 75 mg twice daily) significantly reduced platelet aggregation and prolonged the bleeding times. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness and insomnia; may rarely, cause anxiety, depression, nervousness, or somnolence

Mental Health: Effects on Psychiatric TreatmentEffects of benzodiazepines and antidepressants may be altered. Lithium concentrations may be increased by celecoxib via decreased renal lithium clearance; dose adjustment may be needed.

Cardiovascular ConsiderationsPfizer, Inc, the manufacturer of Celebrex® (celecoxib) has reported an increased risk of cardiovascular events in one clinical trial during an interim analysis. The increased risk was observed in a trial evaluating celecoxib in patients at risk of colon cancer, prompting the National Cancer Institute to end the study. Further analysis of risk factors related to cardiovascular risk appears warranted.

The FDA further notes that these new findings for celecoxib are similar to results with other drugs in this class. Increased cardiovascular risk noted in a study of rofecoxib (Vioxx®) led to a voluntary withdrawal of the product by Merck. In addition, another drug in this class, valdecoxib (Bextra®) demonstrated an increased risk for cardiovascular events in patients following cardiovascular surgery.

Physicians are encouraged to carefully evaluate individual cardiovascular risk profiles prior to prescribing COX-2 inhibitors. COX-2 inhibitors may be appropriate for patients who do not tolerate nonselective NSAIDs, those who are not doing well on NSAIDs, or those with a history of gastrointestinal bleeding. COX-2 inhibitors may not be appropriate in patients with cardiovascular disease or in patients with significant risk factors for cardiovascular disease. If physicians determine that continued use is appropriate for individual patients, the lowest effective dose of celecoxib should be prescribed for the shortest duration of treatment based upon goals.

Medication guides will be required for all prescription products.

Anesthesia and Critical Care Concerns/Other ConsiderationsCelecoxib does not inhibit platelets or prolong bleeding time.

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Steinbach G, Lynch PM, Phillips RK, et al, “The Effect of Celecoxib, a Cyclooxygenase-2 Inhibitor, in Familial Adenomatous Polyposis,” *N Engl J Med*, 2000, 342(26):1946-52.[PubMed 10874062]

International Brand NamesCaditar (PE); Celbexx (PK); Celcox (IL); Celcoxx (PH); Celebra (BR, CN, CR, FI, GT, HN, IL, NI, NO, PA, SE, SV, UY); Celebrex (AE, AR, AU, BD, BE, BF, BG, BH, BJ, CH, CI, CL, CO, CY, CZ, DE, DK, EC, EE, EG, ES, ET, FR, GB, GH, GM, GN, HK, HN, ID, IL, IN, IQ, IR, IT, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, OM, PE, PH, PK, PL, PT, QA, SA, SC, SD, SG, SL, SN, SY, TH, TN, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Celecox (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Celexib (PH); Celib (IN); Coxel (AR); Dolocox (EC); Eliflam (PY); Flamar (PH); Lexfin (CO); Onsenal (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Cellulose (Oxidized Regenerated)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Surgicel® may be confused with Serentil®

Pronunciation(SEL yoo lose, OKS i dyzed re JEN er aye ted)
U.S. Brand NamesSurgicel®; Surgicel® Fibrillar; Surgicel® NuKnit
Pharmacologic CategoryHemostatic Agent
Use: Labeled IndicationsHemostatic; temporary packing for the control of capillary, venous, or small arterial hemorrhage
Use: DentalTo control bleeding created during a dental procedure
Dosing: AdultsBleeding: Topical: Minimal amounts of the fabric strip are laid on the bleeding site or held firmly against the tissues until hemostasis occurs; remove excess material
Dosing: ElderlyRefer to adult dosing.
StorageStore at controlled room temperature. Inactivated by autoclaving; do not resterilize. Do not use if package is damaged. Do not reuse after opening.
ContraindicationsHypersensitivity to any component of the formulation; implantation into bone defects; hemorrhage from large arteries; nonhemorrhagic oozing; use as an adhesion product
Warnings/Precautions

Concerns related to adverse effects:

- Pain/numbness/paralysis: Pain, numbness, or paralysis have been reported if used near a bony or neural space and left inside patient; use minimum amount necessary to achieve hemostasis.

Concurrent drug therapy issues:

- Thrombin: Its hemostatic effect is not enhanced by the addition of thrombin.

Other warnings/precautions:

- Appropriate use: The material should not be moistened before insertion since the hemostatic effect is greater when applied dry. The material should not be impregnated with anti-infective agents. Remove as much of agent as possible after hemostasis is achieved. Do not leave in a contaminated or infected space. Always remove completely following hemostasis if applied in proximity to foramina in bone, areas of bony confine, the spinal cord or optic nerve and chasm; product may swell and exert unwanted pressure.

Pregnancy Risk FactorNo data reported
Adverse ReactionsFrequency not defined.

Central nervous system: Headache

Respiratory: Nasal burning or stinging, sneezing (rhinological procedures)

Miscellaneous: Encapsulation of fluid, foreign body reactions (with or without) infection

Postmarketing and/or case reports: Numbness, pain, paralysis

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Fabric, fibrous (Surgicel® Fibrillar):

1” x 2” (10s)

2” x 4” (10s)

4” x 4” (10s)

Fabric, knitted (Surgicel® NuKnit):

1” x 1” (24s)

1” x 3$^{1}/_{2}$” (10s)

3” x 4” (24s)

6” x 9” (10s)

Fabric, sheer weave (Surgicel®):

$^{1}/_{2}$” x 2” (24s)

2” x 3” (24s)

2” x 14” (24s)

4” x 8” (24s)

Generic AvailableNo

Mechanism of ActionCellulose, oxidized regenerated is saturated with blood at the bleeding site and swells into a brownish or black gelatinous mass which aids in the formation of a clot. When used in small amounts, it is absorbed from the sites of implantation with little or no tissue reaction. In addition to providing hemostasis, oxidized regenerated cellulose also has been shown *in vitro* to have bactericidal properties.

Pharmacodynamics/KineticsAbsorption: 7-14 days

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAbsorbable Cotton; Oxidized Regenerated Cellulose

Cephalexin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cephalexin may be confused with cefaclor, ceFAZolin, cephalothin, ciprofloxacin

Pronunciation(sef a LEKS in)
U.S. Brand NamesKeflex®
Canadian Brand NamesApo-Cephalex®; Keftab®; Novo-Lexin; Nu-Cephalex
Pharmacologic CategoryAntibiotic, Cephalosporin (First Generation)
Use: Labeled IndicationsTreatment of susceptible bacterial infections including respiratory tract infections, otitis media, skin and skin structure infections, bone infections, and genitourinary tract infections, including acute prostatitis; alternative therapy for acute infective endocarditis prophylaxis
Use: DentalProphylaxis in total joint replacement patients undergoing dental procedures which produce bacteremia; alternative oral antibiotic for prevention of infective endocarditis in individuals allergic to penicillins or ampicillin

Note: Individuals allergic to amoxicillin (penicillins) may receive cephalexin provided they have not had an immediate, local, or systemic IgE-mediated anaphylactic allergic reaction to penicillin.

Dosing: Adults

Dosing range: Oral: 250-1000 mg every 6 hours (maximum: 4 g/day)

Cellulitis and mastitis: Oral 500 mg every 6 hours

Furunculosis/skin abscess: Oral: 250 mg 4 times/day

Prophylaxis against infective endocarditis (dental, oral, or respiratory tract procedures): Oral: 2 g 30-60 minutes prior to procedure. **Note:** American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur.

Prophylaxis in total joint replacement patients undergoing dental procedures which produce bacteremia: Oral: 2 g 1 hour prior to procedure

Streptococcal pharyngitis, skin and skin structure infections: Oral: 500 mg every 12 hours

Uncomplicated cystitis: Oral: 500 mg every 12 hours for 7-14 days

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Usual dose: Oral: Children >1 year: Dosing range: 25-100 mg/kg/day in divided doses every 6-8 hours (maximum: 4 g/day)

Furunculosis: Oral: 25-50 mg/kg/day in 4 divided doses

Impetigo: Oral: 25 mg/kg/day in 4 divided doses

Otitis media: 75-100 mg/kg/day in 4 divided doses

Prophylaxis against infective endocarditis (dental, oral, or respiratory tract procedures):

Children >1-15 years: 50 mg/kg 30-60 minutes prior to procedure (maximum: 2 g). **Note:** American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur.

Children >15 years: Refer to adult dosing.

Severe infections: Oral: 50-100 mg/kg/day in divided doses every 6-8 hours

Skin abscess: Oral: 50 mg/kg/day in 4 divided doses (maximum: 4 g)

Streptococcal pharyngitis, skin and skin structure infections: 25-50 mg/kg/day divided every 12 hours

Uncomplicated cystitis: Children >15 years: Refer to adult dosing.

Dosing: Renal ImpairmentAdults:
Cl_{cr} 10-50 mL/minute: 500 mg every 8-12 hours

Cl_{cr} <10: 250-500 mg every 12-24 hours

Hemodialysis: 250 mg every 12-24 hours; moderately dialyzable (20% to 50%); give dose after dialysis session

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralTake without regard to food. If GI distress, take with food. Give around-the-clock to promote less variation in peak and trough serum levels.

Dietary ConsiderationsTake without regard to food. If GI distress, take with food. Panixine DisperDose™ contains phenylalanine 2.8 mg/cephalexin 125 mg.

Storage

Capsule: Store at 15°C to 30°C (59°F to 86°F).

Powder for oral suspension: Refrigerate suspension after reconstitution; discard after 14 days.

ReconstitutionTablets for oral suspension (Panixine DisperDose™): Tablet must be dissolved in ~10 mL water prior to administration.

ContraindicationsHypersensitivity to cephalexin, any component of the formulation, or other cephalosporins

Allergy Considerations

- Cephalosporin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Elevated INR: May be associated with increased INR, especially in nutritionally-deficient patients, prolonged treatment, hepatic or renal disease.
- Penicillin allergy: Use with caution in patients with a history of penicillin allergy, especially IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria).
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; modify dosage in severe impairment.

Geriatric ConsiderationsAdjust dose for renal function.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events were not observed in animal reproduction studies; therefore, cephalexin is classified as pregnancy category B. Cephalexin crosses the placenta and produces therapeutic concentrations in the fetal circulation and amniotic fluid. An increased risk of teratogenic effects has not been observed following maternal use of cephalexin; however, adequate and well-controlled studies have not been completed in pregnant women. Peak concentrations in pregnant patients are similar to those in nonpregnant patients. Prolonged labor may decrease oral absorption.

LactationEnters breast milk (small amounts)/use caution

Breast-Feeding ConsiderationsSmall amounts of cephalexin are excreted in breast milk. The manufacturer recommends that caution be exercised when administering cephalexin to nursing women. Maximum milk concentration occurs ~4 hours after a single oral dose and gradually disappears by 8 hours after administration. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Cephalexin in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Agitation, confusion, dizziness, fatigue, hallucinations, headache

Dermatologic: Angioedema, erythema multiforme (rare), rash, Stevens-Johnson syndrome (rare), toxic epidermal necrolysis (rare), urticaria

Gastrointestinal: Abdominal pain, diarrhea, dyspepsia, gastritis, nausea (rare), pseudomembranous colitis, vomiting (rare)

Genitourinary: Genital pruritus, genital moniliasis, vaginitis, vaginal discharge

Hematologic: Eosinophilia, hemolytic anemia, neutropenia, thrombocytopenia

Hepatic: ALT increased, AST increased, cholestatic jaundice (rare), transient hepatitis (rare)

Neuromuscular & skeletal: Arthralgia, arthritis, joint disorder

Renal: Interstitial nephritis (rare)

Miscellaneous: Allergic reactions, anaphylaxis

Drug Interactions

MetFORMIN: Cephalexin may increase the serum concentration of MetFORMIN. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Cephalosporins. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Peak antibiotic serum concentration is lowered and delayed, but total drug absorbed is not affected. Cephalexin serum levels may be decreased if taken with food.

Test InteractionsPositive direct Coombs', false-positive urinary glucose test using cupric sulfate (Benedict's solution, Clinitest®, Fehling's solution), false-positive serum or urine creatinine with Jaffé reaction, false-positive urinary proteins and steroids

Monitoring ParametersWith prolonged therapy monitor renal, hepatic, and hematologic function periodically; monitor for signs of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, nephrotoxicity). Assess results of laboratory tests, therapeutic response, and adverse reactions (see Adverse Reactions). Advise patients with diabetes about use of Clinitest® (may cause false-positive test). Teach patient possible side effects/appropriate interventions and adverse symptoms to report (eg, opportunistic infection, hypersensitivity reaction).

Monitoring: Lab TestsRenal, hepatic, and hematologic function periodically with prolonged therapy; perform culture and sensitivity studies prior to initiating drug therapy.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, at regular intervals around-the-clock (with or without food). Take complete prescription even if feeling better. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause false test results with Clinitest®; use of another type of glucose testing is preferable. May cause diarrhea (yogurt, boiled milk, or buttermilk may help). Report rash; breathing or swallowing difficulty; persistent diarrhea, nausea, vomiting, or abdominal pain; changes in urinary pattern or pain on urination; opportunistic infection (eg, vaginal itching or drainage, sores in mouth, blood in stool or urine, unusual fever or chills); CNS changes (eg, irritability, agitation, nervousness, insomnia, hallucinations); or other adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 250 mg, 500 mg

Keflex®: 250 mg, 500 mg, 750 mg

Powder for oral suspension: 125 mg/5 mL (100 mL, 200 mL); 250 mg/5 mL (100 mL, 200 mL)

Keflex®: 125 mg/5 mL (100 mL, 200 mL); 250 mg/5 mL (100 mL, 200 mL)

Tablet: 250 mg, 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Cephalexin)

250 mg (30): $13.99

500 mg (30): $12.99

Capsules (Keflex)

250 mg (30): $65.99

750 mg (50): $148.11

Suspension (reconstituted) (Cephalexin)

125 mg/5 mL (100): $7.99

125 mg/5 mL (200): $10.98

250 mg/5 mL (100): $9.99

250 mg/5 mL (200): $19.00

Tablets (Cephalexin)

250 mg (30): $19.99

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: Delayed in young children

Distribution: Widely into most body tissues and fluids, including gallbladder, liver, kidneys, bone, sputum, bile, and pleural and synovial fluids; CSF penetration is poor

Protein binding: 6% to 15%

Half-life elimination: Adults: 0.5-1.2 hours; prolonged with renal impairment

Time to peak, serum: ~1 hour

Excretion: Urine (80% to 100% as unchanged drug) within 8 hours

Related Information

- Cephalosporins by Generation
- Prevention of Infective Endocarditis

Dental Health Professional ConsiderationsCephalexin is effective against anaerobic bacteria, but the sensitivity of alpha-hemolytic *Streptococcus* vary; approximately 10% of strains are resistant. Nearly 70% are intermediately sensitive. Patients allergic to penicillins can use a cephalosporin; the incidence of cross-reactivity between penicillins and cephalosporins is 1% when the allergic reaction to penicillin is delayed. If the patient has a history of immediate reaction to penicillin, the incidence of cross-reactivity is 20%; cephalosporins are contraindicated in these patients.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness; case reports of euphoria, delusion, illusions, and depersonalization with cephalosporins

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine

Cardiovascular ConsiderationsMay be used for prevention of bacterial endocarditis.

Index TermsCephalexin Monohydrate

References

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Smith GH, “Oral Cephalosporins in Perspective,” *DICP*, 1990, 24(1):45-51.[PubMed 2405586]

Wilson W, Taubert KA, Gewitz M, et al, “Prevention of Infective Endocarditis. Guidelines From the American Heart Association. A Guideline From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group,” *Circulation*, 2007, 115. Available at http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.183095v1; last accessed July 26, 2007.[PubMed 17446442]

International Brand NamesAirex (PH); Alexin (IN); Bandax (PH); Bloflex (PH); Cefabiotic (ID); Cefacin-M (HK); Cefadal (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Cefadin (EC); Cefadyl (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Cefalin (ID, PH); Cefalver (MX); Cefaxon (BR); Ceforal (IL); Cefovit (IL); Celexin (TH); Cepastar (PH); Cepexin (AT); Cephalen (SG); Cephalex (DE); Cephalexin (PL); Cephalexin-ratiopharm (PL); Cephalexyl (TH); Cephanmycin (MY, SG); Cephia (TH); Ceporex (AE, AU, BB, BH, BM, BS, BZ, CY, EG, GB, GY, IL, IQ, IR, IT, JM, JO, KW, LB, LY, MX, NL, OM, PE, PH, PT, QA, SA, SR, SY, TT, YE, ZA); Ceporex Forte (PT); Ceporexin (AR); Ceporexine (FR); Ceprax (CO); Cerexin (ZA); CFA (PH); Difagen (PH); Erocetin (PY, UY); Farmalex (TH); Felexin (HK, MY); Fexin (ZA); Ialex (AU); Ibilex (AU, TH); Inphalex (ID); Kefacin (AE, BH, CY, EG, IL, IQ, IR, JO, KP, KW, LB, LY, OM, QA, SA, SY, YE); Kefalex (FI); Kefaxin (IE); Keflex (AT, AU, BB, BF, BJ, BM, BS, BZ, CI, CO, DK, EC, EE, ET, GB, GH, GM, GN, GR, GY, JM, KE, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, PE, PH, PK, PT, SC, SD, SE, SL, SN, SR, TH, TN, TT, TZ, UG, ZA, ZM, ZW); Kefloridina (ES); Keforal (AR, BE, FR, IT, NL, VE); LC-Lexin (PH); Lenocef (ZA); Lexin (PE); Madlexin (ID); Medolexin (MY); Nafacil-S (MX); Neokef (MY); Nufex (IN); Oracef (CZ); Oriphex (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Ospexin (AE, AT, BG, BH, CY, CZ, EG, HK, ID, IL, IQ, IR, JO, KW, LB, LY, MY, OM, QA, SA, SY, YE); Paferxin (MX); Palitrex (ID); Pectril (PH); Pharmexin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Pyassan (HN); Rancef (AU); Relaxin (PH); Respinal (PH); Sanaxin (AT); Sefasin (TH); Sepexin (IN); Septilisin (AR); Servicef (MX); Servispor (MY); Sialexin (TH); Sofilex (HK, MY, SG); Sorlex (PH); Sporahexal (AU); Sporicef (TH); Sporidex (IN, PH); Sporidin (TH); Sporidin AF (TH); Tepaxin (ID); Uphalexin (MY, SG); Voxxim (PH); Zeplex (TH); Zucoflaxin (PH)

CEPP(B)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's

Regimen

Cyclophosphamide: I.V.: 600-650 mg/m^2/day days 1 and 8

[total dose/cycle = 1200-1300 mg/m^2]

Etoposide: I.V.: 70-85 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 210-255 mg/m^2]

Procarbazine: Oral: 60 mg/m^2/day days 1 to 10

[total dose/cycle = 600 mg/m^2]

Prednisone: Oral: 60 mg/m^2/day days 1 to 10

[total dose/cycle = 600 mg/m^2]

Bleomycin: I.V.: 15 units/m^2/day days 1 and 15 (Bleomycin is sometimes omitted)

[total dose/cycle = 30 units/m^2]

Repeat cycle every 28 days

References

Chao NJ, Rosenberg SA, and Horning SJ, âCEPP(B): An Effective and Well-Tolerated Regimen in Poor-Risk, Aggressive Non-Hodgkin's Lymphoma,â *Blood*, 1990, 76(7):1293-8.[PubMed 2207307]

Certolizumab Pegol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Tumor Necrosis Factor: Alpha Blockers Associated with Unrecognized Invasive Fungal Infections - September 4, 2008

The U.S. Food and Drug Administration (FDA) is alerting healthcare professionals of an increased risk for opportunistic fungal infections in patients treated with antitumor necrosis factor (anti-TNF) agents adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), and infliximab (Remicade®). The FDA has received reports of pulmonary and disseminated cases of histoplasmosis, coccidioidomycosis, blastomycosis, and other fungal infections associated with use of these agents. In some cases, the symptoms of fungal infection (eg, fever, cough, malaise, dyspnea, fatigue) were unrecognized and precluded prompt antifungal treatment, resulting in 12 deaths. In response, the FDA is requiring manufacturers of these agents to strengthen the boxed warning statement in the labeling to further emphasize the risk of invasive fungal infection. Patients should be monitored closely for signs and symptoms suggestive of fungal infection, evidence of which should result in prompt discontinuation of the medication and appropriate diagnostic evaluation. Symptomatic patients should be questioned about their residence in or travel from areas of endemic mycoses, which should prompt consideration of empiric antifungal therapy.

Additional information can be found at: http://www.fda.gov/medwatch/safety/2008/safety08.htm#TNF2

Tumor Necrosis Factor (TNF) Blockers and Malignancy Risk - June 5, 2008

The U.S. Food and Drug Administration (FDA) issued an Early Communication to healthcare professionals regarding a possible association between TNF blocker (adalimumab, certolizumb pegol, etanercept, and infliximab) use and the development of malignancies in children and young adults. Over the last 10 years, the FDA has received ~30 reports of cancer in children or young adults who had been treated with TNF blockers prior to the age of 18 years. TNF blockers were given for the treatment of Juvenile Idiopathic Arthritis (JIA [formerly termed Juvenile Rheumatoid Arthritis]), Crohn’s disease, or other indications in combination with other immunosuppressive medications (eg, azathioprine, 6-mercaptopurine or methotrexate). Approximately half of the reported cancers were lymphomas (Hodgkin’s and non-Hodgkin’s), which are cancers involving the cells of the immune system.

TNF blockers work by suppressing the immune system. The prescribing information for each TNF blocker contains warnings regarding the possible association of malignancy development with use. Malignancies may not be detected in short-term studies; long-term studies are necessary to identify the impact of TNF blocker therapy on malignancy development. The manufacturers of the four TNF blockers available in the U.S. are being asked by the FDA to provide information regarding all cases of cancer reported in children taking TNF blockers. The FDA is expected to report its findings in approximately 6 months, after completing a safety review and evaluation.

Additional information is available at http://www.fda.gov/medwatch/safety/2008/safety08.htm#TNF

Pronunciation(cer to LIZ u mab PEG ol)

U.S. Brand NamesCimzia®

Pharmacologic CategoryGastrointestinal Agent, Miscellaneous; Tumor Necrosis Factor (TNF) Blocking Agent

Use: Labeled IndicationsTreatment of moderately- to severely-active Crohn’s disease in patients who have inadequate response to conventional therapy

Dosing: Adults**Note:** Each 400 mg dose should be administered as 2 injections of 200 mg each

Crohn’s disease: SubQ: Initial: 400 mg, repeat dose 2 and 4 weeks after initial dose; Maintenance: 400 mg every 4 weeks

Dosing: ElderlyRefer to adult dosing.

Administration: OtherSubQ: Bring to room temperature prior to administration. Total dose requires 2 vials; after reconstitution, draw each vial into separate syringes, administer each syringe subcutaneously (using provided 23-gauge needle) to separate sites on abdomen or thigh.

StoragePrior to reconstitution, store intact vials under refrigeration at 2°C to 8°C (36°F to 46°F). Reconstituted vials may be retained at room temperature for ≤2 hours or refrigerated for ≤24 hours prior to administration. Do not freeze. Bring to room temperature prior to administration.

ReconstitutionAllow to reach room temperature prior to reconstitution. Using aseptic technique, reconstitute each vial with 1 mL sterile water for injection (provided) to a concentration of ~200 mg/mL; the manufacturer recommends using a 20-gauge needle (provided). Gently swirl to facilitate wetting of powder; do not shake. Allow vials to set undisturbed (may take up to 30 minutes) until fully reconstituted. Reconstituted solutions should not contain visible particles or gels in the solution.

RestrictionsAn FDA-approved medication guide is available, distribute to each patient to whom this medication is dispensed.

ContraindicationsThere are no contraindications listed within the manufacturer’s labeling.

Warnings/Precautions

Boxed warnings:

- Infection: See “Concerns related to adverse effects” below.
- Tuberculosis evaluation: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Autoimmune disorder: Autoantibody formation may develop; rarely resulting in autoimmune disorder, including lupus-like syndrome; monitor and discontinue if symptoms develop.
- Demyelinating CNS disease: Rare cases of optic neuritis, seizure, peripheral neuropathy, and demyelinating disease (new onset or exacerbation) have been reported. Use with caution in patients with pre-existing or recent-onset CNS demyelinating disorders.
- Hematologic effects: Rare cases of pancytopenia and other significant cytopenias, including aplastic anemia, have been reported with TNF-blocking agents. Leukopenia and thrombocytopenia have occurred with certolizumab. Consider discontinuing therapy with significant hematologic abnormalities. Use with caution in patients with underlying hematologic disorders.
- Hepatitis B: Rare and sometimes fatal reactivation of hepatitis B virus (HBV) has occurred in chronic virus carriers. Evaluate prior to initiation, during, and for several months after treatment. Evaluate patients at risk for HBV infection prior to therapy to determine HBV status. Use with extreme caution in patients identified as HBV carriers, use has not been evaluated in this population.
- Hypersensitivity: Hypersensitivity reactions, including angioedema, dyspnea, rash, serum sickness and urticaria have been reported (rarely) with treatment. Discontinue further therapy if hypersensitivity occurs. Use with caution in patients who have experienced hypersensitivity with other TNF blockers.
- Immunogenicity: A small number of patients (8%) develop antibodies to certolizumab during therapy. Antibody-positive patients may have an increased inicidence of adverse events (including injection site pain/erythema, abdominal pain, and erythema nodosom).
- Infections: **[U.S. Boxed Warning]: Serious infections (including tuberculosis, invasive fungal and other opportunistic infections), some with fatalities, have been reported in patients receiving TNF-blocking agents, including certolizumab.** Cases of unrecognized invasive fungal infections (eg, histoplasmosis, blastomycosis, coccidioidomycosis) have also been reported with anti-TNF agent use. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy. Caution should be exercised when considering the use in patients with a history of chronic or recurrent infection, concomitant immunosuppressive therapy, predisposition to infection (eg, diabetes or residence/travel from areas of endemic mycoses). Do not give to patients with an active chronic or localized infection. Patients who develop a new infection while undergoing treatment should be monitored closely. If a patient develops a serious infection, therapy should be discontinued.
- Malignancy: Use of TNF blockers may affect defenses against malignancies; impact on the development and course of malignancies is not fully defined. Chronic immunosuppressant therapy use may be a predisposing factor for malignancy development.
- Tuberculosis evaluation: Tuberculosis has been reported with certolizumab. **[U.S. Boxed Warnings]: Patients should be evaluated for tuberculosis risk factors and latent tuberculosis infection (with a tuberculin skin test) prior to therapy. Treatment of latent tuberculosis should be initiated before use. Patients with initial negative tuberculin skin tests should receive continued monitoring for tuberculosis throughout treatment;** active tuberculosis has developed in this population during treatment. Use with caution in patients who have resided in regions where tuberculosis is endemic. If appropriate, antituberculosis therapy should be considered (prior to certolizumab treatment) in patients with several or with highly significant risk factors for tuberculosis development.

Disease-related concerns:

- Heart failure: Use with caution in heart failure patients; worsening heart failure and new-onset heart failure have been reported with TNF blockers; monitor closely.

Concurrent drug therapy issues:

- Anakinra: The manufacturer does not recommend concurrent use with anakinra due to the risk of serious infections.

Special populations:

- Elderly: Use with caution in the elderly, may be at higher risk for infections.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Immunizations: Patients should be brought up to date with all immunizations before initiating therapy; live vaccines should not be given concurrently. There is no data available concerning the effects of therapy on vaccination or secondary transmission of live vaccines in patients receiving therapy.

Geriatric ConsiderationsStudies to date have insufficient data to make conclusions for use in elderly. Anecdotal reports in clinical settings do not demonstrate any clinical difference between elderly and younger adults. Since elderly have a higher incidence of infection, use with caution and close monitoring.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Central nervous system: Headache (7% to 18%)

Gastrointestinal: Nausea (≤11%)

Respiratory: Upper respiratory infection (20%), nasopharyngitis (4% to 13%)

Miscellaneous: Infection (14% to 38%; serious: 3%)

1% to 10%:

Central nervous system: Dizziness (≤6%), fever (≤5%)

Gastrointestinal: Abdominal pain (≤6%), vomiting (5%)

Genitourinary: Urinary tract infection (≤8%)

Local: Injection site reactions (includes bleeding, burning, erythema, inflammation, pain, rash: ≤7%; incidence higher with placebo)

Neuromuscular & skeletal: Arthralgia (6% to 7%)

Respiratory: Cough (≤6%)

Miscellaneous: Antibody formation (8%), positive ANA (4%)

<1%, postmarketing, and/or case reports: Abdominal mass, abscess, alopecia, anemia, angina, anxiety, aphthous stomatitis, aplastic anemia, arrhythmia, bipolar disorder, blurred vision, cytopenia, demyelinating disorder exacerbation, dermatitis, diarrhea, erythema nodosum, gastroenteritis, heart failure, hepatitis, hepatitis B reactivation; hypersensitivity reaction (eg, allergic dermatitis, angioedema, dizziness [postural], dyspnea, hot flush, hypotension, malaise, serum sickness, syncope); hypertension, leukopenia, lupus-like syndrome, lymphadenopathy, malignancy, menstrual disorder, MI, myocardial ischemia, nephrotic syndrome, optic neuritis, pancytopenia, paralytic ileus, pericardial effusion, pericarditis, peripheral neuropathy, pneumonia, pyelonephritis, rash, rectal hemorrhage, renal failure, retinal hemorrhage, seizure, suicide attempt, thrombocytopenia, thrombophilia, transaminases increased, tuberculosis (pulmonary and disseminated), urticaria, uveitis, vasculitis, visual acuity decreased

Drug Interactions

Abatacept: Anti-TNF Agents may enhance the adverse/toxic effect of Abatacept. An increased risk of serious infection during concomitant use has been reported. *Risk D: Consider therapy modification*

Anakinra: Anti-TNF Agents may enhance the adverse/toxic effect of Anakinra. An increased risk of serious infection during concomitant use has been reported. *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Rilonacept: Anti-TNF Agents may enhance the adverse/toxic effect of Rilonacept. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Echinacea may decrease the therapeutic effects of certolizumab; avoid concurrent use.

Monitoring ParametersSigns and symptoms of infection, signs and symptoms of hypersensitivity reaction, symptoms of lupus-like syndrome; hepatitis B virus and TB screening prior to therapy initiation

Nursing: Physical Assessment/MonitoringPerform tuberculin skin test prior to initiating therapy. Monitor for signs of tuberculosis throughout therapy. Do not initiate therapy if active infection (underlying chronic or localized infection) is occurring. Monitor for signs and symptoms of infection. Assess potential for interactions with other prescriptions, OTC medications, and herbal products patient may be taking. Assess results of laboratory tests (PPD), therapeutic effectiveness, and adverse response at regular intervals during treatment. Teach patient proper use if self-injected (appropriate injection technique and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsHepatitis B virus and TB screening prior to therapy initiation

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, allergies, history of tuberculosis, or any kind of infection you have. Do not take any new medication during therapy without consulting prescriber. If self-administered, follow directions for injection and needle/syringe disposal exactly. You may be more susceptible to infection. Do not have any vaccinations while using this medication without consulting prescriber first. May cause headache or dizziness (use caution when driving or engaged in potentially hazardous tasks); if persistent, consult prescriber for approved analgesic. Report persistent fever; respiratory tract infection; unhealed or infected wounds; urinary tract infection; flu-like symptoms; signs of fluid retention (unusual weight gain of >3-5 lbs per week, swelling of the extremities); shortness of breath; or redness, swelling, or pain at injection site. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Cimzia®: 200 mg [contains sterile water for reconstitution, syringes, and needles]

Generic AvailableNo

ManufacturerUCB, Inc

Mechanism of ActionCertolizumab pegol is a pegylated humanized antibody Fab’ fragment of tumor necrosis factor alpha (TNF-alpha) monoclonal antibody. Certolizumab pegol binds to and selectively neutralizes human TNF-alpha activity. (Elevated levels of TNF-alpha have a role in the inflammatory process associated with Crohn’s disease.) Since it is not a complete antibody (lacks Fc region), it does not induce complement activation, antibody-dependent cell-mediated cytotoxicity, or apoptosis. Pegylation of certolizumab allows for delayed elimination and therefore an extended half-life.

Pharmacodynamics/Kinetics

Distribution: V_{ss}: 6.4 L

Bioavailability: SubQ: ~80% (range: 76% to 88%)

Half-life elimination: ~14 days

Time to peak, plasma: 54-171 hours

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Aphthous ulcers reported in <1% of patients.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusHeadache is common; may cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine, carbamazepine, and valproic acid. May cause GI side effects; concomitant use with SSRIs, lithium, carbamazepine, or valproic acid may produce additive effects.

Index TermsCDP870

References

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Sandborn WJ, Feagan BG, Stoinov S, et al, “Certolizumab Pegol for the Treatment of Crohn's Disease,” *N Engl J Med*, 2007, 357(3):228-38.[PubMed 17634458]

Schreiber S, Khaliq-Kareemi M, Lawrence IC, et al, “Maintenance Therapy With Certolizumab Pegol for Crohn's Disease,” *N Engl J Med*, 2007, 357(3):239-50.[PubMed 17634459]

Schreiber S, Rutgeerts P, Fedorak RN, et al, “A Randomized, Placebo-Controlled Trial of Certolizumab Pegol (CDP870) for Treatment of Crohn's Disease,” *Gastroenterology*, 2005, 129(3):807-18.[PubMed 16143120]

Cetirizine and Pseudoephedrine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Zyrtec® may be confused with Serax®, Xanax®, Zantac®, Zyprexa®

Pronunciation(se TI ra zeen & soo doe e FED rin)

U.S. Brand NamesZyrtec-D 12 Hour® [DSC]; Zyrtec-D® Allergy & Congestion [OTC]

Canadian Brand NamesReactine® Allergy and Sinus

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation

Use: Labeled IndicationsTreatment of symptoms of seasonal or perennial allergic rhinitis

Dosing: AdultsSeasonal/perennial allergic rhinitis: Oral: 1 tablet twice daily

Dosing: ElderlyAdjust dose according to renal dysfunction.

Dosing: PediatricNot indicated for use in children <12 years; see adult dosing for children ≥12 years

Dosing: Renal ImpairmentCl_{cr} 11-31 mL/minute or if patient is on hemodialysis: Oral: 1 tablet once daily

Dosing: Hepatic ImpairmentOral: 1 tablet once daily

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralTablet should be swallowed whole; do not break, crush, or chew.

Dietary ConsiderationsMay be taken without regard to meals.

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to hydroxyzine, adrenergic agents, cetirizine, pseudoephedrine, or any component of the formulation; MAO inhibitor therapy or use within 14 days of discontinuing MAO inhibitor therapy; narrow-angle glaucoma; urinary retention; severe hypertension; severe coronary artery disease

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment required.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Pregnancy Risk FactorC

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsCetirizine and pseudoephedrine are excreted in breast milk. Pseudoephedrine: 0.4% to 0.7% of the dose was estimated to be excreted in breast milk over 24 hours after a single dose; breast milk concentrations were two- to threefold higher than those in plasma.

Adverse ReactionsPercentages reported with combination product. Additional adverse effects reported; refer to individual agents.

1% to 10%:

Central nervous system: Insomnia (4%), fatigue (2%), somnolence (2%), dizziness (1%)

Gastrointestinal: Xerostomia (4%)

Respiratory: Pharyngitis (2%), epistaxis (1%)

Metabolism/Transport EffectsCetirizine: **Substrate** of CYP3A4 (minor)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Cetirizine's absorption and maximal concentration are reduced when taken with food; may be taken without regard to meals.

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid ephedra, yohimbe (may cause hypertension). Avoid valerian, kava kava, gotu kola (may increase CNS depression).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, extended release: Cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg

Zyrtec-D 12 Hour® [DSC], Zyrtec-D® Allergy & Congestion: Cetirizine hydrochloride 5 mg and pseudoephedrine hydrochloride 120 mg

Generic AvailableYes

ManufacturerPfizer Labs

Pricing: U.S. (www.drugstore.com)

Tablet, 12-hour (Zyrtec-D)

5-120 mg (30): $42.99

Mechanism of ActionCetirizine is an antihistamine; exhibits selective inhibition of H_1 receptors. Pseudoephedrine is a sympathomimetic and exerts a decongestant action on nasal mucosa.

Pharmacodynamics/Kinetics

Zyrtec-D 12 Hour™:

Half-life elimination: Cetirizine: 7.9 hours; Pseudoephedrine: 6 hours

Time to peak: Cetirizine: 2.2 hours; Pseudoephedrine: 4.4 hours

Excretion: Urine (70%); feces (10%)

See individual agents.

Related Information

- Cetirizine
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDrowsiness is common; may cause abnormal thinking, agitation, amnesia, anxiety, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, nervousness, paroniria, and sleep disturbances. May also cause aggressive reactions.

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors or within 14 days of discontinuation of MAO inhibitors

Index TermsCetirizine Hydrochloride and Pseudoephedrine Hydrochloride; Pseudoephedrine Hydrochloride and Cetirizine Hydrochloride

International Brand NamesActifedduo LP Rhinite Allergique (FR); Alercet-D (CO, PE); Cetirax D (CO); Cetirivax-D (VE); Cetriler-D (AR); Cipan (AR, BO, BR, BZ, CN, CO, CR, DO, EC, GT, HN, MX, NI, PA, PE, PR, PY, SV, UY, VE); Cirrus (BE, EE, FI, ID, MY); Coolnose (KP); Kossak (KP); Lergium Plus (PE); Remitex-D (CN); Virlix D (MX); Zyrtec-D (AR, BB, BG, BM, BR, BS, BZ, CN, CR, DO, GT, GY, HK, HN, JM, MX, NI, NL, PA, SG, SR, SV, TH, TT)

Cetirizine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Zyrtec® may be confused with Serax®, Xanax®, Zantac®, Zyprexa®

Pronunciation(se TI ra zeen)
U.S. Brand NamesZyrtec® Allergy [OTC]; Zyrtec® [OTC]; Zyrtec®, Children's Allergy [OTC]; Zyrtec®, Children's Hives Relief [OTC]
Canadian Brand NamesApo-Cetirizine®; Reactine™
Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation
Use: Labeled IndicationsPerennial and seasonal allergic rhinitis and other allergic symptoms including urticaria; chronic idiopathic urticaria
Dosing: AdultsPerennial or seasonal allergic rhinitis, chronic urticaria: Oral: 5-10 mg once daily, depending upon symptom severity
Dosing: ElderlyOral: Initial: 5 mg once daily; may increase to 10 mg/day

Note: Manufacturer recommends 5 mg/day in patients ≥77 years of age.

Dosing: Pediatric

Perennial allergic rhinitis, chronic urticaria: Oral:

6-12 months: 2.5 mg once daily

12 months to <2 years: 2.5 mg once daily; may increase to 2.5 mg every 12 hours if needed

Perennial or seasonal allergic rhinitis, chronic urticaria: Oral:

2-5 years: Initial: 2.5 mg once daily; may be increased to 2.5 mg every 12 hours **or** 5 mg once daily

≥6 years: Refer to adult dosing.

Dosing: Renal Impairment

Children <6 years: Cetirizine use not recommended.

Children 6-11 years: <2.5 mg once daily

Children ≥12 and Adults:

Cl_{cr} 11-31 mL/minute or hemodialysis: Administer 5 mg once daily

Cl_{cr} <11 mL/minute, not on dialysis: Cetirizine use not recommended.

Dosing: Hepatic Impairment

Children <6 years: Cetirizine use not recommended.

Children 6-11 years: <2.5 mg once daily

Children ≥12 and Adults: Administer 5 mg once daily

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralMay be administered with or without food.
Dietary ConsiderationsMay be taken with or without food.
Storage

Syrup: Store at room temperature of 15°C to 30°C (59°F to 86°F), or under refrigeration at 2°C to 8°C (36°F to 46°F).

Tablet: Store at room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to cetirizine, hydroxyzine, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment recommended.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Safety and efficacy have not been established in children <6 months of age.

Geriatric ConsiderationsAdjust dose for renal function.
Pregnancy Risk FactorB
Pregnancy ConsiderationsCetirizine was not shown to be teratogenic in animal studies, however, adequate studies have not been conducted in pregnant women. Use during pregnancy only if clearly needed.
LactationEnters breast milk/not recommended
Adverse Reactions

>10%: Central nervous system: Headache (children 11% to 14%, placebo 12%), somnolence (adults 14%, children 2% to 4%)

2% to 10%:

Central nervous system: Insomnia (children 9%, adults <2%), fatigue (adults 6%), malaise (4%), dizziness (adults 2%)

Gastrointestinal: Abdominal pain (children 4% to 6%), dry mouth (adults 5%), diarrhea (children 2% to 3%), nausea (children 2% to 3%, placebo 2%), vomiting (children 2% to 3%)

Respiratory: Epistaxis (children 2% to 4%, placebo 3%), pharyngitis (children 3% to 6%, placebo 3%), bronchospasm (children 2% to 3%, placebo 2%)

<2% (as reported in adults and/or children): Abdomen enlarged, accommodation loss, acne, alopecia, amnesia, anaphylaxis, angioedema, anorexia, anxiety, appetite increased, arthralgia, arthritis, arthrosis, ataxia, back pain, bilirubin increased, blindness, breast pain (female), bronchitis, bullous eruption, cardiac failure, chest pain, cholestasis, concentration impaired, confusion, conjunctivitis, constipation, coordination abnormal, cystitis, deafness, dehydration, depersonalization, depression, dermatitis, diabetes mellitus, dry skin, dysmenorrhea, dyspepsia, dysphonia, dyspnea, dysuria, earache, eczema, edema, emotional lability, eructation, erythematosus rash, euphoria, eye pain, face edema, fever, flatulence, flushing, furunculosis, fussiness, gastritis, glaucoma, glomerulonephritis, hematuria, hemolytic anemia, hemorrhoids, hepatitis, hot flashes, hyperesthesia, hyperkeratosis, hyperkinesia, hypertension, hypertonia, hypertrichosis, hyperventilation, hypoesthesia, hypotension, intermenstrual bleeding, irritability, leg cramps, leg edema, leukorrhea, libido decreased, liver enzymes elevated (transient), liver function abnormal, lymphadenopathy, maculopapular rash, melena, menorrhagia, micturition frequency, migraine, muscle weakness, myalgia, myelitis, nasal polyp, nervousness, ocular hemorrhage, orofacial dyskinesia, ototoxicity, pain, pallor, palpitation, paralysis, paresthesia, paroniria, parosmia, periorbital edema, photosensitivity, pneumonia, polyuria, pruritus, ptosis, purpura, rash, rectal hemorrhage, respiratory disorder, rhinitis, rigors, salivation increased, seborrhea, sinusitis, skin disorder, skin nodule, sleep disorder, sputum increased, stomatitis, sweating, syncope, tachycardia, taste loss, taste perversion, thinking abnormal, thirst, thrombocytopenia, tinnitus, tongue discoloration, tongue edema, tremor, twitching, ulcerative stomatitis, upper respiratory tract infection, urinary incontinence, urinary retention, urinary tract infection, urticaria, vaginitis, vertigo, visual field defect, weakness, weight gain, xerophthalmia

Postmarketing and/or case reports: Aggressive reaction, convulsions, hallucinations, hypotension (severe), suicidal ideation, suicide

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersRelief of symptoms, sedation and anticholinergic effects

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. Breast-feeding is not recommended.

Patient EducationTake as directed; do not exceed recommended dose. Avoid use of other depressants, alcohol, or sleep-inducing medications unless approved by prescriber. You may experience drowsiness or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or dry mouth (frequent small meals, frequent mouth care, chewing gum, or sucking hard candy may help). Report persistent sedation, confusion, or agitation; persistent nausea or vomiting; changes in urinary pattern; blurred vision; chest pain or palpitations; persistent headaches; or lack of improvement or worsening of condition. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Syrup, as hydrochloride: 5 mg/5 mL (120 mL, 473 mL)

Zyrtec®: 5 mg/5 mL (120 mL, 480 mL) [contains propylene glycol; banana-grape flavor]

Zyrtec®, Children's Allergy, Zyrtec®, Children's Hives Relief: 5 mg/5 mL (120 mL) [contains propylene glycol; grape flavor]

Tablet, as hydrochloride: 5 mg, 10 mg

Zyrtec®: 5 mg, 10 mg [DSC]

Zyrtec® Allergy: 10 mg

Tablet, chewable, as hydrochloride:

Zyrtec®: 5 mg, 10 mg [grape flavor] [DSC]

Zyrtec®, Children's Allergy: 5 mg, 10 mg [grape flavor]

Generic AvailableYes

ManufacturerPfizer U.S. Pharmaceuticals Group

Pricing: U.S. (www.drugstore.com)

Tablets (Cetirizine HCl)

10 mg (100): $99.99

Mechanism of ActionCompetes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract

Pharmacodynamics/Kinetics

Onset of action: 15-30 minutes

Absorption: Rapid

Protein binding, plasma: Mean: 93%

Metabolism: Limited hepatic

Half-life elimination: 8 hours

Time to peak, serum: 1 hour

Excretion: Urine (70%); feces (10%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and increased salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause abnormal thinking, agitation, amnesia, anxiety, depersonalization, depression, emotional lability, euphoria, impaired concentration, insomnia, nervousness, paroniria, and sleep disturbances. May also cause aggressive reactions.

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation

Index TermsCetirizine Hydrochloride; P-071; UCB-P071

References

Allegra L, Paupe J, Wieseman HG, et al, "Cetirizine for Seasonal Allergic Rhinitis in Children Aged 2-6 Years. A Double-Blind Comparison With Placebo," *Pediatr Allergy Immunol*, 1993; 4:157-61.

Barnes CL, McKenzie CA, Webster KD, et al, "Cetirizine: A New, Nonsedating Antihistamine," *Ann Pharmacother*, 1993; 27:464-70.

Kaiser HB, "Cetirizine in Allergic Rhinitis," *Pediatr Allergy Immunol*, 1993; 4(Suppl):44-6.

Ramaekers JG, Uiterwijk MM, and O'Hanlon J, "Effects of Loratadine and Cetirizine on Actual Driving and Psychometric Test Performance, and EEG During Driving," *Eur J Clin Pharmacol*, 1992; 42:363-9.

International Brand Names Acer (PL); Aceterin (EE); Adezio (HK, SG); Alercet (CO, PE); Alerid (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Alertop (CN, PY); Alerviden (CO); Aletir (BR); Alled (ID); Aller-Go (TH); Allergy-Care (IL); Allerkid (PH); Allertec (PL); Alzene (AU); Alzytec (SG); Amertil (PL); Cabal (AR); Ceratio (PL); Cerini (ID); Ceritec (MY); Cet-10 (PH); Cetalerg (DE); CetAlergin (PL); Cethis (HK, TH); Cetimin (PH); Cetirin (HK); Cetitev (MX); Cetrimed (TH); Cetrine (CL, EC, SG, TH); Cetrizet (TH); Cetrizin (TH); Cetymin (ID); Ceza (TH); Cistamine (TH); Deallergy (TW); Falergi (ID); Finallerg (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Histatec (CH); Histazine (IL); Histica (TH); Histrine (ID); Incidal-OD (ID); Lergium (PE); Letizen (PL); Nosemin (KP); Ozen (ID); Prixlae (PH); Razene (NZ); Reactine (FR, MX); Risima (ID); Rizine (KP); Ryvel (ID); Ryzen (ID); Sancotec (KP); Setin (TH); Simtec (MY); Sutac (TH); Symitec (TW); Terizin (SG); Terzine (TH); Tirizine (AU); Tolmex (EC); Tradaxin (MX); Triz (IN); Unizef (PH); Virlix (BF, BJ, CI, ES, ET, FR, GH, GM, GN, IT, KE, LR, MA, ML, MR, MU, MW, NE, NG, PH, PL, PT, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Zensil (TH); Zeran (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Zertine (HK, TH); Zicet (MY); Zinex (PH); Zirtek (GB, IE); Zodac (PL); Zyllergy (IL); Zymed (TH); Zyrac (TH); Zyrazine (TH); Zyrcon (TH); Zyrlex (SE); Zyrtec (AR, AT, AU, BE, BG, BR, CH, CN, CR, CZ, DE, DK, DO, ES, FI, FR, GB, GR, GT, HK, HN, HU, IE, IN, IT, KP, LU, MY, NI, NL, NO, PA, PE, PH, PK, PL, PT, RU, SE, SV, TH, TR, TW, UY, VE, ZA)

Cetrorelix

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(set roe REL iks)

U.S. Brand NamesCetrotide®

Canadian Brand NamesCetrotide®

Pharmacologic CategoryGonadotropin Releasing Hormone Antagonist

Use: Labeled IndicationsInhibits premature luteinizing hormone (LH) surges in women undergoing controlled ovarian stimulation

Dosing: Adults

Controlled ovarian stimulation in conjunction with gonadotropins (FSH, HMG): Female: SubQ:

Single-dose regimen: 3 mg given when serum estradiol levels show appropriate stimulation response, usually stimulation day 7 (range days 5-9). If hCG is not administered within 4 days, continue cetrorelix at 0.25 mg/day until hCG is administered.

Multiple-dose regimen: 0.25 mg morning or evening of stimulation day 5, or morning of stimulation day 6; continue until hCG is administered.

Dosing: ElderlyNot intended for use in women ≥65 years of age (Phase 2 and Phase 3 studies included women 19-40 years of age).

Dosing: Renal Impairment

Severe impairment: Use is contraindicated.

Mild-to-moderate impairment: No specific guidelines are available.

Administration: OtherCetrorelix is administered by SubQ injection following proper aseptic technique procedures. Injections should be to the lower abdomen, preferably around the navel (but staying at least 1 inch from the navel). The injection site should be rotated daily. The needle should be inserted completely into the skin at a 45-degree angle.

StorageStore in outer carton. Once mixed, solution should be used immediately.

0.25 mg vials: Store under refrigeration at 2°C to 8°C (36°F to 46°F).

3 mg vials: Store at controlled room temperature at 25°C (77°F).

ContraindicationsHypersensitivity to cetrorelix or any component of the formulation; extrinsic peptide hormones, mannitol, gonadotropin releasing hormone (GnRH) or GnRH analogs; severe renal impairment; pregnancy; breast-feeding

Allergy Considerations

- GnRH Antagonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Monitor carefully after first injection for possible hypersensitivity reactions.

Disease-related concerns:

- Allergies: Use with caution in women with active allergic conditions or a history of allergies; use in women with severe allergic conditions is not recommended.

Special populations:

- Pregnancy: Exclude pregnancy before beginning treatment.

Other warnings/precautions:

- Experienced specialists: Should only be prescribed by fertility specialists.

Pregnancy Risk FactorX

Pregnancy ConsiderationsAnimal studies have shown fetal resorption and implantation losses following administration. Resorption resulting in fetal loss would be expected if used in a pregnant woman.

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions

1% to 10%:

Central nervous system: Headache (1%)

Endocrine & metabolic: Ovarian hyperstimulation syndrome, WHO grade II or III (4%)

Gastrointestinal: Nausea (1%)

Hepatic: ALT, AST, GGT, and alkaline phosphatase increased (1% to 2%)

Postmarketing and/or case reports: Severe anaphylactic reaction (cough, rash, hypotension) occurred in one patient following several months of treatment in a study not related to fertility. Congenital abnormalities and stillbirths have been reported, however, the relationship to cetrorelix treatment has not been established. Local injection site reactions (bruising, erythema, itching, pruritus, redness, swelling) have also been reported.

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersUltrasound to assess follicle size
Nursing: Physical Assessment/MonitoringThis medication should only be prescribed by a fertility specialist. Teach patient proper use if self-administered (appropriate injection technique and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Pregnancy must be excluded before starting medication. Breast-feeding is not recommended.
Patient EducationThis drug can only be given by injection as demonstrated. An instructional leaflet will be provided if you will be administering this medication to yourself. Instructions will be given on how to administer SubQ injections and proper disposal of syringes and needles. Give at a similar time each day as instructed by prescriber. Do not skip any doses. If you miss an injection, do not double next dose; contact your prescriber. You must keep all scheduled ultrasound appointments. Store in refrigerator in outer carton. Solution should be used immediately after mixing. You may experience headache (use of mild analgesic may help); or nausea (small frequent meals, good mouth care, chewing gum, or sucking hard candy may help). Report immediately any sudden or acute abdominal pain; shortness of breath; vaginal bleeding; or pain, itching, or signs of infection at injection site. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this drug. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Cetrotide®: 0.25 mg, 3 mg [contains mannitol]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Kit (Cetrotide)

0.25 mg (1): $122.31

3 mg (1): $606.61

Mechanism of ActionCompetes with naturally-occurring GnRH for binding on receptors of the pituitary. This delays luteinizing hormone surge, preventing ovulation until the follicles are of adequate size.
Pharmacodynamics/Kinetics

Onset of action: 0.25 mg dose: 2 hours; 3 mg dose: 1 hour

Duration: 3 mg dose (single dose): 4 days

Absorption: Rapid

Distribution: V_d: ~1 L/kg

Protein binding: 86%

Metabolism: Transformed by peptidases; cetrorelix and peptides (1-9), (1-7), (1-6), and (1-4) are found in the bile; peptide (1-4) is the predominant metabolite

Bioavailability: 85%

Half-life elimination: 0.25 mg dose: 5 hours; 0.25 mg multiple doses: 20.6 hours; 3 mg dose: 62.8 hours

Time to peak: 0.25 mg dose: 1 hour; 3 mg dose: 1.5 hours

Excretion: Feces (5% to 10% as unchanged drug and metabolites); urine (2% to 4% as unchanged drug); within 24 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsCetrorelix Acetate
International Brand NamesCetrotide (AR, AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IN, IT, KP, MX, MY, NL, NO, PH, PL, PT, RU, SE, TR, TW, VE)

Cetuximab (Biweekly)-Irinotecan

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Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Colorectal Cancer

Regimen Use Colorectal cancer

Index Terms Irinotecan-Biweekly Cetuximab

Regimen

Cycle 1:

Cetuximab: I.V.: 500 mg/m^2 over 120 minutes day 1 (cycle 1 only)

[total dose/cycle = 500 mg/m^2]

Irinotecan: I.V.: 180 mg/m^2 day 1

[total dose/cycle = 180 mg/m^2]

Subsequent cycles:

Cetuximab: I.V.: 500 mg/m^2/day over 60 minutes day 1

[total dose/cycle = 500 mg/m^2]

Irinotecan: I.V.: 180 mg/m^2 day 1

[total dose/cycle = 180 mg/m^2]

Repeat cycle every 14 days

References

Pfeiffer P, Nielsen D, Bjerregaard J, et al, "Biweekly Cetuximab and Irinotecan as Third-Line Therapy in Patients With Advanced Colorectal Cancer After Failure to Irinotecan, Oxaliplatin and 5-Fluorouracil," *Ann Oncol*, 2008, 19(6):1141-5. [PubMed 18281264]

Cetuximab-Carboplatin-Fluorouracil

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Head and Neck Cancer

Regimen UseHead and neck cancer

Index TermsCarboplatin-Fluorouracil-Cetuximab

Regimen

Cycle 1:

Cetuximab: I.V.: 400 mg/m^2 (loading dose) day 1 (week 1, cycle 1 only)

[total loading dose = 400 mg/m^2]

followed by I.V.: 250 mg/m^2/day days 8 and 15

[total dose/cycle 1 = 900 mg/m^2]

Carboplatin: I.V.: AUC 5 day 1

[total dose/cycle = AUC = 5]

Fluorouracil: I.V.: 1000 mg/m2/day continuous infusion days 1-4

[total dose/cycle = 4000 mg/m^2]

Treatment cycle is 3 weeks

Subsequent cycles:

Cetuximab: I.V.: 250 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 750 mg/m^2]

Carboplatin: I.V.: AUC 5 day 1

[total dose/cycle = AUC = 5]

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1-4

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 3 weeks for a total of up to 6 cycles (cetuximab monotherapy may be continued thereafter until disease progression or unacceptable toxicity)

References

Vermorken JB, Mesia R, Rivera F, et al, "Platinum-Based Chemotherapy Plus Cetuximab in Head and Neck Cancer," *N Engl J Med*, 2008, 359(11):1116-27.[PubMed 18784101]

Cetuximab-Cisplatin-Fluorouracil

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Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Head and Neck Cancer

Regimen Use Head and neck cancer

Index Terms Cisplatin-Fluorouracil-Cetuximab

Regimen

Cycle 1:

Cetuximab: I.V.: 400 mg/m^2 (loading dose) day 1 (week 1, cycle 1 only)

[total loading dose = 400 mg/m^2]

followed by I.V.: 250 mg/m^2/day days 8 and 15

[total dose/cycle 1 = 900 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1-4

[total dose/cycle = 4000 mg/m^2]

Treatment cycle is 3 weeks

Subsequent cycles:

Cetuximab: I.V.: 250 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 750 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1-4

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 3 weeks for a total of up to 6 cycles (cetuximab monotherapy may be continued thereafter until disease progression or unacceptable toxicity)

References

Vermorken JB, Mesia R, Rivera F, et al, "Platinum-Based Chemotherapy Plus Cetuximab in Head and Neck Cancer," *N Engl J Med*, 2008, 359(11):1116-27.[PubMed 18784101]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Nonsmall Cell)
Regimen UseLung cancer, nonsmall cell
Index TermsCisplatin-Vinorelbine-Cetuximab
Regimen

Cycle 1:

Cetuximab: I.V.: 400 mg/m^2 (loading dose) day 1 (week 1, cycle 1 only)

[total loading dose = 400 mg/m^2]

followed by I.V.: 250 mg/m^2/dose days 8 and 15

[total dose/cycle 1 = 900 mg/m^2]

Cisplatin: I.V.: 80 mg/m^2/dose day 1

[total dose/cycle = 80 mg/m^2]

Vinorelbine: I.V.: 25 mg/m^2/dose days 1 and 8

[total dose/cycle = 50 mg/m^2]

Treatment cycle is 3 weeks

Subsequent cycles:

Cetuximab: I.V.: 250 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 750 mg/m^2]

Cisplatin: I.V.: 80 mg/m^2 day 1

[total dose/cycle = 80 mg/m^2]

Vinorelbine: I.V.: 25 mg/m^2/dose days 1 and 8

[total dose/cycle = 50 mg/m^2]

Repeat cycle every 3 weeks

References

Pirker R, Szczesna A, von Pawel J, et al, "FLEX: A Randomized, Multicenter, Phase III Study of Cetuximab in Combination With Cisplatin/Vinorelbine (CV) Versus CV Alone in the First-Line Treatment of Patients With Advanced Non-Small Cell Lung Cancer (NSCLC)," *J Clin Oncol*, 2008, 26(Supp) [abstract 3 from 2008 ASCO Annual Meeting].

Rosell R, Robinet G, Szczesna A, et al, "Randomized Phase II Study of Cetuximab Plus Cisplatin/Vinorelbine Compared With Cisplatin/Vinorelbine Alone as First-Line Therapy in EGFR-Expressing Advanced Non-Small-Cell Lung Cancer," *Ann Oncol*, 2008, 19(2):362-9.[PubMed 17947225]

Cetuximab-FOLFOX4

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Colorectal Cancer]

Regimen UseColorectal cancer

Index TermsFOLFOX4-Cetuximab

Regimen

Cycle 1:

Cetuximab: I.V.: 400 mg/m^2 (loading dose) day 1 (week 1, cycle 1 only)

followed by I.V.: 250 mg/m^2/day day 8

[total dose/cycle 1 = 650 mg/m^2]

Oxaliplatin: I.V.: 85 mg/m^2 (over 2 hours) day 1

[total dose/cycle = 85 mg/m^2]

Leucovorin: I.V.: 200 mg/m^2/day (over 2 hours) days 1 and 2

[total dose/cycle = 400 mg/m^2]

Fluorouracil: I.V. bolus: 400 mg/m^2/day days 1 and 2

followed by I.V.: 600 mg/m^2 continuous infusion (over 22 hours) days 1 and 2

[total dose/cycle = 2000 mg/m^2]

Note: Bolus fluorouracil and continuous infusion are both given on each day.

Treatment cycle is 14 days

Subsequent cycles:

Cetuximab: I.V.: 250 mg/m^2/day days 1 and 8

[total dose/cycle = 500 mg/m^2]

Oxaliplatin: I.V.: 85 mg/m^2 day 1

[total dose/cycle = 85 mg/m^2]

Leucovorin: I.V.: 200 mg/m^2/day (over 2 hours) days 1 and 2

[total dose/cycle = 400 mg/m^2]

Fluorouracil: I.V. bolus: 400 mg/m^2/day days 1 and 2

followed by I.V.: 600 mg/m^2 continuous infusion (over 22 hours) days 1 and 2

[total dose/cycle = 2000 mg/m^2]

Note: Bolus fluorouracil and continuous infusion are both given on each day.

Repeat cycle every 14 days

References

Tabernero J, Van Cutsem E, DĂaz-Rubio E, et al, "Phase II Trial of Cetuximab in Combination With Fluorouracil, Leucovorin, and Oxaliplatin in the First-Line Treatment of Metastatic Colorectal Cancer," *J Clin Oncol*, 2007, 25(33):5225-32.[PubMed 18024868]

Cetuximab-Irinotecan

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Colorectal Cancer
Regimen UseColorectal cancer
Index TermsIrinotecan-Cetuximab
RegimenNOTE: Multiple variations are listed below.

Variation 1:

- Cycle 1:
  - Cetuximab: I.V.: 400 mg/m^2 (loading dose) day 1 (week 1, cycle 1 only)
    - [total loading dose = 400 mg/m^2]
      - **followed by** I.V.: 250 mg/m^2/day days 8, 15, 22, 29, and 36
        - [total dose/cycle 1 = 1650 mg/m^2]
  - Irinotecan: I.V.: 125 mg/m^2/day days 1, 8, 15, and 22
    - [total dose/cycle = 500 mg/m^2]
- Subsequent cycles:
  - Cetuximab: I.V.: 250 mg/m^2/day days 1, 8, 15, 22, 29, and 36
    - [total dose/cycle = 1500 mg/m^2]
  - Irinotecan: I.V.: 125 mg/m^2/day days 1, 8, 15, and 22
    - [total dose/cycle = 500 mg/m^2]
- Repeat cycle every 42 days

Variation 2:

- Cycle 1:
  - Cetuximab: I.V.: 400 mg/m^2 (loading dose) day 1 (week 1, cycle 1 only)
    - [total loading dose = 400 mg/m^2]
      - **followed by** I.V.: 250 mg/m^2 day 8
        - [total dose/cycle 1 = 650 mg/m^2]
  - Irinotecan: I.V.: 180 mg/m^2 day 1
    - [total dose/cycle = 180 mg/m^2]
- Subsequent cycles:
  - Cetuximab: I.V.: 250 mg/m^2/day days 1 and 8
    - [total dose/cycle = 500 mg/m^2]
  - Irinotecan: I.V.: 180 mg/m^2 day 1
    - [total dose/cycle = 180 mg/m^2]
- Repeat cycle every 14 days

Variation 3:

- Cycle 1:
  - Cetuximab: I.V.: 400 mg/m^2 (loading dose) day 1 (week 1, cycle 1 only)
    - [total loading dose = 400 mg/m^2]

followed by I.V.: 250 mg/m^2/day days 8 and 15 (cycle 1)

[total dose/cycle 1 = 900 mg/m^2]

Irinotecan: I.V.: 350 mg/m^2 day 1

[total dose/cycle = 350 mg/m^2]

Subsequent cycles:

Cetuximab: I.V.: 250 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 750 mg/m^2]

Irinotecan: I.V.: 350 mg/m^2 day 1

[total dose/cycle = 350 mg/m^2]

Repeat cycle every 21 days

References

Cunningham D, Humblet Y, Siena S, et al, "Cetuximab Monotherapy and Cetuximab Plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer," *N Engl J Med*, 2004, 351(4):337-45.[PubMed 15269313]

Cetuximab

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Cetuximab may be confused with bevacizumab

Pronunciation(se TUK see mab)

U.S. Brand NamesErbitux®

Canadian Brand NamesErbitux®

Pharmacologic CategoryAntineoplastic Agent, Monoclonal Antibody; Epidermal Growth Factor Receptor (EGFR) Inhibitor

Use: Labeled IndicationsTreatment of metastatic colorectal cancer; treatment of squamous cell cancer of the head and neck

Use: Unlabeled/InvestigationalTreatment of EGFR-expressing advanced nonsmall cell lung cancer (NSCLC)

Dosing: Adults **Note:** Premedicate with an H_1 antagonist (eg, diphenhydramine) I.V. 30-60 minutes prior to the first dose; premedication for subsequent doses is based on clinical judgement.

Colorectal cancer: I.V.:

Initial loading dose: 400 mg/m^2 infused over 120 minutes

Maintenance dose: 250 mg/m^2 infused over 60 minutes weekly

Biweekly administration (unlabeled dosing): 500 mg/m^2 every 2 weeks (initial dose infused over 120 minutes, subsequent doses infused over 60 minutes) (Pfeiffer, 2007)

Head and neck cancer: I.V.:

Initial loading dose: 400 mg/m^2 infused over 120 minutes

Maintenance dose: 250 mg/m^2 infused over 60 minutes weekly

Note: If given in combination with radiation therapy, administer loading dose 1 week prior to initiation of radiation course. Weekly maintenance dose should be completed 1 hour prior to radiation for the duration of radiation therapy (6-7 weeks).

NSCLC (unlabeled use): Initial loading dose: 400 mg/m^2, followed by maintenance dose: 250 mg/m^2 weekly (Pirker, 2008)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment required.

Dosing: Hepatic ImpairmentNo adjustment required.

Dosing: Adjustment for Toxicity

Infusion reactions, grade 1 or 2 and nonserious grades 3 or 4: Reduce the infusion rate by 50% and continue to use prophylactic antihistamines

Infusion reactions, severe: Immediately and permanently discontinue treatment

Pulmonary toxicity:

Acute onset or worsening pulmonary symptoms: Hold treatment

Interstitial lung disease: Permanently discontinue

Skin toxicity, mild to moderate: No dosage modification required

Acneiform rash, severe (grade 3 or 4):

- First occurrence: Delay cetuximab infusion 1-2 weeks
  - If improvement, continue at 250 mg/m^2
  - If no improvement, discontinue therapy
- Second occurrence: Delay cetuximab infusion 1-2 weeks
  - If improvement, continue at reduced dose of 200 mg/m^2
  - If no improvement, discontinue therapy

Third occurrence: Delay cetuximab infusion 1-2 weeks

If improvement, continue at reduced dose of 150 mg/m^2

If no improvement, discontinue therapy

Fourth occurrence: Discontinue therapy

Note: Dose adjustments are not recommended for severe **radiation** dermatitis.

Dosing: Combination Regimens

Colorectal cancer:

- Cetuximab (Biweekly)-Irinotecan
- Cetuximab-FOLFOX4
- Cetuximab-Irinotecan

Head and neck cancer:

- Carboplatin-Cetuximab
- Cetuximab-Carboplatin-Fluorouracil
- Cetuximab-Cisplatin-Fluorouracil
- Cisplatin-Cetuximab
- Paclitaxel-Cetuximab

Lung cancer, nonsmall cell: Cetuximab-Cisplatin-Vinorelbine

Calculations

- Body Surface Area: Adults

Administration: I.V.I.V. infusion; loading dose over 2 hours, weekly maintenance dose over 1 hour. Do not administer as I.V. push or bolus. Do not shake or dilute. Administer via infusion pump or syringe pump. Following the infusion, an observation period (1 hour) is recommended; longer observation time (following an infusion reaction) may be required. Premedication with an H_1 antagonist prior to the initial dose is recommended. The maximum infusion rate is 10 mg/minute. Administer through a low protein-binding 0.22 micrometer in-line filter. Use 0.9% NaCl to flush line at the end of infusion.

For biweekly administration (unlabeled frequency and dose), the initial dose was infused over 120 minutes and subsequent doses infused over 60 minutes (Pfeiffer, 2007).

Administration: I.V. DetailpH: 7-7.4; may contain a small amount of visible white, amorphous cetuximab particles

StorageStore unopened vials under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Preparations in infusion containers are stable for up to 12 hours under refrigeration at 2°C to 8°C (36°F to 46°F) and up to 8 hours at room temperature of 20°C to 25°C (68°F to 77°F).

ReconstitutionReconstitution is not required. Appropriate dose should be added to empty sterile container; do not shake or dilute.

ContraindicationsThere are no contraindications listed in the manufacturer's labeling

Warnings/Precautions

Boxed warnings:

- Cardiopulmonary arrest: See "Concerns related to adverse effects" below.
- Infusion/hypersensitivity reactions: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Cardiopulmonary arrest: **[U.S. Boxed Warning]: Cardiopulmonary arrest has been reported in patients receiving radiation therapy in combination with cetuximab.** Closely monitor serum electrolytes (magnesium, potassium, calcium) during and after (for at least 8 weeks) cetuximab therapy. Use caution with history of coronary artery disease, HF, and arrhythmias.
- Dermatologic toxicity: Acneiform rash has been reported in 76% to 88% of patients (severe in 1% to 17%), usually developing within the first 2 weeks of therapy; may require dose modification. Acneiform rash should be treated with topical and/or oral antibiotics; topical corticosteroids are not recommended. Other dermatologic toxicities, including dry skin, fissures, hypertrichosis, paronychial inflammation, and skin infections have been reported; related ocular toxicities (blepharitis, conjunctivitis, keratitis) may also occur. Sunlight may exacerbate skin reactions. In colorectal cancer, the presence of acneiform rash correlates with treatment response and prolonged survival (Cunningham, 2004).
- Electrolyte abnormality: Hypomagnesemia is common; the onset of electrolyte disturbance may occur within days to months after initiation of treatment; monitor.
- Infusion/hypersensitivity reactions: **[U.S. Boxed Warning]: Severe infusion reactions (bronchospasm, stridor, hoarseness, urticaria, hypotension, loss of consciousness, shock, MI, cardiac arrest) have been reported in ~3% of patients; fatal outcome has been reported rarely.** Approximately 90% of reactions occur with the first infusion despite the use of prophylactic antihistamines. **Note:** Although a 20 mg test dose was used in some studies, it did not reliably predict the risk of an infusion reaction, and is not recommended. In case of severe reaction, treatment should be stopped and permanently discontinued. Immediate treatment for anaphylactic/anaphylactoid reactions should

be available during administration. The manufacturer recommends monitoring patients for at least 1 hour following completion of infusion, or longer if a reaction occurs. Mild-to-moderate infusion reactions (chills, fever, dyspnea) are managed by slowing the infusion rate (by 50%) and administering antihistamines. Patients with pre-existing IgE antibody against cetuximab (specific for galactose-α-1,3-galactose) are reported to have a higher incidence of severe hypersensitivity reaction. Severe hypersensitivity reaction has been reported more frequently in patients living in the middle south area of the United States, including North Carolina and Tennessee (O'Neil, 2007; Chung, 2008).

- Interstitial lung disease (ILD): Has been reported; use with caution in patients with pre-existing lung disease. Permanently discontinue with confirmed ILD.

Concurrent drug therapy issues:

- Combination with cisplatin and radiation therapy: Safety and efficacy have not been established when used in combination with radiation therapy and cisplatin.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Anticetuximab antibodies: Non-neutralizing anticetuximab antibodies were detected in 5% of evaluable patients. Relationship between the appearance of antibodies and the safety or antitumor activity of the molecule is unknown.

Pregnancy Risk FactorC

Pregnancy ConsiderationsIn pregnant cynomolgus monkeys, cetuximab was detected in the amniotic fluid and in the serum of embryos. Although teratogenic effects were not observed in animal studies, increases in embryolethality and fetal loss were noted. There are no adequate and well-controlled studies in pregnant women. It is not known whether cetuximab can cause fetal harm or affect reproductive capacity. Because cetuximab inhibits epidermal growth factor (EGF), a component of fetal development, adverse effects on pregnancy would be expected. Cetuximab should only be given to a pregnant woman if the potential benefit justifies the potential risk to the fetus.

LactationExcretion in breast milk is unknown/not recommended

Breast-Feeding ConsiderationsBreast-feeding should be discontinued during treatment and for at least 60 days following the last dose.

Adverse ReactionsExcept where noted, percentages reported for cetuximab monotherapy.

>10%:

Central nervous system: Fatigue (89%), pain (17% to 51%), headache (26% to 33%), insomnia (10% to 30%), fever (27% to 30%), confusion (15%), anxiety (14%), chills/rigors (13%), depression (7% to 13%)

Dermatologic: Acneiform rash (76% to 90%; grades 3/4: 1% to 17%; onset: ≤14 days), rash (89%), dry skin (49%), pruritus (11% to 40%), nail changes/disorder (16% to 21%)

Endocrine & metabolic: Hypomagnesemia (55%; grades 3/4: 6% to 17%)

Gastrointestinal: Abdominal pain (26% to 59%), constipation (26% to 46%), diarrhea (25% to 39%), vomiting (25% to 37%), nausea (mild-to-moderate 29%), weight loss (7% to 27%), anorexia (23%), stomatitis (10% to 25%), xerostomia (11%)

Neuromuscular & skeletal: Weakness (45% to 48%), bone pain (15%)

Respiratory: Dyspnea (17% to 48%), cough (11% to 29%)

Miscellaneous: Infection (13% to 35%), infusion reaction (15% to 21%; grades 3/4: 2% to 5%; 90% of severe reactions occurred with first infusion)

1% to 10%:

Cardiovascular: Peripheral edema (10%), cardiopulmonary arrest (2%; with radiation therapy)

Dermatologic: Alopecia (4%), skin disorder (4%)

Endocrine & metabolic: Dehydration (2% to 10%)

Gastrointestinal: Dyspepsia (6%)

Hematologic: Anemia (9%)

Hepatic: Alkaline phosphatase increased (5% to 10%), transaminases increased (5% to 10%)

Neuromuscular & skeletal: Back pain (10%)

Ocular: Conjunctivitis (7%)

Renal: Renal failure (1%)

Respiratory: Pulmonary embolus (1%)

Miscellaneous: Sepsis (1% to 4%)

<1%, postmarketing, and/or case reports: Abscess formation, arrhythmia, blepharitis, bronchospasm, cardiac arrest, cellulitis, cheilitis, hoarseness, hypertrichosis, hypotension, interstitial lung disease (occurred between the fourth and eleventh doses), keratitis, leukopenia, loss of consciousness, MI, paronychial inflammation, sepsis, shock, skin fissure, skin infection, stridor

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)
Drug InteractionsThere are no known significant interactions.
Monitoring ParametersVital signs during infusion and observe for at least 1 hour postinfusion. Patients developing dermatologic toxicities should be monitored for the development of complications. Periodic monitoring of serum magnesium, calcium, and potassium are recommended to continue over an interval consistent with the half-life (8 weeks); monitor closely (during and after treatment) for cetuximab plus radiation therapy. KRAS genotyping of tumor tissue in patients with colorectal cancer.
Nursing: Physical Assessment/MonitoringUse caution with pre-existing coronary or lung disease. Premedication with antihistamines is recommended. Patient must be monitored closely for adverse reactions (eg, airway obstruction, hives, hypotension) during and for 1 hour following infusion. Treatment for anaphylactic reactions should be available. In case of severe infusion reaction, treatment should be stopped and prescriber notified. Dosing adjustment or permanent discontinuation may be necessary in event of infusion reaction. Evaluate results of laboratory tests prior to and periodically during treatment. Assess therapeutic response and adverse reactions. Teach patient possible side effects/interventions and adverse symptoms to report (eg, skin reactions, cough, dyspnea, gastrointestinal upset, opportunistic infection).
Monitoring: Lab TestsPeriodic monitoring of serum magnesium, calcium, and potassium are recommended to continue over an interval consistent with the half-life (8 weeks); monitor closely (during and after treatment) for cetuximab plus radiation therapy. KRAS genotyping of tumor tissue in patients with colorectal cancer.
Patient EducationDo not take any new prescription, OTC medications, or herbal products during therapy unless approved by prescriber. This medication can only be administered by infusion and you will be closely monitored during each infusion. Report immediately unusual chest tightness; difficulty breathing or swallowing; itching or skin rash; back pain or acute headache; or redness, swelling, or pain at infusion site. Maintain adequate nutrition (small, frequent meals) and hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience feelings of weakness or fatigue (adequate rest is important); nausea, vomiting, or loss of appetite (small, frequent meals, sucking lozenges, or chewing gum may help); diarrhea (boiled milk or yogurt may help); headache or back pain (consult prescriber for appropriate analgesic); skin rash or dryness (avoid sunlight, use protective clothing, use only mild soap, and consult prescriber for approved lotion); or loss of hair or nail disorder (may grow back after therapy). Report immediately chest pain, irregular heart beat, or palpitations; difficulty breathing; persistent gastrointestinal disturbances (pain, constipation, diarrhea, vomiting); CNS changes (depression or insomnia); skin rash, dryness, or cracking; any signs of infection; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed during therapy or for 60 days following completion.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Erbitux®: 2 mg/mL (50 mL, 100 mL)

Generic AvailableNo
ManufacturerImClone (distributed/marketed by Bristol-Myers Squibb)
Pricing: U.S. (www.drugstore.com)

Solution (Erbitux)

100 mg/50 mL (50): $570.00

Mechanism of ActionRecombinant human/mouse chimeric monoclonal antibody which binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands. Binding to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production.
Pharmacodynamics/Kinetics

Distribution: V_d: ~2-3 L/m^2

Half-life elimination: ~112 hours (range: 63-230 hours)

Pharmacotherapy Pearls**Oncology Comment:** EGFR expression is detected in nearly all patients with head and neck cancer; laboratory evidence of EGFR expression is not necessary for head and neck cancers.

The National Comprehensive Cancer Network® (NCCN) guidelines for colon cancer (v.3.2008) recommend genotyping tumor tissue for KRAS mutation in all patients with metastatic colorectal cancer (genotyping may be done on archived specimens). Patients with known codon 12 or 13 KRAS gene mutations are unlikely to respond to EGFR inhibitors and should not receive cetuximab. Favorable progression-free survival and overall survival has been demonstrated with cetuximab in patients with KRAS wild-type (Karapetis, 2008; Van Cutsem, 2008). Because EGFR testing in colorectal tumors does not correlate with response, the NCCN guidelines do not recommend routine EGFR testing in colorectal cancer. Dermatologic toxicity with cetuximab is predictive for response; the presence of acneiform rash correlates with treatment response and prolonged survival (Cunningham, 2004).

The NCCN Non-Small Cell Lung cancer guidelines (v.2.2009) recommend cetuximab in combination with cisplatin and vinorelbine as a first-line therapy option in patients with advanced (stage IIIB or IV disease), with EGFR expression and a performance status of 0-2.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause malaise, insomnia, or depression
Mental Health: Effects on Psychiatric TreatmentGastrointestinal side effects are common; these effects may be additive with concurrent use of SSRIs, acetylcholinesterase inhibitors, aripiprazole, or ziprasidone. May cause anemia and leukopenia; use caution with clozapine and carbamazepine.
Index TermsC225; IMC-C225; NSC-714692
References

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National Comprehensive Cancer Network (NCCN), “Clinical Practice Guidelines in Oncology™: Non-Small Cell Lung Cancer,” Version 2, 2009. Accessible at http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf.

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Reynolds NA and Wagstaff AJ, “Cetuximab: In the Treatment of Metastatic Colorectal Cancer,” *Drugs*, 2004, 64(1):109-18.[PubMed 14723561]

Van Cutsem E, Lang, I, D’haens G, et al, “KRAS Status and Efficacy in the First-Line Treatment of Patients With Metastatic Colorectal Cancer (mCRC) Treated With FOLFIRI With or Without Cetuximab: The CRYSTAL Experience,” *J Clin Oncol*, 2008, 26(Supp) [abstract 2 from 2008 ASCO Annual Meeting].

International Brand NamesErbitux (AR, AT, AU, BE, BG, CH, CL, CN, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, MY, NL, NO, PE, PH, PT, RU, SE, SG, TH, TR, TW)

Cetylpyridinium and Benzocaine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(SEE til peer i DI nee um & BEN zoe kane)
Canadian Brand NamesCepacol速; Kank-A速
Pharmacologic CategoryLocal Anesthetic
Use: Labeled IndicationsSymptomatic relief of sore throat
Use: DentalAntiseptic/anesthetic for oral cavity
Dosing: Adults

Antiseptic/anesthetic: Oral: Dissolve in mouth as needed for sore throat

Antiseptic/anesthetic (dental use): Oral: Dissolve in mouth as needed for pain

Dosing: ElderlyRefer to adult dosing.
RestrictionsNot available in U.S.
Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Pregnancy Risk FactorC
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.
Related Information

- Benzocaine
- Cetylpyridinium

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsBenzocaine and Cetylpyridinium Chloride; Cetylpyridinium Chloride and Benzocaine
International Brand NamesMerocaine (GB, IE); Prodol (ZA); Septolete (EE)

Cetylpyridinium

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(SEE til peer i DI nee um)
U.S. Brand NamesCepacol® Antibacterial Mouthwash Gold [OTC]; DiabetAid Gingivitis Mouth Rinse [OTC]
Pharmacologic CategoryAntiseptic, Oral Mouthwash
Use: Labeled IndicationsAntiseptic to aid in the prevention and reduction of plaque and gingivitis, and to freshen breath
Use: DentalAntiseptic to aid in the prevention and reduction of plaque and gingivitis, and to freshen breath
Dosing: AdultsAntiseptic: Oral (OTC labeling): Rinse or gargle to freshen mouth; may be used before or after brushing
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricAntiseptic: Children ≥6 years: Refer to adult dosing.
ContraindicationsHypersensitivity to cetylpyridinium or any component of the formulation
Warnings/Precautions

Special populations:

- Pediatrics: Not labeled for OTC use in children <6 years of age.

Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined: Gastrointestinal: Tooth and tongue staining, oral irritation
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, as chloride, oral [mouthwash/gargle]:

Cepacol® Antibacterial Mouthwash Gold: 0.05% (360 mL, 720 mL) [contains alcohol 14% and tartrazine; original flavor]

DiabetAid Gingivitis Mouth Rinse: 0.1% (480 mL) [sugar free; contains alcohol and tartrazine]

Generic AvailableNo
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tooth and tongue staining and oral irritation.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsCetylpyridinium Chloride; CPC
International Brand NamesAlgol (IT); Alsol (IT); Angifonil (ES); Bat Zeta (IT); Borocaina (IT); Bronchenolo Gola (IT); Cepacol (BR, CO, HK, NZ, SG, ZA); Cetilsan (IT); Curisol (ES); Dobendan (AT, DE); Farin Gola (IT); Geyderm Sepsi (IT); Golacetin (IT); Halset (AT, PL); Herbagola (IT); Menthosept (PL); Merocets (GB, IE); Neo Cepacol (IT); Neo Coricidin (IT); Neo Formitrol (IT); Novoptine (CH, FR); Pronto G (IT); Pyrisept (NO); Tirocetil (ES)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Rhabdomyosarcoma

Regimen UseRhabdomyosarcoma

Regimen

Carboplatin: I.V.: 500 mg/m^2 day 1

[total dose/cycle = 500 mg/m^2]

Epirubicin: I.V.: 150 mg/m^2 day 1

[total dose/cycle = 150 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2/day days 1 and 7

[total dose/cycle = 3 mg/m^2]

Repeat cycle every 21 days

References

Frascella E, Pritchard-Jones K, Modak S, et al, âResponse of Previously Untreated Metastatic Rhabdomyosarcoma to Combination Chemotherapy With Carboplatin, Epirubicin and Vincristine,â *Eur J Cancer*, 1996, 32A(5):821-5.[PubMed 9081360]

Cevimeline

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Evoxac® may be confused with Eurax®

Pronunciation(se vi ME leen)
U.S. Brand NamesEvoxac®
Canadian Brand NamesEvoxac®
Pharmacologic CategoryCholinergic Agonist
Use: Labeled IndicationsTreatment of symptoms of dry mouth in patients with Sjögren's syndrome
Use: DentalTreatment of symptoms of dry mouth in patients with Sjögren's syndrome
Dosing: AdultsXerostomia (in Sjögren's syndrome): Oral: 30 mg 3 times/day
Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNot studied; no specific dosage adjustment is recommended
Dosing: Hepatic ImpairmentNot studied; no specific dosage adjustment is recommended
Dietary ConsiderationsTake with or without food.
StorageStore at 25°C (77°F).
ContraindicationsHypersensitivity to cevimeline or any component of the formulation; uncontrolled asthma; narrow-angle glaucoma; acute iritis; other conditions where miosis is undesirable
Allergy Considerations

- Cevimeline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Parasympathomimetic effects: May cause a variety of parasympathomimetic effects, which may be particularly dangerous in elderly patients; excessive sweating may lead to dehydration in some patients.

- Visual effects: May cause decreased visual acuity (particularly at night and in patients with central lens changes) and impaired depth perception. Patients should be cautioned about driving at night or performing hazardous activities in reduced lighting.

Disease-related concerns:

- Biliary stones: Use with caution in patients with a history of biliary stones; may may induce smooth muscle spasms, precipitating cholangitis, cholecystitis, or biliary obstruction in susceptible patients.

- Cardiovascular disease: Use with caution in patients with significant cardiovascular disease (including angina, myocardial infarction, or conduction disturbances); may alter cardiac conduction and/or heart rate.

- Nephrolithiasis: Use with caution in patients with a history of nephrolithiasis; may induce smooth muscle spasms, precipitating renal colic or ureteral reflux in susceptible patients.

- Respiratory disease: Use with caution in patients with controlled asthma, COPD, or chronic bronchitis; may increase bronchial smooth muscle tone, airway resistance, and bronchial secretions.

Special populations:

- Patients with CYP2D6 deficiency: Patients with a known or suspected deficiency of CYP2D6 may be at higher risk of adverse effects.

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo specific studies in the elderly are available. However, elderly often have cardiovascular, pulmonary, and gastrointestinal diseases which may restrict or contraindicate the use of this agent. The use of saliva substitutes should be considered initially. Although the clinical studies included elderly patients (>65 years of age), the number of elderly was insufficient to determine any significant differences between young adults and elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use only if potential benefit justifies potential risk to the fetus.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%:

Central nervous system: Headache (14%; placebo 20%)

Gastrointestinal: Nausea (14%), diarrhea (10%)

Respiratory: Rhinitis (11%), sinusitis (12%), upper respiratory infection (11%)

Miscellaneous: Diaphoresis increased (19%)

1% to 10%:

Cardiovascular: Peripheral edema, chest pain, edema, palpitation

Central nervous system: Dizziness (4%), fatigue (3%), pain (3%), insomnia (2%), anxiety (1%), fever, depression, migraine, hypoesthesia, vertigo

Dermatologic: Rash (4%; placebo 6%), pruritus, skin disorder, erythematous rash

Endocrine & metabolic: Hot flashes (2%)

Gastrointestinal: Dyspepsia (8%; placebo 9%), abdominal pain (8%), vomiting (5%), excessive salivation (2%), constipation, salivary gland pain, dry mouth, sialoadenitis, gastroesophageal reflux, flatulence, ulcerative stomatitis, eructation, amylase increased, anorexia, tooth disorder

Genitourinary: Urinary tract infection (6%), vaginitis, cystitis

Hematologic: Anemia

Local: Abscess

Neuromuscular & skeletal: Back pain (5%), arthralgia (4%), skeletal pain (3%), rigors (1%), hypertonia, tremor, myalgia, hyporeflexia, leg cramps

Ocular: Conjunctivitis (4%), abnormal vision, eye pain, eye abnormality, xerophthalmia

Otic: Earache, otitis media

Respiratory: Coughing (6%), bronchitis (4%), pneumonia, epistaxis

Miscellaneous: Flu-like syndrome, infection, fungal infection, allergy, hiccups

<1%: Abnormal ECG, abnormal renal function, aggressive behavior, agitation, alopecia, anemia, angina, anterior chamber hemorrhage, aphasia, apnea, arrhythmia, arthropathy, avascular necrosis (femoral head), blepharitis, bronchospasm, bullous eruption, bundle branch block, bursitis, cataract, cholelithiasis, cholinergic syndrome, coma, confusion, corneal ulceration, costochondritis, CPK increased, deafness, delirium, dementia, impotence, depersonalization, dermatitis, diplopia, dry skin, dyskinesia, dysphagia, dysphonia, dysuria, hematuria, eczema, electrolyte abnormality, emotional lability, enterocolitis, eosinophilia, epididymitis, esophageal stricture, esophagitis, fall, gastric ulcer, gastrointestinal hemorrhage, genital pruritus, gingival hyperplasia, glaucoma, granulocytopenia, hallucination, hyper-/hypotension, hyperkinesia, hypothyroidism, ileus, intestinal obstruction, leukocytosis, leukopenia, lymphadenopathy, lymphocytosis, malaise, manic reaction, melena, menstrual disorder, MI, motion sickness, mucositis, multiple sclerosis (aggravated), nasal ulcer, neuralgia, neuropathy, oliguria, paralysis, paranoia, paresthesia, parosmia, peptic ulcer, pericarditis, peripheral ischemia, photosensitivity reaction, pleural effusion, postural hypotension, pulmonary embolism, pulmonary fibrosis, renal calculus, retinal disorder, scleritis, seizure, sepsis, skin ulceration, somnolence, stomatitis, substernal chest pain, syncope, synovitis, systemic lupus erythematosus, taste perversion, tendonitis, tenosynovitis, thrombocytopenia, thrombocytopenic purpura, thrombophlebitis, tinnitus, tongue discoloration, tongue ulceration, transaminases increased, T-wave inversion, urinary retention, urine flow decreased, vasculitis

Postmarketing and/or case reports: Cholecystitis

Metabolism/Transport Effects**Substrate** (minor) of CYP2D6, CYP3A4
Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor for therapeutic effect and adverse reactions (especially with elderly persons). Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse reactions to report.
Patient EducationTake exactly as directed; do not alter dosage without consulting prescriber. Take with or without food. You may experience decreased visual acuity, especially at night (use caution when driving at night or when engaging in other activities in poorly lighted areas until response to medication is known); GI distress or nausea (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); headache (mild analgesic may help); or diarrhea (boiled milk, yogurt, or buttermilk may help). Report unresolved diarrhea or constipation, abdominal pain, flatulence, anorexia, or excessive salivation; excessive sweating; unresolved respiratory distress, runny nose, cold or flu symptoms; joint, bone, or muscle weakness, pain, tremor, or cramping; chest pain or palpitations, swelling of extremities, weight gain; or other persistent adverse symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 30 mg

Generic AvailableNo
ManufacturerDaiichi Pharmaceutical Corp
Pricing: U.S. (www.drugstore.com)

Capsules (Evoxac)

30 mg (30): $63.99

Mechanism of ActionBinds to muscarinic (cholinergic) receptors, causing an increase in secretion of exocrine glands (including salivary glands)

Pharmacodynamics/Kinetics

Distribution: V_d: 6 L/kg

Protein binding: <20%

Metabolism: Hepatic via CYP2D6 and CYP3A4

Half-life elimination: 5 hours

Time to peak: 1.5-2 hours

Excretion: Urine (as metabolites and unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Excessive salivation, salivary gland pain, xerostomia (normal salivary flow resumes upon discontinuation), ulcerative stomatitis, and tooth disorder.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, insomnia, anxiety, and depression; rare reports of mania

Mental Health: Effects on Psychiatric TreatmentFluoxetine, nefazodone, and paroxetine may increase levels of cevimeline. TCAs, phenothiazine, clozapine, and olanzapine may antagonize the effects of cevimeline.

Index TermsCevimeline Hydrochloride

International Brand NamesEvoxac (JP)

CF

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Head and Neck Cancer

Regimen UseHead and neck cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 3 or 4 weeks

Variation 2:

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 5000 mg/m^2]

Repeat cycle every 3 or 4 weeks

Variation 3:

Cisplatin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Fluorouracil: I.V.: 800 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 14 days

Variation 4:

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Fluorouracil: I.V.: 200 mg/m^2/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

Repeat cycle every 3 weeks

Variation 5:

Cisplatin: I.V.: 80 mg/m^2 continuous infusion day 1

[total dose/cycle = 80 mg/m^2]

Fluorouracil: I.V.: 800 mg/m^2/day continuous infusion days 2 to 6

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 3 weeks

Variation 6:

Cisplatin: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 4 weeks

Variation 7:

Cisplatin: I.V.: 120 mg/m^2 day 1

[total dose/cycle = 120 mg/m^2]

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 5000 mg/m^2]

Repeat cycle every 3 weeks

Variation 8:

Cisplatin: I.V.: 25 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 100 mg/m^2]

Fluorouracil: I.V.: 1000 mg/m^2/day days 1 to 4

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 3 weeks

Variation 9:

Fluorouracil: I.V.: 350 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 1750 mg/m^2]

Cisplatin: I.V.: 50 mg/m^2 day 6

[total dose/cycle = 50 mg/m^2]

Repeat cycle every 3 weeks

Variation 10:

Cisplatin: I.V.: 5 mg/m^2/day continuous infusion days 1 to 14

[total dose/cycle = 70 mg/m^2]

Fluorouracil: I.V.: 200 mg/m^2/day continuous infusion days 1 to 14

[total dose/cycle = 2800 mg/m^2]

With concurrent radiation therapy, cycle does not repeat

References

Variation 1:

Kish J, Drelichman A, Jacobs J, et al, “Clinical Trial of Cisplatin and 5-FU Infusion as Initial Treatment for Advanced Squamous Cell Carcinoma of the Head and Neck,” *Cancer Treat Rep*, 1982, 66(3):471-4.[PubMed 7037180]

Mercier RJ, Neal GD, Mattox DE, et al, “Cisplatin and 5-Fluorouracil Chemotherapy in Advanced or Recurrent Squamous Cell Carcinoma of the Head and Neck,” *Cancer*, 1987, 60(11):2609-12.[PubMed 3676999]

Variation 2:

Rooney M, Kish J, Jacobs J, et al, “Improved Complete Response Rate and Survival in Advanced Head and Neck Cancer After Three-Course Induction Therapy With 120-Hour 5-FU Infusion and Cisplatin,” *Cancer*, 1985, 55(5):1123-8.[PubMed 4038469]

Dasmahapatra KS, Citrin P, Hill GJ, et al, “A Prospective Evaluation of 5-Fluorouracil Plus Cisplatin in Advanced Squamous-Cell Cancer of the Head and Neck,” *J Clin Oncol*, 1985, 3(11):1486-9.[PubMed 4056841]

Variation 3:

Taylor SG 4th, Murthy AK, Showel JL, et al, “Improved Control in Advanced Head and Neck Cancer With Simultaneous Radiation and Cisplatin/5-FU Chemotherapy,” *Cancer Treat Rep*, 1985, 69(9):933-9.[PubMed 3928158]

Variation 4:

Merlano M, Tatarek R, Grimaldi A, et al, “Phase I-II Trial With Cisplatin and 5-FU in Recurrent Head and Neck Cancer: An Effective Outpatient

Schedule," *Cancer Treat Rep*, 1985, 69(9):961-4.[PubMed 4040809]

Variation 5:

Amrein PC and Weitzman SA, "Treatment of Squamous-Cell Carcinoma of the Head and Neck With Cisplatin and 5-Fluorouracil," *J Clin Oncol*, 1985, 3(12):1632-9. [PubMed 2415693]

Variation 6:

Adelstein DJ, Li Y, Adams GL, et al, "An Intergroup Phase III Comparison of Standard Radiation and Two Schedules of Concurrent Chemoradiotherapy in Patients With Unresectable Squamous Cell Head and Neck Cancer," *J Clin Oncol*, 2003, 21(1):92-8.[PubMed 12506176]

Adelstein DJ, Sharan VM, Earle AS, et al, "Chemoradiotherapy as Initial Management in Patients With Squamous Cell Carcinoma of the Head and Neck," *Cancer Treat Rep*, 1986, 70(6):761-7.[PubMed 3731138]

Variation 7:

Paredes J, Hong WK, Felder TB, et al, "Prospective Randomized Trial of High-Dose Cisplatin and Fluorouracil Infusion With or Without Sodium Diethyldithiocarbamate in Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck," *J Clin Oncol*, 1988, 6(6):955-62.[PubMed 2836565]

Variation 8:

Bernal AG, Cruz JJ, Sanchez P, et al, "Four-Day Continuous Infusion of Cisplatin and 5-Fluorouracil in Head and Neck Cancer," *Cancer*, 1989, 63(10):1927-30. [PubMed 2702566]

Variation 9:

Denham JW and Abbott RL, "Concurrent Cisplatin, Infusional Fluorouracil, and Conventionally Fractionated Radiation Therapy in Head and Neck Cancer: Dose-Limiting Mucosal Toxicity," *J Clin Oncol*, 1991, 9(3):458-63.[PubMed 1999716]

Variation 10:

Arcangeli G, Saracino B, Danesi DT, et al, "Accelerated Hyperfractionated Radiotherapy and Concurrent Protracted Venous Infusion Chemotherapy in Locally-Advanced Head and Neck Cancer," *Am J Clin Oncol*, 2002, 25(5):431-7.[PubMed 12393978]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

Regimen

Cyclophosphamide: I.V.: 150 mg/m^2/day days 1 to 5

[total dose/cycle = 750 mg/m^2]

Fluorouracil: I.V.: 300 mg/m^2/day days 1 to 5

[total dose/cycle = 1500 mg/m^2]

Prednisone: Oral: 30 mg/day days 1 to 14 (cycle 1 only)

followed by Oral: 20 mg/day days 15 to 21 (cycle 1 only)

followed by Oral: 10 mg daily thereafter as maintenance

[total dose/cycle = 700 mg in cycle 1; 350 mg in subsequent cycles]

Repeat cycle every 35 days

References

Marschke RF Jr, Ingle JN, Schaid DJ, et al, âRandomized Clinical Trial of CFP Versus CMFP in Women With Metastatic Breast Cancer,â *Cancer*, 1989, 63(10):1931-7.[PubMed 2649221]

CHAMOCA (Modified Bagshawe Regimen)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Gestational Trophoblastic Tumor

Regimen Use Gestational trophoblastic tumor

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Hydroxyurea: Oral: 500 mg every 6 hours, for 4 doses, day 1 (start at 6 AM)

[total dose/cycle = 2000 mg]

Dactinomycin: I.V.: 0.2 mg/day days 1, 2, and 3 (give at 7 PM)

followed by I.V.: 0.5 mg/day days 4 and 5 (give at 7 PM)

[total dose/cycle = 1.6 mg]

Cyclophosphamide: I.V.: 500 mg/m^2/day days 3 and 8 (give at 7 PM)

[total dose/cycle = 1000 mg/m^2]

Vincristine: I.V.: 1 mg/m^2 (maximum 2 mg) day 2 (give at 7 AM)

[total dose/cycle = 1 mg/m^2; maximum 2 mg]

Methotrexate: I.V. bolus: 100 mg/m^2 day 2 (give at 7 PM)

followed by I.V.: 200 mg/m^2 continuous infusion over 12 hours day 2

[total dose/cycle = 300 mg/m^2]

Leucovorin: I.M.: 14 mg every 6 hours, for 6 doses, days 3, 4, and 5 (begin at 7 PM on day 3; start 24 hours after the start of methotrexate)

[total dose/cycle = 84 mg]

Doxorubicin: I.V.: 30 mg/m^2 day 8 (give at 7 PM)

[total dose/cycle = 30 mg/m^2]

Repeat cycle every 18 days or as toxicity permits (cycle may be repeated 10 days after last treatment)

Variation 2:

Hydroxyurea: Oral: 500 mg every 12 hours, for 4 doses, days 1 and 2 (usually started in early morning)

[total dose/cycle = 2000 mg]

Dactinomycin: I.V.: 10 mcg/kg/day days 5, 6, and 7

[total dose/cycle = 30 mcg/kg]

Vincristine: I.V.: 1 mg/m^2 day 3

[total dose/cycle = 1 mg/m^2]

Methotrexate: I.V. bolus: 100 mg/m^2 day 3

followed by I.V.: 200 mg/m^2 continuous infusion over 12 hours day 3

[total dose/cycle = 300 mg/m^2]

Leucovorin: I.M.: 10 mg/m^2 every 12 hours, for 4 doses, days 4 and 5 (start 24 hours after the start of methotrexate)

[total dose/cycle = 40 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 5

[total dose/cycle = 600 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 10

[total dose/cycle = 30 mg/m^2]

Repeat cycle every 3 weeks

Variation 3:

Hydroxyurea: Oral: 500 mg every 12 hours, for 4 doses, days 1 and 2 (usually started in early morning)

[total dose/cycle = 2000 mg/m^2]

Vincristine: I.V.: 1 mg/m^2 day 3

[total dose/cycle = 1 mg/m^2]

Methotrexate: I.V. bolus: 100 mg/m^2 day 3

followed by I.V.: 200 mg/m^{2}continuous infusion over 12 hours day 3

[total dose/cycle = 300 mg/m^2]

Leucovorin: I.M.: 14 mg every 6 hours, for 6 doses, days 4, 5, and 6 (start 24 hours after start of methotrexate)

[total dose/cycle = 84 mg]

Dactinomycin: I.V.: 0.2 mg/day days 2, 3, and 4

followed by I.V.: 0.5 mg/day days 5 and 6

[total dose/cycle = 1.6 mg]

Cyclophosphamide: I.V.: 500 mg/m^2 day 4

[total dose/cycle = 500 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 9

[total dose/cycle = 30 mg/m^2]

Melphalan: I.V.: 6 mg/m^2 day 9

[total dose/cycle = 6 mg/m^2]

Repeat cycle approximately every 3 weeks

Variation 4:

Hydroxyurea: Oral: 500 mg 4 times/day, for 4 doses, day 1

[total dose/cycle = 2000 mg/m^2]

Vincristine: I.V.: 1 mg/m^2 day 2

[total dose/cycle = 1 mg/m^2]

Methotrexate: I.V. bolus: 100 mg/m^2 day 2

followed by I.V.: 200 mg/m^2 continuous infusion over 12 hours day 2

[total dose/cycle = 300 mg/m^2]

Leucovorin: I.M.: 14 mg every 6 hours, for 6 doses, days 3, 4, and 5 (start 24 hours after the start of methotrexate)

[total dose/cycle = 84 mg]

Dactinomycin: I.V.: 0.2 mg days 1, 2, and 3, then 0.5 mg days 4 and 5

[total dose/cycle = 1.6 mg]

Cyclophosphamide: I.V.: 500 mg/m^2 day 3

[total dose/cycle = 500 mg/m^2]

Cyclophosphamide: I.V.: 300 mg/m^2 on day 8

[total dose/cycle = 300 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 8

[total dose/cycle = 30 mg/m^2]

Repeat cycle approximately every 3 weeks

References

Variation 1:

Weed JC Jr, Barnard DE, Currie JL, et al, “Chemotherapy With the Modified Bagshawe Protocol for Poor Prognosis Metastatic Trophoblastic Disease,” *Obstet Gynecol*, 1982, 59(3):377-80.[PubMed 6176924]

Variation 2:

Wong LC, Choo YC, and Ma HK, “Modified Bagshawe's Regimen in High-Risk Gestational Trophoblastic Disease,” *Gynecol Oncol*, 1986, 23(1):87-93.[PubMed 3002917]

Variation 3:

Surwit EA, Suciu TN, Schmidt HJ, et al,“A New Combination Chemotherapy for Resistant Trophoblastic Disease,” *Gynecol Oncol*, 1979, 8(1):110-8. [PubMed 222651]

Variation 4:

Surwit EA and Hammond CB, “Treatment of Metastatic Trophoblastic Disease With Poor Prognosis,” *Obstet Gynecol*, 1980, 55(5):565-70.[PubMed 6245395]

CHAMOMA (Bagshawe Regimen)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Gestational Trophoblastic Tumor
Regimen UseGestational trophoblastic tumor
Regimen

Hydroxyurea: Oral: 500 mg every 12 hours, for 4 doses, days 1 and 2

[total dose/cycle = 2000 mg]

Vincristine: I.V.: 1 mg/m^2 day 3

[total dose/cycle = 1 mg/m^2]

Methotrexate: I.V. bolus: 100 mg/m^2 day 3

followed by I.V.: 200 mg/m^2 continuous infusion over 12 hours day 3

[total dose/cycle = 300 mg/m^2]

Leucovorin: I.M.: 12 mg/m^2 every 12 hours, for 4 doses, days 4 and 5 (start 12 hours after the end of methotrexate infusion)

[total dose/cycle = 48 mg/m^2]

Dactinomycin: I.V.: 10 mcg/kg/day days 5, 6, and 7

[total dose/cycle = 30 mcg/kg]

Cyclophosphamide: I.V.: 600 mg/m^2 day 5

[total dose/cycle = 600 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 10

[total dose/cycle = 30 mg/m^2]

Melphalan: I.V.: 6 mg/m^2 day 10

[total dose/cycle = 6 mg/m^2]

Repeat cycle approximately every 3 weeks

References

Bagshawe KD, âTreatment of Trophoblastic Tumors,â *Ann Acad Med Singapore*, 1976, 5:273-9.

Charcoal, Activated

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Actidose® may be confused with Actos®

Pronunciation(CHAR kole AK tiv ay ted)

U.S. Brand NamesActidose-Aqua® [OTC]; Actidose® with Sorbitol [OTC]; Char-Caps [OTC]; CharcoAid® G [OTC]; Charcoal Plus® DS [OTC]; CharcoCaps® [OTC]; EZ-Char™ [OTC]; Kerr Insta-Char® [OTC]; Requa® Activated Charcoal [OTC]

Canadian Brand NamesCharcadole®; Charcadole® TFS; Charcadole®, Aqueous

Pharmacologic CategoryAntidote

Use: Labeled IndicationsEmergency treatment in poisoning by drugs and chemicals; aids the elimination of certain drugs and improves decontamination of excessive ingestions of sustained-release products or in the presence of bezoars; repetitive doses have proven useful to enhance the elimination of certain drugs (eg, carbamazepine, dapsone, phenobarbital, quinine, or theophylline); repetitive doses for gastric dialysis in uremia to adsorb various waste products; dietary supplement (digestive aid)

Dosing: Adults

Acute poisoning:

Oral: 25-100 g as a single dose; if multiple doses are needed, additional doses may be given as 12.5 g/hour or equivalent (eg, 25 g every 2 hours)

Note: ~10 g of activated charcoal for each 1 g of toxin is considered adequate; this may require multiple doses. If sorbitol is also used, sorbitol dose should not exceed 1.5 g/kg. When using multiple doses of charcoal, sorbitol should be given with every other dose (not to exceed 2 doses/day)

Dietary supplement: Oral: 500-520 mg after meals; may repeat in 2 hours if needed (maximum: 10 g/day)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Acute poisoning: Oral:

Children:

<1 year: 0.5-1 g/kg (10-25 g) as a single dose; if multiple doses are needed, give as 0.25 g/kg/hour or equivalent (eg, 0.5 g/kg every 2 hours)

1-12 years: 0.5-1 g/kg (25-50 g) as a single dose; if multiple doses are needed, give as 0.25 g/kg/hour or equivalent (eg, 0.5 g/kg every 2 hours)

>12 years: Refer to adult dosing.

Note: ~10 g of activated charcoal for each 1 g of toxin is considered adequate; this may require multiple doses. If sorbitol is also used, sorbitol dose should not exceed 1.5 g/kg. When using multiple doses of charcoal, sorbitol should be given with every other dose (not to exceed 2 doses/day).

Administration: OralFlavoring agents (eg, chocolate, concentrated fruit juice) or thickening agents (eg, bentonite, carboxymethylcellulose) can enhance charcoal's palatability. If treatment includes ipecac syrup, induce vomiting prior to administration of charcoal. Often given with a laxative or cathartic; check for presence of bowel sounds before administration. I.V. antiemetics may be required to reduce the risk of vomiting during multiple-dose therapy with charcoal.

StorageAdsorbs gases from air, store in closed container.

ReconstitutionPowder: Dilute with at least 8 mL of water per 1 g of charcoal, or mix in a charcoal to water ratio of 1:4 to 1:8. Mix to form a slurry.

ContraindicationsHypersensitivity to charcoal or any component of the formulation; intestinal obstruction; GI tract not anatomically intact; patients at risk of hemorrhage or GI perforation; patients with an unprotected airway (eg, CNS depression without intubation); if use would increase risk and severity of aspiration

Warnings/Precautions

Concerns related to adverse effects:

- Vomiting: Charcoal may cause vomiting; avoid use in hydrocarbon and caustic ingestions.

Disease-related concerns:

- Decreased peristalsis: Use with caution in patients with decreased peristalsis.

Concurrent drug therapy issues:

- Ipecac: When using ipecac with charcoal, ensure ipecac-induced vomiting has ceased prior to administering charcoal.
- Cathartics (eg, sorbitol, mannitol, magnesium sulfate): Coadministration of a cathartic is not recommended secondary to lack of compelling evidence and the increased morbidity associated with their use. If charcoal is administered with a cathartic, avoid excessive fluid and electrolyte losses, especially in children <1 year of age.

Special populations:

- Pediatrics: Charcoal with sorbitol not recommended in children <1 year of age.

Dosage form specific issues:

- Propylene glycol: Commercial charcoal products may contain propylene glycol.

Other warnings/precautions:

- Appropriate use: Not effective for cyanide, mineral acids, caustic alkalis, organic solvents, iron, ethanol, methanol, or lithium poisoning
- Efficacy: Most effective when administered within 30-60 minutes of ingestion.

Pregnancy Risk FactorC
LactationDoes not enter breast milk/compatible
Adverse ReactionsFrequency not defined.

Endocrine & metabolic: Hypernatremia, hypokalemia, and hypermagnesemia may occur with coadministration of cathartics

Gastrointestinal: Vomiting (incidence may increase with sorbitol), diarrhea (with sorbitol), constipation, swelling of abdomen, bowel obstruction, appendicitis

Respiratory: Aspiration (both gastric contents and charcoal)

Miscellaneous: Fecal discoloration (black)

Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb InteractionsFood: Do not mix with milk, ice cream, sherbet, or marmalade (may reduce charcoal's effectiveness).
Nursing: Physical Assessment/MonitoringMonitor for active bowel sounds prior to administration. If antidote treatment includes ipecac syrup, induce vomiting before administering charcoal. May be administered with sorbitol or chocolate to improve palatability; do not administer with milk products.
Patient EducationCharcoal will cause your stools to turn black. Do not self-administer as an antidote before calling the poison control center, hospital emergency room, or prescriber for instructions (charcoal is not the antidote for all poisons). **Pregnancy precaution:** Inform prescriber if you are pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Char-Caps, CharcoCaps®: 260 mg

Pellets, for suspension:

EZ-Char™: 25 g

Powder for suspension: 30 g, 240 g

CharcoAid® G: 15 g

Suspension:

Actidose-Aqua®: 15 g (72 mL); 25 g (120 mL); 50 g (240 mL)

Kerr Insta-Char®: 25 g (120 mL) [contains sodium benzoate; packaged with cherry flavor (cherry flavor contains propylene glycol and sodium benzoate)]; 50 g (240 mL) [contains sodium benzoate; unflavored or packaged with cherry flavor (cherry flavor contains propylene glycol and sodium benzoate)]

Suspension [with sorbitol]:

Actidose® with Sorbitol: 25 g (120 mL); 50 g (240 mL)

Kerr Insta-Char®: 25 g (120 mL) [contains sodium benzoate; packaged with cherry flavor (cherry flavor contains propylene glycol and sodium benzoate)]; 50 g (240 mL) [contains sodium benzoate; packaged with cherry flavor (cherry flavor contains propylene glycol and sodium benzoate)]

Tablet:

Requa® Activated Charcoal: 250 mg

Tablet, enteric coated:

Charcoal Plus® DS: 250 mg

Generic AvailableYes: Powder

Mechanism of ActionAdsorbs toxic substances or irritants, thus inhibiting GI absorption; adsorbs intestinal gas; the addition of sorbitol results in hyperosmotic laxative action causing catharsis

Pharmacodynamics/KineticsExcretion: Feces (as charcoal)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentDoes not effectively remove lithium

Index TermsActivated Carbon; Activated Charcoal; Adsorbent Charcoal; Liquid Antidote; Medicinal Carbon; Medicinal Charcoal

References

Alaspää AO, Kusima MJ, Hoppu K, et al, “Feasibility Study on Activated Charcoal Given Prehospital by Emergency Medical System (EMS) in Acute Intoxications,” *J Toxicol Clin Toxicol*, 2002, 40(3):312-3.

Bond GR, "The Role of Activated Charcoal and Gastric Emptying in Gastrointestinal Decontamination: A State-of-the-Art Review," *Ann Emerg Med*, 2002, 39(3):273-86.[PubMed 11867980]

Christophersen AB, Hoegberg LC, Angelo HR, et al, “Activated Charcoal in a Simulated Paracetamol Overdose: Downscaling of Dose to 10 Grams - Preliminary Results,” *J Toxicol Clin Toxicol*, 2002, 40(5):696.

Chyka PA, Seger D, Krenzelok EP, et al, American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists, “Position Paper: Single-Dose Activated Charcoal,” *Clin Toxicol (Phila)*, 2005, 43(2):61-87 (review).

Cooper GM, Le Coteur DG, Richardson DB, et al, “A Randomized Clinical Trial of Activated Charcoal for the Routine Management of Oral Drug Overdose,” *Acad Emerg Med*, 2002, 9(5):487.

Dorrington CL, Johnson DW, Brant R, “The Frequency of Complications Associated With the Use of Multiple-Dose Activated Charcoal,” *Ann Emerg Med*, 2003, 41(3):370-7. [PubMed 12605204]

Heard K, "Gastrointestinal Decontamination," *Med Clin N Am*, 2005, 89(6):1067-78 (review).[PubMed 16227054]

Higgins T, Curry S, Brooks D, et al, “Iatrogenic Administration of Propylene Glycol With Activated Charcoal,” *J Toxicol Clin Toxicol*, 2000, 38(5):529.

Holmes C, Schauben J, and Hasan MY, “An Evaluation of the Incidence of Emesis Following Oral Bolus Dosing vs Gradual Administration Regimens of Activated Charcoal,” *J Toxicol Clin Toxicol*, 1998, 36(5):431-2.

Justice HM, Knapp BJ, Pianalto DA, et al, "Failure of Emergency Medical Services Providers to Administer Activated Charcoal Add to Emergency Delay," *Acad Emerg Med*, 2006, 13(5):S180.

Keyes C and DeTamble L, “Prehospital Activated Charcoal: A Prospective Randomized Trial,” *J Toxicol Clin Toxicol*, 1999, 37(5):610.

Merigian KS and Blaho KE, “Single-Dose Oral Activated Charcoal in the Treatment of the Self-Poisoned Patient: A Prospective, Randomized, Controlled Trial,” *Am J Ther*, 2002, 9(4):301-8. [PubMed 12115019]

Seger D, “Single-Dose Activated Charcoal-Backup and Reassess,” *J Toxicol Clin Toxicol*, 2004, 42(1):101-10. [PubMed 15083946]

Vale JA, Krenzelok EP and Barceloux GD et al, American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists, “Position Statement and Practice Guidelines on the Use of Multiple-Dose Activated Charcoal in the Treatment of Acute Poisoning,” *Clin Toxicol*, 1999, 37(6):731-51.

International Brand NamesBekarbon (ID); Ca-R-Bon (TH); Carbo Medicinalis (PL); Carbomix (FR, SE); Carbon Natural (UY); Carbosorb (NZ); Carbosorb S (NZ); Carbosorb X (AU); Carbosorb XS (AU); Carbotural (MX); Charcodote (GB, HK, KP); Charcotrace (AU); Deltacarbon (TH); Mamograf (AR); Norit (IL); RCOL (IN); Ultracarbon (SG)

ChlVPP

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, Hodgkin's Disease

Regimen UseLymphoma, Hodgkin's disease

Regimen

Chlorambucil: Oral: 6 mg/m^2/day (maximum 10 mg) days 1 to 14

[total dose/cycle = 84 mg/m^2]

Vinblastine: I.V.: 6 mg/m^2/day (maximum 10 mg) days 1 and 8

[total dose/cycle = 12 mg/m^2]

Procarbazine: Oral: 100 mg/m^2/day (maximum 150 mg) days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Prednisone: Oral: 40-50 mg/day days 1 to 14

[total dose/cycle = 560-700 mg]

Repeat cycle every 28 days

References

Selby P, Patel P, Milan S, et al, âChlVPP Combination Chemotherapy for Hodgkin's Disease: Long-Term Results,â *Br J Cancer*, 1990, 62(2):279-85.[PubMed 2386744]

CHL + PRED

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Chronic Lymphocytic

Regimen UseLeukemia, chronic lymphocytic

Regimen

Chlorambucil: Oral: 0.4 mg/kg/day for 1 day every other week; increase initial dose of 0.4 mg/kg by 0.1 mg/kg every 2 weeks until toxicity or disease control is achieved

Prednisone: Oral: 100 mg/day for 2 days every other week

References

Han T, Ezdinli EZ, Shimaoka K, et al, âChlorambucil vs Combined Chlorambucil-Corticosteroid Therapy in Chronic Lymphocytic Leukemia,â *Cancer*, 1973,31(3):502-8.[PubMed 4693581]

Chloral Hydrate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(KLOR al HYE drate)
U.S. Brand NamesAquachloral® Supprettes® [DSC]; Somnote®
Canadian Brand NamesPMS-Chloral Hydrate
Pharmacologic CategoryHypnotic, Nonbenzodiazepine
Use: Labeled IndicationsShort-term sedative and hypnotic (<2 weeks); sedative/hypnotic for diagnostic procedures; sedative prior to EEG evaluations
Use: DentalShort-term sedative/hypnotic for dental procedures
Dosing: Adults

Sedation, anxiety: Oral, rectal: 250 mg 3 times/day

Hypnotic: Oral, rectal: 500-1000 mg at bedtime or 30 minutes prior to procedure, not to exceed 2 g/24 hours

Discontinuation: Withdraw gradually over 2 weeks if patient has been maintained on high doses for prolonged period of time. Do not stop drug abruptly; sudden withdrawal may result in delirium.

Dosing: ElderlyHypnotic: Initial: Oral: 250 mg at bedtime; adjust for renal impairment. See Geriatric Considerations.
Dosing: Pediatric

Sedation, anxiety: Oral, rectal: 5-15 mg/kg/dose every 8 hours, maximum: 500 mg/dose

Prior to EEG: Oral, rectal: 20-25 mg/kg/dose, 30-60 minutes prior to EEG; may repeat in 30 minutes to maximum of 100 mg/kg or 2 g total

Hypnotic: Oral, rectal: 20-40 mg/kg/dose up to a maximum of 50 mg/kg/24 hours or 1 g/dose or 2 g/24 hours

Conscious sedation: Oral: 50-75 mg/kg/dose 30-60 minutes prior to procedure; may repeat 30 minutes after initial dose if needed, to a total maximum dose of 120 mg/kg or 1 g total

Discontinuation: Withdraw gradually over 2 weeks if patient has been maintained on high doses for prolonged period of time. Do not stop drug abruptly; sudden withdrawal may result in delirium.

Dosing: Renal Impairment

Cl_{cr} <50 mL/minute: Avoid use.

Hemodialysis effects: Supplemental dose is not necessary; dialyzable (50% to 100%).

Dosing: Hepatic ImpairmentAvoid use in patients with severe hepatic impairment.
Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralChilling the syrup may help to mask unpleasant taste. Do not crush capsule (contains drug in liquid form). Gastric irritation may be minimized by diluting dose in water or other oral liquid.
StorageSensitive to light. Exposure to air causes volatilization. Store in light-resistant, airtight container.
RestrictionsC-IV
ContraindicationsHypersensitivity to chloral hydrate or any component of the formulation; hepatic or renal impairment; gastritis or ulcers; severe cardiac disease
Allergy Considerations

- Chloral Hydrate Allergy

Warnings/Precautions

Disease-related concerns:

- Porphyria: Use with caution in patients with porphyria.

Special populations:

- Elderly: Considered a second line hypnotic agent in the elderly.

- Long-term care facility residents: Recent interpretive guidelines from the Centers for Medicare and Medicaid Services (CMS) discourage the use of chloral hydrate in residents of long-term care facilities.

- Neonates: Use with caution in neonates; drug may accumulate with repeated use and prolonged use in neonates associated with hyperbilirubinemia.

Other warnings/precautions:

- Duration of therapy: Tolerance to hypnotic effect develops, therefore, not recommended for use >2 weeks.

- Metabolite: Trichloroethanol (TCE), a metabolite of chloral hydrate, is a carcinogen in mice; there is no data in humans.

- Withdrawal: Abrupt discontinuance may lead to withdrawal symptoms.

Geriatric ConsiderationsChloral hydrate is considered a second- or third-line hypnotic agent in the elderly. Interpretive guidelines from the Centers for Medicare and Medicaid Services (CMS) discourage the use of chloral hydrate in residents of long-term care facilities.
Pregnancy Risk FactorC
LactationEnters breast milk/compatible
Adverse ReactionsFrequency not defined.

Central nervous system: Ataxia, disorientation, sedation, excitement (paradoxical), dizziness, fever, headache, confusion, lightheadedness, nightmares, hallucinations, drowsiness, “hangover” effect

Dermatologic: Rash, urticaria

Gastrointestinal: Gastric irritation, nausea, vomiting, diarrhea, flatulence

Hematologic: Leukopenia, eosinophilia, acute intermittent porphyria

Miscellaneous: Physical and psychological dependence may occur with prolonged use of large doses

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Flumazenil: May diminish the sedative effect of Hypnotics (Nonbenzodiazepine). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsFalse-positive urine glucose using Clinitest® method; may interfere with fluorometric urine catecholamine and urinary 17-hydroxycorticosteroid tests
Monitoring ParametersVital signs, O_2 saturation and blood pressure with doses used for conscious sedation
Nursing: Physical Assessment/MonitoringFor short-term use. Assess effectiveness and interactions of other medications patient may be taking. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance. Monitor for excessive sedation. Evaluate periodically for need for continued use (symptoms of dependence may resemble alcoholism, but usually there is more gastritis). After long-term use, taper dosage slowly when discontinuing. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor for effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Patient EducationUse exactly as directed; do not increase dose or frequency or discontinue this medication without consulting prescriber. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially, pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, unpleasant taste (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea (buttermilk, boiled milk, yogurt may help). Report skin rash or irritation, CNS changes (confusion, depression, increased sedation, excitation, headache, insomnia, or nightmares), unresolved GI distress, chest pain or palpitations, or ineffectiveness of medication. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

Somnote®: 500 mg

Suppository, rectal: 500 mg

Aquachloral® Supprettes®: 325 mg [contains tartrazine] [DSC]

Syrup: 500 mg/5 mL (5 mL, 480 mL)

Generic AvailableYes: Syrup and suppositories
Pricing: U.S. (www.drugstore.com)

Capsules (Somnote)

500 mg (50): $79.99

Syrup (Chloral Hydrate)

500 mg/5 mL (480): $19.97

Mechanism of ActionCentral nervous system depressant effects are due to its active metabolite trichloroethanol, mechanism unknown
Pharmacodynamics/Kinetics

Onset of action: Time to sleep: 0.5-1 hour

Duration: 4-8 hours

Absorption: Oral, rectal: Well absorbed

Distribution: Crosses placenta; negligible amounts enter breast milk

Metabolism: Rapidly hepatic to trichloroethanol (active metabolite); variable amounts hepatically and renally to trichloroacetic acid (inactive)

Half-life elimination: Active metabolite: 8-11 hours

Excretion: Urine (as metabolites); feces (small amounts)

Related Information

- CMS: Long-Term Care Facility Thresholds
- Depression
- Nonbenzodiazepine Anxiolytics and Hypnotics

Pharmacotherapy PearlsNot an analgesic
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Index TermsChloral; Hydrated Chloral; Trichloroacetaldehyde Monohydrate
References

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Mayers DJ, Hindmarsh KW, Sankaran K, et al, “Chloral Hydrate Disposition Following Single-Dose Administration to Critically Ill Neonates and Children,” *Dev Pharmacol Ther*, 1991, 16(2):71-7. [PubMed 1914781]

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Zeltzer LK, Altman A, Cohen D, et al, “American Academy of Pediatrics Report of the Subcommittee on the Management of Pain Associated With Procedures in Children With Cancer,” *Pediatrics*, 1990, 86(5 Pt 2):826-31.[PubMed 2216645]

International Brand NamesChloradorm (AU); Chloraldurat (CH, DE, NL); Chloralhydrat 500 (ID); Escre (JP); Kloral (DK); Medianox (CH); Pocral (KP); Suppojuvent Sedante (ES); Welldorm (GB)

Chlorambucil

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Chlorambucil may be confused with Chloromycetin®

Leukeran® may be confused with Alkeran®, leucovorin, Leukine®, Myleran®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(klor AM byoo sil)

U.S. Brand NamesLeukeran®

Canadian Brand NamesLeukeran®

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent

Use: Labeled IndicationsManagement of chronic lymphocytic leukemia (CLL), Hodgkin's lymphoma, non-Hodgkin's lymphoma (NHL)

Use: Unlabeled/InvestigationalNephrotic syndrome, Waldenström's macroglobulinemia

Dosing: AdultsRefer to individual protocols.

CLL, NHL: Oral: 0.1 mg/kg/day for 3-6 weeks **or** 0.4 mg/kg (increased by 0.1mg/kg/dose until response/toxicity observed) biweekly **or** 0.4 mg/kg (increased by 0.1mg/kg/dose until response/toxicity observed) monthly **or** 0.03-0.1 mg/kg/day continuously

Hodgkin's lymphoma: Oral: 0.2 mg/kg/day for 3-6 weeks **or** 0.4 mg/kg (increased by 0.1mg/kg/dose until response/toxicity observed) biweekly **or** 0.4 mg/kg (increased by 0.1mg/kg/dose until response/toxicity observed) monthly **or** 0.03-0.1 mg/kg/day continuously

Waldenström's macroglobulinemia (unlabeled use): Oral: 0.1 mg/kg/day (continuously) for at least 6 months **or** 0.3 mg/kg/day for 7 days every 6 weeks for at least 6 months

Dosing: Elderly

Refer to adult dosing. Begin at the lower end of dosing range(s)

Dosing: PediatricRefer to individual protocols. Unlabeled uses:

General short courses: Oral: 0.1-0.2 mg/kg/day for 3-6 weeks **or** maintenance therapy: 0.03-0.1 mg/kg/day

Nephrotic syndrome: Oral: 0.1-0.2 mg/kg/day every day for ~8-12 weeks with low-dose prednisone

Chronic lymphocytic leukemia (CLL): Oral:

Biweekly regimen: Initial: 0.4 mg/kg/dose every 2 weeks; increase dose by 0.1 mg/kg every 2 weeks until a response occurs and/or myelosuppression occurs

Monthly regimen: Initial: 0.4 mg/kg, increase dose by 0.1 mg/kg every 4 weeks until a response occurs and/or myelosuppression occurs

Malignant lymphomas:

Non-Hodgkin's lymphoma: 0.1 mg/kg/day

Hodgkin's lymphoma: 0.2 mg/kg/day

Dosing: Renal ImpairmentThe FDA-appproved labeling does not contain renal dosing adjustment guidelines. The following guidelines have been used by some clinicians (Aronoff, 2007): Adults:

Cl_{cr} 10-50 mL/minute: Administer 75% of dose

Cl_{cr} <10 mL/minute: Administer 50% of dose

Continuous ambulatory peritoneal dialysis (CAPD): Administer 50% of dose

Dosing: Hepatic ImpairmentThe FDA-approved labeling does not contain hepatic dosing adjustment guidelines. Chlorambucil is hepatically metabolized into active and inactive metabolites; dosage adjustment may be needed in patients with hepatic impairment.

Dosing: Adjustment for Toxicity
Skin reactions: Discontinue treatment

Hematologic: Persistent neutropenia, thrombocytopenia, and/or lymphocytosis: Do not exceed 0.1 mg/kg/day

Concurrent or within 4 weeks of chemotherapy/radiotherapy: Initiate treatment cautiously; reduce dose; monitor closely. (May use the usual dose if radiation therapy is small doses of palliative radiation over isolated foci remote from bone marrow.)

Dosing: Combination Regimens

Leukemia, chronic lymphocytic:

CHL + PRED

CP (Leukemia)

Lymphoma, Hodgkin's disease:

ChlVPP

LOPP

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: OralUsually administered as a single dose; preferably on an empty stomach.

StorageStore in refrigerator at 2°C to 8°C (36°F to 46°F). Protect from light.

Extemporaneously PreparedA 2 mg/mL oral suspension can be prepared by crushing sixty 2 mg tablets in a mortar and then mixing in small amounts of methylcellulose (mix in a total of 30 mL of methylcellulose). Next, add a sufficient quantity of syrup to make 60 mL of final product. Transfer to amber container. Label “shake well,” “refrigerate,” and “protect from light.” Refrigerated stability is 7 days.

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, 4th ed, Cincinnati, OH: Harvey Whitney Books Co, 2000.

Dressman JB and Poust RI, “Stability of Allopurinol and of Five Antineoplastics in Suspension,” *Am J Hosp Pharm*, 1983, 40(4):616-8.

ContraindicationsHypersensitivity to chlorambucil or any component of the formulation; hypersensitivity to other alkylating agents (may have cross-hypersensitivity); pregnancy

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Fertility effects: See “Concerns related to adverse effects” below.
- Secondary malignancies: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: May cause bone marrow suppression;** reduce initial dosage if patient has received myelosuppressive or radiation therapy, or has a depressed baseline leukocyte or platelet count within the previous 4 weeks. Lymphopenia may occur.
- Fertility effects: **[U.S. Boxed Warning]: Affects human fertility; probably mutagenic and teratogenic as well;** chromosomal damage has been documented. Fertility effects (reversible and irreversible sterility) include azoospermia (when administered to prepubertal and pubertal males) and amenorrhea.
- Secondary malignancies: **[U.S. Boxed Warning]: Possibly carcinogenic;** acute myelocytic leukemia and secondary malignancies may be associated with chronic therapy.
- Seizures: Have been observed with use; patients with a history of nephrotic syndrome and high pulse doses are at higher risk of seizures.
- Skin reactions: Rare instances of severe skin reactions (eg, erythema multiforme, Stevens-Johnson syndrome) have been reported; discontinue if a reaction occurs.

Disease-related concerns:

- Seizure disorder: Use with caution in patients with a history of seizure disorder or head trauma; seizures have been observed.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Vaccines: Avoid administration of live vaccines to immunocompromised patients.

Geriatric ConsiderationsToxicity to immunosuppressives is increased in the elderly. Start with lowest recommended adult doses. Signs of infection, such as fever and rise in WBCs, may not occur. Lethargy and confusion may be more prominent signs of infection.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenicity. Chlorambucil crosses the human placenta. Following exposure during the first trimester, case reports have noted adverse renal effects (unilateral agenesis). There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should avoid becoming pregnant while receiving treatment. **[U.S. Boxed Warning]: Affects human fertility; probably mutagenic and teratogenic as well**; chromosomal damage has been documented. Fertility effects (reversible and irreversible sterility) include azoospermia (when administered to prepubertal and pubertal males) and amenorrhea.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse ReactionsFrequency not always defined.

Central nervous system: Agitation (rare), ataxia (rare), confusion (rare), drug fever, focal/generalized seizure (rare), hallucinations (rare)

Dermatologic: Angioneurotic edema, erythema multiforme (rare), rash, skin hypersensitivity, Stevens-Johnson syndrome (rare), toxic epidermal necrolysis (rare), urticaria

Endocrine & metabolic: Amenorrhea, infertility, SIADH (rare)

Gastrointestinal: Diarrhea (infrequent), nausea (infrequent), oral ulceration (infrequent), vomiting (infrequent)

Genitourinary: Azoospermia, cystitis (sterile)

Hematologic: Neutropenia (25%; dose- and duration-related; onset: 3 weeks; recovery: 10 days after last dose), bone marrow failure (irreversible), bone marrow suppression, anemia, leukemia (secondary), leukopenia, lymphopenia, pancytopenia, thrombocytopenia

Hepatic: Hepatotoxicity, jaundice

Neuromuscular & skeletal: Flaccid paresis (rare), muscular twitching (rare), myoclonia (rare), peripheral neuropathy, tremor (rare)

Respiratory: Interstitial pneumonia, pulmonary fibrosis

Miscellaneous: Allergic reactions, malignancies (secondary)

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersLiver function tests, CBC with differential and platelets (weekly, with WBC monitored twice weekly during the first 3-6 weeks of treatment), serum uric acid

Nursing: Physical Assessment/MonitoringUse caution in presence of seizure disorder or bone marrow suppression. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, hematologic myelosuppression, hypersensitivity rash, drug fever, seizures, gastrointestinal upset, hepatotoxicity) on a regular basis throughout therapy. Teach patient (or caregiver) proper use, necessity for contraception with sexually-active female patients, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsLiver function tests, CBC with differential and platelets (weekly, with WBC monitored twice weekly during the first 3-6 weeks of treatment), serum uric acid

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid alcohol, acidic, spicy, or hot foods. May cause menstrual irregularities and/or sterility. You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea or vomiting (small, frequent meals, good mouth care, chewing gum or sucking lozenges may help); or mouth sores (use soft toothbrush or cotton swab for oral care). Report CNS changes (agitation, confusion, hallucinations, seizures); easy bruising or bleeding; unusual rash; persistent nausea, vomiting, or mouth sores; menstrual irregularities; yellowing of skin or dark urine; respiratory difficulty; or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during therapy. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for instruction on appropriate contraceptive measures if necessary or if you suspect you might be pregnant. This drug may cause severe fetal defects. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Leukeran®: 2 mg

Generic AvailableNo

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Tablets (Leukeran)

2 mg (30): $87.54

Mechanism of ActionInterferes with DNA replication and RNA transcription by alkylation and cross-linking the strands of DNA

Pharmacodynamics/Kinetics

Absorption: Rapid and complete

Distribution: V_d: 0.14-0.24 L/kg

Protein binding: ~99%

Metabolism: Hepatic; forms a major active metabolite (phenylacetic acid mustard) and inactive metabolites

Bioavailability: Reduced 10% to 20% with food

Half-life elimination: ~1.5 hours; Phenylacetic acid mustard: ~1.8 hours

Time to peak, plasma: Within 1 hour; Phenylacetic acid mustard: 1.2-2.6 hours

Excretion: Urine (15% to 60% primarily as inactive metabolites, <1% as unchanged drug or phenylacetic acid mustard)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May rarely produce agitation, confusion, and hallucinations

Mental Health: Effects on Psychiatric Treatment Myelosuppression is common; use caution with clozapine and carbamazepine

Index TermsCB-1348; Chlorambucilum; Chloraminophene; Chlorbutinum; NSC-3088; WR-139013

References

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Hogg RH, Portman RJ, Milliner D, et al, “Evaluation and Management of Proteinuria and Nephrotic Syndrome in Children: Recommendations From a Pediatric Nephrology Panel Established at the National Kidney Foundation Conference on Proteinuria, Albuminuria, Risk, Assessment, Detection, and Elimination (PARADE),” *Pediatrics*, 2000, 105(6):1242-9.[PubMed 10835064]

Kyle RA, Greipp PR, Gertz MA, et al, “Waldenström's Macroglobulinemia: A Prospective Study Comparing Daily With Intermittent Oral Chlorambucil,” *Br J Haematol*, 2000, 108(4):737-42.[PubMed 10792277]

Robinson RF, Nahata MC, Mahan JD, “Management of Nephrotic Syndrome in Children,” *Pharmacotherapy*, 2003, 23(8):1021-36.[PubMed 12921248]

Rozman C and Montserrat E, “Chronic Lymphocytic Leukemia,” *N Engl J Med*, 1995, 333(16);1052-7. [PubMed 4568395]

Vandenberg SA, Kulig K, Spoerke DG, et al, “Chlorambucil Overdose: Accidental Ingestion of an Antineoplastic Drug,” *J Emerg Med*, 1988, 6(6):495-8.[PubMed 3065402]

Wagner AM, Brunet S, Puig J, et al, “ Chlorambucil-Induced Inappropriate Antidiuresis in Man With Chronic Lymphocytic Leukemia,” *Ann Hemat*, 1999, 78(1):37-8.

International Brand Names Chloraminophene (FR); Leukeran (AE, AR, AT, AU, BB, BD, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PH, PK, PL, PT, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, UY, YE, ZA, ZM, ZW)

Chloramphenicol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Chloromycetin® may be confused with chlorambucil, Chlor-Trimeton®

Pronunciation(klor am FEN i kole)

Canadian Brand NamesChloromycetin®; Chloromycetin® Succinate; Diochloram®; Pentamycetin®

Pharmacologic CategoryAntibiotic, Miscellaneous

Use: Labeled IndicationsTreatment of serious infections due to organisms resistant to other less toxic antibiotics or when its penetrability into the site of infection is clinically superior to other antibiotics to which the organism is sensitive; useful in infections caused by *Bacteroides*, *H. influenzae*, *Neisseria meningitidis*, *Salmonella*, and *Rickettsia*; active against many vancomycin-resistant enterococci

Dosing: AdultsSystemic infections: I.V.: 50-100 mg/kg/day in divided doses every 6 hours; maximum daily dose: 4 g/day.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Other infections:

Neonates: Initial loading dose: I.V. (I.M. administration is not recommended): 20 mg/kg (the first maintenance dose should be given 12 hours after the loading dose)

Maintenance dose: Postnatal age:

≤7 days: 25 mg/kg/day once every 24 hours

>7 days, ≤2000 g: 25 mg/kg/day once every 24 hours

>7 days, >2000 g: 50 mg/kg/day divided every 12 hours

Children: Usual dosing range: I.V.: 50-100 mg/kg/day in divided doses every 6 hours; maximum daily dose: 4 g/day

Meningitis: I.V.: Infants >30 days and Children: 75-100 mg/kg/day divided every 6 hours

Dosing: Renal ImpairmentUse with caution; monitor serum concentrations.

Dosing: Hepatic ImpairmentUse with caution; monitor serum concentrations.

Administration: I.V.Do not administer I.M.; can be administered IVP over at least 1 minute at a concentration of 100 mg/mL, or I.V. intermittent infusion over 15-30 minutes at a final concentration for administration of ≤20 mg/mL.

Administration: I.V. DetailpH: 6.4-7.0

Dietary ConsiderationsMay have increased dietary need for riboflavin, pyridoxine, and vitamin B_{12}. Sodium content of 1 g injection: ~52 mg (2.25 mEq).

StorageStore at room temperature prior to reconstitution. Reconstituted solutions remain stable for 30 days. Use only clear solutions. Frozen solutions remain stable for 6 months.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, fat emulsion 10%, LR, ${}^1/_2NS$, NS.

Y-site administration: Compatible: Acyclovir, cyclophosphamide, enalaprilat, esmolol, foscarnet, hydromorphone, labetalol, magnesium sulfate, meperidine, morphine, perphenazine, tacrolimus. **Incompatible** Fluconazole.

Compatibility in syringe: Compatible: Ampicillin, diatrizoate meglumine and diatrizoate sodium, diatrizoate sodium, heparin, iohexol, iopamidol, iothalamate meglumine, ioxaglate meglumine and ioxaglate sodium, penicillin G sodium. **Incompatible:** Glycopyrrolate, metoclopramide.

Compatibility when admixed: Compatible: Amikacin, aminophylline, ascorbic acid injection, calcium chloride, calcium gluconate, colistimethate, corticotropin, cyanocobalamin, dimenhydrinate, dopamine, ephedrine, heparin, hydrocortisone sodium succinate, kanamycin, lidocaine, lincomycin, magnesium sulfate, metaraminol, methyldopate, methylprednisolone sodium succinate, metronidazole, metronidazole with sodium bicarbonate, nafcillin, oxacillin, oxytocin, penicillin G potassium, penicillin G sodium, pentobarbital, phenylephrine, phenylephrine with sodium bicarbonate, phytonadione, plasma protein fraction, potassium chloride, ranitidine, sodium bicarbonate, thiopental, verapamil. **Incompatible:** Chlorpromazine, hydroxyzine, phenytoin, polymyxin B sulfate, prochlorperazine edisylate, prochlorperazine mesylate, promethazine, vancomycin. **Variable (consult detailed reference):** Ascorbic acid injection, erythromycin lactobionate, promazine, vitamin B complex with C.

ContraindicationsHypersensitivity to chloramphenicol or any component of the formulation; treatment of trivial or viral infections; bacterial prophylaxis

Warnings/Precautions

Boxed warnings:

- Blood dyscrasias: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Blood dyscrasias: **[U.S. Boxed Warning]: Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) have occurred after both short-term and prolonged therapy. Monitor CBC frequently in all patients;** discontinue if evidence of myelosuppression. Irreversible bone marrow suppression may occur weeks or months after therapy. Avoid repeated courses of treatment. Should not be used for minor infections or when less potentially toxic agents are effective.

- Gray syndrome: Characterized by circulatory collapse, cyanosis, acidosis, abdominal distention, myocardial depression, coma, and death. Reaction appears to be associated with serum levels ≥50 mcg/mL. May result from drug accumulation in patients with impaired hepatic or renal function.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; reduced dosage recommended.

- Renal impairment: Use with caution in patients with renal impairment

Special populations:

- Glucose 6-phosphate dehydrogenase deficiency: Use with caution in patients with glucose 6-phosphate dehydrogenase deficiency.

- Neonates: Use with caution in neonates; due to risk of gray syndrome.

Geriatric ConsiderationsChloramphenicol has not been studied in the elderly. It is not necessary to adjust the dose based upon the decrease in renal function associated with age. Chloramphenicol should be reserved for serious infections and the oral form avoided.

Pregnancy ConsiderationsChloramphenicol crosses the placenta producing cord concentrations approaching maternal serum concentrations. An increased risk of teratogenic effects has not been identified for chloramphenicol and there have been no reports of fetal harm related to use of chloramphenicol in pregnancy. "Gray Syndrome" has occurred in premature infants and newborns receiving chloramphenicol. In most cases, chloramphenicol was started during the first 48 hours of life, but it has also occurred in older patients after high doses. Symptoms began after 3-4 days of therapy, starting with abdominal distention and continuing to progressive pallid cyanosis, vasomotor collapse, irregular respiration, and death within a few hours of symptom onset. Stopping therapy can reverse the process and allow complete recovery. There is one case report of an infant with gray baby syndrome after *in utero* exposure to a single maternal dose during labor, followed by a 10-fold overdose of chloramphenicol in the first day of life. The extent of the contribution of the single dose given during labor is unknown. The manufacturer recommends caution if used in a pregnant patient near term or during labor.

LactationEnters breast milk/use with caution (AAP rates “of concern”)

Breast-Feeding ConsiderationsChloramphenicol is excreted in human milk in both the active form and as inactive metabolites. Chloramphenicol is well absorbed following oral administration; however, metabolism and excretion are highly variable in infants and children. The half-life is also significantly prolonged in low birth weight infants. There have been documented toxicities in neonates and preterm infants when chloramphenicol has been used at therapeutic doses. The manufacturer recommends caution if using chloramphenicol in a breast-feeding infant. The AAP considers chloramphenicol to be a drug "for which the effect on nursing infants is unknown but may be of concern." Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Chloramphenicol in Pregnacy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Confusion, delirium, depression, fever, headache

Dermatologic: Angioedema, rash, urticaria

Gastrointestinal: Diarrhea, enterocolitis, glossitis, nausea, stomatitis, vomiting

Hematologic: Aplastic anemia, bone marrow suppression, granulocytopenia, hypoplastic anemia, pancytopenia, thrombocytopenia

Ocular: Optic neuritis

Miscellaneous: Anaphylaxis, hypersensitivity reactions, Gray syndrome

Metabolism/Transport Effects**Inhibits** CYP2C9 (weak), 3A4 (weak)

Drug Interactions

Anticonvulsants (Hydantoin): Chloramphenicol may decrease the metabolism of Anticonvulsants (Hydantoin). Anticonvulsants (Hydantoin) may decrease the serum concentration of Chloramphenicol. Increased chloramphenicol concentrations have also been seen. *Risk D: Consider therapy modification*

Barbiturates: Chloramphenicol may decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

Cyanocobalamin: Chloramphenicol may diminish the therapeutic effect of Cyanocobalamin. The expected hematologic response for the treatment of anemia may be opposed. *Risk D: Consider therapy modification*

Rifampin: May increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

Sulfonylureas: Chloramphenicol may decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: May decrease intestinal absorption of vitamin B_{12} may have increased dietary need for riboflavin, pyridoxine, and vitamin B_{12}.

Test InteractionsMay cause false-positive results in urine glucose tests when using cupric sulfate (Benedict's solution, Clinitest®).

Monitoring ParametersCBC with differential (baseline and every 2 days during therapy), periodic liver and renal function tests, serum drug concentration

Reference Range

Therapeutic levels:

Meningitis:

Peak: 15-25 mcg/mL; toxic concentration: >40 mcg/mL

Trough: 5-15 mcg/mL

Other infections:

Peak: 10-20 mcg/mL

Trough: 5-10 mcg/mL

Timing of serum samples: Draw levels 0.5-1.5 hours after completion of I.V. dose

Nursing: Physical Assessment/MonitoringAssess results of culture/sensitivity tests and patient's allergy history prior to beginning treatment. Assess other pharmacological or herbal products patient may be taking for potential interactions. Assess results of laboratory tests periodically during therapy. Observe closely for adverse reactions during and following therapy (eg, bone marrow depression or aplastic anemia [petechiae, sore throat, fatigue, unusual bleeding or bruising, abdominal or bone pain], circulatory collapse, CNS disturbances, opportunistic infection). Advise patients with diabetes about use of Clinitest® (may cause false-positive test). Teach patient possible side effects/appropriate interventions and adverse symptoms to report (eg, CNS changes, opportunistic infection, aplastic anemia) may occur 3 weeks to 12 months after initial exposure to chloramphenicol.

Monitoring: Lab TestsCBC with differential (baseline and every 2 days during therapy), periodic liver and renal function, serum drug concentration; culture and sensitivity prior to initiating therapy

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by infusion and you will be monitored during each infusion; report immediately unusual chest tightness, difficulty breathing or swallowing; itching or skin rash; back pain or acute headache; or redness, swelling, or pain at infusion site. You may experience a bitter taste during infusion, this will pass. If you have diabetes, drug may cause false test results with Clinitest® glucose monitoring; use alternative glucose monitoring. May cause nausea, vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report persistent rash or diarrhea; pain, burning, or numbness of extremities; petechiae; sore throat; fatigue; unusual bleeding or bruising; vaginal itching or discharge; mouth sores; yellowing of skin or eyes; dark urine or stool discoloration (blue); CNS disturbances (nightmares, acute headache); lack of improvement or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 1 g [contains sodium ~52 mg/g (2.25 mEq/g)]

Generic AvailableYes

Mechanism of ActionReversibly binds to 50S ribosomal subunits of susceptible organisms preventing amino acids from being transferred to growing peptide chains thus inhibiting protein synthesis

Pharmacodynamics/Kinetics

Distribution: To most tissues and body fluids

Chloramphenicol: V_d: 0.5-1 L/kg

Chloramphenicol succinate: V_d: 0.2-3.1 L/kg; decreased with hepatic or renal dysfunction

Protein binding: Chloramphenicol: ~60%; decreased with hepatic or renal dysfunction and in newborn infants

Metabolism:

Chloramphenicol: Hepatic to metabolites (inactive)

Chloramphenicol succinate: Hydrolyzed in the liver, kidney and lungs to chloramphenicol (active)

Bioavailability:

Chloramphenicol: Oral: ~80%

Chloramphenicol succinate: I.V.: ~70%; highly variable, dependant upon rate and extent of metabolism to chloramphenicol

Half-life elimination:

Normal renal function:

Chloramphenicol: Adults: ~4 hours; Children 4-6 hours; Infants: Significantly prolonged

Chloramphenicol succinate: Adults: ~3 hours

End-stage renal disease: Chloramphenicol: 3-7 hours

Hepatic disease: Prolonged

Excretion: Urine (~30% as unchanged chloramphenicol succinate in adults, 6% to 80% in children; 5% to 15% as chloramphenicol)

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Glossitis and stomatitis.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay rarely cause nightmares
Mental Health: Effects on Psychiatric TreatmentMay cause bone marrow suppression; use caution with clozapine and carbamazepine
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Yunis AA, “Chloramphenicol: Relation of Structure to Activity and Toxicity,” *Annu Rev Pharmacol Toxicol*, 1988, 28:83-100.[PubMed 3289495]

International Brand NamesBiophenicol (AT); Cebenicol (FR); Chemicetina (IT); Chloracil (TH); Chloram-P (TH); Chloramphen (FI); Chloramphenicol (BE, CZ, NO); Chloramphenicol Faure, Ophthadoses (CH); Chloramphenicol RIT (BE); Chlorbiotic (ID); Chlornitromycin (BG); Chlorocide S (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Chloromycetin (AR, BF, BJ, CI, CR, DO, EC, ES, ET, GB, GH, GM, GN, GT, HK, HN, IE, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, NI, PA, PE, PK, PT, SC, SD, SL, SN, SV, TN, TZ, UG, ZA, ZM, ZW); Chloromycetin Injection (AU); Chloroptic (GR, IE); Chlorsig (NZ); Cloftal (VE); Cloramfeni Ofteno (MX); Cloran (MX); Cloranfenicol (VE); Cloranfenicol N.T. (EC); Clordil (MX); Cloromisan (PE); Cloroptic (CO); Clovicol (PH); Colain (ID); Colircusi Cloramfenicol (ES); Colsancetine (ID); Cusi Chloramphenicol (PL); Detreomycyna (PL); Enkacetyn (ID); Exacol (MX); Fenicol (ID); Gemitin oftalmico (CN); Globenicol (NL); Helocetin (KP); Ikamicetin (ID); Isopto Fenicol (BE, NZ, PY, SG); Isotic Salmicol (ID); Kalmicetine (IN); Kemicetin (AT); Kemicetine (AE, BH, CY, EG, GB, GR, HK, ID, IL, IQ, IR, JO, KW, LB, LY, MY, OM, PH, PT, QA, SA, SY, YE); Kloramfenicol (DK, SE); Klorfen (PH); Lennacol (ZA); Likoclor (ID); Minims Eye Drops (NZ); New-Lylo (TW); Ofenicol (PY); Oftadil (MX); Oftalmolosa Cusi Chloramphenicol (PL); Oftan-Akvakol (EE); Oleomycetin (DE); Posifenicol C (DE); Quemicitina (BR, CO); Reclor (IN); Reco (ID); Septicol (CH); Septicyn (PH); Solu-Paraxin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Suismycetin (BB, BM, BS, BZ, GY, JM, PR, SR, TT); Synchlolim (TH); Unifenicol (BR); Vanmycetin (IN); Vioclor (UY); Westenicol (MX)

Chlordiazepoxide and Methscopolamine

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English

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Medication Safety Issues

Librax® formulation may be cause for confusion:

In November 2004, Valeant Pharmaceuticals licensed the Librax® trademark to Victory Pharmaceuticals. Subsequently, the product was reformulated to contain chlordiazepoxide and methscopolamine. In January 2006, Valeant Pharmaceuticals began redistributing the original formulation of Librax®, containing clidinium and chlordiazepoxide. Victory Pharmaceuticals has discontinued their product. **Note:** The formulation of Librax® distributed in Canada (Valeant Canada Ltd) always contained clidinium and chlordiazepoxide.

Pronunciation(klor dye az e POKS ide & meth skoe POL a meen)

U.S. Brand NamesLibrax® *[reformulation]* [DSC]

Pharmacologic CategoryAnticholinergic Agent; Benzodiazepine

Use: Labeled IndicationsAdjunctive treatment of peptic ulcer; treatment of irritable bowel syndrome, acute enterocolitis

Dosing: AdultsPeptic ulcer, irritable bowel syndrome, acute enterocolitis: Oral: 1-2 capsules 3-4 times/day; adjust dose based on individual response.

Dosing: ElderlyOral: Initial dose should not exceed 2 capsules/day; adjust dose as tolerated.

Administration: OralAdminister before meals and at bedtime. Do not abruptly discontinue after prolonged use; taper dose gradually.

Dietary ConsiderationsTake before meals.

StorageStore at room temperature of 15°C to 30˚C (59°F to 86˚F).

RestrictionsC-IV

ContraindicationsHypersensitivity to chlordiazepoxide, methscopolamine, or any component of the formulation; glaucoma; prostatic hyperplasia; benign bladder neck obstruction

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.
- Elderly: Use with caution in the elderly.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.
- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsDue to its long-acting metabolite, chlordiazepoxide is not considered a drug of choice in the elderly. The use of anticholinergic agents may cause problems with bladder emptying, constipation, or case confusion. This combination of benzodiazepine and anticholinergic agent may increase the risk of confusion.

Pregnancy Risk FactorC

Pregnancy ConsiderationsSee individual agents.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsSee individual agents.

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersRespiratory and cardiovascular status, monitor for orthostasis; mental status

Nursing: Physical Assessment/MonitoringSee individual agent for Chlordiazepoxide.

Patient EducationSee individual agent for Chlordiazepoxide.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: Chlordiazepoxide hydrochloride 5 mg and methscopolamine nitrate 2.5 mg [DSC]

Generic AvailableNo

ManufacturerVictory Pharmaceuticals

Mechanism of ActionChlordiazepoxide binds to stereospecific benzodiazepine (BZD) binding sites on GABA (A) receptor complexes at several sites within the central nervous system, including the limbic system and reticular formation. BZDs enhance GABA-mediated chloride influx through GABA receptor channels, causing membrane hyperpolarization. The net neuroinhibitory effects result in the observed sedative, hypnotic, anxiolytic, and muscle relaxant properties.

Methscopolamine is a peripheral anticholinergic agent with limited ability to cross the blood-brain barrier and provides a peripheral blockade of muscarinic receptors. This agent reduces the volume and the total acid content of gastric secretions, inhibits salivation, and reduces gastrointestinal motility.

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause dizziness, confusion, amnesia, and insomnia. May rarely be associated with paradoxical reactions that include hyperactive and aggressive behaviors.

Mental Health: Effects on Psychiatric TreatmentConcomitant use with psychotropic agents may produce additive sedative and anticholinergic effects; enzyme inducers (carbamazepine) may decrease the therapeutic effects and inhibitors (nefazodone) may enhance therapeutic effects.

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

Risk factors for abuse include personal or family history of substance abuse and personality disorder.

Index TermsMethscopolamine Nitrate and Chlordiazepoxide Hydrochloride

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ChlordiazePOXIDE

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English English

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Medication Safety Issues

Sound-alike/look-alike issues:

ChlordiazePOXIDE may be confused with chlorproMAZINE

Librium® may be confused with Librax®

Pronunciation(klor dye az e POKS ide)

U.S. Brand NamesLibrium®

Canadian Brand NamesApo-Chlordiazepoxide®

Pharmacologic CategoryBenzodiazepine

Use: Labeled IndicationsManagement of anxiety disorder or for the short-term relief of symptoms of anxiety; withdrawal symptoms of acute alcoholism; preoperative apprehension and anxiety

Dosing: Adults

Anxiety:

Oral: 15-100 mg divided 3-4 times/day

I.M., I.V.: Initial: 50-100 mg followed by 25-50 mg 3-4 times/day as needed

Preoperative anxiety: I.M.: 50-100 mg prior to surgery

Ethanol withdrawal symptoms: Oral, I.V.: 50-100 mg to start, dose may be repeated in 2-4 hours as necessary to a maximum of 300 mg/24 hours

Note: Up to 300 mg may be given I.M. or I.V. during a 6-hour period, but not more than this in any 24-hour period.

Dosing: ElderlyAnxiety: Oral: 5 mg 2-4 times/day; adjust for renal impairment. Avoid use if possible. See Geriatric Considerations.

Dosing: PediatricAnxiety: Oral, I.M.:

<6 years: Not recommended

>6 years: 0.5 mg/kg/24 hours divided every 6-8 hours

Dosing: Renal Impairment

Cl_{cr} <10 mL/minute: Administer 50% of dose.

Not dialyzable (0% to 5%)

Dosing: Hepatic ImpairmentAvoid use.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Administer by deep I.M. injection slowly into the upper outer quadrant of the gluteus muscle. Use only the diluent provided for I.M. use. Solutions made with SWFI or NS cause pain with I.M. administration.

Administration: I.V.Administer slowly over at least 1 minute. Do not use the diluent provided for I.M. use. Air bubbles form during reconstitution.

Administration: I.V. DetailRapid administration may cause symptoms of overdose.

pH: 2.5-3.5 (using I.M. diluent)

pH: 3 (using SWFI or NS as diluent)

StorageInjection: Prior to reconstitution, store under refrigeration and protect from light. Solution should be used immediately following reconstitution.

Reconstitution

I.M. use: Reconstitute by adding 2 mL of provided diluent; agitate gently until dissolved. Provided diluent is **not** for I.V. use.

I.V. use: Reconstitute by adding 5 mL NS or SWFI; agitate gently until dissolved; **do not administer this dilution I.M.**

CompatibilityStable in D_5W; **incompatible (consult detailed reference)** in Ringer's injection, NS.

Y-site administration: Compatible: Heparin, hydrocortisone sodium succinate, potassium chloride, vitamin B complex with C. **Incompatible:** Cefepime.

RestrictionsC-IV

ContraindicationsHypersensitivity to chlordiazepoxide or any component of the formulation (cross-sensitivity with other benzodiazepines may also exist); narrow-angle glaucoma; pregnancy

Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.
- Porphyria: Use with caution in patients with porphyria.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; active metabolites with extended half-lives may lead to delayed accumulation and adverse effects.
- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury. Active metabolites with extended half-lives may lead to delayed accumulation and adverse effects.
- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.
- Pediatrics: Use with caution in children; active metabolites with extended half-lives may lead to delayed accumulation and adverse effects.

Dosage form specific issues:

- Injection: Parenteral administration should be avoided in comatose patients or shock. Adequate resuscitative equipment/personnel should be available, and appropriate monitoring should be conducted at the time of injection and for several hours following administration. The parenteral formulation should be diluted for I.M. administration with the supplied diluent only. This diluent should not be used when preparing the drug for intravenous administration.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.
- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsDue to its long-acting metabolite, chlordiazepoxide is not considered a drug of choice in the elderly. Long-acting benzodiazepines have been associated with falls in the elderly; interpretive guidelines from the Centers for Medicare and Medicaid Services (CMS) discourage the use of this agent in residents of long-term care facilities.

Pregnancy Risk FactorD

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsThere is no significant data for chlordiazepoxide, but a related compound, diazepam, has been shown to accumulate in nursing infants. It is recommended to discontinue nursing or the drug.

Adverse Reactions

>10%:

Central nervous system: Drowsiness, fatigue, ataxia, lightheadedness, memory impairment, dysarthria, irritability

Dermatologic: Rash

Endocrine & metabolic: Libido decreased, menstrual disorders

Gastrointestinal: Xerostomia, salivation decreased, appetite increased or decreased, weight gain/loss

Genitourinary: Micturition difficulties

1% to 10%:

Cardiovascular: Hypotension

Central nervous system: Confusion, dizziness, disinhibition, akathisia

Dermatologic: Dermatitis

Endocrine & metabolic: Libido increased

Gastrointestinal: Salivation increased

Genitourinary: Sexual dysfunction, incontinence

Neuromuscular & skeletal: Rigidity, tremor, muscle cramps

Otic: Tinnitus

Respiratory: Nasal congestion

<1%: Photosensitivity

Metabolism/Transport Effects **Substrate** of CYP3A4 (major)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Serum concentrations/effects may be increased with grapefruit juice, but unlikely because of high oral bioavailability of chlordiazepoxide.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersRespiratory and cardiovascular status, mental status, check for orthostasis

Reference RangeTherapeutic: 0.1-3 mcg/mL (SI: 0-10 µmol/L); Toxic: >23 mcg/mL (SI: >77 µmol/L)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess for CNS depression. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance; periodically evaluate need for continued use. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. **I.V.:** Monitor vital signs frequently during infusion, observe safety precautions, and maintain bedrest for 2-3 hours following infusion.

Patient Education**Oral:** Take exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. Do not use alcohol or other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); or altered sexual drive or ability (reversible). Report persistent CNS effects (eg, euphoria, confusion, increased sedation, depression); chest pain, palpitations, or rapid heartbeat; muscle cramping, weakness, tremors, rigidity, or altered gait; or worsening of condition. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 5 mg, 10 mg, 25 mg

Injection, powder for reconstitution, as hydrochloride: 100 mg [diluent contains benzyl alcohol, polysorbate 80, and propylene glycol]

Generic AvailableYes: Capsule

Pricing: U.S. (www.drugstore.com)

Capsules (Chlordiazepoxide HCl)

5 mg (60): $14.99

10 mg (60): $13.99

25 mg (60): $18.99

Capsules (Librium)

10 mg (60): $98.79

25 mg (30): $65.99

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Distribution: V_d: 3.3 L/kg; crosses placenta; enters breast milk

Protein binding: 90% to 98%

Metabolism: Extensively hepatic to desmethyldiazepam (active and long-acting)

Half-life elimination: 6.6-25 hours; End-stage renal disease: 5-30 hours; Cirrhosis: 30-63 hours

Time to peak, serum: Oral: Within 2 hours; I.M.: Results in lower peak plasma levels than oral

Excretion: Urine (minimal as unchanged drug)

Related Information

- Benzodiazepines
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsAbrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Chlordiazepoxide is poorly and erratically absorbed after I.M. administration; undergoes phase I metabolism. Chlordiazepoxide is a long half-life benzodiazepine. Duration of action after a single dose is determined by redistribution rather than metabolism. Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle-relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include personal or family history of substance abuse and personality disorder.

Anesthesia and Critical Care Concerns/Other ConsiderationsChronic use of this agent may increase the perioperative benzodiazepine dose needed to achieve desired effect. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

Index TermsMethaminodiazepoxide Hydrochloride

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International Brand NamesBenpine (MY, TH); Cetabrium (ID); Chlordiazepoxid L.F.M. (HU); Chlordiazepoxidum (NL); Cozep (TH); Disarim (PT); Elenium (BG, CZ, HN, HU, PK, PL); Eposal (VE); Equilibrium (IN); Klopoxid (DK); Klorpo (PH, SG); Lentotran (PT); Librium (AE, BH, CY, EG, FR, GB, GH, HK, HN, HU, ID, IE, IL, IN, IQ, IR, IT, JO, KE, KW, LB, LY, MY, OM, QA, SA, SY, TW, TZ, UG, YE, ZA, ZM); Nova-Pam (NZ); O.C.M. (AR); Oasil (GR); Omnalio (ES); Paxium (PT); Peast C (JP); Psicosedin (BR); Radepur (AE, BH, CY, DE, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Reliberan (IT); Retcol (JP); Risolid (DK, FI); Seren (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Sophiamin (JP); Trakipearl (JP)

Chlorhexidine Gluconate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Peridex® may be confused with Precedex™

Pronunciation(klor HEKS i deen GLOO koe nate)
U.S. Brand NamesAvagard™ [OTC]; BactoShield® CHG [OTC]; Betasept® [OTC]; ChloraPrep® Frepp® [OTC]; ChloraPrep® Sepp® [OTC]; ChloraPrep® [OTC]; Chlorascrub™ Maxi [OTC]; Chlorascrub™ [OTC]; Dyna-Hex® [OTC]; Hibiclens® [OTC]; Hibistat® [OTC]; Operand® Chlorhexidine Gluconate [OTC]; Peridex®; PerioChip®; PerioGard®
Canadian Brand NamesHibidil® 1:2000; ORO-Clense; Peridex® Oral Rinse
Pharmacologic CategoryAntibiotic, Oral Rinse; Antibiotic, Topical
Use: Labeled IndicationsSkin cleanser for surgical scrub, cleanser for skin wounds, preoperative skin preparation, germicidal hand rinse, and as antibacterial dental rinse. Chlorhexidine is active against gram-positive and gram-negative organisms, facultative anaerobes, aerobes, and yeast.

Orphan drug: Peridex®: Oral mucositis with cytoreductive therapy when used for patients undergoing bone marrow transplant

Use: Dental

Antibacterial dental rinse; chlorhexidine is active against gram-positive and gram-negative organisms, facultative anaerobes, aerobes, and yeast

Chip, for periodontal pocket insertion: Indicated as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis; may be used as part of a periodontal maintenance program

Dosing: Adults

Oral rinse (Peridex®, PerioGard®):

Floss and brush teeth, completely rinse toothpaste from mouth and swish 15 mL (one capful) undiluted oral rinse around in mouth for 30 seconds, then expectorate. Caution patient not to swallow the medicine and instruct not to eat for 2-3 hours after treatment. (Cap on bottle measures 15 mL.)

Treatment of gingivitis: Oral prophylaxis: Swish for 30 seconds with 15 mL chlorhexidine, then expectorate; repeat twice daily (morning and evening). Patient should have a re-evaluation followed by a dental prophylaxis every 6 months.

Periodontal chip: One chip is inserted into a periodontal pocket with a probing pocket depth ≥5 mm. Up to 8 chips may be inserted in a single visit. Treatment is recommended every 3 months in pockets with a remaining depth ≥5 mm. If dislodgment occurs 7 days or more after placement, the subject is considered to have had the full course of treatment. If dislodgment occurs within 48 hours, a new chip should be inserted. The chip biodegrades completely and does not need to be removed. Patients should avoid dental floss at the site of PerioChip® insertion for 10 days after placement because flossing might dislodge the chip.

Insertion of periodontal chip: Pocket should be isolated and surrounding area dried prior to chip insertion. The chip should be grasped using forceps with the rounded edges away from the forceps. The chip should be inserted into the periodontal pocket to its maximum depth. It may be maneuvered into position using the tips of the forceps or a flat instrument.

Cleanser:

Surgical scrub: Scrub 3 minutes and rinse thoroughly, wash for an additional 3 minutes

Hand sanitizer (Avagard™): Dispense 1 pumpful in palm of one hand; dip fingertips of opposite hand into solution and work it under nails. Spread remainder evenly over hand and just above elbow, covering all surfaces. Repeat on other hand. Dispense another pumpful in each hand and reapply to each hand up to the wrist. Allow to dry before gloving.

Hand wash: Wash for 15 seconds and rinse

Hand rinse: Rub 15 seconds and rinse

Dosing: ElderlyRefer to adult dosing.
Administration: OralPeriodontal chip insertion: Pocket should be isolated and surrounding area dried prior to chip insertion. The chip should be grasped using forceps with the rounded edges away from the forceps. The chip should be inserted into the periodontal pocket to its maximum depth. It may be maneuvered into position using the tips of the forceps or a flat instrument. The chip biodegrades completely and does not need to be removed. Patients should avoid dental floss at the site of PerioChip® insertion for 10 days after placement because flossing might dislodge the chip.
Administration: TopicalKeep out of eyes, ears, and mouth. Do not routinely apply to wounds which involve more than superficial layers of skin. Avoid contact with meninges (do not use on lumbar puncture sites). Solutions may be flammable (contain isopropyl alcohol); avoid exposure to open flame and/or ignition source (eg, electrocautery) until completely dry; avoid application to hairy areas which may

significantly delay drying time.

Administration: OtherHand sanitizer (Avagard™): To facilitate drying, continue rubbing hand prep into hands until dry.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).

Avagard™: Avoid excessive heat. Ethanol-containing products are flammable; keep away from flames or fire. Hand lotions and gel hand sanitizers are incompatible. The thickeners used in these products (eg, carbomer) react to form an insoluble salt and cause loss of antibacterial action.

ContraindicationsHypersensitivity to chlorhexidine gluconate or any component of the formulation

Warnings/Precautions

Dosage form specific issues:

- Oral: Staining of oral surfaces (mucosa, teeth, tooth restorations, dorsum of tongue) may occur; may be visible as soon as 1 week after therapy begins and is more pronounced when there is a heavy accumulation of unremoved plaque and when teeth fillings have rough surfaces. Stain does not have a clinically adverse effect, but because removal may not be possible, patient with frontal restoration should be advised of the potential permanency of the stain.

- Topical: For topical use only. Avoid application over large surfaces or into open wounds. Keep out of eyes and ears. May stain fabric. There have been case reports of anaphylaxis following chlorhexidine disinfection. Not for preoperative preparation of face or head; avoid contact with meninges (do not use on lumbar puncture sites). Solutions may be flammable (contain isopropyl alcohol); avoid exposure to open flame and/or ignition source (eg, electrocautery) until completely dry; avoid application to hairy areas which may significantly delay drying time. Avoid use in children <2 months of age due to increased absorption and/or irritation.

Pregnancy Risk FactorB

Adverse Reactions

Oral:

>10%: Tartar on teeth increased, taste changes. Staining of oral surfaces (mucosa, teeth, dorsum of tongue) may be visible as soon as 1 week after therapy begins and is more pronounced when there is a heavy accumulation of unremoved plaque and when teeth fillings have rough surfaces. Stain does not have a clinically adverse effect but because removal may not be possible, patient with frontal restoration should be advised of the potential permanency of the stain.

1% to 10%: Gastrointestinal: Tongue irritation, oral irritation

<1%: Facial edema, nasal congestion, dyspnea

Topical: Skin erythema and roughness, dryness, sensitization, allergic reactions

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Chip, for periodontal pocket insertion:

PerioChip®: 2.5 mg

Liquid, topical [surgical scrub]:

BactoShield® CHG: 2% (120 mL, 480 mL, 750 mL, 960 mL, 3840 mL); 4% (120 mL, 480 mL, 960 mL, 3840 mL) [contains isopropyl alcohol]

Betasept®: 4% (120 mL, 240 mL, 480 mL, 960 mL, 3840 mL) [contains isopropyl alcohol]

ChloraPrep®: 2% (0.67 mL, 1.5 mL, 3 mL, 10.5 mL, 26 mL) [contains isopropyl alcohol 70%; prefilled applicator]

Dyna-Hex®: 2% (120 mL, 480 mL, 960 mL, 3840 mL) [contains isopropyl alcohol]; 4% (120 mL, 480 mL, 960 mL, 3840 mL) [contains isopropyl alcohol]

Hibiclens®: 4% (15 mL, 120 mL, 240 mL, 480 mL, 960 mL, 3840 mL) [contains isopropyl alcohol]

Operand® Chlorhexidine Gluconate: 2% (120 mL); 4% (120 mL, 240 mL, 480 mL, 960 mL, 3840 mL) [contains isopropyl alcohol]

Liquid, oral [rinse]: 0.12% (480 mL)

Peridex®: 0.12% (120 mL, 480 mL, 1920 mL) [contains alcohol 11.6%; mint flavor]

PerioGard®: 0.12% (480 mL) [contains alcohol 11.6%; mint flavor]

Lotion, topical [surgical scrub]:

Avagard™: 1% (500 mL) [contains ethyl alcohol and moisturizers]

Sponge/Brush, topical:

BactoShield® CHG): 4% [contains isopropyl alcohol]

Sponge, topical [surgical scrub]:

ChloraPrep® 3 mL: 2% (25s) [contains isopropyl alcohol; available in clear or Hi-Lite Orange™]

ChloraPrep® 10.5 mL: 2% (25s) [contains isopropyl alcohol; available in clear, Hi-Lite Orange™, and Scrub Teal™]

ChloraPrep® 26 mL: 2% (25s) [contains isopropyl alcohol; available in clear, Hi-Lite Orange™, and Scrub Teal™]

ChloraPrep® Frepp® 1.5 mL: 2% (20s) [contains isopropyl alcohol]

ChloraPrep® Sepp® 0.67 mL: 2% (200s) [contains isopropyl alcohol]

Swab, topical [prep pad]:

Chlorascrub™: 3.15% (100s) [contains isopropyl alcohol]

Swabstick, topical [surgical scrub]:

ChloraPrep® 1.75 mL: 2% (48s) [contains isopropyl alcohol]

ChloraPrep® 5.25 mL: 2% (40s) [contains isopropyl alcohol]

Chlorascrub™ 1.6 mL: 3.15% (50s) [contains isopropyl alcohol]

Chlorascrub™ Maxi 5.1 mL: 3.15% (30s) [contains isopropyl alcohol]

Wipe, topical [towlette]:

Hibistat®: 0.5% (50s) [contains isopropyl alcohol]

Generic AvailableYes: Oral liquid

Pricing: U.S. (www.drugstore.com)

Solution (Chlorhexidine Gluconate)

0.12% (473): $22.00

Solution (Peridex)

0.12% (473): $23.99

Solution (Periogard)

0.12% (473): $15.99

Mechanism of ActionThe bactericidal effect of chlorhexidine is a result of the binding of this cationic molecule to negatively charged bacterial cell walls and extramicrobial complexes. At low concentrations, this causes an alteration of bacterial cell osmotic equilibrium and leakage of potassium and phosphorous resulting in a bacteriostatic effect. At high concentrations of chlorhexidine, the cytoplasmic contents of the bacterial cell precipitate and result in cell death.

Pharmacodynamics/Kinetics

Topical hand sanitizer (Avagard™): Duration of antimicrobial protection: 6 hours

Oral rinse (Peridex®, PerioGard®):

Absorption: ~30% retained in the oral cavity following rinsing and slowly released into oral fluids; poorly absorbed

Time to peak, plasma: Oral rinse: Detectable levels not present after 12 hours

Excretion: Feces (~90%); urine (<1%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Increased tartar on teeth, altered taste perception, staining of oral surfaces (mucosa, teeth, dorsum of tongue), and oral/tongue irritation. Staining may be visible as soon as 1 week after therapy begins and is more pronounced when there is a heavy accumulation of unremoved plaque and when teeth fillings have rough surfaces. Stain does not have a clinically adverse effect but because removal may not be possible, patient with frontal restoration should be advised of the potential permanency of the stain.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms3M™ Avagard™ [OTC]; CHG

References

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International Brand Names AB Antiseptico (PY); Alcloxidine (IL); Alcosept (IL); Blend-A-Med (DE); Bucoglobin (UY); Cetavlon (FR); Chlorhex (TH); Chlorhexamed (CH); Chlorhexidine Mouthwash (AU); Chlorhexidine Obstetric Lotion (AU); Chlorohex gel (AU); Chlorohex gel Forte (AU); Chlorohex Mouth Rinse (AU); Cleardent (IL); Corsodyl (IT, PT, ZA); Diaseptyl (FR); Dosiseptine (FR); Exoseptoplix (FR); Hexol (TH); Hibident (AT, NL); Hibigel (NL); Hibiscrub (FR, HK, NL, TH, TW); Hibisol (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, HK, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Hibitan (KP); Hibitane (AE, BE, BH, CY, DK, EG, FR, HK, ID, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SE, SY, YE); Hibitane Concentrate (MY, TH, TW); Hibitane Cream (GR); Hibitane Dental (NO); Hibitane Solution (GR); Hidine (TH); Klorhexidin (NO); Klorhexol (FI); Orahex (PH); Perio Chip (IL, PH); Perioxidin (MX); Plaqacide Mouthrinse (AU); Savlon (IE); Septalone (IL); Septol (IL); Xylodent (IL)

Chlorophyll

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English

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Pronunciation(KLOR oh fil)
U.S. Brand NamesNulloÂŽ [OTC]
Pharmacologic CategoryGastrointestinal Agent, Miscellaneous
Use: Labeled IndicationsControl fecal odors in colostomy or ileostomy
Dosing: AdultsControl of odors:

Oral: 100-200 mg/day in divided doses; may increase to 300 mg/day if odor is not controlled (maximum: 300 mg/day)

Ostomy: Tablet: May also place 1-2 tablets in empty pouch each time it is reused or changed.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricControl of odors: Oral: Children >12 years: Refer to adult dosing.
Warnings/Precautions

Other warnings/precautions:

âˇ Self-medication (OTC use): Reduce the dose if cramps or diarrhea occur; if symptoms persist, consult healthcare provider. Smallest effective dose should be used.

Adverse ReactionsFrequency not defined: Gastrointestinal: Diarrhea, green stools, abdominal cramping
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet: Chlorophyllin copper complex 100 mg

Tablet: Chlorophyllin copper complex 33.3 mg [DSC]

Generic AvailableNo
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsChlorophyllin

Chlorophyllin, Papain, and Urea

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English

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Special Alerts

Papain-Containing Topical Products: FDA Enforcement Action - November 2008

In September 2008, the U.S. Food and Drug Administration (FDA) ordered companies to discontinue manufacturing papain-containing topical products by November 24, 2008, and to cease shipping of these products by January 21, 2009. At present, all topical products containing papain (~35 products under various trade names) lack FDA approval. Safety concerns have also been raised from reports of serious hypersensitivity reactions, including anaphylaxis, associated with papain use. Hypotension and tachycardia has also been observed in association with these hypersensitivity reactions. In addition, the medical literature also suggests that patients with latex hypersensitivity may also be allergic to papaya, the source of papain.

Papain-containing topical products manufactured prior to the ordered stop date may still be found on pharmacy shelves for a short period of time. However, healthcare providers are reminded that alternative products with FDA approval for the management of wounds are available.

Additional information may be found at http://www.fda.gov/cder/news/papain/qa.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Ziox™ may be confused with Zyvox®

Pronunciation(KLOR oh fil in, pa PAY in, & yoor EE a)

U.S. Brand NamesAllanfil 405; Allanfil Spray; Panafil®; Panafil® SE; Papfyll™; Ziox 405™; Ziox™

Pharmacologic CategoryEnzyme, Topical Debridement

Use: Labeled IndicationsTreatment of acute and chronic lesions, such as venous, diabetic, and decubitus ulcers, burns, postoperative wounds, pilonidal cyst wounds, carbuncles, and miscellaneous traumatic or infected wounds

Dosing: AdultsTopical: Apply with each dressing change; daily or twice daily dressing changes are preferred, but some products may be applied every 2-3 days. Cover with dressing following application.

Foam: Apply a single even layer

Ointment: Apply $^{1}/_{8}$” thickness over the wound with clean applicator.

Spray: Completely cover the wound site so that the wound is not visible.

Dosing: ElderlyRefer to adult dosing.

Administration: TopicalCleanse wound prior to application. May apply under pressure dressings. Initially may require more frequent dressing changes to decrease irritation from enzymatic activity. Avoid cleansing with hydrogen peroxide solution. Avoid using heavy metal containing solutions (lead, mercury, silver). Do not use in or around the eyes.

Foam: Shake well before use. Prime pump (initial use only): Hold spray upright away from patient and depress actuator for 3-5 seconds or until foam begins to dispense. Normal use: Apply directly to wound or dressing; may hold spray at an angle or upright. Wipe actuator clean after each use.

Ointment: Apply directly to wound

Spray:

Panafil®: Shake well before use.

Panafil®, Panafil® SE: Prime pump (initial use only): Hold spray upright directly above the wound and prime the pump 6-8 times. Normal use: Allow a distance of 2-3 inches between the spray container and the wound; may hold spray at an angle or upright.

Storage

Foam: Store upright at room temperature of 15°C to 30°C (59°F to 86°F); do not freeze; protect from heat.

Ointment: Store at room temperature of 15°C to 30°C (59°F to 86°F).

Spray: Store upright at controlled room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to chlorophyllin, papain, urea, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Anaphylaxis and severe hypersensitivity reactions have occurred with papain use. Tachycardia and hypotension, in association with some hypersensitivity reactions, have also been observed.

- Latex hypersensitivity: Inconclusive data suggests a possible cross-sensitivity may exist between patients with natural rubber latex hypersensitivity and papaya, the source of papain.

Other warnings/precautions:

- Administration: For topical use only; not for use in eyes.

Geriatric ConsiderationsPreventive skin care should be instituted in all older patients at high risk for pressure ulcers.

Adverse ReactionsLocal: Burning sensation, skin irritation

Postmarketing and/or case reports: Anaphylaxis, hypersensitivity reactions

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringMonitor therapeutic response and adverse reactions at the beginning and periodically throughout therapy.

Patient EducationFor external use only. Skin should be cleansed prior to use. Hydrogen peroxide should not be used (may inactivate papain). Apply to entire wound area so that wound is not visible. Apply dressing (may use pressure dressings). Dressing changes are recommended once to twice daily. Do not use near eyes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol, topical [foam]:

Papfyll™: Chlorophyllin copper complex sodium 0.5%, papain ≥520,000 USP units/g, and urea 10% (45 g)

Emulsion [spray]:

Panafil® SE: Chlorophyllin copper complex sodium 0.5%, papain ≥521,700 USP units/g, and urea 10% (34 mL)

Ointment:

Allanfil 405, Panafil®: Chlorophyllin copper complex sodium 0.5%, papain ≥521,700 USP units/g, and urea 10% (6 g, 30 g)

Ziox™: Chlorophyllin copper complex sodium 0.5%, papain ≥521,700 units/g, and urea 10% (30 g)

Ziox 405™: Chlorophyllin copper complex sodium 0.5%, papain ≥521,700 USP units/g, and urea 10% (30 g)

Solution [spray]:

Allanfil, Panafil® [DSC]: Chlorophyllin copper complex sodium 0.5%, papain ≥521,700 USP units/g, and urea 10% (33 mL)

Generic AvailableYes: Ointment, solution

Pricing: U.S. (www.drugstore.com)

Ointment (Panafil)

405900-10-0.5 (30): $82.99

Ointment (Ziox)

521.7-10-0.5 units/g-%-% (30): $44.96

Mechanism of Action

Papain: Potent digestant of nonviable protein matter; harmless to viable tissue. Requires activation to exert its function.

Urea: Exposes papain activators (sulfhydryl groups) and denatures nonviable protein matter making it more susceptible to enzymatic digestion.

Chlorophyllin copper complex sodium: Inhibits the hemagglutinating and inflammatory properties of protein degradation products in the wound; the resulting healthy granulation, decreased local inflammation, and decreased wound odor promotes wound healing.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsChlorophyllin Copper Complex Sodium, Papain, and Urea; Papain, Urea, and Chlorophyllin; Urea, Chlorophyllin, and Papain
References

Blanco C, Carrillo T, Castillo R, et al, “Latex Allergy: Clinical Features and Cross-Reactivity With Fruits,” *Ann Allergy*, 1994, 73(4):309-14.[PubMed 7943998]

Focke M, Hemmer W, Wohrl S, et al, “Cross-reactivity Between *Ficus benjamina* Latex and Fig Fruit in Patients With Clinical Fig Allergy,” *Clin Exp Allergy*, 2003, 33(7):971-7.[PubMed 12859455]

Freye HB, “Papain Anaphylaxis: A Case Report,” *Allergy Proc*, 1988, 9(5):571-4.[PubMed 3234762]

Isola S, Ricciardi L, Saitta S, et al, “Latex Allergy and Fruit Cross-Reaction in Subjects Who Are Nonatopic,” *Allergy Asthma Proc*, 2003, 24(3):193-7.[PubMed 12866323]

Chloroprocaine

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Nesacaine® may be confused with Neptazane®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (epidural administration) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(klor oh PROE kane)

U.S. Brand NamesNesacaine®; Nesacaine®-MPF

Canadian Brand NamesNesacaine®-CE

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsInfiltration anesthesia and peripheral and epidural anesthesia

Dosing: AdultsDosage varies with anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, depth of anesthesia required, degree of muscle relaxation required, and duration of anesthesia; range.

Maximum single dose (without epinephrine): 11 mg/kg; maximum dose: 800 mg

Maximum single dose (with epinephrine): 14 mg/kg; maximum dose: 1000 mg

Infiltration and peripheral nerve block:

Mandibular: 2%: 2-3 mL; total dose 40-60 mg

Infraorbital: 2%: 0.5-1 mL; total dose 10-20 mg

Brachial plexus: 2%; 30-40 mL; total dose 600-800 mg

Digital (without epinephrine): 1%; 3-4 mL; total dose: 30-40 mg

Pudendal: 2%; 10 mL each side; total dose: 400 mg

Paracervical: 1%; 3 mL per each of four sites

Caudal block: Preservative-free: 2% or 3%: 15-25 mL; may repeat at 40-60 minute intervals

Lumbar epidural block: Preservative-free: 2% or 3%: 2-2.5 mL per segment; usual total volume: 15-25 mL; may repeat with doses that are 2-6 mL less than initial dose every 40-50 minutes.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDosage varies with anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, depth of anesthesia required, degree of muscle relaxation required, and duration of anesthesia; range.

Children >3 years (normally developed): Maximum dose (without epinephrine): 11 mg/kg; for infiltration, concentrations of 0.5% to 1% are recommended; for nerve block, concentrations of 1% to 1.5% are recommended

Administration: OtherBefore injecting, withdraw syringe plunger to ensure injection is not into vein or artery.

StorageStore at 15°C to 30°C (59°F to 86°F); protect from light and freezing. Discard Nesacaine®-MPF following single use.

ReconstitutionDilute with NS. To prepare 1:200,000 epinephrine-chloroprocaine HCl injection, add 0.1 mL of a 1:1000 epinephrine injection to 20 mL of preservative free chloroprocaine.

ContraindicationsHypersensitivity to chloroprocaine, other ester type anesthetics, or any component of the formulation; myasthenia gravis; do not use for subarachnoid administration

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS toxicity: Careful and constant monitoring of the patient's state of consciousness should be done following each local anesthetic injection; at such times, restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of CNS toxicity. Treatment is primarily symptomatic and supportive.

- Respiratory arrest: Local anesthetics have been associated with rare occurrences of sudden respiratory arrest.

- Seizures: Convulsions due to systemic toxicity leading to cardiac arrest have also been reported, presumably following unintentional intravascular injection.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease or compromised blood supply.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

Special populations:

- Acutely ill patients: Use with caution in acutely ill; reduce dose consistent with age and physical status.

- Debilitated patients: Use with caution in debilitated patients; reduce dose consistent with age and physical status.

- Elderly: Use with caution in the elderly; reduce dose consistent with age and physical status.

- Pediatrics: Use with caution in children; reduce dose consistent with age and physical status.

Dosage form specific issues:

- Preservative-containing solutions: **Do not use solutions containing preservatives for caudal or epidural block.**

Other warnings/precautions;

- Administration: Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

- Test dose: A test dose is recommended prior to epidural administration (prior to initial dose) and all reinforcing doses with continuous catheter technique.

- Trained personnel: Clinicians using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Local anesthetics rapidly cross the placenta and may cause varying degrees of maternal, fetal, and neonatal toxicity. Close maternal and fetal monitoring (heart rate and electronic fetal monitoring advised) are required during obstetrical use. Maternal hypotension has resulted from regional anesthesia. Positioning the patient on her left side and elevating the legs may help. Epidural, paracervical, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. The use of some local anesthetic drugs during labor and delivery may diminish muscle strength and tone for the first day or two of life. Administration as a paracervical block is not recommended with toxemia of pregnancy, fetal distress, or prematurity. Administration of a paracervical block early in pregnancy has resulted in maternal seizures and cardiovascular collapse. Fetal bradycardia and acidosis also have been reported. Fetal depression has occurred following unintended fetal intracranial injection while administering a paracervical and/or pudendal block.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

Frequency not defined.

Cardiovascular: Bradycardia, cardiac arrest, hypotension, ventricular arrhythmia

Central nervous system: Anxiety, dizziness, restlessness, tinnitus, unconsciousness

Dermatologic: Angioneurotic edema, erythema, pruritus, urticaria

Ocular: Blurred vision

Respiratory: Respiratory arrest

Miscellaneous: Allergic reactions, anaphylactoid reactions

<1%: Seizure (0.1%)

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersCardiovascular and respiratory status; mental status

Nursing: Physical Assessment/MonitoringMonitor for effectiveness of anesthesia, and adverse reactions. Monitor for return of sensation. Teach patient adverse reactions to report; use and teach appropriate interventions to promote safety.

Patient EducationThis medication is given to reduce sensation in the injected area. You will experience decreased sensation to pain, heat, or cold in the area and/or decreased muscle strength (depending on area of application) until the effects wear off; use necessary caution to reduce incidence of possible injury until full sensation returns. Immediately report chest pain or palpitations; increased restlessness, confusion, anxiety, or dizziness; respiratory difficulty; chills, shivering, or tremors; ringing in ears; or vision changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride:

Nesacaine®: 1% (30 mL); 2% (30 mL) [contains disodium EDTA and methylparaben]

Injection, solution, as hydrochloride [preservative free]: 2% (20 mL); 3% (20 mL)

Nesacaine®-MPF: 2% (20 mL); 3% (20 mL)

Generic Available Yes

Mechanism of Action Chloroprocaine HCl is benzoic acid, 4-amino-2-chloro-2-(diethylamino) ethyl ester monohydrochloride. Chloroprocaine is an ester-type local anesthetic, which stabilizes the neuronal membranes and prevents initiation and transmission of nerve impulses thereby affecting local anesthetic actions. Local anesthetics including chloroprocaine, reversibly prevent generation and conduction of electrical impulses in neurons by decreasing the transient increase in permeability to sodium. The differential sensitivity generally depends on the size of the fiber; small fibers are more sensitive than larger fibers and require a longer period for recovery. Sensory pain fibers are usually blocked first, followed by fibers that transmit sensations of temperature, touch, and deep pressure. High concentrations block sympathetic somatic sensory and somatic motor fibers. The spread of anesthesia depends upon the distribution of the solution. This is primarily dependent on the volume of drug injected.

Pharmacodynamics/Kinetics

Onset of action: 6-12 minutes

Duration: 30-60 minutes

Distribution: V_d: Depends upon route of administration; high concentrations found in highly perfused organs such as liver, lungs, heart, and brain

Metabolism: Plasma cholinesterases

Excretion: Urine

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause anxiety, restlessness, and dizziness

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Chloroprocaine Hydrochloride

References

Freeman DW and Arnold NI, "Paracervical Block With Low Doses of Chloroprocaine: Fetal and Maternal Effects," *JAMA*, 1975, 231(1):56-7. [PubMed 1243568]

Jankowsky EC, "Pharmacologic Aspects of Local Anesthetic Use," *Anesth Clin North Am*, 1990, 8:1-25.

International Brand Names Ivracain (CH); Nesacaine (CH)

Chloroquine

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English

English

Jump To Field (Select Field Name)

Medication Safety Issues

International issues:

Aralen® may be confused with Oralon® which is a brand name for povidone-iodine in Japan

Aralen® may be confused with Paralen® which is a brand name for acetaminophen in the Czech Republic

Pronunciation(KLOR oh kwin)

U.S. Brand NamesAralen®

Canadian Brand NamesAralen®; Novo-Chloroquine

Pharmacologic CategoryAminoquinoline (Antimalarial)

Use: Labeled IndicationsSuppression or chemoprophylaxis of malaria; treatment of uncomplicated or mild-to-moderate malaria; extraintestinal amebiasis

Use: Unlabeled/InvestigationalRheumatoid arthritis; discoid lupus erythematosus

Dosing: Adults

Malaria, suppression or prophylaxis: Oral: 500 mg/week (300 mg base) on the same day each week; begin 1-2 weeks prior to exposure; continue for 4-6 weeks after leaving endemic area; if suppressive therapy is not begun prior to exposure, double the initial loading dose to 1 g (600 mg base) and administer in 2 divided doses 6 hours apart, followed by the usual dosage regimen.

Malaria, acute attack: Oral: 1 g (600 mg base) on day 1, followed by 500 mg (300 mg base) 6 hours later, followed by 500 mg (300 mg base) on days 2 and 3.

Extraintestinal amebiasis: Oral: 1 g/day (600 mg base) for 2 days followed by 500 mg/day (300 mg base) for at least 2-3 weeks.

Rheumatoid arthritis, lupus erythematosus (unlabeled uses): Oral: 250 mg (150 mg base) once daily; reduce dosage following maximal response (taper to discontinue after response in lupus); generally requires 3-6 weeks. **Note:** Not considered first-line agent.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Malaria, suppression or prophylaxis: Oral: Administer 5 mg base/kg/week on the same day each week (not to exceed 300 mg base/dose); begin 1-2 weeks prior to exposure; continue for 4-6 weeks after leaving endemic area; if suppressive therapy is not begun prior to exposure, double the initial loading dose to 10 mg base/kg and administer in 2 divided doses 6 hours apart, followed by the usual dosage regimen

Malaria, acute attack: Oral: 10 mg/kg (base) on day 1, followed by 5 mg/kg (base) 6 hours later and 5 mg/kg (base) on days 2 and 3

Extraintestinal amebiasis: Oral: 10 mg/kg (base) once daily for 2-3 weeks (up to 300 mg base/day)

Dosing: Renal Impairment

Cl_{cr} <10 mL/minute: Administer 50% of dose.

Hemodialysis effects: Minimally removed by hemodialysis

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralChloroquine phosphate tablets have also been mixed with chocolate syrup or enclosed in gelatin capsules to mask the bitter taste.

Dietary ConsiderationsMay be taken with meals to decrease GI upset.

StorageStore tablets at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Extemporaneously PreparedA 10 mg chloroquine base/mL suspension is made by pulverizing two Aralen® 500 mg phosphate = 300 mg base/tablet, levigating with sterile water, and adding by geometric proportion, a significant amount of the cherry syrup and levigating until a uniform mixture is obtained; qs ad to 60 mL with cherry syrup, stable for up to 4 weeks when stored in the refrigerator or at a temperature of 29°C

Mirochnick M, Barnett E, Clarke DF, et al, “Stability of Chloroquine in an Extemporaneously Prepared Suspension Stored at Three Temperatures,” *Pediatr Infect Dis J*, 1994, 13(9):827-8.

ContraindicationsHypersensitivity to chloroquine or any component of the formulation; retinal or visual field changes

Allergy Considerations

- QuiNIDine/QuiNINE Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiovascular: Chloroquine has been associated with ECG changes, AV block, and cardiomyopathy (rare). Generally these are dose and/or duration dependent.
- Hematologic: Aminoquinolones have been associated with rare hematologic reactions including agranulocytosis, aplastic anemia, and thrombocytopenia; monitoring (CBC) is recommended in prolonged therapy.
- Neuromuscular: Myopathy, neuromyopathy, and progressive weakness have been reported with aminoquinolones (chloroquine); muscle strength (especially proximal muscles) should be assessed periodically during prolonged therapy.
- Ophthalmic effects: Retinopathy has occurred with chloroquine; effect is dose-related and may be reversible if detected early. Other effects include blurred vision or keratopathy. Monitoring is required.

Disease-related concerns:

- Auditory damage: Use with caution in patients with pre-existing auditory damage; discontinue immediately if hearing defects are noted.
- G6PD deficiency: Use with caution in patients with known G6PD; use of 4-aminoquinolines such as chloroquine has been associated with hemolysis and renal impairment in this population.
- Hepatic impairment: Use with caution in patients with hepatic impairment, alcoholism, or concurrent therapy with hepatotoxic agents.
- Porphyria: Use with caution in patients with porphyria; may exacerbate disease symptoms.
- Psoriasis: Use with caution in patients with psoriasis; may exacerbate disease symptoms.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies using chloroquine during pregnancy. However, based on clinical experience and because malaria infection in pregnant women may be more severe than in nonpregnant women, chloroquine prophylaxis may be considered in areas of chloroquine-sensitive *P. falciparum* malaria. Pregnant women should be advised not to travel to areas of *P. falciparum* resistance to chloroquine.

LactationEnters breast milk/not recommended (AAP considers “compatible”)

Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiomyopathy, ECG changes (rare; including T-wave inversion), hypotension (rare)

Central nervous system: Delirium, depression, fatigue, headache, personality changes, psychosis, seizure

Dermatologic: Pruritus, hair bleaching, pleomorphic skin eruptions, alopecia, lichen planus eruptions, alopecia, mucosal pigmentary changes (blue-black), photosensitivity

Gastrointestinal: Abdominal cramps, anorexia, diarrhea, nausea, stomatitis, vomiting

Hematologic: Agranulocytosis (reversible), aplastic anemia, neutropenia, thrombocytopenia

Neuromuscular & skeletal: Rare cases of myopathy, neuromyopathy, proximal muscle atrophy, and depression of deep tendon reflexes have been reported

Ocular: Blurred vision, retinopathy (including irreversible changes in some patients long-term or high-dose therapy)

Otic: Nerve deafness, tinnitus, hearing reduced (risk increased in patients with pre-existing auditory damage)

Metabolism/Transport Effects**Substrate** (major) of CYP2D6, 3A4; **Inhibits** CYP2D6 (moderate)

Drug Interactions

Anthelmintics: Aminoquinolines (Antimalarial) may decrease the serum concentration of Anthelmintics. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): Antimalarial Agents may increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Beta-Blockers: Aminoquinolines (Antimalarial) may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Carteolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Cardiac Glycosides: Aminoquinolines (Antimalarial) may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Mefloquine: Aminoquinolines (Antimalarial) may enhance the adverse/toxic effect of Mefloquine. Specifically, the risk for QTc-prolongation and the risk for convulsions may be increased. Mefloquine may increase the serum concentration of Aminoquinolines (Antimalarial). Management: Avoid concurrent use, and delay administration of mefloquine until at least 12 hours after the last dose of an aminoquinoline antimalarial when possible. *Risk X: Avoid combination*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase GI irritation).

Monitoring ParametersOphthalmic exams at baseline and every 3 months during prolonged therapy. Visual acuity, slit-lamp, fundoscopic and visual field examination are recommended. Evaluate neuormuscular function during prolonged therapy. Periodic CBC in patients receiving prolonged therapy

Nursing: Physical Assessment/Monitoring Assess other pharmacological or herbal products patient may be taking for potential interactions. Assess results of laboratory tests (CBC), therapeutic effectiveness (according to purpose for use), and adverse response (eg, retinopathy, hearing loss, myopathy) regularly during long-term therapy. Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, anemia, muscle weakness, visual or auditory changes).

Monitoring: Lab TestsPeriodic CBC in prolonged therapy.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. It is important to complete full course of therapy, which may take up to 6 months for full effect. May be taken with meals to decrease GI upset and bitter aftertaste. Avoid alcohol. You should have regular ophthalmic exams (every 4-6 months) if using this medication over extended periods. May cause skin discoloration (blue/black), hair bleaching, or skin rash. If you have psoriasis, may cause exacerbation. May turn urine black/brown (normal). May cause headache (if persistent, consult prescriber for analgesic); nausea, vomiting, or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or increased sensitivity to sunlight (wear dark glasses and protective clothing, use sunblock, and avoid direct exposure to sunlight). Report vision changes; rash or itching; persistent diarrhea or GI disturbances; change in hearing acuity or ringing in the ears; chest pain or palpitation; CNS changes; unusual fatigue, easy bruising or bleeding; or any other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as phosphate: 250 mg [equivalent to 150 mg base]; 500 mg [equivalent to 300 mg base]

Aralen®: 500 mg [equivalent to 300 mg base]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Aralen)

500 mg (25): $196.38

Tablets (Chloroquine Phosphate)

250 mg (30): $70.99

500 mg (7): $37.94

Mechanism of ActionBinds to and inhibits DNA and RNA polymerase; interferes with metabolism and hemoglobin utilization by parasites; inhibits prostaglandin effects; chloroquine concentrates within parasite acid vesicles and raises internal pH resulting in inhibition of parasite growth; may involve aggregates of ferriprotoporphyrin IX acting as chloroquine receptors causing membrane damage; may also interfere with nucleoprotein synthesis

Pharmacodynamics/Kinetics

Duration: Small amounts may be present in urine months following discontinuation of therapy

Absorption: Oral: Rapid (~89%)

Distribution: Widely in body tissues (eg, eyes, heart, kidneys, liver, lungs) where retention prolonged; crosses placenta; enters breast milk

Metabolism: Partially hepatic

Half-life elimination: 3-5 days

Time to peak, serum: 1-2 hours

Excretion: Urine (~70% as unchanged drug); acidification of urine increases elimination

Related Information

- Immunization Recommendations
- Malaria Treatment

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause psychosis, delirium, personality changes, and depression
Mental Health: Effects on Psychiatric TreatmentMay cause blood dyscrasias; use caution with clozapine and carbamazepine. May cause seizures; use caution with antipsychotics and antidepressants. May cause widening of QRS complex; use caution with ziprasidone.
Index TermsChloroquine Phosphate
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International Brand NamesAralen (MX); Aralen Phosphate (AE, BF, BH, BJ, CI, CY, EC, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PE, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Arechin (PL); Avloclor (BF, BJ, CI, ET, GB, GH, GM, GN, ID, IE, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Cadiquin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Chemochin (HR); Chlorochin (CH, HR); Chlorofoz (PH); Chloroquini Diphosphas (NL); Chlorquin (AU); Cidanchin (ES); Clo-Kit Junior (IN); Clorochina Bayer (IT); Clorochina Bifosfato (IT); Cloroquina Llorente (ES); Delagil (BB, BM, BS, BZ, CZ, GY, HN, HU, JM, NL, PR, SR, TT); Dichinalex (IT); Diclokin (BR); Diroquine (TH); Emquin (IN); Genocin (TH); Heliopar (FI); Klorokinfosfat (NO, SE); Lagaquin (BB, BF, BJ, BM, BS, BZ, CI, ET, GH, GM, GN, GY, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, PR, SC, SD, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Malaquin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Malarex (AE, BH, CY, DK, EG, ID, IL, IQ, IR, JO, KW, LB, LY, MY, OM, PH, QA, SA, SY, YE); Malarivon (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Malaviron (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Maliaquine (TH); Maquine (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Mexaquin (ID); Nivaquine (AR, BE, FR, LU); Resochin (AE, AT, BF, BG, BH, BJ, CI, CY, DE, EG, ES, ET, GH, GM, GN, HR, ID, IL, IN, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Resochina (PT)

Chlorothiazide

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Medication Safety Issues

International issues:

Diuril® may be confused with Duorol® which is a brand name for acetaminophen in Spain

Pronunciation(klor oh THYE a zide)

U.S. Brand NamesDiuril®; Sodium Diuril®

Canadian Brand NamesDiuril®

Pharmacologic CategoryDiuretic, Thiazide

Use: Labeled IndicationsManagement of mild-to-moderate hypertension; adjunctive treatment of edema

Dosing: Adults**Note:** The manufacturer states that I.V. and oral dosing are equivalent. Some clinicians may use lower I.V. doses; however, because of chlorothiazide's poor oral absorption.

Hypertension: Oral: 500-2000 mg/day divided in 1-2 doses (manufacturer labeling); doses of 125-500 mg/day have also been recommended (JNC 7)

Edema: Oral, I.V.: 500-1000 mg once or twice daily; intermittent treatment (eg, therapy on alternative days) may be appropriate for some patients

ACC/AHA 2005 Heart Failure guidelines:

Oral: 250-500 mg once or twice daily (maximum daily dose: 1000 mg)

I.V.: 500-1000 mg once daily plus a loop diuretic

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** The manufacturer states that I.V. and oral dosing are equivalent. Some clinicians may use lower I.V. doses; however, because of chlorothiazide's poor oral absorption. I.V. dosing in infants and children has not been well established.

Infants <6 months:

Oral: 10-30 mg/kg/day in 2 divided doses (maximum dose: 375 mg/day); anecdotal reports have used up to 40 mg/kg/day (unlabeled).

I.V. (unlabeled): 2-8 mg/kg/day in 2 divided doses; anecdotal reports have used up to 20 mg/kg/day

Infants >6 months and Children:

Oral: 10-20 mg/kg/day in 1-2 divided doses (maximum dose: 375 mg/day in children <2 years or 1 g/day in children 2-12 years)

I.V. (unlabeled route): 4 mg/kg/day in 1-2 divided doses; anecdotal reports have used up to 20 mg/kg/day

Dosing: Renal ImpairmentCl_{cr} <10 mL/minute: Avoid use. Ineffective with Cl_{cr} <30 mL/minute unless in combination with a loop diuretic (Aronoff, 2007)

Note: ACC/AHA 2005 Heart Failure Guidelines suggest that thiazides lose their efficacy when Cl_{cr} <40 mL/minute

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Do **not** administer injection via I.M. or SubQ route.

Administration: I.V. DetailAvoid extravasation of parenteral solution since it is extremely irritating to tissues.

pH: 9.2-10.0 (2.5% solution reconstituted with water for injection)

Dietary ConsiderationsMay need to decrease sodium and calcium, may need to increase potassium, zinc, magnesium, and riboflavin in diet. Sodium content of 500 mg injection: 57.5 mg (2 mEq).

Storage

Powder for injection: Prior to reconstitution, store between 2°C to 25°C (36°F to 77°F). Reconstituted solution is stable for 24 hours at room temperature; precipitation will occur in <24 hours in pH <7.4.

Suspension, tablets: Store at room temperature 15°C to 30°C (59°F to 86°F). Protect from freezing.

ReconstitutionPowder for injection: To reconstitute, add SWFI 18 mL to make 28 mg/mL. May be further diluted with dextrose or sodium chloride solutions. Single use only, discard any unused reconstituted solution.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4$NS, $D_5{}^1/_2$NS, D_5NS, D_5W, D_{10}W, D_{10}NS, LR, ${}^1/_2$NS, NS.

Compatibility when admixed: Compatible: Cimetidine, lidocaine, nafcillin, ranitidine, sodium bicarbonate. **Incompatible:** Amikacin, chlorpromazine, hydralazine, insulin (regular), levorphanol, morphine, multivitamins, norepinephrine, polymyxin B sulfate, procaine, prochlorperazine edisylate, prochlorperazine mesylate, promazine, promethazine, streptomycin, triflupromazine, vancomycin.

ContraindicationsHypersensitivity to chlorothiazide, any component of the formulation, thiazides, or sulfonamide-derived drugs; anuria

Allergy Considerations

- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, hyponatremia, and hypomagnesemia can occur.
- Hypersensitivity reactions: Hypersensitivity reactions may occur.
- Photosensitivity: Photosensitization may occur.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with thiazide or sulfonamide allergy is specifically contraindicated in product labeling. A risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Diabetes: Use with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated.
- Hepatic impairment: Use with caution in patients with hepatic impairment; avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.
- Hypokalemia: Use with caution in patients with hypokalemia; correct before initiating therapy.
- Renal impairment: Avoid in severe renal disease (ineffective). May precipitate azotemia; discontinue or consider withholding if renal impairment occurs.
- Systemic lupus erythematosus (SLE): Can cause SLE exacerbation or activation.

Geriatric ConsiderationsChlorothiazide is minimally effective in patients with a Cl_{cr} <30 mL/minute. This may limit the usefulness of chlorothiazide in the elderly.

Pregnancy Risk FactorC (manufacturer); D (expert analysis)

Pregnancy ConsiderationsCrosses the placenta. Hypoglycemia, thrombocytopenia, hemolytic anemia, electrolyte disturbances reported. May exhibit a tocolytic effect. Generally, use of diuretics during pregnancy is avoided for pregnancy-induced hypertension due to risk of decreased placental perfusion. Use may be considered in select patients with heart disease or chronic hypertension if started prior to gestation.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsCrosses into breast milk; may suppress lactation with high doses. AAP considers **compatible** with breast-feeding.

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension, orthostatic hypotension, necrotizing angiitis

Central nervous system: Dizziness, fever, headache, restlessness, vertigo

Dermatologic: Alopecia, erythema multiforme, exfoliative dermatitis, photosensitivity, purpura, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Endocrine & metabolic: Cholesterol increased, hyperglycemia, hyperuricemia, hypochloremic alkalosis, hypokalemia, hyponatremia, hypomagnesemia, triglycerides increased

Gastrointestinal: Abdominal cramping, anorexia, constipation, diarrhea, gastric irritation, nausea, pancreatitis, sialadenitis, vomiting

Genitourinary: Impotence

Hematologic: Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, thrombocytopenia

Hepatic: Jaundice

Neuromuscular & skeletal: Muscle spasm, paresthesia, weakness

Ocular: Blurred vision, xanthopsia

Renal: Glycosuria, hematuria (I.V.), interstitial nephritis, renal failure, renal dysfunction

Respiratory: Pneumonitis, pulmonary edema, respiratory distress

Miscellaneous: Anaphylactic reactions, systemic lupus erythematosus

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: May increase risk of orthostatic hypotension.

Food: Chlorothiazide serum levels may be increased if taken with food.

Herb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Test InteractionsIncreased creatine phosphokinase [CPK] (S), ammonia (B), amylase (S), calcium (S), chloride (S), cholesterol (S), glucose, increased acid (S), decreased chloride (S), magnesium, potassium (S), sodium (S); may interfere with tests for parathyroid function

Monitoring ParametersSerum electrolytes, renal function, blood pressure; assess weight, I & O reports daily to determine fluid loss

Nursing: Physical Assessment/MonitoringAssess allergy history prior to beginning therapy. Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, blood pressure, fluid status, and electrolyte balance) on a regular basis throughout therapy. Caution patients with diabetes to monitor glucose levels (may reduce effect of oral hypoglycemics). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor C/D:** See Pregnancy Risk Factor for use cautions; determine that patient is not pregnant before beginning treatment. Instruct patients of childbearing age about appropriate barrier contraceptive measures. Note breast-feeding caution.

Monitoring: Lab TestsSerum electrolytes, renal function

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. Take once-daily dose in morning or last of daily doses early in the day to avoid night-time disturbances. You may need to make dietary changes, follow dietary suggestions of prescriber. If using oral hypoglycemics, monitor glucose levels closely (this medication may reduce effect of oral hypoglycemics); contact prescriber with any major changes. May cause sensitivity to sunlight (use sunblock, wear protective clothing, and avoid direct sunlight); dizziness, weakness, or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known); or postural hypotension (use caution when rising from sitting or lying position or when climbing stairs). Report muscle twitching or cramps; acute loss of appetite; GI distress; severe rash, redness, or itching of skin; sexual dysfunction; chest pain or palpitations; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as sodium:

Sodium Diuril®: 500 mg

Suspension, oral:

Diuril®: 250 mg/5 mL (237 mL) [contains alcohol 0.5% and benzoic acid]

Tablet: 250 mg, 500 mg

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Suspension (Diuril)

250 mg/5 mL (237): $14.10

Tablets (Chlorothiazide)

250 mg (30): $12.99

500 mg (30): $7.99

Mechanism of ActionInhibits sodium and chloride reabsorption in the distal tubules causing increased excretion of sodium, chloride, and water resulting in diuresis. Loss of potassium, hydrogen ions, magnesium, phosphate, and bicarbonate also occurs.

Pharmacodynamics/Kinetics

Onset of action: Diuresis: Oral: 2 hours; I.V.: 15 minutes

Duration of diuretic action: Oral: 6-12 hours; I.V.: ~2 hours

Absorption: Oral: Poor

Half-life elimination: 1-2 hours

Time to peak, serum: Oral: ~4 hours; I.V.: 30 minutes

Excretion: Urine (10% to 15% [oral], 96% [I.V.] as unchanged drug)

Related Information

- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentRare reports of agranulocytosis; use caution with clozapine and carbamazepine; thiazides decrease lithium clearance resulting in elevated serum lithium levels and potential toxicity; monitor serum lithium levels

Cardiovascular Considerations

Hypertension: Thiazide diuretics are effective first-line therapeutic agents in the management of hypertension and have proven to be of benefit in terms of cardiovascular outcome. They may act synergistically to lower blood pressure when combined with an ACE inhibitor or beta-blocker. The initial concern about thiazide diuretic-induced hypokalemia, glucose intolerance, and lipid profiles does not appear to be of substantial clinical consequence in the treatment of hypertension. The benefits of this class of agents in the treatment of hypertension is established and compares well with other first-line therapeutic agents. The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The JNC 7 recommends diuretics for the treatment of hypertension with concurrent heart failure where diuresis is also required (loop diuretics may more frequently be required), high coronary disease risk (as in the ALLHAT trial), diabetes (beneficial in reducing CVD and stroke incidence), and recurrent stroke prevention (in combination with an ACE inhibitor). Thiazides are useful in slowing demineralization in osteoporosis, but need to be used cautiously in gout and in patients with significant history of hyponatremia.

Congestive Heart Failure: Diuretics are standard therapy for the management of edema in patients with heart failure. Thiazide diuretics may be preferred in hypertensive heart failure patients with mild fluid retention. Thiazides lose their effectiveness in patients with impaired renal function. Loop diuretics may be the preferred diuretic in heart failure because of their greater ability to increase sodium excretion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThiazide diuretics are effective first-line therapeutic agents in the management of hypertension and have proven to be of benefit in terms of cardiovascular outcome. If given the morning of surgery it may render the patient volume depleted and blood pressure may be labile during general anesthesia.

References

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, "Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)," *JAMA*, 2002, 288(23):2981-97.[PubMed 12479763]

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Hunt SA, Abraham WT, Chin MH , et al, "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the

Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure)," available at http://www.acc.org/qualityandscience/clinical/guidelines/failure/update/index.pdf.

International Brand NamesAzide (AU); Chlorosal (IL); Chlotride (AU, NL); Disalunil (PL); Diurilix (FR); Diurone (AU); Diurosulfona (ES); Hydrochlorothiazidum (PL); Niagar (BE); Saluretil (ES); Saluric (GB, IE); Salutrid (FI); Urinex (FI)

Chloroxine

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Medication Safety Issues

Sound-alike/look-alike issues:

Capitrol速 may be confused with Capital速, captopril

Pronunciation(klor OKS een)
U.S. Brand NamesCapitrol速 [DSC]
Canadian Brand NamesCapitrol速
Pharmacologic CategoryTopical Skin Product
Use: Labeled IndicationsTreatment of dandruff or seborrheic dermatitis of the scalp
Dosing: AdultsDandruff, seborrheic dermatitis of the scalp: Topical: Use twice weekly, massage into wet scalp, avoid contact with eyes, lather should remain on the scalp for approximately 3 minutes, then rinsed; application should be repeated and the scalp rinsed thoroughly
Dosing: ElderlyRefer to adult dosing.
Pregnancy Risk FactorC
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Shampoo, topical: 2% (110 g) [contains benzyl alcohol] [DSC]

Generic AvailableNo
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesEndiaron (CZ); Endiaron N (CZ)

Chlorpheniramine and Acetaminophen

Lexi-Drugs Online

English

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Medication Safety Issues

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(klor fen IR a meen & a seet a MIN oh fen)

U.S. Brand NamesCoricidin HBP速 Cold and Flu [OTC]

Pharmacologic CategoryAnalgesic, Miscellaneous; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of congestion, headache, aches and pains of colds and flu

Dosing: AdultsCold/flu/muscle aches: Oral: 2 tablets every 4 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic ImpairmentUse with caution. Limited, low-dose therapy usually well tolerated in hepatic disease/cirrhosis; however, cases of hepatotoxicity at daily acetaminophen dosages <4 g/day have been reported. Avoid chronic use in hepatic impairment.

Adverse ReactionsSee individual agents.

Metabolism/Transport Effects

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Chlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Chlorpheniramine maleate 2 mg and acetaminophen 325 mg

Generic AvailableNo

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Chronic use of antihistamines will inhibit salivary flow, particularly in elderly patients; this may contribute to periodontal disease and oral discomfort.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause excitability, nervousness, fatigue, or depression

Mental Health: Effects on Psychiatric TreatmentDry mouth and sedation may be exacerbated by concurrent psychotropic use

Index TermsAcetaminophen and Chlorpheniramine

Chlorpheniramine, Ephedrine, Phenylephrine, and Carbetapentane

Lexi-Drugs Online

English English

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Rynatuss® may be confused with Rynatan®

Pronunciation(klor fen IR a meen, e FED rin, fen il EF rin, & kar bay ta PEN tane)

U.S. Brand NamesQuad Tann®; Quad Tann® Pediatric; Rynatuss®; Tetra Tannate Pediatric

Pharmacologic CategoryAlpha/Beta Agonist; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of cough with a decongestant and an antihistamine

Dosing: AdultsCough/rhinitis/nasal congestion: Oral: 1-2 tablets every 12 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricCough/rhinitis/nasal congestion: Oral:

<2 years: Titrate dose individually

2-6 years: 2.5-5 mL every 12 hours

>6 years: 5-10 mL every 12 hours

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children.

Pregnancy Risk FactorC

Metabolism/Transport EffectsChlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension:

Quad Tann® Pediatric: Chlorpheniramine tannate 4 mg, ephedrine tannate 5 mg, phenylephrine tannate 5 mg, and carbetapentane tannate 30 mg per 5 mL (480 mL) [contains sodium benzoate; grape flavor]

Tetra Tannate Pediatric: Chlorpheniramine tannate 4 mg, ephedrine tannate 5 mg, phenylephrine tannate 5 mg, and carbetapentane tannate 30 mg per 5 mL (240 mL, 480 mL) [alcohol free; strawberry flavor]

Tablet:

Rynatuss®: Chlorpheniramine tannage 5 mg, ephedrine tannate 10 mg, phenylephrine tannate 10 mg, and carbetapentane tannate 60 mg

Tablet, long acting:

Quad Tann®: Chlorpheniramine tannage 5 mg, ephedrine tannate 10 mg, phenylephrine tannate 10 mg, and carbetapentane tannate 60 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Suspension (Rynatuss Pediatric)

(120): $107.99

Tablets (Rynatuss)

(30): $147.38

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Chlorpheniramine: Prolonged use will cause significant xerostomia (normal salivary flow resumes upon discontinuation).

Ephedrine: No significant effects or complications reported.

Phenylephrine: Up to 10% of patients could experience tachycardia, palpitations, and xerostomia; use vasoconstrictor with caution.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions

Ephedrine: Use vasoconstrictor with caution since ephedrine may enhance cardiostimulation and vasopressor effects of sympathomimetics

Phenylephrine: Use with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDrowsiness is common; may cause excitability, nervousness, fatigue, or depression
Mental Health: Effects on Psychiatric TreatmentDry mouth and sedation may be exacerbated by concurrent psychotropic use
Index TermsCarbetapentane, Ephedrine, Phenylephrine, and Chlorpheniramine; Ephedrine, Chlorpheniramine, Phenylephrine, and Carbetapentane; Phenylephrine, Ephedrine, Chlorpheniramine, and Carbetapentane

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Chlorpheniramine, Phenylephrine, Codeine, and Potassium Iodide

Lexi-Drugs Online

English

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(klor fen IR a meen, fen il EF rin, KOE deen, & poe TASS ee um EYE oh dide)

U.S. Brand NamesPediacof® [DSC]

Pharmacologic CategoryAlpha/Beta Agonist; Analgesic, Opioid; Antitussive; Expectorant; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of rhinitis, nasal congestion and cough due to colds or allergy

Dosing: PediatricCough, rhinitis, nasal congestion: Children 6 months to 12 years: 1.25-10 mL every 4-6 hours

RestrictionsC-V

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Metabolism/Transport EffectsChlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: Potassium Iodide may enhance the adverse/toxic effect of Lithium. Specifically the hypothyroid/goiter-potentiating effects. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Sodium Iodide I131: Antithyroid Agents may diminish the therapeutic effect of Sodium Iodide I131. Management: Discontinue antithyroid therapy 3-4 days prior to sodium iodide I-131 administration. *Risk X: Avoid combination*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Antithyroid Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Syrup: Chlorpheniramine maleate 0.75 mg, phenylephrine hydrochloride 2.5 mg, codeine phosphate 5 mg, and potassium iodide 75 mg per 5 mL (480 mL) [contains alcohol 5% and sodium benzoate; raspberry flavor] [DSC]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Syrup (Pediacof)

2.5-0.75-5-75 mg/5 mL (120): $19.66

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Chlorpheniramine: Prolonged use will cause significant xerostomia (normal salivary flow resumes upon discontinuation).

Phenylephrine: Up to 10% of patients could experience tachycardia, palpitations, and xerostomia (prolonged use worsens); use vasoconstrictor with caution.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDrowsiness is common; may cause excitability, nervousness, fatigue, or depression

Mental Health: Effects on Psychiatric TreatmentDry mouth and sedation may be exacerbated by concurrent psychotropic use

Index TermsCodeine, Chlorpheniramine, Phenylephrine, and Potassium Iodide; Phenylephrine, Chlorpheniramine, Codeine, and Potassium Iodide; Potassium Iodide, Chlorpheniramine, Phenylephrine, and Codeine

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Chlorpheniramine, Phenylephrine, and Dextromethorphan

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

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- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

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http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(klor fen IR a meen, fen il EF rin, & deks troe meth OR fan)

U.S. Brand NamesC-Phen DM; Ceron-DM; Corfen DM; De-Chlor DM; De-Chlor DR; Dec-Chlorphen DM [DSC]; Dex PC; Donatussin DM [DSC]; Ed A-Hist DM; Father John's® Plus [OTC]; Mintuss DR; Neo DM; Norel DM™; PD-Cof; PE-Hist DM; Phenabid DM®; Poly Tussin DM; Robitussin® Cough and Allergy [OTC]; Robitussin® Cough and Cold Nighttime [OTC]; Robitussin® Pediatric Cough and Cold Nighttime [OTC]; Rondec®-DM ; Sildec PE-DM; Statuss™ DM; Tri-Vent™ DPC [DSC]; Trital DM; Tussplex™ DM

Pharmacologic CategoryAlpha/Beta Agonist; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporary relief of cough and upper respiratory symptoms associated with allergies or the common cold

Dosing: Adults**Relief of cough and cold symptoms:** Oral:

Rondec®-DM syrup: 5 mL every 4-6 hours (maximum: 30 mL/24 hours)

Tri-Vent™ DPC: 10 mL every 6 hours (maximum: 40 mL/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRelief of cough and cold symptoms: Oral:

6-12 months (Rondec®-DM drops): 0.75 mL 4 times/day

1-2 years (Rondec®-DM drops): 1 mL 4 times/day

2-6 years:

Rondec®-DM syrup: 1.25 mL every 4-6 hours (maximum: 7.5 mL/24 hours)

Tri-Vent™ DPC: 2.5 mL every 6 hours (maximum: 10 mL/24 hours)

6-12 years:

Rondec®-DM syrup: 2.5 mL every 4-6 hours (maximum: 15 mL/24 hours)

Tri-Vent™ DPC: 5 mL every 6 hours (maximum: 20 mL/24 hours)

Children ≥12 years: Refer to adult dosing.

Dietary ConsiderationsRobitussion® Cough and Allergy, Robitussin® Cough and Cold Nighttime, and Robitussin® Pediatric Cough and Cold Nighttime contain sodium 3 mg/5 mL. Donatussin DM contains phenylalanine 7 mg/5 mL.

ContraindicationsHypersensitivity to chlorpheniramine, phenylephrine, dextromethorphan, or any component of the formulation; use with or within 14 days of MAO inhibitor; severe hypertension or coronary artery disease; peptic ulcer disease; narrow-angle glaucoma; urinary retention

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Asthma: Use with caution in patients with a history of asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Respiratory disease: Use with caution in patients with asthma or other chronic breathing disorders.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children. Not for OTC use in children <2 years of age.

Other warnings/precautions:

- Self-medication (OTC use): When used for self-medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever, rash, or persistent headache. Discontinue and contact healthcare provider if nervousness, dizziness, or sleeplessness occur.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsSee individual agents.

Metabolism/Transport Effects

Chlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)

Dextromethorphan: **Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Liquid:

Corfen DM: Chlorpheniramine maleate 4 mg, phenylephrine hydrochloride 10 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [grape flavor]

De-Chlor DM: Chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 10 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [strawberry flavor]

De-Chlor DR: Chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 6 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [strawberry flavor]

Father John's® Plus: Chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 5 mg, and dextromethorphan hydrobromide 5 mg per 15 mL (118 mL) [alcohol free]

Norel DM™: Chlorpheniramine maleate 4 mg, phenylephrine hydrochloride 10 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; contains propylene glycol; grape flavor]

Trital DM: Chlorpheniramine maleate 4 mg, phenylephrine hydrochloride 10 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; contains sodium benzoate; grape flavor]

Liquid, oral [drops]:

Ceron DM: Chorpheniramine maleate 1 mg, phenylephrine hydrochloride 3.5 mg, and dextromethorphan hydrobromide 3 mg per 1 mL (30 mL) [alcohol free, sugar free; contains sodium benzoate; grape flavor] [DSC]

C-Phen DM: Chlorpheniramine maleate 1 mg, phenylephrine hydrochloride 3.5 mg, and dextromethorphan hydrobromide 3 mg per 1 mL (30 mL) [grape flavor]

Donatussin DM: Chlorpheniramine maleate 1 mg, phenylephrine hydrochloride 1.5 mg, and dextromethorphan hydrobromide 3 mg per 1 mL (30 mL) [alcohol free, sugar free; contains propylene glycol; bubblegum flavor] [DSC]

Neo DM: Chlorpheniramine maleate 0.75 mg, phenylephrine hydrochloride 1.75 mg, and dextromethorphan hydrobromide 2.75 mg per 1 mL (30 mL) [alcohol free, sugar free; contains propylene glycol; black cherry flavor]

PD-Cof: Chlorpheniramine maleate 1 mg, phenylephrine hydrochloride 3.5 mg, and dextromethorphan hydrobromide 3 mg per 1 mL (30 mL) [alcohol free, sugar free; grape flavor]

Rondec® DM, Sildec PE-DM [DSC]: Chlorpheniramine maleate 1 mg, phenylephrine hydrochloride 3.5 mg, and dextromethorphan hydrobromide 3 mg per 1 mL (30 mL) [alcohol free, sugar free; grape flavor]

Suspension:

Donatussin DM: Dexchlorpheniramine tannate 2 mg, phenylephrine tannate 20 mg, and dextromethorphan tannate 30 mg per 5 mL (480 mL) [alcohol free, sugar free; contains phenylalanine 7 mg/5 mL, propylene glycol; cotton candy strawberry flavor] [DSC]

Syrup:

Ceron-DM: Chlorpheniramine maleate 4 mg, phenylephrine hydrochloride 12.5 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [alcohol free, sugar free; contains sodium benzoate; grape flavor]

C-Phen DM: Chlorpheniramine maleate 4 mg, phenylephrine hydrochloride 12.5 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (120 mL, 480 mL) [grape flavor]

Dec-Chlorphen DM: Chlorpheniramine maleate 4 mg, phenylephrine hydrochloride 12.5 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (120 mL, 480 mL) [alcohol free, dye free, sugar free; grape flavor] [DSC]

Dex PC: Chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 6 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [strawberry flavor]

Ed A-Hist DM: Chlorpheniramine maleate 4 mg, phenylephrine hydrochloride 10 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [alcohol free, sugar free; contains propylene glycol; banana flavor]

Mintuss DR: Chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 6 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [alcohol free; strawberry flavor]

PD-Cof: Chlorpheniramine maleate 4 mg, phenylephrine hydrochloride 12.5 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [alcohol free, sugar free; grape flavor]

PE-Hist DM: Chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 5 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [strawberry flavor]

Poly Tussin DM: Chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 5 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [alcohol free, sugar free]

Robitussion® Cough and Allergy: Chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 5 mg, and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL) [alcohol free; contains sodium 3 mg/5 mL, sodium benzoate, and propylene glycol] [DSC]

Robitussin® Cough and Cold Nighttime: Chlorpheniramine maleate 1 mg, phenylephrine hydrochloride 2.5 mg, and dextromethorphan hydrobromide 5 mg per 5 mL (120 mL) [alcohol free; contains sodium 3 mg/5 mL, sodium benzoate, and propylene glycol]

Robitussin® Pediatric Cough and Cold Nighttime: Chlorpheniramine maleate 1 mg, phenylephrine hydrochloride 2.5 mg, and dextromethorphan hydrobromide 5 mg per 5 mL (120 mL) [alcohol free; contains sodium 3 mg/5 mL, sodium benzoate, and propylene glycol; fruit punch flavor]

Rondec®-DM: Chlorpheniramine maleate 4 mg, phenylephrine hydrochloride 12.5 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (120 mL, 480 mL) [alcohol free, sugar free; contains propylene glycol; grape flavor]

Sildec PE-DM: Chlorpheniramine maleate 4 mg, phenylephrine hydrochloride 12.5 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [grape flavor]

Statuss™: DM: Chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 10 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [alcohol free, sugar free; raspberry flavor]

Tri-Vent™ DPC: Chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 6 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [alcohol free; contains sodium benzoate, propylene glycol; strawberry flavor] [DSC]

Tussplex™ DM: Chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 5 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [alcohol free, sugar free; contains sodium benzoate; strawberry flavor]

Tablet, timed release:

Phenabid DM®: Chlorpheniramine maleate 8 mg, phenylephrine hydrochloride 20 mg, and dextromethorphan hydrobromide 30 mg [scored; dye free, sugar free]

Generic AvailableYes: Excludes timed release tablet

Pricing: U.S. (www.drugstore.com)

Liquid (C-Phen DM)

3.5-1-3 mg/mL (30): $29.96

Syrup (Rondec DM)

12.5-4-15 mg/5 mL (473): $172.27

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment:

Chlorpheniramine: Prolonged use will cause significant xerostomia (normal salivary flow resumes upon discontinuation).

Dextromethorphan: No significant effects or complications reported

Phenylephrine: Up to 10% of patients could experience tachycardia, palpitations, and xerostomia (prolonged use worsens); use vasoconstrictor with caution.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions

Chlorpheniramine, Dextromethorphan: No information available to require special precautions

Phenylephrine: Use with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental Status Drowsiness is common; may cause excitability, nervousness, fatigue, or depression

Mental Health: Effects on Psychiatric Treatment Dry mouth and sedation may be exacerbated by concurrent psychotropic use

Index Terms Dextromethorphan, Chlorpheniramine, and Phenylephrine; Phenylephrine, Chlorpheniramine, and Dextromethorphan

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Chlorpheniramine, Phenylephrine, and Guaifenesin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(klor fen IR a meen, fen il EF rin, & gwye FEN e sin)

U.S. Brand NamesP Chlor GG

Pharmacologic CategoryAlpha/Beta Agonist; Expectorant; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of upper respiratory symptoms associated with infections such as the common cold or allergies

Dosing: PediatricGeneral dosing guidelines; consult specific product labeling.

Antihistamine/decongestant/expectorant: Oral:

Children <3 months: 2-3 drops per month of age every 4-6 hours as needed; not to exceed 4 doses/24 hours

Children 3-6 months: 0.3-0.6 mL every 4-6 hours as needed; not to exceed 4 doses/24 hours

Children 6 months to 1 year: 0.6-1 mL every 4-6 hours as needed; not to exceed 4 doses/24 hours

Children 1-2 years: 1-2 mL every 4-6 hours as needed; not to exceed 4 doses/24 hours

Administration: OralFor oral use only.

StorageStore at room temperature at 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to chlorpheniramine, phenylephrine, guaifenesin, or any components of the formulation; severe hypertension, coronary artery disease; asthma; use with or within 14 days of MAO inhibitor therapy

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Pregnancy Risk FactorC

LactationPhenylephrine enters breast milk/not recommended

Adverse ReactionsFrequency not defined. Also see individual agents.

Cardiovascular: Chest tightness, angina, palpitation, hyper-/hypotension

Central nervous system: Dizziness, drowsiness, headache, insomnia, irritability, nervousness, seizure

Dermatologic: Rash

Gastrointestinal: Abdominal pain, anorexia, constipation, diarrhea, nausea, vomiting, xerostomia

Genitourinary: Dysuria

Hematologic: Leukopenia, thrombocytopenia

Neuromuscular & skeletal: Incoordination, tremor, weakness

Ocular: Visual disturbances

Metabolism/Transport EffectsChlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Test InteractionsGuaifenesin: Possible color interference with determination of 5-HIAA and VMA; discontinue for 48 hours prior to test
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid:

P Chlor GG [drops]: Chlorpheniramine maleate 1 mg, phenylephrine hydrochloride 2 mg, and guaifenesin 20 mg per 1 mL (30 mL) [peach flavor]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Solution (P Chlor GG)

1-20-2 mg/mL (30): $8.99

Pharmacodynamics/KineticsSee individual agents.
Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, insomnia, irritability, or nervousness
Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors or within 14 days of MAO inhibitor
Index TermsChlorpheniramine Maleate, Phenylephrine Hydrochloride, and Guaifenesin; Chlorpheniramine Tannate, Phenylephrine Tannate, and Guaifenesin; Guaifenesin, Phenylephrine, and Chlorpheniramine; Phenylephrine, Chlorpheniramine, and Guaifenesin

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(klor fen IR a meen, fen il EF rin, & fen il tole LOKS a meen)

U.S. Brand NamesChlorex-A; Comhist® [DSC]; Nalex®-A; NoHist-A; Rhinacon A

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of rhinitis and nasal congestion due to colds or allergy

Dosing: AdultsRhinitis and nasal congestion: Oral:

Nalex®-A liquid: 10 mL every 4-6 hours

Nalex®-A tablet: 1 tablet 2-3 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRhinitis and nasal congestion: Oral:

Children:

2-6 years: Nalex®-A liquid: 1.25-2.5 mL every 4-6 hours

6-12 years:

Nalex®-A liquid: 5 mL every 4-6 hours

Nalex®-A tablet: $^{1}/_{2}$ tablet 2-3 times/day

Children >12 years: Refer to adult dosing.

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to chlorpheniramine, phenylephrine, phenyltoloxamine, or any component of the formulation; use with or within 14 days of MAO inhibitor; severe hypertension; narrow-angle glaucoma; acute asthma

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe hypertension.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Respiratory disease: Use with caution in patients with asthma or other chronic breathing disorders.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted for this combination.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension, palpitation

Central nervous system: Headache, dizziness, sedation, excitation (children), nervousness, seizure

Dermatologic: Urticaria, drug rash

Gastrointestinal: Dry mouth, anorexia, nausea, vomiting, diarrhea, constipation, GI upset

Genitourinary: Urinary frequency, urinary retention

Hematologic: Agranulocytosis, leukopenia, thrombocytopenia

Ocular: Blurred vision

Respiratory: Dry nose/throat, thickening of bronchial secretions, wheezing, stuffy nose, tightness of chest

Metabolism/Transport EffectsChlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Liquid: Chlorpheniramine maleate 2.5 mg, phenylephrine hydrochloride 5 mg, and phenyltoloxamine citrate 7.5 mg per 5 mL (480 mL)

Nalex®-A, NoHist-A, Rhinacon A: Chlorpheniramine maleate 2.5 mg, phenylephrine hydrochloride 5 mg, and phenyltoloxamine citrate 7.5 mg per 5 mL (480 mL) [alcohol free, sugar free; cotton candy flavor]

Tablet:

Comhist®: Chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 10 mg, and phenyltoloxamine citrate 25 mg [DSC]

Tablet, extended release:

Rhinacon A: Chlorpheniramine maleate 4 mg, phenylephrine hydrochloride 20 mg, and phenyltoloxamine citrate 40 mg

Tablet, prolonged release:

Nalex®-A: Chlorpheniramine maleate 4 mg, phenylephrine hydrochloride 20 mg, and phenyltoloxamine citrate 40 mg

Tablet, sustained release:

Chlorex-A: Chlorpheniramine maleate 4 mg, phenylephrine hydrochloride 20 mg, and phenyltoloxamine citrate 40 mg

Generic AvailableYes: Liquid
Pricing: U.S. (www.drugstore.com)

Liquid (Chlorphen-Phenyltolox-PE)

2.5-7.5-5 mg/5 mL (473): $28.00

Tablets (Comhist)

2-10-25 mg (30): $32.99

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Chlorpheniramine: Prolonged use will cause significant xerostomia (normal salivary flow resumes upon discontinuation).

Phenylephrine: Up to 10% of patients could experience tachycardia, palpitations, and xerostomia; use vasoconstrictor with caution.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response
Mental Health: Effects on Mental StatusDrowsiness is common; may cause excitability, nervousness, fatigue, or depression
Mental Health: Effects on Psychiatric TreatmentDry mouth and sedation may be exacerbated by concurrent psychotropic use
Index TermsPhenylephrine, Chlorpheniramine, and Phenyltoloxamine; Phenyltoloxamine, Chlorpheniramine, and Phenylephrine

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Chlorpheniramine and Phenylephrine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Rynatan® may be confused with Rynatuss®

Pronunciation(klor fen IR a meen & fen il EF rin)

U.S. Brand NamesAcitfed® Cold & Allergy [OTC] *[reformulation]*; AllanTan Pediatric [DSC]; AlleRx™ Suspension; C-Phen; Ceron; Dallergy Drops; Dallergy®-JR; Dec-Chlorphen; Ed A-Hist™; Ed ChlorPed D; NoHist; P-Tann D; PD-Hist-D; PediaTan™ D; Phenabid®; R-Tanna; R-Tanna Pediatric; Rescon-Jr®; Rinate™ Pediatric; Rondec® ; Rynatan®; Rynatan® Pediatric; Sildec PE [DSC]; Sudafed PE® Sinus & Allergy [OTC]; Tannate Pediatric; Triaminic® Cold and Allergy [OTC]

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporary relief of upper respiratory conditions such as nasal congestion, runny nose, and sneezing due to the common cold, hay fever, or allergic or vasomotor rhinitis

Dosing: Adults

Antihistamine/decongestant: Oral:

AlleRx™: 15 mL every 12 hours

Dallergy®-JR: Two capsules every 12 hours; maximum 4 capsules/24 hours

Dallergy®-JR suspension: 10 mL every 12 hours

Ed A-Hist™: One caplet every 12 hours

R-Tanna: 1-2 tablets every 12 hours

Rondec® syrup: 5 mL every 4-6 hours; maximum 30 mL/24 hours

Rynatan® tablet: 1-2 tablets every 12 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Antihistamine/decongestant:** Oral: Children:

6-12 months: Rondec® drops: 0.75 mL 4 times/day

1-2 years: Rondec® drops: 1 mL 4 times/day

2-6 years:

AlleRx™: 1.25 -2.5 mL every 12 hours

Dallergy®-JR suspension: 2.5 mL every 12 hours

Rondec® syrup: 1.25 mL every 4-6 hours; maximum 7.5 mL/24 hours

Rynatan® suspension: 2.5 -5 mL every 12 hours

6-12 years:

AlleRx™: 2.5- 5 mL every 12 hours

Dallergy®-JR: One capsule every 12 hours; maximum 2 capsules/24 hours

Dallergy®-JR suspension: 5 mL every 12 hours

Ed A-Hist™: One-half caplet every 12 hours

Rondec® syrup: 2.5 mL every 4-6 hours; maximum 15 mL/24 hours

Rynatan® suspension: 5-10 mL every 12 hours

≥12 years: Refer to adult dosing.

Administration: OralShake suspensions well prior to use. Ed A-Hist™ caplets may be broken in half; do not crush or chew.

ContraindicationsHypersensitivity to chlorpheniramine, phenylephrine, or any component of the formulation; severe hypertension; severe cardiovascular disease; use with or within 2 weeks of discontinuing MAO inhibitor; narrow-angle glaucoma; urinary retention; peptic ulcer disease; acute asthma attack; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Respiratory disease: Use with caution in patients with asthma or other chronic breathing disorders.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children. Not for OTC use in children <2 years of age.

Dosage form specific issues:

- Tartrazine: Some products may contain tartrazine.

Other warnings/precautions:

- Self-medication (OTC use): When used for self medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever. Discontinue and contact healthcare provider if nervousness, dizziness or sleeplessness occur.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination.
LactationExcretion in breast milk unknown/contraindicated
Breast-Feeding Considerations Use while breast-feeding is specifically contraindicated by some manufacturers.
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsChlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet, prolonged release:

Ed A-Hist™, NoHist: Chlorpheniramine maleate 8 mg and phenylephrine hydrochloride 20 mg

Capsule, extended release:

Dallergy®-JR: Chlorpheniramine maleate 4 mg and phenylephrine hydrochloride 20 mg

Liquid:

Ed A-Hist™: Chlorpheniramine maleate 4 mg and phenylephrine hydrochloride 10 mg per 5 mL (480 mL) [sugar free; contains alcohol 5%; grape flavor]

Triaminic® Cold and Allergy: Chlorpheniramine maleate 1 mg and phenylephrine hydrochloride 2.5 mg per 5 mL (120 mL) [contains sodium 5 mg/5 mL and benzoic acid; orange flavor]

Liquid, oral [drops]:

Dallergy: Chlorpheniramine maleate 1 mg and phenylephrine hydrochloride 2 mg per 1 mL (30 mL) [alcohol free, sugar free; contains propylene glycol; peach flavor]

Solution, oral [drops]:

C-Phen, PD-Hist-D: Chlorpheniramine maleate 1 mg and phenylephrine hydrochloride 3.5 mg per mL (30 mL) [alcohol free, sugar free; bubblegum flavor]

Ceron: Chlorpheniramine maleate 1 mg and phenylephrine hydrochloride 3.5 mg per mL (30 mL) [raspberry flavor]

Dec-Chlorphen: Chlorpheniramine maleate 1 mg and phenylephrine hydrochloride 3.5 mg per mL (30 mL) [alcohol free, dye free, sugar free; grape flavor]

Rondec®: Chlorpheniramine maleate 1 mg and phenylephrine hydrochloride 3.5 mg per mL (30 mL) [alcohol free, sugar free; contains propylene glycol; bubble gum flavor] [DSC]

Sildec PE: Chlorpheniramine maleate 1 mg and phenylephrine hydrochloride 3.5 mg per 1 mL (30 mL) [alcohol free, sugar free; raspberry flavor] [DSC]

Suspension, oral: Chlorpheniramine tannate 4 mg and phenylephrine tannate 20 mg per 5 mL (473 mL)

AllanTan Pediatric: Chlorpheniramine tannate 4.5 mg and phenylephrine tannate 5 mg per 5 mL (473 mL) [contains sodium benzoate; strawberry flavor] [DSC]

AlleRx™: Chlorpheniramine tannate 3 mg and phenylephrine tannate 7.5 per 5 mL (480 mL) [contains benzoic acid; raspberry flavor]

Dallergy®-JR: Chlorpheniramine tannate 4 mg and phenylephrine tannate 20 mg per 5 mL (480 mL) [contains sodium benzoate; peaches and cream flavor]

P-Tann D, PediaTan™ D: Chlorpheniramine tannate 8 mg and phenylephrine tannate 10 mg per 5 mL (480 mL) [sugar free; contains sodium benzoate; bubblegum flavor]

R-Tanna Pediatric: Chlorpheniramine tannate 4.5 mg and phenylephrine tannate 5 mg per 5 mL (480 mL) [contains benzoic acid and tartrazine]

Rinate™ Pediatric: Chlorpheniramine tannate 4.5 mg and phenylephrine tannate 5 mg per 5 mL (120 mL, 480 mL) [contains sodium benzoate; blueberry flavor]

Rynatan® Pediatric: Chlorpheniramine tannate 4.5 mg and phenylephrine tannate 5 mg per 5 mL (480 mL) [contains benzoic acid and tartrazine; strawberry-currant flavor]

Tannate Pediatric: Chlorpheniramine tannate 4.5 mg and phenylephrine tannate 5 mg per 5 mL (480 mL) [contains sodium benzoate; raspberry flavor]

Suspension, oral [drops]:

Ed ChlorPed D: Chlorpheniramine tannate 2 mg and phenylephrine tannate 6 mg per 1 mL (60 mL) [apple sauce flavor]

Syrup:

C-Phen: Chlorpheniramine maleate 4 mg and phenylephrine hydrochloride 12. 5 mg per 5 mL (120 mL, 480 mL) [alcohol free, sugar free; contains sodium benzoate; bubble gum flavor]

Ceron, Sildec PE: Chlorpheniramine maleate 4 mg and phenylephrine hydrochloride 12. 5 mg per 5 mL (480 mL) [raspberry flavor]

PD-Hist-D: Chlorpheniramine maleate 4 mg and phenylephrine hydrochloride 12. 5 mg per 5 mL (480 mL)[alcohol free, sugar free; bubblegum flavor]

Rondec®: Chlorpheniramine maleate 4 mg and phenylephrine hydrochloride 12.5 mg per 5 mL (120 mL, 480 mL) [alcohol free, sugar free; contains propylene glycol; bubble gum flavor]

Tablet:

Actifed® Cold & Allergy, Sudafed PE® Sinus & Allergy: Chlorpheniramine maleate 4 mg and phenylephrine hydrochloride 10 mg

R-Tanna, Rynatan®: Chlorpheniramine tannate 9 mg and phenylephrine tannate 25 mg

Tablet, chewable:

Rynatan®: Chlorpheniramine tannate 4.5 mg and phenylephrine tannate 5 mg [grape flavor]

Tablet, sustained release:

Rescon-Jr®: Chlorpheniramine maleate 4 mg and phenylephrine hydrochloride 20 mg

Tablet, timed release:

Phenabid®: Chlorpheniramine maleate 8 mg and phenylephrine hydrochloride 20 mg [dye free, sugar free]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsule, 12-hour (Dallergy JR)

4-20 mg (30): $17.70

Suspension (AlleRx)

3-7.5 mg/5 mL (473): $206.28

Suspension (Phenclor Tannate Pediatric)

4.5-5 mg/5 mL (100): $21.99

Suspension (Phenyl Chlor-Tan)

4.5-5 mg/5 mL (100): $21.99

Suspension (Rynatan Pediatric)

4.5-5 mg/5 mL (120): $79.19

Tablets (R-Tanna)

9-25 mg (30): $39.99

Tablets (Rynatan)

9-25 mg (30): $93.63

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Chlorpheniramine: Prolonged use will cause significant xerostomia (normal salivary flow resumes upon discontinuation).

Phenylephrine: Up to 10% of patients could experience tachycardia, palpitations, and xerostomia (prolonged use worsens); use vasoconstrictor with caution.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDrowsiness is common; may cause excitability, nervousness, fatigue, or depression

Mental Health: Effects on Psychiatric TreatmentDry mouth and sedation may be exacerbated by concurrent psychotropic use

Index TermsChlorpheniramine Maleate and Phenylephrine Hydrochloride; Chlorpheniramine Tannate and Phenylephrine Tannate; Phenylephrine and Chlorpheniramine

International Brand NamesRhinathiol Antirhinitis (BE)

Chlorpheniramine, Pseudoephedrine, and Codeine

Lexi-Drugs Online

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Jump To Field (Select Field Name)

Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

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It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(klor fen IR a meen, soo doe e FED rin, & KOE deen)

U.S. Brand NamesDihistine® DH [DSC]

Pharmacologic CategoryAlpha/Beta Agonist; Analgesic, Opioid; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporary relief of cough associated with minor throat or bronchial irritation or nasal congestion due to common cold, allergic rhinitis, or sinusitis

Dosing: AdultsCough, rhinitis and nasal congestion: Oral: 10 mL every 4-6 hours, up to 4 doses in 24-hour period

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricCough, rhinitis and nasal congestion: Oral:

Children:

25-50 lb: 1.25-2.5 mL every 4-6 hours, up to 4 doses in 24-hour period

50-90 lb: 2.5-5 mL every 4-6 hours, up to 4 doses in 24-hour period

RestrictionsC-V
Allergy Considerations

- Opioid Allergy/Hypersensitivity

Pregnancy Risk FactorC
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsChlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Elixir:

Dihistine® DH: Chlorpheniramine maleate 2 mg, pseudoephedrine hydrochloride 30 mg, and codeine phosphate 10 mg per 5 mL (120 mL, 480 mL) [contains alcohol; grape flavor] [DSC]

Generic Available No

Pharmacodynamics/Kinetics See individual agents.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment:

Chlorpheniramine: Significant xerostomia with prolonged use (normal salivary flow resumes upon discontinuation).

Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Use with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental Status Drowsiness is common; may cause excitability, nervousness, fatigue, or depression

Mental Health: Effects on Psychiatric Treatment Dry mouth and sedation may be exacerbated by concurrent psychotropic use

Index Terms Codeine, Chlorpheniramine, and Pseudoephedrine; Pseudoephedrine, Chlorpheniramine, and Codeine

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Chlorpheniramine, Pseudoephedrine, and Dextromethorphan

Lexi-Drugs Online

English English

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It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, "Infant Deaths Associated with Cough and Cold Medications - Two States, 2005," *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(klor fen IR a meen, soo doe e FED rin, & deks troe meth OR fan)

U.S. Brand NamesDicel™ DM; DuraTan™ Forte; Kidkare Children's Cough and Cold [OTC]; Pedia Relief™ [OTC]; Rescon DM [OTC]; Tanafed DMX™; Tannate PD-DM

Pharmacologic CategoryAlpha/Beta Agonist; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporarily relieves nasal congestion, runny nose, cough, and sneezing due to the common cold, hay fever, or allergic rhinitis

Dosing: AdultsGeneral dosing guidelines; consult specific product labeling. Relief of cold symptoms: Oral:

Chlorpheniramine maleate 1 mg, pseudoephedrine 15 mg, and dextromethorphan hydrobromide 7.5 mg per 5 mL: 20 mL every 6 hours

Chlorpheniramine maleate 2 mg, pseudoephedrine 30 mg, and dextromethorphan hydrobromide 10 mg per tablet or 5 mL (Rescon DM): 10 mL every 4-6 hours (maximum: 4 doses/24 hours)

Dexchlorpheniramine tannate 2.5 mg, pseudoephedrine tannate 75 mg, and dextromethorphan tannate 25 mg (Tanafed DMX™): 10-20 mL every

12 hours (maximum: 40 mL/24 hours)

Dexchlorpheniramine tannate 3.5 mg, pseudoephedrine tannate 45 mg, and dextromethorphan tannate 30 mg (DuraTan™ Forte): 5-15 mL every 12 hours (maximum: 30 mL/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricGeneral dosing guidelines; consult specific product labeling.

Relief of cold symptoms: Children: Oral:

2-6 years:

Dexchlorpheniramine tannate 2.5 mg, pseudoephedrine tannate 75 mg, and dextromethorphan tannate 25 mg (Tanafed DMX™): 2.5-5 mL every 12 hours (maximum: 10 mL/24 hours)

Dexchlorpheniramine tannate 3.5 mg, pseudoephedrine tannate 45 mg, and dextromethorphan tannate 30 mg (DuraTan™ Forte): 1.25-2.5 mL every 12 hours (maximum: 5 mL/24 hours)

6-12 years:

Chlorpheniramine maleate 1 mg, pseudoephedrine 15 mg, and dextromethorphan hydrobromide 7.5 mg per 5 mL: 10 mL every 6 hours

Chlorpheniramine maleate 1 mg, pseudoephedrine 15 mg, and dextromethorphan hydrobromide 5 mg per tablet or 5 mL: 2 tablets or 10 mL every 4-6 hours (maximum: 4 doses/24 hours)

Chlorpheniramine maleate 2 mg, pseudoephedrine 30 mg, and dextromethorphan hydrobromide 10 mg per tablet or 5 mL (Rescon DM): 5 mL every 4-6 hours (maximum: 4 doses/24 hours)

Dexchlorpheniramine tannate 2.5 mg, pseudoephedrine tannate 75 mg, and dextromethorphan tannate 25 mg (Tanafed DMX™): 5-10 mL every 12 hours (maximum: 20 mL/24 hours)

Dexchlorpheniramine tannate 3.5 mg, pseudoephedrine tannate 45 mg, and dextromethorphan tannate 30 mg (DuraTan™ Forte): 2.5-5 mL every 12 hours (maximum: 10 mL/24 hours)

>12 years: Refer to adult dosing.

StorageStore at controlled room temperature.

ContraindicationsHypersensitivity to chlorpheniramine, pseudoephedrine, dextromethorphan, or any component of the formulation; use with or within 2 weeks of discontinuing MAO inhibitor

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Respiratory disease: Use with caution in patients with asthma or other chronic breathing disorders.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children. Not labeled for OTC use in children <6 years of age.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.
- Self-medication (OTC use): When used for self-medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever, rash, or persistent headache. Discontinue and contact healthcare provider if nervousness, dizziness, or sleeplessness occur.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination product.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsPseudoephedrine is excreted in breast milk, however, the AAP considers it to be “compatible” with breast-feeding. Information for chlorpheniramine and dextromethorphan is not available.

Adverse ReactionsSee individual agents.

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Liquid: Chlorpheniramine maleate 1 mg, pseudoephedrine hydrochloride 15 mg, and dextromethorphan hydrobromide 5 mg per 5 mL (120 mL)

Kidkare Children's Cough and Cold: Chlorpheniramine maleate 1 mg, pseudoephedrine hydrochloride 15 mg, and dextromethorphan hydrobromide 5 mg per 5 mL (120 mL) [alcohol free; contains propylene glycol and sodium benzoate; cherry flavor]

Pedia Relief™: Chlorpheniramine maleate 1 mg, pseudoephedrine hydrochloride 15 mg, and dextromethorphan hydrobromide 5 mg per 5 mL (120 mL) [alcohol free; contains propylene glycol and sodium benzoate; cherry flavor]

Rescon DM: Chlorpheniramine maleate 2 mg, pseudoephedrine hydrochloride 30 mg, and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL, 480 mL) [dye free; contains propylene glycol; cherry flavor]

Suspension:

Dicel™ DM: Chlorpheniramine tannate 5 mg, pseudoephedrine tannate 75 mg, and dextromethorphan tannate 25 mg per 5 mL (480 mL) [contains sodium benzoate; cotton candy flavor]

DuraTan™ Forte: Dexchlorpheniramine tannate 3.5 mg, pseudoephedrine tannate 45 mg, and dextromethorphan tannate 30 mg per 5 mL (480 mL) [contains sodium benzoate; grape flavor]

Tanafed DMX™: Dexchlorpheniramine tannate 2.5 mg, pseudoephedrine tannate 75 mg, and dextromethorphan tannate 25 mg (120 mL, 480 mL) [contains sodium benzoate; cotton candy flavor]

Tannate PD-DM: Dexchlorpheniramine tannate 3 mg, pseudoephedrine tannate 50 mg, and dextromethorphan tannate 27.5 mg per 5 mL (473 mL) [contains sodium benzoate; grape flavor]

Generic AvailableYes: Liquid
Pricing: U.S. (www.drugstore.com)

Suspension (Tanafed DMX)

75-2.5-25 mg/5 mL (118): $60.83

Mechanism of Action

Chlorpheniramine competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract. Dexchlorpheniramine is the predominant active isomer of chlorpheniramine and is approximately twice as active as the racemic compound.

Pseudoephedrine is a sympathomimetic amine and isomer of ephedrine; acts as a decongestant in respiratory tract mucous membranes with less vasoconstrictor action than ephedrine in normotensive individuals.

Dextromethorphan is a chemical relative of morphine lacking narcotic properties except in overdose; controls cough by depressing the medullary cough center.

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Chlorpheniramine
- Dextromethorphan
- Pseudoephedrine

Pharmacotherapy Pearls

Chlorpheniramine **maleate** is ~70% chlorpheniramine; chlorpheniramine **tannate** is ~44% chlorpheniramine.

Dexchlorpheniramine **maleate** is ~70% dexchlorpheniramine; dexchlorpheniramine **tannate** is ~45% dexchlorpheniramine.

Dextromethorphan **hydrobromide** is ~77% dextromethorphan; dextromethorphan **tannate** is ~42% dextromethorphan.

Pseudoephedrine **hydrochloride** is ~82% pseudoephedrine; pseudoephedrine **tannate** is ~29% pseudoephedrine.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Chlorpheniramine: Significant xerostomia with prolonged use (normal salivary flow resumes upon discontinuation).

Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response
Mental Health: Effects on Mental StatusMay cause anxiety, dizziness, insomnia, restlessness, hallucinations, or depression
Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment; may cause tremor which may be mistaken for EPS; may cause tachycardia; tachycardia is also common with clozapine; monitor vital signs; may cause sedation (concurrent use with psychotropics may produce additive sedative effects)
Index TermsChlorpheniramine Maleate, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide; Chlorpheniramine Tannate, Pseudoephedrine Tannate, and Dextromethorphan Tannate; Dexchlorpheniramine Tannate, Pseudoephedrine Tannate, and Dextromethorphan Tannate; Dextromethorphan, Chlorpheniramine, and Pseudoephedrine; Pseudoephedrine, Chlorpheniramine, and Dextromethorphan

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Chlorpheniramine, Pseudoephedrine, and Methscopolamine

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Pronunciation(klor fen IR a meen, soo doe e FED rin, & meth skoe POL a meen)

U.S. Brand NamesAmdry-C; Coldamine; Durahist™; Hista-Vent® PSE [DSC]

Pharmacologic CategoryAlpha/Beta Agonist; Anticholinergic Agent; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsRelief of symptoms of allergic rhinitis, vasomotor rhinitis, sinusitis, and the common cold

Dosing: AdultsRhinitis, sinusitis, common cold: Oral: Durahist™, Hista-Vent® PSE: One tablet every 12 hours (maximum dose: 2 tablets/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRhinitis, sinusitis, common cold: Oral:

Children 6-11 years: Durahist™, Hista-Vent® PSE: One-half tablet every 12 hours (maximum dose: 1 tablet/24 hours)

Children ≥12 years: Refer to adult dosing.

Administration: OralDurahist™, Hista-Vent® PSE: Swallow whole, do not crush or chew; may split in half

StorageStore at controlled room temperature between 15ºC to 30ºC (59ºF to 86ºF).

ContraindicationsHypersensitivity to chlorpheniramine, pseudoephedrine, methscopolamine, or any component of the formulation; severe hypertension; severe coronary artery disease; use with or within 2 weeks of discontinuing MAO inhibitor; narrow-angle glaucoma; urinary retention; peptic ulcer disease; during an asthmatic attack; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression and blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Neuropathy: Use with caution in patients with autonomic neuropathy.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Renal impairment: Use with caution in patients with renal impairment.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.
- Ulcerative colitis: Use with caution in patients with ulcerative colitis.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children. Safety and efficacy have not been established in children <6 years of age.

Geriatric Considerations

Because of its anticholinergic effects, this product is not considered a treatment of choice in the elderly.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination; see individual agents

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsPseudoephedrine is excreted in breast milk. Excretion of chlorpheniramine or methscopolamine in breast milk is unknown. Breast-feeding with this combination is contraindicated by some manufacturers. See individual agents.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, cardiovascular collapse, flushing, hypotension, pallor, palpitation, tachycardia

Central nervous system: Anxiety, convulsions, CNS depression, dizziness, drowsiness, excitability, fear, giddiness, hallucinations, headache, insomnia, irritability, lassitude, nervousness, restlessness, tremor

Gastrointestinal: Gastric irritation, nausea, xerostomia

Genitourinary: Dysuria, urinary retention

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision

Respiratory: Dry nose, dry throat, respiratory difficulty

Metabolism/Transport EffectsChlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4(major); **Inhibits** CYP2D6 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringAssess for potential interactions with other pharmacological agents patient may be taking (eg, concurrent CNS depressants or anticholinergic psychotropics may cause additive effects). Assess effectiveness of therapy (relief of symptoms) and adverse reactions at beginning of therapy and periodically with long-term use. Teach patient/caregiver appropriate use, possible side effects and interventions to reduce side effects, and adverse symptoms to report.
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed; do not increase dose or take more often than prescribed. Do not chew or crush tablets (may split Durahist™ or Hista-Vent® PSE in half). Avoid excessive alcohol. May cause drowsiness, dizziness, excitability, sleep disturbance, nervousness, restlessness, or blurred vision (do not drive or engage in activities that require alertness and coordination until response to drug is known); dry mouth or gastric irritation (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); urinary retention (void before taking medication). Report chest pain, palpitations or rapid heart beat; excessive or persistent CNS changes (depression, excitability, irritability, insomnia); respiratory difficulties; or lack of improvement or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, extended release:

Coldamine: Chlorpheniramine maleate 8 mg, pseudoephedrine hydrochloride 90 mg, and methscopolamine nitrate 2.5 mg

Tablet, sustained release: Chlorpheniramine maleate 8 mg, pseudoephedrine hydrochloride 60 mg, and methscopolamine nitrate 1.25 mg; chlorpheniramine maleate 8 mg, pseudoephedrine hydrochloride 90 mg, and methscopolamine nitrate 2.5 mg

Amdry-C: Chlorpheniramine maleate 8 mg, pseudoephedrine hydrochloride 120 mg, and methscopolamine nitrate 2.5 mg [scored]

Durahist™: Chlorpheniramine maleate 8 mg, pseudoephedrine hydrochloride 60 mg, and methscopolamine nitrate 1.25 mg [scored]

Hista-Vent® PSE: Chlorpheniramine maleate 8 mg, pseudoephedrine hydrochloride 120 mg, and methscopolamine nitrate 2.5 mg [dye free; scored] [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, 12-hour (Hista-Vent PSE)

8-120-2.5 mg (100): $39.64

Tablet, controlled release (AlleRx Dose Pack)

120-2.5 & 8-2.5 mg (20): $27.33

Mechanism of Action

Chlorpheniramine maleate: Blocks histamine H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract

Pseudoephedrine: Acts as a decongestant in respiratory tract mucous membranes

Methscopolamine nitrate: Derivative of scopolamine, antisecretory effects

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Chlorpheniramine: Significant xerostomia with prolonged use (normal salivary flow resumes upon discontinuation).

Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Methscopolamine: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), and dry throat and nose. Anticholinergic side effects can cause a reduction of saliva production or secretion, contributing to discomfort and dental disease (ie, caries, oral candidiasis and periodontal disease).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause sedation, anxiety, dizziness, giddiness, hallucinations, insomnia, irritability, nervousness, restlessness, or tremor

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 2 weeks of discontinuing an MAO inhibitor. Sedating agent; concurrent use with CNS depressant or alcohol may produce additive effects. Contains an anticholinergic agent; concurrent use with anticholinergic psychotropics may produce additive effects.

Index TermsMethscopolamine, Chlorpheniramine, and Pseudoephedrine; Methscopolamine, Pseudoephedrine, and Chlorpheniramine; Pseudoephedrine Hydrochloride, Methscopolamine Nitrate, and Chlorpheniramine Maleate; Pseudoephedrine, Methscopolamine, and Chlorpheniramine

Chlorpheniramine and Pseudoephedrine

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Allerest® may be confused with Sinarest®

Chlor-Trimeton® may be confused with Chloromycetin®

Sudafed® may be confused with Sufenta®

Pronunciation(klor fen IR a meen & soo doe e FED rin)

U.S. Brand NamesAllerest® Maximum Strength Allergy and Hay Fever [OTC]; Deconamine® SR; Dicel™; Duratuss® DA; Dynahist-ER Pediatric® [DSC]; Histade™ [DSC]; Histex™; LoHist-D; QDALL® [DSC]; Suclor™; Sudafed® Sinus & Allergy [OTC]; SudaHist®; Sudal® 12

Canadian Brand NamesTriaminic® Cold & Allergy

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsRelief of nasal congestion associated with the common cold, hay fever, and other allergies, sinusitis, eustachian tube blockage, and vasomotor and allergic rhinitis

Dosing: AdultsGeneral dosing guidelines; consult specific product labeling.

Rhinitis/nasal decongestant: Oral:

Chlorpheniramine maleate 4 mg and pseudoephedrine hydrochloride 60 mg every 4-6 hours (immediate release products)

Deconamine® SR: Chlorpheniramine maleate 8 mg and pseudoephedrine hydrochloride 120 mg every 12 hours

Chlorpheniramine tannate 4.5 mg and pseudoephedrine tannate 75 mg: 10-20 mL every 12 hours (maximum: 40 mL/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricGeneral dosing guidelines; consult specific product labeling.

Rhinitis/decongestant: Oral: Children:

2-6 years:

Chlorpheniramine maleate 1 mg and pseudoephedrine hydrochloride 15 mg every 4-6 hours

Chlorpheniramine tannate 4.5 mg and pseudoephedrine tannate 75 mg: 2.5-5 mL every 12 hours (maximum: 10 mL/24 hours)

6-12 years: Chlorpheniramine maleate 2 mg and pseudoephedrine hydrochloride 30 mg every 4-6 hours (immediate release products)

Children ≥12 years: Refer to adult dosing.

Administration: OralSwallow sustained release formulations whole, do not crush or chew.

Dietary ConsiderationsTriaminic® Cold and Allergy chewable tablet contains coconut oil, phenylalanine 17.6 mg/tablet, and sodium 5 mg/tablet.

ContraindicationsHypersensitivity to chlorpheniramine, pseudoephedrine, or any component of the formulation; severe hypertension; severe cardiovascular disease; use with or within 2 weeks of discontinuing MAO inhibitor; narrow-angle glaucoma; urinary retention; peptic ulcer disease; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.

- Diabetes: Use with caution in patients with diabetes mellitus.

- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.

- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).

- Respiratory disease: Use with caution in patients with asthma or other chronic breathing disorders.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Antihistamines may cause excitation in young children. Not labeled for OTC use in children <6 years of age.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Other warnings/precautions:

- Self-medication (OTC use): When used for self medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever. Discontinue and contact healthcare provider if nervousness, dizziness or sleeplessness occur.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination product. See individual agents.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsPseudoephedrine is excreted in breast milk. Some manufacturers contraindicate its use; however, the AAP considers it to be “compatible” with breast-feeding. Information for chlorpheniramine is not available. Also see individual agents.

Adverse ReactionsSee individual agents.

Metabolism/Transport Effects

Chlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, extended release: Chlorpheniramine maleate 8 mg and pseudoephedrine hydrochloride 120 mg; chlorpheniramine maleate 12 mg and pseudoephedrine hydrochloride 100 mg

Duratuss® DA: Chlorpheniramine maleate 12 mg and pseudoephedrine hydrochloride 100 mg

Dynahist-ER Pediatric®: Chlorpheniramine maleate 4 mg and pseudoephedrine hydrochloride 60 mg [DSC]

Histade™: Chlorpheniramine maleate 12 mg and pseudoephedrine hydrochloride 120 mg [DSC]

QDALL®: Chlorpheniramine maleate 12 mg and pseudoephedrine hydrochloride 100 mg [DSC]

Suclor™: Chlorpheniramine maleate 8 mg and pseudoephedrine hydrochloride 120 mg

Capsule, sustained release: Chlorpheniramine maleate 8 mg and pseudoephedrine hydrochloride 120 mg

Deconamine® SR: Chlorpheniramine maleate 8 mg and pseudoephedrine hydrochloride 120 mg

Liquid:

Histex™: Chlorpheniramine maleate 2 mg and pseudoephedrine sulfate 30 mg per 5 mL (480 mL) [peach flavor]

LoHist-D: Chlorpheniramine maleate 2 mg and pseudoephedrine hydrochloride 30 mg per 5 mL (480 mL) [alcohol free, dye free; peach flavor]

Suspension:

Dicel™: Chlorpheniramine tannate 5 mg and pseudoephedrine tannate 75 mg per 5 mL (480 mL) [contains sodium benzoate; strawberry banana flavor]

Syrup: Chlorpheniramine maleate 2 mg and pseudoephedrine hydrochloride 30 mg per 5 mL (480 mL)

Tablet: Chlorpheniramine maleate 4 mg and pseudoephedrine hydrochloride 60 mg

Allerest® Maximum Strength Allergy and Hay Fever: Chlorpheniramine maleate 2 mg and pseudoephedrine hydrochloride 30 mg

Sudafed® Sinus & Allergy: Chlorpheniramine maleate 4 mg and pseudoephedrine hydrochloride 60 mg

Tablet, chewable:

Sudal® 12: Chlorpheniramine maleate 4 mg and pseudoephedrine hydrochloride 30 mg [contains phenylalanine 25 mg/tablet; grape flavor]

Tablet, sustained release:

SudaHist: Chlorpheniramine maleate 12 mg and pseudoephedrine hydrochloride 120 mg

Generic AvailableYes: Excludes suspension and chewable tablet

Pricing: U.S. (www.drugstore.com)

Capsule, 12-hour (Histade CR)

12-120 mg (60): $21.99

Capsule, 12-hour (Kronofed-A-Jr)

4-60 mg (30): $24.99

Capsule, 24-hour (QDALL)

12-100 mg (100): $109.23

Capsule, controlled release (Chlorpheniramine-Pseudoeph)

8-120 mg (60): $79.99

Capsule, controlled release (Deconamine SR)

8-120 mg (30): $91.29

Capsule, controlled release (Kronofed-A)

8-120 mg (30): $15.99

Chewable (Sudal 12)

4-30 mg (100): $109.99

Syrup (Chlorpheniramine-Pseudoeph)

2-30 mg/5 mL (473): $48.01

Syrup (Deconamine)

2-30 mg/5 mL (120): $43.99

Tablets (Deconamine)

4-60 mg (60): $104.99

Mechanism of Action

Chlorpheniramine competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract.

Pseudoephedrine is a sympathomimetic amine and isomer of ephedrine; acts as a decongestant in respiratory tract mucous membranes with less vasoconstrictor action than ephedrine in normotensive individuals.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Chlorpheniramine
- Pseudoephedrine

Pharmacotherapy Pearls

Chlorpheniramine **maleate** is ~70% chlorpheniramine; chlorpheniramine **tannate** is ~44% chlorpheniramine.

Pseudoephedrine **hydrochloride** is ~82% pseudoephedrine; pseudoephedrine **tannate** is ~29% pseudoephedrine.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Chlorpheniramine: Prolonged use will cause significant xerostomia (normal salivary flow resumes upon discontinuation).

Pseudoephedrine: Xerostomia (prolonged use worsens; normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDrowsiness is common; may cause excitability, nervousness, fatigue, or depression

Mental Health: Effects on Psychiatric TreatmentDry mouth and sedation may be exacerbated by concurrent psychotropic use

Index TermsChlorpheniramine Maleate and Pseudoephedrine Hydrochloride; Chlorpheniramine Tannate and Pseudoephedrine Tannate; Pseudoephedrine and Chlorpheniramine

International Brand NamesTriaminic Cold & Allergy (CA)

Chlorpheniramine, Pyrilamine, and Phenylephrine

Lexi-Drugs Online

English English

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm.

Pronunciation(klor fen IR a meen, pye RIL a meen, & fen il EF rin)

U.S. Brand NamesAllerTan™; Chlor-Tan A 12 [DSC]; Chlorex-A 12 [DSC]; Conal; MyHist-PD; Nalex A 12; Poly Hist Forte®; Poly Hist PD; Ru-Hist Forte; Tri-Hist; Triplex™ AD

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of rhinitis and nasal congestion due to colds or allergy

Dosing: Adults**Rhinitis, nasal congestion due to colds or allergy:** Oral:

Tablet (Ru-Hist Forte, Poly Hist Forte®): 1 tablet 2-3 times/day

Liquid (MyHist-PD, Poly Hist PD, Triplex™ AD): 5-10 mL every 4-6 hours, not to exceed 40 mL/day

Suspension (AllerTan™, Conal): 5-10 mL every 12 hours, not to exceed 20 mL/day

Dosing: Pediatric**Rhinitis, nasal congestion due to colds or allergy:** Oral:

Tablet (Ru-Hist Forte, Poly Hist Forte®):

Children <6 years: Dosage not established.

Children 6-12 years: $^{1}/_{2}$ tablet 2-3 times/day

Children >12 years: Refer to adult dosing.

Liquid (MyHist-PD, Poly Hist PD):

Children 2-6 years: 2.5 mL every 4-6 hours, not to exceed 10 mL/day

Children 6-12 years: 5 mL every 4-6 hours, not to exceed 20 mL/day

Children >12 years: Refer to adult dosing.

Liquid (Triplex™ AD):

Children <6 years: Dosage not established

Children 6-12 years: 5 mL every 4-6 hours, not to exceed 20 mL/day

Children >12: Refer to adult dosing.

Suspension (AllerTan™, Conal):

Children 2-6 years: 2.5 mL every 12 hours, not to exceed 5 mL/day

Children 6-12 years: 5 mL every 12 hours, not to exceed 10 mL/day

Children >12 years: Refer to adult dosing.

Administration: OralDo not break or crush tablets. Shake liquid suspension well before use.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect liquid from freezing.

ContraindicationsHypersensitivity to phenylephrine, chlorpheniramine, pyrilamine, any sympathomimetic amines, or any component; severe hypertension; severe coronary artery disease; diabetes mellitus; hyperthyroidism; use with or within 14 days of MAO inhibitor; premature or newborn infants; acute asthma

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe hypertension.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or urinary obstruction.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Respiratory disease: Use with caution in patients with asthma or other chronic breathing disorders.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children.

Geriatric ConsiderationsDue to the anticholinergic effects of chlorpheniramine and the sympathomimetic effects of phenylephrine, this product is not recommended for the elderly.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproductive studies have not been conducted with this combination.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Hyper-/hypotension, palpitation

Central nervous system: Dizziness, excitation (children), headache, nervousness, sedation, seizure

Dermatologic: Drug rash, urticaria

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, GI upset, nausea, vomiting

Genitourinary: Urinary frequency, urinary retention

Hematologic: Agranulocytosis, leukopenia, thrombocytopenia

Ocular: Blurred vision

Respiratory: Dry nose/throat, stuffy nose, thickening of bronchial secretions, tightness of chest, wheezing

Metabolism/Transport EffectsChlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, oral:

MyHist-PD: Chlorpheniramine maleate 2 mg, pyrilamine maleate 12.5 mg, and phenylephrine hydrochloride 7.5 mg per 5 mL (473 mL) [dye free, ethanol free, sugar free; bubblegum flavor]

Poly Hist PD: Chlorpheniramine maleate 2 mg, pyrilamine maleate 12.5 mg, and phenylephrine hydrochloride 7.5 mg per 5 mL (480 mL) [dye free, ethanol free, sugar free; contains propylene glycol; bubblegum flavor]

Triplex™ AD: Chlorpheniramine maleate 2 mg, pyrilamine maleate 12.5 mg, and phenylephrine hydrochloride 7.5 mg per 5 mL (473 mL) [dye free, ethanol free, sugar free; contains sodium benzoate; bubblegum flavor]

Suspension, oral:

AllerTan™: Chlorpheniramine maleate 8 mg, pyrilamine maleate 12.5 mg, and phenylephrine hydrochloride 15 mg per 5 mL (473 mL) [contains sodium benzoate; grape flavor]

Chlor-Tan A 12: Chlorpheniramine maleate 2 mg, pyrilamine maleate 12.5 mg, and phenylephrine hydrochloride 5 mg per 5 mL (118 mL) [ethanol free, sugar free; raspberry flavor] [DSC]

Chlorex-A 12: Chlorpheniramine maleate 2 mg, pyrilamine maleate 12.5 mg, and phenylephrine hydrochloride 5 mg per 5 mL (120 mL) [raspberry flavor] [DSC]

Conal: Chlorpheniramine maleate 8 mg, pyrilamine maleate 12.5 mg, and phenylephrine hydrochloride 15 mg per 5 mL (473 mL) [contains phenylalanine 7 mg/5 mL, propylene glycol; raspberry flavor]

Nalex A 12: Chlorpheniramine tannate 2 mg, pyrilamine tannate 12.5 mg, and phenylephrine tannate 5 mg per 5 mL (120 mL) [contains benzoic acid; raspberry flavor]

Tri-Hist: Chlorpheniramine maleate 2 mg, pyrilamine maleate 12.5 mg, and phenylephrine hydrochloride 5 mg per 5 mL (120 mL)

Tablet, sustained release, oral:

Poly Hist Forte®: Chlorpheniramine maleate 4 mg, pyrilamine maleate 25 mg, and phenylephrine hydrochloride 10 mg

Tablet, time-released, oral: Chlorpheniramine maleate 4 mg, pyrilamine maleate 25 mg, and phenylephrine hydrochloride 10 mg

Ru-Hist Forte: Chlorpheniramine maleate 4 mg, pyrilamine maleate 25 mg, and phenylephrine hydrochloride 10 mg

Generic AvailableYes

Pharmacodynamics/KineticsSee individual agents.

Mental Health: Effects on Mental StatusMay cause dizziness, nervousness, sedation, or excitation (children).

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment. May cause CNS depression; concomitant use with psychotropic agents may produce additive effects. May cause agranulocytosis; use with caution in patients receiving clozapine and carbamazepine. May cause anticholinergic side effects; concurrent use with psychotropic agents may produce additive effects. Use may mitigate effects of acetylcholinesterase inhibitors. Tricyclic antidepressants may enhance the vasopressor effect of phenylephrine.

Chlorpheniramine

Lexi-Drugs Online

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Special Alerts

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It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Chlor-Trimeton® may be confused with Chloromycetin®

Pronunciation(klor fen IR a meen)

U.S. Brand NamesAhist™; Aller-Chlor® [OTC]; Chlor-Trimeton® [OTC]; Chlorphen [OTC]; CPM-12; Diabetic Tussin® Allergy Relief [OTC]; PediaTan™; QDALL® AR; Teldrin® HBP [OTC]

Canadian Brand NamesChlor-Tripolon®; Novo-Pheniram

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsPerennial and seasonal allergic rhinitis and other allergic symptoms including urticaria

Use: DentalTreatment of histamine-induced allergic symptoms

Dosing: AdultsAllergic symptoms, allergic rhinitis: Oral: 4 mg every 4-6 hours, not to exceed 24 mg/day or sustained release 8-12 mg every 8-12 hours, not to exceed 24 mg/day

Dosing: ElderlyAllergic symptoms, rhinitis: Oral: 4 mg once or twice daily, or 8 mg sustained release at bedtime. **Note:** Duration of action may be 36 hours or more when serum concentrations are low.

Dosing: Pediatric

Allergic symptoms, allergic rhinitis: Children: Oral: 0.35 mg/kg/day in divided doses every 4-6 hours

2-6 years: 1 mg every 4-6 hours, not to exceed 6 mg in 24 hours

6-12 years: 2 mg every 4-6 hours, not to exceed 12 mg/day or sustained release 8 mg at bedtime

Children >12 years: Refer to adult dosing.

Dosing: Renal ImpairmentHemodialysis: Supplemental dose is not necessary.

Administration: OralTimed release oral forms are to be swallowed whole, not crushed or chewed.

Dietary ConsiderationsMay be taken with food or water.

StorageProtect from light.

ContraindicationsHypersensitivity to chlorpheniramine maleate or any component of the formulation; narrow-angle glaucoma; bladder neck obstruction; symptomatic prostate hypertrophy; during acute asthmatic attacks; stenosing peptic ulcer; pyloroduodenal obstruction. Avoid use in premature and term newborns due to possible association with SIDS.

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Respiratory disease: Use with caution in patients with asthma or other chronic breathing disorders.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children. Not for OTC use in children <2 years of age.

Geriatric ConsiderationsAnticholinergic action may cause significant confusional symptoms, constipation, or problems voiding urine. If an antihistamine is indicated, a second generation nonsedating antihistamine would be a more appropriate choice.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with chlorpheniramine tannate.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Central nervous system: Slight to moderate drowsiness

Respiratory: Thickening of bronchial secretions

1% to 10%:

Central nervous system: Headache, excitability, fatigue, nervousness, dizziness

Gastrointestinal: Nausea, xerostomia, diarrhea, abdominal pain, appetite increase, weight gain

Genitourinary: Urinary retention

Neuromuscular & skeletal: Arthralgia, weakness

Ocular: Diplopia

Renal: Polyuria

Respiratory: Pharyngitis

Metabolism/Transport Effects**Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central).

Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release:

CPM-12: Chlorpheniramine maleate 12 mg

Capsule, variable release, as maleate:

QDALL® AR: Chlorpheniramine 12 mg [immediate release and sustained release]

Suspension, as tannate:

PediaTan™: 8 mg/5 mL (480 mL) [sugar free; contains sodium benzoate; bubble gum flavor]

Syrup, as maleate:

Aller-Chlor®: 2 mg/5 mL (120 mL) [contains alcohol 5%]

Diabetic Tussin® Allergy Relief: 2 mg/5 mL (120 mL) [alcohol free, dye free, sugar free]

Tablet, as maleate: 4 mg

Aller-Chlor®, Chlor-Trimeton®, Chlorphen, Teldrin® HBP: 4 mg

Tablet, extended release, as maleate:

Chlor-Trimeton®: 12 mg

Tablet, long acting, as tannate [scored]:

Ahist™: 12 mg

Generic AvailableYes: Syrup, tablet

Mechanism of ActionCompetes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract

Pharmacodynamics/KineticsHalf-life elimination, serum: 20-24 hours

Pharmacotherapy PearlsNot effective for nasal stuffiness.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Chronic use of antihistamines will inhibit salivary flow, particularly in elderly patients; this may contribute to periodontal disease and oral discomfort.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause excitability, nervousness, fatigue, or depression

Mental Health: Effects on Psychiatric TreatmentDry mouth and sedation may be exacerbated by concurrent psychotropic use

Index TermsChlorpheniramine Maleate; CTM

International Brand NamesAhiston (IL); Alerfin (PY); Alergical (PE); Alergidryl (AR); Alergitrat (AR); Aller (MY); Allerfin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Allergex (ZA); Allergyl (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Allermin (TW); Analerg (UY); Antadex-H (MX); Antamin (PH); Antihistamin (PE); Barominic (PH); Bregamin (MX); Cadistin (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Chloramine (SG); Chlorleate (TH); Chlorpheniramine DHA (HK); Chlorpheno (TH); Chlorphenon (ID); Chlorpyrimine (HK, MY, TH); Chlortrimeton (ZA); Clodryl (CO); Cloro Trimeton (AR); Cloro-Trimeton (MX); Cloroalergan (PE); Clorotrimeton (CO, PE, VE); Cohistan (ID, TH); Com-Trimeton (TW); CTM (ID); Derimeton (MX); Histal (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Histat (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Histatapp (TH); Histavil (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Histin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Istamex (GR); Niramine (TW); Orphen (ID); Pirafene (BG); Piriton (AE, BB, BH, BM, BS, BZ, CY, EG, GB, GY, IE, IL, IQ, IR, JM, JO, KW, LB, LY, MY, NL, OM, PK, PR, QA, SA, SR, SY, TT, YE); Trimeton (IT); Tromine (HK); Valemine (PH)

ChlorproMAZINE

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

Gill SS, Bronskill SE, Normand SL, et al, “Antipsychotic Drug Use and Mortality in Older Adults With Dementia,” *Ann Intern Med*, 2007, 146(11):775-86.[PubMed 17548409]

Schneeweiss S, Setoguchi S, Brookhart A, et al, “Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients,” *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Medication Safety Issues

Sound-alike/look-alike issues:

ChlorproMAZINE may be confused with chlordiazePOXIDE, chlorproPAMIDE, clomiPRAMINE, prochlorperazine, promethazine

Thorazine® may be confused with thiamine, thioridazine

Pronunciation(klor PROE ma zeen)

Canadian Brand NamesLargactil®; Novo-Chlorpromazine

Pharmacologic CategoryAntimanic Agent; Antipsychotic Agent, Typical, Phenothiazine

Use: Labeled IndicationsControl of mania; treatment of schizophrenia; control of nausea and vomiting; relief of restlessness and apprehension before surgery; acute intermittent porphyria; adjunct in the treatment of tetanus; intractable hiccups; combativeness and/or explosive hyperexcitable behavior in children 1-12 years of age and in short-term treatment of hyperactive children

Use: Unlabeled/InvestigationalManagement of psychotic disorders; behavioral symptoms associated with dementia (elderly); psychosis/agitation related to Alzheimer's dementia

Dosing: Adults

Schizophrenia/psychoses:

Oral: Range: 30-800 mg/day in 1-4 divided doses, initiate at lower doses and titrate as needed; usual dose: 200-600 mg/day; some patients may require 1-2 g/day

I.M., I.V.: Initial: 25 mg, may repeat (25-50 mg) in 1-4 hours, gradually increase to a maximum of 400 mg/dose every 4-6 hours until patient is controlled; usual dose: 300-800 mg/day

Intractable hiccups: Oral, I.M.: 25-50 mg 3-4 times/day

Nausea and vomiting:

Oral: 10-25 mg every 4-6 hours

I.M., I.V.: 25-50 mg every 4-6 hours

Dosing: Elderly

Behavioral symptoms associated with dementia (unlabeled use): Initial: 10-25 mg 1-2 times/day; increase at 4- to 7-day intervals by 10-25 mg/day. Increase dose intervals (eg, twice daily, 3 times/day) as necessary to control behavior response or side effects; maximum daily dose: 800 mg; gradual increases (titration) may prevent some side effects or decrease their severity.

Other indications: Refer to adult dosing.

Dosing: Pediatric

Schizophrenia/psychoses: Children ≥6 months:

Oral: 0.5-1 mg/kg/dose every 4-6 hours; older children may require 200 mg/day or higher.

I.M., I.V.: 0.5-1 mg/kg/dose every 6-8 hours; maximum dose for <5 years (22.7 kg): 40 mg/day; maximum for 5-12 years (22.7-45.5 kg): 75 mg/day

Nausea and vomiting: Children ≥6 months:

Oral: 0.5-1 mg/kg/dose every 4-6 hours as needed

I.M., I.V.: 0.5-1 mg/kg/dose every 6-8 hours; maximum dose for <5 years (22.7 kg): 40 mg/day; maximum for 5-12 years (22.7-45.5 kg): 75 mg/day

Dosing: Renal ImpairmentNot dialyzable (0% to 5%)

Dosing: Hepatic ImpairmentAvoid use in severe hepatic dysfunction.

Administration: I.V.Direct of intermittent infusion: Infuse 1 mg or portion thereof over 1 minute. **Note:** Avoid skin contact with solution; may cause contact dermatitis.

StorageInjection: Protect from light. A slightly yellowed solution does not indicate potency loss, but a markedly discolored solution should be discarded. Diluted injection (1 mg/mL) with NS and stored in 5 mL vials remains stable for 30 days.

ReconstitutionDilute injection (1 mg/mL) with NS for I.V. administration.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, ${}^1/_2NS$, NS.

Y-site administration: Compatible: Amsacrine, cisatracurium, cisplatin, cladribine, cyclophosphamide, cytarabine, docetaxel, doxorubicin, doxorubicin liposome, famotidine, filgrastim, fluconazole, gatifloxacin, gemcitabine, granisetron, heparin, hydrocortisone sodium succinate, ondansetron, potassium chloride, propofol, teniposide, thiotepa, vinorelbine, vitamin B complex with C. **Incompatible:** Allopurinol, amifostine, amphotericin B cholesteryl sulfate complex, aztreonam, cefepime, etoposide phosphate, fludarabine, furosemide, linezolid, melphalan, methotrexate, paclitaxel, piperacillin/tazobactam, sargramostim. **Variable (consult detailed reference):** Remifentanil, TPN.

Compatibility in syringe: Compatible: Atropine, benztropine, butorphanol, diphenhydramine, doxapram, droperidol, fentanyl, glycopyrrolate, hydromorphone, hydroxyzine, meperidine, metoclopramide, midazolam, morphine, pentazocine, perphenazine, prochlorperazine edisylate, promazine, promethazine, scopolamine. **Incompatible:** Cimetidine, dimenhydrinate, heparin, pentobarbital, thiopental. **Variable (consult detailed reference):** Ranitidine.

Compatibility when admixed: Compatible: Ascorbic acid injection, ethacrynate, netilmicin, theophylline, vitamin B complex with C. **Incompatible:** Aminophylline, amphotericin B, ampicillin, chloramphenicol, chlorothiazide, floxacillin, furosemide, methohexital, penicillin G potassium, penicillin G sodium, phenobarbital. **Variable (consult detailed reference):** Pentobarbital.

ContraindicationsHypersensitivity to chlorpromazine or any component of the formulation (cross-reactivity between phenothiazines may occur); severe CNS depression; coma

Allergy Considerations

- Phenothiazine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines).
- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to other neuroleptics, chlorpromazine has a moderate potency of cholinergic blockade.
- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).
- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is low-moderate relative to other neuroleptics). Risk of dystonia (and possibly other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Hypotension: Significant hypotension may occur, particularly with parenteral administration.

- Neuroleptic malignant syndrome (NMS): May be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Pigmentary retinopathy: May be associated with pigmentary retinopathy.

- Sedation: Highly sedating which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with bone marrow suppression; blood dyscrasias have occurred. Use only if benefits outweigh risk.

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Dementia: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo. An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Chlorpromazine is not approved for this indication.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for developing tardive dyskinesia.

Dosage form specific issues:

- Sulfites: Injection contains sulfites.

Geriatric ConsiderationsMany elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior. Before initiating antipsychotic medication, the clinician should investigate any possible reversible cause; any stress or stress from any disease can cause acute “confusion” or worsening of baseline nonpsychotic behavior. Most commonly acute changes in behavior are due to increases in drug dose or addition of new drug to regimen; fluid electrolyte loss; infections; and changes in environment.

Any changes in disease status in any organ system can result in behavior changes.

In the treatment of agitated, demented, elderly patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control.

Pregnancy Risk FactorC

LactationEnters breast milk/not recommended (AAP rates “of concern”)

Breast-Feeding ConsiderationsDrowsiness and lethargy have been reported in nursing infants; galactorrhea has been reported in mother.

Adverse ReactionsFrequency not defined.

Cardiovascular: Postural hypotension, tachycardia, dizziness, nonspecific QT changes

Central nervous system: Drowsiness, dystonias, akathisia, pseudoparkinsonism, tardive dyskinesia, neuroleptic malignant syndrome, seizure

Dermatologic: Photosensitivity, dermatitis, skin pigmentation (slate gray)

Endocrine & metabolic: Lactation, breast engorgement, false-positive pregnancy test, amenorrhea, gynecomastia, hyper- or hypoglycemia

Gastrointestinal: Xerostomia, constipation, nausea

Genitourinary: Urinary retention, ejaculatory disorder, impotence

Hematologic: Agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenic purpura

Hepatic: Jaundice

Ocular: Blurred vision, corneal and lenticular changes, epithelial keratopathy, pigmentary retinopathy

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2D6 (major), 3A4 (minor); **Inhibits** CYP2D6 (strong), 2E1 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Analgesics (Opioid): Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antimalarial Agents: May increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Beta-Blockers: Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Strong) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Desmopressin: ChlorproMAZINE may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Haloperidol: May enhance the QTc-prolonging effect of ChlorproMAZINE. ChlorproMAZINE may decrease the metabolism of Haloperidol. *Risk D: Consider therapy modification*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Strong) may decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Valproic Acid: ChlorproMAZINE may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid St John's wort (may decrease chlorpromazine levels, increase photosensitization, or enhance sedative effect). Avoid dong quai (may enhance photosensitization). Avoid kava kava, gotu kola, valerian (may increase CNS depression).

Test InteractionsFalse-positives for phenylketonuria, amylase, uroporphyrins, urobilinogen. May cause false-positive pregnancy test.

Monitoring ParametersVital signs; lipid profile, fasting blood glucose/Hgb A_{1c}; BMI; mental status; abnormal involuntary movement scale (AIMS); extrapyramidal symptoms (EPS)

Reference Range

Therapeutic: 50-300 ng/mL (SI: 157-942 nmol/L)

Toxic: >750 ng/mL (SI: >2355 nmol/L); serum concentrations poorly correlate with expected response

Nursing: Physical Assessment/MonitoringAssess other medications patient is taking for effectiveness and interactions. Review ophthalmic exam and monitor laboratory results, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. **I.V./I.M.:** Significant hypotension may occur. Initiate at lower doses (see Dosing) and taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. **Note:** Chlorpromazine may cause false-positive pregnancy test.

Monitoring: Lab TestsLipid profile, fasting blood glucose/Hgb A_{1c}; BMI

Patient EducationUse exactly as directed; do not increase dose or frequency. Do not discontinue this medication without consulting prescriber. Tablets may be taken with food. Do not take within 2 hours of any antacid. Store away from light. Avoid alcohol or caffeine and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May turn urine red-brown (normal). You may experience excess drowsiness, lightheadedness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); dry mouth, upset stomach, nausea, vomiting, anorexia (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); constipation (increased exercise, fluids, fruit, or fiber may help); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); urinary retention (void before taking medication); ejaculatory dysfunction (reversible); decreased perspiration (avoid strenuous exercise in hot environments); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report persistent CNS effects (trembling fingers, altered gait or balance, excessive sedation, seizures, unusual movements, anxiety, abnormal thoughts, confusion, personality changes); chest pain, palpitations, rapid heartbeat, or severe dizziness; unresolved urinary retention or changes in urinary pattern; altered menstrual pattern, change in libido, swelling or pain in breasts (male or female); vision changes, skin rash, irritation, or changes in color of skin (gray-blue); or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride: 25 mg/mL (1 mL, 2 mL)

Tablet, as hydrochloride: 10 mg, 25 mg, 50 mg, 100 mg, 200 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (ChlorproMAZINE HCl)

10 mg (60): $16.99

25 mg (60): $17.99

50 mg (60): $17.99

100 mg (60): $15.99

200 mg (60): $26.99

Mechanism of ActionChlorpromazine is an aliphatic phenothiazine antipsychotic which blocks postsynaptic mesolimbic dopaminergic receptors in the brain; exhibits a strong alpha-adrenergic blocking effect and depresses the release of hypothalamic and hypophyseal hormones; believed to depress the reticular activating system, thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis

Pharmacodynamics/Kinetics

Onset of action: I.M.: 15 minutes; Oral: 30-60 minutes

Absorption: Rapid

Distribution: V_d: 20 L/kg; crosses the placenta; enters breast milk

Protein binding: 92% to 97%

Metabolism: Extensively hepatic to active and inactive metabolites

Bioavailability: 20%

Half-life, biphasic: Initial: 2 hours; Terminal: 30 hours

Excretion: Urine (<1% as unchanged drug) within 24 hours

Related Information

- Agents Approved for Bipolar Disorder
- Antipsychotic Agents
- CMS: Long-Term Care Facility Thresholds
- Liquid Compatibility

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Xerostomia (normal salivary flow resumes upon discontinuation).

Significant hypotension may occur, especially when the drug is administered parenterally. Orthostatic hypotension is due to alpha-receptor blockade; elderly are at greater risk.

Tardive dyskinesia: Prevalence rate may be 40% in elderly; development of the syndrome and the irreversible nature are proportional to duration and total cumulative dose over time. Extrapyramidal reactions are more common in elderly with up to 50% developing these reactions after 60 years of age. Drug-induced Parkinson's syndrome occurs often; akathisia is the most common extrapyramidal reaction in elderly.

Increased confusion, memory loss, psychotic behavior, and agitation frequently occur as a consequence of anticholinergic effects. Antipsychotic-associated sedation in nonpsychotic patients is extremely unpleasant due to feelings of depersonalization, derealization, and dysphoria.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsMost pharmacology textbooks state that in presence of phenothiazines, systemic doses of epinephrine paradoxically decrease the blood pressure. This is the so called “epinephrine reversal” phenomenon. This has never been observed when epinephrine is given by infiltration as part of the anesthesia procedure. Chlorpromazine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health CommentChlorpromazine is a low-potency typical antipsychotic. Older antipsychotic medications (chlorpromazine, haloperidol), which do not meet specific criteria for “atypical” antipsychotics, are often referred to as typical antipsychotics. Compared to newer "atypical" antipsychotics, typical antipsychotics may have a greater propensity to cause extrapyramidal symptoms (EPS).

These drugs are thought to exert their antipsychotic activity by blocking dopamine D_2 receptors in the mesolimbic dopaminergic pathway. Side effects are often related to their ability to antagonize dopamine receptors in the nigrostriatal and tuberoinfundibular pathways.

Common side effects include sedation and neuroleptic effect (reduced initiative, interest in the environment, and display of emotion or affect). All **typical** antipsychotics are considered to be equally effective if given in equipotent doses. An inverse relationship exists between intrinsic antimuscarinic activity and propensity to cause extrapyramidal side effects. If dystonia or pseudoparkinsonism occurs, antiparkinsonian agents should be considered. If akathisia occurs, beta-blockers (eg, propranolol), benzodiazepines, or antiparkinsonian agents should be considered. Tardive dyskinesia (TD) secondary to typical antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. After this time period, the incidence is estimated to be 2% to 3% per year. Prevalence rates are ~15% to 20%. Female gender and age constitute risk factors for TD. Indeed, prevalence rates have been reported to be as high as 70% in elderly females. No specific treatment exists for TD, however, patients are often initiated on/switched to an atypical antipsychotic because of their lower incidence to cause TD and hopes of suppression.

Typical antipsychotics are usually only indicated for schizophrenia, but are generally effective for mania and psychosis and/or behavioral syndromes secondary to other mental conditions. Nonpsychiatric uses include Tourette's syndrome, Huntington's disease, and occasionally, intractable hiccups, pruritus, nausea, and vomiting.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Index TermsChlorpromazine Hydrochloride; CPZ

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International Brand Names Ampliactil (AR); Aspersinal (AR); Bellacina (PY); Cepezet (ID); Chlorazin (BG, CH, PL); Chlorpromasit (TH); Chlorpromed (TH); Clonazine (IE); Clorpromaz (BR); Clozine (IN); Duncan (TH); Esmind (JP); Fenactil (PL); Hibernal (HN, HU, SE); Klorproman (CZ, FI); Laractyl (PH); Largactil (AE, AT, AU, BB, BE, BF, BH, BJ, BM, BS, BZ, CI, CN, CY, CZ, EG, ES, ET, FR, GB, GH, GM, GN, GR, GY, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, OM, PE, PK, PR, PT, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Largo (SG); Matcine (MY, TH); Megatil (IN); Morefine (TW); Neomazine (KP); Plegomazin (BB, BM, BS, BZ, GY, IQ, JM, NL, PR, SR, SY, TT); Plegomazine (HU); Pogetol (TH); Promactil (ES, ID); Promak (PH); Promexin (JP); Propaphenin (DE); Prozil (DK); Prozin (IT); Psynor (PH); Taroctyl (IL); Thorazine (PH); Winsumin (TW)

ChlorproPAMIDE

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Medication Safety Issues

Sound-alike/look-alike issues:

> ChlorproPAMIDE may be confused with chlorproMAZINE
>
> Diabinese® may be confused with DiaBeta®, Dialume®, Diamox®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(klor PROE pa mide)
U.S. Brand NamesDiabinese® [DSC]
Canadian Brand NamesApo-Chlorpropamide®; Novo-Propamide
Pharmacologic CategoryAntidiabetic Agent, Sulfonylurea
Use: Labeled IndicationsManagement of blood sugar in type 2 diabetes mellitus (noninsulin dependent, NIDDM)
Use: Unlabeled/InvestigationalNeurogenic diabetes insipidus
Dosing: AdultsType 2 diabetes: Oral: The dosage of chlorpropamide is variable and should be individualized based upon the patient's response

Initial dose: 250 mg/day in mild-to-moderate diabetes in middle-aged, stable diabetic; 100-125 mg/day in older patients

Titration: Subsequent dosages may be increased or decreased by 50-125 mg/day at 3- to 5-day intervals

Maintenance dose: 100-250 mg/day; severe patients with diabetes may require 500 mg/day; avoid doses >750 mg/day

Dosing: ElderlyReduce initial dose to 100-125 mg/day in older patients; subsequent dosages may be increased or decreased by 50-125 mg/day at 3- to 5-day intervals (slower upward titration may be appropriate in older patients)
Dosing: Renal Impairment

Cl_{cr} <50 mL/minute: Avoid use.

Hemodialysis: Removed with hemoperfusion.

Peritoneal dialysis: Supplemental dose is not necessary.

Dosing: Hepatic ImpairmentDosage reduction is recommended. Conservative initial and maintenance doses are recommended in patients with liver impairment because chlorpropamide undergoes extensive hepatic metabolism.
Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsDietary modification based on ADA recommendations is a part of therapy. Decreases blood glucose concentration. Hypoglycemia may occur. Must be able to recognize symptoms of hypoglycemia (palpitations, sweaty palms, lightheadedness). May cause GI upset; take with food. Take at the same time each day; eat regularly and do not skip meals.
ContraindicationsHypersensitivity to chlorpropamide, sulfonylureas, sulfonamides, or any component of the formulation; type 1 diabetes mellitus (insulin dependent, IDDM); diabetic ketoacidosis
Allergy Considerations

- Sulfonylurea Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS) have not supported an association.
- Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when ethanol is ingested, or when more than one glucose-lowering drug is used. It is also more likely in elderly patients, malnourished patients and in patients with impaired renal or hepatic function; use with caution.
- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides,

and loop diuretics (except ethacrynic acid). Use in patients with sulfonylurea or sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Disease-related issues:

- Stress-related states: It may be necessary to discontinue therapy and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Long half-life: Patients should be properly instructed in the early detection and treatment of hypoglycemia; long half-life may complicate recovery from excess effects.

Geriatric Considerations Because of chlorpropamide's long half-life, duration of action, drug interactions, and the increased risk for hypoglycemia, it is not considered a hypoglycemic agent of choice in the elderly. How “tightly” a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar of <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well they recognize hypoglycemic or hyperglycemic symptoms, and how to respond to them and their other disease states. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk Factor C

Pregnancy Considerations Animal reproduction studies have not been conducted; therefore, the manufacturer classifies chlorpropamide as pregnancy category C. Chlorpropamide crosses the placenta and measurable serum concentrations can be found in infants exposed *in utero*. Teratogenic effects have been associated with chlorpropamide use in some studies; however, it is unknown if this is related to the medication or uncontrolled diabetes. Nonteratogenic adverse effects (eg, severe neonatal hypoglycemia, increased perianatal mortality) have also been associated with maternal chlorpropamide use. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. The manufacturer recommends if chlorpropamide is used during pregnancy, it should be discontinued at least 1 month before the expected delivery date. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

Lactation Enters breast milk/not recommended

Breast-Feeding Considerations Chlorpropamide is found in breast milk. Breast-feeding is not recommended by the manufacturer. Potentially, hypoglycemia may occur in a nursing infant exposed to a sulfonylurea via breast milk.

Pregnancy & Lactation, In-Depth

- ChlorproPAMIDE in Pregnancy & Lactation

Adverse Reactions Frequency not defined.

Central nervous system: Dizziness, headache

Dermatologic: Erythema multiforme, exfoliative dermatitis, maculopapular eruptions, photosensitivity, pruritus, urticaria

Endocrine & metabolic: Disulfiram-like reactions, hypoglycemia, SIADH

Gastrointestinal: Anorexia, diarrhea, hunger, nausea, proctocolitis, vomiting

Hematologic: Agranulocytosis, aplastic anemia, eosinophilia, hemolytic anemia, leukopenia, pancytopenia, porphyria cutanea tarda, thrombocytopenia

Hepatic: Cholestatic jaundice, hepatic porphyria

Metabolism/Transport Effects **Substrate** of CYP2C9 (minor)

Drug Interactions

Alcohol (Ethyl): Sulfonylureas may enhance the adverse/toxic effect of Alcohol (Ethyl). A flushing reaction may occur. *Risk C: Monitor therapy*

Allopurinol: May increase the serum concentration of ChlorproPAMIDE. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Cyclic Antidepressants: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonylureas may increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Fibric Acid Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Fluconazole: May increase the serum concentration of Sulfonylureas. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the hyperglycemic effect of Sulfonylureas. Quinolone Antibiotics may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Salicylates: May enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. **Exceptions:** Sulfacetamide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (possible disulfiram-like reaction).

Herb/Nutraceutical: Herbs with hypoglycemic properties may enhance the hypoglycemic effect of chlorpropamide. This includes alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, stinging nettle

Monitoring ParametersBlood glucose, Hgb A_{1c}; monitor for signs and symptoms of hypoglycemia (fatigue, sweating, numbness of extremities)

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Monitoring: Lab TestsBlood glucose, Hgb A_{1c}

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: 100 mg, 250 mg

Diabinese®: 100 mg, 250 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (ChlorproPAMIDE)

100 mg (60): $17.24

250 mg (60): $20.99

Tablets (Diabinese)

250 mg (60): $77.27

Mechanism of ActionStimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites

Pharmacodynamics/Kinetics

Onset of action: 1 hour

Peak effect: 3-6 hours

Duration of action: 24 hours

Absorption: Rapid

Distribution: V_d: 0.13-0.23 L/kg

Protein binding: 90%

Metabolism: Extensively hepatic (~80%), primarily via CYP2C9; forms metabolites

Half-life elimination: ~36 hours; prolonged in elderly or with renal impairment

End-stage renal disease: 50-200 hours

Time to peak, serum: 2-4 hours

Excretion: Urine

Related Information

- Diabetes Mellitus Management, Adults
- Sulfonamide Derivatives

Dental Health: Effects on Dental Treatment Chlorpropamide-dependent patients with diabetes (noninsulin dependent, Type 2) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Dizziness is common

Mental Health: Effects on Psychiatric Treatment Rare reports of agranulocytosis; use caution with clozapine and carbamazepine

Cardiovascular Considerations The possibility of higher doses of sulfonylureas eliciting an increase in cardiovascular events, because of their effects on blocking potassium sensitive ATP channels, has been raised. However, there are presently only limited data to support this premise, particularly with newer generation agents. An early study suggested poor cardiovascular outcomes in patients with diabetes treated with tolbutamide. Retrospective studies evaluating cardiovascular outcomes following angioplasty and acute myocardial infarction in patients with diabetes receiving newer sulfonylureas are inconsistent. Longer-term prospective trials of sulfonylurea therapy, such as the UKPDS, do not reveal any increased cardiovascular mortality.

Anesthesia and Critical Care Concerns/Other Considerations Long half-life may complicate recovery from excess effects. Patients previously maintained on insulin at <40 units/day may be directly changed to chlorpropamide. Patients previously receiving larger insulin doses should have their insulin doses decreased by 50% daily for the first few days, then gradually reduced further as necessary.

The possibility of higher doses of sulfonylureas eliciting an increase in cardiovascular events, because of their effects on blocking potassium sensitive ATP channels, has been raised. However, there are presently only limited data to support this premise, particularly with newer generation agents.

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International Brand Names Abemide (JP, TW); Adiaben (HR); Anti-D (SG); Arodoc C (JP); Bioglumin (ES); Chlormide (JP); Chlorpropamid (PL); Chlorpropamide Medochemie (MY); Copamide (IN); Dabinese (VE); Diabeedol (TH); Diabemide (BF, BJ, CI, ET, GH, GM, GN, IT, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Diabenese (AE, AR, BB, BF, BH, BJ, BM, BS, BZ, CI, CO, CR, CY, DO, EG, ET, GB, GH, GM, GN, GR, GT, GY, HN, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NI, NL, NO, OM, PA, PR, PT, QA, SA, SC, SD, SL, SN, SR, SV, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Diabet (ES); Diabexan (IT); Diabines (SE); Diabinese (AU, BE, BR, CH, CN, ES, HK, HR, ID, IE, KP, LU, PE, PH, PK, PL, TH, UY); Diabitex (BB, BM, BS, BZ, GY, JM, NL, SR, TT, ZA); Dibecon (TH); Glicoben (BR); Glycemin (TH); Hypomide (ZA); Insogen (MX); Meldian (HR); Mellitos C (JP); Propamide (MY, TH); Trane (AR)

Chlorthalidone

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Pronunciation(klor THAL i done)
U.S. Brand NamesThalitone®
Canadian Brand NamesApo-Chlorthalidone®
Pharmacologic Category[Diuretic, Thiazide]
Use: Labeled IndicationsManagement of mild-to-moderate hypertension when used alone or in combination with other agents; treatment of edema associated with congestive heart failure or nephrotic syndrome. Recent studies have found chlorthalidone effective in the treatment of isolated systolic hypertension in the elderly.
Use: Unlabeled/InvestigationalPediatric hypertension
Dosing: Adults

Hypertension: Oral: 25-100 mg/day or 100 mg 3 times/week; usual dosage range (JNC 7): 12.5-25 mg/day

Edema: Initial: 50-100 mg/day or 100 mg on alternate days; maximum dose: 200 mg/day

Heart failure-associated edema: 12.5-25 mg once daily; maximum daily dose: 100 mg (ACC/AHA 2005 Heart Failure Guidelines)

Dosing: ElderlyOral: Initial: 12.5-25 mg/day or every other day; there is little advantage to using doses >25 mg/day.
Dosing: PediatricOral: Children (nonapproved): 2 mg/kg/dose 3 times/week or 1-2 mg/kg/day

Hypertension (unlabeled use): Initial: 0.3 mg/kg once daily, up to 2 mg/kg/day; maximum: 50 mg/day

Dosing: Renal ImpairmentCl_{cr} <10 mL/minute: Avoid use. Ineffective with low GFR (Aronoff G, 2002)

Note: ACC/AHA 2005 Heart Failure Guidelines suggest that thiazides lose their efficacy when Cl_{cr} <40 mL/minute

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Dietary ConsiderationsThis product may cause a potassium loss; your healthcare provider may prescribe a potassium supplement, another medication to help prevent the potassium loss, or recommend that you eat foods high in potassium, especially citrus fruits; do not change your diet on your own while taking this medication, especially if you are taking potassium supplements or medications to reduce potassium loss; too much potassium can be as harmful as too little.
ContraindicationsHypersensitivity to chlorthalidone or any component of the formulation; cross-sensitivity with other thiazides or sulfonamides; anuria; renal decompensation; pregnancy
Allergy Considerations

- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, and hyponatremia can occur.
- Photosensitivity: Photosensitization may occur.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with thiazide or sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Diabetes: Use with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated.
- Hepatic impairment: Use with caution in patients with severe hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations.
- Hypokalemia: Use with caution in patients with hypokalemia; correct before initiating therapy.
- Renal impairment: Avoid in severe renal disease (ineffective).

- Systemic lupus erythematosus (SLE): Can cause SLE exacerbation or activation.

Geriatric ConsiderationsStudies have found chlorthalidone effective in the treatment of isolated systolic hypertension in the elderly. The use of chlorthalidone as a step 1 medication reduced the incidence of stroke in the SHEP trial.
Pregnancy Risk FactorB (manufacturer); D (expert analysis)
LactationEnters breast milk/use caution (AAP rates “compatible”)
Adverse Reactions

1% to 10%:

Dermatologic: Photosensitivity

Endocrine & metabolic: Hypokalemia

Gastrointestinal: Anorexia, epigastric distress

<1% (Limited to important or life-threatening): Agranulocytosis, aplastic anemia, cholecystitis, constipation, cutaneous vasculitis, diarrhea, dizziness, glycosuria, headache, hepatic function impairment, hypercalcemia, hyperglycemia, hyperuricemia or gout, hyponatremia, insomnia, leukopenia, muscle cramps or spasm, nausea, necrotizing angiitis, pancreatitis, paresthesia, polyuria, purpura, rash, restlessness, sexual ability (decreased), thrombocytopenia, urticaria, vomiting, vasculitis, weakness

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid dong quai, St John's Wort (may also cause photosensitization). Avoid ephedra, yohimbe, ginseng (may worsen hypertension).
Test InteractionsIncreased creatine phosphokinase [CPK] (S), ammonia (B), amylase (S), calcium (S), chloride (S), cholesterol (S), glucose, increased acid (S), decreased chloride (S), magnesium, potassium (S), sodium (S)
Monitoring ParametersAssess weight, I & O records daily to determine fluid loss; blood pressure, serum electrolytes, renal function
Nursing: Physical Assessment/MonitoringAssess allergy history prior to beginning therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions. Monitor electrolyte balance and renal function on a regular basis throughout therapy. Assess therapeutic effectiveness and adverse response (eg, blood pressure, fluid status) regularly during long-term therapy. Caution patients with diabetes to monitor glucose levels (may reduce effect of oral hypoglycemics). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsSerum electrolytes, renal function
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take once-daily dose in morning or last of daily doses early in the day to avoid night-time disturbances. You may need to make dietary changes (eg, your prescriber may recommend a potassium supplement or foods high in potassium; do not increase your potassium intake unless recommended to do so). If using oral hypoglycemics, monitor glucose levels closely (this medication may reduce effect of oral hypoglycemics); contact prescriber with any major changes. May cause sensitivity to sunlight (use sunblock, wear protective clothing, and avoid direct sunlight); or anorexia or GI distress (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report muscle twitching or cramps; nausea or vomiting; confusion; numbness of extremities; loss of appetite or GI distress; severe rash, redness, or itching of skin; chest pain or palpitations;

respiratory difficulty; unusual weight loss; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 25 mg, 50 mg, 100 mg

Thalitone®: 15 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Chlorthalidone)

25 mg (90): $29.99

50 mg (30): $19.99

100 mg (30): $33.99

Tablets (Thalitone)

15 mg (30): $41.41

Mechanism of ActionSulfonamide-derived diuretic that inhibits sodium and chloride reabsorption in the cortical-diluting segment of the ascending loop of Henle

Pharmacodynamics/Kinetics

Onset of action: Peak effect: 2-6 hours

Duration: 24-72 hours

Absorption: 65%

Distribution: Crosses placenta; enters breast milk

Metabolism: Hepatic

Half-life elimination: 35-55 hours; may be prolonged with renal impairment; Anuria: 81 hours

Excretion: Urine (~50% to 65% as unchanged drug)

Related Information

- Heart Failure (Systolic)
- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentRare reports of blood dyscrasias; use caution with clozapine and carbamazepine; thiazides decrease lithium clearance resulting in elevated serum lithium levels and potential toxicity; monitor serum lithium levels

Cardiovascular Considerations

Hypertension: Thiazide diuretics are effective first-line therapeutic agents in the management of hypertension and have proven to be of benefit in terms of cardiovascular outcome. They may act synergistically to lower blood pressure when combined with an ACE inhibitor or beta-blocker. The initial concern about thiazide diuretic-induced hypokalemia, glucose intolerance, and lipid profiles does not appear to be of substantial clinical consequence in the treatment of hypertension. The benefits of this class of agents in the treatment of hypertension is established and compares well with other first-line therapeutic agents. The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The JNC 7 recommends diuretics for the treatment of hypertension with concurrent heart failure where diuresis is also required (loop diuretics may more frequently be required), high coronary disease risk (as in the ALLHAT trial), diabetes (beneficial in reducing CVD and stroke incidence), and recurrent stroke prevention (in combination with an ACE inhibitor). Thiazides are useful in slowing demineralization in osteoporosis, but need to be used cautiously in gout and in patients with significant history of hyponatremia.

Congestive Heart Failure: Diuretics are standard therapy for the management of edema in patients with heart failure. Thiazide diuretics may be preferred in hypertensive heart failure patients with mild fluid retention. Thiazides lose their effectiveness in patients with impaired renal function. Loop diuretics may be the preferred diuretic in heart failure because of their greater ability to increase sodium excretion.

Index TermsHygroton

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International Brand NamesAquadon (IL); Clortalil (BR); Higroton (BR, MX, VE); Higrotona (ES); Hygroton (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HN, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TN, TR, TT, TZ, UG, YE, ZA, ZM, ZW); Hythalton (IN); Igroton (IT); Saluretin (BG)

Chlorzoxazone

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Parafon Forte® may be confused with Fam-Pren Forte

Pronunciation(klor ZOKS a zone)
U.S. Brand NamesParafon Forte® DSC
Canadian Brand NamesParafon Forte®; Strifon Forte®
Pharmacologic CategorySkeletal Muscle Relaxant
Use: Labeled IndicationsSymptomatic treatment of muscle spasm and pain associated with acute musculoskeletal conditions
Use: DentalTreatment of muscle spasm and pain associated with acute temporomandibular joint pain (TMJ)
Dosing: AdultsMuscle spasm: Oral: 250-500 mg 3-4 times/day up to 750 mg 3-4 times/day
Dosing: ElderlyOral: Initial: 250 mg 2-4 times/day; increase as necessary to 750 mg 3-4 times/day.
Dosing: PediatricMuscle spasm: Oral: 20 mg/kg/day or 600 mg/m^2/day in 3-4 divided doses
Calculations

- Body Surface Area: Pediatrics

ContraindicationsHypersensitivity to chlorzoxazone or any component of the formulation; impaired liver function
Allergy Considerations

- Chlorzoxazone Allergy

Geriatric ConsiderationsNo data available on the use of skeletal muscle relaxants in the elderly. Start dosing low and increase as necessary. The FDA recently approved a stronger warning about hepatotoxicity in the labeling of chlorzoxazone. Because it can cause unpredictable, fatal hepatic toxicity, the use of chlorzoxazone should be avoided.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Central nervous system: Dizziness, drowsiness lightheadedness, paradoxical stimulation, malaise

Dermatologic: Rash, petechiae, ecchymoses (rare), angioneurotic edema

Gastrointestinal: Nausea, vomiting, stomach cramps

Genitourinary: Urine discoloration

Hepatic: Liver dysfunction

Miscellaneous: Anaphylaxis (very rare)

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2A6 (minor), 2D6 (minor), 2E1 (major), 3A4 (minor); **Inhibits** CYP2E1 (weak), 3A4 (weak)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Chlorzoxazone. *Risk C: Monitor therapy*

Isoniazid: May decrease the metabolism of Chlorzoxazone. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Monitoring ParametersPeriodic liver functions tests
Nursing: Physical Assessment/MonitoringAssess results of laboratory tests, therapeutic effectiveness (according to rationale for therapy), and adverse reactions at beginning of therapy and periodically with long-term use. Do not discontinue abruptly; taper dosage slowly. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Monitoring: Lab TestsPeriodic liver functions
Patient EducationTake exactly as directed with food. Do not increase dose or discontinue this medication without consulting prescriber. Do not use alcohol, prescriptive or OTC antidepressants, sedatives, or pain medications without consulting prescriber. May turn urine orange or red (normal). You may experience drowsiness, dizziness, lightheadedness (avoid driving or engaging in tasks that require alertness until response to drug is known); nausea, vomiting, or cramping (small frequent meals, frequent mouth care, or sucking hard candy may help); postural hypotension (change position slowly when rising from sitting or lying or when climbing stairs); or constipation (increased exercise, fluids, fruit, or fiber may help). Report excessive drowsiness or mental agitation; palpitations, rapid heartbeat, or chest pain; skin rash or

swelling of mouth or face; persistent diarrhea or constipation; or unusual weakness or bleeding. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet (Parafon Forte® DSC): 500 mg

Tablet: 250 mg, 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Chlorzoxazone)

250 mg (100): $16.99

500 mg (90): $15.00

Tablets (Parafon Forte DSC)

500 mg (30): $73.01

Mechanism of ActionActs on the spinal cord and subcortical levels by depressing polysynaptic reflexes

Pharmacodynamics/Kinetics

Onset of action: ~1 hour

Duration: 6-12 hours

Absorption: Readily absorbed

Metabolism: Extensively hepatic via glucuronidation

Excretion: Urine (as conjugates)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may produce depression or paradoxical stimulation

Mental Health: Effects on Psychiatric TreatmentMay produce aplastic anemia and leukopenia; use caution with clozapine and carbamazepine

International Brand NamesEscoflex (CH); Klorzoxazon (DK); Matalmin (TW); Muscol (TW); Myoflex (HR); Myoflexin (HN, HU); Paraflex (HR, NO, SE, ZA); Parafon DSC (IN); Parafon Forte (MX, TH); Prolax (TW); Reumophan (MX); Reumophan Alka (MX); Reumophan Vit (MX); Salalin (TW); Solaxin (HK, ID, JP); Tafirol Flex (MX)

Cholecalciferol

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Pronunciation(kole e kal SI fer ole)

U.S. Brand NamesD-3 [OTC]; D3-50™ [OTC]; D3-5™ [OTC]; Delta-D® [OTC]; Maximum D3®; Vitamin D3 [OTC]

Canadian Brand NamesD-Vi-Sol®

Pharmacologic CategoryVitamin D Analog

Use: Labeled IndicationsDietary supplement, treatment of vitamin D deficiency, or prophylaxis of deficiency

Dosing: AdultsDietary supplement: Oral: 400-1000 units/day

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypercalcemia; hypersensitivity to cholecalciferol or any component of the formulation; malabsorption syndrome; evidence of vitamin D toxicity

Geriatric ConsiderationsVitamin D, folate, and B_{12} (cyanocobalamin) have decreased absorption with age (clinical significance unknown); studies in ill geriatrics demonstrated that low serum concentrations of vitamin D result in greater bone loss. Calorie requirements decrease with age and therefore, nutrient density must be increased to ensure adequate nutrient intake, including vitamins and minerals. The use of a daily supplement with a multiple vitamin with minerals is recommended because elderly consume less vitamin D, absorption may be decreased, and many have decreased sun exposure. This is a recommendation of particular need to those with high risk for osteoporosis.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, hyper-/hypotension, cardiac arrhythmia

Central nervous system: Irritability, headache, somnolence, overt psychosis (rare)

Dermatologic: Pruritus

Endocrine & metabolic: Polydipsia

Gastrointestinal: Nausea, vomiting, anorexia, pancreatitis, metallic taste, dry mouth, constipation, weight loss

Genitourinary: Albuminuria, polyuria

Hepatic: Increased liver function test

Neuromuscular & skeletal: Bone pain, myalgia, weakness, muscle pain

Ocular: Conjunctivitis, photophobia

Renal: Azotemia, nephrocalcinosis

Metabolism/Transport Effects**Inhibits** CYP2C9 (weak), 2C19 (weak), 2D6 (weak)

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb Interactions

Food: Olestra may impair the absorption of vitamin D.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, oral:

D-3: 1000 int. units

D3-5™: 5000 int. units

D3-50™: 50,000 int. units

Maximum D3®: 10,000 int. units [contains soybean lecithin]

Capsule, softgel, oral:

D-3: 2000 int. units

Tablet:

Delta-D®: 400 int. units

Generic AvailableYes

Pharmacodynamics/Kinetics

Distribution: Primarily hepatic

Protein binding: Extensively to vitamin D-binding protein

Metabolism: Primary liver and kidney hydroxylation; glucuronidation (minimal)

Half-life elimination: 14 hours

Time to peak, plasma: 11 hours

Excretion: As metabolites, urine (2.4%) and feces (4.9%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Metallic taste and xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause irritability; rare reports of psychosis

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsD$_3$

International Brand NamesArachitol (IN); D!3-Vicotrat (DE); D-Cure (BE, LU); D-Mulsin (DE); Dedrei (DE); Deetipat (FI); Dekristol (DE); Devaron (NL); Devitre (SE); Duvit D!3 (IT); Iper D3 (IT); Laevovit (AT, HU); Neo-Dohyfral D3 (NL); Oleovit D!3 (AT); Ospur D!3 (DE); Ostelavit (PL); Plivit D3 (HR); Quimpe Vitamin D3 (ES); T-Tracetten (DE); Tridelta (IT); Uvedose (FR, LU); Vi-De 3 (AT, CH); Vigantol (CZ, DE, HU, LU, PL, PT); Vigantoletten (AT, DE, LU, PL); Vigorsan (DE); Vit. D3 Agepha (AT); Vitaendil D3 (ES); Vitamin D!3 (HU, HU); Vitamin D!3 Fresenius (HU); Vitamin D!3 Streuli (CH); Vitamin D3-Hevert (DE); Vitamina D3 Berenguer (ES); Vitamine D!3 BON (FR); Vitaminum D3 (PL); Vitamon D3 (BE)

Cholestyramine Resin

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English

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Pronunciation(koe LES teer a meen REZ in)

U.S. Brand NamesPrevalite®; Questran®; Questran® Light

Canadian Brand NamesNovo-Cholamine; Novo-Cholamine Light; PMS-Cholestyramine; Questran®; Questran® Light Sugar Free

Pharmacologic CategoryAntilipemic Agent, Bile Acid Sequestrant

Use: Labeled IndicationsAdjunct in the management of primary hypercholesterolemia; pruritus associated with elevated levels of bile acids; diarrhea associated with excess fecal bile acids; binding toxicologic agents; pseudomembraneous colitis

Dosing: AdultsDyslipidemia: Oral (dosages are expressed in terms of anhydrous resin): 4 g 1-2 times/day to a maximum of 16-24 g/day (and a maximum of 6 times/day)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDyslipidemia: Oral (dosages are expressed in terms of anhydrous resin): Children: 240 mg/kg/day in 3 divided doses; need to titrate dose depending on indication

Dosing: Renal ImpairmentNot removed by hemo- or peritoneal dialysis. Supplemental doses not necessary with dialysis or continuous arteriovenous or venovenous hemofiltration effects.

Administration: OralMix powder with water or other fluid prior to administration; not to be taken in dry form. Suspension should not be sipped or held in mouth for prolonged periods (may cause tooth discoloration or enamel decay).

Dietary ConsiderationsSupplementation of vitamins A, D, E, and K, folic acid, and iron may be required with high-dose, long-term therapy.

Questran® Light contains phenylalanine 14 g/5 g powder.

Prevalite® contains phenylalanine 14.1 g/5.5 g powder.

StorageStore powder at controlled room temperature of 15°C to 30°C (59°F to 86°F). Suspension may be used for up to 48 hours after refrigeration.

ReconstitutionMix contents of 1 packet or 1 level scoop of powder with 4-6 oz of beverage. Allow to stand 1-2 minutes prior to mixing. May also be mixed with highly-fluid soups, cereals, applesauce, etc.

ContraindicationsHypersensitivity to bile acid sequestering resins or any component of the formulation; complete biliary obstruction; bowel obstruction

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: Chronic use may be associated with bleeding problems (especially in high doses).
- Constipation: May produce or exacerbate constipation problems; fecal impaction may occur. Hemorrhoids may be worsened.

Concurrent drug therapy issues:

- Decreased absorption (orally administered drugs): Not to be taken simultaneously with many other medicines (decreased absorption).
- Fat-soluble vitamins/folic acid: May interfere with fat-soluble vitamins (A, D, E, K) and folic acid.

Dosage form specific issues:

- Phenylalanine: Questran® Light contains phenylalanine.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

Geriatric ConsiderationsThe definition of and, therefore, when to treat hyperlipidemia in the elderly is a controversial issue. The National Cholesterol Education Program recommends that all adults maintain a plasma cholesterol <160 mg/dL. Elderly with one additional risk factor, goal LDL would be <130 mg/dL. It is the authors' belief that pharmacologic treatment be reserved for those who are unable to obtain a desirable plasma cholesterol concentration by diet alone and for whom the benefits of treatment are believed to outweigh the potential adverse effects, drug interactions, and cost of treatment.

Pregnancy Risk FactorC

Pregnancy ConsiderationsCholestyramine is not absorbed systemically, but may interfere with vitamin absorption; therefore, regular prenatal supplementation may not be adequate. There are no studies in pregnant women; use with caution.

LactationDoes not enter breast milk/use caution

Adverse Reactions

>10%: Gastrointestinal: Constipation, heartburn, nausea, vomiting, stomach pain

1% to 10%:

Central nervous system: Headache

Gastrointestinal: Belching, bloating, diarrhea

<1% (Limited to important or life-threatening): Hyperchloremic acidosis, gallstones or pancreatitis, GI bleeding, peptic ulcer, steatorrhea or malabsorption syndrome, hypoprothrombinemia (secondary to vitamin K deficiency)

Drug Interactions

Acetaminophen: Cholestyramine Resin may decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

Amiodarone: Bile Acid Sequestrants may decrease the bioavailability of Amiodarone. *Risk D: Consider therapy modification*

Antidiabetic Agents (Thiazolidinedione): Bile Acid Sequestrants may decrease the absorption of Antidiabetic Agents (Thiazolidinedione). *Risk D: Consider therapy modification*

Calcitriol: Bile Acid Sequestrants may decrease the serum concentration of Calcitriol. *Risk C: Monitor therapy*

Cardiac Glycosides: Bile Acid Sequestrants may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

Corticosteroids (Oral): Bile Acid Sequestrants may decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Ezetimibe: Bile Acid Sequestrants may decrease the absorption of Ezetimibe. *Risk C: Monitor therapy*

Fibric Acid Derivatives: Bile Acid Sequestrants may decrease the absorption of Fibric Acid Derivatives. *Risk D: Consider therapy modification*

Loop Diuretics: Bile Acid Sequestrants may decrease the absorption of Loop Diuretics. *Risk D: Consider therapy modification*

Methotrexate: Bile Acid Sequestrants may decrease the absorption of Methotrexate. *Risk C: Monitor therapy*

Methylfolate: Cholestyramine Resin may decrease the serum concentration of Methylfolate. *Risk C: Monitor therapy*

Mycophenolate: Cholestyramine Resin may decrease the serum concentration of Mycophenolate. *Risk X: Avoid combination*

Niacin: Bile Acid Sequestrants may decrease the absorption of Niacin. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: Bile Acid Sequestrants may decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Raloxifene: Bile Acid Sequestrants may decrease the absorption of Raloxifene. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Bile Acid Sequestrants may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Thiazide Diuretics: Bile Acid Sequestrants may decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Thyroid Products: Bile Acid Sequestrants may decrease the absorption of Thyroid Products. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Bile Acid Sequestrants may decrease the absorption of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Cholestyramine (especially high doses or long-term therapy) may decrease the absorption of folic acid, calcium, and iron.

Herb/Nutraceutical: Cholestyramine (especially high doses or long-term therapy) may decrease the absorption of fat-soluble vitamins (vitamins A, D, E, and K).

Test InteractionsIncreased prothrombin time; decreased cholesterol (S), iron (B)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor laboratory results, therapeutic effectiveness, and adverse reactions periodically throughout therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsSerum cholesterol and triglyceride levels before initiating treatment and periodically throughout treatment.

Patient EducationTake once or twice a day as directed. Do not take the powder in its dry form; mix with fluid, applesauce, pudding, or jello. Take other medications 1 hour before or 4-6 hours after cholestyramine. Ongoing medical follow-up and laboratory tests may be required. You may experience GI effects (these should resolve after continued use); nausea and vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or constipation (increased exercise, fluids, fruit, or fiber may help; consult prescriber about use of stool softener or laxative). Report unusual stomach cramping, pain or blood in stool; unresolved nausea, vomiting, or constipation. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for oral suspension: Cholestyramine resin 4 g/5 g packet (60s); cholestyramine resin 4 g/5 g of powder (210 g); cholestyramine resin 4 g/5.7 g packet (60s); cholestyramine resin 4 g/5.7 g of powder (240 g can); cholestyramine resin 4 g/9 g packet (60s); cholestyramine resin 4 g of resin/9 g of powder (378 g)

Prevalite®: Cholestyramine resin 4 g/5.5 g packet (42s, 60s) [contains phenylalanine 14.1 mg/5.5 g; orange flavor]; cholestyramine resin 4 g/5.5 g of powder (231 g) [contains phenylalanine 14.1 mg/5.5 g; orange flavor]

Questran®: Cholestyramine resin 4 g/9 g packet (60s); cholestyramine resin 4 g/9 g of powder (378 g)

Questran® Light: Cholestyramine resin 4 g/5 g packet (60s) [contains phenylalanine 14 mg/5 g]; cholestyramine resin 4 g/5 g of powder (210 g) [contains phenylalanine 14 mg/5 g]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Pack (Cholestyramine)

4 g (60): $122.99

Pack (Cholestyramine Light)

4 g (60): $99.99

Pack (Prevalite)

4 g (60): $144.76

Pack (Questran)

4 g (60): $210.22

Powder (Cholestyramine)

4 g/dose (378): $37.01

Powder (Cholestyramine Light)

4 g/dose (210): $50.00

Powder (Prevalite)

4 g/dose (231): $68.38

Powder (Questran)

4 g/dose (378): $102.25

Powder (Questran Light)

4 g/dose (210): $106.24

4 g/dose (268): $89.99

Mechanism of ActionForms a nonabsorbable complex with bile acids in the intestine, releasing chloride ions in the process; inhibits enterohepatic reuptake of intestinal bile salts and thereby increases the fecal loss of bile salt-bound low density lipoprotein cholesterol

Pharmacodynamics/Kinetics

Onset of action: Peak effect: 21 days

Absorption: None

Excretion: Feces (as insoluble complex with bile acids)

Related Information

- Hyperlipidemia Management
- Lipid-Lowering Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay decrease the absorption of psychotropics including TCAs, beta-blockers, valproic acid, barbiturates

Cardiovascular ConsiderationsCholestyramine alone or when combined with an HMG-CoA reductase inhibitor is effective in lowering cholesterol. Cholestyramine may increase triglycerides, therefore, it should be avoided in patients with triglyceride levels ≥200 mg/dL. Potential factors that may limit patient compliance include GI side effects and the need to separate administration of other medications from cholestyramine.

Anesthesia and Critical Care Concerns/Other ConsiderationsCholestyramine alone or when combined with a statin is effective in lowering cholesterol. Cholestyramine may increase triglycerides, therefore, it should be avoided in patients with triglyceride levels ≥200 mg/dL. Potential factors that may limit patient compliance include GI side effects and the need to space other medications at least 1 hour before or 4 hours after cholestyramine administration.

References

"Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)," *JAMA*, 2001, 285(19):2486-97.[PubMed 11368702]

International Brand NamesCholes (TW); Colestiramina (CN, CO); Colestrol (IT); Lipocol-Merz (DE); Quantalan (CH, PT); Quantalan Zuckerfrei (AT); Questran (BE, BG, CO, DK, EC, EG, FI, FR, GB, GR, HK, HN, ID, IE, IT, KP, MX, NL, NO, SE, TW); Questran Light (AR, BR, CZ, MY, NZ); Questran Lite (AU, PH, ZA); Questran Loc (DK, SE); Resincolestiramina (UY); Vasosan P-Granulat (DE); Vasosan S-Granulat (DE)

Choline Magnesium Trisalicylate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(KOE leen mag NEE zhum trye sa LIS i late)

Pharmacologic CategorySalicylate

Use: Labeled IndicationsManagement of osteoarthritis, rheumatoid arthritis, and other arthritis; acute painful shoulder

Dosing: AdultsArthritis, pain: Oral (based on total salicylate content): 500 mg to 1.5 g 2-3 times/day **or** 3 g at bedtime; usual maintenance dose: 1-4.5 g/day

Dosing: ElderlyUsual dose: 750 mg 3 times/day.

Dosing: PediatricChildren: Oral (based on total salicylate content): <37 kg: 50 mg/kg/day given in 2 divided doses; 2250 mg/day for heavier children

Dosing: Renal ImpairmentAvoid use in severe renal impairment.

Administration: OralLiquid may be mixed with fruit juice just before drinking. Do not administer with antacids. Take with a full glass of water and remain in an upright position for 15-30 minutes after administration.

Dietary ConsiderationsTake with food or large volume of water or milk to minimize GI upset. Liquid may be mixed with fruit juice just before drinking. Hypermagnesemia resulting from magnesium salicylate; avoid or use with caution in renal insufficiency.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to salicylates, other nonacetylated salicylates, other NSAIDs, or any component of the formulation; bleeding disorders; pregnancy (3rd trimester)

Allergy Considerations

- Salicylate Allergy/Sensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Tinnitus: Tinnitus or impaired hearing may indicate toxicity.

Disease-related concerns:

- Asthma: Use with caution in patients with asthma.
- Dehydration: Use with caution in patients with dehydration.
- Gastrointestinal disease: Use with caution in patients with erosive gastritis or peptic ulcer.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Thrombosis (prophylaxis): Salicylate salts may not inhibit platelet aggregation and, therefore, should not be substituted for aspirin in the prophylaxis of thrombosis.

Special populations:

- Elderly: Use lowest effective dose for shortest period possible in the elderly; they are a high-risk population for adverse effects from NSAIDs. As many as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. CNS adverse effects may be observed in the elderly at lower doses than younger adults. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage.
- Pediatrics: Children and teenagers who have or are recovering from chickenpox or flu-like symptoms should not use this product. Changes in behavior (along with nausea and vomiting) may be an early sign of Reye's syndrome; patients should be instructed to contact their healthcare provider if these occur.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from nonsteroidal anti-inflammatory agents. As much as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Avoid use of multiple drugs (OTCs) which contain salicylates (eg, bismuth subsalicylate with other salicylates). Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. There is the consideration that the use of choline magnesium salicylate may cause less gastrointestinal and renal adverse effects than ASA or other NSAIDs in the elderly. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (3rd trimester)

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Due to the known effects of other salicylates (closure of ductus arteriosus), use during late pregnancy should be avoided.

Lactation Enters breast milk/use caution

Breast-Feeding Considerations Excreted in breast milk; peak levels occur 9-12 hours after dose. Use caution if used during breast-feeding.

Adverse Reactions

<20%:

Gastrointestinal: Nausea, vomiting, diarrhea, heartburn, dyspepsia, epigastric pain, constipation

Otic: Tinnitus

<2%:

Central nervous system: Headache, lightheadedness, dizziness, drowsiness, lethargy

Otic: Hearing impairment

<1%: Gastric ulceration, occult bleeding, increased BUN and creatinine, rash, pruritus, anorexia, weight gain, edema, epistaxis, dysgeusia

Postmarketing and/or case reports: Asthma, bruising, confusion, duodenal ulceration, erythema multiforme, esophagitis, hallucinations, hepatic enzymes increased, hearing loss (irreversible)

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: May decrease the rate but not the extent of oral absorption.

Herb/Nutraceutical: Avoid cat's claw, dong quai, evening primrose, feverfew, garlic, ginger, ginkgo, red clover, horse chestnut, green tea, ginseng (all have additional antiplatelet activity). Limit curry powder, paprika, licorice, Benedictine liqueur, prunes, raisins, tea, and gherkins; may cause salicylate accumulation. These foods contain 6 mg salicylate/100 g.

Test Interactions False-negative results for glucose oxidase urinary glucose tests (Clinistix®); false-positives using the cupric sulfate method (Clinitest®); also, interferes with Gerhardt test (urinary ketone analysis), VMA determination; 5-HIAA, xylose tolerance test, and T_3 and

T_4; increased PBI

Monitoring ParametersSerum magnesium with high dose therapy or in patients with impaired renal function; serum salicylate levels, renal function, hearing changes or tinnitus, abnormal bruising, weight gain and response (ie, pain)

Reference RangeSalicylate blood levels for anti-inflammatory effect: 150-300 mcg/mL; analgesia and antipyretic effect: 30-50 mcg/mL

Nursing: Physical Assessment/Monitoring**Do not use for persons with allergic reaction to salicylates or other NSAIDs.** Assess other medications patient may be taking for additive or adverse interactions. Monitor for effectiveness of pain relief. Monitor for signs of adverse reactions or overdose at beginning of therapy and periodically during long-term therapy. Assess knowledge/teach patient appropriate use. Teach patient to monitor for adverse reactions, adverse reactions to report, and appropriate interventions to reduce side effects.

Monitoring: Lab TestsSerum magnesium with high-dose therapy or in patients with impaired renal function, serum salicylate levels, renal function

Patient EducationUse exactly as directed; do not increase dose or frequency. Adverse reactions can occur with overuse. Take with food or milk. While using this medication, do not use alcohol, excessive amounts of vitamin C, or salicylate-containing foods (curry powder, prunes, raisins, tea, or licorice), other prescription or OTC medications containing aspirin or salicylate, or other NSAIDs without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience nausea, vomiting, gastric discomfort (frequent mouth care, small frequent meals, sucking lozenges, or chewing gum may help). GI bleeding, ulceration, or perforation can occur with or without pain. Stop taking medication and report ringing in ears; persistent stomach pain; unresolved nausea or vomiting; respiratory difficulty or shortness of breath; or unusual bruising or bleeding (mouth, urine, stool); or skin rash. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid: 500 mg/5 mL (240 mL) [choline salicylate 293 mg and magnesium salicylate 362 mg per 5 mL; cherry cordial flavor]

Tablet: 500 mg [choline salicylate 293 mg and magnesium salicylate 362 mg]; 750 mg [choline salicylate 440 mg and magnesium salicylate 544 mg]; 1000 mg [choline salicylate 587 mg and magnesium salicylate 725 mg]

Generic AvailableYes

ManufacturerPurdue Frederick Co

Pricing: U.S. (www.drugstore.com)

Tablets (Choline & Mag Trisalicylate)

500 mg (60): $20.99

1000 mg (60): $24.99

Mechanism of ActionWeakly inhibits cyclooxygenase enzymes, which result in decreased formation of prostaglandin precursors; antipyretic, analgesic, and anti-inflammatory properties.

Pharmacodynamics/Kinetics

Onset of action: Peak effect: ~2 hours

Absorption: Stomach and small intestines

Distribution: Readily into most body fluids and tissues; crosses placenta; enters breast milk

Half-life elimination (dose dependent): Low dose: 2-3 hours; High dose: 30 hours

Time to peak, serum: ~2 hours

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation; may rarely cause nervousness or insomnia

Mental Health: Effects on Psychiatric TreatmentMay rarely cause leukopenia; use caution with clozapine and carbamazepine

Anesthesia and Critical Care Concerns/Other ConsiderationsSalicylate salts do not inhibit platelet aggregation and, therefore, should not be substituted for aspirin in the prophylaxis of thrombosis.

Index TermsTricosal

References

Berde C, Ablin A, Glazer J, et al, “American Academy of Pediatrics Report of the Subcommittee on Disease-Related Pain in Childhood Cancer,” *Pediatrics*, 1990, 86(5 Pt 2):818-25. [PubMed 2216644]

Chapman BJ and Proudfoot AT, “Adult Salicylate Poisoning: Deaths and Outcome in Patients With High Plasma Salicylate Concentrations,” *Q J Med*, 1989, 72(268):699-707. [PubMed 2602553]

Department of Health and Human Services, Food and Drug Administration, “Labeling for Oral and Rectal Over-the-Counter Drug Products Containing Aspirin and Nonaspirin Salicylates; Reye's Syndrome Warning; Final Rule, (29 CFR Part 201),” *Fed Regist*, April 17, 2003, 18861-9. [PubMed 10177739]

“Drugs for Pain,” *Med Lett Drugs Ther*, 1998, 40(1033):79-84. [PubMed 9722804]

Dugandric RM, Tierney MG, and Dickinson GE, “Evaluation of the Done Nomogram in the Management of Acute Salicylate Intoxication,” *Ann Emerg Med*, 1989, 18(11):1186-90. [PubMed 2817562]

Hawkey CJ, Karrasch JA, Szczepański L, et al, “Omeprazole Compared With Misoprostol for Ulcers Associated With Nonsteroidal Anti-inflammatory Drugs,” *N Engl J Med*, 1998, 338(11):727-34. [PubMed 9494149]

Vandenberg SA, Smolinske SC, Spoerke DG, et al, “Nonaspirin Salicylates: Conversion Factors for Estimating Aspirin Equivalency,” *Vet Hum*

Toxicol, 1989, 31(1):49-50. [PubMed 2652876]

Verbeeck RK, “Pharmacokinetic Drug Interactions With Nonsteroidal Anti-inflammatory Drugs,” *Clin Pharmacokinet*, 1990, 19(1):44-66. [PubMed 2199127]

Vertrees JE, McWilliams BC, and Kelly HW, “Repeated Oral Administration for Treating Aspirin Overdose in Young Children,” *Pediatrics*, 1990, 85(4):594-8. [PubMed 2314974]

Weissmann G, “Aspirin,” *Sci Am*, 1991, 264(1):84-90.

Yeomans ND, Tulassay Z, Juhasz L, et al, “A Comparison of Omeprazole With Ranitidine for Ulcers Associated With Nonsteroidal Anti-inflammatory Drugs,” *N Engl J Med*, 1998, 338(11):719-26.[PubMed 9494148]

CHOP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen Use Lymphoma, non-Hodgkin's

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Cyclophosphamide: I.V.: 750 mg/m^2 day 1

[total dose/cycle = 750 mg/m^2]

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 (maximum 2 mg) day 1

[total dose/cycle = 1.4 mg/m^2]

Prednisone: Oral: 100 mg/day days 1 to 5

[total dose/cycle = 500 mg]

or 50 mg/m^2/day days 1 to 5

[total dose/cycle = 250 mg/m^2]

or 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Cyclophosphamide: I.V.: 750 mg/m^2 day 1

[total dose/cycle = 750 mg/m^2]

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Vincristine: I.V.: 2 mg day 1

[total dose/cycle = 2 mg]

Prednisone: Oral: 75 mg/day days 1 to 5

[total dose/cycle = 375 mg]

Repeat cycle every 21 days

Variation 3:

Cyclophosphamide: I.V.: 750 mg/m^2/day days 1 and 8

[total dose/cycle = 1500 mg/m^2]

Doxorubicin: I.V.: 25 mg/m^2/day days 1 and 8

[total dose/cycle = 50 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day (maximum 2 mg) days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Prednisone: Oral: 50 mg/m^2/day days 1 to 8

[total dose/cycle = 400 mg/m^2]

Repeat cycle every 28 days

Variation 4 - “mini-CHOP”:

Cyclophosphamide: I.V.: 250 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 750 mg/m^2]

Doxorubicin: I.V.: 16.7 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 50.1 mg/m^2]

Vincristine: I.V.: 0.67 mg/day days 1, 8, and 15

[total dose/cycle = 2.01 mg]

Prednisone: Oral: 75 mg/day days 1 to 5

[total dose/cycle = 375 mg]

Repeat cycle every 21 days

References

Variation 1:

Bezwoda W, Rastogi RB, Erazo Valla A, et al, “Long-Term Results of a Multicentre Randomised, Comparative Phase III Trial of CHOP Versus CNOP Regimens in Patients With Intermediate- and High-Grade Non-Hodgkin's Lymphomas, Novantrone International Study Group,” *Eur J Cancer*, 1995, 31A(6):903-11. [PubMed 7646919]

McKelvey EM, Gottlieb JA, Wilson HE, et al, “Hydroxyldaunomycin (Adriamycin®) Combination Chemotherapy in Malignant Lymphoma,” *Cancer*, 1976, 38(4):1484-93. [PubMed 791473]

Miller TP, Dahlberg S, Cassady JR, et al, “Chemotherapy Alone Compared With Chemotherapy Plus Radiotherapy for Localized Intermediate- and High-Grade Non-Hodgkin's Lymphoma,” *N Engl J Med*, 1998, 339(1):21-6. [PubMed 9647875]

Variation 2 and 4:

Meyer RM, Browman GP, Samosh ML, et al, “Randomized Phase II Comparison of Standard CHOP With Weekly CHOP in Elderly Patients With Non-Hodgkin's Lymphoma,” *J Clin Oncol*, 1995, 13(9):2386-93. [PubMed 7666098]

Variation 3:

Linch DC, Vaughan Hudson B, Hancock BW, et al, “A Randomised Comparison of a Third-Generation Regimen (PACEBOM) With a Standard Regimen (CHOP) in Patients With Histologically Aggressive Non-Hodgkin's Lymphoma: A British National Lymphoma Investigation Report,” *Br J Cancer*, 1996, 74(2):318-22.[PubMed 8688344]

Chorionic Gonadotropin (Human)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(kor ee ON ik goe NAD oh troe pin, HYU man)

U.S. Brand NamesNovarel®; Pregnyl®

Canadian Brand NamesHumegon®; Pregnyl®; Profasi® HP

Pharmacologic CategoryGonadotropin; Ovulation Stimulator

Use: Labeled IndicationsInduces ovulation and pregnancy in anovulatory, infertile females; treatment of hypogonadotropic hypogonadism, prepubertal cryptorchidism; spermatogenesis induction with follitropin alfa

Dosing: Adults

Induction of ovulation: Females: I.M.: 5000-10,000 units 1 day following last dose of menotropins

Spermatogenesis induction associated with hypogonadotropic hypogonadism: Males: Treatment regimens vary (range: 1000-2000 units 2-3 times a week). Administer hCG until serum testosterone levels are normal (may require 2-3 months of therapy), then may add follitropin alfa or menopausal gonadotropin if needed to induce spermatogenesis; continue hCG at the dose required to maintain testosterone levels.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricVarious regimens:

Prepubertal cryptorchidism: I.M.:

4000 units 3 times/week for 3 weeks **or**

5000 units every second day for 4 injections **or**

500 units 3 times/week for 4-6 weeks **or**

15 injections of 500-1000 units given over 6 weeks

Hypogonadotropic hypogonadism: Males: I.M.:

500-1000 units 3 times/week for 3 weeks, followed by the same dose twice weekly for 3 weeks **or**

4000 units 3 times/week for 6-9 months, then reduce dosage to 2000 units 3 times/week for additional 3 months

Administration: I.M.I.M. administration only

ReconstitutionFollowing reconstitution with the provided diluent, solutions are stable for 30-60 days, depending on the specific preparation, when stored at 2°C to 15°C.

ContraindicationsHypersensitivity to chorionic gonadotropin or any component of the formulation; precocious puberty; prostatic carcinoma or similar neoplasms; pregnancy

Warnings/Precautions

Disease-related concerns:

- Asthma: Use with caution in patients with asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Cryptorchidism: May induce precocious puberty in children being treated for cryptorchidism; discontinue if signs of precocious puberty occur.
- Migraine: Use with caution in patients with a history of migraines.
- Obesity: **Not** effective in the treatment of obesity.
- Renal impairment: Use with caution in patients with renal impairment.
- Seizure disorders: Use with caution in patients with a history of seizure disorders.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <4 years of age.

Other warnings/precautions:

- Ovulation induction: Appropriate use: These medications should only be used by physicians who are thoroughly familiar with infertility problems and their management. May cause ovarian hyperstimulation syndrome (OHSS); characterized by severe ovarian enlargement, abdominal pain/distention, nausea, vomiting, diarrhea, dyspnea, and oliguria, and may be accompanied by ascites, pleural effusion, hypovolemia, electrolyte imbalance, hemoperitoneum, and thromboembolic events. If severe hyperstimulation occurs, stop treatment and hospitalize patient. This syndrome develops rapidly with 24 hours to several days and generally occurs during the 7-10 days immediately following treatment. Ovarian enlargement ay be accompanied by abdominal distention or abdominal pain and generally regresses without treatment within 2-3 weeks. If ovaries are abnormally enlarged on the last day of treatment, withhold hCG to reduce the risk of OHSS. In association with and separate from OHSS, thromboembolic events have been reported. May result from the use of these medications; advise patients of the potential risk of multiple births before starting the treatment.

Pregnancy Risk FactorX

Pregnancy ConsiderationsTeratogenic effects (forelimb, CNS) have been noted in animal studies at doses intended to induce superovulation (used in combination with gonadotropin). Testicular tumors in otherwise healthy men have been reported when treating secondary infertility.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Edema

Central nervous system: Depression, fatigue, headache, irritability, restlessness

Endocrine & metabolic: Gynecomastia, precocious puberty

Local: Injection site reaction

Miscellaneous: Hypersensitivity reaction (local or systemic)

Drug InteractionsThere are no known significant interactions.

Monitoring Parameters

Male: Serum testosterone levels, semen analysis

Female: Ultrasound and/or estradiol levels to assess follicle development; ultrasound to assess number and size of follicles; ovulation (basal body temperature, serum progestin level, menstruation, sonography)

Reference RangeDepends on application and methodology; <3 mIU/mL (SI: <3 units/L) usually normal (nonpregnant)

Nursing: Physical Assessment/MonitoringAssess therapeutic effectiveness (according to purpose for use) and adverse response regularly during long-term therapy. Teach patient proper use if self-administered (appropriate injection technique and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab Tests

Male: Serum testosterone levels, semen analysis

Female: Serum progestin level (ovulation)

Patient EducationThis medication can only be administered by injection. If self-administered, follow instruction for reconstitution, injection, and needle disposal. Use exactly as directed; do not alter dosage or miss a dose. May cause headache, depression, irritability, or restlessness (use caution when driving or engaging in potentially hazardous tasks until response to drug is known). Contact prescriber if symptoms are severe or do not resolve with use. Contact prescriber if breasts swell; if you experience swelling of legs or feet; or if there is pain, redness, or swelling at injection site. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 10,000 units [packaged with diluent; diluent contains benzyl alcohol and mannitol]

Novarel®: 10,000 units [packaged with diluent; diluent contains benzyl alcohol and mannitol]

Pregnyl®: 10,000 units [packaged with diluent; diluent contains benzyl alcohol]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Injection (reconstituted) (Novarel)

10,000 unit/10 mL (1): $44.09

Injection (reconstituted) (Pregnyl)

10,000 unit (1): $43.45

Mechanism of ActionLuteinizing hormone obtained from the urine of pregnant women. Stimulates production of gonadal steroid hormones by causing production of androgen by the testes; as a substitute for luteinizing hormone (LH) to stimulate ovulation

Pharmacodynamics/Kinetics

Half-life elimination: Biphasic: Initial: 11 hours; Terminal: 23 hours

Excretion: Urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or depression; rarely may cause restlessness or irritability

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCG; hCG

References

American Association of Clinical Endocrinologists, “American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients – 2002 Update,” *Endocr Pract*, 2002, 8(6):440-56.[PubMed 15260010]

International Brand Names Choragon (MX); Choriomon (MX); Pregnyl (MX)

Chorionic Gonadotropin (Recombinant)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(kor ee ON ik goe NAD oh troe pin ree KOM be nant)
U.S. Brand NamesOvidrel®
Canadian Brand NamesOvidrel®
Pharmacologic CategoryGonadotropin; Ovulation Stimulator
Use: Labeled IndicationsAs part of an assisted reproductive technology (ART) program, induces ovulation in infertile females who have been pretreated with follicle stimulating hormones (FSH); induces ovulation and pregnancy in infertile females when the cause of infertility is functional
Dosing: AdultsAssisted reproductive technologies (ART) and ovulation induction in females: SubQ: 250 mcg given 1 day following the last dose of follicle stimulating agent. Use only after adequate follicular development has been determined. Hold treatment when there is an excessive ovarian response.
Dosing: ElderlySafety and efficacy have not been established.
Dosing: Renal ImpairmentSafety and efficacy have not been established.
Dosing: Hepatic ImpairmentSafety and efficacy have not been established.
Administration: OtherFor SubQ use only; inject into stomach area.
StoragePrefilled syringe: Prior to dispensing, store at 2°C to 8°C (36°F to 46°F). Patient may store at 25°C (77°F) for up to 30 days. Protect from light.
ContraindicationsHypersensitivity to hCG preparations or any component of the formulation; primary ovarian failure; uncontrolled thyroid or adrenal dysfunction; uncontrolled organic intracranial lesion (ie, pituitary tumor); abnormal uterine bleeding, ovarian cyst or enlargement of undetermined origin; sex hormone dependent tumors; pregnancy
Warnings/Precautions

Concerns related to adverse effects:

- Ovarian enlargement: May be accompanied by abdominal distention or abdominal pain and generally regresses without treatment within 2-3 weeks. If ovaries are abnormally enlarged on the last day of treatment, withhold hCG to reduce the risk of ovarian hyperstimulation syndrome (OHSS).

- Ovarian hyperstimulation syndrome (OHSS): OHSS is characterized by severe ovarian enlargement, abdominal pain/distention, nausea, vomiting, diarrhea, dyspnea, and oliguria, and may be accompanied by ascites, pleural effusion, hypovolemia, electrolyte imbalance, hemoperitoneum, and thromboembolic events. If severe hyperstimulation occurs, stop treatment and hospitalize patient. This syndrome develops rapidly with 24 hours to several days and generally occurs during the 7-10 days immediately following treatment.

- Thromboembolism: In association with and separate from ovarian hyperstimulation syndrome (OHSS), arterial thromboembolic events have been reported.

Special populations:

- Elderly: Safety and efficacy have not been established in the elderly.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Experienced physician: These medications should only be used by physicians who are thoroughly familiar with infertility problems and their management.

- Multiple births: May result from the use of these medications; advise patients of the potential risk of multiple births before starting the treatment.

Pregnancy Risk FactorX
Pregnancy ConsiderationsIntrauterine death and impaired birth were observed in animal studies. Ectopic pregnancy, premature labor, postpartum fever, and spontaneous abortion have been reported in clinical trials. Congenital abnormalities have also been observed, however, the incidence is similar during natural conception.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

2% to 10%:

Endocrine & metabolic: Ovarian cyst (3%), ovarian hyperstimulation (<2% to 3%)

Gastrointestinal: Abdominal pain (3% to 4%), nausea (3%), vomiting (3%)

Local: Injection site: Pain (8%), bruising (3% to 5%), reaction (<2% to 3%), inflammation (<2% to 2%)

Miscellaneous: Postoperative pain (5%)

<2%:

Cardiovascular: Cardiac arrhythmia, heart murmur

Central nervous system: Dizziness, emotional lability, fever, headache, insomnia, malaise

Dermatologic: Pruritus, rash

Endocrine & metabolic: Breast pain, hot flashes, hyperglycemia, intermenstrual bleeding, vaginal hemorrhage

Gastrointestinal: Abdominal enlargement, diarrhea, flatulence

Genitourinary: Cervical carcinoma, cervical lesion, dysuria, genital herpes, genital moniliasis, leukorrhea, urinary incontinence, urinary tract infection, vaginal discomfort, vaginal hemorrhage, vaginitis

Hematologic: Leukocytosis

Neuromuscular & skeletal: Back pain, paresthesia

Renal: Albuminuria

Respiratory: Cough, pharyngitis, upper respiratory tract infection

Miscellaneous: Ectopic pregnancy, hiccups

Postmarketing and/or case reports: Allergic reaction

In addition, the following have been reported with menotropin therapy: Adnexal torsion, hemoperitoneum, mild-to-moderate ovarian enlargement, pulmonary and vascular complications. Ovarian neoplasms have also been reported (rare) with multiple drug regimens used for ovarian induction (relationship not established).

Drug InteractionsThere are no known significant interactions.

Test InteractionsMay interfere with interpretation of pregnancy tests; may cross-react with radioimmunoassay of luteinizing hormone and other gonadotropins

Monitoring ParametersUltrasound and/or estradiol levels to assess follicle development; ultrasound to assess number and size of follicles; ovulation (basal body temperature, serum progestin level, menstruation, sonography)

Nursing: Physical Assessment/MonitoringFor use only under the supervision/direction of an infertility prescriber. Monitor for adverse reactions. Teach patient proper use if self-administered (storage, reconstitution, injection technique, needle/syringe disposal; recommend return demonstration), monitoring requirements, interventions to reduce side effects, and adverse reactions to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment and monitor ovulation closely during treatment.

Monitoring: Lab TestsUltrasound and/or estradiol levels to assess follicle development; ultrasound to assess number and size of follicles; ovulation (basal body temperature, serum progestin level, menstruation, sonography)

Patient EducationNote that there is a risk of multiple births associated with treatment. This drug must be administered exactly as scheduled (1 day following last dose of follicle stimulating agent); maintain a calendar of treatment days. Follow administration directions exactly. Keep all ultrasound and laboratory appointments as instructed by prescriber. Avoid strenuous exercise, especially those with pelvic involvement. You may experience nausea, vomiting, or GI upset (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help), hot flashes (cool clothes, cool room, adequate rest may help); if persistent consult prescriber. Report immediately any persistent abdominal pain, vomiting, or acute pelvic pain; chest pain or palpitations; shortness of breath; or urinary tract or vaginal infection or urinary incontinence. **Pregnancy/breast-feeding precautions:** Do not take this medicine if you are pregnant and report to prescriber immediately if you suspect you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Ovidrel®: 257.5 mcg/0.515 mL (0.515 mL) [prefilled syringe; delivers 250 mcg r-hCG/0.5 mL]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Injection (Ovidrel)

250 mcg/0.5 mL (0.5): $84.97

Mechanism of ActionLuteinizing hormone analogue produced by recombinant DNA techniques; stimulates late follicular maturation and intitates rupture of the ovarian follicle once follicular development has occurred

Pharmacodynamics/Kinetics

Distribution: V_d: 21.4L

Bioavailability: 40%

Half-life elimination: Initial: 4 hours; Terminal: 29 hours

Time to peak: 12-24 hours

Excretion: Urine (10% of dose)

Pharmacotherapy PearlsClinical studies have shown r-hCG to be clinically and statistically equivalent to urinary-derived hCG products.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, emotional lability, and insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms Choriogonadotropin Alfa; r-hCG

International Brand Names Ovidrel (AR, AU, BR, ID, KP, MX, MY, PH, SG, TW); Ovitrelle (CH, CZ, DE, DK, EE, ES, FR, GB, IE, IL, IT, NL, SE); Ovitrop (IN)

CI (Neuroblastoma)

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Pharmacologic Category[Chemotherapy Regimen, Neuroblastoma]

Regimen UseNeuroblastoma

Regimen

Ifosfamide: I.V.: 1500 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 4500 mg/m^2]

Mesna: I.V.: 500 mg/m^2 every 3 hours, for 3 doses each day, days 1, 2, and 3

[total dose/cycle = 4500 mg/m^2]

Carboplatin: I.V.: 400 mg/m^2 day 4

[total dose/cycle = 400 mg/m^2]

Repeat cycle every 21-28 days

References

Alvarado CS, Kretschmar C, Joshi VV, et al, âChemotherapy for Patients With Recurrent or Refractory Neuroblastoma: A POG Phase II Study,â *J Pediatr Hematol Oncol*, 1997, 19(1):62-7.[PubMed 9065721]

Ciclesonide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(sye KLES oh nide)
U.S. Brand NamesAlvesco®; Omnaris™
Canadian Brand NamesAlvesco®; Omnaris™
Pharmacologic CategoryCorticosteroid, Inhalant (Oral); Corticosteroid, Nasal
Use: Labeled Indications

Intranasal: Management of seasonal and perennial allergic rhinitis

Oral inhalation: Prophylactic management of bronchial asthma

Dosing: Adults

Asthma: Oral inhalation (Alvesco®): **Note:** Titrate to the lowest effective dose once asthma stability is achieved:

U.S. labeling:

Prior therapy with bronchodilators alone: Initial: 80 mcg twice daily (maximum dose: 320 mcg/day)

Prior therapy with inhaled corticosteroids: Initial: 80 mcg twice daily (maximum dose: 640 mcg/day)

Prior therapy with oral corticosteroids: Initial: 320 mcg twice daily (maximum dose: 640 mcg/day)

Canadian labeling: Initial: 400 mcg once daily; maintenance: 100-800 mcg/day (1-2 puffs once or twice daily)

Perennial allergic rhinitis: Intranasal (Omnaris™): 2 sprays (50 mcg/spray) per nostril once daily; maximum: 200 mcg/day

Seasonal allergic rhinitis: Intranasal (Omnaris™):

U.S. labeling: 2 sprays (50 mcg/spray) per nostril once daily; maximum: 200 mcg/day

Canadian labeling: 2 sprays (50 mcg/spray) per nostril once daily; maximum: 200 mcg/day

Conversion from oral to inhaled steroid: Initiation of oral inhalation therapy should begin in patients who have previously been stabilized on oral corticosteroids (OCS). A gradual dose reduction of OCS should begin ~7-10 days after starting inhaled therapy. U.S. labeling recommends reducing prednisone dose no more rapidly than ≤2.5 mg/day on a weekly basis. The Canadian labeling recommends decreasing the daily dose of prednisone by 1 mg (or equivalent of other OCS) every 7 days in closely monitored patients, and every 10 days in patients whom close monitoring is not possible. In the presence of withdrawal symptoms, resume previous OCS dose for 1 week before attempting further dose reductions.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Asthma: Oral inhalation (Alvesco®): **Note:** Titrate to the lowest effective dose once asthma stability is achieved:

U.S. labeling: Children ≥12 years: Refer to adult dosing.

Canadian labeling: Children ≥12 years: Refer to adult dosing.

Perennial allergic rhinitis: Intranasal (Omnaris™): Children ≥12 years: Refer to adult dosing:

Seasonal allergic rhinitis: Intranasal (Omnaris™):

U.S. labeling: Children ≥6 year: Refer to adult dosing.

Canadian labeling: Children ≥12 years: Refer to adult dosing.

Administration: InhalationOral inhalation: Remove mouthpiece cover, place inhaler in mouth, close lips around mouthpiece, and inhale slowly and deeply. Press down on top of inhaler after slow inhalation has begun. Remove inhaler while holding breath for approximately 10 seconds. Breathe out slowly and replace mouthpiece on inhaler. Do not wash or place inhaler in water. Clean mouthpiece using a dry cloth or tissue once weekly. Discard after the "discard by" date or after labeled number of doses has been used, even if container is not completely empty.

Shaking is not necessary since drug is formulated as a solution aerosol. Prime inhaler prior to initial use or if not in use for ≥1 week by releasing 3 puffs into the air.

Administration: OtherIntranasal: Shake bottle gently before using. Prime pump prior to first use (press 8 times until fine mist appears) or if spray has not been used in 4 consecutive days (press 1 time or until a fine mist appears). Blow nose to clear nostrils. Insert applicator into nostril, keeping bottle upright, and close off the other nostril. Breathe in through nose. While inhaling, press pump to release spray. Avoid spraying directly onto the nasal septum. Nasal applicator may be removed and rinsed with warm water to clean. Discard after the "discard by" date or after labeled number of doses has been used, even if bottle is not completely empty.

StorageStore at 15°C to 30°C (59°F to 86°F); do not freeze. Nasal spray: Use within 4 months after opening aluminum pouch.

ContraindicationsHypersensitivity to ciclesonide or any component of the formulation

Oral inhalation (Alvesco®): Primary treatment of acute asthma or status asthmaticus; moderate-to-severe bronchiectasis

Canadian labeling (Alvesco®): Additional contraindications (not in U.S. labeling): Untreated fungal, bacterial, or tuberculosis infections of the respiratory tract; moderate-to-severe bronchiectasis

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections.

- Bronchospasm: May occur with wheezing after inhalation; if this occurs, stop steroid and treat with a fast-acting bronchodilator.

- Delayed wound healing: Avoid nasal corticosteroid use in patients with recent nasal septal ulcers, nasal surgery or nasal trauma until healing has occurred.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox and measles should be avoided; use caution in patients with active or quiescent TB infections (contraindicated in Canada) or in patients with ocular herpes.

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Thrush: *Candida albicans* infections (mostly mild to moderate) of the mouth and pharynx may occur with orally-inhaled corticosteroid use; interruption of therapy may be necessary at times while antifungal therapy is employed; advise patients to rinse mouth after use.

- Vasculitis: Rare cases of vasculitis (Churg-Strauss syndrome) or other eosinophilic conditions (eg, vasculitic rash, decreased pulmonary function, cardiac complications) can occur.

Disease-related concerns:

- Asthma: Supplemental steroids (oral or parenteral) may be needed during stress or severe asthma attacks. Not to be used in status asthmaticus or for the relief of acute bronchospasm.

- Hepatic impairment: Dosage adjustments are not necessary in hepatic impairment; use with caution in patients with severe hepatic impairment, including cirrhosis.

- Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Consider routine eye exams in chronic users.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Renal impairment: Use in renally-impaired patients has not been studied.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Pediatrics: Orally-inhaled and intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients (~1 cm per year [range 0.3-1.8 cm per year] and related to dose and duration of exposure). To minimize the systemic effects of orally-inhaled and intranasal corticosteroids, each patient should be titrated to the lowest effective dose. Growth should be routinely monitored in pediatric patients. Safety and efficacy of intranasal use have not been established in children <6 years of age and of oral inhalation use in patients <12 years.

Geriatric ConsiderationsNo specific information is available for the elderly patient. Make sure the patient can correctly use the nasal inhaler.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were reported in some, but not all animal studies. There are no adequate and well-controlled studies in pregnant women. The extent of intranasal absorption of ciclesonide systemically is low but variable; use during pregnancy with caution. Hypoadrenalism may occur in infants born to mothers receiving corticosteroids during pregnancy.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Headache (≤11%)

Respiratory: Nasopharyngitis (≤11%)

1% to 10%:

Cardiovascular: Facial edema (≥3%)

Central nervous system: Dizziness (≥3%), fatigue (≥3%)

Dermatologic: Urticaria (≥3%)

Gastrointestinal: Gastroenteritis (≥3%), oral candidiasis (≥3%)

Neuromuscular & skeletal: Arthralgia (≤4%), musculoskeletal chest pain (≥3%), back pain (≥3%), extremity pain (≥3%)

Ocular: Conjunctivitis (≥3%)

Otic: Ear pain (2%)

Respiratory: Upper respiratory infection (≤9%), epistaxis (≤8%), nasal congestion (≤6%), sinusitis (≤6%), pharyngolaryngeal pain (≤ 5%), hoarseness (≥3%), pneumonia (≥3%), paradoxical bronchospasm (2%), dysphonia (1%)

Miscellaneous: Influenza (≥3%)

<1%, postmarketing, and/or case reports: ALT increased, angioedema (with swelling of lip/pharynx/tongue), bruising, candidiasis (nasal/pharyngeal/systemic), cataract, chest discomfort, cough, dry throat, dysgeusia, dyspepsia, GGT increased, intraocular pressure increased, nausea, nasal septum disorder, palpitation, pharyngitis, rash, rhinorrhea, throat irritation, WBC increased, weight gain, xerostomia

Metabolism/Transport Effects **Substrate** of CYP3A4 (major), 2D6 (minor)

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Monitoring Parameters Growth (adolescents) and signs/symptoms of HPA axis suppression/adrenal insufficiency; ocular effects (eg, cataracts, increased intraocular pressure, glaucoma)

Nursing: Physical Assessment/Monitoring Assess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report. Growth should be monitored periodically with long-term use in children. Do not discontinue abruptly after long-term use.

Patient Education Inform prescriber of all prescription medications, OTC medications, or herbal products you are taking. Take exactly as directed. Do not exceed the recommended dosage. Not intended for treatment of acute asthma attacks. Full response to this medication may not be seen for 2-5 weeks. Use regularly. Do not stop treatment, even if feeling better. You may be susceptible to infections. Avoid exposure to chickenpox or measles, crowds, and exposure to other potential infections. Report persistent headache, nosebleeds, or worsening of condition or lack of improvement. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Aerosol for oral inhalation:

Alvesco® [U.S.]: 80 mcg/inhalation (6.1 g) [60 metered actuations]; 160 mcg/inhalation (6.1 g) [60 metered actuations]

Alvesco® [CAN]: 50 mcg/inhalation [30-, 60-, and 120 metered actuations] [not available in the U.S.]; 100 mcg/inhalation [30-, 60-, and 120 metered actuations] [not available in the U.S.]; 200 mcg/inhalation [30-, 60-, and 120 metered actuations] [not available in the U.S.]

Suspension, intranasal [spray]:

Omnaris™: 50 mcg/inhalation (12.5 g) [120 metered actuations]

Generic Available No

Manufacturer Altana

Pricing: U.S. (www.drugstore.com)

Suspension (Omnaris)

50 mcg/ACT (12.5): $80.99

Mechanism of Action Ciclesonide is a nonhalogenated, glucocorticoid prodrug that is hydrolyzed to the pharmacologically active metabolite des-ciclesonide following administration. Des-ciclesonide has a high affinity for the glucocorticoid receptor and exhibits anti-inflammatory activity. The mechanism of action for corticosteroids is believed to be a combination of three important properties – anti-inflammatory activity, immunosuppressive properties, and antiproliferative actions.

Pharmacodynamics/Kinetics

Onset of action: Intranasal: 24-48 hours; further improvement observed over 1-2 weeks in seasonal allergic rhinitis or 5 weeks in perennial allergic rhinitis

Absorption: Intranasal: Minimal systemic absorption; Oral inhalation: 52% (lung deposition)

Distribution: I.V.: V_d: Ciclesonide 2.9 L/kg; Des-ciclesonide 12.1 L/kg

Protein binding: ≥99%

Metabolism: Ciclesonide hydrolyzed to active metabolite, des-ciclesonide via esterases in nasal mucosa and lungs; further metabolism via hepatic CYP3A4 and 2D6

Bioavailability: Intranasal <1%; oral inhalation: >50% (active metabolite)

Half-life elimination: Oral inhalation: ~5-7 hours

Time to peak: Oral inhalation: ~1 hour (active metabolite)

Excretion:

Intranasal: Feces (~66%); urine (≤20%)

Oral inhalation: Feces (78%)

Pharmacotherapy PearlsThe incidence of oral candidiasis, as well as other localized oropharyngeal effects, observed with ciclesonide use has been reported to be approximately one-half of that seen with other commonly inhaled corticosteroids such as budesonide and fluticasone. Small particle size, minimal activation, and deposition in the oropharynx may explain this decreased incidence.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentPatients may experience symptoms of corticosteroid withdrawal (depression) when replacing a systemic agent with a topical corticosteroid.

References

Bateman E, Karpel J, Casale T, et al, “Ciclesonide Reduces the Need for Oral Steroid Use in Adult Patients With Severe, Persistent Asthma,” *Chest*, 2006, 129(5):1176-87.[PubMed 16685007]

Derendorf H, “Pharmacokinetic and Pharmacodynamic Properties of Inhaled Ciclesonide,” *J Clin Pharmacol*, 2007, 47(6):782-9[PubMed 17412829]

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

Nave R, Wingertzahn MA, Brookman S, et al, “Safety, Tolerability, and Exposure of Ciclesonide Nasal Spray in Healthy and Asymptomatic Subjects with Seasonal Allergic Rhinitis,” *J Clin Pharmacol*, 2006, 46 (4):461-7.[PubMed 16554455]

Pearlman DS, Berger WE, Kerwin E, et al, “Once-Daily Ciclesonide Improves Lung Function and is Well Tolerated by Patients With Mild-to-Moderate Persistent Asthma,” *J Allergy Clin Immunol*, 2005, 116(6):1206-12.[PubMed 16337447]

International Brand NamesAlvesco (AR, AU, BR, CH, CN, CO, CZ, DE, EC, EE, FI, GB, HK, IE, MX, MY, NL, NO, PE, SE, VE); Cicletex (AR)

Ciclopirox

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Loprox® may be confused with Lonox®

Pronunciation(sye kloe PEER oks)
U.S. Brand NamesLoprox®; Penlac®
Canadian Brand NamesLoprox®; Penlac®; Stieprox®
Pharmacologic CategoryAntifungal Agent, Topical

Use: Labeled Indications

Cream/suspension: Treatment of tinea pedis (athlete's foot), tinea cruris (jock itch), tinea corporis (ringworm), cutaneous candidiasis, and tinea versicolor (pityriasis)

Gel: Treatment of tinea pedis (athlete's foot), tinea corporis (ringworm); seborrheic dermatitis of the scalp

Lacquer (solution): Topical treatment of mild-to-moderate onychomycosis of the fingernails and toenails due to *Trichophyton rubrum* (not involving the lunula) and the immediately-adjacent skin

Shampoo: Treatment of seborrheic dermatitis of the scalp

Dosing: Adults

Tinea pedis, tinea corporis: Topical:

Cream and suspension: Apply twice daily, gently massage into affected areas; if no improvement after 4 weeks of treatment, re-evaluate the diagnosis.

Gel: Apply twice daily, gently massage into affected areas and surrounding skin; if no improvement after 4 weeks of treatment, re-evaluate diagnosis

Tinea cruris, cutaneous candidiasis, and tinea versicolor: Topical: *Cream and suspension:* Apply twice daily, gently massage into affected areas; if no improvement after 4 weeks of treatment, re-evaluate the diagnosis.

Onychomycosis of the fingernails and toenails: Topical: *Lacquer (solution):* Apply to adjacent skin and affected nails daily (as a part of a comprehensive management program for onychomycosis). Remove with alcohol every 7 days.

Seborrheic dermatitis of the scalp: Topical:

Gel: Apply twice daily, gently massage into affected areas and surrounding skin; if no improvement after 4 weeks of treatment, re-evaluate diagnosis.

Shampoo: Apply ~5 mL (1 teaspoonful) to wet hair; lather, and leave in place ~3 minutes; rinse. May use up to 10 mL for longer hair. Repeat twice weekly for 4 weeks; allow a minimum of 3 days between applications.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Tinea pedis, tinea corporis: Topical:

Cream and suspension: Children >10 years: Refer to adult dosing.

Gel: Children >16 years: Refer to adult dosing.

Tinea cruris, cutaneous candidiasis, and tinea versicolor: Topical: *Cream and suspension:* Children >10 years: Refer to adult dosing.

Onychomycosis of the fingernails and toenails: Topical: *Lacquer (solution):* Children ≥12 years: Refer to adult dosing.

Seborrheic dermatitis of the scalp: Topical: *Gel and shampoo:* Children >16 years: Refer to adult dosing.

Administration: Topical

Cream, suspension: Gently massage into affected areas.

Gel: Gently massage into affected areas and adjacent skin.

Lacquer (solution): Apply evenly over nail and surrounding skin at bedtime (or allow 8 hours before washing); apply daily over previous coat for 7 days; after 7 days, may remove with alcohol and continue cycle.

Shampoo: Apply to wet hair; lather and leave in place for ~3 minutes; rinse.

Storage

Cream, suspension: Store between 5°C to 25°C (41°F to 77°F).

Lacquer (solution): Store at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light. Flammable; keep away from heat and flame.

Gel, shampoo: Store at room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to ciclopirox or any component of the formulation; avoid occlusive wrappings or dressings

Allergy Considerations

- Ciclopirox Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue if sensitivity or irritation occurs.

Special populations:

- Immunocompromised patients: Use has not been evaluated in immunosuppressed or immunocompromised patients.
- Pediatrics: Topical cream and suspension not approved for use in children <10 years of age. Nail lacquer (solution) not approved for use in children <12 years of age. Shampoo and gel not approved for use in children <16 years of age.

Dosage form specific issues:

- Nail lacquer: For topical use only and has not been studied in conjunction with systemic therapy or in patients with type 1 diabetes mellitus (insulin dependent, IDDM).

Other warnings/precautions:

- Appropriate use: For topical use only; avoid contact with eyes.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies, however, there are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

Central nervous system: Headache

Dermatologic: Alopecia, dry skin, erythema, facial edema, hair discoloration (rare; shampoo formulation in light-haired individuals), nail disorder (shape or color change with lacquer), pruritus, rash

Local: Burning sensation (gel: 34%; ≤1% with other forms), irritation, redness, or pain

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, topical, as olamine: 0.77% (15 g, 30 g, 90 g)

Loprox®: 0.77% (15 g, 30 g, 90 g) [contains benzyl alcohol] [DSC]

Gel, topical: 0.77% (30 g, 45 g, 100 g)

Loprox®: 0.77% (30 g, 45 g, 100 g) [contains isopropyl alcohol]

Shampoo, topical:

Loprox®: 1% (120 mL)

Solution, topical [nail lacquer]: 8% (6.6 mL)

Penlac®: 8% (6.6 mL) [contains isopropyl alcohol]

Suspension, topical, as olamine: 0.77% (30 mL, 60 mL)

Loprox®: 0.77% (30 mL, 60 mL) [contains benzyl alcohol] [DSC]

Generic AvailableYes: Excludes shampoo

Pricing: U.S. (www.drugstore.com)

Cream (Ciclopirox Olamine)

0.77% (15): $24.99

0.77% (30): $44.99

0.77% (90): $109.99

Cream (Loprox)

0.77% (30): $107.88

0.77% (90): $254.40

Gel (Loprox)

0.77% (30): $113.57

0.77% (45): $159.02

0.77% (100): $311.74

Shampoo (Loprox)

1% (120): $115.68

Solution (Ciclopirox)

8% (6.6): $29.99

Solution (Penlac)

8% (6.6): $191.82

Suspension (Ciclopirox Olamine)

0.77% (30): $44.99

0.77% (60): $88.46

Suspension (Loprox)

0.77% (30): $105.98

0.77% (60): $211.98

Mechanism of ActionInhibiting transport of essential elements in the fungal cell disrupting the synthesis of DNA, RNA, and protein

Pharmacodynamics/Kinetics

Absorption: Cream, suspension: <2% through intact skin; increased with gel; <5% with lacquer

Distribution: Scalp application: To epidermis, corium (dermis), including hair, hair follicles, and sebaceous glands

Protein binding: 94% to 98%

Half-life elimination: Biologic: 1.7 hours (suspension); elimination: 5.5 hours (gel)

Excretion: Urine (gel: 3% to 10%); feces (small amounts)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCiclopirox Olamine

International Brand NamesBatrafan (IN); Batrafen (AE, AT, BB, BD, BG, BH, BM, BS, BZ, CH, CL, CN, CY, CZ, DE, EC, EE, EG, GR, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KP, KW, LB, LY, MY, NL, NZ, OM, PE, PH, PK, PL, PR, PY, QA, SA, SG, SR, SY, TH, TT, TW, UY, VE, YE); Batrafen Gel (DE); Batrafen Nail Lacquer (IL); Brumixol (IT, TW); Ciclochem (ES); Dafnegin (PL); Fungopirox (PE); Hascofungin (PL); Huanli (CL); Loprox (AR, BR, CR, DO, EC, GT, HN, MX, NI, NL, PA, SV, TH); Loprox Laca (MX); Miclast (IT); Micopirox (AR); Micoxolamina (IT); Mycofen (DK); Mycosten (PL); Mycoster (FR, LU, PT); Nail Batrafen (NZ); Pirolam (PL); Primax (CO); Stieprox (MY, PH, PL, SG, TH, TW); Stiprox (MX)

Cidofovir

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(si DOF o veer)

U.S. Brand NamesVistide®

Pharmacologic CategoryAntiviral Agent

Use: Labeled IndicationsTreatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS). **Note:** Should be administered with probenecid.

Dosing: AdultsTreatment of cytomegalovirus (CMV) retinitis: I.V.:

Induction treatment: 5 mg/kg once weekly for 2 consecutive weeks

Maintenance treatment: 5 mg/kg administered once every 2 weeks

Note: Probenecid must be administered orally with each dose of cidofovir.

Probenecid dose: 2 g 3 hours prior to cidofovir dose, 1 g at 2 hours and 8 hours after completion of the infusion; patients should also receive 1 L of normal saline intravenously prior to each infusion of cidofovir; saline should be infused over 1-2 hours.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Changes in renal function during therapy: If the creatinine increases by 0.3-0.4 mg/dL, reduce the cidofovir dose to 3 mg/kg; discontinue therapy for increases ≥0.5 mg/dL or development of ≥3+ proteinuria

Pre-existing renal impairment: Use is contraindicated with serum creatinine >1.5 mg/dL, Cl_{cr} <55 mL/minute, or urine protein ≥100 mg/dL (≥2+ proteinuria)

Administration: I.V.For I.V. infusion only. Infuse over 1 hour. Hydrate with 1 L of 0.9% NS I.V. prior to cidofovir infusion. A second liter may be administered over a 1- to 3-hour period immediately following infusion, if tolerated.

Administration: I.V. DetailpH: 6.7-7.6

StorageStore at controlled room temperature 20°C to 25°C (68°F to 77°F). Store admixtures under refrigeration for ≤24 hours. Cidofovir infusion admixture should be administered within 24 hours of preparation at room temperature or refrigerated. Admixtures should be allowed to equilibrate to room temperature prior to use.

ReconstitutionDilute dose in NS 100 mL prior to infusion.

CompatibilityStable in $D_5{}^1/_4$NS, D_5W, NS.

ContraindicationsHypersensitivity to cidofovir; history of clinically-severe hypersensitivity to probenecid or other sulfa-containing medications; serum creatinine >1.5 mg/dL; Cl_{cr} <55 mL/minute; urine protein ≥100 mg/dL (≥2+ proteinuria); use with or within 7 days of nephrotoxic agents; direct intraocular injection

Warnings/Precautions

Boxed warnings:

- Appropriate use: See “Other warnings/precautions” below.
- Carcinogenic/teratogenic/fertility effects: See “Concerns related to adverse effects” below.
- Nephrotoxicity: See “Concerns related to adverse effects” below.
- Neutropenia: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Carcinogenic/teratogenic/fertility effects: **[U.S. Boxed Warning]: Possibly carcinogenic and teratogenic based on animal data. May cause hypospermia.**
- Metabolic acidosis: Monitor for signs of metabolic acidosis; decreases $NaHCO_3$, proximal tubule injury, and renal wasting have been reported.
- Nephrotoxicity: **[U.S. Boxed Warning]: Dose-dependent nephrotoxicity requires dose adjustment or discontinuation if changes in renal function occur during therapy (eg, proteinuria, glycosuria, decreased serum phosphate, uric acid or bicarbonate, and elevated creatinine).** Administration must be accompanied by oral probenecid and intravenous saline prehydration.
- Neutropenia: **[U.S. Boxed Warning]: Neutropenia has been reported;** monitor counts during therapy.

- Ocular hypotony: Cases of ocular hypotony have also occurred; monitor intraocular pressure.

Special populations:

- Elderly: Use with caution in the elderly; safety and efficacy have not been established.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: **[U.S. Boxed Warning]: Indicated only for CMV retinitis treatment in HIV patients.**

Geriatric ConsiderationsSince elderly individuals frequently have reduced kidney function, particular attention should be paid to assessing renal function before and frequently during administration.

Pregnancy Risk FactorC

Pregnancy Considerations**[U.S. Boxed Warning]: Possibly carcinogenic and teratogenic based on animal data. May cause hypospermia.** Cidofovir was shown to be teratogenic and embryotoxic in animal studies, some at doses which also produced maternal toxicity. Reduced testes weight and hypospermia were also noted in animal studies. There are no adequate and well-controlled studies in pregnant women; use during pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus. Women of childbearing potential should use effective contraception during therapy and for 1 month following treatment. Males should use a barrier contraceptive during therapy and for 3 months following treatment.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsThe CDC recommends **not** to breast-feed if diagnosed with HIV to avoid postnatal transmission of the virus.

Adverse Reactions

>10%:

Central nervous system: Chills, fever, headache, pain

Dermatologic: Alopecia, rash

Gastrointestinal: Nausea, vomiting, diarrhea, anorexia

Hematologic: Anemia, neutropenia

Neuromuscular & skeletal: Weakness

Ocular: Intraocular pressure decreased, iritis, ocular hypotony, uveitis

Renal: Creatinine increased, proteinuria, renal toxicity

Respiratory: Cough, dyspnea

Miscellaneous: Infection, oral moniliasis, serum bicarbonate decreased

1% to 10%:

Renal: Fanconi syndrome

Respiratory: Pneumonia

<1%: Hepatic failure, metabolic acidosis, pancreatitis

Frequency not defined (limited to important or life-threatening reactions):

Cardiovascular: Cardiomyopathy, cardiovascular disorder, CHF, edema, postural hypotension, shock, syncope, tachycardia

Central nervous system: Agitation, amnesia, anxiety, confusion, convulsion, dizziness, hallucinations, insomnia, malaise, vertigo

Dermatologic: Photosensitivity reaction, skin discoloration, urticaria

Endocrine & metabolic: Adrenal cortex insufficiency

Gastrointestinal: Abdominal pain, aphthous stomatitis, colitis, constipation, dysphagia, fecal incontinence, gastritis, GI hemorrhage, gingivitis, melena, proctitis, splenomegaly, stomatitis, tongue discoloration

Genitourinary: Urinary incontinence

Hematologic: Hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, lymphoma-like reaction, pancytopenia, thrombocytopenia, thrombocytopenic purpura

Hepatic: Hepatomegaly, hepatosplenomegaly, jaundice, liver function tests abnormal, liver damage, liver necrosis

Local: Injection site reaction

Neuromuscular & skeletal: Tremor

Ocular: Amblyopia, blindness, cataract, conjunctivitis, corneal lesion, diplopia, vision abnormal

Otic: Hearing loss

Miscellaneous: Allergic reaction, sepsis

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersRenal function (Cr, BUN, UAs) within 48 hours of each dose, LFTs, WBCs; intraocular pressure and visual acuity, signs and symptoms of uveitis/iritis

Nursing: Physical Assessment/MonitoringAssess patient allergy history (sulfa) prior to beginning therapy. Administration must be accompanied by oral probenecid and intravenous saline prehydration. Assess other pharmacological or herbal products patient may be taking for potential interactions (especially anything that may be nephrotoxic). Infusion site should be monitored closely to avoid extravasation. Assess results of laboratory tests with each dose. Assess therapeutic effectiveness and adverse response (eg, CNS changes, anemia, interocular pressure, renal damage, proteinuria, elevated creatine) regularly during therapy. For patients with diabetes, serum glucose should be monitored closely (may cause hyperglycemia). Teach patient possible side effects/appropriate interventions and adverse symptoms to report (especially any changes in vision or eye pain).

Monitoring: Lab TestsSerum creatinine, serum bicarbonate, acid-base status, urine protein, WBC should be monitored with each dose; monitor intraocular pressure frequently.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. This drug can only be administered I.V. Report immediately any pain, stinging, swelling at infusion site. You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause hair loss (reversible); headache, anxiety, confusion (use caution when driving or engaging in tasks that require alertness until response to drug is known); diarrhea (buttermilk or yogurt may help); nausea, heartburn, or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); constipation (increased exercise, fluids, fruit, or fiber may help); or postural hypotension (use caution changing from lying to sitting or standing position and when climbing stairs). Report severe unresolved vomiting, constipation, or diarrhea; chills, fever, signs of infection; respiratory difficulty or unusual coughing; palpitations, chest pain, or syncope; CNS changes (eg, hallucinations, depression, excessive sedation, amnesia, seizures, insomnia); vision changes; or other severe side effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant and do not get pregnant while taking this medicine. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptives if necessary or if you suspect you might be pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 75 mg/mL (5 mL)

Generic AvailableNo

Mechanism of ActionCidofovir is converted to cidofovir diphosphate which is the active intracellular metabolite; cidofovir diphosphate suppresses CMV replication by selective inhibition of viral DNA synthesis. Incorporation of cidofovir into growing viral DNA chain results in reductions in the rate of viral DNA synthesis.

Pharmacodynamics/KineticsThe following pharmacokinetic data is based on a combination of cidofovir administered with probenecid:

Distribution: V_d: 0.54 L/kg; does not cross significantly into CSF

Protein binding: <6%

Metabolism: Minimal; phosphorylation occurs intracellularly

Half-life elimination, plasma: ~2.6 hours

Excretion: Urine

Related Information

- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis and abnormal taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusAnxiety, confusion, amnesia, and insomnia are common; may cause depression or hallucinations

Mental Health: Effects on Psychiatric TreatmentAnemia and neutropenia are common; use caution with clozapine and carbamazepine

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Lea AP and Bryson HM, “Cidofovir,” *Drugs*, 1996, 52(2):225-30. [PubMed 8841740]

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Whitley RJ, Jacobson MA, Friedberg DN, et al, “Guidelines for the Treatment of Cytomegalovirus Diseases in Patients With AIDS in the Era of Potent Antiretroviral Therapy: Recommendations of an International Panel. International AIDS Society-USA,” *Arch Intern Med*, 1998, 158(9):957-69.[PubMed 9588429]

International Brand NamesVistide (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Cilazapril and Hydrochlorothiazide

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English

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Pronunciation(sye LAY za pril & hye droe klor oh THYE a zide)

Canadian Brand NamesApo-Cilazapril/Hctz; Inhibace® Plus

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of mild-to-moderate hypertension in patients who have been stabilized on the individual agents given in the same proportions; not indicated for initial treatment of hypertension

Dosing: Adults**Note:** Initiate therapy with combination product only after successful titration of individual agents to adequate blood pressure response.

Hypertension: Oral: One tablet administered once daily; dose is individualized (range: Cilazapril: 2.5-10 mg; hydrochlorothiazide: 6.25-25 mg/day)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Mild-to-moderate renal impairment: Use with caution; reduced dosage may be appropriate

Cl_{cr} <30 mL/minute: Not recommended

Calculations

- Creatinine Clearance: Adults

Administration: OralAdminister with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at 15°C to 30°C (59°F to 86°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to cilazapril, hydrochlorothiazide, or any component of the formulation; hypersensitivity to other ACE inhibitors, thiazides or sulfonamide-derived drugs, angioedema related to previous treatment with an ACE inhibitor; anuria; pregnancy; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising the airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Use with extreme caution in patients with idiopathic or hereditary angioedema. Aggressive early and appropriate management is critical. Use in patients with previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Photosensitivity: Photosensitization may occur.
- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.
- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.
- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity. Hydrochlorothiazide can cause systemic lupus erythematosus (SLE) exacerbation or activation.
- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.
- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.
- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.
- Hypovolemia: Use with caution in patients with hypovolemia; hypotension can occur. Carefully monitor blood pressure with the first dose.
- Porphyria: Use with caution in patients with porphyria; acute porphyritic attacks have occurred with hydrochlorothiazide.
- Renal artery stenosis: Use cilazapril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.
- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment. Contraindicated in anuric patients.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: Based on human data, ACE inhibitors can cause injury and death to the developing fetus when used in the second and third trimesters. ACE inhibitors should be discontinued as soon as possible once pregnancy is detected.

Dosage form specific issues:

- Lactose: Contains lactose; avoid use in patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss, or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Pregnancy ConsiderationsUse is contraindicated. See individual agents.
LactationExcretion in breast milk unknown/contraindicated
Adverse Reactions

1% to 10%:

Cardiovascular: Palpitation (1%)

Central nervous system: Dizziness (4%), fatigue (3%), somnolence (1%)

Gastrointestinal: Nausea (1%)

Genitourinary: Polyuria (1%)

Hematologic: Transient neutropenia (1%)

Hepatic: Transaminases increased (≤1%)

Respiratory: Cough (3%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Abdominal pain, acute interstitial pneumonitis, acute pulmonary edema, acute renal failure, agranulocytosis, alkaline phosphatase increased, alopecia, angina, angioedema, anorexia, anxiety, arthralgia, atrial fibrillation, back pain, bleeding time increased, bradycardia, bronchitis, BUN increased, cerebrovascular disorder, cholestatic hepatitis (with or without necrosis), confusion, constipation, depersonalization, depression, dermatitis, diaphoresis, diplopia, dreaming abnormal, dyspepsia, dyspnea, erythema multiforme, extrasystoles, facial edema, fever, flatulence, GGT increased, gout, hemolytic anemia, hot flushes, hyperbilirubinemia, hypoesthesia, hyponatremia, hypotension (including postural), hypothermia, impotence, insomnia, leg cramps, leukorrhea, libido decreased/increased, malaise, melena, MI, myalgia, nervousness, neurosis, nocturia, pain, pancreatitis, paresthesia, paroniria, pemphigus, peripheral edema, peripheral ischemia, pharyngitis, pruritus, pseudoporphyria, purpura, rash, rhinitis, rigors, sinusitis, Stevens-Johnson syndrome, stroke, tachycardia, taste disorder, thrombocytopenia, tinnitus, toxic epidermal necrolysis, transaminases increased, upper respiratory tract infection, vasodilation, vertigo, vision abnormal, vomiting, weakness, weight gain, xerostomia

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure; BUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsBUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet: 5/12.5: Cilazapril monohydrate 5 mg and hydrochlorothiazide 12.5 mg [not available in the U.S.]

Inhibace® Plus 5/12.5 [CAN]: Cilazapril monohydrate 5 mg and hydrochlorothiazide 12.5 mg [not available in the U.S.; contains lactose]

Generic AvailableYes

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Cilazapril
- Hydrochlorothiazide

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or fatigue; may rarely cause sedation, insomnia, or depression

Mental Health: Effects on Psychiatric TreatmentMay decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Hypertension: The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) can be beneficial in patients with hypertension and LVH without symptoms of heart failure. JNC 7 suggests that patients can benefit from treatment with an ACE inhibitor if they have hypertension **and** heart failure, acute myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, history of stroke.

Vascular Disease: The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors can be useful in preventing heart failure in patients who have a history of atherosclerotic vascular disease, diabetes, or hypertension with associated cardiovascular risk factors. The HOPE trial (Heart Outcomes Prevention Evaluation Study Investigators, 2000) investigated the value of an ACE inhibitor (ramipril 5-10 mg daily) versus placebo in patients who had evidence of vascular disease or diabetes (one other cardiovascular risk factor) and were at least 55 years of age. Patients were excluded if they had a low ejection fraction, heart failure, or were on an ACE inhibitor. The primary outcome was a composite of death from cardiovascular cause, myocardial infarction, or stroke; 9297 patients were enrolled and randomized. Ramipril significantly reduced the risk of death from CV causes, MI, or stroke over placebo. New cases of diabetes were also reduced in the ramipril group. In the EUROPA trial, patients with stable coronary artery disease (at low-risk for cardiovascular events) received perindopril or placebo and were evaluated for incidence of cardiovascular events after 4 years of treatment. In this randomized, placebo-controlled, prospective study, 12,218 patients received either perindopril (8 mg/day, n=6110) or placebo (n=6108) and were assessed for the primary endpoint of a cardiovascular event, defined as cardiovascular death, myocardial infarction, or cardiac arrest. The study population was well balanced with respect to baseline demographics and concomitant medication use (including beta-blockers, platelet inhibitors, antihyperlipidemics, calcium channel blockers, nitrates, and diuretics). Intent-to-treat analysis revealed that 603 (10%) of placebo patients experienced the primary endpoint of a cardiovascular event compared to 488 (8%) of perindopril-receiving patients, for a 20% relative risk reduction (p=0.0003). This result was not influenced by the presence of other comorbidities (eg, diabetes, hypertension) or concomitant beta-blocker, calcium channel blocker, or lipid-lowering therapies. Withdrawal from the study (postrandomization) due to adverse reactions was similar between treatment groups. Number needed to treat analysis suggests that treatment of 50 patients over a 4-year period will prevent one major cardiovascular event.

Acute Coronary Syndromes: In the treatment of unstable angina/non-ST-segment elevation MI, ACE inhibitors are recommended when hypertension persists despite treatment with nitroglycerin and a beta-blocker in patients with LV systolic dysfunction or CHF and in ischemic patients with diabetes (Class I). ACE inhibitors are also recommended for all post-ACS individuals (Class IIa). According to 2004 ACC/AHA STEMI guidelines, an ACE inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF <0.4, in the absence of hypotension or known contraindications to this class of medicines. In the emergency management of complicated STEMI, a short-acting ACEI (eg, captopril 1-6.25 mg) may be added once the patient's systolic blood pressure is >100 mm Hg and not <30 mm Hg below baseline. The VALIANT trial evaluated the effects of valsartan (target dose: 160 mg twice daily), captopril (target dose: 50

mg twice daily), and the combination (target doses: valsartan 80 mg twice daily and captopril 150 mg once daily) in a randomized, double-blind trial of patients with acute MI (0.5-10 days post-MI) complicated by left ventricular systolic dysfunction, heart failure, or both. Enrollment in the study numbered 14,703 patients and followed for a median of 24.7 months. There was no difference in the primary endpoint (all cause mortality) among the 3 groups. There was no difference in incidence of CV death, recurrent MI, or hospitalization for heart failure either. Hypotension and renal dysfunction occurred significantly more often in the valsartan group than captopril alone. Cough, rash, and taste disturbances occurred more often in the captopril group. The authors (Pfeffer, 2003) concluded that valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after MI. Combining valsartan with captopril increased the rate of adverse events without improving survival.

Potential Adverse Events: ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. In those patients experiencing cough on an ACE inhibitor, the ACE inhibitor may be discontinued and, if necessary, ARB therapy instituted. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Index TermsCilazapril Monohydrate and Hydrochlorothiazide; Hydrochlorothiazide and Cilazapril

References

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Cilazapril

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(sye LAY za pril)

Canadian Brand NamesApo-Cilazapril®; CO Cilazapril; Gen-Cilazapril; Inhibace®; Novo-Cilazapril; PMS-Cilazapril

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor

Use: Labeled IndicationsManagement of hypertension; treatment of heart failure

Dosing: Adults

Hypertension: Oral: 2.5-5 mg once daily (maximum dose: 10 mg/day)

Congestive heart failure: Oral: Initial: 0.5 mg once daily; if tolerated, after 5 days increase to 1 mg/day (lowest maintenance dose); may increase to maximum of 2.5 mg once daily

Dosing: ElderlyInitial: 1.25 mg once daily; titrate slowly as tolerated

Dosing: Renal Impairment

Hypertension:

Cl_{cr} 10-40 mL/minute: Initial: 0.5 mg once daily (maximum dose: 2.5 mg once daily)

Cl_{cr} <10 mL/minute: 0.25-0.5 mg once or twice weekly

Congestive heart failure:

Cl_{cr} 10-40 mL/minute: Initial: 0.25-0.5 mg once daily (maximum dose: 2.5 mg once daily)

Cl_{cr} <10 mL/minute: 0.25-0.5 mg once or twice weekly

Dosing: Hepatic ImpairmentInitial: ≤0.5 mg once daily (with caution)

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at 15°C to 30°C (59°F to 86°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to cilazapril, any other ACE inhibitor, or any component of the formulation; angioedema related to previous treatment with an ACE inhibitor; ascites; pregnancy; breast-feeding

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising the airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment.

Dosage form specific issues:

- Lactose: Contains lactose; avoid use in patients with galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

Special populations:

- Pregnancy: Based on human data, ACE inhibitors can cause injury and death to the developing fetus when used in the second and third trimesters. Use is contraindicated in pregnancy.

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Pregnancy ConsiderationsCranial defects, hypocalvaria/acalvaria, oligohydramnios, persistent anuria following delivery, hypotension, renal defects, renal dysgenesis/dysplasia, renal failure, pulmonary hypoplasia, limb contractures secondary to oligohydramnios, and fetal death reported. Cilazapril is contraindicated in pregnancy.

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions

1% to 10%:

Cardiovascular: Palpitation (up to 1%), hypotension (symptomatic, up to 1% in CHF patients), orthostatic hypotension (2%)

Central nervous system: Headache (3% to 5%), dizziness (3% to 8%), fatigue (2% to 3%)

Gastrointestinal: Nausea (1% to 3%)

Neuromuscular & skeletal: Weakness (0.3% to 2%)

Renal: Serum creatinine increased

Respiratory: Cough (2% in hypertension, up to 7.5% in CHF patients)

<1%: Angina, angioedema, anorexia, anxiety, arrhythmia, ataxia, atrial fibrillation, AV block, bradycardia, bronchospasm, cardiogenic shock, confusion, constipation, depression, diarrhea, dyspepsia, dyspnea, dysuria, gout, hemolytic anemia, hyperbilirubinemia, hyperglycemia, hyperkalemia, insomnia, leukopenia, MI, neutropenia, nervousness, pancreatitis, paresthesia, pemphigus, polyuria, proteinuria, pruritus, purpura, rash, renal failure, rhinitis, somnolence, Stevens-Johnson syndrome, stroke, syncope, taste perversion, thrombocytopenic purpura, tinnitus, transaminases increased, tremor, urticaria, vomiting

Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Cilazapril serum concentrations may be decreased if taken with food (no apparent effect on activity). Long-term use of ACE inhibitors may result in a zinc deficiency which can result in a decrease in taste perception.

Herb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, california poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Monitoring ParametersBUN, electrolytes, serum creatinine; blood pressure. In patients with renal impairment and/or collagen vascular disease, monitor CBC with differential

Monitoring: Lab TestsBUN, electrolytes, serum creatinine; blood pressure; in patients with renal impairment and/or collagen vascular disease, monitor CBC with differential

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet:

Inhibace® [CAN], Novo-Cilazapril [CAN]: 1 mg, 2.5 mg, 5 mg [not available in the U.S.]

Mechanism of ActionCompetitive inhibitor of angiotensin-converting enzyme (ACE); prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor; results in lower levels of angiotensin II which causes an increase in plasma renin activity and a reduction in aldosterone secretion.

Pharmacodynamics/Kinetics

Onset of action: Antihypertensive: ~1 hour

Duration: Therapeutic effect: 24 hours

Absorption: Rapid

Metabolism: To active form (cilazaprilat)

Bioavailability: 57%

Half-life elimination: Cilazaprilat: Terminal: 36-49 hours

Time to peak: 3-7 hours

Excretion: In urine (91%)

Pharmacotherapy PearlsNot available in U.S.
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness or fatigue; may rarely cause sedation, insomnia, or depression
Mental Health: Effects on Psychiatric TreatmentMay decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels
Cardiovascular Considerations

Congestive Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines recommend that ACE inhibitors be used in patients with a reduced EF (with or without heart failure symptoms) unless contraindicated. ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. In this situation, they decrease hospitalizations for, and retard progression to, congestive heart failure. When used in patients with heart failure, the target dose should be achieved, if possible. Lower daily doses of ACE inhibitors have demonstrated the same mortality effects as high doses, but have not decreased hospitalizations to the extent that high-dose ACE inhibitors have, as demonstrated in the ATLAS study (Packer M, 1999).

Hypertension: The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) can be beneficial in patients with hypertension and LVH without symptoms of heart failure. JNC 7 suggests that patients can benefit from treatment with an ACE inhibitor if they have hypertension **and** heart failure, acute myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, history of stroke.

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Acute Coronary Syndromes: In the treatment of unstable angina/non-ST-segment elevation MI, ACE inhibitors are recommended when hypertension persists despite treatment with nitroglycerin and a beta-blocker in patients with LV systolic dysfunction or CHF and in ischemic patients with diabetes (Class I). ACE inhibitors are also recommended for all post-ACS individuals (Class IIa). According to 2004 ACC/AHA STEMI guidelines, an ACE inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF <0.4, in the absence of hypotension or known contraindications to this class of medicines. In the emergency management of complicated STEMI, a short-acting ACEI (eg, captopril 1-6.25 mg) may be added once the patient's systolic blood pressure is >100 mm Hg and not <30 mm Hg below baseline. The VALIANT trial evaluated the effects of valsartan (target dose: 160 mg twice daily), captopril (target dose: 50 mg twice daily), and the combination (target doses: valsartan 80 mg twice daily and captopril 150 mg once daily) in a randomized, double-blind trial of patients with acute MI (0.5-10 days post-MI) complicated by left ventricular systolic dysfunction, heart failure, or both. Enrollment in the study numbered 14,703 patients and followed for a median of 24.7 months. There was no difference in the primary endpoint (all cause mortality) among the 3 groups. There was no difference in incidence of CV death, recurrent MI, or hospitalization for heart failure either. Hypotension and renal dysfunction occurred significantly more often in the valsartan group than captopril alone. Cough, rash, and taste disturbances occurred more often in the captopril group. The authors (Pfeffer MA, 2003) concluded that valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after MI. Combining valsartan with captopril increased the rate of adverse events without improving survival.

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Drug Interactions: Concomitant indomethacin therapy may blunt the reduction in sitting and 24-hour ambulatory diastolic blood pressure. Use of NSAIDs should be avoided or limited, with monitoring of blood pressure control in this setting. In patients with heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

Index TermsCilazapril Monohydrate

References

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, “Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),” *JAMA*, 2002, 288(23):2981-97.[PubMed 12479763]

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International Brand NamesCilaril (IL); Cilazil (HR); Dynorm (DE); Inhibace (AR, AT, AU, BE, BG, CH, CL, CN, CO, CZ, EE, ES, FI, GR, HK, HN, HU, IT, JP, KP, NL, NZ, PE, PK, PL, PT, SE, TW, UY, VE, ZA); Inibace (LU); Inocar (ES); Justor (FR); Vascace (BR, GB, IE, IL, PH)

Cilostazol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Pletal® may be confused with Plendil®

Pronunciation(sil OH sta zol)

U.S. Brand NamesPletal®

Canadian Brand NamesPletal®

Pharmacologic CategoryAntiplatelet Agent; Phosphodiesterase Enzyme Inhibitor

Use: Labeled IndicationsSymptomatic management of peripheral vascular disease, primarily intermittent claudication

Use: Unlabeled/InvestigationalAdjunct with aspirin and clopidogrel for prevention of stent thrombosis and restenosis after coronary stent placement

Dosing: AdultsPeripheral vascular disease: Oral: 100 mg twice daily

Dosage adjustment for cilostazol with concomitant medications:

CYP2C19 inhibitors (see Drug Interactions): Dosage of cilostazol should be reduced to 50 mg twice daily

CYP3A4 inhibitors (see Drug Interactions): Dosage of cilostazol should be reduced to 50 mg twice daily

Dosing: ElderlyRefer to adult dosing.

Administration: OralAdminister cilostazol 30 minutes before or 2 hours after meals.

Dietary ConsiderationsIt is best to take cilostazol 30 minutes before or 2 hours after meals.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to cilostazol or any component of the formulation; heart failure (HF) of any severity; hemostatic disorders or active bleeding

Allergy Considerations

- Cilostazol Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Leukopenia: Discontinue therapy if leukopenia occurs; progression to agranulocytosis (reversible) has been reported when cilostazol was not immediately stopped.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with underlying heart disease.
- Hepatic impairment: Use with caution in patients with moderate-to-severe hepatic impairment.
- Renal impairment: Use with caution in patients with severe renal impairment (Cl_{cr} <25 mL/minute).
- Thrombocytopenia: Discontinue therapy if thrombocytopenia occurs; progression to agranulocytosis (reversible) has been reported when cilostazol was not immediately stopped.

Concurrent drug therapy issues:

- Clopidogrel: When cilostazol and clopidogrel are used concurrently, manufacturer recommends checking bleeding times.
- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.
- Platelet aggregation inhibitors: Use with caution in patients receiving other platelet aggregation inhibitors.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Elective surgery: Withhold for at least 4-6 half-lives prior to elective surgical procedures.

Geriatric ConsiderationsElderly must be evaluated for cardiac status. Since CHF is common, this disease cannot be overlooked.

Pregnancy Risk FactorC

Pregnancy ConsiderationsIn animal studies, abnormalities of the skeletal, renal and cardiovascular system were increased. In addition, the incidence of stillbirth and decreased birth weights were increased.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known whether cilostazol is excreted in human milk. Because of the potential risk to nursing infants, a decision to discontinue the drug or discontinue nursing should be made.

Adverse Reactions

>10%:

Central nervous system: Headache (27% to 34%)

Gastrointestinal: Abnormal stools (12% to 15%), diarrhea (12% to 19%)

Respiratory: Rhinitis (7% to 12%)

Miscellaneous: Infection (10% to 14%)

2% to 10%:

Cardiovascular: Peripheral edema (7% to 9%), palpitation (5% to 10%), tachycardia (4%)

Central nervous system: Dizziness (9% to 10%), vertigo (up to 3%)

Gastrointestinal: Dyspepsia (6%), nausea (6% to 7%), abdominal pain (4% to 5%), flatulence (2% to 3%)

Neuromuscular & skeletal: Back pain (6% to 7%), myalgia (2% to 3%)

Respiratory: Pharyngitis (7% to 10%), cough (3% to 4%)

<2%: Albuminuria, amblyopia, anemia, anorexia, anxiety, arthralgia, asthma, atrial fibrillation, atrial flutter, blindness, bone pain, bursitis, cardiac arrest, cerebral infarction/ischemia, chills, cholelithiasis, colitis, conjunctivitis, CHF, creatinine increased, cystitis, diabetes mellitus, diplopia, dry skin, duodenal ulcer, duodenitis, ear pain, ecchymosis, edema, epistaxis, esophageal hemorrhage, esophagitis, facial edema, fever, gastritis, GGT increased, gout, gum hemorrhage, hematemesis, hemorrhage, hemoptysis, hyperlipidemia, hyperuricemia, hypotension, insomnia, malaise, melena, myocardial infarction/ischemia, neuralgia, nodal arrhythmia, nuchal rigidity, pelvic pain, periodontal abscess, peptic ulcer, pneumonia, polycythemia, postural hypotension, purpura, rectal hemorrhage, retinal hemorrhage, retroperitoneal hemorrhage, sinusitis, supraventricular tachycardia, syncope, tinnitus, tongue edema, urinary frequency, varicose vein, ventricular extrasystole, ventricular tachycardia

Postmarketing and/or case reports: Agranulocytosis, aplastic anemia, blood pressure increased, blood urea increased, cerebrovascular accident, chest pain, coronary stent thrombosis, extradural hematoma, gastrointestinal hemorrhage, granulocytopenia, hepatic dysfunction, hot flashes, hyperglycemia, interstitial pneumonia, intracranial hemorrhage, jaundice, leukopenia, pain, pulmonary hemorrhage, pruritus, QT_c prolongation, subcutaneous hemorrhage, Stevens-Johnson syndrome, subdural hematoma, thrombocytopenia, thrombosis, torsade de pointes, uric acid increased

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2C19 (minor), 2D6 (minor), 3A4 (major)

Drug Interactions

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Cilostazol. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D:*

Consider therapy modification

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Omeprazole: May enhance the adverse/toxic effect of Cilostazol. *Risk D: Consider therapy modification*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Taking cilostazol with a high-fat meal may increase peak concentration by 90%. Avoid concurrent ingestion of grapefruit juice due to the potential to inhibit CYP3A4.

Herb/Nutraceutical: St John's wort may decrease the levels/effects of cilostazol. Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, chamomile, coleus, cordyceps, dong quai, evening primrose oil, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American), ginseng (Panax), ginseng (Siberian), grape seed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationUse exactly as directed; do not discontinue this medication without consulting prescriber. Beneficial effect may take between 2-12 weeks. Take on empty stomach (30 minutes before or 2 hours after meals). Do not take with grapefruit juice. You may experience nervousness, dizziness, or fatigue (use caution when driving or engaging in tasks requiring alertness until response to treatment is known); nausea, vomiting, or flatulence (small frequent meals, frequent mouth care, chewing gum or sucking hard candy may help); or postural hypotension (change position slowly when rising from sitting or lying position or climbing stairs). Report chest pain, palpitations, unusual heartbeat, or swelling of extremities; unusual bleeding; unresolved GI upset or pain; dizziness, nervousness, sleeplessness, or fatigue; muscle cramping or tremor; unusual cough; or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 50 mg, 100 mg

Pletal®: 50 mg, 100 mg

Generic AvailableYes

ManufacturerOtsuka America Pharmaceutical

Pricing: U.S. (www.drugstore.com)

Tablets (Cilostazol)

50 mg (60): $82.00

100 mg (60): $26.99

Tablets (Pletal)

50 mg (60): $133.00

100 mg (60): $112.20

Mechanism of ActionCilostazol and its metabolites are inhibitors of phosphodiesterase III. As a result, cyclic AMP is increased leading to reversible inhibition of platelet aggregation, vasodilation, and inhibition of vascular smooth muscle cell proliferation.

Pharmacodynamics/Kinetics

Onset of action: 2-4 weeks; may require up to 12 weeks

Protein binding: Cilostazol 95% to 98%; active metabolites 66% to 97%

Metabolism: Hepatic via CYP3A4 (primarily), 1A2, 2C19, and 2D6; at least one metabolite has significant activity

Half-life elimination: 11-13 hours

Excretion: Urine (74%) and feces (20%) as metabolites

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusHeadache and dizziness are common; may rarely cause anxiety or insomnia

Mental Health: Effects on Psychiatric TreatmentCYP3A4 inhibitors (fluvoxamine, fluoxetine, nefazodone, sertraline) may increase the concentrations of cilostazol

Cardiovascular Considerations

Because of its chronotropic effects, arrhythmogenic effects, and similarity to other phosphodiesterase III inhibitors, cilostazol is contraindicated in patients with HF of any severity.

Anesthesia and Critical Care Concerns/Other ConsiderationsConsidered effective treatment in patients with lower extremity peripheral arterial disease (PAD) and intermittent claudication (in the absence of heart failure). A therapeutic trial should be considered in all patients with lifestyle-limiting claudication.

Index TermsOPC-13013

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International Brand NamesAggravan (ID); Agrezol (ID); Alista (ID); Artesol (CN); Cebralat C (BR); Ciletin (PH); Cilosol (KP); Cilostal (CR, DO, EC, GT, HN, NI, PA, PE, SV); Cilotal (KP); Citaz (ID); Clazol (PH); Colidac (IN); KBStazole (KP); Naletal (ID); Pletaal (AR, CL, JP, MY, PK, TH); Pletal (DE); Pletoz (IN); Policor (UY); Qital (ID); Rostal (KP); Sadoxol (UY); Stazol (ID, KP); Trastocir (AR)

Cimetidine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cimetidine may be confused with simethicone

Pronunciation(sye MET i deen)

U.S. Brand NamesTagamet® HB 200 [OTC]

Canadian Brand NamesApo-Cimetidine®; Gen-Cimetidine; Novo-Cimetidine; Nu-Cimet; PMS-Cimetidine; Tagamet® HB

Pharmacologic CategoryHistamine H_2 Antagonist

Use: Labeled IndicationsShort-term treatment of active duodenal ulcers and benign gastric ulcers; long-term prophylaxis of duodenal ulcer; gastric hypersecretory states; gastroesophageal reflux; prevention of upper GI bleeding in critically-ill patients; labeled for OTC use for prevention or relief of heartburn, acid indigestion, or sour stomach

Use: Unlabeled/InvestigationalPart of a multidrug regimen for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence

Dosing: Adults

Short-term treatment of active ulcers:

Oral: 300 mg 4 times/day or 800 mg at bedtime or 400 mg twice daily for up to 8 weeks

Note: Higher doses of 1600 mg at bedtime for 4 weeks may be beneficial for a subpopulation of patients with larger duodenal ulcers (>1 cm defined endoscopically) who are also heavy smokers (≥1 pack/day).

I.M., I.V.: 300 mg every 6 hours or 37.5 mg/hour by continuous infusion; I.V. dosage should be adjusted to maintain an intragastric pH ≥5

Prevention of upper GI bleed in critically-ill patients: 50 mg/hour by continuous infusion; I.V. dosage should be adjusted to maintain an intragastric pH ≥5

Note: Reduce dose by 50% if Cl_{cr} <30 mL/minute; treatment >7 days has not been evaluated.

Duodenal ulcer prophylaxis: Oral: 400 mg at bedtime

Gastric hypersecretory conditions: Oral, I.M., I.V.: 300-600 mg every 6 hours; dosage not to exceed 2.4 g/day

Gastroesophageal reflux disease: Oral: 400 mg 4 times/day or 800 mg twice daily for 12 weeks

Peptic ulcer disease eradication of*Helicobacter pylori*(unlabeled use): Oral: 400 mg twice daily; requires combination therapy with antibiotics

Heartburn, acid indigestion, sour stomach (OTC labeling): Oral: 200 mg up to twice daily; may take 30 minutes prior to eating foods or beverages expected to cause heartburn or indigestion

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Oral, I.M., I.V.: 20-40 mg/kg/day in divided doses every 6 hours

Heartburn, acid indigestion, sour stomach (OTC labeling): Children ≥12 years: Oral: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer 50% of normal dose

Cl_{cr} <10 mL/minute: Administer 25% of normal dose

Slightly dialyzable (5% to 20%); administer after dialysis

Dosing: Hepatic ImpairmentUsual dose is safe in mild liver disease but use with caution and in reduced dosage in severe liver disease. Increased risk of CNS toxicity in cirrhosis suggested by enhanced penetration of CNS.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.May be administered as a slow I.V. push or preferably as an I.V. intermittent or I.V. continuous infusion. Administer each 300 mg (or fraction thereof) over a minimum of 5 minutes when giving I.V. push. Rapid intravenous administration has been associated with rare cases of arrhythmia and/or hypotension. Give intermittent infusion over 15-30 minutes for each 300 mg dose. Intermittent infusions are administered over 15-30 minutes at a final concentration not to exceed 6 mg/mL; for patients with an active bleed, preferred method of administration is continuous infusion.

Administration: I.V. DetailRapid infusion may cause cardiac arrhythmias and hypotension.

pH: 3.8-6.0 (injection); 5-7 (premixed infusion)

Administration: OralGive with meals so that the drug's peak effect occurs at the proper time (peak inhibition of gastric acid secretion occurs at 1 and 3 hours after dosing in fasting subjects and approximately 2 hours in nonfasting subjects. This correlates well with the time food is no longer in the stomach offering a buffering effect). Stagger doses of antacids with cimetidine.

Storage

Tablet: Store between 15°C and 30°C (59°F to 86°F); protect from light.

Solution for injection/infusion: Intact vials should be stored at room temperature, between 15°C and 30°C (59°F to 86°F); protect from light. May precipitate from solution upon exposure to cold, but can be redissolved by warming without degradation.

Stability at room temperature:

Prepared bags: 7 days

Premixed bags: Manufacturer expiration dating and out of overwrap stability: 15 days

Stable in parenteral nutrition solutions for up to 7 days when protected from light.

CompatibilityStable in D_5LR, $D_5\,^1/_4$NS, $D_5\,^1/_2$NS, D_5NS, D_5W, D_{10}W, D_{10}NS, LR, sodium bicarbonate 5%, NS; **variable stability (consult detailed reference)** in TPN.

Y-site administration: Compatible: Acyclovir, amifostine, aminophylline, atracurium, aztreonam, cisatracurium, cisplatin, cladribine, clarithromycin, cyclophosphamide, cytarabine, diltiazem, docetaxel, doxorubicin, doxorubicin liposome, enalaprilat, esmolol, etoposide, filgrastim, fluconazole, fludarabine, foscarnet, gatifloxacin, gemcitabine, granisetron, haloperidol, heparin, hetastarch, idarubicin, inamrinone, labetalol, levofloxacin, linezolid, melphalan, meropenem, methotrexate, midazolam, milrinone, ondansetron, paclitaxel, pancuronium, piperacillin/tazobactam, propofol, remifentanil, sargramostim, tacrolimus, teniposide, theophylline, thiotepa, tolazoline, topotecan, vecuronium, vinorelbine, zidovudine. **Incompatible:** Allopurinol, amphotericin B cholesteryl sulfate complex, amsacrine, cefepime, indomethacin, warfarin. **Variable (consult detailed reference):** TPN.

Compatibility in syringe: Compatible: Atropine, butorphanol, diatrizoate meglumine and diatrizoate sodium, diatrizoate sodium, diazepam, diphenhydramine, doxapram, droperidol, fentanyl, glycopyrrolate, heparin, hydromorphone, hydroxyzine, iohexol, iopamidol, iothalamate meglumine, lorazepam, meperidine, midazolam, morphine, nafcillin, nalbuphine, penicillin G sodium, pentazocine, perphenazine, prochlorperazine edisylate, promazine, promethazine, scopolamine, sodium acetate, sodium chloride, sodium lactate. **Incompatible:** Atropine with pentobarbital, cefamandole, cefazolin, chlorpromazine, ioxaglate meglumine and ioxaglate sodium, pentobarbital, secobarbital.

Compatibility when admixed: Compatible: Acetazolamide, amikacin, aminophylline, ampicillin, atracurium, cefoperazone, cefoxitin, ceftazidime, chlorothiazide, clindamycin, colistimethate, cryptenamine, dexamethasone sodium phosphate, digoxin, epinephrine, erythromycin lactobionate, ethacrynate sodium, floxacillin, flumazenil, furosemide, gentamicin, insulin (regular), isoproterenol, lidocaine, lincomycin, meropenem, metaraminol, methylprednisolone sodium succinate, metoclopramide, norepinephrine, penicillin G potassium, phytonadione, polymyxin B sulfate, potassium chloride, protamine, quinidine gluconate, sodium nitroprusside, tacrolimus, vancomycin, verapamil, vitamin B complex, vitamin B complex with C. **Incompatible:** Amphotericin B, barbiturates. **Variable (consult detailed reference):** Cefamandole, cefazolin.

ContraindicationsHypersensitivity to cimetidine, any component of the formulation, or other H_2 antagonists

Allergy Considerations

- Histamine H_2 Antagonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Confusion: Reversible confusional states, usually clearing within 3-4 days after discontinuation, have been linked to use. Increased age (>50 years) and renal or hepatic impairment are thought to be associated.

Disease-related concerns:

- Gastric malignancy: Relief of symptoms does not preclude the presence of a gastric malignancy.
- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment recommended.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Concurrent drug therapy issues:

- Drugs metabolized through P450 system: Dosage should be adjusted in patients receiving drugs metabolized through the P450 system.

Other warnings/precautions:

- I.V. administration: Rapid intravenous administration has been associated with rare cases of arrhythmia and/or hypotension.
- OTC labeling: Should not be taken by individuals experiencing painful swallowing, vomiting with blood, or bloody or black stools; medical attention should be sought. A healthcare provider should be consulted prior to use when pain in the stomach, shoulder, arms or neck is present; if heartburn has occurred for >3 months; or if unexplained weight loss, or nausea and vomiting occur.

Frequent wheezing, shortness of breath, lightheadedness, or sweating, especially with chest pain or heartburn, should also be reported. Consultation of a healthcare provider should occur by patients if also taking theophylline, phenytoin, or warfarin; if heartburn or stomach pain continues or worsens; or if use is required for >14 days. OTC cimetidine is not approved for use in patients <12 years of age.

Geriatric ConsiderationsPatients diagnosed with PUD should be evaluated for *Helicobacter pylori*. H_2 blockers are the preferred drugs for treating PUD in elderly due to cost and ease of administration. These agents are no less or more effective than any other therapy. The preferred agents, due to favorable pharmacokinetic, side effect and drug interaction profiles are ranitidine, famotidine, and nizatidine. Due to the potential for confusion and drug interactions, cimetidine has been identified by a panel of experts as a drug to avoid in the elderly. Consider evaluating creatinine clearance before initiating H_2-blocker therapy.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic events were not observed in animal studies.

LactationEnters breast milk/not recommended

Adverse Reactions

1% to 10%:

Central nervous system: Headache (2% to 4%), dizziness (1%), somnolence (1%), agitation

Endocrine & metabolic: Gynecomastia (<1% to 4%)

Gastrointestinal: Diarrhea (1%)

Frequency not defined:

Cardiovascular: AV block, bradycardia, hypotension, tachycardia, vasculitis

Central nervous system: Confusion, fever

Dermatologic: Alopecia, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, rash

Endocrine & metabolic: Edema of the breasts, sexual ability decreased

Gastrointestinal: Nausea, pancreatitis, vomiting

Hematologic: Agranulocytosis, aplastic anemia, hemolytic anemia (immune-based), neutropenia, pancytopenia, thrombocytopenia

Hepatic: ALT increased, AST increased, hepatic fibrosis (case report)

Neuromuscular & skeletal: Arthralgia, myalgia, polymyositis

Renal: Creatinine increased, interstitial nephritis

Miscellaneous: Anaphylaxis, pneumonia (causal relationship not established)

Metabolism/Transport Effects**Inhibits** CYP1A2 (moderate), 2C9 (weak), 2C19 (moderate), 2D6 (moderate), 2E1 (weak), 3A4 (moderate)

Drug Interactions

Alfentanil: Cimetidine may decrease the metabolism of Alfentanil. *Risk C: Monitor therapy*

Amiodarone: Cimetidine may decrease the metabolism of Amiodarone. Consider using an alternative H_2 antagonist. *Risk D: Consider therapy modification*

Anticonvulsants (Hydantoin): Cimetidine may decrease the metabolism of Anticonvulsants (Hydantoin). **Exceptions:** Ethotoin. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): H2-Antagonists may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole; Voriconazole. *Risk D: Consider therapy modification*

Atazanavir: H2-Antagonists may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Cimetidine may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers: Cimetidine may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** AmLODIPine; Clevidipine; NiCARdipine. *Risk D: Consider therapy modification*

CarBAMazepine: Cimetidine may increase the serum concentration of CarBAMazepine. The serum carbamazepine concentration might return to normal within one week of starting cimetidine. *Risk C: Monitor therapy*

Carmustine: Cimetidine may decrease the metabolism of Carmustine. *Risk C: Monitor therapy*

Carvedilol: Cimetidine may decrease the metabolism of Carvedilol. *Risk C: Monitor therapy*

Cefpodoxime: H2-Antagonists may decrease the absorption of Cefpodoxime. Separate oral doses by at least 2 hours. *Risk C: Monitor therapy*

Cefuroxime: H2-Antagonists may decrease the absorption of Cefuroxime. Separate oral doses by at least 2 hours. *Risk C: Monitor therapy*

Cisapride: Cimetidine may decrease the metabolism of Cisapride. *Risk D: Consider therapy modification*

Clozapine: Cimetidine may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dasatinib: H2-Antagonists may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Dofetilide: Cimetidine may decrease the excretion of Dofetilide. Cimetidine may decrease the metabolism of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

Erlotinib: H2-Antagonists may decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fosamprenavir: H2-Antagonists may decrease the serum concentration of Fosamprenavir. Cimetidine may also inhibit the metabolism of the active metabolite amprenavir, making its effects on fosamprenavir/amprenavir concentrations difficult to predict. *Risk C: Monitor therapy*

Iron Salts: H2-Antagonists may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

MetFORMIN: Cimetidine may decrease the excretion of MetFORMIN. *Risk C: Monitor therapy*

Moclobemide: Cimetidine may decrease the metabolism of Moclobemide. *Risk D: Consider therapy modification*

Moricizine: Cimetidine may decrease the metabolism of Moricizine. *Risk D: Consider therapy modification*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nicotine: Cimetidine may decrease the metabolism of Nicotine. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Praziquantel: Cimetidine may decrease the metabolism of Praziquantel. *Risk C: Monitor therapy*

Procainamide: Cimetidine may decrease the excretion of Procainamide. *Risk D: Consider therapy modification*

Propafenone: Cimetidine may increase the serum concentration of Propafenone. *Risk D: Consider therapy modification*

QuiNIDine: Cimetidine may decrease the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Saquinavir: H2-Antagonists may increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Cimetidine may decrease the metabolism of Selective Serotonin Reuptake Inhibitors. *Risk D: Consider therapy modification*

Sulfonylureas: Cimetidine may decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Theophylline Derivatives: Cimetidine may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Cimetidine may decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Cimetidine may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Zaleplon: Cimetidine may decrease the metabolism of Zaleplon. *Risk D: Consider therapy modification*

Zolmitriptan: Cimetidine may increase the serum concentration of Zolmitriptan. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Cimetidine may increase serum caffeine levels if taken with caffeine. Cimetidine peak serum levels may be decreased if taken with food.

Herb/Nutraceutical: St John's wort may decrease cimetidine levels.

Monitoring ParametersCBC, gastric pH, occult blood with GI bleeding; monitor renal function to correct dose.

Nursing: Physical Assessment/MonitoringUse caution in presence of renal or hepatic impairment. Assess other pharmacological or herbal products patient may be taking for potential interactions. **I.V.:** Note administration specifics. Assess results of laboratory tests, therapeutic effectiveness (according to purpose for use), and adverse effects (eg, changes in CNS, agitation; gastric bleeding) regularly during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC, gastric pH, occult blood with GI bleeding; monitor renal function to correct dose.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take with meals. Do not increase dose or frequency without consulting prescriber. To be effective, continue to take for the prescribed time (possibly several weeks) even though symptoms may have improved. Smoking decreases the effectiveness of cimetidine (stop smoking if possible). Avoid excess alcohol and caffeine. May cause headache, dizziness, agitation (use caution when driving or engaging in any potentially hazardous tasks until response to drug is known); nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report chest pain or palpitations; CNS changes (confusion, agitation); persistent diarrhea, nausea, vomiting, or heartburn; black tarry stools or coffee ground-like emesis; rash; unusual bleeding or bruising; sore throat; or fever; unexplained weight lose or other adverse effects.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: Strength is expressed as base

Infusion [premixed in NS]: 300 mg (50 mL)

Injection, solution: 150 mg/mL (2 mL, 8 mL)

Solution, oral: 300 mg/5 mL (240 mL, 480 mL)

Tablet: 200 mg [OTC], 300 mg, 400 mg, 800 mg

Tagamet® HB 200: 200 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Cimetidine HCl)

300 mg/5 mL (237): $35.55

Tablets (Cimetidine)

200 mg (30): $19.99

300 mg (180): $29.00

400 mg (90): $25.49

800 mg (30): $17.99

Tablets (Tagamet)

300 mg (60): $71.80

400 mg (60): $114.89

Mechanism of ActionCompetitive inhibition of histamine at H_2 receptors of the gastric parietal cells resulting in reduced gastric acid secretion, gastric volume and hydrogen ion concentration reduced

Pharmacodynamics/Kinetics

Onset of action: 1 hour

Duration: 4-8 hours

Absorption: Rapid

Distribution: Crosses placenta; enters breast milk

Protein binding: 20%

Metabolism: Partially hepatic, forms metabolites

Bioavailability: 60% to 70%

Half-life elimination: Neonates: 3.6 hours; Children: 1.4 hours; Adults: Normal renal function: 2 hours

Time to peak, serum: Oral: 1-2 hours

Excretion: Primarily urine (48% as unchanged drug); feces (some)

Related Information

- Antacid Drug Interactions
- Depression

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause agitation or drowsiness; rare reports of confusion

Mental Health: Effects on Psychiatric TreatmentRare reports of agranulocytosis; use caution with clozapine and carbamazepine; may inhibit the metabolism of TCAs and benzodiazepines; monitor for adverse effects

Cardiovascular ConsiderationsCimetidine has extensive drug interactions, particularly with antiarrhythmics (lidocaine, phenytoin, procainamide, quinidine) and may also increase the likelihood of theophylline and cyclosporine toxicity. Because of inhibition of warfarin metabolism, cimetidine may increase INR in patients on anticoagulation therapy.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2008 Surviving Sepsis Campaign guidelines recommend that stress ulcer prophylaxis using an H_2 blocker (Grade 1A) or proton pump inhibitor (Grade 1B) be given to patients with severe sepsis to prevent upper GI bleed. Benefit of prevention of upper GI bleed must be weighed against potential effect of increased stomach pH on development of ventilator-associated pneumonia.

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International Brand NamesAci-Med (ZA); Acidnor (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Aciloc (DK, FI); Acinil (DK, SE); Ali Veg (ES); Altramet (HR, PL); Apo-Cimetidine (NZ, PL); Azucimet (DE); Belomet (HR, PL); Benomet (ID); Biomag (IT); Brumetidina (IT); Campanex (GR); Cemedin 200 (IL); Cemedin 400 (IL); Cemedin 800 (IL); Cementin (SG); Ciclem (PH); Cidine (TH); Cigamet (TH); Cimbene (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Cimebeta (AU); Cimedine (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Cimegast (PL); Cimehexal (DE, HU, LU); Cimeldine (HU); Cimet (TH); Cimetag (AT); Cimetalgin (AT); Cimetase (MX); Cimetid (NO); Cimetidin (BG, CH, DE); Cimetidin AL (HU); Cimetidina (CN, PY); Cimetidina Inexfa (ES); Cimetidina Merck (ES); Cimetidine (CZ, NL, PL); Cimetidinum (PL); Cimetin (CZ, EC, IN); Cimewell (TW); Cimex (FI); Cimexol (ID); CimLich (LU); Cimulcer (MY, TH); Cinadine (ZA); Cinamet (PL); Cinulcus (ES); Cismetin (KP); Citidine (HK, SG); Citius (AE, BH, CY, EG, ES, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Corsamet (ID); Cytine (NZ); Defense (TW); Dispamet (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Duogastril (ES); Duomet (NZ); Dyspamet (GB); Fremet (ES); Gadol (VE); Gastidine (HK); Gastro H2 (ES); Gastroprotect (DE); Gawei (TW); Geramet (IE); Gerucim (HR); Getidin (PH); H-2 (KP); H2 Blocker-ratiopharm (LU); Haldin (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Hexamet (ZA); Himentin (SG); Histodil (HN, HU, PL); Histodil[inj.] (HU); Lenamet (ZA); Lenamet OTC (ZA); Licomet (ID); Lock 2 (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Magicul (AU); Manomet (TH); Mansal (ES); Maritidine (HK); Meticon (KP); Montidin (PH); Neutronorm (AT); Nuardin (BE, LU); Nulcer (ID); Piovalen (GR); Powegon (TW); Promet (TH); Sanmetidin (ID); Secapine (ZA); Sertidine (TH); Shintamet (MY); Siamidine (TH); Simaglen (HK); Stogamet (TW); Stomakon (BR); Stomedine (FR); Stomet (IT); Tagamet (AE, AR, AU, BB, BF, BH, BJ, BM, BR, BS, BZ, CI, CL, CY, DE, EG, ES, ET, FR, GB, GH, GM, GN, GR, GY, HK, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, OM, PH, PK, PL, PT, QA, SA, SC, SD, SE, SL, SN, SR, SY, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Tedigaster (ES); Thrumetin (KP); Timet (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Tobymet (ID); Ulcedin (IT); Ulcedine (TH); Ulcenon (PH); Ulcerfen (AR); Ulcidine (MY); Ulcim (ZA); Ulcimet (EC, ID, PE, UY); Ulcolind H2 (DE); Ulcomedina (IT); Ulcomet (EE, HK); Ulcumet (ID); Ulsikur (ID); Weisdin (TW); Xepamet (MY)

Cinacalcet

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(sin a KAL cet)

U.S. Brand NamesSensipar®

Canadian Brand NamesSensipar®

Pharmacologic CategoryCalcimimetic

Use: Labeled IndicationsTreatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD) on dialysis; treatment of hypercalcemia in patients with parathyroid carcinoma

Note: In Canada, cinacalcet is approved only for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD) on dialysis

Use: Unlabeled/InvestigationalPrimary hyperparathyroidism

Dosing: Adults**Note:** Do not titrate dose more frequently than every 2-4 weeks.

Secondary hyperparathyroidism: Oral: Initial: 30 mg once daily (maximum daily dose: 180 mg); increase dose incrementally (60 mg, 90 mg, 120 mg, 180 mg once daily) as necessary to maintain iPTH level between 150-300 pg/mL.

Parathyroid carcinoma: Oral: Initial: 30 mg twice daily (maximum daily dose: 360 mg daily as 90 mg 4 times/day); increase dose incrementally (60 mg twice daily, 90 mg twice daily, 90 mg 3-4 times/day) as necessary to normalize serum calcium levels.

Dosing: ElderlyRefer to adult dosing. No adjustment required.

Dosing: Renal ImpairmentNo adjustment required.

Dosing: Hepatic ImpairmentPatients with moderate-to-severe dysfunction (Child-Pugh classes B and C) have an increased exposure to cinacalcet and increased half-life.

Dosing: Adjustment for Toxicity**Dosage adjustment for hypocalcemia:**

If serum calcium >7.5 mg/dL but <8.4 mg/dL **or** if hypocalcemia symptoms occur: Use calcium-containing phosphate binders and/or vitamin D to raise calcium levels.

If serum calcium <7.5 mg/dL **or** if hypocalcemia symptoms persist and the dose of vitamin D cannot be increased: Withhold cinacalcet until serum calcium ≥8 mg/dL and/or symptoms of hypocalcemia resolve. Reinitiate cinacalcet at the next lowest dose.

If iPTH <150-300 pg/mL: Reduce dose or discontinue cinacalcet and/or vitamin D.

Calculations

- Calcium Correction

Administration: OralAdminister with food or shortly after a meal. Do not break tablet; should be taken whole.

Dietary ConsiderationsTake with food or shortly after a meal. May be taken with vitamin D and/or phosphate binders.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to cinacalcet or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Adynamic bone disease: May develop if iPTH levels are suppressed (<100 pg/mL); reduce dose or discontinue use of cinacalcet and/or vitamin D if iPTH levels decrease below 150-300 pg/mL (NKF-K/DOQI guidelines).
- Hypocalcemia: If hypocalcemia develops or symptoms of hypocalcemia (eg, cramps, myalgia, paresthesia, seizure, tetany) occur during treatment, consider initiating supplemental calcium, calcium-based phosphate binder, or vitamin D or temporarily withholding cinacalcet. Serum calcium levels should be ≥8.4 mg/dL prior to initiating treatment. Dosage reductions may be necessary upon reinitiation of cinacalcet treatment.
- Testosterone level reductions: Cinacalcet may cause a decrease in testosterone levels (free and total). Although below normal testosterone levels may occur in patients with end-stage renal disease, the clinical significance has not been determined.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; idiosyncratic hypotension and/or worsening of heart failure have been reported in patients with impaired cardiovascular function.
- Hepatic impairment: Use with caution in patients with moderate-to-severe hepatic impairment (Child-Pugh classes B & C); cinacalcet exposure and half-life are increased; monitor closely.
- Renal impairment: In the U.S., the long-term safety and efficacy of cinacalcet has not been evaluated in chronic kidney disease (CKD) patients with hyperparathyroidism not requiring dialysis. Not indicated for CKD patients not receiving dialysis. Although possibly related to lower baseline calcium levels, clinical studies have shown an increased incidence of hypocalcemia (<8.4 mg/dL) in patients not requiring dialysis.

- Seizure disorder: Use with caution in patients with a history of seizure disorder; seizure threshold is lowered by significant serum calcium reductions. Monitor calcium levels closely.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsIn animal studies, there were no teratogenic effects seen. There are no adequate or well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse effects in the nursing infant, the manufacturer recommends discontinuing nursing or discontinuing cinacalcet.

Adverse Reactions

>10%:

Endocrine & metabolic: Hypocalcemia

Gastrointestinal: Nausea (31%), vomiting (27%), diarrhea (21%)

Neuromuscular & skeletal: Myalgia (15%)

1% to 10%:

Cardiovascular: Hypertension (7%)

Central nervous system: Dizziness (10%), seizure (1%)

Endocrine & metabolic: Testosterone decreased

Gastrointestinal: Anorexia (6%)

Neuromuscular & skeletal: Weakness (7%), chest pain (noncardiac; 6%)

Postmarketing and/or case reports: Adynamic bone disease, heart failure (worsening; in patients with cardiac dysfunction), hypersensitivity reactions, hypotension (idiosyncratic; in patients with cardiac dysfunction), rash

Metabolism/Transport Effects**Substrate** of CYP1A2, 2D6, 3A4; **Inhibits** CYP2D6 (major)

Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Cinacalcet. **Exceptions:** Itraconazole. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Strong) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Tacrolimus: Cinacalcet may decrease the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Strong) may decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

Tetrabenazine: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Tetrabenazine. Specifically, concentrations of the active alpha- and beta-dihydrotetrabenazine metabolites may be increased. Management: Tetrabenazine dose should be reduced by 50% when starting a strong CYP2D6 inhibitor. Maximum tetrabenazine dose is 50mg/day when used with a strong CYP2D6 inhibitor. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Cinacalcet may increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Food increases bioavailability.

Monitoring Parameters

Hyperparathyroidism: Serum calcium and phosphorus levels prior to initiation and within a week of initiation or dosage adjustment; iPTH should be measured 1-4 weeks after initiation or dosage adjustment. After the maintenance dose is established, monthly calcium and phosphorus levels and iPTH every 1-3 months are required. Wait at least 12 hours after dose before drawing PTH levels.

Parathyroid carcinoma: Serum calcium levels prior to initiation and within a week of initiation or dosage adjustment; once maintenance dose is established, obtain serum calcium level every 2 months.

Reference Range

CKD K/DOQI guidelines definition of stages; chronic disease is kidney damage or GFR <60 mL/minute/1.73 m^2 for ≥3 months:

Stage 2: GFR 60-89 mL/minute/1.73 m^2 (kidney damage with mild decrease GFR)

Stage 3: GFR 30-59 mL/minute/1.73 m^2 (moderate decrease GFR)

Stage 4: GFR 15-29 mL/minute/1.73 m^2 (severe decrease GFR)

Stage 5: GFR <15 mL/minute/1.73 m^2 or dialysis (kidney failure)

Target range for iPTH: Adults:

Stage 3 CKD: 35-70 pg/mL

Stage 4 CKD: 70-110 pg/mL

Stage 5 CKD: 150-300 pg/mL

Serum phosphorus: Adults:

Stage 3 and 4 CKD: ≥2.7 to <4.6 mg/dL

Stage 5 CKD: 3.5-5.5 mg/dL

Serum calcium-phosphorus product: Adults: Stage 3-5 CKD: <55 mg^2/dL^2

Nursing: Physical Assessment/MonitoringUse caution with history of seizure disorder; assess serum calcium levels closely prior to initiating therapy or dose change and regularly during maintenance therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions. Assess results of laboratory tests, therapeutic response (calcium levels), and adverse reactions (eg, hypocalcemia [paresthesias, myalgia, cramping, tetany, convulsions]) frequently at beginning of therapy and regularly thereafter. Teach patient possible side effects, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab Tests

Hyperparathyroidism: Serum calcium and phosphorus levels prior to initiation and within a week of initiation or dosage adjustment; iPTH should be measured 1-4 weeks after initiation or dosage adjustment. After the maintenance dose is established, monthly calcium and phosphorus levels and iPTH every 1-3 months are required. Wait at least 12 hours after dose before drawing PTH levels.

Parathyroid carcinoma: Serum calcium levels prior to initiation and within a week of initiation or dosage adjustment; once maintenance dose is established, obtain serum calcium level every 2 months.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed with food; do not break, chew, or crush tablet (swallow whole). Do not take more than prescribed. You may experience dizziness (use caution when driving or engaged in potentially hazards tasks until response to drug is known); nausea, vomiting, or loss of appetite (good mouth care, small frequent meals, sucking lozenges, or chewing gum may help); diarrhea (yogurt or boiled milk may help). Report any muscle cramping, twitches, tremors, or spasms; chest pain or palpitations; unresolved gastrointestinal disturbance, or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Sensipar®: 30 mg, 60 mg, 90 mg

Generic AvailableNo

ManufacturerAmgen

Pricing: U.S. (www.drugstore.com)

Tablets (Sensipar)

30 mg (30): $374.09

60 mg (30): $754.55

90 mg (30): $1038.51

Mechanism of ActionIncreases the sensitivity of the calcium-sensing receptor on the parathyroid gland thereby, concomitantly lowering PTH and serum calcium levels.

Pharmacodynamics/Kinetics

Distribution: V_d: ~1000 L

Protein binding: ~93% to 97%

Metabolism: Hepatic (extensive) via CYP3A4, 2D6, 1A2; forms inactive metabolites

Half-life elimination: Terminal: 30-40 hours; moderate hepatic impairment: prolonged 33%; severe hepatic impairment: prolonged 70%

Time to peak, plasma: Nadir in iPTH levels: 2-6 hours postdose

Excretion: Urine 80% (as metabolites); feces 15%

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDizziness is common
Mental Health: Effects on Psychiatric TreatmentGastrointestinal side effects are common; these effects may be additive with concurrent use of SSRIs, lithium, or valproate. Cinacalcet may increase levels of amitriptyline and nortriptyline; monitor for increased effects and/or serum levels.
Index TermsAMG 073; Cinacalcet Hydrochloride
References

Eknoyan G, Levin A, and Levin NW, “Bone Metabolism and Disease in Chronic Kidney Disease,” *Am J Kidney Dis*, 2003, 42(4 Suppl 3):1-201.

National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Guideline 13: Treatment of Bone Disease in Chronic Kidney Disease. Available at: www.kidney.org/professionals/kdoqi/guidelines_bone/index.htm. Accessed March 18, 2004.

International Brand NamesMimpara (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Parareg (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Sensipar (AU, IL, NZ)

Ciprofloxacin and Dexamethasone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(sip roe FLOKS a sin & deks a METH a sone)

U.S. Brand NamesCiprodex®

Canadian Brand NamesCiprodex®

Pharmacologic CategoryAntibiotic/Corticosteroid, Otic

Use: Labeled IndicationsTreatment of acute otitis media in pediatric patients with tympanostomy tubes or acute otitis externa in children and adults

Dosing: AdultsAcute otitis externa: Otic: Instill 4 drops into affected ear(s) twice daily for 7 days

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAcute otitis media in patients with tympanostomy tubes or acute otitis externa: Otic: Instill 4 drops into affected ear(s) twice daily for 7 days

Administration: OtherOtic: Prior to instillation, bottle should be warmed in hands for 1-2 minutes. Shake suspension well immediately before using. Patient should lie with affected ear upward and remain in this position for 60 seconds following application. Drops should be instilled directly into tympanostomy tube (if present) and tragus should be pumped 5 times to facilitate penetration into the middle ear.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F); do not freeze. Protect from light.

ContraindicationsHypersensitivity to ciprofloxacin, other quinolones, dexamethasone, or any component of the formulation; not for use in viral infection of the external canal

Allergy Considerations

- Corticosteroid Allergy
- Fluoroquinolone Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Special populations:

- Pediatrics: Safety and efficacy have been established in children ≥6 months of age, however, the manufacturer states that there are no safety concerns which would preclude the use of this product in younger children.

Other warnings/precautions:

- Appropriate use: For otic use only; not intended for injection or ophthalmic use. Prior to instillation, suspension should be warmed in hands to prevent dizziness which may occur following use of a cold solution.

Pregnancy Risk FactorC

Pregnancy ConsiderationsRefer to individual agents. Reproduction studies have not been conducted with the otic preparation. Ciprofloxacin is detectable in the serum following otic administration.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if serum levels of ciprofloxacin or dexamethasone are high enough following otic administration to produce detectable quantities in breast milk.

Adverse Reactions

1% to 10%: Otic: Discomfort (3%), pain (<1% to 2%), pruritus (1%)

<1%: Hearing decreased, ear congestion, ear erythema, ear residue, ear tingling, irritability, taste perversion

Metabolism/Transport Effects

Ciprofloxacin: **Inhibits** CYP1A2 (strong), 3A4 (weak)

Dexamethasone: **Substrate** of CYP3A4 (minor); **Induces** CYP2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. **Exceptions:** Sodium

Bicarbonate. *Risk D: Consider therapy modification*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Caffeine: Quinolone Antibiotics may decrease the metabolism of Caffeine. *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Calcium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Calcium Chloride. *Risk D: Consider therapy modification*

Caspofungin: Inducers of Drug Clearance may decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) when coadministered with known inducers of drug clearance. *Risk D: Consider therapy modification*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Quinolone Antibiotics may enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Strong) may decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Didanosine: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents (excludes enteric coated formulation of didanosine). *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Insulin: May enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Lenalidomide: Dexamethasone may enhance the thrombogenic effect of Lenalidomide. *Risk D: Consider therapy modification*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market];

Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methotrexate: Ciprofloxacin may increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

Mycophenolate: Quinolone Antibiotics may decrease the serum concentration of Mycophenolate. Specifically, quinolones may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nisoldipine. *Risk X: Avoid combination*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Pentoxifylline: Ciprofloxacin may enhance the adverse/toxic effect of Pentoxifylline. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Ciprofloxacin may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Probenecid: May increase the serum concentration of Quinolone Antibiotics. *Risk C: Monitor therapy*

QTc-Prolonging Agents: Ciprofloxacin may enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Quinapril: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Ropinirole: Ciprofloxacin may decrease the metabolism of Ropinirole. *Risk C: Monitor therapy*

Ropivacaine: Ciprofloxacin may decrease the metabolism of Ropivacaine. *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Sevelamer: May decrease the absorption of Quinolone Antibiotics. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sulfonylureas: Quinolone Antibiotics may enhance the hyperglycemic effect of Sulfonylureas. Quinolone Antibiotics may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Thalidomide: Dexamethasone may enhance the dermatologic adverse effect of Thalidomide. Dexamethasone may enhance the thrombogenic effect of Thalidomide. *Risk D: Consider therapy modification*

Theophylline Derivatives: Quinolone Antibiotics may decrease the metabolism of Theophylline Derivatives. Ciprofloxacin and enoxacin are of greatest concern. Theophylline/quinolone therapy might augment the seizure-producing potential of each of the individual agents. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

TiZANidine: Ciprofloxacin may decrease the metabolism of TiZANidine. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Quinolone Antibiotics may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Zinc Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, otic: Ciprofloxacin 0.3% and dexamethasone 0.1% (7.5 mL) [contains benzalkonium chloride]

Generic AvailableNo
ManufacturerAlcon, Inc
Pricing: U.S. (www.drugstore.com)

Suspension (Ciprodex)

0.3-0.1% (7.5): $102.06

Mechanism of ActionCiprofloxacin is a quinolone antibiotic; dexamethasone is a corticosteroid used to decrease inflammation accompanying bacterial infections
Pharmacodynamics/Kinetics

Absorption: Otic: Ciprofloxacin: Minor systemic absorption

Time to peak, plasma: Otic: Ciprofloxacin: 15 minutes to 2 hours

Related Information

- Ciprofloxacin
- Dexamethasone

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsCiprofloxacin Hydrochloride and Dexamethasone; Dexamethasone and Ciprofloxacin
International Brand NamesCilodex (CR, GT, HN, IL, MX, NI, PA, SG, SV)

Ciprofloxacin and Hydrocortisone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(sip roe FLOKS a sin & hye droe KOR ti sone)

U.S. Brand NamesCipro® HC

Canadian Brand NamesCipro® HC

Pharmacologic CategoryAntibiotic/Corticosteroid, Otic

Use: Labeled IndicationsTreatment of acute otitis externa, sometimes known as “swimmer's ear”

Dosing: AdultsOtitis externa: Otic: The recommended dosage for all patients is three drops of the suspension in the affected ear twice daily for 7 days; twice-daily dosing schedule is more convenient for patients than that of existing treatments with hydrocortisone, which are typically administered three or four times a day; a twice-daily dosage schedule may be especially helpful for parents and caregivers of young children

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥1 year: Refer to adult dosing.

Allergy Considerations

- Corticosteroid Allergy
- Fluoroquinolone Allergy

Metabolism/Transport Effects

Ciprofloxacin: **Inhibits** CYP1A2 (strong), 3A4 (weak)

Hydrocortisone: **Substrate** of CYP3A4 (minor); **Induces** CYP3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. **Exceptions:** Sodium Bicarbonate. *Risk D: Consider therapy modification*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Caffeine: Quinolone Antibiotics may decrease the metabolism of Caffeine. *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Calcium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Calcium Chloride. *Risk D: Consider therapy modification*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Quinolone Antibiotics may enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Strong) may decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Didanosine: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents (excludes enteric coated formulation of didanosine). *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Insulin: May enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methotrexate: Ciprofloxacin may increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

Mycophenolate: Quinolone Antibiotics may decrease the serum concentration of Mycophenolate. Specifically, quinolones may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Pentoxifylline: Ciprofloxacin may enhance the adverse/toxic effect of Pentoxifylline. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Ciprofloxacin may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Probenecid: May increase the serum concentration of Quinolone Antibiotics. *Risk C: Monitor therapy*

QTc-Prolonging Agents: Ciprofloxacin may enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Quinapril: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Ropinirole: Ciprofloxacin may decrease the metabolism of Ropinirole. *Risk C: Monitor therapy*

Ropivacaine: Ciprofloxacin may decrease the metabolism of Ropivacaine. *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Sevelamer: May decrease the absorption of Quinolone Antibiotics. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider*

therapy modification

Sulfonylureas: Quinolone Antibiotics may enhance the hyperglycemic effect of Sulfonylureas. Quinolone Antibiotics may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Theophylline Derivatives: Quinolone Antibiotics may decrease the metabolism of Theophylline Derivatives. Ciprofloxacin and enoxacin are of greatest concern. Theophylline/quinolone therapy might augment the seizure-producing potential of each of the individual agents. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

TiZANidine: Ciprofloxacin may decrease the metabolism of TiZANidine. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Quinolone Antibiotics may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Zinc Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, otic: Ciprofloxacin hydrochloride 0.2% and hydrocortisone 1% (10 mL) [contains benzyl alcohol]

Generic AvailableNo
ManufacturerBayer Corp (Biological and Pharmaceutical Division)
Pricing: U.S. (www.drugstore.com)

Suspension (Cipro HC)

0.2-1% (10): $99.99

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Ciprofloxacin
- Hydrocortisone

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsCiprofloxacin Hydrochloride and Hydrocortisone; Hydrocortisone and Ciprofloxacin
International Brand NamesCiflox (DK); Cipro HC (BR); Cipro HC Otic (HK); Cipro HC Otico (AR); Ciprobay HC (EE, KP, SG, ZA); Ciproxin HC (CH); Ciproxin HC ear drops (AU); Ciproxin HC Otic Drops (NZ); Ciriax Otic (PE); Oto Eni (MX); Otosec HC (CO)

Ciprofloxacin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Ciprofloxacin may be confused with cephalexin

Ciloxan® may be confused with cinoxacin, Cytoxan®

Cipro® may be confused with Ceftin®

Pronunciation(sip roe FLOKS a sin)

U.S. Brand NamesCiloxan®; Cipro®; Cipro® XR; Proquin® XR

Canadian Brand NamesApo-Ciproflox®; Ciloxan®; Cipro®; Cipro® XL; CO Ciprofloxacin; Dom-Ciprofloxacin; Gen-Ciprofloxacin; Novo-Ciprofloxacin; PHL-Ciprofloxacin; PMS-Ciprofloxacin; RAN™-Ciprofloxacin; ratio-Ciprofloxacin; Riva-Ciprofloxacin; Sandoz-Ciprofloxacin; Taro-Ciprofloxacin

Pharmacologic CategoryAntibiotic, Ophthalmic; Antibiotic, Quinolone

Use: Labeled Indications

Children: Complicated urinary tract infections and pyelonephritis due to *E. coli*. **Note:** Although effective, ciprofloxacin is not the drug of first choice in children.

Children and Adults: To reduce incidence or progression of disease following exposure to aerolized *Bacillus anthracis*. Ophthalmologically, for superficial ocular infections (corneal ulcers, conjunctivitis) due to susceptible strains

Adults: Treatment of the following infections when caused by susceptible bacteria: Urinary tract infections; acute uncomplicated cystitis in females; chronic bacterial prostatitis; lower respiratory tract infections (including acute exacerbations of chronic bronchitis); acute sinusitis; skin and skin structure infections; bone and joint infections; complicated intra-abdominal infections (in combination with metronidazole); infectious diarrhea; typhoid fever due to *Salmonella typhi* (eradication of chronic typhoid carrier state has not been proven); uncomplicated cervical and urethra gonorrhea (due to *N. gonorrhoeae*); nosocomial pneumonia; empirical therapy for febrile neutropenic patients (in combination with piperacillin)

Note: As of April 2007, the CDC no longer recommends the use of fluoroquinolones for the treatment of gonococcal disease.

Use: Unlabeled/InvestigationalAcute pulmonary exacerbations in cystic fibrosis (children); cutaneous/gastrointestinal/oropharyngeal anthrax (treatment, children and adults); disseminated gonococcal infection (adults); chancroid (adults); prophylaxis to *Neisseria meningitidis* following close contact with an infected person; empirical therapy (oral) for febrile neutropenia in low-risk cancer patients; HACEK group endocarditis; infectious diarrhea (children)

Use: DentalUseful as a single agent or in combination with metronidazole in the treatment of periodontitis associated with the presence of *Actinobacillus actinomycetemcomitans* (AA), as well as enteric rods/pseudomonads

Dosing: Adults**Note:** Extended release tablets and immediate release formulations are not interchangeable. Unless otherwise specified, oral dosing reflects the use of immediate release formulations.

Anthrax:

Inhalational (postexposure prophylaxis):

Oral: 500 mg every 12 hours for 60 days

I.V.: 400 mg every 12 hours for 60 days

Cutaneous (treatment, CDC guidelines): Oral: Immediate release formulation: 500 mg every 12 hours for 60 days. **Note:** In the presence of systemic involvement, extensive edema, lesions on head/neck, refer to I.V. dosing for treatment of inhalational/gastrointestinal/oropharyngeal anthrax.

Inhalational/gastrointestinal/oropharyngeal (treatment, CDC guidelines): I.V.: 400 mg every 12 hours. **Note:** Initial treatment should include two or more agents predicted to be effective (per CDC recommendations). Continue combined therapy for 60 days.

Bacterial conjunctivitis:

Ophthalmic solution: Instill 1-2 drops in eye(s) every 2 hours while awake for 2 days and 1-2 drops every 4 hours while awake for the next 5 days

Ophthalmic ointment: Apply a $^{1}/_{2}$" ribbon into the conjunctival sac 3 times/day for the first 2 days, followed by a $^{1}/_{2}$" ribbon applied twice daily for the next 5 days

Bone/joint infections:

Oral: 500-750 mg twice daily for 4-6 weeks

I.V.:

Mild/moderate: 400 mg every 12 hours for 4-6 weeks

Severe/complicated: 400 mg every 8 hours for 4-6 weeks

Chancroid (CDC guidelines): Oral: 500 mg twice daily for 3 days

Corneal ulcer: Ophthalmic solution: Instill 2 drops into affected eye every 15 minutes for the first 6 hours, then 2 drops into the affected eye every 30 minutes for the remainder of the first day. On day 2, instill 2 drops into the affected eye hourly. On days 3-14, instill 2 drops into affected eye every 4 hours. Treatment may continue after day 14 if re-epithelialization has not occurred.

Endocarditis due to HACEK organisms (AHA guidelines, unlabeled use):Note: Not first-line option; use only if intolerant of beta-lactam therapy:

Oral: 500 mg every 12 hours for 4 weeks

I.V.: 400 mg every 12 hours for 4 weeks

Febrile neutropenia*: I.V.: 400 mg every 8 hours for 7-14 days

Gonococcal infections:

Urethral/cervical gonococcal infections: Oral: 250-500 mg as a single dose (CDC recommends concomitant doxycycline or azithromycin due to possible coinfection with *Chlamydia*; **Note:** As of April 2007, the CDC no longer recommends the use of fluoroquinolones for the treatment of uncomplicated gonococcal disease.

Disseminated gonococcal infection (CDC guidelines): Oral: 500 mg twice daily to complete 7 days of therapy (initial treatment with ceftriaxone 1 g I.M./I.V. daily for 24-48 hours after improvement begins); **Note:** As of April 2007, the CDC no longer recommends the use of fluoroquinolones for the treatment of more serious gonococcal disease, unless no other options exist and susceptibility can be confirmed via culture.

Infectious diarrhea: Oral:

Salmonella: 500 mg twice daily for 5-7 days

Shigella: 500 mg twice daily for 3 days

Traveler's diarrhea: Mild: 750 mg for one dose; Severe: 500 mg twice daily for 3 days

Vibrio cholerae: 1 g for one dose

Intra-abdominal*:

Oral: 500 mg every 12 hours for 7-14 days

I.V.: 400 mg every 12 hours for 7-14 days

Lower respiratory tract, skin/skin structure infections:

Oral: 500-750 mg twice daily for 7-14 days

I.V.:

Mild/moderate: 400 mg every 12 hours for 7-14 days

Severe/complicated: 400 mg every 8 hours for 7-14 days

Nosocomial pneumonia: I.V.: 400 mg every 8 hours for 10-14 days

Prostatitis (chronic, bacterial): Oral: 500 mg every 12 hours for 28 days

Sinusitis (acute): Oral: 500 mg every 12 hours for 10 days

Typhoid fever: Oral: 500 mg every 12 hours for 10 days

Urinary tract infection:

Acute uncomplicated, cystitis:

Oral:

Immediate release formulation: 250 mg every 12 hours for 3 days

Extended release formulation (Cipro® XR, Proquin® XR): 500 mg every 24 hours for 3 days

I.V.: 200 mg every 12 hours for 7-14 days

Complicated (including pyelonephritis):

Oral:

Immediate release formulation: 500 mg every 12 hours for 7-14 days

Extended release formulation (Cipro® XR): 1000 mg every 24 hours for 7-14 days

I.V.: 400 mg every 12 hours for 7-14 days

*Combination therapy generally recommended.

Dosing: ElderlyRefer to adult dosing. Adjust dose carefully based on renal function.

Dosing: PediatricSee Warnings/Precautions. **Note:** Extended release tablets and immediate release formulations are not interchangeable. Unless otherwise specified, oral dosing reflects the use of immediate release formulations.

Anthrax:

Inhalational (postexposure prophylaxis):

Oral: 15 mg/kg/dose every 12 hours for 60 days; maximum: 500 mg/dose

I.V.: 10 mg/kg/dose every 12 hours for 60 days; do **not** exceed 400 mg/dose (800 mg/day)

Cutaneous (treatment, CDC guidelines): Oral: 10-15 mg/kg every 12 hours for 60 days (maximum: 1 g/day); amoxicillin 80 mg/kg/day divided every 8 hours is an option for completion of treatment after clinical improvement. **Note:** In the presence of systemic involvement, extensive edema, lesions on head/neck, refer to I.V. dosing for treatment of inhalational/gastrointestinal/oropharyngeal anthrax.

Inhalational/gastrointestinal/oropharyngeal (treatment, CDC guidelines): I.V.: Initial: 10-15 mg/kg every 12 hours for 60 days (maximum: 500 mg/dose); switch to oral therapy when clinically appropriate; refer to adult dosing for notes on combined therapy and duration

Bacterial conjunctivitis:

Ophthalmic solution: Children >1 year: Refer to adult dosing.

Ophthalmic ointment: Children >2 years: Refer to adult dosing.

Corneal ulcer: Children >1 year: Refer to adult dosing.

Cystic fibrosis (unlabeled use): Children 5-17 years:

Oral: 40 mg/kg/day divided every 12 hours administered following 1 week of I.V. therapy has been reported in a clinical trial; total duration of therapy: 10-21 days

I.V.: 30 mg/kg/day divided every 8 hours for 1 week, followed by oral therapy, has been reported in a clinical trial

Urinary tract infection (complicated) or pyelonephritis: Children 1-17 years:

Oral: 20-30 mg/kg/day in 2 divided doses (every 12 hours) for 10-21 days; maximum: 1.5 g/day

I.V.: 6-10 mg/kg every 8 hours for 10-21 days (maximum: 400 mg/dose)

Dosing: Renal ImpairmentAdults:

Cl_{cr} 30-50 mL/minute: Oral: Administer 250-500 mg every 12 hours.

Cl_{cr} <30 mL/minute: Acute uncomplicated pyelonephritis or complicated UTI: Oral: Extended release formulation: 500 mg every 24 hours

Cl_{cr} 5-29 mL/minute:

Oral: Administer 250-500 mg every 18 hours.

I.V.: Administer 200-400 mg every 18-24 hours.

Dialysis: Only small amounts of ciprofloxacin are removed by hemo- or peritoneal dialysis (<10%); usual dose: Oral: 250-500 mg every 24 hours following dialysis.

Continuous renal replacement therapy (CRRT): I.V.:

CVVH: 200 mg every 12 hours

CVVHD or CVVHDF: 200-400 mg every 12 hours

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Administer by slow I.V. infusion over 60 minutes into a large vein.

Administration: I.V. DetailAdminister slowly to reduce the risk of venous irritation (burning, pain, erythema, and swelling).

pH: 3.3-3.9 (vials); 3.5-4.6 (PVC bags)

Administration: OralMay administer with food to minimize GI upset; avoid antacid use; maintain proper hydration and urine output. Administer immediate release ciprofloxacin and Cipro® XR at least 2 hours before or 6 hours after, and Proquin® XR at least 4 hours before or 6 hours after antacids or other products containing calcium, iron, or zinc (including dairy products or calcium-fortified juices). Separate oral administration from drugs which may impair absorption (see Drug Interactions).

Oral suspension: Should not be administered through feeding tubes (suspension is oil-based and adheres to the feeding tube). Patients should avoid chewing on the microcapsules.

Nasogastric/orogastric tube: Crush immediate-release tablet and mix with water. Flush feeding tube before and after administration. Hold tube feedings at least 1 hour before and 2 hours after administration.

Tablet, extended release: Do not crush, split, or chew. May be administered with meals containing dairy products (calcium content <800 mg), but not with dairy products alone. Proquin® XR should be administered with a main meal of the day; evening meal is preferred.

Dietary Considerations

Food: Drug may cause GI upset; take without regard to meals (manufacturer prefers that immediate release tablet is taken 2 hours after meals). Extended release tablet may be taken with meals that contain dairy products (calcium content <800 mg), but not with dairy products alone.

Dairy products, calcium-fortified juices, oral multivitamins, and mineral supplements: Absorption of ciprofloxacin is decreased by divalent and trivalent cations. The manufacturer states that the usual dietary intake of calcium (including meals which include dairy products) has not been shown to interfere with ciprofloxacin absorption. Immediate release ciprofloxacin and Cipro® XR may be taken 2 hours before or 6 hours after, and Proquin® XR may be taken 4 hours before or 6 hours after, any of these products.

Caffeine: Patients consuming regular large quantities of caffeinated beverages may need to restrict caffeine intake if excessive cardiac or CNS stimulation occurs.

Storage

Injection:

Premixed infusion: Store between 5°C to 25°C (41°F to 77°F); avoid freezing. Protect from light.

Vial: Store between 5°C to 30°C (41°F to 86°F); avoid freezing. Protect from light. Diluted solutions of 0.5-2 mg/mL are stable for up to 14 days refrigerated or at room temperature.

Ophthalmic solution/ointment: Store at 36°F to 77°F (2°C to 25°C). Protect from light.

Microcapsules for oral suspension: Prior to reconstitution, store below 25°C (77°F). Protect from freezing. Following reconstitution, store below 30°C (86°F) for up to 14 days. Protect from freezing.

Tablet:

Immediate release: Store below 30°C (86°F).

Extended release: Store at room temperature of 15°C to 30°C (59°F to 86°F).

Reconstitution

Injection, vial: May be diluted with NS, D_5W, SWFI, $D_{10}W$, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, LR.

Compatibility

Stable in $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5W, $D_{10}W$, LR, NS; **variable stability (consult detailed reference)** in peritoneal dialysis solution.

Y-site administration: Compatible: Amifostine, amino acids (dextrose), aztreonam, calcium gluconate, ceftazidime, cisatracurium, clarithromycin, digoxin, diltiazem, diphenhydramine, dobutamine, docetaxel, dopamine, doxorubicin liposome, etoposide phosphate, gemcitabine, gentamicin, granisetron, hydroxyzine, lidocaine, linezolid, lorazepam, metoclopramide, midazolam, midodrine, piperacillin, potassium acetate, potassium chloride, potassium phosphates, promethazine, ranitidine, remifentanil, Ringer's injection (lactated), sodium chloride, tacrolimus, teniposide, thiotepa, tobramycin, verapamil. **Incompatible:** Aminophylline, ampicillin/sulbactam, cefepime, dexamethasone sodium phosphate, furosemide, heparin, hydrocortisone sodium succinate, methylprednisolone sodium succinate, phenytoin, propofol, sodium phosphates, warfarin. **Variable (consult detailed reference):** Magnesium sulfate, sodium bicarbonate, teicoplanin, TPN.

Compatibility when admixed: Compatible: Amikacin, aztreonam, ceftazidime, cyclosporine, gentamicin, metronidazole, netilmicin, piperacillin, potassium chloride, ranitidine, tobramycin, vitamin B complex. **Incompatible:** Aminophylline, clindamycin, floxacillin, heparin.

Restrictions

An FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

Contraindications

Hypersensitivity to ciprofloxacin, any component of the formulation, or other quinolones; concurrent administration of tizanidine

Allergy Considerations

- Fluoroquinolone Allergy

Warnings/Precautions

Boxed Warnings:

- Tendon inflammation/rupture: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Altered cardiac conduction: Fluoroquinolones may prolong QT_c interval; avoid use in patients with a history of QT_c prolongation, uncorrected hypokalemia, hypomagnesemia, or concurrent administration of other medications known to prolong the QT interval (including Class Ia and Class III antiarrhythmics, cisapride, erythromycin, antipsychotics, and tricyclic antidepressants).

- CNS stimulation: Tremor, restlessness, confusion, and very rarely hallucinations or seizures may occur; use with caution in patients with known or suspected CNS disorder. Discontinue in patients who experience significant CNS adverse effects (eg, dizziness, hallucinations, suicidal ideations or actions).

- Crystalluria: Rarely, crystalluria has occurred; urine alkalinity may increase the risk. Ensure adequate hydration during therapy.

- Glucose regulation: Fluoroquinolones have been associated with the development of serious, and sometimes fatal, hypoglycemia. These events have occurred most often in elderly patients with diabetes, but have also been reported in patients without a prior history of diabetes. Prompt identification and treatment of hypoglycemia is essential. Individual quinolones may differ in their potential to cause this effect. It was most evident with gatifloxacin (no longer marketed as s systemic formulation). Hyperglycemia has also been associated with the use of fluoroquinolones. Patients should be monitored closely for signs/symptoms of disordered glucose regulation.

- Hypersensitivity reactions: Severe hypersensitivity reactions, including anaphylaxis, have occurred with quinolone therapy. The spectrum of these reactions can vary widely; reactions may present as typical allergic symptoms (eg, itching, urticaria, rash, edema) after a single dose, or may manifest as severe idiosyncratic dermatologic (eg, Stevens-Johnson, toxic epidermal necrolysis), vascular (eg, vasculitis), pulmonary (eg, pneumonitis), renal (eg, nephritis), hepatic (eg, hepatic failure or necrosis), and/or hematologic (eg, anemia, cytopenias) events, usually after multiple doses. Prompt discontinuation of drug should occur if skin rash or other symptoms arise.

- Peripheral neuropathy: The use of quinolones has been linked to peripheral neuropathy (rare); discontinue if symptoms of sensory or sensorimotor neuropathy occur.

- Phototoxicity: Avoid excessive sunlight and take precautions to limit exposure (eg, loose fitting clothing, sunscreen); may cause moderate-to-severe phototoxicity reactions. Discontinue use if photosensitivity occurs.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

- Tendon inflammation/rupture: **[U.S. Boxed Warning]: There have been reports of tendon inflammation and/or rupture with quinolone antibiotics; risk may be increased with concurrent corticosteroids, organ transplant recipients, and in patients >60 years of age.** Rupture of the Achilles tendon sometimes requiring surgical repair has been reported most frequently; but other tendon sites (eg, rotator cuff, biceps) have also been reported. Strenuous physical activity may be an independent risk factor for tendonitis. Discontinue at first sign of tendon inflammation or pain. May occur even after discontinuation of therapy.

Disease-related concerns:

- Myasthenia gravis: Some quinolones may exacerbate myasthenia gravis, use with caution (rare, potentially life-threatening weakness of respiratory muscles may occur).

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required. May increase risk of tendon rupture.

- Rheumatoid arthritis: Use with caution in patients with rheumatoid arthritis; may increase risk of tendon rupture.

- Seizures: Use with caution in individuals at risk of seizures (CNS disorders or concurrent therapy with medications which may lower seizure threshold). Potential for seizures, although very rare, may be increased with concomitant NSAID therapy.

- Syphilis: Since ciprofloxacin is ineffective in the treatment of syphilis and may mask symptoms, all patients should be tested for syphilis at the time of gonorrheal diagnosis and 3 months later.

Concurrent drug therapy issues:

- CYP1A2 substrates: Ciprofloxacin is a potent inhibitor of CYP1A2. Coadministration of drugs which depend on this pathway may lead to substantial increases in serum concentrations and adverse effects.

Special populations:

- Elderly: Adverse effects (eg, tendon rupture, QT changes) may be increased in the elderly.

- G6PD deficiency: Hemolytic reactions may (rarely) occur with quinolone use in patients with latent or actual G6PD deficiency.

- Pediatrics: Adverse effects, including those related to joints and/or surrounding tissues, are increased in pediatric patients and therefore, ciprofloxacin should not be considered as drug of choice in children (exception is anthrax treatment).

Geriatric ConsiderationsSee Warnings/Precautions regarding tendon rupture in patients >60 years of age. Ciprofloxacin should not be used as first-line therapy unless the culture and sensitivity findings show resistance to usual therapy. The interactions with caffeine and theophylline can result in serious toxicity in the elderly. Adjust dose for renal function.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in some animal studies; therefore, the manufacturer classifies ciprofloxacin as pregnancy category C. Ciprofloxacin crosses the placenta and produces measurable concentrations in the amniotic fluid and cord serum. An increased risk of teratogenic effects has not been observed in animals or humans following ciprofloxacin use during pregnancy; however, because of concerns of cartilage damage in immature animals, ciprofloxacin should only be used during pregnancy if a safer option is not available. Ciprofloxacin is recommended for prophylaxis and treatment of pregnant women exposed to anthrax. Serum concentrations of ciprofloxacin may be lower during pregnancy than in nonpregnant patients.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsCiprofloxacin is excreted in breast milk. Breast-feeding is not recommended by the manufacturer. The AAP considers ciprofloxacin to be “usually compatible with breast-feeding.” Due to the low concentrations in human milk, minimal toxicity would be expected in the nursing infant and infant serum levels were undetectable in one report. Nondose-related effects could include modification of bowel flora. There has been a single case report of perforated pseudomembranous colitis in a breast-feeding infant whose mom was taking ciprofloxacin.

Pregnancy & Lactation, In-Depth

- Ciprofloxacin in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Central nervous system: Neurologic events (children 2%, includes dizziness, insomnia, nervousness, somnolence); fever (children 2%); headache (I.V. administration); restlessness (I.V. administration)

Dermatologic: Rash (children 2%, adults 1%)

Gastrointestinal: Nausea (children/adults 3%); diarrhea (children 5%, adults 2%); vomiting (children 5%, adults 1%); abdominal pain (children 3%, adults <1%); dyspepsia (children 3%)

Hepatic: ALT increased, AST increased (adults 1%)

Local: Injection site reactions (I.V. administration)

Respiratory: Rhinitis (children 3%)

<1%: Abnormal gait, acute renal failure, agitation, allergic reactions, anaphylaxis, anemia, angina pectoris, angioedema, anorexia, arthralgia, ataxia, atrial flutter, breast pain, bronchospasm, candidiasis, cardiopulmonary arrest, cerebral thrombosis, chills, cholestatic jaundice, confusion, chromatopsia, crystalluria (particularly in alkaline urine), cylindruria, depersonalization, depression, dizziness, drowsiness, dyspnea, edema, eosinophilia, erythema nodosum, fever (adults), gastrointestinal bleeding, hallucinations, headache (oral), hematuria, hyperpigmentation, hyper-/hypotension, insomnia, interstitial nephritis, intestinal perforation, irritability, joint pain, laryngeal edema, lightheadedness, lymphadenopathy, malaise, manic reaction, migraine, MI, nephritis, nightmares, palpitation, paranoia, paresthesia, peripheral neuropathy, petechia, photosensitivity, pulmonary edema, seizure, syncope, tachycardia, thrombophlebitis, tinnitus, tremor, urethral bleeding, vaginitis, ventricular ectopy, visual disturbance, weakness

Postmarketing and/or case reports: Agranulocytosis, albuminuria, anaphylactic shock, anosmia, bone marrow depression (life-threatening), candiduria, constipation, delirium, dyspepsia (adults), dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, hemolytic anemia, hepatic failure (some fatal), hepatic necrosis, hyperesthesia, hyperglycemia, hypertonia, jaundice, methemoglobinemia, moniliasis, myalgia, myasthenia gravis, myoclonus, nystagmus, orthostatic hypotension, pancreatitis, pancytopenia (life-threatening or fatal), pneumonitis, prolongation of PT/INR, pseudomembranous colitis, psychosis, renal calculi, serum cholesterol increased, serum glucose increased, serum sickness-like reactions, serum triglycerides increased, Stevens-Johnson syndrome, taste loss, tendon rupture, tendonitis, toxic epidermal necrolysis (Lyell's syndrome), torsade de pointes, twitching, vaginal candidiasis, vasculitis

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Inhibits** CYP1A2 (strong), 3A4 (weak)
Drug Interactions

Antacids: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. **Exceptions:** Sodium Bicarbonate. *Risk D: Consider therapy modification*

Bendamustine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. *Risk C: Monitor therapy*

Caffeine: Quinolone Antibiotics may decrease the metabolism of Caffeine. *Risk C: Monitor therapy*

Calcium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Calcium Chloride. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Quinolone Antibiotics may enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Strong) may decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Didanosine: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents (excludes enteric coated formulation of didanosine). *Risk D: Consider therapy modification*

Insulin: May enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Methotrexate: Ciprofloxacin may increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

Mycophenolate: Quinolone Antibiotics may decrease the serum concentration of Mycophenolate. Specifically, quinolones may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Pentoxifylline: Ciprofloxacin may enhance the adverse/toxic effect of Pentoxifylline. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Ciprofloxacin may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Probenecid: May increase the serum concentration of Quinolone Antibiotics. *Risk C: Monitor therapy*

QTc-Prolonging Agents: Ciprofloxacin may enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Quinapril: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Ropinirole: Ciprofloxacin may decrease the metabolism of Ropinirole. *Risk C: Monitor therapy*

Ropivacaine: Ciprofloxacin may decrease the metabolism of Ropivacaine. *Risk C: Monitor therapy*

Sevelamer: May decrease the absorption of Quinolone Antibiotics. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sulfonylureas: Quinolone Antibiotics may enhance the hyperglycemic effect of Sulfonylureas. Quinolone Antibiotics may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Theophylline Derivatives: Quinolone Antibiotics may decrease the metabolism of Theophylline Derivatives. Ciprofloxacin and enoxacin are of greatest concern. Theophylline/quinolone therapy might augment the seizure-producing potential of each of the individual agents. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

TiZANidine: Ciprofloxacin may decrease the metabolism of TiZANidine. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Quinolone Antibiotics may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zinc Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Food decreases rate, but not extent, of absorption. Ciprofloxacin serum levels may be decreased if taken with dairy products or calcium-fortified juices. Ciprofloxacin may increase serum caffeine levels if taken with caffeine.

Enteral feedings may decrease plasma concentrations of ciprofloxacin probably by >30% inhibition of absorption. Ciprofloxacin should not be administered with enteral feedings. The feeding would need to be discontinued for 1-2 hours prior to and after ciprofloxacin administration. Nasogastric administration produces a greater loss of ciprofloxacin bioavailability than does nasoduodenal administration.

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization).

Test InteractionsSome quinolones may produce a false-positive urine screening result for opiates using commercially-available immunoassay kits. This has been demonstrated most consistently for levofloxacin and ofloxacin, but other quinolones have shown cross-reactivity in certain assay kits. Confirmation of positive opiate screens by more specific methods should be considered.

Monitoring ParametersPatients receiving concurrent ciprofloxacin, theophylline, or cyclosporine should have serum levels monitored; CBC, renal and hepatic function during prolonged therapy

Reference RangeTherapeutic: 2.6-3 mcg/mL; Toxic: >5 mcg/mL

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests prior to beginning therapy. Use caution in patients with known or suspected CNS disorder, current or potential for QT prolongation, renal or hepatic impairment, or diabetes. Assess other pharmacological or herbal products patient may be taking for potential interactions. I.V.: See Administration specifics. Evaluate results of laboratory tests, therapeutic effectiveness (according to purpose for use), and adverse effects (eg, hypersensitivity reactions [severe reactions, including anaphylaxis, have occurred with quinolone therapy]; *C. difficile*-associated colitis [can occur up to 2 months post treatment]; changes in CNS) regularly during prolonged therapy. Teach patient proper use (appropriate for formulation), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC, renal and hepatic function during prolonged therapy; patients receiving concurrent ciprofloxacin, theophylline, or cyclosporine should have serum theophylline or cyclosporine levels monitored. Culture and sensitivity specimen should be taken prior to initiating therapy.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. If administered by infusion, report immediately any redness, swelling, or pain at infusion site; any swelling of mouth, lips, tongue, or throat; chest pain or tightness; respiratory difficulty; back pain; and sudden itching or skin rash. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Oral: Take exactly according to specific directions (eg, timing with meals, dairy products, antacids or products containing calcium, iron or zinc differs with each formulation). Take all of prescribed medication, even if feeling better. Do not crush, split, or chew extended release tablets or chew on microcapsules in oral suspension. Maintain adequate hydration (2-3 L/day) unless instructed to restrict fluid intake. Consult prescriber before having any vaccinations. You may experience nausea, vomiting, or anorexia (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help) or increased sensitivity to sunlight (use sunscreen, wear protective clothing and dark glasses, and avoid direct exposure to sunlight or tanning salons). If tendon inflammation or pain occurs or you experience signs of an allergic reaction (eg, itching, skin rash, respiratory difficulty, facial edema or difficulty swallowing, loss of consciousness, tingling, chest pain, palpitations), discontinue use and contact prescriber immediately. Report persistent GI disturbances; CNS changes (eg, excessive sleepiness, agitation, tremors); vision changes; respiratory difficulty; signs of opportunistic infection (eg, sore throat, chills, fever, burning, itching on urination, vaginal discharge, white plaques in mouth); persistent diarrhea (especially if it lasts or occurs after completing prescription), or worsening of condition.

Ophthalmic: Use exactly as directed. Wash hands prior to instilling eye medication. Do not touch dropper to eye or any other surface. Do not wear contact lenses while using this medication (check with prescriber before using again). Tilt head back, look upward, and pull lower eyelid down to make a pouch. Drop prescribed number of drops directly into eye. Close eye, place one finger at corner of eye near nose, and apply gentle pressure. Do not blink or rub eye. If also using ointment, use drops before ointment. Use for exact time as prescribed; do not discontinue, even if symptoms disappear. May cause temporary stinging or burning. Report persistent eye discomfort, itching, redness, unusual tearing, feeling as if something is in your eye, blurred vision, eye pain, worsening vision, a bad taste in your mouth, sensitivity to light, skin rash, difficulty breathing, or worsening of symptoms.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed in D_5W]: 200 mg (100 mL); 400 mg (200 mL)

Cipro®: 200 mg (100 mL); 400 mg (200 mL)

Injection, solution [concentrate]: 10 mg/mL (20 mL, 40 mL, 120 mL)

Cipro®: 10 mg/mL (20 mL, 40 mL)

Microcapsules for suspension, oral:

Cipro®: 250 mg/5 mL (100 mL); 500 mg/5 mL (100 mL) [strawberry flavor]

Ointment, ophthalmic, as hydrochloride:

Ciloxan®: 3.33 mg/g (3.5 g) [0.3% base]

Solution, ophthalmic, as hydrochloride: 3.5 mg/mL (2.5 mL, 5mL, 10 mL) [0.3% base]

Ciloxan®: 3.5 mg/mL (5 mL) [0.3% base; contains benzalkonium chloride]

Tablet, as hydrochloride: 100 mg [strength expressed as base], 250 mg [strength expressed as base], 500 mg [strength expressed as base], 750 mg [strength expressed as base]

Cipro®: 250 mg [strength expressed as base], 500 mg [strength expressed as base], 750 mg [strength expressed as base]

Tablet, extended release, as base and hydrochloride: 500 mg [strength expressed as base], 1000 mg [strength expressed as base]

Cipro® XR: 500 mg [strength expressed as base], 1000 mg [strength expressed as base]

Tablet, extended release, as hydrochloride:

Proquin® XR: 500 mg [strength expressed as base]

Tablet, extended release, as hydrochloride [dose pack]:

Proquin® XR: 500 mg (3s)

Generic AvailableYes: Excludes ointment, suspension
ManufacturerBayer Corp (Biological and Pharmaceutical Division)
Pricing: U.S. (www.drugstore.com)

Solution (Ciloxan)

0.3% (5): $61.99

Solution (Cipro)

400 mg (40): $259.99

Solution (Ciprofloxacin HCl)

0.3% (2.5): $19.99

0.3% (5): $29.99

0.3% (10): $59.99

Tablet, 24-hour (Cipro XR)

500 mg (20): $187.54

Tablet, 24-hour (Ciprofloxacin-Ciproflox HCl)

500 mg (50): $394.99

Tablet, 24-hour (ProQuin XR)

500 mg (3): $39.99

500 mg (50): $499.99

Tablets (Cipro)

500 mg (30): $177.10

Tablets (Ciprofloxacin HCl)

250 mg (30): $16.99

500 mg (100): $39.99

750 mg (30): $135.99

750 mg (100): $429.99

Mechanism of ActionInhibits DNA-gyrase in susceptible organisms; inhibits relaxation of supercoiled DNA and promotes breakage of double-stranded DNA

Pharmacodynamics/Kinetics

Absorption: Oral: Immediate release tablet: Rapid (~50% to 85%)

Distribution: V_d: 2.1-2.7 L/kg; tissue concentrations often exceed serum concentrations especially in kidneys, gallbladder, liver, lungs, gynecological tissue, and prostatic tissue; CSF concentrations: 10% of serum concentrations (noninflamed meninges), 14% to 37% (inflamed meninges)

Protein binding: 20% to 40%

Metabolism: Partially hepatic; forms 4 metabolites (limited activity)

Half-life elimination: Children: 2.5 hours; Adults: Normal renal function: 3-5 hours

Time to peak: Oral:

Immediate release tablet: 0.5-2 hours

Extended release tablet: Cipro® XR: 1-2.5 hours, Proquin® XR: 3.5-8.7 hours

Excretion: Urine (30% to 50% as unchanged drug); feces (15% to 43%)

Related Information

- Antimicrobial Drugs of Choice
- Desensitization Protocols
- Neutropenic Fever Guidelines
- Treatment of Sexually-Transmitted Infections
- Tuberculosis
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsAlthough the systemic use of ciprofloxacin is only FDA approved in children for the treatment of complicated UTI and postexposure treatment of inhalation anthrax, use of the fluoroquinolones in pediatric patients is increasing. Current recommendations by the American Academy of Pediatrics note that the systemic use of these agents in children should be restricted to infections caused by multidrug resistant pathogens with no safe or effective alternative, and when parenteral therapy is not feasible or other oral agents are not available.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusConvulsions and toxic psychosis have been reported with quinolones. May cause dizziness, confusion, hallucinations, depression, and rarely suicidal ideation and attempts. These reactions may occur after the first dose. Discontinue drug and institute safety measures. Ciprofloxacin may also cause nervousness, agitation, insomnia, anxiety, nightmares or paranoia, phobia, depersonalization, manic reaction, ataxia, irritability, and drowsiness.

Mental Health: Effects on Psychiatric TreatmentInhibits CYP1A2 isoenzyme; use caution with clozapine; monitor for adverse effects. May rarely cause agranulocytosis; monitor with clozapine and carbamazepine. Use caution in patients with CNS disorders that may predispose them to seizures (epilepsy, alcohol/sedative hypnotic withdrawal).

Cardiovascular ConsiderationsCiprofloxacin has been weakly associated with torsade de pointes and/or QT prolongation, but is unlikely to be a risk for torsade de pointes when used in the usual recommended dosages and in patients **without** other risk factors (eg, concomitant QT-prolonging drugs, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit metabolism). Ciprofloxacin should not be used in patients with congenital prolonged QT syndrome.

Index TermsCiprofloxacin Hydrochloride

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International Brand NamesAcire (KP); Alcon Cilox (CO); Arflox (AU); Bacquinor (ID); Bactiflox (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SG, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Bactiflox Lactab (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Baflox (CO); Baquinor (ID); Baxolyn (PH); Baycip (CN, ES); C-Flox (AU, UY); C-Floxacin (TH); Cefaxin (KP); Cenin (HR); Cetraxal (ES, GT, HN, PA); Ciaxone (AU); Ciclodin (PH); Cidroxal (PH); Ciflo (TH); Cifloc (ZA); Ciflox (FR); Cifloxin (HK, MY, TH); Cifran (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, PL, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Cilab (TH); Ciloquin (AU); Cilox (NO); Ciloxan (AR, AT, AU, BE, BF, BG, BJ, BR, CH, CI, CN, CR, CZ, DE, DK, DO, EE, ET, FR, GB, GH, GM, GN, GR, GT, HK, HN, HU, IE, IL, IT, KE, LR, LU, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, PA, PH, PK, PL, PY, SC, SD, SE, SL, SN, SV, TH, TN, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Cimogal (MX); Cinaflox (PE); Cipflox (NZ); Ciphin (PL); Cipio (KP); Ciploc (PK); Ciplox (BF, BJ, CI, ET, GH, GM, GN, HK, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Cipocin (TW); Ciprecu (EC); Ciprinol (BG, HN, HR, PL); Cipro (AR, BR, CO, PY); Ciprobac (MX); Ciprobay (AE, BG, BH, CL, CY, CZ, DE, EG, HN, HR, HU, IL, IQ, IR, JO, KW, LB, LY, MY, OM, PH, PL, QA, SA, SY, TH, YE, ZA); Ciprobay Uro (DE); Ciprobid (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TH, TN, TZ, UG, YE, ZA, ZM, ZW); Ciprobiotic (DO); Ciprocan (KP); Ciprocep (TH); Ciprocin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ciprocinol (BG); Ciprodar (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ciprodex (IL); Ciproflox (BG, MX, PE); Ciprogis (IL); Ciprol (AU); Ciprolet (SG); Ciprolon (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Cipromycin (GR); Cipronex (PL); Cipropharm (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Cipropol (PL); Ciproquinol (PT); Ciprosin Eye (KP); Ciproval (CN); Ciprox (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ciproxan (JP, TH); Ciproxin (AT, AU, CH, DK, EE, FI, GB, GR, HK, ID, IE, IL, IT, NL, NO, NZ, SE, TW); Ciproxina (BB, BM, BS, BZ, CR, DO, EC, GT, GY, HN, JM, MX, NI, NL, PA, PT, SR, SV, TT); Ciproxine (BE, LU); Ciproxyl (HK, TH); Ciprum (PL); Ciriax (PE); Cirok (PH); Citopcin (KP); Cixa (TW); Cobay (TH); Corsacin (ID); Cosflox (IN); Cycin (KP, SG); Cyfloxin (HK); Cypral (VE); Eni (CR, DO, GT, HN, MX, NI, PA, SV); Enoxin (SG, TH); Floroc (PH); Floroxin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Floxager (MX); Floxantina (MX); Floxbio (ID); Floxsid (ID); Grifociprox (PE); H-Next (CO); Iprolan (PH); Isotic (ID); Kenzoflex (MX); Kinoves (PH); Lofucin (KP); Loxan (CO); Medociprin (HK, TH); Mitroken (MX); Novidat (AR); Oftacilox (ES); Opthaflox (TH); Otosec (CO); Probiox (PE); Procin (BR); Proflox (EC, TH); Profloxin (AU); Proksi 250 (GT, HN, SV); Proksi 500 (GT, HN, SV); Proquin (AU); Proxacin (PL); Proxitor (ID); Qilaflox (ID); Qinosyn (PH); Quilox (PH); Quinobiotic (ID); Quintor (PL); Qupron (KP); Serviflox (SG); Sifloks (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Sophixin Ofteno (MX); Superocin (TW); Topistin (SG); Uniflox (FR); Uroxin (HK, SG); Vistaflox (PH); Zipra (MX); Zolina (CR, GT, HN, NI, PA, SV); Zumaflox (ID); Zyflox (PH)

Cisapride

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Propulsid® may be confused with propranolol

Pronunciation(SIS a pride)

U.S. Brand NamesPropulsid®

Pharmacologic CategoryGastrointestinal Agent, Prokinetic

Use: Labeled IndicationsTreatment of nocturnal symptoms of gastroesophageal reflux disease (GERD); has demonstrated effectiveness for gastroparesis, refractory constipation, and nonulcer dyspepsia

Dosing: AdultsGERD or gastrointestinal dysmotility: Oral: Initial: 5-10 mg 4 times/day at least 15 minutes before meals and at bedtime; in some patients the dosage will need to be increased to 20 mg to obtain a satisfactory result.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricGastrointestinal dysmotility: Oral: Children: 0.15-0.3 mg/kg/dose 3-4 times/day; maximum: 10 mg/dose

Dosing: Hepatic ImpairmentInitiate at 50% usual dose.

RestrictionsIn U.S., available via limited-access protocol only (1-800-JANSSEN).

Contraindications

Hypersensitivity to cisapride or any component of the formulations; GI hemorrhage, mechanical obstruction, GI perforation, or other situations when GI motility stimulation is dangerous

Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsade de pointes, and QT prolongation have been reported in patients taking cisapride with other drugs that inhibit CYP3A4. Some of these events have been fatal. Concomitant oral or intravenous administration of the following drugs with cisapride may lead to elevated cisapride blood levels and is contraindicated:

Antibiotics: Oral or I.V. erythromycin, clarithromycin, troleandomycin

Antidepressants: Nefazodone

Antifungals: Oral or I.V. fluconazole, itraconazole, miconazole, oral ketoconazole

Protease inhibitors: Indinavir, ritonavir, amprenavir, atazanavir

Cisapride is also contraindicated for patients with a prolonged electrocardiographic QT intervals (QT_c >450 msec), a history of QT_c prolongation, or known family history of congenital long QT syndrome; clinically significant bradycardia, renal failure, history of ventricular arrhythmias, ischemic heart disease, and congestive heart failure; uncorrected electrolyte disorders (hypokalemia, hypomagnesemia); respiratory failure; and concomitant medications known to prolong the QT interval and increase the risk of arrhythmia, such as certain antiarrhythmics, certain antipsychotics, certain antidepressants, bepridil, sparfloxacin, and terodiline. The preceding lists of drugs are not comprehensive. Cisapride should not be used in patients with uncorrected hypokalemia or hypomagnesemia or who might experience rapid reduction of plasma potassium such as those administered potassium-wasting diuretics and/or insulin in acute settings.

Warnings/Precautions

Special note:

On March 24, 2000, the FDA announced that the manufacturer of cisapride would voluntarily withdraw its product from the U.S. market on July 14, 2000. This decision was based on 341 reports of heart rhythm abnormalities including 80 reports of deaths. The company will continue to make the drug available to patients who meet specific clinical eligibility criteria for a limited-access protocol (contact 1-800-JANSSEN).

Boxed warnings:

- Arrhythmias: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Arrhythmias: **[U.S. Boxed Warning]: Serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsade de pointes, and QT prolongation have been reported in patients taking this drug.** Many of these patients also took drugs expected to increase cisapride blood levels by inhibiting the cytochrome P450 3A4 enzymes that metabolize cisapride. These drugs include clarithromycin, erythromycin, troleandomycin, nefazodone, fluconazole, itraconazole, ketoconazole, indinavir and ritonavir. Some of these events have been fatal. Cisapride is contraindicated in patients taking any of these drugs. **QT prolongation, torsade de pointes (sometimes with syncope), cardiac arrest and sudden death have been reported in patients taking cisapride without the above-mentioned contraindicated drugs.** Most patients had disorders that may have predisposed them to arrhythmias with cisapride. Cisapride is contraindicated for those patients with: history of prolonged electrocardiographic QT intervals; renal failure; history of ventricular arrhythmias, ischemic heart disease, and HF;

uncorrected electrolyte disorders (hypokalemia, hypomagnesemia); respiratory failure; and concomitant medications known to prolong the QT interval and increase the risk of arrhythmia, such as certain antiarrhythmics, including those of Class Ia (such as quinidine and procainamide) and Class III (such as sotalol); tricyclic antidepressants (such as amitriptyline); certain tetracyclic antidepressants (such as maprotiline); certain antipsychotic medications (such as certain phenothiazines and sertindole), protease inhibitors, bepridil, sparfloxacin and terodiline. (The preceding lists of drugs are not comprehensive.) Recommended doses of cisapride should not be exceeded.

Disease-related concerns:

- Electrolyte disturbances: Should not be used in patients with uncorrected hypokalemia or hypomagnesemia, such as those with severe dehydration, vomiting or malnutrition, or those taking potassium-wasting diuretics; should also not be used in patients who might experience rapid reduction of plasma potassium, such as those administered potassium-wasting diuretics and/or insulin in acute settings.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Risk vs. benefit: Potential benefits should be weighed against risks prior administration of cisapride to patients who have or may develop prolongation of cardiac conduction intervals, particularly QT_c. These include patients with conditions that could predispose them to the development of serious arrhythmias, such as multiple organ failure, COPD, apnea and advanced cancer. Patients should have a baseline ECG and an electrolyte panel (magnesium, calcium, potassium) prior to initiating cisapride (see Contraindications).

Geriatric ConsiderationsSteady-state serum concentrations are higher than those in younger adults; however, the therapeutic dose and pharmacologic effects are the same as those in younger adults and no adjustment in dose recommended for elderly.
Pregnancy Risk FactorC
LactationEnters breast milk/use caution (AAP rates “compatible”)
Adverse Reactions

>5%:

Central nervous system: Headache

Dermatologic: Rash

Gastrointestinal: Diarrhea, GI cramping, dyspepsia, flatulence, nausea, xerostomia

Respiratory: Rhinitis

<5%:

Cardiovascular: Tachycardia

Central nervous system: Extrapyramidal effects, somnolence, fatigue, seizure, insomnia, anxiety

Hematologic: Thrombocytopenia, increased LFTs, pancytopenia, leukopenia, granulocytopenia, aplastic anemia

Respiratory: Sinusitis, cough, upper respiratory tract infection, increased incidence of viral infection

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak), 3A4 (weak)
Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amitriptyline: May enhance the arrhythmogenic effect of Cisapride. *Risk X: Avoid combination*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Cisapride. *Risk X: Avoid combination*

Aprepitant: May increase the serum concentration of Cisapride. *Risk X: Avoid combination*

Cimetidine: May decrease the metabolism of Cisapride. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Efavirenz: May enhance the QTc-prolonging effect of Cisapride. *Risk X: Avoid combination*

Fosaprepitant: May increase the serum concentration of Cisapride. The active metabolite aprepitant is likely responsible for this effect. *Risk X: Avoid combination*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Grapefruit Juice: May decrease the metabolism of Cisapride. *Risk D: Consider therapy modification*

Macrolide Antibiotics: May decrease the metabolism of Cisapride. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk X: Avoid combination*

Nefazodone: May decrease the metabolism of Cisapride. *Risk X: Avoid combination*

NIFEdipine: Cisapride may increase the serum concentration of NIFEdipine. Reported with sustained release nifedipine product. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Protease Inhibitors: May decrease the metabolism of Cisapride. The resultant increase in serum cisapride concentrations may result in QTc prolongation and malignant cardiac arrhythmias. *Risk X: Avoid combination*

Protriptyline: May enhance the arrhythmogenic effect of Cisapride. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Coadministration of grapefruit juice with cisapride increases the bioavailability of cisapride and concomitant use should be avoided.

Herb/Nutraceutical: St John's wort may decrease cisapride levels.

Nursing: Physical Assessment/MonitoringEvaluate cardiac status thoroughly prior to therapy (12-lead ECG). Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, anything that may increase risk of cardiac arrhythmias). Assess results of laboratory tests (eg, ECG, electrolyte balance, and renal function), therapeutic effectiveness (relief of symptoms), and adverse response (eg, tachycardia, CNS changes, anemia, viral infection) regularly during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab Tests**A 12-lead ECG should be performed prior to administration of cisapride.** Treatment with cisapride should not be initiated if the QT_c value exceeds 450 milliseconds. Serum electrolytes (potassium, calcium, and magnesium) and creatinine should be assessed prior to administration of cisapride and whenever conditions develop that may affect electrolyte balance or renal function.

Patient EducationIt is absolutely vital that you inform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. Take before meals. Avoid alcohol and grapefruit juice. May cause increased sedation, headache, anxiety (use caution when driving or engaging in hazardous tasks until response to drug is known). Immediately report rapid heartbeat, palpitations, chest pain, or tightness. Report severe abdominal pain, prolonged diarrhea, weight loss, extreme fatigue, or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Generic AvailableNo

ManufacturerJanssen Pharmaceutica Products, LP

Mechanism of ActionEnhances the release of acetylcholine at the myenteric plexus. *In vitro* studies have shown cisapride to have serotonin-4 receptor agonistic properties which may increase gastrointestinal motility and cardiac rate; increases lower esophageal sphincter pressure and lower esophageal peristalsis; accelerates gastric emptying of both liquids and solids.

Pharmacodynamics/Kinetics

Onset of action: 0.5-1 hour

Protein binding: 97.5% to 98%

Metabolism: Extensively hepatic to norcisapride

Bioavailability: 35% to 40%

Half-life elimination: 6-12 hours

Excretion: Urine and feces (<10%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsCisapride is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay cause sedation, insomnia, anxiety, or extrapyramidal symptoms

Mental Health: Effects on Psychiatric TreatmentContraindicated with nefazodone and ziprasidone; may increase cisapride levels which have been associated with QT prolongation and torsade de pointes

Cardiovascular ConsiderationsRecent concerns have arisen regarding the arrhythmogenic potential of cisapride. Cisapride is associated with serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, torsade de pointes, and QT prolongation. For these reasons, cisapride should be avoided in patients with cardiovascular disease, particularly in those patients with a history of arrhythmias or prolonged QT interval, ischemic heart disease, heart failure, respiratory failure, renal failure, and conditions which may predispose to electrolyte imbalances (hypokalemia, hypocalcemia, hypomagnesemia). Cisapride levels and the potential for arrhythmogenic effects may also increase secondary to significant drug interactions (see Drug Interactions). Cisapride therapy is contraindicated with macrolide antibiotics (eg, clarithromycin, erythromycin, troleandomycin), antifungals (eg, fluconazole, itraconazole, ketoconazole), protease inhibitors (eg, indinavir, ritonavir), phenothiazines (eg, prochlorperazine, promethazine), antiarrhythmics (Class Ia agents: quinidine, procainamide, disopyramide and Class III agents: amiodarone, sotalol), and tricyclic antidepressants, nefazodone, maprotiline, sertindole, bepridil, and sparfloxacin.

In the absence of a known disease or drug contraindication, all patients should have a 12-lead ECG and an electrolyte panel (potassium, calcium, and magnesium) completed prior to initiating cisapride therapy. Cisapride is contraindicated in patients with hypokalemia, hypocalcemia, hypomagnesemia, and in patients with a QT_c interval >450 milliseconds. Serum electrolytes and 12-lead ECG should be again evaluated within the first 48 hours of therapy and periodically thereafter. Patients on diuretic and cisapride therapies should be monitored more closely for the development of hypokalemia, hypocalcemia, and hypomagnesemia. Cisapride therapy should be stopped and the patient monitored closely in patients who develop hypokalemia, hypocalcemia, hypomagnesemia, or QT prolongation (QT_c >450 milliseconds).

Anesthesia and Critical Care Concerns/Other Considerations

IMPORTANT NOTE: On March 24, 2000, the FDA announced that the manufacturer of cisapride would voluntarily withdraw its product from the U.S. market on July 14, 2000. This decision was based on 341 reports of heart rhythm abnormalities including 80 reports of deaths. The company will continue to make the drug available to patients who meet specific clinical eligibility criteria for a limited-access protocol (contact 1-800-JANSSEN).

The potential for arrhythmogenic effects may also increase secondary to significant drug interactions (see Drug Interactions).

In the absence of a known disease or drug contraindication, all patients should have a 12-lead ECG and an electrolyte panel (potassium, calcium, and magnesium) completed prior to initiating cisapride therapy. Serum electrolytes and 12-lead ECG should be again evaluated within the first 48 hours of therapy and periodically thereafter. Patients on diuretic and cisapride therapies should be monitored more closely for the development of hypokalemia, hypocalcemia, and hypomagnesemia. Cisapride therapy should be stopped and the patient monitored closely in patients who develop hypokalemia, hypocalcemia, hypomagnesemia, or QT prolongation.

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International Brand NamesAcenalin (JP); Acpulsif (ID); Alimix (GR); Alimix Forte (CZ); Alipride (IN); Cisap (PL); Cisawal (IN); Coordinax (HU, PL); Cyprid (LU); Digenol (HR); Disflux (ID); Enteropride (MX); Esorid (IN); Gasprid (PL); Gastromet (CN, PE); Gastronax (PL); Guarposid (ID); Kineprid (BR); Kinestase (MX); Lornakin (MX); Motilar (VE); Palcid (TH); Prepulsid (AE, AR, AT, AU, BE, BF, BG, BH, BJ, BR, CH, CI, CN, CO, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HN, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, NZ, OM, PE, PH, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SY, TN, TR, TZ, UG, UY, YE, ZA, ZM, ZW); Presistin (MX); Prider (TW); Pridesia (ID); Prisic (TW); Profercol (MX); Pulsar (AR); Refluxin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Risamol (JP); Stimulit (ID); Tadasil (MX); Unamol (MX); Viprasen (GY); Vomipride (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW)

Cisatracurium

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Nimbex® may be confused with Revex®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(sis a tra KYOO ree um)

U.S. Brand NamesNimbex®

Canadian Brand NamesNimbex®

Pharmacologic CategoryNeuromuscular Blocker Agent, Nondepolarizing

Use: Labeled IndicationsAdjunct to general anesthesia to facilitate endotracheal intubation and to relax skeletal muscles during surgery; to facilitate mechanical ventilation in ICU patients; does not relieve pain or produce sedation

Dosing: AdultsNeuromuscular blockade: I.V. (not to be used I.M.):

Operating room administration:

Intubating doses: 0.15-0.2 mg/kg as components of propofol/nitrous oxide/oxygen induction-intubation technique. (**Note:** May produce generally good or excellent conditions for tracheal intubation in 1.5-2 minutes with clinically effective duration of action during propofol anesthesia of 55-61 minutes.) Initial dose after succinylcholine for intubation: 0.1 mg/kg; maintenance dose: 0.03 mg/kg 40-60 minutes after initial dose, then at ~20-minute intervals based on clinical criteria.

Continuous infusion: After an initial bolus, a diluted solution can be given by continuous infusion for maintenance of neuromuscular blockade during extended surgery; adjust the rate of administration according to the patient's response as determined by peripheral nerve stimulation. An initial infusion rate of 3 mcg/kg/minute may be required to rapidly counteract the spontaneous recovery of neuromuscular function; thereafter, a rate of 1-2 mcg/kg/minute should be adequate to maintain continuous neuromuscular block in the 89% to 99% range in most pediatric and adult patients. Consider reduction of the infusion rate by 30% to 40% when administering during stable isoflurane, enflurane, sevoflurane, or desflurane anesthesia. Spontaneous recovery from neuromuscular blockade following discontinuation of infusion of cisatracurium may be expected to proceed at a rate comparable to that following single bolus administration.

Intensive care unit administration: Follow the principles for infusion in the operating room. At initial signs of recovery from bolus dose, begin the infusion at a dose of 3 mcg/kg/minute and adjust rates accordingly; dosage ranges of 0.5-10 mcg/kg/minute have been reported. If patient is allowed to recover from neuromuscular blockade, readministration of a bolus dose may be necessary to quickly re-establish neuromuscular block prior to reinstituting the infusion. See table.

Cisatracurium Besylate Infusion Chart

Drug Delivery Rate (mcg/kg/min)	**Infusion Rate (mL/kg/min) 0.1 mg/mL (10 mg/100 mL)**	**Infusion Rate (mL/kg/min) 0.4 mg/mL (40 mg/100 mL)**
1	0.01	0.0025
1.5	0.015	0.00375
2	0.02	0.005
3	0.03	0.0075
5	0.05	0.0125

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricNeuromuscular blockade: I.V. (not to be used I.M.):

Operating room administration:

Infants 1-23 months: 0.15 mg/kg over 5-10 seconds during either halothane or opioid anesthesia

Children 2-12 years: *Intubating doses:* 0.1-0.15 mg/kg over 5-15 seconds during either halothane or opioid anesthesia. (**Note:** When given during stable opioid/nitrous oxide/oxygen anesthesia, 0.1 mg/kg produces maximum neuromuscular block in an average of 2.8 minutes and clinically effective block for 28 minutes.)

Children ≥2 years: *Continuous infusion:* Refer to adult dosing.

Intensive care unit administration: Refer to adult dosing.

Dosing: Renal ImpairmentBecause slower times to onset of complete neuromuscular block were observed in renal dysfunction patients, extending the interval between the administration of cisatracurium and intubation attempt may be required to achieve adequate intubation conditions.

Calculations

- Cisatracurium

Administration: I.M.Not for I.M. injection, too much tissue irritation.

Administration: I.V.Administer I.V. only. The use of a peripheral nerve stimulator will permit the most advantageous use of cisatracurium, minimize the possibility of overdosage or underdosage and assist in the evaluation of recovery.

Give undiluted as a bolus injection. Continuous administration requires the use of an infusion pump.

StorageRefrigerate intact vials at 2°C to 8°C/36°F to 46°F. Use vials within 21 days upon removal from the refrigerator to room temperature (25°C to 77°F). Dilutions of 0.1-0.2 mg/mL in 0.9% sodium chloride or dextrose 5% in water are stable for up to 24 hours at room temperature.

CompatibilityStable in D_5W, NS, D_5NS; **variable stability (consult detailed reference)** in D_5LR.

Y-site administration: Compatible: Alfentanil, amikacin, aztreonam, bretylium, bumetanide, buprenorphine, butorphanol, calcium gluconate, ceftriaxone, chlorpromazine, cimetidine, ciprofloxacin, clindamycin, dexamethasone sodium phosphate, digoxin, diphenhydramine, dobutamine, dopamine, doxycycline, droperidol, enalaprilat, epinephrine, esmolol, famotidine, fentanyl, fluconazole, gatifloxacin, gentamicin, haloperidol, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, imipenem/cilastatin, inamrinone, isoproterenol, ketorolac, lidocaine, linezolid, lorazepam, magnesium sulfate, mannitol, meperidine, metoclopramide, metronidazole, midazolam, minocycline, morphine, nalbuphine, nitroglycerin, norepinephrine, ofloxacin, ondansetron, phenylephrine, potassium chloride, procainamide, prochlorperazine edisylate, promethazine, ranitidine, remifentanil, sufentanil, theophylline, ticarcillin, tobramycin, vancomycin, zidovudine. **Incompatible:** Amphotericin B cholesteryl sulfate complex, cefoperazone. **Variable (consult detailed reference):** Acyclovir, aminophylline, amphotericin B, ampicillin, ampicillin/sulbactam, cefazolin, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, cefuroxime, diazepam, furosemide, ganciclovir, heparin, methylprednisolone sodium succinate, piperacillin, piperacillin/tazobactam, sodium bicarbonate, sodium nitroprusside, thiopental, ticarcillin/clavulanate, trimethoprim/sulfamethoxazole.

Compatibility when admixed: Compatible: Alfentanil, droperidol, fentanyl, midazolam, sufentanil. **Incompatible:** Ketorolac, propofol.

ContraindicationsHypersensitivity to cisatracurium besylate or any component of the formulation

Allergy Considerations

- Neuromuscular-Blocking Agent Allergy

Warnings/Precautions

Concern related to adverse effects:

- Bradycardia: May be more common with cisatracurium than with other neuromuscular-blocking agents since it has no clinically-significant effects on heart rate to counteract the bradycardia produced by anesthetics.
- Neuromuscular cross-sensitivity: Cross-sensitivity with other neuromuscular-blocking agents may occur; use extreme caution in patients with previous anaphylactic reactions.

Disease-related concerns:

- Burn injury: Resistance may occur in burn patients (>30% of body) for period of 5-70 days postinjury.
- Conditions which may antagonize neuromuscular blockade: Alkalosis, hypercalcemia, demyelinating lesions, peripheral neuropathies, denervation, infection, muscle trauma, and diabetes mellitus may result in antagonism of neuromuscular blockade.
- Conditions which may potentiate neuromuscular blockade: Electrolyte abnormalities, severe hyponatremia, severe hypocalcemia, severe hypokalemia, hypermagnesemia, neuromuscular diseases, acidosis, acute intermittent porphyria, Eaton-Lambert syndrome, myasthenia gravis, renal failure, and hepatic failure may result in potentiation of neuromuscular blockade.

Special populations:

- Elderly: Use with caution in the elderly, effects and duration are more variable.
- Immobilized patients: Resistance may occur in patients who are immobilized.

Other warnings/precautions:

- Appropriate use: Maintenance of an adequate airway and respiratory support is critical.
- Experienced personnel: Should be administered by adequately trained individuals familiar with its use.

Pregnancy Risk FactorB

Lactation Excretion in breast milk unknown/use caution

Adverse Reactions

<1%: Effects are minimal and transient, bradycardia and hypotension, flushing, pruritus, rash, bronchospasm

Postmarketing and/or case reports: Acute quadriplegic myopathy syndrome (prolonged use), myositis ossificans (prolonged use)

Drug Interactions

Acetylcholinesterase Inhibitors: May diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). Acetylcholinesterase Inhibitors may decrease the metabolism of Neuromuscular-Blocking Agents (Nondepolarizing). This is only true for mivacurium in which case the neuromuscular blocking effects might be prolonged. *Risk C: Monitor therapy*

Aminoglycosides: May enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Neuromuscular-Blocking Agents may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Neuromuscular-Blocking Agents may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Calcium Channel Blockers: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Cardiac Glycosides: Neuromuscular-Blocking Agents may enhance the arrhythmogenic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Colistimethate: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Neuromuscular-Blocking Agents (Nondepolarizing) may enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

Inhalational Anesthetics: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Neuromuscular-Blocking Agents (Nondepolarizing). Specifically, episodes of apnea have been reported in patients using this combination. *Risk C: Monitor therapy*

Lincosamide Antibiotics: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Lithium: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Loop Diuretics: May diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Loop Diuretics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Magnesium Salts: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Polymyxin B: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Procainamide: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

QuiNIDine: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Tetracycline Derivatives: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Vancomycin: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Monitoring Parameters Vital signs (heart rate, blood pressure, respiratory rate)

Nursing: Physical Assessment/Monitoring Only clinicians experienced in the use of neuromuscular blocking drugs should administer and/or manage the use of cisatracurium. Dosage and rate of administration should be individualized and titrated to the desired effect, according to relevant clinical factors, premedication, concomitant medications, age, and general condition of the patient. Ventilatory support must be instituted and maintained until adequate respiratory muscle function and/or airway protection are assured. Assess other medications for effectiveness and safety. Other drugs that affect neuromuscular activity may increase/decrease neuromuscular block induced by cisatracurium. This drug does not cause anesthesia or analgesia; pain must be treated with appropriate analgesic agents. Continuous monitoring of vital signs, cardiac status, respiratory status, and degree of neuromuscular block (objective assessment with peripheral external nerve stimulator) is mandatory during infusion and until full muscle tone has returned. Muscle tone returns in a predictable pattern, starting with diaphragm, abdomen, chest, limbs, and finally muscles of the neck, face, and eyes. Safety precautions must be maintained until full muscle tone has returned. **Note:** It may take longer for return of muscle tone in obese or elderly patients or patients with renal or hepatic disease, myasthenia gravis, myopathy, other neuromuscular disease, dehydration, electrolyte imbalance, or severe acid/base imbalance. Provide appropriate patient teaching/support prior to and following administration.

Long-term use: Monitor fluid levels (intake and output) during and following infusion. Reposition patient and provide appropriate skin care, mouth care, and care of patient's eyes every 2-3 hours while sedated. Provide appropriate emotional and sensory support (auditory and environmental).

Patient Education Patient will usually be unconscious prior to administration. Patient education should be appropriate to individual situation. Reassurance of constant monitoring and emotional support to reduce fear and anxiety should precede and follow administration. Following return of muscle tone, do not attempt to change position or rise from bed without assistance. Report immediately any skin rash or hives, pounding heartbeat, respiratory difficulty, or muscle tremors. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 2 mg/mL (5 mL); 10 mg/mL (20 mL)

Injection, solution: 2 mg/mL (10 mL) [contains benzyl alcohol]

Generic AvailableNo

Mechanism of ActionBlocks neural transmission at the myoneural junction by binding with cholinergic receptor sites

Pharmacodynamics/Kinetics

Onset of action: I.V.: 2-3 minutes

Peak effect: 3-5 minutes

Duration: Recovery begins in 20-35 minutes when anesthesia is balanced; recovery is attained in 90% of patients in 25-93 minutes

Metabolism: Undergoes rapid nonenzymatic degradation in the bloodstream (Hofmann elimination), additional metabolism occurs via ester hydrolysis; some active metabolites

Half-life elimination: 22-29 minutes

Related Information

- Neuromuscular-Blocking Agents

Pharmacotherapy PearlsCisatracurium is classified as an intermediate-duration neuromuscular-blocking agent. It does not appear to have a cumulative effect on the duration of blockade. Neuromuscular-blocking potency is 3 times that of atracurium; maximum block is up to 2 minutes longer than for equipotent doses of atracurium.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentConcurrent use with lithium may prolong neuromuscular blockade; conversely, neuromuscular blockade may be diminished if used with carbamazepine

Anesthesia and Critical Care Concerns/Other ConsiderationsCisatracurium is classified as an intermediate duration neuromuscular-blocking agent; does not appear to have a cumulative effect on the duration of blockade; neuromuscular-blocking potency is 3 times that of atracurium.

Critically-Ill Adult Patients:

The 2008 Surviving Sepsis Campaign guidelines recommend avoiding use of neuromuscular blockers if at all possible in the septic patient due to the risk of prolonged neuromuscular blockade following discontinuation. If one is required, monitor the depth of blockade (Grade 1B).

The 2002 ACCM/SCCM/ASHP clinical practice guidelines for sustained neuromuscular blockade in the adult critically-ill patient recommend:

Optimize sedatives and analgesics prior to initiation and monitor and adjust accordingly during course. Neuromuscular blockers do not relieve pain or produce sedation.

Protect patient's eyes from development of keratitis and corneal abrasion by administering ophthalmic ointment and taping eyelids closed or using eye patches. Reposition patient routinely to protect pressure points from breakdown. Address DVT prophylaxis.

Concurrent use of a neuromuscular blocker and corticosteroids appear to increase the risk of certain ICU myopathies; avoid or administer the corticosteroid at the lowest dose possible. Reassess need for neuromuscular blocker daily.

Using daily drug holidays (stopping neuromuscular-blocking agent until patient requires it again) may decrease the incidence of acute quadriplegic myopathy syndrome.

Tachyphylaxis can develop; switch to another neuromuscular blocker (taking into consideration the patient's organ function) if paralysis is still necessary.

Acidosis and severe hypothermia may delay the elimination of atracurium and cisatracurium.

Atracurium or cisatracurium is recommended for patients with significant hepatic or renal disease, due to organ-independent Hofmann elimination.

Monitor patients clinically and via “Train of Four” (TOF) testing with a goal of adjusting the degree of blockade to 1-2 twitches or based upon the patient's clinical condition.

Index TermsCisatracurium Besylate

References

Belmont MR, Lien CA, Quessy S, et al, “The Clinical Neuromuscular Pharmacology of 51W89 in Patients Receiving Nitrous Oxide/Opioid/Barbiturate Anesthesia,” *Anesthesiology*, 1995, 82(5):1139-45. [PubMed 7741288]

Dellinger RP, Levy MM, Carlet JM, et al, “Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008,” *Intensive Care Med*, 2008, 34(1): 17-60. Available at http://www.survivingsepsis.org/system/files/images/2008_20International_20SSC_20Guidelines_1_.pdf[PubMed 18058085]

Konstadt SN, Reich DL, Stanley TE 3d, et al, “A Two Center Comparison of the Cardiovascular Effects of Cisatracurium (Nimbex®) and Vecuronium in Patients With Coronary Artery Disease,” *Anesth Analg*, 1995, 81(5):1010-4. [PubMed 7486039]

Lien CA, Belmont MR, Abalos A, et al, “The Cardiovascular Effects and Histamine-Releasing Properties of 51W89 in Patients Receiving Nitrous Oxide/Opioid/Barbiturate Anesthesia,” *Anesthesiology*, 1995, 82(5):1131-8. [PubMed 7537945]

Murray MJ, Cowen J, DeBlock H, et al, “Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient. Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists, American College of Chest Physicians,” *Crit Care Med*, 2002, 30(1):142-56. Available at: http://www.sccm.org/pdf/NeuromuscularBlockade.pdf. Accessed August 6, 2003. [PubMed 11902255]

Prielipp RC, Coursin DB, Scuderi PE, et al, “Comparison of the Infusion Requirements and Recovery Profiles of Vecuronium and Cisatracurium 51W89 in Intensive Care Unit Patients,” *Anesth Analg*, 1995, 81(1):3-12. [PubMed 7598277]

Sorooshian SS, Stafford MA, Eastwood NB, et al, “Pharmacokinetics and Pharmacodynamics of Cisatracurium in Young and Elderly Adult Patients,” *Anesthesiology*, 1996, 84(5):1083-91.[PubMed 8624002]

International Brand Names Nimbex (AE, AR, AT, AU, BB, BE, BH, BM, BS, BZ, CH, CN, CR, CY, DE, DK, DO, EG, ES, FI, FR, GB, GT, GY, HK, HN, IE, IL, IQ, IR, IT, JM, JO, KW, LB, LU, LY, MX, MY, NI, NL, NO, OM, PA, PL, PT, QA, SA, SE, SR, SV, SY, TH, TT, TW, YE); Nimbex forte (PL); Nimbium (BR)

CISCA

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Bladder Cancer
Regimen UseBladder cancer
Regimen

Cyclophosphamide: I.V.: 650 mg/m^2 day 1

[total dose = 650 mg/m^2]

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose = 50 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 2

[total dose = 100 mg/m^2]

Repeat cycle every 21-28 days

References

Sternberg JJ, Bracken RB, Handel PB, et al, âCombination Chemotherapy (CISCA) for Advanced Urinary Tract Carcinoma. A Preliminary Report,â *JAMA*, 1977, 238(21):2282-7.[PubMed 578848]

Cisplatin-Cetuximab

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Head and Neck Cancer

Regimen UseHead and neck cancer

Index TermsCetuximab-Cisplatin

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cycle 1:

Cetuximab: I.V.: 400 mg/m^2 (loading dose) day 1 (week 1, cycle 1 only)

[total loading dose = 400 mg/m^2]

followed by I.V.: 250 mg/m^2/day days 8, 15, and 22

[total dose/cycle 1 = 1150 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Treatment cycle is 4 weeks

Subsequent cycles:

Cetuximab: I.V.: 250 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 1000 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 4 weeks

Variation 2:

Cycle 1:

Cetuximab: I.V.: 400 mg/m^2 (loading dose) day 1 (week 1, cycle 1 only)

[total loading dose = 400 mg/m^2]

followed by I.V.: 250 mg/m^2/day days 8 and 15

[total dose/cycle 1 = 900 mg/m^2]

Cisplatin: I.V.: 75-100 mg/m^2 day 1

[total dose/cycle = 75-100 mg/m^2]

Treatment cycle is 3 weeks

Subsequent cycles:

Cetuximab: I.V.: 250 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 750 mg/m^2]

Cisplatin: I.V.: 75-100 mg/m^2 day 1

[total dose/cycle = 75-100 mg/m^2]

Repeat cycle every 3 weeks

References

Variation 1:

Burtness B, Goldwasser MA, Flood W, et al, "Phase III Randomized Trial of Cisplatin Plus Placebo Compared With Cisplatin Plus Cetuximab in Metastatic/Recurrent Head and Neck Cancer: An Eastern Cooperative Oncology Group Study," *J Clin Oncol*, 2005, 23(34):8646-54.[PubMed 16314626]

Variation 2:

Herbst RS, Arquette M, Shin DM, et al, "Phase II Multicenter Study of the Epidermal Growth Factor Receptor Antibody Cetuximab and Cisplatin for Recurrent and Refractory Aquamous Cell Carcinoma of the Head and Neck," *J Clin Oncol*, 2005, 23(24):5578-87.[PubMed 16009949]

Cisplatin-Dacarbazine-Carmustine (Melanoma)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Melanoma

Regimen UseMelanoma

Index TermsCarmustine-Cisplatin-Dacarbazine; Dacarbazine-Carmustine-Cisplatin

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cisplatin: I.V.: 25 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Dacarbazine: I.V.: 220 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 660 mg/m^2]

Carmustine: I.V.: 150 mg/m^2 day 1 (every other cycle **[odd cycles]**)

[total dose/**odd** cycles = 150 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Carmustine: I.V.: 150 mg/m^2 day 1

[total dose/cycle = 150 mg/m^2]

Cisplatin: I.V.: 25 mg/m^2/day days 1, 2, 3, 22, 23, and 24

[total dose/cycle = 150 mg/m^2]

Dacarbazine: I.V.: 220 mg/m^2/day days 1, 2, 3, 22, 23, and 24

[total dose/cycle = 1320 mg/m^2]

Repeat cycle every 42 days

References

Variation 1:

Creagan ET, Suman VJ, Dalton RJ, et al, "Phase III Clinical Trial of the Combination of Cisplatin, Dacarbazine, and Carmustine With or Without Tamoxifen in Patients With Advanced Malignant Melanoma," *J Clin Oncol*, 1999, 17(6):1884-90.[PubMed 10561229]

Variation 2:

Rusthoven JJ, Quirt IC, Iscoe NA, et al, "Randomized, Double-Blind, Placebo-Controlled Trial Comparing the Response Rates of Carmustine, Dacarbazine, and Cisplatin With and Without Tamoxifen in Patients With Metastatic Melanoma. National Cancer Institute of Canada Clinical Trials Group," *J Clin Oncol*, 1996, 14(7):2083-90.[PubMed 8683240]

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Melanoma

Regimen Use Melanoma

Index Terms Dacarbazine-Cisplatin-Interferon Alfa-2b-Aldesleukin

Regimen

Cisplatin: I.V.: 25 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Dacarbazine: 250 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 750 mg/m^2]

Interferon Alfa-2b: SubQ: 5 million units/m^2/day days 6, 8, 10, 13, and 15

[total dose/cycle = 25 million units/m^2]

Aldesleukin: I.V.: 18 million units/m^2/day days 6, 7, 8, 9, 10, 13, 14, and 15

[total dose/cycle = 144 million units/m^2]

Repeat cycle every 28 days

References

Flaherty LE, Atkins M, Sosman J, et al, "Outpatient Biochemotherapy With Interleukin-2 and Interferon Alfa-2b in Patients With Metastatic Malignant Melanoma: Results of Two Phase II Cytokine Working Group Trials," *J Clin Oncol*, 2001, 19(13):3194-202.[PubMed 11432886]

Cisplatin-Docetaxel

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Bladder Cancer]

Regimen UseBladder cancer

Regimen

Cisplatin: I.V.: 30 mg/m^2 day 1

[total dose/cycle = 30 mg/m^2]

Docetaxel: I.V.: 40 mg/m^2 day 4

[total dose/cycle = 40 mg/m^2]

Repeat cycle weekly for 8 weeks

References

Varveris H, Delakas D, Anezinis P, et al, âConcurrent Platinum and Docetaxel Chemotherapy and External Radical Radiotherapy in Patients With Invasive Transitional Cell Bladder Carcinoma. A Preliminary Report of Tolerance and Local Control,â *Anticancer Res*, 1997, 17(6D):4771-80.[PubMed 9494605]

Cisplatin-Etoposide (NSCLC)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Nonsmall Cell)

Regimen UseLung cancer, nonsmall cell

Index TermsEtoposide-Cisplatin

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cisplatin: I.V.: 80 mg/m^2 day 1

[total dose/cycle = 80 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 300 mg/m^2]

Repeat cycle every 21 days for a total of 4 cycles

Variation 2:

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 300 mg/m^2]

Repeat cycle every 28 days for a total of 3 cycles

Variation 3:

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 300 mg/m^2]

Repeat cycle every 28 days for a total of 4 cycles

Variation 4:

Cisplatin: I.V.: 120 mg/m^2/day days 1, 29, and 71

[total dose/treatment = 360 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1, 2, 3, 29, 30, 31, 71, 72, and 73

[total dose/treatment = 900 mg/m^2]

Variation 5:

Cisplatin: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 300 mg/m^2]

Repeat cycle every 21 days for up to 10 cycles

References

Variations 1-4:

Arriagada R, Bergman B, Dunant A, et al, "Cisplatin-Based Adjuvant Chemotherapy in Patients With Completely Resected Non-Small-Cell Lung Cancer," *N Engl J Med*, 2004, 350(4):351-60.[PubMed 14736927]

Variation 5:

Belani CP, Lee JS, Socinski MA, et al, "Randomized Phase III Trial Comparing Cisplatin-Etoposide to Carboplatin-Paclitaxel in Advanced or Metastatic Non-Small Cell Lung Cancer," *Ann Oncol*, 2005, 16(7):1069-75.[PubMed 15860487]

Cisplatin-Fluorouracil (Cervical Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Cervical Cancer

Regimen UseCervical cancer

Index TermsFluorouracil-Cisplatin (Cervical Cancer)

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cisplatin: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 4 (96 hours)

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Cisplatin: I.V.: 50 mg/m^2 day 1 starting 4 hours before radiotherapy

[total dose/cycle = 50 mg/m^2]

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 2 to 5 (96 hours)

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 28 days

Variation 3:

Cisplatin: I.V.: 70 mg/m^2 day 1

[total dose/cycle = 70 mg/m^2]

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 4 (96 hours)

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 21 days

References

Variation 1:

Morris M, Eifel PJ, Lu J, et al, “Pelvic Radiation With Concurrent Chemotherapy Compared With Pelvic and Para-aortic Radiation for High-Risk Cervical Cancer,” *N Engl J Med*, 1999, 340(15):1137-43. [PubMed 10202164]

Variation 2:

Whitney CW, Sause W, Bundy BN, et al, “Randomized Comparison of Fluorouracil Plus Cisplatin Versus Hydroxyurea as an Adjunct to Radiation Therapy in Stage IIB-IVA Carcinoma of the Cervix With Negative Para-aortic Lymph Nodes: A Gynecologic Oncology Group and Southwest Oncology Group Study,” *J Clin Oncol*, 1999, 17(5):1339-48.[PubMed 10334517]

Variation 3:

Peters WA 3rd, Liu PY, Barrett RJ 2nd, et al, "Concurrent Chemotherapy and Pelvic Radiation Therapy Compared With Pelvic Radiation Therapy Alone as Adjuvant Therapy After Radical Surgery in High-Risk Early-Stage Cancer of the Cervix," *J Clin Oncol*, 2000, 18(8):1606-13.[PubMed 10764420]

Cisplatin-Fluorouracil (Esophageal Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Esophageal Cancer

Regimen Use Esophageal cancer

Index Terms CF (Esophageal Cancer); Fluorouracil-Cisplatin (Esophageal Cancer)

Regimen NOTE: Multiple variations are listed below.

Variation 1:

- Cisplatin: I.V.: 100 mg/m^2/dose day 1
  - [total dose/cycle = 100 mg/m^2]
- Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 5
  - [total dose/cycle = 5000 mg/m^2]
- Repeat cycle every 28 days

Variation 2:

- Cycles 1 to 3 (prior to surgery):
  - Cisplatin: I.V.: 100 mg/m^2/dose day 1
    - [total dose/cycle = 100 mg/m^2]
  - Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 5
    - [total dose/cycle = 5000 mg/m^2]
  - Treatment cycles 1-3 are 28 days each
- Cycles 4 and 5 (postoperative):
  - Cisplatin: I.V.: 75 mg/m^2/dose day 1
    - [total dose/cycle = 75 mg/m^2]
  - Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 5
    - [total dose/cycle = 5000 mg/m^2]
  - Treatment cycles 4 and 5 are 28 days each

Variation 3 (in combination with radiation therapy):

- Cycle 1:
  - Cisplatin: I.V.: 75 mg/m^2/dose day 1
    - [total dose/cycle = 75 mg/m^2]
  - Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 4
    - [total dose/cycle = 4000 mg/m^2]
  - Treatment cycle is 28 days
- Cycles 2 to 4:
  - Cisplatin: I.V.: 75 mg/m^2/dose day 1
    - [total dose/cycle = 75 mg/m^2]
  - Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 4
    - [total dose/cycle = 4000 mg/m^2]
  - Repeat cycle every 21 days for 3 more cycles (total of 4 cycles)

Variation 4 (in combination with radiation therapy):

- Cisplatin: I.V.: 100 mg/m^2/dose day 1
  - [total dose/cycle = 100 mg/m^2]
- Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 4
  - [total dose/cycle = 4000 mg/m^2]
- Repeat cycle every 28 days for total of 2 cycles

Variation 5 (in combination with radiation therapy):

- Cisplatin: I.V.: 75 mg/m^2/dose day 1
  - [total dose/cycle = 75 mg/m^2]
- Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 4
  - [total dose/cycle = 4000 mg/m^2]
- Repeat cycle every 28 days for 4 cycles

Variation 6 (in combination with radiation therapy):

- Cycles 1 and 2:
  - Cisplatin: I.V.: 75 mg/m^2/dose day 1
    - [total dose/cycle = 75 mg/m^2]
  - Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 4
    - [total dose/cycle = 4000 mg/m^2]
  - Treatment cycles 1 and 2 are 28 days each; cycle 2 is followed by a 2-week rest
- Cycles 3 and 4 (begin cycle 3 at week 11):
  - Cisplatin: I.V.: 75 mg/m^2/dose day 1
    - [total dose/cycle = 75 mg/m^2]
  - Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 4
    - [total dose/cycle = 4000 mg/m^2]
  - Treatment cycles 3 and 4 are 28 days each

Variation 7 (in combination with radiation therapy):

- Cycles 1 to 4:
  - Cisplatin: I.V.: 15 mg/m^2/day days 1 to 5
    - [total dose/cycle = 75 mg/m^2]
  - Fluorouracil: I.V.: 800 mg/m^2/day continuous infusion days 1 to 5
    - [total dose/cycle = 4000 mg/m^2]
  - Repeat cycles 1-4 every 21 days; cycle 4 is followed by a 1-week rest
- Cycles 5 (begin cycle 5 at week 14):
  - Cisplatin: I.V.: 15 mg/m^2/day days 1 to 5
    - [total dose/cycle = 75 mg/m^2]
  - Fluorouracil: I.V.: 800 mg/m^2/day continuous infusion days 1 to 5
    - [total dose/cycle = 4000 mg/m^2]

References

Variation 1:

Ajani JA, Moiseyenko VM, Tjulandin S, et al, "Quality of Life With Docetaxel Plus Cisplatin and Fluorouracil Compared With Cisplatin and

Fluorouracil From a Phase III Trial for Advanced Gastric or Gastroesophageal Adenocarcinoma: The V-325 Study Group," *J Clin Oncol*, 2007, 25(22):3210-6.[PubMed 17664468]

Variation 2:

Kelsen DP, Ginsberg R, Pajak TF, et al, "Chemotherapy Followed by Surgery Compared With Surgery Alone for Localized Esophageal Cancer," *N Engl J Med*, 1998, 339(27):1979-84.[PubMed 9869669]

Variation 3:

Cooper JS, Guo MD, Herskovic A, et al, "Chemoradiotherapy of Locally Advanced Esophageal Cancer: Long-Term Follow-Up of a Prospective Randomized Trial (RTOG 85-01). Radiation Therapy Oncology Group," *JAMA*, 1999, 281(17):1623-7.[PubMed 10235156]

Variation 4:

Tepper J, Krasna MJ, Niedzwiecki D, et al, "Phase III Trial of Trimodality Therapy With Cisplatin, Fluorouracil, Radiotherapy, and Surgery Compared With Surgery Alone for Esophageal Cancer: CALGB 9781," *J Clin Oncol*, 2008, 26(7):1086-92.[PubMed 18309943]

Variation 5 and 6:

Minsky BD, Pajak TF, Ginsberg RJ, et al, "INT 0123 (Radiation Therapy Oncology Group 94-05) Phase III Trial of Combined-Modality Therapy for Esophageal Cancer: High-Dose Versus Standard-Dose Radiation Therapy," *J Clin Oncol*, 2002, 20(5):1167-74.[PubMed 11870157]

Variation 7:

Bedenne L, Michel P, BouchĂŠ O, et al, "Chemoradiation Followed by Surgery Compared With Chemoradiation Alone in Squamous Cancer of the Esophagus: FFCD 9102," *J Clin Oncol*, 2007, 25(10):1160-8.[PubMed 17401004]

Cisplatin-Irinotecan (Small Cell Lung Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Small Cell)

Regimen UseLung cancer, small cell

Index TermsIrinotecan-Cisplatin (Small Cell Lung Cancer)

Regimen

Cisplatin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Irinotecan: I.V.: 60 mg/m^2 days 1, 8, and 15

[total dose/cycle = 180 mg/m^2]

Repeat cycle every 28 days for 4 cycles

References

Noda K, Nishiwaki Y, Kawahara M, et al, "Irinotecan Plus Cisplatin Compared With Etoposide Plus Cisplatin for Extensive Small-Cell Lung Cancer," *N Engl J Med*, 2002, 346(2):85-91.[PubMed 11784874]

Cisplatin-Paclitaxel (Intraperitoneal Regimen)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Ovarian Cancer

Regimen Use Ovarian cancer

Index Terms Paclitaxel-Cisplatin (Intraperitoneal Regimen)

Regimen **Note:** I.P. therapies administered in 2 liters warmed saline

Paclitaxel: I.V.: 135 mg/m^2 continuous infusion (over 24 hours) day 1

[total dose/cycle = 135 mg/m^2]

Cisplatin: I.P.: 100 mg/m^2 day 2

[total dose/cycle = 100 mg/m^2]

Paclitaxel: I.P.: 60 mg/m^2 day 8

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 21 days for 6 cycles

References

Armstrong DK, Bundy B, Wenzel L, et al, "Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer," *N Engl J Med*, 2006, 354(1):34-43.[PubMed 16394300]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Malignant Pleural Mesothelioma

Regimen UseMalignant pleural mesothelioma

Index TermsPemetrexed-Cisplatin (Mesothelioma)

Regimen

Pemetrexed: I.V.: 500 mg/m^2 infused over 10 minutes day 1

[total dose/cycle = 500 mg/m^2]

Cisplatin: I.V.: 75 mg/m^2 infused over 2 hours day 1 (start 30 minutes after pemetrexed)

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 21 days

References

Vogelzang NJ, Rusthoven JJ, Symanowski J, et al, âPhase III Study of Pemetrexed in Combination With Cisplatin Versus Cisplatin Alone in Patients With Malignant Pleural Mesothelioma,â *J Clin Oncol*, 2003, 21(14):2636-44.[PubMed 12860938]

Cisplatin-Vinblastine (NSCLC)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lung Cancer (Nonsmall Cell)
Regimen Use Lung cancer, nonsmall cell
Index Terms Vinblastine-Cisplatin
Regimen NOTE: Multiple variations are listed below.

Variation 1:

Cisplatin: I.V.: 80 mg/m^2/day days 1, 22, 43, and 64

[total dose/treatment = 320 mg/m^2]

Vinblastine: I.V.: 4 mg/m^2/day days 1, 8, 15, 22, 29, 43, and 57

[total dose/treatment = 28 mg/m^2]

Variation 2:

Cisplatin: I.V.: 100 mg/m^2/day days 1, 29, and 57

[total dose/treatment = 300 mg/m^2]

Vinblastine: I.V.: 4 mg/m^2/day days 1, 8, 15, 22, 29, 43, and 57

[total dose/treatment = 28 mg/m^2]

Variation 3:

Cisplatin: I.V.: 100 mg/m^2/day days 1, 29, 57, and 85

[total dose/treatment = 400 mg/m^2]

Vinblastine: I.V.: 4 mg/m^2/day days 1, 8, 15, 22, 29, 43, 57, 71, and 85

[total dose/treatment = 36 mg/m^2]

Variation 4:

Cisplatin: I.V.: 120 mg/m^2/day days 1, 29, and 71

[total dose/treatment = 360 mg/m^2]

Vinblastine: I.V.: 4 mg/m^2/day days 1, 8, 15, 22, 29, 43, 57, and 71

[total dose/treatment = 32 mg/m^2]

References

Arriagada R, Bergman B, Dunant A, et al, "Cisplatin-Based Adjuvant Chemotherapy in Patients With Completely Resected Non-Small-Cell Lung Cancer," *N Engl J Med*, 2004, 350(4):351-60.[PubMed 14736927]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Melanoma

Regimen UseMelanoma

Index TermsCVD; Dacarbazine-Cisplatin-Vinblastine; Vinblastine-Cisplatin-Dacarbazine

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cisplatin: I.V.: 20 mg/m^2/day days 2 to 5

[total dose/cycle = 80 mg/m^2]

Vinblastine: I.V.: 1.6 mg/m^2/day days 1 to 5

[total dose/cycle = 8 mg/m^2]

Dacarbazine: I.V.: 800 mg/m^2 day 1

[total dose/cycle = 800 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 4

[total dose/cycle = 80 mg/m^2]

Vinblastine: I.V.: 2 mg/m^2/day days 1 to 4

[total dose/cycle = 8 mg/m^2]

Dacarbazine: I.V.: 800 mg/m^2 day 1

[total dose/cycle = 800 mg/m^2]

Repeat cycle every 21 days

References

Variation 1:

Legha SS, Ring S, Papadopoulos N, et al, “A Prospective Evaluation of a Triple-Drug Regimen Containing Cisplatin, Vinblastine, and Dacarbazine (CVD) for Metastatic Melanoma,” *Cancer*, 1989, 64(10):2024-9.[PubMed 2804890]

Variation 2:

Eton O, Legha SS, Bedikian AY, et al, “Sequential Biochemotherapy Versus Chemotherapy for Metastatic Melanoma: Results From a Phase III Randomized Trial,” *J Clin Oncol*, 2002, 20(8):2045-52.[PubMed 11956264]

Cisplatin-Vinorelbine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Cervical Cancer

Regimen UseCervical cancer

Regimen

Cisplatin: I.V.: 80 mg/m^2 day 1

[total dose/cycle = 80 mg/m^2]

Vinorelbine: I.V.: 25 mg/m^2/day days 1 and 8

[total dose/cycle = 50 mg/m^2]

Repeat cycle every 21 days

References

Pignata S, Silvestro G, Ferrari E, et al, âPhase II Study of Cisplatin and Vinorelbine as First-Line Chemotherapy in Patients With Carcinoma of the Uterine Cervix,â *J Clin Oncol*, 1999, 17(3):756-60.[PubMed 10071263]

CISplatin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

CISplatin may be confused with CARBOplatin

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Doses >100 mg/m^2 once every 3-4 weeks are rarely used and should be verified with the prescriber.

Pronunciation(SIS pla tin)

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent; Antineoplastic Agent, Platinum Analog

Use: Labeled IndicationsTreatment of bladder, testicular, and ovarian cancer

Use: Unlabeled/InvestigationalTreatment of head and neck, breast, gastric, lung, esophageal, cervical, prostate and small cell lung cancer; Hodgkin's and non-Hodgkin's lymphoma; neuroblastoma; sarcomas, myeloma, melanoma, mesothelioma, and osteosarcoma

Dosing: Adults

Advanced bladder cancer: 50-70 mg/m^2 every 3-4 weeks

Head and neck cancer (unlabeled use): 100-120 mg/m^2 every 3-4 weeks

Malignant pleural mesothelioma in combination with pemetrexed: 75 mg/m^2 on day 1 of each 21-day cycle; see Pemetrexed monograph for additional details

Metastatic ovarian cancer: 75-100 mg/m^2 every 3-4 weeks

Intraperitoneal: Cisplatin has been administered intraperitoneal with systemic sodium thiosulfate for ovarian cancer; doses up to 90-270 mg/m^2 have been administered and retained for 4 hours before draining

Testicular cancer: 10-20 mg/m^2/day for 5 days repeated every 3-4 weeks

High dose BMT: Continuous I.V.: 55 mg/m^2/24 hours for 72 hours; total dose: 165 mg/m^2

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols. **VERIFY ANY CISPLATIN DOSE EXCEEDING 100 mg/m^2 PER COURSE.**

Unlabeled pediatric uses:

Intermittent dosing schedule: 37-75 mg/m^2 once every 2-3 weeks or 50-100 mg/m^2 over 4-6 hours, once every 21-28 days

Daily dosing schedule: 15-20 mg/m^2/day for 5 days every 3-4 weeks

Osteogenic sarcoma or neuroblastoma: 60-100 mg/m^2 on day 1 every 3-4 weeks

Recurrent brain tumors: 60 mg/m^2 once daily for 2 consecutive days every 3-4 weeks

Bone marrow/blood cell transfusion: Continuous Infusion: High dose: 55 mg/m^2/day for 72 hours; total dose = 165 mg/m^2

Dosing: Renal Impairment**Note:** The manufacturer(s) recommend that repeat courses of cisplatin should not be given until serum creatinine is <1.5 mg/dL and/or BUN is <25 mg/dL. The FDA-approved labeling does not contain renal dosing adjustment guidelines. The following guidelines have been used by some clinicians:

Aronoff, 2007:

Cl_{cr} 10-50 mL/minute: Administer 75% of dose

Cl_{cr} <10 mL/minute: Administer 50% of dose

Hemodialysis: Partially cleared by hemodialysis.

Administer 50% of dose posthemodialysis

Continuous ambulatory peritoneal dialysis (CAPD): Administer 50% of dose

Continuous renal replacement therapy (CRRT): Administer 75% of dose

Kintzel, 1995:

Cl_{cr} 46-60 mL/minute: Administer 75% of dose

Cl_{cr} 31-45 mL/minute: Administer 50% of dose

Cl_{cr} <30 mL/minute: Consider use of alternative drug

Dosing: Combination Regimens

Adenocarcinoma, unknown primary: EP (Adenocarcinoma)

Bladder cancer:

- CAP
- CISCA
- Cisplatin-Docetaxel
- CMV
- Gemcitabine-Cisplatin (Bladder Cancer)
- M-VAC (Bladder Cancer)

Brain tumors:

- 8 in 1 (Brain Tumors)
- CDDP/VP-16
- COPE

Breast Cancer:

- Docetaxel-Trastuzumab-Cisplatin
- MVAC (Breast Cancer)

Cervical cancer:

- BIP
- Cisplatin-Fluorouracil (Cervical Cancer
- Cisplatin-Vinorelbine
- Gemcitabine-Cisplatin
- MVAC (Cervical Cancer)
- Paclitaxel-Cisplatin (Cervical Cancer)
- Topotecan-Cisplatin

Colorectal cancer: PFL (Colorectal Cancer)

Endometrial cancer:

- AP
- MVAC (Endometrial Cancer)

Esophageal cancer:

- Irinotecan-Cisplatin
- TCF
- TIP

Gastric cancer:

- Docetaxel-Cisplatin-Fluorouracil (Gastric Cancer)
- EAP
- ECF

EFP

FAP

FUP

Gestational trophoblastic tumor: EP/EMA

Head and neck cancer:

CABO

Cetuximab-Cisplatin-Fluorouracil

Cisplatin-Cetuximab

CF

Docetaxel-Cisplatin-Fluorouracil (Head and Neck Cancer)

MVAC (Head and Neck Cancer)

PFL (Head and Neck Cancer)

PFL + IFN

TIP

Hepatoblastoma:

IPA

PA-CI

Lung cancer (nonsmall cell):

Bevacizumab-Cisplatin-Gemcitabine

Cetuximab-Cisplatin-Vinorelbine

Cisplatin-Etoposide (NSCLC)

Cisplatin-Vinblastine (NSCLC)

Docetaxel-Cisplatin

EP (NSCLC)

EP/PE

Gemcitabine-Cisplatin (NSCLC)

PC (NSCLC)

Pemetrexed-Cisplatin (NSCLC)

Vinorelbine-Cisplatin

Lung cancer (small cell):

Cisplatin-Irinotecan (Small Cell Lung Cancer)

EP (Small Cell Lung Cancer)

Topotecan (Oral)-Cisplatin

VIP (Small Cell Lung Cancer)

VP (Small Cell Lung Cancer)

Lymphoma, non-Hodgkin's:

DHAP

ESHAP

Malignant pleural mesothelioma: Cisplatin-Pemetrexed (Mesothelioma)

Melanoma:

CCDT (Melanoma)

Cisplatin-Dacarbazine-Carmustine (Melanoma)

Cisplatin-Dacarbazine-Interferon Alfa-2b-Aldesleukin

Cisplatin-Vinblastine-Dacarbazine (Melanoma)

Dartmouth Regimen

IL-2 + IFN

Multiple myeloma: DTPACE

Neuroblastoma:

CAV-P/VP

CCDDT (Neuroblastoma)

CCT (Neuroblastoma)

HIPE-IVAD

N6 Protocol

OPEC

OPEC-D

PE-CAdO

Regimen A1

Regimen A2

Osteosarcoma:

MTX-CDDPAdr

POG-8651

Ovarian cancer:

BEP (Ovarian Cancer)

BEP (Ovarian Cancer, Testicular Cancer)

Cisplatin-Paclitaxel (Intraperitoneal Regimen)

CP (Ovarian Cancer)

CT

PAC (CAP)

Retinoblastoma:

8 in 1 (Retinoblastoma)

CCCDE (Retinoblastoma)

Testicular cancer:

BEP (Ovarian Cancer, Testicular Cancer)

BEP (Testicular Cancer)

EP (Testicular Cancer)

Paclitaxel-Ifosfamide-Cisplatin

PVB

VBP

VIP (Etoposide) (Testicular Cancer)

VIP (Vinblastine) (Testicular Cancer)

Oncology: Bone Marrow - High DoseContinuous I.V.: 55 mg/m^2/24 hours for 72 hours; total dose: 165 mg/m^2; generally combined with other high-dose chemotherapy

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Irritant. Perform pretreatment hydration (see Dosage).

I.V.: Rate of administration has varied from a 15- to 120-minute infusion, 1 mg/minute infusion, 6- to 8-hour infusion, 24-hour infusion, or per protocol. Maximum rate of infusion: 1 mg/minute in patients with CHF.

Administration: I.V. DetailpH: 3.5-5.5 (reconstituted solution); 3.7-6.0 (aqueous injection)

Dietary ConsiderationsSodium content: 9 mg/mL (equivalent to 0.9% sodium chloride solution)

StorageStore intact vials at room temperature 15°C to 25°C (59°F to 77°F) and protect from light. Do not refrigerate solution as a precipitate may form. Further dilution **stability is dependent on the chloride ion concentration** and should be mixed in solutions of NS (at least 0.3% NaCl). After initial entry into the vial, solution is stable for 28 days protected from light or for at least 7 days under fluorescent room light at room temperature.

Further dilutions in NS, D$_5$/0.45% NaCl or D$_5$/NS to a concentration of 0.05-2 mg/mL are stable for 72 hours at 4°C to 25°C. The infusion solution should have a final sodium chloride concentration ≥0.2%.

ReconstitutionThe infusion solution should have a final sodium chloride concentration ≥0.2%.

CompatibilityStable in D$_5$^{1}/$_4$NS, D$_5$^{1}/$_2$NS, D$_5$NS, ^{1}/$_4$NS, ^{1}/$_3$NS, ^{1}/$_2$NS, NS; **incompatible** with sodium bicarbonate; **variable stability (consult detailed reference)** in D$_5$W.

Y-site administration: Compatible: Allopurinol, aztreonam, bleomycin, chlorpromazine, cimetidine, cladribine, cyclophosphamide, dexamethasone sodium phosphate, diphenhydramine, doxorubicin, doxorubicin liposome, droperidol, etoposide phosphate, famotidine, filgrastim, fludarabine, fluorouracil, furosemide, ganciclovir, gatifloxacin, gemcitabine, granisetron, heparin, hydromorphone, leucovorin, linezolid, lorazepam, melphalan, methotrexate, methylprednisolone sodium succinate, metoclopramide, mitomycin, morphine, ondansetron, paclitaxel, prochlorperazine edisylate, promethazine, propofol, ranitidine, sargramostim, teniposide, topotecan, vinblastine, vincristine, vinorelbine. **Incompatible:** Amifostine, amphotericin B cholesteryl sulfate complex, cefepime, piperacillin/tazobactam, thiotepa.

Compatibility in syringe: Compatible: Bleomycin, cyclophosphamide, doxapram, doxorubicin, droperidol, fluorouracil, furosemide, heparin, leucovorin, methotrexate, metoclopramide, mitomycin, vinblastine, vincristine.

Compatibility when admixed: Compatible: Carboplatin, cyclophosphamide with etoposide, etoposide, etoposide with floxuridine, floxuridine, floxuridine with leucovorin, hydroxyzine, ifosfamide, ifosfamide with etoposide, leucovorin, magnesium sulfate, mannitol, ondansetron. **Incompatible:** Fluorouracil, mesna, thiotepa. **Variable (consult detailed reference):** Etoposide with mannitol and potassium chloride, paclitaxel.

ContraindicationsHypersensitivity to cisplatin, other platinum-containing compounds, or any component of the formulation (anaphylactic-like reactions have been reported); pre-existing renal insufficiency; myelosuppression; hearing impairment; pregnancy

Allergy Considerations

- Platinum Derivative Allergy

Warnings/Precautions

Boxed warnings:

- Anaphylaxis: See "Concerns related to adverse effects" below.
- Experienced physician: See "Other warnings/precautions" below.
- Medication safety (usual maximum dose per cycle): See "Other warnings/precautions" below.
- Ototoxicity: See "Concerns related to adverse effects" below.
- Renal toxicity: See "Concerns related to adverse effects" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Anaphylaxis: **[U.S. Boxed Warnings]: Anaphylactic-like reactions have been reported; may be managed with epinephrine, corticosteroids, and/or antihistamines.**
- Dose-related toxicities: Myelosuppression, nausea, and vomiting are dose-related toxicities with use.
- Neuropathy: Severe and possibly irreversible neuropathies may occur with higher than recommended doses or more frequent regimen.
- Ototoxicity: **[U.S. Boxed Warnings]: Ototoxicity, especially pronounced in children, is manifested by tinnitus or loss of high frequency hearing and occasionally, deafness.**
- Renal toxicity: **[U.S. Boxed Warning]: Cumulative renal toxicity may be severe.**

Disease-related concerns:

- Renal impairment: Reduce dosage in renal impairment.

Concurrent drug therapy issues:

- Taxane derivatives: When administered as sequential infusions, taxane derivatives (docetaxel, paclitaxel) should be administered before platinum derivatives (carboplatin, cisplatin).

Special populations:

- Elderly: Select dose cautiously and monitor closely in the elderly; may be more susceptible to nephrotoxicity and peripheral neuropathy.

Other warnings/precautions:

- Medication safety (usual maximum dose per cycle): **[U.S. Boxed Warning]: Doses >100 mg/m^2 once every 3-4 weeks are rarely used and should be verified with the prescriber.**
- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**
- Hydration: Patients should receive adequate hydration, with or without diuretics, prior to and for 24 hours after administration; serum electrolytes, particularly magnesium and potassium, should be monitored and replaced as needed during and after therapy.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenicity and embryotoxicity. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid pregnancy. If used in pregnancy, or if patient becomes pregnant during treatment, the patient should be apprised of potential hazard to the fetus.

LactationEnters breast milk/contraindicated

Adverse Reactions

>10%:

Central nervous system: Neurotoxicity: Peripheral neuropathy is dose- and duration-dependent.

Dermatologic: Mild alopecia

Gastrointestinal: Nausea and vomiting (76% to 100%)

Hematologic: Myelosuppression (25% to 30%; mild with moderate doses, mild to moderate with high-dose therapy)

WBC: Mild

Platelets: Mild

Onset: 10 days

Nadir: 14-23 days

Recovery: 21-39 days

Hepatic: Liver enzymes increased

Renal: Nephrotoxicity (acute renal failure and chronic renal insufficiency)

Otic: Ototoxicity (10% to 30%; manifested as high frequency hearing loss; ototoxicity is especially pronounced in children)

1% to 10%:

Gastrointestinal: Diarrhea

Local: Tissue irritation

<1%: Anaphylactic reaction, arrhythmias, blurred vision, bradycardia, hemolytic uremic syndrome, mild alopecia, mouth sores, optic neuritis, orthostatic hypotension, papilledema, phlebitis, SIADH, thrombophlebitis

Oncology: VesicantNo

Oncology: Emetic PotentialHigh (>90%)

Oncology: Bone Marrow - Unique Toxicity

Central nervous system: Autonomic neuropathy, ototoxicity

Gastrointestinal: Highly emetogenic

Hematologic: Myelosuppression

Endocrine & metabolic: Hypokalemia, hypomagnesemia

Neuromuscular & skeletal: Peripheral neuropathy

Ocular: Optic neuropathy, retinal vascular occlusion and myelopathy (concurrent administration of high-dose carmustine)

Renal: Acute renal failure, serum creatinine increased, azotemia

Miscellaneous: Transient pain at tumor, transient autoimmune disorders

Drug Interactions

Aminoglycosides: CISplatin may enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Taxane Derivatives: Platinum Derivatives may enhance the myelosuppressive effect of Taxane Derivatives. Administer Taxane derivative before Platinum derivative when given as sequential infusions to limit toxicity. *Risk D: Consider therapy modification*

Topotecan: Platinum Derivatives may enhance the adverse/toxic effect of Topotecan. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vinorelbine: CISplatin may enhance the adverse/toxic effect of Vinorelbine. Specifically, the combination may be associated with a higher risk of granulocytopenia. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid black cohosh, dong quai in estrogen-dependent tumors.

Monitoring ParametersRenal function (serum creatinine, BUN, Cl_{cr}); electrolytes (particularly magnesium, calcium, potassium) before and within 48 hours after cisplatin therapy; audiography (baseline and prior to each subsequent dose), neurologic exam (with high dose); liver function tests periodically, CBC with differential and platelet count; urine output, urinalysis

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions (especially anything that is ototoxic or nephrotoxic). Patient should be vigorously hydrated prior to and for 24 hours following infusion. Cisplatin is highly emetogenic; antiemetic should be administered prior to each treatment and as needed between infusions. Infusion site must be monitored closely to reduce potential for extravasation. Assess results of laboratory tests and auditory status prior to each treatment and regularly during therapy. Patient response should be closely monitored during and following therapy (eg, acute or chronic renal failure; peripheral neuropathy and ototoxicity, may be irreversible). Teach patient (or caregiver) possible side effects/appropriate interventions (eg, importance of adequate hydration) and adverse symptoms to report.

Monitoring: Lab TestsRenal function (serum creatinine, BUN, Cl_{cr}); electrolytes (particularly magnesium, calcium, potassium) before and within 48 hours after cisplatin therapy; liver function periodically, CBC with differential and platelet count, urinalysis

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by I.V. and numerous side-effects can occur. Report immediately any burning, pain, itching, or redness at infusion site. It is important that you maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and adequate nutrition (small, frequent meals may help). May cause severe nausea or vomiting that can be delayed for up to 48 hours after infusion and last for 1 week (consult prescriber for appropriate antiemetic medication); mouth sores (use soft toothbrush or cotton swabs for mouth care); or loss of hair (reversible). You will be susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). Report promptly any pain, tingling, loss of sensation or cramping in extremities; change in hearing; difficulty breathing or swallowing; fever or chills; unusual fatigue; unusual bruising/bleeding; or any other unusual symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 1 mg/mL (50 mL, 100 mL, 200 mL)

Generic AvailableYes

Mechanism of ActionInhibits DNA synthesis by the formation of DNA cross-links; denatures the double helix; covalently binds to DNA bases and disrupts DNA function; may also bind to proteins; the *cis*-isomer is 14 times more cytotoxic than the *trans*-isomer; both forms cross-link DNA but cis-platinum is less easily recognized by cell enzymes and, therefore, not repaired. Cisplatin can also bind two adjacent guanines on the same strand of DNA producing intrastrand cross-linking and breakage.

Pharmacodynamics/Kinetics

Distribution: I.V.: Rapidly into tissue; high concentrations in kidneys, liver, ovaries, uterus, and lungs

Protein binding: >90%

Metabolism: Nonenzymatic; inactivated (in both cell and bloodstream) by sulfhydryl groups; covalently binds to glutathione and thiosulfate

Half-life elimination: Initial: 20-30 minutes; Beta: 60 minutes; Terminal: ~24 hours; Secondary half-life: 44-73 hours

Excretion: Urine (>90%); feces (10%)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine

Anesthesia and Critical Care Concerns/Other Considerations

Nephrotoxicity: Related to elimination, protein binding, and uptake of cisplatin. Two types of nephrotoxicity: Acute renal failure and chronic renal insufficiency.

Acute renal failure and azotemia is a dose-dependent process and can be minimized with proper administration and prophylaxis. Damage to the proximal tubules by unbound cisplatin is suspected to cause the toxicity. It is manifested as increased BUN/creatinine, oliguria, protein wasting, and potassium, calcium, and magnesium wasting.

Chronic renal dysfunction can develop in patients receiving multiple courses of cisplatin. Slow release of tissue-bound cisplatin may contribute to chronic nephrotoxicity. Manifestations of this toxicity are varied, and can include sodium and water wasting, nephropathy, hyperuricemia, decreased Cl_{cr}, and magnesium wasting.

Recommendations for minimizing nephrotoxicity include:

Prepare cisplatin in saline-containing vehicles.

Infuse dose over 24 hours.

Vigorously hydrate patient (125-150 mL/hour) before, during, and after cisplatin administration.

Simultaneously administer either mannitol or furosemide.

Pretreat with amifostine.

Avoid other nephrotoxic agents (aminoglycosides, amphotericin, etc).

Neurotoxicity: Peripheral neuropathy is dose- and duration-dependent. The mechanism is through axonal degeneration with subsequent damage to the long sensory nerves. Toxicity can first be noted at cumulative doses of 200 mg/m^2, with measurable toxicity at cumulative doses >350 mg/m^2. This process is irreversible and progressive with continued therapy.

Anaphylactic Reaction: Occurs within minutes after intravenous or intraperitoneal administration; can be controlled with epinephrine, antihistamines, and steroids.

Index Terms CDDP

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International Brand Names Abiplatin (AT, IL, TW); Blastolem (CN, PL); Blastolem RU (MX, TH); Cisly (LU); Cispatin (KP); Cisplatin (AU, ID, IN); Cisplatin Ebewe (HU, PL); Cisplatin medac (LU); Cisplatin Teva (HU); Cisplatin-Ebewe (MY); Cisplatin-Knoll (PL); Cisplatine-Lilly (LU); Cisplatino (CO, ES, PE); Cisplatinum (MY, PL, TH); Cisplatinum Cytosafe-Delta West (LU); Cisplatyl (BR, FR, PE, PL); Citoplatino (IT); Cytosplat (PH); Elvecis (AR); Kemoplat (IN, PH); Lederplatin (DK); Neoplatin (ES); Oncotin (PH); P&U Cisplatin (ZA); Placis (ES); Platamine (AE, BH, CY, EG, HR, IL, IQ, IR, IT, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE); Platamine RTU (ID); Platiblastin (AT, CH, DE); Platidiam (BG, CZ, HN, HU, PL); Platimit (HR); Platinex (HR, IT, PL); Platinil (BR); Platinol (AR, BE, CH, EE, FI, GR, LU, NO, PH, PL, SE, TH, TW, UY); Platinol-AQ (NZ); Platinox (ID); Platistil (ES, PT); Platistin (FI, NO, SE); Platistine (LU); Platosin (GB, MY, NL, PH, PK, TH); Randa (JP); Sicatem (PY); Tecnoplatin (MX)

Citalopram

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Celexa® may be confused with Celebrex®, Cerebra®, Cerebyx®, Ranexa™, Zyprexa®

Pronunciation(sye TAL oh pram)

U.S. Brand NamesCelexa®

Canadian Brand NamesApo-Citalopram®; Celexa®; Citalopram-ODAN; CO Citalopram; CTP 30; Dom-Citalopram; Gen-Citalopram; IPG-Citalopram; JAMP-Citalopram; Mint-Citalopram; Novo-Citalopram; PHL-Citalopram; PMS-Citalopram; RAN™-Citalopram; ratio-Citalopram; Riva-Citalopram; Sandoz-Citalopram

Pharmacologic CategoryAntidepressant, Selective Serotonin Reuptake Inhibitor

Use: Labeled IndicationsTreatment of depression

Use: Unlabeled/InvestigationalTreatment of mild dementia-associated agitation in nonpsychotic patients; smoking cessation; ethanol abuse; obsessive-compulsive disorder (OCD) in children; diabetic neuropathy

Dosing: AdultsDepression: Oral: Initial: 20 mg/day, generally with an increase to 40 mg/day; doses of more than 40 mg are not usually necessary. Should a dose increase be necessary, it should occur in 20 mg increments at intervals of no less than 1 week. Maximum dose: 60 mg/day.

Dosing: Elderly

Depression: Oral: Initial: 20 mg once daily; increase dose to 40 mg/day in nonresponsive patients

Alzheimer's dementia-related depression (unlabeled use): Oral: Initial: 5-10 mg/day; may increase at multi-week intervals to maximum of 40 mg/day

Dosing: PediatricChildren and Adolescents: Obsessive-compulsive disorder (unlabeled use): Oral: 10-40 mg/day

Dosing: Renal Impairment

Mild-to-moderate impairment: No dosage adjustment needed.

Severe impairment: Cl_{cr} <20 mL/minute: Use with caution.

Dosing: Hepatic ImpairmentOral: 20 mg once daily; increase dose to 40 mg/day in nonresponsive patients.

Dietary ConsiderationsMay be taken without regard to food.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to citalopram or any component of the formulation; concomitant use with MAO inhibitors or within 2 weeks of discontinuing MAO inhibitors; concomitant use with pimozide

Allergy Considerations

- Selective Serotonin Reuptake Inhibitor (SSRI) Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See "Major psychiatric warnings" below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Citalopram is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Citalopram is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: Relatively devoid of these side effects.

- Bleeding risk: May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin, NSAIDs, warfarin, or other anticoagulants. Bleeding (including GI bleeding) related to SSRI or SNRI use has been reported to range from relatively minor bruising and epistaxis to life-threatening hemorrhage.

- CNS depression: Has a low potential to impair cognitive or motor performance; caution operating hazardous machinery or driving.

- Sexual dysfunction: May cause or exacerbate sexual dysfunction.

- SIADH and hyponatremia: SSRIs and SNRIs have been associated with the development of SIADH; hyponatremia has been reported rarely (including severe cases with serum sodium <110 mmol/L), predominately in the elderly; reversible with discontinuation of treatment. Volume depletion and/or concurrent use of diuretics likely increases risk.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; clearance is decreased and plasma concentrations are increased; a lower dosage may be needed.

- Renal impairment: Use with caution in patients with severe renal impairment.

Concurrent drug therapy issues:

- Anticoagulants/Antiplatelets: Use caution with concomitant use of aspirin, NSAIDs, warfarin, or other drugs that affect coagulation; the risk of bleeding may be potentiated.

- CNS depressants: Use caution with concomitant therapy.

- MAO inhibitors: Potential for severe reaction when used with MAO inhibitors; autonomic instability, coma, death, delirium, diaphoresis, hyperthermia, mental status changes/agitation, muscular rigidity, myoclonus, neuroleptic malignant syndrome features, and seizures may occur.

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce citalopram's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

Special populations:

- Elderly: Use caution in elderly patients; risk of hyponatremia and other adverse events may be increased.

- Pediatrics: Safety and efficacy in children have not been established.

- Pregnancy: Use caution in pregnant patients; high doses of citalopram have been associated with teratogenicity in animals.

Other warnings/precautions:

- Electroconvulsive therapy (ECT): Use with caution; no clinical studies have assessed the combined use of citalopram and electroconvulsive therapy; may increase the risks (eg, cognitive adverse effects) associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

- Withdrawal syndrome: May cause dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Upon discontinuation of citalopram therapy, gradually taper dose. If intolerable symptoms occur following a decrease in dosage or upon discontinuation of therapy, then resuming the previous dose with a more gradual taper should be considered.

Geriatric ConsiderationsIn open-label and placebo-controlled studies, elderly patients with or without dementia have shown significant improvement in depressive symptoms, irritability, anxiety, behavior, and restlessness. Effects on intellectual function have not been consistent. Thus, it appears that citalopram has additional effects in stabilizing emotion. A seven- to eightfold variation in citalopram S(+) (active) and R(-) enantiomer concentrations have been reported in the elderly. The racemic citalopram concentration-to-dose ratio was 1.8 times greater in elderly patients compared to younger patients.

Clearance was decreased, while AUC and half-life were significantly increased in elderly patients and in patients with hepatic impairment. Mild to moderate renal impairment may reduce clearance of citalopram (17% reduction noted in trials). No pharmacokinetic information is available concerning patients with severe renal impairment. The elderly are more prone to SSRI/SNRI-induced hyponatremia.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDue to adverse effects observed in animal studies, citalopram is classified as pregnancy category C. Citalopram and its metabolites cross the human placenta. Nonteratogenic effects in the newborn following SSRI exposure late in the third trimester include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypo- or hypertonia, hyper-reflexia, jitteriness, irritability, constant crying, and tremor. An increased risk of low birth weight and lower APGAR scores have also been reported. Exposure to SSRIs after the twentieth week of gestation has been associated with persistent pulmonary hypertension of the newborn (PPHN). Adverse effects may be due to toxic effects of the SSRI or drug withdrawal without a taper. The long term effects of *in utero* SSRI exposure on infant development and behavior are not known.

Due to pregnancy-induced physiologic changes, women who are pregnant may require increased doses of citalopram to achieve euthymia. Women treated for major depression and who are euthymic prior to pregnancy are more likely to experience a relapse when medication is discontinued as compared to pregnant women who continue taking antidepressant medications. The ACOG recommends that therapy with SSRIs or SNRIs during pregnancy be individualized; treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary healthcare provider, and pediatrician (ACOG, 2007). If treatment during pregnancy is required, consider tapering therapy during the third trimester in order to prevent withdrawal symptoms in the infant. If this is done and the woman is considered to be at risk from her major depressive disorder, the medication can be restarted following delivery, although the dose should be readjusted to that required before pregnancy.

LactationEnters breast milk/consider risk:benefit

Breast-Feeding ConsiderationsCitalopram and its metabolites are excreted in human milk. According to the manufacturer, the decision to continue or discontinue breast-feeding during therapy should take into account the risk of exposure to the infant and the benefits of treatment to the mother. Excessive somnolence, decreased feeding, colic, irritability, restlessness, and weight loss have been reported in breast-fed infants. The long-term effects on development and behavior have not been studied; therefore, citalopram should be prescribed to a mother who is breast-feeding only when the benefits outweigh the potential risks.

Adverse Reactions

>10%:

Central nervous system: Somnolence (18%; dose related), insomnia (15%; dose related)

Gastrointestinal: Nausea (21%), xerostomia (20%)

Miscellaneous: Diaphoresis (11%; dose related)

1% to 10%:

Cardiovascular: Heart rate decreased, postural hypotension, tachycardia

Central nervous system: Fatigue (5%; dose related), anorexia (4%), anxiety (4%), agitation (3%), fever (2%), yawning (2%; dose related), amnesia, apathy, concentration impaired, confusion, depression, migraine, suicide attempt

Dermatologic: Rash, pruritus

Endocrine & metabolic: Libido decreased (1% to 4%), dysmenorrhea (3%), amenorrhea, sexual dysfunction

Gastrointestinal: Diarrhea (8%), dyspepsia (5%), vomiting (4%), abdominal pain (3%), flatulence, salivation increased, taste perversion, weight gain/loss

Genitourinary: Ejaculation disorder (6%), impotence (3%; dose related), polyuria

Neuromuscular & skeletal: Tremor (8%), arthralgia (2%), myalgia (2%), paresthesia

Ocular: Abnormal accommodation

Respiratory: Rhinitis (5%), upper respiratory tract infection (5%), sinusitis (3%), cough

<1% (Limited to important or life threatening): Aggressiveness, alkaline phosphatase increased, alopecia, anemia, angina pectoris, ataxia, cardiac failure, cerebral vascular accident, dyspnea, dystonia, eczema, edema (extremities), epistaxis, extrapyramidal symptoms, extrasystoles, hallucinations, hypertension, leukocytosis, leukopenia, liver enzymes increased, lymphadenopathy, muscle weakness, myocardial infarction, neuralgia, photosensitivity, purpura, rigors, tinnitus, urinary incontinence, urinary retention, urticaria

Postmarketing and/or case reports: Acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, chest pain, delirium, dyskinesia, ecchymosis, epidermal necrolysis, erythema multiforme, gastrointestinal hemorrhage, glaucoma, grand mal seizure, hemolytic anemia, hepatic necrosis, hyponatremia, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolonged, rhabdomyolysis, serotonin syndrome, SIADH, spontaneous abortion, thrombocytopenia, thrombosis, ventricular arrhythmia, torsade de pointes, withdrawal syndrome

Metabolism/Transport Effects**Substrate** of CYP2C19 (major), 2D6 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C19 (weak), 2D6 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha-/Beta-Blockers: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Alpha-/Beta-Blockers. *Risk C: Monitor therapy*

Analgesics (Opioid): May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin Reuptake Inhibitor/Antagonist): Selective Serotonin Reuptake Inhibitors may enhance the serotonergic effect of Antidepressants (Serotonin Reuptake Inhibitor/Antagonist). This may cause serotonin syndrome. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Aspirin: Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Beta-Blockers: Selective Serotonin Reuptake Inhibitors may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Acebutolol; Atenolol; Carteolol; Esmolol; Levobunolol; Metipranolol; Nadolol; Penbutolol. *Risk C: Monitor therapy*

BusPIRone: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. Selective Serotonin Reuptake Inhibitors may decrease the metabolism of BusPIRone. *Risk C: Monitor therapy*

CarBAMazepine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of CarBAMazepine. Specifically those SSRIs that inhibit CYP3A4 isoenzymes. CarBAMazepine may increase the metabolism of Selective Serotonin Reuptake Inhibitors. Specifically those agents metabolized via CYP1A2, 2C, and/or 3A4 isoenzymes. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Selective Serotonin Reuptake Inhibitors. *Risk D: Consider therapy modification*

Clozapine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Cyproheptadine: May diminish the therapeutic effect of Selective Serotonin Reuptake Inhibitors. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dextromethorphan: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Dextromethorphan. *Risk D: Consider therapy modification*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Haloperidol: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Haloperidol. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Iobenguane I 123: Selective Serotonin Reuptake Inhibitors may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Selective Serotonin Reuptake Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methadone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Methadone. Fluvoxamine appears to be the only interacting SSRI. *Risk D: Consider therapy modification*

Mexiletine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Mexiletine. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk D: Consider therapy modification*

NSAID (Nonselective): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Phenytoin: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Pimozide: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Pimozide. *Risk X: Avoid combination*

Propafenone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Propafenone. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Risperidone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Risperidone. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

TraMADol: Selective Serotonin Reuptake Inhibitors may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. TraMADol may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tryptophan: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Selective Serotonin Reuptake Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava, and gotu kola (may increase CNS depression).

Monitoring ParametersMonitor patient periodically for symptom resolution; mental status for depression, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased), anxiety, social functioning, mania, panic attacks; akathisia

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for possible interaction (especially MAO inhibitors, P450 inhibitors, and other CNS active agents). Monitor for effectiveness of therapy and adverse reactions. Assess mental status for depression, suicidal ideation, anxiety, social functioning, mania, or panic attack. Assess knowledge/teach patient appropriate use, interventions to reduce side effects (eg, hypotensive precautions), and adverse symptoms to report.

Monitoring: Lab TestsLiver function tests and CBC with continued therapy

Patient EducationIt may take up to 3 weeks to see therapeutic effects from this medication. Take as directed; do not alter dose or frequency without consulting prescriber. May be taken with or without food. Avoid alcohol, caffeine, and CNS stimulants. Avoid use of aspirin or other NSAIDs unless approved by prescriber (may increase risk of bleeding). You may experience sexual dysfunction (reversible). May cause dizziness, anxiety, or blurred vision (rise slowly from sitting or lying position and use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report confusion or impaired concentration, thoughts of suicide, severe headache, palpitations, rash, insomnia or nightmares, changes in personality, muscle weakness or tremors, altered gait pattern, signs and symptoms of respiratory infection, or excessive perspiration. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral: 10 mg/5 mL (240 mL)

Celexa®: 10 mg/5 mL (240 mL) [alcohol free, sugar free; contains propylene glycol; peppermint flavor]

Tablet: 10 mg, 20 mg, 40 mg

Celexa®: 10 mg, 20 mg, 40 mg

Generic AvailableYes

ManufacturerForest Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Solution (Citalopram Hydrobromide)

10 mg/5 mL (240): $114.00

Tablets (Celexa)

10 mg (30): $95.21

20 mg (30): $96.99

40 mg (30): $103.67

Tablets (Citalopram Hydrobromide)

10 mg (30): $39.99

20 mg (30): $39.99

40 mg (30): $26.99

Mechanism of Action A racemic bicyclic phthalane derivative, citalopram selectively inhibits serotonin reuptake in the presynaptic neurons and has minimal effects on norepinephrine or dopamine. Uptake inhibition of serotonin is primarily due to the *S*-enantiomer of citalopram. Displays little to no affinity for serotonin, dopamine, adrenergic, histamine, GABA, or muscarinic receptor subtypes.

Pharmacodynamics/Kinetics

Onset of action: Depression: The onset of action is within a week, however, individual response varies greatly and full response may not be seen until 8-12 weeks after initiation of treatment.

Distribution: V_d: 12 L/kg

Protein binding, plasma: ~80%

Metabolism: Extensively hepatic, via CYP3A4 and 2C19 (major pathways), and 2D6 (minor pathway); forms metabolites, N-demethylcitalopram (DCT) and didemethylcitalopram (DDCT) which are at least eight times less potent than citalopram

Bioavailability: 80%

Half-life elimination: 24-48 hours (average: 35 hours); doubled with hepatic impairment

Time to peak, serum: 1-6 hours, average within 4 hours

Excretion: Urine (Citalopram 10% and DCT 5%)

Note: Clearance was decreased, while AUC and half-life were significantly increased in elderly patients and in patients with hepatic impairment. Mild-to-moderate renal impairment may reduce clearance (17%) and prolong half-life of citalopram. No pharmacokinetic information is available concerning patients with severe renal impairment.

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Selective Serotonin Reuptake Inhibitors (SSRIs) CYP Profile
- Selective Serotonin Reuptake Inhibitors (SSRIs) FDA-Approved Indications
- Selective Serotonin Reuptake Inhibitors (SSRIs) Pharmacokinetics
- Selective Serotonin Reuptake Inhibitors (SSRIs) Receptor Profile
- Teratogenic Risks of Psychotropic Medications

Dental Health Professional Considerations Problems with SSRI-induced bruxism have been reported and may preclude their use; clinicians attempting to evaluate any patient with bruxism or involuntary muscle movement, who is simultaneously being treated with an SSRI drug, should be aware of the potential association.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Premarketing trials reported abnormal taste. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Although caution should be used in patients taking tricyclic antidepressants, no interactions have been reported with vasoconstrictors and citalopram, a nontricyclic antidepressant which acts to increase serotonin; no precautions appear to be needed

Mental Health: Child/Adolescent Considerations Twenty-three patients with OCD (9-18 years of age) received 10-40 mg/day (40 mg modal) (Thomsen, 1997).

Thomsen PH, “Child and Adolescent Obsessive-Compulsive Disorder Treated With Citalopram: Findings From an Open Trial of 23 Cases,” *J Child Adolesc Psychopharmacol*, 1997, 7(3):157-66.

Wagner KD, Robb AS, Findling RL, et al, "A Randomized, Placebo-Controlled Trial of Citalopram for the Treatment of Major Depression in Children and Adolescents," *Am J Psychiatry*, 2004, 161(6):1079-83.

Mental Health Comment The SSRIs as a class are generally considered to be safe and equally effective. Allow sufficient dose-response time (6-12 weeks). Differences lie in approved indications, receptor profiles, pharmacokinetics, and cytochrome P450 activity profile. Subtle differences exist in adverse effect profiles. All SSRIs have the potential to cause sexual dysfunction. Among the SSRIs, citalopram possesses a mild effect on CYP isoenzymes.

Index Terms Citalopram Hydrobromide; Nitalapram

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Tahir N, “Serotonin Syndrome as a Consequence of Drug-Resistant Infections: An Interaction Between Linezolid and Citalopram, *J Am Med Dir Assoc*, 2004, 5(2):111-3.

Thomsen PH, “Child and Adolescent Obsessive-Compulsive Disorder Treated With Citalopram: Findings From an Open Trial of 23 Cases,” *J Child Adolesc Psychopharmacol*, 1997, 7(3):157-66.[PubMed 9466233]

International Brand NamesCelapram (AU); Ciazil (AU); Cipram (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, HK, ID, IL, IQ, IR, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, PK, QA, SA, SC, SD, SG, SL, SN, SY, TH, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Cipramil (AU, BE, BR, CN, DE, DK, EE, FI, GB, IE, IL, LU, NL, NO, PE, PL, SE, ZA); Cital (HK, PL); Citao (TW); Citopam (IN); Citox (MX); Feliz (PH); Humorap (EC, PY); Kitapram (TW); Lexapro (PL); Lupram (PH); Psiconor (UY); Recital (IL); Sepram (FI); Seropram (AT, BG, CH, CZ, ES, FR, HN, HU, IT, MX, VE); Talam (AU); Xylorane (MX); Zentius (AR, CN, CO)

Citric Acid, Magnesium Carbonate, and Glucono-Delta-Lactone

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Renacidin® may be confused with Remicade®

Pronunciation(SI trik AS id, mag NEE see um KAR bo nate, and GLOO kon o DEL ta LAK tone)

U.S. Brand NamesRenacidin®

Pharmacologic CategoryGenitourinary Irrigant; Urinary Tract Product

Use: Labeled IndicationsPrevention of formation of calcifications of indwelling urinary tract catheters; treatment of renal and bladder calculi of the apatite or struvite type

Dosing: Adults

Dissolution or prevention of calcifications: Irrigation (indwelling urethral catheters): 30-60 mL 2-3 times/day by means of a rubber syringe

Renal calculi: Irrigation: Infuse NS at 60 mL/hour and increase until pain, elevated pressure, or maximum flow rate of 120 mL/hour is reached. Begin flow of solution at maximum rate achieved with NS.

Bladder calculi: 30 mL instilled through urinary catheter; clamp for 30-60 minutes, then release and drain; repeat 4-6 times/day

Dosing: ElderlyRefer to adult dosing.

Administration: OtherDiscontinue irrigation immediately if pain or fever occurs. Maintain patency of irrigating catheter; discontinue if obstructed.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to any component of the formulation; urinary tract infection; treatment of calcium oxalate, uric acid, or cysteine calculi

Warnings/Precautions

Concerns related to adverse effects:

- Hypermagnesemia: Severe hypermagnesemia has occurred; monitor magnesium levels closely.

Disease-related concerns:

- Renal impairment: Use with caution in patients with impaired renal function.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsMagnesium is excreted in human milk; it is not known if the combination of ingredients used by irrigation are excreted in breast milk.

Adverse Reactions

>10%:

Central nervous system: Fever (20% to 40%)

Genitourinary: Urothelial ulceration with or without edema (13%)

Miscellaneous: Transient flank pain

1% to 10%:

Endocrine & metabolic: Hypermagnesemia, hyperphosphatemia

Genitourinary: Urinary tract infection, dysuria, hematuria, bladder irritability

Neuromuscular & skeletal: Back pain

Renal: Creatinine increased

<1%: Septicemia, ileus, vomiting, thrombophlebitis

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Aluminum Hydroxide: Citric Acid Derivatives may increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Antacids may decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Fexofenadine: Antacids may decrease the serum concentration of Fexofenadine. Management: No specific recommendations concerning the time required between their administration are provided. Separate administration of each agent by as much time as possible to decrease the risk of an interaction. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Monitoring ParametersSerum creatinine, serum phosphate, serum magnesium; urine cultures
Monitoring: Lab TestsSerum creatinine, serum phosphate, serum magnesium; urine cultures
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, irrigation: Citric acid 6.602 g, magnesium carbonate 3.177 g, glucono-delta-lactone 0.198 g per 100 mL (500 mL) [contains benzoic acid]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Solution (Renacidin)

(500): $40.00

Mechanism of ActionMagnesium from the irrigating solution is exchanged for calcium in the stone matrix. The magnesium stones are soluble and are able to dissolve in the acidic pH of the solution.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCitric Acid and d-gluconic Acid Irrigant; Citric Acid Bladder Mixture; Citric Acid, Magnesium Hydroxycarbonate, D-Gluconic Acid, Magnesium Acid Citrate, and Calcium Carbonate; Hemiacidrin

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Citric Acid, Sodium Citrate, and Potassium Citrate

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English English

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Pronunciation(SIT rik AS id, SOW dee um SIT rate, & poe TASS ee um SIT rate)
U.S. Brand NamesCytra-3; Polycitra速; Polycitra速-LC; Tricitrates
Pharmacologic CategoryAlkalinizing Agent
Use: Labeled IndicationsConditions where long-term maintenance of an alkaline urine is desirable as in control and dissolution of uric acid and cystine calculi of the urinary tract
Dosing: AdultsAlkalinizing agent/bicarbonate precursor/potassium supplement: Oral: 15-30 mL diluted in water after meals and at bedtime
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricAlkalinizing agent/bicarbonate precursor/potassium supplement: Oral: Children: 5-15 mL diluted in water after meals and at bedtime
Dietary ConsiderationsShould be taken after meals.
Warnings/PrecautionsConversion to bicarbonate may be impaired in patients with hepatic failure, in shock, or who are severely ill.
Pregnancy Risk FactorNot established
Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiac abnormalities

Endocrine & metabolic: Metabolic alkalosis, calcium levels, hyperkalemia, hypernatremia

Gastrointestinal: Diarrhea

Neuromuscular & skeletal: Tetany

Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aluminum Hydroxide: Citric Acid Derivatives may increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral:

Cytra-3: Citric acid 334 mg, sodium citrate 500 mg, and potassium citrate 550 mg per 5 mL (480 mL) [equivalent to potassium 1 mEq, sodium 1 mEq, and bicarbonate 2 mEq per 1 mL; alcohol free, sugar free; contains sodium benzoate and propylene glycol; raspberry flavor]

Polycitra速-LC: Citric acid 334 mg, sodium citrate 500 mg, and potassium citrate 550 mg per 5 mL (480 mL) [equivalent to potassium 1 mEq, sodium 1 mEq, and bicaronate 2 mEq per 1 mL; alcohol free, sugar free]

Tricitrates: Citric acid 334 mg, sodium citrate 500 mg, and potassium citrate 550 mg per 5 mL (480 mL) [equivalent to potassium 1 mEq, sodium 1 mEq, and bicaronate 2 mEq per 1 mL; alcohol free; contains sodium benzoate; raspberry flavor]

Tricitrates: Citric acid 334 mg, sodium citrate 500 mg, and potassium citrate 550 mg per 5 mL (15 mL, 30 mL, 480 mL) [equivalent to potassium 1 mEq, sodium 1 mEq, and bicaronate 2 mEq per 1 mL; alcohol free, sugar free; contains sodiuim benzoate and propylene glycol; raspberry flavor]

Syrup, oral:

Polycitra速: Citric acid 334 mg, sodium citrate 500 mg, and potassium citrate 550 mg per 5 mL (480 mL) [equivalent to potassium 1 mEq, sodium 1 mEq and bicarbonate 2 mEq per 1 mL; alcohol free]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Solution (Polycitra-LC)

334-550-500 mg/5 mL (480): $37.01

Syrup (Polycitra)

334-550-500 mg/5 mL (473): $43.00

Syrup (Tricitrates)

334-550-500 mg/5 mL (480): $32.06

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentSodium chloride intake may decrease serum lithium levels; monitor

Mental Health CommentAlkalization of the urine may increase toxicity of amphetamine, ephedrine, and pseudoephedrine

Index TermsPotassium Citrate, Citric Acid, and Sodium Citrate; Sodium Citrate, Citric Acid, and Potassium Citrate

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Cladribine

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Cladribine may be confused with cleVIDipine, clofarabine

Leustatin® may be confused with lovastatin

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(KLA dri been)

U.S. Brand NamesLeustatin®

Canadian Brand NamesLeustatin®

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite; Antineoplastic Agent, Antimetabolite (Purine Antagonist); Antineoplastic Agent, Antimetabolite (Purine)

Use: Labeled IndicationsTreatment of hairy cell leukemia

Use: Unlabeled/InvestigationalTreatment of chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), non-Hodgkin's lymphomas, progressive multiple sclerosis

Dosing: AdultsRefer to individual protocols.

Hairy cell leukemia: I.V. Continuous infusion:

0.09 mg/kg/day days 1-7; may be repeated every 28-35 days **or**

3.4 mg/m^2/day SubQ days 1-7 (unlabeled dose)

Chronic lymphocytic leukemia (unlabeled use): I.V. Continuous infusion:

0.1 mg/kg/day days 1-7 **or**

0.028-0.14 mg/kg/day as a 2-hour infusion days 1-5

Chronic myelogenous leukemia (unlabeled use): I.V. 15 mg/m^2/day as a 1-hour infusion days 1-5; if no response, increase dose to 20 mg/m^2/day in the second course.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols.

Acute leukemias (unlabeled use): 6.2-7.5 mg/m^2/day continuous infusion for days 1-5; maximum tolerated dose was 8.9 mg/m^2/day.

Dosing: Renal ImpairmentThe FDA-approved labeling recommends that caution should be used in patients with renal impairment; however, no specific dosage adjustment guidelines are available due to lack of data. The following guidelines have been used by some clinicians (Aronoff, 2007):

Children:

Cl$_{cr}$ 10-50 mL/minute: Administer 50% of dose

Cl$_{cr}$ <10 mL/minute: Administer 30% of dose

Hemodialysis: Administer 30% of dose

Continuous renal replacement therapy (CRRT): Administer 50% of dose

Adults:

Cl$_{cr}$ 10-50 mL/minute: Administer 75% of dose

Cl$_{cr}$ <10 mL/minute: Administer 50% of dose

Continuous ambulatory peritoneal dialysis (CAPD): Administer 50% of dose

Dosing: Hepatic ImpairmentThe FDA-approved labeling recommends that caution should be used in patients with hepatic impairment;

however, no specific dosage adjustment guidelines are available due to lack of data.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Administer as a 1- to 2-hour infusion or by continuous infusion

Administration: I.V. DetailpH: 6-6.6

StorageStore intact vials under refrigeration 2°C to 8°C (36°F to 46°F). Protect from light. Dilutions in 500 mL NS are stable for 72 hours. Stable in PVC containers for 24 hours at room temperature of 15°C to 30°C (59°F to 86°F) and 7 days in Pharmacia Deltec® cassettes.

ReconstitutionDilute in 500 mL; dilute to a total volume of 100 mL for 7-day infusion. Solutions for 7-day infusion should be prepared in bacteriostatic NS; the manufacturer recommends filtering with a 0.22 micron filter when preparing 7-day infusions.

CompatibilityStable in NS; **incompatible** with D_5W.

Y-site administration: Compatible: Aminophylline, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, chlorpromazine, cimetidine, cisplatin, cyclophosphamide, cytarabine, dexamethasone sodium phosphate, diphenhydramine, dobutamine, dopamine, doxorubicin, droperidol, enalaprilat, etoposide, famotidine, furosemide, granisetron, haloperidol, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, idarubicin, leucovorin, lorazepam, mannitol, meperidine, mesna, methylprednisolone sodium succinate, metoclopramide, mitoxantrone, morphine, nalbuphine, ondansetron, paclitaxel, potassium chloride, prochlorperazine edisylate, promethazine, ranitidine, sodium bicarbonate, teniposide, vincristine.

ContraindicationsHypersensitivity to cladribine or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.
- Myelosuppression: See “Concerns related to adverse effects” below.
- Neurotoxicity: See “Concerns related to adverse effects” below.
- Renal toxicity: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Fever: May occur, with or without neutropenia.
- Myelosuppression: **[U.S. Boxed Warnings]: Dose-dependent, reversible myelosuppression will occur; use with caution in patients with pre-existing hematologic or immunologic abnormalities.**
- Neurotoxicity: **[U.S. Boxed Warning]: Neurologic toxicity has been reported, usually with higher doses, but may occur at normal doses.**
- Renal toxicity: **[U.S. Boxed Warning]: Acute renal toxicity has been reported with high doses; use caution when administering with other nephrotoxic agents.**
- Tumor lysis syndrome: With high tumor burden, tumor lysis syndrome and subsequent hyperuricemia may occur; consider allopurinol and hydrate accordingly.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenic effects and fetal mortality were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should avoid becoming pregnant.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

>10%:

Central nervous system: Fever (69%; ≥104ºF: 11%), fatigue (11% to 45%), headache (7% to 22%)

Dermatologic: Rash (10% to 27%)

Gastrointestinal: Nausea (28%), appetite decreased (17%), vomiting (13%)

Hematologic: Myelosuppression, common, dose limiting (nadir: 5-10 days, recovery: 4-8 weeks); neutropenia (70%); anemia (37%); thrombocytopenia (12%)

Local: Injection site reactions (9% to 19%)

Respiratory: Abnormal breath sounds (11%)

Miscellaneous: Infection (28%)

1% to 10%:

Cardiovascular: Edema (6%), tachycardia (6%), thrombosis (2%)

Central nervous system: Dizziness (9%), chills (9%), insomnia (7%), malaise (5% to 7%), pain (6%)

Dermatologic: Purpura (10%), petechiae (8%), pruritus (6%), erythema (6%)

Gastrointestinal: Diarrhea (10%), constipation (9%), abdominal pain (6%)

Local: Phlebitis (2%)

Neuromuscular & skeletal: Weakness (9%), myalgia (7%), arthralgia (5%)

Respiratory: Cough (7% to 10%), abnormal chest sounds (9%), dyspnea (7%), epistaxis (5%)

Miscellaneous: Diaphoresis (9%)

<1%, postmarketing and/or case reports: Aplastic anemia, bilirubin increased, hemolytic anemia, hypereosinophilia, myelodysplastic syndrome, neurologic toxicity, opportunistic infections, pancytopenia, paraparesis, pneumonia, polyneuropathy (with high doses), pulmonary interstitial infiltrates, quadriplegia (reported at high doses); renal dysfunction (with high doses), Stevens-Johnson syndrome, toxic epidermal necrolysis, transaminases increased, tumor lysis syndrome, urticaria

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to GI irritation).
Monitoring ParametersCBC with differential, renal and hepatic function; monitor for fever

Periodic assessment of peripheral blood counts, particularly during the first 4-8 weeks post-treatment, is recommended to detect the development of anemia, neutropenia, and thrombocytopenia and for early detection of any potential sequelae (eg, infection or bleeding)

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, myelosuppression, cardiac changes, renal failure) regularly during therapy and following therapy (patients should be considered immunosuppressed for up to 1 year after cladribine therapy). Teach patient (or caregiver) possible side effects/appropriate interventions and adverse symptoms to report.
Monitoring: Lab TestsLiver and renal function tests, CBC with differential, platelets, uric acid
Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. This drug can only be administered by infusion. It is important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition during therapy (small, frequent meals may help). You will be more susceptible to infection during therapy and for up to 1 year following therapy (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); muscle weakness or pain (consult prescriber for mild analgesics); or mouth sores (use frequent mouth care with soft toothbrush or cotton swabs and frequent mouth rinses). Report immediately rash, unusual excessive fatigue, and/or signs of infection. Report rapid heartbeat or palpitations; unusual bruising or bleeding; persistent GI disturbances; diarrhea or constipation; yellowing of eyes or skin; change in color of urine or stool; swelling, warmth, or pain in extremities; or difficult respirations. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Do not breast-feed until prescriber advises it is safe.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 1 mg/mL (10 mL)

Generic AvailableYes
ManufacturerOrtho Biotech, Inc
Mechanism of ActionA purine nucleoside analogue; prodrug which is activated via phosphorylation by deoxycytidine kinase to a 5'-triphosphate derivative. This active form incorporates into DNA to result in the breakage of DNA strand and shutdown of DNA synthesis. This also results in a depletion of nicotinamide adenine dinucleotide and adenosine triphosphate (ATP). Cladribine is cell-cycle nonspecific.
Pharmacodynamics/Kinetics

Absorption: Oral: 55%; SubQ: 100%; Rectal: 20%

Distribution: V_d: 4.52 ± 2.82 L/kg

Protein binding: 20%

Metabolism: Hepatic; 5′-triphosphate moiety-active

Half-life elimination: Biphasic: Alpha: 25 minutes; Beta: 6.7 hours; Terminal, mean: Normal renal function: 5.4 hours

Excretion: Urine (18% to 44%)

Clearance: Estimated systemic: 640 mL/hour/kg

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, or insomnia

Mental Health: Effects on Psychiatric TreatmentMay cause bone marrow suppression; use caution with clozapine and carbamazepine

Index Terms2-CdA; 2-Chlorodeoxyadenosine; NSC-105014

References

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International Brand NamesBiodribin (PL); Intocel (AR); Leustat (AR, GB, IE, UY); Leustatin (AT, AU, BE, BG, BR, CH, CR, CZ, DK, DO, ES, FI, GT, HK, HN, IL, IT, KP, LU, NI, NL, NO, PA, PH, SE, SG, SV, TW); Leustatine (FR); Litak (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Clarithromycin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Clarithromycin may be confused with Claritin®, clindamycin, erythromycin

Pronunciation(kla RITH roe mye sin)

U.S. Brand NamesBiaxin®; Biaxin® XL

Canadian Brand NamesApo-Clarithromycin; Biaxin®; Biaxin® XL; Gen-Clarithromycin; PMS-Clarithromycin; ratio-Clarithromycin; Sandoz-Clarithromycin

Pharmacologic CategoryAntibiotic, Macrolide

Use: Labeled Indications

Children:

Acute otitis media (*H. influenzae*, *M. catarrhalis*, or *S. pneumoniae*)

Community-acquired pneumonia due to susceptible *Mycoplasma pneumoniae*, *S. pneumoniae*, or *Chlamydia pneumoniae* (TWAR)

Pharyngitis/tonsillitis due to susceptible *S. pyogenes*, acute maxillary sinusitis due to susceptible *H. influenzae, S. pneumoniae,* or *Moraxella catarrhalis*, uncomplicated skin/skin structure infections due to susceptible *S. aureus, S. pyogenes,* and mycobacterial infections

Prevention of disseminated mycobacterial infections due to MAC disease in patients with advanced HIV infection

Adults:

Pharyngitis/tonsillitis due to susceptible *S. pyogenes*

Acute maxillary sinusitis and acute exacerbation of chronic bronchitis due to susceptible *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, or *S. pneumoniae*

Community-acquired pneumonia due to susceptible *H. influenzae, H. parainfluenzae, Mycoplasma pneumoniae, S. pneumoniae,* or *Chlamydia pneumoniae* (TWAR), *Moraxella catarrhalis*

Uncomplicated skin/skin structure infections due to susceptible *S. aureus*, *S. pyogenes*

Disseminated mycobacterial infections due to *M. avium* or *M. intracellulare*

Prevention of disseminated mycobacterial infections due to *M. avium* complex (MAC) disease (eg, patients with advanced HIV infection)

Duodenal ulcer disease due to *H. pylori* in regimens with other drugs including amoxicillin and lansoprazole or omeprazole, ranitidine bismuth citrate, bismuth subsalicylate, tetracycline, and/or an H_2 antagonist

Use: Unlabeled/InvestigationalPertussis (CDC guidelines); alternate antibiotic for prophylaxis of infective endocarditis in patients who are allergic to penicillin and undergoing surgical or dental procedures (ACC/AHA guidelines)

Use: DentalAlternate oral antibiotic for prevention of infective endocarditis in individuals allergic to penicillins or ampicillin, when amoxicillin cannot be used; alternate antibiotic in the treatment of common orofacial infections caused by aerobic gram-positive cocci and susceptible anaerobes

Dosing: Adults

Usual dosage range: Oral: 250-500 mg every 12 hours **or** 1000 mg (two 500 mg extended release tablets) once daily for 7-14 days

Acute exacerbation of chronic bronchitis: Oral:

M. catarrhalis and *S. pneumoniae*: 250 mg every 12 hours for 7-14 days **or** 1000 mg (two 500 mg extended release tablets) once daily for 7 days

H. influenzae: 500 mg every 12 hours for 7-14 days or 1000 mg (two 500 mg extended release tablets) once daily for 7 days

H. parainfluenzae: 500 mg every 12 hours for 7 days or 1000 mg (two 500 mg extended release tablets) once daily for 7 days

Acute maxillary sinusitis: Oral: 500 mg every 12 hours **or** 1000 mg (two 500 mg extended release tablets) once daily for 14 days

Mycobacterial infection (prevention and treatment): Oral: 500 mg twice daily (use with other antimycobacterial drugs, eg, ethambutol or rifampin)

Peptic ulcer disease: Eradication of *Helicobacter pylori*: Dual or triple combination regimens with bismuth subsalicylate, amoxicillin, an H_2-receptor antagonist, or proton-pump inhibitor: 500 mg every 8-12 hours for 10-14 days

Pertussis (unlabeled use; CDC guidelines): Oral: 500 mg twice daily for 7 days

Pharyngitis, tonsillitis: Oral: 250 mg every 12 hours for 10 days

Pneumonia: Oral:

C. pneumoniae, *M. pneumoniae*, and *S. pneumoniae*: 250 mg every 12 hours for 7-14 days **or** 1000 mg (two 500 mg extended release tablets) once daily for 7 days

H. influenzae: 250 mg every 12 hours for 7 days **or** 1000 mg (two 500 mg extended release tablets) once daily for 7 days

H. parainfluenzae and *M. catarrhalis*: 1000 mg (two 500 mg extended release tablets) once daily for 7 days

Prophylaxis against infective endocarditis (unlabeled use): Oral: 500 mg 30-60 minutes prior to procedure. **Note:** American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur. As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Skin and skin structure infection, uncomplicated: Oral: 250 mg every 12 hours for 7-14 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Community-acquired pneumonia, sinusitis, bronchitis, skin infections: Oral: 15 mg/kg/day divided every 12 hours for 10 days

Mycobacterial infection (prevention and treatment): Oral: 7.5 mg/kg (up to 500 mg) twice daily. **Note:** Safety of clarithromycin for MAC not studied in children <20 months.

Pertussis (unlabeled use; CDC guidelines): Oral:

Children 1-5 months: 15 mg/kg/day divided every 12 hours for 7 days

Children ≥6 months: 15 mg/kg/day divided every 12 hours for 7 days (maximum: 1 g/day)

Prophylaxis against infective endocarditis (unlabeled use): Oral: 15 mg/kg 30-60 minutes before procedure (maximum: 500 mg). **Note:** American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur. As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Dosing: Renal Impairment

Cl_{cr} <30 mL/minute: Half the normal dose or double the dosing interval.

In combination with ritonavir:

Cl_{cr} 30-60 mL/minute: Reduce dose by 50%.

Cl_{cr} <30 mL/minute: Reduce dose by 75%.

Dosing: Hepatic ImpairmentNo dosing adjustment is needed as long as renal function is normal.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralClarithromycin immediate release tablets and oral solution may be given with or without meals. Give every 12 hours rather than twice daily to avoid peak and trough variation.

Biaxin® XL: Should be given with food. Do not crush or chew extended release tablet.

Dietary ConsiderationsClarithromycin immediate release tablets and oral solution may be given with or without meals. May be taken with milk. Biaxin® XL should be taken with food.

StorageStore tablets and granules for oral suspension at controlled room temperature. Reconstituted oral suspension should not be refrigerated because it might gel. Microencapsulated particles of clarithromycin in suspension is stable for 14 days when stored at room temperature.

ContraindicationsHypersensitivity to clarithromycin, erythromycin, or any macrolide antibiotic; use with ergot derivatives, pimozide, cisapride

Allergy Considerations

- Macrolide Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: Macrolides have been associated with rare QT_c prolongation and ventricular arrhythmias, including torsade de pointes; use with caution in patients at risk of prolonged cardiac repolarization.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Coronary artery disease (CAD): Use with caution in patients with CAD; postmarketing safety trial suggests increased risk of cardiovascular mortality with short-term clarithromycin use (vs placebo) in patients with stable CAD. However, more smokers were randomized to the clarithromycin arm.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms and new onset of symptoms has occurred.

- Renal impairment: Dosage adjustment required with severe renal impairment; decreased dosage or prolonged dosing interval may be appropriate.

Concurrent drug therapy issues:

- Colchicine: Colchicine toxicity (including fatalities) has been reported with concomitant use. Use caution in the elderly and patients with renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 months of age.

Dosage form specific issues:

- Extended release formulation: The extended release formulation consists of drug within a nondeformable matrix; following drug release/absorption, the matrix/shell is expelled in the stool. The use of nondeformable products in patients with known stricture/narrowing of the GI tract has been associated with symptoms of obstruction.

Geriatric ConsiderationsConsidered one of the drugs of choice in the outpatient treatment of community-acquired pneumonia in elderly. After doses of 500 mg every 12 hours for 5 days, 12 healthy elderly subjects had significantly increased C_{max} and C_{min}, elimination half-lives of clarithromycin and 14-OH clarithromycin compared to 12 healthy young subjects. These changes were attributed to a significant decrease in renal clearance; at a dose of 1000 mg twice daily, 100% of 13 elderly subjects experienced an adverse event compared to only 10% taking 500 mg twice daily.

Pregnancy Risk FactorC

Pregnancy ConsiderationsClarithromycin crosses the placenta. Although no teratogenic effects have been reported in humans, adverse fetal effects have been documented in animal studies; therefore, clarithromycin is classified as pregnancy category C. The manufacturer recommends that clarithromycin not be used in a pregnant woman unless there are no alternative therapies. No adequate and well-controlled studies have been completed in pregnant women.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if clarithromycin is excreted in human breast milk, but other macrolides are excreted in human milk and clarithromycin is known to be excreted into animal milk. The manufacturer recommends that caution be exercised when administering clarithromycin to breast-feeding women.

No data is available on infants exposed via human milk. Other macrolides are considered compatible with breast-feeding and clarithromycin is used therapeutically in infants. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Clarithromycin in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Central nervous system: Headache (adults and children 2%)

Dermatologic: Rash (children 3%)

Gastrointestinal: Abnormal taste (adults 3% to 7%), diarrhea (adults 3% to 6%; children 6%), vomiting (children 6%), nausea (adults 3%), abdominal pain (adults 2%; children 3%), dyspepsia (adults 2%)

Hepatic: Prothrombin time increased (1%)

Renal: BUN increased (4%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): *Clostridium difficile* colitis, alkaline phosphatase increased, anaphylaxis, anorexia, anxiety, behavioral changes, bilirubin increased, confusion, disorientation, GGT increased, glossitis, hallucinations, hearing loss (reversible), hepatic dysfunction, hepatic failure, hepatitis, hypoglycemia, insomnia, interstitial nephritis, jaundice, leukopenia, manic behavior, neutropenia, oral moniliasis, pancreatitis, psychosis, QT prolongation, seizure, serum creatinine increased, Stevens-Johnson syndrome, stomatitis, thrombocytopenia, tinnitus, tongue discoloration, tooth discoloration (reversible), torsade de pointes, toxic epidermal necrolysis, transaminases increased, tremor, urticaria, ventricular tachycardia, ventricular arrhythmia, vertigo

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (weak), 3A4 (strong)

Drug Interactions

Alfentanil: Macrolide Antibiotics may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Macrolide Antibiotics may decrease the metabolism of Antifungal Agents (Azole Derivatives, Systemic). Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Macrolide Antibiotics. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Macrolide Antibiotics may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

BusPIRone: Macrolide Antibiotics may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Macrolide Antibiotics may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: Macrolide Antibiotics may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Cardiac Glycosides: Macrolide Antibiotics may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cilostazol: Macrolide Antibiotics may decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Cisapride: Macrolide Antibiotics may decrease the metabolism of Cisapride. *Risk X: Avoid combination*

Clopidogrel: Macrolide Antibiotics may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Clozapine: Macrolide Antibiotics may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

Colchicine: Macrolide Antibiotics may decrease the metabolism of Colchicine. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Macrolide Antibiotics may decrease the metabolism of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

CycloSPORINE: Macrolide Antibiotics may decrease the metabolism of CycloSPORINE. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disopyramide: Macrolide Antibiotics may enhance the QTc-prolonging effect of Disopyramide. Macrolide Antibiotics may decrease the metabolism of Disopyramide. *Risk X: Avoid combination*

Eletriptan: Macrolide Antibiotics may decrease the metabolism of Eletriptan. *Risk D: Consider therapy modification*

Eplerenone: Macrolide Antibiotics may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Macrolide Antibiotics may enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Cabergoline. *Risk D: Consider therapy modification*

Etravirine: May decrease the serum concentration of Macrolide Antibiotics. Clarithromycin AUC is reduced and levels of the active metabolite (14-hydroxy-clarithromycin) are modestly increased. Management: For the treatment of *Mycobacterium avium* complex, consider changing to alternative agent, such as azithromycin. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Macrolide Antibiotics may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Pravastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: Macrolide Antibiotics may decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Macrolide Antibiotics may decrease the metabolism of Pimozide. QTc prolongation is a risk. *Risk X: Avoid combination*

Protease Inhibitors: May diminish the therapeutic effect of Clarithromycin. Specifically, certain protease inhibitors may decrease formation of the active 14-hydroxy-clarithromycin metabolite, which may negatively impact clarithromycin effectiveness vs. H. influenzae and other non-MAC infections. Protease Inhibitors may increase the serum concentration of Clarithromycin. Clarithromycin dose adjustment in renally impaired patients may be needed. Clarithromycin may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Macrolide Antibiotics may decrease the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Macrolide Antibiotics may increase the serum concentration of Repaglinide. *Risk C: Monitor therapy*

Rifamycin Derivatives: Macrolide Antibiotics may decrease the metabolism of Rifamycin Derivatives. **Exceptions:** Rifapentine. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Selective Serotonin Reuptake Inhibitors: Macrolide Antibiotics may decrease the metabolism of Selective Serotonin Reuptake Inhibitors. **Exceptions:** Fluvoxamine; PARoxetine. *Risk C: Monitor therapy*

Sirolimus: Macrolide Antibiotics may decrease the metabolism of Sirolimus. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Tacrolimus: Macrolide Antibiotics may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Temsirolimus: Macrolide Antibiotics may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Theophylline Derivatives: Macrolide Antibiotics may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Macrolide Antibiotics may decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Zopiclone: Macrolide Antibiotics may increase the serum concentration of Zopiclone. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Immediate release: Food delays rate, but not extent of absorption; Extended release: Food increases clarithromycin AUC by ~30% relative to fasting conditions.

Herb/Nutraceutical: St John's wort may decrease clarithromycin levels.

Monitoring ParametersCBC with differential, BUN, creatinine; perform culture and sensitivity studies prior to initiating drug therapy

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's allergy history prior to therapy. Use with caution in presence of severe renal impairment, myasthenia gravis, or coronary artery disease. Assess for potential adverse interactions or toxicity with any other prescription, OTC, or herbal products patient may be taking. Evaluate results of laboratory monitoring with long-term use. Assess therapeutic effectiveness (according to purpose for use) and adverse reactions. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, BUN, creatinine; perform culture and sensitivity studies prior to initiating drug therapy

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take exactly as prescribed and complete full course of therapy, even if feeling better. Tables and suspension may be taken with or without meals or milk. Extended release formulation (XL) should be taken with meals; do not break or chew extended release tablets. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluids. May cause nausea, heartburn, or abnormal taste (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or headaches or abdominal pain (consult prescriber for analgesic). Report rapid heartbeat or palpitations, persistent fever or chills, easy bruising or bleeding, joint pain, severe persistent diarrhea, skin rash, sores in mouth, foul-smelling urine, or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Granules for oral suspension: 125 mg/5 mL (50 mL, 100 mL); 250 mg/5 mL (50 mL, 100 mL)

Biaxin®: 125 mg/5 mL (50 mL, 100 mL); 250 mg/5 mL (50 mL, 100 mL) [fruit punch flavor]

Tablet: 250 mg, 500 mg

Biaxin®: 250 mg, 500 mg

Tablet, extended release: 500 mg

Biaxin® XL: 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Suspension (reconstituted) (Clarithromycin)

125 mg/5 mL (50): $22.53

125 mg/5 mL (100): $41.91

250 mg/5 mL (50): $42.71

250 mg/5 mL (100): $76.72

Tablet, 24-hour (Biaxin XL)

500 mg (20): $115.38

Tablet, 24-hour (Biaxin XL Pac)

500 mg (14): $88.19

Tablets (Biaxin)

250 mg (60): $335.68

500 mg (20): $109.99

Tablets (Clarithromycin)

250 mg (30): $109.99

500 mg (30): $109.99

Mechanism of ActionExerts its antibacterial action by binding to 50S ribosomal subunit resulting in inhibition of protein synthesis. The 14-OH metabolite of clarithromycin is twice as active as the parent compound against certain organisms.

Pharmacodynamics/Kinetics

Absorption: Immediate release: Rapid; food delays rate, but not extent of absorption

Distribution: Widely into most body tissues except CNS

Protein binding: 42% to 50%

Metabolism: Partially hepatic via CYP3A4; converted to 14-OH clarithromycin (active metabolite)

Bioavailability: ~50%

Half-life elimination: Immediate release: Clarithromycin: 3-7 hours; 14-OH-clarithromycin: 5-9 hours

Time to peak: Immediate release: 2-3 hours

Excretion: Primarily urine (20% to 40% as unchanged drug; additional 10% to 15% as metabolite)

Clearance: Approximates normal GFR

Related Information

- ***Helicobacter pylori*** Treatment
- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Prevention of Infective Endocarditis
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health Professional ConsiderationsThe FDA issued a special alert in December 2005 stating that short-term therapy with clarithromycin in patients with stable coronary artery disease may cause significantly higher cardiovascular mortality. The use of 500 mg clarithromycin daily for 14 days in patients with the above condition resulted in significantly higher all-cause mortality compared to patients taking placebo. This information is provided to the dental practitioner on the possible association between short-term use of clarithromycin for infections and increases in mortality in patients with a history of stable coronary artery disease.

Clarithromycin is known to prolong the QT interval. The QT interval is measured as the time and distance between the Q point of the QRS complex and the end of the T wave in the ECG tracing. After adjustment for heart rate, the QT interval is defined as prolonged if it is more than 450 msec in men and 460 msec in women. A long QT syndrome was first described in the 1950s and 60s as a congenital syndrome involving QT interval prolongation and syncope and sudden death. Some of the congenital long QT syndromes were characterized by a peculiar electrocardiographic appearance of the QRS complex involving a premature atria beat followed by a pause, then a subsequent sinus beat showing marked QT prolongation and deformity. This type of cardiac arrhythmia was originally termed “torsade de pointes” (translated from the French as “twisting of the points”).

Prolongation of the QT interval is thought to result from delayed ventricular repolarization. The repolarization process within the myocardial cell is due to the efflux of intracellular potassium. The channels associated with this current can be blocked by many drugs and predispose the electrical propagation cycle to torsade de pointes.

Clarithromycin is considered as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. It is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Abnormal taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsClarithromycin is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution. See Dental Comment.

Mental Health: Effects on Mental StatusMacrolides have been reported to cause nightmares, confusion, anxiety, and mood lability

Mental Health: Effects on Psychiatric TreatmentContraindicated with pimozide; increases carbamazepine and triazolam levels; monitor for signs of toxicity

Cardiovascular ConsiderationsBecause of potential drug interactions, serious arrhythmias may occur when clarithromycin and other macrolides are used in combination with cisapride. Clarithromycin may also increase theophylline, some HMG-CoA reductase inhibitors, digoxin, warfarin, and cyclosporine levels (among others). Clarithromycin may be used in penicillin-allergic patients for prevention of bacterial endocarditis.

The FDA issued an alert for clarithromycin (Biaxin®, Abbott Laboratories) on December 8, 2005. These actions were based upon results of a Danish trial (CLARICOR) that was recently published online in the British Medical Journal (Jesperson, 2005). This was a multicenter, double-blind, randomized, placebo-controlled trial evaluating the effects of clarithromycin (500 mg daily for 14 days) on mortality in patients with stable coronary artery disease. Over 13,000 patients having a discharge diagnosis (from 1993-99) of myocardial infarction or angina pectoris were recruited for the trial. The primary outcome was a composite of all cause mortality, MI, or unstable angina during the three-year follow up. The secondary outcome measure consisted of cardiovascular mortality, MI, or unstable angina. Two thousand one hundred and seventy two patients were randomized to clarithromycin and 2200 to placebo. The groups were well matched except there were more smokers in the clarithromycin group. Compliance was over 90% in both groups. There was no difference between the two groups with regard to the composite outcomes (primary or secondary). All cause mortality was significantly higher in the clarithromycin group (HR 1.27; CI 1.03-1.54; p = 0.03) as a result of a higher cardiovascular mortality (HR 1.45; CI 1.09-1.92; p = 0.01). When a multivariant analysis was done, all cause mortality was insignificantly increased (HR 1.21; CI 0.99-1.48; p = 0.07), but cardiovascular mortality continued to be significantly increased in the clarithromycin group (HR 1.38; CI 1.03-1.85; p = 0.03). One hundred and eighty four patients died in the clarithromycin group (89 from cardiovascular events) and 159 patients died in the placebo group (70 from cardiovascular events). The authors conclude that short-term clarithromycin therapy in patients with stable coronary artery disease may cause significantly higher cardiovascular mortality. This result came as a surprise to the authors who were not evaluating the safety of clarithromycin in patients with CAD. Further study is needed to evaluate the clinical validity of this unexpected finding.

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International Brand NamesAbbotic (ID); Abbotic XL (ID); Adel (MX); Aeroxina (AR); Biaxin HP (DE); Biclar (BE, LU); Binoclar (CR, DO, GT, HK, NI, PA, SV); Binoklar (ID); Bysclas (PH); C-Clarin (KP); Clacine (ID); Clamycin (PH); Clapharma (ID); Clarac (AU); Claranta (PH); Clari (KP, SG); Claribid (IN); Clarid (KP); Claridar (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Clarihexal (AU); Clarimac (IN); Clarimax (CN); Claripen (SG); Claritab (BR); Clarith (JP, TH); Claritrol (CO); Clarix (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Claroma (KP); Claron (TH); Claxin (KP); Cleron (HK, SG); Clormicin (CO); Crixaa (MY); Crixan (SG); Fascar (HK, TH); Fromilid (PL); Gervaken (MX); Hecobac (ID); Heliclar (LU); Heliclo (KP); Kalixocin (AU); Klabax (PL); Klabion (PL); Klacid (AE, AT, AU, BG, BH, CH, CL, CY, CZ, DE, DK, EE, EG, ES, FI, HK, HN, HU, IE, IL, IQ, IR, IT, JO, KP, KW, LB, LY, MY, NL, NO, NZ, OM, PL, PT, QA, SA, SE, SY, TH, YE); Klacid MR (MY); Klacid UNO (PL); Klacid XL (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Klacina (CO); Klarcin (TW); Klaribac (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Klaricid (MX); Klaricid (AR, BB, BM, BR, BS, BZ, CN, CO, EC, GB, GR, GY, JM, JP, KP, NL, PE, PH, PK, PR, PY, SR, TT, TW, UY, VE); Klaricid Pediatric (PH); Klaricid XL (KP); Klarid (PH); Klaridex (IL); Klarin (IL); Klarith (TW); Klarithan (ZA); Klarmyn (MX, PH); Klerimed (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, MY, OM, QA, SA, SG, SY, YE); Klerimid (AE, BH, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Krobicin (MX); Lagur (PE); Larith (KP); Larizin (PH); Lekoklar (PL); Limaclo (KP); Macladin (IT); Maclar (LU, MY); Macrodin (PH); Mavid (DE); Mononaxy (FR); Naxy (FR); Neo-Clarosip (MX); Onexid (PH); Rolicytin (MX); Synclar (HK); Taclar (PL); Veclam (IT); Zeclar (FR)

Clemastine

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Pronunciation(KLEM as teen)

U.S. Brand NamesDayhist® Allergy [OTC]; Tavist® Allergy [OTC]

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsPerennial and seasonal allergic rhinitis and other allergic symptoms including urticaria

Dosing: Adults

Rhinitis or allergic symptoms (including urticaria): Oral:

1.34 mg clemastine fumarate (1 mg base) twice daily to 2.68 mg (2 mg base) 3 times/day; do not exceed 8.04 mg/day (6 mg base)

OTC labeling: 1.34 mg clemastine fumarate (1 mg base) twice daily; do not exceed 2 mg base/24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Rhinitis or other allergic symptoms (including urticaria): Oral:

Infants and Children <6 years: 0.05 mg/kg/day as **clemastine base** or 0.335-0.67 mg/day clemastine fumarate (0.25-0.5 mg base/day) divided into 2 or 3 doses; maximum daily dosage: 1.34 mg (1 mg base)

Children 6-12 years: 0.67-1.34 mg clemastine fumarate (0.5-1 mg base) twice daily; do not exceed 4.02 mg/day (3 mg/day base)

Children ≥12 years: Refer to adult dosing.

ContraindicationsHypersensitivity to clemastine or any component of the formulation; narrow-angle glaucoma

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Asthma: Use with caution in patients with a history of asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Pregnancy Risk FactorB

LactationEnters breast milk/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation, hypotension, tachycardia

Central nervous system: Dyscoordination, sedation, somnolence slight to moderate, sleepiness, confusion, restlessness, nervousness, insomnia, irritability, fatigue, headache, dizziness increased

Dermatologic: Rash, photosensitivity

Gastrointestinal: Diarrhea, nausea, xerostomia, epigastric distress, vomiting, constipation

Genitourinary: Urinary frequency, difficult urination, urinary retention

Hematologic: Hemolytic anemia, thrombocytopenia, agranulocytosis

Ocular: Blurred vision

Otic: Tinnitus

Respiratory: Thickening of bronchial secretions

Miscellaneous: Anaphylaxis

Metabolism/Transport Effects**Inhibits** CYP2D6 (weak), 3A4 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Monitoring ParametersLook for a reduction of rhinitis, urticaria, eczema, pruritus, or other allergic symptoms
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Syrup, as fumarate: 0.67 mg/5 mL (120 mL, 480 mL) [prescription formulation; 0.5 mg base/5 mL]

Tablet, as fumarate: 1.34 mg [1 mg base; OTC], 2.68 mg [2 mg base; prescription formulation]

Dayhist® Allergy, Tavist® Allergy: 1.34 mg [1 mg base]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Syrup (Clemastine Fumarate)

0.67 mg/5 mL (120): $18.98

Tablets (Clemastine Fumarate)

1.34 mg (100): $25.99

2.68 mg (30): $17.99

Tablets (Tavist-1)

1.34 mg (32): $14.99

Mechanism of ActionCompetes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract
Pharmacodynamics/Kinetics

Onset of action: Peak effect: Therapeutic: 5-7 hours

Duration: 8-16 hours

Absorption: Almost complete

Metabolism: Hepatic

Excretion: Urine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDrowsiness is common; may cause nervousness; rare reports of depression
Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may result in additive sedation
Index TermsClemastine Fumarate
References

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Kok TH, Taitz LS, Bennett MJ, et al, “Drowsiness Due to Clemastine Transmitted in Breast Milk,” *Lancet*, 1982, 1:914-5.

International Brand NamesAgasten (BR); Alagyl (JP); Aller-Eze (GB); Aloginan (JP); Alphamin (JP); Anhistan (JP); Arrest (JP); Benanzyl (JP); Clamist (IN); Clemanil (JP); Clemastinum (PL); Darvine (TW); Fuluminol (JP); Fumaresutin (JP); Histaverin (TW); Inbestan (JP); Kinotomin (JP); Lacretin (JP); Langjing (CL); Lecasol (JP); Maikohis (JP); Mallermin-F (JP); Marsthine (JP, PH); Masletine (JP); Piloral (JP); Tandegyl (PK); Tavegil (BB, BM, BS, BZ, DE, ES, GB, GY, IE, IT, JM, LU, NL, SR, TT); Tavegyl (AT, BF, BG, BJ, CH, CI, CO, CZ, DK, EE, EG, ET, GH, GM, GN, HN, HU, ID, KE, LR, MA, ML, MR, MU, MW, NE, NG, NO, PH, PT, SC, SD, SE, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Tavist (PH); Telgin-G (JP); Xolamin (JP)

Clevidipine

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Medication Safety Issues

Sound-alike/look-alike issues:

Clevidipine may be confused with cladribine, clofarabine, clomiPRAMINE

Cleviprex™ may be confused with Claravis™

Pronunciation(klev ID i peen)

U.S. Brand NamesCleviprex™

Pharmacologic CategoryCalcium Channel Blocker

Use: Labeled IndicationsManagement of hypertension when oral treatment is not feasible or not desirable

Dosing: Adults Management of hypertension: I.V.: Initial: 1-2 mg/hour

Titration: Initial: dose may be doubled at 90-second intervals toward blood pressure goal. As blood pressure approaches goal, dose may be increased by less than double every 5-10 minutes. **Note:** For every 1-2 mg/hour increase in dose, an approximate reduction of 2-4 mm Hg in systolic blood pressure may occur.

Usual maintenance: 4-6 mg/hour; maximum: 21 mg/hour (1000 mL within a 24-hour period). There is limited short-term experience with doses up to 32 mg/hour. Data is limited beyond 72 hours.

Dosing: ElderlyRefer to adult dosing. Initiate at the low end of the dosage range. Specific guidelines for adjustment of clevidipine are not available, but careful monitoring is warranted.

Dosing: Renal ImpairmentNo adjustment required with initial infusion rate.

Dosing: Hepatic ImpairmentNo adjustment required with initial infusion rate.

Administration: I.V.I.V.: Maintain aseptic technique. Do not use if contamination is suspected. Do not dilute. Invert vial gently several times to ensure uniformity of emulsion prior to administration. Administer as a slow continuous infusion via central or peripheral line, using infusion device allowing for calibrated infusion rates. Use within 4 hours of puncturing vial; discard any tubing and unused portion, including that currently being infused.

Administration: I.V. DetailpH: 6.0-8.0

Dietary ConsiderationsClevidipine is formulated in an oil-in-water emulsion containing 200 mg/mL of lipid (2 kcal/mL). If on parenteral nutrition, may need to adjust the amount of lipid infused. Emulsion contains soybean oil, egg yolk phospholipids, and glycerin.

StorageStore in refrigerator at 2°C to 8°C (36°F to 46°F). Unopened vials are stable for 2 months at room temperature. Vials are stable for 4 hours once opened. Protect from light during storage. Do not freeze.

CompatibilityDo not mix with or administer in same line with other medications.

Y-site administration: Compatible I.V. solutions: D_5LR, D_5NS, D_5W, LR, NS, 10% amino acids, SWFI

ContraindicationsHypersensitivity to clevidipine or any component of the formulation (soybeans, soy products, eggs, egg products); impaired lipid metabolism (hyperlipidemia with or without acute pancreatitis, lipoid nephrosis); severe aortic stenosis

Allergy Considerations

- Calcium Channel Blocker, Dihydropyridine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Dosage reductions may be necessary.
- Rebound hypertension: May occur with prolonged use in patients not transitioned to other antihypertensive therapy; monitor these patients carefully for at least 8 hours after discontinuation of infusion.
- Reflex tachycardia: May occur with use and may result in angina or myocardial infarction in patients with obstructive coronary disease; dosage reductions may be necessary. Treatment of clevidipine-induced tachycardia with beta-blockers is **not** recommended.

Disease-related concerns:

- Heart failure (HF): Use with caution in patients with HF. Dihydropyridine calcium channel blockers may cause negative inotropic effects and exacerbate heart failure. Monitor carefully.
- Disorders of lipid metabolism: Use with caution in patients with disorders of lipid metabolism. Clevidipine is formulated within a 20% fat emulsion (0.2 g/mL). A reduction in the quantity of concurrently administered lipids may be necessary. Use is contraindicated in patients with impaired lipid metabolism (hyperlipidemia with or without acute pancreatitis, lipoid nephrosis).
- Pheochromocytoma: Use in hypertension associated with pheochromocytoma has not been studied.

Concurrent drug therapy issues:

- Beta-blockers: Avoid abrupt withdrawal of concomitant beta-blocker therapy. Gradually reduce dose of beta-blocker therapy when initiating clevidipine.

Special populations:

- Elderly: Initiate therapy at the low end of the dosage range in the elderly. If clinically indicated, titrate dose upward cautiously.

- Pediatrics: Safety and efficacy have not been established in children less than 18 years of age.

Other warnings/precautions:

- Infection risk: Vials have the potential to support microbial growth. To limit the potential for contamination, maintain aseptic technique while handling.

Geriatric ConsiderationsNo overall differences in safety or efficacy noted in the initial studies in elderly. Doses should be started at low end of dosage range and titrated slowly since elderly may experience a greater hypotensive response, reflecting their greater frequency of renal and cardiac disease with decreased function and concomitant drug therapy.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events were observed in animal reproduction studies. There are no adequate and well-controlled studies in pregnant women. Use only if potential benefit justifies potential risks.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Cardiovascular: Atrial fibrillation (13% to 21%)

Central nervous system: Fever (19%), insomnia (12%)

Gastrointestinal: Nausea (5% to 21%)

1% to 10%:

Central nervous system: Headache (6%)

Gastrointestinal: Vomiting (3%)

Hematologic: Postprocedural hemorrhage (3%)

Renal: Acute renal failure (9%)

Respiratory: Pneumonia (3%), respiratory failure (3%)

<1% (Limited to important or life-threatening): Cardiac arrest, dyspnea, MI, syncope, thrombophlebitis

Drug Interactions

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: Calcium Channel Blockers (Dihydropyridine) may decrease the serum concentration of QuiNIDine. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure, heart rate; patients who receive prolonged infusions of clevidipine and are not transitioned to other antihypertensive therapy should be monitored for at least 8 hours after discontinuation

Nursing: Physical Assessment/MonitoringAssess allergy history prior to treatment (soybeans or soy products, eggs or egg products). Use caution in presence of impaired lipid metabolism or heart failure. Assess other pharmacological or herbal products patient may be taking for potential interactions or toxicity (eg, beta-blockers or agents that may impact blood pressure control). See Administration for I.V. specifics. Assess therapeutic effectiveness (cardiac status and blood pressure) closely and titrate upward carefully, if needed. Patient should be monitored for a minimum of 8 hours after discontinuation (rebound hypertension may occur). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Patient EducationThis medication can only be administered by infusion. Report immediately any pain, burning, or swelling at infusion site or any signs of allergic reaction (eg, respiratory difficulty or swallowing, back pain, chest tightness, rash, hives, swelling of lips or mouth). Ask for assistance when rising or changing position until response to drug is known. Report chest pain or palpitations; headache or dizziness; nausea or vomiting; difficulty breathing; or any other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, emulsion:

Cleviprex™: 0.5 mg/mL (50 mL, 100 mL) [contains eggs, soy products]

Generic AvailableNo

Mechanism of ActionDihydropyridine calcium channel blocker with potent arterial vasodilating activity. Inhibits calcium ion influx through the L-type calcium channels during depolarization in arterial smooth muscle, producing a decrease in mean arterial pressure (MAP) by reducing systemic vascular resistance.

Pharmacodynamics/Kinetics

Onset of action: 2-4 minutes after start of infusion

Duration: I.V.: 5-15 minutes

Distribution: V_{dss}: 0.17 L/kg

Protein binding: >99.5%

Metabolism: Rapid hydrolysis primarily by esterases in blood and extravascular tissues to an inactive carboxylic acid metabolite and formaldehyde

Half-life elimination: Biphasic: Initial: 1 minute (predominant); Terminal: 15 minutes

Excretion: Urine (63% to 74% as metabolites); feces (7% to 22% as metabolites)

Related Information

- Calcium Channel Blockers
- Hypertension
- Postoperative Hypertension

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Although other calcium channel blockers (eg, nifedipine, diltiazem) have been associated with gingival hyperplasia, there are no reports that clevidipine has caused this adverse effect.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia is common

Mental Health: Effects on Psychiatric TreatmentAmphetamines may diminish the antihypertensive effect of clevidipine

Index TermsClevidipine Butyrate

References

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Levy JH, Mancao MY, Gitter R, et al, “Clevidipine Effectively and Rapidly Controls Blood Pressure Preoperatively in Cardiac Surgery Patients: The Results of the Randomized, Placebo-Controlled Efficacy Study of Clevidipine Assessing Its Preoperative Antihypertensive Effect in Cardiac Surgery-1,” *Anesth Analg*, 2007, 105(4):918-25. [PubMed 17898366]

Marik PE and Varon J, “Hypertensive Crises: Challenges and Management,” *Chest*, 2007, 131(6); 1949-62. Available at http://chestjournal.org/cgi/content/abstract/131/6/1949[PubMed 17565029]

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Varon J, “Treatment of Acute Severe Hypertension: Current and Newer Agents,” *Drugs*, 2008, 68(3):283-97. [PubMed 18257607]

Zhang JG, Dehal SS, Ho T, et al, “Human Cytochrome P450 Induction and Inhibition Potential of Clevidipine and Its Primary Metabolite H152/81,” *Drug Metab Dispos*, 2006, 34(5):734-37.[PubMed 16501008]

Clidinium and Chlordiazepoxide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Librax® may be confused with Librium®

Librax® formulation may be cause for confusion:

In November 2004, Valeant Pharmaceuticals licensed the Librax® trademark to Victory Pharmaceuticals. Subsequently, the product was reformulated to contain chlordiazepoxide and methscopolamine. In January 2006, Valeant Pharmaceuticals began redistributing the original formulation of Librax®, containing clidinium and chlordiazepoxide. Victory Pharmaceuticals has discontinued their product. **Note:** The formulation of Librax® distributed in Canada (Valeant Canada Ltd) always contained clidinium and chlordiazepoxide.

Pronunciation(kli DI nee um & klor dye az e POKS ide)

U.S. Brand NamesLibrax® *[original formulation]*

Canadian Brand NamesApo-Chlorax®; Librax®

Pharmacologic CategoryAntispasmodic Agent, Gastrointestinal; Benzodiazepine

Use: Labeled IndicationsAdjunct treatment of peptic ulcer; treatment of irritable bowel syndrome

Dosing: AdultsAdjunct treatment of peptic ulcer; treatment of IBS: Oral: 1-2 capsules 3-4 times/day, before meals or food and at bedtime. **Caution:** Do not abruptly discontinue after prolonged use; taper dose gradually.

Dosing: ElderlyRefer to adult dosing.

Administration: Oral**Caution:** Do not abruptly discontinue after prolonged use; taper dose gradually.

Dietary ConsiderationsShould be taken before meals.

ContraindicationsHypersensitivity to clidinium, chlordiazepoxide, or any component of the formulation; glaucoma; prostatic hyperplasia; benign bladder neck obstruction; pregnancy

Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.
- Elderly: Use with caution in the elderly.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.
- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsThe use of anticholinergic agents may cause problems with bladder emptying, constipation or cause confusion. The addition of chlordiazepoxide may enhance confusion potential. Monitor closely initially.
Pregnancy Risk FactorD
Pregnancy ConsiderationsAn increased risk of congenital malformations has been associated with the use of minor tranquilizers during the 1st trimester. Because use of these drugs is rarely a matter of urgency, their use should be avoided during this period.
LactationEnters breast milk/contraindicated
Adverse Reactions

1% to 10%:

Central nervous system: Drowsiness, ataxia, confusion, anticholinergic side effects

Gastrointestinal: Dry mouth, constipation, nausea

<1% (Limited to important or life-threatening): Agranulocytosis, blood dyscrasias, extrapyramidal symptoms, hepatic dysfunction, jaundice, syncope

Metabolism/Transport EffectsChlordiazepoxide: **Substrate** of CYP3A4 (major)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor for CNS depression. Assess knowledge/teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC, liver function

Patient EducationTake as directed before meals; do not increase dose and do not discontinue this medication without consulting prescriber first. Avoid alcohol and other CNS depressant medications (antihistamines, sleeping aids, antidepressants) unless approved by prescriber. Void before taking medication. This drug may impair mental alertness (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report excessive and persistent anticholinergic effects (blurred vision, headache, flushing, tachycardia, nervousness, constipation, dizziness, insomnia, mental confusion or excitement, dry mouth, altered taste perception, dysphagia, palpitations, bradycardia, urinary hesitancy or retention, impotence, decreased sweating), or change in color of urine or stools. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: Clidinium bromide 2.5 mg and chlordiazepoxide hydrochloride 5 mg

Librax® [original formulation]: Clidinium bromide 2.5 mg and chlordiazepoxide hydrochloride 5 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Clidinium-Chlordiazepoxide)

2.5-5 mg (100): $25.99

Capsules (Librax)

2.5-5 mg (60): $211.17

Related Information

- ChlordiazePOXIDE

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause confusion

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may result in additive sedation

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

Risk factors for abuse include personal or family history of substance abuse and personality disorder.

Index TermsChlordiazepoxide and Clidinium

References

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand NamesApo-Chlorax (SG); Bralix (AE, BB, BH, BM, BS, BZ, CY, EG, GY, IL, IQ, IR, JM, JO, KW, LB, LY, NL, OM, PR, QA, SA, SR, SY, TT, YE); Braxidin (ID); Chlobax (SG); Cliad (ID); Diporax (TW); Epirax (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Equirex (IN); Gastropax (EC); Klidibrax (ID); Kuanium (TW); Lerogin (CN); Librax (AE, AR, BB, BE, BF, BH, BJ, BM, BS, BZ, CH, CI, CR, CY, DO, EG, ET, FI, FR, GH, GM, GN, GR, GT, GY, HK, HN, ID, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NI, NL, OM, PA, PK, PT, QA, SA, SC, SD, SL, SN, SR, SV, SY, TH, TN, TT, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Libraxin (CN); Librocol (CH); Medocalum (SG); Nirvaxal (IL); Poxidium (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Renagas (ID)

Clindamycin and Benzoyl Peroxide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(klin da MYE sin & BEN zoe il peer OKS ide)
U.S. Brand NamesBenzaClin®; Duac® CS; Duac® [DSC]
Canadian Brand NamesBenzaClin®
Pharmacologic CategoryAcne Products; Topical Skin Product; Topical Skin Product, Acne
Use: Labeled IndicationsTopical treatment of acne vulgaris
Dosing: AdultsApply to affected areas after skin has been cleansed and dried:

Acne:*BenzaClin®:* Topical: Apply twice daily (morning and evening)

Inflammatory acne:*Duac® CS:* Topical: Apply once daily in the evening

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren ≥12 years: Refer to adult dosing.
Administration: TopicalSkin should be clean and dry before applying. For external use only; avoid applying to inside nose, mouth, eyes, and mucous membranes.
Storage

BenzaClin®: Store at room temperature of 25°C (77°F). Do not freeze.

Duac® CS: Prior to dispensing, store in refrigerator, between 2°C to 8°C (36°F to 46°F). Once dispensed, may be stored by patient at room temperature of up to 25°C (77°F) if used within 60 days. Do not freeze.

ReconstitutionBenzaClin®: Reconstitute clindamycin with purified water; shake well. Add solution to benzoyl peroxide gel and stir until homogenous in appearance. Discard unused portion after 3 months.
ContraindicationsHypersensitivity to benzoyl peroxide, clindamycin, lincomycin, or any component of the formulation; history of regional enteritis, ulcerative colitis, pseudomembranous colitis or antibiotic-associated colitis
Allergy Considerations

- Lincosamide Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bleaching effects: May bleach hair or colored fabric.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Concurrent drug therapy issues:

- Erythromycin: Concomitant use with erythromycin-containing products is not recommended.
- Topical acne products: Use concomitant topical acne therapy with caution; cumulative irritancy may occur.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Appropriate use: For external use only; avoid contact with mucous membranes and eyes.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted; use during pregnancy only if clearly needed.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsClindamycin is excreted in breast milk following oral and parenteral administration; the extent of excretion, if any, following topical use, in this combination is not known.
Adverse Reactions

>10%: Dermatologic: Erythema (1% to 26%), peeling (2% to 17%), dry skin (1% to 15%)

1% to 10%: Dermatologic: Pruritus (2%), sunburn (1%), burning (<1% to 5%)

Postmarketing and/or case reports: Allergic reactions, anaphylaxis, colitis, diarrhea, pseudomembranous colitis

Drug Interactions

Erythromycin: Lincosamide Antibiotics may diminish the therapeutic effect of Erythromycin. *Risk X: Avoid combination*

Kaolin: May decrease the absorption of Lincosamide Antibiotics. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Lincosamide Antibiotics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Patient EducationReport persistent diarrhea.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Gel, topical:

BenzaClin®: Clindamycin phosphate 1% and benzoyl peroxide 5% (25 g, 50 g)

Duac®: Clindamycin phosphate 1% and benzoyl peroxide 5% (45 g) [DSC]

Duac® CS: Clindamycin phosphate 1% and benzoyl peroxide 5% (45 g) [packaged with SFC™ lotion 107 mL]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Gel (Benzaclin)

1-5% (25): $89.99

1-5% (50): $145.99

Gel (Benzaclin with Pump)

1-5% (50): $152.15

Kit (Duac CS)

1-5% (1): $153.29

Mechanism of ActionClindamycin and benzoyl peroxide have activity against *Propionibacterium acnesin vitro*. This organism has been associated with acne vulgaris. Benzoyl peroxide releases free-radical oxygen which oxidizes bacterial proteins in the sebaceous follicles decreasing the number of anaerobic bacteria and decreasing irritating-type free fatty acids. Clindamycin reversibly binds to 50S ribosomal subunits preventing peptide bond formation thus inhibiting bacterial protein synthesis; bacteriostatic or bactericidal depending on drug concentration, infection site, and organism.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Benzoyl Peroxide
- Clindamycin

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBenzoyl Peroxide and Clindamycin; Clindamycin Phosphate and Benzoyl Peroxide

International Brand NamesBenzaclin (IL, MX); Clindapack (MX); Clindoxyl Gel (DK, FI); DUAC (CZ, DE, EE, ES, GB, IE, NZ, PH, PT, SE); Duac Once Daily (AU, HK); Indoxyl Gel (CN, CO, MX, PE, PY); Klina (CN); Septigel (CR, DO, GT, PA)

Clindamycin and Tretinoin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(klin da MYE sin & TRET i noyn)

U.S. Brand NamesZiana™

Pharmacologic CategoryAcne Products; Retinoic Acid Derivative; Topical Skin Product; Topical Skin Product, Acne

Use: Labeled IndicationsTreatment of acne vulgaris

Dosing: AdultsAcne: Topical: Apply pea-size amount to entire face once daily at bedtime

Dosing: PediatricAcne: Topical: Children ≥12 years: Refer to adult dosing.

Administration: TopicalAt bedtime, clean face with a mild soap and pat dry before applying medication. A pea-size amount should be applied to one fingertip and then dotted on chin, cheeks, nose, and forehead. Gently rub over entire face avoiding eyes, mouth, angles of nose, and mucous membranes.

StorageStore at 15°C to 30°C (68°F to 77°F); do not freeze. Protect from light.

Allergy Considerations

- Retinoid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Photosensitivity: Tretinoin use is associated with increased susceptibility/sensitivity to UV light; avoid sunlamps or excessive sunlight exposure. Daily sunscreen use and other protective measures recommended.
- Skin irritation: Treatment can increase skin sensitivity to weather extremes of wind or cold. Also, concomitant topical medications (eg, medicated or abrasive soaps, cleansers, or cosmetics with a strong drying effect) should be used with caution due to increased skin irritation.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Appropriate use: For external use only; avoid mucous membranes, eyes, mouth, and angles of nose.

Geriatric ConsiderationsHas not been studied in elderly patients.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in topical animal studies. Refer to individual monographs.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Dermatologic: Erythema (26% to 35%), scaling (13% to 17%)

1% to 10%:

Dermatologic: Itching (4% to 10%), burning (2% to 4%), stinging (2%), dry skin (1%)

Gastrointestinal: GI symptoms, unspecified (4%)

Respiratory: Nasopharyngitis (4%)

Drug Interactions

Erythromycin: Lincosamide Antibiotics may diminish the therapeutic effect of Erythromycin. *Risk X: Avoid combination*

Kaolin: May decrease the absorption of Lincosamide Antibiotics. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Lincosamide Antibiotics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel, topical:

Ziana™: Clindamycin phosphate 1.2% and tretinoin 0.025% (30 g, 60 g)

Generic AvailableNo
ManufacturerMedicis
Pricing: U.S. (www.drugstore.com)

Gel (Ziana)

1.2-0.025% (30): $155.90

1.2-0.025% (60): $309.52

Mechanism of ActionClindamycin reversibly binds to 50S ribosomal subunits preventing peptide chain elongation thus inhibiting bacterial protein synthesis. Clindamycin exhibits *in vitro* activity against *Propionibacterium acnes*, an organism associated with acne vulgaris. Topical tretinoin is believed to decrease follicular epithelial cells cohesiveness and increase follicular epithelial cell turnover resulting in decreased microcomedo formation and increased expulsion of comedones.
Pharmacodynamics/KineticsAbsorption: Topical: Tretinoin: Minimal systemic absorption; Clindamycin: Low, but variable systemic absorption
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentDiarrhea may occur with topical clindamycin. Concomitant use with SSRI, lithium, carbamazepine, or valproic acid and derivatives may produce additive effects. Tretinoin and psychotropics are associated with photosensitivity; monitor.
Index TermsClindamycin Phosphate and Tretinoin; Tretinoin and Clindamycin

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Clindamycin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Cleocin® may be confused with bleomycin, Clinoril®, Cubicin®, Lincocin®

Clindamycin may be confused with clarithromycin, Claritin®, vancomycin

Pronunciation(klin da MYE sin)

U.S. Brand NamesCleocin HCl®; Cleocin Pediatric®; Cleocin Phosphate®; Cleocin T®; Cleocin®; Cleocin® Vaginal Ovule; Clindagel®; ClindaMax®; ClindaReach™; Clindesse™; Evoclin®

Canadian Brand NamesAlti-Clindamycin; Apo-Clindamycin®; Clindamycin Injection, USP; Clindoxyl®; Dalacin® C; Dalacin® T; Dalacin® Vaginal; Gen-Clindamycin; Novo-Clindamycin; PMS-Clindamycin; ratio-Clindamycin; Riva-Clindamycin; Taro-Clindamycin

Pharmacologic CategoryAntibiotic, Lincosamide; Topical Skin Product, Acne

Use: Labeled IndicationsTreatment of susceptible bacterial infections, mainly those caused by anaerobes, streptococci, pneumococci, and staphylococci; bacterial vaginosis (vaginal cream, vaginal suppository); pelvic inflammatory disease (I.V.); topically in treatment of severe acne; vaginally for *Gardnerella vaginalis*

Use: Unlabeled/InvestigationalMay be useful in PCP; alternate treatment for toxoplasmosis

Use: DentalAlternate oral antibiotic for prevention of infective endocarditis in individuals allergic to penicillins or ampicillin, when amoxicillin cannot be used; alternate I.M. or I.V. antibiotic for prevention of infective endocarditis in patients allergic to penicillins or ampicillin and unable to take oral medication; alternate oral antibiotic for prophylaxis for dental patients with total joint replacement who are allergic to penicillin; alternate I.V. antibiotic for prophylaxis for dental patients with total joint replacement who are allergic to penicillin and unable to take oral medications; alternate antibiotic in the treatment of common orofacial infections caused by aerobic gram-positive cocci and susceptible anaerobes; treatment of periodontal disease

Dosing: Adults

Usual dose:

Oral: 150-450 mg/dose every 6-8 hours; maximum dose: 1.8 g/day

I.M., I.V.: 1.2-2.7 g/day in 2-4 divided doses; maximum dose: 4.8 g/day

Acne: *Topical:*

Gel, pledget, lotion, solution: Apply a thin film twice daily

Foam (Evoclin®): Apply once daily

Amnionitis:*I.V.:* 450-900 mg every 8 hours

Anthrax:*I.V.:* 900 mg every 8 hours with ciprofloxacin or doxycycline

Babesiosis (unlabeled use):

Oral: 600 mg 3 times/day for 7 days with quinine

I.V.: 1.2 g twice daily for 7 days with quinine

Bacterial vaginosis:*Intravaginal:*

Suppositories: Insert one ovule (100 mg clindamycin) daily into vagina at bedtime for 3 days

Cream:

Cleocin®: One full applicator inserted intravaginally once daily before bedtime for 3 or 7 consecutive days in nonpregnant patients or for 7 consecutive days in pregnant patients

Clindesse™: One full applicator inserted intravaginally as a single dose at anytime during the day in nonpregnant patients

Bite wounds (canine):*Oral:* 300 mg 4 times/day with a fluoroquinolone

Gangrenous pyomyositis:*I.V.:* 900 mg every 8 hours with penicillin G

Group B streptococcus (neonatal prophylaxis):*I.V.:* 900 mg every 8 hours until delivery

Orofacial/parapharyngeal space infections:

Oral: 150-450 mg every 6 hours for at least 7 days; maximum dose: 1.8 g/day

I.V.: 600-900 mg every 8 hours

Pelvic inflammatory disease: *I.V.:* 900 mg every 8 hours with gentamicin 2 mg/kg, then 1.5 mg/kg every 8 hours; continue after discharge with doxycycline 100 mg twice daily to complete 14 days of total therapy

Pneumonia due to*Pneumocystis jiroveci*(unlabeled use): I.V.: 600 mg every 8 hours with primaquineor pentamidine for 21 days

Prophylaxis against infective endocarditis (unlabeled use):

Oral: 600 mg 1 hour before procedure with no follow-up dose needed

I.M., I.V.: 600 mg within 30 minutes before procedure. Intramuscular injections should be avoided in patients who are receiving anticoagulant therapy. In these circumstances, orally administered regimens should be given whenever possible. Intravenously administered antibiotics should be used for patients who are unable to tolerate or absorb oral medications.

Note: American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur. As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Toxic shock syndrome:*I.V.:* 900 mg every 8 hours with penicillin G or ceftriaxone

Toxoplasmosis (unlabeled use):*Oral, I.V.:* 600 mg every 6 hours with pyrimethamine and folinic acid

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Usual dose:

Oral: Infants and Children: 8-20 mg/kg/day as hydrochloride; 8-25 mg/kg/day as palmitate in 3-4 divided doses; minimum dose of palmitate: 37.5 mg 3 times/day

I.M., I.V.:

<1 month: 15-20 mg/kg/day in 3-4 divided doses

>1 month: 20-40 mg/kg/day in 3-4 divided doses

Anthrax:*I.V.:* 7.5 mg/kg every 6 hours

Prophylaxis against infective endocarditis (unlabeled use):

Oral: 20 mg/kg 1 hour before procedure with no follow-up dose needed

I.M., I.V.: 20 mg/kg within 30 minutes before procedure. Intramuscular injections should be avoided in patients who are receiving anticoagulant therapy. In these circumstances, orally administered regimens should be given whenever possible. Intravenously administered antibiotics should be used for patients who are unable to tolerate or absorb oral medications.

Note: American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur. As of April 2007, routine prophylaxis for GI/GU procedures is no longer recommended by the AHA.

Orofacial infections:

Oral: 10-20 mg/kg in 3-4 equally divided doses

I.V.: 15-25 mg/kg in 3-4 equally divided doses

Acne: *Topical:* Children ≥12 years: Refer to adult dosing.

Babesiosis (unlabeled use): *Oral:* 20-40 mg/kg divided every 8 hours for 7 days plus quinine

Dosing: Renal ImpairmentNo adjustment required.
Dosing: Hepatic ImpairmentSystemic use: Adjustment is recommended in patients with severe hepatic disease.
Administration: I.M.Deep I.M. sites, rotate sites. Do not exceed 600 mg in a single injection.
Administration: I.V.**Never administer as bolus**; administer by I.V. intermittent infusion over at least 10-60 minutes, at a rate **not** to exceed 30 mg/minute (do not exceed 1200 mg/hour). Final concentration for administration should not exceed 18 mg/mL.
Administration: I.V. DetailpH: 6.0-6.3 (usual); 5.5-7.0 (range)
Administration: OralAdminister oral dosage form with a full glass of water to minimize esophageal ulceration. Give around-the-clock to promote less variation in peak and trough serum levels.
Administration: TopicalFoam: Dispense directly into cap or onto a cool surface. Do not dispense directly into hands.
Administration: Other

Intravaginal:

Cream: Insertion should be as far as possible into the vagina without causing discomfort.

Ovule: The foil should be removed; if the applicator is used for insertion, it should be washed for additional use.

Dietary ConsiderationsMay be taken with food.

Storage

Capsule: Store at room temperature of 20°C to 25°C (68°F to 77°F).

Cream: Store at room temperature.

Foam: Store at room temperature of 20°C to 25°C (68°F to 77°F). Avoid fire, flame, or smoking during or following application.

Gel: Store at room temperature.

Clindagel®: Do not store in direct sunlight.

I.V.: Infusion solution in NS or D_5W solution is stable for 16 days at room temperature, 32 days refrigerated, or 8 weeks frozen. Prior to use, store vials and premixed bags at controlled room temperature 20°C to 25°C (68°F to 77°F). After initial use, discard any unused portion of vial after 24 hours.

Lotion: Store at room temperature of 20°C to 25°C (68°F to 77°F).

Oral solution: Do not refrigerate reconstituted oral solution (it will thicken). Following reconstitution, oral solution is stable for 2 weeks at room temperature of 20°C to 25°C (68°F to 77°F).

Ovule: Store at room temperature of 15°C to 30°C (68°F to 77°F).

Pledget: Store at room temperature.

Topical solution: Store at room temperature of 20°C to 25°C (68°F to 77°F).

CompatibilityStable in D_5R, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, NS; **variable stability (consult detailed reference)** in peritoneal dialysis solutions.

Y-site administration: Compatible: Acyclovir, amifostine, amiodarone, amphotericin B cholesteryl sulfate complex, amsacrine, anakinra, aztreonam, bivalirudin, cefpirome sulfate, cisatracurium, cyclophosphamide, dexmedetomidine, diltiazem, docetaxel, doxorubicin liposome, enalaprilat, esmolol, etoposide, fenoldopam, fludarabine, foscarnet, gatifloxacin, gemcitabine, granisetron, heparin, hydromorphone, labetalol, levofloxacin, linezolid, magnesium sulfate, melphalan, meperidine, midazolam, milrinone, morphine, multivitamins, nicardipine, ondansetron, pemetrexed, perphenazine, piperacillin/tazobactam, propofol, remifentanil, sargramostim, tacrolimus, teniposide, theophylline, thiotepa, vinorelbine, vitamin B complex with C, zidovudine. **Incompatible:** Allopurinol, azithromycin, doxapram, filgrastim, fluconazole, idarubicin. **Variable (consult detailed reference):** Drotrecogin alfa.

Compatibility in syringe: Compatible: Amikacin, aztreonam, caffeine citrate, dimenhydrinate, gentamicin, heparin. **Incompatible:** Pantoprazole, tobramycin.

Compatibility when admixed: Compatible: Amikacin, ampicillin, aztreonam, cefamandole, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftizoxime, cefuroxime, cimetidine, fluconazole, gentamicin, heparin, hydrocortisone sodium succinate, kanamycin, methylprednisolone sodium succinate, metoclopramide, metronidazole, metronidazole with sodium bicarbonate, ofloxacin, penicillin G, piperacillin, potassium chloride, sodium bicarbonate, tobramycin, verapamil, vitamin B complex with C. **Incompatible:** Aminophylline, ampicillin, barbiturates, calcium gluconate, ceftriaxone, ciprofloxacin, gentamicin with cefazolin, magnesium sulfate, phenytoin. **Variable (consult detailed reference):** Ranitidine.

ContraindicationsHypersensitivity to clindamycin, lincomycin, or any component of the formulation

Topical and vaginal products: Additional contraindications: Previous pseudomembranous colitis, regional enteritis, ulcerative colitis

Allergy Considerations

- Lincosamide Allergy

Warnings/Precautions

Boxed warnings:

- Colitis: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Colitis: **[U.S. Boxed Warning]: Can cause severe and possibly fatal colitis.** Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment. Use with caution in patients with a history of gastrointestinal disease. Discontinue drug if significant diarrhea, abdominal cramps, or passage of blood and mucus occurs.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; monitor hepatic enzymes periodically as dosage adjustments may be necessary in patients with severe impairment.

Special populations:

- Atopic patients: Use with caution in atopic patients.

Dosage form specific issues:

- Benzyl alcohol: Some products may contain benzyl alcohol which has been associated with "gasping syndrome" in neonates.

- Tartrazine: Some products may contain tartrazine, which may cause allergic reactions in certain individuals.

- Vaginal products: May weaken condoms, or contraceptive diaphragms; barrier contraceptives are not recommended concurrently or for 3-5 days (depending on the product) following treatment.

Geriatric ConsiderationsClindamycin has not been studied in the elderly; however, since it is eliminated principally by nonrenal mechanisms, major alteration in its pharmacokinetics are not expected. Elderly patients are often at a higher risk for developing serious colitis and require close monitoring.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsClindamycin is excreted into breast milk. Due to the potential for adverse reactions to neonate, the manufacturer recommends discontinuing the drug taking into account the importance to the mother.

Adverse Reactions

Systemic: Frequency not defined:

Cardiovascular: Cardiac arrest (rare; I.V. administration), hypotension (rare; I.V. administration)

Dermatologic: Erythema multiforme (rare), exfoliative dermatitis (rare), pruritus, rash, Stevens-Johnson syndrome (rare), urticaria

Gastrointestinal: Abdominal pain, diarrhea, esophagitis, nausea, pseudomembranous colitis, vomiting

Genitourinary: Vaginitis

Hematologic: Agranulocytosis, eosinophilia (transient), neutropenia (transient), thrombocytopenia

Hepatic: Jaundice, liver function test abnormal

Local: Induration/pain/sterile abscess (I.M.), thrombophlebitis (I.V.)

Neuromuscular & skeletal: Polyarthritis (rare)

Renal: Renal dysfunction (rare)

Miscellaneous: Anaphylactoid reactions (rare)

Topical:

>10%: Dermatologic: Dryness, burning, itching, scaliness, erythema, or peeling of skin (lotion, solution); oiliness (gel, lotion)

<1% (Limited to important or life-threatening): Pseudomembranous colitis, nausea, vomiting, diarrhea (severe), abdominal pain, folliculitis, hypersensitivity reactions

Vaginal:

>10%: Genitourinary: Vaginal candidiasis (≤13%), vulvovaginal pruritus (from *Candida albicans*)

1% to 10%:

Dermatologic: Pruritus (≤1%)

Genitourinary: Vulvovaginal disorder (3% to 7%), vulvovaginitis (4% to 6%), vaginal pain (≤2%), trichomonal vaginitis (1%)

Miscellaneous: Fungal infection (1% to 2%)

<1% (Limited to important or life-threatening): Abdominal cramps, allergic reaction, atrophic vaginitis, bacterial infection, diarrhea, dizziness, dysuria, endometriosis, epistaxis, erythema, fever, hypersensitivity, hyperthyroidism, local edema, menstrual disorder, metrorrhagia, nausea, pain, pruritus, pyelonephritis, rash, urinary tract infection, urticaria, vaginal burning, vertigo, vomiting

Drug Interactions

Erythromycin: Lincosamide Antibiotics may diminish the therapeutic effect of Erythromycin. *Risk X: Avoid combination*

Kaolin: May decrease the absorption of Lincosamide Antibiotics. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Lincosamide Antibiotics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Peak concentrations may be delayed with food.

Herb/Nutraceutical: St John's wort may decrease clindamycin levels.

Monitoring ParametersObserve for changes in bowel frequency. Monitor for colitis and resolution of symptoms. During prolonged therapy monitor CBC, liver and renal function tests periodically.

Nursing: Physical Assessment/MonitoringAssess previous allergy history prior to beginning therapy. **I.V.:** Cardiac status and blood pressure should be monitored and patient kept recumbent after infusion until blood pressure is stabilized. Assess results of laboratory tests and patient response according to dose, route of administration, and purpose of therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, severe diarrhea, opportunistic infection).

Monitoring: Lab TestsCBC, liver and renal function periodically with prolonged therapy

Patient Education

I.M., I.V.: Report any burning, pain, swelling, or redness at infusion or injection site.

Oral: Take each dose with a full glass of water. Complete full prescription, even if feeling better. You may experience nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report dizziness; persistent GI effects (pain, diarrhea, vomiting); skin redness, rash, or burning; fever; chills; unusual bruising or bleeding; signs of infection; excessive fatigue; yellowing of eyes or skin; change in color of urine or blackened stool; swelling, warmth, or pain in extremities; difficult respirations; bloody or fatty stool (do not take antidiarrheal without consulting prescriber); or lack of improvement or worsening of condition.

Topical, foam: Wash hands thoroughly or wear gloves. Do not dispense directly onto hands or face (foam will begin to melt on contact with warm skin). Dispense an amount the will cover the affected area directly into the cap or onto a cool surface. If can seems warm or foam seems runny, run can under cold water. Pick up small amounts of foam with fingertips and gently massage into affected areas until foam disappears. Wash hands thoroughly. Wait 30 minutes before shaving or applying make-up.

Topical gel, lotion, or solution: Wash hands thoroughly before applying or wear gloves. Apply thin film of gel, lotion, or solution to affected area. May apply porous dressing. Wash hands thoroughly. Wait 30 minutes before shaving or applying make-up. Report persistent burning, swelling, itching, excessive dryness, or worsening of condition.

Vaginal: Wash hands before using. At bedtime: If using applicator, gently insert full applicator into vagina and expel cream. Wash applicator with soap and water following use. If using suppository, insert high into vagina. Remain lying down for 30 minutes following administration. Avoid intercourse during therapy. Report adverse reactions (dizziness, nausea, vomiting, stomach cramps, or headache) or lack of improvement or worsening of condition.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: Strength is expressed as base

Capsule, as hydrochloride: 75 mg, 150 mg, 300 mg

Cleocin HCl®: 75 mg [contains tartrazine], 150 mg [contains tartrazine], 300 mg

Cream, vaginal, as phosphate:

Cleocin®: 2% (40 g) [contains benzyl alcohol and mineral oil; packaged with 7 disposable applicators]

ClindaMax®: 2% (40 g) [contains benzyl alcohol and mineral oil; packaged with 7 disposable applicators]

Clindesse™: 2% (5 g) [contains mineral oil; prefilled single disposable applicator]

Foam, topical, as phosphate:

Evoclin®: 1% (50 g, 100 g) [contains ethanol 58%]

Gel, topical, as phosphate: 1% (30 g, 60 g)

Cleocin T®: 1% (30 g, 60 g)

Clindagel®: 1% (40 mL, 75 mL)

ClindaMax®: 1% (30 g, 60 g)

Granules for oral solution, as palmitate:

Cleocin Pediatric®: 75 mg/5 mL (100 mL) [cherry flavor]

Infusion, as phosphate [premixed in D_5W]:

Cleocin Phosphate®: 300 mg (50 mL); 600 mg (50 mL); 900 mg (50 mL) [contains benzyl alcohol and edetate disodium 0.5 mg/mL]

Injection, solution, as phosphate: 150 mg/mL (2 mL, 4 mL, 6 mL, 60 mL)

Cleocin Phosphate®: 150 mg/mL (2 mL, 4 mL, 6 mL, 60 mL) [contains benzyl alcohol and edetate disodium 0.5 mg/mL]

Lotion, as phosphate: 1% (60 mL)

Cleocin T®, ClindaMax®: 1% (60 mL)

Pledgets, topical: 1% (60s, 69s)

Cleocin T®: 1% (60s) [contains isopropyl alcohol 50%]

ClindaReach™: 1% (120s) [contains isopropyl alcohol 50%; packaged as a kit containing 1 collapsible applicator, 64 appliques, and 64 unmedicated pads]

Solution, topical, as phosphate: 1% (30 mL, 60 mL)

Cleocin T®: 1% (30 mL, 60 mL) [contains isopropyl alcohol 50%]

Suppository, vaginal, as phosphate:

Cleocin® Vaginal Ovule: 100 mg (3s) [contains oleaginous base; single reusable applicator]

Generic AvailableYes: Excludes foam, granules, vaginal suppositories, vaginal cream
Pricing: U.S. (www.drugstore.com)

Capsules (Cleocin)

150 mg (30): $101.84

300 mg (30): $216.68

Capsules (Clindamycin HCl)

150 mg (30): $24.99

300 mg (30): $79.99

Cream (Cleocin)

2% (40): $69.29

Cream (Clindamax)

2% (40): $47.95

Cream (Clindesse)

2% (5.8): $91.20

Foam (Evoclin)

1% (50): $160.05

1% (100): $251.97

Gel (Cleocin-T)

1% (30): $59.99

1% (60): $99.98

Gel (Clindagel)

1% (40): $128.90

1% (75): $210.99

Gel (ClindaMax)

1% (30): $53.73

1% (60): $96.04

Gel (Clindamycin Phosphate)

1% (30): $18.99

1% (60): $51.50

Lotion (Cleocin-T)

1% (60): $77.99

Lotion (ClindaMax)

1% (60): $72.71

Lotion (Clindamycin Phosphate)

1% (60): $45.99

Solution (Cleocin-T)

1% (60): $65.99

Solution (Clindamycin Phosphate)

1% (30): $14.99

1% (60): $16.79

Solution (reconstituted) (Cleocin)

75 mg/5 mL (100): $55.18

Suppository (Cleocin)

100 mg (3): $67.99

Swab (Cleocin-T)

1% (60): $69.99

Swab (Clindamycin Phosphate)

1% (60): $29.98

Mechanism of ActionReversibly binds to 50S ribosomal subunits preventing peptide bond formation thus inhibiting bacterial protein synthesis; bacteriostatic or bactericidal depending on drug concentration, infection site, and organism

Pharmacodynamics/Kinetics

Absorption: Topical: ~10%; Oral: Rapid (90%)

Distribution: High concentrations in bone and urine; no significant levels in CSF, even with inflamed meninges; crosses placenta; enters breast milk

Metabolism: Hepatic

Bioavailability: Topical: <1%

Half-life elimination: Neonates: Premature: 8.7 hours; Full-term: 3.6 hours; Adults: 1.6-5.3 hours (average: 2-3 hours)

Time to peak, serum: Oral: Within 60 minutes; I.M.: 1-3 hours

Excretion: Urine (10%) and feces (~4%) as active drug and metabolites

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Malaria Treatment
- Prevention of Infective Endocarditis
- Treatment of Sexually-Transmitted Infections
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health Professional ConsiderationsClindamycin has not been shown to interfere with oral contraceptive activity; however, it reduces GI microflora, thus, oral contraceptive users should be advised to use additional methods of birth control. About 1% of clindamycin users develop pseudomembranous colitis. Symptoms may occur 2-9 days after initiation of therapy; however, it has never occurred with the 1-dose regimen of clindamycin used to prevent bacterial endocarditis.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine

Cardiovascular ConsiderationsClindamycin may increase the duration of neuromuscular blockade after anesthesia. Clindamycin may also be considered in the prevention of bacterial endocarditis.

Anesthesia and Critical Care Concerns/Other ConsiderationsClindamycin may increase the duration of neuromuscular blockade after anesthesia. In adults, clindamycin injection can usually be dosed effectively on an every-8-hour basis.

Index TermsClindamycin Hydrochloride; Clindamycin Palmitate; Clindamycin Phosphate

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International Brand NamesAclinda (DE); Albiotin (ID); BB (TW); Bexon (CO); Biodaclin (MX); Cleocin HCl (AU, BB, BM, BS, BZ, GY, JM, KP, NL, PK, SR, TT); Cleocin T (KP); Cleocin Vaginal (KP); Clidets (MX); Climadan (ID); Clinacin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Clinamsa (MX); Clinbercin (ID); Clinda (DE); Clindabeta (FR); Clindac (MY); Clindacid (PY); Clindacin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE); Clindacne (PL); Clindagel (SG); Clindal (PH); Clindalin (TH); Clindamax (PE); Clindamycin-MIP (PL); Clindan (TH); Clindatech (HK); Clindavid (TH); Clindo (PL); Clinfol (PE); Clinika (SG); Clinott (TH); Clinott-P (TH); Cliz (PH); Combasin (ID); Cutaclin 1% (MX); Dacin (SG); Daclin (ID, KP); Dalacin (AR, BE, DK, ES, FI, HR, HU, IN, LU, NO, PL, SE, VE); Dalacin C (AE, AT, AU, BE, BF, BG, BH, BJ, BR, CH, CI, CN, CO, CR, CY, CZ, EC, EE, EG, ET, GB, GH, GM, GN, GT, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, OM, PA, PE, PH, PL, PT, QA, SA, SC, SD, SL, SN, SV, SY, TH, TN, TZ, UG, UY, YE, ZA, ZM, ZW); Dalacin T (AE, AR, AU, BE, BF, BH, BJ, BR, CH, CI, CN, CO, CY, CZ, EC, EG, ET, GB, GH, GM, GN, HK, HR, HU, ID, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PE, PL, QA, SA, SC, SD, SL, SN, SY, TH, TN, TZ, UG, YE, ZA, ZM, ZW); Dalacin V (AU, BR, CH, CN, CO, CR, GT, HN, HR, MY, NI, PA, PE, SV); Dalacin VC (ZA); Dalacine (FR); Dalaclin (PH); Dalcap (IN); Damicine (CO); Divanon (EC); Galecin (MX); Inprosyn-HP (PH); Jutaclin (DE); Klamoxyl (MX); Klimicin (HR, HU, PL); Klin-Amsa (MX); Klindamycin (TH); Lacin (TH); Lanacin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Lando (ID); Librodan (ID); Lindan (ID); Lisiken (MX); Luoqing (CL); Millda (TH); Nildacin (ID); Nufaclind (ID); Opiclam (ID); Probiotin (ID); Qualiclinda (HK); Rosil (TH); Sobelin (DE); T3Mycin (SG); Tidact (PH, TW); Topcil (NZ); Topicil (MY); Trexen (MX); Turimycin (DE); Zindaclin (GB, IE, IL, MY); Zindacline (FR)

Clioquinol and Flumethasone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(klye ok KWIN ole & floo METH a sone)
Canadian Brand NamesLocacorten® Vioform®
Pharmacologic CategoryAntibiotic, Topical; Corticosteroid, Topical
Use: Labeled IndicationsTreatment of corticosteroid-responsive dermatoses complicated by infection with bacterial and/or fungal agents
Dosing: Adults

Steroid-responsive otic infection: Otic solution (drops): Instill 2-3 drops into affected ear(s) 2 times/day; generally limit duration to 10 days

Steroid-responsive dermatoses/infection: Topical: Apply in a thin layer to affected area 2-3 times/day; generally limit duration to 7 days

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren >2 years of age: Refer to adult dosing.
Administration: TopicalAvoid use of occlusive dressings. Cleanse affected area before application; can stain skin and fabrics; for external use only; avoid contact with eyes and mucous membranes.
StorageStore between 15°C and 30°C.
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to clioquinol, flumethasone, or any component of the formulation; viral infection of the skin; tuberculosis, syphilis, rosacea, acne vulgaris, or perioral dermatitis; use in children <2 years of age
Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Iodine intolerance: Use with caution in patients with iodine intolerance.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Optic atrophy: Known to cause serious and irreversible optic atrophy.
- Peripheral neuropathy: Known to cause serious and peripheral neuropathy with muscular weakness, sensory loss, spastic paraparesis, and blindness.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Thyroid disease: Use with caution in patients with thyroid abnormalities.

Special populations:

- Pediatrics: Topical application poses a potential risk of toxicity to infants and children; striae and growth suppression have been reported with use of some corticosteroids in infants and children.

Other warnings/precautions:

- Application site: Do not apply to large areas or denuded skin; may irritate sensitized skin.
- Appropriate response: Discontinue therapy if no response within 1 week.

Pregnancy Risk FactorC (based on similar agents)
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Dermatologic: Skin irritation, rash, pigmentary changes, skin atrophy, striae

Endocrine: Potentially associated with excessive/prolonged use: Thyrotoxicosis, HPA axis suppression (rare)

Neuromuscular & skeletal: Peripheral neuropathy

Ocular: Optic atrophy

Drug InteractionsThere are no known significant interactions.
Test InteractionsThyroid function tests (decreased ^{131}I uptake); false-positive ferric chloride test for phenylketonuria
Monitoring ParametersObserve affected area for increased irritation
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Cream, topical (Locacorten® Vioform® [CAN]): Clioquinol 3% and flumethasone pivalate 0.02% (15 g, 50 g) [not available in the U.S.]

Solution, otic (Locacorten® Vioform® [CAN]): Clioquinol 1% and flumethasone pivalate 0.02% (10 mL) [not available in the U.S.]

Generic AvailableNo
Mechanism of ActionFlumethasone is a moderate-potency fluorinated corticosteroid; clioquinol chelates bacterial surface and trace metals needed for bacterial growth
Pharmacodynamics/Kinetics

Absorption: With an occlusive dressing, up to 40% of dose can be absorbed systemically during a 12-hour period; absorption is enhanced when applied under diapers

Half-life elimination: 11-14 hours

Excretion: Conjugated and excreted in urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsFlumethasone and Clioquinol; Iodochlorhydroxyquin and Flumethasone
References

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

International Brand NamesLocacorten-Vioform (DE, DK, FI, NO, SE); Locorten Vioform (NZ); Locorten Vioformo (VE); Locorten-Vioformio (BR); Topicorten V (IL)

Clobazam

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(KLOE ba zam)

Canadian Brand NamesAlti-Clobazam; Apo-Clobazam®; Clobazam-10; Dom-Clobazam; Frisium®; Novo-Clobazam; PMS-Clobazam; ratio-Clobazam

Pharmacologic CategoryBenzodiazepine

Use: Labeled IndicationsAdjunctive treatment of epilepsy

Use: Unlabeled/InvestigationalMonotherapy for epilepsy or intermittent seizures

Dosing: AdultsAnticonvulsant: Oral: Initial: 5-15 mg/day; dosage may be gradually adjusted (based on tolerance and seizure control) to a maximum of 80 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAnticonvulsant: Oral:

<2 years: Initial 0.5-1 mg/kg/day

2-16 years: Initial: 5 mg/day; may be increased (no more frequently than every 5 days) to a maximum of 40 mg/day

Dosing: Hepatic ImpairmentAvoid use in severe hepatic impairment. Use lower doses in mild-to-moderate impairment and monitor closely.

Administration: OralMay be administered with food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at 15°C to 30°C (59°F to 86°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to clobazam or any component of the formulation (cross sensitivity with other benzodiazepines may exist); myasthenia gravis; narrow-angle glaucoma; severe hepatic or respiratory disease; sleep apnea; history of substance abuse; use in pregnancy (particularly 1st trimester); breast-feeding is contraindicated per manufacturer

Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.
- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury.
- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.
- Chronic use: Tolerance and loss of seizure control have been reported with chronic administration.
- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Pregnancy Risk FactorNot assigned; similar agents rated D. Contraindicated in 1st trimester (per manufacturer).

Pregnancy ConsiderationsClobazam crosses the placenta. Oral clefts reported with benzodiazepines, however, more recent data does not support an association between drug and oral clefts. Inguinal hernia, cardiac defects, spina bifida, dysmorphic facial features, skeletal defects, multiple other malformations also reported. Hypotonia and withdrawal symptoms reported following use during 3rd trimester or near time of delivery.

LactationEnters breast milk/contraindicated (AAP rates other benzodiazepines “of concern”); clinical effects on infant include sedation

Breast-Feeding ConsiderationsCrosses into breast milk. Clinical effects on the infant: Sedation. AAP reports that use of other benzodiazepines MAY BE OF CONCERN; manufacturer contraindicates use in breast-feeding.

Adverse Reactions

Central nervous system: Drowsiness (17%), ataxia (4%), dizziness (2%), behavior disorder (1%), confusion, depression, lethargy, slurred speech, tremor, anterograde amnesia. In addition, paradoxical reactions (including excitation, agitation, hallucinations, and psychosis) are known to occur with benzodiazepines.

Dermatologic: Rash, pruritus, urticaria

Gastrointestinal: Weight gain (2%); dose related: Xerostomia, constipation, nausea

Hematologic: Decreased WBCs and other hematologic abnormalities have been rarely associated with benzodiazepines

Neuromuscular & skeletal: Muscle spasm

Ocular: Blurred vision (1%)

Metabolism/Transport Effects**Substrate** (major) of CYP2C19 and 3A4

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin

[Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression). Concomitant administration may increase bioavailability of clobazam by 50%.

Food: Serum concentrations may be increased by grapefruit juice.

Herb/Nutraceutical: St John's wort may decrease benzodiazepine levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Nursing: Physical Assessment/MonitoringFor inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions (see Adverse Reactions) at beginning of therapy and periodically with long-term use.

Patient EducationTake exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or sedatives) without consulting prescriber. Avoid grapefruit juice. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, loss of appetite, or dry mouth (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help). Wear identification that you are taking an antiepileptic medication. Report excessive drowsiness, dizziness, fatigue, or impaired coordination; CNS changes (confusion, depression, increased sedation, excitation, headache, agitation, insomnia, or nightmares) or changes in cognition; respiratory difficulty or shortness of breath; changes in urinary pattern, changes in sexual activity; muscle cramping, weakness, tremors, or rigidity; ringing in ears or visual disturbances, excessive perspiration, or excessive GI symptoms (cramping, constipation, vomiting, anorexia); worsening of seizure activity, or loss of seizure control. **Pregnancy/breast-feeding precautions:** Discuss contraception with prescriber or inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended (contraindicated per manufacturer).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet: 10 mg

Alti-Clobazam [CAN], Apo-Clobazam® [CAN], Clobazam-10 [CAN], Dom-Clobazam [CAN], Frisium® [CAN], Novo-Clobazam [CAN], PMS-Clobazam [CAN], ration-Clobazam [CAN]: 10 mg [not available in the U.S.]

Generic AvailableYes

ManufacturerAventis Pharma (Canada)

Mechanism of ActionClobazam is a 1,5 benzodiazepine which binds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Absorption: Rapid

Protein binding: 85% to 91%

Metabolism: Hepatic via N-dealkylation (likely via CYP) to active metabolite (N-desmethyl), and glucuronidation

Bioavailability: 87%

Half-life elimination: 18 hours; N-desmethyl (active): 42 hours

Time to peak: 15 minutes to 4 hours

Excretion: Urine (90%), as metabolites

Related Information

- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy Pearls Not available in U.S.
Clobazam is a 1,5 benzodiazepine; other benzodiazepines are typically 1,4 substituted.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Paradoxical reactions (including excitation, agitation, hallucinations, and psychosis) are known to occur with benzodiazepines.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health Comment In 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

Risk factors for abuse include personal or family history of substance abuse and personality disorder.

References

Frisium® product monograph, Aventis Pharma Inc, Quebec, October 2001.

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand Names Asabium (ID); Clarmyl (ES); Clobazan (CO); Clopax (ES); Frisium (AT, AU, BE, BR, CZ, DE, DK, FI, GB, GR, HK, HU, ID, IE, IL, IN, IT, LU, NL, PK, PL, TH, TW, UY, VE); Grifoclobam (CN); Karidium (AR); Lucium (PY, UY); Noiafren (ES); Sederlona (ES); Urbadan (CO, EC, NL, PE); Urbanil (BR, PT); Urbanol (ZA); Urbanyl (CH, FR)

Clobetasol

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English

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Medication Safety Issues

International issues:

Clobex® may be confused with Codex® which is a brand name for *Saccharomyces boulardii* in Italy

Pronunciation(kloe BAY ta sol)

U.S. Brand NamesClobevate® [DSC]; Clobex®; Cormax®; Olux-E™; Olux®; Temovate E®; Temovate®

Canadian Brand NamesClobex®; Dermovate®; Gen-Clobetasol; Novo-Clobetasol; Taro-Clobetasol

Pharmacologic CategoryCorticosteroid, Topical

Use: Labeled IndicationsShort-term relief of inflammation of moderate-to-severe corticosteroid-responsive dermatoses (very high potency topical corticosteroid)

Use: DentalShort-term relief of oral mucosal inflammation

Dosing: Adults**Note:** Discontinue when control achieved; if improvement not seen within 2 weeks, reassessment of diagnosis may be necessary.

Oral mucosal inflammation (unlabeled use): Topical: Cream: Apply twice daily for up to 2 weeks (maximum dose: 50 g/week); discontinue application when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary

Steroid-responsive dermatoses: Topical:

Cream, emollient cream, gel, lotion, ointment: Apply twice daily for up to 2 weeks (maximum dose: 50 g/week)

Foam (Olux-E™): Apply to affected area twice daily for up to 2 weeks (maximum dose: 50 g/week); do not apply to face or intertriginous areas

Steroid-responsive dermatoses of the scalp: Topical: Foam (Olux®), solution: Apply to affected scalp twice daily for up to 2 weeks (maximum dose: 50 g or 50 mL/week)

Mild-to-moderate plaque-type psoriasis of nonscalp areas: Topical: Foam (Olux®): Apply to affected area twice daily for up to 2 weeks (maximum dose: 50 g/week); do not apply to face or intertriginous areas

Moderate-to-severe plaque-type psoriasis: Topical:

Emollient cream, lotion: Apply twice daily for up to 2 weeks, has been used for up to 4 weeks when application is <10% of body surface area; use with caution (maximum dose: 50 g/week)

Spray: Apply by spraying directly onto affected area twice daily; should be gently rubbed into skin. Should be used for not longer than 4 weeks; treatment beyond 2 weeks should be limited to localized lesions which have not improved sufficiently. Total dose should not exceed 50 g/week or 59 mL/week.

Scalp psoriasis: Topical: Shampoo: Apply thin film to dry scalp once daily; leave in place for 15 minutes, then add water, lather; rinse thoroughly

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Discontinue when control achieved; if improvement not seen within 2 weeks, reassessment of diagnosis may be necessary. Use in children <12 years is not recommended.

Oral mucosal inflammation (unlabeled use): Children ≥12 years: Topical: Refer to adult dosing.

Steroid-responsive dermatoses: Children ≥12 years: Topical: Refer to adult dosing.

Mild-to-moderate plaque-type psoriasis of nonscalp areas: Children ≥12 years: Topical: Refer to adult dosing.

Moderate-to-severe plaque-type psoriasis: Children ≥16 years: Topical: Refer to adult dosing.

Administration: Topical

Cream, gel, lotion, ointment, shampoo, solution: Apply the smallest amount that will cover affected area. Do not apply to face or intertriginous areas. Total dose should not exceed 50 g/week (or 50 mL/week of lotion, shampoo, or solution).

Foam: Turn can upside down and spray a small amount (golf-ball size) of foam into the cap or another cool surface. If the can is warm or foam is runny, place can under cold, running water. If fingers are warm, rinse with cool water and dry prior to handling (foam will melt on contact with warm skin). Massage foam into affected area.

Spray: Spray directly onto affected area of skin. Gently and completely rub into skin after spraying.

Storage

Cream, emollient cream, ointment: Store at room temperature, between 15°C to 30°C (59°F to 86°F). Do not refrigerate.

Foam: Store at room temperature; do not expose to temperatures >49°C (120°F). Avoid fire, flame, or smoking during and immediately following application.

Gel: Store between 2°C to 30°C (36°F to 86°F).

Lotion, shampoo, spray: Store at room temperature of 20°C to 25°C (68°F to 77°F). Spray is flammable; do not use near open flame.

Solution: Store between 4°C to 25°C (39°F to 77°F). Do not use near an open flame.

ContraindicationsHypersensitivity to clobetasol or any component of the formulation; viral, fungal, or tubercular skin lesions

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Special populations:

- Pediatrics: Use in children <12 years of age is not recommended.

Other warnings/precautions:

- Application site: Do not use on the face, axillae, or groin.

Geriatric ConsiderationsDue to age-related changes in skin, limit use of topical glucocorticosteroids.

Pregnancy Risk FactorC

Pregnancy ConsiderationsExtensive use in pregnant women is not recommended. There are no adequate and well-controlled studies in pregnant women, however, teratogenic effects were observed in animal studies.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if topical application will result in detectable quantities in breast milk.

Adverse ReactionsFrequency not defined; may depend upon formulation used, length of application, surface area covered, and the use of occlusive dressings.

Endocrine & metabolic: Adrenal suppression, Cushing's syndrome, hyperglycemia

Local: Application site: Burning, cracking/fissuring of the skin, dryness, erythema, folliculitis, irritation, numbness, pruritus, skin atrophy, stinging, telangiectasia

Renal: Glucosuria

Effects reported with other high-potency topical steroids: Acneiform eruptions, allergic contact dermatitis, hypertrichosis, hypopigmentation, maceration of the skin, miliaria, perioral dermatitis, secondary infection

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Monitoring ParametersAdrenal suppression with extensive/prolonged use (ACTH stimulation test, morning plasma cortisol test, urinary free cortisol test)

Monitoring: Lab TestsAdrenal suppression with extensive/prolonged use (ACTH stimulation test, morning plasma cortisol test, urinary free cortisol test)

Patient EducationDo not overuse; use only as prescribed and for no longer than the period prescribed. Notify prescriber if condition being treated persists or worsens. Do not bandage or wrap affected area unless instructed to do so by prescriber. Wash hands after applying. Advise prescriber of the use of this medication if surgery is contemplated. This medication is for external use only; avoid use on face, underarms, or groin area unless specifically instructed to use in these areas by prescriber. Avoid contact with eyes or lips.

Cream, gel, lotion, ointment, solution: Apply the smallest amount that will cover affected area. Do not apply to face. A thin film is effective; apply sparingly and rub in lightly.

Foam: Turn can upside down and spray a small amount (golf-ball size) of foam into the cap or another cool surface. If the can is warm or foam is runny, place can under cold, running water. If fingers are warm, rinse with cool water and dry prior to handling (foam will melt on contact with warm skin). Gently massage foam into affected area until foam disappears.

Spray: Spray directly onto affected area of skin. Gently and completely rub into skin after spraying.

Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol, topical, as propionate [foam]: 0.05% (50 g, 100 g)

- Olux®: 0.05% (50 g, 100 g) [contains ethanol 60%]
- Olux-E™: 0.05% (50 g, 100 g)

Cream, as propionate: 0.05% (15 g, 30 g, 45 g, 60 g)

- Cormax®: 0.05% (15 g, 30 g, 45 g)
- Temovate®: 0.05% (30 g, 60 g)

Cream, as propionate [in emollient base]: 0.05% (15 g, 30 g, 60 g)

- Temovate E®: 0.05% (60 g)

Gel, as propionate: 0.05% (15 g, 30 g, 60 g)

- Clobevate®: 0.05% (45 g) [DSC]
- Temovate®: 0.05% (60 g)

Lotion, as propionate:

- Clobex®: 0.05% (30 mL, 59 mL, 118 mL)

Ointment, as propionate: 0.05% (15 g, 30 g, 45 g, 60 g)

- Cormax®: 0.05% (15 g, 45 g)
- Temovate®: 0.05% (15 g, 30 g)

Shampoo, as propionate:

- Clobex®: 0.05% (120 mL) [contains alcohol]

Solution, topical, as propionate [for scalp application]: 0.05% (25 mL, 50 mL)

- Cormax®: 0.05% (25 mL, 50 mL) [contains isopropyl alcohol 40%]
- Temovate®: 0.05% (50 mL) [contains isopropyl alcohol 40%]

Solution, topical, as propionate [spray]:

- Clobex®: 0.05% (60 mL, 125 mL) [contains alcohol]

Generic AvailableYes: Excludes lotion, shampoo, spray

Pricing: U.S. (www.drugstore.com)

Cream (Clobetasol Propionate)

- 0.05% (15): $15.99
- 0.05% (30): $15.99
- 0.05% (60): $29.99

Cream (Cormax)

- 0.05% (15): $41.61
- 0.05% (30): $63.99

Cream (Temovate)

- 0.05% (15): $44.99
- 0.05% (45): $74.99
- 0.05% (60): $158.39

Cream (Temovate E)

- 0.05% (15): $40.99
- 0.05% (60): $164.74

Foam (Olux)

0.05% (50): $201.94

0.05% (100): $374.84

Foam (Olux-E)

0.05% (100): $281.58

Gel (Clobetasol Propionate)

0.05% (15): $25.99

0.05% (30): $29.99

0.05% (60): $43.00

Gel (Temovate)

0.05% (15): $39.99

0.05% (60): $158.40

Liquid (Clobex Spray)

0.05% (59): $205.98

Lotion (Clobex)

0.05% (59): $230.89

Ointment (Clobetasol Propionate)

0.05% (30): $14.99

0.05% (45): $25.88

0.05% (60): $29.99

Ointment (Temovate)

0.05% (15): $63.35

0.05% (30): $91.99

0.05% (45): $74.99

0.05% (60): $89.99

Shampoo (Clobex)

0.05% (118): $229.98

Solution (Clobetasol Propionate)

0.05% (25): $26.99

0.05% (50): $35.99

Solution (Cormax)

0.05% (25): $45.99

0.05% (50): $81.60

Solution (Temovate)

0.05% (50): $95.99

Mechanism of ActionStimulates the synthesis of enzymes needed to decrease inflammation, suppress mitotic activity, and cause vasoconstriction

Pharmacodynamics/Kinetics

Absorption: Percutaneous absorption is variable and dependent upon many factors including vehicle used, integrity of epidermis, dose, and use of occlusive dressings

Metabolism: Hepatic

Excretion: Urine and feces

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsClobetasol Propionate

References

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

International Brand NamesBefurine (TW); Bersol (ID); Betasol (TH); Betavate (KP); Betazol (CO); Butavate (GR); Clarelux Foam (GB, IE); Clobasone (TH); Clobederm (PL); Clobenate (PE); Clobesol (AR, BR, HK, IT, MX); Clobet (TH); Clobex (HK, NZ, PH, SG); Clobexpro (MX); Clobezan (EC); Cloderm (AE, BH, CY, EG, HK, IL, IQ, IR, JO, KP, KW, LB, LY, OM, QA, SA, SY, TH, YE); Clonate (PH); Clonovate (SG); Closderm (PH); Closol (ID); Clovate (ES); Cotaso (TH); Crobate (KP); Decloban (ES); Delor (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Dermasone (PL); Dermatovate (MX); Dermklobal (PL); Dermol (NZ); Dermosol (KP); Dermoval (FR); Dermovat (DK, FI, NO, SE); Dermovate (AE, AT, BB, BD, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CL, CN, CO, CR, CY, CZ, DO, EE, EG, ET, GB, GH, GM, GN, GT, GY, HK, HN, ID, IE, IL, IN, IQ, IR, JM, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, OM, PA, PE, PH, PK, PL, PR, PT, PY, QA, SA, SC, SD, SG, SL, SN, SR, SV, SY, TH, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Dermoxin (DE); Dhabesol (HK, KP, MY); Domo-Horn (KP); Dovate (ZA); Elopro (ID); Eurobetsol (HK); Forderm (ID); Glevate (PH); Karison Creme (DE); Karison Salbe (DE); Kloderma (ID); Klonat (ID); Lamodex (ID); Lobate (IN); Lobesol (MY); Lobevat (MX); Lotasbat (ID); Medodermone (SG); Novate (PL); P-Vate (TH); Pentasol (CO); Powercort (SG); Psoriderm (ID); Rubocort (GR); S.Z. (TW); Stivate (TH); Tenovate (IN); Topifort (IN); Uniderm (HK, KP, TH); Univate (MY); Yihfu (TW); Yugofin (GR)

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cloderm® may be confused with Clocort®

International issues:

Cloderm®: Brand name for clotrimazole in Germany

Pronunciation(kloe KOR toe lone)
U.S. Brand NamesCloderm®
Canadian Brand NamesCloderm®
Pharmacologic CategoryCorticosteroid, Topical
Use: Labeled IndicationsInflammation of corticosteroid-responsive dermatoses (intermediate-potency topical corticosteroid)
Dosing: AdultsSteroid responsive dermatoses: Topical: Apply sparingly and gently; rub into affected area from 1-4 times/day. Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.
Dosing: ElderlyRefer to adult dosing.
ContraindicationsHypersensitivity to clocortolone or any component of the formulation; viral, fungal, or tubercular skin lesions
Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Special populations:

- Pediatrics: Chronic use of corticosteroids in children may interfere with growth and development.

Pregnancy Risk FactorC
Adverse Reactions

1% to 10%:

Dermatologic: Itching, erythema

Local: Burning, dryness, irritation, papular rash

<1%: Hypertrichosis, acneiform eruptions, maceration of skin, skin atrophy, striae, hypopigmentation, perioral dermatitis, miliaria

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Patient EducationA thin film of cream is effective; do not overuse. Use only as prescribed, and for no longer than the period prescribed. Apply sparingly in light film and rub in lightly. Avoid contact with eyes. Notify prescriber if condition being treated persists or worsens. **Pregnancy precaution:** Inform prescriber if you are pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, as pivalate:

Cloderm®: 0.1% (30 g, 45 g, 90 g)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Cream (Cloderm)

0.1% (45): $96.08

Mechanism of ActionStimulates the synthesis of enzymes needed to decrease inflammation, suppress mitotic activity, and cause vasoconstriction

Pharmacodynamics/Kinetics

Absorption: Percutaneous absorption is variable and dependent upon many factors including vehicle used, integrity of epidermis, dose, and use of occlusive dressings; small amounts enter circulatory system via skin

Metabolism: Hepatic

Excretion: Urine and feces

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsClocortolone Pivalate

References

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

International Brand NamesCloderm (CA); Kaban (DE)

Clodronate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(KLOE droh nate)

Canadian Brand NamesBonefos®; Clasteon®

Pharmacologic CategoryBisphosphonate Derivative

Use: Labeled IndicationsManagement of hypercalcemia of malignancy; management of osteolysis due to bone metastases of malignancy

Dosing: Adults

Hypercalcemia of malignancy:

I.V.:

Clasteon®

Single infusion: 1500 mg as a single dose

Multiple infusions: 300 mg/day; should not be prolonged beyond 10 days

Bonefos®: Multiple infusions: 300 mg/day; should not be prolonged beyond 7 days

Oral: Recommended daily maintenance dose following I.V. therapy:

Clasteon®: Range: 1600 mg (4 capsules) to 2400 mg (6 capsules) given in a single or 2 divided doses; maximum recommended daily dose: 3200 mg (8 capsules). Should be taken at least 1 hour before or after food since food may decrease clodronate absorption.

Bonefos®: Range: 1600 mg (4 capsules) to 2400 mg (6 capsules) given in single or 2 divided doses; maximum recommended daily dose: 3200 mg (8 capsules). Should be taken at least 2 hours before or after food since food may decrease clodronate absorption.

Osteolytic bone metastases:

I.V.:

Clasteon®:

Single infusion: 1500 mg as a single dose

Multiple infusions: 300 mg/day; should not be prolonged beyond 10 days

Bonefos®: Multiple infusions: 300 mg/day; should not be prolonged beyond 7 days

Oral:

Clasteon®: Recommended daily maintenance dose following I.V. therapy: Range: 1600 mg (4 capsules) to 2400 mg (6 capsules) given in a single or 2 divided doses; maximum recommended daily dose: 3200 mg (8 capsules). Should be taken at least 1 hour before or after food since food may decrease clodronate absorption.

Bonefos®: Initial: 1600 mg/day; may be increased to a maximum of 3200 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Clasteon®:

Serum creatinine (S_{cr}) >5 mg/dL: Use is contraindicated

S_{cr} ≥2.5-5 mg/dL: Dosage reduction is recommended; no specific guidelines available

Bonefos®:

S_{cr} >5 mg/dL: Use is contraindicated

Cl_{cr}: 50-80 mL/minute: Administer 75% to 100% of normal dose

Cl_{cr}: 12-49 mL/minute: Administer 50% to 75% of normal dose

Cl_{cr}: <12 mL/minute: Administer 50% of normal dose

Administration: I.V.Do not administer as bolus injection; for single infusion therapy administer over at least 4 hours; for multiple-infusion therapy administered once daily, infuse over 2-6 hours. Patients should be adequately hydrated with oral or I.V. fluids prior to infusion.

Administration: OralCapsules: Administer with a glass of plain water at least 2 hours (Bonefos®) or 1 hour (Clasteon®) before or after food.

StorageStore capsules and undiluted ampuls at room temperature (15°C to 30°C).

Clasteon®: Diluted solution should be infused within 12 hours of preparation.

Bonefos®: Diluted solution should be infused within 24 hours of preparation. Once diluted, Bonefos® may be stored up to 24 hours at room temperature.

ReconstitutionInjection must be diluted (in 500 mL of NS or D_5W).

CompatibilityStable in D_5W or 0.9% NS. **Incompatible** with calcium-containing solutions (eg, Ringer's solution).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to clodronate, bisphosphonates, or any component of the formulation; severe GI inflammation; renal impairment (serum creatinine >5 mg/dL, SI 440 µmol/L); concomitant use with other bisphosphonates; pregnancy or breast-feeding

Allergy Considerations

- Bisphosphonate Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bone/joint/muscle pain: Infrequently, severe (and occasionally debilitating) bone, joint, and/or muscle pain have been reported during bisphosphonate treatment. The onset of pain ranged from a single day to several months. Symptoms usually resolve upon discontinuation. Some patients experienced recurrence when rechallenged with same drug or another bisphosphonate; avoid use in patients with a history of these symptoms in association with bisphosphonate therapy.

- Gastrointestinal mucosa irritation: May cause irritation to upper gastrointestinal mucosa. Esophagitis, esophageal ulcers, esophageal erosions, and esophageal stricture (rare) have been reported with oral bisphosphonates; risk increases in patients unable to comply with dosing instructions. Use with caution in patients with dysphagia, esophageal disease, gastritis, duodenitis, or ulcers (may worsen underlying condition).

- Hypocalcemia: Risk of hypocalcemia (often asymptomatic) may be associated with both oral and intravenous use, however chelation of serum calcium observed with intravenous administration can further increase this risk. Interrupting the infusion or reducing the oral dose may be necessary. Correction of severe or symptomatic hypocalcemia may require calcium supplementation.

- Osteonecrosis of the jaw: Bisphosphonate therapy has been associated with osteonecrosis, primarily of the jaw; this has been observed mostly in cancer patients, but also in patients with postmenopausal osteoporosis and other diagnoses. Risk factors include a diagnosis of cancer, with concomitant chemotherapy, radiotherapy, or corticosteroids; anemia, coagulopathy, infection, or pre-existing dental disease. Symptoms included nonhealing extraction socket or an exposed jawbone. There are no data addressing whether discontinuation of therapy reduces the risk of developing osteonecrosis; however, as a precautionary measure, dental exams and preventative dentistry should be performed prior to placing patients with risk factors on chronic bisphosphonate therapy. Invasive dental procedures should be avoided during treatment.

Disease-related concerns:

- Renal impairment: Dose reductions, close monitoring of serum creatinine and BUN, and adequate hydration are required with renal dysfunction. Use is contraindicated when serum creatinine >5 mg/dL, SI 440 µmol/L.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Injection: Dilute prior to use; adequate hydration should be ensured prior to infusion; avoid infiltration/extravasation. May cause hypocalcemia or transient hypophosphatemia. Do not give as bolus injection (may precipitate acute renal failure, severe local reactions, and thrombophlebitis). Monitor renal function during and after intravenous administration. Interrupt infusion in patients experiencing deteriorating renal function during therapy.

Pregnancy ConsiderationsBisphosphonates have been shown to cross the placenta and cause embryo/fetal effects in animals. Bisphosphonates are incorporated into the bone matrix and gradually released over time. Theoretically, there may be a risk of fetal harm when pregnancy follows the completion of therapy. There are no adequate and well-controlled studies in pregnant women; use is contraindicated during pregnancy.

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions

>10%: Hepatic: Transaminases increased (≤18%; >2 x ULN: 2%)

1% to 10%:

Endocrine & metabolic: Hypocalcemia (≤3%)

Gastrointestinal: Vomiting (4%), nausea (≤3%), diarrhea (≤2%), anorexia (1%)

Renal: Serum creatinine increased (1%), BUN increased

<1%, postmarketing, and/or case reports: Alkaline phosphatase increased, bronchospasm, erythematous rash; hypersensitivity reactions (angioedema, pruritus, rash, urticaria); macropapular rash, mouth irritation, oliguria, osteonecrosis (primarily of jaw), parathyroid hormone increased, proteinuria, renal failure, ulcerative pharyngitis

Drug Interactions

Aminoglycosides: May enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Magaldrate; Sodium Bicarbonate. *Risk D: Consider therapy modification*

Calcium Salts: May decrease the absorption of Bisphosphonate Derivatives. *Risk D: Consider therapy modification*

Estramustine: Clodronate may increase the serum concentration of Estramustine. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral iron salts are of concern. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Phosphate Supplements: Bisphosphonate Derivatives may enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: All food and beverages may interfere with absorption. Coadministration with dairy products may decrease absorption. Beverages (especially orange juice and coffee), food, and medications (eg, antacids, calcium, iron, and multivalent cations) may reduce the absorption of bisphosphonates as much as 60%.

Test InteractionsBisphosphonates may interfere with diagnostic imaging agents such as technetium-99m-diphosphonate in bone scans.

Monitoring ParametersSerum electrolytes including calcium, phosphorous, magnesium, and potassium; monitor for hypocalcemia for at least 2 weeks after therapy; serum creatinine, BUN, CBC with differential, hepatic function

Reference RangeCalcium (total): Adults: 9.0-11.0 mg/dL (SI: 2.05-2.54 mmol/L), may slightly decrease with aging; Phosphorus: 2.5-4.5 mg/dL (SI: 0.81-1.45 mmol/L)

Nursing: Physical Assessment/MonitoringAssess history for any previous adverse response to bisphosphonates. Use caution with renal impairment. Correct any hypocalcemia prior to beginning treatment. Assess potential for interactions with other medications patient may be taking. Patients at risk for osteonecrosis (eg, chemotherapy or radiotherapy, corticosteroids, anemia, coagulopathy, poor oral hygiene) should have dental exams and necessary preventive dentistry should be done before beginning bisphosphonate therapy. Assess results of periodic laboratory tests, therapeutic effectiveness, and adverse reactions. Teach appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

I.V.: See specific directions.

Monitoring: Lab TestsSerum electrolytes including calcium, phosphorous, magnesium, and potassium; monitor for hypocalcemia for at least 2 weeks after therapy; serum creatinine, BUN, CBC with differential, hepatic function

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. Certain dental procedures should be avoided if possible while you are taking this medication; consult prescriber. You may experience temporary flatulence, bloating, nausea, or acid regurgitation (small, frequent meals may help); or temporary bone pain (consult prescriber for analgesic). Report persistent muscle or bone pain or leg cramps; acute headache; persistent gastric pain or unresolved GI upset; unusual fever; chills; difficulty swallowing; or pain in mouth, jaws, or teeth. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during therapy. Consult prescriber for instructions on appropriate contraceptive measures. This drug may cause fetal defects. Do not breast-feed.

Oral: Take as directed, with a full glass of water on an empty stomach 2 hours before or 2 hours after eating or taking any other medications.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection:

Bonefos® [CAN]: 60 mg/mL (5 mL) [not available in the U.S.]

Clasteon® [CAN]: 30 mg/mL (10 mL) [not available in the U.S.]

Capsule:

Bonefos® [CAN], Clasteon® [CAN]: 400 mg [not available in the U.S.]

Mechanism of ActionA bisphosphonate which lowers serum calcium by inhibition of bone resorption via actions on osteoclasts or on osteoclast precursors.

Pharmacodynamics/Kinetics

Onset of effect: Within 48 hours

Peak effect: 5-7 days

Duration: 2-3 weeks

Absorption: Oral: Rapid but low absorption (~1% to 3%)

Distribution: V_d: ~20 L; 20% of absorbed clodronate is bound to bone

Protein binding: Variable (2% to 36%)

Bioavailability: Oral: 1% to 3%

Half-life elimination: Terminal: Oral: ~6 hours; I.V.: 13 hours (serum); prolonged in bone tissue

Time to peak, plasma: Oral: 30 minutes

Excretion: Urine (60% to 80% as unchanged drug); feces (as unabsorbed drug)

Dental Health Professional ConsiderationsNovartis Pharmaceuticals Corporation has notified dental health professionals of the risk of **osteonecrosis of the jaw (ONJ)** and the use of the bisphosphonates, pamidronate (Zometa®) and zoledronic acid (Aredia®): *"Dear Dental Health Professional" Letter Issued for Intravenous Bisphosphonates, Pamidronate and Zoledronic Acid, Regarding the Risk of Osteonecrosis of the Jaw (ONJ) in Cancer Patients* – May 2005.

Often observed in patients receiving chemotherapy and corticosteroids, reports of ONJ (the majority being associated with dental procedures) have been documented in cancer patients. Dental exams and preventative dentistry should be performed prior to placing patients with risk factors (chemotherapy, corticosteroids, poor oral hygiene) on intravenous bisphosphonate therapy. Additionally, invasive dental procedures should be avoided during therapy; patients developing ONJ while on bisphosphonate therapy should not have invasive dental procedures because the condition may be exacerbated. It has not been determined whether the discontinuation of bisphosphonate therapy in patients requiring dental surgery decreases the risk of ONJ. The treating healthcare professional is encouraged to assess the benefits and risks.

Bisphosphonates are widely used in the management of metastatic bone disease to treat hypercalcemia associated with malignancies and to treat osteoporosis. It is suggested that because of the trend in the use of chronic bisphosphonate therapy, the observation of an associated risk of osteonecrosis of the jaw should alert practitioners to monitor for this previously unrecognized potential complication.

Additional information is available at http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#zometa2, or by contacting Novartis Oncology Medical Services at 1-888-669-6682.

Estimates of Percent Incidence of ONJ in Treated Cancer Patients

Two reports have attempted to assess the percent of cancer patients developing ONJ after bisphosphonate treatment. Maerevoet et al, reported that among 194 patients treated with Zometa® every 3-4 weeks, nine developed ONJ. Before receiving Zometa®, six had received Aredia® 90 mg every 3-4 weeks. The median duration of treatment with Aredia® was 39 months and for Zometa® 18 months. The incidence of ONJ in these patients was calculated to be 4.6%. Durie et al, described the results of a survey by the International Myeloma Foundation in 2004 to assess the risk factors of ONJ. Out of 1203 respondents, 904 had myeloma and 299 breast cancer. Of the myeloma patients, 62 developed ONJ and 54 had suspicious findings. Of the breast cancer patients, 13 had ONJ and 23 had suspicious findings. The total number of cases of either ONJ or suspicious findings was 152. ONJ developed in 10% of 211 patients receiving Zometa® compared to 4% of 413 receiving Aredia®. The mean time to onset of ONJ among patients taking Zometa® was 18 months; the mean time to onset after Aredia® was 6 years. It should be noted that an early report by authors from Novartis Pharmaceuticals Corporation (Tarassoff, 2003) stressed that Aredia® and Zometa® had been used in 2.5 million patients world wide and reports of ONJ during their extensive use had been rare. In addition, these authors stated that review of the reported cases revealed multiple risk factors for avascular necrosis. McMahon et al, followed up with a report that, along with other factors, bisphosphonates are additional stressors of bone health that can tip the balance to osteonecrosis. They suggested that the prevention of ONJ should be stressed such as the elimination of chronic dental infections prior to chemotherapy and bisphosphonate use in cancer patients.

Dental Health: Effects on Dental TreatmentOsteonecrosis of the jaw (ONJ), generally associated with local infection and/or tooth extraction and often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates. However, some have occurred in patients with postmenopausal osteoporosis taking oral bisphosphonates. Dental surgery may exacerbate ONJ. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentBisphosphonates have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. Use caution in patients receiving lithium.

Index TermsClodronate Disodium

References

American Dental Association Council on Scientific Affairs, “Dental Management of Patients Receiving Oral Bisphosphonate Therapy,” *JADA*, 2006, 137(8):1144-50. Available at http://www.ada.org/prof/resources/pubs/jada/reports/report bisphosphonate.pdf[PubMed 16873332]

Durie BG, Katz M, and Crowley J, "Osteonecrosis of the Jaw and Bisphosphonates," *N Engl J Med*, 2005, 353(1):99-102.[PubMed 16000365]

Maerevoet M, Martin C, and Duck L, "Osteonecrosis of the Jaw and Bisphosphonates," *N Engl J Med*, 2005, 353(1):99-102.[PubMed 16003838]

McMahon RE, Bouquot JE, Glueck CJ, et al, "Osteonecrosis: A Multifactorial Etiology," *J Oral Maxillofac Surg*, 2004, 62(7):904-5.[PubMed 15244000]

Ruggiero S, Gralow J, Marx RE, et al, "Practical Guidelines for the Prevention, Diagnosis, and Treatment of Osteonecrosis of the Jaw in Patients With Cancer," *J Clin Oncol*, 2006, 2(1):7-14.

Tarassoff P and Csermak K, "Avascular Necrosis of the Jaws: Risk Factors in Metastatic Cancer Patients," *J Oral Maxillofac Surg*, 2003, 61(10):1238-9.[PubMed 14586868]

International Brand NamesBonefos (AT, BE, BG, BR, CH, CL, CO, CZ, DE, DK, EE, ES, FI, GB, HK, HN, ID, IE, IL, MX, MY, NL, NO, PE, PH, PK, SE, SG, TH, TW)

Clofarabine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Clofarabine may be confused with cladribine, cleVIDipine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(klo FARE a been)

U.S. Brand NamesClolar™

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite (Purine Antagonist)

Use: Labeled IndicationsTreatment of relapsed or refractory acute lymphoblastic leukemia

Use: Unlabeled/InvestigationalAdults: Relapsed and refractory acute myeloid leukemia (AML), chronic myeloid leukemia (CML) in blast phase, acute lymphocytic leukemia (ALL), myelodysplastic syndrome

Dosing: AdultsALL: Adults ≤21 years: I.V.: Refer to pediatric dosing.

Dosing: PediatricALL: Children and Adults 1-21 years: I.V.: 52 mg/m^2/day days 1 through 5; repeat every 2-6 weeks

Dosing: Renal ImpairmentSafety not established; use with caution.

Dosing: Hepatic ImpairmentSafety not established; use with caution.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Infuse over 2 hours. Continuous I.V. fluids are encouraged to decrease adverse events and tumor lysis effects. Hypotension may be a sign of capillary leak syndrome or systemic inflammatory response syndrome (SIRS). Discontinue if the patient becomes hypotensive during administration. Retreatment should only be considered if the hypotension is not related to capillary leak syndrome or SIRS.

Administration: I.V. DetailpH: 4.5-7.5

StorageStore undiluted and diluted solutions at room temperature of 15°C to 30°C (59°F to 86°F). Solutions diluted in 100-500 mL of D_5W or NS are stable for 24 hours at room temperature.

ReconstitutionClofarabine should be diluted with 100-500 mL NS or D_5W; manufacturer recommends the product be filtered through a 0.2 micrometer filter before dilution.

CompatibilityStable in D_5W or NS.

ContraindicationsHypersensitivity to clofarabine or any component of the formulation

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Myelosuppression (dose-dependent) is common.
- Systemic inflammatory response syndrome (SIRS)/capillary leak syndrome: Cytokine release may develop into systemic inflammatory response syndrome (SIRS)/capillary leak syndrome, and organ dysfunction; discontinuation should be considered with the presentation of SIRS or capillary leak syndrome.
- Tumor lysis syndrome: With use, tumor lysis syndrome may occur (see Tumor Lysis Syndrome)..

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; safety and efficacy have not been established.
- Renal impairment: Use with caution in patients with renal impairment; safety and efficacy have not been established.

Special populations:

- Adults: Safety and efficacy have not been established in adults >21 years of age.
- Pediatrics: Safety and efficacy have not been established in children <1 year of age

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenic effects were observed in animal studies. There are no adequate or well-controlled studies in pregnant women. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant during therapy.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Cardiovascular: Pericardial effusion (35%), tachycardia (34%), hypotension (29%), left ventricular systolic dysfunction (27%), edema (20%), flushing (18%), hypertension (11%)

Central nervous system: Headache (46%), pyrexia (41%), fatigue (36%) anxiety (22%), pain (19%), dizziness (16%), depression (11%), irritability (11%), lethargy (1%)

Dermatologic: Pruritus (47%), dermatitis (41%), petechiae (29%), erythema (18%), palmar-plantar erythrodysesthesia syndrome (13%), oral candidiasis (13%), cellulitis (11%)

Gastrointestinal: Vomiting (83%), nausea (75%), diarrhea (53%), abdominal pain (36%), anorexia (30%), constipation (21%), mucosal inflammation (18%), gingival bleeding (15%), sore throat (14%), appetite decreased (11%)

Genitourinary: Hematuria (17%)

Hematologic: Febrile neutropenia (57%)

Hepatic: ALT increased (44%), AST increased (38%), bilirubin increased (15%), hepatomegaly (15%), jaundice (15%)

Neuromuscular & skeletal: Rigors (38%), pain in limb (29%), myalgia (14%), back pain (13%), arthralgia (11%)

Respiratory: Epistaxis (31%), cough (19%), respiratory distress (14%), dyspnea (13%)

Miscellaneous: Infection (85%), injection site pain (14%), staphylococcal infection (13%), herpes simplex (11%)

1% to 10%:

Central nervous system: Somnolence (10%)

Gastrointestinal: Weight gain (10%)

Genitourinary: Creatinine increased (6%)

Neuromuscular & skeletal: Tremor (10%)

Respiratory: Pleural effusion (10%), pneumonia (10%), systemic inflammatory response syndrome (SIRS)/capillary leak syndrome

Miscellaneous: Transfusion reaction (10%), bacteremia (10%)

Oncology: VesicantNo

Oncology: Emetic PotentialHigh (60% to 90%)

Drug Interactions

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure, cardiac function, and respiratory status during infusion; periodic CBC with platelet count (increase frequency in patients who develop cytopenias); liver and kidney function during 5 days of clofarabine administration; signs and symptoms of tumor lysis syndrome and cytokine release syndrome (tachypnea, tachycardia, hypotension, pulmonary edema); hydration status

Nursing: Physical Assessment/MonitoringAssess other prescriptions, OTCs, or biologicals patient is taking; drugs with known renal or hepatic toxicity should be avoided and renal/hepatic function monitored closely during 5 days of Clolar™ administration. Evaluate laboratory test results at regular intervals during therapy. Monitor for signs of potential systemic inflammatory response syndrome, capillary leak syndrome, and organ dysfunction (eg, tachypnea, tachycardia, hypotension, pulmonary edema - respiratory status, cardiac status, and blood pressure must be closely monitored during infusion). Maintaining adequate hydration with I.V. fluids during administration periods may reduce these and other adverse reactions (see Warnings/Precautions.) Patient should be monitored closely for other adverse reactions on a regular basis for duration of therapy (see Adverse Reactions). Teach patient/caregiver possible side effects, appropriate interventions, adverse symptoms to report, and pregnancy precautions (see Patient Education.)

Patient EducationThis drug can only be administered by intravenous infusion; you will be monitored closely during and following infusions. Immediately report any burning, pain, or swelling at infusion site; any unusual chest pain or tightness, rapid heart beat or palpitations; difficulty breathing; difficulty swallowing; nausea or vomiting; or other adverse symptoms during infusion. Do not take any new medications during therapy without consulting prescriber. You will be more susceptible to infection (avoid crowds and exposure to infection; do not have any vaccinations unless approved by prescriber). It is important that you maintain adequate nutrition and fluid intake; if you experience nausea, vomiting, or loss of appetite, frequent fluid intake and small frequent meals may help. You may experience diarrhea (boiled milk, yogurt may help) or constipation (increased dietary fiber or fluid may help). Report any signs of dehydration (dizziness, lightheadedness, fainting spells, or decreased urine output); chest pain, palpitations, rapid heart beat, swelling of extremities, acute headache or flushing; difficulty breathing or nosebleeds; persistent gastrointestinal upset; signs of infection (fever, sore throat, runny nose, white plaques in mouth, vaginal or rectal discharge); unusual anxiety, depression, irritability, fatigue, or lethargy; new skin rash, eruption, or redness; unusual limb, back, or muscle pain or tremor; change in color or frequency of urine or blood in urine; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. This drug may cause fetal deformities or loss of pregnancy; consult prescriber for appropriate contraceptives. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 1 mg/mL (20 mL)

Generic AvailableNo

ManufacturerAAI Development Services; Genzyme Corp

Mechanism of ActionClofarabine, a purine (deoxyadenosine) nucleoside analog, is metabolized to clofarabine 5'-triphosphate. Clofarabine 5'-triphosphate decreases cell replication and repair as well as causing cell death. To decrease cell replication and repair, clofarabine 5'-triphosphate competes with deoxyadenosine triphosphate for the enzymes ribonucleotide reductase and DNA polymerase. Cell replication is decreased when clofarabine 5'-triphosphate inhibits ribonucleotide reductase from reacting with deoxyadenosine triphosphate to produce deoxynucleotide triphosphate which is needed for DNA synthesis. Cell replication is also decreased when clofarabine 5'-triphosphate competes with DNA polymerase for incorporation into the DNA chain; when done during the repair process, cell repair is affected. To cause cell death, clofarabine 5'-triphosphate alters the mitochondrial membrane by releasing proteins, an inducing factor and cytochrome C.

Pharmacodynamics/Kinetics

Distribution: V_d: 172 L/m^2

Protein binding: 47%

Metabolism: Intracellulary by deoxycytidine kinase and mono- and diphosphokinases to active metabolite clofarabine 5′-triphosphate

Half-life elimination: ~5.2 hours

Excretion: Urine (49% to 60% unchanged)

Related Information

- Tumor Lysis Syndrome

Pharmacotherapy PearlsThe use of prophylactic steroids (hydrocortisone 100 mg/m^2 on days 1-3) may be of benefit in preventing signs of SIRS or capillary leak syndrome; allopurinol may be used if hyperuricemia is anticipated. Dosage should be based on BSA, calculated based upon height and weight prior to each cycle.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucosal inflammation and gingival bleeding.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, dizziness, depression, irritability, and lethargy

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with SSRIs, lithium, valproic acid may produce additive effects.

Index TermsClofarex; NSC606869

References

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Kantarjian H, Gandhi V, Cortes J, et al, “Phase 2 Clinical and Pharmacologic Study of Clofarabine in Patients With Refractory or Relapsed Acute Leukemia,” *Blood*, 2003, 102(7):2379-86.[PubMed 12791647]

Sternberg A, “Clofarabine. Bioenvision/ILEX,” *Curr Opin Investig Drugs*, 2003, 4(12):1479-87.[PubMed 14763136]

International Brand NamesEvoltra (CZ, DK, EE, GB, IE, NO, SE)

ClomiPHENE

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

ClomiPHENE may be confused with clomiPRAMINE, clonidine

Clomid® may be confused with clonidine

Serophene® may be confused with Sarafem™

Pronunciation(KLOE mi feen)

U.S. Brand NamesClomid®; Serophene®

Canadian Brand NamesClomid®; Milophene®; Serophene®

Pharmacologic CategoryOvulation Stimulator; Selective Estrogen Receptor Modulator (SERM)

Use: Labeled IndicationsTreatment of ovulatory failure in patients desiring pregnancy

Dosing: AdultsOvulation induction: Oral: Females:

Initial course: 50 mg once daily for 5 days. Begin on or about the fifth day of cycle if progestin-induced bleeding is scheduled or spontaneous uterine bleeding occurs prior to therapy.

Dose adjustment: Subsequent doses may be increased to 100 mg once daily for 5 days only if ovulation does not occur at the initial dose. A low dose or duration of course is recommended in patients where unusual sensitivity to pituitary gonadotropin is suspected (eg, PCOS).

Repeat courses: If needed, the 5-day cycle may be repeated as early as 30 days after the previous one. Exclude the presence of pregnancy.

Maximum dose: 100 mg once daily for 5 days for 6 cycles. Discontinue if ovulation does not occur after 3 courses of treatment; or if 3 ovulatory responses occur but pregnancy is not achieved. Re-evaluate if menses does not occur following ovulatory response. Doses larger than 150 mg have been reported, however, pregnancy rates are low.

Dosing: ElderlyRefer to adult dosing.

Administration: OralThe total daily dose should be taken at one time to maximize effectiveness.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light, heat, and excessive humidity.

ContraindicationsHypersensitivity to clomiphene citrate or any of its components; liver disease; abnormal uterine bleeding; enlargement or development of ovarian cyst (not due to polycystic ovarian syndrome); uncontrolled thyroid or adrenal dysfunction; presence of an organic intracranial lesion such as pituitary tumor; pregnancy

Allergy Considerations

- ClomiPHENE Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Ovarian enlargement: May be accompanied by abdominal distention or abdominal pain and generally regresses without treatment within 2-3 weeks. Do not continue dosing until ovaries are of normal size.
- Ovarian hyperstimulation syndrome (OHSS): OHSS is characterized by severe ovarian enlargement, abdominal pain/distention, nausea, vomiting, diarrhea, dyspnea, and oliguria, and may be accompanied by ascites, pleural effusion, hypovolemia, electrolyte imbalance, hemoperitoneum, and thromboembolic events. If severe hyperstimulation occurs, stop treatment and hospitalize patient. This syndrome develops rapidly within 24 hours to several days and generally occurs during the 7-10 days immediately following treatment.
- Visual disturbances: Blurring or other visual symptoms can occur; patients with visual disturbances should discontinue therapy and have an eye exam.

Disease-related concerns:

- Polycystic ovarian syndrome (PCOS): Use with caution in patients unusually sensitive to pituitary gonadotropins (eg, POS).

Other warnings/precautions:

- Appropriate use: To minimize risks, use only at the lowest effective dose.
- Multiple births: May result from the use of these medications; advise patient of the potential risk of multiple births before starting the treatment.

Pregnancy Risk FactorX

Pregnancy ConsiderationsEmbryotoxic effects were observed in animal studies. The incidence of adverse fetal effects following maternal use of clomiphene for ovulation induction is similar to those seen in the general population. Clomiphene is not indicated for use in women who are already pregnant.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsClomiphene may decrease lactation.

Adverse Reactions

>10%: Endocrine & metabolic: Ovarian enlargement (14%)

1% to 10%:

Central nervous system: Headache (1%)

Endocrine & metabolic: Hot flashes (10%), breast discomfort (2%), abnormal uterine bleeding (1%)

Gastrointestinal: Distention/bloating/discomfort (6%), nausea (2%), vomiting (2%)

Ocular: Visual symptoms (2%, includes blurring of vision, diplopia, floaters, lights, phosphenes, photophobia, scotomata, waves)

<1%: Acute abdomen, alopecia, appetite increased, constipation, depression, dermatitis, diarrhea, dizziness, dry hair, fatigue, insomnia, lightheadedness, nervousness, rash, urinary frequency/volume increased, vaginal dryness, vertigo, weight gain/loss

Postmarketing/case reports (limited to important or life-threatening): Abnormal accommodation, acne, allergic reaction, arrhythmia, chest pain, edema, endometriosis, erythema multiforme, erythema nodosum, eye pain, fever, hypertension, hypertrichosis, macular edema, migraine, mood changes, neoplasms, optic neuritis, ovarian cyst, ovarian hemorrhage, palpitation, PE, pruritus, retinal hemorrhage, retinal thrombosis, seizure, stroke, syncope, tachycardia, temporary loss of vision, thrombophlebitis, thyroid disorder, tinnitus, transaminase increased, tubal pregnancy, uterine hemorrhage

Drug InteractionsThere are no known significant interactions.

Test InteractionsClomiphene may increase levels of serum thyroxine and thyroxine-binding globulin (TBG)

Monitoring ParametersBasal body temperature, serum progesterone, urinary luteinizing hormone; follicular growth and endometrial thickness may be useful in some cases; pregnancy test prior to repeat courses

Reference RangeSerum progesterone: Ovulation generally occurs with levels ≥3 ng/mL; best results with levels >10 ng/mL

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests, therapeutic effectiveness (according to purpose for use), and adverse response regularly during therapy. Teach patient proper use (eg, measuring basal body temperature and timing intercourse), possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Breast-feeding is contraindicated.

Monitoring: Lab TestsBasal body temperature, serum progesterone, urinary luteinizing hormone; pregnancy test prior to repeat courses

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. There may be a risk of multiple pregnancies with therapy. Do not take any new medication during therapy unless approved by prescriber. Follow recommended schedule of dosing exactly. May cause hot flashes (cool clothes and cool environment may help). Report acute sudden headache; respiratory difficulty; warmth, swelling, pain, or redness in calves; breast enlargement (male) or breast discomfort (female); abnormal menstrual bleeding; vision changes (blurring, diplopia, photophobia, floaters); acute abdominal discomfort; or fever. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as citrate [scored]: 50 mg

Clomid®, Serophene®: 50 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Clomid)

50 mg (5): $75.94

Tablets (ClomiPHENE Citrate)

50 mg (30): $84.99

Tablets (Serophene)

50 mg (5): $55.38

Mechanism of ActionClomiphene is a racemic mixture consisting of zuclomiphene (~38%) and enclomiphene (~62%), each with distinct pharmacologic properties. Enclomiphene is much less potent in inducing ovulation; however, it is more rapidly absorbed and metabolized, allowing the more potent activity of zuclomiphene to predominate. Zuclomiphene acts at the level of the hypothalamus, occupying cell surface and intracellular estrogen receptors (ERs) for longer durations than estrogen. This interferes with receptor recycling, effectively depleting hypothalamic ERs and inhibiting normal estrogenic negative feedback. Impairment of the feedback signal results in increased pulsatile GnRH secretion from the hypothalamus and subsequent pituitary gonadotropin (FSH, LH) release, causing growth of the ovarian follicle, followed by follicular rupture.

Pharmacodynamics/Kinetics

Onset: Ovulation: 5-10 days following course of treatment

Duration: Effects are cumulative; ovulation may occur in the cycle following the last treatment

Metabolism: Hepatic; undergoes enterohepatic recirculation

Half-life elimination: 5-7 days

Time to peak, plasma: ~6 hours

Excretion: Primarily feces; urine (small amounts)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause insomnia, fatigue, or depression
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsClomiphene Citrate
References

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Dickey RP and Holtkamp DE, “Development, Pharmacology, and Clinical Experience With Clomiphene Citrate,” *Hum Reprod Update*, 1996, 2(6):483-506.[PubMed 9111183]

Goldstein SR, Siddhanti S, Ciaccia AV, et al. “A Pharmacological Review of Selective Oestrogen Receptor Modulators,” *Hum Reprod Update*, 2000, 6(3):212-24.[PubMed 10874566]

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Purvin VA, “Visual Disturbance Secondary to Clomiphene Citrate,” *Arch Ophthalmol*, 1995, 113(4):482-4. [PubMed 7710399]

Sokol RZ, “Prevention and Management of Complications Occurring During Treatment With Clomiphene,” *Drug Saf*, 1990, 5(5):313-6. [PubMed 2222865]

Walker AB, Eldridge PR, and MacFarlane IA, “Clomiphene-Induced Pituitary Apoplexy in a Patient With Acromegaly,” *J Endocrinol*, 1995, 144:29.

International Brand NamesAnexin (PY); Biogen (PE); Blesifen (ID); Clombeta (AU); Clomhexal (AU); Clomid (AE, AR, AT, AU, BE, BH, CH, CY, EG, FR, GB, IE, IL, IQ, IR, IT, JO, KW, LB, LY, MY, NL, OM, PH, PK, QA, SA, SY, TH, TW, YE); Clomifen (FI); Clomifil (ID); Clomihexal (ZA); Clomin (GR); Clomiphene Serono (PH); Clomoval (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Clonin (TW); Clostil (PH); Clostilbegyt (AE, BB, BH, BM, BS, BZ, CY, EG, GY, HN, IL, IQ, IR, JM, JO, KW, LB, LY, MY, NL, OM, PR, QA, SA, SR, SY, TT, YE); Dufine (PT); Duinum (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SG, SL, SN, TH, TN, TW, TZ, UG, ZA, ZM, ZW); Dyneric (DE); Fermil (AU); Fertilan (CL, HK); Fertilphen (ID); Fertin (ID); Fertomid (IN); Genoclam (ID); Ikaclomin (IL); Indovar (PT); Mestrolin (ID); Ofertil (ID); Omifin (MX); Ova-Mit (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Ovamit (MY, PH, TH); Ovipreg (IN); Pergotime (BE, DK, FR, NO, SE); Phenate (NZ); Pinfetil (ID); Profertil (ID); Provula (ID); Serofene (AR, MX, VE); Serophene (AE, AT, AU, BH, CH, CY, CZ, EG, HK, IL, IQ, IR, JO, KP, KW, LB, LY, NL, OM, QA, SA, SY, TW, UY, YE); Serpafar (BG, GR); Zimaquin (CN)

ClomiPRAMINE

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

ClomiPRAMINE may be confused with chlorproMAZINE, cleVIDipine, clomiPHENE, desipramine, Norpramin®

Anafranil® may be confused with alfentanil, enalapril, nafarelin

Pronunciation(kloe MI pra meen)

U.S. Brand NamesAnafranil®

Canadian Brand NamesAnafranil®; Apo-Clomipramine®; CO Clomipramine; Gen-Clomipramine

Pharmacologic CategoryAntidepressant, Tricyclic (Tertiary Amine)

Use: Labeled IndicationsTreatment of obsessive-compulsive disorder (OCD)

Use: Unlabeled/InvestigationalDepression, panic attacks, chronic pain

Dosing: Adults**Treatment of OCD:** Oral: Initial: 25 mg/day; may gradually increase as tolerated over the first 2 weeks to 100 mg/day in divided doses; Maintenance: May further increase to recommended maximum of 250 mg/day; may give as a single daily dose at bedtime once tolerated

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Treatment of OCD:** Oral: Children >10 years: Initial: 25 mg/day and gradually increase, as tolerated, to a maximum of 3 mg/kg/day or 200 mg/day, whichever is smaller. **Note:** The safety and efficacy of clomipramine in pediatric patients <10 years of age have not been established and, therefore, dosing recommendations cannot be made.

Administration: OralDuring titration, may divide doses and administer with meals to decrease gastrointestinal side effects. After titration, may administer total daily dose at bedtime to decrease daytime sedation.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to clomipramine, other tricyclic agents, or any component of the formulation; use of MAO inhibitors within 14 days; use in a patient during the acute recovery phase of MI

Allergy Considerations

- Tricyclic Antidepressant and Related Compounds Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Clomipramine is FDA approved for the treatment of OCD in children ≥10 years of age.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Clomipramine is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. The degree of anticholinergic blockade produced by this agent is very high relative to other antidepressants.

- Hematologic effects: TCAs may rarely cause bone marrow suppression; monitor for any signs of infection and obtain CBC if symptoms (eg, fever, sore throat) evident.

- Orthostatic hypotension: May cause orthostatic hypotension (risk is moderate relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is very high relative to other antidepressants.

- Seizures: May cause seizures (relationship to dose and/or duration of therapy); do not exceed maximum doses. Use with caution in patients with a previous seizure disorder or condition predisposing to seizures such as brain damage, alcoholism, or concurrent therapy with other drugs which lower the seizure threshold.

- Sexual dysfunction: Has been associated with a high incidence of male sexual dysfunction.

- Weight gain: May cause weight gain.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk of conduction abnormalities with this agent is high relative to other antidepressants.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

- Thyroid dysfunction: Use with caution in patients with hyperthyroidism or those receiving thyroid supplementation due to concerns of pro-arrhythmogenesis.

Concurrent drug therapy issues:

- Anticholinergic and/or neuroleptic agents: Hyperpyrexia has been observed with TCAs in combination with anticholinergics and/or neuroleptics, particularly during hot weather.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Discontinuation of therapy: Recommended to discontinue prior to elective surgery requiring general anesthesia. Therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

Geriatric ConsiderationsNot approved as an antidepressant, clomipramine's anticholinergic and hypotensive effects limit its use versus other preferred antidepressants. Elderly patients were found to have higher dose-normalized plasma concentrations as a result of decreased demethylation (decreased 50%) and hydroxylation (25%).

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Withdrawal symptoms (including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and/or irritability) have been observed in neonates whose mothers took clomipramine up to delivery. Use in pregnancy only if the benefits to the mother outweigh the potential risks to the fetus.

LactationEnters breast milk/not recommended (AAP rates "of concern")

Breast-Feeding ConsiderationsGenerally, it is not recommended to breast-feed if taking antidepressants because of the long half-life, active metabolites, and the potential for side effects in the infant.

Adverse ReactionsData shown for children reflects both children and adolescents studied in clinical trials.

>10%:

Central nervous system: Dizziness (54%), somnolence (54%), drowsiness, headache (52%; children 28%), fatigue (39%), insomnia (25%; children 11%), malaise, nervousness (18%; children 4%)

Endocrine & metabolic: Libido changes (21%), hot flushes (5%)

Gastrointestinal: Xerostomia (84%, children 63%) constipation (47%; children 22%), nausea (33%; children 9%), dyspepsia (22%; children 13%), weight gain (18%; children 2%), diarrhea (13%; children 7%), anorexia (12%; children 22%), abdominal pain (11%), appetite increased (11%)

Genitourinary: Ejaculation failure (42%), impotence (20%), micturition disorder (14%; children 4%)

Neuromuscular & skeletal: Tremor (54%), myoclonus (13%; children 2%), myalgia (13%)

Ocular: Abnormal vision (18%; children 7%)

Respiratory: Pharyngitis (14%), rhinitis (12%)

Miscellaneous: Diaphoresis increased (29%; children 9%)

1% to 10%:

Cardiovascular: Flushing (8%), postural hypotension (6%), palpitation (4%), tachycardia (4%; children 2%), chest pain (4%), edema (2%)

Central nervous system: Anxiety (9%), memory impairment (9%), twitching (7%), depression (5%), concentration impaired (5%), fever (4%), hypertonia (4%), abnormal dreaming (3%), agitation (3%), confusion (3%), migraine (3%), pain (3%), psychosomatic disorder (3%), speech disorder (3%), yawning (3%), aggressiveness (children 2%), chills (2%), depersonalization (2%), emotional lability (2%), irritability (2%), panic reaction (1%)

Dermatologic: Rash (8%), pruritus (6%), purpura (3%), dermatitis (2%), acne (2%), dry skin (2%), urticaria (1%)

Endocrine & metabolic: Amenorrhea (1%), breast enlargement (2%), breast pain (1%), hot flashes (5%), lactation (nonpuerperal) (4%)

Gastrointestinal: Taste disturbance (8%), vomiting (7%), flatulence (6%), tooth disorder (5%), dysphagia (2%), esophagitis (1%)

Genitourinary: UTI (2% to 6%), micturition frequency (5%), dysuria (2%), leucorrhea (2%), vaginitis (2%), urinary retention (2%)

Neuromuscular & skeletal: Paresthesia (9%), back pain (6%), arthralgia (3%), paresis (children 2%), weakness (1%)

Ocular: Lacrimation abnormal (3%), mydriasis (2%), conjunctivitis (1%)

Otic: Tinnitus (6%)

Respiratory: Sinusitis (6%), coughing (6%), bronchospasm (2%; children 7%), epistaxis (2%)

<1% (Limited to important or life-threatening): Accommodation abnormal, albuminuria, aneurysm, anticholinergic syndrome, aphasia, apraxia, arrhythmia, ataxia, atrial flutter, blepharitis, blood in stool, bradycardia, breast fibroadenosis, bronchitis, bundle branch block, cardiac arrest, cardiac failure, catalepsy, cellulitis, cerebral hemorrhage, cervical dysplasia, cheilitis, cholinergic syndrome, choreoathetosis, chromatopsia, chronic enteritis, coma, conjunctival hemorrhage, cyanosis, deafness, dehydration, delirium, delusion, diabetes mellitus, diplopia, dyskinesia, dysphonia, dystonia, EEG abnormal, encephalopathy, endometrial hyperplasia, endometriosis, epididymitis, erythematous rash, exophthalmos, extrapyramidal disorder, extrasystoles, gastric ulcer, generalized spasm, glaucoma, glycosuria, goiter, gynecomastia, hallucinations, heart block, hematuria, hemiparesis, hemoptysis, hepatitis, hostility, hyperacusis, hypercholesterolemia, hyper-/hypoesthesia, hyperglycemia, hyper-/hypokinesia, hyperreflexia, hyper-/hypothyroidism, hyperuricemia, hyper-/hypoventilation, hypnagogic hallucination, hypokalemia, ideation, intestinal obstruction, irritable bowel syndrome, keratitis, laryngismus, leukemoid reaction, lupus erythematosus rash, lymphadenopathy, lymphoma-like disorder, maculopapular rash, manic reaction, marrow depression, myocardial infarction, myocardial ischemia, myopathy, myositis, neuralgia, neuropathy, oculogyric crisis, oculomotor nerve paralysis, oral/pharyngeal edema, ovarian cyst, paralytic ileus, paranoia, parosmia, peptic ulcer, peripheral ischemia, phobic disorder, photophobia, photosensitivity reaction, pneumonia, polyarteritis nodosa, premature ejaculation, psychosis, pyelonephritis, pyuria, rectal hemorrhage, renal calculus, renal cyst, schizophrenic reaction, scleritis, seizure, sensory disturbance, skin ulceration, strabismus, stupor, suicidal ideation, suicide, suicide attempt, thrombophlebitis, tongue ulceration, tooth caries, torticollis, urinary incontinence, uterine hemorrhage, uterine inflammation, vaginal hemorrhage, vasospasm, ventricular tachycardia, visual field defect, withdrawal syndrome

Metabolism/Transport Effects **Substrate** of CYP1A2 (major), 2C19 (major), 2D6 (major), 3A4 (minor); **Inhibits** CYP2D6 (moderate)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Tricyclic Antidepressants may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Agonists: Tricyclic Antidepressants may enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Alpha2-Agonists: Tricyclic Antidepressants may diminish the antihypertensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Altretamine: May enhance the orthostatic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Amphetamines: Tricyclic Antidepressants may enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Aspirin: Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Beta2-Agonists: Tricyclic Antidepressants may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

CarBAMazepine: May increase the serum concentration of ClomiPRAMINE. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cinacalcet: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Desmopressin: Tricyclic Antidepressants may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dexmethylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

DULoxetine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Iobenguane I 123: Tricyclic Antidepressants may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May enhance the neurotoxic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

NSAID (COX-2 Inhibitor): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Tricyclic Antidepressants may enhance the QTc-prolonging effect of QuiNIDine. QuiNIDine may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

St Johns Wort: May increase the metabolism of Tricyclic Antidepressants. The risk of serotonin syndrome may theoretically be increased. *Risk D: Consider therapy modification*

Sulfonylureas: Cyclic Antidepressants may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Terbinafine: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: Tricyclic Antidepressants may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. *Risk C: Monitor therapy*

Valproic Acid: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Tricyclic Antidepressants may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Serum concentrations/toxicity may be increased by grapefruit juice.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava.

Test InteractionsIncreased glucose

Monitoring ParametersPulse rate and blood pressure prior to and during therapy; ECG/cardiac status in older adults and patients with cardiac disease; suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Observe for clinical worsening, suicidality, or unusual behavior changes, especially during the initial few months of therapy or during dosage changes. If history of cardiac problems, monitor cardiac status closely. Be alert to the potential of new or increased seizure activity. Instruct family or caregiver to observe the patient's behavior closely and communicate any changes to prescriber. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsMonitor ECG/cardiac status in older adults and patients with cardiac disease

Patient EducationTake multiple dose medication with meals to reduce side effects. Take single daily dose at bedtime to reduce daytime sedation. The effect of this drug may take several weeks to appear. Do not use alcohol, caffeine, and other prescriptive or OTC medications without consulting prescriber. May cause weight gain, dizziness, drowsiness, headache, or seizures (use caution when driving or engaging in tasks that require alertness until response to drug is known); dry mouth or unpleasant aftertaste (sucking lozenges and frequent mouth care may help); constipation (increased exercise, fluids, fruit, or fiber may help); or orthostatic hypotension (use caution when rising from lying or sitting to standing position or when climbing stairs). Report unresolved constipation or GI upset, unusual muscle weakness, palpitations, or persistent CNS disturbances (hallucinations, suicidality, seizures, delirium, insomnia, or impaired gait). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 25 mg, 50 mg, 75 mg

Anafranil®: 25 mg, 50 mg, 75 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Anafranil)

50 mg (60): $375.95

Capsules (ClomiPRAMINE HCl)

25 mg (60): $27.99

50 mg (60): $33.99

75 mg (60): $38.99

Mechanism of ActionClomipramine appears to affect serotonin uptake while its active metabolite, desmethylclomipramine, affects norepinephrine uptake

Pharmacodynamics/Kinetics

Absorption: Rapid

Protein binding: 97%, primarily to albumin

Metabolism: Hepatic to desmethylclomipramine (DMI; active); extensive first-pass effect

Half-life elimination: Clomipramine: mean 32 hours (19-37 hours); DMI: mean 69 hours (range 54-77 hours)

Time to peak, plasma: 2-6 hours

Excretion: Urine and feces

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation). Long-term treatment with TCAs, such as clomipramine, increases the risk of caries by reducing salivation and salivary buffer capacity.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution; epinephrine and levonordefrin have been shown to have an increased pressor response in combination with TCAs. Clomipramine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health CommentTricyclic antidepressants may be classified as tertiary (amitriptyline, doxepin, clomipramine, imipramine, trimipramine) or secondary amines (nortriptyline, desipramine, protriptyline). The tertiary amines are not recommended to treat depression in the elderly. If a TCA is used in the elderly, it should be a secondary amine. The tertiary amines are commonly used in low dosages for various conditions associated with pain. Toxicity is generally dose dependent. Relatively small overdoses (1-week supply) can be potentially fatal.

Seizures are dose dependent. The overall cumulative incidence is 0.7%. Doses ≤250 mg/day have an incidence of 0.5% and doses ≥300 mg/day have an incidence of 2.1%.

Index TermsClomipramine Hydrochloride

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International Brand NamesAnafranil (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CY, CZ, DE, DK, EE, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PH, PK, PL, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TR, TT, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Anafranil 25 (ID); Anafranil Retard (AT, DK, FI, NL, SE); Anafranil SR (MY, SG); Anafranil SR 75 (IL); Clofranil (IN); Clopram (AU); Clopran (TW); Clopress (NZ); Equinorm (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Hydiphen (DE, PL); Maronil (IL); Placil (AU)

ClonazePAM

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Medication Safety Issues

Sound-alike/look-alike issues:

ClonazePAM may be confused with clofazimine, cloNIDine, clorazepate, clozapine, LORazepam

Klonopin® may be confused with clofazimine, clonNIDine, clorazepate, clozapine, LORazepam

Pronunciation(kloe NA ze pam)
U.S. Brand NamesKlonopin®; Klonopin® Wafers
Canadian Brand NamesAlti-Clonazepam; Apo-Clonazepam®; Clonapam; CO Clonazepam; Gen-Clonazepam; Klonopin®; Novo-Clonazepam; Nu-Clonazepam; PMS-Clonazepam; Pro-Clonazepam; Rho®-Clonazepam; Rivotril®; Sandoz-Clonazepam
Pharmacologic CategoryBenzodiazepine
Use: Labeled IndicationsAlone or as an adjunct in the treatment of petit mal variant (Lennox-Gastaut), akinetic, and myoclonic seizures; petit mal (absence) seizures unresponsive to succimides; panic disorder with or without agoraphobia
Use: Unlabeled/InvestigationalRestless legs syndrome; neuralgia; multifocal tic disorder; parkinsonian dysarthria; bipolar disorder; adjunct therapy for schizophrenia
Use: DentalBurning mouth syndrome
Dosing: Adults

Seizure disorders: Oral:

Initial daily dose not to exceed 1.5 mg given in 3 divided doses; may increase by 0.5-1 mg every third day until seizures are controlled or adverse effects seen (maximum: 20 mg/day)

Usual maintenance dose: 0.05-0.2 mg/kg; do not exceed 20 mg/day

Panic disorder: Oral: 0.25 mg twice daily; increase in increments of 0.125-0.25 mg twice daily every 3 days; target dose: 1 mg/day (maximum: 4 mg/day)

Discontinuation of treatment: To discontinue, treatment should be withdrawn gradually. Decrease dose by 0.125 mg twice daily every 3 days until medication is completely withdrawn.

Dosing: ElderlyRefer to adult dosing. Initiate with low doses and observe closely.
Dosing: Pediatric

Seizure disorders (see Use): Oral:

Children <10 years or 30 kg:

Initial daily dose: 0.01-0.03 mg/kg/day (maximum: 0.05 mg/kg/day) given in 2-3 divided doses; increase by no more than 0.5 mg every third day until seizures are controlled or adverse effects seen.

Usual maintenance dose: 0.1-0.2 mg/kg/day divided 3 times/day; not to exceed 0.2 mg/kg/day.

Children >10 years or 30 kg: Refer to adult dosing.

Dosing: Renal ImpairmentHemodialysis: Supplemental dose is not necessary.
Administration: OralOrally-disintegrating tablet: Open pouch and peel back foil on the blister; do not push tablet through foil. Use dry hands to remove tablet and place in mouth. May be swallowed with or without water. Use immediately after removing from package.
Extemporaneously PreparedA 0.1 mg/mL oral suspension has been made using five 2 mg tablets, purified water USP (10 mL), and methylcellulose 1% (qs ad 100 mL). The expected stability of this preparation is 2 weeks if stored under refrigeration; shake well before use.

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, 2nd ed, Cincinnati, OH: Harvey Whitney Books Co, 1992.

RestrictionsC-IV
ContraindicationsHypersensitivity to clonazepam or any component of the formulation (cross-sensitivity with other benzodiazepines may exist); significant liver disease; narrow-angle glaucoma; pregnancy
Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

• Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

- Valproic acid: Concurrent use with valproic acid may result in absence status.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.

- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury.

- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties. Worsening of seizures may occur when added to patients with multiple seizure types. Monitoring of CBC and liver function tests has been recommended during prolonged therapy.

- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsHepatic clearance may be decreased allowing accumulation of active drug. Also, metabolites of clonazepam are renally excreted and may accumulate in the elderly as renal function declines with age. Observe for signs of CNS and pulmonary toxicity.

Pregnancy Risk FactorD

Pregnancy ConsiderationsClonazepam was shown to be teratogenic in some animal studies. Clonazepam crosses the placenta. Benzodiazepine use during pregnancy is associated with increased risk of congenital malformations. Nonteratogenic effects (including neonatal flaccidity, respiratory and feeding problems, and withdrawal symptoms) during the postnatal period have also been reported with benzodiazepine use. Epilepsy itself, number of medications, genetic factors, or a combination of these probably influence the teratogenicity of anticonvulsant therapy.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsClonazepam enters breast milk; clinical effects on the infant include CNS depression, respiratory depression reported (no recommendation from the AAP).

Adverse ReactionsReactions reported in patients with seizure and/or panic disorder. Frequency not defined.

Cardiovascular: Edema (ankle or facial), palpitation

Central nervous system: Amnesia, ataxia (seizure disorder ~30%; panic disorder 5%), behavior problems (seizure disorder ~25%), coma, confusion, depression, dizziness, drowsiness (seizure disorder ~50%), emotional lability, fatigue, fever, hallucinations, headache, hypotonia, hysteria, insomnia, intellectual ability reduced, memory disturbance, nervousness; paradoxical reactions (including aggressive behavior, agitation, anxiety, excitability, hostility, irritability, nervousness, nightmares, sleep disturbance, vivid dreams); psychosis, slurred speech, somnolence (panic disorder 37%), suicidal attempt, vertigo

Dermatologic: Hair loss, hirsutism, skin rash

Endocrine & metabolic: Dysmenorrhea, libido increased/decreased

Gastrointestinal: Abdominal pain, anorexia, appetite increased/decreased, coated tongue, constipation, dehydration, diarrhea, gastritis, gum soreness, nausea, weight changes (loss/gain), xerostomia

Genitourinary: Colpitis, dysuria, ejaculation delayed, enuresis, impotence, micturition frequency, nocturia, urinary retention, urinary tract infection

Hematologic: Anemia, eosinophilia, leukopenia, thrombocytopenia

Hepatic: Alkaline phosphatase increased (transient), hepatomegaly, transaminases increased (transient)

Neuromuscular & skeletal: Choreiform movements, coordination abnormal, dysarthria, muscle pain, muscle weakness, myalgia, tremor

Ocular: Blurred vision, eye movements abnormal, diplopia, nystagmus

Respiratory: Chest congestion, cough, bronchitis, hypersecretions, pharyngitis, respiratory depression, respiratory tract infection, rhinitis, rhinorrhea, shortness of breath, sinusitis

Miscellaneous: Allergic reaction, aphonia, dysdiadochokinesis, encopresis, “glassy-eyed” appearance, hemiparesis, lymphadenopathy

Metabolism/Transport Effects

Substrate of CYP3A4 (major)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Clonazepam serum concentration is unlikely to be increased by grapefruit juice because of clonazepam's high oral bioavailability.

Herb/Nutraceutical: St John's wort may decrease clonazepam levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersCBC, liver function tests; observe patient for excess sedation, respiratory depression
Reference RangeRelationship between serum concentration and seizure control is not well established

Timing of serum samples: Peak serum levels occur 1-3 hours after oral ingestion; the half-life is 20-40 hours; therefore, steady-state occurs in 5-7 days

Therapeutic levels: 20-80 ng/mL; Toxic concentration: >80 ng/mL

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess for signs of CNS depression. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance; periodically evaluate need for continued use. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Assess knowledge/teach patient seizure precautions (if administered for seizures), appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Monitoring: Lab TestsRenal function
Patient EducationTake exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, loss of appetite, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help). If medication is used to control seizures, wear identification that you are taking an antiepileptic medication. Report excessive drowsiness, dizziness, fatigue, or impaired coordination; CNS changes (confusion, depression, increased sedation, excitation, headache, agitation, insomnia, or nightmares) or changes in cognition; respiratory difficulty or shortness of breath; changes in urinary pattern, changes in sexual activity; muscle cramping, weakness, tremors, or rigidity; ringing in ears or visual disturbances, excessive perspiration, or excessive GI symptoms (cramping, constipation, vomiting, anorexia); worsening of seizure activity, or loss of seizure control. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 0.5 mg, 1 mg, 2 mg

Klonopin®: 0.5 mg, 1 mg, 2 mg

Tablet, orally disintegrating: 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg

Klonopin® Wafers: 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablet, orally-disintegrating (Clonazepam ODT)

0.125 mg (60): $69.99

0.25 mg (60): $72.99

0.5 mg (60): $70.99

1 mg (60): $65.99

2 mg (60): $100.00

Tablet, orally-disintegrating (Klonopin Wafer)

0.25 mg (30): $54.94

Tablets (Clonazepam)

0.5 mg (30): $13.99

1 mg (30): $11.99

2 mg (30): $12.99

Tablets (Klonopin)

0.5 mg (30): $49.44

1 mg (30): $50.54

2 mg (30): $65.93

Mechanism of ActionThe exact mechanism is unknown, but believed to be related to its ability to enhance the activity of GABA; suppresses the spike-and-wave discharge in absence seizures by depressing nerve transmission in the motor cortex
Pharmacodynamics/Kinetics

Onset of action: 20-60 minutes

Duration: Infants and young children: 6-8 hours; Adults: ≤12 hours

Absorption: Well absorbed

Distribution: Adults: V_d: 1.5-4.4 L/kg

Protein binding: 85%

Metabolism: Extensively hepatic via glucuronide and sulfate conjugation

Half-life elimination: Children: 22-33 hours; Adults: 19-50 hours

Time to peak, serum: 1-3 hours; Steady-state: 5-7 days

Excretion: Urine (<2% as unchanged drug); metabolites excreted as glucuronide or sulfate conjugates

Related Information

- Anticonvulsants by Seizure Type
- Benzodiazepines
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Status Epilepticus
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsEthosuximide or valproic acid may be preferred for treatment of absence (petit mal) seizures. Clonazepam-induced behavioral disturbances may be more frequent in mentally handicapped patients. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms. Flumazenil, a competitive benzodiazepine antagonist at the CNS receptor site, reverses benzodiazepine-induced CNS depression.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), gum soreness, and coated tongue.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Clonazepam is a long half-life benzodiazepine. Duration of action after a single dose is determined by redistribution rather than metabolism. Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include personal or family history of substance abuse and personality disorder.

Anesthesia and Critical Care Concerns/Other ConsiderationsFlumazenil, a competitive benzodiazepine antagonist at the CNS receptor site, reverses benzodiazepine-induced CNS depression. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

References

Barnett AM, “Treatment of Epilepsy With Clonazepam,” *S Afr Med J*, 1973, 47(37):1683-6. [PubMed 4202487]

Bladin PF, “The Use of Clonazepam as an Anticonvulsant - Clinical Evaluation,” *Med J Aust*, 1973, 1(14):683-8.

Brogden RN and Goa KL, “Flumazenil. A Preliminary Review of Its Benzodiazepine Antagonist Properties, Intrinsic Activity, and Therapeutic Use,” *Drugs*, 1988, 35(4):448-67. [PubMed 2839329]

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

Sugai K, “Seizures With Clonazepam: Discontinuation and Suggestions for Safe Discontinuation Rates in Children,” *Epilepsia*, 1993, 34(6):1089-97.[PubMed 8243361]

International Brand NamesAntelepsin (CZ, DE, HU, PL); Clonagin (AR); Clonapilep (MX); Clonazepamum (HU, PL); Clonotril (CY); Clozer (MX); Diocam (AR); Iktorivil (SE); Kenoket (MX); Kriadex (MX); Lonazep (IN); Paxam (AU); Ravotril (CZ, DE); Rivatril (FI, FR); Rivoril (BE); Rivotril (AR, AT, AU, BE, BR, CH, DE, DK, ES, FR, GB, HR, HU, IE, IT, LU, MX, NL, NO, PL, PT); Solfidin (AR); Zymanta (MX)

Clonidine and Chlorthalidone

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Medication Safety Issues

Sound-alike/look-alike issues:

> Combipres® may be confused with Catapres®

Pronunciation(KLON i deen & klor THAL i done)
U.S. Brand NamesClorpres®; Combipres® [DSC]
Pharmacologic CategoryAlpha$_2$-Adrenergic Agonist; Diuretic, Thiazide
Use: Labeled IndicationsManagement of mild-to-moderate hypertension
Dosing: AdultsHypertension: Oral: 1 tablet 1-2 times/day
Dosing: ElderlyMay benefit from lower initial dose; see individual agents.
Allergy Considerations

- Thiazide/Thiazide-Related Diuretic Allergy

Pregnancy Risk FactorC
Pregnancy ConsiderationsRefer to Clonidine monograph.
Lactation

Clonidine: Enters breast milk/not recommended

Chlorthalidone: Enters breast milk/compatible

Adverse ReactionsSee individual agents.
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antidepressants (Alpha2-Antagonist): May diminish the hypotensive effect of Alpha2-Agonists. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Iobenguane I 123: Alpha2-Agonists may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methylphenidate: May enhance the adverse/toxic effect of CloNIDine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: May diminish the antihypertensive effect of Alpha2-Agonists. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

0.1: Clonidine hydrochloride 0.1 mg and chlorthalidone 15 mg

0.2: Clonidine hydrochloride 0.2 mg and chlorthalidone 15 mg

0.3: Clonidine hydrochloride 0.3 mg and chlorthalidone 15 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Clorpres)

0.1-15 mg (60): $64.99

0.2-15 mg (60): $82.96

0.3-15 mg (60): $99.56

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Chlorthalidone
- CloNIDine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Clonidine: Significant xerostomia (normal salivary flow resumes upon discontinuation), orthostatic hypotension, and abnormal taste.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDrowsiness is common
Mental Health: Effects on Psychiatric TreatmentDry mouth, orthostatic hypotension, and sedation may be increased with concurrent psychotropic use; TCAs may antagonize clonidine's hypotensive effect; rare reports of blood dyscrasias; use caution with clozapine and carbamazepine; thiazides decrease lithium clearance resulting in elevated serum lithium levels and potential toxicity; monitor serum lithium levels
Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for clonidine and chlorthalidone combination therapy may include improved compliance and synergistic reductions in blood pressure with an accomplished reduction in side effects. Thiazide therapy improves cardiovascular outcomes in patients with hypertension. See Cardiovascular Considerations for individual agents.
Index TermsChlorthalidone and Clonidine
References

Chobanian AV, Bakris GL, Black HR, et al, “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report,” *JAMA*, 2003, 289(19):2560-71. [PubMed 12748199]

Kaplan NM and Sever PS, “Combination Therapy: A Key to Comprehensive Patient Care,” *Am J Hypertens*, 1997, 10(7 Pt 2):127S. [PubMed 9231887]

Moser M and Black HR, “The Role of Combination Therapy in the Treatment of Hypertension,” *Am J Hypertens*, 1998, 11(6 Pt 2):73S-8S, 95S-100S.[PubMed 9655566]

CloNIDine

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English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.
Special Alerts

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) has issued a statement in April 2008 recommending that all children diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the recommendations due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: Methylphenidate, amphetamine, dextroamphetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children’s Healthcare Quality.

For more information, refer to:

http://americanheart.mediaroom.com/index.php?s=43&item=422

http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1

http://americanheart.mediaroom.com/index.php?s=43&item=398

http://www.fda.gov/medwatch/safety/2007/safety07.htm

http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html

Nissen SE, “ADHD Drugs and Cardiovascular Risk,” *N Engl J Med*, 2006, 354(14):1445-48.

“Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder,” *J Am Acad*

Child Adolesc Psychiatry, 2007, 46(7):894-921.

Vetter VL, Elia J, Erickson CH, et al, "Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing," *Circulation*, 2008, 117:2407-23.

Wilens TE, Prince JB, Spencer TJ, et al, "Stimulants and Sudden Death: What is a Physician to do?" *Pediatrics*, 2006, 118(3):1215-19.

Medication Safety Issues

Sound-alike/look-alike issues:

CloNIDine may be confused with Clomid®, clomiPHENE, clonazePAM, clozapine, Klonopin®, quiNIDine

Catapres® may be confused with Cataflam®, Cetapred®, Combipres®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (epidural administration) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Transdermal patch may contain conducting metal (eg, aluminum); remove patch prior to MRI.

Pronunciation(KLON i deen)
U.S. Brand NamesCatapres-TTS®; Catapres®; Duraclon®
Canadian Brand NamesApo-Clonidine®; Carapres®; Dixarit®; Novo-Clonidine; Nu-Clonidine
Pharmacologic CategoryAlpha$_2$-Adrenergic Agonist
Use: Labeled IndicationsManagement of mild-to-moderate hypertension; either used alone or in combination with other antihypertensives

Orphan drug: Duraclon®: For continuous epidural administration as adjunctive therapy with intraspinal opiates for treatment of cancer pain in patients tolerant to or unresponsive to intraspinal opiates

Use: Unlabeled/InvestigationalHeroin or nicotine withdrawal; severe pain; dysmenorrhea; vasomotor symptoms associated with menopause; ethanol dependence; prophylaxis of migraines; glaucoma; diabetes-associated diarrhea; impulse control disorder, attention-deficit/hyperactivity disorder (ADHD), clozapine-induced sialorrhea
Dosing: Adults

Acute hypertension (urgency): Oral: Initial 0.1-0.2 mg; may be followed by additional doses of 0.1 mg every hour, if necessary, to a maximum total dose of 0.6 mg

Unlabeled route of administration: Sublingual clonidine 0.1-0.2 mg twice daily may be effective in patients unable to take oral medication

Hypertension:

Oral: Initial dose: 0.1 mg twice daily (maximum recommended dose: 2.4 mg/day); usual dose range (JNC 7): 0.1-0.8 mg/day in 2 divided doses

Transdermal: Apply once every 7 days; for initial therapy start with 0.1 mg and increase by 0.1 mg at 1- to 2-week intervals (dosages >0.6 mg do not improve efficacy); usual dose range (JNC 7): 0.1-0.3 mg once weekly

Note: If transitioning from oral to transdermal, overlap oral for 1-2 days. Transdermal route takes 2-3 days to achieve therapeutic effects.

Conversion from oral to transdermal:

Day 1: Place Catapres-TTS® 1; administer 100% of oral dose.

Day 2: Administer 50% of oral dose.

Day 3: Administer 25% of oral dose.

Day 4: Patch remains, no further oral supplement necessary.

Nicotine withdrawal symptoms: 0.1 mg twice daily to maximum of 0.4 mg/day for 3-4 weeks

Pain management: Epidural infusion: Starting dose: 30 mcg/hour; titrate as required for relief of pain or presence of side effects; minimal experience with doses >40 mcg/hour; should be considered an adjunct to intraspinal opiate therapy

Dosing: ElderlyOral: Initial: 0.1 mg once daily at bedtime, increase gradually as needed.
Dosing: Pediatric

Hypertension: Oral: Children ≥12 years: Initial: 0.2 mg/day in 2 divided doses; increase gradually at 5- to 7-day intervals; maximum: 2.4 mg/day

Clonidine tolerance test (growth hormone release from pituitary): Oral: 0.15 mg/m^2 or 4 mcg/kg as single dose

ADHD (unlabeled use): Oral: Initial: 0.05 mg/day, increase every 3-7 days by 0.05 mg/day to 3-5 mcg/kg/day given in divided doses 3-4 times/day; maximum dose: 0.3-0.4 mg/day

Pain management: Epidural infusion: Reserved for patients with severe intractable pain, unresponsive to other analgesics or epidural or spinal opiates: Initial: 0.5 mcg/kg/hour; adjust with caution, based on clinical effect

Dosing: Renal Impairment

Cl_{cr} <10 mL/minute: Administer 50% to 75% of normal dose initially.

Not dialyzable (0% to 5%) via hemo- or peritoneal dialysis; supplemental dose is not necessary.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V. DetailpH: 5-7

Administration: OralDo not discontinue clonidine abruptly. If needed, gradually reduce dose over 2-4 days to avoid rebound hypertension.

Administration: TopicalTransdermal patches should be applied weekly at bedtime to a clean, hairless area of the upper outer arm or chest. Rotate patch sites weekly. Redness under patch may be reduced if a topical corticosteroid spray is applied to the area before placement of the patch.

Dietary ConsiderationsHypertensive patients may need to decrease sodium and calories in diet.

Compatibility

Y-site administration: Compatible: Lorazepam.

Compatibility in syringe: Compatible: Bupivacaine with morphine, fentanyl with lidocaine, ketamine with tetracaine.

ContraindicationsHypersensitivity to clonidine hydrochloride or any component of the formulation

Allergy Considerations

- CloNIDine Allergy

Warnings/Precautions

Boxed warnings:

- Epidural use: See "Dosage form specific issues" below.

Concerns related to adverse effects:

- CNS depression: May cause significant CNS depression; use with caution in patients with pre-existing CNS disease or depression.
- Xerostomia: May cause significant xerostomia.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe coronary insufficiency, including recent MI and conduction disturbances, including sinus node dysfunction.
- Cerebrovascular disease: Use with caution in patients with cerebrovascular disease.
- Renal impairment: Use with caution in patients with chronic renal impairment.

Special populations:

- Elderly: Use with caution in the elderly; may be at greater risk for CNS depressive effects, favoring other agents in this population.
- Surgical patients: Discontinue within 4 hours of surgery then restart as soon as possible after.

Dosage form specific issues:

- Epidural use: **[U.S. Boxed Warning]: Epidural clonidine is not recommended for perioperative, obstetrical, or postpartum pain.** It is not recommended for use in patients with severe cardiovascular disease or hemodynamic instability. In all cases, the epidural route may lead to cardiovascular instability (hypotension, bradycardia). Should be administered via a continuous epidural infusion device.
- Transdermal patch: May contain conducting metal (eg, aluminum); remove patch prior to MRI. Due to the potential for altered electrical conductivity, remove transdermal patch before cardioversion or defibrillation.

Other warnings/precautions:

- Discontinuation of therapy: Gradual withdrawal is needed (over 1 week for oral, 2-4 days with epidural) if drug needs to be stopped. Patients should be instructed about abrupt discontinuation (causes rapid increase in BP and symptoms of sympathetic overactivity). In patients on both a beta-blocker and clonidine where withdrawal of clonidine is necessary, withdraw the beta-blocker first and several days before clonidine. Then slowly decrease clonidine.

Geriatric ConsiderationsBecause of its potential CNS adverse effects, clonidine may not be considered a drug of choice in the elderly. If the decision is to use clonidine, adjust dose based on response and adverse reactions.

Pregnancy Risk FactorC

Pregnancy ConsiderationsClonidine crosses the placenta. Caution should be used with this drug due to the potential of rebound hypertension with abrupt discontinuation.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsEnters breast milk; AAP has NO RECOMMENDATION.

Adverse ReactionsIncidence of adverse events is not always reported.

>10%:

Central nervous system: Drowsiness (35% oral, 12% transdermal), dizziness (16% oral, 2% transdermal)

Dermatologic: Transient localized skin reactions characterized by pruritus, and erythema (15% to 50% transdermal)

Gastrointestinal: Dry mouth (40% oral, 25% transdermal)

1% to 10%:

Cardiovascular: Orthostatic hypotension (3% oral)

Central nervous system: Headache (1% oral, 5% transdermal), sedation (3% transdermal), fatigue (6% transdermal), lethargy (3% transdermal), insomnia (2% transdermal), nervousness (3% oral, 1% transdermal), mental depression (1% oral)

Dermatologic: Rash (1% oral), allergic contact sensitivity (5% transdermal), localized vesiculation (7%), hyperpigmentation (5% at application site), edema (3%), excoriation (3%), burning (3%), throbbing, blanching (1%), papules (1%), and generalized macular rash (1%) has occurred in patients receiving transdermal clonidine.

Endocrine & metabolic: Sodium and water retention, sexual dysfunction (3% oral, 2% transdermal), impotence (3% oral, 2% transdermal)

Gastrointestinal: Nausea (5% oral, 1% transdermal), vomiting (5% oral), anorexia and malaise (1% oral), constipation (10% oral, 1% transdermal), dry throat (2% transdermal), taste disturbance (1% transdermal), weight gain (1% oral)

Genitourinary: Nocturia (1% oral)

Hepatic: Liver function test (mild abnormalities, 1% oral)

Neuromuscular & skeletal: Weakness (10% transdermal)

Miscellaneous: Withdrawal syndrome (1% oral)

<1% (Limited to important or life-threatening): Hepatitis (oral), difficulty in micturition (oral, transdermal), urinary retention (oral), hives (oral, transdermal), angioedema (oral, transdermal), urticaria (oral, transdermal), alopecia (oral, transdermal), parotid pain (oral), gynecomastia (oral, transdermal), transient elevation of blood glucose (oral), elevation of creatinine phosphokinase (oral), palpitation (oral, transdermal), tachycardia (oral, transdermal), bradycardia (oral), sinus bradycardia (oral, transdermal), atrioventricular block (oral, transdermal), CHF (oral, transdermal), ECG abnormalities (oral, transdermal), flushing, pallor, Raynaud's phenomenon (oral, transdermal), chest pain (transdermal), blood pressure increase (transdermal), weakness, muscle or joint pain (0.6% oral), leg cramps (0.3% oral), fever (oral, transdermal), malaise (transdermal), withdrawal syndrome (transdermal), vivid dreams (oral, transdermal), nightmares (oral, transdermal), insomnia (oral), behavioral changes (transdermal), restlessness (oral, transdermal), anxiety (oral, transdermal), mental depression (transdermal), visual and auditory hallucinations (oral, transdermal), delirium (transdermal), CVA (transdermal), irritability (transdermal), weight gain (transdermal), rash (transdermal), orthostatic symptoms (transdermal), syncope (oral, transdermal), agitation (transdermal), contact dermatitis (transdermal), localized hypo- or hyperpigmentation (transdermal), anorexia (transdermal), vomiting (transdermal), loss of libido (transdermal), sexual activity decreased (transdermal), blurred vision (transdermal), burning of eyes (transdermal), dryness of eyes (transdermal), weakly positive Coombs' test (oral), ethanol sensitivity increased (oral), thrombocytopenia (oral), abdominal pain (oral), pseudo-obstruction (oral)

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antidepressants (Alpha2-Antagonist): May diminish the hypotensive effect of Alpha2-Agonists. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Iobenguane I 123: Alpha2-Agonists may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Methylphenidate: May enhance the adverse/toxic effect of CloNIDine. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: May diminish the antihypertensive effect of Alpha2-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersBlood pressure, standing and sitting/supine, mental status, heart rate

When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure (when started and weaned), and consider obtaining ECG prior to initiation (Vetter, 2008).

Reference RangeTherapeutic: 1-2 ng/mL (SI: 4.4-8.7 nmol/L)

Nursing: Physical Assessment/MonitoringUse with caution and monitor closely in presence of pre-existing renal impairment, cardiovascular disease, hemodynamic instability, CNS disease or depression. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, potential for additive hypotension, bradycardia, CNS depression). Monitor blood pressure and mental status, therapeutic effectiveness (according to purpose for use), and adverse response regularly during therapy. Pediatric patients being treated for ADHD should be screened/monitored for cardiovascular risk prior to and during use. Advise patients using oral hypoglycemic agents or insulin to check glucose levels closely; clonidine may decrease the symptoms of hypoglycemia. When discontinuing, monitor blood pressure and taper dose gradually (over 1 week for oral, 2-4 days for epidural). Teach patient proper use (eg, do not discontinue abruptly), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsECG; liver function tests

Patient EducationDo not take any new prescription or over-the-counter medications, or herbal products (especially cough or cold remedies and sleep or stay-awake medications that might affect blood pressure) during treatment unless approved by prescriber. Take as directed, at bedtime. If using patch, check daily for correct placement; rotate patch sites weekly. Do not skip doses or discontinue without consulting prescriber (this drug must be discontinued on a specific schedule to prevent serious adverse effects). This medication may cause drowsiness, dizziness, fatigue, insomnia (use caution when driving or engaging in tasks that require alertness until response is known); decreased libido or sexual function (will resolve when drug is discontinued); postural hypotension (use caution when rising from sitting or lying position or when climbing stairs); constipation (increased exercise, fluids, fruit, and dietary fiber may help); or dry mouth or nausea (frequent mouth care or sucking lozenges may help). Report changes in urinary pattern; persistent nervousness, depression, lethargy, insomnia or nightmares; sudden weight gain (weigh yourself in the same clothes at the same time of day once a week); unusual or persistent swelling of ankles, feet, or extremities; skin reaction to transdermal patch; or other persistent side effects. **Pregnancy precautions:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride [epidural; preservative free]:

Duraclon®: 100 mcg/mL (10 mL); 500 mcg/mL (10 mL)

Tablet, as hydrochloride: 0.1 mg, 0.2 mg, 0.3 mg

Catapres®: 0.1 mg, 0.2 mg, 0.3 mg

Transdermal system, topical [once-weekly patch]:

Catapres-TTS®-1: 0.1 mg/24 hours (4s)

Catapres-TTS®-2: 0.2 mg/24 hours (4s)

Catapres-TTS®-3: 0.3 mg/24 hours (4s)

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Patch weekly (Catapres-TTS-1)

0.1 mg/24 hrs (4): $93.73

Patch weekly (Catapres-TTS-2)

0.2 mg/24 hrs (4): $152.57

Patch weekly (Catapres-TTS-3)

0.3 mg/24 hrs (4): $212.52

Tablets (Catapres)

0.1 mg (60): $74.99

0.2 mg (60): $109.99

0.3 mg (60): $134.99

Tablets (Clonidine HCl)

0.1 mg (100): $23.32

0.2 mg (100): $22.21

0.3 mg (100): $16.08

Mechanism of ActionStimulates alpha$_2$-adrenoceptors in the brain stem, thus activating an inhibitory neuron, resulting in reduced sympathetic outflow from the CNS, producing a decrease in peripheral resistance, renal vascular resistance, heart rate, and blood pressure; epidural clonidine may produce pain relief at spinal presynaptic and postjunctional alpha$_2$-adrenoceptors by preventing pain signal transmission; pain relief occurs only for the body regions innervated by the spinal segments where analgesic concentrations of clonidine exist

Pharmacodynamics/Kinetics

Onset of action: Oral: 0.5-1 hour; Transdermal: Initial application: 2-3 days

Duration: 6-10 hours

Distribution: V_d: Adults: 2.1 L/kg; highly lipid soluble; distributes readily into extravascular sites

Protein binding: 20% to 40%

Metabolism: Extensively hepatic to inactive metabolites; undergoes enterohepatic recirculation

Bioavailability: 75% to 95%

Half-life elimination: Adults: Normal renal function: 6-20 hours; Renal impairment: 18-41 hours

Time to peak: 2-4 hours

Excretion: Urine (65%, 32% as unchanged drug); feces (22%)

Related Information

- Addiction Treatments
- Depression
- Hypertension

Pharmacotherapy PearlsTransdermal clonidine should only be used in patients unable to take oral medication. The transdermal product is much more expensive than oral clonidine and produces no better therapeutic effects.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation), orthostatic hypotension, and abnormal taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common

Mental Health: Effects on Psychiatric TreatmentDry mouth, orthostatic hypotension, and sedation may be increased with concurrent psychotropic use; used to treat clozapine-induced sialorrhea (unlabeled use); TCAs may antagonize clonidine's hypotensive effect

Cardiovascular ConsiderationsTolerance to the blood pressure lowering effects of clonidine may develop with long-term therapy. Abrupt withdrawal from clonidine therapy should be very specifically avoided. The clonidine withdrawal syndrome is more pronounced after abrupt cessation of long-term therapy than after short-term therapy (1-2 months). It has usually been associated with previous administration of high oral doses (>1.2 mg daily) and/or continuation of beta-blocker therapy. The danger of abrupt discontinuation may be increased in patients with hypertension and/or other cardiovascular considerations. Blood pressure may increase 8-24 hours after last dose, but has occurred 60 hours after the last clonidine dose. Rebound hypertension has occurred with discontinuation of transdermal and epidural clonidine.

The advent of the clonidine patch has provided an important alternative to frequent daily dosing. However, it is important that overlap of therapy be maintained for 2-3 days when switching from oral medications to the patch. Important side effects of clonidine include drowsiness. It has also been suggested that clonidine may be useful in promoting smoking cessation.

Note that the use of moxonidine to lower sympathetic activation in patients with heart failure was associated with increased mortality.

Anesthesia and Critical Care Concerns/Other ConsiderationsAbrupt withdrawal from clonidine therapy should be avoided. Clonidine patch has provided an important alternative to frequent daily dosing; may be used in patients unable to take oral medication. Transdermal therapy takes 2-3 days for therapeutic effects.

Index TermsClonidine Hydrochloride

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International Brand NamesArkamin (IN); Aruclonin (HU); Atensina (BR); Catapin (PH); Catapres (AE, AU, BB, BD, BF, BH, BJ, BM, BS, BZ, CI, CL, CY, EG, ET, GB, GH, GM, GN, GY, HK, ID, IE, IL, IN, IQ, IR, JM, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PH, PK, PR, QA, SA, SC, SD, SG, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Catapres TTS (NZ); Catapresan (AR, AT, CH, CN, CO, DE, DK, ES, FI, GR, HR, IT, NL, NO, PE, PL, PT, SE, VE); Catapresan Depot (CZ, DE); Catapresan TTS (IT); Catapressan (BE, FR, LU); Chlophazolin (BG); Clonidina Larjan (AR); Clonidine (TH); Clonidural (AR); Clonilou (ES); Clonipresan (PY); Clonistada (PL); Dixarit (LU); Haemiton (AE, BH, CY, DE, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Hypodine (TH); Iopidine (PL); Iporel (PL); Isoglaucon (ES, HU); Menograine (ZA); Normopresan (IL); Normopresin (UY); Paracefan (BE)

Clopidogrel

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Plavix® may be confused with Elavil®, Paxil®

Pronunciation(kloh PID oh grel)

U.S. Brand NamesPlavix®

Canadian Brand NamesPlavix®

Pharmacologic CategoryAntiplatelet Agent

Use: Labeled IndicationsReduces rate of atherothrombotic events (myocardial infarction, stroke, vascular deaths) in patients with recent MI or stroke, or established peripheral arterial disease; reduces rate of atherothrombotic events in patients with unstable angina or non-ST-segment elevation acute coronary syndromes (unstable angina and non-ST-segment elevation MI) managed medically or through percutaneous coronary intervention (PCI) (with or without stent) or CABG; reduces rate of death and atherothrombotic events in patients with ST-segment elevation MI (STEMI) managed medically

Use: Unlabeled/InvestigationalIn aspirin-allergic patients, initial treatment of acute coronary syndromes (ACS) or prevention of coronary artery bypass graft closure (saphenous vein)

Dosing: Adults

Recent MI, recent stroke, or established arterial disease: Oral: 75 mg once daily

Acute coronary syndrome:

Unstable angina, non-ST-segment elevation myocardial infarction (UA/NSTEMI): Initial: 300 mg loading dose, followed by 75 mg once daily (in combination with aspirin 75-325 mg once daily). **Note:** A loading dose of 600 mg given at least 2 hours (or 24 hours in patients unable to take aspirin) prior to PCI is recommended (*Chest* guidelines, 2008)

ST-segment elevation myocardial infarction (STEMI): 75 mg once daily (in combination with aspirin 75-162 mg/day). CLARITY used a 300 mg loading dose of clopidogrel (with thrombolysis). The duration of therapy was <28 days (usually until hospital discharge) (Sabatine, 2005).

The American College of Chest Physicians (Goodman, 2008) recommends:

Patients ≤75 years: Initial: 300 mg loading dose, followed by 75 mg once daily for up to 28 days (in combination with aspirin)

Patients >75 years: 75 mg once daily for up to 28 days (with or without thrombolysis)

Note:*Coronary artery stents:* Duration of clopidogrel (in combination with aspirin): According to the ACC/AHA/SCAI guidelines, ideally 12 months following drug-eluting stent (DES) placement in patients not at high risk for bleeding; at a minimum, 1, 3, and 6 months for bare metal (BMS), sirolimus eluting, and paclitaxel eluting stents, respectively, for uninterrupted therapy (Smith, 2005). The 2008 *Chest* guidelines recommend for patients who undergo PCI and receive a BMS (with ongoing ACS) or a DES (with or without ongoing ACS) that clopidogrel be continued for at least 12 months. In patients receiving a BMS without ongoing ACS, clopidogrel may be continued for at least 1 month. In patients receiving a DES, therapy with clopidogrel beyond 12 months may be considered in patients without bleeding or tolerability issues (Becker, 2008). Premature interruption of therapy may result in stent thrombosis with subsequent fatal and nonfatal myocardial infarction.

Prevention of coronary artery bypass graft closure (saphenous vein): Aspirin-allergic patients (unlabeled use) [*Chest* guidelines, 2008]: Loading dose: 300 mg 6 hours following procedure; maintenance: 75 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentNo specific guidelines for patients with hepatic impairment; use with caution.

Dietary ConsiderationsMay be taken without regard to meals.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to clopidogrel or any component of the formulation; active pathological bleeding such as peptic ulcer disease (PUD) or intracranial hemorrhage; coagulation disorders

Allergy Considerations

- Thienopyridine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Thrombotic thrombocytopenic purpura (TTP): Cases of thrombotic thrombocytopenic purpura (usually occurring within the first 2 weeks of therapy), resulting in some fatalities, have been reported; urgent plasmapheresis is required.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with platelet disorders, bleeding disorders and/or at increased risk for bleeding (eg, PUD, trauma, or surgery).
- Hepatic impairment: Use with caution in patients with severe hepatic impairment (experience is limited).
- Renal impairment: Use with caution in patients with severe renal impairment (experience is limited).

Concurrent drug therapy issues:

- Anticoagulants and platelet aggregation inhibitors: Use with caution in patients receiving either anticoagulants (eg, heparin, warfarin) or other platelet aggregation inhibitors; bleeding risk is increased.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Coronary artery stents: In patients who have received bare-metal or drug-eluting stents (sirolimus or paclitaxel), interruption of antiplatelet therapy may result in stent thrombosis with subsequent fatal and nonfatal myocardial infarction. Ideally, 12 months following drug-eluting stent placement in patients not at high risk for bleeding is preferred; minimum durations of therapy are 1 month, 3 months, and 6 months for bare metal stents, sirolimus-eluting stents (Cypher®), and paclitaxel-eluting stents (Taxus®), respectively.
- Elective surgery: Consider discontinuing 5 days before elective surgery (except in patients with cardiac stents that have not completed their full course of dual antiplatelet therapy; patient-specific situations need to be discussed with cardiologist; AHA/ACC/SCAI/ACS/ADA Science Advisory provides recommendations).

Geriatric ConsiderationsPlasma concentrations of the main metabolite of clopidogrel were significantly higher in the elderly (≥75 years). This was not associated with changes in bleeding time or platelet aggregation. No dosage adjustment is recommended.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsAs with all drugs which may affect hemostasis, bleeding is associated with clopidogrel. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the concurrent use of multiple agents which alter hemostasis and patient susceptibility.

>10%: Gastrointestinal: The overall incidence of gastrointestinal events (including abdominal pain, vomiting, dyspepsia, gastritis, and constipation) has been documented to be 27% compared to 30% in patients receiving aspirin.

3% to 10%:

Cardiovascular: Chest pain (8%), edema (4%), hypertension (4%)

Central nervous system: Headache (3% to 8%), dizziness (2% to 6%), depression (4%), fatigue (3%), general pain (6%)

Dermatologic: Rash (4%), pruritus (3%)

Endocrine & metabolic: Hypercholesterolemia (4%)

Gastrointestinal: Abdominal pain (2% to 6%), dyspepsia (2% to 5%), diarrhea (2% to 5%), nausea (3%)

Genitourinary: Urinary tract infection (3%)

Hematologic: Bleeding (major 4%; minor 5%), purpura (5%), epistaxis (3%)

Hepatic: Liver function test abnormalities (<3%; discontinued in 0.11%)

Neuromuscular & skeletal: Arthralgia (6%), back pain (6%)

Respiratory: Dyspnea (5%), rhinitis (4%), bronchitis (4%), cough (3%), upper respiratory infection (9%)

Miscellaneous: Flu-like syndrome (8%)

1% to 3%:

Cardiovascular: Atrial fibrillation, cardiac failure, palpitation, syncope

Central nervous system: Fever, insomnia, vertigo, anxiety

Dermatologic: Eczema

Endocrine & metabolic: Gout, hyperuricemia

Gastrointestinal: Constipation, GI hemorrhage, vomiting

Genitourinary: Cystitis

Hematologic: Hematoma, anemia

Neuromuscular & skeletal: Arthritis, leg cramps, neuralgia, paresthesia, weakness

Ocular: Cataract, conjunctivitis

<1% (Limited to important or life-threatening): Agranulocytosis, allergic reaction, anaphylactoid reaction, bilirubinemia, bronchospasm, bullous eruption, fatty liver, granulocytopenia, hematuria, hemoptysis, hemorrhagic stroke (0.1%), hemothorax, hypochromic anemia, intracranial hemorrhage (0.4%), ischemic necrosis, leukopenia, maculopapular rash, menorrhagia, neutropenia (0.05%), ocular hemorrhage, paresthesia, pulmonary hemorrhage, purpura, retroperitoneal bleeding, thrombocytopenia, urticaria

Postmarketing and/or case reports: Acute liver failure, aplastic anemia, angioedema, confusion, erythema multiforme, hallucination, hepatitis, hypersensitivity, interstitial pneumonitis, lichen planus, pancreatitis, pancytopenia, serum sickness, Stevens-Johnson syndrome, stomatitis, taste disorder, thrombotic thrombocytic purpura (TTP), toxic epidermal necrolysis, vasculitis

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 3A4; **Inhibits** CYP2C9 (weak)

Drug Interactions

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Atorvastatin: May diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Calcium Channel Blockers: May diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Macrolide Antibiotics: May diminish the therapeutic effect of Clopidogrel. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Proton Pump Inhibitors: May diminish the therapeutic effect of Clopidogrel. This appears to be due to reduced formation of the active clopidogrel metabolite. *Risk C: Monitor therapy*

Rifamycin Derivatives: May enhance the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Warfarin: Clopidogrel may enhance the anticoagulant effect of Warfarin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, chamomile, coleus, cordyceps, dong quai, evening primrose oil, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American), ginseng (Panax), ginseng (Siberian), grape seed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Monitoring ParametersSigns of bleeding; hemoglobin and hematocrit periodically

Nursing: Physical Assessment/MonitoringAssess effectiveness or interactions of other medications patient may be taking. Clopidogrel is a P450 enzyme inhibitor. Monitor for unusual bleeding. Monitor therapeutic effectiveness and teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsHemoglobin and hematocrit periodically

Patient EducationTake as directed. May cause headache or dizziness; use caution when driving or engaging in tasks that require alertness until response to drug is known. It may take longer than usual to stop bleeding. Small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may reduce nausea or vomiting. Mild analgesics may reduce arthralgia or back pain. Inform prescribers and dentists that you are taking this medication prior to scheduling any surgery or dental procedure. Report immediately unusual or acute chest pain or respiratory difficulties; skin rash; unresolved bleeding, diarrhea, or GI distress; nosebleed; or acute headache. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Plavix®: 75 mg, 300 mg

Generic AvailableNo

ManufacturerSanofi-Aventis

Pricing: U.S. (www.drugstore.com)

Tablets (Plavix)

75 mg (30): $135.99

Mechanism of ActionClopidogrel requires *in vivo* biotransformation to an unidentified active metabolite. This active metabolite irreversibly blocks the $P2Y_{12}$ component of ADP receptors on the platelet surface, which prevents activation of the GPIIb/IIIa receptor complex, thereby reducing platelet aggregation. Platelets blocked by clopidogrel are affected for the remainder of their lifespan.

Pharmacodynamics/Kinetics

Onset of action: Inhibition of platelet aggregation detected: 2 hours after 300 mg administered; after second day of treatment with 50-100 mg/day. At steady-state with 75 mg/day, the average inhibition level observed was 40% to 60%.

Peak effect: 50-100 mg/day: Bleeding time: 5-6 days; Platelet function: 3-7 days

Absorption: Well absorbed

Protein binding: Parent drug: 98%; metabolite: 94%

Metabolism: Extensively hepatic via hydrolysis; biotransformation primarily to carboxyl acid derivative (inactive). The active metabolite that inhibits platelet aggregation has not been isolated.

Half-life elimination: ~8 hours

Time to peak, serum: ~1 hour

Excretion: Urine (50%); feces (46%)

Dental Health Professional ConsiderationsThere is no scientific evidence to warrant the discontinuance of clopidogrel prior to dental surgery. Patients taking one clopidogrel tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with physician.

Dental Health: Effects on Dental TreatmentAspirin and clopidogrel (Plavix®) in combination is the primary prevention strategy against stent thrombosis after placement of drug-eluting metal stents in coronary patients. Premature discontinuation of this combination antiplatelet therapy strongly increases the risk of a catastrophic event of stent thrombosis leading to myocardial infarction and/or death, so says a science advisory issued in January 2007 from the American Heart Association in collaboration with the American Dental Association and other professional healthcare organizations. The advisory stresses a 12-month therapy of aspirin and Plavix® combination after placement of a drug-eluting stent in order to prevent thrombosis at the stent site. Any elective surgery should be postponed for 1 year after stent implantation, and if surgery must be performed, consideration should be given to continuing the antiplatelet therapy during the perioperative period in high-risk patients with drug-eluting stents.

This advisory was issued from a science panel made up of representatives from the American Heart Association (AHA), the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American College of Surgeons, the American Dental Association (ADA), and the American College of Physicians (Grines, 2007).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression, dizziness, confusion, hallucinations, insomnia, or anxiety

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concurrent use with SSRIs and/or valproic acid may produce additive effects. Flu-like syndrome may occur and present like SSRI-discontinuation symptoms. Hematologic side effects have rarely been reported; monitor with clozapine, carbamazepine, and valproate.

Cardiovascular Considerations

Acute Coronary Syndrome (ACS): The 2007 ACC/AHA guidelines for unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) recommend administration of clopidogrel to hospitalized patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance (Class I; level of evidence: A). In certain situations, patients may even be desensitized to aspirin so that they may receive aspirin and clopidogrel concurrently. The CURE trial demonstrated that clopidogrel reduced major cardiovascular events in patients with ACS without ST-segment elevation (Yusuf S, 2001). In this trial, the risk of major bleeding was significantly increased in the clopidogrel group although life-threatening bleeding and hemorrhagic strokes were similar in both groups. In hospitalized UA/NSTEMI patients in whom an early noninvasive strategy is planned, clopidogrel should be added to aspirin and anticoagulant therapy as soon as possible (Class I, Level of evidence A).

In UA/NSTEMI patients in whom an invasive strategy will be employed, antiplatelet therapy should be initiated prior to diagnostic angiography. This can be done with either clopidogrel or a glycoprotein IIb/IIIa inhibitor (eg, eptifibatide) (Class I, Level of evidence A). The PCI-CURE trial, a substudy of the CURE trial, suggested that in patients with ACS undergoing PCI receiving aspirin, a strategy of clopidogrel pretreatment followed by long-term therapy (9 months) is beneficial in reducing major cardiovascular events, compared with placebo (Mehta SR, 2001). In the CREDO trial, long-term (1 year) clopidogrel treatment (75 mg daily) following PCI, significantly reduced the risk of adverse ischemic events (Steinhubl SR, 2002). In CREDO, the issue of timing was evaluated and a 300 mg loading dose of clopidogrel must be given at least 6 hours before PCI. More recently, however, a 600 mg loading dose of clopidogrel was shown to result in maximal platelet inhibition at 2 hours (Hochholzer W, 2005).

In patients taking clopidogrel in whom elective CABG is planned, clopidogrel should be withheld for 5-7 days before elective CABG. If urgent CABG is required, the benefits of surgery should outweigh the risks of incremental bleeding.

ST-Segment Elevation Myocardial Infarction (STEMI): The COMMIT trial (Chen ZM, 2005), randomized 45,852 patients with an acute MI (supporting ECG abnormalities), presenting within 24 hours of onset of symptoms, to clopidogrel 75 mg daily or placebo. All patients received aspirin and standard medical care (eg, thrombolytics if appropriate, ACEI). Clopidogrel was continued for 28 days or until hospital discharge whichever came first. The primary outcome measure was a composite of death, MI, or stroke. Patients in the clopidogrel arm had a significantly lower death rate (7.5% clopidogrel, 8.1% placebo; p=0.002).The CLARITY trial (Scirica BM, 2006) evaluated clopidogrel in the setting of thrombolysis and its relationship to ST-segment resolution. The randomized, double blind, placebo controlled trial included 3491 patients within 12 hours of the onset of STEMI who were candidates for thrombolytic therapy. Patients were randomized to receive clopidogrel (300 mg loading dose, then 75 mg daily) or placebo until angioplasty, discharge, or Day 8. Patients also received aspirin (loading dose followed by 75-162 mg/day). The ECG was monitored at baseline, and 90- and 180 minutes after thrombolysis. There was no difference in ECG resolution (none, partial, complete) between the groups at 90 minutes. Patients with partial (30% to 70%) and complete (>70%) ST-segment resolution on clopidogrel had significantly improved patency on discharge angiogram over placebo patients with similar ST-segment resolution. The clopidogrel group with partial ST segment resolution had a significantly lower rate of in-hospital death and MI than their placebo counterparts. The clopidogrel group with complete resolution of ST-segments showed a trend toward a reduction of in-hospital death and MI but it was not statistically significant (p=0.056). Mortality was followed for 30 days; the clopidogrel group with complete resolution of ST-segment abnormalities had a significant reduction in the rate of death compared to its placebo counterpart.

Percutaneous Coronary Intervention (PCI): The 2004 ACC/AHA guidelines for ST-elevation myocardial infarction (STEMI) suggests that clopidogrel be continued for at least 1 month after bare-metal stent implantation, for several months after drug-eluting stent implantation (3 months for sirolimus, 6 months for paclitaxel), and ideally for up to 12 months in patients who are not at high risk for bleeding.

Coronary Artery Stents: The 2005 ACC/AHA/SCAI guidelines for PCI recommends that along with aspirin, clopidogrel be continued for at least 1 month after bare-metal stent implantation, for several months after drug-eluting stent implantation (3 months for sirolimus, 6 months for paclitaxel), and ideally for up to 12 months in patients who are not at high risk for bleeding. Clopidogrel is the preferred thienopyridine due to its lower incidence of serious side effects (eg, neutropenia) as compared to ticlopidine.

The 2008 *Chest* guidelines recommend for patients who undergo PCI and receive a BMS (with ongoing ACS) or a DES (with or without ongoing ACS) that clopidogrel be continued for at least 12 months. In patients receiving a BMS without ongoing ACS, clopidogrel may be continued for at least 1 month. In patients receiving a DES, therapy with clopidogrel beyond 12 months may be considered in patients without bleeding or tolerability issues (Becker, 2008).

The AHA/ACC/SCAI/ACS/ADA Science Advisory (2007) published recommendations (*Circulation*, February 13, 2007) to prevent premature discontinuation of dual antiplatelet therapy (clopidogrel, aspirin) in patients with coronary artery stents. This advisory panel agreed with the 2004 ACC/AHA guidelines stressing the importance of 12 months of dual antiplatelet therapy after placement of a drug-eluting stent (DES) in patients who are not at high risk of bleeding. The advisory panel included these recommendations. Minor surgery, teeth cleaning, and tooth extraction can usually be performed without increased bleeding on the dual antiplatelet regimen. If increased bleeding is anticipated, then the procedure should be delayed until the antiplatelet regimen is completed. Elective procedures with a significant risk of bleeding should be postponed until the antiplatelet regimen is completed. The Advisory panel recommends healthcare providers who perform invasive or surgical procedures contact the patient's cardiologist before discontinuing antiplatelet therapy. For patients with drug-eluting stents who must undergo a procedure that requires discontinuation of thienopyridine therapy, aspirin should be continued if possible and the thienopyridine restarted as soon as possible after the procedure. "Bridging" stent patients with warfarin, other antithrombins, or glycoprotein IIb/IIIa agents is not supported by the Advisory Committee.

For the complete review and additional recommendations available at
http://www.acc.org/qualityandscience/clinical/pdfs/Final_Dual_Antiplatelet_Statement_010507.pdf.

High Cardiovascular-Event Risk Patients: The CHARISMA trial (Bhatt DL, 2006) evaluated the use of clopidogrel compared to placebo in 15,603 patients receiving low-dose aspirin (75-162 mg/day) who were at high risk of future cardiovascular events. This patient group included those with multiple atherothrombotic risk factors, documented coronary, cerebrovascular, or peripheral vascular disease. The primary outcome measure was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The primary outcome measure occurred in 6.8% of patients receiving clopidogrel and aspirin vs. 7.3% with placebo and aspirin (p=0.22). The rates of the secondary endpoints which included hospitalizations for ischemic events, was 16.7% and 17.9% (p=0.04). The rate of GUSTO-defined severe bleeding was 1.7% and 1.3% (p=0.09). A prespecified subgroup analysis divided patients into a "symptomatic" group (with documented cardiovascular disease) and an "asymptomatic" group (without documented cardiovascular disease). In the patients considered symptomatic, the primary event rate was lower in the clopidogrel group compared to placebo (6.9% vs 7.9%, p=0.046). In patients considered asymptomatic, there was a 20% relative increase in the primary event rate (6.6% vs 5.5%; p=0.20) if receiving clopidogrel. The rate of death from cardiovascular causes was also higher in this group (3.9% vs 2.2%, p=0.01). In summary, clopidogrel in addition to low-dose aspirin is not significantly more effective than low-dose aspirin alone in reducing the rate of MI, stroke, or death from cardiovascular causes. Use of clopidogrel in addition to low-dose aspirin may be harmful in patients with multiple atherothrombotic risk factors without cardiovascular disease. The American College of Chest Physicians recommends against the routine use of clopidogrel (in addition to aspirin) for primary prevention unless the patient has an aspirin allergy and is at moderate-to-high risk for a cardiovascular event (Becker, 2008).

Anesthesia and Critical Care Concerns/Other Considerations **Perioperative Management of Clopidogrel:**

In patients with coronary stents, the risk of stent thrombosis becomes elevated depending on the type of stent deployed (bare metal vs drug-eluting stent) and the time from implantation. According to the American College of Chest Physicians (Becker, 2008), the recommended length of therapy for clopidogrel is at least 12 months in patients with ACS who undergo PCI with a bare metal stent (BMS) or drug-eluting stent (DES). In patients receiving a BMS without ongoing ACS, clopidogrel may be continued for at least 1 month. Early discontinuation of clopidogrel may result in stent thrombosis leading to nonfatal and fatal myocardial infarction. The perioperative recommendations for clopidogrel are below (Douketis, 2008):

Patients undergoing noncardiac surgery (low risk of cardiac event without coronary stent): Clopidogrel and other antiplatelet agents should be temporarily discontinued 5-10 days prior to surgery and resumed ~24 hours (or the next morning) after the procedure when adequate hemostasis is achieved.

Patients without coronary stent undergoing cardiac surgery (eg, CABG) or noncardiac surgery (high risk of cardiac event): Discontinue clopidogrel at least 5 days and, preferably, 10 days prior to surgery while continuing aspirin up to and beyond the time of surgery. If aspirin is interrupted, it should be reinitiated 6-48 hours after surgery; may resume clopidogrel ~24 hours (or the next morning) after the procedure when adequate hemostasis is achieved.

Patients undergoing cardiac surgery (eg, CABG) or noncardiac surgery (with coronary stent): Based on the risk of stent thrombosis, patients with a BMS who require surgery within 6 weeks of implantation or with a DES who require surgery within 12 months of implantation should continue on both aspirin and clopidogrel during the perioperative period.

The AHA/ACC/SCAI/ACS/ADA Science Advisory (2007) published recommendations (*Circulation*, February 13, 2007) to prevent premature discontinuation of dual antiplatelet therapy (clopidogrel and aspirin) in patients with coronary artery stents. The advisory panel agreed with the 2004 ACC/AHA guidelines stressing the importance of 12 months of dual antiplatelet therapy after placement of a drug-eluting stent (DES) in patients who are not at high risk of bleeding. The advisory panel included these recommendations. Minor surgery, teeth cleaning, and tooth extraction can usually be performed without increased bleeding on the dual antiplatelet regimen. If increased bleeding is anticipated, then the procedure should be delayed until the antiplatelet regimen is completed. Elective procedures with a significant risk of bleeding should be postponed until the antiplatelet regimen is completed. The advisory panel recommends healthcare providers who perform invasive or surgical procedures contact the patient's cardiologist before discontinuing antiplatelet therapy. For patients with drug-eluting stents who must undergo a procedure that requires discontinuation of thienopyridine therapy, aspirin should be continued if possible and the thienopyridine restarted as soon as possible after the procedure. "Bridging" stent patients with warfarin, other antithrombins, or glycoprotein IIb/IIIa agents is not supported by the Advisory Committee.

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Index TermsClopidogrel Bisulfate

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International Brand NamesClopilet (IN); Iscover (AR, AT, AU, BE, BG, CH, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Maxgrel (KP); Noclot (PK); Plavix (AR, AT, AU, BB, BD, BE, BF, BG, BJ, BM, BO, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CZ, DE, DK, DO, EC, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, ID, IE, IL, IN, IT, JM, JP, KE, KP, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, PA, PE, PH, PK, PL, PR, PT, PY, RU, SC, SD, SE, SG, SL, SN, SR, SV, TH, TN, TR, TT, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Q.O.L. (KP); Ravalgen (EC)

Clorazepate

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Clorazepate may be confused with clofibrate, clonazepam

Pronunciation(klor AZ e pate)

U.S. Brand NamesTranxene® SD™; Tranxene® SD™-Half Strength; Tranxene® T-Tab®

Canadian Brand NamesApo-Clorazepate®; Novo-Clopate

Pharmacologic CategoryBenzodiazepine

Use: Labeled IndicationsTreatment of generalized anxiety disorder; management of ethanol withdrawal; adjunct anticonvulsant in management of partial seizures

Dosing: Adults

Anxiety:

Regular release tablets (Tranxene® T-Tab®): 7.5-15 mg 2-4 times/day

Sustained release (Tranxene® SD™): 11.25 or 22.5 mg once daily at bedtime

Ethanol withdrawal: Oral: Initial: 30 mg, then 15 mg 2-4 times/day on first day; maximum daily dose: 90 mg; gradually decrease dose over subsequent days.

Seizures (anticonvulsant): Oral: Initial: Up to 7.5 mg/dose 2-3 times/day; increase dose by 7.5 mg at weekly intervals; not to exceed 90 mg/day

Dosing: ElderlyOral: Anxiety: 7.5 mg 1-2 times/day; use is not recommended in the elderly.

Dosing: Pediatric

Seizures (anticonvulsant): Oral:

Children 9-12 years: Initial: 3.75-7.5 mg/dose twice daily; increase dose by 3.75 mg at weekly intervals, not to exceed 60 mg/day in 2-3 divided doses.

Children >12 years: Refer to adult dosing.

RestrictionsC-IV

ContraindicationsHypersensitivity to clorazepate or any component of the formulation (cross-sensitivity with other benzodiazepines may exist); narrow-angle glaucoma; pregnancy

Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

• Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.

• CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

• Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.

Disease-related concerns:

• Depression: Use caution in patients with depression, particularly if suicidal risk may be present.

• Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

• Hepatic impairment: Use with caution in patients with hepatic impairment.

• Impaired gag reflux: Use with caution in patients with an impaired gag reflux.

• Renal impairment: Use with caution in patients with renal impairment.

• Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; active metabolites with extended half-lives may lead to delayed accumulation and adverse effects.
- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury. Active metabolites with extended half-lives may lead to delayed accumulation and adverse effects.
- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.
- Pediatrics: Safety and efficacy have not been established in children <9 years of age.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.
- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsDue to its long-acting metabolite, clorazepate is not considered a drug of choice in the elderly. Long-acting benzodiazepines have been associated with falls in the elderly. Interpretive guidelines from the Centers for Medicare and Medicaid Services (CMS) discourage the use of this agent in residents of long-term care facilities.
Pregnancy Risk FactorD
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsNo specific data for clorazepate; however, other benzodiazepines have been shown to be excreted in breast milk. Therefore, it is recommended not to nurse while taking clorazepate.
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension

Central nervous system: Drowsiness, fatigue, ataxia, lightheadedness, memory impairment, insomnia, anxiety, headache, depression, slurred speech, confusion, nervousness, dizziness, irritability

Dermatologic: Rash

Endocrine & metabolic: Libido decreased

Gastrointestinal: Xerostomia, constipation, diarrhea, salivation decreased, nausea, vomiting, appetite increased or decreased

Neuromuscular & skeletal: Dysarthria, tremor

Ocular: Blurred vision, diplopia

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Serum concentrations/toxicity may be increased by grapefruit juice.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsDecreased hematocrit; abnormal liver and renal function tests

Monitoring ParametersRespiratory and cardiovascular status, excess CNS depression

Reference RangeTherapeutic: 0.12-1 mcg/mL (SI: 0.36-3.01 µmol/L)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess for CNS depression. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance; periodically evaluate need for continued use. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. Do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); altered sexual drive or ability (reversible); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report persistent CNS effects (eg, confusion, depression, increased sedation, excitation, headache, agitation, insomnia or nightmares, dizziness, fatigue, impaired coordination, changes in personality, or changes in cognition); changes in urinary pattern; muscle cramping, weakness, tremors, or rigidity; ringing in ears or visual disturbances; chest pain, palpitations, or rapid heartbeat; excessive perspiration; excessive GI symptoms (cramping, constipation, vomiting, anorexia); or worsening of condition. **Pregnancy/breast-feeding precautions**: Do not get pregnant while using this medication; use appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as dipotassium: 3.75 mg, 7.5 mg, 15 mg

Tranxene® SD™: 22.5 mg [once daily]

Tranxene® SD™-Half Strength: 11.25 mg [once daily]

Tranxene® T-Tab®: 3.75 mg, 7.5 mg, 15 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Tranxene-SD)

11.25 mg (30): $211.03

22.5 mg (30): $268.78

Tablets (Clorazepate Dipotassium)

3.75 mg (90): $68.00

7.5 mg (90): $83.99

15 mg (90): $113.99

Tablets (Tranxene-T)

3.75 mg (90): $260.58

7.5 mg (90): $308.99

15 mg (90): $435.68

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Onset of action: 1-2 hours

Duration: Variable, 8-24 hours

Distribution: Crosses placenta; appears in urine

Metabolism: Rapidly decarboxylated to desmethyldiazepam (active) in acidic stomach prior to absorption; hepatically to oxazepam (active)

Half-life elimination: Adults: Desmethyldiazepam: 48-96 hours; Oxazepam: 6-8 hours

Time to peak, serum: ~1 hour

Excretion: Primarily urine

Related Information

- Benzodiazepines
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Status Epilepticus
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsAbrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Many patients will experience drowsiness; orthostatic hypotension is possible. It is suggested that narcotic analgesics not be given for pain control to patients taking clorazepate due to enhanced sedation.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Clorazepate is a long half-life benzodiazepine. Duration of action after a single dose is determined by redistribution rather than metabolism. Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include personal or family history of substance abuse and personality disorder.

Anesthesia and Critical Care Concerns/Other ConsiderationsAbrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

Index TermsClorazepate Dipotassium; Tranxene T-Tab®

References

Burkhart KK and Kulig KW, “The Diagnostic Utility of Flumazenil (A Benzodiazepine Antagonist) in Coma of Unknown Etiology,” *Ann Emerg Med*, 1990, 19(3):319-21. [PubMed 2106810]

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

Patel DA and Patel AR, “Clorazepate and Congenital Malformations,” *JAMA*, 1980, 244(2):135-6.

International Brand Names Ansiopax (UY); Ansiospaz (PE); Anxidin (FI); Calner (CN); Cloramed (TH); Cloranxen (PL); Clozene (TW); Dipot (TH); Dorken (ES); Flulium (TH); Manotran (TH); Mendon (JP); Nansius (DO); Pazidium (PY); Pomadom (TH); Sanor (MY); Serene (TH); Tencilan (AR); Trancon (TH); Transene (IT); Tranxen (DK, VE); Tranxene (AE, BB, BE, BH, CY, CZ, EC, EG, FR, GB, GR, HK, HN, IE, IL, IQ, IR, JO, KW, LB, LU, LY, MX, MY, NL, OM, PH, PK, PL, PT, QA, SA, SG, SY, TH, TT, TW, YE); Tranxilene (BR); Tranxilium (AR, AT, CH, DE, ES, PL); Uni-Tranxene (LU); Zetran-5 (TH)

Clotrimazole

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Medication Safety Issues

Sound-alike/look-alike issues:

Clotrimazole may be confused with co-trimoxazole

Lotrimin® may be confused with Lotrisone®, Otrivin®

Mycelex® may be confused with Myoflex®

International issues:

Cloderm®: Brand name for clocortolone in the United States

Canesten® [multiple international markets] may be confused with Cenestin® which is a brand name for estrogens (conjugated a/synthetic) in the U.S.

Canesten® [multiple international markets]: Brand name for fluconazole in Great Britain

Mycelex® may be confused with Mucolex® which is a brand name for carbocysteine in Ireland, Portugal, and Thailand; a brand name for guaifenesin in Hong Kong

Pronunciation(kloe TRIM a zole)

U.S. Brand NamesCruex® Cream [OTC]; Gyne-Lotrimin® 3 [OTC]; Gyne-Lotrimin® 7 [OTC]; Lotrimin® AF Athlete's Foot Cream [OTC]; Lotrimin® AF for Her [OTC]; Lotrimin® AF Jock Itch Cream [OTC]; Mycelex®

Canadian Brand NamesCanesten® Topical; Canesten® Vaginal; Clotrimaderm; Trivagizole-3®

Pharmacologic CategoryAntifungal Agent, Oral Nonabsorbed; Antifungal Agent, Topical; Antifungal Agent, Vaginal

Use: Labeled IndicationsTreatment of susceptible fungal infections, including oropharyngeal candidiasis, dermatophytoses, superficial mycoses, and cutaneous candidiasis, as well as vulvovaginal candidiasis; limited data suggest that clotrimazole troches may be effective for prophylaxis against oropharyngeal candidiasis in neutropenic patients

Use: DentalTreatment of susceptible fungal infections, including oropharyngeal candidiasis; limited data suggests that the use of clotrimazole troches may be effective for prophylaxis against oropharyngeal candidiasis in neutropenic patients

Dosing: Adults

Oropharyngeal candidiasis: Oral:

Prophylaxis: 10 mg troche dissolved 3 times/day for the duration of chemotherapy or until steroids are reduced to maintenance levels

Treatment: 10 mg troche dissolved slowly 5 times/day for 14 consecutive days

Dermatophytosis, cutaneous candidiasis: Topical (cream, solution): Apply twice daily; if no improvement occurs after 4 weeks of therapy, re-evaluate diagnosis.

Vulvovaginal candidiasis: Intravaginal:

Cream (1%): Insert 1 applicatorful of 1% vaginal cream daily (preferably at bedtime) for 7 consecutive days.

Cream (2%): Insert 1 applicatorful of 2% vaginal cream daily (preferably at bedtime) for 3 consecutive days.

Tablet: Insert 100 mg/day for 7 days or 500 mg single dose.

Dermatologic infection (superficial): Topical (cream, solution): Apply to affected area twice daily (morning and evening) for 7 consecutive days.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Oropharyngeal candidiasis: Children >3 years: Refer to adult dosing.

Vaginal, Topical infections: Children >12 years: Refer to adult dosing.

Administration: OralTroche: Allow to dissolve slowly over 15-30 minutes.

Administration: TopicalFor external use only. Apply sparingly. Protect hands with latex gloves. Do not use occlusive dressings.

Administration: OtherAvoid contact with eyes.

ContraindicationsHypersensitivity to clotrimazole or any component of the formulation

Allergy Considerations

- Azole Antifungal Allergy

Warnings/Precautions

Disease-related concerns:

- Systemic fungal infection: Clotrimazole should not be used for treatment of systemic fungal infection.

Special populations:

- Pediatrics: Safety and efficacy of clotrimazole lozenges (troches) have not been established in children <3 years of age.

Dosage form specific issues:

- Topical: When using topical formulation, avoid contact with eyes.

Geriatric ConsiderationsLocalized fungal infections frequently follow broad-spectrum antimicrobial therapy. Specifically, oral and vaginal infections due to *Candida*.

Pregnancy Risk FactorB (topical); C (troches)

LactationExcretion in breast milk unknown

Adverse Reactions

Oral:

>10%: Hepatic: Abnormal liver function tests

1% to 10%:

Gastrointestinal: Nausea and vomiting may occur in patients on clotrimazole troches

Local: Mild burning, irritation, stinging to skin or vaginal area

Vaginal:

1% to 10%: Genitourinary: Vulvar/vaginal burning

<1% (Limited to important or life-threatening): Vulvar itching, soreness, edema, or discharge; polyuria; burning or itching of penis of sexual partner

Oncology: Emetic PotentialVery low (<10%)

Metabolism/Transport Effects**Inhibits** CYP1A2 (weak), 2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak), 3A4 (moderate)

Drug Interactions

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Monitoring ParametersPeriodic liver function tests during oral therapy with clotrimazole troche

Nursing: Physical Assessment/MonitoringMonitor laboratory values, effectiveness of treatment, and adverse reactions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. Assess for opportunistic infection.

Monitoring: Lab TestsPeriodic liver function during oral therapy with clotrimazole troche

Patient Education

Oral (troche): Do not swallow oral medication whole; allow to dissolve slowly in mouth. You may experience nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report signs of opportunistic infection (eg, white plaques in mouth, fever, chills, perianal itching, vaginal itching or discharge, fatigue, unhealed wounds or sores).

Topical: Avoid contact with eyes. Wash hands before applying or wear gloves. Apply thin film to affected area. May apply porous dressing. Report persistent burning, swelling, itching, worsening of condition, or lack of response to therapy.

Vaginal: Wash hands before using. Insert full applicator into vagina gently and expel cream, or insert tablet into vagina, at bedtime. Wash applicator with soap and water following use. Remain lying down for 30 minutes following administration. Avoid intercourse during therapy (sexual partner may experience penile burning or itching). Report adverse reactions (eg, vulvar itching, frequent urination), worsening of condition, or lack of response to therapy. Contact prescriber if symptoms do not improve within 3 days or you do not feel well within 7 days. Do not use tampons until therapy is complete. Contact prescriber immediately if you experience abdominal pain, fever, or foul-smelling discharge.

Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, topical: 1% (15 g, 30 g, 45 g)

Cruex®: 1% (15 g) [contains benzyl alcohol]

Lotrimin® AF Athlete's Foot: 1% (12 g) [contains benzyl alcohol]

Lotrimin® AF Jock Itch: 1% (12 g) [contains benzyl alcohol]

Lotrimin® AF for Her: 1% (24 g) [contains benzyl alcohol]

Cream, topical/vaginal: 1% (45 g)

Gyne-Lotrimin® 7: 1% (45 g) [contains benzyl alcohol; packaged with refillable applicator]

Cream, vaginal: 2% (21 g)

Gyne-Lotrimin® 3: 2% (21 g) [contains benzyl alcohol; packaged with 3 disposable applicators]

Solution, topical: 1% (10 mL, 30 mL)

Tablet, vaginal:

Gyne-Lotrimin® 3: 200 mg (3s) [DSC]

Troche, oral: 10 mg

Mycelex®: 10 mg

Generic AvailableYes: Cream, solution, troche

Pricing: U.S. (www.drugstore.com)

Cream (Clotrimazole)

1% (15): $17.99

1% (30): $42.62

1% (45): $55.75

Solution (Clotrimazole)

1% (10): $17.99

1% (30): $24.99

Troche (Clotrimazole)

10 mg (70): $89.99

Troche (Mycelex)

10 mg (70): $122.98

Mechanism of ActionBinds to phospholipids in the fungal cell membrane altering cell wall permeability resulting in loss of essential intracellular elements

Pharmacodynamics/Kinetics

Absorption: Topical: Negligible through intact skin

Time to peak, serum:

Oral topical (troche): Salivary levels occur within 3 hours following 30 minutes of dissolution time

Vaginal cream: High vaginal levels: 8-24 hours

Vaginal tablet: High vaginal levels: 1-2 days

Excretion: Feces (as metabolites)

Related Information

- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

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Hughes D and Kriedman T, “Treatment of Vulvovaginal Candidiasis With a 500 mg Vaginal Tablet of Clotrimazole,” *Clin Ther*, 1984, 6(5):662-8.[PubMed 6383612]

International Brand NamesAgisten (IL); Altenal (MX); Antifungol (LU); Apocanda (DE); Aristen (HK); Baby Agisten (IL); Canazol (TH); Candazole (MY, SG, TH); Candibene (HU); Candid (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Candid-V3 (TH); Candid-V6 (PH); Candimon (MX); Candinox (TH); Candiva (PH); Candizole (ZA); Canesten (AE, AR, AT, AU, BB, BD, BE, BF, BG, BH, BJ, BM, BO, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PK, PL, PR, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SV, SY, TH, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Canesten 1 (KP); Canesten SD (ID); Canesten VT (ID, SG); Canestene (BE, LU); Canifug (DE); Chingazol (TH); Clocreme (NZ); Cloderm (DE); Clofeme (AU); Clomacinvag (PE); Clomazen (TW); Clomizol (DO); Clonea (AU); Clonitia (ID); Clotrihexal (NZ); Clotrimaderm (IL, NZ); Clotrimazol (MX, PL); Clotrimazolum (PL); Cloxy (PH); Clozol (PE); Clozole Vaginal Cream (AU); Cotren (TH); Covospor (ZA); Dermaten (TH); Dermatin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Empecid (AR, PY); Epicort (CO); Esporex (PE); Factodin (GR); Femizol (AU); Fungicare (IL); Fungicon (TH); Fungiderm (ID); Fungistin (PH); Fungizid-ratiopharm (LU, PL); Gino-Lotrimin (CO); Gixaderm (PH); Gyne Lotremin (ID, MY); Gyne-Lotremin (HK); Gynesol (PH); Gyno Canesten (LU); Gyno-Canesten (CL); Gyno-Canestene (BE); Hexal Clotreme Anti-Fungal Cream (AU); Imazol (DE); Kamicin (HK); Kanezin (TW); Klotrimasool (EE); Krema-Rosa (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Lodirtrem (MX); Lotramina (PE); Lotremin (MY); Lotrimin (CO, MX); Medizol (CO); Micoter (PL); Myco-Hermal (IL, SG, TW); Mycocid (IN); Mycoril (SG, TW); Mycoril Spray (HK); Mycozole (TH); Myoderm-C (TH); Nalbix (PT); Oralten Troche (IL); Pan-Fungex (PT); Panmicol (AR); Plimycol (HR, PL); Sastid Anti-Fungal (SG); SD-Hermal (DE); Sinium (IN); Taraten (TH); Topizol (AU); Trimaze (ZA); Vaff (ID); Vagil C (EC); Vanesten (TH); Yeastazol (PH); Zaloc (MX)

Cloxacillin

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Pronunciation(kloks a SIL in)

Canadian Brand NamesApo-Cloxi®; Cloxacillin; Novo-Cloxin; Nu-Cloxi

Pharmacologic CategoryAntibiotic, Penicillin

Use: Labeled IndicationsTreatment of susceptible bacterial infections, including beta-hemolytic streptococci, pneumococci, and penicillinase-producing staphylococci causing respiratory tract, skin and skin structure, bone and joint, urinary tract infections

Use: DentalTreatment of susceptible orofacial infections (notably penicillinase-producing staphylococci)

Dosing: Adults**Note:** Dose and duration of therapy can vary depending on infecting organism, severity of infection, and clinical response of patient. Treat beta-hemolytic streptococcal infections at least 10 days to prevent the occurrence of rheumatic fever or acute glomerulonephritis. Treat severe staphylococcal infections for at least 14 days; endocarditis and osteomyelitis require an extended duration of therapy

Susceptible infections:

Oral: 250-500 mg every 6 hours (manufacturer recommended maximum adult dose: 6 g/day)

I.M., I.V.: 250-500 mg every 6 hours (manufacturer recommended maximum adult dose: 6 g/day)

Dosing recommendations of World Health Organization unless otherwise noted:

Arthritis (septic), methicillin-sensitive *Staphylococcus aureus* (MSSA) (unlabeled dosing): I.M., I.V.: 2 g every 6 hours for 2-3 weeks; **Note:** Oral therapy of 1 g every 6 hours may be used to complete therapy if parenteral therapy is discontinued prior to 2-3 week duration

Endocarditis (MSSA) (unlabeled dosing): I.V.:

Native valve: 2 g every 4 hours for 6 weeks; give with gentamicin for initial 5 days (Choudri, 2000)

Prosthetic valve: 2 g every 4 hours for 6 weeks; give with gentamicin for 2 weeks and rifampin for 6 weeks (Choudri, 2000)

Osteomyelitis (MSSA) (unlabeled dosing): I.M., I.V.: 2 g every 6 hours for 4-6 weeks (preferred) **or** for a minimum of 14 days, **followed by** 1 g every 6 hours orally to complete 4-6 weeks of therapy

Pneumonia (MSSA) (unlabeled dosing): I.M., I.V.: 1-2 g every 6 hours for 10-14 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Dose and duration of therapy can vary depending on infecting organism, severity of infection, and clinical response of patient. Treat beta-hemolytic streptococcal infections at least 10 days to prevent the occurrence of rheumatic fever or acute glomerulonephritis. Treat severe staphylococcal infections for at least 14 days; endocarditis and osteomyelitis require an extended duration of therapy.

Susceptible infections:

Oral:

Children ≤20 kg: 25-50 mg/kg/day in divided doses every 6 hours

Children >20 kg: Refer to adult dosing.

I.M., I.V.:

Children ≤20 kg: 25-50 mg/kg/day in divided doses every 6 hours; up to 200 mg/kg/day has been used in some studies for severe infections

Children >20 kg: Refer to adult dosing.

Dosing recommendations of World Health Organization unless otherwise noted:

Arthritis (septic), methicillin-sensitive *Staphylococcus aureus* (MSSA) (unlabeled dosing):

Children 2 months to 5 years: I.M., I.V.: 25-50 mg/kg every 4-6 hours given with ceftriaxone until clinical improvement, **followed by** oral therapy: 12.5 mg/kg (maximum: 500 mg) every 6 hours; total duration of therapy 2-3 weeks

Children >5 years: I.M., I.V.: 25-50 mg/kg (maximum: 2 g) every 4-6 hours (maximum daily dose: 12 g/day) until clinical improvement, **followed by** oral therapy: 25 mg/kg (maximum: 500 mg) every 6 hours; total duration of therapy 2-3 weeks

Endocarditis (MSSA) (unlabeled dosing): I.V.: 50 mg/kg (maximum: 2 g) every 4 hours for 6 weeks; give with gentamicin for initial 7 days

Osteomyelitis (MSSA) (unlabeled dosing):

Children 2 months to 5 years: I.M., I.V.: 25-50 mg/kg every 4-6 hours given with ceftriaxone until clinical improvement, **followed by** oral therapy: 12.5 mg/kg (maximum: 500 mg) every 6 hours; total duration of therapy 3-4 weeks

Children >5 years: I.M., I.V.: 25-50 mg/kg (maximum: 2 g) every 4-6 hours (maximum daily dose: 12 g/day) until clinical improvement, **followed by** oral therapy: 25 mg/kg (maximum: 500 mg) every 6 hours; total duration of therapy 3-4 weeks

Pneumonia (MSSA) (unlabeled dosing):

Children 2 months to 5 years: Oral: 25-50 mg/kg (maximum: 2 g) every 6 hours for at least 3 weeks with gentamicin

Children >5 years: I.M., I.V.: 50 mg/kg (maximum: 2 g) every 6 hours for 10-14 days

Dosing: Renal ImpairmentNo dosage adjustment necessary.
Administration: I.M. Administer slowly over 2-4 minutes,
Administration: I.V.

I.V. push: Administer slowly over 2-4 minutes.

I.V. infusion: Administer over 30-40 minutes.

Administration: OralAdminister with water 1 hour before or 2 hours after meals.
Dietary ConsiderationsShould be taken 1 hour before or 2 hours after meals with water.
Storage

Capsule: Store at room temperature not exceeding 25˚C (77˚F).

Powder for injection: Store at controlled room temperature not exceeding 25˚C (77˚F). Upon reconstitution the resulting solution is stable for up to 24 hours at controlled room temperature and 48 hours under refrigeration.

I.V. infusion: **Note:** After reconstitution of powder with appropriate volume of sterile water for injection, the manufacturer suggests further dilution to concentrations of 1-2 mg/ml in a compatible solution (eg, D_5W, NS); solutions are stable for up to 12 hours at controlled room temperature.

Powder for oral solution: Prior to mixing, store powder at room temperature not exceeding 25˚C (77˚F). Refrigerate oral solution after reconstitution; discard after 14 days.

Reconstitution

I.M. injection: Vials should be reconstituted with appropriate volume of SWFI to make a final concentration of 125 mg/mL or 250 mg/mL

I.V. injection: Vials should be reconstituted with appropriate volume of SWFI to make a final concentration of 50 mg/mL or 100 mg/mL

I.V. infusion: Infusion is prepared in 2 stages: Initial reconstitution of powder with appropriate volume of SWFI, followed by dilution to final infusion solution.

Compatibility

Solutions: Stable in NS, LR; **variable stability (consult detailed reference):** D_5W.

Compatibility in syringe: Compatible: chloramphenicol, colistimethate, dimenhydrinate, lidocaine, procaine; **incompatible** with erythromycin, gentamicin, pantoprazole, polymyxin B; **variable (consult detailed reference):** Hydromorphone, kanamycin, lincomycin, streptomycin.

Compatibility when admixed: Compatible: Amikacin, floxacillin, furosemide, heparin, hydrocortisone sodium succinate, potassium chloride; **incompatible** with chlorpromazine, gentamicin.

RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to cloxacillin, other penicillins, cephalosporins, or any component of the formulation
Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- CNS effects: Although not reported with cloxacillin, the transport of penicillins across the blood brain barrier may be enhanced by inflamed meninges or during cardiopulmonary bypass. An increased risk of myoclonia, seizures, or reduced consciousness may be observed in these patients (particularly those with renal failure).

- Hematologic effects: Penicillin use has been associated with hematologic disorders (eg, agranulocytosis, neutropenia, thrombocytopenia) believed to be a hypersensitivity phenomena. Reactions are most often reversible upon discontinuing therapy.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; rate of elimination is reduced.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; high serum levels, particularly in the presence of renal impairment, may increase risk for seizures

Special populations:

- Neonates: May have decreased renal clearance of cloxacillin; frequent evaluation of serum levels and of clinical status for adverse effects as well as frequent dosage adjustments may be necessary in this patient population;

Geriatric ConsiderationsDosage change for renal function is not necessary.
Pregnancy ConsiderationsCloxacillin crosses the placenta and distributes into fetal tissue. In general, penicillins as a class are considered safe for use during pregnancy.
LactationEnters breast milk/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension

Central nervous system: Confusion, fever, lethargy, seizure (high doses and/or renal failure)

Dermatologic: Pruritus, rash, urticaria

Gastrointestinal: Abdominal pain, black or hairy tongue, diarrhea, flatulence, nausea, oral candidiasis, pseudomembranous colitis, stomatitis, vomiting

Hematologic: Agranulocytosis, bone marrow depression, eosinophilia, granulocytopenia, hemolytic anemia, leukopenia, neutropenia, thrombocytopenia

Hepatic: Alkaline phosphatase increased, ALT increased, AST increased, hepatotoxicity

Local: Thrombophlebitis

Neuromuscular & skeletal: Arthralgia, myalgia, myoclonus

Renal: Hematuria, interstitial nephritis, proteinuria, renal insufficiency, renal tubular damage

Respiratory: Bronchospasm, laryngeal edema, laryngospasm, sneezing, wheezing

Miscellaneous: Anaphylaxis, angioedema, allergic reaction, serum sickness-like reaction

Drug Interactions

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Decreases cloxacillin absorption; serum levels are reduced by ~50%.
Test InteractionsMay interfere with urinary glucose tests using cupric sulfate (Benedict's solution, Clinitest®); may inactivate aminoglycosides *in vitro*; false-positive urine and serum proteins; false-positive in uric acid, urinary steroids
Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose; CBC with differential (prior to initiating therapy and weekly thereafter), periodic BUN, creatinine, hepatic function
Monitoring: Lab TestsCBC with differential (prior to initiating therapy and weekly thereafter), periodic BUN, creatinine, hepatic function
Patient EducationReport persistent diarrhea.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as sodium: 250 mg, 500 mg [not available in the U.S.]

Injection, powder for reconstitution: 250 mg, 500 mg, 1000 mg, 2000 mg [not available in the U.S.]

Powder for suspension, oral, as sodium: 125 mg/5 mL (60 mL, 100 mL, 200 mL) [not available in the U.S.]

Generic AvailableYes
Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.
Pharmacodynamics/Kinetics

Absorption: Oral: ~50%; reduced by food

Distribution: Widely to most body fluids and bone; penetration into cells, into eye, and across normal meninges is poor; crosses placenta; enters breast milk; inflammation increases amount that crosses blood-brain barrier

Protein binding: ~94% (primarily albumin)

Metabolism: Extensively hepatic to active and inactive metabolites

Half-life elimination: 0.5-1.5 hours; prolonged with renal impairment and in neonates

Time to peak, serum: ~1 hour

Excretion: Urine and feces

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Prolonged use of penicillins may lead to development of oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusPenicillins have been reported to cause apprehension, illusions, agitation, insomnia, depersonalization, and encephalopathy

Mental Health: Effects on Psychiatric TreatmentRare reports of agranulocytosis; use caution with clozapine and carbamazepine

Index TermsCloxacillin Sodium

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International Brand NamesAmpiclox (NL); An Mei Lin (CL); Anaclosil (ES); Bioclox (IN); Caxin (PH); Cloxam (TH); Cloxcin (HK); Cloxgen (TH); Cloxillin (MY); Cloxomed (TW); Corbin (TH); Ekvacillin (NO, SE); Encloxil (PH); Eraclox (PH); Isoxacillin (MY); K-Cil (TH); Klox (IN); Lidoxin (SG); Loxzalin (TH); Meikam (ID); Monoclox (HK, MY, SG); Orbenil (IL); Orbenin (AE, BB, BD, BF, BH, BJ, BM, BS, BZ, CI, CL, CY, EG, ET, GH, GM, GN, GY, HK, ID, IE, IL, IN, IQ, IR, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PH, PK, PR, QA, SA, SC, SD, SG, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Orbenine (FR); Pannox (PH); Penstapho N (BE); Prostafilina A (PE); Prostafilina-A (CO); Prostaphlin-A (HK, PH, TW); Secloxin (PH); Staflocil (FI); Syntarpen (PL); Vaclox (TH); Vamcloxil (PH)

Clozapine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

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Medication Safety Issues

Sound-alike/look-alike issues:

Clozapine may be confused with clofazimine, clonidine, Klonopin®

Clozaril® may be confused with Clinoril®, Colazal®

Pronunciation(KLOE za peen)

U.S. Brand NamesClozaril®; FazaClo®

Canadian Brand NamesApo-Clozapine®; Clozaril®; Gen-Clozapine; PMS-Clozapine

Pharmacologic CategoryAntipsychotic Agent, Atypical

Use: Labeled IndicationsTreatment-refractory schizophrenia; to reduce risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder

Use: Unlabeled/InvestigationalSchizoaffective disorder, bipolar disorder, childhood psychosis, severe obsessive-compulsive disorder; psychosis/agitation related to Alzheimer's dementia

Dosing: Adults

Schizophrenia: Initial: 12.5 mg once or twice daily; increased, as tolerated, in increments of 25-50 mg/day to a target dose of 300-450 mg/day after 2-4 weeks; may require doses as high as 600-900 mg/day

Reduce risk of suicidal behavior: Initial: 12.5 mg once or twice daily; increased, as tolerated, in increments of 25-50 mg/day to a target dose of 300-450 mg/day after 2-4 weeks; median dose is ~300 mg/day (range: 12.5-900 mg)

Termination of therapy: If dosing is interrupted for ≥48 hours, therapy must be reinitiated at 12.5-25 mg/day; may be increased more rapidly than with initial titration, unless cardiopulmonary arrest occurred during initial titration.

In the event of planned termination of clozapine, gradual reduction in dose over a 1- to 2-week period is recommended. If conditions warrant abrupt discontinuation (leukopenia), monitor patient for psychosis and cholinergic rebound (headache, nausea, vomiting, diarrhea).

Patients discontinued on clozapine therapy due to WBC <2000/mm^3 or ANC <1000/mm^3 should not be restarted on clozapine.

Dosing: ElderlyOral: Experience in the elderly is limited; initial dose should be 25 mg/day; increase as tolerated by 25 mg/day to desired response. Maximum daily dose in the elderly should probably be 450 mg. Dose titration to 300-450 mg/day may be attained in 2 weeks if tolerated; however, elderly may require slower titration and daily increases may not be tolerated.

Psychosis/agitation related to Alzheimer’s dementia (unlabeled use): Initial: 12.5 mg/day; if necessary, gradually increase as tolerated not to exceed 75-100 mg/day

Dosing: PediatricChildren and Adolescents: Childhood psychosis (unlabeled use): Oral: Initial: 25 mg/day; increase to a target dose of 25-400 mg/day

Dosing: Adjustment for Toxicity

Moderate leukopenia or granulocytopenia (WBC <3000/mm^3 and/or ANC <1500/mm^3): Discontinue therapy; may rechallenge patient when WBC is >3500/mm^3 and ANC is >2000/mm^3. **Note:** Patient is at greater risk for developing agranulocytosis.

Severe leukopenia or granulocytopenia (WBC <2000/mm^3 and/or ANC <1000/mm^3): Discontinue therapy and do not rechallenge patient.

Calculations

- ANC: Absolute Neutrophil Count

Administration: OralOrally-disintegrating tablet: Should be removed from foil blister by peeling apart (do not push tablet through the foil). Remove immediately prior to use. Place tablet in mouth and allow to dissolve; swallow with saliva. If dosing requires splitting tablet, throw unused portion away.

Dietary ConsiderationsMay be taken without regard to food. Fazaclo™ contains phenylalanine 0.87 mg per 12.5 mg tablet, phenylalanine 1.74 mg per 25 mg tablet, and phenylalanine 6.96 mg per 100 mg tablet.

StorageDispensed in “clozapine patient system” packaging. Store at controlled room temperature. FazaClo™: Protect from moisture; do not remove from package until ready to use.

RestrictionsPatient-specific registration is required to dispense clozapine. Monitoring systems for individual clozapine manufacturers are independent. If a patient is switched from one brand/manufacturer of clozapine to another, the patient must be entered into a new registry (must be completed by the prescriber and delivered to the dispensing pharmacy). Healthcare providers, including pharmacists dispensing clozapine, should verify the patient's hematological status and qualification to receive clozapine with all existing registries. The manufacturer of Clozaril® requests that healthcare providers submit all WBC/ANC values following discontinuation of therapy to the Clozaril National Registry for all nonrechallengable patients until WBC is ≥3500/mm^3 and ANC is ≥2000/mm^3.

ContraindicationsHypersensitivity to clozapine or any component of the formulation; history of agranulocytosis or granulocytopenia with clozapine; uncontrolled epilepsy, severe central nervous system depression or comatose state; paralytic ileus; myeloproliferative disorders or use with other agents which have a well-known risk of agranulocytosis or bone marrow suppression

Warnings/Precautions

Boxed warnings:

- Agranulocytosis: See “Concerns related to adverse effects” below.
- Cardiovascular events: See “Concerns related to adverse effects” below.
- Dementia: See “Disease-related concerns” below.
- Orthostatic hypotension: See “Concerns related to adverse effects” below.
- Seizures: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Agranulocytosis: **[U.S. Boxed Warning]: Significant risk of agranulocytosis, potentially life-threatening.** Therapy should not be initiated in patients with WBC <3500 cells/mm^3 or ANC <2000 cells/mm^3 or history of myeloproliferative disorder. WBC testing should occur periodically on an on-going basis (see prescribing information for monitoring details) to ensure that acceptable WBC/ANC counts are maintained. Initial episodes of moderate leukopenia or granulopoietic suppression confer up to a 12-fold increased risk for subsequent episodes of agranulocytosis. WBCs must be monitored weekly for at least 4 weeks after therapy discontinuation or until WBC is ≥3500/mm^3 and ANC is ≥2000/mm^3. Use with caution in patients receiving other marrow suppressive agents. Eosinophilia has been reported to occur with clozapine and may require temporary or permanent interruption of therapy. Due to the significant risk of agranulocytosis, it is strongly recommended that a patient must fail at least two trials of other primary medications for the treatment of schizophrenia (of adequate dose and duration) before initiating therapy with clozapine.
- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems.
- Cardiovascular events: Myocarditis, pericarditis, pericardial effusion, cardiomyopathy, and HF have also been associated with clozapine. **[U.S. Boxed Warning]: Fatalities due to myocarditis have been reported; highest risk in the first month of therapy, however, later cases also**

reported. Myocarditis or cardiomyopathy should be considered in patients who present with signs/symptoms of heart failure (dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema), chest pain, palpitations, new electrocardiographic abnormalities (arrhythmias, ST-T wave abnormalities), or unexplained fever. Patients with tachycardia during the first month of therapy should be closely monitored for other signs of myocarditis. Discontinue clozapine if myocarditis is suspected; do not rechallenge in patients with clozapine-related myocarditis. The reported rate of myocarditis in clozapine-treated patients appears to be 17-322 times greater than in the general population. Clozapine should be discontinued in patients with confirmed cardiomyopathy unless benefit clearly outweighs risk.

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is generally much lower relative to typical/conventional antipsychotics). Risk of dystonia (and probably other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Hyperglycemia: Atypical antipsychotics have been associated with development of hyperglycemia; in some cases, may be extreme and associated with ketoacidosis, hyperosmolar coma, or death. Use with caution in patients with diabetes or other disorders of glucose regulation; monitor for worsening of glucose control.

- Neuroleptic malignant syndrome (NMS): Use may be associated with neuroleptic malignant syndrome (NMS); monitor for mental status changes, fever, muscle rigidity and/or autonomic instability.

- Orthostatic hypotension: **[U.S. Boxed Warning]: May cause orthostatic hypotension (with or without syncope) and tachycardia;** use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May be moderate to highly sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). Use with caution in patients receiving general anesthesia.

- Seizures: **[U.S. Boxed Warning]: Seizures have been associated with clozapine use in a dose-dependent manner;** use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold. Elderly patients may be at increased risk of seizures due to an increased prevalence of predisposing factors.

- Suicidal ideation: The possibility of a suicide attempt is inherent in psychotic illness or bipolar disorder; use with caution in high-risk patients during initiation of therapy. Prescriptions should be written for the smallest quantity consistent with good patient care.

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

- Thromboembolism: Rare cases of thromboembolism, including pulmonary embolism and stroke resulting in fatalities, have been associated with clozapine in patients with cardiovascular disease.

- Weight gain: Significant weight gain has been observed with antipsychotic therapy; incidence varies with product. Monitor waist circumference and BMI.

Disease-related concerns:

- Dementia: **[U.S. Boxed Warning]: Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo.** An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Clozapine is not approved for this indication.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with hepatic disease or impairment; hepatitis has been reported as a consequence of therapy.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Benzodiazepines: Concurrent use with benzodiazepines may increase the risk of severe cardiopulmonary reactions.

Special populations:

- Elderly: The elderly are more susceptible to adverse effects (including agranulocytosis, cardiovascular, anticholinergic, and tardive dyskinesia).

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt discontinuation: Medication should not be stopped abruptly; taper off over 1-2 weeks. If conditions warrant abrupt discontinuation (leukopenia, myocarditis, cardiomyopathy), monitor patient for psychosis and cholinergic rebound (headache, nausea, vomiting, diarrhea).

Cigarette smoking may enhance the metabolism of clozapine.

Geriatric ConsiderationsNot recommended for use in nonpsychotic patients (eg, dimentia-related psychotic symptoms). Studies in subjects >65 years of age have not been done. Orthostatic hypotension and sustained tachycardia have been noted in up to 25% of patients taking clozapine; therefore, elderly with cardiovascular disease may be at risk. The anticholinergic effects of clozapine may be prominent in elderly (eg, constipation, confusion, urinary retention).

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not seen in animal studies; however, there are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed. Healthcare providers are encouraged to enroll women 18-45 years of age exposed to clozapine during pregnancy in the Atypical Antipsychotics Pregnancy Registry (1-866-961-2388).

LactationEnters breast milk/not recommended (AAP rates “of concern”)

Adverse Reactions

>10%:

Cardiovascular: Tachycardia (25%)

Central nervous system: Drowsiness (39% to 46%), dizziness (19% to 27%), insomnia (2% to 20%)

Gastrointestinal: Constipation (14% to 25%), weight gain (4% to 31%), sialorrhea (31% to 48%), nausea/vomiting (3% to 17%)

1% to 10%:

Cardiovascular: Angina (1%), ECG changes (1%), hypertension (4%), hypotension (9%), syncope (6%)

Central nervous system: Akathisia (3%), seizure (3%), headache (7%), nightmares (4%), akinesia (4%), confusion (3%), myoclonic jerks (1%), restlessness (4%), agitation (4%), lethargy (1%), ataxia (1%), slurred speech (1%), depression (1%), anxiety (1%)

Dermatologic: Rash (2%)

Gastrointestinal: Abdominal discomfort/heartburn (4% to 14%), anorexia (1%), diarrhea (2%), xerostomia (6%), throat discomfort (1%)

Genitourinary: Urinary abnormalities (eg, abnormal ejaculation, retention, urgency, incontinence; 1% to 2%)

Hematologic: Eosinophilia (1%), leukopenia, leukocytosis, agranulocytosis (1%)

Hepatic: Liver function tests abnormal (1%)

Neuromuscular & skeletal: Tremor (6%), hypokinesia (4%), rigidity (3%), hyperkinesia (1%), weakness (1%), pain (1%), spasm (1%)

Ocular: Visual disturbances (5%)

Respiratory: Dyspnea (1%), nasal congestion (1%)

Miscellaneous: Diaphoresis increased, fever, tongue numbness (1%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Amentia, amnesia, anemia, arrhythmia (atrial or ventricular), aspiration, blurred vision, bradycardia, bronchitis, cardiomyopathy (usually dilated), cataplexy, CHF, cholestasis, cyanosis, delusions, diabetes mellitus, difficult urination, edema, erythema multiforme, ESR increased, fecal impaction, gastroenteritis, granulocytopenia, hallucinations, hematemesis, hepatitis, hypercholesterolemia (rare), hyperglycemia, hypertriglyceridemia (rare), hyponatremia, hypothermia, impotence, interstitial nephritis (acute), intestinal obstruction, jaundice, loss of speech, MI, myasthenia syndrome, myocarditis, narrow-angle glaucoma, neuroleptic malignant syndrome, palpitations, pancreatitis (acute), paralytic ileus, Parkinsonism, pericardial effusion, pericarditis, phlebitis, pleural effusion, pneumonia, priapism, pulmonary embolism, rhabdomyolysis, rectal bleeding, salivary gland swelling, sepsis, status epilepticus, stroke, Stevens-Johnson syndrome, tardive dyskinesia, thrombocytopenia, thrombocytosis, thromboembolism, thrombophlebitis, vasculitis, wheezing

Metabolism/Transport Effects**Substrate** of CYP1A2 (major), 2A6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2C19 (weak), 2D6 (moderate), 2E1 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Atypical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Benzodiazepines: May enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Clozapine. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Clozapine. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nefazodone: May decrease the metabolism of Clozapine. *Risk C: Monitor therapy*

Omeprazole: May decrease the serum concentration of Clozapine. Omeprazole may increase the serum concentration of Clozapine. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Clozapine. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: St John's wort may decrease clozapine levels. Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Monitoring ParametersMental status, ECG, WBC (see below), vital signs, fasting lipid profile and fasting blood glucose/Hgb A_{1c} (prior to treatment, at 3 months, then annually; BMI, personal/family history of obesity; waist circumference (weight should be assessed prior to treatment, at 4 weeks, 8 weeks, 12 weeks, and then at quarterly intervals. Consider titrating to a different antipsychotic agent for a weight gain ≥5% of the initial weight); blood pressure; abnormal involuntary movement scale (AIMS).

WBC and ANC should be obtained at baseline and at least weekly for the first 6 months of continuous treatment. If counts remain acceptable (WBC ≥3500/mm^3, ANC ≥2000/mm^3) during this time period, then they may be monitored every other week for the next 6 months. If WBC/ANC continue to remain within these acceptable limits after the second 6 months of therapy, monitoring can be decreased to every 4 weeks. (**Note**: The decrease in monitoring to every 4 weeks is applicable in the United States. Blood monitoring requirements related to the use of clozapine have not changed in Canada). If clozapine is discontinued, a weekly WBC should be conducted for an additional 4 weeks or until WBC is ≥3500/mm^3 and ANC is ≥2000/mm^3. If clozapine therapy is interrupted due to moderate leukopenia, weekly WBC/ANC monitoring is required for 12 months in patients restarted on clozapine treatment. If therapy is interrupted for reasons other than leukopenia/granulocytopenia, the 6-month time period for initiation of biweekly WBCs may need to be reset. This determination depends upon the treatment duration, the length of the break in therapy, and whether or not an abnormal blood event occurred.

Consult full prescribing information for determination of appropriate WBC/ANC monitoring interval (http://www.clozaril.com/index.jsp).

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Initiate at lower doses and taper dosage slowly when discontinuing. Instruct patients with diabetes to monitor blood glucose levels closely (may cause hyperglycemia). Be alert to the potential of cardiac abnormalities. Monitor weight prior to initiating therapy and at least monthly. Consider titrating to a different antipsychotic agent for a weight gain ≥5% of initial weight. Review ophthalmic exam periodically and assess results of weekly laboratory tests. Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate administration, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsECG; WBC (see below), fasting lipid profile and fasting blood glucose/Hgb A_{1c} (prior to treatment, at 3 months, then annually; BMI, personal/family history of obesity; waist circumference (weight should be assessed prior to treatment, at 4 weeks, 8 weeks, 12 weeks, and then at quarterly intervals.

WBC and ANC should be obtained at baseline and at least weekly for the first 6 months of continuous treatment. If counts remain acceptable (WBC ≥3500/mm^3, ANC ≥2000/mm^3) during this time period, then they may be monitored every other week for the next 6 months. If WBC/ANC continue to remain within these acceptable limits after the second 6 months of therapy, monitoring can be decreased to every 4 weeks. (**Note**: The decrease in monitoring to every 4 weeks is applicable in the United States. Blood monitoring requirements related to the use of clozapine have not changed in Canada). If clozapine is discontinued, a weekly WBC should be conducted for an additional 4 weeks or until WBC is ≥3500/mm^3 and ANC is ≥2000/mm^3. If clozapine therapy is interrupted due to moderate leukopenia, weekly WBC/ANC monitoring is required for 12 months in patients restarted on clozapine treatment. If therapy is interrupted for reasons other than leukopenia/granulocytopenia, the 6-month time period for initiation of biweekly WBCs may need to be reset. This determination depends upon the treatment duration, the length

of the break in therapy, and whether or not an abnormal blood event occurred.

Consult full prescribing information for determination of appropriate WBC/ANC monitoring interval (http://www.clozaril.com/index.jsp).

Patient EducationUse exactly as directed; do not increase dose or frequency. Do not discontinue this medication without consulting prescriber. Avoid alcohol or caffeine and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, monitor blood glucose levels frequently. You may experience headache, excess drowsiness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); constipation, diarrhea; dry mouth, nausea, vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing). You may be prone to infections; report fever, sore throat or other possible signs of infection. Report persistent CNS effects (insomnia, depression, altered consciousness); palpitations, rapid heartbeat, severe dizziness; vision changes; hypersalivation, tearing, sweating; respiratory difficulty; or worsening of condition. Report seizures, flu-like symptoms, chest pain, shortness of breath, or excessive fatigue. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 25 mg, 50 mg, 100 mg, 200 mg

Clozaril®: 25 mg [scored], 100 mg [scored]

Tablet, orally disintegrating:

FazaClo®: 12.5 mg [contains phenylalanine 0.87 mg/tablet; mint flavor], 25 mg [contains phenylalanine 1.74 mg/tablet; mint flavor], 100 mg [contains phenylalanine 6.96 mg/tablet; mint flavor]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Clozapine)

25 mg (60): $42.99

100 mg (60): $101.98

Mechanism of ActionClozapine (dibenzodiazepine antipsychotic) exhibits weak antagonism of D_1, D_2, D_3, and D_5 dopamine receptor subtypes, but shows high affinity for D_4; in addition, it blocks the serotonin ($5HT_2$), alpha-adrenergic, histamine H_1, and cholinergic receptors

Pharmacodynamics/Kinetics

Protein binding: 97% to serum proteins

Metabolism: Extensively hepatic; forms metabolites with limited or no activity

Bioavailability: 12% to 81% (not affected by food)

Half-life elimination: Steady state: 12 hours (range: 4-66 hours)

Time to peak: 2.5 hours (range: 1-6 hours)

Excretion: Urine (~50%) and feces (30%) with trace amounts of unchanged drug

Related Information

- Antipsychotic Agents
- Antipsychotic Receptor Profile
- Atypical Antipsychotics
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Sialorrhea and xerostomia (normal salivary flow resumes upon discontinuation). Many patients may experience orthostatic hypotension with clozapine; precautions should be taken; do not use atropine-like drugs for xerostomia in patients taking clozapine due to significant potentiation.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsMost pharmacology textbooks state that in presence of phenothiazines, systemic doses of epinephrine paradoxically decrease the blood pressure. This is the so called “epinephrine reversal” phenomenon. This has never been observed when epinephrine is given by infiltration as part of the local anesthesia procedure.

Mental Health: Child/Adolescent ConsiderationsEleven adolescents with childhood-onset schizophrenia who failed a 6-week trial of haloperidol were treated with clozapine (mean 6-week daily dose: 370 mg) (Frazier, 1994). Twenty-one patients (mean age: 14 ± 2.3 years) with schizophrenia (DSM-III-R) who had been nonresponsive to typical antipsychotics received clozapine 176 ± 149 mg/day (final dose) (Kumra, 1996). Clozapine was evaluated in 11 neuroleptic-resistant children (<13 years of age) mean dosage: 227 mg/day (Turetz, 1997). A 15-year old boy with severe treatment-refractory bipolar disorder type I was treated successfully with clozapine 300 mg/day (Masi, 1998).

Frazier JA, Gordon CT, McKenna K, et al, “An Open Trial of Clozapine in 11 Adolescents With Childhood-Onset Schizophrenia,” *J Am Acad Child Adolesc Psychiatry*, 1994, 33(5):658-63.

Kumra S, Frazier JA, Jacobsen LK, et al, “Childhood-Onset Schizophrenia. A Double-Blind Clozapine-Haloperidol Comparison,” *Arch Gen Psychiatry*, 1996, 53(12):1090-7.

Kumra S, Oberstar JV, Sikich L, et al, “Efficacy and Tolerability of Second-Generation Antipsychotics in Children and Adolescents With Schizophrenia,” *Schizophr Bull*, 2008, 34(1):60-71.

Masi G and Milone A, “Clozapine Treatment in an Adolescent With Bipolar Disorder,” *Panminerva Med*, 1998, 40(3):254-7.

Turetz M, Mozes T, Toren P, et al, “An Open Trial of Clozapine in Neuroleptic-Resistant Childhood-Onset Schizophrenia,” *Br J Psychiatry*, 1997, 170:507-10.

Mental Health Comment

Clozapine is the prototype drug from the antipsychotic class often referred to as atypical. It should be noted that the definition of the term “atypical” is not universally agreed upon. Some prefer to describe antipsychotics based on their pharmacological properties. A common feature of all definitions used to describe “atypical” antipsychotics is the lack of significant acute or subacute EPS, at dosages generally associated with antipsychotic actions. Other experts have included definitions of atypicality that include a) failure to increase serum prolactin levels; b) superior efficacy for positive, negative, and cognitive symptoms; and c) lack of evidence of tardive dyskinesia or dystonia following chronic administration. Clozapine meets all of these criteria and therefore is considered the standard by which other atypical antipsychotics should be compared.

Recently, questions have been raised about its ability (as well as other atypical antipsychotics) to differentiate itself on negative symptom improvement. However, clozapine is considered the drug of choice for treating refractory schizophrenia. Refractory illness is often defined by “Kane” criteria in which patients have failed to respond to at least two antipsychotics from different chemical classes at 1000 mg of chlorpromazine or its equivalent (Kane, 1988).

In a recent trial, clozapine therapy demonstrated superiority over olanzapine therapy in preventing suicide attempts in patients with schizophrenia and schizoaffective disorder at high risk for suicide (Meltzer, 2003). The authors concluded that the use of clozapine for 2 years in this population should lead to a significant reduction in suicidal behavior.

Tardive dyskinesia (TD) secondary to **typical** antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. The incidence of TD associated with the atypical antipsychotics is estimated to be 0.5% to 1%. It is not clear if this estimate represents a risk associated with mental illness or to what extent drug therapy can be implicated. Clozapine appears less likely to cause tardive dyskinesia than typical antipsychotics (fluphenazine, haloperidol), but is generally associated with more weight gain and metabolic abnormalities such as diabetes.

Dose-dependent side effects associated with clozapine include seizures, tachycardia, and sedation.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Kane J, Honigfeld G, Singer J, et al, “Clozapine for the Treatment-Resistant Schizophrenic. A Double-Blind Comparison With Chlorpromazine,” *Arch Gen Psychiatry*, 1988, 45(9):789-96.

Meltzer HY, Alphs L, Green AI, et al, “Clozapine Treatment for Suicidality in Schizophrenia: International Suicide Prevention Trial (InterSePT),” *Arch Gen Psychiatry*, 2003, 60(1):82-91.

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Masi G and Milone A, “Clozapine Treatment in an Adolescent With Bipolar Disorder,” *Panminerva Med*, 1998, 40(3):254-7. [PubMed 9785928]

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Wolf LR, and Otten EJ, “A Case Report of Clozapine Overdose,” *Vet Hum Toxicol*, 1991, 33:370.

International Brand NamesClocinol (PL); Clopin (CH); Clopine (AU, TW); Clopsine (MX); Cloril (TH); Clozamed (TH); Clozapine (PL); Clozaril (AU, GB, HK, ID, IE, KP, MY, PK, TH); Denzapine (GB, IE); Elcrit (DE); Klozapol (PL); Lapenax (AR); Leponex (AE, AT, BE, BG, BH, BR, CH, CN, CO, CY, CZ, DE, DK, EE, EG, ES, FI, FR, GR, HN, IL, IQ, IR, IT, JO, KW, LB, LY, MX, NL, NO, OM, PE, PH, PL, PT, QA, SA, SE, SY, TR, UY, VE, YE); Lozapin (IN); Lozapine (IL); Sizopin (IN); Sizoril (ID); Zapen (CO); Zapine (TW); Ziproc (PH)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

Regimen

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Methotrexate: I.V.: 40 mg/m^2 day 1

[total dose/cycle = 40 mg/m^2]

Fluorouracil: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 21 or 28 days

References

Bonadonna G, Veronesi U, Brambilla C, et al, “Primary Chemotherapy to Avoid Mastectomy in Tumors With Diameters of Three Centimeters or More,” *J Natl Cancer Inst*, 1990, 82(19):1539-45. [PubMed 2402015]

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CMF

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Methotrexate: I.V.: 40 mg/m^2/day days 1 and 8

[total dose/cycle = 80 mg/m^2]

Fluorouracil: I.V.: 600 mg/m^2/day days 1 and 8

[total dose/cycle = 1200 mg/m^2]

Cyclophosphamide: Oral: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Repeat cycle every 28 days

Variation 2 (>60 years of age):

Methotrexate: I.V.: 30 mg/m^2/day days 1 and 8

[total dose/cycle = 60 mg/m^2]

Fluorouracil: I.V.: 400 mg/m^2/day days 1 and 8

[total dose/cycle = 800 mg/m^2]

Cyclophosphamide: Oral: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Repeat cycle every 28 days

References

Variations 1 and 2:

Bonadonna G, Brusamolino E, Valagussa P, et al, "Combination Chemotherapy as an Adjuvant Treatment in Operable Breast Cancer," *N Engl J Med*, 1976, 294(8):405-10. [PubMed 1246307]

Canellos GP, Pocock SJ, Taylor SG III, et al, "Combination Chemotherapy for Metastatic Breast Carcinoma, Prospective Comparison of Multiple Drug Therapy With L-Phenylalanine Mustard," *Cancer*, 1976, 38(5):1882-6.[PubMed 991103]

CMFP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Breast Cancer]

Regimen UseBreast cancer

Regimen

Cyclophosphamide: Oral: 100 mg/m^2/day days 1 to 14

[total dose = 1400 mg/m^2]

Methotrexate: I.V.: 30 or 40 mg/m^2/day days 1 and 8

[total dose = 60 or 80 mg/m^2]

Fluorouracil: I.V.: 400 or 600 mg/m^2/day days 1 and 8

[total dose = 800 or 1200 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14

[total dose = 560 mg/m^2]

Repeat cycle every 28 days

References

Marschke RF Jr, Ingle JN, Schaid DJ, et al, âRandomized Clinical Trial of CFP Versus CMFP in Women With Metastatic Breast Cancer,â *Cancer*, 1989, 63(10):1931-7.[PubMed 2649221]

CMFVP (Cooper Regimen, VPCMF)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer

Regimen Use Breast cancer

Regimen

Cyclophosphamide: Oral: 2 mg/kg/day days 1 to 252

[total dose/cycle = 504 mg/kg]

Methotrexate: I.V.: 0.7 mg/kg day 1, weeks 1 to 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, and 36

[total dose/cycle = 15.4 mg/kg]

Fluorouracil: I.V.: 12 mg/kg day 1, weeks 1 to 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, and 36

[total dose/cycle = 264 mg/kg]

Vincristine: I.V.: 0.035 mg/kg (maximum 2 mg) day 1, weeks 1 to 5, 8, 12, 16, 20, 24, 28, 32, and 36

[total dose/cycle = 0.455 mg/kg]

Prednisone: Oral: 0.75 mg/kg/day days 1 to 10, taper off over next 40 days

Administer one cycle only

References

Cooper RG, Holland JF, and Glidewell O, “Adjuvant Chemotherapy of Breast Cancer,” *Cancer*, 1979, 44(3):793-8.[PubMed 476594]

CMV

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Bladder Cancer]

Regimen UseBladder cancer

Regimen

Cisplatin: I.V.: 100 mg/m^2 infused over 4 hours (start at least 12 hours after methotrexate) day 2

[total dose = 100 mg/m^2]

Methotrexate: I.V.: 30 mg/m^2/day days 1 and 8

[total dose = 60 mg/m^2]

Vinblastine: I.V.: 4 mg/m^2/day days 1 and 8

[total dose = 8 mg/m^2]

Repeat cycle every 21 days

References

Harker WG, Meyers FJ, Freiha FS, et al, âCisplatin, Methotrexate, and Vinblastine (CMV): An Effective Chemotherapy Regimen for Metastatic Transitional Cell Carcinoma of the Urinary Tract. A Northern California Oncology Group Study,â *J Clin Oncol*, 1985, 3(11):1463-70.[PubMed 4056840]

CNF

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

Index TermsCFM; FNC

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cyclophosphamide: I.V.: 500 mg/m^2 day 1

[total dose/cycle = 500 mg/m^2]

Mitoxantrone: I.V.: 10 mg/m^2 day 1

[total dose/cycle = 10 mg/m^2]

Fluorouracil: I.V.: 500 mg/m^2 day 1

[total dose/cycle = 500 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Cyclophosphamide: I.V.: 500-600 mg/m^2 day 1

[total dose/cycle = 500-600 mg/m^2]

Fluorouracil: I.V.: 500-600 mg/m^2 day 1

[total dose/cycle = 500-600 mg/m^2]

Mitoxantrone: I.V.: 10-12 mg/m^2 day 1

[total dose/cycle = 10-12 mg/m^2]

Repeat cycle every 21 days

References

Variation 1:

Bennett JM, Muss HB, Doroshow JH, et al, “A Randomized Multicenter Trial Comparing Mitixantrone, Cyclophosphamide, and Fluorouracil With Doxorubicin, Cyclophosphamide, and Fluorouracil in the Therapy of Metastatic Breast Carcinoma,” *J Clin Oncol*, 1988, 6(10):1611-20. [PubMed 3049953]

Variation 2:

Alonso MC, Tabernero JM, Ojeda B, “A Phase III Randomized Trial of Cyclophosphamide, Mitoxantrone, and 5-Fluorouracil (CNF) Versus Cyclophosphamide, Adriamycin®, and 5-Fluorouracil (CAF) in Patients With Metastatic Breast Cancer,” *Breast Cancer Res Treat*, 1995, 34(1):15-24. [PubMed 7749156]

Casciato DA and Lowitz BB, eds, *Manual of Clinical Oncology*, 3rd ed, Boston, MA: Little, Brown, 1995, 596.

CNOP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's

Regimen

Cyclophosphamide: I.V.: 750 mg/m^2 day 1

[total dose/cycle = 750 mg/m^2]

Mitoxantrone: I.V.: 10 mg/m^2 day 1

[total dose/cycle = 10 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 day 1

[total dose/cycle = 1.4 mg/m^2]

Prednisone: Oral: 50 mg/m^2/day days 1 to 5

[total dose/cycle = 250 mg/m^2]

Repeat cycle every 21 days

References

Pavlovsky S, Santarelli MT, Erazo A, et al, âResults of a Randomized Study of Previously Untreated Intermediate and High Grade Lymphoma Using CHOP Versus CNOP,â *Ann Oncol*, 1992, 3(3):205-9.[PubMed 1586618]

CO

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Retinoblastoma

Regimen UseRetinoblastoma

Regimen

Cyclophosphamide: I.V.: 10 mg/kg/day days 1, 2, and 3

[total dose/cycle = 30 mg/kg]

Vincristine: I.V.: 1.5 mg/m^2 day 1

[total dose/cycle = 1.5 mg/m^2]

Repeat cycle every 21 days

References

Doz F, Khelfaoui F, Mosseri V, et al, âThe Role of Chemotherapy in Orbital Involvement of Retinoblastoma. The Experience of a Single Institution With 33 Patients,â *Cancer*, 1994, 74(2):722-32.[PubMed 8033054]

Coal Tar and Salicylic Acid

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(KOLE tar & sal i SIL ik AS id)
U.S. Brand NamesTarsum® [OTC]; X-Seb T® Pearl [OTC]; X-Seb T® Plus [OTC]
Canadian Brand NamesSebcur/T®
Pharmacologic CategoryTopical Skin Product
Use: Labeled IndicationsSeborrheal dermatitis, dandruff, psoriasis
Dosing: Adults

Psoriasis: Scalp:

Gel: Apply directly to plaques; may leave in place for up to 1 hour. Apply water and work into a lather; rinse.

Shampoo: Apply to wet hair; massage into scalp; rinse.

Dosing: ElderlyRefer to adult dosing.
Pregnancy Risk FactorC
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel [shampoo] (Tarsum®): Coal tar solution 10% [equivalent to coal tar 2%] and salicylic acid (120 mL, 240 mL)

Shampoo, topical:

X-Seb T® Pearl: Coal tar solution 10% [equivalent to coal tar 2%] and salicylic acid (120 mL, 240 mL)

X-Seb T® Plus: Coal tar solution 10% [equivalent to coal tar 2%] and salicylic acid (120 mL, 240 mL) [conditioning shampoo]

Generic AvailableYes
Pharmacodynamics/KineticsSee individual agents.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsSalicylic Acid and Coal Tar
International Brand NamesSebcur/T (CA)

Coal Tar

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Pentrax® may be confused with Permax®

Tegrin® may be confused with Tegretol®

Pronunciation(KOLE tar)

U.S. Brand NamesBalnetar® [OTC]; Betatar® Gel [OTC]; Cutar® [OTC]; Denorex® Original Therapeutic Strength [OTC]; DHS™ Tar [OTC]; DHS™ Targel [OTC]; Doak® Tar [OTC]; Exorex®; Fototar® [OTC]; Ionil T® Plus [OTC] [DSC]; MG 217® Medicated Tar [OTC]; MG 217® [OTC]; Neutrogena® T/Gel Extra Strength [OTC]; Neutrogena® T/Gel Stubborn Itch Control [OTC]; Neutrogena® T/Gel [OTC]; Oxipor® VHC [OTC]; Polytar® [OTC] [DSC]; Reme-T™ [OTC]; Tera-Gel™ [OTC]; Zetar® [OTC]

Canadian Brand NamesBalnetar®; Estar®; Targel®

Pharmacologic CategoryTopical Skin Product

Use: Labeled IndicationsTopically for controlling dandruff, seborrheic dermatitis, or psoriasis

Dosing: Adults

Seborrhea, dermatitis: Topical:

Skin: Apply to the affected area 1-4 times/day; decrease frequency to 2-3 times/week once condition has been controlled

Soap: Use on affected areas in place of regular soap. Work into a lather using warm water; massage into skin; rinse.

Bath: Add appropriate amount to bath water, for adults usually 60-90 mL of a 5% to 20% solution or 15-25 mL of 30% lotion; soak 5-20 minutes, then pat dry; use once daily to 3 days

Dandruff: Shampoo: Rub shampoo onto wet hair and scalp, rinse thoroughly; repeat; leave on 5 minutes; rinse thoroughly; apply twice weekly for the first 2 weeks then once weekly or more often if needed

Psoriasis: Topical:

Scalp psoriasis: Tar oil bath or coal tar solution may be painted sparingly to the lesions 3-12 hours before each shampoo

Psoriasis of the body, arms, legs: Apply at bedtime; if thick scales are present, use product with salicylic acid and apply several times during the day

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to coal tar or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Photosensitivity: May increase photosensitivity; avoid exposure to direct sunlight for 24 hours following application.

Other warnings/precautions:

- Appropriate use: For external use only; avoid contact with eyes, genital/rectal areas.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined: Dermatologic: Dermatitis, folliculitis. irritation, photosensitivity

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream:

Fototar®: Coal tar 2% (85 g, 454 g)

Emulsion, topical:

Cutar®: Coal tar solution 7.5% (180 mL, 3840 mL)

Exorex®: Coal tar 1% (240 mL)

Gel, shampoo:

DHS™ Targel: Coal tar solution 2.9% (240 mL) [equivalent to coal tar 0.5%]

Liquid:

Doak® Tar Distillate: Coal tar 40% (60 mL) [for compounding use only]

Lotion, topical:

MG 217®: Coal tar solution 5% (120 mL) [equivalent to coal tar 1%; contains jojoba]

Oxipor® VHC: Coal tar solution 25% (60 mL, 120 mL) [equivalent to coal tar 5%; contains alcohol 79%]

Oil, topical:

Balnetar®: Coal tar 2.5% (225 mL) [for use in bath]

Doak® Tar: Coal tar distillate 2% (240 mL) [equivalent to coal tar 0.8%; for use in bath]

Ointment, topical:

MG 217®: Coal tar solution 10% (107 g, 430 g) [equivalent to coal tar 2%]

Shampoo, topical:

Betatar Gel®: Coal tar solution 5% (240 mL) [equivalent to coal tar 2.5%; green apple scent]

Denorex® Original Therapeutic Strength: Coal tar solution 12.5% (120 mL, 240 mL, 360 mL) [equivalent to coal tar 2.5%; available with or without conditioner]

DHS™ Tar: Coal tar solution 2.9% (120 mL, 240 mL, 480 mL) [equivalent to coal tar 0.5%]

Doak® Tar: Coal tar distillate 3% (240 mL) [equivalent to coal tar 1.2%]

Ionil T® Plus: Coal tar 2% (240 mL) [DSC]

MG 217® Medicated Tar: Coal tar solution 15% (120 mL, 240 mL) [equivalent to coal tar 3%]

Neutrogena® T/Gel: Coal tar 0.5% (132 mL, 255 mL, 480 mL)

Neutrogena® T/Gel Extra Strength: Coal tar extract 4% (132 mL) [coal tar 1%]

Neutrogena® T/Gel Stubborn Itch Control: Coal tar extract 2% (132 mL) [coal tar 0.5%]

Polytar®: Coal tar 0.5% (177 mL) [DSC]

Reme-T™: Coal tar 5% (236 mL)

Tera-Gel™: Solubilized coal tar 0.5% (120 mL, 240 mL)

Zetar®: Coal tar 1% (180 mL)

Soap, topical:

Polytar®: Coal tar 0.5% (113 g) [DSC]

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCrude Coal Tar; LCD; Pix Carbonis

International Brand NamesAlphosyl (AU); Carbotural (MX); Doak Tar (HK); Evorex Lotion (IE); Linotar (ZA); Linotar Gel 1 (AU); Linotar Gel 2 (AU); Linotar Gel 3 (AU); Medic (AR); Polytar (AU, ZA); Polytar Plus (AU); Tarmed (CN, CO); Tarmed Shampoo (MX)

Cocaine

Lexi-Drugs Online

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Pronunciation(koe KANE)

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsTopical anesthesia for mucous membranes

Dosing: AdultsTopical application (ear, nose, throat, bronchoscopy): Dosage depends on the area to be anesthetized, tissue vascularity, technique of anesthesia, and individual patient tolerance; the lowest dose necessary to produce adequate anesthesia should be used; concentrations of 1% to 10% are used (not to exceed 1 mg/kg). Use reduced dosages for children, elderly, or debilitated patients.

Dosing: ElderlyRefer to adult dosing; use with caution.

Administration: TopicalUse only on mucous membranes of the oral, laryngeal, and nasal cavities. Do not use on extensive areas of broken skin.

StorageStore in well-closed, light-resistant containers.

RestrictionsC-II

ContraindicationsHypersensitivity to cocaine or any component of the topical solution; ophthalmologic anesthesia (causing sloughing of the corneal epithelium); pregnancy (nonmedicinal use)

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Disease-related concerns:

• Cardiovascular disease: Use with caution in patients with cardiovascular disease

• Cocaine abuse: Use with caution in patients with a history of cocaine abuse. In patients being treated for cardiovascular complication of cocaine abuse, avoid beta-blockers for treatment.

Special populations:

• Acutely ill patients: Use with caution in acutely ill; reduce dose consistent with age and physical status.

• Debilitated patients: Use with caution in debilitated patients; reduce dose consistent with age and physical status.

• Elderly: Use with caution in the elderly; reduce dose consistent with age and physical status.

• Pediatrics: Use with caution in children; reduce dose consistent with age and physical status.

Other warnings/precautions:

• Appropriate use: For topical use only. Limit to office and surgical procedures only. Use caution in patients with severely traumatized mucosa and sepsis in the region of the proposed application.

• Trained personnel: Clinicians using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorC/X (nonmedicinal use)

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsIrritability, vomiting, diarrhea, tremors, and seizures have been reported in nursing infants.

Adverse Reactions

>10%:

Central nervous system: CNS stimulation

Gastrointestinal: Loss of taste perception

Respiratory: Rhinitis, nasal congestion

Miscellaneous: Loss of smell

1% to 10%:

Cardiovascular: Heart rate (decreased) with low doses, tachycardia with moderate doses, hypertension, cardiomyopathy, cardiac arrhythmia, myocarditis, QRS prolongation, Raynaud's phenomenon, cerebral vasculitis, thrombosis, fibrillation (atrial), flutter (atrial), sinus bradycardia, CHF, pulmonary hypertension, sinus tachycardia, tachycardia (supraventricular), arrhythmia (ventricular), vasoconstriction

Central nervous system: Fever, nervousness, restlessness, euphoria, excitation, headache, psychosis, hallucinations, agitation, seizure, slurred speech, hyperthermia, dystonic reactions, cerebral vascular accident, vasculitis, clonic-tonic reactions, paranoia, sympathetic storm

Dermatologic: Skin infarction, pruritus, madarosis

Gastrointestinal: Nausea, anorexia, colonic ischemia, spontaneous bowel perforation

Genitourinary: Priapism, uterine rupture

Hematologic: Thrombocytopenia

Neuromuscular & skeletal: Chorea (extrapyramidal), paresthesia, tremor, fasciculations

Ocular: Mydriasis (peak effect at 45 minutes; may last up to 12 hours), sloughing of the corneal epithelium, ulceration of the cornea, iritis, mydriasis, chemosis

Renal: Myoglobinuria, necrotizing vasculitis

Respiratory: Tachypnea, nasal mucosa damage (when snorting), hyposmia, bronchiolitis obliterans organizing pneumonia

Miscellaneous: “Washed-out” syndrome

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP2D6 (strong), 3A4 (weak)
Drug Interactions

Cannabinoids: Cocaine may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Strong) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Cocaine may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Nebivolol: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Strong) may decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

Tetrabenazine: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Tetrabenazine. Specifically, concentrations of the active alpha- and beta-dihydrotetrabenazine metabolites may be increased. Management: Tetrabenazine dose should be reduced by 50% when starting a strong CYP2D6 inhibitor. Maximum tetrabenazine dose is 50mg/day when used with a strong CYP2D6 inhibitor. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Monitoring ParametersVital signs
Reference RangeTherapeutic: 100-500 ng/mL (SI: 330 nmol/L); Toxic: >1000 ng/mL (SI: >3300 nmol/L)
Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for interactions. Monitor adverse effects and teach patient adverse symptoms to report. **Pregnancy risk factor C/X (if nonmedicinal use).** Breast-feeding is contraindicated.
Patient EducationWhen used orally, do not take anything by mouth until full sensation returns. **Ocular:** Use caution when driving or engaging in tasks that require alert vision (mydriasis may last for several hours). At time of use or immediately thereafter, report any unusual cardiovascular, CNS, or respiratory symptoms. Following use, report skin irritation or eruption; alterations in vision, eye pain, or irritation; persistent GI effects; muscle or skeletal tremors, numbness, or rigidity; urinary or genital problems; or persistent fatigue. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Powder, for prescription compounding, as hydrochloride: 1 g, 5 g, 25 g

Solution, topical, as hydrochloride: 4% (4 mL, 10 mL); 10% (4 mL, 10 mL) [DSC]

Generic AvailableYes
Mechanism of ActionEster local anesthetic blocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction; interferes with the uptake of norepinephrine by adrenergic nerve terminals producing vasoconstriction
Pharmacodynamics/KineticsFollowing topical administration to mucosa:

Onset of action: ~1 minute

Peak effect: ~5 minutes

Duration (dose dependent): ≥30 minutes; cocaine metabolites may appear in urine of neonates up to 5 days after birth due to maternal cocaine use shortly before birth

Absorption: Well absorbed through mucous membranes; limited by drug-induced vasoconstriction; enhanced by inflammation

Distribution: Enters breast milk

Metabolism: Hepatic; major metabolites are ecgonine methyl ester and benzoyl ecgonine

Half-life elimination: 75 minutes

Excretion: Primarily urine (<10% as unchanged drug and metabolites)

Pharmacotherapy Pearls Cocaine intoxication of infants who are receiving breast milk from their mothers abusing cocaine has been reported.

Dental Health Professional Considerations The cocaine user, regardless of how the cocaine was administered, presents a potential life-threatening situation in the dental operatory. A patient under the influence of cocaine could be compared to a car going 100 mph. Blood pressure is elevated, heart rate is likely increased, and the use of a local anesthetic with epinephrine may result in a medical emergency. Such patients can be identified by their jitteriness, irritability, talkativeness, tremors, and short, abrupt speech patterns. These same signs and symptoms may also be seen in a normal dental patient with preoperative dental anxiety; therefore, the dentist must be particularly alert in order to identify the potential cocaine abuser. If cocaine use is suspected, the patient should never be given a local anesthetic with vasoconstrictor, for fear of exacerbating the cocaine-induced sympathetic response. Life-threatening episodes of cardiac arrhythmias and hypertensive crises have been reported when local anesthetic with vasoconstrictor was administered to a patient under the influence of cocaine. No local anesthetic, used by any dentist, can interfere with, nor test positive by cocaine in any urine testing screen. Therefore, the dentist does not need to be concerned with any false drug-use accusations associated with dental anesthesia.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Loss of taste perception. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Although plain local anesthetic is not contraindicated, vasoconstrictor is absolutely contraindicated in any patient under the influence of or within 2 hours of cocaine use

Mental Health: Effects on Mental StatusCNS stimulation is common; may cause exacerbation of psychosis, nervousness, euphoria, restlessness, hallucinations, paranoia

Mental Health: Effects on Psychiatric Treatment Concurrent use with MAO inhibitors may result in hypertensive crisis

Cardiovascular Considerations The prevalence of cocaine-induced cardiovascular events is increasing due to recreational use of cocaine. While cocaine is arrhythmogenic, it is also a potent vasospastic agent and may induce marked increases in blood pressure. In young patients presenting with acute myocardial infarction or with severe chest pain with ECG changes suggestive of ischemia, the possibility of antecedent cocaine use should be considered. Alpha blockade may be an option in treating cocaine-induced coronary artery spasm. Avoid use of beta-blockers in patients who are suspected of using cocaine. There is some evidence that the vasospastic effects of cocaine may be enhanced when the drug is used in association with nicotine consumption. Cocaine may also be associated with cerebral vascular accidents in young patients without any previous risk factors.

Anesthesia and Critical Care Concerns/Other Considerations Cocaine may also be associated with cerebral vascular accidents in young patients without any previous risk factors.

Index Terms Cocaine Hydrochloride

References

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Shannon RP, Manders WT, and Shen YT, "Role of Blood Doping in the Coronary Vasoconstrictor Response to Cocaine," *Circulation*, 1995, 92(1):96-105. [PubMed 7788924]

Todd K, Hollander JE, Heilpern K, et al, "Prevalence of the Use of Cocaine in Patients With Chest Pain," *Acad Emerg Med*, 1995, 2:344.

Trabulsy ME, “Cocaine Washed Out Syndrome in a Patient With Acute Myocardial Infarction,” *Am J Emerg Med*, 1995, 13(5):538-9.[PubMed 7662059]

International Brand NamesKokain (DK)

Codeine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Tylenol® With Codeine: Health Canada Issues Warning Concerning Potentially Increased Morphine Levels In Milk of Nursing Mothers - October 9, 2008

Janssen-Ortho Inc, in conjunction with Health Canada, has issued a “Dear Healthcare Professional” letter concerning use of Tylenol® with Codeine (acetaminophen with codeine) products and the risk of elevated morphine levels in the serum and breast milk of nursing women who are ultra-rapid metabolizers of codeine. Consequently, infants of nursing mothers with a certain CYP2D6 (converts codeine to morphine) genotype, may be exposed to potentially dangerous serum levels of morphine as well.

Available data indicates the incidence of this CYP2D6 genotype in the general population varies and is estimated to occur in the following populations as follows: North African, Ethiopian, and Arab (16% to 28%); Chinese, Japanese, and Hispanic (0.5% to 1%); Caucasian (1% to 10%); African American (3%).

When using codeine in nursing women, healthcare providers are urged to prescribe and administer the lowest possible dose for the shortest time necessary to achieve adequate clinical effect. Nursing women should be advised of signs/symptoms of morphine toxicity for themselves (extreme sedation, confusion, shallow breathing) and for their infants (sedation, dyspnea, decreased tone, difficult breastfeeding). The manufacturer will be updating the product labeling to include these new warnings and precautions. A similar warning had previously been released in the U.S. in August 2007.

Additional information can be found at the following websites:

Canada: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/tylenol_codeine_hpc-cps-eng.php

U.S.: http://www.fda.gov/cder/drug/InfoSheets/HCP/codeineHCP.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Codeine may be confused with Cardene®, Cophene®, Cordran®, iodine, Lodine®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(KOE deen)

Canadian Brand NamesCodeine Contin®

Pharmacologic CategoryAnalgesic, Opioid; Antitussive

Use: Labeled IndicationsTreatment of mild-to-moderate pain; antitussive in lower doses; dextromethorphan has equivalent antitussive activity but has much lower toxicity in accidental overdose

Use: DentalTreatment of postoperative pain

Dosing: Adults**Note:** These are guidelines and do not represent the maximum doses that may be required in all patients. Doses should be titrated to pain relief/prevention. Doses >1.5 mg/kg body weight are not recommended.

Pain management (analgesic):

Oral, regular release: 30 mg every 4-6 hours as needed; patients with prior opiate exposure may require higher initial doses. Usual range: 15-120 mg every 4-6 hours as needed

Oral, controlled release formulation (Codeine Contin®, not available in U.S.): 50-300 mg every 12 hours. **Note:** A patient's codeine requirement should be established using prompt release formulations; conversion to long acting products may be considered when chronic, continuous treatment is required. Higher dosages should be reserved for use only in opioid-tolerant patients.

I.M., SubQ: 30 mg every 4-6 hours as needed; patients with prior opiate exposure may require higher initial doses. Usual range: 15-120 mg every 4-6 hours as needed; more frequent dosing may be needed

Cough (antitussive): Oral (for nonproductive cough): 10-20 mg/dose every 4-6 hours as needed; maximum: 120 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** These are guidelines and do not represent the maximum doses that may be required in all patients. Doses should be titrated to pain relief/prevention. Doses >1.5 mg/kg body weight are not recommended.

Analgesic: Oral, I.M., SubQ: Children: 0.5-1 mg/kg/dose every 4-6 hours as needed; maximum: 60 mg/dose

Antitussive: Oral (for nonproductive cough): Children: 1-1.5 mg/kg/day in divided doses every 4-6 hours as needed: Alternative dose according to age:

2-6 years: 2.5-5 mg every 4-6 hours as needed; maximum: 30 mg/day

6-12 years: 5-10 mg every 4-6 hours as needed; maximum: 60 mg/day

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer 75% of dose.

Cl_{cr} <10 mL/minute: Administer 50% of dose.

Dosing: Hepatic ImpairmentDosing adjustment is probably necessary in hepatic insufficiency.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Fentanyl Transdermal Conversion
- Opioid Agonist Conversion

Administration: I.V. DetailpH: 3-6 (codeine phosphate)

StorageStore injection between 15°C to 30°C; avoid freezing. Do not use if injection is discolored or contains a precipitate. Protect injection from light.

Compatibility**Compatibility in syringe: Compatible:** Glycopyrrolate, hydroxyzine.

RestrictionsC-II

ContraindicationsHypersensitivity to codeine or any component of the formulation; pregnancy (prolonged use or high doses at term)

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene-derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Obesity: Use with caution in patients who are morbidly obese.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Renal impairment: Use with caution in patients with severe renal impairment.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- CYP2D6 “ultra-rapid metabolizers”: Use caution in patients with two or more copies of the variant CYP2D6*2 allele; may have extensive conversion to morphine and thus increased opioid-mediated effects.

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Safety and efficacy have not been established for antitussive use in children <2 years of age.

Dosage form specific issues:

- Sulfites: Some preparations contain sulfites which may cause allergic reactions.

Other warnings/precautions:

- Cough control: Not recommended for use for cough control in patients with a productive cough.

- I.V. administration: Not approved for I.V. administration (although this route has been used clinically). If given intravenously, must be given slowly and the patient should be lying down. Rapid intravenous administration of narcotics may increase the incidence of serious adverse effects, in part due to limited opportunity to assess response prior to administration of the full dose. Access to respiratory support should be immediately available.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsThe elderly may be particularly susceptible to CNS depression and confusion as well as the constipating effects of narcotics.

Pregnancy Risk FactorC/D (prolonged use or high doses at term)

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Neonatal abstinence syndrome (NAS) has been observed in the newborn following maternal use of codeine during pregnancy. Symptoms of opiate withdrawal may include excessive crying, diarrhea, fever, hyperreflexia, irritability, tremors, or vomiting. Perinatal stroke has also been reported.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsCodeine and its metabolite (morphine) are found in breast milk and can be detected in the serum of nursing infants. The relative dose to a nursing infant has been calculated to be ~1% of the weight-adjusted maternal dose. Higher levels of morphine may be found in the breast milk of lactating mothers who are “ultra-rapid metabolizers” of codeine; patients with two or more copies of the variant CYP2D6*2 allele may have extensive conversion to morphine and thus increased opioid-mediated effects. In one case, excessively high serum concentrations of morphine were reported in a breastfed infant following maternal use of acetaminophen with codeine. The mother was later found to be an “ultra-rapid metabolizer” of codeine; symptoms in the infant included feeding difficulty and lethargy, followed by death. Because exposure to the nursing infant is generally low, the AAP considers codeine to be “usually compatible with breast-feeding”. However, caution should be used since most persons are not aware if they have the genotype resulting in “ultra-rapid metabolizer” status. When codeine is used in breast-feeding women, it is recommended to use the lowest dose for the shortest duration of time and observe the infant for increased sleepiness, difficulty in feeding or breathing, or limpness.

Adverse Reactions

Frequency not defined: ALT increased, AST increased

>10%:

Central nervous system: Drowsiness

Gastrointestinal: Constipation

1% to 10%:

Cardiovascular: Hypotension, tachycardia or bradycardia

Central nervous system: Confusion, dizziness, false feeling of well being, headache, lightheadedness, malaise, paradoxical CNS stimulation, restlessness

Dermatologic: Rash, urticaria

Gastrointestinal: Anorexia, nausea, vomiting, xerostomia

Genitourinary: Ureteral spasm, urination decreased

Hepatic: LFTs increased

Local: Burning at injection site

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision

Respiratory: Dyspnea

Miscellaneous: Histamine release

<1%: Biliary spasm, convulsions, hallucinations, insomnia, mental depression, muscle rigidity, nightmares, paralytic ileus, stomach cramps

Oncology: VesicantNo

Metabolism/Transport Effects**Substrate** of CYP2D6 (major), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol (may increase CNS depression).

Herb/Nutraceutical: St John's wort may decrease codeine levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsSome quinolones may produce a false-positive urine screening result for opiates using commercially-available immunoassay kits. This has been demonstrated most consistently for levofloxacin and ofloxacin, but other quinolones have shown cross-reactivity in certain assay kits. Confirmation of positive opiate screens by more specific methods should be considered.

Monitoring ParametersPain relief, respiratory and mental status, blood pressure, heart rate

Reference RangeTherapeutic: Not established; Toxic: >1.1 mcg/mL

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for possible additive or adverse interactions. Monitor for effectiveness of pain relief, for signs of overdose, vital signs and CNS status, and adverse reactions at beginning of therapy and at regular intervals with long-term use. May cause physical and/or psychological dependence. For inpatients, implement safety measures. Assess knowledge/teach patient appropriate use (if self-administered). Teach patient to monitor for adverse reactions, adverse reactions to report, and appropriate interventions to reduce side effects.

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause dizziness, drowsiness, confusion, agitation, impaired coordination, or blurred vision (use caution when driving, climbing stairs, or changing position - rising from sitting or lying to standing, or when engaging in tasks requiring alertness until response to drug is known); nausea or vomiting, or loss of appetite (frequent mouth care, small frequent meals, sucking lozenges, or chewing gum may help); or constipation (increased exercise, fluids, fruit, or fiber may help; if unresolved, consult prescriber about use of stool softeners). Report confusion, insomnia, excessive nervousness, excessive sedation or drowsiness, or shakiness; acute GI upset; respiratory difficulty or shortness of breath; facial flushing, rapid heartbeat, or palpitations; urinary difficulty; unusual muscle weakness; or vision changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if you are breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, as phosphate: 15 mg/mL (2 mL); 30 mg/mL (2 mL) [contains sodium metabisulfite]

Powder, for prescription compounding: 10 g, 25 g

Tablet, as phosphate: 30 mg, 60 mg

Tablet, as sulfate: 15 mg, 30 mg, 60 mg

Tablet, controlled release (Codeine Contin®) [CAN]: 50 mg, 100 mg, 150 mg, 200 mg [not available in U.S.]

Generic AvailableYes

Mechanism of ActionBinds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; causes cough supression by direct central action in the medulla; produces generalized CNS depression

Pharmacodynamics/Kinetics

Onset of action: Oral: 0.5-1 hour; I.M.: 10-30 minutes

Peak effect: Oral: 1-1.5 hours; I.M.: 0.5-1 hour

Duration: 4-6 hours

Absorption: Oral: Adequate

Distribution: Crosses placenta; enters breast milk

Protein binding: 7%

Metabolism: Hepatic to morphine (active)

Half-life elimination: 2.5-3.5 hours

Excretion: Urine (3% to 16% as unchanged drug, norcodeine, and free and conjugated morphine)

Related Information

- Narcotic / Opioid Analgesics

Dental Health Professional ConsiderationsIt is recommended that codeine not be used as the sole entity for analgesia because of moderate efficacy along with relatively high incidence of nausea, sedation, and constipation. In addition, codeine has some narcotic addiction liability. Codeine in combination with acetaminophen or aspirin is recommended. Maximum effective analgesic dose of codeine is 60 mg (1 grain). Beyond 60 mg increases respiratory depression only. Sodium thiosulfate is an effective chemical antidote for codeine poisoning.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause euphoria, confusion, insomnia, hallucinations, or depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive toxicity; concurrent use with fluoxetine or paroxetine may result in loss of pain control

Cardiovascular ConsiderationsCodeine may cause constipation which may be problematic in patients with unstable angina, and patients after myocardial infarction. The hemodynamic responses to valsalva-like maneuvers due to straining may have adverse cardiovascular consequences in patients with critical coronary artery disease.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) recommend against using codeine because of its lack of potency, histamine release (may cause hypotension), potential accumulation of active metabolites. The guidelines recommend fentanyl in patients who need immediate pain relief because of its rapid onset of action; fentanyl or hydromorphone is preferred in patients who are hypotensive or have renal dysfunction. Morphine or hydromorphone is recommended for intermittent, scheduled therapy. Both have a longer duration of action requiring less frequent administration.

Index TermsCodeine Phosphate; Codeine Sulfate; Methylmorphine

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International Brand Names Actacode (AU); Antitussivum Burger (DE); Bromophar (BE); Bronchicum (DE); Bronchodine (BE); Bronchosedal Codeine (BE); Codedrill sans sucre (FR); Codein (AR); Codein Knoll (CH); Codein Kwizda (AT); Codein Phosphate (CZ); Codein Slovakofarma (CZ); Codeine Linctus (AU, GB); Codeine Phosphate (AU, CY, CZ, IN); Codeini phosphatis (HR); Codeinsaft von ct (DE); Codeintropfen Ribbeck (DE); Codeintropfen von ct (DE); Codeinum Phosphoricum (PL); Codeinum phosphoricum Berlin-Chemie (DE); Codeinum phosphoricum Compretten (DE); Codeisan (PT); Codenfan (FR); Coderit (MX); codi OPT (DE); Codicaps (DE); Codicompren (DE); Codiforton (DE); Codipertussin (DE); Codipront mono (DE, LU); Compretten (DE); Contrapect (DE); Dicton (DE, LU); Eulyptan (BE); Galcodine (GB); Glottyl (BE, LU); Histaverin (ES); Kaodene (GB); Kodein (NO); Kodein Recip (SE); Kodein ”Dak” (DK); Lertus CD (MX); Neo-Codion[Sirup] (DE); Optipect (DE); Pectinfant (LU); Pectoral Edulcor (LU); Pulmocodeina (EC); Toularynx (BE); Tricodein (DE); Tricodein Solco (AT, CH); Tryasol (DE); Tussamag-Codeinsaft (DE); Tussipan (BE); Tussipect Codein Tropfen Mono (DE); Tussoret (DE); Tussoretard (DE); Tylex CD (MX); Voltaren Forte (MX)

CODOX-M/IVAC

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's (Burkitt's)
Regimen UseLymphoma, non-Hodgkin's (Burkitt's)
Regimen

CODOX-M

Cyclophosphamide: I.V.: 800 mg/m^2/day days 1 and 2

[total dose/cycle = 1600 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day (maximum 2 mg) days 1 and 10

[total dose/cycle = 2.8 mg/m^2; maximum 4 mg/cycle]

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Methotrexate: I.V.: 3 g/m^2 day 10

[total dose/cycle = 3 g/m^2]

Leucovorin: I.V.: 200 mg/m^2 day 11

followed by Oral, I.V.: 15 mg/m^2 every 6 hours until methotrexate level <0.1 Mmol/L

Cytarabine: I.T.: 50 mg/day days 1 and 3

[total dose/cycle = 100 mg]

Methotrexate: I.T.: 12 mg day 1

[total dose/cycle = 12 mg]

Filgrastim: SubQ: Dose not specified, days 3 to 8 and day 12 until ANC >1000 cells/mm^3

Cycle alternates with IVAC (cycles begin when ANC >1000 cells/mm^3)

Note: Hydrocortisone 50 mg may be added to intrathecal therapy to reduce the incidence of side effects/chemical arachnoiditis.

IVAC

Ifosfamide: I.V.: 1500 mg/m^2/day days 1 to 5

[total dose/cycle = 7500 mg/m^2]

Mesna: I.V.: 1500 mg/m^2/day (in divided doses) days 1 to 5

[total dose/cycle = 7500 mg/m^2]

Etoposide: I.V.: 60 mg/m^2/day days 1 to 5

[total dose/cycle = 300 mg/m^2]

Cytarabine: I.V.: 2 g/m^2 every 12 hours, for 4 doses, days 1 and 2

[total dose/cycle = 8 g/m^2]

Methotrexate: I.T.: 12 mg day 5

[total dose/cycle = 12 mg]

Filgrastim: SubQ: Dose not specified, day 6 until ANC >1000 cells/mm^3

Cycle alternates with CODOX-M (cycles begin when ANC >1000 cells/mm^3)

Note: Hydrocortisone 50 mg may be added to intrathecal therapy to reduce the incidence of side effects/chemical arachnoiditis.

References

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CODOX-M

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's

Regimen

Cytarabine: I.T.: 70 mg/day days 1 and 3

[total dose/cycle = 140 mg]

Cyclophosphamide: I.V.: 800 mg/m^2 day 1, then 200 mg/m^2/day days 2 to 5

[total dose/cycle = 1600 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2/day days 1 and 8 (cycle 1); days 1, 8, and 15 (cycle 3)

[total dose/cycle = 3-4.5 mg/m^2]

Doxorubicin: I.V.: 40 mg/m^2 day 1

[total dose/cycle = 40 mg/m^2]

Methotrexate:

I.T.: 12 mg day 15

[total dose/cycle = 12 mg]

I.V.: 1200 mg/m^2 loading dose then 240 mg/m^2/hour for 23 hours day 10

[total dose/cycle = 6720 mg/m^2]

Leucovorin: I.V.: 192 mg/m^2 day 11 then 12 mg/m^2 every 6 hours until methotrexate level <5 X 10^{-8}M (begin 36 hours after the start of methotrexate infusion)

Sargramostim: SubQ: 7.5 mcg/kg/day day 13 until ANC >1000 cells/mm^3

Repeat cycle when ANC >1000 cells/mm^3

References

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Colchicine and Probenecid

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English

Jump To Field (Select Field Name)

Pronunciation(KOL chi seen & proe BEN e sid)

Pharmacologic CategoryAnti-inflammatory Agent; Antigout Agent; Uricosuric Agent

Use: Labeled IndicationsTreatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout

Dosing: AdultsGout: Oral: 1 tablet/day for 1 week, then 1 tablet twice daily thereafter

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentProbenecid may not be effective in patients with chronic renal insufficiency particularly when Cl_{cr} is â¤30 mL/minute.

Administration: OralDo not initiate therapy until acute attack has subsided.

ContraindicationsHypersensitivity to colchicine, probenecid, or any component of the formulation

Allergy Considerations

- Colchicine Allergy

Geriatric ConsiderationsRefer to individual agents.

Pregnancy Risk FactorC

Lactation

Colchicine: Compatible

Probenecid: Excretion in breast milk unknown

Adverse Reactions1% to 10%:

Cardiovascular: Flushing

Central nervous system: Headache, dizziness

Dermatologic: Rash, alopecia

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, abdominal pain

Hematologic: Anemia, leukopenia, aplastic anemia, agranulocytosis

Hepatic: Hepatic necrosis, hepatotoxicity

Neuromuscular & skeletal: Peripheral neuritis, myopathy

Renal: Nephrotic syndrome, uric acid stones, polyuria

Miscellaneous: Hypersensitivity reactions

Metabolism/Transport Effects

Colchicine: **Substrate** of CYP3A4 (major); **Induces** CYP2C8 (weak), 2C9 (weak), 2E1 (weak), 3A4 (weak)

Probenecid: **Inhibits** CYP2C19 (weak)

Drug Interactions

Carbapenems: Uricosuric Agents may decrease the excretion of Carbapenems. Management: Avoid concomitant use of doripenem and probenecid. *Risk C: Monitor therapy*

Cephalosporins: Uricosuric Agents may decrease the excretion of Cephalosporins. **Exceptions:** Ceftobiprole. *Risk C: Monitor therapy*

CycloSPORINE: May enhance the adverse/toxic effect of Colchicine. These include hepatotoxicity and myopathies. Colchicine may increase the serum concentration of CycloSPORINE. Nephrotoxicity and hepatotoxicity may also be increased. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dapsone: Uricosuric Agents may decrease the excretion of Dapsone. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Doripenem: Probenecid may increase the serum concentration of Doripenem. This effect is due to probenecid's ability to decrease the active tubular secretion of doripenem. *Risk D: Consider therapy modification*

Gemifloxacin: Probenecid may decrease the excretion of Gemifloxacin. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Colchicine may enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Ketoprofen: Probenecid may increase the serum concentration of Ketoprofen. *Risk C: Monitor therapy*

Ketorolac: Probenecid may increase the serum concentration of Ketorolac. *Risk X: Avoid combination*

LORazepam: Probenecid may decrease the metabolism of LORazepam. *Risk D: Consider therapy modification*

Macrolide Antibiotics: May decrease the metabolism of Colchicine. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methotrexate: Uricosuric Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Mycophenolate: Probenecid may increase the serum concentration of Mycophenolate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: Probenecid may increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Penicillins: Uricosuric Agents may decrease the excretion of Penicillins. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Quinolone Antibiotics: Probenecid may increase the serum concentration of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: May diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Sodium Benzoate: Probenecid may increase the serum concentration of Sodium Benzoate. Specifically, probenecid may inhibit the renal transport of the hippuric acid metabolite of sodium benzoate. *Risk C: Monitor therapy*

Sodium Phenylacetate: Probenecid may increase the serum concentration of Sodium Phenylacetate. Specifically, probenecid may inhibit the renal transport of the phenylacetylglutamine metabolite of sodium phenylacetate. *Risk C: Monitor therapy*

Theophylline Derivatives: Uricosuric Agents may decrease the excretion of Theophylline Derivatives. **Exceptions:** Aminophylline; Theophylline. *Risk C: Monitor therapy*

Verapamil: May enhance the nephrotoxic effect of Colchicine. Colchicine may increase the serum concentration of Verapamil. *Risk C: Monitor therapy*

Zidovudine: Probenecid may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Colchicine 0.5 mg and probenecid 0.5 g

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Colchicine-Probenecid)

0.5-500 mg (30): $25.99

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Colchicine
- Probenecid

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness
Mental Health: Effects on Psychiatric TreatmentRare reports of agranulocytosis; use caution with clozapine and carbamazepine; CNS depressant effects may be enhanced
Index TermsColBenemid; Probenecid and Colchicine

Colchicine

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Special Alerts

Intravenous Colchicine: U.S. Food and Drug Administration (FDA) Enforcement Action Injectable Product - February 6, 2008

The FDA has ordered companies to stop manufacturing injectable colchicine within 30 days and to stop shipping the product within 180 days. After these dates, all injectable colchicine products must have FDA approval in order to be manufactured or shipped interstate. Injectable colchicine has a narrow therapeutic index and most related toxicities are dose-related. The FDA wants to ensure safety and efficacy of the intravenous product as it has been “grandfathered” into use which did not require evaluation of these endpoints. Serious safety concerns have been associated with intravenous colchicine use; 50 reports of serious adverse events have been reported, including 23 deaths (through June, 2007). Three of these deaths were associated with the use of an improperly compounded I.V. colchicine used to treat chronic back pain, not an accepted practice (*MMWR*, 2007).

Recently (October 2007), the only manufacturer of injectable colchicine voluntarily discontinued production. The FDA also strongly discourages the compounding of injectable colchicine due to serious safety risks. Oral colchicine tablets are not affected by this action.

Additional information can be found at http://www.fda.gov/cder/drug/unapproved_drugs/colchicine_qa.htm.

Medication Safety Issues

Sound-alike/look-alike issues:

Colchicine may be confused with Cortrosyn®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V. formulation) among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(KOL chi seen)

Pharmacologic CategoryColchicine

Use: Labeled IndicationsTreatment of acute gouty arthritis attacks and prevention of recurrences of such attacks

Use: Unlabeled/InvestigationalPrimary biliary cirrhosis; management of familial Mediterranean fever; pericarditis

Dosing: Adults

Familial Mediterranean fever (unlabeled use): Prophylaxis: Oral: 1-2 mg daily in divided doses (occasionally reduced to 0.6 mg/day in patients with GI intolerance)

Gouty arthritis:

Prophylaxis of acute attacks: Oral: 0.6 mg twice daily; initial and/or subsequent dosage may be decreased (ie, 0.6 mg once daily) in patients at risk of toxicity or in those who are intolerant (including weakness, loose stools, or diarrhea); range: 0.6 mg every other day to 0.6 mg 3 times/day

Acute attacks:

Oral: Initial: 0.6-1.2 mg, followed by 0.6 every 1-2 hours; some clinicians recommend a maximum of 3 doses; more aggressive approaches have recommended a maximum dose of up to 6 mg. Wait at least 3 days before initiating another course of therapy

I.V.: Initial: 1-2 mg, then 0.5 mg every 6 hours until response, not to exceed total dose of 4 mg. If pain recurs, it may be necessary to administer additional daily doses. The amount of colchicine administered intravenously in an acute treatment period (generally ~1 week) should not exceed a total dose of 4 mg. Do not administer more colchicine by any route for at least 7 days after a full course of I.V. therapy.

Note: Many experts would avoid use because of potential for serious, life-threatening complications. Should not be administered to patients with renal insufficiency, hepatobiliary obstruction, patients >70 years of age, or recent oral colchicine use. Should be reserved for hospitalized patients who are under the care of a physician experienced in the use of intravenous colchicine.

Surgery: Gouty arthritis, prophylaxis of recurrent attacks: Oral: 0.6 mg/day or every other day; patients who are to undergo surgical procedures may receive 0.6 mg 3 times/day for 3 days before and 3 days after surgery

Primary biliary cirrhosis (unlabeled use): Oral: 0.6 mg twice daily

Pericarditis (unlabeled use): Oral: 0.6 mg twice daily

Dosing: ElderlyRefer to adult dosing. Reduce maintenance/prophylactic dose by 50% in individuals >70 years.

Dosing: PediatricProphylaxis of familial Mediterranean fever (unlabeled use): Oral:

Children ≤5 years: 0.5 mg/day

Children >5 years: 1-1.5 mg/day in 2-3 divided doses

Dosing: Renal Impairment

Gouty arthritis, acute attacks: Oral: Specific dosing recommendations not available from the manufacturer:

Prophylaxis:

Cl_{cr} 35-49 mL/minute: 0.6 mg once daily

Cl_{cr} 10-34 mL/minute: 0.6 mg every 2-3 days

Cl_{cr} <10 mL/minute: Avoid chronic use of colchicine. Use in serious renal impairment is contraindicated by the manufacturer.

Treatment: Cl_{cr} <10 mL/minute: Use in serious renal impairment is contraindicated by the manufacturer. If a decision is made to use colchicine, decrease dose by 75%.

Peritoneal dialysis: Supplemental dose is not necessary

Dosing: Hepatic ImpairmentAvoid in hepatobiliary dysfunction and in patients with hepatic disease.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Injection should be made over 2-5 minutes into tubing of free-flowing I.V. with compatible fluid. Do not administer I.M. or SubQ; severe local irritation can occur following SubQ or I.M. administration. Extravasation can cause tissue irritation.

Administration: OralAdminister tablet orally with water and maintain adequate fluid intake.

Dietary ConsiderationsMay need to supplement with vitamin B_{12}.

StorageProtect tablets from light.

CompatibilityI.V. colchicine is **incompatible** with dextrose or I.V. solutions with preservatives.

ContraindicationsHypersensitivity to colchicine or any component of the formulation; severe renal, gastrointestinal, hepatic, or cardiac disorders; blood dyscrasias; pregnancy (parenteral)

Allergy Considerations

- Colchicine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Gastrointestinal symptoms: Dosage reduction is recommended in patients who develop gastrointestinal symptoms (anorexia, diarrhea, nausea, vomiting) related to drug therapy.

- Local irritation: Severe local irritation can occur following SubQ or I.M. administration; do not administer by these routes.

- Weakness: Dosage reduction is recommended in patients who develop weakness related to drug therapy.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with mild-to-moderate cardiac disease.

- Hepatic impairment: Use with caution in patients with mild-to-moderate hepatic impairment; do not administer I.V. in patients with hepatobiliary obstruction.

- Renal impairment: Use with caution in patients with mild-to-moderate renal impairment; I.V. form should not be administered.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- I.V. administration: Use only with extreme caution; potential for serious, life-threatening complications. Should not be administered to patients with renal insufficiency, hepatobiliary obstruction, patients >70 years of age, or recent oral colchicine use. Should be reserved for hospitalized patients who are under the care of a physician experienced in the use of intravenous colchicine.

Geriatric ConsiderationsColchicine appears to be more toxic in older adults, particularly in the presence of renal, gastrointestinal, or cardiac disease. The most predictable oral side effects are gastrointestinal (eg, vomiting, abdominal pain, and nausea). If colchicine is stopped at this point, other more severe adverse effects may be avoided, such as bone marrow suppression, peripheral neuritis, etc.

Pregnancy Risk FactorC (oral); D (parenteral)

LactationEnters breast milk/use caution (AAP rates “compatible”)

Adverse Reactions

>10%: Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain

1% to 10%:

Dermatologic: Alopecia

Gastrointestinal: Anorexia

<1%: Agranulocytosis, aplastic anemia, arrhythmia (with intravenous administration), azoospermia, bone marrow suppression, dermatosis, hepatotoxicity, hypersensitivity reaction, myopathy, peripheral neuritis, purpura, rash

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Induces** CYP2C8 (weak), 2C9 (weak), 2E1 (weak), 3A4 (weak)

Drug Interactions

CycloSPORINE: May enhance the adverse/toxic effect of Colchicine. These include hepatotoxicity and myopathies. Colchicine may increase the serum concentration of CycloSPORINE. Nephrotoxicity and hepatotoxicity may also be increased. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Colchicine may enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Macrolide Antibiotics: May decrease the metabolism of Colchicine. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Verapamil: May enhance the nephrotoxic effect of Colchicine. Colchicine may increase the serum concentration of Verapamil. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol.

Food: Cyanocobalamin (vitamin B_{12}): Malabsorption of the substrate. May result in macrocytic anemia or neurologic dysfunction.

Herb/Nutraceutical: Vitamin B_{12} absorption may be decreased by colchicine.

Test InteractionsMay cause false-positive results in urine tests for erythrocytes or hemoglobin

Monitoring ParametersCBC and renal function test

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. **I.V.:** Monitor therapeutic effectiveness, laboratory values, and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC and renal function on a regular basis

Patient EducationTake as directed; do not exceed recommended dosage. Consult prescriber about a low-purine diet. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol or aspirin-containing medication without consulting prescriber. You may experience nausea, vomiting, or anorexia (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); hair loss (reversible). Stop medication and report to prescriber if severe vomiting, watery or bloody diarrhea, or abdominal pain occurs. Report muscle tremors or weakness; fatigue; easy bruising or bleeding; yellowing of eyes or skin; or pale stool or dark urine. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 0.5 mg/mL (2 mL)

Tablet: 0.6 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Colchicine)

0.6 mg (30): $12.99

Mechanism of ActionDecreases leukocyte motility, decreases phagocytosis in joints and lactic acid production, thereby reducing the deposition of urate crystals that perpetuates the inflammatory response

Pharmacodynamics/Kinetics

Onset of action: Oral: Pain relief: ~12 hours if adequately dosed

Distribution: Concentrates in leukocytes, kidney, spleen, and liver; does not distribute in heart, skeletal muscle, and brain

Protein binding: 10% to 31%

Metabolism: Partially hepatic via deacetylation

Half-life elimination: 12-30 minutes; End-stage renal disease: 45 minutes

Time to peak, serum: Oral: 0.5-2 hours, declining for the next 2 hours before increasing again due to enterohepatic recycling

Excretion: Primarily feces; urine (10% to 20%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness
Mental Health: Effects on Psychiatric TreatmentRare reports of agranulocytosis; use caution with clozapine and carbamazepine; CNS depressant effects may be enhanced
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International Brand NamesArtrichine (EC); Cholchicin ”Agepha” (AT); Cochic (TH); Colchicin Agepha (AT); Colchicina Lirca (IT); Colchicina Phoenix (AR); Colchicine (IL, NZ); Colchicine capsules (NL); Colchicine Houde (AR, BE, ES, FR, LU, PT); Colchicum-Dispert (BG, DE, HN, HU, PL); Colchily (TH); Colchimedio (CO); Colchine (KP); Colchiquim (MX); Colchis (BR); Colchisol (PE); Colchysat Burger (DE); Colcine (TH); Colgout (AU, HK); Conicine (TW); Goutichine (TH); Goutnil (IN); Kolkisin (NO); Lennon-Colchicine (ZA); Prochic (TH); Recolfar (ID); Sixol (MX); Tolchicine (TH)

Colesevelam

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English

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Pronunciation(koh le SEV a lam)
U.S. Brand NamesWelChol®
Canadian Brand NamesWelChol®
Pharmacologic CategoryAntilipemic Agent, Bile Acid Sequestrant
Use: Labeled IndicationsManagement of elevated LDL in primary hypercholesterolemia (Fredrickson type IIa) when used alone or in combination with an HMG-CoA reductase inhibitor; improve control of type 2 diabetes mellitus (noninsulin dependent, NIDDM) in conjunction with insulin or oral antidiabetic agents
Dosing: Adults

Dyslipidemia: Oral: 3 tablets twice daily with meals or 6 tablets once daily with a meal

Type 2 diabetes:*Combination therapy with insulin or oral antibiabetic agents:* 3 tablets twice daily with meals or 6 tablets once daily with a meal

Dosing: ElderlyRefer to adult dosing.
Administration: OralAdminister with meal(s) and a liquid. Make sure patient understands dietary guidelines.
Dietary ConsiderationsShould be taken with meal(s) and a liquid. Follow dietary guidelines.
StorageStore at room temperature. Protect from moisture.
ContraindicationsHistory of bowel obstruction; serum triglyceride concentration >500 mg/dL; history of hypertriglyceridemia-induced pancreatitis
Warnings/Precautions

Disease-related concerns:

- Gastrointestinal disease: Use with caution in patients with dysphagia, swallowing disorders, severe GI motility disorders or major GI tract surgery.

- Hypertriglyceridemia: Use with caution in treating patients with serum triglyceride concentrations >300 mg/dL (may cause increased concentrations). Discontinue if triglyceride concentrations exceed 500 mg/dL or hypertriglyceridemia-induced pancreatitis occurs.

- Patients susceptible to fat-soluble vitamin deficiencies: Use with caution in patients susceptible to fat-soluble vitamin deficiencies.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy. Minimal effects are seen on HDL-C and triglyceride concentrations.

- Appropriate use: Colesevlam is not indicated for the management of type 1 diabetes mellitus (insulin dependent, IDDM), particularly in the acute management (eg, DKA). It is also not indicated as monotherapy and must be used as an adjunct to insulin or oral antidiabetic agents.

Geriatric ConsiderationsThe definition of and, therefore, when to treat hyperlipidemia in elderly is a controversial issue. The National Cholesterol Education Program recommends that all adults maintain a plasma cholesterol <160 mg/dL. Elderly with one additional risk factor, goal LDL would be <130 mg/dL. It is the authors' belief that pharmacologic treatment be reserved for those who are unable to obtain a desirable plasma cholesterol concentration by diet alone and for whom the benefits of treatment are believed to outweigh the potential adverse effects, drug interactions, and cost of treatment.
Pregnancy Risk FactorB
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women; use only in pregnancy if clearly needed.
LactationExcretion in breast milk unknown
Adverse Reactions

>10%: Gastrointestinal: Constipation (11%)

2% to 10%:

Gastrointestinal: Dyspepsia (8%)

Neuromuscular & skeletal: Weakness (4%), myalgia (2%)

Respiratory: Pharyngitis (3%)

Incidence less than or equal to placebo: Infection, headache, pain, back pain, abdominal pain, flu syndrome, flatulence, diarrhea, nausea, sinusitis, rhinitis, cough

Drug Interactions

Amiodarone: Bile Acid Sequestrants may decrease the bioavailability of Amiodarone. *Risk D: Consider therapy modification*

Antidiabetic Agents (Thiazolidinedione): Bile Acid Sequestrants may decrease the absorption of Antidiabetic Agents (Thiazolidinedione). *Risk D: Consider therapy modification*

Calcitriol: Bile Acid Sequestrants may decrease the serum concentration of Calcitriol. *Risk C: Monitor therapy*

Corticosteroids (Oral): Bile Acid Sequestrants may decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Ethinyl Estradiol: Colesevelam may decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Ezetimibe: Bile Acid Sequestrants may decrease the absorption of Ezetimibe. *Risk C: Monitor therapy*

GlyBURIDE: Colesevelam may decrease the serum concentration of GlyBURIDE. *Risk D: Consider therapy modification*

Loop Diuretics: Bile Acid Sequestrants may decrease the absorption of Loop Diuretics. *Risk D: Consider therapy modification*

Methotrexate: Bile Acid Sequestrants may decrease the absorption of Methotrexate. *Risk C: Monitor therapy*

Niacin: Bile Acid Sequestrants may decrease the absorption of Niacin. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: Bile Acid Sequestrants may decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Norethindrone: Colesevelam may decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

Phenytoin: Colesevelam may decrease the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Raloxifene: Bile Acid Sequestrants may decrease the absorption of Raloxifene. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Bile Acid Sequestrants may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Thiazide Diuretics: Bile Acid Sequestrants may decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Thyroid Products: Bile Acid Sequestrants may decrease the absorption of Thyroid Products. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Bile Acid Sequestrants may decrease the absorption of Vitamin K Antagonists. *Risk C: Monitor therapy*

Monitoring ParametersSerum cholesterol, LDL, and triglyceride levels should be obtained before initiating treatment and periodically thereafter (in accordance with NCEP guidelines)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests prior to and on a regular basis during therapy. Assess knowledge/teach patient appropriate use, possible adverse reactions and interventions, and symptoms to report.

Monitoring: Lab TestsSerum cholesterol, LDL, and triglyceride levels should be obtained before initiating treatment and periodically thereafter (in accordance with NCEP guidelines).

Patient EducationTake medication exactly as directed; do not alter dosage without consulting prescriber. Other medications should be taken 1 hour before or 4 hours after colesevelam. You may experience constipation (increased exercise, increased exercise, fluids, fruit, fiber, or stool softener may help). Report persistent GI upset, skeletal or muscle pain or weakness, or respiratory difficulties. **Breast-feeding precaution:** Inform prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride:

WelChol®: 625 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (WelChol)

625 mg (60): $78.05

Mechanism of ActionColesevelam binds bile acids including glycocholic acid in the intestine, impeding their reabsorption. Increases the fecal loss of bile salt-bound LDL-C

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Therapeutic: ~2 weeks

Absorption: Insignificant

Excretion: Urine (0.05%) after 1 month of chronic dosing

Related Information

- Hyperlipidemia Management
- Lipid-Lowering Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment Constipation is common, concurrent use with psychotropic agents may exacerbate this effect

Cardiovascular Considerations Colesevelam may be 4-6 times as potent as traditional bile acid sequestrants, perhaps because of its greater binding affinity for glycocholic acid (Steinmetz, 2002). Unlike cholestyramine and colestipol, colesevelam appears to reduce LDL cholesterol in a dose-dependent manner. Bile acid sequestrants can cause an undesirable increase in serum triglycerides. No trials are available comparing colesevelam to cholestyramine or colestipol. Colesevelam does not interfere with intestinal absorption of fat-soluble vitamins. Can be taken concurrently with a HMG-CoA reductase inhibitor.

Anesthesia and Critical Care Concerns/Other Considerations Colesevelam alone or when combined with a statin is effective in lowering cholesterol. Colesevelam may increase triglycerides; therefore, it should be used with caution or avoided in patients with triglyceride levels ≥200 mg/dL. Systemic toxicity is low since the drug is not absorbed.

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International Brand Names Cholestagel (DK, EE, NO, SE); Welchol (NO)

Colestipol

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English

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Pronunciation(koe LES ti pole)
U.S. Brand NamesColestid®
Canadian Brand NamesColestid®
Pharmacologic CategoryAntilipemic Agent, Bile Acid Sequestrant
Use: Labeled IndicationsAdjunct in management of primary hypercholesterolemia; regression of arteriolosclerosis; relief of pruritus associated with elevated levels of bile acids; possibly used to decrease plasma half-life of digoxin in toxicity
Dosing: AdultsDyslipidemia: Oral:

Granules: 5-30 g/day given once or in divided doses 2-4 times/day; initial dose: 5 g 1-2 times/day; increase by 5 g at 1- to 2-month intervals

Tablets: 2-16 g/day; initial dose: 2 g 1-2 times/day; increase by 2 g at 1- to 2-month intervals

Dosing: ElderlyRefer to adult dosing.
Administration: OralDry powder should be added to at least 90 mL of liquid and stirred until completely mixed. Other drugs should be administered at least 1 hour before or 4 hours after colestipol.
Dietary ConsiderationsGranules, orange flavor, contain phenylalanine 18.2 mg/7.5 g.
ContraindicationsHypersensitivity to bile acid sequestering resins or any component of the formulation; bowel obstruction
Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: Chronic use may be associated with bleeding problems.

- Constipation: May produce or exacerbate constipation problems; fecal impaction may occur. Hemorrhoids may be worsened.

Concurrent drug therapy issues:

- Decreased absorption (orally administered drugs): Not to be taken simultaneously with many other medicines (decreased absorption).

- Fat-soluble vitamins/folic acid: May interfere with fat-soluble vitamins (A, D, E, K) and folic acid.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

Geriatric ConsiderationsThe definition of and, therefore, when to treat hyperlipidemia in the elderly is a controversial issue. The National Cholesterol Education Program recommends that all adults maintain a plasma cholesterol <160 mg/dL. Elderly with one additional risk factor, goal LDL would be <130 mg/dL. It is the authors' belief that pharmacologic treatment be reserved for those who are unable to obtain a desirable plasma cholesterol concentration by diet alone and for whom the benefits of treatment are believed to outweigh the potential adverse effects, drug interactions, and cost of treatment.
Pregnancy Risk FactorC
LactationNot recommended
Adverse Reactions

>10%: Gastrointestinal: Constipation

1% to 10%:

Central nervous system: Headache, dizziness, anxiety, vertigo, drowsiness, fatigue

Gastrointestinal: Abdominal pain and distention, belching, flatulence, nausea, vomiting, diarrhea

<1% (Limited to important or life-threatening): Peptic ulceration, gallstones, GI irritation and bleeding, anorexia, steatorrhea or malabsorption syndrome, cholelithiasis, cholecystitis, dyspnea

Drug Interactions

Amiodarone: Bile Acid Sequestrants may decrease the bioavailability of Amiodarone. *Risk D: Consider therapy modification*

Antidiabetic Agents (Thiazolidinedione): Bile Acid Sequestrants may decrease the absorption of Antidiabetic Agents (Thiazolidinedione). *Risk*

D: Consider therapy modification

Calcitriol: Bile Acid Sequestrants may decrease the serum concentration of Calcitriol. *Risk C: Monitor therapy*

Cardiac Glycosides: Bile Acid Sequestrants may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

Corticosteroids (Oral): Bile Acid Sequestrants may decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Diltiazem: Colestipol may decrease the absorption of Diltiazem. *Risk C: Monitor therapy*

Ezetimibe: Bile Acid Sequestrants may decrease the absorption of Ezetimibe. *Risk C: Monitor therapy*

Fibric Acid Derivatives: Bile Acid Sequestrants may decrease the absorption of Fibric Acid Derivatives. *Risk D: Consider therapy modification*

Loop Diuretics: Bile Acid Sequestrants may decrease the absorption of Loop Diuretics. *Risk D: Consider therapy modification*

Methotrexate: Bile Acid Sequestrants may decrease the absorption of Methotrexate. *Risk C: Monitor therapy*

Methylfolate: Colestipol may decrease the serum concentration of Methylfolate. *Risk C: Monitor therapy*

Niacin: Bile Acid Sequestrants may decrease the absorption of Niacin. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: Bile Acid Sequestrants may decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Raloxifene: Bile Acid Sequestrants may decrease the absorption of Raloxifene. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Bile Acid Sequestrants may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Thiazide Diuretics: Bile Acid Sequestrants may decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Thyroid Products: Bile Acid Sequestrants may decrease the absorption of Thyroid Products. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Bile Acid Sequestrants may decrease the absorption of Vitamin K Antagonists. *Risk C: Monitor therapy*

Test InteractionsIncreased prothrombin time; decreased cholesterol (S)

Nursing: Physical Assessment/MonitoringAssess other medications the patient may be taking for effectiveness and interactions. Monitor knowledge/teach patient appropriate preparation and use, possible adverse reactions, and symptoms to report. Monitor bowel function. Be alert to potential of constipation or hemorrhoid problems.

Patient EducationTake granules with 3-4 oz of water or fruit juice. Rinse glass with small amount of water to ensure full dose is taken. Take tablets one at a time. Other medications should be taken 1 hour before or 4 hours after colestipol. You may experience constipation (increased exercise, fluids, fruit, fiber, or stool softener may help); or drowsiness or dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report acute gastric pain, tarry stools, or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Granules for suspension, as hydrochloride, oral: 5 g/packet (30s, 90s); 5 g/scoopful (500 g)

Colestid®: 5 g/packet (30s, 90s); 5 g/teaspoon (300 g, 500 g) [unflavored]

Colestid®, flavored: 5 g/packet (60s) [contains phenylalanine (18.2 mg/packet); orange flavor]

Colestid®, flavored: 5 g/scoopful (450 g) [contains phenylalanine (18.2 mg/scoopful); orange flavor]

Tablet, as hydrochloride: 1 g

Tablet, as hydrochloride, oral [micronized]:

Colestid®: 1 g

Generic AvailableYes

ManufacturerPharmacia & Upjohn

Pricing: U.S. (www.drugstore.com)

Granules (Colestid)

5 g (300): $84.60

5 g (500): $137.75

Granules (Colestid Flavored)

5 g (450): $112.19

Pack (Colestid)

5 g (30): $70.94

5 g (90): $199.11

Pack (Colestid Flavored)

5 g/7.5 g (60): $157.37

Tablets (Colestid)

1 g (120): $90.98

Tablets (Colestipol HCl)

1 g (120): $74.99

Mechanism of ActionBinds with bile acids to form an insoluble complex that is eliminated in feces; it thereby increases the fecal loss of bile acid-bound low density lipoprotein cholesterol

Pharmacodynamics/Kinetics

Absorption: None

Excretion: Feces

Related Information

- Lipid-Lowering Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or anxiety

Mental Health: Effects on Psychiatric TreatmentConstipation is common; may be exacerbated by concurrent psychotropic use; may decrease the absorption of TCAs

Cardiovascular ConsiderationsColestipol alone or when combined with an HMG-CoA reductase inhibitor is effective in lowering cholesterol. Colestipol may increase triglycerides, therefore, it should be avoided in patients with triglyceride levels ≥200 mg/dL. Potential factors that may limit patient compliance include GI side effects and the need to separate administration of other medications from colestipol.

Anesthesia and Critical Care Concerns/Other ConsiderationsColestipol alone or when combined with an HMG-CoA reductase inhibitor is effective in lowering cholesterol. Colestipol may increase triglycerides, therefore, it should be avoided in patients with triglyceride levels ≥200 mg/dL.

Index TermsColestipol Hydrochloride

References

“Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III),” *JAMA*, 2001, 285(19):2486-97.[PubMed 11368702]

International Brand NamesCholestabyl (DE); Colestid (AT, AU, BB, BE, BG, BM, BS, BZ, CH, CZ, ES, GB, GY, HN, HR, HU, IE, IL, IT, JM, LU, NL, PL, PT, SR, TT); Lestid (DK, FI, NO, SE)

Colistimethate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(koe lis ti METH ate)

U.S. Brand NamesColy-Mycin® M

Canadian Brand NamesColy-Mycin® M

Pharmacologic CategoryAntibiotic, Miscellaneous

Use: Labeled IndicationsTreatment of infections due to sensitive strains of certain gram-negative bacilli which are resistant to other antibacterials or in patients allergic to other antibacterials

Use: Unlabeled/InvestigationalUsed as nebulized inhalation in the prevention of *Pseudomonas aeruginosa* respiratory tract infections in immunocompromised patients, and used as nebulized inhalation adjunct agent for the treatment of *P. aeruginosa* infections in patients with cystic fibrosis and other seriously ill or chronically ill patients

Dosing: Adults**Note:** Doses should be based on ideal body weight in obese patients; dosage expressed in terms of colistin.

Susceptible infections:

I.M., I.V.: 2.5-5 mg/kg/day in 2-4 divided doses

Inhalation (unlabeled use): 50-75 mg in NS (3-4 mL total) via nebulizer 2-3 times/day

Cystic fibrosis (unlabeled dose): I.V.: 3-8 mg/kg/day in 3 divided doses **or** 60-70 mg every 8 hours, if tolerated, may increase to 80-100 mg every 8 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Doses should be based on ideal body weight in obese patients; dosage expressed in terms of colistin.

Susceptible infections:

I.M., I.V.: 2.5-5 mg/kg/day in 2-4 divided doses

Inhalation (unlabeled use): 50-75 mg in NS (3-4 mL total) via nebulizer 2-3 times/day

Cystic fibrosis (unlabeled dose): I.V.: 3-8 mg/kg/day in 3 divided doses (maximum dose: 70 mg)

Dosing: Renal Impairment

S_{cr} 1.3-1.5 mg/dL: 75-115 mg twice daily (approximately 2.5-3.8 mg/kg/day)

S_{cr} 1.6-2.5 mg/dL: 66-150 mg once or twice daily (approximately 2.5 mg/kg/day)

S_{cr} 2.6-4 mg/dL: 100-150 mg every 36 hours (approximately 1.5 mg/kg/day)

Continuous renal replacement therapy (CRRT): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH or CVVHD/CVVHDF: 2.5 mg/kg every 48 hours

Note: A single case report has demonstrated that the use of 2.5 mg/kg every 48 hours with a dialysate flow rate of 1 L/hour may be inadequate and that dosing every 24 hours was well-tolerated. Based on pharmacokinetic analysis, the authors recommend dosing as frequent as every 12 hours in patients receiving CRRT (Li, 2005).

Administration: I.V.Parenteral: Reconstitute vial with 2 mL SWFI resulting in a concentration of 75 mg colistin/mL; swirl gently to avoid frothing. Administer by I.M., direct I.V. injection over 3-10 minutes, intermittent infusion over 30 minutes, or by continuous I.V. infusion. For continuous I.V. infusion, one-half of the total daily dose is administered by direct I.V. injection over 3-10 minutes followed 1-2 hours later by the remaining one-half of the total daily dose diluted in a compatible I.V. solution infused over 22-23 hours. The final concentration for administration should be based on the patient's fluid needs.

Administration: InhalationUnlabeled: Further dilute dose to a total volume of 3-4 mL in NS and administer via nebulizer. If patient is on a ventilator, place medicine in a T-piece at the midinspiratory circuit of the ventilator. Administer solution promptly following preparation to decrease possibility of high concentrations of colistin from forming which may lead to potentially life-threatening lung toxicity.

StorageStore intact vials (prior to reconstitution) at 20°C to 25°C (68°F to 77°F); reconstituted vials may be refrigerated at 2°C to 8°C (36°F to 46°F) or stored at 20°C to 25°C (68°F to 77°F) for up to 24 hours. Solutions for infusion should be freshly prepared; do not use beyond 24 hours.

ReconstitutionFor I.V. use, reconstitute each vial with 2 mL of SWFI; swirl gently to avoid foaming. May further dilute in D_5W or NS for I.V. infusion. For nebulized inhalation (unlabeled use), reconstitute with NS; should be used promptly after preparation; do not use after 24 hours.

CompatibilityStable in $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, LR, NS.

Compatibility in syringe: Compatible: Ampicillin, penicillin G sodium.

Compatibility when admixed: Compatible: Amikacin, ascorbic acid injection, chloramphenicol, cimetidine, diphenhydramine, heparin, lincomycin, penicillin G potassium, penicillin G sodium, phenobarbital, polymyxin B sulfate, ranitidine, vitamin B complex with C. **Incompatible:** Cefazolin, erythromycin lactobionate, hydrocortisone sodium succinate, kanamycin.

ContraindicationsHypersensitivity to colistimethate, colistin, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- CNS toxicity: Transient, reversible neurological disturbances (eg, dizziness, numbness, paresthesia, tingling, vertigo) may occur.

- Renal toxicity: Dose-dependent nephrotoxicity has been reported, generally reversible upon discontinuation of treatment.

- Respiratory arrest: Respiratory arrest has been reported with use; impaired renal function may increase the risk for neuromuscular blockade and apnea.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with pre-existing renal disease; dosage adjustments may be required. Impaired renal function may increase the risk for respiratory arrest.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in animal reproduction studies; therefore, the manufacturer classifies colistimethate as pregnancy category C. Colistimethate crosses the placenta in humans. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if colistimethate sodium is excreted in human milk, but colistin sulphate (another form of colistin) is excreted in human milk. The manufacturer recommends caution if giving colistimethate sodium to a breast-feeding woman. If colistimethate sodium reaches the breast milk, nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Colistimethate in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Dizziness, fever, headache, slurred speech, vertigo

Dermatologic: Pruritus, rash, urticaria

Gastrintestinal: GI upset

Neuromuscular & skeletal: Paresthesia (extremities, oral); weakness (lower limb)

Renal: BUN increased, creatinine increased, nephrotoxicity, proteinuria, urine output decreased

Respiratory: Apnea, respiratory arrest

Postmarketing, and/or case reports: Lung toxicity (bronchoconstriction, bronchospasm, chest tightness, respiratory distress, acute respiratory failure following inhalation)

Drug Interactions

Aminoglycosides: May enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

Amphotericin B: May enhance the nephrotoxic effect of Colistimethate. *Risk D: Consider therapy modification*

Capreomycin: May enhance the neuromuscular-blocking effect of Colistimethate. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Colistimethate may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Polymyxin B: May enhance the neuromuscular-blocking effect of Colistimethate. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vancomycin: May enhance the nephrotoxic effect of Colistimethate. *Risk D: Consider therapy modification*

Monitoring ParametersSerum creatinine, BUN; urine output; signs of neurotoxicity

Monitoring: Lab TestsSerum creatinine, BUN, urine output

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as colistin base: 150 mg

Coly-Mycin® M: 150 mg

Generic AvailableYes

Mechanism of ActionHydrolyzed to colistin, which acts as a cationic detergent which damages the bacterial cytoplasmic membrane causing leaking of intracellular substances and cell death

Pharmacodynamics/Kinetics

Distribution: Widely, except for CNS, synovial, pleural, and pericardial fluids

Metabolism: Colistimethate is hydrolyzed to colistin

Half-life elimination: I.M., I.V.: 2-3 hours; Anuria: ≤2-3 days

Time to peak: I.V.: 10 minutes

Excretion: Primarily urine (as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other Considerations

Colistimethate: Possible Association of Death Occurring After Off-Label Use of Nebulized Solution - June, 2007

The Food and Drug Administration (FDA) has issued a public health advisory and is notifying clinicians of an investigation surrounding the death of a cystic fibrosis (CF) patient which may be connected to the use of premixed (pharmacy compounded), colistimethate vials for inhalation via a nebulizer.

The FDA is reminding healthcare providers of the proposed mechanism that may have contributed to the death. Colistimethate, an inactive prodrug, is converted to the bioactive colistin by spontaneous hydrolysis once colistimethate is mixed into aqueous solution. Colistin is comprised of 2 components, colistin A (polymyxin E1) and colistin B (polymyxin E2). Polymyxin E1 has been shown to cause localized airway inflammation in animal studies and may result in lung toxicity in humans. Clinicians who continue to prescribe colistimethate for inhalation should be aware of this potentially life-threatening effect and should administer solutions for inhalation promptly following preparation of solution.

On June 12, 2007, the Cystic Fibrosis Foundation issued an alert recommending that patients not use colistimethate for inhalation premixed by pharmacies; patients should prepare their colistimethate nebulizer inhalation solutions immediately prior to use.

Additional information is available at the following websites:

http://www.fda.gov/medwatch/SAFETY/2007/safety07.htm#Colistimethate

http://www.cff.org/aboutCFFoundation/NewsEvents/v

Index TermsColistimethate Sodium; Colistin Methanesulfonate ; Colistin Sulfomethate ; Pentasodium Colistin Methanesulfonate

References

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Bauldoff GS, Nunley DR, Manzetti JD, et al, “Use of Aerosolized Colistin in Cystic Fibrosis Patients Awaiting Lung Transplantation,” *Transplantation*, 1997, 64(5):748-52. [PubMed 9311714]

Beringer P, “The Clinical Use of Colistin in Patients With Cystic Fibrosis,” *Curr Opin Pulm Med*, 2001, 7(6):434-40.[PubMed 11706322]

Bosso JA, Liptak CA, Seilheimer DK, et al, “Toxicity of Colistin in Cystic Fibrosis Patients,” *DCIP*, 1991, 25(11):1168-70.[PubMed 1763528]

Conway SP, Pond MN, Watson A, et al, “Intravenous Colistin Sulphomethate in Acute Respiratory Exacerbations in Adult Patients With Cystic Fibrosis,” *Thorax*, 1997, 52(11):987-93. [PubMed 9487348]

Jensen T, Pederson SS, Garne S, et al, “Colistin Inhalation Therapy in Cystic Fibrosis Patients With Chronic *Pseudomonas aeruginosa* Lung Infection,” *J Antimicrob Chemother*, 1987, 19(6):831-8. [PubMed 3301785]

Li J, Rayner CR, Nation RL, et al, “Pharmacokinetics of Colistin Methanesulfonate and Colistin in a Critically Ill Patient Receiving Continuous Venovenous Hemodiafiltration,” *Antimicrob Agents Chemother*, 2005, 49(11):4814-15.[PubMed 16251342]

McCoy KS, “Compounded Colistimethate as Possible Cause of Fatal Acute Respiratory Distress Syndrome,” *N Engl J Med*, 2007, 357(22):2310-1.[PubMed 18046039]

Reed MD, Stern RC, O'Riordan MA, et al, “The Pharmacokinetics of Colistin in Patients With Cystic Fibrosis,” *J Clin Pharmacol*, 2001, 41(6):645-54.[PubMed 11402633]

Trotman RL, Williamson JC, Shoemaker DM, et al, "Antibiotic Dosing in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy," *Clin Infect Dis*, 2005, 41(8):1159-66.[PubMed 16163635]

Zylberberg H, Vargaftig J, Barbieux C, et al, “Prolonged Efficiency of Secondary Prophylaxis With Colistin Aerosols for Respiratory Infection Due to *Pseudomonas aeruginosa* in Patients Infected With Human Immunodeficiency Virus,” *Clin Infect Dis*, 1996, 23(3):641-3.[PubMed 8879797]

International Brand NamesAlficetin (AR); Colimicina IM (IT); Colimycin (CL, NO); Colimycine (CZ); Coliracin (IL); Colistate (TH); Colistin (CH, DE, NL); Colistin Link (NZ); Colistineb (BE); Colomycin (HN, IE); Coly Mycin M (AU); Promixin (DK, GB, IE)

Collagen (Absorbable/Dental)

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Jump To Field (Select Field Name)

Pronunciation(KOL la jen, ab SORB able / DEN tl)
U.S. Brand NamesCollaCote®; CollaPlug®; CollaTape®
Pharmacologic CategoryHemostatic Agent
Use: Labeled IndicationsHemostatic
Use: DentalControl of bleeding created during dental surgery
Dosing: AdultsControl of bleeding: Topical: A sufficiently large dressing should be selected so as to completely cover the oral wound
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
ContraindicationsNo data reported
Warnings/Precautions

Other warnings/precautions:

- Appropriate use: Should not be used on infected or contaminated wounds.

LactationCompatible
Adverse ReactionsNo data reported.
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Wound dressing:

$^{3}/_{8}$” x $^{3}/_{4}$”

$^{3}/_{4}$” x 1 $^{1}/_{2}$”

1” x 3”

Generic AvailableYes
Mechanism of ActionThe highly porous sponge structure absorbs blood and wound exudate. The collagen component causes aggregation of platelets which bind to collagen fibrils. The aggregated platelets degranulate, releasing coagulation factors that promote the formation of fibrin.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported

Collagen Hemostat

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Medication Safety Issues

Sound-alike/look-alike issues:

Avitene® may be confused with Ativan®

Over 100 reports of paralysis or other neural deficits have been received by the FDA, attributable to collagen hemostat-associated neuronal impingement; see Warnings/Precautions

Pronunciation(KOL la jen HEE moe stat)
U.S. Brand NamesAvitene®; Avitene® Flour; Avitene® Ultrafoam; Avitene® UltraWrap™; EndoAvitene®; Helistat®; Helitene®; Instat™; Instat™ MCH; SyringeAvitene™
Pharmacologic CategoryHemostatic Agent
Use: Labeled IndicationsAdjunct to hemostasis when control of bleeding by ligature is ineffective or impractical
Use: DentalAdjunct to hemostasis when control of bleeding by ligature is ineffective or impractical
Dosing: AdultsHemostasis: Topical: Apply dry directly to source of bleeding; remove excess material after ~10-15 minutes
Dosing: ElderlyRefer to adult dosing.
StorageStore at controlled room temperature. Inactivated by autoclaving; do not resterilize. Do not use if package is damaged. Do not reuse after opening.
ContraindicationsHypersensitivity to any component of the formulation; products of bovine origin; closure of skin incisions, contaminated wounds; application to bone surfaces to which prosthetic materials are attached with methylmethacrylate adhesives
Warnings/Precautions

Concerns related to adverse effects:

- Pain/numbness/paralysis: Pain, numbness, or paralysis have been reported if used near a bony or neural space and left inside patient; use minimum amount necessary to achieve hemostasis.

Other warnings/precautions:

- Appropriate use: Remove as much of agent as possible after hemostasis is achieved. Do not leave in a contaminated or infected space. Fragments of MCH may pass through filters of blood scavenging systems; avoid reintroduction of blood from operative sites treated with MCH. Not intended to treat systemic coagulation disorders. Not for use when origin of bleeding is unknown.

Adverse ReactionsFrequency not defined.

Miscellaneous: Adhesion formation, allergic reaction, edema, foreign body reaction, hematoma, inflammation, potentiation of infection

Postmarketing and/or case reports: Numbness, pain, paralysis, subgaleal seroma; alveolalgia and transient laryngospasm with dental use

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Pad (Instat™) [bovine derived]: 1 inch x 2 inch (24s); 3 inch x 4 inch (24s)

Powder:

Avitene® Flour [microfibrillar product, bovine derived]: 0.5 g, 1 g, 5 g

Helitene® [bovine derived]: 0.5 g, 1 g

Instat™ MCH [microfibrillar product, bovine derived]: 0.5 g, 1 g

SyringeAvitene™ [microfibrillar product, bovine derived, prefilled syringe]: 1 g

Sheet:

Avitene® [microfibrillar product, bovine derived, nonwoven web]: 35 mm x 35 mm (1s); 70 mm x 35 mm (6s, 12s); 70 mm x 70 mm (6s, 12s)

EndoAvitene® [microfibrillar product, bovine derived, preloaded applicator]: 5 mm diameter (6s); 10 mm diameter (6s)

Sponge:

Avitene® Ultrafoam [microfibrillar product, bovine derived]: 2 cm x 6.25 cm x 7 mm (12s); 8 cm x 6.25 cm x 1 cm (6s); 8 cm x 12.5 cm x 1 cm (6s); 8 cm x 12.5 cm x 3 mm (6s)

Avitene® UltraWrap™ [microfibrillar product, bovine derived]: 8 cm x 12.5 cm (6s)

Helistat® [bovine derived]: 0.5 inch x 1 inch x 7 mm (18s) [packaged as 3 strips of 6 sponges]; 3 inch x 4 inch x 5 inch (10s)

Generic Available No

Mechanism of Action Collagen hemostat is an absorbable topical hemostatic agent prepared from purified bovine corium collagen and shredded into fibrils. Physically, microfibrillar collagen hemostat yields a large surface area. Chemically, it is collagen with hydrochloric acid noncovalently bound to some of the available amino groups in the collagen molecules. When in contact with a bleeding surface, collagen hemostat attracts platelets which adhere to its fibrils and undergo the release phenomenon. This triggers aggregation of the platelets into thrombi in the interstices of the fibrous mass, initiating the formation of a physiologic platelet plug.

Pharmacodynamics/Kinetics

Onset: Hemostasis: 2-5 minutes

Absorption: ≥8 weeks

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Collagen; Collagen Absorbable Hemostat; MCH; Microfibrillar Collagen Hemostat

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Collagenase

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English

Jump To Field (Select Field Name)

Pronunciation(KOL la je nase)
U.S. Brand NamesSantyl®
Pharmacologic CategoryEnzyme, Topical Debridement
Use: Labeled IndicationsPromotes debridement of necrotic tissue in dermal ulcers and severe burns

Orphan drug: Injection: Treatment of Peyronie's disease; treatment of Dupytren's disease

Dosing: AdultsDermal ulcers, burns: Topical: Apply once daily.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Administration: TopicalFor external use only. Clean target area of all interfering agents listed above. If infection is persistent, apply powdered antibiotic first. Do not introduce into major body cavities. Monitor debilitated patients for systemic bacterial infections.
ContraindicationsHypersensitivity to collagenase or any component of the formulation
Warnings/Precautions

Special populations:

- Debilitated patients: Monitor debilitated patients for systemic bacterial infections because debriding enzymes may increase the risk of bacteremia.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Administration: For external use only; avoid contact with eyes.

Geriatric ConsiderationsPreventive skin care should be instituted in all older patients at high risk for pressure ulcers. Collagenase is indicated in stage 3 and 4 pressure ulcers.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown
Adverse ReactionsFrequency not defined.

Local: Irritation, pain and burning may occur at site of application

Postmarketing and/or case reports: Hypersensitivity reaction

Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringFor external use only. Clean target area of all interfering agents (eg, detergents, benzalkonium chloride, hexachlorophene, nitrofurazone, tincture of iodine, and heavy metal ions silver and mercury). If infection is persistent, apply powdered antibiotic first. Do not introduce into major body cavities. Monitor debilitated patients for systemic bacterial infections. When applied to large areas or for extensive periods of time, monitor for adverse reactions. Teach patient (or caregiver) appropriate application (if self administered) and adverse symptoms to report.
Patient EducationUse exactly as directed; do not overuse. Clean target area of all interfering agents (eg, detergents, benzalkonium chloride, hexachlorophene, nitrofurazone, tincture of iodine, and heavy metal ions silver and mercury). Wear gloves to apply a thin film to affected area. If dressing is necessary, use a porous dressing. Avoid contact with eyes. Report increased swelling, redness, rash, itching, signs of infection, worsening of condition, or lack of healing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Ointment:

Santyl®: 250 units/g (15 g, 30 g)

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Ointment (Santyl)

250 units/g (15): $55.99

Mechanism of ActionCollagenase is an enzyme derived from the fermentation of *Clostridium histolyticum* and differs from other proteolytic enzymes in that its enzymatic action has a high specificity for native and denatured collagen. Collagenase will not attack collagen in healthy tissue or newly formed granulation tissue. In addition, it does not act on fat, fibrin, keratin, or muscle.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

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International Brand NamesIruxol Mono (BE, BR, ZA); Iruxol Simplex (CO, PE)

COMLA

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Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's

Regimen

Cyclophosphamide: I.V.: 1500 mg/m^2 day 1

[total dose/cycle = 1500 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day (maximum 2 mg) days 1, 8, and 15

[total dose/cycle = 4.2 mg/m^2]

Methotrexate: I.V.: 120 mg/m^2/day days 22, 29, 36, 43, 50, 57, 64, and 71

[total dose/cycle = 960 mg/m^2]

Leucovorin: Oral: 25 mg/m^2 every 6 hours for 4 doses (beginning 24 hours after each methotrexate dose)

[total dose/cycle = 800 mg/m^2]

Cytarabine: I.V.: 300 mg/m^2/day days 22, 29, 36, 43, 50, 57, 64, and 71

[total dose/cycle = 2400 mg/m^2]

Repeat cycle every 85 days

References

Sweet DL, Golomb HM, Ultmann JE, et al, âCyclophosphamide, Vincristine, Methotrexate With Leucovorin Rescue, and Cytarabine (COMLA) Combination Sequential Chemotherapy for Advanced Diffuse Histiocytic Lymphoma,â *Ann Intern Med*, 1980, 92(6):785-90.[PubMed 6992679]

COMP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lymphoma, Hodgkin's Disease
Regimen Use Lymphoma, Hodgkin's disease; Lymphoma, non-Hodgkin's disease
Regimen

Cyclophosphamide: I.V.: 1200 mg/m^2 day 1, cycle 1

[total dose/cycle = 1200 mg/m^2]

followed by I.V.: 1000 mg/m^2 day 1 on subsequent cycles

[total dose/cycle = 1000 mg/m^2]

Vincristine: I.V.: 2 mg/m^2/day (maximum 2 mg) days 3, 10, 17, 24, cycle 1

[total dose/cycle = 8 mg/m^2]

followed by I.V.: 1.5 mg/m^2/day days 1 and 4, on subsequent cycles

[total dose/cycle = 3 mg/m^2]

Methotrexate: I.V.: 300 mg/m^2 day 12

[total dose/cycle = 300 mg/m^2]

Prednisone: Oral: 60 mg/m^2/day (maximum 60 mg) days 3 to 30 then taper over next 7 days, cycle 1

[total dose/cycle = 1680 mg/m^2 + taper over next 7 days]

followed by Oral: 60 mg/m^2 (maximum 60 mg) days 1 to 5, on subsequent cycles

[total dose/cycle = 300 mg/m^2]

Maintenance cycles repeat every 28 days

References

Anderson JR, Wilson JF, Jenkin DT, et al, âChildhood Non-Hodgkin's Lymphoma. The Results of a Randomized Therapeutic Trial Comparing a 4-Drug Regimen (COMP) With a 10-Drug Regimen (LSA2-L2).â *N Engl J Med*, 1983, 308(10):559-65.[PubMed 6338381]

Conivaptan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(koe NYE vap tan)

U.S. Brand NamesVaprisol®

Pharmacologic CategoryVasopressin Antagonist

Use: Labeled IndicationsTreatment of euvolemic and hypervolemic hyponatremia in hospitalized patients

Dosing: AdultsEuvolemic hyponatremia: I.V.:

Loading dose: 20 mg infused over 30 minutes, followed by continuous infusion of 20 mg over 24 hours

Maintenance: 20 mg/day as continuous infusion over 24 hours; may titrate to maximum of 40 mg/day if serum sodium not rising sufficiently; total duration of therapy not to exceed 4 days

Dosing: ElderlyRefer to adult dosing.

Administration: I.V.For intravenous use only; do not administer undiluted; infuse into large veins and change infusion site every 24 hours to minimize vascular irritation

Administration: I.V. DetailpH: 3

StorageStore ampuls in original cardboard container at 15°C to 30°C (59°F to 86°F); protect from light. After dilution, infusion bag (final concentration of 0.08-0.2 mg/mL) is stable at room temperature for 24 hours.

ReconstitutionDilute loading dose of 20 mg in 100 mL D_5W and continuous infusion dose of 20-40 mg in 250 mL D_5W.

CompatibilityStable in D_5W; **incompatible** with LR, NS.

ContraindicationsHypersensitivity to conivaptan or any component of the formulation; use in hypovolemic hyponatremia; concurrent use with strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, ritonavir, indinavir, and clarithromycin)

Warnings/Precautions

Concerns related to adverse effects:

- Hypotension: Discontinue if hypotension occur; may correct and reinitiate if necessary.
- Hypovolemia: Discontinue if hypovolemia occurs; may correct and reinitiate if necessary.
- Injection-site reactions: May cause injection-site reactions.

Disease-related concerns:

- Heart failure: Safety and efficacy have not been established in heart failure patients. Use in 79 hypervolemic, hyponatremic heart failure patients led to increased adverse events, atrial arrhythmias, and sepsis when compared to 10 similar heart failure patients treated with placebo. In other heart failure studies, conivaptan did not show significant improvements in outcomes over placebo.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- High potential for interactions: Use contraindicated in patients taking strong CYP3A4 inhibitors; use caution in patients taking moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions). Consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Monitor closely for rate of serum sodium increase and neurological status; rapid serum sodium correction (>12 mEq/L/24 hours) can lead to permanent neurological damage. Discontinue use if rate of serum sodium increase is undesirable; may reinitiate infusion (at reduced dose) if hyponatremia persists in the absence of neurological symptoms typically associated with rapid sodium rise.

Geriatric ConsiderationsAdverse events in elderly patients were generally similar to those seen in younger patients. In clinical studies, 52% of patients were >65 years of age and 34% were >75 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies indicate that conivaptan accumulates in the placenta (2.2-fold relative to maternal plasma); systemic exposure to fetus is likely. No teratogenic effects have been observed in animal studies; however, these studies have shown decreased neonatal viability and delayed growth and development at doses lower than those required for therapeutic efficacy. There are no adequate and well-controlled studies in pregnant women. Use only if benefit outweighs risk.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

- Cardiovascular: Orthostatic hypotension (6% to 14%)
- Central nervous system: Fever (5% to 11%)
- Endocrine & metabolic: Hypokalemia (10% to 22%)
- Local: Injection site reactions including pain, erythema, phlebitis, swelling (63% to 73%)

1% to 10%:

- Cardiovascular: Hypertension (6% to 8%), hypotension (5% to 8%), edema (3% to 8%), phlebitis (5%), atrial fibrillation (2% to 5%), ECG abnormality (up to 5%)
- Central nervous system: Headache (8% to 10%), insomnia (4% to 5%), confusion (up to 5%), pain (2%)
- Dermatologic: Pruritus (1% to 5%), erythema (3%)
- Endocrine & metabolic: Hyponatremia (3% to 8%), hypomagnesemia (2% to 5%), hyper-/hypoglycemia (3%)
- Gastrointestinal: Constipation (6% to 8%), vomiting (5% to 7%), diarrhea (up to 7%), nausea (5%), dry mouth (4%), dehydration (2%), oral candidiasis (2%)
- Genitourinary: Urinary tract infection (4% to 5%)
- Hematologic: Anemia (4%)
- Renal: Polyuria (5% to 6%), hematuria (2%)
- Respiratory: Pneumonia (2% to 5%)
- Miscellaneous: Thirst (3% to 6%)
- <1%, postmarketing, and/or case reports (limited to important or life-threatening): Atrial arrhythmias, sepsis

Metabolism/Transport Effects **Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (strong)

Drug Interactions

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Conivaptan. *Risk X: Avoid combination*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Digoxin: Conivaptan may increase the serum concentration of Digoxin. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease the levels/effects of conivaptan.

Monitoring ParametersRate of serum sodium increase, blood pressure, volume status, urine output

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (this is a strong inhibitor of CYP3A4; interactions may increase or decrease levels/effects drugs and increase potential for severe toxicity or loss of effectiveness). Assess results of laboratory tests (serum sodium levels [overly-rapid rise in serum sodium concentration may result in serious sequelae]), therapeutic effectiveness, and adverse response (eg, fluid status, blood pressure, neurological status) at beginning of therapy and at regular intervals during therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsRate of serum sodium increase

Patient EducationDo not take any new medication during therapy without consulting prescriber. This drug can only be given by infusion; report immediately any pain, burning, or swelling at infusion site; sudden chest pain; difficulty breathing or swallowing; or chills. May cause headache (consult prescriber for appropriate analgesic); excessive thirst (maintain recommended fluid intake; sucking lozenges may reduce thirst). Report immediately unusual lethargy or restlessness, spastic limb movements, or seizures. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Vaprisol®: 5 mg/mL (4 mL) [single-use ampul; contains propylene glycol and ethanol]

Generic AvailableNo

ManufacturerAstellas Tokai Co, Ltd

Mechanism of ActionConivaptan is an arginine vasopressin (AVP) receptor antagonist with affinity for AVP receptor subtypes V_{1A} and V_2. The antidiuretic action of AVP is mediated through activation of the V_2 receptor, which functions to regulate water and electrolyte balance at the level of the collecting ducts in the kidney. Serum levels of AVP are commonly elevated in euvolemic or hypervolemic hyponatremia, which results in the dilution of serum sodium and the relative hyponatremic state. Antagonism of the V_2 receptor by conivaptan promotes the excretion of free water (without loss of serum electrolytes) resulting in net fluid loss, increased urine output, decreased urine osmolality, and subsequent restoration of normal serum sodium levels.

Pharmacodynamics/Kinetics

Protein binding: 99%

Metabolism: Hepatic via CYP3A4 to four minimally-active metabolites

Half-life elimination: 6.7-8.6 hours

Excretion: Feces (83%); urine (12%, primarily as metabolites)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dry mouth, oral candidiasis, orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusHeadache is common; may cause insomnia or confusion

Mental Health: Effects on Psychiatric TreatmentAdverse effects associated with this agent may mimic those of psychotropic agents (eg, headache with SSRIs or polyuria with lithium). Consider this when evaluating patients' side effect burden. Carbamazepine, phenytoin, and phenobarbital may decrease the effects of conivaptan. Conversely, nefazodone may increase conivaptan levels. Conivaptan may increase levels of benzodiazepines (midazolam and triazolam are contraindicated), mirtazapine, nefazodone, sildenafil, and venlafaxine.

Index TermsConivaptan Hydrochloride; YM087

COP-BLAM

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's

Regimen

Cyclophosphamide: I.V.: 400 mg/m^2 day 1

[total dose/cycle = 400 mg/m^2]

Vincristine: I.V.: 1 mg/m^2 day 1

[total dose/cycle = 1 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 10

[total dose/cycle = 400 mg/m^2]

Bleomycin: I.V.: 15 mg day 14

[total dose/cycle = 15 mg]

Doxorubicin: I.V.: 40 mg/m^2 day 1

[total dose/cycle = 40 mg/m^2]

Procarbazine: Oral: 100 mg/m^2/day days 1 to 10

[total dose/cycle = 1000 mg/m^2]

References

Salles G, Shipp MA, and Coiffier B, “Chemotherapy of Non-Hodgkin's Aggressive Lymphomas,” *Semin Hematol*, 1994, 31(1):46-69. [PubMed 8122135]

Urba WJ, Duffey PL, and Longo DL, “Treatment of Patients With Aggressive Lymphomas: An Overview,” *J Natl Cancer Inst Monogr*, 1990, (10):29-37.[PubMed 2189474]

COPE

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Brain Tumors

Regimen Use Brain tumors

Index Terms Baby Brain I

Regimen

Cycle A:

Vincristine: I.V.: 0.065 mg/kg/day (maximum 1.5 mg) days 1 and 8

[total dose/cycle = 0.13 mg/kg]

Cyclophosphamide: I.V.: 65 mg/kg day 1

[total dose/cycle = 65 mg/kg]

Cycle B:

Cisplatin: I.V.: 4 mg/kg day 1

[total dose/cycle = 4 mg/kg]

Etoposide: I.V.: 6.5 mg/kg/day days 3 and 4

[total dose/cycle = 13 mg/kg]

Repeat cycle every 28 days in the following sequence: AABAAB

References

Duffner PK, Horowitz ME, Krischer JP, et al â Postoperative Chemotherapy and Delayed Radiation in Children Less Than Three Years of Age With Malignant Brain Tumors,â *N Engl J Med*, 1993, 328(24):1725-31.[PubMed 8388548]

COPP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lymphoma, non-Hodgkin's
Regimen Use Lymphoma, non-Hodgkin's
Index Terms C MOPP
Regimen

Cyclophosphamide: I.V.: 450-650 mg/m^2/day days 1 and 8

[total dose/cycle = 900-1300 mg/m^2]

Vincristine: I.V.: 1.4-2 mg/m^2/day (maximum 2 mg) days 1 and 8

[total dose/cycle = 2.8-4 mg/m^2]

Procarbazine: Oral: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14

[total dose/cycle = 560 mg/m^2]

Repeat cycle every 3-4 weeks

References

Brereton HD, Young RC, Longo DL, et al, âA Comparison Between Combination Chemotherapy and Total Body Irradiation Plus Combination Chemotherapy in Non-Hodgkin's Lymphoma,â *Cancer*, 1979, 43(6):2227-31.[PubMed 378350]

Corticorelin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Acthrel® may be confused with Acthar®

Corticorelin may be confused with corticotropin

Pronunciation(kor ti koe REL in)

U.S. Brand NamesActhrel®

Pharmacologic CategoryDiagnostic Agent

Use: Labeled IndicationsDiagnostic test used in adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome to differentiate between pituitary and ectopic production of ACTH

Dosing: AdultsTesting pituitary corticotrophin function: I.V.: 1 mcg/kg; dosages >100 mcg have been associated with an increase in adverse effects

Note: Venous blood samples should be drawn 15 minutes before and immediately prior to corticorelin administration to determine baseline ACTH and cortisol. At 15-, 30-, and 60 minutes after administration, venous blood samples should be drawn again to determine response. **Basal and peak responses differ depending on AM or PM administration; therefore, any repeat evaluations are recommended to be done at the same time of day as initial testing.**

Administration: I.V.Administer I.V. over 30-60 seconds

Administration: I.V. DetailUse of heparin to maintain patency is not recommended.

ContraindicationsHypersensitivity to corticorelin or any component of the formulation

Warnings/Precautions

Concurrent drug therapy issues:

- Heparin: Use of heparin to maintain I.V. patency is not recommended; may increase risk of hypotension.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children (limited data).

Dosage form specific issues:

- Sheep derived: Use with caution in patients with previous reactions to sheep products (lanolin).

Other warnings/precautions:

- Bolus doses: Doses administered as a bolus or in excess of recommendations have been associated with hypotension, transient tachycardia, dyspnea, chest tightness, loss of consciousness. and asystole. Infusion over 30 seconds may reduce the potential for these effects.

- False negative responses: May occur in 5% to 10% of patients.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Cardiovascular: Flushing (face, neck and upper chest, 16%)

1% to 10%:

Gastrointestinal: Metallic taste (transient, 5%)

Respiratory: Dyspnea (urge to inspire, 6%)

<1% (Limited to important or life-threatening): Hypotension (severe), seizure

Drug Interactions

Corticosteroids: May diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Heparin: May enhance the adverse/toxic effect of Corticorelin. Significant hypotension and bradycardia have been previously attributed to this combination. *Risk X: Avoid combination*

Reference Range

High basal plasma ACTH and cortisol (20-40 mcg/dL) resulting in **increased** plasma ACTH and cortisol after administration of test indicates **ACTH-dependent disease of pituitary origin.**

High basal plasma ACTH (may be very high) and cortisol (20-40 mcg/dL) resulting in **little to no change** in plasma ACTH and cortisol after administration of test indicates **ACTH-dependent syndrome of ectopic origin.**

Nursing: Physical Assessment/MonitoringMonitor patient closely when administering medication. Can cause hypotension, transient tachycardia, dyspnea, chest tightness, loss of consciousness, and asystole.

Patient EducationMay cause flushing or metallic taste sensation. Report difficulty breathing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as trifluoroacetate:

Acthrel®: 100 mcg [ovine derived; contains lactose 10 mg]

Generic AvailableNo

ManufacturerFerring Pharmaceuticals

Mechanism of ActionStimulates adrenocorticotropic hormone (ACTH) release from anterior pituitary. ACTH stimulates the adrenal cortex to produce cortisol.

Pharmacodynamics/Kinetics

Onset: I.V.: Plasma ACTH level increases 2 minutes after injection; plasma cortisol level increases within 10 minutes after injection

Duration: I.V.: Plasma ACTH and cortisol levels remain elevated for up to 2 hours

Time to peak, plasma: ACTH: 15-60 minutes; cortisol: 30-120 minutes; both levels show a dose-dependent, biphasic response with a second lower peak 2-3 hours after injection

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCorticorelin Ovine Triflutate; Human Corticotrophin-Releasing Hormone, Analogue; Ovine Corticotrophin-Releasing Hormone

References

Newell-Price J, Bertagna X, Grossman AB, et al, “Cushing’s Syndrome,” *Lancet*, 2006, 367(9522):1605-17.[PubMed 16698415]

Nieman LK, Oldfield EH, Wesley R, et al, “A Simplified Morning Ovine Corticotropin-Releasing Hormone Stimulation Test for the Differential Diagnosis of Adrenocorticotropin-Dependent Cushing’s Syndrome,” *J Clin Endocrinol Metab*, 1993, 77(5):1308-12.[PubMed 8077325]

Corticotropin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Corticotropin may be confused with corticorelin

Pronunciation(kor ti koe TROE pin)
U.S. Brand NamesH.P. Acthar® Gel
Pharmacologic CategoryCorticosteroid, Systemic
Use: Labeled IndicationsAcute exacerbations of multiple sclerosis; diagnostic aid in adrenocortical insufficiency, severe muscle weakness in myasthenia gravis

Cosyntropin is preferred over corticotropin for diagnostic test of adrenocortical insufficiency (cosyntropin is less allergenic and test is shorter in duration)

Dosing: Adults

Acute exacerbation of multiple sclerosis: I.M.: 80-120 units/day for 2-3 weeks

Repository injection: I.M., SubQ: 40-80 units every 24-72 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Anti-inflammatory/immunosuppressant: I.M.: 0.8 units/kg/day or 25 units/m^2/day divided every 12-24 hours

Infantile spasms: Various regimens have been used. Some neurologists recommend low-dose ACTH (5-40 units/day) for short periods (1-6 weeks), while others recommend larger doses of ACTH (40-160 units/day) for long periods of treatment (3-12 months). Well designed comparative dosing studies are needed. Example of low dose regimen:

Initial: I.M.: 20 units/day for 2 weeks, if patient responds, taper and discontinue; if patient does not respond, increase dose to 30 units/day for 4 weeks then taper and discontinue

Usual dosage range: I.M.: 20-40 units/day or 5-8 units/kg/day in 1-2 divided doses; range: 5-160 units/day

Note: Oral prednisone (2 mg/kg/day) was as effective as I.M. ACTH gel (20 units/day) in controlling infantile spasms

Dietary ConsiderationsMay increase renal loss of potassium, calcium, zinc, and vitamin C; may need to increase dietary intake or give supplements.
StorageStore in the refrigerator. Warm gel before administration.
ContraindicationsHypersensitivity to corticotropin or any component of the formulation; scleroderma; osteoporosis; systemic fungal infections; ocular herpes simplex; peptic ulcer
Pregnancy Risk FactorC
Pregnancy ConsiderationsEmbryocidal effects may be observed following corticotropin use during pregnancy. Endogenous ACTH levels are increased during pregnancy. Some studies have shown an association between first trimester systemic corticosteroid use and oral clefts; adverse events in the fetus/neonate have been noted in case reports following large doses of systemic corticosteroids during pregnancy.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsCorticosteroids are excreted in human milk; information specific to corticotropin has not been located.
Adverse ReactionsFrequency not defined.

Central nervous system: Insomnia, nervousness

Dermatologic: Hirsutism

Endocrine & metabolic: Diabetes mellitus

Gastrointestinal: Increased appetite, indigestion

Neuromuscular & skeletal: Arthralgia

Ocular: Cataracts

Respiratory: Epistaxis

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, gelatin: 80 units/mL (5 mL)

Generic AvailableNo

Mechanism of ActionStimulates the adrenal cortex to secrete adrenal steroids (including hydrocortisone, cortisone), androgenic substances, and a small amount of aldosterone

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia and nervousness are common; may cause euphoria or hallucinations

Mental Health: Effects on Psychiatric TreatmentBarbiturates may decrease the levels of corticotropin

Index TermsACTH; Adrenocorticotropic Hormone; Corticotropin, Repository

References

Ostensen M, “Optimisation of Antirheumatic Drug Treatment in Pregnancy,” *Clin Pharmacokinet*, 1994, 27(6):486-503.[PubMed 7882637]

Pradat P, Robert-Gnansia E, Di Tanna GL, et al, “First Trimester Exposure to Corticosteroids and Oral Clefts,” *Birth Defects Res A Clin Mol Teratol*, 2003, 67(12):968-70.[PubMed 14745915]

Smith R, “Parturition,” *N Engl J Med*, 2007, 356(3):271-83. [PubMed 17229954]

International Brand NamesAcortan (DE); ACTH (AT); Acthar (IE, ZA); Acthelea (AR); Trofocortina (IT)

Cortisone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cortisone may be confused with Cortizone®

Pronunciation(KOR ti sone)

Pharmacologic CategoryCorticosteroid, Systemic

Use: Labeled IndicationsManagement of adrenocortical insufficiency

Dosing: AdultsIf possible, administer glucocorticoids before 9 AM to minimize adrenocortical suppression; dosing depends upon the condition being treated and the response of the patient. **Note:** Supplemental doses may be warranted during times of stress in the course of withdrawing therapy.

Anti-inflammatory or immunosuppressive: Oral: 25-300 mg/day in divided doses every 12-24 hours

Physiologic replacement: Oral: 25-35 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricIf possible, administer glucocorticoids before 9 AM to minimize adrenocortical suppression; dosing depends upon the condition being treated and the response of the patient. **Note:** Supplemental doses may be warranted during times of stress in the course of withdrawing therapy.

Anti-inflammatory or immunosuppressive: Oral: 2.5-10 mg/kg/day **or** 20-300 mg/m^2/day in divided doses every 6-8 hours

Physiologic replacement: Oral: 0.5-0.75 mg/kg/day **or** 20-25 mg/m^2/day in divided doses every 8 hours

Dosing: Renal Impairment

Hemodialysis: Supplemental dose is not necessary.

Peritoneal dialysis: Supplemental dose is not necessary.

Calculations

- Corticosteroid Conversion

Administration: OralInsoluble in water.

Dietary ConsiderationsMay need diet with increased potassium, pyridoxine, vitamin C, vitamin D, folate, calcium, and phosphorus and decreased sodium; may be taken with food to decrease GI distress.

ContraindicationsHypersensitivity to cortisone acetate or any component of the formulation; serious infections, except septic shock or tuberculous meningitis; administration of live virus vaccines

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox should be avoided; corticosteroids should not be used to treat ocular herpes simplex. Corticosteroids should not be used for cerebral malaria or viral hepatitis. Close observation is required in patients with latent tuberculosis and/or TB reactivity; restrict use in active TB (only in conjunction with antituberculosis treatment).

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Myopathy: Acute myopathy has been reported with high dose corticosteroids, usually in patients with neuromuscular transmission disorders; may involve ocular and/or respiratory muscles; monitor creatine kinase; recovery may be delayed.

- Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with HF; long-term use has been associated with fluid retention and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.

- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids.

- Myocardial infarction (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Consider routine eye exams in chronic users.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Elderly: Because of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly in the smallest possible effective dose for the shortest duration.

- Pediatrics: May affect growth velocity; growth should be routinely monitored in pediatric patients.

Other warnings/precautions:

- Discontinuation of therapy: Withdraw therapy with gradual tapering of dose.

Geriatric ConsiderationsBecause of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly, in the smallest possible dose, and for the shortest possible time.

Pregnancy ConsiderationsAdverse events have been observed with corticosteroids in animal reproduction studies. Cortisone is found in cord blood; endogenous maternal cortisol (active) is metabolized by placental enzymes to cortisone (inactive), regulating the amount of maternal glucocorticoids reaching the fetus. Some studies have shown an association between first trimester systemic corticosteroid use and oral clefts; adverse events in the fetus/neonate have been noted in case reports following large doses of systemic corticosteroids during pregnancy. Women exposed to cortisone during pregnancy for the treatment of an autoimmune disease may contact the OTIS Autoimmune Diseases Study at 877-311-8972.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Insomnia, nervousness

Gastrointestinal: Increased appetite, indigestion

1% to 10%:

Dermatologic: Hirsutism

Endocrine & metabolic: Diabetes mellitus

Neuromuscular & skeletal: Arthralgia

Ocular: Cataracts, glaucoma

Respiratory: Epistaxis

<1%: Abdominal distention, acne, alkalosis, amenorrhea, bruising, Cushing's syndrome, delirium, edema, euphoria, fractures, glucose intolerance, growth suppression, hallucinations, headache, hyperglycemia, hyperpigmentation, hypersensitivity reactions, hypertension, hypokalemia, mood swings, muscle wasting, myalgia, nausea, osteoporosis, pancreatitis, peptic ulcer, pituitary-adrenal axis suppression, pseudotumor cerebri, psychoses, seizure, skin atrophy, sodium and water retention, ulcerative esophagitis, vertigo, vomiting

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Somatropin: May diminish the therapeutic effect of Cortisone. Growth hormone may reduce the conversion of cortisone to the active cortisol metabolite. *Risk D: Consider therapy modification*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Limit caffeine intake.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as acetate: 25 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Cortisone Acetate)

25 mg (30): $17.99

Mechanism of ActionDecreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Oral: ~2 hours; I.M.: 20-48 hours

Duration: 30-36 hours

Absorption: Slow

Distribution: Muscles, liver, skin, intestines, and kidneys; crosses placenta; enters breast milk

Metabolism: Hepatic to inactive metabolites

Half-life elimination: 0.5-2 hours; End-stage renal disease: 3.5 hours

Excretion: Urine and feces

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentA compromised immune response may occur if patient has been taking systemic cortisone. The need for corticosteroid coverage in these patients should be considered before any dental treatment; consult with physician.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia and nervousness are common; may cause euphoria or hallucinations

Mental Health: Effects on Psychiatric TreatmentBarbiturates may decrease the levels of cortisone

Index TermsCompound E; Cortisone Acetate

References

Beitins IZ, Bayard F, Ances IG, et al, “The Transplacental Passage of Prednisone and Prednisolone in Pregnancy Near Term,” *J Pediatr*, 1972, 81(5):936-45.[PubMed 5086721]

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

McGee S and Hirschmann J, “Use of Corticosteroids in Treating Infectious Diseases,” *Arch Intern Med*, 2008, 168(10):1034-46.[PubMed 18504331]

Ostensen M, “Optimisation of Antirheumatic Drug Treatment in Pregnancy,” *Clin Pharmacokinet*, 1994, 27(6):486-503.[PubMed 7882637]

Pradat P, Robert-Gnansia E, Di Tanna GL, et al, “First Trimester Exposure to Corticosteroids and Oral Clefts,” *Birth Defects Res A Clin Mol Teratol*, 2003, 67(12):968-70.[PubMed 14745915]

Sun K, Adamson SL, Yang K, et al, “Interconversion of Cortiosl and Cortisone by 11Beta-Hydroxysteroid Dehydrogenases Type 1 and 2 in the Perfused Human Placenta,” *Placenta*, 1999, 20(1):13-19.[PubMed 9950140]

International Brand NamesAdreson (BE, HN, HU, LU, NL, PL); Altesona (ES); Colirio Collado Cortioftal (ES); Cortal (SE); Cortate (AU, HK, MY); Cortioftal (ES); Cortisate (DK); Cortison (NL); Cortison Augensalbe Dr. Winzer (DE); Cortison Ciba (CH, DE); Cortison Nycomed (NO); Cortisone (FR, NZ, PL); Cortisone Acetate (CY, IL); Cortistab (GB); Cortisyl (GB, IE); Cortone Acetato (IT); Cortone-Azetat (AT)

Cosyntropin

Lexi-Drugs Online

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Medication Safety Issues

Sound-alike/look-alike issues:

Cortrosyn® may be confused with colchicine, Cotazym®

Pronunciation(koe sin TROE pin)
U.S. Brand NamesCortrosyn®
Canadian Brand NamesCortrosyn®
Pharmacologic CategoryDiagnostic Agent
Use: Labeled IndicationsDiagnostic test to differentiate primary adrenal from secondary (pituitary) adrenocortical insufficiency
Dosing: Adults

Diagnosis of adrenocortical insufficiency: I.M., I.V. (over 2 minutes): Peak plasma cortisol concentrations usually occur 45-60 minutes after cosyntropin administration

0.25-0.75 mg

Note: When greater cortisol stimulation is needed, an I.V. infusion may be used: 0.25 mg administered at 0.04 mg/hour over 6 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Diagnosis of adrenocortical insufficiency: I.M., I.V. (over 2 minutes): Peak plasma cortisol concentrations usually occur 45-60 minutes after cosyntropin administration.

Children <2 years: 0.125 mg

Children >2 years: 0.25 mg

Note: When greater cortisol stimulation is needed, an I.V. infusion may be used: Children >2 years: Refer to adult dosing.

Administration: I.V.Administer I.V. doses over 2 minutes
Storage

Powder for injection: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F).

I.V. infusion: Stable for 12 hours at room temperature; stable for 21 days under refrigeration.

Reconstitution

I.M.: Reconstitute cosyntropin 0.25 mg with NS 1 mL.

I.V. push: Reconstitute cosyntropin 0.25 mg with NS 2-5 mL.

I.V. infusion: Mix in NS or D_5W.

ContraindicationsHypersensitivity to cosyntropin or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Corticotropin allergy: Use with caution in patients with a history of allergic reactions to corticotropin or pre-existing allergic disease.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, hypertension, peripheral edema, tachycardia

Dermatologic: Rash

Local: Whealing with redness at the injection site

Miscellaneous: Anaphylaxis, hypersensitivity reaction

Drug InteractionsThere are no known significant interactions.
Test InteractionsDecreased effect: Spironolactone, hydrocortisone, cortisone, etomidate

Reference RangeNormal baseline cortisol; increase in serum cortisol after cosyntropin injection of >7 mcg/dL or peak response >18 mcg/dL; plasma cortisol concentrations should be measured immediately before and exactly 30 minutes after a dose

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 0.25 mg

Generic AvailableNo

ManufacturerOrganon Inc

Mechanism of ActionStimulates the adrenal cortex to secrete adrenal steroids (including hydrocortisone, cortisone), androgenic substances, and a small amount of aldosterone

Pharmacodynamics/KineticsTime to peak, serum: I.M., IVP: ~1 hour; plasma cortisol levels rise in healthy individuals within 5 minutes

Pharmacotherapy PearlsEach 0.25 mg of cosyntropin is equivalent to 25 units of corticotropin.

Patient should not receive corticosteroids or spironolactone the day prior and the day of the test.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentBarbiturates may decrease the levels of cosyntropin

Anesthesia and Critical Care Concerns/Other Considerations

Septic Shock: A recent randomized, double-blind, placebo-controlled trial assessed whether low-dose corticosteroid administration could improve 28-day survival in patients with septic shock and relative adrenal insufficiency. Relative adrenal insufficiency was defined as an inappropriate response to corticotropin administration (increase of serum cortisol of ≤9 mcg/dL from baseline). Cortisol levels were drawn immediately before corticotropin administration and 30-60 minutes afterwards. Three hundred adult septic shock patients requiring mechanical ventilation and vasopressor support were randomized to either hydrocortisone (50 mg IVP every 6 hours) and fludrocortisone (50 mcg tablet daily via nasogastric tube) or matching placebos for 7 days. In patients who did not appropriately respond to corticotropin (nonresponders), there were significantly fewer deaths in the active treatment group. Vasopressor therapy was withdrawn more frequently in this subset of the active treatment group. Adverse events were similar in both groups. Patients who lack adrenal reserve and thus have relative adrenal insufficiency during the stress of septic shock may benefit from physiologic steroid replacement. However, there was a trend for increased mortality in patients who responded to the corticotropin test (increase serum cortisol >9 mcg/dL from baseline). These patients may not benefit from physiologic steroid replacement. Further study is required to better characterize the patient populations who may benefit.

The 2008 Surviving Sepsis Campaign guidelines recommend doses of corticosteroids comparable to >300 mg hydrocortisone daily **not** be used in severe sepsis or septic shock for the purpose of treating septic shock (Grade 1A). They also recommend corticosteroids **not** be administered for the treatment of sepsis in the absence of shock. There is, however, no contraindication to continuing maintenance steroid therapy or to using stress dose steroids if the patient's endocrine or corticosteroid administration history warrants (Grade 1D).

Index TermsSynacthen; Tetracosactide

References

Annane D, Sebille V, Charpentier C, et al, "Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock," *JAMA*, 2002, 288(7):862-71.[PubMed 12186604]

Dellinger RP, Levy MM, Carlet JM, et al, "Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008," *Intensive Care Med*, 2008, 34(1): 17-60. Available at http://www.survivingsepsis.org/system/files/images/2008_20International_20SSC_20Guidelines_1_.pdf[PubMed 18058085]

International Brand NamesCortrosina (BR); Cortrosina Depot (BR); Cortrosinta Depot (PT); Cortrosyn (BE, HU); Cortrosyn Depot (AE, BE, BF, BG, BH, BJ, CI, CY, CZ, EG, ET, FR, GH, GM, GN, HK, HN, HU, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Nuvacthen Depot (ES); Synacthen (AT, AU, BE, CH, CZ, DE, DK, GB, IE, IT, KP, LU, NO, PL, SE); Synacthen Deposito (VE); Synacthen Depot (AE, AT, AU, BF, BG, BH, BJ, CH, CI, CN, CY, CZ, DK, EG, ET, FI, GB, GH, GM, GN, GR, HN, HR, IE, IL, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, NO, OM, PT, QA, SA, SC, SD, SE, SL, SN, SY, TN, TZ, UG, UY, YE, ZA, ZM, ZW); Synacthene (FR)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Chronic Lymphocytic
Regimen UseLeukemia, chronic lymphocytic
Regimen

Chlorambucil: Oral: 30 mg/m^2 day 1

[total dose/cycle = 30 mg/m^2]

Prednisone: Oral: 80 mg/day days 1 to 5

[total dose/cycle = 400 mg]

Repeat cycle every 14 days

References

Raphael B, Anderson JW, Silber R, et al, âComparison of Chlorambucil and Prednisone Versus Cyclophosphamide, Vincristine, and Prednisone as Initial Treatment for Chronic Lymphocytic Leukemia: Long-Term Follow-up of an Eastern Cooperative Oncology Group Randomized Clinical Trial,â *J Clin Oncol*, 1991, 9(5):770-6.[PubMed 2016618]

CP (Ovarian Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Ovarian Cancer]

Regimen UseOvarian cancer

Regimen

Cyclophosphamide: I.V.: 750 mg/m^2 day 1

[total dose/cycle = 750 mg/m^2]

Cisplatin: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 21 days

References

Hainsworth JD, Grosh WW, Burnett LS, et al, “Advanced Ovarian Cancer: Long-Term Results of Treatment With Intensive Cisplatin-Based Chemotherapy of Brief Duration,” *Ann Intern Med*, 1988, 108(2):165-70. [PubMed 3124679]

Neijt JP, ten Bokkel Huinink WW, van der Burg ME, et al, “Randomized Trial Comparing Two Combination Chemotherapy Regimens (CHAP-5 v CP) in Advanced Ovarian Carcinoma,” *J Clin Oncol*, 1987, 5(8):1157-68. [PubMed 3114434]

Omura GA, Brady MF, Homesley HD, et al, “Long-Term Follow-up and Prognostic Factor Analysis in Advanced Ovarian Carcinoma: The Gynecologic Oncology Group Experience,” *J Clin Oncol*, 1991, 9(7):1138-50.[PubMed 1904477]

Cromolyn

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Intal® may be confused with Endal®

NasalCrom® may be confused with Nasacort®, Nasalide®

Pronunciation(KROE moe lin)

U.S. Brand NamesCrolom®; Gastrocrom®; Intal®; NasalCrom® [OTC]

Canadian Brand NamesApo-Cromolyn®; Intal®; Nalcrom®; Nu-Cromolyn; Opticrom®

Pharmacologic CategoryMast Cell Stabilizer

Use: Labeled Indications

Inhalation: May be used as an adjunct in the prophylaxis of allergic disorders, including asthma; prevention of exercise-induced bronchospasm

Nasal: Prevention and treatment of seasonal and perennial allergic rhinitis

Oral: Systemic mastocytosis

Ophthalmic: Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis

Use: Unlabeled/InvestigationalOral: Food allergy, treatment of inflammatory bowel disease

Dosing: Adults

Allergic rhinitis (treatment and prophylaxis): Nasal: Instill 1 spray in each nostril 3-4 times/day

Asthma: For chronic control of asthma, taper frequency to the lowest effective dose (ie, 4 times/day to 3 times/day to twice daily). **Note:** Not effective for immediate relief of symptoms in acute asthmatic attacks; must be used at regular intervals for 2-4 weeks to be effective.

Nebulization solution: Initial: 20 mg 4 times/day; usual dose: 20 mg 3-4 times/day

Metered spray: Initial: 2 inhalations 4 times/day; usual dose: 2-4 inhalations 3-4 times/day

Prophylaxis of bronchospasm (allergen- or exercise-induced):

Note: Administer 10-15 minutes prior to exercise or allergen exposure but no longer than 1 hour before:

Nebulization solution: Single dose of 20 mg

Metered spray: Single dose of 2 inhalations

Conjunctivitis and keratitis: Ophthalmic: 1-2 drops in each eye 4-6 times/day

Mastocytosis: Oral: 200 mg 4 times/day; given $^{1}/_{2}$ hour prior to meals and at bedtime. If control of symptoms is not seen within 2-3 weeks, dose may be increased to a maximum 40 mg/kg/day

Food allergy and inflammatory bowel disease (unlabeled use): Oral: Initial dose: 200 mg 4 times/day; may double the dose if effect is not satisfactory within 2-3 weeks; up to 400 mg 4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Allergic rhinitis (treatment and prophylaxis): Nasal: Children ≥2 years: Refer to adult dosing.

Asthma: Inhalation:

Note: For chronic control of asthma, taper frequency to the lowest effective dose (ie, 4 times/day to 3 times/day to twice daily):

Nebulization solution: Children >2 years: Initial: 20 mg 4 times/day; usual dose: 20 mg 3-4 times/day

Metered spray:

Children 5-12 years: Initial: 2 inhalations 4 times/day; usual dose: 1-2 inhalations 3-4 times/day

Children ≥12 years: Refer to adult dosing.

Prevention of allergen- or exercise-induced bronchospasm:

Note: Administer 10-15 minutes prior to exercise or allergen exposure but no longer than 1 hour before:

Nebulization solution: Children >2 years: Refer to adult dosing.

Metered spray: Children >5 years: Single dose of 2 inhalations

Systemic mastocytosis: Oral:

Children 2-12 years: 100 mg 4 times/day; not to exceed 40 mg/kg/day; given $^1/_2$ hour prior to meals and at bedtime

Children >12 years: Refer to adult dosing.

Food allergy and inflammatory bowel disease (unlabeled use): Oral:

Children <2 years: Not recommended

Children 2-12 years: Initial dose: 100 mg 4 times/day; may double the dose if effect is not satisfactory within 2-3 weeks; not to exceed 40 mg/kg/day

Children >12 years: Refer to adult dosing.

Note: Once desired effect is achieved, dose may be tapered to lowest effective dose

Dosing: Renal ImpairmentSpecific guidelines not available; consider lower dose of oral product.
Dosing: Hepatic ImpairmentSpecific guidelines not available; consider lower dose of oral product.
Administration: OralOral solution: Open ampul and squeeze contents into glass of water; stir well. Administer at least 30 minutes before meals and at bedtime.
Administration: InhalationOral inhalation: Shake canister gently before use; do not immerse canister in water.
Administration: OtherNasal inhalation: Clear nasal passages by blowing nose prior to use.
Dietary ConsiderationsOral: Should be taken at least 30 minutes before meals.
StorageStore at room temperature of 15°C to 30°C (59°F to 86°F); protect from light. Do not use oral solution if solution becomes discolored or forms a precipitate.
CompatibilityNebulizer solution is **compatible** with metaproterenol sulfate, isoproterenol hydrochloride, 0.25% isoetharine hydrochloride, epinephrine hydrochloride, terbutaline sulfate, and 20% acetylcysteine solution for at least 1 hour after their admixture.
ContraindicationsHypersensitivity to cromolyn or any component of the formulation; acute asthma attacks
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis: Severe anaphylactic reactions may occur rarely

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiac arrhythmias.

Dosage form specific issues:

- Ophthalmic: Transient burning or stinging may occur with ophthalmic use.

- Oral: Use with caution in patients with hepatic or renal impairment; dosage adjustment recommended.

Other warnings/precautions:

- Appropriate use: Prophylactic drug with no benefit for acute situations.

- Withdrawal: Caution should be used when withdrawing the drug or tapering the dose as symptoms may reoccur.

Geriatric ConsiderationsElderly often have difficulty with inhaled and ophthalmic dosage forms.
Pregnancy Risk FactorB
Pregnancy ConsiderationsNo data available on whether cromolyn crosses the placenta or clinical effects on the fetus. Available evidence suggests safe use during pregnancy.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsNo data available on whether cromolyn enters into breast milk or clinical effects on the infant.
Adverse Reactions

Inhalation: >10%: Gastrointestinal: Unpleasant taste in mouth

Nasal:

>10%: Respiratory: Increase in sneezing, burning, stinging, or irritation inside of nose

1% to 10%:

Central nervous system: Headache

Gastrointestinal: Unpleasant taste

Respiratory: Hoarseness, cough, postnasal drip

<1% (Limited to important or life-threatening): Anaphylactic reactions, epistaxis

Ophthalmic: Frequency not defined:

Ocular: Conjunctival injection, dryness around the eye, edema, eye irritation, immediate hypersensitivity reactions, itchy eyes, puffy eyes, styes, rash, watery eyes

Respiratory: Dyspnea

Systemic: Frequency not defined:

Cardiovascular: Angioedema, chest pain, edema, flushing, palpitation, premature ventricular contractions, tachycardia

Central nervous system: Anxiety, behavior changes, convulsions, depression, dizziness, fatigue, hallucinations, headache, irritability, insomnia, lethargy, migraine, nervousness, hypoesthesia, postprandial lightheadedness, psychosis

Dermatologic: Erythema, photosensitivity, pruritus, purpura, rash, urticaria

Gastrointestinal: Abdominal pain, constipation, diarrhea, dyspepsia, dysphagia, esophagospasm, flatulence, glossitis, nausea, stomatitis, unpleasant taste, vomiting

Genitourinary: Dysuria, urinary frequency

Hematologic: Neutropenia, pancytopenia, polycythemia

Hepatic: Liver function test abnormal

Local: Burning

Neuromuscular & skeletal: Arthralgia, leg stiffness, leg weakness, myalgia, paresthesia

Otic: Tinnitus

Respiratory: Dyspnea, pharyngitis

Miscellaneous: Lupus erythematosus

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersPeriodic pulmonary function tests

Nursing: Physical Assessment/MonitoringThis is prophylactic therapy, not to be used for acute situations. Assess results of laboratory tests (long-term use) and adverse reactions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsPeriodic pulmonary function

Patient EducationOral: Use as directed; do not increase dosage or discontinue abruptly without consulting prescriber. Take at least 30 minutes before meals. You may experience dizziness or nervousness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); diarrhea (boiled milk, yogurt, or buttermilk may help); or headache or muscle pain (mild analgesic may offer relief). Report persistent insomnia; skin rash or irritation; abdominal pain or difficulty swallowing; unusual cough, bronchospasm, or respiratory difficulty; decreased urination; or if condition worsens or fails to improve. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Nebulizer: Store nebulizer solution away from light. Prepare nebulizer according to package instructions. Clear as much mucus as possible before use. Rinse mouth following each use to prevent opportunistic infection and reduce unpleasant aftertaste. Report if symptoms worsen or condition fails to improve.

Nasal: Instill 1 spray into each nostril 3-4 times a day. You may experience unpleasant taste (rinsing mouth and frequent oral care may help); or headache (mild analgesic may help). Report increased sneezing, burning, stinging, or irritation inside of nose; sore throat, hoarseness, nosebleed; anaphylactic reaction (skin rash, fever, chills, backache, respiratory difficulty, chest pain); or worsening of condition or lack of improvement.

Ophthalmic: For ophthalmic use only. Wash hands before using. Tilt head back and look upward. Put drops of suspension inside lower eyelid. Close eye and roll eyeball in all directions. Do not blink for $^{1}/_{2}$ minute. Apply gentle pressure to inner corner of eye for 30 seconds. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Do not share medication with anyone else. Temporary stinging or blurred vision may occur. Inform prescriber if condition worsens or fails to improve or if you experience eye pain, redness, burning, watering, dryness, double vision, puffiness around eye, vision changes, or other adverse eye response; or worsening of condition or lack of improvement. Do not wear contact lenses during treatment.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol, for oral inhalation, as sodium:

Intal®: 800 mcg/inhalation (8.1 g) [112 metered inhalations; 56 doses], (14.2 g) [200 metered inhalations; 100 doses]

Solution for nebulization, as sodium: 20 mg/2 mL (60s, 120s)

Intal®: 20 mg/2 mL (60s, 120s)

Solution, intranasal, as sodium [spray]:

NasalCrom®: 40 mg/mL (13 mL, 26 mL) [5.2 mg/inhalation; contains benzalkonium chloride]

Solution, ophthalmic, as sodium: 4% (10 mL)

Crolom®: 4% (10 mL) [contains benzalkonium chloride]

Solution, oral, as sodium [concentrate]:

Gastrocrom®: 100 mg/5 mL (96s)

Generic AvailableYes: Excludes aerosol, oral solution

Pricing: U.S. (www.drugstore.com)

Aerosol solution (Intal)

800 mcg/ACT (8.1): $83.12

800 mcg/ACT (14.2): $126.43

Concentrate (Gastrocrom)

100 mg/5 mL (480): $279.70

Nebulization (Cromolyn Sodium)

20 mg/2 mL (120): $87.29

Solution (Crolom)

4% (10): $45.99

Solution (Cromolyn Sodium)

4% (10): $31.99

Mechanism of ActionPrevents the mast cell release of histamine, leukotrienes, and slow-reacting substance of anaphylaxis by inhibiting degranulation after contact with antigens

Pharmacodynamics/Kinetics

Onset: Response to treatment:

Nasal spray: May occur at 1-2 weeks

Ophthalmic: May be seen within a few days; treatment for up to 6 weeks is often required

Oral: May occur within 2-6 weeks

Absorption:

Inhalation: ~8% reaches lungs upon inhalation; well absorbed

Oral: <1% of dose absorbed

Half-life elimination: 80-90 minutes

Time to peak, serum: Inhalation: ~15 minutes

Excretion: Urine and feces (equal amounts as unchanged drug); exhaled gases (small amounts)

Related Information

- Asthma
- Inhalant Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Inhalation: Unpleasant taste.

Systemic: Glossitis, stomatitis, and unpleasant taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCromoglycic Acid; Cromolyn Sodium; Disodium Cromoglycate; DSCG

References

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Expert Panel Report 3, “Guidelines for the Diagnosis and Management of Asthma,” *Clinical Practice Guidelines*, National Institutes of Health, National Heart, Lung, and Blood Institute, NIH Publication No. 08-4051, prepublication 2007. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

Hargreaves MR and Benson MK, “Inhaled Sodium Cromoglycate in Angiotensin-Converting Enzyme Inhibitor Cough,” *Lancet*, 1995, 345(8941):13-6. [PubMed 7799699]

Slater EF, “Cardiac Tamponade and Peripheral Eosinophilia in a Patient Receiving Cromolyn Sodium,” *Chest*, 1978, 73:838.

Walter SR, Evans ME, Richard AJ, et al, “The Fate of Disodium Cromoglycate in Man,” *J Pharm Pharmacol*, 1972, 24:525-31.[PubMed 4403844]

International Brand NamesAlerbul Nasal (CO); Alerbul Oftalmico (CO); Alercocrom (ES); Alerg (DE); Allergo-comod (DE, TW); Allergocrom (TW); Claroftal (AR, PY); Crom-Ophtal (ID); Cromabak (HK); Cromadoses (FR); Cromal AQ (HK); Cromoftal (VE); Cromohexal (ZA); Cromohexal Nasenspray (TW, ZA); Cromolerg (BR); Cromolux (NZ); Cromolyn (PL); Cromoptic (FR, IL); Cromunal (IL); Cronase (IL); Cusicrom (MY, TW); Cusicrom Fuerte Nasal (ES); Dadcrome (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Epicrom (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Frenal (IT); Ifiral (IN); Intal (AE, AR, AT, BB, BG, BH, BM, BR, BS, BZ, CY, CZ, DE, EG, GB, GY, HN, IE, IL, IQ, IR, JM, JO, JP, KW, LB, LY, MX, NL, NZ, OM, PK, PT, QA, SA, SR, SY, TH, TT, TW, UY, YE); Klonalcrom (AR); Lecrolyn (EE); Lomudal (BE, BF, BJ, CH, CI, DK, ET, FI, FR, GH, GM, GN, GR, IT, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, NO, SC, SD, SE, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Lomudal Gastrointestinum (DK, FI, GR); Lomudal Nasal (FI, SE); Lomudal Nesespray (NO); Lomupren-Nasenspray (AT); Lomusol (AT, BE, FR); Lomusol Forte (NL); Lomusol Nasenspray (AT); Nalcrom (CH, GB, HK, IT, NL, NZ, ZA); Nasotal (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Nazotral (CO); Ningmin (CL); Noaler (CO); Noaler Nasal (CO); Oftacon (CN, PE, UY); Opticrom (AE, AT, AU, BB, BE, BH, BM, BS, BZ, CH, CY, CZ, DE, EG, GB, GY, HN, IL, IQ, IR, JM, JO, KW, LB, LY, MX, NL, OM, PT, QA, SA, SG, SR, SY, TH, TR, TT, YE); Opticron (FR); Rilan Nasal (BR); Rynacrom (AE, AU, BB, BH, BM, BS, BZ, CY, EG, FI, GY, HK, IL, IQ, IR, JM, JO, KP, KW, LB, LY, MX, MY, NL, OM, PR, PT, QA, SA, SR, SY, TT, YE); Rynacrom M (BB, BM, BS, BZ, GY, HK, JM, NL, PR, SG, SR, TT, UY); Vicrom (NZ); Vividrin (PH, TH)

Crotalidae Polyvalent Antivenin (Equine)

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Special Alerts**Product Availability: Although this product has been discontinued and current supplies will expire in October 2008, it may still be available for use.**

Pronunciation(kroe TAL ih die pol i VAY lent an tee VEN in (EE kwine))

U.S. Brand NamesAntivenin Polyvalent [Equine] [DSC]

Pharmacologic CategoryAntivenin

Use: Labeled IndicationsNeutralization of venoms of North, Central, and South American crotalids: Rattlesnakes (*Crotalus*, *Sistrurus*); copperhead and cottonmouth moccasins (*Agkistrodon*), including *A. halys* of Korea and Japan; the Fer-de-lance and other species of *Bothrops*; tropical rattler (*Crotalus durissus*), cantil (*A. bilineatus*); bushmaster (*Lachesis mutus*) of South and Central America

Dosing: AdultsCrotalid envenomation: I.M., I.V.:

Initial sensitivity test: 0.02-0.03 mL of a 1:10 dilution of normal horse serum or antivenin given intracutaneously; also give a control test using normal saline in the opposite extremity. A positive reaction occurs within 5-30 minutes. A negative reaction does not rule out the possibility of an immediate or delayed reaction with treatment.

Minimal envenomation: 20-40 mL (2-4 vials)

Moderate envenomation: 50-90 mL (5-9 vials)

Severe envenomation: ≥100-150 mL (10-15 vials)

Note: Variability in the required dose has been reported (5-43 vials administered). The entire initial dose of antivenin should be administered as soon as possible to be most effective (within 4 hours after the bite). I.V. is the preferred route of administration. When administered I.V., infuse the initial 5-10 mL over 3-5 minutes while carefully observing the patient for signs and symptoms of sensitivity reactions. If no reaction occurs, continue infusion at a safe I.V. fluid delivery rate. Additional doses of antivenin are based on clinical response to the initial dose. If swelling continues to progress, symptoms increase in severity, hypotension occurs, or decrease in hematocrit appears, an additional 10-50 mL (1-5 vials) should be administered.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing. **Note:** Clinical trials included patients as young as 11 years of age. Specific pediatric studies have not been conducted. Because the absolute venom dose is expected to be the same in adults and children, adult dosing should be used. Products contain thimerosal, which in high doses has been associated with neurological and renal toxicity. Very young children are most susceptible.

Administration: I.M.May be used in cases of minimal envenomation; I.V. route is preferred. Administer into a large muscle mass, preferably the gluteal area. Avoid nerve trunks. Do not inject into finger or toe.

Administration: I.V. Infuse the initial 5-10 mL dilution over 3-5 minutes while carefully observing the patient for signs and symptoms of sensitivity reactions. If no reaction occurs, continue infusion at a safe I.V. fluid delivery rate. Total dose should be administered as soon as possible.

StorageStore in refrigerator; avoid temperatures >37°C.

ReconstitutionFor I.V. infusion, reconstitute each vial with 10 mL of bacteriostatic water for injection provided with the antivenin. Mix by gentle swirling; use within 48 hours. For prepare for I.V. use, further prepare a 1:1 to 1:10 dilution of reconstituted antivenin in normal saline or D_5W; use within 24 hours.

ContraindicationsHypersensitivity to any component of the formulation, unless the benefits outweigh the risks and appropriate management for anaphylaxis is available

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity: Anaphylaxis and anaphylactoid reactions are possible due to animal proteins in the antivenin; immediate treatment (including epinephrine 1:1000) should be available. Patients should also be monitored for delayed allergic reactions. Antivenin administration should be stopped in patients who develop severe allergic reactions.

- Delayed serum sickness: Delayed serum sickness may occur 1-3 weeks from administration (especially when large doses are used), even with a negative allergic history and absence of reaction to skin test.

Disease-related concerns:

- Snakebite: Should be used within 4-6 hours of snakebite to prevent clinical deterioration and development of coagulation abnormalities. Coagulation abnormalities are due directly to snake venom interference with the coagulation cascade. Recurrent coagulopathy occurs in approximately 50% of patients and may persist for 1-2 weeks or more. Repeat dosing may be indicated. Patients should be monitored for at least 1 week and evaluated for other pre-existing conditions associated with bleeding disorders. In severe rattlesnake bites, a decrease in platelets may occur, lasting hours to several days. Blood products are generally ineffective as they are rapidly consumed by circulating venom.

Dosage form specific issues:

- Product components: Contains phenol and thimerosal. It is made from horse serum; carefully review allergies and history of exposure to products containing horse serum. History of atopic sensitivity to horses may increase risk of immediate sensitivity reactions; use with caution in patients with asthma, hay fever, or urticaria. Use of beta-blockers may also increase the risk of hypersensitivity. A skin test for horse-serum sensitivity should be done prior to treatment; the absence of a skin hypersensitivity reaction does not exclude anaphylaxis or hypersensitivity following antivenin administration. False-negative rate for skin testing is 10% with similar agents. Conversely, hypersensitivity is not an absolute contraindication in a significantly envenomated patient.

Adverse ReactionsFrequency not always defined.

Cardiovascular: Chest pain, hypotension

Central nervous system: Chills

Gastrointestinal: Anorexia, nausea

Respiratory: Asthma, cough, dyspnea, wheezing

Miscellaneous: Allergic reaction, anaphylaxis, hypersensitivity (23% to 56%), serum sickness (up to 50%)

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersVital signs; CBC, platelet count, prothrombin time, aPTT, fibrinogen levels, fibrin split products, clot retraction, bleeding and coagulation times, BUN, electrolytes, bilirubin, size of bite area (repeat every 15-30 minutes); intake and output, signs and symptoms of anaphylaxis/allergy. CBC, platelet counts, and clotting studies are evaluated at 6-hour intervals until patient is stable.

Monitoring: Lab TestsCBC, platelet count, prothrombin time, aPTT, fibrinogen levels, fibrin split products, clot retraction, bleeding and coagulation times, BUN, electrolytes, bilirubin. CBC, platelet counts, and clotting studies are evaluated at 6-hour intervals until patient is stable.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution:

Antivenin (Crotalidae) polyvalent: Derived from *Crotalus adamanteus*, *C. atrox*, *C. durissus terrificus*, and *Bothrops atrox* snake venoms [contains phenol and thimerosal; packaged with diluent and normal horse serum for sensitivity testing] [DSC]

Generic AvailableNo

Mechanism of ActionA venom-specific fragment of IgG, which binds and neutralizes venom toxin, helping to remove the toxin from the target tissue and eliminate it from the body.

Pharmacodynamics/Kinetics

Time to peak, serum: I.M.: ≥8 hours

Pharmacotherapy Pearls

Minimal envenomation: Swelling, pain, and bruising are limited to immediate bite site; no systemic signs and symptoms; normal coagulation parameters; no clinical evidence of bleeding.

Moderate envenomation: Swelling, pain, and bruising are limited to less than a full extremity (or <50 cm if bite was on head or trunk); systemic signs and symptoms are not life-threatening (nausea, vomiting, oral paresthesia, unusual taste, mild hypotension, mild tachycardia, tachypnea); coagulation parameters may be abnormal; no bleeding other than minor hematuria, gum bleeding, or nosebleeds, if not severe.

Severe envenomation: Swelling, pain, and bruising involve more than the entire extremity or threaten the airway; systemic signs and symptoms are markedly abnormal (severe alteration of mental status, severe hypotension, severe tachycardia, tachypnea, respiratory insufficiency); coagulation parameters are abnormal; serious bleeding or severe threat of bleeding.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCrotalidae Antivenin; Crotaline Antivenin, Polyvalent; North, Central, and South American Antisnake-Bite Serum; Pit Viper Antivenin; Snake (Pit Vipers) Antivenin

References

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Lang DM, "Anaphylactoid and Anaphylactic Reactions. Hazards of Beta-Blockers," *Drug Saf*, 1995, 12(5):299-304.[PubMed 7669259]

Tanen D, Ruha A, Graeme K, et al, "Epidemiology and Hospital Course of Rattlesnake Envenomations Cared for at a Tertiary Referral Center in Central Arizona," *Acad Emerg Med*, 2001, 8(2):177-82.[PubMed 11157295]

White RR 4th and Weber RA, "Poisonous Snakebite in Central Texas. Possible Indicators for Antivenin Treatment," *Ann Surg*, 1991, 213(5):466-71.[PubMed 2025067]

Crotalidae Polyvalent Immune FAB (Ovine)

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English

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Pronunciation(kroe TAL ih die pol i VAY lent i MYUN fab (oh vine))
U.S. Brand NamesCroFab™
Pharmacologic CategoryAntivenin
Use: Labeled IndicationsNeutralization of venoms of North American crotalids: Rattlesnakes (*Crotalus*, *Sistrurus*); copperhead and cottonmouth moccasins (*Agkistrodon*)
Dosing: AdultsCrotalid envenomation: Minimal or moderate envenomation: I.V.:

Initial dose: 4-6 vials, dependent upon patient response. Treatment should begin within 6 hours of snakebite; monitor for 1 hour following infusion. Repeat with an additional 4-6 vials if control is not achieved with initial dose. Continue to treat with 4- to 6-vial doses until complete arrest of local manifestations, coagulation tests, and systemic signs are normal. Monitor closely.

Maintenance dose: Once control is achieved, administer 2 vials every 6 hours for up to 18 hours. Optimal dosing past 18 hours has not been established; however, treatment may be continued if deemed necessary based on the patient's condition.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing. **Note:** Clinical trials included patients as young as 11 years of age. Specific pediatric studies have not been conducted. Because the absolute venom dose is expected to be the same in adults and children, adult dosing should be used. Products contain thimerosal, which in high doses has been associated with neurological and renal toxicity. Very young children are most susceptible.
Administration: I.V.Administer I.V. over 60 minutes at a rate of 25-50 mL/hour for the first 10 minutes. If no allergic reaction is observed, increase rate to 250 mL/hour. Monitor closely. Epinephrine and diphenhydramine should be available during the infusion. Decreasing the rate of infusion may help control some adverse effects.
StorageStore between 2°C to 8°C (36°F to 46°F); do not freeze.
ReconstitutionReconstitute each vial with 10 mL sterile water for injection and mix by gentle swirling. Further dilute total dose in 250 mL NS; use within 4 hours of reconstitution.
ContraindicationsHypersensitivity to any component of the formulation (including papaya or papain), unless the benefits outweigh the risks and appropriate management for anaphylaxis is readily available
Warnings/Precautions

Concern related to adverse effects:

- Hypersensitivity reactions: Derived from sheep plasma; anaphylaxis and anaphylactoid reactions are possible, especially in patients with known allergies to sheep protein. Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available. Incidence of acute hypersensitivity reactions may be lower than previously thought (Cannon, 2008). This product lacks the immunogenic Fc fragments and proteins found in the older equine-derived product. Sensitization may occur with repeated doses.

  Processed with papain and may cause hypersensitivity reactions in patients allergic to papaya, other papaya extracts, papain, chymopapain, or the pineapple-enzyme bromelain. There may also be cross allergenicity with dust mite and latex allergens.

Disease-related concerns:

- Snakebite: Should be used within 4-6 hours of snakebite to prevent clinical deterioration and development of coagulation abnormalities. Coagulation abnormalities are due directly to snake venom interference with the coagulation cascade. Recurrent coagulopathy occurs in approximately 50% of patients and may persist for 1-2 weeks or more. Repeat dosing may be indicated. Patients should be monitored for at least 1 week and evaluated for other pre-existing conditions associated with bleeding disorders. In severe rattlesnake bites, a decrease in platelets may occur, lasting hours to several days. Blood products are generally ineffective as they are rapidly consumed by circulating venom.

Special populations:

- Pediatrics: Product contains thimerosal with 0.11 mg of mercury per vial. Developing fetuses and young children may be at higher risk for mercury-related toxicities.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted. Products contain thimerosal which may be associated with mercury-related toxicities, including neurological and renal toxicities in the fetus and very young children.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not always defined.

Cardiovascular: Hypotension

Central nervous system: Chills

Dermatologic: Pruritus, rash, urticaria

Respiratory: Asthma, cough, dyspnea, wheezing

Miscellaneous: Anaphylaxis, anaphylactoid reaction, hypersensitivity reactions (5% to 19%)

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersVital signs; CBC, platelet count, prothrombin time, aPTT, fibrinogen levels, fibrin split products, clot retraction, bleeding and coagulation times, BUN, electrolytes, bilirubin; size of bite area (repeat every 15-30 minutes); intake and output; signs and symptoms of anaphylaxis/allergy. CBC, platelet counts, and clotting studies are evaluated at 6-hour intervals until patient is stable.
Monitoring: Lab TestsCBC, platelet count, prothrombin time, aPTT, fibrinogen levels, fibrin split products, clot retraction, bleeding and coagulation times, BUN, electrolytes, bilirubin. CBC, platelet counts, and clotting studies are evaluated at 6-hour intervals until patient is stable.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

CroFab™: Derived from *Crotalus adamanteus*, *C. atrox*, *C. scutulatus*, and *Agkistrodon piscivorus* snake venoms [contains thimerosal; derived from or manufactured with papain]

Generic AvailableNo
Mechanism of ActionA venom-specific fragment of IgG, which binds and neutralizes venom toxin, helping to remove the toxin from the target tissue and eliminate it from the body.
Pharmacodynamics/KineticsHalf-life elimination: 12-23 hours (based on limited data)
Pharmacotherapy Pearls

Minimal envenomation: Swelling, pain, and bruising are limited to immediate bite site; no systemic signs and symptoms; normal coagulation parameters; no clinical evidence of bleeding.

Moderate envenomation: Swelling, pain, and bruising are limited to less than a full extremity (or <50 cm if bite was on head or trunk); systemic signs and symptoms are not life-threatening (nausea, vomiting, oral paresthesia, unusual taste, mild hypotension, mild tachycardia, tachypnea); coagulation parameters may be abnormal; no bleeding other than minor hematuria, gum bleeding, or nosebleeds, if not severe.

Severe envenomation: Swelling, pain, and bruising involve more than the entire extremity or threaten the airway; systemic signs and symptoms are markedly abnormal (severe alteration of mental status, severe hypotension, severe tachycardia, tachypnea, respiratory insufficiency); coagulation parameters are abnormal; serious bleeding or severe threat of bleeding.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause nervousness
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsAntivenin (Crotalidae) Polyvalent; Crotaline Antivenin, Polyvalent; FabAV; North American Antisnake-Bite Serum; Snake Antivenin
References

Cannon R, Ruha AM, and Kashani J, "Acute Hypersensitivity Reactions Associated With Administration of Crotalidae Polyvalent Immune Fab Antivenom," *Ann Emerg Med*, 2008, 51(4):407-11.

Crotamiton

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Eurax® may be confused with Efudex®, Eulexin®, Evoxac™, Serax®, Urex®

International issues:

Eurax® may be confused with Urex® which is a brand name for furosemide in Australia

Pronunciation(kroe TAM i tonn)

U.S. Brand NamesEurax®

Pharmacologic CategoryScabicidal Agent

Use: Labeled IndicationsTreatment of scabies (*Sarcoptes scabiei*) and symptomatic treatment of pruritus

Dosing: Adults

Scabies: Topical: Wash thoroughly and scrub away loose scales, then towel dry; apply a thin layer and massage drug onto skin of the entire body from the neck to the toes (with special attention to skin folds, creases, and interdigital spaces). Repeat application in 24 hours. Take a cleansing bath 48 hours after the final application. Treatment may be repeated after 7-10 days if live mites are still present.

Pruritus: Topical: Massage into affected areas until medication is completely absorbed; repeat as necessary

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: TopicalFor external use only. Shake lotion well before using. Avoid contact with face, eyes, mucous membranes, and urethral meatus.

StorageStore at room temperature.

ContraindicationsHypersensitivity to crotamiton or any component of the formulation; patients who manifest a primary irritation response to topical medications

Warnings/Precautions

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: For external use only; avoid contact with face, eyes, mucous membranes, and urethral meatus. Do not apply to acutely inflamed or raw skin.

Geriatric ConsiderationsIf cure is not achieved after 2 doses, use alternative therapy.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted; use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined. Topical:

Dermatologic: Contact dermatitis, pruritus, rash

Local: Local irritation

Miscellaneous: Allergic sensitivity reactions, warm sensation

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringAssess knowledge/teach patient appropriate application and use and adverse symptoms to report.

Patient EducationFor topical use only. Avoid eyes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

When used as scabicide, apply lotion and/or cream to whole body from the chin down being sure to cover all skin folds and creases; apply a second application 24 hours later. Take a bath 48 hours after application. All contaminated clothing and bed linen should be washed to avoid reinfestation. If cure is not achieved after 2 doses, use alternative therapy.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream: 10% (60 g)

Lotion: 10% (60 mL, 480 mL)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Cream (Eurax)

10% (60): $22.99

Lotion (Eurax)

10% (60): $26.39

10% (480): $122.11

Mechanism of ActionCrotamiton has scabicidal activity against *Sarcoptes scabiei*; mechanism of action unknown

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Eichenfield LF, Honig PJ, “Blistering Disorders in Childhood,” *Pediatr Clin North Am*, 1991, 38(4):959-76. [PubMed 1651468]

Hogan DJ, Schachner L, Tanglertsampan C, “Diagnosis and Treatment of Childhood Scabies and Pediculosis,” *Pediatr Clin North Am*, 1991, 38(4):941-57.[PubMed 1870912]

International Brand NamesAcomexol (MX); Congen (PH); Crotamitex (DE); Crotamiton (PL); Crotanol (VE); Crotorax (IN, MY); Eurax (AE, AU, BB, BE, BF, BH, BJ, BM, BS, BZ, CH, CI, CN, CO, CY, EG, ET, FR, GB, GH, GM, GN, GY, HK, HR, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PL, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Eurax-Lotio (AT); Euraxil (DE, ES); Moz-Bite (SG); Scabicin (IL, PT); Scabirax (PH); Ulex (TW); Youlifu (CL)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Ovarian Cancer

Regimen UseOvarian cancer

Regimen

Cisplatin: I.V.: 75 mg/m^2 day 2

[total dose/cycle = 75 mg/m^2]

Paclitaxel: I.V.: 135 mg/m^2 continuous infusion day 1

[total dose/cycle = 135 mg/m^2]

Repeat cycle every 21 days

References

McGuire WP, Hoskins WJ, Brady MF, et al, âCyclophosphamide and Cisplatin Compared With Paclitaxel and Cisplatin in Patients With Stage III and Stage IV Ovarian Cancer,â *N Engl J Med*, 1996, 334(1):1-6.[PubMed 7494563]

CV

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Retinoblastoma]

Regimen UseRetinoblastoma

Regimen

Cyclophosphamide: I.V.: 300 mg/m^2

[total dose/cycle = 300 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2

[total dose/cycle = 1.5 mg/m^2]

Repeat weekly for 6 weeks

followed by

Cyclophosphamide: I.V.: 200 mg/m^2

[total dose/cycle = 200 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2

[total dose/cycle = 1.5 mg/m^2]

Repeat weekly for 42 weeks

References

Zelter M, Damel A, Gonzalez G, et al, âA Prospective Study on the Treatment of Retinoblastoma in 72 Patients,â *Cancer*, 1991, 68(8):1685-90.[PubMed 1913508]

CVP (Leukemia)

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Leukemia, Chronic Lymphocytic]

Regimen UseLeukemia, chronic lymphocytic

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cyclophosphamide: Oral: 400 or 300 mg/m^2/day days 1 to 5

[total dose/cycle = 2000 or 1500 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 (maximum 2 mg) day 1

[total dose/cycle = 1.4 mg/m^2]

Prednisone: Oral: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Cyclophosphamide: I.V.: 800 mg/m^2 day 1

[total dose/cycle = 800 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 (maximum 2 mg) day 1

[total dose/cycle = 1.4 mg/m^2]

Prednisone: Oral: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Repeat cycle every 21 days

References

Variation 1:

Bagley CM, DeVita VT, Berard CW, et al, “Advanced Lymphosarcoma: Intensive Cyclical Combination Chemotherapy With Cyclophosphamide, Vincristine, and Prednisone,” *Ann Int Med*, 1972, 76(2):227-34. [PubMed 5066691]

Raphael B, Anderson JW, Silber R, et al, “Comparison of Chlorambucil and Prednisone Versus Cyclophosphamide, Vincristine, and Prednisone as Initial Treatment for Chronic Lymphocytic Leukemia: Long-Term Follow-up of an Eastern Cooperative Oncology Group Randomized Clinical Trial,” *J Clin Oncol*, 1991, 9(5):770-6. [PubMed 2016618]

Variation 2:

Oken MM and Kaplan ME, “Combination Chemotherapy With Cyclophosphamide, Vincristine, and Prednisone in the Treatment of Refractory Chronic Lymphocytic Leukemia,” *Cancer Treat Rep*, 1979, 63(3):441-7.[PubMed 371799]

CVP (Lymphoma, non-Hodgkin's)

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Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lymphoma, non-Hodgkin's
Regimen Use Lymphoma, non-Hodgkin's
Index Terms Cyclophosphamide-Vincristine-Prednisone (NHL)
Regimen NOTE: Multiple variations are listed below.

Variation 1:

Cyclophosphamide: I.V.: 750 mg/m^2 day 1

[total dose/cycle = 750 mg/m^2]

Vincristine: I.V.: 1.2 mg/m^2 day 1

[total dose/cycle = 1.2 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 5

[total dose/cycle = 200 mg/m^2]

Repeat cycle every 21 days for up to 10 cycles

Variation 2:

Cyclophosphamide: I.V.: 750 mg/m^2 day 1

[total dose/cycle = 750 mg/m^2]

Vincristine: I.V.: 1.2 mg/m^2 day 1 (maximum 2 mg/dose)

[total dose/cycle = 1.2 mg/m^2 (maximum 2 mg/dose)]

Prednisone: Oral: 40 mg/m^2/day days 1 to 5

[total dose/cycle = 200 mg/m^2]

Repeat cycle every 28 days for up to 8 cycles

Variation 3:

Cyclophosphamide: I.V.: 750 mg/m^2 day 1

[total dose/cycle = 750 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 day 1 (maximum 2 mg/dose)

[total dose/cycle = 1.4 mg/m^2 (maximum 2 mg/dose)]

Prednisone: Oral: 40 mg/m^2/day days 1 to 5

[total dose/cycle = 200 mg/m^2]

Repeat cycle every 21 days for up to 8 cycles

Variation 4:

Cyclophosphamide: Oral: 400 mg/m^2/day days 1 to 5

[total dose/cycle = 2000 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 day 1 (maximum 2 mg/dose)

[total dose/cycle = 1.4 mg/m^2 (maximum 2 mg/dose)]

Prednisone: Oral: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Repeat cycle every 21 days

References

Variation 1:

Klasa RJ, Meyer RM, Shustik C, et al, "Randomized Phase III Study of Fludarabine Phosphate Versus Cyclophosphamide, Vincristine, and Prednisone in Patients With Recurrent Low-Grade Non-Hodgkin's Lymphoma Previously Treated With an Alkylating Agent or Alkylator-Containing Regimen," *J Clin Oncol*, 2002, 20(24):4649-54.[PubMed 12488409]

Variation 2:

Hagenbeek A, Eghbali H, Monfardini S, et al, "Phase III Intergroup Study of Fludarabine Phosphate Compared With Cyclophosphamide, Vincristine, and Prednisone Chemotherapy in Newly Diagnosed Patients With Stage III and IV Low-Grade Malignant Non-Hodgkin's Lymphoma," *J Clin Oncol*, 2006, 24(10):1590-6.[PubMed 16575010]

Variation 3:

Marcus R, Imrie K, Belch A, et al, "CVP Chemotherapy Plus Rituximab Compared With CVP as First-Line Treatment for Advanced Follicular Lymphoma," *Blood*, 2005, 105(4):1417-23.[PubMed 15494430]

Variation 4:

Bagley CM Jr, Devita VT Jr, Berard CW, et al, “Advanced Lymphosarcoma: Intensive Cyclical Combination Chemotherapy With Cyclophosphamide, Vincristine, and Prednisone,” *Ann Intern Med*, 1972, 76(2):227-34. [PubMed 5066691]

Portlock CS, Rosenberg SA, Glatstein E, et al, “Treatment of Advanced Non-Hodgkin's Lymphomas With Favorable Histologies: Preliminary Results of a Prospective Trial,” *Blood*, 1976, 47(5):747-56.[PubMed 769864]

Cyanocobalamin

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English English

Jump To Field (Select Field Name)

Pronunciation(sye an oh koe BAL a min)

U.S. Brand NamesCaloMist™; Nascobal®; Twelve Resin-K

Pharmacologic CategoryVitamin, Water Soluble

Use: Labeled IndicationsTreatment of pernicious anemia; vitamin B_{12} deficiency due to dietary deficiencies or malabsorption diseases, inadequate secretion of intrinsic factor, and inadequate utilization of B_{12} (eg, during neoplastic treatment); increased B_{12} requirements due to pregnancy, thyrotoxicosis, hemorrhage, malignancy, liver or kidney disease

CaloMist™: Maintenance of vitamin B_{12} concentrations after initial correction in patients with B_{12} deficiency without CNS involvement

Dosing: Adults

Recommended intake: 2.4 mcg/day

Pregnancy: 2.6 mcg/day

Lactation: 2.8 mcg/day

Vitamin B_{12} deficiency:

Intranasal:

Nascobal®: 500 mcg in one nostril once weekly

CaloMist™: Maintenance therapy (following correction of vitamin B_{12} deficiency): 25 mcg in each nostril daily (50 mcg/day). If inadequate response, 25 mcg in each nostril twice daily (100 mcg/day).

Oral: 250 mcg/day

I.M., deep SubQ: Initial: 30 mcg/day for 5-10 days; maintenance: 100-200 mcg/month

Pernicious anemia: I.M., deep SubQ (administer concomitantly with folic acid if needed, 1 mg/day for 1 month): 100 mcg/day for 6-7 days; if improvement, administer same dose on alternate days for 7 doses, then every 3-4 days for 2-3 weeks; once hematologic values have returned to normal, maintenance dosage: 100 mcg/month. **Note:** Alternative dosing of 1000 mcg/day for 5 days (followed by 500-1000 mcg/month) has been used.

Hematologic remission (without evidence of nervous system involvement):

Intranasal (Nascobal®): 500 mcg in one nostril once weekly

Oral: 1000-2000 mcg/day

I.M., SubQ: 100-1000 mcg/month

Schilling test: I.M.: 1000 mcg

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Adequate intake:

Children:

0-6 months: 0.4 mcg/day

7-12 months: 0.5 mcg/day

Recommended intake:

Children:

1-3 years: 0.9 mcg/day

4-8 years: 1.2 mcg/day

9-13 years: 1.8 mcg/day

Children >14 years: Refer to adult dosing.

Vitamin B_{12} deficiency: I.M., deep SubQ: Dosage in children is not well established: 0.2 mcg/kg for 2 days, followed by 1000 mcg/day for 2-7 days, followed by 100 mcg/week for one month; for malabsorptive causes of B_{12} deficiency, monthly maintenance doses of 100 mcg have been recommended **or** as an alternative 100 mcg/day for 10-15 days, then once or twice weekly for several months

Pernicious anemia: I.M., deep SubQ (administer concomitantly with folic acid if needed, 1 mg/day for 1 month): 30-50 mcg/day for 2 or more weeks (to a total dose of 1000-5000 mcg), then follow with 100 mcg/month as maintenance dosage

Administration: I.M.I.M. or deep SubQ are preferred routes of administration.

Administration: I.V.Not recommended

Administration: I.V. DetailpH: 4.5-7.0

Administration: OralNot recommended due to variable absorption; however, oral therapy of 1000-2000 mcg/day has been effective for anemia if I.M./SubQ routes refused or not tolerated.

Administration: OtherIntranasal: Nasal spray:

Nascobal®: Prior to initial dose, activate (prime) spray nozzle by pumping unit quickly and firmly until first appearance of spray, then prime twice more. The unit must be reprimed once immediately before each subsequent use. Administer 1 hour before or after ingestion of hot foods/liquids.

CaloMist™: Prime unit by spraying 7 times. If ≥5 days since use, reprime with 2 sprays. Separate from other intranasal medications by several hours.

Dietary ConsiderationsStrict vegetarian diets (eg, without eggs or dairy products) may result in vitamin B_{12} deficiency.

Storage

Injection: Clear pink to red solutions are stable at room temperature. Protect from light.

Intranasal spray: Store at 15°C to 30°C (59°F to 86°F); do not freeze. Protect from light.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, $D_{10}NS$, LR, ${}^1/_2NS$, NS; **variable stability (consult detailed reference)** in TPN.

Y-site administration: Compatible: Heparin, hydrocortisone sodium succinate, potassium chloride, vitamin B complex with C.

Compatibility when admixed: Compatible: Ascorbic acid injection, chloramphenicol, metaraminol, vitamin B complex with C. **Incompatible** Chlorpromazine, phytonadione, prochlorperazine edisylate, warfarin.

ContraindicationsHypersensitivity to cyanocobalamin, cobalt, or any component of the formulation

Allergy Considerations

- Cyanocobalamin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Vitamin B_{12} deficiency for >3 months results in irreversible degenerative CNS lesions; neurologic manifestations will not be prevented with folic acid unless vitamin B_{12} is also given. Spinal cord degeneration might also occur when folic acid used as a substitute for vitamin B_{12} in anemia prevention.
- Hypokalemia: Treatment of severe vitamin B_{12} megaloblastic anemia may result in severe hypokalemia, sometimes fatal, due to intracellular potassium shift upon anemia resolution.
- Thrombocytosis: Treatment of severe vitamin B_{12} megaloblastic anemia may result in thrombocytosis.

Disease-related concerns:

- Leber's disease: Use with caution in patients with Leber's disease patients; B_{12} treatment may result in rapid optic atrophy.
- Pernicious anemia: Appropriate use: I.M./SubQ routes are used to treat pernicious anemia; oral and intranasal administration are not indicated until hematologic remission and no signs of nervous system involvement.
- Polycythemia vera: Vitamin B_{12} deficiency masks signs of polycythemia vera; vitamin B_{12} administration may unmask this condition.

Dosage form specific issues:

- Aluminum: Some parenteral products contain aluminum; use caution in patients with impaired renal function and neonates.
- Benzyl alcohol: Some products contain benzyl alcohol which has been associated with "gasping syndrome" in neonates.
- Intranasal administration: Efficacy in patients with nasal pathology or with other concomitant intranasal therapy has not been determined. Use with caution.

Special populations:

- Pediatrics: CaloMist™: Safety and efficacy have not been established in children.

Other warnings/precautions:

- I.V. administration: Avoid intravenous route; anaphylactic shock has occurred.

- Test dose: Intradermal test dose of vitamin B_{12} is recommended for any patient suspected of cyanocobalamin sensitivity prior to intranasal or injectable administration.

Geriatric ConsiderationsThere exists evidence that people, particularly elderly whose serum cobalamin concentrations are <500 pg/mL, should receive replacement parenteral therapy or oral replacement (1000 mcg daily). This recommendation is based upon neuropsychiatric disorders and cardiovascular disorders associated with lower sodium cobalamin concentrations.
Pregnancy Risk FactorA/C (dose exceeding RDA recommendation); C (intranasal)
LactationEnters breast milk/compatible
Breast-Feeding ConsiderationsVegetarian diets which contain no animal products do not supply any vitamin B_{12}. Deficiency recognized in infants of vegetarian mothers who were breast-fed; consider supplementation during breast-feeding.
Adverse ReactionsFrequency not defined.

Cardiovascular: CHF, peripheral vascular disorder, peripheral vascular thrombosis

Central nervous system: Anxiety, dizziness, headache, hypoesthesia, incoordination, pain, nervousness

Dermatologic: Itching, urticaria, exanthema (transient)

Gastrointestinal: Diarrhea, dyspepsia, glossitis, nausea, sore throat, vomiting

Hematologic: Polycythemia vera

Neuromuscular & skeletal: Abnormal gait, arthritis, back pain, myalgia, paresthesia, weakness

Respiratory: Dyspnea, pulmonary edema, rhinitis

Miscellaneous: Anaphylaxis (parenteral) and infection

Drug Interactions

Chloramphenicol: May diminish the therapeutic effect of Cyanocobalamin. The expected hematologic response for the treatment of anemia may be opposed. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Heavy consumption >2 weeks may impair vitamin B_{12} absorption.
Test InteractionsMethotrexate, pyrimethamine, and most antibiotics invalidate folic acid and vitamin B_{12} diagnostic blood assays
Monitoring ParametersVitamin B_{12}, hematocrit, reticulocyte count, folate and iron levels should be obtained prior to treatment; vitamin B_{12} and peripheral blood counts should be monitored 1 month after beginning treatment, then every 3-6 months thereafter.

Megaloblastic anemia: In addition to normal hematological parameters, serum potassium and platelet counts should be monitored during therapy

CaloMist™: If vitamin B_{12} levels declining despite maximum doses then should return to I.M. dosing

Reference RangeNormal range of serum B_{12} is 150-750 pg/mL; this represents 0.1% of total body content. Metabolic requirements are 2-5 mcg/day; years of deficiency required before hematologic and neurologic signs and symptoms are seen. Occasional patients with significant neuropsychiatric abnormalities may have no hematologic abnormalities and normal serum cobalamin levels, 200 pg/mL (SI: >150 pmol/L), or more commonly between 100-200 pg/mL (SI: 75-150 pmol/L).
Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess results of laboratory tests at beginning of therapy and periodically with long-term therapy. Teach patient proper administration, appropriate nutritional counseling, and adverse symptoms to report.
Monitoring: Lab TestsErythrocyte and reticulocyte count, hemoglobin, hematocrit; monitor potassium concentrations during early therapy
Patient EducationUse exactly as directed. Pernicious anemia may require treatment for life. Report skin rash; swelling, pain, or redness of extremities; or acute persistent diarrhea. **Pregnancy precaution:** Inform prescriber if you are pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 1000 mcg/mL (1 mL, 10 mL, 30 mL) [may contain benzyl alcohol]

Lozenge: 50 mcg, 100 mcg, 250 mcg, 500 mcg

Lozenge, sublingual: 500 mcg

Solution, intranasal [spray]:

CaloMist™: 25 mcg/0.1 mL actuation (18 mL) [contains benzyl alcohol, benzalkonium chloride; 60 metered sprays]

Nascobal®: 500 mcg/0.1 mL actuation (2.3 mL) [contains benzalkonium chloride; delivers 8 sprays]

Tablet: 50 mcg, 100 mcg, 250 mcg, 500 mcg, 1000 mcg

Twelve Resin-K: 1000 mcg [may be used as oral, sublingual, or buccal]

Tablet, timed release: 1000 mcg, 1500 mcg

Tablet, sublingual: 1000 mcg, 2500 mcg, 5000 mcg

Generic AvailableYes: Excludes nasal spray
Pricing: U.S. (www.drugstore.com)

Gel (Nascobal)

500 mcg/0.1 mL (2.3): $146.96

Solution (Cyanocobalamin)

1000 mcg/mL (25): $35.99

1000 mcg/mL (30): $19.99

Solution (Nascobal)

500 mcg/0.1 mL (2.3): $213.58

Tablets (Vitamin B-12)

500 mcg (100): $12.99

1000 mcg (100): $12.99

Mechanism of ActionCoenzyme for various metabolic functions, including fat and carbohydrate metabolism and protein synthesis, used in cell replication and hematopoiesis

Pharmacodynamics/Kinetics

Absorption: Oral: Variable from the terminal ileum; requires the presence of calcium and gastric “intrinsic factor” to transfer the compound across the intestinal mucosa

Distribution: Principally stored in the liver and bone marrow, also stored in the kidneys and adrenals

Protein binding: Transcobalamins

Metabolism: Converted in tissues to active coenzymes, methylcobalamin and deoxyadenosylcobalamin; undergoes some enterohepatic recycling

Bioavailability: Intranasal solution: Nascobal®: 6.1% (relative to I.M.)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentAnticonvulsants may decrease the absorption of cyanocobalamin

Cardiovascular ConsiderationsEpidemiological evidence suggests that total plasma homocysteine level may be an independent cardiovascular risk factor. Plasma homocysteine levels are strongly influenced by genetics and diet (folic acid, pyridoxine/vitamin B_6, and cyanocobalamine/vitamin B_{12}). These vitamins help to break down homocysteine in the body.

Schnyder, et al, studied the effects of homocysteine-lowering therapy (folic acid 1 mg/day, vitamin B_6 10 mg/day, vitamin B_{12} 0.4 mg/day) in patients with coronary artery disease after successful angioplasty in the Swiss Heart Study. This randomized, double-blind, placebo-controlled trial looked at a composite endpoint (death, nonfatal MI, repeat revascularization) 6 months and 1 year after angioplasty. Homocysteine-lowering therapy significantly decreased the incidence of major adverse events, primarily due to a reduced rate of target lesion revascularization. Investigators in the Folate After Coronary Intervention Trial randomized patients who underwent successful coronary stenting procedures to placebo or folic acid (1.2 mg/day), vitamin B_6 (4.8 mg/day), and vitamin B_{12} (0.06 mg/day). Vitamin supplementation was associated with increased restenosis in these PCI patients.

Index TermsVitamin B_{12}

References

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“Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline,” (Chapter 9) available at http://books.nap.edu/openbook/0309065542/html/306.html. Last accessed February 22, 2005.

Goodman M, Chen XH, Daarwish D, “Are U.S. Lower Normal B_{12} Limits Too Low?,” *J Am Geriatr Soc*, 1996, 44(10):1274-5.[PubMed 8856015]

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Nelson Textbook of Pediatrics, 17th ed, Behrman RE, Kliegman RM, and Jenson HB, eds, Philadelphia, PA: WB Saunders Co, 2004.

Oh R and Brown DL, “Vitamin B_{12} Deficiency,” *Am Fam Physician*, 2003, 67(5):979-86. [PubMed 12643357]

Olszewski AJ, Szostak WB, Bialkowska M, et al, “Reduction of Plasma Lipid and Homocysteine Levels by Pyridoxine, Folate, Cobalamin, Choline, Riboflavin, and Troxerutin in Atherosclerosis,” *Atherosclerosis*, 1989, 75(1):1-6. [PubMed 2930611]

Rasmussen SA, Fernhoff PM, and Scanlon KS, “Vitamin B_{12} Deficiency in Children and Adolescents,” *J Pediatr*, 2001, 138(1):10-17. [PubMed 11148506]

Regland B, Gottfries CG, and Lindstedt G, “Dementia Patients With Low Serum Cobalamin Concentration: Relationship to Atrophic Gastritis,” *Aging (Milano)*, 1992, 4(1):35-41.

Schjonsby H, “Vitamin B_{12} Absorption and Malabsorption,” *Gut*, 1989, 30(12):1986-91.

Schnyder G, Roffi M, Flammer Y, et al, “Effect of Homocysteine-Lowering Therapy With Folic Acid, Vitamin B12, and Vitamin B6 on Clinical Outcome After Percutaneous Coronary Intervention: The Swiss Heart Study: A Randomized Controlled Trial,” *JAMA*, 2002, 288(8):973-9. [PubMed 12190367]

Silbergleit R and Lee DC, “Bowel Obstruction and Radiopaque Vitamin B_{12} “Pseudobezoar”,” *Am J Emerg Med*, 1995, 13(1):112-3.

International Brand Names Ambe 12 (LU); Ampavit (TH); Arcored (ID); B12 Ankermann (PL); B12 Latino (ES); Bedoc (GR); Bedodeka (IL); Bedoze (PT); Bedozil (BR); Behepan (SE); Betolvex (CH, DK, FI, NO, SE); Betolvex[inj.] (SE); Cianocobalamina B12 Davi (PT); Cincomil Bedoce (ES); Co Vitam B12 (ES); Cobalin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Cobamin Ophth Soln (HK); Creliverol-12 (PE); Cromatonbic B12 (ES); Cytamen (AU, GB, IE, TR); Dobetin (IT, VE); Dolo-Neurobion Retard (MX); Ecovitamine B12 (FR); Isopto B12 (ES); Kiddi Pharmaton (MX); Lagavit B12 (AE, BB, BH, BM, BS, BZ, CY, EG, GY, IL, IQ, IR, JM, JO, KW, LB, LY, NL, OM, PR, QA, SA, SR, SY, TT, YE); Ledoxina (MX); Lifaton B12 (ES); Mono Vitamine B12 (FR); Neurobene (CZ, HN); Norivite-12 (ZA); Noventabedoce (ES); Optovite B12 (ES); Permadoze (PT); Permadoze oral (PT); Redisol (TH); Reedvit 10000 (AR); Reticulogen (ES); Retidex B12 (ES); Rubramin (PH); Sancoba (JP); Sorbevit B12 (ES); Tribedoce DX (MX); Vegevit B12 (PL); Vicapan N (DE); Vitalen (MX); Vitam-Doce (AR); Vitamin B!1!2 (HR, HU); Vitamin B!1!2 Lannacher (AT); Vitamin B12 Recip (SE); Vitamina B12-Ecar (CO); Vitamine B12-Dulcis (LU); Vitaminum B12 (PL); Vitarubin (CH)

Cyclizine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(SYE kli zeen)
U.S. Brand NamesMarezine速 [OTC]
Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation
Use: Labeled IndicationsPrevention and treatment of nausea, vomiting, and vertigo associated with motion sickness; control of postoperative nausea and vomiting
Dosing: AdultsEmesis (prophylaxis and treatment): Oral: 50 mg taken 30 minutes before departure, may repeat in 4-6 hours if needed, up to 200 mg/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricEmesis (prophylaxis and treatment): Oral: Children 6-12 years: 25 mg up to 3 times/day
ContraindicationsHypersensitivity to cyclizine or any component of the formulation
Geriatric ConsiderationsDue to anticholinergic action, use lowest dose in divided doses to avoid side effects and their inconvenience; limit use if possible; may cause confusion or aggravate symptoms of confusion in those with dementia; constipation and difficulty voiding urine may occur
Pregnancy Risk FactorB
Adverse Reactions

>10%:

Central nervous system: Drowsiness

Gastrointestinal: Xerostomia

1% to 10%:

Central nervous system: Headache

Dermatologic: Dermatitis

Gastrointestinal: Nausea

Genitourinary: Urinary retention

Ocular: Diplopia

Renal: Polyuria

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 50 mg

Generic AvailableNo
Mechanism of ActionCyclizine is a piperazine derivative with properties of histamines. The precise mechanism of action in inhibiting the symptoms of motion sickness is not known. It may have effects directly on the labyrinthine apparatus and central actions on the labyrinthine apparatus and on the chemoreceptor trigger zone. Cyclizine exerts a central anticholinergic action.
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may exacerbate the dry mouth and sedation commonly seen with cyclizine

Index TermsCyclizine Hydrochloride; Cyclizine Lactate

International Brand NamesCyclizine FNA (NL); Echnatol (AT); Fortravel (AT); Maremal (ES); Marzine (CH, DK, FI, IT, NL, NO, SE); Nausicalm (NZ); Norizine (ZA); Valoid (GB, IE)

Cyclobenzaprine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

> Cyclobenzaprine may be confused with cycloSERINE, cyproheptadine
>
> Flexeril® may be confused with Floxin®

Pronunciation(sye kloe BEN za preen)
U.S. Brand NamesAmrix®; Fexmid™; Flexeril®
Canadian Brand NamesApo-Cyclobenzaprine®; Flexeril®; Flexitec; Gen-Cyclobenzaprine; Novo-Cycloprine; Nu-Cyclobenzaprine
Pharmacologic CategorySkeletal Muscle Relaxant
Use: Labeled IndicationsTreatment of muscle spasm associated with acute painful musculoskeletal conditions
Use: DentalTreatment of muscle spasm associated with acute temporomandibular joint pain (TMJ)
Dosing: AdultsMuscle spasm (including spasms associated with acute temporomandibular joint pain): Oral: **Note:** Do not use longer than 2-3 weeks

Capsule, extended release: Usual: 15 mg once daily; some patients may require up to 30 mg once daily

Tablet, immediate release: Initial: 5 mg 3 times/day; may increase to 7.5-10 mg 3 times/day if needed

Dosing: Elderly

Capsule, extended release: Use not recommended

Tablet, immediate release: Initial: 5 mg; titrate dose slowly and consider less frequent dosing

Dosing: PediatricMuscle spasm (including spasms associated with acute temporomandibular joint pain):

Capsule, extended release: Children <18 years: Dosage not established.

Tablet, immediate release: Children ≥15 years: Refer to adult dosing.

Dosing: Hepatic Impairment
Capsule, extended release: Mild-to-severe impairment: Use not recommended.

Tablet, immediate release:

> Mild impairment: Initial: 5 mg; use with caution; titrate slowly and consider less frequent dosing
>
> Moderate-to-severe impairment: Use not recommended

Administration: OralExtended release capsules: Administer at the same time each day. Do not crush or chew.
Storage

Amrix®, Flexeril®: Store at room temperature of 15°C to 30°C (59°F to 86°F).

Fexmid™: Store at room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to cyclobenzaprine or any component of the formulation; do not use concomitantly or within 14 days of MAO inhibitors; hyperthyroidism; congestive heart failure, arrhythmias, heart block; acute recovery phase of MI
Allergy Considerations

- Cyclobenzaprine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Toxic potential similar to tricyclic antidepressants: Cyclobenzaprine shares the toxic potentials of the tricyclic antidepressants, including prolongation of conduction time, arrhythmias, and tachycardia; the usual precautions of tricyclic antidepressant therapy should be observed.

Disease-related concerns:

- Glaucoma: Use with caution in patients with angle-closure glaucoma or increased intraocular pressure.

- Hepatic impairment: Use with caution in patients with mild hepatic impairment; plasma concentrations increased twofold in presence of mild impairment. Not recommended in moderate-to-severe hepatic impairment. Extended release capsules not recommended in patients with hepatic impairment of any severity (mild, moderate, or severe).

- Urinary hesitancy/retention: Use with caution in patients with urinary hesitancy or retention.

Concurrent drug therapy issues:

- MAO inhibitors: Do not use concomitantly or within 14 days after MAO inhibitors; combination may cause hypertensive crisis and/or severe convulsions.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; plasma concentrations and incidence of adverse reactions are increased in the elderly compared to younger adults. Extended release capsules not recommended for use in elderly.

- Pediatrics: Safety and efficacy have not been established in patients <15 years of age.

Geriatric ConsiderationsHigh doses in the elderly caused drowsiness and dizziness; therefore, use the lowest dose possible. Because cyclobenzaprine causes anticholinergic effects, it may not be the skeletal muscle relaxant of choice in the elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Drowsiness (29% to 39%), dizziness (1% to 11%)

Gastrointestinal: Xerostomia (6% to 32%)

1% to 10%:

Central nervous system: Fatigue (1% to 6%), confusion (1% to 3%), headache (1% to 3%), irritability (1% to 3%), mental acuity decreased (1% to 3%), nervousness (1% to 3%), somnolence (1% to 2%)

Gastrointestinal: Abdominal pain (1% to 3%), constipation (1% to 3%), diarrhea (1% to 3%), dyspepsia (≤4%), nausea (1% to 3%), unpleasant taste (1% to 3%)

Neuromuscular & skeletal: Weakness (1% to 3%)

Ocular: Blurred vision (1% to 3%)

Respiratory: Pharyngitis (1% to 3%), upper respiratory infection (1% to 3%)

<1% (Limited to important or life-threatening): Ageusia, agitation, anaphylaxis, angioedema, anorexia, anxiety, arrhythmia, ataxia, cholestasis, depression, diaphoresis, diplopia, disorientation, dysarthria, facial edema, flatulence, gastritis, hallucinations, hepatitis (rare), hypertonia, hypotension, insomnia, jaundice, liver function tests abnormal, malaise, muscle twitching, palpitation, paresthesia, pruritus, psychosis, rash, seizure, syncope, tachycardia, thirst, tinnitus, tongue edema, tremor, urinary retention, urticaria, vasodilation, vertigo, vomiting

Metabolism/Transport Effects**Substrate** of CYP1A2 (major), 2D6 (minor), 3A4 (minor)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

MAO Inhibitors: Cyclobenzaprine may enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Food increases bioavailability (peak plasma concentrations increased by 35% and area under the curve by 20%) of the extended release capsule.

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, kava kava, gotu kola (may increase CNS depression).

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy (according to rationale for therapy) and adverse reactions at beginning and periodically during therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects (postural hypotension precautions), and adverse symptoms to report.

Patient EducationTake exactly as directed. Do not increase dose or discontinue this medication without consulting prescriber. Do not use alcohol, prescriptive or OTC antidepressants, sedatives, or pain medications without consulting prescriber. You may experience drowsiness, dizziness, lightheadedness (avoid driving or engaging in tasks that require alertness until response to drug is known); or urinary retention (void before taking medication). Report excessive drowsiness or mental agitation, chest pain, skin rash, swelling of mouth/face, difficulty speaking, ringing in ears, or blurred vision. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release, as hydrochloride:

Amrix®: 15 mg, 30 mg

Tablet, as hydrochloride: 5 mg, 10 mg

Fexmid™: 7.5 mg

Flexeril®: 5 mg, 10 mg

Generic AvailableYes: Excludes capsule

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Amrix)

15 mg (60): $515.98

Tablets (Cyclobenzaprine HCl)

5 mg (30): $13.99

10 mg (30): $13.99

Tablets (Flexeril)

5 mg (30): $55.99

10 mg (30): $58.99

Mechanism of ActionCentrally-acting skeletal muscle relaxant pharmacologically related to tricyclic antidepressants; reduces tonic somatic motor activity influencing both alpha and gamma motor neurons

Pharmacodynamics/Kinetics

Onset of action: Immediate release tablet: ~1 hour

Duration: Immediate release tablet: 12-24 hours

Absorption: Complete

Metabolism: Hepatic via CYP3A4, 1A2, and 2D6; may undergo enterohepatic recirculation

Bioavailability: 33% to 55%

Half-life elimination: Range: 8-37 hours; Immediate release tablet: 18 hours; Extended release capsule: 32 hours

Time to peak, serum: Immediate release tablet: 3-8 hours; Extended release capsule: 7-8 hours

Excretion: Urine (as inactive metabolites); feces (as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and dizziness are common; may cause nervousness or confusion

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors or within 14 days of MAO inhibitor; concurrent use with psychotropics may exacerbate the dry mouth and sedation commonly seen with cyclobenzaprine

Index TermsCyclobenzaprine Hydrochloride

References

Ambre JJ, “Cyclobenzaprine Overdose,” *Ann Intern Med*, 1985, 102(4):559-60.

Heckerling PS, Bartow TJ, “Paradoxical Diaphoresis in Cyclobenzaprine Poisoning,” *Ann Intern Med*, 1984, 101(6):881.

Linden CH, Mitchiner JC, Lindzon RD, et al, “Cyclobenzaprine Overdosage,” *J Toxicol Clin Toxicol*, 1983, 20(3):281-8. [PubMed 6620442]

Spiller HA, Winter ML, Mann KV, et al, “Five Year Multicenter Retrospective Review of Cyclobenzaprine Toxicity,” *Vet Hum Toxicol*, 1994, 36:370.

Theoharides TC, Harris RS, and Weckstein D, “Neuroleptic Malignant-Like Syndrome Due to Cyclobenzaprine?” *J Clin Psychopharmacol*, 1995, 15(1):79-81.[PubMed 7714231]

Winchell GA, King JD, Chavez-Eng CM, et al, “Cyclobenzaprine Pharmacokinetics, Including the Effects of Age, Gender, and Hepatic Insufficiency,” *J Clin Pharmacol*, 2002, 42(1):61-9.[PubMed 11808825]

International Brand Names Ciclamil (CN); Cycloflex (IL); Flexiban (AR, IT, PT); Miosan (BR); Musgud (TW); Tensodox (PE); Yuredol (MX); Yurelax (ES)

Cyclopentolate and Phenylephrine

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Jump To Field (Select Field Name)

Pronunciation(sye kloe PEN toe late & fen il EF rin)
U.S. Brand NamesCyclomydril速
Pharmacologic CategoryOphthalmic Agent, Antiglaucoma
Use: Labeled IndicationsInduce mydriasis greater than that produced with cyclopentolate HCl alone
Dosing: AdultsDiagnostic aid (mydriasis and cycloplegia): Ophthalmic: Instill 1 drop into the eye every 5-10 minutes, for up to 3 doses, approximately 40-50 minutes before the examination
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricDiagnostic aid: Ophthalmic: Neonates, Infants, Children: Refer to adult dosing.
Administration: OtherFinger pressure should be applied to lacrimal sac for 1-2 minutes after instillation to decrease risk of absorption and systemic reactions.
StorageStore in tight containers and protect from light.
Pregnancy Risk FactorC
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic: Cyclopentolate hydrochloride 0.2% and phenylephrine hydrochloride 1% (2 mL, 5 mL) [contains benzalkonium chloride]

Generic AvailableNo
Pharmacodynamics/KineticsSee individual agents.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusCyclopentolate may cause restlessness, hallucinations, psychosis, hyperactivity, seizures, incoherent speech, or ataxia. The 2% solution may result in psychotic reactions and behavioral disturbances in children, usually occurring approximately 30-45 minutes after instillation.
Mental Health: Effects on Psychiatric TreatmentNone reported; may counteract the effects of antipsychotics, especially in children; monitor
Index TermsPhenylephrine and Cyclopentolate

Cyclopentolate

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(sye kloe PEN toe late)
U.S. Brand NamesAK-Pentolate™; Cyclogyl®; Cylate™
Canadian Brand NamesCyclogyl®; Diopentolate®
Pharmacologic CategoryAnticholinergic Agent, Ophthalmic
Use: Labeled IndicationsDiagnostic procedures requiring mydriasis and cycloplegia
Dosing: AdultsDiagnostic aid (mydriasis and cycloplegia): Ophthalmic: Instill 1 drop of 1% followed by another drop in 5 minutes; 2% solution in heavily pigmented iris
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricDiagnostic aid (mydriasis and cycloplegia): Ophthalmic:

Neonates and Infants: **Note:** Cyclopentolate and phenylephrine combination formulation is the preferred agent for use in neonates and infants due to lower cyclopentolate concentration and reduced risk for systemic reactions

Children: Instill 1 drop of 0.5%, 1%, or 2% in eye followed by 1 drop of 0.5% or 1% in 5 minutes, if necessary

StorageStore in tight containers.
ContraindicationsHypersensitivity to cyclopentolate or any component of the formulation; untreated narrow-angle glaucoma; presence of untreated anatomically narrow angles
Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause CNS disturbances, especially with the higher concentrations. May occur with any age group, although children are more susceptible.

- Intraocular pressure: May cause a transient elevation in intraocular pressure.

Disease-related concerns:

- Down syndrome: Patients with Down syndrome are predisposed to angle-closure glaucoma; use with caution.

Special populations:

- Contact lens wearers: Contains benzalkonium chloride which may be adsorbed by contact lenses; remove contacts prior to administration and wait 15 minutes before reinserting.

- Elderly: Use with caution in the elderly; may be predisposed to increased intraocular pressure.

- Pediatrics: May result in psychotic reactions and behavioral disturbances in children, especially with the 2% solution; effects usually occur ~30-45 minutes after instillation; observe infants for at least 30 minutes following instillation. Feeding intolerance may occur in infants; withhold feeding for 4 hours after examination.

Other warnings and precautions:

- Appropriate use: For topical ophthalmic use only. To minimize absorption, use only 1 drop of solution per eye, followed by pressure applied over the nasolacrimal sac for 2-3 minutes.

Pregnancy Risk FactorC
Adverse Reactions1% to 10%:

Cardiovascular: Tachycardia

Central nervous system: Ataxia, hallucinations, hyperactivity, incoherent speech, psychosis, restlessness, seizure

Dermatologic: Burning sensation

Ocular: Intraocular pressure increased, loss of visual accommodation

Miscellaneous: Allergic reaction

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic, as hydrochloride: 1% (2 mL, 15 mL)

AK-Pentolate™, Cylate™: 1% (2 mL, 15 mL) [contains benzalkonium chloride]

Cyclogyl®: 0.5% (15 mL); 1% (2 mL, 5 mL, 15 mL); 2% (2 mL, 5 mL, 15 mL) [contains benzalkonium chloride]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Cyclopentolate HCl)

1% (2): $9.99

1% (15): $8.99

Mechanism of ActionPrevents the muscle of the ciliary body and the sphincter muscle of the iris from responding to cholinergic stimulation, causing mydriasis and cycloplegia

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Cycloplegia: 25-75 minutes; Mydriasis: 30-60 minutes

Duration: ≤24 hours

Related Information

- Cycloplegic Mydriatics

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusCyclopentolate may cause restlessness, hallucinations, psychosis, hyperactivity, seizures, incoherent speech, or ataxia. The 2% solution may result in psychotic reactions and behavioral disturbances in children, usually occurring approximately 30-45 minutes after instillation.

Mental Health: Effects on Psychiatric TreatmentNone reported; may counteract the effects of antipsychotics, especially in children; monitor

Index TermsCyclopentolate Hydrochloride

International Brand NamesChlorhydrate de cyclopentolate (LU); Ciclolato (BR); Ciclolux (IT); Ciclopejico (ES); Ciclopenal (AR, PY); Ciclople (ES); Cicloplegic (ES); Cicloplejico Llorens (ES); Colircusi Cicloplejico (ES); Colirio Ocul Cicloplejic (ES); Cyclogyl (AE, AU, BF, BH, BJ, CH, CI, CY, CZ, DK, EG, ET, GH, GM, GN, GR, IL, IN, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PK, QA, SA, SC, SD, SE, SL, SN, SY, TH, TN, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Cyclomydri (NL); Cyclopent (HU); Cyclopentol (BE, LU); Cyclopentolat (AT, NO, SE); Cyclopentolat Thilo (DE); Cyclopentolate (CZ, GR); Cyclopentolate Eye Drops (HK, PH); Cycogyl (CN, HK); Cyplegin (JP); Humapent (HN, HU); Midriodavi (PT); Minims Cyclopentolate Hydrocloride (AE, AU, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Minims-Cyclopentolate (IE); Mydrilate (GB, IE); Oftan syklo (PL); Oftan-Syklo (FI); Skiacol (FR); Zyklolat EDO (LU); Zyklolat-Edo (DE)

Cyclophosphamide + Doxorubicin

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer

Regimen UseProstate cancer

Regimen

Doxorubicin: I.V.: 40 mg/m^2 day 1

[total dose/cycle = 40 mg/m^2]

Cyclophosphamide: I.V.: 800-2000 mg/m^2 day 1

[total dose/cycle = 800-2000 mg/m^2]

Filgrastim: SubQ: 5 mcg/kg/day days 2 to 10 (or until ANC >10,000 cells/µL)

[total dose/cycle = 45 mcg/kg or until ANC >10,000 cells/µL]

Repeat cycle every 21 days

References

Small EJ, Srinivas S, Egan B, et al, "Doxorubicin and Dose-Escalated Cyclophosphamide With Granulocyte Colony-Stimulating Factor for the Treatment of Hormone-Resistant Prostate Cancer," *J Clin Oncol*, 1996, 14(5):1617-25.[PubMed 8622080]

Cyclophosphamide + Etoposide

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer
Regimen UseProstate cancer
Regimen

Cyclophosphamide: Oral: 100 mg/day days 1 to 14

[total dose/cycle = 1400 mg]

Etoposide: Oral: 50 mg/day days 1 to 14

[total dose/cycle = 700 mg]

Repeat cycle every 28 days

References

Maulard-Durdux C, Dufour B, Hennequin C, et al, âPhase II Study of the Oral Cyclophosphamide and Oral Etoposide Combination in Hormone-Refractory Prostate Carcinoma Patients,â *Cancer*, 1996, 77(6):1144-8.[PubMed 8635136]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer

Regimen UseProstate cancer

Regimen

Cyclophosphamide: Oral: 250 mg/day days 1 to 14

[total dose/cycle = 3500 mg]

Vincristine: I.V.: 1 mg/day days 1, 8, and 15

[total dose/cycle = 3 mg]

Dexamethasone: Oral: 0.75 mg twice daily days 1 to 14

[total dose/cycle = 21 mg]

Repeat cycle every 28 days

References

Daliani DD, Assikis V, Tu SM, et al, âPhase II Trial of Cyclophosphamide, Vincristine, and Dexamethasone in the Treatment of Androgen-Independent Prostate Carcinoma,â *Cancer*, 2003, 97(3):561-7.[PubMed 12548597]

Cyclophosphamide

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cyclophosphamide may be confused with cycloSPORINE, ifosfamide

Cytoxan® may be confused with cefoxitin, Centoxin®, Ciloxan®, cytarabine, CytoGam®, Cytosar®, Cytosar-U®, Cytotec®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(sye kloe FOS fa mide)

U.S. Brand NamesCytoxan® [DSC]

Canadian Brand NamesCytoxan®; Procytox®

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent; Antirheumatic, Miscellaneous

Use: Labeled Indications

Oncologic: Treatment of Hodgkin's and non-Hodgkin's lymphoma, Burkitt's lymphoma, chronic lymphocytic leukemia (CLL), chronic myelocytic leukemia (CML), acute myelocytic leukemia (AML), acute lymphocytic leukemia (ALL), mycosis fungoides, multiple myeloma, neuroblastoma, retinoblastoma, rhabdomyosarcoma, Ewing's sarcoma; breast, testicular, endometrial, ovarian, and lung cancers, and in conditioning regimens for bone marrow transplantation

Nononcologic: Prophylaxis of rejection for kidney, heart, liver, and bone marrow transplants, severe rheumatoid disorders, nephrotic syndrome, Wegener's granulomatosis, idiopathic pulmonary hemosideroses, myasthenia gravis, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, autoimmune hemolytic anemia, idiopathic thrombocytic purpura (ITP), macroglobulinemia, and antibody-induced pure red cell aplasia

Use: DentalTreatment of Wegener's granulomatosis, systemic lupus erythematosus

Dosing: AdultsRefer to individual protocols.

Usual dose:

Oral: 50-100 mg/m^2/day as continuous therapy or 400-1000 mg/m^2 in divided doses over 4-5 days as intermittent therapy

I.V.:

Single doses: 400-1800 mg/m^2 (30-50 mg/kg) per treatment course (1-5 days) which can be repeated at 2- to 4-week intervals

Continuous daily doses: 60-120 mg/m^2 (1-2.5 mg/kg) per day

JRA/vasculitis: I.V.: 10 mg/kg every 2 weeks

High dose BMT:

I.V.:

60 mg/kg/day for 2 days (total dose: 120 mg/kg)

50 mg/kg/day for 4 days (total dose: 200 mg/kg)

1.8 g/m^2/day for 4 days (total dose: 7.2 g/m^2)

Continuous I.V.:

1.5 g/m^2/24 hours for 96 hours (total dose: 6 g/m^2)

1875 mg/m^2/24 hours for 72 hours (total dose: 5625 mg/m^2)

Note: Duration of infusion is 1-24 hours; generally combined with other high-dose chemotherapeutic drugs, lymphocyte immune globulin, or total body irradiation (TBI).

Nephrotic syndrome: Oral: 2-3 mg/kg/day every day for up to 12 weeks when corticosteroids are unsuccessful

Dosing: ElderlyRefer to individual protocols: Initial and maintenance for induction: 1-2 mg/kg/day; adjust for renal clearance.

Dosing: PediatricRefer to individual protocols. Children:

Chemotherapy: Refer to adult dosing.

SLE: I.V.: 500-750 mg/m^2 every month; maximum dose: 1 g/m^2

JRA/vasculitis: I.V.: Refer to adult dosing.

Nephrotic syndrome: Refer to adult dosing.

Dosing: Renal ImpairmentThe FDA-approved labeling states there is insufficiant evidence to recommend dosage adjustment and therefore, does not contain renal dosing adjustment guidelines. The following guidelines have been used by some clinicians (Aronoff, 2007): Children and Adults:

Cl_{cr} <10 mL/minute: Administer 75% of normal dose

Hemodialysis effects: Moderately dialyzable (20% to 50%)

Administer 50% of dose posthemodialysis

Continuous ambulatory peritoneal dialysis (CAPD): Administer 75% of normal dose

Continuous renal replacement therapy (CRRT): Administer 100% of normal dose

Dosing: Hepatic ImpairmentThe pharmacokinetics of cyclophosphamide are not significantly altered in the presence of hepatic insufficiency. The FDA-approved labeling does not contain hepatic dosing adjustment guidelines. The following guidelines have been used by some clinicians (Floyd, 2006):

Serum bilirubin 3.1-5 mg/dL or ALT/AST >3 times ULN: Administer 75% of dose

Serum bilirubin >5 mg/mL: Avoid use

Dosing: Combination Regimens

Bladder cancer:

CAP

CISCA

Brain tumor:

8 in 1 (Brain Tumors)

COPE

Breast cancer:

AC

AC/Paclitaxel (Sequential)

AC-Paclitaxel-Trastuzumab

CAF

CEF

CFP

CMF

CMF-IV

CMFP

CMFVP (Cooper Regimen, VPCMF)

CNF

Docetaxel-Cyclophosphamide (TC)

Docetaxel-FEC

Docetaxel-Trastuzumab-FEC

Dox-CMF (Sequential)

FAC

FEC

TAC

Vinorelbine-FEC

Vinorelbine-Trastuzumab-FEC

Gestational trophoblastic tumor:

- CHAMOCA (Modified Bagshawe Regimen)
- CHAMOMA (Bagshawe Regimen)
- EMA/CO

Leukemia, acute lymphocytic:

- Hyper-CVAD + Imatinib
- Hyper-CVAD (Leukemia, Acute Lymphocytic)
- Larson Regimen
- VAD/CVAD

Leukemia, chronic lymphocytic:

- CVP (Leukemia)
- Fludarabine-Cyclophosphamide (FC)
- Fludarabine-Cyclophosphamide-Rituximab (CLL)
- PCR
- Pentostatin-Cyclophosphamide

Lung cancer (small cell): CAVE

Lymphoma, Hodgkin's disease:

- BEACOPP
- COMP

Lymphoma, non-Hodgkin's:

- CHOP
- CNOP
- COMLA
- COP-BLAM
- COPP
- CVP (Lymphoma, non-Hodgkin's)
- EPOCH
- Fludarabine-Cyclophosphamide-Rituximab (NHL)
- Hyper-CVAD (Lymphoma, non-Hodgkin's)
- MACOP-B
- m-BACOD
- Pro-MACE-CytaBOM
- Rituximab-CHOP
- R-CVP

Lymphoma, non-Hodgkin's (Burkitt's): CODOX-M/IVAC

Lymphoma, non-Hodgkin's (Mantle cell): Hyper-CVAD + Rituximab

Multiple myeloma:

- DTPACE
- Hyper-CVAD (Multiple Myeloma)
- M-2
- VBMCP
- VCAP

Neuroblastoma:

- CAV-P/VP
- CCDDT (Neuroblastoma)
- CCT (Neuroblastoma)
- CE-CAdO
- N4SE Protocol
- N6 Protocol
- OPEC
- OPEC-D
- PE-CAdO
- Regimen A1
- Regimen A2

Osteosarcoma: POG-8651

Ovarian cancer:

- CC
- CP (Ovarian Cancer)
- PAC (CAP)

Prostate cancer:

- Cyclophosphamide + Doxorubicin
- Estramustine-Cyclophosphamide
- Cyclophosphamide + Etoposide
- Cyclophosphamide + Vincristine + Dexamethasone

Retinoblastoma:

- CCCDE (Retinoblastoma)
- CO
- CV
- VAC (Retinoblastoma)

Rhabdomyosarcoma:

- VAC Pulse
- VAC (Rhabdomyosarcoma)

Sarcoma:

- CYVADIC
- VAC Alternating With IE (Ewing's Sarcoma)

Wilms' tumor: ACAV (J)

Oncology: Bone Marrow - High Dose

I.V.:

- 60 mg/kg/day for 2 days (total dose: 120 mg/kg)
- 50 mg/kg/day for 4 days (total dose: 200 mg/kg)
- 1.8 g/m^2/day for 4 days (total dose: 7.2 g/m^2)
- 1875 mg/m^2/24 hours for 72 hours (total dose: 5625 mg/m^2)

Continuous I.V.: 1.5 g/m^2/24 hours for 96 hours (total dose: 6 g/m^2)

Duration of infusion is 1-24 hours; generally combined with other high-dose chemotherapeutic drugs, lymphocyte immune globulin, or total body irradiation (TBI).

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.I.P., intrapleurally, IVPB, or continuous intravenous infusion; I.V. infusions may be administered over 1-24 hours. Doses >500 mg to approximately 2 g may be administered over 20-30 minutes.

To minimize bladder toxicity, increase normal fluid intake during and for 1-2 days after cyclophosphamide dose. Most adult patients will require a fluid intake of at least 2 L/day. High-dose regimens should be accompanied by vigorous hydration with or without mesna therapy.

Administration: I.V. DetailSlow IVP in doses ≤1 g. High-dose regimens should be accompanied by vigorous hydration with or without mesna therapy.

BMT only: Approaches to reduction of hemorrhagic cystitis include infusion of 0.9% NaCl 3 L/m^2/24 hours, infusion of 0.9% NaCl 3 L/m^2/24 hours with continuous 0.9% NaCl bladder irrigation 300-1000 mL/hour, and infusion of 0.9% NaCl 1.5-3 L/m^2/24 hours with intravenous mesna. Hydration should begin at least 4 hours before cyclophosphamide and continue at least 24 hours after completion of cyclophosphamide. The dose of daily mesna used should equal the daily dose of cyclophosphamide. Mesna can be administered as a continuous 24-hour intravenous infusion or be given in divided doses every 4 hours. Mesna should begin at the start of treatment, and continue at least 24 hours following the last dose of cyclophosphamide.

pH: 3-9 (reconstituted solution)

Administration: OralTablets are not scored and should not be cut or crushed. To minimize the risk of bladder irritation, do not administer tablets at bedtime.

Dietary ConsiderationsTablets should be administered during or after meals.

StorageStore intact vials of powder at room temperature of 15°C to 30°C (59°F to 86°F). Reconstituted solutions are stable for 24 hours at room temperature and 6 days under refrigeration 2°C to 8°C (36°F to 46°F). Further dilutions in D_5W or NS are stable for 24 hours at room temperature (25°C) and 6 days at refrigeration.

ReconstitutionReconstitute vials with SWI, NS, or D_5W to a concentration of 20 mg/mL.

CompatibilityStable in D_5LR, D_5NS, D_5W, LR, $^1/_2$NS, NS.

Y-site administration: Compatible: Allopurinol, amifostine, amikacin, ampicillin, azlocillin, aztreonam, bleomycin, cefamandole, cefazolin, cefepime, cefoperazone, cefotaxime, cefoxitin, cefuroxime, chloramphenicol, chlorpromazine, cimetidine, cisplatin, cladribine, clindamycin, co-trimoxazole, dexamethasone sodium phosphate, diphenhydramine, doxorubicin, doxorubicin liposome, doxycycline, droperidol, erythromycin lactobionate, etoposide phosphate, famotidine, filgrastim, fludarabine, fluorouracil, furosemide, ganciclovir, gatifloxacin, gemcitabine, gentamicin, granisetron, heparin, hydromorphone, idarubicin, kanamycin, leucovorin, linezolid, lorazepam, melphalan, methotrexate, methylprednisolone sodium succinate, metoclopramide, metronidazole, minocycline, mitomycin, morphine, nafcillin, ondansetron, oxacillin, paclitaxel, penicillin G potassium, piperacillin, piperacillin/tazobactam, prochlorperazine edisylate, promethazine, propofol, ranitidine, sargramostim, sodium bicarbonate, teniposide, thiotepa, ticarcillin, ticarcillin/clavulanate, tobramycin, topotecan, vancomycin, vinblastine, vincristine, vinorelbine. **Incompatible:** Amphotericin B cholesteryl sulfate complex.

Compatibility in syringe: Compatible: Bleomycin, cisplatin, doxapram, doxorubicin, droperidol, fluorouracil, furosemide, heparin, leucovorin, methotrexate, metoclopramide, mitomycin, vinblastine, vincristine.

Compatibility when admixed: Compatible: Cisplatin with etoposide, dacarbazine, fluorouracil, hydroxyzine, mesna, methotrexate, methotrexate with fluorouracil, mitoxantrone, ondansetron.

Extemporaneously PreparedA 2 mg/mL oral elixir was stable for 14 days when refrigerated when made as follows: Reconstitute a 200 mg vial with aromatic elixir, withdraw the solution, and add sufficient aromatic elixir to make a final volume of 100 mL (store in amber glass container).

Brook D, Davis RE, and Bequette RJ, "Chemical Stability of Cyclophosphamide in Aromatic Elixir U.S.P.," *Am J Health Syst Pharm*, 1973, 30:618-20.

ContraindicationsHypersensitivity to cyclophosphamide or any component of the formulation; pregnancy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Cardiotoxicity: May cause cardiotoxicity (HF, usually with higher doses).
- Fertility effects: May impair fertility; interferes with oogenesis and spermatogenesis.
- Hemorrhagic cystitis: May occur; increased hydration and frequent voiding is recommended.
- Immunosuppression: Monitor for infections; immunosuppression may occur.
- Secondary malignancies: With use secondary malignancies (usually delayed) have been reported.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment may be needed.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment may be needed.

Concurrent drug therapy issues:

- Anthracyclines: May potentiate the cardiotoxicity of anthracyclines.

Geriatric ConsiderationsToxicity to immunosuppressives is increased in the elderly. Start with lowest recommended adult doses. Signs of infection, such as fever and WBC rise, may not occur. Lethargy and confusion may be more prominent signs of infection; adjust dose for renal function.

Pregnancy Risk FactorD

LactationEnters breast milk/contraindicated

Adverse Reactions

>10%:

Dermatologic: Alopecia (40% to 60%) but hair will usually regrow although it may be a different color and/or texture. Hair loss usually begins 3-6 weeks after the start of therapy.

Endocrine & metabolic: Fertility: May cause sterility; interferes with oogenesis and spermatogenesis; may be irreversible in some patients; gonadal suppression (amenorrhea)

Gastrointestinal: Nausea and vomiting (usually beginning 6-10 hours after administration); anorexia, diarrhea, mucositis, and stomatitis are also seen

Genitourinary: Severe, potentially fatal, acute hemorrhagic cystitis or urinary fibrosis (7% to 40%)

Hematologic: Thrombocytopenia and anemia are less common than leukopenia

Onset: 7 days

Nadir: 10-14 days

Recovery: 21 days

1% to 10%:

Cardiovascular: Facial flushing

Central nervous system: Headache

Dermatologic: Skin rash

Renal: SIADH may occur, usually with doses >50 mg/kg (or 1 g/m^2); renal tubular necrosis, which usually resolves with discontinuation of the drug, is also reported

Respiratory: Nasal congestion occurs when I.V. doses are administered too rapidly; patients experience runny eyes, rhinorrhea, sinus congestion, and sneezing during or immediately after the infusion.

<1%, postmarketing, and/or case reports: High-dose therapy may cause cardiac dysfunction manifested as CHF; cardiac necrosis or hemorrhagic myocarditis has occurred rarely, but may be fatal. Interstitial pneumonitis and pulmonary fibrosis are occasionally seen with high doses. Cyclophosphamide may also potentiate the cardiac toxicity of anthracyclines. Other adverse reactions include anaphylactic reactions, darkening of skin/fingernails, dizziness, hemorrhagic colitis, hemorrhagic ureteritis, hepatotoxicity, hyperuricemia, hypokalemia, jaundice, malaise, neutrophilic eccrine hidradenitis, radiation recall, renal tubular necrosis, secondary malignancy (eg, bladder carcinoma), SAIDH, Stevens-Johnson syndrome, toxic epidermal necrolysis, weakness.

Oncology: VesicantNo

Oncology: Emetic Potential

Very high (>90%): >1500 mg/m^2

High (60% to 90%): >750 mg/m^2, ≤1500 mg/m^2

Moderate (30% to 60%): ≤750 mg/m^2

Oral: Moderate (30% to 60%)

Oncology: Bone Marrow - Unique Toxicity

Cardiovascular: Heart failure, cardiac necrosis, pericardial tamponade, heart block

Endocrine & metabolic: Hyponatremia, acquired pseudocholinesterase deficiency, transient diabetes insipidus

Hematologic: Methemoglobinemia

Neuromuscular & skeletal: Rhabdomyolysis

Respiratory: Pleural effusion, interstitial pneumonitis

Metabolism/Transport Effects**Substrate** of CYP2A6 (minor), 2B6 (major), 2C9 (minor), 2C19 (minor), 3A4 (major); **Inhibits** CYP3A4 (weak); **Induces** CYP2B6 (weak), 2C8 (weak), 2C9 (weak)

Drug Interactions

Allopurinol: May enhance the adverse/toxic effect of Cyclophosphamide. Specifically, bone marrow suppression. *Risk C: Monitor therapy*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

CYP2B6 Inducers (Strong): May increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Strong): May decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Etanercept: May enhance the adverse/toxic effect of Cyclophosphamide. An increased risk of solid cancer development may be present. *Risk D: Consider therapy modification*

Mivacurium [Off Market]: Cyclophosphamide may decrease the metabolism of Mivacurium [Off Market]. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Pentostatin: May enhance the cardiotoxic effect of Cyclophosphamide. *Risk C: Monitor therapy*

Succinylcholine: Cyclophosphamide may decrease the metabolism of Succinylcholine. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid black cohosh, dong quai in estrogen-dependent tumors.

Monitoring ParametersCBC with differential and platelet count, BUN, UA, serum electrolytes, serum creatinine

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions (eg, potential for increased or prolonged nephrotoxicity, cardiotoxicity). Note infusion specifics in Administration; including recommendations for pre- and posthydration. Infusion site must be monitored to prevent extravasation. Assess results of laboratory tests (eg, urinalysis, BUN, and serum creatinine [detect nephrotoxicity]; CBC with differential and platelet count [detect myelosuppression]). Evaluate therapeutic effectiveness (according to purpose for use) and adverse response (hemorrhagic cystitis, leukopenia, renal tubular necrosis) prior to each infusion and regularly during therapy. Teach patient (or caregiver) proper use (oral), possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, platelet count, ESR, BUN, UA, serum electrolytes, serum creatinine

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed, during or after meals; do not take at night. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake and void frequently to reduce incidence of bladder irritation. You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause loss of hair (reversible, although regrowth hair may be different color or texture); infertility or amenorrhea; nausea or vomiting (small, frequent meals, good mouth care, chewing gum, or sucking lozenges may help - if persistent consult prescriber for antiemetic); headache (consult prescriber for analgesic); nasal congestion or cold symptoms (consult prescriber for decongestant); or mouth sores (use soft toothbrush or cotton swab for oral care). Report any difficulty or pain with urination; chest pain, rapid heartbeat, or palpitations; easy bruising or bleeding; unusual rash; persistent nausea or vomiting; menstrual irregularities; swelling of extremities; respiratory difficulty; or unusual fatigue. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution: 500 mg, 1 g, 2 g

Cytoxan®: 500 mg, 1 g, 2 g [DSC]

Tablet: 25 mg, 50 mg

Cytoxan®: 25 mg, 50 mg [DSC]

Generic AvailableYes

ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)

Pricing: U.S. (www.drugstore.com)

Tablets (Cyclophosphamide)

25 mg (30): $60.99

50 mg (30): $106.99

Tablets (Cytoxan)

50 mg (30): $125.99

Mechanism of ActionCyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. It is a cell cycle phase nonspecific agent. Cyclophosphamide also possesses potent immunosuppressive activity. Cyclophosphamide is a prodrug that must be metabolized to active metabolites in the liver.

Pharmacodynamics/Kinetics

Absorption: Oral: Well absorbed

Distribution: V_d: 0.48-0.71 L/kg; crosses placenta; crosses into CSF (not in high enough concentrations to treat meningeal leukemia)

Protein binding: 10% to 60%

Metabolism: Hepatic to active metabolites acrolein, 4-aldophosphamide, 4-hydroperoxycyclophosphamide, and nor-nitrogen mustard

Bioavailability: >75%

Half-life elimination: 3-12 hours

Time to peak, serum: Oral: ~1 hour

Excretion: Urine (<30% as unchanged drug, 85% to 90% as metabolites)

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsIn patients with CYP2B6 G516T variant allele, cyclophosphamide metabolism is markedly increased; metabolism is not influenced by CYP2C9 and CYP2C19 isotypes.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine

Cardiovascular ConsiderationsRare but potentially life-threatening cardiovascular side effects may occur at higher doses (>200 mg/m^2) including heart failure, cardiac necrosis, myocarditis, arrhythmias, tamponade, and pulmonary fibrosis. The dose should be based on indications, concomitant diseases (ie, renal dysfunction), and potential drug interactions.

Oncology: Bone Marrow CommentsApproaches to reduction of hemorrhagic cystitis include infusion of 0.9% NaCl 3 L/m^2/24 hours, infusion of 0.9% NaCl 3 L/m^2/24 hours with continuous 0.9% NaCl bladder irrigation 300-1000 mL/hour, and infusion of 0.9% NaCl 1.5-3 L/m^2/24 hours with intravenous mesna. Hydration should begin at least 4 hours before cyclophosphamide and continue at least 24 hours after completion of cyclophosphamide. The dose of daily mesna used should equal the daily dose of cyclophosphamide. Mesna can be administered as a continuous 24-hour intravenous infusion or be given in divided doses every 4 hours. Mesna should begin at the start of treatment, and continue at least 24 hours following the last dose of cyclophosphamide.

Enhanced bioactivation of cyclophosphamide may increase the risk of cardiotoxicity. A 30-minute infusion of thiotepa administered 1 hour before a 60-minute infusion of cyclophosphamide reduced bioactivation of cyclophosphamide to 4-hydroxycyclophosphamide in 20 patients. This effect did not occur with administration of thiotepa 1 hour following infusion of cyclophosphamide. Intravascular red blood cell hemolysis requiring transfusion support occurred during continuous flow plasmapheresis performed 12 hours following infusion of cyclophosphamide 60 mg/kg.

Index TermsCPM; CTX; CYT; Neosar; NSC-26271

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International Brand NamesAlkyroxan (KP); Carloxan (DK); Ciclifen (PY); Ciclofosfamida (CO); Cicloxal (ES); Cryofaxol (MX); Cycloblastin (AU); Cycloblastine (BE, LU); Cyclophosphamid (PL); Cyclophosphamid "Apodan" (DK); Cyclostin (DE); Cyclostin N (DE); Cytoxan (CZ, EC, HU, ID, NZ, PH); Endoxan (AT, BE, BG, CN, DE, EC, EE, GR, HN, HR, HU, IL, IT, LU, NL, PK, PL, PT, RU, SG, TR, UY, ZA); Endoxan-Asta (AE, AR, AU, BH, CH, CY, EG, FR, HK, ID, IL, IN, IQ, IR, IT, JO, KW, LB, LY, MY, OM, PH, PL, QA, SA, SY, TH, TW, YE); Endoxana (GB); Endoxon-Asta (AU); Enduxan (BR); Genoxal (BR); Ledoxan (PH, TH); Ledoxina (MX); Lyophilisate (ID); Sendoxan (DK, FI, NO, SE); Syklofosfamid (FI, TR, TW); Xyclomed (PH)

CycloSERINE

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

CycloSERINE may be confused with cyclobenzaprine, cycloSPORINE

Pronunciation(sye kloe SER een)

U.S. Brand NamesSeromycin®

Pharmacologic CategoryAntibiotic, Miscellaneous; Antitubercular Agent

Use: Labeled IndicationsAdjunctive treatment in pulmonary or extrapulmonary tuberculosis

Use: Unlabeled/InvestigationalTreatment of Gaucher's disease

Dosing: Adults**Note:** Some of the neurotoxic effects may be relieved or prevented by the concomitant administration of pyridoxine.

Tuberculosis: Oral: Initial: 250 mg every 12 hours for 14 days, then give 500 mg to 1 g/day in 2 divided doses for 18-24 months (maximum daily dose: 1 g)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Some of the neurotoxic effects may be relieved or prevented by the concomitant administration of pyridoxine.

Tuberculosis: Oral: Children: 10-20 mg/kg/day in 2 divided doses up to 1000 mg/day for 18-24 months

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer every 12-24 hours.

Cl_{cr} <10 mL/minute: Administer every 24 hours.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Dietary ConsiderationsMay be taken with food; may increase vitamin B_{12} and folic acid dietary requirements.

ContraindicationsHypersensitivity to cycloserine or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Has been associated with CNS toxicity, including seizures, psychosis, depression, and confusion; decrease dosage or discontinue use if occurs.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Alcoholism: Use with caution in patients with a history of chronic alcoholism; increased risk of seizures.

- Mental illness: Use with caution in patients with depression, severe anxiety, and/or psychosis.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Special populations:

- Patients with potential for folate deficiency: Use with caution in patients with potential folate deficiency (malnourished, chronic anticonvulsant therapy, or elderly).

Geriatric ConsiderationsAdjust dose for renal function.

Pregnancy Risk FactorC

LactationEnters breast milk/compatible

Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiac arrhythmia

Central nervous system: Drowsiness, headache, dizziness, vertigo, seizure, confusion, psychosis, paresis, coma

Dermatologic: Rash

Endocrine & metabolic: Vitamin B_{12} deficiency

Hematologic: Folate deficiency

Hepatic: Liver enzymes increased

Neuromuscular & skeletal: Tremor

Drug Interactions

Isoniazid: CycloSERINE may enhance the CNS depressant effect of Isoniazid. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: May increase vitamin B_{12} and folic acid dietary requirements.

Monitoring ParametersPeriodic renal, hepatic, hematological tests, and plasma cycloserine concentrations

Reference RangeToxicity is greatly increased at levels >30 mcg/mL

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, CNS changes, arrhythmias, vitamin B_{12} deficiency, folate deficiency) regularly during therapy. Teach patient proper use, possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report.

Monitoring: Lab TestsPeriodic renal, hepatic, hematological tests, plasma cycloserine concentrations

Patient EducationTake as prescribed; do not discontinue this medication without consulting prescriber. Avoid alcohol. Maintain recommended diet and adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause drowsiness or restlessness (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report skin rash, acute headache, tremors or changes in mentation (confusion, nightmares, depression, or suicide ideation), or fluid retention (respiratory difficulty, swelling of extremities, unusual weight gain). **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 250 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Seromycin)

250 mg (14): $60.99

Mechanism of ActionInhibits bacterial cell wall synthesis by competing with amino acid (D-alanine) for incorporation into the bacterial cell wall; bacteriostatic or bactericidal

Pharmacodynamics/Kinetics

Absorption: ~70% to 90%

Distribution: Widely to most body fluids and tissues including CSF, breast milk, bile, sputum, lymph tissue, lungs, and ascitic, pleural, and synovial fluids; crosses placenta

Half-life elimination: Normal renal function: 10 hours

Metabolism: Hepatic

Time to peak, serum: 3-4 hours

Excretion: Urine (60% to 70% as unchanged drug) within 72 hours; feces (small amounts); remainder metabolized

Related Information

- Antimicrobial Drugs of Choice
- Depression
- Tuberculosis

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, confusion, depression, and psychosis

Mental Health: Effects on Psychiatric TreatmentLow doses (50 mg) have been used to treat negative symptoms of schizophrenia

References

Davidson PT and Le HQ, “Drug Treatment of Tuberculosis - 1992,” *Drugs*, 1992, 43(5):651-73. [PubMed 1379145]

“Drugs for Tuberculosis,” *Med Lett Drugs Ther*, 1993, 35(908):99-101. [PubMed 8412982]

Iseman MD, “Treatment of Multidrug-Resistant Tuberculosis,” *N Engl J Med*, 1993, 329(11):784-91. [PubMed 8350889]

Lev M and Sundaram KS, “Gaucher's Disease,” *N Engl J Med*, 1987, 317(9):572.

International Brand Names Ciclovalidin (IT); Closina (AU); Cyclorine (IN); Cycloserine (GB); Cycosin (IN); Miroseryn (IT); Seromycin (PL); Setavax (ES); Tuberserine (PK)

CycloSPORINE

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

CycloSPORINE may be confused with cyclophosphamide, Cyklokapron®, cycloSERINE

CycloSPORINE modified (Neoral®, Gengraf®) may be confused with cycloSPORINE non-modified (Sandimmne®)

Gengraf® may be confused with Prograf®

Neoral® may be confused with Neurontin®, Nizoral®

Sandimmune® may be confused with Sandostatin®

Pronunciation(SYE kloe spor een)

U.S. Brand NamesGengraf®; Neoral®; Restasis®; Sandimmune®

Canadian Brand NamesNeoral®; Rhoxal-cyclosporine; Sandimmune® I.V.; Sandoz-Cyclosporine

Pharmacologic CategoryImmunosuppressant Agent

Use: Labeled IndicationsProphylaxis of organ rejection in kidney, liver, and heart transplants, has been used with azathioprine and/or corticosteroids; severe, active rheumatoid arthritis (RA) not responsive to methotrexate alone; severe, recalcitrant plaque psoriasis in nonimmunocompromised adults unresponsive to or unable to tolerate other systemic therapy

Ophthalmic emulsion (Restasis®): Increase tear production when suppressed tear production is presumed to be due to keratoconjunctivitis sicca-associated ocular inflammation (in patients not already using topical anti-inflammatory drugs or punctal plugs)

Use: Unlabeled/InvestigationalShort-term, high-dose cyclosporine as a modulator of multidrug resistance in cancer treatment; allogenic bone marrow transplants for prevention and treatment of graft-versus-host disease; also used in some cases of severe autoimmune disease (eg, SLE, myasthenia gravis, inflammatory bowel disease) that are resistant to corticosteroids and other therapy; focal segmental glomerulosclerosis

Use: DentalUsed as an immunosuppressive agent

Dosing: Adults**Neoral®/Genraf® and Sandimmune® are not bioequivalent and cannot be used interchangeably.**

Newly-transplanted patients: Adjunct therapy with corticosteroids is recommended. Initial dose should be given 4-12 hours prior to transplant or may be given postoperatively; adjust initial dose to achieve desired plasma concentration.

Oral: Dose is dependent upon type of transplant and formulation:

Cyclosporine (modified):

Renal: 9 ± 3 mg/kg/day, divided twice daily

Liver: 8 ± 4 mg/kg/day, divided twice daily

Heart: 7 ± 3 mg/kg/day, divided twice daily

Cyclosporine (non-modified): Initial dose: 15 mg/kg/day as a single dose (range 14-18 mg/kg); lower doses of 10-14 mg/kg/day have been used for renal transplants. Continue initial dose daily for 1-2 weeks; taper by 5% per week to a maintenance dose of 5-10 mg/kg/day; some renal transplant patients may be dosed as low as 3 mg/kg/day

Note: When using the non-modified formulation, cyclosporine levels may increase in liver transplant patients when the T-tube is closed; dose may need decreased

I.V.: Manufacturer's labeling: Cyclosporine (non-modified): Initial dose: 5-6 mg/kg/day as a single dose ($^1/_3$ the oral dose), infused over 2-6 hours; use should be limited to patients unable to take capsules or oral solution; patients should be switched to an oral dosage form as soon as possible

Note: Many transplant centers administer cyclosporine as "divided dose" infusions (in 2-3 doses/day) or as a continuous (24-hour) infusion; dosages range from 3-7.5 mg/kg/day. Specific institutional protocols should be consulted.

Note: Conversion to cyclosporine (modified) from cyclosporine (non-modified): Start with daily dose previously used and adjust to obtain preconversion cyclosporine trough concentration. Plasma concentrations should be monitored every 4-7 days and dose adjusted as necessary, until desired trough level is obtained. When transferring patients with previously poor absorption of cyclosporine (non-modified), monitor trough levels at least twice weekly (especially if initial dose exceeds 10 mg/kg/day); high plasma levels are likely to occur.

Rheumatoid arthritis: Oral: Cyclosporine (modified): Initial dose: 2.5 mg/kg/day, divided twice daily; salicylates, NSAIDs, and oral glucocorticoids may be continued (refer to Drug Interactions); dose may be increased by 0.5-0.75 mg/kg/day if insufficient response is seen after 8 weeks of treatment; additional dosage increases may be made again at 12 weeks (maximum dose: 4 mg/kg/day). Discontinue if no benefit is seen by 16 weeks of therapy.

Note: Increase the frequency of blood pressure monitoring after each alteration in dosage of cyclosporine. Cyclosporine dosage should be decreased by 25% to 50% in patients with no history of hypertension who develop sustained hypertension during therapy and, if hypertension persists, treatment with cyclosporine should be discontinued.

Psoriasis: Oral: Cyclosporine (modified): Initial dose: 2.5 mg/kg/day, divided twice daily; dose may be increased by 0.5 mg/kg/day if insufficient response is seen after 4 weeks of treatment; additional dosage increases may be made every 2 weeks if needed (maximum dose: 4 mg/kg/day). Discontinue if no benefit is seen by 6 weeks of therapy. Once patients are adequately controlled, the dose should be decreased to the lowest effective dose. Doses <2.5 mg/kg/day may be effective. Treatment longer than 1 year is not recommended.

Note: Increase the frequency of blood pressure monitoring after each alteration in dosage of cyclosporine. Cyclosporine dosage should be decreased by 25% to 50% in patients with no history of hypertension who develop sustained hypertension during therapy and, if hypertension persists, treatment with cyclosporine should be discontinued.

Focal segmental glomerulosclerosis (unlabeled use): Initial: 3 mg/kg/day divided every 12 hours

Autoimmune diseases (unlabeled use): 1-3 mg/kg/day

Keratoconjunctivitis sicca: Ophthalmic: (Restasis®): Instill 1 drop in each eye every 12 hours

Dosing: ElderlyRefer to adult dosing. **Sandimmune® and Neoral®/Genraf® are not bioequivalent and cannot be used interchangeably.**

Dosing: PediatricTransplant: Refer to adult dosing; children may require, and are able to tolerate, larger doses than adults.

Dosing: Renal ImpairmentFor severe psoriasis:

Serum creatinine levels ≥25% above pretreatment levels: Take another sample within 2 weeks; if the level remains ≥25% above pretreatment levels, decrease dosage of cyclosporine (modified) by 25% to 50%. If two dosage adjustments do not reverse the increase in serum creatinine levels, treatment should be discontinued.

Serum creatinine levels ≥50% above pretreatment levels: Decrease cyclosporine dosage by 25% to 50%. If two dosage adjustments do not reverse the increase in serum creatinine levels, treatment should be discontinued.

Hemodialysis: Supplemental dose is not necessary.

Peritoneal dialysis: Supplemental dose is not necessary.

Dosing: Hepatic ImpairmentDosage adjustment is probably necessary; monitor levels closely

Administration: I.V.The manufacturer recommends that following dilution, intravenous admixture be administered over 2-6 hours. However, many transplant centers administer as divided doses (2-3 doses/day) or as a 24-hour continuous infusion. Patients should be under continuous observation for at least the first 30 minutes of the infusion, and should be monitored frequently thereafter.

Administration: I.V. DetailAnaphylaxis has been reported with I.V. use; reserve for patients who cannot take oral form. Patients should be under continuous observation for at least the first 30 minutes of the infusion, and should be monitored frequently thereafter. Maintain patent airway; other supportive measures and agents for treating anaphylaxis should be present when I.V. drug is given. Discard solution after 24 hours.

Administration: OralOral solution: Do not administer liquid from plastic or styrofoam cup. May dilute Neoral® oral solution with orange juice or apple juice. May dilute Sandimmune® oral solution with milk, chocolate milk, or orange juice. Avoid changing diluents frequently. Mix thoroughly and drink at once. Use syringe provided to measure dose. Mix in a glass container and rinse container with more diluent to ensure total dose is taken. Do not rinse syringe before or after use (may cause dose variation).

Administration: OtherOphthalmic emulsion: Prior to use, invert vial several times to obtain a uniform emulsion. Remove contact lenses prior to instillation of drops; may be reinserted 15 minutes after administration. May be used with artificial tears; allow 15 minute interval between products.

Dietary ConsiderationsAdminister this medication consistently with relation to time of day and meals. Avoid grapefruit juice.

Storage

Capsule: Store at controlled room temperature.

Injection: Store at controlled room temperature; do not refrigerate. Ampuls should be protected from light. Stability of injection of parenteral admixture at room temperature (25°C) is 6 hours in PVC; 24 hours in Excel®, PAB® containers, or glass.

Ophthalmic emulsion: Store at 15°C to 25°C (59°F to 77°F). Vials are single-use; discard immediately following administration.

Oral solution: Store at controlled room temperature; do not refrigerate. Use within 2 months after opening; should be mixed in glass containers.

Reconstitution**Sandimmune® injection:** Injection should be further diluted [1 mL (50 mg) of concentrate in 20-100 mL of D_5W or NS] for administration by intravenous infusion.

CompatibilityStable in D_5W, fat emulsion 10%, fat emulsion 20%, NS.

Y-site administration: Compatible: Alatrofloxacin, gatifloxacin, linezolid, propofol, sargramostim. **Incompatible:** Amphotericin B cholesteryl sulfate complex.

Compatibility when admixed: Compatible: Ciprofloxacin. **Incompatible:** Magnesium sulfate.

ContraindicationsHypersensitivity to cyclosporine or any component of the formulation. Rheumatoid arthritis and psoriasis: Abnormal renal function, uncontrolled hypertension, malignancies. Concomitant treatment with PUVA or UVB therapy, methotrexate, other immunosuppressive agents, coal tar, or radiation therapy are also contraindications for use in patients with psoriasis. Ophthalmic emulsion is contraindicated in patients with active ocular infections.

Allergy Considerations

- CycloSPORINE Allergy

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.
- Hypertension: See “Concerns related to adverse effects” below.
- Infection: See “Concerns related to adverse effects” below.
- Malignancy: See “Concerns related to adverse effects” below.
- Nephrotoxicity: “Concerns related to adverse effects” below.
- Non-interchangeability of modified/non-modified forms: See “Dosage form specific issues” below.
- Skin cancer: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Hepatotoxicity: Increased hepatic enzymes and bilirubin have occurred (when used at high doses); improvement usually seen with dosage reduction.
- Hypertension: **[U.S. Boxed Warning]: May cause hypertension.**
- Infection: **[U.S. Boxed Warning]: Increased risk of infection with use; fatal infections have been reported.**
- Malignancy: **[U.S. Boxed Warning]: Increased risk of lymphomas and other malignancies with use, particulary those of the skin;** risk is related to intensity/duration of therapy and the use of more than one immunosuppressive agent; all patients should avoid excessive sun/UV light exposure.
- Nephrotoxicity: **[U.S. Boxed Warning]: Renal impairment, including structural kidney damage has occurred (when used at high doses); monitor renal function closely.** Use caution with other potentially nephrotoxic drugs (eg, acyclovir, aminoglycoside antibiotics, amphotericin B, ciprofloxacin).
- Skin cancer: **[U.S. Boxed Warning]: Risk of skin cancer may be increased in psoriasis patients with a history of PUVA and possibly methotrexate or other immunosuppressants, UVB, coal tar, or radiation;** increased risk of skin cancer has also been established in transplant patients; risk is related to intensity/duration of therapy and the use of more than one immunosuppressive agent; all patients should avoid excessive sun/UV light exposure.

Disease-related concerns:

- Rheumatoid arthritis: Appropriate use: If receiving other immunosuppressive agents, radiation or UV therapy, concurrent use of cyclosporine is not recommended.

Special populations:

- Pediatrics: Safety and efficacy for use in psoriasis have not been established in children. Safety and efficacy of the ophthalmic emulsion have not been established in children <16 years of age. Safety and efficacy for use in juvenile rheumatoid arthritis have not been established.
- Transplant patients: To be used initially with corticosteroids. May cause significant hyperkalemia and hyperuricemia. May cause seizures, particularly if used with high-dose corticosteroids. Encephalopathy has been reported, predisposing factors include hypertension, hypomagnesemia, hypocholesterolemia, high-dose corticosteroids, high cyclosporine serum concentration, and graft-versus-host disease; may be more common in patients with liver transplant. Make dose adjustments based on cyclosporine blood concentrations. Anaphylaxis has been reported with I.V. use; reserve for patients who cannot take oral form.

Dosage form specific issues:

- Corn oil: Product may contain corn oil.
- Ethanol: Products may contain ethanol.
- Injection: Contains Cremophor® EL (polyoxyethylated castor oil), which has been associated with rare anaphylactic reactions.
- Non-interchangeability of modified/non-modified forms: Use caution when changing dosage forms; products are not equally interchangeable. Cyclosporine (modified) refers to the capsule dosage formulation of cyclosporine in an aqueous dispersion (previously referred to as “microemulsion”). **[U.S. Boxed Warning]: Cyclosporine (modified) has increased bioavailability as compared to cyclosporine (non-modified) and cannot be used interchangeably without close monitoring.**
- Propylene glycol: Products may contain propylene glycol.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Adjustment of dose should only be made under the direct supervision of an experienced physician.**
- Monitoring of concentrations: Monitor cyclosporine concentrations closely following the addition, modification, or deletion of other medications.

- Vaccines: Live, attenuated vaccines may be less effective; use should be avoided.

Geriatric ConsiderationsCyclosporine has not been specifically studied in the elderly. Cyclosporine is being used in combination therapy for the treatment of severe rheumatoid arthritis.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproductive toxicity has been observed in animal studies; mutagenic and teratogenic effects were not observed in the standard test systems following oral administration. In humans, cyclosporine crosses the placenta. Based on clinical use, premature births and low birth weight were consistently observed. Use only if the benefit to the mother outweighs the possible risks to the fetus.

A pregnancy registry has been established for pregnant women taking immunosuppressants following any solid organ transplant (National Transplantation Pregnancy Registry, Temple University, 877-955-6877).

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsThe AAP does not recommend breast-feeding during therapy due to possible immune suppression in the infant as well as the unknown effects on growth or association with carcinogenesis.

Adverse ReactionsAdverse reactions reported with systemic use, including rheumatoid arthritis, psoriasis, and transplantation (kidney, liver, and heart). Percentages noted include the highest frequency regardless of indication/dosage. Frequencies may vary for specific conditions or formulation.

>10%:

Cardiovascular: Hypertension (8% to 53%), edema (5% to 14%)

Central nervous system: Headache (2% to 25%)

Dermatologic: Hirsutism (21% to 45%), hypertrichosis (5% to 19%)

Endocrine & metabolic: Triglycerides increased (15%), female reproductive disorder (9% to 11%)

Gastrointestinal: Nausea (23%), diarrhea (3% to 13%), gum hyperplasia (2% to 16%), abdominal discomfort (<1% to 15%), dyspepsia (2% to 12%)

Neuromuscular & skeletal: Tremor (7% to 55%), paresthesia (1% to 11%), leg cramps/muscle contractions (2% to 12%)

Renal: Renal dysfunction/nephropathy (10% to 38%), creatinine increased (16% to ≥50%)

Respiratory: Upper respiratory infection (1% to 14%)

Miscellaneous: Infection (3% to 25%)

Kidney, liver, and heart transplant only (≤2% unless otherwise noted):

Cardiovascular: Flushes (<1% to 4%), MI

Central nervous system: Convulsions (1% to 5%), anxiety, confusion, fever, lethargy

Dermatologic: Acne (1% to 6%), brittle fingernails, hair breaking, pruritus

Endocrine & metabolic: Gynecomastia (<1% to 4%), hyperglycemia

Gastrointestinal: Nausea (2% to 10%), vomiting (2% to 10%), diarrhea (3% to 8%), abdominal discomfort (<1% to 7%), cramps (0% to 4%), anorexia, constipation, gastritis, mouth sores, pancreatitis, swallowing difficulty, upper GI bleed, weight loss

Hematologic: Leukopenia (<1% to 6%), anemia, thrombocytopenia

Hepatic: Hepatotoxicity (<1% to 7%)

Neuromuscular & skeletal: Paresthesia (1% to 3%), joint pain, muscle pain, tingling, weakness

Ocular: Conjunctivitis, visual disturbance

Otic: Hearing loss, tinnitus

Renal: Hematuria

Respiratory: Sinusitis (<1% to 7%)

Miscellaneous: Lymphoma (<1% to 6%), allergic reactions, hiccups, night sweats

Rheumatoid arthritis only (1% to <3% unless otherwise noted):

Cardiovascular: Hypertension (8%), edema (5%), chest pain (4%), arrhythmia (2%), abnormal heart sounds, cardiac failure, MI, peripheral ischemia

Central nervous system: Dizziness (8%), pain (6%), insomnia (4%), depression (3%), migraine (2%), anxiety, hypoesthesia, emotional lability, impaired concentration, malaise, nervousness, paranoia, somnolence, vertigo

Dermatologic: Purpura (3%), abnormal pigmentation, angioedema, cellulitis, dermatitis, dry skin, eczema, folliculitis, nail disorder, pruritus, skin disorder, urticaria

Endocrine & metabolic: Menstrual disorder (3%), breast fibroadenosis, breast pain, diabetes mellitus, goiter, hot flashes, hyperkalemia, hyperuricemia, hypoglycemia, libido increased/decreased

Gastrointestinal: Vomiting (9%), flatulence (5%), gingivitis (4%), gum hyperplasia (2%), constipation, dry mouth, dysphagia, enanthema, eructation, esophagitis, gastric ulcer, gastritis, gastroenteritis, gingival bleeding, glossitis, peptic ulcer, salivary gland enlargement, taste perversion, tongue disorder, tooth disorder, weight loss/gain

Genitourinary: Leukorrhea (1%), abnormal urine, micturition urgency, nocturia, polyuria, pyelonephritis, urinary incontinence, uterine hemorrhage

Hematologic: Anemia, leukopenia

Hepatic: Bilirubinemia

Neuromuscular & skeletal: Paresthesia (8%), tremor (8%), leg cramps/muscle contractions (2%), arthralgia, bone fracture, joint dislocation, myalgia, neuropathy, stiffness, synovial cyst, tendon disorder, weakness

Ocular: Abnormal vision, cataract, conjunctivitis, eye pain

Otic: Tinnitus, deafness, vestibular disorder

Renal: BUN increased, hematuria, renal abscess

Respiratory: Cough (5%), dyspnea (5%), sinusitis (4%), abnormal chest sounds, bronchospasm, epistaxis

Miscellaneous: Infection (9%), abscess, allergy, bacterial infection, carcinoma, fungal infection, herpes simplex, herpes zoster, lymphadenopathy, moniliasis, diaphoresis increased, tonsillitis, viral infection

Psoriasis only (1% to <3% unless otherwise noted):

Cardiovascular: Chest pain, flushes

Central nervous system: Psychiatric events (4% to 5%), pain (3% to 4%), dizziness, fever, insomnia, nervousness, vertigo

Dermatologic: Hypertrichosis (5% to 7%), acne, dry skin, folliculitis, keratosis, pruritus, rash, skin malignancies

Endocrine & metabolic: Hot flashes

Gastrointestinal: Nausea (5% to 6%), diarrhea (5% to 6%), gum hyperplasia (4% to 6%), abdominal discomfort (3% to 6%), dyspepsia (2% to 3%), abdominal distention, appetite increased, constipation, gingival bleeding

Genitourinary: Micturition increased

Hematologic: Bleeding disorder, clotting disorder, platelet disorder, red blood cell disorder

Hepatic: Hyperbilirubinemia

Neuromuscular & skeletal: Paresthesia (5% to 7%), arthralgia (1% to 6%)

Ocular: Abnormal vision

Respiratory: Bronchospasm (5%), cough (5%), dyspnea (5%), rhinitis (5%), respiratory infection

Miscellaneous: Flu-like syndrome (8% to 10%)

Postmarketing and/or case reports (any indication): Anaphylaxis/anaphylactoid reaction (possibly associated with Cremophor® EL vehicle in injection formulation), benign intracranial hypertension, cholesterol increased, death (due to renal deterioration), encephalopathy, gout, hyperbilirubinemia, hyperkalemia, hypomagnesemia (mild), impaired consciousness, neurotoxicity, papilloedema, pulmonary edema (noncardiogenic), uric acid increased

Ophthalmic emulsion (Restasis®):

>10%: Ocular: Burning (17%)

1% to 10%: Ocular: Hyperemia (conjunctival 5%), eye pain, pruritus, stinging

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP2C9 (weak), 3A4 (moderate)
Drug Interactions

ACE Inhibitors: May enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Aliskiren: CycloSPORINE may increase the serum concentration of Aliskiren. *Risk X: Avoid combination*

Ambrisentan: CycloSPORINE may increase the serum concentration of Ambrisentan. *Risk C: Monitor therapy*

Aminoglycosides: May enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Amiodarone: May decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Amphotericin B: May enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Androgens: May enhance the hepatotoxic effect of CycloSPORINE. Androgens may increase the serum concentration of CycloSPORINE. *Risk D:*

Consider therapy modification

Antacids: May decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Bosentan: CycloSPORINE may increase the serum concentration of Bosentan. Bosentan may decrease the serum concentration of CycloSPORINE. *Risk X: Avoid combination*

Bromocriptine: May increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Calcium Channel Blockers (Dihydropyridine): CycloSPORINE may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. **Exceptions:** Clevidipine. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of CycloSPORINE. CycloSPORINE may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). *Risk D: Consider therapy modification*

CarBAMazepine: May decrease the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Cardiac Glycosides: CycloSPORINE may decrease the metabolism of Cardiac Glycosides. *Risk D: Consider therapy modification*

Carvedilol: May increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Caspofungin: CycloSPORINE may enhance the adverse/toxic effect of Caspofungin. Significant increases in alanine transaminase have been reported. *Risk D: Consider therapy modification*

Colchicine: CycloSPORINE may enhance the adverse/toxic effect of Colchicine. These include hepatotoxicity and myopathies. Colchicine may increase the serum concentration of CycloSPORINE. Nephrotoxicity and hepatotoxicity may also be increased. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): May increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

DOXOrubicin: CycloSPORINE may decrease the metabolism of DOXOrubicin. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

Etoposide: CycloSPORINE may decrease the metabolism of Etoposide. *Risk D: Consider therapy modification*

Etoposide Phosphate: CycloSPORINE may increase the serum concentration of Etoposide Phosphate. CycloSPORINE may decrease the metabolism, via CYP isoenzymes, and decrease the p-glycoprotein-mediated elimination of Etoposide Phosphate. *Risk D: Consider therapy modification*

Ezetimibe: CycloSPORINE may increase the serum concentration of Ezetimibe. Ezetimibe may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fluconazole: May decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Grapefruit Juice: May decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Griseofulvin: May increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: CycloSPORINE may increase the serum concentration of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin. *Risk D: Consider therapy modification*

Imatinib: May increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of CycloSPORINE. **Exceptions:** Dirithromycin [Off Market]; Spiramycin. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Melphalan: May enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Methotrexate: May increase the serum concentration of CycloSPORINE. This may result in nephrotoxicity. CycloSPORINE may increase the serum concentration of Methotrexate. This may result in nausea, vomiting, oral ulcers, hepatotoxicity and/or nephrotoxicity. *Risk D: Consider therapy modification*

Metoclopramide: May increase the absorption of CycloSPORINE. *Risk C: Monitor therapy*

MetroNIDAZOLE: May decrease the metabolism of Calcineurin Inhibitors. *Risk C: Monitor therapy*

Minoxidil: CycloSPORINE may enhance the adverse/toxic effect of Minoxidil. Severe hypertrichosis has been reported. *Risk C: Monitor therapy*

Mycophenolate: CycloSPORINE may decrease the serum concentration of Mycophenolate. Specifically, cyclosporine may decrease concentrations of the active metabolite mycophenolic acid. *Risk D: Consider therapy modification*

Nafcillin: May increase the metabolism of CycloSPORINE. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nonsteroidal Anti-Inflammatory Agents: May enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Norfloxacin: May decrease the metabolism of CycloSPORINE. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Probucol: May decrease the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Pyrazinamide: May decrease the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Quinupristin: May decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Repaglinide: CycloSPORINE may increase the serum concentration of Repaglinide. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of CycloSPORINE. An increased risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA) has been described. CycloSPORINE may increase the serum concentration of Sirolimus. This is of specific concern with cyclosporine [MODIFIED]. *Risk D: Consider therapy modification*

Sitaxsentan: CycloSPORINE may increase the serum concentration of Sitaxsentan. *Risk X: Avoid combination*

Somatostatin Analogs: May decrease the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

St Johns Wort: May increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Sulfinpyrazone [Off Market]: May decrease the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Sulfonamide Derivatives: May enhance the nephrotoxic effect of CycloSPORINE. Sulfonamide Derivatives may decrease the serum concentration of CycloSPORINE. **Exceptions:** Sulfacetamide. *Risk C: Monitor therapy*

Sulfonylureas: May increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of CycloSPORINE. An increased risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA) has been described with concomitant sirolimus use. *Risk D: Consider therapy modification*

Terbinafine: May decrease the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Grapefruit juice increases cyclosporine absorption

Herb/Nutraceutical: Avoid St John's wort; as an enzyme inducer, it may increase the metabolism of and decrease plasma levels of cyclosporine; organ rejection and graft loss have been reported. Avoid cat's claw, echinacea (have immunostimulant properties).

Test InteractionsSpecific whole blood, HPLC assay for cyclosporine may be falsely elevated if sample is drawn from the same line through which dose was administered (even if flush has been administered and/or dose was given hours before).

Monitoring ParametersMonitor blood pressure and serum creatinine after any cyclosporine dosage changes or addition, modification, or deletion of other medications. Monitor plasma concentrations periodically.

Transplant patients: Cyclosporine trough levels, serum electrolytes, renal function, hepatic function, blood pressure, lipid profile

Psoriasis therapy: Baseline blood pressure, serum creatinine (2 levels each), BUN, CBC, serum magnesium, potassium, uric acid, lipid profile. Biweekly monitoring of blood pressure, complete blood count, and levels of BUN, uric acid, potassium, lipids, and magnesium during the first 3 months of treatment for psoriasis. Monthly monitoring is recommended after this initial period. Also evaluate any atypical skin lesions prior to therapy. Increase the frequency of blood pressure monitoring after each alteration in dosage of cyclosporine. Cyclosporine dosage should be decreased by 25% to 50% in patients with no history of hypertension who develop sustained hypertension during therapy and, if hypertension persists, treatment with cyclosporine should be discontinued.

Rheumatoid arthritis: Baseline blood pressure, and serum creatinine (2 levels each); serum creatinine every 2 weeks for first 3 months, then monthly if patient is stable. Increase the frequency of blood pressure monitoring after each alteration in dosage of cyclosporine. Cyclosporine dosage should be decreased by 25% to 50% in patients with no history of hypertension who develop sustained hypertension during therapy and, if hypertension persists, treatment with cyclosporine should be discontinued.

Reference RangeReference ranges are method dependent and specimen dependent; use the same analytical method consistently

Method-dependent and specimen-dependent: Trough levels should be obtained:

Oral: 12-18 hours after dose (chronic usage)

I.V.: 12 hours after dose **or** immediately prior to next dose

Therapeutic range: Not absolutely defined, dependent on organ transplanted, time after transplant, organ function and CsA toxicity:

General range of 100-400 ng/mL

Toxic level: Not well defined, nephrotoxicity may occur at any level

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor kidney and hepatic function closely. Monitor blood pressure and assess for signs of fluid retention periodically. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically throughout therapy. Teach patient appropriate administration, possible side effects, and symptoms to report. **I.V.:** Monitor closely for first 30 minutes of infusion and frequently thereafter to assess for adverse reactions.

Monitoring: Lab TestsCyclosporine levels, serum electrolytes, renal function, hepatic function

Patient Education**Oral:** Take dose at the same time each day. You will be susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). Avoid excessive exposure to sun. Practice good oral hygiene to reduce gum inflammation; see a dentist regularly during treatment. Report severe headache; unusual hair growth or deepening of voice; mouth sores or swollen gums; signs of infection; persistent nausea, vomiting, or abdominal pain; muscle pain or cramping; tremors; unusual swelling of extremities, weight gain, or change in urination; difficulty breathing; or chest pain or rapid heartbeat. Increase in blood pressure or damage to the kidney is possible. Your prescriber will need to monitor you closely. Do not change one brand of cyclosporine for another; any changes must be done by your prescriber. If you are taking this medication for psoriasis, your risk of cancer may be increased when taking additional medications. **Oral solution:** Diluting oral solution improves flavor. Dilute Neoral® with orange juice or apple juice. Dilute Sandimmune® with milk, chocolate milk, or orange juice. Avoid changing what you mix with your cyclosporine. Mix thoroughly and drink at once. Use syringe provided to measure dose. Mix in a glass container (do not use plastic or styrofoam) and rinse container with more juice/milk to ensure total dose is taken. Do not rinse syringe before or after use (may cause dose variation). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule [modified]:

Gengraf®: 25 mg [contains alcohol 12.8%]; 100 mg [contains alcohol 12.8%]

Capsule [non-modified]: 25 mg, 100 mg

Capsule, soft gel [modified]: 25 mg, 50 mg, 100 mg

Neoral®: 25 mg [contains alcohol 11.9% and corn oil]; 100 mg [contains alcohol 11.9% and corn oil]

Capsule, soft gel [non-modified]:

Sandimmune®: 25 mg [contains alcohol 12.7% and corn oil]; 100 mg [contains alcohol 12.7% and corn oil]

Emulsion, ophthalmic [preservative free]:

Restasis®: 0.05% (0.4 mL) [contains 30 single-use vials/box]

Injection, solution [non-modified]: 50 mg/mL (5 mL)

Sandimmune®: 50 mg/mL (5 mL) [contains Cremophor® EL (polyoxyethylated castor oil) and alcohol 32.9%]

Solution, oral [modified]: 100 mg/mL (50 mL)

Gengraf®: 100 mg/mL (50 mL) [contains propylene glycol]

Neoral®: 100 mg/mL (50 mL) [contains alcohol 11.9%, corn oil, and propylene glycol]

Solution, oral [non-modified]: 100 mg/mL (50 mL)

Sandimmune®: 100 mg/mL (50 mL) [contains alcohol 12.5%]

Generic AvailableYes: Excludes ophthalmic emulsion

Pricing: U.S. (www.drugstore.com)

Capsules (CycloSPORINE)

25 mg (60): $84.99

100 mg (60): $299.98

Capsules (CycloSPORINE Modified)

25 mg (30): $34.30

100 mg (30): $141.00

Capsules (Gengraf)

25 mg (60): $85.99

100 mg (60): $319.87

Capsules (Neoral)

25 mg (60): $85.99

100 mg (90): $478.18

Capsules (Sandimmune)

25 mg (60): $121.24

100 mg (60): $452.28

Emulsion (Restasis)

0.05% (30): $114.98

0.05% (32): $111.28

Solution (CycloSPORINE Modified)

100 mg/mL (50): $239.99

Solution (Neoral)

100 mg/mL (50): $301.71

Solution (Sandimmune)

50 mg/mL (5): $38.99

100 mg/mL (50): $384.97

Mechanism of ActionInhibition of production and release of interleukin II and inhibits interleukin II-induced activation of resting T-lymphocytes.

Pharmacodynamics/Kinetics

Absorption:

Ophthalmic emulsion: Serum concentrations not detectable.

Oral:

Cyclosporine (non-modified): Erratic and incomplete; dependent on presence of food, bile acids, and GI motility; larger oral doses are needed in pediatrics due to shorter bowel length and limited intestinal absorption

Cyclosporine (modified): Erratic and incomplete; increased absorption, up to 30% when compared to cyclosporine (non-modified); less dependent on food, bile acids, or GI motility when compared to cyclosporine (non-modified)

Distribution: Widely in tissues and body fluids including the liver, pancreas, and lungs; crosses placenta; enters breast milk

V_{dss}: 4-6 L/kg in renal, liver, and marrow transplant recipients (slightly lower values in cardiac transplant patients; children <10 years have higher values)

Protein binding: 90% to 98% to lipoproteins

Metabolism: Extensively hepatic via CYP3A4; forms at least 25 metabolites; extensive first-pass effect following oral administration

Bioavailability: Oral:

Cyclosporine (non-modified): Dependent on patient population and transplant type (<10% in adult liver transplant patients and as high as 89% in renal transplant patients); bioavailability of Sandimmune® capsules and oral solution are equivalent; bioavailability of oral solution is ~30% of the I.V. solution

Children: 28% (range: 17% to 42%); gut dysfunction common in BMT patients and oral bioavailability is further reduced

Cyclosporine (modified): Bioavailability of Neoral® capsules and oral solution are equivalent:

Children: 43% (range: 30% to 68%)

Adults: 23% greater than with cyclosporine (non-modified) in renal transplant patients; 50% greater in liver transplant patients

Half-life elimination: Oral: May be prolonged in patients with hepatic impairment and shorter in pediatric patients due to the higher metabolism rate

Cyclosporine (non-modified): Biphasic: Alpha: 1.4 hours; Terminal: 19 hours (range: 10-27 hours)

Cyclosporine (modified): Biphasic: Terminal: 8.4 hours (range: 5-18 hours)

Time to peak, serum: Oral:

Cyclosporine (non-modified): 2-6 hours; some patients have a second peak at 5-6 hours

Cyclosporine (modified): Renal transplant: 1.5-2 hours

Excretion: Primarily feces; urine (6%, 0.1% as unchanged drug and metabolites)

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsCyclosporine (modified): Refers to the capsule dosage formulation of cyclosporine in an aqueous dispersion (previously referred to as “microemulsion”). Cyclosporine (modified) has increased bioavailability as compared to cyclosporine (non-modified) and cannot be used interchangeably without close monitoring.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mouth sores, swallowing difficulty, gingivitis, gum hyperplasia, xerostomia (normal salivary flow resumes upon discontinuation), abnormal taste, tongue disorder, tooth disorder, and gingival bleeding.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentCarbamazepine and phenobarbital may increase the clearance of cyclosporine resulting in decreased levels; nefazodone may inhibit the clearance of cyclosporine resulting in increased levels of cyclosporine. There have been reports of serious drug interactions between cyclosporine and St John's wort. This interaction produces a reduction in serum cyclosporine levels resulting in subtherapeutic levels, rejection of transplanted organs, and graft loss.

Cardiovascular ConsiderationsCyclosporine is widely used in the cardiovascular setting, particularly in patients with cardiac transplantation. In these patients, an important consequence of cyclosporine use is hypertension. Because of widespread drug interactions, the concomitant use of other drugs and the addition of new drugs should be carefully evaluated to ensure that these do not influence the concentrations of cyclosporine.

Index TermsCsA; CyA; Cyclosporin A

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International Brand NamesCermox (AR); Cicloral (AU, DE); Cipol (KP); Cipol-N (KP); Consupren (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Cysporin (AU); Deximune (IL); Equoral (TH); Gengraf (BR, HK, MY, SG, TH); Implanta (KP); Imusporin (CO, IN); Modusik-A Ofteno (CR, DO, GT, HN, MX, NI, PA, SV); Neolem (MX); Neoral (FR, NZ, TW); Panimun Bioral (TH); Restasis (EC, IL, KP, MX, PH, TH, TW); Sanda (TH); Sandimmun (AT, AU, BD, BE, BF, BG, BJ, CH, CI, CL, CN, CZ, DE, DK, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, ID, IE, IL, IN, IT, JP, KE, KP, LR, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, PE, PH, PK, PT, RU, SC, SD, SE, SG, SL, SN, TH, TN, TR, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Sandimmun Neoral (AE, AR, AT, AU, BH, BR, CH, CL, CN, CO, CY, CZ, DK, EE, EG, FI, GB, GR, HK, ID, IL, IQ, IR, JO, KP, KW, LB, LY, MX, MY, NO, OM, PE, PH, PY, QA, SA, SE, SY, TH, TR, UY, VE, YE, ZA); Sandimmune (NL); Supremunn (MX)

Cyproheptadine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cyproheptadine may be confused with cyclobenzaprine

Periactin may be confused with Perative®, Percodan®, Persantine®

Pronunciation(si proe HEP ta deen)

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsPerennial and seasonal allergic rhinitis and other allergic symptoms including urticaria

Use: Unlabeled/InvestigationalAppetite stimulation, blepharospasm, cluster headaches, migraine headaches, Nelson's syndrome, pruritus, schizophrenia, spinal cord damage associated spasticity, and tardive dyskinesia

Dosing: Adults

Appetite stimulation (including anorexia nervosa): Oral: 2 mg 4 times/day; may be increased gradually over a 3-week period to 8 mg 4 times/day

Allergic conditions: Oral: 4-20 mg/day divided every 8 hours (not to exceed 0.5 mg/kg/day)

Cluster headaches: Oral: 4 mg 4 times/day

Migraine headaches: Oral: 4-8 mg 3 times/day

Spasticity associated with spinal cord damage: Oral: 4 mg at bedtime; increase by a 4 mg dose every 3-4 days; average daily dose: 16 mg in divided doses; not to exceed 36 mg/day

Dosing: ElderlyOral: Initial: 4 mg twice daily

Dosing: Pediatric

Allergic conditions: Oral: Children: 0.25 mg/kg/day or 8 mg/m^2/day in 2-3 divided doses **or**

2-6 years: 2 mg every 8-12 hours (not to exceed 12 mg/day)

7-14 years: 4 mg every 8-12 hours (not to exceed 16 mg/day)

Migraine headaches: 4 mg 2-3 times/day

Spasticity associated with spinal cord damage: Oral: Children ≥12 years: Refer to adult dosing.

Appetite stimulation (Including anorexia nervosa): Children >13 years: Refer to adult dosing.

Dosing: Hepatic ImpairmentDosage should be reduced in patients with significant hepatic dysfunction.

Calculations

- Body Surface Area: Pediatrics

ContraindicationsHypersensitivity to cyproheptadine or any component of the formulation; narrow-angle glaucoma; bladder neck obstruction; symptomatic prostatic hyperplasia; acute asthmatic attack; stenosing peptic ulcer; GI tract obstruction; concurrent use of MAO inhibitors; avoid use in premature and term newborns due to potential association with SIDS

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Respiratory disease: Use with caution in patients with asthma or other chronic breathing disorders.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Anorexic adults: In case reports, cyproheptadine has promoted weight gain in anorexic adults, though it has not been specifically studied in the elderly. All cases of weight loss or decreased appetite should be adequately assessed.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Antihistamines may cause excitation in young children. Safety and efficacy have not been established in children <2 years of age.

Geriatric ConsiderationsIn case reports, cyproheptadine has promoted weight gain in anorexic adults, though it has not been specifically studied in the elderly. All cases of weight loss or decreased appetite should be adequately assessed. Cyproheptadine may cause less sedation than diphenhydramine or hydroxyzine and, therefore, may be useful for pruritus in elderly; however, elderly may not tolerate anticholinergic effects.
Pregnancy Risk FactorB
LactationExcretion in breast milk unknown/contraindicated
Adverse Reactions

>10%:

Central nervous system: Slight-to-moderate drowsiness

Respiratory: Thickening of bronchial secretions

1% to 10%:

Central nervous system: Dizziness, fatigue, headache, nervousness

Gastrointestinal: Abdominal pain, appetitie stimulation, diarrhea, nausea, xerostomia

Neuromuscular & skeletal: Arthralgia

Respiratory: Pharyngitis

<1%: Allergic reaction, angioedema, bronchospasm, CNS stimulation, depression, edema, epistaxis, hemolytic anemia, hepatitis, leukopenia, myalgia, palpitation, paresthesia, photosensitivity, rash, sedation, seizure, tachycardia, thrombocytopenia

Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Cyproheptadine may diminish the therapeutic effect of Selective Serotonin Reuptake Inhibitors. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS sedation).
Test InteractionsDiagnostic antigen skin test results may be suppressed; false positive serum TCA screen
Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor weight periodically. Monitor effectiveness of therapy and adverse reactions (eg, excess anticholinergic effects) at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Patient EducationTake as directed; do not exceed recommended dose. Avoid use of other depressants, alcohol, or sleep-inducing medications unless approved by prescriber. You may experience drowsiness or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or dry mouth, nausea, or abdominal pain (small frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help). Report persistent sedation, confusion, or agitation; changes in urinary pattern; blurred vision; chest pain or palpitations; sore throat respiratory difficulty or expectorating (thick secretions); significant change in weight; or lack of improvement or worsening or condition. **Breast-feeding precaution:** Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Syrup, as hydrochloride: 2 mg/5 mL (473 mL) [contains alcohol 5%; mint flavor]

Tablet, as hydrochloride: 4 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Syrup (Cyproheptadine HCl)

2 mg/5 mL (120): $14.99

Tablets (Cyproheptadine HCl)

4 mg (30): $11.99

Mechanism of ActionA potent antihistamine and serotonin antagonist, competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract

Pharmacodynamics/Kinetics

Absorption: Completely

Metabolism: Almost completely hepatic

Excretion: Urine (>50% primarily as metabolites); feces (~25%)

Pharmacotherapy PearlsMay stimulate appetite. In case reports, cyproheptadine has promoted weight gain in anorexic adults.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause nervousness or depression

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors; concurrent use with psychotropic may produce additive sedation

Anesthesia and Critical Care Concerns/Other ConsiderationsMay stimulate appetite; in case reports, cyproheptadine has promoted weight gain in anorexic adults.

Index TermsCyproheptadine Hydrochloride; Periactin

References

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International Brand NamesAdekin (GR); Antisemin (TW); Apeton 4 (ID); Cipla-Actin (ZA); Ciplactin (IN); Ciprogal (UY); Ciproral (DE); Ciprovit-A (PE); Complamin (EC); Cyheptine (TH); Cylat (ID); Cypro H (TW); Cyprogin (HK, TH); Cypromin (JP, TW); Cyprono (TH); Cyprosian (TH); Cyprotec (TH); Cyprotin (SG); Cyprotol (BG); Cytadine (TW); Ennamax (ID); Glocyp (ID); Gubamine (AR); Hepdine (TH); Heptasan (ID); Istam-Far (GR); Kulinet (GR); Pangavit Pediátrico (MX); Periactin (AE, AT, AU, BE, BF, BG, BH, BJ, CH, CI, CO, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HN, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PK, PT, QA, RU, SA, SC, SD, SE, SL, SN, SY, TH, TN, TR, TZ, UG, VE, YE, ZA, ZM, ZW); Periactine (FR); Periatin (BR); Peritol (BB, BM, BS, BZ, CZ, GY, HN, HU, IN, JM, NL, PL, PR, SR, TT); Petina (MY); Pilian (MY); Poncohist (ID); Prohessen (ID); Pronicy (ID); Protadina (PL); Showmin (TW); Trimetabol (CO)

Cyproterone and Ethinyl Estradiol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(sye PROE ter one & ETH in il es tra DYE ole)

Canadian Brand NamesCyestra-35; Diane-35®

Pharmacologic CategoryAcne Products; Estrogen and Progestin Combination

Use: Labeled IndicationsTreatment of females with severe acne, unresponsive to other therapies, with associated symptoms of androgenization (including mild hirsutism or seborrhea). **Should not be used solely for contraception;** however, will provide reliable contraception if taken as recommended for approved indications.

Dosing: AdultsFemale: Acne: Oral: One tablet daily for 21 days, followed by 7 days off; first cycle should begin on the first day of menstrual flow. Discontinue therapy 3-4 cycles after symptoms have resolved.

Dosing: Renal ImpairmentSpecific guidelines not available; use with caution.

Dosing: Hepatic ImpairmentContraindicated in hepatic impairment or active liver disease.

Administration: OralAdminister at the same time each day.

StorageStore at controlled room temperature of 25°C (77°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to ethinyl estradiol, cyproterone, or any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); cerebral vascular disease, coronary artery disease, valvular heart disease with complications, severe hypertension; diabetes mellitus with vascular involvement; severe headache with focal neurological symptoms; known or suspected breast carcinoma, endometrial cancer, estrogen-dependent neoplasms, undiagnosed abnormal genital bleeding; hepatic dysfunction or tumor, cholestatic jaundice of pregnancy, jaundice with prior combination hormonal contraceptive use; major surgery with prolonged immobilization; heavy smoking (≥15 cigarettes/day) in patients >35 years of age; ocular lesions resulting from vascular disease; history of otosclerosis with deterioration during pregnancy; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Breast cancer: The use of combination oral contraceptive therapy has been associated with a slight increase in frequency of breast cancer, however, studies are not consistent.
- Glucose intolerance: Combination hormonal contraceptives may cause glucose intolerance.
- Lipid effects: Combination hormonal contraceptives may effect serum triglyceride and lipoprotein levels. Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Thromboembolism: May increase the risk of thromboembolism; users appear to have an elevated risk relative to users of oral contraceptives in some published studies.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with risk factors for coronary artery disease; may lead to increased risk of myocardial infarction. May have a dose-related risk of vascular disease and hypertension; avoid use in hypertensive women.
- Depression: Use with caution in patients with depression.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.
- Gallbladder disease: May have a dose-related risk of gallbladder disease.
- Migraine: Use with caution in patients with a history of migraine.
- Renal impairment: Use with caution in patients with renal disease.

Special populations:

- Smokers: The risk of cardiovascular side effects with oral contraceptives increases in women who smoke cigarettes, especially those who are >35 years of age; women who use combination estrogen/progestin therapy should be strongly advised not to smoke.

Other warnings/precautions:

- Contraceptive properties: Should not be prescribed solely for its contraceptive properties (secondary nonhormonal contraception recommended in patients who may not adhere to dosing). Should not be used in combination with other oral contraceptives. This combination shares many of the risks of oral contraceptive agents.

Pregnancy Risk FactorX

Pregnancy ConsiderationsPregnancy should be ruled out prior to treatment and discontinued if pregnancy occurs. In general, the use of combination hormonal contraceptives when inadvertently taken early in pregnancy have not been associated with teratogenic effects. Due to increased risk of thromboembolism postpartum, combination hormonal contraceptives should not be started earlier than 4-6 weeks following delivery.

LactationEnters breast milk/not recommended

Adverse Reactions**Note:** This listing reflects reactions reported with combination hormonal contraceptives. Percentages specific to this combination are identified in parentheses.

Cardiovascular: Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, edema (2%), hypertension, mesenteric thrombosis, MI

Note: The frequency of venous thromboembolism in users of cyproterone and ethinyl estradiol has been estimated to be from 1.2 to 9.9 events per 10,000 women-years. The incidence of these events in nonusers of any oral contraceptive has been estimated to be 0.5 to 1 event per 10,000 women-years, and increases to 4 events per 10,000 women-years for users of low-dose estrogen combinations.

Central nervous system: Headache (5%), depression (3%), dizziness (1%), nervousness (4%), migraine, premenstrual syndrome, stroke

Dermatologic: Chloasma (4%), acne, erythema multiforme, erythema nodosum, hirsutism, loss of scalp hair, melasma (may persist), rash (allergic)

Endocrine & metabolic: Dysmenorrhea (10%), breast tenderness (7%), libido changes (3%), sex hormone-binding globulins (SHBG) increased, amenorrhea, breakthrough bleeding, breast enlargement, breast secretion, carbohydrate intolerance, lactation decreased (postpartum), glucose tolerance decreased, menstrual flow changes, spotting, temporary infertility (following discontinuation), thyroid-binding globulin increased, triglycerides increased

Gastrointestinal: Nausea (2%), abdominal cramps, appetite changes, bloating, cholestasis, colitis, gallbladder disease, jaundice, vomiting, weight gain/loss

Genitourinary: Cervical erosion changes, cervical secretion changes, cystitis-like syndrome, vaginal candidiasis, vaginitis

Hematologic: Antithrombin III decreased, folate levels decreased, hemolytic uremic syndrome, norepinephrine-induced platelet aggregability increased, porphyria, prothrombin increased; factors VII, VIII, IX, and X increased

Hepatic: Benign liver tumors, Budd-Chiari syndrome, cholestatic jaundice, hepatic adenomas

Local: Thrombophlebitis

Ocular: Cataracts, change in corneal curvature (steepening), contact lens intolerance, optic neuritis, retinal thrombosis

Renal: Renal function impaired

Respiratory: Pulmonary thromboembolism

Miscellaneous: Hemorrhagic eruption

Metabolism/Transport EffectsEthinyl estradiol: **Substrate** of CYP2C9 (minor), 3A4 (major), 3A5-7 (minor); **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C8 (weak), 2C19 (weak), 3A4 (weak)

Drug Interactions

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Armodafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Estrogens) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Colesevelam: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May increase the metabolism of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

LamoTRIgine: Oral Contraceptive (Estrogens) may decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Modafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Average AUC values were unchanged, but there was evidence of substantial patient-to-patient variability in response to this combination. *Risk D: Consider therapy modification*

Nafcillin: May increase the metabolism of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Protease Inhibitors: Oral Contraceptive (Estrogens) may diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Rufinamide: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Estrogens) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

TiZANidine: Oral Contraceptive (Estrogens) may increase the serum concentration of TiZANidine. *Risk C: Monitor therapy*

Topiramate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Oral Contraceptive (Estrogens) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Estrogens). Oral Contraceptive (Estrogens) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: CNS effects of caffeine may be enhanced if combination hormonal contraceptives are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations and would be expected to increase progesterone serum levels as well; clinical implications are unclear.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca. Herbs with progestogenic properties may enhance the adverse/toxic effect of progestins; examples include bloodroot, chasteberry, damiana, oregano, yucca.

Monitoring ParametersSigns/symptoms of venous thromboembolism; blood pressure, breast exam, Pap smear, and pregnancy; lipid profiles in patients being treated for hyperlipidemias; follow-up examination 3 months after initiation of therapy

Monitoring: Lab TestsPap smear, pregnancy; lipid profiles in patients being treated for hyperlipidemias

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. CAN = [Canadian brand name]

Tablet: Diane-35 [CAN]: Cyproterone 2 mg and ethinyl estradiol 0.35 mg (21s) [not available in the U.S.]

ManufacturerBerlex (Canada)

Mechanism of Action

Ethinyl estradiol: Estrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone, and follicle-stimulating hormone through a negative feedback system. Estrogen increases levels of sex hormone-binding globulin (SHBG) and may reduce unbound androgen levels. Ethinyl estradiol is a synthetic derivative of estradiol. The addition of the ethinyl group prevents rapid degradation by the liver.

Cyproterone: Steroidal compound with antiandrogenic, antigonadotropic and progestin-like activity.

Pharmacodynamics/Kinetics

Cyproterone:

Absorption: Rapid and complete

Metabolism: Hepatic; some metabolites have activity

Half-life elimination: 38 hours

Time to peak: 3-4 hours

Excretion: As metabolites: Urine (35%), feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression; use with caution

Mental Health: Effects on Psychiatric TreatmentCarbamazepine phenobarbital, phenytoin, and St John's wort may increase the metabolism of ethinyl estradiol. Concomitant use with benzodiazepines may result in altered clearance of benzodiazepines; monitor. Effects of selegiline and tricyclic antidepressants may be potentiated in combined use with ethinyl estradiol.

Cardiovascular ConsiderationsIt is important to recognize that estrogen/antiandrogen combinations may induce or worsen hypertension. These problems are less severe with low doses. Furthermore, these agents may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on long-term therapy undergo monitoring of blood pressure and avoid cigarette use.

Index TermsEthinyl Estradiol and Cyproterone Acetate

International Brand NamesAlthea (PH); Brenda-35 ED (AU); Claudia (BE); Cyprodiol (BE); Daphne (BE, HK); Diane (EE, FI, IN, MX, NO, SE); Diane 35 (AR, BR, CH, CL, CN, CZ, DE, DK, EE, FR, HK, ID, IL, KP, MY, PE, PH, PK, PY, SG, TH); Diane 35 Diario (ES); Diane-35 (CO, UY, VE, ZA); Diane-35 ED (AU); Dianette (IE); Diva-35 (ZA); Dixi-35 (CN, EC, PE, PY); Estelle -35 (IL, MY, SG); Estelle-35 ED (AU); Eunice-35 (MX); Evepar (FR); Femina-35 (EE); Feminil (NO); Holgyeme (FR); Lady-Ten 35 (CN); Minerva-35 (ZA); Zyrona (SE)

Cyproterone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(sye PROE ter one)
Canadian Brand NamesAndrocur®; Androcur® Depot; Apo-Cyproterone®; Gen-Cyproterone; Novo-Cyproterone
Pharmacologic CategoryAntiandrogen
Use: Labeled IndicationsPalliative treatment of advanced prostate carcinoma
Dosing: AdultsProstatic carcinoma (palliative treatment): Males:

Oral: 200-300 mg/day in 2-3 divided doses; following orchiectomy, reduce dose to 100-200 mg/day; should be taken with meals

I.M. (depot): 300 mg (3 mL) once weekly; reduce dose in orchiectomized patients to 300 mg every 2 weeks

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentUse is contraindicated.
Dosing: Hepatic ImpairmentUse is contraindicated with hepatic impairment or active liver disease.
Administration: OralAdminister at the same time each day. Take with meals.
StorageStore at controlled room temperature of 25°C (77°F).
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to cyproterone or any component of the formulation; active liver disease or hepatic dysfunction; renal impairment
Warnings/Precautions

Concerns related to adverse effects:

- Hepatic toxicity: Has been associated with hepatic toxicity (jaundice, hepatitis, hepatic failure); typically this toxicity develops after several months of therapy. Monitor hepatic function and consider discontinuation of therapy in patients with evidence of hepatic injury.
- Lipid effects: May increase HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Thromboembolism: May increase the risk of thromboembolism.

Disease-related concerns:

- Cardiovascular disease: Use with caution in conditions that may be aggravated by fluid retention, or cardiovascular disease.
- Depression: Use with caution in patients with a history of depression; has been associated with an increased incidence of depression, particularly early in the course of therapy (initial 6-8 weeks).
- Diabetes: Use with caution in patients with diabetes or impaired glucose tolerance, may cause alterations in glucose metabolism.

Pregnancy Risk FactorNot indicated for use in women
Pregnancy ConsiderationsIn males, sperm count and volume of ejaculate will be reduced. After ~2 months of treatment, infertility may be noted.
Adverse ReactionsFrequency not defined.

Cardiovascular: Heart failure, hemorrhage, hypotension, MI, stroke, shock, stroke, syncope, tachycardia, thrombosis (DVT, pulmonary embolism, retinal vein thrombosis)

Central nervous system: Depression, dizziness, encephalopathy, fatigue, headache, lassitude

Dermatologic: Dry skin (sebum reduction), eczema, erythema, exfoliative dermatitis, hirsutism, nodosum, patchy loss of body hair, photosensitivity, pruritus, rash, scleroderma, skin discoloration, urticaria

Endocrine & metabolic: Adrenal suppression (dose related), benign nodular breast hyperplasia, diabetes mellitus, galactorrhea, gynecomastia, hot flashes, hypercalcemia, hyperglycemia, impotence, inhibition of spermatogenesis, libido increased, negative nitrogen balance, weight gain/loss

Gastrointestinal: Anorexia, constipation, diarrhea, dyspepsia, glossitis, nausea, pancreatitis, vomiting

Genitourinary: Bladder carcinoma, hematuria, urinary frequency

Hematologic: Anemia, fibrinogen increased, hemolytic anemia, leukopenia, leukocytosis, PT decreased, thrombocytopenia

Hepatic: Ascites, cholestatic jaundice, cirrhosis, hepatic dysfunction (dose related), hepatic carcinoma, hepatic coma, hepatic failure, hepatic necrosis, hepatitis, hepatoma, hepatomegaly, transaminases increased

Local: Injection site reaction

Neuromuscular and skeletal: Myasthenia, osteoporosis, weakness

Ocular: Abnormal accommodation, abnormal vision, blindness, optic neuritis, optic atrophy, retinal disorder

Renal: Renal failure, serum creatinine increased

Respiratory: Asthma, bronchospasm, cough, dyspnea, pulmonary embolism, pulmonary fibrosis

Miscellaneous: Allergic reaction

Drug Interactions

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: May reduce the effect of cyproterone (not established in the treatment of prostatic carcinoma); avoid concurrent use.

Monitoring Parameters

Liver function tests should be performed at baseline and periodically thereafter, or whenever signs or symptoms suggestive of hepatotoxicity are noted. Adrenal function should be monitored periodically.

Monitoring: Lab Tests

Liver function tests should be performed at baseline and periodically thereafter, or whenever signs or symptoms suggestive of hepatotoxicity are noted. Adrenal function should be monitored periodically.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as acetate (Androcur® Depot): 100 mg/mL (3 mL) [contains benzyl benzoate and castor oil]

Tablet, as acetate (Androcur®): 50 mg

Generic Available

Yes

Mechanism of Action

Cyproterone is a steroidal compound with antiandrogenic, antigonadotropic, and progestin-like activity.

Pharmacodynamics/Kinetics

Absorption: Oral: Rapid and complete

Metabolism: Hepatic, some metabolites have activity

Half-life elimination: Oral: 38 hours; Depot injection: 4 days

Time to peak, plasma: Oral: 3-4 hours; Depot injection: 3 days

Excretion: Urine (35%, as metabolites); feces (60%)

Dental Health: Effects on Dental Treatment

Key adverse event(s) related to dental treatment: Glossitis

Dental Health: Vasoconstrictor/Local Anesthetic Precautions

No information available to require special precautions

Mental Health: Effects on Mental Status

May cause dizziness; associated with an increased incidence of depression early in the course of therapy; use with caution

Mental Health: Effects on Psychiatric Treatment

None reported

Index Terms

Cyproterone Acetate

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Neumann F and Kalmus J, "Cyproterone Acetate in the Treatment of Sexual Disorders: Pharmacological Base and Clinical Experience," *Exp Clin Endocrinol*, 1991, 98(2):71-80.[PubMed 1838080]

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Schroder FH, "Cyproterone Acetate--Mechanism of Action and Clinical Effectiveness in Prostate Cancer Treatment," *Cancer*, 1993, 72(12 Suppl):3810-5.[PubMed 8252496]

International Brand Names

Androcur (AR, AU, BE, BG, BR, CH, CO, CZ, DE, DK, DO, EE, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IT, JP, KP, MX, MY, NL, PE, PK, PL, PT, SE, SG, TH, TW, UY, VE, ZA); Androstat (EC, PE, PY); Armocur (IL); Ciproplex (PY); Ciproterona (CN); Cyprohexal (AU); Cypron 50 (IL); Cyprone (AU); Cyproplex (BE, MY); Cyprostat (AU, GB); Kaliale (FR); Olter (CO); Procur (NZ); Prostaden (UY); Siterone (NZ); Virilit (DE)

Cysteamine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(sis TEE a meen)

U.S. Brand NamesCystagon®

Pharmacologic CategoryAnticystine Agent; Urinary Tract Product

Use: Labeled IndicationsTreatment of nephropathic cystinosis

Dosing: AdultsManagement of nephropathic cystinosis: Oral: Adults (>110 lb): Initiate therapy with $^{1}/_{4}$ to $^{1}/_{6}$ of maintenance dose; titrate slowly upward over 4-6 weeks. **Note:** Dosage may be increased if cystine levels are <1 nmol/$^{1}/_{2}$ cystine/mg protein, although intolerance and incidence of adverse events may be increased.

Maintenance: 2 g/day in 4 divided doses; maximum dose: 1.95 g/m^2/day or 90 mg/kg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricManagement of nephropathic cystinosis: Oral: Initiate therapy with $^{1}/_{4}$ to $^{1}/_{6}$ of maintenance dose; titrate slowly upward over 4-6 weeks. **Note:** Dosage may be increased if cystine levels are <1 nmol/$^{1}/_{2}$ cystine/mg protein, although intolerance and incidence of adverse events may be increased.

Children <12 years: Maintenance: 1.3 g/m^2/day or 60 mg/kg/day divided into 4 doses (maximum dose: 1.95 g/m^2/day or 90 mg/kg/day

Children >12 years and >110 lbs: Refer to adult dosing.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: OralSprinkle capsule contents over food or mix in formula if unable to swallow capsule.

StorageStore at 20°C to 25°C (68°F to 77°F). Protect from light and moisture.

ContraindicationsHypersensitivity to cysteamine, penicillamine, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Bone lesions: Osteopenia, compression fractures, scoliosis, and genu valgum, accompanied by leg pain and joint hyperextension may occur with higher doses; dosage reduction may be required.
- CNS symptoms: Adjust dose if CNS symptoms (eg, depression, lethargy, seizure) related to drug use (rather than the disease) develop. May impair mental alertness; patients should use caution when driving or operating heavy machinery until the effects are known.
- Dermatologic: Withhold if a mild-to-moderate rash develops; restart at a lower dose and titrate to therapeutic dose. Do not rechallenge with severe skin rash (erythema multiforme bullosa or toxic epidermal necrolysis). Skin lesions, appearing as hemorrhagic lesions (on the upper extremities), molluscoid pseudotumors or skin striae have been reported with higher doses; dosage reduction may be required.
- Gastrointestinal symptoms: Gastrointestinal ulcers and bleeding have been reported; promptly evaluate if signs and symptoms occur; adjust dose downward if severe GI symptoms develop (most common during initiation of therapy).
- Hematologic: May cause reversible leukopenia.
- Hepatic: May cause abnormal liver functions studies.
- Intracranial hypertension/papilledema: Intracranial hypertension (pseudotumor cerebri) and/or papilledema have been reported with treatment; may be managed with diuretics.

Pregnancy Risk FactorC

Pregnancy ConsiderationsUse only when the potential benefits outweigh the potential hazards to the fetus; in animal studies, cysteamine is teratogenic and fetotoxic. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is unknown whether cysteamine is excreted in breast milk. Discontinue nursing or discontinue drug during lactation.

Adverse Reactions

>5%:

Central nervous system: Fever (22%), lethargy (11%)

Dermatologic: Rash (7%)

Gastrointestinal: Vomiting (35%), anorexia (31%), diarrhea (16%)

<5%:

Cardiovascular: Hypertension

Central nervous system: Abnormal thinking, ataxia, confusion, depression, dizziness, emotional lability, encephalopathy, hallucinations, headache, impaired cognition, jitteriness, nervousness, nightmares, seizure, somnolence

Dermatologic: Urticaria

Endocrine & metabolic: Dehydration

Gastrointestinal: Abdominal pain, bad breath, constipation, duodenal ulceration, duodenitis, dyspepsia, gastroenteritis, gastrointestinal bleeding, gastrointestinal ulcers, nausea

Hematologic: Anemia, leukopenia

Hepatic: Abnormal LFTs

Neuromuscular & skeletal: Hyperkinesia, tremor

Otic: Hearing decreased

Postmarketing and/or case reports: Compression fracture, genu valgum, hyperthermia, interstitial nephritis, intracranial hypertension (benign), joint hyperextension, leg pain, lethargy, molluscoid pseudotumor, osteopenia, papilledema, pseudotumor cerebri, rash, renal failure, scoliosis, skin fragility, skin lesion, skin striae

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersBlood counts and LFTs during therapy; signs and symptoms of gastrointestinal ulceration and bleeding. Monitor leukocyte cystine measurements every 3 months to determine adequate dosage and compliance (measure 5-6 hours after administration); monitor more frequently when switching salt forms. Ophthalmic examination (periodic).

Reference RangeLeukocyte cystine:

Normal individual: <0.2 $\text{nmol/}^{1}/_{2}$ cystine/mg protein

Cystinosis target: <1 $\text{nmol/}^{1}/_{2}$ cystine/mg protein (if poor tolerability to cysteamine, may still benefit from leukocyte cystine levels <2 $\text{nmol/}^{1}/_{2}$ cystine/mg protein)

Nursing: Physical Assessment/MonitoringMonitor all laboratory results. Monitor or instruct patient to monitor for adverse reactions; especially CNS changes, GI disturbances, or rash. If reactions are noted, medication should be held until reactions clear, and medication started at a lower dose.

Monitoring: Lab TestsBlood counts and LFTs during therapy; monitor leukocyte cystine measurements every 3 months to determine adequate dosage and compliance (measure 5-6 hours after administration); monitor more frequently when switching salt forms

Patient EducationTake as directed. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. It may be necessary to include other medication in treatment regimen. Periodic blood tests will need to be performed. You may experience dizziness, confusion, or lethargy; use caution with tasks that require alertness until response to drug is known; nausea and/or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea (yogurt, boiled milk, or buttermilk may help). Report fever, gastric disturbances, or rash. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Cystagon®: 50 mg, 150 mg

Generic AvailableNo

Mechanism of ActionReacts with cystine within the lysosome to convert it to cysteine and to a cysteine-cysteamine mixed disulfide, both of which can then exit the lysosome in patients with cystinosis, an inherited defect of lysosomal transport

Pharmacodynamics/KineticsAs reported in children:

Onset: 1-1.8 hours

Duration: 6 hours

Distribution: V_d: 156 L

Protein binding: ~52%, predominantly to albumin

Time to peak, plasma: 1.4 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause confusion, nervousness, impaired cognition, and hallucinations

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropic may produce additive sedation

Index TermsCysteamine Bitartrate

References

Gahl WA, Thoene JG, and Schneider JA, “Cystinosis,” *N Engl J Med*, 2002, 347(2):111-21.[PubMed 12110740]

International Brand NamesCystagon (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Jump To Field (Select Field Name)

Pronunciation(SIS te een)
U.S. Brand NamesCysteine-500
Pharmacologic CategoryNutritional Supplement
Use: Labeled IndicationsSupplement to crystalline amino acid solutions, in particular the specialized pediatric formulas (eg, Aminosyn® PF, TrophAmine®) to meet the intravenous amino acid nutritional requirements of infants receiving parenteral nutrition (PN)
Dosing: PediatricNutritional supplement: I.V.: Neonates and Infants (receiving PN): Added as a fixed ratio to crystalline amino acid solution: 40 mg cysteine per g of amino acids; dosage will vary with the daily amino acid dosage (eg, 0.5-2.5 g/kg/day amino acids would result in 20-100 mg/kg/day cysteine). Individual doses of cysteine of 0.8-1 mmol/kg/day have also been added directly to the daily PN solution. The duration of treatment relates to the need for PN. Patients on chronic PN therapy have received cysteine until 6 months of age and in some cases until 2 years of age.
StorageAvoid excessive heat. Do not freeze. When combined with parenteral amino acid solutions, cysteine is relatively unstable. It is intended to be added immediately prior to administration to the patient. Infusion of the admixture should begin within 1 hour of mixing or refrigerated until use. Stable 24 hours in PN solution; opened vials must be used within 4 hours of entry.
ContraindicationsHypersensitivity to cysteine or any component of the formulation; patients with hepatic coma or metabolic disorders involving impaired nitrogen utilization
Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Infants: Metabolic acidosis has occurred in infants related to the “hydrochloride” component of cysteine; each 1 mmol cysteine (175 mg) delivers 1 mEq chloride and 1 mEq hydrogen ion; to balance the extra hydrochloride ions and prevent acidosis addition to the PN solution of a 1 mEq acetate electrolyte salt for each mmol (175 mg) of cysteine may be needed; each 40 mg cysteine (equal to every 1 g amino acid when used in the recommended ratio) adds 0.228 mEq chloride and hydrogen.

Adverse ReactionsFrequency not defined.

Central nervous system: Fever

Endocrine & metabolic: Metabolic acidosis

Gastrointestinal: Nausea

Renal: Azotemia, BUN increased

Monitoring ParametersBUN, ammonia, electrolytes, pH, acid-base balance, serum creatinine, liver function tests, growth curve
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Cysteine-500: 500 mg

Injection, solution, as hydrochloride: 50 mg/mL (10 mL, 50 mL)

Generic AvailableYes
Mechanism of ActionCysteine is a sulfur-containing amino acid synthesized from methionine via the transulfuration pathway. It is a precursor of the tripeptide glutathione and also of taurine. Newborn infants have a relative deficiency of the enzyme necessary to affect this conversion. Cysteine may be considered an essential amino acid in infants.
Pharmacotherapy PearlsAddition of cysteine to PN solutions enhances the solubility of calcium and phosphate by lowering the overall pH of the solution.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsCysteine Hydrochloride

Cytarabine (Liposomal)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Cytarabine may be confused with Cytadren®, Cytosar®, Cytoxan®, vidarabine

Cytarabine liposomal may be confused with conventional cytarabine

DepoCyt® may be confused with Depoject®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(sye TARE a been lip po SOE mal)

U.S. Brand NamesDepoCyt®

Canadian Brand NamesDepoCyt®

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite (Pyrimidine Antagonist)

Use: Labeled IndicationsTreatment of lymphomatous meningitis

Dosing: Adults**Note: Patients should be started on dexamethasone 4 mg twice daily (oral or I.V.) for 5 days, beginning on the day of cytarabine liposomal injection**

Lymphomatous meningitis: I.T.:

Induction: 50 mg every 14 days for a total of 2 doses (weeks 1 and 3)

Consolidation: 50 mg every 14 days for 3 doses (weeks 5, 7, and 9), followed by an additional dose at week 13

Maintenance: 50 mg every 28 days for 4 doses (weeks 17, 21, 25, and 29)

Dosing: ElderlyRefer to adult dosing.

Dosing: Adjustment for ToxicityIf drug-related neurotoxicity develops, reduce dose to 25 mg. If toxicity persists, discontinue treatment.

Administration: OtherFor intrathecal use only. Dose should be removed from vial immediately before administration (must be administered within 4 hours of removal). An in-line filter should **not** be used. Administer directly into the CSF via an intraventricular reservoir or by direct injection into the lumbar sac. Injection should be made slowly (over 1-5 minutes). Patients should lie flat for 1 hour after lumbar puncture.

StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from freezing and avoid aggressive agitation. Solutions should be used within 4 hours of withdrawal from the vial.

ReconstitutionAllow vial to warm to room temperature prior to withdrawal from vial. Particles may settle in diluent over time, and may be resuspended by gentle agitation or inversion of the vial. Further reconstitution or dilution is not required.

ContraindicationsHypersensitivity to cytarabine or any component of the formulation; active meningeal infection

Warnings/Precautions

Boxed warnings:

- Chemical arachnoiditis: See “Concerns related to adverse effects” below.

- Experienced physician: See “Other warnings/precautions” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Chemical arachnoiditis: **[U.S. Boxed Warning]: Chemical arachnoiditis (nausea, vomiting, headache, fever) occurs commonly; may be fatal if untreated. The incidence and severity of chemical arachnoiditis is reduced by coadministration with dexamethasone.** Hydrocephalus has been reported and may be precipitated by chemical arachnoiditis.

- Meningitis: Infectious meningitis may be associated with intrathecal administration.

- Neurotoxicity: May cause neurotoxicity (including myelopathy), which may lead to permanent neurologic deficit; blockage to CSF flow may increase the risk of neurotoxicity. Monitor for neurotoxicity. Reduce subsequent doses; discontinue with persistent neurotoxicity. Peripheral neurotoxicity has also been reported.

Concurrent drug therapy issues:

- Systemic chemotherapy: The risk of adverse events, including neurotoxicity, is increased with concurrent systemic chemotherapy.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Radiation therapy recipients: The risk of adverse events, including neurotoxicity, is increased in patients receiving concurrent radiation therapy.

Other warnings/precautions:

- Administration: For intrathecal use only.
- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsReproductive studies have not been conducted with cytarabine liposomal. Cytarabine, the active component, has been associated with fetal malformations when given as a component of combination chemotherapy during the first trimester. Systemic exposure following intrathecal administration of cytarabine liposomal is negligible. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should avoid becoming pregnant during treatment.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsAlthough the systemic exposure following intrathecal administration of cytarabine liposomal is negligible, breast-feeding is not recommended due to the potential for serious adverse reactions in the nursing infant.

Adverse Reactions

>10%:

Cardiovascular: Peripheral edema (11%)

Central nervous system: Chemical arachnoiditis (without dexamethasone premedication: 100%; with dexamethasone premedication: 33% to 42%; grade 4: 19% to 30%; onset: ≤5 days); headache (56%), confusion (33%), fever (32%), fatigue (25%), seizure (20% to 22%), dizziness (18%), lethargy (16%), insomnia (14%), memory impairment (14%), pain (14%)

Endocrine & metabolic: Dehydration (13%)

Gastrointestinal: Nausea (46%), vomiting (44%), constipation (25%), diarrhea (12%), appetite decreased (11%)

Genitourinary: Urinary tract infection (14%)

Hematologic: Anemia (12%), thrombocytopenia (3% to 11%)

Neuromuscular & skeletal: Weakness (40%), back pain (24%), abnormal gait (23%), limb pain (15%), neck pain (14%), arthralgia (11%), neck stiffness (11%)

Ocular: Blurred vision (11%)

1% to 10%:

Cardiovascular: Tachycardia (9%), hypotension (8%), hypertension (6%), syncope (3%), edema (2%)

Central nervous system: Agitation (10%), hypoesthesia (10%), depression (8%), anxiety (7%), sensory neuropathy (3%)

Dermatologic: Pruritus (2%)

Endocrine & metabolic: Hypokalemia (7%), hyponatremia (7%), hyperglycemia (6%)

Gastrointestinal: Abdominal pain (9%), dysphagia (8%), anorexia (5%), hemorrhoids (3%), mucosal inflammation (3%)

Genitourinary: Incontinence (7%), urinary retention (5%)

Hematologic: Neutropenia (10%), contusion (2%)

Neuromuscular & skeletal: Muscle weakness (10%), tremor (9%), peripheral neuropathy (4%), abnormal reflexes (3%)

Otic: Hypoacusis (6%)

Respiratory: Dyspnea (10%), cough (7%), pneumonia (6%)

Miscellaneous: Diaphoresis (2%)

<1%, postmarketing, and/or case reports: Anaphylaxis, bladder control impaired, blindness, bowel control impaired, cauda equine syndrome, cranial nerve palsies, CSF protein increased, CSF WBC increased, deafness, encephalopathy, hemiplegia, hydrocephalus, infectious meningitis, intracranial pressure increased, myelopathy, neurologic deficit, numbness, papilledema, somnolence, visual disturbance

Oncology: VesicantNo

Oncology: Emetic PotentialModerate (30% to 60%)

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be

increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Test InteractionsSince cytarabine liposomes are similar in appearance to WBCs, care must be taken in interpreting CSF examinations in patients receiving cytarabine liposomal.

Monitoring ParametersMonitor closely for signs of an immediate reaction; neurotoxicity

Nursing: Physical Assessment/MonitoringShould be administered under the supervision of an experienced cancer chemotherapy physician. This medication is only for intrathecal administration. Patient must be monitored continuously for adverse reactions that can be immediate (eg, neurotoxicity [eg, myelopathy, ataxia, confusion, coma] and chemical arachnoiditis [eg, neck pain, neck rigidity, headache, fever, nausea, vomiting, back pain]); potential for adverse reactions increased with concurrent radiation therapy or systemic chemotherapy. Incidence and severity of chemical arachnoiditis is reduced by coadministration with dexamethasone. Provide patient teaching according to patient condition.

Monitoring: Lab TestsSince cytarabine liposomes are similar in appearance to WBCs, care must be taken in interpreting CSF examinations in patients receiving cytarabine liposomal.

Patient EducationPatient instruction will be according to mental status. This medication can only be given by infusion into the spinal cord. You will be monitored closely during and after each infusion. Report immediately any neck pain or rigidity, headache, fever, nausea, or vomiting. Report any swelling of extremities, acute weakness, unusual gait pattern, CNS changes (confusion, speech difficulty), or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension, intrathecal [preservative free]:

Depocyt®: 10 mg/mL (5 mL)

Generic AvailableNo

Mechanism of ActionCytarabine liposomal is a sustained-release formulation of the active ingredient cytarabine, an antimetabolite which acts through inhibition of DNA synthesis and is cell cycle-specific for the S phase of cell division. Cytarabine is converted intracellularly to its active metabolite cytarabine-5'-triphosphate (ara-CTP). Ara-CTP also appears to be incorporated into DNA and RNA; however, the primary action is inhibition of DNA polymerase, resulting in decreased DNA synthesis and repair. The liposomal formulation allows for gradual release, resulting in prolonged exposure.

Pharmacodynamics/Kinetics

Absorption: Systemic exposure following intrathecal administration is negligible since transfer rate from CSF to plasma is slow

Half-life elimination, CSF: 6-82 hours

Time to peak, CSF: Intrathecal: <1 hour

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusCerebellar syndrome is common; may cause dizziness, confusion, or sedation

Mental Health: Effects on Psychiatric TreatmentMyelosuppression is common; use caution with clozapine and carbamazepine. GI side effects are common and dose related; use caution with SSRIs.

References

Cole BF, Glantz MJ, Jaeckle KA, et al, "Quality-of-Life-Adjusted Survival Comparison of Sustained-Release Cytosine Arabinoside Versus Intrathecal Methotrexate for Treatment of Solid Tumor Neoplastic Meningitis," *Cancer*, 2003, 97(12):3053-60.[PubMed 12784341]

Glantz MJ, LaFollette S, Jaeckle KA, et al, "Randomized Trial of a Slow-Release Versus a Standard Formulation of Cytarabine for the Intrathecal Treatment of Lymphomatous Meningitis," *J Clin Oncol*, 1999, 17(10):3110-6.[PubMed 10506606]

Jabbour E, O'Brien S, Kantarjian H, et al, "Neurologic Complications Associated With Intrathecal Liposomal Cytarabine in Combination With High-Dose Methotrexate and Cytarabine to Patients With Acute Lymphocytic Leukemia," *Blood*, 2007, 109(8):3214-8.[PubMed 17209054]

International Brand NamesDepoCyt (CA)

Cytarabine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Cytarabine may be confused with Cytadren®, Cytosar®, Cytoxan®, vidarabine

Cytarabine (conventional) may be confused with cytarabine liposomal

Cytosar-U may be confused with cytarabine, Cytovene®, Cytoxan®, Neosar®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(sye TARE a been)

Canadian Brand NamesCytosar®

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite; Antineoplastic Agent, Antimetabolite (Pyrimidine Analog)

Use: Labeled IndicationsTreatment of acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myelocytic leukemia (CML; blast phase), and lymphomas; prophylaxis and treatment of meningeal leukemia

Dosing: AdultsI.V.: Refer to individual protocols.

Remission induction:

I.V.: 100-200 mg/m^2/day for 5-10 days; a second course, beginning 2-4 weeks after the initial therapy, may be required in some patients.

or 100 mg/m^2/day for 7 days

or 100 mg/m^2/dose every 12 hours for 7 days

I.T.: 5-75 mg/m^2 every 2-7 days until CNS findings normalize

Remission maintenance:

I.V.: 70-200 mg/m^2/day for 2-5 days at monthly intervals

I.M., SubQ: 1-1.5 mg/kg single dose for maintenance at 1- to 4-week intervals

High-dose therapies for leukemia/lymphoma (unlabeled use):

Doses as high as 1-3 g/m^2 have been used for refractory or secondary leukemias or refractory non-Hodgkin's lymphoma.

Doses of 1-3 g/m^2 every 12 hours for up to 12 doses have been used

Bone marrow transplant (unlabeled use): 1.5 g/m^2 continuous infusion over 48 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols.

Remission induction:

I.V.: 75-200 mg/m^2/day for 5- to 10-day therapy course or every day until remission

I.T.: Usual dose 30 mg/m^2/dose every 4 days; range: 5-75 mg/m^2 every 2-7 days until CNS findings normalize **or** age-based dosing (frequency of administration usually defined by protocol):

<1 year of age: 15-20 mg per dose

1-2 years of age: 16-30 mg per dose

2-3 years of age: 20-50 mg per dose

>3 years of age: 24-75 mg per dose

Remission maintenance: Refer to adult dosing.

Dosing: Renal ImpairmentThe FDA-approved labeling does not contain renal dosing adjustment guidelines; the following guidelines have been used by some clinicians:

Aronoff, 2007 (cytarabine 100-200 mg/m^2): Children and Adults: No adjustment necessary

Kintzel, 1995 (high-dose cytarabine 1-3 g/m^2):

- Cl_{cr} 46-60 mL/minute: Administer 60% of dose
- Cl_{cr} 31-45 mL/minute: Administer 50% of dose
- Cl_{cr} <30 mL/minute: Consider use of alternative drug

Smith, 1997 (high-dose cytarabine ≥2 g/m^2/dose):

- Serum creatinine 1.5-1.9 mg/dL or increase (from baseline) of 0.5-1.2 mg/dL: Reduce dose to 1 g/m^2/dose
- Serum creatinine ≥2 mg/dL or increase (from baseline) of >1.2 mg/dL: Reduce dose to 0.1 g/m^2/day as a continuous infusion

Dosing: Hepatic ImpairmentDose may need to be adjusted in patients with liver failure since cytarabine is partially detoxified in the liver. The FDA-approved labeling does not contain hepatic dosing adjustment guidelines; the following guideline has been used by some clinicians:

Floyd, 2006: AST/ALT (any elevation): Administer 50% of dose; may increase subsequent doses in the absence of toxicities

Koren, 1992 (dose level not specified): Bilirubin >2 mg/dL: Administer 50% of dose; may increase subsequent doses in the absence of toxicities

Dosing: Combination Regimens

Brain tumors: 8 in 1 (Brain Tumors)

Leukemia, acute lymphocytic:

- FIS-HAM
- Hyper-CVAD + Imatinib
- Hyper-CVAD (Leukemia, Acute Lymphocytic)
- Linker Protocol
- PVA (POG 8602)

Leukemia, acute myeloid:

- 5 + 2
- 7 + 3 (Daunorubicin)
- 7 + 3 (Idarubicin)
- 7 + 3 (Mitoxantrone)
- 7 + 3 + 7
- CA
- DA
- DAT
- DAV
- EMA 86
- FIS-HAM
- FLAG
- FLAG-IDA
- Idarubicin, Cytarabine, Etoposide (ICE Protocol)
- Idarubicin, Cytarabine, Etoposide (IDA-Based BF12)
- TAD
- V-TAD

Lymphoma, Hodgkin's disease: mini-BEAM

Lymphoma, non-Hodgkin's:

- CODOX-M/IVAC

COMLA

DHAP

ESHAP

Hyper-CVAD (Lymphoma, non-Hodgkin's)

Pro-MACE-CytaBOM

Lymphoma, non-Hodgkin's (Burkitt's): CODOX-M/IVAC

Lymphoma, non-Hodgkin's (Mantle cell): Hyper-CVAD + Rituximab

Neuroblastoma: N4SE Protocol

Retinoblastoma: 8 in 1 (Retinoblastoma)

Oncology: Bone Marrow - High DoseI.V.: 2-3 g/m^2/dose every 12-24 hours for 4-12 doses; duration of infusion is 1-3 hours; maximum single-agent dose: 36 g/m^2; generally combined with other high-dose chemotherapeutic drugs or total body irradiation (TBI).

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.I.V. infusion over 1-3 hours or as a continuous infusion. GI effects may be more pronounced with divided I.V. bolus doses than with continuous infusion.

Administration: I.V. DetailpH: 7.4-7.7

BMT only: Risk of cerebellar toxicity increases with creatinine clearance <60 mL/minute, age older than 50 years, pre-existing CNS lesion, and alkaline phosphatase levels exceeding 3 times the upper limit of normal. Conjunctivitis is prevented and treated with saline or corticosteroid eye drops. As prophylaxis, eye drops should be started 6-12 hours before initiation of cytarabine and continued 24 hours following the last dose.

Administration: OtherMay be administered I.M., I.T., or SubQ at a concentration not to exceed 100 mg/mL.

Storage

Powder for reconstitution: Store intact vials of powder at room temperature 15°C to 30°C (59°F to 86°F). Reconstituted solutions are stable for up to 8 days at room temperature, although the manufacturer recommends use within 48 hours.

Solution: Prior to dilution, store at room temperature, 15°C to 30°C (59°F to 86°F); protect from light. Do not refrigerate solution; precipitate may form.

ReconstitutionReconstitute powder with bacteriostatic water for injection, bacteriostatic 0.9% NaCl.

For I.T. use: Reconstitute with preservative free diluent.

For I.V. infusion: Dilute in 250-1000 mL 0.9% NaCl or D_5W.

Note: Solutions containing bacteriostatic agents should not be used for the preparation of either high doses or intrathecal doses of cytarabine; may be used for I.M., SubQ, and low-dose (100-200 mg/m^2) I.V. solution.

CompatibilityStable in D_5LR, $D_5{}^1/_4NS$, D_5NS, $D_{10}NS$, D_5W, LR, NS.

Y-site administration: Compatible: Amifostine, amsacrine, aztreonam, cefepime, chlorpromazine, cimetidine, cladribine, dexamethasone sodium phosphate, diphenhydramine, doxorubicin liposome, droperidol, etoposide phosphate, famotidine, filgrastim, fludarabine, furosemide, gatifloxacin, gemcitabine, gentamicin, granisetron, heparin, hydrocortisone sodium succinate, hydromorphone, idarubicin, linezolid, lorazepam, melphalan, methotrexate, methylprednisolone sodium succinate, metoclopramide, morphine, ondansetron, paclitaxel, piperacillin/tazobactam, prochlorperazine edisylate, promethazine, propofol, ranitidine, sargramostim, sodium bicarbonate, teniposide, thiotepa, vinorelbine. **Incompatible:** Allopurinol, amphotericin B cholesteryl sulfate complex, ganciclovir.

Compatibility in syringe: Compatible: Metoclopramide.

Compatibility when admixed: Compatible: Corticotropin, dacarbazine, daunorubicin with etoposide, etoposide, hydroxyzine, lincomycin, methotrexate, mitoxantrone, ondansetron, potassium chloride, sodium bicarbonate, vincristine. **Incompatible:** Fluorouracil, heparin, insulin (regular), nafcillin, oxacillin, penicillin G sodium. **Variable (consult detailed reference):** Gentamicin, hydrocortisone sodium succinate, methylprednisolone sodium succinate.

ContraindicationsHypersensitivity to cytarabine or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.
- Myelosuppression: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Cytarabine syndrome: Characterized by fever, myalgia, bone pain, chest pain, maculopapular rash, conjunctivitis, and malaise, cytarabine syndrome may occur 6-12 hours following administration; may be managed with corticosteroids.

- Myelosuppression: **[U.S. Boxed Warning]: Potent myelosuppressive agent;** use with caution in patients with prior bone marrow suppression; monitor for signs of febrile neutropenia.

- Pancreatitis: There have been reports of acute pancreatitis in patients receiving continuous infusion and in patients previously treated with L-asparaginase.

- Tumor lysis syndrome: With high dose therapy, tumor lysis syndrome and subsequent hyperuricemia may occur; consider allopurinol and hydrate accordingly.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; may be at higher risk for CNS toxicities and dosage adjustments may be required.

- Renal impairment: Use with caution in patients with impaired renal function (high dose cytarabine); may be at higher risk for CNS toxicities and dosage adjustments may be required.

Concurrent drug therapy issues:

- Cylcophosphamide: There have been case reports of fatal cardiomyopathy when high-dose cytarabine was used in combination with cyclophosphamide as a preparation regimen for transplantation.

Dosage form specific issues:

- Benzyl alcohol: Some products may contain benzyl alcohol; do not use products containing benzyl alcohol or products reconstituted with bacteriostatic diluent intrathecally or for high-dose cytarabine regimens.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

- High dose treatment: High dose regimens have been associated with GI, CNS, pulmonary, ocular (prophylaxis with ophthalmic corticosteroids is recommended) toxicities, and cardiomyopathy. Neurotoxicity associated with high-dose treatment may present as acute cerebellar toxicity or may be severe with seizure and/or coma; may be delayed, occurring up to 3-8 days after treatment has begun; possibly irreversible. Risk factors for neurotoxicity include cumulative cytarabine dose, prior CNS disease and renal impairment (incidence may be up to 55% in patients with renal impairment).

Pregnancy Risk FactorD

Pregnancy ConsiderationsCytarabine is teratogenic in animal studies. Limb and ear defects have been noted in case reports when cytarabine has been used during pregnancy. The following have also been noted in the neonate: Pancytopenia, WBC depression, electrolyte abnormalities, prematurity, low birth weight, decreased hematocrit or platelets. Risk to the fetus is decreased if therapy is avoided during the 1st trimester; however, women of childbearing potential should be advised of the potential risks.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions**Note:** Frequency not defined.

Frequent:

Central nervous system: Fever

Dermatologic: Rash

Gastrointestinal: Anal inflammation, anal ulceration, anorexia, diarrhea, mucositis, nausea, vomiting

Hematologic: Myelosuppression, neutropenia (onset: 1-7 days; nadir [biphasic]: 7-9 days and at 15-24 days; recovery [biphasic]: 9-12 and at 24-34 days), thrombocytopenia (onset: 5 days; nadir: 12-15 days; recovery 15-25 days), anemia, bleeding, leukopenia, megaloblastosis, reticulocytes decreased

Hepatic: Hepatic dysfunction, transaminases increased (acute)

Local: Thrombophlebitis

Less frequent:

Cardiovascular: Chest pain, pericarditis

Central nervous system: Dizziness, headache, neural toxicity, neuritis

Dermatologic: Alopecia, pruritus, skin freckling, skin ulceration, urticaria

Gastrointestinal: Abdominal pain, bowel necrosis, esophageal ulceration, esophagitis, pancreatitis, sore throat

Genitourinary: Urinary retention

Hepatic: Jaundice

Local: Injection site cellulitis

Ocular: Conjunctivitis

Renal: Renal dysfunction

Respiratory: Dyspnea

Miscellaneous: Allergic edema, anaphylaxis, sepsis

Infrequent and/or case reports: Amylase increased, aseptic meningitis, cardiopulmonary arrest (acute), cerebral dysfunction, cytarabine syndrome (bone pain, chest pain, conjunctivitis, fever, maculopapular rash, malaise, myalgia); exanthematous pustulosis, hyperuricemia, injection site inflammation (SubQ injection), injection site pain (SubQ injection), interstitial pneumonitis, lipase increased, paralysis (intrathecal and I.V. combination therapy), rhabdomyolysis, veno-occlusive liver disease

Adverse events associated with high-dose cytarabine (CNS, gastrointestinal, ocular, and pulmonary toxicities are more common with high-dose regimens):

Cardiovascular: Cardiomegaly, cardiomyopathy (in combination with cyclophosphamide)

Central nervous system: Coma, neurotoxicity (dose-related, cerebellar toxicity may occur in patients receiving high-dose cytarabine [>36-48 g/m^2/cycle]; incidence may up to 55% in patients with renal impairment), personality change, somnolence

Dermatologic: Alopecia (complete), desquamation, rash (severe)

Gastrointestinal: Gastrointestinal ulcer, peritonitis, pneumatosis cystoides intestinalis

Hepatic: Hyperbilirubinemia, liver abscess, liver damage, necrotizing colitis

Neuromuscular & skeletal: Peripheral neuropathy (motor and sensory)

Ocular: Corneal toxicity, hemorrhagic conjunctivitis

Respiratory: Pulmonary edema, syndrome of sudden respiratory distress

Miscellaneous: Sepsis

Adverse events associated with intrathecal cytarabine administration:

Central nervous system: Accessory nerve paralysis, fever, necrotizing leukoencephalopathy (with concurrent cranial irradiation, I.T. methotrexate, and I.T. hydrocortisone), neurotoxicity, paraplegia

Gastrointestinal: Dysphagia, nausea, vomiting

Ocular: Blindness (with concurrent systemic chemotherapy and cranial irradiation), diplopia

Respiratory: Cough, hoarseness

Miscellaneous: Aphonia

Oncology: VesicantNo

Oncology: Emetic Potential

Low dose (<200 mg/m^2): Low (10% to 30%)

High dose (>1 g/m^2): Moderate-to-high (30% to 90%)

Oncology: Bone Marrow - Unique Toxicity

Central nervous system: Cerebellar toxicity which includes nystagmus, dysarthria, disdiadochokinesis, slurred speech; cerebral toxicity which includes somnolence, confusion

Dermatologic: Rash, desquamation may occur

Gastrointestinal: Severe nausea and vomiting, mucositis, diarrhea, ageusia

Ocular: Photophobia, excessive tearing, blurred vision, local discomfort, chemical conjunctivitis, optic neuropathy, visual loss

Respiratory: Noncardiogenic pulmonary edema (onset 22-27 days following completion of therapy)

Miscellaneous: Anosmia

Drug Interactions

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Flucytosine: Cytarabine may diminish the therapeutic effect of Flucytosine. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersLiver function tests, CBC with differential and platelet count, serum creatinine, BUN, serum uric acid

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions (eg, additive myelosuppression, increased risk of cardiomyopathy, pancreatitis). See Administration for I.V. specifics. Premedicate with antiemetic, especially with larger doses. Ocular pain and conjunctivitis reactions may be reduced with premedication. Patient should be monitored closely for anaphylaxis, sudden onset respiratory distress (especially with high doses). Assess results of laboratory tests (BUN, urinalysis, and serum creatinine [hepatic function]; CBC and platelet count [myelosuppression]) prior to therapy and on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions (eg, importance of adequate hydration) and adverse symptoms to report.

Monitoring: Lab TestsLiver function, CBC with differential and platelet count, serum creatinine, BUN, serum uric acid

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug is administered by infusion. You will be monitored closely during infusion. Report immediately any redness, swelling, burning, or pain at injection/infusion site; sudden difficulty breathing or swallowing, chest pain, or chills. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea, vomiting or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help - if ineffective, consult prescriber for antiemetic medication); diarrhea (buttermilk, boiled milk, or yogurt may help - if persistent, consult with prescriber); mouth sores (use soft toothbrush or cotton swabs for oral care); or dizziness, headache, or confusion (use caution when driving or engaging in potentially hazardous tasks until response to drug is known). Report immediately any signs of CNS changes, change in gait, respiratory distress or respiratory difficulty, easy bruising or bleeding, persistent GI upset, yellowing of eyes or skin, change in color of urine or blackened stool, or any other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 100 mg, 500 mg, 1 g, 2 g

Injection, solution: 20 mg/mL (5 mL, 25 mL, 50 mL); 100 mg/mL (20 mL)

Generic AvailableYes

Mechanism of ActionInhibits DNA synthesis. Cytosine gains entry into cells by a carrier process, and then must be converted to its active compound, aracytidine triphosphate. Cytosine is a pyrimidine analog and is incorporated into DNA; however, the primary action is inhibition of DNA polymerase resulting in decreased DNA synthesis and repair. The degree of cytotoxicity correlates linearly with incorporation into DNA; therefore, incorporation into the DNA is responsible for drug activity and toxicity. Cytarabine is specific for the S phase of the cell cycle (blocks progression from the G_1 to the S phase).

Pharmacodynamics/Kinetics

Distribution: V_d: Total body water; widely and rapidly since it enters the cells readily; crosses blood-brain barrier with CSF levels of 40% to 50% of plasma level

Metabolism: Primarily hepatic; metabolized by deoxycytidine kinase and other nucleotide kinases to aracytidine triphosphate (active); about 86% to 96% of dose is metabolized to inactive uracil arabinoside (ARA-U); intrathecal administration results in little conversion to ARA-U due to the low levels of deaminase in the cerebral spinal fluid

Half-life elimination: I.V.: Initial: 7-20 minutes; Terminal: 1-3 hours

Time to peak, plasma: I.M., SubQ: 20-60 minutes

Excretion: Urine (~80%; 90% as metabolite ARA-U) within 24 hours

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsI.V. doses ≥1.5 g/m^2 may produce conjunctivitis which can be ameliorated with prophylactic use of corticosteroid (0.1% dexamethasone) eye drops. Dexamethasone eye drops should be administered at 1-2 drops every 6 hours during and for 2-7 days after cytarabine is done.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation or confusion

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine

Oncology: Bone Marrow CommentsRisk of cerebellar toxicity increases with creatinine clearance <60 mL/minute, age older than 50 years, pre-existing CNS lesion, and alkaline phosphatase levels exceeding 3 times the upper limit of normal. Conjunctivitis is prevented and treated with saline or corticosteroid eye drops. As prophylaxis, eye drops should be started 6-12 hours before initiation of cytarabine and continued 24 hours following the last dose.

Index TermsAra-C; Arabinosylcytosine; Cytarabine (Conventional); Cytarabine Hydrochloride; Cytosar-U; Cytosine Arabinosine Hydrochloride; NSC-63878

References

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International Brand NamesAlcysten (PL); Alexan (AT, BE, BG, BR, CH, CN, CZ, DK, EC, GB, HK, HN, HR, HU, IE, IT, MY, PL, PT, RU, SE, TR, ZA); Ara-C (AR); Arabine (DK, FI, FR); Arabitin (JP); Aracytin (CO, GR, IT, UY); Aracytine (FR); Citafam (AR); Citagenin (PE); Citarabina (ES); Cyclocide (TW); Cylocide (JP); Cytarabin (DE, NO, PL); Cytarabine (AU, PL); Cytarabine Injection (AU, GB); Cytarabinum-Delta West (LU); Cytarine (IN, PH, TH); Cytonal (RU, TR); Cytosa U (KP); Cytosar (AE, AT, BE, BG, BH, CH, CL, CY, CZ, EE, EG, FI, GB, GH, HK, HN, HR, HU, IL, IQ, IR, JO, KE, KW, LB, LY, NL, OM, PH, PK, PL, PT, QA, SA, SY, TZ, UG, YE, ZA, ZM); Cytosar-U (ID, KP, MY, TH, TW, VE); Cytox (PH); Laracit (MX); Medsara (MX); Starasid (JP)

Cytomegalovirus Immune Globulin (Intravenous-Human)

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English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

CytoGam® may be confused with Cytoxan®, Gamimune® N

Pronunciation(sye toe meg a low VYE rus i MYUN GLOB yoo lin in tra VEE nus HYU man)
U.S. Brand NamesCytoGam®
Canadian Brand NamesCytoGam®
Pharmacologic CategoryImmune Globulin
Use: Labeled IndicationsProphylaxis of cytomegalovirus (CMV) disease associated with kidney, lung, liver, pancreas, and heart transplants; concomitant use with ganciclovir should be considered in organ transplants (other than kidney) from CMV seropositive donors to CMV seronegative recipients
Use: Unlabeled/InvestigationalAdjunct therapy in the treatment of CMV disease in immunocompromised patients
Dosing: Adults

Kidney transplant: I.V.:

Initial dose (within 72 hours of transplant): 150 mg/kg/dose

2, 4, 6, and 8 weeks after transplant: 100 mg/kg/dose

12 and 16 weeks after transplant: 50 mg/kg/dose

Liver, lung, pancreas, or heart transplant: I.V.:

Initial dose (within 72 hours of transplant): 150 mg/kg/dose

2, 4, 6, and 8 weeks after transplant: 150 mg/kg/dose

12 and 16 weeks after transplant: 100 mg/kg/dose

Severe CMV pneumonia: I.V.: Various regimens have been used, including 400 mg/kg CMV-IGIV in combination with ganciclovir on days 1, 2, 7, or 8, followed by 200 mg/kg CMV-IGIV on days 14 and 21

Dosing: ElderlyUse with caution in patients >65 years of age; elderly may be at increased risk of renal insufficiency.
Dosing: Renal ImpairmentUse with caution; specific dosing adjustments are not available. Infusion rate should be the minimum practical; do not exceed 180 mg/kg/hour.
Administration: I.V.For I.V. use only. Administer as separate infusion. Infuse beginning at 15 mg/kg/hour, then increase to 30 mg/kg/hour after 30 minutes if no untoward reactions. May titrate up to 60 mg/kg/hour. Do not administer faster than 75 mL/hour. Begin infusion within 6 hours of entering vial, complete infusion within 12 hours.
Administration: I.V. DetailAdminister through an I.V. line containing an in-line filter (pore size 15 micron) using an infusion pump. Do not mix with other infusions; do not use if turbid. Begin infusion within 6 hours of entering vial, complete infusion within 12 hours.

Infuse at 15 mg/kg/hour. If no adverse reactions occur within 30 minutes, may increase rate to 30 mg/kg/hour. If no adverse reactions occur within the second 30 minutes, may increase rate to 60 mg/kg/hour; maximum rate of infusion: 75 mL/hour. When infusing subsequent doses, may decrease titration interval from 30 minutes to 15 minutes. If patient develops nausea, back pain, or flushing during infusion, slow the rate or temporarily stop the infusion. Discontinue if blood pressure drops or in case of anaphylactic reaction.

Dietary Considerations

CytoGam® solution for injection 50 mg (± 10 mg/mL) contains sodium 20-30 mEq/L

StorageStore between 2°C and 8°C (35.6°F and 46.4°F). Use reconstituted product within 6 hours.
ReconstitutionDo not admix with other medications; do not use if turbid. Do not shake vials. Dilution is not recommended.
CompatibilityInfusion with other products is not recommended. If unavoidable, may be piggybacked into an I.V. line of sodium chloride, 2.5% dextrose in water, 5% dextrose in water, 10% dextrose in water, or 20% dextrose in water. Do not dilute more than 1:2. Do not admix with other medications.
ContraindicationsHypersensitivity to CMV-IGIV, other immunoglobulins, or any component of the formulation; immunoglobulin A deficiency
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1:1000) should be available.

- Aseptic meningitis: Aseptic meningitis syndrome (AMS) has been reported with intravenous immune globulin administration (rare); may occur with high doses (≥2 g/kg).

- Hemolysis: Intravenous immune globulin has been associated with antiglobulin hemolysis; monitor for signs of hemolytic anemia.

- Pulmonary edema: Monitor for transfusion-related acute lung injury (TRALI); noncardiogenic pulmonary edema has been reported with intravenous immune globulin use.

- Renal impairment: Acute renal dysfunction (increased serum creatinine, oliguria, acute renal failure) can rarely occur; usually within 7 days of use (more likely with products stabilized with sucrose). Use with caution in the elderly, patients with renal disease, diabetes mellitus, volume depletion, sepsis, paraproteinemia, and nephrotoxic medications due to risk of renal dysfunction. In patients at risk of renal dysfunction, the rate of infusion and concentration of solution should be minimized. discontinue if renal function deteriorates.

- Thrombotic events: Thrombotic events have been reported with administration of intravenous immune globulin; use with caution in patients with cardiovascular risk factors.

Disease-related concerns:

- Hypovolemia: Patients should not be volume depleted prior to therapy.

Special populations:

- Elderly: Use with caution in patients >65 years of age.

Dosage form specific issues:

- Albumin: Product is stabilized with albumin.

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

- Sucrose: Product is stabilized with sucrose.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
LactationExcretion in breast milk unknown
Adverse Reactions

<6%:

Cardiovascular: Flushing

Central nervous system: Chills, fever

Gastrointestinal: Nausea, vomiting

Neuromuscular & skeletal: Arthralgia, back pain, muscle cramps

Respiratory: Wheezing

<1%: Blood pressure decreased

Postmarketing and/or case reports: Acute renal failure, acute tubular necrosis, anaphylactic shock, angioneurotic edema, anuria, aseptic meningitis syndrome (AMS), BUN increased, oliguria, osmotic nephrosis, proximal tubular nephropathy, serum creatinine increased

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

Vaccines (Live): Immune Globulins may diminish the therapeutic effect of Vaccines (Live). **Exceptions:** Influenza Virus Vaccine; Yellow Fever Vaccine. *Risk D: Consider therapy modification*

Monitoring ParametersVital signs (throughout infusion), flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, wheezing, decreased blood pressure, or anaphylaxis; renal function and urine output
Nursing: Physical Assessment/MonitoringAssess for history of previous allergic reactions. Monitor vital signs during infusion and observe for adverse or allergic reactions. Teach patient adverse symptoms to report.
Patient EducationThis medication can only be administered by infusion. You will be monitored closely during the infusion. If you experience nausea, ask for assistance; do not get up alone. Do not have any vaccinations for the next 3 months without consulting prescriber. Immediately report chills, muscle cramping, low back pain, chest pain or tightness, or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

CytoGam®: 50 mg ± 10 mg/mL (50 mL) [contains sodium 20-30 mEq/L, human albumin, and sucrose]

Generic AvailableNo
ManufacturerMassachusetts Public Health Biologic Laboratories/MedImmune, Inc
Mechanism of ActionCMV-IGIV is a preparation of immunoglobulin G derived from pooled healthy blood donors with a high titer of CMV

antibodies; administration provides a passive source of antibodies against cytomegalovirus

Related Information

- Immunization Recommendations

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCMV-IGIV

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International Brand NamesCytotect (PL); Megalotect (IL, TH)

CYVADIC

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Sarcoma]

Regimen UseSarcoma

Regimen

Cyclophosphamide: I.V.: 500 mg/m^2 day 1

[total dose/cycle = 500 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day days 1 and 5

[total dose/cycle = 2.8 mg/m^2]

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Dacarbazine: I.V.: 250 mg/m^2/day days 1 to 5

[total dose/cycle = 1250 mg/m^2]

Repeat cycle every 21 days

References

Pinedo HM, Bramwell VH, Mouridsen HT, et al, âCyvadic in Advanced Soft Tissue Sarcoma: A Randomized Study Comparing Two Schedules. A Study of the EORTC Soft Tissue and Bone Sarcoma Group,â *Cancer*, 1984, 53(9):1825-32.

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Leukemia, Acute Myeloid](#)

Regimen UseLeukemia, acute myeloid (induction)

RegimenInduction:

Daunorubicin: I.V.: 45 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 135 mg/m^2]

Cytarabine: I.V.: 100 mg/m^2/day continuous infusion days 1 to 7

[total dose/cycle = 700 mg/m^2]

References

Rai KR, Holland JF, Glidewell OJ, et al, "Treatment of Acute Myelocytic Leukemia: A Study by Cancer and Leukemia Group B," *Blood*, 1981, 58(6):1203-12.[PubMed 6946847]

Yates J, Glidewell O, Wiernik P, et al, "Cytosine Arabinoside With Daunorubicin or Adriamycin for Therapy of Acute Myelocytic Leukemia: A CALGB Study," *Blood*, 1982, 60(2):454-62.[PubMed 6953986]

Dabigatran Etexilate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(da BIG a tran ett EX ill ate)

Canadian Brand NamesPradax™

Pharmacologic CategoryAnticoagulant, Thrombin Inhibitor

Use: Labeled IndicationsPostoperative thromboprophylaxis in patients who have undergone total hip or knee replacement procedures

Use: Unlabeled/Investigational**Investigational:** Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation

Dosing: Adults**Note:** Therapy should not be initiated until hemostasis has been established. When transitioning from intravenous anticoagulation therapy, initiate oral dabigatran therapy no sooner than time of next regularly scheduled dose of I.V. anticoagulant. When transitioning from dabigatran to I.V. anticoagulation therapy, allow 24 hours after the last dabigatran dose before initiating I.V. anticoagulation therapy.

Postoperative thromboprophylaxis: Oral:

Knee replacement: Initial: 110 mg given 1-4 hours after completion of surgery and establishment of hemostasis **OR** 220 mg as one dose in postoperative patients in whom therapy is not initiated on day of surgery regardless of reason; maintenance: 220 mg once daily (total duration of therapy: 10 days)

Hip replacement: Initial: 110 mg given 1-4 hours after completion of surgery and establishment of hemostasis **OR** 220 mg as one dose in postoperative patients in whom therapy is not initiated on day of surgery regardless of reason; maintenance: 220 mg once daily (total duration of therapy: 28-35 days)

Dosing: Elderly**Postoperative thromboprophylaxis:** Patients >75 years: Oral: Refer to adult dosing. Dosage reduction to 150 mg/day is suggested by the manufacturer. **Note:** Therapy should not be initiated until hemostasis has been established.

Dosing: Renal Impairment

Moderate renal impairment (Cl_{cr} 30-50 mL/minute): Initial: 75 mg given 1-4 hours after completion of surgery and establishment of hemostasis; maintenance: 150 mg/day.

Severe renal impairment (Cl_{cr} < 30 mL/minute): Use is contraindicated.

Dosing: Hepatic Impairment

Mild hepatic impairment: Manufacturer provides no specific recommendations.

Moderate-to-severe hepatic impairment: Use not recommended.

Administration: OralAdminister with water. May be taken without regard to meals.

Dietary ConsiderationsMay be taken without regard to meals.

Storage

Blister: Store between 15°C to 25°C (59°F to 77°F). Protect from moisture.

Bottle: Store between 15°C to 30°C (59°F to 86°F). Protect from moisture; discard 30 days after opening container.

RestrictionsNot available in the U.S.

ContraindicationsHypersensitivity to dabigatran or any component of the formulation; severe renal impairment (Cl_{cr} <30 mL/minute); hemorrhagic manifestations, bleeding diathesis, or patients with spontaneous or pharmacological hemostatic impairment; lesions at risk of clinically significant bleeding (eg, hemorrhagic or ischemic cerebral infarction) within previous 6 months; concomitant therapy with strong P-glycoprotein (Pgp) inhibitors such as quinidine

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: The most common complication is bleeding. Certain patients are at increased risk of bleeding; risk factors include bacterial endocarditis, congenital or acquired bleeding disorders, thrombocytopenia, recent puncture of large vessels or organ biopsy, stroke, intracerebral surgery, or other neuraxial procedure, severe uncontrolled hypertension, renal impairment, recent major surgery, recent major bleeding (intracranial, GI, intraocular, or pulmonary). Monitor for signs and symptoms of bleeding. Avoid use in patients undergoing anesthesia with postoperative indwelling epidural catheters. Hematomas (spinal or epidural) resulting in extended or permanent paralysis may occur. Prior to perispinal procedures, initiate dabigatran therapy only after establishing hemostasis and no sooner than 2 hours after catheter puncture or removal.

Disease-related concerns:

- Hepatic impairment: Use in patients with moderate or severe hepatic impairment (Child-Pugh class B or C) or with elevated hepatic transaminases >2 times the upper limit of normal (ULN) has not been studied. Avoid use in these patients.

- Renal impairment: Use is contraindicated in severe renal impairment (Cl_{cr} <30 mL/minute). Dose reductions are required in patients with moderate impairment (Cl_{cr} 30-50 mL/minute. Discontinue therapy in patients who develop acute renal failure. Evaluate renal function prior to and during therapy.

Concurrent drug therapy issues:

- Anticoagulants: Due to an increased risk of bleeding, avoid use with other direct thrombin inhibitors (eg, bivalirudin), unfractionated heparin or heparin derivatives, low molecular weight heparins (eg, enoxaparin), thienopyridines (eg, clopidogrel, ticlodipine), GPIIb/IIIa antagonists (eg, eptifibatide), aspirin, coumarin derivatives, and sulfinpyrazone. NSAIDs should be used cautiously. Appropriate doses of unfractionated heparin may be used to maintain catheter patency.

Special populations:

- Elderly: Use with caution in patients >75 years of age; dose reductions may be indicated.

- Patients <50 kg: Use with caution in this patient population. Dabigatran exposure is ~25% higher in patients with a body weight of ~48 kg.

- Pediatrics: Safety and efficacy have not been established in patients <18 years of age.

Pregnancy Considerations

Adverse events were observed in some animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Dabigatran etexilate should be used in pregnant women only if clinical benefit outweighs risks of therapy.

Lactation

Excretion in breast milk unknown/not recommended

Adverse Reactions

>10%: Hematologic: Bleeding (8% to 14%; major: ≤2%)

1% to 10%:

Gastrointestinal: GI hemorrhage (≤1%)

Hematologic: Anemia (1% to 4%), hematoma (1% to 2%), hemoglobin decreased (1% to 2%), hemorrhage (postprocedural or wound: 1% to 2%)

Hepatic: ALT increased (≥3 x ULN: 2% to 3%)

Renal: Hematuria (1%)

Miscellaneous: Wound secretion (5%), postprocedural discharge (1%)

<1%, postmarketing, and/or case reports: AST increased, bloody discharge, ecchymosis, epistaxis, hemarthrosis, hematocrit decreased; hemorrhage (catheter site, hemorrhoidal, incision site, rectal); hepatic function abnormal, occult blood positive, thrombocytopenia

Drug Interactions

Amiodarone: May increase the serum concentration of Dabigatran Etexilate. *Risk D: Consider therapy modification*

Antacids: May decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Atorvastatin: May decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Proton Pump Inhibitors: May decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

QuiNIDine: May increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Food has no affect on the bioavailability of dabigatran, but delays the time to peak plasma concentrations by 2 hours.

Herb/Nutraceutical: St John's wort may decrease levels/effects of dabigatran (concomitant use is not recommended). Concomitant use of dabigatran with herbs possessing anticoagulant/antiplatelet properties may increase the risk for bleeding.

Monitoring ParametersActivated partial thromboplastin time (aPTT) (values >2.5 x control may indicate overanticoagulation), ecarin clotting test (ECT) if available, thrombin time (TT), CBC with differential, renal function

Nursing: Physical Assessment/MonitoringUse caution with any condition that increases risk of bleeding. Assess other pharmacological or herbal products patient may be taking for potential interactions or toxicity (especially any agents that may affect coagulation). Assess results of laboratory tests, patient response, and adverse reactions (bleeding) on a regular basis throughout therapy. Teach patient proper use, possible side effects/appropriate interventions (bleeding precautions), and adverse symptoms to report.

Monitoring: Lab TestsActivated partial thromboplastin time (aPTT) (values >2.5 x control may indicate overanticoagulation), ecarin clotting test (ECT) if available, thrombin time (TT), CBC with differential, renal function

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber (including aspirin or other pain medications). Consult prescriber for appropriate pain medication if in pain. Take as directed; do not skip dose or take more than instructed. May be swallowed with water. Store medication as directed; protect from moisture. You may have a tendency to bleed easily while taking this medication (brush teeth with soft brush, use waxed dental floss, use electric razor, avoid scissors or sharp knives, avoid potentially harmful activities). Report any signs of unusual bleeding or bruising (bleeding gums, nosebleed, blood in urine, dark stool, bruises) or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or if you are breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Capsule:

Pradax™ [CAN]: 75 mg, 110 mg [not available in the U.S.]

ManufacturerBoehringer Ingelheim Canada Ltd

Mechanism of ActionProdrug lacking anticoagulant activity that is converted *in vivo* to the active dabigatran, a specific, reversible, direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin. Inhibits coagulation by preventing thrombin-mediated effects, including cleavage of fibrinogen to fibrin monomers, activation of factors V, VIII, XI and XIII, and inhibition of thrombin-induced platelet aggregation.

Pharmacodynamics/Kinetics

Absorption: Rapid; initially slow postoperatively

Distribution: V_d: 60-70 L

Protein binding: 34% to 35% (concentration independent)

Metabolism: Hepatic; dabigatran etexilate is rapidly and completely hydrolyzed to dabigatran (active form) by plasma and hepatic esterases; dabigatran undergoes hepatic glucuronidation to active acylglucuronide isomers

Bioavailability: ~6.5%

Half-life elimination: 11 hours; elderly 14-17 hours

Time to peak, plasma: Dabigatran: 0.5-2 hours; delayed 2 hours by food

Excretion: Urine (85%, primarily as unchanged drug); fecal (6% of total dose)

Dental Health: Effects on Dental TreatmentDabigatran etexilate is converted *in vivo* to the active dabigatran, a specific, reversible, direct thrombin inhibitor. It causes bleeding by preventing thrombin-mediated effects, and by inhibiting thrombin-induced platelet aggregation.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentSt John's wort may decrease levels/effects of dabigatran (concomitant use is not recommended)

Index TermsDabigatran Etexilate Mesilate

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Melanoma]

Regimen UseMelanoma

Regimen

Dacarbazine: I.V.: 750 mg/m^2/day days 1 and 22

[total dose/cycle = 1500 mg/m^2]

Carboplatin: I.V.: 400 mg/m^2/day days 1 and 22

[total dose/cycle = 800 mg/m^2]

Aldesleukin: SubQ: 4,800,000 units every 8 hours days 36 and 57

[total dose/cycle = 28,800,000 units]

then 4,800,000 units every 12 hours days 37 and 58

[total dose/cycle = 19,200,000 units]

then 4,800,000 units/day days 38 to 40, 43 to 47, 50 to 54, 59 to 61, 65 to 68, 71 to 75

[total dose/cycle = 120,000,000 units]

Interferon alpha-2a: SubQ: 6,000,000 units days 38, 40, 43, 45, 47, 50, 52, 54, 59, 61, 64, 66, 68, 71, 73, and 75

[total dose/cycle = 96,000,000 units]

Repeat cycle every 78 days for 3 cycles

References

Ron IG, Mordish Y, Eisenthal A, et al, âA Phase II Study of Combined Administration of Dacarbazine and Carboplatin With Home Therapy of Recombinant Interleukin-2 and Interferon-Alpha 2a in Patients With Advanced Malignant Melanoma,â *Cancer Immunol Immunother*, 1994, 38(6):379-84.[PubMed 8205559]

Dacarbazine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Dacarbazine may be confused with Dicarbosil®, procarbazine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(da KAR ba zeen)

Canadian Brand NamesDTIC®

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent (Triazene)

Use: Labeled IndicationsTreatment of malignant melanoma, Hodgkin's disease, soft-tissue sarcomas, fibrosarcomas, rhabdomyosarcoma, islet cell carcinoma, medullary carcinoma of the thyroid, and neuroblastoma

Dosing: AdultsRefer to individual protocols. Some dosage regimens include:

Intra-arterial: 50-400 mg/m^2 for 5-10 days

Hodgkin's disease, ABVD: 375 mg/m^2 days 1 and 15 every 4 weeks **or** 100 mg/m^2/day for 5 days

Metastatic melanoma (alone or in combination with other agents): I.V.: 150-250 mg/m^2 days 1-5 every 3-4 weeks

Metastatic melanoma: I.V.: 850 mg/m^2 every 3 weeks

High dose: Bone marrow/blood cell transplantation: I.V.: 1-3 g/m^2; maximum dose as a single agent: 3.38 g/m^2; generally combined with other high-dose chemotherapeutic drugs

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols.

Pediatric solid tumors: I.V.: 200-470 mg/m^2/day over 5 days every 21-28 days

Pediatric neuroblastoma: I.V.: 800-900 mg/m^2 as a single dose on day 1 of therapy every 3-4 weeks in combination therapy

Hodgkin's disease, ABVD: I.V.: 375 mg/m^2 on days 1 and 15 of treatment course, repeat every 28 days

Dosing: Renal ImpairmentThe FDA-approved labeling does not contain dosage adjustment guidelines. The following guidelines have been used by some clinicians (Kintzel, 1995):

Cl$_{cr}$ 46-60 mL/minute: Administer 80% of dose

Cl$_{cr}$ 31-45 mL/minute: Administer 75% of dose

Cl$_{cr}$ <30 mL/minute: Administer 70% of dose

Dosing: Hepatic ImpairmentThe FDA-approved labeling does not contain adjustment guidelines. May cause hepatotoxicity; monitor closely for signs of toxicity.

Dosing: Combination Regimens

Brain tumors: 8 in 1 (Brain Tumors)

Lymphoma, Hodgkin's:

ABVD

MOPP/ABVD

Melanoma:

BOLD

BOLD (Melanoma)

BOLD + Interferon

Cisplatin-Dacarbazine-Carmustine (Melanoma)

Cisplatin-Dacarbazine-Interferon Alfa-2b-Aldesleukin

Cisplatin-Vinblastine-Dacarbazine (Melanoma)

Dartmouth Regimen

IL-2 + IFN

Neuroblastoma: CCDDT (Neuroblastoma)

Sarcoma: CYVADIC

Soft tissue sarcoma:

AD

MAID

Oncology: Bone Marrow - High DoseI.V.: 1-3 g/m^2; maximum dose as a single agent: 3.38 g/m^2; generally combined with other high-dose chemotherapeutic drugs.

Calculations

- Body Surface Area: Adults

Administration: I.V.Irritant. Infuse over 30-60 minutes.

Administration: I.V. DetailRapid infusion may cause severe venous irritation.

Extravasation management: Local pain, burning sensation, and irritation at the injection site may be relieved by local application of hot packs. If extravasation occurs, apply cold packs. Protect exposed tissue from light following extravasation.

BMT only: Doses of 6591 mg/m^2 have been administered, although hypotension is considered the nonhematologic dose-limiting side effect for doses >3380 mg/m^2. Infusion-related hypotension may be secondary to calcium chelation by citric acid in formulation.

pH: 3-4

StorageStore intact vials under refrigeration (2°C to 8°C) and protect from light. Vials are stable for 4 weeks at room temperature. Reconstituted solution is stable for 24 hours at room temperature (20°C) and 96 hours under refrigeration (4°C). Solutions for infusion (in D_5W or NS) are stable for 24 hours at room temperature and protected from light. Decomposed drug turns pink.

ReconstitutionThe manufacturer recommends reconstituting 100 mg and 200 mg vials with 9.9 mL and 19.7 mL SWFI, respectively, to a concentration of 10 mg/mL; some institutions use different standard dilutions (eg, 20 mg/mL).

Standard I.V. dilution: Dilute in 250-1000 mL D_5W or NS.

CompatibilityStable in NS, sterile water for injection; **variable stability (consult detailed reference)** in D_5W.

Y-site administration: Compatible: Amifostine, aztreonam, etoposide phosphate, filgrastim, fludarabine, granisetron, melphalan, ondansetron, paclitaxel, sargramostim, teniposide, thiotepa, vinorelbine. **Incompatible:** Allopurinol, cefepime, piperacillin/tazobactam. **Variable (consult detailed reference):** Heparin.

Compatibility when admixed: Compatible: Bleomycin, carmustine, cyclophosphamide, cytarabine, dactinomycin, doxorubicin, fluorouracil, hydrocortisone sodium phosphate, lidocaine, mercaptopurine, methotrexate, ondansetron, vinblastine. **Incompatible:** Hydrocortisone sodium succinate. **Variable (consult detailed reference):** Ondansetron with doxorubicin.

ContraindicationsHypersensitivity to dacarbazine or any component of the formulation

Allergy Considerations

- Dacarbazine (DTIC)/Temozolomide Allergy

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Carcinogenic/teratogenic: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.
- Hepatic effects: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Anaphylaxis: May occur.

- Bone marrow suppression: **[U.S. Boxed Warning]: Bone marrow suppression is a common toxicity;** monitor closely.
- Carcinogenic/teratogenic: **[U.S. Boxed Warning]: May be carcinogenic and/or teratogenic.**
- Extravasation: May result in tissue damage and pain.
- Hepatic effects: **[U.S. Boxed Warning]: Hepatotoxicity with hepatocellular necrosis and hepatic vein thrombosis has been reported,** usually with combination chemotherapy, but may occur with dacarbazine alone.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; half-life is increased, monitor for toxicity and consider dosage reduction.
- Renal impairment: Use with caution in patients with renal impairment; half-life is increased, monitor for toxicity and consider dosage reduction.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorC
Pregnancy Considerations**[U.S. Boxed Warning]: This agent is carcinogenic and/or teratogenic when used in animals.**
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%:

Gastrointestinal: Nausea and vomiting (>90%), can be severe and dose limiting; nausea and vomiting decrease on successive days when dacarbazine is given daily for 5 days; diarrhea

Hematologic: Myelosuppression, leukopenia, thrombocytopenia - dose limiting

Onset: 5-7 days

Nadir: 7-10 days

Recovery: 21-28 days

Local: Pain on infusion, may be minimized by administration through a central line, or by administration as a short infusion (eg, 1-2 hours as opposed to bolus injection)

1% to 10%:

Dermatologic: Alopecia, rash, photosensitivity

Gastrointestinal: Anorexia, metallic taste

Miscellaneous: Flu-like syndrome (fever, myalgia, malaise)

<1%: Anaphylactic reactions, diarrhea (following high-dose bolus injection), eosinophilia, headache, hepatic necrosis, hepatic vein occlusion, liver enzymes increased (transient), paresthesia

Oncology: VesicantNo; irritant
Oncology: Emetic PotentialHigh (>90%)
Oncology: Bone Marrow - Unique Toxicity

Cardiovascular: Hypotension (infusion-related)

Gastrointestinal: Severe nausea and vomiting

Metabolism/Transport Effects**Substrate** (major) of CYP1A2, 2E1
Drug Interactions

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2E1 Inhibitors (Moderate): May decrease the metabolism of CYP2E1 Substrates. *Risk C: Monitor therapy*

CYP2E1 Inhibitors (Strong): May decrease the metabolism of CYP2E1 Substrates. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Sorafenib: May decrease the serum concentration of Dacarbazine. Sorafenib may also increase the concentration of dacarbazine's active metabolite. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (due to GI irritation).

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization).

Monitoring ParametersCBC with differential, liver function

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions. Premedicate with antiemetic (emetic potential is moderately high). Infusion site must be closely monitored; extravasation can cause severe cellulitis or tissue necrosis. Assess results of laboratory tests (CBC with differential, LFTs), therapeutic effectiveness, and adverse response prior to each treatment and on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, liver function

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. This drug can only be given by infusion. Report immediately any pain, burning, or swelling at infusion site. Limit oral intake for 4-6 hours before infusion. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition (small, frequent meals). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea, vomiting, loss of appetite, or diarrhea (consult prescriber for medication); hair loss (reversible); or headache, fever, sinus congestion, or muscles aches (consult prescriber for analgesic). Report immediately any numbness in extremities or change in gait, respiratory distress or respiratory difficulty; rash; easy bruising or bleeding; yellowing of eyes or skin, change in color of urine or blackened stool; or any other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 100 mg, 200 mg

Generic AvailableYes

Mechanism of ActionAlkylating agent which appears to form methylcarbonium ions that attack nucleophilic groups in DNA; cross-links strands of DNA resulting in the inhibition of DNA, RNA, and protein synthesis, the exact mechanism of action is still unclear.

Pharmacodynamics/Kinetics

Onset of action: I.V.: 18-24 days

Distribution: V_d: 0.6 L/kg, exceeding total body water; suggesting binding to some tissue (probably liver)

Protein binding: 5%

Metabolism: Extensively hepatic; hepatobiliary excretion is probably of some importance; metabolites may also have an antineoplastic effect

Half-life elimination: Biphasic: Initial: 20-40 minutes; Terminal: 5 hours

Excretion: Urine (~30% to 50% as unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Metallic taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause headache

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine

Oncology: Bone Marrow CommentsDoses of 6591 mg/m^2 have been administered, although hypotension is considered the nonhematologic dose-limiting side effect for doses >3380 mg/m^2. Infusion-related hypotension may be secondary to calcium chelation by citric acid in formulation.

Index TermsDIC; Dimethyl Triazeno Imidazole Carboxamide; DTIC; Imidazole Carboxamide; Imidazole Carboxamide Dimethyltriazene; WR-139007

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International Brand Names Ai Li Da (CL); D.T.I.C. (DE); D.T.I.C.-Dome (AT, SE, ZA); Dabaz (IN); Dacarb (BR); Dacarbazin (BG, CZ, HN, HU, PL); Dacarbazina (ES); Dacarbazine (NZ); Dacarbazine DBL (MY); Dacarbazine Dome (DK); Dacarbazine For Injection (AU); Dacatic (FI); Dacin (CH); Decarbazine Therabel (PL); Deticene (AR, CN, CZ, EG, FR, GR, HN, HR, IL, IT, MY, NL, PE, PL, PT, RU, TR, UY); Deticine (HU); Detilem (MX); Detimedac (DE); DTI (MY); DTIC (AT, PL, ZA); DTIC-Dome (BE, GB, KP); Duticin (PH, PK); Oncocarbil (AR, PY)

Daclizumab

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(dac KLYE zue mab)

U.S. Brand NamesZenapax®

Canadian Brand NamesZenapax®

Pharmacologic CategoryImmunosuppressant Agent

Use: Labeled IndicationsPart of an immunosuppressive regimen (including cyclosporine and corticosteroids) for the prophylaxis of acute organ rejection in patients receiving renal transplant

Use: Unlabeled/InvestigationalGraft-versus-host disease; prevention of organ rejection after heart transplant

Dosing: Adults

Note: Daclizumab is used adjunctively with other immunosuppressants (eg, cyclosporine, corticosteroids, mycophenolate mofetil, and azathioprine).

Immunoprophylaxis against acute renal allograft rejection: I.V.: 1 mg/kg infused over 15 minutes within 24 hours before transplantation (day 0), then every 14 days for 4 additional doses

Treatment of graft-versus-host disease (unlabeled use, limited data): I.V.: 0.5-1.5 mg/kg, repeat same dosage for transient response. Repeat doses have been administered 11-48 days following the initial dose.

Prevention of organ rejection after heart transplant (unlabeled use): 1 mg/kg up to a maximum of 100 mg; administer within 12 hours after heart transplant and on days 8, 22, 36, and 50 post-transplant

Dosing: ElderlyRefer to adult dosing. Use with caution.

Dosing: PediatricRefer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment needed.

Dosing: Hepatic ImpairmentNo data available for patients with severe impairment.

Administration: I.V.For I.V. administration following dilution. Daclizumab solution should be administered within 4 hours of preparation if stored at room temperature; infuse over a 15-minute period via a peripheral or central vein.

StorageRefrigerate vials at 2°C to 8°C (36°F to 46°F). Do not shake or freeze; protect undiluted solution against direct sunlight. Diluted solution is stable for 24 hours at 4°C or for 4 hours at room temperature.

ReconstitutionDose should be further diluted in 50 mL 0.9% sodium chloride solution. When mixing, gently invert bag to avoid foaming; do not shake. Do not use if solution is discolored.

CompatibilityDo not mix with other medications or infuse other medications through same I.V. line.

ContraindicationsHypersensitivity to daclizumab or any component of the formulation

Allergy Considerations

- Daclizumab Allergy

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Severe hypersensitivity reactions have been rarely reported; anaphylaxis has been observed on initial exposure and following re-exposure; medications for the management of severe allergic reaction should be available for immediate use. Anti-idiotype antibodies have been measured in patients who have received daclizumab (adults 14%; children 34%); detection of antibodies may be influenced by multiple factors and may therefore be misleading.

- Infections: Patients on immunosuppressive therapy are at increased risk for infectious complications; long-term effects on immune function are unknown.

- Secondary malignancy: Patients on immunosuppressive therapy are at increased risk for secondary malignancies; long-term effects on immune function are unknown.

Special populations:

- Cardiac transplant patients: The combined use of daclizumab, cyclosporine, mycophenolate mofetil, and corticosteroids has been associated with an increased mortality in cardiac transplant patients. Higher mortality may be associated with the use of antilymphocyte globulin and a higher incidence of severe infections.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of a physician experienced in immunosuppressive therapy.**

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Generally, IgG molecules cross the placenta. Do not use during pregnancy unless the potential benefit to the mother outweighs the possible risk to the fetus. Women of childbearing potential should use effective contraception before, during, and for 4 months following treatment.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsAlthough reported adverse events are frequent, when daclizumab is compared with placebo the incidence of adverse effects is similar between the two groups. Many of the adverse effects reported during clinical trial use of daclizumab may be related to the patient population, transplant procedure, and concurrent transplant medications. Diarrhea, fever, postoperative pain, pruritus, respiratory tract infection, urinary tract infection, and vomiting occurred more often in children than adults.

≥5%:

Cardiovascular: Chest pain, edema, hyper-/hypotension, tachycardia, thrombosis

Central nervous system: Dizziness, fatigue, fever, headache, insomnia, pain, post-traumatic pain, tremor

Dermatologic: Acne, cellulitis, wound healing impaired

Gastrointestinal: Abdominal distention, abdominal pain, constipation, diarrhea, dyspepsia, epigastric pain, nausea, pyrosis, vomiting

Genitourinary: Dysuria

Hematologic: Bleeding

Neuromuscular & skeletal: Back pain, musculoskeletal pain

Renal: Oliguria, renal tubular necrosis

Respiratory: Cough, dyspnea, pulmonary edema

Miscellaneous: Lymphocele, wound infection

≥2% to <5%:

Central nervous system: Anxiety, depression, shivering

Dermatologic: Hirsutism, pruritus, rash

Endocrine & metabolic: Dehydration, diabetes mellitus, fluid overload

Gastrointestinal: Flatulence, gastritis, hemorrhoids

Genitourinary: Urinary retention, urinary tract bleeding

Local: Application site reaction

Neuromuscular & skeletal: Arthralgia, leg cramps, myalgia, weakness

Ocular: Vision blurred

Renal: Hydronephrosis, renal damage, renal insufficiency

Respiratory: Atelectasis, congestion, hypoxia, pharyngitis, pleural effusion, rales, rhinitis

Miscellaneous: Night sweats, prickly sensation, diaphoresis

<1%, postmarketing, and/or case reports: Severe hypersensitivity reactions (rare): Anaphylaxis, bronchospasm, cardiac arrest, cytokine release syndrome, hypotension, laryngeal edema, pulmonary edema, pruritus, urticaria

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess cardiorespiratory and renal function (fluid overload) and adverse reactions during infusion and periodically between infusions. Be alert to the possibility of the development of infection or malignancies. **Note:** Hypersensitivity reactions can occur;

medications for immediate treatment of severe allergic reactions should be available for immediate use. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Patient EducationThis medication, which may help transplant rejection, can only be administered by infusion. You will be monitored closely during infusion. Report immediately any respiratory or swallowing difficulty; tightness in jaw or throat; chest pain; or rash, pain, burning, redness, or swelling at infusion site. You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake and nutrition (small frequent meals may be advisable). May cause headache, dizziness, fatigue (use caution when driving or engaging in tasks that require alertness until response to drug is known): back pain, leg cramps, or musculoskeletal pain (consult prescriber for approved analgesic); or nausea, vomiting, dyspepsia, or abdominal discomfort (good mouth care, small frequent meals, chewing gum, or sucking lozenges may help). Report changes in urinary pattern; unusual bleeding or bruising; chest pain or palpitations; persistent dizziness, tremors, or headache; respiratory difficulty or unusual cough; rash; opportunistic infection (vaginal itching or drainage, sores in mouth, unusual fever or chills); or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [concentrate; preservative free]:

Zenapax®: 5 mg/mL (5 mL) [contains polysorbate 80]

Generic AvailableNo

ManufacturerRoche Laboratories Inc

Mechanism of ActionDaclizumab is a chimeric (90% human, 10% murine) monoclonal IgG antibody produced by recombinant DNA technology. Daclizumab inhibits immune reactions by binding and blocking the alpha-chain of the interleukin-2 receptor (CD25) located on the surface of activated lymphocytes.

Pharmacodynamics/Kinetics

Distribution: V_d:

Adults: Central compartment: 0.031 L/kg; Peripheral compartment: 0.043 L/kg

Children: Central compartment: 0.067 L/kg; Peripheral compartment: 0.047 L/kg

Half-life elimination (estimated): Adults: Terminal: 20 days; Children: 13 days

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression, anxiety, or insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsA recent international, multicenter trial was published evaluating the use of daclizumab vs placebo with cyclosporine, mycophenolate, and corticosteroids in heart transplant recipients. The primary endpoint was a composite of moderate-severe cellular rejection, hemodynamically significant graft dysfunction, a second transplant, or death. At 6 months, a significantly smaller number of patients in the daclizumab group reached the endpoint when compared to the placebo group (36% vs 48%, $p = 0.007$). Although cytolytic therapy was excluded from the study, 40 patients in the daclizumab arm and 37 patients in the placebo arm received either muromonab-CB3, antithymocyte globulin, or antilymphocyte globulin. Cytolytic therapy was administered because of its renal-sparing properties or for acute rejection in most cases. Six patients in the daclizumab arm who received concurrent cytolytic therapy died from sepsis. No one in the placebo group who received cytolytic therapy died from sepsis. Daclizumab was efficacious as prophylaxis against acute cellular rejection after cardiac transplant. Concurrent or anticipated use of cytolytic therapy with daclizumab should be avoided.

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Wiseman LR and Faulds D, "Daclizumab: A Review of Its Use in the Prevention of Acute Rejection in Renal Transplant Recipients," *Drugs*, 1999, 58(6):1029-42.[PubMed 10651389]

International Brand NamesZenapax (AR, AT, AU, BE, BG, BR, CH, CL, CN, CO, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, MX, NL, NO, PE, PH, PK, PL, PT, PY, RU, SE, TR, TW, UY, VE)

DACTINomycin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

DACTINomycin may be confused with DAPTOmycin, DAUNOrubicin

Actinomycin may be confused with achromycin

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(dak ti noe MYE sin)

U.S. Brand NamesCosmegen®

Canadian Brand NamesCosmegen®

Pharmacologic CategoryAntineoplastic Agent, Antibiotic

Use: Labeled IndicationsTreatment of testicular tumors, melanoma, gestational trophoblastic neoplasm, Wilms' tumor, neuroblastoma, retinoblastoma, rhabdomyosarcoma, uterine sarcomas, Ewing's sarcoma, Kaposi's sarcoma, sarcoma botryoides, and soft tissue sarcoma

Dosing: AdultsRefer to individual protocols.

Note: Medication orders for dactinomycin are commonly written in MICROgrams (eg, 150 mcg) although many regimens list the dose in MILLIgrams (eg, mg/kg or mg/m^2). One-time doses for >1000 mcg, or multiple-day doses for >500 mcg/day are not common. The dose intensity per 2-week cycle for adults and children should not exceed 15 mcg/kg/day for 5 days or 400-600 mcg/m^2/day for 5 days. Some practitioners recommend calculation of the dosage for obese or edematous adult patients on the basis of body surface area in an effort to relate dosage to lean body mass.

Usual doses:

2.5 mg/m^2 in divided doses over 1 week, repeated every 2 weeks **or**

0.75-2 mg/m^2 every 1-4 weeks **or**

400-600 mcg/m^2/day for 5 days, repeated every 3-6 weeks

Testicular cancer: 1000 mcg/m^2 on day 1 (as part of a combination chemotherapy regimen)

Gestational trophoblastic neoplasm: 12 mcg/kg/day for 5 days **or** 500 mcg days 1 and 2 (as part of a combination chemotherapy regimen)

Wilms' tumor, Ewing's sarcoma: 15 mcg/kg/day for 5 days (in various combination regimens and schedules)

Dosing: ElderlyRefer to adult dosing. Elderly patients are at increased risk of myelosuppression; dosing should begin at the low end of the dosing range.

Dosing: PediatricRefer to individual protocols.

Note: Dactinomycin doses are almost ALWAYS expressed in MICROGRAMS rather than milligrams. The dose intensity per 2-week cycle for adults and children should not exceed 15 mcg/kg/day for 5 days or 400-600 mcg/m^2/day for 5 days.

Usual dose: I.V.: Children >6 months: 15 mcg/kg/day **or** 400-600 mcg/m^2/day for 5 days every 3-6 weeks

Wilms' tumor, rhabdomyosarcoma, Ewing's sarcoma: I.V.: Children >6 months: 15 mcg/kg/day for 5 days (in various combination regimens and schedules)

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Combination Regimens

Gestational trophoblastic tumor:

CHAMOCA (Modified Bagshawe Regimen)

CHAMOMA (Bagshawe Regimen)

EMA/CO

EP/EMA

Osteosarcoma: POG-8651

Retinoblastoma: VAC (Retinoblastoma)

Rhabdomyosarcoma:

VAC Pulse

VAC (Rhabdomyosarcoma)

Sarcoma: VAC Alternating With IE (Ewing's Sarcoma)

Wilms' tumor:

AAV (DD)

ACAV (J)

AV (EE)

AV (K)

AV (L)

AV (Wilms' Tumor)

AVD

EE

EE-4A

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Slow I.V. push or infuse over 10-15 minutes. Avoid extravasation. Do not administer I.M. or SubQ. Do not filter with cellulose ester membrane filters.
Administration: I.V. DetailpH: 5.5-7.0 (reconstituted solution)
StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from light and humidity. Solutions in 50 mL D_5W or NS are stable for 24 hours at room temperature.
ReconstitutionDilute with 1.1 mL of preservative-free SWI to yield a final concentration of 500 mcg/mL. Do not use preservative diluent as precipitation may occur. Cellulose ester membrane filters should not be used during preparation.
CompatibilityStable in D_5W, NS, SWFI.

Y-site administration: Compatible: Allopurinol, amifostine, aztreonam, cefepime, etoposide phosphate, fludarabine, gemcitabine, granisetron, melphalan, ondansetron, sargramostim, teniposide, thiotepa, vinorelbine. **Incompatible:** Filgrastim.

Compatibility when admixed: Compatible: Dacarbazine.

ContraindicationsHypersensitivity to dactinomycin or any component of the formulation; patients with concurrent or recent chickenpox or herpes zoster; avoid in infants <6 months of age
Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.
- Hazardous agent: See “Special handling” below.
- Pregnancy: See “Special populations” below.
- Skin irritation/extravasation: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: **[U.S. Boxed Warning]: Avoid inhalation of vapors or contact with skin, mucous membrane, or eyes; use appropriate precautions for handling and disposal.**

Concerns related to adverse effects:

- Secondary malignancies: Long-term observation of cancer survivors is recommended due to the potential for secondary primary tumors following treatment with radiation and antineoplastic agents.
- Skin irritation/extravasation: **[U.S. Boxed Warning]: Extremely irritating to tissues and must be administered I.V.; if extravasation occurs during I.V. use, severe damage to soft tissues will occur.**
- Toxic effects: May be delayed in onset (2-4 days following a course of treatment) and may require 1-2 weeks to reach maximum severity.
- Veno-occlusive disease: May cause veno-occlusive liver disease, increased risk in children <4 years of age; use with caution in hepatobiliary dysfunction.

Special populations:

- Pregnancy: **[U.S. Boxed Warning]: Avoid exposure during pregnancy.**

- Radiation therapy recipients: Potentiates the effects of radiation therapy; use with caution in patients who have received radiation therapy; reduce dosages in patients who are receiving dactinomycin and radiation therapy simultaneously; combination with radiation therapy may result in increased GI toxicity and myelosuppression. Avoid dactinomycin use within 2 months of radiation treatment for right-sided Wilms' tumor, may increase the risk of hepatotoxicity.

Other warnings/precautions:

- Dosage expression: Dosage is usually expressed in **MICRO**grams, **NOT** milligrams, and must be calculated on the basis of body surface area (BSA) in obese or edematous adult patients.

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

- Vaccines: Avoid administration of live vaccines.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenic effects and fetal loss There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential are advised not to become pregnant. Use only when potential benefit justifies potential risk to the fetus. **[U.S. Boxed Warning]: Avoid exposure during pregnancy.**

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if dactinomycin is excreted in human breast milk. Due to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse ReactionsFrequency not defined.

Central nervous system: Fatigue, fever, lethargy, malaise

Dermatologic: Acne, alopecia (reversible), cheilitis; increased pigmentation, sloughing, or erythema of previously irradiated skin; skin eruptions

Endocrine & metabolic: Growth retardation, hypocalcemia

Gastrointestinal: Abdominal pain, anorexia, diarrhea, dysphagia, esophagitis, GI ulceration, mucositis, nausea, pharyngitis, proctitis, stomatitis, vomiting

Hematologic: Agranulocytosis, anemia, aplastic anemia, leukopenia, pancytopenia, reticulocytopenia, thrombocytopenia, myelosuppression (onset: 7 days, nadir: 14-21 days, recovery: 21-28 days)

Hepatic: Ascites, hepatic failure, hepatitis, hepatomegaly, hepatotoxicity, liver function test abnormality, veno-occlusive disease

Local: Erythema, edema, epidermolysis, pain, tissue necrosis, and ulceration (following extravasation)

Neuromuscular & skeletal: Myalgia

Renal: Renal function abnormality

Respiratory: Pneumonitis

Miscellaneous: Anaphylactoid reaction, infection

Oncology: VesicantYes; see Management of Drug Extravasations.

Oncology: Emetic PotentialHigh (60% to 90%)

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Test InteractionsMay interfere with bioassays of antibacterial drug levels

Monitoring ParametersCBC with differential and platelet count, liver function tests, and renal function tests

Nursing: Physical Assessment/MonitoringPatient must be monitored closely during infusion; extravasation is extremely damaging to soft tissue and will cause a severe local reaction. Administer slow I.V. push over 10-15 minutes. Do not give I.M. or SubQ. Assess results of laboratory tests (eg, hematological, renal, and hepatic function), therapeutic response, and adverse reactions (myelosuppression, nausea, vomiting, glossitis, and oral ulceration) prior to each treatment and on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelet count, liver and renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug can only be given by infusion; report immediately any pain, burning, or swelling at infusion site; sudden chest pain; difficulty breathing or swallowing; or chills. Limit oral intake for 4-6 hours immediately before infusion. Between infusions, maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake and nutrition (small frequent meals). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause fatigue or malaise (use caution when driving or engaging in potentially hazardous tasks until response to drug is known); nausea, vomiting, loss of appetite, or diarrhea (consult prescriber for appropriate medication); or hair loss (reversible). Report unresolved nausea, vomiting, diarrhea, or abdominal pain; difficulty swallowing; rash; or any other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Cosmegen®: 0.5 mg [contains mannitol 20 mg]

Generic AvailableNo

Mechanism of ActionBinds to the guanine portion of DNA intercalating between guanine and cytosine base pairs inhibiting DNA and RNA synthesis and protein synthesis

Pharmacodynamics/Kinetics

Distribution: High concentrations found in bone marrow and tumor cells, submaxillary gland, liver, and kidney; crosses placenta; poor CSF penetration

Metabolism: Hepatic, minimal

Half-life elimination: ~36 hours

Time to peak, serum: I.V.: 2-5 minutes

Excretion: Bile (50%); feces (14%); urine (~10% as unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis and mucositis

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine

Index TermsACT; Act-D; Actinomycin; Actinomycin CI; Actinomycin D; DACT; NSC-3053

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International Brand Names Cosmegen, Lyovac (GB, HK); Ac-De (MX, PE); Cosmegen (AR, AT, AU, BE, BG, BR, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PH, PK, PT, PY, RU, SE, TR, TW); Dacmozen (IN); Trepar (PH); Zenapax (DK, IE)

Dalteparin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

2009 National Patient Safety Goals: The Joint Commission on Accreditation of Healthcare Organizations requires healthcare organizations that provide anticoagulant therapy to have a process in place to reduce the risk of anticoagulant-associated patient harm. Patients receiving anticoagulants should receive individualized care through a defined process that includes standardized ordering, dispensing, administration, monitoring and education. This does not apply to routine short-term use of anticoagulants for prevention of venous thromboembolism when the expectation is that the patient's laboratory values will remain within or close to normal values (NPSG.03.05.01).

Pronunciation(dal TE pa rin)

U.S. Brand NamesFragmin®

Canadian Brand NamesFragmin®

Pharmacologic CategoryLow Molecular Weight Heparin

Use: Labeled IndicationsPrevention of deep vein thrombosis which may lead to pulmonary embolism, in patients requiring abdominal surgery who are at risk for thromboembolism complications (eg, patients >40 years of age, obesity, patients with malignancy, history of deep vein thrombosis or pulmonary embolism, and surgical procedures requiring general anesthesia and lasting >30 minutes); prevention of DVT in patients undergoing hip-replacement surgery; patients immobile during an acute illness; acute treatment of unstable angina or non-Q-wave myocardial infarction; prevention of ischemic complications in patients on concurrent aspirin therapy; in patients with cancer, extended treatment (6 months) of acute symptomatic venous thromboembolism (DVT and/or PE) to reduce the recurrence of venous thromboembolism

Use: Unlabeled/InvestigationalActive treatment of deep vein thrombosis (noncancer patients)

Dosing: Adults

Abdominal surgery (DVT prophylaxis):

Low-to-moderate DVT risk: SubQ: 2500 int. units 1-2 hours prior to surgery, then once daily for 5-10 days postoperatively

High DVT risk: SubQ: 5000 int. units the evening prior to surgery and then once daily for 5-10 days postoperatively. Alternatively in patients with malignancy: 2500 int. units 1-2 hours prior to surgery, 2500 int. units 12 hours later, then 5000 int. units once daily for 5-10 days postoperatively.

Total hip surgery (DVT prophylaxis): SubQ: **Note:** Three treatment options are currently available. Dose is given for 5-10 days, although up to 14 days of treatment have been tolerated in clinical trials:

Postoperative start:

Initial: 2500 int. units 4-8 hours* after surgery

Maintenance: 5000 int. units once daily; start at least 6 hours after postsurgical dose

Preoperative (starting day of surgery):

Initial: 2500 int. units within 2 hours before surgery

Adjustment: 2500 int. units 4-8 hours* after surgery

Maintenance: 5000 int. units once daily; start at least 6 hours after postsurgical dose

Preoperative (starting evening prior to surgery):

Initial: 5000 int. units 10-14 hours before surgery

Adjustment: 5000 int. units 4-8 hours* after surgery

Maintenance: 5000 int. units once daily, allowing 24 hours between doses.

***Note:** Dose may be delayed if hemostasis is not yet achieved.

Unstable angina or non-Q-wave myocardial infarction: SubQ: 120 int. units/kg body weight (maximum dose: 10,000 int. units) every 12 hours for 5-8 days with concurrent aspirin therapy. Discontinue dalteparin once patient is clinically stable.

Venous thromboembolism: SubQ: Cancer patients:

Initial (month 1): 200 int. units/kg (maximum dose: 18,000 int. units) once daily for 30 days

Maintenance (months 2-6): ~150 int. units/kg (maximum dose: 18,000 int. units) once daily. If platelet count between 50,000-100,000/mm^3, reduce dose by 2,500 int. units until platelet count recovers to ≥100,000/mm^3. If platelet count <50,000/mm^3, discontinue dalteparin until platelet count recover to >50,000/mm^3.

Immobility/acute illness (DVT prophylaxis): 5000 int. units once daily

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentIn cancer patients, receiving treatment for venous thromboembolism, if Cl_{cr} <30 mL/minute, manufacturer recommends monitoring anti-Xa levels to determine appropriate dose.
Administration: I.M.**Do not give I.M.**
Administration: OtherFor deep SubQ injection only. May be injected in a U-shape to the area surrounding the navel, the upper outer side of the thigh, or the upper outer quadrangle of the buttock. Apply pressure to injection site; do not massage. Use thumb and forefinger to lift a fold of skin when injecting dalteparin to the navel area or thigh. Insert needle at a 45- to 90-degree angle. The entire length of needle should be inserted. Do not expel air bubble from fixed-dose syringe prior to injection. Air bubble (and extra solution, if applicable) may be expelled from graduated syringes.

Administration once daily beginning prior to surgery and continuing 5-10 days after surgery prevents deep vein thrombosis in patients at risk for thromboembolic complications. For unstable angina or non-Q-wave myocardial infarction, dalteparin is administered every 12 hours until the patient is stable (5-8 days).

StorageStore at temperatures of 20°C to 25°C (68°F to 77°F). Multidose vials may be stored for up to 2 weeks at room temperature after entering.
ContraindicationsHypersensitivity to dalteparin or any component of the formulation; thrombocytopenia associated with a positive *in vitro* test for antiplatelet antibodies in the presence of dalteparin; hypersensitivity to heparin or pork products; patients with active major bleeding; patients with unstable angina, non-Q-wave MI, or acute venous thromboembolism undergoing regional anesthesia; not for I.M. or I.V. use
Warnings/Precautions

Boxed warnings:

- Neuraxial anesthesia: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Bleeding: Monitor patient closely for signs or symptoms of bleeding. Certain patients are at increased risk of bleeding. Risk factors include bacterial endocarditis; congenital or acquired bleeding disorders; active ulcerative or angiodysplastic GI diseases; severe uncontrolled hypertension; hemorrhagic stroke; or use shortly after brain, spinal, or ophthalmology surgery; in patient treated concomitantly with platelet inhibitors; recent GI bleeding; thrombocytopenia or platelet defects; severe liver disease; hypertensive or diabetic retinopathy; or in patients undergoing invasive procedures. Discontinue if bleeding occurs.

- Hyperkalemia: Monitor for hyperkalemia. Heparin can cause hyperkalemia by affecting aldosterone; similar reactions could occur with LMWHs.

- Methylparaben/propylparaben hypersensitivity: Use with caution in patients with known hypersensitivity to methylparaben or propylparaben.

- Thrombocytopenia: Rare cases of thrombocytopenia have occurred. Use with extreme caution in patients with history of heparin-induced thrombocytopenia; monitor platelet count closely. Consider discontinuation of therapy in any patient developing significant thrombocytopenia related to initiation of dalteparin. Rare cases of thrombocytopenia with thrombosis have occurred. Use caution in patients with congenital or drug-induced thrombocytopenia or platelet defects.

Disease-related concerns:

- Cancer: Cancer patients with thrombocytopenia may require dose adjustments for treatment of acute venous thromboembolism.

- Renal impairment: Use with caution in patients with severe renal failure (has not been studied).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Multidose vials: Contain benzyl alcohol and should not be used in pregnant women. In neonates, large amounts of benzyl alcohol (>100 mg/kg/day) have been associated with fatal toxicity (gasping syndrome).

Other warnings/precautions:

- Conversion to other products: Not to be used interchangeably (unit for unit) with heparin or any other low molecular weight heparins.

- Neuraxial anesthesia: **[U.S. Boxed Warning]: Patients with recent or anticipated neuraxial anesthesia (epidural or spinal anesthesia) are at risk of spinal or epidural hematoma and subsequent paralysis.** Consider risk versus benefit prior to neuraxial anesthesia; risk is increased by concomitant agents which may alter hemostasis, as well as traumatic or repeated epidural or spinal puncture. Patient should be observed closely for bleeding and signs and symptoms of neurological impairment if therapy is administered during or immediately following diagnostic lumbar puncture, epidural anesthesia, or spinal anesthesia.

Geriatric ConsiderationsNo specific recommendations are necessary for the elderly.
Pregnancy Risk FactorB
Pregnancy ConsiderationsMultiple-dose vials contain benzyl alcohol (avoid in pregnant women due to association with gasping syndrome

in premature infants). Adverse effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationEnters breast milk/use caution

Breast-Feeding Considerations

In lactating women receiving prophylactic doses of dalteparin, small amounts of anti-xa activity was noted in breast milk. The milk/plasma ratio was <0.025 to 0.224. Oral absorption of low molecular weight heparin is extremely low.

Adverse Reactions

Note: As with all anticoagulants, bleeding is the major adverse effect of dalteparin. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables.

>10%:

Hematologic: Bleeding (3% to 14%)

1% to 10%:

Hematologic: Wound hematoma (up to 3%)

Hepatic: AST >3 times upper limit of normal (5% to 9%), ALT >3 times upper limit of normal (4% to 10%)

Local: Pain at injection site (up to 12%), injection site hematoma (up to 7%)

<1% (Limited to important or life-threatening): Thrombocytopenia (including heparin-induced thrombocytopenia), allergic reaction (fever, pruritus, rash, injections site reaction, bullous eruption), alopecia, anaphylactoid reaction, operative site bleeding, gastrointestinal bleeding, hemoptysis, skin necrosis, subdural hematoma, thrombosis (associated with heparin-induced thrombocytopenia). Spinal or epidural hematomas can occur following neuraxial anesthesia or spinal puncture, resulting in paralysis.

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Drotrecogin Alfa: Heparin (Low Molecular Weight) may enhance the adverse/toxic effect of Drotrecogin Alfa. This is of most concern with therapeutic doses of LMW heparin. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose oil, fenugreek, feverfew, garlic, ginger, ginkgo biloba, Ginseng (american), Ginseng (panax), Ginseng (siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (s-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet/anticoagulant activity)

Monitoring ParametersPeriodic CBC including platelet count; stool occult blood tests; monitoring of PT and PTT is not necessary. Once patient has received 3-4 doses, anti-Xa levels, drawn 4-6 hours after dalteparin administration, may be used to monitor effect in patients with severe renal dysfunction or if abnormal coagulation parameters or bleeding should occur.

Reference RangeTreatment: Venous thromboembolism: Target anti-Xa range: 0.5-1.5 int. units/mL

Nursing: Physical Assessment/MonitoringEvaluate for increased bleeding risk prior to beginning treatment. Assess other pharmacological or herbal products patient may be taking for potential interactions (especially anything that will impact coagulation or platelet aggregation). Bleeding precautions should be observed during treatment. Assess results of laboratory tests, therapeutic effectiveness (according to purpose for use), and adverse response (eg, thrombolytic reactions). Teach patient possible side effects/appropriate interventions (eg, bleeding precautions) and adverse symptoms to report.

Monitoring: Lab TestsPeriodic CBC including platelet count; stool occult blood tests; monitoring of PT and PTT is not necessary. Once patient has received 3-4 doses, anti-Xa levels, drawn 4-6 hours after dalteparin administration, may be used to monitor effect in patients with severe renal dysfunction or if abnormal coagulation parameters or bleeding should occur.

Patient EducationDo not take any new medication during therapy unless approved by prescriber (especially anything containing aspirin). This drug can only be administered by injection. You may have a tendency to bleed easily while taking this drug (use caution to prevent falls or bruises or other accidents, brush teeth with soft brush, use waxed dental floss, use electric razor, avoid scissors or sharp knives, and potentially harmful activities). Report unusual fever; unusual bleeding or bruising (bleeding gums, nosebleed, blood in urine, dark stool);

pain in joints or back; severe head pain; skin rash; or redness, swelling, or pain at injection site. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Fragmin®: Antifactor Xa 10,000 int. units per 1 mL (9.5 mL) [contains benzyl alcohol]; antifactor Xa 25,000 units per 1 mL (3.8 mL) [contains benzyl alcohol]

Injection, solution [preservative free]:

Fragmin®: Antifactor Xa 2500 int. units per 0.2 mL (0.2 mL); antifactor Xa 5000 int. units per 0.2 mL (0.2 mL); antifactor Xa 7500 int. units per 0.3 mL (0.3 mL); antifactor Xa 10,000 int. units per 1 mL (1 mL); antifactor Xa 12,500 int. units per 0.5 mL (0.5 mL); antifactor Xa 15,000 int. units per 0.6 mL (0.6 mL); antifactor Xa 18,000 int. units per 0.72 mL (0.72 mL)

Generic Available No

Manufacturer Pharmacia & Upjohn

Pricing: U.S. (www.drugstore.com)

Injection (Fragmin)

2500 units/0.2 mL (0.2): $26.99

5000 units/0.2 mL (2): $342.29

10000 units/mL (1): $69.99

Mechanism of Action Low molecular weight heparin analog with a molecular weight of 4000-6000 daltons; the commercial product contains 3% to 15% heparin with a molecular weight <3000 daltons, 65% to 78% with a molecular weight of 3000-8000 daltons and 14% to 26% with a molecular weight >8000 daltons; while dalteparin has been shown to inhibit both factor Xa and factor IIa (thrombin), the antithrombotic effect of dalteparin is characterized by a higher ratio of antifactor Xa to antifactor IIa activity (ratio = 4)

Pharmacodynamics/Kinetics

Onset of action: 1-2 hours

Duration: >12 hours

Distribution: V_d: 40-60 mL/kg

Bioavailability: SubQ: 81% to 93%

Half-life elimination (route dependent): 2-5 hours

Time to peak, serum: 4 hours

Related Information

- Anticoagulants, Injectable

Pharmacotherapy Pearls Multidose vial contains 14 mg/mL benzyl alcohol.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: As with all anticoagulants, bleeding is the major adverse effect of bivalirudin. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the intensity of anticoagulation and patient susceptibility. Additional adverse effects are often related to idiosyncratic reactions, and the frequency is difficult to estimate. Adverse reactions reported were generally less than those seen with heparin.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Cardiovascular Considerations Low molecular weight heparins (LMWHs) compare favorably to unfractionated heparin (UFH) in the prevention and treatment of venous thromboembolism. LMWHs are associated with less thrombocytopenia, compared to heparin, and do not require routine therapeutic monitoring.

Obesity/Renal Dysfunction: There is no consensus for adjusting/correcting the weight-based dosage of LMWH for patients who are morbidly obese. Monitoring of antifactor Xa concentration 4 hours after injection may be warranted. Patients who have a reduction in calculated creatinine clearance are at risk of accumulated anticoagulant effect when they are treated with certain LMWHs. All LMWHs may not behave the same in patients with renal dysfunction. Some clinicians monitor anti-Xa levels for patients with Cl_{cr} <30 mL/minute.

Anesthesia and Critical Care Concerns/Other Considerations Many critically-ill and surgery patients require preventive measures for venous thromboembolism. LMWHs compare favorably to unfractionated heparin in the prevention and treatment of venous thromboembolism. LMWHs are associated with less thrombocytopenia, compared to heparin, and do not require routine therapeutic monitoring.

Obesity/Renal Dysfunction: There is no consensus for adjusting/correcting the weight-based dosage of LMWH for patients who are morbidly obese. Monitoring of antifactor Xa concentration 4 hours after injection may be warranted. Patients who have a reduction in calculated creatinine clearance are at risk of accumulated anticoagulant effect when they are treated with certain LMWHs. All LMWHs may not behave the same in patients with renal dysfunction. Some clinicians monitor anti-Xa levels for patients with Cl_{cr} <30 mL/minute.

Index Terms Dalteparin Sodium; NSC-714371

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International Brand NamesFragmin (AE, AT, AU, BE, BG, BH, BR, CH, CL, CN, CO, CY, CZ, DE, DK, EC, EG, ES, FI, FR, GB, GR, HK, HN, IE, IL, IN, IQ, IR, IT, JO, KP, KW, LB, LY, NL, NO, OM, PE, PH, PK, PL, PT, QA, RU, SA, SE, SG, SY, TR, TW, YE, ZA); Fragmin P Forte (DE); Fragmine (FR)

Danaparoid

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Orgaran® may be confused with argatroban

Pronunciation(da NAP a roid)

Canadian Brand Names Orgaran®

Pharmacologic Category Anticoagulant

Use: Labeled Indications Prevention of postoperative deep vein thrombosis following elective hip replacement surgery

Use: Unlabeled/Investigational Systemic anticoagulation for patients with heparin-induced thrombocytopenia: factor Xa inhibition is used to monitor degree of anticoagulation if necessary

Dosing: Adults

Prevention of DVT following hip replacement: SubQ: 750 anti-Xa units twice daily; beginning 1-4 hours before surgery and then not sooner than 2 hours after surgery and every 12 hours until the risk of DVT has diminished, the average duration of therapy is 7-10 days

Treatment (unlabeled uses): See table.

Adult Danaparoid Treatment Dosing Regimens (not FDA approved)

	Body Weight (kg)	I.V. Bolus aFXaU	Long-Term Infusion aFXaU	Level of aFXaU/mL	Monitoring
Deep Vein Thrombosis OR Acute Pulmonary Embolism	<55 55-90 >90	1250 2500 3750	400 units/h over 4 h, then 300 units/h over 4 h, then 150-200 units/h maintenance dose	0.5-0.8	Days 1-3 daily, then every alternate day
Deep Vein Thrombosis OR Pulmonary Embolism >5 d old	<90 >90	1250 1250	SubQ: 3 x 750/d SubQ: 3 x 1250/d	<0.5	Not necessary
Embolectomy	<90 >90 and high risk	2500 preoperatively 2500 preoperatively	SubQ: 2 x 1250/d postoperatively 150-200 units/h I.V.; perioperative arterial irrigation, if necessary: 750 units/20 mL NaCl	<0.4 0.5 0.8	Not necessary Days 1-3 daily, then every alternate day
Peripheral Arterial Bypass		2500 preoperatively	150-200 units/h	0.5-0.8	Days 1-3 daily, then every alternate day
Cardiac Catheter	<90 >90	2500 preoperatively 3750 preoperatively			
Surgery (excluding vascular)			SubQ: 750, 1-4 h preoperatively SubQ: 750, 2-5 h	<0.35	Not necessary

			postoperatively, then 2 x 750/d		

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricSubQ: Children: Safety and effectiveness have not been established.

Dosing: Renal ImpairmentAdjustment may be necessary in patients with severe renal impairment. Patients with serum creatinine levels ≥2.0 mg/dL should be carefully monitored. SubQ: Hemodialysis: See table.

Hemodialysis With Danaparoid Sodium

Dialysis on alternate days:	**Dosage prior to dialysis in aFXaU (dosage for body wt <55 kg):**	
First dialysis	3750 (<55 kg 2500)	
Second dialysis	3750 (<55 kg 2000)	
Further dialysis:		
aFXa level before dialysis (eg, day 5)	**Bolus before next dialysis, aFXaU (eg, day 7)**	**aFXa level during dialysis**
<0.3	3000 (<55 kg 2000)	0.5-0.8
0.3-0.35	2500 (<55 kg 2000)	
0.35-0.4	2000 (<55 kg 1500)	
>0.4	No bolus; if fibrin strands occur, 1500 aFXaU I.V.	
Monitoring: 30 minutes before dialysis and after 4 hours of dialysis		
Daily Dialysis		
First dialysis	3750 (<55 kg 2500)	
Second dialysis	2500 (<55 kg 2000)	
Further dialyses	See above	
As with “dialysis on alternate days”, always take the aFXa activity preceding the previous dialysis as a basis for the current dosage.		

Administration: OtherAdminister by subcutaneous injection, **not** I.M. Have patient lie down and administer by deep SubQ injection using a fine needle (25- to 26-gauge). Rotate sites of injection.

StorageStore intact vials or ampuls under refrigeration.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to danaparoid or thrombocytopenia associated with a positive *in vitro* test for antiplatelet antibodies in the presence of danaparoid; hypersensitivity to pork products or to sulfites (contains metabisulfite); patients with active major bleeding; severe hemorrhagic diathesis (hemophilia, idiopathic thrombocytopenic purpura); not for I.M. or I.V. use

Allergy Considerations

- Low Molecular Weight Heparin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: Monitor patient closely for signs or symptoms of bleeding. Certain patients are at increased risk of bleeding; risk factors include bacterial endocarditis; congenital or acquired bleeding disorders; active ulcerative or angiodysplastic GI diseases; severe uncontrolled hypertension; hemorrhagic stroke; or use shortly after brain, spinal, or ophthalmology surgery; in patient treated concomitantly with platelet inhibitors; recent GI bleeding; thrombocytopenia or platelet defects; severe liver disease; hypertensive or diabetic retinopathy; or in patients undergoing invasive procedures. Discontinue if bleeding occurs.

- Hyperkalemia: Monitor for hyperkalemia. Heparin can cause hyperkalemia by affecting aldosterone; similar reactions could occur with danaparoid.

- Methylparaben/propylparaben hypersensitivity: Use with caution in patients with known hypersensitivity to methylparaben or propylparaben.

Disease-related concerns:

- Heparin-induced thrombocytopenia: Use with caution in patients with history of heparin-induced thrombocytopenia.
- Renal impairment: Use with caution in patients with severe renal failure (has not been studied).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Sodium sulfite: This product contains sodium sulfite which may cause allergic-type reactions, including anaphylactic symptoms and life-threatening asthmatic episodes in susceptible people; this is seen more frequently in asthmatics.

Other warnings/precautions:

- Conversion to other products: Not to be used interchangeably (unit for unit) with heparin or any other low molecular weight heparins.
- Neuraxial anesthesia: **Patients with recent or anticipated neuraxial anesthesia (epidural or spinal anesthesia) are at risk of spinal or epidural hematoma and subsequent paralysis.** Consider risk versus benefit prior to neuraxial anesthesia; risk is increased by concomitant agents which may alter hemostasis, as well as traumatic or repeated epidural or spinal puncture. Patient should be observed closely for bleeding if therapy is administered during or immediately following diagnostic lumbar puncture, epidural anesthesia, or spinal anesthesia.

Geriatric ConsiderationsEvaluation of elderly's creatinine serum concentrations is important before initiating therapy.
Pregnancy Risk FactorB
LactationExcretion in breast milk unknown/compatible
Adverse ReactionsAs with all anticoagulants, bleeding is the major adverse effect of danaparoid. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables.

>10%:

Central nervous system: Fever (22%)

Gastrointestinal: Nausea (4% to 14%), constipation (4% to 11%)

1% to 10%:

Cardiovascular: Peripheral edema (3%), edema (3%)

Central nervous system: Insomnia (3%), headache (3%), asthenia (2%), dizziness (2%), pain (9%)

Dermatologic: Rash (2% to 5%), pruritus (4%)

Gastrointestinal: Vomiting (3%)

Genitourinary: Urinary tract infection (3% to 4%), urinary retention (2%)

Hematologic: Anemia (2%)

Local: Injection site pain (8% to 14%), injection site hematoma (5%)

Neuromuscular & skeletal: Joint disorder (3%)

Miscellaneous: Infection (2%)

<1% (Limited to important or life-threatening): Spinal or epidural hematomas can occur following neuraxial anesthesia or spinal puncture, resulting in paralysis. Risk is increased in patients with indwelling epidural catheters or concomitant use of other drugs affecting hemostasis, thrombocytopenia, hyperkalemia, wound infection, skin rash, allergic reaction.

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Drotrecogin Alfa: Danaparoid may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid cat's claw, dong quai, evening primrose, feverfew, garlic, ginger, ginkgo, red clover, horse chestnut, green tea, and ginseng (all have additional antiplatelet activity).

Monitoring ParametersPlatelets, occult blood, and anti-Xa activity, if available; the monitoring of PT and/or PTT is not necessary

Nursing: Physical Assessment/MonitoringSee Contraindications, Warnings/Precautions, and Dosing for use cautions. Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (especially anything that will impact coagulation or platelet aggregation - see Drug Interactions). Assess results of laboratory tests (see above), therapeutic effectiveness, and adverse reactions (eg, thrombolytic reactions - see Adverse Reactions and Overdose/Toxicology). Teach patient possible side effects/appropriate interventions (eg, bleeding precautions) and adverse symptoms to report (see Patient Education).

Monitoring: Lab TestsPlatelets, occult blood, anti-Xa activity, if available; the monitoring of PT and/or PTT is not necessary.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. This drug can only be administered by injection. You may have a tendency to bleed easily while taking this drug (brush teeth with soft brush, floss with waxed floss, use electric razor, avoid scissors or sharp knives and potentially harmful activities). Report unusual fever; unusual bleeding or bruising (bleeding gums, nosebleed, blood in urine, dark stool); pain in joints or back; severe head pain; skin rash; or redness, swelling, or pain at injection site.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, solution:

Orgaran® [CAN]: 750 anti-Xa units/0.6 mL (0.6 mL) [not available in the U.S.]

Generic AvailableNo

ManufacturerOrganon Inc

Mechanism of ActionPrevents fibrin formation in coagulation pathway via thrombin generation inhibition by anti-Xa and anti-IIa effects.

Pharmacodynamics/Kinetics

Onset of action: Peak effect: SubQ: Maximum antifactor Xa and antithrombin (antifactor IIa) activities occur in 2-5 hours

Half-life elimination, plasma: Mean: Terminal: ~24 hours

Excretion: Primarily urine

Related Information

- Anticoagulants, Injectable

Pharmacotherapy PearlsA 750 anti-Xa unit dose of danaparoid is approximately equivalent to 55 mg of danaparoid.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: As with all anticoagulants, bleeding is the major adverse effect of danaparoid. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDanaparoid Sodium

International Brand NamesOrgaran (AT, AU, BE, CH, DE, FI, FR, GB, IT, LU, NL, NO, SE)

Danazol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Danazol may be confused with Dantrium®

Danocrine® may be confused with Dacriose®

Pronunciation(DA na zole)

U.S. Brand NamesDanocrine® [DSC]

Canadian Brand NamesCyclomen®; Danocrine®

Pharmacologic CategoryAndrogen

Use: Labeled IndicationsTreatment of endometriosis, fibrocystic breast disease, and hereditary angioedema

Dosing: Adults

Endometriosis (females): Oral: Initial: 200-400 mg/day in 2 divided doses for mild disease; individualize dosage. Usual maintenance dose: 800 mg/day in 2 divided doses to achieve amenorrhea and rapid response to painful symptoms. Continue therapy uninterrupted for 3-6 months (up to 9 months).

Fibrocystic breast disease (females): Oral: Range: 100-400 mg/day in 2 divided doses

Hereditary angioedema (males/females): Oral: Initial: 200 mg 2-3 times/day; after favorable response, decrease the dosage by 50% or less at intervals of 1-3 months or longer if the frequency of attacks dictates. If an attack occurs, increase the dosage by up to 200 mg/day.

Dosing: ElderlyRefer to adult dosing.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to danazol or any component of the formulation; undiagnosed genital bleeding; pregnancy; breast-feeding; porphyria; markedly impaired hepatic, renal, or cardiac function

Allergy Considerations

- Androgen Allergy

Warnings/Precautions

Boxed warnings:

• Hepatic effects: See “Concerns related to adverse effects” below.

• Intracranial hypertension: See “Concerns related to adverse effects” below.

• Pregnancy: See “Special populations” below.

• Thromboembolic events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

• Androgenic effects: May cause nonreversible androgenic effects.

• Blood lipid changes: Anabolic steroids may cause blood lipid changes with increased risk of arteriosclerosis.

• Hepatic effects: **[U.S. Boxed Warning]: Peliosis hepatis and benign hepatic adenoma have been reported with long-term use** (may be complicated by acute intra-abdominal hemorrhage).

• Intracranial hypertension: **[U.S. Boxed Warning]: May cause benign intracranial hypertension (pseudotumor cerebri);** monitor for headache, nausea/vomiting, visual disturbances and/or papilledema.

• Thromboembolic events: **[U.S. Boxed Warning]: Thromboembolism, thrombotic, and thrombophlebitic events have been reported (including life-threatening or fatal strokes).**

Disease-related concerns:

• Diabetes: Use with caution in patients with diabetes mellitus; monitor carefully.

• Edematous conditions: Use with caution in patients with conditions influenced by edema (eg, cardiovascular disease, migraine, seizure disorder, renal impairment); may cause fluid retention.

- Fibrocystic disease: Breast cancer should be ruled out prior to treatment for fibrocystic breast disease.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Porphyria: Use with caution in patients with a history of porphyria.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: **[U.S. Boxed Warning]: Pregnancy must be ruled out prior to treatment;** a nonhormonal method of contraception should be used during therapy.

Pregnancy Risk FactorX
Pregnancy Considerations**[U.S. Boxed Warning]: Pregnancy should be ruled out prior to treatment** using a sensitive test (beta subunit test, if available). Nonhormonal contraception should be used during therapy. May cause androgenic effects to the female fetus; clitoral hypertrophy, labial fusion, urogenital sinus defect, vaginal atresia, and ambiguous genitalia have been reported.
LactationEnters breast milk/contraindicated
Adverse ReactionsFrequency not defined.

Cardiovascular: Benign intracranial hypertension (rare), edema, flushing, hypertension

Central nervous system: Anxiety (rare), chills (rare), convulsions (rare), depression, dizziness, emotional lability, fainting, fever (rare), Guillain-Barré syndrome, headache, nervousness, sleep disorders, tremor

Dermatologic: Acne, hair loss, mild hirsutism, maculopapular rash, papular rash, petechial rash, pruritus, purpuric rash, seborrhea, Stevens-Johnson syndrome (rare), photosensitivity (rare), urticaria, vesicular rash

Endocrine & metabolic: Amenorrhea (which may continue post therapy), breast size reduction, clitoris hypertrophy, glucose intolerance, HDL decreased, LDL increased, libido changes, nipple discharge, menstrual disturbances (spotting, altered timing of cycle), semen abnormalities (changes in volume, viscosity, sperm count/motility), spermatogenesis reduction

Gastrointestinal: Appetite changes (rare), bleeding gums (rare), constipation, gastroenteritis, nausea, pancreatitis (rare), vomiting, weight gain

Genitourinary: Vaginal dryness, vaginal irritation, pelvic pain

Hematologic: Eosinophilia, erythrocytosis (reversible), leukocytosis, leukopenia, platelet count increased, polycythemia, RBC increased, thrombocytopenia

Hepatic: Cholestatic jaundice, hepatic adenoma, jaundice, liver enzymes increased, malignant tumors (after prolonged use), peliosis hepatis

Neuromuscular & skeletal: Back pain, carpal tunnel syndrome (rare), extremity pain, joint lockup, joint pain, joint swelling, muscle cramps, neck pain, paresthesia, spasms, weakness

Ocular: Cataracts (rare), visual disturbances

Renal: Hematuria

Respiratory: Nasal congestion (rare)

Miscellaneous: Diaphoresis, voice change (hoarseness, sore throat, instability, deepening of pitch)

Metabolism/Transport Effects**Inhibits** CYP3A4 (weak)
Drug Interactions

CarBAMazepine: Danazol may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

CycloSPORINE: Androgens may enhance the hepatotoxic effect of CycloSPORINE. Androgens may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: Danazol may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Pravastatin; Rosuvastatin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Androgens may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Delays time to peak; high-fat meal increases plasma concentration
Test InteractionsTestosterone, androstenedione, dehydroepiandrosterone
Monitoring ParametersSigns and symptoms of intracranial hypertension (papilledema, headache, nausea, vomiting), lipoproteins, androgenic changes, hepatic function
Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions (eg, anticoagulants and hypoglycemic agents). Assess results of laboratory tests, therapeutic effectiveness (according to purpose for use), and adverse response (eg, hypertension, increased LDL, CNS changes, jaundice, hematuria). Caution patients with diabetes to monitor glucose levels closely (may enhance the glucose-lowering effect of hypoglycemic agents). Teach patient proper use, possible side effects/appropriate interventions (eg, good self-breast-exam technique), and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to female patients of childbearing age unless capable of complying with barrier contraceptive use. Instruct patient in appropriate contraceptive measures.
Monitoring: Lab TestsLiver and renal function
Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. Take as directed; do not discontinue without consulting prescriber.

Therapy may take up to several months depending on purpose for therapy. If you have diabetes, monitor serum glucose closely and notify prescriber of changes; this medication can alter hypoglycemic requirements. Consult prescriber for appropriate self-breast-exam technique. May cause headache, sleeplessness, anxiety (use caution when driving or engaging in potentially hazardous tasks until response to drug is known); acne, growth of body hair, deepening of voice, loss of libido, impotence, or menstrual irregularity (usually reversible). Report changes in menstrual pattern; deepening of voice or unusual growth of body hair; persistent penile erections; fluid retention (eg, swelling of ankles, feet, or hands, respiratory difficulty, or sudden weight gain); change in color of urine or stool; yellowing of eyes or skin; unusual bruising or bleeding; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. This drug may cause severe fetal defects. Do not donate blood during or for 1 month following therapy. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule: 50 mg, 100 mg, 200 mg

Danocrine®: 50 mg, 100 mg, 200 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Danazol)

50 mg (30): $52.99

100 mg (30): $68.60

200 mg (30): $110.76

Mechanism of ActionSuppresses pituitary output of follicle-stimulating hormone and luteinizing hormone that causes regression and atrophy of normal and ectopic endometrial tissue; decreases rate of growth of abnormal breast tissue; reduces attacks associated with hereditary angioedema by increasing levels of C4 component of complement

Pharmacodynamics/Kinetics

Onset of action: Therapeutic: ~4 weeks

Metabolism: Extensively hepatic, primarily to 2-hydroxymethylethisterone

Half-life elimination: 4.5 hours (variable)

Time to peak, serum: Within 2 hours

Excretion: Urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

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Makdisi WJ, Cherian R, Vanveldhuizen PJ, et al, “Fatal Peliosis of the Liver and Spleen in a Patient With Agnogenic Myeloid Metaplasia Treated With Danazol,” *Am J Gastroenterol*, 1995, 90(2):317-8. [PubMed 7847311]

Saenger P, “Abnormal Sex Differentiation,” *J Pediatr*, 1984, 104(1):1-17. [PubMed 6361226]

Weinblatt ME, Kochen J, and Ortega J, “Danazol for Children With Immune Thrombocytopenic Purpura,” *Am J Dis Child*, 1988, 142(12):1317-9.[PubMed 3195531]

International Brand NamesAnargil (HK, MY, TH); Azol (AU, MY); Cyclolady (TW); D-Zol (NZ); Danasin (TR); Danatrol (BE, CH, ES, FR, GR, IT, LU, NL, PT); Danazol (KP, PL); Danazol Jean Marie (HK); Danazol-ratiopharm (DE); Danocrine (BB, BM, BS, BZ, DK, FI, GY, HK, ID, JM, NL, NO, PK, SE, SR, TT); Danodiol (AE, BB, BH, BM, BS, BZ, CY, EG, GH, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LY, MU, NL, OM, PR, QA, SA, SR, SY, TT, TZ, YE); Danogar (CN); Danogen (HN, IN, RU); Danokrin (AT); Danol (AE, BH, CY, CZ, EE, EG, GB, HN, IE, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Danol-Danazol (PL); Danoval (BG, HN, HR, HU, PL); Dorink (TW); Ectopal (TH, TW); Gonablok (IN); Ladazol (ZA); Ladogal (AR, BR, CO, MX, MY, PE, PH, TH, TW, UY, VE); Mastodanatrol (PT); Novaprin (MX); Vabon (TH); Winobanin (DE); Zendol (IN)

Dantrolene

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Dantrium® may be confused with danazol, Daraprim®

Pronunciation(DAN troe leen)

U.S. Brand NamesDantrium®

Canadian Brand NamesDantrium®

Pharmacologic CategorySkeletal Muscle Relaxant

Use: Labeled IndicationsTreatment of spasticity associated with spinal cord injury, stroke, cerebral palsy, or multiple sclerosis; treatment of malignant hyperthermia

Use: Unlabeled/InvestigationalNeuroleptic malignant syndrome (NMS)

Dosing: Adults

Spasticity: Oral: 25 mg/day to start, increase frequency to 2-4 times/day, then increase dose by 25 mg every 4-7 days to a maximum of 100 mg 2-4 times/day or 400 mg/day

Malignant hyperthermia:

Preoperative prophylaxis:

Oral: 4-8 mg/kg/day in 4 divided doses, begin 1-2 days prior to surgery with last dose 3-4 hours prior to surgery

I.V.: 2.5 mg/kg ~$1^{1}/_{4}$ hours prior to anesthesia and infused over 1 hour with additional doses as needed and individualized

Crisis: I.V.: 2.5 mg/kg; may repeat dose up to cumulative dose of 10 mg/kg; if physiologic and metabolic abnormalities reappear, repeat regimen

Postcrisis follow-up: Oral: 4-8 mg/kg/day in 4 divided doses for 1-3 days; I.V. dantrolene may be used when oral therapy is not practical; individualize dosage beginning with 1 mg/kg or more as the clinical situation dictates

Neuroleptic malignant syndrome (unlabeled use): I.V.: 1 mg/kg; may repeat dose up to maximum cumulative dose of 10 mg/kg, then switch to oral dosage

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Spasticity: Oral: Initial: 0.5 mg/kg/dose twice daily, increase frequency to 3-4 times/day at 4- to 7-day intervals, then increase dose by 0.5 mg/kg to a maximum of 3 mg/kg/dose 2-4 times/day up to 400 mg/day

Malignant hyperthermia: Refer to adult dosing.

Administration: I.V.Therapeutic or emergency dose can be administered with rapid continuous I.V. push. Follow-up doses should be administered over 2-3 minutes.

Administration: I.V. DetailAvoid extravasation; tissue irritant. 36 vials are needed for adequate hyperthermia therapy.

ReconstitutionReconstitute vial by adding 60 mL of sterile water for injection USP (**not bacteriostatic water for injection**). Protect from light. Use within 6 hours; avoid glass bottles for I.V. infusion.

Extemporaneously PreparedA 5 mg/mL suspension may be made by adding five 100 mg capsules to a citric acid solution (150 mg citric acid powder in 10 mL water) and then adding syrup to a total volume of 100 mL; stable 2 days in refrigerator

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, 1st ed, Cincinnati, OH: Harvey Whitney Books Co, 1990.

ContraindicationsActive hepatic disease; should not be used where spasticity is used to maintain posture or balance

Warnings/Precautions

Boxed warnings:

- Hepatotoxicity: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Hepatotoxicity: **[U.S. Boxed Warning]: Has potential for hepatotoxicity.** Overt hepatitis has been most frequently observed between the third and twelfth month of therapy. Hepatic injury appears to be greater in females and in patients >35 years of age. Idiosyncratic and hypersensitivity reactions (sometimes fatal) of the liver have also occurred.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with impaired cardiac function.
- Respiratory disease: Use with caution in patients with impaired pulmonary function.

Geriatric ConsiderationsThere is little experience with this drug in the elderly.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Central nervous system: Drowsiness, dizziness, lightheadedness, fatigue

Dermatologic: Rash

Gastrointestinal: Diarrhea (mild), nausea, vomiting

Neuromuscular & skeletal: Muscle weakness

1% to 10%:

Cardiovascular: Pleural effusion with pericarditis

Central nervous system: Chills, fever, headache, insomnia, nervousness, mental depression

Gastrointestinal: Diarrhea (severe), constipation, anorexia, stomach cramps

Ocular: Blurred vision

Respiratory: Respiratory depression

<1%: Seizure, confusion, hepatitis, hepatic necrosis

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersMotor performance should be monitored for therapeutic outcomes; nausea, vomiting, and liver function tests should be monitored for potential hepatotoxicity; intravenous administration requires cardiac monitor and blood pressure monitor

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. **I.V.:** Monitor vital signs, cardiac function, respiratory status, and I.V. site (extravasation very irritating to tissues). Monitor effectiveness of therapy and adverse reactions at beginning and periodically during therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsLiver function for potential hepatotoxicity

Patient EducationTake exactly as directed. Do not increase dose or discontinue without consulting prescriber. Do not use alcohol, prescriptive or OTC antidepressants, sedatives, or pain medications without consulting prescriber. You may experience drowsiness, dizziness, lightheadedness (avoid driving or engaging in tasks that require alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, or sucking hard candy may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report excessive confusion; drowsiness or mental agitation; chest pain, palpitations, or respiratory difficulty; skin rash; or vision changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as sodium: 25 mg, 50 mg, 100 mg

Dantrium®: 25 mg, 50 mg, 100 mg

Injection, powder for reconstitution, as sodium:

Dantrium®: 20 mg [contains mannitol 3 g]

Generic AvailableYes: Capsule
ManufacturerProcter & Gamble Co
Pricing: U.S. (www.drugstore.com)

Capsules (Dantrium)

25 mg (45): $58.99

50 mg (45): $81.99

100 mg (45): $99.99

Capsules (Dantrolene Sodium)

25 mg (30): $31.99

50 mg (45): $63.99

100 mg (45): $66.99

Mechanism of ActionActs directly on skeletal muscle by interfering with release of calcium ion from the sarcoplasmic reticulum; prevents or reduces the increase in myoplasmic calcium ion concentration that activates the acute catabolic processes associated with malignant hyperthermia
Pharmacodynamics/Kinetics

Absorption: Oral: Slow and incomplete

Metabolism: Hepatic

Half-life elimination: 8.7 hours

Excretion: Feces (45% to 50%); urine (25% as unchanged drug and metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDrowsiness is common; may cause insomnia, nervousness, confusion, or depression
Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropic may result in additive sedation; use to treat neuroleptic malignant syndrome
Index TermsDantrolene Sodium
References

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Ward A, Chaffman MO, and Sorkin EM, “Dantrolene: A Review of Its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Use in Malignant Hyperthermia, the Neuroleptic Malignant Syndrome and an Update of Its Use in Muscle Spasticity,” *Drugs*, 1986, 32(2):130-68.[PubMed 3527659]

International Brand NamesAnorex (KP); Dantamacrin (AT, BG, CH, DE); Dantrium (AU, BE, CN, DK, FR, GB, GR, IE, IL, IT, JP, LU, NL, PT, ZA); Dantrolen (AR, AT, BG, BR, CZ, PL, RU)

Dapsone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Dapsone may be confused with Diprosone®

Pronunciation(DAP sone)
U.S. Brand NamesAczone®
Pharmacologic CategoryAntibiotic, Miscellaneous; Topical Skin Product, Acne
Use: Labeled IndicationsTreatment of leprosy and dermatitis herpetiformis (infections caused by *Mycobacterium leprae*); topical treatment of acne vulgaris
Use: Unlabeled/InvestigationalProphylaxis of toxoplasmosis in severely-immunocompromised patients; alternative agent for *Pneumocystis carinii* pneumonia prophylaxis (monotherapy) and treatment (in combination with trimethoprim)
Use: DentalUsed in lupus and in selected ulcerative conditions in consult with patient's physician
Dosing: Adults

Acne: Topical: Apply pea-sized amount (approximately) in a thin layer to affected areas twice daily; reevaluate patient if no improvement after 12 weeks of therapy.

Leprosy: Oral: 50-100 mg/day for 3-10 years

Dermatitis herpetiformis: Oral: Initial: 50 mg/day, increase to 300. mg/day, or higher to achieve full control. Reduce dosage to minimum level as soon as possible.

Pneumonia caused by*Pneumocystis carinii*(unlabeled use): Oral:

Prophylaxis: 100 mg/day

Treatment: Adults: 100 mg/day in combination with trimethoprim (15-20 mg/kg/day) for 21 days

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Acne: Topical: Children ≥12 years: Refer to adult dosing.

Leprosy: Oral: Children: 1-2 mg/kg/24 hours, up to a maximum of 100 mg/day

Prophylaxis of*Pneumocystis carinii*pneumonia (unlabeled use): Oral: Children >1 month: 2 mg/kg/day once daily (maximum dose: 100 mg/day) or 4 mg/kg/dose once weekly (maximum dose: 200 mg)

Dosing: Renal ImpairmentNo guidelines are available.
Administration: OralMay administer with meals if GI upset occurs.
Administration: TopicalTopical: Skin should be clean and dry before applying. Rub in gently and completely. Wash hands after applying. Gel may be gritty. For external use only; avoid applying to inside nose, mouth, eyes, and mucous membranes.
Dietary ConsiderationsOral: Do not give with antacids, alkaline foods, or drugs.
StorageStore at 20°C to 25°C (68°F to 76°F). Protect tablets from light. Do not freeze gel.
Extemporaneously PreparedOne report indicated that dapsone may not be well absorbed when administered to children as suspensions made from pulverized tablets

Mirochnick M, Clarke D, Brenn A, et al, "Low Serum Dapsone Concentrations in Children Receiving an Extemporaneously Prepared Oral Formulation," [Abstract Th B 365], APS-SPR, Baltimore, MD: 1992.

Jacobus Pharmaceutical Company (609) 921-7447 makes a 2 mg/mL proprietary liquid formulation available under an IND for the prophylaxis of *Pneumocystis carinii* pneumonia

ContraindicationsHypersensitivity to dapsone or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Blood dyscrasias: Aplastic anemia, agranulocytosis and other severe blood dyscrasias have resulted in death; monitor carefully.
- Dermatologic reactions: Serious dermatologic reactions (including toxic epidermal necrolysis) are rare but potential occurrences.
- Peripheral neuropathy: Motor loss and muscle weakness have been reported with use.
- Sulfonamide allergy: Use with caution in patients with hypersensitivity to other sulfonamides; sulfone reactions may also occur as

potentially fatal hypersensitivity reactions, these, but not leprosy reactional states, require drug discontinuation.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea and pseudomembranous colitis.

Disease-related concerns:

- Anemia: Use with caution in patients with severe anemia; treat prior to therapy.

Special populations:

- G6PD deficiency: Use with caution in patients with G6PD deficiency.

- Hemoglobin M deficiency: Use with caution in patients with hemoglobin M deficiency.

- Methemoglobin reductase deficiency: Use with caution in patients with methemoglobin reductase deficiency.

- Pediatrics: Safety and efficacy of topical dapsone have not been established in children <12 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use during pregnancy when the benefit to the mother outweighs the potential risk to the fetus.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Adverse ReactionsAdverse reactions reported for oral formulation unless otherwise noted.

>10%: Hematologic: Hemolysis (dose related; seen in patients with and without G6PD deficiency), hemoglobin decrease (1-2 g/dL; almost all patients), reticulocyte increase (2% to 12%), methemoglobinemia, red cell life span shortened

Frequency not always defined.

Cardiovascular: Facial edema (topical), tachycardia

Central nervous system: Depression (topical), fever, headache, insomnia, psychosis (oral/topical), suicide attempt (topical), tonic clonic movement (topical), vertigo

Dermatologic: Bullous and exfoliative dermatitis, erythema nodosum, exfoliative dermatitis, morbilliform and scarlatiniform reactions, phototoxicity, Stevens-Johnson syndrome, toxic epidural necrolysis, urticaria

Endocrine & metabolic: Hypoalbuminemia (without proteinuria), male infertility

Gastrointestinal: Abdominal pain (oral/topical), nausea, pancreatitis (oral/topical), vomiting (oral/topical)

Hematologic: Agranulocytosis, anemia, leukopenia, pure red cell aplasia (case report)

Hepatic: Cholestatic jaundice, hepatitis

Neuromuscular & skeletal: Drug-induced lupus erythematosus, lower motor neuron toxicity (prolonged therapy), peripheral neuropathy (rare, nonleprosy patients)

Ocular: Blurred vision

Otic: Tinnitus

Renal: Albuminuria, nephrotic syndrome, renal papillary necrosis

Respiratory: Interstitial pneumonitis, pulmonary eosinophilia, sinusitis (topical 2%)

Miscellaneous: Infectious mononucleosis-like syndrome (rash, fever, lymphadenopathy, hepatic dysfunction)

Metabolism/Transport Effects**Substrate** of CYP2C8 (minor), 2C9 (major), 2C19 (minor), 2E1 (minor), 3A4 (major)

Drug Interactions

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Didanosine: May decrease the absorption of Dapsone. Didanosine enteric coated capsules should not affect dapsone. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Dapsone. *Risk D: Consider therapy modification*

Trimethoprim: May increase the serum concentration of Dapsone. Dapsone may increase the serum concentration of Trimethoprim. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Dapsone. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease dapsone levels.

Monitoring Parameters

Oral: Check G6PD levels prior to initiation. Monitor patients for signs of jaundice and hemolysis; CBC weekly for first month, monthly for 6 months and semiannually thereafter.

Topical: For patients at risk of anemia, monitor with CBC, reticulocyte counts at baseline and routinely thereafter.

Nursing: Physical Assessment/MonitoringUse with caution and monitor closely in patients with severe anemia, G6PD deficiency, hepatic function impairment. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking. Assess results of laboratory tests (CBC and LFT), therapeutic effectiveness (according to purpose for use), and adverse response. Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsLiver function, CBC, reticulocyte counts

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed; do not discontinue without consulting prescriber. Do not take with antacids, alkaline foods, or other medication. Therapy may take 3-10 years for leprosy. Frequent blood tests may be required. If rash develops, discontinue and notify prescriber. Report persistent sore throat, fever, chills; constant fatigue; yellowing of skin or eyes; or easy bruising or bleeding. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel, topical:

Aczone®: 5% (30 g)

Tablet: 25 mg, 100 mg

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Tablets (Dapsone)

25 mg (30): $15.99

100 mg (30): $15.99

Mechanism of ActionCompetitive antagonist of para-aminobenzoic acid (PABA) and prevents normal bacterial utilization of PABA for the synthesis of folic acid

Pharmacodynamics/Kinetics

Absorption:

Oral: Well absorbed

Topical: ~1% of the absorption of 100 mg tablet

Distribution: V_d: 1.5 L/kg; throughout total body water and present in all tissues, especially liver and kidney

Metabolism: Hepatic; forms metabolite

Half-life elimination: 30 hours (range: 10-50 hours)

Excretion: Urine (~85%)

Related Information

- Antimicrobial Drugs of Choice
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDiaminodiphenylsulfone

References

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Stavola JJ and Noel GJ, “Efficacy and Safety of Dapsone Prophylaxis Against *Pneumocystis carinii* Pneumonia in Human Immunodeficiency Virus-Infected Children,” *Pediatr Infect Dis J*, 1993, 12(8):644-7.[PubMed 8414776]

Tracqui A, Gutbub AM, Kintz P, et al, “A Case of Acute Dapsone Poisoning: Toxicological Data and Review of the Literature,” *J Anal Toxicol*, 1995, 19(4):229-35.[PubMed 8531468]

Wynn RF, Laing RB, and Leen CL, “Case Report of Dapsone-Related Thrombocytosis in an AIDS Patient,” *Am J Med*, 1995, 98(6):602.[PubMed 7778582]

International Brand NamesDaps (AR); Dapsoderm-X (MX); Dapson (DK, EG, NL, NO); Dapson-Fatol (DE); Dapsona (PY); Dapsone (AU); Disulone (CZ); Dopsan (TH); Lennon-Dapsone (ZA); Lepravir (PH); Sulfona (PT)

DAPTOmycin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Impurity Found in Daptomycin Stored in ReadyMED® Elastomeric Infusion Pumps - April 2008

Cubist Pharmaceuticals, Inc is informing Healthcare Professionals of the presence of 2-mercaptobenzothiazole (MBT) found in reconstituted daptomycin (Cubicin®) solutions stored in ReadyMED® elastomeric infusion pumps (Cardinal Health, Inc). This impurity has been associated with dermal sensitization (cutaneous exposure) and tumorigenesis (chronic animal exposure) and is believed to leach from rubber components of the pump. Importantly, Cubist investigations have shown that daptomycin is stable, and free from impurities when stored in the Eclipse® pump system (I-Flow Corporation). Additionally, there are no reports of MBT contamination of reconstituted daptomycin used in other standard infusion devices. Until further information is available, the company has advised that daptomycin should not be prepared using the ReadyMED® pump.

Additional information may be found at: http://www.fda.gov/medwatch/safety/2008/safety08.htm#cubicin

Medication Safety Issues

Sound-alike/look-alike issues:

Cubicin® may be confused with Cleocin®

DAPTOmycin may be confused with DACTINomycin

Pronunciation(DAP toe mye sin)
U.S. Brand NamesCubicin®
Canadian Brand NamesCubicin®
Pharmacologic CategoryAntibiotic, Cyclic Lipopeptide
Use: Labeled IndicationsTreatment of complicated skin and skin structure infections caused by susceptible aerobic gram-positive organisms; *Staphylococcus aureus* bacteremia, including right-sided infective endocarditis caused by MSSA or MRSA
Use: Unlabeled/InvestigationalTreatment of severe infections caused by MRSA or VRE
Dosing: Adults

Skin and/or skin structure infections (complicated): I.V.: 4 mg/kg once daily for 7-14 days

Bacteremia, right-sided endocarditis caused by MSSA or MRSA: I.V.: 6 mg/kg once daily for 2-6 weeks

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal Impairment

Cl_{cr} <30 mL/minute:

Skin and soft tissue infections: 4 mg/kg every 48 hours

Staphylococcal bacteremia: 6 mg/kg every 48 hours

Hemodialysis (administer after hemodialysis) and/or CAPD: Dose as in Cl_{cr} <30 mL/minute

Continuous renal replacement therapy (CRRT): Dose as in Cl_{cr} <30 mL/minute

Dosing: Hepatic ImpairmentNo adjustment required for mild-to-moderate impairment (Child-Pugh Class A or B). Not evaluated in severe hepatic impairment.
Calculations

- Creatinine Clearance: Adults

Administration: I.V.Infuse over 30 minutes.
StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F). Reconstituted solution (either in vial or in infusion bag) is stable for a cumulative time of 12 hours at room temperature and 48 hours if refrigerated (2°C to 8°C).
ReconstitutionReconstitute vial with 10 mL NS. Add NS to vial and rotate gently to wet powder. Allow to stand for 10 minutes, then gently swirl to obtain completely reconstituted solution. Do not shake or agitate vial vigorously. Should be further diluted following reconstitution in an appropriate volume of NS.
CompatibilityStable in NS or LR; **incompatible** with dextrose-containing solutions.
ContraindicationsHypersensitivity to daptomycin or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Myopathy: May be associated with an increased incidence of myopathy; discontinue in patients with signs and symptoms of myopathy in conjunction with an increase in CPK (>5 times ULN or 1000 units/L) or in asymptomatic patients with a CPK ≥10 times ULN. Myopathy may occur more frequently at dose and/or frequency in excess of recommended dosages. Use caution in patients receiving other drugs associated with myopathy (eg, HMG-CoA reductase inhibitors).

- Peripheral neuropathy: Symptoms suggestive of peripheral neuropathy have been observed with treatment; monitor for new-onset or worsening neuropathy.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea and pseudomembranous colitis.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Pneumonia use: Not indicated for the treatment of pneumonia due to poor lung penetration.

Geriatric ConsiderationsThe manufacturer reports that in studies of complicated skin and skin structure infections, elderly patients had a lower clinical success rate and a higher incidence of adverse effects (no quantitative data provided in product labeling). Adjust dose in renal impairment.

Pregnancy Risk FactorB

Pregnancy ConsiderationsBecause adverse events were not observed in animal reproduction studies, daptomycin is classified as pregnancy category B. There are no adequate and well-controlled studies in pregnant women

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if daptomycin is excreted in breast milk. The manufacturer recommends caution if daptomycin is used during breast-feeding. The high molecular weight of daptomycin may limit the transfer to the maternal milk. If daptomycin reaches the breast milk, nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- DAPTOmycin in Pregnancy & Lactation

Adverse Reactions

>10%:

Gastrointestinal: Diarrhea (5% to 12%), vomiting (3% to 12%), constipation (6% to 11%)

Hematologic: Anemia (2% to 13%)

1% to 10%:

Cardiovascular: Peripheral edema (7%), chest pain (7%), hypertension (1% to 6%), hypotension (2% to 5%)

Central nervous system: Insomnia (5% to 9%), headache (5% to7%), fever (2% to 7%), dizziness (2% to 6%), anxiety (5%)

Dermatologic: Rash (4% to 7%), pruritus (3% to 6%), erythema (5%)

Endocrine & metabolic: Hypokalemia (9%), hyperkalemia (5%), hyperphosphatemia (3%)

Gastrointestinal: Nausea (6% to 10%), abdominal pain (6%), dyspepsia (1% to 4%), loose stool (4%), GI hemorrhage (2%)

Genitourinary: Urinary tract infection (2% to 7%)

Hematologic: INR increased (2%), eosinophilia (2%)

Hepatic: Transaminases increased (2% to 3%), alkaline phosphatase increased (2%)

Local: Injection site reaction (3% to 6%)

Neuromuscular & skeletal: CPK increased (3% to 9%), limb pain (2% to 9%), back pain (7%), weakness (5%), arthralgia (1% to 3%)

Renal: Renal failure (2% to 3%)

Respiratory: Pharyngolaryngeal pain (8%), pleural effusion (6%), cough (3%), pneumonia (3%), dyspnea (2% to 3%)

Miscellaneous: Osteomyelitis (6%), bacteremia (5%), diaphoresis (5%), sepsis (5%), infection (fungal, 2% to 3%)

<1%: Appetite decreased, arthralgia, atrial fibrillation, atrial flutter, cardiac arrest, dyskinesia, dysphagia, eczema, electrolyte disturbance, eosinophilia, erythema (truncal), eye irritation, fatigue, flatulence, flushing, GI discomfort, gingival pain, hallucination, hives, hypomagnesemia, hypersensitivity, hypoesthesia, jaundice, jitteriness, LDH increased, leukocytosis, lymphadenopathy, mental status change, muscle cramps, muscle weakness, myalgia, osteomyelitis, paresthesia, proteinuria, prothrombin time prolonged, rigors, serum bicarbonate increased, stomatitis, supraventricular arrhythmia, taste disturbance, thrombocytopenia, thrombocythemia, tinnitus, vertigo, vision blurred, xerostomia

Postmarketing and/or case reports: Anaphylaxis, rhabdomyolysis

Drug Interactions

HMG-CoA Reductase Inhibitors: May enhance the adverse/toxic effect of DAPTOmycin. Specifically, the risk of skeletal muscle toxicity may be increased. Management: Consider temporarily stopping HMG-CoA reductase inhibitor therapy prior to daptomycin. If used together, regular (i.e., at least weekly) monitoring of CPK concentrations is recommended. *Risk D: Consider therapy modification*

Test InteractionsDaptomycin may cause false prolongation of the PT and increase of INR with certain reagents. This appears to be a dose-dependent phenomenon. Therefore, it is recommended to obtain blood samples immediately prior to next daptomycin dose (eg, trough). If PT/INR elevated, clinicians should repeat PT/INR and evaluate for other causes of hypocoagulation.

Monitoring ParametersMonitor signs and symptoms of infection. CPK should be monitored at least weekly during therapy; more frequent monitoring if current or prior statin therapy, unexplained CPK increases, and/or renal impairment. Monitor for muscle pain or weakness, especially if noted in distal extremities.

Reference Range

Trough concentrations at steady-state:

4 mg/kg once daily: 5.9 ± 1.6 mcg/mL

6 mg/kg once daily: 6.7 ± 1.6 mcg/mL

Note: Trough concentrations are not predictive of efficacy/toxicity. Drug exhibits concentration-dependent bactericidal activity, so C_{max}:MIC ratios may be a more useful parameter.

Nursing: Physical Assessment/MonitoringUse caution in presence of myopathy. Assess potential for interactions with other pharmacological agents (eg, HMG-CoA reductase inhibitors). Assess results of laboratory tests (CPK), therapeutic effectiveness (eg, signs and symptoms of infection), and adverse reactions at beginning of therapy and on a regular basis during therapy. Should be infused over 30 minutes. Teach patient possible side effects and adverse symptoms to report (eg, rash, hypotension, CNS changes, limb pain, muscle pain or weakness, opportunistic infection).

Monitoring: Lab TestsCPK should be monitored at least weekly during therapy; more frequent monitoring if current or prior statin therapy, unexplained CPK increases, and/or renal impairment

Patient EducationThis medication can only be administered via intravenous infusion. You will be monitored during and after each infusion. Report immediately any burning, pain, or redness at infusion site, any throat tightness, respiratory difficulty, or chest tightness. Use caution when driving or engaging in tasks that require mental alertness until response to drug is known. Report unusual headache, insomnia, nausea or vomiting, persistent diarrhea, limb or joint pain, alteration in urination patterns, itching or pain on urination, or other possible adverse reactions. **Breast-feeding precaution:** Inform prescriber if you are or intend to breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Cubicin®: 500 mg

Generic AvailableNo

ManufacturerCubist Pharmaceutical, Inc

Mechanism of ActionDaptomycin binds to components of the cell membrane of susceptible organisms and causes rapid depolarization, inhibiting intracellular synthesis of DNA, RNA, and protein. Daptomycin is bactericidal in a concentration-dependent manner.

Pharmacodynamics/Kinetics

Distribution: 0.1 L/kg

Protein binding: 90% to 93%; 84% to 88% in patients with Cl_{cr}<30 mL/minute

Half-life elimination: 8-9 hours (up to 28 hours in renal impairment)

Excretion: Urine (78%; primarily as unchanged drug); feces (6%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia or dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause nausea, vomiting, and diarrhea; concurrent use with SSRIs may produce additive effects

Index TermsCidecin; Dapcin; LY146032

References

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Silverman JA, Perlmutter NG, and Shapiro HM, “Correlation of Daptomycin Bactericidal Activity and Membrane Depolarization in *Staphylococcus aureus*,” *Antimicrob Agents Chemother*, 2003, 47(8):2538-44. [PubMed 12878516]

Tedesco KL and Rybak MJ, “Daptomycin,” *Pharmacotherapy*, 2004, 24(1):41-57.[PubMed 14740787]

Trotman RL, Williamson JC, Shoemaker DM, et al, "Antibiotic Dosing in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy," *Clin Infect Dis*, 2005, 41(8):1159-66.[PubMed 16163635]

International Brand Names Cubicin (AR, AT, BE, BG, CH, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HN, IE, IL, IT, NL, NO, PT, RU, SE, TR, TW)

Darbepoetin Alfa

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Erythropoietin (Epogen®/Procrit®) and Darbepoetin (Aranesp®): Labeling Updates, Including Boxed Warning Revisions Regarding Use in Patients With Cancer - Updated September 2008

The U.S. Food and Drug Administration (FDA), Amgen Inc, and Ortho Biotech have issued a “Dear Health Care Professional” letter alerting practitioners of revised labeling for erythropoiesis-stimulating agents (ESAs) (epoetin alfa [Epogen®, Procrit®] and darbepoetin alfa [Aranesp®]). The labeling for these products has been updated, including changes to the indications, boxed warnings, and dosing reflecting that ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is curative and ESA therapy should not be initiated if the hemoglobin level is ≥10 g/dL. Medication guides have been developed to communicate the risks and benefits of ESAs for patients.

Prompted by information from studies on ESA use, over the last year there have been alerts, new labeling and/or “Dear Health Care Professional” letters issued regarding ESA use in both patients with cancer and patients with chronic renal failure. The studies in patients with cancer provided evidence of shortened time to tumor progression and increased mortality (decreased overall survival) in cancer patients (breast, cervical, head and neck, lymphoid, and nonsmall cell lung cancer) who received ESAs; however, in some studies, the ESA doses were targeted to maintain hemoglobin levels ≥12 g/dL. Based on this risk, as well as the risk of serious cardio- and thrombovascular events, labeling revisions have included recommendations from FDA advisory committees on appropriate ESA use in cancer and chronic renal failure patients and have consisted of expanded and/or strengthened boxed warnings, safety information, and revised dosing information. Practitioners are reminded that ESA use is only appropriate in the treatment of anemia in cancer patients due to concomitant chemotherapy, and therapy should be discontinued following completion of chemotherapy.

Boxed warning changes concerning use in chronic renal failure patients have included data from two studies showing an increased risk of death and serious cardiovascular events when ESAs were administered to achieve higher target hemoglobin compared with lower hemoglobin levels (13.5 vs 11.3 g/dL and 14 vs 10 g/dL). Dosing recommendations for chronic renal failure now specify a target hemoglobin range of 10-12 g/dL to achieve and maintain, including guidelines for increasing doses in patients not achieving recommended target hemoglobin range. Additional recommendations have been created for those patients unable to achieve the target hemoglobin range (despite appropriate titrations) with precautions against continuing to increase the dose and a consideration of ESA discontinuation.

The FDA Medwatch alerts and a link to the most recent “Dear Healthcare Professional” letter can be found at

http://www.fda.gov/medwatch/safety/2008/safety08.htm#ESA2

http://www.fda.gov/medwatch/safety/2008/safety08.htm#ESA

Medication Safety Issues

Sound-alike/look-alike issues:

Aranesp® may be confused with Aralast, Aricept®

Darbepoetin alfa may be confused with dalteparin, epoetin alfa, epoetin beta

Pronunciation(dar be POE e tin AL fa)

U.S. Brand NamesAranesp®

Canadian Brand NamesAranesp®

Pharmacologic CategoryColony Stimulating Factor; Growth Factor; Recombinant Human Erythropoietin

Use: Labeled IndicationsTreatment of anemia (elevate/maintain red blood cell level and decrease the need for transfusions) associated with chronic renal failure (including patients on dialysis and not on dialysis); treatment of anemia due to concurrent chemotherapy in patients with metastatic cancer (nonmyeloid malignancies)

Note: Darbepoetin is **not** indicated for use in cancer patients under the following conditions:

- receiving hormonal therapy, therapeutic biologic products, or radiation therapy unless also receiving concurrent myelosuppressive chemotherapy
- receiving myelosuppressive therapy when the expected outcome is curative

Use: Unlabeled/InvestigationalTreatment of symptomatic anemia in myelodysplastic syndrome (MDS)

Dosing: Adults**Note:** Hemoglobin levels should not exceed 12 g/dL and should not rise >1 g/dL per 2-week time period during therapy in any patient.

Anemia associated with CRF: Individualize dosing to achieve and maintain hemoglobin levels to a target range of 10-12 g/dL. Hemoglobin levels should not exceed 12 g/dL.

I.V., SubQ: Initial: 0.45 mcg/kg once weekly; alternative dose for nondialysis patients: 0.75 mcg/kg once every 2 weeks; Maintenance: titrate to maintain hemoglobin levels between 10-12 g/dL as described below (may be administered once weekly or every 2 weeks; nondialysis patients may require lower maintenance doses) **Note:** I.V. route is preferred in hemodialysis patients.

Dosage adjustment:

Decrease dose by ~25%: If hemoglobin approaches 12 g/dL **or** hemoglobin increases >1 g/dL in any 2-week period. If hemoglobin continues to increase, temporarily discontinue therapy until hemoglobin begins to decrease, then resume therapy with a ~25% reduction from previous dose.

Increase dose by ~25%: If hemoglobin does not increase by 1 g/dL after 4 weeks of therapy (with adequate iron stores). Do not increase dose more frequently than at 4-week intervals.

Inadequate or lack of response: If patient does not attain target hemoglobin range of 10-12 g/dL after appropriate dose titrations over 12 weeks:

Do not continue to increase dose and use the minimum effective dose that will maintain a hemoglobin level sufficient to avoid red blood cell transfusions **and** evaluate patient for other causes of anemia.

Monitor hemoglobin closely thereafter and if responsiveness improves, may resume making dosage adjustments as recommended above. If responsiveness does not improve and recurrent red blood cell transfusions continue to be needed, discontinue therapy.

Maintenance dose: Individualize to target hemoglobin range of 10-12 g/dL; limit additional dosage increase to every 4 weeks or longer. Patients generally require lower maintenance doses than initial doses to maintain target range.

Conversion from epoetin alfa: I.V., SubQ: Initial dose: Epoetin alfa doses may be converted to doses ranging from 6.25-200 mcg darbepoetin alfa per week (see conversion table below).

Anemia associated with chemotherapy: Titrate dosage to use the minimum effective dose that will maintain a hemoglobin level sufficient to avoid red blood cell transfusions. Do not initiate therapy if hemoglobin ≥10 g/dL. Discontinue darbepoetin following completion of chemotherapy.

SubQ: Initial: 2.25 mcg/kg once weekly **or** 500 mcg once every 3 weeks

Dosage adjustment:

Increase dose: If hemoglobin does not increase by 1 g/dL after 6 weeks of therapy (for patients receiving weekly therapy), the dose should be increased up to 4.5 mcg/kg once weekly

Decrease dose by 40%: If hemoglobin increases >1g/dL in any 2-week period **or** hemoglobin reaches a level sufficient to avoid red blood cell transfusion.

Withhold dose: If hemoglobin exceeds a level needed to avoid red blood cell transfusion. Resume treatment with a dose 40% below the previous dose when hemoglobin approaches a level where transfusions may be required.

Discontinue: On completion of chemotherapy or if after 8 weeks of therapy there is no hemoglobin response or transfusions still required

Anemia associated with MDS (unlabeled use): Adults: SubQ: 150-300 mcg once weekly

Conversion from epoetin alfa to darbepoetin alfa: See table.

Conversion From Epoetin Alfa to Darbepoetin Alfa (Initial Dose)

Previous Dosage of Epoetin Alfa (units/week)	**Children Darbepoetin Alfa Dosage (mcg/week)**	**Adults Darbepoetin Alfa Dosage (mcg/week)**
<1500	Not established	6.25
1500-2499	6.25	6.25
2500-4999	10	12.5
5000-10,999	20	25

11,000-17,999	40	40
18,000-33,999	60	60
34,000-89,999	100	100
≥90,000	200	200

Note: In patients receiving epoetin alfa 2-3 times per week, darbepoetin alfa is administered once weekly. In patients receiving epoetin alfa once weekly, darbepoetin alfa is administered once every 2 weeks. The darbepoetin dose to be administered every 2 weeks is derived by adding together 2 weekly epoetin alfa doses and then converting to the appropriate darbepoetin dose. Titrate dose to hemoglobin response thereafter.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Hemoglobin levels should not exceed 12 g/dL and should not rise >1 g/dL per 2-week time period during therapy in any patient.

Anemia associated with CRF: I.V. (preferred for hemodialysis patients), SubQ:

Children ≥1 year: Conversion from epoetin alfa: Initial dose: Epoetin alfa doses of 1500 to ≥90,000 units per week may be converted to doses ranging from 6.25-200 mcg darbepoetin alfa per week (see pediatric column in conversion table below).

Children 11-18 years: Initial treatment (unlabeled use): Initial dose: 0.45 mcg/kg once weekly; titrate to hemoglobin response

Anemia associated with chemotherapy: SubQ: Children (unlabeled use): 2.25 mcg/kg once weekly (discontinue following completion of chemotherapy course)

Dosage adjustment: Refer to adult dosing.

Dosing: Renal ImpairmentDosage requirements for patients with chronic renal failure who do not require dialysis may be lower than in dialysis patients. Monitor patients closely during the time period in which a dialysis regimen is initiated, dosage requirement may increase. The National Kidney Foundation Clinical Practice Guidelines for Anemia in Chronic Kidney Disease: 2007 Update of Hemoglobin Target (September, 2007) recommend hemoglobin levels in the range of 11-12 g/dL for dialysis and nondialysis patients receiving ESAs; hemoglobin levels should not be maintained >13 g/dL.

Hemodialysis: I.V. route is preferred in hemodialysis patients.

Calculations

- EPO to Aranesp

Administration: I.V.May be administered by I.V. injection. The I.V. route is recommended in hemodialysis patients. Do not shake; vigorous shaking may denature darbepoetin alfa, rendering it biologically inactive. Do not dilute or administer in conjunction with other drug solutions. Discard any unused portion of the vial; do not pool unused portions.

Administration: OtherMay be administered SubQ.

Dietary ConsiderationsSupplemental iron intake may be required in patients with low iron stores.

StorageStore at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light.

CompatibilityDo not dilute or administer with other solutions.

RestrictionsAn FDA-approved medication guide is available; distribute to each patient to whom this medication is dispensed.

ContraindicationsHypersensitivity to darbepoetin or any component of the formulation; uncontrolled hypertension

Warnings/Precautions

Boxed warnings:

- Cancer patients: See “Disease-related concerns” below.
- Cardiovascular events/mortality/thromboembolic events: See “Concerns related to adverse effects” below.
- Chronic renal failure patients: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Allergic reactions: Potentially serious allergic reactions have been reported, including rash and urticaria.
- Cardiovascular events/mortality/thromboembolic events: **[U.S. Boxed Warning]: ESAs increased the risk of serious cardiovascular events, thromboembolic events, and mortality** in clinical studies; a rapid rise in hemoglobin (>1 g/dL over 2 weeks) or maintaining higher hemoglobin levels may contribute to these risks.
- Pure red cell aplasia (PRCA): Cases of severe anemia and PRCA have been reported, predominantly in patients with CRF receiving SubQ darbepoetin (the I.V. route is preferred for hemodialysis patients). Patients with loss of response should be evaluated for pure red cell aplasia with associated neutralizing antibodies to erythropoietin; discontinue treatment in patients with PRCA secondary to neutralizing antibodies to erythropoietin. Antibodies may cross-react; do not switch to another ESA in patients who develop antibody-mediated anemia.

Disease-related concerns:

- Acute anemia: Due to the delayed onset of erythropoiesis, darbepoetin is of no value in the acute treatment of anemia.

- Cancer patients: **[U.S. Boxed Warning]: A shortened overall survival and/or increased risk of time-to-tumor progression or recurrence has been reported in studies with breast, cervical, head and neck, lymphoid, and nonsmall cell lung cancer patients.** It is of note that in these studies, patients received ESAs to a target hemoglobin of ≥12 g/dL; although risk has not been excluded when dosed to achieve a target hemoglobin of <12 g/dL. **[U.S. Boxed Warnings]: To decrease these risks, and risk of cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusions. Use ESAs in cancer patients only for the treatment of anemia related to concurrent chemotherapy; discontinue ESA following completion of the chemotherapy course. ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is curative.**

- Chronic renal failure patients: **[U.S. Boxed Warning]: An increased risk of death and serious cardiovascular events was reported in patients administered ESAs to target higher versus lower hemoglobin levels (13.5 vs 11.3 g/dL; 14 vs 10 g/dL) in two clinical studies; dosing should be individualized to achieve and maintain hemoglobin levels within 10-12 g/dL range.** Hemoglobin rising >1 g/dL in a 2-week period may contribute to the risk. Chronic renal failure patients who exhibit an inadequate hemoglobin response to ESA therapy may be at a higher risk for cardiovascular events and mortality compared to other patients. ESA therapy may reduce dialysis efficacy (due to increase in red blood cells and decrease in plasma volume); adjustments in dialysis parameters may be needed.

- Hematologic diseases: Safety and efficacy in patients with underlying hematologic diseases have not been established, including porphyria, thalassemia, hemolytic anemia, and sickle cell disease.

- Hypertension/cardiovascular disease: Use with caution in patients with a history of hypertension. An excessive rate of rise of hemoglobin may be possibly associated with the exacerbation of hypertension; decrease the darbepoetin dose if the hemoglobin increase exceeds 1 g/dL in any 2-week period. Blood pressure should be controlled prior to start of therapy and monitored closely throughout treatment. Hypertensive encephalopathy has been reported with patients receiving erythropoietic therapy; monitor closely and control blood pressure

- Perisurgery patients: Increased mortality was observed in patients undergoing coronary artery bypass surgery who received epoetin; these deaths were associated with thrombotic events. An increased risk of DVT has been observed in patients treated with epoetin undergoing surgical orthopedic procedures. Darbepoetin is **not** approved for reduction in red blood cell transfusions in patients scheduled for surgical procedures.

- Seizures: Use with caution in patients with a history of seizures. An excessive rate of rise of hemoglobin may be possibly associated with the exacerbation of seizures; decrease the darbepoetin dose if the hemoglobin increase exceeds 1 g/dL in any 2-week period.

Special populations:

- Pediatrics: Safety and efficacy in children with cancer have not been established; children >1 year of age with CRF have been converted from epoetin alfa to darbepoetin.

Dosage form specific issues:

- Albumin: Product may contain albumin, which confers a theoretical risk of transmission of viral disease or Creutzfeldt-Jakob disease.

- Autoinjectors: Autoinjectors are designed to deliver entire contents; do not use if partial contents are required for dose (use prefilled syringe or vial).

- Latex: The packaging of some formulations may contain latex.

Other warnings/precautions:

- Acute correction: Not recommended for acute correction of severe anemia or as a substitute for transfusion.

- Appropriate use: Hemoglobin levels should not exceed a target range of 10-12 g/dL and should not rise >1 g/dL per 2-week time period during therapy in any patient.

- Factors impairing erythropoiesis: Prior to treatment, correct or exclude deficiencies of iron, vitamin B_{12}, and/or folate, as well as other factors which may impair erythropoiesis (aluminum toxicity, inflammatory conditions, infections). Poor response to therapy should prompt evaluation of potential factors impairing erythropoiesis, as well as possible malignant processes, occult blood loss, hemolysis, and/or bone marrow fibrosis.

- Iron supplementation: Prior to and during therapy, iron stores must be evaluated. Supplemental iron is recommended if serum ferritin <100 mcg/L or serum transferrin saturation <20%.

Pregnancy Risk FactorC
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Darbepoetin alfa should be used in a pregnant woman only if potential benefit justifies the potential risk to the fetus.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%:

Cardiovascular: Edema (21%), hypertension (4% to 20%), hypotension (20%)

Central nervous system: Fatigue (9% to 33%), fever (4% to 19%), headache (12% to 16%), dizziness (7% to 14%)

Gastrointestinal: Diarrhea (14% to 22%), constipation (5% to 18%), vomiting (2% to 14%), nausea (11%)

Neuromuscular & skeletal: Muscle spasm (17%), arthralgia (9% to 13%)

Respiratory: Upper respiratory infection (15%)

Miscellaneous: Infection (24%)

1% to 10%:

Cardiovascular: Peripheral edema (10%), arrhythmia/arrest (8%), angina/chest pain (7% to 8%), fluid overload (6%), thrombosis (6%), CHF (5%), MI (2%)

Central nervous system: Stroke (2%), seizure (≤1%), TIA (≤1%)

Dermatologic: Rash (7%), pruritus (6%)

Endocrine & metabolic: Dehydration (3% to 5%)

Gastrointestinal: Abdominal pain (10%)

Local: Vascular access hemorrhage (7%), injection site pain (6%), vascular access infection (6%), vascular access thrombosis (6%)

Neuromuscular & skeletal: Limb pain (8%), myalgia (8%), back pain (7%), weakness (5%)

Respiratory: Dyspnea (2% to 10%), cough (9%), bronchitis (5%), pneumonia (3%), pulmonary embolism (1%)

Miscellaneous: Death (7% to 10 %; similar to placebo), flu-like syndrome (6%)

<1%, postmarketing, and/or case reports: Abscess, allergic reaction, bacteremia, deep vein thrombosis, GI hemorrhage, hypertensive encephalopathy, peritonitis, pure red cell aplasia (PRCA), sepsis, severe anemia (with or without other cytopenias), thromboembolism, thrombophlebitis, thrombosis, tumor progression (cancer patients)

Oncology: VesicantNo
Oncology: Emetic PotentialLow (10% to 30%)
Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb InteractionsEthanol: Should be avoided due to adverse effects on erythropoiesis.
Monitoring ParametersHemoglobin (at least once per week until maintenance dose established and after dosage changes; monitor at regular intervals at least once per month once hemoglobin is stabilized); iron stores (transferrin saturation and ferritin) prior to and during therapy; serum chemistry (CRF patients); blood pressure
Nursing: Physical Assessment/MonitoringEvaluate history of hypertension or seizures and potential risk for thromboembolism prior to beginning therapy. Blood pressure should be monitored closely and controlled during therapy. If administered by intravenous infusion, lines should be monitored closely for possible clotting. Assess results of laboratory tests prior to and on a regular scheduled basis during therapy (eg, blood chemistries, hemoglobin/hematocrit, serum ferritin, transferrin saturation). Evaluate therapeutic effectiveness (according to purpose for use) and adverse response on a frequent basis during therapy (eg, hyper-/hypotension, edema, thrombosis, stroke, TIA, anemia). Teach patient proper use if self-administered (appropriate SubQ injection technique and syringe/needle disposal), possible side effects/appropriate interventions (importance of maintaining laboratory schedule), and adverse symptoms to report.
Monitoring: Lab TestsHemoglobin (at least once per week until maintenance dose established and after dosage changes; monitor at regular intervals at least once per month once hemoglobin is stabilized); iron stores (transferrin saturation and ferritin) prior to and during therapy; serum chemistry (CRF patients)
Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy unless approved by prescriber. If self-administered, follow exact directions for injection and needle disposal. You will require frequent blood tests to determine appropriate dosage and reduce potential for severe adverse effects; maintaining laboratory testing schedule is vital. Do not make significant changes in your dietary iron without consulting prescriber. You may experience fever; headache; trouble sleeping; itching; skin pain; nausea; and/or vomiting, diarrhea, heartburn, and upper respiratory congestion. Contact prescriber if symptoms persist. Report signs or symptoms of edema (eg, swollen extremities, respiratory difficulty, rapid weight gain); onset of severe headache, unusual dizziness, or blurred vision; chest pain; leg pain and tenderness; muscular tremors or seizure activity; difficulty breathing, coughing, or congestion; or other adverse effects.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Aranesp®: 25 mcg/0.42 mL (0.42 mL); 40 mcg/ 0.4 mL (0.4 mL); 60 mcg/0.3 mL (0.3 mL); 100 mcg/0.5 mL (0.5 mL); 150 mcg/0.3 mL (0.3 mL); 200 mcg/0.4 mL (0.4 mL); 300 mcg/0.6 mL (0.6 mL); 500 mcg/mL (1 mL) [contains polysorbate 80; prefilled syringe; needle cover contains latex]

Aranesp®: 25 mcg/mL (1 mL); 40 mcg/mL (1 mL); 60 mcg/mL (1 mL); 100 mcg/mL (1 mL); 150 mcg/0.75 mL (0.75 mL); 200 mcg/mL (1 mL); 300 mcg/mL (1 mL) [contains polysorbate 80; single-dose vial]

Generic AvailableNo
ManufacturerAmgen, Inc
Pricing: U.S. (www.drugstore.com)

Solution (Aranesp)

25 mcg/mL (4): $516.06

40 mcg/mL (4): $802.77

150 mcg/0.75 mL (3): $2931.27

200 mcg/mL (1): $986.24

300 mcg/mL (1): $1479.36

Solution (Aranesp (Albumin Free))

25 mcg/mL (4): $558.05

60 mcg/mL (4): $1300.95

100 mcg/0.5 mL (2): $1989.59

100 mcg/mL (4): $2082.10

150 mcg/0.75 mL (3): $3430.30

300 mcg/mL (1): $1530.32

Mechanism of ActionInduces erythropoiesis by stimulating the division and differentiation of committed erythroid progenitor cells; induces the release of reticulocytes from the bone marrow into the bloodstream, where they mature to erythrocytes. There is a dose response relationship with this effect. This results in an increase in reticulocyte counts followed by a rise in hematocrit and hemoglobin levels. When administered SubQ or I.V., darbepoetin's half-life is ~3 times that of epoetin alfa concentrations.

Pharmacodynamics/Kinetics

Onset of action: Increased hemoglobin levels not generally observed until 2-6 weeks after initiating treatment

Absorption: SubQ: Slow

Distribution: V_d: 0.06 L/kg

Bioavailability: CRF: SubQ: Adults: ~37% (range: 30% to 50%); Children: 54% (range: 32% to 70%)

Half-life elimination:

- CRF: Adults:
  - I.V.: 21 hours
  - SubQ: Nondialysis patients: 70 hours (range: 35-139 hours); Dialysis patients: 46 hours (range: 12-89 hours)
- Cancer: Adults: SubQ: 74 hours (range: 24-144 hours); Children: 49 hours
- **Note:** Darbepoetin half-life is approximately threefold longer than epoetin alfa following I.V. administration

Time to peak: SubQ:

- CRF: Adults: 48 hours (range: 12-72 hours; independent of dialysis); Children: 36 hours (range: 10-58 hours)
- Cancer: Adults: 71-90 hours (range: 28-123 hours); Children: 71 hours (range: 21-143 hours)

Pharmacotherapy Pearls**Oncology Comment:** The American Society of Hematology (ASH) and American Society of Clinical Oncology (ASCO) 2007 updates to the clinical practice guidelines for the use of erythropoiesis-stimulating agents (ESAs) indicate that ESAs are most appropriate when used according to the dosage parameters within the Food and Drug Administration (FDA) approved labeling for epoetin and darbepoetin (Rizzo, 2008). While the previous guidelines addressed only the use of epoetin, the 2007 guidelines also address the use of darbepoetin, which is assessed as being equivalent to epoetin with respect to safety and efficacy. When used as an option for the treatment of chemotherapy-associated anemia (to increase hemoglobin and decrease red blood cell transfusions), therapy with ESAs should begin as the hemoglobin level approaches or falls below 10 g/dL. The ASH/ASCO guidelines recommend following the FDA approved dosing (and dosing adjustment) guidelines and target hemoglobin ranges as alternate dosing and schedules have not demonstrated consistent differences in effectiveness with regard to hemoglobin response. In patients who do not have a response within 6-8 weeks (hemoglobin rise <1-2 g/dL or no reduction in transfusions) ESA therapy should be discontinued.

The guidelines note that patients with an increased risk of thromboembolism (generally includes previous history of thrombosis, surgery, and/or prolonged periods of immobilization) and patients receiving concomitant medications that may increase thromboembolic risk, should begin ESA therapy only after careful consideration. With the exception of low-risk myelodysplasia-associated anemia (which has evidence supporting the use of ESAs without concurrent chemotherapy), the guidelines do not support the use of ESAs in the absence of concurrent chemotherapy.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation or dizziness

Mental Health: Effects on Psychiatric TreatmentNausea, vomiting, and diarrhea are common; use caution with lithium, valproic acid, and SSRIs

Cardiovascular Considerations

Anemia in Chronic Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines suggest that the benefit of enhancing erythropoiesis in these patients is not established. Although some small studies have shown a benefit from erythropoietin and iron in mild anemia in heart failure, further investigation is required evaluating the risks and benefits. Additionally, darbepoetin has also been evaluated in small numbers of patients with chronic heart failure (Parissis, 2008; van Veldhuisen, 2007); however, larger trials are required to determine the safety and efficacy of darbepoetin in this patient population.

Anesthesia and Critical Care Concerns/Other Considerations

Routine Use in Critically-Ill Patients

A prospective, randomized, double-blind, placebo-controlled, multicenter trial was performed with critically-ill patients assessing the efficacy of recombinant human erythropoietin in reducing red blood cell transfusions (Corwin, 2002). Patients were enrolled from December,1998 through June, 2001. Over 1300 ICU (medical, surgical, or medical/surgical) patients were randomized to receive placebo or 40,000 units of erythropoietin subcutaneously on ICU day 3 and then weekly for a total of 3 doses for patients who remained in the hospital. Inclusion criteria included ICU stay for 3 days, age >18 years, and hematocrit <38%. Exclusion criteria were extensive and included acute ischemic heart disease, acute gastrointestinal bleed, and renal failure with hemodialysis. Each patient's physician determined the need for red blood cell transfusion. Results: The mean baseline hemoglobin was 9.97 g/dL in each group. Patients receiving erythropoietin were less likely to receive transfusions. The median number of units transfused per patient in the placebo group was 2 and in the erythropoietin group was 1 (p<0.001). The erythropoietin group had a 9.9% absolute reduction in RBC transfusions during 28 days (p<0.001, OR 0.67, CI 0.54-0.83). Mortality and adverse clinical events were not significantly different between groups. The authors concluded that weekly administration of erythropoietin in critically-ill patients reduces red blood cell transfusions and increases hemoglobin. The authors also suggest that further study is needed to determine if use of erythropoietin results in improved clinical outcomes.

A restrictive transfusion trial was published after the above Corwin trial was underway (Hebert, 1999). Hebert and his group evaluated a restrictive transfusion strategy (transfuse if hemoglobin <7 g/dL to maintain between 7 and 9 g/dL) versus a liberal strategy (transfuse if hemoglobin <10 g/dL to maintain between 10 and 12 g/dL). Inclusion criteria included anticipated ICU stay >24 hours, hemoglobin ≤9 g/dL with 72 hours of ICU admission, and euvolemia after initial treatment. Exclusion criteria included chronic anemia, active bleeding, or admission after a routine cardiac surgical procedure. The restrictive approach to transfusion was at least as effective as and possibly superior to a liberal transfusion policy in critically-ill patients. The exception to this may be patients with acute myocardial infarction and unstable angina.

More recently, Corwin, et al (2007) once again evaluated the use of recombinant human erythropoietin in the critically ill. In this prospective, randomized, placebo-controlled trial, 1460 medical, surgical, or trauma patients were enrolled between December, 2003 and June, 2006. Patients received either subcutaneous erythropoietin 40,000 units or placebo once weekly for a maximum of 3 doses and were followed for 140 days. The primary endpoint of the study was the percentage of patients who received a red cell transfusion between days 1 and 29. Secondary endpoints included the number of red cell units transfused between days 1 and 29, mortality at day 29 and day 140, and the change in hemoglobin concentration from baseline to day 29. Patients were evaluated for inclusion into the study if they remained in that ICU for 2 days. Inclusion criteria were age >18 years and hemoglobin concentration <12 g/dL. Exclusion criteria were extensive and included acute ischemic heart disease during the ICU stay, acute gastrointestinal bleed, hemodialysis, and patients at risk for thrombosis (history of pulmonary embolism, deep venous thrombosis, ischemic stroke, other arterial or venous thrombosis). Red cell transfusions targeted hemoglobin concentrations between 7 and 9 g/dL, but the need for transfusion was determined by the treating physician (this is more consistent with clinical practice after the Hebert trial was published and different than the previous Corwin trial). Results: The mean baseline hemoglobin for each group was 9.6 g/dL. The use of erythropoietin did not significantly decrease the need for red cell transfusion (46.0% in the erythropoietin group transfused vs 48.3% in the placebo group, p=0.34). The hemoglobin concentration at day 29 increased more in the erythropoietin group compared to placebo (1.6 ± 2.0 g/dL vs 1.2 ± 1.8 g/dL, p<0.001); however, by day 42 the hemoglobin concentrations in both groups were similar. Mortality at day 29 was significantly lower in the group receiving erythropoietin (8.5% vs 11.4%, p=0.02) from the Kaplan-Meier estimate, but no difference was seen in the Cox model in the overall population. Only in the trauma subset was mortality at day 29 significantly lower in the erythropoietin group (3.5% vs 6.6%, p=0.04). At day 140, mortality was not significantly lower in the erythropoietin group. Thrombotic events (eg, DVT and myocardial infarction) were significantly higher in the erythropoietin group as compared to placebo and appeared to be dose-related (16.5% vs 11.5%, p=0.008, HR 1.41, CI 1.06-1.86). However, upon further analysis those patients who did not receive heparin at baseline developed these events more frequently. There was no difference in length of stay or the use of mechanical ventilation between groups. The authors concluded that although erythropoietin does not reduce the incidence of red cell transfusion in critically-ill patients, it may reduce mortality in trauma patients. Further investigation is required to define erythropoietin’s role in this population. The routine use of erythropoietin in critically-ill, nontraumatic surgical or medical patients is not supported by this study.

The 2008 Surviving Sepsis Campaign guidelines do not recommend erythropoietin as a treatment for anemia associated with severe sepsis but suggest that it may be used when septic patients have other therapeutic indications (Grade 1B).

Index TermsErythropoiesis-Stimulating Agent (ESA); Erythropoiesis-Stimulating Protein; NSC-729969

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International Brand NamesAranesp (AU, BE, BG, CH, CZ, DE, DK, EE, FI, FR, GB, HK, IE, IL, IT, NL, NO, SE, SG, TW); Nespo (SE)

Darifenacin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(dar i FEN a sin)

U.S. Brand NamesEnablex®

Canadian Brand NamesEnablex®

Pharmacologic CategoryAnticholinergic Agent

Use: Labeled IndicationsManagement of symptoms of bladder overactivity (urge incontinence, urgency, and frequency)

Dosing: Adults

Symptoms of bladder overactivity: Oral: Initial: 7.5 mg once daily. If response is not adequate after a minimum of 2 weeks, dosage may be increased to 15 mg once daily.

Dosage adjustment with concomitant potent CYP3A4 inhibitors (eg, azole antifungals, erythromycin, isoniazid, protease inhibitors): Daily dosage should not exceed 7.5 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment required.

Dosing: Hepatic Impairment

Moderate impairment (Child-Pugh class B): Daily dosage should not exceed 7.5 mg/day

Severe impairment (Child-Pugh class C): Has not been evaluated; use is not recommended

Administration: OralTablet should be taken with liquid and swallowed whole; do not chew, crush or split tablet. May be taken without regard to food.

Dietary ConsiderationsMay be taken without regard to meals, with or without food.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.

ContraindicationsHypersensitivity to darifenacin or any component of the formulation; uncontrolled narrow-angle glaucoma; urinary retention, paralytic ileus, GI or GU obstruction

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause drowsiness and/or blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Heat prostration: May occur in the presence of increased environmental temperature; use caution in hot weather and/or exercise.

Disease-related concerns:

- Gastrointestinal disease: Use with caution in patients with decreased GI motility, constipation, hiatal hernia, reflux esophagitis, and ulcerative colitis; may decrease GI motility.
- Glaucoma: In patients with controlled narrow-angle glaucoma, darifenacin should be used with extreme caution and only when the potential benefit outweighs risks of treatment.
- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage limitation is required in moderate hepatic impairment (Child-Pugh class B). Not recommended for use in severe hepatic impairment (Child-Pugh class C).
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; may decrease GI motility.
- Prostatic hyperplasia/bladder outlet obstruction: Use with caution in patients with prostatic hyperplasia (nonobstructive) or clinically-significant bladder outlet obstruction; may increase risk of urinary retention.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors (see Drug Interactions); dosage limitation of darifenacin is required.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsThere is a trend for decreased clearance with age, though no change in dose is recommended. The selectivity of darifenacin for the M3 receptor on the bladder may offer an advantage (less CNS and cardiovascular effects) over other anticholinergic agents used in the treatment of overactive bladder.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects and developmental delay were observed in some animal studies. There are no adequate and well-controlled studies in pregnant women; should be used only if potential benefit outweighs possible risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsAlthough human data are not available, darifenacin is excreted in the breast milk in animals.

Adverse Reactions

>10%: Gastrointestinal: Xerostomia (19% to 35%), constipation (15% to 21%)

1% to 10%:

Cardiovascular: Hypertension, peripheral edema

Central nervous system: Headache (7%), dizziness (1% to 2%), pain

Dermatological: Dry skin, pruritus, rash

Gastrointestinal: Dyspepsia (3% to 8%), abdominal pain (2% to 4%), nausea (2% to 4%), diarrhea (1% to 2%), vomiting, weight gain

Genitourinary: Urinary tract infection (4% to 5%), urinary retention, urinary tract disorder, vaginitis

Neuromuscular & skeletal: Weakness (2% to 3%), arthralgia, back pain

Ocular: Dry eyes (2%), abnormal vision

Respiratory: Bronchitis, pharyngitis, rhinitis, sinusitis

Miscellaneous: Flu-like syndrome (1% to 3%), accidental injury (1% to 3%)

Postmarketing and/or case reports: Angioedema, confusion, hallucinations, hypersensitivity reactions

Metabolism/Transport Effects**Substrate** of CYP2D6 (minor), CYP3A4 (major); **Inhibits** CYP2D6 (moderate), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Darifenacin serum concentration may be decreased by St John's wort (avoid concurrent use.)

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Monitor therapeutic effectiveness and adverse reactions. Teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake as directed. Swallow tablet whole. May cause headache (consult prescriber for a mild analgesic); dizziness, nervousness, or sleepiness (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); or abdominal discomfort, diarrhea, constipation (increasing exercise, fluids, fruit/fiber may help); dry mouth, nausea, vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report back pain, muscle spasms, alteration in gait, or numbness of extremities; unresolved or persistent constipation, diarrhea, or vomiting; or symptoms of upper respiratory infection or flu. Report difficulty urinating, or pain on urination, or abdominal pain. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if considering breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, extended release: 7.5 mg, 15 mg

Generic AvailableNo

ManufacturerNovartis

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Enablex)

7.5 mg (30): $120.98

15 mg (30): $123.98

Mechanism of ActionSelective antagonist of the M3 muscarinic (cholinergic) receptor subtype. Blockade of the receptor limits bladder contractions, reducing the symptoms of bladder irritability/overactivity (urge incontinence, urgency and frequency).

Pharmacodynamics/Kinetics

Distribution: V_{dss}: ~163 L

Protein binding: ~98% (primarily alpha$_1$-acid glycoprotein)

Metabolism: Hepatic, via CYP3A4 (major) and CYP2D6 (minor)

Bioavailability: 15% to 19%

Half-life elimination: ~13-19 hours

Time to peak, plasma: ~7 hours

Excretion: As metabolites (inactive); urine (60%), feces (40%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Prolonged xerostomia may contribute to discomfort and dental disease (eg, caries, periodontal disease, and oral candidiasis).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentConcomitant use with acetylcholinesterase inhibitors will mitigate their clinical effects. Concomitant use with psychotropic agents may produce additive anticholinergic effects. Darifenacin may increase levels of fluoxetine, mirtazapine, nefazodone, paroxetine, risperidone, thioridazine, TCAs, and venlafaxine.

Index TermsDarifenacin Hydrobromide; UK-88,525

References

Croom KF and Keating GM, “Darifenacin in the Treatment of Overactive Bladder,” *Drugs Aging*, 2004, 21(13):885-92.[PubMed 15493952]

International Brand NamesEmselex (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Enablex (AU)

Dartmouth Regimen

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Melanoma](#)

Regimen UseMelanoma

Index TermsCarmustine-Cisplatin-Dacarbazine-Tamoxifen; Cisplatin-Dacarbazine-Carmustine-Tamoxifen; Dacarbazine-Carmustine-Cisplatin-Tamoxifen

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cisplatin: I.V.: 25 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Dacarbazine: I.V.: 220 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 660 mg/m^2]

Carmustine: I.V.: 150 mg/m^2 day 1 (every other cycle)

[total dose/cycle = 150 mg/m^2; every other cycle]

Tamoxifen: Oral: 10 mg twice daily (begin 1 week before chemotherapy)

[total dose/cycle = 420 mg]

Repeat cycle every 21 days

Variation 2:

Carmustine: I.V.: 150 mg/m^2 day 1

[total dose/cycle = 150 mg/m^2]

Cisplatin: I.V.: 25 mg/m^2/day days 1, 2, 3, 22, 23, and 24

[total dose/cycle = 150 mg/m^2]

Dacarbazine: I.V.: 220 mg/m^2/day days 1, 2, 3, 22, 23, and 24

[total dose/cycle = 1320 mg/m^2]

Tamoxifen: Oral: 10 mg twice daily days 1 to 42

[total dose/cycle = 840 mg]

Repeat cycle every 42 days

Variation 3:

Carmustine: I.V.: 150 mg/m^2 day 1

[total dose/cycle = 150 mg/m^2]

Cisplatin: I.V.: 25 mg/m^2/day days 1, 2, 3, 22, 23, and 24

[total dose/cycle = 150 mg/m^2]

Dacarbazine: I.V.: 220 mg/m^2/day days 1, 2, 3, 22, 23, and 24

[total dose/cycle = 1320 mg/m^2]

Tamoxifen: Oral: 160 mg/day days -6 to 0 (cycle 1 only)

[total dose/cycle = 1120 mg]

followed by Oral: 40 mg/day days 1 to 42

[total dose/cycle = 1680 mg]

Repeat cycle every 42 days

Variation 4:

Carmustine: I.V.: 150 mg/m^2 day 1

[total dose/cycle = 150 mg/m^2]

Cisplatin: I.V.: 25 mg/m^2/day days 1, 2, 3, 29, 30, and 31

[total dose/cycle = 150 mg/m^2]

Dacarbazine: I.V.: 220 mg/m^2/day days 1, 2, 3, 29, 30, and 31

[total dose/cycle = 1320 mg/m^2]

Tamoxifen: Oral: 10-20 mg twice daily days 1 to 56

[total dose/cycle = 1120-2240 mg]

Repeat cycle every 56 days

Variation 5:

Cisplatin: I.V.: 25 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Dacarbazine: I.V.: 220 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 660 mg/m^2]

Carmustine: I.V.: 100 mg/m^2 day 1 (give in cycles 1, 3, and 6 **only**)

[total dose/cycles 1, 3, and 6 = 100 mg/m^2]

Tamoxifen: Oral: 160 mg loading dose immediately before cycle 1

[total dose/loading dose + cycle 1 = 580 mg]

followed by Oral: 20 mg daily days 1 to 21

[total dose/subsequent cycles = 420 mg]

Repeat cycle every 21 days

Note: Tamoxifen is continued until 3 weeks after last cycle.

References

Variation 1:

Chapman PB, Einhorn LH, Meyers ML, et al, “Phase III Multicenter Randomized Trial of the Dartmouth Regimen Versus Dacarbazine in Patients With Metastatic Melanoma,” *J Clin Oncol*, 1999, 17(9):2745-51. [PubMed 10561349]

Gause BL, Sharfman WH, Janik JE, et al, “A Phase II Study of Carboplatin, Interferon-Alpha, and Tamoxifen for Patients With Metastatic Melanoma,” *Cancer Invest*, 1998, 16(6):374-80. [PubMed 9679527]

McClay EF, Berd D, and Mastrangelo MJ, “The Dartmouth Regimen: Gone or Going Strong?,” *Cancer Invest*, 1998, 16(6):421-3. [PubMed 9679534]

Variation 2

Del Prete SA, Maurer LH, O'Donnell J, et al, “Combination Chemotherapy With Cisplatin, Carmustine, Dacarbazine, and Tamoxifen in Metastatic Melanoma,” *Cancer Treat Rep*, 1984, 68(11):1403-5.[PubMed 6541973]

Variation 3:

Rusthoven JJ, Quirt IC, Iscoe NA, et al, “Randomized, Double-Blind, Placebo-Controlled Trial Comparing the Response Rates of Carmustine, Dacarbazine, and Cisplatin With and Without Tamoxifen in Patients With Metastatic Melanoma,” *J Clin Oncol*, 1996, 14(7):2083-90.[PubMed 8683240]

Variation 4:

McClay EF, Mastrangelo MJ, Berd D, et al, “Effective Combination Chemo/Hormonal Therapy for Malignant Melanoma: Experience With Three Consecutive Trials,” *Int J Cancer*, 1992, 50(4):553-6.[PubMed 1537621]

Variation 5:

Propper DJ, Braybrooke JP, Levitt NC, et al, "Phase II Study of Second-Line Therapy With DTIC, BCNU, Cisplatin and Tamoxifen (Dartmouth Regimen) Chemotherapy in Patients With Malignant Melanoma Previously Treated With Dacarbazine," *Br J Cancer*, 2000, 82(11):1759-63.[PubMed 10839287]

Special Alerts

Hepatotoxicity Associated With Darunavir/Ritonavir Combination - March 13, 2008; Updated May 2008

Tibotec Therapeutics, in conjunction with the U.S. Food and Drug Administration (FDA) and Health Canada, are notifying their respective healthcare professionals of changes to the labeling of darunavir (Prezista®) emphasizing the risk of hepatotoxicity. Use of darunavir/ritonavir during clinical development has been associated with infrequent cases of drug-induced hepatitis. Postmarketing surveillance has confirmed evidence of liver injury, with some fatalities. These events have generally occurred in conjunction with advanced HIV disease (and multiple concomitant medications), hepatitis B or C coinfection and/or immune reconstitution syndrome. Patients' transaminases should be monitored prior to, and during therapy with darunavir/ritonavir. Increased vigilance of monitoring is warranted in patients with risk factors (eg, underlying chronic hepatitis, cirrhosis, previous abnormal liver function tests). Any evidence of new-onset or worsening liver function should prompt interruption or discontinuation of darunavir therapy.

Additional information including a copy of the Dear Healthcare Professional letter can be found at

U.S.: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Prezista.

Canada: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2008/prezista_hpc-cps_e.html

Pronunciation(dar OO na veer)
U.S. Brand NamesPrezista®
Pharmacologic CategoryAntiretroviral Agent, Protease Inhibitor
Use: Labeled IndicationsTreatment of HIV-1 infections in combination with ritonavir and other antiretroviral agents
Dosing: Adults**Treatment of HIV infection:** Oral:

Therapy-naive: 800 mg once daily with food; coadministration with ritonavir 100 mg once daily is required.

Therapy-experienced: 600 mg twice daily with food; coadministration with ritonavir 100 mg twice daily is required.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo adjustment required for mild to moderate impairment. No data available for use in severe renal failure or end-stage renal disease.
Dosing: Hepatic ImpairmentNo adjustment for mild-to-moderate impairment. Not recommended for patients with severe impairment.
Dosing: Adjustment for Toxicity

Severe rash: Discontinue treatment.

New or worsening liver dysfunction: Consider interrupting or discontinuing treatment.

Administration: OralAdminister with food (bioavailability is increased). Coadministration with ritonavir is required.
Dietary ConsiderationsAbsorption increased with food. Take with meals.
StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
ContraindicationsCoadministration with medications highly dependent upon CYP3A4 for clearance and for which increased levels are associated with serious and/or life-threatening events (includes cisapride, ergot alkaloids (eg, dihydroergotamine, ergonovine, ergotamine, methylergonovine), lovastatin, midazolam (oral), pimozide, rifampin, simvastatin, St John's wort, triazolam)
Allergy Considerations

- Darunavir Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Hepatotoxicity: Infrequent cases of drug-induced hepatitis (including acute and cytolytic) have been reported. Liver injury has been reported with use (including some fatalities), though generally in patients on multiple medications, with advanced HIV disease, hepatitis B/C coinfection, and/or immune reconstitution syndrome. Monitor patients closely; consider interrupting or discontinuing therapy if signs/symptoms of liver impairment occur.
- Hypersensitivity reactions: Protease inhibitors have been associated with a variety of hypersensitivity events (some severe), including rash, anaphylaxis (rare), angioedema, bronchospasm, erythema multiforme, and/or Stevens-Johnson syndrome (rare). It is generally

recommended to discontinue treatment if severe rash or moderate symptoms accompanied by other systemic symptoms occur.

- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.

- Increased cholesterol: Increases in total cholesterol and triglycerides have been reported; screening should be done prior to therapy and periodically throughout treatment.

- Sulfonamide allergy: Use with caution in patients with sulfonamide allergy (contains sulfa moiety).

Disease-related concerns:

- Diabetes: Changes in glucose tolerance, hyperglycemia, exacerbation of diabetes, DKA, and new-onset diabetes mellitus have been reported in patients receiving protease inhibitors.

- Hemophilia A or B: Use with caution in patients with hemophilia A or B; increased bleeding during protease inhibitor therapy has been reported.

- Hepatic impairment: May exacerbate pre-existing hepatic dysfunction; use with caution in patients with underlying hepatic disease, such as hepatitis B or C or cirrhosis. Not recommended in severe impairment.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

- Ritonavir: Coadministration with ritonavir is required. Treatment history and resistance data should guide use of darunavir with ritonavir.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsIt is not known if darunavir crosses the human placenta. No teratogenicity has been demonstrated in animal studies. However, there are no adequate and well-controlled studies in pregnant women. Pregnancy and protease inhibitors are both associated with an increased risk of hyperglycemia. Glucose levels should be closely monitored. Women receiving estrogen (as hormonal contraception or replacement therapy) have an increased incidence of rash. Alternative forms of contraception may be needed. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse ReactionsAs a class, protease inhibitors potentially cause dyslipidemias which includes elevated cholesterol and triglycerides and a redistribution of body fat centrally to cause increased abdominal girth, buffalo hump, facial atrophy, and breast enlargement. These agents also cause hyperglycemia. Frequency of adverse events is reported for darunavir/ritonavir. See also Ritonavir monograph.

>10%:

Endocrine & metabolic: Hypercholesterolemia (grade 2: 12% to 24%; grade 3: 1% to 8%), LDL increased (grade 2: 11% to 13%; grade 3: 2% to 7%), triglycerides increased (grade 2: 2% to 11%; grade 3: 1% to 7%; grade 4: ≤2%)

Gastrointestinal: Diarrhea (6% to 12%)

Hematologic: Neutropenia (7% to 12%)

Respiratory: Nasopharyngitis (14%)

2% to 10%:

Central nervous system: Headache (2% to 5%)

Dermatologic: Rash (2% to 10%)

Endocrine & metabolic: Hyperglycemia (grade 2: 6% to 8%; grade 3: ≤1%; grade 4: <1%), hypoglycemia (2% to 4%), hypocalcemia (up to 4%), hyponatremia (1% to 3%), hypernatremia (up to 2%)

Gastrointestinal: Nausea (3% to 7%), amylase increased (grade 2: 4% to 6%; grade 3: 3% to 6%), abdominal pain (4% to 5%), vomiting (2% to 4%), abdominal distention (≤2%), dyspepsia (≤2%), lipase increased (grade 2: 2%; grade 3: ≤2%; grade 4: <1%)

Hematologic: Thromboplastin time increased (4% to 8%), hypoalbuminemia (3% to 4%), prothrombin time increased (1% to 4%), thrombocytopenia (3%)

Hepatic: ALT increased (grade 2: 5% to 6%, grade 3: 2% to 3%; grade 4: ≤1%), AST increased (grade 2: 4% to 6%; grade 3: 2% to 3%; grade 4: <1%)

Neuromuscular & skeletal: Weakness (≤3%)

<2%: Acute renal failure, alkaline phosphatase increased, allergic dermatitis, alopecia, anorexia, anxiety, appetite decreased, arthralgia, confusion, cough, dermatitis medicamentosa, diabetes mellitus, disorientation, dreams abnormal, dyspnea, erythema multiforme, extremity pain; fat redistribution (eg, buffalo hump, increased abdominal girth, breast engorgement, facial atrophy); fatigue, fever,

flatulence, folliculitis, hepatitis (acute and cytolytic), gynecomastia, hiccups, hyperbilirubinemia, hyperhidrosis, hyperlipidemia, hypertension, hyperthermia, hypoesthesia, immune reconstitution syndrome, irritability, lipoatrophy, maculopapular rash, memory impairment, MI, mood changes, myalgia, nephrolithiasis, night sweats, nightmare, obesity, osteopenia, osteoporosis, pancreatitis, paresthesia, peripheral edema, peripheral neuropathy, polydipsia, polyuria, pruritus, renal insufficiency, rigors, skin inflammation, somnolence, Stevens-Johnson syndrome, tachycardia, toxic skin eruption, transient ischemic attack, vertigo, xerostomia

Postmarketing and/or case reports: Hypersensitivity reactions (including facial edema), rhabdomyolysis (coadministration with HMG-CoA reductase inhibitors)

Metabolism/Transport Effects **Substrate** of CYP3A4 (major); **Inhibits** P-glycoprotein

Drug Interactions

Abacavir: Protease Inhibitors may decrease the serum concentration of Abacavir. *Risk C: Monitor therapy*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amiodarone: Protease Inhibitors may decrease the metabolism of Amiodarone. *Risk X: Avoid combination*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Protease Inhibitors may decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Dihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. *Risk D: Consider therapy modification*

CarBAMazepine: May decrease the serum concentration of Darunavir. *Risk X: Avoid combination*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cisapride: Protease Inhibitors may decrease the metabolism of Cisapride. The resultant increase in serum cisapride concentrations may result in QTc prolongation and malignant cardiac arrhythmias. *Risk X: Avoid combination*

Clarithromycin: Protease Inhibitors may diminish the therapeutic effect of Clarithromycin. Specifically, certain protease inhibitors may decrease formation of the active 14-hydroxy-clarithromycin metabolite, which may negatively impact clarithromycin effectiveness vs. H. influenzae and other non-MAC infections. Protease Inhibitors may increase the serum concentration of Clarithromycin. Clarithromycin dose adjustment in renally impaired patients may be needed. Clarithromycin may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): Protease Inhibitors may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk D: Consider therapy modification*

CycloSPORINE: Protease Inhibitors may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

CYP2D6 Substrates: Darunavir may increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Delavirdine: Protease Inhibitors may decrease the serum concentration of Delavirdine. Delavirdine may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Didanosine: Darunavir may decrease the serum concentration of Didanosine. More specifically, this interaction is likely due to the effects of food (with which darunavir/ritonavir are taken) on didanosine, which is supposed to be given on an empty stomach. Management: Didanosine should be administered 1 hour prior to or 2 hours after administration of darunavir/ritonavir (which must be taken with food). *Risk D: Consider therapy modification*

Digoxin: Protease Inhibitors may increase the serum concentration of Digoxin. Increased serum concentrations of digoxin may increase risk of AV nodal blockade. *Risk C: Monitor therapy*

Efavirenz: Darunavir may increase the serum concentration of Efavirenz. Efavirenz may decrease the serum concentration of Darunavir. *Risk C: Monitor therapy*

Enfuvirtide: Protease Inhibitors may increase the serum concentration of Enfuvirtide. Enfuvirtide may increase the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

Eplerenone: Protease Inhibitors may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Protease Inhibitors may decrease the metabolism of Ergot Derivatives. **Exceptions:** Cabergoline. *Risk X: Avoid combination*

Etravirine: Protease Inhibitors may decrease the serum concentration of Etravirine. This effect is anticipated with darunavir & saquinavir (with low-dose ritonavir). Etravirine may increase the serum concentration of Protease Inhibitors. This effect is anticipated with nelfinavir. Protease Inhibitors may increase the serum concentration of Etravirine. This is expected with lopinavir/ritonavir. Management: Low-dose ritonavir boosting MUST be used when these protease inhibitors are used with etravirine. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

FentaNYL: Protease Inhibitors may decrease the metabolism of FentaNYL. *Risk C: Monitor therapy*

Fusidic Acid: Protease Inhibitors may decrease the metabolism of Fusidic Acid. Fusidic Acid may decrease the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Garlic: May decrease the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Protease Inhibitors may increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. **Exceptions:** Fluvastatin. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Lidocaine: Darunavir may increase the serum concentration of Lidocaine. *Risk C: Monitor therapy*

Lopinavir: May decrease the serum concentration of Darunavir. Darunavir may increase the serum concentration of lopinavir *Risk X: Avoid combination*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Meperidine: Protease Inhibitors may enhance the adverse/toxic effect of Meperidine. Protease Inhibitors may decrease the serum concentration of Meperidine. Concentrations of the toxic Normeperidine metabolite may be increased. *Risk D: Consider therapy modification*

Methadone: Protease Inhibitors may decrease the metabolism of Methadone. *Risk C: Monitor therapy*

Nefazodone: Protease Inhibitors may decrease the metabolism of Nefazodone. *Risk C: Monitor therapy*

Nevirapine: May increase the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Norethindrone: Darunavir may decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

PARoxetine: Darunavir may decrease the serum concentration of PARoxetine. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

PHENobarbital: May decrease the serum concentration of Darunavir. *Risk X: Avoid combination*

Phenytoin: May decrease the serum concentration of Darunavir. *Risk X: Avoid combination*

Phosphodiesterase 5 Inhibitors: Protease Inhibitors may decrease the metabolism of Phosphodiesterase 5 Inhibitors. Management: Dose restrictions for tadalafil, and/or sildenafil and vardenafil are recommended in combination with ritonavir, atazanavir, indinavir, darunavir and saquinavir. Consult specific prescribing information for detailed recommendations. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Protease Inhibitors may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Protease Inhibitors: May increase the serum concentration of other Protease Inhibitors. Management: Atazanavir--indinavir combination contraindicated. Amprenavir oral solution not recommended with ritonavir oral solution; tipranavir/ritonavir or atazanavir/ritonavir not recommended with other protease inhibitors. Other combos may require dose changes. *Risk D: Consider therapy modification*

QuiNIDine: Protease Inhibitors may decrease the metabolism of QuiNIDine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: Protease Inhibitors may decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Saquinavir: May decrease the serum concentration of Darunavir. *Risk X: Avoid combination*

Sertraline: Darunavir may decrease the serum concentration of Sertraline. *Risk C: Monitor therapy*

Sirolimus: Protease Inhibitors may increase the serum concentration of Sirolimus. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Protease Inhibitors. *Risk X: Avoid combination*

Tacrolimus: Protease Inhibitors may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Temsirolimus: Protease Inhibitors may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tenofovir: May decrease the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Tenofovir. *Risk C: Monitor therapy*

Theophylline Derivatives: Protease Inhibitors may decrease the serum concentration of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

TraZODone: Protease Inhibitors may increase the serum concentration of TraZODone. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Protease Inhibitors may increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Valproic Acid: Protease Inhibitors may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Voriconazole: Darunavir may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Warfarin: Darunavir may decrease the serum concentration of Warfarin. *Risk C: Monitor therapy*

Zidovudine: Protease Inhibitors may decrease the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Bioavailability is increased with a high-fat meal.

Herb/nutraceutical: St John’s wort may decrease the plasma levels of darunavir (concomitant use not recommended).

Monitoring ParametersViral load, CD4, serum glucose; transaminase levels prior to and during therapy (increase monitoring in patients at risk for liver impairment), cholesterol, triglycerides

Nursing: Physical Assessment/MonitoringUse caution in presence of, or at risk for, hepatic impairment. Assess other pharmacologic or herbal products patient may be taking for potential interactions or toxicity; (multiple liver enzyme interactions may increase or decrease levels/effects drugs and increase potential for toxicity or loss of effectiveness) dosing adjustments may be necessary. Evaluate results of laboratory tests (CD4 count, viral load, transaminase levels, and serum glucose) prior to and at regular intervals during therapy. Assess for adverse reactions (eg, gastrointestinal disturbance [nausea, vomiting, diarrhea] that can lead to dehydration and weight loss, hyperlipidemia and redistribution of body fat). Caution patients with diabetes to monitor glucose levels closely; protease inhibitors may cause hyperglycemia or new-onset diabetes. Teach patient proper use (eg, timing of multiple medications), possible side effects/appropriate interventions (eg, glucose testing), and adverse symptoms to report.

Monitoring: Lab TestsViral load, CD4, serum glucose; transaminase levels prior to and during therapy (increase monitoring in patients at risk for liver impairment), cholesterol, triglycerides

Patient EducationInform prescriber of all medications and over-the-counter products you are currently taking and do not take any new prescription or over-the-counter medications, or herbal products during therapy without consulting prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. This drug is prescribed as one part of a multi drug combination; take exactly as directed, for full course of therapy. Take with food (type of food is not important). Swallow tablets whole with a drink of water or milk. Do not chew tablets. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. You may be susceptible to infection (avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber). Frequent blood tests may be required with prolonged therapy. You may be advised to check your glucose levels (this drug can cause hyperglycemia). May cause body changes due to redistribution of body fat, facial atrophy, or breast enlargement (normal effects of drug); nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea (boiled milk, buttermilk, or yogurt may help); headache (consult prescriber for approved analgesic) Inform prescriber if you experience unresolved persistent vomiting, diarrhea, or abdominal pain; respiratory difficulty or chest pain; unusual bleeding or skin rash; or any persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. If using contraceptive consult prescriber for approved contraceptive. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Prezista®: 300 mg, 400 mg, 600 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Prezista)

300 mg (120): $919.96

Mechanism of ActionDarunavir binds to the HIV-1 protease activity site and inhibits the activity of the enzyme. HIV protease is required for the cleavage of viral Gag-Pol polyprotein precursors into individual functional proteins found in infectious HIV. Inhibition prevents cleavage of these polyproteins, resulting in the formation of immature, noninfectious viral particles.
Pharmacodynamics/KineticsAll kinetic parameters derived in the presence of ritonavir coadministration.

Absorption: Increased 30% with food

Protein binding: ~95%

Metabolism: Hepatic, via CYP3A4 to minimally-active metabolites

Bioavailability: 82% (with ritonavir)

Half-life elimination: ~15 hours (with ritonavir)

Time to peak, plasma: 2.5-4 hours

Excretion: Feces (~80%, 41% as unchanged drug); urine (~14%, 8% as unchanged drug)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Common Toxicity Criteria
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause headache
Mental Health: Effects on Psychiatric TreatmentContraindicated with midazolam, pimozide, and triazolam. Nausea is common; combined use with lithium, valproic acid, carbamazepine, and SSRIs may produce an additive risk. May cause neutropenia; use clozapine and carbamazepine with caution. Carbamazepine may decrease the levels of darunavir. St John's wort may decrease the plasma levels of darunavir. Concomitant use of darunavir and St John's wort is not recommended.
Index TermsDarunavir Ethanolate; TMC-114
References

“Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,” July 8, 2008. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” July 29, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesPrezista (AR, BE, CH, CZ, DE, DK, EE, GB, IE, IL, NZ, SE)

Dasatinib

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(da SA ti nib)

U.S. Brand NamesSprycel®

Canadian Brand NamesSprycel®

Pharmacologic CategoryAntineoplastic Agent, Tyrosine Kinase Inhibitor

Use: Labeled IndicationsTreatment of chronic myelogenous leukemia (CML) in chronic, accelerated or blast (myeloid or lymphoid) phase resistant or intolerant to prior therapy (including imatinib); treatment of Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) resistant or intolerant to prior therapy

Dosing: Adults

CML:

Chronic phase: Oral: 100 mg once daily. In clinical studies, a dose escalation to 140 mg once daily was allowed in patients not achieving cytogenetic response at recommended initial dosage.

Accelerated or blast phase: Oral: 70 mg twice daily. In clinical studies, a dose escalation to 100 mg twice daily was allowed in patients not achieving cytogenetic response at recommended initial dosage.

Ph+ ALL: Oral: 70 mg twice daily. In clinical studies, a dose escalation to 100 mg twice daily was allowed in patients not achieving cytogenetic response at recommended initial dosage.

Dosage adjustment for concomitant CYP3A4 inhibitors/inducers: Dose reductions are likely to be needed when dasatinib is administered concomitantly with a strong CYP3A4 inhibitor (an alternate medication for CYP3A4 enzyme inhibitors should be investigated first). In the event that dasatinib must be administered concomitantly with a potent enzyme inhibitor, consider reducing dasatinib to 20 mg daily with careful monitoring. (Canadian labeling recommend reducing dose to 20-40 mg daily). If reduced dose is not tolerated, the strong CYP3A4 inhibitor must be discontinued or dasatinib therapy temporarily held until concomitant inhibitor use has ceased. When a strong CYP3A4 inhibitor is discontinued, allow a washout period (~1 week) prior to adjusting dasatinib dose upward.

Concomitant administration with CYP3A4 inducers may require increased dasatinib doses, with careful monitoring; alternatives to the enzyme-inducing agent should be utilized first.

Dosing: ElderlyRefer to adult dosing.

Dosing: Adjustment for Toxicity

Hematologic toxicity:

Chronic phase CML (100 mg daily starting dose): For ANC <0.5 x 10^9/L or platelets <50 x 10^9/L, withhold treatment until ANC ≥1 x 10^9/L and platelets ≥50 x 10^9/L; then resume treatment at the original starting dose if recovery occurs in ≤7 days. If platelets <25 x 10^9/L or recurrence of ANC <0.5 x 10^9/L for >7 days, withhold treatment until ANC ≥1 x 10^9/L and platelets ≥50 x 10^9/L; then resume treatment at 80 mg once daily (2nd episode) or discontinue (3rd episode)

Accelerated or blast phase CML and Ph+ ALL (70 mg twice daily starting dose): For ANC <0.5 x 10^9/L or platelets <10 x 10^9/L, if cytopenia unrelated to leukemia, withhold treatment until ANC ≥1 x 10^9/L and platelets ≥20 x 10^9/L; then resume treatment at the original starting dose. If cytopenia recurs, withhold treatment until ANC ≥1 x 10^9/L and platelets ≥20 x 10^9/L; then resume treatment at 50 mg twice daily (2nd episode) or 40 mg twice daily (3rd episode). For cytopenias related to leukemia (confirm with marrow aspirate or biopsy), consider dose escalation to 100 mg twice daily with careful monitoring.

Nonhematologic toxicity: Withhold treatment until toxicity improvement or resolution; if appropriate, resume treatment at a reduced dose based on the event severity.

Calculations

- ANC: Absolute Neutrophil Count

Administration: OralAdminister once daily (morning or evening) or twice daily (morning and evening). May be taken without regard to food. Do not break, crush, or chew tablets.

Dietary ConsiderationsMay be taken without regard to food. Avoid grapefruit juice.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsThere are no contraindications listed within the FDA-approved manufacturer's labeling.

Canadian labeling: Hypersensitivity to dasatinib or any other component of the formulation

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Severe dose-related bone marrow suppression (thrombocytopenia, neutropenia, anemia) is associated with treatment; dosage adjustment or temporary interruption may be required for severe myelosuppression; the incidence of myelosuppression is higher in patients with advanced CML and Ph+ ALL.

- Fluid retention: Fluid retention, including pleural and pericardial effusions, severe ascites, severe pulmonary edema, and generalized edema were reported; may be dose-related. Use with caution in patients where fluid accumulation may be poorly tolerated, such as in cardiovascular disease (HF or hypertension) and pulmonary disease.

- Hemorrhage: Fatal intracranial hemorrhage has been reported in association with dasatinib use; severe hemorrhage (including CNS, GI) may occur due to thrombocytopenia. In addition to thrombocytopenia, dasatinib may also cause platelet dysfunction.

- QT prolongation: May prolong QT interval; use caution in patients at risk for QT prolongation, including patients with long QT syndrome; patients taking antiarrhythmic medications or other medications that lead to QT prolongation or potassium-wasting diuretics; patients with cumulative high-dose anthracycline therapy, and conditions which cause hypokalemia or hypomagnesemia. Correct hypokalemia and hypomagnesemia prior to initiation of therapy.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment due to extensive hepatic metabolism; patients with ALT or AST >2.5 times the upper limit of normal (ULN) or total bilirubin >2 times the ULN were excluded from clinical trials.

Concurrent drug therapy issues:

- Anticoagulants or antiplatelets: Use with caution in patients taking anticoagulants or medications interfering with platelet function; not studied in clinical trials.

- High potential for interactions: Use with caution in patients receiving concurrent therapy which alters CYP3A4 activity; avoid concomitant use or consider dasatinib dosage adjustments.

Special populations:

- Elderly: Elderly may be more likely to experience fluid retention; monitor closely.

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

Geriatric ConsiderationsLimited data available demonstrate no difference in safety or efficacy observed between elderly and younger adults. Elderly may be more sensitive to pharmacologic effects.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated fetal abnormalities (skeletal malformations, reduced ossification, edema, microhepatia) and fetal death. There are no adequate and well-controlled studies in pregnant women. May cause fetal harm if administered to a pregnant woman. Not recommended for use during pregnancy or if contemplating pregnancy. Effective contraception is recommended for men and women of childbearing potential. Pregnant women are advised to avoid contact with crushed or broken tablets.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

≥10%:

- Cardiovascular: Fluid retention (37%; grades 3/4: 8%), superficial edema (20%)

- Central nervous system: Headache (24%), fatigue (21%), fever (13%)

- Dermatologic: Rash (22%; includes erythema, erythema multiforme, erythematous rash, exfoliative rash, follicular rash, heat rash, maculopapular rash, milia, papular rash, pruritic rash, pustular rash, skin exfoliation, skin irritation, systemic lupus erythematosus rash, urticaria vesiculosa, vesicular rash)

- Endocrine & metabolic: Hypophosphatemia (grades 3/4: 6% to 20%), hypocalcemia (grades 3/4: 1% to 16%)

- Gastrointestinal: Diarrhea (31%; grades 3/4: 3%), nausea (22%), vomiting (13%)

- Hematologic: Neutropenia (grades 3/4: 34% to 80%), thrombocytopenia (grades 3/4: 22% to 81%), anemia (grades 3/4: 10% to 75%), hemorrhage (21%; grades 3/4: 6%)

- Neuromuscular & skeletal: Musculoskeletal pain (14%)

- Respiratory: Pleural effusion (22%; grades 3/4: 5%), dyspnea (20%; grades 3/4: 4%)

1% to <10%:

- Cardiovascular: Generalized edema (3%), pericardial effusion (3%; grades 3/4: 1%), CHF/cardiac dysfunction (2%; grades 3/4: 1%; includes cardiac failure, cardiomyopathy, diastolic dysfunction, ejection fraction decreased, left ventricular dysfunction, ventricular failure); arrhythmia, chest pain, flushing, hypertension, palpitation

- Central nervous system: CNS bleeding (1%), chills, depression, dizziness, insomnia, pain, somnolence

Dermatologic: Acne, alopecia, dermatitis, dry skin, eczema, hyperhydrosis, pruritus, urticaria

Gastrointestinal: Abdominal pain (10%), gastrointestinal bleeding (7%; grades 3/4: 4%), abdominal distention, colitis, constipation, dysgeusia, dyspepsia, enterocolitis, gastritis, mucositis/stomatitis, oral soft tissue disorder, weight loss/gain

Hematologic: Contusion, neutropenic fever, pancytopenia

Hepatic: ALT increased (grades 3/4: ≤7%), AST increased (grades 3/4: ≤5%), bilirubin increased (grades 3/4: ≤5%)

Neuromuscular & skeletal: Arthralgia, muscle inflammation, muscle weakness, myalgia, neuropathy, peripheral neuropathy, weakness

Ocular: Visual disorder, xerophthalmia

Renal: Serum creatinine increased (grades 3/4: ≤3%)

Respiratory: Pulmonary edema (2%; grades 3/4: 1%), pulmonary hypertension (1%), cough, lung infiltration, pneumonia, pneumonitis, upper respiratory tract infection/inflammation

Miscellaneous: Infection (bacterial, fungal, viral), herpes virus infection

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Acute coronary syndrome, acute febrile neutrophilic dermatosis, acute respiratory distress syndrome, affect lability, amnesia, anal fissure, angina, ascites, asthma, bronchospasm, bullous conditions, cardiomegaly, cerebrovascular accident, cholecystitis, cholestasis, coagulopathy, confusion, conjunctivitis, creatine phosphokinase increased, dysphagia, erythema nodosum, esophagitis, gynecomastia, hand-foot syndrome, hepatitis, hypersensitivity, hyperuricemia, hypoalbuminemia, hypotension, ileus, libido decreased, livedo reticularis, menstrual irregularities, MI, musculoskeletal stiffness, myocarditis, neutropenic colitis, pancreatitis, panniculitis, pericarditis, periorbital edema, photosensitivity, platelet aggregation abnormal, polyuria, proteinuria, pure red cell aplasia, QT_c prolongation, renal failure, reversible posterior leukoencephalopathy syndrome, rhabdomyolysis, seizure, sepsis, skin ulcer, syncope, tendonitis, thrombophlebitis, TIA, tinnitus, tremor, troponin increased, tumor lysis syndrome, upper gastrointestinal ulcer, ventricular arrhythmia, ventricular tachycardia, vertigo

Oncology: Emetic PotentialVery low (<10%)

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (weak)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Anticoagulants: Dasatinib may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: Dasatinib may enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: Dasatinib may increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

H2-Antagonists: May decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Proton Pump Inhibitors: May decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid St John's wort (may increase metabolism and decrease dasatinib plasma concentration).

Monitoring ParametersCBC with differential (weekly for 2 months, then monthly); bone marrow biopsy; liver function tests, electrolytes including calcium, phosphorus, magnesium; monitor for fluid retention; ECG monitoring if at risk for QT_c prolongation; chest x-ray is recommended for symptoms suggestive of pleural effusion (eg, cough, dyspnea)

Nursing: Physical Assessment/MonitoringMonitor closely any other pharmacological agents or herbal products patient may be taking for effectiveness and possible interactions prior to beginning therapy (eg, anticoagulants, drugs that may affect platelet function, drugs that may prolong QT interval, or CYP3A4 inhibitors); dose adjustments may be necessary. Assess results of laboratory tests on a regular basis (eg, CBC, LFTs, and electrolytes). Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically during therapy (eg, weight and fluid status, gastrointestinal disturbance, hemorrhage, anemia, respiratory or CNS changes). Teach appropriate use, interventions to reduce side effects, and symptoms to report.

Monitoring: Lab TestsCBC with differential (weekly for 2 months, then monthly); liver function tests; electrolytes including calcium, phosphorus, magnesium

Patient EducationDo not take any new prescription or over-the-counter medications, or herbal products during therapy without consulting prescriber. Take exactly as directed; swallow whole; do not break, crush, or chew tablets. May be taken without regard for food; avoid grapefruit juice. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will be required to have regularly scheduled laboratory tests while on this medication. You will be more susceptible to infection (avoid crowds and exposure to infection and do not receive any vaccination unless approved by prescriber). You may experience headache, dizziness, or fatigue (use caution when driving or engaging in tasks requiring alertness until response to drug in known); loss of appetite, nausea, vomiting, or mouth sores (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); or diarrhea (buttermilk, boiled milk, or yogurt may reduce diarrhea); loss of hair (will resolve when therapy is discontinued); muscle or joint pain (consult prescriber for analgesic); loss of libido. Report chest pain, palpitations, swelling of extremities, or weight gain >5 lb; cough, respiratory difficulty, or wheezing; skin rash; persistent muscle or bone pain, tremors, or cramping; persistent fatigue or weakness; easy bruising or unusual bleeding (eg, tarry stools, blood in vomitus, stool, urine, or mouth); changes in vision or hearing; persistent GI problems or pain; or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant. Consult prescriber for appropriate contraception while using this medication. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, oral:

Sprycel®: 20 mg, 50 mg, 70 mg, 100 mg

Generic AvailableNo

ManufacturerBristol Myers Squibb Co

Mechanism of ActionBCR-ABL tyrosine kinase inhibitor; targets most imatinib-resistant BCR-ABL mutations (except the T315I and F317V mutants) by distinctly binding to ABL-kinase. Kinase inhibition halts proliferation of leukemia cells. Also inhibits SRC family (including SRC, LKC, YES, FYN); c-KIT, EPHA2 and platelet derived growth factor receptor (PDGFRβ)

Pharmacodynamics/Kinetics

Distribution: 2505 L

Protein binding: Dasatinib: 96%; metabolite (active): 93%

Metabolism: Hepatic (extensive); metabolized by CYP3A4 (primarily), flavin-containing mono-oxygenase-3 (FOM-3) and uridine diphosphate-glucuronosyltransferase (UGT) to an active metabolite and other inactive metabolites (the active metabolite plays only a minor role in the pharmacology of dasatinib)

Half-life elimination: Terminal: 3-5 hours

Time to peak, plasma: 0.5-6 hours

Excretion: Feces (85%, 19% as unchanged drug); urine (4%, 0.1% as unchanged drug)

Pharmacotherapy Pearls**Oncology Comment:** In a dose finding study in chronic-phase CML, dasatininb 100 mg once daily provided comparable efficacy to the original FDA-approved dose of 70 mg twice daily. The 100 mg once daily dose was better tolerated (lower rates of pleural effusion and grades 3/4 thrombocytopenia), required fewer dose reductions, and fewer dosing interruptions or discontinuations (Shah, 2008).

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis/stomatitis, taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsDasatinib is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusHeadache, fatigue, and dizziness are common; may cause anxiety, confusion, depression, insomnia, or sedation

Mental Health: Effects on Psychiatric TreatmentSevere hemorrhage may occur due to thrombocytopenia; monitor valproic acid and derivatives closely. GI side effects are common; combined use with lithium, valproic acid, carbamazepine, and SSRIs may produce an additive risk. Hematologic side effects are common; use clozapine and carbamazepine with caution. Nefazodone may increase the levels of dasatinib. Concomitant use of dasatinib and nefazodone is not recommended.

Index TermsBMS-354825; NSC-732517

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International Brand NamesSprycel (AR, AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, ID, IE, IT, NL, NO, NZ, PT, RU, SE, TR)

DAT

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid

Regimen UseLeukemia, acute myeloid (induction)

RegimenInduction:

Daunorubicin: I.V. bolus: 45 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 135 mg/m^2]

Cytarabine: I.V. bolus: 200 mg/m^2

[total dose/cycle = 200 mg/m^2]

Thioguanine: Oral: 100 mg/m^2/day days 1 to 7

[total dose/cycle = 700 mg/m^2]

References

Gale RP and Cline MJ, âHigh Remission-Induction Rate in Acute Myeloid Leukaemia,â *Lancet*, 1977, 1(8010):497-9.[PubMed 65605]

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

DAUNOrubicin liposomal may be confused with DACTINomycin, DOXOrubicin, DOXOrubicin liposomal, epirubicin, IDArubicin

Liposomal formulation (DaunoXome®) may be confused with the conventional formulation (Cerubidine®, Rubex®)

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(daw noe ROO bi sin SI trate lip po SOE mal)

U.S. Brand NamesDaunoXome®

Pharmacologic CategoryAntineoplastic Agent, Anthracycline

Use: Labeled IndicationsFirst-line treatment of advanced HIV-associated Kaposi's sarcoma (KS)

Dosing: AdultsRefer to individual protocols.

Advanced HIV-associated Kaposi's sarcoma: I.V.: 40 mg/m^2 every 2 weeks

Dosing: ElderlyRefer to adult dosing. Use with caution.

Dosing: Renal Impairment

S_{cr} 1.2-3 mg/dL: Reduce dose to 75% of normal.

S_{cr} >3 mg/dL: Reduce dose to 50% of normal.

Dosing: Hepatic Impairment

Serum bilirubin 1.2-3 mg/dL: Reduce to 75% of normal dose.

Serum bilirubin >3 mg/dL: Reduce to 50% of normal dose.

Dosing: Adjustment for ToxicityWithhold treatment for ANC <750/mm^3

Dosing: Combination Regimens

Leukemia, acute lymphocytic: Hyper-CVAD (Leukemia, Acute Lymphocytic)

Calculations

- Body Surface Area: Adults

Administration: I.V.Infuse over 1 hour; do not mix with other drugs. Avoid extravasation.

Administration: I.V. DetailpH: 5-6

StorageStore intact vials of solution under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Diluted daunorubicin liposomal for infusion may be refrigerated at 2°C to 8°C (36°F to 46°F) for a maximum of 6 hours. Do not use with in-line filters.

ReconstitutionOnly fluid which may be mixed with DaunoXome® is D_5W. Dilute to a 1:1 solution (1 mg daunorubicin liposomal/mL D_5W). Must **not** be mixed with saline, bacteriostatic agents (such as benzyl alcohol), or any other solution.

CompatibilityStable in D_5W. **Incompatible** with normal saline, sodium bicarbonate and fluorouracil, heparin, dexamethasone.

ContraindicationsHypersensitivity to daunorubicin citrate (liposomal), daunorubicin, or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.
- Hepatic impairment: See “Disease-related concerns” below.
- Infusion-related reactions: See “Concerns related to adverse effects” below.
- Myocardial toxicity: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: May cause bone marrow suppression,** particularly neutropenia; monitor closely for infections.

- Infusion-related reactions: **[U.S. Boxed Warning]: The lipid component is associated with infusion-related reactions (back pain, flushing, chest tightness) usually within the first 5 minutes of infusion;** monitor, interrupt infusion, and resume at reduced infusion rate.

- Myocardial toxicity: **[U.S. Boxed Warning]: Monitor cardiac function regularly; especially in patients with previous therapy with high cumulative doses of anthracyclines, cyclophosphamide, or thoracic radiation, or who have pre-existing cardiac disease.** Although the risk increases with cumulative dose, irreversible cardiotoxicity may occur with anthracycline treatment at any dose level. Patients with pre-existing heart disease, hypertension, concurrent administration of other antineoplastic agents, prior or concurrent chest irradiation, and advanced age are at increased risk. Evaluate left ventricular ejection fraction (LVEF) prior to treatment and periodically during treatment.

Disease-related concerns:

- Hepatic impairment: **[U.S. Boxed Warning]: Use with caution in patients with hepatic impairment;** dosage reduction is recommended.

- Renal impairment: Use with caution in patients with renal impairment; may require dosage reduction.

Special populations:

- Elderly: Use with caution in the elderly; safety and efficacy have not been established.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenic effects and embryotoxicity were noted in animal studies. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should avoid becoming pregnant while receiving treatment.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Cardiovascular: Edema (11%)

Central nervous system: Fatigue (49%), fever (47%), headache (25%), neutropenic fever (17%)

Gastrointestinal: Nausea (54%), diarrhea (38%), abdominal pain (23%), anorexia (23%), vomiting (23%)

Hematologic: Myelosuppression (onset: 7 days; nadir: 14 days; recovery 21 days), neutropenia (up to 55%; grade 4: 15%), anemia (up to 55%; grade 4: 2%), thrombocytopenia (up to 12%; grade 4: 1%)

Neuromuscular & skeletal: Rigors (19%), back pain (16%), neuropathy (13%)

Respiratory: Cough (28%), dyspnea (26%), rhinitis (12%)

Miscellaneous: Opportunistic infections (40%), allergic reactions (24%), diaphoresis (14%), infusion-related reactions (14%; includes back pain, flushing, chest tightness)

1% to 10%:

Cardiovascular: Chest pain (10%), hypertension (≤5%), palpitation (≤5%), syncope (≤5%), tachycardia (≤5%), LVEF decreased (3%), CHF/cardiomyopathy

Central nervous system: Depression (10%), malaise (10%), dizziness (8%), insomnia (6%), abnormal thinking (≤5%), amnesia (≤5%), anxiety (≤5%), ataxia (≤5%), confusion (≤5%), emotional lability (≤5%), hallucination (≤5%), meningitis (≤5%), seizure (≤5%), somnolence (≤5%)

Dermatologic: Alopecia (8%), pruritus (7%), dry skin (≤5%), folliculitis (≤5%), seborrhea (≤5%)

Endocrine & metabolic: Dehydration (≤5%), hot flashes (≤5%)

Gastrointestinal: Stomatitis (10%), constipation (7%), tenesmus (5%), appetite increased (≤5%), dental caries (≤5%), dysphagia (≤5%), gastrointestinal hemorrhage (≤5%), gastritis (≤5%), gingival bleeding (≤5%), hemorrhoids (≤5%), melena (≤5%), splenomegaly (≤5%), taste perversion (≤5%), xerostomia (≤5%)

Genitourinary: Dysuria (≤5%), nocturia (≤5%), polyuria (≤5%)

Hepatic: Hepatomegaly (≤5%)

Local: Injection site inflammation (≤5%)

Neuromuscular & skeletal: Arthralgia (7%), myalgia (7%), gait abnormal (≤5%), hyperkinesia (≤5%), hypertonia (≤5%), tremor (≤5%)

Ocular: Abnormal vision (5%) conjunctivitis (≤5%), eye pain (≤5%)

Otic: Deafness (≤5%), earache (≤5%), tinnitus (≤5%)

Respiratory: Sinusitis (8%), hemoptysis (≤5%), pulmonary infiltrate (≤5%), sputum increased (≤5%)

Miscellaneous: Flu-like syndrome (5%), hiccups (≤5%), lymphadenopathy (≤5%), thirst (≤5%)

Postmarketing and/or case reports: Angina, atrial fibrillation, cardiac arrest, MI, pericardial effusion, pericardial tamponade, pulmonary hypertension, supraventricular tachycardia, ventricular extrasystoles

Oncology: VesicantNo; may be an irritant
Oncology: Emetic PotentialModerate (30% to 60%)
Drug Interactions

Bevacizumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk C: Monitor therapy*

Cardiac Glycosides: May diminish the cardiotoxic effect of Antineoplastic Agents (Anthracycline). Antineoplastic Agents (Anthracycline) may decrease the serum concentration of Cardiac Glycosides. The effects of liposomal formulations may be unique from those of the free drug, as liposomal formulation have unique drug disposition and toxicity profiles, and liposomes themselves may alter digoxin absorption/distribution. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Taxane Derivatives: May enhance the adverse/toxic effect of Antineoplastic Agents (Anthracycline). Taxane Derivatives may increase the serum concentration of Antineoplastic Agents (Anthracycline). Taxane Derivatives may also increase the formation of toxic anthracycline metabolites in heart tissue. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersCBC with differential and platelets (prior to each dose), liver function tests, renal function tests; evaluate cardiac function (baseline left ventricular ejection fraction [LVEF] prior to treatment initiation; repeat LVEF at total cumulative doses of 320 mg/m^2, and every 160 mg/m^2 thereafter; patients with pre-existing cardiac disease, history of prior chest irradiation, or history of prior anthracycline treatment should have baseline LVEF and every 160 mg/m^2 thereafter); signs and symptoms of infection or disease progression; monitor closely for infusion reactions

Nursing: Physical Assessment/MonitoringShould only be administered under the supervision of an experienced cancer chemotherapy physician. Evaluate patient for use cautions prior to beginning therapy (eg, pre-existing bone marrow depressions, impaired hepatic or renal function, or cardiac disease). Infusion site should be closely monitored to avoid extravasation. Patient must be monitored closely during infusions for infusion-related reaction (back pain, flushing, chest tightness). If infusion reaction occurs, interrupt infusion and restart at reduced rate. Evaluate results of laboratory tests, therapeutic response, and adverse reactions prior to each treatment and throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelets (prior to each dose), liver function tests, renal function tests; evaluate cardiac function (baseline left ventricular ejection fraction [LVEF] prior to treatment initiation; repeat LVEF at total cumulative doses of 320 mg/m^2, and every 160 mg/m^2 thereafter; patients with pre-existing cardiac disease, history of prior chest irradiation, or history of prior anthracycline treatment should have baseline LVEF and every 160 mg/m^2 thereafter)

Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. This medication can only be administered by infusion. You will be monitored closely. Report immediately any swelling, pain, burning, or redness at infusion site; chest pain or tightness; or difficulty breathing or swallowing. It is important that you maintain adequate nutrition between treatments (small, frequent meals may help) and adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, or yogurt may help); loss of hair (reversible); or red-pink urine (normal). Report immediately chest pain, palpitations, rapid heartbeat, swelling of extremities, or difficulty breathing. Report unresolved nausea, vomiting, or diarrhea; alterations in urinary pattern (increased or decreased); opportunistic infection (eg, fever, chills, unusual bruising or bleeding, fatigue, purulent vaginal discharge, unhealed mouth sores); CNS changes (depression, insomnia, abnormal thinking, confusion, seizures); abdominal pain or blood in stools; excessive fatigue; or yellowing of eyes or skin. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

DaunoXome®: 2 mg/mL (25 mL) [contains sucrose 2125 mg/25 mL]

Generic AvailableNo

Mechanism of ActionLiposomes have been shown to penetrate solid tumors more effectively, possibly because of their small size and longer circulation time. Once in tissues, daunorubicin is released. Daunorubicin inhibits DNA and RNA synthesis by intercalation between DNA base pairs and by steric obstruction; and intercalates at points of local uncoiling of the double helix. Although the exact mechanism is unclear, it appears that direct binding to DNA (intercalation) and inhibition of DNA repair (topoisomerase II inhibition) result in blockade of DNA and RNA synthesis and fragmentation of DNA.

Pharmacodynamics/Kinetics

Distribution: V_d: 5-8 L

Metabolism: Similar to daunorubicin, but metabolite plasma levels are low

Half-life elimination: Distribution: 4.4 hours; Terminal: 3-5 hours

Excretion: Primarily feces; some urine

Clearance, plasma: 17.3 mL/minute

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay produce myelosuppression; caution with clozapine and carbamazepine

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDAUNOrubicin Liposomal; Liposomal DAUNOrubicin; NSC-697732

References

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Gill PS, Wernz J, Scadden DT, et al, “Randomized Phase III Trial of Liposomal Daunorubicin Versus Doxorubicin, Bleomycin, and Vincristine in AIDS-Related Kaposi's Sarcoma,” *J Clin Oncol*, 1996, 14(8):2353-64. [PubMed 8708728]

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Schurmann D, Dormann A, Grunewald T, et al, “Successful Treatment of AIDS-Related Pulmonary Kaposi's Sarcoma With Liposomal Daunorubicin,” *Eur Respir J*, 1994, 7(4):824-5.[PubMed 8005268]

International Brand NamesDaunoXome (AT, DK, FI, FR, GB, IT, NO, SE)

DAUNOrubicin Hydrochloride

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

DAUNOrubicin may be confused with DACTINomycin, DOXOrubicin, DOXOrubicin liposomal, epirubicin, IDArubicin

Conventional formulation (Cerubidine®, DAUNOrubicin hydrochloride) may be confused with the liposomal formulation (DaunoXome®)

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(daw noe ROO bi sin hye droe KLOR ide)

U.S. Brand NamesCerubidine®

Canadian Brand NamesCerubidine®

Pharmacologic CategoryAntineoplastic Agent, Anthracycline

Use: Labeled IndicationsTreatment of acute lymphocytic (ALL) and nonlymphocytic (ANLL) leukemias

Dosing: AdultsRefer to individual protocols. **Note:** Cumulative dose should not exceed 550 mg/m^2 in adults without risk factors for cardiotoxicity and should not exceed 400 mg/m^2 in adults receiving chest irradiation.

Range: I.V.: 30-60 mg/m^2/day for 3 days, repeat dose in 3-4 weeks

ALL combination therapy: I.V.: 45 mg/m^2/day for 3 days

AML combination therapy (induction): I.V.: Adults <60 years: Induction: 45 mg/m^2/day for 3 days of the first course of induction therapy; subsequent courses: 45 mg/m^2/day for 2 days

Dosing: Elderly

ALL combination therapy: I.V.: 45 mg/m^2/day for 3 days

AML combination therapy (induction): Elderly ≥60 years: Induction: 30 mg/m^2/day for 3 days of the first course of induction therapy; subsequent courses: 30 mg/m^2/day for 2 days

Dosing: PediatricRefer to individual protocols. **Note:** Cumulative dose should not exceed 300 mg/m^2 in children >2 years or 10 mg/kg in children <2 years of age; maximum cumulative doses for younger children are unknown.

ALL combination therapy: I.V.:

Children <2 years or BSA <0.5 m^2: 1 mg/kg/dose per protocol, with frequency dependent on regimen employed

Children ≥2 years and BSA ≥0.5 m^2: Remission induction: 25 mg/m^2 on day 1 every week for up to 4-6 cycles

AML combination therapy (induction): Children ≥2 years and BSA ≥0.5 m^2: I.V. continuous infusion: 30-60 mg/m^2/day on days 1-3 of cycle

Dosing: Renal Impairment

The FDA-approved labeling recommends the following adjustment: S_{cr} >3 mg/dL: Administer 50% of normal dose.

The following guidelines have been used by some clinicians (Aronoff, 2007):

Children:

Cl_{cr} <30 mL/minute: Administer 50% of dose.

Hemodialysis/continuous ambulatory peritoneal dialysis (CAPD): Administer 50% of dose.

Adults: No adjustment recommended.

Dosing: Hepatic Impairment

The FDA-approved labeling recommends the following adjustments:

Serum bilirubin 1.2-3 mg/dL: Administer 75% of dose.

Serum bilirubin >3 mg/dL: Administer 50% of dose.

The following guidelines have been used by some clinicians (Floyd, 2006):

Serum bilirubin 1.2-3 mg/dL: Administer 75% of dose

Serum bilirubin 3.1-5 mg/dL: Administer 50% of dose

Serum bilirubin >5 mg/dL: Avoid use

Dosing: Combination Regimens

Leukemia, acute lymphocytic:

DVP

Larson Regimen

Linker Protocol

PVDA

Leukemia, acute myeloid:

5 + 2

7 + 3 (Daunorubicin)

7 + 3 + 7

DA

DAT

DAV

TAD

V-TAD

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Vesicant. **Never** administer I.M. or SubQ. Administer as slow I.V. push over 1-5 minutes into the tubing of a rapidly infusing I.V. solution of D_5W or NS or dilute in 100 mL of D_5W or NS and infuse over 15-30 minutes.

Administration: I.V. DetailAvoid extravasation, can cause severe tissue damage. Flush with 5-10 mL of I.V. solution before and after drug administration.

pH: 4.5-6.5

StorageStore intact vials of powder for injection at room temperature of 15°C to 30°C (59°F to 86°F); intact vials of solution for injection should be refrigerated at 2°C to 8°C (36°F to 46°F). Protect from light. Reconstituted solution is stable for 4 days at 15°C to 25°C. Further dilution in D_5W, LR, or NS is stable at room temperature (25°C) for up to 4 weeks if protected from light.

ReconstitutionDilute vials of powder for injection with 4 mL SWFI for a final concentration of 5 mg/mL. May further dilute in 100 mL D_5W or NS.

CompatibilityStable in D_5W, LR, NS, sterile water for injection. **Incompatible** with heparin, sodium bicarbonate, fluorouracil, and dexamethasone.

Y-site administration: Compatible: Amifostine, etoposide phosphate, filgrastim, gemcitabine, granisetron, melphalan, methotrexate, ondansetron, sodium bicarbonate, teniposide, thiotepa, vinorelbine. **Incompatible:** Allopurinol, aztreonam, cefepime, fludarabine, piperacillin/tazobactam.

Compatibility when admixed: Compatible: Cytarabine with etoposide, hydrocortisone sodium succinate. **Incompatible:** Dexamethasone sodium phosphate, heparin.

ContraindicationsHypersensitivity to daunorubicin or any component of the formulation

Allergy Considerations

- Anthracycline Allergy

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.

- Hepatic impairment: See “Disease-related concerns” below.

- Myocardial toxicity: See “Concerns related to adverse effects” below.

- Renal impairment: See “Disease-related concerns” below.

- Skin irritation/extravasation: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: May cause severe bone marrow suppression.**

- Myocardial toxicity: **[U.S. Boxed Warning]: May cause cumulative, dose-related myocardial toxicity (concurrent or delayed).** Total cumulative dose should take into account previous or concomitant treatment with cardiotoxic agents or irradiation of chest. The incidence of irreversible myocardial toxicity increases as the total cumulative (lifetime) dosages approach: 550 mg/m^2 in adults; 400 mg/m^2 in adults receiving chest radiation; 300 mg/m^2 in children >2 years of age, or 10 mg/kg in children <2 years of age. Although the risk increases with cumulative dose, irreversible cardiotoxicity may occur at any dose level. Patients with pre-existing heart disease, hypertension, concurrent administration of other antineoplastic agents, prior or concurrent chest irradiation, advanced age; and infants and children are at increased risk. Monitor left ventricular (LV) function (baseline and periodic) with ECHO or MUGA scan; monitor ECG.

- Secondary malignancy: Secondary leukemias may occur when used with combination chemotherapy or radiation therapy.

- Skin irritation/extravasation: **[U.S. Boxed Warning]: For I.V. administration only. Potent vesicant; if extravasation occurs, severe local tissue damage leading to ulceration and necrosis, and pain may occur.**

Disease-related concerns:

- Hepatic impairment: **[U.S. Boxed Warning]: Use with caution in patients with hepatic impairment;** dosage adjustment recommended.

- Renal impairment: **[U.S. Boxed Warning]: Use with caution in patients with renal impairment;** dosage adjustment recommended.

Special populations:

- Radiation recipients: Use with caution in patients who have received radiation therapy; reduce dosage in patients who are receiving radiation therapy simultaneously.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD
Pregnancy ConsiderationsMay cause fetal harm when administered to a pregnant woman. Animal studies have shown an increased incidence of fetal abnormalities.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%:

Cardiovascular: Transient ECG abnormalities (supraventricular tachycardia, S-T wave changes, atrial or ventricular extrasystoles); generally asymptomatic and self-limiting. CHF, dose related, may be delayed for 7-8 years after treatment.

Dermatologic: Alopecia (reversible), radiation recall

Gastrointestinal: Mild nausea or vomiting, stomatitis

Genitourinary: Discoloration of urine (red)

Hematologic: Myelosuppression (onset: 7 days; nadir: 10-14 days; recovery: 21-28 days), primarily leukopenia; thrombocytopenia and anemia

1% to 10%:

Dermatologic: Skin “flare” at injection site; discoloration of saliva, sweat, or tears

Endocrine & metabolic: Hyperuricemia

Gastrointestinal: Abdominal pain, GI ulceration, diarrhea

<1%: Anaphylactoid reaction, bilirubin increased, hepatitis, infertility; local (cellulitis, pain, thrombophlebitis at injection site); MI, myocarditis, nail banding, onycholysis, pericarditis, pigmentation of nailbeds, secondary leukemia, skin rash, sterility, systemic hypersensitivity (including urticaria, pruritus, angioedema, dysphagia, dyspnea); transaminases increased

Oncology: VesicantYes; see Management of Drug Extravasations.
Oncology: Emetic PotentialModerate (30% to 60%)
Drug Interactions

Bevacizumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk C: Monitor therapy*

Cardiac Glycosides: May diminish the cardiotoxic effect of Antineoplastic Agents (Anthracycline). Antineoplastic Agents (Anthracycline) may decrease the serum concentration of Cardiac Glycosides. The effects of liposomal formulations may be unique from those of the free drug, as liposomal formulation have unique drug disposition and toxicity profiles, and liposomes themselves may alter digoxin absorption/distribution. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Taxane Derivatives: May enhance the adverse/toxic effect of Antineoplastic Agents (Anthracycline). Taxane Derivatives may increase the serum concentration of Antineoplastic Agents (Anthracycline). Taxane Derivatives may also increase the formation of toxic anthracycline metabolites in heart tissue. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to GI irritation).

Monitoring ParametersCBC with differential and platelet count, liver function test, ECG, left ventricular ejection function (echocardiography [ECHO] or multigated radionuclide angiography [MUGA] scan), renal function test

Nursing: Physical Assessment/MonitoringUse with caution in presence of pre-existing bone marrow suppression, impaired hepatic or renal function, or cardiac disease. Infusion site must be closely monitored; extravasation can cause severe cellulitis or tissue necrosis. Assess results of laboratory tests (prior to therapy and periodically during treatment), therapeutic response, and adverse effects (tachycardia, cough, dyspnea, gastrointestinal upset) prior to each infusion and on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelet count, liver function test, ECG, left ventricular ejection function (echocardiography [ECHO] or multigated radionuclide angiography [MUGA] scan), renal function test

Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. This medication can only be administered I.V. Report immediately any swelling, pain, burning, or redness at infusion site. Avoid alcohol. It is important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition (small, frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, or yogurt may help); loss of hair (reversible); or red-pink urine (normal). Report immediately chest pain, swelling of extremities, respiratory difficulty, palpitations, or rapid heartbeat. Report unresolved nausea, vomiting, or diarrhea; alterations in urinary pattern (increased or decreased); opportunistic infection (eg, fever, chills, unusual bruising or bleeding fatigue, purulent vaginal discharge, unhealed mouth sores); abdominal pain or blood in stools; excessive fatigue; or yellowing of eyes or skin. **Pregnancy/breast-feeding precautions:** Do not get pregnant or cause a pregnancy (males) while taking this medication. Consult prescriber for appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. **Note: Strength expressed as base**

Injection, powder for reconstitution: 20 mg

Cerubidine®: 20 mg [contains mannitol 100 mg]

Injection, solution: 5 mg/mL (4 mL, 10 mL)

Generic AvailableYes

Mechanism of ActionInhibition of DNA and RNA synthesis by intercalation between DNA base pairs and by steric obstruction. Daunomycin intercalates at points of local uncoiling of the double helix. Although the exact mechanism is unclear, it appears that direct binding to DNA (intercalation) and inhibition of DNA repair (topoisomerase II inhibition) result in blockade of DNA and RNA synthesis and fragmentation of DNA.

Pharmacodynamics/Kinetics

Distribution: Many body tissues, particularly the liver, kidneys, lung, spleen, and heart; not into CNS; crosses placenta; V_d: 40 L/kg

Metabolism: Primarily hepatic to daunorubicinol (active), then to inactive aglycones, conjugated sulfates, and glucuronides

Half-life elimination: Distribution: 2 minutes; Elimination: 14-20 hours; Terminal: 18.5 hours; Daunorubicinol plasma half-life: 24-48 hours

Excretion: Feces (40%); urine (~25% as unchanged drug and metabolites)

Related Information

- Management of Drug Extravasations
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis and discoloration of saliva.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay produce myelosuppression; use caution with clozapine and carbamazepine

Index TermsDaunomycin; NSC-82151; Rubidomycin Hydrochloride

References

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International Brand NamesCerubidin (AE, BH, CY, DK, EG, FI, GB, HN, IE, IL, IQ, IR, JO, KW, LB, LY, MY, NO, OM, QA, SA, SE, SY, YE); Cerubidine (BE, CH, CN, CZ, FR, IL, LU, NL, NZ, PL, RU, TR, UY); Daunobin (IN); Daunoblastin (AT, DE, ZA); Daunoblastina (AE, AR, BH, BR, CL, CY, CZ, EG, ES, GR, HR, IL, IQ, IR, IT, JO, KP, KW, LB, LY, OM, PT, QA, SA, SY, VE, YE); Daunorrubicina (PY); Daunorubicin Injection (AU); Daunorubicin R.P. (DE); DaunoXome (ES, FI, LU); Donobin (PK); Maxidauno (AR); Rubilem (MX, PE)

DAV

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid

Regimen UseLeukemia, acute myeloid

Regimen

Daunorubicin: I.V.: 60 mg/m^2/day days 3, 4, and 5

[total dose/cycle = 180 mg/m^2]

Cytarabine I.V.: 100 mg/m^2/day continuous infusion days 1 and 2

[total dose/cycle = 200 mg/m^2]

followed by I.V.: 100 mg/m^2 over 30 minutes every 12 hours days 3 to 8 (12 doses)

[total dose/cycle = 1200 mg/m^2]

Etoposide: I.V.: 150 mg/m^2/day days 6, 7, and 8

[total dose/cycle = 450 mg/m^2]

Administer one cycle only

References

Creutzig U, Ritter J, and Schellong G, âIdentification of Two Risk Groups in Childhood Acute Myelogenous Leukemia After Therapy Intensification in Study AML-BFM-83 as Compared With Study AML-BFM-78, AML-BFM Study Group,â *Blood*, 1990, 75(10):1932-40.[PubMed 2186819]

Decitabine (Low Dose Regimen)

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Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Leukemia, Chronic Myelogenous; Chemotherapy Regimen, Myelodysplastic Syndrome

Regimen Use Leukemia, chronic myelogenous; Myelodysplastic syndrome

Regimen

Decitabine: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 28 days for at least 3 cycles

References

Kantarjian H, Oki Y, Garcia-Manero G, et al, "Results of a Randomized Study of 3 Schedules of Low-Dose Decitabine in Higher-Risk Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia," *Blood*, 2007, 109(1):52-7.[PubMed 16882708]

Decitabine

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English

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(de SYE ta been)
U.S. Brand NamesDacogen™
Pharmacologic CategoryAntineoplastic Agent, DNA Methylation Inhibitor
Use: Labeled IndicationsTreatment of myelodysplastic syndrome (MDS)
Use: Unlabeled/InvestigationalTreatment of acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), sickle cell anemia
Dosing: Adults

MDS: I.V.: 15 mg/m^2 over 3 hours every 8 hours (45 mg/m^2/day) for 3 days (135 mg/m^2 /cycle) every 6 weeks (treatment is recommended for at least 4 cycles and may continue until the patient no longer continues to benefit) **or**

Low-dose schedule (unlabeled): 20 mg/m^2 over 1 hour daily for 5 days every 28 days

AML (investigational use): I.V.:

5-15 mg/m^2 over 1 hour daily, 5 days/week for 2 weeks (5 days on, 2 days off, 5 days on; 10 doses total) every 6 weeks

or

15 mg/m^2 over 1 hour daily for 10 days every 6 weeks

CML (investigational use): I.V.:

20 mg/m^{2}over 1 hour daily for 5 days every 28 days

or

10-15 mg/m^2 over 1 hour daily, 5 days/week for 2 weeks (5 days on, 2 days off, 5 days on; 10 doses total) every 6 weeks

or

50-75 mg/m^2 over 6 hours every 12 hours for 5 days every 4-8 weeks

Sickle cell anemia (investigational use): I.V., SubQ: 0.15-0.3 mg/kg/day over 2 minutes 5 days/week for 2 weeks (5 days on, 2 days off, 5 days on; 10 doses total) every 6 weeks

Dosing: ElderlyRefer to adult dosing.
Dosing: Adjustment for Toxicity

For delayed hematologic recovery (ANC ≥1000/mm^3 and platelets ≥50,000/mm^3):

Greater than 6 weeks but less than 8 weeks: Delay dose for up to 2 weeks and temporarily reduce dose to 11 mg/m^2 every 8 hours (33 mg/m^2/day) for 3 days

Greater than 8 weeks but less than 10 weeks: Assess for disease progression; if no disease progression, delay dose for up to 2 weeks and reduce dose to 11 mg/m^2 every 8 hours (33 mg/m^2/day) for 3 days; maintain or increase dose with subsequent cycles if clinically indicated

Temporarily hold treatment until resolution for any of the following nonhematologic toxicities:

Serum creatinine ≥2 mg/dL

ALT, bilirubin ≥2 times ULN

Active or uncontrolled infection

Dosing: Combination Regimens

Leukemia, chronic myelogenous: Decitabine (Low Dose Regimen)

Myelodysplastic syndrome: Decitabine (Low Dose Regimen)

Calculations

- ANC: Absolute Neutrophil Count
- Body Surface Area: Adults

Administration: I.V.Infuse over 1-6 hours. Premedication with antiemetics is recommended.
Administration: I.V. DetailpH: 6.7-7.3
StorageStore vials at 15°C to 30°C (59°F to 86°F). Solutions diluted for infusion may be stored for up to 7 hours under refrigeration at 2°C to 8°C (36°F to 46°F) if prepared with cold infusion fluids.
ReconstitutionVials should be reconstituted with 10 mL SWFI to a concentration of 5 mg/mL. Further dilute with 50-250 mL NS, D_5W, or lactated Ringer's to a final concentration of 0.1-1 mg/mL. Solutions not administered within 15 minutes of preparation should be prepared with cold (2°C to 8°C [36°F to 46°F]) infusion solutions.
CompatibilityStable in NS, D_5W, and lactated Ringer's.
ContraindicationsHypersensitivity to decitabine or any component of the formulation
Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: The dose-limiting toxicity is bone marrow suppression; worsening neutropenia is common in first two treatment cycles and may not correlate with progression of underlying MDS; may require growth factor support.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; use not studied in this population.

- Renal impairment: Use with caution in patients with renal impairment; use not studied in this population.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorD
Pregnancy ConsiderationsTeratogenic effects, decreased fetal weight, and increased fetal deaths were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid pregnancy during treatment. In addition, males should be advised to avoid fathering a child while on decitabine therapy and for 2 months after treatment.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.
Adverse Reactions

>10%:

Cardiovascular: Peripheral edema (25%), pallor (23%), edema (18%), cardiac murmur (16%)

Central nervous system: Pyrexia (6% to 53%), headache (28%), insomnia (28%), dizziness (18%), pain (13%), confusion (12%), lethargy (12%), anxiety (11%), hypoesthesia (11%)

Dermatologic: Petechiae (39%), bruising (22%), rash (19%), erythema (14%), cellulitis (12%), lesions (11%), pruritus (11%)

Endocrine & metabolic: Hyperglycemia (33%), hypoalbuminemia (7% to 24%), hypomagnesemia (24%), hypokalemia (22%), hyperkalemia (13%), hyponatremia (13%)

Gastrointestinal: Nausea (42%), constipation (35%), diarrhea (34%), vomiting (25%), anorexia (16%), appetite decreased (16%), abdominal pain (5% to 14%), oral mucosal petechiae (13%), stomatitis (12%), dyspepsia (12%)

Hematologic: Neutropenia (90%; recovery 28-50 days), thrombocytopenia (89%), anemia (82%), febrile neutropenia (29%), leukopenia (28%), lymphadenopathy (12%)

Hepatic: Hyperbilirubinemia (14%), alkaline phosphatase increased (11%)

Local: Tenderness (11%)

Neuromuscular & skeletal: Rigors (22%), arthralgia (20%), limb pain (19%), back pain (17%)

Respiratory: Cough (40%), pneumonia (22%), pharyngitis (16%), lung crackles (14%)

5% to 10%:

Cardiovascular: Chest discomfort (7%), facial swelling (6%), hypotension (6%)

Central nervous system: Malaise (5%)

Dermatologic: Alopecia (8%), urticaria (6%)

Endocrine & metabolic: Hyperuricemia (10%), LDH increased (8%), bicarbonate increased (6%), dehydration (6%), hypochloremia (6%), bicarbonate decreased (5%), hypoproteinemia (5%)

Gastrointestinal: Gingival bleeding (8%), hemorrhoids (8%), loose stools (7%), tongue ulceration (7%), dysphagia (6%), oral candidiasis (6%), lip ulceration (5%), abdominal distension (5%), gastroesophageal reflux (5%), glossodynia (5%)

Genitourinary: Urinary tract infection (7%), dysuria (6%), polyuria (5%)

Hematologic: Hematoma (5%), thrombocythemia (5%), bacteremia (5%)

Hepatic: Ascites (10%), AST increased (10%), hypobilirubinemia (5%)

Local: Catheter infection (8%), catheter site erythema (5%), catheter site pain (5%), injection site swelling (5%)

Neuromuscular & skeletal: Falling (8%), chest wall pain (7%), musculoskeletal discomfort (6%), crepitation (5%), myalgia (5%)

Ocular: Blurred vision (6%)

Respiratory: Breath sounds diminished (10%), hypoxia (10%), rales (8%), pulmonary edema (6%), postnasal drip (5%), sinusitis (5%)

Miscellaneous: Candidal infection (10%), staphylococcal infection (7%), transfusion reaction (7%)

<5%, postmarketing, and/or case reports: Anaphylactic reaction, atrial fibrillation, bronchopulmonary aspergillosis, cardiomyopathy, cardiorespiratory failure, catheter site hemorrhage, chest pain, CHF, cholecystitis, dyspnea, fungal infection, gastrointestinal hemorrhage, gingival pain, hemoptysis, hypersensitivity, intracranial hemorrhage, mental status change, MI, mucosal inflammation, mycobacterium avium complex infection, peridiverticular abscess, pseudomonal lung infection, pulmonary embolism, pulmonary infiltrates, pulmonary mass, renal failure, respiratory arrest, respiratory tract infection, sepsis, splenomegaly, supraventricular tachycardia, urethral hemorrhage, weakness

Oncology: Emetic PotentialLow (10% to 30%)

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersCBC and platelets with each cycle, more frequently if needed; liver enzymes; serum creatinine

Nursing: Physical Assessment/MonitoringPremedication with antiemetic is recommended. Assess results of laboratory tests (CBC with platelets, liver enzymes, serum creatinine) at baseline and with each cycle (more frequently if needed). Assess therapeutic response and adverse reactions (eg, neutropenia, thrombocytopenia, anemia, pulmonary edema, gastrointestinal disturbance, CNS changes, hyperglycemia) prior to each cycle and periodically as indicated during therapy. Advise patients with diabetes to monitor serum glucose closely (may cause hyperglycemia). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC and platelets with each cycle, more frequently if needed; liver enzymes; serum creatinine

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by intravenous infusion. Report immediately any redness, swelling, pain, or burning at infusion site, or any adverse response during infusion (eg, respiratory difficulty, facial edema, pain, restlessness, tremor, wheezing). Maintain adequate hydration (2-3 L/day of fluid) unless instructed to restrict fluid intake and nutrition (small frequent meals). You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). If you have diabetes, you should monitor serum glucose closely; may cause hyperglycemia. May cause lethargy, dizziness, visual changes, confusion, anxiety (avoid driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, loss of appetite, or dry mouth (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help if unresolved, consult prescriber for antiemetic); mouth sores (use soft toothbrush or cotton swabs for mouth care); loss of hair (may grow back when treatment is discontinued); diarrhea or constipation (consult prescriber if persistent). Report respiratory difficulty; chest pain or palpitations; unusual bleeding, bruising or rash; any sign of urinary tract infection (itching or burning) or opportunistic infection (eg, sore throat, fever, chills, fatigue, thrush, vaginal discharge, diarrhea) or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Males should not cause a pregnancy while on therapy and for 2 months after treatment. Consult prescriber for appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Dacogen™: 50 mg

Generic AvailableNo

ManufacturerMGI Pharma

Mechanism of ActionAfter phosphorylation, decitabine is incorporated into DNA and inhibits DNA methyltransferase causing hypomethylation and subsequent cell death.

Pharmacodynamics/Kinetics

Distribution: 63-89 L/m^2

Protein binding: <1%

Metabolism: Extrahepatic; possibly via deamination by cytidine deaminase

Half-life elimination: ~30-35 minutes

Time to peak: At end of infusion

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral mucosal petechiae, stomatitis, gingival bleeding, tongue ulceration, oral candidiasis, lip ulceration, mucosal inflammation, gingival pain have been reported.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia, dizziness, confusion, lethargy, and anxiety are common

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; combined use with lithium, valproic acid, carbamazepine, and SSRIs may produce an additive risk. Neutropenia and thrombocytopenia are common; concomitant use with clozapine, carbamazepine, and valproic acid may produce additive risks.

Index Terms5-Aza-2'-deoxycytidine; 5-AzaC; NSC-127716

References

Cashen AF, Shah AK, Todt L, et al, "Pharmacokinetics of Decitabine Administered as a 3-h Infusion to Patients With Acute Myeloid Leukemia

(AML) or Myelodysplastic Syndrome (MDS)," *Cancer Chemother Pharmacol*, 2008, 61(5):759-66[PubMed 17564707]

DeSimone J, Koshy M, Dorn L, et al, "Maintenance of Elevated Fetal Hemoglobin Levels by Decitabine During Dose Interval Treatment of Sickle Cell Anemia," *Blood*, 2002, 99(11):3905-8.[PubMed 12010787]

Issa JP, Garcia-Manero G, and Giles FJ, "Phase 1 Study of Low-Dose Prolonged Exposure Schedules of the Hypomethylating Agent 5-Aza-2'Deoxycytidine (Decitabine) in Hematopoietic Malignancies," *Blood*, 2004, 103(5):1635-40.[PubMed 14604977]

Issa JP, Gharibyan V, Cortes J, et al, "Phase II Study of Low-Dose Decitabine in Patients With Chronic Myelogenous Leukemia Resistant to Imatinib Mesylate," *J Clin Oncol*, 2005, 23(17):3948-56.[PubMed 15883410]

Kantarjian H, Issa JP, Rosenfeld CS, et al, "Decitabine Improves Patient Outcomes in Myelodysplastic Syndromes," *Cancer*, 2006, 106(8):1794-803.[PubMed 16532500]

Kantarjian HM, O'Brien S, Cortes J, et al, "Results of Decitabine (5-Aza-2'Dexoycytidine) Therapy in 130 Patients With Chronic Myelogenous Leukemia," *Cancer*, 2003, 98(3):522-8.[PubMed 12879469]

Kantarjian H, Oki Y, Garcia-Manero G, et al, "Results of a Randomized Study of 3 Schedules of Low-Dose Decitabine in Higher-Risk Myelodysplastic Syndrome and Chronic Myelomonocytic Leukemia," *Blood*, 2007, 109(1):52-7.[PubMed 16882708]

Momparler RL, "Pharmacology of 5-Aza-2'-Deoxycytidine (Decitabine)," *Semin Hematol*, 2005, 42(3 Suppl 2):9-16.

Deferasirox

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Deferasirox: Postmarketing Reports of Hepatic Failure - December 2007; Health Canada Update - March 2008

Novartis, in conjunction with the U.S. Food and Drug Administration (FDA) and Health Canada have issued respective “Dear Healthcare Professional” letters regarding updates to the warnings, adverse reactions, and dosage and administration sections in the labeling of deferasirox (Exjade®). Labeling changes include clarification and more detailed information concerning serious hepatic reactions (dysfunction/failure) and a recommendation to withhold therapy for severe or persistent hepatic function test abnormalities. The updates were prompted by postmarketing reports of hepatic failure (including fatalities) in association with deferasirox therapy. Most of the reported events occurred in patients >55 years of age with underlying comorbidities, including hepatic cirrhosis and multiorgan failure. The decision to initiate deferasirox therapy to reduce iron overload should be individualized based on the expected benefits/risks of therapy.

Additional information may be found at:

http://www.fda.gov/medwatch/safety/2007/safety07.htm#Exjade

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2008/exjade_2_hpc-cps_e.html

Medication Safety Issues

Sound-alike/look-alike issues:

Deferasirox may be confused with deferoxamine

Pronunciation(de FER a sir ox)

U.S. Brand NamesExjade®

Canadian Brand NamesExjade®

Pharmacologic CategoryAntidote; Chelating Agent

Use: Labeled IndicationsTreatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis)

Dosing: Adults**Chronic iron overload due to blood transfusion:** Oral:

Initial: 20 mg/kg daily (calculate dose to nearest whole tablet)

Maintenance: Adjust dose every 3-6 months based on serum ferritin levels; increase by 5-10 mg/kg/day (calculate dose to nearest whole tablet); titrate. Maximum dose: 30 mg/kg/day; consider interrupting therapy for serum ferritin <500 mcg/L. In clinical trials, doses were individualized based on iron burden determined by liver iron concentrations (LIC); transfusional iron intake should be considered when individualizing maintenance dose. **Note:** Consider dose reduction or interruption for hearing loss or visual disturbances.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥2 years: Refer to adult dosing.

Dosing: Renal ImpairmentInterrupt treatment for progressive increase in serum creatinine above the age-appropriate ULN; once serum creatinine recovers to within the normal range, reinitiate treatment at a reduced dose; gradually escalate the dose if the clinical benefit outweighs potential risk.

Children: For increase in serum creatinine >33% on 2 consecutive measures and above the age-appropriate ULN for 2 consecutive levels, reduce daily dose by 10 mg/kg

Adults: For increase in serum creatinine >33% above the average pretreatment level at 2 consecutive levels (and cannot be attributed to other causes), reduce daily dose by 10 mg/kg

Dosing: Hepatic ImpairmentConsider dose adjustment or discontinuation for severe or persistent elevations in liver function tests.

Dosing: Adjustment for ToxicityConsider dose reduction or interruption for hearing loss or visual disturbances.

Administration: Oral**Do not chew or swallow whole tablets.** Take at same time each day on an empty stomach, 30 minutes before food. Disperse tablets in water, orange juice, or apple juice (use 3.5 ounces for total doses <1 g; 7 ounces for doses ≥1 g); stir to form suspension and drink entire contents. Rinse remaining residue with more fluid; drink. Do not take simultaneously with aluminum-containing antacids.

Dietary ConsiderationsBioavailability increased variably when taken with food; take on empty stomach 30 minutes before a meal.

StorageStore at room temperature of 25°C (77°F); excursions between 15°C and 30°C (59°F and 86°F) permitted. Protect from moisture.

ContraindicationsHypersensitivity to deferasirox or any component of the formulation

Canadian labeling: Additional contraindications (not in U.S. labeling): Cl_{cr} <60 mL/minute

Allergy Considerations

- Deferasirox Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Auditory disturbances: Decreased hearing and high frequency hearing loss have been reported with use; monitor and consider dose reduction or treatment interruption.

- Cytopenias: Cytopenias (including agranulocytosis, neutropenia, and thrombocytopenia) have been reported, predominately in patients with preexisting hematologic disorders; monitor closely. Interrupt treatment for unexplained cytopenias.

- Gastrointestinal effects: Gastrointestinal (GI) irritation, as well as upper GI ulceration and hemorrhage have been reported. Use caution with concurrent medications that may increase risk of adverse GI effects (eg, NSAIDs, corticosteroids, anticoagulants). Monitor patients closely for signs/symptoms of GI ulceration/bleeding.

- Hepatotoxicity: Severe hepatic dysfunction or failure (including fatalities) have occurred (postmarketing reports), mostly in patients >55 years of age with underlying comorbidities (including hepatic cirrhosis and multiorgan failure). Hepatitis and elevated transaminases have also been reported; monitor transaminases and consider dose modification or interruption of therapy with severe or persistent hepatic function test abnormalities. Has not been studied in patients with hepatic impairment, although has been used in patients with baseline transaminases ≤5 times ULN (deferasirox pharmacokinetics were not altered with these transaminase levels). Use with caution.

- Hypersensitivity: Hypersensitivity reactions, including severe reactions (anaphylaxis and angioedema) have been reported, usually within the first month of treatment. Discontinuation of therapy may be necessary.

- Nephrotoxicity: Cases of acute renal failure (some fatal) and dose-related elevations in serum creatinine have been reported. Monitor serum creatinine in patients at risk for renal complications (eg, pre-existing renal conditions, elderly, comorbid conditions, and/or with concurrent medications that may affect renal function); consider dose reduction, interruption, or discontinuation for serum creatinine elevations. Has not been studied in patients with renal impairment; patients with baseline serum creatinine above the upper limit of normal (ULN) were excluded from clinical trials. May cause proteinuria; monitor closely.

- Ocular disturbances: Lens opacities, cataracts, intraocular pressure elevation, and retinal disorders have been reported with use; monitor and consider dose reduction or treatment interruption.

- Rash: May cause skin rash (dose-related); mild-to-moderate rashes may resolve without treatment interruption; for severe rash, interrupt and consider restarting at a lower dose with dose escalation and oral steroids.

Concurrent drug therapy issues:

- Other iron chelation drugs: Do not combine with other iron chelation therapies; safety of combinations has not been established.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Geriatric ConsiderationsStudies to date have not included sufficient numbers of subjects ≥65 years of age. Use caution in patients with liver dysfunction or low serum albumin. Monitor renal function. In general, this drug should be used with caution and close monitoring in elderly due to the greater incidence of decreased hepatic, renal, cardiac function, as well as concomitant disease and drug therapy.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Fever (19%), headache (16%)

Dermatologic: Rash (8% to 11%)

Gastrointestinal: Abdominal pain (21% to 28%), diarrhea (12% to 20%), nausea (11% to 23%), vomiting (10% to 21%)

Renal: Serum creatinine increased (dose related; 7% to 38%), proteinuria (19%)

Respiratory: Cough (14%), nasopharyngitis (13%), pharyngolaryngeal pain (11%)

Miscellaneous: Influenza (11%)

1% to 10%:

Central nervous system: Fatigue (6%)

Dermatologic: Urticaria (4%)

Hepatic: ALT increased (2% to 8%), transaminitis (4%)

Neuromuscular & skeletal: Arthralgia (7%), back pain (6%)

Otic: Ear infection (5%)

Respiratory: Respiratory tract infection (10%), bronchitis (9%), pharyngitis (8%), acute tonsillitis (6%), rhinitis (6%)

<1%, postmarketing, and/or case reports: Acute renal failure, agranulocytosis, anaphylaxis, angioedema, anxiety, ascites, bilirubin increased,

cataract, cholecystitis, cholelithiasis, constipation, cytopenias, dizziness, drug fever, duodenal ulcer, edema, erythema multiforme, esophagitis, gastric ulcer, gastritis, gastrointestinal bleeding, glomerulonephritis, glucosuria, hearing loss (including high frequency), hematuria, Henoch-Schönlein purpura, hepatic dysfunction, hepatic encephalopathy, hepatic failure (including fatalities), hepatic transaminases increased, hepatitis, hyperactivity, hypersensitivity reaction, insomnia, interstitial nephritis, intraocular pressure increased, jaundice, lens opacities, leukocytoclastic vasculitis, maculopathy, neutropenia, optic neuritis, pigment disorder, purpura, renal tubular necrosis, renal tubulopathy, retinal disorder, sleep disorder, thrombocytopenia, visual disturbance

Oncology: Emetic PotentialLow (10% to 30%)
Drug Interactions

Aluminum Hydroxide: May diminish the therapeutic effect of Deferasirox. *Risk D: Consider therapy modification*

CYP3A4 Substrates: Deferasirox may decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Monitoring Parameters

CBC with differential, serum creatinine (twice prior to initiation, then monthly thereafter; monitor patients with renal risk factors or with changes in therapy weekly for the first month and then monthly thereafter, urine protein (monthly), liver function tests (monthly), and serum ferritin (monthly); baseline and annual auditory and ophthalmic function (including slit lamp exam and dilated fundoscopy)

Nursing: Physical Assessment/MonitoringAssess hearing and vision prior to initiating therapy and periodically during treatment. Monitor lab results as indicated. Observe for skin rash. Mild-to-moderate rashes will usually resolve spontaneously. Assess for signs of liver dysfunction (eg, unusual fatigue, easy bruising or bleeding, jaundice) and renal dysfunction (eg, unusual weight gain, swelling of extremities, decrease in urine output). Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.
Monitoring: Lab Tests

CBC with differential, serum creatinine (twice prior to initiation, then monthly thereafter; monitor patients with renal risk factors or with changes in therapy weekly for the first month and then monthly thereafter, urine protein (monthly), liver function tests (monthly), and serum ferritin (monthly); baseline and annual auditory and ophthalmic function (including slit lamp exam and dilated fundoscopy)

Patient EducationTake on an empty stomach at least 30 minutes prior to eating. Do not chew or swallow whole. Disperse in water, orange juice, or apple juice and drink immediately. Any residue remaining should be resuspended in a small volume of liquid and swallowed. Do not take with antacids. Maintain adequate hydration (2-3 L/day) unless instructed to restrict intake by prescriber. You may experience a fever, headache, abdominal pain, nausea, diarrhea, cough, sore throat, or dizziness (use caution when driving or engaging in activities requiring alertness until response to drug is known). Report severe rashes, changes in vision or hearing, weight gain >5 pounds/week, swelling of extremities, decrease in urine output, shortness of breath, unusual bleeding or bruising, change in color of urine or stool, yellowing of skin or eyes, or unusual fatigue. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, for oral suspension:

Exjade®: 125 mg, 250 mg, 500 mg

Generic AvailableNo
ManufacturerNovartis
Mechanism of ActionSelectively binds iron, forming a complex which is excreted primarily through the feces.
Pharmacodynamics/Kinetics

Distribution: Adults: 11.7-17.1 L

Protein binding: ~99% to serum albumin

Metabolism: Hepatic via glucuronidation by UGT1A1(primarily) and UGT1A3; minor oxidation by CYP450; undergoes enterohepatic recirculation

Bioavailability: 70%

Half-life elimination: 8-16 hours

Time to peak, plasma: ~1.5 hours

Excretion: Feces (84%), urine (8%)

Pharmacotherapy PearlsDeferasirox has a low affinity for binding with zinc and copper, may cause variable decreases in the serum concentration of these trace minerals.

Oncology Comment: The National Comprehensive Cancer Network (NCCN) guidelines for myelodysplastic syndromes (MDS) recommend iron chelation therapy in relatively low-risk MDS patients to reverse adverse effects (on cardiac, hepatic and endocrine function) from chronic iron overload due to multiple transfusions. Treatment is generally recommended in MDS patients who have received ≥20 units of RBC transfusions and for those with serum ferritin levels >2500 mcg/L. Although clinical trials in MDS are ongoing, deferasirox may be useful in the management of iron overload of these patients.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness or fatigue; may rarely cause anxiety, hyperactivity, or insomnia
Mental Health: Effects on Psychiatric TreatmentAssociated with dose-related skin rash; monitor patients receiving anticonvulsants (especially lamotrigine). GI side effects are common; concomitant use with SSRIs, lithium, valproic acid, and carbamazepine may produce additive effects.
Index TermsICL670

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International Brand NamesExjade (AR, AT, AU, BE, BG, CH, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IT, KP, MX, MY, NL, NO, NZ, PH, PT, RU, SE, TH, TR, TW)

Deferoxamine

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Deferoxamine may be confused with cefuroxime, deferasirox

Desferal® may be confused with desflurane, Dexferrum®, Disophrol®

International issues:

Desferal® may be confused with Deseril® which is a brand name for methysergide in multiple international markets

Pronunciation(de fer OKS a meen)
U.S. Brand NamesDesferal®
Canadian Brand NamesDesferal®; PMS-Deferoxamine
Pharmacologic CategoryAntidote; Chelating Agent
Use: Labeled IndicationsAcute iron intoxication or when clinical signs of significant iron toxicity exist; chronic iron overload secondary to multiple transfusions
Use: Unlabeled/InvestigationalRemoval of corneal rust rings following surgical removal of foreign bodies; diagnosis or treatment of aluminum induced toxicity associated with chronic kidney disease (CKD)
Dosing: Adults
Acute iron toxicity:

I.M., I.V.: Initial: 1000 mg, may be followed by 500 mg every 4 hours for up to 2 doses; subsequent doses of 500 mg have been administered every 4-12 hours

Maximum recommended dose: 6 g/day (per manufacturer, however, higher doses have been administered)

Note: I.V. route is used when severe toxicity is evidenced by systemic symptoms (coma, shock, metabolic acidosis, or severe gastrointestinal bleeding) or potentially severe intoxications (serum iron level >500 mcg/dL). When severe symptoms are not present, the I.M. route may be preferred (per manufacturer); however, the use of deferoxamine in situations where the serum iron concentration is <500 mcg/dL or when severe toxicity is not evident is a subject of some clinical debate.

Chronic iron overload:

I.M., I.V.: 500-1000 mg/day I.M.; in addition, 2000 mg should be given I.V. with each unit of blood transfused (administer separately from blood); maximum: 1 g/day in absence of transfusions; 6 g/day if patient received transfusions

SubQ: 1-2 g every day or 20-40 mg/kg/day over 8-24 hours

Diagnosis of aluminum induced toxicity with CKD (unlabeled use): I.V.: Test dose: 5 mg/kg during the last hour of dialysis if serum aluminum levels are 60-200 mcg/L and there are clinical signs/symptoms of toxicity. Do not use if aluminum serum levels are >200 mcg/L

Treatment of aluminum toxicity with CKD (unlabeled use): I.V.: 5-10 mg/kg 4-6 hours before dialysis. Administer every 7-10 days with 3-4 dialysis procedures between doses. Do not use if aluminum serum levels are >200 mcg/L.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric
Acute iron toxicity: Children ≥3 years: Refer to "Note" in adult dosing.

I.M.: 90 mg/kg/dose every 8 hours (maximum: 6 g/24 hours)

I.V.: 15 mg/kg/hour (maximum: 6 g/24 hours)

Chronic iron overload: Children ≥3 years:

SubQ: 20-40 mg/kg/day over 8-12 hours (maximum: 1000-2000 mg/day)

I.V.: 15 mg/kg/hour (maximum: 6 g/24 hours)

Diagnosis of aluminum induced toxicity with CKD (unlabeled use): Children ≥3 years: Refer to adult dosing.

Treatment of aluminum toxicity with CKD (unlabeled use): Children ≥3 years: Refer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <10 mL/minute: Administer 50% of dose.
Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Urticaria, hypotension, and shock have occurred following rapid I.V. administration; limiting infusion rate to 15mg/kg/hour may help avoid infusion-related adverse effects.

Acute iron toxicity: The manufacturer states that the I.M. route is preferred; however, the I.V. route is generally preferred in patients with severe toxicity (ie, patients in shock). For the first 1000 mg, infuse at 15 mg/kg/hour (although rates up to 40-50 mg/kg/hour have been given in patients with massive iron intoxication). Subsequent doses may be given over 4-12 hours at a rate not to exceed 125 mg/hour.

Diagnosis or treatment of aluminum induced toxicity with CKD: Administer dose over 1 hour

Administration: OtherSubQ: When administered for chronic iron overload, daily dose should be given over 8-24 hours using portable pump.

Dietary ConsiderationsVitamin C supplements may need to be limited. The manufacturer recommends a maximum of 200 mg/day in adults (given in divided doses) and avoiding use in patients with heart failure.

StoragePrior to reconstitution, do not store above 25˚C (77˚F). Following reconstitution, may be stored at room temperature for 7 days; protect from light. Do not refrigerate reconstituted solution.

Reconstitution

I.M.: Reconstitute with sterile water for injection (500 mg vial with 2 mL to a final concentration of 210 mg/mL; 2000 mg vial with 8 mL to a final concentration of 213 mg/mL)

I.V.: Reconstitute with sterile water for injection to a final solution of 100 mg/mL

SubQ: Reconstitute with sterile water for injection (500 mg vial with 5 mL; 2000 mg vial with 20 mL) to a final concentration of 95 mg/mL

CompatibilityStable in D_5W, LR, NS, sterile water for injection.

ContraindicationsHypersensitivity to deferoxamine or any component of the formulation; patients with severe renal disease or anuria, primary hemochromatosis

Allergy Considerations

- Deferoxamine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adult respiratory distress syndrome (ARDS): Has been associated with ARDS following excessively high-dose treatment of acute intoxication or thalassemia; has also been reported in children.
- Auditory effects: Auditory disturbances have been reported following prolonged administration at high doses, or in patients with low ferritin levels; elderly patients are at increased risk.
- CNS effects: High doses may exacerbate neurological symptoms, including seizure in patients with aluminum-related encephalopathy.
- Dialysis dementia: Associated with dialysis dementia onset.
- Growth retardation: High doses and low ferritin levels are also associated with growth retardation.
- Hypocalcemia: Treatment in patients with aluminum toxicity may cause hypocalcemia and aggravate hyperparathyroidism.
- Infection: Patients with iron overload are at increased susceptibility to infection with *Yersinia enterocolitica* and *Yersinia pseudotuberculosis;* treatment with deferoxamine may enhance this risk; if infection develops, discontinue therapy until resolved.
- Infusion reactions: Flushing, hypotension, urticaria and shock are associated with rapid infusions.
- Mucormycosis: Rare and serious cases of mucormycosis have been reported with use; withhold treatment with signs and symptoms of mucormycosis.
- Ocular effects: Ocular disturbances have been reported following prolonged administration at high doses, or in patients with low ferritin levels; elderly patients are at increased risk.

Concurrent drug therapy issues:

- Ascorbic acid: Combination treatment with ascorbic acid may impair cardiac function (rare). If combination treatment is warranted, therapy may need adjusted; monitor cardiac function. Do not administer deferoxamine in combination with ascorbic acid in patients with pre-existing cardiac failure.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <3 years of age.

Other warnings/precautions:

- Urine discoloration: Patients should be informed that urine may have a reddish color.

Pregnancy Risk FactorC

Pregnancy ConsiderationsSkeletal anomalies and delayed ossification were observed in some but not all animal studies. Toxic amounts of iron or deferoxamine have not been noted to cross the placenta. In case of acute toxicity, treatment during pregnancy should not be withheld.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Flushing, hypotension, tachycardia, shock, edema

Central nervous system: Fever, dizziness, neuropathy, seizure, exacerbation of aluminum-related encephalopathy (dialysis), headache

Dermatologic: Angioedema, rash, urticaria

Endocrine & metabolic: Growth retardation (children), hypocalcemia

Gastrointestinal: Abdominal discomfort, abdominal pain, diarrhea, nausea, vomiting

Genitourinary: Dysuria

Hematologic: Thrombocytopenia, leukopenia

Local: Injection site: Burning, crust, edema, erythema, eschar, induration, infiltration, irritation, pain, pruritus, swelling, vesicles, wheal formation

Neuromuscular & skeletal: Arthralgia, leg cramps, metaphyseal dysplasia (dose related), myalgia, paresthesia

Ocular: Acuity decreased, blurred vision, dichromatopsia, maculopathy, night vision impaired, peripheral vision impaired, visual loss, scotoma, visual field defects, optic neuritis, cataracts, retinal pigmentary abnormalities, night blindness

Otic: Hearing loss, tinnitus

Renal: Renal impairment, urine discoloration (vin-rose color)

Respiratory: Acute/adult respiratory distress syndrome, asthma

Miscellaneous: Anaphylaxis, hypersensitivity reaction, infections (*Yersinia*, mucormycosis)

Drug Interactions

Ascorbic Acid: May enhance the adverse/toxic effect of Deferoxamine. Left ventricular dysfunction is of particular concern. *Risk D: Consider therapy modification*

Test InteractionsTIBC may be falsely elevated with high serum iron concentrations or deferoxamine therapy. Imaging results may be distorted due to rapid urinary excretion of deferoxamine-bound gallium-67; discontinue deferoxamine 48 hours prior to scintigraphy.

Monitoring ParametersSerum iron; ophthalmologic exam (fundoscopy, slit-lamp exam) and audiometry with chronic therapy; growth and body weight in children (every 3 months)

Dialysis patients: Serum aluminum (yearly; every 3 months in patients on aluminum-containing medications)

Aluminum-induced bone disease: Serum aluminum 2 days following test dose; test is considered positive if serum aluminum increases ≥50 mcg/L

Reference Range

Iron, serum: Normal: 50-150 mcg/dL; levels >500 mcg/dL associated with toxicity. Consider treatment with symptomatic patients with levels ≥350 mcg/dL; toxicity cannot be excluded with serum iron levels <350 mcg/dL

Aluminum, serum: <20 mcg/L recommended baseline level in dialysis patients

Nursing: Physical Assessment/MonitoringMonitor laboratory tests. Infuse slowly and monitor infusion site. Monitor for acute reactions; urticaria, hypotension and shock can occur following rapid I.V. administration. With chronic therapy, perform ophthalmologic exam (fundoscopy, slit-lamp exam) and audiometry. Teach patient proper use, including injection technique and syringe/needle disposal. Monitor for adverse reactions (eg, cardiac, respiratory, or CNS symptoms) and teach patient importance of reporting adverse symptoms.

Monitoring: Lab TestsSerum iron, total iron-binding capacity

Patient EducationInstructions depend on patient condition. You will be monitored closely for effects of this medication and frequent blood or urine tests may be necessary. Your urine may show a reddish discoloration. Report chest pain, rapid heartbeat, headache, pain, swelling, or irritation at infusion site; skin rash; changes or loss of hearing or vision; or acute abdominal or leg cramps. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as mesylate: 500 mg, 2 g

Desferal®: 500 mg, 2 g

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Desferal)

500 mg (4): $84.55

Mechanism of ActionComplexes with trivalent ions (ferric ions) to form ferrioxamine, which are removed by the kidneys

Pharmacodynamics/Kinetics

Absorption: I.M.: Erratic

Metabolism: Plasma enzymes; binds with iron to form ferrioxamine

Half-life elimination: Parent drug: 6.1 hours; Ferrioxamine: 5.8 hours

Excretion: Primarily urine (as unchanged drug and ferrioxamine); feces (via bile)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentLoss of consciousness has been reported with concurrent use of prochlorperazine

Index TermsDeferoxamine Mesylate; Desferrioxamine; NSC-644468

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International Brand NamesDesferal (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, OM, PH, PK, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, VE, YE, ZA, ZM, ZW)

Degarelix

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Degarelix may be confused with cetrorelix, ganirelix

Pronunciation(deg a REL ix)

Pharmacologic CategoryAntineoplastic Agent, Gonadotropin-Releasing Hormone Antagonist; Gonadotropin Releasing Hormone Antagonist

Use: Labeled IndicationsTreatment of advanced prostate cancer

Dosing: Adults**Prostate cancer:** SubQ:

Loading dose: 240 mg administered as two 120 mg (3 mL) injections

Maintenance dose: 80 mg every 28 days (beginning 28 days after initial loading dose)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <50 mL/minute: Use with caution.

Dosing: Hepatic Impairment

Mild-to-moderate hepatic impairment: No adjustment required; monitor serum testosterone levels.

Severe hepatic impairment: Has not been studied; use with caution.

Administration: I.V.Not for I.V. use.

Administration: OtherNot for I.V. use. Administer SubQ in the abdominal area by grasping skin and elevating SubQ tissue; inject at an angle ≤45 degrees. Avoid pressure exposed areas (eg, waistband, near ribs); rotate injection site. Inject loading dose as two 3 mL injections (40 mg/mL); maintenance dose should be administered as one 4mL injection (20 mg/mL); begin maintenance dose 28 days after initial loading dose.

Dietary ConsiderationsSupplementation with 500 mg calcium and 400 int. units of vitamin D is recommended (due to the increased risk for osteoporosis with androgen deprivation therapy).

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ReconstitutionUse appropriate precautions (wear gloves for preparation and administration) for handling and disposal. Reconstitute with preservative free sterile water for injection (reconstitute each 120 mg vial with 3 mL; reconstitute the 80 mg vial with 4.2 mL). Swirl gently; do not shake (to prevent foaming). Dissolution may take up to 15 minutes. Keep vial upright at all times. Tilt vial slightly, keeping needle in lowest section of vial to withdraw for administration. Administer within 1 hour of reconstitution.

ContraindicationsHypersensitivity to degarelix or any component of the formulation; pregnancy (or potential to become pregnant)

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Decreased bone mineral density: Androgen deprivation therapy is associated with decreased bone mineral density.
- QT prolongation: Androgen deprivation therapy may prolong the QT interval. Use with caution in patients with a known history of QT prolongation or other risk factors for QT prolongation (eg, concomitant use of medications known to prolong QT interval, heart failure, and/or electrolyte abnormalities).

Disease-related concerns:

- Cardiovascular disease: Androgen deprivation therapy may increase the risk for cardiovascular disease.
- Diabetes: Androgen deprivation therapy may cause obesity and insulin resistance; the risk for diabetes is increased.
- Hepatic impairment: Degarelix exposure is decreased in patients with hepatic impairment, dosage adjustment is not recommended in patients with mild-to-moderate hepatic impairment, although testosterone levels should be monitored. Has not been studied in patients with severe hepatic impairment; use with caution.
- Renal Impairment: Data for use in patients with moderate-to-severe renal impairment (Cl_{cr} <50 mL/minute) is limited; use with caution.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorX

Pregnancy ConsiderationsAnimal studies have demonstrated embryo and fetal loss. Use is contraindicated in women who are or may become pregnant.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Endocrine & metabolic: Hot flashes (26%)

Local: Injections site reactions (35%, grade 3: ≤2%; pain 28%, erythema 17%, swelling 6%, induration 4%, nodule 3%)

1% to 10%:

Cardiovascular: Hypertension (6%)

Central nervous system: Chills (5%), dizziness (1% to 5%), fever (1% to 5%), headache (1% to 5%), insomnia (1% to 5%), fatigue (3%)

Dermatologic: Hyperhydrosis

Endocrine & metabolic: Hypercholesterolemia (3%), gynecomastia, testicular atrophy

Gastrointestinal: Weight gain (9%), constipation (5%), nausea (1% to 5%), diarrhea

Genitourinary: Urinary tract infection (5%), erectile dysfunction

Hepatic: ALT increased (10%; grade 3: <1%), AST increased (5%; grade 3: <1%), GGT increased

Neuromuscular & skeletal: Back pain (6%), arthralgia (5%), weakness (1% to 5%)

Miscellaneous: Antidegarelix antibody formation (10%), night sweats (1% to 5%)

<1%, postmarketing, and/or case reports: Bone metastases worsening, cerebral stroke, depression, injection site pruritus, injection site soreness, lymphoma (malignant), mental status changes, MI, osteoarthritis, QT interval prolongation, squamous cell cancer, unstable angina

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Test InteractionsSuppression of pituitary-gonadal function may affect diagnostic tests of pituitary gonadotropic and gonadal functions.

Monitoring ParametersProstate-specific antigen (PSA) periodically, serum testosterone levels (if PSA increases; in patients with hepatic impairment: monitor testosterone levels monthly until achieve castration levels, then consider monitoring every other month), liver function tests (at baseline), serum electrolytes (calcium, magnesium, potassium, sodium); bone mineral density

Screen for diabetes and cardiovascular risk prior to initiating treatment.

Monitoring: Lab TestsProstate-specific antigen (PSA) periodically, serum testosterone levels (if PSA increases; in patients with hepatic impairment: monitor testosterone levels monthly until achieve castration levels, then consider monitoring every other month), liver function tests (at baseline), serum electrolytes (calcium, magnesium, potassium, sodium); bone mineral density

Product AvailabilityDegarelix (brand name pending): FDA approved December 2008; availability anticipated towards the end of 2009

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as acetate: 80 mg, 120 mg

Generic AvailableNo

ManufacturerFerring Pharmaceuticals, Inc

Mechanism of ActionGonadotropin-releasing hormone (GnRH) antagonist which reversibly binds to GnRH receptors in the anterior pituitary gland, blocking the receptor and decreasing secretion of luteinizing hormone (LH) and follicle stimulation hormone (FSH), resulting in rapid androgen deprivation by decreasing testosterone production, thereby decreasing testosterone levels. Testosterone levels do not exhibit an initial surge, or flare, as is typical with GnRH agonists.

Pharmacodynamics/Kinetics

Onset of action: Rapid; ~96% of patients had testosterone levels ≤50 ng/dL within 3 days (Klotz, 2008)

Distribution: V_d: >1000 L

Protein binding: ~90%

Metabolism: Hepatobiliary, via peptide hydrolysis

Bioavailability: Biphasic release: Rapid release initially, then slow release from depot formed after subcutaneous injection administration (Tornoe, 2007)

Half-life elimination: Loading dose: SubQ: ~53 days

Time to peak, plasma: Loading dose: SubQ: Within 2 days

Excretion: Feces (~70% to 80%, primarily as peptide fragments); urine (~20% to 30%)

Dental Health Professional ConsiderationsDegarelix is known to prolong the QT interval. The QT interval is measured as the time and distance between the Q point of the QRS complex and the end of the T wave in the ECG tracing. After adjustment for heart rate, the QT interval is defined as prolonged if it is more than 450 msec in men and 460 msec in women. A long QT syndrome was first described in the 1950s and 60s as a congenital syndrome involving QT interval prolongation and syncope and sudden death. Some of the congenital long QT syndromes were characterized by a peculiar electrocardiographic appearance of the QRS complex involving a premature atria beat followed by a pause, then a subsequent sinus beat showing marked QT prolongation and deformity. This type of cardiac arrhythmia was originally termed “torsade de pointes” (translated from the French as “twisting of the points”).

Prolongation of the QT interval is thought to result from delayed ventricular repolarization. The repolarization process within the myocardial cell is due to the efflux of intracellular potassium. The channels associated with this current can be blocked by many drugs and predispose the electrical propagation cycle to torsade de pointes.

Degarelix is considered as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. It is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsDegarelix may prolong QT interval; it is suggested that the clinician consult with the physician prior to use of vasoconstrictor in suspected patients; use vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) with caution.

Mental Health: Effects on Mental StatusMay cause dizziness, insomnia, or fatigue; rarely associated with depression

Mental Health: Effects on Psychiatric TreatmentMay prolong QT interval; use caution with paliperidone and ziprasidone. May cause weight gain and insulin resistance; concomitant use with atypical antipsychotics may produce additive effects.

Index TermsDegarelix Acetate; FE200486

References

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National Comprehensive Cancer Network® (NCCN), “Clinical Practice Guidelines in Oncology™: Prostate Cancer,” Version 1, 2009. Available at http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf

Tornoe CW, Agerso H, Senderovitz T, et al, “Population Pharmacokinetic/Pharmacodynamic (PK/PD) Modelling of the Hypothalamic-Pituitary-Gonadal Axis Following Treatment With GnRH Analogues,” *Br J Clin Pharmacol*, 2007, 63(6):648-64.[PubMed 17096678]

Delavirdine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(de la VIR deen)
U.S. Brand NamesRescriptor®
Canadian Brand NamesRescriptor®
Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Non-nucleoside)
Use: Labeled IndicationsTreatment of HIV-1 infection in combination with at least two additional antiretroviral agents
Dosing: AdultsHIV-1 infection (part of combination): Oral: 400 mg 3 times/day
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

HIV-1 infection (part of combination): Adolescents ≥16 years: Refer to adult dosing.

Administration: OralPatients with achlorhydria should take the drug with an acidic beverage. Antacids and delavirdine should be separated by 1 hour. A dispersion of delavirdine may be prepared by adding four 100 mg tablets to at least 3 oz of water. Allow to stand for a few minutes and stir until uniform dispersion. Drink immediately. Rinse glass and mouth, then swallow the rinse to ensure total dose administered. The 200 mg tablets should be taken intact.
Dietary ConsiderationsMay be taken without regard to food.
StorageStore at 20°C to 25°C (68°F to 77°F). Protect from humidity.
Extemporaneously PreparedA dispersion of delavirdine may be prepared by adding four 100 mg tablets to at least 3 oz of water; allow to stand for a few minutes and stir until uniform dispersion; drink immediately; rinse glass and mouth following ingestion to ensure total dose administered
ContraindicationsHypersensitivity to delavirdine or any component of the formulation; concurrent use of alprazolam, cisapride, ergot alkaloids, midazolam, pimozide, rifampin, or triazolam
Warnings/Precautions

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Rash: Occurs frequently, may require discontinuation of therapy; usually occurs within 1-3 weeks and lasts <2 weeks. Most patients may resume therapy following a treatment interruption.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- HIV: Appropriate use: Due to rapid emergence of resistance, delavirdine should not be used as monotherapy; cross-resistance may be conferred to other non-nucleoside reverse transcriptase inhibitors, although potential for cross-resistance with protease inhibitors is low.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Long-term effects: The long-term effects of delavirdine are not known.

Pregnancy Risk FactorC
Pregnancy ConsiderationsIt is not known if delavirdine crosses the human placenta. Delavirdine was shown to be teratogenic in some animal studies. There are no adequate and well-controlled studies in pregnant women and use during pregnancy is not recommended unless other alternatives are not available. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).
LactationExcretion in breast milk unknown/contraindicated
Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse Reactions

Frequency of adverse reactions reported from occurrence in clinical trials with delavirdine when used as part of combination antiretroviral therapy.

>10%:

Central nervous system: Headache (19% to 20%), depressive symptoms (10% to 15%), fever (4% to 12%)

Dermatologic: Rash (16% to 32%)

Gastrointestinal: Nausea (20% to 25%), vomiting (3% to 11%)

1% to 10%:

Central nervous system: Anxiety (6% to 8%)

Endocrine & metabolic: Transaminases increased (2% to 5%), amylase increased (3%), bilirubin increased (2%)

Gastrointestinal: Diarrhea, vomiting, abdominal pain (4% to 6%)

Hematologic: Prothrombin time increased (2%), hemoglobin decreased (1% to 3%)

Respiratory: Bronchitis (6% to 8%)

Frequency not defined (limited to important or life threatening): Abscess, adenopathy, alkaline phosphatase increased, allergic reaction, angioedema, anorexia, arrhythmia, bloody stool, bone pain, bruising, cardiac insufficiency, cardiac rate abnormal, cardiomyopathy, chest congestion, cognitive impairment, colitis, confusion, conjunctivitis, dermal leukocytoclastic vasculitis, desquamation, diverticulitis, dyspnea, emotional lability, eosinophilia, erythema multiforme, fecal incontinence, fungal dermatitis, gamma glutamyl transpeptidase increased, gastroenteritis, gastrointestinal bleeding, granulocytosis, gum hemorrhage, hallucination, hematuria, hepatomegaly, hyperglycemia, hyperkalemia, hypertension, hypertriglyceridemia, hyperuricemia, hypocalcemia, hyponatremia, hypophosphatemia, infection, jaundice, kidney pain, leukopenia, lipase increased, menstrual irregularities, moniliasis (oral/vaginal), pancreatitis, pancytopenia, paralysis, peripheral vascular disorder, pneumonia, postural hypotension, purpura, redistribution of body fat, renal calculi, serum creatinine increased, spleen disorder, Stevens-Johnson syndrome, tetany, thrombocytopenia, urinary tract infection, vertigo

Postmarketing and/or case reports: Acute renal failure, hemolytic anemia, hepatic failure, immune reconstitution syndrome, rhabdomyolysis

Metabolism/Transport Effects

Substrate of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2C9 (strong), 2C19 (strong), 2D6 (strong), 3A4 (strong)

Drug Interactions

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amprenavir: May decrease the serum concentration of Delavirdine. Delavirdine may increase the serum concentration of Amprenavir. *Risk X: Avoid combination*

Antacids: May decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Strong) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

Etravirine: Reverse Transcriptase Inhibitors (Non-Nucleoside) may decrease the serum concentration of Etravirine. This has been observed with the NNRTIs efavirenz and nevirapine. Reverse Transcriptase Inhibitors (Non-Nucleoside) may increase the serum concentration of Etravirine. This has been observed with delavirdine. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fosamprenavir: May decrease the serum concentration of Delavirdine. The active metabolite amprenavir is likely responsible for this effect. Delavirdine may increase the serum concentration of Fosamprenavir. Specifically, delavirdine may increase concentrations of the active metabolite amprenavir. *Risk X: Avoid combination*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nebivolol: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the serum concentration of Delavirdine. Delavirdine may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: Delavirdine may decrease the metabolism of Rifamycin Derivatives. Rifamycin Derivatives may increase the metabolism of Delavirdine. *Risk D: Consider therapy modification*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Strong) may decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

Tetrabenazine: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Tetrabenazine. Specifically, concentrations of the active alpha- and beta-dihydrotetrabenazine metabolites may be increased. Management: Tetrabenazine dose should be reduced by 50% when starting a strong CYP2D6 inhibitor. Maximum tetrabenazine dose is 50mg/day when used with a strong CYP2D6 inhibitor. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Delavirdine serum concentration may be decreased by St John's wort; avoid concurrent use.

Monitoring ParametersLiver function tests if administered with saquinavir

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions or toxicity; dosing adjustments may be necessary. A list of medications that should not be used is available in each bottle and patients should be provided with this information. Assess effectiveness of therapy (decrease in infections and progress of disease; viral load and CD4 count) and adverse reactions periodically during therapy. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions, and adverse symptoms to report (eg, rash, gastrointestinal upset).

Monitoring: Lab TestsLiver function tests if administered with saquinavir; viral load

Patient EducationYou will be provided with a list of specific medications that should not be used during therapy; do not take any new prescriptions, over-the-counter medications, or herbal products (even if they are not on the list) without consulting prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. This drug is prescribed as one part of a multidrug combination; take exactly as directed for full course of therapy. May be taken with or without food. Do not take antacids within 1 hour of delavirdine. Take 200 mg tablets intact (do not chew or dissolve). You may mix four 100 mg tablets in 3-5 oz of water, allow to stand a few minutes and stir; drink immediately; rinse glass and mouth (swallow rinse solution) following ingestion to ensure total dose administered. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. You may be susceptible to infection; avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber. Frequent blood tests may be required with prolonged therapy. May cause nausea or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Consult prescriber if nausea or vomiting persists. Report skin rash or irritation, muscle weakness, persistent headache, fatigue or gastrointestinal upset. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as mesylate: 100 mg, 200 mg

Generic AvailableNo

ManufacturerPharmacia & Upjohn

Pricing: U.S. (www.drugstore.com)

Tablets (Rescriptor)

200 mg (30): $53.99

Mechanism of ActionDelavirdine binds directly to reverse transcriptase, blocking RNA-dependent and DNA-dependent DNA polymerase activities

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: Low concentration in saliva and semen; CSF 0.4% concurrent plasma concentration

Protein binding: ~98%, primarily albumin

Metabolism: Hepatic via CYP3A4 and 2D6 (**Note:** May reduce CYP3A activity and inhibit its own metabolism.)

Bioavailability: Tablet: 85% as tablet; ~100% as oral slurry

Half-life elimination: 5.8 hours (range: 2-11 hours)

Time to peak, plasma: 1 hour

Excretion: Urine (51%, <5% as unchanged drug); feces (44%); nonlinear kinetics exhibited

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV

Pharmacotherapy PearlsPotential compliance problems, frequency of administration, and adverse effects should be discussed with patients before initiating therapy to help prevent the emergence of resistance.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentFluoxetine may increase plasma concentrations of delavirdine; carbamazepine and phenobarbital may decrease plasma concentrations of delavirdine; delavirdine may increase concentrations of alprazolam, midazolam, and triazolam

Index TermsU-90152S

References

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Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” July 29, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesRescriptor (AN, AU, BB, BM, BS, BZ, CA, GY, JM, SR, TT)

Demeclocycline

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(dem e kloe SYE kleen)
U.S. Brand NamesDeclomycin®
Canadian Brand NamesDeclomycin®
Pharmacologic CategoryAntibiotic, Tetracycline Derivative
Use: Labeled IndicationsTreatment of susceptible bacterial infections (acne, gonorrhea, pertussis and urinary tract infections) caused by both gram-negative and gram-positive organisms
Use: Unlabeled/InvestigationalTreatment of chronic syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Dosing: Adults

Susceptible infections: Oral: 150 mg 4 times/day or 300 mg twice daily

SIADH (unlabeled use): Oral: 900-1200 mg/day or 13-15 mg/kg/day divided every 6-8 hours initially, then decrease to 600-900 mg/day

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricSusceptible infections: Oral: ≥8 years: 8-12 mg/kg/day divided every 6-12 hours
Dosing: Renal ImpairmentShould be avoided in patients with renal dysfunction.
Dosing: Hepatic ImpairmentShould be avoided in patients with hepatic dysfunction.
Administration: OralAdminister 1 hour before or 2 hours after food or milk with plenty of fluid.
Dietary ConsiderationsShould be taken 1 hour before or 2 hours after food or milk with plenty of fluid.
StorageTetracyclines form toxic products when outdated or when exposed to light, heat, or humidity (Fanconi-like syndrome).
ContraindicationsHypersensitivity to demeclocycline, tetracyclines, or any component of the formulation; children <8 years of age; concomitant use with methoxyflurane; pregnancy
Allergy Considerations

- Tetracycline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Increased BUN: May be associated with increases in BUN secondary to antianabolic effects; use caution in patients with renal impairment.
- Nephropathy: Outdated drug can cause nephropathy.
- Photosensitivity: May cause photosensitivity; discontinue if skin erythema occurs. Use skin protection and avoid prolonged exposure to sunlight; do not use tanning equipment.
- Pseudotumor cerebri: Has been (rarely) reported with tetracycline use; usually resolves with discontinuation.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Special populations:

- Pediatrics: May cause tissue hyperpigmentation, enamel hypoplasia, or permanent tooth discoloration; use of tetracyclines should be avoided during tooth development (children ≤8 years of age) unless other drugs are not likely to be effective or are contraindicated. However, recommended in treatment of anthrax exposure.
- Pregnancy: Do not use during pregnancy. In addition to affecting tooth development, tetracycline use has been associated with retardation of skeletal development and reduced bone growth.

Geriatric ConsiderationsHas not been studied exclusively in the elderly.
Pregnancy Risk FactorD
Pregnancy ConsiderationsDemeclocycline has been shown to cross the placenta in rats and other tetracyclines cross the placenta in humans causing permanent discoloration of teeth if used during the second or third trimester. Because use during pregnancy may cause fetal harm, demeclocyline is classified as pregnancy category D.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsDemeclocycline has been shown to cause tooth discolorations in newborn rats when exposed to high doses, but not low doses via breast milk. Other tetracyclines are excreted in breast milk. There is no data on the amount of demeclocycline that is

excreted in human breast milk. Breast-feeding is not recommended by the manufacturer.

Tetracyclines, including demeclocycline, bind to calcium. The calcium in maternal milk will significantly decrease the amount of demeclocycline absorbed by the breast-feeding infant. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Demeclocycline in Pregnancy & Lactation

Adverse Reactions

Frequency not defined.

Cardiovascular: Pericarditis

Central nervous system: Bulging fontanels (infants), dizziness, headache, pseudotumor cerebri (adults)

Dermatologic: Angioneurotic edema, erythema multiforme, erythematous rash, maculopapular rash, photosensitivity, pigmentation of skin, Stevens-Johnson syndrome (rare), urticaria

Endocrine & metabolic: Discoloration of thyroid gland (brown/black), nephrogenic diabetes insipidus

Gastrointestinal: Anorexia, diarrhea, dysphagia, enterocolitis, esophageal ulcerations, glossitis, nausea, pancreatitis, vomiting

Genitourinary: Balanitis

Hematologic: Eosinophilia, neutropenia, hemolytic anemia, thrombocytopenia

Hepatic: Hepatitis (rare), hepatotoxicity (rare), liver enzymes increased, liver failure (rare)

Neuromuscular & skeletal: Myasthenic syndrome, polyarthralgia, tooth discoloration (children <8 years, rarely in adults)

Ocular: Visual disturbances

Otic: Tinnitus

Renal: Acute renal failure

Respiratory: Pulmonary infiltrates

Miscellaneous: Anaphylaxis, anaphylactoid purpura, lupus-like syndrome, systemic lupus erythematosus exacerbation

Drug Interactions

Antacids: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Bismuth: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Bismuth Subsalicylate: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Desmopressin: Demeclocycline may diminish the therapeutic effect of Desmopressin. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Tetracycline Derivatives. Only a concern with orally administered products. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Tetracycline Derivatives may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Penicillins: Tetracycline Derivatives may diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Quinapril: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: Tetracycline Derivatives may enhance the adverse/toxic effect of Retinoic Acid Derivatives. The development of pseudotumor cerebri is of particular concern. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Tetracycline Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zinc Salts: May decrease the absorption of Tetracycline Derivatives. Only a concern when both products are administered orally. **Exceptions:** Zinc Chloride. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Demeclocycline serum levels may be decreased if taken with food.

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization).

Test InteractionsMay interfere with tests for urinary glucose (false-negative urine glucose using Clinistix®, Tes-Tape®)

Monitoring ParametersCBC, renal and hepatic function

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's allergy history prior to beginning therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, increased risk of toxicity or decreased effectiveness). Assess results of laboratory tests, therapeutic response, and adverse effects (eg, rash, anaphylactic reactions, anemia, CNS changes) on a regular basis throughout therapy. Advise patients with diabetes about use of Clinitest®. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC, renal and hepatic function; perform culture and sensitivity studies prior to initiating therapy

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. Take on an empty stomach (1 hour before or 2 hours after meals with plenty of fluid). Take at regularly scheduled intervals around-the-clock. Avoid antacids, iron, dairy products, and other medications within 2 hours of taking demeclocycline. May cause photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); dizziness or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea or vomiting (frequent, small meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (buttermilk, yogurt, or boiled milk may help). Report rash or intense itching, yellowing of skin or eyes, change in color of urine or stools, fever or chills, dark urine or pale stools, vaginal itching or discharge, foul-smelling stools, excessive thirst or urination, acute headache, unresolved or persistent diarrhea, or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptives. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 150 mg, 300 mg

Declomycin®: 150 mg, 300 mg

Generic AvailableYes

ManufacturerLederle Laboratories

Pricing: U.S. (www.drugstore.com)

Tablets (Declomycin)

150 mg (30): $329.99

300 mg (48): $978.05

Mechanism of ActionInhibits protein synthesis by binding with the 30S and possibly the 50S ribosomal subunit(s) of susceptible bacteria; may also cause alterations in the cytoplasmic membrane; inhibits the action of ADH in patients with chronic SIADH

Pharmacodynamics/Kinetics

Onset of action: SIADH: Several days

Absorption: ~50% to 80%; reduced by food and dairy products

Protein binding: 41% to 50%

Metabolism: Hepatic (small amounts) to inactive metabolites; undergoes enterohepatic recirculation

Half-life elimination: 10-17 hours

Time to peak, serum: 3-6 hours

Excretion: Urine (42% to 50% as unchanged drug)

Dental Health: Effects on Dental TreatmentTetracyclines are not recommended for use during pregnancy or in children ≤8 years of age since they have been reported to cause enamel hypoplasia and permanent teeth discoloration. Tetracyclines should only be used in these patients if other agents are contraindicated or alternative antimicrobials will not eradicate the organism. Long-term use associated with oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may decrease the effects of demeclocycline. May cause photosensitivity and other dermatological reactions; consider this possibility when individuals are also taking psychotropics (eg, antipsychotics, carbamazepine, lamotrigine) since they may produce similar reactions.

Index TermsDemeclocycline Hydrochloride; Demethylchlortetracycline

References

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Troyer AD, “Demeclocycline. Treatment for Syndrome of Inappropriate Antidiuretic Hormone Secretion,” *JAMA*, 1977, 237(25):2723-6.[PubMed 194065]

International Brand NamesCompleciclin (ES); Ledermicina (IT); Ledermycin (AT, AU, BE, GB, IE, IN, LU, NL, PK); Ledermycine (FR); Perciclina (PT); Provimicina (ES)

Denileukin Diftitox

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(de ni LOO kin DIF ti toks)

U.S. Brand NamesONTAK®

Pharmacologic CategoryAntineoplastic Agent, Miscellaneous

Use: Labeled IndicationsTreatment of persistent or recurrent cutaneous (peripheral) T-cell lymphoma (CTCL) whose malignant cells express the CD25 component of the IL-2 receptor

Use: Unlabeled/InvestigationalTreatment of CTCL types mycosis fungoides (MF) and Sézary syndrome (SS)

Dosing: Adults**Note:** Premedicate with an antihistamine and acetaminophen prior to each infusion; withhold treatment if serum albumin <3 g/dL.

Persistent or recurrent cutaneous T-cell lymphoma: I.V.: 9 or 18 mcg/kg/day days 1 through 5 every 21 days for 8 cycles.

Dosing: ElderlyRefer to adult dosing.

Dosing: Adjustment for Toxicity

Serum albumin <3 g/dL: Withhold treatment

Severe infusion reaction: Permanently discontinue treatment

Administration: I.V.For I.V. use only. Infuse over 30-60 minutes. Should **not** be given as a rapid I.V. bolus. Discontinue or reduce infusion rate for infusion related reactions; discontinue for severe infusion reaction. Do not administer through an in-line filter. Premedicate with an antihistamine and acetaminophen.

Administration: I.V. DetailpH: 6.9-7.2

StorageStore intact vials frozen at or below -10°C (14°F); do not refreeze after thawing. Solutions ≥15 mcg/mL in NS should be used within 6 hours.

ReconstitutionMust be brought to room temperature (25°C or 77°F) before preparing the dose. Do **not** heat vials. Thaw in refrigerator for not more than 24 hours or at room temperature for 1-2 hours. Solution may be mixed by gentle swirling; avoid vigorous agitation. Dilute with NS to a concentration of ≥15 mcg/mL; the concentration must be ≥15 mcg/mL during all steps of preparation. Add drug to the empty sterile I.V. bag first, then add NS. Do not prepare with glass syringes or in glass containers.

ContraindicationsThere are no contraindications listed within the manufacturer’s labeling.

Warnings/Precautions

Boxed warnings:

- Capillary leak syndrome: See “Concerns related to adverse effects” below.
- Infusion reactions: See “Concerns related to adverse effects” below.
- Visual loss: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Capillary leak syndrome: **[U.S. Boxed Warning]: Has been associated with a potentially severe, including life-threatening, capillary leak syndrome; monitor weight, edema, blood pressure, and serum albumin prior to and during treatment.** Symptoms of capillary leak syndrome (hypotension, edema, hypoalbuminemia) may be delayed, occurring up to 2 weeks postinfusion; symptoms may persist or worsen after cessation of denileukin diftitox. Withhold treatment if serum albumin <3 g/dL; pre-existing low serum albumin levels may correlate with capillary leak syndrome.

- Infusion reactions: **[U.S. Boxed Warning]: Serious and fatal infusion reactions have occurred. Administer in a facility appropriate for cardiopulmonary resuscitation. Discontinue immediately and permanently with serious infusion reaction.** Infusion reaction symptoms usually occur within 24 hours of infusion and resolve within 48 hours of last infusion of cycle. Incidence of infusion reaction has been reported to be lower in cycles 3 and 4 (compared to cycles 1 and 2).

- Immunogenicity: May develop immunogenicity; patients with antibodies have a two- to threefold increase in clearance. The presence of antibodies does not correlate with risk for hypersensitivity/infusion related reactions.

- Infection: Monitor closely for infection; may impair immune function; patients with CTCL are predisposed to cutaneous infection.

- Visual loss: **[U.S. Boxed Warning]: Loss of visual acuity, usually associated with loss of color vision (with or without retinal pigment mottling) has been reported.** Most patients have persistent visual impairment.

Special populations:

- Elderly: Use with caution in patients >65 years of age; adverse events (anemia, anorexia, confusion, hypotension, rash, nausea/vomiting) may occur more frequently.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Confirm CD25 expression on malignant cells prior to treatment.

- Experienced physician: Should be administered under the supervision of an experienced cancer chemotherapy physician.

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. There are no adequate and well-controlled studies in pregnant women. Should be given to a pregnant woman only if clearly needed

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsThe excretion of denileukin diftitox in breast milk is unknown, however, it is recommended that a breast-feeding woman who is treated with denileukin diftitox should discontinue nursing.

Adverse Reactions

>10%:

Cardiovascular: Capillary leak syndrome (33%; serious: 11%), peripheral edema (20% to 26%), vasodilation (22%), hypotension (7% to 16%), chest pain (4% to 13%), tachycardia (12%), thrombosis-related events (7% to 11%)

Central nervous system: Fever (49% to 64%), fatigue (44% to 47%), headache (26% to 29%), dizziness (11% to 13%), pain (11% to 13%)

Dermatologic: Rash (20% to 24%), pruritus (16% to 18%)

Endocrine & metabolic: Hypoalbuminemia (14% to 17%)

Gastrointestinal: Nausea (47% to 60%), vomiting (13% to 35%), diarrhea (22%), anorexia (9% to 20%), taste disturbance (11% to 13%)

Hematologic: Lymphopenia (70%; 24% had lymphopenia at baseline)

Hepatic: ALT increased (84%), AST increased (84%)

Neuromuscular & skeletal: Rigors (42% to 47%), myalgia (18% to 20%), weakness (18%), back pain (16% to 18%), arthralgia (13% to 16%)

Respiratory: Cough (18% to 20%), upper respiratory infection (13%), dyspnea (11% to 13%)

Miscellaneous: Antibody formation (76% to 100%) neutralizing antibodies (45% to 97%), flu-like syndrome (≤85%), infusion reaction (71%; serious: 8%), infection (48%)

1% to 10%:

Cardiovascular: Arrhythmia (6%), hypertension (6%)

Hematologic: Leukopenia (grades 3/4: 3% to 6%), neutropenia (grades 3/4: 3%), thrombocytopenia (grades 3/4: 3%)

Local: Injection site reaction (8%)

Ocular: Visual changes (serious: 4%; includes loss of visual acuity)

Renal: Serum creatinine increased (3% to 10%), proteinuria/casts/hematuria (6%)

Postmarketing and/or case reports: Acute renal insufficiency, hyper-/hypothyroidism, oral ulcer, pancreatitis, thyroiditis, thyrotoxicosis, toxic epidermal necrolysis

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersBaseline CD25 expression (on malignant cells); serum albumin level (prior to each treatment), CBC, blood chemistry panel, renal and hepatic function tests (prior to initiation of therapy and weekly during therapy). During the infusion, the patient should be monitored for symptoms of an infusion reaction. After infusion, the patient should be monitored for the development of a delayed capillary leak syndrome (usually in the first 2 weeks), including careful monitoring of weight, blood pressure, and serum albumin.

Information on assay for malignant cell CD25 expression is available at 1-877-873-4724.

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests prior to therapy and weekly during therapy. Patient must be monitored closely for acute hypersensitivity reaction during and for 24 hours following first infusion. Following infusion, patient should be monitored or taught to monitor for delayed vascular leak syndrome (eg, hypotension, edema, or hypoalbuminemia) and other adverse reactions. Teach patient appropriate interventions to reduce side effects and adverse reactions to report.

Monitoring: Lab TestsBaseline CD25 expression (on malignant cells); serum albumin level (prior to each treatment), CBC, blood chemistry panel, renal and hepatic function tests (prior to initiation of therapy and weekly during therapy). Information on assay for malignant cell CD25 expression is available at 1-877-873-4724.

Patient EducationThis medication can only be administered via intravenous infusion. During infusion, report immediately any chills; chest pain, respiratory difficulty, or tightness in throat; or redness, swelling, pain, or burning at infusion site. Maintaining adequate nutrition and hydration is important (2-3 L/day) unless instructed to restrict fluid intake. You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea, vomiting, anorexia, flatulence (small, frequent meals, good mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); diarrhea (buttermilk, boiled milk, or yogurt may help); headache, back or muscle pain (consult prescriber for mild analgesic); dizziness, weakness, or confusion (use caution when driving, engaging in hazardous activities, or climbing stairs until effect of medication is known). Report unresolved GI effects; headache, back or muscle pain; skin dryness, rash, or sores; altered urinary patterns; flu syndrome or infection (eg, weakness, fatigue, white plaques or sores in mouth, vaginal discharge, chills, fever); CNS disturbances (insomnia, dizziness, agitation, confusion, depression); unusual bleeding or bruising, blood in urine or stool; swelling of extremities; or any other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [frozen]:

ONTAK®: 150 mcg/mL (2 mL) [contains EDTA]

Generic AvailableNo

Mechanism of ActionDenileukin diftitox is a fusion protein (a combination of amino acid sequences from diphtheria toxin and interleukin-2) which selectively delivers the cytotoxic activity of diphtheria toxin to targeted cells. It interacts with the high-affinity IL-2 receptor on the surface of malignant cells to inhibit intracellular protein synthesis, rapidly leading to cell death.

Pharmacodynamics/Kinetics

Distribution: V_d: 0.06-0.09 L/kg

Metabolism: Hepatic via proteolytic degradation (animal studies)

Half-life elimination: Distribution: 2-5 minutes; Terminal: 70-80 minutes

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy Pearls**Oncology Comment:** The National Comprehensive Cancer Network (NCCN) Non-Hodgkin's Lymphoma Guidelines (v.3.2008) list denileukin diftitox as a second-line treatment option for systemic therapy of peripheral (cutaneous) T-cell lymphoma in patients who are not candidates for high dose therapy or autologous stem cell rescue. In mycosis fungoides (MF) and Sézary syndrome (SS), denileukin diftitox is a therapy option, either as monotherapy or in combination with bexarotene; participation in a clinical trial is encouraged for this patient population.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and nervousness are common; may cause insomnia or confusion

Mental Health: Effects on Psychiatric TreatmentHypotension and tachycardia are common; use caution with low potency antipsychotics and other psychotropics. Nausea and vomiting are common; use caution with SSRIs.

Index TermsDAB389 Interleukin-2; DAB$_{389}$IL-2; NSC-714744

References

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Foss FM, "DAB(389)IL-2 (denileukin diftitox, ONTAK): A New Fusion Protein Technology," *Clin Lymphoma*, 2000, 1(Suppl 1):27-31.

Foss F, Demierre MF, and DiVenuti F, "A Phase-1 Trial of Bexarotene and Denileukin Diftitox in Patients With Relapsed or Refractory Cutaneous T-Cell Lymphoma," *Blood*, 2005, 106(2):454-7.[PubMed 15811959]

Kuzel TM, "DAB(389)IL-2 (denileukin diftitox, ONTAK): Review of Clinical Trials to Date," *Clin Lymphoma*, 2000, 1(Suppl 1):33-6.

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National Comprehensive Cancer Network (NCCN), "Clinical Practice Guidelines in Oncology™: Non-Hodgkin's Lymphomas," V.3.2008. Available at http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf

Nichols J, Foss F, Kuzel TM, et al, "Interleukin-2 Fusion Protein: An Investigational Therapy for Interleukin-2 Receptor Expressing Malignancies," *Eur J Cancer*, 1997, 33(Suppl 1):34-6.

Olsen E, Duvic M, Frankel A, et al, "Pivotal Phase III Trial of Two Dose Levels of Denileukin Diftitox for the Treatment of Cutaneous T-Cell Lymphoma," *J Clin Oncol*, 2001, 19(2):376-88.[PubMed 11208829]

Polder K, Wang C, Duvic M, et al, "Toxic Epidermal Necrolysis Associated With Denileukin Diftitox (DAB$_{389}$IL-2) Administration in a Patient With

Follicular Large Cell Lymphoma," *Leuk Lymphoma*, 2005, 46(12):1807-11.[PubMed 16263585]

Desflurane

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Desflurane may be confused with Desferal®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(DES flure ane)
U.S. Brand NamesSuprane®
Canadian Brand NamesSuprane®
Pharmacologic CategoryGeneral Anesthetic, Inhalation
Use: Labeled IndicationsInduction and maintenance of general anesthesia (adults); maintenance of anesthesia (intubated children)
Dosing: AdultsInhalation: The minimum alveolar concentration (MAC), the concentration at which 50% of patients do not respond to surgical incision, ranges from 6.0% (45 years of age) to 7.3% (25 years of age). The concentration at which amnesia and loss of awareness occur (MAC - awake) is 2.4%. Surgical levels of anesthesia are achieved with concentrations between 2.5% to 8.5%.

Note: Because of the higher vapor pressure of desflurane, its vaporizer is heated in order to deliver a constant concentration

Dosing: ElderlyMAC is reduced (5.2% at 70 years of age).
Dosing: PediatricAnesthesia maintenance: Children (intubated): Surgical levels of anesthesia range between 5.2% to 10%

Note: Because of the higher vapor pressure of desflurane, its vaporizer is heated in order to deliver a constant concentration

Administration: InhalationVia desflurane-specific calibrated heated vaporizer
ContraindicationsHypersensitivity to desflurane, other halogenated anesthetic agents, or any component of the formulation; known or suspected history of malignant hyperthermia
Warnings/Precautions

Concerns related to adverse effects:

- Decreased blood flow: May cause decrease in hepatic and/or renal blood flow.
- Hepatitis: May cause sensitivity hepatitis in patients who have been sensitized by previous exposure to halogenated anesthetics.
- Hyperkalemia: Use of other inhaled anesthetics has been associated with rare cases of perioperative hyperkalemia; concomitant use of succinylcholine was associated with many of the reported cases, but not all. Risk of hyperkalemia is increased in pediatric patients with underlying neuromuscular disease (eg, Duchenne muscular dystrophy). Other abnormalities may include elevation in CPK and myoglobinuria. Monitor closely for arrhythmias. Aggressively identify and treat hyperkalemia.
- Increased intracranial pressure: May dilate the cerebral vasculature and may, in certain conditions, increase intracranial pressure.
- Malignant hyperthermia: May trigger malignant hyperthermia; avoid use in patients susceptible to malignant hyperthermia.
- Respiratory depression: Causes dose-dependent respiratory depression and blunted ventilatory response to hypoxia and hypercapnia. Hypoxic pulmonary vasoconstriction is blunted which may lead to increased pulmonary shunt. May produce elevated carbon monoxide levels in the presence of a dry carbon dioxide absorbent within the circle breathing system of an anesthetic machine; maintain fresh absorbent as per manufacturer guidelines regardless of state of colorimetric indicator.

Disease-related concerns:

- Cardiovascular disease: Do not use as a single agent to induce anesthesia in patients with CAD or in whom an increase in heart rate or blood pressure should be avoided. Abrupt increases in inspired concentrations >1 MAC can produce a transient increase in blood pressure and heart rate due to increased plasma catecholamine levels. Hypotensive effect due to peripheral vasodilation is dose dependent and increases as anesthesia is deepened.

Special populations:

- Pediatrics: Due to higher incidences of airway irritation (eg, laryngospasm, coughing, breath-holding, increased secretions) in pediatric patients, avoid use to induce and/or maintain anesthesia in nonintubated pediatric patients.

Pregnancy Risk FactorB
Pregnancy ConsiderationsNo adverse events were seen in animal studies. There are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/use caution

Breast-Feeding Considerations Due to rapid washout, desflurane levels in milk most likely have no clinical importance 24 hours after anesthesia.

Adverse Reactions

>10%:

- Gastrointestinal: Nausea (27%), vomiting (16%)
- Respiratory: Cough (3% to 34%), breath-holding (>1% to 30%), apnea (3% to 15%)

1% to 10%:

- Cardiovascular: Bradycardia, hyper-/hypotension, nodal arrhythmia, tachycardia
- Central nervous system: Emergence delirium, headache
- Gastrointestinal: Salivation increased
- Ocular: Conjunctivitis
- Respiratory: Secretions increased (3% to 10%), laryngospasm (3% to 10%), oxyhemoglobin desaturation (3% to 10%), pharyngitis (>1% to 10%)
- Miscellaneous: Shivering

<1% (Limited to important or life-threatening): Agitation, arrhythmia, asthma, bigeminy, dizziness, dyspnea, ECG changes, hemorrhage, hepatic failure, hepatic necrosis, hepatitis, hyperkalemia, hypoxia, malignant hyperthermia, MI, myocardial ischemia, myalgia, pruritus, vasodilation

Drug Interactions

EPINEPHrine: Inhalational Anesthetics may enhance the arrhythmogenic effect of EPINEPHrine. *Risk D: Consider therapy modification*

Methylphenidate: May enhance the hypertensive effect of Inhalational Anesthetics. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): Inhalational Anesthetics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Monitoring Parameters Blood pressure, heart rate and rhythm, temperature, oxygen saturation, end-tidal CO_2 and end-tidal desflurane concentrations should be monitored prior to and throughout anesthesia

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, for inhalation:

- Suprane®: 100% (240 mL) [amber bottle]

Generic Available No

Pharmacodynamics/Kinetics

Onset of action: 1-2 minutes

Duration: Emergence time: Depends on blood concentration when desflurane is discontinued

- The rate of change of anesthetic concentration in the lung is more rapid with desflurane because of its low blood/gas solubility (0.42), which is similar to nitrous oxide.

Metabolism: Hepatic (0.02%)

Excretion: Exhaled gases

Pharmacotherapy Pearls Desflurane has the lowest fat-to-blood solubility of the inhaled anesthetics (desflurane, enflurane, isoflurane, sevoflurane); may be useful in obese patients who are undergoing anesthesia for longer procedures (>2 hours).

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause delirium

Mental Health: Effects on Psychiatric Treatment Hypotension is common; concomitant use with psychotropics may produce additive effects; monitor

Anesthesia and Critical Care Concerns/Other Considerations Use of desflurane for induction of general anesthesia is not recommended due to its irritant properties and unpleasant odor which may cause breath holding and coughing.

References

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Sakai EM, Connolly LA, and Klauck J, "Inhalation Anesthesiology and Volatile Liquid Anesthetics: Focus on Isoflurane, Desflurane, and Sevoflurane," *Pharmacotherapy*, 2005, 25(12):1773-88.[PubMed 16305297]

Yasuda N, Lockhart SH, Eger EI 2nd, et al, "Kinetics of Desflurane, Isoflurane, and Halothane in Humans," *Anesthesiology*, 1991, 74(3):489-98.[PubMed 2001028]

International Brand Names Sulorane (IL); Suprane (AR, AT, AU, BE, CH, CZ, DE, DK, EC, EE, ES, FI, GB, HK, HN, ID, IT, KP, LU, MY, NL, NO, PE, PH, PL, SE, TH, VE)

Desipramine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) has issued a statement in April 2008 recommending that all children diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the recommendations due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: Methylphenidate, amphetamine, dextroamphetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children’s Healthcare Quality.

For more information, refer to:

http://americanheart.mediaroom.com/index.php?s=43&item=422

http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1

http://americanheart.mediaroom.com/index.php?s=43&item=398

http://www.fda.gov/medwatch/safety/2007/safety07.htm

http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html

Nissen SE, “ADHD Drugs and Cardiovascular Risk,” *N Engl J Med*, 2006, 354(14):1445-48.

“Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder,” *J Am Acad*

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Wilens TE, Prince JB, Spencer TJ, et al, “Stimulants and Sudden Death: What is a Physician to do?” *Pediatrics*, 2006, 118(3):1215-19.

Medication Safety Issues

Sound-alike/look-alike issues:

Desipramine may be confused with clomiPRAMINE, deserpidine, diphenhydrAMINE, disopyramide, imipramine, nortriptyline

Norpramin® may be confused with clomiPRAMINE, imipramine, Norpace®, nortriptyline, Tenormin®

International issues:

Norpramin®: Brand name for omeprazole in Spain

Pronunciation(des IP ra meen)

U.S. Brand NamesNorpramin®

Canadian Brand NamesAlti-Desipramine; Apo-Desipramine®; Norpramin®; Nu-Desipramine; PMS-Desipramine

Pharmacologic CategoryAntidepressant, Tricyclic (Secondary Amine)

Use: Labeled IndicationsTreatment of depression

Use: Unlabeled/InvestigationalAnalgesic adjunct in chronic pain; peripheral neuropathies; substance-related disorders (eg, cocaine withdrawal); attention-deficit/hyperactivity disorder (ADHD); depression in children ≤12 years of age

Dosing: Adults

Depression: Oral: Initial: 75 mg/day in divided doses; increase gradually to 150-200 mg/day in divided or single dose; maximum: 300 mg/day

Cocaine withdrawal (unlabeled use): 50-200 mg/day in divided or single dose

Dosing: ElderlyOral: Initial: 10-25 mg/day; increase by 10-25 mg every 3 days for inpatients and every week for outpatients if tolerated; usual maintenance dose: 75-100 mg/day, but doses up to 150 mg/day may be necessary.

Dosing: PediatricDepression: Oral:

Children 6-12 years (unlabeled use): 10-30 mg/day or 1-3 mg/kg/day in divided doses; do not exceed 5 mg/kg/day

Adolescents: Initial: 25-50 mg/day; gradually increase to 100 mg/day in single or divided doses; maximum: 150 mg/day

Dosing: Renal ImpairmentHemodialysis/peritoneal dialysis effects: Supplemental dose is not necessary.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to desipramine, drugs of similar chemical class, or any component of the formulation; use of MAO inhibitors within 14 days; use in a patient during the acute recovery phase of MI; concurrent use of thioridazine

Allergy Considerations

- Tricyclic Antidepressant and Related Compounds Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Desipramine is FDA approved for the treatment of depression in adolescents.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Desipramine is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. The degree of anticholinergic blockade produced by this agent is low relative to other antidepressants.

- Hematologic effects: TCAs may rarely cause bone marrow suppression; monitor for any signs of infection and obtain CBC if symptoms (eg, fever, sore throat) evident.

- Orthostatic hypotension: May cause orthostatic hypotension (risk is moderate relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is low-moderate relative to other antidepressants.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk of conduction abnormalities with this agent is moderate relative to other antidepressants.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose regulation.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

- Thyroid dysfunction: Use with caution in patients with hyperthyroidism or those receiving thyroid supplementation due to concerns of pro-arrhythmogenesis.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be at greater risk of falling or confusional states.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Discontinuation of therapy: Recommended to discontinue prior to elective surgery requiring general anesthesia. Therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

⇧ Geriatric ConsiderationsPreferred agent because of its milder side effect profile; patients may experience excitation or stimulation, in such cases, administer as a single morning dose or divided dose. Data from a clinical trial comparing fluoxetine to tricyclics suggest that fluoxetine is significantly less effective than nortriptyline in hospitalized elderly patients with unipolar major affective disorder, especially those with melancholia and concurrent cardiovascular disease.
⇧ Pregnancy Risk FactorC
⇧ LactationEnters breast milk/not recommended (AAP rates “of concern”)
⇧ Breast-Feeding ConsiderationsGenerally, it is not recommended to breast-feed if taking antidepressants because of the long half-life, active metabolites, and the potential for side effects in the infant.
⇧ Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, edema, flushing, heart block, hyper-/hypotension, MI, palpitation, stroke, tachycardia

Central nervous system: Agitation, anxiety, ataxia, confusion, delirium, disorientation, dizziness, drowsiness, drug fever, exacerbation of psychosis, extrapyramidal symptoms, fatigue, hallucinations, headache, hypomania, incoordination, insomnia, nervousness, parkinsonian syndrome, restlessness, seizure

Dermatologic: Alopecia, itching, petechiae, photosensitivity, skin rash, urticaria

Endocrine & metabolic: Breast enlargement, galactorrhea, hyper-/hypoglycemia, impotence, libido changes, SIADH

Gastrointestinal: Abdominal cramps, anorexia, black tongue, constipation, decreased lower esophageal sphincter tone may cause GE reflux, diarrhea, heartburn, nausea, paralytic ileus, stomatitis, unpleasant taste, vomiting, weight gain/loss, xerostomia

Genitourinary: Difficult urination, polyuria, sexual dysfunction, testicular edema, urinary retention

Hematologic: Agranulocytosis, eosinophilia, purpura, thrombocytopenia

Hepatic: Cholestatic jaundice, hepatitis, liver enzymes increased

Neuromuscular & skeletal: Fine muscle tremor, numbness, paresthesia of extremities, peripheral neuropathy, tingling, weakness

Ocular: Blurred vision, disturbances of accommodation, intraocular pressure increased, mydriasis

Otic: Tinnitus

Miscellaneous: Allergic reaction, diaphoresis (excessive)

Metabolism/Transport Effects **Substrate** of CYP1A2 (minor), 2D6 (major); **Inhibits** CYP2A6 (moderate), 2B6 (moderate), 2D6 (moderate), 2E1 (weak), 3A4 (moderate)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Tricyclic Antidepressants may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Agonists: Tricyclic Antidepressants may enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Alpha2-Agonists: Tricyclic Antidepressants may diminish the antihypertensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Altretamine: May enhance the orthostatic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Amphetamines: Tricyclic Antidepressants may enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Beta2-Agonists: Tricyclic Antidepressants may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cinacalcet: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2A6 Substrates: CYP2A6 Inhibitors (Moderate) may decrease the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inhibitors (Moderate) may decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Desmopressin: Tricyclic Antidepressants may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dexmethylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

DULoxetine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Iobenguane I 123: Tricyclic Antidepressants may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May enhance the neurotoxic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Tricyclic Antidepressants may enhance the QTc-prolonging effect of QuiNIDine. QuiNIDine may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

St Johns Wort: May increase the metabolism of Tricyclic Antidepressants. The risk of serotonin syndrome may theoretically be increased. *Risk D: Consider therapy modification*

Sulfonylureas: Cyclic Antidepressants may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Terbinafine: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: Tricyclic Antidepressants may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. *Risk C: Monitor therapy*

Valproic Acid: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Tricyclic Antidepressants may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Grapefruit juice may inhibit the metabolism of some TCAs and clinical toxicity may result.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava (may increase risk of serotonin syndrome and/or excessive sedation).

Monitoring ParametersMonitor blood pressure and pulse rate prior to and during initial therapy; evaluate mental status, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased); monitor weight; ECG in older adults and those patients with cardiac disease; blood levels are useful for therapeutic monitoring

When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure, and consider obtaining ECG prior to initiation (Vetter, 2008); ensure PR interval ≤200 ms, QRS duration ≤120 ms, and QT_c ≤460 ms.

Reference Range

Plasma levels do not always correlate with clinical effectiveness

Timing of serum samples: Draw trough just before next dose

Therapeutic: 50-300 ng/mL

In elderly patients the response rate is greatest with steady-state plasma concentrations >115 ng/mL

Possible toxicity: >300 ng/mL

Toxic: >1000 ng/mL

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Monitor CNS status. Assess for suicidal tendencies before beginning therapy, during initiation of therapy, or following an increase or decrease of dosage. May cause physiological or psychological dependence, tolerance, or abuse; periodically evaluate need for continued use. Caution patients with diabetes to monitor glucose levels closely; may increase or decrease serum glucose levels. Assess therapeutic response and adverse reactions at beginning of therapy and periodically with long-term use. Taper dose slowly when discontinuing. Teach patient proper use, appropriate interventions to reduce side effects, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results. This medicine may cause physical and/or psychological dependence. Avoid alcohol and grapefruit juice. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); loss of appetite or disturbed taste (small frequent meals, good mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); urinary retention (void before taking medication); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); altered sexual drive or ability (reversible); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report chest pain, palpitations, or rapid heartbeat; persistent adverse CNS effects (eg, suicidal ideation, nervousness, restlessness, insomnia, anxiety, excitation, headache, agitation, impaired coordination, changes in cognition); muscle cramping, weakness, tremors, or rigidity; blurred vision or eye pain; breast enlargement or swelling; yellowing of skin or eyes; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended..

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg

Norpramin®: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg [contains soy oil]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Desipramine HCl)

10 mg (60): $19.99

25 mg (60): $20.99

50 mg (60): $28.99

75 mg (60): $32.99

100 mg (30): $24.99

150 mg (30): $29.99

Tablets (Norpramin)

10 mg (60): $61.84

25 mg (60): $74.85

50 mg (60): $135.62

75 mg (60): $170.34

100 mg (30): $110.46

150 mg (30): $162.74

Mechanism of ActionTraditionally believed to increase the synaptic concentration of norepinephrine (and to a lesser extent, serotonin) in the central nervous system by inhibition of its reuptake by the presynaptic neuronal membrane. However, additional receptor effects have been found including desensitization of adenyl cyclase, down regulation of beta-adrenergic receptors, and down regulation of serotonin receptors.

Pharmacodynamics/Kinetics

Onset of action: 1-3 weeks; Maximum antidepressant effect: >2 weeks

Absorption: Well absorbed

Metabolism: Hepatic

Half-life elimination: Adults: 7-60 hours

Time to peak, plasma: 4-6 hours

Excretion: Urine (70%)

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsLess sedation and anticholinergic effects than with amitriptyline or imipramine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), unpleasant taste, stomatitis, and black tongue. Long-term treatment with TCAs increases the risk of caries by reducing salivation and salivary buffer capacity.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution; epinephrine and levonordefrin have been shown to have an increased pressor response in combination with TCAs. Desipramine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health CommentTricyclic antidepressants may be classified as tertiary (amitriptyline, doxepin, clomipramine, imipramine, trimipramine) or secondary amines (nortriptyline, desipramine, protriptyline). The tertiary amines are not recommended to treat depression in the elderly. If a TCA is used in the elderly, it should be a secondary amine. The tertiary amines are commonly used in low dosages for various conditions associated with pain. Plasma concentrations correlate with clinical response. A linear relationship appears to exist. Toxicity is generally dose dependent. Relatively small overdoses (1-week supply) can be potentially fatal.

Anesthesia and Critical Care Concerns/Other ConsiderationsDesipramine causes less sedation and anticholinergic effects than with amitriptyline or imipramine.

Index TermsDesipramine Hydrochloride; Desmethylimipramine Hydrochloride

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International Brand NamesDeprexan (IL); Norpramin (MX); Nortimil (IT); Pertofran (AT, NL, NZ); Petylyl (CZ, DE, PL, RU)

Desloratadine and Pseudoephedrine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(des lor AT a deen & soo doe e FED rin)

U.S. Brand NamesClarinex-D® 12 Hour; Clarinex-D® 24 Hour

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation

Use: Labeled IndicationsRelief of symptoms of seasonal allergic rhinitis, in children ≥12 years of age and adults

Dosing: AdultsSeasonal or allergic rhinitis: Oral:

Clarinex-D® 12 Hour: One tablet twice daily

Clarinex-D® 24 Hour: One tablet daily

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricSeasonal or allergic rhinitis: Oral: Children ≥12 years: Refer to adult dosing.

Dosing: Renal Impairment

Clarinex-D® 24 Hour: One tablet every other day

Clarinex-D® 12 Hour: Not recommended

Dosing: Hepatic ImpairmentNot recommended

Administration: OralTablet should be swallowed whole; do not break, crush, or chew. Administer with water.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at 15°C to 30°C (59°F to 86°F). Heat sensitive; avoid exposure above 30°C (86°F).

ContraindicationsHypersensitivity to loratadine, desloratadine, pseudoephedrine, or any component of the formulation; narrow-angle glaucoma; urinary retention; during or within 14 days of MAO inhibitor therapy; severe hypertension or coronary artery disease; use in patients experiencing idiosyncratic reactions (eg, insomnia, tremor, dizziness) to adrenergic agents

Warnings/Precautions

Concerns related to adverse effects:

- CNS stimulation: May occur due to sympathomimetic amine (pseudoephedrine); seizures have been reported.
- Tachycardia: May occur due to sympathomimetic amine (pseudoephedrine); cardiovascular collapse with hypotension may also occur.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Diabetes: Use with caution in patients with diabetes mellitus.
- Hepatic impairment: Avoid use in patients with hepatic impairment.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia: Use with caution in patients with prostatic hyperplasia.
- Renal impairment: Avoid the use of Clarinex-D® 12 Hour. Use Clarinex-D® 24 Hour with caution in patients with renal impairment (dosage adjustments are recommended).
- Thyroid dysfunction: Use with caution in patients with hyperthyroidism.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects..
- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. See individual agents.

LactationDesloratadine and pseudoephedrine enter breast milk/not recommended

Adverse ReactionsSee also individual agents. Percentages as reported with the combination products:

1% to 10%:

Central nervous system: Insomnia (5% to 10%), headache (6% to 8%), fatigue (3% to 4%), somnolence (3%), dizziness (2% to 3%), hyperactivity (2%), nervousness (2%)

Gastrointestinal: Xerostomia (8%), anorexia (2%), nausea (2%)

Respiratory: Pharyngitis (3%)

Miscellaneous: Infection (2%)

Postmarketing and/or case reports: Bilirubin increased, hepatitis (rare), hypersensitivity (rare), palpitation, tachycardia, transaminases increased

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Monitoring ParametersCreatinine clearance (pretreatment for product selection and dosing adjustment)

Monitoring: Lab TestsCreatinine clearance (pretreatment for product selection and dosing adjustment)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, variable release:

Clarinex-D® 12 Hour: Desloratadine 2.5 mg [immediate release] and pseudoephedrine 120 mg [extended release]

Clarinex-D® 24 Hour: Desloratadine 5 mg [immediate release] and pseudoephedrine 240 mg [extended release]

Generic AvailableNo

ManufacturerSchering-Plough

Pricing: U.S. (www.drugstore.com)

Tablet, 12-hour (Clarinex-D 12 Hour)

2.5-120 mg (100): $257.55

Tablet, 24-hour (Clarinex-D 24 Hour)

5-240 mg (30): $114.89

Mechanism of Action

Desloratadine, a major metabolite of loratadine, is a long-acting tricyclic antihistamine with selective peripheral histamine H_1 receptor antagonistic activity and additional anti-inflammatory properties.

Pseudoephedrine directly stimulates alpha-adrenergic receptors of respiratory mucosa causing vasoconstriction; directly stimulates beta-adrenergic receptors causing bronchial relaxation, increased heart rate and contractility.

Pharmacodynamics/KineticsAlso see individual agents.

Onset: Antihistaminic activity: 1 hour

Time to peak, plasma: Desloratadine: 4-7 hours; pseudoephedrine: 6-9 hours

Related Information

- Desloratadine
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, insomnia, restlessness, somnolence, or hyperactivity

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor therapy

Index TermsPseudoephedrine and Desloratadine

Desloratadine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(des lor AT a deen)

U.S. Brand NamesClarinex®

Canadian Brand NamesAerius®

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation

Use: Labeled IndicationsRelief of nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR); treatment of chronic idiopathic urticaria (CIU)

Dosing: AdultsSeasonal or perennial allergic rhinitis, chronic idiopathic urticaria: Oral: 5 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricSeasonal or perennial allergic rhinitis, chronic idiopathic urticaria: Oral:

Children:

6-11 months: 1 mg once daily

12 months to 5 years: 1.25 mg once daily

6-11 years: 2.5 mg once daily

Children ≥12 years: Refer to adult dosing.

Dosing: Renal Impairment

Children: Not established

Adults: 5 mg every other day

Dosing: Hepatic Impairment5 mg every other day

Administration: OralMay be taken with or without food.

RediTabs® should be placed on the tongue; tablet will disintegrate immediately. May be taken with or without water.

Syrup: A commercially-available measuring dropper or syringe calibrated to deliver 2 mL or 2.5 mL should be used to administer age-appropriate doses in children.

Dietary ConsiderationsMay be taken with or without food. Orally-disintegrating tablets contain phenylalanine.

StorageSyrup, tablet, orally-disintegrating tablet: Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Protect from moisture and excessive heat (85°F). Use orally-disintegrating tablet immediately after opening blister package. Syrup should be protected from light.

ContraindicationsHypersensitivity to desloratadine, loratadine, or any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment needed.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment needed.

Special populations:

- Pediatrics: Safety and efficacy have not been established for children <6 months of age.
- Slow metabolizers: Use with caution in patients known to be slow metabolizers of desloratadine (incidence of side effects may be increased).

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationEnters breast milk/not recommended

Adverse Reactions

>10%: Central nervous system: Headache (14%)

1% to 10%:

Central nervous system: Fatigue (2% to 5%), somnolence (2%), dizziness (4%)

Endocrine & metabolic: Dysmenorrhea (2%)

Gastrointestinal: Xerostomia (3%), nausea (5%), dyspepsia (3%)

Neuromuscular & skeletal: Myalgia (2% to 3%)

Respiratory: Pharyngitis (3% to 4%)

Postmarketing and/or case reports: Anaphylaxis, bilirubin increased, dyspnea, edema, hepatitis, hypersensitivity reactions, palpitation, pruritus, psychomotor hyperactivity, rash, seizure, tachycardia, transaminases increased, urticaria

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase risk of sedation).

Food: Does not affect bioavailability.

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake as directed; do not exceed recommended dose. Avoid use of other depressants, alcohol, or sleep-inducing medications unless approved by prescriber. You may experience headache, drowsiness, or dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known); or dry mouth, dry throat, or nausea (small frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help). Report rapid heartbeat, shortness of breath, skin rash, persistent flu-like symptoms, or muscle aches. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Syrup:

Clarinex®: 0.5 mg/mL (480 mL) [contains propylene glycol, sodium benzoate; bubble gum flavor]

Tablet:

Clarinex®: 5 mg

Tablet, orally disintegrating:

Clarinex® RediTabs®: 2.5 mg [contains phenylalanine 1.4 mg/tablet; tutti-frutti flavor]; 5 mg [contains phenylalanine 2.9 mg/tablet; tutti-frutti flavor]

Generic AvailableNo

ManufacturerSchering Corporation

Pricing: U.S. (www.drugstore.com)

Syrup (Clarinex)

0.5 mg/mL (473): $182.72

Tablet, orally-disintegrating (Clarinex Reditabs)

2.5 mg (30): $128.18

5 mg (30): $117.79

Tablets (Clarinex)

5 mg (30): $115.99

Mechanism of ActionDesloratadine, a major metabolite of loratadine, is a long-acting tricyclic antihistamine with selective peripheral histamine H_1 receptor antagonistic activity and additional anti-inflammatory properties.

Pharmacodynamics/Kinetics

Protein binding: Desloratadine: 82% to 87%; 3-hydroxydesloratadine: 85% to 89%

Metabolism: Hepatic to active metabolite, 3-hydroxydesloratadine (specific enzymes not identified); undergoes glucuronidation. Decreased in slow metabolizers of desloratadine. Not expected to affect or be affected by medications metabolized by CYP with normal doses.

Half-life elimination: 27 hours

Time to peak: 3 hours

Excretion: Urine and feces (as metabolites)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation, fatigue, or dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause nausea; concurrent use with SSRIs, lithium, and valproic acid may be additive

References

McClellan K and Jarvis B, “Desloratadine,” *Drugs*, 2001, 61(6):789-96.[PubMed 11398910]

International Brand NamesAerius (AR, AT, BE, BG, CH, CL, CN, CO, CR, CZ, DE, DK, DO, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IL, IT, MY, NI, NL, NO, NZ, PA, PE, PH, PL, PT, RU, SE, SV, TH, TR, VE); Aviant (MX); Azomyr (AR, AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, MX, NL, NO, PT, RU, SE, TR); Claramax (AU); Denosin 5 (TW); Desalex (BR, CO); Deslor (IN); Lestacan (CR, DO, GT, HN, NI, PA, SV); Neoclaritine (CN); Neoclarityn (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Supraler (PY)

Desmopressin

Lexi-Drugs Online

English English

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Special Alerts

Desmopressin: Health Canada Issues Warning Concerning Increased Risk of Hyponatremia Associated With Intranasal Use - July 2008

Ferring Pharmaceuticals, in conjunction with Health Canada, has issued a Dear Healthcare Professional letter to Canadian healthcare professionals regarding intranasal use of desmopressin and an increased risk of hyponatremia. This warning is similar to one recently announced by the U.S. Food and Drug Administration (FDA) in December, 2007.

Further information can be found at:

*Canada:*http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/desmopressin_hpc-cps-eng.php

*U.S.:*http://www.fda.gov/cder/drug/InfoSheets/HCP/desmopressinHCP.htm

Pronunciation(des moe PRES in)

U.S. Brand NamesDDAVP®; Stimate®

Canadian Brand NamesApo-Desmopressin®; DDAVP®; DDAVP® Melt; Minirin®; Novo-Desmopressin; Octostim®; PMS-Desmopressin

Pharmacologic CategoryAntihemophilic Agent; Hemostatic Agent; Vasopressin Analog, Synthetic

Use: Labeled Indications

Injection: Treatment of diabetes insipidus; maintenance of hemostasis and control of bleeding in hemophilia A with factor VIII coagulant activity levels >5% and mild-to-moderate classic von Willebrand's disease (type 1) with factor VIII coagulant activity levels >5%

Nasal solutions (DDAVP® Nasal Spray and DDAVP® Rhinal Tube): Treatment of central diabetes insipidus

Nasal spray (Stimate®): Maintenance of hemostasis and control of bleeding in hemophilia A with factor VIII coagulant activity levels >5% and mild to moderate classic von Willebrand's disease (type 1) with factor VIII coagulant activity levels >5%

Tablet: Treatment of central diabetes insipidus, temporary polyuria and polydipsia following pituitary surgery or head trauma, primary nocturnal enuresis

Use: Unlabeled/InvestigationalUremic bleeding associated with acute or chronic renal failure; prevention of surgical bleeding in patients with uremia

Dosing: Adults

Diabetes insipidus:

I.V., SubQ: U.S. labeling: 2-4 mcg/day (0.5-1 mL) in 2 divided doses or $^1/_{10}$ of the maintenance intranasal dose. Fluid restriction should be observed.

I.M., I.V., SubQ: Canadian labeling (not in U.S. labeling): 1-4 mcg (0.25-1 mL) once daily or $^1/_{10}$ of the maintenance intranasal dose. Fluid restriction should be observed.

Intranasal (100 mcg/mL nasal solution): 10-40 mcg/day (0.1-0.4 mL) divided 1-3 times/day; adjust morning and evening doses separately for an adequate diurnal rhythm of water turnover. **Note:** The nasal spray pump can only deliver doses of 10 mcg (0.1 mL) or multiples of 10 mcg (0.1 mL); if doses other than this are needed, the rhinal tube delivery system is preferred. Fluid restriction should be observed.

Oral:

U.S. labeling: Initial: 0.05 mg twice daily; total daily dose should be increased or decreased as needed to obtain adequate antidiuresis (range: 0.1-1.2 mg divided 2-3 times/day). Fluid restriction should be observed.

Canadian labeling (not in U.S. labeling): Initial: 0.1 mg 3 times/day; total daily dose should be increased or decreased as needed to obtain adequate antidiuresis (range: 0.3-1.2 mg divided 3 times/day). Fluid restriction should be observed.

Sublingual formulation: Canadian labeling (not in U.S. labeling): Initial: 60 mcg 3 times/day; total daily dose should be increased or decreased as needed to obtain adequate antidiuresis. Usual maintenance: 60-120 mcg 3 times/day (range: 120-720 mcg divided 2-3 times/day). Fluid restriction should be observed.

Nocturnal enuresis:*Oral:* 0.2 mg at bedtime; dose may be titrated up to 0.6 mg to achieve desired response.

Hemophilia A and mild-to-moderate von Willebrand disease (type 1):

I.V.: 0.3 mcg/kg by slow infusion; if used preoperatively, administer 30 minutes before procedure

Canadian labeling (not in U.S. labeling): Maximum I.V. dose: 20 mcg

Intranasal (using high concentration spray [1.5 mg/mL]): <50 kg: 150 mcg (1 spray); >50 kg: 300 mcg (1 spray each nostril); repeat use is determined by the patient's clinical condition and laboratory work. If using preoperatively, administer 2 hours before surgery.

Uremic bleeding associated with acute or chronic renal failure (unlabeled use) (Watson, 1984): I.V.: 0.4 mcg/kg over 10 minutes

Prevention of surgical bleeding in patients with uremia (unlabeled use) (Mannucci, 1983): I.V.: 0.3 mcg/kg over 30 minutes

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Diabetes insipidus:

I.M., I.V., SubQ: Canadian labeling (not in U.S. labeling): ≥3 months: 0.4 mcg (0.1 mL) once daily or $^1/_{10}$ of the maintenance intranasal dose. Fluid restriction should be observed.

I.V., SubQ:

Children <12 years: No definitive dosing available. Adult dosing should **not** be used in this age group; adverse events such as hyponatremia-induced seizures may occur. Dose should be reduced. Some have suggested an initial dosage range of 0.1-1 mcg in 1 or 2 divided doses (Cheetham, 2002). Initiate at low dose and increase as necessary. Closely monitor serum sodium levels and urine output; fluid restriction is recommended.

Children ≥12 years: Refer to adult dosing.

Intranasal (using 100 mcg/mL nasal solution):

3 months to 12 years: Initial: 5 mcg/day (0.05 mL/day) divided 1-2 times/day; range: 5-30 mcg/day (0.05-0.3 mL/day) divided 1-2 times/day; adjust morning and evening doses separately for an adequate diurnal rhythm of water turnover. **Note:** The nasal spray pump can only deliver doses of 10 mcg (0.1 mL) or multiples of 10 mcg (0.1 mL); if doses other than this are needed, the rhinal tube delivery system is preferred. Fluid restriction should be observed.

Children ≥12 years: Refer to adult dosing.

Oral:

U.S. labeling: ≥4 years: Initial: 0.05 mg twice daily; total daily dose should be increased or decreased as needed to obtain adequate antidiuresis (range: 0.1-1.2 mg divided 2-3 times/day). Fluid restriction should be observed.

Canadian labeling (not in U.S. labeling): ≥5 years: Initial: 0.1 mg 3 times/day; total daily dose should be increased or decreased as needed to obtain adequate antidiuresis (range: 0.3-1.2 mg divided 3 times/day). Divide daily doses so that the evening dose is 2 times higher than the morning or afternoon dose to ensure adequate antidiuresis during the night. Fluid restriction should be observed.

Sublingual formulation: Canadian labeling (not in U.S. labeling): ≥3 months: Initial: 60 mcg 3 times/day; total daily dose should be increased or decreased as needed to obtain adequate antidiuresis. Usual maintenance: 60-120 mcg 3 times/day (range: 120-720 mcg divided 2-3 times/day); divide daily doses so that the evening dose is 2 times higher than the morning or afternoon dose to ensure adequate antidiuresis during the night. Fluid restriction should be observed.

Hemophilia A and von Willebrand disease (type 1):

I.V.: ≥3 months: 0.3 mcg/kg by slow infusion; may repeat dose if needed; if used preoperatively, administer 30 minutes before procedure

Canadian labeling (not in U.S. labeling): Maximum I.V. dose: 20 mcg

Note: Adverse events such as hyponatremia-induced seizures have been reported especially in young children using this dosing regimen (Das, 2005; Molnar, 2005; Smith, 1989; Thumfart, 2005; Weinstein, 1989). Fluid restriction and careful monitoring of serum sodium levels and urine output are necessary.

Intranasal (using high concentration spray [1.5 mg/mL]): ≥11 months: Refer to adult dosing.

Nocturnal enuresis:

Oral:

Children ≥6 years: 0.2 mg at bedtime. Dose may be titrated up to 0.6 mg to achieve desired response. Fluid intake should be limited 1 hour prior to dose until the next morning, or at least 8 hours after administration. **Note:** In the Canadian labeling, use is approved for patients ≥5 years.

Children >12 years: Refer to adult dosing.

Sublingual: Canadian labeling (not in U.S. labeling): ≥5 years: Initial: 120 mcg at bedtime; dose may be titrated up to 360 mcg to achieve desired response. Fluid intake should be limited 1 hour prior to dose until the next morning, or at least 8 hours after administration.

Dosing: Renal ImpairmentCl$_{cr}$ <50 mL/minute: Use is contraindicated according to the manufacturer; however, has been used in acute and chronic renal failure patients experiencing uremic bleeding or for prevention of surgical bleeding (unlabeled uses; Mannuccio, 1983; Watson, 1984).

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Central diabetes insipidus: Withdraw dose from ampul into appropriate syringe size (eg, insulin syringe). Further dilution is not required. Administer as direct injection.

Administration: I.V.

I.V. push: Central diabetes insipidus: Withdraw dose from ampul into appropriate syringe size (eg, insulin syringe). Further dilution is not required. Administer as direct injection.

I.V. infusion:

Hemophilia A, von Willebrand disease (type 1), and prevention of surgical bleeding in patients with uremia (unlabeled; Mannucci, 1983): Infuse over 15-30 minutes

Acute uremic bleeding (unlabeled; Watson, 1984): May infuse over 10 minutes

Administration: Other

Intranasal:

DDAVP®: Nasal pump spray: Delivers 0.1 mL (10 mcg); for doses <10 mcg or for other doses which are not multiples, use rhinal tube. DDAVP® Nasal spray delivers fifty 10 mcg doses. For 10 mcg dose, administer in one nostril. Any solution remaining after 50 doses should be discarded. Pump must be primed prior to first use.

DDAVP® Rhinal tube: Insert top of dropper into tube (arrow marked end) in downward position. Squeeze dropper until solution reaches desired calibration mark. Disconnect dropper. Grasp the tube $^3/_4$ inch from the end and insert tube into nostril until the fingertips reach the nostril. Place opposite end of tube into the mouth (holding breath). Tilt head back and blow with a strong, short puff into the nostril (for very young patients, an adult should blow solution into the child's nose). Reseal dropper after use.

SubQ: Central diabetes insipidus: Withdraw dose from ampul into appropriate syringe size (eg, insulin syringe). Further dilution is not required. Administer as direct injection.

Storage

DDAVP®:

Nasal spray: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Keep nasal spray in upright position.

Rhinal Tube solution: Store refrigerated at 2°C to 8°C (36°F to 46°F). May store at controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 3 weeks.

Solution for injection: Store refrigerated at 2°C to 8°C (36°F to 46°F).

Tablet: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F).

DDAVP® Melt (CAN; not available in U.S.): Store at 15°C to 25°C (59°F to 77°F) in original container. Protect from moisture.

Stimate® nasal spray: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Keep nasal spray in upright position. Discard 6 months after opening.

ReconstitutionDDAVP®: Dilute solution for injection in 10-50 mL NS for I.V. infusion (10 mL for children ≤10 kg: 50 mL for adults and children >10 kg).

CompatibilityStable in NS.

ContraindicationsHypersensitivity to desmopressin or any component of the formulation; hyponatremia or a history of hyponatremia; moderate-to-severe renal impairment (Cl_{cr}<50 mL/minute)

Canadian labeling: Additional contraindications (not in U.S. labeling): Type 2B or platelet-type (pseudo) von Willebrand's disease (injection, intranasal, oral, sublingual); known hyponatremia, habitual or psychogenic polydipsia, cardiac insufficiency or other conditions requiring diuretic therapy (intranasal, sublingual); nephrosis, severe hepatic dysfunction (sublingual); primary nocturnal enuresis (intranasal)

Allergy Considerations

- Desmopressin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Allergic reactions (injectable and intranasal formulations): Severe reactions resembling hypersensitivity (eg, anaphylaxis) reactions have occurred rarely with I.V. and intranasal administration.
- Hyponatremia: Use may rarely lead to hyponatremia and extreme decreases in plasma osmolality, resulting in seizures, coma, and death. Risk factors for hyponatremia with desmopressin use include cystic fibrosis, renal dysfunction, heart failure, young age, advanced age, inappropriate high fluid intake with desmopressin administration, a larger than recommended dose, and concomitant use of medications known to either increase thirst or cause syndrome of inappropriate ADH secretion (SIADH). Fluid restriction during use is recommended.
- Thrombotic events: Acute cerebrovascular thrombosis and acute myocardial infarction have occurred (rare); use with caution in patients predisposed to thrombus formation.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery insufficiency or hypertensive cardiovascular disease; may increase or decrease blood pressure leading to changes in heart rate.

- Polydipsia (habitual or psychogenic): Use with caution in patients with habitual or psychogenic polydipsia. These patients are at greater risk of hyponatremia. Use in these patients is contraindicated in Canadian labeling.

- von Willebrand's disease type 2B: Patients with type 2B von Willebrand's disease requiring hemostasis should not be treated with desmopressin since use may result in platelet aggregation, thrombocytopenia, and possibly thrombosis.

Special populations:

- Elderly: Fluid intake should be adjusted downward in the elderly to decrease the possibility of water intoxication and hyponatremia.

- Pediatrics: Fluid intake should be adjusted downward in very young patients to decrease the possibility of water intoxication and hyponatremia.

Dosage form specific issues:

- Injection and high concentration spray (1.5 mg/mL): Not for use in hemophilia B, type 2B von Willebrand disease, severe classic von Willebrand disease (type 1), or in patients with factor VIII antibodies. In general, the injection and high concentration spray are also not recommended for use in patients with ≤5% factor VIII activity level, although it may be considered in selected patients with activity levels between 2% and 5%.

- Intranasal: Consider alternative route of administration (I.V.) if changes in the nasal mucosa (scarring, edema) occur leading to unreliable absorption.

- Tablet: Patients should be instructed to restrict fluid intake from 1 hour before to 8 hours after taking desmopressin tablets. Consider alternative route of administration (I.V. or intranasal) with inadequate therapeutic response at maximum recommended oral doses.

Appropriate use:

- Interruption of therapy: Therapy should be interrupted if the patient experiences an acute illness (eg, fever, recurrent vomiting or diarrhea), vigorous exercise, or any condition associated with an increase in water consumption.

Other warnings/precautions:

- Long-term effects: Some patients may demonstrate a change in response after long-term therapy (>6 months) characterized as decreased response or a shorter duration of response.

Geriatric ConsiderationsElderly patients should be cautioned not to increase their fluid intake beyond that sufficient to satisfy their thirst in order to avoid water intoxication and hyponatremia. Under experimental conditions, elderly have been shown to have a decreased responsiveness to vasopressin with respect to its effects on water homeostasis.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events were not observed in animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Anecdotal reports suggest congenital anomalies and low birth weight. However, causal relationship has not been established. Desmopressin has been used safely during pregnancy.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency may not be defined (may be dose or route related).

Cardiovascular: Blood pressure increased/decreased (I.V.), facial flushing

Central nervous system: Headache (2% to 5%), dizziness (intranasal; ≤3%), chills (intranasal; 2%)

Dermatologic: Rash

Endocrine & metabolic: Hyponatremia, water intoxication

Gastrointestinal: Abdominal pain (intranasal; 2%), gastrointestinal disorder (intranasal; ≤2%), nausea (intranasal; ≤2%), abdominal cramps, sore throat

Hepatic: Transient increases in liver transaminases (associated primarily with tablets)

Local: Injection: Burning pain, erythema, and swelling at the injection site

Neuromuscular & Skeletal: Weakness (intranasal; ≤2%)

Ocular: Conjunctivitis (intranasal; ≤2%), eye edema (intranasal; ≤2%), lacrimation disorder (intranasal; ≤2%)

Respiratory: Rhinitis (intranasal; 3% to 8%), epistaxis (intranasal; ≤3%), nostril pain (intranasal; ≤2%), cough, nasal congestion, upper respiratory infection

<1%, postmarketing, and/or case reports: Acute cerebrovascular thrombosis (I.V.), acute MI (I.V.), agitation, allergic reactions (rare), anaphylaxis (rare), balanitis, chest pain, coma, diarrhea, dyspepsia, edema, insomnia, itching eyes, light-sensitive eyes, pain, palpitation, seizure, somnolence, tachycardia, thinking abnormal, vomiting, vulval pain, warmth

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Analgesics (Opioid): May enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

CarBAMazepine: May enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

ChlorproMAZINE: May enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Demeclocycline: May diminish the therapeutic effect of Desmopressin. *Risk C: Monitor therapy*

LamoTRIgine: May enhance the adverse/toxic effect of Desmopressin. LamoTRIgine may enhance the therapeutic effect of Desmopressin. *Risk C: Monitor therapy*

Lithium: May diminish the therapeutic effect of Desmopressin. Desmopressin may increase the serum concentration of Lithium. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may decrease antidiuretic effect).

Monitoring ParametersBlood pressure and pulse should be monitored during I.V. infusion

Note: For all indications, fluid intake, urine volume, and signs and symptoms of hyponatremia should be closely monitored especially in high-risk patient subgroups (eg, young children, elderly, patients with heart failure).

Diabetes insipidus: Urine specific gravity, plasma and urine osmolality, serum electrolytes

Hemophilia A: Factor VIII coagulant activity, factor VIII ristocetin cofactor activity, and factor VIII antigen levels, aPTT

von Willebrand disease: Factor VIII coagulant activity, factor VIII ristocetin cofactor activity, and factor VIII von Willebrand antigen levels, bleeding time

Nocturnal enuresis: Serum electrolytes if used for >7 days

Nursing: Physical Assessment/MonitoringEvaluate for any history of or potential for hyponatremia or renal impairment prior to beginning therapy. Assess results of laboratory tests on a regular basis during therapy. Assess therapeutic effectiveness (according to rationale for use) and adverse reactions (eg, thromboembolism, hyponatremia, water intoxication) regularly throughout therapy. Teach patient proper use (if self-administered), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsFor all indications, fluid intake, urine volume, and signs and symptoms of hyponatremia should be closely monitored especially in high-risk patient subgroups (eg, young children, elderly, patients with heart failure).

Diabetes insipidus: Urine specific gravity, plasma and urine osmolality, serum electrolytes

Hemophilia A: Factor VIII coagulant activity, factor VIII ristocetin cofactor activity, and factor VIII antigen levels, aPTT

von Willebrand disease: Factor VIII coagulant activity, factor VIII ristocetin cofactor activity, and factor VIII von Willebrand antigen levels, bleeding time

Nocturnal enuresis: Serum electrolytes if used for >7 days

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Use specific product as directed. Avoid alcohol; may decrease effect of medication. Diabetes insipidus: Avoid overhydration. Weigh yourself daily at the same time in the same clothes. Report increased weight or swelling of extremities. If using intranasal product, inspect nasal membranes regularly. Report swelling, redness, irritation, or increased nasal congestion.

All uses: Report unresolved headache; chest pain or palpitation; respiratory difficulty; acute heartburn, nausea, vomiting, or abdominal cramping; vulval pain; CNS changes (agitation, chills, coma, dizziness, insomnia, confusion); rash; or other adverse effects. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian product

Injection, solution, as acetate: 4 mcg/mL (1 mL, 10 mL)

DDAVP®: 5 mcg/mL (1 mL, 10 mL)

Solution, intranasal, as acetate: 100 mcg/mL (2.5 mL)

DDAVP®: 100 mcg/mL (2.5 mL) [contains benzalkonium chloride; with rhinal tube]

Solution, as acetate, intranasal [spray]: 100 mcg/mL (5 mL)

DDAVP®: 100 mcg/mL (5 mL) [contains benzalkonium chloride; delivers 10 mcg/spray]

Stimate®: 1.5 mg/mL (2.5 mL) [delivers 150 mcg/spray]

Tablet, as acetate, oral: 0.1 mg, 0.2 mg

DDAVP®: 0.1 mg, 0.2 mg [scored]

Tablet, as acetate, sublingual:

DDAVP® Melt (CAN) [not available in U.S.]: 60 mcg, 120 mcg, 240 mcg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (DDAVP)

0.01% (5): $208.44

4 mcg/mL (10): $372.11

Solution (DDAVP Rhinal Tube)

0.01% (2.5): $121.54

Solution (Desmopressin Ace Rhinal Tube)

0.01% (2.5): $85.99

Solution (Desmopressin Ace Spray Refrig)

0.01% (5): $107.99

Tablets (DDAVP)

0.1 mg (30): $119.34

0.2 mg (30): $145.89

Tablets (Desmopressin Acetate)

0.1 mg (30): $86.99

0.2 mg (90): $325.99

Mechanism of ActionIn a dose dependent manner, desmopressin increases cyclic adenosine monophosphate (cAMP) in renal tubular cells which increases water permeability resulting in decreased urine volume and increased urine osmolality; increases plasma levels of von Willebrand factor, factor VIII, and t-PA contributing to a shortened activated partial thromboplastin time (aPTT) and bleeding time.

Pharmacodynamics/Kinetics

Onset of action:

Intranasal: Antidiuretic: 15-30 minutes; Increased factor VIII and von Willebrand factor (vWF) activity (dose related): 30 minutes

Peak effect: Antidiuretic: 1 hour; Increased factor VIII and vWF activity: 1.5 hours

I.V. infusion: Increased factor VIII and vWF activity: 30 minutes (dose related)

Peak effect: 1.5-2 hours

Oral tablet: Antidiuretic: ~1 hour

Peak effect: 4-7 hours

Duration of action: Intranasal, I.V. infusion, Oral tablet: ~6-14 hours

Absorption: Sublingual: Rapid

Bioavailability: Intranasal: ~3.5%; Oral tablet: 5% compared to intranasal, 0.16% compared to I.V.

Half-life elimination: Intranasal: ~3.5 hours; I.V. infusion: 3 hours; Oral tablet: 2-3 hours

Renal impairment: ≤9 hours

Excretion: Urine

Pharmacotherapy Pearls10 mcg of desmopressin acetate is equivalent to 40 int. units

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay decrease lithium's effect on ADH, however, hydrochlorothiazide or amiloride are better choices

Cardiovascular ConsiderationsWhen administered I.V., desmopressin is a vasoconstrictor and may cause acute hypertension.

Anesthesia and Critical Care Concerns/Other ConsiderationsIf desmopressin I.V. is given preoperatively, administer 30 minutes prior to surgery. If desmopressin intranasal is given preoperatively, administer 2 hours prior to surgery.

Index Terms1-Deamino-8-D-Arginine Vasopressin; Desmopressin Acetate

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Weinstein RE, Bona RD, Altman AJ, et al, “Severe Hyponatremia after Repeated Intravenous Administration of Desmopressin,” *Am J Hematol*, 1989, 32(4):258-61.[PubMed 2816922]

International Brand NamesAdin Spray (IL); Adiuretin (PL); Adiuretin SD (HU); Adiuretin-SD (CZ, HN); D-VOID (IN); DDAVP (BR, CN, IT, TW); DDAVP Desmopressin (PT); Defirin (GR); Desmomelt (GB, IE); Desmopresin DDAVP (AR); Desmospray (GB, IE); Desmotab (GB, IE); Minirin (AT, AU, BG, CH, CL, CO, DE, DK, EE, FI, FR, HR, HU, IL, LU, MY, NO, PH, PK, PL, PY, SE, TR, TW); Minirin DDAVP (AE, BH, CY, EG, GR, HK, IL, IQ, IR, IT, JO, KW, LB, LY, OM, QA, SA, SY, TH, YE); Minirin Nasal Spray (AU); Minirinmelt (FR, KP); Minrin (BE, LU, NL); Minurin (ES); Nafiset (MX); Noctisson (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Octim (FR); Octim Nasal Spray (GB, IE); Octostim (AE, AR, AU, BH, CH, CO, CY, EG, ES, FI, HK, HU, IL, IQ, IR, JO, KW, LB, LY, MX, NL, NO, NZ, OM, QA, SA, SE, SY, YE); Octostim Nasal Spray (KP); Octostin (AR); Pizzard (MX); Presinex (GB, IE, IL); Uremin (KP)

Desonide

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English

English

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Pronunciation(DES oh nide)

U.S. Brand NamesDesonate™; DesOwen®; LoKara™; Verdeso™

Canadian Brand NamesDesocort®; PMS-Desonide

Pharmacologic CategoryCorticosteroid, Topical

Use: Labeled IndicationsAdjunctive therapy for inflammation in acute and chronic corticosteroid responsive dermatosis (low potency corticosteroid); mild-to-moderate atopic dermatitis

Dosing: Adults

Corticosteroid responsive dermatoses: Topical: Therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Cream, ointment: Apply 2-4 times/day sparingly

Lotion: Apply 2-3 times/day sparingly

Atopic dermatitis: Aerosol, gel: Apply 2 times/day sparingly. Therapy should be discontinued when control is achieved. If no improvement is seen within 4 weeks, reassessment of diagnosis may be necessary.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Corticosteroid responsive dermatoses:** Refer to adult dosing.

Atopic dermatitis: Children ≥3 months: Refer to adult dosing.

Administration: TopicalDo not use on open wounds; apply sparingly using smallest amount needed to adequately cover the affected area. Use of occlusive dressings is not recommended.

Aerosol, lotion: Shake well before use.

ContraindicationsHypersensitivity to desonide or any component of the formulation

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Special populations:

- Pediatrics: Chronic use of corticosteroids in children may interfere with growth and development.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic events were not observed in rats or rabbits following topical administration of the cream in doses similar to the maximum human dose, based on body surface area. Teratogenic events have been reported following systemic use of corticosteroids.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsSystemic corticosteroids are excreted in human milk. The extent of topical absorption is variable. Use with caution while breast-feeding.

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypertension, peripheral edema

Central nervous system: Asthma, cough, headache, irritability

Dermatologic: Dry skin, erythema (transient, intense), folliculitis, peeling of skin, pruritus, rash, scaly skin, telangiectasia

Endocrine & metabolic: HPA axis suppression, hyperglycemia

Genitourinary: Xerostomia

Hepatic: Liver function abnormality

Local: Application site: Atrophy, burning, dermatitis, stinging

Respiratory: Pharyngitis, upper respiratory tract infection

Miscellaneous: Infection

Reported with other topical corticosteroids, may occur more frequently with occlusive dressings: Acneiform eruptions, allergic contact dermatitis, Cushing's syndrome (children), growth retardation (children), hypopigmentation, intracranial hypertension (children), miliaria, perioral dermatitis, secondary infection, skin atrophy, striae, weight gain delayed (children)

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Patient Education

A thin film is effective; do not overuse. Rub in lightly. Do not cover or use occlusive bandaging. Do not use tight-fitting diapers or plastic pants on children being treated in the diaper area. Use only as prescribed and for no longer than the period prescribed. Avoid contact with eyes; notify prescriber if condition being treated persists or worsens. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol, topical [foam]:

Verdeso®: 0.05% (50 g, 100 g)

Cream, topical: 0.05% (15 g, 60 g)

DesOwen®: 0.05% (60 g)

Gel, topical [aqueous]:

Desonate™: 0.05% (15 g [DSC], 30 g [DSC], 60 g)

Lotion, topical: 0.05% (60 mL, 120 mL)

DesOwen® [DSC], LoKara™: 0.05% (60 mL, 120 mL)

Ointment, topical: 0.05% (15 g, 60 g)

DesOwen®: 0.05% (60 g)

Generic Available

Yes: Excludes aerosol, gel

Pricing: U.S. (www.drugstore.com)

Cream (Desonide)

0.05% (15): $12.99

0.05% (60): $17.99

Cream (DesOwen)

0.05% (60): $148.35

Foam (Verdeso)

0.05% (100): $256.78

Kit (DesOwen Lot w/Cetaphil Cream)

0.05% (1): $114.99

Lotion (Desonide)

0.05% (59): $26.99

0.05% (118): $39.99

Lotion (DesOwen)

0.05% (59): $116.27

0.05% (118): $157.52

Lotion (LoKara)

0.05% (59): $88.90

Ointment (Desonide)

0.05% (15): $13.99

0.05% (60): $27.99

Ointment (Tridesilon)

0.05% (60): $39.99

Mechanism of ActionStimulates the synthesis of enzymes needed to decrease inflammation, suppress mitotic activity, and cause vasoconstriction

Pharmacodynamics/Kinetics

Absorption: Extensive from scalp, face, axilla, and scrotum; adequate through epidermis on appendages; may be increased with inflammation or occlusion

Metabolism: Hepatic

Excretion: Primarily urine

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

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International Brand NamesApolar (FI, ID, NO, SE); Dermades (ID); Dermanide (ID); Dermonide (KP); Dermosupril (PE); Desoclin (KP); Desolex (ID); Desowen (AR, AU, BR, CN, HK, IN, MX, PH, PY, SG, UY, VE); Deswon Lotion (KP); Dong Koo Dermo Lotion (KP); Locapred (CH); Locatop (CH, PL); Nufapolar (ID); Prenacid (PE); Reticus (IT); Sine-Fluor (ES); Sterax (BE, CH, DE, LU); Topifug (DE); Tresilen (CO); Tridesilon (CR, DE, EC, GB, GT, HN, NI, PA, SV); Tridesonit (FR); Zotinar (PT)

Desoximetasone

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Desoximetasone may be confused with dexamethasone

Topicort® may be confused with Topic®

Pronunciation(des oks i MET a sone)

U.S. Brand NamesTopicort®; Topicort®-LP

Canadian Brand NamesTaro-Desoximetasone; Topicort®

Pharmacologic CategoryCorticosteroid, Topical

Use: Labeled IndicationsRelieves inflammation and pruritic symptoms of corticosteroid-responsive dermatosis (intermediate- to high-potency topical corticosteroid)

Use: DentalShort-term relief of inflammation of moderate to severe corticosteroid-responsive dermatosis (intermediate- to high-potency topical corticosteroid)

Dosing: AdultsSteroid-response dermatoses: Topical: Apply a thin film to affected area twice daily

Note: Desoximetasone is a potent fluorinated topical corticosteroid. Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricSteroid-response dermatoses: Topical:

Cream, gel: Refer to adult dosing.

Ointment: Children ≥10 years: Refer to adult dosing.

Administration: TopicalFor external use only; apply sparingly to occlusive dressings; should not be used in the presence of open or weeping lesions.

ContraindicationsHypersensitivity to desoximetasone or any component of the formulation; topical fungal infections; tuberculosis of skin herpes simplex

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Special populations:

- Pediatrics: Safety and efficacy of desoximetasone ointment have not been established in children <10 years of age. Chronic use of corticosteroids in children may interfere with growth and development.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. However, topical desoximetasone is teratogenic in animals; use during pregnancy with caution. In general, the use of large amounts, or prolonged use, of topical corticosteroids during pregnancy should be avoided.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions<1%: Acneiform eruptions, allergic contact dermatitis, burning, dry skin, erythema, folliculitis, folliculopustular lesions, hypertrichosis, hypopigmentation, itching; local burning, irritation, miliaria; perioral dermatitis, secondary infection, skin atrophy, skin maceration, striae, vesiculation

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Patient EducationA thin film is effective; do not overuse. Rub in lightly. Do not use tight-fitting diapers or plastic pants on children being treated in the diaper area. Use only as prescribed and for no longer than the period prescribed. Avoid contact with eyes; notify prescriber if condition being treated persists or worsens. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical: 0.25% (15 g, 60 g); 0.05% (15 g, 60 g)

Topicort®: 0.25% (15 g, 60 g)

Topicort®-LP: 0.05% (15 g, 60 g)

Gel, topical: 0.05% (15 g, 60 g)

Topicort®: 0.05% (15 g, 60 g) [contains alcohol]

Ointment, topical: 0.25% (15 g, 60 g)

Topicort®: 0.25% (15 g, 60 g) [contains coconut oil]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Cream (Desoximetasone)

0.05% (15): $39.43

0.05% (60): $170.18

0.25% (15): $28.04

0.25% (60): $99.60

Cream (Topicort)

0.25% (15): $64.99

0.25% (60): $206.81

Gel (Desoximetasone)

0.05% (15): $50.89

0.05% (60): $117.82

Gel (Topicort)

0.05% (15): $51.30

Ointment (Desoximetasone)

0.25% (15): $64.36

0.25% (60): $174.92

Ointment (Topicort)

0.25% (15): $67.16

Mechanism of ActionStimulates the synthesis of enzymes needed to decrease inflammation, suppress mitotic activity, and cause vasoconstriction

Pharmacodynamics/Kinetics

Absorption: May be increased with occlusion, inflammation, or vary with site of application

Ointment: Systemic absorption with occlusion: 7%

Metabolism: Hepatic

Half-life elimination: Emollient cream: 15-17 hours

Excretion: Urine, feces

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Goedert JJ, Vitale F, Lauria C, et al, "Risk Factors for Classical Kaposi's Sarcoma," *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

Reed BR, "Dermatologic Drugs, Pregnancy, and Lactation. A Conservative guide," *Arch Dermato*, 1997, 133(7):894-8.[PubMed 9236528]

International Brand Names

Actiderm (AR); Cendexsone (TH); Decilone (PH); Decilone Forte (PH); Deoxon Gel (KP); Deoxon Lotion (KP); Dercason (ID); Desicort (IL); Desome (ID); Dethasone (KP); Dexocort (ID); Esperson (BD, BG, BR, CL, HK, ID, IN, JP, KP, MY, PH, PK, PT, SG, TH, TW); Flubason (ES, IT); Ibaril (BG, DK, FI, NL, NO); Inerson (ID); Pyderma (ID); Soderma (ID); Stiedex (GB); Topcort (ID); Topicorte (AE, BE, BH, CY, EG, FR, IL, IQ, IR, JO, KW, LB, LU, LY, MY, NL, OM, PT, QA, SA, SY, TH, YE); Topisolon (AT, BB, BM, BS, BZ, CH, DE, GY, IE, JM, NL, PR, SE, SR, TT, ZA)

Desvenlafaxine

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English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(des ven la FAX een)

U.S. Brand NamesPristiq™

Pharmacologic CategoryAntidepressant, Serotonin/Norepinephrine Reuptake Inhibitor

Use: Labeled IndicationsTreatment of major depressive disorder

Dosing: Adults**Depression:** Oral: 50 mg once daily; up to 400 mg once daily have been studied; however, the manufacturer states there is no evidence that higher doses confer any additional benefit. A flat dose response curve for efficacy between 50-400 mg/day has been noted as well as an increase in adverse events.

Note: Gradually taper dose (by increasing dosing interval) if discontinuing.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} ≥30 mL/minute: No dosage adjustment required.

Cl_{cr} <30 mL/minute: 50 mg every other day (maximum).

Hemodialysis: 50 mg every other day (maximum). Supplemental doses not required after HD.

Dosing: Hepatic ImpairmentUsual adult dose recommended; maximum dose: 100 mg/day

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralMay be taken with or without food. Swallow tablet whole; do not crush, chew, break, or dissolve. When discontinuing therapy, extend dosing interval to taper.

Dietary ConsiderationsMay be taken with or without food.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.wyeth.com/content/showlabeling.asp?id=498.

ContraindicationsHypersensitivity to desvenlafaxine, venlafaxine or any component of the formulation; use of MAO inhibitors within 14 days; should not initiate MAO inhibitor within 7 days of discontinuing desvenlafaxine

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor for clinical worsening, suicidality, or unusual changes in behavior; the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants in children and teenagers should be dispensed with each prescription. **Desvenlafaxine is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Desvenlafaxine is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anxiety/insomnia: May cause increase in anxiety, nervousness, and insomnia.
- Bleeding risk: May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin or NSAIDs due to ulcerogenic potential. Data are inconclusive regarding extent of bleeding risk of SNRIs in combination with warfarin or other anticoagulants. Bleeding related to SNRI use has been reported to range from relatively minor bruising and epistaxis to life-threatening hemorrhage.
- CNS depression: Has a low potential to impair cognitive or motor performance; caution operating hazardous machinery or driving.
- Dyslipidemia: May cause significant dose-related increases in total cholesterol, LDL, and triglycerides; monitor.
- Hypertension: Dose-related increases in systolic and diastolic blood pressure have been documented. Monitor blood pressure regularly, and if sustained increases noted, consider dose reduction or discontinuation.
- Pulmonary events: Interstitial lung disease and eosinophilic pneumonia have been rarely reported with venlafaxine (the parent drug of desvenlafaxine). May present as progressive dyspnea, cough, and/or chest pain. Prompt evaluation and possible discontinuation of therapy may be necessary.
- Sexual dysfunction: May cause or exacerbate sexual dysfunction.
- SIADH and hyponatremia: SSRIs and SNRIs have been associated with the development of SIADH; hyponatremia has been reported rarely (including severe cases with serum sodium <110 mmol/L). Age (the elderly), volume depletion and/or concurrent use of diuretics likely increases risk. Discontinue treatment in patients with symptomatic hyponatremia.

Disease-related concerns:

- Cardiovascular disease: May cause sustained increase in blood pressure or heart rate. Control pre-existing hypertension prior to initiation of desvenlafaxine. Use caution in patients with recent history of MI, unstable heart disease, or cerebrovascular disease. Hypertensive effect is dose related.
- Hepatic impairment: Use caution.
- Narrow-angle glaucoma: May cause mydriasis; use caution in patients with increased intraocular pressure or at risk of acute narrow-angle glaucoma.
- Renal impairment: Use caution; clearance is decreased and plasma concentrations are increased; dosage reduction recommended in patients with severe renal impairment or end-stage renal disease.
- Seizure disorders: Use caution in patients with a previous seizure disorder.

Concurrent drug therapy issues:

- MAO inhibitors (MAO-I): Potential for serotonin syndrome when used with MAO inhibitors; autonomic instability, coma, death, delirium, diaphoresis, hyperthermia, mental status changes/agitation, muscular rigidity, myoclonus, neuroleptic malignant syndrome features, and seizures may occur. Concurrent use with MAO inhibitors is contraindicated. Do not begin desvenlafaxine within 14 days of terminating MAO-I therapy
- Proserotonergic drugs: Serotonin syndrome (eg, symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia) may occur with concomitant use of proserotonergic drugs (ie, SSRIs/SNRIs or triptans). Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.
- Weight loss agents: Agents causing weight loss or anorectic effects should be avoided.

Special populations:

- Pediatrics: Safety and efficacy have not been established.

Other warnings/precautions:

- Withdrawal syndrome: Abrupt discontinuation or dosage reduction has been associated with a wide range of reactions, including (but not limited to) dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, impaired coordination/balance, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. When discontinuing therapy, gradually taper dose. If intolerable symptoms occur following a decrease in dosage or upon discontinuation of therapy, then resuming the previous dose with a more gradual taper should be considered.

Geriatric ConsiderationsNo dose adjustment is necessary for age alone; adjust dose for renal function in the elderly. According to desvenlafaxine's manufacturer, 5% of the 3292 patients in clinical trials were 65 years of age or older. No differences in safety or efficacy were reported between younger and older adults. The elderly are more prone to SSRI/SNRI-induced hyponatremia.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDesvenlafaxine is classified as pregnancy category C due to adverse effects observed in animal studies. Nonteratogenic effects in the newborn following SSRI/SNRI exposure late in the third trimester include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hyper- or hypotonia, hyper-reflexia, jitteriness, irritability, constant crying, and tremor. The long-term effects on neurobehavior have not been studied.

Women treated for major depression and who are euthymic prior to pregnancy are more likely to experience a relapse when medication is discontinued as compared to pregnant women who continue taking antidepressant medications. The ACOG recommends that therapy with SSRIs or SNRIs during pregnancy be individualized; treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary healthcare provider, and pediatrician. If treatment during pregnancy is required, consider tapering therapy during the third trimester in order to prevent withdrawal symptoms in the infant. If this is done and the woman is considered to be at risk from her major depressive disorder, the medication can be restarted following delivery, although the dose should be readjusted to that required before pregnancy.

Desvenlafaxine is the major active metabolite of venlafaxine; also refer to the venlafaxine monograph.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsDesvenlafaxine is found in human milk. The manufacturer recommends breast-feeding during therapy only if the expected benefits to the mother outweigh any potential risk to the infant.

Adverse ReactionsReported for 50-100 mg/day.

>10%:

Central nervous system: Dizziness (10% to 13%), insomnia (9% to 12%)

Gastrointestinal: Nausea (22% to 26%), xerostomia (11% to 17%), constipation (9% to 11%), diarrhea (9% to 11%)

Miscellaneous: Diaphoresis (10% to 14%)

1% to 10%:

Cardiovascular: Palpitation (≤3%), orthostatic hypotension (<2%), syncope (<2%), hypertension (dose related; ≤1% of patients taking 50-100 mg daily had sustained diastolic BP ≥90 mm Hg)

Central nervous system: Somnolence (≤9%), fatigue (7%), anxiety (3% to 5%), abnormal dreams (2% to 3%), irritability (2%), depersonalization (<2%), extrapyramidal symptoms (<2%), hypomania (<2%), seizures (<2%), concentration decreased (≤1%)

Dermatologic: Rash (1%)

Endocrine & metabolic: Libido decreased (males 4% to 5%), cholesterol (increased by ≥50 mg/dL and ≥261 mg/dL: 3% to 4%), anorgasmia (females 1%), low density lipoprotein cholesterol (increased by ≥50 mg/dL and ≥190 mg/dL: ≤1%), sexual dysfunction (males ≤1%)

Gastrointestinal: Anorexia (5% to 8%), vomiting (≤4%), weight loss (≤2%)

Genitourinary: Urinary hesitancy (≤1%)

Hepatic: Liver function tests abnormal (≤2%)

Neuromuscular & skeletal: Tremor (≤ 3%), paresthesia (≤2%), weakness (≤2%)

Ocular: Blurred vision (3% to 4%), mydriasis (2%)

Otic: Tinnitus (2%)

Renal: Proteinuria (6% to 8%)

Respiratory: Epistaxis (<2%)

Miscellaneous: Ejaculation retarded (1% to 5%), erectile dysfunction (3% to 6%), hypersensitivity reaction (<2%), ejaculation failure (≤1%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Myocardial infarction, myocardial ischemia

Metabolism/Transport Effects**Substrate** of 3A4 (minor); **Inhibits** 3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha-/Beta-Agonists: Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Aspirin: Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Iobenguane I 123: Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the serotonergic effect of Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor). This may cause serotonin syndrome. *Risk X: Avoid combination*

NSAID (Nonselective): Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS effects).

Herb/Nutraceutical: Avoid St John's wort (may increase risk of serotonin syndrome and/or excessive sedation).

Monitoring ParametersRenal function for dosing purposes; blood pressure should be regularly monitored, especially in patients with a high baseline blood pressure; lipid panel (eg, total cholesterol, LDL, triglycerides); mental status for depression, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased). Intraocular pressure should be monitored in those with baseline elevations or a history of glaucoma.

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness according to rationale for therapy and adverse reactions at beginning of therapy and periodically with long-term use. Observe for clinical worsening, suicidality, or unusual behavior changes; especially during the initial few months of therapy or during dosage changes. Monitor vital signs at the beginning and periodically throughout therapy. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsLipid panel

Patient EducationTake exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results. Extended release capsules should be swallowed whole; do not crush or chew. Avoid alcohol, caffeine, and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience excess drowsiness or insomnia, lightheadedness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); headache, nausea, vomiting, anorexia, dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); diarrhea (buttermilk, yogurt, or boiled milk may help); postural hypotension (use caution when climbing stairs or changing position from lying or sitting to standing); urinary retention (void before taking medication); or sexual dysfunction (reversible). Report persistent CNS effects (eg, insomnia, restlessness, fatigue, anxiety, abnormal thoughts, suicidal ideation, confusion, personality changes, impaired cognitive function); muscle cramping or tremors; chest pain, palpitations, rapid heartbeat, unusual bleeding or bruising, or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, extended release:

Pristiq™: 50 mg, 100 mg

Generic AvailableNo

ManufacturerWyeth Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Pristiq)

50 mg (30): $119.96

100 mg (30): $124.99

Mechanism of ActionDesvenlafaxine is a potent and selective serotonin and norepinephrine reuptake inhibitor.

Pharmacodynamics/Kinetics

Distribution: V_d: 3.4 L/kg

Protein binding: 30%

Metabolism: Hepatic via conjugation, and oxidation via CYP3A4 (minor pathway)

Bioavailability: 80%

Half-life elimination: 11 hours; prolonged in renal failure

Time to peak, serum: 7.5 hours

Excretion: Urine (45% as unchanged drug; ~24% as metabolites)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsPart of the mechanism of desvenlafaxine is to block reuptake of norepinephrine along with dopamine. Because of the potential for norepinephrine elevation within CNS synapses, it is suggested that vasoconstrictor be administered with caution and to monitor vital signs in dental patients taking antidepressants that affect norepinephrine in this way. This is particularly important in patients taking desvenlafaxine, which has been noted to cause a sustained increase in blood pressure or heart rate. Dose-related increase in systolic and diastolic blood pressure have also been reported.

Mental Health CommentDesvenlafaxine is the active metabolite of venlafaxine (Effexor®). Both agents inhibit the reuptake of serotonin and norepinephrine and are referred to as serotonin/norepinephrine reuptake inhibitors (SNRIs). Both agents lack significant affinity for the muscarinic cholinergic, H_1-histaminergic, and alpha$_1$-adrenergic receptors. They also do not possess MAO inhibitory activity.

Parks et al, conducted a dose-finding study of desvenlafaxine in doses up to 750 mg and found that it was associated with less nausea than venlafaxine 150 mg extended release. Ahmed et al, conducted an open-label study in which patients were switched from venlafaxine extended release or placebo to desvenlafaxine. They found a low incidence of adverse reactions in the group switching from venlafaxine to desvenlafaxine, compared with the group switching from placebo to desvenlafaxine (nausea 4% vs 35%; $p<0.001$).

Overall, compared to venlafaxine, desvenlafaxine may be associated with an improved adverse effect profile and fewer drug-drug interactions, but head-to-head studies between these two agents are necessary to establish its place in therapy (Sproule, 2008).

Ahmed S, Zitek B, Ninan PT, et al, "Switch From Venlafaxine to Desvenlafaxine Succinate is Well Tolerated in Patients With Major Depressive Disorder," [abstract from the 160th Annual Meeting of the American Psychiatric Association, May 19-24, 2007, San Diego, CA] Available at: http://www.psych.org/edu/other_res/lib_archives/archives/meetings/AMS/2007saps.pdf.

Parks V, Patat A, Behrle J, et al, "Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Ascending Single Doses of Desvenlafaxine (DVS-233 SR) in Healthy Subjects," *Clin Pharmacol Ther*, 2005, 77:P28.

Sproule BA, Hazra M, and Pollock BG, "Desvenlafaxine Succinate for Major Depressive Disorder," *Drugs Today (Barc)*, 2008, 44(7):475-87.

Index Terms O-desmethylvenlafaxine; ODV

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American Psychiatric Association, “Treatment Recommendations for Patients With Major Depressive Disorder,” Second Edition, January 2000; http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx

Boyer EW and Shannon M, “The Serotonin Syndrome,” *N Engl J Med*, 2005, 352(11):1112-20.[PubMed 15784664]

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“Use of Psychoactive Medication During Pregnancy and Possible Effects on the Fetus and Newborn. Committee on Drugs. American Academy of Pediatrics,” *Pediatrics*, 2000, 105(4 Pt 1):880-7. [PubMed 10742343]

Dexamethasone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Dexamethasone may be confused with desoximetasone, dextroamphetamine

Decadron® may be confused with Percodan®

Maxidex® may be confused with Maxzide®

Pronunciation(deks a METH a sone)

U.S. Brand NamesDexamethasone Intensol™; DexPak® 10 Day TaperPak®; DexPak® TaperPak®; Maxidex®

Canadian Brand NamesApo-Dexamethasone®; Dexasone®; Diodex®; Maxidex®; PMS-Dexamethasone

Pharmacologic CategoryAnti-inflammatory Agent; Anti-inflammatory Agent, Ophthalmic; Antiemetic; Corticosteroid, Ophthalmic; Corticosteroid, Otic; Corticosteroid, Systemic

Use: Labeled Indications

Systemic: Primarily as an anti-inflammatory or immunosuppressant agent in the treatment of a variety of diseases including those of allergic, dermatologic, endocrine, hematologic, inflammatory, neoplastic, nervous system, renal, respiratory, rheumatic, and autoimmune origin; may be used in management of cerebral edema, septic shock, chronic swelling, as a diagnostic agent, diagnosis of Cushing's syndrome, antiemetic

Ophthalmic: Treatment of palpebral and bulbar conjunctivitis; corneal injury from chemical, radiation, thermal burns, or foreign body penetration

Otic: Treatment of inflammation of external auditory meatus; treatment of edema associated with infective otitis externa

Use: Unlabeled/Investigational

Dexamethasone suppression test: General indicator consistent with depression and/or suicide

Accelerate fetal lung maturation in patients with preterm labor

Use: DentalTreatment of a variety of oral diseases of allergic, inflammatory or autoimmune origin

Dosing: Adults

Anti-inflammatory:

Oral, I.M., I.V.: 0.75-9 mg/day in divided doses every 6-12 hours

Intra-articular, intralesional, or soft tissue: 0.4-6 mg/day

Extubation or airway edema: Oral, I.M., I.V.: 0.5-2 mg/kg/day in divided doses every 6 hours beginning 24 hours prior to extubation and continuing for 4-6 doses afterwards

Antiemetic:

Prophylaxis: Oral, I.V.: 10-20 mg 15-30 minutes before treatment on each treatment day

Continuous infusion regimen: Oral or I.V.: 10 mg every 12 hours on each treatment day

Mildly emetogenic therapy: Oral, I.M., I.V.: 4 mg every 4-6 hours

Delayed nausea/vomiting: Oral: 4-10 mg 1-2 times/day for 2-4 days **or**

8 mg every 12 hours for 2 days; then

4 mg every 12 hours for 2 days **or**

20 mg 1 hour before chemotherapy; then

10 mg 12 hours after chemotherapy; then

8 mg every 12 hours for 4 doses; then

4 mg every 12 hours for 4 doses

Ophthalmic anti-inflammatory:

Ophthalmic solution: Instill 1-2 drops into conjunctival sac every hour during the day and every other hour during the night; gradually reduce dose to every 3-4 hours, then to 3-4 times/day.

Ophthalmic suspension: Instill 1-2 drops into conjunctival sac up to 4-6 times per day; may use hourly in severe disease; taper prior to discontinuation.

Otic anti-inflammatory: Instill 3-4 drops 2-3 times a day; reduce dose gradually prior to discontinuation.

Multiple myeloma: Oral, I.V.: 40 mg/day, days 1 to 4, 9 to 12, and 17 to 20, repeated every 4 weeks (alone or as part of a regimen)

Cerebral edema: I.V. 10 mg stat, 4 mg I.M./I.V. (should be given as sodium phosphate) every 6 hours until response is maximized, then switch to oral regimen, then taper off if appropriate; dosage may be reduced after 24 days and gradually discontinued over 5-7 days

Dexamethasone suppression test (depression/suicide indicator) (unlabeled use): Oral: 1 mg at 11 PM, draw blood at 8 AM the following day for plasma cortisol determination

Cushing's syndrome, diagnostic: Oral: 1 mg at 11 PM, draw blood at 8 AM; greater accuracy for Cushing's syndrome may be achieved by the following:

Dexamethasone 0.5 mg by mouth every 6 hours for 48 hours (with 24-hour urine collection for 17-hydroxycorticosteroid excretion)

Differentiation of Cushing's syndrome due to ACTH excess from Cushing's due to other causes: Oral: Dexamethasone 2 mg every 6 hours for 48 hours (with 24-hour urine collection for 17-hydroxycorticosteroid excretion)

Multiple sclerosis (acute exacerbation): Oral: 30 mg/day for 1 week, followed by 4-12 mg/day for 1 month

Treatment of shock:

Addisonian crisis/shock (eg, adrenal insufficiency/responsive to steroid therapy): I.V.: 4-10 mg as a single dose, which may be repeated if necessary

Unresponsive shock (eg, unresponsive to steroid therapy): I.V.: 1-6 mg/kg as a single I.V. dose or up to 40 mg initially followed by repeat doses every 2-6 hours while shock persists

Physiological replacement: Oral, I.M., I.V. (should be given as sodium phosphate): 0.03-0.15 mg/kg/day **or** 0.6-0.75 mg/m^2/day in divided doses every 6-12 hours

Dosing: ElderlyRefer to adult dosing. Use cautiously in the elderly in the smallest possible dose.

Dosing: Pediatric

Antiemetic (prior to chemotherapy): I.V.: 10 mg/m^2 (initial dose) followed by 5 mg/m^2 every 6 hours as needed **or** 5-20 mg given 15-30 minutes before treatment

Anti-inflammatory and/or immunosuppressant: Oral, I.M., I.V.: 0.08-0.3 mg/kg/day **or** 2.5-10 mg/m^2/day in divided doses every 6-12 hours

Extubation or airway edema: Oral, I.M., I.V.: 0.5-2 mg/kg/day in divided doses every 6 hours beginning 24 hours prior to extubation and continuing for 4-6 doses afterwards

Cerebral edema: I.V.: Loading dose: 1-2 mg/kg/dose as a single dose; maintenance: 1-1.5 mg/kg/day (maximum: 16 mg/day) in divided doses every 4-6 hours, taper off over 1-6 weeks

Bacterial meningitis in infants and children >2 months: I.V.: 0.6 mg/kg/day in 4 divided doses every 6 hours for the first 4 days of antibiotic treatment; start dexamethasone at the time of the first dose of antibiotic

Physiologic replacement: Oral, I.M., I.V.: 0.03-0.15 mg/kg/day or 0.6-0.75 mg/m^2/day in divided doses every 6-12 hours

Ophthalmic inflammation: Refer to adult dosing.

Dosing: Renal ImpairmentHemodialysis or peritoneal dialysis: Supplemental dose is not necessary.

Dosing: Combination Regimens

Leukemia, acute lymphocytic:

Hyper-CVAD + Imatinib

Hyper-CVAD (Leukemia, Acute Lymphocytic)

TVTG

VAD/CVAD

Leukemia, acute myeloid: TVTG

Lymphoma, non-Hodgkin's:

DHAP

Hyper - CVAD (Lymphoma, non-Hodgkin's)

m-BACOD

Lymphoma, non-Hodgkin's (Mantle cell): Hyper-CVAD + Rituximab

Multiple myeloma:

Bortezomib-Dexamethasone

Bortezomib-Doxorubicin-Dexamethasone

Bortezomib-Doxorubicin (Liposomal)-Dexamethasone

DTPACE

Doxorubicin (Liposomal) - Vincristine - Dexamethasone

Hyper - CVAD (Multiple Myeloma)

Lenalidomide-Dexamethasone

Lenalidomide-Dexamethasone (Low Dose)

Thalidomide-Dexamethasone

VAD

Prostate cancer: Cyclophosphamide + Vincristine + Dexamethasone

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Corticosteroid Conversion

Administration: I.V.Administer as a 5-10 minute bolus; rapid injection is associated with a high incidence of perineal discomfort.
Administration: I.V. DetailpH: 7.0-8.5
Administration: OralAdminister oral formulation with meals to decrease GI upset.
Administration: TopicalTopical formulation is for external use. Do not use on open wounds.
Administration: Other

Ophthalmic: Remove soft contact lenses prior to using solutions containing benzalkonium chloride. Do not touch tip of container to eye.

Otic: Use ophthalmic solution for otic administration. Instill directly into aural canal or may pack canal with gauze saturated with solution. Keep wick moist and remove after 12-24 hours.

Dietary ConsiderationsMay be taken with meals to decrease GI upset. May need diet with increased potassium, pyridoxine, vitamin C, vitamin D, folate, calcium, and phosphorus.

Storage

Injection solution: Store at room temperature; protect from light and freezing.

Stability of injection of parenteral admixture at room temperature (25°C): 24 hours.

Stability of injection of parenteral admixture at refrigeration temperature (4°C): 2 days; protect from light and freezing.

ReconstitutionInjection should be diluted in 50-100 mL NS or D_5W.

CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, amikacin, amphotericin B cholesteryl sulfate complex, amsacrine, aztreonam, cefepime, cefpirome, cisatracurium, cisplatin, cladribine, cyclophosphamide, cytarabine, docetaxel, doxorubicin, doxorubicin liposome, etoposide phosphate, famotidine, filgrastim, fluconazole, fludarabine, foscarnet, gatifloxacin, gemcitabine, granisetron, heparin, heparin with hydrocortisone sodium succinate, levofloxacin, linezolid, lorazepam, melphalan, meperidine, meropenem, morphine, ondansetron, paclitaxel, piperacillin/tazobactam, potassium chloride, propofol, remifentanil, sargramostim, sodium bicarbonate, sufentanil, tacrolimus, teniposide, theophylline, thiotepa, vinorelbine, vitamin B complex with C, zidovudine. **Incompatible:** Ciprofloxacin, idarubicin, midazolam, topotecan. **Variable (consult detailed reference):** Methotrexate.

Compatibility in syringe: Compatible: Granisetron, metoclopramide, palonosetron, ranitidine, sufentanil. **Incompatible:** Doxapram, glycopyrrolate. **Variable (consult detailed reference):** Diphenhydramine, hydromorphone, ondansetron.

Compatibility when admixed: Compatible: Aminophylline, bleomycin, cimetidine, floxacillin, furosemide, granisetron, lidocaine, meropenem, mitomycin, nafcillin, netilmicin, ondansetron, palonosetron, prochlorperazine edisylate, ranitidine, verapamil. **Incompatible:** Daunorubicin, diphenhydramine with lorazepam and metoclopramide, metaraminol, vancomycin. **Variable (consult detailed reference):** Amikacin.

ContraindicationsHypersensitivity to dexamethasone or any component of the formulation; systemic fungal infections, cerebral malaria; ophthalmic use in viral (active ocular herpes simplex), fungal, or tuberculosis diseases of the eye

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox should be avoided; corticosteroids should not be used to treat ocular herpes simplex. Corticosteroids should not be used for cerebral malaria or viral hepatitis. Close observation is required in patients with latent tuberculosis and/or TB reactivity; restrict use in active TB (only in conjunction with antituberculosis treatment).
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Myopathy: Acute myopathy has been reported with high dose corticosteroids, usually in patients with neuromuscular transmission disorders; may involve ocular and/or respiratory muscles; monitor creatine kinase; recovery may be delayed.
- Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

Disease-related concerns:

- Adrenal insufficiency: Dexamethasone does not provide adequate mineralocorticoid activity in adrenal insufficiency (may be employed as a single dose while cortisol assays are performed). The lowest possible dose should be used during treatment; discontinuation and/or dose reductions should be gradual.
- Cardiovascular disease: Use with caution in patients with HF; long-term use has been associated with fluid retention and hypertension.
- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.
- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.
- Head injury: Increased mortality was observed in patients receiving high-dose I.V. methylprednisolone. High-dose corticosteroids should not be used for the management of head injury.
- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids.
- Myocardial infarction (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.
- Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Consider routine eye exams in chronic users.
- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.
- Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur.
- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.
- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Elderly: Because of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly in the smallest possible effective dose for the shortest duration.
- Pediatrics: May affect growth velocity; growth should be routinely monitored in pediatric patients.

Other warnings/precautions:

- Discontinuation of therapy: Withdraw therapy with gradual tapering of dose.

Geriatric ConsiderationsBecause of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly in the smallest possible dose, and for the shortest possible time.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed with corticosteroids in animal reproduction studies. Dexamethasone crosses the placenta; and is partially metabolized to an inactive metabolite by placental enzymes. Due to its positive effect on stimulating fetal lung maturation, the injection is often used in patients with premature labor (24-34 weeks gestation). Some studies have shown an association between first trimester systemic corticosteroid use and oral clefts; adverse events in the fetus/neonate have been noted in case reports following large doses of systemic corticosteroids during pregnancy. Women exposed to dexamethasone during pregnancy for the treatment of an autoimmune disease may contact the OTIS Autoimmune Diseases Study at 877-311-8972.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsCorticosteroids are excreted in human milk; information specific to dexamethasone has not been located.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, bradycardia, cardiac arrest, cardiomyopathy, CHF, circulatory collapse, edema, hypertension, myocardial rupture (post-MI), syncope, thromboembolism, vasculitis

Central nervous system: Depression, emotional instability, euphoria, headache, intracranial pressure increased, insomnia, malaise, mood swings, neuritis, personality changes, pseudotumor cerebri (usually following discontinuation), psychic disorders, seizure, vertigo

Dermatologic: Acne, allergic dermatitis, alopecia, angioedema, bruising, dry skin, erythema, fragile skin, hirsutism, hyper-/hypopigmentation, hypertrichosis, perianal pruritus (following I.V. injection), petechiae, rash, skin atrophy, skin test reaction impaired, striae, urticaria, wound healing impaired

Endocrine & metabolic: Adrenal suppression, carbohydrate tolerance decreased, Cushing's syndrome, diabetes mellitus, glucose intolerance decreased, growth suppression (children), hyperglycemia, hypokalemic alkalosis, menstrual irregularities, negative nitrogen balance, pituitary-adrenal axis suppression, protein catabolism, sodium retention

Gastrointestinal: Abdominal distention, appetite increased, gastrointestinal hemorrhage, gastrointestinal perforation, nausea, pancreatitis, peptic ulcer, ulcerative esophagitis, weight gain

Genitourinary: Altered (increased or decreased) spermatogenesis

Hepatic: Hepatomegaly, transaminases increased

Local: Postinjection flare (intra-articular use), thrombophlebitis

Neuromuscular & skeletal: Arthropathy, aseptic necrosis (femoral and humoral heads), fractures, muscle mass loss, myopathy (particularly in conjunction with neuromuscular disease or neuromuscular-blocking agents), neuropathy, osteoporosis, parasthesia, tendon rupture, vertebral compression fractures, weakness

Ocular: Cataracts, exophthalmos, glaucoma, intraocular pressure increased

Renal: Glucosuria

Respiratory: Pulmonary edema

Miscellaneous: Abnormal fat deposition, anaphylactoid reaction, anaphylaxis, avascular necrosis, diaphoresis, hiccups, hypersensitivity, impaired wound healing, infections, Kaposi's sarcoma, moon face, secondary malignancy

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%); may cause nausea/indigestion if taken orally on an empty stomach

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Induces** CYP2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 3A4 (strong)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Caspofungin: Inducers of Drug Clearance may decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) when coadministered with known inducers of drug clearance. *Risk D: Consider therapy modification*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Lenalidomide: Dexamethasone may enhance the thrombogenic effect of Lenalidomide. *Risk D: Consider therapy modification*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nisoldipine. *Risk X: Avoid combination*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Thalidomide: Dexamethasone may enhance the dermatologic adverse effect of Thalidomide. Dexamethasone may enhance the thrombogenic effect of Thalidomide. *Risk D: Consider therapy modification*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

↑ Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Dexamethasone interferes with calcium absorption. Limit caffeine.

Herb/Nutraceutical: Avoid cat's claw, echinacea (have immunostimulant properties).

Monitoring ParametersHemoglobin, occult blood loss, serum potassium, and glucose; intraocular pressure (with use >6 weeks)
Reference RangeDexamethasone suppression test, overnight: 8 AM cortisol <6 mcg/100 mL (dexamethasone 1 mg); plasma cortisol determination should be made on the day after giving dose
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic response, and adverse effects, according to indications for therapy, dose, route, and duration of therapy. When used for long-term therapy (>10-14 days), do not discontinue abruptly; decrease dosage incrementally. With systemic administration, caution patients with diabetes to monitor glucose levels closely (corticosteroids may alter glucose levels). Teach patient proper use (according to formulation), side effects/appropriate interventions, and symptoms to report.
Monitoring: Lab TestsHemoglobin, occult blood loss, serum potassium, glucose

Dexamethasone suppression test, overnight: 8 AM cortisol <6 mg/100 mL (dexamethasone 1 mg). Plasma cortisol determination should be made on the day after giving dose.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed, do not increase dose or discontinue abruptly without consulting prescriber.

Oral: Take with or after meals. Avoid alcohol and limit intake of caffeine or stimulants. Prescriber may recommend increased dietary vitamins, minerals, or iron. If you have diabetes, monitor glucose levels closely (antidiabetic medication may need to be adjusted). Inform prescriber if you are experiencing greater-than-normal levels of stress (medication may need adjustment). You may be more susceptible to infection (avoid crowds and persons with contagious or infective conditions and do not have any vaccinations unless approved by prescriber). Some forms of this medication may cause GI upset (small frequent meals and frequent mouth care may help). Report promptly excessive nervousness or sleep disturbances; signs of infection (eg, sore throat, unhealed injuries); excessive growth of body hair or loss of skin color; vision changes; excessive or sudden weight gain (>3 lb/week); swelling of face or extremities; respiratory difficulty; muscle weakness; tarry stool, persistent abdominal pain; worsening of condition or failure to improve. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Ophthalmic: For use in eyes only. Wash hands before using. Lie down or tilt your head back and look upward. Put drops of suspension or solution inside lower eyelid. Close eye and roll eyeball in all directions. Do not blink for $^1/_2$ minute. Apply gentle pressure to inner corner of eye for 30 seconds. Do not use any other eye preparation for at least 10 minutes. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Do not share medication with anyone else. Wear sunglasses when in sunlight; you may be more sensitive to bright light. Inform prescriber if condition worsens, fails to improve, or if you experience eye pain, disturbances of vision, or other adverse eye response.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Elixir, as base: 0.5 mg/5 mL (240 mL)

Injection, solution, as sodium phosphate: 4 mg/mL (1 mL, 5 mL, 30 mL); 10 mg/mL (10 mL)

Injection, solution, as sodium phosphate [preservative free]: 10 mg/mL (1 mL)

Solution, ophthalmic, as sodium phosphate [drops]: 0.1% (5 mL)

Solution, oral: 0.5 mg/5 mL (500 mL)

Solution, oral [concentrate]:

Dexamethasone Intensol™: 1 mg/mL (30 mL) [dye free, sugar free; contains alcohol 30% and propylene glycol]

Suspension, ophthalmic [drops]:

Maxidex®: 0.1% (5 mL) [contains benzalkonium chloride]

Tablet [scored]: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, 6 mg

DexPak® 10 Day TaperPak®: 1.5 mg [35 tablets on taper dose card]

DexPak® TaperPak®: 1.5 mg [51 tablets on taper dose card]

Generic AvailableYes: Excludes ophthalmic suspension
Pricing: U.S. (www.drugstore.com)

Elixir (Dexamethasone)

0.5 mg/5 mL (120): $47.70

Solution (Dexamethasone Sodium Phosphate)

0.1% (5): $19.99

4 mg/mL (25): $41.99

Suspension (Maxidex)

0.1% (5): $45.08

0.1% (15): $86.99

Tablets (Dexamethasone)

1 mg (30): $19.99

2 mg (30): $21.99

6 mg (30): $22.99

Mechanism of ActionDecreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response. Dexamethasone's mechanism of antiemetic activity is unknown.

Pharmacodynamics/Kinetics

Onset of action: Acetate: Prompt

Duration of metabolic effect: 72 hours; acetate is a long-acting repository preparation

Metabolism: Hepatic

Half-life elimination: Normal renal function: 1.8-3.5 hours; Biological half-life: 36-54 hours

Time to peak, serum: Oral: 1-2 hours; I.M.: ~8 hours

Excretion: Urine and feces

Related Information

- Corticosteroids
- Inhalant Agents

Pharmacotherapy PearlsEffects of inhaled/intranasal steroids on growth have been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally-inhaled and intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied.

Withdrawal/tapering of therapy: Corticosteroid tapering following short-term use is limited primarily by the need to control the underlying disease state; tapering may be accomplished over a period of days. Following longer-term use, tapering over weeks to months may be necessary to avoid signs and symptoms of adrenal insufficiency and to allow recovery of the HPA axis. Testing of HPA axis responsiveness may be of value in selected patients. Subtle deficits in HPA response may persist for months after discontinuation of therapy, and may require supplemental dosing during periods of acute illness or surgical stress.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia and nervousness are common; may cause euphoria, confusion, or hallucinations

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may decrease dexamethasone effects

Cardiovascular ConsiderationsLong-term steroid therapy is associated with a fluid retention and hypertension. Glucocorticoid agents have some mineralocorticoid activity with consequent hemodynamic effects. Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. In discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia.

Oral and intravenous steroid therapy in patients with heart failure should be administered cautiously with special attention given to signs and symptoms of fluid retention.

Although glucocorticoids can provide relief from pericarditis postmyocardial infarctions, these drugs may cause thinning of the developing scar and myocardial rupture. Avoid use in acute myocardial infarction; may cause wall rupture.

Anesthesia and Critical Care Concerns/Other ConsiderationsDexamethasone is a long-acting corticosteroid with minimal sodium-retaining potential.

Neuromuscular Effects: ICU-acquired paresis was recently studied in 5 ICUs (3 medical and 2 surgical ICUs) at 4 French hospitals. All ICU patients without pre-existing neuromuscular disease admitted from March 1999 through June 2000 were evaluated (De Jonghe, 2002). Each patient had to be mechanically ventilated for ≥7 days and was screened daily for awakening. The first day the patient was considered awake was Study Day 1. Patients with severe muscle weakness on Study Day 7 were considered to have ICU-acquired paresis. Among the 95 patients who were evaluable, about 25% developed ICU-acquired paresis. Independent predictors included: female gender, the number of days with ≥2 organ dysfunction, and administration of corticosteroids. Further studies may be required to verify and characterize the association between the development of ICU-acquired paresis and use of corticosteroids. Concurrent use of a corticosteroid and muscle relaxant appear to increase the risk of certain ICU myopathies; avoid or administer the corticosteroid at the lowest dose possible (De Jonghe, 2002).

Adrenal Insufficiency: Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. When discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that the steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia. Patients on long-term steroid supplementation will require higher corticosteroid doses when subject to stress (ie, trauma, surgery, severe infection). Guidelines for glucocorticoid replacement during various surgical procedures has been published (Coursin, 2002; Salem, 1994).

Head Injury: The use of high-dose corticosteroids in acute head injury has been investigated in an international, double-blind, placebo-controlled trial. The purpose of this trial was to evaluate the effect of early administration of a 48-hour infusion of methylprednisolone on the risk of death and disability after a head injury. Adults (≥16 years of age) were randomized within 8 hours of a head injury if they had a Glasgow coma score of 14 or less and had no clear indication or contraindication for corticosteroid use. Ten thousand and eight patients were randomized to either placebo or 2 g of methylprednisolone infused over 1 hour, followed by a continuous infusion of 0.4 g per hour for 48 hours. Primary outcome measures were death from any cause within 2 weeks of injury and the composite of death or disability after 6 months. Patients that received methylprednisolone had a higher relative risk of death at two weeks and at 6 months. The risk of death or disability at 6 months was higher in the methylprednisolone group but this result was not statistically significant. There were also no subsets of patients (time since injury, severity of injury) that benefited from corticosteroid treatment. The investigators concluded that corticosteroids should not be routinely used in the treatment of acute head injury (Roberts, 2004; Edwards, 2005).

Recent guidelines from the Brain Trauma Foundation for the management of severe traumatic brain injury state that steroids are not recommended for improving outcome or reducing intracranial pressure. The use of high dose methyprednisolone in patients with moderate-to-severe traumatic brain injury is associated with increased mortality and is contraindicated (Bratton, 2007).

Septic Shock: A recent randomized, double-blind, placebo controlled trial assessed whether low dose corticosteroid administration could improve 28-day survival in patients with septic shock and relative adrenal insufficiency. Relative adrenal insufficiency was defined as an inappropriate response to corticotropin administration (increase of serum cortisol of ≤9 mcg/dL from baseline). Cortisol levels were drawn immediately before corticotropin administration and 30-60 minutes afterwards. Three hundred adult septic shock patients requiring mechanical ventilation and vasopressor support were randomized to either hydrocortisone (50 mg IVP every 6 hours) and fludrocortisone (50 mcg tablet daily via nasogastric tube) or matching placebos for 7 days. In patients who did not appropriately respond to corticotropin (nonresponders), there were significantly fewer deaths in the active treatment group. Vasopressor therapy was withdrawn more frequently in this subset of the active treatment group. Adverse events were similar in both groups. Patients who lack adrenal reserve and thus have relative adrenal insufficiency during the stress of septic shock may benefit from physiologic steroid replacement. However, there was a trend for increased mortality in patients who responded to the corticotropin test (increase serum cortisol >9 mcg/dL from baseline). These patients may not benefit from physiologic steroid replacement. Further study is required to better characterize the patient populations who may benefit (Annane, 2002).

The 2008 Surviving Sepsis Campaign guidelines recommend doses of corticosteroids comparable to >300 mg hydrocortisone daily **not** be used in severe sepsis or septic shock for the purpose of treating septic shock (Grade 1A). They also recommend corticosteroids **not** be administered for the treatment of sepsis in the absence of shock. There is, however, no contraindication to continuing maintenance steroid therapy or to using stress dose steroids if the patient's endocrine or corticosteroid administration history warrants (Grade 1D).

Index TermsDexamethasone Sodium Phosphate

References

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International Brand NamesAacidexam (LU); Alfalyl (CO); Alin (CR, DO, GT, MX, NI, PA, SV); Aphtasolon (JP); BiDexol (TH); Brulin (MX); Cetadexon (ID); Cortidex (ID); Danasone (ID); Decadron (BF, BJ, CI, ET, GB, GH, GM, GN, GR, HK, IT, KE, LR, LU, MA, ML, MR, MU, MW, MX, NE, NG, NO, PK, PT, PY, RU, SC, SD, SL, SN, TN, TW, TZ, UG, ZA, ZM, ZW); Decadron A.L. (AR); Decadron Depot (NL); Decadronal (BR, MX); Decdan (IN); Decilone (PH); Decorex (MX); Dectancyl (AE, BH, CY, EG, FR, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Desalark (IT); Dexa-Mamallet (JP); Dexabene (LU); Dexacort (PE); Dexacortal (SE); Dexafrin Ofteno (MX); Dexagel (TH, TW); Dexalien (UY); Dexamed (SG); Dexametason (FI); Dexamethason (HN, PL); Dexamethasone (GR, IL, NZ); Dexamethasone-Organon (LU); Dexano (TH); Dexapolcort (PL); Dexapro (TH); Dexasolone (KP); Dexasone (HK, TH); Dexi Siozwo (DE); Dexmethsone (HK); Dexona (AE, BH, CY, EG, IL, IN, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Dextrasone (MY); Dibasona (MX); Etacortilen (MX); Examsa (MX); Fortecortin (AT, BG, CH, CZ, ES, LU, RU); Loverine (JP); Maxidex (AU, DK, EE, GB, HR, IE, LU); Metax (MX); Moco (JP); Oftan-Dexa (FI); Oradexon (AE, BE, BF, BH, BJ, CI, CN, CY, EG, ET, FI, GH, GM, GN, GR, HN, HU, ID, IL, IQ, IR, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, OM, PE, QA, SA, SC, SD, SL, SN, SY, TN, TR, TW, TZ, UG, YE, ZA, ZM, ZW); Pidexon (ID); Santeson (JP, PH); Sawasone (JP); Spersadex (NO); Steralol (JP); Thilodexine (GR); Vexamet (PH); Visumetazone (IT); Wymesone (IN)

Dexbrompheniramine and Pseudoephedrine

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English

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Pronunciation(deks brom fen EER a meen & soo doe e FED rin)

U.S. Brand NamesDrixoral速 Cold & Allergy [OTC]

Canadian Brand NamesDrixoral速

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsRelief of symptoms of upper respiratory mucosal congestion in seasonal and perennial nasal allergies, acute rhinitis, rhinosinusitis and eustachian tube blockage

Dosing: AdultsAllergy symptoms, rhinitis, and nasal congestion: Oral: 1 timed release tablet every 12 hours, may require 1 tablet every 8 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren >12 years: Refer to adult dosing.

Administration: OralSwallow tablet whole; do not crush or chew.

Dietary ConsiderationsMay be taken with food or water.

Pregnancy Risk FactorB

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, sustained action: Dexbrompheniramine maleate 6 mg and pseudoephedrine sulfate 120 mg

Generic AvailableYes

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause drowsiness, anxiety, and nervousness

Mental Health: Effects on Psychiatric TreatmentDry mouth is common; this effect may be worsened by concurrent psychotropic use

Index TermsPseudoephedrine and Dexbrompheniramine

International Brand NamesDisofrol (ES); Drixoral (HK, ID, SG, TW); Rinafort (MY)

Dexchlorpheniramine and Pseudoephedrine

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English English

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state "Do not use in children under four years of age." In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, "Infant Deaths Associated with Cough and Cold Medications - Two States, 2005," *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(deks klor fen EER a meen & soo doe e FED rin)

U.S. Brand NamesAllerDur™; Duotan PD [DSC]; SuTan

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsRelief of nasal congestion associated with the common cold, hay fever, and other allergies, sinusitis, and vasomotor and allergic rhinitis

Dosing: AdultsRhinitis/decongestant: Oral:

AllerDur™: 15 mL every 12 hours (maximum: 30 mL/24 hours)

DuoTan PD: 10-20 mL every 12 hours (maximum: 40 mL/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRhinitis/decongestant: Oral: Children:

2-6 years:

AllerDur™: 2.5-5 mL every 12 hours (maximum: 10 mL/24 hours)

DuoTan PD: 2.5-5 mL every 12 hours (maximum: 10 mL/24 hours)

6-12 years:

AllerDur™: 5-7.5 mL every 12 hours (maximum: 15 mL/24 hours)

DuoTan PD: 5-10 mL every 12 hours (maximum: 20 mL/24 hours)

≥12 years: Refer to adult dosing.

Administration: OralShake suspension well prior to use.

ContraindicationsHypersensitivity to dexchlorpheniramine, pseudoephedrine, or any component of the formulation; severe hypertension; severe cardiovascular disease; use with or within 2 weeks of discontinuing MAO inhibitor; narrow-angle glaucoma; urinary retention; peptic ulcer disease; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease). Use is contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Respiratory disease: Use with caution in patients with asthma or other chronic breathing disorders.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children. Safety and efficacy have not been established in children <2 years of age.

Geriatric ConsiderationsElderly patients should be counseled about the proper use of over-the-counter cough and cold preparations. Elderly are more predisposed to adverse effects of sympathomimetics since they frequently have cardiovascular diseases and diabetes mellitus as well as multiple drug therapies. It may be advisable to treat with a short-acting/immediate-release formulation before initiating sustained-release/long-acting formulations. Anticholinergic action may cause significant confusional symptoms, constipation, or problems voiding urine.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Refer to individual agents.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsPseudoephedrine is excreted in breast milk. The manufacturers do not recommend its use while breast-feeding; however, the AAP considers it to be “compatible” with breast-feeding. Information for dexchlorpheniramine is not available.

Adverse ReactionsSee individual agents.

Metabolism/Transport EffectsSee individual monographs for dexchlorpheniramine and pseudoephedrine.

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Suspension:

AllerDur™: Dexchlorpheniramine tannate 3 mg and pseudoephedrine tannate 50 mg per 5 mL (480 mL) [sugar free; contains sodium benzoate; candy-apple flavor]

Duotan PD: Dexchlorpheniramine tannate 2.5 mg and pseudoephedrine tannate 75 mg per 5 mL (120 mL, 480 mL) [contains sodium benzoate; strawberry-banana flavor] [DSC]

SuTan: Dexchlorpheniramine tannate 3 mg and pseudoephedrine tannate 50 mg per 5 mL (480 mL) [candy-apple flavor]

Generic AvailableYes
Mechanism of Action

Chlorpheniramine competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract. Dexchlorpheniramine is the predominant active isomer of chlorpheniramine and is approximately twice as active as the racemic compound.

Pseudoephedrine is a sympathomimetic amine and isomer of ephedrine; acts as a decongestant in respiratory tract mucous membranes with less vasoconstrictor action than ephedrine in normotensive individuals.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation)
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusSedation is common; may cause nervousness, depression, or confusion
Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment. Concomitant use with psychotropics may produce additive sedation.
Index TermsPseudoephedrine Tannate and Dexchlorpheniramine Tannate

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Dexchlorpheniramine

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English

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Pronunciation(deks klor fen EER a meen)

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsPerennial and seasonal allergic rhinitis and other allergic symptoms including urticaria

Dosing: AdultsAllergy symptoms: Oral: 2 mg every 4-6 hours or 4-6 mg timed release at bedtime or every 8-10 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAllergy symptoms: Oral:

2-5 years: 0.5 mg every 4-6 hours (do not use timed release)

6-11 years: 1 mg every 4-6 hours or 4 mg timed release at bedtime

Dietary ConsiderationsMay be taken with food or water.

ContraindicationsHypersensitivity to dexchlorpheniramine or any component of the formulation; narrow-angle glaucoma

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children.

Geriatric ConsiderationsAnticholinergic action may cause significant confusional symptoms, constipation, or problems voiding urine.

Pregnancy Risk FactorB

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Central nervous system: Slight to moderate drowsiness

Respiratory: Thickening of bronchial secretions

1% to 10%:

Central nervous system: Headache, fatigue, nervousness, dizziness

Gastrointestinal: Appetite increase, weight gain, nausea, diarrhea, abdominal pain, xerostomia

Neuromuscular & skeletal: Arthralgia

Respiratory: Pharyngitis

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake as directed; do not exceed recommended dose. Do not chew or crush sustained release tablet. Take with food or water. Avoid use of other depressants, alcohol, or sleep-inducing medications unless approved by prescriber. You may experience drowsiness or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or dry mouth, nausea, or abdominal pain (small frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help). Report persistent sedation, confusion, or agitation; changes in urinary pattern; blurred vision; sore throat, respiratory difficulty or expectorating (thick secretions); or lack of improvement or worsening or condition. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Syrup, as maleate: 2 mg/5 mL (480 mL) [contains alcohol 6%; orange flavor]

Tablet, sustained action, as maleate: 4 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Syrup (Dexchlorpheniramine Maleate)

2 mg/5 mL (120): $20.99

Mechanism of ActionCompetes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract. Dexchlorpheniramine is the predominant active isomer of chlorpheniramine and is approximately twice as active as the racemic compound.

Pharmacodynamics/Kinetics

Onset of action: ~1 hour

Duration: 3-6 hours

Absorption: Well absorbed

Metabolism: Hepatic

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause nervousness and depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may cause additive sedation

Index TermsDexchlorpheniramine Maleate

International Brand NamesAfeme (AR); Dapriton (HK); Delamin (TW); Destramin (BG); Dexferin (TW); Dextramine (SG); Isomerine (AR); Isomerine Repetabs (PY); Liramin (VE); Polamec (ID); Polamine (MY); Polaramin (DK, IT, NO, SE); Polaramin Prolong Depottab (NO); Polaramin Prolongatum (SE); Polaramine (BB, BE, BF, BJ, BM, BR, BS, BZ, CH, CI, CO, ES, ET, FR, GH, GM, GN, GY, HK, ID, IN, JM, KE, LR, LU, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, PR, SC, SD, SL, SN, SR, TN, TT, TW, TZ, UG, ZA, ZM, ZW); Polaramine (non-prescription) (AU); Polaramine Repetabs (FR, GR); Polarist (ID); Polaronil (AT); Rhiniramine (SG); Rhiniramine SR (HK, SG); Somin (MY, SG); Tomin (TW); Trenelone (PT)

Dexmedetomidine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Precedex® may be confused with Peridex®

Pronunciation(deks MED e toe mi deen)
U.S. Brand NamesPrecedex®
Canadian Brand NamesPrecedex®
Pharmacologic CategoryAlpha$_2$-Adrenergic Agonist; Sedative
Use: Labeled IndicationsSedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting; sedation prior to and/or during surgical or other procedures of nonintubated patients; duration of infusion should not exceed 24 hours
Use: Unlabeled/InvestigationalUnlabeled uses include premedication prior to anesthesia induction with thiopental; relief of pain and reduction of opioid dose following laparoscopic tubal ligation; as an adjunct anesthetic in ophthalmic surgery; treatment of shivering; premedication to attenuate the cardiostimulatory and postanesthetic delirium of ketamine; use in children
Dosing: AdultsIndividualized and titrated to desired clinical effect; duration of infusion should not exceed 24 hours.

ICU sedation: I.V.: Initial: Loading infusion of 1 mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2-0.7 mcg/kg/hour; adjust rate to desired level of sedation

Procedural sedation: I.V.: Initial: Loading infusion of 1 mcg/kg (or 0.5 mcg/kg for less invasive procedures [eg, ophthalmic]) over 10 minutes, followed by a maintenance infusion of 0.6 mcg/kg/hour, titrate to desired effect; usual range: 0.2-1 mcg/kg/hour

Fiberoptic intubation (awake): I.V. Initial: Loading infusion of 1 mcg/kg over 10 minutes, followed by a maintenance infusion of 0.7 mcg/kg/hour until endotracheal tube is secured.

Dosing: Elderly

ICU sedation: I.V.: Refer to adult dosing. Dosage reduction may need to be considered. No specific guidelines available. Dose selections should be cautious, at the low end of dosage range; titration should be slower, allowing adequate time to evaluate response.

Procedural sedation: I.V.: Refer to adult dosing: Initial: Loading infusion of 0.5 mcg/kg over 10 minutes; Maintenance infusion: Dosage reduction should be considered.

Dosing: Renal ImpairmentDosage reduction may need to be considered. No specific guidelines available.
Dosing: Hepatic ImpairmentDosage reduction may need to be considered. No specific guidelines available.
Administration: I.V.Administer using a controlled infusion device. Must be diluted in 0.9% sodium chloride solution to achieve the required concentration (4 mcg/mL) prior to administration. Advisable to use administration components made with synthetic or coated natural rubber gaskets. Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. If loading dose used, administer over 10 minutes; may extend to 20 minutes to further reduce vasoconstrictive effects.
StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
ReconstitutionAdd 2 mL (200 mcg) of dexmedetomidine to 48 mL of 0.9% sodium chloride for a total volume of 50 mL (4 mcg/mL). Shake gently to mix.
CompatibilityStable in D$_5$W, LR, 0.9% NS, 20% mannitol, plasma substitute

Y-site administration: Compatible: Alfentanil, amikacin, aminophylline, amiodarone, ampicillin, ampicillin and sulbactam, atracurium, atropine, azithromycin, aztreonam, bumetanide, butorphanol, calcium gluconate, cefazolin, cefepime, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, chlorpromazine, cimetidine, ciprofloxacin, cisatracurium, clindamycin, dexamethasone, digoxin, diltiazem, diphenhydramine, dobutamine, dolasetron, dopamine, doxycycline, droperidol, enalaprilat, ephedrine, epinephrine, erythromycin, esmolol, etomidate, famotidine, fenoldopam, fentanyl, fluconazole, furosemide, gentamicin, glycopyrrolate, granisetron, haloperidol, heparin, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, inamrinone, isoproterenol, ketorolac, labetalol, levofloxacin, lidocaine, linezolid, lorazepam, magnesium sulfate, meperidine, methylprednisolone sodium succinate, metoclopramide, metronidazole, midazolam, milrinone, mivacurium, morphine, nalbuphine, nitroglycerin, nitroprusside, norepinephrine, ofloxacin, ondansetron, pancuronium, phenylephrine, piperacillin, piperacillin and tazobactam, potassium chloride, procainamide, prochlorperazine, promethazine, propofol, ranitidine, rapacuronium, remifentanil, rocuronium, sodium bicarbonate, succinylcholine, sufentanil, sulfamethoxazole and trimethoprim, theophylline, thiopental, ticarcillin and clavulanate, tobramycin, vancomycin, vecuronium, verapamil. **Incompatible:** Amphotericin B, diazepam

May adsorb to certain types of natural rubber; use components made with synthetic or coated natural rubber gaskets whenever possible.

ContraindicationsThere are no contraindications listed in the manufacturer's labeling.
Allergy Considerations

- Dexmedetomidine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Transient hypertension: Has been primarily observed during loading dose administration and is associated with the initial peripheral vasoconstrictive effects of dexmedetomidine. Treatment of this is generally unnecessary; however, reduction of infusion rate may be required.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with heart block, bradycardia, severe ventricular dysfunction, hypovolemia, or chronic hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; cardiovascular adverse events (eg, bradycardia, hypotension) may be more pronounced.

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage reductions recommended.

Concurrent drug therapy issues:

- Vasodilators: Use with caution in patients receiving vasodilators or drugs which decrease heart rate.

Special populations:

- Elderly: Use with caution in the elderly; cardiovascular events (eg, bradycardia, hypotension) may be more pronounced. Dose reduction may be necessary.

Other warnings/precautions:

- Arousability: Patients may be arousable and alert when stimulated. This alone should not be considered as lack of efficacy in the absence of other clinical signs/symptoms.

- Experienced personnel: Should be administered only by persons skilled in management of patients in intensive care setting or operating room. Patients should be continuously monitored.

- Rapid I.V. administration: Episodes of bradycardia, hypotension, and sinus arrest have been associated with rapid I.V. administration (eg, bolus administration) or when given to patients with high vagal tone. If medical intervention is required, treatment may include stopping or decreasing the infusion; increasing the rate of I.V. fluid administration, use of pressor agents, and elevation of the lower extremities.

- Withdrawal: When withdrawn abruptly in patients who have received >24 hours, withdrawal symptoms similar to clonidine withdrawal may result (eg, hypertension, nervousness, agitation, headaches). Use for >24 hours is not recommended.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Cardiovascular: Hypotension (24% to 54%), bradycardia (5% to 14%)

Respiratory: Respiratory depression (37%)

1% to 10%:

Cardiovascular: Atrial fibrillation (4% to 5%), hypovolemia (3%)

Endocrine & metabolic: Hypocalcemia (1%)

Gastrointestinal: Nausea (3% to 9%), xerostomia (3% to 4%)

Renal: Urine output decreased (1%)

Respiratory: Pleural effusion (32%), wheezing (≤1%)

Postmarketing and/or case reports: Abdominal pain, abnormal vision, acidosis, agitation, alkaline phosphatase increased, ALT increased, anemia, apnea, arrhythmia, AST increased, atrioventricular block, BUN increased, bronchospasm, cardiac arrest, confusion, delirium, diaphoresis, diarrhea, dizziness, dyspnea, extrasystoles, fever, GGT increased, hallucination, headache, heart block, hemorrhage, hepatic impairment, hyperbilirubinemia, hypercapnia, hyperkalemia, hypertension, hypoglycemia, hypoventilation, hypoxia, illusion, MI, neuralgia, neuritis, oliguria, pain, photopsia, pulmonary congestion, respiratory acidosis, rigors, seizure, speech disorder, supraventricular tachycardia, tachycardia, thirst, T-wave inversion, ventricular arrhythmia, ventricular tachycardia, vomiting

Metabolism/Transport Effects**Substrate** of CYP2A6 (major); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2D6 (strong), 3A4 (weak)

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antidepressants (Alpha2-Antagonist): May diminish the hypotensive effect of Alpha2-Agonists. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

CYP2A6 Inhibitors (Moderate): May decrease the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2A6 Inhibitors (Strong): May decrease the metabolism of CYP2A6 Substrates. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Iobenguane I 123: Alpha2-Agonists may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: May diminish the antihypertensive effect of Alpha2-Agonists. *Risk D: Consider therapy modification*

Monitoring ParametersLevel of sedation; heart rate, respiration, rhythm, blood pressure; pain control

Nursing: Physical Assessment/MonitoringAdministration should be managed by professionals experienced in anesthesia. Dosage and rate of administration should be individualized and titrated to the desired effect, according to relevant clinical factors, premedication, concomitant medications, age, and general condition of patient. Assess other medications for effectiveness and safety. Other drugs that cause CNS depression may increase CNS depression induced by dexmedetomidine (monitor and adjust dosage as necessary). Continuous monitoring of vital signs, cardiac and respiratory status, and level of sedation is mandatory during infusion and until full consciousness is regained. Safety precautions must be maintained until patient is fully alert. Dexmedetomidine is an anesthetic; pain must be treated with appropriate analgesic agents. Do not discontinue abruptly (may result in rapid awakening associated with anxiety, agitation, and resistance to mechanical ventilation). Titrate infusion rate so patient awakes slowly. Monitor fluid levels (intake and output) during and following infusion. Reposition patient and provide appropriate skin, mouth, and eye care every 2-3 hours, while sedated. Provide appropriate emotional and sensory support (auditory and environmental).

Patient EducationThis is an anesthetic. Patient education should be appropriate to individual situation. Following return of consciousness, do not attempt to change position or rise from bed without assistance. Report immediately any pounding or unusual heartbeat, respiratory difficulty, or acute dizziness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Precedex®: 100 mcg/mL (2 mL)

Generic AvailableNo

Mechanism of ActionSelective alpha$_2$-adrenoceptor agonist with anesthetic and sedative properties thought to be due to activation of G-proteins by apha$_{2a}$-adrenoceptors in the brainstem resulting in inhibition of norepinephrine release; peripheral alpha$_{2b}$-adrenoceptors are activated at high doses or with rapid I.V. administration resulting in vasoconstriction.

Pharmacodynamics/Kinetics

Onset of action: Rapid

Distribution: V$_{ss}$: ~118 L; rapid

Protein binding: ~94%

Metabolism: Hepatic via N-glucuronidation, N-methylation, and CYP2A6

Half-life elimination: ~6 minutes; Terminal: ~2 hours

Excretion: Urine (95%); feces (4%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common

Mental Health: Effects on Psychiatric TreatmentHypotension and sedation are common; concurrent use with psychotropics may produce additive hypotension and sedation; monitor

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Dexmedetomidine causes minimal respiratory depression, inhibits salivation, and is analgesic-sparing. Assess the patient for pain during infusion; the sedation produced by this agent is not equivalent to analgesia. Adequate pain management should be addressed. Dexmedetomidine does not provide adequate and reliable amnesia; therefore, use of additional agents with amnestic properties may be necessary.

Hemodynamic effects: Dexmedetomidine is associated with hypotension and bradycardia due to inhibition of norepinephrine release from presynaptic neurons. Hypertension due to stimulation of peripheral vascular alpha$_{2b}$-adrenoceptors may also occur with rapid I.V. administration or high-dose infusion rates. In addition, rapid I.V. administration may also induce bradycardia. The loading infusion may be administered over a longer period of time (eg, 20-30 minutes) or may be omitted. Initiation of a maintenance infusion without administration of the loading infusion achieves similar levels of sedation without the undesirable hemodynamic effects (Ickeringill, 2004).

At low concentrations, mean arterial pressure (MAP) may be reduced without changes in other hemodynamic parameters (eg, pulmonary artery occlusion pressure [PAOP]); however, at higher concentrations (>1.9 ng/mL), MAP, CVP, PAOP, PVR, and SVR increase. An infusion rate of 0.7 mcg/kg/hour, the higher end of the manufacturer recommended dosing range, results in plasma concentrations of ~1.25 ng/mL.

Infusion duration: Infusion durations >24 hours are not recommended by the manufacturer due to the potential for the development of withdrawal symptoms (eg, hypertension, agitation). However,a study conducted in 20 critically ill patients with a mean APACHE II score of 23 (±9) demonstrated that although patients received prolonged infusions (median: 71.5 hours; range: 35-168 hours), dexmedetomidine did not produce cardiovascular rebound upon abrupt discontinuation. However, SBP and HR did increase by 7% and 11%, respectively. Patients were monitored for 24 hours after discontinuation (Shehabi, 2004).

Evidence-Based Information: In a prospective, observational study of 12 ventilator-dependent patients, dexmedetomidine was assessed as a sedative. Patients received a loading dose infusion of 1 mcg/kg over 10 minutes followed by the manufacturer's recommended infusion rate (0.2-0.7 mcg/kg/hour) for up to 7 days. Some patients required higher maintenance infusion rates than recommended by the manufacturer. Mean infusion rate was 1 ± 0.7 mcg/kg/hour. The maximum rate was 2.5 mcg/kg/hour. Adverse cardiovascular events were most frequently related to the initial loading infusion. These investigators suggest using a lower loading infusion. Higher maintenance infusions may be required in some patients. Patients did not experience a withdrawal syndrome when the infusion was discontinued (Venn, 2003).

Index Terms Dexmedetomidine Hydrochloride

References

Baddigam K, Russo P, Russo J, et al, "Dexmedetomidine in the Treatment of Withdrawal Syndromes in Cardiothoracic Surgery Patients," *J Intensive Care Med*, 2005, 20(2):118-23.[PubMed 15855224]

Gerlach AT and Dasta JF, "Dexmedetomidine: An Updated Review," *Ann Pharmacother*, 2007, 41(2):245-52.[PubMed 17299013]

Ickeringill M, Shehabi Y, Adamson H, et al, "Dexmedetomidine Infusion Without Loading Dose in Surgical Patients Requiring Mechanical Ventilation: Haemodynamic Effects and Efficacy," *Anaesth Intensive Care*, 2004, 32(6):741-5.[PubMed 15648981]

Phan H and Nahata MC, “Clinical Uses of Dexmedetomidine in Pediatric Patients,” *Paediatr Drugs*, 2008, 10(1):49-69.[PubMed 18162008]

Shehabi Y, Ruettimann U, Adamson H, et al, "Dexmedetomidine Infusion for More Than 24 Hours in Critically Ill Patients: Sedative and Cardiovascular Effects," *Intensive Care Med*, 2004, 30(12):2188-96.[PubMed 15338124]

Venn M, Newman J, and Grounds M, “A Phase II Study To Evaluate the Efficacy of Dexmedetomidine for Sedation in the Medical Intensive Care Unit,” *Intensive Care Med*, 2003, 29(2):201-7.[PubMed 12594584]

International Brand Names Precedex (MX, PL)

Dexmethylphenidate

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) has issued a statement in April 2008 recommending that all children diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the recommendations due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: Methylphenidate, amphetamine, dextroamphetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children's Healthcare Quality.

For more information, refer to:

http://americanheart.mediaroom.com/index.php?s=43&item=422

http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1

http://americanheart.mediaroom.com/index.php?s=43&item=398

http://www.fda.gov/medwatch/safety/2007/safety07.htm

http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html

Nissen SE, "ADHD Drugs and Cardiovascular Risk," *N Engl J Med*, 2006, 354(14):1445-48.

"Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder," *J Am Acad*

Child Adolesc Psychiatry, 2007, 46(7):894-921.

Vetter VL, Elia J, Erickson CH, et al, “Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing,” *Circulation*, 2008, 117:2407-23.

Wilens TE, Prince JB, Spencer TJ, et al, “Stimulants and Sudden Death: What is a Physician to do?” *Pediatrics*, 2006, 118(3):1215-19.

Medication Safety Issues

Sound-alike/look-alike issues:

Dexmethylphenidate may be confused with methadone

Pronunciation(dex meth il FEN i date)
U.S. Brand NamesFocalin®; Focalin® XR
Pharmacologic CategoryCentral Nervous System Stimulant
Use: Labeled IndicationsTreatment of attention-deficit/hyperactivity disorder (ADHD)
Dosing: Adults

Treatment of ADHD: Patients not currently taking methylphenidate: Oral:

Tablet: Initial: 2.5 mg twice daily; dosage may be adjusted in increments of 2.5-5 mg at weekly intervals (maximum dose: 20 mg/day); doses should be taken at least 4 hours apart

Capsule: Initial: 10 mg/day; dosage may be adjusted in increments of 10 mg/day at weekly intervals (maximum dose: 20 mg/day)

Note:

Conversion to dexmethylphenidate from methylphenidate: Tablet, capsule: Initial: Half the total daily dose of racemic methylphenidate (maximum dexmethylphenidate dose: 20 mg/day)

Conversion from dexmethylphenidate immediate release to dexmethylphenidate extended release: When changing from Focalin® tablets to Focalin® XR capsules, patients may be switched to the same daily dose using Focalin® XR (maximum dose: 20 mg/day)

Dose reductions and discontinuation: Reduce dose or discontinue in patients with paradoxical aggravation of symptoms. Discontinue if no improvement is seen after 1 month of treatment.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Treatment of ADHD:**
Children ≥6 years: Patients not currently taking methylphenidate: Oral:

Tablet: Initial: 2.5 mg twice daily; dosage may be adjusted in increments of 2.5-5 mg at weekly intervals (maximum dose: 20 mg/day); doses should be taken at least 4 hours apart

Capsule: Initial: 5 mg/day; dosage may be adjusted in increments of 5 mg/day at weekly intervals (maximum dose: 20 mg/day)

See "Note" in adult dosing.

Dosing: Renal ImpairmentNo data available. However, considering extensive metabolism to inactive compounds, renal insufficiency expected to have minimal effect on kinetics of dexmethylphenidate.
Dosing: Hepatic ImpairmentNo data available.
Administration: Oral

Capsule: Should be administered once daily in the morning; do not crush or chew. Capsules may be opened and contents sprinkled over a spoonful of applesauce; consume immediately; do not store for future use.

Tablet: Should be administered at least 4 hours apart; may be taken with or without food.

Dietary ConsiderationsMay be taken with or without food. Food effects on Focalin® XR have not been studied and may need to be individually adjusted.
StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light and moisture.
RestrictionsC-II

An FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to dexmethylphenidate, methylphenidate, or any component of the formulation; marked anxiety, tension, and agitation; glaucoma, motor tics, family history or diagnosis of Tourette's syndrome; use with or within 14 days following MAO inhibitor therapy
Allergy Considerations

- Amphetamine Allergy

Warnings/Precautions

Boxed warnings:

- Drug abuse: See "Disease-related concerns" below.

Concerns related to adverse effects:

- Cardiovascular events: CNS stimulant use has been associated with serious cardiovascular events including sudden death in patients with pre-existing structural cardiac abnormalities or other serious heart problems (sudden death in children and adolescents; sudden death, stroke, and MI in adults). These products should be avoided in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that could increase the risk of sudden death that these conditions alone carry. Patients should be carefully evaluated for cardiac disease prior to initiation of therapy.

- Visual disturbance: Difficulty in accommodation and blurred vision has been reported with the use of stimulants.

Disease-related concerns:

- ADHD treatment: Appropriate use: Recommended to be used as part of a comprehensive treatment program for attention deficit disorders.

- Drug abuse: **[U.S. Boxed Warning]: Potential for drug dependency exists; avoid abrupt discontinuation in patients who have received for prolonged periods.** Use caution in patients with history of ethanol or drug abuse.

- Hypertension: Use with caution in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases in blood pressure or heart rate.

- Psychiatric disorders: Use with caution in patients with pre-existing psychosis or bipolar disorder (may induce mixed/manic episode). May exacerbate symptoms of behavior and thought disorder in psychotic patients; new onset psychosis or mania may occur with stimulant use; observe for symptoms of aggression and/or hostility.

- Seizure disorder: Use with caution in patients with a history of seizure disorder; may lower seizure threshold leading to new onset or breakthrough seizure activity.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 years of age. Use of stimulants has been associated with suppression of growth; monitor growth rate during treatment.

Other warnings/precautions:

- Long-term use: Safety and efficacy of long-term use of methylphenidate have not yet been established.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were noted in animal studies. There are no adequate and well-controlled studies in pregnant women. Use only if the potential benefit to the mother outweighs the possible risks to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Headache (25% to 26%), restlessness (12%)

Gastrointestinal: Appetite decreased (30%), abdominal pain (15%)

1% to 10%:

Cardiovascular: Tachycardia (3%)

Central nervous system: Dizziness (6%), anxiety (5% to 6%), fever (5%)

Gastrointestinal: Nausea (9%), dyspepsia (5% to 8%), xerostomia (7%), anorexia (6%), pharyngolaryngeal pain (4%)

Frequency not defined: Ocular: Accommodation difficulties, blurred vision

Also refer to Methylphenidate for adverse effects seen with other methylphenidate products.

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Dexmethylphenidate. *Risk X: Avoid combination*

Phenytoin: Dexmethylphenidate may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Dexmethylphenidate may decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause CNS depression).

Food: High-fat meal may increase time to peak concentration.

Herb/Nutraceutical: Avoid ephedra (may cause hypertension or arrhythmias) and yohimbe (also has CNS stimulatory activity).

Monitoring ParametersBlood pressure and heart rate (especially in hypertensive patients), CBC with differential, platelet count; growth in children. Patients should be re-evaluated at appropriate intervals to assess continued need of the medication. Observe for signs/symptoms of aggression or hostility, or depression.

When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure, and consider obtaining ECG prior to initiation (Vetter, 2008).

Nursing: Physical Assessment/MonitoringThis drug should be used as part of a comprehensive treatment program for ADHD. Monitor closely any other medication patient may be taking for effectiveness and possible interactions prior to beginning therapy. Perform careful cardiovascular assessment prior to initiating therapy. In children, monitor growth pattern. If growth/weight gain is not as expected, may need to discontinue medication. Assess results of laboratory tests for effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage when discontinuing from long-term therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and importance of reporting adverse symptoms promptly.

Monitoring: Lab TestsCBC with differential, ECG, platelet count

Patient EducationTake exactly as directed; do not change dosage or discontinue without consulting prescriber. Response may take some time. Avoid alcohol, caffeine, or other stimulants. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience decreased appetite or weight loss (small frequent meals may help maintain adequate nutrition); or restlessness, impaired judgment, or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Report unresolved rapid heartbeat; seizures; blurred vision; excessive agitation, nervousness, insomnia, tremors, or dizziness; blackened stool; skin rash or irritation; or altered gait or movement. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release:

Focalin® XR: 5 mg, 10 mg, 15 mg, 20 mg [bimodal release]

Tablet, as hydrochloride: 2.5 mg, 5 mg, 10 mg

Focalin®: 2.5 mg, 5 mg; 10 mg [dye free]

Generic AvailableYes: Tablet

ManufacturerMikart, Inc for Novartis Pharmaceuticals Corporation

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Focalin XR)

5 mg (20): $79.86

10 mg (20): $82.05

20 mg (20): $87.91

Tablets (Dexmethylphenidate HCl)

2.5 mg (30): $21.99

Tablets (Focalin)

5 mg (20): $26.99

10 mg (20): $34.55

Mechanism of ActionDexmethylphenidate is the more active, *d-threo*-enantiomer, of racemic methylphenidate. It is a CNS stimulant; blocks the reuptake of norepinephrine and dopamine, and increases their release into the extraneuronal space.

Pharmacodynamics/Kinetics

Duration of action: Capsule: 12 hours

Absorption: Tablet: Rapid; Capsule: Bimodal

Distribution: V_d: 1.54-3.76 L/kg

Protein binding: 12% to 15%

Metabolism: Via de-esterification to inactive metabolite, *d*-α-phenyl-piperidine acetate (*d*-ritalinic acid)

Bioavailability: 22% to 25%

Half-life elimination: Immediate release: Adults: 2-4.5 hours; Children: 2-3 hours

Time to peak: Fasting:

Tablet: 1-1.5 hours

Capsule: First peak: 1.5 hours (range: 1-4 hours); Second peak: 6.5 hours (range: 4.5-7 hours)

Excretion: Urine (90%, primarily as inactive metabolite)

Related Information

- Methylphenidate
- Stimulant Agents Used for ADHD

Pharmacotherapy PearlsFocalin® XR capsules use a bimodal release where $^1/_2$ the dose is provided in immediate release beads and $^1/_2$ the dose is in delayed release beads. A single, once-daily dose of a capsule provides the same amount of dexmethylphenidate as two tablets given 4 hours apart.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index TermsDexmethylphenidate Hydrochloride

References

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Vetter VL, Elia J, Erickson CH, et al, “Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing,” *Circulation*, 2008, 117:2407-23.[PubMed 18427125]

Jump To Field (Select Field Name)

Pronunciation(deks PAN the nole)

Pharmacologic CategoryGastrointestinal Agent, Stimulant; Topical Skin Product

Use: Labeled IndicationsProphylactic use to minimize paralytic ileus; treatment of postoperative distention; topical to relieve itching and to aid healing of minor dermatoses

Dosing: Adults

Prevention of postoperative ileus: I.M.: 250-500 mg stat, repeat in 2 hours, followed by doses every 6 hours until danger passes

Paralytic ileus: I.M.: 500 mg stat, repeat in 2 hours, followed by doses every 6 hours, if needed

Dosing: ElderlyRefer to adult dosing.

Administration: I.M.Usual route of administration is I.M.

Administration: I.V.If I.V. administration is needed, may be added to a large volume of D_5W or lactated Ringer's and infused slowly.

StorageInjection: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from freezing.

ReconstitutionInjection may be diluted with D_5W or lactated Ringer's if I.V. administration is needed.

ContraindicationsHypersensitivity to dexpanthenol or any component of the formulation; mechanical obstruction of ileus

Warnings/Precautions

Other warnings/precautions:

- Appropriate use: Treatment of adynamic ileus should include correction of fluid and electrolyte imbalance, anemia, hypoproteinemia, infection and the avoidance of drugs which decrease motility.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women; use only if possible benefit outweighs potential risk to the fetus

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Slight drop in blood pressure

Central nervous system: Agitation

Dermatologic: Dermatitis, irritation, itching, urticaria

Gastrointestinal: Diarrhea, hyperperistalsis, vomiting

Neuromuscular & skeletal: Paresthesia

Respiratory: Dyspnea

Miscellaneous: Allergic reactions

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 250 mg/mL (2 mL)

Generic AvailableYes

Mechanism of ActionA pantothenic acid B vitamin analog that is converted to coenzyme A internally; coenzyme A is essential to normal fatty acid synthesis, amino acid synthesis and acetylation of choline in the production of the neurotransmitter, acetylcholine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPantothenyl Alcohol

International Brand NamesBepanten (IT); Bepanthen (AT, AU, BE, BG, CH, DE, EE, FI, HN, ID, KP, LU, PL); Bepanthene (ES, FR, PT, TR, UY); Bepanthol (EC); Bepantol (BR, ZA); Corneregel (HU, LU, PL); Dermopanten (PL); Pantenol (PY); Panthenol (CZ, DE, HN, HU, PL, RU); Pasquam (ID)

Dexrazoxane

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Zinecard® may be confused with Gemzar®

Pronunciation(deks ray ZOKS ane)

U.S. Brand NamesTotect™; Zinecard®

Canadian Brand NamesZinecard®

Pharmacologic CategoryAntidote; Cardioprotectant

Use: Labeled Indications

Zinecard®: Reduction of the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m^2 and who would benefit from continuing therapy with doxorubicin. (Not recommended for use with initial doxorubicin therapy.)

Totect™: Treatment of anthracycline-induced extravasation.

Use: Unlabeled/InvestigationalReduction of the incidence and severity of cardiomyopathy associated with doxorubicin administration (cumulative doses >300 mg/m^2) in patients with malignancies other than metastatic breast cancer who would benefit from continuing therapy with doxorubicin; reduction of the incidence and severity of cardiomyopathy associated with continued epirubicin administration for advanced breast cancer

Dosing: Adults

Prevention of doxorubicin cardiomyopathy: I.V.: A 10:1 ratio of dexrazoxane:doxorubicin (500 mg/m^2 dexrazoxane: 50 mg/m^2 doxorubicin). Note: Cardiac monitoring should continue during dexrazoxane therapy; doxorubicin/dexrazoxane should be discontinued in patients who develop a decline in LVEF or clinical CHF.

Treatment of anthracycline extravasation: 1000 mg/m^2 on days 1 and 2 (maximum dose: 2000 mg), followed by 500 mg/m^2 on day 3 (maximum dose: 1000 mg); begin treatment as soon as possible, within 6 hours of extravasation

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentModerate-to-severe (Cl_{cr}<40 mL/minute):

Prevention of cardiomyopathy: Reduce dose by 50%, using a 5:1 ratio (250 mg/m^2 dexrazoxane: 50 mg/m^2 doxorubicin)

Anthracycline-induced extravasation: Reduce dose by 50%

Dosing: Hepatic ImpairmentSince doxorubicin dosage is reduced in hyperbilirubinemia, a proportional reduction in dexrazoxane dosage is recommended (maintain ratio of 10:1).

Calculations

- Body Surface Area: Adults
- Creatinine Clearance: Adults

Administration: I.V.

Prevention of doxorubicin cardiomyopathy: Administer by slow I.V. push or rapid (5-15 minutes) I.V. infusion. Administer doxorubicin within 30 minutes after beginning the infusion with dexrazoxane.

Treatment of anthracycline extravasation: Administer over 1-2 hours; begin infusion as soon as possible, within 6 hours of extravasation. Infuse in a large vein in an area remote from the extravasation. If extravasation is also being managed with cooling, withhold cooling beginning 15 minutes before dexrazoxane infusion; continue withholding cooling until 15 minutes after infusion is completed. Day 2 and 3 doses should be administered at approximately the same time (±3 hours) as the dose on day 1. For I.V. administration; **not** for local infiltration into extravasation

StorageStore intact vials at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light. According to the manufacturers, infusion solutions diluted in 1000 mL NS (Totect™) are stable for 4 hours when stored at temperatures <25°C (<77°F); solutions diluted in D_5W or NS (Zinecard®) are stable for 6 hours at room temperature of 15°C to 30°C (59°F to 86°F) or under refrigeration at 2°C to 8°C (36°F to 46°F). When studied as a 24-hour continuous infusion for the prevention of cardiomyopathy, solutions diluted to a final concentration of 0.1 or 0.5 mg/mL in D_5W were found to retain ≥90% of their initial concentration when stored at room temperature (ambient light conditions) for ≤24 hours (Tetef, 2007).

ReconstitutionMust be reconstituted with 0.167 Molar (M/6) sodium lactate injection to a concentration of 10 mg dexrazoxane/mL sodium lactate. Reconstituted dexrazoxane solution may be diluted with either 0.9% sodium chloride injection or 5% dextrose injection to a final concentration of 1.3-5 mg/mL in intravenous infusion bags for prevention of cardiomyopathy. For anthracycline-induced extravasation, add the reconstituted solution to 1000 mL NS. Use appropriate precautions for handling and disposal.

CompatibilityStable in NS, D_5W.

Y-site administration: Compatible: Gemcitabine, pemetrexed.

ContraindicationsHypersensitivity to dexrazoxane or any component of the formulation; use with chemotherapy regimens that do not contain an anthracycline

Allergy Considerations

- Dexrazoxane Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: May cause mild myelosuppression activity; myelosuppression may be additive with concurrently administered chemotherapeutic agents.
- Cardioprotection: Does not eliminate the potential for anthracycline-induced cardiac toxicity; carefully monitor cardiac function.

Disease-related concerns:

- Hepatic impairment: Due to dosage adjustments for doxorubicin in hepatic impairment, a proportional dose reduction in dexrazoxane is recommended to maintain the dosage ratio of 10:1.
- Renal impairment: Use with caution in patients with renal dysfunction; dosage adjustment required for Cl_{cr} <40 mL/minute.

Concurrent drug therapy issues:

- Dimethylsulfoxide (DMSO): Do not use DMSO in patients receiving dexrazoxane for anthracycline-induced extravasation; may diminish dexrazoxane efficacy.
- Tumor response: Dexrazoxane may interfere with the antitumor effect of chemotherapy when given concurrently with fluorouracil, doxorubicin, and cyclophosphamide (FAC).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Administration: For I.V. administration; **not** for local infiltration into extravasation site.
- Administration sequence: When used for the prevention of cardiomyopathy, doxorubicin should be administered 30 minutes after the beginning of the dexrazoxane infusion.

Pregnancy Risk FactorC (Zinecard®) / D (Totect™)

Pregnancy ConsiderationsEmbryotoxicity and teratogenicity were observed in animal studies; maternal toxicity was also noted. There are no adequate and well-controlled studies in pregnant women. Avoid use in pregnant women unless the potential benefit justifies the potential risk to the fetus.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, discontinue nursing during dexrazoxane therapy.

Adverse Reactions Adverse reactions listed are those which were greater in the dexrazoxane arm in a trial comparison of dexrazoxane plus fluorouracil, doxorubicin, and cyclophosphamide (FAC) to FAC alone for the prevention of cardiomyopathy. Most adverse reactions are thought to be attributed to chemotherapy, except for increased myelosuppression, pain at injection site, and phlebitis.

Central nervous system: Fatigue/malaise, fever

Dermatologic: Alopecia, streaking/erythema

Endocrine & metabolic: Serum amylase increased, serum calcium decreased, serum triglycerides increased

Hematologic: Anemia, granulocytopenia, hemorrhage, leukopenia, myelosuppression, thrombocytopenia

Hepatic: ALT increased, AST increased, bilirubin increased

Local: Injection site pain (12% to 16%), phlebitis (6% to 8%), extravasation,

Neuromuscular & skeletal: Neurotoxicity

Miscellaneous: Infection, sepsis

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersSince dexrazoxane will always be used with cytotoxic drugs, and since it may add to the myelosuppressive effects of cytotoxic drugs, frequent complete blood counts are recommended; liver function; serum creatinine; cardiac function (repeat monitoring at 400 mg/m^2, 500 mg/m^2 and with every 50 mg/m^2 of doxorubicin thereafter); monitor site of extravasation

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor cardiac function closely. Assess infusion site frequently. Avoid extravasation. Monitor for effectiveness of therapy and adverse effects.

Monitoring: Lab TestsFrequent complete blood counts are recommended; liver function; serum creatinine

Patient EducationThis I.V. medication is given to reduce incidence of cardiac complications with doxorubicin. Report promptly any pain at infusion site. You will be more susceptible to infections. Avoid crowds and exposure to infections whenever possible. Report shortness of breath, chest discomfort, unusual bleeding, fever, or swelling of extremities. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 250 mg, 500 mg

Totect™: 500 mg [provided with 0.167 Molar sodium lactate injection, USP]

Zinecard®: 250 mg, 500 mg [provided with 0.167 Molar sodium lactate injection, USP]

Generic AvailableYes

Mechanism of ActionDerivative of EDTA; potent intracellular chelating agent. The mechanism of cardioprotectant activity is not fully understood. Appears to be converted intracellularly to a ring-opened chelating agent that interferes with iron-mediated oxygen free radical generation thought to be responsible, in part, for anthracycline-induced cardiomyopathy. In the management of anthracycline-induced extravasation, dexrazoxane may act by reversibly inhibiting topoisomerase II, protecting tissue from anthracycline cytotoxicity, thereby decreasing tissue damage.

Pharmacodynamics/Kinetics

Distribution: V_d: 22 L/m^2

Protein binding: None

Half-life elimination: 2-2.5 hours

Excretion: Urine (42%)

Clearance, renal: 3.35 L/hour/m^2; Plasma: 6.25-7.88 L/hour/m^2

Related Information

- Management of Drug Extravasations
- Safe Handling of Hazardous Drugs

Pharmacotherapy Pearls**Oncology Comment:** Guidelines from the American Society of Clinical Oncology (ASCO) for the use of chemotherapy and radiotherapy protectants (Schuchter, 2002; Hensley, 2008 [update]) recommend the use of dexrazoxane as a cardioprotectant in patients with metastatic breast cancer who may benefit from further doxorubicin-based chemotherapy after a cumulative doxorubicin dose >300 mg/m^2 has been reached. In patients with metastatic breast cancer who had previously received >300 mg/m^2 doxorubicin in the adjuvant setting, the decision to use dexrazoxane should be individualized, weighing the benefits of cardioprotection against the possibility of decreased response rates (due to dexrazoxane). Dexrazoxane use is not recommended in patients with metastatic breast cancer receiving doxorubicin as initial therapy. In the adjuvant setting, dexrazoxane use is not recommended outside of a clinical trial. Dexrazoxane may be considered for reduction of the incidence and severity of cardiomyopathy associated with continued epirubicin administration in patients with advanced breast cancer. In adults with malignancies other than breast cancer, dexrazoxane may be considered in patients who have received >300 mg/m^2 of doxorubicin-based therapy. Cardiac monitoring should continue during dexrazoxane therapy; discontinue doxorubicin/dexrazoxane in patients who develop a decline in LVEF or clinical CHF.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause granulocytopenia; use caution with clozapine or carbamazepine

Index TermsICRF-187; NSC-169780

References

Hellmann K, “Overview and Historical Development of Dexrazoxane,” *Semin Oncol*, 1998, 25(4 Suppl 10):48-54.

Hensley ML, Hagerty KL, Kewalramani T, et al, “American Society of Clinical Oncology 2008 Clinical Practice Guideline Update: Use of Chemotherapy and Radiotherapy Protectants,” *J Clin Oncol*, 2008 [epub ahead of print][PubMed 19018081]

Hochster HS, “Clinical Pharmacology of Dexrazoxane,” *Semin Oncol*, 1998, 25(4 Suppl 10):37-42. [PubMed 9768822]

Kwok JC and Richardson DR, “The Cardioprotective Effect of the Iron Chelator Dexrazoxane (ICRF-187) on Anthracycline-Mediated Cardiotoxicity,” *Redox Rep*, 2000, 5(6):317-24. [PubMed 11140743]

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Langer SW, Thougaard AV, Sehested M, et al, “Treatment of Anthracycline Extravasation in Mice With Dexrazoxane With or Without DMSO and Hydrocortisone,” *Cancer Chemother Pharmacol*, 2006, 57(1):125-8.[PubMed 16001176]

Lopez M and Vici P, “European Trials With Dexrazoxane in Amelioration of Doxorubicin and Epirubicin-Induced Cardiotoxicity,” *Semin Oncol*, 1998, 25(4 Suppl 10):55-60. [PubMed 9768825]

Mouridsen HT, Langer SW, Buter J, et al, “Treatment of Anthracycline Extravasation With Savene (Dexrazoxane): Results From Two Prospective

Clinical Multicentre Studies," *Ann Oncol*, 2007, 18(3):546-50.[PubMed 17185744]

Schuchter LM, Hensley ML, Meropol NJ, et al, "2002 Update of Recommendations for the Use of Chemotherapy and Radiotherapy Protectants: Clinical Practice Guidelines of the American Society of Clinical Oncology," *J Clin Oncol*, 2002, 20(12):2895-903.[PubMed 12065567]

Sehested M, et al, "Dexrazoxane for Protection Against Cardiotoxic Effects of Anthracyclines," *J Clin Oncol*, 1996, 14:2884.

Tetef ML, Synold TW, Chow W, et al, "Phase I Trial of 96-Hour Continuous Infusion of Dexrazoxane I Patients With Advanced Malignancies," *Clin Cancer Res*, 2001, 7(6):1569-76.[PubMed 11410492]

Wiseman LR and Spencer CM, "Dexrazoxane. A Review of Its Use as a Cardioprotective Agent in Patients Receiving Anthracycline-Based Chemotherapy," *Drugs*, 1998. 56(3):385-403.[PubMed 9777314]

International Brand NamesCardioxane (AR, BG, BR, CN, CZ, DK, EC, ES, FI, FR, GB, HN, IL, IT, KP, MX, PE, PL, PY, UY, VE); Dexarazoxane Martian (AR); Dexrazoxane Chiron (AR); Savene (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Dextran 1

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Dextran may be confused with Dexatrim®, Dexedrine®

Pronunciation(DEKS tran won)
U.S. Brand NamesPromit® [DSC]
Pharmacologic CategoryPlasma Volume Expander
Use: Labeled IndicationsProphylaxis of serious anaphylactic reactions to I.V. infusion of dextran
Dosing: AdultsProphylaxis of severe reactions to dextran infusions: I.V.: 20 mL 1-2 minutes before infusion of dextran. Administer 1 dose only prior to dextran. Give 1-2 minutes before I.V. infusion of dextran. Time between dextran 1 and dextran solution should not exceed 15 minutes.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricProphylaxis of severe adverse reactions to dextran: I.V. (time between dextran 1 and dextran solution should not exceed 15 minutes): Children: 0.3 mL/kg 1-2 minutes before I.V. infusion of dextran
Administration: I.V.Infuse over 1 minute.
StorageProtect from freezing.
CompatibilityDo not dilute or admix with dextrans.
ContraindicationsHypersensitivity to dextrans or any component of the formulation; **dextran** contraindicated
Allergy Considerations

- Dextran Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis: Mild dextran-induced anaphylactic reactions are not prevented.

- Cardiovascular effects: Severe hypotension and bradycardia can occur. If any reaction occurs, do not administer dextran.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown
Adverse Reactions<1% (Limited to important or life-threatening): Mild hypotension, tightness of chest, wheezing
Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringDextran 1 is to be infused not more than 15 minutes before dextran for prophylaxis of serious anaphylactic reactions to dextran infusions. Patient should be monitored closely during infusion; hypotension and bradycardia may occur. If reaction occurs, dextran should not be given. Patient teaching should be appropriate to patient condition.
Patient EducationSince this medication is generally administered in emergency situations, patient education should be supportive and appropriate to patient condition.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution:

Promit®: 150 mg/mL (20 mL) [DSC]

Generic AvailableNo
Mechanism of ActionBinds to dextran-reactive immunoglobulin without bridge formation and no formation of large immune complexes
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Cardiovascular ConsiderationsDextran use in patients with restrictive cardiovascular disease or renal and hepatic impairment should be used with extreme caution. Dextran can also result in an anaphylactoid reaction. Patients should be observed closely during the first several minutes of the infusion in case anaphylactoid reaction occurs.
References

Renck H, Ljungstrom KG, Hedin H, et al, “Prevention of Dextran-Induced Anaphylactic Reactions by Hapten Inhibition,” *Acta Chir Scand*, 1983, 149(4):355-60.[PubMed 6193667]

Dextran

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Dextran may be confused with Dexatrim®, Dexedrine®

Pronunciation(DEKS tran)

U.S. Brand NamesGentran®; LMD®

Canadian Brand NamesGentran®

Pharmacologic CategoryPlasma Volume Expander

Use: Labeled IndicationsBlood volume expander used in treatment of shock or impending shock when blood or blood products are not available; dextran 40 is also used as a priming fluid in cardiopulmonary bypass and for prophylaxis of venous thrombosis and pulmonary embolism in surgical procedures associated with a high risk of thromboembolic complications

Dosing: Adults

Volume expansion/shock:

Dextran 40: 500-1000 mL at a rate of 20-40 mL/minute (maximum: 20 mL/kg/day for first 24 hours); 10 mL/kg/day thereafter; therapy should not be continued beyond 5 days

Dextran 70: 500-1000 mL at a rate of 20-40 mL/minute (maximum: 20 mL/kg/day for first 24 hours)

Pump prime:*Dextran 40:* Varies with the volume of the pump oxygenator; generally, the 10% solution is added in a dose of 1-2 g/kg

Prophylaxis of venous thrombosis/pulmonary embolism:*Dextran 40:* Begin during surgical procedure and give 50-100 g on the day of surgery; an additional 50 g (500 mL) should be administered every 2-3 days during the period of risk (up to 2 weeks postoperatively); usual maximum infusion rate for nonemergency use: 4 mL/minute

Dosing: ElderlyUse with extreme caution in patients with renal or hepatic impairment.

Dosing: PediatricTreatment of shock or impending shock (when blood or blood products are not available): I.V. (requires an infusion pump): *Dextran 40 or 70:* Total dose should not be >20 mL/kg during first 24 hours

Dosing: Renal ImpairmentUse with extreme caution.

Dosing: Hepatic ImpairmentUse with extreme caution.

Administration: I.V.For I.V. infusion only (use an infusion pump). Infuse initial 500 mL at a rate of 20-40 mL/minute if hypervolemic. Reduce rate for additional infusion to 4 mL/minute. **Observe patients closely for anaphylactic reaction.**

Administration: I.V. DetailHave other means of maintaining circulation with epinephrine and diphenhydramine available should dextran therapy result in an anaphylactoid reaction.

pH: 3-7 (dextran 40 10% in dextrose 5%); 3.5-7 (dextran 40 10% in sodium chloride)

StorageStore at room temperature. Discard partially used containers.

Compatibility

Dextran 40: Stable in D_5W, NS.

Y-site administration: Compatible: Enalaprilat, famotidine.

Compatibility when admixed: Incompatible: Amoxicillin.

Do not add any drugs to dextran solution. To prevent coagulation of blood, flush tubing well or change I.V. tubing before infusing blood after dextran.

ContraindicationsHypersensitivity to dextran or any component of the formulation; marked hemostatic defects (thrombocytopenia, hypofibrinogenemia) of all types including those caused by drugs; marked cardiac decompensation; renal disease with severe oliguria or anuria

Allergy Considerations

- Dextran Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Decreased hematocrit: Exercise care to prevent a depression of hematocrit <30% (can cause hemodilution); observe for signs of bleeding.

- Fluid overload: Administration can cause fluid overload; use with caution in patients with hypovolemia.

- Hypersensitivity reactions: Have been reported (dextran 40 rarely causes a reaction), usually early in the infusion. Monitor closely during infusion initiation for signs or symptoms of a hypersensitivity reaction. Dextran 1 is indicated for prophylaxis of serious anaphylactic reactions to dextran infusions.

- Renal failure: Has been reported; fluid status including urine output should be monitored closely.

Disease-related concerns:

- Hemorrhage: Use with caution in patients with active hemorrhage.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown
Adverse Reactions<1% (Limited to important or life-threatening): Mild hypotension, tightness of chest, wheezing
Drug Interactions

Abciximab: Dextran may enhance the anticoagulant effect of Abciximab. *Risk X: Avoid combination*

Monitoring ParametersObserve patient for signs of circulatory overload and/or monitor central venous pressure; observe patients closely during the first minute of infusion and have other means of maintaining circulation should dextran therapy result in an anaphylactoid reaction; monitor hemoglobin and hematocrit, electrolytes, serum protein
Nursing: Physical Assessment/MonitoringPatient should be monitored closely for fluid overload, anaphylactoid reaction, and bleeding (eg, fluid status [oliguria/anuria], vital signs, and CVP) during first 15 minutes of first hour and periodically thereafter. Other means of maintaining circulation (eg, with epinephrine and diphenhydramine) should be available in the event of an anaphylactoid reaction. Patient teaching should be appropriate to patient condition.
Monitoring: Lab TestsHemoglobin and hematocrit, electrolytes, serum protein
Patient EducationSince this medication is generally used in emergency situations, patient education should be appropriate to patient condition.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed in D_5W; low molecular weight]:

LMD®: 10% Dextran 40 (500 mL)

Infusion [premixed in NS; high molecular weight]:

Gentran®: 6% Dextran 70 (500 mL)

Infusion [premixed in NS; low molecular weight]:

LMD®: 10% Dextran (500 mL)

Generic AvailableNo
Mechanism of ActionProduces plasma volume expansion by virtue of its highly colloidal starch structure, similar to albumin
Pharmacodynamics/Kinetics

Onset of action: Minutes to 1 hour (depending upon the molecular weight polysaccharide administered)

Excretion: Urine (~75%) within 24 hours

Pharmacotherapy PearlsDextran 40 is known as low molecular weight dextran (LMD®) and has an average molecular weight of 40,000; dextran 75 has an average molecular weight of 75,000. Dextran 70 has an average molecular weight of 70,000; sodium content of 500 mL is 77 mEq, with pH ranging from 3.0-7.0.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Cardiovascular ConsiderationsDextran use in patients with restrictive cardiovascular disease, renal or hepatic impairment should be used with extreme caution. Dextran can also result in an anaphylactoid reaction. Patients should be observed closely during the first several minutes of the infusion in case anaphylactoid reaction occurs. Use caution with concurrent use of antiplatelet medications. Monitor closely for bleeding.
Anesthesia and Critical Care Concerns/Other ConsiderationsDextran should be used with extreme caution in patients with restrictive cardiovascular disease and renal or hepatic impairment. Patients should be observed closely during the first several minutes of the infusion in case anaphylactoid reaction occurs.

Dextran 40 is known as low molecular weight dextran (LMD®) and has an average molecular weight of 40,000.

Dextran 75 has an average molecular weight of 75,000.

Dextran 70 has an average molecular weight of 70,000.

Index TermsDextran 40; Dextran 70; Dextran, High Molecular Weight; Dextran, Low Molecular Weight
International Brand NamesDekstran 40000 (PL); Dekstran 70000 (PL); Dextran 40 Injection (AU); Dextran 40 Vifor (CH); Dextran 70 Injection (AU); Dextran 70 Vifor (CH); Dextran Spofa (CZ); Dextran-1 B. Braun (CH); Dextril 70 (FI); Dialens (CH); Eudextran (IT); Fluidex (CZ); Gentran 40 (LU, NL); Gentran 70 (LU, NL); Hyskon (DE); Infukoll M 40 (DE); Lacrima Plus (MX); LM Dextran (ID); LM Dextran L (ID); Longasteril 40° (DE, LU); Macrodex (DE, NL); Macrodex 6% (GB); Onkovertin N (DE); Plander (IT); Plander R (IT); Promit (CH, DE); Promiten (LU, NO); Rheodextran Infusia (CZ); Rheodextran Spofa (CZ); Rheomacrodex (BR, CZ, DE, DK, EC, FR, LU, NL, NO, SE); Rheomacrodex 10% (AT, GB); Solplex 40 (IT); Solplex 70 (IT); Soludeks 1 (HR);

Soludeks 40 (HR); Soludeks 70 (HR); Tears Naturale (PL); Thomaedex 40 (DE)

Dextroamphetamine and Amphetamine

Lexi-Drugs Online

English

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) has issued a statement in April 2008 recommending that all children diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the recommendations due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: Methylphenidate, amphetamine, dextroamphetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children's Healthcare Quality.

For more information, refer to:

- http://americanheart.mediaroom.com/index.php?s=43&item=422
- http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1
- http://americanheart.mediaroom.com/index.php?s=43&item=398
- http://www.fda.gov/medwatch/safety/2007/safety07.htm
- http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html

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"Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder," *J Am Acad*

Child Adolesc Psychiatry, 2007, 46(7):894-921.

Vetter VL, Elia J, Erickson CH, et al, “Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing,” *Circulation*, 2008, 117:2407-23.

Wilens TE, Prince JB, Spencer TJ, et al, “Stimulants and Sudden Death: What is a Physician to do?” *Pediatrics*, 2006, 118(3):1215-19.

Medication Safety Issues

Sound-alike/look-alike issues:

Adderall® may be confused with Inderal®

Pronunciation(deks troe am FET a meen & am FET a meen)
U.S. Brand NamesAdderall XR®; Adderall®
Canadian Brand NamesAdderall XR®
Pharmacologic CategoryStimulant
Use: Labeled IndicationsAttention-deficit/hyperactivity disorder (ADHD); narcolepsy
Dosing: Adults**Note:** Use lowest effective individualized dose; administer first dose as soon as awake; use intervals of 4-6 hours between additional doses.

ADHD: Oral:

Adderall®: Initial: 5 mg once or twice daily; increase daily dose in 5 mg increments at weekly intervals until optimal response is obtained; usual maximum dose: 40 mg/day given in 1-3 divided doses per day.

Adderall XR®: Initial: 20 mg once daily in the morning; higher doses (up to 60 mg once daily) have been evaluated; however, there is not adequate evidence that higher doses afforded additional benefit

Narcolepsy:*Adderall®*: Oral: Initial: 10 mg/day; increase daily dose in 10 mg increments at weekly intervals until optimal response is obtained; maximum dose: 60 mg/day given in 1-3 divided doses per day with intervals of 4-6 hours between doses.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Note: Use lowest effective individualized dose; administer first dose as soon as awake

ADHD: Oral:

Children: <3 years: Not recommended.

Children: 3-5 years (Adderall®): Initial 2.5 mg/day given every morning; increase daily dose in 2.5 mg increments at weekly intervals until optimal response is obtained; maximum dose: 40 mg/day given in 1-3 divided doses per day. Use intervals of 4-6 hours between additional doses.

Children: ≥6 years:

Adderall®: Initial: 5 mg once or twice daily; increase daily dose in 5 mg increments at weekly intervals until optimal response is obtained; usual maximum dose: 40 mg/day given in 1-3 divided doses per day. Use intervals of 4-6 hours between additional doses.

Adderall XR®: 5-10 mg once daily in the morning; if needed, may increase daily dose in 5-10 mg increments at weekly intervals (maximum dose: 30 mg/day)

Adolescents 13-17 years (Adderall XR®): 10 mg once daily in the morning; maybe increased to 20 mg/day after 1 week if symptoms are not controlled; higher doses (up to 60 mg)/day have been evaluated; however, there is not adequate evidence that higher doses afforded additional benefit.

Narcolepsy:*Adderall®*: Oral:

Children: 6-12 years: Initial: 5 mg/day; increase daily dose in 5 mg increments at weekly intervals until optimal response is obtained; maximum dose: 60 mg/day given in 1-3 divided doses per day with intervals of 4-6 hours between doses.

Children >12 years: Refer to adult dosing.

Administration: Oral

Adderall®: To avoid insomnia, last daily dose should be administered no less than 6 hours before retiring.

Adderall XR®: Should be given by noon. Capsule may be swallowed whole or it may be opened and the contents sprinkled on applesauce. Applesauce should be consumed immediately without chewing. Do not divide the contents of the capsule.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.
RestrictionsC-II

An FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to dextroamphetamine, amphetamine, or any component of the formulation; advanced arteriosclerosis; symptomatic cardiovascular disease; moderate to severe hypertension; hyperthyroidism; hypersensitivity or idiosyncrasy to the sympathomimetic amines; glaucoma; agitated states; patients with a history of drug abuse; with or within 14 days following MAO inhibitor (hypertensive crisis)

Allergy Considerations

- Amphetamine Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Drug abuse: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Cardiovascular events: **[U.S. Boxed Warning]: Use has been associated with serious cardiovascular events including sudden death in patients with pre-existing structural cardiac abnormalities or other serious heart problems (sudden death in children and adolescents; sudden death, stroke and MI in adults).** These products should be avoided in the patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that could increase the risk of sudden death that these conditions alone carry. Patients should be carefully evaluated for cardiac disease prior to initiation of therapy.
- CNS effects: Amphetamines may impair the ability to engage in potentially hazardous activities.
- Visual disturbance: Difficulty in accommodation and blurred vision has been reported with the use of stimulants.

Disease-related concerns:

- Drug abuse: **[U.S. Boxed Warning]: Potential for drug dependency exists; prolonged use may lead to drug dependency.** Use is contraindicated in patients with history of ethanol or drug abuse. Prescriptions should be written for the smallest quantity consistent with good patient care to minimize possibility of overdose.
- Hypertension: Use with caution in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases in blood pressure or heart rate. Use is contraindicated in patients with moderate to severe hypertension.
- Psychiatric disorders: Use with caution in patients with pre-existing psychosis or bipolar disorder (may induce mixed/manic episode). May exacerbate symptoms of behavior and thought disorder in psychotic patients; new onset psychosis or mania may occur with stimulant use; observe for symptoms of aggression and/or hostility.
- Seizure disorder: Use with caution in patients with a history of seizure disorder; may lower seizure threshold leading to new onset or breakthrough seizure activity.
- Tourette's syndrome: Use with caution in patients with Tourette's syndrome; stimulants may unmask tics.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <3 years of age. Appetite suppression may occur; monitor weight during therapy, particularly in children. Use of stimulants has been associated with suppression of growth; monitor growth rate during treatment.

Other warnings/precautions:

- Discontinuation of therapy: Abrupt discontinuation following high doses or for prolonged periods may result in symptoms for withdrawal.

Pregnancy Risk FactorC

Pregnancy ConsiderationsUse during pregnancy may lead to increased risk of premature delivery and low birth weight. Infants may experience symptoms of withdrawal. Teratogenic effects were reported when taken during the 1st trimester.

LactationEnters breast milk/contraindicated

Adverse Reactions

As reported with Adderall XR®:

>10%:

Central nervous system: Insomnia (12% to 27%), headache (up to 26% in adults)

Gastrointestinal: Appetite decreased (22% to 36%), abdominal pain (11% to 14%), dry mouth (2% to 35%), weight loss (4% to 11%)

1% to 10%:

Cardiovascular: Tachycardia (up to 6% in adults), palpitation (2% to 4%)

Central nervous system: Emotional lability (2% to 9%), agitation (up to 8% in adults), anxiety (8%), dizziness (2% to 7%), nervousness (6%), fever (5%), somnolence (2% to 4%)

Dermatologic: Photosensitization (2% to 4%)

Endocrine & metabolic: Dysmenorrhea (2% to 4%), impotence (2% to 4%), libido decreased (2% to 4%)

Gastrointestinal: Nausea (2% to 8%), vomiting (2% to 7%), diarrhea (2% to 6%), constipation (2% to 4%), dyspepsia (2% to 4%), tooth disorder (2% to 4%)

Genitourinary: Urinary tract infection (5%)

Neuromuscular & skeletal: Twitching (2% to 4%), weakness (2% to 6%)

Respiratory: Dyspnea (2% to 4%)

Miscellaneous: Diaphoresis (2% to 4%), infection (2% to 4%), speech disorder (2% to 4%)

<1% (Limited to important or life-threatening): MI, seizure, stroke, sudden death

Adverse reactions reported with other amphetamines include: Anaphylaxis, angioedema, anorexia, cardiomyopathy, depression, dyskinesia, dysphoria, euphoria, exacerbation of motor and phonic tics, exacerbation of Tourette's syndrome, hypertension, MI, overstimulation, psychosis, rash, restlessness, seizure, stroke, taste disturbance, tremor, urticaria

Metabolism/Transport EffectsAmphetamine: **Inhibits** CYP2D6 (weak)

Drug Interactions

Alkalinizing Agents: May decrease the excretion of Amphetamines. *Risk D: Consider therapy modification*

Ammonium Chloride: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

Analgesics (Opioid): Amphetamines may enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Antihistamines: Amphetamines may diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antipsychotics: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Amphetamines. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Ethosuximide: Amphetamines may diminish the therapeutic effect of Ethosuximide. Amphetamines may decrease the serum concentration of Ethosuximide. *Risk C: Monitor therapy*

Gastrointestinal Acidifying Agents: May decrease the serum concentration of Amphetamines. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Methenamine: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

PHENobarbital: Amphetamines may decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Phenytoin: Amphetamines may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Dextroamphetamine serum levels may be altered if taken with acidic food, juices, or vitamin C. Avoid caffeine.

Herb/Nutraceutical: Avoid ephedra (may cause hypertension or arrhythmias).

Test InteractionsMay interfere with urinary steroid testing

Monitoring ParametersCNS activity, blood pressure, pulse; height, weight, growth parameters; appetite; signs/symptoms of tolerance or dependence

When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure, and consider obtaining ECG prior to initiation (Vetter, 2008).

Nursing: Physical Assessment/MonitoringSee individual agent for Dextroamphetamine.

Patient EducationSee individual agent for Dextroamphetamine.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release:

- Adderall XR®:
  - 5 mg [dextroamphetamine sulfate 1.25 mg, dextroamphetamine saccharate 1.25 mg, amphetamine aspartate monohydrate 1.25 mg, amphetamine sulfate 1.25 mg (equivalent to amphetamine base 3.1 mg)]
  - 10 mg [dextroamphetamine sulfate 2.5 mg, dextroamphetamine saccharate 2.5 mg, amphetamine aspartate monohydrate 2.5 mg, amphetamine sulfate 2.5 mg (equivalent to amphetamine base 6.3 mg)]
  - 15 mg [dextroamphetamine sulfate 3.75 mg, dextroamphetamine saccharate 3.75 mg, amphetamine aspartate monohydrate 3.75 mg, amphetamine sulfate 3.75 mg (equivalent to amphetamine base 9.4 mg)]
  - 20 mg [dextroamphetamine sulfate 5 mg, dextroamphetamine saccharate 5 mg, amphetamine aspartate monohydrate 5 mg, amphetamine sulfate 5 mg (equivalent to amphetamine base 12.5 mg)]
  - 25 mg [dextroamphetamine sulfate 6.25 mg, dextroamphetamine saccharate 6.25 mg, amphetamine aspartate monohydrate 6.25 mg, amphetamine sulfate 6.25 mg (equivalent to amphetamine base 15.6 mg)]
  - 30 mg [dextroamphetamine sulfate 7.5 mg, dextroamphetamine saccharate 7.5 mg, amphetamine aspartate monohydrate 7.5 mg, amphetamine sulfate 7.5 mg (equivalent to amphetamine base 18.8 mg)]

Tablet:

- 5 mg [dextroamphetamine sulfate 1.25 mg, dextroamphetamine saccharate 1.25 mg, amphetamine aspartate monohydrate 1.25 mg, amphetamine sulfate 1.25 mg (equivalent to amphetamine base 3.13 mg)]
- 7.5 mg [dextroamphetamine 1.875 mg, dextroamphetamine saccharate 1.875 mg, amphetamine aspartate monohydrate 1.875 mg, amphetamine sulfate 1.875 mg (equivalent to amphetamine base 4.7 mg)]
- 10 mg [dextroamphetamine sulfate 2.5 mg, dextroamphetamine saccharate 2.5 mg, amphetamine aspartate monohydrate 2.5 mg, amphetamine sulfate 2.5 mg (equivalent to amphetamine base 6.3 mg)]
- 12.5 mg [dextroamphetamine sulfate 3.125 mg, dextroamphetamine saccharate 3.125 mg, amphetamine aspartate monohydrate 3.125 mg, amphetamine sulfate 3.125 mg (equivalent to amphetamine base 7.8 mg)]
- 15 mg [dextroamphetamine sulfate 3.75 mg, dextroamphetamine saccharate 3.75 mg, amphetamine aspartate monohydrate 3.75 mg, amphetamine sulfate 3.75 mg (equivalent to amphetamine base 9.4 mg)]
- 20 mg [dextroamphetamine sulfate 5 mg, dextroamphetamine saccharate 5 mg, amphetamine aspartate monohydrate 5 mg, amphetamine sulfate 5 mg (equivalent to amphetamine base 12.6 mg)]
- 30 mg [dextroamphetamine sulfate 7.5 mg, dextroamphetamine saccharate 7.5 mg, amphetamine aspartate monohydrate 7.5 mg, amphetamine sulfate 7.5 mg (equivalent to amphetamine base 18.8 mg)]
- Adderall®:
  - 5 mg [dextroamphetamine sulfate 1.25 mg, dextroamphetamine saccharate 1.25 mg, amphetamine aspartate monohydrate 1.25 mg, amphetamine sulfate 1.25 mg (equivalent to amphetamine base 3.13 mg)]
  - 7.5 mg [dextroamphetamine 1.875 mg, dextroamphetamine saccharate 1.875 mg, amphetamine aspartate monohydrate 1.875 mg, amphetamine sulfate 1.875 mg (equivalent to amphetamine base 4.7 mg)]
  - 10 mg [dextroamphetamine sulfate 2.5 mg, dextroamphetamine saccharate 2.5 mg, amphetamine aspartate monohydrate 2.5 mg, amphetamine sulfate 2.5 mg (equivalent to amphetamine base 6.3 mg)]
  - 12.5 mg [dextroamphetamine sulfate 3.125 mg, dextroamphetamine saccharate 3.125 mg, amphetamine aspartate monohydrate 3.125 mg, amphetamine sulfate 3.125 mg (equivalent to amphetamine base 7.8 mg)]
  - 15 mg [dextroamphetamine sulfate 3.75 mg, dextroamphetamine saccharate 3.75 mg, amphetamine aspartate monohydrate 3.75 mg, amphetamine sulfate 3.75 mg (equivalent to amphetamine base 9.4 mg)]
  - 20 mg [dextroamphetamine sulfate 5 mg, dextroamphetamine saccharate 5 mg, amphetamine aspartate monohydrate 5 mg, amphetamine sulfate 5 mg (equivalent to amphetamine base 12.6 mg)]
  - 30 mg [dextroamphetamine sulfate 7.5 mg, dextroamphetamine saccharate 7.5 mg, amphetamine aspartate monohydrate 7.5 mg, amphetamine sulfate 7.5 mg (equivalent to amphetamine base 18.8 mg)]

Generic AvailableYes: Tablet
ManufacturerShire
Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Adderall XR)

- 5 mg (20): $94.08
- 10 mg (20): $94.08
- 15 mg (20): $94.08
- 20 mg (20): $94.08
- 25 mg (20): $94.08
- 30 mg (20): $94.08

Tablets (Adderall)

5 mg (20): $67.09

10 mg (20): $61.99

15 mg (20): $64.99

20 mg (20): $65.99

30 mg (20): $65.99

Tablets (Amphetamine Salt Combo)

5 mg (20): $26.66

7.5 mg (20): $25.99

10 mg (20): $26.99

12.5 mg (20): $25.99

15 mg (20): $25.99

20 mg (20): $26.66

30 mg (20): $26.66

Mechanism of ActionBlocks reuptake of dopamine and norepinephrine from the synapse, thus increases the amount of circulating dopamine and norepinephrine in cerebral cortex to reticular activating system; inhibits the action of monoamine oxidase and causes catecholamines to be released. Peripheral actions include elevation of blood pressure, weak bronchodilation, and respiratory stimulation.

Pharmacodynamics/Kinetics

Onset: 30-60 minutes

Duration: 4-6 hours

Absorption: Well-absorbed

Distribution: V_d: Adults: 3.5-4.6 L/kg; concentrates in breast milk (avoid breast-feeding); distributes into CNS, mean CSF concentrations are 80% of plasma

Half-life elimination:

Children 6-12 years: d-amphetamine: 9 hours; l-amphetamine: 11 hours

Adolescents 13-17 years: d-amphetamine: 11 hours; l-amphetamine: 13-14 hours

Adults: d-amphetamine: 10 hours; l-amphetamine: 13 hours

Metabolism: Hepatic via cytochrome P450 monooxygenase and glucuronidation

Time to peak: T_{max}: Adderall®: 3 hours; Adderall XR®: 7 hours

Excretion: Urine (highly dependent on urinary pH); 70% of a single dose is eliminated within 24 hours; excreted as unchanged amphetamine (30%, may range from ~1% in alkaline urine to ~75% in acidic urine), benzoic acid, hydroxyamphetamine, hippuric acid, norephedrine, and *p*-hydroxynorephedrine

Related Information

- Stimulant Agents Used for ADHD

Pharmacotherapy PearlsTreatment of ADHD may include "drug holidays" or periodic discontinuation of medication in order to assess the patient's requirements, decrease tolerance, and limit suppression of linear growth and weight; the combination of equal parts of *d*, *l*-amphetamine aspartate, *d*, *l*-amphetamine sulfate, dextroamphetamine saccharate and dextroamphetamine sulfate results in a 75:25 ratio of the dextro and levo isomers of amphetamine.

The duration of action of Adderall® is longer than methylphenidate; behavioral effects of a single morning dose of Adderall® may last throughout the school day; a single morning dose of Adderall® has been shown in several studies to be as effective as twice daily dosing of methylphenidate for the treatment of ADHD (see Pelham et al, *Pediatrics*, 1999, 104(6):1300-11; Manos 1999; Pliszka 2000).

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tooth disorder; up to 10% of patients taking dextroamphetamines may present with hypertension. Monitor blood pressure prior to using local anesthetic with vasoconstrictors.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse vasoconstrictor with caution in patients taking dextroamphetamine. Amphetamines enhance the sympathomimetic response of epinephrine and norepinephrine leading to potential hypertension and cardiotoxicity.

Cardiovascular ConsiderationsAmphetamines should be avoided in patients with known or suspected cardiovascular disease. They may precipitate marked increases in blood pressure, tachycardia, and tachyarrhythmias. These drugs are often used recreationally and inappropriately, particularly for appetite suppressant effects. Recreational use of amphetamines should be considered in otherwise healthy patients with new onset hypertension, tachycardia, or tachyarrhythmias.

There have been cases of sudden death, heart-related death, and stroke in children and adults taking regular recommended doses of Adderall® and Adderall XR®. In Canada, sales of Adderall XR® were suspended for about six months, but have now resumed. Education and additional surveillance will be done of all stimulants used to treat attention deficit hyperactivity disorder. According to the FDA, five of the 12 reported cases of sudden death in pediatric patients occurred in children with cardiac risk factors, including undiagnosed cardiac abnormalities. The other seven cases were complicated by other illness, rigorous exercise, or family history of ventricular arrhythmia. In addition, unexplained or unusual drug accumulation (resulting in toxic levels despite usual dosing) has been noted in several cases. The drug should not be used in patients with structural heart disease. Further information is available at the following websites:

http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005_01.html

http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#Adderall

http://www.fda.gov/bbs/topics/news/2005/NEW01156.html

Index Terms Amphetamine and Dextroamphetamine

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English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Dextroamphetamine 5 mg Tablets: Recall Due to Potential for Oversized Tablets - October 2008; Updated November 2008: Dextroamphetamine 10 mg Tablets Recalled

Certain lots of generic dextroamphetamine tablets have been recalled due to possibility of oversized tablets. Oversized tablets may contain up to twice the amount of the active ingredient which may cause serious or life-threatening effects.

For information, please refer to the FDA MedWatch alert:

> http://www.fda.gov/medwatch/safety/2008/safety08.htm#Dextroamphetamine
>
> http://www.fda.gov/medwatch/safety/2008/safety08.htm#Ethex

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) has issued a statement in April 2008 recommending that all children diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the recommendations due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: Methylphenidate, amphetamine, dextroamphetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children’s Healthcare Quality.

For more information, refer to:

http://americanheart.mediaroom.com/index.php?s=43&item=422

http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1

http://americanheart.mediaroom.com/index.php?s=43&item=398

http://www.fda.gov/medwatch/safety/2007/safety07.htm

http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html

Nissen SE, "ADHD Drugs and Cardiovascular Risk," *N Engl J Med*, 2006, 354(14):1445-48.

"Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder," *J Am Acad Child Adolesc Psychiatry*, 2007, 46(7):894-921.

Vetter VL, Elia J, Erickson CH, et al, "Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing," *Circulation*, 2008, 117:2407-23.

Wilens TE, Prince JB, Spencer TJ, et al, "Stimulants and Sudden Death: What is a Physician to do?" *Pediatrics*, 2006, 118(3):1215-19.

Medication Safety Issues

Sound-alike/look-alike issues:

Dexedrine® may be confused with dextran, Excedrin®

Dextroamphetamine may be confused with dexamethasone

Pronunciation(deks troe am FET a meen)
U.S. Brand NamesDexedrine®; DextroStat®; Liquadd™
Canadian Brand NamesDexedrine®
Pharmacologic CategoryStimulant
Use: Labeled IndicationsNarcolepsy; attention-deficit/hyperactivity disorder (ADHD)
Use: Unlabeled/InvestigationalExogenous obesity; depression; abnormal behavioral syndrome in children (minimal brain dysfunction)
Dosing: Adults

Narcolepsy: Oral: Initial: 10 mg/day, may increase at 10 mg increments in weekly intervals until side effects appear; maximum: 60 mg/day

Exogenous obesity (short-term adjunct): Oral: 5-30 mg/day in divided doses of 5-10 mg 30-60 minutes before meals

Dosing: ElderlyRefer to adult dosing; start at lowest dose. Use with caution.
Dosing: Pediatric

Narcolepsy: Oral: Children 6-12 years: Initial: 5 mg/day, may increase at 5 mg increments in weekly intervals until side effects appear; maximum dose: 60 mg/day

Attention-deficit/hyperactivity disorder (ADHD): Oral:

Children 3-5 years: Initial: 2.5 mg/day given every morning; increase by 2.5 mg/day in weekly intervals until optimal response is obtained, usual range: 0.1-0.5 mg/kg/dose every morning with maximum of 40 mg/day

Children ≥6 years: 5 mg once or twice daily; increase in increments of 5 mg/day at weekly intervals until optimal response is reached, usual range: 0.1-0.5 mg/kg/dose every morning (5-20 mg/day) with maximum of 40 mg/day

Administration: OralDo not crush sustained release drug product. Administer as single dose in morning or as divided doses with breakfast and lunch. Should be administered 30 minutes before meals and at least 6 hours before bedtime.
Dietary ConsiderationsShould be taken 30 minutes before meals and at least 6 hours before bedtime.
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light.
RestrictionsC-II

An FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity or idiosyncrasy to dextroamphetamine, other sympathomimetic amines, or any component of the formulation; advanced arteriosclerosis, symptomatic cardiovascular disease, moderate-to-severe hypertension; hyperthyroidism; glaucoma; agitated states; patients with a history of drug abuse; during or within 14 days following MAO inhibitor therapy
Allergy Considerations

- Amphetamine Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Drug abuse: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Cardiovascular events: **[U.S. Boxed Warning]: Use has been associated with serious cardiovascular events including sudden death in patients with pre-existing structural cardiac abnormalities or other serious heart problems (sudden death in children and adolescents; sudden death, stroke and MI in adults).** These products should be avoided in the patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that could increase the risk of sudden death that these conditions alone carry. Patients should be carefully evaluated for cardiac disease prior to initiation of therapy.
- CNS effects: Amphetamines may impair the ability to engage in potentially hazardous activities (driving, operating machinery).
- Visual disturbance: Difficulty in accommodation and blurred vision has been reported with the use of stimulants.

Disease-related concerns:

- Drug abuse: **[U.S. Boxed Warning]: Potential for drug dependency exists; prolonged use may lead to drug dependency.** Use is contraindicated in patients with history of ethanol or drug abuse. Prescriptions should be written for the smallest quantity consistent with good patient care to minimize possibility of overdose.
- Hypertension: Use with caution in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases in blood pressure or heart rate. Use is contraindicated in patients with moderate to severe hypertension.
- Psychiatric disorders: Use with caution in patients with pre-existing psychosis or bipolar disorder (may induce mixed/manic episode). May exacerbate symptoms of behavior and thought disorder in psychotic patients; new onset psychosis or mania may occur with stimulant use; observe for symptoms of aggression and/or hostility.
- Seizure disorder: Use with caution in patients with a history of seizure disorder; may lower seizure threshold leading to new onset or breakthrough seizure activity.
- Tourette's syndrome: Use with caution in patients with Tourette's syndrome; stimulants may unmask tics.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <3 years of age; Dexedrine® is not recommended for use in children <6 years of age. Appetite suppression may occur; monitor weight during therapy, particularly in children. Use of stimulants has been associated with suppression of growth; monitor growth rate during treatment.

Dosage form specific issues:

- Tartrazine: Products may contain tartrazine; use with caution in potentially sensitive individuals.

Other warnings/precautions:

- Discontinuation of therapy: Abrupt discontinuation following high doses or for prolonged periods may result in symptoms for withdrawal.

Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic and embryocidal effects have been observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use only if potential benefit justifies the potential risk to the fetus.
LactationEnters breast milk/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiomyopathy, hypertension, palpitation, tachycardia

Central nervous system: Aggression, dizziness, dyskinesia, dysphoria, euphoria, exacerbation of motor and phonic tics, headache, insomnia, mania, overstimulation, psychosis, restlessness, Tourette's syndrome

Dermatologic: Rash, urticaria

Endocrine & metabolic: Libido changes

Gastrointestinal: Anorexia, constipation, diarrhea, unpleasant taste, weight loss, xerostomia

Genitourinary: Impotence

Neuromuscular & skeletal: Tremor

Ocular: Accommodation abnormalities, blurred vision

Drug Interactions

Alkalinizing Agents: May decrease the excretion of Amphetamines. *Risk D: Consider therapy modification*

Ammonium Chloride: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

Analgesics (Opioid): Amphetamines may enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Antihistamines: Amphetamines may diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antipsychotics: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Amphetamines. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Ethosuximide: Amphetamines may diminish the therapeutic effect of Ethosuximide. Amphetamines may decrease the serum concentration of Ethosuximide. *Risk C: Monitor therapy*

Gastrointestinal Acidifying Agents: May decrease the serum concentration of Amphetamines. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Methenamine: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

PHENobarbital: Amphetamines may decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Phenytoin: Amphetamines may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Dextroamphetamine serum levels may be altered if taken with acidic food, juices, or vitamin C.

Herb/Nutraceutical: Avoid ephedra (may cause hypertension or arrhythmias).

Test InteractionsAmphetamines may elevate plasma corticosteroid levels; may interfere with urinary steroid determinations.

Monitoring ParametersCardiac evaluation should be completed on any patient who develops chest pain, unexplained syncope, and any symptom of cardiac disease during treatment with stimulants; growth in children and CNS activity in all

When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure, and consider obtaining ECG prior to initiation (Vetter, 2008).

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess for history of psychopathology, homicidal or suicidal tendencies, or addiction; long-term use can result in dependence, abuse, or tolerance. Perform careful cardiovascular assessment prior to initiating therapy. Periodically evaluate the need for continued use. Monitor therapeutic effectiveness, vital signs, and adverse reactions at start of therapy, when changing dosage, and at regular intervals during therapy. Monitor serum glucose closely in patients with diabetes (amphetamines may alter antidiabetic requirements). Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, possible side effects, and symptoms to report.

Patient EducationTake exactly as directed; do not increase dose or frequency without consulting prescriber. Drug may cause physical and/or psychological dependence. Take early in day to avoid sleep disturbance, 30 minutes before meals. Avoid alcohol, caffeine, or OTC medications that act as stimulants. You may experience restlessness, false sense of euphoria, or impaired judgment (use caution when driving or engaging in tasks requiring alertness until response to drug is known); dry mouth (frequent mouth care, sucking lozenges, or chewing gum may help); nausea or vomiting (small frequent meals, frequent mouth care may help); constipation (increased exercise, fluids, fruit, or fiber may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or altered libido (reversible). Patients with diabetes need to monitor serum glucose closely (may alter antidiabetic medication requirements). Report chest pain, palpitations, or irregular heartbeat; extreme fatigue or depression; CNS changes (aggressiveness, restlessness, euphoria, sleep disturbances); severe unremitting abdominal distress or cramping; blackened stool; changes in sexual activity; or blurred vision. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release, as sulfate: 5 mg, 10 mg, 15 mg

Capsule, sustained release, as sulfate:

Dexedrine® Spansule®: 5 mg, 10 mg, 15 mg

Tablet, as sulfate: 5 mg, 10 mg

DextroStat®: 5 mg, 10 mg [contains tartrazine]

Solution, oral, as sulfate:

Liquadd™: 5 mg/5 mL (480 mL) [contains benzoic acid; bubblegum flavor]

Generic AvailableYes: Excludes oral suspension

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Dexedrine)

10 mg (20): $53.50

15 mg (20): $50.66

Capsule, 24-hour (Dextroamphetamine Sulfate CR)

10 mg (20): $39.99

15 mg (20): $49.99

Tablets (Dextroamphetamine Sulfate)

5 mg (20): $11.99

10 mg (20): $14.99

Tablets (DextroStat)

10 mg (20): $17.99

Mechanism of Action

Amphetamines are noncatecholamine, sympathomimetic amines. Blocks reuptake of dopamine and norepinephrine from the synapse, thus increases the amount of circulating dopamine and norepinephrine in cerebral cortex to reticular activating system; inhibits the action of monoamine oxidase and causes catecholamines to be released. Peripheral actions include elevated blood pressure, weak bronchodilator, and respiratory stimulant action.

Pharmacodynamics/Kinetics

Onset of action: 1-1.5 hours

Distribution: V_d: Adults: 3.5-4.6 L/kg; distributes into CNS; mean CSF concentrations are 80% of plasma; enters breast milk

Metabolism: Hepatic via CYP monooxygenase and glucuronidation

Half-life elimination: Adults: 10-13 hours

Time to peak, serum: T_{max}: Immediate release: ~3 hours; sustained release: ~8 hours

Excretion: Urine (as unchanged drug and inactive metabolites)

Related Information

- Stimulant Agents Used for ADHD

Dental Health: Effects on Dental Treatment

Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Up to 10% of patients taking dextroamphetamines may present with hypertension. Monitor blood pressure prior to using local anesthetic with vasoconstrictors.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions

Use vasoconstrictor with caution in patients taking dextroamphetamine. Amphetamines enhance the sympathomimetic response of epinephrine and norepinephrine leading to potential hypertension and cardiotoxicity.

Cardiovascular Considerations

Amphetamines should be avoided in patients with known or suspected cardiovascular disease. They may precipitate marked increases in blood pressure, tachycardia, and tachyarrhythmias. These drugs are often used recreationally and inappropriately, particularly for appetite suppressant effects. Recreational use of amphetamines should be considered in otherwise healthy patients with new onset hypertension, tachycardia, or tachyarrhythmias.

Index Terms

Dextroamphetamine Sulfate

References

Grinstead GF, “Ranitidine and High Concentrations of Phenylpropanolamine Cross React in the EMIT Monoclonal Amphetamine/Methamphetamine Assay,” *Clin Chem*, 1989, 35(9):1998-9.

Mattson RH and Calverley JR, “Dextroamphetamine-Sulfate-Induced Dyskinesias,” *JAMA*, 1968, 204(5):400-2. [PubMed 5694457]

Richards CF, Clark RF, Holbrook T, et al, “The Effect of Cocaine and Amphetamines on Vital Signs in Trauma Patients,” *J Emerg Med*, 1995, 13(1):59-63. [PubMed 7782627]

Segar DL, “Substances of Abuse: Topics,” *Emerg Med*, 1985, 7:18-30.

Vetter VL, Elia J, Erickson CH, et al, “Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing,” *Circulation*, 2008, 117:2407-23.[PubMed 18427125]

Warden C and Winger J, “Choreoathetoid Reaction Associated With a Methylphenidate Ingestion in a Toddler,” *Clin Toxicol*, 1995, 33(5):522.

International Brand Names

Dexamphetamine (AU); Dexamphetamini Sulfas (CH); Dexedrine (GB, NO)

Dextromethorphan, Chlorpheniramine, Phenylephrine, and Guaifenesin

Lexi-Drugs Online

English

English

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(deks troe meth OR fan, klor fen IR a meen, fen il EF rin, & gwye FEN e sin)

U.S. Brand NamesChlordex GP; Donatussin; Quartuss™

Pharmacologic CategoryAlpha/Beta Agonist; Antitussive; Expectorant; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of dry, nonproductive cough and upper respiratory symptoms associated with infections such as the common cold, bronchitis, or sinusitis

Dosing: AdultsCough, cold symptoms (Donatussin): Oral: 10 mL every 6 hours as needed (maximum: 40 mL/24 hours)

Dosing: Elderly

Refer to adult dosing.

Dosing: PediatricCough, cold symptoms (Donatussin): Oral:

Children 2-6 years: 2.5 mL every 6 hours as needed (maximum: 10 mL/24 hours)

Children 6-12 years: 5 mL every 6 hours as needed (maximum: 20 mL/24 hours)

Children ≥12 years: Refer to adult dosing.

Administration: OralAdminister with water.
Dietary ConsiderationsTake with food, water or milk to decrease stomach upset.
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).
ContraindicationsHypersensitivity to dextromethorphan, chlorpheniramine, phenylephrine, guaifenesin, sympathomimetic amines, or any component of the formulation; hypertension; hyperthyroidism, prostatic hyperplasia; use with or within 14 days of discontinuing MAO inhibitor
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; contraindicated in patients with hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus.

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.

- Peripheral vascular disease: Use with caution in patients with peripheral vascular disease.

- Respiratory disease: Use with caution in patients with asthma or other chronic respiratory disorders.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Antihistamines may cause excitation in young children. Safety and efficacy have not been established in children <2 years of age.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. See individual agents.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsPhenylephrine is excreted in breast milk. See individual agents.
Adverse ReactionsSee individual agents.
Metabolism/Transport Effects

Chlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)

Dextromethorphan: **Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Test InteractionsGuaifenesin: Possible color interference with determination of 5-HIAA and VMA; discontinue for 48 hours prior to test
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Syrup:

Chlordex GP®: Dextromethorphan hydrobromide 7.5 mg, chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 10 mg, and guaifenesin 100 mg per 5 mL (480 mL) [grape flavor]

Donatussin: Dextromethorphan hydrobromide 15 mg, chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 10 mg, and guaifenesin 100 mg per 5 mL (480 mL) [alcohol free; contains propylene glycol; cherry flavor]

Quartuss™: Dextromethorphan hydrobromide 15 mg, chlorpheniramine maleate 2 mg, phenylephrine hydrochloride 10 mg, and guaifenesin 100 mg per 5 mL (480 mL) [alcohol free, sugar free; contains sodium benzoate, propylene glycol; cherry flavor]

Generic AvailableYes
Mechanism of ActionSee individual agents.
Pharmacodynamics/KineticsSee individual agents.
Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, insomnia, irritability, or nervousness
Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors or within 14 days of MAO inhibitor
Index TermsChlorpheniramine, Dextromethorphan, Phenylephrine, and Guaifenesin; Guaifenesin, Chlorpheniramine, Phenylephrine, and Dextromethorphan; Phenylephrine Hydrochloride, Chlorpheniramine maleate, Dextromethorphan Hydrobromide, and Guaifenesin

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Dextromethorphan and Chlorpheniramine

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- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(deks troe meth OR fan & klor fen IR a meen)

U.S. Brand NamesCoricidin® HBP Cough & Cold [OTC]; Dimetapp® Children’s Long Acting Cough Plus Cold [OTC]; Robitussin® Children’s Cough & Cold Long-Acting [OTC]; Robitussin® Cough & Cold Long-Acting [OTC]; Scot-Tussin® DM Maximum Strength [OTC]

Pharmacologic CategoryAntitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of runny nose, sneezing, itchy/watery eyes, cough, and other upper respiratory symptoms associated with hay fever, common cold, or upper respiratory allergies

Dosing: AdultsGeneral dosing guidelines; consult specific product labeling.

Cough, cold symptoms: Oral: Dextromethorphan 30 mg and chlorpheniramine 4 mg every 6 hours as needed (maximum: 120 mg dextromethorphan and 16 mg chlorpheniramine/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricGeneral dosing guidelines; consult specific product labeling.

Cough, cold symptoms: Oral:

Children 6-11 years: Dextromethorphan 15 mg and chlorpheniramine 2 mg every 6 hours as needed (maximum: 60 mg dextromethorphan and 8 mg chlorpheniramine/24 hours)

Children ≥12 years: Refer to adult dosing.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsUse with or within 14 days of discontinuing MAO inhibitor

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Pediatrics: Antihistamines may cause excitation in young children. Do not exceed pediatric dosing recommendations. If no recommendations exist on OTC labeling for patient's age, the product should **not** be administered without the guidance of a physician. Not for OTC use in children <6 years of age.

Other warnings/precautions:

- Self-medication (OTC use): Patients with glaucoma or prostatic hyperplasia should consult healthcare provider prior to use. Patients with chronic cough (associated with COPD or smoking) and/or productive cough (eg, copious amounts of phlegm) should be evaluated by a healthcare provider prior to use. Ask healthcare provider prior to using with sedatives. If cough does not improve, is accompanied by rash, fever, or headache, or persists >7 days during use, discontinue use and consult a physician. Do not exceed recommended dose.

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. See individual agents.

Adverse ReactionsSee individual agents.

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Syrup:

Dimetapp® Children’s Long Acting Cough Plus Cold: Dextromethorphan hydrobromide 7.5 mg and chlorpheniramine maleate 1 mg per 5 mL (118 mL) [alcohol free, sugar free; contains sodium benzoate, propylene glycol; grape flavor]

Robitussin® Children’s Cough and Cold Long-Acting: Dextromethorphan hydrobromide 15 mg and chlorpheniramine maleate 2 mg per 5 mL (118 mL) [alcohol free, sugar free; contains sodium benzoate, propylene glycol, fruit punch flavor]

Robitussin® Cough and Cold Long-Acting: Dextromethorphan hydrobromide 7.5 mg and chlorpheniramine maleate 1 mg per 5 mL (118 mL) [alcohol free, sugar free; contains sodium benzoate, propylene glycol]

Scot-Tussin® DM Maximum Strength: Dextromethorphan hydrobromide 15 mg and chlorpheniramine maleate 2 mg per 5 mL (118 mL) [alcohol free, sugar free, cherry-strawberry flavor]

Tablet:

Coricidin® HBP Cough and Cold: Dextromethorphan hydrobromide 30 mg and chlorpheniramine maleate 4 mg

Generic AvailableNo

Mechanism of Action

Chlorpheniramine maleate: Antihistamine with H_1-receptor activity

Dextromethorphan: A non-narcotic antitussive, increases cough threshold by its activity on the medulla oblongata

Pharmacodynamics/KineticsSee individual agents.

Mental Health: Effects on Mental StatusMay cause sedation, dizziness, excitability, nervousness

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment. May cause sedation; concurrent use with psychotropics may produce additive effects. Combined use with serotoninergic agents may cause serotonin syndrome. The anticholinergic effects of chlorpheniramine may decrease the effects of acetylcholinesterase inhibitors. However, when combined with psychotropic agents, anticholinergic effects may be additive. Nefazodone may potentiate the effects of chlorpheniramine.

Index TermsChlorpheniramine and Dextromethorphan; Chlorpheniramine Maleate and Dextromethorphan Hydrobromide; Dextromethorphan Hydrobromide and Chlorpheniramine Maleate

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Dextromethorphan

Lexi-Drugs Online

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

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- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

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For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Benylin® may be confused with Benadryl®, Ventolin®

Delsym® may be confused with Delfen®, Desyrel®

Pronunciation(deks troe meth OR fan)

U.S. Brand NamesBabee® Cof Syrup [OTC]; Creo-Terpin® [OTC]; Creomulsion® Cough [OTC]; Creomulsion® for Children [OTC]; Delsym® [OTC]; ElixSure® Cough [OTC]; Hold® DM [OTC]; PediaCare® Infants' Long-Acting Cough [OTC] [DSC]; Robitussin® CoughGels™ [OTC]; Robitussin® Maximum Strength Cough [OTC]; Robitussin® Pediatric Cough [OTC]; Scot-Tussin DM® Cough Chasers [OTC] [DSC]; Silphen DM® [OTC]; Triaminic® Thin Strips™ Long Acting Cough [OTC]; Vicks® 44® Cough Relief [OTC]

Pharmacologic CategoryAntitussive

Use: Labeled IndicationsSymptomatic relief of coughs caused by minor viral upper respiratory tract infections or inhaled irritants; most effective for a chronic nonproductive cough

Use: Unlabeled/Investigational*N*-methyl-D-aspartate (NMDA) antagonist in cerebral injury

Dosing: AdultsCough suppressant: Oral: 10-20 mg every 4 hours or 30 mg every 6-8 hours; extended release: 60 mg twice daily; maximum: 120 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricCough suppressant: Oral:

<2 years: Use only as directed by a physician

2-6 years (syrup): Oral: 2.5-7.5 mg every 4-8 hours; extended release is 15 mg twice daily (maximum: 30 mg/24 hours)

6-12 years: 5-10 mg every 4 hours or 15 mg every 6-8 hours; extended release is 30 mg twice daily (maximum: 60 mg/24 hours)

Children >12 years: Refer to adult dosing.

Dietary Considerations

Delsym® contains sodium 6 mg/5 mL.

Vicks® 44® Cough Relief contains sodium 10 mg/5 mL.

ContraindicationsHypersensitivity to dextromethorphan or any component of the formulation; do not use with or within 2 weeks of an MAO inhibitor

Warnings/Precautions

Special populations:

- Debilitated patients: Use with caution in patients who are sedated, debilitated or confined to a supine position.
- Pediatrics: Use with caution in atopic children. Not for OTC use in children <2 years of age.

Dosage form specific issues:

- Coconut: Some products may contain coconut oil.
- Tartrazine: Some products may contain tartrazine.

Other warnings/precautions:

- Self-medication (OTC use): When used for self medication (OTC) notify healthcare provider if symptoms do not improve within 7 days, or are accompanied by fever, rash or persistent headache. Do not use for persistent or chronic cough (as with smoking, asthma, chronic bronchitis, emphysema) or if cough is accompanied b excessive phlegm unless directed to do so by healthcare provider.

Pregnancy Risk FactorC

Adverse Reactions<1%: Drowsiness, dizziness, coma, respiratory depression, nausea, GI upset, constipation, abdominal discomfort

Metabolism/Transport Effects**Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Gelcap, as hydrobromide:

Robitussin® CoughGels™: 15 mg [contains coconut oil]

Liquid, as hydrobromide:

Creo-Terpin®: 10 mg/15 mL (120 mL) [contains alcohol 25% and tartrazine]

Vicks® 44® Cough Relief: 10 mg/5 mL (120 mL) [contains alcohol, sodium 10 mg/5 mL, sodium benzoate]

Liquid, oral, as hydrobromide [drops]:

PediaCare® Infants' Long-Acting Cough: 7.5 mg/0.8 mL (15 mL) [alcohol free, dye free; contains sodium benzoate; grape flavor] [DSC]

Lozenge, as hydrobromide:

Hold® DM: 5 mg (10s) [cherry or original flavor]

Scot-Tussin DM® Cough Chasers: 5 mg (20s) [DSC]

Strips, oral, as hydrobromide:

Triaminic® Thin Strips™ Long Acting Cough: 7.5 mg [equivalent to dextromethorphan 5 mg; cherry flavor]

Suspension, extended release:

Delsym®: Dextromethorphan polistirex [equivalent to dextromethorphan hydrobromide 30 mg/5 mL] (78 mL, 148 mL) [contains sodium 6 mg/5 mL; orange flavor]

Syrup, as hydrobromide:

Babee® Cof Syrup: 7.5 mg/5 mL (120 mL) [alcohol free, dye free; cherry flavor]

Creomulsion® Cough: 20 mg/15 mL (120 mL) [alcohol free; contains sodium benzoate]

Creomulsion® for Children: 5 mg/5 mL (120 mL) [alcohol free; contains sodium benzoate; cherry flavor]

ElixSure® Cough: 7.5 mg/5 mL (120 mL) [cherry bubble gum flavor]

Robitussin® Maximum Strength Cough: 15 mg/5 mL (120 mL, 240 mL) [contains alcohol, sodium benzoate]

Robitussin® Pediatric Cough: 7.5 mg/5 mL (120 mL) [alcohol free; contains sodium benzoate; fruit punch flavor]

Silphen DM®: 10 mg/5 mL (120 mL) [strawberry flavor]

Generic AvailableYes: Excludes strip, liquid freezer pop

Mechanism of ActionChemical relative of morphine lacking narcotic properties except in overdose; controls cough by depressing the medullary cough center

Pharmacodynamics/Kinetics

Onset of action: Antitussive: 15-30 minutes

Duration: ≤6 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or depression

Mental Health: Effects on Psychiatric TreatmentUse with MAO inhibitors may cause hypertensive crisis; avoid combination

International Brand NamesAcodin (PL); Akindex (BE, FR, LU, PL, PT); Argotussin (PL); Aricodil (IT); Arpha (DE); Astho-Med Husten (CH); Athos (MX); Atuxane (FR); Bechilar (IT); Benylin (NL, ZA); Benylin Antitusivo (ES); Bexin (CH); Bronchenolo Tosse (IT); Bronchosedal (BE, LU); Bronchydex (FR); Brudex (MX); Calmasan (CH); Calmerphan (CH); Calmerphan-L (CH); Calmesin-Mepha (CH); Canfodian (IT); Capsyl (BE, LU); Cinfatos (ES); Codotussyl toux seche (FR); Dampo Bij Droge Hoest (NL); Darolan Hoestprikkeldempend (NL); Daromefan (NL); Delsym (IE); Destrometorfano Bromidrato (IT); Dexatussin (PL); Dexir (BE, FR); Dexofan (DK); Dextphan (JP); Dextrogel Oral (CH); Dextromephar (BE); Dextrometorfano Fabra (AR); Dextrotos (AR); Emedrin N (CH); Fluprim (IT); Formitrol (IT); Formulatus (ES); Humex (BE, ES); Hustenstiller-ratiopharm (DE); Hustep (JP); Kibon S (JP); Lagun (FI); Methorcon (JP); Metorfan (IT); NeoTussan (DE, LU); Nodex (FR); Notuxal (BE); Nucosef (AU); Pectofree (BE); Pulmofor (CH); Rami Dextromethorfan Hoestdrank (NL); Resilar (FI); Rhinathiol (FR, LU); Rivodex (CH); Rivolyn (CH); Robitussin (AU, ES, IE, PL); Romilar (AR, BE, ES, LU, MX); Sanabronchiol (IT); Sebrane (FR); Siepex (ES); Sisaal (JP); Soludril Toux seches (LU); Strepsils (AU); Tesafilm (MX); Tip (ES); Tosfriol (ES); Tosion retard (NL); Tossoral (IT); Touxium Antitussivum (BE, LU); Trimpus (JP); Tusitinas (ES); Tusorama (DE, ES); Tuss Hustenstiller (DE); Tussal Antitussicom (PL); Tussidex (PL); Tussidril (ES); Tussidrill (PL); Tussinol (AU); Tussipect (BE, LU); Tussycalm (IT); Tuxium (FR); Valatux (IT); Valdatos (ES); Vicks (CH, FR); Vicks Hustensirup mit Dextromethorphan (CH); Vicks sirop contre la toux, avec dextromethorphane (CH); Vicks Tosse Pastiglie (IT); Vicks Tosse Sedativo (IT); Vicks Vaposiroop (NL); Vicks Vaposyrup (BE); Wick Formel 44 Husten-Pastillen S (AT, DE); Wick Formel 44 Hustenstiller (AT, DE); Wick Formula 44 Plus S (PL)

Dextrose

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Glutose™ may be confused with Glutofac®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (hypertonic solutions ≥20%) among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(DEKS trose)

U.S. Brand NamesB-D™ Glucose [OTC]; Dex4® Glucose [OTC]; Enfamil® Glucose; Glutol™ [OTC]; Glutose™ [OTC]; Insta-Glucose® [OTC]; Similac® Glucose

Pharmacologic CategoryHyperglycemic Agent; Intravenous Nutritional Therapy

Use: Labeled Indications

Oral: Treatment of hypoglycemia

5% and 10% solutions: Peripheral infusion to provide calories and fluid replacement

25% (hypertonic) solution: Treatment of acute symptomatic episodes of hypoglycemia in infants and children to restore depressed blood glucose levels; adjunctive treatment of hyperkalemia when combined with insulin

50% (hypertonic) solution: Treatment of insulin-induced hypoglycemia (hyperinsulinemia or insulin shock) and adjunctive treatment of hyperkalemia in adolescents and adults

≥10% solutions: Infusion after admixture with amino acids for nutritional support

Dosing: Adults

Treatment of hypoglycemia: Doses may be repeated in severe cases

Oral: 10-20 g as single dose; repeat in 10 minutes if necessary

I.V.: 10-25 g (40-100 mL of 25% solution or 20-50 mL of 50% solution)

Treatment of hyperkalemia: I.V. (in combination with insulin): 25-50 g dextrose (250-500 mL $D_{10}W$) combined with 10 units regular insulin administered over 30-60 minutes; repeat as needed or as an alternative 25 g dextrose (50 mL $D_{50}W$) combined with 5-10 units regular insulin infused over 5 minutes; repeat as needed

Note: More rapid infusions (<30 minutes) may be associated with hyperglycemia and hyperosmolality and will exacerbate hyperkalemia; avoid use in patients who are already hyperglycemic

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Treatment of hypoglycemia: Doses may be repeated in severe cases

Oral: Children >2 years: Refer to adult dosing.

I.V.:

Infants ≤6 months: 0.25-0.5 g/kg/dose (1-2 mL/kg/dose of 25% solution); maximum: 25 g/dose

Infants >6 months and Children: 0.5-1g/kg/dose (2-4 mL/kg/dose of 25% solution); maximum: 25 g/dose

Adolescents: Refer to adult dosing.

Treatment of hyperkalemia: I.V. (in combination with insulin):

Infants and Children: 0.5-1 g/kg (using 25% or 50% solution) combined with regular insulin 1 unit for every 4-5 g dextrose given; infuse over 2 hours (infusions as short as 30 minutes have been recommended); repeat as needed

Adolescents: Refer to adult dosing.

Administration: I.V.Not for SubQ or I.M. administration; dilute concentrated dextrose solutions for peripheral venous administration to a maximum concentration of 12.5%; in emergency situations, 25% dextrose has been used peripherally; for direct I.V. infusion, infuse at a maximum rate of 200 mg/kg over 1 minute; continuous infusion rates very with tolerance and range from 4.5-15 mg/kg/minute; hyperinsulinemic neonates may require up to 15-25 mg/kg/minute infusion rates

Administration: OralMust be swallowed to be absorbed (see Warnings)
StorageStable at room temperature. Protect from freezing and extreme heat. Store oral dextrose in airtight containers.
ContraindicationsHypersensitivity to corn or corn products; diabetic coma with hyperglycemia; hypertonic solutions in patients with intracranial or intraspinal hemorrhage; patients with delirium tremens and dehydration; patients with anuria, hepatic coma, or glucose-galactose malabsorption syndrome
Allergy Considerations

- Dextrose Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hyperglycemia: An unexpected rise in blood glucose level in an otherwise stable patient may be an early symptom of infection. Rapid administration of hypertonic solutions may produce significant hyperglycemia, glycosuria, and shifts in electrolytes; this may result in dehydration, hyperosmolar syndrome, coma, and death especially in patients with chronic uremia or carbohydrate intolerance.

- Hypokalemia: Administration of potassium free I.V. dextrose solutions may result in significant hypokalemia, particularly if highly concentrated dextrose solutions are used; monitor closely and/or add potassium to dextrose solutions for patients with adequate renal function.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; hyperglycemia and glycosuria may be functions of the rate of administration of dextrose; to minimize these effects, reduce the rate of infusion; addition of insulin may be necessary.

Special populations:

- Very low birth weight infants: Excessive or rapid dextrose administration in very low birth weight infants has been associated with increased serum osmolality and possible intracerebral hemorrhage.

Dosage form specific issues:

- Aluminium: Parenteral dextrose solutions contain aluminum which may accumulate to toxic levels with prolonged administration particularly in patients with impaired renal function. Patients with impaired renal function including premature neonates who receive aluminum at >4-5 mcg/kg/day accumulate aluminum at levels associated with CNS and bone toxicity.

- Oral forms: Do not use oral forms in unconscious patients.

Other warnings/precautions:

- Abrupt withdrawal: Rebound hypoglycemia may be associated with abrupt withdrawal.

- Administration: Hypertonic solutions (>10%) may cause thrombosis if infused via peripheral veins; administer hypertonic solutions via a central venous catheter.

Pregnancy Risk FactorC/A (oral)
Adverse ReactionsFrequency not defined. **Note:** Most adverse effects are associated with excessive dosage or rate of infusion.

Cardiovascular: Venous thrombosis, phlebitis, hypovolemia, hypervolemia, dehydration, edema

Central nervous system: Fever, mental confusion, unconsciousness, hyperosmolar syndrome

Endocrine & metabolic: Hyperglycemia, hypokalemia, acidosis, hypophosphatemia, hypomagnesemia

Genitourinary: Polyuria, glycosuria, ketonuria

Gastrointestinal: Polydipsia, nausea, diarrhea (oral)

Local: Pain, vein irritation, tissue necrosis

Respiratory: Tachypnea, pulmonary edema

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersBlood and urine sugar, serum electrolytes, I & O, caloric intake
Reference RangeNormal blood sugar:

Children 0-2 years: 60-105 mg/dL

Children >2 years and Adults: 70-110 mg/dL

Monitoring: Lab TestsBlood and urine sugar, serum electrolytes
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel, oral:

Glutose™: 40% (37.5 g) [provides dextrose 15 g/tube; lemon flavor]; (112.5 g) [provides dextrose 45 g/tube; lemon flavor]

Insta-Glucose®: 40% (30 g) [provides dextrose 12 g and additional carbohydrates 12 g/tube; cherry flavor]

Infusion:

Generics:

- 2.5% (1000 mL)
- 5% (25 mL, 50 mL, 100 mL, 150 mL, 250 mL, 500 mL, 1000 mL)
- 10% (250 mL, 500 mL, 1000 mL)
- 20% (500 mL, 1000 mL)
- 30% (500 mL, 1000 mL)
- 40% (500 mL, 1000 mL)
- 50% (500 mL, 1000 mL, 2000 mL)
- 60% (500 mL, 1000 mL)
- 70% (500 mL, 1000 mL, 2000 mL)

Injection, solution: 10% (3 mL, 5 mL); 25% (10 mL); 50% (50 mL)

Solution, oral:

Enfamil® Glucose: 5% (89 mL) [provides dextrose 4 g/bottle]; 10% (89 mL) [provides dextrose 9 g/bottle]

Glutol™: 55% (180 mL) [dextrose 100 g/180 mL]

Similac® Glucose: 5% (60 mL, 120 mL); 10% (60 mL, 120 mL)

Tablet, chewable:

B-D™ Glucose: 5 g (6s) [orange flavor]

Dex4® Glucose: 4 g (10s, 50s) [grape, raspberry, orange, and watermelon flavor]

Generic AvailableYes

Mechanism of ActionDextrose, a monosaccharide, is a source of calories and fluid for patients unable to obtain an adequate oral intake; may decrease body protein and nitrogen losses; promotes glycogen deposition in the liver. When used in the treatment of hyperkalemia (combined with insulin), dextrose stimulates the uptake of potassium by cells, especially in muscle tissue, lowering serum potassium.

Pharmacodynamics/Kinetics

Onset of action: Treatment of hypoglycemia: Oral: 10 minutes

Maximum effect: Treatment of hyperkalemia: I.V.: 30 minutes

Absorption: Oral: Rapidly from the small intestine by an active mechanism

Metabolism: Metabolized to carbon dioxide and water

Time to peak, serum: Oral: 40 minutes

Pharmacotherapy PearlsEach g of I.V. dextrose contains 3.4 kcal; glucose monohydrate 1 g is equal to 1 g anhydrous dextrose; osmolarity of 10% dextrose is 505 mOsm/L and 25% dextrose is 1330 mOsm/L. Normal body fluid osmolarity is 310 mOsm/L.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAnhydrous Glucose; $D_{10}W$; $D_{25}W$; $D_{30}W$; $D_{40}W$; $D_{50}W$; $D_{5}W$; $D_{60}W$; $D_{70}W$; Dextrose Monohydrate; Glucose; Glucose Monohydrate; Glycosum

References

AACE Diabetes Mellitus Clinical Practice Guidelines Task Force, "American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus," *Endocr Pract*, 2007, 13(Suppl 1):1-68.[PubMed 17613449]

American Diabetes Association, "Standards of Medical Care in Diabetes Mellitus - 2008," *Diabetes Care*, 2008, 30(Suppl 1):12-54.[PubMed 18165335]

International Brand NamesDextrevit (MX); Glucose Braun (PL); Glucosum (PL); Glukoza (PL); Glukoza Braun (PL); Injectio Glucosi (PL)

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen Use Lymphoma, non-Hodgkin's

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Dexamethasone: I.V. or Oral: 40 mg/day days 1 to 4

[total dose/cycle = 160 mg]

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Cytarabine: I.V.: 2000 mg/m^2 every 12 hours for 2 doses day 2 (begins at the end of the cisplatin infusion)

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 3-4 weeks for 6-10 cycles (salvage therapy) or 1-2 cycles (mobilization prior to high-dose therapy with peripheral hematopoietic progenitor cell support)

Variation 2:

Dexamethasone: I.V. or Oral: 40 mg/day days 1 to 4

[total dose/cycle = 160 mg]

Oxaliplatin: I.V.: 130 mg/m^2 day 1

[total dose/cycle = 130 mg/m^2]

Cytarabine: I.V.: 2000 mg/m^2 every 12 hours for 2 doses day 2

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 3 weeks

References

Variation 1:

Velasquez WS, Cabanillas F, Salvador P, et al, “Effective Salvage Therapy for Lymphoma With Cisplatin in Combination With High-Dose Ara-C and Dexamethasone (DHAP),” *Blood*, 1988, 71(1):117-22. [PubMed 3334893]

Variation 2:

Chau I, Webb A, Cunningham D, et al, “An Oxaliplatin-Based Chemotherapy in Patients With Relapsed or Refractory Intermediate and High-Grade Non-Hodgkin's Lymphoma,” *Br J Haematol*, 2001, 115(4):786-92.[PubMed 11843810]

English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(dye a tri ZOE ate MEG loo meen & dye a tri ZOE ate SOW dee um)

U.S. Brand NamesGastrografin®; MD-76®R; MD-Gastroview®; RenoCal-76® [DSC]; Renografin®-60

Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Ionic, High Osmolality)

Use: Labeled Indications

Oral/rectal: Examination of GI tract; adjunct to contrast enhancement in computed tomography of the torso

Injection: Angiocardiography, aortography, central venography, cerebral angiography, cholangiography, digital arteriography, excretory urography, nephrotomography, peripheral angiography, peripheral arteriography, renal arteriography, renal venography, splenoportography, visceral arteriography; contrast enhancement of computed tomographic imaging

Dosing: Adults

Radiographic exam of GI tract segments:

Oral: 30-90 mL

Rectal enema: Dilute 240 mL in 1000 mL tap water

Tomography: Oral: 25-77 mL in 1000 mL tap water 15-30 minutes prior to imaging

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Radiographic exam of GI tract segments:**

Oral:

Children <5 years: 30 mL , dilute 1:1 (if <10 kg or debilitated, dilute 1:3)

Children 5-10 years: 60 mL , dilute 1:1 (if <10 kg or debilitated, dilute 1:3)

Rectal enema:

Children <5 years: Dilute 1:5 in tap water

Children >5 years: Dilute 90 mL in 500 mL tap water

Administration: OralMay be diluted 1:1 with water, carbonated beverage, milk, or mineral oil for children and cachectic elderly; for very young (<10kg) and debilitated children, dilute 1:3 in water.

StorageStore at 20°C to 25°C (68°F to 77°F). Protect from light.

ContraindicationsHypersensitivity to diatrizoate or any component of the formulation; injection is not intended for intrathecal use

Refer to product labeling for procedure-specific contraindications.

Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Contrast dye/iodine hypersensitivity: Use with caution in patients with history of previous reaction to contrast dye or iodine.
- Laxative effect: Solutions may be hypertonic and may cause mucosal irritation and intraluminal water movement resulting in laxative effect.

Disease-related concerns:

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction; hyperthyroidism has been reported.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.

- Pediatrics: Use with caution in children.

Other warnings/precautions:

- Monitoring: Monitor hydration and electrolyte status.

Pregnancy Risk FactorB/C (manufacturer dependent)

Pregnancy ConsiderationsDiatrizoate salts cross the placenta and may enter fetal circulation. Abnormal neonatal opacification of the small intestine and colon have been reported in the newborn 4-6 days after delivery. In general, iodinated contrast media agents are avoided during pregnancy unless essential for diagnosis.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsDiatrizoate salts are reported to be excreted in human milk. One manufacturer recommends bottle feedings for 24 hours following administration.

Adverse ReactionsFrequency not defined.

Cardiovascular: Tachyarrhythmia

Dermatologic: Urticaria

Gastrointestinal: Diarrhea, nausea, vomiting

Respiratory: Dyspnea, hypoxia

Miscellaneous: Anaphylaxis

Drug Interactions

MetFORMIN: Iodinated Contrast Agents may enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Test InteractionsThyroid function tests (protein bound iodine uptake studies) may be inaccurate for up to 1 year after administration; may cause false low trypsin values (determined spectrophotometrically).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, injection:

MD-76®R: Diatrizoate meglumine 660 mg and diatrizoate sodium 100 mg per 1 mL (50 mL, 100 mL, 200 mL) [provides organically-bound iodine 370 mg/mL; contains edetate calcium disodium, sodium 3.65 mg (0.16 mEq)/mL]

RenoCal-76®: Diatrizoate meglumine 660 mg and diatrizoate sodium 100 mg per 1 mL (50 mL) [provides organically-bound iodine 370 mg/mL; contains edetate calcium disodium, sodium 3.69 mg (0.16 mEq)/mL] [DSC]

Renografin®-60: Diatrizoate meglumine 520 mg and diatrizoate sodium 80 mg per 1 mL (50 mL) [provides organically-bound iodine 292.5 mg/mL; contains edetate disodium, sodium 3.76 mg (0.16 mEq)/mL]

Solution, oral/rectal:

Gastrografin®: Diatrizoate meglumine 660 mg and diatrizoate sodium 100 mg per 1 mL (30 mL, 120 mL) [provides organically-bound iodine 367 mg/mL; contains edetate disodium, sodium 4.8 mg (0.21 mEq)/mL; lemon flavor]

MD-Gastroview®: Diatrizoate meglumine 660 mg and diatrizoate sodium 100 mg per 1 mL (30 mL, 120 mL, 240 mL) [provides organically-bound iodine 367 mg/mL; contains edetate disodium, sodium 4.8 mg (0.21 mEq)/mL; lemon-vanilla flavor]

Generic AvailableNo

Manufacturer

Bracco Diagnostics Inc; Mallinckrodt Inc

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDiatrizoate Sodium and Diatrizoate Meglumine

References

ACOG Committee on Obstetric Practice, “ACOG Committee Opinion. Guidelines for Diagnostic Imaging During Pregnancy,” *Obstet Gynecol*, 2004, 104(3):647-51.[PubMed 15339791]

International Brand NamesGastrografin (AU, CL, FI, GR); MD 60 (AU); MD 76 (AU); MD Gastroview (AU); MD-76R (AR); Pielograf (CO)

Diatrizoate Meglumine and Iodipamide Meglumine

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English

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(dye a tri ZOE ate MEG loo meen & eye oh DI pa mide MEG loo meen)

U.S. Brand NamesSinografin®

Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Ionic, Low Osmolality)

Use: Labeled IndicationsHysterosalpingography

Dosing: AdultsHysterosalpingography: Intrauterine: Usual dose: 3-4 mL administered in fractional doses of ~1 mL; may give additional 3-4 mL to visualize tubes; total dosage range: 1.5-10 mL

Administration: OtherFor intrauterine use only; administer in fractional doses of ~1 mL

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light. If crystallization occurs, place vial in hot water, and shake gently for several minutes until the solids redissolve. Allow to cool to body temperature before administering. Discard if cloudiness persists.

ContraindicationsHypersensitivity to any component of the formulation; during or within 6 months following pregnancy termination; infection of external genitalia or genital tract; during menstrual period; within 30 days of curettage or conization

Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Allergic reactions: Use extreme caution with history of previous reaction to contrast dye or iodine-based contrast media or asthma. Severe, potentially life-threatening reactions and delayed reactions may occur. Pretreatment with corticosteroids (eg, prednisone) and antihistamines (eg, diphenhydramine) may be beneficial to decrease the frequency/severity of allergic reactions in "at risk" patients. Equipment for resuscitation and trained personnel experienced in handling emergencies should be immediately available. Monitor closely after injection.

Disease-related concerns:

- Uterine cancer: Use with caution in patients with uterine or uterine tube cancer; procedure may cause dispersion of cancer cells.

Pregnancy ConsiderationsThe procedure for which this product is indicated is contraindicated during or within 6 months of pregnancy. Diatrizoate meglumine crosses the placenta and enters the fetal circulation. Also refer to individual agents.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsDiatrizoate meglumine and iodipamide meglumine have been found in breast milk following intravascular administration.

Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia (rare), cardiac arrest (rare), hypotension, syncope

Central nervous system: Chills, dizziness, fever

Gastrointestinal: Abdominal pain, abdominal tenderness, nausea, vomiting

Miscellaneous: Anaphylactoid reactions, hypersensitivity reactions (including sweating, flushing, pruritus, urticaria, rash, arthralgia, respiratory distress, and circulatory collapse)

Drug Interactions

MetFORMIN: Iodinated Contrast Agents may enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Test InteractionsThyroid function tests (protein bound iodine and radioactive iodine uptake) may be inaccurate after administration. If necessary, T_3 resin uptake or free thyroxine assays can be used after iodinated contrast agents to evaluate thyroid function.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [for intrauterine instillation]:

> Sinografin®: Diatrizoate meglumine 527 mg and iodipamide meglumine 268 mg per mL (10 mL) [provides organically-bound iodine 380 mg/mL; contains edetate disodium, sodium 0.91 mg (0.04 mEq)/mL]

Generic AvailableNo

ManufacturerBracco Diagnostics

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsIodipamide Meglumine and Diatrizoate Meglumine

Diatrizoate Meglumine

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(dye a tri ZOE ate MEG loo meen)

U.S. Brand NamesCystografin®; Cystografin® Dilute; Reno-30®; Reno-60® [DSC]; Reno-Dip®

Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Ionic, High Osmolality)

Use: Labeled Indications

Solution for instillation: Retrograde cystourethrography; retrograde or ascending pyelography

Solution for injection: Arthrography, cerebral angiography, direct cholangiography, discography, drip infusion pyelography, excretory urography, peripheral arteriography, splenoportography, venography; contrast enhancement of computed tomographic head and body imaging

Dosing: AdultsDosing is based upon route of administration, type of examination, age of patient, and product used. Consult specific product information for detailed dosing.

Dosing: PediatricRefer to adult dosing.

Administration: I.V.Administer slower in the elderly and heart failure patients. Slow infusion if nausea or flushing occurs. For intravenous use, should be at body temperature for administration. In angiography, use meticulous intravascular administration technique to minimize thrombotic events including frequent catheter flushing, and close attention to catheter and guidewire manipulation. **Note:** Some products (eg, Cystografin®, Reno-30®) are intended only for instillation and are not to be administered I.V.; consult product labeling to avoid inadvertent erroneous administration.

StorageProtect from light. Store at 20°C to 25°C (68°F to 77°F); Hypaque™ should be stored at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to diatrizoate or any component of the formulation; solutions for instillation should not be used for intravascular injection; solutions for injection are not for intrathecal use

Refer to product labeling for procedure-specific contraindications.

Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Intrathecal use: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Allergic reactions: Use extreme caution with history of previous reaction to contrast dye or iodine-based contrast media. Severe, potentially life-threatening, reactions and delayed reactions may occur. Monitor closely after injection.

- Extravasation: Use meticulous intravascular administration technique.

Disease-related concerns:

- Heart failure: Use caution in heart failure.

- Hepatic disease: Use caution in severe hepatic failure. Avoid diagnostic infusion studies in patients with hepatic or biliary disease who have recently taken cholecystographic contrast agent.

- Hypertension: Use caution in hypertension.

- Hyperthyroidism: Use caution; thyroid storm following use of intravascular iodinated contrast agents has been rarely reported.

- Multiple myeloma: Use caution in multiple myeloma; use of intravascular contrast agents may lead to renal dysfunction, especially with concurrent dehydration.

- Pheochromocytoma: Use extreme caution in pheochromocytoma; monitor blood pressure closely.

- Renal disease: Use caution in renal disease. May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in diabetics, the elderly, and those who are dehydrated.

- Sickle cell disease: May exacerbate sickle cell disease.

- Subarachnoid hemorrhage: Use caution in subarachnoid hemorrhage; reports of clinical deterioration have occurred with administration of contrast media.

- Thromboembolism: Serious, rarely fatal, thromboembolic events causing myocardial infarction (MI) and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Ionic iodinated contrast media may inhibit blood coagulation. Use meticulous intravascular administration techniques during angiographic procedures.

Dosage form specific issues:

- Instillation: Some products (eg, Cystografin®, Reno-30®) are intended only for instillation and are not to be administered I.V.; consult product labeling to avoid inadvertent erroneous administration.

Other warnings/precautions:

- Intrathecal: **[U.S. Boxed Warning]:** Injectable solution should never be used intrathecally.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Diatrizoate salts cross the placenta and may enter fetal circulation. Abnormal neonatal opacification of the small intestine and colon have been reported in the newborn 4-6 days after delivery. In general, iodinated contrast media agents are avoided during pregnancy unless essential for diagnosis.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsDiatrizoate salts are reported to be excreted in human milk

Adverse Reactions

<10%:

Cardiovascular: Flushing (49%)

Gastrointestinal: Taste perversion (11%)

Local: Injection site reaction (12%)

Renal: Nephrosis (excretory urography: 23%)

1% to 10%:

Cardiovascular: Edema, hypertension

Central nervous system: Dizziness (5%), agitation, chills, fever, headache

Dermatologic: Urticaria (1%)

Gastrointestinal: Nausea (6%), vomiting (3%)

Local: Extravasation

Neuromuscular & skeletal: Parasthesia (6%)

Renal: Hematuria (retrograde GU procedures), urinary tract infections (retrograde GU procedures)

Respiratory: Cough (2%), rhinitis (1%), sneezing

Miscellaneous: Allergic reaction, diaphoresis

<1%: Anaphylactic shock, anemia, angioneurotic edema, anuria, apnea, asthma, bradycardia (sinus), bronchospasm, BUN (increased), cardiac arrest, cardiorespiratory failure, chest pain, coma, confusion, conjunctival irritation, creatinine (increased), cyanosis, dyspnea, fibrillation (ventricular), gangrene (extremities), hematoma (cerebral), hypotension, itching eyes, lacrimation, laryngeal edema, leukopenia, neutropenia, oliguria, pain, paresis, parotid glands swelling, petechiae, pruritus, pulmonary edema, pulmonary embolism, rash, renal colic (retrograde GU procedures), renal failure, respiratory arrest, seizure, shock (urography), speech disorder, syncope, tachycardia (reflex), thrombocytopenia, thrombophlebitis, uremia, urinary tract spasm (retrograde GU procedures), ventricular fibrillation

Drug Interactions

MetFORMIN: Iodinated Contrast Agents may enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, for instillation:

Cystografin®: 30% (100 mL, 300 mL) [provides organically-bound iodine 141 mg/mL; contains edetate disodium 0.4 mg/mL]

Cystografin® Dilute: 18% (300 mL) [provides organically-bound iodine 85 mg/mL; contains edetate disodium 0.4 mg/mL]

Reno-30®: 30% (50 mL) [provides organically-bound iodine 141 mg/mL; contains edetate disodium 0.4 mg/mL]

Solution, injection:

Reno-60®: 60% (50 mL) [provides organically-bound iodine 282 mg/mL; contains edetate disodium 0.4 mg/mL, sodium 0.91 mg (0.04 mEq)/mL] [DSC]

Reno-Dip®: 30% (300 mL) [provides organically-bound iodine 141 mg/mL; contains edetate disodium 0.4 mg/mL, sodium 0.049 mg (0.002 mEq)/mL]

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

ACOG Committee on Obstetric Practice, “ACOG Committee Opinion. Guidelines for Diagnostic Imaging During Pregnancy,” *Obstet Gynecol*, 2004, 104(3):647-51.[PubMed 15339791]

Diatrizoate Sodium

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English

English

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Pronunciation(dye a tri ZOE ate SOW dee um)
U.S. Brand NamesHypaque™ Sodium
Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Ionic, High Osmolality)
Use: Labeled IndicationsRadiographic examination of GI tract
Dosing: Adults Radiographic imaging:

Oral: 25% to 40% solution: 90-180 mL

Rectal: Enema: 15% to 25% solution: 500-1000 mL

Dosing: PediatricRadiographic imaging: Infants and Children:

Oral: 20% to 40% solution: 30-75 mL

Rectal: Enema: 10% to 15% solution: 100-500 mL depending on weight of patient

Administration: OralUse immediately after mixing.
Administration: OtherRectal: Use immediately after mixing.
ReconstitutionOral solution: Mix powder with 100 mL of water, milk or carbonated drink. Carbonated diluents should be avoided when gas artifacts are undesirable. Solutions may be sweetened or flavored (eg, with vanilla, lemon, chocolate).

To make 10% solution, mix 1 level measuring spoonful (10 g) of powder in 100 mL of liquid.

ContraindicationsHypersensitivity to diatrizoate or any component of the formulation
Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Contrast dye/iodine hypersensitivity: Use with caution in patients with history of previous reaction to contrast dye or iodine.
- Laxative effect: Solutions may be hypertonic and may cause mucosal irritation and intraluminal water movement resulting in laxative effect.
- Serious reactions: Parenteral administration of radiopaque media has been associated with serious reactions; may also occur with oral administration.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Patients at risk for aspiration: Should not be used in patients who are at risk of aspiration, including patients with esophagotracheal fistula.
- Renal impairment: Use with caution in patients with severe renal impairment.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.
- Pediatrics: Use with caution in children.

Other warnings/precautions:

- Monitoring: Monitor hydration and electrolyte status.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Diatrizoate salts cross the placenta and may enter fetal circulation. Abnormal neonatal opacification of the small intestine and colon have been reported in the newborn 4-6 days after delivery. In general, iodinated contrast media agents are avoided during pregnancy unless essential for diagnosis.
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsDiatrizoate salts are reported to be excreted in human milk.
Adverse ReactionsFrequency not defined.

Dermatologic: Urticaria

Gastrointestinal: Diarrhea, nausea, vomiting

Hematologic: Eosinophilia

Miscellaneous: Anaphylactic reaction

Drug Interactions

MetFORMIN: Iodinated Contrast Agents may enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for solution, oral/rectal:

Hypaque™ Sodium: 100% (250 g) [provides organically-bound iodine 600 mg/g]

Generic AvailableNo

ManufacturerAmersham Health

Mechanism of ActionWhen administered orally or given as an enema, the medium produces excellent opacification and delineation of the upper and lower gastrointestinal tract; however, because of dilution, contrast in the small bowel may be unsatisfactory.

Pharmacodynamics/KineticsAbsorption: Oral: Minimal; Rectal: May result in increased absorption

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

ACOG Committee on Obstetric Practice, “ACOG Committee Opinion. Guidelines for Diagnostic Imaging During Pregnancy,” *Obstet Gynecol*, 2004, 104(3):647-51.[PubMed 15339791]

Diazepam

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Medication Safety Issues

Sound-alike/look-alike issues:

Diazepam may be confused with diazoxide, Ditropan®, LORazepam

Valium® may be confused with Valcyte™

Pronunciation(dye AZ e pam)

U.S. Brand NamesDiastat®; Diastat® AcuDial™; Diazepam Intensol®; Valium®

Canadian Brand NamesApo-Diazepam®; Diastat®; Diastat® Rectal Delivery System; Diazemuls®; Novo-Dipam; Valium®

Pharmacologic CategoryBenzodiazepine

Use: Labeled IndicationsManagement of anxiety disorders, ethanol withdrawal symptoms; skeletal muscle relaxant; status epilepticus; muscle spasm associated with tetanus

Rectal gel: Management of selected, refractory epilepsy patients on stable regimens of antiepileptic drugs (AEDs) requiring intermittent use of diazepam to control episodes of increased seizure activity

Use: Unlabeled/InvestigationalPanic disorders; preoperative sedation, light anesthesia, amnesia

Use: DentalOral medication for preoperative dental anxiety; sedative component in I.V. conscious sedation in oral surgery patients; skeletal muscle relaxant

Dosing: Adults**Note:** Oral absorption is more reliable than I.M.

Acute ethanol withdrawal:*Oral:* 10 mg 3-4 times during first 24 hours, then decrease to 5 mg 3-4 times/day as needed

Anticonvulsant (acute treatment):*Rectal gel:* 0.2 mg/kg. **Note:** Dosage should be rounded upward to the next available dose, 2.5, 5, 7.5, 10, 12.5, 15, 17.5, and 20 mg/dose; dose may be repeated in 4-12 hours if needed; do not use for more than 5 episodes per month or more than one episode every 5 days.

Anxiety (symptoms/disorders):

Oral: 2-10 mg 2-4 times/day

I.M., I.V.: 2-10 mg, may repeat in 3-4 hours if needed

Muscle spasm:*I.V., I.M.:* Initial: 5-10 mg; then 5-10 mg in 3-4 hours, if necessary. Larger doses may be required if associated with tetanus.

Sedation in the ICU patient:*I.V.:* 0.03-0.1 mg/kg every 30 minutes to 6 hours

Skeletal muscle relaxant (adjunct therapy):*Oral:* 2-10 mg 3-4 times/day

Status epilepticus:

I.V.: 5-10 mg every 5-10 minutes given over ≤5 mg/minute (maximum dose: 30 mg)

Rectal gel: Premonitory/out-of-hospital treatment: 10 mg once; may repeat once if necessary

Rapid tranquilization of agitated patient (administer every 30-60 minutes): *Oral:* 5-10 mg; average total dose for tranquilization: 20-60 mg

Dosing: Elderly**Oral absorption is more reliable than I.M.**. Elderly and/or debilitated patients:

Oral: 2-2.5 mg 1-2 times/day initially; increase gradually as needed and tolerated.

Rectal gel: Due to the increased half-life in elderly and debilitated patients, consider reducing dose.

Dosing: Pediatric

Anticonvulsant (acute treatment):*Rectal gel:*

Children <2 years: Safety and efficacy have not been studied

Children 2-5 years: 0.5 mg/kg

Children 6-11 years: 0.3 mg/kg

Children ≥12 years: Refer to adult dosing.

Note: Dosage should be rounded upward to the next available dose, 2.5, 5, 7.5, 10, 12.5, 15, 17.5, and 20 mg/dose; dose may be repeated in 4-12 hours if needed; do not use for more than 5 episodes per month or more than one episode every 5 days.

Conscious sedation for procedures:

Oral:

Children: 0.2-0.3 mg/kg (maximum dose: 10 mg) 45-60 minutes prior to procedure

Adolescents: 10 mg

I.V.: Adolescents: 5 mg; may repeat with 2.5 mg if needed

Febrile seizure prophylaxis:*Oral:* Children: 1 mg/kg/day divided every 8 hours; initiate therapy at first sign of fever and continue for 24 hours after fever is gone

Muscle spasm associated with tetanus:*I.V., I.M.:*

Infants >30 days: 1-2 mg/dose every 3-4 hours as needed

Children ≥5 years: 5-10 mg/dose every 3-4 hours as needed

Sedation or muscle relaxation or anxiety:

Oral: Children: 0.12-0.8 mg/kg/day in divided doses every 6-8 hours

I.M., I.V.: Children: 0.04-0.3 mg/kg/dose every 2-4 hours to a maximum of 0.6 mg/kg within an 8-hour period if needed

Status epilepticus:

I.V.: Infants >30 days and Children: 0.1-0.3 mg/kg given over ≤5 mg/minute; may repeat dose after 5-10 minutes; maximum: 10 mg/dose (Hegenbarth, 2008)

Rectal: 0.5 mg/kg/dose then 0.25 mg/kg/dose in 10 minutes if needed (prepare dose using parenteral formulation)

Dosing: Renal ImpairmentNo dose adjustment recommended; decrease dose if administered for prolonged periods.

I.V.: Risk of propylene glycol toxicity; monitor closely if using for prolonged periods or at high doses.

Hemodialysis: Not dialyzable (0% to 5%); supplemental dose is not necessary.

Dosing: Hepatic ImpairmentUse caution.

Administration: I.V.Continuous infusion is not recommended because of precipitation in I.V. fluids and absorption of drug into infusion bags and tubing. In children, do not exceed 1-2 mg/minute IVP; in adults 5 mg/minute.

Administration: I.V. DetailpH: 6.2-6.9

Administration: OralIntensol® should be diluted before use.

Administration: OtherRectal gel: Prior to administration, confirm that prescribed dose is visible and correct, and that the green “ready” band is visible. Patient should be positioned on side (facing person responsible for monitoring), with top leg bent forward. Insert rectal tip (lubricated) into rectum and push in plunger gently over 3 seconds. Remove tip of rectal syringe after 3 additional seconds. Buttocks should be held together for 3 seconds after removal. Dispose of syringe appropriately.

Storage

Injection: Store at 20° to 25°C (68° to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light. Potency is retained for up to 3 months when kept at room temperature. Most stable at pH 4-8; hydrolysis occurs at pH <3.

Rectal gel: Store at 25°C (77°F); excursion permitted to 15°C to 30°C (59°F to 86°F).

Tablet: Store at 15°C to 30°C (59°F to 86°F).

ReconstitutionPer manufacturer, do not mix I.V. product with other medications.

CompatibilityPer manufacturer, do not mix I.V. product with other medications. **Variable stability (consult detailed reference)** in D_5W, LR, NS.

Y-site administration: Compatible: Dobutamine, fentanyl, morphine sulfate, nafcillin, quinidine gluconate, sufentanil. **Incompatible:** Amphotericin B cholesteryl sulfate complex, atracurium, cefepime, dexmedetomidine, diltiazem, fluconazole, foscarnet, gatifloxacin, heparin, heparin with hydrocortisone sodium succinate, hetastarch, hydromorphone, linezolid, meropenem, pancuronium, potassium chloride, propofol, vecuronium, vitamin B complex with C. **Variable (consult detailed reference):** Cisatracurium, remifentanil.

Compatibility in syringe: Compatible: Cimetidine. **Incompatible:** Doxapram, glycopyrrolate, heparin, hydromorphone, nalbuphine, sufentanil. **Variable (consult detailed reference):** Ketorolac, ranitidine.

Compatibility when admixed: Compatible: Verapamil. **Incompatible:** Bleomycin, buprenorphine, dobutamine, doxorubicin, floxacillin, fluorouracil, furosemide.

RestrictionsC-IV

ContraindicationsHypersensitivity to diazepam or any component of the formulation (cross-sensitivity with other benzodiazepines may exist); myasthenia gravis; severe respiratory insufficiency; severe hepatic insufficiency; sleep apnea syndrome; acute narrow-angle glaucoma; not for use in children <6 months of age (oral)

Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Psychiatric and paradoxical reactions: Reactions, including hyperactive or aggressive behavior, hallucinations, and psychoses, have been reported with benzodiazepines, particularly in adolescent/pediatric or elderly patients. Diazepam should be discontinued if reactions occur.

Disease-related concerns:

- Convulsive disorders: When used as an adjunct in treating convulsive disorders, an increase in frequency/severity of grand mal seizures may occur and require dose adjustment of anticonvulsant. Abrupt withdrawal may result in a temporary increase of seizures.

- Depression: Use caution in patients with depression or anxiety associated with depression, particularly if suicidal risk may be present.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use (generally >10 days).

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with respiratory disease; a lower dose is recommended for chronic respiratory insufficiency.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 and CYP2C19 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

- Narcotics: The dosage of narcotics should be reduced by approximately one-third when diazepam is added.

Special populations:

- Debilitated/elderly patients: Use with caution; active metabolites with extended half-lives may lead to delayed accumulation and adverse effects; limit dose to smallest effective amount (2-2.5 mg once or twice daily initially, to be increased gradually and as tolerated) to avoid adverse reactions.

- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.

- Neonates: Safety and efficacy of the injection have not been established in children <1 month of age. Solution for injection may contain sodium benzoate, benzyl alcohol, or benzoic acid. Large amounts have been associated with “gasping syndrome” in neonates.

- Obese patients: Use with caution in obese patients; may have prolonged action when discontinued.

- Pediatrics: Safety and efficacy of oral use have not been established in children <6 months of age. Safety and efficacy in rectal gel have not been established in children <2 years of age.

- Psychotic patients: Use of diazepam is not recommended in place of appropriate therapy.

Dosage form specific issues:

- Parenteral: Acute hypotension, muscle weakness, apnea, and cardiac arrest have occurred with parenteral administration. Acute effects may be more prevalent in patients receiving concurrent barbiturates, narcotics, or ethanol. Appropriate resuscitative equipment and qualified personnel should be available during administration and monitoring. Avoid use of the injection in patients with shock, coma, or acute ethanol intoxication. Intra-arterial injection or extravasation of the parenteral formulation should be avoided. Parenteral formulation contains propylene glycol, which has been associated with toxicity when administered in high dosages.

- Propylene glycol: Parenteral formulation contains propylene glycol. May be associated with toxicity in high-dose and/or longer-term therapy.

- Rectal gel: Administration of rectal gel should only be performed by individuals trained to recognize characteristic seizure activity for which the product is indicated, and capable of monitoring response to determine need for additional medical intervention.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.

- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsDue to its long-acting metabolite, diazepam is not considered a drug of choice in the elderly. Long-acting benzodiazepines have been associated with falls in the elderly. Interpretive guidelines from the Centers for Medicare and Medicaid Services (CMS) strongly discourage the use of this agent in residents of long-term care facilities.

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenic effects have been reported in animal studies. In humans, diazepam crosses the placenta. An increased risk of congenital malformations and other developmental abnormalities have been associated with diazepam; epilepsy itself may also increase the risk. Hypotonia, hypothermia, withdrawal symptoms, respiratory and feeding difficulties have been reported in the infant following maternal use of benzodiazepines near time of delivery.

LactationEnters breast milk/contraindicated (AAP rates “of concern”)

Breast-Feeding ConsiderationsClinical effects on the infant include sedation; AAP reports that USE MAY BE OF CONCERN.

Adverse ReactionsFrequency not defined. Adverse reactions may vary by route of administration.

Cardiovascular: Hypotension, vasodilatation

Central nervous system: Amnesia, ataxia, confusion, depression, drowsiness, fatigue, headache, slurred speech, paradoxical reactions (eg, aggressiveness, agitation, anxiety, delusions, hallucinations, inappropriate behavior, increased muscle spasms, insomnia, irritability, psychoses, rage, restlessness, sleep disturbances, stimulation), vertigo

Dermatologic: Rash

Endocrine & metabolic: Libido changes

Gastrointestinal: Constipation, diarrhea, nausea, salivation changes (dry mouth or hypersalivation)

Genitourinary: Incontinence, urinary retention

Hepatic: Jaundice

Local: Phlebitis, pain with injection

Neuromuscular & skeletal: Dysarthria, tremor, weakness

Ocular: Blurred vision, diplopia

Respiratory: Apnea, asthma, respiratory rate decreased

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2B6 (minor), 2C9 (minor), 2C19 (major), 3A4 (major); **Inhibits** CYP2C19 (weak), 3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Diazepam serum levels may be increased if taken with food. Diazepam effect/toxicity may be increased by grapefruit juice; avoid concurrent use.

Herb/Nutraceutical: St John's wort may decrease diazepam levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsFalse-negative urinary glucose determinations when using Clinistix® or Diastix®

Monitoring ParametersRespiratory, cardiovascular, and mental status; check for orthostasis

Reference RangeTherapeutic: Diazepam: 0.2-1.5 mcg/mL (SI: 0.7-5.3 µmol/L); N-desmethyldiazepam (nordiazepam): 0.1-0.5 mcg/mL (SI: 0.35-1.8 µmol/L)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance; periodically evaluate need for continued use. Monitor blood pressure, CNS status. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Assess knowledge/teach patient seizure precautions (if administered for seizures), appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, loss of appetite, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help). If medication is used to control seizures, wear identification that you are taking an antiepileptic medication. Report CNS changes (confusion, depression, increased sedation, excitation, headache, agitation, insomnia or nightmares, dizziness, fatigue, or impaired coordination) or changes in cognition; respiratory difficulty or shortness of breath; changes in urinary pattern; changes in sexual activity; muscle cramping, weakness, tremors, or rigidity; ringing in ears or visual disturbances; excessive perspiration; excessive GI symptoms (cramping, constipation, vomiting, anorexia); or worsening of seizure activity or loss of seizure control. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel, rectal:

Diastat®: Pediatric rectal tip [4.4 cm]: 5 mg/mL (2.5 mg, 5 mg) [contains ethyl alcohol 10%, sodium benzoate, benzyl alcohol 1.5%; twin pack]

Diastat® AcuDial™ delivery system:

10 mg: Pediatric/adult rectal tip [4.4 cm]: 5 mg/mL (delivers set doses of 5 mg, 7.5 mg, and 10 mg) [contains ethyl alcohol 10%, sodium benzoate, benzyl alcohol 1.5%; twin pack]

20 mg: Adult rectal tip [6 cm]: 5 mg/mL (delivers set doses of 10 mg, 12.5 mg, 15 mg, 17.5 mg, and 20 mg) [contains ethyl alcohol 10%, sodium benzoate, benzyl alcohol 1.5%; twin pack]

Injection, solution: 5 mg/mL (2 mL, 10 mL)

Solution, oral: 5 mg/5 mL (5 mL, 500 mL)

Solution, oral concentrate:

Diazepam Intensol®: 5 mg/mL (30 mL)

Tablet: 2 mg, 5 mg, 10 mg

Valium®: 2 mg, 5 mg, 10 mg

Generic AvailableYes: Injection, tablet, solution only

Pricing: U.S. (www.drugstore.com)

Gel (Diastat AcuDial)

10 mg (1): $384.99

Gel (Diastat Universal)

10 mg (1): $211.99

Solution (Diazepam)

1 mg/mL (60): $15.99

Tablets (Diazepam)

2 mg (30): $11.99

5 mg (30): $11.99

10 mg (30): $12.99

Tablets (Valium)

2 mg (30): $54.04

5 mg (30): $81.64

10 mg (30): $121.89

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

I.V.: Status epilepticus:

Onset of action: Almost immediate

Duration: 20-30 minutes

Absorption: Oral: 85% to 100%, more reliable than I.M.

Protein binding: 98%

Metabolism: Hepatic

Half-life elimination: Parent drug: Adults: 20-50 hours; increased half-life in neonates, elderly, and those with severe hepatic disorders; Active major metabolite (desmethyldiazepam): 50-100 hours; may be prolonged in neonates

Related Information

- Benzodiazepines
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Status Epilepticus
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsDiazepam does not have any analgesic effects.

Diastat® AcuDial™: When dispensing, consult package information for directions on setting patient's dose; confirm green "ready" band is visible prior to dispensing product.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Diazepam is a long half-life benzodiazepine. Duration of action after a single dose is determined by redistribution rather than metabolism.

Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include personal or family history of substance abuse and personality disorder.

Diazepam is the most rapidly absorbed benzodiazepine; poorly and erratically absorbed after I.M. administration; undergoes phase I metabolism; injection contains propylene glycol which may cause hypotension and bradycardia when injected rapidly. Therefore, maximum rate of infusion is 5 mg/minute.

Cardiovascular ConsiderationsHypotension may result in orthostatic lightheadedness or syncope. Benzodiazepines, as a class, may depress respiration. These medications may often be prescribed for difficulty in sleeping but may exacerbate sleep-disordered breathing.

Anesthesia and Critical Care Concerns/Other ConsiderationsOral absorption more reliable than intramuscular. Intensol® should be diluted before use. Diazepam does not have any analgesic effects. Chronic use of this agent may increase the perioperative benzodiazepine dose needed to achieve desired effect. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms. Hypotension may result in orthostatic lightheadedness or syncope. Benzodiazepines, as a class, may depress respiration. The 2002 ACCM/SCCM guidelines for the sustained use of sedatives and analgesics in critically-ill adults recommend diazepam or midazolam for rapid sedation of acutely-agitated patients.

Status Epilepticus: A randomized, double-blind trial (Treiman, 1998) evaluated the efficacy of four treatments in overt status epilepticus. Treatment arms were designed based upon accepted practices of North American neurologists. The treatments were: 1) lorazepam 0.1 mg/kg, 2) diazepam 0.15 mg/kg followed by phenytoin 18 mg/kg, 3) phenytoin 18 mg/kg alone, and 4) phenobarbital 15 mg/kg. Treatment was considered successful if the seizures were terminated (clinically and by EEG) within 20 minutes of start of therapy without seizure recurrence within 60 minutes from the start of therapy. Patients who failed the first treatment received a second and a third, if necessary. Patients did not receive randomized treatments after the first one but the treating physician remained blinded. Treatment success: Lorazepam 64.9%, phenobarbital 58.2%, diazepam/phenytoin 55.8%, and phenytoin alone 43.6%. Using an “intention-to-treat” analysis, there was no statistical difference between the groups. Results of subsequent treatments in patients who failed the first therapy indicated that response rate significantly dropped regardless of treatment. Aggregate response rate to the second treatment was 7.0% and third treatment 2.3%.

Guidelines are available for status epilepticus (Kälviäinen, 2007).

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Zeltzer LK, Altman A, Cohen D, et al, “Report of the Subcommittee on the Management of Pain Associated With Procedures in Children With Cancer,” *Pediatrics*, 1990, 86(5 Pt 2):826-31.[PubMed 2216645]

International Brand NamesAliseum (IT); Ansiolin (IT); Antenex (AU); Apaurin (HR); Apo-diazepam (CZ); Apozepam (DK); Assival (IL); Azepan

(AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Benzopin (ZA); Calmpose (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Cercine (JP); Ceregulart (JP); Compaz (BR); Condition (JP); D-Pam (NZ); Dialag (BB, BF, BJ, BM, BS, BZ, CI, ET, GH, GM, GN, GY, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, SC, SD, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Diano (TH); Diapam (FI, RU, TH, TR); Diapin (TW); Diapine (MY, TH); Diapo (MY, SG); Diaz (IL); Diazem (TR); Diazemuls (GB, IT, NL); Diazepam (HK, PL); Diazepam Desitin (HU); Diazepam RecTubes (PL); Diazepam-Eurogenerics (LU); Diazepam-Lipuro (PL); Diazepam-ratiopharm (LU); Diazepan (AE, BF, BH, BJ, CI, CY, EG, ES, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Diazer (AU); Diazerekt (PL); Dipaz (EC); Dipezona (AR); Doval (ZA); Ducene (AU); Dupin (TW); DZP (MY); Elcion CR (IN); Euphorin (JP); Gewacalm (AT); Horizon (JP); Ifa Fonal (MX); Kratium (BB, BF, BJ, BM, BS, BZ, CI, ET, GH, GM, GN, GY, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, SC, SD, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Kratium 2 (HK); Lembrol (AR); Melode (KP); Mentalium (ID); Nivalen (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Nixtensyn (PH); Noan (BR, IT); Normabel (HR); Ortopsique (MX); Paceum (CH); Pacitran (PE); Pax (ZA); Paxum (IN); Placidox 10 (IN); Placidox 2 (IN); Placidox 5 (IN); Plidan (AR); Propam (NZ); Psychopax (AT, CH); Radizepam (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Relanium (BG, PL, RU); Relsed (PL); Renborin (JP); Seduxen (BB, BM, BS, BZ, EE, GY, HN, HU, JM, NL, SR, TT); Serenzin (JP); Sipam (TH); Stesolid (AE, BH, CH, CY, DE, DK, EG, FI, HN, ID, IL, IQ, IR, JO, KW, LB, LY, NL, NO, OM, QA, SA, SE, SY, TW, YE); Stesolid Rectal Tube (DE, HK); Sunzepam (MX); Tranquirit (IT); Valaxona (DK); Valdimex (ID); Valiquid (DE); Valisanbe (ID); Valium (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CY, CZ, DE, DK, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HN, HR, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PH, PK, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Valiuzam (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Valpam (AE, AU, BH, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Vanconin (TW); Vatran (IT)

Diazoxide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Diazoxide may be confused with diazepam, Dyazide®

Pronunciation(dye az OKS ide)
U.S. Brand NamesProglycem®
Canadian Brand NamesProglycem®
Pharmacologic CategoryAntidote, Hypoglycemia; Vasodilator, Direct-Acting
Use: Labeled IndicationsHypoglycemia related to islet cell adenoma, carcinoma, hyperplasia, or adenomatosis; nesidioblastosis; leucine sensitivity; extrapancreatic malignancy
Dosing: Adults**Hyperinsulinemic hypoglycemia:** Oral: Initial dose: 3 mg/kg/day; dosing range: 3-8 mg/kg/day in divided doses every 8-12 hours. **Note:** In certain instances, patients with refractory hypoglycemia may require higher doses.
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Hyperinsulinemic hypoglycemia:** Oral:

Newborns and Infants: Initial dose: 10 mg/kg/day; dosing range: 8-15 mg/kg/day in divided doses every 8-12 hours

Children: Refer to adult dosing.

Dosing: Renal ImpairmentHalf-life may be prolonged with renal impairment; a reduced dose should be considered.
StorageSuspension: Store at controlled room temperature of 25°C (77°F). Protect from light.
ContraindicationsHypersensitivity to diazoxide, thiazides, or other sulfonamide derivatives; functional hypoglycemia
Allergy Considerations

- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Disease-related concerns:

- Heart failure: Use may lead to increased fluid retention and may precipitate congestive heart failure in patients with compromised cardiac reserve.
- Gout: Use with caution in patients with hyperuricemia or a history of gout.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment; a reduced dose should be considered.

Concerns related to adverse effects:

- Hyperosmolar coma: Nonketotic hyperosmolar coma may occur during treatment; usually in patients with concomitant illness. Transient cataracts have been reported which subside following correction of hyperosmolarity.
- Ketoacidosis: Ketoacidosis may occur during treatment, usually in patients with concomitant illness.

Special populations:

- Newborns: May displace bilirubin from albumin; use caution in newborns with hyperbilirubinemia.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAdverse events have been observed in animal studies. Diazoxide crosses the human placenta. Altered carbohydrate metabolism, hyperbilirubinemia, or thrombocytopenia have been reported in the fetus or neonate. Alopecia and hypertrichosis lanuginosa have also been reported in infants following maternal use of diazoxide during the last 19-60 days of pregnancy.
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension, palpitation, tachycardia

Central nervous system: Anxiety, dizziness, fever, headache, insomnia, malaise, polyneuritis

Dermatologic: Hirsutism, pruritus, purpura, rash, scalp hair loss

Endocrine & metabolic: Breast lump enlargement, diabetic ketoacidosis, fluid retention, galactorrhea, gout, hyperglycemia, hyperosmolar nonketotic coma, sodium retention

Gastrointestinal: Abdominal pain, anorexia, diarrhea, ileus, nausea, pancreatitis, pancreatic necrosis, taste loss (transient), vomiting

Hematologic: Bleeding (excessive), eosinophilia, hemoglobin/hematocrit decreased, neutropenia (transient), thrombocytopenia

Hepatic: Alkaline phosphatase increased, AST increased

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision, cataracts (transient), diplopia, lacrimation, ring scotoma, subconjunctival hemorrhage

Renal: Albuminuria, azotemia, creatinine clearance decreased, glucosuria, hematuria, nephrotic syndrome (reversible), uric acid increased, urinary output decreased

Miscellaneous: Abnormal facial features (children with chronic use), IgG decreased, lymphadenopathy

Drug Interactions

Antihypertensives: Diazoxide may enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Phenytoin: Diazoxide may decrease the serum concentration of Phenytoin. Total phenytoin concentrations may be affected more than free phenytoin concentrations. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid herbs with hypotensive properties (black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse); may enhance the hypotensive effect of diazoxide. Avoid herbs with hypertensive properties (bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng [American], kola, licorice); may diminish the antihypertensive effect of diazoxide.

Test InteractionsFalse-negative insulin response to glucagon

Monitoring ParametersBlood glucose, serum uric acid, BUN, creatinine clearance, CBC with differential, AST; urine glucose and ketones

Monitoring: Lab TestsBlood glucose, serum uric acid, BUN, creatinine clearance, CBC with differential, AST; urine glucose and ketones

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, oral:

Proglycem®: 50 mg [not available in the U.S.]

Suspension, oral:

Proglycem®: 50 mg/mL (30 mL) [contains ethanol 7.25%, sodium benzoate, propylene glycol; chocolate-mint flavor]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Suspension (Proglycem)

50 mg/mL (30): $154.43

Mechanism of ActionActivates potassium channels. Inhibits insulin release from the pancreas

Pharmacodynamics/Kinetics

Onset of action: Hyperglycemic: Oral: ~1 hour

Duration: Hyperglycemic: Oral: Normal renal function: 8 hours

Protein binding: >90%

Half-life elimination: Oral: Children: 9-24 hours; Adults: 24-36 hours

Excretion: Urine

Related Information

- Hypertension

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness; may rarely cause extrapyramidal symptoms

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine

References

Lancaster-Smith M, Leigh NI, and Thompson HM, “Death Following Nonketotic Hyperglycemic Coma During Diazoxide Therapy and Peritoneal Dialysis,” *Postgrad Med J*, 1974, 50:175-9.

International Brand NamesEudemine (GB); Hyperstat (BE, CZ, ES, HR, HU, LU, SE); Hypertonalum (DE); Naxproglycem (KP); Proglicem (AR, CH, DE, FR, IT, NL, NO); Proglycem (GR)

English English

Jump To Field (Select Field Name)

Pronunciation(DYE byoo kane)

U.S. Brand NamesNupercainal® [OTC]

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsFast, temporary relief of pain and itching due to hemorrhoids, minor burns

Use: DentalAmide derivative local anesthetic for minor skin conditions

Dosing: AdultsLocal pain (local anesthetic): Topical: Apply gently to the affected areas; no more than 30 g for adults or 7.5 g for children should be used in any 24-hour period

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren: Topical: Refer to adult dosing.

StorageDarkens on light exposure.

ContraindicationsHypersensitivity to amide-type anesthetics, ophthalmic use

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Pregnancy Risk FactorC

Breast-Feeding ConsiderationsNo data reported; however, topical administration is probably compatible.

Adverse Reactions1% to 10%:

Dermatologic: Angioedema, contact dermatitis

Local: Burning

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Ointment, topical: 1% (30 g)

Nupercainal®: 1% (30 g, 60g) [contains sodium bisulfite]

Generic AvailableYes

Mechanism of ActionLocal anesthetics bind selectively to the intracellular surface of sodium channels to block influx of sodium into the axon. As a result, depolarization necessary for action potential propagation and subsequent nerve function is prevented. The block at the sodium channel is reversible. When drug diffuses away from the axon, sodium channel function is restored and nerve propagation returns.

Pharmacodynamics/Kinetics

Onset of action: ~15 minutes

Duration: 2-4 hours

Absorption: Poor through intact skin; well absorbed through mucous membranes and excoriated skin

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Dichlorodifluoromethane and Trichloromonofluoromethane

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Jump To Field (Select Field Name)

Pronunciation(dye klor oh dye flor oh METH ane & tri klor oh mon oh flor oh METH ane)

U.S. Brand NamesFluori-Methane®

Pharmacologic CategoryAnalgesic, Topical

Use: Labeled IndicationsManagement of pain associated with injections

Use: DentalTopical application in the management of myofascial pain, restricted motion, and muscle spasm

Dosing: AdultsMyofascial pain, muscle spasm, pain associated with injections: Topical: Invert bottle over treatment area approximately 12" away from site of application; open dispenseal spring valve completely, allowing liquid to flow in a stream from the bottle. The rate of spraying is approximately 10 cm/second and should be continued until entire muscle has been covered.

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to dichlorofluoromethane and/or trichloromonofluoromethane, or any component of the formulation; patients having vascular impairment of the extremities

Warnings/Precautions

Other warnings/precautions:

- Appropriate use: For external use only; care should be taken to minimize inhalation of vapors, especially with application to head and neck; avoid contact with eyes; should not be applied to the point of frost formation.

Adverse ReactionsNo data reported.

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol, topical: Dichlorodifluoromethane 15% and trichloromonofluoromethane 85% (103 mL) [contains chlorofluorocarbons]

Generic AvailableNo

Pharmacodynamics/KineticsNo data reported

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsTrichloromonofluoromethane and Dichlorodifluoromethane

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Dichlorphenamide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Daranide® may be confused with Daraprim®

Pronunciation(dye klor FEN a mide)

U.S. Brand NamesDaranide®

Canadian Brand NamesDaranide®

Pharmacologic CategoryCarbonic Anhydrase Inhibitor; Diuretic, Carbonic Anhydrase Inhibitor; Ophthalmic Agent, Antiglaucoma

Use: Labeled IndicationsAdjunct in treatment of open-angle glaucoma and perioperative treatment for angle-closure glaucoma

Dosing: AdultsGlaucoma: Oral: 100-200 mg to start followed by 100 mg every 12 hours until desired response is obtained; maintenance dose: 25-50 mg 1-3 times/day

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to dichlorphenamide or any component of the formulation; severe pulmonary obstruction; severe renal impairment

Allergy Considerations

- Carbonic Anhydrase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonylurea allergy is specifically contraindicated in product labeling; however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Geriatric ConsiderationsMalaise, complaints of tiredness, and myalgia are signs of excessive dosing and acidosis in the elderly.

Pregnancy Risk FactorC

Adverse Reactions

>10%:

Central nervous system: Fatigue, malaise

Gastrointestinal: Anorexia, diarrhea, metallic taste

Genitourinary: Polyuria

1% to 10%:

Central nervous system: Drowsiness, mental depression

Renal: Renal calculi

Drug Interactions

Alpha-/Beta-Agonists: Carbonic Anhydrase Inhibitors may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amphetamines: Carbonic Anhydrase Inhibitors may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Barbiturate): Carbonic Anhydrase Inhibitors may enhance the adverse/toxic effect of Anticonvulsants (Barbiturate). Specifically, osteomalacia and rickets. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Carbonic Anhydrase Inhibitors may enhance the adverse/toxic effect of Anticonvulsants (Hydantoin). Specifically, osteomalacia and rickets. *Risk C: Monitor therapy*

CarBAMazepine: Carbonic Anhydrase Inhibitors may increase the serum concentration of CarBAMazepine. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Flecainide: Carbonic Anhydrase Inhibitors may decrease the excretion of Flecainide. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Memantine: Carbonic Anhydrase Inhibitors may decrease the excretion of Memantine. *Risk C: Monitor therapy*

Methenamine: Carbonic Anhydrase Inhibitors may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Primidone: Carbonic Anhydrase Inhibitors may enhance the adverse/toxic effect of Primidone. Specifically, osteomalacia and rickets. Carbonic Anhydrase Inhibitors may decrease the serum concentration of Primidone. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: Carbonic Anhydrase Inhibitors may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Trientine: Carbonic Anhydrase Inhibitor Diuretics may decrease the serum concentration of Trientine. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 50 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Daranide)

50 mg (30): $20.99

Related Information

- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Metallic taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause bone marrow suppression; use caution with clozapine and carbamazepine; may increase the excretion of lithium but should not be used to treat lithium toxicity

Index TermsDiclofenamide

International Brand NamesAntidrasi (IT); Barastonin (JP); Daranide (AU, GB, IE); Diclofenamid (DE); Fenamide (IT); Glajust (JP); Glaucol (AT, CZ); Glauconide (ES); Glaumid (IT); Oratrol (BE, CH, CZ, DK, ES, GR, HK, LU); Tensodilen (ES)

Diclofenac and Misoprostol

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(dye KLOE fen ak & mye soe PROST ole)

U.S. Brand NamesArthrotec®

Canadian Brand NamesArthrotec®

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral; Prostaglandin

Use: Labeled IndicationsThe diclofenac component is indicated for the treatment of osteoarthritis and rheumatoid arthritis; the misoprostol component is indicated for the prophylaxis of NSAID-induced gastric and duodenal ulceration

Dosing: Adults

Osteoarthritis: Oral: Arthrotec® 50: 1 tablet 2-3 times/day

Rheumatoid arthritis: Oral: Arthrotec® 50: 1 tablet 3-4 times/day

> **Note:** For both regimens, if not tolerated by patient, the dose may be reduced to 1 tablet twice daily. Arthrotec® 75 may be used in patients who cannot tolerate full daily Arthrotec® 50 regimens. Dose: 1 tablet twice daily. However, the use of these tablets may not be as effective at preventing GI ulceration.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot recommended for use in patients with advanced renal disease. In renal insufficiency, diclofenac should be used with caution due to potential detrimental effects on renal function, and misoprostol dosage reduction may be required if adverse effects occur (misoprostol is renally eliminated).

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to diclofenac, misoprostol, other prostaglandins, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery; pregnancy

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.
- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Aseptic meningitis: May increase the risk of aseptic meningitis, especially in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to

reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Porphyria: Avoid use in patients with hepatic porphyria.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Misoprostol is not to be used in pregnant women or women of childbearing potential unless capable of complying with effective contraceptive measures; therapy is normally begun on the second or third day of next normal menstrual period.** Uterine perforation and/or rupture have been reported in association with intravaginal use to induce labor or with combined oral/intravaginal use to induce abortion. Should not be used as a cervical-ripening agent for induction of labor or termination of pregnancy.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from nonsteroidal anti-inflammatory agents. As much as 60% of the elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorX

Pregnancy Considerations**[U.S. Boxed Warning]: Exposure to NSAIDs late in pregnancy may lead to premature closure of the ductus arteriosus and may inhibit uterine contractions. Misoprostol is an abortifacient. Administration by any route is contraindicated in pregnancy.** Reports of fetal death and congenital anomalies have been received after the use of misoprostol as an abortifacient. Arthrotec® should not be used in women of childbearing potential without a negative serum pregnancy test within 2 weeks prior to therapy and unless capable of complying with effective contraception. Therapy should begin on the 2nd or 3rd day of the next normal menstrual period. Written and verbal warnings concerning the hazards of misoprostol should be provided. Pregnancy should be avoid for one month or through one complete menstrual cycle after therapy is discontinued.

LactationEnters breast milk/not recommended

Adverse ReactionsAlso see individual agents.

>10%: Gastrointestinal: Abdominal pain (21%), diarrhea (19%), dyspepsia (14%), nausea (11%)

1% to 10%:

Endocrine & metabolic: Transaminases increased

Gastrointestinal: Flatulence (9%)

Hematologic: Anemia

Miscellaneous: Anaphylactic reactions

Postmarketing and/or case reports (associated with misoprostol): Uterine rupture, fetal or infant death (when used during pregnancy)

Metabolism/Transport EffectsDiclofenac: **Substrate** (minor) of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4; **Inhibits** CYP1A2 (moderate), 2C9 (weak), 2E1 (weak), 3A4 (weak)

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Latanoprost: NSAID (Ophthalmic) may diminish the therapeutic effect of Latanoprost. *Risk C: Monitor therapy*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Oxytocin: Misoprostol may enhance the therapeutic effect of Oxytocin. *Risk D: Consider therapy modification*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Voriconazole: May increase the serum concentration of Diclofenac. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Diclofenac sodium 50 mg and misoprostol 200 mcg; diclofenac sodium 75 mg and misoprostol 200 mcg

Generic AvailableNo

ManufacturerSearle

Pricing: U.S. (www.drugstore.com)

Tablets (Arthrotec 50)

50-200 mg-mcg (60): $146.99

Tablets (Arthrotec 75)

75-200 mg-mcg (60): $153.28

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Diclofenac
- Misoprostol

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness or dizziness; may rarely cause depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause may agranulocytosis; use caution with clozapine and carbamazepine; may decrease the clearance of lithium resulting in elevated serum levels and potential toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A meta-analysis (Pope, 1993) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 chronic heart failure guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Index TermsMisoprostol and Diclofenac

References

Conlin P, Moore T, Swartz S, et al, “Effect of Indomethacin on Blood Pressure Lowering by Captopril and Losartan in Hypertensive Patients,” *Hypertension*, 2000, 36(3):461-5. [PubMed 10988282]

Hunt SA, Abraham WT, Chin MH , et al, "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure)," available at http://www.acc.org/qualityandscience/clinical/guidelines/failure/update/index.pdf.

Morgan TO, Anderson A, and Bertram D, “Effect of Indomethacin on Blood Pressure in Elderly People With Essential Hypertension Well Controlled on Amlodipine or Enalapril,” *Am J Hypertens*, 2000, 13(11):1161-7.[PubMed 11078175]

Pope JE, Anderson JJ, and Felson DT, “A Meta-analysis of the Effects of Nonsteroidal Anti-inflammatory Drugs on Blood Pressure,” *Arch Intern Med*, 1993, 153(4):477-84. [PubMed 8435027]

International Brand NamesArthrotec (AE, BF, BG, BH, BJ, CI, CY, CZ, DK, EE, EG, ET, FI, GB, GH, GM, GN, GR, HK, HN, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, NO, OM, QA, SA, SC, SD, SE, SL, SN, SY, TN, TZ, UG, VE, YE, ZA, ZM, ZW); Arthrotec 50 (AU); Artotec (FR, RU); Artrotec (ES, IT, MX, PE)

Diclofenac

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Diclofenac may be confused with Diflucan®, Duphalac®

Cataflam® may be confused with Catapres®

Voltaren® may be confused with traMADol, Ultram®, Verelan®

Pronunciation(dye KLOE fen ak)

U.S. Brand NamesCataflam®; Flector®; Solaraze®; Voltaren Ophthalmic®; Voltaren®; Voltaren® Gel; Voltaren®-XR

Canadian Brand NamesApo-Diclo Rapide®; Apo-Diclo SR®; Apo-Diclo®; Cataflam®; Dom-Diclofenac; Dom-Diclofenac SR; Novo-Difenac; Novo-Difenac K; Novo-Difenac-SR; Nu-Diclo; Nu-Diclo-SR; Pennsaid®; PMS-Diclofenac; PMS-Diclofenac SR; Pro-Diclo-Rapide; Riva-Diclofenac; Riva-Diclofenac-K; Sab-Diclofenac; Sandoz-Diclofenac; Voltaren Ophtha®; Voltaren Rapide®; Voltaren®

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID); Nonsteroidal Anti-inflammatory Drug (NSAID), Ophthalmic; Nonsteroidal Anti-inflammatory Drug (NSAID), Oral; Nonsteroidal Anti-inflammatory Drug (NSAID), Topical

Use: Labeled Indications

Immediate release tablet: Ankylosing spondylitis; primary dysmenorrhea; acute and chronic treatment of rheumatoid arthritis, osteoarthritis

Delayed-release tablet: Acute and chronic treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis

Extended-release tablet: Chronic treatment of osteoarthritis, rheumatoid arthritis

Ophthalmic solution: Postoperative inflammation following cataract extraction; temporary relief of pain and photophobia in patients undergoing corneal refractive surgery

Topical gel 1%: Relief of osteoarthritis pain in joints amenable to topical therapy (eg, ankle, elbow, foot, hand, knee, wrist)

Topical gel 3%: Actinic keratosis (AK) in conjunction with sun avoidance

Topical patch: Acute pain due to minor strains, sprains, and contusions

Use: Unlabeled/InvestigationalJuvenile rheumatoid arthritis

Use: DentalImmediate-release tablets: Acute treatment of mild to moderate pain

Dosing: Adults

Analgesia/primary dysmenorrhea: Oral: Starting dose: 50 mg 3 times/day; maximum dose: 150 mg/day

Rheumatoid arthritis: Oral: 150-200 mg/day in 2-4 divided doses (100 mg/day of sustained release product)

Osteoarthritis:

Oral: 100-150 mg/day in 2-3 divided doses (100-200 mg/day of sustained release product)

Topical (Voltaren® Gel): **Note:** Maximum total body dose of 1% gel should not exceed 32 g per day

Lower extremities: Apply 4 g of 1% gel to affected area 4 times daily (maximum: 16 g per joint per day)

Upper extremities: Apply 2 g of 1% gel to affected area 4 times daily (maximum: 8 g per joint per day)

Ankylosing spondylitis: Oral: 100-125 mg/day in 4-5 divided doses

Cataract surgery: Ophthalmic: Instill 1 drop into affected eye 4 times/day beginning 24 hours after cataract surgery and continuing for 2 weeks

Corneal refractive surgery: Ophthalmic: Instill 1-2 drops into affected eye within the hour prior to surgery, within 15 minutes following surgery, and then continue for 4 times/day, up to 3 days

Actinic keratosis (AK): Topical (Solaraze® Gel): Apply 3% gel to lesion area twice daily for 60-90 days

Acute pain (strains, sprains, contusions): Topical (patch): Apply 1 patch twice daily to most painful area of skin

Dosing: ElderlyRefer to adult dosing. No specific dosing recommendations; elderly may demonstrate adverse effects at lower doses than younger adults, and >60% may develop asymptomatic peptic ulceration with or without hemorrhage; monitor renal function.

Dosing: Renal ImpairmentNot recommended in patients with advanced renal disease or significant renal impairment.

Dosing: Hepatic ImpairmentNo adjustment necessary.

Administration: OralDo not crush tablets. Administer with food or milk to avoid gastric distress. Take with full glass of water to enhance absorption.

Administration: Topical

Topical gel:

1% formulation: Apply gel to affected joint and rub into skin gently, making sure to apply to entire joint. Do not cover area with occlusive dressings or apply sunscreens, cosmetics, or other medications to affected area. Do not wash area for one hour following application. Wash hands immediately after application (unless hands are treated joint).

3% formulation: Apply to lesion with gel and smooth into skin gently. Do not cover lesion with occlusive dressings or apply sunscreens, cosmetics, or other medications to affected area.

Topical patch: Apply to intact, nondamaged skin. Remove transparent liner prior to applying to skin. Wash hands after applying as well as after removal of patch. May tape down edges of patch, if peeling occurs. Should not be worn while bathing or showering. Fold used patches so the adhesive side sticks to itself; dispose of used patches out of reach of children and pets.

Administration: OtherOphthalmic: Wait at least 5 minutes before administering other types of eye drops.

Dietary ConsiderationsOral formulations may be taken with food to decrease GI distress.

Diclofenac potassium = Cataflam®; potassium content: 5.8 mg (0.15 mEq) per 50 mg tablet

Storage

Ophthalmic solution: Store at 15°C to 25°C (59°F to 77°F).

Tablet: Store below 30°C (86°F). Protect from moisture; store in tight container.

Topical gel: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F); do not freeze.

Topical patch: Store at controlled room temperature 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Keep envelope sealed when not being used.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to diclofenac, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Topical patch: Do not apply to nonintact or damaged skin (eg, exudative dermatitis, eczema, infected lesions, burns or wounds)

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, HF, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.
- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery (CABG): **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Rarely, severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use; discontinue all formulations if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics and ACEI, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, and renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Ophthalmic drops: Monitor patients for 1 year following application of ophthalmic drops for corneal refractive procedures. Patients using ophthalmic drops should not wear soft contact lenses. Ophthalmic drops may slow/delay healing or prolong bleeding time following surgery.

- Topical gel: Do not apply topical gel to the eyes, mucous membranes, open wounds, infected areas, or to exfoliative dermatitis. Avoid use of occlusive dressings. Should not be used concomitantly with sunscreens, cosmetics, lotions, moisturizers, insect repellents, or other topical medication on the same skin sites. Avoid sunlight exposure to treated areas.

- Topical patch: Do not apply topical patch to the eyes, mucous membranes, open wounds, infected areas, or to exudative dermatitis. Patch should not be worn during bathing or showering.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from nonsteroidal anti-inflammatory agents. As much as 60% of the elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorB (topical gel 3%); C (oral, topical gel 1%, topical patch); D (3rd trimester)

Pregnancy ConsiderationsSafety and efficacy in pregnant women have not been established. Exposure late in pregnancy may lead to premature closure of the ductus arteriosus and may inhibit uterine contractions. Avoid use of diclofenac (all forms) in late pregnancy.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

Ophthalmic solution (drops):

>10%: Ocular: Lacrimation (30%), keratitis (28%), intraocular pressure increased (15%), transient burning/stinging (15%)

1% to 10%:

Cardiovascular: Facial edema (≤3%)

Central nervous system: ≤3%: Dizziness, fever, headache, insomnia, pain

Gastrointestinal: ≤3%: Abdominal pain, nausea, vomiting

Neuromuscular & skeletal: ≤3%: Pain, weakness

Ocular: 5%: Abnormal vision, blurred vision, conjunctivitis, corneal deposits, corneal edema, corneal lesions, corneal opacity, discharge, eyelid swelling, injection, iritis, irritation, itching, lacrimation disorder, ocular allergy

Respiratory: Rhinitis (≤3%)

Miscellaneous: Viral infection (≤3%)

<1%, postmarketing, and/or case reports: Corneal erosion, corneal infiltrates, corneal perforation, corneal thinning, corneal ulceration, epithelial breakdown, superficial punctuate keratitis

Oral:

1% to 10%:

- Cardiovascular: Edema
- Central nervous system: Dizziness, headache
- Dermatologic: Pruritus, rash
- Endocrine & metabolic: Fluid retention
- Gastrointestinal: Abdominal distension, abdominal pain, constipation, diarrhea, dyspepsia, flatulence, GI perforation, heartburn, nausea, peptic ulcer/GI bleed, vomiting
- Hematologic: Anemia, bleeding time increased
- Hepatic: Liver enzyme abnormalities
- Otic: Tinnitus
- Renal: Renal function abnormal

<1%, postmarketing, and/or case reports: Abnormal coordination, agranulocytosis, alopecia, amblyopia, anaphylactoid reactions, anaphylaxis, anxiety, angioedema, aphthous stomatitis, aplastic anemia, appetite changes, arrhythmia, aseptic meningitis, asthma, azotemia, blurred vision, bruising, chest pain, cirrhosis, CHF, colitis, confusion, coma, cystitis, depression, dermatitis, diaphoresis, diplopia, disorientation, drowsiness, dyspnea, epistaxis, eructation, erythema multiforme, esophageal lesions, exfoliative dermatitis, dysuria, flushing, hallucination, hearing impairment, hearing loss, hematuria, hemoglobin decreased, hemolytic anemia, hepatitis, hepatic failure, hepatic necrosis, hyper-/hypotension, hyper-/hypoglycemia, hyperventilation, impotence, infection, interstitial nephritis, intestinal perforation, jaundice, laryngeal edema, leukopenia, lymphadenopathy, malaise, melena, memory disturbance, meningitis, MI, nervousness, night blindness, nocturia, oliguria, palpitation, pancreatitis, pancytopenia, paresthesia, pharynx edema, photosensitivity, pneumonia, polyuria, purpura, psychotic reactions, PVCs, rectal bleeding, renal failure, respiratory depression, scotoma, seizure, sepsis, somnolence, Stevens-Johnson syndrome, swelling of lips and tongue, stomatitis, syncope, tachycardia, taste disorder, thrombocytopenia, tic, toxic epidermal necrolysis, tremor, urinary frequency, urticaria, vaginal bleeding, vertigo, vitreous floaters, weight change, weakness, vasculitis, xerostomia

Topical gel:

>10%: Local: Application site reactions (incidence increased with 3% gel): Pruritus (≤52%), rash (35% to 46%), contact dermatitis (4% to 33%), dry skin (≤27%), pain (15% to 26%), exfoliation (3% gel; 6% to 24%), paresthesia (≤20%)

1% to 10% (reported for 3% gel):

- Cardiovascular: Chest pain, hypertension
- Central nervous system: Headache, pain
- Dermatologic: Pruritus, rash, skin ulcer
- Endocrine & metabolic: Hypercholesterolemia, hyperglycemia
- Gastrointestinal: Abdominal pain, diarrhea, dyspepsia
- Genitourinary: Hematuria
- Hepatic: Liver enzymes increased
- Local: Alopecia, edema, photosensitivity
- Neuromuscular and skeletal: Arthralgia, arthrosis, back pain, CPK increased, hypokinesia, myalgia, neck pain, weakness
- Ocular: Conjunctivitis
- Respiratory: Asthma, dyspnea, pneumonia, sinusitis
- Miscellaneous: Flu-like syndrome

Topical patch:

1% to 10%:

- Central nervous system: Dizziness, hypaesthesia
- Dermatologic: Dermatitis (2%), dermal allergic reaction
- Gastrointestinal: Nausea (3%), dysgeusia (2%), abdominal pain, constipation, diarrhea, gastritis, vomiting, xerostomia
- Local: Application site dryness, irritation, erythema, atrophy, discoloration, hyperhidrosis, and vesicles, edema, itching
- Neuromuscular & skeletal: Hyperkinesia

Metabolism/Transport Effects **Substrate** (minor) of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4; **Inhibits** CYP1A2 (moderate), 2C9 (weak), 2E1 (weak), 3A4 (weak)

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Latanoprost: NSAID (Ophthalmic) may diminish the therapeutic effect of Latanoprost. *Risk C: Monitor therapy*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Voriconazole: May increase the serum concentration of Diclofenac. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, grapeseed, green tea, ginseng (Siberian), guggul, horse chestnut, horseradish, licorice, prickly ash, red clover, reishi, SAMe (s-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Monitoring ParametersMonitor CBC, liver enzymes; monitor urine output and BUN/serum creatinine; occult blood loss, hemoglobin, hematocrit

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess other medications patient may be taking for effectiveness and interactions. Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (systemic or ophthalmic) at beginning of therapy and periodically throughout therapy. Schedule ophthalmic evaluations for patients who develop eye complaints during long-term NSAID therapy. Assess knowledge/teach patient appropriate use (oral, ophthalmic, gel), interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC, liver enzymes, urine output and BUN/serum creatinine in patients receiving diuretics, occult blood loss

Patient EducationOral: Take this medication exactly as directed; do not increase dose without consulting prescriber. Do not crush or chew tablets. Take with 8 oz of water, along with food or milk products to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid alcohol, aspirin and aspirin-containing medication, or any other anti-inflammatory medications unless consulting prescriber. You may experience dizziness, nervousness, or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, dry mouth, or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or constipation (increased exercise, fluids, fruit, or fiber may help). GI bleeding, ulceration, or perforation can occur with or without pain; discontinue medication and contact prescriber if persistent abdominal pain or cramping, or blood in stool occurs. Report chest pain or palpitations; breathlessness or respiratory difficulty; unusual bruising/bleeding or blood in urine, stool, mouth, or vomitus; unusual fatigue; skin rash or itching; jaundice, unusual weight gain, or swelling of extremities; change in urinary pattern; change in vision or hearing (ringing in ears). **Pregnancy/breast-feeding precautions:** Consult prescriber if you are pregnant. This drug should not be used in the 3rd trimester of pregnancy. Consult prescriber if you are breast-feeding.

Ophthalmic: For ophthalmic use only. Apply prescribed amount as often as directed. Wash hands before using. Tilt head back and look upward. Gently pull down lower lid and put drop(s) in inner corner of eye. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Close eye and roll eyeball in all directions. Do not blink for $^1/_2$minute. Apply gentle pressure to inner corner of eye for 30 seconds. Wipe away excess from skin around eye. Do not use any other eye preparation for at least 10 minutes. Do not share medication with anyone else. May cause sensitivity to bright light (dark glasses may help); temporary stinging or blurred vision may occur. Inform prescriber if you experience eye pain, redness, burning, watering, dryness, double vision, puffiness around eye, vision changes, other adverse eye response, worsening of condition, or lack of improvement.

Gel: This preparation is for topical use only. Treatment may take up to 3 months. Do not use more often than recommended; use at regular intervals. Wash hands before and after use. Follow directions on prescription label. Gently apply enough of the gel to cover the lesion. Advise prescriber if you are using any other skin preparations. Avoid direct sunlight and sunlamps while using this medication. You may experience dry skin, itching, peeling, swelling, or tingling at site of application. If severe skin reaction develops, stop applications and notify your prescriber at once.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Gel, as sodium:

    Solaraze®: 3% (50 g, 100 g)

    Voltaren® Gel: 1% (100 g)

Solution, ophthalmic, as sodium [drops]: 0.1% (2.5 mL, 5 mL)

    Voltaren Ophthalmic®: 0.1% (2.5 mL, 5 mL)

Tablet, as potassium: 50 mg

    Cataflam®: 50 mg

Tablet, delayed release, enteric coated, as sodium: 50 mg, 75 mg

    Voltaren®: 25 mg [DSC], 50 mg [DSC], 75 mg

Tablet, extended release, as sodium: 100 mg

    Voltaren®-XR: 100 mg

Transdermal system, topical, as epolamine:

    Flector®: 1.3% (30s) [180 mg]

Generic AvailableYes: Excludes gel, patch

Pricing: U.S. (www.drugstore.com)

Gel (Solaraze)

    3% (50): $205.80

    3% (100): $350.74

Gel (Voltaren)

1% (100): $32.99

Patch (Flector)

1.3% (30): $155.99

Solution (Voltaren)

0.1% (2.5): $49.11

0.1% (5): $76.99

Tablet, 24-hour (Diclofenac Sodium CR)

100 mg (30): $74.92

Tablet, 24-hour (Voltaren-XR)

100 mg (30): $175.43

Tablet, EC (Diclofenac Sodium)

25 mg (60): $42.38

50 mg (90): $35.99

75 mg (60): $26.99

Tablet, EC (Voltaren)

25 mg (60): $58.09

75 mg (60): $174.97

Tablets (Cataflam)

50 mg (100): $328.51

Tablets (Diclofenac Potassium)

50 mg (60): $39.99

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: Cataflam® is more rapid than sodium salt (Voltaren®) because it dissolves in the stomach instead of the duodenum

Absorption: Topical gel: 6% to 10%

Protein binding: 99% to albumin

Metabolism: Hepatic to several metabolites

Half-life elimination: 2 hours; Patch: ~12 hours

Time to peak, serum: Cataflam®: ~1 hour; Flector®: 10-20 hours; Solaraze® Gel: ~5 hours; Voltaren®: ~2 hours; Voltaren® Gel: 10-14 hours

Excretion: Urine (65%); feces (35%)

Related Information

- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness or dizziness; may rarely cause depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease the clearance of lithium resulting in elevated serum levels and potential toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A meta-analysis (Pope, 1993) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 chronic heart failure guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

Index TermsDiclofenac Epolamine; Diclofenac Potassium; Diclofenac Sodium

References

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International Brand NamesAbdiflam (ID); Abitren (IL); Acuflam (PH); Alflam (ID); Allvoran (DE); Almiral (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, HK, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Almiral Gel (SG); Almiral SR (HK, MY); Apo-Diclo (PL); Arcanafenac (ZA); Arthrifen (PH); Artren (CO, EC); Artrites (CO); Artrites Retard (CO); Berafen Gel (PY); Berifen (CR, DO, GT, HN, ID, NI, PA, SV); Berifen Gel (CR, DO, GT, HN, NI, PA, SV); Betaren (IL); Biofenak (PL); Cataflam (AE, BB, BE, BH, BM, BS, BZ, CN, CY, EG, GR, GY, HK, HN, ID, IL, IQ, IR, JM, JO, KW, LB, LY, MX, NL, OM, PE, PL, PT, QA, SA, SR, SY, TR, TT, TW, YE); Cataflam DD (EC); Cataflam Drops (MY); Cataflam Emulgel (BR, CN, VE); Cencenag (TH); Clofec (TH); Clonaren (PH); Cordralan (PE); Coyenpin (TW); Curinflam (AR, HK); Declophen (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Decrol (KP); Deflam-K (TW); Deflox (MX); Depain Plaster (KP); Diceus (TW); Diclac (PL); Diclax SR (NZ); Diclo (SG); Diclobene (AT); Dicloberl (PL); Diclobeta (AU); Diclobion (PL); Dicloced (FR); Diclodoc (DE); DicloDuo (PL); Diclofen (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, TW, YE); Diclofen Cremogel (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Diclofenac (CO, PL); Diclofenac Sodium E/C (PL); Diclofenac Stada (PL); Dicloflam (ZA); Diclohexal (AU); Diclomax (IN); Diclomol (TH); Diclon (DK); Diclophlogont (PL); Dicloran Gel (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Dicloratio (PL); Dicloren (TW); Dicloreum (PL); Diclosan SR (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Diclosian (TH); Diclowal (CR, DO, GT, HN, NI, PA, SV); Difadol (PL); Difen (TH); Difena (TW); Difenac (TH); Difengesic Gel (TH); Difenol Gel (HK); Difnal K (MY); Diklofen (PL); Diklonat P (PL); Dinac (TH); Dioxaflex (CO, CR, DO, GT, HN, NI, PA, SV); Divoltar (ID); Doflex (IN); Doloflam (PH); Dolotren (DO, GT, HN, NI, PA, SV, TW); Dolotren Gel (TW); Dosanac (TH); Dycon SR (PH); E (GR); Ecofenac (CH); Epifenac (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Eurofenac (HK); Feloran (PL); Fenac (AU); Fenadium (MY); Fenaspec (PH); Flameril (NZ); Flamquit (TW); Flankol (MX); Flector (FR); Flexagen (ZA); Flexy Gel (TH); Flogofenac (HK); Flogosin D (UY); Flogozan (CR, DO, GT, HN, NI, PA, SV); Fortfen SR (ZA); Imflac (AU); Inac (SG); Inac gel (SG); Inflamac (CH); Inflanac (HK, TH); Jonac Gel (IN); Kadiflam (ID); Klotaren (ID); Lesflam (SG); Lofenac (TH); Magluphen (AT); Majamil (PL); Majamil prolongatum (PL); Merflam (ID); Monoflam (CZ, DE); Myfenax (TH); N-Zen (MY); N-Zen Gel (TH); Nac Gel (IN); Naclof (HK, KP, PH, PL, TH, TW); Nadifen (ID); Naklofen (PL); Nepenthe (PH); Novo-Difenac (HK); Ofenac (KP); Olfen (HK, MY, PE, PL); Olfen Gel (SG); Olfen-75 SR (HK, MY); Optanac (ID, KP); Osteoflam (IN); Painstop (TW); Panamor (ZA); Physicare Gel (IL); Profenac (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ratiogel (PL); Relaxyl Gel (IN); Remethan (DE, MY, SG); Remethan Gel (TW); Ren (HK); Renvol Emulgel (ID); Rewodina (DE, MY, PL, RU); Rhewlin (SG); Rhewlin Forte (SG); Rhewlin SR (SG); Sefnac (TH); Sodinac (KP); Soproxen (TH); Staren (TW); Sting Gel (SG); Taks (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Toraren (KP); Uniclonax (PH); Uniren (SG); Vartelon (HK); Vartelon Gel (HK); Veral (PL); Vesconac (TH); Voldic (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Voldic Emulgel (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Volna-K (TW); Volta (TH); Voltadex Emulgel (ID); Voltaflam (PK); Voltalen (HK, NZ); Voltalen Emulgel (NZ); Voltareactigo (FR); Voltaren (AE, AR, AT, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CO, CY, CZ, DE, DK, EC, EE, EG, ES, ET, FI, GH, GM, GN, GY, HK, ID, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PH, PL, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Voltaren Acti-Go (IL); Voltaren Colirio (PY); Voltaren Dolo (FR); Voltaren Emulgel (AE, AU, BB, BH, BM, BR, BS, BZ, CH, CN, CO, CY, CZ, DE, EG, ES, FI, GR, GY, ID, IL, IQ, IR, JM, JO, KW, LB, LY, MY, NL, OM, PE, PH, PL, QA, SA, SR, SY, TR, TT, TW, YE); Voltaren Forte (PH); Voltaren K Migraine (DE); Voltaren Ofta (DE, IT); Voltaren Oftalmico (CO, UY, VE); Voltaren Ophtha (AT, AU, BE, CH, DK, HK, IL, KP, MY, NO, PH, SE, TH); Voltaren Rapid (AU); Voltaren Retard (CO); Voltaren SR (HK, NZ, PH, PL); Voltarene (FR, GR); Voltarene Emulgel (FR); Voltarol (GB, IE); Voltarol Emulgel (GB, IE); Voltarol Ophtha (IE); Voltenac (PL); Voltine (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Voltrix (BR); Voren (ID, PH, TW); Votalen (HK); Votalen SR (NZ); Votalin (CL); Votalin Emulgel (CL); Voveran (IN); Voveran Emulgel (IN); Vurdon (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Yuren (TW); Zolterol (MY); Zolterol SR (SG)

Dicloxacillin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(dye kloks a SIL in)
Canadian Brand NamesDycill®; Pathocil®
Pharmacologic CategoryAntibiotic, Penicillin
Use: Labeled IndicationsTreatment of systemic infections such as pneumonia, skin and soft tissue infections, and osteomyelitis caused by penicillinase-producing staphylococci
Use: DentalTreatment of susceptible orofacial infections (notably penicillinase-producing staphylococci)
Dosing: Adults

Susceptible infections: Oral: 125-500 mg every 6 hours

Erysipelas, furunculosis, mastitis, otitis externa, septic bursitis, skin abscess: Oral: 500 mg every 6 hours

Impetigo: 250 mg every 6 hours

Prosthetic joint (long-term suppression therapy): Oral: 250 mg twice daily

Staphylococcus aureus, **methicillin susceptible infection if no I.V. access:** Oral: 500-1000 mg every 6-8 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricUse in newborns is not recommended.

Susceptible infections: Oral:

Children <40 kg: 12.5-25 mg/kg/day divided every 6 hours; doses of 50-100 mg/kg/day in divided doses every 6 hours have been used for therapy of osteomyelitis

Children >40 kg: 125-250 mg every 6 hours

Furunculosis: Oral: 25-50 mg/kg/day divided every 6 hours

Osteomyelitis: Oral: 50-100 mg/kg/day in divided doses every 6 hours

Dosing: Renal Impairment

Dosage adjustment is not necessary.

Not dialyzable (0% to 5%); supplemental dose is not necessary.

Peritoneal dialysis effects: Supplemental dose is not necessary.

Continuous arteriovenous or venovenous hemofiltration: Supplemental dose is not necessary.

Administration: OralAdminister 1 hour before or 2 hours after meals. Administer around-the-clock to promote less variation in peak and trough serum levels.
Dietary ConsiderationsAdminister on an empty stomach 1 hour before or 2 hours after meals. Sodium content of 250 mg capsule: 13 mg (0.6 mEq).
ContraindicationsHypersensitivity to dicloxacillin, penicillin, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea and pseudomembranous colitis.

Concurrent drug therapy issues:

- Warfarin: Monitor PT if patient is concurrently on warfarin.

Special populations:

- Neonates: Use with caution in neonates; elimination of drug is slow.

Geriatric ConsiderationsNo dosage adjustment for renal function is necessary.
Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, dicloxacillin is classified as pregnancy category B. Dicloxacillin crosses the placenta. Teratogenic effects have not been reported with dicloxacillin, but adequate and well-controlled studies of dicloxacillin have not been completed in pregnant women. Other penicillins are considered safe for use in pregnancy.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if dicloxacillin crosses into human milk. The manufacturer recommends that caution be exercised when administering dicloxacillin to nursing women. Other penicillins distribute into human milk and are considered safe for use during breast-feeding. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Dicloxacillin in Pregnancy & Lactation

Adverse Reactions

1% to 10%: Gastrointestinal: Nausea, diarrhea, abdominal pain

<1%: Fever, seizure with extremely high doses and/or renal failure, rash (maculopapular to exfoliative), vomiting, pseudomembranous colitis, vaginitis, eosinophilia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, anemia, hemolytic anemia, prolonged PT, hepatotoxicity, transient elevated LFTs, hematuria, interstitial nephritis, increased BUN/creatinine, serum sickness-like reactions, hypersensitivity

Metabolism/Transport Effects**Induces** CYP3A4 (weak)

Drug Interactions

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Dicloxacillin may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Decreases drug absorption rate; decreases drug serum concentration.

Test InteractionsFalse-positive urine and serum proteins; false-positive in uric acid, urinary steroids; may interfere with urinary glucose tests using cupric sulfate (Benedict's solution, Clinitest®); may inactivate aminoglycosides *in vitro*

Monitoring ParametersMonitor prothrombin time if patient concurrently on warfarin; monitor for signs of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringAssess allergy history prior to beginning therapy. Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions on a regular basis throughout therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating therapy.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take medication as directed, with a large glass of water 1 hour before or 2 hours after meals. Take at regular intervals around-the-clock and take for length of time prescribed. If you have diabetes, drug may cause false test results with Clinitest® urine glucose monitoring; use of another type of glucose monitoring is preferable. May cause some gastric distress (small, frequent meals may help) and diarrhea (if this persists, consult prescriber). Report fever, vaginal itching, persistent diarrhea, sores in the mouth, loose foul-smelling stools, yellowing of skin or eyes, or change in color of urine or stool. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 250 mg, 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Dicloxacillin Sodium)

500 mg (30): $21.99

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: 35% to 76%; rate and extent reduced by food

Distribution: Throughout body with highest concentrations in kidney and liver; CSF penetration is low

Protein binding: 96%

Half-life elimination: 0.6-0.8 hour; slightly prolonged with renal impairment

Time to peak, serum: 0.5-2 hours

Excretion: Feces; urine (56% to 70% as unchanged drug); prolonged in neonates

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Prolonged use of penicillins may lead to development of oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusPenicillins have been reported to cause apprehension, illusions, agitation, insomnia, depersonalization, and encephalopathy

Mental Health: Effects on Psychiatric TreatmentRarely may cause agranulocytosis; use caution with clozapine and carbamazepine

Index TermsDicloxacillin Sodium

References

Donowitz GR and Mandell GL, “Beta-Lactam Antibiotics,” *N Engl J Med*, 1988, 318(7):419-26 and 318(8):490-500. [PubMed 3277054]

Pacifici GM, Viani A, Taddeucci-Brunelli G, et al, “Plasma Protein Binding of Dicloxacillin: Effects of Age and Diseases,” *Int J Clin Pharmacol Ther Toxicol*, 1987, 25(11):622-6. [PubMed 3429065]

Wright AJ, “The Penicillins,” *Mayo Clin Proc*, 1999, 74(3):290-307.[PubMed 10090000]

International Brand NamesBrispen (MX); Cloxydin (TH); Dacocilin (TW); Di-K-Cil (TH); Diamsalina (MX); Diclex (TH); Diclo (IT); Diclocil (AU, CO, DK, FI, GR, HK, NO, PT, SE, TH, VE); Diclox (TH); Dicloxapen (PY); Dicloxin (TH); Dicloxno (TH); Dicloxsig (AU); Diloxin (TH); Distaph (AU); Ditterolina (MX); Dixalin (EC); H.G. Dicloxacil (EC); Posipen (MX, PE); Ziefmycin (TW)

Dicyclomine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Dicyclomine may be confused with diphenhydrAMINE, doxycycline, dyclonine

Bentyl® may be confused with Aventyl®, Benadryl®, Bontril®, Cantil®, Proventil®, Trental®

Pronunciation(dye SYE kloe meen)
U.S. Brand NamesBentyl®
Canadian Brand NamesBentylol®; Formulex®; Lomine; Riva-Dicyclomine
Pharmacologic CategoryAnticholinergic Agent
Use: Labeled IndicationsTreatment of functional bowel/irritable bowel syndrome
Use: Unlabeled/InvestigationalUrinary incontinence
Dosing: AdultsGastrointestinal motility disorders/irritable bowel:

Oral: Initiate with 80 mg/day in 4 equally divided doses, then increase up to 160 mg/day

I.M. **(should not be used I.V.)**: 80 mg/day in 4 divided doses (20 mg/dose)

Dosing: Elderly10-20 mg 4 times/day; increasing as necessary to 160 mg/day
Administration: I.M.Administer solution for injection as I.M. injection only.
Administration: I.V.Do not administer I.V.
Administration: OralAdminister 30-60 minutes before a meal.
StorageProtect from light.
ContraindicationsHypersensitivity to dicyclomine or any component of the formulation; obstructive diseases of the GI tract; severe ulcerative colitis; reflux esophagitis; unstable cardiovascular status in acute hemorrhage; obstructive uropathy; narrow-angle glaucoma; myasthenia gravis; breast-feeding; should not be used in infants <6 months of age
Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause drowsiness and/or blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Diarrhea: May be a sign of incomplete intestinal obstruction, treatment should be discontinued if this occurs.
- Heat prostration: May occur in the presence of increased environmental temperature; use caution in hot weather and/or exercise.
- Psychosis: Has been reported in patients with an extreme sensitivity to anticholinergic effects or at excessive dosages.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease, tachyarrhythmias, heart failure, or hypertension; evaluate tachycardia prior to administration.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hiatal hernia: Use with caution in patients with hiatal hernia.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Neuropathy: Use with caution in patients with autonomic neuropathy.
- Prostatic hyperplasia: Use with caution in patients with prostatic hyperplasia (known or suspected).
- Renal impairment: Use with caution in patients with renal impairment.
- Ulcerative colitis: Use with caution in patients with mild-moderate ulcerative colitis.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for anticholinergic effects, confusion, and hallucinations.
- Pediatrics: Safety and efficacy have not been established in children. Serious respiratory reactions, central nervous symptoms, and deaths have been reported following administration to infants; use in infants <6 months of age is contraindicated).

Geriatric ConsiderationsLong-term use of antispasmodics should be avoided in the elderly. The potential for a toxic reaction is greater than the potential benefit. In addition, the anticholinergic effects of dicyclomine are not well tolerated in the elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects have not been observed in animal studies.

LactationEnters breast milk/contraindicated

Adverse ReactionsAdverse reactions are included here that have been reported for pharmacologically similar drugs with anticholinergic/antispasmodic action.

Cardiovascular: Palpitation, syncope, tachycardia

Central nervous system: Dizziness (29%), lightheadedness (11%), drowsiness (9%), tingling, headache, nervousness (6%), numbness, mental confusion and/or excitement, dyskinesia, lethargy, speech disturbance, insomnia

Dermatologic: Rash, urticaria, itching, and other dermal manifestations

Endocrine & metabolic: Suppression of lactation

Gastrointestinal: Xerostomia (33%), nausea (14%), vomiting, constipation, bloated feeling, abdominal pain, taste loss, anorexia

Genitourinary: Urinary hesitancy, urinary retention, impotence

Local: Irritation (injection), focal coagulation necrosis (injection)

Neuromuscular & skeletal: Weakness (7%)

Ocular: Blurred vision (27%), diplopia, mydriasis, cycloplegia, increased ocular tension

Respiratory: Dyspnea, apnea, asphyxia, nasal stuffiness or congestion, sneezing, throat congestion

Miscellaneous: Anaphylaxis, diaphoresis decreased, severe allergic reaction

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersPulse, anticholinergic effect, urinary output, GI symptoms

Nursing: Physical Assessment/MonitoringSee Contraindications and Warnings/Precautions for use cautions. Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (see Drug Interactions). Assess effectiveness of therapy and adverse response (see Adverse Reactions and Overdose/Toxicology - eg, anticholinergic response). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (see Patient Education). Breast-feeding is contraindicated.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber (especially antihistamines, sleeping aids, or antidepressants). Take as directed before meals; do not increase dose and do not discontinue without consulting prescriber. Avoid alcohol. Void before taking medication. This drug may impair mental alertness (use caution when driving or engaging in tasks that require alertness until response to drug is known); or constipation (increased exercise, fluids, fruit, or fiber may help). Report excessive and persistent anticholinergic effects (blurred vision, headache, flushing, tachycardia, nervousness, dizziness, insomnia, mental confusion or excitement, dry mouth, altered taste perception, dysphagia, palpitations, bradycardia, urinary hesitancy or retention, impotence, decreased sweating); change in color of urine or stools; or irritation or redness at injection site. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 10 mg

Bentyl®: 10 mg

Injection, solution, as hydrochloride: 10 mg/mL (2 mL)

Bentyl®: 10 mg/mL (2 mL)

Syrup, as hydrochloride:

Bentyl®: 10 mg/5 mL (480 mL)

Tablet, as hydrochloride: 20 mg

Bentyl®: 20 mg

Generic AvailableYes: Excludes syrup

Pricing: U.S. (www.drugstore.com)

Capsules (Bentyl)

10 mg (30): $14.99

Capsules (Dicyclomine HCl)

10 mg (30): $13.99

Tablets (Dicyclomine HCl)

20 mg (30): $11.99

Mechanism of ActionBlocks the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands and the CNS

Pharmacodynamics/Kinetics

Onset of action: 1-2 hours

Duration: ≤4 hours

Absorption: Oral: Well absorbed

Metabolism: Extensive

Half-life elimination: Initial: 1.8 hours; Terminal: 9-10 hours

Excretion: Urine (small amounts as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness, excitement, insomnia, confusion, drowsiness, dyskinesia

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation and dry mouth

Index TermsDicyclomine Hydrochloride; Dicycloverine Hydrochloride

References

Fick DM, Cooper JW, Wade WE, et al "Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults: Results of a U.S. Consensus Panel of Experts," *Arch Intern Med*, 2003, 163(22):2716-24.[PubMed 14662625]

International Brand NamesBabyspasmil (AR); Bentyl (BR, MX, PH, TW); Blisscolic (PK); Clomin (TH); Cyclominol (IN); Dicomin (TH); Dicymine (HK, TH); Dilomin (PH); Merbentyl (GB, NZ); Nomcramp (ZA); Notensyl (IL); Spasdon Drops (PH); Swityl (TW)

Didanosine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

FDA Early Communication: Increased Risk of Myocardial Infarction Observed - March 2008

The Food and Drug Administration (FDA) has issued an Early Communication to patients, caregivers, and healthcare professionals informing them of new evidence regarding the use of abacavir (Ziagen®) and didanosine (Videx®) and the risk of myocardial infarction (MI). Analysis from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study, an observational study aimed at investigating the adverse effects of certain nucleoside reverse transcriptase inhibitors (NRTI) involving over 33,000 patients, suggests that patients taking Ziagen® or Videx® appear to be at an increased risk for MI in comparison to other NRTIs. The risk of MI appears to be greatest with recent use (within 6 months) and in patients with existing risk factors for heart disease (eg, hypercholesterolemia, hypertension, diabetes, smoking, and age). In addition, the risk of MI appears to be reversible upon discontinuation of the offending agents. Patients taking didanosine (Videx®) may have up to a 49% increase in their risk of MI according to study results.

The FDA emphasizes that these are preliminary results of the D:A:D study and urges healthcare providers to weigh the potential risks and benefits of every treatment option until further results become available.

Additional information is available at http://www.fda.gov/cder/drug/early_comm/abacavir.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Videx® may be confused with Lidex®

Pronunciation(dye DAN oh seen)

U.S. Brand NamesVidex®; Videx® EC

Canadian Brand NamesVidex®; Videx® EC

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)

Use: Labeled IndicationsTreatment of HIV infection; always to be used in combination with at least two other antiretroviral agents

Dosing: Adults**Treatment of HIV infection:** Oral (administer on an empty stomach):
Dosing based on patient weight:

Pediatric powder for oral solution (Videx®):

<60 kg: 125 mg twice daily (preferred) or 250 mg once daily

≥60 kg: 200 mg twice daily (preferred) or 400 mg once daily

Delayed release capsule (Videx® EC):

25 kg to <60 kg: 250 mg once daily

≥60 kg; 400 mg once daily

When taken with tenofovir:

<60 kg and Cl_{cr} ≥60 mL/minute: 200 mg once daily

≥60 kg and Cl_{cr} ≥60 mL/minute: 250 mg once daily

Dosing: ElderlyRefer to adult dosing. Elderly patients have a higher frequency of pancreatitis (10% versus 5% in younger patients); monitor renal function and dose accordingly

Dosing: Pediatric**Treatment of HIV infection:** Oral (administer on an empty stomach):

Pediatric powder for oral solution (Videx®):

Infants 2 weeks to 8 months: 100 mg/m^2 twice daily is recommended by the manufacturer; 50 mg/m^2 may be considered in infants 2 weeks to 4 months (AIDSinfo guidelines)

Infants and Children >8 months: 120 mg/m^2 twice daily is recommended by the manufacturer. **Note:** AIDSinfo guidelines suggest a range of 90-150 mg/m^2 twice daily

Children 3-21 years (AIDSinfo guidelines): Treatment-naive: 240 mg/m^2/dose once daily (maximum: 400 mg/dose)

Delayed release capsule (Videx® EC):

20 kg to <25 kg: 200 mg once daily

25 kg to <60 kg: 250 mg once daily

≥60 kg: 400 mg once daily

Dosing: Renal ImpairmentChildren: No specific guidelines available; consider dosage reduction.Adults: Dosing based on patient weight, creatinine clearance, and dosage form: See table.

Recommended Dose (mg) of Didanosine by Body Weight – Adults

Creatinine Clearance (mL/min)	**≥60 kg**		**<60 kg**	
	Powder for Oral Solution	**Delayed Release Capsule**	**Powder for Oral Solution**	**Delayed Release Capsule**
≥60	400 mg daily or 200 mg twice daily	400 mg daily	250 mg daily or 125 mg twice daily	250 mg daily
30-59	200 mg daily or 100 mg twice daily	200 mg daily	150 mg daily or 75 mg twice daily	125 mg daily
10-29	150 mg daily	125 mg daily	100 mg daily	125 mg daily
<10	100 mg daily	125 mg daily	75 mg daily	See Note.
Note: Per manufacturer, not suitable for use in patients <60 kg with Cl_{cr} <10 mL/minute; use alternate formulation.				

Patients requiring hemodialysis or CAPD: Dose per Cl_{cr} <10 mL/minute. No didanosine removed via CAPD.

Hemodialysis: Minimal amount of dose (≤7%) removed by hemodialysis; no supplemental dosing necessary

Dosing: Hepatic ImpairmentShould be considered; monitor for toxicity.

Calculations

- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralPediatric powder for oral solution: Prior to dispensing, the powder should be mixed with purified water USP to an initial concentration of 20 mg/mL and then further diluted with an appropriate antacid suspension to a final mixture of 10 mg/mL. Shake well prior to use. Videx® EC: Administer on an empty stomach at least 1 hour before or 2 hours after eating; swallow capsule whole.

Dietary ConsiderationsVidex® EC: Take on an empty stomach; administer at least 1 hour before or 2 hours after eating

StorageDelayed release capsules should be stored in tightly closed bottles at controlled room temperature of 25°C (77°F). Unreconstituted powder should be stored at 15°C to 30°C (59°F to 86°F). Reconstituted pediatric solution is stable for 30 days if refrigerated.

ReconstitutionVidex® pediatric powder: Add 100 mL or 200 mL purified water, USP to the 2 g or 4 g container, respectively, to achieve a 20 mg/mL solution. Immediately mix the resulting solution with an equal volume of Mylanta® Maximum Strength (or equivalent) to achieve a final concentration of 10 mg/mL.

ContraindicationsThere are no contraindications listed in manufacturer's labeling.

Warnings/Precautions

Boxed warnings:

- Lactic acidosis/hepatomegaly: See "Concerns related to adverse effects" below.

- Pancreatitis: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).

- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.

- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).

- Ocular effects: Retinal changes (including retinal depigmentation) and optic neuritis have been reported in adults and children using didanosine; patients should undergo retinal examination every 6-12 months.

- Pancreatitis: **[U.S. Boxed Warning]: Pancreatitis (sometimes fatal) has been reported;** incidence is dose related. Risk factors for developing pancreatitis may include a previous history of the condition, concurrent cytomegalovirus or *Mycobacterium avium-intracellulare* infection, renal impairment, advanced age, and concomitant use of stavudine, pentamidine, or hydroxyurea; discontinue if clinical signs of pancreatitis occur.

- Peripheral neuropathy: Occurs in ~20% of patients receiving the drug; if symptomatic, discontinue therapy; after resolution of symptoms, reinitiation of therapy at a reduced dose may be tolerated. Permanently discontinue if neuropathy recurs.

Disease-related concerns:

- Heart failure/edema: Use with caution in patients with HF, edema and/or patients on sodium-restricted diets.

- Hepatic impairment: Use with caution in patients with hepatic impairment; safety and efficacy have not been established in patients with significant hepatic disease. Patients on combination antiretroviral therapy with hepatic impairment may be at increased risk of potentially severe and fatal hepatic toxicity; consider interruption or discontinuation of therapy if hepatic impairment worsens.

- Hyperuricemia: Use with caution in patients with hyperuricemia; asymptomatic hyperuricemia has occurred.

- Renal impairment: Use with caution in patients with renal impairment; dose reduction recommended for Cl_{cr} <60 mL/minute.

Concurrent drug therapy issues:

- Hydroxyurea and stavudine: Fatal cases of hepatotoxicity have been reported in HIV patients treated with didanosine in combination with hydroxyurea and stavudine; combination should be avoided.

Dosage form specific issues:

- Delayed release capsules: Didanosine delayed release capsules are indicated for once-daily use.

Geriatric ConsiderationsSince the elderly often have a creatinine clearance <60 mL/minute, monitor closely for adverse reactions and adjust dose accordingly to maintain efficacy (CD4 counts).

Pregnancy Risk FactorB

Pregnancy ConsiderationsCases of fatal and nonfatal lactic acidosis, with or without pancreatitis, have been reported in pregnant women. It is not known if pregnancy itself potentiates this known side effect; however, pregnant women may be at increased risk of lactic acidosis and liver damage. Hepatic enzymes and electrolytes should be monitored frequently during the 3rd trimester of pregnancy. Use during pregnancy only if the potential benefit to the mother outweighs the potential risk of this complication. Didanosine has been shown to cross the placenta. Preliminary information from the antiretroviral pregnancy registry note an increased risk of birth defects with 1st trimester exposure compared to exposure later in pregnancy; no pattern of defects have been noted. Pharmacokinetics are not significantly altered during pregnancy; dose adjustments are not needed. The Perinatal HIV Guidelines Working Group considers didanosine to be an alternative NRTI in dual nucleoside combination regimens; use with stavudine only if no other alternatives are available. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse ReactionsAs reported in monotherapy studies; risk of toxicity may increase when combined with other agents.

>10%:

Gastrointestinal: Diarrhea (19% to 28%), amylase increased (15% to 17%), abdominal pain (7% to 13%)

Neuromuscular & skeletal: Peripheral neuropathy (17% to 20%)

1% to 10%:

Dermatologic: Rash/pruritus (7% to 9%)

Endocrine & metabolic: Uric acid increased (2% to 3%)

Gastrointestinal: Pancreatitis (1% to 7% dose dependent); patients >65 years of age had a higher frequency of pancreatitis than younger patients

Hepatic: Alkaline phosphatase increased (1% to 4%), ALT increased (6% to 9%), AST increased (6% to 9%)

Postmarketing and/or reports: Acute renal impairment, alopecia, anaphylactoid reaction, anemia, anorexia, arthralgia, chills/fever, diabetes mellitus, dry eyes, dyspepsia, flatulence, granulocytopenia, hepatic steatosis, hepatitis, hyper-/hypoglycemia, hyperlactatemia (symptomatic), hypersensitivity, immune reconstitution syndrome, lactic acidosis/hepatomegaly, leukopenia, lipodystrophy, liver failure, MI, myalgia, myopathy, optic neuritis, pain, parotid gland enlargement, retinal depigmentation, rhabdomyolysis, seizure, sialoadenitis, thrombocytopenia, weakness, xerostomia

Drug Interactions

Allopurinol: May decrease the metabolism of Didanosine. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): Didanosine may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). Enteric coated didanosine capsules are not expected to affect these antifungals. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Atazanavir: Didanosine may decrease the absorption of Atazanavir. Only the buffered formulations of didanosine are of concern. Atazanavir may decrease the serum concentration of Didanosine. Reported with enteric coated didanosine capsules. *Risk D: Consider therapy modification*

Dapsone: Didanosine may decrease the absorption of Dapsone. Didanosine enteric coated capsules should not affect dapsone. *Risk D: Consider therapy modification*

Darunavir: May decrease the serum concentration of Didanosine. More specifically, this interaction is likely due to the effects of food (with which darunavir/ritonavir are taken) on didanosine, which is supposed to be given on an empty stomach. Management: Didanosine should be administered 1 hour prior to or 2 hours after administration of darunavir/ritonavir (which must be taken with food). *Risk D: Consider therapy modification*

Ganciclovir-Valganciclovir: May enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. *Risk D: Consider therapy modification*

Hydroxyurea: Didanosine may enhance the adverse/toxic effect of Hydroxyurea. An increased risk of pancreatitis, hepatotoxicity and/or neuropathy may exist. *Risk C: Monitor therapy*

Indinavir: Didanosine may decrease the serum concentration of Indinavir. Management: Indinavir should be administered on an empty stomach at least 1 hour apart from administration of buffer-containing formulations of didanosine. *Risk D: Consider therapy modification*

Lopinavir: May decrease the serum concentration of Didanosine. This interaction refers only to lopinavir/ritonavir oral solution, which must be taken with food, and is principally the result of a food-didanosine interaction. Management: Didanosine should be administered 1 hour prior to or 2 hours after administration of lopinavir/ritonavir oral solution (which must be taken with food). Didanosine and lopinavir/ritonavir tablets can be administered together. *Risk D: Consider therapy modification*

Methadone: May decrease the serum concentration of Didanosine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Didanosine may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents (excludes enteric coated formulation of didanosine). *Risk D: Consider therapy modification*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Stavudine: May enhance the adverse/toxic effect of Didanosine. Lactic acidosis (possibly fatal) is of particular concern. *Risk D: Consider therapy modification*

Tenofovir: May diminish the therapeutic effect of Didanosine. Tenofovir may increase the serum concentration of Didanosine. *Risk D: Consider therapy modification*

Tipranavir: May decrease the serum concentration of Didanosine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (increases risk of pancreatitis).

Food: Decreases AUC and C_{max}. Didanosine serum levels may be decreased by 55% if taken with food.

Monitoring ParametersSerum potassium, uric acid, creatinine; hemoglobin, CBC with neutrophil and platelet count, CD4 cells; viral load; liver function tests, amylase; weight gain; perform dilated retinal exam every 6 months

Nursing: Physical Assessment/MonitoringEvaluate risk factors for heart disease. Assess other pharmacological or herbal products patient may be taking for potential interactions; dosing adjustments may be necessary. A list of medications that should not be used is available in each bottle and patients should be provided with this information. Assess results of laboratory tests, effectiveness of therapy (decrease in infections and progress of disease, viral load and CD4 count) and adverse reactions (peripheral neuropathy, hepatotoxicity, optic neuritis) periodically during therapy. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions (including need for annual or semiannual retinal examinations), and adverse symptoms to report.

Monitoring: Lab TestsSerum potassium, uric acid, creatinine, hemoglobin, CBC with neutrophil, platelet count, CD4 cells, liver function, amylase; viral load

Patient EducationYou will be provided with a list of specific medications that should not be used during therapy; do not take any new prescription or over-the-counter medications, or herbal products during therapy (even if they are not on the list) without consulting prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. This drug is prescribed as one part of a multidrug combination; take exactly as directed for full course of therapy. Videx® EC: Take on an empty stomach; administer at least 1 hour before or 2 hours after eating. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. You may be susceptible to infection (avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber). Frequent blood tests may be required with prolonged therapy. You will need a retinal examination every 6 -12 months. May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help; consult prescriber if nausea or vomiting persists); diarrhea (boiled milk, yogurt or buttermilk may help); changes in body fat (increased in upper back, neck, breast and around trunk, decreased from legs, arms, and face). Seek immediate emergency care if you experience unusual chest pain, palpitations, erratic heart beat or if you suspect you are having a heart attack. Report immediately any loss of sensation, numbness, or tingling in fingers, toes, or feet; persistent unresolved abdominal distress (pain, nausea, vomiting, diarrhea); or signs of infection (burning on urination, perineal itching, white plaques in mouth, unhealed sores, persistent sore throat or cough).
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, delayed release, enteric coated pellets: 200 mg, 250 mg, 400 mg

Capsule, delayed release, enteric coated beadlets:

Videx® EC: 125 mg, 200 mg, 250 mg, 400 mg

Powder for oral solution, pediatric:

Videx®: 2 g, 4 g [makes 10 mg/mL solution after final mixing]

Generic AvailableYes: Delayed release capsule

Pricing: U.S. (www.drugstore.com)

Capsule, delayed release (Didanosine)

200 mg (30): $158.38

250 mg (30): $173.99

400 mg (30): $253.42

Capsule, delayed release (Videx EC)

250 mg (30): $230.99

400 mg (30): $347.97

Solution (reconstituted) (Videx)

2 g (100): $53.99

4 g (200): $105.98

Mechanism of ActionDidanosine, a purine nucleoside (adenosine) analog and the deamination product of dideoxyadenosine (ddA), inhibits HIV replication *in vitro* in both T cells and monocytes. Didanosine is converted within the cell to the mono-, di-, and triphosphates of ddA. These ddA triphosphates act as substrate and inhibitor of HIV reverse transcriptase substrate and inhibitor of HIV reverse transcriptase thereby blocking viral DNA synthesis and suppressing HIV replication.

Pharmacodynamics/Kinetics

Absorption: Subject to degradation by acidic pH of stomach; some formulations are buffered to resist acidic pH; ≤50% reduction in peak plasma concentration is observed in presence of food. Delayed release capsules contain enteric-coated beadlets which dissolve in the small intestine.

Distribution: V_d: Children: 28 L/m^2; Adults: 1.08 L/kg

Protein binding: <5%

Metabolism: Has not been evaluated in humans; studies conducted in dogs show extensive metabolism with allantoin, hypoxanthine, xanthine, and uric acid being the major metabolites found in urine

Bioavailability: Children: 25%; Adults: 42%

Half-life elimination:

Children and Adolescents: 0.8 hour

Adults: Normal renal function: 1.5 hours; active metabolite, ddATP, has an intracellular half-life >12 hours *in vitro*; Renal impairment: 2.5-5 hours

Time to peak: Delayed release capsules: 2 hours; Powder for suspension: 0.25-1.5 hours

Excretion: Urine (~55% as unchanged drug)

Clearance: Total body: Averages 800 mL/minute

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV

Pharmacotherapy PearlsA high rate of early virologic nonresponse was observed when didanosine, lamivudine, and tenofovir were used as the initial regimen in treatment-naive patients. Use of this combination is not recommended; patients currently on this regimen should be closely monitored for modification of therapy. Early virologic failure was also observed with tenofovir and didanosine delayed release capsules, plus either efavirenz or nevirapine; use caution in treatment-naive patients with high baseline viral loads.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusAnxiety; irritability and insomnia are common; may produce depression

Mental Health: Effects on Psychiatric TreatmentMay cause granulocytopenia; use caution with clozapine and carbamazepine

Index TermsddI; Dideoxyinosine

References

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International Brand NamesBandotan (AR); Bristol-Videx EC (CO); Cipladinex 100 (CO); Didasten (MX); Didax (BR); Dinex (IN); Vidanovir (HN); Viden DDI (CO); Videx (AT, AU, BE, BG, BR, CH, CL, CN, CZ, DE, DK, EG, ES, FI, FR, GB, GR, HN, ID, IE, IT, MY, NL, NO, PE, PL, PT, RU, SE, TR, TW, UY, VE, ZA); Videx EC (BG, CH, EC, EE, FI, HK, IE, MX, MY, NO, NZ, SE, SG, TH, TW); Videx EC SR (KP); Videx Pediatric (HK)

Diethylene Triamine Penta-Acetic Acid

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Jump To Field (Select Field Name)

Pronunciation(dye ETH i leen TRYE a meen PEN ta a SEE tik AS id)

Pharmacologic CategoryAntidote

Use: Labeled IndicationsTreatment of known or suspected internal contamination with plutonium, americium, or curium

Dosing: AdultsInternal contamination with plutonium, americium, or curium: Ca-DTPA is the preferred initial agent; sequential administration of Ca-DTPA then Zn-DTPA is recommended. I.V.:

Initial: Ca-DTPA: 1 g/day

Pregnancy: Zn-DTPA 1 g/day should be used for the initial dose in pregnant women **except** in cases of high internal contamination,

Maintenance: Zn-DTPA: 1 g/day; length of therapy depends on patient response and degree of contamination. **Note:** An equivalent dose of Ca-DTPA should be used for maintenance therapy only if Zn-DTPA is not available.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricInternal contamination with plutonium, americium, or curium: Ca-DTPA is the preferred initial agent; sequential administration of Ca-DTPA then Zn-DTPA is recommended. I.V.:

Children <12 years:

Initial: Ca-DTPA: 14 mg/kg/day (maximum dose: 1 g/day)

Maintenance: Zn-DTPA: 14 mg/kg/day (maximum: 1 g/day); length of therapy depends on patient response and degree of contamination. **Note:** An equivalent dose of Ca-DTPA should be used for maintenance therapy only if Zn-DTPA is not available.

Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentDose adjustment not needed. Dialysis may be used to increase rate of elimination after the initial dose. If Ca-DTPA is not available, substitute Zn-DTPA as initial therapy.

Administration: I.V.Dose should be administered once daily.

Infusion: Administer over 30 minutes.

I.V. push: Administer over 3-4 minutes.

Administration: I.V. DetailpH: Ca-DTPA: 7.3-8.3; Zn-DTPA: 6.5-7.5

Administration: InhalationNebulization: Dose should be administered once daily. Patients should be instructed not to swallow any expectorant.

Dietary ConsiderationsFluids should be consumed liberally to promote dilution and excretion of radioactive chelate and minimize radiation exposure to bladder. Supplemental zinc or other vitamins and minerals may be needed.

StorageCa-DTPA, Zn-DTPA: Store between 15°C to 30°C (59°F to 86°F).

ReconstitutionCa-DTPA, Zn-DTPA:

I.V. infusion: Dilute 1 g into 100-250 mL D_5W, NS, or LR.

Nebulization: Dilute to a 1:1 ratio with SWFI or NS.

Warnings/Precautions

Special populations:

- Pediatrics: Safety and efficacy for use by nebulization have not been established in children.

Dosage form specific issues:

- Calcium DTPA (Ca-DTPA): Use is associated with depletion of endogenous trace metals (zinc, magnesium, manganese). Amount of depletion is dependent upon length of therapy; supplements should be provided. The initial treatment dose should be with Ca-DTPA; if additional doses are needed, zinc-DTPA should be used if available due to safety concerns. Use caution with severe hemochromatosis.

- Zinc DTPA (Zn-DTPA): Long-term use may be associated with depletion of magnesium and manganese; supplements should be provided.

Other warnings/precautions:

- Administration: For I.V. administration. May be administered by nebulization in adults whose contamination is only by inhalation within the last 24 hours. When administered by nebulization, use caution with asthma.

- Appropriate use: Treatment is most effective if begun within 24 hours but should be started as soon as available. Treatment with diethylene triamine penta-acetic acid (DTPA) is not effective for uranium, neptunium, or iodine exposure. Appropriate safety measures should be taken to minimize contamination of others.

Pregnancy Risk FactorC (Ca-DTPA)/B (Zn-DTPA)

Pregnancy ConsiderationsTeratogenic effects have been reported with Ca-DTPA in animal studies. Multiple doses during pregnancy may increase adverse effects to the fetus due to zinc depletion. Reproduction studies with Zn-DTPA did not show teratogenic effects in animals; there are no well-controlled studies in pregnant women. Except in cases of high internal contamination, treatment should be initiated and maintained with Zn-DTPA during pregnancy.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsRadiocontaminants such as plutonium, americium, or curium can be found in breast milk; excretion of Ca-DTPA or Zn-DTPA is unknown. Women suspected of internal contamination, regardless of treatment, should not breast feed and precautions should be taken when discarding breast milk.

Adverse ReactionsFrequency not defined.

Cardiovascular: Chest pain

Central nervous system: Headache, lightheadedness

Dermatologic: Dermatitis

Gastrointestinal: Diarrhea, metallic taste, nausea

Local: Injection site reactions

Neuromuscular & skeletal: Pelvic pain

Respiratory: Cough and/or wheezing (using Ca-DTPA following nebulization in patients with asthma)

Miscellaneous: Allergic reaction, magnesium depletion, manganese depletion, metalloproteinases, zinc depletion

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersCBC with differential, BUN, urinalysis, blood and urine radioassays (baseline and throughout therapy); blood, urine, and fecal radioactivity (weekly); serum zinc levels should also be monitored with Ca-DTPA

Nursing: Physical Assessment/MonitoringAssess other prescription and OTC medications the patient may be taking. Monitor laboratory tests. Instruct patient in appropriate measures to use to discard of body fluids and feces. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Monitoring: Lab TestsCBC with differential, BUN, urinalysis, blood and urine radioassays (baseline and throughout therapy); blood, urine, and fecal radioactivity (weekly); serum zinc levels should also be monitored with Ca-DTPA

Patient EducationRadioactive metals are known to be excreted in the urine, feces, and breast milk. When possible, use toilet instead of urinal, and flush several times after each use. Spilled urine or feces should be cleaned up immediately. Wash hands thoroughly. If blood or urine comes in contact with clothing or linens, wash separately. If coughing productively, dispose of expectorant carefully and avoiding swallowing if possible. It is important to maintain liberal fluid intake (at least 2-3 L/day) unless instructed to restrict intake by prescriber. You may experience headache, lightheadedness, dermatitis, metallic taste, nausea, and diarrhea. Report chest pain, any allergic reactions, coughing and/or wheezing. **Pregnancy/breast-feeding precaution:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended. Use precautions when disposing of breast milk.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Ca-DTPA: 200 mg/mL (5 mL)

Zn-DTPA: 200 mg/mL (5 mL)

Generic AvailableNo

ManufacturerHameln Pharmaceuticals

Mechanism of ActionCa-DTPA and Zn-DTPA form chelates with metal ions. The radioactive chelates are then excreted in the urine. Treatment is most effective when radiocontaminants are in circulation or interstitial fluids. Radiocontaminants eventually sequester in liver and bone, therefore, effectiveness of treatment decreases with time after exposure.

Pharmacodynamics/Kinetics

Absorption:

Ca-DTPA: Oral: Poor (~5%); Inhalation: 20%

Zn-DTPA: Oral: Poor (~5%)

Distribution: Ca-DTPA, Zn-DTPA: Distributed throughout extracellular fluid; not found to accumulate in organs

Metabolism: Ca-DTPA, Zn-DTPA: Minimal

Half-life elimination: Ca-DTPA, Zn-DTPA: May be increased by renal impairment

Excretion: Ca-DTPA, Zn-DTPA: Urine; Rate of excretion may be decreased by renal impairment Ca-DTPA provides a 10-fold higher rate of elimination than Zn-DTPA within the first 24 hours; after 24 hours rate of radioactivity elimination is comparable.

Pharmacotherapy PearlsThe manufacturer provides a Patient Data Form that should be completed for all patients receiving treatment. Information collected will be used to develop long-term response data and information concerning risk of late malignancy development. Procedures for proper collection and disposal of radioactive body fluids (sputum, urine) and dialysis fluid should be followed.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Metallic taste

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness

Mental Health: Effects on Psychiatric Treatment May cause magnesium depletion; use caution with ziprasidone as magnesium depletion may predispose patient to torsade de pointes.

Index Terms Ca-DTPA; Diethylenetriamine Pentaacetic Acid; DTPA; Pentetate Calcium Trisodium; Pentetate Zinc Trisodium; Trisodium Calcium Diethylenetriaminepentaacetate (Ca-DTPA); Zinc Diethylenetriaminepentaacetate (Zn-DTPA); Zn-DTPA

Diethylpropion

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(dye eth il PROE pee on)

Canadian Brand NamesTenuate®; Tenuate® Dospan®

Pharmacologic CategoryAnorexiant; Sympathomimetic

Use: Labeled IndicationsShort-term (few weeks) adjunct in the management of exogenous obesity

Dosing: AdultsObesity (short-term adjunct): Oral:

Tablet: 25 mg 3 times/day before meals or food

Tablet, controlled release: 75 mg at midmorning

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren >16 years: Refer to adult dosing.

Calculations

- Body Mass Index

Administration: OralDose should not be administered in evening or at bedtime.

Tablet: Administer 1 hour before meals.

Tablet, controlled release: Do not crush tablet; administer at midmorning.

Dietary ConsiderationsMost effective when combined with a low calorie diet and behavior modification counseling.

StorageStore at room temperature, below 30°C (86°F).

RestrictionsC-IV

Pharmacotherapy for weight loss is recommended only for obese patients with a body mass index ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of other risk factors such as hypertension, diabetes, and/or dyslipidemia or a high waist circumference; therapy should be used in conjunction with a comprehensive weight management program. Rule out organic causes of obesity (eg, untreated hypothyroidism) prior to use.

Note: Diethylpropion is not approved for long-term use. The limited usefulness of medications in this class should be weighed against possible risks associated with their use. Consult weight loss guidelines for current pharmacotherapy recommendations.

ContraindicationsHypersensitivity or idiosyncrasy to diethylpropion or other sympathomimetic amines; advanced arteriosclerosis, severe hypertension; pulmonary hypertension; hyperthyroidism; glaucoma; agitated states, history of drug abuse; during or within 14 days following MAO inhibitor therapy, concurrent use with other anorectic agents

Allergy Considerations

- Amphetamine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Amphetamines may impair the ability to engage in potentially hazardous activities.
- Primary pulmonary hypertension (PPH): A rare, frequently fatal disease of the lungs, PPH has been found to occur with increased frequency in patients receiving some anorexigens.
- Valvular heart disease: The use of some anorexigens, including diethylpropion, has been associated with the development of valvular heart disease. Avoid stimulants in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that could increase the risk of sudden death that these conditions alone carry.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; antidiabetic agent requirements may be altered with anorexigens and concomitant dietary restrictions.
- Hypertension: Use with caution in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases in blood pressure or heart rate.
- Seizure disorders: Use with caution in patients with a history of seizure disorders; seizures have been reported with use.
- Tourette's syndrome: Use with caution in patients with Tourette's syndrome; stimulants may unmask tics.

Concurrent drug therapy issues:

- Anorexigens: Safety and efficacy have not been established for use with other weight loss medications, including over-the-counter or herbal products. Not recommended for use in patients who have used other anorectic agents within the past year.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children ≤16 years of age.

Other warnings/precautions:

- Abuse potential: Diethylpropion is pharmacologically related to the amphetamines, which have a high abuse potential; prolonged use may lead to dependency. Prescriptions should be written for the smallest quantity consistent with good patient care to minimize possibility of overdose.

- Discontinuation of therapy: Discontinue if satisfactory weight loss has not occurred within the first 4 weeks of treatment, or if tolerance develops.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects have not been observed in animal studies. Crosses the human placenta; spontaneous reports of congenital malformations have been reported, but an association with diethylpropion has not been established. Withdrawal symptoms may occur in the neonate following maternal use of diethylpropion.

LactationEnters breast milk/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, ECG changes, hypertension, palpitation, precordial pain, pulmonary hypertension, tachycardia, valvulopathy

Central nervous system: Anxiety, CVA, depression, dizziness, drowsiness, dysphoria, euphoria, headache, insomnia, jitteriness, malaise, nervousness, overstimulation, psychosis, restlessness, seizure

Dermatologic: Alopecia, ecchymosis, erythema, rash, urticaria

Endocrine & metabolic: Libido changes, gynecomastia, menstrual irregularities

Gastrointestinal: Abdominal discomfort, constipation, diarrhea, nausea, unpleasant taste, vomiting, xerostomia

Genitourinary: Dysuria, impotence, polyuria

Hematologic: Bone marrow depression, agranulocytosis, leukopenia

Neuromuscular & skeletal: Dyskinesia, muscle pain, tremor

Ocular: Blurred vision, mydriasis

Respiratory: Dyspnea

Miscellaneous: Diaphoresis, tachyphylaxis

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersBaseline cardiac evaluation (for preexisting valvular heart disease, pulmonary hypertension); echocardiogram during therapy; weight, waist circumference, blood pressure; renal function in elderly patients

Reference Range

Adult classification of weight by BMI (kg/m^2):

Underweight: <18.5

Normal: 18.5-24.9

Overweight: 25-29.9

Obese, class I: 30-34.9

Obese, class II: 35-39.9

Extreme obesity (class III): ≥40

Waist circumference: In adults with a BMI of 25-34.9 kg/m^2, high-risk waist circumference is defined as:

Men >102 cm (>40 in)

Women >88 cm (>35 in)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess for history of psychopathology, homicidal or suicidal tendencies, or addiction; long-term use can result in dependence, abuse, or tolerance. Periodically evaluate the need for continued use. Monitor therapeutic effectiveness, vital signs, and adverse reactions at start of therapy, when changing dosage, and at regular intervals during therapy. Monitor serum glucose closely in patients with diabetes (amphetamines may alter antidiabetic requirements). Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, possible side effects, and symptoms to report.

Patient EducationTake exactly as directed; do not increase dose or frequency without consulting prescriber. Drug may cause physical and/or psychological dependence. Do not crush or chew extended release tablets. Take early in day to avoid sleep disturbance, 1 hour before meals. Avoid alcohol, caffeine, or OTC medications that act as stimulants. You may experience restlessness, false sense of euphoria, or impaired judgment (use caution when driving or engaging in tasks requiring alertness until response to drug is known); dry mouth (frequent mouth care, sucking lozenges, or chewing gum may help); nausea or vomiting (small frequent meals, frequent mouth care may help); constipation (increased exercise, fluids, fruit, or fiber may help); or diarrhea (buttermilk, boiled milk, or yogurt may help); or altered libido (reversible). Patients with diabetes need to monitor serum glucose closely (may alter antidiabetic medication requirements). Report chest pain, palpitations, or irregular heartbeat; muscle weakness or tremors; extreme fatigue or depression; CNS changes (aggressiveness, restlessness, euphoria, sleep disturbances); severe unremitting abdominal distress or cramping; changes in sexual activity; changes in urinary pattern; or blurred vision. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 25 mg

Tablet, controlled release, as hydrochloride: 75 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Diethylpropion HCl CR)

75 mg (30): $29.99

Tablets (Diethylpropion HCl)

25 mg (90): $25.99

Tablets (Tenuate)

25 mg (90): $59.99

Mechanism of ActionDiethylpropion s a sympathomimetic amine with pharmacologic properties similar to the amphetamines. It is also structurally similar to bupropion. The mechanism of action in reducing appetite appears to be secondary to CNS effects, including stimulation of the hypothalamus to release norepinephrine

Pharmacodynamics/Kinetics

Metabolism: Forms active metabolites via N-dealkylation and reduction

Half-life elimination: Aminoketone metabolites: ~4-6 hours

Excretion: Urine

Related Information

- Obesity Treatment Guidelines for Adults

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), and metallic taste (the use of local anesthetic without vasoconstrictor is recommended in these patients).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse vasoconstrictor with caution in patients taking diethylpropion. Amphetamine-like drugs such as diethylpropion enhance the sympathomimetic response of epinephrine and norepinephrine leading to potential hypertension and cardiotoxicity.

Mental Health: Effects on Mental StatusInsomnia, nervousness, and euphoria are common; may cause confusion, depression, or psychosis

Mental Health: Effects on Psychiatric TreatmentConcurrent use with MAO inhibitors may cause hypertensive crisis; avoid combination; antipsychotics may blunt effect of diethylpropion. May cause bone marrow depression; use caution with clozapine.

Index TermsAmfepramone; Diethylpropion Hydrochloride

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International Brand NamesAnorex (FR); Apisate (IE); Atractil (LU); Bonumin (FI); Delgamer (ES); Dietil Retard (BE); Dietil-retard (LU); Dipion (KP); Dobesin (DK); Linea (GR, IT); Lipomin (ES); Moderatan (FR); Neobes (CR, DO, GT, HN, PA, SV); Nulobes (AR); Prefamone (CH, FR, LU);

Prefamone Chronule (BE); Prothin (HK); Regenon (AT, BE, LU); Regenon Reard (DE); Sacin (CN); Tenuate (AU, FR); Tenuate Dospan (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, NZ, OM, PE, QA, SA, SY, YE); Wellpion (KP)

Difenoxin and Atropine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(dye fen OKS in & A troe peen)
U.S. Brand NamesMotofen® [DSC]
Pharmacologic CategoryAntidiarrheal
Use: Labeled IndicationsTreatment of diarrhea
Dosing: AdultsDiarrhea: Oral: Initial: 2 tablets (each tablet contains difenoxin hydrochloride 1 mg and atropine sulfate 0.025 mg), then 1 tablet after each loose stool; 1 tablet every 3-4 hours, up to 8 tablets in a 24-hour period; if no improvement after 48 hours, continued administration is not indicated
Dosing: ElderlyRefer to adult dosing; use with caution.
StorageStore at room temperature 15°C to 30°C (59°C to 86°C).
RestrictionsC-IV
ContraindicationsHypersensitivity to difenoxin, atropine, or any component of the formulation; severe liver disease; jaundice; dehydrated patient; angle-closure glaucoma; children <2 years of age; diarrhea associated with organisms that penetrate the intestinal mucosa (toxigenic *E. coli*, *Salmonella* sp, *Shigella*), and pseudomembranous colitis associated with broad spectrum antibiotics
Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Dehydration/electrolyte imbalance: In case of severe dehydration or electrolyte imbalance, withhold difenoxin/atropine treatment until corrective therapy has been initiated. Use in conjunction with fluid and electrolyte therapy when appropriate. Inhibiting peristalsis may lead to fluid retention in the intestine aggravating dehydration and electrolyte imbalance.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

- Ulcerative colitis: Use with caution in patients with acute ulcerative colitis; may induce toxic megacolon. Discontinue promptly with abdominal distention.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age; contraindicated in children <2 years of age.

Other warnings/precautions:

- Dosage recommendations: Strictly adhere to dosage recommendations.

Pregnancy Risk FactorC
LactationEnters breast milk/contraindicated
Breast-Feeding ConsiderationsPotential for serious adverse reactions in nursing infants.
Adverse Reactions1% to 10%:

Central nervous system: Dizziness, drowsiness, lightheadedness, headache

Gastrointestinal: Nausea, vomiting, xerostomia, epigastric distress

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy*

modification

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Nursing: Physical Assessment/MonitoringSee individual agent for Atropine.
Patient EducationSee individual agent for Atropine.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, oral:

Motofen®: Difenoxin hydrochloride 1 mg and atropine sulfate 0.025 mg [DSC]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Motofen)

1-0.025 mg (15): $16.46

Pharmacodynamics/Kinetics

Absorption: Rapid and well absorbed

Metabolism: To inactive hydroxylated metabolite

Time to peak, plasma: Within 40-60 minutes

Excretion: Urine and feces (primarily as conjugates)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation)
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness; confusion
Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropic may cause additive sedation or dry mouth
Index TermsAtropine and Difenoxin

Diflorasone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

International issues:

Florone® may be confused with Fluoron® which is a brand name for fluorine in Canada

Florone® may be confused with Flogene® which is a brand name for fentiazac in Italy and a brand name for piroxicam in Brazil

Pronunciation(dye FLOR a sone)
U.S. Brand NamesApexiCon™; ApexiCon™ E
Pharmacologic CategoryCorticosteroid, Topical
Use: Labeled IndicationsRelieves inflammation and pruritic symptoms of corticosteroid-responsive dermatosis (high to very high potency topical corticosteroid)
Dosing: AdultsCorticosteroid-responsive dermatosis: Topical: Apply ointment sparingly 1-3 times/day; apply cream sparingly 2-4 times/day. Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.
Dosing: ElderlyRefer to adult dosing.
ContraindicationsHypersensitivity to diflorasone
Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC
Adverse Reactions<1%: Arthralgia, burning, dryness, folliculitis, itching, maceration, muscle atrophy, secondary infection
Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Patient EducationA thin film of cream or ointment is effective; do not overuse. Do not use tight-fitting diapers or plastic pants on children being treated in the diaper area. Use only as prescribed, and for no longer than the period prescribed. Apply sparingly in light film. Rub in lightly. Avoid contact with eyes. Notify prescriber if condition being treated persists or worsens. **Pregnancy precaution:** Inform prescriber if you are pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, as diacetate: 0.05% (15 g, 30 g, 60 g)

ApexiCon™ E: 0.05% (30 g, 60 g)

Ointment, as diacetate: 0.05% (15 g, 30 g, 60 g)

ApexiCon™: 0.05% (30 g, 60 g)

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Cream (ApexiCon E)

0.05% (60): $89.87

Cream (Diflorasone Diacetate)

0.05% (15): $27.99

0.05% (30): $37.99

0.05% (60): $67.99

Ointment (Diflorasone Diacetate)

0.05% (15): $30.99

0.05% (30): $37.99

0.05% (60): $67.99

Mechanism of ActionDecreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability

Pharmacodynamics/Kinetics

Absorption: Negligible, around 1% reaches dermal layers or systemic circulation; occlusive dressings increase absorption percutaneously

Metabolism: Primarily hepatic

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDiflorasone Diacetate

References

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

International Brand NamesFlorone (DE); Taesun Cream (KP)

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Dolobid® (discontinued U.S. brand name [generics available]) may be confused with Slo-Bid®

International issues: Dolobid® (brand name product available in multiple international markets) may be confused with Slo-Bid®

Pronunciation(dye FLOO ni sal)

Canadian Brand NamesApo-Diflunisal®; Novo-Diflunisal; Nu-Diflunisal

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsManagement of inflammatory disorders usually including rheumatoid arthritis and osteoarthritis; can be used as an analgesic for treatment of mild-to-moderate pain

Use: DentalTreatment of postoperative pain

Dosing: Adults

Mild-to-moderate pain: Oral: Initial: 500-1000 mg followed by 250-500 mg every 8-12 hours; maximum daily dose: 1.5 g

Arthritis: Oral: 500-1000 mg/day in 2 divided doses; maximum daily dose: 1.5 g

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Use with caution; Cl_{cr} <50 mL/minute: Administer 50% of normal dose (Aronoff, 1998)

Hemodialysis: No supplement required

CAPD: No supplement require

CAVH: Dose for GFR 10-50

Calculations

- Creatinine Clearance: Adults

Administration: OralTablet should be swallowed whole; do not crush or chew.

Dietary ConsiderationsShould be taken with food to decrease GI distress.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to diflunisal, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy

should be monitored for anemia.

- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin's cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.

- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Hypersensitivity syndrome: A hypersensitivity syndrome has been reported; monitor for constitutional symptoms and cutaneous findings; other organ dysfunction may be involved.

- Reye's syndrome: Diflunisal is a derivative of acetylsalicylic acid and therefore may be associated with Reye's syndrome.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsThe elderly are a high-risk population for adverse effects from nonsteroidal anti-inflammatory agents. As much as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC (1st and 2nd trimesters)/D (3rd trimester)

Pregnancy ConsiderationsTeratogenic effects have been documented in animal studies. However, known effects of NSAIDs suggest the potential for premature ductus arteriosus closure, particularly in late pregnancy. There are no adequate and well-controlled studies in pregnant women.

LactationEnters breast milk/not recommended

Adverse Reactions

1% to 10%:

Central nervous system: Headache (3% to 9%), dizziness (1% to 3%), insomnia (1% to 3%), somnolence (1% to 3%), fatigue (1% to 3%)

Dermatologic: Rash (3% to 9%)

Gastrointestinal: Nausea (3% to 9%), dyspepsia (3% to 9%), GI pain (3% to 9%), diarrhea (3% to 9%), constipation (1% to 3%), flatulence (1% to 3%), vomiting (1% to 3%), GI ulceration

Otic: Tinnitus (1% to 3%)

<1%: Acute anaphylactic reaction, agranulocytosis, allergic reactions, angioedema, anorexia, blurred vision, bronchospasm, confusion, chest pain, cholestasis, cystitis, depression, diaphoresis, disorientation, dry mucous membranes, dyspnea, dysuria, edema, eructation, erythema multiforme, esophagitis, exfoliative dermatitis, flushing, gastritis, GI bleeding, GI perforation, hallucinations, hearing decreased, hearing loss, hematuria, hemolytic anemia, hepatitis, hypersensitivity syndrome, hypersensitivity vasculitis, interstitial nephritis, itching, jaundice, mental depression, muscle cramps, necrotizing fasciitis, nephrotic syndrome, nervousness, palpitation,

paresthesia, peptic ulcer, peripheral neuropathy, photosensitivity, proteinuria, pruritus, renal impairment, renal failure, seizure, Stevens-Johnson syndrome, stomatitis, syncope, tachycardia, thrombocytopenia, toxic epidermal necrolysis, trembling, urticaria, vasculitis, vertigo, weakness, wheezing

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Test InteractionsFalsely elevated increase in serum salicylate levels

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. **Assess patient for allergic reaction to salicylates or other NSAIDs.** Assess other medications patient may be taking for additive or adverse interactions. Monitor blood pressure at the beginning of therapy and periodically during use. Monitor therapeutic effectiveness and signs of adverse reactions or overdose at beginning of therapy and periodically during long-term therapy. Schedule ophthalmic evaluations for patients who develop eye complaints during long-term NSAID therapy. Assess knowledge/teach patient appropriate use, appropriate interventions to reduce side effects, and adverse reactions to report.

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Adverse reactions can occur with overuse. Consult your prescriber before use if you have hypertension or heart failure. Do not take longer than 3 days for fever, or 10 days for pain without consulting medical advisor. Take with food or milk. While using this medication, do not use alcohol, excessive amounts of vitamin C, or salicylate-containing foods (curry powder, prunes, raisins, tea, or licorice), other prescription or OTC medications containing aspirin or salicylate, or other NSAIDs without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience nausea, vomiting, gastric discomfort (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help). GI bleeding, ulceration, or perforation can occur with or without pain. Stop taking medication and report ringing in ears; persistent stomach pain; unresolved nausea or vomiting; respiratory difficulty or shortness of breath; unusual bruising or bleeding (mouth, urine, stool); skin rash; flu-like symptoms; unexplained weight gain; unusual swelling of extremities; chest pain; or palpitations. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Diflunisal)

500 mg (60): $59.99

Tablets (Dolobid)

500 mg (60): $84.98

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has analgesic and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: Analgesic: ~1 hour; maximal effect: 2-3 hours

Duration: 8-12 hours

Absorption: Well absorbed

Protein binding: >99%

Distribution: Enters breast milk

Metabolism: Extensively hepatic; metabolic pathways are saturable

Half-life elimination: 8-12 hours; prolonged with renal impairment

Time to peak, serum: 2-3 hours

Excretion: Urine (~3% as unchanged drug, 90% as glucuronide conjugates) within 72-96 hours

Related Information

- Nonsteroidal Anti-inflammatory Agents

Pharmacotherapy PearlsDiflunisal is a salicylic acid derivative which is chemically different than aspirin and is not metabolized to salicylic acid. It is not considered a salicylate. Diflunisal 500 mg is equal in analgesic efficacy to aspirin 650 mg, acetaminophen 650 mg, and acetaminophen 650 mg/propoxyphene napsylate 100 mg, but has a longer duration of effect (8-12 hours). Not recommended as an antipyretic. Not found to be clinically useful to treat fever; at doses ≥2 g/day, platelets are reversibly inhibited in function. Diflunisal is uricosuric at 500-750 mg/day; causes less GI and renal toxicity than aspirin and other NSAIDs; fecal blood loss is $^{1}/_{2}$ that of aspirin at 2.6 g/day.

Dental Health Professional ConsiderationsThe advantage of diflunisal as a pain reliever is its 12-hour duration of effect. In many cases, this long effect will ensure a full night sleep during the postoperative pain period.

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®). See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness; rarely may cause insomnia, nervousness, depression, and hallucinations

Mental Health: Effects on Psychiatric Treatment May rarely cause may agranulocytosis; use caution with clozapine and carbamazepine; may decrease the clearance of lithium resulting in elevated serum levels and potential toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A recent meta-analysis (see References) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 chronic heart failure guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents including ibuprofen and naproxen may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin’s inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other Considerations The 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

Diflunisal is a salicylic acid derivative which is chemically different than aspirin and is not metabolized to salicylic acid. Diflunisal 500 mg is equal in analgesic efficacy to aspirin 650 mg, acetaminophen 650 mg, and acetaminophen 650 mg/propoxyphene napsylate 100 mg, but has a longer duration of effect (8-12 hours). It is not recommended as an antipyretic. At doses ≥2 g/day, platelets are reversibly inhibited in function. Diflunisal is uricosuric at 500-750 mg/day. It causes less GI and renal toxicity than aspirin and other NSAIDs. Fecal blood loss is $^1/_2$ that of aspirin at 2.6 g/day.

Index Terms Dolobid

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International Brand NamesAnaleric (GR); Ansal (NZ); Diflonid (NO); Dolobid (BF, BJ, CI, CZ, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MX, NE, NG, PT, RU, SC, SD, SL, SN, TH, TN, TW, TZ, UG, ZA, ZM, ZW); Dolocid (NL); Donobid (NO, SE); Flunidor (PT); Ilacen (TW); Senta (TW)

Difluprednate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(dye floo PRED nate)

U.S. Brand NamesDurezol™

Pharmacologic Category[Corticosteroid, Ophthalmic]()

Use: Labeled IndicationsTreatment of inflammation and pain following ocular surgery

Dosing: Adults**Anti-inflammatory:** Ophthalmic: Adults: Instill 1 drop in conjunctival sac of the affected eye(s) 4 times/day beginning 24 hours after surgery, continue for 2 weeks, then decrease to 2 times/day for 1 week, then taper based on response

Dosing: ElderlyRefer to adult dosing.

StorageStore at 15°C to 25°C (59°F to 77°F); do not freeze. Protect from light.

ContraindicationsActive viral (including herpes simplex keratitis, vaccinia, varicella) infections of the cornea or conjunctiva, fungal infection of ocular structures, or mycobacterial ocular infections

Warnings/Precautions

Concerns related to adverse effects:

- Infection: Steroids may mask infection or enhance existing ocular infection; prolonged use may result in secondary infections due to immunosuppression. If signs and symptoms of infection do not improve after 2 days, patient should be re-evaluated.

- Ocular effects: Prolonged use may result in glaucoma and injury to the optic nerve, as well as, visual defects in acuity and field of vision. Posterior subcapsular cataracts may form after long-term use. Use with caution in presence of glaucoma (steroids increase intraocular pressure). Perforation may occur with topical steroids in diseases which thin the cornea or sclera. Steroid use may delay healing after cataract surgery. Intraocular pressure should be monitored if this product is used ≥10 days.

Special populations:

- Contact lens wearers: Contains sorbic acid which may be adsorbed by contact lenses; it is not recommended to wear contacts while using difluprednate.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: For ophthalmic use only; not for intraocular administration. Initial prescription and renewal of medication for >28 days should be made by healthcare provider only after examination with the aid of magnification such as slit lamp biomicroscopy or fluorescein staining (if appropriate).

Geriatric ConsiderationsEvaluate patient's ability to self-administer eye drops.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

5% to 15%: Ocular: Anterior chamber cells/flare, blepharitis, ciliary and conjunctival hyperemia, conjunctival/corneal edema, pain, photophobia, posterior capsule opacification

1% to 5%: Ocular: Inflammation, iritis, punctuate keratitis, visual acuity reduced

<1%: Application site discomfort/irritation, cataracts, corneal pigmentation and striae, episcleritis, eyelid crusting, foreign body sensation, intraocular pressure increased, lacrimation increased, macular edema, ocular pruritus, optic nerve damage, perforation of globe, sclera hyperemia, secondary ocular infection, uveitis

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Monitoring ParametersIntraocular pressure and periodic examination of lens (with prolonged use >28 days)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Emulsion, ophthalmic:

Durezol™: 0.05% (5 mL) [contains sorbic acid]

Generic AvailableNo

ManufacturerSirion Therapeutics, Inc

Mechanism of ActionCorticosteroids inhibit the inflammatory response including edema, capillary dilation, leukocyte migration, and scar formation. Difluprednate penetrates cells readily to induce the production of lipocortins. These proteins modulate the activity of prostaglandins and leukotrienes.

Pharmacodynamics/KineticsAbsorption: Systemic: Limited

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Digoxin Immune Fab

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Jump To Field (Select Field Name)

Pronunciation(di JOKS in i MYUN fab)

U.S. Brand Names Digibind®; DigiFab™

Canadian Brand Names Digibind®

Pharmacologic Category Antidote

Use: Labeled Indications Treatment of life-threatening or potentially life-threatening digoxin intoxication, including:

- acute digoxin ingestion (ie, >10 mg in adults or >4 mg in children)
- chronic ingestions leading to steady-state digoxin concentrations >6 ng/mL in adults or >4 ng/mL in children
- manifestations of digoxin toxicity due to overdose (life-threatening ventricular arrhythmias, progressive bradycardia, second- or third-degree heart block not responsive to atropine, serum potassium >5 mEq/L in adults or >6 mEq in children)

Dosing: Adults Each vial of Digibind® 38 mg or DigiFab™ 40 mg will bind ~0.5 mg of digoxin or digitoxin.

Note: Estimation of the dose is based on the body burden of digitalis. This may be calculated if the amount ingested is known or the postdistribution serum drug level is known (round dose to the nearest whole vial). If the amount of ingestion is unknown, general dosing guidelines should be used.

Acute ingestion of unknown amount: I.V.: 20 vials is adequate to treat most life-threatening ingestions. May give as a single dose or give 10 vials, observe response, and give a second 10 vial dose if indicated.

Acute ingestion of known amount: I.V.:

Based on number of tablets/capsules ingested:

Step 1:

Total body load (mg) = Amount (mg) digoxin capsules/digitoxin ingested

Step 2:

Dose (vials) = Total body load (mg) / (0.5 mg digitalis bound/vial)

Alternatively, the following table gives an estimation of the number of vials needed based on the number of digoxin tablets or capsules ingested.

Number of Digoxin Tablets or Capsules Ingested[1]	Dose of Digoxin Immune Fab (# of Vials)
25	10
50	20
75	30
100	40
150	60
200	80
[1] 250 mcg tablets with 80% bioavailability or 200 mcg Lanoxicaps® capsules with 100% bioavailability.	

Based on steady-state serum digoxin concentration: Adults:

Step 1:

Dose (vials) = [(serum digoxin concentration [ng/mL] x weight [kg]) / 100

Alternatively, the following table gives an estimation of the number of vials needed based on the steady-state serum digoxin concentration.

Adult Dose Estimates of Digibind® (in # of Vials) From Steady-State Serum Digoxin Concentration

Patient Weight (kg)	Serum Digoxin Concentration (ng/mL)						
	1	**2**	**4**	**8**	**12**	**16**	**20**
40	0.5 v	1 v	2 v	3 v	5 v	7 v	8 v
60	0.5 v	1 v	3 v	5 v	7 v	10 v	12 v
70	1 v	2 v	3 v	6 v	9 v	11 v	14 v
80	1 v	2 v	3 v	7 v	10 v	13 v	16 v
100	1 v	2 v	4 v	8 v	12 v	16 v	20 v
v = vials.							

Based on steady-state digitoxin concentration: Children and Adults: If the calculated dose based on the digitoxin concentration is different than that for the digoxin concentration, use the higher dose.

Step 1:

Dose (vials) = [serum digitoxin concentration (ng/mL) x weight (kg)] / 1000

Chronic toxicity (serum digoxin concentration unavailable): I.V.: Adults: 6 vials is adequate to reverse most cases of toxicity

⇧ Dosing: ElderlyRefer to adult dosing.

⇧ Dosing: PediatricEach vial of Digibind® 38 mg or DigiFab™ 40 mg will bind ~0.5 mg of digoxin or digitoxin.

Note: Estimation of the dose is based on the body burden of digitalis. This may be calculated if the amount ingested is known or the postdistribution serum drug level is known (round dose to the nearest whole vial). If the amount of ingestion is unknown, general dosing guidelines should be used.

Acute ingestion of unknown amount: I.V.: Refer to adult dosing.

Acute ingestion of known amount: I.V.: Refer to adult dosing.

Based on steady-state serum digoxin concentration: Infants and Children ≤20 kg: May require smaller doses; calculate dose in milligrams, reconstitute with NS, and administer dose via tuberculin syringe

Step 1:

Dose (mg) = [(serum digoxin concentration [ng/mL] x weight [kg]) / 10] x (mg/vial)[1]

[1] Digibind® 38 mg/vial or DigiFab™ 40 mg/vial

Alternatively, the following table gives an estimation of the amount of **Digibind®** needed based on the steady-state serum digoxin concentration.

Infants and Small Children Dose Estimates of Digibind® (in mg) From Steady-State Serum Digoxin Concentration

Patient Weight (kg)	Serum Digoxin Concentration (ng/mL)						
	1	**2**	**4**	**8**	**12**	**16**	**20**
1	0.4 mg[1]	1 mg[1]	1.5 mg[1]	3 mg[1]	5 mg	6 mg	8 mg
3	1 mg[1]	2 mg[1]	5 mg	9 mg	14 mg	18 mg	23 mg
5	2 mg[1]	4 mg	8 mg	15 mg	23 mg	30 mg	38 mg

10	4 mg	8 mg	15 mg	30 mg	46 mg	61 mg	76 mg
20	8 mg	15 mg	30 mg	61 mg	91 mg	122 mg	152 mg

[1] Dilution of reconstituted vial to 1 mg/mL may be desirable.

Alternatively, the following table gives an estimation of the amount of **DigiFab™** needed based on the steady-state serum digoxin concentration.

Infants and Small Children Dose Estimates of DigiFab™ (in mg) From Steady-State Serum Digoxin Concentration

Patient Weight (kg)	Serum Digoxin Concentration (ng/mL)						
	1	**2**	**4**	**8**	**12**	**16**	**20**
1	0.4 mg[1]	1 mg[1]	1.5 mg[1]	3 mg[1]	5 mg	6.5 mg	8 mg
3	1 mg[1]	2.5 mg[1]	5 mg	10 mg	14 mg	19 mg	24 mg
5	2 mg[1]	4 mg	8 mg	16 mg	24 mg	32 mg	40 mg
10	4 mg	8 mg	16 mg	32 mg	48 mg	64 mg	80 mg
20	8 mg	16 mg	32 mg	64 mg	96 mg	128 mg	160 mg

[1] Dilution of reconstituted vial to 1 mg/mL may be desirable.

Based on steady-state digitoxin concentration: Refer to adult dosing.

Chronic toxicity (serum digoxin concentration unavailable): I.V.: Infants and Children ≤20 kg: 1 vial is adequate to reverse most cases of toxicity

Dosing: Renal ImpairmentRenal elimination of complexed digoxin may be decreased in renal failure. Potential "rebound" may occur when immune fragments are hepatically metabolized, leaving unbound digoxin.
Administration: I.V.Continuous I.V. infusion over ≥30 minutes is preferred. May give by bolus injection if cardiac arrest is imminent. Small doses (infants/small children) may be administered using tuberculin syringe.
Administration: I.V. DetailStopping the infusion and restarting at a slower rate may help if infusion-related reactions occur.
StorageShould be refrigerated at 2°C to 8°C.
Reconstitution Digibind®: Reconstitute by adding 4 mL sterile water, resulting in 9.5 mg/mL for I.V. infusion. Reconstituted solutions should be used within 4 hours if refrigerated. For very small doses, reconstituted vial can be further diluted by adding an additional 34 mL of sterile isotonic saline to achieve a final concentration of 1 mg/mL.

DigiFab™: Reconstitute by adding 4 mL sterile water, resulting in 10 mg/mL for I.V. infusion. Reconstituted solutions should be used within 4 hours if refrigerated. For very small doses, reconstituted vial can be further diluted by adding an additional 36 mL of sterile isotonic saline to achieve a final concentration of 1 mg/mL.

ContraindicationsHypersensitivity to digoxin immune Fab, sheep products, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Hypersensitivity reactions can occur; immediate treatment (including epinephrine 1:1000) should be available.

Disease-related concerns:

- Heart failure: If digoxin was being used to treat heart failure, may see exacerbation of symptoms as digoxin level is reduced.
- Overdose: Consider other drug toxicities as well (eg, suicidal attempts often involve multiple drugs). Monitor for recurrence of digoxin toxicity.
- Renal impairment: Use with caution in patients with renal failure (experience limited); the complex will be removed from the body more slowly.

Dosage form specific issues:

- Papain: Processed with papain and may cause hypersensitivity reactions in patients allergic to papaya, other papaya extracts, papain, chymopapain, or the pineapple enzyme bromelain. There may also be cross allergy with dust mite and latex allergens.

Other warnings/precautions:

- Failure to respond to treatment: Failure of response to adequate treatment may call diagnosis of digitalis toxicity into question.

- Monitoring parameters: Serum potassium levels should be monitored, especially during the first few hours after administration. Total serum digoxin concentrations will rise precipitously following administration of this drug (has no clinical meaning; avoid monitoring serum concentrations).

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Safety and efficacy in pregnant women have not been established. Use during pregnancy only if clearly needed.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Effects (due to withdrawal of digitalis) include exacerbation of heart failure, rapid ventricular response in patients with atrial fibrillation; postural hypotension

Endocrine & metabolic: Hypokalemia

Local: Phlebitis

Miscellaneous: Allergic reactions, serum sickness

Drug InteractionsThere are no known significant interactions.
Test InteractionsDigibind® will interfere with digitalis immunoassay measurements - this will result in clinically misleading serum digoxin concentrations fragment is eliminated from the body (several days to >1 week after Digibind® administration).
Monitoring ParametersSerum potassium, serum digoxin concentration prior to first dose of digoxin immune Fab; **digoxin levels will greatly increase with digoxin immune Fab use and are not an accurate determination of body stores** (has no clinical meaning; avoid monitoring serum concentrations); standard digoxin concentration measurements may be misleading until Fab fragments are eliminated from the body.

Patients with renal failure should be monitored for a prolonged period for reintoxication with digoxin following the rerelease of bound digoxin into the blood.

Nursing: Physical Assessment/MonitoringAssess allergy history prior to administration. Assess results of laboratory tests, cardiac status, vital signs, blood pressure, and adverse reactions during and following infusion. Monitor for signs of reoccurrence of cardiac toxicity.
Monitoring: Lab TestsSerum potassium, serum digoxin concentration prior to first dose of digoxin immune Fab; **digoxin levels will greatly increase with digoxin immune Fab use and are not an accurate determination of body stores** (has no clinical meaning; avoid monitoring serum concentrations); standard digoxin concentration measurements may be misleading until Fab fragments are eliminated from the body.

Patients with renal failure should be monitored for a prolonged period for reintoxication with digoxin following the rerelease of bound digoxin into the blood.

Patient EducationPatient education and instruction will be determined by patient condition and ability to understand. Immediately report dizziness, palpitations, cramping, respiratory difficulty, rash, or itching. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [ovine derived]:

Digibind®: 38 mg [derived from or manufactured using papain]

DigiFab™: 40 mg [derived from or manufactured using papain]

Generic AvailableNo
ManufacturerGlaxoSmithKline
Mechanism of ActionDigoxin immune antigen-binding fragments (Fab) are specific antibodies for the treatment of digitalis intoxication in carefully selected patients; binds with molecules of digoxin or digitoxin and then is excreted by the kidneys and removed from the body
Pharmacodynamics/Kinetics

Onset of action: I.V.: Improvement in 2-30 minutes for toxicity

Half-life elimination: 15-20 hours; prolonged with renal impairment

Excretion: Urine; undetectable amounts within 5-7 days

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsAntidigoxin Fab Fragments, Ovine
References

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International Brand NamesDigibind (GB, NO); Digoxin Immune FAB (Ovine) Digibind (AU)

Digoxin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Digitek® (digoxin tablets, USP) Recalled (Actavis Totowa LLC) - April 28, 2008

Actavis Totowa LLC, manufacturer of Digitek® (digoxin) tablets, has initiated a voluntary recall of all lots of the tablets due to the possibility they may contain twice the amount of digoxin. The tablets may be double the appropriate thickness. Digitek® is distributed by Mylan and UDL under the Bertek and UDL labels (Mylan affiliates). To date there have been several recent reports of digoxin toxicity after taking the product.

Healthcare providers must be aware of the signs of digoxin toxicity which include anorexia, nausea, vomiting, dizziness, bradycardia, and heart block. Severe digoxin toxicity, if left untreated, may result in death. Patients at highest risk of digoxin toxicity include patients who have renal disease.

For more information, refer to the following: http://www.fda.gov/oc/po/firmrecalls/actavis04_08.html

Medication Safety Issues

Sound-alike/look-alike issues:

Digoxin may be confused with Desoxyn®, doxepin

Lanoxin® may be confused with Lasix®, Levoxyl®, Levsinex®, Lomotil®, Lonox®, Mefoxin®, Xanax®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

International issues:

Dilacor®: Brand name for diltiazem in the U.S.; brand name for verapamil in Brazil; brand name for barnidipine in Argentina

Lanoxin® may be confused with Lemoxin® which is a brand bane for cefuroxime in Mexico

Lanoxin® may be confused with Limoxin® which is a brand name for amoxicillin in Mexico

Pronunciation(di JOKS in)

U.S. Brand NamesDigitek®; Lanoxicaps® [DSC]; Lanoxin®

Canadian Brand NamesApo-Digoxin®; Digoxin CSD; Lanoxicaps®; Lanoxin®; Novo-Digoxin; Pediatric Digoxin CSD

Pharmacologic CategoryAntiarrhythmic Agent, Class IV; Cardiac Glycoside

Use: Labeled IndicationsTreatment of congestive heart failure and to slow the ventricular rate in tachyarrhythmias such as atrial fibrillation, atrial flutter, and supraventricular tachycardia (paroxysmal atrial tachycardia); cardiogenic shock

Dosing: Adults

Note: When changing from oral (tablets or liquid) or I.M. to I.V. therapy, dosage should be reduced by 20% to 25%.

Atrial dysrhythmias (rate control), CHF:

Initial: Total digitalizing dose: Give $^{1}/_{2}$ of the total digitalizing dose (TDD) in the initial dose, then give $^{1}/_{4}$ of the TDD in each of two subsequent doses at 6- to 8-hour intervals. Obtain ECG 6 hours after each dose to assess potential toxicity.

Oral: 0.75-1.5 mg

I.V. or I.M.: 0.5-1 mg

Daily maintenance dose: Give once daily to children >10 years of age and adults.

Oral: 0.125-0.5 mg

I.V. or I.M.: 0.1-0.4 mg

Dosing: ElderlyDose is based on lean body weight and normal renal function for age. Decrease dose in patients with decreased renal function (see Dosing in Renal Impairment).

Dosing: PediatricAtrial dysrhythmias (rate control), CHF: When changing from oral (tablets or liquid) or I.M. to I.V. therapy, dosage should be reduced by 20% to 25%. See table.

Dosage Recommendations for Digoxin

Age	Total Digitalizing Dose[2] (mcg/kg[1])		Daily Maintenance Dose[3] (mcg/kg[1])	
	P.O.	I.V. or I.M.	P.O.	I.V. or I.M.
Preterm infant[1]	20-30	15-25	5-7.5	4-6
Full-term infant[1]	25-35	20-30	6-10	5-8
1 mo - 2 y[1]	35-60	30-50	10-15	7.5-12
2-5 y[1]	30-40	25-35	7.5-10	6-9
5-10 y[1]	20-35	15-30	5-10	4-8
>10 y[1]	10-15	8-12	2.5-5	2-3

[1] Based on lean body weight and normal renal function for age. Decrease dose in patients with ↓ renal function; digitalizing dose often not recommended in infants and children.

[2] Give one-half of the total digitalizing dose (TDD) in the initial dose, then give one-quarter of the TDD in each of two subsequent doses at 6- to 8-hour intervals. Obtain ECG 6 hours after each dose to assess potential toxicity.

[3] Divided every 12 hours in infants and children <10 years of age. Given once daily to children >10 years of age and adults.

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer 25% to 75% of dose or every 36 hours.

Cl_{cr} <10 mL/minute: Administer 10% to 25% of dose or every 48 hours.

Reduce loading dose by 50% in ESRD.

Not dialyzable (0% to 5%)

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Inject no more than 2 mL per injection site. May cause intense pain.

Administration: I.V.May be administered undiluted or diluted fourfold in D_5W, NS, or SWFI for direct injection. Less than fourfold dilution may lead to drug precipitation. Inject slowly over ≥5 minutes

Administration: I.V. DetailpH: 6.8-7.2

Dietary ConsiderationsMaintain adequate amounts of potassium in diet to decrease risk of hypokalemia (hypokalemia may increase risk of digoxin toxicity).

StorageProtect elixir and injection from light.

CompatibilityStable in $D_5{}^1/_2NS$ with KCl 20 mEq, D_5W, $D_{10}W$, LR, ${}^1/_2NS$, and NS. May be diluted fourfold in D_5W, NS, or SWFI for direct injection (or may be administered undiluted).

Y-site administration: Compatible: Ciprofloxacin, cisatracurium, diltiazem, famotidine, gatifloxacin, heparin with hydrocortisone sodium succinate, inamrinone, linezolid, meperidine, meropenem, midazolam, milrinone, morphine, potassium chloride, remifentanil, tacrolimus, vitamin B complex with C. **Incompatible:** Amphotericin B cholesteryl sulfate complex, fluconazole, foscarnet, propofol. **Variable (consult detailed reference):** Insulin (regular).

Compatibility in syringe: Compatible: Heparin, milrinone. **Incompatible:** Doxapram.

Compatibility when admixed: Compatible: Bretylium, cimetidine, floxacillin, furosemide, lidocaine, ranitidine, verapamil. **Incompatible:** Dobutamine.

ContraindicationsHypersensitivity to digoxin or any component of the formulation; hypersensitivity to cardiac glycosides (another may be tried); history of toxicity; ventricular tachycardia or fibrillation; idiopathic hypertrophic subaortic stenosis; constrictive pericarditis; amyloid disease; second- or third-degree heart block (except in patients with a functioning artificial pacemaker); Wolff-Parkinson-White syndrome and atrial fibrillation concurrently

Allergy Considerations

- Digitalis Glycoside Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Proarrhythmic effects: Watch for proarrhythmic effects (especially with digoxin toxicity)

Disease-related concerns:

- Acute MI: Use with caution in patients with an acute MI (within 6 months).
- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.
- Heart failure (HF): Withdrawal in HF patients may lead to recurrence of HF symptoms.
- Hypermetabolic states: Atrial arrhythmias associated with hypermetabolic states are very difficult to treat.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment needed.
- Sinus nodal disease: Use with caution in patients with sinus nodal disease; may worsen.

Concurrent drug therapy issues:

- Amiodarone/quinidine/verapamil: Adjust dose when amiodarone, quinidine, or verapamil are added to a patient on digoxin.
- Calcium: Especially when administered rapidly I.V., calcium can produce serious arrhythmias in digitalized patients.

Other warnings/precautions:

- CAST trial: In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, non-life-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide. An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. Antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.
- Elective electrical cardioversion: Reduce or hold dose 1-2 days before elective electrical cardioversion.
- Rate control: When using digoxin for rate control, it works best in a sedentary patient.
- Serum monitoring: Serum concentration monitoring should be done before the next dose (patient can hold AM dose for blood test) for an accurate assessment.

Geriatric ConsiderationsDigitalis preparations (primarily digoxin) are frequently used to treat common cardiac diseases in the elderly (congestive heart failure, atrial fibrillation). Elderly are at risk for toxicity due to age-related changes; volume of distribution is diminished significantly; half-life is increased as a result of decreased total body clearance. Additionally, elderly frequently have concomitant diseases which affect the pharmacokinetics in digitalis glycosides; hypo- and hyperthyroidism and renal function decline will affect clearance of digoxin. Exercise in elderly will reduce serum concentrations of digoxin due to increased skeletal muscle uptake. Therefore, a knowledge of the physical activity of elderly helps interpret serum assays. Must be observant for noncardiac signs of toxicity in elderly such as anorexia, vision changes (blurred), confusion, and depression. Changes in dose may be necessary with declining renal function with age; monitor closely.

Pregnancy Risk FactorC

LactationEnters breast milk (small amounts)/compatible

Adverse ReactionsIncidence not always reported.

Cardiovascular: Heart block; first-, second- (Wenckebach), or third-degree heart block; asystole; atrial tachycardia with block; AV dissociation; accelerated junctional rhythm; ventricular tachycardia or ventricular fibrillation; PR prolongation; ST segment depression

Central nervous system: Visual disturbances (blurred or yellow vision), headache (3%), dizziness (5%), apathy, confusion, mental disturbances (4%), anxiety, depression, delirium, hallucinations, fever

Dermatologic: Maculopapular rash (2%), erythematous, scarlatiniform, papular, vesicular or bullous rash, urticaria, pruritus, facial, angioneurotic or laryngeal edema, shedding of fingernails or toenails, alopecia

Gastrointestinal: Nausea (3%), vomiting (2%), diarrhea (3%), abdominal pain

Neuromuscular & skeletal: Weakness

<1% (Limited to important or life-threatening): Gynecomastia, thrombocytopenia, palpitation, unifocal or multiform ventricular premature contractions (especially bigeminy or trigeminy), anorexia, abdominal pain, intestinal ischemia, hemorrhagic necrosis of the intestines, increase plasma estrogen and decreased serum luteinizing hormone in men and postmenopausal women and decreased plasma testosterone in men, vaginal cornification, eosinophilia, sexual dysfunction, diaphoresis

Children are more likely to experience cardiac arrhythmia as a sign of excessive dosing. The most common are conduction disturbances or tachyarrhythmia (atrial tachycardia with or without block) and junctional tachycardia. Ventricular tachyarrhythmia are less common. In infants, sinus bradycardia may be a sign of digoxin toxicity. Any arrhythmia seen in a child on digoxin should be considered as digoxin toxicity. The gastrointestinal and central nervous system symptoms are not frequently seen in children.

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)

Drug Interactions

5-ASA Derivatives: May decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

Acarbose: May decrease the serum concentration of Digoxin. *Risk C: Monitor therapy*

Aminoglycosides: May decrease the absorption of Cardiac Glycosides. **Exceptions:** Amikacin; Gentamicin; Streptomycin; Tobramycin. *Risk C: Monitor therapy*

Aminoquinolines (Antimalarial): May increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Amiodarone: May increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Cardiac Glycosides. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antineoplastic Agents: May decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Alitretinoin; Altretamine; Aminoglutethimide; Anastrozole; Asparaginase; AzaCITIDine; Busulfan; Capecitabine; CARBOplatin; Chlorambucil; CISplatin; Cladribine; Cytarabine (Liposomal); Dacarbazine; DACTINomycin; DAUNOrubicin Citrate (Liposomal); DAUNOrubicin Hydrochloride; Denileukin Diftitox; Docetaxel; Epirubicin; Estramustine; Etoposide; Etoposide Phosphate; Exemestane; Fludarabine; Fluorouracil; Gemcitabine; Goserelin; Hydroxyurea; IDArubicin; Ifosfamide; Irinotecan; Letrozole; Leuprolide; Lomustine; Mechlorethamine; Megestrol; Mercaptopurine; Mitomycin; Mitotane; Mitoxantrone; Nilutamide; Paclitaxel; Pegaspargase; Pentostatin; Polyestradiol; Porfimer; RiTUXimab; Streptozocin; Tamoxifen; Temozolomide; Teniposide; Thioguanine; Thiotepa; Topotecan; Toremifene; Tretinoin (Oral); Valrubicin; VinBLAStine; Vinorelbine. *Risk C: Monitor therapy*

Antineoplastic Agents (Anthracycline): Cardiac Glycosides may diminish the cardiotoxic effect of Antineoplastic Agents (Anthracycline). Antineoplastic Agents (Anthracycline) may decrease the serum concentration of Cardiac Glycosides. The effects of liposomal formulations may be unique from those of the free drug, as liposomal formulation have unique drug disposition and toxicity profiles, and liposomes themselves may alter digoxin absorption/distribution. *Risk C: Monitor therapy*

Atorvastatin: May increase the serum concentration of Digoxin. *Risk C: Monitor therapy*

Beta-Blockers: May enhance the bradycardic effect of Cardiac Glycosides. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Cardiac Glycosides. **Exceptions:** Colesevelam. *Risk C: Monitor therapy*

Calcitriol: May enhance the arrhythmogenic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the AV-blocking effect of Cardiac Glycosides. Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Cardiac Glycosides. *Risk D: Consider therapy modification*

Carvedilol: May increase the serum concentration of Digoxin. *Risk C: Monitor therapy*

Conivaptan: May increase the serum concentration of Digoxin. *Risk C: Monitor therapy*

CycloSPORINE: May decrease the metabolism of Cardiac Glycosides. *Risk D: Consider therapy modification*

Kaolin: May decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

Macrolide Antibiotics: May increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Midodrine: Cardiac Glycosides may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nefazodone: May increase the serum concentration of Cardiac Glycosides. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: May enhance the arrhythmogenic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Penicillamine: May decrease the serum concentration of Digoxin. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May diminish the therapeutic effect of Cardiac Glycosides. Specifically, the inotropic effects. *Risk C: Monitor therapy*

Propafenone: May increase the serum concentration of Cardiac Glycosides. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of Digoxin. Increased serum concentrations of digoxin may increase risk of AV nodal blockade. *Risk C: Monitor therapy*

QuiNIDine: May increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

QuiNINE: May increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Ranolazine: May increase the serum concentration of Digoxin. *Risk C: Monitor therapy*

St Johns Wort: May decrease the serum concentration of Cardiac Glycosides. *Risk C: Monitor therapy*

Telmisartan: May increase the serum concentration of Cardiac Glycosides. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Digoxin peak serum levels may be decreased if taken with food. Meals containing increased fiber (bran) or foods high in pectin may decrease oral absorption of digoxin.

Herb/Nutraceutical: Avoid ephedra (risk of cardiac stimulation). Avoid natural licorice (causes sodium and water retention and increases potassium loss).

Monitoring Parameters

When to draw serum digoxin concentrations: Digoxin serum concentrations are monitored because digoxin possesses a narrow therapeutic serum range; the therapeutic endpoint is difficult to quantify and digoxin toxicity may be life-threatening. Digoxin serum levels should be drawn **at least 4 hours after an intravenous dose** and **at least 6 hours after an oral dose (optimally 12-24 hours after a dose).**

Initiation of therapy:

If a loading dose is given: Digoxin serum concentration may be drawn within 12-24 hours after the initial loading dose administration. Levels drawn this early may confirm the relationship of digoxin plasma levels and response but are of little value in determining maintenance doses.

If a loading dose is not given: Digoxin serum concentration should be obtained after 3-5 days of therapy.

Maintenance therapy:

Trough concentrations should be followed just prior to the next dose or at a minimum of 4 hours after an I.V. dose and at least 6 hours after an oral dose.

Digoxin serum concentrations should be obtained within 5-7 days (approximate time to steady-state) after any dosage changes. Continue to obtain digoxin serum concentrations 7-14 days after any change in maintenance dose. **Note:** In patients with end-stage renal disease, it may take 15-20 days to reach steady-state.

Additionally, patients who are receiving potassium-depleting medications such as diuretics, should be monitored for potassium, magnesium, and calcium levels.

Digoxin serum concentrations should be obtained whenever any of the following conditions occur:

Questionable patient compliance or to evaluate clinical deterioration following an initial good response

Changing renal function

Suspected digoxin toxicity

Initiation or discontinuation of therapy with drugs (amiodarone, quinidine, verapamil) which potentially interact with digoxin; if quinidine therapy is started, the digoxin dose should be reduced by 25% to 50% and digoxin levels should be monitored closely. Any disease changes (hypothyroidism)

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Heart rate and rhythm should be monitored along with periodic ECGs to assess both desired effects and signs of toxicity

Follow closely (especially in patients receiving diuretics or amphotericin) for decreased serum potassium and magnesium or increased calcium, all of which predispose to digoxin toxicity

Assess renal function

Be aware of drug interactions

Observe patients for noncardiac signs of toxicity, confusion, and depression

Reference Range

Digoxin therapeutic serum concentrations:

Congestive heart failure: 0.5-0.8 ng/mL

Arrhythmias: 0.8-2 ng/mL

Adults: <0.5 ng/mL; probably indicates underdigitalization unless there are special circumstances

Toxic: >2.5 ng/mL

Digoxin-like immunoreactive substance (DLIS) may cross-react with digoxin immunoassay. DLIS has been found in patients with renal and liver disease, congestive heart failure, neonates, and pregnant women (3rd trimester).

Nursing: Physical Assessment/MonitoringClosely assess effects and interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests (when beginning or changing dosage, especially with I.V. administration and when patients are receiving diuretics or amphotericin). Monitor therapeutic effectiveness and adverse reactions at beginning of therapy, periodically throughout therapy, or when changing dosage. Monitor for signs of digoxin toxicity. **I.V.:** Monitor ECG continuously. **Oral:** Monitor apical pulse before administering any dose. Assess knowledge/teach patient appropriate use, adverse reactions to report, and appropriate interventions to reduce side effects.

Monitoring: Lab Tests

When to draw serum digoxin concentrations: Digoxin serum levels should be drawn **at least 4 hours after an intravenous dose** and **at least 6 hours after an oral dose (optimally 12-24 hours after a dose).**

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Any disease changes (hypothyroidism)

Patient EducationTake as directed; do not discontinue without consulting prescriber. Maintain adequate dietary intake of potassium (do not increase without consulting prescriber). Adequate dietary potassium will reduce risk of digoxin toxicity. Take pulse at the same time each day, hold medication as directed by prescriber. Notify prescriber of acute changes in pulse. Report loss of appetite, nausea, vomiting, persistent diarrhea, swelling of extremities, palpitations, "yellowing" or blurred vision, mental confusion or depression, or unusual fatigue. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name; [DSC] = Discontinued product

Capsule:

Lanoxicaps®: 100 mcg [contains ethanol; DSC]; 200 mcg [contains ethanol; DSC]

Injection, solution: 250 mcg/mL (1 mL, 2 mL)

Lanoxin®: 250 mcg/mL (2 mL) [contains ethanol 10% and propylene glycol 40%]

Injection, solution [pediatric]: 100 mcg/mL (1 mL)

Solution, oral: 50 mcg/mL (2.5 mL, 5 mL, 60 mL)

Tablet: 125 mcg, 250 mcg

Digitek®, Lanoxin®: 125 mcg, 250 mcg

Apo-Digoxin® [CAN]: 62.5 mcg, 125 mcg, 250 mcg

Generic AvailableYes: Excludes capsule

Pricing: U.S. (www.drugstore.com)

Capsules (Lanoxicaps)

0.1 mg (100): $39.99

Tablets (Digoxin)

0.125 mg (30): $13.99

Tablets (Lanoxin)

0.125 mg (30): $19.99

0.25 mg (30): $17.99

Mechanism of Action

Congestive heart failure: Inhibition of the sodium/potassium ATPase pump which acts to increase the intracellular sodium-calcium exchange to increase intracellular calcium leading to increased contractility

Supraventricular arrhythmias: Direct suppression of the AV node conduction to increase effective refractory period and decrease conduction velocity - positive inotropic effect, enhanced vagal tone, and decreased ventricular rate to fast atrial arrhythmias. Atrial fibrillation may decrease sensitivity and increase tolerance to higher serum digoxin concentrations.

Pharmacodynamics/Kinetics

Onset of action: Oral: 1-2 hours; I.V.: 5-30 minutes

Peak effect: Oral: 2-8 hours; I.V.: 1-4 hours

Duration: Adults: 3-4 days both forms

Absorption: By passive nonsaturable diffusion in the upper small intestine; food may delay, but does not affect extent of absorption

Distribution:

Normal renal function: 6-7 L/kg

V_d: Extensive to peripheral tissues, with a distinct distribution phase which lasts 6-8 hours; concentrates in heart, liver, kidney, skeletal muscle, and intestines. Heart/serum concentration is 70:1. Pharmacologic effects are delayed and do not correlate well with serum concentrations during distribution phase.

Hyperthyroidism: Increased V_d

Hyperkalemia, hyponatremia: Decreased digoxin distribution to heart and muscle

Hypokalemia: Increased digoxin distribution to heart and muscles

Concomitant quinidine therapy: Decreased V_d

Chronic renal failure: 4-6 L/kg

Decreased sodium/potassium ATPase activity - decreased tissue binding

Neonates, full-term: 7.5-10 L/kg

Children: 16 L/kg

Adults: 7 L/kg, decreased with renal disease

Protein binding: 30%; in uremic patients, digoxin is displaced from plasma protein binding sites

Metabolism: Via sequential sugar hydrolysis in the stomach or by reduction of lactone ring by intestinal bacteria (in ~10% of population, gut bacteria may metabolize up to 40% of digoxin dose); metabolites may contribute to therapeutic and toxic effects of digoxin; metabolism is reduced with CHF

Bioavailability: Oral (formulation dependent): Elixir: 75% to 85%; Tablet: 70% to 80%

Half-life elimination (age, renal and cardiac function dependent):

Neonates: Premature: 61-170 hours; Full-term: 35-45 hours

Infants: 18-25 hours

Children: 35 hours

Adults: 38-48 hours

Adults, anephric: 4-6 days

Half-life elimination: Parent drug: 38 hours; Metabolites: Digoxigenin: 4 hours; Monodigitoxoside: 3-12 hours

Time to peak, serum: Oral: ~1 hour

Excretion: Urine (50% to 70% as unchanged drug)

Related Information

- Antacid Drug Interactions
- Antiarrhythmic Drugs
- Heart Failure (Systolic)

Dental Health: Effects on Dental TreatmentSensitive gag reflex may cause difficulty in taking a dental impression.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse vasoconstrictor with caution due to risk of cardiac arrhythmias with digoxin

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentPhenytoin may decrease levels of digoxin; monitor levels

Cardiovascular ConsiderationsDigoxin has been used for many years in treatment of heart failure. Even though digoxin has a very narrow therapeutic index, it remains an important therapeutic strategy when added to standard therapy. When used in heart failure, it should be used only for systolic dysfunction and not diastolic dysfunction. While the long-term trials show no convincing reduction in cardiovascular mortality, digoxin therapy is associated with a decrease in frequency in hospitalizations for exacerbations of heart failure. A potential mechanism of benefit in heart failure is that digoxin may improve baroreflex sensitivity.

Digoxin use for ventricular rate control in patients with atrial fibrillation is a particularly useful strategy in those patients with coexisting systolic dysfunction. It is important to consider, however, that while digoxin may control ventricular response rate for atrial fibrillation at rest, the medication is less effective for rate control during exercise.

Digoxin toxicity may be potentiated in patients with hypokalemia, hypomagnesemia, and hypercalcemia. Digoxin may also rapidly approach toxic levels in patients with renal failure. For patients with renal failure, the loading dose is unchanged but maintenance doses may be adjusted and levels should be monitored very carefully. Signs of digoxin toxicity include both brady- and tachyarrhythmias. Bidirectional VT induced by digitalis toxicity indicates imminent development of ventricular fibrillation. The recent development of digoxin antibodies (Digibind®) allows rapid intervention for acute digoxin toxicity. However, it is important to note that after administration of Digibind®, measured digoxin levels cannot be used to follow effectiveness of antibody therapy because they seem to rise rapidly.

Anesthesia and Critical Care Concerns/Other ConsiderationsElderly are at risk for toxicity due to age-related changes; volume of distribution is diminished significantly; half-life is increased as a result of decreased total body clearance. Digoxin toxicity may be potentiated in patients with hypokalemia, hypomagnesemia, and hypercalcemia. Digoxin may also rapidly approach toxic levels in patients with renal failure. Signs of digoxin toxicity include both brady- and tachyarrhythmias. Bidirectional VT induced digitalis indicates imminent development of ventricular fibrillation.

Digoxin has been used for many years in treatment of heart failure. Digoxin therapy is associated with a decrease in frequency in hospitalizations for exacerbations of heart failure. Digoxin use for ventricular rate control in patients with atrial fibrillation is a particularly useful strategy in those patients with coexisting systolic dysfunction. While digoxin may control ventricular response rate for atrial fibrillation at rest, the medication is less effective for rate control during exercise.

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International Brand NamesCardiacin (TW); Cardiogoxin (AR); Cardioxin (IN, PH); Cardoxin (IL); Digomal (IT); Digosin (JP); Digoxin (PL); Digoxin ”Dak” (DK); Digoxin-Sandoz (BF, BJ, CH, CI, ET, GH, GM, GN, ID, JP, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Digoxin-Zori (IL); Digoxina (ES, PE); Digoxina Boehringer (ES); Digoxine Nativelle (LU); Digoxine Navtivelle (FR); Dilacor (BG); Dilanacin (CY, EG, IQ, JO, SD); Eudigox (IT); Fargoxin (ID); Grexin (TH); Lanacordin (ES); Lanicor (AE, AR, AT, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, CZ, DE, EG, ET, GH, GM, GN, GR, GY, HR, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PT, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, VE, YE, ZA, ZM, ZW); Lanikor (RU); Lanox (PH); Lanoxin (AE, AR, AU, BB, BE, BF, BH, BJ, BM, BR, BS, BZ, CI, CY, EG, ET, GB, GH, GM, GN, GR, GY, HK, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PH, PK, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Lenoxin (DE); Mapluxin (MX); Purgoxin (ZA); Sigmaxin (AU); Toloxin (TH); Vidaxil (MX)

Dihydrocodeine, Aspirin, and Caffeine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Synalgos®-DC may be confused with Synagis®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(dye hye droe KOE deen, AS pir in, & KAF een)

U.S. Brand NamesSynalgos®-DC

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled IndicationsManagement of mild to moderate pain that requires relaxation

Use: DentalManagement of postoperative pain

Dosing: AdultsPain: Oral: 1-2 capsules every 4-6 hours as needed

Dosing: ElderlyInitial dosing should be cautious (low end of adult dosing range).

RestrictionsC-III

ContraindicationsHypersensitivity to dihydrocodeine or any component of the formulation; pregnancy (prolonged use or high doses at term)

Allergy Considerations

- Opioid Allergy/Hypersensitivity
- Salicylate Allergy/Sensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).
- Salicylate sensitivity: Patients with sensitivity to tartrazine dyes, nasal polyps, and asthma may have an increased risk of salicylate sensitivity.
- Tinnitus: Discontinue use if tinnitus or impaired hearing occurs.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- Bleeding disorders: Use with caution in patients with platelet and bleeding disorders.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Ethanol use: Heavy ethanol use (>3 drinks/day) can increase bleeding risks.
- Gastrointestinal disease: Use with caution in patients with erosive gastritis or peptic ulcer disease.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Renal impairment: Use with caution in patients with severe renal impairment.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other

obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- Surgical patients: ASA should be avoided (if possible) in surgical patients for 1-2 weeks prior to surgery, to reduce the risk of excessive bleeding (except in patients with cardiac stents that have not completed their full course of dual antiplatelet therapy [aspirin, clopidogrel]; patient specific situations need to be discussed with cardiologist; AHA/ACC/SCAI/ACS/ADA Science Advisory provides recommendations).

Dosage form specific issues:

- Sulfites: Some preparations contain sulfites which may cause allergic reactions.

Other warnings/precautions:

- Alternative antitussive: Dextromethorphan has equivalent antitussive activity but has much lower toxicity in accidental overdose.

Pregnancy Risk FactorB/D (prolonged use or high doses at term)
LactationExcretion in breast milk unknown/use caution
Breast-Feeding Considerations

Acetaminophen: May be taken while breast-feeding.

Aspirin: Use cautiously due to potential adverse effects in nursing infants.

Dihydrocodeine: No data reported.

Adverse Reactions

>10%:

Central nervous system: Lightheadedness, dizziness, drowsiness, sedation

Dermatologic: Pruritus, skin reactions

Gastrointestinal: Nausea, vomiting, constipation

1% to 10%:

Cardiovascular: Hypotension, palpitation, bradycardia, peripheral vasodilation

Central nervous system: Increased intracranial pressure

Endocrine & metabolic: Antidiuretic hormone release

Gastrointestinal: Biliary tract spasm

Genitourinary: Urinary tract spasm

Ocular: Miosis

Respiratory: Respiratory depression

Miscellaneous: Histamine release, physical and psychological dependence with prolonged use

Metabolism/Transport Effects**Substrate** of CYP2D6 (minor) based on dihydrocodeine
Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

QuiNIDine: May diminish the analgesic effect of Dihydrocodeine. *Risk D: Consider therapy modification*

Quinolone Antibiotics: May decrease the metabolism of Caffeine. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Ofloxacin; Sparfloxacin; Trovafloxacin. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Regadenoson: Caffeine may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Nursing: Physical Assessment/MonitoringSee individual agents for Aspirin and Caffeine.
Patient EducationSee individual agents for Aspirin and Caffeine.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: Dihydrocodeine bitartrate 16 mg, aspirin 356.4 mg, and caffeine 30 mg

Generic AvailableNo
Mechanism of ActionBinds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; causes cough suppression by direct central action in the medulla; produces generalized CNS depression
Pharmacodynamics/Kinetics

Onset of action: 10-30 minutes

Duration: 4-6 hours

Metabolism: Hepatic

Half-life elimination, serum: 3.8 hours

Time to peak, serum: 30-60 minutes

Dental Health Professional ConsiderationsThere is no scientific evidence to warrant discontinuance of aspirin prior to dental surgery. Patients taking one aspirin tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with the physician before removal of the aspirin relative to prevention of postoperative bleeding.

The Food and Drug Administration (FDA), has issued a letter updating information and considerations regarding the use of ibuprofen (400 mg doses) in patients who are taking low dose aspirin (81 mg, immediate release; not enteric coated) for cardioprotection and stroke prevention. Ibuprofen, at these doses, may interfere with aspirin’s antiplatelet effect depending upon when it is administered. Patients initiated on aspirin first (for ~1 week) then ibuprofen (400 mg 3 times/day for 10 days) seem to maintain aspirin’s platelet effect (Cryer B, 2005). Ibuprofen has the greatest impact on aspirin if administered less than 8 hours before aspirin (Catella-Lawson F, 2001).

Patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. With occasional use of ibuprofen, a clinically-significant interaction with aspirin in unlikely. To avoid interference during chronic dosing, a single dose of ibuprofen should be taken 30-120 minutes after aspirin ingestion or at least 8 hours should elapse after ibuprofen dosing before giving aspirin (FDA, 2006; Catella-Lawson F, 2001).

The clinical implications of the interaction are unclear. There have not been any clinical endpoint studies conducted at this time. Avoidance of this interaction is potentially important because aspirin’s vascular protection could be decreased or negated.

Other nonselective NSAIDs may have potential for a similar interaction with aspirin. Such has been described with naproxen (Capone ML, 2005). Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin. Other clinical scenarios (use of smaller ibuprofen doses, other aspirin products, other doses of aspirin) have not been evaluated.

Additional information is available at: http://www.fda.gov/cder/drug/infopage/aspirin/default.htm

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dihydrocodeine: nausea, followed by sedation and constipation. Elderly are a high-risk population for adverse effects from nonsteroidal anti-inflammatory agents. As many as 60% of elderly patients with GI complications from NSAIDs can develop peptic ulceration and/or hemorrhage asymptomatically. Concomitant disease and drug use contribute to the risk of GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age.

Aspirin: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity (see Dental Comment).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common

Mental Health: Effects on Psychiatric TreatmentConcurrent use with MAO inhibitors may produce additive side effects

Cardiovascular ConsiderationsDihydrocodeine compound may cause constipation which may be problematic in patients with unstable angina, and patients after myocardial infarction. The hemodynamic responses to valsalva-like maneuvers due to straining may have adverse cardiovascular consequences in patients with critical coronary artery disease.

Index TermsDihydrocodeine Compound

References

Capone ML, Sciulli MG, Tacconelli S, et al, “Pharmacodynamic Interaction of Naproxen With Low-Dose Aspirin in Healthy Subjects,” *J Am Coll Cardiol*, 2005, 45(8):1295-1301.[PubMed 15837265]

Catella-Lawson F, Reilly MP, Kapoor SC, et al, “Cyclooxygenase Inhibitors and the Antiplatelet Effects of Aspirin,” *N Engl J Med*, 2001, 345(25):1809-17.[PubMed 11752357]

Cryer B, Verlin RG, Cooper SA, et al, “Double-Blind, Randomized, Parallel, Placebo-Controlled Study of Ibuprofen Effects on Thromboxane B2 Concentrations in Aspirin-Treated Healthy Adult Volunteers,” *Clin Ther*, 2005, 27(2):185-191.[PubMed 15811481]

“Drugs for Pain,” *Med Lett Drugs Ther*, 2000, 42(1085):73-8. [PubMed 10951654]

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand NamesCodicontin (BE, CH, LU); Codidol (AT); Contugesic (ES); DF 118 (IE); DF 118 Forte (GB); DHC Continus (GB, HU, IE, PL); DHC Mundipharma (DE); Dicodin (FR); Dihydrocodeine (CY, GB); Dolcontin (GR); Hydol (IE); Hydrocodin (HU); Paracodin (AT, AU, CH, DE, IE); Paracodina (ES, IT, PT); Paracodine (BE); Paracodin[gtt.] (AT, CH, DE, IE); Remedacen (DE); Rikodeine (AU); Tiamon (DE); Tosidrin (ES)

Dihydrocodeine, Chlorpheniramine, and Phenylephrine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(dye hye droe KOE deen, klor fen IR a meen, & fen il EF rin)

U.S. Brand NamesBaltussin; Coldcough PD; Novahistine DH

Pharmacologic CategoryAlpha/Beta Agonist; Analgesic, Opioid; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of cough and congestion associated with the upper respiratory tract

Dosing: Adults**Cough and congestion:** Oral:

Baltussin: 5 mL every 4-6 hours as needed

Novahistine DH: 5-10 mL every 4-6 hours as needed (maximum: 40 mL/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Cough and congestion:** Oral:

Children 2-6 years (Novahistine DH): 1.25-2.5 mL every 4-6 hours as needed (maximum: 10 mL/24 hours)

Children 6-12 years:

Baltussin: 2.5 mL every 4-6 hours as needed

Novahistine DH: 2.5-5 mL every 4-6 hours as needed (maximum: 20 mL/24 hours)

Children ≥12 years: Refer to adult dosing.

StorageStore at controlled room temperature.
RestrictionsC-III/C-V
ContraindicationsHypersensitivity to dihydrocodeine, chlorpheniramine, phenylephrine, codeine, sympathomimetic amines, antihistamines, or any component of the formulation; significant respiratory depression (in unmonitored settings), acute asthma, severe bronchial asthma, hypercapnia; paralytic ileus, peptic ulcer; use with or within 14 days of MAO inhibitors; severe hypertension, severe coronary artery disease; narrow angle glaucoma; urinary retention; pregnancy
Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients not able to maintain blood pressure.
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene-derivative opioid agonists (eg, hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease). Use is contraindicated with severe disease.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Delirium tremens: Use caution in patients with delirium tremens.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Respiratory disease: Use with caution in patients with pulmonary disease or decreased ventilatory function; dose-related respiratory depression occurs.
- Seizures: Use caution in patients with a history of seizure disorders.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children. Safety and efficacy have not been established in children <2 years of age.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. This combination is contraindicated by some manufacturers during pregnancy. Also See individual monographs for codeine, chlorpheniramine, and phenylephrine.
LactationExcretion in breast milk unknown/use caution

Adverse ReactionsSee individual agents.

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May diminish the analgesic effect of Dihydrocodeine. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsSee individual monographs for Codeine, Chlorpheniramine, and Phenylephrine.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid:

Novahistine DH: Dihydrocodeine bitartrate 7.5 mg, chlorpheniramine maleate 2 mg and phenylephrine hydrochloride 5 mg per 5 mL (480 mL) [alcohol free, sugar free; contains propylene glycol; strawberry flavor; C-III]

Syrup:

Baltussin: Dihydrocodeine bitartrate 3 mg, chlorpheniramine maleate 5 mg, and phenylephrine hydrochloride 20 mg per 5 mL (480 mL) [alcohol free, sugar free; contains propylene glycol; fruit flavor; C-III]

Coldcough PD: Dihydrocodeine bitartrate 3 mg, chlorpheniramine maleate 2 mg, and phenylephrine hydrochloride 7.5 mg per 5 mL (120 mL) [alcohol free, sugar free; grape flavor; C-V]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Syrup (Pancof PD)

7.5-2-3 mg/5 mL (480): $94.99

Mechanism of Action

Dihydrocodeine: Binds to opiate receptors in the CNS; suppresses cough in medullary center; produces generalized CNS depression

Chlorpheniramine: Competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract

Phenylephrine: Potent, direct-acting alpha-adrenergic stimulator with weak beta-adrenergic activity; causes vasoconstriction of the arterioles of the nasal mucosa and conjunctiva

Related Information

- Chlorpheniramine
- Codeine
- Phenylephrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:
Chlorpheniramine: Prolonged use will cause significant xerostomia (normal salivary flow resumes upon discontinuation).

Phenylephrine: Up to 10% of patients could experience tachycardia, palpitations, and xerostomia; use vasoconstrictor with caution.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause paradoxical excitation in pediatric patients. Sedation is common; may cause anxiety, euphoria, confusion, insomnia, nervousness, fatigue, hallucinations, or depression.

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitors. Concomitant use with psychotropics may produce additive sedation or hypotensive effects. May result in loss of pain control if used with fluoxetine or paroxetine.

Index TermsChlorpheniramine Maleate, Dihydrocodeine Bitartrate, and Phenylephrine Hydrochloride; Phenylephrine, Chlorpheniramine, and Dihydrocodeine

Dihydrocodeine, Pseudoephedrine, and Guaifenesin

Lexi-Drugs Online

English English

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(dye hye droe KOE deen, soo doe e FED rin, & gwye FEN e sin)

U.S. Brand NamesDiHydro-GP; Hydro-Tussin™ EXP [DSC]; Pancof®-EXP

Pharmacologic CategoryAntitussive/Decongestant/Expectorant

Use: Labeled IndicationsTemporary relief of cough and congestion associated with upper respiratory tract infections and allergies

Dosing: Adults

Cough/congestion: Oral (Hydro-Tussin™ EXP, Pancof®-EXP): 5-10 mL every 4-6 hours as needed

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Cough/congestion: Oral (Hydro-Tussin™ EXP, Pancof®-EXP): Children:

2-6 years: 1.25-2.5 mL every 4-6 hours as needed

6-12 years 2.5-5 mL every 4-6 hours as needed

≥12 years: Refer to adult dosing.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to dihydrocodeine, codeine, pseudoephedrine, guaifenesin, or any component of the formulation; severe respiratory depression; acute asthma or hypercapnia; paralytic ileus; severe hypertension; severe cardiac disease; narrow-angle glaucoma; bronchial asthma; urinary retention; peptic ulcer; use with or within 14 days of MAO inhibitors; pregnancy

Allergy Considerations

- GuaiFENesin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension.
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with pulmonary disease or decrease ventilatory function; dose-related respiratory depression occurs.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Use with caution in children; may be more sensitive to adverse effects. Safety and efficacy have not been established in children <2 years of age.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Geriatric ConsiderationsElderly may be particularly susceptible to CNS depression and confusion, as well as the constipating effects of narcotics. Elderly are more predisposed to adverse effects of sympathomimetics since they frequently have cardiovascular disease and diabetes, as well as multiple drug therapies.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Refer to individual monographs for Codeine, Pseudoephedrine, and Guaifenesin for additional information. Use during pregnancy is contraindicated.

Breast-Feeding ConsiderationsRefer to individual monographs for Codeine, Pseudoephedrine, and Guaifenesin.

Adverse ReactionsRefer to individual agents.

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

QuiNIDine: May diminish the analgesic effect of Dihydrocodeine. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Test InteractionsRefer to individual monographs for Pseudoephedrine and Guaifenesin.

Nursing: Physical Assessment/MonitoringSee individual agents for Pseudoephedrine and Guaifenesin.

Patient EducationSee individual agents for Pseudoephedrine and Guaifenesin.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Syrup:

DiHydro-GP: Dihydrocodeine bitartrate 7.5 mg, pseudoephedrine hydrochloride 15 mg, and guaifenesin 100 mg per 5 mL (480 mL) [vanilla flavor]

Hydro-Tussin™ EXP [DSC], Pancof®-EXP: Dihydrocodeine bitartrate 7.5 mg, pseudoephedrine hydrochloride 15 mg, and guaifenesin 100 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free]

Generic AvailableYes

Mechanism of Action

Dihydrocodeine is an antitussive and analgesic chemically related to codeine. Codeine binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; causes cough supression by direct central action in the medulla; produces generalized CNS depression.

Pseudoephedrine directly stimulates alpha-adrenergic receptors of respiratory mucosa causing vasoconstriction; directly stimulates beta-adrenergic receptors causing bronchial relaxation, increased heart rate and contractility.

Guaifenesin is thought to act as an expectorant by irritating the gastric mucosa and stimulating respiratory tract secretions, thereby increasing respiratory fluid volumes and decreasing phlegm viscosity.

Related Information

- Codeine
- GuaiFENesin
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDizziness, nervousness, and insomnia are common; may cause CNS depression; concomitant use with psychotropic agents may produce additive effects; may rarely cause hallucinations

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor use

Index TermsGuaifenesin, Dihydrocodeine, and Pseudoephedrine; Pseudoephedrine Hydrochloride, Guaifenesin, and Dihydrocodeine Bitartrate

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Dihydroergotamine

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(dye hye droe er GOT a meen)

U.S. Brand NamesD.H.E. 45®; Migranal®

Canadian Brand NamesMigranal®

Pharmacologic CategoryAntimigraine Agent; Ergot Derivative

Use: Labeled IndicationsTreatment of migraine headache with or without aura; injection also indicated for treatment of cluster headaches

Use: Unlabeled/InvestigationalAdjunct for DVT prophylaxis for hip surgery, for orthostatic hypotension, xerostomia secondary to antidepressant use, and pelvic congestion with pain

Dosing: Adults

Migraine, cluster headache:

I.M., SubQ: 1 mg at first sign of headache; repeat hourly to a maximum dose of 3 mg total; maximum dose: 6 mg/week

I.V.: 1 mg at first sign of headache; repeat hourly up to a maximum dose of 2 mg total; maximum dose: 6 mg/week

Intranasal: 1 spray (0.5 mg) of nasal spray should be administered into each nostril; if needed, repeat after 15 minutes, up to a total of 4 sprays. **Note:** Do not exceed 3 mg (6 sprays) in a 24-hour period and no more than 8 sprays in a week.

Dosing: ElderlyRefer to adult dosing. Patients >65 years of age were not included in controlled clinical studies.

Dosing: Renal ImpairmentContraindicated in severe renal impairment

Dosing: Hepatic ImpairmentDosage reductions are probably necessary but specific guidelines are not available; contraindicated in severe hepatic dysfunction.

Administration: OtherPrior to administration of nasal spray, the nasal spray applicator must be primed (pumped 4 times); in order to let the drug be absorbed through the skin in the nose, patients should not inhale deeply through the nose while spraying or immediately after spraying; for best results, treatment should be initiated at the first symptom or sign of an attack; however, nasal spray can be used at any stage of a migraine attack

Storage

Injection: Store below 25°C (77°F); do not refrigerate or freeze. Protect from heat and light.

Nasal spray: Prior to use, store below 25°C (77°F); do not refrigerate or freeze. Once spray applicator has been prepared, use within 8 hours; discard any unused solution.

ContraindicationsHypersensitivity to dihydroergotamine or any component of the formulation; high-dose aspirin therapy; uncontrolled hypertension, ischemic heart disease, angina pectoris, history of MI, silent ischemia, or coronary artery vasospasm including Prinzmetal's angina; hemiplegic or basilar migraine; peripheral vascular disease; sepsis; severe hepatic or renal dysfunction; following vascular surgery; avoid use within 24 hours of sumatriptan, zolmitriptan, other serotonin agonists, or ergot-like agents; avoid during or within 2 weeks of discontinuing MAO inhibitors; ergot alkaloids are contraindicated with potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics); pregnancy

Allergy Considerations

- Ergot Alkaloid Allergy

Warnings/Precautions

Boxed warnings:

- CYP3A4 inhibitors: See “Concurrent drug therapy issues” below.

Concerns related to adverse effects:

- Cardiac valvular fibrosis: Ergot alkaloids have been associated with fibrotic valve thickening (eg, aortic, mitral, tricuspid); usually associated with long-term, chronic use.
- Cardiovascular effects: Vasospasm or vasoconstriction can occur, possibly resulting in decreased cerebral blood flow, ECG changes, and hypertension; sustained vasoconstriction may also lead to ischemic colitis, intermittent claudication, aggravation of angina, or precipitation of MI. Do not use is any patient at risk or predisposed to vascular effects of ergot alkaloids.
- Cerebrovascular events: Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have also occurred (in some cases resulted in fatalities) following use of the injection.
- Ergotism: Ergot alkaloid use may result in ergotism (intense vasoconstriction) resulting in peripheral vascular ischemia and possible gangrene. Ergotism is usually associated with overdosage or prolonged chronic use; do not exceed dosing guidelines and avoid prolonged administration.

- Pleural/retroperitoneal fibrosis: Rare cases of pleural and/or retroperitoneal fibrosis have been reported with prolonged daily use.

Disease-related concerns:

- Cardiovascular disease: Do not give to patients with risk factors for CAD until a cardiovascular evaluation has been performed; if evaluation is satisfactory, the healthcare provider should administer the first dose and cardiovascular status should be periodically evaluated.

Concurrent drug therapy issues:

- CYP3A4 inhibitors: **[U.S. Boxed Warning]: Ergot alkaloids are contraindicated with potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics); concomitant use associated with acute ergot toxicity (ergotism).**

Special populations:

- Elderly: Use with extreme caution or avoid use in the elderly; due to vasoconstrictive properties and cardiovascular adverse effects associated with ergot alkaloids.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Migranal® Nasal Spray: Local irritation to nose and throat (usually transient and mild-moderate in severity) can occur; long-term consequences on nasal or respiratory mucosa have not been extensively evaluated.

Geriatric ConsiderationsMonitor cardiac and peripheral effects closely in the elderly since they often have cardiovascular disease and peripheral vascular impairment (ie, diabetes mellitus, PVD) that will complicate therapy and monitoring for adverse effects.

Pregnancy Risk FactorX

Pregnancy ConsiderationsDihydroergotamine is oxytocic and should not be used during pregnancy.

LactationMay be excreted in breast milk/contraindicated

Breast-Feeding ConsiderationsErgot derivatives inhibit prolactin and it is known that ergotamine is excreted in breast milk (vomiting, diarrhea, weak pulse, and unstable blood pressure have been reported in nursing infants). It is not known if dihydroergotamine would also cause these effects, however, it is likely that it is excreted in human breast milk. Do not use in nursing women.

Adverse Reactions

>10%: Nasal spray: Respiratory: Rhinitis (26%)

1% to 10%: Nasal spray:

Central nervous system: Dizziness (4%), somnolence (3%)

Endocrine & metabolic: Hot flashes (1%)

Gastrointestinal: Nausea (10%), taste disturbance (8%), vomiting (4%), diarrhea (2%)

Local: Application site reaction (6%)

Neuromuscular & skeletal: Weakness (1%), stiffness (1%)

Respiratory: Pharyngitis (3%)

<1% (Limited to important or life-threatening): Injection and nasal spray: Abdominal pain, anxiety, cerebral hemorrhage, coronary artery vasospasm, cramps, diaphoresis increased, diarrhea, dizziness, edema, flushing, headache, hyperkinesis, hypertension, muscular weakness, myalgia, MI, myocardial ischemia, palpitation, paresthesia, peripheral ischemia, peripheral cyanosis, rash, stroke, subarachnoid hemorrhage, transient ventricular tachycardia, tremor, ventricular fibrillation

Postmarketing and/or case reports: Injection: Pleural and retroperitoneal fibrosis have been reported following prolonged use; cardiac valvular fibrosis has been associated with ergot alkaloids

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (weak)

Drug Interactions

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Efavirenz: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically, the risk for peripheral vasospasm and ischemia may be increased. *Risk X: Avoid combination*

Macrolide Antibiotics: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Posaconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Protease Inhibitors: May decrease the metabolism of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: Ergot Derivatives may enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Ergot Derivatives. This may cause serotonin syndrome. *Risk X: Avoid combination*

Voriconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Reference RangeMinimum concentration for vasoconstriction is reportedly 0.06 ng/mL

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic response and adverse effects on a regular basis. Teach patient proper use for either nasal spray or injection (storage, administration, injection technique, and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to women of childbearing age, unless patient is capable of complying with contraceptive use.

Patient EducationTake this drug as rapidly as possible when first symptoms occur. May cause rare feelings of numbness or tingling of fingers, toes, or face (use caution and avoid injury) or drowsiness (use caution when driving or engaging in potentially hazardous tasks until response to drug is known). Report heart palpitations, severe nausea or vomiting, and severe numbness of fingers or toes.

Nasal spray: Follow directions for use on package insert. Wait 15 minutes between inhalations. Use no more than 4 inhalations (2 mg) for a single administration; do not use >3 mg (6 sprays) in a 24-hour period and no more than 8 sprays in a week.

I.M.: Follow directions for injections and needle disposal.

Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as mesylate: 1 mg/mL (1 mL) [contains ethanol 6.2%]

D.H.E. 45®: 1 mg/mL (1 mL) [contains ethanol 6.2%]

Solution, intranasal spray, as mesylate (Migranal®): 4 mg/mL [0.5 mg/spray] (1 mL) [contains caffeine 10 mg/mL]

Generic AvailableYes: Injection

Pricing: U.S. (www.drugstore.com)

Solution (D.H.E. 45)

1 mg/mL (5): $369.30

Solution (Migranal)

4 mg/mL (4): $119.99

Mechanism of ActionErgot alkaloid alpha-adrenergic blocker directly stimulates vascular smooth muscle to vasoconstrict peripheral and cerebral vessels; also has effects on serotonin receptors

Pharmacodynamics/Kinetics

Onset of action: 15-30 minutes

Duration: 3-4 hours

Distribution: V_d: 14.5 L/kg

Protein binding: 93%

Metabolism: Extensively hepatic

Half-life elimination: 1.3-3.9 hours

Time to peak, serum: I.M.: 15-30 minutes

Excretion: Primarily feces; urine (10% mostly as metabolites)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Rhinitis and abnormal taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsUse is contraindicated in patients with cardiovascular disease because of its potent vasoconstrictor action. Administration may elicit marked increases in blood pressure and cardiac, cerebral, or peripheral vascular ischemia. Long-term use (injectable) has resulted in cardiac valvular fibrosis.

Index TermsDHE; Dihydroergotamine Mesylate

International Brand NamesAdhaegon (AT); Cervasal (BG); Dergott (JP); Detemes Retard (AT); Detms (LU); DH-Ergotamin (PL); DHE (IN); DHT (AR); Diergospray (FR); Dihydergot (AU, BE, BF, BJ, BR, CH, CI, CZ, DE, ES, ET, GH, GM, GN, GR, ID, IL, IN, KE, LR, LU, MA, ML, MR, MU, MW, NE, NG, NL, NO, PE, SC, SD, SL, SN, TN, TR, TZ, UG, VE, ZA, ZM, ZW); Dihydergot Sandoz (AT); Dihydroergotamin "Dak" (DK); Dihydroergotaminum Methansulfonicum (PL); Dihydroergotaminum Tartaricum (PL); Ditamin (HR, PL); Dystonal (BE); Ergotamina (PY); Ergovasan (AT); Ikaran (FR, IT, LU, PT); Ikaran LP (FR); Migranal (GB); Neomigran (HU, PL); Orstanorm (FI, SE); Parsel (MX); Seglor (AR, FR, IT, LU, TW); Seglor Retard (PT); Tamik (FR); Tenuatina (ES); Tonopan (MX); Verladyn (DE); Verteblan (GR)

Dihydrotachysterol

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English

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Pronunciation(dye hye droe tak ISS ter ole)
U.S. Brand NamesDHT™ Intensol™ [DSC]; DHT™ [DSC]; Hytakerol® [DSC]
Canadian Brand NamesHytakerol®
Pharmacologic CategoryVitamin D Analog
Use: Labeled IndicationsTreatment of hypocalcemia associated with hypoparathyroidism; prophylaxis of hypocalcemic tetany following thyroid surgery
Dosing: Adults

Hypoparathyroidism: Oral: Initial: 0.8-2.4 mg/day for several days followed by maintenance doses of 0.2-1 mg/day

Nutritional rickets: Oral: 0.5 mg as a single dose or 13-50 mcg/day until healing occurs

Renal osteodystrophy: Oral: Maintenance: 0.25-0.6 mg/24 hours adjusted as necessary to achieve normal serum calcium levels and promote bone healing

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricHypoparathyroidism: Oral:

Infants and young Children: Initial: 1-5 mg/day for 4 days, then 0.1-0.5 mg/day

Older Children: Refer to adult dosing.

StorageProtect from light.
ContraindicationsHypersensitivity to dihydrotachysterol or any component of the formulation; hypercalcemia; pregnancy (dose exceeding RDA)
Warnings/Precautions

Concerns related to adverse effects:

- Hypercalcemia: Use is contraindicated in patients with hypercalcemia.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease.
- Renal impairment: Use with caution in patients with decreased renal function (especially with secondary hyperparathyroidism) or renal stones.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Calcium-phosphate product: Serum calcium and phosphorus product must not exceed 70.

Geriatric ConsiderationsRecommended daily allowances (RDA) have not been developed for persons >65 years of age; vitamin D, folate, and B_{12} (cyanocobalamin) have decreased absorption with age, but the clinical significance is yet unknown. Calorie requirements decrease with age and therefore, nutrient density must be increased to ensure adequate nutrient intake, including vitamins and minerals. Therefore, the use of a daily supplement with a multiple vitamin with minerals is recommended. Elderly consume less vitamin D, absorption may be decreased, and many elderly have decreased sun exposure; therefore, elderly should receive supplementation with 800 units of vitamin D (20 mcg)/day. This is a recommendation of particular need to those with high risk for osteoporosis.
Pregnancy Risk FactorA/D (dose exceeding RDA recommendation)
LactationEnters breast milk/compatible
Adverse Reactions

>10%:

Endocrine & metabolic: Hypercalcemia

Renal: Serum creatinine increased, hypercalciuria

<1%: Convulsions, polydipsia, nausea, vomiting, anorexia, weight loss, polyuria, anemia, weakness, metastatic calcification, renal damage

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersMonitor renal function, serum calcium, and phosphate concentrations; if hypercalcemia is encountered, discontinue agent until serum calcium returns to normal

Reference RangeCalcium (serum): 9-10 mg/dL (4.5-5 mEq/L)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess results of laboratory tests, effectiveness of therapy, and adverse effects at beginning of therapy and regularly with long-term use. Assess knowledge/teach patient appropriate use, appropriate nutritional counseling, possible side effects/interventions, and adverse symptoms to report.

Monitoring: Lab TestsRenal function, serum calcium, and phosphate concentrations. If hypercalcemia is encountered, discontinue agent until serum calcium returns to normal.

Patient EducationTake exact dose prescribed; do not take more than recommended. Your prescriber may recommend a special diet. Do not increase calcium intake without consulting prescriber. Avoid magnesium supplements or magnesium-containing antacids. You may experience nausea, vomiting, or metallic taste (small frequent meals, frequent mouth care, or sucking hard candy may help); or hypotension (use caution when rising from sitting or lying position or when climbing stairs or bending over). Report chest pain or palpitations; acute headache, dizziness, or feeling of weakness; unresolved nausea or vomiting; persistent metallic taste; unrelieved muscle or bone pain; or CNS irritability. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule (Hytakerol®): 0.125 mg [contains sesame oil] [DSC]

Solution, oral concentrate (DHT™ Intensol™): 0.2 mg/mL (30 mL) [contains alcohol 20%] [DSC]

Tablet (DHT™): 0.125 mg, 0.2 mg, 0.4 mg [DSC]

Generic AvailableNo

Mechanism of ActionSynthetic analogue of vitamin D with a faster onset of action; stimulates calcium and phosphate absorption from the small intestine, promotes secretion of calcium from bone to blood; promotes renal tubule resorption of phosphate

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Calcium: 2-4 weeks

Duration: ≤9 weeks

Absorption: Well absorbed

Distribution: Stored in liver, fat, skin, muscle, and bone

Excretion: Feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentConcurrent use with phenytoin or phenobarbital may decrease effectiveness

Index TermsDichysterol

References

Letsou AP and Price LS, “Health Aging and Nutrition: An Overview,” *Clin Geriatr Med*, 1987, 3(2):253-60. [PubMed 3555761]

Myrianthopoulos M, “Dietary Treatment of Hyperlipidemia in the Elderly,” *Clin Geriatr Med*, 1987, 3(2):343-59. [PubMed 3581018]

Riggs BL and Melton LJ, “The Prevention and Treatment of Osteoporosis,” *N Engl J Med*, 1992, 327(9):620-7.[PubMed 1640955]

International Brand NamesA.T. 10 (HR, HU, LU, ZA); A.T.10 (AT, BE, BG, CH, DE, HN, RU); AT 10 (GB, IE, IT); AT-10 (AU); Dihydral (LU, NL); Dygratyl (DK, FI, SE); Hytakerol (JP); Tachystin (CZ, HU)

Diloxanide Furoate

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(dye LOKS ah nide FYOOR oh ate)
U.S. Brand NamesFuramide®
Pharmacologic CategoryAmebicide
Use: Labeled IndicationsTreatment of amebiasis (asymptomatic cyst passers)
RestrictionsNot commercially available in U.S.
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.
Generic AvailableNo
Pharmacotherapy PearlsNot commercially available in U.S.; available from:

The Centers for Disease Control Drug and Immunobiologic Service

1600 Clifton Road

Building 1 Room 1259

Atlanta, GA 30333

Monday-Friday 8 AM to 4:30 PM: (404) 639-3670

Nonbusiness hours (emergencies only): (404) 639-2888

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
References

"Drugs for Parasitic Infections," *Med Lett Drugs Ther*, 1993, 35(911):111-22.[PubMed 8246830]

Diltiazem

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cardizem® may be confused with Cardene®, Cardene SR®, Cardizem CD®, Cardizem SR®, cardiem

Cartia XT™ may be confused with Procardia XL®

Diltiazem may be confused with Dilantin®

Tiazac® may be confused with Tigan®, Tiazac® XC [CAN], Ziac®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V. formulation) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Significant differences exist between oral and I.V. dosing. Use caution when converting from one route of administration to another.

International issues:

Cardizem® may be confused with Cardem® which is a brand name for celiprolol in Spain

Cartia XT™ may be confused with Cartia® which is a brand name for aspirin in multiple international markets

Dilacor®: Brand name for digoxin in Serbia, a brand name for verapamil in Brazil, and a brand name for barnidipine in Argentina

Tiazac® may be confused with Tazac® which is a brand name for nizatidine in Australia

Tiazac® may be confused with Tiazac® XC which is a brand name for diltiazem available in Canada (not available in U.S.)

Pronunciation(dil TYE a zem)

U.S. Brand NamesCardizem®; Cardizem® CD; Cardizem® LA; Cartia XT™; Dilacor® XR; Dilt-CD; Dilt-XR; Taztia XT™; Tiazac®

Canadian Brand NamesAlti-Diltiazem CD; Apo-Diltiaz CD®; Apo-Diltiaz SR®; Apo-Diltiaz TZ®; Apo-Diltiaz®; Apo-Diltiaz® Injectable; Cardizem®; Cardizem® CD; Cardizem® SR; Diltiazem HCl ER®; Diltiazem Hydrochloride Injection; Gen-Diltiazem; Gen-Diltiazem CD; Med-Diltiazem; Novo-Diltazem; Novo-Diltazem-CD; Novo-Diltiazem HCl ER; Nu-Diltiaz; Nu-Diltiaz-CD; ratio-Diltiazem CD; Rhoxal-diltiazem CD; Rhoxal-diltiazem SR; Rhoxal-diltiazem T; Sandoz-Diltiazem CD; Sandoz-Diltiazem T; Syn-Diltiazem®; Tiazac® ; Tiazac® XC

Pharmacologic CategoryCalcium Channel Blocker

Use: Labeled Indications

Oral: Essential hypertension; chronic stable angina or angina from coronary artery spasm

Injection: Atrial fibrillation or atrial flutter; paroxysmal supraventricular tachycardia (PSVT)

Use: Unlabeled/InvestigationalInvestigational: Therapy of Duchenne muscular dystrophy

Dosing: Adults

Angina: Oral:

Capsule, extended release (Cardizem® CD, Cartia XT™, Dilacor® XR, Tiazac®): Initial: 120-180 mg once daily (maximum dose: 480 mg/day)

Tablet, extended release (Cardizem® LA, Tiazac® XC [CAN; not available in U.S.]): 180 mg once daily; may increase at 7- to 14-day intervals (maximum recommended dose: 360 mg/day)

Tablet, immediate release (Cardizem®): Usual starting dose: 30 mg 4 times/day; usual range: 180-360 mg/day

Hypertension: Oral:

Capsule, extended release (Cardizem® CD, Cartia XT™, Dilacor® XR, Tiazac®): Initial: 180-240 mg once daily; dose adjustment may be made after 14 days; usual dose range (JNC 7): 180-420 mg/day; Tiazac®: usual dose range: 120-540 mg/day

Capsule, sustained release: Initial: 60-120 mg twice daily; dose adjustment may be made after 14 days; usual range: 240-360 mg/day

Tablet, extended release (Cardizem® LA, Tiazac® XC [CAN; not available in U.S.]): Initial: 180-240 mg once daily; dose adjustment may be made after 14 days; usual dose range (JNC 7): 120-540 mg/day

Atrial fibrillation, atrial flutter, PSVT: I.V.:

Initial bolus dose: 0.25 mg/kg actual body weight over 2 minutes (average adult dose: 20 mg)

Repeat bolus dose (may be administered after 15 minutes if the response is inadequate): 0.35 mg/kg actual body weight over 2 minutes (average adult dose: 25 mg)

Continuous infusion (requires an infusion pump; infusions >24 hours or infusion rates >15 mg/hour are not recommended): Initial infusion rate of 10 mg/hour; rate may be increased in 5 mg/hour increments up to 15 mg/hour as needed; some patients may respond to an initial rate of 5 mg/hour.

If diltiazem injection is administered by continuous infusion for >24 hours, the possibility of decreased diltiazem clearance, prolonged elimination half-life, and increased diltiazem and/or diltiazem metabolite plasma concentrations should be considered.

Conversion from I.V. diltiazem to oral diltiazem:

Oral dose (mg/day) is approximately equal to [rate (mg/hour) x 3 + 3] x 10.

3 mg/hour = 120 mg/day

5 mg/hour = 180 mg/day

7 mg/hour = 240 mg/day

11 mg/hour = 360 mg/day

Dosing: ElderlyRefer to adult dosing. **Note:** Patients ≥60 years may respond to a lower initial dose (eg, 120 mg once daily using extended release capsule)

Dosing: Pediatric

Children: Minimal information available; some centers use the following:

Hypertension (unlabeled use): Oral: Initial: 1.5-2 mg/kg/day in 3 divided doses (maximum: 6 mg/kg/day, up to 360 mg/day)

Note: Doses up to 8 mg/kg/day given in 4 divided doses have been used for investigational therapy of Duchenne muscular dystrophy

Adolescents: Refer to adult dosing.

Dosing: Renal ImpairmentUse with caution as diltiazem is extensively metabolized by the liver and excreted in the kidneys and bile. Not removed by hemo- or peritoneal dialysis; supplemental dose is not necessary.

Dosing: Hepatic ImpairmentUse with caution as diltiazem is extensively metabolized by the liver and excreted in the kidneys and bile.

Calculations

- Diltiazem

Administration: I.V.Bolus doses given over 2 minutes with continuous ECG and blood pressure monitoring. Continuous infusion should be via infusion pump.

Administration: I.V. DetailResponse to bolus may require several minutes to reach maximum. Response may persist for several hours after infusion is discontinued.

pH: 3.7-4.1

Administration: OralDo not crush long acting dosage forms.

Taztia XT™, Tiazac®: Capsules may be opened and sprinkled on a spoonful of applesauce. Applesauce should be swallowed without chewing, followed by drinking a glass of water.

Tiazac® XC [CAN; not available in U.S.]: Administer at bedtime

Storage

Capsule, tablet: Store at 15°C to 30°C (59°F to 86°F). Protect from light.

Solution for injection: Store in refrigerator at 2°C to 8°C (36°F to 46°F). May be stored at room temperature for up to 1 month; do not freeze. Following dilution with $D_5$1/2NS, D_5W, or NS, solution is stable for 24 hours at room temperature or under refrigeration.

CompatibilityStable in $D_5{}^1/_2$NS, D_5W, NS.

Y-site administration: Compatible: Albumin, amikacin, amphotericin B, aztreonam, bretylium, bumetanide, cefazolin, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, cimetidine, ciprofloxacin, clindamycin, digoxin, dobutamine, dopamine, doxycycline, epinephrine, erythromycin lactobionate, esmolol, fentanyl, fluconazole, gentamicin, hetastarch, hydromorphone, imipenem/cilastatin, labetalol, lidocaine, lorazepam, meperidine, metoclopramide, metronidazole, midazolam, milrinone, morphine, multivitamins, nicardipine, nitroglycerin, norepinephrine, oxacillin, penicillin G potassium, pentamidine, piperacillin, potassium chloride, potassium phosphates, ranitidine, sodium nitroprusside, theophylline, ticarcillin, ticarcillin/clavulanate potassium, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, vecuronium. **Incompatible:** Diazepam, furosemide, phenytoin, rifampin, thiopental. **Variable (consult detailed reference):** Acetazolamide, acyclovir, aminophylline, ampicillin, ampicillin/sulbactam, cefamandole, cefoperazone, heparin, hydrocortisone sodium succinate, insulin (regular), methylprednisolone sodium succinate, nafcillin, procainamide, sodium bicarbonate.

Extemporaneously PreparedA 12 mg/mL oral liquid preparation made from tablets (regular, not sustained release) and 3 different vehicles (cherry syrup, a 1:1 mixture of Ora-Sweet® and Ora-Plus®, or a 1:1 mixture of Ora-Sweet® SF and Ora-Plus®) was stable for 60 days when stored in amber plastic prescription bottles in the dark at room temperature (25°C) or under refrigeration (5°C); grind sixteen 90 mg tablets in a mortar into a fine powder; add 10 mL of the vehicle and mix well to form a uniform paste; mix while adding the vehicle in geometric proportions to **almost** 120 mL; transfer to a calibrated bottle and qs ad with vehicle to 120 mL; label “shake well” and “protect from light”.

Allen LV and Erickson MA, “Stability of Baclofen, Captopril, Diltiazem Hydrochloride, Dipyridamole, and Flecainide Acetate in Extemporaneously Compounded Oral Liquids,” *Am J Health Syst Pharm*, 1996, 53(18):2179-84.

Contraindications

Oral: Hypersensitivity to diltiazem or any component of the formulation; sick sinus syndrome; second- or third-degree AV block (except in patients with a functioning artificial pacemaker); severe hypotension (systolic <90 mm Hg); acute MI and pulmonary congestion

Intravenous (I.V.): Hypersensitivity to diltiazem or any component of the formulation; sick sinus syndrome; second- or third-degree AV block (except in patients with a functioning artificial pacemaker); severe hypotension (systolic <90 mm Hg); acute MI and pulmonary congestion; administration concomitantly or within a few hours of the administration of I.V. beta-blockers; atrial fibrillation or flutter associated with accessory bypass tract (eg, Wolff-Parkinson-White syndrome); ventricular tachycardia (with wide-complex tachycardia, must determine whether origin is supraventricular or ventricular)

Canadian labeling: Additional contraindications (not in U.S. labeling): I.V. and oral: Pregnancy; use in women of childbearing potential

Allergy Considerations

- Diltiazem Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Conduction abnormalities: May cause first-, second-, and third-degree AV block or sinus bradycardia; risk increases with agents known to slow cardiac conduction.
- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition.
- Peripheral edema: The most common side effect is peripheral edema; occurs within 2-3 weeks of starting therapy.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; may require lower starting dose.
- Hypertrophic obstructive cardiomyopathy (HOCM): Use with caution in patients with HOCM.
- Left ventricular dysfunction: Use with caution in left ventricular dysfunction; due to negative inotropic effects, may exacerbate condition.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy:

- Beta-blockers: Concomitant use with beta-blockers can result in conduction disturbances, hypotension, and worsened LV function; I.V. administration concomitantly or within a few hours of I.V. beta-blockers is contraindicated.
- Digoxin: Concomitant use with digoxin can result in conduction disturbances.

Geriatric ConsiderationsElderly may experience a greater hypotensive response; constipation may be encountered more often in elderly. Calcium channel blockers are no more effective in elderly than other therapies; however, they do not cause significant CNS effects which is an advantage over other antihypertensive agents (eg, beta-blockers, clonidine).

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic and embryotoxic effects have been demonstrated in small animals. There are no adequate and well-controlled studies in pregnant women.

LactationEnters breast milk/not recommended (AAP considers “compatible”)

Breast-Feeding ConsiderationsFreely diffuses into breast milk; however, the AAP considers diltiazem to be **compatible** with breast-feeding. Available evidence suggests safe use during breast-feeding.

Adverse Reactions**Note:** Frequencies represent ranges for various dosage forms. Patients with impaired ventricular function and/or conduction abnormalities may have higher incidence of adverse reactions.

>10%:

Cardiovascular: Edema (2% to 15%)

Central nervous system: Headache (5% to 12%)

2% to 10%:

Cardiovascular: AV block (first degree 2% to 8%), edema (lower limb, 2% to 8%), pain (6%), bradycardia (2% to 6%), hypotension (<2% to 4%), vasodilation (2% to 3%), extrasystoles (2%), flushing (1% to 2%), palpitation (1% to 2%)

Central nervous system: Dizziness (3% to 10%), nervousness (2%)

Dermatologic: Rash (1% to 4%)

Endocrine & metabolic: Gout (1% to 2%)

Gastrointestinal: Dyspepsia (1% to 6%), constipation (<2% to 4%), vomiting (2%), diarrhea (1% to 2%)

Local: Injection site reactions: Burning, itching (4%)

Neuromuscular & skeletal: Weakness (1% to 4%), myalgia (2%)

Respiratory: Rhinitis (<2% to 10%), pharyngitis (2% to 6%), dyspnea (1% to 6%), bronchitis (1% to 4%), sinus congestion (1% to 2%)

<2%: Albuminuria, alkaline phosphatase increased, allergic reaction, ALT increased, AST increased, amblyopia, amnesia, angina, anorexia, arrhythmia, AV block (second or third degree), bruising, bundle branch block, CHF, CPK increased, crystalluria, depression, dreams abnormal, dry mouth, dysgeusia, ECG abnormalities, epistaxis, gait abnormality, gynecomastia, hallucination, hyperglycemia, hyperuricemia, impotence, insomnia, LDH increased, muscle cramps, nausea, neck rigidity, nocturia, pain, paresthesia, personality change, petechiae, photosensitivity, polyuria, pruritus, somnolence, syncope, tachycardia, thirst, tinnitus, tremor, ventricular extrasystoles, weight gain

Postmarketing and/or case reports: Alopecia, angioedema, asystole, bleeding time increased, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, leukopenia, purpura, retinopathy, Stevens-Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis

Metabolism/Transport Effects **Substrate** of CYP2C9 (minor), 2D6 (minor), 3A4 (major); **Inhibits** CYP2C9 (weak), 2D6 (weak), 3A4 (moderate)

Drug Interactions

Alfentanil: Diltiazem may increase the serum concentration of Alfentanil. *Risk C: Monitor therapy*

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amiodarone: Calcium Channel Blockers (Nondihydropyridine) may enhance the bradycardic effect of Amiodarone. Sinus arrest has been reported. *Risk D: Consider therapy modification*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Calcium Channel Blockers (Nondihydropyridine). Anilidopiperidine Opioids may enhance the hypotensive effect of Calcium Channel Blockers (Nondihydropyridine). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Diltiazem. Diltiazem may increase the serum concentration of Aprepitant. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Beta-Blockers: Calcium Channel Blockers (Nondihydropyridine) may enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

BusPIRone: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Dihydropyridine): Calcium Channel Blockers (Nondihydropyridine) may enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of CarBAMazepine. CarBAMazepine may increase the metabolism of Calcium Channel Blockers (Nondihydropyridine). *Risk D: Consider therapy modification*

Cardiac Glycosides: Calcium Channel Blockers (Nondihydropyridine) may enhance the AV-blocking effect of Cardiac Glycosides. Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Cardiac Glycosides. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Colestipol: May decrease the absorption of Diltiazem. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of CycloSPORINE. CycloSPORINE may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eletriptan: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Eletriptan. *Risk C: Monitor therapy*

Eplerenone: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Diltiazem. The active metabolite aprepitant is likely responsible for this effect. Diltiazem may increase the serum concentration of Fosaprepitant. Specifically, diltiazem may increase the concentration of the active metabolite aprepitant. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Pravastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Lithium: Calcium Channel Blockers (Nondihydropyridine) may enhance the neurotoxic effect of Lithium. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Lithium. Decreased or unaltered lithium concentrations have also been reported with this combination. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Calcium Channel Blockers (Nondihydropyridine) may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. *Risk D: Consider therapy modification*

QuiNIDine: Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of QuiNIDine. *Risk D: Consider therapy modification*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Ranolazine: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: Calcium Channel Blockers (Nondihydropyridine) may enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Tacrolimus: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Tacrolimus. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase risk of hypotension or vasodilation).

Food: Diltiazem serum levels may be elevated if taken with food. Serum concentrations were not altered by grapefruit juice in small clinical trials.

Herb/Nutraceutical: St John's wort may decrease diltiazem levels. Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice, yohimbe (may worsen hypertension). Avoid black cohosh, California poppy, coleus, garlic, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Monitoring ParametersLiver function tests, blood pressure, ECG

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions (eg, increased risk of bradycardia, conduction delays, decreased cardiac output). I.V. requires use of infusion pump and continuous cardiac and hemodynamic monitoring. Assess therapeutic effectiveness according to purpose for use (hypertension, angina, atrial fib/flutter or PSVT) and adverse reactions when beginning therapy, when changing dose, and periodically during long-term therapy. Teach patient appropriate use (oral), interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsLiver function tests

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Oral: Take as directed; do not alter dosage or discontinue therapy without consulting prescriber. Do not crush or chew extended release form. Avoid (or limit) alcohol and caffeine. May cause dizziness or lightheadedness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report chest pain, palpitations, irregular heartbeat; unusual cough, respiratory difficulty; swelling of extremities; muscle tremors or weakness; confusion or acute lethargy; skin rash; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Capsule, extended release, as hydrochloride [once-daily dosing]: 120 mg, 180 mg, 240 mg, 300 mg, 360 mg, 420 mg

Cardizem® CD: 120 mg, 180 mg, 240 mg, 300 mg, 360 mg

Cartia XT™: 120 mg, 180 mg, 240 mg, 300 mg

Dilacor® XR, Dilt-XR: 120 mg, 180 mg, 240 mg

Dilt-CD: 120 mg, 180 mg, 240 mg, 300 mg

Taztia XT™: 120 mg, 180 mg, 240 mg, 300 mg, 360 mg

Tiazac®: 120 mg, 180 mg, 240 mg, 300 mg, 360 mg, 420 mg

Capsule, extended release, as hydrochloride [twice-daily dosing]: 60 mg, 90 mg, 120 mg

Injection, solution, as hydrochloride: 5 mg/mL (5 mL, 10 mL, 25 mL)

Injection, powder for reconstitution, as hydrochloride: 100 mg

Tablet, as hydrochloride: 30 mg, 60 mg, 90 mg, 120 mg

Cardizem®: 30 mg, 60 mg, 90 mg, 120 mg

Tablet, extended release, as hydrochloride:

Cardizem® LA: 120 mg, 180 mg, 240 mg, 300 mg, 360 mg, 420 mg

Tiazac® XC [CAN; not available in U.S.]: 120 mg, 180 mg, 240 mg, 300 mg, 360 mg

Generic AvailableYes: Excludes extended release tablet

Pricing: U.S. (www.drugstore.com)

Capsule, 12-hour (Diltiazem HCl CR)

60 mg (60): $35.99

90 mg (60): $45.99

120 mg (60): $71.51

Capsule, 24-hour (Cardizem CD)

120 mg (30): $92.57

180 mg (30): $108.44

240 mg (30): $149.42

300 mg (30): $145.99

360 mg (30): $204.98

Capsule, 24-hour (Cartia XT)

120 mg (30): $23.99

180 mg (30): $27.99

240 mg (30): $43.99

300 mg (30): $58.99

Capsule, 24-hour (Dilacor XR)

120 mg (30): $65.31

180 mg (30): $86.39

240 mg (30): $86.39

Capsule, 24-hour (Diltia XT)

120 mg (30): $27.99

180 mg (30): $32.99

240 mg (30): $34.99

Capsule, 24-hour (Diltiazem HCl Coated Beads)

120 mg (30): $29.99

180 mg (30): $34.99

300 mg (30): $58.99

Capsule, 24-hour (Diltiazem HCl CR)

240 mg (90): $65.99

Capsule, 24-hour (Diltiazem HCl ER Beads)

120 mg (30): $25.99

180 mg (30): $29.99

240 mg (30): $38.99

300 mg (30): $46.99

360 mg (30): $47.99

420 mg (90): $136.98

Capsule, 24-hour (Taztia XT)

120 mg (30): $33.99

180 mg (30): $39.99

240 mg (30): $49.99

300 mg (30): $64.99

360 mg (30): $65.99

Capsule, 24-hour (Tiazac)

120 mg (30): $47.83

180 mg (30): $53.50

240 mg (30): $74.20

300 mg (30): $93.68

360 mg (30): $94.89

Tablet, 24-hour (Cardizem LA)

120 mg (30): $65.93

180 mg (30): $82.99

240 mg (30): $89.99

300 mg (30): $126.78

360 mg (30): $133.78

420 mg (30): $140.09

Tablets (Cardizem)

30 mg (90): $50.99

60 mg (90): $76.00

90 mg (90): $105.99

Tablets (Diltiazem HCl)

30 mg (90): $12.99

60 mg (90): $22.50

90 mg (90): $22.00

120 mg (90): $29.99

Mechanism of ActionInhibits calcium ion from entering the “slow channels” or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary vascular smooth muscle and coronary vasodilation; increases myocardial oxygen delivery in patients with vasospastic angina

Pharmacodynamics/Kinetics

Onset of action: Oral: Immediate release tablet: 30-60 minutes

Absorption: Immediate release tablet: >90%; Extended release capsule: ~93%

Distribution: V_d: 3-13 L/kg

Protein binding: 70% to 80%

Metabolism: Hepatic; extensive first-pass effect; following single I.V. injection, plasma concentrations of N-monodesmethyldiltiazem and desacetyldiltiazem are typically undetectable; however, these metabolites accumulate to detectable concentrations following 24-hour constant rate infusion. N-monodesmethyldiltiazem appears to have 20% of the potency of diltiazem; desacetyldiltiazem is about 25% to 50% as potent as the parent compound.

Bioavailability: Oral: ~40% (undergoes extensive first-pass metabolism)

Half-life elimination: Immediate release tablet: 3-4.5 hours, may be prolonged with renal impairment; Extended release tablet: 6-9 hours; Extended release capsules: 5-10 hours

Time to peak, serum: Immediate release tablet: 2-4 hours; Extended release tablet: 11-18 hours; Extended release capsule: 10-14 hours

Excretion: Urine (2% to 4% as unchanged drug; 6% to 7% as metabolites); feces

Related Information

- Antiarrhythmic Drugs
- Calcium Channel Blockers
- Hypertension

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Diltiazem has been reported to cause >10% incidence of gingival hyperplasia; usually disappears with discontinuation (consultation with physician is suggested).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, insomnia, nervousness, or sedation

Mental Health: Effects on Psychiatric TreatmentMay produce leukopenia; use caution with clozapine and carbamazepine; lithium levels may be increased or decreased; monitor serum lithium levels; benzodiazepines (midazolam, triazolam), buspirone, and carbamazepine levels may be increased; monitor for increased side effects

Cardiovascular ConsiderationsDiltiazem is an effective antihypertensive alone or in combination with other agents. Antihypertensive therapy should be individualized with consideration given to the patient's concomitant diseases and compelling indications for therapy.

In the treatment of acute myocardial infarction, diltiazem may be used to treat hypertension or ongoing ischemia if beta-blocker therapy is ineffective or contraindicated and in the absence of left ventricular dysfunction, pulmonary congestion, or AV block. In this setting, diltiazem may be beneficial. Diltiazem should be avoided in patients with left ventricular dysfunction or pulmonary congestion.

Diltiazem may be administered intravenously in the acute setting to attain ventricular rate control in patients with atrial fibrillation or flutter. Patients who respond, defined in general as at least a 20% decrease in ventricular response rate or attaining a rate <100 beats/minute, can be continued on oral therapy to maintain control. It is important to consider the potential drug interaction with digoxin, as these agents are both used in this setting.

In the treatment of unstable angina/non-ST-segment elevation MI, a nondihydropyridine calcium antagonist (diltiazem or verapamil) may be considered in patients with continuing or frequently recurring ischemia when beta-blockers are contraindicated (Class I). Oral long-acting calcium antagonists may also be considered in addition to beta-blockers and nitrates (Class IIa).

Anesthesia and Critical Care Concerns/Other ConsiderationsDiltiazem may be administered intravenously in the acute setting to attain ventricular rate control in patients with atrial fibrillation or flutter. Patients who respond, defined in general as at least a 20% decrease in ventricular response rate or attaining a rate <100 beats/minute, can be continued on oral therapy to maintain control.

Index TermsDiltiazem Hydrochloride

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International Brand NamesAcalix (AR, PY, VE); Adizem (IE, LU); Adizem-CD (IL); Adizem-XL (IE); Aldizem (HR, PL); Altiazem (BG, HK, IT); Altiazem Retard (IT); Altiazem RR (EE, RU); Angiotrofen (CR, DO, GT, HN, NI, PA, SV); Angiotrofin (CO, MX); Angiotrofin Retard (MX); Angiozem (PH); Angizem (IT); Apo-Diltiaz (PL); Apo-diltiazem (NZ); Balcor (BR); Beatizem (SG); Bi-Tildiem (FR); Blocalcin (HU, PL); Calcicard (GB); Calnurs (JP); Cardcal (AU); Cardiazem (KP); Cardil (BG, DK, MY, RU); Cardil Retard (GR); Cardiosta LP (FR); Cardizem (AU, BR, DK, FI, ID, NO, SE); Cardizem CD (AU, BR); Cardizem Retard (DK, FI, SE, TW); Cardizem SR (BR); Cardizem Unotard (TW); Cartia XT (TW); Cascor XL (MY, TH); Coras (AU); Cordizem (ID, MY); Dasav (MX); Dazil (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Deltazen (FR); Diacor LP (FR); Diacordin (PL); Diladel (IT); Dilatam (IL, PH, SG, ZA); Dilatam 120 (IL); Dilatame (AT); Dilcard (NZ); Dilcardia (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Dilcor (DK); Dilem SR (TH); Dilfar (PT); Dilren (RU); Dilrene (CZ, FR, HN, HU); Dilso (MY); Dilta-Hexal (LU); Diltahexal (DE, LU); Diltam (IE); Diltan (BB, BM, BS, BZ, GY, HU, JM, NL, SR, TT); Diltan SR (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Diltelan (KP, TW); Diltelan Depot (IE); Diltiasyn (CO); Diltiazem (PL); Diltiazem-B (HU); Diltiazem-Ethypharm (LU); Diltiazem-Xl (LU); Diltime (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Dilzanton (DE); Dilzem (AE, AT, AU, BG, BH, CH, CY, CZ, DE, EG, FI, HN, HR, HU, IE, IL, IN, IQ, IR, JO, KW, LB, LY, NZ, OM, PH, PK, PL, QA, RU, SA, SY, TH, YE); Dilzem CD (AU); Dilzem Retard (AE, AT, BG, BH, CY, CZ, DE, EG, HN, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Dilzem RR (CH); Dilzem SR (GB, NZ); Dilzene (IT); Dilzereal 90 Retard (DE); Dilzicardin (DE); Dinisor (ES); Dinisor Retard (ES); DTM (IN); Dyalac (PH); Entrydil (IE); Ergolan (CL); Filazem (PH); Gadoserin (JP); Grifodilzem (PE); Hagen (TW); Helsibon (JP); Herben (KP); Herbesser (ID, JP, MY, TH, TW); Herbesser 180 SR (HK); Herbesser 60 (MY, TH); Herbesser 90 SR (HK, MY, TH); Herbesser R100 (HK, JP); Herbesser R200 (HK, JP); Herbessor (SG); Herbessor 30 (MY); Hesor (TW); Iski (IN); Iski-90 SR (IN); Kaizem CD (IN); Lanodil (ID); Levodex (IL); Lytelsen (JP); Masdil (ES); Metazem (IE); Mono-Tildiem (LU); Mono-Tildiem SR (SG); Monotildiem (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Myonil (DK); Myonil Retard (DK); Oxycardil (PL); Pazeadin (JP); Progor (TH, TW); Surazem (LU); Tazem (TW); Tiadil (PT); Tilazem (AR, CN, CO, EC, MX, PE, UY, ZA); Tilazem 90 (ZA); Tildiem (BE, CH, CN, FR, GB, GR, IE, IT, LU, MY, NL); Tildiem CR (NL); Tildiem LA (GB); Tildiem Retard (GR); Vasmulax (PH); Vasocardol CD (AU); Zandil (PH); Zemtrial (PH); Zilden (PL); Ziruvate (JP)

DimenhyDRINATE

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English English

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Medication Safety Issues

Sound-alike/look-alike issues:

DimenhyDRINATE may be confused with diphenhydrAMINE

Pronunciation(dye men HYE dri nate)

U.S. Brand NamesDramamine® [OTC]; Driminate® [OTC]; TripTone® [OTC]

Canadian Brand NamesApo-Dimenhydrinate®; Children's Motion Sickness Liquid; Dinate®; Gravol®; Jamp® Travel Tablet; Nauseatol; Novo-Dimenate; SAB-Dimenhydrinate

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTreatment and prevention of nausea, vertigo, and vomiting associated with motion sickness

Dosage forms available in Canada (not available in the U.S.), including parenteral formulations and suppositories, are also approved for the treatment of postoperative nausea and vomiting and treatment of radiation sickness.

Use: Unlabeled/InvestigationalTreatment of Meniere's disease

Dosing: Adults

Motion sickness (prevention/treatment): Oral: 50-100 mg every 4-6 hours, not to exceed 400 mg/day

Gravol® L/A (not available in the U.S.): Oral: 75-150 mg every 8-12 hours, up to a maximum of five 75 mg caplets or three 100 mg caplets in 24 hours

Additional formulations/uses (approved in Canada) for parenteral/suppository formulations (not available in U.S.):

Postoperative nausea and vomiting: I.M., I.V., rectal: 50-100 mg administered 30-60 minutes prior to radiation therapy; may be repeated as needed up to a maximum of 400 mg in 24 hours

Radiation sickness: I.M., I.V., rectal: 50-100 mg administered 30-60 minutes prior to radiation therapy. May be repeated as needed up to a maximum of 400 mg in 24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricMotion sickness (prevention/treatment): Oral:

2-5 years: 12.5-25 mg every 6-8 hours, maximum: 75 mg/day

6-12 years: 25-50 mg every 6-8 hours, maximum: 150 mg/day

Dietary ConsiderationsMay be taken with food or water.

ContraindicationsHypersensitivity to dimenhydrinate or any component

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or angle-closure glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Antihistamines may cause excitation in young children. Not for OTC use in children <2 years of age.

Dosage form specific issues:

- Parenteral formulations: (Not available in the U.S.): Intended for I.V. and I.M. use are distinct and should not be confused. The I.M. formulation can be used for I.V. administration only after dilution.

- Phenylalanine: Some products may contain phenylalanine.

- Tartrazine: Some products may contain tartrazine.

Geriatric Considerations

Monitor for anticholinergic side effects (confusion, constipation, etc); if possible, limit use to short-term therapy

Pregnancy Risk FactorB

Adverse Reactions

>10%:

Central nervous system: Slight to moderate drowsiness

Respiratory: Thickening of bronchial secretions

1% to 10%:

Central nervous system: Dizziness, fatigue, headache, nervousness

Gastrointestinal: Abdominal pain, diarrhea, increased appetite, nausea, weight gain, xerostomia

Neuromuscular & skeletal: Arthralgia

Respiratory: Pharyngitis

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Capsule, softgel (Gravol®) [CAN]: 50 mg [not available in the U.S.]

Capsule, long-acting (Gravol® L/A) [CAN]: 75 mg, 100 mg [not available in the U.S.]

Injection, solution: 50 mg/mL (1 mL)

Gravol® I.M. [CAN]: 50 mg/mL (1 mL, 5 mL) [not available in the U.S.]

Gravol® I.V. [CAN]: 10 mg/mL (5 mL) [not available in the U.S.]

Solution, oral (Gravol® [CAN], Children’s Motion Sickness [CAN]): 3 mg/mL (75 mL) [not available in the U.S.]

Suppository, rectal (Gravol® [CAN], Sab-Dimenhydrinate [CAN]): 75 mg, 100 mg [not available in the U.S.]

Tablet:

Dinate® [CAN], Jamp® Travel Tablet [CAN], Nauseatol® [CAN]: 50 mg

Dramamine®: 50 mg

Driminate®: 50 mg [scored]

Gravol® Filmkote Jr [CAN]: 25 mg [not available in the U.S.]

Gravol® Filmkote [CAN]: 50 mg [not available in the U.S.]

TripTone®: 50 mg

Tablet, chewable:

Dramamine®: 50 mg [contains phenylalanine 1.5 mg/tablet and tartrazine; orange flavor]

Gravol® Chewable for Children [CAN]: 25 mg [not available in the U.S.]

Gravol® Chewable for Adults [CAN]: 50 mg [not available in the U.S.]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Triptone)

50 mg (30): $8.99

Mechanism of ActionCompetes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract; blocks chemoreceptor trigger zone, diminishes vestibular stimulation, and depresses labyrinthine function through its central anticholinergic activity
Pharmacodynamics/Kinetics

Onset of action: Oral: ~15-30 minutes

Absorption: Oral: Well absorbed

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDrowsiness is common; may cause depression, nervousness, or paradoxical CNS stimulation
Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropic may result in additive sedation
International Brand NamesAgolene (BE); Amosyt (SE); Anautin (DK, EC); Antemin (CH); Antivomit (FI); Aviomarin (PL); Biodramina (CR, ES, GT, PA, SV); Cinfamar (ES, TW); Contramareo (ES); Daedalon (HU); Dekatravel (BE); Denim (TH); Devom (PK); Dimenate (HK, MY); Dimenhidrinato (MX); Dimenidrinato (IT); Dimicaps (MX); Dimin (TH); Divonal (PE); Dramamine (AR, AU, BB, BD, BF, BJ, BM, BS, BZ, CI, CL, ET, GH, GM, GN, GY, HK, ID, IN, JM, JP, KE, KP, LR, MA, ML, MR, MU, MW, MY, NE, NG, NL, PH, PK, PR, SC, SD, SG, SL, SN, SR, TH, TN, TT, TW, TZ, UG, VE, ZA, ZM, ZW); Dramamine (BE, GB, IE, LU, MX); Dramasan (PE); Dramavir (ES); Dramin (BR); Dramina (HR); Driminate Supp (MY); Dromyl (NO); Emedyl (AT); Garcol (HK); Gravol (CR, DO, GT, HK, IN, NI, PA, PE, PH, SV, TH); Hydrinate (MY); Lomarin (IT); Mareol (CO); Mareosan (ES); Marolin (ES); Menito (TW); Motozina (IT); Nausamine (TH); Nausicalm (FR); Novomin (HK, MY); Paranausine (BE, LU); Pasedol (CO); Phrachedi (TH); RubieMen (DE); Setmenate (HK); Travamin (IL); Travel Well (ES); Travel-Gum (AT, CZ, IT); Trawell (CH); Trimin (TW); Vagomine (BE, LU); Valontan (ES, IT); Vertirosan (AT); Vomidrine (PT); Vomisin (MX); Votmine (MY); Xamamina (IT)

Dimercaprol

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Pronunciation(dye mer KAP role)

U.S. Brand NamesBAL in Oil®

Pharmacologic CategoryAntidote

Use: Labeled IndicationsAntidote to gold, arsenic (except arsine), or acute mercury poisoning (except nonalkyl mercury); adjunct to edetate CALCIUM disodium in lead poisoning

Dosing: Adults**Note:** Premedication with a histamine H_1 antagonist (eg, diphenhydramine) is recommended.

Mild arsenic or gold poisoning: Deep I.M.: 2.5 mg/kg every 6 hours for 2 days, then every 12 hours for 1 day, followed by once daily for 10 days

Severe arsenic or gold poisoning: Deep I.M.: 3 mg/kg every 4 hours for 2 days, then every 6 hours for 1 day, followed every 12 hours for 10 days

Mercury poisoning: Deep I.M.: 5 mg/kg initially, followed by 2.5 mg/kg 1-2 times/day for 10 days

Lead poisoning: Deep I.M.: **Note:** For the treatment of high blood lead levels in children, the CDC recommends chelation treatment when blood lead levels are >45 mcg/dL (CDC, 2002). Combination parenteral therapy is indicated when blood lead levels are ≥70 mcg/dL, or patients are symptomatic (AAP, 2005). In adults, available guidelines recommend chelation therapy with blood lead levels >50 mcg/dL and significant symptoms; chelation therapy may also be indicated with blood lead levels ≥100 mcg/dL and/or symptoms. (Kosnett, 2007).

Lead encephalopathy (in conjunction with edetate CALCIUM disodium): Dimercaprol 4 mg/kg (75 mg/m^2) loading dose, followed by dimercaprol 4 mg/kg (75 mg/m^2) every 4 hours for 2-7 days (edetate CALCIUM disodium is **not** administered with the loading dose; begin edetate CALCIUM disodium with the second dose)

Symptomatic lead poisoning or blood lead levels ≥70 mcg/dL (in conjunction with edetate CALCIUM disodium): Dimercaprol 4 mg/kg (75 mg/m^2) loading dose, followed by dimercaprol 3 mg/kg/dose (50 mg/m^2) every 4 hours for 2-7 days (edetate CALCIUM disodium is **not** administered with the loading dose; begin edetate CALCIUM disodium with the second dose)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Premedication with a histamine H_1 antagonist (eg, diphenhydramine) is recommended. Refer to adult dosing.

Administration: I.M.Administer all injections deep I.M. at different sites. Keep urine alkaline to protect renal function. When used in the treatment of lead poisoning, administer in a separate site from edetate CALCIUM disodium.

StorageStore at 20°C to 25°C (68°F to 77°F).

ContraindicationsHepatic insufficiency (unless due to arsenic poisoning); iron, cadmium, or selenium poisoning

Warnings/Precautions

Concerns related to adverse effects:

- Nephrotoxicity: Potentially a nephrotoxic drug; use with caution in patients with oliguria. Keep urine alkaline to protect kidneys (prevents dimercaprol-metal complex breakdown). Discontinue or use with extreme caution if renal insufficiency develops during treatment. Hemodialysis may be used to remove dimercaprol-metal chelate in patients with renal dysfunction

Special populations:

- Glucose 6-phosphate dehydrogenase deficiency: Use with caution in patients with glucose 6-phosphate dehydrogenase deficiency; may increase risk of hemolytic anemia.

- Pediatrics: Fevers may occur in ~30% of children and may persist for the duration of therapy.

Disease related concerns:

- Lead poisoning: Investigate, identify, and remove sources of lead exposure prior to treatment.

- Heavy metal poisoning: Primary care providers should consult experts in chemotherapy of heavy metal toxicity before using chelation drug therapy.

Dosage form specific issues:

- Peanut oil: Product contains peanut oil; use with caution in patients with peanut allergy; medication for the treatment of hypersensitivity reactions should be available for immediate use.

Other warnings/precautions:

- Administration: Administer all injections deep I.M. at different sites.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. There are no adequate and well-controlled studies in pregnant women.

Lead poisoning: Following maternal occupational exposure, lead was found to cross the placenta in amounts related to maternal plasma levels. Possible outcomes of maternal lead exposure >10 mcg/dL include spontaneous abortion, postnatal developmental delay, and reduced birth weight. Chelation therapy during pregnancy is for maternal benefit only and should be limited to the treatment of severe, symptomatic lead poisoning.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding Considerations

It is not known if dimercaprol is excreted in breast milk; however, it is not absorbed orally, which would limit the exposure to a nursing infant. When used for the treatment of lead poisoning, the amount of lead in breast milk may range from 0.6% to 3% of the maternal serum concentration. Calcium supplementation may reduce the amount of lead in breast milk.

Adverse Reactions

Frequency not always defined.

Cardiovascular: Chest pain, hypertension (dose related), tachycardia (dose related)

Central nervous system: Anxiety, fever (children ~30%), headache, nervousness

Dermatologic: Abscess

Gastrointestinal: Abdominal pain, burning sensation (lips, mouth, throat), nausea, salivation, throat irritation/pain, vomiting

Genitourinary: Burning sensation (penis)

Hematologic: Leukopenia (polymorphonuclear)

Local: Injection site pain

Neuromuscular & skeletal: Paresthesias (hand), weakness

Ocular: Blepharospasm, conjunctivitis, lacrimation

Renal: Acute renal insufficiency

Respiratory: Rhinorrhea, throat constriction

Miscellaneous: Diaphoresis

Drug Interactions

Iron Salts: Dimercaprol may enhance the nephrotoxic effect of Iron Salts. *Risk X: Avoid combination*

Test InteractionsIodine ^{131}I thyroidal uptake values may be decreased

Monitoring ParametersRenal function, urine pH, infusion-related reactions

For lead poisoning: Blood lead levels (baseline and 7-21 days after completing chelation therapy); hemoglobin or hematocrit, iron status, free erythrocyte protoporphyrin or zinc protoporphyrin; neurodevelopmental changes

Monitoring: Lab TestsRenal function, urine pH

For lead poisoning: Blood lead levels (baseline and 7-21 days after completing chelation therapy); hemoglobin or hematocrit, iron status, free erythrocyte protoporphyrin or zinc protoporphyrin; neurodevelopmental changes

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, oil:

BAL in Oil®: 100 mg/mL (3 mL) [contains benzyl benzoate and peanut oil]

Generic AvailableNo

Mechanism of ActionSulfhydryl group combines with ions of various heavy metals to form relatively stable, nontoxic, soluble chelates which are excreted in urine

Pharmacodynamics/Kinetics

Absorption: I.M.: Rapid; Oral: Not absorbed

Distribution: To all tissues including the brain

Metabolism: Rapidly hepatic to inactive metabolites

Time to peak, serum: 0.5-1 hour

Excretion: Urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness

Mental Health: Effects on Psychiatric TreatmentMay produce neutropenia; use caution with clozapine and carbamazepine

Index Terms BAL; British Anti-Lewisite; Dithioglycerol

References

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“Lead Exposure in Children: Prevention, Detection, and Management. American Academy of Pediatrics Committee on Environmental Health,” *Pediatrics*, 2005, 116(4):1036-46.[PubMed 16199720]

Shannon M, “Severe Lead Poisoning in Pregnancy,” *Ambul Pediatr*, 2003, 3(1):37-9.[PubMed 12540252]

International Brand Names B.A.L. (DE, FR, IT); BAL (IE, IN); BAL In Oil (GR, MY); Dicaptol (HU); DMPS-Heyl (NO); Sulfactin (PL); Unithiol (PL)

Dimethyl Sulfoxide

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English

Jump To Field (Select Field Name)

Pronunciation(dye meth il sul FOKS ide)

U.S. Brand NamesRimso-50®

Canadian Brand NamesDimethyl Sulfoxide Irrigation, USP; Kemsol®; Rimso-50®

Pharmacologic CategoryUrinary Tract Product

Use: Labeled IndicationsSymptomatic relief of interstitial cystitis

Dosing: AdultsInterstitial cystitis: Instill 50 mL directly into bladder and allow to remain for 15 minutes; repeat every 2 weeks until symptoms are relieved, then increase intervals between treatments **or** 50 mL directly into bladder for 15-20 minutes every 1-2 weeks for 4-8 treatments (Chancellor, 2004)

Dosing: ElderlyRefer to adult dosing.

Administration: Other**Not for I.V. or I.M. use.** Intravesical: Instill directly into the bladder via catheter or syringe. To reduce bladder spasm it is recommended to apply an analgesic lubricant (eg, lidocaine jelly) to urethra prior to catheter insertion; belladonna and opium suppositories may be of benefit.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

ContraindicationsThere are no contraindications listed within the manufacturer's labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: May cause hypersensitivity reactions (rare).
- Ophthalmic effects: Lens changes and opacities have been observed in animal studies; precaution is advised in humans and eye exams (prior to use and periodically) are recommended.

Disease-related concerns:

- Urinary tract malignancy: Use with caution in patients with urinary tract malignancy; may be harmful due to vasodilatory effects.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate administration: For bladder instillation only; do not administer I.V./I.M.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Gastrointestinal: Garlic-like breath (may persist for up to 72 hours), garlic-like taste (may persist for several hours)

Genitourinary: Cystitis (transient)

Local: Discomfort (moderate-to-severe)

Miscellaneous: Skin odor (may persist for up to 72 hours)

Postmarketing and/or case reports: Contact dermatitis, eosinophilic cystitis, hypersensitivity reactions, lens deposits

Drug Interactions

Sulindac: Dimethyl Sulfoxide may decrease the metabolism of Sulindac. Specifically, the concentrations of the active sulfide metabolite are decreased. *Risk C: Monitor therapy*

Monitoring ParametersCBC, liver and renal function tests about every 6 months; eye examinations and slit lamp examinations (baseline and periodically)

Nursing: Physical Assessment/MonitoringFor bladder instillation only. Assess knowledge/teach patient interventions to reduce side effects and adverse symptoms to report.

Monitoring: Lab TestsCBC, liver and renal function tests about every 6 months

Patient EducationThis medication is only for use as a bladder instillation. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Report persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Note breast-feeding caution.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, intravesical:

Rimso-50®: 50% [500 mg/mL] (50 mL)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Rimso-50)

50% (50): $111.20

Mechanism of ActionExact mechanism unknown; reported to induce and alter inflammatory tissue responses, modulate collagen disposition, influence nerve conduction and neurotransmission, and alter cell proliferation in fibroblasts and hepatocytes; thus exerting an anti-inflammatory, analgesic, and muscle relaxant effect. It may also interact with free radicals forming formaldehyde, possibly contributing to fixative effect on biological tissues.

Pharmacodynamics/Kinetics

Absorption: Well absorbed (topical administration)

Distribution: Body fluids and tissues (topical administration)

Metabolism: Oxidation to dimethyl sulfone; reduction to dimethyl sulfide

Excretion: Urine and feces (as unchanged drug and dimethyl sulfone); skin and lungs (dimethyl sulfoxide)

Pharmacotherapy PearlsDimethyl sulfoxide (≥99%) is used as a cryopreservative solution.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDMSO

References

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Perez-Marrero R, Emerson LE, and Feltis JT, "A Controlled Study of Dimethyl Sulfoxide in Interstitial Cystitis," *J Urol*, 1988, 140(1):36-9.[PubMed 3288775]

Rowley S and Baer R, "Lens Deposits Associated With RIMSO-50 (Dimethylsulphoxide)," *Eye*, 2001, 15(pt 3):332-3.[PubMed 11450733]

International Brand NamesDemsodrox (ES); Dermialgida Liquido (ES); Dolobene (PL); Intran DMSO-Losung (AT); Rheumabene (DE); Rimso-50 (GB)

Dinoprostone

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Prepidil® may be confused with Bepridil®

International issues:

Cervidil®: Brand name for gemeprost in Italy

Pronunciation(dye noe PROST one)

U.S. Brand NamesCervidil®; Prepidil®; Prostin E_2®

Canadian Brand NamesCervidil®; Prepidil®; Prostin E_2®

Pharmacologic CategoryAbortifacient; Prostaglandin

Use: Labeled Indications

Gel: Promote cervical ripening in patients at or near term in whom there is a medical or obstetrical indication for the induction of labor

Suppositories: Terminate pregnancy from 12th through 20th week of gestation; evacuate uterus in cases of missed abortion or intrauterine fetal death up to 28 weeks of gestation; manage benign hydatidiform mole (nonmetastatic gestational trophoblastic disease)

Vaginal insert: Initiation and/or continuation of cervical ripening in patients at or near term in whom there is a medical or obstetrical indication for the induction of labor

Dosing: Adults

Abortifacient:*Vaginal suppository:* Insert 20 mg (1 suppository) high in vagina, repeat at 3- to 5-hour intervals until abortion occurs; continued administration for longer than 2 days is not advisable

Cervical ripening:

Endocervical gel: Using catheter supplied with gel, insert 0.5 mg into the cervical canal. May repeat every 6 hours if needed. Maximum cumulative dose: 1.5 mg/24 hours

Vaginal insert: Insert 10 mg transversely into the posterior fornix of the vagina (to be removed at the onset of active labor or after 12 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricFemales of reproductive age: Refer to adult dosing.

Administration: Other

Endocervical gel: Bring to room temperature just prior to use. Do not force the warming process (eg, water bath, microwave). Avoid contact with skin while handling; wash hands thoroughly with soap and water after administration. For cervical ripening, patient should be supine in the dorsal position. The appropriate catheter length should be based on degree of effacement; 20 mm for no effacement; 10 mm if 50% effaced. Patient should remain supine for 15-30 minutes following administration.

Vaginal insert: One vaginal insert is placed transversely in the posterior fornix of the vagina immediately after removal from its foil package. Patients should remain in the recumbent position for 2 hours after insertion, but thereafter may be ambulatory. Do not use without retrieval system. Product does not need warmed prior to use. A water miscible lubricant may be used to facilitate insertion (avoid excessive use of lubricant). Ensure complete removal of system at completion of therapy.

Vaginal suppository: Bring to room temperature just prior to use. Patient should remain supine for 10 minutes following insertion.

StorageSuppositories must be kept frozen; store in freezer not above -20°C (-4°F). Cervical gel should be stored under refrigeration 2°C to 8°C (36°F to 46°F). Vaginal insert should be stored in freezer between -20°C and -10°C (-4°F and 14°F).

Contraindications

Gel, vaginal insert: Hypersensitivity to prostaglandins or any component of the formulation; fetal distress (suspicion or clinical evidence unless delivery is imminent); unexplained vaginal bleeding during this pregnancy; strong suspicion of marked cephalopelvic disproportion; patients in whom oxytocic drugs are contraindicated or when prolonged contraction of the uterus may be detrimental to fetal safety or uterine integrity (including previous cesarean section or major uterine surgery); >6 previous term pregnancies; patients already receiving oxytocic drugs; hyperactive or hypotonic uterine patterns; when vaginal delivery is not indicated (vasa previa, active herpes genitalia); obstetrical emergencies when surgical intervention would be favorable

Suppository: Hypersensitivity to dinoprostone or any component of the formulation; acute pelvic inflammatory disease; active cardiac, pulmonary, renal or hepatic disease

Warnings/Precautions

Boxed warnings:

- Trained personnel: See “Other warnings/precautions” below.

Dosage form specific issues:

- Gel, vaginal insert: Use caution with ruptured membranes; nonvertex or nonsingleton pregnancy; previous uterine hypertony; glaucoma; history of asthma. Vaginal insert must be removed prior to administration of oxytocin; in case of hyperstimulation or if labor begins; fetal or maternal distress; and prior to amniotomy.

- Suppository: Transient pyrexia and decreased blood pressure may be observed with treatment. Use caution with history of asthma; hypotension or hypertension; cardiovascular, renal, or hepatic disease; anemia; jaundice; diabetes; epilepsy; compromised uteri; cervicitis, endocervical infections or acute vaginitis. Measures should be taken to ensure complete abortion. Commercially available suppositories should not be used for extemporaneous preparation of any other dosage form of drug. Do not use for cervical ripening or other indications in patients with term pregnancy.

Other warnings/precautions:

- Trained personnel: **[U.S. Boxed Warning]: Dinoprostone should be used only by medically-trained personnel in a hospital.**

Pregnancy Risk FactorC

Pregnancy ConsiderationsSkeletal anomalies and embryotoxicity have been observed in animal studies. Although these effects would not be expected in humans when administered after the period of organogenesis, a sustained increase in uterine tone may have increased risks of adverse events to the fetus.

Fetal distress without corresponding maternal uterine hyperstimulation was observed in 3% to 4% of infants exposed to Cervidil® *in utero.* No adverse effects on physical or psychomotor function were observed in a 3 year follow-up study of exposed infants. Abnormal fetal heart rates were observed in 17% of infants exposed to Prepidil® gel *in utero.* Deceleration, intrauterine fetal sepsis, fetal depression and fetal acidosis have also been reported with administration of the gel.

When used for termination of pregnancy, dinoprostone is not considered feticidal, but is used to terminate pregnancy due to its ability to stimulate uterine contractions; do not use if fetus has reached the stage of viability.

LactationExcretion in breast milk unknown

Breast-Feeding ConsiderationsEndogenous PGE_2 can be detected in breast milk. High levels have been associated with diarrhea in nursing infants.

Adverse Reactions

Gel:

1% to 10%:

Central nervous system: Fever (1%)

Gastrointestinal: GI upset (6%)

Genitourinary: Abnormal uterine contractions (7%), warm feeling in vagina (2%)

Neuromuscular & skeletal: Back pain (3%)

Postmarketing and/or case reports: Amnionitis, premature rupture of membranes, uterine rupture (with intracervical administration)

Suppository:

Frequency not defined:

Cardiovascular: Arrhythmia, chest pain, chest tightness, hypotension, syncope

Central nervous system: Chills, dizziness, fever, headache, shivering, tension

Dermatologic: Rash, skin discoloration

Endocrine & metabolic: Breast tenderness, endometritis, hot flashes

Gastrointestinal: Dehydration, diarrhea, nausea, vomiting

Genitourinary: uterine rupture, urinary retention, vaginal pain, vaginismus, vaginitis, vulvitis

Neuromuscular & skeletal: Arthralgia, backache, joint inflammation/pain (new or exacerbated), leg cramps (nocturnal), muscle cramp/pain, myalgia, paresthesia, stiff neck, tremor, weakness

Ocular: Blurred vision, eye pain

Otic: Hearing impairment

Respiratory: Cough, dyspnea, laryngitis, pharyngitis, wheezing

Miscellaneous: Diaphoresis

Postmarketing and/or case reports: MI

Vaginal insert:

1% to 10%: Genitourinary: Uterine hyperstimulation *without* fetal distress (2% to 5%), uterine hyperstimulation *with* fetal distress (3%)

<1%: Abdominal pain, diarrhea, fever, nausea, vomiting

Postmarketing and/or case reports: Uterine rupture

Drug Interactions

Oxytocin: Dinoprostone may enhance the therapeutic effect of Oxytocin. *Risk D: Consider therapy modification*

Monitoring Parameters

Gel, insert: Fetal heart rate and uterine activity

Suppository: Confirmation of fetal death

Nursing: Physical Assessment/MonitoringMonitor temperature, uterine tone, and vaginal discharge closely throughout procedure and postprocedure. Monitor abortion for completeness (other measures may be necessary if incomplete). Assess knowledge/teach patient interventions to reduce side effects and adverse symptoms to report.

Patient EducationNausea and vomiting, cramping or uterine pain, or fever may occur. Report acute pain, respiratory difficulty, or skin rash. Closely monitor for vaginal discharge for several days. Report vaginal bleeding, itching, malodorous or bloody discharge, or severe cramping. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel, endocervical (Prepidil®): 0.5 mg/3 g syringe [each package contains a 10 mm and 20 mm shielded catheter]

Insert, vaginal (Cervidil®): 10 mg [releases 0.3 mg/hour]

Suppository, vaginal (Prostin E_2®): 20 mg

Generic AvailableNo

Mechanism of ActionA synthetic prostaglandin E_2 abortifacient that stimulates uterine contractions similar to those seen during natural labor. Prostaglandin E_2 plays a role in cervical ripening, which allows the fetus to pass through the birth canal.

Pharmacodynamics/Kinetics

Onset of action (uterine contractions): Vaginal suppository: Within 10 minutes

Duration: Vaginal insert: 0.3 mg/hour over 12 hours; Vaginal suppository: Up to 2-3 hours

Absorption: Vaginal suppository: Slow

Metabolism: In many tissues including lungs, liver, and kidney

Half-life elimination: 2.5-5 minutes

Time to peak, plasma: Gel: 30-45 minutes

Excretion: Primarily urine; feces (small amounts)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPGE_2; Prostaglandin E_2

References

Novakov A, Segedi D, Milasinovic L, et al, “Induction of Labor by Endocervical Application of Prostaglandins and Intravenous Infusion of Oxytocin in Post-term Pregnancy,” *Med Pregl*, 1998, 51(9-10):419-26.[PubMed 9863332]

International Brand NamesCervidil (NZ); Cerviprime (IN); Cerviprost (AT, RU); Minprostin (NO, SE); Minprostin E(2) (DE, DK); Prandin E2 (ZA); Prepidil (AE, AT, BE, BG, BH, CO, CY, CZ, EG, ES, FR, HN, HR, HU, IL, IQ, IR, IT, JO, KW, LB, LU, LY, MY, NL, OM, PK, PL, QA, SA, SY, YE, ZA); Primiprost (IN); Prolisina E2 (AR); Propess (FI, FR, IL, SE); Prostaglandina E2 (ES); Prostarmon E (TW); Prostenon (EE); Prostin 3 (MY); Prostin E2 (AE, AT, BE, BF, BG, BH, BJ, CH, CI, CY, EG, ET, GB, GH, GM, GN, HK, HN, HR, HU, ID, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PL, PT, QA, SA, SC, SD, SG, SL, SN, SY, TH, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Prostin E2 Vaginal Cream (AU); Prostin E2 Vaginal Gel (NZ); Prostin VR (LU); Prostine (FR)

Diphenhydramine and Phenylephrine

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English English

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(dye fen HYE dra meen & fen il EF rin)

U.S. Brand NamesAldex® CT; D-Tann; Dimetapp® Children’s Nighttime Cold & Congestion [OTC]; Robitussin® Night Time Cough & Cold [OTC]

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporary relief of symptoms of allergic rhinitis, sinusitis, and other upper respiratory conditions, including sinus/nasal congestion, sneezing, stuffy/runny nose, itchy/watery eyes, and cough

Dosing: Adults**Allergic symptoms, nasal congestion:** Oral:

Aldex® CT: 1-2 tablets every 6 hours

D-Tann: 5-10 mL **or** 1-2 tablets every 12 hours

OTC labeling: 20 mL every 4 hours as needed, maximum 6 doses/24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Allergic symptoms, nasal congestion:** Oral:

Aldex® CT:

Children 6-11 years: One-half to 1 tablet every 6 hours

Children ≥12 years: Refer to adult dosing.

D-Tann:

Children 2-5 years: 1.25-2.5 mL every 12 hours

Children 6-11 years: 2.5-5 mL **or** $^{1}/_{2}$ to 1 tablet every 12 hours

Children ≥12 years: Refer to adult dosing.

OTC labeling:

Children <6 years: Use not recommended

Children 6-11 years (Dimetapp® Children's Nighttime Cold and Congestion): 10 mL every 4 hours as needed, maximum 6 doses/24 hours

Children ≥12 years: Refer to adult dosing.

Dietary ConsiderationsD-Tann chewable tablets contain phenylalanine 5.7 mg per tablet.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to diphenhydramine, phenylephrine, or any component of the formulation; concurrent use with other products containing diphenhydramine (including topical); use with or within 14 days of MAO inhibitors; newborns; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Asthma: Use with caution in patients with asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or narrow-angle glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Use with caution in children; may cause excitability. Do not exceed pediatric dosing recommendations. If no recommendations exist on OTC labeling for patient’s age, the product should **not** be administered without the guidance of a physician. Not for OTC use in children <6 years of age.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Other warnings/precautions:

- Self-medication (OTC use): Patients with hypertension, thyroid disease, diabetes mellitus, glaucoma, cardiovascular disease, or prostatic hyperplasia should consult healthcare provider prior to use. Patients with chronic cough (associated with COPD or smoking) and/or productive cough (eg, copious amounts of phlegm) should be evaluated by a healthcare provider prior to use. Ask healthcare provider prior to using with sedatives. If symptoms or cough do not improve, are accompanied by fever, or persist >7 days during use, consult a physician. Do not exceed recommended dose.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Also refer to Diphenhydramine monograph.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsIt is not known if phenylephrine is found in breast milk. Diphenhydramine is excreted in breast milk. Use of this combination is contraindicated by the manufacturers while breast-feeding. Also refer to Diphenhydramine monograph.

Adverse ReactionsFrequency not defined.

Cardiovascular: Chest tightness, extrasystoles, hypotension, palpitation, tachycardia

Central nervous system: Chills, confusion, coordination impaired, dizziness, drowsiness, euphoria, excitation, fatigue, headache, insomnia, irritability, nervousness, neuritis, restlessness, sedation, seizure, vertigo

Dermatologic: Photosensitivity, rash, urticaria

Endocrine & metabolic: Early menses

Gastrointestinal: Anorexia, constipation, diarrhea, dry mucous membranes, epigastric distress, nausea, vomiting, xerostomia

Genitourinary: Dysuria, polyuria, urinary retention

Hematologic: Agranulocytosis, hemolytic anemia, thrombocytopenia

Neuromuscular & skeletal: Paresthesia, tremor

Ocular: Blurred vision, diplopia

Otic: Labyrinthitis, tinnitus

Respiratory: Bronchial secretions (thickening), nasal congestion, throat tightness, wheezing

Miscellaneous: Anaphylaxis, diaphoresis

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension:

D-Tann: Diphenhydramine tannate 25 mg and phenylephrine tannate 7.5 mg per 5 mL [118 mL] [contains sodium benzoate, bubblegum flavor]

Syrup:

Dimetapp® Children's Nighttime Cold and Congestion: Diphenhydramine hydrochloride 6.25 mg and phenylephrine hydrochloride 2.5 mg per 5 mL [120 mL] [alcohol free, sugar free; grape flavor]

Robitussin® Night Time Cough and Cold: Diphenhydramine hydrochloride 6.25 mg and phenylephrine hydrochloride 2.5 mg per 5 mL [120 mL] [alcohol free, contains sodium benzoate]

Tablet, chewable:

Aldex® CT: Diphenhydramine hydrochloride 12.5 mg and phenylephrine hydrochloride 5 mg [strawberry flavor]

D-Tann: Diphenhydramine tannate 25 mg and phenylephrine tannate 10 mg [contains phenylalanine 5.7 mg/tablet, berry flavor]

Generic AvailableNo

Mechanism of Action

Diphenhydramine is an H_1-receptor antagonist.

Phenylephrine is a potent, direct-acting alpha-adrenergic stimulator.

Pharmacodynamics/KineticsSee individual agents.

Mental Health: Effects on Mental StatusMay cause sedation, confusion, dizziness, euphoria, excitation, insomnia, irritability, nervousness, and restlessness

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment. May cause sedation; concurrent use with psychotropics may produce additive effects

Index TermsDiphenhydramine Hydrochloride and Phenylephrine Hydrochloride; Diphenhydramine Tannate and Phenylephrine Tannate; Phenylephrine and Diphenhydramine; Phenylephrine Hydrochloride and Diphenhydramine Hydrochloride; Phenylephrine Tannate and Diphenhydramine Tannate

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Diphenhydramine and Pseudoephedrine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Benadryl® may be confused with benazepril, Bentyl®, Benylin®, Caladryl®

Pronunciation(dye fen HYE dra meen & soo doe e FED rin)

U.S. Brand NamesBenadryl-D™ Allergy and Sinus Fastmelt™ [OTC]; Benadryl-D™ Children's Allergy and Sinus [OTC]; Benadryl® Children's Allergy and Cold Fastmelt™ [OTC]

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsRelief of symptoms of upper respiratory mucosal congestion in seasonal and perennial nasal allergies, acute rhinitis, rhinosinusitis, and eustachian tube blockage

Dosing: AdultsAllergic symptoms, nasal congestion:

Based on **pseudoephedrine** component:

Adults: Oral: 60 mg every 4-6 hours, maximum: 240 mg/day

Dosing: ElderlyRefer to adult dosing.

Adverse ReactionsSee individual agents.

Metabolism/Transport EffectsDiphenhydramine: **Inhibits** CYP2D6 (moderate)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid:

Benadryl-D™ Children's Allergy and Sinus: Diphenhydramine hydrochloride 12.5 mg and pseudoephedrine hydrochloride 30 mg per 5 mL [alcohol free, sugar free; contains sodium 10 mg/5 mL and sodium benzoate; grape flavor]

Tablet, quick dissolving:

Benadryl® Children's Allergy and Cold Fastmelt™, Benadryl-D™ Allergy and Sinus Fastmelt™: Diphenhydramine citrate 19 mg [equivalent to diphenhydramine hydrochloride 12.5 mg] and pseudoephedrine 30 mg [contains phenylalanine 4.6 mg/tablet; cherry flavor]

Generic AvailableNo

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation). Chronic use of antihistamines will inhibit salivary flow, particularly in elderly patients; this may contribute to periodontal disease and oral discomfort.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDiphenhydramine may cause paradoxical excitation in pediatric patients, and can result in hallucinations, coma, and death in overdose. May cause sedation, sleepiness, dizziness, disturbed coordination, headache, fatigue, nervousness, paradoxical excitement, insomnia, euphoria, or confusion. Pseudoephedrine may cause dizziness, drowsiness, nervousness, and insomnia; may rarely cause hallucinations.

Mental Health: Effects on Psychiatric TreatmentRare reports of agranulocytosis and thrombocytopenia; use caution with clozapine, carbamazepine, and valproic acid; may increase gastric degradation of levodopa and decrease the amount of levodopa absorbed by delaying gastric emptying. Therapeutic effects of cholinergic agents (tacrine, donepezil, rivastigmine, galantamine) and neuroleptics may be antagonized. Central and/or peripheral anticholinergic syndrome can occur when administered with amantadine, rimantadine, narcotic analgesics, phenothiazines, and other antipsychotics (especially with high anticholinergic activity), tricyclic antidepressants and antihistamines. Pseudoephedrine is contraindicated with MAO inhibitors.

Index TermsPseudoephedrine and Diphenhydramine

DiphenhydrAMINE

Lexi-Drugs Online

English English

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Special Alerts

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

DiphenhydrAMINE may be confused with desipramine, dicyclomine, dimenhyDRINATE

Benadryl® may be confused with benazepril, Bentyl®, Benylin®, Caladryl®

Pronunciation(dye fen HYE dra meen)

U.S. Brand NamesAler-Cap [OTC]; Aler-Dryl [OTC]; Aler-Tab [OTC]; AllerMax® [OTC]; Altaryl [OTC]; Banophen® Anti-Itch [OTC]; Banophen® [OTC]; Ben-Tann; Benadryl® Allergy [OTC]; Benadryl® Children's Allergy Fastmelt® [OTC]; Benadryl® Children's Allergy [OTC]; Benadryl® Children's Dye-Free Allergy [OTC]; Benadryl® Itch Stopping Extra Strength [OTC]; Benadryl® Itch Stopping [OTC]; Compoz® Nighttime Sleep Aid [OTC]; Dermamycin® [OTC]; Diphenhist [OTC]; Diphen® AF [OTC]; Diphen® [OTC]; Dytan™; Genahist® [OTC]; Hydramine® [OTC]; Nytol® Quick Caps [OTC]; Nytol® Quick Gels [OTC]; Siladryl® Allergy [OTC]; Silphen® [OTC]; Simply Sleep® [OTC]; Sleep-ettes D [OTC]; Sleepinal® [OTC]; Sominex® Maximum Strength [OTC]; Sominex® [OTC]; Triaminic® Thin Strips™ Cough and Runny Nose [OTC]; Twilite® [OTC]; Unisom® Maximum Strength SleepGels® [OTC]

Canadian Brand NamesAllerdryl®; Allernix; Benadryl®; Nytol®; Nytol® Extra Strength; PMS-Diphenhydramine; Simply Sleep®

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of allergic symptoms caused by histamine release including nasal allergies and allergic dermatosis; adjunct to epinephrine in the treatment of anaphylaxis; nighttime sleep aid; prevention or treatment of motion sickness; antitussive; management of Parkinsonian syndrome including drug-induced extrapyramidal symptoms; topically for relief of pain and itching associated with insect bites, minor cuts and burns, or rashes due to poison ivy, poison oak, and poison sumac

Use: DentalSymptomatic relief of nasal mucosal congestion

Dosing: Adults **Note:** Dosages are expressed as the hydrochloride salt.

Allergic reactions or motion sickness:

Oral: 25-50 mg every 6-8 hours

I.M., I.V.: 10-50 mg per dose; single doses up to 100 mg may be used if needed; not to exceed 400 mg/day

Antitussive: Oral: 25 mg every 4 hours; maximum 150 mg/24 hours

Nighttime sleep aid: Oral: 50 mg at bedtime

Dystonic reaction: I.M., I.V.: 50 mg in a single dose; may repeat in 20-30 minutes if necessary

Relief of pain and itching: Topical: Apply 1% or 2% to affected area up to 3-4 times/day

Dosing: ElderlyInitial: 25 mg 2-3 times/day increasing as needed

Dosing: Pediatric**Note:** Dosages are expressed as the hydrochloride salt.

Allergic reactions or motion sickness: Oral, I.M., I.V.: 5 mg/kg/day or 150 mg/m^2/day in divided doses every 6-8 hours, not to exceed 300 mg/day

Alternate dosing by age: Oral:

2 to <6 years: 6.25 mg every 4-6 hours; maximum: 37.5 mg/day

6 to <12 years: 12.5-25 mg every 4-6 hours; maximum: 150 mg/day

≥12 years: 25-50 mg every 4-6 hours; maximum: 300 mg/day

Night-time sleep aid: Oral: Children ≥12 years: 50 mg at bedtime

Antitussive: Oral:

2 to <6 years: 6.25 mg every 4 hours; maximum 37.5 mg/day

6 to <12 years: 12.5 mg every 4 hours; maximum 75 mg/day

≥12 years: 25 mg every 4 hours; maximum 150 mg/day

Treatment of dystonic reactions: I.M., I.V.: 0.5-1 mg/kg/dose

Relief of pain and itching: Topical: Children ≥2 years: Apply 1% or 2% to affected area up to 3-4 times/day

Calculations

- Body Surface Area: Pediatrics

Administration: I.V.Injection solution: For I.V. or I.M. administration only. Local necrosis may result with SubQ or intradermal use. For I.V. administration, inject at a rate ≤25 mg/minute.

Administration: I.V. DetailpH: 5-6

Administration: OralWhen used to prevent motion sickness, first dose should be given 30 minutes prior to exposure.

Dietary Considerations

Benadryl® Allergy strips contain sodium 4 mg per 25 mg strip.

Benadryl® Children's Allergy chewable tablets contain phenylalanine 4.2 mg, magnesium 15 mg, and sodium 2 mg per 12.5 mg tablet.

Benadryl® Children's Allergy Fastmelt® contains phenylalanine 4.5 mg/tablet and soy protein isolate (contraindicated in patients with soy protein allergies; use caution in peanut allergic individuals, ~10% are estimated to also have soy protein allergies).

Dytan™ chewable tablets contain phenylalanine.

StorageInjection: Store at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light and freezing

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, fat emulsion 10%, LR, $^1/_2NS$, NS.

Y-site administration: Compatible: Acyclovir, aldesleukin, amifostine, amsacrine, aztreonam, ciprofloxacin, cisatracurium, cisplatin, cladribine, cyclophosphamide, cytarabine, docetaxel, doxorubicin, doxorubicin liposome, etoposide phosphate, famotidine, filgrastim, fluconazole, fludarabine, gatifloxacin, gemcitabine, granisetron, heparin, hydrocortisone sodium succinate, idarubicin, linezolid, melphalan, meperidine, meropenem, methotrexate, ondansetron, paclitaxel, piperacillin/tazobactam, potassium chloride, propofol, remifentanil, sargramostim, sufentanil, tacrolimus, teniposide, thiotepa, vinorelbine, vitamin B complex with C. **Incompatible:** Allopurinol, amphotericin B cholesteryl sulfate complex, cefepime, foscarnet.

Compatibility in syringe: Compatible: Atropine, butorphanol, chlorpromazine, cimetidine, diatrizoate meglumine, diatrizoate meglumine 34.3% and diatrizoate sodium 35%, diatrizoate sodium, diatrizoate sodium 75%, dimenhydrinate, droperidol, fentanyl, fluphenazine, glycopyrrolate, hydromorphone, hydroxyzine, iohexol, iopamidol, iothalamate meglumine, iothalamate meglumine 60%, iothalamate sodium 80%, meperidine, metoclopramide, midazolam, morphine, nalbuphine, pentazocine, perphenazine, prochlorperazine edisylate, promazine, promethazine, ranitidine, scopolamine, sufentanil. **Incompatible:** Diatrizoate meglumine 52% and diatrizoate sodium 8%, diatrizoate sodium 60%, haloperidol, iodipamide meglumine, iodipamide meglumine 52%, ioxaglate meglumine 39.3% and ioxaglate sodium 19.6%, pentobarbital, thiopental. **Variable (consult detailed reference):** Dexamethasone sodium phosphate, diatrizoate meglumine 52% and diatrizoate sodium 8%.

Compatibility when admixed: Compatible: Amikacin, aminophylline, ascorbic acid injection, bleomycin, buprenorphine, colistimethate, erythromycin lactobionate, hydrocortisone sodium succinate, lidocaine, methyldopate, nafcillin, netilmicin, penicillin G potassium , penicillin G sodium, polymyxin B, vitamin B complex with C. **Incompatible:** Amobarbital, amphotericin B, dexamethasone sodium phosphate with lorazepam and metoclopramide, iodipamide meglumine, phenytoin, phenobarbital, thiopental. **Variable (consult detailed reference):** Heparin in solution.

ContraindicationsHypersensitivity to diphenhydramine or any component of the formulation; acute asthma; neonates or premature infants; breast-feeding; use as a local anesthetic (injection)

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Asthma: Use with caution in patients with a history of asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or angle-closure glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.
- Soy protein: Some preparations contain soy protein; avoid use in patients with soy protein or peanut allergies.

Other warnings/precautions:

- Self-medication (OTC use): Do not use with other products containing diphenhydramine, even ones used on the skin. Oral products are not for OTC use in children <6 years of age. Topical products should not be used on large areas of the body, or on chicken pox or measles. Healthcare provider should be contacted if topical use is needed for >7 days. Topical products are not for OTC use in children <2 years of age.

Geriatric ConsiderationsDiphenhydramine has high sedative and anticholinergic properties, so it may not be considered the antihistamine of choice for prolonged use in the elderly. Its use as a sleep aid is discouraged due to its anticholinergic effects; interpretive guidelines from the Centers for Medicare and Medicaid Services (CMS) discourage the use of diphenhydramine as a sedative or anxiolytic in long-term care facilities.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Diphenhydramine crosses the human placenta. One retrospective study showed an increased risk of cleft palate formation following maternal use of diphenhydramine during the 1st trimester of pregnancy; however, later studies have not confirmed this finding. Signs of toxicity and symptoms of withdrawal have been reported in infants following high doses or chronic maternal use close to term. Diphenhydramine has been evaluated for the treatment of hyperemesis gravidarum. It is generally not considered the antihistamine of choice for treating allergic rhinitis or nausea and vomiting during pregnancy.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsInfants may be more sensitive to the effects of antihistamines. Use while breast-feeding is contraindicated by the manufacturer.

Adverse ReactionsFrequency not defined.

Cardiovascular: Chest tightness, extrasystoles, hypotension, palpitation, tachycardia

Central nervous system: Chills, confusion, convulsion, disturbed coordination, dizziness, euphoria, excitation, fatigue, headache, insomnia, irritability, nervousness, paradoxical excitement, restlessness, sedation, sleepiness, vertigo

Dermatologic: Photosensitivity, rash, urticaria

Endocrine & metabolic: Menstrual irregularities (early menses)

Gastrointestinal: Anorexia, constipation, diarrhea, dry mucous membranes, epigastric distress, nausea, throat tightness, vomiting, xerostomia

Genitourinary: Difficult urination, urinary frequency, urinary retention

Hematologic: Agranulocytosis, hemolytic anemia, thrombocytopenia

Neuromuscular & skeletal: Neuritis, paresthesia, tremor

Ocular: Blurred vision, diplopia

Otic: Labyrinthitis (acute), tinnitus

Respiratory: Nasal stuffiness, thickening of bronchial secretions, wheezing

Miscellaneous: Anaphylactic shock, diaphoresis

Metabolism/Transport Effects**Inhibits** CYP2D6 (moderate)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsMay suppress the wheal and flare reactions to skin test antigens
Monitoring ParametersRelief of symptoms, mental alertness
Reference Range

Antihistamine effects at levels >25 ng/mL

Drowsiness at levels 30-40 ng/mL

Mental impairment at levels >60 ng/mL

Therapeutic: Not established

Toxic: >0.1 mcg/mL

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Patient EducationTake as directed; do not exceed recommended dose. Avoid use of other depressants, alcohol, or sleep-inducing medications unless approved by prescriber. You may experience drowsiness or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or dry mouth, nausea, or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help). Report persistent sedation, confusion, or agitation; changes in urinary pattern; blurred vision; sore throat, respiratory difficulty, or expectorating (thick secretions); or lack of improvement or worsening or condition. **Breast-feeding precaution:** Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet, as hydrochloride: 25 mg, 50 mg

Aler-Dryl, AllerMax®, Compoz® Nighttime Sleep Aid, Sleep-ettes D, Sominex® Maximum Strength, Twilite®: 50 mg

Nytol® Quick Caps, Simply Sleep®: 25 mg

Capsule, as hydrochloride: 25 mg, 50 mg

Aler-Cap, Banophen®, Benadryl® Allergy, Diphen®, Diphenhist, Genahist®: 25 mg

Sleepinal®: 50 mg

Capsule, softgel, as hydrochloride: 50 mg

Benadryl® Dye-Free Allergy: 25 mg [dye-free]

Compoz® Nighttime Sleep Aid, Nytol® Quick Gels, Sleepinal®, Unisom® Maximum Strength SleepGels®: 50 mg

Captab, as hydrochloride:

Diphenhist®: 25 mg

Cream, as hydrochloride: 2% (30 g)

Banophen® Anti-Itch: 2% (30 g) [contains zinc acetate 0.1%]

Benadryl® Itch Stopping: 1% (30 g) [contains zinc acetate 0.1%]

Benadryl® Itch Stopping Extra Strength: 2% (30 g) [contains zinc acetate 0.1%]

Diphenhist®: 2% (30 g) [contains zinc acetate 0.1%]

Elixir, as hydrochloride:

Altaryl: 12.5 mg/5 mL (120 mL, 480 mL, 3840 mL) [cherry flavor]

Banophen®: 12.5 mg/5 mL (120 mL)

Diphen AF: 12.5 mg/5 mL (240 mL, 480 mL) [alcohol free; cherry flavor]

Gel, topical, as hydrochloride:

Benadryl® Itch Stopping Extra Strength: 2% (120 mL)

Injection, solution, as hydrochloride: 50 mg/mL (1 mL, 10 mL)

Liquid, as hydrochloride:

AllerMax®: 12.5 mg/5 mL (120 mL)

Benadryl® Allergy: 12.5 mg/5 mL (120 mL, 240 mL) [alcohol free; contains sodium benzoate; cherry flavor]

Benadryl® Children's Dye-Free Allergy: 12.5 mg/5 mL (120 mL) [alcohol free, dye free, sugar free; contains sodium benzoate; bubble gum flavor]

Genahist®: 12.5 mg/5 mL (120 mL) [alcohol free, sugar free; contains sodium benzoate; cherry flavor]

Hydramine®: 12.5 mg/5 mL (120 mL, 480 mL) [alcohol free]

Siladryl® Allergy: 12.5 mg/5 mL (120 mL, 240 mL, 480 mL) [alcohol free, sugar free; black cherry flavor]

Liquid, topical, as hydrochloride [stick]:

Benadryl® Itch Stopping Extra Strength: 2% (14 mL) [contains zinc acetate 0.1% and alcohol]

Solution, oral, as hydrochloride:

Diphenhist: 12.5 mg/5 mL (120 mL, 480 mL) [alcohol free; contains sodium benzoate]

Solution, topical, as hydrochloride [spray]:

Benadryl® Itch Stopping Extra Strength: 2% (60 mL) [contains zinc acetate 0.1% and alcohol]

Dermamycin®: 2% (60 mL) [contains menthol 1%]

Strips, oral, as hydrochloride:

Benadryl® Allergy: 25 mg (10s) [contains sodium 4 mg/strip; vanilla mint flavor]

Benadryl® Children’s Allergy: 12.5 mg (10s) [vanilla mint flavor]

Triaminic® Thin Strips™ Cough and Runny Nose: 12. 5 mg (16s) [grape flavor]

Suspension, as tannate:

Ben-Tann: 25 mg/5 mL (120 ml) [contains sodium benzoate; strawberry flavor]

Dytan™: 25 mg/5 mL (120 mL) [strawberry flavor] [DSC]

Syrup, as hydrochloride:

Silphen® Cough: 12.5 mg/5 mL (120 mL, 240 mL, 480 mL) [contains alcohol; 5%; strawberry flavor]

Tablet, as hydrochloride: 25 mg, 50 mg

Aler-Tab, Benadryl® Allergy, Genahist®, Sominex®: 25 mg

Tablet, chewable, as hydrochloride:

Benadryl® Children's Allergy: 12.5 mg [contains phenylalanine 4.2 mg, magnesium 15 mg, and sodium 2 mg per tablet; grape flavor]

Tablet, chewable, as tannate:

Dytan™: 25 mg [contains phenylalanine; strawberry flavor]

Tablet, orally disintegrating, as citrate:

Benadryl® Children's Allergy Fastmelt®: 19 mg [equivalent to diphenhydramine hydrochloride 12.5 mg; contains phenylalanine 4.5 mg/tablet and soy protein isolate; cherry flavor]

Generic AvailableYes: Excludes chewable tablet, gel, orally-disintegrating tablet, stick, strip

Pricing: U.S. (www.drugstore.com)

Capsules (DiphenhydrAMINE HCl)

25 mg (100): $11.99

50 mg (100): $13.99

Chewable (Dytan)

25 mg (60): $76.55

Liquid (Q-Dryl)

12.5 mg/5 mL (473): $13.01

Solution (DiphenhydrAMINE HCl)

50 mg/mL (25): $35.99

Mechanism of ActionCompetes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract; anticholinergic and sedative effects are also seen

Pharmacodynamics/Kinetics

Onset of action: Maximum sedative effect: 1-3 hours

Duration: 4-7 hours

Distribution: V_d: 3-22 L/kg

Protein binding: 78%

Metabolism: Extensively hepatic n-demethylation via CYP2D6; minor demethylation via CYP1A2, 2C9 and 2C19; smaller degrees in pulmonary and renal systems; significant first-pass effect

Bioavailability: Oral: ~40% to 70%

Half-life elimination: 2-10 hours; Elderly: 13.5 hours

Time to peak, serum: 2-4 hours

Excretion: Urine (as unchanged drug)

Related Information

- Antiparkinsonian Agents
- CMS: Long-Term Care Facility Thresholds
- Contrast Media Reactions, Premedication for Prophylaxis
- Discontinuation of Psychotropic Drugs
- Nonbenzodiazepine Anxiolytics and Hypnotics
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsDiphenhydramine citrate 19 mg is equivalent to diphenhydramine hydrochloride 12.5 mg

Dental Health Professional Considerations25-50 mg of diphenhydramine orally every 4-6 hours can be used to treat mild dermatologic manifestations of allergic reactions to penicillin and other antibiotics. Diphenhydramine is not recommended as local anesthetic for either infiltration route or nerve block since the vehicle has caused local necrosis upon injection. A 50:50 mixture of diphenhydramine liquid (12.5

mg/5 mL) in Kaopectate® or Maalox® is used as a local application for recurrent aphthous ulcers; swish 1 tablespoonful for 2 minutes 4 times/day.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and dry mucous membranes. Chronic use of antihistamines will inhibit salivary flow, particularly in elderly patients; may contribute to periodontal disease and oral discomfort. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentAlong with benztropine, considered the drug of choice for patients with acute dystonic reactions. The usual adult dosage is I.M. 50 mg. In an emergency situation (laryngeal spasm), it should be given intravenously. It is the most sedating antihistamine used to treat drug-induced EPS. Generally not a first-line agent for insomnia, but often utilized in individuals where benzodiazepines are contraindicated (eg, patients with a history of substance abuse).

Anesthesia and Critical Care Concerns/Other ConsiderationsDiphenhydramine's use as a sleep aid is discouraged due to its anticholinergic effects.

Index TermsDiphenhydramine Citrate; Diphenhydramine Hydrochloride; Diphenhydramine Tannate

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Weston MV, “Lovelorn and Snakebite,” *Hosp Pract (Off Ed)*, 1986, 21(3A):140-3.

International Brand NamesAlerace (PH); Allerin AH (PH); Allermin (JP); Bedorma (CH); Bena (HK); Benadryl (AR, CO, EC, GR, ID, IN, MX, PH, TH, VE); Benadryl A (UY); Benadryl Allergy (PE); Benadryl for the Family Original (AU); Benocten (CH, CR); Benzhydraminum Hydrochloricum (PL); Broncho D (IL); Brudifen (MX); Calmaben (BG); Cathejell (IL); Dermodrin (PL); Diamine (TW); Dibrondrin (AT); Dimedrol (EE); Dormutil (DE); Dormutil N (NO); Drafen (MX); Dramelin (PH); Histergan (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PR, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Indumir (MX); Nytol (IL); Otede (ID); Pasifen (CN); R Calm (BE); ratioAllerg (DE); Recodryl (ID); Resmin (JP); Sleepia (DE); Snuzaid (AU); Somol (CN); Therafilm (MX); Unisom Sleepgels (AU, HK); Vena (JP); Venasmin (JP); Vicnite (MX)

Diphenoxylate and Atropine

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Medication Safety Issues

Sound-alike/look-alike issues:

Lomotil® may be confused with Lamictal®, Lamisil®, lamotrigine, Lanoxin®, Lasix®, ludiomil

Lonox® may be confused with Lanoxin®, Loprox®

International issues:

Lomotil® may be confused with Lemesil® which is a brand name for nimesulide in Greece

Lonox® may be confused with Flomox® which is a brand of cefcapene in Japan

Pronunciation(dye fen OKS i late & A troe peen)
U.S. Brand NamesLomotil®; Lonox®
Canadian Brand NamesLomotil®
Pharmacologic CategoryAntidiarrheal
Use: Labeled IndicationsTreatment of diarrhea
Dosing: AdultsDiarrhea: Oral: Diphenoxylate 5 mg 4 times/day until control achieved (maximum: 20 mg/day), then reduce dose as needed; some patients may be controlled on doses of 5 mg/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricDiarrhea: Oral: Children 2-12 years (use with caution in young children due to variable responses): Liquid: Diphenoxylate 0.3-0.4 mg/kg/day in 4 divided doses until control achieved (maximum: 10 mg/day), then reduce dose as needed; some patients may be controlled on doses as low as 25% of the initial daily dose
Administration: OralIf there is no response within 48 hours of continuous therapy, this medication is unlikely to be effective and should be discontinued; if chronic diarrhea is not improved symptomatically within 10 days at maximum dosage, control is unlikely with further use. Use of the liquid preparation is recommended in children <13 years of age; use plastic dropper provided when measuring liquid.
RestrictionsC-V
ContraindicationsHypersensitivity to diphenoxylate, atropine, or any component of the formulation; obstructive jaundice; diarrhea associated with pseudomembranous enterocolitis or enterotoxin-producing bacteria; not for use in children <2 years of age
Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Dehydration/electrolyte imbalance: In case of severe dehydration or electrolyte imbalance, withhold diphenoxylate/atropine treatment until corrective therapy has been initiated. Use in conjunction with fluid and electrolyte therapy when appropriate. Inhibiting peristalsis may lead to fluid retention in the intestine aggravating dehydration and electrolyte imbalance.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Ulcerative colitis: Use with caution in patients with acute ulcerative colitis.

Special populations:

- Pediatrics: Use with caution in children. Younger children may be predisposed to toxicity; signs of atropinism may occur even at recommended doses, especially in patients with Down syndrome. Overdose in children may result in severe respiratory depression, coma, and possibly permanent brain damage.

Other warnings/precautions:

- Appropriate use: If there is no response within 48 hours, this medication is unlikely to be effective and should be discontinued; if chronic diarrhea is not improved symptomatically within 10 days at maximum dosage, control is unlikely with further use. Reduction of intestinal motility may be deleterious in diarrhea resulting from *Shigella, Salmonella*, toxigenic strains of *E. coli*, and pseudomembranous enterocolitis associated with broad-spectrum antibiotics; use is not recommended.
- Dependence: Physical and psychological dependence have been reported with higher than recommended dosing.

Geriatric ConsiderationsElderly are particularly sensitive to fluid and electrolyte loss. This generally results in lethargy, weakness, and confusion. Repletion and maintenance of electrolytes and water are essential in the treatment of diarrhea. Drug therapy must be limited in order to avoid toxicity with this agent.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not noted in animal studies; decreased maternal weight, fertility and litter sizes were observed. There are no adequate and well-controlled studies in pregnant women.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsAtropine is excreted in breast milk (refer to Atropine monograph); the manufacturer states that diphenoxylic acid may be excreted in breast milk.

Adverse ReactionsFrequency not defined.

Cardiovascular: Tachycardia

Central nervous system: Confusion, depression, dizziness, drowsiness, euphoria, flushing, headache, hyperthermia, lethargy, malaise, restlessness, sedation

Dermatologic: Angioneurotic edema, dry skin, pruritus, urticaria

Gastrointestinal: Abdominal discomfort, anorexia, gum swelling, nausea, pancreatitis, paralytic ileus, toxic megacolon, vomiting, xerostomia

Genitourinary: Urinary retention

Neuromuscular & skeletal: Numbness

Miscellaneous: Anaphylaxis

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersWatch for signs of atropinism (dryness of skin and mucous membranes, tachycardia, thirst, flushing); monitor number and consistency of stools; observe for signs of toxicity, fluid and electrolyte loss, hypotension, and respiratory depression

Nursing: Physical Assessment/MonitoringSee individual agent for Atropine.

Patient EducationSee individual agent for Atropine.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral: Diphenoxylate hydrochloride 2.5 mg and atropine sulfate 0.025 mg per 5 mL (5 mL, 10 mL, 60 mL)

Lomotil®: Diphenoxylate hydrochloride 2.5 mg and atropine sulfate 0.025 mg per 5 mL (60 mL) [contains alcohol 15%; cherry flavor]

Tablet: Diphenoxylate hydrochloride 2.5 mg and atropine sulfate 0.025 mg

Lomotil®, Lonox®: Diphenoxylate hydrochloride 2.5 mg and atropine sulfate 0.025 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Liquid (Diphenoxylate-Atropine)

2.5-0.025 mg/5 mL (60): $19.99

Liquid (Lomotil)

2.5-0.025 mg/5 mL (60): $29.39

Tablets (Diphenoxylate-Atropine)

2.5-0.025 mg (30): $13.99

Tablets (Lomotil)

2.5-0.025 mg (30): $35.99

Tablets (Lonox)

2.5-0.025 mg (60): $27.99

Mechanism of ActionDiphenoxylate inhibits excessive GI motility and GI propulsion; commercial preparations contain a subtherapeutic amount of atropine to discourage abuse

Pharmacodynamics/Kinetics

Atropine: See Atropine monograph.

Diphenoxylate:

Onset of action: Antidiarrheal: 45-60 minutes

Duration: Antidiarrheal: 3-4 hours

Absorption: Well absorbed

Metabolism: Extensively hepatic via ester hydrolysis to diphenoxylic acid (active)

Half-life elimination: Diphenoxylate: 2.5 hours; Diphenoxylic acid: 12-14 hours

Time to peak, serum: 2 hours

Excretion: Primarily feces (49% as unchanged drug and metabolites); urine (~14%, <1% as unchanged drug)

Related Information

- Atropine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness, restlessness, drowsiness, or insomnia; rarely may produce euphoria

Mental Health: Effects on Psychiatric TreatmentConcurrent use with MAO inhibitors may result in hypertensive crisis; additive sedation and dry mouth with psychotropics; use with benztropine or other anticholinergic agents may result in ileus

Index TermsAtropine and Diphenoxylate

References

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McCarron MM, Challoner KR, and Thompson GA, "Diphenoxylate-Atropine (Lomotil®) Overdose in Children: An Update (Report of Eight Cases and Review of the Literature)," *Pediatrics*, 1991, 87(5):694-700.[PubMed 2020516]

International Brand NamesBeamotil (MY, SG); Dhamotil (HK, MY); Diarase (MY); Diarsed (FR); Diastop (NZ); Dimotil (HK); Diphenoxylate A (MY); Lofenoxal (AU); Lomotil (AU, BB, BF, BJ, BR, CI, CO, EG, ET, GB, GH, GM, GN, HK, IN, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, PE, PT, SC, SD, SL, SN, TH, TN, TR, TT, TZ, UG, ZA, ZM, ZW); Lomotine (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Reasec (CH, CZ, DE, HN)

Diphtheria and Tetanus Toxoids, and Acellular Pertussis Vaccine

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Medication Safety Issues

Carefully review product labeling to prevent inadvertent administration of Tdap when DTaP is indicated. Tdap contains lower amounts of diphtheria toxoid and some pertussis antigens than DTaP.

Tdap is not indicated for use in children <10 years of age

DTaP is not indicated for use in persons ≥7 years of age

Guidelines are available in case of inadvertent administration of these products; refer to ACIP recommendations, February 2006 available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr55e223a1.htm

Note:

DTaP: Diphtheria and tetanus toxoids and acellular pertussis vaccine

DTP: Diphtheria and tetanus toxoids and pertussis vaccine (unspecified pertussis antigens)

DTwP: Diphtheria and tetanus toxoids and whole-cell pertussis vaccine (no longer available on U.S. market)

Tdap: Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine

Pronunciation(dif THEER ee a & TET a nus TOKS oyds & ay CEL yoo lar per TUS sis vak SEEN)
U.S. Brand NamesAdacel®; Boostrix®; Daptacel®; Infanrix®; Tripedia®
Canadian Brand NamesAdacel®
Pharmacologic CategoryVaccine, Inactivated (Bacterial)
Use: Labeled Indications
Daptacel®, Infanrix®, Tripedia® (DTaP): Active immunization against diphtheria, tetanus, and pertussis from age 6 weeks through 6 years of age (prior to seventh birthday)

Adacel®, Boostrix® (Tdap): Active booster immunization against diphtheria, tetanus, and pertussis

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for the following:

Children 6 weeks to <7 years (DTaP): For primary immunization against diphtheria, tetanus and pertussis

Adolescents 11-18 years (Tdap) (Adacel®, Boostrix®):

- A single dose of Tdap as a booster dose in adolescents who have completed the recommended childhood DTaP vaccination series (preferred age of administration is 11-12 years)
- A single dose of Tdap should be given to replace a single dose of Td if the last dose of Td was ≥5 years earlier; lesser intervals may be used if the benefit outweighs the risk (not for multiple administrations; recommendations are for the replacement of a single dose of Td only)
- Persons wounded in bombings or similar mass casualty events and who cannot confirm receipt of a tetanus booster within the previous 5 years and who have penetrating injuries or nonintact skin exposure should receive a single dose of Tdap

Adults aged 19-64 (Adacel®): A single dose of Tdap should be given to replace a single dose of Td if the last dose of Td was ≥10 years earlier (not for multiple administrations; recommendations are for the replacement of a single dose of Td only). A shorter interval (<10 years but at least 2 years since last dose of Td) may be considered in the following situations:

- To protect against pertussis
- To protect against pertussis transmission to infants in adults who anticipate close contact with children <12 months of age; Tdap should be administered at least 2 weeks prior to beginning close contact
- Healthcare providers with direct patient contact
- Persons wounded in bombings or similar mass casualty events and who cannot confirm receipt of a tetanus booster within the previous 5 years and who have penetrating injuries or non-intact skin exposur, should receive a single dose of Tdap

Dosing: Adults

Booster immunization:

ACIP recommendations: I.M.: Adults 19-64 years (Adacel®): 0.5 mL. A single dose should be given instead of Td in adults if they received their last dose of Td ≥10 years previous. Shorter intervals (as short as 2 years) may used among healthcare providers, adults in contact with infants, or others in settings with increased risk for pertussis, including during pertussis outbreaks. Adacel® should only be used to replace a single booster dose of Td.

Manufacturer's labeling: I.M.: Adults ≤64 years (Adacel®): 0.5 mL as a single dose, administered 5 years after last dose of DTwP or DTaP vaccine.

Wound management: Adacel® (in patients 11-64 years of age) or Boostrix® (in patients 10-18 years of age) may be used as an alternative to Td vaccine when a tetanus toxoid-containing vaccine is needed for wound management, and in whom the pertussis component is also indicated.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Primary immunization: Children 6 weeks to <7 years: I.M.: **Note:** Whenever possible, the same product should be used for all doses. Interruption of recommended schedule does not require starting the series over; a delay between doses should not interfere with final immunity.

Daptacel®, Infanrix®, Tripedia®: 0.5 mL per dose, total of 5 doses administered as follows:

Three doses, usually given at 2-, 4-, and 6 months of age; may be given as early as 6 weeks of age and repeated every 6-8 weeks

Fourth dose: Given at ~15-20 months of age, but at least 6 months after third dose

Fifth dose: Given at 4-6 years of age, prior to starting school or kindergarten; if the fourth dose is given at ≥4 years of age, the fifth dose may be omitted

Booster immunization:

ACIP recommendations: Adolescents 11-18 years: I.M.: 0.5 mL. A single dose of Tdap should be given instead of Td in adolescents who have completed the recommended childhood DTP/DTaP series and have not received Td or Tdap; preferred age of vaccination with Tdap is 11-12 years. Adolescents who received Td but not Tdap and who have completed the recommended childhood DTP/DTaP series are encouraged to receive Tdap; an interval of at least 5 years between Td and Tdap is recommended, but lesser intervals may be used if the benefit outweighs the risk.

Manufacturer's labeling:

Children 10-18 years (Boostrix®): I.M.: 0.5 mL as a single dose, administered 5 years after last dose of DTwP or DTaP vaccine.

Children ≥11 years (Adacel®): I.M.: Refer to adult dosing.

Wound management: Refer to adult dosing.

Administration: I.M.Shake suspension well.
Adacel®, Boostrix®: Administer only I.M. in deltoid muscle of upper arm.

Daptacel®, Infanrix®, Tripedia®: Administer only I.M. in anterolateral aspect of thigh or deltoid muscle of upper arm.

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

Administration with other vaccines:

Diphtheria and Tetanus Toxoids, and Acellular Pertussis vaccine with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Diphtheria and Tetanus Toxoids, and Acellular Pertussis vaccine with live vaccines: May be given simultaneously or at any interval between doses.

Vaccine administration with antibody-containing products: Diphtheria and Tetanus Toxoids, and Acellular Pertussis vaccine may be given simultaneously at different sites or at any interval between doses. Examples of antibody containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StorageRefrigerate at 2°C to 8°C (35°F to 46°F). Do not freeze.
ContraindicationsHypersensitivity to diphtheria, tetanus toxoids, pertussis, or any component of the formulation; history of any of the following effects from previous administration of pertussis-containing vaccine - progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy or progressive epilepsy (postpone until condition stabilized); encephalopathy occurring within 7 days of administration and not attributable to another cause
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

- Arthus-type hypersensitivity: Td or Tdap vaccines and emergency doses of Td vaccine should not be given more frequently than every 10 years in patients who have experienced a serious Arthus-type hypersensitivity reaction following a prior use of tetanus toxoid even if the wound is not clean or minor; these patients generally have high serum antitoxin levels.

- Reactions from previous dose: Carefully consider use in patients with history of any of the following effects from previous administration of whole-cell DTP or acellular pertussis vaccine: Fever ≥105°F (40.5°C) within 48 hours of unknown cause; seizures with or without fever occurring within 3 days; persistent, inconsolable crying episodes lasting ≥3 hours and occurring within 48 hours; shock or collapse within 48 hours.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).
- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.
- Guillain-Barré syndrome: Continue use with caution if Guillain-Barré syndrome occurs within 6 weeks of prior tetanus toxoid.
- Neurologic disorders: Use with caution in patients with history of seizure disorder, progressive neurologic disease, or conditions predisposing to seizures; ACIP and APP guidelines recommend deferring immunization until health status can be assessed and condition stabilized.
- Poliomyelitis: Defer administration during outbreaks of poliomyelitis.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Adults: Safety and efficacy of Boostrix® have not been established in patients >18 years of age.
- Elderly: Safety and efficacy of Adacel® have not been established adults ≥65 years of age.
- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination. May be used in patients with HIV infection.
- Pediatrics: Safety and efficacy of Adacel® have not been established in children <11 years. Safety and efficacy of Boostrix® have not been established in patients <7 years of age. Safety and efficacy of Daptacel®, Infanrix®, Tripedia® have not been established in children <6 weeks of age or ≥7 years of age.

Dosage form specific issues:

- Adacel®: Formulated with the same antigens found in Daptacel®, but with reduced quantities of tetanus and pertussis. Use in the primary immunization series or to complete the primary series has not been evaluated.
- Boostrix®: Formulated with the same antigens found in Infanrix®, but in reduced quantities. Use in the primary immunization series or to complete the primary series has not been evaluated.
- Latex: Packaging may contain natural latex rubber.
- Thimerosal: Products may contain thimerosal.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. It is not known whether the vaccine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Daptacel®, Infanrix®, and Tripedia® are not recommended for use in a pregnant woman or any patient ≥7 years of age. Although pregnancy itself is generally not considered a contraindication to Tdap (Adacel®, Boostrix®) vaccination, Td is preferred to Tdap when vaccination cannot be delayed during pregnancy. In order to help prevent pertussis exposure among infants, the use of Tdap, is recommended in women of childbearing potential prior to pregnancy. Due to lack of information with Tdap, a pregnancy registry has been established for women who may become exposed to Boostrix® (888-825-5249) or Adacel® (800-822-2463) while pregnant.

Breast-Feeding ConsiderationsBreast-feeding is not a contraindication to vaccine administration. Women who have not previously had a dose of Tdap should receive a dose postpartum to help prevent pertussis in infants <12 months of age.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Daptacel®, Infanrix®, Tripedia® (incidence of erythema, swelling, and fever increases with successive doses):

Frequency not defined:

Central nervous system: Drowsiness, fever, fussiness, irritabililty, lethargy

Gastrointestinal: Appetite decreased, vomiting

Local: Pain, redness, swelling, tenderness

Miscellaneous: Prolonged or persistent crying, refusal to play

Postmarketing and/or case reports: Allergic reaction, anaphylactic reactions, cellulitis, cyanosis, diarrhea, ear pain, encephalopathy, erythema, hypersensitivity, hypotonia, hypotonic-hyporesponsive episode, idiopathic thrombocytopenic purpura, infantile spasm, injection site reaction (abscess, cellulitis, mass, nodule, rash), intussusception, irritability, limb swelling, lymphadenopathy, nausea, pruritus, rash, respiratory tract infection, seizure, screaming, somnolence, sudden infant death syndrome, thrombocytopenia, urticaria

Adacel®, Boostrix®: Note: Ranges presented, actual percent varies by product and age group

>10%:

Central nervous system: Fatigue, tiredness (24% to 37%; grade 3/severe: 1% to 4%), headache (34% to 44%; grade 3/severe: 2% to 4%), chills (8% to 15%; severe: <1%)

Gastrointestinal: Gastrointestinal symptoms, includes abdominal pain, diarrhea, nausea and/or vomiting (3% to 26%; grade 3/severe: ≤3%)

Local: Injection site pain (66% to 78%; grade 3/severe: 1% to 5%), arm circumference increased (28%; >40 mm: 0.5%), redness (21% to 25%; ≥50 mm: 2% to 4%), swelling (21%; ≥50 mm: 3%)

Neuromuscular & skeletal: Body aches/muscle weakness (22% to 30%; severe: 1%), soreness/swollen joints (9% to 11%; severe: <1%)

1% to 10%:

Central nervous system: Fever ≥38°C (≥100.4˚F: 1% to 5%)

Dermatologic: Rash (2% to 3%)

Miscellaneous: Lymph node swelling (7%; severe: <1%)

Postmarketing and/or case reports: Arthralgia, back pain, bruising, diabetes mellitus, encephalitis, exanthema, facial palsy, Henoch-Schönlein purpura, injection site reaction (induration, inflammation, mass, nodule, warmth), limb swelling (extensive), lymphadenitis, lymphadenopathy, myalgia, myocarditis, nerve compression, paresthesia, pruritus, seizure, sterile abscess, urticaria

Additional adverse reactions associated with diphtheria, tetanus, and/or pertussis antigens: Arthus hypersensitivity, brachial neuritis, GBS, peripheral/central mononeuropathies

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension [Tdap, booster formulation]:

Adacel®: Diphtheria 2 Lf units, tetanus 5 Lf units, and acellular pertussis antigens (detoxified pertussis toxin 2.5 mcg, filamentous hemagglutinin 5 mcg, pertactin 3 mcg, fimbriae [types 2 and 3] 5 mcg) per 0.5 mL (0.5 mL) [contains aluminum]

Boostrix®: Diphtheria 2.5 Lf units, tetanus 5 Lf units, and acellular pertussis antigens (inactivated pertussis toxin 8 mcg, filamentous hemagglutinin 8 mcg, pertactin 2.5 mcg) per 0.5 mL (0.5 mL) [preservative free; contains aluminum and polysorbate 80; prefilled syringes contain natural rubber/natural latex]

Injection, suspension [DTaP, active immunization formulation]:

Daptacel®: Diphtheria 15 Lf units, tetanus 5 Lf units, and acellular pertussis antigens (detoxified pertussis toxin 10 mcg, filamentous hemagglutinin 5 mcg, pertactin 3 mcg, fimbriae [types 2 and 3] 5 mcg) per 0.5 mL (0.5 mL) [contains aluminum; contains natural rubber/natural latex in packaging]

Infanrix®: Diphtheria 25 Lf units, tetanus 10 Lf units, and acellular pertussis antigens (inactivated pertussis toxin 25 mcg, filamentous hemagglutinin 25 mcg, pertactin 8 mcg) per 0.5 mL (0.5 mL) [contains aluminum and polysorbate 80; prefilled syringes contain natural rubber/natural latex]

Tripedia®: Diphtheria 6.7 Lf units, tetanus 5 Lf units, and acellular pertussis antigens (inactivated pertussis toxin 23.4 mcg, filamentous hemagglutinin 23.4 mcg) per 0.5 mL (0.5 mL) [contains aluminum, natural rubber/natural latex in packaging, polysorbate 80, and thimerosal (trace amounts)]

Note: Tripedia® vaccine is also used to reconstitute ActHIB® to prepare TriHIBit® vaccine (diphtheria, tetanus toxoids, and acellular pertussis and *Haemophilus influenzae* b conjugate vaccine combination)

Generic AvailableNo

Mechanism of ActionPromotes active immunity to diphtheria, tetanus, and pertussis by inducing production of specific antibodies.

Related Information

- Immunization Recommendations
- Prophylaxis for Patients Exposed to Common Communicable Diseases

Pharmacotherapy PearlsDTaP may be given for the fourth and fifth doses in children who started immunization with DTP vaccine. In patients who cannot be given pertussis vaccine, DT for pediatric use should be given to complete the series.

TriHIBit® is Tripedia® vaccine used to reconstitute ActHIB® (*Haemophilus* b conjugate) vaccine. The combination can be used for the DTaP dose given at 15-18 months when Tripedia® was used for the initial doses and a primary series of HIB vaccine has been given.

Adacel® is formulated with the same antigens found in Daptacel® but with reduced quantities of pertussis and tetanus. It is intended for use as a booster dose in children and adults, 11-64 years of age, and **not** for primary immunization.

Boostrix® is formulated with the same antigens found in Infanrix® but in reduced quantities. It is intended for use as a booster dose in children 10-18 years, and is **not** for primary immunization.

The ACIP considers Adacel® and Boostrix® to be interchangeable when administered to adolescents for childhood vaccination according to the Child and Adolescent Immunization Schedule.

Acetaminophen or ibuprofen may reduce or prevent fever; the child's medical record should document that the small risk of postvaccination seizure and the benefits of the pertussis vaccination were discussed with the patient; parents or guardians should be questioned prior to administration of vaccine as to any adverse reactions from previous dose. Provide Vaccine Information Materials, as required by National Childhood Vaccine Injury Act of 1986, prior to immunization.

Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title and address be entered into the patient's permanent medical record.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDTaP; dTpa; Tdap; Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis, Adsorbed

References

Centers for Disease Control, “Notice to Readers: Update: Supply of Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine,” *MMWR*, 2002, 50(51):1159.

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Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.[PubMed 17136024]

Pichichero ME, Rennels MB, Edwards KM, et al, "Combined Tetanus, Diphtheria, and 5-Component Pertussis Vaccine for Use in Adolescents and Adults," *JAMA*, 2005, 293:3003-11.[PubMed 15933223]

“Use of Diphtheria Toxoid-Tetanus Toxoid-Acellular Pertussis Vaccine as a Five-Dose Series,” *MMWR Recomm Rep*, 2000, 49(RR-13);1-8.

International Brand NamesAcelluvax DTP (TH); Adacel (AU); Adsorbed DT COQ (HK, TW); Anatoxal Di Te Per Berna (PE); Boostrix (AU, HK, IL); D.T. COQ (MY); Dif per tet all (IT, MY, PH, TH); DiTePer Anatoxal Berna Vaccine (HK, MY, PH); DPT (TW); Infanrix (AT, AU, BB, BE, BM, BS, BZ, GY, IT, JM, MX, NL, SE, SR, TT, TW); P.D.T. Vax Purified (KP); TRIAcelluvax (DE); Tripacel (AU, HK, TW); Tripvac (IN)

Haemophilus influenzae b Conjugate Vaccine'; return;">
Diphtheria and Tetanus Toxoids, Acellular Pertussis and *Haemophilus influenzae* b Conjugate Vaccine

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Pronunciation(dif THEER ee a & TET a nus TOKS oyds, ay CEL yoo lar per TUS sis & hem OF fi lus in floo EN za bee KON joo gate vak SEEN)
U.S. Brand NamesTriHIBit®
Pharmacologic CategoryVaccine, Inactivated (Bacterial)
Use: Labeled IndicationsActive immunization of children 15-18 months of age for prevention of diphtheria, tetanus, pertussis, and invasive disease caused by *H. influenzae* type b

The Advisory Committee on Immunization Practices (ACIP) recommends the use of TriHIBit® for the fourth dose of the diphtheria, tetanus, pertussis, and *Haemophilus* vaccine series. Whenever feasible, the same manufacturer should be used to provide the pertussis component; however, vaccination should not be deferred if a specific brand is not known or is not available.

Dosing: PediatricImmunization: Children 15-18 months: I.M.: 0.5 mL: **Note:** For use as the fourth dose of the DTaP and Hib series (see individual vaccines). May be used as a booster in children 12-20 months of age as long as 6 months have elapsed since the third dose.
Administration: I.M.For I.M use only; do not administer I.V. or SubQ. Administer in the anterolateral aspects of the thigh or the deltoid muscle of the upper arm. Do not inject in the gluteal area or where there may be a major nerve trunk. Do not administer additional vaccines or immunoglobulins at the same site or using the same syringe.

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends "it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection."

Administration with other vaccines:

DTaP/Hib with live vaccines: May be given simultaneously or at any interval between doses.

DTaP/Hib with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Vaccine administration with antibody-containing products: DTaP/Hib may be given simultaneously at different sites or at any interval between doses. Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StorageRefrigerate ActHIB® and Tripedia® at 2°C to 8°C (35°F to 46°F). Do not freeze. Suspension should be used within 30 minutes of reconstitution.
ReconstitutionAgitate vial of Tripedia®, then withdraw 0.6 mL to reconstitute ActHIB® powder; agitate thoroughly to form a suspension. **Tripedia® should not be used to reconstitute any vaccines other than ActHIB®.**
ContraindicationsHypersensitivity to diphtheria, tetanus toxoids, pertussis, *Haemophilus*, or any component of the formulation; history of any of the following effects from previous administration of pertussis-containing vaccine: Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive epilepsy (postpone until condition stabilized); encephalopathy occurring within 7 days of administration and not attributable to another cause
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

- Reactions from previous pertussis vaccine: Carefully consider use in patients with history of any of the following effects from previous administration of whole-cell DTP or acellular pertussis vaccine: Fever ≥105°F (40.5°C) within 48 hours of unknown cause; seizures with or without fever occurring within 3 days; persistent, inconsolable crying episodes lasting ≥3 hours and occurring within 48 hours; shock or collapse (hypotonic-hyporesponsive episode [HHE]) occurring within 48 hours.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).

- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.

- Guillain-Barré syndrome: Use with caution if Guillain-Barré syndrome occurred within 6 weeks of prior tetanus toxoid.

- Neurologic disorders: Use with caution in patients with history of seizure disorder, progressive neurologic disease, or conditions predisposing to seizures; ACIP and AAP guidelines recommend deferring immunization until health status can be assessed and condition stabilized. Antipyretics should be administered at the time of and for 24 hours following vaccination to patients at high risk for seizures.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Adults: This combination is not for use in adults.
- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy [including high-dose corticosteroids]); may have a reduced response to vaccination. May be used in patients with HIV infection.
- Pediatrics: This combination is not for use in children <12 months or >20 months of age

Dosage form specific issues:

- Latex: Packaging may contain natural latex rubber.
- Thimerosal: Products may contain thimerosal.

Appropriate use:

- TriHIBit® combination: TriHIBit® is Tripedia® vaccine used to reconstitute ActHIB® (*Haemophilus* b conjugate) vaccine. The combination can be used for the DTaP dose given at 15-18 months when Tripedia® was used for the initial doses and a primary series of HIB vaccine has been given. It should not be used for primary immunization.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Refer to individual agents. When administered as the combination formed with TriHIBit®, adverse reactions were less than those seen with ActHIB® and Tripedia® administered separately.

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension [preservative free]:

TriHIBit®: Diphtheria 6.7 Lf units, tetanus 5 Lf units, acellular pertussis antigens [inactivated pertussis toxin 23.4 mcg, filamentous hemagglutinin 23.4 mcg], and *Haemophilus* b capsular polysaccharide 10 mcg [bound to tetanus toxoid 24 mcg] per 0.5 mL (0.5 mL) [contains aluminum, natural rubber/natural latex in packaging, polysorbate 80, sucrose, and trace amounts of thimerosal; Tripedia® vaccine used to reconstitute ActHIB® forms TriHIBit®]

Generic AvailableNo
ManufacturerSanofi Pasteur Inc
Related Information

- Immunization Recommendations

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index Terms*Haemophilus influenzae* b Conjugate Vaccine and Diphtheria, Tetanus Toxoids, and Acellular Pertussis Vaccine; DTaP/Hib
References

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International Brand NamesDesopam (JP); Modrenal (GB)

Diphtheria and Tetanus Toxoids, Acellular Pertussis, and Poliovirus Vaccine

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Pronunciation(dif THEER ee a & TET a nus TOKS oyds, ay CEL yoo lar per TUS sis & POE lee oh VYE rus vak SEEN)

U.S. Brand NamesKinrix™

Pharmacologic Category[Vaccine, Inactivated (Bacterial)](); [Vaccine, Inactivated (Viral)]()

Use: Labeled IndicationsActive immunization against diphtheria, tetanus, pertussis, and poliomyelitis, used as the 5th dose in the DTaP series and the 4th dose in the IPV series

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for use as the fifth dose in the DTaP series and the fourth dose in the IPV series in children who received DTaP (Infanrix®) and/or DTaP-Hepatitis B-IPV (Pediarix®) as the first 3 doses and DTaP (Infanrix®) as the fourth dose. Whenever feasible, the same manufacturer should be used to provide the pertussis component; however, vaccination should not be deferred if a specific brand is not known or is not available.

Dosing: Pediatric**Immunization:** I.M.: Children 4-6 years: 0.5 mL; **Note:** For use as the 5th dose in the DTaP series and the 4th dose in the IPV series

Administration: I.M.For I.M. use only; do not administer intradermally, I.V., or SubQ. Shake well prior to use; do not use unless a homogeneous, turbid, white suspension forms. Administer in the deltoid muscle of the upper arm. Do not administer additional vaccines or immunoglobulins at the same site, or using the same syringe.

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

Acetaminophen or other appropriate antipyretic should be administered every 4 hours for 24 hours following vaccination to children with history of seizure with DTaP vaccination to decrease the possibility of postvaccination fever.

Administration with other vaccines:

DTaP-IPV with other inactivated vaccines: May be given simultaneously or at any interval between doses.

DTaP-IPV with live vaccines: May be given simultaneously or at any interval between doses.

Vaccine administration with antibody-containing products: DTaP-IPV may be given simultaneously at different sites or at any interval between doses. Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StorageStore under refrigeration of 2°C to 8°C (36°F to 46°F); do not freeze. Discard if frozen.

CompatibilityDo not mix with other vaccines or injections.

ContraindicationsHypersensitivity to diphtheria and tetanus toxoids, pertussis, poliovirus vaccine, or any component of the vaccine; encephalopathy occurring within 7 days of a previous pertussis vaccine not (not attributable to another identifiable cause); progressive neurologic disorders (including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy)

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.
- Reactions from previous pertussis vaccination: Carefully consider use in patients with history of any of the following effects from previous administration of whole-cell DTP or acellular pertussis vaccine: Fever 40.5°C (≥105°F) within 48 hours of unknown cause; seizures with or without fever occurring within 3 days; persistent, inconsolable crying episodes lasting ≥3 hours and occurring within 48 hours; shock or collapse (hypotonic-hyporesponsive episode [HHE]) occurring within 48 hours.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).
- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.
- Guillain-Barré syndrome: Use with caution if Guillain-Barré syndrome occurred within 6 weeks of prior tetanus toxoid.
- Neurologic disorders: Use with caution in patients with history of seizure disorder, progressive neurologic disease, or conditions

predisposing to seizures; ACIP and AAP guidelines recommend deferring immunization until health status can be assessed and condition stabilized. Antipyretics should be administered at the time of and for 24 hours following vaccination to patients at high risk for seizures.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Adults: Safety and efficacy have not been established for use in adults.

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy [including high-dose corticosteroids]); may have a reduced response to vaccination.

- Pediatrics: Safety and efficacy have not been established for use in children <4 years of age and children ≥7 years of age. If inadvertently administered to children ≥7 years of age earlier than the fifth dose in the series, it may be counted as a valid dose, provided the minimum interval requirements were met.

Dosage form specific issues:

- Aluminum: Product may contain aluminum.

- Latex: Packaging may contain natural latex rubber.

- Neomycin: Product may contain neomycin.

- Polymyxin B: Product may contain polymyxin B.

- Polysorbate 80: Product may contain polysorbate 80.

Geriatric ConsiderationsSince protective tetanus and diphtheria antibodies decline with age, only 28% of persons >70 years of age in the U.S. are believed to be immune to tetanus, and most of the tetanus-induced deaths occur in people >60 years of age, it is advisable to offer Td, especially to elderly, concurrent with their influenza and other immunization programs if history of vaccination is unclear; boosters should be given at 10-year intervals; earlier for wounds. For the elderly who cannot document a primary immunization series or at risk due to contact or travel, administer the initial series. Boosters may be necessary for travel since antibody titers may diminish with age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted; not indicated for women of childbearing age.

Breast-Feeding ConsiderationsNot indicated for use by patients ≥7 years of age

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Adverse events reported within 4 days of vaccination:

>10%:

Central nervous system: Drowsiness (19%, grade 3: 1%), fever (≥99.5°F: 16%, >100.4: 7%, >104: <1%)

Gastrointestinal: Loss of appetite (16%; grade 3: 1%)

Local: Injection site: Pain (57%; grade 3: 2%), redness (37%; ≥50 mm: 18%, ≥110 mm: 3%), arm circumference increase (36%, >20 mm: 7%, >30 mm: 2%), swelling (26%; ≥50 mm: 10%, ≥110 mm: 1%)

<1%, postmarketing, and/or case reports: Cellulitis, cerebrovascular accident, constipation, dehydration, gastroenteritis, hypernatremia, injection site vesicles, pruritus

Additional postmarketing events associated with Infanrix®: Allergic reactions, anaphylactoid reactions, anaphylaxis, angioedema, apnea, hypotonic-hyporesponsive episode, lymphadenopathy, seizures, thrombocytopenia, urticaria

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringEvaluate patient's prior immunization history, current state of health, and appropriateness for vaccination prior to therapy (deferring treatment should be considered in presence of acute illness or fever). Treatment for anaphylactic reactions should be immediately available during vaccine use. For I.M. use only; see Administration for specifics. All serious adverse reactions must be reported to the U.S. DHHS. Date of administration, name of manufacturer, lot number, and administering person's name, title, and address should be recorded in patient's permanent medical record. Teach patient/caregiver possible side effects/appropriate interventions and adverse symptoms to report.

Patient EducationNotify prescriber immediately of any acute reaction to vaccination (eg, difficulty breathing or swallowing, chest pain or palpitations, acute headache, rash, seizures, high fever). Follow directions for care of injection site; report persistent redness, swelling, or signs of infection at injection site. May cause drowsiness or loss of appetite; if these persist beyond 1-2 days or become severe, consult prescriber.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension [preservative free]:

Kinrix™: Diphtheria toxoid 25 Lf, tetanus toxoid 10 Lf, PT 25 mcg, FHA 25 mcg, pertactin 8 mcg, poliovirus type 1 40 DU, poliovirus type 2 8 DU, and poliovirus type 3 32 DU per 0.5 mL (0.5 mL) [contains aluminum, neomycin sulfate, polymyxin B, polysorbate 80, natural rubber/natural latex in packaging]

Generic AvailableNo

ManufacturerGlaxoSmithKline Biologicals

Mechanism of ActionPromotes active immunity to diphtheria, tetanus, pertussis, and poliovirus (types 1, 2 and 3) by inducing production of specific antibodies and antitoxins.

Pharmacodynamics/KineticsOnset of action: Immune response observed to all components ~1 month following vaccination

Related Information

- Immunization Recommendations

Pharmacotherapy PearlsFederal law requires that the date of administration, name of the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Contains the following three pertussis antigens: Inactivated pertussis toxin (PT), filamentous hemagglutinin (FHA), and pertactin. Contains the same diphtheria, tetanus toxoids, and pertussis antigens found in Infanrix® and Pediarix®. Contains the same poliovirus antigens found in Infanrix®.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDiphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, and Inactivated Poliovirus Vaccine Combined; Diphtheria, Tetanus Toxoids, Acellular Pertussis (DTaP); DTaP-IPV; Poliovirus, inactivated (IPV)

References

Centers for Disease Control, "Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization," *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.[PubMed 17136024]

Centers for Disease Control and Prevention (CDC), "Licensure of a Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine and Guidance for Use as a Booster Dose," *MMWR Morb Mortal Wkly Rep*, 2008, 57(39):1078-9.[PubMed 18830212]

Pronunciation(dif THEER ee a & TET a nus TOKS oyds ay CEL yoo lar per TUS sis POE lee oh VYE rus & hem OF fi lus in floo EN za bee KON joo gate vak SEEN)
U.S. Brand NamesPentacel®
Pharmacologic CategoryVaccine, Inactivated (Bacterial); Vaccine, Inactivated (Viral)
Use: Labeled IndicationsActive immunization against diphtheria, tetanus, pertussis, poliomyelitis, and invasive disease caused by *H. influenzae* type b in children 6 weeks through 4 years of age

Advisory Committee on Immunization Practices (ACIP) recommends that Pentacel® (DTaP-IPV/Hib) may be used to provide the recommended DTaP, IPV, and Hib immunization in children <5 years of age. Whenever feasible, the same manufacturer should be used to provide the pertussis component; however, vaccination should not be deferred if a specific brand is not known or is not available. The Hib component in Pentacel® contains a tetanus toxoid conjugate. A Hib vaccine containing the PRP-OMP conjugate (PedvaxHIB®) may provide a more rapid seroconversion following the first dose and may be preferable to use in certain populations (eg, American Indian or Alaska Native children).

Dosing: PediatricPrimary immunization: Children 6 weeks to ≤4 years: I.M.: 0.5 mL per dose administered at 2, 4, 6 and 15-18 months of age (total of 4 doses). The first dose may be administered as early as 6 weeks of age. Following completion of the 4-dose series, children should receive a dose of DTaP vaccine at 4-6 years of age (Daptacel® recommended due to same pertussis antigen used in both products).

Children previously vaccinated with ≥1 dose of Daptacel® or IPV vaccines: Pentacel® may be used to complete the first 4 doses of the DTaP or IPV series in children scheduled to receive the other components in the vaccine.

Children previously vaccinated with ≥1 dose of *Haemophilus* b Conjugate vaccine: Pentacel® may be used to complete the series in children scheduled to receive the other components in the vaccine; however, if different brands of *Haemophilus* b Conjugate vaccine are administered to complete the series, 3 primary immunizing doses are needed, followed by a booster dose.

Note: Completion of 3 doses of Pentacel® provides primary immunization against diphtheria, tetanus, *H. influenzae* type B, and poliomyelitis. Completion of the 4-dose series with Pentacel® provides primary immunization against pertussis. It also provides a booster vaccination against diphtheria, tetanus, *H. influenzae* type B, and poliomyelitis.

Administration: I.M.For I.M. administration only. Do not administer I.V. or SubQ. Administer in the anterolateral aspect of thigh in children <1 year of age or deltoid muscle of upper arm in older children. Do not administer to gluteal area or areas near a major nerve trunk. Do not administer additional vaccines or immunoglobulins at the same site or using the same syringe.

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends: "It should be administered intramuscularly if, in the opinion of the physician familiar with the patient's bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23-gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection."

Acetaminophen or other appropriate antipyretic should be administered every 4 hours for 24 hours following vaccination to children with history of seizure with DTaP vaccination to decrease the possibility of postvaccination fever.

Administration with other vaccines:

DTaP-IPV/Hib with live vaccines: May be given simultaneously or at any interval between doses.

DTaP-IPV/Hib with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Vaccine administration with antibody-containing products: DTaP-IPV/Hib may be given simultaneously at different sites or at any interval between doses. Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StorageStore at 2°C to 8°C (35°F to 46°F). Do not freeze; discard if product has been frozen. Use immediately after reconstitution.
ReconstitutionGently shake vial containing DTaP-IPV component. Withdraw liquid contents and inject into vial containing Hib powder; shake until uniform suspension results.
ContraindicationsSevere allergic reaction to any vaccine containing diphtheria toxoid, tetanus toxoid, pertussis, poliovirus, or *Haemophilus* b, or any component of this vaccine; encephalopathy occurring within 7 days of a previous pertussis vaccine not (not attributable to another identifiable cause); progressive neurologic disorders (including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy)
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

- Reactions from previous pertussis vaccine: Carefully consider use in patients with history of any of the following effects from previous administration of a pertussis-containing vaccine: Fever ≥105°F (40.5°C) within 48 hours of unknown cause; seizures with or without fever occurring within 3 days; persistent, inconsolable crying episodes lasting ≥3 hours and occurring within 48 hours; shock or collapse (hypotonic-hyporesponsive episode [HHE]) occurring within 48 hours.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).

- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.

- Guillain-Barré syndrome: Use with caution if Guillain-Barré syndrome occurred within 6 weeks of prior tetanus toxoid.

- Neurologic disorders: Use with caution in patients with history of seizure disorder, progressive neurologic disease, or conditions predisposing to seizures; ACIP and AAP guidelines recommend deferring immunization until health status can be assessed and condition stabilized. Antipyretics should be administered at the time of and for 24 hours following vaccination to patients at high risk for seizures.

Special populations:

- Adults: Safety and efficacy have not been established in adults.

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high-dose corticosteroids); may have a reduced response to vaccination.

- Pediatrics: Safety and efficacy have not been established in children <6 weeks or ≥5 years of age. If inadvertently administered to children ≥5 years as a booster dose, it may be counted as a valid dose.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted for this combination product. This product is not indicated for use in women of childbearing age.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

>10%:

Central nervous system: Fussiness/irritability (54% to 77%; >3 hours 4% to 5%), crying inconsolable crying (36% to 60%; >3 hours ≤2%), lethargy/decreased activity (24% to 46%; severe ≤3%), fever ≥38°C (6% to 16%)

Local: Injection site reactions: Tenderness (39% to 56%; severe 1% to 5%), arm circumference increase >5 mm (34%; >40 mm <1%), redness >5 mm (7% to 17%)

1% to 10%: Local: Injection site reaction: Swelling >5 mm (5% to 10%)

<1%, postmarketing, and/or case reports: Apnea, appetite decreased, asthma, bronchiolitis, consciousness decreased, cough, cyanosis, dehydration, diarrhea, encephalopathy, erythema, gastroenteritis, hypersensitivity reactions, hypotonia, hypotonic-hyporesponsive episodes, injection site reactions (abscess, extensive swelling of injected limb, inflammation, mass), pallor, pneumonia, screaming, seizure, skin discoloration, somnolence, vomiting

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension:

Pentacel®: Diphtheria toxoid 15 Lf, tetanus toxoid 5 Lf, acellular pertussis antigens (pertussis toxin detoxified 20 mcg, filamentous hemagglutinin 20 mcg, pertactin 3 mcg, fimbriae [types 2 and 3] 5 mcg), poliovirus (type 1: 40 D-antigen units; type 2: 8 D antigen units; type 3: 32 D antigen units), and *Haemophilus* b capsular polysaccharide 10 mcg (bound to tetanus toxoid 24 mcg) per 0.5 mL (0.5 mL) [contains albumin, aluminum, neomycin, polymyxin B sulfate, and polysorbate 80; supplied in two vials, one containing DTaP-IPV liquid and one containing Hib powder]

Generic AvailableNo

ManufacturerSanofi Pasteur Limited

Related Information

- Immunization Recommendations

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record. Lot numbers are different for each component of the DTaP-IPV/Hib vaccine; numbers should be recorded separately for the DTaP-IPV and Hib components. The vaccine components should not be administered separately.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Drowsiness is common

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms *Haemophilus* B Conjugate (Hib); *Haemophilus* B Polysaccharide ; Diphtheria Toxoid; Diphtheria, Tetanus Toxoids, Acellular Pertussis (DTaP); DTaP-IPV/Hib; Pertussis, Acellular (Adsorbed); Poliovirus, Inactivated (IPV); Tetanus Toxoid

References

Centers for Disease Control and Prevention (CDC), "Licensure of a Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus, and *Haemophilus* B Conjugate Vaccine and Guidance for Use in Infants and Children," *MMWR Morb Mortal Wkly Rep*, 2008, 57(39):1079-80.[PubMed 18830213]

Kroger AT, Atkinson WL, Marcuse EK, et al, "General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP)," *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.[PubMed 17136024]

Diphtheria and Tetanus Toxoids

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(dif THEER ee a & TET a nus TOKS oyds)

U.S. Brand NamesDecavac®

Canadian Brand NamesTd Adsorbed

Pharmacologic CategoryVaccine, Inactivated (Bacterial)

Use: Labeled Indications

Diphtheria and tetanus toxoids adsorbed for pediatric use (DT): Infants and children through 6 years of age: Active immunization against diphtheria and tetanus when pertussis vaccine is contraindicated

Tetanus and diphtheria toxoids adsorbed for adult use (Td) (Decavac™): Children ≥7 years of age and Adults: Active immunization against diphtheria and tetanus; tetanus prophylaxis in wound management

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for the following:

- Adults and children ≥7 years should receive a booster dose of Td every 10 years; persons <65 years of age may substitute a single Td booster dose with Tdap
- Children 7-10 years, adults, and the elderly (≥65 years) who are wounded in bombings or similar mass casualty events who have penetrating injuries or nonintact skin exposure and who cannot confirm receipt of a tetanus booster within the previous 5 years, may also receive a single dose of Td; children ≥11 years may also received Td if Tdap is unavailable

Dosing: Adults

Primary immunization: I.M.: Patients previously not immunized should receive 2 primary doses of 0.5 mL each, given at an interval of 4-6 weeks; third (reinforcing) dose of 0.5 mL 6-12 months later

Booster immunization: I.M.: 0.5 mL every 10 years; to be given to children 11-12 years of age if at least 5 years have elapsed since last dose of toxoid containing vaccine. Subsequent routine doses are not recommended more often than every 10 years.

Tetanus prophylaxis in wound management; use of tetanus toxoid (Td) and/or tetanus immune globulin (TIG) depends upon the number of prior tetanus toxoid doses and type of wound: I.M.: See table.

Tetanus Prophylaxis in Wound Management

Number of Prior Tetanus Toxoid Doses	**Clean, Minor Wounds**		**All Other Wounds**	
	Td[1]	**TIG**[2]	**Td**[1]	**TIG**[2]
Unknown or <3	Yes	No	Yes	Yes
≥3[3]	No[4]	No	No[5]	No
[1]Adult tetanus and diphtheria toxoids; use pediatric preparations (DT or DTP) if the patient is <7 years old.				
[2]Tetanus immune globulin.				
[3]If only three doses of fluid tetanus toxoid have been received, a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.				
[4]Yes, if >10 years since last dose.				
[5]Yes, if >5 years since last dose.				
Adapted from Centers for Disease Control, “Diphtheria, Tetanus, and Pertussis: Recommendations for Vaccine Use and Other Preventive Measures: Recommendations				

of the Immunization Practices Advisory Committee (ACIP)," *MMWR* 1991:40(RR-10).

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Primary immunization: I.M.:

Infants and Children ≤6 years (DT):

6 weeks to 1 year: Three 0.5 mL doses at least 4 weeks apart; administer a reinforcing dose 6-12 months after the third injection

1-6 years: Two 0.5 mL doses at least 4-8 weeks apart; reinforcing dose 6-12 months after second injection; if final dose is given after seventh birthday, use adult preparation

4-6 years (booster immunization): 0.5 mL; not necessary if the fourth dose was given after fourth birthday; routinely administer booster doses at 10-year intervals with the adult preparation

Children ≥7 years: Refer to adult dosing. The ACIP prefers Tdap for use in adolescents 11-18 years; refer to Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine monograph for additional information.

Tetanus prophylaxis in wound management: Children ≥7 years: Use of tetanus toxoid (Td) and/or tetanus immune globulin (TIG) depends upon the number of prior tetanus toxoid doses and type of wound: See table.

Administration: I.M.Prior to use, shake suspension well

Td: Administer in the deltoid muscle; do not inject in the gluteal area

DT: Administer in the anterolateral aspect of the thigh or the deltoid muscle; do not inject in the gluteal area

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends "it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection."

Administration with other vaccines:

Diphtheria and Tetanus Toxoids vaccine with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Diphtheria and Tetanus Toxoids vaccine with live vaccines: May be given simultaneously or at any interval between doses.

Vaccine administration with antibody-containing products: Diphtheria and tetanus toxoids vaccine may be given simultaneously at different sites or at any interval between doses. Examples of antibody containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StorageStore at 2°C to 8°C (35°F to 46°F). Do not freeze. Discard if product has been frozen.

ContraindicationsHypersensitivity to diphtheria, tetanus toxoid, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.
- Arthus-type hypersensitivity: Td or Tdap vaccines and emergency doses of Td vaccine should not be given more frequently than every 10 years in patients who have experienced a serious Arthus-type hypersensitivity reaction following a prior use of tetanus toxoid.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).
- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.
- Guillain-Barré syndrome: Continue use with caution if Guillain-Barré syndrome occurs within 6 weeks of prior tetanus toxoid.
- Poliomyelitis: Defer administration during outbreaks of poliomyelitis.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Adults: Td should be administered adults.
- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination.

- Pediatrics: Safety and efficacy of DT have not been established in children <6 weeks of age; Td should be administered to children ≥7 years of age.

Dosage form specific issues:

- DT confused with Td: Do not confuse pediatric diphtheria and tetanus (DT) with adult tetanus and diphtheria (Td).
- Latex: Some products may contain natural latex/natural rubber.
- Thimerosal: Some products may contain thimerosal.

Geriatric ConsiderationsSince protective tetanus and diphtheria antibodies decline with age, only 28% of persons >70 years of age in the U.S. are believed to be immune to tetanus, and most of the tetanus-induced deaths occur in people >60 years of age, it is advisable to offer Td, especially to elderly, concurrent with their influenza and other immunization programs if history of vaccination is unclear; boosters should be given at 10-year intervals; earlier for wounds.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. DT is not recommended for use in persons ≥7 years of age. The Advisory Committee on Immunization Practices (ACIP) recommends booster injections for previously vaccinated pregnant women who have not had Td vaccination within the past 10 years. Pregnant women who are not immunized or are only partially immunized should complete the primary series. Vaccination may be deferred until the postpartum period in women who are likely to have sufficient diphtheria and tetanus protection until delivery; Tdap may be substituted for Td after delivery to add extra protection against pertussis. Td should be administered during pregnancy to women who do not have sufficient tetanus immunity to protect against maternal and neonatal tetanus, and if booster protection for diphtheria is required (eg, travel to where diphtheria is endemic). Tetanus immune globulin and a tetanus toxoid containing vaccine are recommended by the ACIP as part of the standard wound management to prevent tetanus in pregnant women; the use of Td during pregnancy is recommended for wound management if ≥5 years have passed since the last Td vaccination.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

>10%: Local: Injection site (adolescents and adults): Pain (81% to 85%), redness (5% to 21%), swelling (10% to 16%)

Frequency not defined; reactions reported with adult and pediatric preparations

Cardiovascular: EEG disturbances

Central nervous system: Brachial neuritis, dizziness, Guillain-Barré syndrome, paresthesia, seizure

Dermatologic: Rash

Gastrointestinal: Nausea, vomiting

Local: Injection site: Persistent nodules; local reactions (erythema, cellulitis, swelling)

Neuromuscular & skeletal: Arthralgia, myalgia

Miscellaneous: Allergic/anaphylactic reactions, Arthus-type hypersensitivity reaction (severe local reaction starting 2-8 hours after injection)

Note: Other neurological conditions reported in temporal association with vaccine administration have not been demonstrated to be causally related to the vaccine. These have included demyelinating CNS diseases, mononeuropathies, and encephalopathy.

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension [Td, adult]: Diphtheria 2 Lf units and tetanus 2 Lf units per 0.5 mL (5 mL, 7.5 mL); Diphtheria 2 Lf units and tetanus 5 Lf units per 0.5 mL (5 mL, 7.5 mL)

Injection, suspension [Td, adult; preservative free]: Diphtheria 2 Lf units and tetanus 2 Lf units per 0.5 mL (0.5 mL); diphtheria 2 Lf units and tetanus 5 Lf units per 0.5 mL (0.5 mL)

Decavac®: Diphtheria 2 Lf units and tetanus 5 Lf units per 0.5 mL (0.5 mL) [contains aluminum, thimerosal (may have trace amounts)]

Injection, suspension [Dt, pediatric; preservative free]: Diphtheria 6.7 Lf units and tetanus 5 Lf units per 0.5 mL (0.5 mL)

Generic AvailableYes

Related Information

- Immunization Recommendations
- Skin Tests

Pharmacotherapy PearlsPediatric dosage form should only be used in patients ≤6 years of age. Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Since protective tetanus and diphtheria antibodies decline with age, only 28% of persons >70 years of age in the U.S. are believed to be immune to tetanus, and most of the tetanus-induced deaths occur in people >60 years of age, it is advisable to offer Td especially to the elderly concurrent with their influenza and other immunization programs if history of vaccination is unclear; boosters should be given at 10-year intervals; earlier for wounds

DT contains higher proportions of diphtheria toxoid than Td.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsDT; Td; Tetanus and Diphtheria Toxoid
References

Bentley DW, “Vaccinations,” *Clin Geriatr Med*, 1992, 8(4):745-60. [PubMed 1423132]

Centers for Disease Control, “Preventing Tetanus, Diphtheria, and Pertussis Among Adolescents: Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP),” *MMWR*, 2006, 55(early release);1-34.

Centers for Disease Control, “Prevention of Pertussis, Tetanus, and Diphtheria Among Pregnant and Postpartum Women and Their Infants, Recommendations of the Advisory Committee on Immunization Practices (ACIP),” *MMWR Recomm Rep*, 2008, 57(early release):1-47. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e0514a1.htm?s_cid=rr57e0514a1_e

Centers for Disease Control, “Recommendations for Postexposure Interventions to Prevent Infection With Hepatitis B Virus, Hepatitis C Virus, or Human Immunodeficiency Virus, and Tetanus in Persons Wounded During Bombings and Other Mass-Casualty Events -- United States, 2008: Recommendations of the Centers For Disease Control And Prevention (CDC),” *MMWR Recomm Rep*, 2008, 57(RR-6):1-21.[PubMed 18668022]

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.[PubMed 17136024]

Gardner P and Schaffner W, “Immunization of Adults,” *N Engl J Med*, 1993, 328(17):1242-8.

International Brand NamesAcelluvax DTP (PH); Adsorbed DT VAX (HK); CDT Vaccine (AU, NZ); D.T. Vax (FR, MY); Dif tet all (IT, MY, PH); Diftavax (FR); DITE Anatoxal Berna (HK, MY, PH, TH); DiTe Anatoxal Berna Adults (NZ); DiTe Anatoxal Berna Children (NZ); diTe Booster (DK); Dual Antigen (IN); Imovax d.T. Adult (EE)

Diphtheria Antitoxin

Lexi-Drugs Online

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Pronunciation(dif THEER ee a an tee TOKS in)
Pharmacologic CategoryAntitoxin
Use: Labeled IndicationsTreatment of diphtheria (neutralizes unbound toxin, available from CDC)
Dosing: AdultsDiphtheria treatment: I.M. or slow I.V. infusion: Dosage varies; range: 20,000-120,000 units
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Restrictions

Diphtheria antitoxin is not currently licensed by the Food and Drug Administration (FDA) and is only available in the U.S. under an investigational new drug (IND) protocol through the Centers for Disease Control and Prevention (CDC). Physicians may contact the CDC Drug Service at 404-639-3670 (Monday-Friday 8:00 a.m. to 4:30 p.m. eastern/standard time) or by contacting the CDC Emergency Operations Center at 770-488-7100. Additional information may be found at http://www.cdc.gov/vaccines/vpd-vac/diphtheria/dat/dat-main.htm

Pregnancy Risk FactorD
Drug InteractionsThere are no known significant interactions.
Generic AvailableNo
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported

Diphtheria, Tetanus Toxoids, Acellular Pertussis, Hepatitis B (Recombinant), and Poliovirus Vaccine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(dif THEER ee a, TET a nus TOKS oyds, ay CEL yoo lar per TUS sis, hep a TYE tis bee, & POE lee oh VYE rus, in ak ti VAY ted vak SEEN)
U.S. Brand NamesPediarix®
Canadian Brand NamesPediarix®
Pharmacologic CategoryVaccine, Inactivated (Bacterial); Vaccine, Inactivated (Viral)
Use: Labeled IndicationsCombination vaccine for the active immunization against diphtheria, tetanus, pertussis, hepatitis B virus (all known subtypes), and poliomyelitis (caused by poliovirus types 1, 2, and 3)

The Advisory Committee on Immunization Practices (ACIP) recommends Pediarix® for the following:

- Primary vaccination for DTaP, Hep B, and IPV in children at 2-, 4-, and 6 months of age.

- To complete the primary vaccination series in children who have received DTaP (Infanrix®) and who are scheduled to received the other components of the vaccine. Whenever feasible, the same manufacturer should be used to provide the pertussis component; however, vaccination should not be deferred if a specific brand is not known or is not available. HepB and IPV from different manufacturers are interchangeable.

Dosing: Pediatric

Primary immunization: Children 6 weeks to <7 years: I.M.: 0.5 mL; repeat in 6-8 week intervals (preferably 8-week intervals) for a total of 3 doses. Vaccination usually begins at 2 months, but may be started as early as 6 weeks of age.

Use in children previously vaccinated with one or more component, and who are also scheduled to receive all vaccine components:

Hepatitis B vaccine: Infants born of HBsAg-negative mothers who received 1 dose of hepatitis B vaccine at birth may be given Pediarix® (safety data limited); use in infants who received more than 1 dose of hepatitis B vaccine has not been studied. Infants who received 1 or more doses of hepatitis B vaccine (recombinant) may be given Pediarix® to complete the hepatitis B series (safety and efficacy not established).

Diphtheria and tetanus toxoids, and acellular pertussis vaccine (DTaP): Infants previously vaccinated with 1 or 2 doses of Infanrix® may use Pediarix® to complete the first 3 doses of the series (safety and efficacy not established); use of Pediarix® to complete DTaP vaccination started with products other than Infanrix® is not recommended.

Inactivated polio vaccine (IPV): Infants previously vaccinated with 1 or 2 doses of IPV may use Pediarix® to complete the first 3 doses of the series (safety and efficacy not established).

Administration: I.M.For I.M. use only; do not administer I.V. or SubQ. Shake well prior to use; do not use unless a homogeneous, turbid, white suspension forms. Administer in the anterolateral aspects of the thigh or the deltoid muscle of the upper arm. Do not inject in the gluteal area (suboptimal hepatitis B immune response) or where there may be a major nerve trunk. Do not administer additional vaccines or immunoglobulins at the same site, or using the same syringe.

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

Administration with other vaccines:

DTaP/IPV/HepB with live vaccines: May be given simultaneously or at any interval between doses.

DTaP/IPV/HepB with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Vaccine administration with antibody-containing products: DTaP/IPV/HepB may be given simultaneously at different sites or at any interval between doses. Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StorageStore under refrigeration of 2°C to 8°C (36°F to 46°F); do not freeze. Discard if frozen.
CompatibilityDo not mix with other vaccines or injections.
ContraindicationsHypersensitivity to diphtheria and tetanus toxoids, pertussis, hepatitis B, poliovirus vaccine, or any component of the vaccine; encephalopathy occurring within 7 days of a previous pertussis vaccine not (not attributable to another identifiable cause); progressive neurologic disorders (including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy)
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

- Reactions from previous pertussis vaccine: Carefully consider use in patients with history of any of the following effects from previous administration of whole-cell DTP or acellular pertussis vaccine: Fever ≥105°F (40.5°C) within 48 hours of unknown cause; seizures with or without fever occurring within 3 days; persistent, inconsolable crying episodes lasting ≥3 hours and occurring within 48 hours; shock or collapse (hypotonic-hyporesponsive episode [HHE]) occurring within 48 hours.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).

- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.

- Guillain-Barré syndrome: Use with caution if Guillain-Barré syndrome occurred within 6 weeks of prior tetanus toxoid.

- Neurologic disorders: Use with caution in patients with history of seizure disorder, progressive neurologic disease, or conditions predisposing to seizures; ACIP and AAP guidelines recommend deferring immunization until health status can be assessed and condition stabilized. Antipyretics should be administered at the time of and for 24 hours following vaccination to patients at high risk for seizures.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Adults: Safety and efficacy have not been established for use in adults.

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy [including high-dose corticosteroids]); may have a reduced response to vaccination.

- Pediatrics: Safety and efficacy have not been established for use in children <6 weeks and children ≥7 years of age. Infants born of HBsAg-positive mothers should receive monovalent hepatitis B vaccine and hepatitis B immune globulin; infants born of HBsAg-unknown mothers should receive monovalent hepatitis B vaccine; use of combination product in these patients to complete the hepatitis B vaccination series has not been studied but is considered acceptable by the ACIP.

Dosage form specific issues:

- Aluminum: Product may contain aluminum.

- Latex: Packaging may contain natural latex rubber.

- Neomycin: Product may contain neomycin.

- Polymyxin B: Product may contain polymyxin B.

- Polysorbate 80: Product may contain polysorbate 80.

- Yeast protein: Product may contain yeast protein.

Other warnings/precautions:

- Booster dose: Not for use as a booster dose following the 3-dose primary series.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted; not indicated for women of childbearing age.
Breast-Feeding ConsiderationsNot indicated for women of childbearing age.
Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Adverse events reported within 4 days of vaccination at 2-, 4-, and 6 months of age in patients given Pediarix® concomitantly with Hib conjugate vaccine and PCV7 vaccine.

>10%:

Central nervous system: Central nervous system: Irritability/fussiness (61% to 65%; grade 3: 3% to 4%), drowsiness (41% to 57%), fever ≥100.4°F (28% to 39%)

Gastrointestinal: Loss of appetite (26% to 31%; grade 3: <1%)

Local: Injection site: Redness (25% to 40%; >20 mm: 2% to 3%), pain (31% to 36%; grade 3: 2% to 3%), swelling (17% to 29%; >20 mm: 2% to 3%)

1% to 10%: Central nervous system: Fever >103.1°F (<1%)

Additional and postmarketing events: Anaphylactic/anaphylactoid reaction, angioedema, anorexia, apnea, arthus-type hypersensitivity reactions, brachial neuritis, bronchitis, bulging fontanelle, consciousness depressed, cranial mononeuropathy, crying, cyanosis, demyelinating disease, dermatitis, diarrhea, dyspnea, erythema, fatigue, febrile convulsion, Guillain-Barré syndrome, hypersensitivity reaction, hypotonia, hypotonic-hyporesposnive episode, injection site reactions (cellulitis, induration, itching, nodule, warmth), insomnia, lethargy, limb pain, limb swelling, liver function test abnormalities, nervousness, pallor, peripheral mononeuropathy, petechiae, rash, restlessness, screaming, seizure, SIDS, somnolence, upper respiratory tract infection, urticaria, vomiting

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringChildren who are moderately to severely ill (with or without fever) should not get this vaccination until they have recovered. Assess any hypersensitivity history prior to administering. Treatment for anaphylactic/anaphylactoid reaction should be available during vaccine use. See Contraindications, Warnings/Precautions, Dosing, and Administration for specific use cautions. Before administering, see Drug Interactions. Antipyretics should be administered at time of and for 24 hours following vaccination to patients at high-risk for seizures. **Note:** All serious adverse reactions must be reported the the US DHHS (see Adverse Reactions). Record date of administration, name of manufacturer, lot number, and administering person's name, title, and address into patient's permanent medical record. Teach caregiver possible side effects/appropriate interventions, and adverse symptoms to report (see Patient Education). **Pregnancy risk factor C** - not for women of childbearing age.

Patient EducationChildren who are moderately to severely ill (with or without fever) should not get this vaccination until they have recovered. Inform prescriber of all previous allergic reactions and any other medications being used. Three doses will be required for effective immunity; consult prescriber for appropriate schedule of vaccinations. May cause increased sleeping, restlessness, fussiness, decreased appetite, or fever (use antipyretic if directed by prescriber, or consult prescriber for appropriate antipyretic). May cause some redness, pain, or swelling at injection site; consult prescriber if excessive or persistent. Notify prescriber immediately of any excessive or persistent reactions (eg, fever >105°F within 48 hours, inconsolable crying that occurs within 48 hours and lasts 3 hours, seizures that occur within 3 days).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension [preservative free]:

Pediarix®: Diphtheria toxoid 25 Lf, tetanus toxoid 10 Lf, acellular pertussis antigens [inactivated pertussis toxin 25 mcg, filamentous hemagglutin 25 mcg, pertactin 8 mcg, HBsAg 10 mcg, type 1 poliovirus 40 D antigen units, type 2 poliovirus 8 D antigen units and type 3 poliovirus 32 D antigen units] per 0.5 mL (0.5 mL) [contains aluminum, neomycin sulfate (trace amounts), polymyxin B (trace amounts), polysorbate 80, and yeast protein ≤5%; prefilled syringes contain natural rubber/natural latex]

Generic AvailableNo

ManufacturerGlaxoSmithKline Biologicals

Mechanism of ActionPromotes active immunity to diphtheria, tetanus, pertussis, hepatitis B and poliovirus (types 1, 2 and 3) by inducing production of specific antibodies and antitoxins.

Pharmacodynamics/KineticsOnset of action: Immune response observed to all components 1 month following the 3-dose series

Related Information

- Immunization Recommendations

Pharmacotherapy PearlsFederal law requires that the date of administration, name of the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Contains the following three pertussis antigens: Inactivated pertussis toxin (PT), filamentous hemagglutinin (FHA) and pertactin. Contains the same diphtheria and tetanus toxoids and pertussis antigens found in Infanrix®. Contains the same hepatitis B surface antigen (HBsAg) found in Engerix-B® (recombinant vaccine).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation and restlessness are common

Mental Health: Effects on Psychiatric TreatmentContraindicated in patients with progressive neurologic disorders

Index TermsDiphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined; DTaP/IPV/HepB

References

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.[PubMed 17136024]

Centers for Disease Control and Prevention (CDC), “FDA Licensure of Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant), and Poliovirus Vaccine Combined, (PEDIARIX) for Use in Infants,” *MMWR Morb Mortal Wkly Rep*, 2003, 52(10):203-4.

Dipivefrin

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English

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Pronunciation(dye PI ve frin)

U.S. Brand NamesPropine®

Canadian Brand NamesOphtho-Dipivefrin™; PMS-Dipivefrin; Propine®

Pharmacologic CategoryAlpha/Beta Agonist; Ophthalmic Agent, Antiglaucoma; Ophthalmic Agent, Vasoconstrictor

Use: Labeled IndicationsReduces elevated intraocular pressure in chronic open-angle glaucoma; also used to treat ocular hypertension, low tension, and secondary glaucomas

Dosing: AdultsGlaucoma: Ophthalmic: Instill 1 drop every 12 hours into the eyes

Dosing: ElderlyRefer to adult dosing.

StorageAvoid exposure to light and air. Discolored or darkened solutions indicate loss of potency.

ContraindicationsHypersensitivity to dipivefrin, any component of the formulation, or epinephrine; angle-closure glaucoma

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Hypertension: Use with caution in patients with hypertension.

Special populations:

- Aphakic patients: Use with caution in aphakic patients.

Dosage form specific issues:

- Sodium metabisulfite: Product may contain sodium metabisulfite.

Geriatric ConsiderationsUse with caution in patients with heart disease. Assess patient's ability to self-administer drops.

Pregnancy Risk FactorB

Adverse Reactions

1% to 10%:

Central nervous system: Headache

Local: Burning, stinging

Ocular: Ocular congestion, photophobia, mydriasis, blurred vision, ocular pain, bulbar conjunctival follicles, blepharoconjunctivitis, cystoid macular edema

<1%: Arrhythmias, hypertension

Drug Interactions

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Patient EducationDiscolored solutions should be discarded. May cause transient burning or stinging

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic, as hydrochloride: 0.1% (5 mL, 10 mL, 15 mL) [contains benzalkonium chloride]

Propine®: 0.1% (5 mL [DSC], 10 mL, 15 mL) [contains benzalkonium chloride]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Dipivefrin HCl)

0.1% (5): $13.99

0.1% (10): $15.99

0.1% (15): $19.99

Mechanism of Action Dipivefrin is a prodrug of epinephrine which is the active agent that stimulates alpha- and/or beta-adrenergic receptors increasing aqueous humor outflow

Pharmacodynamics/Kinetics

Ocular pressure effect:

Onset of action: ~30 minutes

Duration: ≥12 hours

Mydriasis:

Onset of action: ~30 minutes

Duration: Several hours

Absorption: Rapid into aqueous humor

Metabolism: Converted to epinephrine

Related Information

- Glaucoma Drug Therapy

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Anesthesia and Critical Care Concerns/Other Considerations Systemic absorption can occur, although minimal.

Index Terms Dipivalyl Epinephrine; Dipivefrin Hydrochloride; DPE

International Brand NamesD Epifrin (DE); D'epifrin (PL); Difrin (IL); Diopine (ES, GR, NL); Diopine-C (MX); Dipoquin (NZ); Glaucothil (AT, DE); Glaudrops (ES); Oftanex (PL); Pivepol (PL); Propine (AE, AU, BE, BH, BR, CY, EG, FI, FR, GB, IE, IL, IN, IQ, IR, IT, JO, KW, LB, LY, NO, OM, PT, QA, SA, SY, TH, TR, TW, YE)

Dipyridamole

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English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Dipyridamole may be confused with disopyramide

Persantine® may be confused with Periactin®, Permitil®

Pronunciation(dye peer ID a mole)
U.S. Brand NamesPersantine®
Canadian Brand NamesApo-Dipyridamole FC®; Dipyridamole For Injection; Persantine®
Pharmacologic CategoryAntiplatelet Agent; Vasodilator
Use: Labeled Indications

Oral: Used with warfarin to decrease thrombosis in patients after artificial heart valve replacement

I.V.: Diagnostic agent in CAD

Dosing: Adults

Adjunctive therapy for prophylaxis of thromboembolism with cardiac valve replacement: Oral: 75-100 mg 4 times/day

Evaluation of coronary artery disease: I.V.: 0.14 mg/kg/minute for 4 minutes; maximum dose: 60 mg

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Adjunctive therapy for prophylaxis of thromboembolism with cardiac valve replacement: Oral: Children ≥12 years: Refer to adult dosing.

Administration: I.V.I.V.: Infuse diluted solution over 4 minutes; following dipyridamole infusion, inject thallium-201 within 5 minutes. **Note:** Aminophylline should be available for urgent/emergent use; dosing of 50-100 mg (range: 50-250 mg) IVP over 30-60 seconds.
Administration: OralAdminister with water 1 hour before meals.
Dietary ConsiderationsShould be taken with water 1 hour before meals.
StorageI.V.: Store between 15°C to 25°C (59°F to 77°F). Do not freeze, protect from light.
ReconstitutionPrior to administration, dilute solution for injection to a ≥1:2 ratio in NS, $^1/_2$NS, or D$_5$W. Total volume should be ~20-50 mL.
CompatibilityStable in $^1/_2$NS, D$_5$W, NS. Do not mix with other drugs in syringe or infusion container.
Extemporaneously PreparedA 10 mg/mL oral suspension has been made using four 25 mg tablets and purified water USP qs ad to 10 mL; expected stability is 3 days. Dipyridamole 10 mg/mL was stable for up to 60 days at 5°C and 25°C in 1:1 mixtures of Ora-Sweet® and Ora-Plus®, Ora-Sweet® SF and Ora-Plus® and in cherry syrup

Allen LV and Erickson III MA, “Stability of Baclofen, Captopril, Diltiazem, Hydrochloride, Dipyridamole, and Flecainide Acetate in Extemporaneously Compounded Oral Liquids,” *Am J Health Syst Pharm*, 1996, 53:2179-84.

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, 2nd ed, Cincinnati, OH: Harvey Whitney Books Co, 1992.

ContraindicationsHypersensitivity to dipyridamole or any component of the formulation
Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with in patients with hypotension, unstable angina, and/or recent MI.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

Concurrent drug therapy issues:

- Antiplatelet agents/anticoagulants: Use with caution in patients on other antiplatelet agents or anticoagulation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Dosage form specific issues:

- Injection: Severe adverse reactions have occurred rarely with I.V. administration. Use the I.V. form with caution in patients with bronchospastic disease or unstable angina. Have aminophylline ready in case of urgency or emergency with I.V. use.

Geriatric ConsiderationsSince evidence suggests that clinically used doses are ineffective for prevention of platelet aggregation, consideration for low-dose aspirin (81-325 mg/day) alone may be necessary. This will decrease cost as well as inconvenience.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsExcretion in breast milk is reported to be minimal.

Adverse Reactions

Oral:

>10%: Dizziness (14%)

1% to 10%:

Central nervous system: Headache (2%)

Dermatologic: Rash (2%)

Gastrointestinal: Abdominal distress (6%)

Frequency not defined: Diarrhea, vomiting, flushing, pruritus, angina pectoris, liver dysfunction

Postmarketing and/or case reports: Alopecia, arthritis, cholelithiasis, dyspepsia, fatigue, hepatitis, hypersensitivity reaction, hypotension, larynx edema, malaise, myalgia, nausea, palpitation, paresthesia, tachycardia, thrombocytopenia

I.V.:

>10%:

Cardiovascular: Exacerbation of angina pectoris (20%)

Central nervous system: Dizziness (12%), headache (12%)

1% to 10%:

Cardiovascular: Hypotension (5%), hypertension (2%), blood pressure lability (2%), ECG abnormalities (ST-T changes, extrasystoles; 5% to 8%), pain (3%), tachycardia (3%)

Central nervous system: Flushing (3%), fatigue (1%)

Gastrointestinal: Nausea (5%)

Neuromuscular & skeletal: Paresthesia (1%)

Respiratory: Dyspnea (3%)

<1% (Limited to important or life-threatening): Abdominal pain, abnormal coordination, appetite increased; arrhythmia (ventricular tachycardia, bradycardia, AV block, SVT, atrial fibrillation, asystole); arthralgia, asthenia, back pain, breast pain, bronchospasm, cardiomyopathy, cough, depersonalization, diaphoresis, dry mouth, dysgeusia, dyspepsia, dysphagia, earache, ECG abnormalities (unspecified), edema, eructation, flatulence, hypertonia, hyperventilation, injection site reaction, intermittent claudication leg cramping, malaise, MI, myalgia, orthostatic hypotension, palpitation, perineal pain, pharyngitis, pleural pain, renal pain, rhinitis, rigor, syncope, tenesmus, thirst, tinnitus, tremor, vertigo, vision abnormalities, vomiting

Postmarketing and/or case reports: Allergic reaction, pruritus, rash, urticaria

Drug Interactions

Adenosine: Dipyridamole may enhance the therapeutic effect of Adenosine. Dose reduction of adenosine may be needed. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Beta-Blockers: Dipyridamole may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Regadenoson: Dipyridamole may enhance the therapeutic effect of Regadenoson. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Topotecan: BCRP/ABCG2 Inhibitors may increase the serum concentration of Topotecan. *Risk D: Consider therapy modification*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid cat's claw, dong quai, evening primrose, feverfew, garlic, ginger, ginkgo, red clover, horse chestnut, green tea, ginseng (all have additional antiplatelet activity).

Monitoring ParametersBlood pressure, heart rate, ECG (stress test)

Nursing: Physical Assessment/MonitoringMonitor therapeutic effectiveness (dependent on purpose for use) and adverse reactions. Observe bleeding precautions. **Oral:** Monitor blood pressure on a regular basis. **I.V.:** Continuous ECG and blood pressure monitoring during infusion. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake tablet exactly as directed, with water 1 hour before meals. You may experience mild headache, transient diarrhea, or temporary dizziness (sit or lie down when taking medication). You may have a tendency to bleed easily; use caution with sharps, needles, or razors. Report chest pain, redness around mouth, acute abdominal cramping or severe diarrhea, acute and persistent headache or dizziness, rash, respiratory difficulty, or swelling of extremities. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 5 mg/mL (2 mL, 10 mL)

Tablet: 25 mg, 50 mg, 75 mg

Persantine®: 25 mg, 50 mg, 75 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Dipyridamole)

25 mg (100): $28.99

Tablets (Persantine)

25 mg (100): $68.18

50 mg (100): $105.79

75 mg (100): $140.14

Mechanism of ActionInhibits the activity of adenosine deaminase and phosphodiesterase, which causes an accumulation of adenosine, adenine nucleotides, and cyclic AMP; these mediators then inhibit platelet aggregation and may cause vasodilation; may also stimulate release of prostacyclin or PGD_2; causes coronary vasodilation

Pharmacodynamics/Kinetics

Absorption: Readily, but variable

Distribution: Adults: V_d: 2-3 L/kg

Protein binding: 91% to 99%

Metabolism: Hepatic

Half-life elimination: Terminal: 10-12 hours

Time to peak, serum: 2-2.5 hours

Excretion: Feces (as glucuronide conjugates and unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsDipyridamole is frequently used in CV stress testing because it increases endogenous adenosine levels and thereby induces myocardial vasodilation in vessels that do not have fixed stenotic lesions. Thus, areas of ischemia are identified. May enhance exercise induced myocardial ischemia in patients with chronic stable angina.

Anesthesia and Critical Care Concerns/Other ConsiderationsFor patients undergoing CABG, the Seventh American College of Chest Physicians Consensus Conference recommended against the addition of dipyridamole to aspirin therapy.

References

Antman EM, Anbe SC, Alpert JS, et al, “ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction - Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction),” *Circulation*, 2004, 110(5):588-636. Available at: http://www.circulationaha.org/cgi/content/full/110/5/588. Last accessed October 26, 2004. [PubMed 15289388]

Stein PD, Schunemann HJ, Dalen JE, et al, “Antithrombotic Therapy in Patients With Saphenous Vein and Internal Mammary Artery Bypass Grafts: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy,” *Chest*, 2004, 126(3 Suppl):600-08.

International Brand NamesAdezan (GR); Agremol (TH); Anginal (JP); Anti-Plate 75 (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Atrombin (FI); Biocardin (BG); Cardoxin (IL); Cardoxin Forte (IL); Cleridium (PH); Coronair (BE); Cortab (ID); Curantyl (PL); Dipyridamol Forte-Ratiopharm (PL); Dipyrol (ZA); Ethrine (GR); Miosen (ES); Novodil (IT); Parotin (TW); Persantin (AE, AR, AT, AU, BB, BD, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PH, PK, PL, PR, PT, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Persantin 100 (AU); Persantin 75 (CO); Persantin Depot (AT, FI); Persantin Forte (DE); Persantin PL (NZ); Persantin Prolonguets (PT); Persantin Retard (IE, NL); Persantin SR (AU); Persantine (BE, FR); Plato (ZA); Posanin (TH); PosLinlen (TW); Procardin (HK, SG); Pytazen SR (NZ); Sandel (TW); Solantin (TW); Tovincocard (IT); Vasokor (ID)

Disopyramide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Disopyramide may be confused with desipramine, dipyridamole

Norpace® may be confused with Norpramin®

Pronunciation(dye soe PEER a mide)

U.S. Brand NamesNorpace®; Norpace® CR

Canadian Brand NamesNorpace®; Rythmodan®; Rythmodan®-LA

Pharmacologic CategoryAntiarrhythmic Agent, Class Ia

Use: Labeled IndicationsSuppression and prevention of unifocal and multifocal atrial and premature, ventricular premature complexes, coupled ventricular tachycardia; effective in the conversion of atrial fibrillation, atrial flutter, and paroxysmal atrial tachycardia to normal sinus rhythm and prevention of the recurrence of these arrhythmias after conversion by other methods

Use: Unlabeled/InvestigationalHypertrophic obstructive cardiomyopathy (HOCM)

Dosing: Adults

Dysrhythmia: Oral:

<50 kg: 100 mg every 6 hours or 200 mg every 12 hours (controlled release)

>50 kg: 150 mg every 6 hours or 300 mg every 12 hours (controlled release); if no response, may increase to 200 mg every 6 hours; maximum dose required for patients with severe refractory ventricular tachycardia is 400 mg every 6 hours.

Hypertrophic obstructive cardiomyopathy (unlabeled use): Oral: Initial: Controlled release: 200 mg twice daily. If symptoms do not improve, increase by 100 mg/day at 2-week intervals to a maximum daily dose of 600 mg.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAntiarrhythmic: Oral:

<1 year: 10-30 mg/kg/24 hours in 4 divided doses

1-4 years: 10-20 mg/kg/24 hours in 4 divided doses

4-12 years: 10-15 mg/kg/24 hours in 4 divided doses

12-18 years: 6-15 mg/kg/24 hours in 4 divided doses

Dosing: Renal ImpairmentOral: 100 mg (nonsustained release) given at the following intervals, based on creatinine clearance (mL/minute):

Cl_{cr} 30-40 mL/minute: Administer every 8 hours

Cl_{cr} 15-30 mL/minute: Administer every 12 hours

Cl_{cr} <15 mL/minute: Administer every 24 hours

or alter the dose as follows:

Cl_{cr} 30-<40 mL/minute: Reduce dose 50%

Cl_{cr} 15-30 mL/minute: Reduce dose 75%

Not dialyzable (0% to 5%) by hemo- or peritoneal methods; supplemental dose is not necessary.

Dosing: Hepatic ImpairmentAdminister 100 mg every 6 hours or 200 mg every 12 hours (controlled release).

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralDo not break or chew controlled release capsules. Administer around-the-clock to promote less variation in peak and trough serum levels.

Dietary ConsiderationsShould be taken on an empty stomach.

StorageExtemporaneously prepared suspension is stable for 4 weeks refrigerated.

Extemporaneously PreparedExtemporaneous suspensions in cherry syrup (1 mg/mL and 10 mg/mL) are stable for 4 weeks in amber glass bottles stored at 5°C, 30°C, or at room temperature; shake well before use; do not use extended release capsules for this suspension

Mathur LK, Lai PK, and Shively CD, "Stability of Disopyramide Phosphate in Cherry Syrup," *Am J Hosp Pharm*, 1982, 39(2):309-10.

ContraindicationsHypersensitivity to disopyramide or any component of the formulation; cardiogenic shock; pre-existing second- or third-degree heart block (except in patients with a functioning artificial pacemaker); congenital QT syndrome; sick sinus syndrome

Warnings/Precautions

Boxed warnings:

- CAST trial: See "Other warnings/precautions" below.

Concerns related to adverse effects:

- Hypotension: May occur during the initiation of therapy; monitor closely.
- Proarrhythmic effects: Watch for proarrhythmic effects; monitor and adjust dose to prevent QT_c prolongation.

Disease-related concerns:

- Atrial fibrillation/flutter: Appropriate use: In patients with atrial fibrillation or flutter, block the AV node before initiating.
- BPH/urinary retention: Do not use in patients with BPH and/or urinary retention due to significant anticholinergic effects.
- Conduction disturbances: Use with caution in patients with bundle branch block or heart block.
- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.
- Glaucoma: Do not use in patients with glaucoma due to significant anticholinergic effects.
- Heart failure (HF): Use with caution in patients with HF; may precipitate or exacerbate condition.
- Hepatic impairment: Use with caution in patients with hepatic impairment; reduced dosage recommended.
- Myasthenia gravis: Do not use in patients with myasthenia gravis due to significant anticholinergic effects.
- Renal impairment: Use with caution in renal impairment; reduced dosage recommended. The extended release form is not recommended for Cl_{cr} <40 mL/minute.
- Wolff-Parkinson-White syndrome: Use with caution in patients with Wolff-Parkinson-White syndrome.

Concurrent drug therapy issues:

- Drugs with QT prolongation potential: Avoid concurrent use with other drugs known to prolong QT_c interval or decrease myocardial contractibility.

Other warnings/precautions:

- CAST trial: **[U.S. Boxed Warning]: In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, non-life-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide.** An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. Antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Geriatric ConsiderationsDue to changes in total clearance (decreased) in the elderly, monitor closely; the anticholinergic action may be intolerable and require discontinuation; monitor for CNS anticholinergic effects (confusion, agitation, hallucinations, etc). **Note:** Dose needs to be altered with Cl_{cr} <40 mL/minute which may be found frequently in older adults.

Clinical studies of Norpace®/Norpace® CR did not include sufficient numbers of subjects ≥65 years of age to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Because of its anticholinergic activity, disopyramide phosphate should not be used in patients with glaucoma, urinary retention, or benign prostatic hyperplasia (medical conditions commonly associated with the elderly) unless adequate overriding measures are taken. In the event of increased anticholinergic side effects, plasma levels of disopyramide should be monitored and the dose of the drug adjusted accordingly. A reduction of the dose by one third, from the recommended 600 mg/day to 400 mg/day, would be reasonable, without changing the dosing interval. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Pregnancy Risk FactorC

LactationEnters breast milk/compatible

Adverse ReactionsThe most common adverse effects are related to cholinergic blockade. The most serious adverse effects of disopyramide are hypotension and CHF.

>10%:

- Gastrointestinal: Xerostomia (32%), constipation (11%)
- Genitourinary: Urinary hesitancy (14% to 23%)

1% to 10%:

- Cardiovascular: CHF, hypotension, cardiac conduction disturbance, edema, syncope, chest pain
- Central nervous system: Fatigue, headache, malaise, dizziness, nervousness
- Dermatologic: Rash, generalized dermatoses, pruritus
- Endocrine & metabolic: Hypokalemia, elevated cholesterol, elevated triglycerides
- Gastrointestinal: Dry throat, nausea, abdominal distension, flatulence, abdominal bloating, anorexia, diarrhea, vomiting, weight gain
- Genitourinary: Urinary retention, urinary frequency, urinary urgency, impotence (1% to 3%)
- Neuromuscular & skeletal: Muscle weakness, muscular pain
- Ocular: Blurred vision, dry eyes
- Respiratory: Dyspnea

<1% (Limited to important or life-threatening): Agranulocytosis, arrhythmia (new or worsened, proarrhythmic effect); AV block, BUN increased, cholestatic jaundice, creatinine increased, depression, dysuria, fever, gynecomastia, hematocrit decreased, hemoglobin decreased, hepatotoxicity, hypoglycemia, insomnia, numbness, paresthesia, psychotic reaction, respiratory distress, serum creatinine increased, thrombocytopenia, tingling, transaminases increased. Rare cases of lupus have been reported (generally in patients previously receiving procainamide).

Postmarketing and/or case reports: Peripheral neuropathy, psychosis, pupillary dilation, toxic cutaneous blisters

Metabolism/Transport Effects

Substrate of CYP3A4 (major)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amiodarone: Antiarrhythmic Agents (Class Ia) may enhance the QTc-prolonging effect of Amiodarone. Amiodarone may increase the metabolism of Antiarrhythmic Agents (Class Ia). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Beta-Blockers: Disopyramide may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Lidocaine: Disopyramide may enhance the arrhythmogenic effect of Lidocaine. Disopyramide may increase the serum concentration of Lidocaine. Specifically, the unbound/free fraction of lidocaine. *Risk C: Monitor therapy*

Macrolide Antibiotics: May enhance the QTc-prolonging effect of Disopyramide. Macrolide Antibiotics may decrease the metabolism of Disopyramide. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk X: Avoid combination*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Phenytoin: May increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: St John's wort may decrease disopyramide levels. Avoid ephedra (may worsen arrhythmia).

Monitoring ParametersECG, blood pressure, urinary retention, CNS anticholinergic effects (confusion, agitation, hallucinations, etc)

Reference Range

Therapeutic concentration:

Atrial arrhythmias: 2.8-3.2 mcg/mL

Ventricular arrhythmias 3.3-7.5 mcg/mL

Toxic concentration: >7 mcg/mL

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions when beginning therapy, when titrating dosage, and periodically during long-term therapy. **Note:** Disopyramide has a low toxic:therapeutic ratio and overdose may easily produce severe and life threatening reactions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsECG, disopyramide drug level

Patient EducationTake as directed, at regular intervals around-the-clock on an empty stomach. Do not alter dosage or discontinue therapy without consulting prescriber. Do not crush or chew extended release form. Avoid (or limit) alcohol and caffeine. You may experience dizziness or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or dry mouth (frequent mouth care or sucking on lozenges may help). Report any change in urinary pattern or difficulty urinating; chest pain, palpitations, irregular heartbeat; unusual cough, respiratory difficulty, swelling of extremities; muscle tremors or weakness; confusion or acute lethargy; or skin rash. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule (Norpace®): 100 mg, 150 mg

Capsule, controlled release (Norpace® CR): 100 mg, 150 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsule, 12-hour (Disopyramide Phosphate)

150 mg (30): $43.10

Capsule, 12-hour (Norpace CR)

100 mg (60): $92.99

150 mg (60): $107.27

Capsules (Disopyramide Phosphate)

100 mg (90): $36.99

150 mg (30): $19.99

Capsules (Norpace)

100 mg (90): $128.69

150 mg (30): $51.99

Mechanism of ActionClass Ia antiarrhythmic: Decreases myocardial excitability and conduction velocity; reduces disparity in refractory between normal and infarcted myocardium; possesses anticholinergic, peripheral vasoconstrictive, and negative inotropic effects

Pharmacodynamics/Kinetics

Onset of action: 0.5-3.5 hours

Duration: 1.5-8.5 hours

Absorption: 60% to 83%

Protein binding (concentration dependent): 20% to 60%

Metabolism: Hepatic to inactive metabolites

Half-life elimination: Adults: 4-10 hours; prolonged with hepatic or renal impairment

Excretion: Urine (40% to 60% as unchanged drug); feces (10% to 15%)

Related Information

- Antiarrhythmic Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsDisopyramide is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay cause drowsiness or nervousness; rare reports of depression and psychosis

Mental Health: Effects on Psychiatric TreatmentContraindicated with ziprasidone; use cautiously with TCAs; may cause AV block or QT prolongation; phenobarbital and carbamazepine may decrease the effects of disopyramide via enzyme induction

Cardiovascular ConsiderationsDisopyramide has limited antiarrhythmic effects and has a very narrow therapeutic index. Close monitoring of ECG, particularly of the QT interval, should be conducted when initiating therapy. Increases in QT >25% over baseline should result in cessation or reduction in disopyramide dosing. In patients with pre-existing cardiovascular disease, the incidence of proarrhythmic effects and mortality may be increased with Class Ia antiarrhythmic agents.

Disopyramide has significant anticholinergic effects which also limits its role in patients with cardiovascular disease. Disopyramide is being used experimentally for the treatment of vasovagal syncope.

Disopyramide may be used in the treatment of HOCM as it significantly reduces the left ventricular outflow gradient and improves symptoms. Some patients may not tolerate the anticholinergic effects such as dry mouth or urinary retention, frequency, and urgency. Up to $^{1}/_{3}$ may not improve and will require other nonpharmacologic interventions.

Anesthesia and Critical Care Concerns/Other ConsiderationsIn patients with pre-existing cardiovascular disease, the incidence of proarrhythmic effects and mortality may be increased with Class Ia antiarrhythmic agents. Disopyramide has significant anticholinergic effects which also limits its role in patients with cardiovascular disease.

Index TermsDisopyramide Phosphate

References

Buxton AE, Lee KL, Fisher JD, et al, “A Randomized Study of the Prevention of Sudden Death in Patients With Coronary Artery Disease. Multicenter Unsustained Tachycardia Trial Investigators,” *N Engl J Med*, 1999, 341(25):1882-90. [PubMed 10601507]

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Flaker GC, Blackshear JL, McBride R, et al, “Antiarrhythmic Drug Therapy and Cardiac Mortality in Atrial Fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators,” *J Am Coll Cardiol*, 1992, 20(3):527-32. [PubMed 1512329]

Maron BJ, "Hypertrophic Cardiomyopathy: A Systematic Review," *JAMA*, 2002, 287(10):1308-20.[PubMed 11886323]

Morganroth J and Goin JE, “Quinidine-Related Mortality in the Short-to-Medium Term Treatment of Ventricular Arrhythmias," *Circulation*, 1991, 84(5):1977-83.[PubMed 1834365]

Sherrid MV, Barac I, McKenna WJ, et al, "Multicenter Study of the Efficacy and Safety of Disopyramide in Obstructive Hypertrophic Cardiomyopathy," *J Am Coll Cardiol*, 2005, 45(8):1251-8.[PubMed 15837258]

International Brand NamesDicorantil-F (BR); Dicorynan (ES); Dimodan (MX); Dirytmin (BE, LU, NL, SE); Disocor (PL); Disomet (FI); Durbis (DK, SE); Durbis Retard (NO, SE); Durbis[inj.] (DK); Norpace (BB, CH, DE, DK, HR, IE, IN, KP, MY, NL, PH, SR, TR, TT, ZA); Norpace CR (TW); Norpace Retard (HK, PH, ZA); Norpaso (AR); Palpitin (HN, HU, PL); Pyramide (NZ); Ritmodan (IT, PT); Ritmoforine (NL); Rythmical (IL); Rythmodan (AE, AT, AU, BE, BH, CY, CZ, EG, FR, GB, GR, IE, IL, IQ, IR, JO, KW, LB, LU, LY, NL, OM, PL, QA, RU, SA, SY, YE, ZA); Rythmodan Retard (PL, ZA); Rythmodul (DE); Rytmilen (BG, CZ, PL, RU)

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Disulfiram may be confused with Diflucan®

Antabuse® may be confused with Anturane®

Pronunciation(dye SUL fi ram)

U.S. Brand NamesAntabuse®

Pharmacologic CategoryAldehyde Dehydrogenase Inhibitor

Use: Labeled IndicationsManagement of chronic alcoholism

Dosing: Adults**Note:** Do not administer until the patient has abstained from ethanol for at least 12 hours.

Alcoholism: Oral: Initial: 500 mg/day as a single dose for 1-2 weeks; maximum daily dose is 500 mg. Average maintenance dose: 250 mg/day; range: 125-500 mg; duration of therapy is to continue until the patient is fully recovered socially and a basis for permanent self control has been established. Maintenance therapy may be required for months or even years.

Dosing: ElderlyRefer to adult dosing.

Administration: OralAdministration of any medications containing alcohol, including topicals, is contraindicated. Do not administer disulfiram if ethanol has been consumed within the prior 12 hours.

ContraindicationsHypersensitivity to disulfiram and related compounds or any component of the formulation; patients receiving or using ethanol, metronidazole, paraldehyde, or ethanol-containing preparations like cough syrup or tonics; psychosis; severe myocardial disease and coronary occlusion

Warnings/Precautions

Boxed warnings:

- Ethanol intoxication: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Hepatotoxicity: Severe (sometimes fatal) hepatitis and/or hepatic failure have been associated with use; may occur in patients with or without prior history of abnormal hepatic function.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus.
- Hepatic impairment: Use with caution in patients with hepatic cirrhosis or impairment.
- Hypothyroidism: Use with caution in patients with hypothyroidism.
- Nephritis: Use with caution in patients with acute or chronic nephritis.
- Seizures: Use with caution in patients with a history of seizure disorder.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Ethanol intoxication: **[U.S. Boxed Warning]: Should never be administered to a patient when he/she is in a state of ethanol intoxication, or without his/her knowledge.**
- Patient information: Patients must receive appropriate counseling, including information on “disguised” forms of ethanol (tonics, mouthwashes, etc) and the duration of the drug's activity (up to 14 days).

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined.

Central nervous system: Drowsiness, headache, fatigue, psychosis

Dermatologic: Rash, acneiform eruptions, allergic dermatitis

Gastrointestinal: Metallic or garlic-like aftertaste

Genitourinary: Impotence

Hepatic: Hepatitis (cholestatic and fulminant), hepatic failure (multiple case reports)

Neuromuscular & skeletal: Peripheral neuritis, polyneuritis, peripheral neuropathy

Ocular: Optic neuritis

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 2A6, 2B6, 2D6, 2E1, 3A4; **Inhibits** CYP1A2 (weak), 2A6 (weak), 2B6 (weak), 2C9 (weak), 2D6 (weak), 2E1 (strong), 3A4 (weak)

Drug Interactions

Alcohol (Ethyl): Disulfiram may enhance the adverse/toxic effect of Alcohol (Ethyl). A disulfiram-like reaction may occur. *Risk X: Avoid combination*

Amprenavir: Disulfiram may enhance the adverse/toxic effect of Amprenavir. This is specifically related to the propylene glycol contained in amprenavir oral solution, not capsules. Management: Specifically, concurrent amprenavir oral solution and disulfiram is contraindicated due to the large amount of propylene glycol in the oral solution. *Risk X: Avoid combination*

Benzodiazepines (metabolized by oxidation): Disulfiram may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Chlorzoxazone: Disulfiram may decrease the metabolism of Chlorzoxazone. *Risk C: Monitor therapy*

CYP2E1 Substrates: CYP2E1 Inhibitors (Strong) may decrease the metabolism of CYP2E1 Substrates. *Risk D: Consider therapy modification*

MetroNIDAZOLE: Disulfiram may enhance the adverse/toxic effect of MetroNIDAZOLE. *Risk D: Consider therapy modification*

Phenytoin: Disulfiram may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Ritonavir: Disulfiram may enhance the adverse/toxic effect of Ritonavir. This is specific for the lopinavir/ritonavir (Kaletra) oral solution due to its alcohol content (42%). Management: Concomitant use of Kaletra (lopinavir/ritonavir) oral solution and disulfiram should be avoided. Kaletra contains 42% alcohol. *Risk X: Avoid combination*

Sertraline: Disulfiram may enhance the adverse/toxic effect of Sertraline. This is specifically related to sertraline oral concentrate due to its alcohol content (12%). Management: Sertraline Oral Concentrate contains 12% alcohol, and its use should be avoided with disulfiram. *Risk X: Avoid combination*

Theophylline Derivatives: Disulfiram may increase the serum concentration of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tipranavir: Disulfiram may enhance the adverse/toxic effect of Tipranavir. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Disulfiram may increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Disulfiram inhibits ethanol's usual metabolism. Avoid all ethanol. Patients can have a disulfiram reaction (headache, nausea, vomiting, chest, or abdominal pain) if they drink ethanol concurrently. Avoid cough syrups and elixirs containing ethanol. Avoid vinegars, cider, extracts, and foods containing ethanol.

Monitoring ParametersHypokalemia; liver function tests at baseline and after 10-14 days of treatment; CBC, serum chemistries, liver function tests should be monitored during therapy

Nursing: Physical Assessment/MonitoringAssess for adverse drug interactions with other prescription or OTC drugs. Do not administer until the patient has abstained from ethanol for 12 hours. Assess results of laboratory tests and for CNS changes at beginning of therapy and periodically with long-term therapy. Advise patient about disulfiram reaction if alcohol is ingested. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsMonitor liver function before, 10-14 days after beginning therapy, and every 6 months during therapy.

Patient EducationTablets can be crushed or mixed with water or juice. Metallic aftertaste may occur; this will go away. Do not drink any alcohol, including products containing alcohol (such as cough and cold syrups or some mouthwashes), or use alcohol-containing skin products while taking this medication and for at least 3 days (preferably 14 days) after stopping this medication. Drowsiness, tiredness, or visual changes may occur. Use care when driving or engaging in tasks requiring alertness until response to drug is known. Notify prescriber of any respiratory difficulty, weakness, nausea, vomiting, decreased appetite, yellowing of skin or eyes, or dark-colored urine. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Antabuse®: 250 mg, 500 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Antabuse)

250 mg (30): $105.59

Mechanism of ActionDisulfiram is a thiuram derivative which interferes with aldehyde dehydrogenase. When taken concomitantly with alcohol, there is an increase in serum acetaldehyde levels. High acetaldehyde causes uncomfortable symptoms including flushing, nausea, thirst, palpitations, chest pain, vertigo, and hypotension. This reaction is the basis for disulfiram use in postwithdrawal long-term care of alcoholism.

Pharmacodynamics/Kinetics

Onset of action: Full effect: 12 hours

Duration: ~1-2 weeks after last dose

Absorption: Rapid

Metabolism: To diethylthiocarbamate

Excretion: Feces and exhaled gases (as metabolites)

Related Information

- Addiction Treatments
- Depression

Dental Health: Effects on Dental Treatment No significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions
Mental Health: Effects on Mental Status Psychotic reactions have been noted

References

Motte S, Vincent JL, and Gillet JB, “Refractory Hyperdynamic Shock Associated With Alcohol and Disulfiram,” *Am J Emerg Med*, 1986, 4(4):323-5. [PubMed 3718622]

Pompidou A, Delsaux MC, Telvi L, et al, “Isoprinosine and Imuthiol, Two Potentially Active Compounds in Patients With AIDS-Related Complex Symptoms,” *Cancer Res*, 1985, 45(9 Suppl):4671-3.

International Brand Names Abstensyl (AR); Alcobuse (TH); Alcohol Stop (KP); Antabus (AT, CH, CN, DE, DK, EC, ES, FI, HN, HR, NL, NO, SE, TR); Antabuse (AU, BE, GB, IE, IT, LU, MX, ZA); Antaethyl (HU); Anticol (PL); Antietanol (BR); Busetal (PE); Deadict (IN); Difiram (TH); Disulfiram (PL); Esperal (BG, FR, IN, PL, RU); Refusal (NL); Tetidis (HR); Tetradin (PT)

DOBUTamine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

DOBUTamine may be confused with DOPamine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(doe BYOO ta meen)

Canadian Brand NamesDobutamine Injection, USP; Dobutrex®

Pharmacologic CategoryAdrenergic Agonist Agent

Use: Labeled IndicationsShort-term management of patients with cardiac decompensation

Use: Unlabeled/InvestigationalPositive inotropic agent for use in myocardial dysfunction of sepsis

Dosing: AdultsCardiac decompensation: I.V. infusion: 2.5-20 mcg/kg/minute; maximum: 40 mcg/kg/minute, titrate to desired response; see table.

Infusion Rates of Various Dilutions of Dobutamine

Desired Delivery Rate (mcg/kg/min)	**Infusion Rate (mL/kg/min)**	
	500 mcg/mL[1]	**1000 mcg/mL**[2]
2.5	0.005	0.0025
5.0	0.01	0.005
7.5	0.015	0.0075
10.0	0.02	0.01
12.5	0.025	0.0125
15.0	0.03	0.015
[1] 500 mg per liter or 250 mg per 500 mL of diluent.		
[2] 1000 mg per liter or 250 mg per 250 mL of diluent.		

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricCardiac decompensation: Refer to adult dosing.

Calculations

- Dobutamine

Administration: I.V.Always administer via infusion device; administer into large vein.

Administration: I.V. DetailpH: 2.5-5.5

StorageStore reconstituted solution under refrigeration for 48 hours or 6 hours at room temperature. Stability of parenteral admixture at room temperature (25°C) is 48 hours; at refrigeration (4°C) stability is 7 days.

ReconstitutionRemix solution every 24 hours. Pink discoloration of solution indicates slight oxidation but **no** significant loss of potency.

Standard adult diluent: 250 mg/500 mL D_5W; 500 mg/500 mL D_5W.

CompatibilityStable in D_5LR, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, $^1/_2NS$, NS, mannitol 20%; **incompatible** with sodium bicarbonate 5%; **variable stability (consult detailed reference)** in peritoneal dialysis solutions.

Y-site administration: Compatible: Amifostine, amiodarone, atracurium, aztreonam, bretylium, calcium chloride, calcium gluconate, ciprofloxacin, cisatracurium, cladribine, clarithromycin, diazepam, diltiazem, docetaxel, dopamine, dopamine with lidocaine, dopamine with nitroglycerin, dopamine with sodium nitroprusside, doxorubicin liposome, enalaprilat, epinephrine, etoposide, famotidine, fentanyl, fluconazole, gatifloxacin, gemcitabine, granisetron, haloperidol, hydromorphone, inamrinone, insulin (regular), labetalol, levofloxacin, lidocaine, lidocaine with nitroglycerin, lidocaine with sodium nitroprusside, linezolid, lorazepam, magnesium sulfate, meperidine, milrinone, morphine, nicardipine, nitroglycerin, nitroglycerin with sodium nitroprusside, norepinephrine, pancuronium, potassium chloride, propofol, ranitidine, remifentanil, sodium nitroprusside, streptokinase, tacrolimus, theophylline, thiotepa, tolazoline, vecuronium, verapamil, zidovudine. **Incompatible:** Acyclovir, alatrofloxacin, alteplase, aminophylline, amphotericin B cholesteryl sulfate complex, cefepime, foscarnet, indomethacin, phytonadione, piperacillin/tazobactam, thiopental, warfarin. **Variable (consult detailed reference):** Furosemide, heparin, midazolam.

Compatibility in syringe: Compatible: Heparin, ranitidine. **Incompatible:** Doxapram.

Compatibility when admixed: Compatible: Amiodarone, atracurium, atropine, dopamine, enalaprilat, epinephrine, flumazenil, hydralazine, isoproterenol, lidocaine, meperidine, meropenem, metaraminol, morphine, nitroglycerin, norepinephrine, phentolamine, phenylephrine, procainamide, propranolol, ranitidine. **Incompatible:** Acyclovir, alteplase, aminophylline, bumetanide, calcium gluconate, diazepam, digoxin, floxacillin, furosemide, insulin (regular), magnesium sulfate, phenytoin, potassium phosphates, sodium bicarbonate. **Variable (consult detailed reference):** Bretylium, calcium chloride, heparin, nitroglycerin with sodium nitroprusside, potassium chloride, verapamil.

ContraindicationsHypersensitivity to dobutamine or sulfites (some contain sodium metabisulfate), or any component of the formulation; idiopathic hypertrophic subaortic stenosis (IHSS)

Warnings/Precautions

Concerns related to adverse effects:

- Blood pressure effects: An increase in blood pressure is more common, but occasionally a patient may become hypotensive.
- Tachycardia: May increase heart rate.
- Ventricular ectopy: May exacerbate ventricular ectopy.

Disease-related concerns:

- Aortic stenosis: Ineffective therapeutically in the presence of mechanical obstruction such as severe aortic stenosis.
- Atrial fibrillation: Patients with atrial fibrillation may experience an increase in ventricular response.
- Hypovolemia: If needed, correct hypovolemia first to optimize hemodynamics.
- Myocardial infarct (post): Use with caution in patients post-MI; can increase myocardial oxygen demand.

Concurrent drug therapy issues:

- Monoamine oxidase inhibitors (MAO-I): Use with extreme caution in patients taking MAO inhibitors; prolong hypertension may result from concurrent use.

Dosage form specific issues:

- Sodium sulfite: Product may contain sodium sulfite.

Special populations:

- Elderly: Use with caution in the elderly; start at lower end of the dosage range.

Other warnings/precautions:

- Diagnostic testing: Dobutamine in combination with stress echo may be used diagnostically.

Geriatric ConsiderationsA recent study demonstrated beneficial hemodynamic effects in elderly patients; monitor closely.

Pregnancy Risk FactorB

LactationExcretion in breast milk unknown

Adverse ReactionsIncidence of adverse events is not always reported.

Cardiovascular: Increased heart rate, increased blood pressure, increased ventricular ectopic activity, hypotension, premature ventricular beats (5%, dose related), anginal pain (1% to 3%), nonspecific chest pain (1% to 3%), palpitation (1% to 3%)

Central nervous system: Fever (1% to 3%), headache (1% to 3%), paresthesia

Endocrine & metabolic: Slight decrease in serum potassium

Gastrointestinal: Nausea (1% to 3%)

Hematologic: Thrombocytopenia (isolated cases)

Local: Phlebitis, local inflammatory changes and pain from infiltration, cutaneous necrosis (isolated cases)

Neuromuscular & skeletal: Mild leg cramps

Respiratory: Dyspnea (1% to 3%)

Drug Interactions

Calcium Salts: May diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

COMT Inhibitors: May decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure, ECG, heart rate, CVP, RAP, MAP, urine output; if pulmonary artery catheter is in place, monitor CI, PCWP, and SVR; also monitor serum potassium

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Infusion pump and continuous cardiac and hemodynamic monitoring are required. Monitor therapeutic effectiveness and adverse reactions. Instruct patient on adverse symptoms to report.

Monitoring: Lab TestsSerum glucose, renal function

Patient EducationWhen administered in emergencies, patient education should be appropriate to the situation. If patient is aware, instruct to promptly report chest pain, palpitations, rapid heartbeat, headache, nervousness, or restlessness, nausea or vomiting, or respiratory difficulty. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion, as hydrochloride [premixed in dextrose]: 1 mg/mL (250 mL, 500 mL); 2 mg/mL (250 mL); 4 mg/mL (250 mL)

Injection, solution, as hydrochloride: 12.5 mg/mL (20 mL, 40 mL, 100 mL) [contains sodium bisulfite]

Generic AvailableYes

Mechanism of ActionStimulates beta$_1$-adrenergic receptors, causing increased contractility and heart rate, with little effect on beta$_2$- or alpha-receptors

Pharmacodynamics/Kinetics

Onset of action: I.V.: 1-10 minutes

Peak effect: 10-20 minutes

Metabolism: In tissues and hepatically to inactive metabolites

Half-life elimination: 2 minutes

Excretion: Urine (as metabolites)

Related Information

- Hemodynamic Support, Intravenous

Pharmacotherapy PearlsDobutamine lowers central venous pressure and wedge pressure but has little effect on pulmonary vascular resistance.

Dobutamine therapy should be avoided in patients with stable heart failure due to an increase in mortality. In patients with intractable heart failure, dobutamine may be used as a short-term infusion to provide symptomatic benefit. It is not known whether short-term dobutamine therapy in end-stage heart failure has any outcome benefit.

Dobutamine infusion during echocardiography is used as a cardiovascular stress. Wall motion abnormalities developing with increasing doses of dobutamine may help to identify ischemic and/or hibernating myocardium.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsDobutamine therapy should be avoided in patients with stable heart failure due to an increase in mortality. In patients with intractable heart failure, dobutamine may be used as a short-term infusion to provide symptomatic benefit. It is not known whether short-term dobutamine therapy in end-stage heart failure has any outcome benefit.

Dobutamine infusion during echocardiography is used as a cardiovascular stress. Wall motion abnormalities developing with increasing doses of dobutamine may help to identify ischemic and/or hibernating myocardium.

Anesthesia and Critical Care Concerns/Other Considerations**Septic Shock:** Septic patients who have been adequately fluid resuscitated and have an adequate mean arterial pressure but low cardiac index (<2.5 L/minute/m^2) may require dobutamine. Dobutamine may help reverse tissue hypoperfusion by increasing cardiac output. Increasing cardiac output beyond the normal range has not been shown in clinical trials to improve patient outcome. The 2008 Surviving Sepsis Campaign guidelines recommend the use of dobutamine infusion when myocardial dysfunction is present with the goal of normalizing cardiac output. Avoid trying to increase cardiac index to supranormal levels (Grade 1C).

Early goal-directed therapy in the treatment of severe sepsis and septic shock provides significant survival benefits to this subset of patients. About 14% of the patients in the early goal-directed group received dobutamine. The early goal-directed patients received significantly more fluid, red-cell transfusions, and inotropic support during the initial 6 hours of their visit (Rivers, 2001). The 2008 Surviving Sepsis Campaign guidelines suggest that if central venous (superior vena cava) or mixed venous oxygen saturation of ≥70% or ≥65%, respectively, is not achieved (central venous pressure 8-12 mm Hg) within the first 6 hours of resuscitation, then transfuse packed red blood cells to a hematocrit of ≥30% and/or administer dobutamine (up to 20 mcg/kg/minute) to achieve this goal (Grade 2C).

Index Terms Dobutamine Hydrochloride

References

Bax JJ, Poldermans D, Elhendy A, et al, “Improvement of Left Ventricular Ejection Fraction, Heart Failure Symptoms and Prognosis After Revascularization in Patients With Chronic Coronary Artery Disease and Viable Myocardium Detected by Dobutamine Stress Echocardiography,” *J Am Coll Cardiol*, 1999, 34(1):163-9. [PubMed 10400006]

Dellinger RP, Levy MM, Carlet JM, et al, “Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008,” *Intensive Care Med*, 2008, 34(1):17-60.[PubMed 18058085]

Leier CV, Webel J, and Bush CA, “The Cardiovascular Effects of the Continuous Infusion of Dobutamine in Patients With Severe Cardiac Failure,” *Circulation*, 1977, 56(3):468-72. [PubMed 884803]

Patel MB, Kaplan IV, Patni RN, et al, “Sustained Improvement in Flow-Mediated Vasodilation After Short-Term Administration of Dobutamine in Patients With Severe Congestive Heart Failure,” *Circulation*, 1999, 99(1):60-4. [PubMed 9884380]

Paulman PM, Cantral K, Meade JG, et al, “Dobutamine Overdose,” *JAMA*, 1990, 264(18):2386-7. [PubMed 2231992]

“Practice Parameters for Hemodynamic Support of Sepsis in Adult Patients in Sepsis. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine,” *Crit Care Med*, 1999, 27(3):639-60. Available at: http://www.sccm.org/pdf/Hemodynamic%20Support.pdf. Accessed August 13, 2003. [PubMed 10199548]

Rich MN, Woods WL, Davila-Roman VG, et al, “A Randomized Comparison of Intravenous Amrinone Versus Dobutamine in Older Patients With Decompensated Congestive Heart Failure,” *J Am Geriatr Soc*, 1995, 43(3):271-4. [PubMed 7884117]

Rivers E, Nguyen B, Havstad S, et al, “Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock," *N Engl J Med*, 2001, 345(19):1368-77.[PubMed 11794169]

International Brand Names Butamine (IL); Cardiject (ID, IN, TH, ZA); Dobamin (KP); Dobucard (MY); Dobucor (ES); Dobuject (CZ, DK, FI, ID, IL, KP, MX, PH, PK, PL, RU, SE, TH, TW); Doburan (KP, VE); Dobutamin Hexal (DE, HU, PL); Dobutamin-Ratiopharm (DE); Dobutamina Abbott (ES); Dobutamina Inibsa (ES); Dobutamina Rovi (ES); Dobutamine (PL); Dobutamine Aguettant (FR); Dobutamine Hydrochloride (GB); Dobutamine Panpharma (FR); Dobutrex (AT, AU, BE, BF, BG, BJ, BR, CH, CI, CL, CZ, DK, ES, ET, FR, GB, GH, GM, GN, HN, HR, HU, ID, IE, IN, IT, KE, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, PH, PL, RU, SC, SD, SE, SL, SN, TN, TR, TZ, UG, ZA, ZM, ZW); Dobutrim (PH); Doxa (PY); Duvig (AR); Gendobu (TW); Inotrex (GR, PT); Inotrop (ID); Posiject (GB, IE)

Docetaxel (Weekly Regimen)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer

Regimen UseProstate cancer

Regimen

Docetaxel: I.V.: 40 mg/m^2 days 1, 8, and 15

[total dose/cycle = 120 mg/m^2]

Repeat cycle every 4 weeks

References

Joshua AM, Nordman I, Venkataswaran R, et al, âWeekly Docetaxel as Second Line Treatment After Mitozantrone for Androgen-Independent Prostate Cancer,â *Intern Med J*, 2005, 35(8):468-72.[PubMed 16176469]

Docetaxel (Weekly)-Trastuzumab

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Breast Cancer]

Regimen UseBreast cancer

Index TermsTrastuzumab-Docetaxel (Weekly)

Regimen

Cycle 1:

Docetaxel: I.V.: 35 mg/m^2/day days 1, 8, and 15

[total dose/cycle 1 = 105 mg/m^2]

Trastuzumab: I.V.: 4 mg/kg (loading dose) day 0 cycle 1

followed by I.V.: 2 mg/kg/day days 8 and 15 cycle 1

[total dose/cycle 1 = 8 mg/kg]

Treatment cycle is 28 days

Subsequent cycles:

Docetaxel: I.V.: 35 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 105 mg/m^2]

Trastuzumab: I.V.: 2 mg/kg/day days 1, 8, and 15

[total dose/cycle = 6 mg/kg]

Repeat cycle every 28 days

References

Esteva FJ, Valero V, Booser D, et al, "Phase II Study of Weekly Docetaxel and Trastuzumab for Patients With HER-2-Overexpressing Metastatic Breast Cancer," *J Clin Oncol*, 2002, 20(7):1800-8.[PubMed 11919237]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer
Regimen UseBreast cancer
Index TermsBevacizumab-Docetaxel
RegimenNOTE: Multiple variations are listed below.

Variation 1:

Docetaxel: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Bevacizumab: I.V.: 7.5 mg/kg day 1

[total dose/cycle = 7.5 mg/kg]

Repeat cycle every 21 days (administer docetaxel for up to 9 cycles, bevacizumab until disease progression or unacceptable toxicity)

Variation 2:

Docetaxel: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Bevacizumab: I.V.: 15 mg/kg day 1

[total dose/cycle = 15 mg/kg]

Repeat cycle every 21 days (administer docetaxel for up to 9 cycles, bevacizumab until disease progression or unacceptable toxicity)

References

Miles D, Chan A, Romieu G, et al, "Randomized, Double-Blind, Placebo-Controlled, Phase III Study of Bevacizumab With Docetaxel or Docetaxel With Placebo as First-Line Therapy for Patients With Locally Recurrent or Metastatic Breast Cancer (mBC): AVADO," [LBA1011abstract from 2008 ASCO Annual Meeting]

Docetaxel-Carboplatin (Ovarian Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Ovarian Cancer

Regimen UseOvarian cancer

Index TermsCarboplatin-Docetaxel (Ovarian Cancer)

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Docetaxel: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Carboplatin: I.V.: Target AUC 6

[total dose/cycle = AUC = 6]

Repeat cycle every 21 days for 6 cycles

Variation 2:

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Carboplatin: I.V.: AUC 5 day 1

[total dose/cycle = AUC = 5]

Repeat cycle every 21 days for 6 cycles

References

Variation 1:

Markman M, Kennedy A, Webster K, et al, "Combination Chemotherapy With Carboplatin and Docetaxel in the Treatment of Cancers of the Ovary and Fallopian Tube and Primary Carcinoma of the Peritoneum," *J Clin Oncol*, 2001, 19(7):1901-5.[PubMed 11283121]

Variation 2:

Vasey PA, Jayson GC, Gordon A, et al, "Phase III Randomized Trial of Docetaxel-Carboplatin Versus Paclitaxel-Carboplatin as First-line Chemotherapy for Ovarian Carcinoma," *J Natl Cancer Inst*, 2004, 96(22):1682-91.[PubMed 15547181]

Docetaxel-Cisplatin-Fluorouracil (Gastric Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Gastric Cancer]

Regimen UseGastric cancer

Index TermsDCF

Regimen

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Cisplatin: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Fluorouracil: I.V.: 750 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 3750 mg/m^2]

Repeat cycle every 21 days

References

Ajani JA, Fodor MB, Tjulandin SA, et al, âPhase II Multi-Institutional Randomized Trial of Docetaxel Plus Cisplatin With or Without Fluorouracil in Patients With Untreated, Advanced Gastric, or Gastroesophageal Adenocarcinoma,â *J Clin Oncol*, 2005, 23(24):5660-7.[PubMed 16110025]

Docetaxel-Cisplatin-Fluorouracil (Head and Neck Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Head and Neck Cancer]
Regimen UseHead and neck cancer
Index TermsTPF
RegimenNOTE: Multiple variations are listed below.

Variation 1:

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Cisplatin: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Fluorouracil: I.V.: 750 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 3750 mg/m^2]

Repeat cycle every 21 days for 4 cycles

Variation 2:

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Cisplatin: I.V.: 75-100 mg/m^2 day 1

[total dose/cycle = 75-100 mg/m^2]

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 21 days for total of 3 cycles

References

Variation 1:

Schrijvers D, van Herpen C, Kerger J, et al, âDocetaxel, Cisplatin and 5-Fluorouracil in Patients With Locally Advanced Unresectable Head and Neck Cancer: A Phase I-II Feasibility Study,â *Ann Oncol*, 2004, 15(4):638-45.[PubMed 15033673]

Vermorken JB, Remenar E, van Herpen C, et al, "Cisplatin, Fluorouracil, and Docetaxel in Unresectable Head and Neck Cancer," *N Engl J Med*, 2007, 357(17):1695-1704.[PubMed 17960012]

Variation 2:

Posner MR, Glisson B, Frenette G, et al, "Multicenter Phase I-II Trial of Docetaxel, Cisplatin, and Fluorouracil Induction Chemotherapy for Patients With Locally Advanced Squamous Cell Cancer of the Head and Neck," *J Clin Oncol*, 2001, 19(4):1096-104.[PubMed 11181674]

Posner MR, Hershock DM, Blajman CR, et al, "Cisplatin and Fluorouracil Alone or With Docetaxel in Head and Neck Cancer," *N Engl J Med*, 2007, 357(17):1705-15.[PubMed 17960013]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Nonsmall Cell)

Regimen UseLung cancer, nonsmall cell

Regimen

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Cisplatin: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 21 days

References

Zalcberg J, Millward M, Bishop J, et al, âPhase II Study of Docetaxel and Cisplatin in Advanced Nonsmall-Cell Lung Cancer,â *J Clin Oncol*, 1998, 16(5):1948-53.[PubMed 9586914]

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer

Regimen Use Breast cancer

Index TermsTC

Regimen

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 21 days for 4 cycles

References

Jones SE, Savin MA, Holmes FA, et al, "Phase III Trial Comparing Doxorubicin Plus Cyclophosphamide With Docetaxel Plus Cyclophosphamide as Adjuvant Therapy for Operable Breast Cancer," *J Clin Oncol*, 2006, 24(34):5381-7.[PubMed 17135639]

Docetaxel-FEC

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Breast Cancer]

Regimen UseBreast cancer

Index TermsFEC-Docetaxel

Regimen

Cycles 1, 2, and 3:

Docetaxel: I.V.: 80-100 mg/m^2 day 1

[total dose/cycle = 80-100 mg/m^2]

Repeat cycle every 21 days for 3 cycles

Cycles 4, 5, and 6 (FEC):

Fluorouracil: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Epirubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat FEC cycle every 21 days for total of 3 cycles

References

Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al, "Adjuvant Docetaxel or Vinorelbine With or Without Trastuzumab for Breast Cancer," *N Engl J Med*, 2006, 354(8):809-20.[PubMed 16495393]

Docetaxel-Prednisone

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer
Regimen UseProstate cancer
Regimen

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Prednisone: Oral: 5 mg twice daily

[total dose/cycle = 210 mg]

Repeat cycle every 21 days for up to 10 cycles

References

Dagher R, Li N, Abraham S, et al, “Approval Summary: Docetaxel in Combination With Prednisone for the Treatment of Androgen-Independent Hormone-Refractory Prostate Cancer,” *Clin Cancer Res*, 2004, 10(24):8147-51.[PubMed 15623588]

Tannock IF, de Wit R, Berry WR, et al, “Docetaxel Plus Prednisone or Mitoxantrone Plus Prednisone for Advanced Prostate Cancer,” *N Engl J Med*, 2004, 351(15):1502-12[PubMed 15470213]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer

Regimen UseProstate cancer

Regimen

Docetaxel: I.V.: 30 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 90 mg/m^2]

Thalidomide: Oral: 200 mg daily (at bedtime)

[total dose/cycle = 5600 mg]

Repeat cycle every 28 days

References

Dahut WL, Gulley JL, Arlen PM, et al, âRandomized Phase II Trial of Docetaxel Plus Thalidomide in Androgen-Independent Prostate Cancer,â *J Clin Oncol*, 2004, 22(13):2532-9.[PubMed 15226321]

Docetaxel-Trastuzumab-Carboplatin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer

Regimen Use Breast cancer

Index Terms Trastuzumab-Docetaxel-Carboplatin

Regimen

Cycle 1:

Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1 cycle 1

followed by I.V.: 2 mg/kg/day days 8 and 15 cycle 1

[total dose/cycle 1 = 8 mg/kg]

Docetaxel: I.V.: 75 mg/m^2 day 2

[total dose/cycle 1 = 75 mg/m^2]

Carboplatin: I.V.: AUC 6 day 2

[total dose/cycle 1 = AUC = 6]

Treatment cycle is 21 days

Subsequent cycles:

Trastuzumab: I.V.: 2 mg/kg/day days 1, 8, and 15

[total dose/cycle = 6 mg/kg]

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Carboplatin: I.V.: AUC 6 day 1

[total dose/cycle = AUC = 6]

Repeat cycle every 21 days for a total of ~6 cycles (continue weekly trastuzumab for 1 year after chemotherapy, or until disease progression or unacceptable toxicity)

References

Pegram MD, Pienkowski T, Northfelt DW, et al, "Results of Two Open-Label, Multicenter Phase II Studies of Docetaxel, Platinum Salts, and Trastuzumab in HER2-Positive Advanced Breast Cancer," *J Natl Cancer Inst*, 2004, 96(10):759-69.[PubMed 15150304]

Docetaxel-Trastuzumab-Cisplatin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer

Regimen Use Breast cancer

Index Terms Trastuzumab-Docetaxel-Cisplatin

Regimen

Cycle 1:

- Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1 cycle 1
    - **followed by** I.V.: 2 mg/kg/day days 8 and 15 cycle 1
        - [total dose/cycle 1 = 8 mg/kg]
- Docetaxel: I.V.: 75 mg/m^2 day 2
    - [total dose/cycle 1 = 75 mg/m^2]
- Cisplatin: I.V.: 75 mg/m^2 day 2
    - [total dose/cycle 1 = 75 mg/m^2]
- Treatment cycle is 21 days

Subsequent cycles:

- Trastuzumab: I.V.: 2 mg/kg/day days 1, 8, and 15
    - [total dose/cycle = 6 mg/kg]
- Docetaxel: I.V.: 75 mg/m^2 day 1
    - [total dose/cycle = 75 mg/m^2]
- Cisplatin: I.V.: 75 mg/m^2 day 1
    - [total dose/cycle = 75 mg/m^2]
- Repeat cycle every 21 days for a total of ~6 cycles (continue weekly trastuzumab for 1 year after chemotherapy, or until disease progression or unacceptable toxicity)

References

Pegram MD, Pienkowski T, Northfelt DW, et al, "Results of Two Open-Label, Multicenter Phase II Studies of Docetaxel, Platinum Salts, and Trastuzumab in HER2-Positive Advanced Breast Cancer," *J Natl Cancer Inst*, 2004, 96(10):759-69.[PubMed 15150304]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

Index TermsTrastuzumab-Docetaxel-FEC

Regimen

Cycle 1:

Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1 cycle 1

followed by I.V.: 2 mg/kg/day days 8 and 15 cycle 1

[total dose/cycle 1 = 8 mg/kg]

Docetaxel: I.V.: 80-100 mg/m^2 day 1

[total dose/cycle 1 = 80-100 mg/m^2]

Treatment cycle is 21 days

Cycles 2 and 3:

Trastuzumab: I.V.: 2 mg/kg/day days 1, 8, and 15

[total dose/cycle = 6 mg/kg]

Docetaxel: I.V.: 80-100 mg/m^2 day 1

[total dose/cycle = 80-100 mg/m^2]

Treatment cycle is 21 days

Cycles 4, 5, and 6 (FEC):

Fluorouracil: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Epirubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat FEC cycle every 21 days for total of 3 cycles

References

Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al, "Adjuvant Docetaxel or Vinorelbine With or Without Trastuzumab for Breast Cancer," *N Engl J Med*, 2006, 354(8):809-20.[PubMed 16495393]

Docetaxel-Trastuzumab

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer
Regimen Use Breast cancer
Index Terms Trastuzumab-Docetaxel
Regimen

Cycle 1:

Docetaxel: I.V.: 100 mg/m^2 day 1

[total dose/cycle 1 = 100 mg/m^2]

Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1 cycle 1

followed by I.V.: 2 mg/kg/day days 8 and 15 cycle 1

[total dose/cycle 1 = 8 mg/kg]

Treatment cycle is 21 days

Subsequent cycles:

Docetaxel: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Trastuzumab: I.V.: 2 mg/kg/day days 1, 8, and 15

[total dose/cycle = 6 mg/kg]

Repeat cycle every 21 days for a total of at least 6 cycles (continue weekly trastuzumab until disease progression)

References

Marty M, Cognetti F, Maraninchi D, et al, "Randomized Phase II Trial of the Efficacy and Safety of Trastuzumab Combined With Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Administered as First-Line Treatment: The M77001 Study Group," *J Clin Oncol*, 2005, 23(19):4265-74.[PubMed 15911866]

Docetaxel

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Taxotere® may be confused with Taxol®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(doe se TAKS el)

U.S. Brand NamesTaxotere®

Canadian Brand NamesTaxotere®

Pharmacologic CategoryAntineoplastic Agent, Antimicrotubular; Antineoplastic Agent, Natural Source (Plant) Derivative; Antineoplastic Agent, Taxane Derivative

Use: Labeled IndicationsTreatment of breast cancer; locally-advanced or metastatic nonsmall cell lung cancer (NSCLC); hormone refractory, metastatic prostate cancer; advanced gastric adenocarcinoma; locally-advanced squamous cell head and neck cancer

Use: Unlabeled/InvestigationalTreatment of bladder cancer, ovarian cancer, small cell lung cancer, and soft tissue sarcoma

Dosing: Adults**Note:** Premedicate with corticosteroids, beginning the day before docetaxel administration, (administer for 1-5 days) to reduce the severity of hypersensitivity reactions and pulmonary/peripheral edema. Refer to individual protocols:

Breast cancer: I.V.:

Locally-advanced or metastatic: 60-100 mg/m^2 every 3 weeks; patients initially started at 60 mg/m^2 who do not develop toxicity may tolerate higher doses

Operable, node-positive (adjuvant treatment): 75 mg/m^2 every 3 weeks for 6 courses (in combination with doxorubicin and cyclophosphamide)

Nonsmall cell lung cancer: I.V.: 75 mg/m^2 every 3 weeks (as monotherapy or in combination with cisplatin)

Prostate cancer: I.V.: 75 mg/m^2 every 3 weeks (in combination with prednisone)

Gastric adenocarcinoma: I.V.: 75 mg/m^2 every 3 weeks (in combination with cisplatin and fluorouracil)

Head and neck cancer: I.V.: 75 mg/m^2 every 3 weeks (in combination with cisplatin and fluorouracil) for 3 or 4 cycles, followed by radiation therapy

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentDocetaxel has minimal renal excretion; dosage adjustments for renal dysfunction may not be needed.

Dosing: Hepatic Impairment

The FDA-approved labeling recommends the following adjustments:

Total bilirubin greater than the ULN, or AST/ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN: Docetaxel **generally should not be administered**.

Hepatic impairment dosing adjustment specific for gastric adenocarcinoma:

AST/ALT >2.5 to ≤5 times ULN and alkaline phosphatase ≤2.5 times ULN: Administer 80% of dose

AST/ALT >1.5 to ≤5 times ULN and alkaline phosphatase >2.5 to ≤5 times ULN: Administer 80% of dose

AST/ALT >5 times ULN and /or alkaline phosphatase >5 times ULN: Discontinue docetaxel

The following guidelines have been used by some clinicians (Floyd, 2006):

AST/ALT 1.6-6 times ULN: Administer 75% of dose

AST/ALT >6 times ULN: Use clinical judgment

Dosing: Adjustment for Toxicity**Note:** Toxicity includes febrile neutropenia, neutrophils ≤500/mm^3 for >1 week, severe or cumulative cutaneous reactions; in nonsmall cell lung cancer, this may also include platelets <25,000/mm^3 and other grade 3/4 nonhematologic toxicities.

Breast cancer: Patients dosed initially at 100 mg/m^2; reduce dose to 75 mg/m^2; **Note:** If the patient continues to experience these adverse reactions, the dosage should be reduced to 55 mg/m^2 or therapy should be discontinued; discontinue for peripheral neuropathy ≥ grade 3

Breast cancer, adjuvant treatment: TAC regimen should be administered when neutrophils are ≥1500 cells/mm^3. Patients experiencing febrile neutropenia should receive G-CSF in all subsequent cycles. Patients with persistent febrile neutropenia (while on G-CSF) or patients experiencing severe/cumulative cutaneous reactions or moderate neurosensory effects (signs/symptoms) should receive a reduced dose (60 mg/m^2) of docetaxel. Patients who experience grade 3 or 4 stomatitis should also receive a reduced dose (60 mg/m^2) of docetaxel. Discontinue therapy with persistent toxicities after dosage reduction.

Nonsmall cell lung cancer:

Monotherapy: Patients dosed initially at 75 mg/m^2 should have dose held until toxicity is resolved, then resume at 55 mg/m^2; discontinue for peripheral neuropathy ≥ grade 3.

Combination therapy (with cisplatin): Patients dosed initially at 75 mg/m^2 should have the docetaxel dosage reduced to 65 mg/m^2 in subsequent cycles; if further adjustment is required, dosage may be reduced to 50 mg/m^2

Prostate cancer: Reduce dose to 60 mg/m^2; discontinue therapy if toxicities persist at lower dose.

Gastric cancer, head and neck cancer: **Note:** Cisplatin may require dose reductions/therapy delays for peripheral neuropathy, ototoxicity, and /or nephrotoxicity. Patients experiencing febrile neutropenia, documented infection with neutropenia or neutropenia >7 days should receive G-CSF in all subsequent cycles. For neutropenic complications despite G-CSF use, further reduce dose to 60 mg/m^2. Neutropenic complications in subsequent cycles should be further dose reduced to 45 mg/m^2. Patients who experience grade 4 thrombocytopenia should receive a dose reduction from 75 mg/m^2 to 60 mg/m^2. Discontinue therapy for persistent toxicities.

Gastrointestinal toxicity for docetaxel in combination with cisplatin and fluorouracil for treatment of gastric cancer or head and neck cancer:

Diarrhea, grade 3:

First episode: Reduce fluorouracil dose by 20%

Second episode: Reduce docetaxel dose by 20%

Diarrhea, grade 4:

First episode: Reduce fluorouracil and docetaxel doses by 20%

Second episode: Discontinue treatment

Stomatitis, grade 3:

First episode: Reduce fluorouracil dose by 20%

Second episode: Discontinue fluorouracil for all subsequent cycles

Third episode: Reduce docetaxel dose by 20%

Stomatitis, grade 4:

First episode: Discontinue fluorouracil for all subsequent cycles

Second episode: Reduce docetaxel dose by 20%

Dosing: Combination Regimens

Bladder cancer:

Cisplatin-Docetaxel

Gemcitabine-Docetaxel (Bladder Cancer)

Breast cancer:

AT

Capecitabine + Docetaxel (Breast Cancer)

Docetaxel-Bevacizumab

Docetaxel-Cyclophosphamide (TC)

Docetaxel-FEC

Docetaxel-Trastuzumab

Docetaxel-Trastuzumab-Carboplatin

Docetaxel-Trastuzumab-Cisplatin

Docetaxel-Trastuzumab-FEC

Docetaxel (Weekly)-Trastuzumab

TAC

TEX (Capecitabine + Docetaxel + Epirubicin)

Gastric cancer:

Capecitabine + Docetaxel (Gastric Cancer)

Docetaxel-Cisplatin-Fluorouracil (Gastric Cancer)

Head and neck cancer: Docetaxel-Cisplatin-Fluorouracil (Head and Neck Cancer)

Lung cancer (nonsmall cell):

Capecitabine + Docetaxel (NSCLC)

Docetaxel-Cisplatin

Osteosarcoma: Gemcitabine-Docetaxel (Sarcoma)

Prostate cancer:

Docetaxel-Prednisone

Docetaxel-Thalidomide

Docetaxel (Weekly Regimen)

Estramustine + Docetaxel

Estramustine + Docetaxel + Calcitriol

Estramustine + Docetaxel + Carboplatin

Estramustine + Docetaxel + Hydrocortisone

Estramustine + Docetaxel + Prednisone

Soft tissue sarcoma: Gemcitabine-Docetaxel (Sarcoma)

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Administer I.V. infusion over 1-hour through nonsorbing polyethylene lined (non-DEHP) tubing; in-line filter is not necessary (the use of a filter during administration is not recommended by the manufacturer). **Note:** Premedication with corticosteroids for 1-5 days, beginning the day before docetaxel administration, is recommended to prevent hypersensitivity reactions and pulmonary/peripheral edema (see Additional Information).

StorageIntact vials should be stored at 2°C to 25°C (36°F to 77°F) and protected from light. Freezing does not adversely affect the product. If refrigerated, vials should be stored at room temperature for approximately 5 minutes before using. Diluted solutions in the vial are stable for 8 hours at room temperature or under refrigeration. Solutions diluted for infusion in D_5W or NS are stable for up to 4 weeks at room temperature of 15°C to 25°C (59°F to 77°F) in polyolefin containers; however, the manufacturer recommends use within 4 hours.

ReconstitutionVials should be diluted with 13% (w/w) ethanol/water (provided with the drug) to a final concentration of 10 mg/mL. Do not shake. The solution should be further diluted in 250-1000 mL of NS or D_5W to a final concentration of 0.3-0.9 mg/mL (although the manufacturer recommends a final concentration of 0.3-0.74) and dispensed in a non-DEHP container (eg, glass, polypropylene, polyolefin).

CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Acyclovir, amifostine, amikacin, aminophylline, ampicillin, ampicillin/sulbactam, anidulafungin, aztreonam, bumetanide, buprenorphine, butorphanol, calcium gluconate, cefazolin, cefepime, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, chlorpromazine, cimetidine, ciprofloxacin, clindamycin, co-trimoxazole, dexamethasone sodium phosphate, diphenhydramine, dobutamine, dopamine, doxycycline, droperidol, enalaprilat, famotidine, fluconazole, furosemide, ganciclovir, gemcitabine, gentamicin, granisetron, haloperidol, heparin, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, imipenem/cilastatin, leucovorin calcium, lorazepam, magnesium sulfate, mannitol, meperidine, meropenem, mesna, metoclopramide, metronidazole, morphine, ofloxacin, ondansetron, oxaliplatin, palonosetron, pemetrexed, piperacillin, piperacillin/tazobactam, potassium chloride, prochlorperazine edisylate, promethazine, ranitidine, Ringer's injection (lactated), sodium bicarbonate, ticarcillin/clavulanate, tobramycin, vancomycin, zidovudine. **Incompatible:** Amphotericin B, doxorubicin liposome, methylprednisolone sodium succinate, nalbuphine.

ContraindicationsHypersensitivity to docetaxel or any component of the formulation; prior hypersensitivity to medications containing polysorbate 80; pre-existing bone marrow suppression (neutrophils <1500 cells/mm^3)

Allergy Considerations

- Taxane Allergy

Warnings/Precautions

Boxed warnings:

- Fluid retention syndrome: See “Concerns related to adverse effects” below.

- Hepatic impairment: See "Disease-related concerns" below.
- Hypersensitivity reactions: See "Concerns related to adverse effects" below.
- Neutropenia: See "Concerns related to adverse effects" below.
- Treatment-related mortality: See "Concerns related to adverse effects" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Cutaneous reactions: With use, cutaneous reactions including erythema and desquamation have been reported; may require dose reduction.
- Fluid retention: **[U.S. Boxed Warning]: Fluid retention syndrome characterized by pleural effusions, ascites, edema, and weight gain (2-15 kg) has also been reported.** The incidence and severity of the syndrome increase sharply at cumulative doses ≥400 mg/m^2. Patients should be premedicated with a corticosteroid to prevent fluid retention; severity is reduced with dexamethasone premedication starting one day prior to docetaxel administration.
- Hypersensitivity reactions: **[U.S. Boxed Warning]: Severe hypersensitivity reactions characterized by rash/erythema, hypotension, bronchospasms, or anaphylaxis may occur;** minor reactions including flushing or localized skin reactions may also occur. Patients should be premedicated with a corticosteroid to prevent hypersensitivity reactions; severity is reduced with dexamethasone premedication starting one day prior to docetaxel administration.
- Neurosensory symptoms: Dosage adjustment is recommended with severe neurosensory symptoms (paresthesia, dysesthesia, pain); persistent symptoms may require discontinuation.
- Neutropenia: **[U.S. Boxed Warning]: Patients with an absolute neutrophil count <1500 cells/mm^3 should not receive docetaxel.** The dose-limiting toxicity is neutropenia; however, this rarely results in treatment delays and prophylactic colony stimulating factors have not been routinely used. Patients with increased liver function tests experienced more episodes of neutropenia with a greater number of severe infections. When administered as sequential infusions, taxane derivatives (docetaxel, paclitaxel) should be administered before platinum derivatives (carboplatin, cisplatin) to limit myelosuppression and to enhance efficacy.
- Treatment-related mortality: **[U.S. Boxed Warning]: Patients with abnormal liver function, those receiving higher doses, and patients with nonsmall cell lung cancer and a history of prior treatment with platinum derivatives who receive docetaxel doses higher than 100 mg/m^2 are at higher risk for treatment-related mortality.**

Disease-related concerns:

- Hepatic impairment: **[U.S. Boxed Warning]: Avoid use in patients with bilirubin exceeding upper limit of normal (ULN) or AST and/or ALT >1.5 times ULN in conjunction with alkaline phosphatase >2.5 times ULN.** Use caution in hepatic disease; patients with abnormal liver function are at increased risk of treatment-related adverse events.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated embryotoxicity, fetal toxicity, and maternal toxicity. There are no adequate and well-controlled studies in pregnant women; however, fetal harm may occur. Women of childbearing potential should avoid becoming pregnant. A pregnancy registry is available for all cancers diagnosed during pregnancy at Cooper Health (856-757-7876).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in nursing the infant, breast-feeding is not recommended.

Adverse ReactionsPercentages reported for docetaxel monotherapy; frequency may vary depending on diagnosis, dose, liver function, prior treatment, and premedication. The incidence of adverse events was usually higher in patients with elevated liver function tests.

>10%:

Cardiovascular: Fluid retention (13% to 60%; dose dependent)

Central nervous system: Neurosensory events (20% to 58%; including neuropathy), fever (31% to 35%), neuromotor events (16%)

Dermatologic: Alopecia (56% to 76%), cutaneous events (20% to 48%), nail disorder (11% to 41%)

Gastrointestinal: Stomatitis (19% to 53%; severe 1% to 8%), diarrhea (23% to 43%; severe: 5% to 6%), nausea (34% to 42%), vomiting (22% to 23%)

Hematologic: Neutropenia (84% to 99%; grade 4: 75% to 86%; onset: 4-7 days, nadir: 5-9 days, recovery: 21 days; dose dependent), leukopenia (84% to 99%; grade 4: 32% to 44%), anemia (65% to 94%; dose dependent; grades 3/4: 8% to 9%), thrombocytopenia (8% to 14%; grade 4: 1%; dose dependent), febrile neutropenia (6% to 12%; dose dependent)

Hepatic: Transaminases increased (4% to 19%)

Neuromuscular & skeletal: Weakness (53% to 66%; severe 13% to 18%), myalgia (3% to 23%)

Respiratory: Pulmonary events (41%)

Miscellaneous: Infection (1% to 34%; dose dependent), hypersensitivity (1% to 21%; with premedication 15%)

1% to 10%:

- Cardiovascular: Left ventricular ejection fraction decreased (prostate cancer: 10%; metastatic breast cancer: 8%), hypotension (3%)
- Dermatologic: Rash/erythema (2%)
- Gastrointestinal: Taste perversion (6%)
- Hepatic: Bilirubin increased (9%), alkaline phosphatase increased (4% to 7%)
- Local: Infusion-site reactions (4%, including hyperpigmentation, inflammation, redness, dryness, phlebitis, extravasation, swelling of the vein)
- Neuromuscular and skeletal: Arthralgia (3% to 9%)
- Ocular: Epiphora associated with canalicular stenosis (≤77% with weekly administration; ≤1% with every-3-week administration)

<1%, postmarketing and/or case reports (limited to important or life-threatening): Acute myeloid leukemia (AML), acute respiratory distress syndrome (ARDS), anaphylactic shock, angina, ascites, atrial fibrillation, atrial flutter, bleeding episodes, bronchospasm, cardiac tamponade, chest pain, chest tightness, colitis, conjunctivitis, constipation, cutaneous lupus erythematosus, deep vein thrombosis, dehydration, disseminated intravascular coagulation (DIC), drug fever, duodenal ulcer, dyspnea, dysrhythmia, ECG abnormalities, erythema multiforme, esophagitis, gastrointestinal hemorrhage, gastrointestinal obstruction, gastrointestinal perforation, hand and foot syndrome, hearing loss, heart failure, hepatitis, hypertension, ileus, interstitial pneumonia, ischemic colitis, lacrimal duct obstruction, loss of consciousness (transient), MI, multiorgan failure, myelodysplastic syndrome, neutropenic enterocolitis, ototoxicity, pleural effusion, pruritus, pulmonary edema, pulmonary embolism, pulmonary fibrosis, radiation pneumonitis, radiation recall, renal insufficiency, seizure, sepsis, sinus tachycardia, Stevens-Johnson syndrome, syncope, toxic epidermal necrolysis, tachycardia, thrombophlebitis, unstable angina, visual disturbances (transient)

Oncology: VesicantNo; may be an irritant

Oncology: Emetic PotentialLow (10% to 30%)

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (weak)

Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Docetaxel. *Risk D: Consider therapy modification*

Antineoplastic Agents (Anthracycline): Taxane Derivatives may enhance the adverse/toxic effect of Antineoplastic Agents (Anthracycline). Taxane Derivatives may increase the serum concentration of Antineoplastic Agents (Anthracycline). Taxane Derivatives may also increase the formation of toxic anthracycline metabolites in heart tissue. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Platinum Derivatives: May enhance the myelosuppressive effect of Taxane Derivatives. Administer Taxane derivative before Platinum derivative when given as sequential infusions to limit toxicity. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (due to GI irritation).

Herb/Nutraceutical: Avoid St John's wort (may decrease docetaxel levels).

Monitoring ParametersCBC with differential, liver function tests, bilirubin, alkaline phosphatase, renal function; monitor for hypersensitivity reactions, fluid retention, epiphora, and canalicular stenosis

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, drugs that may increase or decrease levels/effects of docetaxel). **Caution:** Severe hypersensitivity reactions have been reported; premedication with dexamethasone may be advisable. Patient should be monitored continuously during infusion; dosing adjustment may be necessary. Assess results of laboratory tests, therapeutic response, and adverse effects (eg, neutropenia, severe fluid retention, pleural effusion, opportunistic infections, anemia) prior to each infusion and on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, liver function tests, bilirubin, alkaline phosphatase, renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by infusion; report immediately any pain, burning, swelling, or redness at infusion site, difficulty breathing or swallowing, chest pain, or sudden chills. It is important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake and adequate nutrition (small frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); loss of hair (reversible); or diarrhea (buttermilk, boiled milk, or yogurt may help; if unresolved, contact prescriber for medication relief). Report immediately swelling of extremities, respiratory difficulty, unusual weight gain, abdominal distention, chest pain, palpitations, fever, chills, unusual bruising or bleeding, signs of infection, excessive fatigue, or rash. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this drug. Consult prescriber for appropriate contraceptives. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [concentrate]:

Taxotere®: 20 mg/0.5 mL (0.5 mL, 2 mL) [contains Polysorbate 80®; diluent contains ethanol 13%]

Generic AvailableNo

Mechanism of ActionDocetaxel promotes the assembly of microtubules from tubulin dimers, and inhibits the depolymerization of tubulin which stabilizes microtubules in the cell. This results in inhibition of DNA, RNA, and protein synthesis. Most activity occurs during the M phase of the cell cycle.

Pharmacodynamics/KineticsExhibits linear pharmacokinetics at the recommended dosage range

Distribution: Extensive extravascular distribution and/or tissue binding; V_d: 80-90 L/m^2, V_{dss}: 113 L (mean steady state)

Protein binding: ~94% to 97%, primarily to alpha$_1$-acid glycoprotein, albumin, and lipoproteins

Metabolism: Hepatic; oxidation via CYP3A4 to metabolites

Half-life elimination: Terminal: 11 hours

Excretion: Feces (75%, <8% as unchanged drug); urine (6%); ~80% within 48 hours

Clearance: Total body: Mean: 21 L/hour/m^2

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsPremedication with oral corticosteroids is recommended to decrease the incidence and severity of fluid retention and severity of hypersensitivity reactions. Dexamethasone 8-10 mg orally twice daily for 3-5 days, starting the day before docetaxel administration, is usually recommended. When prednisone is part of the antineoplastic regimen (eg, prostate cancer), the prednisone is sometimes withheld on the days dexamethasone is administered.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis, stomatitis, and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause confusion

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine

Index TermsNSC-628503; RP-6976

References

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International Brand Names Daxotel (PH); Dexotel (IN); Docetax-20 (BG); Hentaxel (PH); Oncodocel (CO); Taxoter (RU); Taxotere (AR, AT, AU, BD, BE, BF, BG, BJ, BO, BR, CH, CI, CL, CN, CO, CR, CZ, DE, DK, DO, EC, EG, ET, FI, FR, GB, GH, GM, GN, GR, GT, HK, HN, ID, IE, IL, IN, IT, JP, KE, KP, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, PA, PE, PH, PK, PL, PR, PT, PY, RU, SC, SD, SE, SG, SL, SN, SV, TH, TN, TR, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Texot (AR)

Docosanol

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(doe KOE san ole)
U.S. Brand NamesAbreva® [OTC]
Pharmacologic CategoryAntiviral Agent, Topical
Use: Labeled IndicationsTreatment of herpes simplex of the face or lips
Use: DentalTreatment of herpes simplex of the face or lips
Dosing: AdultsHerpes simplex (face/lips): Topical: Apply 5 times/day to affected area of face or lips. Start at first sign of cold sore or fever blister and continue until healed.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricHerpes simplex: Children ≥12 years: Refer to adult dosing.
StorageStore at 20°C to 25°C (68°F to 77°F); do not freeze.
ContraindicationsHypersensitivity to docosanol or any component of the formulation
Warnings/Precautions

Special populations:

- Pediatrics: Not for use in children <12 years of age.

Other warnings/precautions:

- Appropriate use: For external use only; do not apply to inside of mouth or around eyes.

Adverse ReactionsLimited information; headache reported (frequency similar to placebo)
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical:

Abreva®: 10% (2 g) [contains benzyl alcohol]

Generic AvailableNo
Mechanism of ActionPrevents viral entry and replication at the cellular level
Dental Health Professional ConsiderationsWash hands before and after applying cream. Begin treatment at first tingle of cold sore or fever blister. Rub into area gently, but completely. Do not apply directly to inside of mouth or around eyes. Contact healthcare provider if sore gets worse or does not heal within 10 days. Do not share this product with others, may spread infection. Notify healthcare professional if pregnant or breast-feeding.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Anesthesia and Critical Care Concerns/Other ConsiderationsDo not apply directly to inside of mouth or around eyes.
Index Terms*n*-Docosanol; Behenyl Alcohol
International Brand NamesAbrax (IL); Healip (DK, FI, SE); Heloc (NO)

Docusate and Senna

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Senokot® may be confused with Depakote®

Pronunciation(DOK yoo sate & SEN na)
U.S. Brand NamesPeri-Colace® [OTC]; Senokot-S® [OTC]; SenoSol™-SS [OTC]
Pharmacologic CategoryLaxative, Stimulant; Stool Softener
Use: Labeled IndicationsShort-term treatment of constipation
Use: Unlabeled/InvestigationalEvacuate the colon for bowel or rectal examinations; management/prevention of opiate-induced constipation
Dosing: AdultsConstipation: OTC ranges: Oral: Initial: 2 tablets (17.2 mg sennosides plus 100 mg docusate) once daily (maximum: 4 tablets twice daily)
Dosing: ElderlyConstipation: OTC ranges: Oral: Consider half the initial dose in older, debilitated patients
Dosing: PediatricConstipation: OTC ranges: Oral: Children:

2-6 years: Initial: 4.3 mg sennosides plus 25 mg docusate ($^1/_2$ tablet) once daily (maximum: 1 tablet twice daily)

6-12 years: Initial: 8.6 sennosides plus 50 mg docusate (1 tablet) once daily (maximum: 2 tablets twice daily)

≥12 years: Refer to adult dosing.

Administration: OralOnce-daily doses should be taken at bedtime.
Dietary ConsiderationsSenokot-S®: Sodium content: 3 mg per tablet
ContraindicationsHypersensitivity to any component; intestinal obstruction; acute intestinal inflammation (eg, Crohn's disease); ulcerative colitis; appendicitis; abdominal pain of unknown origin; concurrent use of mineral oil; pregnancy (per Commission E for senna)
Allergy Considerations

- Anthraquinone Allergy

Warnings/Precautions

Other warnings/precautions:

- OTC labeling: Not recommended for over-the-counter (OTC) use in patients experiencing stomach pain, nausea, vomiting, or a sudden change in bowel movements which lasts >2 weeks. Not recommended for use longer than 1 week. Not recommended for use in children <2 years of age.

Geriatric ConsiderationsThe chronic use of stimulant cathartics is inappropriate and should be avoided. Although the elderly commonly complain of constipation, such complaints require evaluation; short-term use of stimulant cathartics is best. If prophylaxis is desired, then the use of bulk agents (eg, psyllium), stool softeners, and hyperosmotic agents (eg, sorbitol 70%) is preferred. Stool softeners are unnecessary if stools are well-hydrated (as in use of hyperosmotics), soft or “mushy”. Patients should be instructed for proper dietary fiber and fluid intake, as well as regular exercise. Monitor closely for fluid/electrolyte imbalance, CNS signs of fluid/electrolyte loss, and hypotension.
Adverse ReactionsFrequency not defined.

Gastrointestinal: Nausea, vomiting, diarrhea, abdominal cramps

Genitourinary: Urine discoloration (red/brown)

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Docusate sodium 50 mg and sennosides 8.6 mg

Peri-Colace®: Docusate sodium 50 mg and sennosides 8.6 mg

Senokot-S®: Docusate sodium 50 mg and sennosides 8.6 mg [sugar free; contains sodium 4 mg/tablet]

SenoSol™-SS: Docusate sodium 50 mg and sennosides 8.6 mg [contains sodium 3 mg/tablet]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Senna S)

8.6-50 mg (100): $12.99

Mechanism of ActionDocusate is a stool softener; sennosides are laxatives
Pharmacotherapy PearlsIndividual product labeling should be consulted prior to dosing.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentGI side effects are common; use caution with SSRIs
Index TermsSenna and Docusate; Senna-S

Docusate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Colace® may be confused with Calan®, Cozaar®

Docusate may be confused with Doxinate®

Surfak® may be confused with Surbex®

Pronunciation(DOK yoo sate)

U.S. Brand NamesColace® [OTC]; Correctol® [OTC]; D-S-S® [OTC]; Diocto® [OTC]; Docu-Soft [OTC]; Docusoft-S™ [OTC]; DOK™ [OTC]; DOS® [OTC]; Dulcolax® Stool Softener [OTC]; Enemeez® Plus [OTC]; Enemeez® [OTC]; Fleet® Sof-Lax® [OTC]; Genasoft® [OTC]; Phillips'® Stool Softener Laxative [OTC]; Silace [OTC]; Surfak® [OTC]

Canadian Brand NamesApo-Docusate-Sodium®; Colace®; Colax-C®; Novo-Docusate Calcium; Novo-Docusate Sodium; PMS-Docusate Calcium; PMS-Docusate Sodium; Regulex®; Selax®; Soflax™

Pharmacologic CategoryStool Softener

Use: Labeled IndicationsStool softener in patients who should avoid straining during defecation and constipation associated with hard, dry stools; prophylaxis for straining (Valsalva) following myocardial infarction. A safe agent to be used in elderly; some evidence that doses <200 mg are ineffective; stool softeners are unnecessary if stool is well hydrated or "mushy" and soft; shown to be ineffective used long-term.

Use: Unlabeled/InvestigationalCeruminolytic

Dosing: Adults**Note:** Docusate salts are interchangeable; the amount of sodium, calcium, or potassium per dosage unit is clinically insignificant.

Stool softener:

Oral: 50-500 mg/day in 1-4 divided doses

Rectal: Add 50-100 mg of docusate liquid to enema fluid (saline or water); give as retention or flushing enema

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Docusate salts are interchangeable; the amount of sodium, calcium, or potassium per dosage unit is clinically insignificant.

Stool softener:

Oral:

- Infants and Children <3 years: 10-40 mg/day in 1-4 divided doses
- Children:
    - 3-6 years: 20-60 mg/day in 1-4 divided doses
    - 6-12 years: 40-150 mg/day in 1-4 divided doses
- Adolescents: Refer to adult dosing.

Rectal: Older Children: Refer to adult dosing.

Administration: OralEnsure adequate fluid intake. Docusate syrup should be administered with 6-8 ounces of milk, juice, or infant formula to mask the bitter taste.

Dietary ConsiderationsEnsure adequate fluid intake.

Syrup: Should be taken with 6-8 ounces of milk, juice, or infant formula.

ContraindicationsHypersensitivity to docusate or any component of the formulation; concomitant use of mineral oil; intestinal obstruction, acute abdominal pain, nausea, or vomiting

Warnings/Precautions

Concerns related to adverse effects:

- Dependence: Prolonged, frequent or excessive use may result in dependence.
- Electrolyte imbalance: Prolonged, frequent or excessive use may result in electrolyte imbalance.

Geriatric ConsiderationsA safe agent to be used in the elderly. Some evidence that doses <200 mg are ineffective. Stool softeners are unnecessary if stool is well hydrated or “mushy” and soft; shown to be ineffective used long-term.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/compatible

Adverse Reactions1% to 10%:

Gastrointestinal: Intestinal obstruction, diarrhea, abdominal cramping

Miscellaneous: Throat irritation

Drug InteractionsThere are no known significant interactions.

Test InteractionsDecreased potassium (S), decreased chloride (S)

Nursing: Physical Assessment/MonitoringMonitor for effectiveness and instruct patient in proper use (avoid excessive or prolonged use) and adverse effects to report.

Patient EducationMaintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not chew or break caplets; swallow whole. Docusate should be taken with a full (6-8 oz) glass of milk, fruit juice, or infant formula. Do not use if abdominal pain, nausea, or vomiting are present. Laxative use should be used for a short period of time (<1 week). Prolonged use may result in abuse, dependence, as well as fluid and electrolyte loss. Report bleeding or constipation. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, oral, as calcium: 240 mg

Capsule, oral, as sodium: 100 mg, 250 mg [DSC]

Colace®: 50 mg [contains sodium 3 mg/capsule]; 100 mg [contains sodium 5 mg/capsule]

Capsule, liquid, oral, as calcium:

Surfak®: 240 mg

Capsule, liquid, oral, as sodium:

Docusoft-S™: 100 mg [contains sodium 5 mg/capsule]

Capsule, softgel, oral, as calcium: 240 mg

Capsule, softgel, oral, as sodium: 100 mg, 250 mg

Correctol®: 100 mg

Docu-Soft: 100 mg

DOK™: 100 mg, 250 mg

Dulcolax® Stool Softener: 100 mg [contains sodium 5 mg/softgel]

Fleet® Sof-Lax®: 100 mg [contains sodium 5 mg/softgel]

DOS®, D-S-S®: 100 mg, 250 mg

Genasoft®: 100 mg

Phillips'® Stool Softener Laxative: 100 mg [contains sodium 5.2 mg/softgel]

Liquid, oral, as sodium: 150 mg/15 mL (480 mL)

Colace®: 150 mg/15 mL (30 mL) [contains propylene glycol, sodium 1 mg/mL]

Diocto®: 150 mg/15 mL (480 mL)

Silace: 150 mg/15 mL (480 mL) [lemon-vanilla flavor]

Solution, rectal, as sodium [enema]:

Enemeez®: 283 mg/5 mL

Enemeez® Plus: 283 mg/5 mL [contains benzocaine]

Syrup, oral, as sodium: 60 mg/15 mL (480 mL)

Colace®: 60 mg/15 mL (480 mL) [alcohol free, sugar free; contains sodium 36 mg/5 mL]

Diocto®: 60 mg/15 mL (480 mL)

Silace: 20 mg/5 mL (480 mL) [peppermint flavor]

Generic AvailableYes: Excludes gelcap

Pricing: U.S. (www.drugstore.com)

Capsules (Colace)

100 mg (60): $25.99

Capsules (Docusate Sodium)

100 mg (100): $11.99

250 mg (100): $13.99

Syrup (Doc-Q-Lace)

60 mg/15 mL (473): $8.99

Mechanism of ActionReduces surface tension of the oil-water interface of the stool resulting in enhanced incorporation of water and fat allowing for stool softening

Pharmacodynamics/Kinetics

Onset of action: 12-72 hours

Excretion: Feces

Related Information

- Laxatives, Classification and Properties

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Throat irritation.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDioctyl Calcium Sulfosuccinate; Dioctyl Sodium Sulfosuccinate; Docusate Calcium; Docusate Potassium; Docusate Sodium; DOSS; DSS

References

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Schindler AM, “Isolated Neonatal Hypomagnesaemia Associated With Maternal Overuse of Stool Softener,” *Lancet*, 1984, 2(8406):822.

Singer AJ, Sauris E, and Viccellio AS, “Ceruminolytic Effects of Docusate Sodium: A Randomized, Controlled Trial,” *Ann Emerg Med*, 2000, 36(3):228-32.[PubMed 10969225]

International Brand NamesCellubril (IN); Colace (CL); Coloxyl (AU); Cusate (TH); Dama-Lax (ES); Dioctyl (GB); Dipolaxan (PL); Docusaat FNA (NL); Docusoft (IL); Docusol (GB); Doslax (IN); Emtix (FI); Jamylene (FR); Klyx (FI, NL, NO, SE); Lambanol (IT); Laxadine (ID); Laxicon (IN); Laxol (PL); Laxopol (PL); Molcer (GB); Norgalax (AE, BE, BH, CH, CY, DE, EG, GB, IE, IL, IQ, IR, JO, KW, LB, LU, LY, NL, OM, QA, RU, SA, SY, YE); Norgalax Micro-enema (GB); Purgeron (JP); Regutol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Softon (HK); Soliwax (GB); Soluwax Ear Drops (SG); Tirolaxo (ES); Wasserlax (ES); Waxsol (AU, GB, IE)

Dofetilide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(doe FET il ide)

U.S. Brand NamesTikosyn®

Canadian Brand NamesTikosyn®

Pharmacologic CategoryAntiarrhythmic Agent, Class III

Use: Labeled IndicationsMaintenance of normal sinus rhythm in patients with chronic atrial fibrillation/atrial flutter of longer than 1-week duration who have been converted to normal sinus rhythm; conversion of atrial fibrillation and atrial flutter to normal sinus rhythm

Dosing: Adults **Note:** QT_c must be determined prior to first dose

Antiarrhythmic: Oral:

Initial: 500 mcg orally twice daily. Initial dosage must be adjusted in patients with estimated Cl_{cr} <60 mL/minute. Dofetilide may be initiated at lower doses than recommended based on physician discretion.

Modification of dosage in response to initial dose: QT_c interval should be measured 2-3 hours after the initial dose. If the QT_c >15% of baseline, or if the QT_c is >500 msec (550 msec in patients with ventricular conduction abnormalities), dofetilide should be adjusted. If the starting dose is 500 mcg twice daily, then adjust to 250 mcg twice daily. If the starting dose was 250 mcg twice daily, then adjust to 125 mcg twice daily. If the starting dose was 125 mcg twice daily, then adjust to 125 mcg every day.

Continued monitoring for doses 2-5: QT_c interval must be determined 2-3 hours after each subsequent dose of dofetilide for in-hospital doses 2-5. If the measured QT_c is >500 msec (550 msec in patients with ventricular conduction abnormalities) dofetilide should be stopped.

Dosing: ElderlyRefer to adult dosing. No specific dosage adjustments are recommended based on age; however, careful assessment of renal function is particularly important in this population. See Special Geriatric Considerations.

Dosing: Renal Impairment

Cl_{cr} >60 mL/minute: Administer 500 mcg twice daily.

Cl_{cr} 40-60 mL/minute: Administer 250 mcg twice daily.

Cl_{cr} 20-39 mL/minute: Administer 125 mcg twice daily.

Cl_{cr} <20 mL/minute: Contraindicated in this group

Dosing: Hepatic ImpairmentNo dosage adjustments required in Child-Pugh class A and B; patients with severe hepatic impairment were not studied.

Calculations

- Creatinine Clearance: Adults

Administration: OralDo not open capsules.

RestrictionsTikosyn® is only available to prescribers and hospitals that have confirmed their participation in a designated Tikosyn® Education Program. The program provides comprehensive education about the importance of in-hospital treatment initiation and individualized dosing.

T.I.P.S. is the Tikosyn® In Pharmacy System designated to allow retail pharmacies to stock and dispense Tikosyn® once they have been enrolled. A participating pharmacy must confirm receipt of the T.I.P.S. program materials and educate its pharmacy staff about the procedures required to fill an outpatient prescription for Tikosyn®. The T.I.P.S. enrollment form is available at www.tikosyn.com. Tikosyn® is only available from a special mail order pharmacy, and enrolled retail pharmacies. Pharmacists must verify that the hospital/prescriber is a confirmed participant before Tikosyn® is provided. For participant verification, the pharmacist may call 1-800-788-7353 or use the web site located at www.tikosynlist.com. Further details and directions on the program are provided at www.tikosyn.com.

Dofetilide therapy must be initiated/adjusted in a hospital setting with proper monitoring under the guidance of experienced personnel.

ContraindicationsHypersensitivity to dofetilide or any component of the formulation; patients with congenital or acquired long QT syndromes, do not use if a baseline QT interval or QT_c is >440 msec (500 msec in patients with ventricular conduction abnormalities); severe renal impairment (estimated Cl_{cr} <20 mL/minute); concurrent use with verapamil, cimetidine, hydrochlorothiazide (alone or in combinations), trimethoprim (alone or in combination with sulfamethoxazole), itraconazole, ketoconazole, prochlorperazine, or megestrol; baseline heart rate <50 beats/minute; other drugs that prolong QT intervals (phenothiazines, cisapride, bepridil, tricyclic antidepressants, moxifloxacin; hypokalemia or hypomagnesemia; concurrent amiodarone, clarithromycin, or erythromycin

Allergy Considerations

- Dofetilide Allergy

Warnings/Precautions

Boxed warnings:

- Arrhythmias: Appropriate use: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Proarrhythmic effects: Watch for proarrhythmic effects; monitor and adjust dose to prevent QT_c prolongation. Torsade de pointes significantly increases with doses >500 mcg twice daily.

Disease-related concerns:

- Arrhythmias: Appropriate use: Reserve for patients who are highly symptomatic with atrial fibrillation/atrial flutter. **[U.S. Boxed Warning]: Must be initiated (or reinitiated) in a setting with continuous monitoring and staff familiar with the recognition and treatment of life-threatening arrhythmias. Patients must be monitored with continuous ECG for a minimum of 3 days,** or for a minimum of 12 hours after electrical or pharmacological cardioversion to normal sinus rhythm, whichever is greater. Patients should be readmitted for continuous monitoring if dosage is later increased.

- Conduction disturbances: Patients with second or third-degree heart block and/or sick sinus syndrome should not receive unless a functional pacemaker is in place. Defibrillation threshold is reduced in patients with ventricular tachycardia or ventricular fibrillation undergoing implantation of a cardioverter-defibrillator device.

- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Drugs with QT prolongation potential: Concurrent use with other drugs known to prolong QT_c interval is not recommended. Hold class I or class III antiarrhythmics for at least three half-lives prior to starting dofetilide; use in patients on amiodarone therapy only if serum amiodarone level is <0.3 mg/L or if amiodarone was stopped for >3 months previously.

- Potassium-depleting diuretics: Risk of hypokalemia and/or hypomagnesemia may be increased by potassium-depleting diuretics, increasing the risk of malignant arrhythmias such as torsade de pointes.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- CAST trial: In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, non-life-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide. An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. Antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Geriatric ConsiderationsNo specific dosage adjustments are recommended based on age; however, evaluation for use of this drug in the elderly is imperative. A complete review of medications, to assure there is no inadvertent use of contraindicated medications and those with potential drug interactions, can be re-evaluated for continued need. Laboratory values must be assessed prior to initiating medication; careful assessment of renal function is particularly important in the elderly population.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDofetilide has been shown to adversely affect *in utero* growth, organogenesis, and survival of rats and mice. There are no adequate and well-controlled studies in pregnant women. Dofetilide should be used with extreme caution in pregnant women and in women of childbearing age only when the benefit to the patient unequivocally justifies the potential risk to the fetus.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

Supraventricular arrhythmia patients (incidence > placebo)

>10%: Central nervous system: Headache (11%)

2% to 10%:

Central nervous system: Dizziness (8%), insomnia (4%)

Cardiovascular: Ventricular tachycardia (2.6% to 3.7%), chest pain (10%), torsade de pointes (3.3% in CHF patients and 0.9% in patients with a recent MI; up to 10.5% in patients receiving doses in excess of those recommended). Torsade de pointes occurs most frequently within the first 3 days of therapy.

Dermatologic: Rash (3%)

Gastrointestinal: Nausea (5%), diarrhea (3%), abdominal pain (3%)

Neuromuscular & skeletal: Back pain (3%)

Respiratory: Dyspnea (6%), respiratory tract infection (7%)

Miscellaneous: Flu syndrome (4%)

<2%:

Central nervous system: CVA, facial paralysis, flaccid paralysis, migraine, paralysis

Cardiovascular: AV block (0.4% to 1.5%), ventricular fibrillation (0% to 0.4%), bundle branch block, heart block, edema, heart arrest, myocardial infarct, sudden death, syncope

Dermatologic: Angioedema

Gastrointestinal: Liver damage

Neuromuscular & skeletal: Paresthesia

Respiratory: Cough

>2% (incidence ≤ placebo): Anxiety, pain, angina, atrial fibrillation, hypertension, palpitation, supraventricular tachycardia, peripheral edema, urinary tract infection, weakness, arthralgia, diaphoresis

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Dofetilide. *Risk X: Avoid combination*

Cimetidine: May decrease the excretion of Dofetilide. Cimetidine may decrease the metabolism of Dofetilide. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the QTc-prolonging effect of Dofetilide. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thiazide Diuretics: May enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Trimethoprim: May decrease the excretion of Dofetilide. *Risk X: Avoid combination*

Verapamil: May increase the serum concentration of Dofetilide. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease dofetilide levels. Avoid ephedra (may worsen arrhythmia).

Monitoring ParametersECG monitoring with attention to QT_c and occurrence of ventricular arrhythmias, baseline serum creatinine and changes in serum creatinine. Check serum potassium and magnesium levels if on medications where these electrolyte disturbances can occur, or if patient has a history of hypokalemia or hypomagnesemia. QT or QT_c must be monitored at specific times prior to the first dose and during the first 3 days of therapy. Thereafter, QT or QT_c and creatinine clearance must be evaluated at 3-month intervals.

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Must be initiated or reinitiated by a cardiologist in a setting with continuous ECG monitoring for a period of time at beginning or adjustment of therapy. Monitor for signs of electrolyte imbalance. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and on a regular basis with long-term therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse reactions to report.

Monitoring: Lab TestsSerum creatinine; check serum potassium and magnesium levels if on medications where these electrolyte disturbances can occur, or if patient has a history of hypokalemia or hypomagnesemia.

Patient EducationTake exactly as directed; do not take additional doses or discontinue without consulting prescriber. Do not open capsules. If you miss a dose, take your normal amount at the next scheduled time. You will need regular cardiac checkups and blood tests when taking this medication. You may experience headache, dizziness, or difficulty sleeping (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or abdominal pain, diarrhea, or nausea (small frequent meals and increased dietary bulk may help). Inform prescriber immediately if you experience fainting; severe GI discomfort or diarrhea; chest palpitations, irregular heartbeat, or chest pain; increased thirst; respiratory difficulty; skin rash; back pain; or alteration in muscle strength or gait. **Pregnancy/breast-feeding precautions:** Inform your prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 125 mcg, 250 mcg, 500 mcg

Generic AvailableNo
ManufacturerPfizer U.S. Pharmaceuticals Group
Pricing: U.S. (www.drugstore.com)

Capsules (Tikosyn)

500 mcg (60): $176.76

Mechanism of ActionVaughan Williams Class III antiarrhythmic activity. Blockade of the cardiac ion channel carrying the rapid component of the delayed rectifier potassium current. Dofetilide has no effect on sodium channels, adrenergic alpha-receptors, or adrenergic beta-receptors. It increases the monophasic action potential duration due to delayed repolarization. The increase in the QT interval is a function of prolongation of both effective and functional refractory periods in the His-Purkinje system and the ventricles. Changes in cardiac conduction velocity and sinus node function have not been observed in patients with or without structural heart disease. PR and QRS width remain the same in patients with pre-existing heart block and or sick sinus syndrome.
Pharmacodynamics/Kinetics

Absorption: >90%

Distribution: V_d: 3 L/kg

Protein binding: 60% to 70%

Metabolism: Hepatic via CYP3A4, but low affinity for it; metabolites formed by N-dealkylation and N-oxidation

Bioavailability: >90%

Half-life elimination: 10 hours

Time to peak: Fasting: 2-3 hours

Excretion: Urine (80%, 80% as unchanged drug, 20% as inactive or minimally active metabolites); renal elimination consists of glomerular filtration and active tubular secretion via cationic transport system

Related Information

- Antiarrhythmic Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsDofetilide is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.
Mental Health: Effects on Mental StatusInsomnia is common
Mental Health: Effects on Psychiatric TreatmentContraindicated with drugs that prolong QT_c (phenothiazines, TCAs, ziprasidone)
Cardiovascular ConsiderationsThe management of atrial fibrillation deserves careful consideration in patients with heart failure, because the loss of atrial assistance to ventricular filling may have greater negative effects on cardiac output. The choice of antiarrhythmic is important because of the risk that antiarrhythmic therapy may increase mortality in this setting.

The two DIAMOND studies were 3-year trials comparing mortality between dofetilide and placebo in patients with left ventricular dysfunction. One study included patients with moderate to severe CHF (60% of participants were NYHA Class III or IV) and the other study looked at patients with a recent MI (40% had NYHA class III or IV CHF). Dofetilide was an effective therapy for atrial fibrillation in carefully selected and monitored heart failure patients. Mortality was similar between those who received placebo and dofetilide; fewer patients on dofetilide were hospitalized for heart failure. It seems prudent, therefore, to carefully select and monitor patients in this situation.

There are limited studies evaluating the efficacy of dofetilide in patients with paroxysmal atrial fibrillation (PAF). While the efficacy data have not been statistically significant, positive trends have been noted and further study is required. In heart failure patients, dofetilide has been reported to preserve inotropic and end-systolic indices. Considering the neutral survival data from the DIAMOND trials and the positive influence on hemodynamic function, dofetilide is recommended by the most recently published ACC/AHA/ESC guidelines as an appropriate second- or third-line agent for PAF, particularly in the setting of ventricular dysfunction.

Dofetilide can cause life-threatening ventricular arrhythmias and should therefore be used in select patients in whom atrial fibrillation/flutter is highly symptomatic. Hospitals and physicians need to complete their Tikosyn® educational program before dofetilide can be prescribed and dispensed.

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International Brand NamesTikosyn (CA)

Dolasetron

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Anzemet® may be confused with Aldomet® and Avandamet®

Dolasetron may be confused with granisetron, ondansetron, palonosetron

Pronunciation(dol A se tron)

U.S. Brand NamesAnzemet®

Canadian Brand NamesAnzemet®

Pharmacologic CategoryAntiemetic; Selective 5-HT$_3$ Receptor Antagonist

Use: Labeled IndicationsPrevention of nausea and vomiting associated with emetogenic cancer chemotherapy; prevention of postoperative nausea and vomiting; treatment of postoperative nausea and vomiting (injectable form only).

Note: In Canada, the use of dolasetron is contraindicated for all uses in children <18 years of age or in the treatment of postoperative nausea and vomiting in adults. These are not labeled contraindications in the U.S.

Dosing: Adults**Note:** In Canada, the use of dolasetron is contraindicated in the treatment of postoperative nausea and vomiting in adults. These are not labeled contraindications in the U.S.

Prevention of chemotherapy-associated nausea and vomiting:

Oral:100 mg single dose 1 hour prior to chemotherapy

I.V.: 1.8 mg/kg or 100 mg 30 minutes prior to chemotherapy

Postoperative nausea and vomiting:

Prevention:

Oral: 100 mg within 2 hours before surgery (doses of 25-200 mg have been used)

I.V.: 12.5 mg ~15 minutes before stopping anesthesia

Treatment: I.V. (only): 12.5 mg as soon as needed

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** In Canada, the use of dolasetron is contraindicated in children <18 years of age.
Prevention of chemotherapy-associated nausea and vomiting (including initial and repeat courses): Children 2-16 years:

Oral: 1.8 mg/kg within 1 hour before chemotherapy; maximum: 100 mg/dose

I.V.: 1.8 mg/kg ~30 minutes before chemotherapy; maximum: 100 mg/dose

Postoperative nausea and vomiting: Children 2-16 years:

Prevention:

Oral: 1.2 mg/kg within 2 hours before surgery; maximum: 100 mg/dose

I.V.: 0.35 mg/kg (maximum: 12.5 mg) ~15 minutes before stopping anesthesia

Treatment: I.V. (only): 0.35 mg/kg as soon as needed

Administration: I.V.I.V. injection may be given either undiluted IVP over 30 seconds or diluted in 50 mL of compatible fluid and infused over 15 minutes. Line should be flushed, prior to and after, dolasetron administration.

Administration: I.V. DetailpH: 3.2-3.8

Administration: OralDolasetron injection may be diluted in apple or apple-grape juice and taken orally; this dilution is stable for 2 hours at room temperature.

StorageStore intact vials and tablets at room temperature. Protect from light. A 20 mg/mL solution in syringes is stable for 8 months at room temperature. Solutions diluted for infusion are stable at room temperature for 24 hours or under refrigeration for 48 hours.

ReconstitutionDilute in 50-100 mL of a compatible solution (ie, 0.9% NS, D_5W, $D_5{}^1/_2NS$, D_5LR, LR, and 10% mannitol injection).

CompatibilityStable in 0.9% NS, D_5W, $D_5{}^1/_2NS$, D_5LR, LR, and 10% mannitol injection.

Extemporaneously PreparedDolasetron injection may be diluted in apple or apple-grape juice and taken orally; this dilution is stable for 2 hours at room temperature.

ContraindicationsHypersensitivity to dolasetron or any component of the formulation

Note: In Canada, the use of dolasetron is contraindicated for all uses in children <18 years of age or in the treatment of postoperative nausea and vomiting in adults. These are not labeled contraindications in the U.S.

Allergy Considerations

- Serotonin 5-HT$_3$ Antagonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Allergic reactions: Use with caution in patients allergic to other 5-HT$_3$ receptor antagonists; cross-reactivity has been reported.

- ECG effects: Dolasetron has been associated with a number of dose-dependent increases in ECG intervals (eg, PR, QRS duration, QT/QT$_c$, JT), usually occurring 1-2 hours after I.V. administration and lasting 6-8 hours; however, may last ≥24 hours. May rarely lead to heart block or arrhythmia. Clinically relevant QT interval prolongation may occur resulting in torsade de pointes, when used in conjunction with other agents that prolong the QT interval (eg, Class I and III antiarrhythmics). Use with caution in patients at risk of QT prolongation and/or ventricular arrhythmia. Reduction in heart rate may also occur with the 5-HT$_3$ antagonists. I.V. formulations of 5-HT$_3$ antagonists have more association with ECG interval changes, compared to oral formulations.

Disease-related concerns:

- Long QT syndrome: Use with caution in patients with congenital long QT syndrome or other risk factors for QT prolongation (eg, medications known to prolong QT interval, electrolyte abnormalities [hypokalemia or hypomagnesemia], and cumulative high-dose anthracycline therapy).

Special populations:

- Pediatrics: Use with caution in children and adolescents who have or may develop QT$_c$ prolongation; rare cases of supraventricular and ventricular arrhythmias, cardiac arrest, and MI have been reported in this population. Safety and efficacy have not been established in children <2 years of age.

Other warnings/precautions:

- Chemotherapy-related emesis: **For chemotherapy, should be used on a scheduled basis, not on an "as needed" (PRN) basis,** since data support the use of this drug only in the prevention of nausea and vomiting (due to antineoplastic therapy) and not in the rescue of nausea and vomiting. Not intended for treatment of nausea and vomiting or for chronic continuous therapy.

Geriatric ConsiderationsIn controlled trials, no difference in overall safety and efficacy were observed between elderly and younger adults. Pharmacokinetics are similar in younger adults and elderly. No dosage adjustment necessary.

Pregnancy Risk FactorB

Pregnancy Considerations

Teratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsAdverse events may vary according to indication

>10%:

Central nervous system: Headache (7% to 24%)

Gastrointestinal: Diarrhea (2% to 12%)

1% to 10%:

Cardiovascular: Bradycardia (4% to 5%), hypotension (5%), hypertension (2% to 3%), tachycardia (2% to 3%)

Central nervous system: Dizziness (1% to 6%), fatigue (3% to 6%), fever (4% to 5%), pain (≤3%), chills/shivering (1% to 2%), sedation (2%)

Dermatological: Pruritus (3% to 4%)

Gastrointestinal: Dyspepsia (2% to 3%), abdominal pain (≤3%)

Hepatic: Abnormal hepatic function (4%)

Neuromuscular & skeletal: Pain (3%)

Renal: Oliguria (1% to 3%)

<1% (Limited to important or life-threatening): Abnormal vision, abnormal dreaming, acute renal failure, alkaline phosphatase increased, ALT increased, anaphylactic reaction, anemia, anorexia, anxiety, arrhythmia (supraventricular and ventricular), AST increased, ataxia, AV block, bronchospasm, cardiac arrest, cardiac conduction abnormalities, chest pain, confusion, constipation, diaphoresis, dyspnea, dysuria, edema, epistaxis, facial edema, flushing, GGT increased, heart block, hematuria, hyperbilirubinemia, ischemia (peripheral), local injection site reaction, MI, myocardial ischemia, orthostatic hypotension, palpitation, pancreatitis, paresthesia, peripheral edema, photophobia, polyuria; prolonged PR, QRS, JT, and QT$_c$ intervals; prothrombin time increased, PTT increased, purpura/hematoma, rash, sleep disorder, syncope, taste perversion, thrombocytopenia, thrombophlebitis/phlebitis, tinnitus, tremor, twitching, urticaria, vertigo

Oncology: VesicantNo

Metabolism/Transport Effects**Substrate** (minor) of CYP2C9, 3A4; **Inhibits** CYP2D6 (weak)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Apomorphine: Antiemetics (5HT3 Antagonists) may enhance the hypotensive effect of Apomorphine. *Risk X: Avoid combination*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Monitoring ParametersLiver function tests, blood pressure and pulse, and ECG in patients with cardiovascular disease

Nursing: Physical Assessment/MonitoringAssess allergy history (selective 5-HT$_3$ receptor antagonists) prior to administering. Use with caution in presence of, or potential for, cardiac conduction abnormalities (eg, QT prolongation, medication known to prolong QT interval, electrolyte abnormalities). I.V.: Follow infusion specifics. **Note:** Oral and I.V. doses have different schedules and should not be administered on "PRN" basis. Assess therapeutic effectiveness and adverse reactions on a regular basis. Teach patient possible side effects and adverse symptoms to report.

Patient EducationThis drug is given to reduce the incidence of nausea and vomiting. Do not take any other medication for nausea and vomiting with this medication unless approved by prescriber. If this medication is given by intravenous infusion you will be monitored during infusion. Report immediately any chest pain, respiratory difficulty, pain or itching at infusion site. Self-administered oral doses must be taken exactly as directed. You may experience headache, drowsiness, or dizziness (request assistance when getting up or changing position and do not perform activities requiring alertness [including driving] until response to drug is known). Report chest pain or palpitations; persistent headache; excessive drowsiness; fever; or changes in elimination patterns (constipation or diarrhea) or other adverse effects. **Breast-feeding precaution:** Consult prescriber if you are or intend to breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as mesylate:

Anzemet®: 20 mg/mL (0.625 mL) [single-use Carpuject® or vial; contains mannitol 38.2 mg/mL]; 20 mg/mL (5 mL) [single-use vial; contains mannitol 38.2 mg/mL]; 20 mg/mL (25 mL) [multidose vial; contains mannitol 29 mg/mL]

Tablet, as mesylate:

Anzemet®: 50 mg, 100 mg

Generic AvailableNo

ManufacturerSanofi-Aventis Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Anzemet)

50 mg (5): $272.90

100 mg (5): $355.44

Mechanism of ActionSelective serotonin receptor (5-HT$_3$) antagonist, blocking serotonin both peripherally (primary site of action) and centrally at the chemoreceptor trigger zone

Pharmacodynamics/Kinetics

Absorption: Rapid and complete

Distribution: Hydrodolasetron: 5.8 L/kg

Protein binding: Hydrodolasetron: 69% to 77% (50% bound to alpha$_1$-acid glycoprotein)

Metabolism: Hepatic; reduction by carbonyl reductase to hydrodolasetron (active metabolite); further metabolized by CYP2D6, CYP3A, and flavin monooxygenase

Bioavailability: 75%

Half-life elimination: Dolasetron: 10 minutes; hydrodolasetron: Adults: 6-8 hours; Children: 4-6 hours

Time to peak, plasma: Hydrodolasetron: I.V.: 0.6 hours; Oral: 1 hour

Excretion: Urine ~67% (53% to 61% as active metabolite hydrodolasetron); feces ~33%

Pharmacotherapy PearlsEfficacy of dolasetron, for chemotherapy treatment, is enhanced with concomitant administration of dexamethasone 20 mg (increases complete response by 10% to 20%). Oral administration of the intravenous solution is equivalent to tablets.

A single I.V. dose of dolasetron mesylate (1.8 or 2.4 mg/kg) has comparable safety and efficacy to a single 32 mg I.V. dose of ondansetron in patients receiving cisplatin chemotherapy.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste alterations.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsDolasetron is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness

Mental Health: Effects on Psychiatric TreatmentContraindicated with ziprasidone

Anesthesia and Critical Care Concerns/Other ConsiderationsOral administration of the intravenous solution is equivalent to tablets.

Index TermsDolasetron Mesylate; MDL 73,147EF

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International Brand NamesAnemet (DE, HN); Anzemet (AR, AT, AU, BG, BR, CH, FR, GB, IT, KP, MX, NL, PL, SE, VE)

Domperidone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(dom PE ri done)

Canadian Brand NamesApo-Domperidone®; Dom-Domperidone; Novo-Domperidone; Nu-Domperidone; PHL-Domperidone; PMS-Domperidone; RAN™-Domperidone; ratio-Domperidone

Pharmacologic CategoryDopamine Antagonist; Gastrointestinal Agent, Prokinetic

Use: Labeled IndicationsSymptomatic management of upper GI motility disorders associated with chronic and subacute gastritis and diabetic gastroparesis; prevention of GI symptoms associated with use of dopamine-agonist anti-Parkinson agents

Dosing: Adults

GI motility disorders: Oral: 10 mg 3-4 times/day, 15-30 minutes before meals

Severe/resistant cases: 20 mg 3-4 times/day, 15-30 minutes before meals

Nausea/vomiting associated with dopamine-agonist anti-Parkinson agents: Oral: 20 mg 3-4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentDecrease dose to 10-20 mg 1-2 times/day

Administration: OralIn GI motility disorders, administer 15-30 minutes prior to meals.

Dietary ConsiderationsIn GI motility disorders, should be taken 15-30 minutes prior to meals.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light and moisture.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to domperidone or any component of the formulation; patients with GI hemorrhage, mechanical obstruction, or perforation; patients with prolactin-releasing pituitary tumor

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: QT_c prolongation, life-threatening tachyarrhythmias, and cardiac arrest have been reported after use; these adverse effects may be precipitated in hypokalemic patients.
- Elevated prolactin levels: May increase prolactin levels (dose-dependent response); may be asymptomatic (clinical consequence of chronically-elevated prolactin is unknown) or may present symptomatically as galactorrhea, gynecomastia, amenorrhea, or impotence (reversible upon decreasing dose or discontinuing drug).

Disease-related concerns:

- Breast cancer: Use caution when administering to patients with a personal or family history of breast cancer.
- Hepatic impairment: Use with caution in patients with hepatic impairment.

Concurrent drug therapy issues:

- MAO inhibitors: Use with caution in patients concomitantly taking MAO inhibitors.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have not shown drug-related teratogenic or primary embryotoxic effects on animal fetuses, however, comparative studies have not been done in humans. Use only when benefit outweighs potential risk in a pregnant woman.

LactationEnters breast milk/not recommended (AAP rates as “compatible”)

Breast-Feeding ConsiderationsDomperidone is excreted in low concentrations in breast milk, therefore, caution should be exercised when administered to a breast-feeding woman. Use in a breast-feeding woman is not recommended by the manufacturer; AAP rates as “compatible.”

Adverse Reactions

1% to 10%:

Central nervous system: Headache/migraine (1%); does not cross blood-brain barrier; fewer CNS effects compared to metoclopramide

Gastrointestinal: Xerostomia (2%)

<1%: Abdominal cramps, constipation, diarrhea, dizziness, dysuria, edema, extrapyramidal symptoms (EPS) rarely, galactorrhea, gynecomastia, heartburn, hot flashes, insomnia, irritability, nervousness, thirst, lethargy, leg cramps, mastalgia, menstrual irregularities, nausea, palpitation, prolactin increased, pruritus, rash, regurgitation, stomatitis, urinary frequency, urticaria, weakness

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Monitoring ParametersAgitation, irritability, confusion, and rarely EPS

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet: 10 mg [domperidone maleate 12.72 mg; not available in the U.S.]

Alti-Domperidone [CAN], Apo-Domperidone® [CAN], Dom-Domperidone [CAN], Novo-Domperidone [CAN], Nu-Domperidone [CAN], PHL-Domperidone [CAN], PMS-Domperidone [CAN], ratio-Domperidone [CAN]: 10 mg [not available in the U.S.]

Generic AvailableYes

ManufacturerPharmascience Inc (Canada)

Mechanism of ActionDomperidone has peripheral dopamine receptor blocking properties. It increases esophageal peristalsis and increases lower esophageal sphincter pressure, increases gastric motility and peristalsis, and enhances gastroduodenal coordination, therefore, facilitating gastric emptying and decreasing small bowel transit time.

Pharmacodynamics/Kinetics

Protein binding: 93%

Metabolism: Hepatic via N-dealkylation (CYP3A4) and hydroxylation

Half-life elimination: 7 hours

Time to peak serum concentration: 30 minutes

Excretion: Feces (66%); urine (31%)

Pharmacotherapy PearlsNot available in U.S.

The Food and Drug Administration (FDA) has issued a warning concerning the off-label use of domperidone to increase milk production in breast-feeding women. Domperidone is not available for any use in the United States and does not have approval for this indication in other countries. However, the FDA is aware that women are obtaining domperidone from U.S. compounding pharmacies and foreign sources for this purpose. The FDA notes that there are health risks associated with the use of this product that is why it has been removed from marketing.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsDomperidone is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Index TermsDomperidone Maleate

References

da Silva OP, Knoppert DC, Angelini MM, et al, “Effect of Domperidone on Milk Production in Mothers of Premature Newborns: A Randomized, Double-Blind, Placebo-Controlled Trial,” *CMAJ*, 2001, 164(1):17-21. [PubMed 11202662]

Drolet B, Rousseau G, Daleau P, et al, “Domperidone Should Not be Considered a No-Risk Alternative to Cisapride in the Treatment of Gastrointestinal Motility Disorders,” *Circulation*, 2000, 102(16):1883-5. [PubMed 11034933]

“FDA Warns Against Women Using Unapproved Drug, Domperidone, to Increase Milk Production,” FDA Talk Paper T04-17, June 7, 2004, available at http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01292.html, last accessed February 8, 2005.

pms-Domperidone product monograph, Pharmascience Inc, Quebec, October 1997.

International Brand NamesAlmedon (PK); Bropasmo (PY); Cilroton (GR); Costi (HK, TW); Domerdon (TH); Domperine (KP); Dompil (KP); Domstal (IN); Dosin (CN); Ecuamon (AR); Euciton (AR); Galflux (ID); Gasdol (CN); Harmetone (CO); Idon (PY); Mirax (TH); Modomed (TH); Mogasinte (PT); Moperidona (AR); Motilium (AR, AT, AU, BE, BG, BR, CH, CL, CY, CZ, DE, DK, EE, FR, GB, HK, HN, HU, ID, IE, IL, IT, LU, MX, MY, NL, PE, PH, PK, PT, PY, SG, TW, ZA); Motilium M (KP); Motilium [tabs.] (PL); Motinorm (IN); Nauzelin (ES, JP); Netaf (PE); Nordonil (PT); Peptomet (CY); Peridon (IT); Peridys (FR); Perinal (KP); Rabugen (HK); Remotil (PT); Seronex (MX); Siligaz (CN); Tametil (HR); Tilidon (ID); Vometa (ID, PH); Vomitil (PK); Zidon-DT (IN); Zilium (BE)

Donepezil

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Aricept® may be confused with AcipHex®, Ascriptin®, and Azilect®

Pronunciation(doh NEP e zil)
U.S. Brand NamesAricept®; Aricept® ODT
Canadian Brand NamesAricept®; Aricept® RDT
Pharmacologic CategoryAcetylcholinesterase Inhibitor (Central)
Use: Labeled IndicationsTreatment of mild, moderate, or severe dementia of the Alzheimer's type
Use: Unlabeled/InvestigationalAttention-deficit/hyperactivity disorder (ADHD); behavioral syndromes in dementia; mild-to-moderate dementia associated with Parkinson's disease; Lewy body dementia
Dosing: AdultsAlzheimer's disease: Oral: Initial: 5 mg/day at bedtime; may increase to 10 mg/day at bedtime after 4-6 weeks.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricADHD (unlabeled use): Oral: 5 mg/day
Administration: OralAdminister at bedtime without regard to food.

Aricept® ODT: Allow tablet to dissolve completely on tongue and follow with water.

Dietary ConsiderationsMay take with or without food.
StorageStore at 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to donepezil, piperidine derivatives, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Diarrhea: May cause diarrhea which may be dose-related; usually resolves in 1-3 weeks.
- Nausea/vomiting: May cause nausea, and/or vomiting, which may be dose-related; usually resolves in 1-3 weeks.
- Vagotonic effects: Cholinesterase inhibitors may have vagotonic effects which may cause bradycardia and/or heart block with or without a history of cardiac disease; syncopal episodes have been associated with donepezil.

Disease-related concerns:

- Cardiac conduction abnormalities: Use with caution in patients with sick-sinus syndrome, bradycardia, or conduction abnormalities. Alzheimer's treatment guidelines consider bradycardia to be a relative contraindication for use of centrally-active cholinesterase inhibitors.
- Peptic ulcer disease: Use with caution in patients at risk of ulcer disease (eg, previous history or NSAID use); may increase gastric acid secretion. Monitor for symptoms of bleeding.
- Respiratory disease: Use with caution in patients with COPD and/or asthma.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.
- Urinary tract obstruction: Use with caution in patients with bladder outlet obstruction or prostatic hyperplasia; cholinomimetics may cause or worsen outflow obstructions, including possible exacerbation of BPH symptoms.

Concurrent drug therapy issues:

- Depolarizing neuromuscular-blocking agents: May exaggerate neuromuscular blockade effects of depolarizing neuromuscular-blocking agents like succinylcholine.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%:

Central nervous system: Insomnia (5% to 14%)

Gastrointestinal: Nausea (5% to 19%), diarrhea (8% to 15%)

Miscellaneous: Accident (7% to 13%), infection (11%)

1% to 10%:

Cardiovascular: Hypertension (3%), chest pain (2%), hemorrhage (2%), syncope (2%), hypotension, atrial fibrillation, bradycardia, ECG abnormal, edema, heart failure, hot flashes, peripheral edema, vasodilation

Central nervous system: Headache (4% to 10%), pain (3% to 9%), fatigue (3% to 8%), dizziness (2% to 8%), abnormal dreams (3%), depression (2% to 3%), hostility (3%), nervousness (3%), hallucinations (3%), confusion (2%), emotional lability (2%), personality disorder (2%), fever (2%), somnolence (2%), abnormal crying, aggression, agitation, anxiety, aphasia, delusions, irritability, restlessness, seizure

Dermatologic: Bruising (4% to 5%), eczema (3%), pruritus, rash, skin ulcer, urticaria

Endocrine & metabolic: Dehydration (2%), hyperlipemia (2%), libido increased

Gastrointestinal: Anorexia (3% to 8%), vomiting (3% to 8%), weight loss (3%), abdominal pain, constipation, dyspepsia, fecal incontinence, gastroenteritis, GI bleeding, bloating, epigastric pain, toothache

Genitourinary: Urinary frequency (2%), urinary incontinence (2%), hematuria, glycosuria, nocturia, UTI

Hematologic: Anemia

Hepatic: Alkaline phosphatase increased

Neuromuscular & skeletal: Muscle cramps (3% to 8%), back pain (3%), CPK increased (3%), arthritis (2%), ataxia, bone fracture, gait abnormal, lactate dehydrogenase increased, paresthesia, tremor, weakness

Ocular: Blurred vision, cataract, eye irritation

Respiratory: Cough increased, dyspnea, bronchitis, pharyngitis, pneumonia, sore throat

Miscellaneous: Diaphoresis, fungal infection, flu symptoms, wandering

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Abscess, breast fibroadenosis, cellulitis, cerebrovascular accident, CHF, cholecystitis, conjunctival hemorrhage, conjunctivitis, deep vein thrombosis, diabetes mellitus, diverticulitis, ear pain, eosinophilia, fibrocystic breast, gastrointestinal ulcer, glaucoma, goiter, heart block, hemolytic anemia, hepatitis, hostility, hyperglycemia, hypertonia, hypokalemia, hypokinesia, hyponatremia, hypoxia, intracranial hemorrhage, jaundice, LFTs increased, MI, neuroleptic malignant syndrome, pancreatitis, pleurisy, pulmonary collapse, pulmonary congestion, pyelonephritis, renal failure, retinal hemorrhage, SVT, thrombocythemia, thrombocytopenia, tongue edema, transient ischemic attack, vision abnormal

Metabolism/Transport Effects**Substrate** (minor) of CYP2D6, 3A4

Drug Interactions

Anticholinergics: May diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotics: Acetylcholinesterase Inhibitors (Central) may enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Beta-Blockers: Acetylcholinesterase Inhibitors may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Cholinergic Agonists: Acetylcholinesterase Inhibitors may enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Ginkgo Biloba: May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): Acetylcholinesterase Inhibitors may diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). Acetylcholinesterase Inhibitors may decrease the metabolism of Neuromuscular-Blocking Agents (Nondepolarizing). This is only true for mivacurium in which case the neuromuscular blocking effects might be prolonged. *Risk C: Monitor therapy*

Succinylcholine: Acetylcholinesterase Inhibitors may enhance the neuromuscular-blocking effect of Succinylcholine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease donepezil levels. Gingko biloba may increase adverse effects/toxicity of acetylcholinesterase inhibitors.

Monitoring ParametersBehavior, mood, bowel function, cognitive function, general function (eg, activities of daily living)

Nursing: Physical Assessment/MonitoringAssess bladder adequacy prior to administering medication. Assess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effect, and adverse reactions (eg, cholinergic crisis). Monitor pulse. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationThis medication will not cure the disease, but may help reduce symptoms. Use as directed; do not increase dose or discontinue without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause dizziness, sedation, or hypotension (rise slowly from sitting or lying position and use caution when driving or climbing stairs); vomiting or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea (boiled milk, yogurt, or buttermilk may help). Report persistent abdominal discomfort; significantly increased salivation, sweating, tearing, or urination; flushed skin; chest pain or palpitations; acute headache; unresolved diarrhea; excessive fatigue, insomnia, dizziness, or depression; increased muscle, joint, or body pain; vision changes or blurred vision; or shortness of breath or wheezing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride:

Aricept®: 5 mg, 10 mg

Tablet, orally disintegrating, as hydrochloride:

Aricept® ODT: 5 mg, 10 mg

Generic AvailableNo

ManufacturerPfizer U.S. Pharmaceuticals Group

Pricing: U.S. (www.drugstore.com)

Tablet, orally-disintegrating (Aricept ODT)

5 mg (30): $188.62

Tablets (Aricept)

5 mg (30): $169.99

10 mg (30): $169.99

Mechanism of ActionAlzheimer's disease is characterized by cholinergic deficiency in the cortex and basal forebrain, which contributes to cognitive deficits. Donepezil reversibly and noncompetitively inhibits centrally-active acetylcholinesterase, the enzyme responsible for hydrolysis of acetylcholine. This appears to result in increased concentrations of acetylcholine available for synaptic transmission in the central nervous system.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Protein binding: 96%, primarily to albumin (75%) and α_1-acid glycoprotein (21%)

Metabolism: Extensively to four major metabolites (two are active) via CYP2D6 and 3A4; undergoes glucuronidation

Bioavailability: 100%

Half-life elimination: 70 hours; time to steady-state: 15 days

Time to peak, plasma: 3-4 hours

Excretion: Urine 57% (17% as unchanged drug); feces 15%

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Child/Adolescent ConsiderationsFive children (8-17 years of age) with ADHD showed improvement when treated with donepezil (Wilens, 2000). Four of 8 patients with autism (mean age: 11 years of age; range: 7-19 years) showed significant improvement in behaviors in a retrospective pilot study (Hardan, 2002). A retrospective chart review case series of 8 individuals (10-17 years of age) with pervasive developmental disorder showed improvement in ADHD-like symptoms upon treatment with donepezil (Doyle, 2006). Mean treatment duration was 18 weeks and dosing ranged from 2.5-30 mg/day. However, a 12-week, open-label, adjunctive trial of donepezil (dose range: 2.5-10 mg/day) in 7 children and 6 adults with stimulant-stabilized ADHD showed no significant improvement in ADHD rating scale or Executive Function Checklist (Wilens, 2005).

An 18-week, prospective, open-label, dose-escalation study of donepezil (2.5 mg, 5 mg, 10 mg daily) in 20 patients 8-14 years of age with tics (including Tourette’s syndrome) and comorbid ADHD showed significant improvement of tics at the 10 mg dose (Cubo, 2008). No improvement of ADHD was evident and a large number (65%) experienced adverse events, including a 50% study dropout rate.

Cubo E, Fern Ndez Jaén A, Moreno C, et al, “Donepezil Use in Children and Adolescents With Tics and Attention-Deficit/Hyperactivity Disorder: An 18-Week, Single-Center, Dose-Escalating, Prospective, Open-Label Study,” *Clin Ther*, 2008, 30(1):182-9.

Doyle RL, Frazier J, Spencer TJ, et al, “Donepezil in the Treatment of ADHD-Like Symptoms in Youths With Pervasive Developmental Disorder: A Case Series,” *J Atten Disord*, 2006, 9(3):543-9.

Hardan AY and Handen BL, “A Retrospective Open Trial of Adjunctive Donepezil in Children and Adolescents With Autistic Disorder,” *J Child Adolesc Psychopharmacol*, 2002, 12(3): 237-41.

Wilens TE, Biederman J, Wong J, et al, “Adjunctive Donepezil in Attention Deficit Hyperactivity Disorder Youth: Case Series,” *J Child Adolesc Psychopharmacol*, 2000, 10(3):217-22.

Wilens TE, Waxmonsky J, Scott M, et al, “An Open Trial of Adjunctive Donepezil in Attention-Deficit/Hyperactivity Disorder,” *J Child Adolesc Psychopharmacol*, 2005, 15(6):947-55.

Mental Health CommentBe mindful of other medications (and their intrinsic anticholinergic activity) that an individual is receiving. The effects of donepezil may be completely mitigated. If tolerated, increase dosage from 5 mg/day to 10 mg/day after 4-6 weeks.

Index Terms E2020

References

Hardan AY and Handen BL, “A Retrospective Open Trial of Adjunctive Donepezil in Children and Adolescents With Autistic Disorder,” *J Child Adolesc Psychopharmacol*, 2002, 12(3):237-41. [PubMed 12427297]

Hoopes SP, “Donepezil for Tourette's Disorder and ADHD,” *J Clin Psychopharmacol*, 1999, 19(4):381-2. [PubMed 10440471]

Rabins PV, Blacker D, Rovner BW, et al, “Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias,” October, 2007. Available at http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm

Rogers SL and Friedhoff LT, “The Efficacy and Safety of Donepezil in Patients With Alzheimer's Disease: Results of a U.S. Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial,” *Dementia*, 1996, 7(6):293-303. [PubMed 8915035]

Wilens TE, Biederman J, Wong J, et al, “Adjunctive Donepezil in Attention Deficit Hyperactivity Disorder Youth: Case Series,” *J Child Adolesc Psychopharmacol*, 2000, 10(3):217-22.[PubMed 11052411]

International Brand Names Alzaimax (AR); Alzim (ID); Aricept (AE, AT, AU, BD, BE, BF, BG, BH, BJ, CH, CI, CL, CY, DE, DK, EE, EG, ES, ET, FI, FR, GB, GH, GM, GN, HK, HN, HU, ID, IE, IL, IN, IQ, IR, IT, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NO, OM, PH, PK, PL, PT, QA, SA, SC, SD, SE, SG, SL, SN, SY, TH, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Aricept-D (NZ); Asenta (IL); Donaz (IN); Eranz (AR, BR, CN, CO, CR, GT, HN, MX, NI, PA, SV, VE); Fordesia (ID); Memorit (IL); Piridon (UY); Yasnal (PL)

DOPamine

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

DOPamine may be confused with DOBUTamine, Dopram®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(DOE pa meen)

Pharmacologic CategoryAdrenergic Agonist Agent

Use: Labeled IndicationsAdjunct in the treatment of shock (eg, MI, open heart surgery, renal failure, cardiac decompensation) which persists after adequate fluid volume replacement

Use: Unlabeled/InvestigationalSymptomatic bradycardia or heart block unresponsive to atropine or pacing

Dosing: Adults

Hemodynamic support: I.V. infusion: 1-5 mcg/kg/minute up to 50 mcg/kg/minute, titrate to desired response; infusion may be increased by 1-4 mcg/kg/minute at 10- to 30-minute intervals until optimal response is obtained

Note: If dosages >20-30 mcg/kg/minute are needed, a more direct-acting vasopressor may be more beneficial (ie, epinephrine, norepinephrine).

Hemodynamic effects of dopamine are dose dependent:

Low-dose: 1-5 mcg/kg/minute, increased renal blood flow and urine output

Intermediate-dose: 5-15 mcg/kg/minute, increased renal blood flow, heart rate, cardiac contractility, and cardiac output

High-dose: >15 mcg/kg/minute, alpha-adrenergic effects begin to predominate, vasoconstriction, increased blood pressure

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricHemodynamic support: I.V. infusion:

Children: 1-20 mcg/kg/minute, maximum: 50 mcg/kg/minute continuous infusion, titrate to desired response.

Calculations

- Dopamine

Administration: I.V.Vesicant. **Must be diluted prior to use**. Do not discontinue suddenly - sudden discontinuation may lead to marked hypotension.

Administration: I.V. DetailMonitor continuously for free flow. Administration into an umbilical arterial catheter is not recommended; central line administration.

Extravasation management: Due to short half-life, withdrawal of drug is often only necessary treatment. Use phentolamine as antidote. Mix 5 mg with 9 mL of NS; inject a small amount of this dilution into extravasated area. Blanching should reverse immediately. Monitor site. If blanching should recur, additional injections of phentolamine may be needed.

pH: 3.3-3.6

StorageProtect from light. Solutions that are darker than slightly yellow should not be used.

CompatibilityStable in D_5LR, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, mannitol 20%, NS; **incompatible** with sodium bicarbonate 5%, and alkaline solutions or iron salts.

Y-site administration: Compatible: Alatrofloxacin, aldesleukin, amifostine, amiodarone, atracurium, aztreonam, cefpirome, ciprofloxacin, cisatracurium, cladribine, clarithromycin, diltiazem, dobutamine, dobutamine with lidocaine, dobutamine with nitroglycerin, dobutamine with sodium nitroprusside, docetaxel, doxorubicin liposome, enalaprilat, epinephrine, esmolol, etoposide, famotidine, fentanyl, fluconazole, foscarnet, gatifloxacin, gemcitabine, granisetron, haloperidol, heparin, hydrocortisone sodium succinate, hydromorphone, inamrinone, labetalol, levofloxacin, lidocaine, lidocaine with nitroglycerin, lidocaine with sodium nitroprusside, linezolid, lorazepam, meperidine, methylprednisolone sodium succinate, metronidazole, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroglycerin with sodium nitroprusside, norepinephrine, ondansetron, pancuronium, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, sargramostim, sodium nitroprusside, streptokinase, tacrolimus, theophylline, thiotepa, tirofiban, tolazoline, vecuronium, verapamil, vitamin B complex with C, warfarin, zidovudine. **Incompatible:** Acyclovir, alteplase, amphotericin B cholesteryl sulfate complex, cefepime, indomethacin, insulin (regular), thiopental. **Variable (consult detailed reference):** Furosemide, TPN.

Compatibility in syringe: Compatible: Doxapram, heparin, ranitidine.

Compatibility when admixed: Compatible: Aminophylline, atracurium, bretylium, calcium chloride, chloramphenicol, dobutamine, enalaprilat, flumazenil, heparin, hydrocortisone sodium succinate, kanamycin, lidocaine, meropenem, methylprednisolone sodium succinate, nitroglycerin, oxacillin, potassium chloride, propafenone, ranitidine, verapamil. **Incompatible:** Acyclovir, alteplase, amphotericin B, ampicillin, metronidazole with sodium bicarbonate, penicillin G potassium. **Variable (consult detailed reference):** Gentamicin.

Contraindications Hypersensitivity to sulfites (commercial preparation contains sodium bisulfite); pheochromocytoma; ventricular fibrillation

Warnings/Precautions

Boxed warnings:

- Extravasation: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Arrhythmias: May cause increases in arrhythmias.
- Tachycardia: May cause increases in heart rate.
- Tissue necrosis: Avoid infiltration - may cause severe tissue necrosis.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease, cardiac arrhythmias and/or occlusive vascular disease.
- Myocardial infarct (post): Use with caution in patients post-MI.

Concurrent drug therapy issues:

- Monoamine oxidase inhibitors (MAO-I): Use with extreme caution in patients taking MAO inhibitors; prolong hypertension may result from concurrent use.

Dosage form specific issues:

- Sodium metabisulfite: Product may contain sodium metabisulfite.

Other warnings/precautions:

- Appropriate use: Assure adequate circulatory volume to minimize need for vasoconstrictors. Avoid hypertension; monitor blood pressure closely and adjust infusion rate.
- Extravasation: Avoid extravasation; infuse into a large vein if possible. Avoid infusion into leg veins. Watch I.V. site closely. **[U.S. Boxed Warning]: If extravasation occurs, infiltrate the area with diluted phentolamine (5-10 mg in 10-15 mL of saline) with a fine hypodermic needle. Phentolamine should be administered as soon as possible after extravasation is noted.**

Geriatric Considerations Has not been specifically studied in the elderly; monitor closely, especially due to increase in cardiovascular disease with age.

Pregnancy Risk Factor C

Lactation Excretion in breast milk unknown

Adverse Reactions Frequency not defined.

Most frequent:

Cardiovascular: Ectopic beats, tachycardia, anginal pain, palpitation, hypotension, vasoconstriction

Central nervous system: Headache

Gastrointestinal: Nausea and vomiting

Respiratory: Dyspnea

Infrequent:

Cardiovascular: Aberrant conduction, bradycardia, widened QRS complex, ventricular arrhythmia (high dose), gangrene (high dose), hypertension

Central nervous system: Anxiety

Endocrine & metabolic: Piloerection, serum glucose increased (usually not above normal limits)

Local: Extravasation of dopamine can cause tissue necrosis and sloughing of surrounding tissues

Ocular: Intraocular pressure increased, dilated pupils

Renal: Azotemia, polyuria

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

COMT Inhibitors: May decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure, ECG, heart rate, CVP, RAP, MAP, urine output; if pulmonary artery catheter is in place, monitor CI, PCWP, SVR, and PVR

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Infusion pump, continuous cardiac and hemodynamic monitoring, and frequent assessment of I.V. site is required for inpatient therapy. Low-dose home infusion therapy requires frequent monitoring of cardiac and renal status and adverse reactions. Monitor therapeutic effectiveness and adverse reactions. Instruct patient on adverse symptoms to report.

Monitoring: Lab TestsSerum glucose, renal function

Patient EducationWhen administered in emergencies, patient education should be appropriate to the situation. If patient is aware, instruct to promptly report chest pain, palpitations, rapid heartbeat, headache, nervousness or restlessness, nausea or vomiting, or respiratory difficulty.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion, as hydrochloride [premixed in D_5W]: 0.8 mg/mL (250 mL, 500 mL); 1.6 mg/mL (250 mL, 500 mL); 3.2 mg/mL (250 mL)

Injection, solution, as hydrochloride: 40 mg/mL (5 mL, 10 mL); 80 mg/mL (5 mL); 160 mg/mL (5 mL) [contains sodium metabisulfite]

Generic AvailableYes

Mechanism of ActionStimulates both adrenergic and dopaminergic receptors, lower doses are mainly dopaminergic stimulating and produce renal and mesenteric vasodilation, higher doses also are both dopaminergic and beta$_1$-adrenergic stimulating and produce cardiac stimulation and renal vasodilation; large doses stimulate alpha-adrenergic receptors

Pharmacodynamics/Kinetics

Children: Dopamine has exhibited nonlinear kinetics in children; with medication changes, may not achieve steady-state for ~1 hour rather than 20 minutes

Onset of action: Adults: 5 minutes

Duration: Adults: <10 minutes

Metabolism: Renal, hepatic, plasma; 75% to inactive metabolites by monoamine oxidase and 25% to norepinephrine

Half-life elimination: 2 minutes

Excretion: Urine (as metabolites)

Clearance: Neonates: Varies and appears to be age related; clearance is more prolonged with combined hepatic and renal dysfunction

Related Information

- Hemodynamic Support, Intravenous

Pharmacotherapy PearlsDopamine is most frequently used for treatment of hypotension because of its peripheral vasoconstrictor action. In this regard, dopamine is often used together with dobutamine and minimizes hypotension secondary to dobutamine-induced vasodilation. Thus, pressure is maintained by increased cardiac output (from dobutamine) and vasoconstriction (by dopamine). It is critical neither dopamine nor dobutamine be used in patients in the absence of correcting any hypovolemia as a cause of hypotension.

Low-dose dopamine is often used in the intensive care setting for presumed beneficial effects on renal function. However, there is no clear evidence that low-dose dopamine confers any renal or other benefit. Indeed, dopamine may act on dopamine receptors in the carotid bodies causing chemoreflex suppression. In patients with heart failure, dopamine may inhibit breathing and cause pulmonary shunting. Both these mechanisms would act to decrease minute ventilation and oxygen saturation. This could potentially be deleterious in patients with respiratory compromise and patients being weaned from ventilators.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentDopamine's effects may be enhanced by MAO inhibitors

Cardiovascular ConsiderationsDopamine is most frequently used for treatment of hypotension because of its peripheral vasoconstrictor action. In this regard, dopamine is often used together with dobutamine and minimizes hypotension secondary to dobutamine-induced vasodilation. Thus, pressure is maintained by increased cardiac output (from dobutamine) and vasoconstriction (by dopamine). It is critical neither dopamine nor dobutamine be used in patients in the absence of correcting any hypovolemia as a cause of hypotension.

Low-dose dopamine is often used in the intensive care setting for presumed beneficial effects on renal function. However, there is no clear evidence that low-dose dopamine confers any renal or other benefit. Indeed, dopamine may act on dopamine receptors in the carotid bodies causing chemoreflex suppression. In patients with heart failure, dopamine may inhibit breathing and cause pulmonary shunting. Both these mechanisms would act to decrease minute ventilation and oxygen saturation. This could potentially be deleterious in patients with respiratory compromise and patients being weaned from ventilators.

Anesthesia and Critical Care Concerns/Other Considerations

Low-Dose Dopamine: There is no clear evidence that low-dose dopamine confers any renal benefit. The 2004 ACCM/SCCM Practice Parameters for Hemodynamic Support of Sepsis in Adult Patients recommends against the use of low doses of dopamine to maintain renal function. Low-dose dopamine may increase renal blood flow in some patients requiring norepinephrine. Kellum and Decker (2001) reviewed 58 studies in a meta-analysis focused on determining if low-dose dopamine reduced the severity of acute renal failure, the need for dialysis, or mortality in critically-ill patients. They concluded that the use of low-dose dopamine for the treatment or prevention of acute renal failure cannot be justified. A more recent randomized, double-blind, placebo-controlled trial came to a similar conclusion (Australian and New Zealand Intensive Care Society Clinical Trials Group, 2000). This study enrolled over 300 ICU patients with clinical evidence of renal dysfunction. They were randomized to low-dose dopamine (2 mcg/kg/minute) or placebo. The investigators found no difference in serum creatinine, renal replacement therapy, intensive care length of stay, hospital stay, or mortality between the groups. The 2008 Surviving Sepsis Campaign guidelines also recommend against the use of low-dose dopamine for renal protection (Grade 1A).

Septic Shock: In septic shock, dopamine is effective in increasing mean arterial pressure in patients who remain hypotensive after adequate volume expansion. Undesirable effects include tachycardia, increased pulmonary shunt, and decreased P_aO_2. As catecholamine stores are depleted, tachyphylaxis may occur. The 2004 ACCM/SCCM Practice Parameters for Hemodynamic Support of Sepsis in Adult Patients recommend either norepinephrine or dopamine as vasopressor therapy. Norepinephrine has a wider dosage range than dopamine.

The 2008 Surviving Sepsis Campaign guidelines recommend using either norepinephrine or dopamine as the first-choice vasopressor agent in adult patients (Grade 1C). Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in septic shock. In pediatric patients with hypotension refractory to fluid resuscitation, the Surviving Sepsis Campaign guidelines suggest dopamine as the first choice of support (Grade 2C).

Index TermsDopamine Hydrochloride; Intropin

References

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International Brand NamesCardiofast (PH); Cardiopal (CO); Catabon (JP); Cetadop (ID); Cordodopa Forte (PT); Docard (IL, PH); Dopacris (BR); Dopamex (TH); Dopamin (BG, CH, NO, PL); Dopamin AWD (HN); Dopamin Giulini (HU, LU); Dopamin Guilini (AT, DE, ID); Dopamin Natterman (BG); Dopamina (ES); Dopamine (FR, NL); Dopamine Injection (AU); Dopamine Pierre Fabre (LU); Dopaminex (TH); Dopaminum Hydrochloricum (PL); Dopavate (TW); Dopinga (IN); Dopmin (CZ, DK, EE, FI, MY, PL, TR); Dopmin E (RU); Drynalken (MX); Dynatra (BE, LU); Dynos (ZA); Giludop (DK, SE, TR); Inopin (TH); Inotropin (AR); Inovan (JP); Intropin (GB, IE, PE, PH, TW, UY, ZA); Intropin IV (MY); Medopa (PT); Myocard (PH); Pre Dopa (JP); Revivan (IT); Tropin (KP, PK); Uramin (TW)

Doripenem

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(dore i PEN em)

U.S. Brand NamesDoribax™

Pharmacologic Category[Antibiotic, Carbapenem]

Use: Labeled IndicationsTreatment of complicated intra-abdominal infections and complicated urinary tract infections (including pyelonephritis) due to susceptible gram-positive, gram-negative (including *Pseudomonas aeruginosa*), and anaerobic bacteria

Use: Unlabeled/InvestigationalTreatment of nosocomial pneumonia

Dosing: Adults

Intra-abdominal infection (complicated): I.V.: 500 mg every 8 hours for 5-14 days

Urinary tract infection (complicated) or pyelonephritis: I.V.: 500 mg every 8 hours for 10-14 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 30-50 mL/minute: 250 mg every 8 hours

Cl_{cr} 11-29 mL/minute: 250 mg every 12 hours

Hemodialysis: Dialyzable (~52% of dose removed during 4-hour session in ESRD patients)

Calculations

- Creatinine Clearance: Adults

Administration: I.V.Infuse over 1 hour

StorageStore dry powder vials at 15°C to 30°C (59°F to 86°F). Stability of solution (concentration: 4.5 mg/mL) when diluted in NS is 8 hours at room temperature or 24 hours under refrigeration; stability in D_5W is 4 hours at room temperature and 24 hours under refrigeration.

ReconstitutionReconstitute 500 mg vial with 10 mL of SWFI or NS. Shake gently until clear. Further dilute for infusion with 100 mL of NS or D_5W. Reconstituted vial may be stored for up to 1 hour prior to preparation of infusion solution.

Renal impairment: For preparation of a 250 mg dose in renal impairment, reconstitute 500 mg vial with 10 mL of SWFI or NS and further dilute with 100 mL of compatible solution as above, but remove and discard 55 mL from the infusion bag to leave the remaining solution containing the 250 mg dose (concentration: 4.5 mg/mL).

ContraindicationsKnown serious hypersensitivity to doripenem or other carbapenems (eg, imipenem, ertapenem, meropenem); anaphylactic reactions to beta-lactam antibiotics

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Serious hypersensitivity reactions, including anaphylaxis, and skin reactions have been reported in patients receiving beta-lactams.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required in patients with moderate-to-severe renal dysfunction.

Concurrent drug therapy issues:

- Valproic acid: Levels of valproic acid may be decreased to subtherapeutic levels during concomitant use, increasing potential for breakthrough seizures.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

Other warnings/precautions:

- Appropriate use: Administer via intravenous infusion only. Per manufacturer's labeling, investigational experience of doripenem via inhalation resulted in pneumonitis.

Geriatric ConsiderationsCareful attention to dose adjustment based on renal function, as well as monitoring renal function during treatment is recommended. According to the manufacturer, 28% of clinical trial patients were ≥65 years and 12% were ≥75 years, with no differences in overall age-related safety findings.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, the manufacturer classifies doripenem as pregnancy category B. There are no adequate and well-controlled studies completed in pregnant women.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if doripenem is excreted into breast milk. The manufacturer recommends that caution be exercised when administering doripenem to nursing women.

Pregnancy & Lactation, In-Depth

- Doripenem in Pregnancy & Lactation

Adverse Reactions

>10%:

Central nervous system: Headache (4% to 16%)

Gastrointestinal: Nausea (4% to 12%), diarrhea (6% to 11%)

1% to 10%:

Dermatologic: Rash (1% to 5%; includes allergic/bullous dermatitis, erythema, macular/papular eruptions, urticaria, and erythema multiforme), pruritus (≤3%)

Gastrointestinal: Oral candidiasis (1%)

Hematologic: Anemia (2% to 10%)

Hepatic: Transaminases increased (1% to 2%)

Local: Phlebitis (4% to 8%)

Renal: Renal impairment/failure (≤1%)

Miscellaneous: Vulvomycotic infection (1% to 2%)

Postmarketing and/or case reports: Anaphylaxis, interstitial pneumonia, Stevens-Johnson syndrome, seizure, toxic epidermal necrolysis

Drug Interactions

Probenecid: May increase the serum concentration of Doripenem. This effect is due to probenecid's ability to decrease the active tubular secretion of doripenem. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Carbapenems. Management: Avoid concomitant use of doripenem and probenecid. *Risk C: Monitor therapy*

Valproic Acid: Carbapenems may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Monitoring ParametersMonitor for signs of anaphylaxis during first dose; periodic renal assessment; consider hematologic monitoring during prolonged therapy

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient history of previous allergies or adverse drug reactions. Use caution in presence of renal impairment. Assess all other pharmacological or herbal products patient may be taking for potential adverse interactions. Patient must be monitored closely for adverse reactions, especially anaphylaxis or skin reactions. Teach patient interventions to reduce side effects and adverse symptoms to report.

Monitoring: Lab TestsPeriodic renal assessment; consider hematologic monitoring during prolonged therapy

Patient EducationThis medication can only be administered intravenously. Report warmth, swelling, or irritation at infusion site; difficulty breathing; facial swelling; or acute anxiety. Maintain adequate nutrition and hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Report prolonged GI effects (diarrhea, nausea); unusual skin rash; excessive or persistent fatigue or weakness; or other persistent adverse effects. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Doribax™: 500 mg

Generic AvailableNo

ManufacturerJohnson and Johnson

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to several of the penicillin-binding proteins, which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis; bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Distribution: V_d: 16.8 L

Protein binding: 8% to 9%

Metabolism: Non-CYP-mediated metabolism via dehydropeptidase-I to doripenem-M1 (inactive metabolite)

Half-life elimination: ~1 hour

Excretion: Urine (70% as unchanged drug; 15% as doripenem-M1 metabolite); feces (<1%)

Dental Health: Effects on Dental TreatmentProlonged use of doripenem may lead to development of oral candidiasis.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with SSRIs, carbamazepine, valproic acid, and lithium may produce additive effects. Doripenem may decrease valproic acid levels resulting in breakthrough seizures.
Index TermsS-4661
References

Doribax™ prescribing information, Ortho-McNeil Pharmaceutical, Inc, Raritan, NJ, October 2007.

English English

Jump To Field (Select Field Name)

Pronunciation(DOOR nase AL fa)
U.S. Brand NamesPulmozyme®
Canadian Brand NamesPulmozyme®
Pharmacologic CategoryEnzyme
Use: Labeled IndicationsManagement of cystic fibrosis patients to reduce the frequency of respiratory infections that require parenteral antibiotics in patients with FVC ≥40% of predicted; in conjunction with standard therapies, to improve pulmonary function in patients with cystic fibrosis
Dosing: AdultsMucolytic: Inhalation: 2.5 mg once daily through selected nebulizers
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Mucolytic (cystic fibrosis): Inhalation:

Children ≥3 months: 2.5 mg once daily through selected nebulizers; experience in children <5 years is limited

Note: Patients unable to inhale or exhale orally throughout the entire treatment period may use Pari-Baby™ nebulizer. Some patients may benefit from twice daily administration.

StorageMust be stored in the refrigerator at 2°C to 8°C (36°F to 46°F) and protected from strong light.
CompatibilityShould not be diluted or mixed with any other drugs in the nebulizer; this may inactivate the dornase alfa.
ContraindicationsHypersensitivity to dornase alfa, Chinese hamster ovary cell products, or any component of the formulation
Warnings/Precautions

Disease-related concerns:

- Decreased pulmonary function: In patients with pulmonary function <40% of normal, dornase alfa does not significantly reduce the risk of respiratory infections that require parenteral antibiotics.

Special populations:

- Pediatrics: Safety studies included children ≥3 months, however experience is limited in children <5 years of age.

Other warnings/precautions:

- Prolonged therapy: Safety and efficacy have not been established for daily administration >12 months.

Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsMeasurable amounts would not be expected in breast milk following inhalation; however, it is not known if dornase alfa is excreted in human milk.
Adverse ReactionsAdverse events were similar in children using the PARI BABY™ nebulizer (facemask as opposed to mouthpiece) with the addition of cough (45% in children 3 months to <5 years; 30% in children 5 to ≤10 years).

>10%:

Cardiovascular: Chest pain (18% to 25%)

Central nervous system: Fever (32% in patients with FVC <40%)

Dermatologic: Rash (3% to 12%)

Respiratory: Pharyngitis (32% to 40%), rhinitis (30% in patients with FVC <40%); FVC decrease ≥10% of predicted (22% in patients with FVC <40%), dyspnea (17% in patients with FVC <40%)

Miscellaneous: Voice alteration (12% to 18%)

1% to 10%:

Gastrointestinal: Dyspepsia (≤3%)

Ocular: Conjunctivitis (1% to 5%)

Respiratory: Laryngitis (3% to 4%)

Miscellaneous: Dornase alfa serum antibodies (2% to 4%)

Postmarketing and/or case reports: Headache, urticaria

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringAssess effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Teach patient or caregiver appropriate use of nebulizer, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationInform prescriber of any allergies you have. Use exactly as directed by prescriber (see following administration information). Report any signs of adverse response, skin rash, sore throat, respiratory difficulty, wheezing, or cough. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Self-administered nebulizer: Store in refrigerator, away from light. Do not combine with any other medications in the nebulizer. Wash hands before and after treatment. Wash and dry nebulizer after each treatment. Twist open the top of one unit dose vial and squeeze contents into nebulizer reservoir. Connect nebulizer reservoir to the mouthpiece or face mask. Connect nebulizer to compressor. Sit in comfortable, upright position. Put on face mask and turn on compressor. Avoid leakage around the mask to avoid mist getting into eyes. Breathe calmly and deeply until no more mist is formed in nebulizer (about 5 minutes). At this point treatment is finished.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution for nebulization [preservative free]:

Pulmozyme®: 1 mg/mL (2.5 mL) [derived from Chinese hamster cells]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Pulmozyme)

1 mg/mL (75): $1785.65

Mechanism of ActionThe hallmark of cystic fibrosis lung disease is the presence of abundant, purulent airway secretions composed primarily of highly polymerized DNA. The principal source of this DNA is the nuclei of degenerating neutrophils, which is present in large concentrations in infected lung secretions. The presence of this DNA produces a viscous mucous that may contribute to the decreased mucociliary transport and persistent infections that are commonly seen in this population. Dornase alfa is a deoxyribonuclease (DNA) enzyme produced by recombinant gene technology. Dornase selectively cleaves DNA, thus reducing mucous viscosity and as a result, airflow in the lung is improved and the risk of bacterial infection may be decreased.

Pharmacodynamics/Kinetics

Onset of action: Nebulization: Enzyme levels are measured in sputum in ~15 minutes

Duration: Rapidly declines

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pharyngitis

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsRecombinant Human Deoxyribonuclease; rhDNase

References

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International Brand NamesPulmozyme (AR, AT, AU, BB, BE, BG, BM, BR, BS, BZ, CH, CO, CZ, DE, DK, ES, FI, FR, GB, GR, GY, HN, HU, IE, IL, IT, JM, LU, MX, NL, NO, PL, PT, RU, SE, SR, TR, TT)

Dorzolamide and Timolol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(dor ZOLE a mide & TYE moe lole)
U.S. Brand NamesCosopt®
Canadian Brand NamesCosopt®; Preservative-Free Cosopt®
Pharmacologic CategoryBeta Blocker, Nonselective; Carbonic Anhydrase Inhibitor; Ophthalmic Agent, Antiglaucoma
Use: Labeled IndicationsTreatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma
Dosing: Adults**Reduction of intraocular pressure:** Ophthalmic: Instill 1 drop in affected eye(s) twice daily
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Reduction of intraocular pressure: Ophthalmic: Children ≥2 years: Refer to adult dosing.

Administration: OtherIf using additional topical ophthalmic preparations, separate administration by at least 10 minutes. Remove contact lens prior to administration and wait 15 minutes before reinserting. Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Ocular solutions can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may occur from using contaminated solutions.
StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light.
ContraindicationsHypersensitivity to dorzolamide, timolol, or any component of the formulation; sinus bradycardia, heart block greater than first degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; uncompensated cardiac failure; bronchospastic disease or asthma; history of bronchial asthma; severe COPD. Also see individual agents.
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

- Bacterial keratitis: Inadvertent contamination of multiple-dose ophthalmic solutions has caused bacterial keratitis.

- Ocular effects: Local ocular adverse effects (conjunctivitis and lid reactions) were reported with chronic administration; many resolved upon discontinuation of drug therapy. Choroidal detachment has been reported after filtration procedures. Patients with low endothelial cell counts may have increased risk for corneal edema; use caution.

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is not specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

- Systemic effects: Systemic absorption and adverse effects (similar to sulfonamides) including blood dyscrasias, Stevens-Johnson syndrome, toxic epidermal necrolysis, and fulminant hepatic necrosis may occur with ophthalmic use. Bradycardia and/or hypotension may also occur due to beta-blockade.

Disease-related concerns:

- Angle-closure glaucoma: Appropriate use: Should not be used alone in angle-closure glaucoma (has no effect on pupillary constriction).

- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.

- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.

- Heart failure (HF): Use with caution in patients with compensated heart failure and monitor for a worsening of the condition.

- Hepatic impairment: Use with caution in patients with hepatic impairment; not evaluated.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; may worsen disease or other myasthenic symptoms (diplopia, ptosis).

- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).

- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

- Renal impairment: Use with caution in patients with renal impairment; not recommended with severe impairment (Cl_{cr} <30 mL/minute).

- Respiratory disease: In general, patients with mild-to-moderate COPD or bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.

- Thyroid disease: Signs of hyperthyroidism (eg, tachycardia) may be masked by beta-blockers. Avoid abrupt withdrawal if thyrotoxicosis is suspected (may precipitate thyroid storm).

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents which decrease myocardial function.
- Calcium channel blockers: Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur.
- Oral carbonic anhydrase inhibitors: Concurrent use with oral carbonic anhydrase inhibitors is not recommended.

Special populations:

- Contact lens wearers: Some products may contain benzalkonium chloride which may be absorbed by soft contact lenses; remove lens prior to administration and wait 15 minutes before reinserting.
- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.

Also see individual agents.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women with the combination product. Use only if benefit outweighs risk. See individual agents.

LactationExcreted in breast milk (timolol)/not recommended

Breast-Feeding ConsiderationsTimolol is excreted in breast milk following oral and ophthalmic administration, and is considered compatible by the AAP. However, it is unknown whether dorzolamide is also excreted. Therefore, use of the combination product during lactation cannot be recommended at this time.

Adverse ReactionsPercentages as reported with combination product. Also see individual agents.

>5%:

Gastrointestinal: Taste perversion (≤30%)

Ocular: Burning/stinging (≤30%), blurred vision (5% to 15%), conjunctival hyperemia (5% to 15%), itching (5% to 15%), superficial punctuate keratitis (5% to 15%)

1% to 5%:

Cardiovascular: Hypertension

Central nervous system: Dizziness, headache

Gastrointestinal: Abdominal pain, dyspepsia, nausea

Genitourinary: Urinary tract infection

Neuromuscular & skeletal: Back pain

Ocular: Blepharitis, cloudy vision, conjunctival discharge, conjunctival edema, conjunctival follicles, conjunctivitis, corneal erosion, corneal staining, cortical lens opacity, dryness, eye debris, eye/eyelid discharge, eye/eyelid pain, eyelid edema, eyelid erythema, eyelid exudate/scales, foreign body sensation, glaucomatous cupping, lens nucleus discoloration, lens opacity, post-subcapsular cataract, tearing, visual field defect, vitreous detachment

Respiratory: Bronchitis, cough, pharyngitis, sinusitis, upper respiratory infection

Miscellaneous: Flu

<1%, postmarketing, and/or case reports: Bradycardia, cardiac failure, cerebral vascular accident, chest pain, choroidal detachment (following filtration procedures), depression, diarrhea, dyspnea, heart block, hypotension, iridocyclitis, MI, nasal congestion, paresthesia, photophobia, respiratory failure, skin rash, urolithiasis, vomiting, xerostomia

Metabolism/Transport Effects

Dorzolamide: **Substrate** (minor) of CYP2C8/9, 3A4

Timolol: **Substrate** of CYP2D6 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Memantine: Carbonic Anhydrase Inhibitors may decrease the excretion of Memantine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Monitoring ParametersOphthalmic exams and IOP periodically

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, ophthalmic: Dorzolamide hydrochloride 2% (as base) and timolol maleate 0.5% (as base) (10 mL)

Cosopt®: Dorzolamide hydrochloride 2% (as base) and timolol maleate 0.5% (as base) (5 mL [DSC]; 10 mL) [contains benzalkonium chloride]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Cosopt)

2-0.5% (5): $58.99

2-0.5% (10): $123.89

Mechanism of Action

Dorzolamide: Inhibits carbonic anhydrase in the ciliary processes of the eye resulting decreased bicarbonate ion formation which decreases sodium and fluid transport, thus decreasing aqueous humor secretion and reduces intraocular pressure.

Timolol: Blocks both beta$_1$- and beta$_2$-adrenergic receptors, reduces intraocular pressure by reducing aqueous humor production or possibly outflow

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, or fatigue; may rarely cause anxiety, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may decrease the effects of beta-blockers

Index TermsTimolol and Dorzolamide

References

Lang DM, “Anaphylactoid and Anaphylactic Reactions. Hazards of Beta-Blockers,” *Drug Saf*, 1995, 12(5):299-304.[PubMed 7669259]

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand NamesCosopt (AR, AU, BE, BR, CH, CN, CO, DK, EC, ES, FI, FR, HK, HN, IL, IT, KP, MX, MY, NL, PH, PK, SE, SG, TH, TW, UY, VE); Dorzoflax (PY); Timpilo (AU, BE, CH, CZ, DE, DK, FR, GR, HN, NL, RU, SE)

Dorzolamide

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English English

Jump To Field (Select Field Name)

Pronunciation(dor ZOLE a mide)
U.S. Brand NamesTrusopt®
Canadian Brand NamesTrusopt®
Pharmacologic CategoryCarbonic Anhydrase Inhibitor; Ophthalmic Agent, Antiglaucoma
Use: Labeled IndicationsTreatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma
Dosing: AdultsReduction of intraocular pressure: Ophthalmic: Instill 1 drop in the affected eye(s) 3 times/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Administration: OtherIf more than one topical ophthalmic drug is being used, administer the drugs at least 10 minutes apart. Remove contact lens prior to administration and wait 15 minutes before reinserting. Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Ocular solutions can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may occur from using contaminated solutions.
StorageStore at room temperature 15°C to 30°C (59°F to 86°F). Protect from light.
ContraindicationsHypersensitivity to dorzolamide or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Bacterial keratitis: Inadvertent contamination of multiple-dose ophthalmic solutions, has caused bacterial keratitis.

- Ocular effects: Local ocular adverse effects (conjunctivitis and lid reactions) were reported with chronic administration; many resolved upon discontinuation of drug therapy. Choroidal detachment has been reported after filtration procedures. Patients with low endothelial cell counts may have increased risk for corneal edema; use caution.

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is not specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

- Systemic effects: Systemic absorption and adverse effects (similar to sulfonamides) including, blood dyscrasias, Stevens-Johnson syndrome, toxic epidermal necrolysis, and fulminant hepatic necrosis may occur with ophthalmic use.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; not evaluated.

- Renal impairment: Use with caution in patients with renal impairment; not recommended with severe impairment (Cl_{cr} <30 mL/minute).

Concurrent drug therapy issues:

- Oral carbonic anhydrase inhibitors: Concurrent use with oral carbonic anhydrase inhibitors is not recommended.

Special populations:

- Contact lens wearers: Product contains benzalkonium chloride which may be absorbed by soft contact lenses; remove lens prior to administration and wait 15 minutes before reinserting.

Geriatric ConsiderationsThe oral carbonic anhydrase inhibitors are useful for patients who have difficulty administering ophthalmic drops, who do not achieve sufficient lowering of IOP, or who cannot tolerate other agents. Dorzolamide is an important addition that may be useful in the latter two groups, but with better tolerance than its oral counterpart.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%:

Gastrointestinal: Bitter taste following administration (25%)

Ocular: Burning, stinging or discomfort immediately following administration (33%); superficial punctate keratitis (10% to 15%); signs and symptoms of ocular allergic reaction (10%)

1% to 5%: Ocular: Blurred vision, conjunctivitis, dryness, lid reactions, photophobia, redness, tearing

<1%, postmarketing and/or case reports: Allergic reaction (systemic), angioedema, bronchospasm, choriodal detachment (following filtration procedures), contact dermatitis, dizziness, dyspnea, epistaxis, eyelid crusting, fatigue, headache, iridocyclitis (rare), myopia (transient), nausea, ocular pain, paresthesia, pharyngitis, pruritus, rash (rare), throat irritation, urolithiasis (rare), urticaria, weakness, xerostomia

Metabolism/Transport Effects**Substrate** (minor) of CYP2C9, 3A4

Drug Interactions

Memantine: Carbonic Anhydrase Inhibitors may decrease the excretion of Memantine. *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Monitoring ParametersOphthalmic exams and IOP periodically

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic response and adverse effects. Teach patient proper use, side effects/appropriate interventions, and symptoms to report.

Patient EducationFor use in eyes only. If serious or unusual reactions or signs of hypersensitivity occur, discontinue use of the product. If any ocular reactions, particularly conjunctivitis and lid reactions, discontinue use and notify prescriber. If an intercurrent ocular condition (eg, trauma, ocular surgery, infection) occur, immediately seek your prescriber's advice concerning the continued use of the present multidose container. Avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Take out contact lenses before using medicine. Lenses can be replaced 15 minutes after medicine is given. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic: 2% (10 mL)

Trusopt®: 2% (10 mL) [contains benzalkonium chloride]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Trusopt)

2% (10): $74.12

Mechanism of ActionReversible inhibition of the enzyme carbonic anhydrase resulting in reduction of hydrogen ion secretion at renal tubule and an increased renal excretion of sodium, potassium, bicarbonate, and water to decrease production of aqueous humor; also inhibits carbonic anhydrase in central nervous system to retard abnormal and excessive discharge from CNS neurons

Pharmacodynamics/Kinetics

Onset of action: Peak effect: 2 hours

Duration: 8-12 hours

Absorption: Topical: Reaches systemic circulation where it accumulates in RBCs during chronic dosing as a result of binding to CA-II

Distribution: In RBCs during chronic administration

Protein binding: 33%

Metabolism: To N-desethyl metabolite (less potent than parent drug)

Half-life elimination: Terminal RBC: 147 days; washes out of RBCs nonlinearly, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half-life of about 4 months

Excretion: Urine (as unchanged drug and metabolite, N-desethyl)

Related Information

- Glaucoma Drug Therapy

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDorzolamide Hydrochloride

References

Biollaz J, Munafo A, Buclin T, et al, “Whole Blood Pharmacokinetics and Metabolic Affects of the Topical Carbonic Anhydrase Inhibitor Dorzolamide,” *Eur J Clin Pharmacol*, 1995, 47(5):455-60. [PubMed 7720769]

Wilkerson M, Cyrlin M, Lippa EA, et al, “Four-Week Safety and Efficacy Study of Dorzolamide, a Novel, Active, Topical Carbonic Anhydrase Inhibitor,” *Arch Ophthalmol*, 1993, 111(10):1343-50.[PubMed 8216014]

International Brand NamesTrusopt (MX, PL)

Dox-CMF (Sequential)

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Breast Cancer]
Regimen UseBreast cancer
Regimen

Doxorubicin: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 21 days for 4 cycles

followed by (after completing Cycle 4)

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Methotrexate: I.V.: 40 mg/m^2 day 1

[total dose/cycle = 40 mg/m^2]

Fluorouracil: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 21 days for 8 cycles

References

Bonadonna G, Zambetti M, Velagussa P, “Sequential or Alternating Doxorubicin and CMF Regimens in Breast Cancer With More Than Three Positive Nodes. Ten-Year Results,” *JAMA*, 1995, 273(7):542-7.[PubMed 7837388]

Doxapram

Lexi-Drugs Online

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Medication Safety Issues

Sound-alike/look-alike issues:

> Doxapram may be confused with doxacurium, doxazosin, doxepin, Doxinate®, DOXOrubicin
>
> Dopram® may be confused with DOPamine

Pronunciation(DOKS a pram)
U.S. Brand NamesDopram®
Pharmacologic CategoryRespiratory Stimulant; Stimulant
Use: Labeled IndicationsRespiratory and CNS stimulant for respiratory depression secondary to anesthesia, drug-induced CNS depression; acute hypercapnia secondary to COPD
Dosing: Adults

Respiratory depression following anesthesia:

Intermittent injection: Initial: 0.5-1 mg/kg; may repeat at 5-minute intervals (only in patients who demonstrate initial response); maximum total dose: 2 mg/kg

I.V. infusion: Initial: 5 mg/minute until adequate response or adverse effects seen; decrease to 1-3 mg/minute; maximum total dose: 4 mg/kg

Drug-induced CNS depression:

Intermittent injection: Initial: Priming dose of 1-2 mg/kg; repeat after 5 minutes; may repeat at 1-2 hour intervals (until sustained consciousness); maximum 3 g/day. May repeat in 24 hours if necessary.

I.V. infusion: Initial: Priming dose of 1-2 mg/kg repeated in 5 minutes. If no response, wait 1-2 hours and repeat. If some stimulation is noted, initiate infusion at 1-3 mg/minute (depending on size of patient/depth of CNS depression); suspend infusion if patient begins to awaken. Infusion should not be continued for >2 hours. May reinstitute infusion as described above, including bolus, after rest interval of 30 minutes to 2 hours; maximum: 3 g/day

Acute hypercapnia secondary to COPD: I.V. infusion: Initial: Initiate infusion at 1-2 mg/minute (depending on size of patient/depth of CNS depression); may increase to maximum rate of 3 mg/minute; infusion should not be continued for >2 hours. Monitor arterial blood gases prior to initiation of infusion and at 30-minute intervals during the infusion (to identify possible development of acidosis/CO_2 retention). Additional infusions are not recommended (per manufacturer).

Dosing: ElderlyRefer to adult dosing.
Administration: I.V.Avoid rapid infusion.
StorageStore at 20°C to 25°C (68°F to 77°F).
Reconstitution

Drug-induced CNS depression or postanesthesia: Mix doxapram 250 mg in 250 mL of D_5W, $D_{10}W$, or NS.

COPD-associated hypercapnia: Mix doxapram 400 mg in 180 mL of D_5W, $D_{10}W$, or NS (final concentration: 2 mg/mL).

CompatibilityStable in D_5W, $D_{10}W$, NS.

Compatibility in syringe: Compatible: Amikacin, bumetanide, chlorpromazine, cimetidine, cisplatin, cyclophosphamide, dopamine, doxycycline, epinephrine, hydroxyzine, isoniazid, lincomycin, methotrexate, phytonadione, pyridoxine, terbutaline, thiamine, tobramycin, vincristine. **Incompatible:** Aminophylline, ascorbic acid injection, cefoperazone, cefotaxime, cefotetan, cefuroxime, dexamethasone sodium phosphate, diazepam, digoxin, dobutamine, folic acid, furosemide, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, ketamine, methylprednisolone sodium succinate, minocycline, thiopental, ticarcillin.

Compatibility when admixed: Incompatible: Aminophylline, sodium bicarbonate, thiopental.

ContraindicationsHypersensitivity to doxapram or any component of the formulation; cardiovascular disease, cerebral edema, cerebral vascular accident, epilepsy, head injury, hyperthyroidism, mechanical disorders of ventilation, mechanical ventilation or neuromuscular blockade, pheochromocytoma, pulmonary embolism, or severe hypertension
Warnings/Precautions

Concerns related to adverse effects:

- CNS toxicity: May cause severe CNS toxicity, including seizures.

Disease-related concerns:

- Cerebrovascular disease: Use with caution in patients with cerebral disease; lowered pCO_2 induced by hyperventilation produces cerebral vasoconstriction and decreased circulation.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in treating pulmonary disease; a pressor effect on pulmonary circulation may result in a fall in arterial pO_2.

Concurrent drug therapy issues:

- Volatile anesthetics: If patient has received anesthesia with a volatile agent known to sensitize the myocardium to catecholamines, avoid use of doxapram until anesthetic has been eliminated.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Dosage form specific issues:

- Benzyl alcohol: Solution contains benzyl alcohol which has been associated with "gasping syndrome" in neonates.

Other warnings/precautions:

- Administration: Hemolysis may result from rapid infusion.

- Appropriate use: Adequate airway required; consider airway protection in case of vomiting. Resuscitative equipment (in addition to anticonvulsants and oxygen) should be readily available. Doxapram is neither a nonspecific CNS depressant antagonist nor an opiate antagonist.

Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, blood pressure increased, chest pain, chest tightness, flushing, heart rate changes, T waves lowered, ventricular tachycardia, ventricular fibrillation

Central nervous system: Apprehension, Babinski turns positive, disorientation, dizziness, hallucinations, headache, hyperactivity, pyrexia, seizure

Dermatologic: Burning sensation, pruritus

Gastrointestinal: Defecation urge, diarrhea, nausea, vomiting

Genitourinary: Spontaneous voiding, urinary retention

Hematologic: Hematocrit decreased, hemoglobin decreased, hemolysis, red blood cell count decreased

Local: Phlebitis

Neuromuscular & skeletal: Clonus, deep tendon reflexes increase, fasciculations, involuntary muscle movement, muscle spasm, paresthesia

Ocular: Pupillary dilatation

Renal: Albuminuria, BUN increased

Respiratory: Bronchospasm, cough, dyspnea, hiccups, hyperventilation, laryngospasm, rebound hypoventilation, tachypnea

Miscellaneous: Diaphoresis

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Monitoring ParametersMonitor heart rate, blood pressure, reflexes, CNS status, ECG, arterial blood gases (COPD)
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride: 20 mg/mL (20 mL) [contains benzyl alcohol]

Generic AvailableYes
Mechanism of ActionStimulates respiration through action on respiratory center in medulla or indirectly on peripheral carotid chemoreceptors
Pharmacodynamics/Kinetics

Onset of action: Respiratory stimulation: I.V.: 20-40 seconds

Peak effect: 1-2 minutes

Duration: 5-12 minutes

Half-life elimination, serum: Adults: Mean: 3.4 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause CNS stimulation, restlessness, irritability, or hallucinations
Mental Health: Effects on Psychiatric TreatmentMay cause hypertensive crisis if used with MAO inhibitors
Anesthesia and Critical Care Concerns/Other ConsiderationsBecause of doxapram's transient effect, doxapram should not be used as a drug of choice to treat anesthesia-induced respiratory depression.
Index TermsDoxapram Hydrochloride
References

Barrington KJ, Finer NN, Torok-Both G, et al, “Dose-Response Relationship of Doxapram in the Therapy for Refractory Idiopathic Apnea of Prematurity,” *Pediatrics*, 1987, 80(1):22-7.[PubMed 3110729]

International Brand NamesCaropraml (IN); Docatone (ES); Dopram (AT, AU, BE, CH, DE, DK, FI, FR, GB, GR, IE, NL, NO, ZA)

Doxazosin

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Doxazosin may be confused with doxapram, doxepin, DOXOrubicin

Cardura® may be confused with Cardene®, Cordarone®, Cordran®, Coumadin®, K-Dur®, Ridaura®

Pronunciation(doks AY zoe sin)
U.S. Brand NamesCardura®; Cardura® XL
Canadian Brand NamesAlti-Doxazosin; Apo-Doxazosin®; Cardura-1™; Cardura-2™; Cardura-4™; Gen-Doxazosin; Novo-Doxazosin
Pharmacologic CategoryAlpha $_1$ Blocker
Use: Labeled IndicationsTreatment of hypertension alone or in conjunction with diuretics, ACE inhibitors, beta-blockers, or calcium antagonists; treatment of urinary outflow obstruction and/or obstructive and irritative symptoms associated with benign prostatic hyperplasia (BPH), particularly useful in patients with troublesome symptoms who are unable or unwilling to undergo invasive procedures, but who require rapid symptomatic relief; can be used in combination with finasteride
Use: Unlabeled/InvestigationalPediatric hypertension
Dosing: Adults

Hypertension: Oral: Immediate release: 1 mg once daily in morning or evening; may be increased to 2 mg once daily. Thereafter titrate upwards, if needed, over several weeks, balancing therapeutic benefit with doxazosin-induced postural hypotension. Maximum dose: 16 mg/day

BPH: Oral:

Immediate release: 1 mg once daily in morning or evening; may be increased to 2 mg once daily. Thereafter titrate upwards, if needed, over several weeks, balancing therapeutic benefit with doxazosin-induced postural hypotension. Goal: 4-8 mg/day; maximum dose: 8 mg/day

Extended release: 4 mg once daily with breakfast; titrate based on response and tolerability every 3-4 weeks to maximum recommended dose of 8 mg/day. Reinitiation of therapy: If therapy is discontinued for several days, restart at 4 mg dose and titrate as before.

Note: Conversion to extended release from immediate release: Initiate with 4 mg once daily; omit final evening dose of immediate release prior to starting morning dosing with extended release product.

Dosing: ElderlyImmediate release: Oral: Initial: 0.5 mg once daily
Dosing: PediatricHypertension (unlabeled use): Oral: Immediate release: Initial: 1 mg once daily; maximum: 4 mg/day
Dosing: Hepatic ImpairmentUse with caution in mild-to-moderate hepatic dysfunction. Do not use with severe impairment.
Administration: OralCardura ® XL: Tablets should be swallowed whole; do not crush, chew, or divide.
Dietary ConsiderationsCardura® XL: Take with morning meal.
ContraindicationsHypersensitivity to quinazolines (prazosin, terazosin), doxazosin, or any component of the formulation
Allergy Considerations

- Alpha-Blocker, Piperazinyl Quinazoline Allergy

Warnings/Precautions

Concerns related to adverse effects:

• Angina: Discontinue if symptoms of angina occur or worsen.

• Floppy iris syndrome: Intraoperative floppy iris syndrome has been observed in cataract surgery patients who were on or were previously treated with alpha$_1$-blockers; causality has not been established and there appears to be no benefit in discontinuing alpha-blocker therapy prior to surgery.

• Orthostatic hypotension/syncope: Can cause significant orthostatic hypotension and syncope, especially with first dose; anticipate a similar effect if therapy is interrupted for a few days, if dosage is rapidly increased, or if another antihypertensive drug (particularly vasodilators) or a PDE-5 inhibitor is introduced. Patients should be cautioned about performing hazardous tasks when starting new therapy or adjusting dosage upward.

Disease-related concerns:

• Hepatic impairment: Use with caution in patients with mild to moderate hepatic impairment; not recommended in severe dysfunction.

• Prostate cancer: Should rule out prostatic carcinoma before beginning therapy.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Extended release formulation: Consists of drug within a nondeformable matrix; following drug release/absorption, the matrix/shell is expelled in the stool. The use of nondeformable products in patients with known stricture/narrowing of the GI tract has been associated with symptoms of obstruction. Use caution in patients with increased GI retention (eg, chronic constipation) as doxazosin exposure may be increased. Extended release formulation is not approved for the treatment of hypertension.

Geriatric ConsiderationsAdverse reactions such as dry mouth and urinary problems can be particularly bothersome in the elderly. In studies of the extended-release tablets, the incidence of hypotension was higher in the elderly compared to younger patients.

Pregnancy Risk FactorC

Pregnancy ConsiderationsSome studies demonstrated embryolethality resulting from doxazosin exposure during organogenesis. Delayed postnatal development was also noted. There are no adequate and well-controlled studies in pregnant women. Use only if benefit outweighs risk.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions**Note:** Type and frequency of adverse reactions reflect combined data from trials with immediate release and extended release products.

>10%: Central nervous system: Dizziness (5% to 19%), headache (5% to 14%)

1% to 10%:

Cardiovascular: Orthostatic hypotension (dose related; 0.3% up to 2%), edema (3% to 4%), hypotension (2%), palpitation (1% to 2%), chest pain (1% to 2%), arrhythmia (1%), syncope (2%), flushing (1%)

Central nervous system: Fatigue (8% to 12%), somnolence (1% to 5%), nervousness (2%), pain (2%), vertigo (2% to 4%), insomnia (1%), anxiety (1%), paresthesia (1%), movement disorder (1%), ataxia (1%), hypertonia (1%), depression (1%)

Dermatologic: Rash (1%), pruritus (1%)

Endocrine & metabolic: Sexual dysfunction (2%)

Gastrointestinal: Abdominal pain (2%), diarrhea (2%), dyspepsia (1% to 2%), nausea (1% to 3%), xerostomia (1% to 2%), constipation (1%), flatulence (1%)

Genitourinary: Urinary tract infection (1%), impotence (1%), polyuria (2%), incontinence (1%)

Neuromuscular & skeletal: Back pain (2% to 3%), weakness (1% to 7%), arthritis (1%), muscle weakness (1%), myalgia (≤1%), muscle cramps (1%)

Ocular: Abnormal vision (1% to 2%), conjunctivitis (1%)

Otic: Tinnitus (1%)

Respiratory: Respiratory tract infection (5%), rhinitis (3%), dyspnea (1% to 3%), respiratory disorder (1%), epistaxis (1%)

Miscellaneous: Diaphoresis increased (1%), flu-like syndrome (1%)

<1% (Limited to important or life-threatening): Abnormal lacrimation, abnormal thinking, agitation, alopecia, amnesia, angina, anorexia, appetite, bradycardia, breast pain, bronchospasm, confusion, cough, depersonalization, dry skin, earache, eczema, emotional lability, fecal incontinence, fever, gastroenteritis, gout, hot flashes, hypoesthesia, hypokalemia, impaired concentration, infection, leukopenia, lymphadenopathy, migraine, MI, neutropenia, pallor, paranoia, paresis, parosmia, peripheral ischemia, purpura, renal calculus, rigors stroke, syncope, tachycardia

Postmarketing and/or case reports: Allergic reaction, cataplexy, cerebrovascular accident, cholestasis, enuresis, hematuria, hepatitis, intraoperative floppy iris syndrome (cataract surgery), jaundice, liver function tests increased, micturition abnormality, nocturia, paresthesia, priapism, purpura, systemic lupus erythematosus, thrombocytopenia, vomiting

Drug Interactions

Alfuzosin: Alpha1-Blockers may enhance the antihypertensive effect of Alfuzosin. Risk of orthostatic hypotension or syncope may be increased. Alfuzosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Alpha1-Blockers may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: May enhance the hypotensive effect of Alpha1-Blockers. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tamsulosin: Alpha1-Blockers may enhance the antihypertensive effect of Tamsulosin. Risk of orthostatic hypotension or syncope may be increased. Tamsulosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid saw palmetto when used for BPH (due to limited experience with this combination). Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure, standing and sitting/supine; syncope may occur usually within 90 minutes of the initial dose

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness (blood pressure), and adverse reactions (eg, hypotension, CNS changes, urinary retention) at beginning of therapy and on a regular basis with long-term therapy. When discontinuing, blood pressure should be closely monitored and dose tapered slowly over 1 week or more. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsWhite blood count

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, at bedtime. Do not skip dose or discontinue without consulting prescriber. Do not crush or chew extended release forms, swallow whole. Tablet shell may be visible in the stool. Follow recommended diet and exercise program. May cause drowsiness, dizziness, or impaired judgment (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from sitting or lying position or when climbing stairs); or dry mouth or nausea (frequent mouth care or sucking lozenges may help). Report increased nervousness or depression; sudden weight gain (weigh yourself in the same clothes at the same time of day once a week); unusual or persistent swelling of ankles, feet, or extremities; palpitations or rapid heartbeat; muscle weakness, fatigue, or pain; or other persistent side effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 1 mg, 2 mg, 4 mg, 8 mg

Cardura®: 1 mg, 2 mg, 4 mg, 8 mg

Tablet, extended release:

Cardura® XL: 4 mg, 8 mg

Generic AvailableYes: Excludes extended release tablet

ManufacturerPfizer U.S. Pharmaceuticals Group

Pricing: U.S. (www.drugstore.com)

Tablets (Cardura)

1 mg (30): $47.32

2 mg (30): $47.32

4 mg (30): $50.10

8 mg (30): $53.54

Tablets (Doxazosin Mesylate)

1 mg (30): $17.99

2 mg (30): $19.99

4 mg (30): $21.99

8 mg (30): $23.99

Mechanism of Action

Hypertension: Competitively inhibits postsynaptic alpha$_1$-adrenergic receptors which results in vasodilation of veins and arterioles and a decrease in total peripheral resistance and blood pressure; ~50% as potent on a weight by weight basis as prazosin.

BPH: Competitively inhibits postsynaptic alpha$_1$-adrenergic receptors in prostatic stromal and bladder neck tissues. This reduces the sympathetic tone-induced urethral stricture causing BPH symptoms.

Pharmacodynamics/KineticsNot significantly affected by increased age

Duration: >24 hours

Protein binding: Extended release: 98%

Metabolism: Extensively hepatic to active metabolites; primarily via CYP3A4; secondary pathways involve CYP2D6 and 2C19

Bioavailability: Extended release relative to immediate release: 54% to 59%

Half-life elimination: 15-22 hours

Time to peak, serum: Immediate release: 2-3 hours; extended release: 8-9 hours

Excretion: Feces (63% primarily as metabolites); urine (9%)

Pharmacotherapy Pearls First-dose hypotension occurs less frequently with doxazosin as compared to prazosin; this may be due to its slower onset of action.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and orthostatic hypotension

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Dizziness is common.

Mental Health: Effects on Psychiatric Treatment Psychotropics may potentiate the hypotensive effects of doxazosin

Cardiovascular Considerations Doxazosin may be used in combination with other agents for the treatment of hypertension or alone in select patients who fail to respond or have contraindications to other agents. Patients with BPH may derive an extra benefit from therapy. Recently, the doxazosin treatment arm of ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) was prematurely stopped due to a significantly higher incidence (25%) of cardiovascular events, particularly heart failure events, compared to the diuretic (chlorthalidone) treatment arm. This unfavorable difference was also present when doxazosin was compared to the amlodipine and lisinopril treatment arms. This study does not address cardiovascular outcomes when doxazosin is combined with other antihypertensive medications.

Index Terms Doxazosin Mesylate

References

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“Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin vs Chlorthalidone: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Collaborative Research Group,” *JAMA*, 2000, 283(15):1967-75. [PubMed 10789664]

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National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, “The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents,” *Pediatrics*, 2004, 114(2 Suppl):555-76.[PubMed 15286277]

International Brand Names Alfadil (SE); Alfamedin (DE); Apo-Doxan (PL); Cadex (IL); Cadlin (KP); Cardenalin (JP); Cardoral (IL); Cardoxan (NZ); Cardular (DE); Cardular PP (DE); Cardular Uro (DE); Cardura (AE, AR, BG, BH, CN, CR, CY, CZ, DO, EC, EG, GB, GT, HK, HN, HU, ID, IE, IL, IQ, IR, JO, KW, LB, LY, MX, MY, NI, NL, OM, PA, PE, PK, PL, PT, QA, RU, SA, SG, SV, SY, TH, TR, UY, VE, YE, ZA, ZM); Cardura CR (CH); Cardura XL (CL, CN, EE, HK, MY, PL, TH); Cardura-XL S.R. (KP); Carduran (AU, BR, CO, ES, NO); Carduran Neo (ES); Carduran Retard (DK); Carxasin (TH); Cazosin (TH); Dedralen (IT); Diblocin (DE); Diblocin PP (DE); Diblocin Uro (DE); Dophilin (TW); Dosabin (TW); Dosan (NZ); Doxaben (TW); Doxaben XL (TW); Doxacard (IN); Doxagamma (DE); Doxaloc (IL); Doxanorm (PL); Doxar (PL); Doxaratio (PL); Doxasyn (HK); Doxatensa (ES); Doxazone XL SR (KP); Doxazosina Alter (ES); Doxazosina Cinfa (ES); Doxazosina Combino Pharm (ES); Doxazosina Geminis (ES); Doxazosina Normon (ES); Doxazosina Pharmagenus (ES); Doxazosina Ratiopharm (ES); Doxazosina Ur (ES); Doxolbran (AR); Dozozin (TH); Genzosin (TW); Jutalar (DE); Kamiren (PL); Kinxasen (TW); Maguran (GR); Magurol (MY); Pencor (HK, SG, TH); Progandol (ES); Progandol Neo (ES); Prostatic (PL); Saxobin (TW); Supressin (AT); Tensiobas (ES); Tonocardin (HR); Tonokardin (HR); Uriduct (DE); Xadosin (TW); Zoxan LP (FR); Zoxon (PL)

Doxepin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Doxepin may be confused with digoxin, doxapram, doxazosin, Doxidan®, doxycycline

Sinequan® may be confused with saquinavir, Serentil®, Seroquel®, Singulair®

Zonalon® may be confused with Zone-A Forte®

International issues:

Doxal® [Finland] may be confused with Doxil® which is a brand name for doxorubicin in the U.S.

Doxal® [Finland]: Brand name for doxycycline in Austria; brand name for pyridoxine/thiamine in Brazil

Pronunciation(DOKS e pin)

U.S. Brand NamesPrudoxin™; Sinequan® [DSC]; Zonalon®

Canadian Brand NamesApo-Doxepin®; Novo-Doxepin; Sinequan®; Zonalon®

Pharmacologic CategoryAntidepressant, Tricyclic (Tertiary Amine); Topical Skin Product

Use: Labeled Indications

Oral: Depression

Topical: Short-term (<8 days) management of moderate pruritus in adults with atopic dermatitis or lichen simplex chronicus

Use: Unlabeled/InvestigationalAnalgesic for certain chronic and neuropathic pain; anxiety

Use: DentalCream: Treatment of burning mouth syndrome and neuropathic pain

Dosing: Adults

Depression and/or anxiety (unlabeled use): Oral: Initial: 25-150 mg/day at bedtime or in 2-3 divided doses; may gradually increase up to 300 mg/day; single dose should not exceed 150 mg; select patients may respond to 25-50 mg/day.

Chronic urticaria, angioedema, nocturnal pruritus: Oral: 10-30 mg/day

Pruritus: Topical: Apply a thin film 4 times/day with at least 3- to 4-hour interval between applications; not recommended for use >8 days. (Oral administration of doxepin 25-50 mg has also been used, but systemic adverse effects are increased.)

Dosing: Elderly

Depression and/or anxiety (unlabeled use): Oral: Initial: 10-25 mg at bedtime; increase by 10-25 mg every 3 days for inpatients and weekly for outpatients if tolerated. Rarely does the maximum dose required exceed 75 mg/day; a single bedtime dose is recommended.

Pruritus: Topical: Refer to adult dosing.

Dosing: Pediatric

Depression and/or anxiety: Oral:

Children (unlabeled use): 1-3 mg/kg/day in single or divided doses

Adolescents: Initial: 25-50 mg/day in single or divided doses; gradually increase to 100 mg/day

Dosing: Hepatic ImpairmentUse a lower dose and adjust gradually.

Administration: OralDo not mix oral concentrate with carbonated beverages (physically incompatible).

Administration: TopicalApply thin film to affected area; use of occlusive dressings is not recommended.

StorageProtect from light.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to doxepin, drugs from similar chemical class, or any component of the formulation; narrow-angle glaucoma; urinary retention; use of MAO inhibitors within 14 days; use in a patient during acute recovery phase of MI

Allergy Considerations

- Tricyclic Antidepressant and Related Compounds Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Doxepin is approved for treatment of depression in adolescents.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Doxepin is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. The degree of anticholinergic blockade produced by this agent is high relative to other antidepressants.

- Orthostatic hypotension: May cause orthostatic hypotension (risk is moderate relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is very high relative to other antidepressants.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk conduction abnormalities with this agent is moderate relative to other antidepressants.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

- Thyroid dysfunction: Use with caution in patients with hyperthyroidism or those receiving thyroid supplementation.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly.

Dosage form specific issues:

- Topical: Cream formulation is for external use only (not for ophthalmic, vaginal, or oral use). Do not use occlusive dressings. Use for >8 days may increase risk of contact sensitization. Doxepin is significantly absorbed following topical administration; plasma levels may be similar to those achieved with oral administration.

Other warnings/precautions:

- Discontinuation of therapy: Therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

Geriatric ConsiderationsThe oral form is the preferred agent when sedation is a desired property. Less potential for anticholinergic effects than amitriptyline and less orthostatic hypotension than imipramine. However, dosing should be approached cautiously, initiated at the low end of the dosage range. The pharmacokinetics of doxepin have not been studied in elderly patients. Data from a clinical trial comparing fluoxetine to tricyclics suggest that fluoxetine is significantly less effective than nortriptyline in hospitalized elderly patients with unipolar major affective disorder, especially those with melancholia and concurrent cardiovascular disease.

Pregnancy Risk FactorB (cream); C (all other forms)

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; however, there are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationEnters breast milk/not recommended (AAP rates "of concern")

Breast-Feeding ConsiderationsGenerally, it is not recommended to breast-feed if taking antidepressants because of the long half-life, active metabolites, and the potential for side effects in the infant.

Adverse Reactions

Oral: Frequency not defined.

Cardiovascular: Hyper-/hypotension, tachycardia

Central nervous system: Drowsiness, dizziness, headache, disorientation, ataxia, confusion, seizure

Dermatologic: Alopecia, photosensitivity, rash, pruritus

Endocrine & metabolic: Blood sugar increased/decreased, breast enlargement, galactorrhea, libido increased/decreased, SIADH

Gastrointestinal: Xerostomia, constipation, vomiting, indigestion, anorexia, aphthous stomatitis, nausea, unpleasant taste, weight gain, diarrhea, trouble with gums, lower esophageal sphincter tone decrease may cause GE reflux

Genitourinary: Urinary retention, testicular edema

Hematologic: Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, purpura

Neuromuscular & skeletal: Weakness, tremor, numbness, paresthesia, extrapyramidal symptoms, tardive dyskinesia

Ocular: Blurred vision

Otic: Tinnitus

Miscellaneous: Diaphoresis (excessive), allergic reactions

Topical:

>10%:

Central nervous system: Drowsiness (22%)

Dermatologic: Stinging/burning (23%)

1% to 10%:

Cardiovascular: Edema: (1%)

Central nervous system: Dizziness (2%), emotional changes (2%)

Gastrointestinal: Xerostomia (10%), taste alteration (2%)

<1%: Contact dermatitis, tongue numbness, anxiety

Metabolism/Transport Effects**Substrate** (major) of CYP1A2, 2D6, 3A4

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Tricyclic Antidepressants may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Agonists: Tricyclic Antidepressants may enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Alpha2-Agonists: Tricyclic Antidepressants may diminish the antihypertensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Altretamine: May enhance the orthostatic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Amphetamines: Tricyclic Antidepressants may enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Aspirin: Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Beta2-Agonists: Tricyclic Antidepressants may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cinacalcet: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Tricyclic Antidepressants may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dexmethylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

DULoxetine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Iobenguane I 123: Tricyclic Antidepressants may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May enhance the neurotoxic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

NSAID (COX-2 Inhibitor): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Tricyclic Antidepressants may enhance the QTc-prolonging effect of QuiNIDine. QuiNIDine may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

St Johns Wort: May increase the metabolism of Tricyclic Antidepressants. The risk of serotonin syndrome may theoretically be increased. *Risk D: Consider therapy modification*

Sulfonylureas: Cyclic Antidepressants may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Terbinafine: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

TraMADol: Tricyclic Antidepressants may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. *Risk C: Monitor therapy*

Valproic Acid: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Tricyclic Antidepressants may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Grapefruit juice may inhibit the metabolism of some TCAs and clinical toxicity may result.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava (may increase risk of serotonin syndrome and/or excessive sedation).

Test InteractionsIncreased glucose

Monitoring ParametersMonitor blood pressure and pulse rate prior to and during initial therapy; monitor mental status, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased); weight; ECG in older adults; adverse effects may be increased if topical formulation is applied to >10% of body surface area

Reference RangeProposed therapeutic concentration (doxepin plus desmethyldoxepin): 110-250 ng/mL. Toxic concentration (doxepin plus desmethyldoxepin): >500 ng/mL. Utility of serum level monitoring is controversial.

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. Monitor CNS status. Be alert for signs of clinical worsening, suicidal ideation, or other changes in behavior. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient Education**Oral:** Take exactly as directed; do not increase dose or frequency. It may take several weeks to achieve desired results. Avoid alcohol, caffeine, and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); constipation (increased exercise, fluids, fruit, or fiber may help); urinary retention (void before taking medication); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); altered sexual drive or ability (reversible); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report persistent CNS effects (eg, nervousness, restlessness, insomnia, anxiety, excitation, suicide ideation, headache, agitation, impaired coordination, changes in cognition); muscle cramping, weakness, tremors, or rigidity; chest pain, palpitations, or irregular heartbeat; blurred vision or eye pain; yellowing of skin or eyes; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Topical: Use as directed. Apply in thin layer; do not overuse. Report increased skin irritation, worsening of condition or lack of improvement.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, as hydrochloride: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg

Sinequan®: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg [DSC]

Cream, as hydrochloride:

Prudoxin™: 5% (45 g) [contains benzyl alcohol]

Zonalon®: 5% (30 g, 45 g) [contains benzyl alcohol]

Solution, oral concentrate, as hydrochloride: 10 mg/mL (120 mL)

Sinequan®: 10 mg/mL (120 mL) [DSC]

Generic AvailableYes: Capsule, solution

Pricing: U.S. (www.drugstore.com)

Capsules (Doxepin HCl)

10 mg (90): $19.00

25 mg (60): $13.99

50 mg (60): $14.99

75 mg (30): $8.99

100 mg (30): $13.99

Capsules (Sinequan)

50 mg (60): $55.84

Concentrate (Doxepin HCl)

10 mg/mL (120): $16.00

Cream (Prudoxin)

5% (45): $95.14

Cream (Zonalon)

5% (30): $116.58

5% (45): $138.60

Mechanism of ActionIncreases the synaptic concentration of serotonin and norepinephrine in the central nervous system by inhibition of their reuptake by the presynaptic neuronal membrane

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Antidepressant: Usually >2 weeks; Anxiolytic: may occur sooner

Absorption: Following topical application, plasma levels may be similar to those achieved with oral administration

Distribution: Crosses placenta; enters breast milk

Protein binding: 80% to 85%

Metabolism: Hepatic; metabolites include desmethyldoxepin (active)

Half-life elimination: Adults: 6-8 hours

Excretion: Urine

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Dental Health Professional ConsiderationsDoxepin is known to prolong the QT interval. The QT interval is measured as the time and distance between the Q point of the QRS complex and the end of the T wave in the ECG tracing. After adjustment for heart rate, the QT interval is defined as prolonged if it is more than 450 msec in men and 460 msec in women. A long QT syndrome was first described in the 1950s and 60s as a congenital syndrome involving QT interval prolongation and syncope and sudden death. Some of the congenital long QT syndromes were characterized by a peculiar electrocardiographic appearance of the QRS complex involving a premature atria beat followed by a pause, then a subsequent sinus beat showing marked QT prolongation and deformity. This type of cardiac arrhythmia was originally termed “torsade de pointes” (translated from the French as “twisting of the points”).

Prolongation of the QT interval is thought to result from delayed ventricular repolarization. The repolarization process within the myocardial cell is due to the efflux of intracellular potassium. The channels associated with this current can be blocked by many drugs and predispose the electrical propagation cycle to torsade de pointes.

Doxepin is considered as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. It is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation)

Oral: Aphthous stomatitis, unpleasant taste, trouble with gums

Topical: Taste alteration

Long-term treatment with TCAs increases the risk of caries by reducing salivation and salivary buffer capacity.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsDoxepin is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution. See Dental Comment.

Mental Health CommentTricyclic antidepressants may be classified as tertiary (amitriptyline, doxepin, clomipramine, imipramine, trimipramine) or secondary amines (nortriptyline, desipramine, protriptyline). The tertiary amines are not recommended to treat depression in the elderly. If a TCA is used in the elderly, it should be a secondary amine. The tertiary amines are commonly used in low dosages for various conditions associated with pain. Toxicity is generally dose dependent. Relatively small overdoses (1-week supply) can be potentially fatal.

Index TermsDoxepin Hydrochloride

References

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Ware MR, "Tricyclic Antidepressant Overdose: Pharmacology and Treatment," *South Med J*, 1987, 80(11):1410-5. [PubMed 3317897]

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International Brand NamesAnten (NZ); Aponal (DE); Deptran (AU); Doneurin (DE); Doxal (FI); Doxederm (AR); Doxepin (PL); Doxin (IN); Expan (CO); Gilex (IL); Mareen (DE); Poldoxin (PL); Qualiquan (HK); Quitaxon (BE, BF, BJ, CI, ET, FR, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, PT, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Sagalon (SG); Sinepin (GB); Sinequan (AE, AT, AU, BB, BE, BH, BM, BS, BZ, CY, EG, GR, GY, HK, IL, IQ, IR, JM, JO, KW, LB, LY, MX, NL, NO, OM, PL, PT, QA, RU, SA, SR, SY, TH, TT, TW, YE); Sinquan (CH, DE, DK); Spectra (IN); Xepin (GB)

Doxercalciferol

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English

Jump To Field (Select Field Name)

Pronunciation(doks er kal si fe FEER ole)

U.S. Brand NamesHectorol®

Canadian Brand NamesHectorol®

Pharmacologic CategoryVitamin D Analog

Use: Labeled IndicationsTreatment of secondary hyperparathyroidism in patients with chronic kidney disease

Dosing: AdultsSecondary hyperparathyroidism:

Oral:

Dialysis patients: Dose should be titrated to lower iPTH to 150-300 pg/mL; dose is adjusted at 8-week intervals (maximum dose: 20 mcg 3 times/week)

Initial dose: iPTH >400 pg/mL: 10 mcg 3 times/week at dialysis

Dose titration:

iPTH level decreased by 50% and >300 pg/mL: Dose can be increased to 12.5 mcg 3 times/week for 8 more weeks; this titration process can continue at 8-week intervals; each increase should be by 2.5 mcg/dose

iPTH level 150-300 pg/mL: Maintain current dose

iPTH level <100 pg/mL: Suspend doxercalciferol for 1 week; resume at a reduced dose; decrease each dose (not weekly dose) by at least 2.5 mcg

Predialysis patients: Dose should be titrated to lower iPTH to 35-70 pg/mL with stage 3 disease or to 70-110 pg/mL with stage 4 disease: Dose may be adjusted at 2-week intervals (maximum dose: 3.5 mcg/day)

Initial dose: 1 mcg/day

Dose titration:

iPTH level >70 pg/mL with stage 3 disease or >110 pg/mL with stage 4 disease: Increase dose by 0.5 mcg every 2 weeks as necessary

iPTH level 35-70 pg/mL with stage 3 disease or 70-110 pg/mL with stage 4 disease: Maintain current dose

iPTH level is <35 pg/mL with stage 3 disease or <70 pg/mL with stage 4 disease: Suspend doxercalciferol for 1 week, then resume at a reduced dose (at least 0.5 mcg lower)

I.V.:

Dialysis patients: Dose should be titrated to lower iPTH to 150-300 pg/mL; dose is adjusted at 8-week intervals (maximum dose: 18 mcg/week)

Initial dose: iPTH level >400 pg/mL: 4 mcg 3 times/week after dialysis, administered as a bolus dose

Dose titration:

iPTH level decreased by <50% and >300 pg/mL: Dose can be increased by 1-2 mcg at 8-week intervals, as necessary

iPTH level decreased by >50% and >300 pg/mL: Maintain current dose

iPTH level 150-300 pg/mL: Maintain the current dose

iPTH level <100 pg/mL: Suspend doxercalciferol for 1 week; resume at a reduced dose (at least 1 mcg lower)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is required.

Dosing: Hepatic ImpairmentUse caution in these patients; no guidelines for dosage adjustment.

Dietary ConsiderationsBased on serum levels, dietary phosphorus may be restricted and/or controlled with calcium-based phosphorus binders. The daily combined calcium intake (dietary and calcium based phosphate binder) should be 1.5-2 g. Additional vitamin D supplements and magnesium-containing antacids should be avoided. Capsules contain coconut oil.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). The injection should be protected from light.

ContraindicationsHypersensitivity to any component of the formulation; history of hypercalcemia or evidence of vitamin D toxicity

Warnings/Precautions

Concerns related to adverse effects:

- Excessive vitamin D: Excessive vitamin D administration may lead to over suppression of PTH, progressive or acute hypercalcemia, hypercalciuria, hyperphosphatemia and adynamic bone disease.

- Hypercalcemia: Progressive and/or acute hypercalcemia may increase risk of cardiac arrhythmias and seizures; chronic hypercalcemia may lead to generalized vascular and other soft-tissue calcification. Phosphate and vitamin D (and its derivatives) should be withheld during therapy to avoid hypercalcemia.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Hyperphosphatemia: Should be corrected before initiating therapy; exacerbates secondary hyperparathyroidism, diminishing the effect of doxercalciferol.

Concurrent drug therapy issues:

- Cardiac glycosides: Use with caution in patients taking cardiac glycosides; digitalis toxicity is potentiated by hypocalcemia.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Injection: Intended for I.V. use only.

Other warnings/precautions:

- Appropriate use: Other forms of vitamin D should be discontinued when doxercalciferol is started.

Geriatric ConsiderationsNo special changes in dose are required. Caution should be used in the elderly using magnesium products (MOM, magnesium containing antacids, etc). These should be stopped if possible before initiating doxercalciferol.

Pregnancy Risk FactorB

Pregnancy ConsiderationsReproduction in animals (usual and high dose) do not reveal teratogenic or fetotoxic effects.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsExcretion in breast milk is unknown. Other vitamin D derivatives are excreted in breast milk; there is a potential for adverse effects. Therefore, the manufacturer recommends that breast-feeding be discontinued or doxercalciferol discontinued, depending upon importance of the drug to the mother.

Adverse Reactions

Note: As reported in dialysis patients.

>10%:

Cardiovascular: Edema (34%)

Central nervous system: Headache (28%), malaise (28%), dizziness (12%)

Gastrointestinal: Nausea/vomiting (24%)

Respiratory: Dyspnea (12%)

1% to 10%:

Cardiovascular: Bradycardia (7%)

Central nervous system: Sleep disorder (3%)

Dermatologic: Pruritus (8%)

Gastrointestinal: Anorexia (5%), constipation (3%), dyspepsia (5%), weight gain (5%)

Neuromuscular & skeletal: Arthralgia (5%)

Miscellaneous: Abscess (3%)

Drug InteractionsThere are no known significant interactions.

Monitoring Parameters

Dialysis patients: Before initiating, check iPTH, serum calcium and phosphorus. Check weekly thereafter until stable. Serum iPTH, calcium, phosphorus, and alkaline phosphatase should be monitored.

Predialysis patients: iPTH, serum calcium and phosphorus every 2 weeks for 3 months following initiation and dose adjustments, then monthly for 3 months, then every 3 months

Reference RangeSerum calcium times phosphorus product should be >55 mg^2/dL^2 with chronic kidney disease

Target range by stage of chronic kidney disease:

Stage 3:

GFR 30-59 mL/minute: iPTH 35-70 pg/mL

Serum phosphorus: 2.7-4.6 mg/dL

Stage 4:

GFR 15-29 mL/minute: iPTH 70-110 pg/mL

Serum phosphorus: 2.7-4.6 mg/dL

Stage 5:

GFR <15 mL/minute or dialysis: iPTH 150-300 pg/mL

Serum phosphorus: 3.5-5.5 mg/dL

Nursing: Physical Assessment/MonitoringMonitor therapeutic effectiveness (laboratory results), adverse reactions. Monitor for fluid retention. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse reactions to report.

Monitoring: Lab Tests

Dialysis patients: Before initiating, check iPTH, serum calcium and phosphorus. Check weekly thereafter until stable. Serum iPTH, calcium, phosphorus, and alkaline phosphatase should be monitored.

Predialysis patients: iPTH, serum calcium and phosphorus every 2 weeks for 3 months following initiation and dose adjustments, then monthly for 3 months, then every 3 months.

Patient EducationBe clear on dose and directions for taking. Stop other vitamin D products. Do not miss doses. Avoid magnesium-containing antacids and supplements. Report headache, dizziness, weakness, sleepiness, severe nausea, vomiting, dry mouth, loss of appetite, constipation, metallic taste, muscle and/or bone pain, significant fluid retention, malaise, shortness of breath, and difficulty thinking or concentrating to your prescriber. Do not take over-the-counter medicines or supplements without first consulting your prescriber. Follow diet and calcium supplements as directed by your prescriber.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, softgel:

Hectorol®: 0.5 mcg, 2.5 mcg [contains coconut oil]

Injection, solution:

Hectorol®: 2 mcg/mL (2 mL) [contains disodium edetate]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Hectorol)

0.5 mcg (50): $251.26

2.5 mcg (50): $875.96

Mechanism of ActionDoxercalciferol is metabolized to the active form of vitamin D. The active form of vitamin D controls the intestinal absorption of dietary calcium, the tubular reabsorption of calcium by the kidneys, and in conjunction with PTH, the mobilization of calcium from the skeleton.

Pharmacodynamics/Kinetics

Metabolism: Hepatic via CYP27

Half-life elimination: Active metabolite: 32-37 hours; up to 96 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and malaise are common; may cause confusion or sleep disorders

Mental Health: Effects on Psychiatric TreatmentNausea and vomiting are common; use caution with SSRIs

Index Terms1α-Hydroxyergocalciferol

References

Eknoyan G, Levin A, and Levin NW, “Bone Metabolism and Disease in Chronic Kidney Disease,” *Am J Kidney Dis*, 2003, 42(4 Suppl 3):1-201.

International Brand NamesHectorol (CA)

Pharmacologic CategoryChemotherapy Regimen, Multiple Myeloma
Regimen UseMultiple myeloma
Index TermsDVd; DVD
RegimenNOTE: Multiple variations are listed below.

Variation 1:

Doxorubicin, liposomal: I.V.: 40 mg/m^2 day 1

[total dose/cycle = 40 mg/m^2]

Vincristine: I.V.: 2 mg day 1

[total dose/cycle = 2 mg]

Dexamethasone: Oral or I.V.: 40 mg/day days 1 to 4

[total dose/cycle = 160 mg]

Repeat cycle every 4 weeks

Variation 2:

Doxorubicin, liposomal: I.V.: 40 mg/m^2 day 1

[total dose/cycle = 40 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 (maximum 2 mg) day 1

[total dose/cycle = 1.4 mg/m^2; maximum 2 mg]

Dexamethasone: Oral: 40 mg/day days 1 to 4

[total dose/cycle = 160 mg]

Repeat cycle every 4 weeks

References

Variation 1:

Hussein MA, Wood L, Hsi E, et al, âA Phase II Trial of Pegylated Liposomal Doxorubicin, Vincristine, and Reduced-Dose Dexamethasone Combination Therapy in Newly Diagnosed Multiple Myeloma Patients,â *Cancer*, 2002, 95(10):2160-8.[PubMed 2412170]

Variation 2:

Rifkin RM, Gregory SA, Mohrbacher A, et al, "Pegylated Liposomal Doxorubicin, Vincristine, and Dexamethasone Provide Significant Reduction in Toxicity Compared With Doxorubicin, Vincristine, and Dexamethasone in Patients With Newly Diagnosed Multiple Myeloma: A Phase III Multicenter Randomized Trial," *Cancer*, 2006, 106(4):848-58.[PubMed 16404741]

DOXOrubicin (Liposomal)

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

DOXOrubicin liposomal may be confused with DACTINomycin, DAUNOrubicin, DAUNOrubicin liposomal, doxacurium, doxapram, doxazosin, DOXOrubicin, epirubicin, IDArubicin

DOXOrubicin liposomal may be confused with DAUNOrubicin liposomal

Doxil® may be confused with Doxy®, Paxil®

Liposomal formulation (Doxil®) may be confused with the conventional formulation (Adriamycin PFS®, Adriamycin RDF®)

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Use caution when selecting product for preparation and dispensing; indications, dosages and adverse event profiles differ between conventional DOXOrubicin hydrochloride solution and DOXOrubicin liposomal. Both formulations are the same concentration. As a result, serious errors have occurred. Liposomal formulation of doxorubicin should NOT be substituted for doxorubicin hydrochloride on a mg-per-mg basis.

Pronunciation(doks oh ROO bi sin lip pah SOW mal)

U.S. Brand NamesDoxil®

Canadian Brand NamesCaelyx®

Pharmacologic CategoryAntineoplastic Agent, Anthracycline

Use: Labeled IndicationsTreatment of ovarian cancer, multiple myeloma, and AIDS-related Kaposi's sarcoma

Use: Unlabeled/InvestigationalTreatment of metastatic breast cancer

Dosing: AdultsRefer to individual protocols. **Liposomal formulations of doxorubicin should NOT be substituted for conventional doxorubicin hydrochloride on a mg-per-mg basis.**

AIDS-related Kaposi's sarcoma: I.V.: 20 mg/m^2/dose once every 3 weeks

Breast cancer (unlabeled use): I.V.: 50 mg/m^2/dose every 4 weeks

Multiple myeloma: I.V.: 30 mg/m^2/dose every 3 weeks (in combination with bortezomib) **or**

Unlabeled dosing: I .V.: 40 mg/m^2/dose every 4 weeks (in combination with vincristine and dexamethasone)

Ovarian cancer: I.V.: 50 mg/m^2/dose every 4 weeks

Dosing: ElderlyRefer to adult dosing.

Liposomal formulations of doxorubicin should NOT be substituted for conventional doxorubicin hydrochloride on a mg-per-mg basis.

Dosing: Hepatic Impairment **Liposomal formulations of doxorubicin should NOT be substituted for conventional doxorubicin hydrochloride on a mg-per-mg basis.**

ALT/AST 2-3 times ULN: Administer 75% of dose

ALT/AST >3 times ULN **or** bilirubin 1.2-3 mg/dL (20-51 µmol/L): Administer 50% of dose

Bilirubin 3.1-5 mg/dL (51-85 µmol/L): Administer 25% of dose

Bilirubin >5 mg/dL (85 µmol/L): Do not administer

Dosing: Adjustment for Toxicity

Liposomal formulations of doxorubicin should NOT be substituted for conventional doxorubicin hydrochloride on a mg-per-mg basis.

Toxicity Grade 1

ANC 1500-1900; platelets 75,000-150,000: Resume treatment with no dose reduction

Toxicity Grade 2

ANC 1000-<1500; platelets 50,000-<75,000: Wait until ANC ≥1500 and platelets ≥75,000; redose with no dose reduction

Toxicity Grade 3

ANC 500-999; platelets 25,000-<50,000: Wait until ANC ≥1500 and platelets ≥75,000; redose with no dose reduction

Toxicity Grade 4

ANC <500; platelets <25,000: Wait until ANC ≥1500 and platelets ≥75,000; redose at 25% dose reduction or continue full dose with cytokine support

Dosing adjustment for toxicity in treatment with bortezomib (for multiple myeloma) (see Bortezomib monograph for bortezomib dosage reduction with toxicity guidelines):

Fever ≥38°C and ANC <1000/mm^3*:* If prior to doxorubicin liposomal treatment (day 4), do not administer; if after doxorubicin liposomal administered, reduce dose by 25% in next cycle.

ANC<500/mm^3*, platelets <25,000/mm*^{3}*, hemoglobin <8 g/dL:* If prior to doxorubicin liposomal treatment (day 4); do not administer; if after doxorubicin liposomal administered, reduce dose by 25% in next cycle if bortezomib dose reduction occurred for hematologic toxicity.

Grade 3 or 4 nonhematologic toxicity: Delay dose until resolved to grade <2; reduce dose by 25% for all subsequent doses.

Neuropathic pain or peripheral neuropathy: No dose reductions needed for doxorubicin liposomal, refer to Bortezomib monograph for bortezomib dosing adjustment.

Dosing: Combination Regimens

Lymphoma, Hodgkin's: Gemcitabine-Vinorelbine-Doxorubicin (Liposomal)

Multiple myeloma:

Bortezomib-Doxorubicin (Liposomal)

Bortezomib-Doxorubicin (Liposomal)-Dexamethasone

Doxorubicin (Liposomal)-Vincristine-Dexamethasone

Calculations

- Body Surface Area: Adults

Administration: I.V.Irritant; avoid extravasation. Administer IVPB over 60 minutes; manufacturer recommends administering at initial rate of 1 mg/minute to minimize risk of infusion reactions until the absence of a reaction has been established, then increase the infusion rate for completion over 1 hour. **Do not administer intramuscular or subcutaneous**. **Do not infuse with in-line filters.**

Administration: I.V. DetailFlush with 5-10 mL of D$_5$W solution before and after drug administration, incompatible with heparin flushes. Monitor for local erythematous streaking along vein and/or facial flushing (may indicate rapid infusion rate).

StorageStore intact vials of solution under refrigeration at 2°C to 8°C (36°F to 46°F); avoid freezing. Prolonged freezing may adversely affect liposomal drug products, however, short-term freezing (<1 month) does not appear to have a deleterious effect. Diluted doxorubicin hydrochloride liposome injection may be refrigerated at 2°C to 8°C (36°F to 46°F); administer within 24 hours. **Do not infuse with in-line filters.**

ReconstitutionDoses of doxorubicin liposomal ≤90 mg must be diluted in 250 mL of D$_5$W prior to administration. Doses >90 mg should be diluted in 500 mL D$_5$W.

CompatibilityStable in D$_5$W.

Y-site administration: Compatible: Acyclovir, allopurinol, aminophylline, ampicillin, aztreonam, bleomycin, butorphanol, calcium gluconate, carboplatin, cefazolin, cefepime, cefoxitin, ceftizoxime, ceftriaxone, chlorpromazine, cimetidine, ciprofloxacin, cisplatin, clindamycin, co-trimoxazole, cyclophosphamide, cytarabine, dexamethasone sodium phosphate, diphenhydramine, dobutamine, dopamine, droperidol, enalaprilat, etoposide, famotidine, fluconazole, ganciclovir, gentamicin, granisetron, haloperidol, hydrocortisone sodium succinate, hydromorphone, ifosfamide, leucovorin, lorazepam, magnesium sulfate, mesna, methotrexate, methylprednisolone sodium succinate, metronidazole, netilmicin, ondansetron, piperacillin, potassium chloride, prochlorperazine edisylate, ranitidine, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, vinblastine, vincristine, vinorelbine, zidovudine. **Incompatible:** Amphotericin B, amphotericin B cholesteryl sulfate complex, buprenorphine, cefoperazone, ceftazidime, docetaxel, fluorouracil, furosemide, heparin, hydroxyzine, mannitol, meperidine, metoclopramide, mitoxantrone, morphine, ofloxacin, paclitaxel, piperacillin/tazobactam, promethazine, sodium bicarbonate.

ContraindicationsHypersensitivity to doxorubicin, other anthracyclines, or any component of the formulation; breast-feeding

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Hepatic impairment: See “Disease-related concerns” below.
- Infusion-related reactions: See “Concerns related to adverse effects” below.
- Liposomal vs. conventional doxorubicin dosing: “Dosage form specific issues” below.
- Myocardial toxicity: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: Severe myelosuppression may occur.** Delay in treatment or dosage modification may be required.

- Hand-foot syndrome: Palmar-plantar erythrodysesthesia has been reported in up to 51% of patients with ovarian cancer, 19% of patients with multiple myeloma, and ~3% in patients with Kaposi's sarcoma. May occur early in treatment, but is usually seen after 2-3 treatment cycles. Dosage modification may be required. In severe cases, treatment discontinuation may be required.

- Infusion-related reactions: **[U.S. Boxed Warning]: Acute infusion reactions may occur, some may be serious/life-threatening**, including fatal allergic/anaphylactoid-like reactions. May include flushing, dyspnea, facial swelling, chills, back pain, hypotension and/or tightness of chest/throat. Medication for the treatment of reactions should be readily available. Infuse doxorubicin liposomal at 1 mg/minute initially to minimize risk of infusion reaction.

- Myocardial toxicity: **[U.S. Boxed Warning]: Doxorubicin may cause cumulative, dose-related myocardial toxicity (concurrent or delayed).** Doxorubicin liposomal should be used cautiously in patients with high cumulative doses of anthracyclines. Total cumulative dose should take into account previous or concomitant treatment with cardiotoxic agents or irradiation of chest. The incidence of irreversible myocardial toxicity increases as the total cumulative (lifetime) dosages approach 450-550 mg/m^2. Although the risk increases with cumulative dose, irreversible cardiotoxicity may occur with anthracycline treatment at any dose level. Patients with pre-existing heart disease, hypertension, concurrent administration of other antineoplastic agents, prior or concurrent chest irradiation, and advanced age are at increased risk. Evaluate left ventricular ejection fraction (LVEF) prior to treatment and periodically during treatment. The onset of symptoms of anthracycline-induced HF and/or cardiomyopathy may be delayed.

- Radiation therapy: Radiation recall reaction has been reported with doxorubicin liposomal treatment after radiation therapy. Radiation-induced toxicity (to the myocardium, mucosa, skin, and liver) may be increased by doxorubicin.

Disease-related concerns:

- Hepatic impairment: **[U.S. Boxed Warning]: Use with caution in patients with hepatic impairment;** dosage reduction is recommended. Safety and efficacy in hepatic dysfunction have not been established.

Concurrent drug therapy issues:

- Toxicity potentiation: Doxorubicin may potentiate the toxicity of cyclophosphamide (hemorrhagic cystitis) and mercaptopurine (hepatotoxicity).

Special populations:

- Pediatrics: Safety and efficacy in children have not been established.

Dosage form specific issues:

- Liposomal vs. conventional doxorubicin hydrochloride dosing: **[U.S. Boxed Warning]: Liposomal formulations of doxorubicin should NOT be substituted for conventional doxorubicin hydrochloride on a mg-per-mg basis.**

Pregnancy Risk FactorD
Pregnancy ConsiderationsMay cause fetal harm if administered during pregnancy. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should avoid becoming pregnant during treatment.
LactationExcretion in breast milk unknown/contraindicated
Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is contraindicated.
Adverse Reactions

>10%:

Cardiovascular: Peripheral edema (≤11%)

Central nervous system: Fever (8% to 21%), headache (≤11%), pain (≤21%)

Dermatologic: Alopecia (9% to 19%); palmar-plantar erythrodysesthesia/hand-foot syndrome (≤51% in ovarian cancer, 3% in Kaposi's sarcoma), rash (≤29% in ovarian cancer, ≤5% in Kaposi's sarcoma)

Gastrointestinal: Stomatitis (5% to 41%), vomiting (8% to 33%), nausea (17% to 46%), mucositis (≤14%), constipation (≤30%), anorexia (≤20%), diarrhea (5% to 21%), dyspepsia (≤12%), intestinal obstruction (≤11%)

Hematologic: Myelosuppression (onset: 7 days; nadir: 10-14 days; recovery: 21-28 days), neutropenia (12% to 62%; grade 4: 4%), leukopenia (36%), thrombocytopenia (13% to 65%), anemia (6% to 74%; grade 4: <1%)

Neuromuscular & skeletal: Weakness (7% to 40%), back pain (≤12%)

Respiratory: Pharyngitis (≤16%), dyspnea (≤15%)

Miscellaneous: Infection (≤11%)

1% to 10%:

Cardiovascular: Cardiac arrest, chest pain, edema, hypotension, pallor, tachycardia, vasodilation

Central nervous system: Agitation, anxiety, chills, confusion, depression, dizziness, emotional lability, insomnia, somnolence, vertigo

Dermatologic: Acne, bruising, dry skin (6%), dermatitis (exfoliative and fungal), furunculosis, maculopapular rash, pruritus, skin discoloration, vesiculobullous rash

Endocrine & metabolic: Dehydration, hyperbilirubinemia, hypercalcemia, hyperglycemia, hypokalemia, hyponatremia

Gastrointestinal: Abdomen enlarged, anorexia, ascites, cachexia, dyspepsia, dysphagia, esophagitis, flatulence, gingivitis, glossitis, ileus, mouth ulceration, oral moniliasis, rectal bleeding, taste perversion, weight loss, xerostomia

Genitourinary: Cystitis, dysuria, leukorrhea, pelvic pain, polyuria, urinary incontinence, urinary tract infection, urinary urgency, vaginal bleeding, vaginal moniliasis

Hematologic: Hemolysis, prothrombin time increased

Hepatic: ALT increased

Local: Thrombophlebitis

Neuromuscular & skeletal: Arthralgia, hypertonia, myalgia, neuralgia, neuritis (peripheral), neuropathy, paresthesia (≤10%), pathological fracture

Ocular: Conjunctivitis, dry eyes, retinitis

Otic: Ear pain

Renal: Albuminuria, hematuria

Respiratory: Apnea, cough (≤10%), epistaxis, pleural effusion, pneumonia, rhinitis, sinusitis

Miscellaneous: Allergic reaction; infusion-related reactions (7%; includes bronchospasm, chest tightness, chills, dyspnea, facial edema, flushing, headache, herpes simplex/zoster, hypotension, pruritus); moniliasis, diaphoresis

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Abscess, acute brain syndrome, abnormal vision, acute myeloid leukemia (secondary), alkaline phosphatase increased, anaphylactic or anaphylactoid reaction, asthma, balanitis, blindness, bone pain, bronchitis, BUN increased, bundle branch block, cardiomegaly, cardiomyopathy, cellulitis, CHF, colitis, creatinine increased, cryptococcosis, diabetes mellitus, erythema multiforme, erythema nodosum, eosinophilia, fecal impaction, flu-like syndrome, gastritis, glucosuria, hemiplegia, hemorrhage, hepatic failure, hepatitis, hepatosplenomegaly, hyperkalemia, hypernatremia, hyperuricemia, hyperventilation, hypoglycemia, hypolipidemia, hypomagnesemia, hypophosphatemia, hypoproteinemia, hypothermia, injection site hemorrhage, injection site pain, jaundice, ketosis, lactic dehydrogenase increased, kidney failure, lymphadenopathy, lymphangitis, migraine, myositis, optic neuritis, palpitation, pancreatitis, pericardial effusion, petechia, pneumothorax, pulmonary embolism, radiation injury, sclerosing cholangitis, seizure, sepsis, skin necrosis, skin ulcer, syncope, tenesmus, thromboplastin decreased, thrombosis, tinnitus, urticaria, visual field defect, ventricular arrhythmia

Oncology: VesicantNo; may be an irritant

Oncology: Emetic PotentialLow (10% to 30%)

Metabolism/Transport Effects**Substrate** (major) of CYP2D6, 3A4; **Inhibits** CYP2B6 (moderate), 2D6 (weak), 3A4 (weak)

Drug Interactions

Bevacizumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk C: Monitor therapy*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Cardiac Glycosides: May diminish the cardiotoxic effect of Antineoplastic Agents (Anthracycline). Antineoplastic Agents (Anthracycline) may decrease the serum concentration of Cardiac Glycosides. The effects of liposomal formulations may be unique from those of the free drug, as liposomal formulation have unique drug disposition and toxicity profiles, and liposomes themselves may alter digoxin absorption/distribution. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inhibitors (Moderate) may decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Stavudine: DOXOrubicin (Liposomal) may diminish the therapeutic effect of Stavudine. *Risk D: Consider therapy modification*

Taxane Derivatives: May enhance the adverse/toxic effect of Antineoplastic Agents (Anthracycline). Taxane Derivatives may increase the serum concentration of Antineoplastic Agents (Anthracycline). Taxane Derivatives may also increase the formation of toxic anthracycline metabolites in heart tissue. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Zidovudine: DOXOrubicin (Liposomal) may enhance the adverse/toxic effect of Zidovudine. DOXOrubicin (Liposomal) may diminish the therapeutic effect of Zidovudine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (due to GI irritation).

Herb/Nutraceutical: St John's wort may decrease doxorubicin levels.

Monitoring ParametersCBC with differential and platelet count, liver function tests (ALT/AST, bilirubin, alkaline phosphatase); monitor for infusion reactions

Cardiac function should be carefully monitored; echocardiography, left ventricular ejection fraction (LVEF), MUGA scan may be used during therapy. Endomyocardial biopsy is the most definitive test for anthracycline myocardial injury.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, potential to reduce or increase levels/effects of doxorubicin). See Administration infusion specifics. Premedication with antiemetic is recommended (especially with larger doses). Infusion site must be closely monitored; extravasation can cause sloughing or tissue necrosis. Patient must be monitored for infusion reactions (eg, flushing, dyspnea, fever, chills, tachycardia, hypotension, chest tightness, facial swelling, difficulty swallowing) during and following infusion; medication/equipment for treating reactions should be readily available. Assess results of laboratory tests and patient response prior to each treatment and on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions (eg, importance of adequate hydration) and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, platelet count, echocardiogram, liver function tests (ALT/AST, bilirubin, alkaline phosphatase)

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. This medication can only be administered by infusion. Report immediately any swelling, pain, burning, or redness at infusion site. Avoid alcohol (may cause gastrointestinal irritation). It is important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and adequate nutrition (small, frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); sore mouth or gums (use soft toothbrush); diarrhea (buttermilk, boiled milk, or yogurt may help); loss of hair (reversible); or red-pink urine (normal). Report immediately chest pain, swelling of extremities, respiratory difficulty, palpitations, or rapid heartbeat. Report unresolved nausea, vomiting, or diarrhea; alterations in urinary pattern (increased or decreased); opportunistic infection (fever, chills, unusual bruising or bleeding fatigue, purulent vaginal discharge, unhealed mouth sores); abdominal pain or blood in stools; excessive fatigue; redness, swelling, pain or blisters on palms of hands or soles of feet; or yellowing of eyes or skin. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication or for the first several months following therapy. Consult prescriber for appropriate contraceptives. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride: 2 mg/mL (10 mL, 25 mL)

Generic AvailableNo

Mechanism of ActionDoxorubicin inhibits DNA and RNA synthesis by intercalating between DNA base pairs causing steric obstruction and inhibits topoisomerase-II at the point of DNA cleavage. Doxorubicin is also a powerful iron chelator. The iron-doxorubicin complex can bind DNA and cell membranes, producing free hydroxyl (OH) radicals that cleave DNA and cell membranes. Active throughout entire cell cycle. Doxorubicin liposomal is a pegylated formulation which protects the liposomes, and thereby increases blood circulation time.

Pharmacodynamics/Kinetics

Distribution: V_{dss}: 2.7-2.8 L/m^2

Protein binding, plasma: Unknown; nonliposomal (conventional) doxorubicin: 70%

Half-life elimination: Terminal: Distribution: 4.7-5.2 hours, Elimination: 44-55 hours

Metabolism: Hepatic and in plasma to doxorubicinol and the sulfate and glucuronide conjugates of 4-demethyl,7-deoxyaglycones

Excretion: Urine (5% as doxorubicin or doxorubicinol)

Related Information

- Common Toxicity Criteria
- Management of Drug Extravasations
- Management of Nausea and Vomiting

Pharmacotherapy Pearls**Oncology Comment:** Pegylated liposomal doxorubicin is listed within National Comprehensive Cancer Network (NCCN) guidelines for the treatment of the following malignancies: Breast cancer (as a preferred single-agent therapy for recurrent or metastatic breast cancer), ovarian cancer (an acceptable second-line agent for recurrent ovarian cancer), and multiple myeloma, (as primary induction therapy for both transplant candidates and nontransplant candidates [in combination with vincristine and dexamethasone]).

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes

upon discontinuation), mucositis, gingivitis, glossitis, mouth ulceration, taste perversion, and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMyelosuppression is common; use caution with clozapine and carbamazepine

Index TermsDOXOrubicin Hydrochloride (Liposomal); Liposomal DOXOrubicin; NSC-712227; Pegylated Liposomal DOXOrubicin

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International Brand NamesA.D.Mycin (KP); Adriablastin (AT, CH, HN); Adriablastina (CZ, GR, PT); Adriablastina R.D. (TH); Adriacin (JP); Adriamicine (RU); Adriamycin (AU, CZ, DK, FI, GB, HK, NO, SE, TH); Adriamycin P.F.S. (KP); Adriamycin R.D.F. (KP); Adriblastin (RU); Adriblastina (AE, AR, BE, BF, BG, BH, BJ, CI, CR, CY, DO, EG, ET, GH, GM, GN, GT, HN, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NI, NL, OM, PA, PE, PH, QA, SA, SC, SD, SL, SN, SV, SY, TN, TR, TW, TZ, UG, YE, ZA, ZM, ZW); Adriblastina CS (CO); Adriblastina PFS (IL); Adriblastina RD (BR); Adriblastina RTU (CN); Adriblastine (FR); Adrim (IN, PH); Adrimedac (DE); Adrubicin (KP); Amminac (TH); Caelyx (AR, AT, AU, BE, BG, CH, CN, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IT, MX, MY, NI, NL, NO, PA, PE, PH, PT, RU, SE, SG, SV, TH, TR, TW, UY, VE); Carcinocin (ID); Dicladox (PE); Doxolem (CR, DO, GT, HN, MX, NI, PA, SV, TH); Doxor Lyo (TW); Doxorubicin (IN); Doxorubicin Meiji (IN); Doxorubin (NZ, TH); Lipo-Dox (TH); Myocet (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Rubidox (PH)

Doxorubicin + Ketoconazole/Estramustine + Vinblastine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Prostate Cancer

Regimen Use Prostate cancer

Regimen

Doxorubicin: I.V.: 20 mg/m^2/day days 1, 15, and 29

[total dose/cycle = 60 mg/m^2]

Ketoconazole: Oral: 400 mg 3 times/day days 1 to 7, 15 to 21, and 29 to 35

[total dose/cycle = 25,200 mg]

Estramustine: Oral: 140 mg 3 times/day days 8 to 14, 22 to 28, and 36 to 42

[total dose/cycle = 8820 mg]

Vinblastine: I.V.: 5 mg/m^2/day days 8, 22, and 36

[total dose/cycle = 15 mg/m^2]

Repeat cycle every 8 weeks

References

Ellerhorst JA, Tu SM, Amato RJ, et al, âPhase II Trial of Alternating Weekly Chemohormonal Therapy for Patients With Androgen-Independent Prostate Cancer,â *Clin Cancer Res*, 1997, 3(12 Pt 1):2371-6.[PubMed 9815636]

Doxorubicin + Ketoconazole

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer

Regimen UseProstate cancer

Regimen

Doxorubicin: I.V.: 20 mg/m^2 continuous infusion day 1

[total dose/cycle = 20 mg/m^2]

Ketoconazole: Oral: 400 mg 3 times/day days 1 to 7

[total dose/cycle = 8400 mg]

Repeat cycle every 7 days

References

Sella A, Kilbourn R, Amato R, et al, âPhase II Study of Ketoconazole Combined With Weekly Doxorubicin in Patients With Androgen-Independent Prostate Cancer,â *J Clin Oncol*, 1994, 12(4):683-8.[PubMed 7512126]

DOXOrubicin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

DOXOrubicin may be confused with DACTINomycin, DAUNOrubicin, DAUNOrubicin liposomal, doxacurium, doxapram, doxazosin, DOXOrubicin liposomal, epirubicin, IDArubicin

Adriamycin PFS® may be confused with achromycin, Aredia®, Idamycin®

Conventional formulation (Adriamycin PFS®, Adriamycin RDF®) may be confused with the liposomal formulation (Doxil®)

Use caution when selecting product for preparation and dispensing; indications, dosages and adverse event profiles differ between conventional DOXOrubicin hydrochloride solution and DOXOrubicin liposomal. Both formulations are the same concentration. As a result, serious errors have occurred.

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

ADR is an error-prone abbreviation

International issues:

Doxil® may be confused with Doxal® which is a brand name for doxepin in Finland, a brand name for doxycycline in Austria, and a brand name for pyridoxine/thiamine combination in Brazil

Rubex®: Brand name for ascorbic acid in Ireland

Pronunciation(doks oh ROO bi sin)

U.S. Brand NamesAdriamycin®; Rubex® [DSC]

Canadian Brand NamesAdriamycin®

Pharmacologic CategoryAntineoplastic Agent, Anthracycline

Use: Labeled IndicationsTreatment of leukemias, lymphomas, multiple myeloma, osseous and nonosseous sarcomas, mesotheliomas, germ cell tumors of the ovary or testis, and carcinomas of the head and neck, thyroid, lung, breast, stomach, pancreas, liver, ovary, bladder, prostate, uterus, neuroblastoma, and Wilms' tumor.

Dosing: AdultsRefer to individual protocols. **Note:** Lower dosage should be considered for patients with inadequate marrow reserve (due to old age, prior treatment or neoplastic marrow infiltration).

Usual or typical dosages: I.V.: 60-75 mg/m^2/dose every 21 days **or**

60 mg/m^2/dose every 2 weeks (dose dense) **or**

40-60 mg/m^2/dose every 3-4 weeks **or**

20-30 mg/m^2/day for 2-3 days every 4 weeks **or**

20 mg/m^2/dose once weekly

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols. **Note:** Lower dosage should be considered for patients with inadequate marrow reserve (due to prior treatment or neoplastic marrow infiltration).

Usual/typical dosages: Children: I.V.:

35-75 mg/m^2/dose every 21 days **or**

20-30 mg/m^2/dose once weekly **or**

60-90 mg/m^2 given as a continuous infusion over 96 hours every 3-4 weeks

Dosing: Renal Impairment

Adjustments are not required.

Hemodialysis: Supplemental dose is not necessary.

Dosing: Hepatic Impairment

The FDA-approved labeling recommends the following adjustments:

- Serum bilirubin 1.2-3 mg/dL: Administer 50% of dose
- Serum bilirubin 3.1-5 mg/dL: Administer 25% of dose
- Severe hepatic impairment: Use is contraindicated

The following guidelines have been used by some clinicians: Floyd, 2006:

- ALT/AST 2-3 times ULN: Administer 75% of dose
- ALT/AST >3 times ULN or serum bilirubin 1.2-3 mg/dL: Administer 50% of dose
- Serum bilirubin 3.1-5 mg/dL: Administer 25% of dose
- Serum bilirubin >5 mg/dL: Do not administer

Dosing: Adjustment for ToxicityThe following delays and/or dose reductions have been used:

Neutropenic fever/infection: Consider reducing to 75% of dose in subsequent cycles

ANC <1000/mm^3: Delay treatment until ANC recovers to ≥1000/mm^3

Platelets <100,000/mm^3: Delay treatment until platelets recover to ≥100,000/mm^3

Dosing: Combination Regimens

Bladder cancer:

- CAP
- CISCA
- M-VAC (Bladder Cancer)

Breast cancer:

- AT
- AC
- AC/Paclitaxel (Sequential)
- AC-Paclitaxel-Trastuzumab
- CAF
- Dox-CMF (Sequential)
- FAC
- MVAC (Breast Cancer)
- TAC
- VATH
- VD

Cervical cancer: MVAC (Cervical Cancer)

Endometrial cancer:

- AP
- MVAC (Endometrial Cancer)

Gastric cancer:

- EAP
- FAM
- FAMe
- FAP

FAMTX

Gestational trophoblastic tumor:

CHAMOCA (Modified Bagshawe Regimen)

CHAMOMA (Bagshawe Regimen)

Head and Neck cancer: MVAC (Head and Neck Cancer)

Hepatoblastoma:

IPA

PA-CI

Leukemia, acute lymphocytic:

Hyper-CVAD + Imatinib

Hyper-CVAD (Leukemia, Acute Lymphocytic)

VAD/CVAD

Lung cancer (small cell): CAVE

Lymphoma, Hodgkin's:

ABVD

BEACOPP

CAD/MOPP/ABV

Etoposide-Vinblastine-Doxorubicin (Hodgkin's)

MOPP/ABV Hybrid

MOPP/ABVD

OPA

OPPA

Stanford V Regimen

Lymphoma, non-Hodgkin's:

CHOP

CODOX-M/IVAC

COP-BLAM

EPOCH

Hyper-CVAD (Lymphoma, non-Hodgkin's)

MACOP-B

m-BACOD

Pro-MACE-CytaBOM

Rituximab-CHOP

Lymphoma, non-Hodgkin's (Burkitt's): CODOX-M/IVAC

Lymphoma, non-Hodgkin's (Mantle cell): Hyper-CVAD + Rituximab

Multiple Myeloma:

Bortezomib-Doxorubicin-Dexamethasone

DTPACE

Hyper-CVAD (Multiple Myeloma)

VAD

VBAP

VCAP

Neuroblastoma:

CAV-P/VP

CCDDT (Neuroblastoma)

CE-CAdO

HIPE-IVAD

N4SE Protocol

N6 Protocol

OPEC-D

PE-CAdO

Regimen A1

Regimen A2

Osteosarcoma:

MTX-CDDPAdr

POG-8651

Ovarian cancer: PAC (CAP)

Pancreatic cancer: FAM

Prostate cancer:

Cyclophosphamide + Doxorubicin

Doxorubicin + Ketoconazole

Doxorubicin + Ketoconazole/Estramustine + Vinblastine

Retinoblastoma: CCCDE (Retinoblastoma)

Sarcoma:

CYVADIC

VAC Alternating With IE (Ewing's Sarcoma)

Sarcoma, soft tissue:

AD

AI

MAID

Wilms' tumor:

AAV (DD)

ACAV (J)

AVD

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Vesicant. I.V. push over at least 3-5 minutes or IVPB over 15-60 minutes. Infusion via central venous line recommended.
Administration: I.V. DetailMay be further diluted in either NS of D_5W for I.V. administration. Avoid extravasation associated with severe ulceration and soft tissue necrosis. Flush with 5-10 mL of I.V. solution before and after drug administration. Incompatible with heparin. Monitor for local erythematous streaking along vein and/or facial flushing (may indicate rapid infusion rate).

pH: 3.8-6.5 (lyophilized doxorubicin HCl reconstituted with sodium chloride 0.9%); 2.5-4.5 (adjusted solution)

StorageStore intact vials of solution under refrigeration at 2°C to 8°C and protected from light. Store intact vials of lyophilized powder at room temperature (15°C to 30°C). Reconstituted vials are stable for 7 days at room temperature (25°C) and 15 days under refrigeration (5°C) when protected from light. Infusions are stable for 48 hours at room temperature (25°C) when protected from light. Solutions diluted in 50-1000 mL D_5W or NS are stable for 48 hours at room temperature (25°C) when protected from light.
ReconstitutionReconstitute lyophilized powder with NS to a final concentration of 2 mg/mL (may further dilute in 50-1000 mL D_5W or NS for infusion). Unstable in solutions with a pH <3 or >7.
CompatibilityStable in D_5W, LR, NS.

Y-site administration: Compatible: Amifostine, aztreonam, bleomycin, chlorpromazine, cimetidine, cisplatin, cladribine, cyclophosphamide, dexamethasone sodium phosphate, diphenhydramine, droperidol, etoposide phosphate, famotidine, filgrastim, fludarabine, fluorouracil, gatifloxacin, gemcitabine, granisetron, hydromorphone, leucovorin, linezolid, lorazepam, melphalan, methotrexate, methylprednisolone sodium succinate, metoclopramide, mitomycin, morphine, ondansetron, paclitaxel, prochlorperazine edisylate, promethazine, ranitidine, sargramostim, sodium bicarbonate, teniposide, thiotepa, topotecan, vinblastine, vincristine, vinorelbine. **Incompatible:** Allopurinol, amphotericin B cholesteryl sulfate complex, cefepime, ganciclovir, piperacillin/tazobactam, propofol. **Variable (consult detailed reference):** Furosemide, heparin.

Compatibility in syringe: Compatible: Bleomycin, cisplatin, cyclophosphamide, droperidol, leucovorin, methotrexate, metoclopramide, mitomycin, vinblastine, vincristine. **Incompatible:** Furosemide, heparin. **Variable (consult detailed reference):** Fluorouracil.

Compatibility when admixed: Compatible: Dacarbazine, ondansetron, ondansetron with vincristine, paclitaxel, vinblastine. **Incompatible:** Aminophylline, diazepam, fluorouracil. **Variable (consult detailed reference):** Dacarbazine with ondansetron, etoposide with vincristine.

ContraindicationsHypersensitivity to doxorubicin, any component of the formulation, or to other anthracyclines or anthracenediones; recent MI, severe myocardial insufficiency, severe arrhythmia; previous therapy with high cumulative doses of doxorubicin, daunorubicin, idarubicin, or other anthracycline and anthracenediones; baseline neutrophil count <1500/mm^3; severe hepatic impairment

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See "Concerns related to adverse effects" below.
- Experienced physician: See "Other warnings/precautions" below.
- Hepatic impairment: See "Disease-related concerns" below.
- Myocardial toxicity: See "Concerns related to adverse effects" below.
- Secondary malignancy: See "Concerns related to adverse effects" below.
- Skin irritation/extravasation: See "Concerns related to adverse effects" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: May cause severe myelosuppression;** dose-limiting, primarily leukopenia and neutropenia.
- Myocardial toxicity: **[U.S. Boxed Warning]: May cause cumulative, dose-related, myocardial toxicity (early or delayed).** Cardiotoxicity is dose-limiting. Total cumulative dose should take into account previous or concomitant treatment with cardiotoxic agents or irradiation of chest. The incidence of irreversible myocardial toxicity increases as the total cumulative (lifetime) dosages approach 450-500 mg/m^2. Although the risk increases with cumulative dose, irreversible cardiotoxicity may occur at any dose level. Patients with pre-existing heart disease, hypertension, concurrent administration of other antineoplastic agents, prior or concurrent chest irradiation, advanced age; and infants and children are at increased risk. Alternative administration schedules (weekly or continuous infusions) are associated with less cardiotoxicity. Baseline and periodic monitoring of ECG and LVEF (with either ECHO or MUGA scan) is recommended. Children are at increased for developing delayed cardiotoxicity.
- Secondary malignancy: **[U.S. Boxed Warnings]: Secondary acute myelogenous leukemia and myelodysplastic syndrome have been reported following treatment.**
- Skin irritation/extravasation: **[U.S. Boxed Warning]: I.V. administration only. Potent vesicant; if extravasation occurs, severe local tissue damage leading to ulceration and necrosis, and pain may occur.**
- Tumor lysis syndrome: May cause tumor lysis syndrome and hyperuricemia (in patients with rapidly growing tumors).

Disease-related concerns:

- Hepatic impairment: **[U.S. Boxed Warning]: Use with caution in patients with hepatic impairment;** toxicities may be increased in patients with hepatic impairment; dosage adjustment recommended. Use with caution in patients with hepatobiliary dysfunction.

Special populations:

- Pediatrics: Children are at increased risk for developing delayed cardiotoxicity; follow-up cardiac function monitoring is recommended. Doxorubicin may contribute to prepubertal growth failure in children; may also contribute to gonadal impairment (usually temporary). Radiation recall pneumonitis has been reported in children receiving concomitant dactinomycin and doxorubicin.
- Radiation recipients: Use with caution in patients who have received radiation therapy; reduce dosage in patients who are receiving radiation therapy simultaneously.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**
- Vaccines: Administration of live vaccines to immunosuppressed patients may be hazardous.

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenicity and embryotoxicity were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Advise patients to avoid becoming pregnant (females) and to avoid causing pregnancy (males) during treatment. According to the National Comprehensive Cancer Network (NCCN) breast cancer guidelines, doxorubicin, if indicated, may be administered to pregnant women with breast cancer as part of a combination chemotherapy regimen, although chemotherapy should not be administered during the first trimester or after 35 weeks gestation.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsDoxorubicin and its metabolites are found in breast milk. Due to the potential for serious adverse reactions in the nursing infant, breast-feeding should be discontinued during treatment.

Adverse ReactionsFrequency not defined.

Cardiovascular:

Acute cardiotoxicity: Atrioventricular block, bradycardia, bundle branch block, ECG abnormalities, extrasystoles (atrial or ventricular), sinus tachycardia, ST-T wave changes, supraventricular tachycardia, tachyarrhythmia, ventricular tachycardia

Delayed cardiotoxicity: LVEF decreased, CHF (manifestations include ascites, cardiomegaly, dyspnea, edema, gallop rhythm, hepatomegaly, oliguria, pleural effusion, pulmonary edema, tachycardia); myocarditis, pericarditis

Central nervous system: Malaise

Dermatologic: Alopecia, itching, photosensitivity, radiation recall, rash; discoloration of saliva, sweat, or tears

Endocrine & metabolic: Amenorrhea, dehydration, infertility (may be temporary), hyperuricemia

Gastrointestinal: Abdominal pain, anorexia, colon necrosis, diarrhea, GI ulceration, mucositis, nausea, vomiting

Genitourinary: Discoloration of urine

Hematologic: Leukopenia/neutropenia (75%; nadir: 10-14 days; recovery: by day 21); thrombocytopenia and anemia

Local: Skin “flare” at injection site, urticaria

Neuromuscular & skeletal: Weakness

Postmarketing and/or case reports: Anaphylaxis, azoospermia, bilirubin increased, chills, coma (when in combination with cisplatin or vincristine), conjunctivitis, fever, gonadal impairment (children), growth failure (prepubertal), hepatitis, hyperpigmentation (nail, skin & oral mucosa), infection, keratitis, lacrimation, myelodysplastic syndrome, neutropenic fever, oligospermia, onycholysis, peripheral neurotoxicity (with intra-arterial doxorubicin), phlebosclerosis, radiation recall pneumonitis (children), secondary acute myelogenous leukemia, seizure (when in combination with cisplatin or vincristine), sepsis, shock, systemic hypersensitivity (including urticaria, pruritus, angioedema, dysphagia, and dyspnea), transaminases increased, urticaria

Oncology: VesicantYes; see Management of Drug Extravasations.

Oncology: Emetic PotentialModerate (30% to 60%)

Metabolism/Transport Effects**Substrate** (major) of CYP2D6, 3A4; **Inhibits** CYP2B6 (moderate), 2D6 (weak), 3A4 (weak)

Drug Interactions

Bevacizumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk C: Monitor therapy*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Cardiac Glycosides: May diminish the cardiotoxic effect of Antineoplastic Agents (Anthracycline). Antineoplastic Agents (Anthracycline) may decrease the serum concentration of Cardiac Glycosides. The effects of liposomal formulations may be unique from those of the free drug, as liposomal formulation have unique drug disposition and toxicity profiles, and liposomes themselves may alter digoxin absorption/distribution. *Risk C: Monitor therapy*

CycloSPORINE: May decrease the metabolism of DOXOrubicin. *Risk D: Consider therapy modification*

CYP2B6 Substrates: CYP2B6 Inhibitors (Moderate) may decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Sorafenib: May increase the serum concentration of DOXOrubicin. *Risk C: Monitor therapy*

Stavudine: DOXOrubicin may diminish the therapeutic effect of Stavudine. *Risk D: Consider therapy modification*

Taxane Derivatives: May decrease the metabolism of DOXOrubicin. **Exceptions:** Docetaxel. *Risk D: Consider therapy modification*

Taxane Derivatives: May enhance the adverse/toxic effect of Antineoplastic Agents (Anthracycline). Taxane Derivatives may increase the serum concentration of Antineoplastic Agents (Anthracycline). Taxane Derivatives may also increase the formation of toxic anthracycline metabolites in heart tissue. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zidovudine: DOXOrubicin may enhance the adverse/toxic effect of Zidovudine. DOXOrubicin may diminish the therapeutic effect of Zidovudine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid St John's wort (may decrease doxorubicin levels). Avoid black cohosh, dong quai in estrogen-dependent tumors.

Monitoring ParametersCBC with differential and platelet count; liver function tests (bilirubin, ALT/AST, alkaline phosphatase); serum uric acid, calcium, potassium, phosphate and creatinine; cardiac function (baseline, periodic, and followup): ECG, left ventricular ejection fraction (echocardiography [ECHO] or multigated radionuclide angiography [MUGA])

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, potential to reduce or increase levels/effects of doxorubicin). See Administration infusion specifics. Premedication with antiemetic is recommended (especially with larger doses). Infusion site must be closely monitored; extravasation can cause sloughing or tissue necrosis (do not apply heat or sodium bicarbonate). Assess results of laboratory tests and patient response prior to each treatment and on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions (eg, importance of adequate hydration) and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelet count; liver function tests (bilirubin, ALT/AST, alkaline phosphatase); serum uric acid, calcium, potassium, phosphate and creatinine; cardiac function (baseline, periodic, and followup): ECG, left ventricular ejection fraction (echocardiography [ECHO] or multigated radionuclide angiography [MUGA])

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered intravenously. Report immediately any swelling, pain, burning, or redness at infusion site. Maintain adequate nutrition (small, frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, or yogurt may help); loss of hair (reversible); or darker yellow urine (normal). Report immediately chest pain, swelling of extremities, respiratory difficulty, palpitations, or rapid heartbeat. Report unresolved nausea, vomiting, or diarrhea; alterations in urinary pattern (increased or decreased); opportunistic infection (fever, chills, unusual bruising or bleeding fatigue, purulent vaginal discharge, unhealed mouth sores); abdominal pain or blood in stools; excessive fatigue; or yellowing of eyes or skin. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication or for 1 month following therapy. Consult prescriber for appropriate barrier contraceptives. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as hydrochloride: 10 mg, 50 mg

Adriamycin®: 10 mg, 20 mg, 50 mg, [contains lactose]

Rubex®: 50 mg, 100 mg [contains lactose] [DSC]

Injection, solution, as hydrochloride: 2 mg/mL (5 mL, 10 mL, 25 mL, 100 mL)

Adriamycin®: 2 mg/mL (5 mL, 10 mL, 25 mL, 100 mL)

Generic AvailableYes

Mechanism of ActionInhibition of DNA and RNA synthesis by intercalation between DNA base pairs by inhibition of topoisomerase II and by steric obstruction. Doxorubicin intercalates at points of local uncoiling of the double helix. Although the exact mechanism is unclear, it appears that direct binding to DNA (intercalation) and inhibition of DNA repair (topoisomerase II inhibition) result in blockade of DNA and RNA synthesis and fragmentation of DNA. Doxorubicin is also a powerful iron chelator; the iron-doxorubicin complex can bind DNA and cell membranes and produce free radicals that immediately cleave the DNA and cell membranes.

Pharmacodynamics/Kinetics

Absorption: Oral: Poor (<50%)

Distribution: V_d: 809-1214 L/m^2; to many body tissues, particularly liver, spleen, kidney, lung, heart; does not distribute into the CNS; crosses placenta

Protein binding, plasma: 70% to 76%

Metabolism: Primarily hepatic to doxorubicinol (active), then to inactive aglycones, conjugated sulfates, and glucuronides

Half-life elimination:

Distribution: 5-10 minutes

Elimination: Doxorubicin: 1-3 hours; Metabolites: 3-3.5 hours

Terminal: 17-48 hours

Male: 54 hours; Female: 35 hours

Excretion: Feces (~40% to 50% as unchanged drug); urine (~5% to 12% as unchanged drug and metabolites)

Clearance: Male: 113 L/hour; Female: 44 L/hour

Related Information

- Management of Drug Extravasations
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis and mucositis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMyelosuppression is common; use caution with clozapine and carbamazepine

Index TermsADR (error-prone abbreviation); Adria; Doxorubicin Hydrochloride; Hydroxydaunomycin Hydrochloride; Hydroxyldaunorubicin Hydrochloride; NSC-123127

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International Brand Names A.D.Mycin (TH); Adriablastina (BG, CO); Adriablastina RD (HR, SG); Adriacin (JP); Adriamycin (AU, DK, FI, GB, NO, SE); Adriblastin (AT, CH, IL); Adriblastina (AR, BE, CZ, HU, IT, LU, NL, PK, PL, VE); Adriblastina PFS (EE); Adriblastina RD (MX); Adriblastina Soluzione Pronta (IT); Adriblastine (FR); AdriCept (DE); Adrim (IN); Adrimedac (DE); Axibin (PH); Biorubina (PL); Caelyx (AR, CH, DE, DK, ES, FR, IT, MX, PL, PT); Colhidrol (AR); Dicladox (AR); DOXO-cell (DE); Doxocris (AR); Doxolem (PL); Doxolem RU (MX); Doxopeg (MX); Doxorbin (AR); Doxorubicin (IN); Doxorubicin Azupharma (DE); Doxorubicin Bigmar (CH); Doxorubicin Bristol (CH); Doxorubicin Ebewe (CH, PL); Doxorubicin Hexal (DE); Doxorubicin Knoll (PL); Doxorubicin Meiji (IN); Doxorubicin NC (DE); Doxorubicin R.P. (DE); Doxorubicin ”Paranova” (DK); Doxorubicina (ES); Doxorubicina Asofarma (AR); Doxorubicina Delta Farma (AR); Doxorubicina Faulding (AR); Doxorubicina Filaxis (AR); Doxorubicina Gador (AR); Doxorubicine Asta (FR); Doxorubicine Dakota (FR); Doxorubin (CH, DK, NL); Doxosol (FI); Doxotec (MX); Doxtie (EC, MX, TH); Farmiblastina (ES); Flavicina (AR); Leubex (AR); Nagun (AR); Pallagicin (HU); Quimotus (AR); Rastocin (HR, PL); Ribodoxo (DE); Roxorin (PY, UY); Rubex (BR); Rubidox (ID); Urokit Doxo-cell (DE)

Doxycycline Hyclate Periodontal Extended-Release Liquid

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(doks i SYE kleen HI klayt per ee oh DON tal ik STEN did ri LES LIK wid)
U.S. Brand NamesAtridox™
Canadian Brand NamesAtridox™
Pharmacologic Category[Antibiotic, Tetracycline Derivative]
Use: Labeled IndicationsUsed exclusively in dental applications
Use: DentalTreatment of chronic adult periodontitis for gain in clinical attachment, reduction in probing depth, and reduction in bleeding upon probing
Dosing: Adults

Periodontitis: Subgingival application: Dose depends on size, shape and number of pockets treated. Contains 50 mg doxycycline per 500 mg of formulation in each final blended syringe product. Application may be repeated four months after initial treatment.

Atridox™ subgingival controlled-release product: The delivery system consists of 2 separate syringes in a single pouch. Syringe A contains 450 mg of a bioabsorbable polymer gel; syringe B contains doxycycline hyclate 50 mg. To prepare for instillation, couple syringe A to syringe B. Inject contents of syringe A (purple stripe) into syringe B, then push contents back into syringe A. Repeat this mixing cycle at a rate of one cycle per second for 100 cycles. If syringes are stored prior to use (a maximum of 3 days), repeat mixing cycle 10 times before use. After appropriate mixing, contents should be in syringe A. Holding syringes vertically, with syringe A at the bottom, pull back on the syringe A plunger, allowing contents to flow down barrel for several seconds. Uncouple syringes and attach enclosed blunt cannula to syringe A. Local anesthesia is not required for placement. Cannula tip may be bent to resemble periodontal probe and used to explore pocket. Express product from syringe until pocket is filled. To separate tip from formulation, turn tip towards the tooth and press against tooth surface to achieve separation. An appropriate dental instrument may be used to pack gel into the pocket. Pockets may be covered with either Coe-Pak™ or Octyldent™ dental adhesive.

Dosing: ElderlyRefer to adult dosing.
Administration: OralAtridox™ subgingival controlled-release product: The delivery system consists of 2 separate syringes in a single pouch. Syringe A contains 450 mg of a bioabsorbable polymer gel; syringe B contains doxycycline hyclate 50 mg. To prepare for instillation, couple syringe A to syringe B. Inject contents of syringe A (purple stripe) into syringe B, then push contents back into syringe A. Repeat this mixing cycle at a rate of one cycle per second for 100 cycles. If syringes are stored prior to use (a maximum of 3 days), repeat mixing cycle 10 times before use. After appropriate mixing, contents should be in syringe A. Holding syringes vertically, with syringe A at the bottom, pull back on the syringe A plunger, allowing contents to flow down barrel for several seconds. Uncouple syringes and attach enclosed blunt cannula to syringe A. Local anesthesia is not required for placement. Cannula tip may be bent to resemble periodontal probe and used to explore pocket. Express product from syringe until pocket is filled. To separate tip from formulation, turn tip towards the tooth and press against tooth surface to achieve separation. An appropriate dental instrument may be used to pack gel into the pocket. Pockets may be covered with either Coe-Pak™ or Octyldent™ dental adhesive.
Dietary ConsiderationsMay be taken with food, milk, or water.
StorageDental gel: Store at 2°C to 8°C (36°F to 46°F). After mixing, coupled syringes may be stored for a maximum of 3 days at room temperature.
ContraindicationsHypersensitivity to doxycycline, tetracycline or any component of the formulation; children <8 years of age; severe hepatic dysfunction; pregnancy
Allergy Considerations

- Tetracycline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Photosensitivity: May cause photosensitivity; discontinue if skin erythema occurs. Use skin protection and avoid prolonged exposure to sunlight; do not use tanning equipment.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Special populations:

- Pediatrics: May cause tissue hyperpigmentation, enamel hypoplasia, or permanent tooth discoloration; use of tetracyclines should be avoided during tooth development (children ≤8 years of age) unless other drugs are not likely to be effective or are contraindicated. However, recommended in treatment of anthrax exposure.

- Pregnancy: Do not use during pregnancy. In addition to affecting tooth development, tetracycline use has been associated with retardation of skeletal development and reduced bone growth.

Other warnings/precautions:

- Appropriate use: For subgingival application: This product has not been evaluated or tested in immunocompromised patients, in patients with oral candidiasis, or in conditions characterized by severe periodontal defects with little remaining periodontium. May result in overgrowth of nonsusceptible organisms, including fungi. Effects of treatment >6 months have not been evaluated. Has not been evaluated for use in regeneration of alveolar bone.

Pregnancy Risk FactorD

Adverse Reactions

>10%: Discoloration of teeth in children

<1%: Gastrointestinal: Nausea, diarrhea

Rare adverse effects of tetracyclines: Glossitis, vomiting, dysphagia, hepatotoxicity, esophageal ulceration (if capsule forms are taken before lying down), rash, anaphylaxis, exfoliative dermatitis, photosensitivity, exacerbations of SLE, hemolytic anemia, neutropenia and thrombocytopenia

Doxycycline periodontal gel (Atridox™): The adverse effects reported in clinical trials were similar in incidence between doxycycline-containing product and vehicle alone. In addition, these effects were comparable to standard therapies including scaling and root planing or oral hygiene. Events associated with application reported with an incidence >1% included: gum discomfort (18%), toothache (14%), periodontal abscess (10%), tooth sensitivity (8%), broken tooth (5%), tooth mobility (2%), endodontic abscess (2%) and jaw pain (1%). Systemic adverse events included headache (27%), muscle aches (7%), diarrhea (3%), upset stomach (4%), and nausea (2%). Although there is no known relationship between doxycycline and hypertension, unspecified essential hypertension was noted in 1.6% of the doxycycline gel group, as compared to 0.2% in the vehicle group. Allergic reactions to the vehicle were also reported in two patients.

Drug InteractionsThere are no known significant interactions.

Patient Education

Report persistent diarrhea.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel, subgingival: 50 mg in each 500 mg of blended formulation [2-syringe system includes doxycycline syringe (50 mg) and delivery system syringe (450 mg) with a blunt cannula]

Generic AvailableNo

Mechanism of ActionInhibits protein synthesis by binding with the 30S and possibly the 50S ribosomal subunit(s) of susceptible bacteria; may also cause alterations in the cytoplasmic membrane

Doxycycline inhibits collagenase *in vitro* and has been shown to inhibit collagenase in the gingival crevicular fluid in adults with periodontitis

Pharmacodynamics/KineticsSystemic absorption from dental subgingival gel may occur, but is limited by the slow rate of dissolution from this formulation over 7 days.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Discoloration of teeth (in children), gum discomfort, toothache, periodontal abscess, tooth sensitivity, broken tooth, tooth mobility, endodontic abscess, and jaw pain

Mechanical oral hygiene procedures (ie, tooth brushing, flossing) should be avoided in any treated area for 7 days.

Effects reported in clinical trials were similar in incidence between doxycycline-containing product and vehicle alone; comparable to standard therapies including scaling and root planing or oral hygiene. Although there is no known relationship between doxycycline and hypertension, unspecified essential hypertension was noted in 1.6% of the doxycycline gel group, as compared to 0.2% in the vehicle group (allergic reactions to the vehicle were also reported in two patients).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause photosensitivity and other dermatological reactions; consider this possibility when individuals are also taking psychotropics since this may produce similar reactions. Carbamazepine and barbiturates may decrease the effectiveness of doxycycline.

International Brand NamesAtridox® (CA)

Doxycycline

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Doxycycline may be confused with dicyclomine, doxepin, doxylamine

Doxy-100® may be confused with Doxil®

Monodox® may be confused with Maalox®

Oracea™ may be confused with Orencia®

Vibramycin® may be confused with vancomycin

Pronunciation(doks i SYE kleen)
U.S. Brand NamesAdoxa®; Doryx®; Doxy-100®; Monodox®; Oracea™; Periostat®; Vibra-Tabs®; Vibramycin®
Canadian Brand NamesApo-Doxy Tabs®; Apo-Doxy®; Doxycin; Doxytec; Novo-Doxylin; Nu-Doxycycline; Periostat®; Vibra-Tabs®
Pharmacologic CategoryAntibiotic, Tetracycline Derivative
Use: Labeled IndicationsPrincipally in the treatment of infections caused by susceptible *Rickettsia*, *Chlamydia*, and *Mycoplasma*; alternative to mefloquine for malaria prophylaxis; treatment for syphilis, uncomplicated *Neisseria gonorrhoeae*, *Listeria*, *Actinomyces israelii*, and *Clostridium* infections in penicillin-allergic patients; used for community-acquired pneumonia and other common infections due to susceptible organisms; anthrax due to *Bacillus anthracis,* including inhalational anthrax (postexposure); treatment of infections caused by uncommon susceptible gram-negative and gram-positive organisms including *Borrelia recurrentis*, *Ureaplasma urealyticum*, *Haemophilus ducreyi*, *Yersinia pestis*, *Francisella tularensis*, *Vibrio cholerae*, *Campylobacter fetus*, *Brucella* spp, *Bartonella bacilliformis*, and *Calymmatobacterium granulomatis,* Q fever, Lyme disease; treatment of inflammatory lesions associated with rosacea; intestinal amebiasis; severe acne
Use: Unlabeled/InvestigationalSclerosing agent for pleural effusion injection; vancomycin-resistant enterococci (VRE)
Use: DentalTreatment of periodontitis associated with presence of *Actinobacillus actinomycetemcomitans* (AA); Atridox™ is indicated for the treatment of chronic adult periodontitis for gain in clinical attachment, reduction in probing depth, and reduction in bleeding on probing; Periostat® is indicated for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in adult periodontitis (systemic levels are subinhibitory against bacteria)
Dosing: Adults

Usual dosage range: Oral, I.V.: 100-200 mg/day in 1-2 divided doses

Anthrax:

Inhalational (postexposure prophylaxis): Oral, I.V. (use oral route when possible): 100 mg every 12 hours for 60 days (*MMWR*, 2001, 50:889-93).

Cutaneous (treatment): Oral: 100 mg every 12 hours for 60 days. **Note:** In the presence of systemic involvement, extensive edema, lesions on head/neck, refer to I.V. dosing for treatment of inhalational/gastrointestinal/oropharyngeal anthrax

Inhalational/gastrointestinal/oropharyngeal (treatment): I.V.: Initial: 100 mg every 12 hours; switch to oral therapy when clinically appropriate; some recommend initial loading dose of 200 mg, followed by 100 mg every 8-12 hours (*JAMA*, 1997, 278:399-411).

Note: Initial treatment should include two or more agents predicted to be effective (per CDC recommendations). Agents suggested for use in conjunction with doxycycline or ciprofloxacin include rifampin, vancomycin, imipenem, penicillin, ampicillin, chloramphenicol, clindamycin, and clarithromycin. May switch to oral antimicrobial therapy when clinically appropriate. Continue combined therapy for 60 days.

Brucellosis: Oral: 100 mg twice daily for 6 weeks with rifampin or streptomycin

Chlamydial infections, uncomplicated: Oral: 100 mg twice daily for ≥7 days

Community-acquired pneumonia, bronchitis: Oral, I.V.: 100 mg twice daily

Endometritis, salpingitis, parametritis, or peritonitis: I.V.: 100 mg twice daily with cefoxitin 2 g every 6 hours for 4 days and for ≥48 hours after patient improves; then continue with oral therapy 100 mg twice daily to complete a 10- to 14-day course of therapy

Gonococcal infection, acute (PID) in combination with another antibiotic: I.V.: 100 mg every 12 hours until improved, followed by 100 mg orally twice daily to complete 14 days

Lyme disease, Q fever, or Tularemia: Oral: 100 mg twice daily for 14-21 days

Malaria prophylaxis: 100 mg/day. Start 1-2 days prior to travel to endemic area; continue daily during travel and for 4 weeks after leaving endemic area

Nongonococcal urethritis: Oral: 100 mg twice daily for 7 days

Periodontitis: Oral (Periostat®): 20 mg twice daily as an adjunct following scaling and root planing; may be administered for up to 9 months. Safety beyond 12 months of treatment and efficacy beyond 9 months of treatment have not been established.

Rickettsial disease or ehrlichiosis: Oral, I.V.: 100 mg twice daily for 7-14 days

Rosacea: (Oracea™): Oral: 40 mg once daily in the morning

Sclerosing agent for pleural effusion injection (unlabeled use): Irrigation: 500 mg as a single dose in 30-50 mL of NS or SWI

Syphilis:

Early syphilis: Oral, I.V.: 200 mg/day in divided doses for 14 days

Late syphilis: Oral, I.V.: 200 mg/day in divided doses for 28 days

***Yersinia pestis*(plague):** Oral: 100 mg twice daily for 7 days

Vibrio cholerae: Oral: 300 mg as a single dose

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Usual dosage range:

Children >8 years (<45 kg): Oral, I.V.: 2-5 mg/kg/day in 1-2 divided doses, not to exceed 200 mg/day

Children >8 years (>45 kg): Oral, I.V.: Refer to adult dosing.

Anthrax:

Inhalational (postexposure prophylaxis) (*MMWR*, 2001, 50:889-93): Oral, I.V. (use oral route when possible):

≤8 years: 2.2 mg/kg every 12 hours for 60 days

>8 years and ≤45 kg: 2.2 mg/kg every 12 hours for 60 days

>8 years and >45 kg: 100 mg every 12 hours for 60 days

Cutaneous (treatment): Oral: See dosing for "Inhalational (postexposure prophylaxis)"

Note: In the presence of systemic involvement, extensive edema, and/or lesions on head/neck, doxycycline should initially be administered I.V.

Inhalational/gastrointestinal/oropharyngeal (treatment): I.V.: Refer to dosing for inhalational anthrax (postexposure prophylaxis); switch to oral therapy when clinically appropriate.

Note: Initial treatment should include two or more agents predicted to be effective (per CDC recommendations). Agents suggested for use in conjunction with doxycycline or ciprofloxacin include rifampin, vancomycin, imipenem, penicillin, ampicillin, chloramphenicol, clindamycin, and clarithromycin. May switch to oral antimicrobial therapy when clinically appropriate. Continue combined therapy for 60 days

Malaria prophylaxis: Children ≥8 years: 2 mg/kg/day (maximum 100 mg/day). Start 1-2 days prior to travel to endemic area; continue daily during travel and for 4 weeks after leaving endemic area

Chlamydial infections, uncomplicated: Children ≥8 years and >45 kg: Oral: 100 mg twice daily for ≥7 days

Lyme disease, Q fever, or tularemia: Children ≥8 years and >45 kg: Oral: 100 mg twice daily for 14-21 days

Rickettsial disease or ehrlichiosis: Children ≥8 years and >45 kg: Oral, I.V.: 100 mg twice daily for 7-14 days

Dosing: Renal ImpairmentNo adjustment necessary.

Not dialyzable; 0% to 5% by hemo- and peritoneal methods or by continuous arteriovenous or venovenous hemofiltration; supplemental dose is not necessary.

Administration: I.V.Infuse slowly, usually over 1-4 hours. Avoid extravasation.

Administration: I.V. DetailAvoid extravasation. Very irritating to vein; use central line if possible.

pH: 1.8-3.3 (reconstituted solution)

Administration: OralMay give with meals to decrease GI upset. Capsule and tablet: Administer with at least 8 ounces of water and have patient sit up for at least 30 minutes after taking to reduce the risk of esophageal irritation and ulceration.

Oracea™: Take on an empty stomach 1 hour before or 2 hours after meals.

Doryx®: May be administered by carefully breaking up the tablet and sprinkling tablet contents on a spoonful of cold applesauce. The delayed release pellets must not be crushed or damaged when breaking up tablet. Should be administered immediately after preparation and without chewing.

Dietary Considerations

Tetracyclines (in general): Take with food if gastric irritation occurs. While administration with food may decrease GI absorption of doxycycline by up to 20%, administration on an empty stomach is not recommended due to GI intolerance. Of currently available tetracyclines, doxycycline has the least affinity for calcium.

Oracea™: Take on an empty stomach 1 hour before or 2 hours after meals.

Doryx®: 75 mg, 100 mg, and 150 mg tablets contain sodium 4.5 mg, 6 mg, and 9 mg respectively.

Storage

Capsule, tablet: Store at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.

I.V. infusion: Protect from light. Stability varies based on solution.

ReconstitutionI.V. infusion: Following reconstitution with sterile water for injection, dilute to a final concentration of 0.1-1 mg/mL using a compatible solution.

CompatibilitySolutions for I.V. infusion are stable in NS, D_5W, Ringer's injection, LR, D_5LR.

Y-site administration: Compatible: Acyclovir, amifostine, amiodarone, aztreonam, bivalirudin, cisatracurium, cyclophosphamide, dexmedetomidine, diltiazem, docetaxel, etoposide, fenoldopam, filgrastim, fludarabine, gemcitabine, granisetron, hetastarch, hydromorphone, linezolid, magnesium sulfate, melphalan, meperidine, morphine, ondansetron, perphenazine, propofol, remifentanil, sargramostim, tacrolimus, teniposide, theophylline, thiotepa, vinorelbine. **Incompatible:** Allopurinol, heparin, pemetrexed, piperacillin/tazobactam. **Variable (consult detailed reference):** Meropenem.

Compatibility in syringe: Compatible: Doxapram.

Compatibility when admixed: Compatible: Ranitidine. **Variable (consult detailed reference):** Meropenem.

Extemporaneously PreparedIf liquid doxycycline is unavailable for the treatment of anthrax, emergency doses may be prepared for children using the tablets.

Crush one 100 mg tablet and grind into a fine powder. Mix with 4 teaspoons of food or drink (lowfat milk, chocolate milk, chocolate pudding, or apple juice). Appropriate dose may be taken from this mixture. Mixture may be stored for up to 24 hours. Dairy mixtures should be refrigerated; apple juice may be stored at room temperature.

U.S. Food and Drug Administration, Center for Drug Evaluation and Research, "How to Prepare Emergency Dosages of Doxycycline at Home for Infants and Children," April 25, 2003, viewable at http://www.fda.gov/cder/drug/infopage/penG_doxy/doxycyclinePeds.htm, last accessed May 8, 2003.

ContraindicationsHypersensitivity to doxycycline, tetracycline or any component of the formulation; children ≤8 years of age, except in treatment of anthrax (including inhalational anthrax postexposure prophylaxis)

Allergy Considerations

- Tetracycline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Autoimmune syndromes: Have been reported.
- Hepatotoxicity: Rarely occurs; if symptomatic, conduct LFT and discontinue drug.
- Increased BUN: May be associated with increases in BUN secondary to antianabolic effects; use caution in patients with renal impairment.
- Photosensitivity: May cause photosensitivity; discontinue if skin erythema occurs. Use skin protection and avoid prolonged exposure to sunlight; do not use tanning equipment.
- Pseudotumor cerebri: Has been (rarely) reported with tetracycline use; usually resolves with discontinuation.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Special populations:

- Pediatrics: May cause tissue hyperpigmentation, enamel hypoplasia, or permanent tooth discoloration; use of tetracyclines should be avoided during tooth development (children ≤8 years of age) unless other drugs are not likely to be effective or are contraindicated. However, recommended in treatment of anthrax exposure.
- Pregnancy: Do not use during pregnancy. In addition to affecting tooth development, tetracycline use has been associated with retardation of skeletal development and reduced bone growth.

Dosage form specific issues:

- Oracea™: Should not be used for the treatment or prophylaxis of bacterial infections, since the lower dose of drug per capsule may be subefficacious and promote resistance.
- Periostat®: Effectiveness has not been established in patients with coexistent oral candidiasis; use with caution in patients with a history or predisposition to oral candidiasis.
- Syrup: Contains sodium metabisulfite.

Geriatric ConsiderationsDose adjustment for renal function is not necessary.

Pregnancy Risk FactorD

Pregnancy ConsiderationsBecause use during pregnancy may cause fetal harm, doxycycline is classified as pregnancy category D. Exposure to tetracyclines during the second or third trimester may cause permanent discoloration of the teeth. Most reports do not show an increase risk for teratogenicity with the exception of a potential small increased risk for cleft palate or esophageal atresia/stenosis. When considering treatment for life-threatening infection and/or prolonged duration of therapy (such as in anthrax), the potential risk to the fetus must be balanced against the severity of the potential illness.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsTetracyclines, including doxycycline, are excreted in breast milk and therefore, breast-feeding is not recommended by the manufacturer.

Doxycycline is less bound to the calcium in maternal milk which may lead to increased absorption compared to other tetracyclines. Only minimal amounts of doxycycline are excreted in human milk and the relative amount of tooth staining has been reported to be lower when compared to other tetracycline analogs. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Doxycycline in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Cardiovascular: Intracranial hypertension, pericarditis

Dermatologic: Angioneurotic edema, exfoliative dermatitis (rare), photosensitivity, rash, skin hyperpigmentation, urticaria

Endocrine & metabolic: Brown/black discoloration of thyroid gland (no dysfunction reported), hypoglycemia

Gastrointestinal: Anorexia, diarrhea, dysphagia, enterocolitis, esophagitis (rare), esophageal ulcerations (rare), glossitis, inflammatory lesions in anogenital region, nausea, oral (mucosal) pigmentation, pseudomembranous colitis, tooth discoloration (children), vomiting

Hematologic: Eosinophilia, hemolytic anemia, neutropenia, thrombocytopenia

Hepatic: Hepatotoxicity (rare)

Renal: BUN increased (dose related)

Miscellaneous: Anaphylactoid purpura, anaphylaxis, bulging fontanels (infants), serum sickness, SLE exacerbation

Note: Adverse effects in clinical trials with Periostat® occurring at a frequency more than 1% greater than placebo included nausea, dyspepsia, joint pain, diarrhea, menstrual cramp, and pain.

Metabolism/Transport Effects**Inhibits** CYP3A4 (moderate)

Drug Interactions

Antacids: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Barbiturates: May decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Bismuth: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Bismuth Subsalicylate: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

CarBAMazepine: May decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Tetracycline Derivatives. Only a concern with orally administered products. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Tetracycline Derivatives may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Penicillins: Tetracycline Derivatives may diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Phenytoin: May decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Quinapril: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: Tetracycline Derivatives may enhance the adverse/toxic effect of Retinoic Acid Derivatives. The development of pseudotumor cerebri is of particular concern. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Tetracycline Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Chronic ethanol ingestion may reduce the serum concentration of doxycycline.

Food: Doxycycline serum levels may be slightly decreased if taken with food or milk. Administration with iron or calcium may decrease doxycycline absorption. May decrease absorption of calcium, iron, magnesium, zinc, and amino acids.

Herb/Nutraceutical: St John's wort may decrease doxycycline levels. Avoid dong quai, St John's wort (may also cause photosensitization).

Test InteractionsFalse elevations of urine catecholamine levels; false-negative urine glucose using Clinistix®, Tes-Tape®

Monitoring ParametersPerform culture and sensitivity testing prior to initiating therapy. CBC, renal and liver function tests periodically with prolonged therapy.

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity test and patient's allergy history prior to beginning therapy. Assess potential for interactions with other pharmacologic agents or herbal products patient may be taking. **IV:** Infusion site must be closely monitored; extravasation can be very irritating to veins (use of central line is preferable). Assess therapeutic effectiveness (according to purpose for use) and adverse response on a regular basis throughout therapy. Advise patients with diabetes about use of Clinistix® (may cause false-negative). Teach patient appropriate use/administration (oral), possible side effects, interventions to reduce side effects (eg, importance of adequate hydration, photosensitivity precautions), and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity testing prior to initiating therapy. CBC, renal and liver function tests periodically with prolonged therapy.

Patient EducationIf administered by infusion, report immediately any acute back pain, difficulty breathing or swallowing, chest tightness, pain, redness, or swelling at infusion site. **Oral:** Do not take any new medication during therapy unless approved by prescriber. Take entire prescription as directed, even if you are feeling better. Follow exact directions for administering the form of drug you are using (eg, tablet, capsules, liquid, or delayed release). Generally, the medication may be taken with food if gastric irritation occurs. Avoid alcohol and maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, drug may cause false test results with Clinistix® urine glucose monitoring; use of another form of glucose monitoring is recommended. You may be sensitive to sunlight (use sunblock, wear protective clothing and eyewear, or avoid exposure to direct sunlight). May cause nausea or vomiting (small frequent meals, frequent mouth care, or sucking lozenges may help) or diarrhea (buttermilk, boiled milk, or yogurt may help). Report skin rash or itching; easy bruising or bleeding; yellowing of skin or eyes; pale stool or dark urine; unhealed mouth sores; vaginal itching or discharge; persistent diarrhea; and fever, chills, or unusual cough. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate barrier contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Note: Strength expressed as base.

Capsule, as hyclate: 50 mg, 100 mg

Vibramycin®: 100 mg

Capsule, as monohydrate: 50 mg, 100 mg

Monodox®: 50 mg, 75 mg, 100 mg

Capsule, variable release:

Oracea™: 40 mg [30 mg (immediate-release) and 10 mg (delayed-release)]

Injection, powder for reconstitution, as hyclate: 100 mg

Doxy-100®: 100 mg

Powder for oral suspension, as monohydrate: 25 mg/5 mL (60 mL)

Vibramycin®: 25 mg/5 mL (60 mL) [raspberry flavor]

Syrup, as calcium:

Vibramycin®: 50 mg/5 mL (480 mL) [contains sodium metabisulfite; raspberry-apple flavor]

Tablet, as hyclate: 20 mg, 100 mg

Periostat®: 20 mg

Vibra-Tabs®: 100 mg

Tablet, as monohydrate: 50 mg, 75 mg, 100 mg, 150 mg

Adoxa®: 50 mg, 75 mg, 100 mg

Adoxa® Pak™ 1/75 [unit-dose pack]: 75 mg (31s)

Adoxa® Pak™ 1/100 [unit-dose pack]: 100 mg (31s)

Adoxa® Pak™ 1/150 [unit-dose pack]: 150 mg (30s)

Adoxa® Pak™ 2/100 [unit-dose pack]: 100 mg (60s)

Tablet, delayed-release coated pellets, as hyclate:

Doryx®: 75 mg [contains sodium 4.5 mg (0.196 mEq); 100 mg [contains sodium 6 mg (0.261 mEq)]; 150 mg [contains sodium 9 mg (0.392 mEq)]

Generic AvailableYes: Excludes capsule (variable release), syrup

Pricing: U.S. (www.drugstore.com)

Capsule, delayed release (Oracea)

40 mg (30): $231.24

Capsules (Doxycycline Hyclate)

50 mg (20): $12.99

100 mg (30): $12.99

Capsules (Doxycycline Monohydrate)

50 mg (30): $29.99

Capsules (Monodox)

75 mg (100): $774.48

100 mg (50): $563.96

Capsules (Vibramycin)

100 mg (20): $129.13

Suspension (reconstituted) (Vibramycin)

25 mg/5 mL (60): $32.98

Syrup (Vibramycin)

50 mg/5 mL (480): $251.95

Tablet, EC (Doryx)

75 mg (30): $214.27

100 mg (30): $249.97

Tablets (Adoxa)

75 mg (30): $228.79

100 mg (30): $243.69

Tablets (Adoxa Pak 1/100)

100 mg (31): $231.97

Tablets (Adoxa Pak 1/150)

150 mg (30): $372.81

Tablets (Adoxa Pak 2/100)

100 mg (60): $465.83

Tablets (Doxycycline Hyclate)

20 mg (30): $31.99

100 mg (20): $13.99

Tablets (Periostat)

20 mg (100): $337.47

Tablets (Vibra-Tabs)

100 mg (20): $129.13

Mechanism of ActionInhibits protein synthesis by binding with the 30S and possibly the 50S ribosomal subunit(s) of susceptible bacteria; may also cause alterations in the cytoplasmic membrane

Periostat® capsules (proposed mechanism): Has been shown to inhibit collagenase activity *in vitro*. Also has been noted to reduce elevated collagenase activity in the gingival crevicular fluid of patients with periodontal disease. Systemic levels do not reach inhibitory concentrations against bacteria.

Pharmacodynamics/Kinetics

Absorption: Oral: Almost complete

Distribution: Widely into body tissues and fluids including synovial, pleural, prostatic, seminal fluids, and bronchial secretions; saliva, aqueous humor, and CSF penetration is poor

Protein binding: 90%

Metabolism: Not hepatic; partially inactivated in GI tract by chelate formation

Half-life elimination: 12-15 hours (usually increases to 22-24 hours with multiple doses); End-stage renal disease: 18-25 hours

Time to peak, serum: 1.5-4 hours

Excretion: Feces (30%); urine (23%)

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Immunization Recommendations
- Malaria Treatment
- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Glossitis and tooth discoloration (children). Opportunistic “superinfection” with *Candida albicans*; tetracyclines are not recommended for use during pregnancy or in children ≤8 years of age since they have been reported to cause enamel hypoplasia and permanent teeth discoloration. The use of tetracyclines should only be used in these patients if other agents are contraindicated or alternative antimicrobials will not eradicate the organism.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusTetracyclines have been reported to cause memory disturbance, mood stabilizing and antidepressant effects

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine; barbiturates and carbamazepine increase the clearance of doxycycline

Index TermsDoxycycline Calcium; Doxycycline Hyclate; Doxycycline Monohydrate

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International Brand NamesAmermycin (HK, TH); Azudoxat (DE); Bactidox (PH); Banndoclin (ID); Bassado (IT); Biodoxi (IN); Biomixin (MX); Bronmycin (MY); Ciclonal (MX); Cyclidox (ZA); Cytragen (PH); Dagracycline (NL); Dagramycine (LU); Dentistar (KP); Deoxymykoin (CZ); Docyl (TH); Doinmycin (TW); Doksiciklin (HR); Doline (MY); Domiken (MX); Doryx (AU, NZ); Dotur (PL); Doxacin (ID); Doxat (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Doxibiotic (IL); Doxiclat (ES); Doxilin-100 (SG); Doximed (FI); Doximycin (CZ, FI); Doxin (ID, PH, TH); Doxine (NZ, SG); Doxsig (AU); Doxy (HK, MY, NZ); Doxy 200 (LU); Doxy Komb (LU); Doxy M (EE); Doxy SMB (LU); Doxy-1 (IN); Doxy-100 (DE, NZ); Doxycap (SG); Doxycline (LU, TH); Doxycyclin AL (HU); Doxycyclin Stada (PL); Doxycycline (BE); Doxycycline-Ethypharm (LU); Doxycycline-Eurogenerics (LU); Doxycyclinum (PL); Doxyhexal (AU, HU, LU); Doxylag (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Doxylcap (TH); Doxylets (LU); Doxylin (AU, IL, NO, TH); Doxyline (SG); Doxylis (FR); Doxymycin (NL, TW, ZA); Doxymycine (LU); Doxypharm (HU); Doxyratio (PL); Dumoxin (AE, BH, CY, EG, ID, IL, IQ, IR, JO, KW, LB, LY, NL, NO, OM, QA, SA, SY, YE); Etidoxina (CO); Frakas (AU); Genobiotic-Doxi (MX); Gewacyclin (AT); Granudoxy (FR, LU); Harvellin (PH); Hiramicin (HR); Interdoxin (ID); Linexine (PE); Madoxy (TH); Medomycin (BF, BJ, CI, ET, GH, GM, GN, HK, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SG, SL, SN, TH, TN, TW, TZ, UG, ZA, ZM, ZW); Miraclin (IT); Monocin (KP); Monodox (CO); Periostat (GB, IE, IL); Radox (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Remycin (TW); Servidoxine (EC); Servidoxyne (MY, TH); Siadocin (TH); Sigadoxin (AT, PT); Supracyclin (AT, CH, PL); Supramycina (CR, DO, GT, HN, NI, PA, PY, SV); Tenutan (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Tetradox (PL); Tolexine (FR); Tolexine Ge (FR); Torymycin (TH); Unidox (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE); Veemycin (TH); Viadoxin (ID); Vibra-S (NL); Vibra-Tabs (AU); Vibrabiotic (GR); Vibradox (DK, PT); Vibramicina (AR, CO, CR, DO, GT, HN, MX, NI, PA, PE, PT, SV, UY); Vibramicina C (VE); Vibramycin (AE, AT, AU, BB, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CY, CZ, DE, EG, ET, GB, GH, GM, GN, GR, GY, HK, HN, HU, ID, IE, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PH, PK, PL, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Vibramycin-N (KP); Vibramycine (BE, FR); Vibratab (HN); Vibraveineuse (FR); Vibravenos (DE); Vivradoxil (MX); Wanmycin (HK); Zadorin (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW)

Doxylamine and Pyridoxine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Doxylamine may be confused with doxycycline

Pronunciation(dox IL a meen & peer i DOX een)

Canadian Brand NamesDiclectin®

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation; Vitamin, Water Soluble

Use: Labeled IndicationsTreatment of pregnancy-associated nausea and vomiting

Dosing: AdultsNausea and vomiting associated with pregnancy: Oral: Two delayed release tablets (a total of doxylamine 20 mg and pyridoxine 20 mg) at bedtime. In severe cases or in cases with nausea/vomiting during the day, dosage may be increased by 1 tablet in the morning and/or afternoon.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment required.

Administration: OralMain dose should be taken at bedtime to provide relief in the early morning hours.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to doxylamine, pyridoxine, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or angle-closure glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Pregnancy Risk FactorA

Pregnancy ConsiderationsDoxylamine has been approved for use in pregnancy-associated nausea and vomiting.

LactationExcretion in breast milk unknown

Breast-Feeding ConsiderationsDoxylamine may be excreted in breast milk, potentially resulting in sedative effects in nursing infants. Approved use of the combination of doxylamine and pyridoxine is limited to the prenatal period.

Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation, tachycardia

Central nervous system: Disorientation, dizziness, drowsiness, headache, paradoxical CNS stimulation, vertigo

Gastrointestinal: Anorexia, constipation, diarrhea, dry mucous membranes, epigastric pain, xerostomia

Genitourinary: Dysuria, urinary retention

Ocular: Blurred vision, diplopia

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Altretamine: Pyridoxine may diminish the therapeutic effect of Altretamine. Specifically when altretamine is used in combination with Cisplatin the response duration may be diminished. *Risk D: Consider therapy modification*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Barbiturates: Pyridoxine may increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Levodopa: Pyridoxine may diminish the therapeutic effect of Levodopa. *Risk D: Consider therapy modification*

Phenytoin: Pyridoxine may increase the metabolism of Phenytoin. This is most apparent in high pyridoxine doses (eg, 80 mg to 200 mg daily) *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Nursing: Physical Assessment/Monitoring See Contraindications, Warnings/Precautions, and Dosing for use cautions. Assess potential for interactions with other prescription, OTC medications, or herbal products patient may be using (see Drug Interactions). Assess therapeutic effectiveness and adverse reactions (see Adverse Reactions) on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report (see Patient Education). Note breast-feeding caution.

Patient Education Inform prescriber of all other prescriptions, OTC medications, or herbal products you are taking and any allergies you have. Take exactly as directed; do not take more than recommended. May cause drowsiness, headache, disorientation, or double vision (use caution when driving or engaged is tasks requiring alertness until response to drug is known); mouth sores, gastrointestinal upset, lack of appetite (small frequent meals, frequent mouth care, or sucking lozenges may help). Report rapid heart beat, palpitations; change in urinary pattern (urinary retention); unusual CNS changes; or other persistent adverse reactions.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet, delayed release:

Diclectin® [CAN]: Doxylamine 10 mg and pyridoxine 10 mg [not available in the U.S.]

ManufacturerDuchesnay (Canada)

Mechanism of Action Doxylamine competes with histamine for H_1-receptor sites on effector cells; blocks chemoreceptor trigger zone, diminishes vestibular stimulation, and depresses labyrinthine function through its central anticholinergic activity. Pyridoxine is a vitamin which may have modest antiemetic effects.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: V_d: 2.5 L/kg

Metabolism: Via multiple metabolic pathways including N-demethylation, oxidation, hydroxylation, N-acetylation to metabolites including nordoxylamine, dinordoxylamine

Half-life elimination: 10-12 hours

Excretion: Urine (primarily as metabolites)

Mental Health: Effects on Mental Status May cause drowsiness, dizziness, disorientation, and paradoxical excitement

Mental Health: Effects on Psychiatric Treatment Concomitant use with psychotropic agents (including valerian, St John's wort, and kava kava) will produce additive sedative and anticholinergic effects. Conversely, the effects of cholinergic agonist will be ameliorated.

Index Terms Doxylamine Succinate and Pyridoxine Hydrochloride; Pyridoxine and Doxylamine

International Brand Names Diclectin (CA)

Doxylamine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Doxylamine may be confused with doxycycline

Pronunciation

(dox IL a meen)

U.S. Brand NamesAldex® AN; Good Sense Sleep Aid [OTC]; Unisom® SleepTabs® [OTC]
Canadian Brand NamesUnisom®-2
Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation
Use: Labeled IndicationsTreatment of short-term insomnia
Dosing: AdultsInsomnia: Oral: One tablet 30 minutes before bedtime; once daily or as instructed by healthcare professional
Dosing: Renal ImpairmentNo dosage adjustment required.
StorageStore at 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to doxylamine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Sleeplessness: If sleeplessness persists for >2 weeks, consult healthcare provider.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or angle-closure glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Respiratory disease: Use with caution in patients with asthma or other chronic breathing disorders.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Geriatric ConsiderationsBecause of its considerable anticholinergic and sedative properties, this medication is not recommended for use in the elderly.
Pregnancy Risk FactorB
Pregnancy ConsiderationsDoxylamine has been approved for used in pregnancy-associated nausea and vomiting.
LactationExcretion in breast milk unknown
Breast-Feeding ConsiderationsDoxylamine may be excreted in breast milk, potentially resulting in sedative effects in nursing infants.
Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation, tachycardia

Central nervous system: Dizziness, disorientation, drowsiness, headache, paradoxical CNS stimulation, vertigo

Gastrointestinal: Anorexia, dry mucous membranes, diarrhea, constipation, epigastric pain, xerostomia

Genitourinary: Dysuria, urinary retention

Ocular: Blurred vision, diplopia

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescription, OTC medications, or herbal products patient may be using. Assess therapeutic effectiveness and adverse reactions on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Patient EducationInform prescriber of all other prescriptions, OTC medications, or herbal products you are taking and any allergies you have. Take exactly as directed; do not take more than recommended. May cause drowsiness, headache, disorientation, or double vision (use caution when driving or engaged is tasks requiring alertness until response to drug is known); mouth sores, gastrointestinal upset, lack of appetite (small frequent meals, frequent mouth care, or sucking lozenges may help). Report rapid heart beat, palpitations; change in urinary pattern (urinary retention); unusual CNS changes; or other persistent adverse reactions. **Breast-feeding precaution:** Consult prescriber before breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as succinate:

Good Sense Sleep Aid, Unisom® SleepTabs®: 25 mg

Tablet, chewable, as succinate:

Aldex® AN: 5 mg [orange flavor]

Generic AvailableYes

Mechanism of ActionDoxylamine competes with histamine for H_1-receptor sites on effector cells; blocks chemoreceptor trigger zone, diminishes vestibular stimulation, and depresses labyrinthine function through its central anticholinergic activity.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: V_d: 2.5 L/kg

Metabolism: Via multiple metabolic pathways including N-demethylation, oxidation, hydroxylation, N-acetylation to metabolites including nordoxylamine, dinordoxylamine

Half-life elimination: 10-12 hours

Excretion: Urine (primarily as metabolites)

Related Information

- Nonbenzodiazepine Anxiolytics and Hypnotics

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dry mucous membranes and significant xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, disorientation, and paradoxical excitement

Mental Health: Effects on Psychiatric TreatmentConcomitant use with psychotropic agents (including valerian, St John's wort, and kava kava) will produce additive sedative and anticholinergic effects. Conversely, the effects of cholinergic agonist will be ameliorated.

Index TermsDoxylamine Succinate

References

Fick DM, Cooper JW, Wade WE, et al "Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults: Results of a US Consensus Panel of Experts," *Arch Intern Med*, 2003, 163(22):2716-24.[PubMed 14662625]

International Brand NamesCalmex (CN); Donormyl (FR); Dozile (NZ); Restavit (AU); Sedaplus (DE); Sleep Aid (IL); Sominar (TH); Somnil (ZA); Tonight (IL); Unisom (IL, PH); Unsono (PT); Zarcop (CN)

Dronabinol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Dronabinol may be confused with droperidol

Pronunciation(droe NAB i nol)
U.S. Brand NamesMarinol®
Canadian Brand NamesMarinol®
Pharmacologic CategoryAntiemetic; Appetite Stimulant
Use: Labeled IndicationsChemotherapy-associated nausea and vomiting refractory to other antiemetic(s); AIDS-related anorexia
Use: Unlabeled/InvestigationalCancer-related anorexia
Dosing: Adults

Antiemetic: Oral: 5 mg/m^2 1-3 hours before chemotherapy, then give 5 mg/m^2/dose every 2-4 hours after chemotherapy for a total of 4-6 doses/day; dose may be increased up to a maximum of 15 mg/m^2/dose if needed (dosage may be increased by 2.5 mg/m^2 increments).

Appetite stimulant (AIDS-related): Oral: Initial: 2.5 mg twice daily (before lunch and dinner); titrate up to a maximum of 20 mg/day.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricAntiemetic: Oral: Refer to adult dosing.
Dosing: Hepatic ImpairmentUsual dose should be reduced in patients with severe liver failure.
Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Dietary ConsiderationsCapsules contain sesame oil.
StorageStore under refrigeration (or in a cool environment) between 8°C and 15°C (46°F and 59°F). Protect from freezing.
RestrictionsC-III
ContraindicationsHypersensitivity to dronabinol, cannabinoids, sesame oil, or any component of the formulation, or marijuana; should be avoided in patients with a history of schizophrenia
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists (drug is psychoactive substance in marijuana). Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment; reduce dosage with severe impairment.
- Psychiatric disorders: Use with caution in patients with mania, depression, or schizophrenia; careful psychiatric monitoring is recommended.
- Seizure disorder: Use with caution in patients with a history of seizure disorder; may lower seizure threshold.

Concurrent drug therapy issues:

- CNS depressants: Effects may be potentiated when used with other psychoactive drugs, sedatives and/or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may cause postural hypotension.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Withdrawal: May cause withdrawal symptoms upon abrupt discontinuation.

Geriatric ConsiderationsElderly patients may be more sensitive to the CNS effects and postural hypotensive effects of dronabinol. Titrate the dose slowly and monitor for adverse effects.

Pregnancy Risk FactorC
LactationEnters breast milk/contraindicated
Adverse ReactionsFrequency not always specified.

>1%:

Cardiovascular: Palpitations, tachycardia, vasodilation/facial flushing

Central nervous system: Euphoria (8% to 24%, dose related), abnormal thinking (3% to 10%), dizziness (3% to 10%), paranoia (3% to 10%), somnolence (3% to 10%), amnesia, anxiety, ataxia, confusion, depersonalization, hallucination

Gastrointestinal: Abdominal pain (3% to 10%), nausea (3% to 10%), vomiting (3% to 10%)

Neuromuscular & skeletal: Weakness

<1%, postmarketing, and/or case reports: Conjunctivitis, depression, diarrhea, fatigue, fecal incontinence, flushing, hypotension, myalgia, nightmares, seizure, speech difficulties, tinnitus, vision difficulties

Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Anticholinergic Agents: May enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Cocaine: May enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Ritonavir: May increase the serum concentration of Dronabinol. *Risk C: Monitor therapy*

Sympathomimetics: Cannabinoids may enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Administration with high-lipid meals may increase absorption.

Herb/Nutraceutical: St John's wort may decrease dronabinol levels.

Test InteractionsDecreased FSH, LH, growth hormone, and testosterone
Monitoring ParametersCNS effects, heart rate, blood pressure, behavioral profile
Reference RangeAntinauseant effects: 5-10 ng/mL
Nursing: Physical Assessment/MonitoringUse caution in the presence of heart disease, hepatic disease, or seizure disorders. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking. Assess effectiveness of therapy according to purpose for use. Monitor closely for adverse psychotic reactions; this drug is the psychoactive substance in marijuana. Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.
Patient EducationDo not take any new medication during therapy unless approved by prescriber (especially barbiturates and benzodiazepines). Take exactly as directed; do not increase dose or take more often than prescribed. Avoid alcohol. May cause psychotic reaction, impaired coordination or judgment, faintness, dizziness, or drowsiness (do not drive or engage in activities that require alertness and coordination until response to drug is known); or clumsiness, unsteadiness, or muscular weakness (change position slowly and use caution when climbing stairs). Report excessive or persistent CNS changes (euphoria, anxiety, depression, memory lapse, bizarre thought patterns, excitability, inability to control thoughts or behavior, fainting); respiratory difficulties; rapid heartbeat; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, soft gelatin: 2.5 mg, 5 mg, 10 mg

Marinol®: 2.5 mg, 5 mg, 10 mg [contains sesame oil]

Generic AvailableYes
ManufacturerRoxane Laboratories, Inc
Pricing: U.S. (www.drugstore.com)

Capsules (Dronabinol)

2.5 mg (60): $259.98

5 mg (60): $679.93

10 mg (60): $959.96

Capsules (Marinol)

2.5 mg (30): $200.01

10 mg (30): $723.16

Mechanism of ActionUnknown, may inhibit endorphins in the brain's emetic center, suppress prostaglandin synthesis, and/or inhibit medullary activity through an unspecified cortical action. Some pharmacologic effects appear to involve sympathimometic activity;

tachyphylaxis to some effect (eg, tachycardia) may occur, but appetite-stimulating effects do not appear to wane over time. Antiemetic activity may be due to effect on cannabinoid receptors (CB1) within the central nervous system.

Pharmacodynamics/Kinetics

Onset of action: Within 1 hour

Peak effect: 2-4 hours

Duration: 24 hours (appetite stimulation)

Absorption: Oral: 90% to 95%; 10% to 20% of dose gets into systemic circulation

Distribution: V_d: 10 L/kg; dronabinol is highly lipophilic and distributes to adipose tissue

Protein binding: 97% to 99%

Metabolism: Hepatic to at least 50 metabolites, some of which are active; 11-hydroxy-delta-9-tetrahydrocannabinol (11-OH-THC) is the major metabolite; extensive first-pass effect

Half-life elimination: Dronabinol: 25-36 hours (terminal); Dronabinol metabolites: 44-59 hours

Time to peak, serum: 0.5-4 hours

Excretion: Feces (50% as unconjugated metabolites, 5% as unchanged drug); urine (10% to 15% as acid metabolites and conjugates)

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and orthostatic hypotension

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Drowsiness, anxiety, confusion, and mood changes are common; may cause depression or hallucinations

Mental Health: Effects on Psychiatric Treatment Concurrent use with barbiturates and benzodiazepines produce additive sedation

Index Terms Delta-9 THC; Delta-9-tetrahydro-cannabinol; Tetrahydrocannabinol; THC

References

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Cat LK and Coleman RL, “Treatment for HIV Wasting Syndrome,” *Ann Pharmacother*, 1994, 28(5):595-7. [PubMed 8068997]

Plasse TF, Gorter RW, Krasnow SH, et al, "Recent Clinical Experience with Dronabinol," *Pharmacol Biochem Behav*, 1991, 40(3):695-700. [PubMed 1666930]

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Tramer MR, Carroll D, Campbell FA, et al, “Cannabinoids for Control of Chemotherapy Induced Nausea and Vomiting: Quantitative Systematic Review,” *BMJ*, 2001, 323(7303):16-21.[PubMed 11440936]

Voth EA and Schwartz RH, “Medicinal Applications of Delta-9-Tetrahydrocannabinol and Marijuana,” *Ann Intern Med*, 1979, 126(10):791-8.[PubMed 9148653]

International Brand Names Elevat (ZA); Marinol (DE)

Droperidol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Droperidol may be confused with dronabinol

Inapsine® may be confused with Nebcin®

Pronunciation(droe PER i dole)

U.S. Brand NamesInapsine®

Canadian Brand NamesDroperidol Injection, USP

Pharmacologic CategoryAntiemetic; Antipsychotic Agent, Typical

Use: Labeled IndicationsAntiemetic in surgical and diagnostic procedures; preoperative medication in patients when other treatments are ineffective or inappropriate

Dosing: AdultsTitrate carefully to desired effect: Prevention of postoperative nausea and vomiting (PONV): I.M., I.V.: Initial: 0.625-2.5 mg; additional doses of 1.25 mg may be administered to achieve desired effect; administer additional doses with caution. Consensus guidelines recommend 0.625-1.25 mg I.V. administered after surgery (Gan, 2003).

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricTitrate carefully to desired effect: Children 2-12 years: Nausea and vomiting: I.M., I.V.: 0.05-0.06 mg/kg (maximum initial dose: 0.1 mg/kg); additional doses may be repeated to achieve effect; administer additional doses with caution

Administration: I.V.Administer I.M. or I.V.; according to the manufacturer, I.V. push administration should be slow (generally regarded as 2-5 minutes); however, many clinicians administer I.V. doses rapidly (over 30-60 seconds) in an effort to reduce the incidence of EPS. The effect, if any, of rapid administration on QT prolongation is unclear. For I.V. infusion, dilute in 50-100 mL NS or D_5W; ECG monitoring for 2-3 hours after administration is recommended regardless of rate of infusion.

Administration: I.V. DetailpH: 3.0-3.8

StorageDroperidol ampuls/vials should be stored at room temperature and protected from light. Solutions diluted in NS or D_5W are stable at room temperature for up to 7 days.

CompatibilityStable in D_5W, LR, NS.

Y-site administration: Compatible: Alatrofloxacin, amifostine, aztreonam, bleomycin, cisatracurium, cisplatin, cladribine, cyclophosphamide, cytarabine, docetaxel, doxorubicin, doxorubicin liposome, etoposide phosphate, famotidine, filgrastim, fluconazole, fludarabine, gatifloxacin, gemcitabine, granisetron, hydrocortisone sodium succinate, idarubicin, linezolid, melphalan, meperidine, metoclopramide, mitomycin, ondansetron, paclitaxel, potassium chloride, propofol, remifentanil, sargramostim, teniposide, thiotepa, vinblastine, vincristine, vinorelbine, vitamin B complex with C. **Incompatible:** Allopurinol, amphotericin B cholesteryl sulfate complex, cefepime, fluorouracil, foscarnet, furosemide, leucovorin, nafcillin, piperacillin/tazobactam. **Variable (consult detailed reference):** Heparin, methotrexate.

Compatibility in syringe: Compatible: Atropine, bleomycin, butorphanol, chlorpromazine, cimetidine, cisplatin, cyclophosphamide, dimenhydrinate, diphenhydramine, doxorubicin, fentanyl, glycopyrrolate, hydroxyzine, meperidine, metoclopramide, midazolam, mitomycin, morphine, nalbuphine, pentazocine, perphenazine, prochlorperazine edisylate, promazine, promethazine, scopolamine, vinblastine, vincristine. **Incompatible:** Fluorouracil, furosemide, heparin, leucovorin, methotrexate, ondansetron, pentobarbital.

ContraindicationsHypersensitivity to droperidol or any component of the formulation; known or suspected QT prolongation, including congenital long QT syndrome (prolonged QT_c is defined as >440 msec in males or >450 msec in females)

Allergy Considerations

- Butyrophenone Allergy

Warnings/Precautions

Boxed warnings:

- Altered cardiac conduction: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Altered cardiac conduction: **[U.S. Boxed Warning]: Cases of QT prolongation and torsade de pointes, including some fatal cases, have been reported.** Use extreme caution in patients with bradycardia (<50 bpm), cardiac disease, concurrent MAO inhibitor therapy, Class I and Class III antiarrhythmics or other drugs known to prolong QT interval, and electrolyte disturbances (hypokalemia or hypomagnesemia), including concomitant drugs which may alter electrolytes (diuretics).
- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, urinary retention, BPH, xerostomia, or visual problems. Relative to other neuroleptics, droperidol has a low potency of cholinergic blockade.

- Esophageal dysmotility/aspiration: Has been associated with antipsychotic use; use with caution in patients at risk of pneumonia (eg, Alzheimer's disease).

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is high relative to other neuroleptics). Risk of dystonia (and possibly other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Neuroleptic malignant syndrome (NMS): Use may be associated with neuroleptic malignant syndrome (NMS); monitor for mental status changes, fever, muscle rigidity and/or autonomic instability.

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Pigmentary retinopathy: May be associated with pigmentary retinopathy.

- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended. Relative to other neuroleptics, droperidol has a low potency of cholinergic blockade.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade. Relative to other neuroleptics, droperidol has a low potency of cholinergic blockade.

- Pheochromocytoma: Use with caution in patients with pheochromocytoma; severe hypertension and/or tachycardia may occur.

- Prolactin-dependent tumors: Use with caution in breast cancer or other prolactin-dependent tumors; may elevate prolactin levels.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizures: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

Special populations:

- Elderly: Use with caution in the elderly; reduce initial dose.

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Dosage form specific issues:

- Benzyl alcohol: Injection contains benzyl alcohol which has been associated with "gasping syndrome" in neonates.

- Sulfites: Injection contains sulfites which may cause allergic reaction.

Geriatric ConsiderationsMany elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior although the use of droperidol is seldom used for this indication. Since elderly frequently have cardiac disease which may result in QT prolongation, evaluation should be made prior to considering use of this agent.
Pregnancy Risk FactorC
Pregnancy ConsiderationsCrosses the placenta
LactationExcretion in breast milk unknown
Adverse Reactions

>10%:

Cardiovascular: QT_c prolongation (dose dependent)

Central nervous system: Restlessness, anxiety, extrapyramidal symptoms, dystonic reactions, pseudoparkinsonian signs and symptoms, tardive dyskinesia, seizure, altered central temperature regulation, sedation, drowsiness

Endocrine & metabolic: Swelling of breasts

Gastrointestinal: Weight gain, constipation

1% to 10%:

Cardiovascular: Hypotension (especially orthostatic), tachycardia, abnormal T waves with prolonged ventricular repolarization, hypertension

Central nervous system: Hallucinations, persistent tardive dyskinesia, akathisia

Gastrointestinal: Nausea, vomiting

Genitourinary: Dysuria

<1%: Adynamic ileus, agranulocytosis, alopecia, amenorrhea, arrhythmia, blurred vision, cholestatic jaundice, contact dermatitis, galactorrhea, gynecomastia, heat stroke, hyperpigmentation, laryngospasm, leukopenia (usually with large doses for prolonged periods), neuroleptic malignant syndrome (NMS), obstructive jaundice, overflow incontinence, photosensitivity (rare), priapism, pruritus, rash, respiratory depression, retinal pigmentation, sexual dysfunction, tardive dystonia, torsade de pointes, urinary retention, ventricular tachycardia, visual acuity decreased (may be irreversible), xerostomia

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Monitoring ParametersTo identify QT prolongation, a 12-lead ECG prior to use is recommended; continued ECG monitoring for 2-3 hours following administration is recommended. Vital signs; lipid profile, fasting blood glucose/Hgb A_{1c}, serum magnesium and potassium; BMI; mental status, abnormal involuntary movement scale (AIMS); observe for dystonias, extrapyramidal side effects, and temperature changes
Nursing: Physical Assessment/MonitoringAssess other medications the patient may be taking for effectiveness and interactions. Monitor vital signs; cardiac and respiratory status on a frequent basis and especially immediately following administration and for several hours afterward. Monitor for extrapyramidal symptoms for 24-48 hours after therapy. Teach and use safety precautions until the patient is stable. Teach adverse reactions to report.
Monitoring: Lab TestsTo identify QT prolongation, a 12-lead ECG prior to use is recommended; ECG monitoring for 2-3 hours following administration is recommended. Lipid profile, fasting blood glucose/Hgb A_{1c}, serum magnesium and potassium; BMI
Patient EducationThis drug may cause you to feel very sleepy; do not attempt to get up without assistance. May cause orthostatic hypotension (use caution when changing position from lying or sitting to standing). You may experience constipation, (increasing exercise, fluids, fruit/fiber may help). Immediately report any respiratory difficulty, confusion, loss of thought processes, or palpitations.
Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 2.5 mg/mL (1 mL, 2 mL)

Inapsine®: 2.5 mg/mL (1 mL, 2 mL)

Generic AvailableYes
Mechanism of ActionDroperidol is a butyrophenone antipsychotic; antiemetic effect is a result of blockade of dopamine stimulation of the chemoreceptor trigger zone. Other effects include alpha-adrenergic blockade, peripheral vascular dilation, and reduction of the pressor effect of epinephrine resulting in hypotension and decreased peripheral vascular resistance; may also reduce pulmonary artery pressure
Pharmacodynamics/Kinetics

Onset of action: Peak effect: Parenteral: ~30 minutes

Duration: Parenteral: 2-4 hours, may extend to 12 hours

Absorption: I.M.: Rapid

Distribution: Crosses blood-brain barrier and placenta

V_d: Children: ~0.25-0.9 L/kg; Adults: ~2 L/kg

Protein binding: Extensive

Metabolism: Hepatic, to *p*-fluorophenylacetic acid, benzimidazolone, *p*-hydroxypiperidine

Half-life elimination: Adults: 2.3 hours

Excretion: Urine (75%, <1% as unchanged drug); feces (22%, 11% to 50% as unchanged drug)

Related Information

- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsDoes not possess analgesic effects; has little or no amnesic properties.

Dental Health: Effects on Dental TreatmentSee Warnings/Precautions. Key adverse event(s) related to dental treatment: Orthostatic hypotension

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsManufacturer's information states that droperidol may block vasopressor activity of epinephrine. This has not been observed during use of epinephrine as a vasoconstrictor in local anesthesia. Droperidol is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Psychiatric TreatmentContraindicated with ziprasidone

Mental Health CommentPrimarily reserved as an agent in acute or intensive care setting for patients in whom rapid control of symptoms/behavior is needed.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Cardiovascular ConsiderationsWarnings concerning QT prolongation have altered recommendations concerning perioperative use and monitoring. Baseline 12-lead ECG screening is recommended, and continued ECG monitoring for 2-3 hours postadministration is advised. Use should be limited to patients in whom alternatives are unacceptable. May cause hypotension and reflex tachycardia. This is more pronounced when the drug is given intravenously. For these reasons, use with caution in patients with angina. Has been associated with cases of QT prolongation and deaths associated with torsade de pointes. These events have occurred at or even below the normal dosage range.

Anesthesia and Critical Care Concerns/Other ConsiderationsMay cause hypotension and reflex tachycardia; this is more pronounced when the drug is given intravenously. Warnings concerning QT prolongation have altered recommendations concerning perioperative use and monitoring. Baseline 12-lead ECG screening is recommended, and continued ECG monitoring for 2-3 hours postadministration is advised. Droperidol does not possess analgesic effects and has little or no amnesic properties.

Index TermsDehydrobenzperidol

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International Brand NamesDehidrobenzoperidol (PT); Dehidrobenzperidol (ES); Dehydrobenzperidol (AE, AT, BE, BH, CY, CZ, DE, DK, EG, FI, IL, IQ, IR, JO, KW, LB, LU, LY, NL, OM, QA, SA, SY, TH, TR, TW, YE); Dridol (NO, SE); Droleptan (AU, FR, GB, IE); Dropedol (TW); Dropel (TW); Droperidol (PL); Droperol (IN); Inapsin (ZA); Sintodian (IT)

Drospirenone and Estradiol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(droh SPYE re none & es tra DYE ole)

U.S. Brand NamesAngeliq®

Canadian Brand NamesAngeliq®

Pharmacologic CategoryEstrogen and Progestin Combination

Use: Labeled IndicationsTreatment of moderate-to-severe vasomotor symptoms associated with menopause; treatment of vulvar and vaginal atrophy associated with menopause

Dosing: Adults

Moderate-to-severe vasomotor symptoms associated with menopause: Oral: One tablet daily; re-evaluate patients at 3- and 6-month intervals to determine if treatment is still necessary.

Atrophic vaginitis in females with an intact uterus: Oral: One tablet daily; re-evaluate patients at 3- and 6-month intervals to determine if treatment is still necessary.

Note: The lowest dose of estrogen/progestin that will control symptoms should be used; medication should be discontinued as soon as possible.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentUse in contraindicated.

Dosing: Hepatic ImpairmentUse in contraindicated.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to drospirenone, estradiol, or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); carcinoma of the breast; estrogen-dependent tumor; hepatic or renal dysfunction or disease; adrenal insufficiency; pregnancy

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.
- Dementia: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Breast cancer: Estrogens may increase the risk of breast cancer. An increased risk of invasive breast cancer was observed in postmenopausal women using CEE in combination with MPA; a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy. Estrogen use may lead to severe hypercalcemia in patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs.
- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in women ≥65 years of age taking CEE alone or in combination with MPA.
- Hyperkalemia: Drospirenone has antimineralocorticoid activity that may lead to hyperkalemia in patients with renal insufficiency, hepatic dysfunction, or adrenal insufficiency; use caution with medications that may increase serum potassium.
- Lipid effects: Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Endometrial carcinoma: Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women. Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent coronary heart disease.** Use caution with cardiovascular disease or dysfunction. May increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA). Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CEE (eg, for prostate cancer).

- Cholestatic jaundice: Use caution with history of cholestatic jaundice associated with past estrogen use or pregnancy.

- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes, or renal dysfunction.

- Gallbladder disease: Use with caution in patients with gallbladder disease.

- Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.

- Hypocalcemia: Use with caution in patients with severe hypocalcemia.

- Porphyria: Use with caution in patients with porphyria.

- SLE: Use with caution in patients with SLE.

Special populations:

- Premenopausal women: Not for use prior to menopause.

- Surgical patients: Whenever possible, estrogens should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- Risks vs. benefits: Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.

- Vulvar and vaginal atrophy use: When used solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should be considered.

Geriatric ConsiderationsBefore prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible side effects and the return of menstrual bleeding (when cycled with a progestin), and be involved in the decision to prescribe. A higher incidence of stroke and invasive breast cancer was observed in women >75 years in a WHI substudy. Oral therapy may be more convenient for vaginal atrophy and urinary incontinence.

Pregnancy ConsiderationsUse is contraindicated during pregnancy

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsFollowing administration of an oral contraceptive agent containing drospirenone, ~0.02% of the dose was detected in breast milk, resulting in a maximum of ~3 mcg/day drospirenone to the infant. Estrogens may decrease the quality and quantity of breast milk.

Adverse Reactions

>10%:

Endocrine & metabolic: Breast pain (19%)

Gastrointestinal: Abdominal pain (11%)

Respiratory: Upper respiratory tract infection (19%)

1% to 10%:

Cardiovascular: Peripheral edema (2%)

Central nervous system: Headache (10%), pain (8%)

Gastrointestinal: Abdomen enlarged (7%)

Genitourinary: Vaginal hemorrhage (9%), endometrial disorder (2%), leukorrhea (1%)

Neuromuscular & skeletal: Back pain (7%)

Respiratory: Flu-like syndrome (7%), sinusitis (5%)

Additional adverse effects reported with estrogens and/or progestins: Abdominal cramps, acne, abnormal uterine bleeding, aggravation of porphyria, amenorrhea, anaphylactoid reactions, anaphylaxis, antifactor Xa decreased, antithrombin III decreased, appetite changes, bloating, breast enlargement, breast tenderness, cerebral embolism, cerebral thrombosis, chloasma, cholestatic jaundice, cholecystitis, cholelithiasis, chorea, contact lens intolerance, corneal curvature steepening, cystitis-like syndrome, decreased carbohydrate tolerance, depression, dementia, dizziness, dysmenorrhea; factors VII, VIII, IX, X, XII, VII-X complex, and II-VII-X complex increased; endometrial hyperplasia, erythema multiforme, erythema nodosum, galactorrhea, hemorrhagic eruption, fatigue, fibrinogen increased, impaired glucose tolerance, HDL-cholesterol increased, hirsutism, hypertension, gallbladder disease, insomnia, LDL-cholesterol decreased, libido changes, melasma, migraine, mood disturbances, nausea, nervousness, optic neuritis, pancreatitis, platelet aggregability and platelet count increased, premenstrual-like syndrome, PT and PTT accelerated, pulmonary embolism, pyrexia, retinal thrombosis, scalp hair loss, somnolence, stroke, thrombophlebitis, thyroid-binding globulin increased, total thyroid hormone (T_4) increased, triglycerides increased, urticaria, uterine leiomyomata size increased, vaginal candidiasis, vomiting, weight gain/loss

Metabolism/Transport Effects

Drospirenone: **Substrate** of CYP3A4 (minor); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2C19 (weak), 3A4 (weak)

Estradiol: **Substrate** of CYP1A2 (major), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2C8 (weak); **Induces** CYP3A4 (weak)

Drug Interactions

ACE Inhibitors: Potassium-Sparing Diuretics may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Ammonium Chloride: Potassium-Sparing Diuretics may enhance the adverse/toxic effect of Ammonium Chloride. Specifically the risk of systemic acidosis. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Cardiac Glycosides: Potassium-Sparing Diuretics may diminish the therapeutic effect of Cardiac Glycosides. Specifically, the inotropic effects. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Mitotane: Potassium-Sparing Diuretics may diminish the therapeutic effect of Mitotane. High dose diuretics (eg, Cushings syndrome) may present significantly higher risk than low doses (eg, CHF). *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy*

modification

Potassium Salts: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Drospirenone may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: Potassium-Sparing Diuretics may diminish the therapeutic effect of QuiNIDine. *Risk C: Monitor therapy*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Somatropin: Estrogen Derivatives may diminish the therapeutic effect of Somatropin. Shown to be a concern with oral hormone replacement therapy in postmenopausal women. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (routine use increases estrogen level and risk of breast cancer). Ethanol may also increase the risk of osteoporosis.

Test InteractionsPathologist should be advised of estrogen/progesterone therapy when specimens are submitted. Reduced response to metyrapone test.

Monitoring ParametersYearly physical examination that includes blood pressure and Papanicolaou smear, breast exam, mammogram. Monitor for signs of endometrial cancer. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals.

Nursing: Physical Assessment/MonitoringSee individual agent for Estradiol.

Monitoring: Lab TestsGlycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy

Patient EducationSee individual agent for Estradiol.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Drospirenone 0.5 mg and estradiol 1 mg

Generic AvailableNo

ManufacturerBerlix, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Angeliq)

0.5-1 mg (28): $64.99

Mechanism of Action

Drospirenone is a synthetic progestin and spironolactone analog with antimineralocorticoid and antiandrogenic activity. Counteracts estrogen effects causing endometrial thinning.

Estrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principal intracellular human estrogen and is more potent than estrone and estriol at the receptor level; it is the primary estrogen secreted prior to menopause. Following menopause, estrone and estrone sulfate are more highly produced. Estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone, and follicle-stimulating hormone through a negative feedback system; estrogen replacement reduces elevated levels of these hormones in postmenopausal women.

Pharmacodynamics/Kinetics

Distribution: Drospirenone: 4.2 L/kg

Protein binding:

Drospirenone: 97%; does not bind to sex hormone binding globulin or corticosteroid binding globulin

Estradiol: 37% bound to sex hormone binding globulin; 61% bound to albumin

Metabolism: Hepatic

Drospirenone forms two metabolites (inactive)

Estradiol: Converted to estrone and estriol; also undergoes enterohepatic recirculation; estrone sulfite is the main metabolite in postmenopausal women

Bioavailability: Drospirenone: 76% to 85%

Time to peak, plasma: Drospirenone: 1 hour; Estradiol: 6-8 hours

Dental Health: Effects on Dental TreatmentWhen prescribing antibiotics, patient must be warned to use additional methods of birth control if on oral contraceptives.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression or other mood disturbances

Mental Health: Effects on Psychiatric TreatmentCombined use with carbamazepine, felbamate, phenobarbital, phenytoin, or topiramate may increase the metabolism of ethinyl estradiol and/or some progestins, leading to possible decrease in contraceptive effectiveness. Estrogens may elevate triglycerides; combined use with clozapine, olanzapine, or quetiapine may produce additive risks; monitor lipid profile.

Mental Health CommentThe role of hormone replacement therapy for postmenopausal women continues to evolve, given findings from a large-scale women's health initiative, which suggested a small but significant increased risk of dementia. Seizure frequency may also be increased in menopausal women with epilepsy.

Index TermsE2 and DRSP; Estradiol and Drospirenone

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International Brand NamesAngeliq (CA)

Drotrecogin Alfa

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(dro TRE coe jin AL fa)

U.S. Brand NamesXigris®

Canadian Brand NamesXigris®

Pharmacologic CategoryProtein C (Activated)

Use: Labeled IndicationsReduction of mortality from severe sepsis (associated with organ dysfunction) in adults at high risk of death (eg, APACHE II score ≥25)

Use: Unlabeled/InvestigationalPurpura fulminans

Dosing: Adults

Purpura fulminans (unlabeled use): 24 mcg/kg/hour

Severe sepsis: I.V.: 24 mcg/kg/hour for a total of 96 hours; stop infusion **immediately** if clinically-important bleeding is identified. **Note:** Use actual body weight for dosing.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricPurpura fulminans (unlabeled use): Refer to adult dosing.

Dosing: Renal ImpairmentNo specific adjustment recommended.

Calculations

- Drotrecogin Alfa

Administration: I.V.Administer via infusion pump. Administration must be completed within 12 hours of solution preparation. Suspend administration for 2 hours prior to invasive procedures or other procedure with significant bleeding risk; may continue treatment immediately following uncomplicated, minimally-invasive procedures, but delay for 12 hours after major invasive procedures/surgery.

Administration: I.V. DetailCompatible with 0.9% sodium chloride; normal saline, dextrose, lactated Ringer's or dextrose/saline mixtures may be infused through the same infusion line. Compatible with ceftriaxone, cisatracurium, fluconazole, nitroglycerin, potassium chloride, and vasopressin.

StorageStore vials under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light. Do not freeze.

ReconstitutionReconstitute 5 mg vials with 2.5 mL and 20 mg vials with 10 mL sterile water for injection (resultant solution ~2 mg/mL). Must be further diluted (within 3 hours of reconstitution) in 0.9% sodium chloride, typically to a concentration between 100 mcg/mL and 200 mcg/mL when using infusion pump and between 100 mcg/mL and 1000 mcg/mL when infused via syringe pump. Although product information states administration must be completed within 12 hours of preparation, additional studies (data on file, Lilly Research Laboratories) show that the final solution is stable for 14 hours at 15°C to 30°C (59°F to 86°F). If not used immediately, a prepared solution may be stored in the refrigerator for up to 12 hours. The total expiration time (refrigeration and administration) should be ≤24 hours from time of preparation.

CompatibilityStable in NS; only NS, dextrose, LR, or dextrose/saline mixtures may be infused through the same line.

Y-site administration: Compatible: Ceftriaxone, cisatracurium, fluconazole, nitroglycerin, potassium chloride, vasopressin. **Incompatible:** Amiodarone, ampicillin/sulbactam sodium, ceftazidime, ciprofloxacin, clindamycin, cyclosporine, dobutamine hydrochloride, dopamine hydrochloride, epinephrine hydrochloride, fosphenytoin, furosemide, gentamicin sulfate, heparin sodium, human serum albumin, imipenem/cilastatin sodium, insulin human (regular), levofloxacin, magnesium sulfate, metronidazole, midazolam hydrochloride, nitroprusside sodium, norepinephrine bitartrate, piperacillin/tazobactam sodium, potassium phosphate, ranitidine hydrochloride, ticarcillin/clavulanate, tobramycin sulfate, vancomycin hydrochloride.

ContraindicationsHypersensitivity to drotrecogin alfa or any component of the formulation; active internal bleeding; recent hemorrhagic stroke (within 3 months); severe head trauma (within 2 months); recent intracranial or intraspinal surgery (within 2 months); intracranial neoplasm or mass lesion; evidence of cerebral herniation; presence of an epidural catheter; trauma with an increased risk of life-threatening bleeding

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: Increases risk of bleeding; careful evaluation of risks and benefit is required prior to initiation. Bleeding risk is increased in patients receiving concurrent therapeutic heparin, oral anticoagulants, glycoprotein IIb/IIIa antagonists, platelet aggregation inhibitors, or aspirin at a dosage of >650 mg/day (within 7 days). In addition, an increased bleeding risk is associated with prolonged INR (>3), gastrointestinal bleeding (within 6 weeks), decreased platelet count (<30,000/mm^3), thrombolytic therapy (within 3 days), recent ischemic stroke (within 3 months), intracranial AV malformation or aneurysm, known bleeding diathesis, severe hepatic disease (chronic), or other condition where bleeding is a significant hazard or difficult to manage due to its location. Discontinue if significant bleeding occurs (may consider continued use after stabilization). Suspend administration for 2 hours prior to invasive procedures or other procedure with significant bleeding risk; may continue treatment immediately following uncomplicated, minimally-invasive procedures, but delay for 12 hours after major invasive procedures/surgery. During treatment, aPTT cannot be used to assess coagulopathy (PT/INR not affected).

Disease-related concerns:

- Conditions excluded from clinical trial: Efficacy not established in adult patients at a low risk of death (APACHE II score <25). Patients with pre-existing nonsepsis-related medical conditions with a poor prognosis (anticipated survival <28 days), patients with acute pancreatitis (no established source of infection), HIV-infected patients with a CD4 count ≤50 cells/mm^3, chronic dialysis patients, pre-existing hypercoagulable conditions, and patients who had received bone marrow, liver, lung, pancreas, or small bowel transplants were excluded from the clinical trial which established benefit. In addition, patients weighing >135 kg were not evaluated.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsAs with all drugs which may affect hemostasis, bleeding is the major adverse effect associated with drotrecogin alfa. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the dosage administered, concurrent use of multiple agents which alter hemostasis, and patient predisposition.

>10%:

Dermatologic: Bruising

Gastrointestinal: Gastrointestinal bleeding

1% to 10%: Hematologic: Bleeding (serious 2.4% during infusion vs 3.5% during 28-day study period; individual events listed as <1%)

<1%: Gastrointestinal hemorrhage, intrathoracic hemorrhage, retroperitoneal bleeding, genitourinary bleeding, intracranial hemorrhage (0.2%; frequencies up to 2% noted in a previous trial without placebo control), skin/soft tissue bleeding, immune reaction (antibody production)

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Antithrombin III: May enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Danaparoid: May enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Fondaparinux: Drotrecogin Alfa may enhance the adverse/toxic effect of Fondaparinux. Bleeding may occur. *Risk D: Consider therapy modification*

Heparin: May enhance the adverse/toxic effect of Drotrecogin Alfa. This is of concern with therapeutic dosages of heparin. Bleeding may occur. *Risk D: Consider therapy modification*

Heparin (Low Molecular Weight): May enhance the adverse/toxic effect of Drotrecogin Alfa. This is of most concern with therapeutic doses of LMW heparin. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Thrombolytic Agents: May enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): May enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Recent use/intake of herbs with anticoagulant or antiplatelet activity (including cat's claw, feverfew, garlic, ginkgo, ginseng, and horse chestnut seed) may increase the risk of bleeding.

Test InteractionsMay interfere with one-stage coagulation assays based on the aPTT (such as factor VIII, IX, and XI assays).

Monitoring ParametersMonitor for signs and symptoms of bleeding, hemoglobin/hematocrit, PT/INR, platelet count

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (especially drugs affecting coagulation or platelet activity). Assess results of laboratory tests prior to, during, and following therapy. Patient must be monitored very closely for bleeding during and following infusion (hemorrhage may occur at virtually any site). If significant bleeding occurs, infusion should be stopped and prescriber notified immediately. Bleeding precautions must be observed. Patient instruction should be according to patient condition.

Monitoring: Lab TestsHemoglobin/hematocrit, PT/INR, platelet count

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. This medication can only be administered by infusion. You will be monitored closely. Report immediately any unusual or acute abdominal pain or headache, or respiratory difficulty. You will be more susceptible to bleeding and bruising; remain in bed and ring for assistance to avoid falling or injuring yourself. Avoid sharps of any kind (knives, scissors, needles, nail clippers, etc; shave with a safety razor). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]: 5 mg [contains sucrose 31.8 mg], 20 mg [contains sucrose 124.9 mg]

Generic AvailableNo

ManufacturerEli Lilly and Co

Mechanism of ActionInhibits factors Va and VIIIa, limiting thrombotic effects. Additional *in vitro* data suggest inhibition of plasminogen activator inhibitor-1 (PAF-1) resulting in profibrinolytic activity, inhibition of macrophage production of tumor necrosis factor, blocking of leukocyte adhesion, and limitation of thrombin-induced inflammatory responses. Relative contribution of effects on the reduction of mortality from sepsis is not completely understood.

Pharmacodynamics/Kinetics

Duration: Plasma nondetectable within 2 hours of discontinuation

Metabolism: Inactivated by endogenous plasma protease inhibitors; mean clearance: 40 L/hour; increased with severe sepsis (~50%)

Half-life elimination: 1.6 hours

Pharmacotherapy PearlsPrepared by recombinant DNA technology in human cell line

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: As with all drugs which may affect hemostasis, bleeding is the major adverse effect associated with drotrecogin alfa. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables, including the dosage administered, concurrent use of multiple agents which alter hemostasis, and patient predisposition.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentConcomitant use with ginkgo and ginseng may increase the risk of bleeding

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2008 Surviving Sepsis Campaign guidelines suggest that adult patients with sepsis-induced organ dysfunction (APACHE II ≥25 or multiple organ failure) receive drotrecogen alfa if there are no contraindications (Grade 2B except for patients within 30 days of surgery [Grade 2C]). Relative contraindications need to be considered also. The guidelines recommend that adult patients with severe sepsis and low risk of death (APACHE II <20) or one organ failure should not receive drotrecogen alfa (Grade 1A).

PROWESS trial: The inclusion criteria for the PROWESS trial (Bernard, 2001) may help in patient selection since it is the first clinical trial evaluating a fixed dose of drotrecogin alfa in severe sepsis. The patients included had a known or suspected infection, three or more signs of systemic inflammatory syndrome (SIRS), and sepsis-induced acute organ dysfunction. Indicators of infection included: White cells in a normally sterile body fluid, perforated viscus, radiographic evidence of pneumonia in association with purulent sputum, a syndrome associated with a high risk of infection (eg, ascending cholangitis). Modified (SIRS) criteria (needed ≥3 criteria): A core temperature of ≥38°C (100.4°F) or ≤36°C (96.8°F); heart rate ≥90 bpm except in patients with a medical condition known to increase the heart rate or those receiving treatment that would prevent tachycardia; respiratory rate ≥20 breaths/minute, a $PaCO_2$ ≤32 mm Hg, or the use of mechanical ventilation; WBC count ≥12,000/mm^3, ≤4000/mm^3, or a differential count with >10% immature neutrophils. Criteria for organ dysfunction included arterial blood pressure ≤90 mm Hg or a MAP ≤70 mm Hg for at least 1 hour despite adequate fluid resuscitation, adequate intravascular volume status, or the use of vasopressors; urine output <0.5 mL/kg/hour for 1 hour despite adequate fluid resuscitation; PaO_2/FiO_2 ≤250 in the presence of other dysfunctional organ systems or ≤200 if the lung is the only dysfunctional organ; platelet count <80,000/mm^3 or acute decrease by 50%; unexplained metabolic acidosis with a high plasma lactate level.

Severe sepsis and a low risk of death: Recently a randomized, double-blind, placebo-controlled, multicenter, international trial (Abraham, 2005) was conducted to evaluate the safety and efficacy of drotrecogin alfa in adult patients with severe sepsis and a low risk of death (APACHE II score <25 or single-organ failure). Patients were randomized to a 96 hour infusion of normal saline or drotrecogin alfa at the FDA approved dose; 2640 patients were enrolled in the study. There was no statistical difference between the groups in 28-day mortality. Hemorrhage accounted for 2 deaths (0.9%) in the placebo group and 7 deaths (2.9%) in the drotrecogin alfa group (p = 0.02) during the infusion. Drotrecogin alfa should not be used in patients with severe sepsis who are at low risk of death because of a lack of efficacy and an increased incidence of bleeding. There was no difference in mortality between active treatment and placebo in these-low risk patients after one year of follow up (Laterre, 2007).

Stability: Drotrecogin alfa has a shorter stability time than was originally suggested. This may lead to some confusion. Additional studies (data on file, Lilly Research Laboratories) show that the final solution is stable for 14 hours at controlled room temperature 15°C to 30°C (59°F to 86°F). If not used immediately, a prepared solution may be stored in the refrigerator for up to 12 hours. The total expiration time (refrigeration and administration) should be ≤24 hours from time of preparation. Due to brief stability consider these dilutions for infusion pumps: 5 mg/50 mL, 10 mg/100 mL, 15 mg/150 mL, 20 mg/200 mL.

Index TermsActivated Protein C, Human, Recombinant; Drotrecogin Alfa, Activated; Protein C (Activated), Human, Recombinant

References

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International Brand NamesXigris (AR, AT, AU, BE, BG, BR, CH, CN, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IN, IT, MX, MY, NL, NO, PE, PL, PT, PY, RU, SE, SG, TR, TW, VE)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Multiple Myeloma

Regimen UseMultiple myeloma

Regimen

Dexamethasone: Oral: 40 mg/day days 1 to 4

[total dose/cycle = 160 mg]

Thalidomide: Oral: 400 mg/day

[total dose/cycle = 11,200 - 16,800 mg]

Cisplatin: I.V.: 10 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 40 mg/m^2]

Doxorubicin: I.V.: 10 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 40 mg/m^2]

Cyclophosphamide: I.V.: 400 mg/m^2 continuous infusion days 1 to 4

[total dose/cycle = 1600 mg/m^2]

Etoposide: I.V.: 40 mg/m^2 continuous infusion days 1 to 4

[total dose/cycle = 160 mg/m^2]

Repeat cycle every 4-6 weeks

References

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DULoxetine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

DULoxetine may be confused with FLUoxetine

Pronunciation(doo LOX e teen)

U.S. Brand NamesCymbalta®

Canadian Brand NamesCymbalta®

Pharmacologic CategoryAntidepressant, Serotonin/Norepinephrine Reuptake Inhibitor

Use: Labeled IndicationsAcute and maintenance treatment of major depressive disorder (MDD); treatment of generalized anxiety disorder (GAD); management of pain associated with diabetic neuropathy; management of fibromyalgia

Use: Unlabeled/InvestigationalTreatment of stress incontinence; management of chronic pain syndromes

Dosing: Adults

Major depressive disorder: Oral: Initial: 40-60 mg/day; dose may be divided (ie, 20 or 30 mg twice daily) or given as a single daily dose of 60 mg; maintenance: 60 mg once daily; for doses >60 mg/day, titrate dose in increments of 30 mg/day over 1 week as tolerated to a maximum dose: 120 mg/day. **Note:** Doses >60 mg/day have not been demonstrated to be more effective.

Diabetic neuropathy: Oral: 60 mg once daily; lower initial doses may be considered in patients where tolerability is a concern and/or renal impairment is present. **Note:** Doses up to 120 mg/day administered in clinical trials offered no additional benefit and were less well tolerated than dose of 60 mg/day.

Fibromyalgia: Oral: Initial: 30 mg/day for 1 week, then increase to 60 mg/day as tolerated. **Note:** Doses up to 120 mg/day administered in clinical trials offered no additional benefit and were less well tolerated than dose of 60 mg/day.

Generalized anxiety disorder: Oral: Initial: 30-60 mg/day as a single daily dose; patients initiated at 30 mg/day should be titrated to 60 mg/day after 1 week; maximum dose: 120 mg/day. **Note:** Doses >60 mg/day have not been demonstrated to be more effective.

Chronic pain syndromes (unlabeled use): Oral: 60 mg once daily

Stress incontinence (unlabeled use): Oral: 40 mg twice daily

Dosing: Elderly

Major depressive disorder: Oral: Manufacturer does not recommend specific dosage adjustment. Conservatively, may initiate at a dose of 20 mg 1-2 times/day; increase to 40-60 mg/day as a single daily dose or in divided doses **or** initiate therapy at 30 mg/day for 1 week then increase to 60 mg/day as tolerated.

Other indications: Refer to adult dosing.

Dosing: Renal ImpairmentNot recommended for use in Cl_{cr} <30 mL/minute or ESRD (contraindicated in Canadian labeling). In mild-moderate impairment, lower initial doses may be considered with titration guided by response and tolerability.

Dosing: Hepatic ImpairmentNot recommended for use in hepatic impairment (contraindicated in Canadian labeling).

Calculations

- Creatinine Clearance: Adults

Administration: OralCapsule should be swallowed whole; do not break open or crush.

Dietary ConsiderationsMay be taken without regard to meals.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsConcomitant use or within 2 weeks of MAO inhibitors; uncontrolled narrow-angle glaucoma

Canadian labeling: Additional contraindications (not in U.S. labeling): Hypersensitivity to duloxetine or any component of the formulation; hepatic impairment; severe renal impairment (eg, Cl_{cr} <30 mL/minute) or end-stage renal disease (ESRD); concomitant use with thioridazine or with CYP1A2 inhibitors

Allergy Considerations

- DULoxetine Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor for clinical worsening, suicidality, or unusual changes in behavior; the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants in children and teenagers should be dispensed with each prescription. **Duloxetine is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial (generally first 1-2 months) few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Duloxetine is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Bleeding risk: May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin or NSAIDs due to ulcerogenic potential. Data are inconclusive regarding extent of bleeding risk of SNRIs in combination with warfarin or other anticoagulants. Bleeding related to SNRI use has been reported to range from relatively minor bruising and epistaxis to life-threatening hemorrhage.

- CNS depression: Has a low potential to impair cognitive or motor performance; caution operating hazardous machinery or driving.

- Hepatotoxicity: Avoid use in patients with substantial ethanol intake, evidence of chronic liver disease or hepatic impairment (contraindicated in Canadian labeling). Rare cases of hepatic failure (including fatalities) have been reported with use. Hepatitis with abdominal pain, hepatomegaly, elevated transaminase levels >20 times the upper limit of normal (ULN) with and without jaundice have all been observed. Discontinue therapy with the presentation of jaundice or other signs of hepatic dysfunction and do not reinitiate therapy unless another source or cause is identified.

- Hyperglycemia: Modest increases in serum glucose and hemoglobin A_{1c} (Hb A_{1c}) levels have been observed in some diabetic patients receiving duloxetine therapy for diabetic peripheral neuropathy (DPN).

- Orthostatic hypotension/syncope: May cause orthostatic hypotension/syncope, especially within the first week of therapy and after dose increases. Carefully monitor blood pressure with initiation of therapy, dose increases (especially in patients receiving >60 mg/day), or when using concomitant vasodilators or CYP1A2 inhibitors.

- Sexual dysfunction: May cause or exacerbate sexual dysfunction.

- SIADH and hyponatremia: SSRIs and SNRIs have been associated with the development of SIADH; hyponatremia has been reported rarely (including severe cases with serum sodium <110 mmol/L), predominately in the elderly. Volume depletion and/or concurrent use of diuretics likely increases risk.

- Urinary hesitancy: May cause increased urinary resistance; advise patient to report symptoms of urinary hesitation/difficulty.

Disease-related concerns:

- Hypertension: Use caution in patients with hypertension. Although no statistically significant differences in the frequency of sustained elevations of blood pressure were observed in clinical trials when compared with placebo, modest increases in blood pressure have been reported with use. Additionally, rare cases of hypertensive crisis have been reported in patients with pre-existing hypertension; blood pressure should be evaluated prior to initiating therapy and periodically thereafter; consider dose reduction or gradual discontinuation of therapy in individuals with sustained hypertension during therapy

- Narrow-angle glaucoma: Associated with an increased risk of mydriasis in patients with controlled narrow-angle glaucoma.

- Renal impairment: Use with caution; clearance is decreased and plasma concentrations are increased; not recommended for use when Cl_{cr} <30 mL/minute or ESRD (contraindicated in Canadian labeling).

- Seizure disorders: Use caution with a previous seizure disorder or condition predisposing to seizures such as brain damage or alcoholism.

Concurrent drug therapy issues:

- Agents which lower seizure threshold: Concurrent therapy with other drugs which lower the seizure threshold.

- Anticoagulants/antiplatelets: Use caution with concomitant use of NSAIDs, ASA, or other drugs that affect coagulation; the risk of bleeding may be potentiated.

- CNS depressants: Use caution with concomitant therapy.
- CYP1A2 inhibitors (eg, fluvoxamine, ciprofloxacin): Concomitant use with duloxetine may increase levels/adverse effects of duloxetine and is not recommended (contraindicated in Canadian labeling).
- MAO inhibitors: Potential for severe reaction when used with MAO inhibitors; autonomic instability, coma, death, delirium, diaphoresis, hyperthermia, mental status changes/agitation, muscular rigidity, myoclonus, neuroleptic malignant syndrome features, and seizures may occur.
- Serotonin modulators: Serotonin syndrome with symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, nausea/vomiting, diarrhea, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce duloxetine's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.
- Thioridazine: Concomitant use is contraindicated in Canadian labeling.

Special populations:

- Sucrose intolerance: Formulation contains sucrose; patients with fructose intolerance, glucose-galactose malabsorption, or sucrose-isomaltase deficiency should avoid use

Other warnings/precautions:

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.
- Withdrawal syndrome: May cause dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. To discontinue therapy with duloxetine, gradually taper dose. If intolerable symptoms occur following a decrease in dosage or upon discontinuation of therapy, then resuming the previous dose with a more gradual taper should be considered.

Geriatric ConsiderationsIn an 8-week study of elderly patients with a history of recurrent major depressive disorder, improvements in verbal learning and memory, and depression response and remission rates were significantly greater in subjects randomized to duloxetine 60 mg per day compared to placebo. Duloxetine was well tolerated. No dose adjustment is necessary for age alone; adjust dose for renal function in the elderly. Higher doses are generally required for treatment of general anxiety disorder, neuropathic pain and stress urinary incontinence (unlabeled use). The elderly are more prone to SSRI/SNRI-induced hyponatremia.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDuloxetine is classified as pregnancy category C due to adverse effects observed in animal studies. Nonteratogenic effects in the newborn following SSRI/SNRI exposure late in the third trimester include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hyper- or hypotonia, hyper-reflexia, jitteriness, irritability, constant crying, and tremor. The long-term effects on neurobehavior have not been studied.

Women treated for major depression and who are euthymic prior to pregnancy are more likely to experience a relapse when medication is discontinued as compared to pregnant women who continue taking antidepressant medications. The ACOG recommends that therapy with SSRIs or SNRIs during pregnancy be individualized; treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary healthcare provider, and pediatrician. If treatment during pregnancy is required, consider tapering therapy during the third trimester in order to prevent withdrawal symptoms in the infant. If this is done and the woman is considered to be at risk of relapse from her major depressive disorder, the medication can be restarted following delivery, although the dose should be readjusted to that required before pregnancy.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsDuloxetine is excreted in human milk. The average relative dose to the infant was calculated to be ~0.14% (maximum: 0.25%) of the weight-adjusted maternal dose. Duloxetine is not stable at an acidic pH; therefore, any drug which reaches the stomach of the breast-feeding infant may degrade, thus decreasing the amount reaching the systemic circulation. Breast-feeding is not recommended by the manufacturer. The long term effects on neurobehavior have not been studied, thus one should prescribe duloxetine to a mother who is breast-feeding only when the benefits outweigh the potential risks.

Pregnancy & Lactation, In-Depth

- DULoxetine in Pregnancy & Lactation

Adverse Reactions

>10%:

Central nervous system: Fatigue (2% to 15%), somnolence (7% to 21%), dizziness (6% to 17%), headache (13% to 20%), insomnia (8% to 16%)

Gastrointestinal: Nausea (14% to 30%), xerostomia (5% to 18%), diarrhea (7% to 13%), constipation (5% to 15%), appetite decreased (3% to 11%)

1% to 10%:

Cardiovascular: Palpitation (1% to 2%)

Central nervous system: Agitation (5% to 6%), anxiety (3%), sleep disorder (3%), dreams abnormal (2% to 3%), fever (1% to 3%), yawning (1% to 2%), hypoesthesia (1%), lethargy (1%), nightmares (1%), vertigo (1%)

Dermatologic: Hyperhydrosis (6% to 8%), rash (4%), pruritus (3%)

Endocrine & metabolic: Libido decreased (2% to 4%), orgasm abnormality (3%), hot flushes (2% to 3%), anorgasmia (1%)

Gastrointestinal: Vomiting (5% to 6%), dyspepsia (4% to 5%), anorexia (3% to 5%), loose stools (2% to 3%), taste abnormal (1% to 3%), weight gain/loss (2%), flatulence (1%)

Genitourinary: Erectile dysfunction (1% to 5%), pollakiuria (1% to 5%), ejaculatory dysfunction (2% to 4%), ejaculation delayed (3%), penis disorder (2%)

Hepatic: ALT >3x ULN (1%)

Neuromuscular & skeletal: Weakness (2% to 8%), musculoskeletal pain (1% to 5%), muscle cramp (4% to 5%), muscle spasms (4%), tremor (3% to 4%), myalgia (1% to 4%), paresthesia (1%), rigors (1%)

Ocular: Blurred vision (1% to 3%)

Respiratory: Nasopharyngitis (7% to 9%), upper respiratory infection (7%), cough (3% to 6%), pharyngolaryngeal pain (1% to 6%)

Miscellaneous: Diaphoresis increased (6%), seasonal allergies (3%)

<1%, postmarketing, and/or case reports: Abdominal pain, acne, agitation, aggression, alkaline phosphatase increased, alopecia, anaphylactic reaction, anger, anemia, angioneurotic edema, aphthous stomatitis, ataxia, atrial fibrillation, bloody stools, bundle branch block, CHF, colitis, CPK increased, dehydration, diastolic blood pressure increased, diplopia, disorientation, diverticulitis, dysarthria, dyskinesia, dyslipidemia, dysphagia, dysuria, ecchymosis, eczema, edema (peripheral), erythema, erythema multiforme, esophageal stenosis, EPS, facial edema, flu-like syndrome, flushing, gastric emptying impaired, gastric ulcer, gastritis, gastroenteritis, GI bleeding, gingivitis, glaucoma, hallucinations, Hb A_{1c} increased, hematochezia, hepatic failure, hepatic steatosis, hepatitis, hepatomegaly, hyperbilirubinemia, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypersensitivity, hypertensive crisis, hyponatremia, hypothyroidism, irritability, irritable bowel syndrome, jaundice, keroconjunctivitis sicca, laryngitis, leukopenia, lymphadenopathy, macular degeneration, maculopathy, malaise, mania, melena, MI, micturition urgency, mood swings, muscle spasm, muscle tightness, muscle twitching, nephropathy, night sweats, nocturia, oropharyngeal edema, orthostatic hypotension, peripheral coldness, phlebitis, photosensitivity, polyuria, retinal detachment, seizure, serotonin syndrome, sexual dysfunction, SIADH, Stevens-Johnson syndrome, stomatitis, suicide, supraventricular arrhythmia, syncope, systolic blood pressure increased, tachycardia, thirst, throat tightness, thrombocytopenia, tinnitus, transaminases increased, trismus, urinary retention, urticaria, visual disturbance; withdrawal syndrome (including headache, dizziness, nightmares, irritability, paresthesia, and/or vomiting)

Metabolism/Transport Effects **Substrate** (major) of CYP1A2, 2D6; **inhibits** CYP2D6 (moderate)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha-/Beta-Agonists: Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Aspirin: Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Fluvoxamine: May decrease the metabolism of DULoxetine. *Risk C: Monitor therapy*

Iobenguane I 123: Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the serotonergic effect of Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor). This may cause serotonin syndrome. *Risk X: Avoid combination*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

NSAID (Nonselective): Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

PARoxetine: May decrease the metabolism of DULoxetine. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Tricyclic Antidepressants: DULoxetine may decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression and/or hepatotoxic potential of duloxetine).

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava, and gotu kola (may increase CNS depression).

Monitoring ParametersBlood pressure should be checked prior to initiating therapy and then regularly monitored, especially in patients with a high baseline blood pressure; mental status for depression, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased), anxiety, social functioning, mania, panic attacks; glucose levels and Hb A_{1c} levels in diabetic patients, creatinine, BUN, transaminases

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and potential interactions. Monitor blood pressure (can cause elevation or orthostatic hypotension) at the beginning of treatment and periodically throughout treatment. Monitor for worsening of depression and suicide ideation. Taper dosage slowly when discontinuing. Do not discontinue abruptly. Assess knowledge/teach appropriate use of this medication, interventions to reduce side effects and adverse reactions.

Monitoring: Lab TestsGlucose levels and Hb A_{1c} levels in diabetic patients, creatinine, BUN, transaminases

Patient EducationTake exactly as directed. Swallow capsule whole; do not open or crush. It may take 2-3 weeks to achieve desired results. Inform prescriber of all prescription medications, OTC medications, or herbal products you are taking. Maintain adequate hydration (2-3 L/day of fluid) unless instructed to restrict fluid intake by prescriber. Avoid alcohol use. If you have diabetes, monitor blood glucose levels closely. May cause increase in glycemic levels. Can cause drowsiness, dizziness, fatigue, insomnia (use caution when driving or engaging in activities requiring alertness until response to drug is known). You may experience headache, nausea, diarrhea (buttermilk, yogurt, or boiled milk may help), constipation (increased exercise, fluids, fruit, or fiber may help), appetite decrease, or xerostomia. Report persistent insomnia, dizziness, headache, thoughts of suicide, worsening of anxiety, panic attacks, agitation, irritability, akathisia, hostility, hypomania, mania. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber before breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, delayed release, enteric coated pellets:

Cymbalta®: 20 mg, 30 mg, 60 mg

Generic AvailableNo

ManufacturerEli Lilly and Co

Pricing: U.S. (www.drugstore.com)

Capsule, enteric pellets (Cymbalta)

20 mg (30): $120.83

30 mg (30): $130.32

60 mg (30): $131.39

Mechanism of ActionDuloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a weak inhibitor of dopamine reuptake. Duloxetine has no significant activity for muscarinic cholinergic, H_1-histaminergic, or alpha$_2$-adrenergic receptors. Duloxetine does not possess MAO-inhibitory activity.

Pharmacodynamics/Kinetics

Absorption: Well absorbed, 2-hour delay in absorption after ingestion; food decreases extent of absorption ~10% (no effect on C_{max})

Distribution: 1640 L (range: 701-3800 L)

Protein binding: >90%; primarily to albumin and α_1-acid glycoprotein

Metabolism: Hepatic, via CYP1A2 and CYP2D6; forms multiple metabolites (inactive)

Half-life elimination: 12 hours (range 8-17 hours)

Time to peak: 6 hours; 10 hours when ingested with food

Excretion: As metabolites; urine (72%), feces (19%)

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAlthough duloxetine is not a tricyclic antidepressant, it does block norepinephrine reuptake within the CNS synapses as part of its mechanism. It has been suggested that vasoconstrictors be administered with caution and to monitor vital signs in dental patients taking antidepressants that affect norepinephrine in this way.

Index Terms(+)-(*S*)-*N*-Methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine Hydrochloride; Duloxetine Hydrochloride; LY248686

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International Brand NamesAriclaim (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Cymbalta (AR, AT, BE, BG, BR, CH, CL, CN, CO, CR, CZ, DE, DK, DO, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IL, IT, MX, MY, NI, NL, NO, PA, PE, PH, PT, RU, SE, SG, SV, TH, TR, TW); Xeristar (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Yentreve (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, MX, NL, NO, PT, RU, SE, TR, TW)

Dutasteride

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(doo TAS teer ide)

U.S. Brand NamesAvodart®

Canadian Brand NamesAvodart®

Pharmacologic Category5 Alpha-Reductase Inhibitor

Use: Labeled IndicationsTreatment of symptomatic benign prostatic hyperplasia (BPH) as monotherapy or combination therapy with tamsulosin

Use: Unlabeled/InvestigationalTreatment of male patterned baldness

Dosing: AdultsMales: Benign prostatic hyperplasia: Oral: 0.5 mg once daily alone or in combination with tamsulosin

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is required.

Dosing: Hepatic ImpairmentUse caution; no specific adjustments recommended.

Administration: OralMay be administered with or without food. Capsule should be swallowed whole; do not chew or open; contact with opened capsule can cause oropharyngeal irritation. Should not be touched or handled by women who are pregnant or are of childbearing age.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to dutasteride, other 5α-reductase inhibitors (eg, finasteride), or any component of the formulation; not indicated for use in women or children; pregnant women or women trying to conceive should not handle the product

Allergy Considerations

- Dutasteride Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.
- Women/pregnancy: Women can absorb the active ingredient through the skin and should always use caution whenever handling. Pregnant women or women trying to conceive should not handle the product; dutasteride may negatively impact fetal development.

Disease-related concerns:

- Diminished urinary flow: Carefully monitor patients with a large residual urinary volume or severely diminished urinary flow for obstructive uropathy; these patients may not be candidates for dutasteride therapy.
- Hepatic impairment: Use with caution in patients with hepatic impairment.

Concurrent drug therapy issues:

- CYP3A4 inhibitors: Use with caution with concurrent use of potent, chronic CYP3A4 inhibitors.

Other warnings/precautions:

- Appropriate use: Other urological diseases including cancer should be ruled out before initiating therapy.
- Blood donation: Avoid donating blood during or for 6 months following treatment due to risk of administration to a pregnant female transfusion recipient.
- PSA monitoring: Reduces prostate specific antigen (PSA) by 40% following 3 months of use and 50% after 6-24 months of use. If following serial PSAs, re-establish a new baseline after 3-6 months of use. If interpreting an isolated PSA value in a patient treated for 6 months, then double the PSA value for comparison.

Pregnancy Risk FactorX

Pregnancy ConsiderationsPreclinical data (animal studies) suggests that the suppression of circulating levels of dihydrotestosterone may inhibit the development of the external genital organs and lead to feminization of a male fetus carried by a woman exposed to dutasteride. Pregnant woman and those who may become pregnant should not handle the capsules because dutasteride is absorbed through the skin. It is distributed into the semen.

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions

>10%: Endocrine & metabolic: Serum testosterone increased, thyroid-stimulating hormone increased

1% to 10%: Endocrine & metabolic: Impotence (1% to 5%), libido decreased (≤3%), ejaculation disorders (≤1%), gynecomastia (including breast tenderness, breast enlargement; ≤1%)

<1%, postmarketing, and/or case reports: Allergic reaction, angioedema, dizziness, edema (localized), hypersensitivity, pruritus, rash, skin

reactions (serious), urticaria

Note: Frequency of adverse events (except gynecomastia) tends to decrease with continued use (>6 months).

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)
Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb Interactions

Ethanol: No effect or interaction noted.

Food: Maximum serum concentrations reduced by 10% to 15% when taken with food; not clinically significant.

Herb/Nutraceutical: St John's wort may decrease dutasteride levels. Avoid saw palmetto (concurrent use has not been adequately studied).

Test InteractionsPSA levels decrease in treated patients. After 6 months of therapy, PSA levels stabilize to a new baseline that is ~50% of pretreatment values. If following serial PSAs in a patient, re-establish a new baseline after 3-6 months of use. If interpreting an isolated PSA value in a patient treated for 6 months, then double the PSA value for comparison.
Monitoring ParametersObjective and subjective signs of relief of benign prostatic hyperplasia, including improvement in urinary flow, reduction in symptoms of urgency, and relief of difficulty in micturition; new baseline PSA level after 3-6 months of therapy
Monitoring: Lab Tests

New baseline PSA level after 3-6 months of therapy

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, softgel:

Avodart®: 0.5 mg

Generic AvailableNo
ManufacturerGlaxoSmithKline
Pricing: U.S. (www.drugstore.com)

Capsules (Avodart)

0.5 mg (30): $98.26

Mechanism of ActionDutasteride is a 4-azo analog of testosterone and is a competitive, selective inhibitor of both reproductive tissues (type 2) and skin and hepatic (type 1) 5α-reductase. This results in inhibition of the conversion of testosterone to dihydrotestosterone and markedly suppresses serum dihydrotestosterone levels.
Pharmacodynamics/Kinetics

Absorption: Via skin when handling capsules

Distribution: V_d: 300-500 L, ~12% of serum concentrations partitioned into semen

Protein binding: 99% to albumin; ~97% to α_1-acid glycoprotein; >96% to semen protein

Metabolism: Hepatic via CYP3A4 isoenzyme; forms metabolites: 6-hydroxydutasteride has activity similar to parent compound, 4'-hydroxydutasteride and 1,2-dihydrodutasteride are much less potent than parent *in vitro*

Bioavailability: ~60% (range: 40% to 94%)

Half-life elimination: Terminal: ~5 weeks

Time to peak: 2-3 hours

Excretion: Feces (40% as metabolites, 5% as unchanged drug); urine (<1% as unchanged drug); 55% of dose unaccounted for

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNefazodone may increase dutasteride levels
International Brand NamesAvidart (ES); Avodart (AR, BE, BG, CH, CN, CZ, DE, DK, EE, FI, FR, GB, HK, HN, ID, IE, IL, IT, KP, MX, MY, NL, NO, PH, PT, SE, SG, TH, TW); Duprost (IN)

DVP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Leukemia, Acute Lymphocytic]

Regimen UseLeukemia, acute lymphocytic

RegimenInduction:

Daunorubicin: I.V.: 25 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 75 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2/day (maximum 2 mg) days 1, 8, 15, and 22

[total dose/cycle = 6 mg/m^2]

Prednisone: Oral: 60 mg/m^2/day days 1 to 28 then taper over next 14 days

[total dose/cycle = 1680 mg/m^2 + taper over next 14 days]

Administer single cycle; used in conjunction with intrathecal chemotherapy

References

Belasco JB, Luery N, and Scher C, âMultiagent Chemotherapy in Relapsed Acute Lymphoblastic Leukemia in Children,â *Cancer*, 1990, 66(12):2492-7.[PubMed 2249189]

Dyclonine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Dyclonine may be confused with dicyclomine

Pronunciation(DYE kloe neen)
U.S. Brand NamesCēpacol® Dual Action Maximum Strength [OTC]; Sucrets® [OTC]
Pharmacologic CategoryLocal Anesthetic, Oral
Use: Labeled IndicationsTemporary relief of pain associated with oral mucosa
Dosing: AdultsTemporary relief of pain: Oral topical:

Lozenge: One lozenge every 2 hours as needed (maximum: 10 lozenges/day)

Spray: 1-4 sprays, up to 4 times a day

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricTemporary relief of pain: Oral topical:

Lozenge: Children ≥2 years: Refer to adult dosing.

Spray:

Children ≥3-12 years: 1-3 sprays, up to 4 times a day

Children ≥12 years: Refer to adult dosing.

Administration: OralAllow lozenge to slowly dissolve in mouth.
Dietary ConsiderationsTopical anesthetics may impair swallowing or eating.
ContraindicationsHypersensitivity to dyclonine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Aspiration: Topical anesthetics may impair swallowing, eating, and may enhance the danger of aspiration.

Special populations:

- Acutely ill/debilitated patients: Use with caution in acutely ill or debilitated patients; risks of systemic toxicity (CNS exacerbation, myocardial depression) may be increased, particularly at excessive dosages.

- Elderly: Use with caution in the elderly; may be at increased risk of adverse effects.

- Pediatrics: Use with caution in children; may be at increased risk of adverse effects.

Other warnings/precautions:

- Area of application: Topical anesthetics should be used with caution in patients with sepsis or traumatized mucosa in the area of application to avoid rapid systemic absorption.

- Self-medication (OTC use): When used for self-medication (OTC) patients should contact healthcare provider if symptoms worsen or last for >7 days. When treating a severe sore throat, patients should contact healthcare provider if symptoms lasts >2 days, occur with fever, headache, rash, nausea, or vomiting. Not for OTC use in children <2 years of age.

Adverse ReactionsThe following were reported with the previously available 0.5% and 1% topical solutions; effects are similar to other local anesthetic agents and are generally dose related; frequency not defined:

Cardiovascular: Bradycardia, hypotension

Central nervous system: Apprehension, confusion, convulsion, dizziness, drowsiness, euphoria, lightheadedness, nervousness

Gastrointestinal: Vomiting

Neuromuscular & skeletal: Numbness, tremor, twitching

Ocular: Blurred vision, double vision

Otic: Tinnitus

Respiratory: Respiratory depression

Miscellaneous: Allergic reactions, cold/heat sensation

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringMonitor for effectiveness of anesthesia and for adverse or toxic reactions. Monitor for return of sensation. Teach patient adverse reactions to report; use and teach appropriate interventions to promote safety.

Patient EducationThis medication is given to reduce sensation in the injected area. When used in mouth or throat; do not eat or drink anything for at least 1 hour following treatment. Take small sips of water at first to ensure that you can swallow without difficulty. Your tongue and mouth may be numb, use caution to avoid biting yourself. Immediately report swelling of face, lips, tongue; chest pain or palpitations; increased restlessness, confusion, anxiety, or dizziness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Lozenge, as hydrochloride (Sucrets®): 1.2 mg [children’s cherry flavor]; 2 mg [wild cherry and assorted flavors]; 3 mg [vapor black cherry and wintergreen flavors]

Spray, oral, as hydrochloride (Cēpacol® Dual Action Maximum Strength): 0.1% (120 mL) [contains glycerin 33%; cherry, honey lemon and cool menthol flavors]

Generic AvailableNo

Pharmacodynamics/Kinetics

Onset of action: Local anesthetic: 2-10 minutes

Duration: ~30 minutes

Absorption: Systemic absorption increased in presence of severely traumatized mucosa

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusRare reports of drowsiness, dizziness, nervousness, and excitation

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDyclonine Hydrochloride

References

Carnel SB, Blakeslee DB, Oswald SG, et al, “Treatment of Radiation- and Chemotherapy-Induced Stomatitis,” *Otolaryngol Head Neck Surg*, 1990, 102(4):326-30. [PubMed 2113258]

Gargiulo AV, Burns GM, and Huck CP, “Dyclonine Hydrochloride - A Topical Agent for Managing Pain,” *Ill Dent J*, 1992, 61(4):303-4. [PubMed 1286862]

Kinzie BJ, “Treatment of Stomatitis Associated With Antineoplastic Drug Therapy,” *Clin Pharm*, 1988, 7:14-7.

Nelson LA, “Nonprescription Drug Screening. Dyclonine Hydrochloride,” *Am Pharm*, 1987, NS27(9):27-9.

Dyphylline and Guaifenesin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(DYE fi lin & gwye FEN e sin)
U.S. Brand NamesCOPD; Difil-G; Difil®-G Forte; Dilex-G; Dilor-G®; Lufyllin®-GG
Pharmacologic CategoryExpectorant; Theophylline Derivative
Use: Labeled IndicationsTreatment of bronchial asthma and reversible bronchospasm associated with chronic bronchitis and emphysema
Dosing: AdultsAsthma/bronchospasm: Oral:

Elixir: Lufyllin®-GG: 30 mL 4 times/day

Syrup:

Dilex-G: 5-10 mL 4 times/day

Difil®-G Forte: 5-10 mL 3 or 4 times/day; may double or triple (in severe cases) according to patient response

Tablet: Difil®-G, Dilex-G, Lufyllin®-GG: One tablet 3 or 4 times/day

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricAsthma/bronchospasm: Oral:

Children 6-12 years:

Elixir: Lufyllin®-GG: 15-30 mL 3 or 4 times/day

Syrup: Dilex-G:

18-27 kg: 1.25-1.6 mL 4 times/day

27-36 kg: 2.5-3.3 mL 4 times/day

36.5-45 kg: 3.3-3.7 mL 4 times/day

Tablet: Lufyllin®-GG: $^1/_2$ -1 tablet 3 or 4 times/day

Children >12 years: Refer to adult dosing.

Dosing: Renal ImpairmentDosage reduction should be considered in severe renal impairment. Half-life of dyphylline is significantly prolonged in anuria.
Administration: OralAdminister after meals to decrease stomach irritation.
StorageStore at room temperature.
ContraindicationsHypersensitivity to dyphylline, guaifenesin, or any component of the formulation
Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiac disease including, acute myocardial injury, hypertension, and heart failure.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Peptic ulcer disease: Use with caution in patient with peptic ulcer disease.
- Renal impairment: Use with caution in patients with severe renal impairment.
- Status asthmaticus: Xanthine derivatives, including theophylline, are not indicated for the management of status asthmaticus.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Geriatric ConsiderationsThere is a lack of significant studies to document the efficacy of guaifenesin. Best to encourage adequate hydration to enhance response to guaifenesin since elderly have a blunted thirst reflex. Elderly are at greater risk for toxicity due to concomitant disease (eg, CHF, arrhythmias); therefore, start at lowest recommended doses.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination. Use during pregnancy only when clearly needed.
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsDyphylline is present in breast milk at approximately twice the maternal plasma concentration.

Adverse ReactionsFrequency not defined. Also see individual agents.

Cardiovascular: Circulatory failure, extrasystoles, flushing, hypotension, palpitation, tachycardia, ventricular arrhythmias

Central nervous system: Agitation, dizziness, drowsiness, headache, hyperexcitability, insomnia, irritability, restlessness, seizure (generalized tonic-clonic)

Endocrine & metabolic: Hyperglycemia, SIADH, uric acid serum concentration decreased

Gastrointestinal: Diarrhea, epigastric pain, hematemesis, nausea, vomiting

Neuromuscular: Muscle twitching

Renal: Albuminuria, diuresis, hematuria

Respiratory: Tachypnea

Drug Interactions

Adenosine: Theophylline Derivatives may diminish the therapeutic effect of Adenosine. *Risk D: Consider therapy modification*

Benzodiazepines: Theophylline Derivatives may diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Uricosuric Agents: May decrease the excretion of Theophylline Derivatives. *Risk C: Monitor therapy*

Test InteractionsGuaifenesin: Possible color interference with determination of 5-HIAA and VMA; discontinue for 48 hours prior to test.

Nursing: Physical Assessment/MonitoringSee individual agent for Guaifenesin.

Patient EducationSee individual agent for Guaifenesin.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Elixir: Dyphylline 100 mg and guaifenesin 100 mg per 15 mL (480 mL)

Lufyllin®-GG: Dyphylline 100 mg and guaifenesin 100 mg per 15 mL (480 mL) [contains alcohol 17%; wine-like flavor]

Liquid: Dyphylline 100 mg and guaifenesin 100 mg per 5 mL (480 mL)

Difil®-G Forte: Dyphylline 100 mg and guaifenesin 100 mg per 5 mL (240 mL) [menthol flavor]

Syrup:

Dilex-G: Dyphylline 100 mg and guaifenesin 200 mg per 5 mL (480 mL) [alcohol free, dye free, and sugar free]

Tablet: Dyphylline 200 mg and guaifenesin 200 mg

COPD, Lufyllin®-GG: Dyphylline 200 mg and guaifenesin 200 mg

Difil®-G: Dyphylline 200 mg and guaifenesin 300 mg

Dilex-G: Dyphylline 200 mg and guaifenesin 400 mg

Generic AvailableYes: Excludes syrup

Pricing: U.S. (www.drugstore.com)

Elixir (Lufyllin-GG)

100-100 mg/15 mL (480): $228.96

Tablets (Dyphylline-Guaifenesin)

200-200 mg (100): $39.47

Tablets (Lufyllin-GG)

200-200 mg (120): $400.97

Mechanism of Action

Dyphylline primarily causes bronchodilation by competitively inhibiting phosphodiesterases resulting in the increase of cyclic AMP and the relaxation of bronchial smooth muscles.

Guaifenesin is thought to act as an expectorant by irritating the gastric mucosa and stimulating respiratory tract secretions, thereby increasing respiratory fluid volumes and decreasing phlegm viscosity.

Pharmacodynamics/Kinetics See individual agents.

Mental Health: Effects on Mental Status May cause agitation, dizziness, drowsiness, hyperexcitability, insomnia, irritability, nervousness, or restlessness

Mental Health: Effects on Psychiatric Treatment May decrease serum lithium levels, monitor; barbiturates and carbamazepine may decrease dyphylline levels; may antagonize effects of benzodiazepines

Index Terms Guaifenesin and Dyphylline

Dyphylline

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

International issues:

Dilor® [Canada] may be confused with Dilar® which is a brand name for paramethasone in France and Mexico

Pronunciation(DYE fi lin)

U.S. Brand NamesDylix; Lufyllin®

Canadian Brand NamesDilor®; Lufyllin®

Pharmacologic CategoryTheophylline Derivative

Use: Labeled IndicationsBronchodilator in reversible airway obstruction due to asthma, chronic bronchitis, or emphysema

Dosing: AdultsBronchoconstriction (asthma, COPD): Oral: Up to 15 mg/kg 4 times/day, individualize dosage

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 50-80 mL/minute: Administer 75% of normal dose.

Cl_{cr} 10-50 mL/minute: Administer 50% of normal dose.

Cl_{cr} <10 mL/minute: Administer 25% of normal dose.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsShould be taken with water 1 hour before or 1 hour after meals.

StorageStore at controlled room temperature.

ContraindicationsHypersensitivity to dyphylline, xanthine compounds, or any component of the formulation; status asthmaticus

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiac disease including, acute myocardial injury, hypertension, and heart failure.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Peptic ulcer disease: Use with caution in patient with peptic ulcer disease.
- Renal impairment: Use with caution in patients with renal impairment; dose adjustment may be required.
- Status asthmaticus: Xanthine derivatives, including theophylline, are not indicated for the management of status asthmaticus.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsBreast milk concentrations are ~2 times the maternal serum concentration.

Adverse ReactionsFrequency not defined. Reactions reported with other xanthine derivatives and may be dose related.

Cardiovascular: Circulatory failure, extrasystoles, flushing, hypotension, palpitation, tachycardia, ventricular arrhythmias

Central nervous system: Agitation, convulsion, fever, headache, hyperexcitability, insomnia, irritability, restlessness

Endocrine & metabolic: ADH syndrome, dehydration, hyperglycemia

Gastrointestinal: Diarrhea, epigastric pain, hematemesis, nausea, vomiting

Neuromuscular & skeletal: Muscle twitching

Renal: Albuminuria, diuresis, hematuria

Respiratory: Respiratory arrest, tachypnea

Drug Interactions

Adenosine: Theophylline Derivatives may diminish the therapeutic effect of Adenosine. *Risk D: Consider therapy modification*

Benzodiazepines: Theophylline Derivatives may diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Uricosuric Agents: May decrease the excretion of Theophylline Derivatives. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Elixir:

Dylix: 100 mg/15 mL (473 mL) [contains alcohol 20%]

Tablet:

Lufyllin®: 200 mg, 400 mg

Generic AvailableYes: Elixir

Pricing: U.S. (www.drugstore.com)

Tablets (Lufyllin)

200 mg (120): $308.16

400 mg (120): $451.51

Mechanism of ActionCauses bronchodilatation, through phosphodiesterase inhibition which increases concentrations of cyclic adenine monophosphate (cAMP) and produces relaxation of bronchial smooth muscle.

Pharmacodynamics/Kinetics

Metabolism: Not converted to free theophylline *in vivo*

Half-life elimination: ~2 hours

Time to peak, plasma: ~45 minutes

Excretion: Urine (88% as unchanged drug)

Related Information

- Theophylline

Dental Health: Effects on Dental TreatmentDo not prescribe any erythromycin product to patients taking theophylline products. Erythromycin will delay the normal metabolic inactivation of theophyllines leading to increased blood levels; this has resulted in nausea, vomiting and CNS restlessness.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness, restlessness, or insomnia

Mental Health: Effects on Psychiatric TreatmentMay decrease serum lithium levels; monitor; barbiturates and carbamazepine may decrease dyphylline levels; may antagonize effects of benzodiazepines

Index TermsDihydroxypropyl Theophylline

International Brand NamesDilor (CA); Diprophylline (RU); Dydilene (KR); Lufyllin (CA); Neophyllin-M (KR); Neutraphylline (BE)

EAP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Gastric Cancer

Regimen Use Gastric cancer

Regimen

Etoposide: I.V.: 120 mg/m^2/day days 4, 5, and 6

[total dose/cycle = 360 mg/m^2]

Doxorubicin: I.V.: 20 mg/m^2/day days 1 and 7

[total dose/cycle = 40 mg/m^2]

Cisplatin: I.V.: 40 mg/m^2/day days 2 and 8

[total dose/cycle = 80 mg/m^2]

Repeat cycle every 22-28 days

References

Preusser P, Wilke H, Achterrath W, et al, “Phase II Study With the Combination Etoposide, Doxorubicin, and Cisplatin in Advanced Measurable Gastric Cancer,” *J Clin Oncol*, 1989, 7(9):1310-17.[PubMed 2671287]

Wilke H, Preusser P, Fink U, et al, “New Developments in the Treatment of Gastric Carcinoma,” *Semin Oncol*, 1990, 17(1 Suppl 2):61-70. [PubMed 2305269]

Wilke H, Preusser P, Fink U, et al, “Preoperative Chemotherapy in Locally Advanced and Nonresectable Gastric Cancer: A Phase II Study With Etoposide, Doxorubicin, and Cisplatin,” *J Clin Oncol*, 1989, 7(9):1318-26.[PubMed 2769330]

EC (NSCLC)

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Nonsmall Cell)

Regimen UseLung cancer, nonsmall cell

Regimen

Etoposide: I.V.: 120 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 360 mg/m^2]

Carboplatin: I.V.: AUC 6 day 1

[total dose/cycle = AUC = 6]

Repeat cycle every 21-28 days

References

Birch R, Weaver CH, Hainsworth JD, et al, âA Randomized Study of Etoposide and Carboplatin With or Without Paclitaxel in the Treatment of Small Cell Lung Cancer,â *Semin Oncol*, 1997, 24(4 Suppl 12):S12-135, 137.[PubMed 9331138]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Small Cell)

Regimen UseLung cancer, small cell

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Etoposide: I.V.: 100-120 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 300-360 mg/m^2]

Carboplatin: I.V.: 325-400 mg/m^2 day 1

[total dose/cycle = 325-400 mg/m^2]

Repeat cycle every 28 days

Variation 2:

Etoposide: I.V.: 120 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 360 mg/m^2]

Carboplatin: I.V.: AUC 6 day 1

[total dose/cycle = AUC = 6]

Repeat cycle every 21-28 days

References

Variation 1:

Kosmidis PA, Samantas E, Fountzilas G, et al, "Cisplatin/Etoposide Versus Carboplatin/Etoposide Chemotherapy and Irradiation in Small Cell Lung Cancer: A Randomized Phase III Study. Hellenic Cooperative Oncology Group for Lung Cancer Trials," *Semin Oncol*, 1994, 1(3 Suppl 6):23-30. [PubMed 8052870]

Variation 2:

Birch R, Weaver CH, Hainsworth JD, et al, "A Randomized Study of Etoposide and Carboplatin With or Without Paclitaxel in the Treatment of Small Cell Lung Cancer," *Semin Oncol*, 1997, 24(4 Suppl 12):135, 137.[PubMed 9331138]

ECF

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Gastric Cancer

Regimen UseGastric cancer

Regimen

Epirubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Cisplatin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 3 weeks

Fluorouracil: I.V.: 200 mg/m^2/day continuous infusion for up to 6 months

[total dose/cycle = 36,000 mg/m^2]

References

Webb A, Cunningham D, Scarffe JH, et al, âRandomized Trial Comparing Epirubicin, Cisplatin, and Fluorouracil Versus Fluorouracil, Doxorubicin, and Methotrexate in Advanced Esophagogastric Cancer,â *J Clin Oncol*, 1997, 15(1):261-7. [PubMed 8996151]

Echothiophate Iodide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(ek oh THYE oh fate EYE oh dide)

U.S. Brand NamesPhospholine Iodide®

Pharmacologic CategoryAcetylcholinesterase Inhibitor; Ophthalmic Agent, Antiglaucoma; Ophthalmic Agent, Miotic

Use: Labeled IndicationsUsed as miotic in treatment of chronic, open-angle glaucoma; may be useful in specific cases of angle-closure glaucoma (postiridectomy or where surgery refused/contraindicated); postcataract surgery-related glaucoma; accommodative esotropia

Dosing: Adults**Open-angle or secondary glaucoma:** Ophthalmic:

Initial: Instill 1 drop (0.03%) twice daily into eyes with 1 dose just prior to bedtime

Maintenance: Some patients have been treated with 1 dose daily or every other day

Conversion from other ophthalmic agents: If IOP control was unsatisfactory, patients may be expected to require higher doses of echothiophate (eg, ≥0.06%); however, patients should be initially started on the 0.03% strength for a short period to better tolerance.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Accommodative esotropia:** Ophthalmic:

Diagnosis: Instill 1 drop (0.125%) once daily into both eyes at bedtime for 2-3 weeks

Treatment: Usual dose: 1 drop of 0.06% once daily or 0.125% every other day (maximum: 0.125% daily). **Note:** Use lowest concentration and frequency which gives satisfactory response; if necessary, doses >0.125% daily may be used for short periods of time.

Administration: Other

Proper administration technique is required for maximal benefit. The nasolacrimal duct(s) should be compressed for 1-2 minutes after instillation of the drops. Excess fluid around the eye should be blotted with tissue, and any contact of medication to the hands should be immediately washed off.

StorageStore undiluted vials at room temperature of 2°C to 8°C (36°F to 46°F). Reconstituted solutions remain stable for 30 days at room temperature or 6 months when refrigerated.

ContraindicationsHypersensitivity to echothiophate or any component of the formulation; most cases of angle-closure glaucoma; active uveal inflammation

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac irregularities: Discontinue if cardiac irregularities occur.
- Cholinergic effects: Discontinue if symptoms of excess cholinergic activity (eg, salivation, sweating, urinary incontinence); overdosage may result in cholinergic crisis, which must be distinguished from myasthenic crisis.
- Cholinesterase levels: May depress plasma and erythrocyte cholinesterase levels after a few weeks of therapy.

Disease-related concerns:

- Asthma: Not generally recommended for use in patients with asthma.
- Cardiovascular disease: Not generally recommended for use in patients with bradycardia, hypotension or recent MI.
- GI disease: Not generally recommended for use in patients with GI disease, including peptic ulcer disease.
- Ocular: Appropriate use: Baseline measurement of anterior chamber angle recommended; routine lens examinations (for opacities) should be conducted. Do not use for tonometric glaucoma, or with active or history of uveitis, or retinal detachment. Use cautiously prior to ophthalmic surgery due to risk of blood in the anterior chamber.
- Parkinsonism: Not generally recommended for use in patients with parkinsonism.
- Seizure disorder: Not generally recommended for use in patients with a history of seizure disorder.
- Vagotonia: Not generally recommended for use in patients with vagotonia.

Concurrent drug therapy issues:

- Anticholinesterase agents: Use with caution in patients on concomitant anticholinesterase agents; warn patients of possible additive effects if chronically exposed to organophosphate/carbamate pesticides/insecticides.
- Succinylcholine: If general anesthesia required, use succinylcholine with great caution due to potential for respiratory or cardiovascular collapse.

Other warnings/precautions:

- Tolerance: Patients may develop tolerance after prolonged use; a rest period restores response to the drug.

Geriatric ConsiderationsAssess patient's ability to self-administer eye drops.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproductive studies have not been conducted. There are no adequate and well-controlled studies in pregnant women. Use only if clearly needed.
Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, cardiac irregularities, flushing, hypotension

Gastrointestinal: Diarrhea, nausea, vomiting

Neurologic & skeletal: Muscle weakness

Ocular: Blurred vision, browache, burning eyes, ciliary redness, conjunctival redness/thickening, intraocular pressure increases (paradoxical), iris cysts, lacrimation, lid muscle twitching, miosis, myopia, latent iritis or uveitis activation, lens opacities, retinal detachment, stinging

Respiratory: Dyspnea

Miscellaneous: Diaphoresis, nasolacrimal canal obstruction

Drug Interactions

Succinylcholine: Echothiophate Iodide may decrease the metabolism of Succinylcholine. *Risk D: Consider therapy modification*

Patient EducationBe sure of solution expiration date. Local irritation and headache may occur. Notify prescriber if abdominal cramps, diarrhea, or salivation occurs. Use caution if driving at night or performing hazardous tasks. Do not touch dropper to eye. Report any change in vision to prescriber. **Pregnancy precaution:** Inform prescriber if you are pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for reconstitution, ophthalmic:

Phospholine Iodide®: 6.25 mg (5 mL) [0.125%; packaged with sterile diluent containing mannitol]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Injection (reconstituted) (Phospholine Iodide)

0.125% (5): $69.99

Mechanism of ActionLong-acting inhibition of cholinesterase enhances activity of endogenous acetylcholine. Reduced degradation of acetylcholine leads to continuous stimulation of the ciliary muscle producing miosis; other effects include potentiation of accommodation and facilitation of aqueous humor outflow, with attendant reduction in intraocular pressure.
Pharmacodynamics/Kinetics

Onset of action: Miosis: 10-30 minutes; Intraocular pressure decrease: 4-8 hours

Peak effect: Intraocular pressure decrease: 24 hours

Duration: Miosis: 1-4 weeks

Related Information

- Glaucoma Drug Therapy

Pharmacotherapy PearlsTolerance may develop after prolonged use; a rest period restores response to the drug.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Anesthesia and Critical Care Concerns/Other ConsiderationsTolerance may develop after prolonged use; a rest period restores response to the drug.
Index TermsEcostigmine Iodide
International Brand NamesPhospholine Iodide (IL); Phospholine Jodide (HN); Phospholinjodid (AT)

English

Jump To Field (Select Field Name)

Pronunciation(e KONE a zole)
U.S. Brand NamesSpectazole® [DSC]
Pharmacologic CategoryAntifungal Agent, Topical
Use: Labeled IndicationsTopical treatment of tinea pedis (athlete's foot), tinea cruris (jock itch), tinea corporis (ringworm), tinea versicolor, and cutaneous candidiasis
Dosing: Adults

Tinea pedis: Apply sufficient amount to cover affected areas once daily for 1 month

Tinea cruris, tinea corporis, tinea versicolor: Apply sufficient amount to cover affected areas once daily for 2 weeks

Cutaneous candidiasis: Apply sufficient quantity twice daily (morning and evening) for 2 weeks

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Administration: TopicalOccasionally, longer treatment periods may be required. For external use only. Avoid contact with the eyes.
ContraindicationsHypersensitivity to econazole or any component of the formulation
Allergy Considerations

- Azole Antifungal Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue if sensitivity or irritation occurs.

Other warnings/precautions:

- Appropriate use: For topical use only; avoid contact with eyes, mouth, nose, or other mucous membranes

Pregnancy Risk FactorC
Pregnancy ConsiderationsFetotoxic and embryotoxic events were observed in animal studies. The manufacturer does not recommend use during pregnancy.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

1% to 10%: Dermatologic: Burning (3%), erythema (3%), itching (3%), stinging (3%)

Postmarketing and/or case reports: Pruritic rash

Metabolism/Transport Effects**Inhibits** CYP2E1 (weak)
Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringAssess effectiveness at regular intervals, especially extended use. Teach patient appropriate application, possible side effects/appropriate interventions, and adverse symptoms to report.
Patient EducationThis mediation is for external use only; avoid contact with eyes, mouth, nose, or other mucous membranes. Apply in sufficient quantity to cover affected area as often as directed by prescriber. Do not cover with occlusive dressings or wrapping unless otherwise directed. Continue applications as long as directed even if area appears to be improved. May cause temporary burning, itching, or stinging. Report if these persist, if condition worsen or persists, or if infection occurs. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical, as nitrate: 1% (15 g, 30 g, 85 g)

Spectazole®: 1% (15 g, 30 g, 85 g) [DSC]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Cream (Econazole Nitrate)

1% (15): $14.99

1% (15): $15.99

1% (30): $26.99

1% (85): $49.99

Mechanism of ActionAlters fungal cell wall membrane permeability; may interfere with RNA and protein synthesis, and lipid metabolism

Pharmacodynamics/Kinetics

Absorption: <10%

Metabolism: Hepatic to more than 20 metabolites

Excretion: Urine (<1%); feces (<1%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsEconazole Nitrate

International Brand NamesBismultin (GR); Derma-Coryl (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Dermazole (AU); Ecalin (HR); Ecanol (IN); Ecoderm (ZA); Econ (TH); Econaderm (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Ecostatin (GB, IE); Ecreme (NZ); Epi-Pevaryl (DE); Gyno (EE); Gyno-Coryl (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Gyno-Pevaryl (HU, LU, PL); Italconazol (EC); Micolis (AR, CN, PE, PY, UY); Micos (IT); Micostyl (BR); Myleugyn LP (FR); Penicomb (GR); Pevaryl (AT, AU, BE, BF, BG, BH, BJ, CH, CI, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, HU, IE, IL, IT, JO, KE, LR, LU, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, PH, PT, RU, SC, SD, SE, SL, SN, TN, TR, TZ, UG, VE, ZA, ZM, ZW); Pevaryl Lipogel (HU, MX, PL); Pevaryl P.v. (HU); Pevaryl P.V. (PL); Pevaryl Powder (PL); Pevaryl Spray Powder (PL); Pevazol (PL); Polycain (JP)

Eculizumab

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Eculizumab may be confused with efalizumab

Pronunciation(e kue LIZ oo mab)

U.S. Brand NamesSoliris™

Pharmacologic CategoryMonoclonal Antibody; Monoclonal Antibody, Complement Inhibitor

Use: Labeled IndicationsTreatment of paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis

Dosing: AdultsPNH: I.V.: 600 mg once weekly (±2 days) for 4 weeks, followed by 900 mg 1 week (±2 days) later; then maintenance: 900 mg every 2 weeks (±2 days) thereafter

Note: Patients must receive meningococcal vaccine at least 2 weeks prior to treatment initiation; revaccinate according to current guidelines.

Treatment should be administered at the recommended time interval, however, the administration day may be varied by ±2 days if serum LDH levels suggest increased hemolysis before the end of the dosing interval.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot studied in renal dysfunction.

Dosing: Hepatic ImpairmentNot studied in hepatic dysfunction.

Administration: I.V.Allow to warm to room temperature prior to administration. Infuse over 35 minutes. Decrease infusion rate or discontinue for infusion reactions; do not exceed a maximum 2-hour duration of infusion. Monitor for at least 1 hour following completion of infusion.

Administration: I.V. DetailpH: 7

StoragePrior to dilution, store vials at 2°C to 8°C (36°F to 46°F). Protect from light; do not freeze; do not shake. Following dilution, store at room temperature or refrigerate; protect from light; use within 24 hours.

ReconstitutionDilute with an equal volume of D_5W, sodium chloride 0.9% sodium chloride 0.45%, or Ringer's injection to a final concentration of 5 mg/mL. (eg, 600 mg in a total volume of 120 mL or 900 mg in a total volume of 180 mL). Gently invert bag to mix.

Compatibility**Compatible** with D_5W, sodium chloride 0.9%, sodium chloride 0.45%, Ringer's injection

RestrictionsPatients and providers must enroll with Soliris™ OneSource™ (1-888-765-4747) prior to treatment initiation.

An FDA-approved medication guide is available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm; distribute to each patient to whom this medication is dispensed.

ContraindicationsHypersensitivity to eculizumab or any component of the formulation; unresolved serious *Neisseria meningitidis* infection; use in patients who have not received *Neisseria meningitidis* vaccination at least 2 weeks prior to first treatment

Warnings/Precautions

Boxed warnings:

- Meningococcal infection: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Infections: In addition to meningitis, the risk of other infections, especially with encapsulated bacteria (eg, *Streptococcus pneumoniae, H. influenzae*) is increased with eculizumab treatment.
- Infusion reactions: Infusion reactions, including anaphylaxis or hypersensitivity, may occur; interrupt infusion for severe reaction. Continue monitoring for 1 hour after completion of infusion.
- Meningococcal infection: **[U.S. Boxed Warning]: The risk for meningococcal*(Neisseria meningitides)*infections (septicemia and/or meningitis) is increased with PNH and may be further increased in patients receiving eculizumab; vaccinate with meningococcal vaccine at least 2 weeks prior to initiation of treatment;** revaccinate according to current guidelines. Quadravalent, conjugated meningococcal vaccines are recommended. Meningococcal infections developed in some patients despite vaccination. Monitor for early signs of meningococcal infections; evaluate and treat promptly. Consider withholding eculizumab during the treatment of serious meningococcal infections.

Disease-related concerns:

- Systemic infections: Use caution in patients with any concurrent systemic infection.

Concurrent drug therapy issues:

- Anticoagulation: In clinical trials, anticoagulant therapy was continued in patients who were receiving these agents prior to initiation of eculizumab. The effect of anticoagulant therapy withdrawal is unknown.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Discontinuation: Patients with PNH who discontinue eculizumab treatment may be at increased risk for serious hemolysis; monitor closely for at least 8 weeks after treatment discontinuation.

- Immunizations: Patients should be brought up to date with all immunizations before initiating therapy.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have demonstrated fetal abnormalities. Human IgG is known to cross the placenta; therefore, eculizumab (a recombinant IgG molecule) may also. There are no adequate and well-controlled studies in pregnant women. Pregnant women with PNH and their fetuses have high rates of morbidity and mortality during pregnancy and the postpartum period. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if eculizumab is excreted in human milk. However, human IgG is excreted in breast milk, and therefore, eculizumab may also be excreted in milk. The risks to the infant from gastrointestinal or limited systemic exposure are unknown.

Adverse Reactions

>10%:

Central nervous system: Headache (2% to 44%), fatigue (12%)

Gastrointestinal: Nausea (16%)

Neuromuscular & skeletal: Back pain (19%)

Respiratory: Nasopharyngitis (23%), cough (12%)

1% to 10%:

Central nervous system: Fever (2%)

Gastrointestinal: Constipation (7%)

Hematologic: Anemia (2%)

Neuromuscular & skeletal: Limb pain (7%), myalgia (7%)

Respiratory: Respiratory tract infection (7%), sinusitis (7%)

Miscellaneous: Herpes infections (7%), flu-like syndrome (5%), viral infection (2%), meningococcal infection (1%)

<1%, postmarketing, and/or case reports: Chills, dizziness, infusion reaction, vomiting

Oncology: Emetic PotentialVery low (<10%)

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersSigns and symptoms of infusion reaction (during infusion and for 1 hour after infusion complete); CBC with differential, lactic dehydrogenase (LDH), AST, urinalysis

After discontinuation: Signs and symptoms of intravascular hemolysis, serum LDH (monitor for at least 8 weeks after discontinuation)

Nursing: Physical Assessment/MonitoringPatient should receive the meningococcal vaccine at least 2 weeks prior to starting therapy. Monitor closely during infusion and for 1hour post infusion. Monitor therapeutic response and adverse reactions at the beginning and periodically throughout therapy.

Monitoring: Lab TestsCBC with differential, lactic dehydrogenase (LDH), AST, urinalysis; after discontinuation, serum LDH (monitor for at least 8 weeks after discontinuation)

Patient EducationYou may experience headache, fatigue, nausea (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help), back pain, sore throat, cough, pain in extremities, muscle pain, nausea, or constipation. You may be at increased risk for meningitis. Menningococcal vaccination is recommended at least 2 weeks prior to starting therapy and repeated per clinical guidelines. Report immediately if you have a moderate-to-severe headache with nausea or vomiting, high fever, stiff neck or back, rash, confusion, severe muscle aches with flu-like symptoms, or eyes sensitive to light. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Soliris™: 10 mg/mL (30 mL) [contains polysorbate 80]

Generic AvailableNo

ManufacturerAlexion Pharmaceuticals, Inc

Mechanism of ActionEculizumab is a humanized monoclonal IgG antibody that binds to complement protein C5, preventing cleavage into C5a and C5b. Blocking the formation of C5b inhibits the subsequent formation of terminal complex C5b-9 or membrane attack complex (MAC). Terminal complement-mediated intravascular hemolysis is a key clinical feature of paroxysmal nocturnal hemoglobinuria. Blocking the formation of MAC results in stabilization of hemoglobin and a reduction in the need for RBC transfusions.

Pharmacodynamics/Kinetics

Onset of action: PNH: Reduced hemolysis: ≤1 week

Distribution: 7.7 L

Half-life elimination: ~11 days (range: ~8-15 days)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue or dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

References

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Hill A, Hillmen P, Richards SJ, et al, “Sustained Response and Long-Term Safety of Eculizumab in Paroxysmal Nocturnal Hemoglobinuria,” *Blood*, 2005, 106(7):2559-65.[PubMed 15985537]

Hillmen P, Hall C, Marsh JC, et al, “Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients With Paroxysmal Nocturnal Hemoglobinuria,” *N Engl J Med*, 2004, 350(6):552-9.[PubMed 14762182]

Hillmen P, Young NS, Schubert J, et al, “The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria,” *N Engl J Med*, 2006, 355(12):1233-43.[PubMed 16990386]

International Brand NamesSolirus (GB, SE)

Edetate CALCIUM Disodium

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Sound-Alike Look-Alike Issues - January, 2008

The U.S. Food and Drug Administration (FDA) has issued a public health advisory alerting healthcare professionals, patients, and caregivers about the possibility of serious outcomes that may result from the improper use of edetate disodium. Edetate disodium (Na$_2$EDTA) may be confused with edetate CALCIUM disodium (CaEDTA). Fatalities have been reported in children and adults who were inadvertently given edetate disodium instead of edetate CALCIUM disodium or when edetate disodium was used for “chelation therapy” and other non-FDA-approved uses. The FDA is currently evaluating the risk/benefit profile of edetate disodium; until further information is available, the following recommendations have been released by the FDA in attempt to reduce the risk of serious medication errors:

- Hospitals should evaluate the need to maintain stock of edetate disodium. If need for edetate disodium is **not** established, remove the entire supply from the pharmacy to reduce the risk of serious medication errors.
- Do **not** use edetate disodium or edetate CALCIUM disodium for unlabeled uses which have no proven benefit (eg, “chelation therapy” other than edetate CALCIUM disodium for lead poisoning, coronary artery disease, and autism).
- Patients with lead poisoning should **only** be treated with the edetate CALCIUM disodium form.
- Do **not** use the abbreviation “EDTA” when prescribing or dispensing either drug.
- Consider **always** including the indication for use on prescriptions for either drug.
- Hospitals, pharmacies, and healthcare providers should **always** double-check the diagnosis, prescription, and drug label at each step of dispensing and medication administration to ensure the correct medication is dispensed and administered to patients.

For more information, refer to the following FDA website: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Edetate

Medication Safety Issues

Sound-alike look-alike issues:

To avoid potentially serious errors, the abbreviation “EDTA” should **never** be used.

Edetate CALCIUM disodium (CaEDTA) may be confused with edetate disodium (Na$_2$EDTA). CDC recommends that edetate disodium should **never** be used for chelation therapy in children. Fatal hypocalcemia may result if edetate disodium is used for chelation therapy instead of edetate calcium disodium. ISMP recommends confirming the diagnosis to help distinguish between the two drugs prior to dispensing and/or administering either drug.

Edetate CALCIUM disodium may be confused with etomidate

Pronunciation(ED e tate KAL see um dye SOW dee um)

U.S. Brand NamesCalcium Disodium Versenate®

Pharmacologic CategoryChelating Agent

Use: Labeled IndicationsTreatment of symptomatic acute and chronic lead poisoning or for symptomatic patients with high blood lead levels

Use: Unlabeled/InvestigationalPossibly useful in poisoning by zinc, manganese, and certain heavy radioisotopes

Dosing: Adults

Treatment of lead poisoning: In adults, available guidelines recommend chelation therapy with blood lead levels >50 mcg/dL and significant symptoms; chelation therapy may also be indicated with blood lead levels ≥100 mcg/dL and/or symptoms (Kosnett, 2007). Depending upon the blood lead level, additional courses may be necessary; repeat at least 2-4 days and preferably 2-4 weeks apart:

Asymptomatic lead poisoning with blood lead level >20 mcg/dL and <70 mcg/dL (manufacturer labeling): I.M., I.V.: 1000 mg/m^2/day (25-50 mg/kg/day) for 5 days. **Note:** the AAP recommends succimer as the drug used for initial management in asymptomatic children when blood lead levels are >45 mcg/dL and <70 mcg/dL. Edetate CALCIUM disodium can be used in children allergic to to succimer (AAP, 2005).

Symptomatic lead poisoning or blood lead levels ≥70 mcg/dL: I.M., I.V.: 1000 mg/m^2/day (25-50 mg/kg/day) for 5 days. Edetate CALCIUM disodium should be administered 4 hours after the initial dimercaprol dose. Edetate CALCIUM disodium should be used in conjunction with dimercaprol when blood lead levels are >70 mcg/dL or when symptoms of lead poisoning are present.

Lead encephalopathy: I.M., I.V.: 1500 mg/m^2/day (50-75 mg/kg/day). Edetate CALCIUM disodium should be administered 4 hours after the initial dimercaprol dose. Edetate CALCIUM disodium should be used in conjunction with dimercaprol when blood lead levels are >70 mcg/dL or when symptoms of lead poisoning are present.

Lead nephropathy: An alternative dosing regimen reflecting the reduction in renal clearance is based upon the serum creatinine. Dose of edetate CALCIUM disodium based on serum creatinine (Morgan, 1975): **Note:** Repeat regimen monthly until lead levels are reduced to an acceptable level:

S_{cr} >2-3 mg/dL / Cl_{cr} 30-50 mL/minute: Reduce recommended dose by 50% and administer daily

S_{cr} >3-4 mg/dL / Cl_{cr} 20-30 mL/minute: Reduce recommended dose by 50% and administer every 48 hours

S_{cr} >4 mg/dL / Cl_{cr} <20 mL/minute: Reduce recommended dose by 50% and administer once weekly

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Treatment of lead poisoning:** For the treatment of high blood lead levels in children, the CDC recommends chelation treatment when blood lead levels are >45 mcg/dL (CDC, 2002). Refer to adult dosing.

Dosing: Renal ImpairmentDose should be reduced with pre-existing mild renal disease. Limiting daily dose to 1 g in children and 2 g in adults may decrease risk of nephrotoxicity, although larger doses may be needed in the treatment of lead encephalopathy.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.M.For I.M. or I.V. use; I.V. is generally preferred, however, I.M. route is preferred when cerebral edema is present.

For I.M. injection: Daily dose should be divided into 2-3 equal doses spaced 8-12 hours apart. Procaine hydrochloride or lidocaine may be added to edetate CALCIUM disodium to minimize pain at injection site. Administer by deep I.M. injection. When used in conjunction with dimercaprol, inject in a separate site.

Administration: I.V.For I.M. or I.V. use; I.V. is generally preferred, however, I.M. route is preferred when cerebral edema is present.

I.V. infusion: Administer daily dose in diluted solution over 8-12 hours or continuously over 24 hours

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ReconstitutionFor I.V. infusion, dilute total daily dose into 250-500 mL of 0.9% sodium chloride or D_5W. Concentrations >0.5% (5 mg/mL) should be avoided. Procaine or lidocaine may be added to solutions given by I.M. injection.

CompatibilityStable in D_5W, NS; **incompatible** with $D_{10}W$, LR, Ringer's injection.

Compatibility when admixed: Incompatible: Amphotericin B, hydralazine.

Contraindications

Active renal disease or anuria; hepatitis

Allergy Considerations

- Bisphosphonate Allergy

Warnings/Precautions

Boxed warnings:

- Cerebral edema: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Hypocalcemia: Fatal hypocalcemia may result if edetate disodium is used for the treatment of lead poisoning instead of edetate CALCIUM disodium.

- Nephrotoxicity: Edetate CALCIUM disodium is potentially nephrotoxic; renal tubular acidosis and fatal nephrosis may occur, especially with high doses; ECG changes may occur during therapy; do not exceed recommended daily dose. If anuria, increasing proteinuria, or hematuria occurs during therapy, discontinue edetate CALCIUM disodium. Minimize nephrotoxicity by adequate hydration, establishment of good urine output, avoidance of excessive doses, and limitation of continuous administration to ≤5 days.

Disease-related concerns:

- Cerebral edema: **[U.S. Boxed Warning]: Use with extreme caution in patients with lead encephalopathy and cerebral edema.** In these patients, I.V. infusion has been associated with lethal increase in intracranial pressure; I.M. injection is preferred.

- Lead poisoning: Investigate, identify, and remove sources of lead exposure prior to treatment. Primary care providers should consult experts in chemotherapy of lead toxicity before using chelation drug therapy.

- Renal impairment: Use with caution in patients with renal impairment; reduced dose recommended.

Other warnings/precautions:

- Potential for name confusion: Exercise caution in the ordering, dispensing, and administration of this drug. Edetate CALCIUM disodium (CaEDTA) may be confused with edetate disodium (Na_2EDTA). The CDC and FDA recommend that edetate disodium should never be used for chelation therapy (especially in children). Death has occurred following the use of edetate disodium for chelation therapy in pediatric patients with autism.

Pregnancy Risk FactorB
Pregnancy ConsiderationsAdverse events were observed in some animal reproduction studies; there are no well controlled studies of edetate CALCIUM disodium in pregnant women. Following maternal occupational exposure, lead was found to cross the placenta in amounts related to maternal plasma levels. Possible outcomes of maternal lead exposure >10 mcg/dL includes spontaneous abortion, postnatal developmental delay, and reduced birth weight. Chelation therapy during pregnancy is for maternal benefit only and should be limited to the treatment of severe, symptomatic lead poisoning.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding Considerations

If present in breast milk, oral absorption of edetate CALCIUM disodium is poor (<5%) which would limit exposure to a nursing infant. However, edetate CALCIUM disodium is not used orally because it may increase lead absorption from the GI tract. The amount of lead in breast milk may range from 0.6% to 3% of the maternal serum concentration. Calcium supplementation may reduce the amount of lead in breast milk.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, ECG changes, hypotension

Central nervous system: Chills, fatigue, fever, headache, malaise

Dermatologic: Cheilosis, dermatitis, rash

Endocrine & metabolic: Hypercalcemia

Gastrointestinal: Anorexia, GI upset, nausea, thirst (excessive), vomiting

Hematologic: Anemia, bone marrow suppression (transient)

Hepatic: Liver function test increased (mild)

Local: Thrombophlebitis following I.V. infusion (when concentration >5 mg/mL), pain at injection site following I.M. injection

Neuromuscular & skeletal: Arthralgia, myalgia, numbness, tremor

Ocular: Lacrimation

Renal: Glucosuria, nephrotoxicity, renal tubular necrosis, microscopic hematuria, proteinuria, urinary frequency/urgency

Respiratory: Nasal congestion, sneezing

Miscellaneous: Iron, magnesium, and/or zinc deficiency (with chronic therapy)

Drug Interactions

Insulin: Edetate CALCIUM Disodium may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Test InteractionsIf edetate CALCIUM disodium is given as a continuous I.V. infusion, stop the infusion for at least 1 hour before blood is drawn for lead concentration to avoid a falsely elevated value
Monitoring ParametersUrinary output; ECG changes (with I.V. therapy); blood lead levels (baseline and 7-21 days after completing chelation therapy); hemoglobin or hematocrit, iron status, free erythrocyte protoporphyrin or zinc protoporphyrin; neurodevelopmental changes
Monitoring: Lab TestsBlood lead levels (baseline and 7-21 days after completing chelation therapy); hemoglobin or hematocrit, iron status, free erythrocyte protoporphyrin or zinc protoporphyrin
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 200 mg/mL (5 mL)

Generic AvailableNo
Mechanism of ActionCalcium is displaced by divalent and trivalent heavy metals, forming a nonionizing soluble complex that is excreted in urine
Pharmacodynamics/Kinetics

Onset of action: Chelation of lead: I.V.: 1 hour

Absorption: I.M., SubQ: Well absorbed; Oral: <5%

Distribution: Into extracellular fluid; minimal CSF penetration (~5%)

Half-life elimination, plasma: 20-60 minutes

Excretion: Urine (as metal chelates or unchanged drug); decreased GFR decreases elimination

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentBest to avoid concomitant ziprasidone use due to ECG changes associated with therapy
Index TermsCaEDTA ; Calcium Disodium Edetate; Edetate Disodium CALCIUM; EDTA (CALCIUM Disodium) (error-prone abbreviation)
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American Academy of Pediatrics Committee on Environmental Health, "Lead Exposure in Children: Prevention, Detection, and Management," *Pediatrics*, 2005, 116(4):1036-46.[PubMed 16199720]

Centers for Disease Control and Prevention (CDC), “Deaths Associated With Hypocalcemia From Chelation Therapy --Texas, Pennsylvania, and Oregon, 2003-2005,” *MMWR Morb Mortal Wkly Rep*, 2006, 55(8):204-7.[PubMed 16511441]

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International Brand NamesCalcium Disodium Versenate (AU, HK); Calcium Edetate de Sodium (FR); Ledclair (GB); Versenato calcio disodico (CN)

Edetate Disodium

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Sound-Alike Look-Alike Issues - January, 2008

The U.S. Food and Drug Administration (FDA) has issued a public health advisory alerting healthcare professionals, patients, and caregivers about the possibility of serious outcomes that may result from the improper use of edetate disodium. Edetate disodium (Na_2EDTA) may be confused with edetate CALCIUM disodium (CaEDTA). Fatalities have been reported in children and adults who were inadvertently given edetate disodium instead of edetate CALCIUM disodium or when edetate disodium was used for "chelation therapy" and other non-FDA-approved uses. The FDA is currently evaluating the risk/benefit profile of edetate disodium; until further information is available, the following recommendations have been released by the FDA in attempt to reduce the risk of serious medication errors:

- Hospitals should evaluate the need to maintain stock of edetate disodium. If need for edetate disodium is **not** established, remove the entire supply from the pharmacy to reduce the risk of serious medication errors.
- Do **not** use edetate disodium or edetate CALCIUM disodium for unlabeled uses which have no proven benefit (eg, "chelation therapy" other than edetate CALCIUM disodium for lead poisoning, coronary artery disease, and autism).
- Patients with lead poisoning should **only** be treated with the edetate CALCIUM disodium form.
- Do **not** use the abbreviation "EDTA" when prescribing or dispensing either drug.
- Consider **always** including the indication for use on prescriptions for either drug.
- Hospitals, pharmacies, and healthcare providers should **always** double-check the diagnosis, prescription, and drug label at each step of dispensing and medication administration to ensure the correct medication is dispensed and administered to patients.

For more information, refer to the following FDA website: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Edetate

Medication Safety Issues

Sound-alike look-alike issues:

To avoid potentially serious errors, the abbreviation "EDTA" should **never** be used.

Edetate disodium (Na_2EDTA) may be confused with edetate calcium disodium (CaEDTA). CDC recommends that edetate disodium should **never** be used for chelation therapy in children. Fatal hypocalcemia may result if edetate disodium is used for chelation therapy instead of edetate calcium disodium. ISMP recommends confirming the diagnosis to help distinguish between the two drugs prior to dispensing and/or administering either drug.

Edetate disodium may be confused with etomidate

Pronunciation(ED e tate dye SOW dee um)

U.S. Brand NamesEndrate® [DSC]

Pharmacologic CategoryChelating Agent

Use: Labeled IndicationsEmergency treatment of hypercalcemia in adults

Use: Unlabeled/InvestigationalEmergency treatment of hypercalcemia in children

Dosing: Adults**Note:** Confirm the diagnosis prior to dispensing.

Hypercalcemia: I.V.: 50 mg/kg/day over 3 or more hours to a maximum of 3 g/24 hours; a suggested regimen of 5 days followed by 2 days without drug and repeated courses up to 15 total doses

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Confirm the diagnosis prior to dispensing.

Hypercalcemia (unlabeled use): I.V.: 40-70 mg/kg/day slow infusion over 3-4 hours or more to a maximum of 3 g/24 hours; administer for 5 days and allow 5 days between courses of therapy.

Administration: I.M.Not for I.M. use

Administration: I.V.Must be diluted before I.V. use in D_5W or NS to a maximum concentration of 30 mg/mL (3%) and infused over at least 3 hours; avoid extravasation

Dietary ConsiderationsSodium content of 1 g: 5.4 mEq

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, $D_5{}^1/_4$NS, $D_5{}^1/_2$NS, D_5NS, D_5W, D_{10}W, D_{10}NS, ${}^1/_2$NS, NS.
ContraindicationsHypersensitivity to edetate disodium or any component of the formulation; severe renal disease or anuria
Allergy Considerations

- Bisphosphonate Allergy

Warnings/Precautions

Boxed warnings:

- Appropriate use: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Hypocalcemia: Fatal hypocalcemia may result if edetate disodium is used for the treatment of lead poisoning instead of edetate CALCIUM disodium.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; may decrease blood glucose.
- Hypokalemia: Use with caution in patients with hypokalemia; monitor closely.
- Intracranial lesions: Use with caution in patients with intracranial lesions.
- Renal impairment: Use with caution in patients with renal impairment.
- Seizures: Use with caution in patients with a history of seizure disorder.
- Vascular disease: Not recommended for the treatment of atherosclerotic cardiovascular disease; no evidence of a beneficial effect with chelation therapy.

Special populations:

- Pediatrics: Safety and efficacy have not been established in pediatric patients. The CDC and FDA recommend that edetate disodium should never be used for chelation therapy in children. Death has occurred following the use of edetate disodium for chelation therapy in pediatric patients with autism.

Other warnings/precautions:

- Appropriate use: **[U.S. Boxed Warning]: Use of this drug is recommended only when the severity of the clinical condition justifies the aggressive measures associated with this type of therapy.**
- Potential for name confusion: Exercise caution in the ordering, dispensing, and administration of this drug. Edetate disodium (Na_2EDTA) may be confused with edetate CALCIUM disodium (CaEDTA). The CDC and FDA recommend that edetate disodium should never be used for chelation therapy (especially in children).
- Infusion reactions: Rapid I.V. administration or excessive doses may cause a sudden drop in serum calcium concentration which may lead to hypocalcemic tetany, seizure, arrhythmia, and death from respiratory arrest. Do not exceed recommended dosage and rate of administration.

Pregnancy Risk FactorC
Adverse ReactionsFrequency not always defined.

Gastrointestinal: Nausea, vomiting, abdominal cramps, diarrhea

<1%: Arrhythmias, transient hypotension, acute tubular necrosis, seizure, fever, headache, tetany, chills, eruptions, dermatologic lesions, hypomagnesemia, hypokalemia, anemia, thrombophlebitis, pain at the site of injection, paresthesia, back pain, muscle cramps, nephrotoxicity, death from respiratory arrest

Drug Interactions

Insulin: Edetate Disodium may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Monitoring ParametersECG monitoring; blood pressure during infusion; renal function should be assessed before and during therapy; monitor calcium, magnesium, and potassium levels
Monitoring: Lab TestsCalcium, magnesium, and potassium levels
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution: 150 mg/mL (20 mL)

Endrate®: 150 mg/mL (20 mL) [DSC]

Generic AvailableYes
Mechanism of ActionChelates with divalent or trivalent metals to form a soluble complex that is then eliminated in urine
Pharmacodynamics/Kinetics

Metabolism: None

Half-life elimination: 20-60 minutes

Time to peak: I.V.: 24-48 hours

Excretion: Following chelation: Urine (95%); chelates within 24-48 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsEdathamil Disodium; EDTA (Disodium) (error-prone abbreviation); Na_2EDTA; Sodium Edetate

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International Brand NamesOpti-Free Express (MX)

Edrophonium and Atropine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(ed roe FOE nee um & A troe peen)
U.S. Brand NamesEnlon-Plus™ [DSC]
Pharmacologic CategoryAnticholinergic Agent; Antidote; Cholinergic Agonist
Use: Labeled IndicationsReversal of nondepolarizing neuromuscular blockers; adjunct treatment of respiratory depression caused by curare overdose
Dosing: AdultsReversal of neuromuscular blockade: I.V.: 0.05 mL/kg given over 45-60 seconds. The dose delivered is 0.5-1 mg/kg of edrophonium and 0.007-0.015 mg/kg of atropine. An edrophonium dose of 1 mg/kg should rarely be exceeded. **Note:** Monitor closely for bradyarrhythmias. Have atropine on hand in case needed.
Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentAdjustment not required.
Dosing: Hepatic ImpairmentAdjustment not required.
Administration: I.V. DetailpH: 4-5
StorageStore at 15°C to 26°C (59°F to 78°F).
ContraindicationsHypersensitivity to edrophonium, atropine, sulfites, or any component of the formulation; GI or GU obstruction. Atropine is contraindicated in acute glaucoma, adhesions (synechiae) between the iris and the lens of the eye, and pyloric stenosis.
Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anticholinesterase insensitivity: if patient becomes insensitive to the drug, reduce dose or discontinue edrophonium until patient sensitive again.
- Respiratory arrest: Rare reports of respiratory arrest have occurred with edrophonium.
- Tissue irritation: May cause tissue irritation if extravasated.

Disease-related concerns:

- Arrhythmias: Use with caution in patients with cardiac arrhythmias (eg, bradyarrhythmias).
- Asthma: Use with caution in patients with bronchial asthma.
- Chronic lung disease: Use with caution in patients with chronic lung disease.
- Prostatic hyperplasia: Use with caution in patients with prostatic hyperplasia.
- Myasthenia gravis: Avoid use in myasthenia gravis; may exacerbate muscular weakness.

Concurrent drug therapy issues:

- Anticholinergics: Consider additive adverse effects with concurrent use of atropine and other anticholinergics (eg, tricyclic antidepressants, antipsychotics, some antihistamines, anti-Parkinson drugs).
- Atropine: Patients who are bradycardic or at risk of being bradycardic (eg, those on a beta-blocker or cardiovascular patients who received anesthesia with a narcotic and nitrous oxide only) should first receive atropine prior to edrophonium-atropine combination. Most arrhythmias occur within 2 minutes of administration and reverse shortly thereafter. Atropine should be available for immediate use in case of severe cholinergic reaction. Bradyarrhythmias respond to small doses of atropine.
- Nondepolarizing muscle relaxants: Should not be administered before any nondepolarizing muscle relaxant.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Sodium sulfite: Products may contain sodium sulfite.

Geriatric ConsiderationsNot enough elderly patients were included in clinical trials to determine differences in response from younger adults. Initiate dose at the lower end of the dosing range.
Pregnancy Risk FactorC
Pregnancy ConsiderationsSee Atropine monograph.
Breast-Feeding ConsiderationsSee Atropine monograph.

Adverse ReactionsAlso see individual agents.

>10%: Cardiovascular: Bradycardia, junctional rhythm, tachycardia

1% to 10%: Cardiovascular: Atrial premature contractions (3% to 10%), first-degree AV block (3% to 10%), P-wave changes (3% to 10%), second-degree AV block (3% to 10%), third-degree AV block (1% to 3%), premature ventricular contractions (1% to 3%)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Monitoring ParametersVital signs, ECG, and ventilatory support; neuromuscular function
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution:

Enlon-Plus™: Edrophonium chloride 10 mg/mL and atropine sulfate 0.14 mg/mL (5 mL, 15 mL) [contains sodium sulfite] [DSC]

Generic AvailableNo
ManufacturerBaxter
Mechanism of Action

Edrophonium: Inhibits destruction of acetylcholine by acetylcholinesterase. This facilitates transmission of impulses across myoneural junction and results in increased cholinergic response.

Atropine: Minimizes or prevents the muscarinic cholinergic effects caused by edrophonium (eg, bradycardia, bronchocontriction, and increased secretions).

Pharmacodynamics/KineticsSee individual agents.

Onset of action: Edrophonium: Antagonism of nondepolarizing muscle relaxants: 3 minutes; Atropine: Heart rate: Immediate

Duration: Edrophonium: Antagonism of nondepolarizing muscle relaxants: 70 minutes; Atropine: Heart rate: 170 minutes

Protein binding: Atropine: 14%

Half-life elimination: Edrophonium: Adults: 1.2-2.4 hours; Anephric patients: 2.4-4.4 hours

Time to peak, plasma: Edrophonium: Antagonism of nondepolarizing muscle relaxants: 1.2 minutes; Atropine: Heart rate: 2-16 minutes

Excretion: Edrophonium: Primarily urine (67%)

Related Information

- Atropine
- Edrophonium

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsBradyarrhythmias, tachycardia, and premature ventricular contractions have been reported; use vasoconstrictor with caution
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentAtropine is highly anticholinergic; concurrent use of atropine and other anticholinergics (eg, tricyclic antidepressants, antipsychotics, some antihistamines, antiparkinson drugs) may produce additive effects. Avoid use in myasthenia gravis; myasthenic weakness may be a symptom of anticholinesterase overdose. Concomitant use with propranolol may produce additive bradycardia.
Index TermsAtropine Sulfate and Edrophonium Chloride; Edrophonium Chloride and Atropine Sulfate

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Edrophonium

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(ed roe FOE nee um)
U.S. Brand NamesEnlon® [DSC]
Canadian Brand NamesEnlon®; Tensilon®
Pharmacologic CategoryAntidote; Cholinergic Agonist; Diagnostic Agent
Use: Labeled IndicationsDiagnosis of myasthenia gravis; differentiation of cholinergic crises from myasthenia crises; reversal of nondepolarizing neuromuscular blockers; adjunct treatment of respiratory depression caused by curare overdose
Dosing: AdultsUsually administered I.V., however, if not possible, I.M. or SubQ may be used.

Diagnosis of Myasthenia gravis:

I.V.: 2 mg test dose administered over 15-30 seconds; 8 mg given 45 seconds later if no response is seen. Test dose may be repeated after 30 minutes.

I.M.: Initial: 10 mg; if no cholinergic reaction occurs, give 2 mg 30 minutes later to rule out false-negative reaction.

Titration of oral anticholinesterase therapy: 1-2 mg given 1 hour after oral dose of anticholinesterase; if strength improves, an increase in neostigmine or pyridostigmine dose is indicated.

Differentiation of cholinergic from myasthenic crisis: I.V.: 1 mg; may repeat after 1 minute. **Note:** Intubation and controlled ventilation may be required if patient has cholinergic crisis.

Reversal of nondepolarizing neuromuscular blocking agents (neostigmine with atropine usually preferred): I.V.: 10 mg over 30-45 seconds; may repeat every 5-10 minutes up to 40 mg.

Termination of paroxysmal atrial tachycardia: I.V. rapid injection: 5-10 mg

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricUsually administered I.V., however, if not possible, I.M. or SubQ may be used:

Infants:

I.M.: 0.5-1 mg

I.V.: Initial: 0.1 mg, followed by 0.4 mg if no response; total dose = 0.5 mg

Children:

Diagnosis: Initial: 0.04 mg/kg over 1 minute followed by 0.16 mg/kg if no response, to a maximum total dose of 5 mg for children <34 kg, or 10 mg for children >34 kg **or**

Alternative dosing (manufacturer's recommendation):

≤34 kg: 1 mg; if no response after 45 seconds, repeat dosage in 1 mg increments every 30-45 seconds, up to a total of 5 mg

>34 kg: 2 mg; if no response after 45 seconds, repeat dosage in 1 mg increments every 30-45 seconds, up to a total of 10 mg

I.M.:

<34 kg: 1 mg

>34 kg: 5 mg

Titration of oral anticholinesterase therapy: 0.04 mg/kg once given 1 hour after oral intake of the drug being used in treatment. If strength improves, an increase in neostigmine or pyridostigmine dose is indicated.

Dosing: Renal ImpairmentDose may need to be reduced in patients with chronic renal failure.
Administration: I.V. DetailpH: 5.4
Compatibility**Y-site administration: Compatible:** Heparin, hydrocortisone sodium succinate, potassium chloride, vitamin B complex with C.
ContraindicationsHypersensitivity to edrophonium, sulfites, or any component of the formulation; GI or GU obstruction
Warnings/Precautions

Concerns related to adverse effects:

- Cholinergic crisis: Overdosage can cause cholinergic crisis which may be fatal. Atropine should always be readily available as an antagonist and for treatment of cholinergic reactions.

Disease-related concerns:

- Arrhythmias: Use with caution in patients with cardiac arrhythmias (eg, bradyarrhythmias).
- Asthma: Use with caution in patients with bronchial asthma.
- Myasthenia gravis: Avoid use in myasthenia gravis; may exacerbate muscular weakness.

Concurrent drug therapy issues:

- Cardiac glycosides: Use with caution in patients receiving a cardiac glycoside; may enhance AV block.

Dosage form specific issues:

- Sodium sulfite: Products may contain sodium sulfite.

Geriatric ConsiderationsMany elderly will have diseases which may influence the use of edrophonium. Also, many elderly will need doses reduced 50% due to creatinine clearances in the 10-50 mL/minute range (common in the aged). Side effects or concomitant disease may warrant use of pyridostigmine.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias (especially bradycardia), AV block, cardiac arrest, decreased carbon monoxide, flushing, hypotension, nodal rhythm, nonspecific ECG changes, syncope, tachycardia

Central nervous system: Convulsions, dizziness, drowsiness, dysarthria, dysphonia, headache, loss of consciousness

Dermatologic: Skin rash, thrombophlebitis (I.V.), urticaria

Gastrointestinal: Diarrhea, dysphagia, flatulence, hyperperistalsis, nausea, salivation, stomach cramps, vomiting

Genitourinary: Urinary urgency

Neuromuscular & skeletal: Arthralgias, fasciculations, muscle cramps, spasms, weakness

Ocular: Lacrimation, small pupils

Respiratory: Bronchiolar constriction, bronchospasm, dyspnea, bronchial secretions increased, laryngospasm, respiratory arrest, respiratory depression, respiratory muscle paralysis

Miscellaneous: Allergic reactions, anaphylaxis, diaphoresis increased

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Test InteractionsIncreased aminotransferase [ALT/AST] (S), amylase (S)

Monitoring ParametersPre- and postinjection strength (cranial musculature is most useful); heart rate, respiratory rate, blood pressure

Nursing: Physical Assessment/MonitoringAdministration of edrophonium for MG diagnosis is supervised by a neurologist and use as a neuromuscular blocking agent is supervised by an anesthesiologist. Patient must be monitored closely during and following procedure, especially for cholinergic crisis; keep atropine at hand for antidote. Patients receiving the medication for MG testing will have been advised by their neurologist about drug effects. Those patients receiving medication for neuromuscular block will be unaware of drug effects. Patient should never be left alone until all drug effects and the possibility of cholinergic crisis have passed.

Patient Education**Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as chloride:

Enlon®: 10 mg/mL (15 mL) [contains sodium sulfite]

Generic AvailableNo

Mechanism of ActionInhibits destruction of acetylcholine by acetylcholinesterase. This facilitates transmission of impulses across myoneural junction and results in increased cholinergic responses such as miosis, increased tonus of intestinal and skeletal muscles, bronchial and ureteral constriction, bradycardia, and increased salivary and sweat gland secretions.

Pharmacodynamics/Kinetics

Onset of action: I.M.: 2-10 minutes; I.V.: 30-60 seconds

Duration: I.M.: 5-30 minutes: I.V.: 10 minutes

Distribution: V_d: Adults: 1.1 L/kg

Half-life elimination: Adults: 1.2-2.4 hours; Anephric patients: 2.4-4.4 hours

Excretion: Adults: Primarily urine (67%)

Pharmacotherapy PearlsAtropine should be administered along with edrophonium when reversing the effects of nondepolarizing agents to antagonize the cholinergic effects at the muscarinic receptors, especially bradycardia. It is important to recognize the difference in dose for diagnosis of myasthenia gravis versus reversal of muscle relaxant, a much larger dose is needed for desired effect of reversal of muscle paralysis.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other ConsiderationsAtropine should be administered along with edrophonium when reversing the effects of nondepolarizing agents to antagonize the cholinergic effects at the muscarinic receptors, especially bradycardia; important to recognize the difference in dose for diagnosis of myasthenia gravis versus reversal of muscle relaxant, a much larger dose is needed for desired effect of reversal of muscle paralysis

Index TermsEdrophonium Chloride

References

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International Brand NamesAnticude (ES); Camsilon (GB)

EE-4A

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Wilms' Tumor

Regimen Use Wilms' tumor

Regimen

Dactinomycin: I.V.: 45 mcg/kg day 1 of weeks 0, 3, 6, 9, 12, 15, and 18

[total dose/cycle = 315 mcg/kg]

Vincristine: I.V.: 2 mg/m^2 day 1 of weeks 1-10, 12, 15, and 18

[total dose/cycle = 26 mg/m^2]

References

Green DM, Breslow NE, Beckwith JB, et al, “Effect of Duration of Treatment on Treatment Outcome and Cost of Treatment for Wilms' Tumor: A Report From the National Wilms' Tumor Study Group,” *J Clin Oncol*, 16(12):3744-51.[PubMed 9850017]

EE

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Wilms' Tumor

Regimen UseWilms' tumor

Regimen

Dactinomycin: I.V.: 15 mcg/kg/day days 1 to 5 of weeks 0, 5, 13, and 24

[total dose/cycle = 300 mcg/kg]

Vincristine: I.V.: 1.5 mg/m^2 day 1 of weeks 1-10, 13, 14, 24, and 25

[total dose/cycle = 21 mg/m^2]

References

Green DM, Breslow NE, Beckwith JB, et al, “Effect of Duration of Treatment on Treatment Putcome and Cost of Treatment for Wilms' Tumor: A Report From the National Wilms' Tumor Study Group,” *J Clin Oncol*, 16(12):3744-51.[PubMed 9850017]

Efalizumab

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Efalizumab: New Boxed Warnings (Associated With Life-threatening Infections, Including Progressive Multifocal Leukoencephalopathy) - October 20, 2008

The Food and Drug Administration (FDA) has informed healthcare professionals regarding the addition of black boxed warnings to the efalizumab prescribing information related to the development of progressive multifocal leukoencephalopathy (PML) and other life-threatening infections (bacterial, viral, fungal and other opportunistic infections).

Prior to this labeling change, Genentech, Inc issued a “Dear Healthcare Professional” letter informing of a case of PML, reported in a patient who had received efalizumab (for >4 years) for the treatment of plaque psoriasis. This patient was not receiving other immunosuppressants. PML is a demyelinating central nervous system disease due to latent JC virus. Any neurological change in patients receiving efalizumab should be evaluated promptly; if clinically indicated, consider neurology consultation, brain MRI and lumbar puncture for suspected PML. Discontinue efalizumab in patients who develop PML.

Labeling changes also include addition of data from juvenile murine studies, which suggests a risk for permanent immunosuppression in association with repeat efalizumab administration in children. Efalizumab is not approved for use in patients under the age of 18 years.

A medication guide regarding these safety concerns will be available in the near future.

For more information, see:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Raptiva

http://www.gene.com/gene/products/information/pdf/raptiva_dhcp.pdf

Medication Safety Issues

Sound-alike/look-alike issues:

Efalizumab may be confused with eculizumab

Raptiva® maybe confused with Rapaflo®

Pronunciation(e fa li ZOO mab)

U.S. Brand NamesRaptiva®

Pharmacologic CategoryImmunosuppressant Agent; Monoclonal Antibody

Use: Labeled IndicationsTreatment of chronic moderate-to-severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy

Dosing: AdultsPsoriasis: SubQ: Initial: 0.7 mg/kg, followed by weekly dose of 1 mg/kg (maximum: 200 mg/dose)

Dosing: ElderlyRefer to adult dosing.

Administration: OtherFor SubQ injection in the abdomen, buttocks, thigh, or upper arm. Rotate injection sites.

StoragePowder should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light. Following reconstitution, solution should be stored at room temperature and used within 8 hours. Discard unused solution.

ReconstitutionSlowly inject 1.3 mL of the provided diluent into vial. Gently swirl to mix; do not shake.

ContraindicationsHypersensitivity to efalizumab or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Infections: See “Concerns related to adverse effects” below.
- Progressive multifocal leukoencephalopathy: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- First dose reactions: Have been reported; a lower, conditioning dose is recommended to reduce the incidence and severity of reactions.
- Hemolytic anemia: May occur after 4-6 months of treatment, has been reported; discontinue if signs and symptoms of hemolytic anemia

occur.

- Infections: **[U.S. Boxed Warning]: Infections (bacterial, viral, fungal and other opportunistic infections), some serious and even fatal, have been reported with efalizumab use.** May result in increased susceptibility to infections or reactivation of latent infection; use caution with chronic infections, history of recurrent infection, or the elderly. Avoid administration to patients with clinically important infection; discontinue therapy if serious infection develops.

- Neurologic events: Neurologic events (including chronic inflammatory demyelinating polyneuropathy, facial palsy, Guillain-Barré syndrome, and transverse myelitis) have been observed; discontinue therapy if signs of a neurologic event occurs.

- Progressive multifocal leukoencephalopathy (PML): **[U.S. Boxed Warning]: Progressive multifocal leukoencephalopathy (PML), a demyelinating central nervous system disease due to latent JC virus infection, has been reported with efalizumab use.** Evaluate any neurological change promptly; if clinically indicated, consider neurology consultation, brain MRI, and lumbar puncture for suspected PML. Discontinue efalizumab in patients who develop PML.

- Thrombocytopenia: Has been reported (rare) and may require treatment; discontinue if thrombocytopenia develops.

Disease-related concerns:

- Hepatic impairment: Safety and efficacy have not been established in patients with hepatic impairment.

- Malignancy: Use with caution in patients at high risk for malignancy or history of malignancy; effects of efalizumab on the development of malignancies is unknown.

- Renal impairment: Safety and efficacy have not been established in patients with renal impairment.

Concurrent drug therapy issues:

- Immunosuppressants: Concomitant use with other immunosuppressant agents is not recommended.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Hamster cell: Produced in a Chinese hamster cell medium.

- Immunizations: Patients should be brought up to date with all immunizations before initiating therapy. Live vaccines should not be given concurrently; there is no data available concerning secondary transmission of live vaccines in patients receiving therapy. Inactivated immunizations may not elicit adequate response to prevent disease.

- Worsening of condition: Psoriasis and/or arthritis may worsen with treatment or following discontinuation (rare).

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. A decreased ability to mount an antibody response was observed in the offspring of female mice who received efalizumab during toxicity studies. There are no adequate and well-controlled studies in pregnant women. Healthcare providers are encouraged to enroll patients who may become pregnant during therapy or within 6 weeks of discontinuing treatment in the Raptiva® registry (877-727-8482).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsA decrease in the ability to mount an antibody response was observed in the offspring of lactating mice. It is not known if efalizumab is excreted in human milk. However, since maternal immunoglobulins are present, and animal data suggest possible adverse effects in the nursing infant, it is recommended to discontinue nursing or discontinue efalizumab.

Adverse Reactions

>10%:

Central nervous system: Headache (32%), chills (13%)

Gastrointestinal: Nausea (11%)

Hematologic: Lymphocytosis (40%), leukocytosis (26%)

Miscellaneous: First-dose reaction (29%, described as chills, fever, headache, myalgia, and nausea occurring within 2 days of the first injection; percent reported in patients receiving a 1 mg/kg dose; severity decreased with 0.7 mg/kg dose); infection (29%, serious infection <1%)

1% to 10%:

Cardiovascular: Peripheral edema (1% to 2%)

Central nervous system: Pain (10%), fever (7%)

Dermatologic: Acne (4%), psoriasis (1% to 2%), urticaria (1%)

Hepatic: Alkaline phosphatase increased (4%)

Neuromuscular & skeletal: Myalgia (8%), back pain (4%), arthralgia (1% to 2%), weakness (1% to 2%)

Miscellaneous: Antibodies to efalizumab (6%); hypersensitivity reaction, including asthma, dyspnea, angioedema, urticaria, or maculopapular rash (8%); flu-like syndrome (7%)

<1%, postmarketing and/or case reports: Arthritis, aseptic meningitis, asthma, bacterial sepsis (with seeding of distant sites), bronchiolitis obliterans, chronic inflammatory demyelinating polyneuropathy, drug eruption (allergic), erythema multiforme, facial palsy, fungal infection, Guillain-Barré syndrome, hemolytic anemia (immune mediated), inflammatory arthritis, idiopathic hepatitis, interstitial pneumonitis, laryngospasm, lymphoma, malignancies, necrotizing fasciitis, opportunistic infection, photoallergic dermatitis, photosensitivity, pneumonia (severe with neutropenia), progressive multifocal leukoencephalopathy (PML), serious psoriasis events (include erythrodermic, guttate, and pustular subtypes); psoriatic arthritis, serum sickness-like reaction, sialadenitis, sensorineural hearing loss, thrombocytopenia (immune mediated), toxic epidermal necrolysis, transverse myelitis, tuberculous pneumonia, viral infection

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Test InteractionsIncreased lymphocytes (related to mechanism of action)

Monitoring ParametersPlatelet counts (at least monthly at the start of treatment, every 3 months as therapy continues); signs of infection; worsening of psoriasis; any neurologic impairment

Signs or symptoms of progressive multifocal leukoencephalopathy (focal neurologic deficits, which may present as hemiparesis, visual field deficits, cognitive impairment, aphasia, ataxia, and/or cranial nerve deficits); if PML is suspected, obtain brain MRI scan and lumbar puncture

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests. Be alert to the possibility of the development of infection or malignancy. Assess therapeutic effectiveness and adverse reactions on a regular basis throughout therapy. Do not administer any immunizations with acellular, live, or live-attenuated vaccines during therapy with efalizumab. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsPlatelet counts (at least monthly at the start of treatment, every 3 months as therapy continues)

Patient EducationThis medication can only be given by injection. Do not take any new medications during therapy without consulting prescriber. You may be more susceptible to infection while on this therapy; avoid crowds and exposure to infections, and do not have any immunizations while on this therapy. Notify prescriber of any allergic response (headache, chills, muscle pain, rash, difficulty breathing, or swelling around mouth within 3 days of first dose). May cause mild edema in extremities; back or muscle pain or flu-like syndrome (consult prescriber for appropriate analgesic). Report unusual infection or bleeding; weight gain >5 pounds in 1 week; persistent muscle or joint pain or weakness; other persistent reactions or worsening of psoriasis. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to be pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Raptiva®: 150 mg [contains sucrose 123.2 mg/vial; delivers 125 mg/1.25 mL; packaged with prefilled syringe containing sterile water for injection]

Generic AvailableNo

ManufacturerGenentech, Inc

Mechanism of ActionEfalizumab is a recombinant monoclonal antibody which binds to CD11a, a subunit of leukocyte function antigen-1 (LFA-1) found on leukocytes. By binding to CD11a, efalizumab blocks multiple T-cell mediated responses involved in the pathogenesis of psoriatic plaques.

Pharmacodynamics/Kinetics

Onset: Reduction of CD11a expression and free CD11a-binding sites seen 1-2 days after the first dose; time to steady state serum concentration: 4 weeks

Response to therapy (75% reduction from baseline of PASI score): Observed after 12 weeks

Duration: CD11a expression was ~74% of baseline at 5-13 weeks after discontinuing dose; free CD11a binding sites were at ~86% of baseline at 8-13 weeks following discontinuation; response to therapy (75% reduction from baseline PASI score) continued 1-2 months after discontinuation

Bioavailability: SubQ: 50%

Excretion: Time to eliminate (at steady state): 25 days (range: 13-35 days)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentNausea is common; concurrent use with SSRIs and/or valproic acid may produce additive effects. May cause acne or psoriasis; lithium may produce similar side effects; monitor. Flu-like syndrome has been reported and may present similarly to SSRI-discontinuation symptoms. May rarely cause thrombocytopenia; monitor with high-dose valproic acid use.

Index TermsAnti-CD11a; hu1124

References

Papp K, Bissonnette R, Krueger JG, et al, “The Treatment of Moderate to Severe Psoriasis With a New Anti-CD11a Monoclonal Antibody,” *J Am Acad Dermatol*, 2001, 45:665-74.[PubMed 11606914]

International Brand NamesRaptiva (AR, AT, AU, BE, BG, BR, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, MX, MY, NL, NO, PT, RU, SE, SG, TR)

Efavirenz, Emtricitabine, and Tenofovir

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(e FAV e renz, em trye SYE ta been, & te NOE fo veer)

U.S. Brand NamesAtripla®

Canadian Brand NamesAtripla®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Non-nucleoside); Antiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside); Antiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleotide)

Use: Labeled IndicationsTreatment of HIV infection

Dosing: AdultsHIV infection: Oral: One tablet once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentModerate-to-severe renal impairment (Cl_{cr} <50 mL/minute): Use not recommended.

Calculations

- Creatinine Clearance: Adults

Administration: OralShould be taken on an empty stomach, normally at bedtime to increase gastrointestinal tolerance and decrease nervous system manifestations.

Dietary ConsiderationsShould be taken on an empty stomach. In patients with history of bone fracture or osteopenia, consider calcium and vitamin D supplementation.

StorageStore 15°C to 30°C (59°F to 86°F). Dispense only in original container.

ContraindicationsHypersensitivity to efavirenz, emtricitabine, or tenofovir, or any component of the formulation; concurrent use of cisapride, midazolam, triazolam, voriconazole, ergot alkaloids (includes dihydroergotamine, ergotamine, ergonovine, methylergonovine), St John's wort, pimozide; concurrent use of other tenofovir-, efavirenz-, or lamivudine-containing formulations

Warnings/Precautions

Boxed warnings:

- Chronic hepatitis B: See “Disease-related concerns” below.
- Lactic acidosis/hepatomegaly: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- CNS depression: May cause CNS depression (eg, impaired concentration, dizziness or drowsiness); avoid potentially hazardous tasks such as driving or operating machinery.
- Decreased bone mineral density: Use has been associated with decreases in bone mineral density (~5% to 7%) and osteomalacia. Consider monitoring of bone density in patients at risk for osteopenia or with a history of pathologic fractures; consider calcium and vitamin D supplementation.
- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis). Persistent elevations of serum transaminases >5 times the upper limit of normal should prompt evaluation - benefit of continued therapy should be weighed against possible risk of hepatotoxicity.
- Psychiatric effects: Serious psychiatric side effects have been associated with use, including severe depression, suicide, paranoia, and mania; use with caution in patients with a history of mental illness/drug abuse (predisposition to psychological reactions).
- Rash: Discontinue if severe rash (involving blistering, desquamation, mucosal involvement or fever) develops. Children are more susceptible to development of rash; prophylactic antihistamines may be used.
- Renal toxicity: May cause renal toxicity (acute renal failure and/or Fanconi syndrome); avoid use with concurrent or recent nephrotoxic therapy; monitor renal function during therapy.

Disease-related concerns:

- Chronic hepatitis B: **[U.S. Boxed Warning]: Safety and efficacy during coinfection of HIV and HBV have not been established; acute, severe exacerbations of HBV have been reported following discontinuation of antiretroviral therapy. Not indicated for treatment of chronic hepatitis B.** All patients with HIV should be tested for HBV prior to initiation of treatment. Caution in patients with known or suspected hepatitis B or

C infection (monitoring of liver function is recommended). In HBV coinfected patients, monitor hepatic function closely for several months following discontinuation.

- Hepatic impairment: Use caution in hepatic impairment.

- Renal impairment: Product is a fixed-dose combination and is not appropriate for use in renal impairment (Cl_{cr} <50 mL/minute).

- Seizure disorder: Use with caution in patients with a history of seizure disorder; seizures have been associated with use.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

Special populations:

- Pediatrics: Fixed dose combination product; safety and efficacy have not been established in patients <18 years of age. In children <40 kg, the dose of efavirenz would be excessive.

- Pregnancy: Avoid pregnancy; women of childbearing potential should undergo pregnancy testing prior to initiation of therapy.

Pregnancy Risk FactorD

Pregnancy ConsiderationsSee individual agents.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse ReactionsThe complete adverse reaction profile of combination therapy has not been established. **See individual agents.** The following adverse effects were noted in clinical trials with combination therapy:

>10%: Endocrine & metabolic: Hypercholesterolemia (22%)

1% to 10%:

Central nervous system: Depression (9%), fatigue (9%), dizziness (8%), headache (6%), anxiety (5%), insomnia (5%), somnolence (4%), abnormal dreams

Dermatologic: Rash (7%)

Endocrine & metabolic: Triglycerides increased (4%), hyperglycemia (2%)

Gastrointestinal: Nausea (9%), diarrhea (9%), serum amylase increased (8%), vomiting (2%)

Hematologic: Neutropenia (3%)

Hepatic: AST increased (3%), ALT increased (2%), alkaline phosphatase increased (1%)

Neuromuscular & skeletal: Creatine increased (9%)

Renal: Hematuria (3%)

Respiratory: Sinusitis (8%), upper respiratory infection (8%), nasopharyngitis (5%)

<1%: Glycosuria

Metabolism/Transport Effects

Efavirenz: **Substrate** (major) of CYP2B6, 3A4; **Inhibits** CYP2C9 (moderate), 2C19 (moderate), 3A4 (moderate); **Induces** CYP2B6 (weak), 3A4 (strong)

Tenofovir: **Inhibits** CYP1A2 (weak)

Drug Interactions

Acyclovir-Valacyclovir: May decrease the excretion of Tenofovir. *Risk C: Monitor therapy*

Adefovir: May diminish the therapeutic effect of Tenofovir. Specifically, adefovir-associated mutations in Hepatitis B viral reverse transcriptase may decrease viral susceptibility to tenofovir. Tenofovir may increase the serum concentration of Adefovir. Similarly, Adefovir may increase the concentration of Tenofovir. *Risk D: Consider therapy modification*

Atazanavir: Tenofovir may decrease the serum concentration of Atazanavir. Atazanavir may increase the serum concentration of Tenofovir. Management: When combined use required, tenofovir 300mg and atazanavir 300mg should be used together with ritonavir 100mg, all given as a single daily dose with food. Atazanavir without ritonavir should not be used with tenofovir. *Risk D: Consider therapy modification*

Atazanavir: Efavirenz may decrease the serum concentration of Atazanavir. *Risk D: Consider therapy modification*

Caspofungin: Inducers of Drug Clearance may decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) when coadministered with known inducers of drug clearance. *Risk D: Consider therapy modification*

Cisapride: Efavirenz may enhance the QTc-prolonging effect of Cisapride. *Risk X: Avoid combination*

CYP2B6 Inducers (Strong): May increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of Efavirenz. Efavirenz may decrease the serum concentration of Darunavir. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Didanosine: Tenofovir may diminish the therapeutic effect of Didanosine. Tenofovir may increase the serum concentration of Didanosine. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

Ergot Derivatives: Efavirenz may enhance the adverse/toxic effect of Ergot Derivatives. Specifically, the risk for peripheral vasospasm and ischemia may be increased. *Risk X: Avoid combination*

Etravirine: Reverse Transcriptase Inhibitors (Non-Nucleoside) may decrease the serum concentration of Etravirine. This has been observed with the NNRTIs efavirenz and nevirapine. Reverse Transcriptase Inhibitors (Non-Nucleoside) may increase the serum concentration of Etravirine. This has been observed with delavirdine. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Ganciclovir-Valganciclovir: May enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. *Risk D: Consider therapy modification*

Ganciclovir-Valganciclovir: May decrease the excretion of Tenofovir. *Risk C: Monitor therapy*

Itraconazole: Efavirenz may decrease the serum concentration of Itraconazole. *Risk D: Consider therapy modification*

LamiVUDine: May enhance the adverse/toxic effect of Emtricitabine. *Risk X: Avoid combination*

Lopinavir: Efavirenz may decrease the serum concentration of Lopinavir. Management: An increased dose of lopinavir/ritonavir to 500mg/125mg (for tablets) or 533mg/133mg (for oral solution) twice daily is recommended when used concurrently with efavirenz. Avoid once daily use of lopinavir/ritonavir when used with efavirenz. *Risk D: Consider therapy modification*

Lopinavir: May enhance the nephrotoxic effect of Tenofovir. Lopinavir may increase the serum concentration of Tenofovir. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Reverse Transcriptase Inhibitors (Non-Nucleoside) may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Midazolam: Efavirenz may increase the serum concentration of Midazolam. *Risk X: Avoid combination*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Phenytoin: May decrease the serum concentration of Efavirenz. Efavirenz may increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Efavirenz may enhance the arrhythmogenic effect of Pimozide. *Risk X: Avoid combination*

Posaconazole: Efavirenz may decrease the serum concentration of Posaconazole. *Risk X: Avoid combination*

Protease Inhibitors: Efavirenz may increase the metabolism of Protease Inhibitors. This specifically includes amprenavir, indinavir, and saquinavir. Efavirenz may increase the serum concentration of Protease Inhibitors. This specifically includes nelfinavir and ritonavir. *Risk D: Consider therapy modification*

Protease Inhibitors: Tenofovir may decrease the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Tenofovir. **Exceptions:** Saquinavir. *Risk C: Monitor therapy*

Raltegravir: Efavirenz may decrease the serum concentration of Raltegravir. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Rifabutin: Efavirenz may decrease the serum concentration of Rifabutin. Rifabutin may decrease the serum concentration of Efavirenz. Management: If efavirenz is to be used with daily rifabutin, increase the planned rifabutin dose by 50%. If used with regimens where rifabutin is administered 2-3 times per week, consider doubling the rifabutin dose. *Risk D: Consider therapy modification*

Rifampin: May decrease the serum concentration of Efavirenz. Management: Efavirenz dose adjustment (to 800mg daily) may be required, particularly for patients weighing more than 60kg. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Sertraline: Efavirenz may decrease the serum concentration of Sertraline. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

St Johns Wort: May decrease the serum concentration of Efavirenz. *Risk X: Avoid combination*

Triazolam: Efavirenz may increase the serum concentration of Triazolam. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Efavirenz may increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Voriconazole: Reverse Transcriptase Inhibitors (Non-Nucleoside) may decrease the serum concentration of Voriconazole. Voriconazole may increase the serum concentration of Reverse Transcriptase Inhibitors (Non-Nucleoside). Management: Efavirenz and voriconazole should not be coadministered at standard doses. Concurrent therapy is acceptable if voriconazole is dosed at 400 mg every 12 hours and efavirenz is dosed at 300 mg daily throughout the course of therapy. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (hepatic and CNS adverse effects).

Food: Avoid high-fat meals (increase the absorption of efavirenz). Food decreases peak plasma concentrations of emtricitabine, but does not alter the extent of absorption or overall systemic exposure. Fatty meals may increase the bioavailability of tenofovir.

Herb/Nutraceutical: St John's wort may decrease efavirenz serum levels. Concurrent use is contraindicated.

Test InteractionsFalse-positive test for cannabinoids have been reported when the CEDIA DAU Multilevel THC assay is used in patients receiving efavirenz. False-positive results with other assays for cannabinoids have not been observed.

Monitoring ParametersTesting for HBV is recommended prior to the initiation of antiretroviral therapy. Monitor CBC with differential, reticulocyte count, serum creatine kinase, CD4 count, HIV RNA plasma levels, renal and hepatic function tests, cholesterol, triglycerides, bone density (long-term), serum phosphorus. Serum transaminases (discontinuation of treatment should be considered for persistent elevations >5 times ULN).

Patients with HIV and HBV coinfection should have hepatic function monitored for several months following discontinuation.

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsTesting for HBV is recommended prior to the initiation of antiretroviral therapy. Monitor CBC with differential, reticulocyte count, serum creatine kinase, CD4 count, HIV RNA plasma levels, renal and hepatic function tests, cholesterol, triglycerides, bone density (long-term), serum phosphorus. Serum transaminases (discontinuation of treatment should be considered for persistent elevations >5 times ULN).

Patients with HIV and HBV coinfection should have hepatic function monitored for several months following discontinuation.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Atripla™: Efavirenz 600 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg

ManufacturerBristol-Myers Squibb

Pricing: U.S. (www.drugstore.com)

Tablets (Atripla)

600-200-300 mg (30): $1555.09

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Efavirenz alone has caused xerostomia (normal salivary flow resumes upon discontinuation) and abnormal taste (see individual monograph). No significant effects or complications reported with combination drug.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause severe depression, suicidal ideation, paranoia, or mania. May also cause dizziness, drowsiness, and impaired concentration.

Mental Health: Effects on Psychiatric TreatmentContraindicated with midazolam, triazolam, and ergot alkaloids. Concurrent use with St John's wort is not recommended. Levels of citalopram, fluoxetine, and sertraline may be increased; monitor response.

Index TermsEmtricitabine, Efavirenz, and Tenofovir; FTC, TDF, and EFV; Tenofovir Disoproxil Fumarate, Efavirenz, and Emtricitabine

References

Gallant JE, DeJesus E, Arribas JR, et al, “Tenofovir DF, Emtricitabine, and Efavirenz vs Zidovudine, Lamivudine, and Efavirenz for HIV,” *N Engl J Med*, 2006, 354(3):251-60.[PubMed 16421366]

“Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection,” January 29, 2008. Available at http://www.aidsinfo.nih.gov

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” July 29, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesAtripla (CA)

Efavirenz

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(e FAV e renz)

U.S. Brand NamesSustiva®

Canadian Brand NamesSustiva®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Non-nucleoside)

Use: Labeled IndicationsTreatment of HIV-1 infections in combination with at least two other antiretroviral agents

Dosing: Adults

HIV infection (as part of combination): Oral: 600 mg once daily

Dosage adjustment for concomitant voriconazole: Reduce efavirenz dose to 300 mg once daily and increase voriconazole to 400 mg every 12 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDosage is based on body weight.

HIV infection (as part of combination): Oral: Children ≥3 years:

10 kg to <15 kg: 200 mg once daily

15 kg to <20 kg: 250 mg once daily

20 kg to <25 kg: 300 mg once daily

25 kg to <32.5 kg: 350 mg once daily

32.5 kg to <40 kg: 400 mg once daily

≥40 kg: 600 mg once daily

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentLimited clinical experience - use with caution.

Administration: OralAdminister on an empty stomach. Dosing at bedtime is recommended to limit central nervous system effects. Tablets should not be broken. Capsules may be opened and added to liquid or food.

Dietary ConsiderationsShould be taken on an empty stomach.

StorageStore at controlled room temperature of 25°C (77°F), excursion permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to efavirenz or any component of the formulation; concurrent use of cisapride, midazolam, pimozide, triazolam, voriconazole (with standard [eg, unadjusted] voriconazole and efavirenz doses), or ergot alkaloids (includes dihydroergotamine, ergotamine, ergonovine, methylergonovine)

Allergy Considerations

- Efavirenz Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression (eg, impaired concentration, dizziness or drowsiness); avoid potentially hazardous tasks such as driving or operating machinery.
- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Hypercholesterolemia: Increases in total cholesterol and triglycerides have been reported; screening should be done prior to therapy and periodically throughout treatment.
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Psychiatric effects: Serious psychiatric side effects have been associated with use, including severe depression, suicide, paranoia, and mania; use with caution in patients with a history of mental illness/drug abuse (predisposition to psychological reactions).
- Rash: Discontinue if severe rash (involving blistering, desquamation, mucosal involvement or fever) develops. Children are more susceptible to development of rash; prophylactic antihistamines may be used.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment, including known or suspected hepatitis B or C infection; monitoring is recommended. Persistent elevations of serum transaminases >5 times the upper limit of normal should prompt evaluation - benefit of continued therapy should be weighed against possible risk of hepatotoxicity.

- Seizure disorder: Use with caution in patients with a history of seizure disorder; seizures have been associated with use.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

- Sedatives: CNS effects may be potentiated when used with other sedative drugs or ethanol.

- St John's wort: May decrease the therapeutic efficacy of efavirenz; concurrent use not recommended.

Special populations:

- Pregnancy: Avoid pregnancy; women of childbearing potential should undergo pregnancy testing prior to initiation of therapy.

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenic effects have been observed in Primates receiving efavirenz. Severe CNS defects have been reported in infants following efavirenz exposure in the first trimester. Pregnancy should be avoided and alternate therapy should be considered in women of childbearing potential. Women of childbearing potential should undergo pregnancy testing prior to initiation of efavirenz. Barrier contraception should be used in combination with other (hormonal) methods of contraception and for 12 weeks after efavirenz is discontinued. If therapy with efavirenz is administered during pregnancy, avoid use during the first trimester. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion is breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse Reactions

Unless otherwise noted, frequency of adverse events is as reported in adults receiving combination antiretroviral therapy.

>10%:

Central nervous system: Dizziness (2% to 28%; children 16%), fever (children 21%), depression (up to 19%; severe: 1% to 2%), insomnia (up to 16%), anxiety (2% to 13%), pain (1% to 13%; children 14%), headache (2% to 8%; children 11%)

Dermatologic: Rash (5% to 26%, grade 3/4: <1%; children up to 46%, grade 3/4: 2% to 4%)

Endocrine & metabolic: HDL increased (25% to 35%), total cholesterol increased (20% to 40%), triglycerides increased (≥751 mg/dL: 6% to 11%)

Gastrointestinal: Diarrhea (3% to 14%; children: up to 39%), nausea (2% to 12%; children 12%), vomiting (3% to 6%; children 12%)

Respiratory: Cough (children 16%)

1% to 10%:

Central nervous system: Impaired concentration (up to 8%), somnolence (up to 7%), fatigue (up to 8%), abnormal dreams (1% to 6%), nervousness (2% to 7%), hallucinations (1%)

Dermatologic: Pruritus (up to 9%)

Endocrine & metabolic: Hyperglycemia (>250 mg/dL: 2% to 5%)

Gastrointestinal: Dyspepsia (up to 4%), abdominal pain (2% to 3%), anorexia (up to 2%), amylase increased (grade 3/4: up to 6%)

Hematologic: Neutropenia (grade 3/4: 2% to 10%)

Hepatic: Transaminases increased (grade 3/4: 2% to 8%, incidence higher with hepatitis B and/or C coinfection)

Miscellaneous: Diaphoresis increased (1% to 2%)

<1%, postmarketing, and/or case reports: Allergic reaction, aggressive reaction, agitation, arthralgia, ataxia, balance disturbances, body fat accumulation/redistribution, cerebellar coordination disturbances, constipation, coordination abnormal, delusions, dermatitis (photoallergic), dyspnea, emotional lability, erythema multiforme, flushing, gynecomastia, hepatic failure, hepatitis, hypoesthesia, immune reconstitution syndrome, malabsorption, mania, myalgia, myopathy, nail disorder, neuropathy, neurosis, palpitation, paranoia, paresthesia, psychosis, seizure, skin discoloration, Stevens-Johnson syndrome, suicide attempts, suicidal ideation, tinnitus, tremor, visual abnormality, weakness

Metabolism/Transport Effects**Substrate** (major) of CYP2B6, 3A4; **Inhibits** CYP2C9 (moderate), 2C19 (moderate), 3A4 (moderate); **Induces** CYP2B6 (weak), 3A4 (strong)

Drug Interactions

Atazanavir: Efavirenz may decrease the serum concentration of Atazanavir. *Risk D: Consider therapy modification*

Caspofungin: Inducers of Drug Clearance may decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70mg daily in adults (or $70mg/m^2$, up to a maximum of 70mg, daily in pediatric patients) when coadministered with known inducers of drug clearance. *Risk D: Consider therapy modification*

Cisapride: Efavirenz may enhance the QTc-prolonging effect of Cisapride. *Risk X: Avoid combination*

CYP2B6 Inducers (Strong): May increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of Efavirenz. Efavirenz may decrease the serum concentration of Darunavir. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

Ergot Derivatives: Efavirenz may enhance the adverse/toxic effect of Ergot Derivatives. Specifically, the risk for peripheral vasospasm and ischemia may be increased. *Risk X: Avoid combination*

Etravirine: Reverse Transcriptase Inhibitors (Non-Nucleoside) may decrease the serum concentration of Etravirine. This has been observed with the NNRTIs efavirenz and nevirapine. Reverse Transcriptase Inhibitors (Non-Nucleoside) may increase the serum concentration of Etravirine. This has been observed with delavirdine. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Itraconazole: Efavirenz may decrease the serum concentration of Itraconazole. *Risk D: Consider therapy modification*

Lopinavir: Efavirenz may decrease the serum concentration of Lopinavir. Management: An increased dose of lopinavir/ritonavir to 500mg/125mg (for tablets) or 533mg/133mg (for oral solution) twice daily is recommended when used concurrently with efavirenz. Avoid once daily use of lopinavir/ritonavir when used with efavirenz. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Reverse Transcriptase Inhibitors (Non-Nucleoside) may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Midazolam: Efavirenz may increase the serum concentration of Midazolam. *Risk X: Avoid combination*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Phenytoin: May decrease the serum concentration of Efavirenz. Efavirenz may increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Efavirenz may enhance the arrhythmogenic effect of Pimozide. *Risk X: Avoid combination*

Posaconazole: Efavirenz may decrease the serum concentration of Posaconazole. *Risk X: Avoid combination*

Protease Inhibitors: Efavirenz may increase the metabolism of Protease Inhibitors. This specifically includes amprenavir, indinavir, and saquinavir. Efavirenz may increase the serum concentration of Protease Inhibitors. This specifically includes nelfinavir and ritonavir. *Risk D: Consider therapy modification*

Raltegravir: Efavirenz may decrease the serum concentration of Raltegravir. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Rifabutin: Efavirenz may decrease the serum concentration of Rifabutin. Rifabutin may decrease the serum concentration of Efavirenz. Management: If efavirenz is to be used with daily rifabutin, increase the planned rifabutin dose by 50%. If used with regimens where rifabutin is administered 2-3 times per week, consider doubling the rifabutin dose. *Risk D: Consider therapy modification*

Rifampin: May decrease the serum concentration of Efavirenz. Management: Efavirenz dose adjustment (to 800mg daily) may be required, particularly for patients weighing more than 60kg. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Sertraline: Efavirenz may decrease the serum concentration of Sertraline. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

St Johns Wort: May decrease the serum concentration of Efavirenz. *Risk X: Avoid combination*

Triazolam: Efavirenz may increase the serum concentration of Triazolam. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Efavirenz may increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Voriconazole: Reverse Transcriptase Inhibitors (Non-Nucleoside) may decrease the serum concentration of Voriconazole. Voriconazole may increase the serum concentration of Reverse Transcriptase Inhibitors (Non-Nucleoside). Management: Efavirenz and voriconazole should not be coadministered at standard doses. Concurrent therapy is acceptable if voriconazole is dosed at 400 mg every 12 hours and efavirenz is dosed at 300 mg daily throughout the course of therapy. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (hepatic and CNS adverse effects).

Food: Avoid high-fat meals (increase the absorption of efavirenz).

Herb/Nutraceutical: St John's wort may decrease efavirenz serum levels. Avoid concurrent use.

Test InteractionsFalse-positive test for cannabinoids have been reported when the CEDIA DAU Multilevel THC assay is used. False-positive results with other assays for cannabinoids have not been observed.

Monitoring ParametersSerum transaminases (discontinuation of treatment should be considered for persistent elevations greater than five times the upper limit of normal), cholesterol, triglycerides, signs and symptoms of infection

Nursing: Physical Assessment/MonitoringUse caution in presence of or history of hepatic impairment or mental illness/drug abuse (increased risk of serious psychiatric side effects). Assess other pharmacological or herbal products patient may be taking for potential interactions or toxicity (multiple liver enzyme interactions may increase or decrease levels/effects of drugs and increase potential for severe toxicity or loss of effectiveness); dosing adjustments may be necessary. A list of medications that should not be used in conjunction with this agent is available in each bottle and patient should be provided with that information. Evaluate results of laboratory tests prior to beginning therapy and periodically throughout therapy. Assess effectiveness of therapy (decrease in infections and progress of disease - viral load and CD4 count) and adverse reactions (eg, CNS effects, redistribution of body fat, hyperglycemia, hyperlipidemia, cushingoid appearance) periodically during therapy. Teach patient proper use (eg, timing of multiple medications), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsMonitor serum transaminases (discontinuation of treatment should be considered for persistent elevations greater than five times the upper limit of normal), cholesterol, and triglycerides.

Patient EducationYou will be provided with a list of specific medications that should not be used during therapy: Do not take any new prescription or over-the-counter medications or herbal products during therapy - even if they are not on the list - without consulting prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. This medication will be prescribed with a combination of other medications; time these medications as directed by prescriber. Take exactly as directed (usually at bedtime) on an empty stomach; swallow capsules or tablets whole with water. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. You may be susceptible to infection (avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber). Frequent blood tests may be required with prolonged therapy. You may be advised to check your glucose levels; this drug can cause hyperglycemia. May cause dizziness, insomnia, or impaired concentration (use caution when driving or engaging in tasks that require alertness until response to medication is known); nausea, vomiting, or abdominal pain (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (boiled milk, yogurt, or buttermilk may help). May cause changes in body fat; increased fat in upper back and neck and around trunk; and loss of fat from extremities and face. Report immediately any CNS changes (depression, anxiety, suicidal ideation, abnormal dreams, hallucinations, nervousness, impaired concentration). Report rash, persistent gastrointestinal upset, or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptives; some contraceptives are contraindicated with this medication. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

Sustiva®: 50 mg; 100 mg [DSC]; 200 mg

Tablet:

Sustiva®: 600 mg

Generic AvailableNo

ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)

Pricing: U.S. (www.drugstore.com)

Capsules (Sustiva)

50 mg (90): $135.76

100 mg (90): $272.08

200 mg (90): $546.03

Tablets (Sustiva)

600 mg (30): $545.97

Mechanism of ActionAs a non-nucleoside reverse transcriptase inhibitor, efavirenz has activity against HIV-1 by binding to reverse transcriptase. It consequently blocks the RNA-dependent and DNA-dependent DNA polymerase activities including HIV-1 replication. It does not require intracellular phosphorylation for antiviral activity.

Pharmacodynamics/Kinetics

Absorption: Increased by fatty meals

Distribution: CSF concentrations exceed free fraction in serum

Protein binding: >99%, primarily to albumin

Metabolism: Hepatic via CYP3A4 and 2B6 to inactive hydroxylated metabolites; may induce its own metabolism

Half-life elimination: Single dose: 52-76 hours; Multiple doses: 40-55 hours

Time to peak: 3-5 hours

Excretion: Feces (16% to 61% primarily as unchanged drug); urine (14% to 34% as metabolites)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV

Pharmacotherapy PearlsEfavirenz oral solution is available only through an expanded access (compassionate use) program. Enrollment information may be obtained by calling 1-877-372-7097.

Early virologic failure was observed with tenofovir and didanosine delayed release capsules, plus either efavirenz or nevirapine; use caution in treatment-naive patients with high baseline viral loads.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Abnormal taste

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSerious psychiatric adverse effects have been reported. May cause severe depression, suicidal ideation, aggressive behavior, paranoia, and mania. Patients with a psychiatric history appear to be at a greater risk for these psychiatric effects. May cause difficulty in concentration, insomnia, abnormal dreams, sedation, nervousness, and fatigue. May rarely cause hallucinations, psychosis, anxiety, euphoria, emotional lability, agitation.

Mental Health: Effects on Psychiatric TreatmentShould not be administered with other drugs known to be metabolized by the CYP3A4 system (midazolam, triazolam, ergot alkaloids) as combination may lead to life-threatening adverse effects. Coadministration with St John's wort is expected to substantially decrease NNRTI concentrations, and may result in suboptimal levels and lead to loss of virologic response and possible resistance to efavirenz or to the class of NNRTIs.

References

Adkins JC and Noble S, “Efavirenz,” *Drugs*, 1998, 56(6):1055-64. [PubMed 9878993]

“Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection,” January 29, 2008. Available at http://www.aidsinfo.nih.gov

“Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,” July 8, 2008, 1-96. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” February 28, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesEfavir (IN, PY); Estavirenz (PE); Filginase (AR); Stocrin (AT, AU, BE, BG, BR, CH, CL, CN, CO, CZ, DE, DK, EC, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, MX, MY, NL, NO, PL, PT, RU, SE, SG, TH, TR, TW, UY, VE); Sustiva (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Virorrever (AR)

Eflornithine

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Vaniqa™ may be confused with Viagra®

Pronunciation(ee FLOR ni theen)
U.S. Brand NamesVaniqa™
Canadian Brand NamesVaniqa™
Pharmacologic CategoryAntiprotozoal; Topical Skin Product
Use: Labeled IndicationsCream: Females ≥12 years: Reduce unwanted hair from face and adjacent areas under the chin

Orphan status: Injection: Treatment of meningoencephalitic stage of *Trypanosoma brucei gambiense* infection (sleeping sickness)

Dosing: Adults

Unwanted facial hair (Females): Topical: Apply thin layer of cream to affected areas of face and adjacent chin twice daily, at least 8 hours apart.

Treatment of infections caused by*Trypanosoma*: I.V. infusion (orphan drug): 100 mg/kg/dose given every 6 hours (over at least 45 minutes) for 14 days.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricUnwanted facial hair (females): Children ≥12 years: Refer to adult dosing.
Dosing: Renal ImpairmentInjection: Dose should be adjusted although no specific guidelines are available.
Administration: I.M.Not for I.M. use.
Administration: I.V.Can only be administered I.V.; infuse over 45 minutes.
Administration: OtherApply thin layer of eflornithine cream to affected areas of face and adjacent chin area twice daily, at least 8 hours apart. Rub in thoroughly. Hair removal techniques must still be continued; wait at least 5 minutes after removing hair to apply cream. Do not wash affected area for at least 8 hours following application.
Storage

Injection: Must be diluted before use and used within 24 hours of preparation.

Cream: Store at controlled room temperature 25°C (77°F); do not freeze.

ContraindicationsHypersensitivity to eflornithine or any component of the formulation
Warnings/Precautions

Dosage form specific issues:

- Cream: For topical use by females only; discontinue if hypersensitivity occurs; safety and efficacy in children <12 years of age have not been studied.
- Injection: For I.V. use only; not for I.M. administration. Must be diluted before use; frequent monitoring for myelosuppression should be done; use with caution in patients with a history of seizures and in patients with renal impairment; serial audiograms should be obtained; due to the potential for relapse, patients should be followed up for at least 24 months.

Pregnancy Risk FactorC
Pregnancy ConsiderationsThere are no adequate and well-controlled studies of topical eflornithine cream in pregnant women. The potential benefits to the mother versus the possible risks to the fetus should be considered prior to use.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

Injection:

>10%: Hematologic (reversible): Anemia (55%), leukopenia (37%), thrombocytopenia (14%)

1% to 10%:

Central nervous system: Seizure (may be due to the disease) (8%), dizziness

Dermatologic: Alopecia

Gastrointestinal: Vomiting, diarrhea

Hematologic: Eosinophilia

Otic: Hearing impairment

<1%: Abdominal pain, anorexia, facial edema, headache, weakness

Topical:

>10%: Dermatologic: Acne (11% to 21%), pseudofolliculitis barbae (5% to 15%)

1% to 10%:

Central nervous system: Headache (4% to 5%), dizziness (1%), vertigo (0.3% to 1%)

Dermatologic: Pruritus (3% to 4%), burning skin (2% to 4%), tingling skin (1% to 4%), dry skin (2% to 3%), rash (1% to 3%), facial edema (0.3% to 3%), alopecia (1% to 2%), skin irritation (1% to 2%), erythema (0% to 2%), ingrown hair (0.3% to 2%), folliculitis (0% to 1%)

Gastrointestinal: Dyspepsia (2%), anorexia (0.7% to 2%)

<1%: Bleeding skin, cheilitis, contact dermatitis, herpes simplex, lip swelling, nausea, numbness, rosacea, weakness

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersCBC with platelet counts

Nursing: Physical Assessment/MonitoringLaboratory tests and results should be monitored on regular basis during therapy. Serial audiograms are recommended. Monitor effectiveness according to purpose for use. Patient should be monitored for adverse reactions, especially with infusion administration. Assess knowledge/teach patient appropriate use, adverse reactions and possible interventions, and adverse reactions to report.

Monitoring: Lab TestsCBC with platelet counts

Patient EducationI.V.: This medication can only be administered I.V.; you will be closely monitored during therapy. Report immediately any signs of acute GI upset, seizures, altered hearing. You may lose your hair, however, it will grow back when therapy is discontinued.

Cream: This medication is for external use only. It will not prevent hair growth, but may decrease rate of growth. You will still need to use hair removal techniques while using eflornithine cream. Use only as directed; do not use more often or discontinue without consulting prescriber. Wait at least 5 minutes after removing hair to apply cream. Wash hands thoroughly prior to using cream. Apply thin lay of cream to affected areas of face and chin twice daily (at least 8 hours apart). Rub in thoroughly. Wash hands thoroughly after rubbing cream in. Do not wash area for 8 hours following application. Once cream has dried you may apply make-up over the affected area. Improvement may be seen in 4-8 weeks. Following discontinuation of therapy you may see hair growth return in about 8 weeks. You may be required to have blood tests if used for extended period of time. Report any skin irritation, rash, tingling, or skin eruptions; persistent headache, dizziness; or GI disturbances.

Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical, as hydrochloride: 13.9% (30 g)

Injection, solution, as hydrochloride: 200 mg/mL (100 mL) [orphan drug status]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Cream (Vaniqa)

13.9% (30): $44.99

Mechanism of ActionEflornithine exerts antitumor and antiprotozoal effects through specific, irreversible (“suicide”) inhibition of the enzyme ornithine decarboxylase (ODC). ODC is the rate-limiting enzyme in the biosynthesis of putrescine, spermine, and spermidine, the major polyamines in nucleated cells. Polyamines are necessary for the synthesis of DNA, RNA, and proteins and are, therefore, necessary for cell growth and differentiation. Although many microorganisms and higher plants are able to produce polyamines from alternate biochemical pathways, all mammalian cells depend on ornithine decarboxylase to produce polyamines. Eflornithine inhibits ODC and rapidly depletes animal cells of putrescine and spermidine; the concentration of spermine remains the same or may even increase. Rapidly dividing cells appear to be most susceptible to the effects of eflornithine. Topically, the inhibition of ODC in the skin leads to a decreased rate of hair growth.

Pharmacodynamics/Kinetics

Absorption: Topical: <1%

Half-life elimination: I.V.: 3-3.5 hours; Topical: 8 hours

Excretion: Primarily urine (as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common

Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; use caution with clozapine and carbamazepine

Index TermsDFMO; Eflornithine Hydrochloride

References

Barbarash RA, Toll L, and Sahn SA, “Alpha-Difluoromethylornithine Infusion and Cardiac Arrest,” *Ann Intern Med*, 1986, 105(1):141-2.

“Drugs for Parasitic Infections,” *Med Lett Drugs Ther*, 1993, 35(911):111-22. [PubMed 8246830]

Haegele KD, Alken RG, Grove J, et al, “Kinetics of α-Difluoromethylornithine: An Irreversible Inhibitor of Ornithine Decarboxylase,” *Clin Pharmacol Ther*, 1981, 30(2):210-7.[PubMed 6788425]

International Brand NamesVaniqa (AU, ES, GB, IE, IL)

EFP

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Pharmacologic CategoryChemotherapy Regimen, Gastric Cancer

Regimen UseGastric cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Etoposide: I.V.: 90 mg/m^2/day days 1, 3, and 5

[total dose/cycle = 270 mg/m^2]

Fluorouracil: I.V.: 900 mg/m^2/day (20-hour infusion) days 1 to 5

[total dose/cycle = 4500 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 24-28 days

Variation 2:

Etoposide: I.V.: 100 mg/m^2/day days 1, 3, and 5

[total dose/cycle = 300 mg/m^2]

Fluorouracil: I.V.: 800 mg/m^2/day (12-hour infusion) days 1 to 5

[total dose/cycle = 4000 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 3 weeks

References

Variation 1:

Ajani JA, Roth JA, Ryan B, et al, “Evaluation of Pre- and Postoperative Chemotherapy for Resectable Adenocarcinoma of the Esophagus or Gastroesophageal Junction,” *J Clin Oncol*, 1990, 8(7):1231-8.[PubMed 2358838]

Variation 2:

Ryoo BY, Kang YK, Im YH, et al, “Adjuvant (Cisplatin, Etoposide, and 5-Fluorouracil) Chemotherapy After Curative Resection of Gastric Adenocarcinomas Involving the Esophagogastric Junction,” *Am J Clin Oncol*, 1999, 22(3):253-7. [PubMed 10362331]

Electrolyte Solution, Renal Replacement

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ee LEK trow lite soe LOO shun REE nil ree PLASE ment)

U.S. Brand NamesNormocarb HF™; PrismaSol

Pharmacologic CategoryAlkalinizing Agent; Electrolyte Supplement

Use: Labeled IndicationsUsed as a replacement solution to replenish water, correct electrolytes, and adjust acid-base balance depleted by hemofiltration or hemodiafiltration (continuous renal replacement therapy [CRRT])

Dosing: Adults**Note:** If using PrismaSol™, ensure that compartment A and B are mixed.

Continuous renal replacement circuit: Pre- or post-filter: Volume of solution administered depends upon the patient's fluid balance, target fluid balance, body weight, and amount of fluid removed during hemofiltration process.

Post-filter replacement: Volume infused/hour should not be greater than $^1/_3$ of blood flow rate (eg, blood flow rate 100 mL/minute [6000 mL/hour], post-filter replacement rate ≤2000 mL/hour)

Dosing: PediatricRefer to adult dosing.

Dosing: Hepatic ImpairmentAbility to convert lactate to bicarbonate may be impaired; use solutions containing lactate cautiously.

Administration: OtherMay heat to ≤40°C (104°F) before administration.

Normocarb HF™ (pH 8.3-8.8, osmolarity: 283 mOsm/L): Dilute by adding to 3 L bag of sterile water for injection before use.

PrismaSol™ (pH 7-8.5, osmolarity: 287-300 mOsm/L [depending on mixture]): Mix compartments A and B together before use.

Storage

Normocarb HF™: Store undiluted solution at 20°C to 25°C (68°F to 77°F). Do not freeze. Diluted solution can be stored at room temperature or refrigerated at 2°C to 30°C (36°F to 86°F); use within 24 hours.

PrismaSol™: Store solution at 15°C to 30°C (59°F to 86°F). Once the overwrap is removed, PrismaSol™ should be mixed and used within 24 hours.

ReconstitutionEvaluate final solutions for precipitate.

Normocarb HF™: Must be diluted with sterile water for injection before use. Do not use normal saline, lactated Ringer's, or any other diluent. Add 240 mL vial to 3 L bag of sterile water for injection. Final volume: 3.24 L. Additional additives may be incorporated in the final solution, using aseptic technique. Do not exceed concentration guidelines of additives. Potassium ≤4 mEq/L, calcium ≤2.5 mEq/L, D_{50} W ≤6 g (12 mL), and/or phosphate ≤1.2 mmol/L may be added. Total potassium concentration should be ≤4 mEq/L.

PrismaSol™: Electrolyte solution (compartment A containing 250 mL) must be mixed with buffer solution (compartment B containing 4750 mL) before use. Final volume: 5 L. Additional additives may be incorporated in the final solution, using aseptic technique. Do not exceed concentration guidelines of additives. Potassium ≤4 mEq/L and/or phosphate ≤1.2 mmol/L may be added. Total potassium concentration should be ≤4 mEq/L.

ContraindicationsThere are no contraindications listed in manufacturer's labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Continuous renal replacement therapy: Can cause hypokalemia, hypocalcemia, hypophosphatemia, and hypoglycemia. Monitor closely and correct with appropriate replacement solution.

Disease-related concerns:

- Diabetes mellitus or glucose intolerance: May require insulin adjustment when using the PrismaSol™ solutions as some contain dextrose. Adjusting solutions or rates of administration may cause changes in dextrose delivery.

Concurrent drug therapy issues:

- Anticoagulants: Citrate, when used as an anticoagulant, can contribute to the base load and cause hypocalcemia.

Dosage form specific issues:

- Normocarb HF™: Dilute prior to use.

- PrismaSol™: Mix compartment A and B prior to use. If not mixed, patient may experience severe reductions in electrolytes (magnesium, calcium)/glucose.

Other warnings/precautions:

- Appropriate use: Only for use as replacement fluid in patients receiving continuous renal replacement therapy under direct supervision of an intensivist. Use only with continuous extracorporeal blood purification equipment in CRRT.

Adverse ReactionsFrequency not defined: Endocrine & metabolic: Acid/base abnormalities; electrolyte (potassium, calcium, phosphorous) abnormalities; fluid imbalances; glucose abnormalities

Monitoring ParametersHemodynamic status, electrolyte and acid-base balance, serum glucose. Fluid balance record extremely important as this system requires hourly calculations of replacement fluids to be given.

Monitoring: Lab TestsHemodynamic status, electrolyte and acid-base balance, serum glucose. Fluid balance record extremely important as this system requires hourly calculations of replacement fluids to be given.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [concentrate; preservative free]:

Normocarb HF™ 25: Bicarbonate 25 mEq/L, chloride 116.5 mEq/L, magnesium 1.5 mEq/L, sodium 140 mEq/L (240 mL) [strength represents final solution after mixing; when diluted as directed, makes 3240 mL of infusate]

Normocarb HF™ 35: Bicarbonate 35 mEq/L, chloride 106.5 mEq/L, magnesium 1.5 mEq/L, sodium 140 mEq/L (240 mL) [strength represents final solution after mixing; when diluted as directed, makes 3240 mL of infusate]

Injection, solution [preservative free]:

PrismaSol BGK 0/2.5: Bicarbonate 32 mEq/L, calcium 2.5 mEq/L, chloride 109 mEq/L, dextrose 100 mg/dL, lactate 3 mEq/L, magnesium 1.5 mEq/L, sodium 140 mEq/L (5000 mL) [strength represents final solution after mixing]

PrismaSol BGK 2/0: Bicarbonate 32 mEq/L, chloride 108 mEq/L, dextrose 100 mg/dL, lactate 3 mEq/L, magnesium 1 mEq/L, potassium 2 mEq/L, sodium 140 mEq/L (5000 mL) [strength represents final solution after mixing]

PrismaSol BGK 2/3.5: Bicarbonate 32 mEq/L, calcium 3.5 mEq/L, chloride 111.5 mEq/L, dextrose 100 mg/dL, lactate 3 mEq/L, magnesium 1 mEq/L, potassium 2 mEq/L, sodium 140 mEq/L (5000 mL) [strength represents final solution after mixing]

PrismaSol BGK 4/2.5: Bicarbonate 32 mEq/L, calcium 2.5 mEq/L, chloride 113 mEq/L, dextrose 100 mg/dL, lactate 3 mEq/L, magnesium 1.5 mEq/L, potassium 4 mEq/L, sodium 140 mEq/L (5000 mL) [strength represents final solution after mixing]

PrismaSol BK 0/3.5: Bicarbonate 32 mEq/L, calcium 3.5 mEq/L, chloride 109.5 mEq/L, lactate 3 mEq/L, magnesium 1 mEq/L, sodium 140 mEq/L (5000 mL) [strength represents final solution after mixing]

Mechanism of ActionReplacement fluids achieve fluid and electrolyte balance by substituting for the ultrafiltrate removed during some forms of continuous renal replacement therapies. Replacement solutions may vary in composition and may include a buffer and electrolytes to manage acid-base disorders and electrolyte imbalances.

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsContinuous Renal Replacement Therapy; CRRT; Renal Replacement Solution

References

Culley CM, Bernardo JF, Gross PR, et al, “Implementing a Standardized Safety Procedure for Continuous Renal Replacement Therapy Solutions,” *Am J Health Syst Pharm*, 2006, 63(8):756-63.[PubMed 16595818]

Mehta RL, “Continuous Renal Replacement Therapy in the Critically Ill Patient,” *Kidney Int*, 2005, 67(2):781-95.[PubMed 15673337]

Eletriptan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(el e TRIP tan)
U.S. Brand NamesRelpax®
Canadian Brand NamesRelpax®
Pharmacologic CategoryAntimigraine Agent; Serotonin 5-$HT_{1B, 1D}$ Receptor Agonist
Use: Labeled IndicationsAcute treatment of migraine, with or without aura
Dosing: AdultsAcute migraine: Oral: 20-40 mg; if the headache improves but returns, dose may be repeated after 2 hours have elapsed since first dose; maximum 80 mg/day

Note: If the first dose is ineffective, diagnosis needs to be re-evaluated. Safety of treating >3 headaches/month has not been established.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo dosing adjustment needed; monitor for increased blood pressure.
Dosing: Hepatic Impairment

Mild-to-moderate impairment: No adjustment necessary.

Severe impairment: Use is contraindicated.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to eletriptan or any component of the formulation; ischemic heart disease or signs or symptoms of ischemic heart disease (including Prinzmetal's angina, angina pectoris, MI, silent myocardial ischemia); cerebrovascular syndromes (including strokes, transient ischemic attacks); peripheral vascular syndromes (including ischemic bowel disease); uncontrolled hypertension; use within 24 hours of ergotamine derivatives; use within 24 hours of another 5-HT_1 agonist; use within 72 hours of potent CYP3A4 inhibitors; management of hemiplegic or basilar migraine; prophylactic treatment of migraine; severe hepatic impairment
Allergy Considerations

- Serotonin 5-$HT_{1B,1D}$ Receptor Agonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac events: Coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia/fibrillation, cardiac arrest, and death have been reported with 5-HT_1 agonist administration. Patients who experience sensations of chest pain/pressure/tightness or symptoms suggestive of angina following dosing should be evaluated for coronary artery disease or Prinzmetal's angina before receiving additional doses.

- Cerebrovascular events: Cerebral/subarachnoid hemorrhage and stroke have been reported with 5-HT_1 agonist administration.

- Elevated blood pressure: Significant elevation in blood pressure, including hypertensive crisis, has also been reported on rare occasions in patients with and without a history of hypertension.

- Vasospasm-related events: Peripheral vascular ischemia and colonic ischemia have been reported with 5-HT_1 agonist.

Disease-related concerns:

- Coronary artery disease: Should not be given to patients who have risk factors for CAD (eg, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, menopause, male >40 years of age) without adequate cardiac evaluation. Patients with suspected CAD should have cardiovascular evaluation to rule out CAD before considering use; if cardiovascular evaluation “is satisfactory,” first dose should be given in the healthcare provider's office. Periodic evaluation of cardiovascular status should be done in all patients.

- Hepatic impairment: Use with caution in patients with hepatic impairment. Drug clearance may be reduced leading to increased plasma concentrations; dosage reduction is recommended. Do not use with severe impairment.

Concurrent drug therapy issues:

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce eletriptan's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

Other warnings/precautions:

- Appropriate use: Only indicated for treatment of acute migraine; if a patient does not respond to the first dose, the diagnosis of migraine should be reconsidered.

Geriatric ConsiderationsSince elderly often have cardiovascular disease, careful evaluation of the use of 5-HT agonists is needed to avoid complications with the use of these agents. Safety and efficacy in elderly >65 years of age have not been established, however, pharmacokinetic disposition is similar to that in younger adults. Use lowest recommended doses initially.
Pregnancy Risk FactorC
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women; use during pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus. Teratogenic effects were observed in animal studies.
LactationEnters breast milk/use caution
Adverse Reactions

1% to 10%:

Cardiovascular: Chest pain/tightness (1% to 4%; placebo 1%), palpitation

Central nervous system: Dizziness (3% to 7%; placebo 3%), somnolence (3% to 7%; placebo 4%), headache (3% to 4%; placebo 3%), chills, pain, vertigo

Gastrointestinal: Nausea (4% to 8%; placebo 5%), xerostomia (2% to 4%, placebo 2%), dysphagia (1% to 2%), abdominal pain/discomfort (1% to 2%; placebo 1%), dyspepsia (1% to 2%; placebo 1%)

Neuromuscular & skeletal: Weakness (4% to 10%), paresthesia (3% to 4%), back pain, hypertonia, hypoesthesia

Respiratory: Pharyngitis

Miscellaneous: Diaphoresis

<1% (Limited to important or life-threatening): Agitation, allergic reaction, angina, arrhythmia, ataxia, confusion, constipation, CPK increased, depersonalization, depression, diarrhea, dreams (abnormal), dyspnea, edema, emotional lability, esophagitis, euphoria, hyperesthesia, hyperkinesia, hypertension, impotence, incoordination, insomnia, lacrimation disorder, liver function tests abnormal, myalgia, myasthenia, nervousness, peripheral vascular disorder, photophobia, polyuria, pruritus, rash, salivation increased, shock, speech disorder, stupor, tachycardia, taste perversion, thrombophlebitis, tinnitus, tongue edema, tremor, urinary frequency, vasospasm, vision abnormal

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)
Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Eletriptan. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Eletriptan. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ergot Derivatives: May enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Fluconazole: May decrease the metabolism of Eletriptan. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Eletriptan. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: High-fat meal increases bioavailability.
Nursing: Physical Assessment/MonitoringFor use with clear diagnosis of migraine. Assess for potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, ergot-containing drugs, other 5-HT$_1$ agonists). Assess therapeutic effectiveness (relief of migraine) and adverse response (hypertension, cardiac events). Teach patient proper use, possible side effects/appropriate interventions and adverse symptoms to report.
Patient EducationThis drug is to be used to reduce your migraine, not to prevent the number of attacks. Follow exact instructions for use. Do not crush, break, or chew tablet. Do not take within 24 hours of any other medication without first consulting prescriber. If headache improves but returns, dose may be repeated after 2 hours. Do not exceed two doses in 24 hours (may take either 20 mg or 40 mg twice daily). If you have no relief with the first dose, do not take a second dose without consulting prescriber. May cause dizziness or drowsiness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or abdominal pain. Report immediately any chest pain, tightness, or palpitations; muscle weakness or tremors; back pain; respiratory difficulty; changes in CNS (abnormal thought processes, depression, insomnia, confusion, agitation); swelling of eyelids, face, lips, throat; rash, hives, or any other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrobromide: 20 mg, 40 mg [as base]

Generic AvailableNo
ManufacturerPfizer, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Relpax)

20 mg (6): $119.29

40 mg (6): $119.68

Mechanism of ActionSelective agonist for serotonin (5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1F}$ receptors) in cranial arteries; causes vasoconstriction and reduce sterile inflammation associated with antidromic neuronal transmission correlating with relief of migraine

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: V$_d$: 138 L

Protein binding: ~85%

Metabolism: Hepatic via CYP3A4; forms one metabolite (active)

Bioavailability: ~50%, increased with high-fat meal

Half-life elimination: 4 hours (Elderly: 4.4-5.7 hours); Metabolite: ~13 hours

Time to peak, plasma: 1.5-2 hours

Related Information

- Antimigraine Drugs: 5-HT1 Receptor Agonists

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Cardiovascular ConsiderationsCoronary vasospasm has been associated with 5-HT$_{1B/1D}$ agonists. These agents are contraindicated in patients with documented ischemic of vasospastic coronary artery disease. Patients with risk factors for CAD may receive these agents, provided a cardiovascular evaluation yields satisfactory evidence that the patient is free of cardiovascular disease. In patients with risk factors for CAD, administration of the initial dose in a medically staffed/equipped facility (ie, physician's office) is recommended. In addition, ECG monitoring after the initial dose should be considered. Patients who acquire risk factors for CAD, or long-term users of agents from this class of medications, should undergo periodic cardiovascular evaluation.

Index TermsEletriptan Hydrobromide

References

Boyer EW and Shannon M, “The Serotonin Syndrome,” *N Engl J Med*, 2005, 352:1112-20.[PubMed 15784664]

International Brand NamesRelert (BE, CR, GT, HN, IL, NI, PA, PT, SV); Relpax (AU, BG, BR, CH, CN, CO, CZ, DE, DK, EE, ES, FR, GB, HN, IE, IT, MX, NL, NO, PL, SE, SG, ZA)

ELF

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Gastric Cancer

Regimen UseGastric cancer

Regimen

Leucovorin calcium: I.V.: 300 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 900 mg/m^2]

followed by

Etoposide: I.V.: 120 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 360 mg/m^2]

followed by

Fluorouracil: I.V.: 500 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 1500 mg/m^2]

Repeat cycle every 21-28 days

References

Wilke H, Preusser P, Fink U, et al, âNew Developments in the Treatment of Gastric Carcinoma,â *Semin Oncol*, 1990, 17(1 Suppl 2):61-70.[PubMed 2305269]

Eltrombopag

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(el TROM boe pag)

U.S. Brand NamesPromacta®

Pharmacologic CategoryColony Stimulating Factor; Thrombopoietic Agent

Use: Labeled IndicationsTreatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) at risk for bleeding who have had insufficient response to corticosteroids, immune globulin, or splenectomy

Dosing: Adults**Note:** Discontinue if platelet count does not respond to a level that avoids clinically important bleeding after 4 weeks at the maximum daily dose of 75 mg.

ITP: Oral: Initial: 50 mg once daily; adjust dose to achieve and maintain platelet count ≥50,000/mm^3 to reduce the risk of bleeding; Maximum dose: 75 mg once daily

Dosage adjustment recommendations:

Platelet count <50,000/mm^3 (after at least 2 weeks): Increase daily dose by 25 mg; maximum dose: 75 mg/day

Platelet count >200,000/mm^3 (at any time): Reduce daily dose by 25 mg; reassess in 2 weeks

Platelet count >400,000/mm^3: Withhold dose; assess platelet count twice weekly; when platelet count <150,000/mm3, resume with the daily dose reduced by 25 mg

Platelet count >400,000/mm^3 after 2 weeks at the lowest dose: Permanently discontinue

Dosage adjustment for patients of East-Asian ethnicity (eg, Chinese, Japanese, Korean, Taiwanese): Initial dose: 25 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentHas not been evaluated in patients with renal impairment; monitor closely.

Dosing: Hepatic Impairment

Mild impairment: No adjustment required.

Moderate-to-severe impairment: Initial dose: 25 mg once daily.

Dosing: Adjustment for Toxicity

ALT levels ≥3 times the upper limit of normal (ULN) **and** which are progressive, or persistent (≥4 weeks), or accompanied by increased direct bilirubin, or accompanied by clinical signs of liver injury or evidence of hepatic decompensation: Discontinue treatment.

New or worsening cellular abnormalities or cytopenias: Discontinue treatment.

Administration: OralAdminister on an empty stomach, 1 hour before or 2 hours after a meal. Do not administer concurrently with antacids, foods high in calcium, or minerals (eg, iron, calcium, aluminum, magnesium, selenium, zinc); separate by at least 4 hours.

Dietary ConsiderationsTake on an empty stomach (1 hour before or 2 hours after a meal). Food, especially dairy products, may decrease the absorption of eltrombopag; allow at least 4 hours between dosing of eltrombopag and polyvalent cation intake (eg, dairy products, calcium-rich foods, multivitamins with minerals).

StorageStore at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

RestrictionsEltrombopag is approved for marketing under a Food and Drug Administration (FDA) approved, risk management, and restricted distribution program called Promacta® Cares™ (1-877-977-6622). Patients, prescribers, and pharmacies must be enrolled in the program.

An FDA-approved medication guide is available, distribute to each patient to whom this medication is dispensed.

ContraindicationsThere are no contraindications listed within the manufacturer’s labeling.

Warnings/Precautions

Box warnings:

- Hepatotoxicity: See “Concerns related to adverse effects” below.
- Restricted access: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Bone marrow reticulin: May increase the risk for bone marrow reticulin formation or progression; collagen fibrosis (not associated with cytopenias) was observed in clinical trials. Monitor peripheral blood smear for cellular morphologic abnormalities; discontinue treatment with onset of new or worsening abnormalities or cytopenias and consider bone marrow biopsy.

- Cataract formation: Cataract formation or worsening was observed in clinical trials. Monitor regularly for signs and symptoms of cataracts; obtain ophthalmic exam at baseline and during therapy. Use with caution in patients at risk for cataracts (eg, advanced age, long-term glucocorticoid use).

- Hepatotoxicity: **[U.S. Boxed Warning]: May cause hepatotoxicity; obtain ALT/AST and bilirubin prior to treatment initiation, every 2 weeks during adjustment phase, then monthly. Obtain fractionation for elevated bilirubin levels. Repeat abnormal liver function tests within 3-5 days; if confirmed abnormal, monitor weekly until resolves, stabilizes, or returns to baseline. Discontinue treatment for ALT levels ≥3 times the upper limit of normal (ULN) and which are progressive, or persistent (≥4 weeks), or accompanied by increased direct bilirubin, or accompanied by clinical signs of liver injury or evidence of hepatic decompensation**. Reinitiation is not recommended; hepatotoxicity usually recurred with retreatment after therapy interruption. Use with caution in patients with pre-existing hepatic impairment; dosage reductions are recommended in patients moderate-to-severe hepatic dysfunction; monitor closely.

- Malignancy/tumorigenicity: Stimulation of cell surface thrombopoietin (TPO) receptors may increase the risk for hematologic malignancies.

- Rebound thrombocytopenia: Upon discontinuation of therapy, thrombocytopenia may worsen. Severity may be greater than pretreatment level. Risk of bleeding is increased, particularly in patients receiving anticoagulants or antiplatelet agents; monitor closely. Monitor for at least 4 weeks after treatment discontinuation.

- Thromboembolism: Thromboembolism may occur with excess increases in platelet levels. Use with caution in patients with known risk factors for thromboembolism (eg, Factor V Leiden, AT deficiency, antiphospholipid syndrome).

Disease-related concerns:

- Hepatic impairment: Clearance may be reduced in patients with hepatic impairment; use with caution; reduced starting doses are recommended in patients with moderate-to-severe hepatic impairment.

- Renal impairment: Safety and efficacy in renal impairment have not been established.

Concurrent drug therapy issues:

- Antacids/calcium/cation mineral supplements: May reduce eltrombopag levels; allow at least 4 hours between dosing of eltrombopag and antacids, minerals (eg, iron, calcium, aluminum, magnesium, selenium, zinc), or foods high in calcium.

Special populations:

- East-Asian ethnicity (eg, Chinese, Japanese, Korean, Taiwanese): May have greater drug exposure (compared to non-east Asians); therapy should be initiated with lower starting doses.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Indicated only when the degree of thrombocytopenia and clinical conditions increase the risk for bleeding; use the lowest dose necessary to achieve and maintain platelet count ≥50,000/mm^3. Do not use to normalize platelet counts. Discontinue if platelet count does not respond to a level to avoid clinically important bleeding after 4 weeks at the maximum recommended dose.

- Restricted access: **[U.S. Boxed Warning]: Eltrombopag is available through a restricted access program called Promacta Cares™; prescribers, pharmacies and patients must be registered with the program.** The program maintains a patient registry and requires prescribers to monitor and report baseline and periodic safety information related to hepatotoxicity, thromboembolic events, bone marrow reticulin events, rebound thrombocytopenia (after cessation), and malignancies.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse effects were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus. A Promacta® pregnancy registry has been established to monitor outcomes of women exposed to eltrombopag during pregnancy (1-888-825-5249).

LactationExcretion in breast milk unknown/ not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse effects in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

1% to 10%:

Dermatologic: Rash (≤7%), bruising (2%)

Endocrine & metabolic: Menorrhagia (4%)

Gastrointestinal: Nausea (6%), vomiting (4%), dyspepsia (2%)

Hematologic: Rebound thrombocytopenia (10%), thrombocytopenia (2%)

Hepatic: Liver function tests abnormal (10%), ALT increased (2%), AST increased (2%)

Neuromuscular & skeletal: Limb pain (≤7%), myalgia (3%), paresthesia (3%)

Ocular: Cataract (3%), conjunctival hemorrhage (2%)

<1%, postmarketing, and/or case reports: Bone marrow collagen fiber deposits, bone marrow reticulin fiber deposits, cataract worsening, epistaxis, headache, hemorrhage (due to thrombocytopenia or rebound thrombocytopenia), non-Hodgkin’s lymphoma, thrombotic/thromboembolic complications

Metabolism/Transport Effects

Substrate of CYP1A2, CYP2C8, UGT 1A1, UGT1A3; **Inhibits** OATP1B1, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15

Drug Interactions

Antacids: May decrease the absorption of eltrombopag; separate administration by at least 4 hours.

Cation mineral supplements (eg, iron, calcium, aluminum, magnesium, selenium, zinc): May reduce eltrombopag absorption; separate administration by at least 4 hours

OATP1B1 substrates (eg, rosuvastatin): Eltrombopag may decrease the metabolism of rosuvastatin; dose reductions of rosuvastatin (50%) may be required.

Ethanol/Nutrition/Herb InteractionsFood: Food, especially dairy products, may decrease the absorption of eltrombopag; allow at least 4 hours between dosing of eltrombopag and polyvalent cation intake (eg, dairy products, calcium-rich foods, multivitamins with minerals).

Monitoring ParametersLiver tests, including ALT, AST, and bilirubin (baseline, every 2 weeks during dosage titration, then monthly; monitor weekly if retreating [not recommended] after therapy interruption for hepatotoxicity); bilirubin fractionation (for elevated bilirubin); CBC with differential and platelet count (weekly at initiation and during dosage titration, then monthly when stable; continue monitoring for ≥4 weeks after cessation); peripheral blood smear (baseline and monthly when stable), bone marrow biopsy (if peripheral blood smear reveals abnormality); ophthalmic exam (baseline and during treatment)

Reference RangeTarget platelet count (with treatment) of 50,000-200,000/mm^3; platelet life span: 8-11 days

Monitoring: Lab TestsLiver tests, including ALT, AST, and bilirubin (baseline, every 2 weeks during dosage titration, then monthly; monitor weekly if retreating [not recommended] after therapy interruption for hepatotoxicity); bilirubin fractionation (for elevated bilirubin); CBC with differential and platelet count (weekly at initiation and during dosage titration, then monthly when stable; continue monitoring for ≥4 weeks after cessation); peripheral blood smear (baseline and monthly when stable)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Promacta®: 25 mg, 50 mg

Generic AvailableNo

ManufacturerGlaxo SmithKline, Inc

Mechanism of ActionThrombopoietin (TPO) nonpeptide agonist which increases platelet counts by binding to and activating the human TPO receptor. Activates intracellular signal transduction pathways to increase proliferation and differentiation of marrow progenitor cells. Does not induce platelet aggregation or activation.

Pharmacodynamics/Kinetics

Onset of action: Platelet count increase: Within 1-2 weeks

Peak platelet count increase: 14-16 days

Duration of action: Platelets return to baseline: 1-2 weeks after last dose

Protein binding: >99%

Metabolism: Extensive hepatic metabolism; via CYP 1A2, 2C8 oxidation and UGT 1A1, 1A3 glucuronidation

Bioavailability: ~52%

Half-life elimination: ~21-32 hours in healthy individuals; ~26-35 hours in patients with ITP

Time to peak, plasma: 2-6 hours

Excretion: Feces (~59%, 20% as unchanged drug, 21% glutathione-related conjugates); urine (31%, 20% glucuronide of the phenypyrazole moiety)

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsEltrombopag Olamine; Revolade®; SB-497115; SB-497115-GR

References

Bussel JB, Cheng G, Saleh MN, et al, “Eltrombopag for the Treatment of Chronic Idiopathic Thrombocytopenic Purpura,” *N Engl J Med*, 2007, 357(22):2237-47.[PubMed 18046028]

Jenkins JM, Williams D, Deng Y, et al, “Phase 1 Clinical Study of Eltrombopag, An Oral, Nonpeptide Thrombopoietin Receptor Agonist,” *Blood*, 2007, 109(11):4739-41. [PubMed 17327409]

Kuter DJ, “New Thrombopoietic Growth Factors,” *Blood*, 2007, 109(11):4607-16.[PubMed 17289815]

McHutchison JG, Dusheiko G, Schiffman ML, et al, “Eltrombopag for Thrombocytopenia in Patients With Cirrhosis Associated With Hepatitis C,” *N Engl J Med*, 2007, 357(22):2227-36.[PubMed 18046027]

EMA 86

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid

Regimen UseLeukemia, acute myeloid

Regimen

Mitoxantrone: I.V.: 12 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 36 mg/m^2]

Etoposide: I.V.: 200 mg/m^2/day continuous infusion days 8, 9, and 10

[total dose/cycle = 600 mg/m^2]

Cytarabine: I.V.: 500 mg/m^2/day continuous infusion days 1, 2, and 3 and days 8, 9, and 10

[total dose/cycle = 3000 mg/m^2]

Administer one cycle only

References

Archimbaud E, Fenaux P, Reiffers J, et al, âGranulocyte-Macrophage Colony-Stimulating Factor in Association to Timed-Sequential Chemotherapy With Mitoxantrone, Etoposide, and Cytarabine for Refractory Acute Myelogenous Leukemia,â *Leukemia*, 1993, 7(3):372-7.[PubMed 8445942]

EMA/CO

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Gestational Trophoblastic Tumor

Regimen Use Gestational trophoblastic tumor

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Etoposide: I.V.: 100 mg/m^2/day days 1 and 2

[total dose/cycle = 200 mg/m^2]

Methotrexate: I.V.: 300 mg/m^2 continuous infusion over 12 hours day 1

[total dose/cycle = 300 mg/m^2]

Dactinomycin: I.V. push: 0.5 mg/day days 1 and 2

[total dose/cycle = 1 mg]

Leucovorin: Oral, I.M.: 15 mg twice daily for 2 days (start 24 hours after the start of methotrexate) days 2 and 3

[total dose/cycle = 60 mg]

Alternate weekly with:

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Vincristine: I.V. push: 0.8 mg/m^2 (maximum 2 mg) day 1

[total dose/cycle = 0.8 mg/m^2]

Repeat cycle every 2 weeks

Variation 2:

Dactinomycin: I.V.: 0.5 mg/day days 1 and 2

[total dose/cycle = 1 mg]

Etoposide: I.V.: 100 mg/m^2/day days 1 and 2

[total dose/cycle = 200 mg/m^2]

Methotrexate: I.V. bolus: 100 mg/m^2 then 200 mg/m^2 continuous infusion over 12 hours day 1

[total dose/cycle = 300 mg/m^2]

Leucovorin: Oral, I.M.: 15 mg every 12 hours for 4 doses (start 24 hours after methotrexate) days 2 and 3

[total dose/cycle = 60 mg]

Vincristine: I.V.: 1 mg/m^2 day 8

[total dose/cycle = 1 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 8

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 2 weeks

Variation 3:

Dactinomycin: I.V.: 0.5 mg/day days 1 and 2

[total dose/cycle = 1 mg]

Etoposide: I.V.: 100 mg/m^2/day days 1 and 2

[total dose/cycle = 200 mg/m^2]

Methotrexate: I.V.: 300 mg/m^2 continuous infusion over 12 hours day 1

[total dose/cycle = 300 mg/m^2]

Leucovorin: Oral, I.M.: 15 mg every 12 hours for 4 doses (start 24 hours after start of methotrexate) days 2 and 3

[total dose/cycle = 60 mg]

Vincristine: I.V.: 1 mg/m^2 day 8

[total dose/cycle = 1 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 8

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 2 weeks

Variation 4:

Dactinomycin: I.V.: 0.35 mg/m^2/day days 1 and 2

[total dose/cycle = 0.7 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1 and 2

[total dose/cycle = 200 mg/m^2]

Methotrexate: I.V. bolus: 100 mg/m^2 then 200 mg/m^2 continuous infusion over 12 hours day 1

[total dose/cycle = 300 mg/m^2]

Leucovorin: Oral, I.M.: 15 mg every 12 hours for 4 doses (start 24 hours after start of methotrexate) days 2 and 3

[total dose/cycle = 60 mg]

Vincristine: I.V.: 1 mg/m^2 day 8

[total dose/cycle = 1 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 8

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 2 weeks

Variation 5 (patients with brain metastases):

Dactinomycin: I.V.: 0.5 mg/day days 1 and 2

[total dose/cycle = 1 mg]

Etoposide:I.V.: 100 mg/m^2/day days 1 and 2

[total dose/cycle = 200 mg/m^2]

Methotrexate: I.V.: 1 g/m^2 continuous infusion over 12 hours day 1

[total dose/cycle = 1 g/m^2]

Leucovorin: I.M.: 20 mg/m^2 every 6 hours for 12 doses (start 24 hours after start of methotrexate) days 2, 3, and 4

[total dose/cycle = 240 mg/m^2]

Vincristine: I.V.: 1 mg/m^2 day 8

[total dose/cycle = 1 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 8

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 2 weeks

Variation 6 (patients with brain metastases):

Dactinomycin: I.V.: 0.5 mg/day days 1 and 2

[total dose/cycle = 1 mg]

Etoposide: I.V.: 100 mg/m^2/day days 1 and 2

[total dose/cycle = 200 mg/m^2]

Methotrexate: I.V.: 1 g/m^2 continuous infusion over 12 hours day 1

[total dose/cycle = 1 g/m^2]

Leucovorin: Oral, I.M.: 30 mg/m^2 every 12 hours for 6 doses (start 32 hours after start of methotrexate) days 2, 3, and 4

[total dose/cycle = 180 mg/m^2]

Vincristine: I.V.: 1 mg/m^2 day 8

[total dose/cycle = 1 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 8

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 2 weeks

Variation 7:

Dactinomycin: I.V.: 0.5 mg/day days 1 and 2

[total dose/cycle = 1 mg]

Etoposide: I.V.: 100 mg/m^2/day days 1 and 2

[total dose/cycle = 200 mg/m^2]

Methotrexate: I.V.: 1 g/m^2 continuous infusion over 24 hours day 1

[total dose/cycle = 1 g/m^2]

Leucovorin: Oral, I.M.: 15 mg every 8 hours for 9 doses (start 32 hours after start of methotrexate) days 2, 3, and 4

[total dose/cycle = 135 mg/m^2]

Vincristine: I.V.: 1 mg/m^2 day 8

[total dose/cycle = 1 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 8

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 2 weeks

Variation 8 (patients with lung metastases):

Dactinomycin: I.V.: 0.5 mg/day days 1 and 2

[total dose/cycle = 1 mg]

Etoposide: I.V.: 100 mg/m^2/day days 1 and 2

[total dose/cycle = 200 mg/m^2]

Methotrexate: I.V. bolus: 100 mg/m^2 then 200 mg/m^2 continuous infusion over 12 hours day 1

[total dose/cycle = 300 mg/m^2]

Leucovorin: Oral, I.M.: 15 mg every 12 hours for 4 doses (start 24 hours after start of methotrexate) days 2 and 3

[total dose/cycle = 60 mg]

Vincristine: I.V.: 1 mg/m^2 day 8

[total dose/cycle = 1 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 8

[total dose/cycle = 600 mg/m^2]

Methotrexate: I.T.: 10 mg day 1 (every other cycle)

[total dose/cycle = 10 mg, every other cycle]

Repeat cycle every 2 weeks

Variation 9 (patients with lung metastases):

Dactinomycin: I.V.: 0.5 mg/day days 1 and 2

[total dose/cycle = 1 mg]

Etoposide: I.V.: 100 mg/m^2/day days 1 and 2

[total dose/cycle = 200 mg/m^2]

Methotrexate: I.V. bolus: 100 mg/m^2 then 200 mg/m^2 continuous infusion over 12 hours day 1

[total dose/cycle = 300 mg/m^2]

Leucovorin: Oral, I.M.: 15 mg every 12 hours for 4 doses (start 24 hours after start of methotrexate) days 2 and 3

[total dose/cycle = 60 mg]

Vincristine: I.V.: 1 mg/m^2 day 8

[total dose/cycle = 1 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 8

[total dose/cycle = 600 mg/m^2]

Methotrexate: I.T.: 12.5 mg day 8

[total dose/cycle = 12.5 mg]

Repeat cycle every 2 weeks

References

Variation 1:

Bagshawe KD, “High-Risk Metastatic Trophoblastic Disease,” *Obstet Gynecol Clin North Am*, 1988, 15(3):531-43.[PubMed 2852333]

Variation 2:

Newlands ES, Bagshawe KD, Begent RH, et al, “Developments in Chemotherapy for Medium- and High-Risk Patients With Gestational Trophoblastic Tumours (1979-1984),” *Br J Obstet Gynaecol*, 1986, 93(1):63-9.[PubMed 3002420]

Variation 3:

Newlands ES, Bagshawe KD, Begent RH, et al, “Results With the EMA/CO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Vincristine) Regimen in High-Risk Gestational Trophoblastic Tumours, 1979 to 1989,” *J Obstet Gynaecol*, 1991, 98(6):550-7.[PubMed 1651757]

Variation 4:

Soper JT, Evans AC, Clarke-Pearson DL, et al, “Alternating Weekly Chemotherapy With Etoposide-Methotrexate-Dactinomycin/Cyclophosphamide-Vincristine for High-Risk Gestational Trophoblastic Disease,” *Obstet Gynecol*, 1994, 83(1):113-7. [PubMed 8272290]

Variation 5:

Bolis G, Bonazzi C, Landoni F, et al, “EMA/CO Regimen in High-Risk Gestational Trophoblastic Tumor (GTT),” *Gynecol Oncol*, 1988, 31(3):439-44. [PubMed 2846414]

Variation 6:

Schink JC, Singh Dk, Rademaker AW, et al, “Etoposide, Methotrexate, Actinomycin-D, Cyclophosphamide, and Vincristine for the Treatment of Metastatic, High-Risk Gestational Trophoblastic Disease,” *Obstet Gynecol*, 1992, 80(5):817-20.[PubMed 1328977]

Variation 7:

Newlands ES, Bagshawe KD, Begent RH, et al, “Results With the EMA/CO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Vincristine) Regimen in High-Risk Gestational Trophoblastic Tumours, 1979 to 1989,” *Br J Obstet Gynaecol*, 1991, 98(6):550-7.[PubMed 1651757]

Variation 8:

Bolis G, Bonazzi C, Landoni F, et al, “EMA/CO Regimen in High-Risk Gestational Trophoblastic Tumor (GTT),”*Gynecol Oncol*, 1988, 31(3):439-44. [PubMed 2846414]

Variation 9:

Newlands ES, Bagshawe KD, Begent RH, et al, “Developments in Chemotherapy for Medium- and High-Risk Patients With Gestational Trophoblastic Tumours (1979-1984),” *Br J Obstet Gynaecol*, 1986, 93(1):63-9.[PubMed 3002420]

Emedastine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(em e DAS teen)
U.S. Brand NamesEmadine®
Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation
Use: Labeled IndicationsTreatment of allergic conjunctivitis
Dosing: AdultsAllergic conjunctivitis: Ophthalmic: Instill 1 drop in affected eye up to 4 times/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren ≥3 years: Refer to adult dosing.
Administration: OtherEmadine® is for topical ophthalmic use only, **not** for injection. Soft contact lenses should not be worn during treatment if eyes are red; if there is no redness, wait 10 minutes following emedastine instillation before inserting contact lenses. Do not allow dropper tip to touch eyelids or surrounding area of the eye.
StorageStore at 4°C to 30°C (39°F to 86°F). Solution should not be used if it becomes discolored.
ContraindicationsHypersensitivity to emedastine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Bacterial keratitis: Inadvertent contamination of multiple-dose ophthalmic solutions has caused bacterial keratitis.

Special populations:

- Contact lens wearers: Contains benzalkonium chloride which may be absorbed by contact lenses; remove contact lenses prior to use and wait 15 minutes before reinserting.

- Pediatrics: Safety and efficacy have not been established in children <3 years of age.

Other warnings/precautions:

- Appropriate use: For topical ophthalmic use only.

Pregnancy Risk FactorB
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%: Central nervous system: Headache (11%)

1% to 10%:

Cardiovascular: Hyperemia

Central nervous system: Abnormal dreams

Dermatologic: Dermatitis, keratitis, pruritus

Gastrointestinal: Taste (unpleasant)

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision, corneal infiltrates, corneal staining, dry eyes, transient burning or stinging

Respiratory: Rhinitis, sinusitis

Miscellaneous: Tearing

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic, as difumarate: 0.05% (5 mL) [contains benzalkonium chloride]

ManufacturerAlcon Laboratories, Inc
Pricing: U.S. (www.drugstore.com)

Solution (Emadine)

0.05% (5): $70.99

Mechanism of ActionSelective histamine H_1-receptor antagonist for topical ophthalmic use
Pharmacodynamics/Kinetics

Absorption: Ocular: Minimal

Half-life elimination: Oral: Plasma: 3-4 hours

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause drowsiness or abnormal dreams

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Emedastine Difumarate

International Brand Names Daren (JP); Emadine (AT, BE, BG, BR, CH, CL, CZ, DE, DK, EE, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, NL, NO, PK, PL, PT, RU, SE, TH, TR, TW, ZA); Remicut SR (KP)

Emtricitabine and Tenofovir

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(em trye SYE ta been & te NOE fo veer)

U.S. Brand NamesTruvada®

Canadian Brand NamesTruvada®

Pharmacologic Category[Antiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)](); [Antiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleotide)]()

Use: Labeled IndicationsTreatment of HIV infection in combination with other antiretroviral agents

Dosing: AdultsHIV: Oral: One tablet (emtricitabine 200 mg and tenofovir 300 mg) once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 30-49 mL/minute: Increase interval to every 48 hours.

Cl_{cr} <30 mL/minute or hemodialysis: Not recommended.

Calculations

- [Creatinine Clearance: Adults]()

Administration: OralMay be administered with or without food. If used with didanosine; refer to didanosine monograph for additional information.

Dietary ConsiderationsMay be taken without regard to meals. Consider calcium and vitamin D supplementation in patients with history of bone fracture or osteopenia.

StorageStore tablets at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to emtricitabine, tenofovir, or any component of the formulation; severe renal impairment (Cl_{cr} <30 mL/minute); concurrent use of single-agent tenofovir (Viread®) or other tenofovir-containing combination formulations (eg, Atripla™)

Warnings/Precautions

Boxed warnings:

- Chronic hepatitis B: See “Disease-related concerns” below.
- Lactic acidosis/hepatomegaly: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Decreased bone mineral density: Use has been associated with decreases in bone mineral density (~5% to 7%) and osteomalacia. Consider monitoring of bone density in patients at risk for osteopenia or with a history of pathologic fractures; consider calcium and vitamin D supplementation.
- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).
- Renal toxicity: May cause renal toxicity (acute renal failure and/or Fanconi syndrome); avoid use with concurrent or recent nephrotoxic therapy. Calculate creatinine clearance prior to initiation of therapy and monitor renal function (including recalculation of creatinine clearance and serum phosphorus) during therapy. Dosage adjustment required in patients with Cl_{cr} <50 mL/minute.

Disease-related concerns:

- Chronic hepatitis B: **[U.S. Boxed Warning]: Safety and efficacy during coinfection of HIV and HBV have not been established; acute, severe exacerbations of HBV have been reported following discontinuation of antiretroviral therapy.** All patients with HIV should be tested for HBV prior to initiation of treatment. Caution in patients with known or suspected hepatitis B or C infection (monitoring of liver function is recommended). In HBV coinfected patients, monitor hepatic function closely for several months following discontinuation.
- Hepatic impairment: Use with caution in patients with hepatic impairment. No dosage adjustment is required; limited studies indicate the pharmacokinetics of tenofovir are not altered in hepatic dysfunction.

- HIV: Appropriate use: Not recommended as a component of a triple nucleoside regimen.
- Renal impairment: Use with caution in patients with renal impairment (Cl_{cr} <50 mL/minute); dosage adjustment required.

Special populations:

- Pediatrics: Safety and efficacy have not been established in pediatric patients.

Pregnancy Risk FactorB
Pregnancy ConsiderationsRefer to individual agents.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsHIV-infected women are discouraged from breast-feeding to decrease the potential transmission of HIV.
Adverse ReactionsThe adverse reaction profile of combination therapy has not been established. See individual agents.
Drug Interactions

Acyclovir-Valacyclovir: May decrease the excretion of Tenofovir. *Risk C: Monitor therapy*

Adefovir: May diminish the therapeutic effect of Tenofovir. Specifically, adefovir-associated mutations in Hepatitis B viral reverse transcriptase may decrease viral susceptibility to tenofovir. Tenofovir may increase the serum concentration of Adefovir. Similarly, Adefovir may increase the concentration of Tenofovir. *Risk D: Consider therapy modification*

Atazanavir: Tenofovir may decrease the serum concentration of Atazanavir. Atazanavir may increase the serum concentration of Tenofovir. Management: When combined use required, tenofovir 300mg and atazanavir 300mg should be used together with ritonavir 100mg, all given as a single daily dose with food. Atazanavir without ritonavir should not be used with tenofovir. *Risk D: Consider therapy modification*

Didanosine: Tenofovir may diminish the therapeutic effect of Didanosine. Tenofovir may increase the serum concentration of Didanosine. *Risk D: Consider therapy modification*

Ganciclovir-Valganciclovir: May enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. *Risk D: Consider therapy modification*

Ganciclovir-Valganciclovir: May decrease the excretion of Tenofovir. *Risk C: Monitor therapy*

LamiVUDine: May enhance the adverse/toxic effect of Emtricitabine. *Risk X: Avoid combination*

Lopinavir: May enhance the nephrotoxic effect of Tenofovir. Lopinavir may increase the serum concentration of Tenofovir. *Risk C: Monitor therapy*

Protease Inhibitors: Tenofovir may decrease the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Tenofovir. **Exceptions:** Saquinavir. *Risk C: Monitor therapy*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Food decreases peak plasma concentrations, but does not alter the extent of absorption or overall systemic exposure.
Monitoring ParametersCBC with differential, reticulocyte count, serum creatine kinase, CD4 count, HIV RNA plasma levels, renal and hepatic function tests, bone density (long-term), serum phosphorus; testing for HBV is recommended prior to the initiation of antiretroviral therapy

Patients with HIV and HBV coinfection should be monitored for several months following tenofovir discontinuation.

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg

Generic AvailableNo
ManufacturerGilead
Pricing: U.S. (www.drugstore.com)

Tablets (Truvada)

200-300 mg (30): $904.13

Mechanism of ActionNucleoside and nucleotide reverse transcriptase inhibitor combination; emtricitabine is a cytosine analogue while tenofovir disoproxil fumarate (TDF) is an analog of adenosine 5'-monophosphate. Each drug interferes with HIV viral RNA dependent DNA polymerase resulting in inhibition of viral replication.
Pharmacodynamics/KineticsRefer to individual monographs.
Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDepression, insomnia, and dizziness are common; may cause abnormal dreams and anxiety
Mental Health: Effects on Psychiatric TreatmentGI side effects are common; combined use with SSRIs (lithium or valproic acid) may produce

additive effects. May cause increases in serum triglycerides; monitor in patients receiving concurrent psychotropic medication especially, clozapine, olanzapine, quetiapine, or mirtazapine. May cause glucose abnormalities; use caution with clozapine, olanzapine, quetiapine, and risperidone. May cause neutropenia; use caution with clozapine and carbamazepine.

Index TermsTenofovir and Emtricitabine

International Brand NamesTruvada (AR, AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, MX, NL, NO, NZ, PT, RU, SE, TR)

Emtricitabine

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(em trye SYE ta been)

U.S. Brand NamesEmtriva®

Canadian Brand NamesEmtriva®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)

Use: Labeled IndicationsTreatment of HIV infection in combination with at least two other antiretroviral agents

Use: Unlabeled/InvestigationalHepatitis B (with HIV coinfection)

Dosing: AdultsHIV infection: Oral:

Capsule: 200 mg once daily

Solution: 240 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricHIV infection: Oral:

Children: 0-3 months: Solution: 3 mg/kg/day

Children: 3 months to 17 years:

Capsule: Children >33 kg: 200 mg once daily

Solution: 6 mg/kg once daily; maximum: 240 mg/day

Dosing: Renal ImpairmentAdults (consider similar adjustments in children):

Cl_{cr} 30-49 mL/minute: Capsule: 200 mg every 48 hours; solution: 120 mg every 24 hours

Cl_{cr} 15-29 mL/minute: Capsule: 200 mg every 72 hours; solution: 80 mg every 24 hours

Cl_{cr} <15 mL/minute (including hemodialysis patients): Capsule: 200 mg every 96 hours; solution: 60 mg every 24 hours; administer after dialysis on dialysis days

Dosing: Hepatic ImpairmentNo adjustment required.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore capsules at 15°C to 30°C (59°F to 86°F). Solution should be stored under refrigeration at 2°C to 8°C (36°F to 46°F). Once dispensed, may be stored at 15°C to 30°C (59°F to 86°F) if used within 3 months.

ContraindicationsHypersensitivity to emtricitabine or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Chronic hepatitis B: See “Disease-related concerns” below.
- Lactic acidosis/hepatomegaly: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).

Disease-related concerns:

- Chronic hepatitis B: **[U.S. Boxed Warning]: Safety and efficacy during coinfection of HIV and HBV have not been established; acute, severe exacerbations of HBV have been reported following discontinuation of antiretroviral therapy. Not indicated for treatment of chronic hepatitis B.** All patients with HIV should be tested for HBV prior to initiation of treatment. Caution in patients with known or suspected hepatitis B or C infection (monitoring of liver function is recommended). In HBV coinfected patients, monitor hepatic function closely for several months following discontinuation.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required.

Pregnancy Risk FactorB

Pregnancy Considerations Adverse events were not observed in animal studies, however, there are no studies of emtricitabine during human pregnancy. Cases of fatal and nonfatal lactic acidosis, with or without pancreatitis, have been reported in pregnant women receiving reverse transcriptase inhibitors. It is not known if pregnancy itself potentiates this known side effect; however, pregnant women may be at increased risk of lactic acidosis and liver damage. Hepatic enzymes and electrolytes should be monitored frequently during the 3rd trimester of pregnancy. The Perinatal HIV Guidelines Working Group considers emtricitabine to be an alternative NRTI in dual nucleoside combination regimens. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected women are discouraged from breast-feeding to decrease the potential transmission of HIV.

Adverse Reactions Clinical trials were conducted in patients receiving other antiretroviral agents, and it is not possible to correlate frequency of adverse events with emtricitabine alone. The range of frequencies of adverse events is generally comparable to comparator groups, with the exception of hyperpigmentation, which occurred more frequently in patients receiving emtricitabine. Unless otherwise noted, percentages are as reported in adults.

>10%:

Central nervous system: Dizziness (4% to 25%), headache (6% to 22%), fever (children 18%), insomnia (5% to 16%), abnormal dreams (2% to 11%)

Dermatologic: Hyperpigmentation (children 32%; adults 2% to 4%; primarily of palms and/or soles but may include tongue, arms, lip and nails; generally mild and nonprogressive without associated local reactions such as pruritus or rash); rash (17% to 30%; includes pruritus, maculopapular rash, vesiculobullous rash, pustular rash, and allergic reaction)

Gastrointestinal: Diarrhea (children 20%; adults 9% to 23%), vomiting (children 23%; adults 9%), nausea (13% to 18%), abdominal pain (8% to 14%), gastroenteritis (children 11%)

Neuromuscular & skeletal: Weakness (12% to 16%), CPK increased (grades 3/4: 11% to 12%)

Otic: Otitis media (children 23%)

Respiratory: Cough (children 28%; adults 14%), rhinitis (children 20%; adults 12% to 18%), pneumonia (children 15%)

Miscellaneous: Infection (children 44%)

1% to 10%:

Central nervous system: Depression (6% to 9%), neuropathy/neuritis (4%)

Endocrine & metabolic: Serum triglycerides increased (grades 3/4: 4% to 10%), disordered glucose homeostasis (grades 3/4: 2% to 3%), serum amylase increased (grades 3/4: children 9%; adults 2% to 5%), serum lipase increased (grades 3/4: ≤1%)

Gastrointestinal: Dyspepsia (4% to 8%), serum amylase increased (grades 3/4: 8%)

Genitourinary: Hematuria (grades 3/4: 3%)

Hematologic: Anemia (children: 7%), neutropenia (grades 3/4: children 2%; adults 5%)

Hepatic: Transaminases increased (grades 3/4: 2% to 6%), alkaline phosphatase increased (>550 units/L: 1%), bilirubin increased (grades 3/4: 1%)

Neuromuscular & skeletal: Creatinine kinase increased (grades 3/4: 9%), myalgia (4% to 6%), paresthesia (5% to 6%), arthralgia (3% to 5%)

Respiratory: Upper respiratory tract infection (8%), sinusitis (8%), pharyngitis (5%)

Drug Interactions

Ganciclovir-Valganciclovir: May enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. *Risk D: Consider therapy modification*

LamiVUDine: May enhance the adverse/toxic effect of Emtricitabine. *Risk X: Avoid combination*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions Food: Food decreases peak plasma concentrations, but does not alter the extent of absorption or overall systemic exposure.

Monitoring Parameters Viral load, CD4, liver function tests; hepatitis B testing is recommended prior to initiation of therapy

Nursing: Physical Assessment/Monitoring Assess other pharmacologic or herbal products patient may be taking for potential interactions or toxicity; dosing adjustments may be necessary. Assess results of laboratory tests, effectiveness of therapy (viral load and CD4 count), and adverse reactions (eg, Lactic Acidosis) periodically during therapy. Teach patient proper use (eg, timing of multiple medications), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsViral load, CD4, liver function tests; hepatitis B testing is recommended prior to initiation of therapy

Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV. Use appropriate precautions to prevent spread to other people. This drug is prescribed as one part of a multi-drug combination; time multiple medications exactly as directed for full course of therapy. Take with or without food. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. You may be susceptible to infection (avoid crowds and exposure to known infections, and do not have any vaccinations without consulting prescriber). Frequent blood tests may be required with prolonged therapy. May cause hyperpigmentation of hands, soles, or lips (normal). May cause headache, dizziness, or insomnia (use care when driving or engaged in potentially hazardous tasks until response to drug is know); nausea, vomiting, or abdominal pain (small frequent meals, chewing gum, good mouth care, or sucking lozenges may help); and diarrhea (boiled milk, yogurt, or buttermilk may help). Report persistent fast or rapid heartbeat, weakness or tiredness, muscle pain, respiratory difficulty, gastrointestinal upset, rash, or diarrhea; signs of infection (burning on urination, perineal itching, white plaques in mouth, unhealed sores, persistent sore throat, or cough); yellowing of skin or eyes, dark urine, or light stool; or other adverse side effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Emtriva®: 200 mg

Solution:

Emtriva®: 10 mg/mL (170 mL) [contains propylene glycol; cotton candy flavor]

Generic AvailableNo

ManufacturerGilead Sciences

Pricing: U.S. (www.drugstore.com)

Capsules (Emtriva)

200 mg (30): $392.65

Mechanism of ActionNucleoside reverse transcriptase inhibitor; emtricitabine is a cytosine analogue which is phosphorylated intracellularly to emtricitabine 5'-triphosphate which interferes with HIV viral RNA dependent DNA polymerase resulting in inhibition of viral replication.

Pharmacodynamics/Kinetics

Absorption: Rapid, extensive

Protein binding: <4%

Metabolism: Limited, via oxidation and conjugation (not via CYP isoenzymes)

Bioavailability: Capsule: 93%; solution: 75%

Half-life elimination: Normal renal function: Adults: 10 hours; children: 5-18 hours

Time to peak, plasma: 1-2 hours

Excretion: Urine (86% primarily as unchanged drug, 13% as metabolites); feces (14%)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia and dizziness are common; may cause depression and abnormal dreams

Mental Health: Effects on Psychiatric TreatmentGI side effects are common. Combined use with SSRIs may produce additive effects. May cause increases in serum triglycerides. Monitor in patients receiving concurrent psychotropic medication especially, clozapine, olanzapine, quetiapine, or mirtazapine. May cause glucose abnormalities; use caution with clozapine, olanzapine, and quetiapine, and risperidone.

Index TermsBW524W91; Coviracil; FTC

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International Brand NamesEmtriva (AR, AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, MX, NL, NO, PL, PT, RU, SE, TR)

Enalapril and Felodipine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(e NAL a pril & fe LOE di peen)

U.S. Brand NamesLexxel® [DSC]

Canadian Brand NamesLexxel®

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Calcium Channel Blocker

Use: Labeled IndicationsTreatment of hypertension, however, not indicated for initial treatment of hypertension; replacement therapy in patients receiving separate dosage forms (for patient convenience); when monotherapy with one component fails to achieve desired antihypertensive effect, or when dose-limiting adverse effects limit upward titration of monotherapy

Dosing: AdultsHypertension: Oral: Enalapril 5-20 mg and felodipine 2.5-10 mg once daily

Dosing: ElderlyRecommended initial dose of felodipine is 2.5 mg daily. Titration of individual components is preferred.

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute: Recommended initial dose of enalapril is 2.5 mg/day. Titration of individual components is preferred.

Dosing: Hepatic ImpairmentRecommended initial dose of felodipine is 2.5 mg daily. Titration of individual components is preferred.

ContraindicationsHypersensitivity to felodipine, enalapril or any other component of the formulation; history of angioedema related to previous ACE inhibitor therapy; idiopathic or hereditary angioedema

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity
- Calcium Channel Blocker, Dihydropyridine Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angina/MI: Increased angina and/or MI has occurred with initiation or dosage titration of dihydropyridine calcium channel blockers; reflex tachycardia may occur resulting in angina and/or MI in patients with obstructive coronary disease especially in the absence of concurrent beta-blockade.

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with idiopathic or hereditary angioedema or previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Peripheral edema: The most common side effect of felodipine (dose dependent) is peripheral edema; occurs within 2-3 weeks of starting therapy.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with extreme caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use enalapril with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.

- Heart failure: Use with caution in patients with heart failure. Safety and efficacy has not been established.

- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use enalapril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use ACE inhibitors with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment.

Special populations:

- Elderly: Felodipine should be initiated at lower doses in elderly patients.

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss, or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Pregnancy Risk FactorC/D (2nd and 3rd trimesters)
Pregnancy ConsiderationsSee Enalapril monograph.
LactationEnters breast milk/use caution
Adverse ReactionsSee individual agents.
Metabolism/Transport Effects

Enalapril: **Substrate** of CYP3A4 (minor)

Felodipine: **Substrate** of CYP3A4 (major); **Inhibits** CYP2C8 (moderate), 2C9 (weak), 2D6 (weak), 3A4 (weak)

Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

CycloSPORINE: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk D: Consider therapy modification*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure; serum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsSerum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, extended release:

Lexxel® 5/2.5: Enalapril maleate 5 mg and felodipine 2.5 mg [DSC]

Lexxel® 5/5: Enalapril maleate 5 mg and felodipine 5 mg [DSC]

Generic AvailableNo

ManufacturerAstraZeneca Pharmaceuticals LP

Pricing: U.S. (www.drugstore.com)

Tablet, controlled release (Lexxel)

5-5 mg (30): $71.38

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Enalapril
- Felodipine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Gingival hyperplasia (fewer reports with felodipine than with other CCBs); resolves upon discontinuation (consultation with physician is suggested).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness and dizziness; rarely may cause nervousness, insomnia, confusion, or depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels; carbamazepine may decrease felodipine effect

Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for enalapril and felodipine combination therapy may include improved compliance and synergistic reductions in blood pressure with an accompanied reduction in side effects. ACE inhibitors are standard therapy for left ventricular systolic dysfunction. Felodipine has neutral effects on mortality in this setting and therefore may be considered for the treatment of hypertension or angina in patients with heart failure.

Index TermsEnalapril Maleate and Felodipine; Felodipine and Enalapril

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International Brand NamesLexxel (CA)

Enalapril and Hydrochlorothiazide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(e NAL a pril & hye droe klor oh THYE a zide)

U.S. Brand NamesVaseretic®

Canadian Brand NamesVaseretic®

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension

Dosing: AdultsHypertension: Oral: Enalapril 5-10 mg and hydrochlorothiazide 12.5-25 mg once daily (maximum: 40 mg/day [enalapril]; 50 mg/day [hydrochlorothiazide])

Dosing: ElderlyRefer to dosing in individual monographs; adjust for renal impairment.

Dosing: Renal Impairment

Cl_{cr} >30 mL/minute: Administer usual dose.

Severe renal failure: Avoid; loop diuretics are recommended.

ContraindicationsHypersensitivity to enalapril, hydrochlorothiazide, sulfonamide-derived drugs, or any component of the formulation; angioedema related to previous treatment with an ACE inhibitor; patients with hereditary or idiopathic angioedema; anuria

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with idiopathic or hereditary angioedema or previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Electrolyte disturbances: Hyperkalemia may occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use enalapril with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity. Hydrochlorothiazide can cause systemic lupus erythematosus (SLE) exacerbation or activation.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use enalapril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use ACE inhibitors with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment. Avoid hydrochlorothiazide in severe renal disease (ineffective). Contraindicated in anuric patients.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Pregnancy Risk FactorC/D (2nd and 3rd trimesters)
Pregnancy Considerations**U.S. Boxed Warning: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.** See individual agents.
LactationEnters breast milk (both ingredients)/compatible
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsEnalapril: **Substrate** of CYP3A4 (major)
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure; BUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential
Nursing: Physical Assessment/MonitoringSee individual agents.
Monitoring: Lab TestsBUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

5/12.5: Enalapril maleate 5 mg and hydrochlorothiazide 12.5 mg

10/25: Enalapril maleate 10 mg and hydrochlorothiazide 25 mg

Vaseretic®:

10/25: Enalapril maleate 10 mg and hydrochlorothiazide 25 mg

Generic AvailableYes

ManufacturerMerck & Co

Pricing: U.S. (www.drugstore.com)

Tablets (Enalapril-Hydrochlorothiazide)

5-12.5 mg (30): $23.99

10-25 mg (30): $26.99

Tablets (Vaseretic)

5-12.5 mg (30): $42.34

10-25 mg (30): $85.95

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Enalapril
- Hydrochlorothiazide

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness and dizziness; rarely may cause insomnia, confusion, and depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for enalapril and hydrochlorothiazide combination therapy may include improved compliance and synergistic reductions in blood pressure with an accompanied reduction in side effects. ACE inhibitors and thiazides are also standard therapy for left ventricular systolic dysfunction. See Cardiovascular Considerations for individual agents.

Index TermsEnalapril Maleate and Hydrochlorothiazide; Hydrochlorothiazide and Enalapril

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International Brand NamesAcesistem (IT); Actensil Plus (ES); Angiozide (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Co-Renitec (AE, AT, BE, BF, BG, BH, BJ, BR, CI, CY, CZ, EG, ET, FR, GH, GM, GN, GR, HK, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NZ, OM, PK, QA, SA, SC, SD, SG, SL, SN, SY, TN, TZ, UG, VE, YE, ZA, ZM, ZW); Co-Reniten (CH); Corenitec (AR, DK, NL); Ecaprinil-D (CR, DO, GT, HN, NI, PA, SV); Enace-D (IN); Enap HL (SG); Esalfon-D (CN); Gliotenzide (SG); Innozide (GB, IE); Invozide (IN); Lotrial D (AR, PE, PY, UY); Naprizide (IL); Nariplus

(KP); Pres Plus (DE); Pressel H (BR); Renacor (DE); Renidur (PT); Renitec Comp (FI, NO); Renitec Plus (EE); Renitec Plus 20/6 (AU); Tenazide (ID); Vaseretic (CO, EC); Vasoretic (IT)

Enalapril

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Enalapril may be confused with Anafranil®, Elavil®, Eldepryl®, nafarelin, ramipril

Significant differences exist between oral and I.V. dosing. Use caution when converting from one route of administration to another.

International issues:

Acepril® [Hungary, Switzerland] may be confused with Accupril® which is a brand name for quinapril in the U.S.

Acepril®: Brand name for lisinopril in Denmark; brand name for captopril in Great Britain

Nacor® [Spain] may be confused with Niacor® which is a brand name for niacin in the U.S.

Pronunciation(e NAL a pril)

U.S. Brand NamesVasotec®

Canadian Brand NamesApo-Enalapril®; CO Enalapril; Gen-Enalapril; Novo-Enalapril; PMS-Enalapril; Pro-Enalapril; ratio-Enalapril; Riva-Enalapril; Sandoz-Enalapril; Taro-Enalapril; Vasotec®; Vasotec® I.V.

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor

Use: Labeled IndicationsTreatment of hypertension; treatment of symptomatic heart failure; treatment of asymptomatic left ventricular dysfunction

Use: Unlabeled/Investigational

Unlabeled: To delay the progression of nephropathy and reduce risks of cardiovascular events in hypertensive patients with type 1 or 2 diabetes mellitus; hypertensive crisis, diabetic nephropathy, hypertension secondary to scleroderma renal crisis, diagnosis of aldosteronism, idiopathic edema, Bartter's syndrome, postmyocardial infarction for prevention of ventricular failure

Investigational: Severe congestive heart failure in infants, neonatal hypertension, acute cardiogenic pulmonary edema (enalaprilat)

Dosing: AdultsUse lower listed initial dose in patients with hyponatremia, hypovolemia, severe congestive heart failure, decreased renal function, or in those receiving diuretics.

Asymptomatic left ventricular dysfunction: Oral: 2.5 mg twice daily, titrated as tolerated to 20 mg/day

Hypertension:

Oral: 2.5-5 mg/day then increase as required, usually at 1- to 2-week intervals; usual dose range (JNC 7): 2.5-40 mg/day in 1-2 divided doses. **Note:** Initiate with 2.5 mg if patient is taking a diuretic which cannot be discontinued. May add a diuretic if blood pressure cannot be controlled with enalapril alone.

I.V. (Enalaprilat): 1.25 mg/dose, given over 5 minutes every 6 hours; doses as high as 5 mg/dose every 6 hours have been tolerated for up to 36 hours. **Note:** If patients are concomitantly receiving diuretic therapy, begin with 0.625 mg I.V. over 5 minutes; if the effect is not adequate after 1 hour, repeat the dose and administer 1.25 mg at 6-hour intervals thereafter; if adequate, administer 0.625 mg I.V. every 6 hours.

Heart failure:

Oral: Initial: 2.5 mg once or twice daily (usual range: 5-40 mg/day in 2 divided doses). Titrate slowly at 1- to 2-week intervals. Target dose: 10-20 mg twice daily (ACC/AHA 2005 Heart Failure Guidelines)

I.V.: Avoid I.V. administration in patients with unstable heart failure or those suffering acute myocardial infarction.

Conversion from I.V. to oral therapy if not concurrently on diuretics: 5 mg once daily; subsequent titration as needed; if concurrently receiving diuretics and responding to 0.625 mg I.V. every 6 hours, initiate with 2.5 mg/day.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Hypertension: Oral: Children 1 month to 17 years: Initial: 0.08 mg/kg/d (up to 5 mg) in 1-2 divided doses; adjust dosage based on patient response; doses >0.58 mg/kg (40 mg) have not been evaluated in pediatric patients

Heart failure (non-FDA approved):

Infants and Children:

Oral (Enalapril): Initial: 0.1 mg/kg/day in 1-2 divided doses; increase as required over 2 weeks to maximum of 0.5 mg/kg/day; mean dose required for CHF improvement in 39 children (9 days to 17 years) was 0.36 mg/kg/day; investigationally, select individuals have been treated with doses up to 0.94 mg/kg/day

I.V. (Enalaprilat): 5-10 mcg/kg/dose administered every 8-24 hours (as determined by blood pressure readings); monitor patients carefully; select patients may require higher doses

Adolescents: Refer to adult dosing.

Dosing: Renal Impairment

Oral: Enalapril: Hypertension:

Cl_{cr} 30-80 mL/minute: Administer 5 mg/day titrated upwards to maximum of 40 mg.

Cl_{cr} <30 mL/minute: Administer 2.5 mg day titrated upward until blood pressure is controlled up to a maximum of 40 mg.

For heart failure patients with sodium <130 mEq/L or serum creatinine >1.6 mg/dL, initiate dosage with 2.5 mg/day, increasing to twice daily as needed; increase further in increments of 2.5 mg/dose at >4-day intervals to a maximum daily dose of 40 mg.

I.V.: Enalaprilat:

Cl_{cr} >30 mL/minute: Initiate with 1.25 mg every 6 hours and increase dose based on response.

Cl_{cr} <30 mL/minute: Initiate with 0.625 mg every 6 hours and increase dose based on response.

Moderately dialyzable (20% to 50%)

Administer dose postdialysis (eg, 0.625 mg I.V. every 6 hours) or administer 20% to 25% supplemental dose following dialysis; Clearance: 62 mL/minute

Peritoneal dialysis effects: Supplemental dose is not necessary, although some removal of drug occurs.

Dosing: Hepatic ImpairmentHydrolysis of enalapril to enalaprilat may be delayed and/or impaired in patients with severe hepatic impairment, but the pharmacodynamic effects of the drug do not appear to be significantly altered. No dosage adjustment is necessary.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Give direct IVP over at least 5 minutes or dilute up to 50 mL and infuse.

Dietary ConsiderationsLimit salt substitutes or potassium-rich diet.

StorageEnalaprilat: Clear, colorless solution which should be stored at <30°C. I.V. is stable for 24 hours at room temperature in D_5W or NS.

CompatibilityStable in dextran 40 10% in dextrose, D_5LR, D_5NS, D_5W, hetastarch 6%, NS.

Y-site administration: Compatible: Allopurinol, amifostine, amikacin, aminophylline, ampicillin, ampicillin/sulbactam, aztreonam, butorphanol, calcium gluconate, cefazolin, cefoperazone, ceftazidime, ceftizoxime, chloramphenicol, cimetidine, cisatracurium, cladribine, clindamycin, dextran 40, dobutamine, docetaxel, dopamine, doxorubicin liposome, erythromycin lactobionate, esmolol, etoposide, famotidine, fentanyl, filgrastim, ganciclovir, gatifloxacin, gemcitabine, gentamicin, granisetron, heparin, hetastarch, hydrocortisone sodium succinate, labetalol, lidocaine, linezolid, magnesium sulfate, melphalan, meropenem, methylprednisolone sodium succinate, metronidazole, morphine, nafcillin, nicardipine, penicillin G potassium, phenobarbital, piperacillin, piperacillin/tazobactam, potassium chloride, potassium phosphates, propofol, ranitidine, remifentanil, sodium acetate, sodium nitroprusside, teniposide, thiotepa, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, vinorelbine. **Incompatible:** Amphotericin B, amphotericin B cholesteryl sulfate complex, cefepime, phenytoin.

Compatibility when admixed: Compatible: Dobutamine, dopamine, heparin, meropenem, nitroglycerin, potassium chloride, sodium nitroprusside.

Extemporaneously Prepared

An enalapril oral suspension (0.2 mg/mL) has been made using one 2.5 mg tablet and 12.5 mL sterile water; stability unknown; suspension should be used immediately and the remaining amount discarded

Young TE and Mangum OB, “Neofax®, '95: A Manual of Drugs Used in Neonatal Care,” 8th ed, Columbus, OH: Ross Products Division, Abbott Laboratories, 1995, 85.

An enalapril oral suspension (1 mg/mL) has been made using 20 mg tablets and Bicitra®. Add 50 mL Bicitra® to a polyethylene terephthalate (PET) bottle containing ten 20 mg tablets and shake for at least 2 minutes. Let concentrate stand for 60 minutes. Following the 60-minute hold time, shake the concentration for an additional minute. Add 150 mL Bicitra® to the concentrate and shake the suspension to disperse the ingredients. The suspension should refrigerated at 2°C to 8°C (36°F to 46°F); it can be stored for up to 30 days. Shake suspension well before use.

Package labeling, Merck & Co, Inc, issued October 2000.

ContraindicationsHypersensitivity to enalapril or enalaprilat; angioedema related to previous treatment with an ACE inhibitor; patients with idiopathic or hereditary angioedema

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with idiopathic or hereditary angioedema or previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment.

Special populations:

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsDue to frequent decreases in glomerular filtration (also creatinine clearance) with aging, elderly patients may have exaggerated responses to ACE inhibitors; differences in clinical response due to hepatic changes are not observed. ACE inhibitors may be preferred agents in elderly patients with congestive heart failure and diabetes mellitus. Diabetic proteinuria is reduced and insulin sensitivity is enhanced. In general, the side effect profile is favorable in the elderly and causes little or no CNS confusion; use lowest dose recommendations initially; adjust dose for renal function in the elderly. Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.

Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)

Pregnancy ConsiderationsDue to adverse events observed in some animal studies, enalapril is considered pregnancy category C during the first trimester. Based on human data, enalapril is considered pregnancy category D if used during the second and third trimesters (per the manufacturer; however, one study suggests that fetal injury may occur at anytime during pregnancy). Enalaprilat, the active metabolite of enalapril, crosses the placenta. First trimester exposure to ACE inhibitors may cause major congenital malformations. An increased risk of cardiovascular and/or central nervous system malformations was observed in one study; however, an increased risk of teratogenic events was not observed in other studies. Second and third trimester use of an ACE inhibitor is associated with oligohydramnios. Oligohydramnios due to decreased fetal renal function may lead to fetal limb contractures, craniofacial deformation, and hypoplastic lung development. The use of ACE inhibitors during the second and third trimesters is also associated with anuria, hypotension, renal failure (reversible or irreversible), skull hypoplasia, and death in the fetus/neonate. Chronic maternal hypertension itself is also associated with adverse events in the fetus/infant. ACE inhibitors are not recommended during pregnancy to treat maternal hypertension or heart failure. Those who are planning a pregnancy should be considered for other medication options if an ACE inhibitor is currently prescribed or the ACE inhibitor should be discontinued as soon as possible once pregnancy is detected. The exposed fetus should be monitored for fetal growth, amniotic fluid volume, and organ formation. Infants exposed to an ACE inhibitor *in utero*, especially during the second and third trimester, should be monitored for hyperkalemia, hypotension, and oliguria.

[U.S. Boxed Warning]: Based on human data, ACE inhibitors can cause injury and death to the developing fetus when used in the second and third trimesters. ACE inhibitors should be discontinued as soon as possible once pregnancy is detected.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsEnalapril and enalaprilat are excreted in breast milk. Breast-feeding is not recommended by the manufacturer. The AAP considers enalapril to be “usually compatible with breast-feeding.”

Pregnancy & Lactation, In-Depth

- Enalapril in Pregnancy & Lactation

Adverse Reactions**Note:** Frequency ranges include data from hypertension and heart failure trials. Higher rates of adverse reactions have generally been noted in patients with CHF. However, the frequency of adverse effects associated with placebo is also increased in this population.

1% to 10%:

Cardiovascular: Hypotension (0.9% to 7%), chest pain (2%), syncope (0.5% to 2%), orthostasis (2%), orthostatic hypotension (2%)

Central nervous system: Headache (2% to 5%), dizziness (4% to 8%), fatigue (2% to 3%)

Dermatologic: Rash (2%)

Gastrointestinal: Abnormal taste, abdominal pain, vomiting, nausea, diarrhea, anorexia, constipation

Neuromuscular & skeletal: Weakness

Renal: Serum creatinine increased (0.2% to 20%), worsening of renal function (in patients with bilateral renal artery stenosis or hypovolemia)

Respiratory (1% to 2%): Bronchitis, cough, dyspnea

<1% (Limited to important or life-threatening): Agranulocytosis, alopecia, anaphylactoid reaction, angina pectoris, angioedema, ataxia, atrial fibrillation, atrial tachycardia, bone marrow suppression, bradycardia, bronchospasm, cardiac arrest, cerebral vascular accident, cholestatic jaundice, depression, eosinophilic pneumonitis, erythema multiforme, exfoliative dermatitis, flushing, giant cell arteritis, gynecomastia, hallucinations, hemolysis with G6PD, Henoch-Schönlein purpura, hepatitis, ileus, impotence, jaundice, lichen-form reaction, melena, MI, neutropenia, ototoxicity, pancreatitis, paresthesia, pemphigus, pemphigus foliaceus, peripheral neuropathy, photosensitivity, psychosis, pulmonary edema, pulmonary embolism, pulmonary infiltrates, Raynaud’s phenomenon, sicca syndrome, somnolence, Stevens-Johnson syndrome, systemic lupus erythematosus, thrombocytopenia, toxic epidermal necrolysis, toxic pustuloderma, vertigo.

A syndrome which may include arthralgia, elevated ESR, eosinophilia and positive ANA, fever, interstitial nephritis, myalgia, rash, and vasculitis has been reported for enalapril and other ACE inhibitors.

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)

Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, california poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Test InteractionsPositive Coombs' [direct]; may cause false-positive results in urine acetone determinations using sodium nitroprusside reagent

Monitoring ParametersBlood pressure; serum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (especially anything that may impact fluid balance or cardiac status). **Infusion:** See Administration details. Blood pressure should be closely monitored with first dose or change in dose. Assess results of laboratory tests closely during first 3 months of therapy and regularly thereafter. Assess therapeutic effectiveness according to purpose for use and adverse response on a regular basis during therapy (eg, anaphylactic reaction, hypovolemia, angioedema, postural hypotension). Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Do not use potassium supplement or salt substitutes without consulting prescriber. Take exactly as directed; do not discontinue without consulting prescriber. Take first dose at bedtime. Take all doses on an empty stomach, 1 hour before or 2 hours after meals. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); or nausea, vomiting, abdominal pain, dry mouth, or transient loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report persistent nausea and vomiting; chest pain or palpitations; mouth sores; fever or chills; swelling of extremities, face, mouth, or tongue; skin rash; numbness, tingling, or pain in muscles; respiratory difficulty or unusual cough; or other persistent adverse reactions. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as enalaprilat: 1.25 mg/mL (1 mL, 2 mL) [contains benzyl alcohol]

Tablet, as maleate (Vasotec®): 2.5 mg, 5 mg, 10 mg, 20 mg

Generic AvailableYes
ManufacturerMerck & Co
Pricing: U.S. (www.drugstore.com)

Tablets (Enalapril Maleate)

2.5 mg (30): $12.99

5 mg (30): $10.99

10 mg (30): $11.99

20 mg (30): $11.99

Tablets (Vasotec)

2.5 mg (60): $122.97

10 mg (30): $85.95

20 mg (30): $112.40

Mechanism of ActionCompetitive inhibitor of angiotensin-converting enzyme (ACE); prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor; results in lower levels of angiotensin II which causes an increase in plasma renin activity and a reduction in aldosterone secretion
Pharmacodynamics/Kinetics

Onset of action: Oral: ~1 hour

Duration: Oral: 12-24 hours

Absorption: Oral: 55% to 75%

Protein binding: 50% to 60%

Metabolism: Prodrug, undergoes hepatic biotransformation to enalaprilat

Half-life elimination:

Enalapril: Adults: Healthy: 2 hours; Congestive heart failure: 3.4-5.8 hours

Enalaprilat: Infants 6 weeks to 8 months of age: 6-10 hours; Adults: 35-38 hours

Time to peak, serum: Oral: Enalapril: 0.5-1.5 hours; Enalaprilat (active): 3-4.5 hours

Excretion: Urine (60% to 80%); some feces

Related Information

- Angiotensin Agents
- Heart Failure (Systolic)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Abnormal taste and orthostatic hypotension
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness and dizziness; rarely may cause insomnia, confusion, depression
Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels
Cardiovascular Considerations

Congestive Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines recommend that ACE inhibitors be used in patients with a reduced EF (with or without heart failure symptoms) unless contraindicated. ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. In this situation, they decrease hospitalizations for, and retard progression to, congestive heart failure. When used in patients with heart failure, the target dose should be achieved, if possible. Lower daily doses of ACE inhibitors have demonstrated the same mortality effects as high doses, but have not decreased hospitalizations to the extent that high-dose ACE inhibitors have, as demonstrated in the ATLAS study (Packer M, 1999).

Hypertension: The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) can be beneficial in patients with hypertension and LVH without symptoms of heart failure. JNC 7 suggests that patients can benefit from treatment with an ACE inhibitor if they have hypertension **and** heart failure, acute myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, or history of stroke.

Vascular Disease: The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors can be useful in preventing heart failure in patients who have a history of atherosclerotic vascular disease, diabetes, or hypertension with associated cardiovascular risk factors. The HOPE trial (Heart Outcomes Prevention Evaluation Study Investigators, 2000) investigated the value of an ACE inhibitor (ramipril 5-10 mg daily) versus placebo in patients who had evidence of vascular disease or diabetes (one other cardiovascular risk factor) and were at least 55 years of age. Patients were excluded if they had a low ejection fraction, heart failure, or were on an ACE inhibitor. The primary outcome was a composite of death from cardiovascular cause, myocardial infarction, or stroke; 9297 patients were enrolled and randomized. Ramipril significantly reduced the risk of death from CV causes, MI, or stroke over placebo. New cases of diabetes were also reduced in the ramipril group. In the EUROPA trial, patients with stable coronary artery disease (at low risk for cardiovascular events) received perindopril or placebo and were evaluated for incidence of cardiovascular events after four years of treatment. In this randomized, placebo-controlled, prospective study, 12,218 patients received either perindopril (8 mg/day, n=6110) or placebo (n=6108) and were assessed for the primary endpoint of a cardiovascular event, defined as cardiovascular death, myocardial infarction, or cardiac arrest. The study population was well balanced with respect to baseline demographics and concomitant medication use (including beta-blockers, platelet inhibitors, antihyperlipidemics, calcium channel blockers, nitrates, and diuretics). Intent-to-treat analysis revealed that 603 (10%) of placebo patients experienced the primary endpoint of a cardiovascular event compared to 488 (8%) of perindopril-receiving patients, for a 20% relative risk reduction (p=0.0003). This result was not influenced by presence of other comorbidities (eg, diabetes, hypertension) or concomitant beta-blocker, calcium channel blocker, or lipid-lowering therapies. Withdrawal from the study (postrandomization) due to adverse reactions was similar between treatment groups. Number needed to treat analysis suggests that treatment of 50 patients over a 4-year period will prevent one major cardiovascular event.

Acute Coronary Syndromes: In the treatment of unstable angina/non-ST-segment elevation MI, ACE inhibitors are recommended when hypertension persists despite treatment with nitroglycerin and a beta-blocker in patients with LV systolic dysfunction or CHF and in ischemic patients with diabetes (Class I). ACE inhibitors are also recommended for all post-ACS individuals (Class IIa). According to 2004 ACC/AHA STEMI guidelines, an ACE inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF <0.4, in the absence of hypotension or known contraindications to this class of medicines. In the emergency management of complicated STEMI, a short-acting ACEI (eg, captopril 1-6.25 mg) may be added once the patient's systolic blood pressure is >100 mm Hg and not <30 mm Hg below baseline. The VALIANT trial evaluated the effects of valsartan (target dose: 160 mg twice daily), captopril (target dose: 50 mg twice daily), and the combination (target doses: valsartan 80 mg twice daily and captopril 150 mg once daily) in a randomized, double-blind trial of patients with acute MI (0.5-10 days post-MI) complicated by left ventricular systolic dysfunction, heart failure, or both. Enrollment in the study numbered 14,703 patients and followed for a median of 24.7 months. There was no difference in the primary endpoint (all cause mortality) among the 3 groups. There was no difference in incidence of CV death, recurrent MI, or hospitalization for heart failure either. Hypotension and renal dysfunction occurred significantly more often in the valsartan group than captopril alone. Cough, rash, and taste disturbances occurred more often in the captopril group. The authors (Pfeffer MA, 2003) concluded that valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after MI. Combining valsartan with captopril increased the rate of adverse events without improving survival.

Potential Adverse Events: ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. In those patients experiencing cough on an ACE inhibitor, the ACE inhibitor may be discontinued and, if necessary, ARB therapy instituted. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Drug Interactions: Concomitant indomethacin therapy may blunt the reduction in sitting and 24-hour ambulatory diastolic blood pressure. Use of NSAIDs should be avoided or limited, with monitoring of blood pressure control in this setting. In patients with heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

Anesthesia and Critical Care Concerns/Other ConsiderationsSevere hypotension may occur in patients who are sodium and/or volume depleted, initiate lower doses and monitor closely when starting therapy in these patients

ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. In this situation, they decrease hospitalizations for, and retard progression to, congestive heart failure. ACE inhibitors are also indicated in patients postmyocardial infarction in whom left ventricular ejection fraction is <40%. When used in patients with heart failure, the target dose of 10 mg twice daily should be achieved, if possible. Lower daily doses of ACE inhibitors have not demonstrated the same cardioprotective effects.

ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension.

Index TermsEnalapril Maleate; Enalaprilat

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International Brand NamesAcebitor (PH); Acetec (MY); Acetensil (ES); Alapren (ZA); Alphapril (AU); Amprace (AU); Analept (BG, GR); Anapril (SG); Auspril (AU); Bajaten (CN); Beartec (KP); Benalapril (PL); Benalipril (DE); Biocronil (CO); BQL (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Cardiopril (PE); Co-Renitec (CY); Converten (IN); Convertin (IL); Corprilor (SG); Ednyt (BB, BM, BS, BZ, GY, HU, JM, NL, PL, SR, TT); Elfonal (KP); Enahexal (AU); Enalabell (AU); Enalagamma (DE); Enalapril (ES, PL); Enaldun (HK); Enaloc (FI); Enap (HR, HU, PL); Enap i.v. (HR); Enap [inj.] (HU); Enapren (IT); Enapress (PL); Enapril (TH); Enaprin (KP); Enaratio (PL); Enarenal (PL); Enaril (KP, TH); Enatec (BB, BM, BS, BZ, GY, JM, NL, PL, SR, TT); Enazil (PL); Enetil (CO); Enpril (KP); Envas (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Epril (PL); Espron (KP); Glioten (BR, CN, CO, CR, DO, EC, GT, HN, NI, PA, PE, PY, SG, SV); Hipertal (PH); Hypace (PH); Hytrol (IN); Ileveran (MX); Innovace (GB, IE); Invoril (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SG, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Korandil (CY); Lapril (TH); Lenipril (KP); Lotrial (AR, PE, UY); Lowtril (KP); Malepril (KP); Mapryl (PL); Meipril (ID); Naprilate (PH); Naprilene (IT); Naritec (TH); Neopril (KP); Nuril (IN); Olivin (HR); Pharmapress (HK); Pres (DE); Presil (CO); Renallapin (KP); Renitec (AR, AT, AU, BE, BF, BG, BJ, BR, CI, CL, CO, CR, CZ, DK, EC, EE, EG, ES, ET, FI, FR, GH, GM, GN, GR, GT, HK, HN, HU, KE, LR, LU, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, NO, NZ, PA, PE, PH, PK, PT, SC, SD, SE, SL, SN, SV, TH, TN, TR, TW, TZ, UG, VE, ZA, ZM, ZW); Renitek (RU); Reniten (CH); Renivace (JP); Tenace (ID); Unaril (TH, TW); Unipril (CO); Vasopress (PH); Xanef (DE)

Enflurane

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Enflurane may be confused with isoflurane

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(EN floo rane)

U.S. Brand NamesCompound 347™; Ethrane®

Pharmacologic CategoryGeneral Anesthetic, Inhalation

Use: Labeled IndicationsMaintenance of general anesthesia

Dosing: AdultsGeneral anesthesia: Inhalation: Minimum alveolar concentration (MAC), the concentration at which 50% of patients do not respond to surgical incision, is 1.6% for enflurane. The concentration at which amnesia and loss of awareness occur (MAC - awake) is 0.4%. Surgical levels of anesthesia are achieved with concentrations between 0.5% to 3%.

Dosing: ElderlyMAC is reduced in the elderly.

Administration: InhalationVia enflurane-specific calibrated vaporizers

ContraindicationsHypersensitivity to enflurane or any component of the formulation; known or suspected history of malignant hyperthermia

Warnings/Precautions

Concerns related to adverse effects:

- Cardiovascular effects: Decrease in blood pressure is dose dependent, primarily due to peripheral vasodilation. Enflurane does not depress cardiac conduction nor does it sensitize the myocardium to catecholamine-induced arrhythmias like halothane.
- Decreased blood flow: May cause decrease in hepatic, renal and splenic blood flow.
- Hyperkalemia: Use of other inhaled anesthetics has been associated with rare cases of perioperative hyperkalemia; concomitant use of succinylcholine was associated with many of the reported cases, but not all. Risk of hyperkalemia is increased in pediatric patients with underlying neuromuscular disease (eg, Duchenne muscular dystrophy). Other abnormalities may include elevation in CPK and myoglobinuria. Monitor closely for arrhythmias. Aggressively identify and treat hyperkalemia.
- Increased intracranial pressure: May dilate the cerebral vasculature and may, in certain conditions, increase intracranial pressure.
- Malignant hyperthermia: May trigger malignant hyperthermia; avoid use in patients susceptible to malignant hyperthermia.
- Respiratory depression: Respiration is depressed with a $PaCO_2$ of 55 mm Hg at 1 MAC. Hypoxic pulmonary vasoconstriction is blunted. Hypoxia induced increase in ventilation is abolished at low concentrations.

Disease-related concerns:

- Seizure disorder: Not recommended in patients with a history of seizure disorders; EEG seizure complexes have been seen with higher doses especially associated with hypocarbia.

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension, myocardial depression, tachycardia

Central nervous system: Seizure activity during or after emergence from enflurane anesthesia; motor activity and/or seizure, especially with hypocapnia, malignant hyperthermia

Gastrointestinal: Nausea, vomiting

Hepatic: Hepatic injury, hepatic failure (rare), necrosis

Renal: Renal dysfunction, nephrotoxicity

Respiratory: Respiratory depression/arrest, hypoxemia, breath holding, cough

Miscellaneous: Shivering

Metabolism/Transport Effects**Substrate** of CYP2E1 (major)

Drug Interactions

CYP2E1 Inhibitors (Moderate): May decrease the metabolism of CYP2E1 Substrates. *Risk C: Monitor therapy*

CYP2E1 Inhibitors (Strong): May decrease the metabolism of CYP2E1 Substrates. *Risk D: Consider therapy modification*

EPINEPHrine: Inhalational Anesthetics may enhance the arrhythmogenic effect of EPINEPHrine. *Risk D: Consider therapy modification*

Methylphenidate: May enhance the hypertensive effect of Inhalational Anesthetics. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): Inhalational Anesthetics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure, heart rate and rhythm, temperature, oxygen saturation, end-tidal CO_2 and end-tidal enflurane concentrations should be monitored prior to and throughout anesthesia

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, for inhalation: >99.9% (250 mL)

Generic AvailableNo

Pharmacodynamics/Kinetics

Onset of action: 7-10 minutes

Duration: Emergence time: Depends on blood concentration when enflurane is discontinued

Metabolism: Hepatic (2% to 10%)

Excretion: Exhaled gases

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNot recommended for use in patients with a seizure disorder. Minimum alveolar concentration may be decreased with concomitant use with a benzodiazepine or opioid. Disulfiram may increase the levels of enflurane.

Anesthesia and Critical Care Concerns/Other ConsiderationsUse of enflurane for induction of general anesthesia is not recommended due to its airway irritant properties and unpleasant odor which may cause breath holding and coughing.

References

Campagna JA, Miller KW, and Forman SA, “Mechanisms of Action of Inhaled Anesthetics,” *N Engl J Med*, 2003, 348(21):2110-24. [PubMed 12761368]

Cousins MJ, Greenstein LR, Hitt BA, et al, “Metabolism and Renal Effects of Enflurane in Man,” *Anesthesiology*, 1976, 44(1):44-53. [PubMed 1244774]

Gion H and Saidman LJ, “The Minimum Alveolar Concentration of Enflurane in Man,” *Anesthesiology*, 1971, 35(4):361-4.[PubMed 5114398]

International Brand NamesAlyrane (AU, BE, DK, KP, LU, NO, ZA); Compound 347 (ID, KP); Efrane (FI, NO, SE); Enfluran (CH); Enforan (AR); Enfran (MX); Ethrane (AT, AU, BE, CH, CL, DE, ID, IE, IL, IT, LU, MY, NL, PH, PK, RU, TR, UY, VE); Etrane (BR); Gerolan (KP); Inhelthran (PY)

Enfuvirtide

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English English

Jump To Field (Select Field Name)

Pronunciation(en FYOO vir tide)
U.S. Brand NamesFuzeon®
Canadian Brand NamesFuzeon®
Pharmacologic CategoryAntiretroviral Agent, Fusion Protein Inhibitor
Use: Labeled IndicationsTreatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy
Dosing: Adults**HIV treatment:** SubQ: 90 mg twice daily
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**HIV treatment:** SubQ:

Children 6-16 years: 2 mg/kg twice daily (maximum dose: 90 mg twice daily)

Adolescents ≥16 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} >35 mL/minute: Clearance not affected; no dosage adjustment required.

Cl_{cr} ≤35 mL/minute: Limited data showed decreased clearance; however, no dosage adjustment recommended.

End-stage renal disease (on dialysis): Limited data showed decreased clearance; however, no dosage adjustment recommended.

Dosing: Hepatic ImpairmentNo dosage adjustment required.
Administration: OtherInject subcutaneously into upper arm, abdomen, or anterior thigh. Do not inject into moles, the navel, over a blood vessel or skin abnormalities such as scar tissue, surgical scars, bruises, or tattoos. In addition, do not inject in or near sites where large nerves are close to the skin including the elbow, knee, groin, or buttocks. Rotate injection site, give injections at a site different from the preceding injection site; do not inject into any site where an injection site reaction is evident. Bioequivalence was found to be similar in a study comparing standard administration using a needle versus a needle-free device.
StorageStore powder at 15°C to 30°C (59°F to 86°F). Reconstituted solutions should be refrigerated and must be used within 24 hours.
ReconstitutionReconstitute with 1.1 mL SWFI; tap vial for 10 seconds and roll gently to ensure contact with diluent; then allow to stand until solution is completed; may require up to 45 minutes to form solution.
ContraindicationsHypersensitivity to enfuvirtide or any component of the formulation
Allergy Considerations

- Enfuvirtide Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: May cause hypersensitivity reactions (symptoms may include rash, fever, nausea, vomiting, hypotension, and elevated transaminases).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Injection site reactions: Local injection site reactions are common. Administration using a needle-free device has been associated with nerve pain (including neuralgia and/or paresthesia lasting up to 6 months), bruising, and hematomas when administered at sites where large nerves are close to the skin; only administer medication in recommended sites.
- Pneumonia: Monitor closely for signs/symptoms of pneumonia; associated with an increased incidence during clinical trials, particularly in patients with a low CD4 cell count, high initial viral load, I.V. drug use, smoking, or a history of lung disease.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with coagulation disorders (eg, hemophilia) or receiving anticoagulants; increased risk of bleeding at injection site.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies, however, there are no adequate and well-controlled studies in pregnant women. An antiretroviral registry has been established to monitor maternal and fetal outcomes in women receiving antiretroviral drugs. Physicians are encouraged to register patients at 1-800-258-4263 or www.APRegistry.com.

LactationExcretion in breast milk unknown/contraindicated
Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.
Adverse Reactions

>10%:

Central nervous system: Fatigue (20%), insomnia (11%)

Gastrointestinal: Diarrhea (32%), nausea (23%)

Local: Injection site reactions (98%; may include pain, erythema, induration, pruritus, ecchymosis, nodule or cyst formation)

1% to 10%:

Dermatologic: Folliculitis (2%)

Gastrointestinal: Weight loss (7%), abdominal pain (4%), appetite decreased (3%), pancreatitis (3%), anorexia (2%), xerostomia (2%)

Hematologic: Eosinophilia (2% to 9%)

Hepatic: Transaminases increased (4%, grade 4: 1%)

Local: Injection site infection (2%)

Neuromuscular & skeletal: CPK increased (3% to 7%), limb pain (3%), myalgia (3%)

Ocular: Conjunctivitis (2%)

Respiratory: Sinusitis (6%), cough (4%), pneumonia (3%)

Miscellaneous: Infections (4% to 6%), herpes simplex (4%), flu-like syndrome (2%)

<1%: Abacavir hypersensitivity worsening, amylase increased, angina, anxiety, constipation, depression, GGT increased, glomerulonephritis, Guillain-Barré syndrome, hepatic steatosis, hyperglycemia; hypersensitivity reactions (symptoms may include rash, fever, nausea, vomiting, hypotension, and transaminase increases); insomnia, lipase increased, lymphadenopathy, neutropenia, peripheral neuropathy, pneumopathy, renal failure, renal insufficiency, respiratory distress, sepsis, sixth nerve palsy, suicide attempt, taste disturbances, thrombocytopenia, toxic hepatitis, triglycerides increased, tubular necrosis, weakness

Drug Interactions

Protease Inhibitors: May increase the serum concentration of Enfuvirtide. Enfuvirtide may increase the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringUse caution and monitor closely for symptoms of pneumonia with history of I.V. drug use, smoking, or lung disease. Assess therapeutic response (CD4 level and viral load) and adverse reactions (pneumonia, neuropathy, CNS changes) on a regular basis throughout therapy. Teach patient or caregiver proper use (eg, reconstitution, injection procedure, needle/syringe disposal, and proper timing of medications). Teach patient possible side effects/appropriate interventions and adverse symptoms to report (eg, hypersensitivity reactions, injection site infection).
Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. This drug is prescribed as one part of a multidrug combination; take exactly as directed for full course of therapy. This drug can only be administered by injection, follow exact injection instructions that come with your medication. Do not mix any other medications in the same syringe. Inject into the upper arm, abdomen, or anterior thigh; do not inject in the same area you did the time before and do not inject around the naval, into scar tissues, a bruise, a mole, or where there is an injection site reaction. Make sure you have an adequate supply of medications on hand; do not allow supply to run out. Do not miss or skip a dose; if you miss a dose, take the missed dose as soon as you can and take the next dose as scheduled. If it is close to the time for the next dose, wait and take the next dose as regularly scheduled. Do not take two doses at the same time. Frequent blood tests may be required with prolonged therapy. May cause injection site reactions such as itching, swelling, redness, pain, hardened skin, or bumps (usually last for <7 days). May cause insomnia, anorexia (small, frequent meals may help), or constipation (increased dietary fiber, fruit, fluids, or exercise may help). Notify prescriber immediately if you experience a hypersensitivity reaction (rash, fever, nausea, vomiting, hypotension, blood in urine) or injection site becomes infected (red, painful, swollen, drainage). Report CNS disturbances (depression, anxiety); weakness, loss of feeling, or muscle pain; respiratory infections, difficulty breathing, flu-like symptoms, unusual cough, fever, alteration in urinary pattern; swelling of legs or feet; or any other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Notify prescriber if you are or intend to become pregnant. Do not breast feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Fuzeon®: 108 mg [90 mg/mL following reconstitution; available in convenience kit of 60 vials, SWFI, syringes, alcohol wipes, patient instructions]

Generic AvailableNo
ManufacturerRoche
Mechanism of ActionBinds to the first heptad-repeat (HR1) in the gp41 subunit of the viral envelope glycoprotein. Inhibits the fusion of HIV-1 virus with CD4 cells by blocking the conformational change in gp41 required for membrane fusion and entry into CD4 cells
Pharmacodynamics/Kinetics

Distribution: V_d: 5.5 L

Protein binding: 92%

Metabolism: Proteolytic hydrolysis (CYP isoenzymes do not appear to contribute to metabolism)

Clearance: Adults: 24.8 mL/hour/kg

Bioavailability: 84% ± 16%

Half-life elimination: 3.8 hours

Time to peak: 4-8 hours

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and taste disturbance

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia is common; may cause depression and anxiety. Suicide attempts have been reported.

Mental Health: Effects on Psychiatric TreatmentMay cause an increase in triglycerides; use caution with clozapine, olanzapine, quetiapine, and mirtazapine. Smokers have an increased risk of pneumonia; monitor. May rarely cause neutropenia and thrombocytopenia; use caution with clozapine, carbamazepine, and valproic acid

Index TermsT-20

References

"Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States," November 2, 2007, 1-96. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

True AL, Chiu YY, Demasi RA, et al, "Pharmacokinetic Bioequivalence of Enfuvirtide Using a Needle-Free Device Versus Standard Needle Administration," *Pharmacotherapy*, 2006, 26(12):1679-86.[PubMed 17125431]

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection," February 28, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesFuzeon (AR, AT, AU, BE, BG, BR, CH, CN, CO, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HN, IE, IL, IT, MX, NL, NO, PE, PL, PT, RU, SE, TR, TW, UY)

Enoxaparin

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Lovenox® may be confused with Levaquin®, Lotronex®, Protonix®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

International issues:

Lovenox® may be confused with Lotanax® which is a brand name for terfenadine in the Czech Republic

2009 National Patient Safety Goals: The Joint Commission on Accreditation of Healthcare Organizations requires healthcare organizations that provide anticoagulant therapy to have a process in place to reduce the risk of anticoagulant-associated patient harm. Patients receiving anticoagulants should receive individualized care through a defined process that includes standardized ordering, dispensing, administration, monitoring and education. This does not apply to routine short-term use of anticoagulants for prevention of venous thromboembolism when the expectation is that the patient’s laboratory values will remain within or close to normal values (NPSG.03.05.01).

Pronunciation(ee noks a PA rin)

U.S. Brand NamesLovenox®

Canadian Brand NamesEnoxaparin Injection; Lovenox®; Lovenox® HP

Pharmacologic CategoryLow Molecular Weight Heparin

Use: Labeled Indications

Acute coronary syndromes: Unstable angina (UA), non-ST-elevation (NSTEMI), and ST-elevation myocardial infarction (STEMI)

DVT prophylaxis: Following hip or knee replacement surgery, abdominal surgery, or in medical patients with severely-restricted mobility during acute illness who are at risk for thromboembolic complications

DVT treatment (acute): Inpatient treatment (patients with and without pulmonary embolism) and outpatient treatment (patients without pulmonary embolism)

Note: High-risk patients include those with one or more of the following risk factors: >40 years of age, obesity, general anesthesia lasting >30 minutes, malignancy, history of deep vein thrombosis or pulmonary embolism

Use: Unlabeled/InvestigationalProphylaxis and treatment of thromboembolism in children; anticoagulant bridge therapy during temporary interruption of vitamin K antagonist therapy in patients at high risk for thromboembolism; DVT prophylaxis following moderate-risk general surgery, major gynecologic surgery and following higher-risk general surgery for cancer; management of venous thromboembolism (VTE) during pregnancy (Hirsh, 2008)

Dosing: Adults

DVT prophylaxis: SubQ:

Hip replacement surgery:

Twice-daily dosing: 30 mg every 12 hours, with initial dose within 12-24 hours after surgery, and every 12 hours for at least 10 days or until risk of DVT has diminished or the patient is adequately anticoagulated on warfarin.

Once-daily dosing: 40 mg once daily, with initial dose within 9-15 hours before surgery, and daily for at least 10 days (or up to 35 days postoperatively) or until risk of DVT has diminished or the patient is adequately anticoagulated on warfarin.

Knee replacement surgery: 30 mg every 12 hours, with initial dose within 12-24 hours after surgery, and every 12 hours for at least 10 days or until risk of DVT has diminished or the patient is adequately anticoagulated on warfarin.

Abdominal surgery: 40 mg once daily, with initial dose given 2 hours prior to surgery; continue until risk of DVT has diminished (usually 7-10 days).

Medical patients with severely-restricted mobility during acute illness: 40 mg once daily; continue until risk of DVT has diminished (usually 6-11 days).

DVT treatment (acute): SubQ: **Note:** Start warfarin on the first treatment day and continue enoxaparin until INR is between 2 and 3 (usually 5-7 days).

Inpatient treatment (with or without pulmonary embolism): 1 mg/kg/dose every 12 hours or 1.5 mg/kg once daily.

Outpatient treatment (without pulmonary embolism): 1 mg/kg/dose every 12 hours.

ST-elevation MI (STEMI):

Patients <75 years of age: Initial: 30 mg I.V. single bolus plus 1 mg/kg (maximum 100 mg for the first 2 doses only) SubQ every 12 hours. The first SubQ dose should be administered with the I.V. bolus. Maintenance: After first 2 doses, administer 1 mg/kg SubQ every 12 hours.

Patients ≥75 years of age: Initial: SubQ: 0.75 mg/kg every 12 hours (**Note:** No I.V. bolus is administered in this population); a maximum dose of 75 mg is recommended for the first 2 doses. Maintenance: After first 2 doses, administer 0.75 mg/kg SubQ every 12 hours

Additional notes on STEMI treatment: Therapy was continued for 8 days or until hospital discharge; optimal duration not defined. Unless contraindicated, all patients received aspirin (75-325 mg daily) in clinical trials. In patients with STEMI receiving thrombolytics, initiate enoxaparin dosing between 15 minutes before and 30 minutes after fibrinolytic therapy. In patients undergoing PCI, if balloon inflation occurs ≤8 hours after the last SubQ enoxaparin dose, no additional dosing is needed. If balloon inflation occurs 8-12 hours after last SubQ enoxaparin dose, a single I.V. dose of 0.3 mg/kg should be administered.

Unstable angina or non-ST-elevation MI (NSTEMI): 1 mg/kg every 12 hours in conjunction with oral aspirin therapy (100-325 mg once daily); continue until clinical stabilization (a minimum of at least 2 days)

Dosing: ElderlySubQ: Refer to adult dosing. Increased incidence of bleeding with doses of 1.5 mg/kg/day or 1 mg/kg every 12 hours; injection-associated bleeding and serious adverse reactions are also increased in the elderly. Careful attention should be paid to elderly patients, particularly those <45 kg. **Note:** Dosage alteration/adjustment may be required.

Dosing: PediatricThromboembolism (unlabeled use; Monagle, 2008): SubQ:

Infants <2 months: Initial:

Prophylaxis: 0.75 mg/kg every 12 hours

Treatment: 1.5 mg/kg every 12 hours

Infants >2 months and Children ≤18 years: Initial:

Prophylaxis: 0.5 mg/kg every 12 hours

Treatment: 1 mg/kg every 12 hours

Maintenance: See **Dosage Titration** table:

Enoxaparin Pediatric Dosage Titration

Antifactor Xa	**Dose Titration**	**Time to Repeat Antifactor Xa Level**
<0.35 units/mL	Increase dose by 25%	4 h after next dose
0.35-0.49 units/mL	Increase dose by 10%	4 h after next dose
0.5-1 unit/mL	Keep same dosage	Next day, then 1 wk later, then monthly (4 h after dose)
1.1-1.5 units/mL	Decrease dose by 20%	Before next dose
1.6-2 units/mL	Hold dose for 3 h and decrease dose by 30%	Before next dose, then 4 h after next dose
>2 units/mL	Hold all doses until antifactor Xa is 0.5 units/mL, then decrease dose by 40%	Before next dose and every 12 h until antifactor Xa <0.5 units/mL

Modified from Monagle P, Michelson AD, Bovill E, et al, “Antithrombotic Therapy in Children,” *Chest*, 2001, 119:344S-70S.

Dosing: Renal Impairment

Cl$_{cr}$ ≥30 mL/minute: No specific adjustment recommended (per manufacturer); monitor closely for bleeding.

Cl$_{cr}$ <30 mL/minute:

DVT prophylaxis in abdominal surgery, hip replacement, knee replacement, or in medical patients during acute illness: SubQ: 30 mg once daily

DVT treatment (inpatient or outpatient treatment in conjunction with warfarin): SubQ: 1 mg/kg once daily

STEMI:

<75 years: Initial: I.V.: 30 mg as a single dose with the first dose of the SubQ maintenance regimen administered at the same time as the I.V. bolus

≥75 years of age: Omit I.V. bolus; Maintenance: SubQ: 1 mg/kg every 24 hours in all patients

Unstable angina, NSTEMI: SubQ: 1 mg/kg once daily

Dialysis: Enoxaparin has not been FDA approved for use in dialysis patients. It's elimination is primarily via the renal route. Serious bleeding complications have been reported with use in patients who are dialysis dependent or have severe renal failure. LMWH administration at fixed doses without monitoring has greater unpredictable anticoagulant effects in patients with chronic kidney disease. If used, dosages should be reduced and anti-Xa levels frequently monitored, as accumulation may occur with repeated doses. Many clinicians would not use enoxaparin in this population especially without timely anti-Xa levels.

Hemodialysis: Supplemental dose is not necessary.

Peritoneal dialysis: Significant drug removal is unlikely based on physiochemical characteristics.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Do **not** administer I.M.

Administration: I.V.May be administered I.V. as part of treatment for ST-elevation myocardial infarction (STEMI) only in patients <75 years of age or during PCI. The manufacturer recommends using the multiple-dose vial to prepare I.V. doses. Do not mix or coadminister with other medications.

Administration: I.V. DetailpH: 5.5-7.5

Administration: OtherShould be administered by deep SubQ injection to the left or right anterolateral and left or right posterolateral abdominal wall. To avoid loss of drug from the 30 mg and 40 mg syringes, do not expel the air bubble from the syringe prior to injection. In order to minimize bruising, do not rub injection site. An automatic injector (Lovenox EasyInjector™) is available with the 30 mg and 40 mg syringes to aid the patient with self-injections. **Note:** Enoxaparin is available in 100 mg/mL and 150 mg/mL concentrations.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F); do not freeze.

CompatibilityStable in D_5W, NS; do not mix with other injections or infusions.

ContraindicationsHypersensitivity to enoxaparin, heparin, or any component of the formulation; thrombocytopenia associated with a positive *in vitro* test for antiplatelet antibodies in the presence of enoxaparin; hypersensitivity to pork products; active major bleeding; not for I.M. use

Allergy Considerations

- Low Molecular Weight Heparin Allergy

Warnings/Precautions

Boxed warnings:

- Neuraxial anesthesia: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Bleeding: Monitor patient closely for signs or symptoms of bleeding. Certain patients are at increased risk of bleeding. Risk factors include bacterial endocarditis; congenital or acquired bleeding disorders; active ulcerative or angiodysplastic GI diseases; severe uncontrolled hypertension; history of hemorrhagic stroke; or use shortly after brain, spinal, or ophthalmic surgery; in patients treated concomitantly with platelet inhibitors; recent GI bleeding; thrombocytopenia or platelet defects; severe liver disease; hypertensive or diabetic retinopathy; or in patients undergoing invasive procedures. Discontinue if bleeding occurs.

- Hyperkalemia: Monitor for hyperkalemia; can cause hyperkalemia by suppressing aldosterone production. Most commonly occurs in patients with risk factors for the development of hyperkalemia (eg, renal dysfunction, concomitant use of potassium-sparing diuretics or potassium supplements, hematoma in body tissues).

- Thrombocytopenia: Rare cases of thrombocytopenia have occurred. Use with caution in patients with history of heparin-induced thrombocytopenia; monitor platelet count closely. Discontinue therapy and consider alternative treatment if platelets are <100,000/mm^3 and/or thrombosis develops. Rare cases of thrombocytopenia with thrombosis have occurred. Use caution in patients with congenital or drug-induced thrombocytopenia or platelet defects.

Disease-related concerns:

- Prosthetic heart valves: Cannot be recommended for long-term thromboprophylaxis in patients with prosthetic heart valves (especially pregnant women) due to insufficient evidence.

- Renal impairment: Use with caution in patients with renal failure; dosage adjustment needed if Cl_{cr} <30 mL/minute.

Special populations:

- Elderly: Use with caution in the elderly; delayed elimination may occur. Dosage alteration/adjustment may be required (eg, omission of I.V. bolus in acute STEMI in patients ≥75 years of age).

- Low weight patients: Risk of bleeding may be increased in women <45 kg and in men <57 kg.

Dosage form specific issues:

- Multidose vials: Contain benzyl alcohol and should not be used in pregnant women. In neonates, large amounts of benzyl alcohol (>100 mg/kg/day) have been associated with fatal toxicity (gasping syndrome).

Other warnings/precautions:

- Administration: Do **not** administer intramuscularly.

- Conversion to other products: Not to be used interchangeably (unit for unit) with heparin or any other low molecular weight heparins.

- Neuraxial anesthesia: **[U.S. Boxed Warning]: Patients with recent or anticipated neuraxial anesthesia (epidural or spinal anesthesia) are at risk of spinal or epidural hematoma and subsequent paralysis.** Consider risk versus benefit prior to neuraxial anesthesia; risk is increased by concomitant agents which may alter hemostasis or by the use of indwelling epidural catheters for analgesia, as well as traumatic or repeated epidural or spinal puncture. Patient should be observed closely for bleeding and signs and symptoms of neurological impairment if therapy is administered during or immediately following diagnostic lumbar puncture, epidural anesthesia, or spinal anesthesia.

Geriatric ConsiderationsNo specific dosage adjustment recommendations for most indications, however, total clearance is lower and elimination is delayed in patients with renal failure. Adjustment may be necessary if renal impairment is present. In the treatment of STEMI, a lower dosage (0.75 mg/kg every 12 hours) and omission of the I.V. bolus, are recommended in patients ≥75 years of age.

Over 2800 patients, ≥65 years of age, have received enoxaparin sodium in pivotal clinical trials. The efficacy of enoxaparin injection in elderly (≥65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between elderly and younger patients when 30 mg every 12 hours or 40 mg once daily doses of enoxaparin injection was administered at doses of 1.5 mg/kg/day or 1 mg/kg every 12 hours. The risk of enoxaparin injection associated bleeding increased with age. Serious adverse events increased with age for patients receiving enoxaparin injections. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of enoxaparin injection between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Monitoring of elderly patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAnimal studies have not shown teratogenic or fetotoxic effects. Pregnancy itself increases the risk of thromboembolism. Pregnant women with a history of thromboembolic disease are at increased risk of maternal and fetal complications. Enoxaparin does not cross the placenta. Use may be recommended in pregnant women for the management of VTE. Monitoring antifactor Xa levels is recommended. Risk of adverse events may be increased in pregnant women with mechanical heart valves; use is controversial and has not been adequately studied. Postmarketing reports include congenital abnormalities (cause and effect not established) and also fetal death when used in pregnant women. Multiple-dose vials contain benzyl alcohol; use caution in pregnant women.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsThis drug has a high molecular weight that would minimize excretion in breast milk and is inactivated by the GI tract which further reduces the risk to the infant.

Adverse ReactionsAs with all anticoagulants, bleeding is the major adverse effect of enoxaparin. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables. At the recommended doses, single injections of enoxaparin do not significantly influence platelet aggregation or affect global clotting time (ie, PT or aPTT).

1% to 10%:

Central nervous system: Fever (5% to 8%), confusion, pain

Dermatologic: Erythema, bruising

Gastrointestinal: Nausea (3%), diarrhea

Hematologic: Hemorrhage (major, <1% to 4%; includes cases of intracranial, retroperitoneal, or intraocular hemorrhage; incidence varies with indication/population), thrombocytopenia (moderate 1%; severe 0.1% - see note below), anemia (<2%)

Hepatic: ALT, increased, AST increased

Local: Injection site hematoma (9%), local reactions (irritation, pain, ecchymosis, erythema)

Renal: Hematuria (<2%)

<1% and/or postmarketing case reports (limited to important or life-threatening): Allergic reaction, anaphylactoid reaction, cutaneous vasculitis (hypersensitive), eczematous plaques, hematoma (see note on "Spinal or epidural hematomas" below), hyperkalemia, hyperlipidemia, hypertriglyceridemia, intracranial hemorrhage (up to 0.8%), erythematous pruritic patches, pruritus, purpura, retroperitoneal bleeding, skin necrosis, thrombocytopenia with thrombosis, thrombocytosis, urticaria, vesicobullous rash

Notes:

Spinal or epidural hematomas: Can occur following neuraxial anesthesia or spinal puncture, resulting in paralysis. Risk is increased in patients with indwelling epidural catheters or concomitant use of other drugs affecting hemostasis. Prosthetic valve thrombosis, including fatal cases, has been reported in pregnant women receiving enoxaparin as thromboprophylaxis.

Thrombocytopenia with thrombosis: Cases of heparin-induced thrombocytopenia (some complicated by organ infarction, limb ischemia, or death) have been reported.

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Drotrecogin Alfa: Heparin (Low Molecular Weight) may enhance the adverse/toxic effect of Drotrecogin Alfa. This is of most concern with therapeutic doses of LMW heparin. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid cat's claw, dong quai, evening primrose, feverfew, garlic, ginger, ginkgo, red clover, horse chestnut, green tea, ginseng (all have additional antiplatelet activity).

Monitoring ParametersPlatelets, occult blood, anti-Xa levels, serum creatinine; monitoring of PT and/or aPTT is not necessary. Routine monitoring of anti-Xa levels is not required, but has been utilized in patients with obesity and/or renal insufficiency. Monitoring anti-Xa levels is recommended in pregnant women receiving therapeutic doses of enoxaparin (Hirsh, 2008).

Reference RangeThe following therapeutic ranges for anti-Xa levels have been suggested, but have not been validated in a controlled trial. Anti-Xa level measured 4 hours post dose.

DVT treatment (every-12-hour dosing): 0.6-1 units/mL

DVT treatment (once-daily dosing): 1-2 units/mL

Nursing: Physical Assessment/MonitoringUse caution in presence or history of conditions that increase risk of bleeding. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (especially anything that will impact coagulation or platelet aggregation). Note specific injection directions. Monitor results of laboratory tests, therapeutic effectiveness according to purpose for use, and adverse response (eg, bleeding, thrombosis). Teach patient possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPlatelets, occult blood, anti-Xa levels, serum creatinine; monitoring of PT and/or aPTT is not necessary. Routine monitoring of anti-Xa levels is not required, but has been utilized in patients with obesity and/or renal insufficiency. Monitoring anti-Xa levels is recommended in pregnant women receiving therapeutic doses of enoxaparin (Hirsh, 2008).

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. This drug can only be administered by injection. If self-administered, follow exact directions for injection and needle disposal. Do not make major changes to your diet unless recommended by prescriber. You may have a tendency to bleed easily while taking this drug (brush teeth with soft brush, use waxed dental floss, use electric razor, avoid scissors or sharp knives, and potentially harmful activities). Report chest pain; persistent constipation; persistent erection; unusual bleeding or bruising (bleeding gums, nosebleed, blood in urine, dark stool); pain in joints or back; or redness, swelling, burning, or pain at injection site. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sodium [graduated prefilled syringe; preservative free]:

Lovenox®: 60 mg/0.6 mL (0.6 mL); 80 mg/0.8 mL (0.8 mL); 100 mg/mL (1 mL); 120 mg/0.8 mL (0.8 mL); 150 mg/mL (1 mL)

Injection, solution, as sodium [multidose vial]:

Lovenox®: 100 mg/mL (3 mL) [contains benzyl alcohol]

Injection, solution, as sodium [prefilled syringe; preservative free]:

Lovenox®: 30 mg/0.3 mL (0.3 mL); 40 mg/0.4 mL (0.4 mL)

Generic AvailableNo

ManufacturerSanofi-Aventis U.S. LLC

Pricing: U.S. (www.drugstore.com)

Solution (Lovenox)

30 mg/0.3 mL (3): $232.61

40 mg/0.4 mL (4): $321.27

60 mg/0.6 mL (6): $438.21

80 mg/0.8 mL (8): $555.99

100 mg/mL (10): $724.96

150 mg/mL (10): $1088.07

300 mg/3 mL (3): $229.98

Mechanism of ActionStandard heparin consists of components with molecular weights ranging from 4000-30,000 daltons with a mean of 16,000 daltons. Heparin acts as an anticoagulant by enhancing the inhibition rate of clotting proteases by antithrombin III impairing normal hemostasis and inhibition of factor Xa. Low molecular weight heparins have a small effect on the activated partial thromboplastin time and strongly inhibit factor Xa. Enoxaparin is derived from porcine heparin that undergoes benzylation followed by alkaline depolymerization. The average molecular weight of enoxaparin is 4500 daltons which is distributed as (≤20%) 2000 daltons (≥68%) 2000-8000 daltons, and (≤15%) >8000 daltons. Enoxaparin has a higher ratio of antifactor Xa to antifactor IIa activity than unfractionated heparin.

Pharmacodynamics/Kinetics

Onset of action: Peak effect: SubQ: Antifactor Xa and antithrombin (antifactor IIa): 3-5 hours

Duration: 40 mg dose: Antifactor Xa activity: ~12 hours

Distribution: 4.3 L (based on antifactor Xa activity)

Metabolism: Hepatic, to lower molecular weight fragments (little activity)

Protein binding: Does not bind to heparin binding proteins

Half-life elimination, plasma: 2-4 times longer than standard heparin, independent of dose; based on anti-Xa activity: 4.5-7 hours

Excretion: Urine (40% of dose; 10% as active fragments)

Related Information

- Anticoagulants, Injectable

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: As with all anticoagulants, bleeding is the major adverse effect of enoxaparin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables. At the recommended doses, single injections of enoxaparin do not significantly influence platelet aggregation or affect global clotting time (ie, PT or aPTT).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause confusion

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsLow molecular weight heparins (LMWHs) compare favorably to unfractionated heparin (UFH) in the prevention and treatment of venous thromboembolism. LMWHs are associated with less thrombocytopenia, compared to heparin, and do not require routine therapeutic monitoring. In patients with unstable angina and non-ST-elevation myocardial infarction (UA/NSTEMI), the 2002 ACC/AHA guidelines recommend anticoagulation with subcutaneous LMWH or intravenous UFH be added to antiplatelet therapy with aspirin and/or clopidogrel. Enoxaparin is preferable to UFH as an anticoagulant unless CABG is planned within 24 hours (Class IIa recommendation; level of evidence: A). In patients with ST-elevation myocardial infarction, most studies are limited to small numbers of patients treated with dalteparin or enoxaparin. Control groups (placebo, UFH), dosing, primary endpoints (composite ones), and bleeding definitions vary. In general, the studies suggest equivalent or superior outcomes with these LMWHs and less major bleeding. Preliminary results of a larger trial comparing prehospital dosing of enoxaparin (30 mg I.V. bolus; 1 mg/kg SubQ twice daily for a maximum of 7 days) versus UFH in patients receiving tenecteplase suggests a higher incidence of major bleeding and intracranial hemorrhage in the enoxaparin group (Wallentin L, 2003). Almost all cases of intracranial hemorrhage were confined to patients >75 years of age. Another ongoing trial will address this safety issue. In the 2004 ACC/AHA guideline for patients with ST-elevation MI (STEMI), a low molecular weight heparin might be considered an acceptable alternative to unfractionated heparin for patients <75 years of age who are receiving fibrinolytic therapy. The patient must have reasonable renal function (serum creatinine <2.5 mg/dL in men and <2 mg/dL in women). Enoxaparin in combination with full-dose tenecteplase is the best studied regimen (Wallentin L, 2003).

Obesity/Renal Dysfunction: There is no consensus for adjusting/correcting the weight-based dosage of LMWH for patients who are morbidly obese. Anti-Xa levels are increased to appropriate levels when enoxaparin is dosed on actual body weight in obese patients weighing up to 144 kg (Sanderink, 2002). Monitoring of anti-Xa levels 4 hours after injection may be warranted. Patients who have a reduction in calculated creatinine clearance are at risk of accumulated anticoagulant effect when they are treated with certain LMWHs. All LMWHs may not behave the same in patients with renal dysfunction. Some clinicians monitor anti-Xa levels in patients with Cl_{cr} <30 mL/minute if assay results are readily available. Patients requiring dialysis should not receive enoxaparin due to an increased risk of bleeding resulting from drug accumulation.

Anesthesia and Critical Care Concerns/Other ConsiderationsMany critically-ill and surgical patients require preventative measures for venous thromboembolism. Low molecular weight heparins (LMWHs) compare favorably to unfractionated heparin in the prevention and treatment of venous thromboembolism. LMWHs are associated with less thrombocytopenia, compared to heparin, and do not require routine therapeutic monitoring. The anticoagulant effect of LMWHs is not reliably reversed with protamine. Therefore, consideration should be given to enoxaparin’s duration of action when invasive procedures (eg, surgery, line placement) are required.

Obesity/Renal Dysfunction: There is no consensus for adjusting/correcting the weight-based dosage of LMWH for patients who are morbidly obese. Anti-Xa levels are increased to appropriate levels when enoxaparin is dosed on actual body weight in obese patients weighing up to 144 kg (Sanderink, 2002). Monitoring of anti-Xa levels 4 hours after injection may be warranted. Patients who have a reduction in calculated creatinine clearance are at risk of accumulated anticoagulant effect when they are treated with certain LMWHs. All LMWHs may not behave the same in patients with renal dysfunction. Some clinicians monitor anti-Xa levels in patients with Cl_{cr} <30 mL/minute if assay results are readily available. Patients requiring dialysis should not receive enoxaparin due to an increased risk of bleeding resulting from drug accumulation.

Index TermsEnoxaparin Sodium

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International Brand NamesClexane (AR, AU, BE, CH, CZ, DE, ES, GB, HU, IE, IT, LU, MX, NL, PL); Clexane Forte (PL); Decipar (ES); Klexane (DK, FI, SE); Lovenox (AT, CH, FR, PT); Plaucina (ES); Trombenox (IT)

Entacapone

Lexi-Drugs Online

English

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Pronunciation(en TA ka pone)

U.S. Brand NamesComtan®

Canadian Brand NamesComtan®

Pharmacologic CategoryAnti-Parkinson's Agent, COMT Inhibitor

Use: Labeled IndicationsAdjunct to levodopa/carbidopa therapy in patients with idiopathic Parkinson's disease who experience “wearing-off” symptoms at the end of a dosing interval

Dosing: AdultsParkinson's disease: Oral: 200 mg with each dose of levodopa/carbidopa, up to a maximum of 8 times/day (maximum daily dose: 1600 mg/day). To optimize therapy, the dosage of levodopa may need reduced or the dosing interval may need extended. Patients taking levodopa ≥800 mg/day or who had moderate-to-severe dyskinesias prior to therapy required an average decrease of 25% in the daily levodopa dose.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is required; dialysis patients were not studied.

Dosing: Hepatic ImpairmentDosage adjustment in chronic therapy with standard treatment has not been studied.

Dietary ConsiderationsMay be taken with or without food.

ContraindicationsHypersensitivity to entacapone or any of component of the formulation

Allergy Considerations

- COMT Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Diarrhea: Has been associated with delayed development of diarrhea (onset after 2-12 weeks); use with caution in patients with lower gastrointestinal disease or an increased risk of dehydration.
- Hallucinations: May cause hallucinations, which may improve with reduction in levodopa therapy.
- Neuroleptic malignant syndrome: Entacapone, in conjunction with other drug therapy that alters brain biogenic amine concentrations (eg, MAO inhibitors, SSRIs), has been associated with a syndrome resembling neuroleptic malignant syndrome (hyperpyrexia and confusion - some fatal) on abrupt withdrawal or dosage reduction. Concomitant use of tolcapone and nonselective MAO inhibitors should be avoided.
- Orthostatic hypotension: May cause orthostatic hypotension and syncope; Parkinson's disease patients appear to have an impaired capacity to respond to a postural challenge; use with caution in patients at risk of hypotension (such as those receiving antihypertensive drugs) or where transient hypotensive episodes would be poorly tolerated (cardiovascular disease or cerebrovascular disease). Parkinson's patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation, and should be informed of this risk.
- Pleural/retroperitoneal fibrosis: Dopaminergic agents from the ergot class have been associated with fibrotic complications, such as retroperitoneal fibrosis, pulmonary infiltrates or effusion and pleural thickening. It is unknown whether non-ergot, pro-dopaminergic agents like tolcapone confer this risk.
- Rhabdomyolysis: Severe rhabdomyolysis has been reported with use.

Disease-related concerns:

- Dyskinesia: Use with caution in patients with pre-existing dyskinesias; exacerbation of pre-existing dyskinesia has been reported. Levodopa dosage reduction may be required, particularly in patients with levodopa dosages >600 mg daily or with moderate-to-severe dyskinesia prior to initiation.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with severe renal impairment.

Concurrent drug therapy issues:

- MAO inhibitors: Concomitant use of tolcapone and nonselective MAO inhibitors should be avoided. Selegiline is a selective MAO type B inhibitor (when given orally at ≤10 mg/day) and can be taken with entacapone.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Discontinuation of therapy: Do not withdraw therapy abruptly.

Geriatric ConsiderationsNo difference in adverse effects was noted in the elderly. Monitor levodopa dose.
Pregnancy Risk FactorC
Pregnancy ConsiderationsNot recommended
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%:

Gastrointestinal: Nausea (14%)

Neuromuscular & skeletal: Dyskinesia (25%), placebo (15%)

1% to 10%:

Cardiovascular: Orthostatic hypotension (4%), syncope (1%)

Central nervous system: Dizziness (8%), fatigue (6%), hallucinations (4%), anxiety (2%), somnolence (2%), agitation (1%)

Dermatologic: Purpura (2%)

Gastrointestinal: Diarrhea (10%), abdominal pain (8%), constipation (6%), vomiting (4%), dry mouth (3%), dyspepsia (2%), flatulence (2%), gastritis (1%), taste perversion (1%)

Genitourinary: Brown-orange urine discoloration (10%)

Neuromuscular & skeletal: Hyperkinesia (10%), hypokinesia (9%), back pain (4%), weakness (2%)

Respiratory: Dyspnea (3%)

Miscellaneous: Bacterial infection (1%), diaphoresis increased (2%)

<1%: Hyperpyrexia and confusion (resembling neuroleptic malignant syndrome), pulmonary fibrosis, rhabdomyolysis, retroperitoneal fibrosis

Metabolism/Transport Effects**Inhibits** CYP1A2 (weak), 2A6 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak), 3A4 (weak)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

COMT Substrates: COMT Inhibitors may decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

MAO Inhibitors: COMT Inhibitors may enhance the adverse/toxic effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS adverse effects).

Food: Entacapone has been reported to chelate iron and decreasing serum iron levels were noted in clinical trials; however, clinically significant anemia has not been observed.

Monitoring ParametersSigns and symptoms of Parkinson's disease; liver function tests, blood pressure, patient's mental status; serum iron (if signs of anemia)
Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness and adverse reactions. Monitor blood pressure. Taper dosage when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse reactions to report.
Monitoring: Lab TestsLiver function tests, serum iron (if signs of anemia)
Patient EducationTake exactly as directed; do not alter dosage or discontinue without consulting prescriber. May be taken with food. Notify prescriber if any other prescription medications you are taking. Avoid all alcohol or OTC medications unless approved by your prescriber. Orange-brown urine is normal with this medication. You may experience dizziness, fatigue, or sleepiness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); postural hypotension (rise slowly when getting up from chair or bed, when climbing stairs); or unusual taste, nausea, vomiting, flatulence, or upset stomach (small frequent meals, good mouth care, chewing gum, or sucking hard candy may help). Report any increased or abnormal skeletal movements or pain; unresolved sedation, nausea, diarrhea, constipation, or GI distress; signs of infection; persistent dizziness or sleepiness; or other unusual responses. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 200 mg

Generic AvailableNo
ManufacturerNovartis Pharmaceuticals Corp
Pricing: U.S. (www.drugstore.com)

Tablets (Comtan)

200 mg (30): $87.19

Mechanism of ActionEntacapone is a reversible and selective inhibitor of catechol-O-methyltransferase (COMT). When entacapone is taken with levodopa, the pharmacokinetics are altered, resulting in more sustained levodopa serum levels compared to levodopa taken alone. The resulting levels of levodopa provide for increased concentrations available for absorption across the blood-brain barrier, thereby providing for increased CNS levels of dopamine, the active metabolite of levodopa.

Pharmacodynamics/Kinetics

Onset of action: Rapid

Peak effect: 1 hour

Absorption: Rapid

Distribution: I.V.: V_{dss}: 20 L

Protein binding: 98%, primarily to albumin

Metabolism: Isomerization to the *cis*-isomer, followed by direct glucuronidation of the parent and *cis*-isomer

Bioavailability: 35%

Half-life elimination: B phase: 0.4-0.7 hours; Y phase: 2.4 hours

Time to peak, serum: 1 hour

Excretion: Feces (90%); urine (10%)

Related Information

- Antiparkinsonian Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension and abnormal taste. Dopaminergic therapy in Parkinson's disease (ie, treatment with levodopa) is associated with orthostatic hypotension. Entacapone enhances levodopa bioavailability and may increase the occurrence of hypotension/syncope in the dental patient. The patient should be carefully assisted from the chair and observed for signs of orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

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International Brand NamesAdcapone (IN); Comtade (CO); Comtan (AR, AT, AU, BE, BG, BR, CH, CL, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IT, KP, MX, MY, NL, NO, PE, PH, PL, PT, PY, RU, SE, TH, TR, UY, VE); Comtess (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Entecavir

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(en TE ka veer)

U.S. Brand NamesBaraclude®

Canadian Brand NamesBaraclude®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)

Use: Labeled IndicationsTreatment of chronic hepatitis B infection in adults with evidence of active viral replication and either evidence of persistent transaminase elevations or histologically-active disease

Dosing: AdultsTreatment of chronic hepatitis B infection: Oral:

Nucleoside treatment naive: 0.5 mg daily

Lamivudine-resistant viremia (or known lamivudine- or telbivudine-resistant mutations): 1 mg daily

Note: Usual treatment duration is at least 1 year and varies with HBeAg status; consult current guidelines and literature.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAdolescents ≥16 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 30-49 mL/minute: Administer 50% of usual dose daily or administer the normal dose every 48 hours

Cl_{cr} 10-29 mL/minute: Administer 30% of usual dose daily or administer the normal dose every 72 hours

Cl_{cr} <10 mL/minute (including hemodialysis and CAPD): Administer 10% of usual dose daily or administer the normal dose every 7 days; administer after hemodialysis

Dosing: Hepatic ImpairmentNo adjustment necessary.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister on an empty stomach. Do not dilute or mix oral solution with water or other beverages; use calibrated oral dosing syringe. Oral solution and tablet are bioequivalent on a mg-to-mg basis.

Dietary ConsiderationsTake on an empty stomach (2 hours before or after a meal).

StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect oral solution from light.

ContraindicationsHypersensitivity to entecavir or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Chronic hepatitis B: See “Disease-related concerns” below.
- Human immunodeficiency virus (HIV): See “Disease-related concerns” below.
- Lactic acidosis/hepatomegaly: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).

Disease-related concerns:

- Chronic hepatitis B: **[U.S. Boxed Warning]: Severe, acute exacerbation of hepatitis B may occur upon discontinuation.** Monitor liver function several months after stopping treatment; reinitiation of antihepatitis B therapy may be required.
- HIV: **[U.S. Boxed Warning]: May cause the development of HIV resistance in chronic hepatitis B patients with unrecognized or untreated HIV infection.** Determine HIV status prior to initiating treatment with entecavir. Not recommended for HIV/HBV coinfected patients unless also receiving highly active antiretroviral therapy (HAART). The manufacturer's labeling states that entecavir does not exhibit any clinically-relevant activity against human immunodeficiency virus (HIV type 1). However, a small number of case reports have indicated declines in virus levels during entecavir therapy. Reports of HIV resistance to a common HIV drug has been reported in an HIV/HBV-infected patient receiving entecavir as monotherapy for HBV.

- Renal impairment: Use with caution in patients with renal impairment or patients receiving concomitant therapy which may reduce renal function; dose adjustment recommended for Cl_{cr} <50 mL/minute.

Special populations:

- Liver transplant recipients: Safety and efficacy have not been established in liver transplant patients; monitor renal function before and during treatment in liver transplant patients receiving concurrent therapy of cyclosporine or tacrolimus; entecavir dosage may need to be adjusted.

- Pediatrics: Safety and efficacy have not been established in patients <16 years of age.

Other warnings/precautions:

- Resistance: Cross-resistance may develop in patients failing previous therapy with lamivudine.

Geriatric ConsiderationsSee dosing for renal impairment.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects have been observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use only if benefit outweighs risk. Pregnant women taking entecavir should enroll in the pregnancy registry by calling 1-800-258-4263.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%: Hepatic: ALT increased (>5 x ULN: 11% to 12%; post-treatment flare [lamivudine refractory]: >10 x ULN and >2 x baseline: 12%)

1% to 10%:

Central nervous system: Headache (2% to 4%), fatigue (1% to 3%), dizziness

Endocrine & metabolic: Hyperglycemia (2% to 3%)

Gastrointestinal: Lipase increased (7%), amylase increased (2% to 3%), diarrhea (≤1%), dyspepsia (≤1%), nausea

Hepatic: Bilirubin increased (2% to 3%), ALT increased (>10 x ULN and >2 x baseline: 2%; post-treatment flare [nucleoside-naive]: >10 x ULN and >2 x baseline: 2% to 8%)

Renal: Hematuria (9%), glycosuria (4%), creatinine increased (1% to 2%)

<1% (Limited to important or life-threatening): Anaphylactoid reaction, hypoalbuminemia, insomnia, rash, somnolence, thrombocytopenia, vomiting

Drug Interactions

Ganciclovir-Valganciclovir: May enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. *Risk D: Consider therapy modification*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Food delays absorption and reduces AUC by 18% to 20%.

Monitoring ParametersHIV status (prior to initiation of therapy); liver function tests, renal function; in HBV/HIV-coinfected patients, monitor HIV viral load and CD4 count
Monitoring: Lab TestsHIV status (prior to initiation of therapy); liver function tests, renal function; in HBV/HIV-coinfected patients, monitor HIV viral load and CD4 count
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Oral solution:

Baraclude®: 0.05 mg/mL (210 mL) [orange flavor]

Tablet:

Baraclude®: 0.5 mg, 1 mg

Generic AvailableNo
ManufacturerBristol-Myers Squibb
Pricing: U.S. (www.drugstore.com)

Tablets (Baraclude)

0.5 mg (30): $779.98

Mechanism of ActionEntecavir is intracellularly phosphorylated to guanosine triphosphate which competes with natural substrates to effectively inhibit hepatitis B viral polymerase; enzyme inhibition blocks reverse transcriptase activity thereby reducing viral DNA synthesis.
Pharmacodynamics/Kinetics

Distribution: Extensive (V_d in excess of body water)

Protein binding: ~13%

Metabolism: Minor hepatic glucuronide/sulfate conjugation

Half-life elimination: Terminal: ~5-6 days; accumulation: ~24 hours

Time to peak, plasma: 0.5-1.5 hours

Excretion: Urine (60% to 73% as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Lok AS and McMahon BJ, “Chronic Hepatitis B,” *Hepatology*, 2007, 45(2):507-39.[PubMed 17256718]

International Brand NamesBaraclude (AR, AT, AU, BE, BG, CH, CL, CN, CO, CR, CZ, DE, DK, DO, ES, FI, FR, GB, GR, GT, HN, ID, IE, IT, KP, MY, NI, NL, NO, PA, PE, PH, PT, RU, SE, SG, SV, TH, TR)

EP (Adenocarcinoma)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Adenocarcinoma (Unknown Primary)

Regimen Use Adenocarcinoma, unknown primary

Regimen

Cisplatin: I.V.: 60-100 mg/m^2 day 1

[total dose = 60-100 mg/m^2]

Etoposide: I.V.: 80-100 mg/m^2/day days 1, 2, and 3

[total dose = 240-300 mg/m^2]

Repeat cycle every 21 days

References

Sulkes A, Uziely B, Isacson R, et al, “Combination Chemotherapy in Metastatic Tumors of Unknown Origin. 5-Fluorouracil, Adriamycin® and Mitomycin C for Adenocarcinomas and Adriamycin®, Vinblastine, and Mitomycin C for Anaplastic Carcinomas,” *Isr J Med Sci*, 1988, 24(9-10):604-10.[PubMed 3204009]

EP (NSCLC)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Nonsmall Cell)

Regimen UseLung cancer, nonsmall cell

Regimen

Etoposide: I.V.: 80-120 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 240-360 mg/m^2]

Cisplatin: I.V.: 80-100 mg/m^2 day 1

[total dose/cycle = 80-100 mg/m^2]

Repeat cycle every 21-28 days

References

Goldhirsch A, Joss RA, Cavalli F, et al, âCis-Dichlorodiammineplatinum (II) and VP 16-213 Combination Chemotherapy for Nonsmall-Cell Lung Cancer,â *Med Pediatr Oncol*, 1981, 9(3):205-8.[PubMed 6264280]

EP (Small Cell Lung Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Small Cell)

Regimen UseLung cancer, small cell

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Etoposide: I.V.: 100 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 300 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Etoposide: I.V.: 80 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 240 mg/m^2]

Cisplatin: I.V.: 80 mg/m^2 day 1

[total dose/cycle = 80 mg/m^2]

Repeat cycle every 21-28 days

References

Variation 1:

Goodman GE, Crowley JJ, Blasko JC, et al, “Treatment of Limited Small-Cell Lung Cancer With Etoposide and Cisplatin Alternating With Vincristine, Doxorubicin, and Cyclophosphamide Versus Concurrent Etoposide, Vincristine, Doxorubicin, and Cyclophosphamide and Chest Radiotherapy: A Southwest Oncology Group Study,” *J Clin Oncol*, 1990, 8(1):39-47. [PubMed 2153194]

Variation 2:

Perng RP, Chen YM, Ming-Liu J, et al, “Gemcitabine Versus the Combination of Cisplatin and Etoposide in Patients With Inoperable Nonsmall Cell Lung Cancer in a Phase II Randomized Study,” *J Clin Oncol*, 1997, 15(5):2097-102.[PubMed 9164223]

EP (Testicular Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Testicular Cancer
Regimen UseTesticular cancer
RegimenNOTE: Multiple variations are listed below.

Variation 1:

Etoposide: I.V.: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Etoposide: I.V.: 120 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 360 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 3 or 4 weeks

Variation 3:

Etoposide: I.V.: 120 mg/m^2/day days 1, 3, and 5

[total dose/cycle = 360 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 3 weeks

References

Variation 1:

Hainsworth JD, Williams SD, Einhorn LH, et al, "Successful Treatment of Resistant Germinal Neoplasms With VP-16 and Cisplatin: Results of a Southeastern Cancer Study Group Trial," *J Clin Oncol*, 1985, 3(5):666-71. [PubMed 2582097]

Variation 2:

Peckham MJ, Horwich A, Blackmore C, et al, "Etoposide and Cisplatin With or Without Bleomycin as First-Line Chemotherapy for Patients With Small-Volume Metastases of Testicular Nonseminoma," *Cancer Treat Rep*, 1985, 69(5):483-8. [PubMed 2408750]

Variation 3:

de Wit R, Stoter G, Kaye SB, et al, "Importance of Bleomycin in Combination Chemotherapy for Good-Prognosis Testicular Nonseminoma: A Randomized Study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group," *J Clin Oncol*, 1997, 15(5):1837-43.[PubMed 9164193]

EP/EMA

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Gestational Trophoblastic Tumor]
Regimen Use Gestational trophoblastic tumor
Index Terms EMA/EP
Regimen NOTE: Multiple variations are listed below.

Variation 1:

Etoposide: I.V.: 150 mg/m^2 day 1

[total dose/cycle = 150 mg/m^2]

Cisplatin: I.V.: 25 mg/m^2 infused over 4 hours for 3 consecutive doses, day 1

[total dose/cycle = 75 mg/m^2]

Alternate weekly with:

Etoposide: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Methotrexate: I.V.: 300 mg/m^2 infused over 12 hours day 1

[total dose/cycle = 300 mg/m^2]

Dactinomycin: I.V. push: 0.5 mg day 1

[total dose/cycle = 0.5 mg]

Leucovorin: Oral, I.M.: 15 mg twice daily for 2 days (start 24 hours after the start of methotrexate) days 2 and 3

[total dose/cycle = 60 mg]

Variation 2:

Dactinomycin: I.V.: 0.5 mg/day days 1 and 2

[total dose/cycle = 1 mg]

Etoposide: I.V.: 100 mg/m^2/day days 1 and 2

[total dose/cycle = 200 mg/m^2]

Methotrexate: I.V.: 300 mg/m^2 continuous infusion over 12 hours day 1

[total dose/cycle = 300 mg/m^2]

Leucovorin: Oral, I.M.: 15 mg every 12 hours for 4 doses (start 24 hours after start of methotrexate) days 2 and 3

[total dose/cycle = 60 mg]

Etoposide: I.V.: 150 mg/m^2 day 8

[total dose/cycle = 150 mg/m^2]

Cisplatin: I.V.: 75 mg/m^2 day 8

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 2 weeks

References

Variation 1:

Newlands ES, Bower M, Holden L, et al, “Management of Resistant Gestational Trophoblastic Tumors,” *J Reprod Med*, 1998, 43(2):111-8.[PubMed 9513872]

Variation 2:

Newlands ES, Bagshawe KD, Begent RH, et al, “Results With the EMA/CO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Vincristine) Regimen in High Risk Gestational Trophoblastic Tumours, 1979 to 1989,” *J Obstet Gynaecol*, 1991, 98(6):550-7.[PubMed 1651757]

EP/PE

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Nonsmall Cell)

Regimen UseLung cancer, nonsmall cell

Regimen

Etoposide: I.V.: 120 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 360 mg/m^2]

Cisplatin: I.V.: 60-120 mg/m^2 day 1

[total dose/cycle = 60-120 mg/m^2]

Repeat cycle every 21-28 days

References

Weick JK, Crowley J, Natale RB, et al, âA Randomized Trial of Five Cisplatin-Containing Treatments in Patients With Metastatic Nonsmall-Cell Lung Cancer: A Southwest Oncology Group Study,â *J Clin Oncol*, 1991, 9(7):1157-62.[PubMed 1646292]

EPHEDrine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

EPHEDrine may be confused with Epifrin®, EPINEPHrine

Pronunciation(e FED rin)
U.S. Brand NamesPretz-D® [OTC]
Pharmacologic CategoryAlpha/Beta Agonist
Use: Labeled IndicationsTreatment of bronchial asthma, nasal congestion, acute bronchospasm, idiopathic orthostatic hypotension, hypotension induced by spinal anesthesia
Dosing: Adults

Asthma, nasal congestion, acute bronchospasm, idiopathic orthostatic hypotension, hypotension induced by anesthesia:

Oral: 25-50 mg every 3-4 hours as needed

I.M., SubQ: 25-50 mg, parenteral adult dose should not exceed 150 mg in 24 hours

I.M.: 25 mg

I.V.: 5-25 mg/dose slow I.V. push repeated after 5-10 minutes as needed, then every 3-4 hours not to exceed 150 mg/24 hours

Nasal congestion: Nasal spray: 2-3 sprays into each nostril, not more frequently than every 4 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Bronchospasm, nasal congestion:

Oral, SubQ: 3 mg/kg/day or 25-100 mg/m^2/day in 4-6 divided doses every 4-6 hours

I.M., slow I.V. push: 0.2-0.3 mg/kg/dose every 4-6 hours

Nasal congestion: Nasal spray:

Children 6-12 years: 1-2 sprays into each nostril, not more frequently than every 4 hours

Children ≥12 years: Refer to adult dosing.

Calculations

- Body Surface Area: Pediatrics

Administration: I.V.Do not administer unless solution is clear.
Administration: I.V. DetailpH: 4.5-7.0
StorageProtect all dosage forms from light.
CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, ${}^1/_2NS$, NS.

Y-site administration: Compatible: Etomidate, propofol. **Incompatible:** Thiopental.

Compatibility in syringe: Compatible: Pentobarbital. **Incompatible:** Thiopental.

Compatibility when admixed: Compatible: Chloramphenicol, lidocaine, metaraminol, nafcillin, penicillin G potassium. **Incompatible:** Hydrocortisone sodium succinate, pentobarbital, phenobarbital. **Variable (consult detailed reference):** Thiopental.

ContraindicationsHypersensitivity to ephedrine or any component of the formulation; cardiac arrhythmias; angle-closure glaucoma; concurrent use of other sympathomimetic agents
Warnings/Precautions

Concerns related to adverse effects:

- Hypertension: May cause hypertension.
- Psychiatric disorders: Long-term use may cause anxiety and symptoms of paranoid schizophrenia.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease such as coronary artery disease, arrhythmias, and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Seizures: Use with caution in patients with a history of seizure disorder.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

- Vasomotor symptoms: Use with caution in patients with unstable vasomotor symptoms.

Concurrent drug therapy issues:

- Monoamine oxidase inhibitors (MAO-I): Use with extreme caution in patients taking MAO inhibitors; prolonged hypertension may result from concurrent use.

Special populations:

- Elderly: Use with caution in the elderly, since it crosses the blood-brain barrier and may cause confusion.

Dosage form specific issues:

- Injectable: Blood volume depletion should be corrected before I.V./I.M. therapy is instituted.

Other warnings/precautions:

- Bronchodilator use: Avoid as a bronchodilator; generally not used as a bronchodilator since other beta$_2$-agents are less toxic.

Geriatric ConsiderationsAvoid as a bronchodilator. Use caution since it crosses the blood-brain barrier and may cause confusion.
Pregnancy Risk FactorC
LactationEnters breast milk/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, chest pain, elevation or depression of blood pressure, hypertension, palpitation, tachycardia, unusual pallor

Central nervous system: Agitation, anxiety, apprehension, CNS stimulating effects, dizziness, excitation, fear, headache hyperactivity, insomnia, irritability, nervousness, restlessness, tension

Gastrointestinal: Anorexia, GI upset, nausea, vomiting, xerostomia

Genitourinary: Painful urination

Neuromuscular & skeletal: Trembling, tremor (more common in the elderly), weakness

Respiratory: Dyspnea

Miscellaneous: Diaphoresis increased

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid ephedra, yohimbe (may cause CNS stimulation).
Test InteractionsCan cause a false-positive amphetamine EMIT assay
Monitoring ParametersInjection solution: Monitor blood pressure, pulse
Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness and adverse reactions when initiating therapy and at regular intervals with long-term therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Patient EducationUse this medication exactly as directed; do not take more than recommended dosage. Avoid other stimulant prescriptive or OTC medications to avoid serious overdose reactions. Store this medication away from light. You may experience dizziness, blurred vision, restlessness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or difficulty urinating (empty bladder immediately before taking this medication). Report excessive nervousness or excitation, inability to sleep, facial flushing, pounding

heartbeat, muscle tremors or weakness, chest pain or palpitations, bronchial irritation or coughing, or increased sweating. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as sulfate: 25 mg

Injection, solution, as sulfate: 50 mg/mL (1 mL, 10 mL)

Solution, intranasal spray, as sulfate (Pretz-D®): 0.25% (50 mL)

Generic AvailableYes

Mechanism of ActionReleases tissue stores of epinephrine and thereby produces an alpha- and beta-adrenergic stimulation; longer-acting and less potent than epinephrine

Pharmacodynamics/Kinetics

Onset of action: Oral: Bronchodilation: 0.25-1 hour

Duration: Oral: 3-6 hours

Distribution: Crosses placenta; enters breast milk

Metabolism: Minimally hepatic

Half-life elimination: 2.5-3.6 hours

Excretion: Urine (60% to 77% as unchanged drug) within 24 hours

Related Information

- Contrast Media Reactions, Premedication for Prophylaxis

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse vasoconstrictor with caution since ephedrine may enhance cardiostimulation and vasopressor effects of sympathomimetics such as epinephrine

Mental Health: Effects on Mental StatusNervousness, anxiety, agitation, restlessness, and insomnia are common

Mental Health: Effects on Psychiatric TreatmentUse with MAO inhibitors may produce hypertensive crisis; avoid combination

Anesthesia and Critical Care Concerns/Other ConsiderationsFor I.V. administration, give the undiluted injection slowly. Additional I.V. doses may be given every 5-10 minutes if needed. Do not exceed adult parenteral dose of 150 mg/24 hours. Do not exceed pediatric dose of 3 mg/kg/24 hours. Use the smallest effective dose. Anesthesiologists may administer to treat nausea and vomiting in adults that has failed traditional antiemetic therapy and might be caused by hypotension (Gan, 2003).

Index TermsEphedrine Sulfate

References

Gan TJ, Meyer T, Apfel CC, et al, “Consensus Guidelines for Managing Postoperative Nausea and Vomiting,” *Anesth Analg*, 2003, 97(1):62-71.[PubMed 12818945]

Pickup ME, May CS, Sendagire R, et al, “The Pharmacokinetics of Ephedrine After Oral Dosage in Asthmatics Receiving Acute and Chronic Treatment,” *Br J Clin Pharmacol*, 1976, 3(1):123-34. [PubMed 973934]

Stein GC, “Requirements for Pharmacists Dispensing Ephedrine Products,” *Am J Health Syst Pharm*, 1995, 52(15):1630.[PubMed 7583823]

International Brand NamesCoderit (MX); Efrinol (PL); Endrine (IN); Ephedrinum hydrochloridum (PL); Ephedrivo (CH); Kemeol (CH); Piralgina (MX)

Epinastine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(ep i NAS teen)
U.S. Brand NamesElestat™
Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation
Use: Labeled IndicationsTreatment of allergic conjunctivitis
Dosing: AdultsAllergic conjunctivitis: Ophthalmic: Instill 1 drop into each eye twice daily. Continue throughout period of exposure, even in the absence of symptoms.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricAllergic conjunctivitis: Ophthalmic: Children ≥3 years: Refer to adult dosing.
Administration: OtherFor ophthalmic use only; avoid touching tip of applicator to eye or other surfaces. Contact lenses should be removed prior to application, may be reinserted after 10 minutes. Do not wear contact lenses if eyes are red.
StorageStore at controlled room temperature of 15°C to 25°C (59°F to 77°F). Keep tightly closed.
ContraindicationsHypersensitivity to epinastine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Bacterial keratitis: Inadvertent contamination of multiple-dose ophthalmic solutions has caused bacterial keratitis.

Special populations:

- Contact lens wearers: Contains benzalkonium chloride which may be absorbed by contact lenses; remove contact lenses prior to use and wait 15 minutes before reinserting.

- Pediatrics: Safety and efficacy have not been established in children <3 years of age.

Other warnings/precautions:

- Appropriate use: For topical ophthalmic use only. Not for the treatment of contact lens irritation; do not wear contact lenses if eye is red.

Geriatric ConsiderationsNo difference in safety and efficacy was observed between elderly and younger patients.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions1% to 10%:

Central nervous system: Headache (1% to 3%)

Ocular: Burning sensation, folliculosis, hyperemia, pruritus

Respiratory: Cough (1% to 3%), pharyngitis (1% to 3%), rhinitis (1% to 3%), sinusitis (1% to 3%)

Miscellaneous: Infection (10%; defined as cold symptoms and upper respiratory infection)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringFor ophthalmic use only. Assess therapeutic effectiveness and adverse reactions on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.
Patient EducationFor ophthalmic use only. Use exactly as directed. Do not wear contact lenses if eyes are red. May cause headache (consult prescriber for analgesic if persistent). Report unusual or persistent cough of cold symptoms related to use, or if condition does not improve. Wash hands before using. Remove contact lenses before application (may be reinserted after 10 minutes). Gently pull lower eyelid forward and instill prescribed amount in lower eyelid. Avoid touching tip of dropper to eye. Close eye and roll eyeball in all directions. May cause blurred vision, temporary stinging or burning sensation.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic, as hydrochloride: 0.05% (5 mL) [contains benzalkonium chloride]

Generic AvailableNo
ManufacturerAllergan, Inc
Pricing: U.S. (www.drugstore.com)

Solution (Elestat)

0.05% (5): $90.94

Mechanism of ActionSelective H_1-receptor antagonist; inhibits release of histamine from the mast cell
Pharmacodynamics/Kinetics

Onset of action: 3-5 minutes

Duration: 8 hours

Absorption: Low systemic absorption following topical application

Distribution: Does not cross blood-brain barrier

Protein binding: 64%

Metabolism: <10% metabolized

Half-life elimination: 12 hours

Excretion: I.V.: Urine (55%); feces (30%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsEpinastine Hydrochloride
International Brand NamesAlket (AR); Aresten (KP); Flurinol (CN, CO, CR, DO, GT, HN, NI, PA, PE, PY, SV, UY, VE); Furinol (MX); Purivist (FR); Relestat (BE, CH, DE, ES, FI, GB, HK, HN, IE, IL, IT, PT, SE, TW); Talerc (BR)

Jump To Field (Select Field Name)

Pronunciation(ep i NEF rin, ra SEE mik and a LOO mi num poe TASS ee um SUL fate)
U.S. Brand NamesVan R Gingibraid®
Pharmacologic CategoryAdrenergic Agonist Agent; Alpha/Beta Agonist; Astringent; Vasoconstrictor
Use: DentalGingival retraction
Dosing: AdultsGingival retraction: Pass the impregnated yarn around the neck of the tooth and place into gingival sulcus; normal tissue moisture, water, or gingival retraction solutions activate impregnated yarn. Limit use to one quadrant of the mouth at a time; recommended use is for 3-8 minutes in the mouth.
Dosing: ElderlyRefer to adult dosing.
ContraindicationsHypersensitivity to epinephrine or any component of the formulation; cardiovascular disease, hyperthyroidism, or diabetes; do not apply to areas of heavy or deep bleeding or over exposed bone
Warnings/Precautions

Other warnings/precautions:

- Appropriate use: Caution should be exercised whenever using gingival retraction cords with epinephrine since it delivers vasoconstrictor doses of racemic epinephrine to patients; the general medical history should be thoroughly evaluated before using in any patient.

Adverse ReactionsNo data reported.
Drug InteractionsNo data reported.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Yarn, saturated in solution of 8% racemic epinephrine and 7% aluminum potassium sulfate:

Type “0e”: 0.20 ± 0.10 mg epinephrine/inch

Type “1e”: 0.40 ± 0.20 mg epinephrine/inch

Type “2e”: 0.60 ± 0.20 mg epinephrine/inch

Generic AvailableNo
Mechanism of ActionEpinephrine stimulates alpha$_1$ adrenergic receptors to cause vasoconstriction in blood vessels in gingiva; aluminum potassium sulfate, precipitates tissue and blood proteins
Pharmacodynamics/KineticsNo data reported.
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tissue retraction around base of the tooth (therapeutic effect)..
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsAluminum Potassium Sulfate and Epinephrine (Racemic) (Dental)

Epinephrine and Chlorpheniramine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(ep i NEF rin & klor fen IR a meen)

U.S. Brand NamesAna-Kit速

Pharmacologic CategoryAntidote

Use: Labeled IndicationsAnaphylaxis emergency treatment of insect bites or stings by the sensitive patient that may occur within minutes of insect sting or exposure to an allergic substance

Dosing: AdultsInsect stings (Children and Adults): I.M. or SubQ:

Epinephrine:

<2 years: 0.05-0.1 mL

2-6 years: 0.15 mL

6-12 years: 0.2 mL

>12 years : 0.3 mL

Chlorpheniramine:

<6 years: 1 tablet

6-12 years: 2 tablets

>12 years: 4 tablets

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

StorageStore at room temperature; do not freeze. Protect from light.

Pregnancy ConsiderationsRefer to Epinephrine monograph.

Metabolism/Transport EffectsChlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

COMT Inhibitors: May decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Inhalational Anesthetics: May enhance the arrhythmogenic effect of EPINEPHrine. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Kit: Epinephrine hydrochloride 1:1000 [prefilled syringe, delivers two 0.3 mL doses; contains sodium bisulfite] (1 mL), chlorpheniramine maleate chewable tablet 2 mg (4), sterile alcohol pads [isopropyl alcohol 70%] (2), tourniquet (1)

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness or restlessness

Mental Health: Effects on Psychiatric TreatmentNone reported. However, use cautiously with psychotropics that block alpha-receptors (phenothiazines); may produce paradoxical hypotension.

Index TermsInsect Sting Kit

EPINEPHrine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

EPINEPHrine may be confused with ePHEDrine

Epifrin® may be confused with ephedrine, EpiPen®

EpiPen® may be confused with Epifrin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Medication errors have occurred due to confusion with epinephrine products expressed as ratio strengths (eg, 1:1000 vs 1:10,000).

Epinephrine 1:1000 = 1 mg/mL and is most commonly used I.M.

Epinephrine 1:10,000 = 0.1 mg/mL and is used I.V.

International issues:

EpiPen® may be confused with Epigen® which is a brand name for glycyrrhizinic acid in Mexico

EpiPen® may be confused with Epopen® which is a brand name for epoetin alfa in Spain

Pronunciation(ep i NEF rin)

U.S. Brand NamesAdrenalin®; EpiPen®; EpiPen® Jr; Primatene® Mist [OTC]; Raphon [OTC]; S2® [OTC]; Twinject™

Canadian Brand NamesAdrenalin®; EpiPen®; EpiPen® Jr; Twinject™

Pharmacologic CategoryAlpha/Beta Agonist; Antidote

Use: Labeled IndicationsTreatment of bronchospasms, bronchial asthma, nasal congestion, viral croup, anaphylactic reactions, cardiac arrest; added to local anesthetics to decrease systemic absorption of local anesthetics and increase duration of action; decrease superficial hemorrhage

Use: Unlabeled/InvestigationalACLS guidelines: Ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) unresponsive to initial defibrillatory shocks; pulseless electrical activity, asystole, hypotension unresponsive to volume resuscitation; symptomatic bradycardia or hypotension unresponsive to atropine or pacing; inotropic support

Use: DentalEmergency drug for treatment of anaphylactic reactions; used as vasoconstrictor to prolong local anesthesia

Dosing: Adults

Asystole/pulseless arrest, bradycardia, VT/VF:

I.V., I.O.: 1 mg every 3-5 minutes; if this approach fails, higher doses of epinephrine (up to 0.2 mg/kg) may be indicated for treatment of specific problems (eg, beta-blocker or calcium channel blocker overdose)

Intratracheal: Administer 2-2.5 mg for VF or pulseless VT if I.V./I.O. access is delayed or cannot be established; dilute in 5-10 mL NS or distilled water. **Note:** Absorption is greater with distilled water, but causes more adverse effects on PaO_2.

Bradycardia (symptomatic) or hypotension (not responsive to atropine or pacing):*I.V. infusion:* 2-10 mcg/minute; titrate to desired effect

Bronchodilator:

SubQ: 0.3-0.5 mg **(1:1000)** every 20 minutes for 3 doses

Nebulization: 1-3 inhalations up to every 3 hours using solution prepared with 10 drops of the **1:100** product (solution for oral inhalation [Adrenalin®])

S2® (racepinephrine, OTC labeling): 0.5 mL up to every 3-4 hours if needed. Solution should be diluted if using jet nebulizer.

Inhalation: Primatene® Mist (OTC labeling): One inhalation, wait at least 1 minute; if not relieved, may use once more. Do not use again for at least 3 hours.

Decongestant:*Intranasal:* Apply 1:1000 locally as drops or spray or with sterile swab

Hypersensitivity reaction:

SubQ, I.M.: 0.3-0.5 mg (1:1000) every 15-20 minutes if condition requires (I.M. route is preferred)

I.V.: 0.1 mg (1:10,000) over 5 minutes. May infuse at 1-4 mcg/minute to prevent the need to repeat injections frequently.

Self-administration following severe allergic reactions (eg, insect stings, food): **Note:** The World Health Organization (WHO) and Anaphylaxis Canada recommend the availability of one dose for every 10 to 20 minutes of travel time to a medical emergency facility. More than 2 doses should only be administered under direct medical supervision.

Twinject™: SubQ, I.M.: 0.3 mg

EpiPen®: I.M.: 0.3 mg

Shock, fluid-resistant (unlabeled use): *I.V. infusion:* 2-10 mcg/minute, titrate dose to blood pressure effect (AHA, 2005)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Cardiac arrest: I.V.: Neonates: 0.01-0.03 mg/kg (0.1-0.3 mL/kg of **1:10,000** solution) every 3-5 minutes as needed. Although I.V. route is preferred, may consider administration of doses up to 0.1 mg/kg through the endotracheal tube until I.V. access established; dilute intratracheal doses to 1-2 mL with normal saline.

Asystole/pulseless arrest, bradycardia, VT/VF (after failed defibrillations):

I.V., I.O.: Infants and Children: 0.01 mg/kg (0.1 mL/kg of **1:10,000** solution) every 3-5 minutes as needed (maximum: 1 mg)

Intratracheal: Infants and Children: 0.1 mg/kg (0.1 mL/kg of **1:1000** solution) every 3-5 minutes (maximum: 10 mg)

Continuous I.V. infusion: Infants and Children: 0.1-1 mcg/kg/minute; doses <0.3 mcg/kg/minute generally produce β-adrenergic effects and higher doses generally produce α-adrenergic vasoconstriction; titrate dosage to desired effect

Bronchodilator:

SubQ: Infants and Children: 0.01 mg/kg (0.01 mL/kg of **1:1000**) (single doses not to exceed 0.5 mg) every 20 minutes for 3 doses

Nebulization:

Infants and Children: 1-3 inhalations up to every 3 hours using solution prepared with 10 drops of **1:100** (solution for oral inhalation [Adrenalin®])

Children <4 years: S2® (racepinephrine, OTC labeling): Croup: 0.05 mL/kg (max 0.5 mL/dose); dilute in NS 3 mL. Administer over ~15 minutes; do not administer more frequently than every 2 hours.

Inhalation: Children ≥4 years: Primatene® Mist: Refer to adult dosing.

Decongestant: Children ≥6 years: Refer to adult dosing.

Hypersensitivity reaction:

SubQ, I.V.: 0.01 mg/kg every 20 minutes; larger doses or continuous infusion may be needed for some anaphylactic reactions

Self-administration following severe allergic reactions (eg, insect stings, food): **Note:** World Health Organization (WHO) and Anaphylaxis Canada recommend the availability of 1 dose for every 10-20 minutes of travel time to a medical emergency facility:

Twinject™: SubQ, I.M.:

Children 15-30 kg: 0.15 mg

Children >30 kg: 0.3 mg

EpiPen® Jr: I.M.: Children <30 kg: 0.15 mg

EpiPen®: I.M.: Children ≥30 kg: 0.3 mg

Shock, fluid-resistant (unlabeled use): *Continuous I.V. infusion:* 0.1-1 mcg/kg/minute; doses up to 5 mcg/kg/minute may rarely be necessary (Hegenbarth, 2008)

Calculations

- Epinephrine
- Epinephrine, Weight-Based

Administration: I.M.I.M. administration into the buttocks should be avoided.

Administration: I.V.Central line administration only. I.V. infusions require an infusion pump. Epinephrine solutions for injection can be administered SubQ, I.M., I.V., I.O.

Administration: I.V. Detail **Extravasation management:** Use phentolamine as antidote. Mix 5 mg with 9 mL of NS. Inject a small amount of this dilution into extravasated area. Blanching should reverse immediately. Monitor site. If blanching should recur, additional injections of phentolamine may be needed.

pH: 2.5-5.0

Administration: InhalationS2®: Administer over ~15 minutes; must be diluted if using jet nebulizer.

Administration: OtherIntratracheal: Dilute in NS or distilled water. Absorption is greater with distilled water, but causes more adverse effects on PaO_2. Pass catheter beyond tip of tracheal tube, stop compressions, spray drug quickly down tube. Follow immediately with several quick insufflations and continue chest compressions.

StorageEpinephrine is sensitive to light and air. Protection from light is recommended. Oxidation turns drug pink, then a brown color. **Solutions should not be used if they are discolored or contain a precipitate.**

Adrenalin®: Store between 15°C to 25°C (59°F to 77°F); do not freeze. Protect from light. The 1:1000 solution should be discarded 30 days after initial use.

Raphon: Store between 2°C to 25°C (36°F to 77°F). Refrigerate after opening.

Twinject™: Store between 20°C to 25°C (68°F to 77°F); do not freeze or refrigerate. Protect from light.

Stability of injection of parenteral admixture at room temperature (25°C) or refrigeration (4°C) is 24 hours.

Reconstitution

Standard I.V. diluent: 1 mg/250 mL NS.

Preparation of adult I.V. infusion: Dilute 1 mg in 250 mL of D_5W or NS (4 mcg/mL).

S2®: Dilution not required when administered via hand-nebulizer; dilute with NS 3-5 mL if using jet nebulizer.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, $D_{10}NS$, LR, NS; **incompatible** with sodium bicarbonate 5%.

Y-site administration: Compatible: Atracurium, calcium chloride, calcium gluconate, cisatracurium, diltiazem, dobutamine, dopamine, famotidine, fentanyl, furosemide, heparin, hydrocortisone sodium succinate, hydromorphone, inamrinone, labetalol, levofloxacin, lorazepam, midazolam, milrinone, morphine, nicardipine, nitroglycerin, norepinephrine, pancuronium, phytonadione, potassium chloride, propofol, ranitidine, remifentanil, vecuronium, vitamin B complex with C, warfarin. **Incompatible:** Ampicillin, thiopental.

Compatibility in syringe: Compatible: Diatrizoate meglumine 52%, diatrizoate sodium 8%, diatrizoate sodium 60%, doxapram, heparin, iohexol, iopamidol, iothalamate meglumine 60%, ioxaglate 39.3%, ioxaglate sodium 19.6%, milrinone. **Variable (consult detailed reference):** Sodium bicarbonate.

Compatibility when admixed: Compatible: Amikacin, bupivacaine, cimetidine, dobutamine, fentanyl, floxacillin, furosemide, metaraminol, ranitidine, verapamil. **Incompatible:** Aminophylline, hyaluronidase, mephentermine, sodium bicarbonate.

ContraindicationsHypersensitivity to epinephrine or any component of the formulation; cardiac arrhythmias; angle-closure glaucoma

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular diseases (angina, tachycardia, myocardial infarction).
- Cerebrovascular disease: Use with caution in patients with cerebrovascular disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Parkinson's disease: Use with caution in patients with Parkinson's disease.
- Thyroid disease: Use with caution in patients with thyroid disease.

Concurrent drug therapy issues:

- Monoamine oxidase inhibitors (MAO-I): Use with extreme caution in patients taking MAO inhibitors; prolong hypertension may result from concurrent use.

Special populations:

- Elderly: Use with caution in the elderly.

Dosage form specific issues:

- I.V. infusion: Rapid I.V. infusion may cause death from cerebrovascular hemorrhage or cardiac arrhythmias.
- Oral inhalation: Oral inhalation of epinephrine is **not** the preferred route of administration.
- Sulfites: Some products contain sulfites as preservatives.
- Topical: Avoid topical application where reduced perfusion could lead to ischemic tissue damage (eg, penis, ears, digits).

Geriatric ConsiderationsThe use of epinephrine in the treatment of acute exacerbations of asthma was studied in the elderly. A dose of 0.3 mg SubQ every 20 minutes for three doses was well tolerated in elderly patients with no history of angina or recent myocardial infarction. There was no significant difference in the incidence of ventricular arrhythmias in elderly versus younger adults.

Pregnancy Risk FactorC

Pregnancy ConsiderationsCrosses the placenta. Reported association with malformations in 1 study; may be secondary to severe maternal disease.

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined.

Cardiovascular: Angina, cardiac arrhythmia, chest pain, flushing, hypertension, increased myocardial oxygen consumption, pallor, palpitation, sudden death, tachycardia (parenteral), vasoconstriction, ventricular ectopy

Central nervous system: Anxiety, dizziness, headache, insomnia, lightheadedness, nervousness, restlessness

Gastrointestinal: Dry throat, nausea, vomiting, xerostomia

Genitourinary: Acute urinary retention in patients with bladder outflow obstruction

Neuromuscular & skeletal: Trembling, weakness

Ocular: Allergic lid reaction, burning, eye pain, ocular irritation, precipitation of or exacerbation of narrow-angle glaucoma, transient stinging

Renal: Decreased renal and splanchnic blood flow

Respiratory: Dyspnea, wheezing

Miscellaneous: Diaphoresis increased

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. *Risk D: Consider therapy modification*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

COMT Inhibitors: May decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

Inhalational Anesthetics: May enhance the arrhythmogenic effect of EPINEPHrine. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid ephedra, yohimbe (may cause CNS stimulation).

Test InteractionsIncreased bilirubin (S), catecholamines (U), glucose, uric acid (S)

Monitoring ParametersPulmonary function, heart rate, blood pressure, site of infusion for blanching, extravasation; cardiac monitor and blood pressure monitor required. If using to treat hypotension, assess intravascular volume and support as needed.

Reference RangeTherapeutic: 31-95 pg/mL (SI: 170-520 pmol/L)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness (according to purpose for use) and adverse reactions. Monitor vital signs. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. I.V. central line with infusion pump and continuous cardiac/hemodynamic monitoring is necessary.

Patient EducationUse this medication exactly as directed; do not take more than recommended dosage. Avoid other stimulant prescriptive or OTC medications to avoid serious overdose reactions. You may experience dizziness, blurred vision, restlessness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or difficulty urinating (empty bladder immediately before taking this medication). Report excessive nervousness or excitation, inability to sleep, facial flushing, pounding heartbeat, muscle tremors or weakness, chest pain or palpitations, bronchial irritation or coughing, or increased sweating.

Aerosol: Use aerosol or nebulizer as per instructions. Clear as much mucus as possible before use. Rinse mouth following each use. If more than one inhalation is necessary, wait 1 minute between inhalations. May cause restlessness or nervousness; use caution when driving or engaging in hazardous activities until response to medication is known. Report persistent nervousness, restlessness, sleeplessness, palpitations, tachycardia, chest pain, muscle tremors, dizziness, flushing, or if breathing difficulty persists.

Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol for oral inhalation:

Primatene® Mist: 0.22 mg/inhalation (15 mL, 22.5 mL) [contains CFCs]

Injection, solution [prefilled auto injector]:

EpiPen®: 0.3 mg/0.3 mL (2 mL) [1:1000 solution; delivers 0.3 mg per injection; contains sodium metabisulfite; available as single unit or in double-unit pack with training unit]

EpiPen® Jr: 0.15 mg/0.3 mL (2 mL) [1:2000 solution; delivers 0.15 mg per injection; contains sodium metabisulfite; available as single unit or in double-unit pack with training unit]

Twinject™: 0.15 mg/0.15 mL (1.1 mL) [1:1000 solution; delivers 0.15 mg per injection; contains sodium bisulfite; two 0.15 mg doses per injector]; 0.3 mg/0.3 mL (1.1 mL) [1:1000 solution; delivers 0.3 mg per injection; contains sodium bisulfite; two 0.3 mg doses per injector]

Injection, solution, as hydrochloride: 0.1 mg/mL (10 mL) [1:10,000 solution]; 1 mg/mL (1 mL) [1:1000 solution]

Adrenalin®: 1 mg/mL (1 mL) [1:1000 solution; contains sodium bisulfite]

Adrenalin®: 1 mg/mL (30 mL) [1:1000 solution; contains chlorobutanol, sodium bisulfite]

Solution for oral inhalation, as hydrochloride:

Adrenalin®: 1% (7.5 mL) [10 mg/mL, 1:100 solution; contains sodium bisulfite]

Solution for oral inhalation [racepinephrine; preservative free]:

S2®: 2.25% (0.5 mL) [as d-epinephrine 1.125% and l-epinephrine 1.125%]

Solution, intranasal, as hydrochloride [drops, spray]:

Adrenalin®: 1 mg/mL [1:1000 solution; contains sodium bisulfite]

Solution, topical [racepinephrine]:

Raphon: 2.25% (15 mL) [as d-epinephrine 1.125% and l-epinephrine 1.125%; contains benzoic acid, metabisulfites]

Generic AvailableYes: Solution for injection

Pricing: U.S. (www.drugstore.com)

Device (EpiPen)

0.3 MG/0.3ML (1:1000) (1): $61.99

Device (EpiPen 2-Pak)

0.3 MG/0.3ML (1:1000) (2): $115.99

Device (EpiPen Jr)

0.15 MG/0.3ML (1:2000) (1): $64.99

Device (EpiPen Jr 2-Pak)

0.15 MG/0.3ML (1:2000) (2): $109.99

Device (Twinject)

0.15 mg/dose (1): $86.63

Nebulization (S-2)

2.25% (15): $27.99

Solution (EPINEPHrine HCl)

1 mg/mL (3): $8.99

Mechanism of ActionStimulates alpha-, beta$_1$-, and beta$_2$-adrenergic receptors resulting in relaxation of smooth muscle of the bronchial tree, cardiac stimulation, and dilation of skeletal muscle vasculature; small doses can cause vasodilation via beta$_2$-vascular receptors; large doses may produce constriction of skeletal and vascular smooth muscle

Pharmacodynamics/Kinetics

Onset of action: Bronchodilation: SubQ: ~5-10 minutes; Inhalation: ~1 minute

Distribution: Crosses placenta

Metabolism: Taken up into the adrenergic neuron and metabolized by monoamine oxidase and catechol-o-methyltransferase; circulating drug hepatically metabolized

Excretion: Urine (as inactive metabolites, metanephrine, and sulfate and hydroxy derivatives of mandelic acid, small amounts as unchanged drug)

Pharmacotherapy PearlsTwinject® and EpiPen® are not interchangeable due to packaging considerations.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and dry throat.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNervousness and restlessness are common; may cause insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported; however, use cautiously with psychotropics that block alpha-receptors (phenothiazines); may produce paradoxical hypotension

Anesthesia and Critical Care Concerns/Other Considerations

Septic Shock: Epinephrine's use may be limited by its effects on renal and gastric blood flow and its propensity to increase lactic acid concentrations.

Cardiac Arrest: Epinephrine can be given by endotracheal route during cardiac resuscitation. High-intravenous dose epinephrine (0.1 mg/kg) has not shown to improve survival or neurological outcomes. May have more postresuscitation complications than survivors who receive standard dose epinephrine. Eight randomized clinical studies (>9000 patients) have found no improvement in survival to hospital discharge or neurological outcomes compared with standard epinephrine.

A prospective, multicenter, double-blind randomized, controlled trial evaluated the efficacy of vasopressin or epinephrine when administered to adult patients who suffered an out-of-hospital cardiac arrest (Wenzel, 2004). For inclusions, patients presented with ventricular fibrillation, pulseless electrical activity, or asystole. They were excluded if they were successfully defibrillated without the administration of a vasopressor, had a terminal illness or had a DNR order, a lack of intravenous access, hemorrhagic shock, pregnancy, cardiac arrest due to trauma, or were <18 years of age. Eligible patients were randomized to intravenous vasopressin (40 units) or epinephrine (1 mg). Each patient received an injection of the study drug, if spontaneous circulation was not restored in 3 minutes they received a second dose (same amount) of the same study drug. If there was no response, the managing physician had the option of giving epinephrine. Patients with ventricular fibrillation were randomized after the first three attempts at defibrillation failed; all others were randomized immediately. The primary endpoint was survival to hospital admission; the secondary endpoint was survival to hospital discharge. Five hundred and eighty-nine patients were randomized to vasopressin and five hundred and ninety-seven patients were randomized to epinephrine. There was no significant difference in the rate of hospital admission between the vasopressin group and the epinephrine group if they had ventricular fibrillation (46.2% vs 43% respectively, p: 0.48) or pulseless electrical activity (33.7% vs 30.5% respectively, p: 0.65). Patients with asystole responded significantly better to vasopressin; having higher rates of hospital admission (29% vs 20.3% in the epinephrine group, p: 0.02) and hospital discharge (4.7% vs 1.5% in the epinephrine group, p: 0.04). Patients who failed vasopressin therapy and received additional epinephrine had significant improvement in survival to hospital admission (25.7% vs 16.4% in the epinephrine group, p: 0.002) and discharge (6.2% vs 1.7%, p: 0.002). Similar patients who were randomized to epinephrine and failed to respond did not improve with additional epinephrine. Cerebral performance among all patients who survived to discharge was similar in both groups. In this trial, vasopressin was superior to epinephrine in patients with asystole. Vasopressin followed by epinephrine may be more effective than epinephrine alone in refractory out-of-hospital cardiac arrest.

A small in-hospital cardiac arrest study evaluated the efficacy of vasopressin or epinephrine in 200 patients. These investigators did not find any differences between the two treatment groups with regard to survival, discharge, or cerebral performance (Stiell, 2001).

Index TermsAdrenaline; Epinephrine Bitartrate; Epinephrine Hydrochloride; Racepinephrine

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International Brand NamesAdreject (ES); Adrenalin (BG, DE, FI, LU, SE, TR); Adrenalin Jenapharm (DE); Adrenalin Medihaler (DE); Adrenalina

(AR, ES, IT); Adrenalina Apolo (AR); Adrenalina Biol (AR); Adrenalina Braun (ES); Adrenalina Fada (AR); Adrenalina Larjan (AR); Adrenalina Level (ES); Adrenalina Miro (ES); Adrenalina Sintetica (CH); Adrenaline (GR, RU); Adrenaline Aguettant (FR); Adrenaline Injection (AU); Adrenaline-Parke-Davis (LU); Adrenalini Bitarticas (ID); Adrenin (PH); Ana-Guard (ZA); Anapen (FR); Anaphylaxie-Besteck (DE); Bosmin (TW); Clorhidrato de adrenalina Richmond (AR); Diopine (DE); Epifrin (LU); Epinefrina (CN); Epipen (AU, BE, CZ, DK, IL, MY, NO, PT); EpiPen (NL); Epipen Jr. 0.15mg Adrenaline Auto-Injector (AU); Epipen Junior (IL, MY); Eppy (IE, IT, ZA); Eppystabil (AT); Fastjekt (DE, LU, PL); Fastjekt Injektor (DE); Infectokrupp (DE); Injectio Adrenalini (PL); L-Adrenalin (AT); Medihaler-Iso (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Posumin (TW); Sanepi (JP); Simplene (GB, IE, ZA); Suprarenin (AT, DE, HR); Tonogen (HU); Weimer Adrenaline (HK, PH); Weradren (PH); Xylodont (PL)

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Esophageal Cancer

Regimen Use Esophageal cancer

Index Terms ECX (Esophageal Cancer)

Regimen

Epirubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Cisplatin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Capecitabine: Oral: 625 mg/m^2 twice daily days 1 to 21

[total dose/cycle = 26,250 mg/m^2]

Repeat cycle every 21 days for up to 8 cycles

References

Cunningham D, Starling N, Rao S, et al, "Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer," *N Engl J Med*, 2008, 358(1):36-46.[PubMed 18172173]

Epirubicin-Oxaliplatin-Capecitabine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Esophageal Cancer; Chemotherapy Regimen, Gastric Cancer

Regimen Use Esophageal cancer; Gastric cancer

Index Terms Capecitabine-Oxaliplatin-Epirubicin; EOX; Oxaliplatin-Capecitabine-Epirubicin

Regimen

Epirubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Oxaliplatin: I.V.: 130 mg/m^2 day 1

[total dose/cycle = 130 mg/m^2]

Capecitabine: Oral: 625 mg/m^2 twice daily days 1 to 21

[total dose/cycle = 26,250 mg/m^2]

Repeat cycle every 21 days for up to 8 cycles

References

Cunningham D, Starling N, Rao S, et al, "Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer," *N Engl J Med*, 2008, 358(1):36-46.[PubMed 18172173]

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Esophageal Cancer

Regimen Use Esophageal cancer

Index Terms EOF (Esophageal Cancer)

Regimen

Epirubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Oxaliplatin: I.V.: 130 mg/m^2 day 1

[total dose/cycle = 130 mg/m^2]

Fluorouracil: I.V.: 200 mg/m^2/day continuous infusion days 1 to 21

[total dose/cycle = 4200 mg/m^2]

Repeat cycle every 21 days for up to 8 cycles

References

Cunningham D, Starling N, Rao S, et al, "Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer," *N Engl J Med*, 2008, 358(1):36-46.[PubMed 18172173]

Epirubicin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Epirubicin may be confused with DOXOrubicin, DAUNOrubicin, idarubicin

Ellence® may be confused with Elase®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ep i ROO bi sin)

U.S. Brand NamesEllence®

Canadian Brand NamesEllence®; Pharmorubicin®

Pharmacologic CategoryAntineoplastic Agent, Anthracycline

Use: Labeled IndicationsAdjuvant therapy for primary breast cancer

Dosing: AdultsI.V.: 100-120 mg/m^2 once weekly every 3-4 weeks **or** 50-60 mg/m^2 days 1 and 8 every 3-4 weeks

Breast cancer:

CEF-120: 60 mg/m^2 on days 1 and 8 every 28 days for 6 cycles

FEC-100: 100 mg/m^2 on day 1 every 21 days for 6 cycles

Note: Patients receiving 120 mg/m^2/cycle as part of combination therapy should also receive prophylactic therapy with sulfamethoxazole/trimethoprim or a fluoroquinolone.

Dosage modifications:

Delay day 1 dose until platelets are ≥100,000/mm^3, ANC ≥1500/mm^3, and nonhematologic toxicities have recovered to ≤grade 1

Reduce day 1 dose in subsequent cycles to 75% of previous day 1 dose if patient experiences nadir platelet counts <50,000/mm^3, ANC <250/mm^3, neutropenic fever, or grade 3/4 nonhematologic toxicity during the previous cycle

For divided doses (day 1 and day 8), reduce day 8 dose to 75% of day 1 dose if platelet counts are 75,000-100,000/mm^3 and ANC is 1000-1499/mm^3; omit day 8 dose if platelets are <75,000/mm^3, ANC <1000/mm^3, or grade 3/4 nonhematologic toxicity

Dosage adjustment in bone marrow dysfunction: Heavily-treated patients, patients with pre-existing bone marrow depression or neoplastic bone marrow infiltration: Lower starting doses (75-90 mg/mm^2) should be considered.

Dosing: ElderlyPlasma clearance of epirubicin in elderly female patients was noted to be reduced by 35%. Although no initial dosage reduction is specifically recommended, particular care should be exercised in monitoring toxicity and adjusting subsequent dosage in elderly patients (particularly females >70 years of age).

Dosing: Renal ImpairmentThe FDA-approved labeling recommends that in patients with severe renal impairment (serum creatinine >5 mg/dL), lower doses should be considered. Aronoff (2007) recommends no dosage adjustment needed for Cl_{cr} <50 mL/minute.

Dosing: Hepatic ImpairmentThe FDA-approved labeling recommends the following guidelines (based on clinical trial information):

Bilirubin 1.2-3 mg/dL or AST 2-4 times the upper limit of normal: Administer 50% of recommended starting dose.

Bilirubin >3 mg/dL or AST >4 times the upper limit of normal: Administer 25% of recommended starting dose.

Severe hepatic impairment: Use is contraindicated.

Dosing: Combination Regimens

Breast cancer:

CEF

Docetaxel-FEC

Docetaxel-Trastuzumab-FEC

FEC

Tamoxifen-Epirubicin

TEX (Capecitabine + Docetaxel + Epirubicin)

Vinorelbine-FEC

Vinorelbine-Trastuzumab-FEC

Esophageal cancer: Epirubicin-Oxaliplatin-Capecitabine

Gastric cancer:

ECF

Epirubicin-Oxaliplatin-Capecitabine

Rhabdomyosarcoma: CEV

Calculations

- ANC: Absolute Neutrophil Count
- Body Surface Area: Adults

Administration: I.V.Infuse over 15-20 minutes or slow I.V. push (for lower doses [due to dose modification or organ dysfunction]) over 3-10 minutes

StorageStore intact vials of solution under refrigeration at 2°C to 8°C (36°F to 46°F). Store intact vials of lyophilized powder at room temperature 15°C to 30°C (59°F to 86°F). Protect from light. Reconstituted solutions and solutions for infusion are stable for 24 hours when stored at 2°C to 8°C (36°F to 46°F).

Reconstitution Reconstitute lyophilized powder with SWFI to a final concentration of 2 mg/mL. May administer undiluted for IVP or dilute in 50-250 mL NS or D_5W for infusion.

CompatibilityStable in D_5W, LR, NS; **incompatible** with heparin, fluorouracil, or any solution of alkaline pH.

Compatibility in syringe: Compatible: Ifosfamide. **Incompatible:** Fluorouracil, heparin, ifosfamide with mesna, any solution of alkaline pH.

ContraindicationsHypersensitivity to epirubicin or any component of the formulation, other anthracyclines, or anthracenediones; previous anthracycline treatment up to maximum cumulative dose; severe myocardial insufficiency, severe arrhythmias; recent myocardial infarction; severe hepatic dysfunction; baseline neutrophil count 1500 cells/mm^3; pregnancy

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See "Concerns related to adverse effects" below.
- Experienced physician: See "Other warnings/precautions" below.
- Hepatic impairment: See "Disease-related concerns" below.
- Myocardial toxicity: See "Concerns related to adverse effects" below.
- Secondary malignancy: See "Concerns related to adverse effects" below.
- Skin irritation/extravasation: See "Concerns related to adverse effects" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: May cause severe myelosuppression;** neutropenia is the dose-limiting toxicity; severe thrombocytopenia or anemia may occur.
- Myocardial toxicity: **[U.S. Boxed Warning]: May cause cumulative dose-related myocardial toxicity (concurrent or delayed);** particularly in patients who have received prior anthracyclines, prior or concomitant radiotherapy to the mediastinal/pericardial area, or who have pre-existing cardiac disease. Acute toxicity (primarily arrhythmias) and delayed toxicity (HF) have been described. Delayed toxicity usually develops late in the course of therapy or within 2-3 months after completion, however, events with an onset of several months to years after termination of treatment have been described. The risk of delayed cardiotoxicity increases more steeply with cumulative doses >900 mg/m^2, and this dose should be exceeded only with extreme caution. (The risk of HF is ~0.9% at a cumulative dose of 550 mg/m^2, ~1.6% at a cumulative dose of 700 mg/m^2, and ~3.3% at a cumulative dose of 900 mg/m^2.) Toxicity may be additive with other anthracyclines or anthracenediones, and may be increased in pediatric patients. Regular monitoring of LVEF and discontinuation at the first sign of impairment is recommended especially in patients with cardiac risk factors or impaired cardiac function.
- Secondary malignancy: **[U.S. Boxed Warning]: Treatment with anthracyclines may increase the risk of secondary leukemias.**
- Skin irritation/extravasation: **[U.S. Boxed Warning]: For I.V. administration only. Vesicant; if extravasation occurs, severe local tissue damage and necrosis may occur.**
- Thromboembolic events: Thrombophlebitis and thromboembolic phenomena (including pulmonary embolism) have occurred.

- Tumor lysis syndrome: May cause tumor lysis syndrome.

Disease-related concerns:

- Hepatic impairment: **[U.S. Boxed Warning]: Use with caution in patients with mild-to-moderate hepatic impairment;** dosage reduction is recommended.
- Renal impairment: Use with caution in patients with renal impairment (serum creatinine >5 mg/dL).

Special populations:

- Elderly: Women ≥70 years of age should be especially monitored for toxicity.
- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: Women of childbearing age should be advised to avoid becoming pregnant.
- Radiation recipients: Epirubicin may have radiosensitizing activity; radiation recall has also been reported.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenic effects and embryotoxicity were noted in animal studies. There are no adequate and well-controlled studies in pregnant women. If a pregnant woman is treated with epirubicin, or if a woman becomes pregnant while receiving this drug, she should be informed of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant. Men undergoing treatment should use effective contraception.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsExcretion in human breast milk is unknown, however, other anthracyclines are excreted. Breast-feeding is contraindicated.

Adverse ReactionsPercentages reported as part of combination chemotherapy regimens.

>10%:

Central nervous system: Lethargy (1% to 46%)

Dermatologic: Alopecia (69% to 96%)

Endocrine & metabolic: Amenorrhea (69% to 72%), hot flashes (5% to 39%)

Gastrointestinal: Nausea/vomiting (83% to 92%), mucositis (9% to 59%), diarrhea (7% to 25%)

Hematologic: Leukopenia (50% to 80%; grades 3/4: 2% to 59%), neutropenia (54% to 80%; grades 3/4: 11% to 67%; nadir: 10-14 days; recovery: 21 days), anemia (13% to 72%; grades 3/4: 6%), thrombocytopenia (5% to 49%; grades 3/4: 5%)

Local: Injection site reactions (3% to 20%)

Ocular: Conjunctivitis (1% to 15%)

Miscellaneous: Infection (15% to 21%)

1% to 10%:

Cardiovascular: CHF (0.4% to 1.5%), decreased LVEF (asymptomatic) (1% to 2%); recommended maximum cumulative dose: 900 mg/m^2

Central nervous system: Fever (1% to 5%)

Dermatologic: Rash (1% to 9%), skin changes (1% to 5%)

Gastrointestinal: Anorexia (2% to 3%)

Hematologic: Neutropenic fever (grades 3/4: 6%)

<1%, postmarketing, case reports, and/or frequency not defined: Acute lymphoid leukemia; acute myelogenous leukemia (0.3% at 3 years, 0.5% at 5 years, 0.6% at 8 years); anaphylaxis, atrioventricular block, bradycardia, bundle-branch block, cardiomyopathy, ECG abnormalities, hypersensitivity, myelodysplastic syndrome, photosensitivity, premature menopause, premature ventricular contractions, pulmonary embolism, radiation recall, sinus tachycardia, skin and nail hyperpigmentation, ST-T wave changes (nonspecific), tachyarrhythmias, thromboembolism, thrombophlebitis, transaminases increased, urticaria, ventricular tachycardia

Oncology: VesicantYes

Oncology: Emetic PotentialModerate-to-high (30% to 90%)

Drug Interactions

Bevacizumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk C: Monitor therapy*

Cardiac Glycosides: May diminish the cardiotoxic effect of Antineoplastic Agents (Anthracycline). Antineoplastic Agents (Anthracycline) may decrease the serum concentration of Cardiac Glycosides. The effects of liposomal formulations may be unique from those of the free drug, as liposomal formulation have unique drug disposition and toxicity profiles, and liposomes themselves may alter digoxin absorption/distribution. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Taxane Derivatives: May enhance the adverse/toxic effect of Antineoplastic Agents (Anthracycline). Taxane Derivatives may increase the serum concentration of Antineoplastic Agents (Anthracycline). Taxane Derivatives may also increase the formation of toxic anthracycline metabolites in heart tissue. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (due to GI irritation).

Herb/Nutraceutical: Avoid black cohosh, dong quai in estrogen-dependent tumors.

Monitoring ParametersMonitor injection site during infusion for possible extravasation or local reactions; CBC with differential and platelet count, liver function tests, renal function, ECG, and left ventricular ejection fraction. Monitor during therapy for potential cardiotoxicity with ECHO or with MUGA scans (patients with higher cumulative doses).

Nursing: Physical Assessment/MonitoringAssess potential for interactions with herbal products patient may taking (see Nutritional/Ethanol Interactions). Note infusion specifics in Administration. Premedication with an antiemetic may be useful (emetogenic). Infusion site must be monitored closely to prevent extravasation; severe local tissue necrosis will result if extravasation occurs. Evaluate results of laboratory tests and patient response prior to each treatment and on a regular basis during therapy (eg, acute nausea and vomiting, anemia, infection, bleeding, and cardiotoxicity) (Note: cardiotoxicity may occur 1 to several months after termination of treatment). Teach patient possible side effects/appropriate interventions (eg, importance of adequate hydration) and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelet count, liver function tests, renal function, ECG, and left ventricular ejection fraction (baseline and repeated measurement). The method used for assessment of LVEF (echocardiogram or MUGA) should be consistent during routine monitoring.

Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. This medication can only be administered by infusion. Report immediately any swelling, pain, burning, or redness at infusion site, sudden difficulty breathing or swallowing, chest pain, or chills. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and adequate nutrition (small, frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, or yogurt may help); loss of hair (reversible); hyperpigmentation of skin or nails; mouth sores (frequent mouth care, soft toothbrush may help); or changes in menstrual cycle (consult prescriber). Report chest pain, swelling of extremities, palpitations, or rapid heartbeat; respiratory difficulty or unusual cough; pain, redness, unusual warmth in extremities; unresolved nausea, vomiting, or diarrhea; alterations in urinary pattern (increased or decreased); opportunistic infection (fever, chills, unusual bruising or bleeding, fatigue, purulent vaginal discharge, unhealed mouth sores); skin rash; abdominal pain; blood in urine or stool; or other unresolved reactions. **Pregnancy/breast-feeding precautions:** Female: Do not get pregnant while taking this medication and for 1 month following therapy. Male undergoing treatment: Do not cause a pregnancy. This drug may cause severe fetal defects. Consult prescriber for appropriate barrier contraceptives. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as hydrochloride, [preservative free]: 50 mg, 200 mg [contains lactose]

Injection, solution, as hydrochloride [preservative free]: 2 mg/mL (5 mL, 25 mL, 75 mL, 100 mL)

Ellence®: 2 mg/mL (25 mL, 100 mL)

Generic AvailableYes

Mechanism of ActionEpirubicin is an anthracycline antibiotic; known to inhibit DNA and RNA synthesis by steric obstruction after intercalating between DNA base pairs; active throughout entire cell cycle. Intercalation triggers DNA cleavage by topoisomerase II, resulting in cytocidal activity. Also inhibits DNA helicase, and generates cytotoxic free radicals.

Pharmacodynamics/Kinetics

Distribution: V_{ss}: 21-27 L/kg

Protein binding: 77% to albumin

Metabolism: Extensively via hepatic and extrahepatic (including RBCs) routes

Half-life elimination: Triphasic; Mean terminal: 33 hours

Excretion: Feces (34% to 35%); urine (20% to 27%)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusLethargy is common

Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; use caution with clozapine and carbamazepine

Index TermsEpirubicin Hydrochloride; NSC-256942; Pidorubicin; Pidorubicin Hydrochloride

References

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Trudeau M and Pagani O, “Epirubicin in Combination With the Taxanes,” *Semin Oncol*, 2001, 28(4 Suppl 12):41-50.

International Brand NamesAnthracin (TH); Binarin (MX); Bioepicyna (PL); E.P.Mycin (TH); Epicin (TW); Epidoxo (PY); Epifil (AR); Epilem (MX, TH); Farmorrubicina RTU (CN); Farmorubicin (AE, AT, BG, BH, CH, CY, CZ, DE, DK, EG, FI, GR, HN, HR, HU, IL, IN, IQ, IR, JO, JP, KW, LB, LU, LY, MX, NO, OM, PK, PL, QA, RU, SA, SE, SY, TR, VE, YE, ZA); Farmorubicin CSU (ZA); Farmorubicin PFS (BG, EE); Farmorubicin RD (EE, ID, MX, TH, ZA); Farmorubicina (ES, IT, PE, PT); Farmorubicina CS (BR, CO, EC); Farmorubicina R.D. (BR); Farmorubicine (BE, FR, NL); Neoquabin (PH); Pharmorubicin (AU, GB, HK, IE, MY, PH); Pharmorubicin PDF (KP); Pharmorubicin PFS (KP, TW); Pharmorubucin RD (CL)

Medication Safety Issues

Sound-alike/look-alike issues:

Inspra™ may be confused with Spiriva®

Pronunciation(e PLER en one)

U.S. Brand NamesInspra™

Pharmacologic CategorySelective Aldosterone Blocker

Use: Labeled IndicationsTreatment of hypertension (may be used alone or in combination with other antihypertensive agents); treatment of heart failure (HF) following acute MI

Dosing: Adults

Hypertension: Oral: Initial: 50 mg once daily; may increase to 50 mg twice daily if response is not adequate; may take up to 4 weeks for full therapeutic response. Doses >100 mg/day are associated with increased risk of hyperkalemia and no greater therapeutic effect.

Dose modification during concurrent use with moderate CYP3A4 inhibitors: Initial: 25 mg once daily

Heart failure (post-MI): Oral: Initial: 25 mg once daily; dosage goal: Titrate to 50 mg once daily within 4 weeks, as tolerated

Dosage adjustment per serum potassium concentrations for HF (post-MI):

<5.0 mEq/L:

Increase dose from 25 mg every other day to 25 mg daily **or**

Increase dose from 25 mg daily to 50 mg daily

5.0-5.4 mEq/L: No adjustment needed

5.5-5.9 mEq/L:

Decrease dose from 50 mg daily to 25 mg daily **or**

Decrease dose from 25 mg daily to 25 mg every other day **or**

Decrease dose from 25 mg every other day to withhold medication

≥6.0 mEq/L: Withhold medication until potassium <5.5 mEq/L, then restart at 25 mg every other day

Dosing: ElderlyRefer to adult dosing. Also see Geriatric Considerations.

Dosing: Renal Impairment

Hypertension: Cl_{cr} <50 mL/minute or serum creatinine >2.0 mg/dL in males or >1.8 mg/dL in females: Use is contraindicated; risk of hyperkalemia increases with declining renal function

All other indications: Cl_{cr} ≤30 mL/minute: Use is contraindicated.

Dosing: Hepatic ImpairmentNo dosage adjustment needed for mild-to-moderate impairment. Safety and efficacy not established for severe impairment.

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken with or without food. Do not use salt substitutes containing potassium.

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsSerum potassium >5.5 mEq/L at initiation; Cl_{cr} ≤30 mL/minute; concomitant use of strong CYP3A4 inhibitors (see Drug Interactions for details)

The following additional contraindications apply to patients with hypertension: Type 2 diabetes mellitus (noninsulin dependent, NIDDM) with microalbuminuria; serum creatinine >2.0 mg/dL in males or >1.8 mg/dL in females; Cl_{cr} <50 mL/minute; concomitant use with potassium supplements or potassium-sparing diuretics

Warnings/Precautions

Concerns related to adverse effects:

- Hyperkalemia: Monitor closely for hyperkalemia; increases in serum potassium were dose related during clinical trials and rates of hyperkalemia also increased with declining renal function.

Disease-related concerns:

- Diabetes: Use with caution in heart failure patients post-MI with diabetes (especially if patient has proteinuria); risk of hyperkalemia is increased.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment; safety and efficacy have not been established.

- Renal impairment: Risk of hyperkalemia is increased with declining renal function. Use with caution in patients with mild renal impairment; contraindicated with moderate-severe impairment (HTN: Cl_{cr} <50 mL/minute; other indications: Cl_{cr} ≤30 mL/minute).

Concurrent drug therapy issues:

- High potential for interactions: Dosage adjustment needed for patients on moderate CYP3A4 inhibitors.

Geriatric ConsiderationsSince this medication is contraindicated in patients with a Cl_{cr} <50 mL/minute, it will have limited use in the elderly. Due to physiologic changes, elderly may be at increased risk of hyperkalemia when using this medication.

Pregnancy Risk FactorB

Pregnancy ConsiderationsNo teratogenic effects were seen in animal studies, however, there are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%: Endocrine & metabolic: Hyperkalemia ([HF post-MI: K >5.5 mEq/L: 16%; K ≥6 mEq/L: 6%] [HTN: K >5.5 mEq/L at doses ≤100 mg: ≤1%; doses >100 mg: 9%]), hypertriglyceridemia (1% to 15%, dose related)

1% to 10%:

Central nervous system: Dizziness (3%), fatigue (2%)

Endocrine & metabolic: Hyponatremia (2%, dose related), breast pain (males <1% to 1%), gynecomastia (males <1% to 1%), hypercholesterolemia (<1% to 1%)

Gastrointestinal: Diarrhea (2%), abdominal pain (1%)

Genitourinary: Abnormal vaginal bleeding (<1% to 2%)

Renal: Creatinine increased (HF post-MI: 6%), albuminuria (1%)

Respiratory: Cough (2%)

Miscellaneous: Flu-like syndrome (2%)

<1%, postmarketing, and/or case reports: Angioneurotic edema, BUN increased, liver function tests increased, rash, uric acid increased

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)

Drug Interactions

ACE Inhibitors: Eplerenone may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: Eplerenone may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Eplerenone. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Eplerenone. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Potassium Salts: Eplerenone may enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Eplerenone may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Grapefruit juice increases eplerenone AUC ~25%.

Herb/Nutraceutical: St John's wort may decrease levels of eplerenone. Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse(may have increased antihypertensive effect). Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may diminish the antihypertensive effect).

Monitoring ParametersBlood pressure; serum potassium (levels monitored prior to therapy, within the first week, and at 1 month after start of treatment or dose adjustment, then periodically [monthly in clinical trials]); renal function

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking; (eg, increased risk of toxicity). Assess results of laboratory tests prior to and periodically during therapy (potassium levels, renal function), therapeutic effectiveness (blood pressure), and adverse response at beginning of and at regular intervals during therapy (eg, hypotension, hyperkalemia). Teach patient proper use, possible side effects/appropriate interventions, and adverse reactions to report.

Monitoring: Lab TestsSerum potassium (levels monitored prior to therapy, within the first week, and at 1 month after start of treatment or dose adjustment, then periodically [monthly in clinical trials]); renal function

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take exactly as directed at the same time of day, without regard for meals. Do not alter dose or discontinue without consulting prescriber; it may take up to 4 weeks to achieve desired results. Do not use potassium supplement or salt substitutes without consulting prescriber. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause dizziness, fainting, lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); diarrhea (boiled milk, buttermilk, or yogurt may help); breast pain (males); abnormal vaginal bleeding. Report chest pain, palpitations; unusual cough or flu-like symptoms; or other persistent or severe adverse effects. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 25 mg, 50 mg

Inspra™: 25 mg, 50 mg

Generic AvailableYes

ManufacturerPfizer

Pricing: U.S. (www.drugstore.com)

Tablets (Inspra)

25 mg (30): $122.00

50 mg (30): $121.79

Mechanism of ActionAldosterone, a mineralocorticoid, increases blood pressure primarily by inducing sodium and water retention. Overexpression of aldosterone is thought to contribute to myocardial fibrosis (especially following myocardial infarction) and vascular fibrosis. Mineralocorticoid receptors are located in the kidney, heart, blood vessels, and brain. Eplerenone selectively blocks mineralocorticoid receptors reducing blood pressure in a dose-dependent manner and appears to prevent myocardial and vascular fibrosis.

Pharmacodynamics/Kinetics

Distribution: V_d: 43-90 L

Protein binding: ~50%; primarily to $alpha_1$-acid glycoproteins

Metabolism: Primarily hepatic via CYP3A4; metabolites inactive

Bioavailability: 69%

Half-life elimination: 4-6 hours

Time to peak, plasma: ~1.5 hours; may take up to 4 weeks for full antihypertensive effect

Excretion: Urine (~67%); feces (32%); <5% as unchanged drug in urine and feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentHypertriglyceridemia is common; monitor when used with clozapine, olanzapine, quetiapine, and mirtazapine. Lithium levels should be monitored for possible effects on serum concentrations. Fluoxetine, fluvoxamine, and nefazodone may increase levels of eplerenone; initial dose should be 25 mg/day.

Cardiovascular Considerations

Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines suggest that the addition of an aldosterone antagonist is reasonable in selected patients with moderately severe to severe symptoms of heart failure (HF) and reduced LVEF who can be carefully monitored (renal function and serum potassium). When evaluating a heart failure patient for aldosterone antagonist treatment, creatinine should be ≤2.5 mg/dL in men or ≤2 mg/dL in women and potassium <5 mEq/L. Patients are not candidates for such therapy if they are unable to comply with the monitoring required. In addition, the routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended in patients with current or prior symptoms of HF and reduced LVEF. In severe heart failure, spironolactone (25 mg/day), when combined with maximal standard therapy, resulted in a striking improvement in cardiovascular outcome (Pitt B, 1999). In the RALES trial, potassium supplementation was stopped with the initiation of spironolactone unless the patient was hypokalemic. The aldosterone antagonist, eplerenone, was recently studied in patients with acute MI complicated by left ventricular dysfunction and heart failure (Pitt B, 2003). Patients were randomly assigned to eplerenone (initially 25 mg daily; titrated to 50 mg daily) or placebo, in addition to standard therapy. During a mean follow-up of 16 months, 478 deaths in the eplerenone group occurred and 554 deaths in the placebo group (CI 0.75-0.96; p = 0.008). The addition of eplerenone to optimal medical therapy reduces morbidity and mortality in this patient population.

Monitoring Issues: The ACC/AHA 2005 Heart Failure Guidelines emphasize factors to consider in minimizing the risk of hyperkalemia with use of aldosterone antagonists such as initial dosages to use, avoidance of NSAIDs, discontinuing or reducing potassium supplements, and following monitoring guidelines. They suggest that potassium levels and renal function be checked in 3 days and at 1 week after initiation of therapy and at least monthly for the first 3 months. If serum potassium increases to a level >5.4 mEq/L while on an aldosterone antagonist, dose reduction is suggested.

Hypertension: Aldosterone antagonists may add additional antihypertensive benefits in patients who have severe LV dysfunction (NYHA class III and IV), but only after ACE inhibitors and beta-blockers have been instituted (if no contraindications or intolerances exist).

References

Chobanian AV, Bakris GL, Black HR, et al, “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report,” *JAMA*, 2003, 289(19):2560-71. [PubMed 12748199]

Pitt B, Zannad F, Remme WJ, et al, “The Effect of Spironolactone on Morbidity and Mortality in Patients With Severe Heart Failure. Randomized Aldactone Evaluation Study Investigators,” *N Engl J Med*, 1999, 341(10):709-17. [PubMed 10471456]

Pitt B, Remme W, Zannad F, et al, “Eplerenone, A Selective Aldosterone Blocker, in Patients With Left Ventricular Dysfunction After Myocardial Infarction,” *N Engl J Med*, 2003, 348(14):1309-21.[PubMed 12668699]

International Brand NamesElecor (ES); Inspra (BG, CH, CZ, DE, DK, EE, FI, FR, GB, HK, IE, IL, NL, NO, NZ, SE); Inspra IC (MX)

EPOCH

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lymphoma, non-Hodgkin's
Regimen Use Lymphoma, non-Hodgkin's
Regimen

Etoposide: I.V.: 50 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 200 mg/m^2]

Vincristine: I.V.: 0.4 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 1.6 mg/m^2]

Doxorubicin: I.V.: 10 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 40 mg/m^2]

Cyclophosphamide: I.V.: 750 mg/m^2 day 6

[total dose/cycle = 750 mg/m^2]

Prednisone: Oral: 60 mg/m^2/day days 1 to 6

[total dose/cycle = 360 mg/m^2]

Repeat cycle every 21 days

References

Wilson WH, Bryant G, Bates S, et al, âEPOCH Chemotherapy: Toxicity and Efficacy in Relapsed and Refractory Non-Hodgkin's Lymphoma,â *J Clin Oncol*, 1993, 11(8):1573-82.[PubMed 7687667]

Epoetin Alfa

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Epoetin: Ongoing Safety Review - Updated September 26, 2008

Erythropoietin (Epogen®/Procrit®) and Darbepoetin (Aranesp®): Labeling Updates, Including Boxed Warning Revisions Regarding Use in Patients With Cancer - Updated September 2008

The U.S. Food and Drug Administration (FDA), Amgen Inc, and Ortho Biotech have issued a “Dear Health Care Professional” letter alerting practitioners of revised labeling for erythropoiesis-stimulating agents (ESAs) (epoetin alfa [Epogen®, Procrit®] and darbepoetin alfa [Aranesp®]). The labeling for these products has been updated, including changes to the indications, boxed warnings, and dosing reflecting that ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is curative and ESA therapy should not be initiated if the hemoglobin level is ≥10 g/dL. Medication guides have been developed to communicate the risks and benefits of ESAs for patients.

Prompted by information from studies on ESA use, over the last year there have been alerts, new labeling and/or “Dear Health Care Professional” letters issued regarding ESA use in both patients with cancer and patients with chronic renal failure. The studies in patients with cancer provided evidence of shortened time to tumor progression and increased mortality (decreased overall survival) in cancer patients (breast, cervical, head and neck, lymphoid, and nonsmall cell lung cancer) who received ESAs; however, in some studies, the ESA doses were targeted to maintain hemoglobin levels ≥12 g/dL. Based on this risk, as well as the risk of serious cardio- and thrombovascular events, labeling revisions have included recommendations from FDA advisory committees on appropriate ESA use in cancer and chronic renal failure patients and have consisted of expanded and/or strengthened boxed warnings, safety information, and revised dosing information. Practitioners are reminded that ESA use is only appropriate in the treatment of anemia in cancer patients due to concomitant chemotherapy, and therapy should be discontinued following completion of chemotherapy.

Boxed warning changes concerning use in chronic renal failure patients have included data from two studies showing an increased risk of death and serious cardiovascular events when ESAs were administered to achieve higher target hemoglobin compared with lower hemoglobin levels (13.5 vs 11.3 g/dL and 14 vs 10 g/dL). Dosing recommendations for chronic renal failure now specify a target hemoglobin range of 10-12 g/dL to achieve and maintain, including guidelines for increasing doses in patients not achieving recommended target hemoglobin range. Additional recommendations have been created for those patients unable to achieve the target hemoglobin range (despite appropriate titrations) with precautions against continuing to increase the dose and a consideration of ESA discontinuation.

The FDA is also aware of preliminary findings from a German trial of epoetin (at doses higher than recommended for anemia) to treat acute ischemic stroke. Although analysis is ongoing, preliminary findings show increased mortality in the epoetin group, when compared to the placebo group.

The FDA Medwatch alerts and a link to the most recent “Dear Healthcare Professional” letter can be found at

http://www.fda.gov/medwatch/safety/2008/safety08.htm#ESA2

http://www.fda.gov/medwatch/safety/2008/safety08.htm#ESA3

http://www.fda.gov/medwatch/safety/2008/safety08.htm#ESA

Medication Safety Issues

Sound-alike/look-alike issues:

Epoetin alfa may be confused with darbepoetin alfa, epoetin beta

Epogen® may be confused with Neupogen®

International issues:

Epopen® [Spain] may be confused with EpiPen® which is a brand name for epinephrine in the U.S.

Pronunciation(e POE e tin AL fa)

U.S. Brand NamesEpogen®; Procrit®

Canadian Brand NamesEprex®

Pharmacologic CategoryColony Stimulating Factor

Use: Labeled IndicationsTreatment of anemia (elevate/maintain red blood cell level and decrease the need for transfusions) associated with HIV (zidovudine) therapy, chronic renal failure (including patients on dialysis and not on dialysis); reduction of allogeneic blood transfusion for elective, noncardiac, nonvascular surgery; treatment of anemia due to concurrent chemotherapy in patients with metastatic cancer (nonmyeloid malignancies)

Note: Erythropoietin is **not** indicated for use in cancer patients under the following conditions:

- receiving hormonal therapy, therapeutic biologic products, or radiation therapy unless also receiving concurrent myelosuppressive chemotherapy
- receiving myelosuppressive therapy when the expected outcome is curative
- anemia due to other factors (eg, iron deficiency, folate deficiency or gastrointestinal bleed)

Use: Unlabeled/InvestigationalTreatment of anemia associated with critical illness; anemia of prematurity; symptomatic anemia in myelodysplastic syndrome (MDS)

Dosing: AdultsIndividuals with anemia due to iron deficiency, sickle cell disease, autoimmune hemolytic anemia, and bleeding, generally have appropriate endogenous EPO levels to drive erythropoiesis and would not ordinarily be candidates for EPO therapy. **Note:** Hemoglobin levels should not exceed 12 g/dL and should not rise >1 g/dL per 2-week time period during therapy in any patient.

Chronic renal failure patients: SubQ, I.V. (preferred for hemodialysis patients): Initial dose: 50-100 units/kg 3 times/week. Individualize dosing to achieve and maintain hemoglobin levels between 10-12 g/dL. Hemoglobin levels should not exceed a target range of 10-12 g/dL.

Dosage adjustment:

Decrease dose by 25%: If hemoglobin approaches 12 g/dL **or** hemoglobin increases >1 g/dL in any 2-week period. If hemoglobin continues to increase, temporarily discontinue therapy until hemoglobin begins to decrease, then resume therapy with a ~25% reduction from previous dose.

Increase dose by 25%: If hemoglobin <10 g/dL and does not increase by 1 g/dL after 4 weeks of therapy (with adequate iron stores) **or** hemoglobin decreases below 10 g/dL. If transferrin saturation >20%, may increase epoetin dose. Do not increase dose more frequently than at 4-week intervals, unless clinically indicated (hemoglobin response time for dose increases may be 2-6 weeks).

Inadequate or lack of response: If patient does not attain target hemoglobin range of 10-12 g/dL after appropriate dose titrations over 12 weeks:

Do not continue to increase dose and use the minimum effective dose that will maintain a hemoglobin level sufficient to avoid red blood cell transfusions **and** evaluate patient for other causes of anemia.

Monitor hemoglobin closely thereafter, and if responsiveness improves, may resume making dosage adjustments as recommended above. If responsiveness does not improve and recurrent red blood cell transfusions continue to be needed, discontinue therapy.

Maintenance dose: Individualize to target hemoglobin range of 10-12 g/dL; limit additional dosage increases to every 4 weeks (or longer)

Dialysis patients: Median dose: 75 units/kg 3 times/week

Nondialysis patients: Dosing range: 75-150 units/kg/week

Zidovudine-treated, HIV-infected patients (with serum erythropoietin levels ≤500 and zidovudine doses ≤4200 mg/week; patient with erythropoietin levels >500 mU/mL is unlikely to respond). Titrate dosage to use the minimum effective dose that will maintain a hemoglobin level sufficient to avoid red blood cell transfusions. Hemoglobin levels should not exceed 12 g/dL

I.V.: 100 units/kg 3 times/week for 8 weeks

Dosage adjustment:

Increase dose by 50-100 units/kg 3 times/week: If response is not satisfactory in terms of reducing transfusion requirements or increasing hemoglobin after 8 weeks of therapy. Evaluate response every 4-8 weeks thereafter and adjust the dose accordingly by 50-100 units/kg increments 3 times/week. If patient has not responded satisfactorily to 300 unit/kg dose 3 times/week, a response to higher doses is unlikely.

Withhold dose: If hemoglobin exceeds 12 g/dL and resume treatment at a 25% dose reduction when hemoglobin drops below 11g/dL.

Cancer patient on chemotherapy: Treatment of patients with erythropoietin levels >200 mU/mL is **not recommended by the manufacturer.** Titrate dosage to use the minimum effective dose that will maintain a hemoglobin level sufficient to avoid red blood cell transfusions. Do not initiate therapy if hemoglobin ≥10 g/dL. Discontinue erythropoietin following completion of chemotherapy.

SubQ: Initial dose: 150 units/kg 3 times/week or 40,000 units once weekly; commonly used doses range from 10,000 units 3 times/week to 40,000-60,000 units once weekly.

Dosage adjustment:

Increase dose: If response is not satisfactory after a sufficient period of evaluation (no reduction in transfusion requirements or increase in hemoglobin after 8 weeks of 3 times/week therapy) **or** (no increase in hemoglobin by ≥1 g/dL after 4 weeks of once-weekly therapy), the dose may be increased every 4 weeks (or longer) to 300 units/kg 3 times/week, **or** when dosed weekly, increased all at once to 60,000 units weekly. If patient does not respond, a response to higher doses is unlikely.

Withhold dose: If hemoglobin exceeds a level needed to avoid red blood cell transfusion. Resume treatment with a 25% dose reduction when hemoglobin approaches a level where transfusions may be required.

Reduce dose by 25%: If hemoglobin increases >1 g/dL in any 2-week period **or** hemoglobin reaches a level sufficient to avoid red blood cell transfusion.

Discontinue: If after 8 weeks of therapy there is no response (ie, increased hemoglobin levels) or transfusions still required.

Surgery patients: Prior to initiating treatment, obtain a hemoglobin to establish that it is >10 g/dL and ≤13 g/dL: SubQ: Initial dose: 300 units/kg/day for 10 days before surgery, on the day of surgery, and for 4 days after surgery

Alternative dose: 600 units/kg in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery

Anemia of critical illness (unlabeled use): SubQ: 40,000 units once weekly

Symptomatic anemia associated with MDS (unlabeled use): SubQ: 40,000-60,000 units 1-3 times/ week

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Hemoglobin levels should not exceed 12 g/dL and should not rise >1 g/dL per 2-week time period during therapy in any patient.

Anemia of prematurity (unlabeled use): Infants: SubQ, I.V.: Dosing range: 500-1250 units/kg/week; commonly used dose: 250 units/kg 3 times/week; supplement with oral iron therapy 3-8 mg/kg/day

Chronic renal failure patients: SubQ, I.V. (preferred for hemodialysis patients): Initial dose: 50 units/kg 3 times/week. Individualize dosing to achieve and maintain hemoglobin levels between 10-12 g/dL. Hemoglobin levels should not exceed 12 g/dL.

Dosage adjustment:

Decrease dose by 25%: If hemoglobin approaches 12 g/dL **or** hemoglobin increases >1 g/dL in any 2-week period. If hemoglobin continues to increase, temporarily discontinue therapy until hemoglobin begins to decrease, then resume therapy with a ~25% reduction from previous dose.

Increase dose by 25%: If hemoglobin <10 g/dL and does not increase by 1 g/dL after 4 weeks of therapy (with adequate iron stores) **or** hemoglobin decreases below 10 g/dL. If transferrin saturation >20%, may increase epoetin dose. Do not increase dose more frequently than at 4-week intervals, unless clinically indicated (hemoglobin response time for dose increases may be 2-6 weeks).

Inadequate or lack of response: If patient does not attain target hemoglobin range of 10-12 g/dL after appropriate dose titrations over 12 weeks:

Do not continue to increase dose and use the minimum effective dose that will maintain a hemoglobin level sufficient to avoid red blood cell transfusions **and** evaluate patient for other causes of anemia.

Monitor hemoglobin closely thereafter, and if responsiveness improves, may resume making dosage adjustments as recommended above. If responsiveness does not improve and recurrent red blood cell transfusions continue to be needed, discontinue therapy.

Maintenance dose: Individualize to target hemoglobin range of 10-12 g/dL; limit additional dosage increases to every 4 weeks (or longer)

Dialysis patients: 167 units/kg/week (hemodialysis) **or** 76 units/kg/week (peritoneal dialysis), in 2-3 divided doses per week

Nondialysis patients: Dosing range: 50-250 units/kg 1-3 times/week

Zidovudine-treated, HIV-infected patients (patient with erythropoietin levels >500 mU/mL is unlikely to respond): SubQ, I.V.: Limited data available; reported dosing range: 50-400 units/kg 2-3 times/week.

Note: Titrate dosage to use the minimum effective dose that will maintain a hemoglobin level sufficient to avoid red blood cell transfusions. Hemoglobin levels should not exceed 12 g/dL.

Cancer patients on chemotherapy: I.V.: 600 units/kg once weekly (maximum: 40,000 units). Treatment of patients with erythropoietin levels >200 mU/mL is **not recommended by the manufacturer.** Titrate dosage to use the minimum effective dose that will maintain a hemoglobin level sufficient to avoid red blood cell transfusions. Do not initiate therapy if hemoglobin ≥10 g/dL. Discontinue erythropoietin following completion of chemotherapy.

Dosage adjustment:

Increase dose: If response is not satisfactory after a sufficient period of evaluation (no increase in hemoglobin by ≥1 g/dL after 4 weeks of once-weekly therapy), the dose may be increased every 4 weeks (or longer) to 900 units/kg/week; maximum 60,000 units. If patient does not respond, a response to higher doses is unlikely.

Withhold dose: If hemoglobin exceeds a level needed to avoid red blood cell transfusion. Resume treatment with a 25% dose reduction when hemoglobin approaches a level where transfusions may be required.

Reduce dose by 25%: If hemoglobin increases >1 g/dL in any 2-week period **or** hemoglobin reaches a level sufficient to avoid red blood cell transfusion.

Discontinue: If after 8 weeks of therapy there is no response (ie, increased hemoglobin levels) or transfusions still required.

Dosing: Renal ImpairmentThe National Kidney Foundation Clinical Practice Guideline for Anemia in Chronic Kidney Disease: 2007 Update of Hemoglobin Target (September, 2007) recommend hemoglobin levels in the range of 11-12 g/dL for dialysis and nondialysis patients receiving ESAs; hemoglobin levels should not be >13 g/dL.

Hemodialysis: Supplemental dose is not necessary. I.V. route is preferred for hemodialysis patients.

Peritoneal dialysis: Supplemental dose is not necessary.

Calculations

- EPO to Aranesp

Administration: I.V.

Patients with CRF on dialysis: I.V. route preferred; may be administered I.V. bolus into the venous line after dialysis.

Patients with CRF not on dialysis: May be administered I.V. or SubQ

Administration: I.V. DetailpH: 6.6-7.2 (single dose vial); 5.8-6.4 (multidose vial)
Administration: OtherSubQ:

Patients with CRF on dialysis: I.V. route preferred.

Patients with CRF not on dialysis: May be administered I.V. or SubQ

StorageVials should be stored at 2°C to 8°C (36°F to 46°F); **do not freeze or shake**. Protect from light.

Single-dose 1 mL vial contains no preservative: Use one dose per vial. Do not re-enter vial; discard unused portions.

> Single-dose vials (except 40,000 units/mL vial) are stable for 2 weeks at room temperature. Single-dose 40,000 units/mL vial is stable for 1 week at room temperature.

Multidose 1 mL or 2 mL vial contains preservative. Store at 2°C to 8°C after initial entry and between doses. Discard 21 days after initial entry.

> Multidose vials (with preservative) are stable for 1 week at room temperature.
>
> Prefilled syringes containing the 20,000 units/mL formulation with preservative are stable for 6 weeks refrigerated (2°C to 8°C).
>
> Dilutions of 1:10 in $D_{10}W$ with human albumin 0.05% or 0.1% are stable for 24 hours.

ReconstitutionPrior to SubQ administration, preservative free solutions may be mixed with bacteriostatic NS containing benzyl alcohol 0.9% in a 1:1 ratio.
CompatibilityStable in $D_{10}W$ with albumin 0.05%, $D_{10}W$ with albumin 0.1%; **incompatible** with $D_{10}W$ with albumin 0.01%, $D_{10}W$, NS; **variable stability (consult detailed reference)** in TPN.
RestrictionsAn FDA-approved medication guide is available; distribute to each patient to whom this medication is dispensed.
ContraindicationsHypersensitivity to albumin (human) or mammalian cell-derived products; uncontrolled hypertension
Warnings/Precautions

Boxed warnings:

- Cancer patients: See “Disease-related concerns” below.
- Cardiovascular events/mortality/thromboembolic events: See “Concerns related to adverse effects” below.
- Chronic renal failure patients: See “Disease-related concerns” below.
- Perisurgery patients: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Cardiovascular events/mortality/thromboembolic events: **[U.S. Boxed Warning]: ESAs increased the risk of serious cardiovascular events, thromboembolic events, and mortality** in clinical studies; a rapid rise in hemoglobin (>1 g/dL over 2 weeks) or maintaining higher hemoglobin levels may contribute to these risks. Patients treated with epoetin may require increased heparinization during dialysis to prevent clotting of the artificial kidney.
- Pure red cell aplasia (PRCA): Cases of severe anemia and PRCA have been reported, predominantly in patients with CRF receiving SubQ epoetin (the I.V. route is preferred for hemodialysis patients), Patients with loss of response should be evaluated for pure red cell aplasia with associated neutralizing antibodies to erythropoietin; discontinue treatment in patients with PRCA secondary to neutralizing antibodies to erythropoietin. Antibodies may cross-react; do not switch to another ESA in patients who develop antibody-mediated anemia.

Disease-related concerns:

- Cancer patients: **[U.S. Boxed Warning]: A shortened overall survival and/or increased risk of tumor progression or recurrence has been reported in studies with breast, cervical, head and neck, lymphoid, and nonsmall cell lung cancer patients.** It is of note that in these studies, patients received ESAs to a target hemoglobin of ≥12 g/dL; although risk has not been excluded when dosed to achieve a target hemoglobin of <12 g/dL. **[U.S. Boxed Warnings]: To decrease these risks, and risk of cardio and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusions. Use ESAs in cancer patients only for the treatment of anemia related to concurrent chemotherapy; discontinue ESA following completion of the chemotherapy course. ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is curative.**
- Chronic renal failure patients: **[U.S. Boxed Warning]: An increased risk of death and serious cardiovascular events was reported in patients administered ESAs to target higher versus lower hemoglobin levels (13.5 vs 11.3 g/dL; 14 vs 10 g/dL) in two clinical studies; dosing should be individualized to achieve and maintain hemoglobin levels within 10-12 g/dL range.** Hemoglobin rising >1 g/dL in a 2-week period may contribute to the risk. Chronic renal failure patients who exhibit an inadequate hemoglobin response to ESA therapy may be at a

higher risk for cardiovascular events and mortality compared to other patients. ESA therapy may reduce dialysis efficacy (due to increase in red blood cells and decrease in plasma volume); adjustments in dialysis parameters may be needed.

- Hematologic diseases: Safety and efficacy in patients with underlying hematologic diseases have not been established, including hypercoagulation disorders and sickle cell disease.

- Hypertension/cardiovascular disease: Use with caution in patients with a history of hypertension. An excessive rate of rise of hemoglobin is associated with hypertension or exacerbation of hypertension; decrease the epoetin dose if the hemoglobin increase exceeds 1 g/dL in any 2-week period. Blood pressure should be controlled prior to start of therapy and monitored closely throughout treatment. Hypertensive encephalopathy has been reported with patients receiving erythropoietic therapy; monitor closely and control blood pressure.

- Perisurgery patients: **[U.S. Boxed Warning]: Epoetin alfa increased the rate of DVT in patients not receiving anticoagulant prophylaxis; consider DVT prophylaxis in surgery patients.** Increased mortality was also observed in patients undergoing coronary artery bypass surgery who received epoetin alfa; these deaths were associated with thrombotic events. Epoetin is **not** approved for reduction of red blood cell transfusion in patients undergoing cardiac or vascular surgery.

- Porphyria: Use caution with porphyria, exacerbation of porphyria has been reported in patients with chronic renal failure.

- Seizures: Use with caution in patients with a history of seizures. An excessive rate of rise of hemoglobin may be possibly associated with the exacerbation of seizures; decrease the epoetin dose if the hemoglobin increase exceeds 1 g/dL in any 2-week period.

Special populations:

- Pediatrics: Safety and efficacy in children <1 month of age have not been established.

Dosage form specific issues:

- Albumin: Product may contain albumin, which confers a theoretical risk of transmission of viral disease or Creutzfeldt-Jakob disease.

- Benzyl alcohol: Multidose vials contain benzyl alcohol which has been associated with "gasping syndrome" in neonates.

Other warnings/precautions:

- Acute correction: Not recommended for acute correction of severe anemia or as a substitute for transfusion.

- Appropriate use: Hemoglobin levels should not exceed a target range of 10-12 g/dL and should not rise >1 g/dL per 2-week time period during therapy in any patient.

- Factors impairing erythropoiesis: Prior to treatment, correct or exclude deficiencies of iron, vitamin B_{12}, and/or folate, as well as other factors which may impair erythropoiesis (aluminum toxicity, inflammatory conditions, infections). Poor response to therapy should prompt evaluation of potential factors impairing erythropoiesis, as well as possible malignant processes, occult blood loss, hemolysis, and/or bone marrow fibrosis.

- Iron supplementation: Prior to and periodically during therapy, iron stores must be evaluated. Supplemental iron is recommended if serum ferritin <100 mcg/L or serum transferrin saturation <20%.

Geriatric ConsiderationsThere is limited information about the use of epoetin alfa in the elderly. Endogenous erythropoietin secretion has been reported to be decreased in elderly with normocytic or iron deficiency anemias or those with a serum hemoglobin concentration <12 g/dL; one study did not find such a relationship in the elderly with chronic anemia. A blunted erythropoietin response to anemia has been reported in patients with cancer, rheumatoid arthritis, and AIDS.

Pregnancy Risk FactorC

Pregnancy ConsiderationsEpoetin alfa has been shown to have adverse effects (decreased weight gain, delayed development, delayed ossification) in animal studies. Studies suggest that *r*HuEPO-α does not cross the human placenta. Based on case reports, treatment with *r*HuEPO-α may be an option in pregnant women with ESRD on dialysis. Amenorrheic premenopausal women should be cautioned that menstruation may resume following treatment with *r*HuEPO-α and contraception should be considered if pregnancy is to be avoided.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsWhen administered enterally to neonates (mixed with human milk or infant formula), *r*HuEPO-α did not significantly increase serum EPO concentrations. If passage via breast milk does occur, risk to a nursing infant appears low.

Adverse Reactions

>10%:

Cardiovascular: Hypertension (5% to 24%), thrombotic/vascular events (coronary artery bypass graft surgery: 23%), edema (6% to 17%), deep vein thrombosis (3% to 11%)

Central nervous system: Fever (29% to 51%), dizziness (<7% to 21%), insomnia (13% to 21%), headache (10% to 19%)

Dermatologic: Pruritus (14% to 22%), skin pain (4% to 18%), rash (≤16%)

Gastrointestinal: Nausea (11% to 58%), constipation (42% to 53%), vomiting (8% to 29%), diarrhea (9% to 21%), dyspepsia (7% to 11%)

Genitourinary: Urinary tract infection (3% to 12%)

Local: Injection site reaction (<10% to 29%)

Neuromuscular & skeletal: Arthralgia (11%), paresthesia (11%)

Respiratory: Cough (18%), congestion (15%), dyspnea (13% to 14%), upper respiratory infection (11%)

1% to 10%:

Central nervous system: Seizure (1% to 3%)

Local: Clotted vascular access (7%)

<1%, postmarketing, and/or case reports: Allergic reaction, anemia (severe; with or without other cytopenias), CVA, flu-like syndrome, hyperkalemia, hypersensitivity reactions, hypertensive encephalopathy, microvascular thrombosis, MI, myalgia, neutralizing antibodies, pulmonary embolism, pure red cell aplasia (PRCA), renal vein thrombosis, retinal artery thrombosis, tachycardia, temporal vein thrombosis, thrombophlebitis, thrombosis, TIA, urticaria

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersBlood pressure; hemoglobin, CBC with differential and platelets, transferrin saturation and ferritin, serum chemistry (CRF patients)

Suggested tests to be monitored and their frequency: See table.

Test	Initial Phase Frequency	Maintenance Phase Frequency
Hemoglobin	1-2 x/week	2-4 x/month
Blood pressure	3 x/week	3 x/week
Serum ferritin	Monthly	Quarterly
Transferrin saturation	Monthly	Quarterly
Serum chemistries including CBC with differential, creatinine, blood urea nitrogen, potassium, phosphorous	Regularly per routine	Regularly per routine

Reference Range

Zidovudine-treated HIV patients: Available evidence indicates patients with endogenous serum erythropoietin levels >500 mU/mL are unlikely to respond

Cancer chemotherapy patients: Measurement of endogenous serum erythropoietin levels in patients with cancer is generally not recommended (NCCN Cancer- and Chemotherapy-Induced Anemia Guidelines, v2.2009). Treatment of patients with endogenous serum erythropoietin levels >200 mU/mL is not recommended according to the manufacturer.

Nursing: Physical Assessment/MonitoringEvaluate history of hypertension or seizures and potential risk for thromboembolism prior to beginning therapy. Blood pressure should be monitored closely and controlled during therapy. If administered by intravenous infusion, lines should be monitored closely for possible clotting. Assess results of laboratory tests prior to and on a regular scheduled basis during therapy (eg, blood chemistries, hemoglobin/hematocrit, serum ferritin, transferrin saturation); dosage adjustment and iron supplements may be necessary. Evaluate therapeutic effectiveness (according to purpose for use) and adverse response on a frequent basis during therapy (eg, hypertension, thrombotic events, edema, anemia). Teach patient proper use if self-administered (appropriate SubQ injection technique and syringe/needle disposal), possible side effects/appropriate interventions (importance of maintaining laboratory schedule), and adverse symptoms to report.

Monitoring: Lab TestsSee table.

Test	Initial Phase Frequency	Maintenance Phase Frequency
Hemoglobin	1-2 x/week	2-4 x/month
Blood pressure	3 x/week	3 x/week
Serum ferritin	Monthly	Quarterly
Transferrin saturation	Monthly	Quarterly
Serum chemistries including CBC with differential, creatinine, blood urea nitrogen, potassium, phosphorous	Regularly per routine	Regularly per routine

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy unless approved by prescriber. If self-administered, follow exact directions for injection and needle disposal. You will require frequent blood tests to determine appropriate dosage and reduce potential for severe adverse effects; maintaining laboratory testing schedule is vital. Do not make significant changes in your dietary iron without consulting prescriber. You may experience fever; headache; trouble sleeping; itching; skin pain; nausea; and/or vomiting, diarrhea, heartburn, and upper respiratory congestion. Contact prescriber if symptoms persist. Report signs or symptoms of edema (eg, swollen extremities, respiratory difficulty, rapid weight gain); onset of severe headache, unusual dizziness, or blurred vision; chest pain; leg pain and tenderness; muscular tremors or seizure activity; difficulty breathing, coughing, or congestion; or other adverse effects.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Epogen®, Procrit®: 2000 units/mL (1 mL); 3000 units/mL (1 mL); 4000 units/mL (1 mL); 10,000 units/mL (1 mL); 40,000 units/mL (1 mL) [contains human albumin]

Injection, solution [with preservative]:

Epogen®, Procrit®: 10,000 units/mL (2 mL); 20,000 units/mL (1 mL) [contains human albumin and benzyl alcohol]

Generic AvailableNo

ManufacturerAmgen Inc

Pricing: U.S. (www.drugstore.com)

Solution (Epogen)

2000 units/mL (1): $36.71

3000 units/mL (1): $47.99

4000 units/mL (1): $53.50

10000 units/mL (2): $272.93

10000 units/mL (10): $1290.27

20000 units/mL (10): $2572.89

40000 units/mL (10): $5348.60

Solution (Procrit)

2000 units/mL (6): $182.98

3000 units/mL (6): $274.48

4000 units/mL (6): $363.90

10000 units/mL (6): $855.99

10000 units/mL (12): $1810.41

20000 units/mL (6): $1804.21

40000 units/mL (4): $2394.33

Mechanism of ActionInduces erythropoiesis by stimulating the division and differentiation of committed erythroid progenitor cells; induces the release of reticulocytes from the bone marrow into the bloodstream, where they mature to erythrocytes. There is a dose response relationship with this effect. This results in an increase in reticulocyte counts followed by a rise in hematocrit and hemoglobin levels.

Pharmacodynamics/Kinetics

Onset of action: Several days

Peak effect: 2-3 weeks

Distribution: V_d: 9 L; rapid in the plasma compartment; concentrated in liver, kidneys, and bone marrow

Metabolism: Some degradation does occur

Bioavailability: SubQ: ~21% to 31%; intraperitoneal epoetin: 3% (a few patients)

Half-life elimination: Cancer: SubQ: 16-67 hours; Chronic renal failure: I.V.: 4-13 hours

Time to peak, serum: Chronic renal failure: SubQ: 5-24 hours

Excretion: Feces (majority); urine (small amounts, 10% unchanged in normal volunteers)

Pharmacotherapy Pearls

Factors limiting response to epoetin alfa: Delayed onset of erythropoiesis (2-6 weeks to increase hemoglobin), iron deficiency (most patients require iron supplementation); underlying infection, inflammatory or malignant process; blood loss (occult), underlying hematologic disease (thalassemia, refractory anemia, MDS); vitamin deficiency (folic acid or cyanocobalamin), hemolysis, aluminum overload, osteitis fibrosa cystica, and PRCA

Oncology Comment: The American Society of Hematology (ASH) and American Society of Clinical Oncology (ASCO) 2007 updates to the clinical practice guidelines for the use of erythropoiesis-stimulating agents (ESAs) indicate that ESAs are most appropriate when used according to the dosage parameters within the Food and Drug Administration (FDA) approved labeling for epoetin and darbepoetin (Rizzo, 2008). While the previous guidelines addressed only the use of epoetin, the 2007 guidelines also address the use of darbepoetin, which is assessed as being equivalent to epoetin with respect to safety and efficacy. When used as an option for the treatment of chemotherapy-associated anemia (to increase hemoglobin and decrease red blood cell transfusions), therapy with ESAs should begin as the hemoglobin level approaches or falls below 10 g/dL. The ASH/ASCO guidelines recommend following the FDA approved dosing (and dosing adjustment) guidelines and target hemoglobin ranges as alternate dosing and schedules have not demonstrated consistent differences in effectiveness with regard to hemoglobin response. In patients who do not have a response within 6-8 weeks (hemoglobin rise <1-2 g/dL or no reduction in transfusions) ESA therapy should be discontinued.

The guidelines note that patients with an increased risk of thromboembolism (generally includes previous history of thrombosis, surgery, and/or prolonged periods of immobilization) and patients receiving concomitant medications that may increase thromboembolic risk, should begin ESA therapy only after careful consideration. With the exception of low-risk myelodysplasia-associated anemia (which has evidence supporting the use of ESAs without concurrent chemotherapy), the guidelines do not support the use of ESAs in the absence of concurrent chemotherapy.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsThe ACC/AHA 2005 Heart Failure Guidelines suggest that the benefit of enhancing erythropoiesis in these patients is not established. Although some small studies have shown a benefit from erythropoietin and iron in mild anemia in heart failure, further investigation is required evaluating the risks and benefits.

Anesthesia and Critical Care Concerns/Other Considerations**Routine Use in Critically-Ill Patients**

A prospective, randomized, double-blind, placebo-controlled, multicenter trial was performed with critically-ill patients assessing the efficacy of recombinant human erythropoietin in reducing red blood cell transfusions (Corwin, 2002). Patients were enrolled from December,1998 through June, 2001. Over 1300 ICU (medical, surgical, or medical/surgical) patients were randomized to receive placebo or 40,000 units of erythropoietin subcutaneously on ICU day 3 and then weekly for a total of 3 doses for patients who remained in the hospital. Inclusion criteria included ICU stay for 3 days, age >18 years, and hematocrit <38%. Exclusion criteria were extensive and included acute ischemic heart disease, acute gastrointestinal bleed, and renal failure with hemodialysis. Each patient's physician determined the need for red blood cell transfusion. Results: The mean baseline hemoglobin was 9.97 g/dL in each group. Patients receiving erythropoietin were less likely to receive transfusions. The median number of units transfused per patient in the placebo group was 2 and in the erythropoietin group was 1 (p<0.001). The erythropoietin group had a 9.9% absolute reduction in RBC transfusions during 28 days (p<0.001, OR 0.67, CI 0.54-0.83). Mortality and adverse clinical events were not significantly different between groups. The authors concluded that weekly administration of erythropoietin in critically-ill patients reduces red blood cell transfusions and increases hemoglobin. The authors also suggest that further study is needed to determine if use of erythropoietin results in improved clinical outcomes.

A restrictive transfusion trial was published after the above Corwin trial was underway (Hebert, 1999). Hebert and his group evaluated a restrictive transfusion strategy (transfuse if hemoglobin <7 g/dL to maintain between 7 and 9 g/dL) versus a liberal strategy (transfuse if hemoglobin <10 g/dL to maintain between 10 and 12 g/dL). Inclusion criteria included anticipated ICU stay >24 hours, hemoglobin ≤9 g/dL with 72 hours of ICU admission, and euvolemia after initial treatment. Exclusion criteria included chronic anemia, active bleeding, or admission after a routine cardiac surgical procedure. The restrictive approach to transfusion was at least as effective as and possibly superior to a liberal transfusion policy in critically-ill patients. The exception to this may be patients with acute myocardial infarction and unstable angina.

More recently, Corwin, et al (2007) once again evaluated the use of recombinant human erythropoietin in the critically ill. In this prospective, randomized, placebo-controlled trial, 1460 medical, surgical, or trauma patients were enrolled between December, 2003 and June, 2006. Patients received either subcutaneous erythropoietin 40,000 units or placebo once weekly for a maximum of 3 doses and were followed for 140 days. The primary endpoint of the study was the percentage of patients who received a red cell transfusion between days 1 and 29. Secondary endpoints included the number of red cell units transfused between days 1 and 29, mortality at day 29 and day 140, and the change in hemoglobin concentration from baseline to day 29. Patients were evaluated for inclusion into the study if they remained in that ICU for 2 days. Inclusion criteria were age >18 years and hemoglobin concentration <12 g/dL. Exclusion criteria were extensive and included acute ischemic heart disease during the ICU stay, acute gastrointestinal bleed, hemodialysis, and patients at risk for thrombosis (history of pulmonary embolism, deep venous thrombosis, ischemic stroke, other arterial or venous thrombosis). Red cell transfusions targeted hemoglobin concentrations between 7 and 9 g/dL, but the need for transfusion was determined by the treating physician (this is more consistent with clinical practice after the Hebert trial was published and different than the previous Corwin trial). Results: The mean baseline hemoglobin for each group was 9.6 g/dL. The use of erythropoietin did not significantly decrease the need for red cell transfusion (46.0% in the erythropoietin group transfused vs 48.3% in the placebo group, p=0.34). The hemoglobin concentration at day 29 increased more in the erythropoietin group compared to placebo (1.6 ± 2.0 g/dL vs 1.2 ± 1.8 g/dL, p<0.001); however, by day 42 the hemoglobin concentrations in both groups were similar. Mortality at day 29 was significantly lower in the group receiving erythropoietin (8.5% vs 11.4%, p=0.02) from the Kaplan-Meier estimate, but no difference was seen in the Cox model in the overall population. Only in the trauma subset was mortality at day 29 significantly lower in the erythropoietin group (3.5% vs 6.6%, p=0.04). At day 140, mortality was not significantly lower in the erythropoietin group. Thrombotic events (eg, DVT and myocardial infarction) were significantly higher in the erythropoietin group as compared to placebo and appeared to be dose-related (16.5% vs 11.5%, p=0.008, HR 1.41, CI 1.06-1.86). However, upon further analysis those patients who did not receive heparin at baseline developed these events more frequently. There was no difference in length of stay or the use of mechanical ventilation between groups. The authors concluded that although erythropoietin does not reduce the incidence of red cell transfusion in critically-ill patients, it may reduce mortality in trauma patients. Further investigation is required to define erythropoietin’s role in this population. The routine use of erythropoietin in critically-ill, nontraumatic surgical or medical patients is not supported by this study.

The 2008 Surviving Sepsis Campaign guidelines do not recommend erythropoietin as a treatment for anemia associated with severe sepsis, but suggest that it may be used when septic patients have other therapeutic indications (Grade 1B).

Index Terms*r*HuEPO-α; EPO; Erythropoiesis-Stimulating Agent (ESA); Erythropoietin; NSC-724223

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International Brand NamesEPIAO (TH); Epokine (PH, TH); Eposino (PH); Eprex (AE, AR, AU, BD, BE, BG, BH, CH, CL, CR, CY, CZ, DK, DO, EE, EG, ES, FI, FR, GB, GR, GT, HK, HN, HR, HU, ID, IL, IN, IQ, IR, IT, JO, JP, KP, KW, LB, LY, MX, MY, NI, NL, NO, OM, PA, PE, PH, PK, PL, PY, QA, RU, SA, SE, SG, SV, SY, TH, TR, TW, UY, VE, YE); Erypo (AT, DE); Espo (JP); Espogen (TH); Hemapo (ID); Hypercrit (BR, CN); Neorecormon (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Renogen (PH, TH)

Epoprostenol

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(e poe PROST en ole)

U.S. Brand NamesFlolan®

Canadian Brand NamesFlolan®

Pharmacologic CategoryProstacyclin; Prostaglandin; Vasodilator

Use: Labeled IndicationsTreatment of idiopathic pulmonary arterial hypertension (IPAH); pulmonary hypertension associated with the scleroderma spectrum of disease (SSD) in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy

Dosing: AdultsIPAH or SSD: I.V.: Initial: 1-2 ng/kg/minute, increase dose in increments of 1-2 ng/kg/minute every 15 minutes or longer until dose-limiting side effects are noted or tolerance limit to epoprostenol is observed. Significant patient variability in optimal dose exists. Maximum dose with chronic therapy has not been defined; however, doses as high as 195 ng/kg/minute have been described in children (Rosenzweig, 1999).

Note: The need for increased doses should be expected with chronic use; incremental increases occur more frequently during the first few months after the drug is initiated.

Dose adjustment:

Increase dose in 1-2 ng/kg/minute increments at intervals of at least 15 minutes if symptoms persist or recur following improvement. In clinical trials, dosing increases occurred at intervals of 24-48 hours.

Decrease dose in 2 ng/kg/minute decrements at intervals of at least 15 minutes in case of dose-limiting pharmacologic events. Avoid abrupt withdrawal or sudden large dose reductions.

Lung transplant: In patients receiving lung transplants, epoprostenol may be tapered after the initiation of cardiopulmonary bypass.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricUnlabeled use; refer to adult dosing.

Administration: I.V.The ambulatory infusion pump should be small and lightweight, be able to adjust infusion rates in 2 ng/kg/minute increments, have occlusion, end of infusion, and low battery alarms, have ± 6% accuracy of the programmed rate, and have positive continuous or pulsatile pressure with intervals ≤3 minutes between pulses. The reservoir should be made of polyvinyl chloride, polypropylene, or glass. The infusion pump used in the most recent clinical trial was CADD-1 HFX 5100 (Pharmacia Deltec). Immediate access to back up pump, infusion sets and medication is essential to prevent treatment interruptions. Assess patient's and family's ability to manage a central venous catheter in the home setting. Clinicians should routinely review with patient the importance of infection control practices for the management of a central venous catheter.

Administration: I.V. DetailWhen given on an ongoing basis, must be infused through a central venous catheter. Peripheral infusion may be used temporarily until central line is established. Infuse using an infusion pump. Avoid abrupt withdrawal (including interruptions in delivery) or sudden large reductions in dosing.

pH: 10.2-10.8

StoragePrior to use, store vials at 15°C to 25°C (59°F to 77°F); do not freeze. Protect from light. Following reconstitution, solution must be stored under refrigeration at 2°C to 8°C (36°F to 46°F) if not used immediately; do not freeze. Protect from light. Discard if refrigerated for >48 hours. During use, a single reservoir of solution may be used at room temperature for a total duration of 8 hours, or used with a cold pouch for administration up to 24 hours. Cold packs should be changed every 12 hours.

Reconstitution Reconstitute only with provided sterile diluent. See table.

Preparation of Epoprostenol Infusion

Note: Only prepare with sterile diluent provided.	
To make 100 mL of solution with concentration:	**Directions**
3000 ng/mL	Dissolve one 0.5 mg vial with 5 mL supplied diluent, withdraw 3 mL, and add to a sufficient volume of supplied diluent to make a total of 100 mL.
5000 ng/mL	Dissolve one 0.5 mg vial with 5 mL supplied diluent, withdraw entire vial contents, and add to a sufficient

	volume of supplied diluent to make a total of 100 mL.
10,000 ng/mL	Dissolve two 0.5 mg vials each with 5 mL supplied diluent, withdraw entire vial contents, and add to a sufficient volume of supplied diluent to make a total of 100 mL.
15,000 ng/mL	Dissolve one 1.5 mg vial with 5 mL supplied diluent, withdraw entire vial contents, and add to a sufficient volume of supplied diluent to make a total of 100 mL.

CompatibilityOnly prepare with sterile diluent provided. Do not mix or administer with any other drugs or solutions prior to or during administration.

RestrictionsOrders for epoprostenol are distributed by two sources in the United States. Information on orders or reimbursement assistance may be obtained from either Accredo Health, Inc (1-800-935-6526) or TheraCom, Inc (1-877-356-5264).

ContraindicationsHypersensitivity to epoprostenol or to structurally-related compounds; chronic use in patients with heart failure due to severe left ventricular systolic dysfunction; patients who develop pulmonary edema during dose initiation

Warnings/Precautions

Concerns related to adverse effects:

- Pulmonary edema: Some patients with primary pulmonary hypertension have developed pulmonary edema during dosing adjustment, which may be associated with pulmonary veno-occlusive disease.
- Rebound pulmonary hypertension: Abrupt interruptions or large sudden reductions in dosage may result in rebound pulmonary hypertension. Avoid abrupt withdrawal.

Disease-related concerns:

- Conditions that increase bleeding risk: Epoprostenol is an inhibitor of platelet aggregation. Use with caution in patients with risk factors for bleeding.

Concurrent drug therapy issues:

- Anticoagulants: During chronic use, unless contraindicated, anticoagulants should be coadministered to reduce the risk of thromboembolism.

Other warnings/precautions:

- Infection: Chronic continuous I.V. infusion of epoprostenol via a chronic indwelling central venous catheter has been associated with local infections and serious blood stream infections.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not reported in animal studies. There are no adequate and well-controlled studies in pregnant women. Pregnant women with IPAH are encouraged to avoid pregnancy.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

Note: Adverse events reported during dose initiation and escalation include flushing (58%), headache (49%), nausea/vomiting (32%), hypotension (16%), anxiety/nervousness/agitation (11%), chest pain (11%), dizziness, abdominal pain, bradycardia, musculoskeletal pain, dyspnea, back pain, diaphoresis, dyspepsia, hypoesthesia/paresthesia, and tachycardia are also reported. The following adverse events have been reported during chronic administration for IPAH. Although some may be related to the underlying disease state, anxiety, diarrhea, flu-like syndrome, flushing, headache, jaw pain, nausea, nervousness, and vomiting are clearly contributed to epoprostenol.

>10%:

Cardiovascular: Chest pain (52% to 67%), palpitation (63%), tachycardia (35% to 43%), flushing (23% to 42%), arrhythmia (27%), bradycardia (15%), hypotension (13%)

Central nervous system: Dizziness (83%), headache (46% to 83%), chills/fever/sepsis/flu-like syndrome (13% to 25%), anxiety/nervousness/tremor (7% to 21%), depression/depression psychotic (13%)

Dermatologic: Skin ulcer (39%), eczema/rash/urticaria (25%)

Gastrointestinal: Nausea/vomiting (41% to 67%), anorexia (66%), diarrhea (37% to 50%), weight loss (27%)

Hematologic: Hemorrhage (11% to 19%)

Hepatic: Ascites (23%)

Local: Injection site reactions: Infection (21%), pain (13%)

Neuromuscular & skeletal: Weakness (87% to 100%), pain/neck pain/arthralgia (84%), jaw pain (54% to 75%), arthritis (52%), myalgia (44%), musculoskeletal pain (35%; predominantly involving legs and feet), back pain (13%), hypoesthesia/hyperparesthesia/paresthesia (5% to 12%)

Respiratory: Dyspnea (90%)

Miscellaneous: Diaphoresis (41%)

1% to 10%:

Cardiovascular: Supraventricular tachycardia (8%), cerebrovascular accident (4%), MI (4%)

Central nervous system: Insomnia (9%), seizure (4%), somnolence (4%)

Dermatologic: Rash (10%), pruritus (4%)

Endocrine & metabolic: Hypokalemia (6%), hyperkalemia (4%)

Gastrointestinal: Abdominal pain (14%), constipation (4% to 6%), weight gain (6%), flatulence (5%), abdominal enlargement (4%)

Genitourinary: Urinary tract infection (7%)

Hematologic: Thrombocytopenia (4%)

Ocular: Amblyopia (8%), vision abnormality (4%)

Renal: Hematuria (5%)

Respiratory: Epistaxis (4% to 9%), pleural effusion (4% to 7%), pharyngitis (5%), pneumonia (5%), pneumothorax (4%), pulmonary edema (4%)

<1%, postmarketing, and/or case reports: Anemia, hepatic failure, hypersplenism, hyperthyroidism, pancytopenia, pulmonary embolism, splenomegaly

Drug Interactions

Anticoagulants: Prostacyclin Analogues may enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Antihypertensives: Prostacyclin Analogues may enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Antiplatelet Agents: Prostacyclin Analogues may enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Monitoring ParametersMonitor for improvements in pulmonary function, decreased exertional dyspnea, fatigue, syncope and chest pain, pulmonary vascular resistance, pulmonary arterial pressure and quality of life. In addition, the pump device and catheters should be monitored frequently to avoid “system” related failure. Monitor arterial pressure; assess all vital functions. Hypoxia, flushing, and tachycardia may indicate overdose.

Nursing: Physical Assessment/Monitoring**Institutional:** Continuous pulmonary and hemodynamic arterial monitoring, protimes. **Noninstitutional:** Avoid sudden rate reduction or abrupt withdrawal or interruption of therapy. When adjustment in rate is made, monitor blood pressure (standing and supine) and pulse for several hours to ensure tolerance to new rate. Monitor for bleeding. Monitor (or teach appropriate caregiver or patient to monitor) vital signs on 3 times/day basis. Monitor for improved pulmonary function and improved quality of life. Be alert for any infusion pump malfunction. Assess for signs of overdose (eg, hypoxia, flushing, tachycardia, fever, chills, anxiety, acute headache, tremor, vomiting, diarrhea).

Patient EducationTherapy on this drug will probably be prolonged, possibly for years. You may experience mild headache, nausea or vomiting, diarrhea, weight loss, nervousness, dizziness (use caution when driving or engaging in activities requiring alertness) and some muscular pains (use of a mild analgesia may be recommended by your prescriber). Report immediately any signs or symptoms of acute or severe headache; back pain; increased difficult breathing; flushing; fever or chills; any unusual bleeding or bruising; chest pain; palpitations; irregular, slow or fast pulse; flushing; loss of sensation; or any onset of unresolved diarrhea. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 0.5 mg, 1.5 mg [provided with 50 mL sterile diluent]

Flolan®: 0.5 mg, 1.5 mg

Generic AvailableYes

ManufacturerGlaxoSmithKline

Mechanism of ActionEpoprostenol is also known as prostacyclin and PGI_2. It is a strong vasodilator of all vascular beds. In addition, it is a potent endogenous inhibitor of platelet aggregation. The reduction in platelet aggregation results from epoprostenol's activation of intracellular adenylate cyclase and the resultant increase in cyclic adenosine monophosphate concentrations within the platelets. Additionally, it is capable of decreasing thrombogenesis and platelet clumping in the lungs by inhibiting platelet aggregation.

Pharmacodynamics/Kinetics

Metabolism: Rapidly hydrolyzed; subject to some enzymatic degradation; forms one active metabolite and 13 inactive metabolites

Half-life elimination: 6 minutes

Excretion: Urine (84%); feces (4%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported. Epoprostenol is an inhibitor of platelet aggregation and may enhance the risk of bleeding with other antiplatelet agents (such as aspirin and/or NSAIDs).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusAnxiety, nervousness are common; may cause confusion, insomnia, or depression

Mental Health: Effects on Psychiatric TreatmentHypotensive effects may be exacerbated by low potency antipsychotics (chlorpromazine) and TCAs

Cardiovascular ConsiderationsThe primary role of epoprostenol is in the treatment of primary pulmonary hypertension in patients unresponsive to other therapy. Response to initial therapy is evaluated in a controlled setting before chronic therapy is administered. The role of epoprostenol in the treatment of heart failure confers a negative impact on cardiovascular morbidity and mortality. Clinical trials showed improvement of heart failure symptoms and exercise tolerance, but an increase in mortality.

Index TermsEpoprostenol Sodium; PGI_2; PGX; Prostacyclin

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International Brand NamesFlolan (AT, AU, BE, CH, CZ, DK, EE, ES, FR, GB, IE, IL, IT, NL, PL, SG)

Eprosartan and Hydrochlorothiazide

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English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ep roe SAR tan & hye droe klor oh THYE a zide)

U.S. Brand NamesTeveten® HCT

Canadian Brand NamesTeveten® HCT; Teveten® Plus

Pharmacologic CategoryAngiotensin II Receptor Blocker; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension (not indicated for initial treatment)

Dosing: AdultsHypertension: Oral: Dose is individualized (combination substituted for individual components)

Usual recommended dose: Eprosartan 600 mg/hydrochlorothiazide 12.5 mg once daily (maximum dose: Eprosartan 600 mg/hydrochlorothiazide 25 mg once daily)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentInitial dose adjustments not recommended by manufacturer; carefully monitor patient. Hydrochlorothiazide is ineffective in patients with Cl_{cr} <30 mL/minute.

Dosing: Hepatic ImpairmentInitial dose adjustments not recommended by manufacturer; carefully monitor patient.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsMay be taken with or without food.

StorageStore between 20°C and 25°C (68°F and 77°F)

ContraindicationsHypersensitivity to eprosartan, hydrochlorothiazide, or any component of the formulation; sulfonamide-derived drugs; anuria

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See "Special populations" below.

Concerns related to adverse effects:

- Electrolyte disturbances: Hyperkalemia may occur with angiotensin II receptor antagonists; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use caution in patients with moderate hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.

- Renal artery stenosis: Use eprosartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use eprosartan with caution with pre-existing renal insufficiency and severe renal impairment. Avoid hydrochlorothiazide in severe renal disease (ineffective); may precipitate azotemia; discontinue or consider withholding if renal impairment occurs.

- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Pregnancy Risk FactorC/D (2nd and 3rd trimesters)
Pregnancy ConsiderationsSee individual agents.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsExcretion of eprosartan in breast milk is not known and use during nursing is not recommended; hydrochlorothiazide is excreted in breast milk
Adverse ReactionsPercentages reported with combination product; other reactions have been reported (see individual agents for additional information).

1% to 10%:

Central nervous system: Dizziness (4%), headache (3%), fatigue (2%)

Hematologic: Neutrophil count decreased (1%)

Neuromuscular & skeletal: Back pain (3%)

Renal: BUN increased (1%)

<1%: Anemia, hyperkalemia (0.9%), hypotension, liver enzyme (ALT) increased, myalgia, orthostasis, thrombocytopenia, upper respiratory tract infection; rhabdomyolysis has been reported (rarely) with angiotensin-receptor antagonists

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure; serum electrolytes, BUN, creatinine
Nursing: Physical Assessment/MonitoringSee individual agents.
Monitoring: Lab TestsSerum electrolytes, BUN, creatinine
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

600 mg/12.5 mg: Eprosartan 600 mg and hydrochlorothiazide 12.5 mg

600 mg/25 mg: Eprosartan 600 mg and hydrochlorothiazide 25 mg

Generic AvailableNo
ManufacturerSolvay Pharmaceuticals
Pricing: U.S. (www.drugstore.com)

Tablets (Teveten HCT)

600-12.5 mg (30): $73.62

Mechanism of Action**Hydrochlorothiazide** inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions. **Eprosartan** blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland.
Pharmacodynamics/KineticsSee individual agents.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness, fatigue, and depression
Mental Health: Effects on Psychiatric TreatmentMay decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels
Cardiovascular Considerations

Hypertension: According to the 2003 JNC 7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 m Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Index TermsEprosartan Mesylate and Hydrochlorothiazide; Hydrochlorothiazide and Eprosartan
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International Brand NamesCo Teveten (FR); Futuran Plus (ES); Teveten Comp (DK, FI, NO, SE); Teveten Plus (AU, BE, BG, CH, DE, EE, HK, IE, KP, PH, PT); Teveten Plus H (CZ); Tevetens Plus (ES)

Eprosartan

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ep roe SAR tan)

U.S. Brand NamesTeveten®

Canadian Brand NamesTeveten®

Pharmacologic CategoryAngiotensin II Receptor Blocker

Use: Labeled IndicationsTreatment of hypertension; may be used alone or in combination with other antihypertensives

Dosing: AdultsHypertension: Oral: Dosage must be individualized. Can administer once or twice daily with total daily doses of 400-800 mg. Usual starting dose is 600 mg once daily as monotherapy in patients who are euvolemic. Limited clinical experience with doses >800 mg.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo starting dosage adjustment is necessary; however, carefully monitor the patient.

Dosing: Hepatic ImpairmentNo starting dosage adjustment is necessary; however, carefully monitor the patient.

ContraindicationsHypersensitivity to eprosartan or any component of the formulation

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Hyperkalemia: May occur; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.
- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.
- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.
- Renal artery stenosis: Use eprosartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.
- Renal impairment: Use with with pre-existing renal insufficiency and severe renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Geriatric ConsiderationsNo specific dose adjustments are necessary in the elderly due to the drug's major route of elimination. However, since many elderly may be volume depleted due to their “blunted thirst reflex” and use of diuretics, care and monitoring of blood pressure and volume status are necessary upon initiation.

Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)

Pregnancy ConsiderationsMedications which act on the renin-angiotensin system are reported to have the following fetal/neonatal effects: Hypotension, neonatal skull hypoplasia, anuria, renal failure, and death; oligohydramnios is also reported. These effects are reported to occur with exposure during the second and third trimesters. There are no adequate and well-controlled studies in pregnant women. **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

LactationNot recommended

Adverse Reactions

1% to 10%:

Central nervous system: Fatigue (2%), depression (1%)

Endocrine & metabolic: Hypertriglyceridemia (1%)

Gastrointestinal: Abdominal pain (2%)

Genitourinary: Urinary tract infection (1%)

Respiratory: Upper respiratory tract infection (8%), rhinitis (4%), pharyngitis (4%), cough (4%)

Miscellaneous: Viral infection (2%), injury (2%)

<1% (Limited to important or life-threatening): Abnormal ECG, abnormal vision, aggravated arthritis, albuminuria, anemia, angina pectoris, anorexia, anxiety, arthritis, arthrosis, asthma, ataxia, atrial fibrillation, back pain, bradycardia, BUN increased, conjunctivitis, constipation, creatine phosphokinase increased, creatinine increased, cystitis, diabetes mellitus, diaphoresis increased, dry mouth, eczema, epistaxis, esophagitis, ethanol intolerance, extrasystoles, facial edema, fatigue, fever, flatulence, furunculosis, gastritis, gastroenteritis, gingivitis, glycosuria, gout, hematuria, herpes simplex, hot flushes, hypercholesterolemia, hyperglycemia, hyper-/hypokalemia, hyponatremia, hypotension, influenza-like symptoms, insomnia, leg cramps, leukopenia, maculopapular rash, malaise, micturition frequency, migraine, nausea, nervousness, neuritis, neutropenia, orthostasis, otitis externa, otitis media, pain, palpitation, paresthesia, periodontitis, peripheral edema, peripheral ischemia, polyuria, pruritus, purpura, rash, renal calculus, rigors, skeletal pain, somnolence, substernal chest pain, tachycardia, tendonitis, thrombocytopenia, tinnitus, toothache, transaminases increased, tremor, urinary incontinence, vertigo, vomiting, weakness, xerophthalmia

Rhabdomyolysis has been reported (rarely) with angiotensin-receptor antagonists.

Metabolism/Transport Effects**Inhibits** CYP2C9 (weak)

Drug Interactions

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Nursing: Physical Assessment/MonitoringUse caution in presence of renal impairment. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (especially anything that may impact blood pressure). Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, hypotension) on a regular basis during therapy. Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsElectrolytes, serum creatinine, BUN, urinalysis

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed and do not discontinue without consulting prescriber. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); or postural hypotension (use caution when rising from lying or sitting position or climbing stairs). Report chest pain or palpitations; respiratory infection or cold symptoms; unusual cough; swelling of face, tongue, lips, or extremities; changes in urinary pattern; extreme fatigue; or other adverse response. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 400 mg, 600 mg

Generic AvailableNo
ManufacturerSmithKline Beecham Pharmaceuticals
Pricing: U.S. (www.drugstore.com)

Tablets (Teveten)

400 mg (30): $64.18

Mechanism of ActionAngiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Eprosartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis. Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because eprosartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Eprosartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.
Pharmacodynamics/Kinetics

Protein binding: 98%

Metabolism: Minimally hepatic

Bioavailability: 300 mg dose: 13%

Half-life elimination: Terminal: 5-9 hours

Time to peak, serum: Fasting: 1-2 hours

Excretion: Feces (90%); urine (7%, mostly as unchanged drug)

Clearance: 7.9 L/hour

Related Information

- Angiotensin Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause fatigue or depression
Mental Health: Effects on Psychiatric TreatmentRisk of lithium toxicity may be increased by eprosartan; monitor lithium levels
Cardiovascular Considerations

Hypertension: According to the 2003 JNC 7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe angiotensin II receptor antagonists appear to have similar indications as the ACE inhibitors. In heart failure, the angiotensin II antagonists are especially useful in providing an alternative therapy in those patients who have intractable cough in response to ACE inhibitor therapy. Candesartan has been studied as an alternative therapy in chronic heart failure patients who cannot tolerate an ACE-I (CHARM-Alternative) and as an added therapy in heart failure patients who are maintained on an ACE-I (CHARM-Added). In both studies, the combined endpoint of cardiovascular death or heart failure hospitalizations was significantly improved over the placebo-treated group. Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.
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International Brand NamesFuturan (ES); Teveten (AT, AU, BE, BG, CH, CZ, DE, DK, EE, FI, FR, GB, GR, HK, HN, IE, KP, NL, NO, PH, PK, PL, PT, SE, TH, TW); Tevetens (ES); Tevetenz (IT)

Eptifibatide

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English

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ep TIF i ba tide)

U.S. Brand NamesIntegrilin®

Canadian Brand NamesIntegrilin®

Pharmacologic CategoryAntiplatelet Agent, Glycoprotein IIb/IIIa Inhibitor

Use: Labeled IndicationsTreatment of patients with acute coronary syndrome (unstable angina/non-Q wave myocardial infarction [UA/NQMI]), including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI including angioplasty, intracoronary stenting)

Dosing: Adults

Acute coronary syndrome: I.V.: Bolus of 180 mcg/kg (maximum: 22.6 mg) over 1-2 minutes, begun as soon as possible following diagnosis, followed by a continuous infusion of 2 mcg/kg/minute (maximum: 15 mg/hour) until hospital discharge or initiation of CABG surgery, up to 72 hours. Concurrent aspirin and heparin therapy (target aPTT 50-70 seconds) are recommended.

Percutaneous coronary intervention (PCI) with or without stenting: I.V.: Bolus of 180 mcg/kg (maximum: 22.6 mg) administered immediately before the initiation of PCI, followed by a continuous infusion of 2 mcg/kg/minute (maximum: 15 mg/hour). A second 180 mcg/kg bolus (maximum: 22.6 mg) should be administered 10 minutes after the first bolus. Infusion should be continued until hospital discharge or for up to 18-24 hours, whichever comes first. Concurrent aspirin (160-325 mg 1-24 hours before PCI and daily thereafter) and heparin therapy (ACT 200-300 seconds during PCI) are recommended. Heparin infusion after PCI is discouraged. In patients who undergo coronary artery bypass graft surgery, discontinue infusion prior to surgery.

Dosing: ElderlyRefer to adult dosing. No dosing adjustment for the elderly appears to be necessary; adjust carefully to renal function.

Dosing: Renal ImpairmentDialysis is a contraindication to use.

Note: The Cockroft-Gault equation using actual body weight sould be used to estimate renal function.

Acute coronary syndrome: Cl_{cr} <50 mL/minute: Use 180 mcg/kg bolus (maximum: 22.6 mg) and 1 mcg/kg/minute infusion (maximum: 7.5 mg/hour)

Percutaneous coronary intervention (PCI) with or without stenting: Cl_{cr} <50 mL/minute: Use 180 mcg/kg bolus (maximum: 22.6 mg) administered immediately before the initiation of PCI and followed by a continuous infusion of 1 mcg/kg/minute (maximum: 7.5 mg/hour). A second 180 mcg/kg (maximum: 22.6 mg) bolus should be administered 10 minutes after the first bolus.

Calculations

- Creatinine Clearance: Adults
- Eptifibatide

Administration: I.V.Do not shake vial. Administer bolus doses by I.V. push over 1-2 minutes. Begin continuous infusion immediately following bolus administration; administer directly from the 100 mL vial.

Administration: I.V. DetailVisually inspect for discoloration or particulate matter prior to administration. The bolus dose should be withdrawn from the 10 mL vial into a syringe. The 100 mL vial should be spiked with a vented infusion set.

StorageVials should be stored refrigerated at 2°C to 8°C (36°F to 46°F). Vials can be kept at room temperature for 2 months. Protect from light until administration. Do not use beyond the expiration date. Discard any unused portion left in the vial.

CompatibilityMay be administered in same I.V. line as alteplase, atropine, dobutamine, heparin, lidocaine, meperidine, metoprolol, midazolam, morphine, nitroglycerin, verapamil, normal saline (infusion may contain up to 60 mEq/L KCl), normal saline/D_5W (infusion may contain up to 60 mEq/L KCl).

ContraindicationsHypersensitivity to eptifibatide or any component of the product; active abnormal bleeding or a history of bleeding diathesis within the previous 30 days; history of CVA within 30 days or a history of hemorrhagic stroke; severe hypertension (systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg) not adequately controlled on antihypertensive therapy; major surgery within the preceding 6 weeks; current or planned administration of another parenteral GP IIb/IIIa inhibitor; thrombocytopenia; dependency on renal dialysis

Allergy Considerations

- Glycoprotein (GP) IIb/IIIa Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: The most common complication is bleeding, including retroperitoneal, pulmonary, and spontaneous GI and/or GU bleeding;

watch closely for bleeding, especially the arterial access site for the cardiac catheterization. Use with extreme caution in patients with platelet counts <150,000/mm^3, patients with hemorrhagic retinopathy, previous history of GI disease, recent thrombolytic therapy and in chronic dialysis patients. Use caution with administration of other drugs affecting hemostasis. Minimize other procedures including arterial and venous punctures, I.M. injections, nasogastric tubes, etc.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal dysfunction (estimated Cl_{cr} <50 mL/minute); dosage adjustment required.

Concurrent drug therapy issues:

- Thrombolytic agents: Concurrent use with thrombolytics has not been established as safe.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Sheath removal: Prior to pulling the sheath, heparin should be discontinued for 3-4 hours and ACT <180 seconds or aPTT <45 seconds. Use standard compression techniques after sheath removal. Watch the site closely afterwards for further bleeding.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsBleeding is the major drug-related adverse effect. Access site is often primary source of bleeding complications. Incidence of bleeding is also related to heparin intensity. Patients weighing <70 kg may have an increased risk of major bleeding.

>10%: Hematologic: Bleeding (major: 1% to 11%; minor: 3% to 14%; transfusion required: 2% to 13%)

1% to 10%:

Cardiovascular: Hypotension (up to 7%)

Hematologic: Thrombocytopenia (1% to 3%)

Local: Injection site reaction

<1% (Limited to important or life-threatening): Anaphylaxis, intracranial hemorrhage (0.5% to 0.7%), stroke

Postmarketing and/or case reports: Acute profound thrombocytopenia, fatal bleeding events, GI hemorrhage, pulmonary hemorrhage

Drug Interactions

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, coleus, cordyceps, dong quai, evening primrose oil, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American), ginseng (Panax), ginseng (Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, same (s-adenosylmethionine), sweet clover, turmeric, and white willow (all have additional antiplatelet activity).

Monitoring ParametersCoagulation parameters, signs/symptoms of excessive bleeding. Laboratory tests at baseline and monitoring during therapy: hematocrit and hemoglobin, platelet count, serum creatinine, PT/aPTT (maintain aPTT between 50-70 seconds unless PCI is to be performed), and ACT with PCI (maintain ACT between 200-300 seconds during PCI).

Assess sheath insertion site and distal pulses of affected leg every 15 minutes for the first hour and then every 1 hour for the next 6 hours. Arterial access site care is important to prevent bleeding. Care should be taken when attempting vascular access that only the anterior wall of the femoral artery is punctured, avoiding a Seldinger (through and through) technique for obtaining sheath access. Femoral vein sheath placement should be avoided unless needed. While the vascular sheath is in place, patients should be maintained on complete bedrest with the head of the bed at a 30° angle and the affected limb restrained in a straight position.

Observe patient for mental status changes, hemorrhage, assess nose and mouth mucous membranes, puncture sites for oozing, ecchymosis and hematoma formation, and examine urine, stool and emesis for presence of occult or frank blood; gentle care should be provided when removing dressings.

Nursing: Physical Assessment/MonitoringAssess other medications (including herbal products) for possible interactions or additive effects. Monitor vital signs and laboratory results prior to, during, and after therapy. Monitor closely for signs of excessive/unusual bleeding. Observe and teach patient bleeding precautions and adverse reactions to report.

Monitoring: Lab TestsLaboratory tests at baseline and monitoring during therapy: Hematocrit and hemoglobin, platelet count, serum creatinine, PT/aPTT (maintain aPTT between 50-70 seconds unless PCI is to be performed), and ACT with PCI (maintain ACT between 200-300 seconds during PCI). Prior to sheath removal, the aPTT or ACT should be checked (do not remove unless aPTT is <45 seconds or the ACT <150 seconds).

Patient EducationEmergency use may dictate depth of patient education. This medication can only be administered intravenously. You will have a tendency to bleed easily following this medication. Use caution to prevent injury (use electric razor, use soft toothbrush, use caution with sharps). If bleeding occurs, apply pressure to bleeding spot until bleeding stops completely. Report unusual bruising or bleeding (eg, blood in urine, stool, or vomitus, bleeding gums), dizziness or vision changes, or back pain. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 0.75 mg/mL (100 mL); 2 mg/mL (10 mL, 100 mL)

Generic AvailableNo

ManufacturerCOR Therapeutics

Mechanism of ActionEptifibatide is a cyclic heptapeptide which blocks the platelet glycoprotein IIb/IIIa receptor, the binding site for fibrinogen, von Willebrand factor, and other ligands. Inhibition of binding at this final common receptor reversibly blocks platelet aggregation and prevents thrombosis.

Pharmacodynamics/Kinetics

Onset of action: Within 1 hour

Duration: Platelet function restored ~4 hours following discontinuation

Protein binding: ~25%

Half-life elimination: 2.5 hours

Excretion: Primarily urine (as eptifibatide and metabolites); significant renal impairment may alter disposition of this compound

Clearance: Total body: 55-58 mL/kg/hour; Renal: ~50% of total in healthy subjects

Related Information

- Glycoprotein Antagonists

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Bleeding; patients weighing <70 kg may have an increased risk of major bleeding.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentContraindicated in patients with a recent stroke (within 30 days)

Cardiovascular Considerations

Acute Coronary Syndromes (ACS): The 2002 ACC/AHA unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) guidelines recommend administration of intravenous glycoprotein IIb/IIIa inhibitors (along with aspirin and heparin) in patients with non-ST-segment elevation ACS with high-risk features (eg, positive biochemical markers of infarction, ST-segment depression, or signs of LV dysfunction) or refractory ischemia. Eptifibatide or tirofiban (with ASA and LMWH or UFH) should be chosen in patients who have high-risk features where an invasive management strategy is not planned. In addition, a glycoprotein IIb/IIIa inhibitor is recommended for patients who will undergo percutaneous coronary intervention (PCI).

Platelet Effects: Eptifibatide has a short duration of action and hemostasis is restored within ~4 hours after discontinuation in patients with normal renal function. Acute profound thrombocytopenia has been associated with eptifibatide use. (Nagge J, 2003; Rezkalla SH, 2003; Salengro E, 2003)

Anesthesia and Critical Care Concerns/Other ConsiderationsEptifibatide has a short duration of action and hemostasis is restored within about 4 hours after discontinuation in patients with normal renal function. Acute profound thrombocytopenia has been associated with eptifibatide use. (Nagge, 2003; Rezkalla, 2003; Salengro, 2003)

Index TermsIntrifiban

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International Brand Names Integrilin (AR, AT, AU, BE, BG, CH, CN, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, MY, NL, NO, PH, PL, PT, RU, SE, SG, TH, TR)

Ergocalciferol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Calciferol™ may be confused with calcitriol

Drisdol® may be confused with Drysol™

Pronunciation(er goe kal SIF e role)
U.S. Brand NamesDrisdol®
Canadian Brand NamesDrisdol®; Ostoforte®
Pharmacologic Category[Vitamin D Analog]
Use: Labeled IndicationsTreatment of refractory rickets, hypophosphatemia, hypoparathyroidism; dietary supplement
Use: Unlabeled/InvestigationalPrevention and treatment of vitamin D deficiency in patients with chronic kidney disease (CKD)
Dosing: Adults**Note:** 1 mcg = 40 int. units

Adequate intake: Oral:

18-50 years: 5 mcg/day (200 int. units/day)

51-70 years: 10 mcg/day (400 int. units/day)

Elderly >70 years: 15 mcg/day (600 int. units/day)

Dietary supplementation: Oral: 10 mcg/day (400 int. units/day)

Vitamin D deficiency/insufficiency in patients with CKD stages 3-4 (K/DOQI guidelines): **Note:** Dose is based on 25-hydroxyvitamin D serum level [25(OH) D]: Oral (treatment duration should be a total of 6 months):

Serum 25(OH)D <5 ng/mL:

50,000 int. units/week for 12 weeks, then 50,000 int. units/month

Serum 25(OH)D 5-15 ng/mL:

50,000 int. units/week for 4 weeks, then 50,000 int. units/month

Serum 25(OH)D 16-30 ng/mL:

50,000 int. units/month

Hypoparathyroidism: Oral: 625 mcg to 5 mg/day (25,000-200,000 int. units) and calcium supplements

Nutritional rickets and osteomalacia: Oral:

Adults with normal absorption: 25-125 mcg/day (1000-5000 int. units)

Adults with malabsorption: 250-7500 mcg (10,000-300,000 int. units)

Vitamin D-*dependent* rickets: Oral: 250 mcg to 1.5 mg/day (10,000-60,000 int. units)

Vitamin D-*resistant* rickets: Oral: 12,000-500,000 int. units/day

Familial hypophosphatemia: Oral: 10,000-60,000 int. units plus phosphate supplements

Dosing: ElderlyRefer to adult dosing (see Geriatric Considerations and Additional Information).

Adequate intake (each 1 mcg = 40 int. units): >70 years: Oral: 15 mcg/day (600 int. units/day)

Dosing: Pediatric**Note:** 1 mcg = 40 int. units

Adequate intake: Oral: Infants and Children: 5 mcg/day (200 int. units/day)

Dietary supplementation: Infants and Children: Oral: 10 mcg/day (400 int. units/day)

Vitamin D deficiency/insufficiency in patients with CKD stages 3-4 (K/DOQI guidelines): **Note:** Dose is based on 25-hydroxyvitamin D serum level [25(OH) D]: Oral (treatment duration should be a total of 3 months):

Serum 25(OH)D <5 ng/mL:

8000 int. units/day for 4 weeks, then 4000 int. units/day for 2 months **or**

50,000 int. units/week for 4 weeks, then 50,000 int. units twice a month for 2 months

Serum 25(OH)D 5-15 ng/mL:

4000 int units/day **or**

50,000 int units every other week

Serum 25(OH)D 16-30 ng/mL:

2000 int. units/day **or**

50,000 int. units every 4 weeks

Hypoparathyroidism: Oral: 1.25-5 mg/day (50,000-200,000 int. units) and calcium supplements

Nutritional rickets and osteomalacia: Oral:

Children with normal absorption: 25-125 mcg/day (1000-5000 int. units)

Children with malabsorption: 250-625 mcg/day (10,000-25,000 int. units)

Vitamin D-*dependent* rickets: Oral: 75-125 mcg/day (3000-5000 int. units); maximum: 1500 mcg/day

Vitamin D-*resistant* rickets: Oral: 12,000-500,000 int. units/day

Familial hypophosphatemia: Oral: 40,000-80,000 int. units plus phosphate supplements; dose may be reduced once growth is complete

Dietary ConsiderationsVitamin D is found in fish, fortified milk, fortified cereal, and infant formulas; it is also produced by exposure to sunlight. Multivitamin supplements containing vitamin D may be needed for infants who are exclusively breastfed or who receive <500 mL/day of formula, and children/adolescents without regular sunlight exposure or who are not ingesting at least 500 mL/day of fortified milk.

Supplemental calcium and/or phosphorous may be required depending on the indication for therapy. Alternately, a low phosphate diet and/or the use of a nonaluminum-binding agent may be required.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

ContraindicationsHypersensitivity to ergocalciferol or any component of the formulation; hypercalcemia; malabsorption syndrome; hypervitaminosis D or abnormal sensitivity to the toxic effects of vitamin D

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Renal impairment: Use with caution in patients with renal impairment or diseases that may impair vitamin D metabolism.
- Rickets: The range between therapeutic and toxic doses is narrow in vitamin D-resistant rickets; adjust dose based on clinical response to avoid toxicity.

Dosage form specific issues:

- Tartrazine: Products may contain tartrazine, which may cause allergic reactions in certain individuals.

Other warnings/precautions:

- Appropriate use: Adequate calcium supplementation is required; calcium and phosphorous levels must be monitored during therapy.
- Toxicity: Effects of vitamin D can last ≥2 months after therapy is discontinued.

Geriatric ConsiderationsVitamin D, folate, and B_{12} (cyanocobalamin) have decreased absorption with age (clinical significance unknown); studies in ill geriatrics demonstrated that low serum concentrations of vitamin D result in greater bone loss. Calorie requirements decrease with age and therefore, nutrient density must be increased to ensure adequate nutrient intake, including vitamins and minerals. The use of a daily supplement with a multiple vitamin with minerals is recommended because elderly consume less vitamin D, absorption may be decreased, and many have decreased sun exposure. This is a recommendation of particular need to those with high risk for osteoporosis.

Pregnancy Risk FactorC (manufacturer); A/C (dose exceeding RDA recommendation; per expert analysis)

Pregnancy ConsiderationsAbnormalities have been observed in animal studies with maternal doses causing hypervitaminosis D. Doses larger than the RDA should be avoided during pregnancy.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsSmall quantities of vitamin D are found in breast milk following normal maternal exposure via sunlight and diet. The amount in breast milk does not correlate with serum levels in the infant. Hypercalcemia has been noted in a breast-feeding infant following maternal use of large doses of ergocalciferol.

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypertension, vascular calcification

Central nervous system: Mental retardation

Endocrine & metabolic: Acidosis, growth suppression (children), hyperphosphatemia, polydypsia

Gastrointestinal: Anorexia, constipation, nausea, weight loss

Hematologic: Anemia

Neuromuscular & skeletal: Aches, osteoporosis (adults), stiffness, weakness

Renal: Azotemia (reversible), hypercalciuria, nephrocalcinosis, nocturia, polyuria, renal dysfunction

Miscellaneous: Dwarfism (children); soft tissue calcification (blood vessels, heart, lungs, renal tubules)

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersSerum calcium, creatinine, BUN, and phosphorus every 1-2 weeks; x-ray bones monthly until stabilized; signs and symptoms of vitamin D intoxication

Vitamin D deficiency/insufficiency in patients with CKD stages 3-4: Measure serum 25(OH)D levels after 3 months of treatment in children or after 6 months in adults. Discontinue ergocalciferol (or any vitamin D supplements) if the corrected total serum calcium level is >10.2 mg/dL.

Reference Range

Serum calcium times phosphorus should not exceed 70 mg^2/dL^2 to avoid ectopic calcification

Vitamin D insufficiency: Serum 25(OH)D <27-32 ng/mL

CKD K/DOQI guidelines definition of stages; chronic disease is kidney damage or GFR <60 mL/minute/1.73 m^2 for ≥3 months:

Stage 2: GFR 60-89 mL/minute/1.73 m^2 (kidney damage with mild decrease GFR)

Stage 3: GFR 30-59 mL/minute/1.73 m^2 (moderate decrease GFR)

Stage 4: GFR 15-29 mL/minute/1.73 m^2 (severe decrease GFR)

Stage 5: GFR <15 mL/minute/1.73 m^2 or dialysis (kidney failure)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse effects at beginning of therapy and regularly with long-term use. Monitor growth in children. Teach patient appropriate nutritional counseling, possible side effects/interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum calcium, creatinine, BUN, phosphorus every 1-2 weeks

Vitamin D deficiency/insufficiency in patients with CKD stages 3-4: measure serum 25(OH)D levels after 3 months of treatment in children or after 6 months in adults. Discontinue ergocalciferol (or any vitamin D supplements) if the corrected total serum calcium level is >10.2 mg/dL.

Patient EducationTake exact dose prescribed; do not take more than recommended. Your prescriber may recommend a special diet; do not increase calcium intake without consulting prescriber. Avoid magnesium supplements or magnesium-containing antacids. You may experience nausea, vomiting, or metallic taste (small frequent meals, frequent mouth care, or sucking hard candy may help). Report chest pain or palpitations; acute headache, dizziness, or feeling of weakness; unresolved nausea or vomiting; persistent metallic taste; unrelieved muscle or bone pain; or CNS irritability. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Drisdol®: 50,000 int. units [1.25 mg; contains tartrazine and soybean oil]

Liquid, oral [drops]:

Drisdol®: 8000 int. units/mL (60 mL) [200 mcg/mL; OTC]

Tablet: 400 int. units [10 mcg; OTC]

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Capsules (Vitamin D)

50000 unit (30): $48.17

Solution (Calciferol)

8000 units/mL (60): $91.99

Mechanism of ActionStimulates calcium and phosphate absorption from the small intestine, promotes secretion of calcium from bone to blood; promotes renal tubule phosphate resorption

Pharmacodynamics/Kinetics

Onset of action: Peak effect: ~1 month following daily doses

Absorption: Readily; requires bile

Metabolism: Inactive until hydroxylated hepatically and renally to calcifediol and then to calcitriol (most active form)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Metallic taste and xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause irritability or drowsiness; may rarely cause psychosis

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsActivated Ergosterol; Viosterol; Vitamin D_2

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International Brand NamesAdekon (MX); Aderowest (MX); AFI-D2 forte (NO); Aquasol AD (MX); Axed (MX); Biocatines D2 (ES); Calciferol (CZ); D-forte (FI); Devitol (AT, FI); Endo-D (IT); Ergosterina Irradiata (IT); Farmobion D2 (IT); Infadin (CZ); Jekovit (FI); One-Alpha (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PR, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Ostelin (AU, IT); Pharmaton Complex (MX); Raquiferol (AR); Raquiferol D3 (PE); Sterogyl (BE, LU); Sterogyl-15 (FR); Uvesterol D (FR); Vigantol (ES); Vigantolo (IT); Vitamina D2 Salf (IT); Vitaminol (GR)

English

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Pronunciation(ER goe loid MES i lates)

Canadian Brand NamesHydergine®

Pharmacologic CategoryErgot Derivative

Use: Labeled IndicationsTreatment of cerebrovascular insufficiency in primary progressive dementia, Alzheimer's dementia, and senile onset

Dosing: AdultsPrimary progressive dementia, Alzheimer's dementia: Oral: 1 mg 3 times/day up to 4.5-12 mg/day; up to 6 months of therapy may be necessary

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsShould not eat or drink while tablet dissolves under tongue.

ContraindicationsHypersensitivity to ergot or any component of the formulation; acute or chronic psychosis; ergot alkaloids are contraindicated with potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics)

Allergy Considerations

- Ergot Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac valvular fibrosis: Ergot alkaloids have been associated with fibrotic valve thickening (eg, aortic, mitral, tricuspid); usually associated with long-term, chronic use.
- Pleural/retroperitoneal fibrosis: Rare cases of pleural and/or retroperitoneal fibrosis have been reported with prolonged daily use.

Concurrent drug therapy issues:

- CYP3A4 inhibitors: Concomitant use with potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics) and ergot alkaloids has been associated with acute ergot toxicity (ergotism); certain ergot alkaloids (eg, ergotamine and dihydroergotamine) are contraindicated by the manufacturer.

Special populations:

- Elderly: Use with caution.
- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsErgoloid mesylates have no role in the treatment of dementia. Many clinicians regard it as no better than placebo and most patients do not experience significant benefits. Improvement in social function has been shown in some studies, but no consistent improvement in memory or cognitive function was reported.

Pregnancy Risk FactorC

Adverse ReactionsAdverse effects are minimal; most common include transient nausea, gastrointestinal disturbances and sublingual irritation with SL tablets; other common side effects include:

Cardiovascular: Orthostatic hypotension, bradycardia

Dermatologic: Skin rash, flushing

Ocular: Blurred vision

Respiratory: Nasal congestion

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)

Drug Interactions

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Efavirenz: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically, the risk for peripheral vasospasm and ischemia may be increased. *Risk X: Avoid combination*

Macrolide Antibiotics: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Posaconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Protease Inhibitors: May decrease the metabolism of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: Ergot Derivatives may enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Ergot Derivatives. This may cause serotonin syndrome. *Risk X: Avoid combination*

Voriconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 1 mg

Tablet, sublingual: 1 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Sublingual (Ergoloid Mesylates)

1 mg (30): $21.99

Tablets (Ergoloid Mesylates)

1 mg (30): $85.99

Mechanism of ActionErgoloid mesylates do not have the vasoconstrictor effects of the natural ergot alkaloids; exact mechanism in dementia is unknown; originally classed as peripheral and cerebral vasodilator, now considered a “metabolic enhancer”; there is no specific evidence which clearly establishes the mechanism by which ergoloid mesylate preparations produce mental effects, nor is there conclusive evidence that the drug particularly affects cerebral arteriosclerosis or cerebrovascular insufficiency

Pharmacodynamics/Kinetics

Absorption: Rapid yet incomplete

Half-life elimination, serum: 3.5 hours

Time to peak, serum: ~1 hour

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentContraindicated in individuals with psychosis

Index TermsDihydroergotoxine; Dihydrogenated Ergot Alkaloids; Hydergine [DSC]

International Brand NamesAlergot (TH); Cirloid (ID); Crinadex (ID); Elmesatt (TW); Ergohydrin (CH); Ergomed (AT); Ergotika (ID); Hodrin (TW); Hyceral (TH); Hydergin (AT, CH, FI, ID, IL); Hydergina (CN, MX, UY, VE); Hydergine (AE, BE, BF, BH, BJ, BR, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PH, QA, SA, SC, SD, SE, SL, SN, SY, TH, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Redergam (HN); Redergin (HR); Togine (TH); Trigogine (CL, SG); Vasian (TH)

Ergonovine

Lexi-Drugs Online

English

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Pronunciation(er goe NOE veen)

U.S. Brand NamesErgotrate®

Pharmacologic CategoryErgot Derivative

Use: Labeled IndicationsPrevention and treatment of postpartum and postabortion hemorrhage caused by uterine atony or subinvolution

Use: Unlabeled/InvestigationalDiagnostically to identify Prinzmetal's angina

Dosing: AdultsTreatment/prevention of postpartum or postabortion hemorrhage:

I.M., I.V. (I.V. should be reserved for emergency use only): 0.2 mg, may repeat dose in 2-4 hours if needed

Oral, SL:

Immediate post-partum: 0.2 mg (usually given I.M. or I.V)

Late post-partum: 0.2-0.4 mg every 6-12 hours until danger of uterine atony has passed (usually ~48 hours)

Dosing: ElderlyRefer to adult dosing.

Administration: I.V.I.V. use should be limited to patients with severe uterine bleeding or other life-threatening emergency situations. I.V. doses should be administered over a period of not <1 minute.

Administration: I.V. DetailDilute in NS to 5 mL for I.V. administration.

pH: 2.7-3.5

Administration: OralOral tablets may also be administered sublingually.

Storage

Injection: Store at <46°F; protect from light. May store at room temperature for up to 60 days. Do not use if discoloration occurs.

Tablet: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F).

Compatibility**Compatibility when admixed: Compatible:** Amikacin, sodium bicarbonate.

ContraindicationsHypersensitivity to ergonovine or any component of the formulation; ergot alkaloids are contraindicated with potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics); induction of labor, threatened spontaneous abortion, pregnancy

Allergy Considerations

- Ergot Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac valvular fibrosis: Ergot alkaloids have been associated with fibrotic valve thickening (eg, aortic, mitral, tricuspid); usually associated with long-term, chronic use.
- Ergotism: Ergot alkaloid use may result in ergotism (intense vasoconstriction) resulting in peripheral vascular ischemia and possible gangrene. Ergotism is usually associated with overdosage or prolonged chronic use; do not exceed dosing guidelines and avoid prolonged administration.
- Pleural/retroperitoneal fibrosis: Rare cases of pleural and/or retroperitoneal fibrosis have been reported with prolonged daily use.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (eg, hypertension).
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hypocalcemia: Restore uterine responsiveness in calcium-deficient patients who do not respond to ergonovine by I.V. calcium administration.
- Renal impairment: Use with caution in patients with renal impairment.
- Sepsis: Use with caution in patients with sepsis.
- Vascular disease: Use with caution in patients with obliterative vascular disease.

Concurrent drug therapy issues:

- CYP3A4 inhibitors: Concomitant use with potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics) and ergot alkaloids has been associated with acute ergot toxicity (ergotism); certain ergot alkaloids (eg, ergotamine and dihydroergotamine) are contraindicated by the manufacturer.

Special populations:

- Elderly: Use with extreme caution or avoid use in the elderly; due to vasoconstrictive properties and cardiovascular adverse effects associated with ergot alkaloids.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- I.V. administration: Use with extreme caution when administering intravenously; risk of inducing sudden hypertensive and cerebrovascular accidents.

Pregnancy ConsiderationsAdministration causes hyperstimulation of the uterus and may cause uterine tetany, decreased uteroplacental blood flow, uterine rupture, cervical and perineal lacerations, amniotic fluid embolism, and possible trauma to the infant. Ergonovine is used in the third stage of labor for the prevention and treatment of postpartum hemorrhage; use is contraindicated during pregnancy.

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypertension, MI, shock

Gastrointestinal: Nausea, vomiting

Miscellaneous: Allergic reactions, ergotism

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)

Drug Interactions

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Efavirenz: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically, the risk for peripheral vasospasm and ischemia may be increased. *Risk X: Avoid combination*

Macrolide Antibiotics: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Posaconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Protease Inhibitors: May decrease the metabolism of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: Ergot Derivatives may enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Ergot Derivatives. This may cause serotonin syndrome. *Risk X: Avoid combination*

Voriconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Monitoring ParametersBlood pressure, pulse, uterine response; cramping, if severe, may justify a need for dose reduction (oral)

Nursing: Physical Assessment/MonitoringBlood pressure should be monitored, especially with I.V. use. For postpartum use, character and amount of vaginal bleeding should be monitored. Assess therapeutic effectiveness and adverse reactions, including ergotamine toxicity (eg, headache, ringing in ears, nausea and vomiting, diarrhea, numbness or coldness of extremities, confusion, hallucinations, dyspnea, chest pain, convulsions). When used to test for Prinzmetal's angina during coronary arteriography, emergency equipment, including nitroglycerin, must be on hand. When used at any time other than postpartum, determine that patient is not pregnant.

Patient EducationFor angina diagnosis, cardiologist will instruct patient about what to expect. For postpartum hemorrhage (an emergency situation), patient needs to know why the drug is being given and what side effects she might experience (eg, mild nausea and vomiting, dizziness, headache, ringing ears) and be instructed to report respiratory difficulty, acute headache, numbness or cold feeling in extremities, or severe abdominal cramping. **Pregnancy/breast-feeding precautions:** If used for angina diagnosis, inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, as maleate:

Ergotrate®: 0.2 mg/mL (1 mL)

Tablet, as maleate:

Ergotrate®: 0.2 mg

Generic AvailableNo

Mechanism of ActionSimilar smooth muscle actions as seen with ergotamine; however, it affects primarily uterine smooth muscles producing sustained contractions and thereby shortens the third stage of labor.

Pharmacodynamics/Kinetics

Onset of action: I.M.: ~2-5 minutes; Oral: 6-15 minutes

Duration: I.M.: Uterine effect: 3 hours; I.V.: ~45 minutes; Oral: 3 hours

Absorption: Oral: Rapid

Metabolism: Hepatic

Half-life elimination: I.V.: 120 minutes

Excretion: Primarily feces; urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness
Mental Health: Effects on Psychiatric TreatmentNone reported
Cardiovascular ConsiderationsFor variant angina, ergonovine with an intravenous test dose of 50 mcg followed by 0.1-0.4 mg every 5 minutes can be used (Fuster V, 2004).
Index TermsErgometrine Maleate; Ergonovine Maleate
References

Dargaville PA and Campbell NT, “Ergonovine Overdose in the Neonate,” *Ped Res*, 1997, 41(4):144.

de Groot AN, van Dongen PW, Vree TB, et al, “Ergot Alkaloids. Current Status and Review of Clinical Pharmacology and Therapeutic Use Compared With Other Oxytocics in Obstetrics and Gynaecology,” *Drugs*, 1998, 56(4):523-35.

Fuster V, Topol EJ, and Nabel EG, eds, *Atherothrombosis and Coronary Artery Disease*, 2nd ed, Philadelphia, PA: Lippincott Williams & Wilkens, 2004.

Soriano D, Dulitzki M, Schiff E, et al, “A Prospective Cohort Study of Oxytoxin Plus Ergometrine Compared With Oxytocin Alone for Prevention of Postpartum Heamorrhage,” *Br J Obstet Gynaecol*, 1996, 103(11):1068-73.

International Brand NamesErgotrate (MX)

Ergotamine and Caffeine

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Cafergot® may be confused with Carafate®

Pronunciation(er GOT a meen & KAF een)

U.S. Brand NamesCafergot®; Migergot

Canadian Brand NamesCafergor®

Pharmacologic CategoryAntimigraine Agent; Ergot Derivative; Stimulant

Use: Labeled IndicationsAbort or prevent vascular headaches, such as migraine, migraine variants, or so-called “histaminic cephalalgia”

Dosing: AdultsMigraine:

Oral: Two tablets at onset of attack; then 1 tablet every 30 minutes as needed; maximum: 6 tablets per attack; do not exceed 10 tablets/week.

Rectal: One suppository rectally at first sign of an attack; follow with second dose after 1 hour, if needed; maximum: 2 per attack; do not exceed 5/week.

Storage

Suppositories: Store below 25°C (77°F) in sealed foil. Protect from moisture.

Tablet: Store at room temperature 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to ergotamine, caffeine, or any component of the formulation; peripheral vascular disease; hepatic or renal disease; coronary artery disease; hypertension; sepsis; ergot alkaloids are contraindicated with strong inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics); pregnancy

Allergy Considerations

- Ergot Alkaloid Allergy

Warnings/Precautions

Boxed warnings:

- CYP3A4 inhibitors: See “Concurrent drug therapy issues” below.

Concerns related to adverse effects:

- Cardiac valvular fibrosis: Ergot alkaloids have been associated with fibrotic valve thickening (eg, aortic, mitral, tricuspid); usually associated with long-term, chronic use.

- Cardiovascular effects: Vasospasm or vasoconstriction can occur, possibly resulting in decreased cerebral blood flow, ECG changes, and hypertension; sustained vasoconstriction may also lead to ischemic colitis, intermittent claudication, aggravation of angina, or precipitation of MI. Do not use is any patient at risk or predisposed to vascular effects of ergot alkaloids.

- Ergotism: Ergot alkaloid use may result in ergotism (intense vasoconstriction) resulting in peripheral vascular ischemia and possible gangrene. Ergotism is usually associated with overdosage or prolonged chronic use; do not exceed dosing guidelines and avoid prolonged administration.

- Pleural/retroperitoneal fibrosis: Rare cases of pleural and/or retroperitoneal fibrosis have been reported with prolonged daily use.

Concurrent drug therapy issues:

- CYP3A4 inhibitors: **[U.S. Boxed Warning]: Ergot alkaloids are contraindicated with potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics); concomitant use associated with acute ergot toxicity (ergotism).**

Special populations:

- Elderly: Use with extreme caution or avoid use in the elderly; due to vasoconstrictive properties and cardiovascular adverse effects associated with ergot alkaloids.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Withdrawal: Discontinuation after extended use may result in withdrawal symptoms (eg, rebound headache).

Geriatric ConsiderationsNot recommended for use in the elderly. May be harmful due to reduction in cerebral blood flow. May precipitate angina, myocardial infarction, or aggravate intermittent claudication.

Pregnancy Risk FactorX

Pregnancy ConsiderationsMay cause prolonged constriction of the uterine vessels and/or increased myometrial tone leading to reduced placental blood flow. This has contributed to fetal growth retardation in animals.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsErgotamine is excreted in breast milk and may cause vomiting, diarrhea, weak pulse, and unstable blood pressure in the nursing infant. Consider discontinuing the drug or discontinuing nursing.

Adverse ReactionsFrequency not defined.

Cardiovascular: Absence of pulse, bradycardia, cardiac valvular fibrosis, cyanosis, edema, ECG changes, gangrene, hypertension, ischemia, precordial distress and pain, tachycardia, vasospasm

Central nervous system: Vertigo

Dermatologic: Itching

Gastrointestinal: Anal or rectal ulcer (with overuse of suppository), nausea, vomiting

Genitourinary: Retroperitoneal fibrosis

Neuromuscular & skeletal: Muscle pain, numbness, paresthesia, weakness

Respiratory: Pleuropulmonary fibrosis

Miscellaneous: Cold extremities

Metabolism/Transport Effects

Ergotamine: **Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (weak)

Caffeine: **Substrate** of CYP1A2 (major), 2C9 (minor), 2D6 (minor), 2E1 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 3A4 (moderate)

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Efavirenz: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically, the risk for peripheral vasospasm and ischemia may be increased. *Risk X: Avoid combination*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Macrolide Antibiotics: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Posaconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Protease Inhibitors: May decrease the metabolism of Ergot Derivatives. *Risk X: Avoid combination*

Quinolone Antibiotics: May decrease the metabolism of Caffeine. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Ofloxacin; Sparfloxacin; Trovafloxacin. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Regadenoson: Caffeine may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Serotonin 5-HT1D Receptor Agonists: Ergot Derivatives may enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Ergot Derivatives. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Voriconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: Avoid tea, cola, and coffee (caffeine may increase GI absorption of ergotamine). Grapefruit juice may cause increased blood levels of ergotamine, leading to increased toxicity.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, anything that adds to peripheral vasoconstriction). Assess therapeutic effectiveness and adverse response on a regular basis during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Do not give to women of childbearing unless woman is capable of complying with appropriate contraceptive measures 1 month prior to therapy, during therapy, and for 1 month following therapy. Instruct patient on appropriate contraceptive measures. Breast-feeding is not recommended.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy without consulting prescriber. Take this drug as directed; do not increase dose or use more often than prescribed. If relief is not obtained, contact your prescriber. Avoid products that contain caffeine (eg, tea, coffee, colas, cocoa); caffeine increases GI absorption of ergotamines. May cause drowsiness (avoid activities requiring alertness until effects of medication are known); mild nausea or vomiting (consult prescriber for approved antiemetic); or mild weakness or numbness of extremities (avoid activities that may have a potential for injury). Inspect your extremities for coldness, numbness, or injury. Report immediately any extreme numbness, pain, tingling or weakness in extremities (toes, fingers); severe unresolved nausea or vomiting; or respiratory difficulty or irregular heartbeat. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant 1 month before, during, or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not donate blood during or for 1 month following therapy. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suppository, rectal:

Migergot: Ergotamine tartrate 2 mg and caffeine 100 mg (12s)

Tablet: Ergotamine tartrate 1 mg and caffeine 100 mg

Cafergot®: Ergotamine tartrate 1 mg and caffeine 100 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Suppository (Migergot)

2-100 mg (12): $72.99

Mechanism of ActionHas partial agonist and/or antagonist activity against tryptaminergic, dopaminergic and alpha-adrenergic receptors depending upon their site; is a highly active uterine stimulant; it causes constriction of peripheral and cranial blood vessels and produces depression of central vasomotor centers

Pharmacodynamics/Kinetics

Absorption: Ergotamine: Oral, rectal: Erratic; enhanced by caffeine coadministration

Metabolism: Extensively hepatic

Time to peak, serum: Ergotamine: 0.5-3 hours

Half-life elimination: 2 hours

Excretion: Feces (90% as metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and dizziness are common

Mental Health: Effects on Psychiatric TreatmentUse caution with propranolol; vasoconstriction has been reported; coadministration with strong CYP3A4 inhibitors has been associated with serious adverse events (some weaker inhibitors include nefazodone, fluoxetine and fluvoxamine)

Cardiovascular ConsiderationsThis drug should be used extremely carefully because of its potent vasoconstrictor action. Administration may elicit marked increases in blood pressure and intracranial hemorrhage. Use should be avoided in patients with cardiovascular disease, including hypertension, coronary artery disease and peripheral vascular disease.

Index TermsCaffeine and Ergotamine; Ergotamine Tartrate and Caffeine

References

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Husum B, Metz P, and Rasmussen JP, “Nitroglycerin Infusion for Ergotism,” *Lancet*, 1979, 2(8146):794-5.

McGuigan MA, “Ergot Alkaloids,” *Clin Toxicol Rev*, 1984, 6:1-2.

Orton DA and Richardson RJ, “Ergotamine Absorption and Toxicity,” *Postgrad Med J*, 1982, 58(675):6-11.[PubMed 7088766]

International Brand NamesAvamigran (TH); Cafergot (AE, AR, AT, AU, BE, BF, BH, BJ, CI, CY, EG, ET, GB, GH, GM, GN, GR, HK, ID, IL, IQ, IR, IT, JO, JP, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, OM, QA, RU, SA, SC, SD, SE, SL, SN, SY, TH, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Cafergot N (DE); Degran (TH); Enxak (BR); Ergam (HU); Ergofein (CZ); Ergokoffin (DK); Ergosanol (LU); Ergosanol SL (CH); Ergosanol Spezial N (LU); Ergoton (TW); Ericaf (ID); Gynergene Cafeine (FR); Lingraine (IE); Migana (TH); Migrexa (HR); Polygot (TH); Sydolil (MX); Tofago (TH); Trinergot (MX)

Ergotamine

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(er GOT a meen)

U.S. Brand NamesErgomar®

Pharmacologic CategoryAntimigraine Agent; Ergot Derivative

Use: Labeled IndicationsAbort or prevent vascular headaches, such as migraine, migraine variants, or so-called “histaminic cephalalgia”

Dosing: AdultsMigraine: Sublingual: One tablet under tongue at first sign, then 1 tablet every 30 minutes if needed; maximum dose: 3 tablets/24 hours, 5 tablets/week

Dosing: ElderlySee Special Geriatric Considerations.

Administration: OralDo not crush sublingual tablets.

StorageStore sublingual tablet at room temperature. Protect from light and heat.

ContraindicationsHypersensitivity to ergotamine or any component of the formulation; peripheral vascular disease; hepatic or renal disease; coronary artery disease; hypertension; sepsis; ergot alkaloids are contraindicated with strong inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics); pregnancy

Allergy Considerations

- Ergot Alkaloid Allergy

Warnings/Precautions

Boxed warnings:

- CYP3A4 inhibitors: See “Concurrent drug therapy issues” below.

Concerns related to adverse effects:

- Cardiac valvular fibrosis: Ergot alkaloids have been associated with fibrotic valve thickening (eg, aortic, mitral, tricuspid); usually associated with long-term, chronic use.
- Cardiovascular effects: Vasospasm or vasoconstriction can occur, possibly resulting in decreased cerebral blood flow, ECG changes, and hypertension; sustained vasoconstriction may also lead to ischemic colitis, intermittent claudication, aggravation of angina, or precipitation of MI. Do not use is any patient at risk or predisposed to vascular effects of ergot alkaloids.
- Ergotism: Ergot alkaloid use may result in ergotism (intense vasoconstriction) resulting in peripheral vascular ischemia and possible gangrene. Ergotism is usually associated with overdosage or prolonged chronic use; do not exceed dosing guidelines and avoid prolonged administration.
- Pleural/retroperitoneal fibrosis: Rare cases of pleural and/or retroperitoneal fibrosis have been reported with prolonged daily use.

Concurrent drug therapy issues:

- CYP3A4 inhibitors: **[U.S. Boxed Warning]: Ergot alkaloids are contraindicated with potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics); concomitant use associated with acute ergot toxicity (ergotism).**

Special populations:

- Elderly: Use with extreme caution or avoid use in the elderly; due to vasoconstrictive properties and cardiovascular adverse effects associated with ergot alkaloids.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Withdrawal: Discontinuation after extended use may result in withdrawal symptoms (eg, rebound headache).

Geriatric ConsiderationsNot recommended for use in the elderly. May be harmful due to reduction in cerebral blood flow. May precipitate angina, myocardial infarction, or aggravate intermittent claudication.

Pregnancy Risk FactorX

Pregnancy ConsiderationsMay cause prolonged constriction of the uterine vessels and/or increased myometrial tone leading to reduced placental blood flow. This has contributed to fetal growth retardation in animals.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsErgotamine is excreted in breast milk and may cause vomiting, diarrhea, weak pulse, and unstable blood pressure in the nursing infant. Consider discontinuing the drug or discontinuing nursing.

Adverse ReactionsFrequency not defined.

Cardiovascular: Absence of pulse, bradycardia, cardiac valvular fibrosis, cyanosis, edema, ECG changes, gangrene, hypertension, ischemia, precordial distress and pain, tachycardia, vasospasm

Central nervous system: Vertigo

Dermatologic: Itching

Gastrointestinal: Nausea, vomiting

Genitourinary: Retroperitoneal fibrosis

Neuromuscular & skeletal: Muscle pain, numbness, paresthesia, weakness

Respiratory: Pleuropulmonary fibrosis

Miscellaneous: Cold extremities

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); Inhibits CYP3A4 (weak)
Drug Interactions

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Efavirenz: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically, the risk for peripheral vasospasm and ischemia may be increased. *Risk X: Avoid combination*

Macrolide Antibiotics: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Posaconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Protease Inhibitors: May decrease the metabolism of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: Ergot Derivatives may enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Ergot Derivatives. This may cause serotonin syndrome. *Risk X: Avoid combination*

Voriconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: Avoid tea, cola, and coffee (caffeine may increase GI absorption of ergotamine). Grapefruit juice may cause increased blood levels of ergotamine, leading to increased toxicity.
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic effectiveness and adverse response on a regular basis during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. Abrupt discontinuation after long-term use may result in withdrawal symptoms (eg, rebound headache). **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Do not give to women of childbearing unless woman is capable of complying with contraceptive measures 1 month prior to therapy, during therapy, and for 1 month following therapy. Instruct patient on appropriate contraceptive measures. Breast-feeding is not recommended.
Patient EducationDo not take any new medication during therapy without consulting prescriber. Take this drug as directed; do not increase dose or use more often than prescribed. If relief is not obtained, contact your prescriber. Avoid products that contain caffeine (eg, tea, coffee, colas, cocoa); caffeine increases GI absorption of ergotamines. May cause drowsiness (avoid activities requiring alertness until effects of medication are known); mild nausea or vomiting (consult prescriber for approved antiemetic); or mild weakness or numbness of extremities (avoid activities that may have a potential for injury). Inspect your extremities for coldness, numbness, or injury. Report immediately any extreme numbness, pain, tingling or weakness in extremities (toes, fingers); severe unresolved nausea or vomiting; or respiratory difficulty or irregular heartbeat. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant 1 month before, during, or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not donate blood during or for 1 month following therapy. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, sublingual, as tartrate:

Ergomar®: 2 mg [peppermint flavor]

Generic AvailableNo
Mechanism of ActionHas partial agonist and/or antagonist activity against tryptaminergic, dopaminergic and alpha-adrenergic receptors depending upon their site; is a highly active uterine stimulant; it causes constriction of peripheral and cranial blood vessels and produces depression of central vasomotor centers
Pharmacodynamics/Kinetics

Absorption: Oral: Erratic; enhanced by caffeine coadministration

Metabolism: Extensively hepatic

Time to peak, serum: 0.5-3 hours

Half-life elimination: 2 hours

Excretion: Feces (90% as metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and dizziness are common

Mental Health: Effects on Psychiatric TreatmentUse caution with propranolol; vasoconstriction has been reported; coadministration with strong CYP3A4 inhibitors has been associated with serious adverse events (some weaker inhibitors include nefazodone, fluoxetine and fluvoxamine)

Cardiovascular ConsiderationsThis drug should be used extremely carefully because of its potent vasoconstrictor action. Administration may elicit marked increases in blood pressure and intracranial hemorrhage. Use should be avoided in patients with cardiovascular disease, including hypertension, coronary artery disease and peripheral vascular disease.

Index TermsErgotamine Tartrate

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International Brand NamesAvamigran (PH); Cafergot (MX, SE); Caftar (MX); Clavigrenin akut (DE); Cornutamin (CZ); Enxak (BR); Ergam (HU); ergo sanol (DE); Ergo-Kranit (DE); Ergocaf (MX); Ergodryl Mono (AU); Ergokapton (AT); Ergosanol (DE, LU); Ergosanol SL (CH); Ergosanol Spezial N (LU); Ergotamin (DE); Ergotamin Medihaler (DK); Ergotamin ”Dak” (DK); Ergotamina tartrato (IT); Ergotaminum Tartaricum (PL); Ergotan (IT); Ergotartrat (AT); Gynergen (IT); Lingraine (GB, IE); Medihaler Ergotamine (NZ); Medihaler-Ergotamine (GB); Migretamine (JP); Migrexa (DE, HR); RubieNex (DE); Secagyn (IL); Sydolil (MX); Tetralgin Haler (AR); Trinergot (MX)

Erlotinib

Lexi-Drugs Online

English

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Special Alerts

Erlotinib: Health Canada Issues Warning Concerning Hepatoxicity - December, 2008

Hoffmann-La Roche Limited, in conjunction with Health Canada, has issued a “Dear Healthcare Professional” letter regarding important safety information concerning erlotinib (Tarceva®) use in patients with hepatic impairment. The warning is similar to that released previously by the U.S. Food and Drug Administration (FDA). Further information may be found at:

Canada: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/tarceva_hpc-cps-eng.php

U.S.: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Tarceva

Erlotinib: Reports of Hepatic Failure and Hepatorenal Syndrome - September 2008

OSI Pharmaceuticals, Inc and Genetech, Inc, in conjunction with the U.S. Food and Drug Administration (FDA), have issued a “Dear Healthcare Professional” letter regarding erlotinib (Tarceva®) use in patients with hepatic impairment. Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported, particularly in patients with baseline hepatic impairment. Closely monitor all patients with hepatic impairment (total bilirubin greater than upper limit of normal [ULN] or any Child-Pugh class) receiving erlotinib, especially those with total bilirubin >3 times ULN. Dosage modifications (therapy interruption or discontinuation) may be necessary for severe changes in liver function. The FDA-approved labeling has been updated to include related changes to warnings and dosage modifications for hepatic disease.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Tarceva

Medication Safety Issues

Sound-alike/look-alike issues:

Erlotinib may be confused with gefitinib

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(er LOE tye nib)

U.S. Brand NamesTarceva®

Canadian Brand NamesTarceva®

Pharmacologic CategoryAntineoplastic Agent, Tyrosine Kinase Inhibitor; Epidermal Growth Factor Receptor (EGFR) Inhibitor

Use: Labeled IndicationsTreatment of locally advanced or metastatic nonsmall cell lung cancer (NSCLC) as monotherapy; locally advanced, unresectable or metastatic pancreatic cancer (first-line therapy in combination with gemcitabine)

Dosing: Adults**Note:** Dose adjustments are likely to be needed when erlotinib is administered concomitantly with strong CYP3A4 inducers or inhibitors.

NSCLC: 150 mg once daily

Pancreatic cancer: 100 mg once daily in combination with gemcitabine

Dosage adjustment for concomitant CYP3A4 inhibitors/inducers:

CYP3A4 inhibitors: Dose reductions are more likely to be needed for severe adverse reactions when erlotinib is administered concomitantly with strong CYP3A4 inhibitors (eg, azole antifungals, clarithromycin, erythromycin, nefazodone, protease inhibitors, telithromycin). Dose reduction (if required) should be done in decrements of 50 mg.

CYP3A4 inducers: Concomitant administration with CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifamycins, and St John’s wort) may require increased doses (increase as tolerated at 2-week intervals); doses >150 mg/day should be considered with rifampin; alternatives to the enzyme-inducing agent should be utilized first.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentInterrupt treatment for renal disease due to dehydration; may resume after euvolemia re-established.

Dosing: Hepatic Impairment

The manufacturer recommends the following guidelines:

Patients with normal hepatic function at baseline: Total bilirubin >3 times ULN and/or transaminases >5 times ULN: Interrupt or discontinue treatment

Patients with baseline hepatic impairment:

Total bilirubin >3 times ULN: Use extreme caution

Worsening liver function (not yet severe): Interrupt treatment and/or reduce dose

Severe changes in liver function (eg, doubling of total bilirubin and/or tripling of transaminases): Interrupt or discontinue treatment

A reduced starting dose (75 mg once daily) has been recommended in patients with hepatic dysfunction (AST ≥3 times ULN or direct bilirubin 1-7 mg/dL), with individualized dosage escalation if tolerated (Miller, 2007).

Dosing: Adjustment for ToxicityDose reductions should be made in 50 mg decrements.

Diarrhea: Manage with loperamide; Severe diarrhea: Reduce dose or temporarily interrupt treatment

Pulmonary symptoms: Acute onset (or worsening) of pulmonary symptoms (eg, dyspnea, cough, fever): Interrupt treatment and evaluate for drug-induced interstitial lung disease; discontinue permanently with development of interstitial lung disease

Severe skin reaction: Reduce dose or temporarily interrupt treatment

Dosing: Combination Regimens

Pancreatic cancer: Gemcitabine-Erlotinib

Administration: OralThe manufacturer recommends administration on an empty stomach (at least 1 hour before or 2 hours after the ingestion of food) even though this reduces drug absorption by approximately 40%. Administration after a meal results in nearly 100% absorption.

Dietary ConsiderationsTake this medicine an empty stomach, 1 hour before or 2 hours after a meal. Avoid grapefruit juice.

StorageStore at room temperature of 25°C (77°F); excursions permitted to 15°C and 30°C (59°F and 86°F).

ContraindicationsThere are no contraindications listed within the manufacturer’s labeling.

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Cardiovascular events: Cerebrovascular accidents, MI, and myocardial ischemia have been reported; use with caution in patients with cardiovascular disease.

- Hematologic effects: Microangiopathic hemolytic anemia (MAHA) with thrombocytopenia has been reported (rarely) with erlotinib in combination with gemcitabine.

- Pulmonary toxicity: Rare, sometimes fatal, pulmonary toxicity (interstitial pneumonia, interstitial lung disease [ILD], obliterative bronchiolitis, pulmonary fibrosis) has occurred; symptoms may begin within 5 days to more than 9 months after treatment initiation. Interrupt therapy for unexplained pulmonary symptoms (dyspnea, cough, and fever); discontinue for confirmed ILD.

- Skin reaction: Generalized or severe acneiform, erythematous or maculopapular rash may occur. Skin rash may correlate with treatment response and prolonged survival (Saif, 2008). Management should include alcohol-free lotions, topical antibiotics or topical corticosteroids, or if necessary, oral antibiotics and systemic corticosteroids; avoid sunlight. Severe skin reactions may require dosage modification.

Disease-related concerns:

- Hepatic impairment: Liver enzyme elevations have been reported. Hepatic failure and hepatorenal syndrome have also been reported, particularly in patients with baseline hepatic impairment. Monitor patients with any hepatic impairment (total bilirubin >ULN; Child-Pugh class A, B, or C) closely, including those with hepatic disease due to tumor burden. Use with extreme caution in patients with total bilirubin >3 times ULN. Dosage reduction, interruption or discontinuation may be recommended for changes in hepatic function.

- Renal impairment: Acute renal failure, renal insufficiency, and hepatorenal syndrome have been reported; use with caution in patients with or at risk for renal impairment. Monitor closely for dehydration.

Concurrent drug therapy issues:

- Anticoagulants: Use caution with concomitant anticoagulant therapy; elevated INR and bleeding events have been reported.

- Gemcitabine: MI, CVA, and microangiopathic hemolytic anemia with thrombocytopenia have been noted in patients receiving concomitant erlotinib and gemcitabine.

- High potential for interactions: Concurrent use with CYP3A4 inhibitors and moderate or strong CYP3A4 inducers may affect erlotinib levels. Consider alternative agents to CYP3A4 inducers to avoid the potential for CYP-mediated interactions; use with caution in patients taking strong CYP3A4 inhibitors.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Smokers: Erlotinib levels may be lower in patients who smoke; advise patients to stop smoking.

Geriatric ConsiderationsIn clinical trials, there was no significant difference between older and younger adults in survival benefit, safety, or pharmacokinetics. No dosage adjustment necessary in elderly patients.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated fetal harm and abortion. There are no well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid pregnancy; adequate contraception is recommended during treatment and for 2 weeks after treatment has been completed.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

Adverse reactions reported with monotherapy:

>10%:

Central nervous system: Fatigue (52% to 79%)

Dermatologic: Rash (75% to 76%; grade 3: 8%; grade 4: <1%; median onset: 8 days), pruritus (13%), dry skin (12%)

Gastrointestinal: Diarrhea (54% to 55%; grade 3: 6%; grade 4: <1%; median onset: 12 days), anorexia (52% to 69%), nausea (33% to 40%), vomiting (23% to 25%), stomatitis (17% to 19%), abdominal pain (11%)

Ocular: Conjunctivitis (12%), keratoconjunctivitis sicca (12%)

Respiratory: Dyspnea (41%), cough (33%)

Miscellaneous: Infection (24% to 34%)

1% to 10%:

Hepatic: ALT increased (grade 2: 4%)

Respiratory: Pneumonitis/pulmonary infiltrate (3%), pulmonary fibrosis (3%)

Significant adverse reactions reported with combination (erlotinib plus gemcitabine) therapy:

Cardiovascular: Deep venous thrombosis (4%), cerebrovascular accident (2%; including cerebral hemorrhage), MI/myocardial ischemia (2%), arrhythmia, syncope

Central nervous system: Fever (36%), depression (19%), headache (15%)

Dermatologic: Rash (69%)

Gastrointestinal: Diarrhea (48%), weight loss (39%), stomatitis (22%), ileus, pancreatitis

Hematologic: Hemolytic anemia, microangiopathic hemolytic anemia with thrombocytopenia (1%)

Hepatic: ALT increased (grade 2: 31%, grade 3: 13%, grade 4: <1%), AST increased (grade 2: 24%, grade 3: 10%, grade 4 <1%), hyperbilirubinemia (grade 2: 17%, grade 3: 10%, grade 4: <1%)

Renal: Renal insufficiency

Respiratory: Dyspnea (24%), cough (16%), ILD-like events (3%)

Miscellaneous: Infection (39%)

Mono- or combination therapy: <1%, postmarketing, and/or case reports: Acute renal failure, bronchiolitis, corneal ulcerations, episcleritis, epistaxis, gastritis, gastroduodenal ulcers, gastrointestinal bleeding, gastrointestinal hemorrhage, hair/nail disorders (alopecia, brittle/loose nails, eyelash/brow changes, hirsutism, paronychia), hearing loss, hematemesis, hematochezia, hepatic failure, hepatorenal syndrome, hepatotoxicity, interstitial lung disease, melena, peptic ulcer bleeding, pulmonary fibrosis, pulmonary infiltrates, rash (acneiform; sparing prior radiation field), tympanic membrane perforation

Oncology: Emetic PotentialVery low (<10%)

Metabolism/Transport EffectsSubstrate of CYP1A2 (minor), 3A4 (major)

Drug Interactions

Antacids: May decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Erlotinib. *Risk C: Monitor therapy*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

H2-Antagonists: May decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Proton Pump Inhibitors: May decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Rifampin: May increase the metabolism of Erlotinib. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Erlotinib bioavailability is increased with food. Avoid grapefruit or grapefruit juice (may decrease the metabolism and increase erlotinib levels). Avoid grapefruit juice.

Herb/Nutraceutical: Avoid St John's wort (may increase metabolism and decrease erlotinib concentrations).

Monitoring ParametersPeriodic liver function tests (transaminases, bilirubin, and alkaline phosphatase); periodic renal function tests and serum electrolytes (in patients at risk for dehydration); hydration status

Nursing: Physical Assessment/MonitoringEvaluate hepatic and renal status prior to beginning therapy. Assess potential for interactions or toxicity with other pharmacological agents or herbal products patient may be taking (especially CYP3A4 inhibitors or inducers); dose adjustments may be necessary. Assess laboratory test results, therapeutic response, and adverse reactions (eg, pulmonary toxicity, poorly tolerated diarrhea, severe skin reactions). Teach patient possible side effects, appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPeriodic liver function tests (transaminases, bilirubin, and alkaline phosphatase); renal function, electrolytes (in patients at risk for dehydration)

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take exactly as directed; 1 hour before or 2 hours after food. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and adequate nutrition (small frequent meals may help). May cause fatigue (regular, adequate rest periods may help reduce fatigue); rash or dry skin (use nonirritating skin lotion that does not contain alcohol or other irritants); loss of hair (may grow back when treatment is completed); nausea or anorexia (small frequent meals, good mouth care, or sucking lozenges may help); diarrhea (boiled milk, yogurt). Report any persistent gastrointestinal changes (including diarrhea, abdominal pain, nausea, or vomiting); conjunctivitis or visual changes; any difficulty breathing, unusual cough or fever; signs of infection; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication or for two weeks after discontinuing. This drug may cause fetal deformities or loss of pregnancy; see prescriber for appropriate contraceptives. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Tarceva®: 25 mg, 100 mg, 150 mg

Generic AvailableNo

ManufacturerOSI Inc and Genetech Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Tarceva)

25 mg (30): $1279.77

100 mg (30): $3487.86

150 mg (30): $3965.25

Mechanism of ActionThe mechanism of erlotinib's antitumor action is not fully characterized. The drug is known to inhibit overall epidermal growth factor receptor (HER1/EGFR)- tyrosine kinase. Active competitive inhibition of adenosine triphosphate inhibits downstream signal transduction of ligand dependent HER1/EGFR activation.

Pharmacodynamics/Kinetics

Absorption: Oral: 60% on an empty stomach; almost 100% on a full stomach

Distribution: 94-232 L

Protein binding: 92% to 95% to albumin and α_1-acid glycoprotein

Metabolism: Hepatic, via CYP3A4 (major), CYP1A1 (minor), CYP1A2 (minor), and CYP1C (minor)

Bioavailability: Almost 100% when given with food; 60% without food

Half-life elimination: 24-36 hours

Time to peak, plasma: 1-7 hours

Excretion: Primarily as metabolites: Feces (83%; 1% as unchanged drug); urine (8%)

Pharmacotherapy Pearls **Oncology Comment:** According to the National Comprehensive Cancer Network (NCCN) pancreatic adenocarcinoma guidelines, gemcitabine combination therapy (including gemcitabine plus erlotinib) is an option for patients with good performance status in the treatment of locally-advanced or metastatic pancreatic cancer.

The NCCN guidelines for NSCLC recommend erlotinib as single agent treatment for disease progression after failure of first- or second-line treatment in patients with a performance status of 0-2. Erlotinib may be considered for patients with a performance status of 3. Erlotinib is considered a first-line therapy (alone or in combination with chemotherapy) in patients with advanced or metastatic NSCLC who have never smoked and have known active EGFR mutation or gene amplification.

Factors (in patients with NSCLC) which correlate positively with response to EGFR-tyrosine kinase inhibitor (TKI) therapy include skin rash (due to EGFR-TKI therapy), patients who have never smoked, EGFR mutation, and patients of Asian origin. KRAS mutation correlated with poorer outcome with EGFR-TKI therapy in patients with NSCLC. (Cooley, 2008; Jackman, 2008; Masarelli, 2007; Shepherd, 2005)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), mucositis, abnormal taste, and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common

Mental Health: Effects on Psychiatric TreatmentGI side effects and sedation are common. Concomitant use with lithium, SSRIs, or valproic acid may produce additive effects. Concomitant use with psychotropic agents may produce additive sedative effects; monitor. Carbamazepine, phenobarbital, phenytoin, and St John's wort may decrease the effects of erlotinib; monitor. Nefazodone may increase the effects of erlotinib secondary to enzyme inhibition; monitor.

Index TermsCP358774; Erlotinib Hydrochloride; NSC-718781; OSI-774; R 14-15

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International Brand Names Tarceva (AR, AT, AU, BE, BG, CH, CL, CN, CO, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, MX, NL, NO, PE, PH, PT, RU, SE, SG, TH, TR, TW, UY)

Ertapenem

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Ertapenem may be confused with imipenem, meropenem

Invanz® may be confused with Avinza™

Pronunciation(er ta PEN em)

U.S. Brand NamesInvanz®

Canadian Brand NamesInvanz®

Pharmacologic CategoryAntibiotic, Carbapenem

Use: Labeled IndicationsTreatment of the following moderate-severe infections: Complicated intra-abdominal infections, complicated skin and skin structure infections (including diabetic foot infections without osteomyelitis), complicated UTI (including pyelonephritis), acute pelvic infections (including postpartum endomyometritis, septic abortion, post surgical gynecologic infections), and community-acquired pneumonia. Prophylaxis of surgical site infection following elective colorectal surgery. Antibacterial coverage includes aerobic gram-positive organisms, aerobic gram-negative organisms, anaerobic organisms.

Note: Methicillin-resistant *Staphylococcus*, *Enterococcus* spp, penicillin-resistant strains of *Streptococcus pneumoniae*, beta-lactamase-positive strains of *Haemophilus influenzae* are **resistant** to ertapenem, as are most *Pseudomonas aeruginosa*.

Dosing: Adults**Note:** I.V. therapy may be administered for up to 14 days; I.M. for up to 7 days

Community-acquired pneumonia and complicated urinary tract infections (including pyelonephritis): I.M., I.V.: 1 g/day; duration of total antibiotic treatment: 10-14 days (**Note:** Duration includes possible switch to appropriate oral therapy after at least 3 days of parenteral treatment, once clinical improvement demonstrated.)

Intra-abdominal infection: I.M., I.V.: 1 g/day for 5-14 days

Pelvic infections (acute): I.M., I.V.: 1 g/day for 3-10 days

Prophylaxis of surgical site following colorectal surgery: 1 g given 1 hour preoperatively

Skin and skin structure infections (including diabetic foot infections): I.M., I.V.: 1 g/day for 7-14 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** I.V. therapy may be administered for up to 14 days; I.M. therapy for up to 7 days

Children 3 months to 12 years:

Community-acquired pneumonia and complicated urinary tract infections (including pyelonephritis): I.M., I.V.: 15 mg/kg twice daily (maximum: 1 g/day); duration of total antibiotic treatment: 10-14 days (**Note:** Duration includes possible switch to appropriate oral therapy after at least 3 days of parenteral treatment, once clinical improvement demonstrated.)

Intra-abdominal infection: I.M., I.V.: 15 mg/kg twice daily (maximum: 1 g/day) for 5-14 days

Pelvic infections (acute): I.M., I.V.: 15 mg/kg twice daily (maximum: 1 g/day) for 3-10 days

Skin and skin structure infections: I.M., I.V.: 15 mg/kg twice daily (maximum: 1 g/day) for 7-14 days

Children ≥13 years: Refer to adult dosing.

Dosing: Renal Impairment

Children: No data available for pediatric patients with renal insufficiency.

Adults:

Cl_{cr} >30 mL/minute/1.73 m^2: No adjustment required

Cl_{cr} ≤30 mL/minute/1.73 m^2 and ESRD: 500 mg/day

Hemodialysis: When the daily dose is given within 6 hours prior to hemodialysis, a supplementary dose of 150 mg is required following hemodialysis.

Dosing: Hepatic ImpairmentAdjustments cannot be recommended (lack of experience and research in this patient population).

Calculations

- Creatinine Clearance: Adults

Administration: I.M.Avoid injection into a blood vessel. Make sure patient does not have an allergy to lidocaine or another anesthetic of the amide type. Administer by deep I.M. injection into a large muscle mass (eg, gluteal muscle or lateral part of the thigh). Do not administer I.M. preparation or drug reconstituted for I.M. administration intravenously.

Administration: I.V.Infuse over 30 minutes

Administration: I.V. DetailpH 7.5

Dietary ConsiderationsSodium content: 137 mg (~6 mEq) per gram of ertapenem

StorageBefore reconstitution store at ≤25°C (77°F).

I.M.: Use within 1 hour after preparation.

I.V.: Reconstituted I.V. solution may be stored at room temperature and must be used within 6 hours **or** refrigerated, stored for up to 24 hours and used within 4 hours after removal from refrigerator. Do not freeze.

Reconstitution

I.M.: Reconstitute 1 g vial with 3.2 mL of 1% lidocaine HCl injection (without epinephrine). Shake well.

I.V.: Reconstitute 1 g vial with 10 mL of water for injection, 0.9% sodium chloride injection, or bacteriostatic water for injection. Shake well. For adults, transfer dose to 50 mL of 0.9% sodium chloride injection; for children, dilute dose with NS to a final concentration ≤20 mg/mL.

CompatibilityDo not mix with other medications or use diluents containing dextrose.

Y-site: Compatible: Dextran 40, dextran 70, heparin, hetastarch in NS, potassium chloride

ContraindicationsHypersensitivity to ertapenem, other carbapenems, or any component of the formulation; anaphylactic reactions to beta-lactam antibiotics. If using intramuscularly, known hypersensitivity to local anesthetics of the amide type (lidocaine is the diluent).

Allergy Considerations

- Carbapenem Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Serious hypersensitivity reactions, including anaphylaxis, have been reported (some without a history of previous allergic reactions to beta-lactams).
- CNS effects: Has been associated with CNS adverse effects, including confusional states and seizures; use caution with CNS disorders (eg, brain lesions, history of seizures, or renal impairment).
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required in patients with moderate-to-severe renal dysfunction. Increased seizure risk has been reported in patients with renal dysfunction.

Concurrent drug therapy issues:

- Valproic acid: Serum concentrations may be reduced to subtherapeutic levels with concomitant use; monitor frequently.

Special populations:

- Elderly: Lower doses (based upon renal function) are often required in the elderly.
- Pediatrics: Safety and efficacy have not been established in children <3 months of age.

Other warnings/precautions:

- I.M. administration: Doses for I.M. administration are mixed with lidocaine; consult Lidocaine information for associated Warnings/Precautions.

Geriatric ConsiderationsAccording to the package insert, the total and unbound AUCs were increased 37% and 67%, respectively, in healthy men and women ≥65 years of age compared to younger adults. No dose adjustment is required for patients with normal age-adjusted renal function.

Pregnancy Risk FactorB

Pregnancy ConsiderationsWith the exception of slightly decreased fetal weights in mice, teratogenic effects and fetal harm have not been shown in animal studies. Adequate and well-controlled studies have not been conducted in pregnant women and it is not known whether ertapenem can cause fetal harm.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsErtapenem is excreted in breast milk. The low concentrations in milk and low oral bioavailability suggest minimal exposure risk to the infant. Although the manufacturer recommends that caution be exercised when administering ertapenem to nursing women, most penicillins and carbapenems are safe for use in breast-feeding. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Ertapenem in Pregnancy & Lactation

Adverse Reactions **Note:** Percentages reported in adults.

1% to 10%:

Cardiovascular: Swelling/edema (3%), chest pain (1% to 2%), hypertension (1% to 2%), hypotension (1% to 2%), tachycardia (1% to 2%)

Central nervous system: Headache (6% to 7%), altered mental status (eg, agitation, confusion, disorientation, decreased mental acuity, changed mental status, somnolence, stupor) (3% to 5%), fever (2% to 5%), insomnia (3%), dizziness (2%), fatigue (1%), anxiety (1%)

Dermatologic: Rash (2% to 3%), pruritus (1% to 2%), erythema (1% to 2%)

Endocrine & metabolic: Hypokalemia (2%), hyperglycemia (1% to 2%), hyperkalemia (≤1%)

Gastrointestinal: Diarrhea (9% to 10%), nausea (6% to 9%), abdominal pain (4%), vomiting (4%), constipation (3% to 4%), acid regurgitation (1% to 2%), dyspepsia (1%), oral candidiasis (≤1%)

Genitourinary: Urine WBCs increased (2% to 3%), urine RBCs increased (1% to 3%), vaginitis (1% to 3%)

Hematologic: Platelet count increased (3% to 7%), hematocrit/hemoglobin decreased (3% to 5%), eosinophils increased (1% to 2%), leukopenia (1% to 2%), neutrophils decreased (1% to 2%), platelet count decreased (1%), prothrombin time increased (<1%)

Hepatic: Hepatic enzyme increased (5% to 9%), alkaline phosphatase increase (3% to 7%), albumin decreased (1% to 2%), bilirubin (total) increased (1% to 2%)

Local: Infused vein complications (5% to 7%), phlebitis/thrombophlebitis (2%), extravasation (1% to 2%)

Neuromuscular & skeletal: Leg pain (≤1%), weakness (1%)

Renal: Serum creatinine increased (1%)

Respiratory: Dyspnea (1% to 3%), cough (1% to 2%), pharyngitis (1%), rales/rhonchi (1%), respiratory distress (≤1%)

<1%, postmarketing, and/or case reports: Abdominal distention, aggressive behavior, anaphylactoid reactions, anaphylaxis, anorexia, arrhythmia, asthma, asystole, atrial fibrillation, bicarbonate (serum) decreased, bilirubin (direct and indirect) increased, bladder dysfunction, bradycardia, bronchoconstriction, BUN increased, *C. difficile*-associated diarrhea, candidiasis, cardiac arrest, chills, cholelithiasis, dehydration, depression, dermatitis, desquamation, diaphoresis, duodenitis, dysphagia, epistaxis, epithelial (urine) cells increased, esophagitis, facial edema, flank pain, flatulence, flushing, gastritis, gastrointestinal hemorrhage, gout, hallucinations, heart failure, heart murmur, hematoma, hematuria, hemoptysis, hemorrhoids, hiccups, hypoesthesia, hypoxemia, ileus, injection site induration, injection site pain, jaundice, malaise, monocytes increased, mouth ulcer, muscle spasm, necrosis, nervousness, oliguria/anuria, pain, pancreatitis, paresthesia, pharyngeal discomfort, pleural effusion, pleuritic pain, pseudomembranous colitis, PTT increased, pyloric stenosis, renal insufficiency, seizure (0.5%), septicemia, septic shock, sodium (serum) increased, spasm, stomatitis, subdural hemorrhage, syncope, taste perversion, tremor, urinary retention, urticaria, vaginal candidiasis, vaginal pruritus, ventricular tachycardia, vertigo, voice disturbance, vulvovaginitis, weight loss

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Carbapenems. Management: Avoid concomitant use of doripenem and probenecid. *Risk C: Monitor therapy*

Valproic Acid: Carbapenems may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Monitoring Parameters Periodic renal, hepatic, and hematopoietic assessment during prolonged therapy; neurological assessment

Nursing: Physical Assessment/Monitoring Assess results of culture and sensitivity tests and patient history of previous allergies or adverse drug reactions. Use caution in presence of impaired renal function; CNS disorder. Patient must be monitored closely for adverse reactions, especially CNS adverse effects (history of seizures, head injuries, or other CNS events increases risk). Teach patient interventions to reduce side effects and adverse symptoms to report.

Patient Education This medication can only be administered intravenously or by intramuscular injections; report warmth, swelling, irritation at infusion or injection site. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition. Report unresolved nausea or vomiting (small, frequent meals, frequent mouth care, and sucking hard candy may help). Report immediately any CNS changes (eg, dizziness, disorientation, visual disturbances, headaches, confusion, or seizures). Report prolonged GI effects, persistent diarrhea, vomiting, abdominal pain; change in respirations or respiratory difficulty; chest pain or palpitations; skin rash; foul-smelling vaginal discharge; or white plaques in mouth. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Invanz®: 1 g [contains sodium 137 mg/g (~6 mEq/g)]

Generic Available No

Manufacturer Merck & Co

Mechanism of Action Inhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins; which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: I.M.: Almost complete

Distribution: V_{dss}:

Children 3 months to 12 years: ~0.2 L/kg

Children 13-17 years: ~0.16 L/kg

Adults: ~0.12 L/kg

Protein binding (concentration dependent, primarily to albumin): 85% at 300 mcg/mL, 95% at <100 mcg/mL

Metabolism: Non-CYP-mediated hydrolysis to inactive metabolite

Bioavailability: I.M.: ~90%

Half-life elimination:

Children 3 months to 12 years: ~2.5 hours

Children ≥13 years and Adults: ~4 hours

Time to peak: I.M.: ~2.3 hours

Excretion: Urine (~80% as unchanged drug and metabolite); feces (~10%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral candidiasis

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause agitation, confusion, disorientation, decreased mental acuity, sedation, stupor, insomnia, dizziness, or anxiety

Mental Health: Effects on Psychiatric TreatmentNausea and diarrhea are common; use caution with lithium, valproic acid, and SSRIs. May increase hepatic enzymes; use caution with olanzapine and valproic acid.

Index TermsErtapenem Sodium; L-749,345; MK0826

References

American Thoracic Society and Infectious Diseases Society of America, “Guidelines for the Management of Adults With Hospital-Acquired, Ventilator-Associated, and Healthcare-Associated Pneumonia,” *Am J Respir Crit Care Med*, 2005, 171(4):388-416.[PubMed 15699079]

Lunde JL, Nelson RE, and Storandt HF, “Acute Seizures in a Patient Receiving Divalproex Sodium After Starting Ertapenem Therapy,” *Pharmacotherapy*, 2007, 27(8):1202-5.[PubMed 17655519]

Seto AH, Song JC, and Guest SS, “Ertapenem-Associated Seizures in a Peritoneal Dialysis Patient,” *Ann Pharmacother* , 2005, 39(2):352-6.[PubMed 15644469]

International Brand NamesInvanz (AR, AT, AU, BE, BG, BO, BR, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, HK, HN, IE, IL, IT, KP, MX, MY, NI, NL, NO, PA, PE, PH, PL, PR, PT, PY, RU, SE, SG, SV, TH, TR, UY, VE)

Erythromycin and Benzoyl Peroxide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(er ith roe MYE sin & BEN zoe il per OKS ide)
U.S. Brand NamesBenzamycin®; Benzamycin® Pak
Pharmacologic CategoryAcne Products; Topical Skin Product, Acne
Use: Labeled IndicationsTopical control of acne vulgaris
Dosing: AdultsAcne: Topical: Apply twice daily, morning and evening.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricAdolescents ≥12 years: Refer to adult dosing.
Allergy Considerations

- Macrolide Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bleaching effects: May bleach hair or colored fabric.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment. Stop the drug if significant diarrhea occurs.

Concurrent drug therapy issues:

- Topical acne products: Use concomitant topical acne therapy with caution; cumulative irritancy may occur.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Appropriate use: For external use only; avoid contact with mucous membranes and eyes.

Also see Erythromycin monograph.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Metabolism/Transport EffectsErythromycin: **Substrate** of CYP2B6 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 3A4 (moderate)
Drug Interactions

Alfentanil: Macrolide Antibiotics may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Macrolide Antibiotics may decrease the metabolism of Antifungal Agents (Azole Derivatives, Systemic). Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Macrolide Antibiotics. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Macrolide Antibiotics may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

BusPIRone: Macrolide Antibiotics may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Macrolide Antibiotics may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: Macrolide Antibiotics may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Cardiac Glycosides: Macrolide Antibiotics may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Cilostazol: Macrolide Antibiotics may decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Cisapride: Macrolide Antibiotics may decrease the metabolism of Cisapride. *Risk X: Avoid combination*

Clopidogrel: Macrolide Antibiotics may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Clozapine: Macrolide Antibiotics may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

Colchicine: Macrolide Antibiotics may decrease the metabolism of Colchicine. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Macrolide Antibiotics may decrease the metabolism of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

CycloSPORINE: Macrolide Antibiotics may decrease the metabolism of CycloSPORINE. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disopyramide: Macrolide Antibiotics may enhance the QTc-prolonging effect of Disopyramide. Macrolide Antibiotics may decrease the metabolism of Disopyramide. *Risk X: Avoid combination*

Eletriptan: Macrolide Antibiotics may decrease the metabolism of Eletriptan. *Risk D: Consider therapy modification*

Eplerenone: Macrolide Antibiotics may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Macrolide Antibiotics may enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Cabergoline. *Risk D: Consider therapy modification*

Etravirine: May decrease the serum concentration of Macrolide Antibiotics. Clarithromycin AUC is reduced and levels of the active metabolite (14-hydroxy-clarithromycin) are modestly increased. Management: For the treatment of *Mycobacterium avium* complex, consider changing to alternative agent, such as azithromycin. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fexofenadine: Erythromycin may increase the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Macrolide Antibiotics may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Pravastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Lincosamide Antibiotics: May diminish the therapeutic effect of Erythromycin. *Risk X: Avoid combination*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: Macrolide Antibiotics may decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Macrolide Antibiotics may decrease the metabolism of Pimozide. QTc prolongation is a risk. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Macrolide Antibiotics may decrease the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Repaglinide: Macrolide Antibiotics may increase the serum concentration of Repaglinide. *Risk C: Monitor therapy*

Rifamycin Derivatives: Macrolide Antibiotics may decrease the metabolism of Rifamycin Derivatives. **Exceptions:** Rifapentine. *Risk D: Consider therapy modification*

Rivaroxaban: Erythromycin may increase the serum concentration of Rivaroxaban. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Macrolide Antibiotics may decrease the metabolism of Selective Serotonin Reuptake Inhibitors. **Exceptions:** Fluvoxamine; PARoxetine. *Risk C: Monitor therapy*

Sirolimus: Macrolide Antibiotics may decrease the metabolism of Sirolimus. *Risk D: Consider therapy modification*

Tacrolimus: Macrolide Antibiotics may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Temsirolimus: Macrolide Antibiotics may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Theophylline Derivatives: Macrolide Antibiotics may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Macrolide Antibiotics may decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zafirlukast: Erythromycin may decrease the serum concentration of Zafirlukast. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Zopiclone: Macrolide Antibiotics may increase the serum concentration of Zopiclone. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringSee individual agent for Erythromycin.

Patient EducationSee individual agent for Erythromycin.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel, topical: Erythromycin 30 mg and benzoyl peroxide 50 mg per g (23 g, 47 g)

Benzamycin®: Erythromycin 30 mg and benzoyl peroxide 50 mg per g (47 g) [contains alcohol 20%]

Benzamycin® Pak: Erythromycin 30 mg and benzoyl peroxide 50 mg per 0.8 g packet (60s) [supplied with diluent containing alcohol]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Gel (Benzamycin)

5-3% (46.6): $183.11

Gel (Benzoyl Peroxide-Erythromycin)

5-3% (23.3): $54.11

5-3% (46.6): $100.99

Pack (BenzamycinPak)

5-3% (60): $119.90

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Benzoyl Peroxide
- Erythromycin

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBenzoyl Peroxide and Erythromycin

International Brand NamesBenzac Eritromicina (BR); Benzac Kombi (CO); Benzac Plus (CR, DO, GT, HN, NI, PA, PE, SV); Benzamycin (AR, BE, GR, MX, MY, PH, SG); Erimicin (AR, CN, PY, UY)

Erythromycin and Sulfisoxazole

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Pediazole® may be confused with Pediapred®

Pronunciation(er ith roe MYE sin & sul fi SOKS a zole)
U.S. Brand NamesE.S.P.®
Canadian Brand NamesPediazole®
Pharmacologic CategoryAntibiotic, Macrolide; Antibiotic, Macrolide Combination; Antibiotic, Sulfonamide Derivative
Use: Labeled IndicationsTreatment of susceptible bacterial infections of the upper and lower respiratory tract, otitis media in children caused by susceptible strains of *Haemophilus influenzae*, and many other infections in patients allergic to penicillin
Dosing: AdultsSusceptible infections: Oral (dosage recommendation is based on the product's erythromycin content): 400 mg erythromycin and 1200 mg sulfisoxazole every 6 hours
Dosing: ElderlyNot recommended for use in the elderly.
Dosing: PediatricSusceptible infections: Oral (dosage recommendation is based on the product's erythromycin content): ≥2 months: 50 mg/kg/day erythromycin and 150 mg/kg/day sulfisoxazole in divided doses every 6 hours; not to exceed 2 g erythromycin/day or 6 g sulfisoxazole/day for 10 days
Dosing: Renal ImpairmentSulfisoxazole must be adjusted in renal impairment.

Cl_{cr} 10-50 mL/minute: Administer every 8-12 hours.

Cl_{cr} <10 mL/minute: Administer every 12-24 hours.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

StorageReconstituted suspension is stable for 14 days when refrigerated.
ContraindicationsHypersensitivity to erythromycin, sulfonamides, or any component of the formulation; hepatic dysfunction; infants <2 months of age (sulfas compete with bilirubin for binding sites); porphyria; concurrent use with pimozide or cisapride
Allergy Considerations

- Macrolide Allergy
- Sulfonamide Antibiotic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: Macrolides have been associated with rare QT_c prolongation and ventricular arrhythmias, including torsade de pointes; use with caution in patients at risk of prolonged cardiac repolarization.

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). In patients with allergy to one of these compounds, a risk of cross-reaction exists; avoid use when previous reaction has been severe.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- G6PD deficiency: Use with caution in patients with G6PD deficiency; hemolysis may occur.

- Hepatic impairment: Use with caution in patients with pre-existing liver disease; hepatic impairment, including hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been observed. Discontinue if symptoms of malaise, nausea, vomiting, abdominal colic, and fever.

- Myasthenia gravis: Erythromycin has been associated with aggravation of weakness associated with myasthenia gravis.

- Renal impairment: Use with caution in patients with renal impairment.

Pregnancy Risk FactorC
LactationEnters breast milk/compatible
Adverse ReactionsFrequency not defined.

Cardiovascular: Ventricular arrhythmia,

Central nervous system: Headache, fever

Dermatologic: Rash, Stevens-Johnson syndrome, toxic epidermal necrolysis

Gastrointestinal: Abdominal pain, cramping, nausea, vomiting, oral candidiasis, hypertrophic pyloric stenosis, diarrhea, pseudomembranous colitis

Hematologic: Agranulocytosis, aplastic anemia, eosinophilia

Hepatic: Hepatic necrosis, cholestatic jaundice

Local: Phlebitis at the injection site, thrombophlebitis

Renal: Toxic nephrosis, crystalluria

Miscellaneous: Hypersensitivity reactions

Metabolism/Transport Effects

Erythromycin: **Substrate** of CYP2B6 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 3A4 (moderate)

Sulfisoxazole: **Substrate** of CYP2C8/9 (major); **Inhibits** CYP2C8/9 (strong)

Drug Interactions

Alfentanil: Macrolide Antibiotics may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Macrolide Antibiotics may decrease the metabolism of Antifungal Agents (Azole Derivatives, Systemic). Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Macrolide Antibiotics. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Macrolide Antibiotics may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

BusPIRone: Macrolide Antibiotics may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Macrolide Antibiotics may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: Macrolide Antibiotics may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Cardiac Glycosides: Macrolide Antibiotics may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Cilostazol: Macrolide Antibiotics may decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Cisapride: Macrolide Antibiotics may decrease the metabolism of Cisapride. *Risk X: Avoid combination*

Clopidogrel: Macrolide Antibiotics may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Clozapine: Macrolide Antibiotics may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

Colchicine: Macrolide Antibiotics may decrease the metabolism of Colchicine. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Macrolide Antibiotics may decrease the metabolism of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

CycloSPORINE: Macrolide Antibiotics may decrease the metabolism of CycloSPORINE. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonamide Derivatives may enhance the nephrotoxic effect of CycloSPORINE. Sulfonamide Derivatives may decrease the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disopyramide: Macrolide Antibiotics may enhance the QTc-prolonging effect of Disopyramide. Macrolide Antibiotics may decrease the metabolism of Disopyramide. *Risk X: Avoid combination*

Eletriptan: Macrolide Antibiotics may decrease the metabolism of Eletriptan. *Risk D: Consider therapy modification*

Eplerenone: Macrolide Antibiotics may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Macrolide Antibiotics may enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Cabergoline. *Risk D: Consider therapy modification*

Etravirine: May decrease the serum concentration of Macrolide Antibiotics. Clarithromycin AUC is reduced and levels of the active metabolite (14-hydroxy-clarithromycin) are modestly increased. Management: For the treatment of *Mycobacterium avium* complex, consider changing to alternative agent, such as azithromycin. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fexofenadine: Erythromycin may increase the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Macrolide Antibiotics may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Pravastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Lincosamide Antibiotics: May diminish the therapeutic effect of Erythromycin. *Risk X: Avoid combination*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methotrexate: Sulfonamide Derivatives may enhance the adverse/toxic effect of Methotrexate. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Sulfonamide Derivatives may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: Macrolide Antibiotics may decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Macrolide Antibiotics may decrease the metabolism of Pimozide. QTc prolongation is a risk. *Risk X: Avoid combination*

Procaine: May diminish the therapeutic effect of Sulfonamide Derivatives. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Macrolide Antibiotics may decrease the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Repaglinide: Macrolide Antibiotics may increase the serum concentration of Repaglinide. *Risk C: Monitor therapy*

Rifamycin Derivatives: Macrolide Antibiotics may decrease the metabolism of Rifamycin Derivatives. **Exceptions:** Rifapentine. *Risk D: Consider therapy modification*

Rivaroxaban: Erythromycin may increase the serum concentration of Rivaroxaban. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Macrolide Antibiotics may decrease the metabolism of Selective Serotonin Reuptake Inhibitors. **Exceptions:** Fluvoxamine; PARoxetine. *Risk C: Monitor therapy*

Sirolimus: Macrolide Antibiotics may decrease the metabolism of Sirolimus. *Risk D: Consider therapy modification*

Sulfonylureas: Sulfonamide Derivatives may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Tacrolimus: Macrolide Antibiotics may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Temsirolimus: Macrolide Antibiotics may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Theophylline Derivatives: Macrolide Antibiotics may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Sulfonamide Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Macrolide Antibiotics may decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zafirlukast: Erythromycin may decrease the serum concentration of Zafirlukast. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Zopiclone: Macrolide Antibiotics may increase the serum concentration of Zopiclone. *Risk D: Consider therapy modification*

Test InteractionsFalse-positive urinary protein
Monitoring ParametersCBC and periodic liver function test
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for oral suspension: Erythromycin ethylsuccinate 200 mg and sulfisoxazole acetyl 600 mg per 5 mL (100 mL, 150 mL, 200 mL)

E.S.P.®: Erythromycin ethylsuccinate 200 mg and sulfisoxazole acetyl 600 mg per 5 mL (100 mL, 150 mL, 200 mL) [cheri beri flavor]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Suspension (reconstituted) (Erythromycin-Sulfisoxazole)

200-600 mg/5 mL (100): $10.99

200-600 mg/5 mL (150): $26.00

200-600 mg/5 mL (200): $31.00

Suspension (reconstituted) (Pediazole)

200-600 mg/5 mL (100): $20.99

200-600 mg/5 mL (150): $29.99

200-600 mg/5 mL (200): $37.98

Mechanism of ActionErythromycin inhibits bacterial protein synthesis; sulfisoxazole competitively inhibits bacterial synthesis of folic acid from para-aminobenzoic acid
Pharmacodynamics/KineticsSee individual agents.
Related Information

- Erythromycin
- SulfiSOXAZOLE

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral candidiasis.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMacrolides have been reported to cause nightmares, confusion, anxiety, and mood lability; dizziness is common with sulfisoxazole; sulfonamides reported to cause restlessness, irritability, depression, euphoria, disorientation, panic, hallucinations, and delusions
Mental Health: Effects on Psychiatric TreatmentErythromycin is contraindicated with pimozide; may increase concentration of bromocriptine, carbamazepine, and triazolam; photosensitivity is common with sulfisoxazole; use caution with concurrent psychotropics; may cause leukopenia; caution with clozapine and carbamazepine
Index TermsSulfisoxazole and Erythromycin
References

Rodriguez WJ, Schwartz RH, Sait T, et al, “Erythromycin-Sulfisoxazole vs Amoxicillin in the Treatment of Acute Otitis Media in Children,” *Am J Dis Child*, 1985, 139(8):766-70. [PubMed 3895889]

Tartaglione TA, “Therapeutic Options for the Management and Prevention of *Mycobacterium avium* Complex Infection in Patients With the

Acquired Immunodeficiency Syndrome,” *Pharmacotherapy*, 1996, 16(2):171-82.[PubMed 8820462]

International Brand NamesBioquin (CN); Erisul (CO); Pediazole (AE, BH, CN, CY, EC, EG, FR, GR, IL, IQ, IR, JO, KW, LB, LY, MX, MY, OM, PE, PH, PK, QA, SA, SY, TW, VE, YE)

Erythromycin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Erythromycin may be confused with azithromycin, clarithromycin, Ethmozine®

Akne-Mycin® may be confused with AK-Mycin®

E.E.S.® may be confused with DES®

Eryc® may be confused with Emcyt®, Ery-Tab®

Ery-Tab® may be confused with Eryc®

Erythrocin® may be confused with Ethmozine®

Pronunciation(er ith roe MYE sin)

U.S. Brand NamesAkne-Mycin®; E.E.S.®; Ery-Tab®; Eryc® [DSC]; Eryderm® [DSC]; Erygel® [DSC]; EryPed®; Erythro-RX; Erythrocin®; PCE®; Romycin®

Canadian Brand NamesApo-Erythro Base®; Apo-Erythro E-C®; Apo-Erythro-ES®; Apo-Erythro-S®; Diomycin®; EES®; Erybid™; Eryc®; Novo-Rythro Estolate; Novo-Rythro Ethylsuccinate; Nu-Erythromycin-S; PCE®; PMS-Erythromycin; Sans Acne®

Pharmacologic CategoryAcne Products; Antibiotic, Macrolide; Antibiotic, Ophthalmic; Antibiotic, Topical; Topical Skin Product; Topical Skin Product, Acne

Use: Labeled Indications

Systemic: Treatment of susceptible bacterial infections including *S. pyogenes*, some *S. pneumoniae,* some *S. aureus*, *M. pneumoniae*, *Legionella pneumophila*, diphtheria, pertussis, *Chlamydia*, erythrasma, *N. gonorrhoeae*, *E. histolytica*, syphilis and nongonococcal urethritis, and *Campylobacter* gastroenteritis; used in conjunction with neomycin for decontaminating the bowel

Ophthalmic: Treatment of superficial eye infections involving the conjunctiva or cornea; neonatal ophthalmia

Topical: Treatment of acne vulgaris

Use: Unlabeled/InvestigationalSystemic: Treatment of gastroparesis, chancroid; preoperative gut sterilization

Use: DentalSystemic: Alternative to penicillin VK for treatment of orofacial infections

Dosing: Adults**Note:** Due to differences in absorption, 400 mg erythromycin ethylsuccinate produces the same serum levels as 250 mg erythromycin base or stearate.

Usual dosage range:

Ophthalmic: Instill $^{1}/_{2}$" (1.25 cm) 2-6 times/day depending on the severity of the infection

Topical: Apply over the affected area twice daily after the skin has been thoroughly washed and patted dry

Oral:

Base: 250-500 mg every 6-12 hours

Ethylsuccinate: 400-800 mg every 6-12 hours

I.V.: Lactobionate: 15-20 mg/kg/day divided every 6 hours or 500 mg to 1 g every 6 hours, or given as a continuous infusion over 24 hours (maximum: 4 g/24 hours)

Indication-specific dosing:

***Bartonella sp*infections (bacillary angiomatosis [BA], peliosis hepatis [PH]) (unlabeled use):** Oral: 500 mg (base) 4 times/day for 3 months (BA) or 4 months (PH)

Chancroid (unlabeled use): Oral: 500 mg (base) 3 times/day for 7 days; Note: Not a preferred agent; isolates with intermediate resistance have been documented

Gastrointestinal prokinetic (unlabeled use): I.V.: 200 mg initially followed by 250 mg (base) orally 3 times/day 30 minutes before meals. Lower dosages have been used in some trials.

Granuloma inguinale*(K. granulomatis)*(unlabeled use): Oral: 500 mg (base) 4 times/day for 21 days

Legionnaires' disease: Oral: 1.6-4 g (ethylsuccinate)/day or 1-4 g (base)/day in divided doses for 21 days. **Note:** No longer preferred therapy and only used in nonhospitalized patients.

Lymphogranuloma venereum: Oral: 500 mg (base) 4 times/day for 21 days

Nongonococcal urethritis (including coinfection with*C. trachomatis*): Oral: 500 mg (base) 4 times/day for 7 days or 800 mg (ethylsuccinate) 4 times/day for 7 days. **Note:** May use 250 mg (base) or 400 mg (ethylsuccinate) 4 times/day for 14 days if gastrointestinal intolerance.

Pelvic inflammatory disease: I.V.: 500 mg every 6 hours for 3 days, followed by 1000 mg (base)/day orally in 2-4 divided doses for 7 days. **Note:** Not recommended therapy per current treatment guidelines.

Pertussis: Oral: 500 mg (base) every 6 hours for 14 days

Preop bowel preparation (unlabeled use): Oral: 1 g erythromycin base at 1, 2, and 11 PM on the day before surgery combined with mechanical cleansing of the large intestine and oral neomycin

Syphilis, primary: Oral: 48-64 g (ethylsuccinate) or 30-40 g (base) in divided doses over 10-15 days. **Note:** Not recommended therapy per current treatment guidelines.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Due to differences in absorption, 400 mg erythromycin ethylsuccinate produces the same serum levels as 250 mg erythromycin base or stearate.

Usual dosage range: Infants and Children:

Oral:

Base: 30-50 mg/kg/day in 2-4 divided doses; maximum: 2 g/day

Ethylsuccinate: 30-50 mg/kg/day in 2-4 divided doses; maximum: 3.2 g/day

Stearate: 30-50 mg/kg/day in 2-4 divided doses; maximum: 2 g/day

I.V.: Lactobionate: 15-50 mg/kg/day divided every 6 hours, not to exceed 4 g/day

Ophthalmic: Refer to adult dosing.

Topical: Refer to adult dosing.

Indication-specific dosing:

***Bartonella sp*infections (bacillary angiomatosis [BA], peliosis hepatis [PH]) (unlabeled use):** Oral: 40 mg/kg/day (ethylsuccinate) in 4 divided doses (maximum: 2 g/day) for 3 months (BA) or 4 months (PH)

Conjunctivitis, neonatal*(C. trachomatis):* Oral: 50 mg/kg/day (base or ethylsuccinate) in 4 divided doses for 14 days

Mild/moderate infection: Oral: 30-50 mg/kg/day in divided doses every 6-12 hours

Pertussis: Oral: 40-50 mg/kg/day in 4 divided doses for 14 days; maximum 2 g/day (not preferred agent for infants <1 month due to IHPS)

Pharyngitis, tonsillitis (streptococcal): Oral: 20 mg (base)/kg/day or 40 mg (ethylsuccinate)/kg/day in 2 divided doses for 10 days. **Note:** No longer preferred therapy due to increased organism resistance.

Pneumonia*(C. trachomatis):* Oral: 50 mg/kg/day (base or ethylsuccinate) in 4 divided doses for 14-21 days

Preop bowel preparation: Oral: 20 mg (base)/kg at 1, 2, and 11 PM on the day before surgery combined with mechanical cleansing of the large intestine and oral neomycin

Severe infection: I.V.: 15-50 mg/kg/day; maximum: 4 g/day

Dosing: Renal ImpairmentSlightly dialyzable (5% to 20%); supplemental dose is not necessary in hemo- or peritoneal dialysis or in continuous arteriovenous or venovenous hemofiltration.

Administration: I.V.Infuse 1 g over 20-60 minutes.

Administration: I.V. DetailI.V. infusion may be very irritating to the vein. If phlebitis/pain occurs with used dilution, consider diluting further (eg, 1:5) if fluid status of the patient will tolerate, or consider administering in larger available vein. The addition of lidocaine or bicarbonate does not decrease the irritation of erythromycin infusions.

pH: Erythromycin lactobionate: 6.5-7.5 (reconstituted with sterile water for injection or D_5W to a 50 mg/mL concentration)

Administration: OralDo not crush enteric coated drug product. GI upset, including diarrhea, is common. May be administered with food to decrease GI upset. Do not give with milk or acidic beverages.

Administration: OtherAvoid contact of tip of ophthalmic ointment tube with affected eye.

Dietary Considerations

Systemic: Drug may cause GI upset; may take with food.

E.E.S.® granules for oral suspension contain sodium 25.9 mg (1.1 mEq)/5 mL

EryPed® powder for oral suspension contains sodium 117.5 mg (5.1 mEq)/5 mL; powder for oral suspension (drops) contains sodium 58.8 mg (2.6 mEq)/dropperful dose

Storage

Injection: Store unreconstituted vials at 15°C to 30°C (59°F to 86°F). Reconstituted solution is stable for 2 weeks when refrigerated or for 8 hours at room temperature. Erythromycin I.V. infusion solution is stable at pH 6-8; stability of lactobionate is pH dependent; I.V. form has longest stability in NS. Stability of parenteral admixture at room temperature (25°C) and at refrigeration temperature (4°C) is 24 hours.

Oral suspension:

Granules: After mixing, store under refrigeration and use within 10 days.

Powder: Refrigerate to preserve taste. Erythromycin ethylsuccinate may be stored at room temperature if used within 14 days. EryPed® drops should be used within 35 days following reconstitution. May store at room temperature or under refrigeration.

Tablet and capsule formulations: Store at <30°C (<86°F).

Topical and ophthalmic formulations: Store at room temperature.

Reconstitution Erythromycin lactobionate should be reconstituted with sterile water for injection without preservatives to avoid gel formation. I.V. form has the longest stability in NS and should be prepared in this base solution whenever possible. Do not use D_5W as a diluent unless sodium bicarbonate is added to solution. If I.V. must be prepared in D_5W, 0.5 mL of the 8.4% sodium bicarbonate solution should be added per each 100 mL of D_5W.

Standard diluent: 500 mg/250 mL D_5W/NS; 750 mg/250 mL D_5W/NS; 1 g/250 mL D_5W/NS.

Compatibility

Erythromycin lactobionate: Stable in NS; **incompatible** with D_5LR, $D_{10}W$; **variable stability (consult detailed reference)** in D_5NS, D_5W, LR.

Y-site administration: Compatible: Acyclovir, amiodarone, cyclophosphamide, diltiazem, enalaprilat, esmolol, famotidine, foscarnet, heparin, hydromorphone, idarubicin, labetalol, lorazepam, magnesium sulfate, meperidine, midazolam, morphine, multivitamins, perphenazine, tacrolimus, theophylline, vitamin B complex with C, zidovudine. **Incompatible:** Fluconazole.

Compatibility in syringe: Incompatible: Ampicillin, heparin.

Compatibility when admixed: Compatible: Aminophylline, ampicillin, cimetidine, diphenhydramine, hydrocortisone sodium succinate, lidocaine, penicillin G potassium, penicillin G sodium, pentobarbital, polymyxin B sulfate, potassium chloride, prochlorperazine edisylate, promazine, ranitidine, sodium bicarbonate, verapamil. **Incompatible:** Colistimethate, floxacillin, furosemide, heparin, metaraminol, metoclopramide, riboflavin, vitamin B complex with C. **Variable (consult detailed reference):** Ascorbic acid injection.

Contraindications Hypersensitivity to erythromycin or any component of the formulation

Systemic: Concomitant use with pimozide or cisapride

Allergy Considerations

- Macrolide Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: Macrolides have been associated with rare QT_c prolongation and ventricular arrhythmias, including torsade de pointes; use with caution in patients at risk of prolonged cardiac repolarization.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with pre-existing liver disease; hepatic impairment, including hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been observed. Discontinue if symptoms of malaise, nausea, vomiting, abdominal colic, and fever.
- Myasthenia gravis: Erythromycin has been associated with aggravation of weakness associated with myasthenia gravis.

Concurrent drug therapy issues:

- Major inhibitor of CYP3A4: Use caution with any agents with substantial metabolism through the CYP3A4 pathway; high potential for drug interactions exists.

Special populations:

- Infants: Use of erythromycin has been associated with infantile hypertrophic pyloric stenosis (IHPS); observe for non-bilious vomiting or irritability with feeding.
- Elderly: May be at increased risk of adverse events, including hearing loss and/or torsade de pointes when dosage ≥4 g/day, particularly if concurrent renal/hepatic impairment.

Geriatric Considerations Dose does not need to be adjusted unless there is severe renal or hepatic impairment. Elderly may be at an increased risk for torsade de pointes, ototoxicity (particularly when dose is ≥4 g/day in conjunction with renal or hepatic impairment).

Pregnancy Risk Factor B

Pregnancy Considerations Adverse events were not observed in animal studies; therefore, erythromycin is classified as pregnancy category B. Low levels of erythromycin have been shown to cross the placenta and erythromycin is considered the drug of choice for certain illnesses in pregnant women. Most studies do not support a link between prenatal exposure to erythromycin and pyloric stenosis in the neonate. No increased risk for congenital abnormalities has been documented, with the exception of a possible slight increase in risk for cardiovascular anomalies. No adequate and well-controlled studies have been completed in pregnant women. The estolate form of erythromycin should not be used in pregnancy due to a potential increased risk for hepatic toxicity.

LactationEnters breast milk/use caution (AAP considers “compatible”)

Breast-Feeding ConsiderationsErythromycin is excreted in breast milk; therefore, the manufacturer recommends that caution be exercised when administering erythromycin to breast-feeding women.

Due to the low concentrations in human milk, minimal toxicity would be expected in the nursing infant. One case report and a cohort study raise the possibility for a connection with pyloric stenosis in neonates exposed to erythromycin via breast milk and an alternative antibiotic may be preferred for breast-feeding mothers of infants in this age group. Nondose-related effects could include modification of bowel flora. The AAP considers erythromycin to be “usually compatible with breast-feeding.”

Pregnancy & Lactation, In-Depth

- Erythromycin in Pregnancy & Lactation

Adverse ReactionsFrequency not defined. Incidence may vary with formulation.

Systemic:

Cardiovascular: QT_c prolongation, torsade de pointes, ventricular arrhythmia, ventricular tachycardia

Central nervous system: Seizure

Dermatitis: Pruritus, rash

Gastrointestinal: Abdominal pain, anorexia, diarrhea, infantile hypertrophic pyloric stenosis, nausea, oral candidiasis, pancreatitis, pseudomembranous colitis, vomiting

Hepatic: Cholestatic jaundice (most common with estolate), hepatitis, liver function tests abnormal

Local: Phlebitis at the injection site, thrombophlebitis

Neuromuscular & skeletal: Weakness

Otic: Hearing loss

Miscellaneous: Allergic reactions, anaphylaxis, hypersensitivity reactions, urticaria

Topical: 1% to 10%: Dermatologic: Erythema, desquamation, dryness, pruritus

Metabolism/Transport Effects**Substrate** of CYP2B6 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 3A4 (moderate)

Drug Interactions

Alfentanil: Macrolide Antibiotics may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Macrolide Antibiotics may decrease the metabolism of Antifungal Agents (Azole Derivatives, Systemic). Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Macrolide Antibiotics. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Macrolide Antibiotics may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

BusPIRone: Macrolide Antibiotics may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Macrolide Antibiotics may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: Macrolide Antibiotics may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Cardiac Glycosides: Macrolide Antibiotics may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Cilostazol: Macrolide Antibiotics may decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Cisapride: Macrolide Antibiotics may decrease the metabolism of Cisapride. *Risk X: Avoid combination*

Clopidogrel: Macrolide Antibiotics may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Clozapine: Macrolide Antibiotics may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

Colchicine: Macrolide Antibiotics may decrease the metabolism of Colchicine. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Macrolide Antibiotics may decrease the metabolism of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

CycloSPORINE: Macrolide Antibiotics may decrease the metabolism of CycloSPORINE. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disopyramide: Macrolide Antibiotics may enhance the QTc-prolonging effect of Disopyramide. Macrolide Antibiotics may decrease the metabolism of Disopyramide. *Risk X: Avoid combination*

Eletriptan: Macrolide Antibiotics may decrease the metabolism of Eletriptan. *Risk D: Consider therapy modification*

Eplerenone: Macrolide Antibiotics may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Macrolide Antibiotics may enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Cabergoline. *Risk D: Consider therapy modification*

Etravirine: May decrease the serum concentration of Macrolide Antibiotics. Clarithromycin AUC is reduced and levels of the active metabolite (14-hydroxy-clarithromycin) are modestly increased. Management: For the treatment of *Mycobacterium avium* complex, consider changing to alternative agent, such as azithromycin. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fexofenadine: Erythromycin may increase the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Macrolide Antibiotics may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Pravastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Lincosamide Antibiotics: May diminish the therapeutic effect of Erythromycin. *Risk X: Avoid combination*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: Macrolide Antibiotics may decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Macrolide Antibiotics may decrease the metabolism of Pimozide. QTc prolongation is a risk. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Macrolide Antibiotics may decrease the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Repaglinide: Macrolide Antibiotics may increase the serum concentration of Repaglinide. *Risk C: Monitor therapy*

Rifamycin Derivatives: Macrolide Antibiotics may decrease the metabolism of Rifamycin Derivatives. **Exceptions:** Rifapentine. *Risk D: Consider therapy modification*

Rivaroxaban: Erythromycin may increase the serum concentration of Rivaroxaban. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Macrolide Antibiotics may decrease the metabolism of Selective Serotonin Reuptake Inhibitors. **Exceptions:** Fluvoxamine; PARoxetine. *Risk C: Monitor therapy*

Sirolimus: Macrolide Antibiotics may decrease the metabolism of Sirolimus. *Risk D: Consider therapy modification*

Tacrolimus: Macrolide Antibiotics may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Temsirolimus: Macrolide Antibiotics may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Theophylline Derivatives: Macrolide Antibiotics may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Macrolide Antibiotics may decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zafirlukast: Erythromycin may decrease the serum concentration of Zafirlukast. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Zopiclone: Macrolide Antibiotics may increase the serum concentration of Zopiclone. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may decrease absorption of erythromycin or enhance ethanol effects).

Food: Erythromycin serum levels may be altered if taken with food (formulation-dependent).

Herb/Nutraceutical: St John's wort may decrease erythromycin levels.

Test InteractionsFalse-positive urinary catecholamines

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's previous allergy history prior to therapy. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking. Assess therapeutic effectiveness and adverse reactions. Teach patient proper use (according to formulation and purpose for use), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy.

Patient EducationDo not take any new prescription or OTC medications, or herbal products during therapy without consulting prescriber. Take exactly as directed:

Ophthalmic: Preparations should be used exactly as directed. Always wash hands before applying ophthalmic preparations and do not let tip of applicator touch eye or become contaminated.

Suspension: Mix granules exactly as directed and store in refrigerator after mixing; mix powder as directed; store at room temperature or in refrigerator.

Tablets/capsules: Take as directed, around-the-clock, with a full glass of water (not juice or milk); may take with food to reduce GI upset. Do not chew or crush extended release capsules or tablets.

Topical: Apply as directed after skin has been cleansed and gently dried.

Take complete prescription even if you are feeling better. Avoid alcohol (may cause adverse response). May cause nausea, vomiting, or mouth sores (small, frequent meals, frequent mouth care may help). Report immediately any unusual malaise, nausea, vomiting, abdominal colic, or fever; skin rash or itching; easy bruising or bleeding; vaginal itching or discharge; watery or bloody diarrhea; yellowing of skin or eyes, pale stool or dark urine; persistent diarrhea; white plaques, sores, or fuzziness in mouth; or any change in hearing.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product; [CAN] = Canadian brand name

Note: Strength expressed as base

Capsule, delayed release, enteric-coated pellets, as base: 250 mg

Eryc®: 250 mg [DSC]

Gel, topical: 2% (30 g, 60 g)

Erygel®: 2% (30 g, 60 g) [DSC] [contains alcohol 92%]

Granules for oral suspension, as ethylsuccinate:

E.E.S.®: 200 mg/5 mL (100 mL, 200 mL) [contains sodium 25.9 mg (1.1 mEq)/5 mL; cherry flavor]

Injection, powder for reconstitution, as lactobionate:

Erythrocin®: 500 mg, 1 g

Ointment, ophthalmic: 0.5% [5 mg/g] (1 g, 3.5 g)

Romycin®: 0.5% [5 mg/g] (3.5 g)

Ointment, topical:

Akne-Mycin®: 2% (25 g)

Powder for oral suspension, as ethylsuccinate:

EryPed®: 200 mg/5 mL (100 mL, 200 mL [DSC]) [contains sodium 117.5 mg (5.1 mEq)/5 mL; fruit flavor]; 400 mg/5 mL (100 mL, 200 mL [DSC]) [contains sodium 117.5 mg (5.1 mEq)/5 mL; banana flavor]

Powder for oral suspension, as ethylsuccinate [drops]:

EryPed®: 100 mg/2.5 mL (50 mL) [DSC] [contains sodium 58.8 mg (2.6 mEq)/dropperful; fruit flavor]

Powder, for prescription compounding:

Erythro-RX: USP (50 g)

Solution, topical: 2% (60 mL)

Eryderm®: 2% (60 mL) [contain alcohol] [DSC]

Sans acne [CAN]: 2% (60 mL) [contains ethyl alcohol 44%; not available in U.S.]

Suspension, oral, as ethylsuccinate: 200 mg/5 mL (480 mL) [DSC]; 400 mg/5 mL (480 mL) [DSC]

E.E.S.®: 200 mg/5 mL (100 mL, 480 mL) [fruit flavor] [DSC]; 400 mg/5 mL (100 mL, 480 mL) [orange flavor]

Tablet, as base: 250 mg, 500 mg

Tablet, as base [polymer-coated particles]:

PCE®: 333 mg, 500 mg

Tablet, as ethylsuccinate: 400 mg

E.E.S.®: 400 mg [DSC]

Tablet, as stearate: 250 mg, 500 mg

Erythrocin®: 250 mg, 500 mg

Tablet, delayed release, enteric coated, as base:

Ery-Tab®: 250 mg, 333 mg, 500 mg

Generic AvailableYes: Capsule, gel, ophthalmic ointment, topical solution, suspension (as ethylsuccinate), swab, tablet (as base, ethylsuccinate, and stearate)

Pricing: U.S. (www.drugstore.com)

Capsule, enteric pellets (Erythromycin Base)

250 mg (30): $13.99

Gel (Erygel)

2% (30): $35.99

Gel (Erythromycin)

2% (30): $18.65

2% (60): $38.65

Ointment (Erythromycin)

5 mg/g (3.5): $11.99

Solution (Eryderm)

2% (60): $25.99

Solution (Erythromycin)

2% (60): $26.13

Suspension (E.E.S. 200)

200 mg/5 mL (200): $13.18

Suspension (E.E.S. 400)

400 mg/5 mL (100): $12.99

Suspension (Erythromycin Ethylsuccinate)

200 mg/5 mL (200): $15.00

400 mg/5 mL (100): $10.99

Suspension (reconstituted) (E.E.S. Granules)

200 mg/5 mL (100): $12.99

200 mg/5 mL (200): $20.98

Tablet, EC (Ery-Tab)

250 mg (40): $17.99

333 mg (30): $16.99

500 mg (20): $15.99

Tablet, EC (PCE)

333 mg (30): $70.04

500 mg (20): $61.79

Tablets (E.E.S. 400)

400 mg (40): $12.99

Tablets (Erythrocin Stearate)

250 mg (30): $13.99

500 mg (20): $13.99

Tablets (Erythromycin Base)

250 mg (30): $13.99

500 mg (30): $16.99

Tablets (Erythromycin Ethylsuccinate)

400 mg (40): $16.99

Mechanism of ActionInhibits RNA-dependent protein synthesis at the chain elongation step; binds to the 50S ribosomal subunit resulting in blockage of transpeptidation

Pharmacodynamics/Kinetics

Absorption: Oral: Variable but better with salt forms than with base form; 18% to 45%; ethylsuccinate may be better absorbed with food

Distribution:

Relative diffusion from blood into CSF: Minimal even with inflammation

CSF:blood level ratio: Normal meninges: 2% to 13%; Inflamed meninges: 7% to 25%

Protein binding: Base: 73% to 81%

Metabolism: Demethylation primarily via hepatic CYP3A4

Half-life elimination: Peak: 1.5-2 hours; End-stage renal disease: 5-6 hours

Time to peak, serum: Base: 4 hours; Ethylsuccinate: 0.5-2.5 hours; delayed with food due to differences in absorption

Excretion: Primarily feces; urine (2% to 15% as unchanged drug)

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Treatment of Sexually-Transmitted Infections

Dental Health Professional ConsiderationsErythromycin is known to prolong the QT interval. The QT interval is measured as the time and distance between the Q point of the QRS complex and the end of the T wave in the ECG tracing. After adjustment for heart rate, the QT interval is defined as prolonged if it is more than 450 msec in men and 460 msec in women. A long QT syndrome was first described in the 1950s and 60s as a congenital syndrome involving QT interval prolongation and syncope and sudden death. Some of the congenital long QT syndromes were characterized by a peculiar electrocardiographic appearance of the QRS complex involving a premature atria beat followed by a pause, then a subsequent sinus beat showing marked QT prolongation and deformity. This type of cardiac arrhythmia was originally termed “torsade de pointes” (translated from the French as “twisting of the points”).

Prolongation of the QT interval is thought to result from delayed ventricular repolarization. The repolarization process within the myocardial cell is due to the efflux of intracellular potassium. The channels associated with this current can be blocked by many drugs and predispose the electrical propagation cycle to torsade de pointes.

Erythromycin is considered as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. It is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Many patients cannot tolerate erythromycin because of abdominal pain and nausea; the mechanism of this adverse effect appears to be the motilin agonistic properties of erythromycin in the GI tract. For these patients, clindamycin is indicated as the alternative antibiotic for treatment of orofacial infections.

HMG-CoA reductase inhibitors, also known as the statins, effectively decrease the hepatic cholesterol biosynthesis resulting in the reduction of blood LDL-cholesterol concentrations. The AUC of atorvastatin (Lipitor®) was increased 33% by erythromycin administration. Combination of erythromycin and lovastatin (Mevacor®) has been associated with rhabdomyolysis (Ayanian, et al). The mechanism of erythromycin is inhibiting the CYP3A4 metabolism of atorvastatin, lovastatin, and cerivastatin. Simvastatin (Zocor®) would likely be affected in a similar manner by the coadministration of erythromycin. Clarithromycin (Biaxin®) may exert a similar effect as erythromycin on atorvastatin, lovastatin, cerivastatin, and simvastatin.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsErythromycin is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution. See Dental Comment.

Mental Health: Effects on Mental StatusSystemic: Macrolides have been reported to cause nightmares, confusion, anxiety, and mood lability

Mental Health: Effects on Psychiatric TreatmentSystemic: Contraindicated with pimozide; may increase concentration of bromocriptine, carbamazepine, and triazolam

Cardiovascular ConsiderationsErythromycin, when used with drugs that affect the QT interval (eg, cisapride, quinidine) or when administered to patients with a prolonged QT interval, may further increase the QT interval and the risk of torsade de pointes (proarrhythmias).

Anesthesia and Critical Care Concerns/Other ConsiderationsErythromycin, when used with drugs that affect the QT interval (eg, cisapride, ergot derivatives, pimozide) or when administered to patients with a prolonged QT interval, may further increase the QT interval and the risk of torsade de pointes (proarrhythmias).

Index TermsErythromycin Base; Erythromycin Ethylsuccinate; Erythromycin Lactobionate; Erythromycin Stearate

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International Brand NamesAbomacetin (JP); Acnecin (PL); Acneryne (LU); Akne-mycin (CL); Akne-Mycin (LU, SG); Aknemycin (HU, LU, PL); Bannthrocin (ID); Cetathrocin (ID); Cusi Erythromycin (PL); Davercin (PL); Duramycin (ID); E-Mycin (PK); EES 400 (PR); EES Granules (PR); Emu-V E (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Emycin (KP); ERA (NZ); Erase (IN); Eribiotic (BR); Erigran (PY); Eritimix (VE); Eritrocap (MX); Eritrocina (PT); Eritrolag (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Eritromicin (HR); Eritromicina (CO); Eritropharma-S (MX); Erixyl (DO); Eromel (ZA); Ery (LU); Ery-Hexal (LU); Eryacne (SG); Eryacnen 4 (MX); Eryc (HU, KP, PL); Erycin (MY, TH, TW); Eryderm (LU); Eryfluid (LU); Eryhexal (LU); Erymycin AF (ZA); Erytab-S (MY); Eryth-Mycin (TH); Erythran (HU); Erythro (LU); Erythrocin (AE, AT, BB, BH, BM, BS, BZ, CY, DE, EG, GB, GR, GY, HK, IE, IL, IQ, IR, JM, JO, KW, LB, LY, NL, OM, PH, PR, QA, SA, SR, SY, TT, TW, YE); Erythrocin I.V. (AU); Erythrocin Lactobionate (HU); Erythrocine (LU, NL); Erythrocine[inj.] (LU); Erythrogenat (DE); Erythromil (AT, BE, BF, BG, BJ, CH, CI, CZ, DE, DK, ES, ET, FI, FR, GB, GH, GM, GN, GR, HN, IE, IT, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, NO, PT, RU, SC, SD, SE, SL, SN, TN, TR, TZ, UG, ZA, ZM, ZW); Erythromycin (DE); Erythromycin-ratiopharm DB (LU); Erythromycine-Ethypharm (LU); Erythromycinum (NL, PL); Erythromycinum Intravenosum (PL); Erythromycinum pro Suspensione (PL); Erythropen (GR); Erythrotrop (HU); Etocin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Etrola (TH); Etrotab (MY); Farmicina (UY); Hexabiotin (DK); Ilosone (HU, LU, MX); Inderm (LU); Iretron (MX); Lauritran (MX); Macromycine (LU); Meromycin (HU); Monomycin (LU); Oftalmolets (AR); Oftalmolosa Cusi Erythromycin (PL); Optomicin (MX); Panamicyn (CO); Pantomicina (CN, EC, MX, PE); Roug-mycin (GR); Rycin (HK); Ryebact (PH); Rythocin (TH); Sansacné (MX); Servitrocin (HK, HU); Sorestin (PH); Stiemcyn (MX); Stiemycin (CR, DO, GT, KP, LU, NI, PA, SV); Tropharma (MX); Urycin (TW); Zineryt (LU)

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Lexapro® may be confused with Loxitane®

Pronunciation(es sye TAL oh pram)

U.S. Brand NamesLexapro®

Canadian Brand NamesCipralex®

Pharmacologic CategoryAntidepressant, Selective Serotonin Reuptake Inhibitor

Use: Labeled IndicationsTreatment of major depressive disorder; generalized anxiety disorders (GAD)

Use: Unlabeled/Investigational

Treatment of mild dementia-associated agitation in nonpsychotic patients

Dosing: AdultsMajor depressive disorder, generalized anxiety disorder: Oral: Initial: 10 mg/day; dose may be increased to 20 mg/day after at least 1 week

Dosing: ElderlyDepression: Oral: 10 mg once daily

Dosing: Renal Impairment

Mild-to-moderate impairment: No dosage adjustment needed.

Severe impairment: Cl_{cr} <20 mL/minute: Use with caution.

Dosing: Hepatic Impairment10 mg/day

Administration: OralAdminister once daily (morning or evening), with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to escitalopram, citalopram, or any component of the formulation; concomitant use with pimozide; concomitant use or within 2 weeks of MAO inhibitors

Allergy Considerations

- Selective Serotonin Reuptake Inhibitor (SSRI) Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Escitalopram is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Escitalopram is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: Relatively devoid of these side effects.
- Bleeding risk: May impair platelet aggregation resulting in increased risk of bleeding events (including GI bleeding), particularly if used concomitantly with aspirin, NSAIDs, warfarin, or other anticoagulants. Bleeding related to SSRI or SNRI use has been reported to range from relatively minor bruising and epistaxis to life-threatening hemorrhage.
- CNS depression: Has a low potential to impair cognitive or motor performance; caution operating hazardous machinery or driving.
- Sexual dysfunction: May cause or exacerbate sexual dysfunction.
- SIADH and hyponatremia: SSRIs and SNRIs have been associated with the development of SIADH; hyponatremia has been reported rarely (including severe cases with serum sodium <110 mmol/L), predominately in the elderly. Hyponatremia is reversible with discontinuation of treatment. Volume depletion and/or concurrent use of diuretics likely increases risk.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; clearance is decreased and plasma concentrations are increased; a lower dosage may be needed.
- Renal impairment: Use with caution in patients with renal impairment.
- Seizure disorders: Use with caution in patients with a previous seizure disorder or condition predisposing to seizures such as brain damage or alcoholism.

Concurrent drug therapy issues:

- Agents which lower seizure threshold: Concurrent therapy with other drugs which lower the seizure threshold.
- Anticoagulants/Antiplatelets: Use caution with concomitant use of aspirin, NSAIDs, warfarin, or other drugs that affect coagulation; the risk of bleeding may be potentiated.
- CNS depressants: Use caution with concomitant therapy.
- MAO inhibitors: Potential for severe reaction when used with MAO inhibitors; autonomic instability, coma, death, delirium, diaphoresis, hyperthermia, mental status changes/agitation, muscular rigidity, myoclonus, neuroleptic malignant syndrome features, and seizures may occur.
- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce escitalopram's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

Special populations:

- Elderly: Use caution in elderly patients; risk of hyponatremia and other adverse events may be increased. Bioavailability and half-life are increased by 50% in the elderly.
- Pediatrics: Safety and efficacy in children have not been established.
- Pregnancy: Use caution in pregnant patients; high doses of citalopram have been associated with teratogenicity in animals.

Other warnings/precautions:

- Electroconvulsive therapy (ECT): Use with caution; no clinical studies have assessed the combined use of escitalopram and electroconvulsive therapy; may increase the risks (eg, cognitive adverse effects) associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.
- Withdrawal syndrome: May cause dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Upon discontinuation of escitalopram therapy, gradually taper dose. If intolerable symptoms occur following a decrease in dosage or upon discontinuation of therapy, then resuming the previous dose with a more gradual taper should be considered.

Geriatric ConsiderationsBioavailability and half-life are increased by 50% in the elderly. The elderly are more prone to SSRI/SNRI-induced hyponatremia.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDue to adverse effects observed in animal studies, escitalopram is classified as pregnancy category C. Escitalopram is distributed into the amniotic fluid. Limited data is available concerning the use of escitalopram during pregnancy. Nonteratogenic effects in the newborn following SSRI exposure late in the third trimester include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypo- or hypertonia, hyper-reflexia, jitteriness, irritability, constant crying, and tremor. An increased risk of low birth weight and lower APGAR scores have also been reported. Exposure to SSRIs after the twentieth week of gestation has been associated with persistent pulmonary hypertension of the newborn (PPHN). Adverse effects may be due to toxic effects of the SSRI or drug withdrawal without a taper. The long-term effects of *in utero* SSRI exposure on infant development and behavior are not known. Escitalopram is the S-enantiomer of the racemic derivative citalopram; also refer to the Citalopram monograph.

Women treated for major depression and who are euthymic prior to pregnancy are more likely to experience a relapse when medication is discontinued as compared to pregnant women who continue taking antidepressant medications. The ACOG recommends that therapy with

SSRIs or SNRIs during pregnancy be individualized; treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary healthcare provider, and pediatrician (ACOG, 2007). If treatment during pregnancy is required, consider tapering therapy during the third trimester in order to prevent withdrawal symptoms in the infant. If this is done and the woman is considered to be at risk from her major depressive disorder, the medication can be restarted following delivery, although the dose should be readjusted to that required before pregnancy.

LactationEnters breast milk/consider risk:benefit

Breast-Feeding ConsiderationsEscitalopram and its metabolite are excreted into breast milk. Limited data is available concerning the effects escitalopram may have in the nursing infant and the long-term effects on development and behavior have not been studied. According to the manufacturer, the decision to continue or discontinue breast-feeding during therapy should take into account the risk of exposure to the infant and the benefits of treatment to the mother. Escitalopram is the S-enantiomer of the racemic derivative citalopram; also refer to the Citalopram monograph.

Adverse Reactions

>10%:

Central nervous system: Headache (24%), somnolence (6% to 13%), insomnia (9% to 12%)

Gastrointestinal: Nausea (15% to 18%)

Genitourinary: Ejaculation disorder (9% to 14%)

1% to 10%:

Cardiovascular: Chest pain, hypertension, palpitation

Central nervous system: Fatigue (5% to 8%), dizziness (5%), dreaming abnormal (3%), lethargy (1% to 3%), yawning (2%), concentration impaired, fever, irritability, lightheadedness, migraine

Dermatologic: Rash

Endocrine & metabolic: Libido decreased (3% to 7%), anorgasmia (2% to 6%), menstrual disorder (2%), hot flashes, menstrual cramps

Gastrointestinal: Xerostomia (6% to 9%), diarrhea (8%), constipation (3% to 5%), appetite decreased (3%), indigestion (3%), vomiting (3%), abdominal pain (2%), flatulence (2%), toothache (2%), abdominal cramps, appetite increased, gastroenteritis, heartburn, weight gain

Genitourinary: Impotence (2% to 3%), urinary tract infection, urinary frequency

Neuromuscular & skeletal: Neck/shoulder pain (3%), paresthesia (2%), arthralgia, limb pain, muscle cramp, myalgia

Ocular: Blurred vision

Otic: Earache, tinnitus

Respiratory: Rhinitis (5%), sinusitis (3%), bronchitis, cough, nasal or sinus congestion, sinus headache

Miscellaneous: Diaphoresis (4% to 5%), flu-like syndrome (5%), allergy

<1% (Limited to important or life threatening): Abdominal discomfort, agitation, amnesia, anaphylaxis, anemia, anxiety attack, apathy, arthritis, arthropathy, asthma, auditory hallucination, back discomfort, bilirubin increased, bradycardia, bruxism, carpal tunnel syndrome, chest tightness, chills, confusion, conjunctivitis, coordination abnormal, depersonalization, depression aggravated, depression, dermatitis, disorientation, dyspepsia, dyspnea, dysuria, ECG abnormal, eczema, edema, emotional lability, excitability, eye infection, flushing, folliculitis, furunculosis, gastritis, GERD, gout, hematoma, hematuria, hypercholesterolemia, hyperglycemia, hyper-reflexia, kidney stone, leg pain, lipoma, liver enzymes increased, malaise, menorrhagia, muscle contractions (involuntary), muscle stiffness, muscle weakness, muscular tone increased, nervousness, nosebleed, panic reaction, pneumonia, pruritus, pupils dilated, restless legs, restlessness aggravated, shaking, spotting between menses, suicidal tendency, suicide attempt, syncope, tachycardia, taste alteration, tics, tracheitis, tremor, tremulousness nervous, twitching, urinary urgency, varicose vein, vertigo, vision abnormal, visual disturbance, weakness, weight loss

Postmarketing and/or case reports: Acute renal failure, aggression, akathisia, allergic reaction, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dyskinesia, dystonia, ecchymosis, erythema multiforme, glaucoma, grand mal seizure, hallucination, hemolytic anemia, hepatic necrosis, hepatitis, INR increased, liver failure, myocardial infarction, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, pulmonary embolism, QT prolonged, rhabdomyolysis, serotonin syndrome, SIADH, spontaneous abortion, Stevens-Johnson syndrome, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, withdrawal syndrome

Metabolism/Transport Effects**Substrate** (major) of CYP2C19, 3A4; **Inhibits** CYP2D6 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha-/Beta-Blockers: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Alpha-/Beta-Blockers. *Risk C: Monitor therapy*

Analgesics (Opioid): May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin Reuptake Inhibitor/Antagonist): Selective Serotonin Reuptake Inhibitors may enhance the serotonergic effect of Antidepressants (Serotonin Reuptake Inhibitor/Antagonist). This may cause serotonin syndrome. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Aspirin: Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Beta-Blockers: Selective Serotonin Reuptake Inhibitors may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Acebutolol; Atenolol; Carteolol; Esmolol; Levobunolol; Metipranolol; Nadolol; Penbutolol. *Risk C: Monitor therapy*

BusPIRone: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. Selective Serotonin Reuptake Inhibitors may decrease the metabolism of BusPIRone. *Risk C: Monitor therapy*

CarBAMazepine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of CarBAMazepine. Specifically those SSRIs that inhibit CYP3A4 isoenzymes. CarBAMazepine may increase the metabolism of Selective Serotonin Reuptake Inhibitors. Specifically those agents metabolized via CYP1A2, 2C, and/or 3A4 isoenzymes. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Selective Serotonin Reuptake Inhibitors. *Risk D: Consider therapy modification*

Clozapine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Cyproheptadine: May diminish the therapeutic effect of Selective Serotonin Reuptake Inhibitors. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dextromethorphan: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Dextromethorphan. *Risk D: Consider therapy modification*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Haloperidol: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Haloperidol. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Iobenguane I 123: Selective Serotonin Reuptake Inhibitors may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Selective Serotonin Reuptake Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methadone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Methadone. Fluvoxamine appears to be the only interacting SSRI. *Risk D: Consider therapy modification*

Mexiletine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Mexiletine. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk D: Consider therapy modification*

NSAID (Nonselective): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Phenytoin: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Pimozide: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Pimozide. *Risk X: Avoid combination*

Propafenone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Propafenone. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Risperidone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Risperidone. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

TraMADol: Selective Serotonin Reuptake Inhibitors may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. TraMADol may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tryptophan: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Selective Serotonin Reuptake Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava, and gotu kola (may increase CNS depression).

Monitoring ParametersMental status for depression, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased), anxiety, social functioning, mania, panic attacks; akathisia

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, MAO inhibitors and other SSRIs). Assess therapeutic effectiveness and adverse reactions at the beginning of therapy and on a regular basis throughout therapy (eg, suicidal ideation, mania, hypomania, anxiety, or panic attacks). Teach patient proper use, possible side effects, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take exactly as directed; do not alter dose or discontinue without consulting prescriber (effects of medication may take up to 3 weeks to occur). Avoid other stimulants: caffeine or alcohol. May cause dizziness, lightheadedness, insomnia, impaired concentration, headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, loss or increase of appetite, indigestion, or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); constipation (increased dietary fluid, fruit, fiber, and increased exercise may help); sexual dysfunction (reversible when drug is discontinued); hot flashes or menstrual cramps; or muscle pain, cramps, or tremor (consult prescriber for approved analgesia). Report immediately any CNS changes such as increased depression, confusion, impaired concentration, severe headache, insomnia, nightmares, irritability, acute anxiety, panic attacks, or thoughts of suicide; persistent GI changes; chest pain or palpitations; blurred vision or vision changes; ringing in ears; unusual cough; or other persistent adverse effects.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral:

Lexapro®: 1 mg/mL (240 mL) [contains propylene glycol; peppermint flavor]

Tablet:

Lexapro®: 5 mg, 10 mg, 20 mg

Note: Cipralex® [CAN] is available only in 10 mg and 20 mg strengths.

Generic AvailableNo

ManufacturerForest Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Solution (Lexapro)

5 mg/5 mL (240): $140.86

Tablets (Lexapro)

5 mg (30): $82.99

10 mg (30): $85.99

20 mg (30): $89.99

Mechanism of ActionEscitalopram is the S-enantiomer of the racemic derivative citalopram, which selectively inhibits the reuptake of serotonin with little to no effect on norepinephrine or dopamine reuptake. It has no or very low affinity for 5-HT$_{1-7}$, alpha- and beta-adrenergic, D$_{1-5}$, H$_{1-3}$, M$_{1-5}$, and benzodiazepine receptors. Escitalopram does not bind to or has low affinity for Na^{+}, K^{+}, Cl^{-}, and Ca^{++} ion channels.

Pharmacodynamics/Kinetics

Onset of action: Depression: The onset of action is within a week, however, individual response varies greatly and full response may not be seen until 8-12 weeks after initiation of treatment.

Protein binding: 56% to plasma proteins

Metabolism: Hepatic via CYP2C19 and 3A4 to an active metabolite, S-desmethylcitalopram (S-DCT; 1/7 the activity); S-DCT is metabolized to S-didesmethylcitalopram (S-DDCT; active; 1/27 the activity) via CYP2D6

Half-life elimination: Escitalopram: 27-32 hours; S-desmethylcitalopram: 59 hours

Time to peak: Escitalopram: ~5 hours; S-desmethylcitalopram: 14 hours

Excretion: Urine (Escitalopram: 8%; S-DCT: 10%)

Clearance: Total body: 37-40 L/hour; Renal: Escitalopram: 2.7 L/hour; S-desmethylcitalopram: 6.9 L/hour

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Selective Serotonin Reuptake Inhibitors (SSRIs) CYP Profile
- Selective Serotonin Reuptake Inhibitors (SSRIs) FDA-Approved Indications
- Selective Serotonin Reuptake Inhibitors (SSRIs) Pharmacokinetics
- Selective Serotonin Reuptake Inhibitors (SSRIs) Receptor Profile
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsThe tablet and oral solution dosage forms are bioequivalent. Clinically, escitalopram 20 mg is equipotent to citalopram 40 mg. Do not coadminister with citalopram.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and toothache

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAlthough caution should be used in patients taking tricyclic antidepressants, no interactions have been reported with vasoconstrictors and escitalopram, a nontricyclic antidepressant which acts to increase serotonin; no precautions appear to be needed

Mental Health CommentThe SSRIs as a class are generally considered to be safe and equally effective. Allow sufficient dose-response time (6-12 weeks). Differences lie in approved indications, receptor profiles, pharmacokinetics, and cytochrome P450 activity profile. Subtle differences exist in adverse effect profiles. All SSRIs have the potential to cause sexual dysfunction. Escitalopram is the s-isomer of citalopram and therefore, similar to citalopram. Among the SSRIs, escitalopram possesses the lowest effects on CYP isoenzymes.

Index TermsEscitalopram Oxalate; Lu-26-054; S-Citalopram

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International Brand Names Cipralex (AE, BG, BH, CH, CY, CZ, DE, DK, EE, EG, ES, FI, GB, HN, ID, IL, IN, IQ, IR, IT, JO, KW, LB, LY, NO, OM, PK, PT, QA, SA, SE, SY, YE); Esipram (AU); Ipran (CN); Lexapro (AR, AU, BR, CO, EC, HK, IE, KP, MY, NL, PE, PH, PL, SG, TH, TW); Seroplex (FR); Sipralexa (BE)

ESHAP

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Etoposide: I.V.: 40 mg/m^2/day days 1 to 4

[total dose/cycle = 160 mg/m^2]

Methylprednisolone: I.V.: 250-500 mg/day days 1 to 5

[total dose/cycle = 1250-2500 mg]

Cytarabine: I.V.: 2000 mg/m^2 day 5

[total dose/cycle = 2000 mg/m^2]

Cisplatin: I.V.: 25 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21-28 days

Variation 2:

Etoposide: I.V.: 40 mg/m^2/day days 1 to 4

[total dose/cycle = 160 mg/m^2]

Methylprednisolone: I.V.: 500 mg/day days 1 to 5

[total dose/cycle = 2500 mg]

Cytarabine: I.V.: 2000 mg/m^2 day 5

[total dose/cycle = 2000 mg/m^2]

Cisplatin: I.V.: 25 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21-28 days

Variation 3:

Etoposide: I.V.: 60 mg/m^2/day days 1 to 4

[total dose/cycle = 240 mg/m^2]

Methylprednisolone: I.V.: 500 mg/day days 1 to 4

[total dose/cycle = 2000 mg]

Cytarabine: I.V.: 2000 mg/m^2 day 5

[total dose/cycle = 2000 mg/m^2]

Cisplatin: I.V.: 25 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21 days

References

Variation 1:

Velasquez WF, McLaughlin P, Tucker S, et al, “ESHAP - An Effective Chemotherapy Regimen in Refractory and Relapsing Lymphoma: A 4-Year

Follow-up Study,” *J Clin Oncol*, 1994, 12(6):1169-76. [PubMed 8201379]

Variation 2:

Wang WS, Chiou TJ, Liu JH, et al, “ESHAP as Salvage Therapy for Refractory Non-Hodgkin's Lymphoma: Taiwan Experience,” *Jpn J Clin Oncol*, 1999, 29(1):33-7. [PubMed 10073149]

Variation 3:

Rodriguez MA, Cabanillas FC, Velasquez W, et al, “Results of a Salvage Treatment Program for Relapsing Lymphoma: MINE Consolidated With ESHAP,” *J Clin Oncol*, 1995, 13(7):1734-41.[PubMed 7602363]

Esmolol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Esmolol may be confused with Osmitrol®

Brevibloc® may be confused with bretylium, Brevital®, Bumex®, Buprenex®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ES moe lol)

U.S. Brand NamesBrevibloc®

Canadian Brand NamesBrevibloc®

Pharmacologic CategoryAntiarrhythmic Agent, Class II; Beta Blocker, Beta$_1$ Selective

Use: Labeled IndicationsTreatment of supraventricular tachycardia (SVT) and atrial fibrillation/flutter (control ventricular rate); treatment of tachycardia and/or hypertension (especially intraoperative or postoperative); treatment of noncompensatory sinus tachycardia

Use: Unlabeled/InvestigationalIn children, for SVT and postoperative hypertension

Dosing: Adults **Infusion requires an infusion pump** (must be adjusted to individual response and tolerance):

Intraoperative tachycardia and/or hypertension (immediate control): I.V.: Initial bolus: 80 mg (~1 mg/kg) over 30 seconds, followed by a 150 mcg/kg/minute infusion, if necessary. Adjust infusion rate as needed to maintain desired heart rate and/or blood pressure, up to 300 mcg/kg/minute.

For control of postoperative hypertension, as many as one-third of patients may require higher doses (250-300 mcg/kg/minute) to control blood pressure; the safety of doses >300 mcg/kg/minute has not been studied.

Supraventricular tachycardia or gradual control of postoperative tachycardia/hypertension: I.V.: Loading dose: 500 mcg/kg over 1 minute; follow with a 50 mcg/kg/minute infusion for 4 minutes; response to this initial infusion rate may be a rough indication of the responsiveness of the ventricular rate.

Infusion may be continued at 50 mcg/kg/minute or, if the response is inadequate, titrated upward in 50 mcg/kg/minute increments (increased no more frequently than every 4 minutes) to a maximum of 200 mcg/kg/minute.

Note: To achieve more rapid response, following the initial loading dose and 50 mcg/kg/minute infusion, rebolus with a second 500 mcg/kg loading dose over 1 minute, and increase the maintenance infusion to 100 mcg/kg/minute for 4 minutes. If necessary, a third (and final) 500 mcg/kg loading dose may be administered, prior to increasing to an infusion rate of 150 mcg/kg/minute. After 4 minutes of the 150 mcg/kg/minute infusion, the infusion rate may be increased to a maximum rate of 200 mcg/kg/minute (without a bolus dose).

Supraventricular tachycardias (SVT); usual dose range: Usual dosage range: 50-200 mcg/kg/minute with average dose of 100 mcg/kg/minute.

Guidelines for transfer to oral therapy (beta-blocker, calcium channel blocker):

Infusion should be reduced by 50% 30 minutes following the first dose of the alternative agent

Manufacturer suggests following the second dose of the alternative drug, patient's response should be monitored and if control is adequate for the first hours, esmolol may be discontinued.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Supraventricular tachycardias (unlabeled use): I.V.: A limited amount of information regarding esmolol use in pediatric patients is currently available. Some centers have utilized doses of 100-500 mcg/kg given over 1 minute for control of supraventricular tachycardias.

Postoperative hypertension (unlabeled use): I.V.: Loading doses of 500 mcg/kg/minute over 1 minute with maximal doses of 50-250 mcg/kg/minute (mean = 173) have been used in addition to nitroprusside to treat postoperative hypertension after coarctation of aorta repair.

Dosing: Renal ImpairmentNot removed by hemo- or peritoneal dialysis. Supplemental dose is not necessary.

Calculations

- Esmolol

Administration: I.V.The 250 mg/mL ampul is **not** for direct I.V. injection, but rather must first be diluted to a final concentration of 10 mg/mL (ie, 2.5 g in 250 mL or 5 g in 500 mL). Concentrations >10 mg/mL or infusion into small veins or through a butterfly catheter should be avoided (can cause thrombophlebitis).

Administration: I.V. DetailInfusions must be administered with an infusion pump. Decrease or discontinue infusion if hypotension, congestive heart failure occur.

pH: 3.5-5.5 (concentrate); 4.5-5.5 (ready to use)

StorageClear, colorless to light yellow solution which should be stored at 15°C to 30°C (59°F to 85°F); do not freeze. Protect fromexcessive heat.

CompatibilityStable in D_5LR, $D_5{}^1/_2$NS, D_5NS, D_5W, D_5W with KCl 40 mEq/L, LR, ${}^1/_2$NS, NS.

Y-site administration: Compatible: Amikacin, aminophylline, amiodarone, ampicillin, atracurium, butorphanol, calcium chloride, cefazolin, cefoperazone, ceftazidime, ceftizoxime, chloramphenicol, cimetidine, cisatracurium, clindamycin, diltiazem, dopamine, enalaprilat, erythromycin lactobionate, famotidine, fentanyl, gatifloxacin, gentamicin, heparin, hydrocortisone sodium succinate, insulin (regular), labetalol, linezolid, magnesium sulfate, methyldopate, metronidazole, midazolam, morphine, nafcillin, nitroglycerin, norepinephrine, pancuronium, penicillin G potassium, phenytoin, piperacillin, polymyxin B sulfate, potassium chloride, potassium phosphates, propofol, ranitidine, remifentanil, sodium acetate, sodium nitroprusside, streptomycin, tacrolimus, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, vecuronium. **Incompatible:** Amphotericin B cholesteryl sulfate complex, furosemide, warfarin.

Compatibility when admixed: Compatible: Aminophylline, atracurium, bretylium, digoxin, dopamine, heparin, lidocaine. **Incompatible:** Diazepam, procainamide, sodium bicarbonate, thiopental.

ContraindicationsHypersensitivity to esmolol or any component of the formulation; sinus bradycardia; heart block greater than first degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; bronchial asthma (relative); uncompensated cardiac failure; hypotension; pregnancy (2nd and 3rd trimesters)

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.
- Hypotension: Can commonly occur; patients need close blood pressure monitoring.
- Skin necrosis: Extravasation can lead to skin necrosis and sloughing.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; however, esmolol, with B_1 selectivity, has been used cautiously with close monitoring.
- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.
- Heart failure (HF): Use with caution in patients with compensated heart failure and monitor for a worsening of the condition.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis.
- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).
- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.
- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.
- Renal impairment: Use with caution in patients with renal impairment; active metabolite retained.

Concurrent drug therapy issues:

- Calcium channel blockers: Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur. Avoid concurrent I.V. use of both agents.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Administration: Concentrations >10 mg/mL or infusion into small veins or through a butterfly catheter should be avoided; can cause thrombophlebitis.
- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.
- Hypertension associated with hypothermia: Do not use in the treatment of hypertension associated with vasoconstriction related to hypothermia.

Geriatric ConsiderationsDue to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (ie, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20% to 50% in elderly populations. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults.

Pregnancy Risk FactorC (manufacturer); D (2nd and 3rd trimesters - expert analysis)

Pregnancy ConsiderationsTeratogenic effects are not noted in animal studies. Fetal bradycardia can occur when administered in the 3rd trimester of pregnancy or at delivery.

LactationExcretion in breast milk unknown/use with caution

Adverse Reactions

>10%:

Cardiovascular: Asymptomatic hypotension (dose related: 25% to 38%), symptomatic hypotension (dose related: 12%)

Miscellaneous: Diaphoresis (10%)

1% to 10%:

Cardiovascular: Peripheral ischemia (1%)

Central nervous system: Dizziness (3%), somnolence (3%), confusion (2%), headache (2%), agitation (2%), fatigue (1%)

Gastrointestinal: Nausea (7%), vomiting (1%)

Local: Pain on injection (8%), infusion site reaction

<1% (Limited to important or life-threatening): Abdominal discomfort, abnormal thinking, acne, alopecia, anorexia, anxiety, bradycardia, bronchospasm, chest pain, CHF, constipation, depression, dyspepsia, dyspnea, eczema, edema, erythema, exfoliative dermatitis, fever, flushing, heart block, lightheadedness, midcapsular pain, nasal congestion, pallor, paresthesia, pruritus, psoriasis, pulmonary edema, rigors, seizure, severe bradycardia/asystole (rare), skin discoloration, skin irritation, skin necrosis (from extravasation), syncope, taste perversion, thrombophlebitis, urinary retention, vision change, weakness, wheezing, xerostomia

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Theophylline Derivatives: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Test InteractionsIncreases cholesterol (S), glucose

Monitoring ParametersBlood pressure, heart rate, MAP, ECG, respiratory rate, I.V. site; cardiac monitor and blood pressure monitor required

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Requires continuous cardiac, hemodynamic, and infusion site monitoring (extravasation). If you have diabetes, may mask signs of hypoglycemia. Monitor blood sugars closely. Monitor therapeutic effectiveness and adverse reactions.

Patient EducationEsmolol is administered in emergencies, patient education should be appropriate to the situation. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Infusion [premixed in sodium chloride; preservative free]:

Brevibloc®: 2000 mg (100 mL) [20 mg/mL; double strength]; 2500 mg (250 mL) [10 mg/mL]

Injection, solution, as hydrochloride: 10 mg/mL (10 mL)

Brevibloc®:

10 mg/mL (10 mL) [alcohol free; premixed in sodium chloride]

20 mg/mL (5 mL, 100 mL) [alcohol free; double strength; premixed in sodium chloride]

250 mg/mL (10 mL) [contains alcohol 25%, propylene glycol 25%; concentrate] [DSC]

Generic AvailableYes: Excludes infusion

Mechanism of ActionClass II antiarrhythmic: Competitively blocks response to beta$_1$-adrenergic stimulation with little or no effect of beta$_2$-receptors except at high doses, no intrinsic sympathomimetic activity, no membrane stabilizing activity

Pharmacodynamics/Kinetics

Onset of action: Beta-blockade: I.V.: 2-10 minutes (quickest when loading doses are administered)

Duration of hemodynamic effects: 10-30 minutes; prolonged following higher cumulative doses, extended duration of use

Protein binding: 55%

Metabolism: In blood by red blood cell esterases

Half-life elimination: Adults: 9 minutes; elimination of metabolite decreases with end stage renal disease

Excretion: Urine (~69% as metabolites, 2% unchanged drug)

Related Information

- Antiarrhythmic Drugs
- Beta-Blockers
- Hypertension

Dental Health: Effects on Dental TreatmentEsmolol is a cardioselective beta-blocker. Local anesthetic with vasoconstrictor can be safely used in patients medicated with esmolol. Nonselective beta-blockers (ie, propranolol, nadolol) enhance the pressor response to epinephrine, resulting in hypertension and bradycardia; this has not been reported for esmolol. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, confusion, fatigue, or depression

Mental Health: Effects on Psychiatric TreatmentBarbiturates may decease effects of esmolol

Cardiovascular ConsiderationsEsmolol provides an important mechanism for close titration of rate control in patients with atrial fibrillation. Esmolol may also be beneficial in allowing close blood pressure control. Esmolol should only be administered in intensive care or closely monitored situations. Potential adverse effects include hypotension and bradyarrhythmias. These are usually short-lived because of esmolol's short half-life (9 minutes).

Anesthesia and Critical Care Concerns/Other ConsiderationsEsmolol 250 mg/mL contains propylene glycol 258 mg/mL (25% v/v).

This agent is also used to blunt sympathetic response during intubation, in “at-risk” patients such as those with coronary artery disease (CAD), angina, uncontrolled hypertension, and hyperthyroidism. Esmolol may lose beta$_1$ specificity after higher doses. It should be used with caution in patients with pulmonary disease and diabetes.

Esmolol provides an important mechanism for close titration of rate control in patients with atrial fibrillation; may also be beneficial in allowing close blood pressure control. Esmolol should only be administered in intensive care or closely monitored situations. Potential adverse effects include hypotension and bradyarrhythmias (usually short-lived due to short half-life of 9 minutes).

Index TermsEsmolol Hydrochloride

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International Brand NamesBreviblo (PK); Brevibloc (AR, AT, AU, BE, BR, CH, CZ, DK, ES, FI, FR, GB, HN, HU, IE, IT, KP, MX, NL, NO, SE, TW, UY); Esbloc (KP); Escard (IN)

Esomeprazole

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Proton Pump Inhibitors (Esomeprazole, Omeprazole): Evidence Does Not Suggest Increased Rates of Cardiac Events - Results of FDA Analysis - Updated, February 2008

The U.S. Food and Drug Administration (FDA) and Health Canada reviews of esomeprazole (Nexium®) and omeprazole (Prilosec® [U.S.]/Losec® [CAN]) find no evidence of increased risk of cardiac events related to these medications. In May 2007, AstraZeneca, the manufacturer of Nexium® (esomeprazole) and Prilosec® (U.S.)/Losec® (CAN) (omeprazole), notified both regulatory agencies of concerns regarding a possible association between long-term use of esomeprazole or omeprazole and cardiovascular side effects based on the results of two small, nonblinded, long-term, European clinical trials of patients with GERD. Patients in these trials were randomized to antireflux surgery (fundoplication) or esomeprazole or omeprazole treatment. In these trials, initial data suggested that patients using either of these proton pump inhibitors experienced more heart attacks, heart failure, and cardiac deaths than patients who had surgery. As a result, the FDA and Health Canada issued public notifications regarding these results in August 2007.

The FDA and Health Canada evaluated the two studies, other published trials, and an analysis of postmarketing safety data from the FDA and WHO since that time, and issued independent statements saying that preliminary reviews do not confirm the existence of cardiovascular risk. Upon further analysis of additional information submitted to the FDA and Health Canada by the manufacturer, both regulatory agencies have confirmed their respective preliminary reviews of the evidence, and are recommending that healthcare providers continue to prescribe (and patients continue to use) these products as described within their labeling.

For more information, healthcare professionals may refer to the following FDA and Health Canada websites:

http://www.fda.gov/cder/drug/early_comm/omeprazole_esomepazole_update.htm

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_34_e.html

Medication Safety Issues

Sound-alike/look-alike issues:

Nexium® may be confused with Nexavar®

Pronunciation(es oh ME pray zol)

U.S. Brand NamesNexium®

Canadian Brand NamesNexium®

Pharmacologic CategoryProton Pump Inhibitor; Substituted Benzimidazole

Use: Labeled Indications

Oral: Short-term (4-8 weeks) treatment of erosive esophagitis; maintaining symptom resolution and healing of erosive esophagitis; treatment of symptomatic gastroesophageal reflux disease (GERD); as part of a multidrug regimen for *Helicobacter pylori* eradication in patients with duodenal ulcer disease (active or history of within the past 5 years); prevention of gastric ulcers in patients at risk (age ≥60 years and/or history of gastric ulcer) associated with continuous NSAID therapy; long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome

Canadian labeling: Additional use (not in U.S. labeling): Oral: Treatment of nonerosive reflux disease (NERD)

I.V.: Short-term (≤10 days) treatment of gastroesophageal reflux disease (GERD) when oral therapy is not possible or appropriate

Dosing: Adults

Erosive esophagitis (healing): Oral: Initial: 20-40 mg once daily for 4-8 weeks; if incomplete healing, may continue for an additional 4-8 weeks; maintenance: 20 mg once daily

Maintenance of healing of erosive esophagitis: Oral: 20 mg once daily; clinical trials evaluated therapy for ≤6 months

Nonerosive reflux disease (NERD) (Canadian labeling): Initial: 20 mg once daily for 2-4 weeks; lack of symptom control after 4 weeks warrants further evaluation; maintenance (in patients with successful initial therapy): 20 mg once daily as needed

Symptomatic gastroesophageal reflux: Oral: 20 mg once daily for 4 weeks; may consider an additional 4 weeks of treatment if symptoms do not resolve

Treatment of GERD (short-term): I.V.: 20 mg or 40 mg once daily for ≤10 days; change to oral therapy as soon as appropriate

Peptic ulcer disease: Eradication of*Helicobacter pylori*: Oral: 40 mg once daily for 10 days; requires combination therapy. **Note:** Various regimens available:

Canadian labeling: 20 mg twice daily for 7 days; requires combination therapy

Prevention of NSAID-induced gastric ulcers: 20-40 mg once daily for up to 6 months

Treatment of NSAID-induced gastric ulcers (Canadian labeling): 20 mg once daily for 4-8 weeks.

Pathological hypersecretory conditions (Zollinger-Ellison syndrome): 40 mg twice daily; adjust regimen to individual patient needs; doses up to 240 mg/day have been administered

Dosing: ElderlyRefer to adult dosing. No dosage adjustment needed.

Dosing: Pediatric

Children 1-11 years: Oral: **Note:** Safety and efficacy of doses >1 mg/kg/day and/or therapy beyond 8 weeks have not been established.

Symptomatic GERD: 10 mg once daily for up to 8 weeks

Erosive esophagitis (healing):

<20 kg: 10 mg once daily for 8 weeks

≥20 kg: 10-20 mg once daily for 8 weeks

Nonerosive reflux disease (NERD) (Canadian labeling): 10 mg once daily for up to 8 weeks

Adolescents 12-17 years: Oral:

Symptomatic GERD: 20-40 mg once daily for up to 8 weeks

NERD (Canadian labeling): 20 mg once daily for 2-4 weeks

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentSafety and efficacy not established in children with hepatic impairment.

Mild-to-moderate hepatic impairment (Child-Pugh class A or B): No dosage adjustment needed.

Severe hepatic impairment (Child-Pugh class C): Dose should not exceed 20 mg/day.

Administration: I.V.May be administered by injection (≥3 minutes) or infusion (10-30 minutes). Flush line prior to and after administration with NS, LR, or D_5W.

Administration: I.V. DetailpH: 9-11

Administration: Oral

Capsule: Should be swallowed whole and taken at least 1 hour before eating (best if taken before breakfast). Capsule can be opened and contents mixed with 1 tablespoon of applesauce. Swallow immediately; mixture should not be chewed or warmed. For patients with difficulty swallowing, use of granules may be easiest.

Granules: Empty into container with 1 tablespoon of water and stir; leave 2-3 minutes to thicken. Stir and drink within 30 minutes. If any medicine remains after drinking, add more water, stir and drink immediately.

Tablet (Canadian formulation, not available in U.S.): Swallow whole or may be dispersed in a half a glass of noncarbonated water. Stir until tablets disintegrate, leaving a liquid containing pellets. Drink contents within 30 minutes. Do not chew or crush pellets. After drinking, rinse glass with water and drink.

Administration: OtherNasogastric tube:

Capsule: Open capsule and place intact granules into a 60 mL syringe; mix with 50 mL of water. Replace plunger and shake vigorously for 15 seconds. Ensure that no granules remain in syringe tip. Do not administer if pellets dissolve or disintegrate. Use immediately after preparation. After administration, flush nasogastric tube with additional water.

Granules: Delayed release oral suspension granules can also be given by nasogastric or gastric tube. Add 15 mL of water to a syringe, add granules from packet. Shake the syringe, leave 2-3 minutes to thicken. Shake the syringe and administer through nasogastric or gastric tube (French size 6 or greater) within 30 minutes. Refill the syringe with 15 mL of water, shake and flush nasogastric/gastric tube.

Tablet (Canadian formulation, not available in U.S.): Disperse tablets in 50 mL of noncarbonated water. Stir until tablets disintegrate leaving a liquid containing pellets. After administration, flush with additional 25-50 mL of water to clear the syringe and tube.

Dietary ConsiderationsTake at least 1 hour before meals; best if taken before breakfast. The contents of the capsule may be mixed in applesauce or water; pellets also remain intact when exposed to orange juice, apple juice, and yogurt.

Storage

Capsule, granules: Store at 15°C to 30°C (59°F to 86°F). Keep container tightly closed.

Powder for injection: Store at 15°C to 30°C (59°F to 86°F). Protect from light. Following reconstitution, solution for injection prepared in NS, and solution for infusion prepared in NS or LR should be used within 12 hours. Following reconstitution, solution for infusion prepared in D_5W should be used within 6 hours. Refrigeration is not required following reconstitution.

ReconstitutionPowder for injection:

For I.V. injection: Reconstitute powder with 5 mL NS.

For I.V. infusion: Initially reconstitute powder with 5 mL of NS, LR, or D_5W, then further dilute to a final volume of 50 mL.

ContraindicationsHypersensitivity to esomeprazole, substituted benzimidazoles (ie, lansoprazole, omeprazole, pantoprazole, rabeprazole), or any component of the formulation

Allergy Considerations

- Proton Pump Inhibitor, Benzimidazole Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Atrophic gastritis: Long-term omeprazole therapy has caused atrophic gastritis (by biopsy); this may also occur with esomeprazole.
- Carcinoma: No reports of enterochromaffin-like (ECL) cell carcinoids, dysplasia, or neoplasia have occurred.

Disease-related concerns:

- Gastric malignancy: Relief of symptoms does not preclude the presence of a gastric malignancy.
- Hepatic impairment: Patients with severe liver dysfunction may require dosage reductions.

Dosage form specific issues:

- Intravenous: Safety and efficacy of I.V. treatment beyond 10 days have not been established; transition from I.V. to oral therapy as soon possible.

Geriatric ConsiderationsDose adjustment is not necessary.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. However, there are no adequate and well-controlled studies in pregnant women. Congenital abnormalities have been reported sporadically following omeprazole use during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsEsomeprazole excretion into breast milk has not been studied. However, omeprazole is excreted in breast milk, and therefore considered likely that esomeprazole is similarly excreted; breast-feeding is not recommended.

Adverse ReactionsUnless otherwise specified, percentages represent adverse reactions identified in clinical trials evaluating the oral formulation.

>10%: Central nervous system: Headache (I.V. 11%; oral ≤8%)

1% to 10%:

Cardiovascular: Hypertension (≤3%), chest pain (>1%)

Central nervous system: Pain (4%), dizziness (oral >1%; I.V. 3%), anxiety (2%), insomnia (2%), pyrexia (2%), fatigue (>1%)

Dermatologic: Rash (>1%), pruritus (I.V. ≤1%)

Endocrine & metabolic: Hypercholesterolemia (2%)

Gastrointestinal: Flatulence (oral ≤5%; I.V. 10%), diarrhea (oral ≤7%; I.V. 4%), abdominal pain (oral ≤6%; I.V. 6%), nausea (oral 5%; I.V. 6%), dyspepsia (oral > 1%; I.V. 6%), gastritis (≤6%), constipation (oral 2%; I.V. 3%), vomiting (≤3%), benign GI neoplasm (>1%), dyspepsia (>1%), duodenitis (>1%), epigastric pain (>1%), esophageal disorder (>1%), gastroenteritis (>1%), GI mucosal discoloration (>1%), serum gastrin increased (>1%), tooth disorder (>1%), xerostomia (1%)

Genitourinary: Urinary tract infection (4%)

Hematologic: Anemia (>1%)

Hepatic: Transaminases increased (>1%)

Local: Local: Injection site reaction (I.V. 2%)

Neuromuscular & skeletal: Arthralgia (3%), back pain (>1%), fracture (>1%), arthropathy (1%), myalgia (1%)

Respiratory: Respiratory infection (oral ≤9%; I.V. 1%), bronchitis (4%), sinusitis (oral ≤4%; I.V. 2%), coughing (>1%), rhinitis (>1%), dyspnea (1%)

Miscellaneous: Accident/injury (≤8%), viral infection (4%), allergy (2%), ear infection (2%), hernia (>1%), flu-like syndrome (1%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Abdominal rigidity, aggression, agitation, agranulocytosis, albuminuria, alkaline phosphatase increased, alopecia, anaphylactic reaction/shock, angioedema, anorexia, arthritis exacerbation, asthma exacerbation, benign polyps/nodules, bilirubinemia, blurred vision, bronchospasm, candidiasis (GI and genital), carcinoid tumor of stomach, cervical lymphadenopathy, conjunctivitis, cramps, creatinine increased, cystitis, dehydration, depression, dermatitis, dysmenorrhea, dysphagia, dysuria, edema (including facial, peripheral and tongue), epigastric pain, epistaxis, erythema multiforme, esophageal varices, fibromyalgia syndrome, flushing, fungal infection, gastric retention, GI dysplasia, glycosuria, goiter, gynecomastia, hallucinations, hematuria, hepatic encephalopathy, hepatic failure, hepatitis, hyperhidrosis, hyperparathyroidism, hypertonia, hyperuricemia, hypoesthesia, hypokalemia, hypomagnesemia, hyponatremia, impotence, interstitial nephritis, jaundice, larynx edema, leukocytosis, leukopenia, malaise, micturition increased, migraine, muscular weakness, nervousness, osteoporosis, otitis media, pancreatitis, pancytopenia, paresthesia, pharyngolaryngeal pain, pharyngitis, photosensitivity, polymyalgia rheumatica, polyuria, proteinuria, pruritus ani, rhinorrhea, rigors, sleep disorder, somnolence, Stevens-Johnson syndrome, stomatitis, tachycardia, taste disturbances, thrombocytopenia, thyroid-stimulating hormone increased, tinnitus, total bilirubin increased, toxic epidermal necrolysis, tremor, urticaria, vaginitis, vertigo, vitamin B_{12} deficiency, weight changes

Metabolism/Transport Effects**Substrate** of CYP2C19 (major), 3A4 (major); **Inhibits** CYP2C19 (moderate)
Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): Proton Pump Inhibitors may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Atazanavir: Proton Pump Inhibitors may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Proton Pump Inhibitors may increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clopidogrel: Proton Pump Inhibitors may diminish the therapeutic effect of Clopidogrel. This appears to be due to reduced formation of the active clopidogrel metabolite. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: Proton Pump Inhibitors may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Proton Pump Inhibitors may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Erlotinib: Proton Pump Inhibitors may decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Indinavir: Proton Pump Inhibitors may decrease the absorption of Indinavir. *Risk C: Monitor therapy*

Iron Salts: Proton Pump Inhibitors may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk C: Monitor therapy*

Methotrexate: Proton Pump Inhibitors may decrease the excretion of Methotrexate. Antirheumatic doses of methotrexate probably hold minimal risk. *Risk C: Monitor therapy*

Mycophenolate: Proton Pump Inhibitors may decrease the serum concentration of Mycophenolate. Specifically, concentrations of the active mycophenolic acid may be reduced. *Risk C: Monitor therapy*

Saquinavir: Proton Pump Inhibitors may increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

Tipranavir: May decrease the serum concentration of Proton Pump Inhibitors. These data are derived from studies with Ritonavir-boosted Tipranavir. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Absorption is decreased by 43% to 53% when taken with food.
Monitoring ParametersSusceptibility testing recommended in patients who fail *H. pylori* eradication regimen (esomeprazole, clarithromycin, and amoxicillin)
Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions (especially those dependent on cytochrome P450 metabolism or those dependent on an acid environment for absorption). Monitor response and adverse reactions at beginning of therapy and periodically throughout therapy. Assess knowledge/teach appropriate use of this medication, interventions to reduce side effects, and adverse symptoms to report.
Monitoring: Lab TestsSusceptibility testing is recommended in patients who fail *H. pylori* eradication regimen (esomeprazole, clarithromycin, and amoxicillin).
Patient EducationTake as directed, 1 hour before eating at same time each day. Swallow capsule whole; do not crush or chew. If you cannot swallow capsule whole, open capsule, mix contents with 1 tablespoon of applesauce, and swallow immediately; do not chew mixture. Do not store for future use. You may experience headache; constipation (increased exercise, fluids, fruit, or fiber may help); diarrhea (boiled milk, yogurt, or buttermilk may help); or abdominal pain (should diminish with use). Report persistent headache, diarrhea, constipation, abdominal pain, changes in urination or pain on urination, CNS changes, persistent muscular aches or pain, ringing in ears or visual changes, or other adverse reactions. **Breast-feeding precaution:** Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian availability

Note: Strength expressed as base

Capsule, delayed release, as magnesium:

Nexium®: 20 mg, 40 mg

Granules, for oral suspension, delayed release, as magnesium:

Nexium®: 10 mg/packet (30s); 20 mg/packet (30s); 40 mg/packet (30s)

Nexium® [CAN]: 10 mg/packet (28s)

Injection, powder for reconstitution, as sodium:

Nexium®: 20 mg, 40 mg [contains edetate sodium]

Tablet, extended release, as magnesium:

Nexium® [CAN]: 20 mg, 40 mg [not available in U.S.]

Generic AvailableNo
ManufacturerAstraZeneca Pharmaceuticals LP
Pricing: U.S. (www.drugstore.com)

Capsule, delayed release (Nexium)

20 mg (30): $169.25

40 mg (30): $154.99

Mechanism of ActionProton pump inhibitor suppresses gastric acid secretion by inhibition of the H^+/K^+-ATPase in the gastric parietal cell

Pharmacodynamics/Kinetics

Distribution: V_{dss}: 16 L

Protein binding: 97%

Metabolism: Hepatic via CYP2C19 and 3A4 enzymes to hydroxy, desmethyl, and sulfone metabolites (all inactive)

Bioavailability: Oral: 90% with repeat dosing

Half-life elimination: ~1-1.5 hours

Time to peak: Oral: 1.5-2 hours

Excretion: Urine (80%, primarily as inactive metabolites; <1% as active drug); feces (20%)

Pharmacotherapy PearlsEsomeprazole is the S-isomer of omeprazole.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause headache

Mental Health: Effects on Psychiatric TreatmentThe clearance of diazepam is decreased by 45% with concomitant use, resulting in increased diazepam levels and potential for toxicity; monitor

Anesthesia and Critical Care Concerns/Other Considerations**Acute ulcer: Postendoscopy therapy:** Intravenous omeprazole has been studied in prevention of rebleeding in ulcer patients who are at high risk for rebleeding (endoscopic findings of active bleeding or nonbleeding visible vessel) after successful hemostasis (Lin, 1998; Lau, 2000).

Lin and his group treated 100 ulcer patients (actively bleeding ulcers or ulcers with nonbleeding visible vessels) endoscopically and then randomized them to cimetidine (300 mg bolus followed by 50 mg/hour infusion) or omeprazole (40 mg bolus, ~7 mg/hour infusion) for 72 hours. Patients were discharged on the oral form of the drug arm they were assigned to. The omeprazole group maintained an intragastric pH >6 for about 84% of the infusion duration, while the cimetidine group maintained their pH >6 only about 50% of the time. Rebleeding occurred significantly more often in the cimetidine group.

Lau and his colleagues treated patients with actively bleeding ulcers or ulcers with nonbleeding visible vessels with an epinephrine infusion followed by thermocoagulation. They were then randomized to omeprazole (80 mg bolus followed by a continuous infusion of 8 mg/hour for 72 hours) or placebo. All patients were discharged on oral omeprazole (20 mg/day) for 8 weeks and received *H. pylori* treatment if indicated. The primary goal was to evaluate the rate of rebleeding during the first 30 days after endoscopy. Two hundred and forty patients were enrolled with randomization of 120 into each group. Bleeding recurred in significantly more patients receiving placebo than omeprazole infusion. The authors concluded that after endoscopic therapy, omeprazole reduces the risk of rebleeding in patients with actively bleeding ulcers or ulcers with nonbleeding visible vessels.

Acute ulcer: Pre-endoscopy therapy: Lau and associates (2007) evaluated the effects of preemptive infusion of omeprazole before endoscopy in upper gastrointestinal bleeding. Consecutive patients (638) were stabilized and then randomly assigned to intravenous omeprazole (80 mg bolus followed by a continuous infusion of 8 mg/hour) or placebo infusion before endoscopy the next morning. The primary endpoint was the need for endoscopic therapy (eg, epinephrine, thermocoagulation). Seven patients were excluded from the analysis. The need for endoscopic treatment was significantly lower in the omeprazole group (60/314 patients; 19%) than in the placebo group (90/317; 28%). The active treatment group had a significantly shorter hospital stay. Duration of infusion before endoscopy was similar in both groups (~8-21 hours).

Stress ulcer prophylaxis: The 2008 Surviving Sepsis Campaign guidelines recommend that stress ulcer prophylaxis using an H_2 blocker (Grade 1A) or proton pump inhibitor (Grade 1B) be given to patients with severe sepsis to prevent upper GI bleed. Benefit of prevention of upper GI bleed must be weighed against potential effect of increased stomach pH on development of ventilator-associated pneumonia.

Index TermsEsomeprazole Magnesium; Esomeprazole Sodium

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International Brand NamesEsoprax (CO); Inexium (FR); Nexiam (BE); Nexium (AR, AU, BB, BF, BG, BJ, BM, BO, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CZ, DE, DK, DO, EC, EE, ES, ET, FI, GB, GH, GM, GN, GT, GY, HK, HN, ID, IE, IL, IT, JM, KE, KP, LR, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, NO, PA, PE, PH, PL, PR, PT, PY, SC, SD, SE, SG, SL, SN, SR, SV, TN, TT, TZ, UG, UY, VE, ZA, ZM, ZW); Nexium IV (MX); Nexium-MUPS (MX); Nexum (PK); Sompraz (IN)

Estazolam

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

ProSom® may be confused with PhosLo®, Proscar®, Pro-Sof® Plus, Prozac®, Psorcon®

Pronunciation(es TA zoe lam)
U.S. Brand NamesProSom® [DSC]
Pharmacologic CategoryBenzodiazepine
Use: Labeled IndicationsShort-term management of insomnia
Dosing: AdultsInsomnia: Oral: 1 mg at bedtime, some patients may require 2 mg; start at doses of 0.5 mg in debilitated patients.
Dosing: ElderlyStart at doses of 0.5 mg in small elderly patients.
Dosing: Hepatic ImpairmentAdjustment may be necessary.
RestrictionsC-IV
ContraindicationsHypersensitivity to estazolam or any component of the formulation (cross-sensitivity with other benzodiazepines may exist); pregnancy

Note: Manufacturer states concurrent therapy with itraconazole or ketoconazole is contraindicated.

Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypersensitivity reactions: Postmarketing studies have indicated that the use of hypnotic/sedative agents for sleep has been associated with hypersensitivity reactions including anaphylaxis as well as angioedema.
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.
- Sleep-related activities: An increased risk for hazardous sleep-related activities such as sleep-driving; cooking and eating food, and making phone calls while asleep have also been noted.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.
- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.

- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury.

- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.

Other warning/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.

- Hypnotic: Appropriate use: As a hypnotic, should be used only after evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric or medical illness.

- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsThere has been little experience with this drug in the elderly, but because of its lack of active metabolites, estazolam would be a reasonable choice for elderly patients when a benzodiazepine hypnotic is indicated.
Pregnancy Risk FactorX
LactationEnters breast milk/contraindicated
Adverse Reactions

>10%:

Central nervous system: Somnolence

Neuromuscular & skeletal: Weakness

1% to 10%:

Cardiovascular: Flushing, palpitation

Central nervous system: Anxiety, confusion, dizziness, hypokinesia, abnormal coordination, hangover effect, agitation, amnesia, apathy, emotional lability, euphoria, hostility, seizure, sleep disorder, stupor, twitch

Dermatologic: Dermatitis, pruritus, rash, urticaria

Gastrointestinal: Xerostomia, constipation, appetite increased/decreased, flatulence, gastritis, perverse taste

Genitourinary: Frequent urination, menstrual cramps, urinary hesitancy, urinary frequency, vaginal discharge/itching

Neuromuscular & skeletal: Paresthesia

Ocular: Photophobia, eye pain, eye swelling

Respiratory: Cough, dyspnea, asthma, rhinitis, sinusitis

Miscellaneous: Diaphoresis

<1%: Allergic reactions, chills, drug dependence, fever, muscle spasm, myalgia, neck pain

Postmarketing and/or case reports: Anaphylaxis, angioedema, complex sleep-related behavior (sleep-driving, cooking or eating food, making phone calls)

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Serum levels and/or toxicity may be increased by grapefruit juice.

Monitoring ParametersRespiratory and cardiovascular status

Nursing: Physical Assessment/MonitoringFor short-term use. Assess effectiveness and interactions of other medications patient may be taking. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance. Be alert to possibility of anaphylaxis any time during therapy. Evaluate periodically for need for continued use. After long-term use, taper dosage slowly when discontinuing. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to sexually-active female patients unless capable of complying with contraceptive use. Breast-feeding is contraindicated.

Monitoring: Lab TestsCBC, liver function with long-term therapy

Patient EducationUse exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol or other prescription or OTC medications (especially, pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or GI upset (take with water or milk). Report CNS changes (confusion, depression, increased sedation, excitation, headache, abnormal thinking, insomnia, or nightmares); altered voiding patterns or blood in urine; respiratory difficulty, chest pain, or palpitations; unusual swelling, especially on face or neck; altered gait pattern; or ineffectiveness of medication. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during therapy or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: 1 mg, 2 mg

ProSom®: 1 mg, 2 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Estazolam)

1 mg (30): $24.99

2 mg (30): $27.99

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Onset of action: ~1 hour

Duration: Variable

Metabolism: Extensively hepatic

Half-life elimination: 10-24 hours (no significant changes in elderly)

Time to peak, serum: 0.5-1.6 hours

Excretion: Urine (<5% as unchanged drug)

Related Information

- Benzodiazepines
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsAbrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Estazolam is a short half-life benzodiazepine. Duration of action after a single dose is determined by redistribution rather than metabolism. Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include personal or family history of substance abuse and personality disorder.

Anesthesia and Critical Care Concerns/Other ConsiderationsAbrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

References

Busto U, Bendayan R, and Sellers EM, “Clinical Pharmacokinetics of Nonopiate Abuse Drugs,” *Clin Pharmacokinet*, 1989, 16(1):1-26.

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand NamesDomnamid (DK, NO); Esilgan (ID, IT, JP, PH, PK); Eslam (TW); Estazolam (PL); Eszo 2 (TW); Eurodin (JP, TW); Kainever (PT); Kinzolam (TW); Noctal (BR); Nuctalon (FR); Sedarest (PE); Somnatrol (AR); Tasedan (MX)

Estradiol and Levonorgestrel

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Transdermal patch may contain conducting metal (eg, aluminum); remove patch prior to MRI.

Pronunciation(es tra DYE ole & LEE voe nor jes trel)

U.S. Brand NamesClimaraPro®

Pharmacologic CategoryEstrogen and Progestin Combination

Use: Labeled IndicationsWomen with an intact uterus: Treatment of moderate-to-severe vasomotor symptoms associated with menopause; prevention of postmenopausal osteoporosis

Dosing: Adults

Treatment of moderate-to-severe vasomotor symptoms associated with menopause or prevention of postmenopausal osteoporosis: Adult females with an intact uterus:

Transdermal: Estradiol 0.045 mg/levonorgestrel 0.015 mg: Apply one patch weekly

Dosing: ElderlyRefer to adult dosing.

Administration: TopicalApply once weekly to a clean, dry, fold-free area of the lower abdomen; avoid application to waistline. Do not apply to irritated or broken skin. Do not apply to breasts. Rotate site with each application. Avoid touching adhesive with fingers. Hold system in place for ~10 seconds to ensure proper application. If patch falls off during the week, may reapply same patch or apply a new patch to another area of the lower abdomen. Remove patch slowly to avoid irritating the skin. Allow skin to dry for 15 minutes, then gently rub area with an oil-based cream or lotion if needed to remove any remaining adhesive. Prior to discarding, fold patch so that it sticks to itself.

Dietary ConsiderationsEnsure adequate calcium and vitamin D intake when used for the prevention of osteoporosis.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Pouch should remain sealed until ready to use.

ContraindicationsHypersensitivity to estradiol, levonorgestrel, or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); carcinoma of the breast; estrogen-dependent tumor; hepatic dysfunction or disease; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.
- Dementia: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Breast cancer: Estrogens may increase the risk of breast cancer. An increased risk of invasive breast cancer was observed in postmenopausal women using CEE in combination with MPA; a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy. Estrogen use may lead to severe hypercalcemia in patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs.
- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in women ≥65 years of age taking CEE alone or in combination with MPA.
- Endometrial cancer: Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women. Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy.
- Lipid effects: Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent coronary heart disease.** Use caution with cardiovascular disease or dysfunction. May increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA). Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CEE (eg, for prostate cancer).

- Cholestatic jaundice: Use caution with history of cholestatic jaundice associated with past estrogen use or pregnancy.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes, or renal dysfunction.
- Gallbladder disease: Use with caution in patients with gallbladder disease.
- Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.
- Hypocalcemia: Use with caution in patients with severe hypocalcemia.
- Porphyria: Use with caution in patients with porphyria.
- SLE: Use with caution in patients with SLE.

Special populations:

- Premenopausal women: Not for use prior to menopause.
- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Dosage form specific issues:

- Transdermal patch: May contain conducting metal (eg, aluminum); remove patch prior to MRI. Following application, avoid exposure of the transdermal patch to prolonged periods of sunlight.

Other warnings/precautions:

- Osteoporosis use: When used solely for the prevention of osteoporosis in women at significant risk, nonestrogen treatment options should be considered.
- Risks vs. benefits: Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.

Pregnancy ConsiderationsUse of this combination is contraindicated during pregnancy. Estrogens are not indicated for use during pregnancy or immediately postpartum. Increased risk of fetal reproductive tract disorders and other birth defects have been observed with diethylstilbestrol (DES). Epidemiologic studies have not shown an increased risk of birth defects when levonorgestrel is used prior to pregnancy or inadvertently during early pregnancy, although rare reports of congenital anomalies have been reported. This product is intended to be used only in postmenopausal women.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsEstradiol and levonorgestrel are both excreted in breast milk. Estrogen has been shown to decrease the quantity and quality of human milk; use only if clearly needed; monitor the growth of the infant closely.

Adverse ReactionsPercentages reported as greater in ClimaraPro™ when compared to estradiol alone:

>10%:

Central nervous system: Depression (12%)

Endocrine & metabolic: Breast pain (40%)

Genitourinary: Vaginal bleeding (78%)

Local: Application site reaction (86%)

Neuromuscular & skeletal: Back pain (13%)

Respiratory: Upper respiratory tract infection (28%)

1% to 10%: Cardiovascular: Edema (8%)

Other adverse events reported with **estrogen and/or estrogen/progestin** therapy: Abdominal cramps, acne, abnormal uterine bleeding, aggravation of porphyria, amenorrhea, anaphylactoid reactions, anaphylaxis, angioedema, antifactor Xa decreased, antithrombin III decreased, appetite changes, bloating, breast enlargement, breast tenderness, carbohydrate tolerance decreased, cerebral embolism, cerebral thrombosis, chloasma, cholestatic jaundice, cholecystitis, cholelithiasis, chorea, contact lens intolerance, corneal curvature steepening, cystitis-like syndrome, dizziness; factors VII, VIII, IX, X, XII, VII-X complex, and II-VII-X complex increased; endometrial hyperplasia, erythema multiforme, erythema nodosum, galactorrhea, hemorrhagic eruption, fatigue, fibrinogen increased, glucose tolerance impaired, HDL-cholesterol increased, hirsutism, hypertension, gallbladder disease, insomnia, LDL-cholesterol decreased, libido changes, melasma, migraine, nervousness, optic neuritis, pancreatitis, platelet aggregability and platelet count increased, premenstrual-like syndrome, PT and PTT accelerated, pulmonary embolism, pyrexia, retinal thrombosis, scalp hair loss, size of uterine leiomyomata increased, somnolence, thrombophlebitis, thyroid-binding globulin increased, total thyroid hormone (T_4) increased, triglycerides increased, urticaria, vaginal candidiasis, vomiting, weight gain/loss

Metabolism/Transport Effects

Estradiol: **Substrate** of CYP1A2 (major), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2C8 (weak); **Induces** CYP3A4 (weak)

Levonorgestrel: **Substrate** of CYP3A4 (major)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Somatropin: Estrogen Derivatives may diminish the therapeutic effect of Somatropin. Shown to be a concern with oral hormone replacement therapy in postmenopausal women. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Monitoring ParametersYearly physical examination that includes blood pressure and Papanicolaou smear, breast exam, mammogram. Monitor for signs of endometrial cancer. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Prevention of osteoporosis: Bone density measurement

Nursing: Physical Assessment/Monitoring Assess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests prior to beginning therapy and regularly during therapy. Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Teach patient importance of monthly blood pressure checks, and annual physical assessment, Pap smear, and vision assessment; appropriate use, interventions to reduce side effects (eg, alcohol and smoking cessation), and adverse symptoms to report. Determine that patient is not pregnant before starting therapy.

Monitoring: Lab TestsYearly Papanicolaou smear, mammogram. Monitor for signs of endometrial cancer. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take anything new without consulting prescriber. Apply as directed ,once weekly (see below) Annual gynecologic and breast exams are important. May cause nausea or vomiting (small, frequent meals may help); abdominal pain, dizziness or mental depression; headache; breast pain or back pain; increased/decreased libido. Report significant swelling of extremities or weight gain >5 lb/week; sudden acute pain in legs or calves, chest or abdomen; shortness of breath; severe headache or vomiting; sudden blindness; weakness or numbness of arm or leg; unusual vaginal bleeding; yellowing of skin or eyes; or unusual bruising or bleeding. See individual monographs for additional information. **Pregnancy precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this drug; may cause fetal defects and should not be used during pregnancy.

Application: Apply weekly to clean, dry skin in fold-free area of lower abdomen; do not apply at waistline. Do not apply to irritated or broken skin. Rotate site each week. Avoid touching adhesive with fingers. Hold patch in place for 10 seconds. If patch falls off during week; reapply same patch or apply a new patch. When changing patch, remove old patch slowly to avoid irritating skin. Allow ski to dry for 15 minutes then rub area gently with an oil-based cream of lotion if needed to remove any remaining adhesive. Fold used patch so that it sticks to itself and discard.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Transdermal system: Estradiol 0.045 mg/24 hours and levonorgestrel 0.015 mg/24 hours (4s) [once-weekly patch; 22 cm^2; contains estradiol 4.4 mg and levonorgestrel 1.39 mg]

ManufacturerBerlex

Pricing: U.S. (www.drugstore.com)

Patch weekly (Climara Pro)

0.045-0.015 mg/day (4): $57.55

Mechanism of ActionEstrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principle intracellular human estrogen and is more potent than estrone and estriol at the receptor level; it is the primary estrogen secreted prior to menopause. Following menopause, estrone and estrone sulfate are more highly produced. Estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone, and follicle-stimulating hormone through a negative feedback system; estrogen replacement reduces elevated levels of these hormones in postmenopausal women.

Levonorgestrel inhibits gonadotropin production; when used in this combination, it counteracts the proliferative effects of estradiol on the endometrium.

Pharmacodynamics/Kinetics

Protein binding: Estradiol and levonorgestrel: Bind to sex hormone-binding globulin and albumin

Metabolism:

Estradiol: Hepatic via oxidation and conjugation in GI tract; hydroxylated via CYP3A4 to metabolites; first-pass effect; enterohepatic recirculation; reversibly converted to estrone and estriol

Levonorgestrel: Hepatic involving CYP3A4; undergoes reduction and conjugation followed by hydroxylation; forms metabolites

Half-life elimination: Estradiol: 3 ± 0.67 hours; Levonorgestrel: 28 ± 6.4 hours

Time to peak, serum: Topical: Estradiol (mean): 2-2.5 days; Levonorgestrel: 2.5 days

Excretion:

Estradiol: Primarily urine (as metabolites estrone and estriol); feces (small amounts)

Levonorgestrel: Primarily urine

Related Information

- Estradiol
- Levonorgestrel

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentThe Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Index TermsLevonorgestrel and Estradiol

References

American Academy of Pediatrics Committee on Drugs, “The Transfer of Drugs and Other Chemicals Into Human Milk,” *Pediatrics*, 2001, 108(3):776-89. [PubMed 11533352]

Rossouw JE, Anderson GL, Prentice RL, et al, “Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principle Results From the Women's Health Initiative Randomized Controlled Trial,”*JAMA*, 2002, 288(3):321-33.[PubMed 12117397]

Shumaker SA, Legault C, Rapp SR, et al, “WHIMS Investigators. Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial,” *JAMA*, 2003, 289(20):2651-62. [PubMed 12771112]

U.S. Food and Drug Administration, Department of Health and Human Services, “FDA Approves New Labels for Estrogen and Estrogen With Progestin Therapies for Postmenopausal Women Following Review of Women's Health Initiative Data,” January 8, 2003. Available at: http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#prempr. Accessed April 17, 2003.

Estradiol and Norethindrone

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Transdermal patch may contain conducting metal (eg, aluminum); remove patch prior to MRI.

Pronunciation(es tra DYE ole & nor eth IN drone)

U.S. Brand NamesActivella®; CombiPatch®

Canadian Brand NamesEstalis-Sequi®; Estalis®

Pharmacologic CategoryEstrogen and Progestin Combination

Use: Labeled IndicationsWomen with an intact uterus:

Tablet: Treatment of moderate-to-severe vasomotor symptoms associated with menopause; treatment of vulvar and vaginal atrophy; prophylaxis for postmenopausal osteoporosis

Transdermal patch: Treatment of moderate-to-severe vasomotor symptoms associated with menopause; treatment of vulvar and vaginal atrophy; treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure

Dosing: Adults**Note:** Patients should be treated with the lowest effective dose and for the shortest duration, consistent with treatment goals.

Hypoestrogenism: Transdermal (patch):

Continuous combined regimen: Apply one patch twice weekly

Continuous sequential regimen: Apply estradiol-only patch for first 14 days of cycle, followed by one CombiPatch® applied twice weekly for the remaining 14 days of a 28-day cycle.

Osteoporosis, prevention in postmenopausal females (Activella®): Oral: 1 tablet daily

Menopause (moderate-to-severe vasomotor symptoms); vulvar and vaginal atrophy:

Oral (Activella®): 1 tablet daily

Transdermal (patch):

Continuous combined regimen: Apply one patch twice weekly

Continuous sequential regimen: Apply estradiol-only patch for first 14 days of cycle, followed by one CombiPatch® applied twice weekly for the remaining 14 days of a 28-day cycle.

Transdermal patch, combination pack (product-specific dosing for Canadian formulation):

Estalis®: Continuous combined regimen: Apply a new patch twice weekly during a 28-day cycle

Estalis-Sequi®: Continuous sequential regimen: Apply estradiol-only patch (Vivelle®) for first 14 days, followed by one Estalis® patch applied twice weekly during the last 14 days of a 28-day cycle

Note: In women previously receiving oral estrogens, initiate upon reappearance of menopausal symptoms following discontinuation of oral therapy.

Dosing: ElderlyRefer to adult dosing.

Administration: OtherTransdermal patch: Apply to clean dry skin. Do not apply transdermal patch to breasts; apply to lower abdomen, avoiding waistline. Rotate application sites.

ContraindicationsHypersensitivity to estrogens, progestins, or any components; carcinoma of the breast; estrogen-dependent tumor; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); hysterectomy; hepatic dysfunction or disease; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Breast cancer: See “Concerns related to adverse effects” below.
- Cardiovascular disease: See “Disease-related concerns” below.

- Dementia: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Breast cancer: **[U.S. Boxed Warning]: Estrogens may increase the risk of breast cancer.** An increased risk of invasive breast cancer was observed in postmenopausal women using CEE in combination with MPA; a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy. Estrogen use may lead to severe hypercalcemia in patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs.

- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in women ≥65 years of age taking CEE alone or in combination with MPA.

- Endometrial cancer: Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women. Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy.

- Lipid effects: Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.

- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent coronary heart disease.** Use caution with cardiovascular disease or dysfunction. May increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA). Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CEE (eg, for prostate cancer).

- Cholestatic jaundice: Use caution with history of cholestatic jaundice associated with past estrogen use or pregnancy.

- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes, or renal dysfunction.

- Gallbladder disease: Use with caution in patients with gallbladder disease.

- Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.

- Hypocalcemia: Use with caution in patients with severe hypocalcemia.

- Porphyria: Use with caution in patients with porphyria.

- SLE: Use with caution in patients with SLE.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Dosage form specific issues:

- Transdermal patch: May contain conducting metal (eg, aluminum); remove patch prior to MRI.

Other warnings/precautions:

- Osteoporosis use: When used solely for the prevention of osteoporosis in women at significant risk, nonestrogen treatment options should be considered.

- Risks vs. benefits: Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.

- Vulvar and vaginal atrophy use: When used solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should be considered.

Pregnancy ConsiderationsNot for use prior to menopause; use during pregnancy is contraindicated.
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsEstrogens may decrease the quality and quantity of breast milk.
Adverse ReactionsFrequency not defined.

Cardiovascular: Altered blood pressure, cardiovascular accident, edema, MI, stroke, venous thromboembolism, thrombophlebitis

Central nervous system: Dementia, dizziness, emotional lability, fatigue, headache, insomnia, irritability, mental depression, migraine, mood changes, nervousness, seizure

Dermatologic: Chloasma, erythema multiforme, erythema nodosum, hemorrhagic eruption, hirsutism, itching, loss of scalp hair, melasma, pruritus, seborrhea, skin rash

Endocrine & metabolic: Breast cancer, breast enlargement, breast tenderness, breast pain, fibrocystic breast changes, galactorrhea, hypocalcemia, libido changes, nipple discharge, triglycerides increased

Gastrointestinal: Abdominal pain, bloating, changes in appetite, cramps, flatulence, gallbladder disease, gastroenteritis, nausea, pancreatitis, vomiting, weight gain/loss

Genitourinary: Alterations in frequency and flow of menses, changes in cervical secretions, cystitis-like syndrome, endometrial cancer, endometrial hyperplasia, endometrial thickening, endometriosis exacerbation, genital moniliasis, ovarian cancer, ovarian cyst, postmenopausal bleeding, premenstrual-like syndrome, size of uterine leiomyomata increased, uterine fibroid, vaginal candidiasis, vaginal hemorrhage, vaginitis

Hematologic: Aggravation of porphyria

Hepatic: Cholestatic jaundice

Local: Application site reaction (transdermal patch)

Neuromuscular & skeletal: Arthralgia, back pain, chorea, extremity pain, leg cramps, myalgia, weakness

Ocular: Contact lens intolerance, corneal curvature steepening, retinal vascular thrombosis

Respiratory: Asthma exacerbation, nasopharyngitis, pharyngitis, pulmonary thromboembolism, rhinitis, sinusitis, upper respiratory tract infection

Miscellaneous: Allergic reactions, carbohydrate intolerance, flu-like syndrome, viral infection

Metabolism/Transport Effects

Estradiol: **Substrate** of CYP1A2 (major), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2C8 (weak); **Induces** CYP3A4 (weak)

Norethindrone: **Substrate** of CYP3A4 (major); **Induces** CYP2C19 (weak)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Colesevelam: May decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Darunavir: May decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Rufinamide: May decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Somatropin: Estrogen Derivatives may diminish the therapeutic effect of Somatropin. Shown to be a concern with oral hormone replacement therapy in postmenopausal women. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (routine use increases estrogen level and risk of breast cancer). Ethanol may also increase the risk of osteoporosis.

Food: Folic acid absorption may be decreased

Herb/Nutraceutical: St John's wort may decrease estradiol levels. Avoid black cohosh, dong quai (has estrogenic activity). Avoid red clover, saw palmetto, ginseng.

Monitoring ParametersRoutine physical examination that includes blood pressure and Papanicolaou smear, breast exam, mammogram. Monitor for signs of endometrial cancer. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Prevention of osteoporosis: Bone density measurement

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Combination pack:

Estalis-Sequi® 140/50 [CAN; not available in U.S.]:

Transdermal system (Vivelle®): Estradiol 50 mcg per day (4s) [14.5 sq cm; total estradiol 4.33 mg]

Transdermal system (Estalis®): Norethindrone acetate 140 mcg and estradiol 50 mcg per day (4s) [9 sq cm; total norethindrone acetate 2.7 mg, total estradiol 0.62 mg; not available in U.S.]

Estalis-Sequi® 250/50 [CAN; not available in U.S.]:

Transdermal system (Vivelle®): Estradiol 50 mcg per day (4s) [14.5 sq cm; total estradiol 4.33 mg]

Transdermal system (Estalis®): Norethindrone acetate 250 mcg and estradiol 50 mcg per day (4s) [16 sq cm; total norethindrone acetate 4.8 mg, total estradiol 0.51 mg; not available in U.S.]

Tablet:

Activella® 0.5/0.1: Estradiol 0.5 mg and norethindrone acetate 0.1mg (28s)

Activella® 1/0.5: Estradiol 1 mg and norethindrone acetate 0.5 mg (28s)

Transdermal system:

CombiPatch®:

0.05/0.14: Estradiol 0.05 mg and norethindrone acetate 0.14 mg per day (8s) [9 sq cm]

0.05/0.25: Estradiol 0.05 mg and norethindrone acetate 0.25 mg per day (8s) [16 sq cm]

Estalis® [CAN]:

140/50: Norethindrone acetate 140 mcg and estradiol 50 mcg per day (8s) [9 sq cm; total norethindrone acetate 2.7 mg, total estradiol 0.62 mg; not available in U.S.]

250/50 Norethindrone acetate 250 mcg and estradiol 50 mcg per day (8s) [16 sq cm; total norethindrone acetate 4.8 mg, total estradiol 0.51 mg; not available in U.S.]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Patch, twice-weekly (CombiPatch)

0.05-0.14 mg/day (8): $55.99

0.05-0.25 mg/day (8): $55.99

Tablets (Activella)

0.5-0.1 mg (28): $56.17

1-0.5 mg (28): $67.03

Pharmacodynamics/Kinetics

Activella®:

Bioavailability: Estradiol: 50%; Norethindrone: 100%

Half-life elimination: Estradiol: 12-14 hours; Norethindrone: 8-11 hours

Time to peak: Estradiol: 5-8 hours

See individual agents.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentThe Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Index TermsNorethindrone and Estradiol

References

Shumaker SA, Legault C, Rapp SR, et al, “WHIMS Investigators. Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial,” *JAMA*, 2003, 289(20):2651-62. [PubMed 12771112]

Rossouw JE, Anderson GL, Prentice RL, et al, “Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principle Results From the Women's Health Initiative Randomized Controlled Trial,”*JAMA*, 2002, 288(3):321-33.[PubMed 12117397]

U.S. Food and Drug Administration, Department of Health and Human Services, “FDA Approves New Labels for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women Following Review of Women's Health Initiative Data,” January 8, 2003. Available at: http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#prempr. Accessed April 17, 2003.

International Brand NamesEstalis (CA); Estalis-Sequi (CA)

Estradiol and Norgestimate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(es tra DYE ole & nor JES ti mate)

U.S. Brand NamesPrefest™

Pharmacologic CategoryEstrogen and Progestin Combination

Use: Labeled IndicationsWomen with an intact uterus: Treatment of moderate to severe vasomotor symptoms associated with menopause; treatment of atrophic vaginitis; prevention of osteoporosis

Dosing: AdultsFemales with an intact uterus:

Treatment of menopausal symptoms, atrophic vaginitis, prevention of osteoporosis: Oral: Treatment is cyclical and consists of the following: One tablet of estradiol 1 mg (pink tablet) once daily for 3 days, followed by 1 tablet of estradiol 1 mg and norgestimate 0.09 mg (white tablet) once daily for 3 days; repeat sequence continuously. **Note:** This dose may not be the lowest effective combination for these indications. In case of a missed tablet, restart therapy with next available tablet in sequence (taking only 1 tablet each day).

Dosing: ElderlyRefer to adult dosing.

Administration: OralIn case of a missed tablet, restart therapy with next available tablet in sequence (taking only 1 tablet each day).

Dietary ConsiderationsEnsure adequate calcium and vitamin D intake when used for the prevention of osteoporosis.

StorageStore at 25°C (77°F).

ContraindicationsHypersensitivity to estradiol, norgestimate, or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); carcinoma of the breast; estrogen-dependent tumor; hepatic dysfunction or disease; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.

- Dementia: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Breast cancer: Estrogens may increase the risk of breast cancer. An increased risk of invasive breast cancer was observed in postmenopausal women using CEE in combination with MPA; a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy. Estrogen use may lead to severe hypercalcemia in patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs.

- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in women ≥65 years of age taking CEE alone or in combination with MPA.

- Endometrial cancer: Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women. Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy.

- Lipid effects: Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.

- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent coronary heart disease.** Use caution with cardiovascular disease or dysfunction. May increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA). Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CEE (eg, for prostate cancer).

- Cholestatic jaundice: Use caution with history of cholestatic jaundice associated with past estrogen use or pregnancy.

- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes, or renal dysfunction.

- Gallbladder disease: Use with caution in patients with gallbladder disease.
- Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.
- Hypocalcemia: Use with caution in patients with severe hypocalcemia.
- Porphyria: Use with caution in patients with porphyria.
- SLE: Use with caution in patients with SLE.

Special populations:

- Premenopausal women: Not for use prior to menopause.
- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- Osteoporosis use: When used solely for the prevention of osteoporosis in women at significant risk, nonestrogen treatment options should be considered.
- Risks vs. benefits: Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.
- Vulvar and vaginal atrophy use: When used solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should be considered.

Geriatric ConsiderationsSee Estradiol monograph.
Pregnancy Risk FactorX
Pregnancy ConsiderationsEstrogens are not indicated for use during pregnancy or immediately postpartum. Increased risk of fetal reproductive tract disorders and other birth defects have been observed with diethylstilbestrol (DES); do not use during pregnancy. Progestins are associated with fetal genital abnormalities when used during the first trimester; not recommended for use during pregnancy.
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsEstrogens and progestins are excreted in breast milk. Estrogens decrease the quality and quantity of breast milk.
Adverse Reactions

>10%:

Central nervous system: Headache (23%)

Endocrine & metabolic: Breast pain (16%)

Gastrointestinal: Abdominal pain (12%)

Neuromuscular & skeletal: Back pain (12%)

Respiratory: Upper respiratory tract infection (21%)

Miscellaneous: Flu-like syndrome (11%)

1% to 10%:

Central nervous system: Fatigue (6%), pain (6%), depression (5%), dizziness (5%)

Endocrine & metabolic: Vaginal bleeding (9%), dysmenorrhea (8%), vaginitis (7%)

Gastrointestinal: Nausea (6%), flatulence (5%)

Neuromuscular & skeletal: Arthralgia (9%), myalgia (5%)

Respiratory: Sinusitis (8%), pharyngitis (7%), cough (5%)

Miscellaneous: Viral infection (6%)

Additional adverse effects associated with **estrogens and progestins**; frequency not defined:

Cardiovascular: Edema, hypertension, MI, stroke, venous thrombosis

Central nervous system: Anxiety, epilepsy exacerbation, insomnia, irritability, migraine, mood disturbances, nervousness, pyrexia, somnolence

Dermatologic: Acne, chloasma, erythema multiforme, erythema nodosum, hemorrhagic eruptions, hirsutism, itching, melasma, pruritus, rash, scalp hair loss, urticaria

Endocrine & metabolic: Amenorrhea, breast cancer, breast discharge, breast enlargement, Breast tenderness, carbohydrate tolerance decreased, endometrial cancer, endometrial hyperplasia, fibrocystic breast changes, galactorrhea, hypocalcemia, libido changes, ovarian cancer, triglycerides increased

Gastrointestinal: Abdominal cramps, appetite changes, bloating, gallbladder disease, pancreatitis, vomiting, weight gain/loss

Genitourinary: Abnormal withdrawal bleeding/flow, breakthrough bleeding, cervical secretion changes, cystitis syndrome, uterine leiomyomata size increased, vaginal candidiasis, vaginal bleeding/spotting

Hematologic: Anemia, porphyria

Hepatic: Cholestatic jaundice

Local: Thrombophlebitis

Neuromuscular & skeletal: Chorea

Ocular: Contact lens intolerance, corneal curvature steepening, neuro-ocular lesions

Respiratory: Asthma exacerbation, pulmonary embolism

Miscellaneous: Anaphylaxis

Metabolism/Transport Effects

Estradiol: **Substrate** of CYP1A2 (major), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2C8 (weak); **Induces** CYP3A4 (weak)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Somatropin: Estrogen Derivatives may diminish the therapeutic effect of Somatropin. Shown to be a concern with oral hormone replacement therapy in postmenopausal women. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (routine use increases estrogen level and risk of breast cancer). Ethanol may also increase the risk of osteoporosis.

Food: CNS effects of caffeine may be enhanced if combination estrogen/progestins are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations and would be expected to increase progesterone serum levels as well; clinical implications are unclear.

Herb/Nutraceutical: St John's wort may decrease the plasma levels of combination estrogen/progestin combinations by inducing hepatic enzymes. Avoid dong quai and black cohosh (have estrogen activity). Avoid saw palmetto, red clover, ginseng.

Test InteractionsPathologist should be advised of estrogen/progesterone therapy when specimens are submitted. Reduced response to metyrapone test.

Monitoring ParametersYearly physical examination that includes blood pressure and Papanicolaou smear, breast exam, mammogram. Monitor for signs of endometrial cancer. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Prevention of osteoporosis: Bone density measurement

Monitoring: Lab TestsYearly Papanicolaou smear, mammogram. Monitor for signs of endometrial cancer. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Prevention of osteoporosis: Bone density measurement

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Estradiol 1 mg [15 pink tablets] and estradiol 1 mg and norgestimate 0.09 mg [15 white tablets] (supplied in blister card of 30)

Generic AvailableNo

ManufacturerOrtho-McNeil Pharmaceutical, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Prefest)

1/1-0.09 mg (30): $44.90

Mechanism of ActionEstrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principle intracellular human estrogen and is more potent than estrone and estriol at the receptor level; it is the primary estrogen secreted prior to menopause. Following menopause, estrone and estrone sulfate are more highly produced. Estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone, and follicle-stimulating hormone through a negative feedback system; estrogen replacement reduces elevated levels of these hormones in postmenopausal women.

Progestins inhibit gonadotropin production which then prevents follicular maturation and ovulation. In women with adequate estrogen, progestins transform a proliferative endometrium into a secretory endometrium; when administered with estradiol, reduces the incidence of endometrial hyperplasia and risk of adenocarcinoma.

Pharmacodynamics/Kinetics

Estradiol: See Estradiol monograph.

Norgestimate:

Protein binding: 17-deacetylnorgestimate: 99%

Metabolism: Forms 17-deacetylnorgestimate (major active metabolite) and other metabolites; first-pass effect

Half-life elimination: 17-deacetylnorgestimate: 37 hours

Excretion: Norgestimate metabolites: Urine and feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentMay cause flu-like symptoms, take this into consideration if also concerned about SSRI discontinuation syndrome. Carbamazepine and topiramate may increase the metabolism of estradiol, leading to a decrease in serum concentrations. Estrogens may inhibit the metabolism of some benzodiazepines (alprazolam, chlordiazepoxide, diazepam), TCAs, and selegiline. Estrogens may increase the clearance of lorazepam, oxazepam, and temazepam.

The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Index TermsEstradiol and NGM; Norgestimate and Estradiol; Ortho Prefest

References

Shumaker SA, Legault C, Rapp SR, et al, “WHIMS Investigators. Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial,” *JAMA*, 2003, 289(20):2651-62. [PubMed 12771112]

Rossouw JE, Anderson GL, Prentice RL, et al, “Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principle Results From the Women's Health Initiative Randomized Controlled Trial,”*JAMA*, 2002, 288(3):321-33.[PubMed 12117397]

U.S. Food and Drug Administration, Department of Health and Human Services, “FDA Approves New Labels for Estrogen and Estrogen With Progestin Therapies for Postmenopausal Women Following Review of Women's Health Initiative Data,” January 8, 2003. Available at: http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#prempr. Accessed April 17, 2003.

Estradiol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Alora® may be confused with Aldara®

Elestrin™ may be confused with alosetron

Estraderm® may be confused with Testoderm®

International issues:

Vivelle®: Brand name for ethinyl estradiol and norgestimate in Austria

Estring® may be confused with Estrena® [Finland]

Estrena® [Finland] may be confused with estrone in the U.S.

Transdermal patch may contain conducting metal (eg, aluminum); remove patch prior to MRI.

Pronunciation(es tra DYE ole)

U.S. Brand NamesAlora®; Climara®; Delestrogen®; Depo®-Estradiol; Divigel®; Elestrin™; Estrace®; Estraderm®; Estrasorb™; Estring®; EstroGel®; Evamist™; Femring®; Femtrace®; Gynodiol® [DSC]; Menostar®; Vagifem®; Vivelle-Dot®; Vivelle® [DSC]

Canadian Brand NamesClimara®; Depo®-Estradiol; Estrace®; Estraderm®; Estradot®; Estring®; EstroGel®; Menostar®; Oesclim®; Sandoz-Estradiol Derm 100; Sandoz-Estradiol Derm 50; Sandoz-Estradiol Derm 75; Vagifem®

Pharmacologic CategoryEstrogen Derivative

Use: Labeled IndicationsTreatment of moderate-to-severe vasomotor symptoms associated with menopause; treatment of vulvar and vaginal atrophy; hypoestrogenism (due to hypogonadism, castration, or primary ovarian failure); prostatic cancer (palliation), breast cancer (palliation), osteoporosis (prophylaxis); abnormal uterine bleeding due to hormonal imbalance; postmenopausal urogenital symptoms of the lower urinary tract (urinary urgency, dysuria)

Dosing: AdultsAll dosage needs to be adjusted based upon the patient's response:

Atrophic vaginitis, vulvar/vaginal atrophy:

Intravaginal:

Vaginal cream: Atrophic vaginitis, kraurosis vulvae: Insert 2-4 g/day for 2 weeks then gradually reduce to $^1/_2$ the initial dose for 2 weeks followed by a maintenance dose of 1 g 1-3 times/week

Vaginal ring:

Postmenopausal vaginal atrophy, urogenital symptoms (Estring®): 2 mg intravaginally; following insertion, ring should remain in place for 90 days

Vulvar/vaginal atrophy (Femring®): 0.05 mg intravaginally; following insertion, ring should remain in place for 3 months; dose may be increased to 0.1 mg if needed

Vaginal tablets (Vagifem®); Atrophic vaginitis: Initial: Insert 1 tablet once daily for 2 weeks; maintenance: Insert 1 tablet twice weekly. Attempts to discontinue or taper medication should be made at 3- to 6-month intervals

Topical gel: Vulvar/vaginal atrophy:

Elestrin™: 0.87 g/day applied at the same time each day

EstroGel®: 1.25 g/day applied at the same time each day

Transdermal: Refer to product-specific dosing (below)

Breast cancer (females; inoperable, progressing): Oral: 10 mg 3 times/day for at least 3 months

Hypogonadism:

Oral: 1-2 mg/day in a cyclic regimen for 3 weeks on drug, then 1 week off drug

I.M.: Cypionate: 1.5-2 mg monthly; Valerate: 10-20 mg every 4 weeks

Transdermal: Refer to product-specific dosing (below)

Osteoporosis prevention (females):

Oral: 0.5 mg/day in a cyclic regimen (3 weeks on and 1 week off of drug)

Transdermal: Refer to product-specific dosing (below)

Prostate cancer:

I.M. (valerate): ≥30 mg or more every 1-2 weeks

Oral (androgen-dependent, inoperable, progressing): 10 mg 3 times/day for at least 3 months

Vasomotor symptoms (moderate to severe) associated with menopause:

Oral (in addition to I.M. dosing): 1-2 mg daily, adjusted as necessary to limit symptoms. Administrations should be cyclic (3 weeks on, 1 week off). Patients should be re-evaluated at 3-6 month intervals to determine if treatment is still necessary

I.M.: Cypionate: 1-5 mg every 3-4 weeks; Valerate: 10-20 mg every 4 weeks

Topical emulsion: 3.84 g applied once daily in the morning

Topical gel:

Divigel®: 0.25 g/day; adjust dose based on patient response. Dosing range: 0.25-1 g/day

Elestrin™: 0.87 g/day applied at the same time each day

EstroGel®: 1.25 g/day applied at the same time each day

Topical spray: (Evamist™): Initial: One spray (1.53 mg) per day. Adjust dose based on patient response. Dosing range: 1-3 sprays per day.

Vaginal ring (Femring®): 0.05 mg intravaginally; following insertion, ring should remain in place for 3 months; dose may be increased to 0.1 mg if needed

Transdermal: See product-specific dosing (below)

Transdermal product-specific dosing:

Note: Indicated dose may be used continuously in patients without an intact uterus. May be given continuously or cyclically (3 weeks on, 1 week off) in patients with an intact uterus **(exception - Menostar®, see specific dosing instructions).** When changing patients from oral to transdermal therapy, start transdermal patch 1 week after discontinuing oral hormone (may begin sooner if symptoms reappear within 1 week):

Transdermal once-weekly patch:

Moderate-to-severe vasomotor symptoms associated with menopause, vulvar and vaginal atrophy associated with menopause, female hypoestrogenism (Climara®): Apply 0.025 mg/day patch once weekly. Adjust dose as necessary to control symptoms. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary.

Prevention of osteoporosis in postmenopausal women:

Climara®: Apply patch once weekly; minimum effective dose 0.025 mg/day; adjust dosage based on response to therapy as indicated by biological markers and bone mineral density.

Menostar®: Apply patch once weekly. In women with a uterus, also administer a progestin for 14 days every 6-12 months.

Transdermal twice-weekly patch (Alora®, Estraderm®, Vivelle®):

Moderate to severe vasomotor symptoms associated with menopause, vulvar/vaginal atrophy, female hypogonadism: Titrate to lowest dose possible to control symptoms, adjusting initial dose after the first month of therapy; re-evaluate therapy at 3- to 6-month intervals to taper or discontinue medication:

Alora®, Esclim®, Estraderm®, Vivelle-Dot®: Apply 0.05 mg patch twice weekly

Vivelle®: Apply 0.0375 mg patch twice weekly

Prevention of osteoporosis in postmenopausal women:

Alora®, Vivelle®, Vivelle-Dot®: Apply 0.025 mg patch twice weekly, increase dose as necessary

Estraderm®: Apply 0.05 mg patch twice weekly

Dosing: ElderlyRefer to adult dosing.

Administration: I.M.Injection for intramuscular administration only.

Administration: Topical

Emulsion: Apply to clean dry skin while in a sitting position. Contents of two pouches (total 3.48 g) are to be applied individually, once daily in the morning. Apply contents of first pouch to left thigh, massage into skin of left thigh and calf until thoroughly absorbed (~3 minutes). Apply excess from both hands to the buttocks. Apply contents of second pouch to the right thigh, massage into skin of right thigh and calf until thoroughly absorbed (~3 minutes). Apply excess from both hands to buttocks. Wash hands with soap and water. Allow skin to dry before covering legs with clothing. Do not apply to other areas of body. Do not apply to red or irritated skin.

Gel: Apply to clean, dry, unbroken skin at the same time each day. Allow to dry for 5 minutes prior to dressing. Gel is flammable; avoid fire or flame until dry. After application, wash hands with soap and water. Prior to the first use, pump must be primed. Do not apply gel to breast.

Divigel®: Apply entire contents of packet to right or left upper thigh each day (alternate sites). Do not apply to face, breasts, vaginal area or irritated skin. Apply over an area ~5x7 inches. Do not wash application site for 1 hour. Allow gel to dry before dressing

Elestrin™: Apply to upper arm and shoulder area using two fingers to spread gel. Apply after bath or shower; allow at least 2 hours between applying gel and going swimming. Wait at least 25 minutes before applying sunscreen to application area. Do not apply sunscreen to application area for ≥7 days (may increase absorption of gel).

EstroGel®: Apply gel to the arm, from the wrist to the shoulder. Spread gel as thinly as possible over one arm.

Spray: Evamist™: Prior to first use, prime pump by spraying 3 sprays with the cover on. To administer dose, hold container upright and vertical and rest the plastic cone flat against the skin while spraying. Spray to the inner surface of the forearm, starting near the elbow. If more than one spray is needed, apply to adjacent but not overlapping areas. Apply at the same time each day. Allow spray to dry for ~2 minutes. Do not wash application site for 30 minutes. Apply to clean, dry, unbroken skin. Do not apply to skin other than that of the forearm. Solution contained in the spray is flammable; avoid fire, flame, or smoking until spray has dried. If needed, sunscreen should be applied ~1 hour prior to application of Evamist™.

Transdermal patch: Aerosol topical corticosteroids applied under the patch may reduce allergic reactions. Do not apply transdermal system to breasts, but place on trunk of body (preferably abdomen). Rotate application sites allowing a 1-week interval between applications at a particular site. Do not apply to oily, damaged or irritated skin; avoid waistline or other areas where tight clothing may rub the patch off. Apply patch immediately after removing from protective pouch. In general, if patch falls off, the same patch may be reapplied or a new system may be used for the remainder of the dosing interval. Swimming, bathing, or showering are not expected to affect use of the patch. Note the following exceptions:

Estraderm®: Do not apply to an area exposed to direct sunlight.

Menostar®: Swimming, bathing, or wearing patch while in a sauna have not been studied; adhesion of patch may be decreased or delivery of estradiol may be affected. Remove patch slowly after use to avoid skin irritation. If any adhesive remains on the skin after removal, first allow skin to dry for 15 minutes, then gently rub area with an oil-based cream or lotion. If patch falls off, a new patch should be applied for the remainder of the dosing interval.

Administration: Other

Vaginal ring: Exact positioning is not critical for efficacy, however, patient should not feel anything once inserted. In case of discomfort, ring should be pushed further into vagina. If ring is expelled prior to 90 days, it may be rinsed off and reinserted.

Vaginal tablet: Insert tablet with supplied applicator at the same time each day. Once inserted, depress plunger until a click is heard, then remove applicator and discard. If tablet comes out of applicator prior to insertion, do not replace; use a new tablet filled applicator instead.

Dietary ConsiderationsEnsure adequate calcium and vitamin D intake when used for the prevention of osteoporosis.

ContraindicationsHypersensitivity to estradiol or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); carcinoma of the breast, except in appropriately selected patients being treated for metastatic disease; estrogen-dependent tumor; hepatic dysfunction or disease; porphyria; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.
- Dementia: See “Concerns related to adverse effects” below.
- Endometrial carcinoma: See “Concerns related to adverse effects” below.
- Risks vs benefits: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Breast cancer: Estrogens may increase the risk of breast cancer. An increased risk of invasive breast cancer was observed in postmenopausal women using conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA); a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy. Estrogen use may lead to severe hypercalcemia in patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs.

- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in women ≥65 years of age taking CEE alone or in combination with MPA.

- Endometrial carcinoma: **[U.S. Boxed Warning]: Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women with an intact uterus.** The use of a progestin should be considered when administering estrogens to postmenopausal women with an intact uterus. Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy. Consider adding a progestin in women with residual endometriosis posthysterectomy.

- Lipid effects: Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.

- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent coronary heart disease.** Use caution with cardiovascular disease or dysfunction. May increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using CEE in combination with MPA. Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CEE (eg, for prostate cancer).

- Cholestatic jaundice: Use caution with history of cholestatic jaundice associated with past estrogen use or pregnancy.

- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.

- Gallbladder disease: Use with caution in patients with gallbladder disease.

- Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.

- Hypocalcemia: Use with caution in patients with severe hypocalcemia.

- Porphyria: Use with caution in patients with porphyria; use is contraindicated with certain products.

- SLE: Use with caution in patients with SLE.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children. Prior to puberty, estrogens may cause premature closure of the epiphyses, premature breast development in girls or gynecomastia in boys. Vaginal bleeding and vaginal cornification may also be induced in girls.

- Surgical patients: Whenever possible, estrogens should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Dosage form specific issues:

- Topical emulsion, gel, spray: Absorption of the topical emulsion (Estrasorb™) and topical gel (Elestrin™) is increased by application of sunscreen; do not apply sunscreen within close proximity of estradiol. When sunscreen is applied ~1 hour prior to the topical spray (Evamist™), no change in absorption was observed (estradiol absorption was decreased when sunscreen is applied 1 hour after Evamist™). Application of Divigel® or EstroGel® with sunscreen has not been evaluated.

- Transdermal patch: May contain conducting metal (eg, aluminum); remove patch prior to MRI.

- Vaginal ring: Use may not be appropriate in women with narrow vagina, vaginal stenosis, vaginal infections, cervical prolapse, rectoceles, cystoceles, or other conditions which may increase the risk of vaginal irritation, ulceration, or increase the risk of expulsion. Remove ring if vaginal infection develops; reinsert only after infection has been appropriately treated. Ring should also be removed in case of ulceration, erosion, or adherence to vaginal wall; do not reinsert until healing is complete.

Other warnings/precautions:

- Osteoporosis use: When used solely for prevention of osteoporosis in women at significant risk, nonestrogen treatment options should be considered.

- Risks vs. benefits: **[U.S. Boxed Warning]: Estrogens with or without progestin should be used for shortest duration possible at the lowest effective dose consistent with treatment goals.** Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Conduct periodic risk:benefit assessments.

- Vulvar and vaginal atrophy use: When used solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should be considered. Use caution applying topical products to severely atrophic vaginal mucosa.

Geriatric ConsiderationsBefore prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Data in women ≥80 years are minimal and it is unclear if the reduced risk is applicable to women in this age group. Women should be informed of these risks and benefits, as well as possible side effects and the return of menstrual bleeding (when cycled with a progestin), and be involved in the decision to prescribe. Oral therapy may be more convenient for vaginal atrophy and urinary incontinence.

Pregnancy Risk FactorX

Pregnancy ConsiderationsEstrogens are not indicated for use during pregnancy or immediately postpartum. Increased risk of fetal reproductive tract disorders and other birth defects have been observed with diethylstilbestrol (DES). In general, the use of estrogen and progestin as in combination hormonal contraceptives have not been associated with teratogenic effects when inadvertently taken early in pregnancy. These products are not intended to be used during pregnancy.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsThe AAP considers ethinyl estradiol, an estrogen derivative, to be “usually compatible” with breast-feeding. Estrogen has been shown to decrease the quantity and quality of human milk; use only if clearly needed; monitor the growth of the infant closely.

Adverse ReactionsFrequency not defined. Some adverse reactions observed with estrogen and/or progestin combination therapy.

Cardiovascular: Chest pain, DVT, edema, hypertension, MI, stroke, syncope, venous thromboembolism

Central nervous system: Anxiety, dementia, dizziness, epilepsy exacerbation, headache, insomnia, irritability, mental depression, migraine, mood disturbances, nervousness

Dermatologic: Angioedema, chloasma, dermatitis, erythema multiforme, erythema nodosum, hemorrhagic eruption, hirsutism, loss of scalp hair, melasma, rash, pruritus, urticaria

Endocrine & metabolic: Breast cancer, breast enlargement, breast pain, breast tenderness, fibrocystic breast changes, HDL-cholesterol increased, galactorrhea, glucose intolerance, hot flashes, hypocalcemia, LDL-cholesterol decreased, libido changes, nipple pain, serum triglycerides/phospholipids increased, thyroid-binding globulin increased, total thyroid hormone (T_4) increased

Gastrointestinal: Abdominal cramps, abdominal distension, abdominal pain, bloating, cholecystitis, cholelithiasis, diarrhea, dyspepsia, flatulence, gallbladder disease, gastritis, nausea, pancreatitis, vomiting, weight gain/loss

Genitourinary: Alterations in frequency and flow of menses, cervical secretion changes, cystitis, dysmenorrhea, dysuria, endometrial cancer, endometrial hyperplasia, genital eruption, metrorrhagia, ovarian cancer, Pap smear suspicious, urinary tract infection, uterine leiomyomata size increased, leukorrhea, uterine pain, urinary incontinence, urogenital eruption/pruritus, vaginal candidiasis, vaginal discharge, vaginal moniliasis, vaginitis

Vaginal: Trauma from applicator insertion may occur in women with severely atrophic vaginal mucosa; skin hypertrophy, vaginal discomfort, vaginal hemorrhage, vaginal pain

Hematologic: Aggravation of porphyria, antithrombin III and antifactor Xa decreased, fibrinogen levels increased, platelet aggregability increased, platelet count increased, prothrombin increased; factors VII, VIII, IX, X increased

Hepatic: Cholestatic jaundice, hepatic hemangioma enlargement

Local: Thrombophlebitis

Gel, spray: Application site reaction

Transdermal patches: Burning, erythema, irritation

Neuromuscular & skeletal: Arthralgia, arthritis, back pain, chorea, leg cramps, muscle cramps, skeletal pain

Ocular: Contact lens intolerance, corneal curvature steepening, retinal vascular thrombosis, vision abnormal

Respiratory: Asthma exacerbation, pulmonary thromboembolism

Miscellaneous: Anaphylactoid/anaphylactic reactions

Postmarketing and/or case reports: Liver function tests increased (rare), leg pain

Vaginal ring: Bowel obstruction, ring adherence to vaginal wall, toxic shock syndrome

Metabolism/Transport Effects **Substrate** of CYP1A2 (major), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2C8 (weak); **Induces** CYP3A4 (weak)

Drug Interactions

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Somatropin: Estrogen Derivatives may diminish the therapeutic effect of Somatropin. Shown to be a concern with oral hormone replacement therapy in postmenopausal women. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (routine use increases estrogen level and risk of breast cancer). Ethanol may also increase the risk of osteoporosis.

Food: Folic acid absorption may be decreased

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca.

Test InteractionsPathologist should be advised of estrogen/progesterone therapy when specimens are submitted. Reduced response to metyrapone test.

Monitoring ParametersRoutine physical examination that includes blood pressure and Papanicolaou smear, breast exam, mammogram. Monitor for signs of endometrial cancer in female patients with uterus. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy.

When using Menostar® in a woman with a uterus, endometrial sampling is recommended at yearly intervals or when clinically indicated.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Prevention of osteoporosis: Bone density measurement

Reference Range

Children: <10 pg/mL (SI: <37 pmol/L)

Male: 10-50 pg/mL (SI: 37-184 pmol/L)

Female:

Premenopausal: 30-400 pg/mL (SI: 110-1468 pmol/L)

Postmenopausal: 0-30 pg/mL (SI: 0-110 pmol/L)

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, increased or decreased levels/effects of estradiol or increased potential for toxicity or thrombolic events). Assess results of annual gynecological exam, therapeutic effectiveness (dependent on rationale for use), need for continued therapy, and adverse effects (eg, thromboembolism, hypertension, edema, CNS changes) on a regular basis during therapy. **Note:** Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals and periodic assessment of risk:benefit should be made. Caution patients with diabetes to monitor glucose levels closely (may impair glucose tolerance). Teach patient proper use and application (according to formulation), possible side effects/appropriate interventions, and adverse symptoms to report. Remind patient about the importance of frequent self-breast exams and the need for annual gynecological exam. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to females of childbearing age unless patient is capable of complying with contraceptive use. Advise patient about contraceptive measures as appropriate.

Monitoring: Lab TestsRoutine Papanicolaou smear, mammogram. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Follow directions for timing and application of your prescription (see product insert or consult prescriber). Wash hands thoroughly prior to and following application; do not apply topical agent to damaged, reddened, or irritated skin; do not allow agent to come in contact with face or eyes. Routine use of alcohol may increase estrogen level and risk of breast cancer. Annual gynecologic and regular self-breast exams are important. If you have diabetes, monitor glucose levels closely (may impair glucose tolerance). You may experience nausea, vomiting, or abdominal pain (small, frequent meals may help); dizziness or mental depression (use caution when driving); rash; hair loss; headache; or breast pain, increased/decreased libido, enlargement/tenderness of breasts, or difficult/painful menstrual cycles. Report unusual swelling of extremities; sudden acute pain in legs or calves, chest, or abdomen; shortness of breath; severe headache or vomiting; sudden blindness or change in visual acuity; weakness or numbness of arm or leg; unusual vaginal bleeding; yellowing of skin or eyes; unusual bruising or bleeding; skin rash; or other persistent adverse reactions. You may become intolerant to wearing contact lenses; notify prescriber if this occurs. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. This medication may cause fetal defects and should not be used during pregnancy. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, vaginal:

Estrace®: 0.1 mg/g (42.5 g)

Emulsion, topical, as hemihydrate:

Estrasorb™: 2.5 mg/g (56s) [each pouch contains 4.35 mg estradiol hemihydrate; contents of two pouches delivers estradiol 0.05 mg/day]

Gel, topical:

Divigel®: 0.1% (0.25 g) [delivers estradiol 0.25 mg/packet]; (0.5 g) [delivers 0.5 mg estradiol/packet]; (1 g) [delivers estradiol 1 mg/packet]

Elestrin™: 0.06% (144 g) [delivers estradiol 0.52 mg/0.87 g; 100 actuations]

EstroGel®: 0.06% (50 g) [delivers estradiol 0.75 mg/1.25 g; 32 actuations; contains ethanol]

Injection, oil, as cypionate:

Depo®-Estradiol: 5 mg/mL (5 mL) [contains chlorobutanol, cottonseed oil]

Injection, oil, as valerate: 10 mg/mL (5 mL); 20 mg/mL (5 mL); 40 mg/mL (5 mL)

Delestrogen®:

10 mg/mL (5 mL) [contains chlorobutanol, sesame oil]

20 mg/mL (5 mL) [contains benzyl alcohol, castor oil]

40 mg/mL (5 mL) [contains benzyl alcohol, castor oil]

Ring, vaginal, as base:

Estring®: 2 mg (1s) [total estradiol 2 mg; releases 7.5 mcg/day over 90 days]

Ring, vaginal, as acetate:

Femring®: 0.05 mg/day (1s) [total estradiol 12.4 mg; releases 0.05 mg/day over 3 months]; 0.1 mg/day (1s) [total estradiol 24.8 mg; releases 0.1 mg/day over 3 months]

Solution, topical [spray]:

Evamist™: 1.53 mg/spray (8.1 mL) [contains 56 sprays after priming; contains ethanol]

Tablet, oral, as acetate:

Femtrace®: 0.45 mg, 0.9 mg, 1.8 mg

Tablet, oral, micronized: 0.5 mg, 1 mg, 2 mg

Estrace®: 0.5 mg, 1 mg, 2 mg [2 mg tablets contain tartrazine]

Gynodiol®: 0.5 mg [DSC], 1 mg [DSC], 1.5 mg [DSC], 2 mg [DSC]

Tablet, vaginal, as base:

Vagifem®: 25 mcg

Transdermal system: 0.025 mg/24 hours (4s) [once-weekly patch]; 0.0375 mg/24 hours (4s) [once-weekly patch]; 0.05 mg/24 hours (4s) [once-weekly patch]; 0.06 mg/24 hours (4s) [once-weekly patch]; 0.075 mg/24 hours [once-weekly patch]; 0.1 mg/24 hours (4s) [once-weekly patch]

Alora® [twice-weekly patch]:

0.025 mg/24 hours (8s) [9 cm^2, total estradiol 0.77 mg]

0.05 mg/24 hours (8s, 24s [DSC]) [18 cm^2, total estradiol 1.5 mg]

0.075 mg/24 hours (8s) [27 cm^2, total estradiol 2.3 mg]

0.1 mg/24 hours (8s) [36 cm^2, total estradiol 3.1 mg]

Climara® [once-weekly patch]:

0.025 mg/24 hours (4s) [6.5 cm^2, total estradiol 2.04 mg]

0.0375 mg/24 hours (4s) [9.375 cm^2, total estradiol 2.85 mg]

0.05 mg/24 hours (4s) [12.5 cm^2, total estradiol 3.8 mg]

0.06 mg/24 hours (4s) [15 cm^2, total estradiol 4.55 mg]

0.075 mg/24 hours (4s) [18.75 cm^2, total estradiol 5.7 mg]

0.1 mg/24 hours (4s) [25 cm^2, total estradiol 7.6 mg]

Estraderm® [twice-weekly patch]:

0.05 mg/24 hours (8s) [10 cm^2, total estradiol 4 mg]

0.1 mg/24 hours (8s) [20 cm^2, total estradiol 8 mg]

Menostar® [once-weekly patch]: 0.014 mg/24 hours (4s) [3.25 cm^2, total estradiol 1 mg]

Vivelle® [twice-weekly patch]:

0.05 mg/24 hours (8s) [14.5 cm^2, total estradiol 4.33 mg] [DSC]

0.1 mg/24 hours (8s) [29 cm^2, total estradiol 8.66 mg] [DSC]

Vivelle-Dot® [twice-weekly patch]:

0.025 mg/day (24s) [2.5 cm^2, total estradiol 0.39 mg]

0.0375 mg/day (24s) [3.75 cm^2, total estradiol 0.585 mg]

0.05 mg/day (24s) [5 cm^2, total estradiol 0.78 mg]

0.075 mg/day (24s) [7.5 cm^2, total estradiol 1.17 mg]

0.1 mg/day (24s) [10 cm^2, total estradiol 1.56 mg]

Generic AvailableYes: Oral tablet, patch, valerate oil for injection
Pricing: U.S. (www.drugstore.com)

Cream (Estrace)

0.1 mg/g (42.5): $108.49

Emulsion (ESTRASORB TOP EMUL)

4.35 mg/1.74 g (10.44): $15.99

Gel (Divigel)

0.25 mg/0.25gm (30): $69.99

Gel (Elestrin)

0.52 MG/0.87 GM (0.06%) (144): $118.64

Gel (Estrogel)

0.75 MG/1.25 GM (0.06%) (50): $68.94

Oil (Delestrogen)

10 mg/mL (5): $79.56

20 mg/mL (5): $111.99

40 mg/mL (5): $177.99

Oil (Depo-Estradiol)

5 mg/mL (5): $45.99

Patch weekly (Climara)

0.025 mg/24 hrs (4): $57.55

0.0375 mg/24 hrs (4): $57.55

0.05 mg/24 hrs (4): $57.55

0.06 mg/24 hrs (4): $57.55

0.075 mg/24 hrs (4): $57.55

0.1 mg/24 hrs (4): $57.55

Patch weekly (Estradiol)

0.025 mg/24 hrs (4): $36.99

0.0375 mg/24 hrs (4): $39.35

0.05 mg/24 hrs (4): $36.99

0.06 mg/24 hrs (4): $39.99

0.075 mg/24 hrs (4): $35.99

0.1 mg/24 hrs (4): $35.99

Patch weekly (Menostar)

14 mcg/24 hrs (4): $60.99

Patch, twice-weekly (Alora)

0.05 mg/24 hrs (8): $49.67

0.075 mg/24 hrs (8): $44.15

0.1 mg/24 hrs (8): $49.68

Patch, twice-weekly (Estraderm)

0.05 mg/24 hrs (8): $54.99

0.1 mg/24 hrs (8): $59.99

Patch, twice-weekly (Vivelle)

0.05 mg/24 hrs (8): $49.99

Patch, twice-weekly (Vivelle-Dot)

0.025 mg/24 hrs (8): $51.99

0.0375 mg/24 hrs (8): $51.64

0.05 mg/24 hrs (8): $54.94

0.075 mg/24 hrs (8): $54.92

0.1 mg/24 hrs (8): $54.94

Ring (Estring)

2 mg (1): $156.19

Ring (Femring)

0.05 mg/24 hrs (1): $154.06

0.1 mg/24 hrs (1): $171.88

Solution (Evamist)

1.53 mg/spray (8.1): $54.99

Tablets (Estrace)

0.5 mg (30): $57.49

1 mg (30): $59.66

2 mg (30): $64.99

Tablets (Estradiol)

0.5 mg (30): $12.99

1 mg (30): $11.99

2 mg (90): $17.99

Tablets (Femtrace)

0.45 mg (100): $165.59

0.9 mg (100): $160.99

1.8 mg (100): $201.41

Tablets (Gynodiol)

0.5 mg (30): $9.99

1 mg (30): $18.99

1.5 mg (30): $22.99

2 mg (30): $15.99

Tablets (Vagifem)

25 mcg (8): $44.92

25 mcg (18): $90.46

Mechanism of ActionEstrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principle intracellular human estrogen and is more potent than estrone and estriol at the receptor level; it is the primary estrogen secreted prior to menopause. Following menopause, estrone and estrone sulfate are more highly produced. Estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone, and follicle-stimulating hormone through a negative feedback system; estrogen replacement reduces elevated levels of these hormones in postmenopausal women.

Pharmacodynamics/Kinetics

Absorption: Oral, topical: Well absorbed

Protein binding: 37% to sex hormone-binding globulin; 61% to albumin

Metabolism: Hepatic via oxidation and conjugation in GI tract; hydroxylated via CYP3A4 to metabolites; first-pass effect; enterohepatic recirculation; reversibly converted to estrone and estriol

Excretion: Primarily urine (as metabolites estrone and estriol); feces (small amounts)

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric Treatment The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Cardiovascular Considerations It is important to recognize that estrogens may induce or worsen hypertension. These problems are less severe with lower doses. Furthermore, estrogens may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on long-term estrogens undergo monitoring of blood pressure and avoid cigarette use.

Several observational trials evaluating the use of estrogen in primary prevention of coronary artery disease in women found a decrease in cardiovascular events. However, a recent trial (HERS) found that women with coronary disease derived no cardiovascular protection compared to those treated with placebo. Substantial evidence suggests that estrogen therapy increases bone mineralization and therefore may be of added benefit in patients with osteoporosis. Estrogen also has a favorable effect on lipids (decreases total cholesterol and LDL, increases HDL) but increases triglycerides. Therapy should be initiated after careful evaluation of risk:benefit for therapy.

Index Terms Estradiol Acetate; Estradiol Cypionate; Estradiol Hemihydrate; Estradiol Transdermal; Estradiol Valerate

References

American College of Physicians, “Guidelines for Counseling Postmenopausal Women About Preventive Hormone Therapy,” *Ann Intern Med*, 1992, 117(12):1038-41. [PubMed 1443972]

Belchetz PE, “Hormone Treatment for Postmenopausal Women,” *N Engl J Med*, 1994, 330(15):1062-71. [PubMed 8127335]

Ettinger B, Friedman GD, Bush T, et al, “Reduced Mortality Associated With Long-Term Postmenopausal Estrogen Therapy,” *Obstet Gynecol*, 1996, 87(1):6-12. [PubMed 8532268]

Grodstein F, Stampfer MJ, Colditz GA, et al, “Postmenopausal Hormone Therapy and Mortality,” *N Engl J Med*, 1997, 336(25):1769-75. [PubMed 9187066]

Hulley S, Grady D, Bush T, et al, “Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group,” *JAMA*, 1998, 280(7):605-13. [PubMed 9718051]

Rossouw JE, Anderson GL, Prentice RL, et al, “Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principle Results From the Women's Health Initiative Randomized Controlled Trial,”*JAMA*, 2002, 288(3):321-33.[PubMed 12117397]

Shumaker SA, Legault C, Rapp SR, et al, “WHIMS Investigators. Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial,” *JAMA*, 2003, 289(20):2651-62. [PubMed 12771112]

Stallard S, Litherland JC, Cordiner CM, et al, “Effect of Hormone Replacement Therapy on the Pathological Stage of Breast Cancer: Population Based, Cross Sectional Study,” *BMJ*, 2000, 320(7231):348-9. [PubMed 10657329]

U.S. Food and Drug Administration, Department of Health and Human Services, “FDA Approves New Labels for Estrogen and Estrogen With Progestin Therapies for Postmenopausal Women Following Review of Women's Health Initiative Data,” January 8, 2003. Available at: http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#prempr. Accessed April 17, 2003.

International Brand Names Bisteron 2 (TW); Calidiol (PL); Climaderm (BR, MX); Climara (LU, PL); Dermestril (HU, LU, PL); Dermestril-Septem (PL); Divigel (LU, PL); Enadiol (CN, PE); Estrade (TW); Estraderm (HR, NO); Estraderm MX (HU, PL); Estraderm TTS (AE, BB, BH, BM, BR, BS, BZ, CY, CZ, EG, ES, GY, HN, HR, HU, IN, IQ, IR, JM, JO, KW, LB, LU, LY, NZ, OM, PL, PY, QA, SA, SR, SY, TR, TT, UY, VE, YE); Estradiol Depot (PL); Estradiol-Depot (KP); Estradot (PL); Estramon (HU); Estreva (PL); Estring (NO, PL); Estrium (PL); Estro-Pause (ZA); Estrofem (BR, CZ, HR, HU, LU, NZ, PL); Estrofem Forte (PL); Estrofem Mite (PL); Estromikron (PL); Estropatch (LU); Estroplast (PL); Evorel (MX); Fem7 (PL); FemTab (GB, IE); Femtran (NZ); Ginedisc (MX); Gynokadin (DE); Lumelin 2 (TW); Menorest (LU, PL); Merimono (DE); Oesclim (PL); Oestradiolum benzoicum (PL); Oestrogel (HU, LU, MX); Primogyn Depot (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Primogyna (CN); Progynon (DK, SE); Progynon Amp Depot (GR); Progynon C (PL); Progynon Depot (AR, AT, BG, CH, DE, IT, NL, PE, PT, TH, TW); Progynon-Depot (DK); Progynova (AR, AT, AU, BE, CH, CL, CO, FI, FR, GB, HK, ID, IE, IL, MY, NL, NO, PL, PT, RU, TH, ZA); Progynova 2 (IL, PH, SG); Progynova 21 (DE); Prosu 2 (TW); Sandrena (MX); Systen (HU, LU, MX, PL); Vagifem (EE, HR, HU, LU, PL, UY); Zumenon (LU)

Estramustine-Cyclophosphamide

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Prostate Cancer

Regimen Use Prostate cancer

Index Terms Cyclophosphamide-Estramustine

Regimen

Cyclophosphamide: Oral: 2 mg/kg/day days 1 to 14

[total dose/cycle = 28 mg/kg]

Estramustine: Oral: 10 mg/kg/day days 1 to 14

[total dose/cycle = 140 mg/kg]

Repeat cycle every 28 days

References

Bracarda S, Tonato M, Rosi P, âOral Estramustine and Cyclophosphamide in Patients With Metastatic Hormone Refractory Prostate Carcinoma: A Phase II Study,â *Cancer*, 2000, 88(6):1438-44.[PubMed 10717628]

Estramustine + Docetaxel + Calcitriol

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer
Regimen UseProstate cancer
Regimen

Cycle 1:

Calcitriol: Oral: 60 mcg (in divided doses) day 1

[total dose/cycle = 60 mcg]

Estramustine: Oral: 280 mg 3 times/day days 1 to 5

[total dose/cycle = 4200 mg]

Docetaxel: I.V.: 60 mg/m^2 day 2

[total dose/cycle = 60 mg/m^2]

Treatment cycle is 21 days

Subsequent cycles:

Calcitriol: Oral: 60 mcg (in divided doses) day 1

[total dose/cycle = 60 mcg]

Estramustine: Oral: 280 mg 3 times/day days 1 to 5

[total dose/cycle = 4200 mg]

Docetaxel: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Repeat cycle every 21 days for up to 12 cycles

References

Tiffany NM, Ryan CW, Garzotto M, et al, âHigh Dose Pulse Calcitriol, Docetaxel and Estramustine for Androgen Independent Prostate Cancer: A Phase I/II Study,â *J Urol*, 2005, 174(3):888-92.[PubMed 16093981]

Estramustine + Docetaxel + Carboplatin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Prostate Cancer

Regimen Use Prostate cancer

Regimen

Docetaxel: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Estramustine: Oral: 280 mg 3 times/day days 1 to 5

[total dose/cycle = 4200 mg]

Carboplatin: I.V.: Target AUC 5 day 2

[total dose/cycle = AUC = 5]

Repeat cycle every 3 weeks

References

Oh WK, Halabi S, Kelly WK, et al, “A Phase II Study of Estramustine, Docetaxel, and Carboplatin (EDC) with G-CSF Support in Men With Hormone Refractory Prostate Cancer: CALGB 99813,” *Proc Am Soc Clin Oncol*, 2002, 21:195a.[PubMed 14669278]

Oh WK, Halabi S, Kelly WK, et al, “A Phase II Study of Estramustine, Docetaxel, and Carboplatin With Granulocyte-Colony-Stimulating Factor Support in Patients With Hormone-Refractory Prostate Carcinoma: Cancer and Leukemia Group B 99813,” *Cancer*, 2003, 98(12):2592-8.[PubMed 14669278]

Estramustine + Docetaxel + Hydrocortisone

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer

Regimen UseProstate cancer

Regimen

Docetaxel: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Estramustine: Oral: 10 mg/kg/day days 1 to 5

[total dose/cycle = 50 mg/kg]

Hydrocortisone: Oral: 40 mg daily

[total dose/cycle = 840 mg]

Repeat cycle every 3 weeks

References

Savarese DM, Halabi S, Hars V, et al, âPhase II Study of Docetaxel, Estramustine, and Low-Dose Hydrocortisone in Men With Hormone-Refractory Prostate Cancer: A Final Report of CALGB 9780. Cancer and Leukemia Group B,â *J Clin Oncol*, 2001, 19(9):2509-16.[PubMed 11331330]

Estramustine + Docetaxel + Prednisone

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Prostate Cancer]

Regimen UseProstate cancer

Regimen

Estramustine: Oral: 280 mg 3 times/day days 1 to 5 and days 7 to 11

[total dose/cycle = 8400 mg]

Docetaxel: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Prednisone: Oral: 10 mg daily

[total dose/cycle = 210 mg]

Repeat cycle every 21 days for up to 6 cycles

References

Boehmer A, Anastasiadis AG, Feyerabend S, et al, âDocetaxel, Estramustine and Prednisone for Hormone-Refractory Prostate Cancer: A Single-Center Experience,â *Anticancer Res*, 2005, 25(6C):4481-6.[PubMed 16334130]

Estramustine + Docetaxel

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer

Regimen UseProstate cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Docetaxel: I.V.: 20-80 mg/m^2 day 2

[total dose/cycle = 20-80 mg/m^2]

Estramustine: Oral: 280 mg 3 times/day days 1 to 5

[total dose/cycle = 4200 mg]

Repeat cycle every 21 days

Variation 2:

Docetaxel: I.V.: 20-80 mg/m^2 day 2

[total dose/cycle = 20-80 mg/m^2]

Estramustine: Oral: 14 mg/kg/day days 1 to 21

[total dose/cycle = 294 mg/kg]

Repeat cycle every 21 days

Variation 3:

Docetaxel: I.V.: 35 mg/m^2/day days 2 and 9

[total dose/cycle = 70 mg/m^2]

Estramustine: Oral: 420 mg 3 times/day for 4 doses, then 280 mg 3 times/day for 5 doses days 1, 2, 3, 8, 9, and 10

[total dose/cycle = 6160 mg]

Repeat cycle every 21 days

Variation 4:

Docetaxel: I.V.: 60 mg/m^2 day 2 cycle 1

[total dose/cycle = 60 mg/m^2]

followed by I.V.: 60-70 mg/m^2 day 2 (subsequent cycles)

[total dose/cycle = 60-70 mg/m^2]

Estramustine: Oral: 280 mg 3 times/day days 1 to 5

[total dose/cycle = 4200 mg]

Repeat cycle every 21 days for up to 12 cycles

References

Variation 1:

Petrylak DP, Macarthur RB, O'Connor J, et al, “Phase I Trial of Docetaxel With Estramustine in Androgen-Independent Prostate Cancer,” *J Clin Oncol*, 1999, 17(3):958-67. [PubMed 10071290]

Variation 2:

Kreis W, Budman DR, Fetten J, et al, “Phase I Trial of The Combination of Daily Estramustine Phosphate and Intermittent Docetaxel in Patients With Metastatic Hormone Refractory Prostate Carcinoma,” *Ann Oncol*, 1999, 10(1):33-8. [PubMed 10076719]

Variation 3:

Sitka Copur M, Ledakis P, Lynch J, et al, “Weekly Docetaxel and Estramustine in Patients With Hormone-Refractory Prostate Cancer,” *Semin Oncol*,

2001, 28(4 Suppl 15):16-21.[PubMed 11685724]

Variation 4:

Petrylak DP, Tangen CM, Hussain MH, et al, “Docetaxel and Estramustine Compared With Mitoxantrone and Prednisone for Advanced Refractory Prostate Cancer,” *N Engl J Med*, 2004, 351(15):1513-20.[PubMed 15470214]

Estramustine + Etoposide

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Prostate Cancer]

Regimen UseProstate cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Estramustine: Oral: 15 mg/kg/day days 1 to 21

[total dose/cycle = 315 mg/kg]

Etoposide: Oral: 50 mg/m^2/day days 1 to 21

[total dose/cycle = 1050 mg/m^2]

Repeat cycle every 4 weeks

Variation 2:

Estramustine: Oral: 10 mg/kg/day days 1 to 21

[total dose/cycle = 210 mg/kg]

Etoposide: Oral: 50 mg/m^2/day days 1 to 21

[total dose/cycle = 1050 mg/m^2]

Repeat cycle every 4 weeks

Variation 3:

Estramustine: Oral: 140 mg 3 times/day days 1 to 21

[total dose/cycle = 8820 mg]

Etoposide: Oral: 50 mg/m^2/day days 1 to 21

[total dose/cycle = 1050 mg/m^2]

Repeat cycle every 4 weeks

References

Variation 1:

Pienta KJ, Redman B, Hussain M, et al, "Phase II Evaluation of Oral Estramustine and Oral Etoposide in Hormone-Refractory Adenocarcinoma of the Prostate," *J Clin Oncol*, 1994, 12(10):2005-12. [PubMed 7523606]

Variation 2:

Pienta KJ, Redman BG, Bandekar R, et al, "A Phase II Trial of Oral Estramustine and Oral Etoposide in Hormone Refractory Prostate Cancer," *Urology*, 1997, 50(3):401-6; discussion 406-7. [PubMed 9301705]

Variation 3:

Dimopoulos MA, Panopoulos C, Bamia C, et al, "Oral Estramustine and Oral Etoposide for Hormone-Refractory Prostate Cancer," *Urology*, 1997, 50(5):754-8.[PubMed 9372887]

Estramustine-Paclitaxel

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Prostate Cancer]

Regimen UseProstate cancer

Index TermsPaclitaxel-Estramustine; PE (Prostate Cancer)

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Paclitaxel: I.V.: 30-35 mg/m^2/day continuous infusion (given in 2-3 divided doses daily) either days 1 to 4 or days 2 to 5

[total dose/cycle = 120-140 mg/m^2]

Estramustine: Oral: 600 mg/m^2/day days 1 to 21

[total dose/cycle = 12,600 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Paclitaxel: I.V. 60-107 mg/m^2 infused over 3 hours weekly for 6 weeks

[total dose/cycle = 360-642 mg/m^2]

Estramustine: Oral: 280 mg twice daily 3 days/week for 6 weeks

[total dose/cycle = 3360 mg]

Repeat cycle every 8 weeks

Variation 3:

Paclitaxel: I.V. 150 mg/m^2/day days 2, 9, and 16

[total dose/cycle = 450 mg/m^2]

Estramustine: Oral: 280 mg 3 times/day days 1, 2, 3, 8, 9, 10, 15, 16, and 17

[total dose/week = 7560 mg/m^2]

Repeat cycle every 4 weeks

Variation 4:

Paclitaxel: I.V.: 100 mg/m^2/day days 2, 9, and 16

[total dose/cycle = 300 mg/m^2]

Estramustine: Oral: 280 mg 3 times/day days 1, 2, 3, 8, 9, 10, 15, 16, and 17

[total dose/cycle = 7560 mg]

Repeat cycle every 4 weeks

References

Variation 1:

Hudes GR, Nathan FE, Khater C, et al, “Paclitaxel Plus Estramustine in Metastatic Hormone-Refractory Prostate Cancer,” *Semin Oncol*, 1995, 22(5 Suppl 12):41-5. [PubMed 7481860]

Hudes GR, Nathan F, Khater C, et al, “Phase II Trial of 96-Hour Paclitaxel Plus Oral Estramustine Phosphate in Metastatic Hormone-Refractory Prostate Cancer,” *J Clin Oncol*, 1997, 15(9):3156-63. [PubMed 9294479]

Variation 2:

Haas N, Roth B, Garay C, et al, “Phase I Trial of Weekly Paclitaxel Plus Oral Estramustine Phosphate in Patients With Hormone-Refractory Prostate Cancer,” *Urology*, 2001, 58(1):59-64 [PubMed 11445480]

Variation 3:

Vaishampayan U, Fontana J, Du W, et al, “An Active Regimen of Weekly Paclitaxel and Estramustine in Metastatic Androgen-Independent Prostate Cancer,” *Urology*, 2002, 60(6):1050-4. [PubMed 12475668]

Variation 4:

Berry W, Gregurich M, Dakhil S, et al, “Phase II Randomized Trial of Weekly Paclitaxel With or Without Estramustine Phosphate in Patients With Symptomatic, Hormone-Refractory Metastatic Carcinoma of the Prostate.” *Proc Am Soc Clin Oncol*, 2001, 20:175a. [PubMed 15479494]

Estramustine-Vinblastine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Prostate Cancer](#)

Regimen UseProstate cancer

Index TermsEV

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Estramustine: Oral: 10 mg/kg/day days 1 to 42

[total dose/cycle = 420 mg/kg]

Vinblastine: I.V.: 4 mg/m^2/day days 1, 8, 15, 22, 29, and 36

[total dose/cycle = 24 mg/m^2]

Repeat cycle every 8 weeks

Variation 2:

Estramustine: Oral: 600 mg/m^2/day days 1 to 42

[total dose/cycle = 25,200 mg/m^2]

Vinblastine: I.V.: 4 mg/m^2/day days 1, 8, 15, 22, 29, and 36

[total dose/cycle = 24 mg/m^2]

Repeat cycle every 8 weeks

References

Variation 1:

Seidman AD, Scher HI, Petrylak D, et al, "Estramustine and Vinblastine: Use of Prostate Specific Antigen as a Clinical Trial Endpoint for Hormone Refractory Prostatic Cancer," *J Urol*, 1992, 147(3 Pt 2):931-4. [PubMed 1371564]

Variation 2:

Hudes GR, Greenberg R, Krigel RL, et al, "Phase II Study of Estramustine and Vinblastine, Two Microtubule Inhibitors, in Hormone-Refractory Prostate Cancer," *J Clin Oncol*, 1992, 10(11):1754-61.[PubMed 1383436]

Estramustine + Vinorelbine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer
Regimen UseProstate cancer
RegimenNOTE: Multiple variations are listed below.

Variation 1:

Estramustine: Oral: 140 mg 3 times/day days 1 to 14

[total dose/cycle = 5880 mg]

Vinorelbine: I.V.: 25 mg/m^2/day days 1 and 8

[total dose/cycle = 50 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Estramustine: Oral: 280 mg 3 times/day days 1, 2, and 3

[total dose/cycle = 2520 mg/m^2]

Vinorelbine: I.V.: 15 or 20 mg/m^2 day 2

[total dose/cycle = 15 or 20 mg/m^2]

Repeat cycle weekly for 8 weeks, then every other week

References

Variation 1:

Smith MR, Kaufman D, Oh W, et al, “Vinorelbine and Estramustine in Androgen-Independent Metastatic Prostate Cancer: A Phase II Study,” *Cancer*, 2000, 89(8):1824-8. [PubMed 11042579]

Variation 2:

Sweeney CJ, Monaco FJ, Jung SH, et al, “A Phase II Hoosier Oncology Group Study of Vinorelbine and Estramustine Phosphate in Hormone-Refractory Prostate Cancer,” *Ann Oncol*, 2002, 13(3):435-40.[PubMed 11996476]

Estramustine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Emcyt® may be confused with Eryc®

Estramustine may be confused with exemestane.

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(es tra MUS teen)

U.S. Brand NamesEmcyt®

Canadian Brand NamesEmcyt®

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent; Antineoplastic Agent, Hormone; Antineoplastic Agent, Hormone (Estrogen/Nitrogen Mustard)

Use: Labeled IndicationsPalliative treatment of progressive or metastatic prostate cancer

Dosing: AdultsDetails concerning dosing in combination regimens should also be consulted.

Prostate cancer: Oral: Males: 14 mg/kg/day (range: 10-16 mg/kg/day) in 3 or 4 divided doses

Combination therapy with docetaxel (unlabeled dose): 280 mg 3 times/day for 5 days (days 1 through 5) of a 21-day treatment cycle for up to 12 cycles (Petrylak, 2004)

Dosing: ElderlyRefer to adult dosing.

Dosing: Combination Regimens

Prostate cancer:

Estramustine-Cyclophosphamide

Doxorubicin + Ketoconazole/Estramustine + Vinblastine

Estramustine + Docetaxel

Estramustine + Docetaxel + Calcitriol

Estramustine + Docetaxel + Carboplatin

Estramustine + Docetaxel + Hydrocortisone

Estramustine + Docetaxel + Prednisone

Estramustine + Etoposide

Estramustine-Vinblastine

Estramustine + Vinorelbine

Paclitaxel + Estramustine + Carboplatin

Paclitaxel + Estramustine + Etoposide

Estramustine-Paclitaxel

Administration: OralAdminister on an empty stomach, at least 1 hour before or 2 hours after eating.

Dietary ConsiderationsShould be taken at least 1 hour before or 2 hours after eating. Milk products and calcium-rich foods or supplements may impair the oral absorption of estramustine phosphate sodium.

StorageRefrigerate at 2°C to 8°C (36°F to 46°F).

ContraindicationsHypersensitivity to estramustine, estradiol, nitrogen mustard, or any component of the formulation; active thrombophlebitis or thromboembolic disorders (except where tumor mass is the cause of thromboembolic disorder and the benefit may outweigh the risk)

Canadian labeling: Additional contraindications (not in the U.S. labeling): Severe hepatic or cardiac disease

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Allergic reaction: Allergic reactions and angioedema, including airway involvement, have been reported.
- Cardiovascular effects: Elevated blood pressure or congestive heart disease may occur. Estrogen treatment for prostate cancer is associated with an increased risk of thrombosis or MI.
- Estrogenic effects: Estrogen use may cause gynecomastia and/or impotence.
- Fluid retention: Peripheral edema (new onset or exacerbation) or congestive heart disease may occur. Use with caution in patients where fluid accumulation may be poorly tolerated, including cardiovascular disease (HF or hypertension), migraine, seizure disorder or renal dysfunction.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (eg, thrombophlebitis, thrombosis, or thromboembolic disease) and cerebrovascular or coronary artery disease.
- Diabetes: Use with caution in patients with diabetes mellitus; may decrease glucose tolerance.
- Hepatic impairment: Use with caution in patients with hepatic impairment (may be metabolized poorly).
- Metabolic bone disease: Use with caution in patients with metabolic bone diseases due to the effects on calcium and phosphorus homeostasis.
- Osteoblastic metastases: Patients with osteoblastic metastases should have their calcium monitored regularly.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Immunization: Avoid vaccination with live vaccines during treatment (risk of infection may be increased due to immunosuppression). Although the response to vaccines may be diminished, inactivated vaccines may be administered during treatment.

Other warnings/precautions:

- Monitoring: Patients with prostate cancer should have their calcium monitored regularly.

Pregnancy ConsiderationsEstramustine is not indicated for use in women. Men who were impotent on estrogen therapy have regained potency while taking estramustine; effective contraception should be used for male patients with partners of childbearing potential.

Breast-Feeding ConsiderationsEstramustine is not indicated for use in women.

Adverse Reactions

>10%:

Cardiovascular: Edema (20%)

Endocrine & metabolic: Gynecomastia (75%), breast tenderness (71%), libido decreased

Gastrointestinal: Nausea (16%), diarrhea (13%), gastrointestinal upset (12%)

Hepatic: LDH increased (2% to 33%), AST increased (2% to 33%)

Respiratory: Dyspnea (12%)

1% to 10%:

Cardiovascular: CHF (3%), MI (3%), cerebrovascular accident (2%), chest pain (1%), flushing (1%)

Central nervous system: Lethargy (4%), insomnia (3%), emotional lability (2%), anxiety (1%), headache (1%)

Dermatologic: Bruising (3%), dry skin (2%), pruritus (2%), hair thinning (1%), rash (1%), skin peeling (1%)

Gastrointestinal: Anorexia (4%), flatulence (2%), burning throat (1%), gastrointestinal bleeding (1%), thirst (1%), vomiting (1%)

Hematologic: Leukopenia (4%), thrombocytopenia (1%)

Hepatic: Bilirubin increased (1% to 2%)

Local: Thrombophlebitis (3%)

Neuromuscular & skeletal: Leg cramps (9%)

Ocular: Tearing (1%)

Respiratory: Pulmonary embolism (2%), upper respiratory discharge (1%), hoarseness (1%)

<1%, postmarketing, and/or case reports: Allergic reactions, anemia, angina, angioedema, cerebrovascular ischemia, confusion, coronary ischemia, depression, glucose tolerance decreased, hyper-/hypocalcemia, hypertension, impotence, muscle weakness, venous thrombosis

Oncology: Emetic PotentialLow (10% to 30%)
Drug Interactions

Calcium Salts: May decrease the absorption of Estramustine. **Exceptions:** Calcium Chloride. *Risk D: Consider therapy modification*

Clodronate: May increase the serum concentration of Estramustine. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: Estramustine serum levels may be decreased if taken with milk and other dairy products, calcium supplements, and vitamins containing calcium.
Monitoring ParametersSerum calcium, liver function tests; blood pressure
Nursing: Physical Assessment/MonitoringUse caution in presence of renal or hepatic impairment, metabolic disease, seizure disorders, or migraine history. Assess results of laboratory tests (serum calcium levels, LFTs), therapeutic effectiveness, and adverse response (eg, hypertension, CNS changes, thromboembolism) on a regular basis during therapy. Caution patients with diabetes to monitor glucose carefully; glucose tolerance may be decreased. Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsSerum calcium, liver function tests
Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. It may take several weeks to manifest effects of this medication. Store capsules in refrigerator. Take on empty stomach, 1 hour before or 2 hours after meals or any supplements containing calcium; do not take with milk or milk products. Patients with diabetes should use caution and monitor glucose carefully; glucose tolerance may be decreased. May cause nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); flatulence; diarrhea (buttermilk, boiled milk, or yogurt may help); decreased libido (reversible); or breast tenderness or enlargement. Report sudden acute pain or cramping in legs or calves, unusual swelling in legs or feet, chest pain, shortness of breath, weakness or numbness of arms or legs, respiratory difficulty, or other adverse side effects. **Pregnancy precaution:** Not indicated for use in women. Males who were impotent on estrogen therapy have regained potency while taking estramustine. Males with partners of childbearing potential should consult prescriber for instruction on appropriate barrier contraceptive measures. This drug may cause severe fetal defects.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as phosphate sodium:

Emcyt®: 140 mg

Generic AvailableNo
ManufacturerPfizer
Pricing: U.S. (www.drugstore.com)

Capsules (Emcyt)

140 mg (150): $752.64

Mechanism of ActionCombines the effects of estradiol and nitrogen mustard. It appears to bind to microtubule proteins, preventing normal tubulin function. The antitumor effect may be due solely to an estrogenic effect. Estramustine causes a marked decrease in plasma testosterone and an increase in estrogen levels.
Pharmacodynamics/Kinetics

Absorption: Oral: 75%

Metabolism:

GI tract: Initial dephosphorylation

Hepatic: Oxidation and hydrolysis; metabolites include estramustine, estrone analog, estrone, and estradiol

Half-life elimination: Terminal: 15-24 hours

Time to peak, serum: 2-3 hours

Excretion: Feces (2.9% to 4.8% as unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause sedation or insomnia; rarely may cause depression
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsEstramustine Phosphate; Estramustine Phosphate Sodium; NSC-89199

References

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Hudes GR, “Estramustine-Based Chemotherapy,” *Semin Urol Oncol*, 1997, 15(1):13-9. [PubMed 9050135]

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Perry CM and McTavish D, “Estramustine Phosphate Sodium. A Review of Its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Prostate Cancer,” *Drugs Aging*, 1995, 7(1):49-74.[PubMed 7579781]

Petrylak DP, Tangen CM, Hussain MH, et al, “Docetaxel and Estramustine Compared With Mitoxantrone and Prednisone for Advanced Refractory Prostate Cancer,” *N Engl J Med*, 2004, 351(15):1513-20.[PubMed 15470214]

International Brand Names Emcyt (MX); Estracyt (AE, AR, AT, BE, BG, BH, CH, CL, CN, CO, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, HK, HN, IE, IL, IQ, IR, IT, JO, JP, KP, KW, LB, LY, MY, NL, NO, OM, PL, PT, QA, RU, SA, SE, SY, TR, VE, YE, ZA); Multosin (DE); X-Trant (IN)

Estrogens (Conjugated A/Synthetic)

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Cenestin® may be confused with Senexon®

International issues:

Cenestin® may be confused with Canesten® which is a brand name for clotrimazole in multiple international markets and a brand name for fluconazole in Great Britain

Pronunciation(ES troe jenz, KON joo gate ed, aye, sin THET ik)

U.S. Brand NamesCenestin®

Canadian Brand NamesCenestin

Pharmacologic CategoryEstrogen Derivative

Use: Labeled IndicationsTreatment of moderate-to-severe vasomotor symptoms of menopause; treatment of vulvar and vaginal atrophy

Dosing: AdultsThe lowest dose that will control symptoms should be used. Medication should be discontinued as soon as possible.

Menopause, moderate-to-severe vasomotor symptoms: Oral: 0.45 mg/day; may be titrated up to 1.25 mg/day; attempts to discontinue medication should be made at 3- to 6-month intervals

Vulvar and vaginal atrophy: Oral: 0.3 mg/day

Dosing: ElderlyRefer to adult dosing. A higher incidence of stroke and invasive breast cancer were observed in women >75 years in a WHI substudy using conjugated equine estrogen.

StorageStore at room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to estrogens or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); carcinoma of the breast; estrogen-dependent tumor; hepatic dysfunction or disease; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.
- Dementia: See “Concerns related to adverse effects” below.
- Endometrial carcinoma: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Breast cancer: Estrogens may increase the risk of breast cancer. An increased risk of invasive breast cancer was observed in postmenopausal women using CEE in combination with MPA; a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy. Estrogen use may lead to severe hypercalcemia in patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs.
- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in women ≥65 years of age taking CEE alone or in combination with MPA.
- Endometrial carcinoma: **[U.S. Boxed Warning]: Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women.** Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy. Consider adding a progestin in women with residual endometriosis posthysterectomy.
- Lipid effects: Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent coronary heart disease.** Use caution with cardiovascular disease or dysfunction. May increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA). Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CEE (eg, for prostate cancer).

- Cholestatic jaundice: Use caution with history of cholestatic jaundice associated with past estrogen use or pregnancy.

- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.

- Gallbladder disease: Use with caution in patients with gallbladder disease.

- Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.

- Hypocalcemia: Use with caution in patients with severe hypocalcemia.

- Porphyria: Use with caution in patients with porphyria.

- SLE: Use with caution in patients with SLE.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children. Prior to puberty, estrogens may cause premature closure of the epiphyses, premature breast development in girls or gynecomastia in boys. Vaginal bleeding and vaginal cornification may also be induced in girls.

- Surgical patients: Whenever possible, estrogens should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- Osteoporosis use: When used solely for prevention of osteoporosis in women at significant risk, nonestrogen treatment options should be considered.

- Risks vs. benefits: Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.

- Vulvar and vaginal atrophy use: When used solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should be considered.

Geriatric ConsiderationsBefore prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible side effects and the return of menstrual bleeding (when cycled with a progestin), and be involved in the decision to prescribe. A higher incidence of stroke and invasive breast cancer were observed in women >75 years in a WHI substudy using conjugated equine estrogen. Oral therapy may be more convenient for vaginal atrophy and urinary incontinence.

Pregnancy ConsiderationsUse during pregnancy is contraindicated.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsThe AAP considers ethinyl estradiol, an estrogen derivative, to be “usually compatible” with breast-feeding. Estrogen has been shown to decrease the quantity and quality of human milk. Use only if clearly needed. Monitor the growth of the infant closely.

Adverse Reactions

>10%:

Central nervous system: Headache (11% to 68%), dizziness (11%), pain (11%)

Endocrine & metabolic: Breast pain (29%), endometrial thickening (19%), metrorrhagia (14%)

Gastrointestinal: Abdominal pain (9% to 28%), nausea (9% to 18%)

Neuromuscular & skeletal: Paresthesia (8% to 33%), back pain (14%)

Respiratory: Upper respiratory tract infection (13%)

Miscellaneous: Infection (2% to 14%)

1% to 10%:

Central nervous system: Anxiety (6%), fever (1%)

Gastrointestinal: Dyspepsia (10%), vomiting (7%), constipation (6%), diarrhea (6%), weight gain (6%)

Genitourinary: Vaginitis (8%)

Neuromuscular & skeletal: Leg cramps (10%), hypertonia (6%)

Respiratory: Rhinitis (6% to 8%), cough (6%)

In addition, the following have been reported with estrogen and/or progestin therapy:

Cardiovascular: Edema, hypertension, MI, stroke, venous thromboembolism

Central nervous system: Epilepsy exacerbation, irritability, mental depression, migraine, mood disturbances, nervousness

Dermatologic: Angioedema, chloasma, erythema multiforme, erythema nodosum, hemorrhagic eruption, hirsutism, melasma, pruritus, rash, scalp hair loss, urticaria

Endocrine & metabolic: Breast cancer, breast enlargement, breast tenderness, glucose tolerance impaired, HDL-cholesterol increased, hyper-/hypocalcemia, LDL-cholesterol decreased, libido changes, serum triglycerides/phospholipids increased, thyroid-binding globulin increased, total thyroid hormone (T_4) increased

Gastrointestinal: Abdominal cramps, bloating, cholecystitis, cholelithiasis, gallbladder disease, pancreatitis, weight gain/loss

Genitourinary: Alterations in frequency and flow of menses, cervical secretion changes, endometrial cancer, endometrial hyperplasia, uterine leiomyomata size increased, vaginal candidiasis

Hematologic: Aggravation of porphyria, antithrombin III and antifactor Xa decreased, fibrinogen levels increased, platelet aggregability and platelet count increased; prothrombin and factors VII, VIII, IX, X increased

Hepatic: Cholestatic jaundice, hepatic hemangiomas enlarged

Neuromuscular & skeletal: Arthralgias, chorea, leg cramps

Local: Thrombophlebitis

Ocular: Contact lens intolerance, retinal vascular thrombosis, corneal curvature steepening

Respiratory: Asthma exacerbation, pulmonary thromboembolism

Miscellaneous: Anaphylactoid/anaphylactic reactions, carbohydrate intolerance

Metabolism/Transport Effects Based on estradiol and estrone: **Substrate** of CYP1A2 (major), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak); **Induces** CYP3A4 (weak)

Drug Interactions

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Somatropin: Estrogen Derivatives may diminish the therapeutic effect of Somatropin. Shown to be a concern with oral hormone replacement therapy in postmenopausal women. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (routine use increases estrogen level and risk of breast cancer).

Food: Grapefruit juice may increase estrogen levels, leading to increased adverse effects.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca.

Test Interactions Pathologist should be advised of estrogen/progesterone therapy when specimens are submitted. Reduced response to metyrapone test observed with conjugated estrogens (equine).

Monitoring Parameters Yearly physical examination that includes blood pressure and Papanicolaou smear, breast exam, mammogram. Monitor for signs of endometrial cancer in female patients with uterus. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Nursing: Physical Assessment/Monitoring Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, increased potential for decreased levels/effects or increased potential for toxicity or thrombolic events). Assess results of annual gynecological exam, therapeutic effectiveness, need for continued treatment, and adverse effects (eg, thromboembolism, hypertension, edema, CNS changes) on a regular basis during therapy. **Note:** Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals and periodic assessment of risk:benefit should be made. Caution patients with diabetes to monitor glucose levels closely (may impair glucose tolerance). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. Remind patient about the importance of frequent self-breast exams and the need for annual gynecological exam. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to females of childbearing age unless patient is capable of complying with contraceptive use. Advise patient about contraceptive measures as appropriate.

Monitoring: Lab TestsYearly Papanicolaou smear, mammogram. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take exactly as directed. Routine use of alcohol may increase estrogen level and risk of breast cancer. Annual gynecologic and regular self-breast exams are important. If you have diabetes, monitor glucose levels closely (may impair glucose tolerance). You may experience nausea, vomiting or abdominal pain (small, frequent meals may help); dizziness or mental depression (use caution when driving); rash; hair loss; headache; or breast pain, increased/decreased libido, or enlargement/tenderness of breasts. difficult/painful menstrual cycles. Report significant swelling of extremities; sudden acute pain in legs or calves, chest, or abdomen; shortness of breath; severe headache or vomiting; sudden blindness; weakness or numbness of arm or leg; unusual vaginal bleeding; yellowing of skin or eyes; unusual bruising or bleeding; any alteration or decrease in mental alertness or acuity; or other persistent adverse reactions. You may become intolerant to wearing contact lenses, notify prescriber if this occurs. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. This medication may cause fetal defects and should not be used during pregnancy. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg

Generic AvailableNo

ManufacturerDuramed Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Cenestin)

0.3 mg (30): $51.99

0.45 mg (30): $52.99

0.625 mg (30): $51.99

0.9 mg (30): $51.33

1.25 mg (30): $51.99

Mechanism of ActionConjugated A/synthetic estrogens contain a mixture of 9 synthetic estrogen substances, including sodium estrone sulfate, sodium equilin sulfate, sodium 17 alpha-dihydroequilin, sodium 17 alpha-estradiol and sodium 17 beta-dihydroequilin. Estrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principle intracellular human estrogen and is more potent than estrone and estriol at the receptor level; it is the primary estrogen secreted prior to menopause. Following menopause, estrone and estrone sulfate are more highly produced. Estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone, and follicle-stimulating hormone through a negative feedback system; estrogen replacement reduces elevated levels of these hormones in postmenopausal women.

Pharmacodynamics/Kinetics

Absorption: Well absorbed over a period of several hours

Protein-binding: Sex hormone-binding globulin (SHBG) and albumin

Metabolism: Hepatic via CYP3A4; estradiol is converted to estrone and estriol; also undergoes enterohepatic recirculation; estrone sulfate is the main metabolite in postmenopausal women

Excretion: Urine (primarily estriol, also as estradiol, estrone, and conjugates)

Pharmacotherapy PearlsNot biologically equivalent to conjugated estrogens from equine source. Contains 9 unique estrogenic compounds (equine source contains at least 10 active estrogenic compounds).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentThe Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Cardiovascular ConsiderationsIt is important to recognize that estrogens may induce or worsen hypertension. These problems are less severe with lower doses. Furthermore, estrogens may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on long-term estrogens undergo monitoring of blood pressure and avoid cigarette use.

Conjugated estrogens (alone or in combination with a progestin) should not be used to prevent coronary heart disease. The HERS trial found that women with coronary disease derived no cardiovascular protection compared to those treated with placebo. In the Women's Health

Initiative trial, a conjugated estrogen/progestin combination did not offer protection against heart disease. No cardiovascular benefits were seen; in fact, more coronary heart disease was observed in the treatment group. Substantial evidence suggests that estrogen therapy increases bone mineralization and therefore may be of added benefit in patients with osteoporosis. Estrogen also has a favorable effect on lipids (decreases total cholesterol and LDL, increases HDL) but increases triglycerides. Therapy should be initiated after careful evaluation of risk:benefit for therapy.

References

Grodstein F, Stampfer MJ, Colditz GA, et al, “Postmenopausal Hormone Therapy and Mortality,” *N Engl J Med*, 1997, 336(25):1769-75. [PubMed 9187066]

Hulley S, Grady D, Bush T, et al, “Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group,” *JAMA*, 1998, 280(7):605-13. [PubMed 9718051]

Rossouw JE, Anderson GL, Prentice RL, et al, “Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principle Results From the Women's Health Initiative Randomized Controlled Trial,”*JAMA*, 2002, 288(3):321-33.[PubMed 12117397]

Shumaker S, Legault C, Thal L, et al, “Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial,” *JAMA*, 2003, 289:2651-62. [PubMed 12771112]

U.S. Food and Drug Administration, Department of Health and Human Services, “FDA Approves New Labels for Estrogen and Estrogen With Progestin Therapies for Postmenopausal Women Following Review of Women's Health Initiative Data,” January 8, 2003. Available at: http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#prempr. Accessed January 9, 2003.

International Brand NamesCenestin (CA)

Estrogens (Conjugated B/Synthetic)

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ES troe jenz, KON joo gate ed, bee, sin THET ik)

U.S. Brand NamesEnjuvia™

Pharmacologic Category[Estrogen Derivative]()

Use: Labeled IndicationsTreatment of moderate-to-severe vasomotor symptoms of menopause; treatment of vulvar and vaginal atrophy associated with menopause; treatment of moderate-to-severe vaginal dryness and pain with intercourse associated with menopause

Dosing: AdultsThe lowest dose that will control symptoms should be used. Medication should be discontinued as soon as possible.

Menopause, moderate-to-severe vasomotor symptoms: Oral: 0.3 mg/day; may be titrated up to 1.25 mg/day. Attempts to discontinue medication should be made at 3- to 6-month intervals.

Vaginal dryness/vulvar and vaginal atrophy associated with menopause: Oral: 0.3 mg/day. Attempts to discontinue medication should be made at 3- to 6-month intervals.

Dosing: ElderlyRefer to adult dosing. A higher incidence of stroke and invasive breast cancer were observed in women >75 years in a WHI substudy using conjugated equine estrogen.

StorageStore at room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to estrogens or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); carcinoma of the breast; estrogen-dependent tumor; hepatic dysfunction or disease; pregnancy

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.
- Dementia: See “Concerns related to adverse effects” below.
- Endometrial carcinoma: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Breast cancer: Estrogens may increase the risk of breast cancer. An increased risk of invasive breast cancer was observed in postmenopausal women using conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA); a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy. Estrogen use may lead to severe hypercalcemia in patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs.
- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in women ≥65 years of age taking CEE alone or in combination with MPA.
- Endometrial carcinoma: **[U.S. Boxed Warning]: Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women.** Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy. Consider adding a progestin in women with residual endometriosis posthysterectomy.
- Lipid effects: Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent coronary heart disease.** Use caution with cardiovascular disease or dysfunction. May increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using CEE in combination with MPA. Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CEE (eg, for prostate cancer).
- Cholestatic jaundice: Use caution with history of cholestatic jaundice associated with past estrogen use or pregnancy.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.
- Gallbladder disease: Use with caution in patients with gallbladder disease.
- Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.

- Hypocalcemia: Use with caution in patients with severe hypocalcemia.
- Porphyria: Use with caution in patients with porphyria.
- SLE: Use with caution in patients with SLE.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children. Prior to puberty, estrogens may cause premature closure of the epiphyses, premature breast development in girls or gynecomastia in boys. Vaginal bleeding and vaginal cornification may also be induced in girls.
- Surgical patients: Whenever possible, estrogens should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- Risks vs. benefits: Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.
- Vaginal dryness/atrophy: When used solely for the treatment of vaginal dryness and pain with intercourse, or vulvar and vaginal atrophy, topical vaginal products should be considered.

Geriatric ConsiderationsEnjuvia™ has not been studied in an elderly population. Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible side effects and the return of menstrual bleeding (when cycled with a progestin), and be involved in the decision to prescribe. A higher incidence of stroke and invasive breast cancer was observed in women >75 years of age in a WHI substudy. Oral therapy may be more convenient for vaginal atrophy and urinary incontinence.

Pregnancy ConsiderationsUse during pregnancy is contraindicated.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsThe AAP considers ethinyl estradiol, an estrogen derivative, to be “usually compatible” with breast-feeding. Estrogen has been shown to decrease the quantity and quality of human milk. Use only if clearly needed. Monitor the growth of the infant closely.

Adverse Reactions

>10%:

Central nervous system: Headache (15% to 25%), pain (10% to 19%)

Endocrine & metabolic: Breast pain (up to 14%)

Gastrointestinal: Abdominal pain (4% to 15%), nausea (7% to 12%)

1% to 10%:

Central nervous system: Dizziness (1% to 7%)

Endocrine & metabolic: Dysmenorrhea (1% to 8%)

Gastrointestinal: Flatulence (4% to 7%)

Genitourinary: Vaginitis (2% to 7%)

Neuromuscular & skeletal: Paresthesia (up to 6%)

Respiratory: Bronchitis (up to 7%), rhinitis (4% to 7%), sinusitis (3% to 7%)

Miscellaneous: Flu-like syndrome (4% to 7%)

In addition, the following have been reported with estrogen and/or progestin therapy:

Cardiovascular: Edema, hypertension, MI, stroke, venous thromboembolism

Central nervous system: Epilepsy exacerbation, irritability, mental depression, migraine, mood disturbances, nervousness

Dermatologic: Angioedema, chloasma, erythema multiforme, erythema nodosum, hemorrhagic eruption, hirsutism, loss of scalp hair, melasma, pruritus, rash, urticaria

Endocrine & metabolic: Breast cancer, breast enlargement, breast tenderness, HDL-cholesterol increased, hyper-/hypocalcemia, impaired glucose tolerance, LDL-cholesterol decreased, libido (changes in), serum triglycerides/phospholipids increased, thyroid-binding globulin increased, total thyroid hormone (T_4) increased

Gastrointestinal: Abdominal cramps, bloating, cholecystitis, cholelithiasis, gallbladder disease, pancreatitis, weight gain/loss

Genitourinary: Alterations in frequency and flow of menses, changes in cervical secretions, endometrial cancer, endometrial hyperplasia, increased size of uterine leiomyomata, vaginal candidiasis

Hematologic: Aggravation of porphyria; antithrombin III and antifactor Xa decreased; fibrinogen levels increased; platelet aggregability and platelet count increased; prothrombin and factors VII, VIII, IX, X increased

Hepatic: Cholestatic jaundice, hepatic hemangiomas enlarged

Local: Thrombophlebitis

Neuromuscular & skeletal: Arthralgias, chorea, leg cramps

Ocular: Contact lens intolerance, corneal curvature steepening, retinal vascular thrombosis

Respiratory: Asthma exacerbation, pulmonary thromboembolism

Miscellaneous: Anaphylactoid/anaphylactic reactions, carbohydrate intolerance

Metabolism/Transport EffectsBased on estradiol and estrone: **Substrate** of CYP1A2 (major), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak); **Induces** CYP3A4 (weak)

Drug Interactions

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Somatropin: Estrogen Derivatives may diminish the therapeutic effect of Somatropin. Shown to be a concern with oral hormone replacement therapy in postmenopausal women. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (routine use increases estrogen level and risk of breast cancer).

Food: Grapefruit juice may increase estrogen levels, leading to increased adverse effects.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, and yucca.

Test InteractionsPathologist should be advised of estrogen/progesterone therapy when specimens are submitted. Reduced response to metyrapone test observed with conjugated estrogens (equine).

Monitoring ParametersYearly physical examination that may include blood pressure and Papanicolaou smear, breast exam, mammogram. Monitor for signs of endometrial cancer in female patients with uterus. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, increased potential for decreased levels/effects or increased potential for toxicity or thrombolic events). Assess results of annual gynecological exam, therapeutic effectiveness, need for continued treatment, and adverse effects (eg, thromboembolism, hypertension, edema, CNS changes) on a regular basis during therapy. **Note:** Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals and periodic assessment of risk:benefit should be made. Caution patients with diabetes to monitor glucose levels closely (may impair glucose tolerance). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. Remind patient about the importance of frequent self-breast exams and the need for annual gynecological exam. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to females of childbearing age unless patient is capable of complying with contraceptive use. Advise patient about contraceptive measures as appropriate.

Monitoring: Lab TestsPapanicolaou smear, mammogram. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take exactly as directed. Routine use of alcohol may increase estrogen level and risk of breast cancer. Annual gynecologic and regular self-breast exams are important. If you have diabetes, monitor glucose levels closely (may impair glucose tolerance). You may experience nausea, vomiting or abdominal pain (small, frequent meals may help); dizziness or mental depression (use caution when driving); rash; hair loss; headache; or breast pain, increased/decreased libido, or enlargement/tenderness of breasts. difficult/painful menstrual cycles. Report significant swelling of extremities; sudden acute pain in legs or calves, chest, or abdomen; shortness of breath; severe headache or vomiting; sudden blindness; weakness or numbness of arm or leg; unusual vaginal bleeding; yellowing of skin or eyes; unusual bruising or bleeding; any alteration or decrease in mental alertness or acuity; or other persistent adverse reactions. You may become intolerant to wearing contact lenses, notify prescriber if this occurs. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. This medication may cause fetal defects and should not be used during pregnancy. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Enjuvia™: 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Enjuvia)

0.3 mg (30): $49.23

0.45 mg (100): $154.87

0.625 mg (100): $155.61

1.25 mg (100): $154.87

Mechanism of ActionConjugated B/synthetic estrogens contain a mixture of 10 synthetic estrogen substances, including sodium estrone sulfate, sodium equilin sulfate, sodium 17-alpha-dihydroequilin, sodium 17-alpha-estradiol, and sodium 17-beta-dihydroequilin. Estrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principle intracellular human estrogen and is more potent than estrone and estriol at the receptor level; it is the primary estrogen secreted prior to menopause. Following menopause, estrone and estrone sulfate are more highly produced. Estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone, and follicle-stimulating hormone through a negative feedback system; estrogen replacement reduces elevated levels of these hormones in postmenopausal women.
Pharmacodynamics/Kinetics

Absorption: Well absorbed over a period of several hours

Protein-binding: Sex hormone-binding globulin (SHBG) and albumin

Metabolism: Hepatic via CYP3A4; estradiol is converted to estrone and estriol; also undergoes enterohepatic recirculation; estrone sulfate is the main metabolite in postmenopausal women

Half-life elimination: Conjugated estrone: 8-20 hours; conjugated equilin: 5-17 hours

Excretion: Urine (primarily estriol, also as estradiol, estrone, and conjugates)

Pharmacotherapy PearlsNot biologically equivalent to conjugated estrogens from equine source. Contains 10 unique estrogenic compounds (equine source contains at least 10 active estrogenic compounds).
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness, irritability, depression, mood disturbances, and nervousness
Mental Health: Effects on Psychiatric TreatmentThe risk of dementia may be increased in postmenopausal women. Increased incidence of dementia was observed in women ≥65 years of age who were taking conjugated equine estrogens alone or in combination with medroxyprogesterone acetate. May increase triglycerides; combined use with clozapine, olanzapine, and quetiapine may produce an additive risk. Nausea is common; combined use with lithium, valproic acid, carbamazepine, and SSRIs may produce an additive risk. Carbamazepine and St John's wort may reduce the effectiveness or estrogens.
References

Grodstein F, Stampfer MJ, Colditz GA, et al, “Postmenopausal Hormone Therapy and Mortality,” *N Engl J Med*, 1997, 336(25):1769-75. [PubMed 9187066]

Hulley S, Grady D, Bush T, et al, “Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group,” *JAMA*, 1998, 280(7):605-13. [PubMed 9718051]

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Shumaker S, Legault C, Thal L, et al, “Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial,” *JAMA*, 2003, 289:2651-62. [PubMed 12771112]

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Estrogens (Conjugated/Equine) and Medroxyprogesterone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Premphase® may be confused with Prempro™

Prempro™ may be confused with Premphase®

Pronunciation(ES troe jenz KON joo gate ed/EE kwine & me DROKS ee proe JES te rone)

U.S. Brand NamesPremphase®; Prempro™

Canadian Brand NamesPremphase®; Premplus®; Prempro™

Pharmacologic CategoryEstrogen and Progestin Combination

Use: Labeled IndicationsWomen with an intact uterus: Treatment of moderate-to-severe vasomotor symptoms associated with menopause; treatment of atrophic vaginitis; osteoporosis (prophylaxis)

Dosing: Adults

Treatment of moderate-to-severe vasomotor symptoms associated with menopause or treatment of atrophic vaginitis in females with an intact uterus: (**Note:** The lowest dose that will control symptoms should be used; medication should be discontinued as soon as possible): Oral:

Premphase®: One maroon conjugated estrogen 0.625 mg tablet daily on days 1 through 14 and one light blue conjugated estrogen 0.625 mg/MPA 5 mg tablet daily on days 15 through 28; re-evaluate patients at 3- and 6-month intervals to determine if treatment is still necessary; monitor patients for signs of endometrial cancer; rule out malignancy if unexplained vaginal bleeding occurs

Prempro™: One conjugated estrogen 0.3 mg/MPA 1.5 mg tablet daily; re-evaluate at 3-and 6-month intervals to determine if therapy is still needed; dose may be increased to a maximum of one conjugated estrogen 0.625 mg/MPA 5 mg tablet daily in patients with bleeding or spotting, once malignancy has been ruled out

Osteoporosis prophylaxis in females with an intact uterus: Oral:

Premphase®: One maroon conjugated estrogen 0.625 tablet daily on days 1 through 14 and one light blue conjugated estrogen 0.625 mg/MPA 5 mg tablet daily on days 15 through 28; monitor patients for signs of endometrial cancer; rule out malignancy if unexplained vaginal bleeding occurs

Prempro™: One conjugated estrogen 0.3 mg/MPA 1.5 mg tablet daily; dose may be increased to one conjugated estrogen 0.625 mg/MPA 5 mg tablet daily; in patients with bleeding or spotting, once malignancy has been ruled out

Dosing: ElderlyRefer to adult dosing. A higher incidence of stroke and breast cancer was observed in women >75 years in a WHI substudy.

Dietary ConsiderationsAdministration with food decreases nausea, administer with food. Ensure adequate calcium and vitamin D intake when used for the prevention of osteoporosis.

StorageStore at room temperature 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to conjugated estrogens, medroxyprogesterone (MPA), or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); carcinoma of the breast; estrogen-dependent tumor; hepatic dysfunction or disease; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.
- Dementia: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Breast cancer: Estrogens may increase the risk of breast cancer. An increased risk of invasive breast cancer was observed in postmenopausal women using CEE in combination with MPA; a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy. Estrogen use may lead to severe hypercalcemia in patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs.
- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in

women ≥65 years of age taking CEE alone or in combination with MPA.

- Endometrial cancer: Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women. Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy.

- Lipid effects: Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.

- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent coronary heart disease.** Use caution with cardiovascular disease or dysfunction. May increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA). Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CEE (eg, for prostate cancer).

- Cholestatic jaundice: Use caution with history of cholestatic jaundice associated with past estrogen use or pregnancy.

- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes, or renal dysfunction.

- Gallbladder disease: Use with caution in patients with gallbladder disease.

- Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.

- Hypocalcemia: Use with caution in patients with severe hypocalcemia.

- Porphyria: Use with caution in patients with porphyria.

- SLE: Use with caution in patients with SLE.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children. Prior to puberty, estrogens may cause premature closure of the epiphyses, premature breast development in girls, or gynecomastia in boys. Vaginal bleeding and vaginal cornification may also be induced in girls.

- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- Osteoporosis use: When used solely for the prevention of osteoporosis in women at significant risk, nonestrogen treatment options should be considered.

- Risks vs. benefits: Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.

- Vulvar and vaginal atrophy use: When used solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should be considered.

Geriatric ConsiderationsBefore prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible side effects and the return of menstrual bleeding (when cycled with a progestin), and be involved in the decision to prescribe. A higher incidence of stroke and invasive breast cancer was observed in women >75 years in a WHI substudy. Oral therapy may be more convenient for vaginal atrophy and urinary incontinence.
Pregnancy ConsiderationsSee individual agents; use of this combination is contraindicated during pregnancy
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsSee individual agents.
Adverse Reactions

>10%:

Central nervous system: Headache (28% to 37%), pain (11% to 13%), depression (6% to 11%)

Endocrine & metabolic: Breast pain (32% to 38%), dysmenorrhea (8% to 13%)

Gastrointestinal: Abdominal pain (16% to 23%), nausea (9% to 11%)

Neuromuscular & skeletal: Back pain (13% to 16%)

Respiratory: Pharyngitis (11% to 13%)

Miscellaneous: Infection (16% to 18%), flu-like syndrome (10% to 13%)

1% to 10%:

Cardiovascular: Peripheral edema (3% to 4%)

Central nervous system: Dizziness (3% to 5%)

Dermatologic: Pruritus (5% to 10%), rash (4% to 6%)

Endocrine & metabolic: Leukorrhea (5% to 9%)

Gastrointestinal: Flatulence (8% to 9%), diarrhea (5% to 6%), dyspepsia (5% to 6%)

Genitourinary: Vaginitis (5% to 7%), cervical changes (4% to 5%), vaginal hemorrhage (1% to 3%)

Neuromuscular & skeletal: Weakness (6% to 10%), arthralgia (7% to 9%), leg cramps (3% to 5%), hypertonia (3% to 4%)

Respiratory: Sinusitis (7% to 8%), rhinitis (6% to 8%)

Additional adverse effects reported with conjugated estrogens and/or progestins: Abdominal cramps, acne, abnormal uterine bleeding, aggravation of porphyria, amenorrhea, anaphylactoid reactions, anaphylaxis, antifactor Xa decreased, antithrombin III decreased, appetite changes, bloating, breast enlargement, breast tenderness, cerebral embolism, cerebral thrombosis, chloasma, cholestatic jaundice, cholecystitis, cholelithiasis, chorea, contact lens intolerance, cystitis-like syndrome, decreased carbohydrate tolerance, dizziness; factors VII, VIII, IX, X, XII, VII-X complex, and II-VII-X complex increased; endometrial hyperplasia, erythema multiforme, erythema nodosum, galactorrhea, hemorrhagic eruption, fatigue, fibrinogen increased, impaired glucose tolerance, HDL-cholesterol increased, hirsutism, hypertension, increase in size of uterine leiomyomata, gallbladder disease, insomnia, LDL-cholesterol decreased, libido changes, loss of scalp hair, melasma, migraine, nervousness, optic neuritis, pancreatitis, platelet aggregability and platelet count increased, premenstrual like syndrome, PT and PTT accelerated, pulmonary embolism, pyrexia, retinal thrombosis, somnolence, steepening of corneal curvature, thrombophlebitis, thyroid-binding globulin increased, total thyroid hormone (T_4) increased, triglycerides increased, urticaria, vaginal candidiasis, vomiting, weight gain/loss

Metabolism/Transport Effects

Based on estradiol and estrone: **Substrate** of CYP1A2 (major), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2C8 (weak); **Induces** CYP3A4 (weak)

Medroxyprogesterone: **Substrate** of CYP3A4 (major); **Induces** CYP3A4 (weak)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Somatropin: Estrogen Derivatives may diminish the therapeutic effect of Somatropin. Shown to be a concern with oral hormone replacement therapy in postmenopausal women. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (routine use increases estrogen level and risk of breast cancer). Ethanol may also increase the risk of osteoporosis.

Food: Folic acid absorption may be decreased.

Herb/Nutraceutical: St John's wort may decrease levels. Avoid black cohosh, dong quai (has estrogenic activity). Avoid red clover, saw palmetto, ginseng (due to potential hormonal effects).

Test InteractionsPathologist should be advised of estrogen/progesterone therapy when specimens are submitted. Reduced response to metyrapone test.

Monitoring ParametersYearly physical examination that includes blood pressure and Papanicolaou smear, breast exam, mammogram. Monitor for signs of endometrial cancer. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Prevention of osteoporosis: Bone density measurement

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsSerum cholesterol, HDL, LDL triglycerides

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Premphase® [therapy pack contains 2 separate tablet formulations]: Conjugated estrogens 0.625 mg [14 maroon tablets] and conjugated estrogen 0.625 mg/medroxyprogesterone acetate 5 mg [14 light blue tablets] (28s)

Prempro™:

0.3/1.5: Conjugated estrogens 0.3 mg and medroxyprogesterone acetate 1.5 mg (28s)

0.45/1.5: Conjugated estrogens 0.45 mg and medroxyprogesterone acetate 1.5 mg (28s)

0.625/2.5: Conjugated estrogens 0.625 mg and medroxyprogesterone acetate 2.5 mg (28s)

0.625/5: Conjugated estrogens 0.625 mg and medroxyprogesterone acetate 5 mg (28s)

Generic AvailableNo

ManufacturerWyeth-Ayerst Laboratories

Pricing: U.S. (www.drugstore.com)

Tablets (Prempro)

0.3-1.5 mg (28): $62.33

0.45-1.5 mg (28): $62.33

0.625-2.5 mg (28): $62.33

0.625-5 mg (28): $60.25

Mechanism of Action

Conjugated estrogens contain a mixture of estrone sulfate, equilin sulfate, 17 alpha-dihydroequilin, 17 alpha-estradiol, and 17 beta-dihydroequilin. Estrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principle intracellular human estrogen and is more potent than estrone and estriol at the receptor level; it is the primary estrogen secreted prior to menopause. Following menopause, estrone and estrone sulfate are more highly produced. Estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone, and follicle-stimulating hormone through a negative feedback system; estrogen replacement reduces elevated levels of these hormones in postmenopausal women.

MPA inhibits gonadotropin production which then prevents follicular maturation and ovulation. In women with adequate estrogen, MPA transforms a proliferative endometrium into a secretory endometrium; when administered with conjugated estrogens, reduces the incidence of endometrial hyperplasia and risk of adenocarcinoma.

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric Treatment Barbiturates and carbamazepine may decrease the effects of estrogens; estrogens may affect metabolism of benzodiazepines; monitor for clinical effect. The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Cardiovascular Considerations It is important to recognize that estrogens may induce or worsen hypertension. These problems are less severe with lower doses. Furthermore, estrogens may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on long-term estrogens undergo monitoring of blood pressure and avoid cigarette use.

Conjugated estrogens (alone or in combination with a progestin) should not be used to prevent coronary heart disease. The HERS trial found that women with coronary disease derived no cardiovascular protection compared to those treated with placebo. In the Women's Health Initiative trial, a conjugated estrogen/progestin combination did not offer protection against heart disease. No cardiovascular benefits were seen; in fact, more coronary heart disease was observed in the treatment group. Substantial evidence suggests that estrogen therapy increases bone mineralization and therefore may be of added benefit in patients with osteoporosis. Estrogen also has a favorable effect on lipids (decreases total cholesterol and LDL, increases HDL) but increases triglycerides. Therapy should be initiated after careful evaluation of risk:benefit for therapy.

Index Terms Medroxyprogesterone and Estrogens (Conjugated); MPA and Estrogens (Conjugated)

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International Brand Names Climatrol (PE); Climatrol Continuo (CN); Climatrol HT (CO); Climatrol HT Ciclico (VE); Climatrol HT Continuo (CO); Climatrol HT Continuo Plus (CO); Climatrol HT Plus (CO); Climopax (DE); Monosedan Ciclo (BR); Monosedan Fase (BR); Novofac 30 Simple (UY); Plentiva (KP, TW); Plentiva Cycle (KP, TW); Premelle (CO, HK, KP, MX, MY, PE, PH, SG, TW); Premelle Ciclico (AR); Premelle Continuo (AR); Premelle Cycle 5 (SG); Premelle Lite (TW); Premelle Right (KP); Premia (NZ); Prempak (EC, HK, TH); Profemina M.P. (PY)

Estrogens (Conjugated/Equine)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Premarin® may be confused with Primaxin®, Provera®, Remeron®

Pronunciation(ES troe jenz KON joo gate ed, EE kwine)

U.S. Brand NamesPremarin®

Canadian Brand NamesC.E.S.®; Premarin®

Pharmacologic CategoryEstrogen Derivative

Use: Labeled IndicationsTreatment of moderate-to-severe vasomotor symptoms associated with menopause; treatment of vulvar and vaginal atrophy; hypoestrogenism (due to hypogonadism, castration, or primary ovarian failure); prostatic cancer (palliation); breast cancer (palliation); osteoporosis (prophylaxis, postmenopausal women at significant risk only); abnormal uterine bleeding; moderate-to-severe dyspareunia (pain during intercourse) due to vaginal/vulvar atrophy of menopause

Use: Unlabeled/InvestigationalUremic bleeding

Dosing: Adults

Breast cancer palliation, metastatic disease in selected patients (male and female): Oral: 10 mg 3 times/day for at least 3 months

Uremic bleeding (unlabeled use): I.V.: 0.6 mg/kg/day for 5 days

Androgen-dependent prostate cancer palliation (males): Oral: 1.25-2.5 mg 3 times/day

Prevention of postmenopausal osteoporosis: Oral: Initial: 0.3 mg/day, cyclically* or daily, depending on medical assessment of patient. Dose may be adjusted based on bone mineral density and clinical response. The lowest effective dose should be used.

Menopause (moderate to severe vasomotor symptoms): Oral: Initial: 0.3 mg/day. May be given cyclically* or daily, depending on medical assessment of patient. The lowest dose that will control symptoms should be used. Medication should be discontinued as soon as possible.

Vulvar and vaginal atrophy: Oral: Initial: 0.3 mg/day. The lowest dose that will control symptoms should be used. May be given cyclically* or daily, depending on medical assessment of patient. Medication should be discontinued as soon as possible.

Vaginal cream: Intravaginal: 0.5-2 g/day given cyclically*

Moderate-to-severe dyspareunia: Intravaginal: Vaginal cream: 0.5 g twice weekly (eg, Monday and Thursday) or once daily cyclically*

Female hypogonadism: Oral: 0.3-0.625 mg/day given cyclically*; dose may be titrated in 6- to 12-month intervals; progestin treatment should be added to maintain bone mineral density once skeletal maturity is achieved.

Female castration, primary ovarian failure: Oral: 1.25 mg/day given cyclically*; adjust according to severity of symptoms and patient response. For maintenance, adjust to the lowest effective dose.

Abnormal uterine bleeding:

Acute/heavy bleeding:

Oral (unlabeled route): 1.25 mg, may repeat every 4 hours for 24 hours, followed by 1.25 mg once daily for 7-10 days

I.M., I.V.: 25 mg, may repeat in 6-12 hours if needed

Note: Treatment should be followed by a low-dose oral contraceptive; medroxyprogesterone acetate along with or following estrogen therapy can also be given

Nonacute/lesser bleeding: Oral (unlabeled route): 1.25 mg once daily for 7-10 days

***Cyclic administration:** Either 3 weeks on, 1 week off **or** 25 days on, 5 days off

Dosing: ElderlyRefer to adult dosing. A higher incidence of stroke and breast cancer was observed in women >75 years in a WHI substudy.

Dosing: PediatricAdolescents: Refer to adult dosing.

Dosing: Hepatic Impairment

Mild to moderate liver impairment: Dosage reduction of estrogens is recommended.

Severe liver impairment: **Not recommended.**

Administration: I.M.May be administered intramuscularly.
Administration: I.V.Administer I.V. doses slowly to avoid a flushing reaction.
Administration: OralAdminister at bedtime to minimize adverse effects. May be administered without regard to meals.
Administration: OtherVaginal cream: Administer at bedtime to minimize adverse effects. To clean applicator, remove plunger from barrel. Wash with mild soap and warm water; do not boil or use hot water.
Dietary ConsiderationsEnsure adequate calcium and vitamin D intake when used for the prevention of osteoporosis. Powder for reconstitution for injection (25 mg) contains lactose 200 mg.
Storage

Injection: Refrigerate at 2°C to 8°C (36°F to 46°F) prior to reconstitution. Use immediately following reconstitution.

Tablets, vaginal cream: Store at room temperature 20°C to 25°C (68°F to 77°F).

ReconstitutionInjection: Reconstitute with sterile water for injection; slowly inject diluent against side wall of the vial. Agitate gently; do not shake violently.
CompatibilityStable in D_5W and NS.

Y-site administration: Compatible: Heparin with hydrocortisone sodium succinate, potassium chloride, vitamin B complex with C.

Compatibility when admixed: Incompatible: Ascorbic acid.

ContraindicationsHypersensitivity to estrogens or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); carcinoma of the breast (except in appropriately selected patients being treated for metastatic disease); estrogen-dependent tumor; hepatic dysfunction or disease; pregnancy
Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.

- Dementia: See “Concerns related to adverse effects” below.

- Endometrial carcinoma: See “Concerns related to adverse effects” below.

- Risks vs benefits: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Breast cancer: Estrogens may increase the risk of breast cancer. An increased risk of invasive breast cancer was observed in postmenopausal women using conjugated estrogens (CE) in combination with medroxyprogesterone acetate (MPA); a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy. Estrogen use may lead to severe hypercalcemia in patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs.

- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in women ≥65 years of age taking CE alone or in combination with MPA.

- Endometrial carcinoma: [**U.S. Boxed Warning]: Adequate diagnostic measures, including endometrial sampling (if indicated), should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women with an intact uterus.** Risk appears to be associated with long-term use. The use of a progestin should be considered when administering estrogens to postmenopausal women with an intact uterus.

- Lipid effects: Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.

- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

- Vaginal bleeding: Presentation of irregular, unresolving vaginal bleeding warrants further evaluation including endometrial sampling, if indicated, to rule out malignancy

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent cardiovascular disease.** Use caution with cardiovascular disease or dysfunction. May increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using CE alone or in combination with MPA. Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CE (eg, for prostate cancer).

- Cholestatic jaundice: Use caution with history of cholestatic jaundice associated with past estrogen use or pregnancy.

- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes, heart failure, or renal dysfunction.

- Endometriosis: Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy. Consider adding a progestin in women with residual endometriosis posthysterectomy.

- Gallbladder disease: Use with caution in patients with gallbladder disease.

- Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.

- Hypocalcemia: Use with caution in patients with severe hypocalcemia.

- Porphyria: Use with caution in patients with porphyria.

- SLE: Use with caution in patients with SLE.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children. Prior to puberty, estrogens may cause premature closure of the epiphyses, premature breast development in girls or gynecomastia in boys. Vaginal bleeding and vaginal cornification may also be induced in girls.

- Surgical patients: Whenever possible, estrogens should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Dosage form specific issues:

- Vaginal cream: Use of the vaginal cream may weaken latex found in condoms, diaphragms or cervical caps.

Other warnings/precautions:

- Osteoporosis use: When used solely for prevention of osteoporosis in women at significant risk, nonestrogen treatment options should be considered.

- Risks vs benefits: **[U.S. Boxed Warning]: Estrogens with or without progestin should be used for shortest duration possible at the lowest effective dose consistent with treatment goals.** Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.

- Vulvar and vaginal atrophy use: When used solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should be considered. Use caution applying topical products to severely atrophic vaginal mucosa.

Geriatric ConsiderationsBefore prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible side effects and the return of menstrual bleeding (when cycled with a progestin), and be involved in the decision to prescribe. A higher incidence of stroke and invasive breast cancer was observed in women >75 years in a WHI substudy. Oral therapy may be more convenient for vaginal atrophy and urinary incontinence.

Pregnancy ConsiderationsEstrogens are not indicated for use during pregnancy or immediately postpartum. In general, the use of estrogen and progestin as in combination hormonal contraceptives have not been associated with teratogenic effects when inadvertently taken early in pregnancy. These products are contraindicated for use during pregnancy. Use of the vaginal cream may weaken latex found in condoms, diaphragms or cervical caps.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsThe AAP considers ethinyl estradiol, an estrogen derivative, to be “usually compatible” with breast-feeding. Estrogen has been shown to decrease the quantity and quality of human milk. Use only if clearly needed. Monitor the growth of the infant closely.

Adverse Reactions

Note: Percentages reported in postmenopausal women following oral use.

>10%:

Central nervous system: Headache (26% to 32%; placebo 28%)

Endocrine & metabolic: Breast pain (7% to 12%; placebo 9%)

Gastrointestinal: Abdominal pain (15% to 17%)

Genitourinary: Vaginal hemorrhage (2% to 14%)

Neuromuscular & skeletal: Back pain (13% to 14%)

1% to 10%:

Central nervous system: Nervousness (2% to 5%)

Dermatologic: Pruritus (4% to 5%)

Gastrointestinal: Flatulence (6% to 7%)

Genitourinary: Vaginitis (5% to 7%), leukorrhea (4% to 7%), vaginal moniliasis (5% to 6%)

Neuromuscular & skeletal: Weakness (7% to 8%), leg cramps (3% to 7%)

Additional adverse reactions reported with injection or vaginal cream; frequency not defined:

Genitourinary: Cystis-like syndrome, genital pruritus, vulvovaginal discomfort

Local: injection site: Edema, pain, phlebitis

In addition, the following have been reported with estrogen and/or progestin therapy:

Cardiovascular: DVT, edema, hypertension, MI, stroke, superficial venous thrombosis

Central nervous system: Dementia, dizziness, epilepsy exacerbation, headache, irritability, mental depression, migraine, mood disturbances, nervousness

Dermatologic: Angioedema, chloasma, erythema multiforme, erythema nodosum, hemorrhagic eruption, hirsutism, loss of scalp hair, melasma, pruritus, rash, urticaria

Endocrine & metabolic: Breast cancer, breast discharge, breast enlargement, breast tenderness, dysmenorrhea, fibrocystic breast changes, galactorrhea, glucose intolerance, HDL-cholesterol increased, hyper-/hypocalcemia, LDL-cholesterol decreased, libido (changes in), ovarian cancer, serum triglycerides/phospholipids increased, thyroid-binding globulin increased, total thyroid hormone (T_4) increased

Gastrointestinal: Abdominal cramps, bloating, cholecystitis, cholelithiasis, gallbladder disease, ischemic colitis, nausea, pancreatitis, vomiting, weight gain/loss

Genitourinary: Abnormal uterine bleeding/spotting, changes in cervical ectropion, changes in cervical secretions, endometrial cancer, endometrial hyperplasia, increased size of uterine leiomyomata, vaginal candidiasis

Hematologic: Aggravation of porphyria, antithrombin III and antifactor Xa decreased; factors II, II-VII-X complex, VII, VIII, VII-X complex, IX, X , and XII increased; increased beta-thromboglobulin, fibrinogen levels, plasminogen/plasminogen activity, platelet aggregability, platelet count, and prothrombin

Hepatic: Cholestatic jaundice, hepatic hemangiomas enlarged

Neuromuscular & skeletal: Arthralgias, chorea, leg cramps

Local: Thrombophlebitis

Ocular: Contact lens intolerance, corneal curvature steepening, retinal vascular thrombosis

Respiratory: Asthma exacerbation, pulmonary thromboembolism

Miscellaneous: Anaphylactoid/anaphylactic reactions, benign meningioma growth potentiation

Metabolism/Transport Effects

Based on estradiol and estrone: **Substrate** of CYP1A2 (major), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (minor), 2E1 (minor), 3A4 (major); Inhibits CYP1A2 (weak), 2C8 (weak); Induces CYP3A4 (weak)

Drug Interactions

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Somatropin: Estrogen Derivatives may diminish the therapeutic effect of Somatropin. Shown to be a concern with oral hormone replacement therapy in postmenopausal women. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (routine use increases estrogen level and risk of breast cancer). Ethanol may also increase the risk of osteoporosis.

Food: Folic acid absorption may be decreased.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca.

Test InteractionsPathologist should be advised of estrogen/progesterone therapy when specimens are submitted. Reduced response to metyrapone test.

Monitoring ParametersRoutine physical examination that includes blood pressure and Papanicolaou smear, breast exam, mammogram. Monitor for signs of endometrial cancer in female patients with uterus. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Prevention of osteoporosis: Bone density measurement

Uremic bleeding: Bleeding time

Reference Range

Children: <10 mcg/24 hours (SI: <35 µmol/day) (values at Mayo Medical Laboratories)

Adults:

Male: 15-40 mcg/24 hours (SI: 52-139 µmol/day)

Female:

Menstruating: 15-80 mcg/24 hours (SI: 52-277 µmol/day)

Postmenopausal: <20 mcg/24 hours (SI: <69 µmol/day)

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, increased potential for decreased levels/effects or increased potential for toxicity or thrombolic events). Assess results of annual gynecological exam, therapeutic effectiveness (dependent on rationale for use), need for continued therapy, and adverse effects (eg, thromboembolism, hypertension, edema, CNS changes) on a regular basis during therapy. **Note:** Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals and periodic assessment of risk:benefit should be made. Caution patients with diabetes to monitor glucose levels closely (may impair glucose tolerance). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. Remind patient about the importance of frequent self-breast exams and the need for annual gynecological exam. Determine that patient is not pregnant before starting therapy. Do not give to females of childbearing age unless patient is capable of complying with contraceptive use. Advise patient about appropriate contraceptive measures as appropriate.

Monitoring: Lab TestsRoutine physical examination that includes blood pressure and Papanicolaou smear. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Uremic bleeding: Bleeding time

Patient EducationDo not take any new medication during therapy without consulting prescriber. Use/apply exactly as directed and maintain prescribed cycles or term as prescribed. Routine use of alcohol may increase estrogen level and risk of breast cancer. Annual gynecologic exams and regular self-breast exams are important. If you have diabetes, monitor glucose levels closely (may impair glucose tolerance). You may experience nausea, vomiting, bloating, or abdominal pain (small, frequent meals may help); dizziness or mental depression (use caution when driving); rash; hair loss; headache; breast pain, increased/decreased libido, or enlargement/tenderness of breasts; or difficult/painful menstrual cycles. Report significant swelling of extremities; sudden acute pain in legs, chest, or abdomen; shortness of breath; severe headache or vomiting; CNS changes (dementia, mood disturbances, irritability, nervousness); sudden blindness; weakness or numbness of arm or leg; unusual vaginal bleeding; yellowing of skin or eyes; unusual bruising or bleeding; or other persistent adverse reactions. You may become intolerant to wearing contact lenses; notify prescriber if this occurs. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, vaginal:

Premarin®: 0.625 mg/g (42.5 g)

Injection, powder for reconstitution:

Premarin®: 25 mg [contains benzyl alcohol (in diluent), lactose 200 mg]

Tablet:

Premarin®: 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Cream (Premarin)

0.625 mg/g (42.5): $95.99

Tablets (Premarin)

0.3 mg (30): $56.99

0.45 mg (30): $51.99

0.625 mg (30): $50.97

0.9 mg (30): $49.99

1.25 mg (30): $49.99

Mechanism of ActionConjugated estrogens contain a mixture of estrone sulfate, equilin sulfate, 17 alpha-dihydroequilin, 17 alpha-estradiol and 17 beta-dihydroequilin. Estrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principle intracellular human estrogen and is more potent than estrone and estriol at the receptor level; it is the primary estrogen secreted prior to menopause. Following menopause, estrone and estrone sulfate are more highly produced. Estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone, and follicle-stimulating hormone through a negative feedback system; estrogen replacement reduces elevated levels of these hormones in postmenopausal women.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Protein binding: Binds to sex-hormone-binding globulin and albumin

Metabolism: Hepatic via CYP3A4; estradiol is converted to estrone and estriol; also undergoes enterohepatic recirculation (avoided with vaginal administration); estrone sulfite is the main metabolite in postmenopausal women

Half-life elimination: Total estrone: 27 hours

Time to peak, plasma: Total estrone: 7 hours

Excretion: Urine (primarily estriol, also as estradiol, estrone, and conjugates

Related Information

- Depression

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may decrease estrogen levels. The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Cardiovascular ConsiderationsIt is important to recognize that estrogens may induce or worsen hypertension. These problems are less severe with lower doses. Furthermore, estrogens may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on long-term estrogens undergo monitoring of blood pressure and avoid cigarette use.

Conjugated estrogens (alone or in combination with a progestin) should not be used to prevent coronary heart disease. The HERS trial found that women with coronary disease derived no cardiovascular protection compared to those treated with placebo. In the Women's Health Initiative trial, a conjugated estrogen/progestin combination did not offer protection against heart disease. No cardiovascular benefits were seen; in fact, more coronary heart disease was observed in the treatment group. Substantial evidence suggests that estrogen therapy increases bone mineralization and therefore may be of added benefit in patients with osteoporosis. Estrogen also has a favorable effect on lipids (decreases total cholesterol and LDL, increases HDL) but increases triglycerides. Therapy should be initiated after careful evaluation of risk:benefit for therapy.

Index TermsC.E.S.; CE; CEE; Conjugated Estrogen; Estrogenic Substances, Conjugated

References

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Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial," *JAMA*, 2003, 289:2651-62.

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International Brand NamesC.E.S (MX); Premarin (MX)

Estrogens (Esterified) and Methyltestosterone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Estratest® may be confused with Eskalith®, Estratab®, Estratest® H.S.

Estratest® H.S. may be confused with Eskalith®, Estratab®, Estratest®

Pronunciation(ES troe jenz es TER i fied & meth il tes TOS te rone)

U.S. Brand NamesCovaryx™; Covaryx™ HS; E.E.M.T. D.S.; E.E.M.T. H.S.; Estratest®; Estratest® H.S.; Syntest D.S. [DSC]; Syntest H.S. [DSC]

Canadian Brand NamesEstratest®

Pharmacologic CategoryEstrogen and Progestin Combination

Use: Labeled IndicationsVasomotor symptoms of menopause

Dosing: AdultsMenopause (vasomotor symptoms): Oral: Lowest dose that will control symptoms should be chosen, normally given 3 weeks on and 1 week off

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsShould be taken with food at same time each day.

ContraindicationsHypersensitivity to estrogens, methyltestosterone, or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); carcinoma of the breast, except in appropriately selected patients being treated for metastatic disease; estrogen-dependent tumor; hepatic dysfunction or disease; pregnancy; breast-feeding

Allergy Considerations

- Androgen Allergy
- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.
- Dementia: See “Concerns related to adverse effects” below.
- Endometrial carcinoma: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Breast cancer: Estrogens may increase the risk of breast cancer. An increased risk of invasive breast cancer was observed in postmenopausal women using CEE in combination with MPA; a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy. Estrogen use may lead to severe hypercalcemia in patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs.
- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in women ≥65 years of age taking CEE alone or in combination with MPA.
- Endometrial cancer: **[U.S. Boxed Warning]: Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women**. Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy.
- Lipid effects: Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent coronary heart disease.** Use caution with cardiovascular disease or dysfunction. May increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA). Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CEE (eg, for prostate cancer).

- Cholestatic jaundice: Use caution with history of cholestatic jaundice associated with past estrogen use or pregnancy.

- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes, or renal dysfunction.

- Gallbladder disease: Use with caution in patients with gallbladder disease.

- Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.

- Hypocalcemia: Use with caution in patients with severe hypocalcemia.

- Porphyria: Use with caution in patients with porphyria.

- SLE: Use with caution in patients with SLE.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children. Prior to puberty, estrogens may cause premature closure of the epiphyses, premature breast development in girls, or gynecomastia in boys. Vaginal bleeding and vaginal cornification may also be induced in girls.

- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- Risks vs. benefits: Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.

Pregnancy Risk FactorX
Pregnancy ConsiderationsRefer to Estrogens (Esterified) monograph.
Adverse Reactions1% to 10%:

Cardiovascular: Increase in blood pressure, edema, thromboembolic disorder

Central nervous system: Depression, headache

Dermatologic: Chloasma, melasma

Endocrine & metabolic: Breast tenderness, change in menstrual flow, hypercalcemia

Gastrointestinal: Nausea, vomiting

Hepatic: Cholestatic jaundice

Metabolism/Transport EffectsBased on estrone: **Substrate** of CYP1A2 (major), 2B6 (minor), 2C9 (minor), 2E1 (minor), 3A4 (major)
Drug Interactions

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Androgens may enhance the hepatotoxic effect of CycloSPORINE. Androgens may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Somatropin: Estrogen Derivatives may diminish the therapeutic effect of Somatropin. Shown to be a concern with oral hormone replacement therapy in postmenopausal women. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Androgens may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Monitoring ParametersYearly physical examination that includes blood pressure and Papanicolaou smear, breast exam, mammogram. Monitor for signs of endometrial cancer. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Monitoring: Lab TestsYearly Papanicolaou smear, mammogram. Monitor for signs of endometrial cancer. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: Esterified estrogens 1.25 mg and methyltestosterone 2.5 mg [contains tartrazine]; esterified estrogen 0.625 mg and methyltestosterone 1.25 mg

Covaryx™: Esterified estrogens 1.25 mg and methyltestosterone 2.5 mg [contains tartrazine]

Covaryx™ H.S.: Esterified estrogens 1.25 mg and methyltestosterone 2.5 mg [contains tartrazine]

Estratest®: Esterified estrogen 1.25 mg and methyltestosterone 2.5 mg

Estratest® H.S.: Esterified estrogen 0.625 mg and methyltestosterone 1.25 mg

E.E.M.T. D.S., Syntest D.S. [DSC]: Esterified estrogen 1.25 mg and methyltestosterone 2.5 mg

E.E.M.T. H.S., Syntest H.S. [DSC]: Esterified estrogen 0.625 mg and methyltestosterone 1.25 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Est Estrogens-Methyltest DS)

1.25-2.5 mg (30): $46.96

Tablets (Est Estrogens-Methyltest HS)

0.625-1.25 mg (30): $43.76

Tablets (Estratest)

1.25-2.5 mg (30): $113.18

Tablets (Estratest H.S.)

0.625-1.25 mg (30): $97.80

Mechanism of Action

Conjugated estrogens: Activate estrogen receptors (DNA protein complex) located in estrogen-responsive tissues. Once activated, regulate transcription of certain genes leading to observed effects.

Testosterone: Increases synthesis of DNA, RNA, and various proteins in target tissues

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may decrease the effects of estrogens; estrogens may affect metabolism of benzodiazepines; monitor for clinical effect. The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Index TermsConjugated Estrogen and Methyltestosterone; Esterified Estrogen and Methyltestosterone

References

Shumaker SA, Legault C, Rapp SR, et al, "WHIMS Investigators. Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial," *JAMA*, 2003, 289(20):2651-62. [PubMed 12771112]

Rossouw JE, Anderson GL, Prentice RL, et al, "Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principle Results From the Women's Health Initiative Randomized Controlled Trial,"*JAMA*, 2002, 288(3):321-33.[PubMed 12117397]

U.S. Food and Drug Administration, Department of Health and Human Services, "FDA Approves New Labels for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women Following Review of Women's Health Initiative Data," January 8, 2003. Available at: http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#prempr. Accessed April 17, 2003.

International Brand NamesEstratest (CA)

Estrogens (Esterified)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

> Estratab® may be confused with Estratest®, Estratest® H.S.

Pronunciation(ES troe jenz, es TER i fied)

U.S. Brand NamesMenest®

Canadian Brand NamesEstratab®; Menest®

Pharmacologic CategoryEstrogen Derivative

Use: Labeled IndicationsTreatment of moderate to severe vasomotor symptoms associated with menopause; treatment of vulvar and vaginal atrophy; hypoestrogenism (due to hypogonadism, castration, or primary ovarian failure); prostatic cancer (palliation); breast cancer (palliation); osteoporosis (prophylaxis, in women at significant risk only)

Dosing: Adults

Prostate cancer (palliation): Oral: 1.25-2.5 mg 3 times/day

Female hypogonadism: Oral: 2.5-7.5 mg of estrogen daily for 20 days followed by a 10-day rest period. Administer cyclically (3 weeks on and 1 week off). If bleeding does not occur by the end of the 10-day period, repeat the same dosing schedule; the number of courses dependent upon the responsiveness of the endometrium. If bleeding occurs before the end of the 10-day period, begin an estrogen-progestin cyclic regimen of 2.5-7.5 mg esterified estrogens daily for 20 days. During the last 5 days of estrogen therapy, give an oral progestin. If bleeding occurs before regimen is concluded, discontinue therapy and resume on the fifth day of bleeding.

Menopause, moderate to severe vasomotor symptoms: Oral: 1.25 mg/day administered cyclically (3 weeks on and 1 week off). If patient has not menstruated within the last 2 months or more, cyclic administration is started arbitrary. If the patient is menstruating, cyclical administration is started on day 5 of the bleeding. For short-term use only and should be discontinued as soon as possible. Re-evaluate at 3- to 6-month intervals for tapering or discontinuation of therapy.

Atopic vaginitis and kraurosis vulvae: Oral: 0.3 to ≥1.25 mg/day, depending on the tissue response of the individual patient. Administer cyclically. For short-term use only and should be discontinued as soon as possible. Re-evaluate at 3- to 6-month intervals for tapering or discontinuation of therapy.

Breast cancer (palliation): Oral: 10 mg 3 times/day for at least 3 months

Osteoporosis in postmenopausal women: Oral: Initial: 0.3 mg/day and increase to a maximum daily dose of 1.25 mg/day; initiate therapy as soon as possible after menopause; cyclically or daily, depending on medical assessment of patient. Monitor patients with an intact uterus for signs of endometrial cancer; rule out malignancy if unexplained vaginal bleeding occurs

Female castration and primary ovarian failure: Oral: 1.25 mg/day, cyclically. Adjust dosage upward or downward, according to the severity of symptoms and patient response. For maintenance, adjust dosage to lowest level that will provide effective control.

Dosing: ElderlyRefer to adult dosing. A higher incidence of stroke and invasive breast cancer were observed in women >75 years in a WHI substudy using conjugated equine estrogen.

Dosing: Hepatic Impairment

Mild to moderate liver impairment: Dosage reduction of estrogens is recommended.

Severe liver impairment: **Not recommended**.

Dietary ConsiderationsShould be taken with food at same time each day. Ensure adequate calcium and vitamin D intake when used for the prevention of osteoporosis.

StorageStore below 30°C (86°F). Protect from moisture.

ContraindicationsHypersensitivity to estrogens or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); carcinoma of the breast, except in appropriately selected patients being treated for metastatic disease; estrogen-dependent tumor; hepatic dysfunction or disease; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.

- Dementia: See "Concerns related to adverse effects" below.
- Endometrial carcinoma: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Breast cancer: Estrogens may increase the risk of breast cancer. An increased risk of invasive breast cancer was observed in postmenopausal women using CEE in combination with MPA; a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy. Estrogen use may lead to severe hypercalcemia in patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs.
- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in women ≥65 years of age taking CEE alone or in combination with MPA.
- Endometrial carcinoma: **[U.S. Boxed Warning]: Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women.** Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy. Consider adding a progestin in women with residual endometriosis posthysterectomy.
- Lipid effects: Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent coronary heart disease.** Use caution with cardiovascular disease or dysfunction. May increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA). Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CEE (eg, for prostate cancer).
- Cholestatic jaundice: Use caution with history of cholestatic jaundice associated with past estrogen use or pregnancy.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.
- Gallbladder disease: Use with caution in patients with gallbladder disease.
- Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.
- Hypocalcemia: Use with caution in patients with severe hypocalcemia.
- Porphyria: Use with caution in patients with porphyria.
- SLE: Use with caution in patients with SLE.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children. Prior to puberty, estrogens may cause premature closure of the epiphyses, premature breast development in girls or gynecomastia in boys. Vaginal bleeding and vaginal cornification may also be induced in girls.
- Surgical patients: Whenever possible, estrogens should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- Osteoporosis use: When used solely for prevention of osteoporosis in women at significant risk, nonestrogen treatment options should be considered.
- Risks vs. benefits: Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.
- Vulvar and vaginal atrophy use: When used solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should be considered.

Geriatric ConsiderationsBefore prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible side effects and the return of menstrual bleeding (when cycled with a progestin), and be involved in the decision to prescribe. A higher incidence of stroke and invasive breast cancer were observed in women >75 years in a WHI substudy using conjugated equine estrogen. Oral therapy may be more convenient for vaginal atrophy and urinary incontinence.

Pregnancy Risk FactorX

Pregnancy ConsiderationsIncreased risk of fetal reproductive tract disorders and other birth defects; do not use during pregnancy.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsThe AAP considers ethinyl estradiol, an estrogen derivative, to be "usually compatible" with breast-feeding. Estrogen has been shown to decrease the quantity and quality of human milk; use only if clearly needed; monitor the growth of the infant closely.

Adverse ReactionsFrequency not defined.

Cardiovascular: Edema, hypertension, venous thromboembolism

Central nervous system: Dizziness, headache, mental depression, migraine

Dermatologic: Chloasma, erythema multiforme, erythema nodosum, hemorrhagic eruption, hirsutism, loss of scalp hair, melasma

Endocrine & metabolic: Breast enlargement, breast tenderness, libido (changes in), increased thyroid-binding globulin, increased total thyroid hormone (T_4), increased serum triglycerides/phospholipids, increased HDL-cholesterol, decreased LDL-cholesterol, impaired glucose tolerance, hypercalcemia

Gastrointestinal: Abdominal cramps, bloating, cholecystitis, cholelithiasis, gallbladder disease, nausea, pancreatitis, vomiting, weight gain/loss

Genitourinary: Alterations in frequency and flow of menses, changes in cervical secretions, endometrial cancer, increased size of uterine leiomyomata, vaginal candidiasis

Hematologic: Aggravation of porphyria, decreased antithrombin III and antifactor Xa, increased levels of fibrinogen, increased platelet aggregability and platelet count; increased prothrombin and factors VII, VIII, IX, X

Hepatic: Cholestatic jaundice

Neuromuscular & skeletal: Chorea

Ocular: Contact lens intolerance, corneal curvature steepening

Respiratory: Pulmonary thromboembolism

Miscellaneous: Carbohydrate intolerance

Metabolism/Transport EffectsBased on estrone: **Substrate** of CYP1A2 (major), 2B6 (minor), 2C9 (minor), 2E1 (minor), 3A4 (major)

Drug Interactions

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Somatropin: Estrogen Derivatives may diminish the therapeutic effect of Somatropin. Shown to be a concern with oral hormone replacement therapy in postmenopausal women. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (routine use increases estrogen level and risk of breast cancer). Ethanol may also increase the risk of osteoporosis.

Food: Folic acid absorption may be decreased.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca.

Test InteractionsPathologist should be advised of estrogen/progesterone therapy when specimens are submitted. Reduced response to metyrapone test.

Monitoring ParametersYearly physical examination that includes blood pressure and Papanicolaou smear, breast exam, mammogram. Monitor for signs of endometrial cancer in female patients with uterus. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Prevention of osteoporosis: Bone density measurement

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, increased potential for decreased levels/effects or increased potential for toxicity or thrombolic events). Assess results of annual gynecological exam, therapeutic effectiveness (dependent on rationale for use), need for continued treatment, and adverse effects (eg, thromboembolism, hypertension, edema, CNS changes) on a regular basis during therapy. **Note:** Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals and periodic assessment of risk:benefit should be made. Caution patients with diabetes to monitor glucose levels closely (may impair glucose tolerance). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. Remind patient about the importance of frequent self-breast exams and the need for annual gynecological exam. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to females of childbearing age unless patient is capable of complying with contraceptive use. Advise patient about contraceptive measures as appropriate.

Monitoring: Lab TestsYearly Papanicolaou smear, mammogram. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take exactly as directed and maintain prescribed cycles or term as prescribed. Routine use of alcohol may increase estrogen level and risk of breast cancer. Annual gynecologic and regular self-breast exams are important. If you have diabetes, monitor glucose levels closely (may impair glucose tolerance). You may experience nausea, vomiting or abdominal pain (small, frequent meals may help); dizziness or mental depression (use caution when driving); rash; hair loss; headache; or breast pain, increased/decreased libido, or enlargement/tenderness of breasts. difficult/painful menstrual cycles. Report significant swelling of extremities; sudden acute pain in legs or calves, chest, or abdomen; shortness of breath; severe headache or vomiting; sudden blindness; weakness or numbness of arm or leg; unusual vaginal bleeding; yellowing of skin or eyes; unusual bruising or bleeding, or other persistent adverse reactions. You may become intolerant to wearing contact lenses, notify prescriber if this occurs. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. This medication may cause fetal defects and should not be used during pregnancy. Consult prescriber if breast-feeding.

Dosage FormsTablet: 0.3 mg, 0.625 mg, 1.25 mg, 2.5 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Menest)

0.3 mg (30): $27.99

0.625 mg (30): $32.69

1.25 mg (30): $41.15

2.5 mg (30): $61.72

Mechanism of ActionEsterified estrogens contain a mixture of estrogenic substances; the principle component is estrone. Preparations contain 75% to 85% sodium estrone sulfate and 6% to 15% sodium equilin sulfate such that the total is not <90%. Estrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principle intracellular human estrogen and is more potent than estrone and estriol at the receptor level; it is the primary estrogen secreted prior to menopause. In males and following menopause in females, estrone and estrone sulfate are more highly produced. Estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone, and follicle-stimulating hormone through a negative feedback system; estrogen replacement reduces elevated levels of these hormones.

Pharmacodynamics/Kinetics

Absorption: Readily

Metabolism: Rapidly hepatic to estrone sulfate, conjugated and unconjugated metabolites; first-pass effect

Excretion: Urine (as unchanged drug and as glucuronide and sulfate conjugates)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentThe Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Cardiovascular ConsiderationsIt is important to recognize that estrogens may induce or worsen hypertension. These problems are less severe with lower doses. Furthermore, estrogens may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on long-term estrogens undergo monitoring of blood pressure and avoid cigarette use.

Conjugated estrogens (alone or in combination with a progestin) should not be used to prevent coronary heart disease. The HERS trial found that women with coronary disease derived no cardiovascular protection compared to those treated with placebo. In the Women's Health Initiative trial, a conjugated estrogen/progestin combination did not offer protection against heart disease. No cardiovascular benefits were seen; in fact, more coronary heart disease was observed in the treatment group. Substantial evidence suggests that estrogen therapy increases bone mineralization and therefore may be of added benefit in patients with osteoporosis. Estrogen also has a favorable effect on lipids (decreases total cholesterol and LDL, increases HDL) but increases triglycerides. Therapy should be initiated after careful evaluation of risk:benefit for therapy.

Index TermsEsterified Estrogens

References

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Hulley S, Grady D, Bush T, et al, “Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group,” *JAMA*, 1998, 280(7):605-13. [PubMed 9718051]

Rossouw JE, Anderson GL, Prentice RL, et al, “Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principle Results From the Women's Health Initiative Randomized Controlled Trial,”*JAMA*, 2002, 288(3):321-33.[PubMed 12117397]

Shumaker SA, Legault C, Rapp SR, et al, “WHIMS Investigators. Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial,” *JAMA*, 2003, 289(20):2651-62. [PubMed 12771112]

Winship KA, “Unopposed Oestrogens,” *Adverse Drug React Acute Poisoning Rev*, 1987, 6(1):37-66. [PubMed 3303864]

U.S. Food and Drug Administration, Department of Health and Human Services, “FDA Approves New Labels for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women Following Review of Women's Health Initiative Data,” January 8, 2003. Available at: http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#prempr. Accessed January 9, 2003.

International Brand NamesEstratab (CA); Menest (AR, CA)

Estropipate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ES troe pih pate)

U.S. Brand NamesOgen®; Ortho-Est®

Canadian Brand NamesOgen®

Pharmacologic CategoryEstrogen Derivative

Use: Labeled IndicationsTreatment of moderate to severe vasomotor symptoms associated with menopause; treatment of vulvar and vaginal atrophy; hypoestrogenism (due to hypogonadism, castration, or primary ovarian failure); osteoporosis (prophylaxis, in women at significant risk only)

Dosing: Adults

Menopause, moderate to severe vasomotor symptoms: Oral: Usual dosage range: 0.75-6 mg estropipate daily. Use the lowest dose and regimen that will control symptoms, and discontinue as soon as possible. Attempt to discontinue or taper medication at 3- to 6-month intervals. If a patient with vasomotor symptoms has not menstruated within the last ≥2 months, start the cyclic administration arbitrarily. If the patient has menstruated, start cyclic administration on day 5 of bleeding.

Female hypogonadism: Oral: 1.5-9 mg estropipate daily for the first 3 weeks, followed by a rest period of 8-10 days; use the lowest dose and regimen that will control symptoms. Repeat if bleeding does not occur by the end of the rest period. The duration of therapy necessary to product the withdrawal bleeding will vary according to the responsiveness of the endometrium. If satisfactory withdrawal bleeding does not occur, give an oral progestin in addition to estrogen during the third week of the cycle.

Female castration or primary ovarian failure: Oral: 1.5-9 mg estropipate daily for the first 3 weeks of a theoretical cycle, followed by a rest period of 8-10 days; use the lowest dose and regimen that will control symptoms

Osteoporosis prophylaxis (females): Oral: 0.75 mg estropipate daily for 25 days of a 31-day cycle

Atrophic vaginitis or kraurosis vulvae: Oral: 0.75-6 mg estropipate daily; administer cyclically. Use the lowest dose and regimen that will control symptoms; discontinue as soon as possible.

Dosing: ElderlyRefer to adult dosing. A higher incidence of stroke and invasive breast cancer were observed in women >75 years in a WHI substudy using conjugated equine estrogen.

Dosing: Hepatic Impairment

Mild to moderate liver impairment: Dosage reduction of estrogens is recommended.

Severe liver impairment: **Not recommended.**

Dietary ConsiderationsEnsure adequate calcium and vitamin D intake when used for the prevention of osteoporosis.

StorageTablet: Store below 25°C (77°F).

ContraindicationsHypersensitivity to estrogens or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); carcinoma of the breast, except in appropriately selected patients being treated for metastatic disease; estrogen-dependent tumor; hepatic dysfunction or disease; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.
- Dementia: See “Concerns related to adverse effects” below.
- Endometrial carcinoma: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Breast cancer: Estrogens may increase the risk of breast cancer. An increased risk of invasive breast cancer was observed in postmenopausal women using CEE in combination with MPA; a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy. Estrogen use may lead to severe hypercalcemia in patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs.
- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in women ≥65 years of age taking CEE alone or in combination with MPA.

- Endometrial carcinoma: **[U.S. Boxed Warning]: Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women.** Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy. Consider adding a progestin in women with residual endometriosis posthysterectomy.

- Lipid effects: Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.

- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent coronary heart disease.** Use caution with cardiovascular disease or dysfunction. May increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA). Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CEE (eg, for prostate cancer).

- Cholestatic jaundice: Use caution with history of cholestatic jaundice associated with past estrogen use or pregnancy.

- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.

- Gallbladder disease: Use with caution in patients with gallbladder disease.

- Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.

- Hypocalcemia: Use with caution in patients with severe hypocalcemia.

- Porphyria: Use with caution in patients with porphyria.

- SLE: Use with caution in patients with SLE.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children. Prior to puberty, estrogens may cause premature closure of the epiphyses, premature breast development in girls or gynecomastia in boys. Vaginal bleeding and vaginal cornification may also be induced in girls.

- Surgical patients: Whenever possible, estrogens should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precaution:

- Osteoporosis use: When used solely for prevention of osteoporosis in women at significant risk, nonestrogen treatment options should be considered.

- Risks vs. benefits: Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.

- Vulvar and vaginal atrophy use: When used solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should be considered.

Pregnancy Risk FactorX

Pregnancy ConsiderationsIncreased risk of fetal reproductive tract disorders and other birth defects; do not use during pregnancy.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsThe AAP considers ethinyl estradiol, an estrogen derivative, to be “usually compatible” with breast-feeding. Estrogen has been shown to decrease the quantity and quality of human milk; monitor the growth of the infant closely.

Adverse ReactionsFrequency not defined.

Cardiovascular: Edema, hypertension, venous thromboembolism

Central nervous system: Dizziness, headache, mental depression, migraine

Dermatologic: Chloasma, erythema multiforme, erythema nodosum, hemorrhagic eruption, hirsutism, loss of scalp hair, melasma

Endocrine & metabolic: Breast enlargement, breast tenderness, libido (changes in), increased thyroid-binding globulin, increased total thyroid hormone (T_4), increased serum triglycerides/phospholipids, increased HDL-cholesterol, decreased LDL-cholesterol, impaired glucose tolerance, hypercalcemia

Gastrointestinal: Abdominal cramps, bloating, cholecystitis, cholelithiasis, gallbladder disease, nausea, pancreatitis, vomiting, weight gain/loss

Genitourinary: Alterations in frequency and flow of menses, changes in cervical secretions, endometrial cancer, increased size of uterine leiomyomata, vaginal candidiasis

Hematologic: Aggravation of porphyria, decreased antithrombin III and antifactor Xa, increased levels of fibrinogen, increased platelet aggregability and platelet count; increased prothrombin and factors VII, VIII, IX, X

Hepatic: Cholestatic jaundice

Neuromuscular & skeletal: Chorea

Ocular: Ocular: Contact lens intolerance, corneal curvature steepening

Respiratory: Pulmonary thromboembolism

Miscellaneous: Carbohydrate intolerance

Metabolism/Transport EffectsBased on estrone: **Substrate** of CYP1A2 (major), 2B6 (minor), 2C9 (minor), 2E1 (minor), 3A4 (major)

Drug Interactions

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Somatropin: Estrogen Derivatives may diminish the therapeutic effect of Somatropin. Shown to be a concern with oral hormone replacement therapy in postmenopausal women. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Routine use increases estrogen level and risk of breast cancer; avoid ethanol. Ethanol may also increase the risk of osteoporosis.

Food: Folic acid absorption may be decreased.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca.

Test InteractionsPathologist should be advised of estrogen/progesterone therapy when specimens are submitted. Reduced response to metyrapone test.

Monitoring ParametersYearly physical examination that includes blood pressure and Papanicolaou smear, breast exam, mammogram. Monitor for signs of endometrial cancer in female patients with uterus. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Monitor for loss of vision, sudden onset of proptosis, diplopia, migraine; signs and symptoms of thromboembolic disorders; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Prevention of osteoporosis: Bone density measurement

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, increased potential for decreased levels/effects or increased potential for toxicity or thromboembolic events). Assess results of annual gynecological exam, therapeutic effectiveness (dependent on rationale for use), need for continued therapy, and adverse effects (eg, thromboembolism, hypertension, edema, CNS changes) on a regular basis during therapy. **Note:** Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals and periodic assessment of risk:benefit should be made. Caution patients with diabetes to monitor glucose levels closely (may impair glucose tolerance). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. Remind patient about the importance of frequent self-breast exams and the need for annual gynecological exam. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to females of childbearing age unless patient is capable of complying with barrier contraceptive use. Advise patient about contraceptive measures as appropriate.

Monitoring: Lab TestsYearly Papanicolaou smear, mammogram

Patient EducationDo not take any new medication during therapy without consulting prescriber. Use/apply exactly as directed and maintain prescribed cycles or term as prescribed. Routine use of alcohol may increase estrogen level and risk of breast cancer. Annual gynecologic exams and regular self-breast exams are important. If you have diabetes, monitor glucose levels closely (may impair glucose tolerance). You may experience nausea, vomiting or abdominal pain (small, frequent meals may help); dizziness or mental depression (use caution when driving); rash; hair loss; headache; or breast pain, change in libido, enlargement and/or tenderness of breasts; difficult or painful menstrual cycles. Report significant swelling of extremities; sudden acute pain in legs or calves, chest, or abdomen; shortness of breath; severe headache or vomiting; sudden blindness; weakness or numbness of arm or leg; unusual vaginal bleeding; yellowing of skin or eyes; unusual bruising or bleeding, or other persistent adverse reactions. You may become intolerant to wearing contact lenses, notify prescriber if this occurs. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. This medication may cause fetal defects and should not be used during pregnancy. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 0.625 mg [estropipate 0.75 mg]; 1.25 mg [estropipate 1.5 mg]; 2.5 mg [estropipate 3 mg]

Ogen®: 0.625 mg [estropipate 0.75 mg]; 1.25 mg [estropipate 1.5 mg]; 2.5 mg [estropipate 3 mg]

Ortho-Est®: 0.625 mg [estropipate 0.75 mg]; 1.25 mg [estropipate 1.5 mg]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Estropipate)

0.75 mg (30): $12.99

1.5 mg (30): $15.99

3 mg (30): $24.99

Tablets (Ogen 0.625)

0.75 mg (30): $39.99

Tablets (Ogen 1.25)

1.5 mg (30): $52.99

Tablets (Ogen 2.5)

3 mg (30): $82.99

Tablets (Ortho-Est 0.625)

0.75 mg (30): $18.76

Tablets (Ortho-Est 1.25)

1.5 mg (30): $24.99

Mechanism of ActionEstrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principle intracellular human estrogen and is more potent than estrone and estriol at the receptor level; it is the primary estrogen secreted prior to menopause. In males and following menopause in females, estrone and estrone sulfate are more highly produced. Estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone, and follicle-stimulating hormone through a negative feedback system; estrogen replacement reduces elevated levels of these hormones. Estropipate is prepared from purified crystalline estrone that has been solubilized as the sulfate and stabilized with piperazine.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Metabolism: Hepatic and in target tissues; first-pass effect

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentThe Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Index TermsOrtho Est; Piperazine Estrone Sulfate

References

Shumaker SA, Legault C, Rapp SR, et al, “WHIMS Investigators. Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial,” *JAMA*, 2003, 289(20):2651-62. [PubMed 12771112]

Rossouw JE, Anderson GL, Prentice RL, et al, “Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principle Results From the Women's Health Initiative Randomized Controlled Trial,”*JAMA*, 2002, 288(3):321-33.[PubMed 12117397]

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International Brand NamesGenoral (AU); Harmogen (CH, GB, IE); Ogen (AU, BB, BM, BS, BZ, GY, ID, JM, NL, SR, TT); Ortho-Est (ZA)

Eszopiclone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Lunesta® may be confused with Neulasta®

Pronunciation(es zoe PIK lone)
U.S. Brand NamesLunesta®
Pharmacologic Category[Hypnotic, Nonbenzodiazepine]
Use: Labeled IndicationsTreatment of insomnia
Use: DentalNot established at this time
Dosing: Adults

Insomnia: Oral: Initial: 2 mg immediately before bedtime (maximum dose: 3 mg)

Concurrent use with strong CYP3A4 inhibitor: 1 mg immediately before bedtime; if needed, dose may be increased to 2 mg

Dosing: Elderly

Difficulty **falling** asleep: Initial: 1 mg before immediately bedtime; maximum dose: 2 mg.

Difficulty **staying** asleep: 2 mg immediately before bedtime.

Dosing: Renal ImpairmentNo adjustment required.
Dosing: Hepatic Impairment

Mild-to-moderate: Use with caution; dosage adjustment unnecessary

Severe: Initial dose: 1 mg; maximum dose: 2 mg

Administration: OralBecause of the rapid onset of action, eszopiclone should be administered immediately prior to bedtime or after the patient has gone to bed and is having difficulty falling asleep. Do not take with, or immediately following, a high-fat meal. Do not crush or break tablet.
Dietary ConsiderationsAvoid taking after a heavy meal; may delay onset.
StorageStore at controlled room temperature of 25°C (77°F).
RestrictionsC-IV

An FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsThere are no contraindications listed within the manufacturer's labeling.
Allergy Considerations

- Eszopiclone Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Abnormal thinking/behavioral changes: Hypnotics/sedatives have been associated with abnormal thinking and behavior changes including decreased inhibition, aggression, bizarre behavior, agitation, hallucinations, and depersonalization. These changes may occur unpredictably and may indicate previously unrecognized psychiatric disorders; evaluate appropriately.
- Amnesia: Can occur, do not take unless a full night's sleep and clearance of the drug from the body are possible.
- CNS depression: May cause CNS depression impairing physical and mental capabilities; patients must be cautioned about performing tasks, which require mental alertness (operating machinery or driving).
- Hypersensitivity reactions: Postmarketing studies have indicated that the use of hypnotic/sedative agents for sleep has been associated with hypersensitivity reactions including anaphylaxis as well as angioedema.
- Sleep-related activities: An increased risk for hazardous sleep-related activities such as sleep-driving; cooking and eating food, and making phone calls while asleep have also been noted.

Disease-related concerns:

- Depression: Use with caution in patients with depression; worsening of depression, including suicidal ideation has been reported with the use of hypnotics. Intentional overdose may be an issue in this population; prescribe least amount of medication needed.
- Drug abuse: Use with caution in patients with a history of drug dependence.
- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment required with severe impairment.
- Respiratory disease: Use with caution in patients with respiratory compromise, COPD or sleep apnea.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.
- CYP3A4 inhibitors: Use with caution in patients taking strong CYP3A4 inhibitors.

Special populations:

- Elderly: Use with caution in the elderly; dosage adjustment recommended.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Symptomatic treatment of insomnia should be initiated only after careful evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric and/or medical illness.
- Duration of therapy: Tolerance, as assessed by sleep measurement, did not develop over 6 months of use.
- Rapid onset: Because of the rapid onset of action, administer immediately prior to bedtime or after the patient has gone to bed and is having difficulty falling asleep.
- Withdrawal: Abrupt discontinuance may lead to withdrawal symptoms.

Geriatric ConsiderationsIn subjects >65 years of age, the AUC was increased by 41%. The manufacturer reports that in studies, the pattern of adverse reactions in elderly subjects was not different from that seen in younger adults.
Pregnancy Risk FactorC
Pregnancy ConsiderationsNo evidence of teratogenicity in animal models (high dose). There are no adequate or well-controlled studies in pregnant women; use only if clearly needed.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%:

Central nervous system: Headache (15% to 21%)

Gastrointestinal: Unpleasant taste (8% to 34%)

1% to 10%:

Cardiovascular: Chest pain, peripheral edema

Central nervous system: Somnolence (8% to 10%), dizziness (5% to 7%), pain (4% to 5%), nervousness (up to 5%), depression (1% to 4%), confusion (up to 3%), hallucinations (1% to 3%), anxiety (1% to 3%), abnormal dreams (1% to 3%), migraine

Dermatologic: Rash (3% to 4%), pruritus (1% to 4%)

Endocrine & metabolic: Libido decreased (up to 3%), dysmenorrhea (up to 3%), gynecomastia (males up to 3%)

Gastrointestinal: Xerostomia (3% to 7%), dyspepsia (2% to 6%), nausea (4% to 5%), diarrhea (2% to 4%), vomiting (up to 3%)

Genitourinary: Urinary tract infection (up to 3%)

Neuromuscular & skeletal: Neuralgia (up to 3%)

Miscellaneous: Infection (5% to 10%), viral infection (3%), accidental injury (up to 3%)

<1% (Limited to life-threatening or important): Abnormal gait, agitation, alopecia, allergic reaction, amenorrhea, anorexia, asthma, ataxia, breast enlargement, breast neoplasm, bronchitis, cholelithiasis, colitis, conjunctivitis, contact dermatitis, cystitis, dehydration, diaphoresis, dry eyes, dyspnea, dysphagia, dysuria, eczema, emotional lability, epistaxis, erythema multiforme, euphoria, facial edema, fever, gout, heat stroke, hematuria, hepatitis, hepatomegaly, herpes zoster, hostility, hypercholesterolemia, hypertension, hypokalemia, kidney calculus, kidney pain, liver damage, maculopapular rash, malaise, mastitis, melena, memory impairment, menorrhagia, myasthenia, mydriasis, myopathy, neck rigidity, neuritis, neuropathy, neurosis, nystagmus, oliguria, paresthesia, photophobia, photosensitivity, pyelonephritis, rectal hemorrhage, reflexes decreased, stomach ulcer, swelling, thrombophlebitis, tinnitus, tongue edema, tremor, twitching, ulcerative stomatitis, urinary frequency, urinary incontinence, urticaria, urethritis, vaginal hemorrhage, vaginitis, vestibular disorder, vertigo, vesiculobullous rash

Postmarketing and/or case reports: Anaphylaxis, angioedema, complex sleep-related behavior (sleep-driving, cooking or eating food, making phone calls)

Metabolism/Transport Effects**Substrate** of CYP2E1 (minor), 3A4 (major)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Eszopiclone. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Flumazenil: May diminish the sedative effect of Hypnotics (Nonbenzodiazepine). *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Use caution with concurrent use. Effects are additive and may decrease psychomotor function.

Food: Onset of action may be reduced if taken with or immediately after a heavy meal.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Nursing: Physical Assessment/MonitoringEvaluate potential causes of insomnia prior to initiating medication. Assess effectiveness and interactions of other medications patient may be taking Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance. After long-term use, taper dosage slowly when discontinuing. Be alert to possibility of anaphylaxis any time during therapy. Monitor for CNS depression, abnormal thinking, and behavior changes. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor for effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationUse exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol or other prescription or OTC medications (especially, pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Take immediately prior to bedtime (quick onset) or when having difficulty falling asleep. Do not use unless you are able to get 8 or more hours of sleep before you must be active again. Swallow whole, do not crush or break tablet. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, lightheadedness, or difficulty with coordination (use caution when driving or engaging in tasks requiring alertness until response to drug is known); headache, or unpleasant taste. Report CNS changes (confusion, depression, increased sedation, excitation, severe headache, abnormal thinking, insomnia, or nightmares); respiratory difficulty; or unusual swelling, especially on face or neck. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 1 mg, 2 mg, 3 mg

Generic AvailableNo

ManufacturerSepracor Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Lunesta)

1 mg (30): $167.00

2 mg (30): $168.77

3 mg (30): $168.78

Mechanism of ActionMay interact with GABA-receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors.

Pharmacodynamics/Kinetics

Absorption: Rapid; high-fat/heavy meal may delay absorption

Protein binding: 52% to 59%

Metabolism: Hepatic via oxidation and demethylation (CYP2E1, 3A4); 2 primary metabolites; one with activity less than parent.

Half-life elimination: ~6 hours; Elderly (≥65 years): ~9 hours

Time to peak, plasma: ~1 hour

Excretion: Urine (up to 75%, primarily as metabolites; <10% as parent drug)

Related Information

- CMS: Long-Term Care Facility Thresholds
- Nonbenzodiazepine Anxiolytics and Hypnotics

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Unpleasant taste and xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep. Eszopiclone may be associated with a lower potential for abuse compared to benzodiazepines.

References

Krystal AD, Walsh JK, Laska E, et al, “Sustained Efficacy of Eszopiclone Over 6 Months of Nightly Treatment: Results of a Randomized, Double-Blind, Placebo-Controlled Study in Adults With Chronic Insomnia,” *Sleep*, 2003, 26(7):793-9.[PubMed 14655910]

Etanercept

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Tumor Necrosis Factor: Alpha Blockers Associated with Unrecognized Invasive Fungal Infections - September 4, 2008

The U.S. Food and Drug Administration (FDA) is alerting healthcare professionals of an increased risk for opportunistic fungal infections in patients treated with antitumor necrosis factor (anti-TNF) agents adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), and infliximab (Remicade®). The FDA has received reports of pulmonary and disseminated cases of histoplasmosis, coccidioidomycosis, blastomycosis, and other fungal infections associated with use of these agents. In some cases, the symptoms of fungal infection (eg, fever, cough, malaise, dyspnea, fatigue) were unrecognized and precluded prompt antifungal treatment, resulting in 12 deaths. In response, the FDA is requiring manufacturers of these agents to strengthen the boxed warning statement in the labeling to further emphasize the risk of invasive fungal infection. Patients should be monitored closely for signs and symptoms suggestive of fungal infection, evidence of which should result in prompt discontinuation of the medication and appropriate diagnostic evaluation. Symptomatic patients should be questioned about their residence in or travel from areas of endemic mycoses, which should prompt consideration of empiric antifungal therapy.

Additional information can be found at: http://www.fda.gov/medwatch/safety/2008/safety08.htm#TNF2

Tumor Necrosis Factor (TNF) Blockers and Malignancy Risk - June 5, 2008

The U.S. Food and Drug Administration (FDA) issued an Early Communication to healthcare professionals regarding a possible association between TNF blocker (adalimumab, certolizumb pegol, etanercept, and infliximab) use and the development of malignancies in children and young adults. Over the last 10 years, the FDA has received ~30 reports of cancer in children or young adults who had been treated with TNF blockers prior to the age of 18 years. TNF blockers were given for the treatment of Juvenile Idiopathic Arthritis (JIA [formerly termed Juvenile Rheumatoid Arthritis]), Crohn’s disease, or other indications in combination with other immunosuppressive medications (eg, azathioprine, 6-mercaptopurine or methotrexate). Approximately half of the reported cancers were lymphomas (Hodgkin’s and non-Hodgkin’s), which are cancers involving the cells of the immune system.

TNF blockers work by suppressing the immune system. The prescribing information for each TNF blocker contains warnings regarding the possible association of malignancy development with use. Malignancies may not be detected in short-term studies; long-term studies are necessary to identify the impact of TNF blocker therapy on malignancy development. The manufacturers of the four TNF blockers available in the U.S. are being asked by the FDA to provide information regarding all cases of cancer reported in children taking TNF blockers. The FDA is expected to report its findings in approximately 6 months, after completing a safety review and evaluation.

Additional information is available at http://www.fda.gov/medwatch/safety/2008/safety08.htm#TNF

Etanercept (Enbrel®): Revised Prescribing Information With the Addition of a Boxed Warning Concerning the Risk of Infection, Including Tuberculosis - May 2008

These product labeling changes have previously been incorporated into the etanercept Lexi-Comp monograph.

The FDA MedWatch alert can be found at: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Enbrel

Pronunciation(et a NER sept)

U.S. Brand NamesEnbrel®

Canadian Brand NamesEnbrel®

Pharmacologic CategoryAntirheumatic, Disease Modifying; Tumor Necrosis Factor (TNF) Blocking Agent

Use: Labeled IndicationsTreatment of moderately- to severely-active rheumatoid arthritis (RA); moderately- to severely-active polyarticular juvenile idiopathic arthritis (JIA); psoriatic arthritis; active ankylosing spondylitis (AS); moderate-to-severe chronic plaque psoriasis

Dosing: Adults

Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis: SubQ:

Once-weekly dosing: 50 mg once weekly

Twice-weekly dosing: 25 mg given twice weekly (individual doses should be separated by 72-96 hours)

Plaque psoriasis:

Initial: 50 mg twice weekly, 3-4 days apart (starting doses of 25 or 50 mg once weekly have also been used successfully); maintain initial dose for 3 months

Maintenance dose: 50 mg once weekly

Dosing: ElderlySubQ: Refer to adult dosing. Although greater sensitivity of some elderly patients cannot be ruled out, no overall differences in safety or effectiveness were observed.
Dosing: Pediatric**Juvenile idiopathic arthritis:** Children 2-17 years: SubQ:

Once-weekly dosing: 0.8 mg/kg (maximum: 50 mg/dose) once weekly

Twice-weekly dosing: 0.4 mg/kg (maximum: 25 mg/dose) twice weekly (individual doses should be separated by 72-96 hours)

Administration: OtherAdminister subcutaneously. Rotate injection sites. New injections should be given at least one inch from an old site and never into areas where the skin is tender, bruised, red, or hard. **Note:** If the physician determines that it is appropriate, patients may self-inject after proper training in injection technique.

Powder for reconstitution: Follow package instructions carefully for reconstitution. The maximum amount injected at any single site should not exceed 25 mg.

Solution for injection: May be allowed to reach room temperature prior to injection.

StorageStore prefilled syringes at 2°C to 8°C (36°F to 46°F); protect from light; do not freeze or shake. Powder for reconstitution must be refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze. Reconstituted vials of etanercept should be administered as soon as possible after reconstitution. If not administered immediately after reconstitution, etanercept may be stored in the vial at 2°C to 8°C (36°F to 46°F) for up to 14 days.
ReconstitutionReconstitute lyophilized powder aseptically with 1 mL sterile bacteriostatic water for injection, USP (supplied); swirl gently, do not shake. Do not filter reconstituted solution during preparation or administration.
Restrictions

An FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to etanercept or any component of the formulation; patients with sepsis (mortality may be increased); active infections (including chronic or local infection)
Warnings/Precautions

Boxed warnings:

• Infections: See "Concerns related to adverse effects" below.

• Tuberculosis: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Allergic reactions may occur, but anaphylaxis has not been observed. If an anaphylactic reaction or other serious allergic reaction occurs, administration should be discontinued immediately and appropriate therapy initiated.

- Autoimmune disorder: Positive antinuclear antibody titers have been detected in patients (with negative baselines). Rare cases of autoimmune disorder, including lupus-like syndrome or autoimmune hepatitis, have been reported; monitor and discontinue if symptoms develop.

- Hepatitis B: Rare reactivation of hepatitis B has occurred in chronic carriers of the virus; evaluate prior to initiation and during treatment in patients at risk for hepatitis B infection.

- Infections: **[U.S. Boxed Warning]: Serious and potentially fatal infections have been reported including bacterial sepsis and tuberculosis.** Cases of unrecognized invasive fungal infections (eg, histoplasmosis, blastomycosis, coccidioidomycosis) have also been reported with anti-TNF agent use. Discontinue administration if patient develops a serious infection or sepsis. Caution should be exercised when considering the use in patients with chronic infection, history of recurrent infection, or predisposition to infection (eg, poorly-controlled diabetes or residence/travel from areas of endemic mycoses). Do not give to patients with an active chronic or localized infection. Patients should be educated about the symptoms of infection and closely monitored for signs and symptoms while undergoing treatment.

- Malignancy: Use may affect defenses against malignancies; impact on the development and course of malignancies is not fully defined. As compared to the general population, an increased risk of lymphoma has been noted in clinical trials; however, rheumatoid arthritis has been previously associated with an increased rate of lymphoma.

- Tuberculosis: **[U.S. Boxed Warning]: Tuberculosis (disseminated or extrapulmonary) has been reported in patients receiving etanercept; both reactivation of latent infection and new infections have been reported.** Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test prior to starting therapy. Treatment of latent tuberculosis should be initiated before therapy is used. Some patients who tested negative prior to therapy have developed active infection; monitor for signs and symptoms of tuberculosis in all patients.

Disease-related concerns:

- Demyelinating CNS disease: Use with caution in patients with pre-existing or recent onset CNS demyelinating disorders; rare cases of new onset or exacerbation of CNS demyelinating disorders have occurred; may present with mental status changes and some may be associated with permanent disability. Optic neuritis, transverse myelitis, multiple sclerosis, and new onset or exacerbation of seizures have been reported.

- Heart failure: Use with caution in patients with heart failure or decreased left ventricular function; worsening and new-onset heart failure has been reported.
- Hematologic disorders: Use with caution in patients with a history of significant hematologic abnormalities; has been associated with pancytopenia and aplastic anemia (rare cases in postmarketing experience). Patients must be advised to seek medical attention if they develop signs and symptoms suggestive of blood dyscrasias; discontinue if significant hematologic abnormalities are confirmed.
- Wegener's granulomatosis: Use is not recommended for use in patients with Wegener's granulomatosis who are receiving immunosuppressive therapy due to higher incidence of noncutaneous solid malignancies.

Concurrent drug therapy issues:

- Anakinra: Due to higher incidence of serious infections, should not be used in combination with anakinra unless no satisfactory alternatives exist, and then only with extreme caution.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.
- Varicella virus exposure: Patients with a significant exposure to varicella virus should temporarily discontinue therapy; treatment with varicella zoster immune globulin should be considered.

Dosage form specific issues:

- Latex: Some dosage forms may contain dry natural rubber (latex).

Other warnings/precautions:

- Immunizations: Patients should be brought up to date with all immunizations before initiating therapy. Live vaccines should not be given concurrently; there is no data available concerning secondary transmission of live vaccines in patients receiving therapy.

Geriatric ConsiderationsClinical trials including those ≥65 years of age with rheumatoid arthritis have not demonstrated any differences in safety and efficacy between elderly and younger adults to date. Since elderly have a higher incidence of infections in general, caution should be used, with close monitoring and patient education.

Pregnancy Risk FactorB

Pregnancy ConsiderationsDevelopmental toxicity studies performed in animals have revealed no evidence of harm to the fetus. There are no studies in pregnant women; this drug should be used during pregnancy only if clearly needed. A pregnancy registry has been established to monitor outcomes of women exposed to etanercept during pregnancy (877-311-8972).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known whether etanercept is excreted in human milk. Because many immunoglobulins are excreted in human milk and the potential for serious adverse reactions exists, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Adverse ReactionsPercentages reported for adults except where specified.

>10%:

Central nervous system: Headache (17%; children 19%)

Gastrointestinal: Abdominal pain (5%; children 19%), vomiting (3%; children 13%)

Local: Injection site reaction (14% to 37%; erythema, itching, pain or swelling)

Respiratory: Respiratory tract infection (upper; 12% to 29%), rhinitis (12% to 16%)

Miscellaneous: Infection (35%; children 63%), positive ANA (11%), positive antidouble-stranded DNA antibodies (15% by RIA, 3% by *Crithidia luciliae* assay)

≥3% to 10%:

Cardiovascular: Edema (2% to 8%)

Central nervous system: Dizziness (7%)

Dermatologic: Rash (5%)

Gastrointestinal: Dyspepsia (4%), nausea (children 9%)

Neuromuscular & skeletal: Weakness (5%)

Respiratory: Pharyngitis (7%), respiratory disorder (5%), sinusitis (3%), cough (6%)

<3%, postmarketing, and/or case reports: Abscess, adenopathy, allergic reactions, alopecia, anemia, angioedema, anorexia, aplastic anemia, appendicitis, aseptic meningitis, bursitis, cerebral ischemia, chest pain, cholecystitis, coagulopathy; demyelinating CNS disorders (suggestive of multiple sclerosis, transverse myelitis, or optic neuritis); deep vein thrombosis, depression, diarrhea, dyspnea, erythema multiforme, fatigue, fever, flushing, flu-like syndrome, gastrointestinal hemorrhage, heart failure, hepatitis (autoimmune), hydrocephalus (with normal pressure), hyper-/hypotension; infections (bacterial, fungal, protozoal, viral); interstitial lung disease, intestinal perforation, joint pain, leukopenia, lupus-like syndrome, lymphadenopathy, malignancies (including lymphoma), membranous glomerulopathy, MI, mouth ulcer, multiple sclerosis, myocardial ischemia, neutropenia, ocular inflammation, optic neuritis,

pancytopenia, pancreatitis, paresthesia, polymyositis, pruritus, psoriasis exacerbation, pulmonary disease, pulmonary embolism, renal calculus, sarcoidosis, seizure, stroke, Stevens-Johnson syndrome, subcutaneous nodules, taste disturbances, thrombocytopenia, thrombophlebitis, toxic epidermal necrolysis, transaminases increased, tuberculosis, tuberculous arthritis, urinary tract infection, urticaria, vasculitis (cutaneous), weight gain, xerophthalmia, xerostomia

Drug Interactions

Abatacept: Anti-TNF Agents may enhance the adverse/toxic effect of Abatacept. An increased risk of serious infection during concomitant use has been reported. *Risk D: Consider therapy modification*

Anakinra: Anti-TNF Agents may enhance the adverse/toxic effect of Anakinra. An increased risk of serious infection during concomitant use has been reported. *Risk X: Avoid combination*

Cyclophosphamide: Etanercept may enhance the adverse/toxic effect of Cyclophosphamide. An increased risk of solid cancer development may be present. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Rilonacept: Anti-TNF Agents may enhance the adverse/toxic effect of Rilonacept. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Echinacea may decrease the therapeutic effects of etanercept (avoid concurrent use).

Monitoring Parameters

Signs and symptoms of infection (prior to and during therapy); latent TB screening prior to therapy initiation

Nursing: Physical Assessment/MonitoringMonitor for signs and symptoms of infection. Assess for liver dysfunction. Monitor effectiveness of therapy (eg, pain, range of motion, mobility, ADL function, inflammation). Assess knowledge/teach patient appropriate administration (injection technique and needle disposal if self-administered), possible side effects/interventions, and adverse symptoms to report.

Monitoring: Lab Tests

Latent TB screening prior to therapy initiation

Patient EducationIf self-injecting, follow instructions for injection and disposal of needles exactly. If redness, swelling, or irritation appears at the injection site, contact prescriber. Do not have any vaccinations while using this medication without consulting prescriber first. You may experience headache or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known). If stomach pain or cramping; unusual bleeding or bruising; persistent fever; paleness; blood in vomitus, stool, or urine occurs, stop medication and contact prescriber **immediately**. Also immediately report skin rash, unusual muscle or bone weakness, or signs of respiratory flu or other infection (eg, chills, fever, sore throat, easy bruising or bleeding, mouth sores, unhealed sores). **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Enbrel®: 25 mg [contains sucrose 10 mg; diluent contains benzyl alcohol]

Injection, solution [preservative free]:

Enbrel®: 50 mg/mL (0.51 mL, 0.98 mL) [contains sucrose 1%; natural rubber/natural latex in packaging]

Generic AvailableNo

ManufacturerImmunex Corp

Pricing: U.S. (www.drugstore.com)

Kit (Enbrel)

25 mg (4): $748.92

Solution (Enbrel)

50 mg/mL (3.92): $1471.69

Solution (Enbrel SureClick)

50 mg/mL (3.92): $1541.98

Mechanism of ActionEtanercept is a recombinant DNA-derived protein composed of tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. Etanercept binds tumor necrosis factor (TNF) and blocks its interaction with cell surface receptors. TNF plays an important role in the inflammatory processes and the resulting joint pathology of rheumatoid arthritis (RA), polyarticular-course juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), and plaque psoriasis.

Pharmacodynamics/Kinetics

Onset of action: ~2-3 weeks; RA: 1-2 weeks

Half-life elimination: RA: SubQ: 72-132 hours

Time to peak: RA: SubQ: 35-103 hours

Excretion: Clearance: Children: 45.9 mL/hour/m^2; Adults: 89 mL/hour (52 mL/hour/m^2)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDizziness is common; may cause depression
Mental Health: Effects on Psychiatric TreatmentNone reported
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International Brand NamesEnbrel (AR, AT, AU, BE, BG, BR, CH, CN, CO, CR, CZ, DE, DK, ES, FI, FR, GB, GR, GT, HK, HN, IE, IL, IN, IT, KP, MX, MY, NI, NL, NO, PA, PE, PH, PL, PT, RU, SE, SG, SV, TH, TR, VE)

Ethacrynic Acid

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Edecrin® may be confused with Eulexin®, Ecotrin®

Pronunciation(eth a KRIN ik AS id)

U.S. Brand NamesEdecrin®

Canadian Brand NamesEdecrin®

Pharmacologic CategoryDiuretic, Loop

Use: Labeled IndicationsManagement of edema associated with congestive heart failure; hepatic cirrhosis or renal disease; short-term management of ascites due to malignancy, idiopathic edema, and lymphedema

Dosing: AdultsI.V. formulation should be diluted in D_5W or NS (1 mg/mL) and infused over several minutes.

Edema:

Oral: 50-100 mg/day in 1-2 divided doses; may increase in increments of 25-50 mg at intervals of several days to a maximum of 400 mg/24 hours.

I.V.: 0.5-1 mg/kg/dose (maximum: 100 mg/dose); repeat doses not routinely recommended; however, if indicated, repeat doses every 8-12 hours.

Dosing: ElderlyOral: Initial: 25-50 mg/day

Dosing: Pediatric

Edema: Oral: Children: 1 mg/kg/dose once daily; increase at intervals of 2-3 days as needed, to a maximum of 3 mg/kg/day.

Dosing: Renal Impairment

Cl_{cr} <10 mL/minute: Avoid use.

Not removed by hemo- or peritoneal dialysis; supplemental dose is not necessary.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Injection should **not** be given SubQ or I.M. due to local pain and irritation. Single I.V. doses should not exceed 100 mg. Administer each 10 mg over a minute.

Administration: I.V. DetailIf a second dose is needed, it is recommended to use a new injection site to avoid possible thrombophlebitis.

pH: 6.3-7.7

Dietary ConsiderationsThis product may cause a potassium loss. Your healthcare provider may prescribe a potassium supplement, another medication to help prevent the potassium loss, or recommend that you eat foods high in potassium, especially citrus fruits. Do not change your diet on your own while taking this medication, especially if you are taking potassium supplements or medications to reduce potassium loss. Too much potassium can be as harmful as too little.

CompatibilityStable in D_5NS, D_5W, LR, NS.

Incompatible with whole blood or its derivatives.

Y-site administration: Compatible: Heparin with hydrocortisone sodium succinate, potassium chloride, vitamin B complex with C.

Compatibility when admixed: Compatible: Chlorpromazine, cimetidine, prochlorperazine, promazine. **Incompatible:** Hydralazine, procainamide, ranitidine, tolazoline, triflupromazine.

Extemporaneously PreparedTo make a 1 mg/mL suspension: Dissolve 120 mg ethacrynic acid powder in a small amount of 10% alcohol. Add a small amount of 50% sorbitol solution and stir. Adjust pH to 7 with 0.1N sodium hydroxide solution. Add sufficient 50% sorbitol solution to make a final volume of 120 mL. (Methylparaben 6 mg and propylparaben 2.4 mg are added as preservatives.) Stable 220 days at room temperature.

Handbook on Extemporaneous Formulations, Bethesda, MD: American Society of Hospital Pharmacists, 1987.

ContraindicationsHypersensitivity to ethacrynic acid or any component of the formulation; anuria; history of severe watery diarrhea caused by this product; infants

Warnings/Precautions

Concerns related to adverse effects:

- Fluid/electrolyte loss: Loop diuretics are potent diuretics; excess amounts can lead to profound diuresis with fluid and electrolyte loss; close medical supervision and dose evaluation are required. Watch for and correct electrolyte disturbances; adjust dose to avoid dehydration.

- Hypersensitivity reactions: Can rarely occur, however, ethacrynic acid has no cross-reactivity to sulfonamides or sulfonylureas.

- Nephrotoxicity: Monitor fluid status and renal function in an attempt to prevent oliguria, azotemia, and reversible increases in BUN and creatinine; close medical supervision of aggressive diuresis required.

- Ototoxicity: Rapid I.V. administration, renal impairment, excessive doses, and concurrent use of other ototoxins is associated with ototoxicity; has been associated with a higher incidence of ototoxicity than other loop diuretics.

Disease-related concerns:

- Cirrhosis: In cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

Concurrent drug therapy issues:

- Antihypertensives: Coadministration of antihypertensives may increase the risk of hypotension.

Geriatric ConsiderationsEthacrynic acid is rarely used because of its increased incidence of ototoxicity as compared to the other loop diuretics.

Pregnancy Risk FactorB

Pregnancy ConsiderationsNo data available. Generally, use of diuretics during pregnancy is avoided due to risk of decreased placental perfusion.

LactationContraindicated

Adverse ReactionsFrequency not defined.

Central nervous system: Headache, fatigue, apprehension, confusion, fever, chills, encephalopathy (patients with pre-existing liver disease); vertigo

Dermatologic: Skin rash, Henoch-Schönlein purpura (in patient with rheumatic heart disease)

Endocrine & metabolic: Hyponatremia, hyperglycemia, variations in phosphorus, CO_2 content, bicarbonate, and calcium; reversible hyperuricemia, gout, hyperglycemia, hypoglycemia (occurred in two uremic patients who received doses above those recommended)

Gastrointestinal: Anorexia, malaise, abdominal discomfort or pain, dysphagia, nausea, vomiting, and diarrhea, gastrointestinal bleeding, acute pancreatitis (rare)

Genitourinary: Hematuria

Hepatic: Jaundice, abnormal liver function tests

Hematology: Agranulocytosis, severe neutropenia, thrombocytopenia

Local: Thrombophlebitis (with intravenous use), local irritation and pain

Ocular: Blurred vision

Otic: Tinnitus, temporary or permanent deafness

Renal: Serum creatinine increased

Drug Interactions

ACE Inhibitors: Loop Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Loop Diuretics may enhance the adverse/toxic effect of Allopurinol. Loop Diuretics may increase the serum concentration of Allopurinol. Specifically, Loop Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoglycosides: Loop Diuretics may enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Loop Diuretics. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dofetilide: Loop Diuretics may enhance the QTc-prolonging effect of Dofetilide. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Loop Diuretics may diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Loop Diuretics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Phenytoin: May diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Monitoring ParametersBlood pressure, renal function, serum electrolytes, and fluid status closely, including weight and I & O daily; hearing

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (especially anything that would impact blood pressure or add to risk of ototoxicity). **Infusion:** See Administration. Assess results of laboratory tests, therapeutic effectiveness (according to purpose for use), and adverse response (eg, dehydration, electrolyte imbalance, CNS changes) on a regular basis during therapy. Caution patients with diabetes to monitor glucose levels closely (may cause hyper/hypoglycemia). Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsRenal function, serum electrolytes

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy without consulting prescriber. Take prescribed dose with food early in day. Include orange juice or bananas (or other potassium-rich foods) in your diet, but do not take potassium supplements without consulting prescriber. If you have diabetes, monitor serum glucose closely (this medication may alter glucose levels). May cause postural hypotension (use caution when rising from lying or sitting position, when climbing stairs, or when driving); lightheadedness, dizziness, or drowsiness (use caution driving or when engaging in hazardous activities); diarrhea (buttermilk, boiled milk, or yogurt may help); or decreased accommodation to heat (avoid excessive exercise in hot weather). Report hearing changes (ringing in ears); persistent headache; unusual confusion or nervousness; abdominal pain or blood stool (black stool); palpitations, chest pain, rapid heartbeat; flu-like symptoms; skin rash or itching; blurred vision; swelling of ankles or feet; weight changes of more than 3 lb/day; increased fatigue; or joint/muscle swelling, pain, cramping, or trembling. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as ethacrynate sodium: 50 mg

Tablet: 25 mg

Generic AvailableNo

ManufacturerMerck & Co

Pricing: U.S. (www.drugstore.com)

Tablets (Edecrin)

25 mg (100): $112.49

Mechanism of ActionInhibits reabsorption of sodium and chloride in the ascending loop of Henle and distal renal tubule, interfering with the chloride-binding cotransport system, thus causing increased excretion of water, sodium, chloride, magnesium, and calcium

Pharmacodynamics/Kinetics

Onset of action: Diuresis: Oral: ~30 minutes; I.V.: 5 minutes

Peak effect: Oral: 2 hours; I.V.: 30 minutes

Duration: Oral: 12 hours; I.V.: 2 hours

Absorption: Oral: Rapid

Protein binding: >90%

Metabolism: Hepatic (35% to 40%) to active cysteine conjugate

Half-life elimination: Normal renal function: 2-4 hours

Excretion: Feces and urine (30% to 60% as unchanged drug)

Related Information

- Heart Failure (Systolic)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness; may rarely cause drowsiness, nervousness, or confusion

Mental Health: Effects on Psychiatric TreatmentRare reports of agranulocytosis; use caution with clozapine and carbamazepine; may increase serum lithium levels, however, more likely with thiazide diuretic

Cardiovascular ConsiderationsLimited use over other loop diuretics because of increased risk of ototoxicity. Hypotensive effect of ethacrynic acid may be more pronounced in patients previously on a diuretic therapy or who have volume depletion.

Anesthesia and Critical Care Concerns/Other ConsiderationsEthacrynic acid has limited use over other loop diuretics because of increased risk of ototoxicity. If given the morning of surgery, it may render the patient volume depleted and blood pressure may be labile during general anesthesia.

Index TermsEthacrynate Sodium

References

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Lant A, “Diuretics: Clinical Pharmacology and Therapeutic Use,” *Drugs*, 1985, 29(1):57-87.

International Brand NamesEdecril (AU, NL); Edecrin (AT, CZ, GB, IE, IT, NL); Edecrina (SE); Hydromedin (DE); Hydromedin i.v.[inj.] (DE); Reomax (IT); Uregyt (CZ, DE, HU)

Ethambutol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Myambutol® may be confused with Nembutal®

Pronunciation(e THAM byoo tole)

U.S. Brand NamesMyambutol®

Canadian Brand NamesEtibi®

Pharmacologic CategoryAntitubercular Agent

Use: Labeled IndicationsTreatment of tuberculosis and other mycobacterial diseases in conjunction with other antituberculosis agents

Dosing: Adults

Tuberculosis, active (suggested doses by lean body weight): Oral:

Daily therapy: 15-25 mg/kg

40-55 kg: 800 mg

56-75 kg: 1200 mg

76-90 kg: 1600 mg (maximum dose regardless of weight)

Twice weekly directly observed therapy (DOT): 50 mg/kg

40-55 kg: 2000 mg

56-75 kg: 2800 mg

76-90 kg: 4000 mg (maximum dose regardless of weight)

Three times/week DOT: 25-30 mg/kg (maximum: 2.5 g)

40-55 kg: 1200 mg

56-75 kg: 2000 mg

76-90 kg: 2400 mg (maximum dose regardless of weight)

Note: Used as part of a multidrug regimen. Treatment regimens consist of an initial 2 month phase, followed by a continuation phase of 4 or 7 additional months; frequency of dosing may differ depending on phase of therapy.

Disseminated*Mycobacterium avium*complex (MAC) in patients with advanced HIV infection: Oral: 15 mg/kg ethambutol in combination with azithromycin 600 mg daily

Nontuberculous mycobacterium (*M. kansasii*) (unlabeled use; IDSA guidelines): Oral: 15 mg/kg/day for duration to include 12 months of culture-negative sputum; typically used in combination with rifampin and isoniazid; **Note:** Previous recommendations stated to use 25 mg/kg/day for the initial 2 months of therapy; however, IDSA guidelines state this may be unnecessary given the success of rifampin-based regimens with ethambutol 15 mg/kg/day or omitted altogether.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Treatment of tuberculosis Oral:

Daily therapy: 15-20 mg/kg/day (maximum: 1 g/day)

Twice weekly directly observed therapy (DOT): 50 mg/kg (maximum: 4 g/dose)

See “Note” in adult dosing.

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer every 24-36 hours.

Cl_{cr} <10 mL/minute: Administer every 48 hours.

Slightly dialyzable (5% to 20%); administer dose postdialysis.

Peritoneal dialysis: Dose as for Cl_{cr} <10 mL/minute.

Continuous arteriovenous or venovenous hemofiltration: Administer every 24-36 hours.

Calculations

- Adjusted Body Weight
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Ideal Body Weight: Adults

Dietary ConsiderationsMay be taken with food as absorption is not affected, may cause gastric irritation.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to ethambutol or any component of the formulation; optic neuritis; use in children, unconscious patients, or any other patient who may be unable to discern and report visual changes

Warnings/Precautions

Concerns related to adverse effects:

- Hepatic toxicity: Has been reported, possibly due to concurrent therapy.

- Optic neuritis: May cause optic neuritis, resulting in decreased visual acuity or other vision changes. Discontinue promptly in patients with changes in vision, color blindness, or visual defects (effects normally reversible, but reversal may require up to a year).

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage modification recommended.

Special populations:

- Pediatrics: Use only in children whose visual acuity can accurately be determined and monitored (not recommended for use in children <13 years of age unless the benefit outweighs the risk).

Geriatric ConsiderationsSince most elderly patients acquired their tuberculosis before current antituberculin regimens were available, ethambutol is only indicated when patients are from areas where drug resistant *M. tuberculosis* is endemic, in HIV-infected elderly patients, and when drug resistant *M. tuberculosis* is suspected (see dose adjustments for renal impairment).

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women; teratogenic effects have been seen in animals. Ethambutol has been used safely during pregnancy.

LactationEnters breast milk/use caution (AAP considers “compatible”)

Breast-Feeding ConsiderationsThe manufacturer suggests use during breast-feeding only if benefits to the mother outweigh the possible risk to the infant. Some references suggest that exposure to the infant is low and does not produce toxicity, and breast-feeding should not be discouraged. Other references recommend if breast-feeding, monitor the infant for rash, malaise, nausea, or vomiting.

Adverse ReactionsFrequency not defined.

Cardiovascular: Myocarditis, pericarditis

Central nervous system: Headache, confusion, disorientation, malaise, mental confusion, fever, dizziness, hallucinations

Dermatologic: Rash, pruritus, dermatitis, exfoliative dermatitis

Endocrine & metabolic: Acute gout or hyperuricemia

Gastrointestinal: Abdominal pain, anorexia, nausea, vomiting

Hematologic: Leukopenia, thrombocytopenia, eosinophilia, neutropenia, lymphadenopathy

Hepatic: Abnormal LFTs, hepatotoxicity (possibly related to concurrent therapy), hepatitis

Neuromuscular & skeletal: Peripheral neuritis, arthralgia

Ocular: Optic neuritis; symptoms may include decreased acuity, scotoma, color blindness, or visual defects (usually reversible with discontinuation, irreversible blindness has been described)

Renal: Nephritis

Respiratory: Infiltrates (with or without eosinophilia), pneumonitis

Miscellaneous: Anaphylaxis, anaphylactoid reaction; hypersensitivity syndrome (rash, eosinophilia, and organ-specific inflammation)

Drug Interactions

Aluminum Hydroxide: May decrease the absorption of Ethambutol. *Risk D: Consider therapy modification*

Monitoring ParametersBaseline and periodic (monthly) visual testing (each eye individually, as well as both eyes tested together) in patients receiving >15 mg/kg/day; baseline and periodic renal, hepatic, and hematopoietic tests

Nursing: Physical Assessment/MonitoringUse caution in presence of renal insufficiency. Assess results of baseline and periodic laboratory tests, therapeutic effectiveness, and adverse response (eg, CNS changes, neuritis, and ocular changes) on a regular basis during therapy. Teach patient appropriate use (need to adhere to dosing program), possible side effects/appropriate interventions (regular ophthalmic evaluations), and adverse symptoms to report.

Monitoring: Lab TestsBaseline and periodic (monthly) visual testing (each eye individually, as well as both eyes tested together) in patients receiving >15 mg/kg/day; baseline and periodic renal, hepatic, and hematopoietic tests

Patient EducationTake as scheduled, with meals. Avoid missing doses and do not discontinue without consulting prescriber. Avoid aluminum-containing antacids for at least 4 hours following ethambutol. May cause GI distress (small, frequent meals and good oral care may help), dizziness, disorientation, drowsiness (avoid driving or engaging in tasks that require alertness until response to drug is known). You will need to have frequent ophthalmic exams and periodic medical check-ups to evaluate drug effects. Report vision changes, numbness or tingling of extremities, or persistent loss of appetite. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 100 mg, 400 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Ethambutol HCl)

400 mg (30): $55.99

Mechanism of ActionSuppresses mycobacteria multiplication by interfering with RNA synthesis

Pharmacodynamics/Kinetics

Absorption: ~80%

Distribution: Widely throughout body; concentrated in kidneys, lungs, saliva, and red blood cells

Relative diffusion from blood into CSF: Adequate with or without inflammation (exceeds usual MICs)

CSF:blood level ratio: Normal meninges: 0%; Inflamed meninges: 25%

Protein binding: 20% to 30%

Metabolism: Hepatic (20%) to inactive metabolite

Half-life elimination: 2.5-3.6 hours; End-stage renal disease: 7-15 hours

Time to peak, serum: 2-4 hours

Excretion: Urine (~50%) and feces (20%) as unchanged drug

Related Information

- Antimicrobial Drugs of Choice
- Depression
- Desensitization Protocols
- Tuberculosis

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause confusion and disorientation

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsEthambutol Hydrochloride

References

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International Brand NamesAlthocin (GR); Ambutol (MY); Arbutol (ID); Bacbutol (ID); Blomison (GR); Clobutol (PT); Combutol (IN); Corsabutol (ID); Dexambutol (FR); Ebutol (TW); EMB (DE); EMB-Fatol (HK); Etambutol (BG, BR, HR); Etambutol Northia (AR); Etambutol Richet (AR); Etambutol Richmond (AR); Etapiam (IT); ETH Ciba 400 (ID); Etham (TH); Ethambin-PIN (PH); Ethambutol (PL); Ethbutol (TH); Etibi (AT, ID, IT); Interbutol (PH); Lambutol (TH); Manzida (MX); Myambutol (AT, AU, BE, BF, BJ, CH, CI, DE, DK, ES, ET, FR, GB, GH, GM, GN, GR, IE, IN, KE, KP, LR, LU, MA, ML, MR, MU, MW, MY, NE, NG, NL, PK, PT, SC, SD, SE, SL, SN, TH, TN, TW, TZ, UG, ZA, ZM, ZW); Mycobutol (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Odetol (PH); Oributol (FI); Purderal (ZA); Servambutol (PE); Stambutol (FI); Sural (CZ, HN, HU); Tibigon (ID); Tibitol (ID, IN); Tibutol (PE); Tobutol (TH)

Ethanolamine Oleate

Lexi-Drugs Online

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Medication Safety Issues

Sound-alike/look-alike issues:

Ethamolin® may be confused with ethanol

Pronunciation(ETH a nol a meen OH lee ate)
U.S. Brand NamesEthamolin®
Pharmacologic CategorySclerosing Agent
Use: Labeled Indications**Orphan drug:** Sclerosing agent used for bleeding esophageal varices
Dosing: AdultsEsophageal varices (sclerotherapy): Injection: 1.5-5 mL per varix, up to 20 mL total or 0.4 mL/kg for a 50 kg patient; doses should be decreased in patients with severe hepatic dysfunction and should receive less than recommended maximum dose
Dosing: ElderlyRefer to adult dosing.
ContraindicationsHypersensitivity to agent or oleic acid
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis: Fatal anaphylactic shock has been reported following administration.
- Aspiration pneumonia: Fatal aspiration pneumonia has occurred.

Disease-related concerns:

- Cardiorespiratory disease: Use with caution in patients with concomitant cardiorespiratory disease.
- Hepatic impairment: Use with caution in patients with significant liver dysfunction (Child class C); decreased dose recommended.

Special populations:

- Critically-ill patients: Use with caution in critically-ill patients.
- Elderly: Use with caution in the elderly.
- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC
Adverse Reactions

1% to 10%:

Central nervous system: Pyrexia (1.8%)

Gastrointestinal: Esophageal ulcer (2%), esophageal stricture (1.3%)

Respiratory: Pleural effusion (2%), pneumonia (1.2%)

Miscellaneous: Retrosternal pain (1.6%)

<1%: Esophagitis, perforation, injection necrosis, acute renal failure, anaphylaxis

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 5% [50 mg/mL] (2 mL) [contains benzyl alcohol]

Generic AvailableNo
Mechanism of ActionDerived from oleic acid and similar in physical properties to sodium morrhuate; however, the exact mechanism of the hemostatic effect used in endoscopic injection sclerotherapy is not known. Intravenously injected ethanolamine oleate produces a sterile inflammatory response resulting in fibrosis and occlusion of the vein; a dose-related extravascular inflammatory reaction occurs when the drug diffuses through the venous wall. Autopsy results indicate that variceal obliteration occurs secondary to mural necrosis and fibrosis. Thrombosis appears to be a transient reaction.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsMonoethanolamine

Ethinyl Estradiol and Desogestrel

Lexi-Drugs Online

English

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Apri® may be confused with Apriso™

Ortho-Cept® may be confused with Ortho-Cyclen®

Pronunciation(ETH in il es tra DYE ole & des oh JES trel)

U.S. Brand NamesApri®; Cesia™; Cyclessa®; Desogen®; Kariva™; Mircette®; Ortho-Cept®; Reclipsen™; Solia™; Velivet™

Canadian Brand NamesCyclessa®; Linessa®; Marvelon®; Ortho-Cept®

Pharmacologic CategoryContraceptive; Estrogen and Progestin Combination

Use: Labeled IndicationsPrevention of pregnancy

Use: Unlabeled/InvestigationalTreatment of hypermenorrhea (menorrhagia); pain associated with endometriosis; dysmenorrhea; dysfunctional uterine bleeding

Dosing: AdultsFemales: Contraception: Oral:

Schedule 1 (Sunday starter): Dose begins on first Sunday after onset of menstruation; if the menstrual period starts on Sunday, take first tablet that very same day. **With a Sunday start, an additional method of contraception should be used until after the first 7 days of consecutive administration.**

For 21-tablet package: Dosage is 1 tablet daily for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken.

For 28-tablet package: Dosage is 1 tablet daily without interruption.

Schedule 2 (Day 1 starter): Dose starts on first day of menstrual cycle taking 1 tablet daily.

For 21-tablet package: Dosage is 1 tablet daily for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken.

For 28-tablet package: Dosage is 1 tablet daily without interruption.

If all doses have been taken on schedule and one menstrual period is missed, continue dosing cycle. If two consecutive menstrual periods are missed, pregnancy test is required before new dosing cycle is started.

Missed doses **monophasic formulations** (refer to package insert for complete information):

One dose missed: Take as soon as remembered or take 2 tablets next day

Two consecutive doses missed in the first 2 weeks: Take 2 tablets as soon as remembered or 2 tablets next 2 days. **An additional method of contraception should be used for 7 days after missed dose.**

Two consecutive doses missed in week 3 or three consecutive doses missed at any time: Schedule 1 (Sunday starter): Continue to take 1 tablet daily until Sunday, then discard the rest of the pack, and a new pack is started that same day. Schedule 2 (Day 1 starter): Current pack should be discarded, and a new pack started that same day. **An additional method of contraception should be used for 7 days after missed dose.**

Missed doses **biphasic/triphasic formulations** (refer to package insert for complete information):

One dose missed: Take as soon as remembered or take 2 tablets next day.

Two consecutive doses missed in week 1 or week 2 of the pack: Take 2 tablets as soon as remembered and 2 tablets the next day. Resume taking 1 tablet daily until the pack is empty. **An additional method of contraception should be used for 7 days after a missed dose.**

Two consecutive doses missed in week 3 of the pack; **an additional method of contraception must be used for 7 days after a missed dose**:

Schedule 1 (Sunday starter): Take 1 tablet every day until Sunday. Discard the remaining pack and start a new pack of pills on the same day.

Schedule 2 (Day 1 starter): Discard the remaining pack and start a new pack the same day.

Three or more consecutive doses missed; **an additional method of contraception must be used for 7 days after a missed dose**:

Schedule 1 (Sunday starter): Take 1 tablet every day until Sunday; on Sunday, discard the pack and start a new pack.

Schedule 2 (Day 1 starter): Discard the remaining pack and begin new pack of tablets starting on the same day.

Dosing: PediatricFemales: Contraception: Oral: See adult dosing; not to be used prior to menarche.

Dosing: Renal ImpairmentSpecific guidelines not available; use with caution and monitor blood pressure closely. Consider other forms of contraception.

Dosing: Hepatic ImpairmentContraindicated in patients with hepatic impairment.

Administration: OralAdminister at the same time each day.

Dietary ConsiderationsShould be taken at same time each day.

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to ethinyl estradiol, etonogestrel, desogestrel, or any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); cerebral vascular disease, coronary artery disease, valvular heart disease with complications, severe hypertension; diabetes mellitus with vascular involvement; severe headache with focal neurological symptoms; known or suspected breast carcinoma, endometrial cancer, estrogen-dependent neoplasms, undiagnosed abnormal genital bleeding; hepatic dysfunction or tumor, cholestatic jaundice of pregnancy, jaundice with prior combination hormonal contraceptive use; major surgery with prolonged immobilization; heavy smoking (≥15 cigarettes/day) in patients >35 years of age; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Smokers: See “Special populations” below.

Concerns related to adverse effects:

- Breast cancer: The use of combination hormonal contraceptives has been associated with a slight increase in frequency of breast cancer, however, studies are not consistent.
- Glucose intolerance: Combination hormonal contraceptives may cause glucose intolerance.
- Lipid effects: Combination hormonal contraceptives may effect serum triglyceride and lipoprotein levels. Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis (has been reported rarely with combination hormonal contraceptives); discontinue permanently if papilledema or retinal vascular lesions are observed on examination.
- Thromboembolism: May increase the risk of thromboembolism.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with risk factors for coronary artery disease; may lead to increased risk of myocardial infarction. May have a dose-related risk of vascular disease and hypertension; women with hypertension should be encouraged to use another form of contraception.
- Depression: Use with caution in patients with depression.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.
- Gallbladder disease: May have a dose-related risk of gallbladder disease.
- Migraine: Use with caution in patients with a history of migraine.
- Renal impairment: Women with renal disease should be encouraged to use another form of contraception.

Special populations:

- Pediatrics: Not for use prior to menarche.
- Smokers: **[U.S. Boxed Warning]: The risk of cardiovascular side effects increases in women who smoke cigarettes, especially those who are >35 years of age; women who use combination hormonal contraceptives should be strongly advised not to smoke.**
- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- HIV infection protection: Combination hormonal contraceptives do not protect against HIV infection or other sexually-transmitted diseases.
- Minimum effective dosage: The minimum dosage combination of estrogen/progestin that will effectively treat the individual patient should be used. New patients should be started on products containing ≤0.035 mg of estrogen per tablet.

Pregnancy Risk FactorX

Pregnancy ConsiderationsPregnancy should be ruled out prior to treatment and discontinued if pregnancy occurs. In general, the use of combination hormonal contraceptives when inadvertently taken early in pregnancy have not been associated with teratogenic effects. Due to increased risk of thromboembolism postpartum, combination hormonal contraceptives should not be started earlier than 4-6 weeks following delivery. Hormonal contraceptives may be less effective in obese patients. An increase in oral contraceptive failure was noted in women with a BMI >27.3. Similar findings were noted in patients weighing ≥90 kg (198 lb) using the contraceptive patch.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsJaundice and breast enlargement in the nursing infant have been reported following the use of combination hormonal contraceptives. May decrease the quality and quantity of breast milk; a nonhormonal form of contraception is recommended.

Adverse ReactionsThe following reactions have been associated with oral contraceptive use:

Increased risk or evidence of association with use:

Cardiovascular: Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, hypertension, mesenteric thrombosis, MI, venous thrombosis (with or without embolism)

Gastrointestinal: Gallbladder disease

Hepatic: Hepatic adenomas, liver tumors (benign)

Local: Thrombophlebitis

Ocular: Retinal thrombosis

Respiratory: Pulmonary embolism

Adverse reactions considered drug related:

Cardiovascular: Edema, varicose vein aggravation

Central nervous system: Depression, migraine, mood changes

Dermatologic: Chloasma, melasma, rash (allergic)

Endocrine & metabolic: Amenorrhea, breakthrough bleeding, breast changes (enlargement, pain, secretion, tenderness), fluid retention, infertility (temporary), lactation decreased (with use immediately postpartum), menstrual flow changes, spotting

Gastrointestinal: Abdominal bloating, abdominal cramps, abdominal pain, appetite changes, nausea, weight changes, vomiting

Genitourinary: Cervical ectropion, cervical secretion, vaginal candidiasis, vaginitis

Hematologic: Folate decreased, porphyria exacerbation

Hepatic: Cholestatic jaundice

Neuromuscular & skeletal: Chorea exacerbation

Ocular: Contact lens intolerance, corneal curvature changes (steepening)

Miscellaneous: Anaphylactic/anaphylactoid reactions (including angioedema, circulatory collapse, respiratory collapse, urticaria), SLE exacerbation

Adverse reactions in which association is not confirmed or denied: Acne, Budd-Chiari syndrome, cataracts, colitis, cystitis-like syndrome, dizziness, dysmenorrhea, erythema multiforme, erythema nodosum, headache, hemolytic uremic syndrome, hemorrhagic eruption, hirsutism, libido changes, nervousness, optic neuritis (with or without partial or complete loss of vision), pancreatitis, premenstrual syndrome, renal function impaired, scalp hair loss

Metabolism/Transport Effects

Ethinyl estradiol: **Substrate** of CYP2C9 (minor), 3A4 (major), 3A5-7 (minor); **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C8 (weak), 2C19 (weak), 3A4 (weak)

Desogestrel: **Substrate** of CYP2C19 (major)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Armodafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Estrogens) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Colesevelam: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Griseofulvin: May increase the metabolism of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

LamoTRIgine: Oral Contraceptive (Estrogens) may decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Modafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Average AUC values were unchanged, but there was evidence of substantial patient-to-patient variability in response to this combination. *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

Nafcillin: May increase the metabolism of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Protease Inhibitors: Oral Contraceptive (Estrogens) may diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Rufinamide: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Estrogens) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy*

modification

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

TiZANidine: Oral Contraceptive (Estrogens) may increase the serum concentration of TiZANidine. *Risk C: Monitor therapy*

Topiramate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Oral Contraceptive (Estrogens) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Estrogens). Oral Contraceptive (Estrogens) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: CNS effects of caffeine may be enhanced if combination hormonal contraceptives are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations and would be expected to increase progesterone serum levels as well; clinical implications are unclear.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca. Herbs with progestogenic properties may enhance the adverse/toxic effect of progestins; examples include bloodroot, chasteberry, damiana, oregano, yucca.

Monitoring ParametersBefore starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision, sudden onset of proptosis, diplopia, migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Nursing: Physical Assessment/MonitoringMonitor blood pressure on a regular basis. Assess for adverse reactions and potential drug interactions. Assess knowledge/teach importance of regular (monthly) blood pressure checks and annual physical assessment, Pap smear, and vision assessment. Teach importance of maintaining prescribed schedule of dosing. **Pregnancy risk factor X:** Do not use if patient is pregnant.

Patient EducationOral contraceptives do not protect against HIV infection or other sexually-transmitted diseases. Take exactly as directed by prescriber (see package insert). You are at risk of becoming pregnant if doses are missed. Detailed and complete information on dosing and missed doses can be found in the package insert. Be aware that some medications may reduce the effectiveness of oral contraceptives; an alternate form of contraception may be needed. Check all medicines (prescription and over-the-counter), herbal and alternative products with prescriber. It is important that you check your blood pressure monthly (same day each month) and that you have an annual physical assessment, Pap smear, and vision exam while taking this medication. Avoid smoking while taking this medication; smoking increases risk of adverse effects, including thromboembolic events and heart attacks. You may experience loss of appetite (small frequent meals will help); or constipation (increased exercise, fluids, fruit, fiber, or stool softeners may help). If you have diabetes, use accurate serum glucose testing to identify any changes in glucose tolerance; notify prescriber of significant changes so antidiabetic medication can be adjusted if necessary. Report immediately pain or muscle soreness; warmth, swelling, pain, or redness in calves; shortness of breath; sudden loss of vision; unresolved leg/foot swelling; change in menstrual pattern (unusual bleeding, amenorrhea, breakthrough spotting); breast tenderness that does not go away; acute abdominal cramping; signs of vaginal infection (drainage, pain, itching); CNS changes (blurred vision, confusion, acute anxiety, or unresolved depression); chest pain; severe headache or vomiting; weakness in arm or leg; severe abdominal pain or tenderness; jaundice; or significant weight gain (>5 lb/week). Notify prescriber of changes in contact lens tolerance. **Pregnancy/breast-feeding precautions:** This medication should not be used during pregnancy. If you suspect you may become pregnant, contact prescriber immediately.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, low-dose formulations:

Kariva™:

Day 1-21: Ethinyl estradiol 0.02 mg and desogestrel 0.15 mg [21 white tablets]

Day 22-23: 2 inactive light green tablets

Day 24-28: Ethinyl estradiol 0.01 mg [5 light blue tablets] (28s)

Mircette®:

Day 1-21: Ethinyl estradiol 0.02 mg and desogestrel 0.15 mg [21 white tablets]

Day 22-23: 2 inactive green tablets

Day 24-28: Ethinyl estradiol 0.01 mg [5 yellow tablets] (28s)

Tablet, monophasic formulations:

Apri® 28: Ethinyl estradiol 0.03 mg and desogestrel 0.15 mg (28s) [21 rose tablets and 7 white inactive tablets]

Desogen®, Reclipsen™, Solia™: Ethinyl estradiol 0.03 mg and desogestrel 0.15 mg (28s) [21 white tablets and 7 green inactive tablets]

Ortho-Cept® 28: Ethinyl estradiol 0.03 mg and desogestrel 0.15 mg (28s) [21 orange tablets and 7 green inactive tablets]

Tablet, triphasic formulations:

Cesia™, Cyclessa®:

Day 1-7: Ethinyl estradiol 0.025 mg and desogestrel 0.1 mg [7 light yellow tablets]

Day 8-14: Ethinyl estradiol 0.025 mg and desogestrel 0.125 mg [7 orange tablets]

Day 14-21: Ethinyl estradiol 0.025 mg and desogestrel 0.15 mg [7 red tablets]

Day 21-28: 7 green inactive tablets (28s)

Velivet™:

Day 1-7: Ethinyl estradiol 0.025 mg and desogestrel 0.1 mg [7 beige tablets]

Day 8-14: Ethinyl estradiol 0.025 mg and desogestrel 0.125 mg [7 orange tablets]

Day 14-21: Ethinyl estradiol 0.025 mg and desogestrel 0.15 mg [7 pink tablets]

Day 21-28: 7 white inactive tablets (28s)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Cyclessa)

(28): $56.39

Tablets (Desogen)

0.15-30 mg-mcg (28): $59.61

Tablets (Kariva)

0.15-0.02/0.01 mg (28): $56.15

Tablets (Mircette)

0.15-0.02/0.01 mg (28): $65.99

Tablets (Ortho-Cept (28))

0.15-30 mg-mcg (28): $54.99

Tablets (Reclipsen)

0.15-30 mg-mcg (28): $32.99

Tablets (Velivet)

(28): $30.28

Mechanism of ActionCombination hormonal contraceptives inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of gonadotropin secretion of a follicle-stimulating hormone (FSH) and luteinizing hormone by the anterior pituitary. The follicular phase FSH and midcycle surge of gonadotropins are inhibited. In addition, combination hormonal contraceptives produce alterations in the genital tract, including changes in the cervical mucus, rendering it unfavorable for sperm penetration even if ovulation occurs. Changes in the endometrium may also occur, producing an unfavorable environment for nidation. Combination hormonal contraceptive drugs may alter the tubal transport of the ova through the fallopian tubes. Progestational agents may also alter sperm fertility.

Pharmacodynamics/Kinetics

Absorption: Desogestrel and ethinyl estradiol: Rapid and complete

Protein binding: Etonogestrel (active metabolite): 98%, primarily to sex hormone-binding globulin; Ethinyl estradiol: primarily bound to albumin

Metabolism:

Desogestrel: Hepatic via CYP2C9 to active metabolite etonogestrel (3-keto-desogestrel); etonogestrel metabolized via CYP3A4

Ethinyl estradiol: Hepatic; forms metabolites

Half-life elimination: Etonogestrel: ~38 hours; Ethinyl estradiol: ~26 hours

Excretion: Etonogestrel and ethinyl estradiol: Urine and feces (as metabolites)

Pharmacotherapy PearlsThe World Health Organization (WHO) has issued revised management recommendations for missed combined oral contraceptive pills. Refer to the following reference for a complete presentation and discussion of the guidelines:

> Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit, "Faculty Statement from the CEU on a New Publication: WHO Selected Practice Recommendations for Contraceptive Use Update. Missed Pills: New Recommendations," *J Fam Plann Reprod Health Care*, 2005, 31(2):153-5.

Dental Health: Effects on Dental TreatmentWhen prescribing antibiotics, patient must be warned to use additional methods of birth control if on oral contraceptives.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentBarbiturates decrease the effects of oral contraceptives; may increase the toxicity of the benzodiazepines and TCAs. The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Cardiovascular ConsiderationsIt is important to recognize that hormone-based contraceptives may induce or worsen hypertension. These problems are less severe with low-dose ones. Furthermore, hormone-based contraceptives may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on these contraceptives long-term undergo monitoring of blood pressure and avoid cigarette use.

Index TermsDesogestrel and Ethinyl Estradiol; Ortho Cept

References

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“Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection,” August 13, 2001. Available at: http://www.aidsinfo.nih.gov. Accessed September 5, 2001.

Holt VL, Scholes D, Wicklund KG, et al, “Body Mass Index, Weight, and Oral Contraceptive Failure Risk,” *Obstet Gynecol*, 2005, 105(1):46-52. [PubMed 15625141]

Orme ML, Back DJ, and Breckenridge AM, “Clinical Pharmacokinetics of Oral Contraceptive Steroids,” *Clin Pharmacokinet*, 1983, 8(2):95-136. [PubMed 6342899]

Shenfield GM and Griffin JM, “Clinical Pharmacokinetics of Contraceptive Steroids. An Update,” *Clin Pharmacokinet*, 1991, 20(1):15-37.[PubMed 2029800]

International Brand NamesCiclidon (CN); Desmin (DE); Desolett (TR); Desolett 28 (SE); Gracial 28 (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PH, QA, SA, SY, YE); Lamuna (DE); Lovina (DE); Marvelon (AE, AR, AT, BE, BF, BG, BH, BJ, CH, CI, CL, CN, CO, CY, CZ, DE, DK, EC, EE, EG, ET, FI, GB, GH, GM, GN, GR, HK, HN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PK, PT, PY, QA, RU, SA, SC, SD, SL, SN, SY, TN, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Marvelon 21 (NZ, TH, TW); Marvelon 28 (AU, DK, ID, NZ, PH, TH); Marviol (IE); Mercilon (FR, PH); Microdiol (BR, IL); Miravelle Suave (CO); Novelon (IN); Novynette (BB, BM, BS, BZ, GY, HK, JM, NL, SR, TT); Oilezz (TH); Primera 30 (BR); Regulon (BG, MY); Varnoline (FR)

Ethinyl Estradiol and Drospirenone

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English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ETH in il es tra DYE ole & droh SPYE re none)

U.S. Brand NamesOcella™; Yasmin®; Yaz®

Canadian Brand NamesYasmin®

Pharmacologic CategoryContraceptive; Estrogen and Progestin Combination

Use: Labeled IndicationsFemales: Prevention of pregnancy; treatment of premenstrual dysphoric disorder (PMDD); treatment of acne

Use: Unlabeled/InvestigationalTreatment of hypermenorrhea (menorrhagia); pain associated with endometriosis; dysmenorrhea; dysfunctional uterine bleeding

Dosing: Adults

Acne (Yaz®): Females: Oral: Refer to dosing for contraception.

Contraception (Yasmin®, Yaz®), PMDD (Yaz®): Female: Oral: Dosage is 1 tablet daily for 28 consecutive days. Dose should be taken at the same time each day, either after the evening meal or at bedtime. Dosing may be started on the first day of menstrual period (Day 1 starter) or on the first Sunday after the onset of the menstrual period (Sunday starter).

Day 1 starter: Dose starts on first day of menstrual cycle taking 1 tablet daily.

Sunday starter: Dose begins on first Sunday after onset of menstruation; if the menstrual period starts on Sunday, take first tablet that very same day. **With a Sunday start, an additional method of contraception should be used until after the first 7 days of consecutive administration.**

If all doses have been taken on schedule and one menstrual period is missed, continue dosing cycle. If two consecutive menstrual periods are missed, pregnancy test is required before new dosing cycle is started.

If doses have been missed during the first 3 weeks and the menstrual period is missed, pregnancy should be ruled out prior to continuing treatment.

Missed doses (monophasic formulations) (refer to package insert for complete information):

One dose missed: Take as soon as remembered or take 2 tablets next day

Two consecutive doses missed in the first 2 weeks: Take 2 tablets as soon as remembered or 2 tablets next 2 days. **An additional method of contraception should be used for 7 days after missed dose.**

Two consecutive doses missed in week 3 or three consecutive doses missed at any time: **An additional method of contraception must be used for 7 days after a missed dose.**

Day 1 starter: Current pack should be discarded, and a new pack should be started that same day.

Sunday starter: Continue dose of 1 tablet daily until Sunday, then discard the rest of the pack, and a new pack should be started that same day.

Any number of doses missed in week 4: Continue taking one pill each day until pack is empty; no back-up method of contraception is needed

Dosing: Pediatric

Acne (Yaz®): Females: Children ≥14 years: Oral: Refer to adult dosing.

Contraception (Yasmin®, Yaz®), PMDD (Yaz®): Females: Oral: Refer to adult dosing; not to be used prior to menarche.

Dosing: Renal ImpairmentContraindicated in patients with renal dysfunction (Cl_{cr} ≤50 mL/minute).

Dosing: Hepatic ImpairmentContraindicated in patients with hepatic dysfunction.

Calculations

- Creatinine Clearance: Adults

Administration: OralTo be taken at the same time each day, either after the evening meal or at bedtime

StorageStore at 25°C (77°F).

ContraindicationsHypersensitivity to ethinyl estradiol, drospirenone, or to any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); cerebral vascular disease, coronary artery disease, severe hypertension, valvular heart disease with thrombogenic complications; diabetes with vascular involvement; headache with focal neurological symptoms; known or suspected breast carcinoma, endometrial cancer, estrogen-dependent neoplasms, undiagnosed abnormal genital bleeding; renal insufficiency, hepatic dysfunction or tumor, adrenal insufficiency, cholestatic jaundice of pregnancy, jaundice with prior oral contraceptive use; major surgery with prolonged immobilization; heavy smoking (≥15 cigarettes/day) in patients >35 years of age; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Smokers: See “Special populations” below.

Concerns related to adverse effects:

- Breast cancer: The use of combination hormonal contraceptives has been associated with a slight increase in frequency of breast cancer, however, studies are not consistent.
- Glucose intolerance: Combination hormonal contraceptives may cause glucose intolerance.
- Hyperkalemia: Drospirenone has antimineralocorticoid activity that may lead to hyperkalemia in patients with renal insufficiency, hepatic dysfunction, or adrenal insufficiency; use caution with medications that may increase serum potassium.
- Lipid effects: Combination hormonal contraceptives may effect serum triglyceride and lipoprotein levels. Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis (has been reported rarely with combination hormonal contraceptives); discontinue permanently if papilledema or retinal vascular lesions are observed on examination.
- Thromboembolism: May increase the risk of thromboembolism.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with risk factors for coronary artery disease; may lead to increased risk of myocardial infarction. May have a dose-related risk of vascular disease and hypertension; women with hypertension should be encouraged to use another form of contraception.
- Depression: Use with caution in patients with depression.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.
- Gallbladder disease: May have a dose-related risk of gallbladder disease.
- Migraine: Use with caution in patients with a history of migraine.

Special populations:

- Pediatrics: Not for use prior to menarche.
- Smokers: **[U.S. Boxed Warning]: The risk of cardiovascular side effects increases in women who smoke cigarettes, especially those who are >35 years of age; women who use combination hormonal contraceptives should be strongly advised not to smoke.**
- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- Acne use: For use only in females ≥14 years of age who have reached menarche, who also desire combination hormonal contraceptive therapy, are unresponsive to topical acne treatments, and have no contraindications to combination hormonal contraceptive use.
- HIV infection protection: Oral contraceptives do not protect against HIV infection or other sexually-transmitted diseases.
- Minimum effective dosage: The minimum dosage combination of estrogen/progestin that will effectively treat the individual patient should be used.
- PMDD use: For use only in females who desire combination hormonal contraceptive therapy; use for more than 3 menstrual cycles has not been evaluated. Has not been evaluated for the treatment of premenstrual syndrome.

Pregnancy Risk FactorX

Pregnancy ConsiderationsIn general, the use of oral contraceptives when inadvertently taken early in pregnancy have not been associated with teratogenic effects. Esophageal atresia was reported in one infant with a single-cycle exposure to ethinyl estradiol and drospirenone *in utero* (association not known). Pregnancy should be ruled out prior to treatment and discontinued if pregnancy occurs. Due to increased risk of thromboembolism postpartum, do not start oral contraceptives earlier than 4-6 weeks following delivery. Hormonal contraceptives may be less effective in obese patients. An increase in oral contraceptive failure was noted in women with a BMI >27.3. Similar findings were noted in patients weighing ≥90 kg (198 lb) using the contraceptive patch.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsThe amount of drospirenone excreted in breast milk is ~0.02%, resulting in a maximum of ~3 mcg/day drospirenone to the infant. Jaundice and breast enlargement in the nursing infant have been reported following the use of other oral contraceptives. In addition, may decrease the quality and quantity of breast milk. Other forms of contraception are recommended while breast-feeding.

Adverse Reactions

>1%:

Central nervous system: Depression, dizziness, emotional lability, fever, headache, migraine, nervousness, pain

Dermatologic: Acne, pruritus, rash

Endocrine & metabolic: Amenorrhea, breast pain, dysmenorrhea, hyperlipidemia, intermenstrual bleeding, libido decreased, menstrual irregularities

Gastrointestinal: Abdomen enlarged, abdominal pain, diarrhea, dyspepsia, gastroenteritis, nausea, tooth disorder, vomiting, weight gain

Genitourinary: Cystitis, leukorrhea, papanicolaou smear suspicious, pelvic pain, UTI, vaginal moniliasis, vaginitis

Neuromuscular & skeletal: Back pain, extremity pain, weakness

Respiratory: Bronchitis, cough, pharyngitis, rhinitis, sinusitis, upper respiratory infection

Miscellaneous: Allergic reaction, flu-like syndrome, infection

Adverse reactions reported with other oral contraceptives: Appetite changes, antithrombin III decreased, arterial thromboembolism, benign liver tumors, breast changes, Budd-Chiari syndrome, carbohydrate intolerance, cataracts, cerebral hemorrhage, cerebral thrombosis, cervical changes, change in corneal curvature (steepening), cholestatic jaundice, colitis, contact lens intolerance, decreased lactation (postpartum), deep vein thrombosis, diplopia, edema, erythema multiforme, erythema nodosum; factors VII, VIII, IX, X increased; folate serum concentrations decreased, gallbladder disease, glucose intolerance, hemolytic uremic syndrome, hemorrhagic eruption, hepatic adenomas, hirsutism, hypercalcemia, hyperglycemia, hypertension, melasma, mesenteric thrombosis, MI, papilledema, platelet aggregability increased, porphyria, premenstrual syndrome, proptosis, prothrombin increased, pulmonary thromboembolism, renal function impairment, retinal thrombosis, sex hormone-binding globulin increased, thrombophlebitis, thyroid-binding globulin increased, total thyroid hormone (T_4) increased, triglycerides/phospholipids increased, vaginal candidiasis

Metabolism/Transport Effects

Ethinyl estradiol: **Substrate** of CYP2C9 (minor), 3A4 (major), 3A5-7 (minor); **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C8 (weak), 2C19 (weak), 3A4 (weak)

Drospirenone: **Substrate** of CYP3A4 (minor); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2C19 (weak), 3A4 (weak)

Drug Interactions

ACE Inhibitors: Potassium-Sparing Diuretics may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Ammonium Chloride: Potassium-Sparing Diuretics may enhance the adverse/toxic effect of Ammonium Chloride. Specifically the risk of systemic acidosis. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Aprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Armodafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Estrogens) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Cardiac Glycosides: Potassium-Sparing Diuretics may diminish the therapeutic effect of Cardiac Glycosides. Specifically, the inotropic effects. *Risk C: Monitor therapy*

Colesevelam: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Griseofulvin: May increase the metabolism of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

LamoTRIgine: Oral Contraceptive (Estrogens) may decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Mitotane: Potassium-Sparing Diuretics may diminish the therapeutic effect of Mitotane. High dose diuretics (eg, Cushings syndrome) may present significantly higher risk than low doses (eg, CHF). *Risk D: Consider therapy modification*

Modafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Average AUC values were unchanged, but there was evidence of substantial patient-to-patient variability in response to this combination. *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

Nafcillin: May increase the metabolism of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Potassium Salts: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Drospirenone may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: Oral Contraceptive (Estrogens) may diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

QuiNIDine: Potassium-Sparing Diuretics may diminish the therapeutic effect of QuiNIDine. *Risk C: Monitor therapy*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Rufinamide: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Estrogens) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

TiZANidine: Oral Contraceptive (Estrogens) may increase the serum concentration of TiZANidine. *Risk C: Monitor therapy*

Topiramate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Oral Contraceptive (Estrogens) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Estrogens). Oral Contraceptive (Estrogens) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: CNS effects of caffeine may be enhanced if oral contraceptives are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations; clinical implications are unclear.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca. Herbs with progestogenic properties may enhance the adverse/toxic effect of progestins; examples include bloodroot, chasteberry, damiana, oregano, yucca.

Monitoring ParametersBefore starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision, sudden onset of proptosis, diplopia, migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; serum potassium in high-risk patients and those on medications with potassium-retaining properties. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Nursing: Physical Assessment/MonitoringMonitor or teach patient to monitor blood pressure on a regular (monthly) basis, and the importance of annual physical examinations (including Pap smear and vision exam). Assess knowledge/teach patient the importance of maintaining prescribed schedule of dosing, possible side effects, appropriate interventions, and adverse reactions to report. **Pregnancy risk factor X:** Determine patient is not pregnant prior to prescribing.

Patient EducationTake exactly as directed by prescriber (see package insert). An additional form of contraception should be used until after the first 7 consecutive days of administration. You are at risk of becoming pregnant if doses are missed. If you miss a dose, take as soon as possible or double the dose the next day. If two or more consecutive doses are missed, contact prescriber for restarting directions. Detailed and complete information on dosing and missed doses can be found in the package insert. If any number of doses are missed in week 4, continue taking one pill each day until pack is empty; no back-up method of contraception is needed. Be aware that some medications may reduce the effectiveness of oral contraceptives; an alternate form of contraception may be needed (see Drug Interactions). It is important that you check your blood pressure monthly (on same day each month) and report any increased blood pressure to prescriber. Have an annual physical assessment, Pap smear, and vision exam while taking this medication. Avoid smoking while taking this medication; smoking increases risk of adverse effects, including thromboembolic events and heart attacks. You may experience loss of appetite (small frequent meals will help); or constipation (increased exercise, fluids, fruit, fiber, or stool softeners may help). If you have diabetes, you should use accurate serum glucose testing to identify any changes in glucose tolerance; notify prescriber of significant changes so antidiabetic medication can be adjusted if necessary. Report immediately pain or muscle soreness; warmth, swelling, pain, or redness in calves; shortness of breath; sudden loss of vision; unresolved leg/foot swelling or weight gain (>5 lb); change in menstrual pattern (unusual bleeding, amenorrhea, breakthrough spotting); breast tenderness that does not go away; acute abdominal cramping; signs of vaginal infection (drainage, pain, itching); CNS changes (blurred vision, confusion, acute anxiety, or unresolved depression); chest pain; severe headache or vomiting; severe abdominal pain or tenderness; weakness in arm or leg; jaundice; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Ocella™: Ethinyl estradiol 0.03 mg and drospirenone 3 mg (28s) [21 yellow active tablets and 7 white inactive tablets]

Yasmin®: Ethinyl estradiol 0.03 mg and drospirenone 3 mg (28s) [21 yellow active tablets and 7 white inactive tablets]

Yaz®: Ethinyl estradiol 0.02 mg and drospirenone 3 mg (28s) [24 light pink tablets and 4 white inactive tablets]

Generic AvailableNo

ManufacturerBerlex Laboratories, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Ocella)

3-0.03 mg (28): $54.99

Tablets (Yasmin 28)

3-0.03 mg (28): $65.99

Tablets (YAZ)

3-0.02 mg (28): $57.99

Mechanism of ActionCombination oral contraceptives inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of gonadotropin secretion of a follicle-stimulating hormone (FSH) and luteinizing hormone by the anterior pituitary. The follicular phase FSH and midcycle surge of gonadotropins are inhibited. In addition, oral contraceptives produce alterations in the genital tract, including changes in the cervical mucus, rendering it unfavorable for sperm penetration even if ovulation occurs. Changes in the endometrium may also occur, producing an unfavorable environment for nidation. Oral contraceptive drugs may alter the tubal transport of the ova through the fallopian tubes. Progestational agents may also alter sperm fertility. Drospirenone is a spironolactone analogue with antimineralocorticoid and antiandrogenic activity.

Pharmacodynamics/Kinetics

Distribution: Drospirenone: 4 L/kg; Ethinyl estradiol: 4-5 L/kg

Protein binding: Drospirenone: Serum proteins (excluding sex hormone-binding globulin and corticosteroid-binding globulin): 97%; Ethinyl estradiol: ~98%

Metabolism: Drospirenone: To inactive metabolites, minor metabolism hepatically via CYP3A4; Ethinyl estradiol: Hepatic via CYP3A4; forms metabolites; undergoes enterohepatic circulation

Bioavailability: Drospirenone: 76%; Ethinyl estradiol: 40%

Half-life elimination: Drospirenone: 30 hours; Ethinyl estradiol: ~24 hours

Time to peak: 1-3 hours

Excretion: Drospirenone, ethinyl estradiol: Urine and feces

Pharmacotherapy PearlsThe World Health Organization (WHO) has issued revised management recommendations for missed combined oral contraceptive pills. Refer to the following reference for a complete presentation and discussion of the guidelines:

Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit, "Faculty Statement from the CEU on a New Publication: WHO Selected Practice Recommendations for Contraceptive Use Update. Missed Pills: New Recommendations," *J Fam Plann Reprod Health Care*, 2005, 31(2):153-5.

Dental Health: Effects on Dental TreatmentWhen prescribing antibiotics, patient must be warned to use additional methods of birth control if on oral contraceptives.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentMay cause flu-like symptoms, take this into consideration if also concerned about SSRI discontinuation syndrome. Carbamazepine and topiramate may increase the metabolism of estradiol, leading to a decrease in serum concentrations. Estrogens may inhibit the metabolism of some benzodiazepines (alprazolam, chlordiazepoxide, diazepam), TCAs, and selegiline. Estrogens may increase the clearance of lorazepam, oxazepam, and temazepam. The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Index TermsDrospirenone and Ethinyl Estradiol

References

Burkman R, Schlesselman JJ, and Zieman M, “Safety Concerns and Health Benefits Associated With Oral Contraception,” *Am J Obstet Gynecol*, 2004, 190(4 Suppl):5-22.

Holt VL, Scholes D, Wicklund KG, et al, “Body Mass Index, Weight, and Oral Contraceptive Failure Risk,” *Obstet Gynecol*, 2005, 105(1):46-52.[PubMed 15625141]

Pearlstein TB, Bachmann GA, Zacur HA, et al, “Treatment of Premenstrual Dysphoric Disorder With a New Drospirenone-Containing Oral Contraceptive Formulation,” *Contraception*, 2005, 72(6):414-21.[PubMed 16307962]

International Brand NamesAngeliq (AU, EE, FR, GB, HK, ID, IE, IL, MY, PH, TH); Dileva (EC); Jasmine (FR); Jasminelle (FR); Yadine (HN); Yasmin (AR, AU, BR, CH, CN, CO, DK, ES, FI, GB, HK, ID, IE, IL, MX, MY, NL, NO, PE, PH, PT, PY, SE, SG, TH, TW, UY, VE, ZA); Yasminelle (BE, BG, CH, CZ, EE, NO, PT)

Ethinyl Estradiol and Ethynodiol Diacetate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Demulen® may be confused with Dalmane®, Demerol®

Pronunciation(ETH in il es tra DYE ole & e thye noe DYE ole dye AS e tate)

U.S. Brand NamesKelnor™; Zovia®

Canadian Brand NamesDemulen® 30

Pharmacologic Category[Contraceptive](); [Estrogen and Progestin Combination]()

Use: Labeled IndicationsPrevention of pregnancy

Use: Unlabeled/InvestigationalTreatment of hypermenorrhea (menorrhagia); pain associated with endometriosis; dysmenorrhea; dysfunctional uterine bleeding

Dosing: Adults

Females: Contraception: Oral:

- Schedule 1 (Sunday starter): Dose begins on first Sunday after onset of menstruation; if the menstrual period starts on Sunday, take first tablet that very same day. **With a Sunday start, an additional method of contraception should be used until after the first 7 days of consecutive administration:**
  - For 21-tablet package: 1 tablet/day for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken
  - For 28-tablet package: 1 tablet/day without interruption
- Schedule 2 (Day-1 starter): Dose starts on first day of menstrual cycle taking 1 tablet/day:
  - For 21-tablet package: 1 tablet/day for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken
  - For 28-tablet package: 1 tablet/day without interruption
- If all doses have been taken on schedule and one menstrual period is missed, continue dosing cycle. If two consecutive menstrual periods are missed, pregnancy test is required before new dosing cycle is started.
- Missed doses **monophasic formulations** (refer to package insert for complete information):
  - One dose missed: Take as soon as remembered or take 2 tablets next day
  - Two consecutive doses missed in the first 2 weeks: Take 2 tablets as soon as remembered or 2 tablets next 2 days. **An additional method of contraception should be used for 7 days after missed dose.**
  - Two consecutive doses missed in week 3 or three consecutive doses missed at any time: **An additional method of contraception must be used for 7 days after a missed dose:**
    - Schedule 1 (Sunday starter): Continue dose of 1 tablet daily until Sunday, then discard the rest of the pack, and a new pack should be started that same day.
    - Schedule 2 (Day-1 starter): Current pack should be discarded, and a new pack should be started that same day.

Dosing: PediatricFemales: Contraception: Oral: Refer to adult dosing; not to be used prior to menarche.

Dosing: Renal ImpairmentSpecific guidelines not available; use with caution and monitor blood pressure closely. Consider other forms of contraception.

Dosing: Hepatic ImpairmentContraindicated in patients with hepatic impairment.

Administration: OralAdminister at the same time each day.

Dietary ConsiderationsShould be taken with food at same time each day.

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to ethinyl estradiol, ethynodiol diacetate, or any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); cerebral vascular disease, coronary artery disease, valvular heart disease with complications, severe hypertension; diabetes mellitus with vascular involvement; severe headache with focal neurological symptoms; known or suspected breast carcinoma, endometrial cancer, estrogen-dependent neoplasms, undiagnosed abnormal genital bleeding; hepatic dysfunction or tumor, cholestatic jaundice of pregnancy, jaundice with prior combination hormonal contraceptive use; major surgery with prolonged immobilization; heavy smoking (≥15 cigarettes/day) in patients >35 years of age; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Smokers: See “Special populations” below.

Concerns related to adverse effects:

- Breast cancer: The use of combination hormonal contraceptives has been associated with a slight increase in frequency of breast cancer, however, studies are not consistent.
- Glucose intolerance: Combination hormonal contraceptives may cause glucose intolerance.
- Lipid effects: Combination hormonal contraceptives may effect serum triglyceride and lipoprotein levels. Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis (has been reported rarely with combination hormonal contraceptives); discontinue permanently if papilledema or retinal vascular lesions are observed on examination.
- Thromboembolism: May increase the risk of thromboembolism.

Disease-related adverse effects:

- Cardiovascular disease: Use with caution in patients with risk factors for coronary artery disease; may lead to increased risk of myocardial infarction. May have a dose-related risk of vascular disease and hypertension; women with hypertension should be encouraged to use a nonhormonal form of contraception.
- Depression: Use with caution in patients with depression.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.
- Gallbladder disease: May have a dose-related risk of gallbladder disease.
- Migraine: Use with caution in patients with a history of migraine.
- Renal impairment: Women with renal disease should be encouraged to use a nonhormonal form of contraception.

Special populations:

- Pediatrics: Not for use prior to menarche.
- Smokers: **[U.S. Boxed Warning]: The risk of cardiovascular side effects increases in women who smoke cigarettes, especially those who are >35 years of age; women who use combination hormonal contraceptives should be strongly advised not to smoke.**
- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- HIV infection protection: Oral contraceptives do not protect against HIV infection or other sexually-transmitted diseases.
- Minimum effective dosage: The minimum dosage combination of estrogen/progestin that will effectively treat the individual patient should be used. New patients should be started on products containing ≤0.035 mg of estrogen per tablet.

Pregnancy Risk FactorX

Pregnancy ConsiderationsPregnancy should be ruled out prior to treatment and discontinued if pregnancy occurs. In general, the use of combination hormonal contraceptives when inadvertently taken early in pregnancy have not been associated with teratogenic effects. Due to increased risk of thromboembolism postpartum, combination hormonal contraceptives should not be started earlier than 4-6 weeks following delivery. Hormonal contraceptives may be less effective in obese patients. An increase in oral contraceptive failure was noted in women with a BMI >27.3. Similar findings were noted in patients weighing ≥90 kg (198 lb) using the contraceptive patch.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsJaundice and breast enlargement in the nursing infant have been reported following the use of combination hormonal contraceptives. May decrease the quality and quantity of breast milk; a nonhormonal form of contraception is recommended.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, edema, hypertension, mesenteric thrombosis, MI

Central nervous system: Depression, dizziness, headache, migraine, nervousness, premenstrual syndrome, stroke

Dermatologic: Acne, erythema multiforme, erythema nodosum, hirsutism, loss of scalp hair, melasma (may persist), rash (allergic)

Endocrine & metabolic: Amenorrhea, breakthrough bleeding, breast enlargement, breast secretion, breast tenderness, carbohydrate intolerance, lactation decreased (postpartum), glucose tolerance decreased, libido changes, menstrual flow changes, sex hormone-binding globulins (SHBG) increased, spotting, temporary infertility (following discontinuation), thyroid-binding globulin increased, triglycerides increased

Gastrointestinal: Abdominal cramps, appetite changes, bloating, cholestasis, colitis, gallbladder disease, jaundice, nausea, vomiting, weight gain/loss

Genitourinary: Cervical erosion changes, cervical secretion changes, cystitis-like syndrome, vaginal candidiasis, vaginitis

Hematologic: Antithrombin III decreased, folate levels decreased, hemolytic uremic syndrome, norepinephrine induced platelet aggregability increased, porphyria, prothrombin increased; factors VII, VIII, IX, and X increased

Hepatic: Benign liver tumors, Budd-Chiari syndrome, cholestatic jaundice, hepatic adenomas

Local: Thrombophlebitis

Ocular: Cataracts, change in corneal curvature (steepening), contact lens intolerance, optic neuritis, retinal thrombosis

Renal: Impaired renal function

Respiratory: Pulmonary thromboembolism

Miscellaneous: Hemorrhagic eruption

Metabolism/Transport EffectsEthinyl estradiol: **Substrate** of CYP2C9 (minor), 3A4 (major), 3A5-7 (minor); **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C8 (weak), 2C19 (weak), 3A4 (weak)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Armodafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Estrogens) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Colesevelam: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Griseofulvin: May increase the metabolism of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

LamoTRIgine: Oral Contraceptive (Estrogens) may decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Modafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Average AUC values were unchanged, but there was evidence of substantial patient-to-patient variability in response to this combination. *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

Nafcillin: May increase the metabolism of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Protease Inhibitors: Oral Contraceptive (Estrogens) may diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Rufinamide: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Estrogens) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

TiZANidine: Oral Contraceptive (Estrogens) may increase the serum concentration of TiZANidine. *Risk C: Monitor therapy*

Topiramate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Oral Contraceptive (Estrogens) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Estrogens). Oral Contraceptive (Estrogens) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: CNS effects of caffeine may be enhanced if combination hormonal contraceptives are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations and would be expected to increase progesterone serum levels as well; clinical implications are unclear.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca. Herbs with progestogenic properties may enhance the adverse/toxic effect of progestins; examples include bloodroot, chasteberry, damiana, oregano, yucca.

Monitoring ParametersBefore starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision, sudden onset of proptosis, diplopia, migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Nursing: Physical Assessment/MonitoringMonitor or teach patient to monitor blood pressure on a regular basis. Monitor or teach patient to monitor for occurrence of adverse effects and symptoms to report. Assess knowledge/teach importance of regular (monthly) blood pressure checks and annual physical assessment, Pap smear, and vision assessment. Teach importance of maintaining prescribed schedule of dosing. **Pregnancy risk factor X:** Do not use if patient is pregnant.

Patient EducationOral contraceptives do not protect against HIV or other sexually-transmitted diseases. Take exactly as directed by prescriber (also see package insert). You are at risk of becoming pregnant if doses are missed. Detailed and complete information on dosing and missed doses can be found in the package insert. Be aware that some medications may reduce the effectiveness of oral contraceptives; an alternate form of contraception may be needed. Check all medicines (prescription and OTC), herbal, and alternative products with prescriber. It is important that you check your blood pressure monthly (on same day each month) and that you have an annual physical assessment, Pap smear, and vision assessment while taking this medication. Avoid smoking while taking this medication; smoking increases risk of adverse effects, including thromboembolic events and heart attacks. You may experience loss of appetite (small frequent meals will help); or constipation (increased exercise, fluids, fruit, fiber, or stool softeners may help). If you have diabetes, use accurate serum glucose testing to identify any changes in glucose tolerance; notify prescriber of significant changes so antidiabetic medication can be adjusted if necessary. Report immediately pain or muscle soreness; warmth, swelling, pain, or redness in calves; shortness of breath; sudden loss of vision; unresolved leg/foot swelling; change in menstrual pattern (unusual bleeding, amenorrhea, breakthrough spotting); breast tenderness that does not go away; acute abdominal cramping; signs of vaginal infection (drainage, pain, itching); CNS changes (blurred vision, confusion, acute anxiety, or unresolved depression); chest pain; severe headache or vomiting; weakness in arm or leg; severe abdominal pain or tenderness; jaundice; or significant weight gain (>5 lb/week). Notify prescriber of changes in contact lens tolerance. **Pregnancy/breast-feeding precautions:** This medication should not be used during pregnancy. If you suspect you may become pregnant, contact prescriber immediately. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, monophasic formulations:

Kelnor™ 1/35: Ethinyl estradiol 0.035 mg and ethynodiol diacetate 1 mg [21 light yellow tablets and 7 white inactive tablets] (28s)

Zovia® 1/35-28: Ethinyl estradiol 0.035 mg and ethynodiol diacetate 1 mg [21 light pink tablets and 7 white inactive tablets] (28s)

Zovia® 1/50-28: Ethinyl estradiol 0.05 mg and ethynodiol diacetate 1 mg [21 pink tablets and 7 white inactive tablets] (28s)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Kelnor 1/35)

1-35 mg-mcg (28): $28.99

Tablets (Zovia 1/35E (28))

1-35 mg-mcg (28): $32.99

Tablets (Zovia 1/50E (28))

1-50 mg-mcg (28): $33.99

Mechanism of ActionCombination hormonal contraceptives inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of gonadotropin secretion of a follicle-stimulating hormone (FSH) and luteinizing hormone by the anterior pituitary. The follicular phase FSH and midcycle surge of gonadotropins are inhibited. In addition, combination hormonal contraceptives produce alterations in the genital tract, including changes in the cervical mucus, rendering it unfavorable for sperm penetration even if ovulation occurs. Changes in the endometrium may also occur, producing an unfavorable environment for nidation. Combination hormonal contraceptive drugs may alter the tubal transport of the ova through the fallopian tubes. Progestational agents may also alter sperm fertility.

Pharmacodynamics/Kinetics

Ethynodiol diacetate (converted to norethindrone)

Metabolism: Hepatic conjugation

Half-life elimination: Terminal: 5-14 hours

See Norethindrone monograph.

Pharmacotherapy PearlsThe World Health Organization (WHO) has issued revised management recommendations for missed combined oral contraceptive pills. Refer to the following reference for a complete presentation and discussion of the guidelines:

Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit, "Faculty Statement from the CEU on a New Publication: WHO Selected Practice Recommendations for Contraceptive Use Update. Missed Pills: New Recommendations," *J Fam Plann Reprod Health Care*, 2005, 31(2):153-5.

Dental Health: Effects on Dental TreatmentWhen prescribing antibiotics, patient must be warned to use additional methods of birth control if on oral contraceptives.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric Treatment The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Cardiovascular Considerations It is important to recognize that hormone-based contraceptives may induce or worsen hypertension. These problems are less severe with low-dose ones.Furthermore, hormone-based contraceptives may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on these contraceptives long-term undergo monitoring of blood pressure and avoid cigarette use.

Index Terms Ethynodiol Diacetate and Ethinyl Estradiol

References

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Burkman R, Schlesselman JJ, and Zieman M, “Safety Concerns and Health Benefits Associated With Oral Contraception,” *Am J Obstet Gynecol*, 2004, 190(4 Suppl):5-22.

“Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection,” August 13, 2001. Available at: http://www.aidsinfo.nih.gov. Accessed September 5, 2001.

Holt VL, Scholes D, Wicklund KG, et al, “Body Mass Index, Weight, and Oral Contraceptive Failure Risk,” *Obstet Gynecol*, 2005, 105(1):46-52. [PubMed 15625141]

Orme ML, Back DJ, and Breckenridge AM, “Clinical Pharmacokinetics of Oral Contraceptive Steroids,” *Clin Pharmacokinet*, 1983, 8(2):95-136. [PubMed 6342899]

Shenfield GM and Griffin JM, “Clinical Pharmacokinetics of Contraceptive Steroids. An Update,” *Clin Pharmacokinet*, 1991, 20(1):15-37.[PubMed 2029800]

International Brand Names Ovulen 50 (NL)

Ethinyl Estradiol and Etonogestrel

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ETH in il es tra DYE ole & et oh noe JES trel)

U.S. Brand NamesNuvaRing®

Canadian Brand NamesNuvaRing®

Pharmacologic CategoryContraceptive; Estrogen and Progestin Combination

Use: Labeled IndicationsPrevention of pregnancy

Use: Unlabeled/InvestigationalTreatment of hypermenorrhea (menorrhagia); pain associated with endometriosis; dysmenorrhea; dysfunctional uterine bleeding

Dosing: AdultsFemales: Contraception: Vaginal: One ring, inserted vaginally and left in place for 3 consecutive weeks, then removed for 1 week. A new ring is inserted 7 days after the last was removed (even if bleeding is not complete) and should be inserted at approximately the same time of day the ring was removed the previous week.

Initial treatment should begin as follows (pregnancy should always be ruled out first):

No hormonal contraceptive use in the past month: Insert ring on the first day of menstrual cycle (“Day 1”). May also insert on days 2-5 even if bleeding is not complete, however, **a spermicide or barrier method of contraception should be used for the following 7 days.***

Switching from combination oral contraceptive: Ring can be inserted on any day within 7 days after the last **active** tablet in the cycle was taken and no later than the first day a new cycle of tablets would begin. Additional forms of contraception are not needed.

Switching from progestin-only contraceptive: **A spermicide or barrier method of contraception should be used for the following 7 days with any of the following.***

If previously using a progestin-only mini-pill, insert the ring on any day of the month; do not skip days between the last pill and insertion of the ring.

If previously using an implant, insert the ring on the same day of implant removal.

If previously using a progestin-containing IUD, insert the ring on day of IUD removal.

If previously using a progestin injection, insert the ring on the day the next injection would be given.

Following complete 1st trimester abortion: Insert ring within the first 5 days of abortion. If not inserted within 5 days, follow instructions for “No hormonal contraceptive use within the past month” and instruct patient to use a nonhormonal contraceptive in the interim.

Following delivery or 2nd trimester abortion: Insert ring 4 weeks postpartum (in women who are not breast-feeding) or following 2nd trimester abortion. **A spermicide or barrier method of contraception should be used for the following 7 days.***

If the ring is accidentally removed from the vagina at anytime during the 3-week period of use, it may be rinsed with cool or lukewarm water (not hot) and reinserted as soon as possible. If the ring is not reinserted within 3 hours, contraceptive effectiveness will be decreased. **A spermicide or barrier method of contraception should be used until the ring has been in place for 7 consecutive days.***

If the ring has been removed for longer than 1 week, pregnancy must be ruled out prior to restarting therapy. **A spermicide or barrier method of contraception should be used for the following 7 days.***

If the ring has been left in place for >3 weeks, a new ring should be inserted following a 1-week (ring-free) interval. Protection continues during week 4, however, if the ring is left in place >4 weeks, pregnancy must be ruled out prior to insertion and **a spermicide or barrier method of contraception should be used for the following 7 days.***

Disconnected ring: In the event the ring disconnects at the weld joint, discard and replace with a new ring.

***Note:** Diaphragms may interfere with proper ring placement, and therefore, are not recommended for use as an additional form of contraception.

Dosing: PediatricFemales: Contraception: Vaginal: Refer to adult dosing; not to be used prior to menarche.

Dosing: Renal ImpairmentSpecific guidelines not available; use with caution and monitor blood pressure closely. Consider other forms of contraception.

Dosing: Hepatic ImpairmentContraindicated in patients with hepatic impairment

Administration: OtherVaginal: Wash hands and remove ring from protective pouch (keep pouch for later ring disposal). Press sides of ring together between thumb and index finger and insert folded ring into vagina. Specific placement is not required for ring to be effective, but ring should be inserted far enough into the vagina as to be comfortable. To remove, hook index finger around rim and pull out. Vaginal ring **cannot** be disposed of in the toilet. New rings should be inserted at approximately the same time of day the ring was removed the previous week. If the ring accidentally falls out, it may be rinsed with cool or warm (not hot) water and replaced. However, it must be replaced within 3 hours. Refer to dosing if ring is out of place for >3 hours. Tampons do not interfere with the effectiveness of the ring; caution should be used when removing tampon not to remove ring. The ring may interfere with correct placement of diaphragms; diaphragms should not be used as a back-up method of contraception. Ensure proper vaginal placement of the ring to avoid inadvertent urinary bladder insertion.

Storage Prior to dispensing, store under refrigeration, 2°C to 8°C (36°F to 46°F). After dispensing, may be stored at room temperature of 25°C (77°F) for up to 4 months. Avoid direct sunlight or temperatures >30˚C (86˚F).

Contraindications Hypersensitivity to ethinyl estradiol, etonogestrel, or any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); major surgery with prolonged immobilization, cerebral vascular disease, coronary artery disease, valvular heart disease with complications, severe hypertension; diabetes mellitus with vascular involvement; severe headache with focal neurological symptoms; known or suspected breast carcinoma or personal history of breast cancer, endometrial cancer, estrogen-dependent neoplasms, undiagnosed abnormal genital bleeding; active liver disease or tumor, cholestatic jaundice of pregnancy, jaundice with prior combination hormonal contraceptive use; heavy smoking (≥15 cigarettes/day) in patients >35 years of age; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Smokers: See "Special populations" below.

Concerns related to adverse effects:

- Breast cancer: The use of combination hormonal contraceptives has been associated with a slight increase in frequency of breast cancer, however, studies are not consistent.
- Carbohydrate intolerance: May have adverse effects on glucose tolerance; use caution in women with diabetes.

Disease-related concerns:

- Lipid effects: Combination hormonal contraceptives may effect serum triglyceride and lipoprotein levels. Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis (has been reported rarely with combination hormonal contraceptives); discontinue permanently if loss of vision occurs, or if papilledema or retinal vascular lesions are observed on examination.
- Thromboembolism: May increase the risk of thromboembolism.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with risk factors for coronary artery disease; may lead to increased risk of myocardial infarction. May have a dose-related risk of vascular disease and hypertension; women with hypertension should be encouraged to use a nonhormonal form of contraception.
- Depression: Use with caution in patients with depression.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.
- Gallbladder disease: May have a dose-related risk of gallbladder disease.
- Hepatic impairment: Combination hormonal contraceptives may be poorly metabolized in women with hepatic impairment.
- Migraine: Use with caution in patients with a history of migraine.
- Renal impairment: Women with renal disease should be encouraged to use a nonhormonal form of contraception.

Special populations:

- Pediatrics: Not for use prior to menarche.
- Smokers: **[U.S. Boxed Warning]: The risk of cardiovascular side effects increases in women who smoke cigarettes, especially those who are >35 years of age; women who use combination hormonal contraceptives should be strongly advised not to smoke.**
- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Dosage form specific issues:

- Vaginal preparation: Vaginally-administered combination hormonal contraceptive agents may have a similar adverse effects associated with oral contraceptive products. In order to reduce some of the possible risks, the minimum dosage combination of estrogen/progestin that will effectively treat the individual patient should be used. May not be appropriate for use in women with conditions that make the vagina susceptible to irritation or ulceration. Ensure proper vaginal placement of the ring to avoid inadvertent urinary bladder insertion.

Other warnings/precautions:

- HIV infection protection: Combination hormonal contraceptives do not protect against HIV infection or other sexually-transmitted diseases.

Pregnancy Risk Factor X

Pregnancy Considerations Pregnancy should be ruled out prior to treatment and discontinued if pregnancy occurs. In general, the use of combination hormonal contraceptives, when inadvertently used early in pregnancy, have not been associated with teratogenic effects. Due to increased risk of thromboembolism postpartum, do not start earlier than 4-6 weeks following delivery. Hormonal contraceptives may be less effective in obese patients. An increase in oral contraceptive failure was noted in women with a BMI >27.3. Similar findings were noted in patients weighing ≥90 kg (198 lb) using the contraceptive patch.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsJaundice and breast enlargement in the nursing infant have been reported following the use of combination hormonal contraceptives. May decrease the quality and quantity of breast milk; alternative form of contraception is recommended.

Adverse Reactions

The most common adverse reactions associated with NuvaRing® (5% to 14%): Headache, nausea, sinusitis, upper respiratory tract infection, vaginal secretion, vaginitis, and weight gain. The following reactions have been associated with combination hormonal contraceptive use:

Increased risk or evidence of association with use:

Cardiovascular: Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, hypertension, mesenteric thrombosis, MI, venous thrombosis (with or without embolism)

Gastrointestinal: Gallbladder disease

Hepatic: Hepatic adenomas, liver tumors (benign)

Local: Thrombophlebitis

Ocular: Retinal thrombosis

Respiratory: Pulmonary embolism

Adverse reactions considered drug related:

Cardiovascular: Edema, varicose vein aggravation

Central nervous system: Depression, migraine, mood changes

Dermatologic: Chloasma, melasma, rash (allergic)

Endocrine & metabolic: Amenorrhea, breakthrough bleeding, breast changes (enlargement, pain, secretion, tenderness), fluid retention, infertility (temporary), lactation decreased (with use immediately postpartum), menstrual flow changes, spotting

Gastrointestinal: Abdominal bloating, abdominal cramps, abdominal pain, appetite changes, nausea, weight changes, vomiting

Genitourinary: Cervical ectropion, cervical secretion, vaginal candidiasis, vaginitis

Hematologic: Folate decreased, porphyria exacerbation

Hepatic: Cholestatic jaundice

Neuromuscular & skeletal: Chorea exacerbation

Ocular: Contact lens intolerance, corneal curvature changes (steepening)

Miscellaneous: Anaphylactic/anaphylactoid reactions (including angioedema, circulatory collapse, respiratory collapse, urticaria), SLE exacerbation

Adverse reactions in which association is not confirmed or denied: Acne, Budd-Chiari syndrome, cataracts, colitis, cystitis-like syndrome, dizziness, dysmenorrhea, erythema multiforme, erythema nodosum, headache, hemolytic uremic syndrome, hemorrhagic eruption, hirsutism, libido changes, nervousness, optic neuritis (with or without partial or complete loss of vision), pancreatitis, premenstrual syndrome, renal function impaired, scalp hair loss

Metabolism/Transport Effects

Ethinyl estradiol: **Substrate** of CYP2C9 (minor), 3A4 (major), 3A5-7 (minor); **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C8 (weak), 2C19 (weak), 3A4 (weak)

Etonogestrel: **Substrate** of CYP3A4 (minor)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Armodafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Estrogens) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Colesevelam: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Griseofulvin: May increase the metabolism of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

LamoTRIgine: Oral Contraceptive (Estrogens) may decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Modafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Average AUC values were unchanged, but there was evidence of substantial patient-to-patient variability in response to this combination. *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

Nafcillin: May increase the metabolism of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Protease Inhibitors: Oral Contraceptive (Estrogens) may diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Rufinamide: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Estrogens) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

TiZANidine: Oral Contraceptive (Estrogens) may increase the serum concentration of TiZANidine. *Risk C: Monitor therapy*

Topiramate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Oral Contraceptive (Estrogens) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Estrogens). Oral Contraceptive (Estrogens) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: CNS effects of caffeine may be enhanced if combination hormonal contraceptives are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations and would be expected to increase progesterone serum levels as well; clinical implications are unclear.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca. Herbs with progestogenic properties may enhance the adverse/toxic effect of progestins; examples include bloodroot, chasteberry, damiana, oregano, yucca.

Monitoring ParametersBefore starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision, sudden onset of proptosis, diplopia, migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. In patients with persistent urinary symptoms, assess for inadvertent urinary bladder insertion if ring is not otherwise located.

Monitoring: Lab TestsBlood pressure, breast exam, Pap smear, and pregnancy; lipid profiles in patients being treated for hyperlipidemias

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Ring, vaginal:

NuvaRing®: Ethinyl estradiol 0.015 mg/day and etonogestrel 0.12 mg/day (1s) [3-week duration]

Generic AvailableNo

ManufacturerOrganon Inc

Pricing: U.S. (www.drugstore.com)

Ring (NuvaRing)

0.12-0.015 mg/24 hrs (1): $65.03

Mechanism of ActionCombination hormonal contraceptives inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of gonadotropin secretion of a follicle-stimulating hormone (FSH) and luteinizing hormone by the anterior pituitary. The follicular phase FSH and midcycle surge of gonadotropins are inhibited. In addition, combination hormonal contraceptives produce alterations in the genital tract, including changes in the cervical mucus, rendering it unfavorable for sperm penetration even if ovulation occurs. Changes in the endometrium may also occur, producing an unfavorable environment for nidation. Combination hormonal contraceptive drugs may alter the tubal transport of the ova through the fallopian tubes. Progestational agents may also alter sperm fertility.

Pharmacodynamics/Kinetics

Duration: Serum levels (contraceptive effectiveness) decrease after 3 weeks of continuous use

Absorption: Ethinyl estradiol and etonogestrel: Rapid

Tampons do not interfere with absorption.

Protein binding:

Ethinyl estradiol: 98%, primarily to albumin

Etonogestrel: 32% to sex hormone-binding globulin (SHBG) and 66% to albumin; SHBG capacity is affected by plasma ethinyl estradiol levels

Metabolism:

Ethinyl estradiol: Hepatic via CYP3A4; forms metabolites (weak estrogenic activity)

Etonogestrel: Hepatic via CYP3A4; forms metabolites (activity not known)

Bioavailability: Vaginal: Ethinyl estradiol: ~56% Etonogestrel: 100%

Half-life elimination: Ethinyl estradiol: 45 hours; Etonogestrel: 29 hours

Time to peak: Vaginal: Ethinyl estradiol: 60 hours; Etonogestrel: 200 hours

Excretion: Ethinyl estradiol and etonogestrel: Urine, bile, and feces

Dental Health: Effects on Dental TreatmentWhen prescribing antibiotics, patient must be warned to use additional methods of birth control if on oral contraceptives.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentMay cause flu-like symptoms, take this into consideration if also concerned about SSRI discontinuation syndrome. Carbamazepine and topiramate may increase the metabolism of estradiol, leading to a decrease in serum concentrations. Estrogens may inhibit the metabolism of some benzodiazepines (alprazolam, chlordiazepoxide, diazepam), TCAs, and selegiline. Estrogens may increase the clearance of lorazepam, oxazepam, and temazepam. The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Index TermsEtonogestrel and Ethinyl Estradiol

References

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Orme ML, Back DJ, and Breckenridge AM, “Clinical Pharmacokinetics of Oral Contraceptive Steroids,” *Clin Pharmacokinet*, 1983, 8(2):95-136. [PubMed 6342899]

Shenfield GM and Griffin JM, “Clinical Pharmacokinetics of Contraceptive Steroids. An Update,” *Clin Pharmacokinet*, 1991, 20(1):15-37.[PubMed 2029800]

International Brand NamesNuvaRing (AU, BE, BR, CH, CN, DE, DK, EE, FI, FR, HN, IE, IL, IT, KP, MX, NL, SE)

Ethinyl Estradiol and Levonorgestrel

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Alesse® may be confused with Aleve®

Nordette® may be confused with Nicorette®

PREVEN® may be confused with Prevnar®

Seasonale® may be confused with Seasonique™

Seasonique™ may be confused with Seasonale®

Tri-Levlen® may be confused with Trilafon®

Triphasil® may be confused with Tri-Norinyl®

Pronunciation(ETH in il es tra DYE ole & LEE voe nor jes trel)

U.S. Brand NamesAlesse®; Aviane™; Enpresse™; Jolessa™; Lessina™; Levlen®; Levlite™; Levora®; Lutera™; Lybrel™; Nordette®; Portia™; Quasense™; Seasonale®; Seasonique™; Sronyx™; Triphasil®; Trivora®

Canadian Brand NamesAlesse®; Aviane®; Min-Ovral®; Seasonale®; Triphasil®; Triquilar®

Pharmacologic CategoryContraceptive; Estrogen and Progestin Combination

Use: Labeled IndicationsPrevention of pregnancy; postcoital contraception

Use: Unlabeled/InvestigationalTreatment of hypermenorrhea (menorrhagia); pain associated with endometriosis; dysmenorrhea; dysfunctional uterine bleeding

Dosing: AdultsFemales:

Contraception, 28-day cycle: Oral:

Schedule 1 (Sunday starter): Dose begins on first Sunday after onset of menstruation; if the menstrual period starts on Sunday, take first tablet that very same day. With a Sunday start, an additional method of contraception should be used until after the first 7 days of consecutive administration:

For 21-tablet package: 1 tablet/day for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken

For 28-tablet package: 1 tablet/day without interruption

Schedule 2 (Day-1 starter): Dose starts on first day of menstrual cycle taking 1 tablet/day:

For 21-tablet package: 1 tablet/day for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken

For 28-tablet package: 1 tablet/day without interruption

If all doses have been taken on schedule and one menstrual period is missed, continue dosing cycle. If two consecutive menstrual periods are missed, pregnancy test is required before new dosing cycle is started.

Missed doses **monophasic formulations** (refer to package insert for complete information):

One dose missed: Take as soon as remembered or take 2 tablets next day

Two consecutive doses missed in the first 2 weeks: Take 2 tablets as soon as remembered or 2 tablets next 2 days. An additional method of contraception should be used for 7 days after missed dose.

Two consecutive doses missed in week 3 or three consecutive doses missed at any time: An additional method of contraception must be used for 7 days after a missed dose:

Schedule 1 (Sunday starter): Continue dose of 1 tablet daily until Sunday, then discard the rest of the pack, and a new pack should be started that same day.

Schedule 2 (Day-1 starter): Current pack should be discarded, and a new pack should be started that same day.

Missed doses **biphasic/triphasic formulations** (refer to package insert for complete information):

One dose missed: Take as soon as remembered or take 2 tablets next day.

Two consecutive doses missed in week 1 or week 2 of the pack: Take 2 tablets as soon as remembered and 2 tablets the next day. Resume taking 1 tablet daily until the pack is empty. An additional method of contraception should be used for 7 days after a missed dose.

Two consecutive doses missed in week 3 of the pack: An additional method of contraception must be used for 7 days after a missed dose.

Schedule 1 (Sunday starter): Take 1 tablet every day until Sunday. Discard the remaining pack and start a new pack of pills on the same day.

Schedule 2 (Day-1 starter): Discard the remaining pack and start a new pack the same day.

Three or more consecutive doses missed: An additional method of contraception must be used for 7 days after a missed dose.

Schedule 1 (Sunday starter): Take 1 tablet every day until Sunday; on Sunday, discard the pack and start a new pack.

Schedule 2 (Day-1 starter): Discard the remaining pack and begin new pack of tablets starting on the same day.

Contraception, 91-day cycle (extended cycle regimen): Dose begins on first Sunday after onset of menstruation; if the menstrual period starts on Sunday, take first tablet that very same day. An additional method of contraception should be used until after the first 7 days of consecutive administration:

Seasonale®: One active tablet/day for 84 consecutive days, followed by 1 inactive tablet/day for 7 days; if all doses have been taken on schedule and one menstrual period is missed, pregnancy should be ruled out prior to continuing therapy.

Seasonique™: One active tablet/day for 84 consecutive days, followed by 1 low dose estrogen tablet/day for 7 days; if all doses have been taken on schedule and one menstrual period is missed, pregnancy should be ruled out prior to continuing therapy.

Missed doses:

One dose missed: Take as soon as remembered or take 2 tablets the next day

Two consecutive doses missed: Take 2 tablets as soon as remembered or 2 tablets the next 2 days. An additional nonhormonal method of contraception should be used for 7 consecutive days after the missed dose.

Three or more consecutive doses missed: Do not take the missed doses; continue taking 1 tablet/day until pack is complete. Bleeding may occur during the following week. An additional nonhormonal method of contraception should be used for 7 consecutive days after the missed dose.

Any number of pills during week 13: Throw away the missed pills and keep taking scheduled pills until the pack is finished. A back-up method of contraception is not needed

Contraception, continuous use (extended cycle regimen): Oral: Lybrel™: Take one tablet daily, at the same time each day, without a tablet-free interval. Therapy should be initiated as follows:

No previous contraception: Begin on the first day of menstrual cycle. Back-up contraception is not needed.

Previously taking a 21-day or 28-day combination hormonal contraceptive: Begin on day 1 of the withdrawal bleed (at the latest, 7 days after the last active tablet). Back-up contraception is not needed.

Previously using a progestin-only pill: Begin the day after taking a progestin only pill. Back-up contraception is needed for the first 7 days of therapy.

Previously using contraceptive implant: Begin the day of implant removal. Back-up contraception is needed for the first 7 days of therapy.

Previously using contraceptive injection: Begin when the next injection is due. Back-up contraception is needed for the first 7 days of therapy.

Missed doses:

One dose missed: Take as soon as remembered then take the next tablet at the regular time (2 tablets in 1 day). An additional nonhormonal method of contraception should also be used for 7 consecutive days.

Two consecutive doses missed: If remembered the day of the second missed tablet, take 2 tablets as soon as remembered, then 1 tablet the next day. If remembered the day after the second tablet is missed, take 2 tablets the day remembered, then 2 tablets the next day. An additional nonhormonal method of contraception should also be used for 7 consecutive days.

Three or more consecutive doses missed: Take 1 tablet daily and contact healthcare provider; do not take the missed pills. An additional nonhormonal method of contraception should also be used for 7 consecutive days.

Dosing: PediatricFemales: Contraception or emergency contraception: Oral: Refer to adult dosing; not to be used prior to menarche.

Dosing: Renal ImpairmentSpecific guidelines not available; use with caution and monitor blood pressure closely. Consider other forms of contraception.

Dosing: Hepatic ImpairmentContraindicated in patients with hepatic impairment.

Administration: OralAdminister at the same time each day.

Dietary ConsiderationsShould be taken at the same time each day.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to ethinyl estradiol, levonorgestrel, or any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); cerebral vascular disease, coronary artery disease, valvular heart disease with complications, severe/uncontrolled hypertension, thrombogenic rhythm disorders, hereditary or acquired thrombophilias; diabetes mellitus with vascular involvement; severe headache with focal neurological symptoms; known or suspected breast carcinoma, endometrial cancer, estrogen-dependent neoplasms, undiagnosed abnormal genital bleeding; hepatic dysfunction or tumor, cholestatic jaundice of pregnancy, jaundice with prior combination hormonal contraceptive use; major surgery with prolonged immobilization; heavy smoking (≥15 cigarettes/day) in patients >35 years of age; pregnancy

Canadian-labeling: Additional contraindication: Ocular lesions due to ophthalmic vascular disease including partial or complete loss of vision or defect in visual fields; severe dyslipoproteinemia; hereditary or acquired predisposition for venous or arterial thrombosis

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Smokers: See “Special populations” below.

Concerns related to adverse effects:

- Breast cancer: The use of combination hormonal contraceptives has been associated with a slight increase in frequency of breast cancer, however, studies are not consistent.
- Carbohydrate intolerance: May have adverse effects on glucose tolerance; use caution in women with diabetes.
- Lipid effects: Combination hormonal contraceptives may affect serum triglyceride and lipoprotein levels. Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis (has been reported rarely with combination hormonal contraceptives); discontinue permanently if papilledema or retinal vascular lesions are observed on examination.
- Thromboembolism: May increase the risk of thromboembolism.
- Vaginal bleeding: Presentation of irregular, unresolving vaginal bleeding warrants further evaluation including endometrial sampling, if indicated, to rule out malignancy; evaluate hypothalamic-pituitary-function in women with persistent (≥6 months) amenorrhea (especially associated with breast secretion) following discontinuation of therapy.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with risk factors for coronary artery disease; may lead to increased risk of myocardial infarction. May have a dose-related risk of vascular disease and hypertension; women with hypertension should be encouraged to use a nonhormonal form of contraception.
- Depression: Use with caution in patients with depression.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.
- Fibroids: Discontinue use with the onset of sudden enlargement, pain, or tenderness of fibroids (leiomyomata).
- Gallbladder disease: May have a dose-related risk of gallbladder disease; may worsen existing gallbladder disease.
- Hepatic adenomas: Extremely rare adenomas and focal nodular hyperplasia resulting in fatal intra-abdominal hemorrhage have been reported in association with long-term oral contraceptive use. Presentation of an abdominal mass, acute abdominal pain, or intra-abdominal bleeding warrants further evaluation to rule out source.
- Migraine: Use with caution in patients with a history of migraine.
- Renal impairment: Women with renal disease should be encouraged to use a nonhormonal form of contraception.

Special populations:

- Pediatrics: Not for use prior to menarche.
- Smokers: **[U.S. Boxed Warning]: The risk of cardiovascular side effects increases in women who smoke cigarettes, especially those who are >35 years of age; women who use combination hormonal contraceptives should be strongly advised not to smoke.**
- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- HIV infection protection: Combination hormonal contraceptives do not protect against HIV infection or other sexually-transmitted diseases.
- Extended cycle regimen: Contraceptives with an extended cycle regimen provide more hormonal exposure per year than conventional monthly contraceptives.
- Minimum effective dosage: The minimum dosage combination of estrogen/progestin that will effectively treat the individual patient should be used. New patients should be started on products containing ≤0.035 mg of estrogen per tablet.

Pregnancy Risk FactorX

Pregnancy ConsiderationsPregnancy should be ruled out prior to treatment and discontinued if pregnancy occurs. In general, the use of combination hormonal contraceptives when inadvertently taken early in pregnancy have not been associated with teratogenic effects. Due to increased risk of thromboembolism postpartum, combination hormonal contraceptives should not be started earlier than 4-6 weeks following delivery. Hormonal contraceptives may be less effective in obese patients. An increase in oral contraceptive failure was noted in women with a BMI >27.3. Similar findings were noted in patients weighing ≥90 kg (198 lb) using the contraceptive patch.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsJaundice and breast enlargement in the nursing infant have been reported following the use of combination hormonal contraceptives. May decrease the quality and quantity of breast milk; alternative form of contraception is recommended.

Adverse ReactionsThe following reactions have been associated with oral contraceptive use:

Increased risk or evidence of association with use:

Cardiovascular: Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, hypertension, mesenteric thrombosis, MI, venous thrombosis (with or without embolism)

Gastrointestinal: Gallbladder disease

Hepatic: Hepatic adenomas, liver tumors (benign)

Local: Thrombophlebitis

Ocular: Retinal thrombosis

Respiratory: Pulmonary embolism

Adverse reactions considered drug related:

Cardiovascular: Edema, varicose vein aggravation

Central nervous system: Depression, migraine, mood changes

Dermatologic: Chloasma, melasma, rash (allergic)

Endocrine & metabolic: Amenorrhea, breakthrough bleeding, breast changes (enlargement, pain, secretion, tenderness), carbohydrate tolerance decreased, fluid retention, infertility (temporary), lactation decreased (with use immediately postpartum), menstrual flow changes, spotting

Gastrointestinal: Abdominal bloating, abdominal cramps, abdominal pain, appetite changes, nausea, weight changes, vomiting

Genitourinary: Cervical ectropion, cervical secretion/erosion, endocervical hyperplasia, fibroid enlargement, vaginal candidiasis, vaginitis

Hematologic: Folate decreased, porphyria exacerbation

Hepatic: Cholestatic jaundice, focal nodular hyperplasia

Neuromuscular & skeletal: Chorea exacerbation

Ocular: Contact lens intolerance, corneal curvature changes (steepening)

Respiratory: Rhinitis

Miscellaneous: Anaphylactic/anaphylactoid reactions (including angioedema, circulatory collapse, respiratory collapse, urticaria), SLE exacerbation

Adverse reactions in which association is not confirmed or denied: Acne, auditory disturbances, Budd-Chiari syndrome, cataracts, cervical smear abnormal, colitis, cystitis-like syndrome, dizziness, dysmenorrhea, erythema multiforme, erythema nodosum, headache, hemolytic uremic syndrome, hemorrhagic eruption, hirsutism, libido changes, nervousness, optic neuritis (with or without partial or complete loss of vision), pancreatitis, premenstrual syndrome, renal function impaired, scalp hair loss

Metabolism/Transport Effects

Ethinyl estradiol: **Substrate** of CYP2C9 (minor), 3A4 (major), 3A5-7 (minor); **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C8 (weak), 2C19 (weak), 3A4 (weak)

Levonorgestrel: **Substrate** of CYP3A4 (major)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Armodafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy*

modification

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Estrogens) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Colesevelam: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Griseofulvin: May increase the metabolism of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

LamoTRIgine: Oral Contraceptive (Estrogens) may decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Modafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Average AUC values were unchanged, but there was evidence of substantial patient-to-patient variability in response to this combination. *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

Nafcillin: May increase the metabolism of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Protease Inhibitors: Oral Contraceptive (Estrogens) may diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Rufinamide: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Estrogens) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

TiZANidine: Oral Contraceptive (Estrogens) may increase the serum concentration of TiZANidine. *Risk C: Monitor therapy*

Topiramate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Oral Contraceptive (Estrogens) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Estrogens). Oral Contraceptive (Estrogens) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: CNS effects of caffeine may be enhanced if combination hormonal contraceptives are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations and would be expected to increase progesterone serum levels as well; clinical implications are unclear.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca. Herbs with progestogenic properties may enhance the adverse/toxic effect of progestins; examples include bloodroot, chasteberry, damiana, oregano, yucca. Impaired folate metabolism and reduced serum levels of cyanocobalamin have been reported with oral contraceptive use; increased dietary intake or supplementation may be necessary.

Test InteractionsIncreased prothrombin and factors VII, VIII, IX, X; increased platelet aggregability, thyroid-binding globulin, total thyroid hormone (T4), serum triglycerides/phospholipids, AST, Alkaline Phosphatase, GGT; decreased serum folate concentration; pathologist should be advised of estrogen/progesterone therapy when specimens are submitted. Oral contraceptives suppress LH and FSH levels; wait at least 2 weeks after discontinuing use of contraceptive before measuring.

Monitoring ParametersBefore starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision, sudden onset of proptosis, diplopia, migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Nursing: Physical Assessment/MonitoringSee Levonorgestrel monograph.

Patient EducationSee Levonorgestrel monograph.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, low-dose formulations:

Alesse® 28: Ethinyl estradiol 0.02 mg and levonorgestrel 0.1 mg (28s) [21 pink tablets and 7 light green inactive tablets]

Aviane™ 28: Ethinyl estradiol 0.02 mg and levonorgestrel 0.1 mg (28s) [21 orange tablets and 7 light green inactive tablets]

Lessina™ 28, Levlite™ 28: Ethinyl estradiol 0.02 mg and levonorgestrel 0.1 mg (28s) [21 pink tablets and 7 white inactive tablets]

Lutera™, Sronyx™: Ethinyl estradiol 0.02 mg and levonorgestrel 0.1 mg (28s) [21 white tablets and 7 peach inactive tablets]

Lybrel™: Ethinyl estradiol 0.02 mg and levonorgestrel 0.09 mg (28s) [28 yellow tablets]

Tablet, monophasic formulations:

Levlen® 28: Ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg (28s) [21 light orange tablets and 7 pink inactive tablets]

Levora® 28: Ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg (28s) [21 white tablets and 7 peach inactive tablets]

Nordette® 28: Ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg (28s) [21 light orange tablets and 7 pink inactive tablets]

Portia™ 28: Ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg (28s) [21 pink tablets and 7 white inactive tablets]

Tablet, monophasic formulations [extended cycle regimen]:

Jolessa™, Seasonale®: Ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg (91s) [84 pink tablets and 7 white inactive tablets]

Quasense™: Ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg (91s) [84 white tablets and 7 peach inactive tablets]

Seasonique™: Ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg (91s) [84 light blue-green tablets] and ethinyl estradiol 0.01 mg [7 yellow tablets]

Tablet, triphasic formulations:

Enpresse™:

Day 1-6: Ethinyl estradiol 0.03 mg and levonorgestrel 0.05 mg [6 pink tablets]

Day 7-11: Ethinyl estradiol 0.04 mg and levonorgestrel 0.075 mg [5 white tablets]

Day 12-21: Ethinyl estradiol 0.03 mg and levonorgestrel 0.125 mg [10 orange tablets]

Day 22-28: 7 light green inactive tablets (28s)

Triphasil® 28:

Day 1-6: Ethinyl estradiol 0.03 mg and levonorgestrel 0.05 mg [6 brown tablets]

Day 7-11: Ethinyl estradiol 0.04 mg and levonorgestrel 0.075 mg [5 white tablets]

Day 12-21: Ethinyl estradiol 0.03 mg and levonorgestrel 0.125 mg [10 light yellow tablets]

Day 22-28: 7 light green inactive tablets (28s)

Trivora® 28:

Day 1-6: Ethinyl estradiol 0.03 mg and levonorgestrel 0.05 mg [6 blue tablets]

Day 7-11: Ethinyl estradiol 0.04 mg and levonorgestrel 0.075 mg [5 white tablets]

Day 12-21: Ethinyl estradiol 0.03 mg and levonorgestrel 0.125 mg [10 pink tablets]

Day 22-28: 7 peach inactive tablets (28s)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Aviane)

0.1-20 mg-mcg (28): $31.29

Tablets (Lessina-28)

0.1-20 mg-mcg (28): $35.99

Tablets (Levlen (28))

0.15-30 mg-mcg (28): $45.99

Tablets (Levora 0.15/30 (28))

0.15-30 mg-mcg (28): $32.99

Tablets (Lutera)

0.1-20 mg-mcg (28): $29.99

Tablets (Lybrel)

90-20 mcg (28): $55.99

Tablets (Nordette (28))

0.15-30 mg-mcg (28): $69.95

Tablets (Portia-28)

0.15-0.03 mg (28): $29.99

Tablets (Quasense)

0.15-0.03 mg (91): $109.99

Tablets (Seasonale)

0.15-0.03 mg (91): $196.54

Tablets (Seasonique)

0.15-0.03 &0.01 mg (91): $176.10

Tablets (Sronyx)

0.1-20 mg-mcg (28): $29.99

Tablets (Tri-Levlen (28))

(28): $39.99

Tablets (Trivora (28))

(28): $29.99

Mechanism of ActionCombination hormonal contraceptives inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of gonadotropin secretion of a follicle-stimulating hormone (FSH) and luteinizing hormone by the anterior pituitary. The follicular phase FSH and midcycle surge of gonadotropins are inhibited. In addition, combination hormonal contraceptives produce alterations in the genital tract, including changes in the cervical mucus, rendering it unfavorable for sperm penetration even if ovulation occurs. Changes in the endometrium may also occur, producing an unfavorable environment for nidation. Combination hormonal contraceptive drugs may alter the tubal transport of the ova through the fallopian tubes. Progestational agents may also alter sperm fertility.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: Ethinyl estradiol: 4.3 L/kg; Levonorgestrel: 1.8 L/kg

Protein binding:

Ethinyl estradiol: 95% to 97% to albumin

Levonorgestrel: 97% to 99% primarily to sex hormone binding globulin (SHBG), lesser amounts to albumin

Metabolism:

Ethinyl estradiol: Hepatic via CYP3A4; undergoes first-pass metabolism; forms metabolites

Levonorgestrel: Forms conjugated in unconjugated metabolites

Bioavailability: Ethinyl estradiol: 38% to 48%; Levonorgestrel: 100%

Half-life elimination: Ethinyl estradiol: 12-23 hours; Levonorgestrel: 22-49 hours

Excretion:

Ethinyl estradiol: Urine and feces

Levonorgestrel: Urine (40% to 68%, parent drug and metabolites); feces (16% to 48% as metabolites)

Pharmacotherapy PearlsThe World Health Organization (WHO) has issued revised management recommendations for missed combined oral contraceptive pills. Refer to the following reference for a complete presentation and discussion of the guidelines:

Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit, "Faculty Statement from the CEU on a New Publication: WHO Selected Practice Recommendations for Contraceptive Use Update. Missed Pills: New Recommendations," *J Fam Plann Reprod Health Care*, 2005, 31(2):153-5.

Dental Health: Effects on Dental TreatmentWhen prescribing antibiotics, patient must be warned to use additional methods of birth control if on oral contraceptives.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentBarbiturates decrease the effects of oral contraceptives; may increase the toxicity of the benzodiazepines and TCAs. The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Cardiovascular ConsiderationsIt is important to recognize that hormone-based contraceptives may induce or worsen hypertension. These problems are less severe with low-dose ones. Furthermore, hormone-based contraceptives may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on these contraceptives long-term undergo monitoring of blood pressure and avoid cigarette use.

Index TermsLevonorgestrel and Ethinyl Estradiol

References

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“Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection,” August 13, 2001. Available at: http://www.aidsinfo.nih.gov. Accessed September 5, 2001.

Holt VL, Scholes D, Wicklund KG, et al, “Body Mass Index, Weight, and Oral Contraceptive Failure Risk,” *Obstet Gynecol*, 2005, 105(1):46-52. [PubMed 15625141]

Orme ML, Back DJ, and Breckenridge AM, “Clinical Pharmacokinetics of Oral Contraceptive Steroids,” *Clin Pharmacokinet*, 1983, 8(2):95-136. [PubMed 6342899]

Shenfield GM and Griffin JM, “Clinical Pharmacokinetics of Contraceptive Steroids. An Update,” *Clin Pharmacokinet*, 1991, 20(1):15-37.[PubMed 2029800]

International Brand NamesAlesse 28 (CO); Anulette (CN, PE, PY); Biphasil (ZA); Ciclo 21 (BR); Daily Ge (FR); E-Gen-C (ZA); Evelea MD (AR); Gynatrol (DK); Klimonorm (HK); Lady (PH); Levlen ED (AU); Loette (MY, SG); Loette 21 (SG); Logynon (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PH, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Logynon ED (AU, BB, BM, BS, BZ, GY, JM, NL, SR, TT, ZA); Ludeal Ge (FR); Microfemin (CO); Microfemin CD (CO); Microgest ED (TH); Microgyn (DK); Microgynon (CO, CZ, DK, FI, GR, ID, IL, IT, MX, NO, PE, PH, UY); Microgynon 20 ED (AU); Microgynon 21 (DE); Microgynon 28 (DE); Microgynon 30 (AE, AT, AU, BB, BE, BF, BH, BJ, BM, BS, BZ, CH, CI, CY, EG, ET, GB, GH, GM, GN, GY, HK, IE, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NZ, OM, PH, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Microgynon 30 ED (AU, BB, BM, BS, BZ, GY, HK, JM, NL, NZ, SR, TH, TT); Microgynon CD (CO, MX); Microlenyn 30 ED (TH); Minidril (FR); Minivlar 30 (KP); Neogynon 21 (DE); Nordet (MX); Nordette (AR, BF, BJ, CI, CN, ET, GH, GM, GN, GR, HK, IL, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, PE, PH, SC, SD, SL, SN, TN, TW, TZ, UG, ZA, ZM, ZW); Nordette 21 (NZ, TH); Nordette 28 (AU, CO, TH); Norvetal (CO, EC); Novastep (DE); Ovoplex 30-150 (ES); Ovranette (AT, GB); Pil Keluarga Berencana (ID); Planak (ID); Rigevidon (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, MY, OM, QA, SA, SY, YE); Rigevidon 21+7 (HK, MY, PH); Seif (PH); Stediril 30 (BE, CZ, NL); Triciclor (ES); Trifeme 28 (AU); Trigoa (DE); Trigynon (AT, BE); Trinordiol (AR, AT, BE, BF, BJ, BR, CI, CN, CZ, DE, DK, ET, FI, GB, GH, GM, GN, GR, HK, HN, IE, IT, KE, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, PH, RU, SC, SD, SE, SL, SN, TN, TW, TZ, UG, ZA, ZM, ZW); Trinordiol 21 (DE, ID); Trinordiol 28 (ID); Triphasil (ZA); Triphasil 21 (NZ); Triphasil 28 (AU); Triquilar (AE, BH, CL, CY, CZ, DE, EG, GR, IL, IN, IQ, IR, JO, KP, KW, LB, LY, MX, OM, PE, PY, QA, SA, SY, UY, VE, YE); Triquilar ED (AU, ID, MY, NZ, TH); Trolit (PE)

Ethinyl Estradiol and Norelgestromin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Ortho Evra® and Venous Thromboembolism - January, 2008

The Food and Drug Administration (FDA) has notified healthcare professionals of updated labeling related to the use of Ortho Evra® (ethinyl estradiol and norelgestromin). Results from a third study that illustrates the increased risk of venous thromboembolism (VTE) with the use of the contraceptive patch have been released.

Product labeling now contains information from three epidemiologic studies based on information obtained from electronic healthcare claims data. The first study found the risk of nonfatal VTE associated with the use of Ortho Evra® patch was similar to the risk associated with use of oral contraceptive pills containing ethinyl estradiol 35 mcg and norgestimate. The second study found an approximate twofold increase in the risk of medically verified VTE events in users of Ortho Evra® compared to users of norgestimate-containing oral contraceptives containing ethinyl estradiol 35 mcg. The third study found an increased risk of VTE in women using Ortho Evra® compared to those using oral contraceptives containing ethinyl estradiol 30 mcg and levonorgestrel.

Although the results and methods of the studies differ, two of the studies support the FDA's concerns regarding the potential for Ortho Evra® use to increase the risk of blood clots in some women.

Women with concerns or risk factors for thromboembolic disease should consult with their healthcare providers for appropriate contraceptive options.

For additional information, refer to the following FDA website: http://www.fda.gov/medwatch/safety/2008/safety08.htm#orthoevrapatch

Medication Safety Issues

Transdermal patch may contain conducting metal (eg, aluminum); remove patch prior to MRI.

Pronunciation(ETH in il es tra DYE ole & nor el JES troe min)

U.S. Brand NamesOrtho Evra®

Canadian Brand NamesEvra®

Pharmacologic CategoryContraceptive; Estrogen and Progestin Combination

Use: Labeled IndicationsPrevention of pregnancy

Dosing: AdultsFemales: Contraception: Topical:

Apply one patch each week for 3 weeks (21 total days); followed by one week that is patch-free. Each patch should be applied on the same day each week (“patch change day”) and only one patch should be worn at a time. No more than 7 days should pass during the patch-free interval.

Schedule 1 (Sunday starter): Dose begins on first Sunday after onset of menstruation; if the menstrual period starts on Sunday, apply one patch that very same day. **With a Sunday start, an additional method of contraception (nonhormonal) should be used until after the first 7 days of consecutive administration.** Each patch change will then occur on Sunday.

Schedule 2 (Day 1 starter): Dose starts on first day of menstrual cycle, applying one patch during the first 24 hours of menstrual cycle. No back-up method of contraception is needed as long as the patch is applied on the first day of cycle. Each patch change will then occur on that same day of the week.

Additional dosing considerations:

No bleeding during patch-free week/missed menstrual period: If patch has been applied as directed, continue treatment on usual “patch change day”. If used correctly, no bleeding during patch-free week does not necessarily indicate pregnancy. However, if no withdrawal bleeding occurs for 2 consecutive cycles, pregnancy should be ruled out. If patch has not been applied as directed, and one menstrual period is missed, pregnancy should be ruled out prior to continuing treatment.

If a patch becomes partially or completely detached for <24 hours: Try to reapply to same place, or replace with a new patch immediately. Do not reapply if patch is no longer sticky, if it is sticking to itself or another surface, or if it has material sticking to it.

If a patch becomes partially or completely detached for >24 hours (or time period is unknown): Apply a new patch and use this day of the week as the new “patch change day” from this point on. **An additional method of contraception (nonhormonal) should be used until after the first 7 days of consecutive administration.**

Switching from oral contraceptives: Apply first patch on the first day of withdrawal bleeding. If there is no bleeding within 5 days of taking the last active tablet, pregnancy must first be ruled out. If patch is applied later than the first day of bleeding, **an additional method of contraception (nonhormonal) should be used until after the first 7 days of consecutive administration**

Use after childbirth: Therapy should not be started <4 weeks after childbirth. Pregnancy should be ruled out prior to treatment if menstrual periods have not restarted. **An additional method of contraception (nonhormonal) should be used until after the first 7 days of consecutive administration.**

Use after abortion or miscarriage: Therapy may be started immediately if abortion/miscarriage occur within the first trimester. If therapy is not started within 5 days, follow instructions for first time use. If abortion/miscarriage occur during the second trimester, therapy should not be started for at least 4 weeks. Follow directions for use after childbirth.

Dosing: PediatricFemales: Contraception: Topical: Refer to adult dosing; not to be used prior to menarche.
Dosing: Renal ImpairmentSpecific guidelines not available; use with caution and monitor blood pressure closely. Consider other forms of contraception
Dosing: Hepatic ImpairmentContraindicated in patients with hepatic impairment.
Administration: TopicalNew patches should be applied on the same day each week. Apply to clean, dry, intact, healthy skin on the buttock, abdomen, upper arm, or upper torso. Avoid areas that will be rubbed by tight clothing. Do not apply to the breasts or to skin that is red, irritated, or cut. Do not apply make-up, creams, lotions, powders, or other topical products to the skin where the patch will be placed. Remove the patch and the plastic liner from the foil pouch, being careful not to remove the clear liner when removing the patch. Apply patch by first peeling back half of the clear protective liner. Avoid touching surface of patch. Apply patch to skin and remove the rest of the liner. Press patch down firmly onto skin using palm of the hand; apply pressure for 10 seconds. When changing the patch each week, the new patch may be applied in the same anatomic area but should be applied to a new spot in that area. Do not use supplemental adhesives or wraps to hold patch into place.

Forgetting to apply the patch at the start of cycle (week 1/day 1): Apply first patch as soon as remembering, using this day of the week as the new “patch change day” from this point on. An additional method of contraception (nonhormonal) should be used until after the first 7 days of consecutive administration.

Forgetting to change patch in the middle of the cycle (week 2/day 8 or week 3/day 15): If <48 hours from normal “patch change day,” apply new patch immediately. No back-up contraception is needed. If >48 hours from normal “patch change day,” apply a new patch and use this day of the week as the new “patch change day” from this point on. An additional method of contraception (nonhormonal) should be used until after the first 7 days of consecutive administration.

Forgetting to remove patch at end of cycle (week 4/day 22): Take off as soon as remembering, start new cycle on usual “patch change day.”

Changing the “patch change day”: The “patch change day” can be changed to an earlier day in the week by first completing the current cycle. Then, during the “patch-free interval”, select an earlier day to start the new cycle. Do not allow >7 consecutive patch-free days.

Skin irritation: If patch is in an uncomfortable location, it can be removed and a new patch applied to a different location until the next “patch change day.”

StorageStore at controlled room temperature of 25°C (77°F); do not refrigerate or freeze.
ContraindicationsHypersensitivity to ethinyl estradiol, norelgestromin, or any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); cerebral vascular disease, coronary artery disease, valvular heart disease with complications, severe hypertension; diabetes mellitus with vascular involvement; severe headache with focal neurological symptoms; known or suspected breast carcinoma, endometrial cancer, estrogen-dependent neoplasms, undiagnosed abnormal genital bleeding; hepatic dysfunction or tumor, cholestatic jaundice of pregnancy, jaundice with prior combination hormonal contraceptive use; major surgery with prolonged immobilization; heavy smoking (≥15 cigarettes/day) in patients >35 years of age; pregnancy
Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Smokers: See “Special populations” below.

Concerns related to adverse effects:

- Breast cancer: The use of combination hormonal contraceptives has been associated with a slight increase in frequency of breast cancer, however, studies are not consistent.

- Carbohydrate intolerance: May have adverse effects on glucose tolerance; use caution in women with diabetes.

- Lipid effects: Combination hormonal contraceptives may effect serum triglyceride and lipoprotein levels. Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.

- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis (has been reported rarely with combination hormonal contraceptives); discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

- Thromboembolism: Combination hormonal contraceptive use may increase the risk of venous thromboembolism; risk may be increased with use of the contraceptive patch.

- Vaginal bleeding: Presentation of irregular, unresolving vaginal bleeding warrants further evaluation including endometrial sampling, if indicated, to rule out malignancy; evaluate hypothalamic-pituitary-function in women with persistent (≥6 months) amenorrhea (especially associated with breast secretion) following discontinuation of therapy.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with risk factors for coronary artery disease; may lead to increased risk of myocardial infarction. May have a dose-related risk of vascular disease and hypertension; women with hypertension should be encouraged to use a nonhormonal form of contraception.

- Depression: Use with caution in patients with depression.

- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.

- Gallbladder disease: May have a dose-related risk of gallbladder disease.

- Hepatic adenomas: Extremely rare adenomas and focal nodular hyperplasia resulting in fatal intra-abdominal hemorrhage have been reported in association with long-term oral contraceptive use. Presentation of an abdominal mass, acute abdominal pain, or intra-abdominal bleeding warrants further evaluation to rule out source.

- Migraine: Use with caution in patients with a history of migraine.

- Renal impairment: Women with renal disease should be encouraged to use a nonhormonal form of contraception.

Special populations:

- Pediatrics: Not for use prior to menarche.

- Smokers: **[U.S. Boxed Warning]: The risk of cardiovascular side effects increases in women who smoke cigarettes, especially those who are >35 years of age; women who use combination hormonal contraceptives should be strongly advised not to smoke.**

- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Dosage form specific issues:

- Transdermal patch: The amount of ethinyl estradiol absorbed from the transdermal patch results in higher but more variable exposure than achieved if administered orally. The increased estrogen exposure may increase the risk of adverse events, including venous thromboembolism. The combination hormonal contraceptive patch may have adverse effects similar to those associated with oral contraceptive products. Risk of complications increases with other risk factors such as hypertension, hyperlipidemias, obesity and diabetes. The topical patch may be less effective in patients weighing ≥90 kg (198 lb) and an increased incidence of pregnancy has been reported in this population; consider another form of contraception. Transdermal patch may contain conducting metal (eg, aluminum); remove patch prior to MRI.

Other warnings/precautions:

- HIV infection protection: Combination hormonal contraceptives do not protect against HIV infection or other sexually-transmitted diseases.

- Minimum effective dosage: The minimum dosage combination of estrogen/progestin that will effectively treat the individual patient should be used.

Pregnancy Risk FactorX
Pregnancy ConsiderationsPregnancy should be ruled out prior to treatment and discontinued if pregnancy occurs. In general, the use of combination hormonal contraceptives when inadvertently taken early in pregnancy have not been associated with teratogenic effects. Due to increased risk of thromboembolism postpartum, combination hormonal contraceptives should not be started earlier than 4-6 weeks following delivery. The topical patch may be less effective in patients weighing ≥90 kg (198 lb) and an increased incidence of pregnancy has been reported in this population; consider another form of contraception.
LactationEnters breast milk/not recommended (AAP rates “compatible”)
Breast-Feeding ConsiderationsJaundice and breast enlargement in the nursing infant have been reported following the use of combination hormonal contraceptives. May decrease the quality and quantity of breast milk; a nonhormonal form of contraception is recommended.
Adverse ReactionsThe following reactions have been reported with the contraceptive patch. Adverse reactions associated with oral combination hormonal contraceptive agents are also likely to appear with the topical contraceptive patch (frequency difficult to anticipate). Refer to individual oral contraceptive monographs for additional information.

9% to 22%: Abdominal pain, application site reaction, breast symptoms, headache, menstrual cramps, nausea, upper respiratory infection

The following reactions have been associated with combination hormonal contraceptive use:

Increased risk or evidence of association with use:

Cardiovascular: Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, hypertension, mesenteric thrombosis, MI, venous thrombosis (with or without embolism)

Gastrointestinal: Gallbladder disease

Hepatic: Hepatic adenomas, liver tumors (benign)

Local: Thrombophlebitis

Ocular: Retinal thrombosis

Respiratory: Pulmonary embolism

Adverse reactions considered drug related:

Cardiovascular: Edema, varicose vein aggravation

Central nervous system: Depression, migraine, mood changes

Dermatologic: Chloasma, melasma, rash (allergic)

Endocrine & metabolic: Amenorrhea, breakthrough bleeding, breast changes (enlargement, pain, secretion, tenderness), fluid retention, infertility (temporary), lactation decreased (with use immediately postpartum), menstrual flow changes, spotting

Gastrointestinal: Abdominal bloating, abdominal cramps, abdominal pain, appetite changes, nausea, weight changes, vomiting

Genitourinary: Cervical ectropion, cervical secretion, endocervical hyperplasia, fibroid enlargement, vaginal candidiasis, vaginitis

Hematologic: Folate decreased, porphyria exacerbation

Hepatic: Cholestatic jaundice

Neuromuscular & skeletal: Chorea exacerbation

Ocular: Contact lens intolerance, corneal curvature changes (steepening)

Respiratory: Rhinitis

Miscellaneous: Anaphylactic/anaphylactoid reactions (including angioedema, circulatory collapse, respiratory collapse, urticaria), SLE exacerbation

Adverse reactions in which association is not confirmed or denied: Acne, auditory disturbances, Budd-Chiari syndrome, cataracts, cervical smear abnormal, colitis, cystitis-like syndrome, dizziness, dysmenorrhea, erythema multiforme, erythema nodosum, headache, hemolytic uremic syndrome, hemorrhagic eruption, hirsutism, libido changes, nervousness, optic neuritis (with or without partial or complete loss of vision), pancreatitis, premenstrual syndrome, renal function impaired, scalp hair loss

Metabolism/Transport Effects

Ethinyl estradiol: **Substrate** of CYP2C9 (minor), 3A4 (major), 3A5-7 (minor); **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C8 (weak), 2C19 (weak), 3A4 (weak)

Norelgestromin: **Substrate** of CYP3A4 (minor)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Armodafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Estrogens) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Colesevelam: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Griseofulvin: May increase the metabolism of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

LamoTRIgine: Oral Contraceptive (Estrogens) may decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Modafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Average AUC values were unchanged, but there was evidence of substantial patient-to-patient variability in response to this combination. *Risk D: Consider therapy modification*

Nafcillin: May increase the metabolism of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Protease Inhibitors: Oral Contraceptive (Estrogens) may diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Rufinamide: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Estrogens) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

TiZANidine: Oral Contraceptive (Estrogens) may increase the serum concentration of TiZANidine. *Risk C: Monitor therapy*

Topiramate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Oral Contraceptive (Estrogens) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Estrogens). Oral Contraceptive (Estrogens) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: CNS effects of caffeine may be enhanced if combination hormonal contraceptives are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations and would be expected to increase progesterone serum levels as well; clinical implications are unclear.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca. Herbs with progestogenic properties may enhance the adverse/toxic effect of progestins; examples include bloodroot, chasteberry, damiana, oregano, yucca.

Monitoring ParametersBefore starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision, sudden onset of proptosis, diplopia, migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Note: The formulation available in Canada differs from the U.S. product in both composition and the manufacturing process (although delivery rates appear similar).

Patch, transdermal:

Ortho Evra®: Ethinyl estradiol 0.75 mg and norelgestromin 6 mg [releases ethinyl estradiol 20 mcg and norelgestromin 150 mcg per day] (1s, 3s)

Evra® [CAN]: Ethinyl estradiol 0.6 mg and norelgestromin 6 mg [releases ethinyl estradiol 20 mcg and norelgestromin 150 mcg per day] (1s, 3s) [Not available in U.S.]

Pricing: U.S. (www.drugstore.com)

Patch weekly (Ortho Evra)

150-20 mcg/24 hrs (3): $62.99

Mechanism of ActionCombination hormonal contraceptives inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of gonadotropin secretion of a follicle-stimulating hormone (FSH) and luteinizing hormone by the anterior pituitary. The follicular phase FSH and midcycle surge of gonadotropins are inhibited. In addition, combination hormonal contraceptives produce alterations in the genital tract, including changes in the cervical mucus, rendering it unfavorable for sperm penetration even if ovulation occurs. Changes in the endometrium may also occur, producing an unfavorable environment for nidation. Combination hormonal contraceptive drugs may alter the tubal transport of the ova through the fallopian tubes. Progestational agents may also alter sperm fertility.

Pharmacodynamics/Kinetics

Ortho Evra®:

Absorption: Topical: Equivalent when applied to abdomen, buttock, upper outer arm, and upper torso

Ethinyl estradiol and norelgestromin: Rapid; reaches plateau by ~48 hours. Absorption of ethinyl estradiol may be increased with heat exposure due to sauna, whirlpool, or treadmill.

The amount of ethinyl estradiol absorbed is 20 mcg/day and results in greater exposure than produced by oral ethinyl estradiol 20 mcg. In contrast, peak levels of ethinyl estradiol are higher in women taking oral tablets.

Protein binding:

Ethinyl estradiol: Albumin

Norelgestromin and norgestrel: >97%; norelgestromin to albumin and norgestrel to sex-hormone-binding globulin

Metabolism: Topical:

Ethinyl estradiol: First-pass effect avoided; forms metabolites

Norelgestromin: Hepatic to norgestrel and others; first-pass effect avoided

Bioavailability: Ethinyl estradiol: ~60% greater using the topical patch when compared to oral tablets.

Half-life elimination: Topical:

Ethinyl estradiol: 17 hours

Norelgestromin: 28 hours

Excretion: Metabolites of ethinyl estradiol and norelgestromin: Urine and feces

Pharmacotherapy PearlsPatches are available in boxes of 3 patches and also in single-patch cartons, intended for use as a replacement patch in case a patch is lost or destroyed. Approximately 5% of patches need to be replaced; ~2% because they fall off, ~3% because of partial detachment.

Dental Health: Effects on Dental TreatmentWhen prescribing antibiotics, patient must be warned to use additional methods of birth control if on oral contraceptives.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentMay cause flu-like symptoms, take this into consideration if also concerned about SSRI discontinuation syndrome. Carbamazepine and topiramate may increase the metabolism of estradiol, leading to a decrease in serum concentrations. Estrogens may inhibit the metabolism of some benzodiazepines (alprazolam, chlordiazepoxide, diazepam), TCAs, and selegiline. Estrogens may increase the clearance of lorazepam, oxazepam, and temazepam. The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Index Terms Norelgestromin and Ethinyl Estradiol; Ortho-Evra

References

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“Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection,” August 13, 2001. Available at: http://www.aidsinfo.nih.gov. Accessed September 5, 2001.

Hendeles S, Galand N, Schwers J, “Metabolism of Orally-Administered D-norgestrel in Women,” *Acta Endocrinol (Copenh)*, 1972, 71(3):557-68.

Orme ML, Back DJ, and Breckenridge AM, “Clinical Pharmacokinetics of Oral Contraceptive Steroids,” *Clin Pharmacokinet*, 1983, 8(2):95-136.[PubMed 6342899]

International Brand Names Evra (KP)

Ethinyl Estradiol and Norethindrone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

femhrt® may be confused with Femara®

Modicon® may be confused with Mylicon®

Norinyl® may be confused with Nardil®

Tri-Norinyl® may be confused with Triphasil®

International issues:

Notrel™ may be confused with Nostril® which is a brand name for chlorhexidine and cetrimonium in France

Pronunciation(ETH in il es tra DYE ole & nor eth IN drone)

U.S. Brand NamesAranelle™; Balziva™; Brevicon®; Estrostep® Fe; Femcon™ Fe; femhrt®; Junel™; Junel™ Fe; Leena™; Loestrin®; Loestrin® 24 Fe; Loestrin® Fe; Microgestin™; Microgestin™ Fe; Modicon®; Necon® 0.5/35; Necon® 1/35; Necon® 10/11; Necon® 7/7/7; Norinyl® 1+35; Nortrel™; Nortrel™ 7/7/7; Ortho-Novum®; Ovcon®; Tilia™ Fe; Tri-Norinyl®; Zenchent™

Canadian Brand NamesBrevicon® 0.5/35; Brevicon® 1/35; FemHRT®; Loestrin™ 1.5/30; Minestrin™ 1/20; Ortho® 0.5/35; Ortho® 1/35; Ortho® 7/7/7; Select™ 1/35; Synphasic®

Pharmacologic CategoryContraceptive; Estrogen and Progestin Combination

Use: Labeled IndicationsPrevention of pregnancy; treatment of acne; moderate-to-severe vasomotor symptoms associated with menopause; prevention of osteoporosis (in women at significant risk only)

Use: Unlabeled/InvestigationalTreatment of hypermenorrhea (menorrhagia); pain associated with endometriosis, dysmenorrhea; dysfunctional uterine bleeding

Dosing: Adults

Adolescents ≥15 years and Adults: Females: Acne: Estrostep® Fe: Oral: Refer to dosing for contraception

Moderate-to-severe vasomotor symptoms associated with menopause: Initial: femhrt® 0.5/2.5: Oral: 1 tablet daily; patient should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary; patient should be maintained on lowest effective dose

Prevention of osteoporosis: Initial: femhrt® 0.5/2.5: Oral: 1 tablet daily; patient should be maintained on lowest effective dose

Contraception: Oral:

Schedule 1 (Sunday starter): Dose begins on first Sunday after onset of menstruation; if the menstrual period starts on Sunday, take first tablet that very same day. With a Sunday start, an additional method of contraception should be used until after the first 7 days of consecutive administration.

For 21-tablet package: Dosage is 1 tablet daily for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken.

For 28-tablet package: Dosage is 1 tablet daily without interruption.

Schedule 2 (Day 1 starter): Dose starts on first day of menstrual cycle taking 1 tablet daily.

For 21-tablet package: Dosage is 1 tablet daily for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken.

For 28-tablet package: Dosage is 1 tablet daily without interruption.

If all doses have been taken on schedule and one menstrual period is missed, continue dosing cycle. If two consecutive menstrual periods are missed, pregnancy test is required before new dosing cycle is started.

Missed doses **monophasic formulations** (refer to package insert for complete information):

One dose missed: Take as soon as remembered or take 2 tablets next day Two consecutive doses missed in the first 2 weeks: Take 2 tablets as soon as remembered or 2 tablets next 2 days. An additional method of contraception should be used for 7 days after missed dose.

Two consecutive doses missed in week 3 or three consecutive doses missed at any time: An additional method of contraception must be used for 7 days after a missed dose.

Schedule 1 (Sunday starter): Continue dose of 1 tablet daily until Sunday, then discard the rest of the pack, and a new pack should be started that same day.

Schedule 2 (Day 1 starter): Current pack should be discarded, and a new pack should be started that same day.

Missed doses **biphasic/triphasic formulations** (refer to package insert for complete information):

One dose missed: Take as soon as remembered or take 2 tablets next day.

Two consecutive doses missed in week 1 or week 2 of the pack: Take 2 tablets as soon as remembered and 2 tablets the next day. Resume taking 1 tablet daily until the pack is empty. An additional method of contraception should be used for 7 days after a missed dose.

Two consecutive doses missed in week 3 of the pack: An additional method of contraception must be used for 7 days after a missed dose.

Schedule 1 (Sunday Starter): Take 1 tablet every day until Sunday. Discard the remaining pack and start a new pack of pills on the same day.

Schedule 2 (Day 1 starter): Discard the remaining pack and start a new pack the same day.

Three or more consecutive doses missed: An additional method of contraception must be used for 7 days after a missed dose.

Schedule 1 (Sunday Starter): Take 1 tablet every day until Sunday; on Sunday, discard the pack and start a new pack.

Schedule 2 (Day 1 Starter): Discard the remaining pack and begin new pack of tablets starting on the same day.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricFemales:

Acne: Oral (Estrostep® Fe): For use in females ≥15 years; refer to adult dosing for contraception

Contraception: Oral: Refer to adult dosing; not to be used prior to menarche.

Dosing: Renal ImpairmentSpecific guidelines not available; use with caution and monitor blood pressure closely. Consider other forms of contraception.
Dosing: Hepatic ImpairmentContraindicated in patients with hepatic impairment.
Administration: OralAdminister at the same time each day.
Dietary ConsiderationsShould be taken at same time each day. May be taken with or without food. Ensure adequate calcium and vitamin D intake when used for the prevention of osteoporosis.
StorageStore at controlled room temperature of 25°C (77°F).

Estrostep®: Protect from light.

ContraindicationsHypersensitivity to ethinyl estradiol, norethindrone, norethindrone acetate, or any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); cerebral vascular disease, coronary artery disease, uncontrolled hypertension; diabetes mellitus with vascular involvement; severe headache with focal neurological symptoms; known or suspected breast carcinoma, endometrial cancer, estrogen-dependent neoplasms, undiagnosed abnormal genital bleeding; hepatic dysfunction or tumor, cholestatic jaundice of pregnancy, jaundice with prior combination hormonal contraceptive use; major surgery with prolonged immobilization; heavy smoking (≥15 cigarettes/day) in patients >35 years of age; pregnancy
Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.
- Dementia: See “Concerns related to adverse effects” below.
- Risks vs benefits: See “Other warnings/precautions” below.
- Smokers: See “Special populations” below.

Concerns related to adverse effects:

- Breast cancer: Estrogens may increase the risk of breast cancer. The use of combination hormonal contraceptives has been associated with a slight increase in frequency of breast cancer, however studies are not consistent. An increased risk of invasive breast cancer was observed in postmenopausal women using conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA); a smaller increase in risk was seen with estrogen therapy alone in observational studies. An increase in abnormal mammograms has also been reported with estrogen and progestin therapy in postmenopausal women. Estrogen use may lead to severe hypercalcemia in postmenopausal patients with breast cancer and bone metastases; discontinue estrogen if hypercalcemia occurs

- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in women ≥65 years of age taking CEE alone or in combination with MPA.

- Endometrial carcinoma: Adequate diagnostic measures, including endometrial sampling (if indicated), should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Unopposed estrogens may increase the risk of endometrial carcinoma in postmenopausal women with an intact uterus. Risk appears to be associated with long-term use. The use of a progestin should be considered when administering estrogens to postmenopausal women with an intact uterus.

- Lipid effects: Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.

- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Estrogens with or without progestin should not be used to prevent cardiovascular disease.** Use caution with cardiovascular disease or dysfunction. May increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using CEE in combination with MPA. Nonfatal MI, PE, and thrombophlebitis have also been reported in males taking high doses of CEE (eg, for prostate cancer). An increased risk of MI has been noted with use of combination hormonal contraceptives, primarily in women with underlying risk factors; women with hypertension or renal disease should be encouraged to use another form of contraception.

- Cholestatic jaundice: Use femhrt™ with caution with history of cholestatic jaundice associated with past estrogen use or pregnancy. Combination oral contraceptives are contraindicated with a history of cholestatic jaundice of pregnancy or jaundice with prior combination hormonal contraceptive use.

- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes, or renal dysfunction.

- Endometriosis: Estrogens may exacerbate endometriosis. Malignant transformation of residual endometrial implants has been reported posthysterectomy with estrogen only therapy. Consider adding a progestin in women with residual endometriosis posthysterectomy.

- Gallbladder disease: Use with caution in patients with gallbladder disease.

- Hepatic hemangiomas: Use with caution in patients with hepatic hemangiomas.

- Hypocalcemia: Use with caution in patients with severe hypocalcemia.

- Porphyria: Use with caution in patients with porphyria.

- Renal impairment: Women with renal disease should be encouraged to use a nonhormonal form of contraception.

- SLE: Use with caution in patients with SLE.

Special populations:

- Pediatrics: Not for use prior to menarche.

- Smokers: **[U.S. Boxed Warning]: The risk of cardiovascular side effects increases in women who smoke cigarettes, especially heavy smokers (≥15 cigarettes/day) and those who are >35 years of age; women who use combination hormonal contraceptives should be strongly advised not to smoke.**

- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- Acne use: When used for acne, use only in females ≥15 years, who also desire combination hormonal contraceptive therapy, are unresponsive to topical treatments, and have no contraindications to combination hormonal contraceptive use.

- HIV infection protection: Combination hormonal contraceptives do not protect against HIV infection or other sexually-transmitted diseases.

- Minimum effective dosage: Combination hormonal contraceptives: The minimum dosage combination of estrogen/progestin that will effectively treat the individual patient should be used. New patients should be started on products containing ≤0.035 mg of estrogen per tablet.

- Osteoporosis use: When used solely for the prevention of osteoporosis in women at significant risk, nonestrogen treatment options should be considered.

- Risks vs. benefits: **Postmenopausal women: [U.S. Boxed Warning]: Estrogens with or without progestin should be used for shortest duration possible at the lowest effective dose consistent with treatment goals.** Before prescribing estrogen therapy to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of progestin when added to estrogen therapy. Estrogens with or without progestin should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.

Pregnancy Risk FactorX

Pregnancy ConsiderationsPregnancy should be ruled out prior to treatment and discontinued if pregnancy occurs. In general, the use of combination hormonal contraceptives when inadvertently taken early in pregnancy have not been associated with teratogenic effects. Due to increased risk of thromboembolism postpartum, combination hormonal contraceptives should not be started earlier than 4-6 weeks following delivery. Hormonal contraceptives may be less effective in obese patients. An increase in oral contraceptive failure was noted in women with a BMI >27.3. Similar findings were noted in patients weighing ≥90 kg (198 lb) using the contraceptive patch.

LactationEnters breast milk/not recommended

Breast-Feeding Considerations

Jaundice and breast enlargement in the nursing infant have been reported following the use of combination hormonal contraceptives. May decrease the quality and quantity of breast milk; alternative form of contraception is recommended.

Adverse Reactions

The following reactions have been associated with oral contraceptive use:

Increased risk or evidence of association with use:

Cardiovascular: Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, hypertension, mesenteric thrombosis, MI, venous thrombosis (with or without embolism)

Gastrointestinal: Gallbladder disease

Hepatic: Hepatic adenomas, liver tumors (benign)

Local: Thrombophlebitis

Ocular: Retinal thrombosis

Renal: Impaired renal function

Respiratory: Pulmonary embolism

Adverse reactions considered drug related:

Cardiovascular: Edema, varicose vein aggravation

Central nervous system: Depression, migraine, mood changes

Dermatologic: Chloasma, melasma, rash (allergic)

Endocrine & metabolic: Amenorrhea, breakthrough bleeding, breast changes (enlargement, pain, secretion, tenderness), fluid retention, infertility (temporary), lactation decreased (with use immediately postpartum), menstrual flow changes, spotting

Gastrointestinal: Abdominal bloating, abdominal cramps, abdominal pain, appetite changes, nausea, weight changes, vomiting

Genitourinary: Cervical ectropion, cervical secretion, vaginal candidiasis, vaginitis

Hematologic: Folate decreased, porphyria exacerbation

Hepatic: Cholestatic jaundice

Neuromuscular & skeletal: Chorea exacerbation

Ocular: Contact lens intolerance, corneal curvature changes (steepening)

Miscellaneous: Anaphylactic/anaphylactoid reactions (including angioedema, circulatory collapse, respiratory collapse, urticaria), SLE exacerbation

Adverse reactions in which association is not confirmed or denied: Acne, Budd-Chiari syndrome, cataracts, colitis, cystitis-like syndrome, dizziness, dysmenorrhea, erythema multiforme, erythema nodosum, headache, hemolytic uremic syndrome, hemorrhagic eruption, hirsutism, libido changes, nervousness, optic neuritis (with or without partial or complete loss of vision), pancreatitis, premenstrual syndrome, renal function impaired, scalp hair loss

The following have been associated with femhrt® and in general, are similar to placebo. Also refer to adverse reactions observed with oral contraceptives for additional reactions observed with estrogen/progestin therapy:

>10%: Central nervous system: Headache (15% to 18%)

1% to 10%:

Central nervous system: Depression (4% to 6%), nervousness (2% to 5%)

Endocrine & metabolic: Breast pain (8% to 9%)

Gastrointestinal: Abdominal pain (8% to 10%), nausea/vomiting (5% to 7%), diarrhea (4% to 6%), dyspepsia (3% to 5%)

Genitourinary: Urinary tract infection (4% to 6%), vaginitis (5%)

Respiratory: Sinusitis (8% to 9%)

Metabolism/Transport Effects

Ethinyl estradiol: **Substrate** of CYP2C9 (minor), 3A4 (major), 3A5-7 (minor); **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C8 (weak), 2C19 (weak), 3A4 (weak)

Norethindrone: **Substrate** of CYP3A4 (major); Induces CYP2C19 (weak)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Armodafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Estrogens) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Colesevelam: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Colesevelam: May decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Darunavir: May decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Griseofulvin: May increase the metabolism of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

LamoTRIgine: Oral Contraceptive (Estrogens) may decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Modafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Average AUC values were unchanged, but there was evidence of substantial patient-to-patient variability in response to this combination. *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

Nafcillin: May increase the metabolism of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Protease Inhibitors: Oral Contraceptive (Estrogens) may diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C:*

Monitor therapy

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Rufinamide: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Rufinamide: May decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Estrogens) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

TiZANidine: Oral Contraceptive (Estrogens) may increase the serum concentration of TiZANidine. *Risk C: Monitor therapy*

Topiramate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Oral Contraceptive (Estrogens) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Estrogens). Oral Contraceptive (Estrogens) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Routine use increases estrogen level and risk of breast cancer; avoid ethanol. Ethanol may also increase the risk of osteoporosis.

Food: CNS effects of caffeine may be enhanced if combination hormonal contraceptives are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations and would be expected to increase progesterone serum levels as well; clinical implications are unclear. Norethindrone absorption is increased by 27% following administration with food.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca. Herbs with progestogenic properties may enhance the adverse/toxic effect of progestins; examples include bloodroot, chasteberry, damiana, oregano, yucca.

Test InteractionsIncreased prothrombin and factors VII, VIII, IX, X; increased platelet aggregability, thyroid-binding globulin, total thyroid hormone (T_4), serum triglycerides/phospholipids; decreased antithrombin III, serum folate concentration; pathologist should be advised of estrogen/progesterone therapy when specimens are submitted

Monitoring ParametersBefore starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision, sudden onset of proptosis, diplopia, migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias; thyroid function in patients on thyroid hormone replacement therapy. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Menopausal symptoms: Assess need for therapy at 3- to 6-month intervals

Prevention of osteoporosis: Bone density measurement

Nursing: Physical Assessment/MonitoringSee individual agent for Norethindrone.

Patient EducationSee individual agent for Norethindrone.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

femhrt® 1/5: Ethinyl estradiol 5 mcg and norethindrone acetate 1 mg [white tablets]

femhrt® 0.5/2.5: Ethinyl estradiol 2.5 mcg and norethindrone acetate 0.5 mg [white tablets]

Tablet, monophasic formulations:

Balziva™: Ethinyl estradiol 0.035 mg and norethindrone 0.4 mg (28s) [21 light peach tablets and 7 white inactive tablets]

Brevicon®: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg (28s) [21 blue tablets and 7 orange inactive tablets]

Junel™ 21 1/20: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg (21s) [yellow tablets]

Junel™ 21 1.5/30: Ethinyl estradiol 0.03 mg and norethindrone acetate 1.5 mg (21s) [pink tablets]

Junel™ Fe 1/20: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg (28s) [21 yellow tablets] and ferrous fumarate 75 mg [7 brown tablets]

Junel™ Fe 1.5/30: Ethinyl estradiol 0.03 mg and norethindrone acetate 1.5 mg (28s) [21 pink tablets] and ferrous fumarate 75 mg [7 brown tablets]

Loestrin® 21 1/20, Microgestin™ 1/20: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg (21s) [white tablets]

Loestrin® 21 1.5/30, Microgestin™ 1.5/30: Ethinyl estradiol 0.03 mg and norethindrone acetate 1.5 mg (21s) [green tablets]

Loestrin® 24 Fe: 1/20: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg (28s) [24 white tablets] and ferrous fumarate 75 mg [4 brown tablets]

Loestrin® Fe 1/20, Microgestin™ Fe 1/20: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg (28s) [21 white tablets] and ferrous fumarate 75 mg [7 brown tablets]

Loestrin® Fe 1.5/30, Microgestin™ Fe 1.5/30: Ethinyl estradiol 0.03 mg and norethindrone acetate 1.5 mg (28s) [21 green tablets] and ferrous fumarate 75 mg [7 brown tablets]

Modicon® 28: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg (28s) [21 white tablets and 7 green inactive tablets]

Necon® 0.5/35-28: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg (28s) [21 light yellow tablets and 7 white inactive tablets]

Necon® 1/35-28: Ethinyl estradiol 0.035 mg and norethindrone 1 mg (28s) [21 dark yellow tablets and 7 white inactive tablets]

Norinyl® 1+35: Ethinyl estradiol 0.035 mg and norethindrone 1 mg (28s) [21 yellow-green tablets and 7 orange inactive tablets]

Nortrel™ 0.5/35 mg:

Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg (21s) [light yellow tablets]

Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg (28s) [21 light yellow tablets and 7 white inactive tablets]

Nortrel™ 1/35 mg:

Ethinyl estradiol 0.035 mg and norethindrone 1 mg (21s) [yellow tablets]

Ethinyl estradiol 0.035 mg and norethindrone 1 mg (28s) [21 yellow tablets and 7 white inactive tablets]

Ortho-Novum® 1/35 28: Ethinyl estradiol 0.035 mg and norethindrone 1 mg (28s) [21 peach tablets and 7 green inactive tablets]

Ovcon® 35 21-day: Ethinyl estradiol 0.035 mg and norethindrone 0.4 mg (21s) [peach tablets]

Ovcon® 35 28-day: Ethinyl estradiol 0.035 mg and norethindrone 0.4 mg (28s) [21 peach tablets and 7 green inactive tablets]

Ovcon® 50: Ethinyl estradiol 0.05 mg and norethindrone 1 mg (28s) [21 yellow tablets and 7 green inactive tablets]

Zenchent™: Ethinyl estradiol 0.035 mg and norethindrone 0.4 mg (28s) [21 light peach tablets and 7 white inactive tablets]

Tablet, chewable, monophasic formulations:

Femcon™ Fe: Ethinyl estradiol 0.035 mg and norethindrone 0.4 mg (28s) [21 white tablets and 7 brown inactive tablets] [spearmint flavor]

Tablet, biphasic formulations:

Necon® 10/11-28:

Day 1-10: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [10 light yellow tablets]

Day 11-21: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [11 dark yellow tablets]

Day 22-28: 7 white inactive tablets (28s)

Ortho-Novum® 10/11-28:

Day 1-10: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [10 white tablets]

        - Day 11-21: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [11 peach tablets]
        - Day 22-28: 7 green inactive tablets (28s)

Tablet, triphasic formulations:

- Aranelle™:
    - Day 1-7: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [7 light yellow tablets]
    - Day 8-16: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [9 white tablets]
    - Day 17-21: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [5 light yellow tablets]
    - Day 22-28: 7 peach inactive tablets (28s)
- Estrostep® Fe:
    - Day 1-5: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg [5 white triangular tablets]
    - Day 6-12: Ethinyl estradiol 0.03 mg and norethindrone acetate 1 mg [7 white square tablets]
    - Day 13-21: Ethinyl estradiol 0.035 mg and norethindrone acetate 1 mg [9 white round tablets]
    - Day 22-28: Ferrous fumarate 75 mg [7 brown tablets] (28s)
- Leena™:
    - Day 1-7: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [7 light blue tablets]
    - Day 8-16: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [9 light yellow-green tablets]
    - Day 17-21: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [5 light blue tablets]
    - Day 22-28: 7 orange inactive tablets (28s)
- Necon® 7/7/7, Ortho-Novum® 7/7/7 28:
    - Day 1-7: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [7 white tablets]
    - Day 8-14: Ethinyl estradiol 0.035 mg and norethindrone 0.75 mg [7 light peach tablets]
    - Day 15-21: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [7 peach tablets]
    - Day 22-28: 7 green inactive tablets (28s)
- Nortrel™ 7/7/7 28:
    - Day 1-7: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [7 light yellow tablets]
    - Day 8-14: Ethinyl estradiol 0.035 mg and norethindrone 0.75 mg [7 blue tablets]
    - Day 15-21: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [7 peach tablets]
    - Day 22-28: 7 white inactive tablets (28s)
- Ortho-Novum® 7/7/7 28:
    - Day 1-7: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [7 white tablets]
    - Day 8-14: Ethinyl estradiol 0.035 mg and norethindrone 0.75 mg [7 light peach tablets]
    - Day 15-21: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [7 peach tablets]
    - Day 22-28: 7 green inactive tablets (28s)
- Tilia™ Fe:
    - Day 1-5: Ethinyl estradiol 0.02 mg and norethindrone acetate 1 mg [5 white triangular tablets]
    - Day 6-12: Ethinyl estradiol 0.03 mg and norethindrone acetate 1 mg [7 white square tablets]
    - Day 13-21: Ethinyl estradiol 0.035 mg and norethindrone acetate 1 mg [9 white round tablets]
    - Day 22-28: Ferrous fumarate 75 mg [7 brown tablets] (28s)
- Tri-Norinyl® 28:
    - Day 1-7: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [7 blue tablets]
    - Day 8-16: Ethinyl estradiol 0.035 mg and norethindrone 1 mg [9 yellow-green tablets]
    - Day 17-21: Ethinyl estradiol 0.035 mg and norethindrone 0.5 mg [5 blue tablets]

Day 22-28: 7 orange inactive tablets (28s)

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Chewable (Femcon Fe)

0.4-35 mg-mcg (28): $62.69

Tablets (Balziva)

0.4-35 mg-mcg (28): $42.99

Tablets (Brevicon (28))

0.5-35 mg-mcg (28): $52.99

Tablets (Estrostep Fe)

1-20/1-30/1-35 mg-mcg (28): $75.94

Tablets (Femhrt 1/5)

1-5 mg-mcg (28): $64.19

1-5 mg-mcg (30): $65.72

Tablets (Femhrt Low Dose)

0.5-2.5 mg-mcg (30): $66.24

Tablets (Junel 1/20)

1-20 mg-mcg (21): $27.99

Tablets (Junel FE 1.5/30)

1.5-30 mg-mcg (28): $29.99

Tablets (Junel FE 1/20)

1-20 mg-mcg (28): $27.99

Tablets (Leena)

0.5/1/0.5-35 mg-mcg (28): $29.99

Tablets (Loestrin 1.5/30 (21))

1.5-30 mg-mcg (21): $69.95

Tablets (Loestrin 1/20 (21))

1-20 mg-mcg (21): $69.95

Tablets (Loestrin Fe 1.5/30)

1.5-30 mg-mcg (28): $69.95

Tablets (Loestrin Fe 1/20)

1-20 mg-mcg (28): $69.95

Tablets (Microgestin 1.5/30)

1.5-30 mg-mcg (21): $29.99

Tablets (Microgestin 1/20)

1-20 mg-mcg (21): $29.99

Tablets (Microgestin FE 1.5/30)

1.5-30 mg-mcg (28): $29.99

Tablets (Microgestin FE 1/20)

1-20 mg-mcg (28): $29.99

Tablets (Modicon (28))

0.5-35 mg-mcg (28): $59.99

Tablets (Necon 0.5/35 (28))

0.5-35 mg-mcg (28): $32.99

Tablets (Necon 1/35 (28))

1-35 mg-mcg (28): $31.99

Tablets (Necon 10/11 (28))

35 mcg (28): $35.99

Tablets (Necon 7/7/7)

0.5/0.75/1-35 mg-mcg (28): $33.99

Tablets (Norinyl 1+35 (28))

1-35 mg-mcg (28): $55.99

Tablets (Nortrel 1/35 (28))

1-35 mg-mcg (28): $25.99

Tablets (Nortrel 7/7/7)

0.5/0.75/1-35 mg-mcg (28): $28.99

Tablets (Ortho-Novum 1/35 (28))

1-35 mg-mcg (28): $55.99

Tablets (Ortho-Novum 10/11 (28))

35 mcg (28): $53.96

Tablets (Ortho-Novum 7/7/7 (28))

0.5/0.75/1-35 mg-mcg (28): $55.99

Tablets (Ovcon-35 (28))

0.4-35 mg-mcg (28): $65.09

Tablets (Ovcon-50)

50-1 mcg-mg (28): $71.54

Tablets (Tilia Fe)

1-20/1-30/1-35 mg-mcg (28): $45.99

Tablets (Tri-Norinyl (28))

0.5/1/0.5-35 mg-mcg (28): $53.99

Tablets (Zenchent)

0.4-35 mg-mcg (28): $39.99

Mechanism of ActionCombination oral contraceptives inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of gonadotropin secretion of a follicle-stimulating hormone (FSH) and luteinizing hormone by the anterior pituitary. The follicular phase FSH and midcycle surge of gonadotropins are inhibited. In addition, combination hormonal contraceptives produce alterations in the genital tract, including changes in the cervical mucus, rendering it unfavorable for sperm penetration even if ovulation occurs. Changes in the endometrium may also occur, producing an unfavorable environment for nidation. Combination hormonal contraceptive drugs may alter the tubal transport of the ova through the fallopian tubes. Progestational agents may also alter sperm fertility.

In postmenopausal women, exogenous estrogen is used to replace decreased endogenous production. The addition of progestin reduces the incidence of endometrial hyperplasia and risk of endometrial cancer in women with an intact uterus.

Pharmacodynamics/Kinetics

Norethindrone: See individual monograph.

Ethinyl estradiol:

Absorption: Rapid

Bioavailability: 43% to 55%

Distribution: V_d: 2-4 L/kg

Protein binding: >95% to albumin

Metabolism: Hepatic via oxidation and conjugation in GI tract; hydroxylated via CYP3A4 to metabolites; first-pass effect; enterohepatic recirculation; reversibly converted to estrone and estriol

Half-life elimination: 19-24 hours

Excretion: Urine (as estradiol, estrone, and estriol); feces

Pharmacotherapy Pearls Norethindrone acetate 1 mg is equivalent to ethinyl estradiol 2.8 mcg.

The World Health Organization (WHO) has issued revised management recommendations for missed combined oral contraceptive pills. Refer to the following reference for a complete presentation and discussion of the guidelines:

Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit, "Faculty Statement from the CEU on a New Publication: WHO Selected Practice Recommendations for Contraceptive Use Update. Missed Pills: New Recommendations," *J Fam Plann Reprod Health Care*, 2005, 31(2):153-5.

Dental Health: Effects on Dental Treatment When prescribing antibiotics, patient must be warned to use additional methods of birth control if on oral contraceptives.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric Treatment Barbiturates decrease the effects of oral contraceptives; may increase the toxicity of the benzodiazepines and TCAs. The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Cardiovascular Considerations It is important to recognize that hormone-based contraceptives may induce or worsen hypertension. These problems are less severe with low-dose ones. Furthermore, hormone-based contraceptives may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on these contraceptives long-term undergo monitoring of blood pressure and avoid cigarette use.

Index Terms Norethindrone Acetate and Ethinyl Estradiol; Ortho Novum

References

Burkman R, Schlesselman JJ, and Zieman M, “Safety Concerns and Health Benefits Associated With Oral Contraception,” *Am J Obstet Gynecol*, 2004, 190(4 Suppl):5-22.

“Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection,” August 13, 2001. Available at: http://www.aidsinfo.nih.gov. Accessed September 5, 2001.

Holt VL, Scholes D, Wicklund KG, et al, “Body Mass Index, Weight, and Oral Contraceptive Failure Risk,” *Obstet Gynecol*, 2005, 105(1):46-52. [PubMed 15625141]

Orme ML, Back DJ, and Breckenridge AM, “Clinical Pharmacokinetics of Oral Contraceptive Steroids,” *Clin Pharmacokinet*, 1983, 8(2):95-136. [PubMed 6342899]

Rossouw JE, Anderson GL, Prentice RL, et al, “Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principle Results From the Women's Health Initiative Randomized Controlled Trial,”*JAMA*, 2002, 288(3):321-33.[PubMed 12117397]

Shenfield GM and Griffin JM, “Clinical Pharmacokinetics of Contraceptive Steroids. An Update,” *Clin Pharmacokinet*, 1991, 20(1):15-37. [PubMed 2029800]

U.S. Food and Drug Administration, Department of Health and Human Services, “FDA Approves New Labels for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women Following Review of Women's Health Initiative Data,” January 8, 2003. Available at: http://www.fda.gov/medwatch/SAFETY/2003/safety03.htm#prempr. Accessed January 9, 2003.

International Brand Names Activelle (AR, CH, DK, FI, FR, HK, IL, KP, MY, SE, SG, TH, TW, UY); Cliane (NZ); Clinorette (GB, IE); Covina (TW); Esdiol-half (KP); Estalis continuous (AU); Estalis Sequi (AU); Estracomb (AE, BH, CO, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Estragest TTS (AE, BH, CY, DE, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Eveclin Half (KP); Eveprem (KP); Eviclin (KP); Evorel Cont (IL); Evorel Conti (AR); Evorel Sequi (IL); Evorelconti (MX); Kliogest (BF, BJ, CI, ET, GH, GM, GN, KE, KP, LR, MA, ML, MR, MU, MW, MY, NE, NG, PK, SC, SD, SG, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Kliovance (AU); Novofem (EE, GB, HK, IE); Tri-Sequens (CO, KP, SG); Trisekvens (SE); Trisequens (BF, BJ, BR, CH, CI, CN, ET, FR, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, PE, PY, SC, SD, SL, SN, TN, TZ, UG, UY, ZA, ZM, ZW); Trisequens Forte (IL)

Ethinyl Estradiol and Norgestimate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Ortho-Cyclen® may be confused with Ortho-Cept®

Pronunciation(ETH in il es tra DYE ole & nor JES ti mate)

U.S. Brand NamesMonoNessa™; Ortho Tri-Cyclen®; Ortho Tri-Cyclen® Lo; Ortho-Cyclen®; Previfem™; Sprintec™; Tri-Previfem™; Tri-Sprintec™; TriNessa™

Canadian Brand NamesCyclen®; Tri-Cyclen® ; Tri-Cyclen® Lo

Pharmacologic CategoryContraceptive; Estrogen and Progestin Combination

Use: Labeled IndicationsPrevention of pregnancy; treatment of acne

Use: Unlabeled/InvestigationalTreatment of hypermenorrhea (menorrhagia); pain associated with endometriosis; dysmenorrhea; dysfunctional uterine bleeding

Dosing: AdultsFemales:

Acne (Ortho Tri-Cyclen®): Oral: Refer to dosing for contraception

Contraception: Oral:

Schedule 1 (Sunday starter): Dose begins on first Sunday after onset of menstruation; if the menstrual period starts on Sunday, take first tablet that very same day. **With a Sunday start, an additional method of contraception should be used until after the first 7 days of consecutive administration.**

For 21-tablet package: Dosage is 1 tablet daily for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken.

For 28-tablet package: Dosage is 1 tablet daily without interruption.

Schedule 2 (Day 1 starter): Dose starts on first day of menstrual cycle taking 1 tablet daily.

For 21-tablet package: Dosage is 1 tablet daily for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken.

For 28-tablet package: Dosage is 1 tablet daily without interruption.

If all doses have been taken on schedule and one menstrual period is missed, continue dosing cycle. If two consecutive menstrual periods are missed, pregnancy test is required before new dosing cycle is started.

Missed doses **monophasic formulations** (refer to package insert for complete information):

One dose missed: Take as soon as remembered or take 2 tablets next day

Two consecutive doses missed in the first 2 weeks: Take 2 tablets as soon as remembered or 2 tablets next 2 days. **An additional method of contraception should be used for 7 days after missed dose.**

Two consecutive doses missed in week 3 or three consecutive doses missed at any time: **An additional method of contraception must be used for 7 days after a missed dose:**

Schedule 1 (Sunday starter): Continue dose of 1 tablet daily until Sunday, then discard the rest of the pack, and a new pack should be started that same day.

Schedule 2 (Day 1 starter): Current pack should be discarded, and a new pack should be started that same day.

Missed doses **biphasic/triphasic formulations** (refer to package insert for complete information):

One dose missed: Take as soon as remembered or take 2 tablets next day.

Two consecutive doses missed in week 1 or week 2 of the pack: Take 2 tablets as soon as remembered and 2 tablets the next day. Resume taking 1 tablet daily until the pack is empty. **An additional method of contraception must be used for 7 days after a missed dose.**

Two consecutive doses missed in week 3 of the pack. **An additional method of contraception must be used for 7 days after a missed dose.**

Schedule 1 (Sunday starter): Take 1 tablet every day until Sunday. Discard the remaining pack and start a new pack of pills on the same day.

Schedule 2 (Day 1 starter): Discard the remaining pack and start a new pack the same day.

Three or more consecutive doses missed. **An additional method of contraception must be used for 7 days after a missed dose.**

Schedule 1 (Sunday starter): Take 1 tablet every day until Sunday; on Sunday, discard the pack and start a new pack.

Schedule 2 (Day 1 starter): Discard the remaining pack and begin new pack of tablets starting on the same day.

Dosing: PediatricFemales:

Acne: Oral: Children ≥15 years; refer to adult dosing for contraception

Contraception: Oral: Refer to adult dosing; not to be used prior to menarche.

Dosing: Renal ImpairmentSpecific guidelines not available; use with caution and monitor blood pressure closely. Consider other forms of contraception.

Dosing: Hepatic ImpairmentContraindicated in patients with hepatic impairment.

Administration: OralAdminister at the same time each day.

Dietary ConsiderationsShould be taken at same time each day.

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to ethinyl estradiol, norgestimate, or any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); cerebral vascular disease, coronary artery disease, valvular heart disease with complications, severe hypertension; diabetes with vascular involvement; severe headache with focal neurological symptoms; known or suspected breast carcinoma, endometrial cancer, estrogen-dependent neoplasms, undiagnosed abnormal genital bleeding; hepatic dysfunction or tumor, cholestatic jaundice of pregnancy, jaundice with prior combination hormonal contraceptive use; major surgery with prolonged immobilization; heavy smoking (≥15 cigarettes/day) in patients >35 years of age; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Smokers: See “Special populations” below.

Concerns related to adverse effects:

- Breast cancer: The use of combination hormonal contraceptives has been associated with a slight increase in frequency of breast cancer, however, studies are not consistent.
- Glucose intolerance: Combination hormonal contraceptives may cause glucose intolerance.
- Lipid effects: Combination hormonal contraceptives may effect serum triglyceride and lipoprotein levels. Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis (has been reported rarely with combination hormonal contraceptives); discontinue permanently if papilledema or retinal vascular lesions are observed on examination.
- Thromboembolism: May increase the risk of thromboembolism.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with risk factors for coronary artery disease; may lead to increased risk of myocardial infarction. May have a dose-related risk of vascular disease and hypertension; women with hypertension should be encouraged to use a nonhormonal form of contraception.
- Depression: Use with caution in patients with depression.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.
- Gallbladder disease: May have a dose-related risk of gallbladder disease.
- Migraine: Use with caution in patients with a history of migraine.
- Renal impairment: Women with renal disease should be encouraged to use a nonhormonal form of contraception.

Special populations:

- Pediatrics: Not for use prior to menarche.
- Smokers: **[U.S. Boxed Warning]: The risk of cardiovascular side effects increases in women who smoke cigarettes, especially those who are >35 years of age; women who use combination hormonal contraceptives should be strongly advised not to smoke.**
- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- Acne use: For use only in females ≥15 years, who also desire combination hormonal contraceptive therapy, are unresponsive to topical treatments, and have no contraindications to combination hormonal contraceptive use.

- HIV infection protection: Combination hormonal contraceptives do not protect against HIV infection or other sexually-transmitted diseases.

- Minimum effective dosage: The minimum dosage combination of estrogen/progestin that will effectively treat the individual patient should be used. New patients should be started on products containing ≤0.035 mg of estrogen per tablet.

Pregnancy Risk FactorX

Pregnancy ConsiderationsPregnancy should be ruled out prior to treatment and discontinued if pregnancy occurs. In general, the use of combination hormonal contraceptives when inadvertently taken early in pregnancy have not been associated with teratogenic effects. Due to increased risk of thromboembolism postpartum, combination hormonal contraceptives should not be started earlier than 4-6 weeks following delivery. Hormonal contraceptives may be less effective in obese patients. An increase in oral contraceptive failure was noted in women with a BMI >27.3. Similar findings were noted in patients weighing ≥90 kg (198 lb) using the contraceptive patch.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsJaundice and breast enlargement in the nursing infant have been reported following the use of combination hormonal contraceptives. May decrease the quality and quantity of breast milk; a nonhormonal form of contraception is recommended.

Adverse ReactionsThe following reactions have been associated with oral contraceptive use:

Increased risk or evidence of association with use:

Cardiovascular: Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, hypertension, mesenteric thrombosis, MI, venous thrombosis (with or without embolism)

Gastrointestinal: Gallbladder disease

Hepatic: Hepatic adenomas, liver tumors (benign)

Local: Thrombophlebitis

Ocular: Retinal thrombosis

Respiratory: Pulmonary embolism

Adverse reactions considered drug related:

Cardiovascular: Edema, varicose vein aggravation

Central nervous system: Depression, migraine, mood changes

Dermatologic: Chloasma, melasma, rash (allergic)

Endocrine & metabolic: Amenorrhea, breakthrough bleeding, breast changes (enlargement, pain, secretion, tenderness), fluid retention, infertility (temporary), lactation decreased (with use immediately postpartum), menstrual flow changes, spotting

Gastrointestinal: Abdominal bloating, abdominal cramps, abdominal pain, appetite changes, nausea, weight changes, vomiting

Genitourinary: Cervical ectropion, cervical secretion, vaginal candidiasis, vaginitis

Hematologic: Folate decreased, porphyria exacerbation

Hepatic: Cholestatic jaundice

Neuromuscular & skeletal: Chorea exacerbation

Ocular: Contact lens intolerance, corneal curvature changes (steepening)

Miscellaneous: Anaphylactic/anaphylactoid reactions (including angioedema, circulatory collapse, respiratory collapse, urticaria), SLE exacerbation

Adverse reactions in which association is not confirmed or denied: Acne, Budd-Chiari syndrome, cataracts, colitis, cystitis-like syndrome, dizziness, dysmenorrhea, erythema multiforme, erythema nodosum, headache, hemolytic uremic syndrome, hemorrhagic eruption, hirsutism, libido changes, nervousness, optic neuritis (with or without partial or complete loss of vision), pancreatitis, premenstrual syndrome, renal function impaired, scalp hair loss

Metabolism/Transport EffectsEthinyl estradiol: **Substrate** of CYP2C9 (minor), 3A4 (major), 3A5-7 (minor); **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C8 (weak), 2C19 (weak), 3A4 (weak)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Armodafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Estrogens) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Colesevelam: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Griseofulvin: May increase the metabolism of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

LamoTRIgine: Oral Contraceptive (Estrogens) may decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Modafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Average AUC values were unchanged, but there was evidence of substantial patient-to-patient variability in response to this combination. *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

Nafcillin: May increase the metabolism of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Protease Inhibitors: Oral Contraceptive (Estrogens) may diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Rufinamide: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Estrogens) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

TiZANidine: Oral Contraceptive (Estrogens) may increase the serum concentration of TiZANidine. *Risk C: Monitor therapy*

Topiramate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Oral Contraceptive (Estrogens) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Estrogens). Oral Contraceptive (Estrogens) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: CNS effects of caffeine may be enhanced if combination hormonal contraceptives are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations and would be expected to increase progesterone serum levels as well; clinical implications are unclear.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca. Herbs with progestogenic properties may enhance the adverse/toxic effect of progestins; examples include bloodroot, chasteberry, damiana, oregano, yucca.

Monitoring ParametersBefore starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision, sudden onset of proptosis, diplopia, migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Nursing: Physical Assessment/MonitoringAssess for adverse reactions and potential drug interactions. Emphasize importance of regular (monthly) blood pressure checks and annual physical assessment, Pap smear, and vision assessment. Teach importance of maintaining prescribed schedule of dosing. **Pregnancy risk factor X:** Do not use if patient is pregnant.

Patient EducationOral contraceptives do not protect against HIV or other sexually-transmitted diseases. Take exactly as directed by prescriber (also see package insert). You are at risk of becoming pregnant if doses are missed. Detailed and complete information on dosing and missed doses can be found in the package insert. Be aware that some medications may reduce the effectiveness of oral contraceptives; an alternate form of contraception may be needed. Check all medicines (prescription and OTC), herbal, and alternative products with prescriber. It is important that you check your blood pressure monthly (on same day each month) and that you have an annual physical assessment, Pap smear, and vision assessment while taking this medication. Avoid smoking while taking this medication; smoking increases risk of adverse effects, including thromboembolic events and heart attacks. You may experience loss of appetite (small frequent meals will help); or constipation (increased exercise, fluids, fruit, fiber, or stool softeners may help). If you have diabetes, use accurate serum glucose testing to identify any changes in glucose tolerance; notify prescriber of significant changes so antidiabetic medication can be adjusted if necessary. Report immediately pain or muscle soreness; warmth, swelling, pain, or redness in calves; shortness of breath; sudden loss of vision; unresolved leg/ foot swelling; change in menstrual pattern (unusual bleeding, amenorrhea, breakthrough spotting); breast tenderness that does not go away; acute abdominal cramping; signs of vaginal infection (drainage, pain, itching); CNS changes (blurred vision, confusion, acute anxiety, or unresolved depression); chest pain; severe headache or vomiting; weakness in arm or leg; severe abdominal pain or tenderness; jaundice; or significant weight gain (>5 lb/week). Notify prescriber of changes in contact lens tolerance. **Pregnancy/breast-feeding precautions:** This medication should not be used during pregnancy. If you suspect you may become pregnant, contact prescriber immediately. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, monophasic formulations:

MonoNessa™, Ortho-Cyclen®: Ethinyl estradiol 0.035 mg and norgestimate 0.25 mg (28s) [21 blue tablets and 7 green inactive tablets]

Previfem™: Ethinyl estradiol 0.035 mg and norgestimate 0.25 mg (28s) [21 blue tablets and 7 teal inactive tablets]

Sprintec™: Ethinyl estradiol 0.035 mg and norgestimate 0.25 mg (28s) [21 blue tablets and 7 white inactive tablets]

Tablet, triphasic formulations:

Ortho Tri-Cyclen®, TriNessa™:

Day 1-7: Ethinyl estradiol 0.035 mg and norgestimate 0.18 mg [7 white tablets]

Day 8-14: Ethinyl estradiol 0.035 mg and norgestimate 0.215 mg [7 light blue tablets]

Day 15-21: Ethinyl estradiol 0.035 mg and norgestimate 0.25 mg [7 blue tablets]

Day 22-28: 7 green inactive tablets (28s)

Tri-Previfem™:

Day 1-7: Ethinyl estradiol 0.035 mg and norgestimate 0.18 mg [7 white tablets]

Day 8-14: Ethinyl estradiol 0.035 mg and norgestimate 0.215 mg [7 light blue tablets]

Day 15-21: Ethinyl estradiol 0.035 mg and norgestimate 0.25 mg [7 blue tablets]

Day 22-28: 7 teal inactive tablets (28s)

Tri-Sprintec™:

Day 1-7: Ethinyl estradiol 0.035 mg and norgestimate 0.18 mg [7 gray tablets]

Day 8-14: Ethinyl estradiol 0.035 mg and norgestimate 0.215 mg [7 light blue tablets]

Day 15-21: Ethinyl estradiol 0.035 mg and norgestimate 0.25 mg [7 blue tablets]

Day 22-28: 7 white inactive tablets (28s)

Ortho Tri-Cyclen® Lo:

Day 1-7: Ethinyl estradiol 0.025 mg and norgestimate 0.18 mg [7 white tablets]

Day 8-14: Ethinyl estradiol 0.025 mg and norgestimate 0.215 mg [7 light blue tablets]

Day 15-21: Ethinyl estradiol 0.025 mg and norgestimate 0.25 mg [7 dark blue tablets]

Day 22-28: 7 green inactive tablets (28s)

Generic AvailableYes
ManufacturerOrtho-McNeil Pharmaceutical, Inc
Pricing: U.S. (www.drugstore.com)

Tablets (Mononessa)

0.25-35 mg-mcg (28): $28.99

Tablets (Ortho Tri-Cyclen (28))

0.035 mg (28): $47.99

Tablets (Ortho Tri-Cyclen Lo)

0.025 mg (28): $62.99

Tablets (Ortho-Cyclen (28))

0.25-35 mg-mcg (28): $55.99

Tablets (Sprintec 28)

0.25-35 mg-mcg (28): $26.99

Tablets (Tri-Previfem)

0.035 mg (28): $34.99

Tablets (Tri-Sprintec)

0.035 mg (28): $34.99

Tablets (TriNessa (28))

0.035 mg (28): $27.99

Mechanism of ActionCombination hormonal contraceptives inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of gonadotropin secretion of a follicle-stimulating hormone (FSH) and luteinizing hormone by the anterior pituitary. The follicular phase FSH and midcycle surge of gonadotropins are inhibited. In addition, combination hormonal contraceptives produce alterations in the genital tract, including changes in the cervical mucus, rendering it unfavorable for sperm penetration even if ovulation occurs. Changes in the endometrium may also occur, producing an unfavorable environment for nidation. Combination hormonal contraceptive drugs may alter the tubal transport of the ova through the fallopian tubes. Progestational agents may also alter sperm fertility.

Pharmacodynamics/Kinetics

Absorption: Ethinyl estradiol (EE) and norgestimate (NGM): Rapid and well absorbed

Protein binding:

EE: >97% to albumin

Norelgestromin (NGMN): >97% to albumin

Norgestrel (NG): >97% to sex hormone-binding globulin (SHBG); SHBG capacity is affected by plasma ethinyl estradiol levels

Metabolism:

EE: Hepatic; forms metabolites

NGM: Hepatic; forms NGMN (major active metabolite) which is further metabolized to NG (active) and other metabolites

Half-life elimination:

EE: 10-16 hours

NGMN: 18-25 hours

NG: 38-45 hours

Time to peak, plasma: EE and NGM: ~2 hours

Excretion:

EE: Urine and feces

NGM: Urine (~47%) and feces (~37%) as metabolites

Pharmacotherapy PearlsThe World Health Organization (WHO) has issued revised management recommendations for missed combined oral contraceptive pills. Refer to the following reference for a complete presentation and discussion of the guidelines:

Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit, "Faculty Statement from the CEU on a New Publication: WHO Selected Practice Recommendations for Contraceptive Use Update. Missed Pills: New Recommendations," *J Fam Plann Reprod Health Care*, 2005, 31(2):153-5.

Dental Health: Effects on Dental TreatmentWhen prescribing antibiotics, patient must be warned to use additional methods of birth control if on oral contraceptives.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentBarbiturates decrease the effects of oral contraceptives; may increase the toxicity of the benzodiazepines and TCAs. The Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Cardiovascular ConsiderationsIt is important to recognize that hormone-based contraceptives may induce or worsen hypertension. These problems are less severe with low-dose ones. Furthermore, hormone-based contraceptives may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on these contraceptives long-term undergo monitoring of blood pressure and avoid cigarette use.

Index TermsEthinyl Estradiol and NGM; Norgestimate and Ethinyl Estradiol; Ortho Cyclen; Ortho Tri Cyclen

References

Burkman R, Schlesselman JJ, and Zieman M, “Safety Concerns and Health Benefits Associated With Oral Contraception,” *Am J Obstet Gynecol*, 2004, 190(4 Suppl):5-22.

“Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection,” August 13, 2001. Available at: http://www.aidsinfo.nih.gov. Accessed September 5, 2001.

Holt VL, Scholes D, Wicklund KG, et al, “Body Mass Index, Weight, and Oral Contraceptive Failure Risk,” *Obstet Gynecol*, 2005, 105(1):46-52. [PubMed 15625141]

Orme ML, Back DJ, and Breckenridge AM, “Clinical Pharmacokinetics of Oral Contraceptive Steroids,” *Clin Pharmacokinet*, 1983, 8(2):95-136. [PubMed 6342899]

Shenfield GM and Griffin JM, “Clinical Pharmacokinetics of Contraceptive Steroids. An Update,” *Clin Pharmacokinet*, 1991, 20(1):15-37.[PubMed 2029800]

International Brand NamesCilest (AR, BE, BG, CH, CO, CR, CZ, DE, DK, DO, EE, FI, FR, GB, GT, HN, IE, MX, NI, NL, PA, PE, PY, SE, SK, SV, TH, UY); Cileste (AT); Edelsin (ES); Ortho Cyclen (IL); Ortrel (VE); Tri-Cilest (CO); Triafemi (FR); Tricilest (FR, TH)

Ethinyl Estradiol and Norgestrel

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English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ETH in il es tra DYE ole & nor JES trel)

U.S. Brand NamesCryselle™; Lo/Ovral®; Low-Ogestrel®; Ogestrel®

Canadian Brand NamesOvral®

Pharmacologic CategoryContraceptive; Estrogen and Progestin Combination

Use: Labeled IndicationsPrevention of pregnancy; postcoital contraceptive or “morning after” pill

Use: Unlabeled/InvestigationalTreatment of hypermenorrhea (menorrhagia); pain associated with endometriosis; dysmenorrhea; dysfunctional uterine bleeding

Dosing: Adults

Females: Contraception: Oral:

Schedule 1 (Sunday starter): Dose begins on first Sunday after onset of menstruation; if the menstrual period starts on Sunday, take first tablet that very same day. **With a Sunday start, an additional method of contraception should be used until after the first 7 days of consecutive administration.**

For 21-tablet package: Dosage is 1 tablet daily for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken.

For 28-tablet package: Dosage is 1 tablet daily without interruption.

Schedule 2 (Day 1 starter): Dose starts on first day of menstrual cycle taking 1 tablet daily.

For 21-tablet package: Dosage is 1 tablet daily for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken.

For 28-tablet package: Dosage is 1 tablet daily without interruption.

If all doses have been taken on schedule and one menstrual period is missed, continue dosing cycle. If two consecutive menstrual periods are missed, pregnancy test is required before new dosing cycle is started.

Missed doses **monophasic formulations** (refer to package insert for complete information):

One dose missed: Take as soon as remembered or take 2 tablets next day

Two consecutive doses missed in the first 2 weeks: Take 2 tablets as soon as remembered or 2 tablets next 2 days. **An additional method of contraception should be used for 7 days after missed dose.**

Two consecutive doses missed in week 3 or three consecutive doses missed at any time:

Schedule 1 (Sunday starter): Continue to take 1 tablet daily until Sunday, then discard the rest of the pack, and a new pack is started that same day.

Schedule 2 (Day 1 starter): Current pack should be discarded, and a new pack started that same day. **An additional method of contraception should be used for 7 days after missed dose.**

Females: Postcoital contraception: Oral:

Ethinyl estradiol 0.03 mg and norgestrel 0.3 mg formulation: 4 tablets within 72 hours of unprotected intercourse and 4 tablets 12 hours after first dose

Ethinyl estradiol 0.05 mg and norgestrel 0.5 mg formulation: 2 tablets within 72 hours of unprotected intercourse and 2 tablets 12 hours after first dose

Dosing: PediatricFemales: Contraception or postcoital contraception: Oral: See adult dosing; not to be used prior to menarche.

Dosing: Renal ImpairmentSpecific guidelines not available; use with caution and monitor blood pressure closely. Consider other forms of contraception.

Dosing: Hepatic ImpairmentContraindicated in patients with hepatic impairment.

Administration: OralAdminister at the same time each day.

Dietary ConsiderationsShould be taken at same time each day.

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to ethinyl estradiol, norgestrel, or any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); cerebral vascular disease, coronary artery disease, valvular heart disease with complications, severe hypertension; diabetes mellitus with vascular involvement; severe headache with focal neurological symptoms; known or suspected breast carcinoma, endometrial cancer, estrogen-dependent neoplasms, undiagnosed abnormal genital bleeding; hepatic dysfunction or tumor, cholestatic jaundice of pregnancy, jaundice with prior combination hormonal contraceptive use; major surgery with prolonged immobilization; heavy smoking (≥15 cigarettes/day) in patients >35 years of age; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Smokers: See “Special populations” below.

Concerns related to adverse effects:

- Breast cancer: The use of combination hormonal contraceptives has been associated with a slight increase in frequency of breast cancer, however, studies are not consistent.
- Glucose intolerance: Combination hormonal contraceptives may cause glucose intolerance.
- Lipid effects: Combination hormonal contraceptives may effect serum triglyceride and lipoprotein levels. Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis (has been reported rarely with combination hormonal contraceptives); discontinue permanently if papilledema or retinal vascular lesions are observed on examination.
- Thromboembolism: May increase the risk of thromboembolism.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with risk factors for coronary artery disease; may lead to increased risk of myocardial infarction. May have a dose-related risk of vascular disease and hypertension; women with hypertension should be encouraged to use a nonhormonal form of contraception.
- Depression: Use with caution in patients with depression.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.
- Gallbladder disease: May have a dose-related risk of gallbladder disease.
- Migraine: Use with caution in patients with a history of migraine.
- Renal impairment: Women with renal disease should be encouraged to use a nonhormonal form of contraception.

Special populations:

- Pediatrics: Not for use prior to menarche.
- Smokers: **[U.S. Boxed Warning]: The risk of cardiovascular side effects increases in women who smoke cigarettes, especially those who are >35 years of age; women who use combination hormonal contraceptives should be strongly advised not to smoke.**
- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- HIV infection protection: Combination hormonal contraceptives do not protect against HIV infection or other sexually-transmitted diseases.
- Minimum effective dosage: The minimum dosage combination of estrogen/progestin that will effectively treat the individual patient should be used. New patients should be started on products containing ≤0.035 mg of estrogen per tablet.

Pregnancy Risk FactorX

Pregnancy ConsiderationsPregnancy should be ruled out prior to treatment and discontinued if pregnancy occurs. In general, the use of combination hormonal contraceptives when inadvertently taken early in pregnancy have not been associated with teratogenic effects. Due to increased risk of thromboembolism postpartum, combination hormonal contraceptives should not be started earlier than 4-6 weeks following delivery. Hormonal contraceptives may be less effective in obese patients. An increase in oral contraceptive failure was noted in women with a BMI >27.3. Similar findings were noted in patients weighing ≥90 kg (198 lb) using the contraceptive patch.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsJaundice and breast enlargement in the nursing infant have been reported following the use of combination hormonal contraceptives. May decrease the quality and quantity of breast milk; a nonhormonal form of contraception is recommended.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, edema, hypertension, mesenteric thrombosis, MI

Central nervous system: Depression, dizziness, headache, migraine, nervousness, premenstrual syndrome, stroke

Dermatologic: Acne, erythema multiforme, erythema nodosum, hirsutism, loss of scalp hair, melasma (may persist), rash (allergic)

Endocrine & metabolic: Amenorrhea, breakthrough bleeding, breast enlargement, breast secretion, breast tenderness, carbohydrate intolerance, lactation decreased (postpartum), glucose tolerance decreased, libido changes, menstrual flow changes, sex hormone-binding globulins (SHBG) increased, spotting, temporary infertility (following discontinuation), thyroid-binding globulin increased, triglycerides increased

Gastrointestinal: Abdominal cramps, appetite changes, bloating, cholestasis, colitis, gallbladder disease, jaundice, nausea, vomiting, weight gain/loss

Genitourinary: Cervical erosion changes, cervical secretion changes, cystitis-like syndrome, vaginal candidiasis, vaginitis

Hematologic: Antithrombin III decreased, folate levels decreased, hemolytic uremic syndrome, norepinephrine induced platelet aggregability increased, porphyria, prothrombin increased; factors VII, VIII, IX, and X increased

Hepatic: Benign liver tumors, Budd-Chiari syndrome, cholestatic jaundice, hepatic adenomas

Local: Thrombophlebitis

Ocular: Cataracts, change in corneal curvature (steepening), contact lens intolerance, optic neuritis, retinal thrombosis

Renal: Impaired renal function

Respiratory: Pulmonary thromboembolism

Miscellaneous: Hemorrhagic eruption

Metabolism/Transport Effects

Ethinyl estradiol: **Substrate** of CYP2C9 (minor), 3A4 (major), 3A5-7 (minor); **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C8 (weak), 2C19 (weak), 3A4 (weak)

Norgestrel: **Substrate** of CYP3A4 (major)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Armodafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Estrogens) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Colesevelam: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Griseofulvin: May increase the metabolism of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy*

modification

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

LamoTRIgine: Oral Contraceptive (Estrogens) may decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Modafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Average AUC values were unchanged, but there was evidence of substantial patient-to-patient variability in response to this combination. *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

Nafcillin: May increase the metabolism of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Protease Inhibitors: Oral Contraceptive (Estrogens) may diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Rufinamide: May decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Estrogens) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

TiZANidine: Oral Contraceptive (Estrogens) may increase the serum concentration of TiZANidine. *Risk C: Monitor therapy*

Topiramate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Oral Contraceptive (Estrogens) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Estrogens). Oral Contraceptive (Estrogens) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: CNS effects of caffeine may be enhanced if combination hormonal contraceptives are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations and would be expected to increase progesterone serum levels as well; clinical implications are unclear.

Herb/Nutraceutical: St John's wort may decrease levels. Herbs with estrogenic properties may enhance the adverse/toxic effect of estrogen derivatives; examples include alfalfa, black cohosh, bloodroot, hops, kudzu, licorice, red clover, saw palmetto, soybean, thyme, wild yam, yucca. Herbs with progestogenic properties may enhance the adverse/toxic effect of progestins; examples include bloodroot, chasteberry, damiana, oregano, yucca.

Monitoring ParametersBefore starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision, sudden onset of proptosis, diplopia, migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, monophasic formulations:

Cryselle™: Ethinyl estradiol 0.03 mg and norgestrel 0.3 mg [21 white tablets and 7 light green inactive tablets] (28s)

Low-Ogestrel® 28: Ethinyl estradiol 0.03 mg and norgestrel 0.3 mg [21 white tablets and 7 peach inactive tablets] (28s)

Lo/Ovral® 28: Ethinyl estradiol 0.03 mg and norgestrel 0.3 mg [21 white tablets and 7 pink inactive tablets] (28s)

Ogestrel® 28: Ethinyl estradiol 0.05 mg and norgestrel 0.5 mg [21 white tablets and 7 peach inactive tablets] (28s)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Cryselle-28)

0.3-30 mg-mcg (28): $26.99

Tablets (Lo/Ovral (28))

0.3-30 mg-mcg (28): $62.98

Tablets (Low-Ogestrel)

0.3-30 mg-mcg (28): $31.99

Tablets (Ogestrel)

0.5-50 mg-mcg (28): $41.99

Tablets (Ovral (28))

0.5-50 mg-mcg (28): $52.07

Mechanism of ActionCombination hormonal contraceptives inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of gonadotropin secretion of a follicle-stimulating hormone (FSH) and luteinizing hormone by the anterior pituitary. The follicular phase FSH and midcycle surge of gonadotropins are inhibited. In addition, combination hormonal contraceptives produce alterations in the genital tract, including changes in the cervical mucus, rendering it unfavorable for sperm penetration even if ovulation occurs. Changes in the endometrium may also occur, producing an unfavorable environment for nidation. Combination hormonal contraceptive drugs may alter the tubal transport of the ova through the fallopian tubes. Progestational agents may also alter sperm fertility.

Pharmacotherapy PearlsThe World Health Organization (WHO) has issued revised management recommendations for missed combined oral contraceptive pills. Refer to the following reference for a complete presentation and discussion of the guidelines:

Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit, "Faculty Statement from the CEU on a New Publication: WHO Selected Practice Recommendations for Contraceptive Use Update. Missed pills: New Recommendations," *J Fam Plann Reprod Health Care*, 2005, 31(2):153-5.

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Cardiovascular ConsiderationsIt is important to recognize that hormone-based contraceptives may induce or worsen hypertension. These problems are less severe with low-dose ones.Furthermore, hormone-based contraceptives may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on these contraceptives long-term undergo monitoring of blood pressure and avoid cigarette use.

Index TermsMorning After Pill; Norgestrel and Ethinyl Estradiol

References

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Burkman R, Schlesselman JJ, and Zieman M, “Safety Concerns and Health Benefits Associated With Oral Contraception,” *Am J Obstet Gynecol*, 2004, 190(4 Suppl):5-22.

“Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection,” August 13, 2001. Available at: http://www.aidsinfo.nih.gov. Accessed September 5, 2001.

Hendeles SM, Galand N, and Schwers J, “Metabolism of Orally Administered D-norgestrel in Women,” *Acta Endocrinol (Copenh)*, 1972, 71(3):557-68.

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“Prescription Drug Products; Certain Combined Oral Contraceptives for Use as Postcoital Emergency Contraception,” *Fed Regist*, 1997, 62(37):8610-12 (Notice).

Shenfield GM and Griffin JM, “Clinical Pharmacokinetics of Contraceptive Steroids. An Update,” *Clin Pharmacokinet*, 1991, 20(1):15-37.[PubMed 2029800]

International Brand NamesAnfertil (BR); Duoluton (AR, BE, IN, JP, TW); Duoluton-L (IN); Eugynon 28 (DE); Eugynon 30 (IE); Femenal (PH); Microdiol (ID); Ovral (AR, BB, BF, BJ, BM, BS, BZ, CI, ET, GH, GM, GN, GR, GY, IN, JM, KE, LR, MA, ML, MR, MU, MW, MX, NE, NG, NL, PE, PK, SC, SD, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Planovar (JP); Stediril (BE, FR)

Ethionamide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(e thye on AM ide)

U.S. Brand NamesTrecator®

Canadian Brand NamesTrecator®

Pharmacologic CategoryAntitubercular Agent

Use: Labeled IndicationsTreatment of tuberculosis and other mycobacterial diseases, in conjunction with other antituberculosis agents, when first-line agents have failed or resistance has been demonstrated

Dosing: AdultsTuberculosis: Oral: 15-20 mg/kg/day; initiate dose at 250 mg/day for 1-2 days, then increase to 250 mg twice daily for 1-2 days, with gradual increases to highest tolerated dose; average adult dose: 750 mg/day (maximum: 1 g/day in 3-4 divided doses)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricTuberculosis: Oral: 15-20 mg/kg/day in 2 divided doses, not to exceed 1 g/day

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute: 250-500 mg/day

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralNeurotoxic effects may be relieved by the administration of pyridoxine (6-100 mg daily, lower doses are more common). May be taken with or without meals. Gastrointestinal adverse effects may be decreased by administration at bedtime, decreased dose, or giving antiemetics.

Dietary ConsiderationsHealthcare provider may recommend an increase in dietary intake of pyridoxine to prevent neurotoxic effects of ethionamide. Avoid alcohol.

ContraindicationsHypersensitivity to ethionamide or any component of the formulation; severe hepatic impairment

Warnings/Precautions

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; may cause hypoglycemia.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction; hypothyroidism has been reported.

Concurrent drug therapy issues:

- Cycloserine: Use with caution in patients receiving cycloserine.

- Isoniazid: Use with caution in patients receiving isoniazid.

Dosage form specific issues:

- Product interchangeability: Use caution when switching patients from the sugar-coated tablet formulation (Trecator®-SC) to film-coated tablet (Trecator®); the dosage may need retitrated in order to avoid intolerance.

Other warnings/precautions:

- Eye exams: Periodic eye exams are recommended.

Geriatric ConsiderationsSince many elderly have Cl_{cr} <50 mL/minute, adjust dose for renal function.

Pregnancy Risk FactorC

Pregnancy ConsiderationsEthionamide crosses the placenta; teratogenic effects were observed in animal studies. Use during pregnancy is not recommended.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIf ethionamide is used while breast-feeding, monitor the infant for adverse effects.

Adverse ReactionsFrequency not defined.

Cardiovascular: Postural hypotension

Central nervous system: Depression, dizziness, drowsiness, headache, psychiatric disturbances, restlessness, seizure

Dermatologic: Acne, alopecia, photosensitivity, purpura, rash

Endocrine & metabolic: Gynecomastia, hypoglycemia, hypothyroidism or goiter, pellagra-like syndrome

Gastrointestinal: Abdominal pain, anorexia, diarrhea, excessive salivation, metallic taste, nausea, stomatitis, vomiting, weight loss

Genitourinary: Impotence

Hematologic: Thrombocytopenia

Hepatic: Hepatitis, jaundice, liver function tests increased

Neuromuscular & skeletal: Peripheral neuritis, weakness (common)

Ocular: Blurred vision, diplopia, optic neuritis

Respiratory: Olfactory disturbances

Miscellaneous: Hypersensitivity reaction

Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid excessive ethanol ingestion; psychotic reaction may occur.

Monitoring ParametersInitial and periodic serum ALT and AST; ophthalmic exams; thyroid function
Nursing: Physical Assessment/MonitoringSee Contraindications, Warnings/Precautions, Drug Interactions, and Dosing for use cautions. Assess results of laboratory tests (see above), therapeutic effectiveness, and adverse response (eg, CNS changes, neuritis, and ocular changes - see Adverse Reactions) on a regular basis during therapy. Teach patient appropriate use (eg, need to adhere to dosing program), possible side effects/appropriate interventions, and adverse symptoms to report (see Patient Education). **Pregnancy risk factor C** - benefits of use should outweigh possible risks. Note breast-feeding caution.
Monitoring: Lab TestsInitial and periodic serum ALT and AST
Patient EducationTake this medication as prescribed; avoid missing doses and do not discontinue without contacting prescriber. Avoid excessive alcohol intake (may cause severe psychotic reaction). You will need to schedule regular medical checkups which will include blood tests. May cause GI upset (small, frequent meals may help); metallic taste and increased salivation (lozenges, frequent mouth care); dizziness, blurred vision (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (change position slowly); or impotence and/or menstrual difficulties (these will go away when drug is discontinued). Report acute unresolved GI upset, vision changes, numbness or pain in extremities, or unusual bleeding or bruising. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 250 mg

Generic AvailableNo
ManufacturerWyeth-Ayerst Laboratories
Pricing: U.S. (www.drugstore.com)

Tablets (Trecator-SC)

250 mg (60): $160.98

Mechanism of ActionInhibits peptide synthesis
Pharmacodynamics/Kinetics

Absorption: Rapid, complete

Distribution: Crosses placenta; V_d: 93.5 L

Protein binding: ~30%

Metabolism: Extensively hepatic to active and inactive metabolites

Bioavailability: 80%

Half-life elimination: 2-3 hours

Time to peak, serum: 1 hour

Excretion: Urine (<1% as unchanged drug; as active and inactive metabolites)

Related Information

- Antimicrobial Drugs of Choice
- Tuberculosis

Pharmacotherapy PearlsNeurotoxic effects may be relieved by the administration of pyridoxine.
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Postural hypotension, metallic taste, and stomatitis.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness; case reports of depression and psychosis
Mental Health: Effects on Psychiatric TreatmentNone reported
References

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Davidson PT and Le HQ, “Drug Treatment of Tuberculosis - 1992,” *Drugs*, 1992, 43(5):651-73. [PubMed 1379145]

Donald PR and Seifart HI,“Cerebrospinal Fluid Concentrations of Ethionamide in Children With Tuberculous Meningitis,” *J Pediatr*, 1989, 115(3):483-6. [PubMed 2769511]

"Drugs for Tuberculosis," *Med Lett Drugs Ther*, 1993, 35(908):99-101. [PubMed 8412982]

Iseman MD, "Treatment of Multidrug-Resistant Tuberculosis," *N Engl J Med*, 1993, 329(11):784-91. [PubMed 8350889]

Pattyn SR, Janssens L, Bourland J, et al, "Hepatotoxicity of the Combination of Rifampin-Ethionamide in the Treatment of Multibacillary Leprosy," *Int J Lepr Other Mycobact Dis*, 1984, 52(1):1-6. [PubMed 6368424]

Starke JR and Correa AG, "Management of Mycobacterial Infection and Disease in Children," *Pediatr Infect Dis J*, 1995, 14(6):455-69.[PubMed 7667049]

International Brand NamesEthatyl (ZA); Myobid (IN); Trecator (FR)

Ethosuximide

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - February, 2008

The U.S. Food and Drug Administration (FDA) is informing healthcare professionals of an increased risk of suicidality (suicidal behavior or ideation) observed from analysis of clinical studies using various antiepileptic medications compared to placebo. The analysis was performed on 199 placebo-controlled studies involving 43,892 patients (27,863 treated patients versus 16,029 placebo patients) aged ≥5 years receiving one of the following 11 drugs: carbamazepine (Carbatrol®, Equetro™, Tegretol®, Tegretol® XR), felbamate (Felbatol®), gabapentin (Neurontin®), lamotrigine (Lamictal®), levetiracetam (Keppra®), oxcarbazepine (Trileptal®), pregabalin (Lyrica®), tiagabine (Gabitril®), topiramate (Topamax®), valproate (Depakote®, Depakote® ER, Depakene®, Depacon®), and zonisamide (Zonegran®). Studies examined medication efficacy in a variety of disorders, including epilepsy, psychiatric disorders (eg, depression, bipolar disorder), and other conditions (eg, migraine, neuropathic pain). According to the FDA, the results revealed a statistically significant increased risk of suicidality in 0.43% treated patients compared to 0.22% placebo patients, or an estimated 2.1 per 1000 (95% CI: 0.7, 4.2) more patients in the treated groups relative to placebo. This increased risk was reported anywhere from 1 week of therapy through 24 weeks. However, most trials were ≤24 weeks duration and the risk of suicide extending beyond 24 weeks is currently unknown. The relative risk of suicidal behavior or ideation in the treated patients was higher for patients with epilepsy (RR=3.6) compared to patients treated for psychiatric (RR=1.6) or other conditions (RR=2.3). Overall, the incidence of suicidal behavior or ideation occurred consistently across all demographic subgroups and with each of the drugs studied. Of note, four patients receiving an antiepileptic committed suicide relative to none in the placebo groups.

Forthcoming product labeling changes are likely to extend to all antiepileptic drugs and not limited to the drugs used in the studies, pending discussions scheduled for the upcoming advisory committee meeting. Healthcare professionals and family members/caregivers are encouraged to monitor patients receiving any antiepileptic medication for signs/symptoms of suicidality (eg, anxiety, depression, behavior changes). Patients should not stop taking their antiepileptic therapy unless advised by a healthcare professional.

Additional information can be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

Ethosuximide may be confused with methsuximide

Zarontin® may be confused with Xalatan®, Zantac®, Zaroxolyn®

Pronunciation(eth oh SUKS i mide)
U.S. Brand NamesZarontin®
Canadian Brand NamesZarontin®
Pharmacologic CategoryAnticonvulsant, Succinimide
Use: Labeled IndicationsManagement of absence (petit mal) seizures
Dosing: Adults**Management of absence (petit mal) seizures:** Oral: Initial: 500 mg/day; increase by 250 mg as needed every 4-7 days up to 1.5 g/day in divided doses
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Absence (petit mal) seizures: Oral:

Children 3-6 years: Initial: 250 mg/day; increase every 4-7 days; usual maintenance dose: 20 mg/kg/day; maximum dose: 1.5 g/day in divided doses.

Children >6 years: Refer to adult dosing.

Dosing: Renal ImpairmentUse with caution.
Dosing: Hepatic ImpairmentUse with caution.
Administration: OralAdminister with food or milk to avoid GI upset.
Dietary ConsiderationsIncrease dietary intake of folate; may be administered with food or milk.
ContraindicationsHypersensitivity to ethosuximide, other succinimides, or any component of the formulation
Allergy Considerations

- Succinimide Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Blood dyscrasias: Succinimides have been associated with severe blood dyscrasias.

- SLE: Succinimides have been associated with cases of systemic lupus erythematosus (SLE).

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Infection: Consider evaluation of blood counts in patients with signs/symptoms of infection.

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <3 years of age.

Other warnings/precautions:

- Appropriate use: Must be used in combination with other anticonvulsants in patients with both absence and tonic-clonic seizures. May increase tonic-clonic seizures in patients with mixed seizure disorders.

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsNo specific studies with the use of this medication in the elderly. Consider renal function and proceed slowly with dosing increases; monitor closely.
Pregnancy Considerations

Ethosuximide crosses the placenta. Cases of birth defects have been reported in infants. Epilepsy itself, the number of medications, genetic factors, or a combination of these probably influence the teratogenicity of anticonvulsant therapy. Health professionals and patients are encouraged to contact the North American Antiepileptic Drug Pregnancy registry to monitor outcomes of pregnant women exposed to ethosuximide and other antiepileptic drugs (888-233-2334).

LactationEnters breast milk/use caution (AAP rates “compatible”)
Adverse ReactionsFrequency not defined.

Central nervous system: Aggressiveness, ataxia, disturbance in sleep, dizziness, drowsiness, euphoria, fatigue, headache, hyperactivity, inability to concentrate, irritability, lethargy, mental depression (with cases of overt suicidal intentions), night terrors, paranoid psychosis

Dermatologic: Hirsutism, pruritus, rash, Stevens-Johnson syndrome, urticaria

Endocrine & metabolic: Libido increased

Gastrointestinal: Abdominal pain, anorexia, cramps, diarrhea, epigastric pain, gastric upset, gum hypertrophy, nausea, tongue swelling, vomiting, weight loss

Genitourinary: Hematuria (microscopic), vaginal bleeding

Hematologic: Agranulocytosis, eosinophilia, leukopenia, pancytopenia

Ocular: Myopia

Miscellaneous: Hiccups, systemic lupus erythematosus

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the therapeutic effect of Ethosuximide. Amphetamines may decrease the serum concentration of Ethosuximide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Valproic Acid: Ethosuximide may decrease the serum concentration of Valproic Acid. Valproic Acid may increase the serum concentration of Ethosuximide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: St John's wort may decrease ethosuximide levels.

Monitoring ParametersSeizure frequency, trough serum concentrations; CBC, platelets, liver enzymes, urinalysis

Reference RangeTherapeutic: 40-100 mcg/mL

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness, laboratory values, and adverse reactions at beginning of therapy and periodically with long-term use. Observe and teach seizure/safety precautions. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsTrough serum concentrations, CBC, platelets, liver enzymes, urinalysis

Patient EducationTake exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, loss of appetite, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help). Wear identification of epileptic status and medications. Report CNS changes, mentation changes, or changes in cognition; muscle cramping, weakness, tremors, or changes in gait; persistent GI symptoms (cramping, constipation, vomiting, anorexia); rash or skin irritations; unusual bruising or bleeding (mouth, urine, stool); signs or symptoms of an infection (eg, sore throat, fever) or worsening of seizure activity or loss of seizure control. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber before breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 250 mg

Zarontin®: 250 mg

Syrup: 250 mg/5 mL (473 mL)

Zarontin®: 250 mg/5 mL [contains sodium benzoate; raspberry flavor]

Generic AvailableYes

ManufacturerPfizer Inc

Pricing: U.S. (www.drugstore.com)

Capsules (Ethosuximide)

250 mg (30): $42.99

Capsules (Zarontin)

250 mg (60): $85.04

Solution (Ethosuximide)

250 mg/5 mL (474): $57.97

Solution (Zarontin)

250 mg/5 mL (300): $93.45

Mechanism of ActionIncreases the seizure threshold and suppresses paroxysmal spike-and-wave pattern in absence seizures; depresses nerve transmission in the motor cortex

Pharmacodynamics/Kinetics

Distribution: Adults: V_d: 0.62-0.72 L/kg

Metabolism: Hepatic (~80% to 3 inactive metabolites)

Half-life elimination, serum: Children: 30 hours; Adults: 50-60 hours

Time to peak, serum: Capsule: ~2-4 hours; Syrup: <2-4 hours

Excretion: Urine, slowly (50% as metabolites, 10% to 20% as unchanged drug); feces (small amounts)

Related Information

- Anticonvulsants by Seizure Type
- Status Epilepticus

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause sedation, euphoria, insomnia, or hallucinations; may rarely cause depression

Mental Health: Effects on Psychiatric Treatment Barbiturates and carbamazepine may decrease the clinical effects of ethosuximide

References

Marbury TC, Lee CS, Perchalski RJ, et al, "Hemodialysis Clearance of Ethosuximide in Patients With Chronic Renal Disease," *Am J Hosp Pharm*, 1981, 38(11):1757-60. [PubMed 7304633]

Marquardt ED, Ishisaka DY, Batra KK, et al, "Removal of Ethosuximide and Phenobarbital by Peritoneal Dialysis in a Child," *Clin Pharm*, 1992, 11(12):1030-1.[PubMed 1286553]

International Brand Names Asamid (HR); Emeside (GB, IE); Ethymal (NL); Etomal (FI); Etosuximida (ES); Fluozoid (MX); Petimid (TR); Petinimid (AT, CH, CZ, PL); Petnidan (DE, HU, LU); Ronton (PL); Suxilep (BG, DE, HU, RU); Suximal (PT); Suxinutin (AT, CN, FI, HN, HU, PL, SE); Zarondan (DK, NO); Zarontin (AE, AR, AU, BE, BH, CY, EG, ES, FR, GB, GR, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LU, LY, MY, NL, OM, QA, SA, SY, UY, YE, ZA, ZW)

Ethotoin

Lexi-Drugs Online

English

English

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Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - February, 2008

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Forthcoming product labeling changes are likely to extend to all antiepileptic drugs and not limited to the drugs used in the studies, pending discussions scheduled for the upcoming advisory committee meeting. Healthcare professionals and family members/caregivers are encouraged to monitor patients receiving any antiepileptic medication for signs/symptoms of suicidality (eg, anxiety, depression, behavior changes). Patients should not stop taking their antiepileptic therapy unless advised by a healthcare professional.

Additional information can be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Pronunciation(ETH oh toyn)

U.S. Brand NamesPeganone®

Canadian Brand NamesPeganone®

Pharmacologic CategoryAnticonvulsant, Hydantoin

Use: Labeled IndicationsGeneralized tonic-clonic or complex-partial seizures

Dosing: AdultsGeneralized tonic-clonic or complex-partial seizures: Oral: Initial dose: ≤1 g/day; usual maintenance dose: 2-3 g/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAnticonvulsant: Children ≥1 year: Oral: Maximum initial dose: 750 mg/day; usual maintenance dose: 0.5-1 g/day; maximum dose: 3 g/day

Administration: OralAdminister with food to decrease GI distress. Administer in 4-6 divided doses daily, spaced as evenly as practical.

Dietary ConsiderationsShould be taken after meals.

StorageStore below 25˚C (77˚F).

ContraindicationsHypersensitivity to ethotoin or any component of the formulation; hepatic abnormalities; hematologic disorders

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Anemia: Hydantoin-like compounds may interfere with folic acid metabolism precipitating megaloblastic anemia.

- Hypersensitivity reactions: May occur with therapy.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <1 year of age.

Other warnings/precautions:

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Pregnancy Risk FactorD

Pregnancy ConsiderationsMaternal ingestion of antiepileptic agents has been associated with neonatal coagulation defects/bleeding usually within 24 hours of birth. Congenital malformations (including a pattern of malformations termed the “fetal hydantoin syndrome” or “fetal anticonvulsant syndrome”) have been reported with the use of other hydantoin derivatives, however, case reports using ethotoin during pregnancy are few. Epilepsy itself, the number of medications, genetic factors, or a combination of these probably influence the teratogenicity of anticonvulsant therapy.

A pregnancy registry is available for women exposed to antiepileptic drugs (including ethotoin) at the Genetics and Teratology Unit Massachusetts General Hospital, 1-888-233-2334.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsThe manufacturer recommends discontinuing breast-feeding during ethotoin therapy.

Adverse ReactionsFrequency not defined.

Cardiovascular: Chest pain

Central nervous system: Ataxia, dizziness, fatigue, fever, headache, insomnia

Dermatologic: Skin rash, Stevens-Johnson syndrome

Gastrointestinal: Diarrhea, gingival hyperplasia, nausea, vomiting

Hematologic: Blood dyscrasias

Neuromuscular & skeletal: Numbness

Ocular: Diplopia, nystagmus

Miscellaneous: Lymphadenopathy, SLE-like syndrome

Metabolism/Transport Effects**Inhibits** CYP2C19 (weak)

Drug Interactions

Acetaminophen: Anticonvulsants (Hydantoin) may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May enhance the adverse/toxic effect of Anticonvulsants (Hydantoin). Specifically, osteomalacia and rickets. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Anticonvulsants (Hydantoin). Anticonvulsants (Hydantoin) may decrease the serum concentration of Chloramphenicol. Increased chloramphenicol concentrations have also been seen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersCBC, urinalysis

Monitoring: Lab TestsCBC, urinalysis

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Peganone®: 250 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Peganone)

250 mg (120): $91.08

Mechanism of ActionStabilizes the seizure threshold and prevents the spread of seizure activity
Pharmacodynamics/Kinetics

Absorption: Rapid

Metabolism: Hepatic; forms metabolites

Half-life elimination: 3-9 hours

Excretion: Urine, feces, saliva (minimal)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDrowsiness and dizziness are common; may cause insomnia or confusion
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsEthylphenylhydantoin
International Brand NamesPeganone (CA)

Jump To Field (Select Field Name)

Pronunciation(ETH il KLOR ide & dye klor oh te tra floo or oh ETH ane)
U.S. Brand NamesFluro-Ethyl® [DSC]
Pharmacologic CategoryLocal Anesthetic
Use: Labeled IndicationsTopical refrigerant anesthetic to control pain associated with minor surgical procedures, dermabrasion, injections, contusions, and minor strains
Dosing: AdultsLocal anesthetic: Topical (spray): Press gently on side of spray valve allowing the liquid to emerge as a fine mist approximately 2” to 4” from site of application
Dosing: ElderlyRefer to adult dosing.
Pregnancy Risk FactorC
Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/Monitoring
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol: Ethyl chloride 25% and dichlorotetrafluoroethane 75% (148 mL) [DSC]

Generic AvailableNo
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsDichlorotetrafluoroethane and Ethyl Chloride

Ethyl Chloride

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(ETH il KLOR ide)

U.S. Brand NamesGebauer's Ethyl ChlorideÂŽ

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsLocal anesthetic in minor operative procedures and to relieve pain caused by insect stings and burns, and irritation caused by myofascial and visceral pain syndromes

Dosing: AdultsDosage varies with use

Dosing: ElderlyRefer to adult dosing.

StorageRefrigerate. Store in airtight containers preferably hermetically sealed at a temperature not exceeding 15Â°C. Protect from light.

Pregnancy Risk FactorC

Adverse Reactions1% to 10%: Mucous membrane irritation, freezing may alter skin pigment

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol: 100% (103 mL) [available as a fine-point or medium spray]

Generic AvailableNo

Dental Health Professional ConsiderationsSpray for a few seconds to the point of frost formation when the tissue becomes white; avoid prolonged spraying of skin beyond this point

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucous membrane irritation. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsChloroethane

International Brand NamesAethylum Chloratum (PL); athylchlorid Sintetica (CH); Chloraethyl (DE); Chloraethyl Adroka (CH); Cloretilo Chemirosa (ES); Holsten aktiv (DE); WariActiv (DE)

Etidronate Disodium

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Bisphosphonates: Safety Update Regarding Possible Association With Atrial Fibrillation - November 2008

The Food and Drug Administration (FDA) has been reviewing placebo-controlled trials of the 7 bisphosphonates currently marketed in the US. This review is in response to study results associating an increased incidence of atrial fibrillation (AF) with alendronate or zoledronic acid use in women (65-89 years of age) with osteoporosis.

The FDA reviewed all the submitted data (19,687 bisphosphonate-treated patients and 18,358 placebo-treated patients) from these studies. Overall, the occurrence of AF was rare in each study with an absolute difference in event rates between each of the bisphosphonate and placebo arms of 0-3 per 1000. A zoledronic acid study showed a statistically significant increase in the rate of AF in the active treatment arm. However, no clear association between bisphosphonate use and AF could be established. In this study, AF events were diagnosed more than 30 days after receiving zoledronic acid in 47 of the 50 patients diagnosed with AF. According to the FDA, healthcare providers should not alter their prescribing patterns for bisphosphonates and patients should not stop taking their medication.

The FDA will continue monitoring the safety of bisphosphonates through postmarketing reports and is assessing the need for additional epidemiologic studies.

Further information is available at http://www.fda.gov/cder/drug/early_comm/bisphosphonates_update_200811.htm

Bisphosphonates: Possible Association with Severe Musculoskeletal Pain - January, 2008

The Food and Drug Administration (FDA) is informing healthcare practitioners of the possible association between bisphosphonate use and the development of severe (possibly incapacitating) bone, muscle, and/or joint pain. The severe musculoskeletal pain may develop days, months, or years after initiating a bisphosphonate. This is a distinct event from the acute phase response (eg, fever, chills, bone pain, myalgia, arthralgia) that may occur following initial bisphosphonate administration which generally resolves within several days of continued use.

Frequency of and contributing risk factors between severe musculoskeletal pain and bisphosphonate use are currently unknown.

Further information is available at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Bisphosphonates

Medication Safety Issues

Sound-alike/look-alike issues:

> Etidronate may be confused with etidocaine, etomidate, etretinate

Pronunciation(e ti DROE nate dye SOW dee um)

U.S. Brand NamesDidronel®

Canadian Brand NamesDidronel®; Gen-Etidronate

Pharmacologic Category[Bisphosphonate Derivative]()

Use: Labeled IndicationsSymptomatic treatment of Paget's disease; prevention and treatment of heterotopic ossification due to spinal cord injury or after total hip replacement

Use: Unlabeled/InvestigationalPostmenopausal osteoporosis

Dosing: Adults

Paget's disease: Oral:

> *Initial:* 5-10 mg/kg/day (not to exceed 6 months) or 11-20 mg/kg/day (not to exceed 3 months). Doses >20 mg/kg/day are **not** recommended.
>
> *Retreatment:* Initiate only after etidronate-free period ≥90 days. Monitor patients every 3-6 months. Retreatment regimens are the same as for initial treatment.

Heterotopic ossification: Oral:

> *Caused by spinal cord injury:* 20 mg/kg/day for 2 weeks, then 10 mg/kg/day for 10 weeks; total treatment period: 12 weeks
>
> *Complicating total hip replacement:* 20 mg/kg/day for 1 month preoperatively then 20 mg/kg/day for 3 months postoperatively; total treatment

period is 4 months

Postmenopausal osteoporosis (unlabeled use): Oral: 400 mg/day for 2 weeks, followed by 13-week period with no etidronate, then repeat cycle. Maintain adequate calcium and vitamin D intake during the entire 15-week treatment cycle

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentUse with caution; specific guidelines are not available, however consider dose reduction.
Administration: OralAdminister tablet on an empty stomach 2 hours before food.
Dietary ConsiderationsAdminister tablet with water or fruit juice on an empty stomach; avoid administering foods/supplements with calcium, iron, or magnesium within 2 hours of drug; maintain adequate intake of calcium and vitamin D.
StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to bisphosphonates or any component of the formulation; overt osteomalacia
Allergy Considerations

- Bisphosphonate Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bone/joint/muscle pain: Infrequently, severe (and occasionally debilitating) bone, joint, and/or muscle pain have been reported during bisphosphonate treatment. The onset of pain ranged from a single day to several months. Symptoms usually resolve upon discontinuation. Some patients experienced recurrence when rechallenged with same drug or another bisphosphonate; avoid use in patients with a history of these symptoms in association with bisphosphonate therapy.

- Gastrointestinal mucosa irritation: May cause irritation to upper gastrointestinal mucosa. Esophagitis, esophageal ulcers, esophageal erosions, and esophageal stricture (rare) have been reported with oral bisphosphonates; risk increases in patients unable to comply with dosing instructions. Use with caution in patients with dysphagia, esophageal disease, gastritis, duodenitis, or ulcers (may worsen underlying condition).

- Osteonecrosis of the jaw: Bisphosphonate therapy has been associated with osteonecrosis, primarily of the jaw; this has been observed mostly in cancer patients, but also in patients with postmenopausal osteoporosis and other diagnoses. Risk factors include a diagnosis of cancer, with concomitant chemotherapy, radiotherapy, or corticosteroids; anemia, coagulopathy, infection, or pre-existing dental disease. Symptoms included nonhealing extraction socket or an exposed jawbone. There are no data addressing whether discontinuation of therapy reduces the risk of developing osteonecrosis; however, as a precautionary measure, dental exams and preventative dentistry should be performed prior to placing patients with risk factors on chronic bisphosphonate therapy. Invasive dental procedures should be avoided during treatment.

Disease-related concerns:

- Enterocolitis: Use with caution in patients with enterocolitis; diarrhea has been reported at high doses and therapy may need to be withheld.

- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Bone mineralization: May retard mineralization of bone; treatment may need delayed or interrupted until callus is present.

- Calcium/vitamin D intake: Ensure adequate calcium and vitamin D intake.

Geriatric ConsiderationsMonitor serum electrolytes periodically since the elderly are often receiving diuretics which can result in decreases in serum calcium, potassium, and magnesium
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects have been reported in some but not all animal studies. There are no adequate and well-controlled studies in pregnant women. Bisphosphonates are incorporated into the bone matrix and gradually released over time. Theoretically, there may be a risk of fetal harm when pregnancy follows the completion of therapy. Based on limited case reports with pamidronate, serum calcium levels in the newborn may be altered if administered during pregnancy.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Gastrointestinal: Diarrhea, nausea

Neuromuscular & skeletal: Bone pain

Postmarketing and/or case reports: Agranulocytosis, alopecia, amnesia, angioedema, arthralgia, arthritis, asthma exacerbation, bone fracture, confusion, depression, esophagitis, follicular eruption, gastritis, glossitis, hallucination, headache, hypersensitivity reactions, leg cramps, leukopenia, macular rash, maculopapular rash, musculoskeletal pain (sometimes severe and/or incapacitating), osteomalacia, pancytopenia, paresthesia, peptic ulcer disease exacerbation, pruritus, Stevens-Johnson syndrome, urticaria

Oncology: Emetic PotentialLow
Drug Interactions

Aminoglycosides: May enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Magaldrate; Sodium Bicarbonate. *Risk D: Consider therapy modification*

Calcium Salts: May decrease the absorption of Bisphosphonate Derivatives. *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral iron salts are of concern. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Phosphate Supplements: Bisphosphonate Derivatives may enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Food decreases the absorption and bioavailability of the drug.

Test InteractionsBisphosphonates may interfere with diagnostic imaging agents such as technetium-99m-diphosphonate in bone scans.

Monitoring ParametersSerum calcium and phosphorous; serum creatinine and BUN

Reference RangeCalcium (total): Adults: 9.0-11.0 mg/dL

Nursing: Physical Assessment/MonitoringAssess history for any previous adverse response to bisphosphonates and ability to comply with administration instructions. Use caution with renal impairment. Correct any hypocalcemia prior to beginning treatment. Patients at risk for osteonecrosis (eg, chemotherapy, corticosteroids, poor oral hygiene) should have dental exams and necessary preventive dentistry should be done before beginning bisphosphonate therapy. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, immediate or long-term musculoskeletal pain). Teach appropriate use and specific administration directions, lifestyle and dietary changes according to purpose for use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take with water or fruit juice on an empty stomach at least 30 minutes before any food. Do not take within 2 hours of food or dietary supplements containing calcium, iron, or magnesium. Consult prescriber to determine necessity of dietary supplements of calcium or increased dietary vitamin D. Certain dental procedures should be avoided if possible while you are taking this medication; consult prescriber. You may experience temporary nausea or vomiting (small frequent meals may help); diarrhea (boiled milk or yogurt may help); or bone pain (consult prescriber for analgesic). Report muscle twitching, unusual fever, convulsions, difficulty breathing, rash, bloody stool, pain in mouth, jaws or teeth, acute or lasting bone pain, or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or if you are breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 200 mg, 400 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Didronel)

200 mg (30): $105.99

400 mg (30): $209.99

Mechanism of ActionDecreases bone resorption by inhibiting osteocystic osteolysis; decreases mineral release and matrix or collagen breakdown in bone

Pharmacodynamics/Kinetics

Onset of action: 1-3 months

Duration: Can persist for 12 months without continuous therapy

Absorption: ~3%

Metabolism: None

Half-life elimination: 1-6 hours

Excretion: Primarily urine (as unchanged drug); feces (as unabsorbed drug)

Dental Health Professional ConsiderationsThere is no data on the incidence of ONJ associated with use of etidronate disodium. A report by the Council of Scientific Affairs of the American Dental Association (accessed at: http://www.ada.org/prof/resources/topics/osteonecrosis.asp) as of July 2006 gave an estimated incidence of 0.7 cases for every 100,000 person-years of exposure to alendronate (Fosamax®). This translates to one case for every 142,857 person-years exposure. This figure from the ADA report was based on information received from Merck & Co citing 170 worldwide cases for alendronate (Fosamax®). In addition, Procter & Gamble Pharmaceuticals has cited 20 cases for risedronate (Actonel®) and Roche Laboratories has cited one case for ibandronate (Boniva®).

Consumer Reports On Health stated that the risk of jaw bone osteoporosis due to alendronate (Fosamax®), risedronate (Actonel®), or ibandronate (Boniva®) taken to prevent osteoporosis is very low and is estimated to be one out of every 20,000 users. That report mentioned that tooth extraction or implants increase the risk of developing osteonecrosis in patients taking any of these drugs for osteoporosis. The report also recommended that patients should stop taking any of these oral drugs 1-2 months before and after such dental treatment. No evidence was presented to support this statement.

In terms of length of exposure to oral bisphosphonates prior to onset of ONJ, data from large population studies or controlled studies is lacking. A report by Marx et al, observed that of three cases of ONJ associated with Fosamax® exposure, one patient had been taking 10 mg/day by mouth for 6 years and the other two patients 10 mg/day by mouth for 3 and 2 years respectively. In contrast, they observed that in cancer patients receiving intravenous bisphosphonates, the time period between the first doses of the bisphosphonate to first recognition of exposed bone either by the patients or by the clinician, was 9.4 months for zoledronate (Zometa®), 14.3 months for pamidronate (Aredia®), and 12.1 months for pamidronate then to zoledronate.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Abnormal taste.

Osteonecrosis of the jaw (ONJ), generally associated with local infection and/or tooth extraction and often with delayed healing, has been reported in patients taking bisphosphonates. Symptoms included nonhealing extraction socket or an exposed jawbone. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates. However, some have occurred in patients with postmenopausal osteoporosis taking oral bisphosphonates. Dental surgery may exacerbate ONJ. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Patients who develop ONJ while on bisphosphonate therapy should receive care by an oral surgeon. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentBisphosphonates have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. Use caution in patients receiving lithium.

Index TermsEHDP; Sodium Etidronate

References

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French AE, Kaplan N, Lishner M, et al, “Taking Bisphosphonates During Pregnancy,” *Can Fam Physician*, 2003, 49:1281-2. [PubMed 14594094]

Gray RE, “Severe Reaction to Diphosphonate,” *BMJ*, 1988, 297(6655):1042.

Marx RE, Sawatari Y, Fortin M, et al, “Bisphosphonate-Induced Exposed Bone (Osteonecrosis/Osteopetrosis) of the Jaws: Risk Factors, Recognition, Prevention, and Treatment,” *J Oral Maxillofac Surg*, 2005, 63(11):1567-75.[PubMed 16243172]

Storm T, Thamsborg G, Steiniche T, et al, “Effect of Intermittent Cyclical Etidronate Therapy on Bone Mass and Fracture Rate in Women With Postmenopausal Osteoporosis,” *N Engl J Med*, 1990, 322(18):1265-71. [PubMed 2109197]

Watts NB, Harris ST, Genant HK, et al, “Intermittent Cyclical Etidronate Treatment of Postmenopausal Osteoporosis,” *N Engl J Med*, 1990, 323(2):73-9.[PubMed 2113611]

International Brand NamesDidronat (TR); Didronate (DK, FI, NO, SE); Didronel (AT, AU, CH, DE, FR, GB, GR, HK, IE, IT, JP, LU, NL, PT); Difosfen (AR, CO, MY, PL, SG, TH, UY); Dinol (KP); Diphos (DE); Disonate (IN); Etibon (TW); Etidrate (NZ); Etidronat Jenapharm (DE); Luodi (CL); Oestrodidronel (BE); Ostedron (PL); Osteotop (CN, PE); Osteum (ES)

Etidronate and Calcium

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(e ti DROE nate & KAL see um)

Canadian Brand NamesDidrocal™

Pharmacologic CategoryBisphosphonate Derivative; Calcium Salt

Use: Labeled IndicationsTreatment and prevention of postmenopausal osteoporosis; prevention of corticosteroid-induced osteoporosis

Dosing: Adults**Note:** 90-day treatment regimen involves sequential administration of two products within the packaging; not to be taken concurrently. The first blister card contains white tablets containing etidronate disodium, while the remaining four blister cards contains blue, capsule-shaped tablets containing calcium carbonate.

Osteoporosis: Oral: Etidronate disodium 400 mg once daily for 14 days, followed by calcium carbonate 1250 mg (500 mg elemental calcium) once daily for 76 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot recommended for treatment in renally-impaired patients.

Administration: OralAdminister etidronate tablets with a full glass of water on an empty stomach 2 hours before meals. The calcium carbonate tablets may be administered with food.

Dietary Considerations

Etidronate: Administer tablet with water on an empty stomach; avoid administering foods/supplements with calcium, iron, or magnesium within 2 hours of drug; maintain adequate intake of calcium and vitamin D.

Calcium: As a dietary supplement, should be given with meals to increase absorption. May decrease iron absorption, so should be administered 1-2 hours before or after iron supplementation; limit intake of with bran, foods high in oxalates, or whole grain cereals which may decrease calcium absorption. Dietary calcium should be adjusted to supply at least 1500 mg/day (Didrocal™ supplies 500 mg/day), and dietary vitamin D intake should provide 400 int. units/day.

StorageStore at 15°C to 30°C (59°F to 86°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to etidronate disodium, bisphosphonates, or any component of the formulation; clinically-overt osteomalacia (appropriate treatment to resolve osteomalacia should be initiated before prescribing Didrocal™ therapy).

Warnings/Precautions

Concerns related to adverse effects:

- Bone/joint/muscle pain: Infrequently, severe (and occasionally debilitating) bone, joint, and/or muscle pain have been reported during bisphosphonate treatment. The onset of pain ranged from a single day to several months. Symptoms usually resolve upon discontinuation. Some patients experienced recurrence when rechallenged with same drug or another bisphosphonate; avoid use in patients with a history of these symptoms in association with bisphosphonate therapy.

- Gastrointestinal mucosa irritation: May cause irritation to upper gastrointestinal mucosa. Esophagitis, esophageal ulcers, esophageal erosions, and esophageal stricture (rare) have been reported with oral bisphosphonates; risk increases in patients unable to comply with dosing instructions. Use with caution in patients with dysphagia, esophageal disease, gastritis, duodenitis, or ulcers (may worsen underlying condition).

- Osteonecrosis of the jaw: Bisphosphonate therapy has been associated with osteonecrosis, primarily of the jaw; this has been observed mostly in cancer patients, but also in patients with postmenopausal osteoporosis and other diagnoses. Risk factors include a diagnosis of cancer, with concomitant chemotherapy, radiotherapy, or corticosteroids; anemia, coagulopathy, infection, or pre-existing dental disease. Symptoms included nonhealing extraction socket or an exposed jawbone. There are no data addressing whether discontinuation of therapy reduces the risk of developing osteonecrosis; however, as a precautionary measure, dental exams and preventative dentistry should be performed prior to placing patients with risk factors on chronic bisphosphonate therapy. Invasive dental procedures should be avoided during treatment.

Disease-related concerns:

- Hypoparathyroidism: While hypercalcemia and hypercalciuria may result when therapeutic replacement amounts are given for prolonged periods, they are most likely to occur in hypoparathyroid patients receiving high doses of vitamin D.

- Renal impairment: Use with caution in patients with renal impairment; I.V. form of etidronate has been noted to be nephrotoxic; therefore, this drug should be used with caution, if at all, in patients with impaired renal function or a history of kidney stones. There is no specific experience to guide cyclic therapy in patients with renal impairment or a history of renal calculi; monitor urine calcium and other relevant parameters if therapy is implemented.

Special populations:

- Calcium/vitamin D restricted patients: Use with caution in patients with restricted calcium and vitamin D intake.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Absorption: Calcium carbonate absorption is impaired in achlorhydria (common in elderly); administer calcium component with food.

Pregnancy Risk FactorC (based on U.S. labeling)
Pregnancy ConsiderationsEtidronate: Teratogenic effects have been reported in some but not all animal studies. There are no adequate and well-controlled studies in pregnant women. Bisphosphonates are incorporated into the bone matrix and gradually released over time. Theoretically, there may be a risk of fetal harm when pregnancy follows the completion of therapy. Based on limited case reports with pamidronate, serum calcium levels in the newborn may be altered if administered during pregnancy.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%:

Central nervous system: Dizziness (16%), headache (13%)

Gastrointestinal: Diarrhea (37%), nausea (18%), flatulence (17%), constipation (13%), dyspepsia (12%), vomiting (11%)

<1%, postmarketing, and/or case reports: Agranulocytosis, alopecia, amnesia, angioedema, arthropathies, asthma exacerbation, bone fracture, burning tongue, confusion, depression, erythema multiforme, esophagitis, follicular eruption, glossitis, hallucinations, leukopenia, leukemia (1 in 100,000 patients), musculoskeletal pain, pancytopenia, paresthesia, peptic ulcer disease (exacerbation), rash (maculopapular), Stevens-Johnson syndrome, urticaria

Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb Interactions

Food: Food decreases the absorption and bioavailability of the etidronate.

Test InteractionsBisphosphonates may interfere with diagnostic imaging agents such as technetium-99m-diphosphonate in bone scans.
Monitoring ParametersBone mass should be monitored; if not stabilized within 4 cycles (1 year) of therapy, consider discontinuation of treatment
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Combination package [each package contains five blister cards (90-day supply)]:

Didrocal™ [CAN; not available in the U.S.]

Tablet, etidronate disodium 400 mg (14s) [first card (white tablets)]

Tablet, calcium carbonate: 1250 mg (76s) [equivalent to elemental calcium 500 mg; remaining cards (blue tablets)]

ManufacturerProcter & Gamble Pharmaceuticals Canada
Mechanism of ActionSee individual agents.
Pharmacodynamics/KineticsSee individual agents.
Related Information

- Calcium Carbonate
- Etidronate Disodium

Dental Health Professional ConsiderationsSee Etidronate Disodium monograph.
Dental Health: Effects on Dental TreatmentOsteonecrosis of the jaw (ONJ), generally associated with local infection and/or tooth extraction and often with delayed healing, has been reported in patients taking bisphosphonates. Symptoms included nonhealing extraction socket or an exposed jawbone. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates. However, some have occurred in patients with postmenopausal osteoporosis taking oral bisphosphonates. Dental surgery may exacerbate ONJ. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Patients who develop ONJ while on bisphosphonate therapy should receive care by an oral surgeon. See Dental Comment in Etidronate Disodium monograph.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness
Mental Health: Effects on Psychiatric TreatmentBisphosphonates have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. use caution in patients receiving lithium. GI side effects are common, concurrent use with SSRIs, lithium, valproic acid, or carbamazepine may produce additive effects.
Index TermsCalcium Carbonate and Etidronate Disodium
References

Ruggiero SL, Mehrotra B, Rosenberg TJ, et al, "Osteonecrosis of the Jaws Associated With the Use of Bisphosphonates: A Review of 63 Cases," *J Oral Maxillofac Surg*, 2004, 62(5):527-34. [PubMed 15122554]

International Brand NamesDidronate + Calcium (NO); Didronel PMO (GB, IE)

Etodolac

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Lodine® may be confused with codeine, iodine, Iopidine®, Lopid®

Pronunciation(ee toe DOE lak)

Canadian Brand NamesApo-Etodolac®; Utradol™

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsAcute and long-term use in the management of signs and symptoms of osteoarthritis; rheumatoid arthritis and juvenile rheumatoid arthritis; management of acute pain

Use: DentalManagement of postoperative pain

Dosing: Adults **Note:** For chronic conditions, response is usually observed within 2 weeks.

Acute pain: Oral: 200-400 mg every 6-8 hours, as needed, not to exceed total daily doses of 1000 mg

Rheumatoid arthritis, osteoarthritis: Oral: 400 mg 2 times/day **or** 300 mg 2-3 times/day **or** 500 mg 2 times/day (doses >1000 mg/day have not been evaluated)

Lodine® XL: 400-1000 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric **Note:** For chronic conditions, response is usually observed within 2 weeks.

Juvenile rheumatoid arthritis (Lodine® XL): Oral: Children 6-16 years:

20-30 kg: 400 mg once daily

31-45 kg: 600 mg once daily

46-60 kg: 800 mg once daily

Children >60 kg: 1000 mg once daily

Dosing: Renal Impairment
Mild to moderate: No adjustment required

Severe: Use not recommended; use with caution

Hemodialysis: Not removed

Dosing: Hepatic ImpairmentNo adjustment required.

Dietary ConsiderationsMay be taken with food to decrease GI distress.

StorageStore at 20°C to 25°C (68°F to 77°F). Protect from moisture.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to etodolac, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

• Cardiovascular events: See “Concerns related to adverse effects” below.

• Coronary artery bypass graft surgery: See “Disease-related concerns” below.

• Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.

- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.

- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin's cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.

- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly are at greater risk for renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Extended release formulation: Use of extended release product consisting of a nondeformable matrix should be avoided in patients with stricture/narrowing of the GI tract; symptoms of obstruction have been associated with nondeformable products.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsThe elderly are a high-risk population for adverse effects from nonsteroidal anti-inflammatory agents. As much as 60% of older adults who experience GI side effects can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute.

Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but older adults may demonstrate these adverse effects at lower doses than younger adults. In patients ≥65 years, no substantial differences in the pharmacokinetics or side-effects profile were seen compared with the general population. Studies with etodolac in elderly demonstrated no difference in safety or efficacy compared to younger adults. No dosing adjustment necessary in elderly.

Pregnancy Risk FactorC/D (3rd trimester)
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

1% to 10%:

Central nervous system: Dizziness (3% to 9 %), chills/fever (1% to 3%), depression (1% to 3%), nervousness (1% to 3%)

Dermatologic: Rash (1% to 3%), pruritus (1% to 3%)

Gastrointestinal: Abdominal cramps (3% to 9%), nausea (3% to 9%), vomiting (1% to 3%), dyspepsia (10%), diarrhea (3% to 9%), constipation (1% to 3%), flatulence (3% to 9%), melena (1% to 3%), gastritis (1% to 3%)

Genitourinary: Dysuria (1% to 3%)

Neuromuscular & skeletal: Weakness (3% to 9%)

Ocular: Blurred vision (1% to 3%)

Otic: Tinnitus (1% to 3%)

Renal: Polyuria (1% to 3%)

<1%: Agranulocytosis, allergic reaction, allergic/necrotizing vasculitis, alopecia, anaphylactic/anaphylactoid reactions, anemia, angioedema, anorexia, arrhythmia, aseptic meningitis, asthma, bleeding time increased, CHF, confusion, conjunctivitis, CVA, cystitis, duodenitis, dyspnea, ecchymosis, edema, erythema multiforme, esophagitis (+/- stricture or cardiospasm), exfoliative dermatitis, GI ulceration, hallucination, headache, hearing decreased, hematemesis, hematuria, hepatic failure, hepatitis, hyperglycemia (in controlled patients with diabetes), hyperpigmentation, hypertension, infection, insomnia, interstitial nephritis, irregular uterine bleeding, jaundice, LFTs increased, leukopenia, MI, palpitation, pancreatitis, pancytopenia, paresthesia, peptic ulcer (+/- bleeding/perforation), peripheral neuropathy, photophobia, photosensitivity, pulmonary infiltration (eosinophilia), rectal bleeding, renal calculus, renal failure, renal insufficiency, shock, Stevens-Johnson syndrome, syncope, thrombocytopenia, toxic epidermal necrolysis, ulcerative stomatitis, urticaria, vesiculobullous rash, renal papillary necrosis, visual disturbances

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of

Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Etodolac peak serum levels may be decreased if taken with food.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Test InteractionsFalse-positive for urinary bilirubin and ketone

Monitoring ParametersMonitor CBC and chemistry profile, liver enzymes; in patients with an increased risk for renal failure (CHF or decreased renal function, taking ACE inhibitors or diuretics, elderly), monitor urine output and BUN/serum creatinine

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess effectiveness and interactions of other medications patient may be taking. Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests and therapeutic and adverse reactions at beginning of therapy and periodically throughout therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC, liver enzymes; in patients receiving diuretics, monitor BUN/serum creatinine.

Patient EducationTake this medication exactly as directed; do not increase dose without consulting prescriber. Do not crush tablets or break capsules. Take with food or milk to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol, aspirin or aspirin-containing medication, or any other anti-inflammatory medications without consulting prescriber. You may experience anorexia, nausea, vomiting, or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); drowsiness, dizziness, nervousness, or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or fluid retention (weigh yourself weekly and report unusual [3-5 lb/week] weight gain). GI bleeding, ulceration, or perforation can occur with or without pain; discontinue medication and contact prescriber if persistent abdominal pain or cramping, or blood in stool occurs. Report breathlessness, respiratory difficulty, or unusual cough; chest pain, rapid heartbeat, palpitations; unusual bruising/bleeding; blood in urine, stool, mouth, or vomitus; swollen extremities; skin rash, blisters, or itching; acute fatigue; fever; jaundice; abdominal tenderness; flu-like symptoms; or hearing changes (ringing in ears). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 200 mg, 300 mg

Tablet: 400 mg, 500 mg

Tablet, extended release: 400 mg, 500 mg, 600 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Etodolac)

300 mg (60): $31.99

Tablet, 24-hour (Etodolac CR)

400 mg (30): $32.99

500 mg (30): $34.99

600 mg (30): $64.99

Tablets (Etodolac)

400 mg (60): $38.99

500 mg (60): $37.00

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: Analgesic: 2-4 hours; Maximum anti-inflammatory effect: A few days

Absorption: ≥80%

Distribution: V_d:

Immediate release: Adults:0.4 L/kg

Extended release: Adults: 0.57 L/kg; Children (6-16 years): 0 .08 L/kg

Protein binding: ≥99%, primarily albumin

Metabolism: Hepatic

Half-life elimination: Terminal: Adults: 5-8 hours

Extended release: Children (6-16 years): 12 hours

Time to peak, serum:

Immediate release: Adults: 1-2 hours

Extended release: Extended release: 5-7 hours, increased 1.4-3.8 hours with food

Excretion: Urine 73% (1% unchanged); feces 16%

Related Information

- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness; rarely produces confusion, depression, insomnia, or hallucinations

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease the clearance of lithium resulting in elevated serum levels and potential toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A recent meta-analysis (see References) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 chronic heart failure guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin's inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. May precipitate renal failure in dehydrated patients.

Index TermsEtodolic Acid

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International Brand Names Eccoxolac (GB); Ecridoxan (GR); Entrang (KP); Etodol (KP); Etoflam (PH); Etonox (TH); Etopan (IL); Etopan XL (GB, IL);

Flancox (BR); Hypen (JP); Jenac (TW); Lacoxa (TW); Lodine (AT, CH, FI, FR, IT, KP, MX, PK, TR, VE); Lodine Retard (MX); Lodine SR (GB); Lodine XL (CL); Lonene (ID); Lonine (GR); Osteluc (JP); Sodolac (PT); Todo (TW); Todolac (DK); Toselac (KP)

Etomidate

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Medication Safety Issues

Sound-alike/look-alike issues:

Etomidate may be confused with etidronate

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(e TOM i date)

U.S. Brand NamesAmidate®

Canadian Brand NamesAmidate®

Pharmacologic CategoryGeneral Anesthetic

Use: Labeled IndicationsInduction and maintenance of general anesthesia

Use: Unlabeled/InvestigationalSedation for diagnosis of seizure foci

Dosing: AdultsAnesthesia: I.V.: Initial: 0.2-0.6 mg/kg over 30-60 seconds for induction of anesthesia; maintenance: 5-20 mcg/kg/minute

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren >10 years: Refer to adult dosing.

Administration: I.V.Administer I.V. push over 30-60 seconds. Solution is highly irritating; avoid administration into small vessels; in some cases, preadministration of lidocaine may be considered.

StorageStore at room temperature.

Compatibility

Y-site administration: Compatible: Alfentanil, atracurium, atropine, doxacurium, ephedrine, fentanyl, lidocaine, lorazepam, midazolam, mivacurium, morphine, pancuronium, phenylephrine, succinylcholine, sufentanil. **Incompatible:** Ascorbic acid, vecuronium.

ContraindicationsHypersensitivity to etomidate or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal steroid production: Etomidate inhibits 11-B-hydroxylase, an enzyme important in adrenal steroid production. A single induction dose blocks the normal stress-induced increase in adrenal cortisol production for 4-8 hours, up to 24 hours in elderly and debilitated patients. Continuous infusion of etomidate for sedation in the ICU may increase mortality because patients may not be able to respond to stress. No increase in mortality has been identified with a single dose for induction of anesthesia. Consider exogenous corticosteroid replacement in patients undergoing severe stress.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <10 years of age.

Pregnancy Risk FactorC

Adverse Reactions

>10%:

Endocrine & metabolic: Adrenal suppression

Gastrointestinal: Nausea, vomiting on emergence from anesthesia

Local: Pain at injection site (30% to 80%)

Neuromuscular & skeletal: Myoclonus (33%), transient skeletal movements, uncontrolled eye movements

1% to 10%: Hiccups

<1%: Apnea, arrhythmia, bradycardia, cortisol synthesis decreased, hyper-/hypotension, hyper-/hypoventilation, laryngospasm, tachycardia

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersCardiac monitoring and blood pressure required

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effect, and adverse/toxic effects, particularly for signs of adrenal insufficiency (including hypotension, hyperkalemia). Monitor respiratory status (for conscious sedation, includes pulse oximetry), cardiovascular status, CNS status (when used for procedures monitor sedation score); cardiac monitor and blood pressure monitor required. Infusion site should be monitored closely due to potential irritation (see Administration).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 2 mg/mL (10 mL, 20 mL) [contains propylene glycol 35% v/v]

Generic AvailableYes
Mechanism of ActionUltrashort-acting nonbarbiturate hypnotic (benzylimidazole) used for the induction of anesthesia; chemically, it is a carboxylated imidazole which produces a rapid induction of anesthesia with minimal cardiovascular effects; produces EEG burst suppression at high doses
Pharmacodynamics/Kinetics

Onset of action: 30-60 seconds

Peak effect: 1 minute

Duration: 3-5 minutes; terminated by redistribution

Distribution: V_d: 2-4.5 L/kg

Protein binding: 76%;

Metabolism: Hepatic and plasma esterases

Half-life elimination: Terminal: 2.6 hours

Pharmacotherapy PearlsEtomidate decreases cerebral metabolism and cerebral blood flow while maintaining perfusion pressure. Premedication with opioids or benzodiazepines can decrease myoclonus. Etomidate can enhance somatosensory evoked potential recordings.
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Hiccups.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Cardiovascular ConsiderationsEtomidate is a relatively safe anesthetic for use in patients with stable cardiovascular disease.
Anesthesia and Critical Care Concerns/Other ConsiderationsEtomidate 2 mg/mL contains propylene glycol 362.6 mg/mL (35% v/v).

Etomidate decreases cerebral metabolism and cerebral blood flow while maintaining perfusion pressure; can enhance somatosensory evoked potential recordings. Premedication with opioids or benzodiazepines can decrease myoclonus. Etomidate is a relatively safe anesthetic for use in patients with stable cardiovascular disease.

International Brand NamesEtomidat-Lipuro (CH, LU); Etomidate-Lipuro (PL); Etomidato-Lipuro (AR); Hypnomidate (AT, BE, BG, BR, CH, CZ, DE, ES, FR, GB, GR, HR, IE, LU, MX, NL, PL, PT, PY, RU, TR, TW, ZA); Radenarcon (PL)

Etonogestrel

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(e toe noe JES trel)

U.S. Brand NamesImplanon™

Pharmacologic CategoryContraceptive; Progestin

Use: Labeled IndicationsPrevention of pregnancy; for use in women who request long-acting (up to 3 years) contraception

Dosing: AdultsContraception: Subdermal: Implant 1 rod in the inner side of the upper, nondominant arm. Remove no later than 3 years after the date of insertion. After ruling out pregnancy, timing of insertion is based on the patient's contraceptive history:

No hormonal contraceptives within the past month: Insert between days 1 through 5 of menstruation, even if woman is still bleeding

Switching from combination hormonal contraceptive:

Oral tablet: Insert anytime within 7 days after the last active tablet

Vaginal ring: Insert anytime during the 7-day ring-free period

Transdermal system: Insert anytime during the 7-day patch-free period

Switching from a progestin-only contraceptive:

Oral pill: Any day during the month; do not skip days between the last pill and implant insertion

Implant: Insert on same day as removal of implant

IUD: Insert on same day as removal of IUD

Injection: Insert on day next injection is due

First trimester abortion or miscarriage: Insert immediately. If not inserted within first 5 days follow directions for “no hormonal contraception within the past month”

Following delivery or second trimester abortion: May insert between 21 and 28 days (if not exclusively breast-feeding) or after 4 weeks (if exclusively breast-feeding). Patients should use a second form of contraception for the first 7 days if insertion occurs at >4 weeks.

Note: If following above insertion schedule, no back-up contraception needed. If deviating, use back-up method for 7 days postinsertion.

Dosing: ElderlyNot for use after menopause

Dosing: PediatricNot for use prior to menarche

Dosing: Renal ImpairmentUse with caution; formal studies have not been conducted.

Dosing: Hepatic ImpairmentUse is contraindicated.

Administration: OtherSubdermal: For insertion under local anesthesia by healthcare providers trained in the insertion and removal procedure. Rod must be palpable after insertion. Deep insertion may require surgery to remove. If rod is impalpable, ultrasound should be used to locate the rod; MRI may also be useful if ultrasound is not successful. A pressure bandage should be applied and left in place for 24 hours after insertion to decrease bruising; a small bandage placed over the insertion site should remain in place for 3-5 days.

StorageStore at controlled room temperature 15°C to 30°C (59°F to 86°F). Protect from light.

RestrictionsOnly healthcare providers who have undergone training in the insertion and removal procedures will be able to order Implanon™.

ContraindicationsHypersensitivity to etonogestrel or any component of the formulation; undiagnosed abnormal uterine bleeding; active hepatic disease or malignant tumors; active thrombophlebitis or thromboembolic disorders (current or history of); known or suspected carcinoma of the breast; concomitant use with chronic potent hepatic enzyme inducers; pregnancy

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding irregularities: Abnormal bleeding should be evaluated as required to exclude pathologic conditions or pregnancy.
- Ectopic pregnancy: Rarely, may occur more commonly than in women using no contraception.
- Thromboembolism: Combination hormonal contraceptives may increase the risk of thromboembolism (also reported with etonogestrel).

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Hepatic enzyme inducers: Etonogestrel serum levels and contraceptive efficacy may be significantly decreased by potent hepatic enzyme inducer; the manufacturer does not recommend use in women chronically taking hepatic enzyme inducers.

Special populations:

- Obesity: Use with caution in overweight women; women >130% of ideal body weight were not included in clinical studies.
- Pediatrics: Not for use prior to menarche.

Other warnings/precautions:

- Appropriate use: Improper insertion may lead to unintended pregnancy or may cause difficult or impossible removal. Failure to properly remove may lead to infertility, ectopic pregnancy, or continued adverse reactions. Menstrual bleeding patterns are likely to be altered; patients should be counseled prior to implant insertion.
- HIV infection protection: Use does not protect against HIV infection or other sexually-transmitted diseases.

Additional concerns reported with combination oral contraceptives:

- Breast cancer: Use has been associated with a slight increase in frequency of breast cancer, however, studies are not consistent.
- Cardiovascular disease: Use with caution in patients with risk factors for coronary artery disease; may lead to increased risk of myocardial infarction. May have a dose-related risk of vascular disease and hypertension; women with hypertension should be encouraged to use a nonhormonal form of contraception.
- Depression: Use with caution in patients with depression.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.
- Gallbladder disease: May have a dose-related risk of gallbladder disease.
- Glucose intolerance: May cause glucose intolerance.
- Lipid effects: May effect serum triglyceride and lipoprotein levels. Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.
- Migraine: Use with caution in patients with a history of migraine.
- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis (has been reported rarely with combination hormonal contraceptives); discontinue permanently if papilledema or retinal vascular lesions are observed on examination.
- Smokers: The risk of cardiovascular side effects increases in women who smoke cigarettes, especially those who are >35 years of age; women who use combination hormonal contraceptives should be strongly advised not to smoke.
- Surgical patients: Whenever possible, therapy should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

⇧ Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Not for use during pregnancy; remove implant if pregnancy is detected. Ovulation may return within 1 week of implant removal; alternate forms of contraception may be required. In a multicenter clinical trial, 11 out of 46 women no longer using contraception became pregnant between 1 and 18 weeks following removal of the implant. Do not insert <21 days postpartum. Women weighing >130% of their ideal body weight were not included in clinical studies. With oral combination hormonal contraceptives, an increase in contraceptive failure was noted in women with a BMI >27.3. Similar findings were noted in patients weighing ≥90 kg (198 lb) using the contraceptive patch.

⇧ LactationEnters breast milk/use caution

⇧ Breast-Feeding ConsiderationsEtonogestrel was not found to affect the quality or quantity of breast milk. Do not insert <21 days postpartum. Levels of etonogestrel are highest during the first month following insertion (~2.2% of the weight-adjusted maternal daily dose).

⇧ Adverse Reactions

>10%:

Central nervous system: Headache (25%)

Dermatologic: Acne (14%)

Endocrine & metabolic: Infrequent menstrual bleeding (<3 episodes/90 days: 34%), amenorrhea (no bleeding in 90 days: 22%), prolonged menstrual bleeding (lasting >14 days: 18%), breast pain (13%), menstrual bleeding irregularities requiring discontinuation (11%)

Gastrointestinal: Weight gain (14%), abdominal pain (11%)

Genitourinary: Vaginitis (15%)

Respiratory: Upper respiratory tract infection (13%), pharyngitis (11%)

5% to 10%:

Central nervous system: Dizziness (7%), emotional lability (7%), depression (6%), nervousness (6%), pain (6%)

Endocrine & metabolic: Dysmenorrhea (7%), frequent menstrual bleeding (>5 episodes/90 days: 7%)

Gastrointestinal: Nausea (6%)

Genitourinary: Leukorrhea (10%)

Local: Insertion site pain (5%)

Neuromuscular & skeletal: Back pain (7%)

Respiratory: Sinusitis (6%)

Miscellaneous: Flu-like syndrome (8%)

<5% (Limited to important or life-threatening): Allergic reaction, alopecia, anorexia, anxiety, appetite increased, arthralgia, asthma, breast discharge, breast enlargement, breast fibroadenosis, cervical smear test positive, constipation, coughing, crying, diarrhea, dyspepsia, dysuria, edema, fatigue, fever, flatulence, gastritis, hot flushes, hypertension, hypoesthesia, injection site reaction, insomnia, lactation nonpuerperal, libido decreased, migraine, myalgia, otitis media, ovarian cyst, pelvic cramping, premenstrual tension, pruritus, rash, rhinitis, sexual function abnormal, skeletal pain, somnolence, vaginal discomfort, varicose vein, vision abnormal, vomiting, weakness, weight loss

Metabolism/Transport Effects **Substrate** of CYP3A4 (minor)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Herb/Nutraceutical: St John's wort (an enzyme inducer) may decrease serum levels of etonogestrel. Concomitant use is not recommended. Bloodroot, chasteberry, damiana, oregano, and yucca may enhance the adverse/toxic effect of progestins.

Test Interactions

Sex hormone-binding globulin: Serum concentrations may be decreased for first 6 months following implantation.

Thyroxine: Serum concentrations may be slightly decreased initially.

Monitoring Parameters Before starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision, sudden onset of proptosis, diplopia, migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Reference RangeEtonogestrel: A release rate of 25-30 mcg/day is required to inhibit ovulation

Nursing: Physical Assessment/MonitoringAssess insertion site. Monitor therapeutic response and adverse reactions at the beginning and periodically thoughout therapy. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Monitoring: Lab TestsBefore starting therapy, a Papanicolaou smear; pregnancy should be ruled out prior to use; monitor glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias

Patient EducationInform prescriber of all prescription medications, OTC medications, or herbal products you are taking. Do not take any new medications without consulting prescriber. Does not protect against HIV or other sexually transmitted diseases. Regular (as directed by prescriber) gynecological and regular self-breast exams are important. Changes in menstrual periods may occur (change in frequency, length, or spotting between periods). Use of a backup method of birth control (ie, condom) is recommended for 7 days after insertion. Periodically check for the presence of the device. If the device cannot be felt, use an alternative form of birth control until your prescriber confirms its presence. You will be given a user card to document the insertion of the device. Keep with your health records and keep track of the removal date. You may experience acne, breast pain, weight gain, vaginal discharge, back pain, dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known), or nausea (small, frequent meals, frequent oral care, sucking lozenges, or chewing gum may help). Report excessive vaginal bleeding, depression or severe mood swings, persistent or severe headaches, chest pain, coughing up blood, shortness of breath, pain in legs, or abdominal pain. **Pregnancy/breast-feeding precautions:** Inform prescriber if you become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Rod, subdermal:

Implanon™: 68 mg [latex free]

Generic AvailableNo

ManufacturerOrganon

Mechanism of ActionEtonogestrel is the active metabolite of desogestrel. It prevents pregnancy by suppressing ovulation, increasing the viscosity of cervical mucous, and inhibiting endometrial proliferation.

Pharmacodynamics/Kinetics

Onset of action: Serum levels sufficient to inhibit ovulation: ≤8 hours of implant

Duration: Implant: Each rod maintains etonogestrel levels sufficient to inhibit ovulation for 3 years

Distribution: V_d: 201 L

Protein binding: Albumin (66%) and sex hormone-binding globulin (32%)

Metabolism: Hepatic via CYP3A4; forms metabolites (activity not known)

Bioavailability: Implant: 100%

Half-life, elimination: 25 hours

Excretion: Urine (primarily); feces

Pharmacotherapy PearlsFor subdermal insertion by healthcare providers trained on the insertion and removal procedure. For use in women who request long-acting (up to 3 years) contraception. A User Card (to give to the patient), consent form (to keep on file), and a medication guide (for the patient) are provided with the device.

The rod releases etonogestrel at a rate of 60-70 mcg/day, decreasing to 35-45 mcg/day after the first year, 30-40 mcg/day after the second year, and 25-30 mcg/day at the end of the third year. Following removal of rod, levels decrease rapidly and are less than the level of detection within 1 week.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Until more is known about the mechanism of interaction, use caution in prescribing antibiotics to female patients taking progestin-only contraceptives.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusHeadache is common; may cause dizziness, depression, nervousness, or mood lability

Mental Health: Effects on Psychiatric TreatmentEtonogestrel is not recommended for patients receiving potent enzyme inducers (eg, phenobarbital, carbamazepine, St John's wort). Weight gain is common; concomitant use with psychotropics may produce additive effects.

Index Terms3-Keto-desogestrel; ENG

References

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Funk S, Miller MM, Mishell DR Jr, et al, "Safety and Efficacy of Implanon™, a Single-Rod Implantable Contraceptive Containing Etonogestrel," *Contraception*, 2005, 71(5):319-26.[PubMed 15854630]

Merki-Feld GS, Brekenfeld C, Migge B, et al, "Nonpalpable Ultrasonographically Not Detectable Implanon™ Rods Can be Localized by Magnetic Resonance Imaging," *Contraception*, 2001, 63(6):325-8.[PubMed 11672555]

International Brand NamesImplanon (AU, BE, BR, CH, CN, CO, CZ, DE, DK, ES, FI, FR, GB, HN, ID, IE, IT, KP, MX, MY, NL, NO, PE, PT, SE, SG, TH)

Etoposide Phosphate

Lexi-Drugs Online

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Etoposide may be confused with teniposide

Etoposide phosphate is a prodrug of etoposide and is rapidly converted in the plasma to etoposide. To avoid confusion or dosing errors, **dosage should be expressed as the desired etoposide dose,** not as the etoposide phosphate dose (eg, etoposide phosphate equivalent to ____ mg etoposide).

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(e toe POE side FOS fate)

U.S. Brand NamesEtopophos®

Pharmacologic CategoryAntineoplastic Agent, Podophyllotoxin Derivative

Use: Labeled IndicationsTreatment of refractory testicular tumors; treatment of small cell lung cancer

Dosing: AdultsRefer to individual protocols. **Note:** Etoposide phosphate is a prodrug of etoposide, doses should be expressed as the desired **ETOPOSIDE** dose; **not** as the etoposide phosphate dose. (eg, etoposide phosphate equivalent to ____ mg etoposide).

Small cell lung cancer: I.V. (in combination with other approved chemotherapeutic drugs): Etoposide 35 mg/m^2/day for 4 days to 50 mg/m^2/day for 5 days. Courses are repeated at 3- to 4-week intervals after adequate recovery from any toxicity.

Testicular cancer: I.V. (in combination with other approved chemotherapeutic agents): Etoposide 50-100 mg/m^2/day on days 1-5 to 100 mg/m^2/day on days 1, 3, and 5. Courses are repeated at 3- to 4-week intervals after adequate recovery from any toxicity.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Manufacturer recommended guidelines:

Cl$_{cr}$ 15-50 mL/minute: Administer 75% of normal dose

Cl$_{cr}$ <15 mL minute: Data are available; consider further dose reductions

Aronoff, 1999:

Cl$_{cr}$ 10-50 mL/minute: Administer 75% of normal dose

Cl$_{cr}$ <10 mL minute: Administer 50% of normal dose

Hemodialysis: Supplemental dose is not necessary

Peritoneal dialysis: Supplemental dose is not necessary

CAPD effects: Unknown

CAVH effects: Dose for Cl$_{cr}$ 10-50 mL/minute (Aronoff, 1999)

Dosing: Hepatic Impairment

Bilirubin 1.5-3 mg/dL or AST 60-180 units: Reduce dose by 50%.

Bilirubin 3-5 mg/dL or AST >180 units: Reduce dose by 75%.

Bilirubin >5 mg/dL: Do not administer.

Oncology: Bone Marrow - High DoseI.V.: 0.5-2 g/m^2 divided into 2 daily doses; maximum single-dose agent: 3.2 g/m^2; generally combined with other high-dose chemotherapeutic drugs.

Calculations

- Body Surface Area: Adults
- Creatinine Clearance: Adults

Administration: I.V.Infuse over 5-210 minutes.

Administration: I.V. Detail

BMT only: In contrast to etoposide, metabolic acidosis is not a frequent adverse effect of high-dose etoposide phosphate.

pH: 2.9 (reconstituted with sterile water for injection)

StorageStore intact vials of injection under refrigeration 2°C to 8°C (36°F to 46°F). Protect from light. Reconstituted etoposide phosphate is stable refrigerated at 2°C to 8°C (36°F to 47°F) for 7 days. Undiluted solutions are stable for 24 hours at room temperature of 20°C to 25°C (68°F to 77°F) when reconstituted with SWI, D_5W or NS; and stable for 48 hours at room temperature when reconstituted with bacteriostatic SWI or NS. Further diluted solutions are stable at room temperature 20°C to 25°C (68°F to 77°F) or under refrigeration 2°C to 8°C (36°F to 47°F) for up to 24 hours.

ReconstitutionReconstitute vials with 5 mL or 10 mL SWI, D_5W, NS, bacteriostatic SWI, or bacteriostatic NS to a concentration of 20 mg/mL or 10 mg/mL etoposide equivalent. These solutions may be administered without further dilution or may be diluted in 50-500 mL of D_5W or NS to a concentration as low as 0.1 mg/mL.

CompatibilityStable in D_5W, NS, sterile water for injection.

Y-site administration: Compatible: Acyclovir, amikacin, aminophylline, ampicillin, ampicillin/sulbactam, aztreonam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, carmustine, cefazolin, cefoperazone, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cimetidine, ciprofloxacin, cisplatin, clindamycin, co-trimoxazole, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, dexamethasone sodium phosphate, diphenhydramine, dobutamine, dopamine, doxorubicin, doxycycline, droperidol, enalaprilat, famotidine, floxuridine, fluconazole, fludarabine, fluorouracil, furosemide, ganciclovir, gatifloxacin, gemcitabine, gentamicin, granisetron, haloperidol, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, idarubicin, ifosfamide, leucovorin, linezolid, lorazepam, magnesium sulfate, mannitol, meperidine, mesna, methotrexate, metoclopramide, metronidazole, minocycline, mitoxantrone, morphine, nalbuphine, netilmicin, ofloxacin, ondansetron, paclitaxel, piperacillin, piperacillin/tazobactam, plicamycin, potassium chloride, promethazine, ranitidine, sodium bicarbonate, streptozocin, teniposide, thiotepa, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, vinblastine, vincristine, zidovudine. **Incompatible:** Amphotericin B, cefepime, chlorpromazine, imipenem/cilastatin, methylprednisolone sodium succinate, mitomycin, prochlorperazine edisylate.

ContraindicationsHypersensitivity to etoposide, etoposide phosphate, or any component of the formulation; pregnancy

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See "Concerns related to adverse effects" below.
- Experienced physician: See "Other warnings/precautions" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Anaphylactic reaction: May cause anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension (higher concentrations were associated with higher rates of reactions in children). Infusion should be interrupted and medications for the treatment of anaphylaxis should be available for immediate use.
- Bone marrow suppression: **[U.S. Boxed Warning]: Severe myelosuppression with resulting infection or bleeding may occur.** Treatment should be withheld for platelets <50,000/mm^3 or absolute neutrophil count (ANC) <500/mm^3.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage should be adjusted.
- Hypoalbuminemia: Use with caution in patients with low serum albumin; may increase risk for toxicities.
- Renal impairment: Use with caution in patients with renal impairment; dosage should be adjusted.

Special populations:

- Elderly: Use with caution in elderly patients; may be more likely to develop severe myelosuppression and/or GI effects.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Dosage: Doses of etoposide phosphate >175 mg/m^2 have not been evaluated.
- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Geriatric ConsiderationsElderly patients may be more susceptible to severe myelosuppression. Other adverse effects including GI toxicity, infectious complications, weakness, and alopecia may occur more frequently in elderly.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenicity and fetal loss. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid pregnancy.

LactationEnters breast milk/contraindicated

Adverse Reactions**Note:** Also see adverse reactions for **etoposide**. Since etoposide phosphate is converted to etoposide, adverse reactions experienced with etoposide would also be expected with etoposide phosphate.

>10%:

Central nervous system: Chills/fever (24%)

Dermatologic: Alopecia (33% to 44%)

Gastrointestinal: Nausea/vomiting (37%), anorexia (16%), mucositis (11%)

Hematologic: Leukopenia (91%; grade 4: 17%), neutropenia (88%; grade 4: 37%), anemia (72%; grades 3/4: 19%), thrombocytopenia (23%; grade 4: 9%)

Neuromuscular & skeletal: Weakness/malaise (39%)

1% to 10%:

Cardiovascular: Hypotension (5%), hypertension (3%), facial flushing (2%)

Central nervous system: Dizziness (5%)

Dermatologic: Skin rash (3%)

Gastrointestinal: Constipation (8%), abdominal pain (7%), diarrhea (6%), taste perversion (6%)

Local: Extravasation/phlebitis (5%)

Miscellaneous: Anaphylactic-type reactions (3%; including chills, diaphoresis, fever, rigor, tachycardia, bronchospasm, dyspnea, pruritus)

<1%, postmarketing, and/or case reports: Acute leukemia (with/without preleukemia phase), anaphylactic-like reactions, back pain, blindness (transient, cortical), cough, cyanosis, diaphoresis, dysphagia, erythema, facial swelling, hepatic toxicity, hyperpigmentation, hypersensitivity-associated apnea, infection, interstitial pneumonitis, laryngospasm, maculopapular rash, neutropenic fever, optic neuritis, perivasculitis, pruritus, pulmonary fibrosis, radiation recall dermatitis, seizure, Stevens-Johnson syndrome, taste perversion, tongue swelling, toxic epidermal necrolysis, urticaria

Oncology: VesicantNo
Oncology: Emetic PotentialMild (10% to 30%)
Oncology: Bone Marrow - Unique ToxicityGastrointestinal: Nausea, vomiting, mucositis
Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP2C9 (weak), 3A4 (weak)
Drug Interactions

Barbiturates: May decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

CycloSPORINE: May increase the serum concentration of Etoposide Phosphate. CycloSPORINE may decrease the metabolism, via CYP isoenzymes, and decrease the p-glycoprotein-mediated elimination of Etoposide Phosphate. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May decrease the serum concentration of Etoposide Phosphate. Phenytoin may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase GI irritation).

Herb/Nutraceutical: Avoid St John's wort (may decrease etoposide levels).

Monitoring ParametersCBC with differential, platelet count, bilirubin, renal function

Nursing: Physical Assessment/MonitoringUse caution in presence of hepatic or renal impairment. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (potential for increasing/decreasing levels or effects of etoposide). See Reconstitution for specific directions. Assess results of laboratory tests and renal function, therapeutic effectiveness, and adverse response prior to each treatment and on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report (refer to Patient Education).

Monitoring: Lab TestsCBC with differential, platelet count, bilirubin, renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is administered by infusion. Report immediately any swelling, pain, burning, or redness at infusion site. Avoid alcohol. It is important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and adequate nutrition (small, frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, or yogurt may help); loss of hair (reversible); or mouth sores (use soft toothbrush or cotton swabs for oral care and rinse mouth frequently). Report immediately chest pain, swelling of extremities, respiratory difficulty, palpitations, or rapid heartbeat. Report extreme fatigue, pain or numbness in extremities, severe GI upset or diarrhea, bleeding or bruising, fever, chills, sore throat, vaginal discharge, respiratory difficulty, yellowing of eyes or skin, or changes in color of urine or stool. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate barrier contraceptive measures to use during and for 1 month following therapy. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Etopophos®: 100 mg

Generic AvailableNo

Mechanism of ActionEtoposide phosphate is converted *in vivo* to the active moiety, etoposide, by dephosphorylation. Etoposide inhibits mitotic activity; inhibits cells from entering prophase; inhibits DNA synthesis. Initially thought to be mitotic inhibitors similar to podophyllotoxin, but actually have no effect on microtubule assembly. However, later shown to induce DNA strand breakage and inhibition of topoisomerase II (an enzyme which breaks and repairs DNA); etoposide acts in late S or early G2 phases.

Pharmacodynamics/Kinetics

Distribution: Average V_d: 7-17 L/m^2; poor penetration across blood-brain barrier; concentrations in CSF being <10% that of plasma

Protein binding: 94% to 97%

Metabolism:

Etoposide phosphate: Rapidly and completely converted to etoposide in plasma

Etoposide: Hepatic, via CYP3A4, to hydroxy acid and cislactone metabolites

Half-life elimination: Terminal: 4-11 hours; Children: Normal renal/hepatic function: 6-8 hours

Excretion: Urine (56%; 45% as etoposide); feces (44% as etoposide and metabolites)

Children: I.V.: Urine (≤55% as etoposide)

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsEtoposide phosphate 113.5 mg is equivalent to etoposide 100 mg. Dosages should always be expressed, and calculated, as the desired **etoposide** dose.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis (especially at high doses), stomatitis, and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine

Oncology: Bone Marrow CommentsIn contrast to etoposide, metabolic acidosis is not a frequent adverse effect of high-dose etoposide phosphate. Etoposide 800 mg/m^2 was pharmacokinetically equivalent to etoposide phosphate 910 mg/m^2 in patients with refractory hematologic malignancies.

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International Brand NamesEtopofos (DK, FI, NO, SE); Etopophos (AU, CH, GB, IE, NL, ZA); Etopos (BR, MX); Fytosid (PH, TH); Posyd (ID)

Etoposide-Vinblastine-Doxorubicin (Hodgkin's)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, Hodgkin's Disease

Regimen UseLymphoma, Hodgkin's disease

Index TermsEVA (Hodgkin's)

Regimen

Etoposide: I.V.: 100 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 300 mg/m^2]

Vinblastine: I.V.: 6 mg/m^2 day 1

[total dose/cycle = 6 mg/m^2]

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Repeat cycle every 28 days

References

Canellos GP, Petroni GR, Barcos M, et al, âEtoposide, Vinblastine, and Doxorubicin: An Active Regimen for the Treatment of Hodgkin's Disease in Relapse Following MOPP. Cancer and Leukemia Group B,â *J Clin Oncol*, 1995, 13(8):2005-11.[PubMed 7636541]

Etoposide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Etoposide may be confused with teniposide

VePesid速 may be confused with Versed

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(e toe POE side)

U.S. Brand NamesToposar速; VePesid速 [DSC]

Canadian Brand NamesVePesid速

Pharmacologic CategoryAntineoplastic Agent, Podophyllotoxin Derivative

Use: Labeled IndicationsTreatment of refractory testicular tumors; treatment of small cell lung cancer

Use: Unlabeled/InvestigationalTreatment of lymphomas, acute nonlymphocytic leukemia (ANLL); lung, bladder, and prostate carcinoma; hepatoma, rhabdomyosarcoma, uterine carcinoma, neuroblastoma, mycosis fungoides, Kaposi's sarcoma, histiocytosis, gestational trophoblastic disease, Ewing's sarcoma, Wilms' tumor, brain tumors

Dosing: AdultsRefer to individual protocols.

Small cell lung cancer (in combination with other approved chemotherapeutic drugs):

Oral: Due to poor bioavailability, oral doses should be twice the I.V. dose, rounded to the nearest 50 mg given once daily

I.V.: 35 mg/m^2/day for 4 days or 50 mg/m^2/day for 5 days every 3-4 weeks

IVPB: 60-100 mg/m^2/day for 3 days (with cisplatin)

CIV: 500 mg/m^2 over 24 hours every 3 weeks

Testicular cancer (in combination with other approved chemotherapeutic drugs):

IVPB: 50-100 mg/m^2/day for 5 days repeated every 3-4 weeks

I.V.: 100 mg/m^2 every other day for 3 doses repeated every 3-4 weeks

BMT/relapsed leukemia (unlabeled uses): I.V.: 2.4-3.5 g/m^2 or 25-70 mg/kg administered over 4-36 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols.

Children (unlabeled uses): I.V.: 60-120 mg/m^2/day for 3-5 days every 3-6 weeks

AML: I.V.:

Remission induction: 150 mg/m^2/day for 2-3 days for 2-3 cycles

Intensification or consolidation: 250 mg/m^2/day for 3 days, courses 2-5

Brain tumor: I.V.: 150 mg/m^2/day on days 2 and 3 of treatment course

Neuroblastoma: I.V.: 100 mg/m^2/day over 1 hour on days 1-5 of cycle; repeat cycle every 4 weeks

BMT conditioning regimen used in patients with rhabdomyosarcoma or neuroblastoma: I.V. continuous infusion: 160 mg/m^2/day for 4 days

Conditioning regimen for allogenic BMT: I.V.: 60 mg/kg/dose as a single dose

Dosing: Renal Impairment

The FDA-approved labeling recommends the following adjustments:

Cl$_{cr}$ 15-50 mL/minute: Administer 75% of dose

- Cl_{cr} <15 mL minute: Data not available; consider further dose reductions

The following guidelines have been used by some clinicians:

- Aronoff, 2007:
  - Cl_{cr} 10-50 mL/minute: Children and Adults: Administer 75% of dose
  - Cl_{cr} <10 mL minute: Children and Adults: Administer 50% of dose
  - Hemodialysis:
    - Children: Administer 50% of dose
    - Adults: Supplemental dose is not necessary
  - Continuous ambulatory peritoneal dialysis (CAPD):
    - Children: Administer 50% of dose
    - Adults: Supplemental dose is not necessary
  - Continuous renal replacement therapy (CRRT): Children and Adults: Administer 75% of dose
- Kintzel, 1995:
  - Cl_{cr} 46-60 mL/minute: Administer 85% of dose
  - Cl_{cr} 31-45 mL/minute: Administer 80% of dose
  - Cl_{cr} <30 mL/minute: Administer 75% of dose

Dosing: Hepatic Impairment

The FDA-approved labeling does not contain dosing adjustment guidelines. The following adjustments have been used by some clinicians:

Donelli, 1998: Liver dysfunction may reduce the metabolism and increase the toxicity of etoposide. Normal doses of I.V. etoposide should be given to patients with liver dysfunction (dose reductions may result in subtherapeutic concentrations); however, use caution with concomitant liver dysfunction (severe) and renal dysfunction as the decreased metabolic clearance cannot be compensated by increased renal clearance.

Floyd, 2006: Bilirubin 1.5-3 mg/dL or AST >3 times ULN: Administer 50% of dose

King, 2001: Bilirubin 1.5-3 mg/dL or ALT or AST >180 units/L: Administer 50% of dose

Koren, 1992: Bilirubin 1.5-3 mg/dL or AST >180 units/L: Administer 50% of dose

Perry, 1982:

- Bilirubin 1.5-3 mg/dL or AST 60-180 units/L: Administer 50% of dose
- Bilirubin >3 mg/dL or AST >180 units/L: Avoid use

Dosing: Combination Regimens

Adenocarcinoma, unknown primary:

- EP (Adenocarcinoma)
- Paclitaxel-Carboplatin-Etoposide
- PCE

Brain tumors:

- CDDP/VP-16
- COPE

Breast cancer: ICE-T

Gastric cancer:

- EAP
- EFP
- ELF

Gestational trophoblastic tumor:

- EMA/CO
- EP/EMA

Leukemia, acute lymphocytic: Hyper-CVAD (Leukemia, Acute Lymphocytic)

Leukemia, acute myeloid:

- 7 + 3 + 7
- DAV
- EMA 86
- Idarubicin, Cytarabine, Etoposide (ICE Protocol)
- Idarubicin, Cytarabine, Etoposide (IDA-Based BF12)
- MV
- V-TAD

Lung cancer (small cell):

- CAVE
- EC (Small Cell Lung Cancer)
- EP (Small Cell Lung Cancer)
- VIP (Small Cell Lung Cancer)
- VP (Small Cell Lung Cancer)

Lung cancer (nonsmall cell):

- Cisplatin-Etoposide (NSCLC)
- EC (NSCLC)
- EP (NSCLC)
- EP/PE

Lymphoma, Hodgkin's:

- BEACOPP
- Etoposide-Vinblastine-Doxorubicin (Hodgkin's)
- mini-BEAM
- Stanford V Regimen

Lymphoma, non-Hodgkin's:

- CEPP(B)
- CODOX-M/IVAC
- EPOCH
- ESHAP
- ICE (Lymphoma, non-Hodgkin's)
- IMVP-16
- IVAC
- MINE
- MINE-ESHAP
- Pro-MACE-CytaBOM
- RICE

Lymphoma, non-Hodgkin's (Burkitt's): CODOX-M/IVAC

Multiple myeloma: DTPACE

Neuroblastoma:

- CAV-P/VP
- CDDP/VP-16
- CE (Neuroblastoma)

CE-CAdO

HIPE-IVAD

N6 Protocol

Regimen A2

Osteosarcoma: ICE (Sarcoma)

Ovarian cancer:

BEP (Ovarian Cancer)

BEP (Ovarian Cancer, Testicular Cancer)

Prostate cancer:

Cyclophosphamide + Etoposide

Estramustine + Etoposide

Paclitaxel + Estramustine + Etoposide

Retinoblastoma:

CCCDE (Retinoblastoma)

CE (Retinoblastoma)

Sarcoma: VAC Alternating With IE (Ewing's Sarcoma)

Sarcoma, soft tissue:

ICE (Sarcoma)

ICE-T

IE

Testicular cancer:

BEP (Ovarian Cancer, Testicular Cancer)

BEP (Testicular Cancer)

EP (Testicular Cancer)

VIP (Etoposide) (Testicular Cancer)

Oncology: Bone Marrow - High DoseI.V.: 750-2400 mg/m^2; 10-60 mg/kg; duration of infusion is 1-4 hours to 24 hours; generally combined with other high-dose chemotherapeutic drugs or total body irradiation (TBI).

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Do not administer I.M. or SubQ (severe tissue necrosis).

Administration: I.V.Irritant. Administer lower doses IVPB over at least 30 minutes to minimize the risk of hypotensive reactions. Etoposide injection contains polysorbate 80 which may cause leaching of diethylhexyl phthalate (DEHP), a plasticizer contained in polyvinyl chloride (PVC) tubing. Administration through non-PVC (low sorbing) tubing will minimize patient exposure to DEHP.

Administration: I.V. DetailConcentrations >0.4 mg/mL are very unstable and may precipitate within a few minutes. For large doses, where dilution to ��.4 mg/mL is not feasible, consideration should be given to slow infusion of the undiluted drug through a running normal saline, dextrose or saline/dextrose infusion; or use of etoposide phosphate. Etoposide solutions of 0.1-0.4 mg/mL may be filtered through a 0.22 micron filter without damage to the filter or significant loss of drug.

pH: 3-4

BMT only: The etoposide formulation contains ethanol 30.3% (v/v). Etoposide 2.4 mg/m^2 delivers ethanol 45 g/m^2 I.V. Adverse effects may be increased with administration of etoposide to patients with decreased creatinine clearance.

Administration: OralDoses ��00 mg/day as a single once daily dose; doses >400 mg should be given in 2-4 divided doses. If necessary, the injection may be used for oral administration.

StorageStore intact vials of injection at 15属C to 30属C (59属F to 86属F). Protect from light. Store oral capsules at 2属C to 8属C (36属F to 46属F). Solutions for infusion, at room temperature, in D_5W or NS in polyvinyl chloride, the concentration is stable as follows:

0.2 mg/mL: 96 hours

0.4 mg/mL: 24 hours

Etoposide injection contains polysorbate 80 which may cause leaching of diethylhexyl phthalate (DEHP), a plasticizer contained in polyvinyl chloride (PVC) bags and tubing. Higher concentrations and longer storage time after preparation in PVC bags may increase DEHP leaching. Preparation in glass or polyolefin containers will minimize patient exposure to DEHP.

Etoposide injection diluted for oral use to 10 mg/mL in NS may be stored for 22 days in plastic oral syringes at room temperature. Mix with orange juice, apple juice, or lemonade to a concentration of ��.4 mg/mL, and use within a 3-hour period.

ReconstitutionEtoposide should be diluted to a concentration of 0.2-0.4 mg/mL in D_5W or NS for administration. Diluted solutions have concentration-dependent stability: More concentrated solutions have shorter stability times. Precipitation may occur with concentrations >0.4 mg/mL.

Compatibility**Variable stability (consult detailed reference)** in D_5W, LR, NS.

Y-site administration: Compatible: Allopurinol, amifostine, aztreonam, cladribine, doxorubicin liposome, fludarabine, gemcitabine, granisetron, melphalan, ondansetron, paclitaxel, piperacillin/tazobactam, sargramostim, sodium bicarbonate, teniposide, thiotepa, topotecan, vinorelbine. **Incompatible:** Cefepime, filgrastim, idarubicin.

Compatibility when admixed: Compatible: Carboplatin, cisplatin, cisplatin with cyclophosphamide, cisplatin with floxuridine, cytarabine, cytarabine with daunorubicin, floxuridine, fluorouracil, hydroxyzine, ifosfamide, ifosfamide with carboplatin, ifosfamide with cisplatin, ondansetron. **Variable (consult detailed reference):** Cisplatin with mannitol and potassium chloride, doxorubicin with vincristine.

ContraindicationsHypersensitivity to etoposide or any component of the formulation; pregnancy

Allergy Considerations

- Epidophyllotoxin Allergy

Warnings/Precautions

Boxed warnings:

��Bone marrow suppression: See ��oncerns related to adverse effects��below.

��Experienced physician: See ��ther warnings/precautions��below.

Special handling:

��Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

��Anaphylactic reaction: May cause anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension. In children, the use of concentrations higher than recommended were associated with higher rates of anaphylactic-like reactions. Infusion should be interrupted and medications for the treatment of anaphylaxis should be available for immediate use.

��Bone marrow suppression: **[U.S. Boxed Warning]: Severe myelosuppression with resulting infection or bleeding may occur.** Treatment should be withheld for platelets <50,000/mm^3 or absolute neutrophil count (ANC) <500/mm^3.

Disease-related concerns:

��Hepatic impairment: Use with caution in patients with hepatic impairment; dosage should be adjusted.

��Renal impairment: Use with caution in patients with renal impairment; dosage should be adjusted.

Dosage form specific issues:

��Benzyl alcohol: May contain benzyl alcohol which has been associated with "gasping syndrome" in neonates.

��Polysorbate 80: Injectable formula contains polysorbate 80; do not use in premature infants.

Other warnings/precautions:

��Administration: Must be diluted; do not give I.V. push, infuse over at least 30-60 minutes; hypotension is associated with rapid infusion.

��Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenicity and fetal loss. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid pregnancy.

LactationEnters breast milk/contraindicated

Adverse Reactions

>10%:

Dermatologic: Alopecia (8% to 66%)

Endocrine & metabolic: Ovarian failure (38%), amenorrhea

Gastrointestinal: Nausea/vomiting (31% to 43%), anorexia (10% to 13%), diarrhea (1% to 13%), mucositis/esophagitis (with high doses)

Hematologic: Leukopenia (60% to 91%; grade 4: 3% to 17%; onset: 5-7 days; nadir: 7-14 days; recovery: 21-28 days), thrombocytopenia (22% to

41%; grades 3/4: 1% to 20%; nadir 9-16 days), anemia (up to 33%)

1% to 10%:

Cardiovascular: Hypotension (1% to 2%; due to rapid infusion)

Gastrointestinal: Stomatitis (1% to 6%), abdominal pain (up to 2%)

Hepatic: Hepatic toxicity (up to 3%)

Neuromuscular & skeletal: Peripheral neuropathy (1% to 2%)

Miscellaneous: Anaphylactic-like reaction (I.V. infusion: 1% to 2%; including chills, fever, tachycardia, bronchospasm, dyspnea)

<1%: Anovulatory cycles, back pain; blindness (transient, cortical); CHF, constipation, cough, cyanosis, diaphoresis, dysphagia, erythema; extravasation (induration, necrosis, swelling); facial swelling, fatigue, fever, headache, hepatic toxicity, hepatitis, hyperpigmentation, hypersensitivity, hypersensitivity-associated apnea, hypomenorrhea, interstitial pneumonitis, laryngospasm, maculopapular rash, malaise, metabolic acidosis, MI, optic neuritis, perivasculitis, pruritus, pulmonary fibrosis, radiation-recall dermatitis, rash, seizure, somnolence, Stevens-Johnson syndrome, tachycardia, taste perversion, thrombophlebitis, tongue swelling, toxic epidermal necrolysis, urticaria, weakness

Oncology: Vesicant

No; irritant

Oncology: Emetic Potential

Low (10% to 30%)

Etoposide (oral): Moderate-to-high (30% to 90%)

Oncology: Bone Marrow - Unique Toxicity

Cardiovascular: Hypotension (infusion-related)

Central nervous system: Confusion, somnolence, seizure activity increased

Dermatologic: Skin lesions resembling Stevens-Johnson syndrome, alopecia

Endocrine & metabolic: Metabolic acidosis, parotitis

Gastrointestinal: Severe nausea and vomiting, mucositis

Hepatic: Hepatitis

Neuromuscular & skeletal: Peripheral neuropathy, motor deficits exacerbated

Miscellaneous: Secondary malignancy, ethanol intoxication (infusion-related)

Metabolism/Transport Effects

Substrate of CYP1A2 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP2C9 (weak), 3A4 (weak)

Drug Interactions

Barbiturates: May increase the metabolism of Etoposide. *Risk C: Monitor therapy*

CycloSPORINE: May decrease the metabolism of Etoposide. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Etoposide may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase GI irritation).

Herb/Nutraceutical: Avoid concurrent St John's wort; may decrease etoposide levels.

Monitoring ParametersCBC with differential, platelet count, and hemoglobin, vital signs (blood pressure), bilirubin, and renal function tests

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, potential for increasing/decreasing levels or effects of etoposide). Patient should be monitored closely for anaphylactic reaction (chills, fever, tachycardia, bronchospasm, dyspnea, hypotension). Emergency equipment should be available. Assess results of laboratory tests and renal function, therapeutic effectiveness, and adverse response prior to each treatment and on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, platelet count, bilirubin, renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication may be administered by infusion. Report immediately any swelling, pain, burning, or redness at infusion site; swelling of extremities; palpitations, rapid heartbeat, sudden difficulty breathing or swallowing; chest pain or chills. It is important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and adequate nutrition (small, frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, or yogurt may help); loss of hair (reversible); or mouth sores (use soft toothbrush or cotton swabs for oral care and rinse mouth frequently). Report extreme fatigue, pain or numbness in extremities, severe GI upset or diarrhea, bleeding or bruising, fever, sore throat, vaginal discharge, yellowing of eyes or skin, or any changes in color of urine or stool. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures to use during and for 1 month following therapy. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, softgel: 50 mg

VePesid速: 50 mg [DSC]

Injection, solution: 20 mg/mL (5 mL, 25 mL, 50 mL)

Toposar速: 20 mg/mL (5 mL, 25 mL, 50 mL) [contains alcohol 33% and polysorbate 80]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (VePesid)

50 mg (20): $1088.98

Mechanism of ActionEtoposide has been shown to delay transit of cells through the S phase and arrest cells in late S or early G_2 phase. The drug may inhibit mitochondrial transport at the NADH dehydrogenase level or inhibit uptake of nucleosides into HeLa cells. It is a topoisomerase II inhibitor and appears to cause DNA strand breaks. Etoposide does not inhibit microtubular assembly.

Pharmacodynamics/Kinetics

Absorption: Oral: 25% to 75%; significant inter- and intrapatient variation

Distribution: Average V_d: 7-17 L/m^2; poor penetration across the blood-brain barrier; CSF concentrations <10% of plasma concentrations

Protein binding: 94% to 97%

Metabolism: Hepatic to hydroxy acid and cislactone metabolites

Bioavailability: Oral: ��0% (range 25% to 75%)

Half-life elimination: Terminal: 4-11 hours; Children: Normal renal/hepatic function: 6-8 hours

Time to peak, serum: Oral: 1-1.5 hours

Excretion:

Children: Urine (��5% as unchanged drug)

Adults: Urine (42% to 67%; 8% to 35% as unchanged drug) within 24 hours; feces (up to 44%)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis (especially at high doses) and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine

Oncology: Bone Marrow CommentsThe etoposide formulation contains ethanol 30.3% (v/v). Etoposide 2.4 mg/m^2 delivers ethanol 45 g/m^2 I.V. Adverse effects may be increased with administration of etoposide to patients with decreased creatinine clearance. Etoposide 400-1600 mg/m^2 has been drawn into plastic syringes undiluted (20 mg/mL) for administration over 3-4 hours. Etoposide 800 mg/m^2 was pharmacokinetically equivalent to etoposide phosphate 910 mg/m^2 in patients with refractory hematologic malignancies.

Index TermsEpipodophyllotoxin; VP-16; VP-16-213

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International Brand NamesCelltop (FR); Citodox (AR); Cryosid (MX); Eposin (MY, TH, TW); Epsidox (CN); Etonco (MX); Etopophos (PL); Etopos (MX, PE, TH); Etoposid (IL); Etoposid Ebewe (PL); Etoposid Knoll (PL); Etoposide (AU, IL, PL); Etoposide Pierre Fabre (LU, PL); Etoposide Teva (HU, PL); Etoposido (CO); Etosid (IN); Lastet (CN, HU, IN, JP, MY, PH, PL, SG, TH, TW); Lastet-S (KP); Nexvep (BR); Posid (PH); Sintopozid (PL); Topresid (PH); Vepesid (AR, AT, BE, BG, CH, CL, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HK, HN, IE, IT, JP, NL, NO, PH, PK, PT, RU, SE, TH, TR, TW, UY, ZA); VePesid (AU, HR, HU, LU, PL); Vepeside (FR); VP-Gen (EC); VP-TEC (MX)

Etravirine

Lexi-Drugs Online

English

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Pronunciation(et ra VIR een)
U.S. Brand NamesIntelence™
Canadian Brand NamesIntelence™
Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Non-nucleoside)
Use: Labeled IndicationsTreatment of HIV-1 infection in combination with at least two additional antiretroviral agents in treatment-experienced patients exhibiting viral replication with documented non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance
Dosing: AdultsTreatment of HIV-1 infection: Oral: 200 mg twice daily after meals
Dosing: Renal ImpairmentDue to minimal renal clearance, dose adjustment likely unnecessary in renal impairment.
Dosing: Hepatic ImpairmentNo adjustment required for mild-to-moderate (Child-Pugh class A/B) impairment; no data in severe impairment.
Administration: OralAdminister after meals. If unable to swallow tablets, may disperse tablets in glass of water; stir well prior to drinking (swallow completely) and rinse glass several times to ensure administration of complete dose.
Dietary ConsiderationsTake after meals. May disperse tablets in glass of water; stir well prior to drinking and rinse glass several times to ensure administration of complete dose.
StorageStore at USP controlled room temperature of 25°C (77°F).
ContraindicationsThere are no contraindications listed in the manufacturer's labeling.
Warnings/Precautions

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).

- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.

- Rash: Severe and possibly life-threatening reactions, including Stevens-Johnson syndrome, hypersensitivity reactions and erythema multiforme have been rarely reported; discontinue if severe rash develops. Self-limiting (with continued therapy) mild-to-moderate rashes (higher incidence in women) were also observed in clinical trials, usually during second week of therapy initiation.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking major CYP3A4, 2C9, or 2C19 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

- Not recommended for use with: Other NNRTIs, unboosted protease inhibitors, high-dose ritonavir, tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, enzyme-inducing anticonvulsants, clarithromycin, St John's wort, rifampin, or rifapentine.

Special populations:

- Appropriate use: Not for use in treatment-naive patients, or experienced patients without evidence of viral mutations conferring resistance to NNRTIs and PIs.

- Pediatrics: Safety and efficacy have not been established in pediatric patients.

Pregnancy Risk FactorB
Pregnancy ConsiderationsNo evidence of fetal toxicity has been noted in animal reproduction studies. However, there are no adequate and well-controlled studies in pregnant women, and use during pregnancy is not recommended unless other alternatives are not available. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).
LactationExcretion in breast milk unknown/contraindicated
Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.
Adverse Reactions

>10%:

Dermatologic: Rash (17%; ≥ grade 2: 9%)

Endocrine & metabolic: Cholesterol (total) increased (≤300 mg/dL: 18%; >300 mg/dL: 6%); hyperglycemia (≤250 mg/dL: 13%; 251-500 mg/dL: 3%), LDL increased (≤190 mg/dL: 12%)

Gastrointestinal: Nausea (14%; ≥ grade 2: 5%)

2% to 10%:

Cardiovascular: Hypertension (3%)

Endocrine & metabolic: Triglycerides increased (≤750 mg/dL: 7%; >750 mg/dL: 3% to 4%)

Gastrointestinal: Abdominal pain (3%), vomiting (≥ grade 2: 2%)

Hepatic: ALT increased (≤5 x ULN: 5%; >5 x ULN: 2%)

Neuromuscular & skeletal: Peripheral neuropathy (3%)

Renal: Creatinine increased (≤1.8 x ULN: 5%; >1.8 x ULN: 2%)

<2% (Limited to important or life-threatening): Amnesia, anemia (including hemolytic), angina, angioedema, anorexia, atrial fibrillation, bronchospasm, confusion, constipation, diabetes mellitus, dyspnea, erythema multiforme, gastritis, gynecomastia, haemorrhagic stroke, hematemesis, hepatic steatosis, hepatitis, hepatomegaly, hypersensitivity reaction, hypersomnia, hypoesthesia, immune reconstitution syndrome, insomnia, lipohypertrophy/dystrophy, MI, pancreatitis, paresthesia, renal failure, seizure, Stevens-Johnson syndrome, stomatitis, syncope, vertigo

Metabolism/Transport Effects **Substrate** of CYP3A4, 2C9, 2C19; **Inhibits** CYP2C9, 2C19; **Induces** CYP3A4

Drug Interactions

Atazanavir: May increase the serum concentration of Etravirine. Etravirine may decrease the serum concentration of Atazanavir. *Risk X: Avoid combination*

CarBAMazepine: May decrease the serum concentration of Etravirine. Management: The manufacturer of etravirine states these drugs should not be used in combination. *Risk X: Avoid combination*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fosamprenavir: Etravirine may increase the serum concentration of Fosamprenavir. *Risk X: Avoid combination*

HMG-CoA Reductase Inhibitors: Etravirine may decrease the serum concentration of HMG-CoA Reductase Inhibitors. This applies to atorvastatin, lovastatin and simvastatin. Conversely, levels of fluvastatin may be increased. Management: Dose adjustment of the HMG-CoA reductase inhibitor may be warranted. No interaction is expected with rosuvastatin or pravastatin. **Exceptions:** Pravastatin; Rosuvastatin. *Risk C: Monitor therapy*

Macrolide Antibiotics: Etravirine may decrease the serum concentration of Macrolide Antibiotics. Clarithromycin AUC is reduced and levels of the active metabolite (14-hydroxy-clarithromycin) are modestly increased. Management: For the treatment of *Mycobacterium avium* complex, consider changing to alternative agent, such as azithromycin. **Exceptions:** Azithromycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Etravirine may decrease the serum concentration of Methadone. *Risk C: Monitor therapy*

PHENobarbital: May decrease the serum concentration of Etravirine. Management: The manufacturer of etravirine states these drugs should not be used in combination *Risk X: Avoid combination*

Phenytoin: May decrease the serum concentration of Etravirine. Management: The manufacturer of etravirine states these drugs should not be used in combination *Risk X: Avoid combination*

Phosphodiesterase 5 Inhibitors: Etravirine may decrease the serum concentration of Phosphodiesterase 5 Inhibitors. Management: No empiric dosage adjustments are recommended with concomitant therapy; however, dose of the phosphodiesterase inhibitor may need to be altered based on clinical response. *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the serum concentration of Etravirine. This effect is anticipated with darunavir & saquinavir (with low-dose ritonavir). Etravirine may increase the serum concentration of Protease Inhibitors. This effect is anticipated with nelfinavir. Protease Inhibitors may increase the serum concentration of Etravirine. This is expected with lopinavir/ritonavir. Management: Low-dose ritonavir boosting MUST be used when these protease inhibitors are used with etravirine. **Exceptions:** Amprenavir; Atazanavir; Fosamprenavir; Ritonavir; Tipranavir. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Reverse Transcriptase Inhibitors (Non-Nucleoside): May decrease the serum concentration of Etravirine. This has been observed with the NNRTIs efavirenz and nevirapine. Reverse Transcriptase Inhibitors (Non-Nucleoside) may increase the serum concentration of Etravirine. This has been observed with delavirdine. *Risk X: Avoid combination*

Rifabutin: May decrease the serum concentration of Etravirine. Management: Avoid concomitant use with rifabutin if a protease inhibitor/ritonavir combination is also used. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Etravirine. **Exceptions:** Rifabutin. *Risk X: Avoid combination*

Ritonavir: May decrease the serum concentration of Etravirine. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Tipranavir: May decrease the serum concentration of Etravirine. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Increases absorption of etravirine by ~50%.

Herb/Nutraceutical: St John's wort (*Hypericum perforatum*) may decrease the levels/effects of etravirine; do not coadminister.

Monitoring ParametersCholesterol, triglycerides, serum glucose; signs of skin rash, signs and symptoms of infection

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions or toxicity; changing drugs or dosing adjustments may be necessary. Assess effectiveness of therapy (decrease in infections and progress of disease; viral load and CD4 count) and adverse reactions (eg, skin rash, may be severe and require discontinuing drug) periodically during therapy. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions, and adverse symptoms to report (eg, rash, gastrointestinal upset).

Monitoring: Lab TestsCholesterol, triglycerides, serum glucose

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. This drug is prescribed as one part of a multi-drug combination; take exactly as directed for full course of therapy. Take after meals. May disperse tablets in glass of water if unable to swallow whole; stir well prior to drinking, then rinse glass several times and swallow each rinse to ensure total dose administered. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. You may be susceptible to infection (avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber). Frequent blood tests may be required with prolonged therapy. You may experience nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help; consult prescriber if nausea or vomiting persists) or changes in body fat (increased in upper back and neck and around trunk; decreased from extremities and face). Report immediately any sign of skin rash or irritation. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Intelence™: 100 mg

Generic AvailableNo

ManufacturerJanssen Cilag S.p.A., Latina, IT

Pricing: U.S. (www.drugstore.com)

Tablets (Intelence)

100 mg (120): $739.92

Mechanism of ActionAs a non-nucleoside reverse transcriptase inhibitor, etravirine has activity against HIV-1 by binding to reverse transcriptase. It consequently blocks the RNA-dependent and DNA-dependent DNA polymerase activities, including HIV-1 replication. It does not require intracellular phosphorylation for antiviral activity.

Pharmacodynamics/Kinetics

Absorption: Increased 50% with food

Protein binding: 99.9%

Metabolism: Hepatic, primarily by CYP3A4, 2C9, and 2C19; major metabolites exhibit ~10% of parent drug activity against HIV

Half-life elimination: 41 hours (± 20 hours)

Time to peak, plasma: 2.5-4 hours

Excretion: Feces (94%, up to 86% as unchanged drug); urine (1%)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis has been reported.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause amnesia, confusion, insomnia, and hypersomnia

Mental Health: Effects on Psychiatric TreatmentEtravirine is associated with Stevens-Johnson syndrome; monitor patients also receiving lamotrigine. May cause elevations in lipid panel; concomitant use with atypical antipsychotics may produce additive effects. GI side effects are common; concomitant use with lithium, SSRIs, valproic acid, and carbamazepine may produce additive effects. Associated with a high potential for drug-drug interactions; monitor. Carbamazepine, phenobarbital, and St John's wort may decrease the levels/effects of etravirine; do not coadminister. Etravirine may increase the levels/effects of citalopram, diazepam, fluoxetine, propranolol, and sertraline. Etravirine may decrease the levels/effects of benzodiazepines, methadone, mirtazapine, nefazodone, and venlafaxine.

Index TermsTMC125

References

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Madruga JV, Cahn P, Grinsztejn B, et al, “Efficacy and Safety of TMC125 (Etravirine) in Treatment-Experienced HIV-1-Infected Patients in DUET-1: 24-Week Results From a Randomised, Double-Blind, Placebo-Controlled Trial,” *Lancet*, 2007, 370(9581):29-38.[PubMed 17617270]

Exemestane

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Exemestane may be confused with estramustine.

Pronunciation(ex e MES tane)
U.S. Brand NamesAromasin®
Canadian Brand NamesAromasin®
Pharmacologic CategoryAntineoplastic Agent, Aromatase Inactivator
Use: Labeled IndicationsTreatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy; adjuvant treatment of postmenopausal estrogen receptor-positive early breast cancer following 2-3 years of tamoxifen (for a total of 5 years of adjuvant therapy)
Dosing: AdultsBreast cancer: Oral: 25 mg once daily

Dosage adjustment with CYP3A4 inducers: 50 mg once daily when used with potent inducers (eg, rifampin, phenytoin)

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentSafety of chronic dosing in renal impairment has not been established.
Dosing: Hepatic ImpairmentSafety of chronic dosing in hepatic impairment has not been established.
Administration: OralAdminister after a meal.
Dietary ConsiderationsTake after a meal; patients on aromatase inhibitor therapy should receive vitamin D and calcium supplements.
StorageStore at 25°C (77°F)
ContraindicationsHypersensitivity to exemestane or any component of the formulation; pregnancy
Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concurrent drug therapy issues:

- Estrogen-containing drugs: Should not be administered concurrently with estrogen-containing drugs.

Special populations:

- Premenopausal women: Not recommended for use in premenopausal women.

Geriatric ConsiderationsIn pharmacokinetic trials, no significant changes were seen in women <68 years of age.
Pregnancy Risk FactorD
Pregnancy ConsiderationsExemestane has been associated with prolonged gestation, abnormal or difficult labor, increased resorption, reduced number of live fetuses, decreased fetal weight, and retarded ossification in rats. It is not indicated for premenopausal women, but if exposure occurred during pregnancy, risk to the fetus and potential risk for loss of the pregnancy should be discussed.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%:

Cardiovascular: Hypertension (5% to 15%)

Central nervous system: Fatigue (8% to 22%), insomnia (11% to 14%), pain (13%), headache (7% to 13%), depression (6% to 13%)

Dermatological: Hyperhidrosis (4% to 18%), alopecia (15%)

Endocrine & metabolic: Hot flashes (13% to 21%)

Gastrointestinal: Nausea (9% to 18%), abdominal pain (6% to 11%)

Hepatic: Alkaline phosphatase increased (14% to 15%)

Neuromuscular & skeletal: Arthralgia (15% to 29%)

1% to 10%:

Cardiovascular: Edema (6% to 7%); cardiac ischemic events (2%: MI, angina, myocardial ischemia); chest pain

Central nervous system: Dizziness (8% to 10%), anxiety (4% to 10%), fever (5%), confusion, hypoesthesia

Dermatologic: Dermatitis (8%), itching, rash

Endocrine & metabolic: Weight gain (8%)

Gastrointestinal: Diarrhea (4% to 10%), vomiting (7%), anorexia (6%), constipation (5%), appetite increased (3%), dyspepsia

Genitourinary: Urinary tract infection

Hepatic: Bilirubin increased (5% to 7%)

Neuromuscular & skeletal: Back pain (9%), limb pain (9%), osteoarthritis (6%), weakness (6%), osteoporosis (5%), pathological fracture (4%), paresthesia (3%), carpal tunnel syndrome (2%), cramps (2%)

Ocular: Visual disturbances (5%)

Renal: Creatinine increased (6%)

Respiratory: Dyspnea (10%), cough (6%), bronchitis, pharyngitis, rhinitis, sinusitis, upper respiratory infection

Miscellaneous: Influenza-like symptoms (6%), diaphoresis (6%), lymphedema, infection

<1%: Cardiac failure, endometrial hyperplasia, GGT increased, neuropathy, osteochondrosis, thromboembolism, transaminases increased, trigger finger, uterine polyps

A dose-dependent decrease in sex hormone-binding globulin has been observed with daily doses of 25 mg or more. Serum luteinizing hormone and follicle-stimulating hormone levels have increased with this medicine.

Oncology: Emetic PotentialLow (10% to 30%)
Metabolism/Transport Effects**Substrate** of CYP3A4 (major)
Drug Interactions

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Rifampin: May increase the metabolism of Exemestane. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Plasma levels increased by 40% when exemestane was taken with a fatty meal.

Herb/Nutraceutical: St John's wort may decrease exemestane levels. Avoid black cohosh, dong quai in estrogen-dependent tumors.

Nursing: Physical Assessment/MonitoringNot indicated for women who are premenopausal or those taking any estrogen containing products. Assess patient response prior to each treatment and on a regular basis throughout therapy. Teach patient proper use, possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take after meals at approximately the same time each day; may cause indigestion (small, frequent meals, and frequent mouth care may reduce GI upset). You may be more susceptible to infection (avoid crowds or exposure to infection and do not have any vaccinations unless approved by prescriber). May cause headache, dizziness, confusion, fatigue, anxiety, insomnia (use caution when driving or engaging in tasks requiring alertness until response to medication is known); nausea, vomiting, loss of appetite (small, frequent meals, good mouth care, chewing gum, or sucking hard candy may help); or hot flashes (cool dark room or cold compresses may help). Report chest pain, palpitations; acute headache, visual disturbances; unresolved GI problems; itching or burning on urination, vaginal discharge; acute joint, back, bone, or muscle pain; respiratory difficulty, unusual cough, respiratory infection; or other adverse response. **For use in postmenopausal women only.**

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 25 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Aromasin)

25 mg (30): $310.27

Mechanism of ActionExemestane is an irreversible, steroidal aromatase inactivator. It prevents conversion of androgens to estrogens by tying up the enzyme aromatase. In breast cancers where growth is estrogen-dependent, this medicine will lower circulating estrogens.
Pharmacodynamics/Kinetics

Absorption: Rapid and moderate (~42%) following oral administration; absorption increases ~40% following high-fat meal

Distribution: Extensive

Protein binding: 90%, primarily to albumin and α_1-acid glycoprotein

Metabolism: Extensively hepatic; oxidation (CYP3A4) of methylene group, reduction of 17-keto group with formation of many secondary metabolites; metabolites are inactive

Half-life elimination: 24 hours

Time to peak: Women with breast cancer: 1.2 hours

Excretion: Urine (<1% as unchanged drug, 39% to 45% as metabolites); feces (36% to 48%)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Drowsiness, depression, insomnia, and anxiety are common; may cause confusion

Mental Health: Effects on Psychiatric Treatment None reported

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International Brand Names Aromasil (ES); Aromasin (AE, AR, AU, BE, BG, BH, BR, CH, CL, CN, CO, CR, CY, CZ, DE, DK, EC, EE, EG, FI, GB, GT, HK, HN, ID, IE, IL, IQ, IR, IT, JO, KP, KW, LB, LY, MY, NI, NL, NO, OM, PA, PE, PH, PL, PT, QA, SA, SE, SG, SV, SY, TH, VE, YE, ZA); Aromasine (FR)

Exenatide

Lexi-Drugs Online

English

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Special Alerts

Exenatide (Byetta®): Hemorrhagic or Necrotizing Pancreatitis - August 2008

The Food and Drug Administration (FDA) has issued an update regarding the incidence of pancreatitis associated with the use of exenatide (Byetta®). In addition to previously reported postmarketing cases of acute pancreatitis, the FDA has received six case reports (including two fatalities) of hemorrhagic or necrotizing pancreatitis in patients receiving exenatide therapy. As a result, the FDA is working with the manufacturer of exenatide, Amylin Pharmaceuticals, to update the prescribing information to strengthen warnings concerning the risk for acute hemorrhagic or necrotizing pancreatitis.

In addition, the FDA is reminding healthcare professionals that exenatide therapy should be promptly discontinued in patients in whom pancreatitis is suspected. If pancreatitis is confirmed, administer appropriate treatment as indicated and do not restart exenatide therapy. Alternative antidiabetic therapy should be considered in patients with a prior history of pancreatitis.

Additional information can be found at http://www.fda.gov/cder/drug/InfoSheets/HCP/exenatide2008HCP.htm

Pronunciation(ex EN a tide)

U.S. Brand NamesByetta®

Pharmacologic CategoryAntidiabetic Agent, Incretin Mimetic

Use: Labeled IndicationsManagement (adjunctive) of type 2 diabetes mellitus (noninsulin dependent, NIDDM) in patients receiving a sulfonylurea, thiazolidinedione, or metformin (or a combination of these agents)

Dosing: Adults**Adjunctive therapy of type 2 diabetes:** SubQ: Initial: 5 mcg twice daily within 60 minutes prior to a meal; after 1 month, may be increased to 10 mcg twice daily (based on response)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} ≥30 mL/minute: No adjustment necessary.

Cl_{cr} <30 mL/minute: Not recommended

Calculations

- Creatinine Clearance: Adults

Administration: OtherShould be administered subcutaneously in the upper arm, thigh, or abdomen. Administer within 60 minutes prior to morning and evening meal (or prior to the 2 main meals of the day, approximately ≥6 hours apart). Set up each new pen before the first use by priming it. See pen user manual for further details. Dial the dose into the dose window before each administration.

StoragePrior to initial use, store under refrigeration at 2°C to 8°C (36°F to 46°F); after initial use, may be stored at a temperature ≤25° (≤77°F). Do not freeze (discard if freezing occurs). Protect from light. Pen should be discarded 30 days after initial use.

ContraindicationsHypersensitivity to exenatide or any component of the formulation; type 1 diabetes; diabetic ketoacidosis

Warnings/Precautions

Concerns related to adverse effects:

- Anti-exenatide antibodies: Use may be associated with the development of anti-exenatide antibodies; low titers are not associated with a loss of efficacy, however high titers (observed in 6% of patients in clinical studies) may result in an attenuation of response.
- GI symptoms: Most common reactions are gastrointestinal related; these symptoms may be dose-related and may decrease in frequency/severity with gradual titration and continued use.
- Pancreatitis: Cases of acute pancreatitis (including hemorrhagic and necrotizing with some fatalities) have been reported; monitor for unexplained severe abdominal pain, and if pancreatitis is suspected, discontinue use. Do not resume unless an alternative etiology of pancreatitis is confirmed. Consider alternative antidiabetic therapy in patients with a history of pancreatitis.
- Weight loss: Use may be associated with weight loss (due to reduced intake) independent of the change in hemoglobin A_{1c}.

Disease-related concerns:

- Diabetes, type 1: Mechanism requires the presence of insulin, therefore use in type 1 diabetes (insulin dependent, IDDM) or diabetic ketoacidosis is not recommended; it is not a substitute for insulin in insulin-requiring patients.
- Gastrointestinal disease: Not recommended to be used in patients with gastroparesis or severe gastrointestinal disease; due to frequent gastrointestinal adverse effects.

- Renal impairment: Use not recommended in severe renal impairment (Cl_{cr} <30 mL/minute).

Concurrent drug therapy issues:

- Insulin/other hypoglycemic agents: Concurrent use with other hypoglycemic agents and/or insulin therapy has not been evaluated.
- Sulfonylureas: In combination with a sulfonylurea, may increase the risk of hypoglycemia (risk not increased when added to metformin monotherapy); this risk is related to the dosage of both exenatide and the sulfonylurea.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsIntensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDue to adverse events observed in some animal studies, exenatide is classified as pregnancy category C. Based on *in vitro* data, exenatide has a low potential to cross the placenta. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of exenatide is generally not recommended in the routine management of diabetes mellitus during pregnancy. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy. A registry has been established for women exposed to exenatide during pregnancy (1-800-633-9081).

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if exenatide is present in breast milk. The manufacturer recommends that caution be exercised when administering exenatide to nursing women.

Pregnancy & Lactation, In-Depth

- Exenatide in Pregnancy & Lactation

Adverse Reactions

>10%:

Endocrine & metabolic: Hypoglycemia (with concurrent sulfonylurea therapy 14% to 36%; frequency similar to placebo with metformin therapy)

Gastrointestinal: Nausea (44%), vomiting (13%), diarrhea (13%)

Miscellaneous: Anti-exenatide antibodies (low titers 38%, high titers 6%)

1% to 10%:

Central nervous system: Dizziness (9%), headache (9%)

Endocrine & metabolic: Appetite decreased (<5%)

Gastrointestinal: Dyspepsia (6%), GERD (<5%)

Neuromuscular & skeletal: Weakness (<5%)

Miscellaneous: Feeling jittery (9%), diaphoresis increased (<5%)

Postmarketing and/or case reports: Abdominal distension, abdominal pain, acute pancreatitis (including hemorrhagic and necrotizing), anaphylactic reaction, angioedema, chest pain, constipation, dysgeusia, eructation, flatulence, hypersensitivity pneumonitis, injection site reaction, macular or papular rash, pruritus, renal failure, serum creatinine increased, somnolence, urticaria

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsEthanol: Caution with ethanol (may cause hypoglycemia)

Monitoring ParametersSerum glucose, hemoglobin A_{1c}, and renal function

Nursing: Physical Assessment/MonitoringAssess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Teach appropriate injection technique and disposal of needles. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Monitoring: Lab TestsSerum glucose, hemoglobin A_{1c}, and renal function

Patient EducationTake as directed. Administer injection within 60 minutes of meals. Do not administer after meal. Consume alcohol with caution; may cause hypoglycemia. It is important to follow dietary and lifestyle recommendations of prescriber. You may experience nausea (small, frequent meals, frequent oral care, sucking lozenges, or chewing gum may help), feeling jittery, dizziness, or lightheadedness (use caution when driving or engaging in activities requiring alertness until response to drug is known). Maintain adequate hydration (2-3 L/day) unless instructed to restrict intake by prescriber. Report persistent nausea, diarrhea, abdominal pain, or dizziness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Byetta®: 250 mcg/mL (1.2 mL [5 mcg/0.02 mL; 60-dose pen]); (2.4 mL [10 mcg/0.04 mL; 60-dose pen])

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Solution (Byetta 10 MCG Pen)

10 mcg/0.04 mL (2.4): $229.97

Solution (Byetta 5 MCG Pen)

5 mcg/0.02 mL (1.2): $213.03

Mechanism of ActionExenatide is an analog of the hormone incretin (glucagon-like peptide 1 or GLP-1) which increases insulin secretion, increases B-cell growth/replication, slows gastric emptying, and may decrease food intake. When added to sulfonylureas, thiazolidinediones, and/or metformin, it results in additional lowering of hemoglobin A_{1c} by approximately 0.5% to 1%.
Pharmacodynamics/Kinetics

Distribution: V_d: 28.3 L

Metabolism: Minimal systemic metabolism; proteolytic degradation may occur following glomerular filtration

Half-life elimination: 2.4 hours

Time to peak, plasma: SubQ: 2.1 hours

Excretion: Urine (majority of dose)

Pharmacotherapy PearlsA dosing strategy which employs progressive dose escalation of exenatide (initiating at 0.02 mcg/kg 3 times daily and increasing in increments of 0.02 mcg/kg every 3 days) has been described, limiting the frequency and severity of gastrointestinal adverse effects. The complexity of this regimen may limit its clinical application.

In animal models, exenatide has been a useful adjunctive therapy when added to immunotherapy protocols, resulting in recovery of beta cell function and sustained remission.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness
Mental Health: Effects on Psychiatric Treatment

GI side effects are common; use caution with SSRIs, lithium, and valproic acid

Index TermsAC 2993; AC002993; Exendin-4 ; LY2148568
References

Buse JB, Henry RR, Han J , et al, "Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Sulfonylurea-Treated Patients With Type-2 Diabetes," *Diabetes Care*, 2004, 27(11):2628-35. [PubMed 15504997]

Defronzo RA, Ratner RE, Han J, et al, "Effects of Exenatide (Exendin-4) on Glycemic Control and Weight Over 30 Weeks in Metformin-Treated Patients With Type-2 Diabetes," *Diabetes Care*, 2005, 28(5):1092-1100. [PubMed 15855572]

Fineman MS, Shen LZ, Taylor K, et al, "Effectiveness of Progressive Dose-Escalation of Exenatide (Exendin-4) in Reducing Dose-Limiting Side Effects in Subjects With Type 2 Diabetes," *Diabetes Metab Res Rev* , 2004, 20(5):411-7. [PubMed 15343588]

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Kendall DM, Riddle MC, Rosenstock J, et al, "Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Patients With Type 2 Diabetes Treated With Metformin and a Sulfonylurea," *Diabetes Care*, 2005, 28(5):1083-91. [PubMed 15855571]

Movassat J, Beattie GM, Lopez AD, et al, "Exendin 4 Up-Regulates Expression of PDX 1 and Hastens Differentiation and Maturation of Human Fetal Pancreatic Cells," *J Clin Endocrinol Metab,* 2002, 87(10):4775-8.[PubMed 12364473]

Ogawa N, List JF, Habener JF, et al, "Cure of Overt Diabetes in NOD Mice by Transient Treatment With Anti-Lymphocyte Serum and Exendin-4," *Diabetes*, 2004, 53(7):1700-5.[PubMed 15220193]

International Brand NamesByetta (AR, AT, BE, BG, CH, CN, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IL, IT, NL, NO, NZ, PH, PT, RU, SE, TR)

Ezetimibe and Simvastatin

Lexi-Drugs Online

English

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Special Alerts

HMG-CoA Reductase Inhibitors: Evidence Does Not Suggest Increased Incidence of Amyotrophic Lateral Sclerosis (ALS) - Results of FDA Analysis - September 30, 2008

The U.S. Food and Drug Administration's (FDA) review of 41 long-term controlled clinical trials of HMG-CoA reductase inhibitors finds no evidence of an increased incidence of ALS (also known as Lou Gehrig's disease) related to these medications. This analysis occurred after the FDA had received notice of numerous adverse events of which 109 of these reports mentioned ALS, Lou Gehrig's disease, or motor neurone disease. The clinical trials included in the analysis had a median duration of treatment of 3.3 years (range of duration: 6 months to 5 years) and involved 120,964 patients. The analysis identified a total of 19 cases of ALS – 9 cases per 64,602 patients (0.014%) with statin therapy and 10 cases per 56,362 patients (0.017%) with placebo. The incidence rates, based on approximately 400,000 person-years, were 4.2 per 100,000 person-years in the statin-treated group and 5 per 100,000 person-years in the placebo-treated group.

The FDA recommends that health care providers continue to prescribe, and patients continue to use these products as described within their labeling.

For more information, healthcare professionals may refer to the following:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Statin

Colman E, Szarfman A, Wyeth J, et al, "An Evaluation of a Data Mining Signal for Amyotrophic Lateral Sclerosis and Statins Detected in FDA's Spontaneous Adverse Event Reporting System," *Pharmacoepidemiol Drug Saf*, 2008 (epub ahead of print)

Ezetimibe (Zetia®), Simvastatin (Zocor®), and Ezetimibe/Simvastatin (Vytorin®): Preliminary Results From the SEAS Trial - Updated September 2008

The U.S. Food and Drug Administration (FDA) has communicated important information regarding an ongoing safety review of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial. The SEAS trial (Rossebo, 2008), recently available online, evaluated the effects of the combination ezetimibe/simvastatin (Vytorin®) on clinical outcomes in patients with mild-to-moderate asymptomatic aortic stenosis. The 5-year trial demonstrated that ezetimibe/simvastatin was no better than placebo in reducing the primary composite outcomes – major cardiovascular events (eg, death from cardiovascular causes, aortic-valve replacement, heart failure) or the composite outcome of aortic-valve-related clinical events and ischemia. Additionally, a higher incidence of newly diagnosed cancer of any type (105 patients taking ezetimibe/simvastatin vs 70 patients taking placebo, p=0.01) and cancer-related death (39 patients taking ezetimibe/simvastatin vs 23 patients taking placebo, p=0.05) was observed in the patients receiving ezetimibe/simvastatin compared to those receiving placebo. Of note, 8 patients diagnosed with cancer prior to randomization experienced recurrence (3 in the ezetimibe/simvastatin group vs 5 in the placebo group).

Subsequently, an interim analysis of the ongoing Study of Heart and Renal Protection (SHARP) trial and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) with a total of 20,617 randomized patients demonstrated no overall excess of cancer (313 active-treatment vs 326 control, p=0.61) (Peto, 2008). The SHARP trial randomized patients with chronic kidney disease to either ezetimibe/simvastatin or placebo. The IMPROVE-IT trial randomized patients with acute coronary syndrome to either ezetimibe/simvastatin or simvastatin alone. When the SEAS trial data is included in this analysis, there still is no significant excess of cancer (414 active-treatment vs 391 control, p=0.46). However, cancer-associated deaths were significantly higher when compared to controls (134 vs 92, respectively; p=0.007). Previous trials and meta-analyses involving the use of ezetimibe, simvastatin, or ezetimibe/simvastatin also have not shown an increased risk of cancer.

The FDA estimates that it will take approximately 6 months to fully evaluate the clinical trial data after receipt of the final SEAS trial report. At this time, the FDA recommends that patients continue taking their cholesterol-lowering medications.

For more information, U.S. healthcare professionals may refer to the following:

FDA: http://www.fda.gov/medwatch/safety/2008/safety08.htm#ezetimibe2

Peto R, Emberson J, Landray M, et al, "Analysis of Cancer Data From Three Ezetimibe Trials," *N Engl J Med*, 2008, http://content.nejm.org/cgi/content/full/NEJMsa0806603

Rossebo AB, Pederson TR, Boman K, et al, "Intensive Lipid Lowering With Simvastatin and Ezetimibe in Aortic Stenosis," *N Engl J Med*, 2008, http://content.nejm.org/cgi/content/full/NEJMoa0804602

Simvastatin and Amiodarone Concurrent Therapy: Dose-Related Increased Risk of Rhabdomyolysis - August 2008

The U.S. Food and Drug Administration (FDA) has issued an alert to remind practitioners of a dose-related increased risk of rhabdomyolysis when amiodarone is used concurrently with simvastatin at doses >20 mg. If patients require simvastatin >20 mg, an alternative HMG-CoA reductase inhibitor (statin) should be used. This information has previously been incorporated into the Lexi-Comp monograph.

Additional information may be found at http://www.fda.gov/cder/drug/InfoSheets/HCP/simvastatin_amiodaroneHCP.htm

Ezetimibe/Simvastatin (Vytorin®), Ezetimibe (Zetia®), and Simvastatin (Zocor®): ENHANCE Results - January, 2008

The U.S. Food and Drug Administration (FDA) is communicating important information regarding the preliminary results of the Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) trial, originally released on January 14, 2008, by Merck/Schering Plough. This multinational, randomized, double-blind trial was conducted in 720 patients with heterozygous familial hypercholesterolemia (HeFH) over a two-year period. Patients were randomized to either ezetimibe 10 mg/simvastatin 80 mg (Vytorin®) or simvastatin 80 mg alone (Zocor®). The primary endpoint of the trial was mean change in carotid intima-media thickness (CIMT) which is a surrogate endpoint believed to translate in a reduction of future cardiovascular events. It is important to note that this was an imaging trial and was not powered for clinical outcomes (eg, MI, stroke). Although ezetimibe/simvastatin lowered LDL cholesterol more effectively as compared to simvastatin alone, there was no difference seen in mean change in CIMT. Adverse events were similar between both groups.

Upon completion of full data analysis, the manufacturer will submit a final report to the FDA. Once the report is received, the FDA estimates it will take about 6 months to fully evaluate the data and decide whether or not further regulatory action is necessary. Three large clinical outcome trials evaluating the use of ezetimibe/simvastatin will be presented over the next 2-3 years.

At this point in time, patients should not stop taking their ezetimibe/simvastatin (Vytorin®), ezetimibe (Zetia®), or simvastatin (Zocor®). Instead patients should talk with their healthcare provider if they have questions about the ENHANCE trial.

For more information, U.S. healthcare professionals may refer to the following:

FDA: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Ezetimibe

American College of Cardiology (ACC) Statement on ENHANCE Trial: http://www.acc.org/enhance.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Vytorin® may be confused with Vyvanse™

Pronunciation(ez ET i mibe & SIM va stat in)

U.S. Brand NamesVytorin®

Pharmacologic CategoryAntilipemic Agent, 2-Azetidinone; Antilipemic Agent, HMG-CoA Reductase Inhibitor

Use: Labeled IndicationsUsed in combination with dietary modification for the treatment of primary hypercholesterolemia and homozygous familial hypercholesterolemia

Dosing: Adults

Homozygous familial hypercholesterolemia: Ezetimibe 10 mg and simvastatin 40 mg once daily or ezetimibe 10 mg and simvastatin 80 mg once daily in the evening. Dosing range: Ezetimibe 10 mg and simvastatin 10-80 mg once daily.

Hyperlipidemias: Oral: Initial: Ezetimibe 10 mg and simvastatin 20 mg once daily in the evening; those patients requiring less aggressive LDL-C reductions can start with ezetimibe 10 mg and simvastatin 10 mg once daily

Patients who require less aggressive reduction in LDL-C: Initial: Ezetimibe 10 mg and simvastatin 10 mg once daily

Patients who require >55% reduction in LDL-C: Initial: Ezetimibe 10 mg and simvastatin 40 mg once daily

Dosage adjustment with concomitant medications: Oral:

Amiodarone or verapamil: Dose should not exceed ezetimibe 10 mg and simvastatin 20 mg once daily.

Danazol or cyclosporine: Patient must first demonstrate tolerance to simvastatin ≥5 mg once daily. Dose should not exceed ezetimibe 10 mg and simvastatin 10 mg once daily.

Gemfibrozil: Although concurrent use is not recommended by manufacturer, dose should not exceed ezetimibe 10 mg and simvastatin 10 mg once daily.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentDosage adjustment unnecessary in mild to moderate renal dysfunction. In severe dysfunction, start only if patient tolerates 5 mg daily of simvastatin; monitor closely.

Dosing: Hepatic ImpairmentDosage adjustment unnecessary in mild hepatic dysfunction.

Dietary ConsiderationsMay be taken with or without food. Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg of rice.

StorageStore at 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to ezetimibe, simvastatin, or any component of the formulation; acute liver disease; unexplained persistent elevations of serum transaminases; pregnancy; breast-feeding

Allergy Considerations

- HMG-CoA Reductase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Myopathy/rhabdomyolysis: Patients receiving HMG-CoA reductase inhibitors have developed rhabdomyolysis with acute renal failure and/or myopathy; patients should be monitored closely. This risk is dose-related and is increased with concurrent use of other lipid lowering medications. Temporarily discontinue for elective major surgery, acute medical or surgical conditions, or in any patient experiencing an acute or serious condition predisposing to renal failure (eg, sepsis, hypotension, trauma, uncontrolled seizures). Based upon current evidence, HMG-CoA reductase inhibitor therapy should be continued in the perioperative period unless risk outweighs cardioprotective benefit. Use caution in patients with renal impairment, inadequately treated hypothyroidism, and those taking other drugs associated with myopathy (eg, colchicine); these patients are predisposed to myopathy. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine.

Disease-related concerns:

- Hepatic impairment: Use ezetimibe with caution in patients with mild hepatic impairment; not recommended for use with moderate or severe hepatic impairment. Use simvastatin with caution in patients who consume large amounts of ethanol or have a history of liver disease.

Concurrent drug therapy issues:

- High potential for interactions: Use simvastatin with caution in patients taking strong CYP3A4 inhibitors (see drug interactions); consider alternative agents that avoid or lessen potential for CYP-mediated interactions.

Special populations:

- Elderly: Use with caution in patients with advanced age, these patients are predisposed to myopathy.

- Pediatrics: Safety and efficacy have not been established in patients <10 years of age or premenarcheal girls.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

- Liver function tests: Must be monitored by periodic laboratory assessment.

Geriatric ConsiderationsClinical studies of Vytorin® included a total of 792 patients >65 years of age with 176 of these patients ≥75 years. The safety in this group was similar to the younger patients. No adjustment of dose is necessary for initiation of treatment in the elderly.

Pregnancy Risk FactorX

Pregnancy ConsiderationsSee individual agents.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsSee individual agents.

Adverse ReactionsPercentages below refer to combination Vytorin®. Also see individual agents.

1% to 10%:

Central nervous system: Headache (7%)

Neuromuscular & skeletal: Myalgia (4%), pain in extremity (2%)

Respiratory: Upper respiratory infection (4%)

Miscellaneous: Influenza (3%)

Metabolism/Transport EffectsSimvastatin: **Substrate** of CYP3A4 (major); **Inhibits** CYP2C8 (weak), 2C9 (weak), 2D6 (weak)

Drug Interactions

Amiodarone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. Management: Dose of HMG-CoA reductase inhibitor may need to be reduced (e.g., simvastatin prescribing information recommends not exceeding 20 mg/day during concurrent therapy). *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Ezetimibe. *Risk C: Monitor therapy*

Bosentan: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Colchicine: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CycloSPORINE: May increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CycloSPORINE: May increase the serum concentration of Ezetimibe. Ezetimibe may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Danazol: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

DAPTOmycin: HMG-CoA Reductase Inhibitors may enhance the adverse/toxic effect of DAPTOmycin. Specifically, the risk of skeletal muscle toxicity may be increased. Management: Consider temporarily stopping HMG-CoA reductase inhibitor therapy prior to daptomycin. If used together, regular (i.e., at least weekly) monitoring of CPK concentrations is recommended. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Etravirine: May decrease the serum concentration of HMG-CoA Reductase Inhibitors. This applies to atorvastatin, lovastatin and simvastatin. Conversely, levels of fluvastatin may be increased. Management: Dose adjustment of the HMG-CoA reductase inhibitor may be warranted. No interaction is expected with rosuvastatin or pravastatin. *Risk C: Monitor therapy*

Fenofibrate: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fibric Acid Derivatives: May increase the serum concentration of Ezetimibe. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Gemfibrozil: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Gemfibrozil may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Grapefruit Juice: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Imatinib: May decrease the metabolism of Simvastatin. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Niacin: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Niacinamide: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Protease Inhibitors: May increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. *Risk D: Consider therapy modification*

Ranolazine: May increase the serum concentration of Simvastatin. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Sildenafil: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

St Johns Wort: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): HMG-CoA Reductase Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid excessive ethanol consumption (due to potential hepatic effects).

Food: Simvastatin serum concentration may be increased when taken with grapefruit juice; avoid concurrent intake of large quantities (>1 quart/day). Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice. Ezetimibe did not cause meaningful reductions in fat-soluble vitamin concentrations during a 2-week clinical trial. Effects of long-term therapy have not been evaluated.

Herb/Nutraceutical: St John's wort may decrease simvastatin levels.

Monitoring ParametersCreatine phosphokinase levels due to possibility of myopathy; serum cholesterol (total and fractionated)

Obtain liver function tests prior to initiation, dosage increase, and thereafter when clinically indicated. Patients titrated to the simvastatin 80 mg dose should be tested prior to initiation and 3 months after initiating the 80 mg dose. Thereafter, periodic monitoring (ie, semiannually) is recommended for the first year of treatment. Patients with elevated transaminase levels should have a second (confirmatory) test and frequent monitoring until values normalize. Discontinue if increase in ALT/AST is persistently >3 times ULN.

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

10/10: Ezetimibe 10 mg and simvastatin 10 mg

10/20: Ezetimibe 10 mg and simvastatin 20 mg

10/40: Ezetimibe 10 mg and simvastatin 40 mg

10/80: Ezetimibe 10 mg and simvastatin 80 mg

Generic AvailableNo

ManufacturerMerck/Schering-Plough Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Vytorin)

10-10 mg (30): $103.99

10-20 mg (30): $100.99

10-40 mg (30): $100.99

10-80 mg (30): $100.99

Mechanism of Action

Ezetimibe: Inhibits absorption of cholesterol at the brush border of the small intestine, leading to a decreased delivery of cholesterol to the liver. Ezetimibe inhibits the enzyme Niemann-Pick C1-Like1 (NPC1L1), a sterol transporter.

Simvastatin: A methylated derivative of lovastatin that acts by competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis.

Pharmacodynamics/KineticsSee individual agents.

Bioavailability: Vytorin® is equivalent to coadministered ezetimibe and simvastatin.

Related Information

- Ezetimibe
- Hyperlipidemia Management
- Lipid-Lowering Agents
- Simvastatin

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or fatigue; may rarely cause anxiety, depression, insomnia, or memory loss

Mental Health: Effects on Psychiatric TreatmentRhabdomyolysis with acute renal failure has occurred; risk increased with concurrent use of fluvoxamine, nefazodone, and verapamil

Cardiovascular ConsiderationsHMG-CoA reductase inhibitors are effective in primary and secondary prevention of cardiovascular events in patients with hyperlipidemia. For primary prevention, a patient's major risk factors (cigarette smoking, hypertension or currently taking antihypertensives, low HDL-C, family history, age, gender) should be evaluated. Patients with multiple risk factors (≥2) require more intensive therapy guided by the calculation of a 10-year absolute CHD risk (eg, the percent probability of having a CHD event in next 10 years). An individual's 10-year absolute CHD risk can be calculated at www.med-decisions.com/cvtool/phys/phys.html. LDL cholesterol goals, therapeutic lifestyle changes, and drug therapy are determined based upon a patient's risk factor profile.

Primary prevention trials show that cholesterol-lowering drugs reduce the risk of major coronary events, coronary death, and cerebrovascular events even in the first 6-12 months of use. The WOSCOP trial suggested a trend towards enhanced survival using pravastatin in their patients (mean LDL-cholesterol of 192 mg/dL and no history of MI). In a recent trial (Sever, 2003), patients with HTN and at least three other risk factors were randomized to 10 mg daily of atorvastatin or placebo. These patients had a total nonfasting cholesterol <250 mg/dL before treatment. LDL-C levels were 132 mg/dL before treatment and fell to an average of 90 mg/dL in the atorvastatin-treated group. There was a significant reduction in stroke, cardiovascular events, and coronary events in the atorvastatin-treated group as compared to the placebo group. There was no difference in mortality between the groups.

Secondary prevention trials indicate that “statin” therapy reduces mortality, major coronary events, coronary artery procedures, and stroke. The Heart Protection Study proved that lowering serum cholesterol levels reduces the rate of major vascular events among high-risk individuals with documented vascular disease (CHD, cerebrovascular, peripheral vascular) or diabetes regardless of initial cholesterol concentrations. PROVE IT is a randomized, double-blind trial evaluating hospitalized patients with acute coronary syndrome to determine the effects of intense LDL-C lowering therapy. Four thousand patients with an LDL-C levels of 106 mg/dL were randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily. After 2 years, the combined cardiovascular endpoint (death, MI, unstable angina requiring hospitalization, revascularization and stroke) was ~26% in the pravastatin patients (median LDL-C 95 mg/dL) and ~22% in the atorvastatin treated patients (median LDL-C 62 mg/dL).

LaRosa and colleagues assessed the efficacy and safety of lowering LDL cholesterol <100 mg/dL in patients with stable coronary heart disease (LaRosa, 2005). Ten thousand and one patients with baseline LDL levels <130 mg/dL were randomized to atorvastatin 10 mg or 80 mg daily and followed for a median of 4.9 years. The primary endpoint was the occurrence of the first major cardiovascular event (death from CVD, MI, resuscitation after cardiac arrest, or stroke). A primary event occurred in 434 patients (8.7%) receiving 80 mg daily (mean LDL 77 mg/dL) and 548 patients (10.9%) receiving 10 mg dose (mean LDL 101 mg/dL) (95% CI, 0.69-0.89; p <0.001). There was no mortality difference between the two treatment groups.

HMG-CoA reductase inhibitors decrease levels of high-sensitivity C-reactive protein (hs-CRP). They also possess pleiotropic properties including improved endothelial function, reduced inflammation at the site of the coronary plaque, inhibition of platelet aggregation, and anticoagulant effects. These nonlipid effects may be beneficial when HMG-CoA reductase inhibitors are introduced early in the management of acute coronary syndromes (de Denus, 2002).

Myopathy: Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years of age), women more frequently than men, small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, drug interactions (use with caution or avoid). The combination of a HMG-CoA reductase inhibitor plus nicotinic acid seems to carry a lower risk of myopathy than does a HMG-CoA reductase inhibitor plus a fibrate. Other medications, when used concurrently, may enhance the risk of myopathy associated with statins; these include drugs that inhibit CYP3A4 isoenzymes (lovastatin, simvastatin, atorvastatin) or CYP2C9 isoenzymes (fluvastatin). HMG-CoA reductase inhibitors may exacerbate exercise-induced skeletal muscle injury. Many experts favor getting a baseline creatine kinase (CK) measurement before initiating therapy (asymptomatic CK elevations are common). Obtain a CK measurement if patient complains of muscle soreness, tenderness, or pain.

Anesthesia and Critical Care Concerns/Other ConsiderationsBased on the simvastatin component: **Myopathy:** Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years), gender (occurs in women more frequently than men), small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, and drug interactions (use with caution or avoid).

Based on current research, HMG-CoA reductase inhibitors should be continued in the perioperative period. Postoperative discontinuation of statin therapy is associated with an increased risk of cardiac morbidity and mortality.

Index TermsSimvastatin and Ezetimibe

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International Brand NamesAdacai (CR, DO, GT, HN, NI, PA, SV); Inegy (AT, BE, CH, CZ, DE, DK, EE, ES, FI, FR, GB, IE, IL, NL, PT); Maxetibe Plus (PY); Starstat-EZ (IN); Vytorin (AR, AU, BR, EC, ES, HK, ID, KP, MX, MY, PE, PH, SG, TH, TW); Zintrepid (CN, CO, EC, MX)

Ezetimibe

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Special Alerts

Ezetimibe (Zetia®), Simvastatin (Zocor®), and Ezetimibe/Simvastatin (Vytorin®): Preliminary Results From the SEAS Trial - Updated September 2008

The U.S. Food and Drug Administration (FDA) has communicated important information regarding an ongoing safety review of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial. The SEAS trial (Rossebo, 2008), recently available online, evaluated the effects of the combination ezetimibe/simvastatin (Vytorin®) on clinical outcomes in patients with mild-to-moderate asymptomatic aortic stenosis. The 5-year trial demonstrated that ezetimibe/simvastatin was no better than placebo in reducing the primary composite outcomes – major cardiovascular events (eg, death from cardiovascular causes, aortic-valve replacement, heart failure) or the composite outcome of aortic-valve-related clinical events and ischemia. Additionally, a higher incidence of newly diagnosed cancer of any type (105 patients taking ezetimibe/simvastatin vs 70 patients taking placebo, p=0.01) and cancer-related death (39 patients taking ezetimibe/simvastatin vs 23 patients taking placebo, p=0.05) was observed in the patients receiving ezetimibe/simvastatin compared to those receiving placebo. Of note, 8 patients diagnosed with cancer prior to randomization experienced recurrence (3 in the ezetimibe/simvastatin group vs 5 in the placebo group).

Subsequently, an interim analysis of the ongoing Study of Heart and Renal Protection (SHARP) trial and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) with a total of 20,617 randomized patients demonstrated no overall excess of cancer (313 active-treatment vs 326 control, p=0.61) (Peto, 2008). The SHARP trial randomized patients with chronic kidney disease to either ezetimibe/simvastatin or placebo. The IMPROVE-IT trial randomized patients with acute coronary syndrome to either ezetimibe/simvastatin or simvastatin alone. When the SEAS trial data is included in this analysis, there still is no significant excess of cancer (414 active-treatment vs 391 control, p=0.46). However, cancer-associated deaths were significantly higher when compared to controls (134 vs 92, respectively; p=0.007). Previous trials and meta-analyses involving the use of ezetimibe, simvastatin, or ezetimibe/simvastatin also have not shown an increased risk of cancer.

The FDA estimates that it will take approximately 6 months to fully evaluate the clinical trial data after receipt of the final SEAS trial report. At this time, the FDA recommends that patients continue taking their cholesterol-lowering medications.

For more information, U.S. healthcare professionals may refer to the following:

FDA: http://www.fda.gov/medwatch/safety/2008/safety08.htm#ezetimibe2

Peto R, Emberson J, Landray M, et al, "Analysis of Cancer Data From Three Ezetimibe Trials," *N Engl J Med*, 2008, http://content.nejm.org/cgi/content/full/NEJMsa0806603

Rossebo AB, Pederson TR, Boman K, et al, "Intensive Lipid Lowering With Simvastatin and Ezetimibe in Aortic Stenosis," *N Engl J Med*, 2008, http://content.nejm.org/cgi/content/full/NEJMoa0804602

Ezetimibe/Simvastatin (Vytorin®), Ezetimibe (Zetia®), and Simvastatin (Zocor®): ENHANCE Results - January 2008

The U.S. Food and Drug Administration (FDA) is communicating important information regarding the preliminary results of the Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) trial, originally released on January 14, 2008, by Merck/Schering Plough. This multinational, randomized, double-blind trial was conducted in 720 patients with heterozygous familial hypercholesterolemia (HeFH) over a two-year period. Patients were randomized to either ezetimibe 10 mg/simvastatin 80 mg (Vytorin®) or simvastatin 80 mg alone (Zocor®). The primary endpoint of the trial was mean change in carotid intima-media thickness (CIMT) which is a surrogate endpoint believed to translate in a reduction of future cardiovascular events. It is important to note that this was an imaging trial and was not powered for clinical outcomes (eg, MI, stroke). Although ezetimibe/simvastatin lowered LDL cholesterol more effectively as compared to simvastatin alone, there was no difference seen in mean change in CIMT. Adverse events were similar between both groups.

Upon completion of full data analysis, the manufacturer will submit a final report to the FDA. Once the report is received, the FDA estimates it will take about 6 months to fully evaluate the data and decide whether or not further regulatory action is necessary. Three large clinical outcome trials evaluating the use of ezetimibe/simvastatin will be presented over the next 2-3 years.

At this point in time, patients should not stop taking their ezetimibe/simvastatin (Vytorin®), ezetimibe (Zetia®), or simvastatin (Zocor®). Instead patients should talk with their healthcare provider if they have questions about the ENHANCE trial.

For more information, U.S. healthcare professionals may refer to the following:

FDA: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Ezetimibe

American College of Cardiology (ACC) Statement on ENHANCE Trial: http://www.acc.org/enhance.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Zetia® may be confused with Zebeta®, Zestril®

Pronunciation(ez ET i mibe)
U.S. Brand NamesZetia®
Canadian Brand NamesEzetrol®
Pharmacologic CategoryAntilipemic Agent, 2-Azetidinone
Use: Labeled IndicationsUse in combination with dietary therapy for the treatment of primary hypercholesterolemia (as monotherapy or in combination with HMG-CoA reductase inhibitors); homozygous sitosterolemia; homozygous familial hypercholesterolemia (in combination with atorvastatin or simvastatin); mixed hyperlipidemia (in combination with fenofibrate)
Dosing: Adults**Hyperlipidemias, sitosterolemia:** Oral: 10 mg/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren ≥10 years: Refer to adult dosing.
Dosing: Renal ImpairmentAUC increased with severe impairment (Cl_{cr} <30 mL/minute); no dosing adjustment recommended.
Dosing: Hepatic Impairment AUC increased with hepatic impairment:

Mild impairment (Child-Pugh class A): No dosing adjustment necessary.

Moderate-to-severe impairment (Child-Pugh classes B and C): Use of ezetimibe not recommended.

Administration: OralMay be administered without regard to meals. May be taken at the same time as HMG-CoA reductase inhibitors. Administer ≥2 hours before or ≥4 hours after bile acid sequestrants.
Dietary ConsiderationsMay be taken without regard to meals. Before initiation of therapy, patients should be placed on a standard cholesterol-lowering diet for 6 weeks and the diet should be continued during drug therapy.
StorageStore at controlled room temperature of 25°C (77°F). Protect from moisture.
ContraindicationsHypersensitivity to ezetimibe or any component of the formulation; concomitant use with an HMG-CoA reductase inhibitor in patients with active hepatic disease, unexplained persistent elevations in serum transaminases; pregnancy; breast-feeding
Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with mild hepatic impairment (Child-Pugh class A); not recommended for use with moderate or severe hepatic impairment (Child-Pugh classes B and C).

- Renal impairment: Use with caution in patients with severe renal impairment (Cl_{cr} <30 mL/minute).

Concurrent drug therapy issues:

- Fibric acid derivatives (eg, fenofibrate, gemfibrozil): Concurrent use of fibric acid derivatives may increase the risk of cholelithiasis.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <10 years of age.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

Pregnancy Risk FactorC
Pregnancy ConsiderationsSafety and efficacy have not been established; use during pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

1% to 10%:

Central nervous system: Fatigue (2%)

Gastrointestinal: Diarrhea (4%)

Hepatic: Transaminases increased (with HMG-CoA reductase inhibitors) (≥3 x ULN, 1%)

Neuromuscular & skeletal: Arthralgia (3%), pain in extremity (3%)

Respiratory: Upper respiratory tract infection (4%), sinusitis (3%)

Miscellaneous: Influenza (2%)

Postmarketing and/or case reports: Anaphylaxis, angioedema, autoimmune hepatitis (Stolk, 2006), cholecystitis, cholelithiasis, cholestatic hepatitis (Stolk, 2006), CPK increased, depression, dizziness, hepatitis, hypersensitivity reactions, myalgia, myopathy, nausea, pancreatitis, paresthesia, rash, rhabdomyolysis, thrombocytopenia, urticaria

Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Ezetimibe. *Risk C: Monitor therapy*

CycloSPORINE: May increase the serum concentration of Ezetimibe. Ezetimibe may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Fibric Acid Derivatives: May increase the serum concentration of Ezetimibe. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Ezetimibe did not cause meaningful reductions in fat-soluble vitamin concentrations during a 2-week clinical trial. Effects of long-term therapy have not been evaluated.

Monitoring ParametersTotal cholesterol profile prior to therapy, and when clinically indicated and/or periodically thereafter. When used in combination with fenofibrate, monitor LFTs and signs and symptoms of cholelithiasis.

Nursing: Physical Assessment/MonitoringUse caution in presence of renal or hepatic impairment. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, timing of concurrent medication). Assess results of laboratory tests (lipid profile), therapeutic effectiveness, and adverse response at beginning of and at regular intervals during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse reactions to report (eg, signs of hepatic, muscle, or pancreatic adverse reactions).

Monitoring: Lab TestsTotal cholesterol profile prior to therapy, and when clinically indicated and/or periodically thereafter. When used in combination with fenofibrate, monitor LFTs and signs and symptoms of cholelithiasis.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take at the same time of day, without regard for meals. Take 2 hours before or 4 hours after bile acid binding agents (ie, Questran®). This medication does not replace the need for dietary and exercise recommendations of prescriber. May cause headache, dizziness, or fatigue (use caution when driving or engaged in potentially hazardous tasks until response to drug is known); diarrhea (boiled milk, buttermilk, or yogurt may help); abdominal pain. Report any yellowing of skin or sclera; dark urine or pale stools; excessive tiredness; chest pain or palpitations; muscle, skeletal, or joint pain; twitching or numbness; increased perspiration; changes in urinary pattern; or other persistent side effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Zetia®: 10 mg

Generic AvailableNo

ManufacturerMerck/Schering-Plough Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Zetia)

10 mg (30): $99.98

Mechanism of ActionInhibits absorption of cholesterol at the brush border of the small intestine via the sterol transporter, Niemann-Pick C1-Like1 (NPC1L1). This leads to a decreased delivery of cholesterol to the liver, reduction of hepatic cholesterol stores and an increased clearance of cholesterol from the blood; decreases total C, LDL-cholesterol (LDL-C), ApoB, and triglycerides (TG) while increasing HDL-cholesterol (HDL-C).

Pharmacodynamics/Kinetics

Protein binding: >90% to plasma proteins

Metabolism: Undergoes glucuronide conjugation in the small intestine and liver; forms metabolite (active); may undergo enterohepatic recycling

Bioavailability: Variable

Half-life elimination: 22 hours (ezetimibe and metabolite)

Time to peak, plasma: 4-12 hours

Excretion: Feces (78%, 69% as ezetimibe); urine (11%, 9% as metabolite)

Related Information

- Hyperlipidemia Management
- Lipid-Lowering Agents

Pharmacotherapy PearlsWhen studied in combination with fenofibrate for mixed hyperlipidemia, the dose of fenofibrate was 160 mg daily.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness and fatigue

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsEzetimibe decreases cholesterol concentrations by inhibiting the oral absorption of cholesterol. More specifically, ezetimibe inhibits the cholesterol transport system located within intestinal cell walls. Ezetimibe lowers LDL-C by ~18%. Additionally, it lowers TGs by ~5% and raises HDL-C by ~3%. Peak effects of ezetimibe are reached at 2 weeks. Ezetimibe does not interfere with the absorption of fat soluble vitamins. Ezetimibe can be taken concurrently with an HMG-CoA reductase inhibitor or fenofibrate. Asymptomatic increase in transaminase elevations (>3 times ULN) occurs at a slightly higher incidence (1.3%) when used concurrently with a HMG-CoA reductase inhibitor than with the HMG-CoA reductase inhibitor alone (0.4%). Use of ezetimibe and fenofibrate (160 mg daily) may increase rate of cholecystectomy.

Given the lack of clinical outcome data, the use of ezetimibe as initial monotherapy in treating hyperlipidemia would not be expected unless a patient was intolerant to HMG-CoA reductase inhibitor treatment. Ezetimibe enhances the LDL-C lowering effect of HMG-CoA reductase inhibitors by an additional 15% to 20%; and therefore, may be helpful in combination with an HMG-CoA reductase inhibitor to reach therapeutic goals. Ezetimibe may also be useful as combined therapy in patients who require a lower dose of HMG-CoA reductase inhibitor because they developed side effects when using a higher dose. Ezetimibe is also indicated in the treatment of sitosterolemia.

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International Brand NamesEzetib (IN); Ezetrol (AR, AU, BE, BG, CH, CN, CO, CZ, DE, DK, EC, EE, ES, FI, FR, GB, HK, HN, ID, IE, IL, KP, MX, MY, NL, NO, PE, PT, SE, TH, TW); Maxetibe (PY); Zemitra (PK); Zetavim (UY); Zetia (BR, CR, DO, GT, HN, NI, PA, SV); Zient (MX)

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Pharmacologic CategoryChemotherapy Regimen, Breast Cancer
Regimen UseBreast cancer
Index TermsCAF-IV; IVCAF
RegimenNOTE: Multiple variations are listed below.

Variation 1:

Fluorouracil: I.V.: 500 mg/m^2/day days 1 and 8

[total dose/cycle = 1000 mg/m^2]

or 500 mg/m^2 day 1

[total dose/cycle = 500 mg/m^2]

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Cyclophosphamide: I.V.: 500 mg/m^2 day 1

[total dose/cycle = 500 mg/m^2]

Repeat cycle every 21-28 days

Variation 2:

Fluorouracil: I.V.: 200 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 600 mg/m^2]

Doxorubicin: I.V.: 40 mg/m^2 day 1

[total dose/cycle = 40 mg/m^2]

Cyclophosphamide: I.V.: 400 mg/m^2 day 1

[total dose/cycle = 400 mg/m^2]

Repeat cycle every 28 days

Variation 3:

Fluorouracil: I.V.: 400 mg/m^2/day days 1 and 8

[total dose/cycle = 800 mg/m^2]

Doxorubicin: I.V.: 40 mg/m^2 day 1

[total dose/cycle = 40 mg/m^2]

Cyclophosphamide: I.V.: 400 mg/m^2 day 1

[total dose/cycle = 400 mg/m^2]

Repeat cycle every 28 days

Variation 4:

Fluorouracil: I.V.: 600 mg/m^2/day days 1 and 8

[total dose/cycle = 1200 mg/m^2]

Doxorubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 28 days

Variation 5:

Fluorouracil: I.V.: 300 mg/m^2/day days 1 and 8

[total dose/cycle = 600 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 1

[total dose/cycle = 30 mg/m^2]

Cyclophosphamide: I.V.: 300 mg/m^2 day 1

[total dose/cycle = 300 mg/m^2]

Repeat cycle every 28 days

References

Variation 1:

Smalley RV, Carpenter J, Bartolucci A, et al, "A Comparison of Cyclophosphamide, Adriamycin®, 5-Fluorouracil (CAF), and Cyclophosphamide, Methotrexate, 5-Fluorouracil, Vincristine, Prednisone (CMFVP) in Patients With Metastatic Breast Cancer: A Southeastern Cancer Study Group Project," *Cancer*, 1977, 40(2):625-32. [PubMed 329975]

Swenerton KD, Legha SS, Smith T, et al, "Prognostic Factors in Metastatic Breast Cancer Treated With Combination Chemotherapy," *Cancer Res*, 1979, 39(5):1552-62. [PubMed 427797]

Variation 2:

Nemoto T, Horton J, Simon R, et al, "Comparison of Four-Combination Chemotherapy Programs in Metastatic Breast Cancer: Comparison of Multiple Drug Therapy With Cytoxan, 5-FU, and Prednisone, Versus Cytoxan and Adriamycin, Versus Cytoxan, 5-FU, and Adriamycin, Versus Cytoxan, 5-FU, and Prednisone Alternation With Cytoxan and Adriamycin," *Cancer*, 1982, 49(10):1988-93. [PubMed 7074523]

Variation 3-5:

Wood WC, Budman DR, Korzun AH, et al, "Dose and Dose Intensity of Adjuvant Chemotherapy for State II, Node-Positive Breast Carcinoma," *N Engl J Med*, 1994, 330(18):1253-9.[PubMed 8080512]

Factor IX Complex (Human)

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English English

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Pronunciation(FAK ter nyne KOM pleks HYU man)

U.S. Brand NamesBebulin® VH; Profilnine® SD; Proplex® T [DSC]

Pharmacologic CategoryAntihemophilic Agent; Blood Product Derivative; Prothrombin Complex Concentrate (PCC)

Use: Labeled IndicationsControl bleeding in patients with factor IX deficiency (hemophilia B or Christmas disease) **Note:** Factor IX concentrate containing **only** factor IX is also available and preferable for this indication.

Use: Unlabeled/InvestigationalEmergency correction of the coagulopathy of warfarin excess in critical situations.**Note:** Products contain low or nontherapeutic levels of factor VII component.

Dosing: Adults

Bleeding in factor IX deficiency: I.V. (only):

Note: Dosage is expressed in units of factor IX activity and must be individualized.

Formula for units required to raise blood level %:

Total blood volume (mL blood/kg) = 70 mL/kg (adults), 80 mL/kg (children)

Plasma volume = total blood volume (mL) x [1 - Hct (in decimals)]

For example, for a 70 kg adult with a Hct = 40%: Plasma volume = [70 kg x 70 mL/kg] x [1 - 0.4] = 2940 mL

To calculate number of units needed to increase level to desired range (highly individualized and dependent on patient's condition): Number of units = desired level increase [desired level - actual level] x plasma volume (in mL)

For example, for a 100% level in the above patient who has an actual level of 20%: Number of units needed = [1 (for a 100% level) - 0.2] x 2940 mL = 2352 units

As a general rule, the level of factor IX required for treatment of different conditions is listed below:

Minor Spontaneous Hemorrhage, Prophylaxis:

Desired levels of factor IX for hemostasis: 15% to 25%

Initial loading dose to achieve desired level: <20-30 units/kg

Frequency of dosing: Once; repeated in 24 hours if necessary

Duration of treatment: Once; repeated if necessary

Major Trauma or Surgery:

Desired levels of factor IX for hemostasis: 25% to 50%

Initial loading dose to achieve desired level: <75 units/kg

Frequency of dosing: Every 18-30 hours, depending on half-life and measured factor IX levels

Duration of treatment: Up to 10 days, depending upon nature of insult

Anticoagulant overdosage (unlabeled use): I.V.: 15 units/kg

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: I.V.I.V. administration only; should be infused **slowly**. Rate should not exceed 2 mL/minute for Bebulin® VH, 3 mL/minute for Proplex® T, or 10 mL/minute for Profilnine® SD.

StorageWhen stored at refrigerator temperature, 2°C to 8°C (36°F to 46°F), coagulation factor IX is stable for the period indicated by the expiration date on its label. Avoid freezing which may damage container for the diluent. Once diluted, should be used promptly; stable for up to 3 hours.

Reconstitution

Refer to instructions for individual products. Diluent and factor IX complex should come to room temperature before combining. Diluent vial should be inverted over concentrate vial. After diluent is pulled, disconnect. The provided filter needle should be used to withdraw concentrate. Remove needle and attach to infusion set or replace needle for infusion.

ContraindicationsLiver disease with signs of intravascular coagulation or fibrinolysis; not for use in factor VII deficiencies, patients undergoing elective surgery

Warnings/Precautions

Concerns related to adverse effects:

- Thrombotic events: Thromboembolic complications rarely occur; more likely to occur during postoperative period or in patients with risk factors.

- Unstable vital signs: Treatment should stop if respiratory distress or any changes in blood pressure or pulse rate occur.

Disease-related concerns:

- Hepatic impairment: Use with extreme caution in patients with hepatic impairment.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

Pregnancy Risk FactorC

Adverse Reactions

1% to 10%:

Central nervous system: Fever, headache, chills

Neuromuscular & skeletal: Tingling

Miscellaneous: Following rapid administration: Transient fever

<1%: Disseminated intravascular coagulation (DIC), flushing, nausea, somnolence, thrombosis (following high dosages because of presence of activated clotting factors), tightness in chest, tightness in neck, urticaria, vomiting

Drug Interactions

Aminocaproic Acid: May enhance the adverse/toxic effect of Factor IX Complex (Human). Specifically, use of this combination may increase the risk of thrombosis. *Risk X: Avoid combination*

Monitoring ParametersLevels of factors being replaced (eg, VII or IX), PT, PTT

Reference RangeAverage normal factor VII and factor IX levels are 50% to 150%; patients with severe hemophilia will have levels <1%, often undetectable. Moderate forms of the disease have levels of 1% to 10% while some mild cases may have 11% to 49% of normal factor IX.

Maintain factor IX plasma level at least 20% until hemostasis achieved after acute joint or muscle bleeding.

In preparation for and following surgery:

Level to prevent spontaneous hemorrhage: 5%

Minimum level for hemostasis following trauma and surgery: 30% to 50%

Severe hemorrhage: >60%

Major surgery: >60% prior to procedure, 30% to 50% for several days after surgery, and >20% for 7-10 days thereafter

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution (**Note:** Exact potency labeled on each vial):

Bebulin® VH [single-dose vial; vapor heated; supplied with sterile water for injection]

Profilnine® SD [single-dose vial; solvent detergent treated]

Proplex® T [single-dose vial; heat treated; supplied with sterile water for injection] [DSC]

Generic AvailableNo

Mechanism of ActionReplaces deficient clotting factor including factor X; hemophilia B, or Christmas disease, is an X-linked recessively inherited disorder of blood coagulation characterized by insufficient or abnormal synthesis of the clotting protein factor IX. Factor IX is a vitamin K-dependent coagulation factor which is synthesized in the liver. Factor IX is activated by factor XIa in the intrinsic coagulation pathway. Activated factor IX (IXa), in combination with factor VII:C, activates factor X to Xa, resulting ultimately in the conversion of prothrombin to thrombin and the formation of a fibrin clot. The infusion of exogenous factor IX to replace the deficiency present in hemophilia B temporarily restores hemostasis.

Pharmacodynamics/Kinetics

Half-life elimination:

VII component: Initial: 4-6 hours; Terminal: 22.5 hours

IX component: 24 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay rarely cause sedation
Mental Health: Effects on Psychiatric TreatmentNone reported
Anesthesia and Critical Care Concerns/Other Considerations

Management of Intracerebral Hemorrhage (ICH) Due to Warfarin: Overall management of ICH is similar regardless of cause, however, iatrogenic spontaneous ICH may have specific treatments. According to the 2007 ACC/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage, warfarin-related ICH should be treated with I.V. vitamin K at a dose of 10 mg given slowly (not to exceed 1 mg/minute) (Class I recommendation). It is important to also administer fresh frozen plasma (FFP) since vitamin K may take several hours to normalize INR. Other options besides FFP include prothrombin complex concentrate (PCC) which contains high levels of vitamin K-dependent factors (II, VII, and X) and factor IX complex which contains factors II, VII, IX, and X (Class IIb recommendation). Use of rFVIIa has shown promise for this indication. Advantages to rFVIIa include faster onset of action compared to FFP and vitamin K and a 50% lower volume is required compared to FFP. Disadvantages include a short half-life (~2.6 hours) requiring multiple doses to maintain a normalized INR and an increased risk of thromboembolic complications. Dosing of rFVIIa ranges between 15-90 mcg/kg. The use of factor-containing products has a risk of thromboembolism.

Index TermsProthrombin Complex Concentrate
References

Broderick J, Connolly S, Feldmann E, et al, "Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults: 2007 Update: A Guideline From the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group," *Stroke*, 2007, 38(6):2001-23. Available at http://stroke.ahajournals.org/cgi/content/short/STROKEAHA.107.183689.[PubMed 17478736]

Lusher JM, “Thrombogenicity Associated With Factor IX Complex Concentrates,” *Semin Hematol*, 1991, 28(3 Suppl 6):3-5.

International Brand NamesAlphanine SD (BR, HK, MY, SG, TW); Bebulin S-Tim 4 (AT); Bebulin Team 4 (RU); Bebulin TIM 4 (HN); Benefix (AR, AT, AU, BE, BG, BR, CH, CN, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Betafact (IL); Facnyne (KP); Factor IX S-TIM (DE); Haemosolvex (ZA); Immunine (DE, SE, TH); Inmunine (VE); MonoFIX-VF (AU); Mononine (BE, CZ, DE, FR, GB, IE, NL, SE); Nonafact (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Octanine F (UY); Profilnine SD (MY, SG, TH); Proplex T (ID); Prothrombinex-HT (NZ); Replenine VF (IL, MY, SG); Replenine-VF (MX)

Factor IX

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(FAK ter nyne)

U.S. Brand NamesAlphaNine® SD; BeneFix®; Mononine®

Canadian Brand NamesBeneFix®; Immunine® VH; Mononine®

Pharmacologic CategoryAntihemophilic Agent; Blood Product Derivative

Use: Labeled IndicationsControl bleeding in patients with factor IX deficiency (hemophilia B or Christmas disease)

Dosing: Adults**Control bleeding in patients with factor IX deficiency (hemophilia B or Christmas disease):** Dosage is expressed in int. units of factor IX activity; dosing must be individualized based on severity of factor IX deficiency, extent and location of bleeding, and clinical status of patient:

Formula for int. units required to raise blood level %:

AlphaNine® SD, Mononine®: I.V.:

Number of factor IX int. units required = body weight (in kg) x desired factor IX level increase (int. units/dL or % of normal) x 1 int. unit/kg

For example, for a 100% level a patient who has an actual level of 20%: Number of factor IX int. units needed = 70 kg x 80% x 1 int. unit/kg = 5600 int. units

BeneFix®: I.V.: Number of factor IX int. units required = body weight (in kg) x desired factor IX level increase (int. units/dL or % of normal) x 1.3 int. units/kg

Guidelines: As a general rule, the level of factor IX required for treatment of different conditions is listed below:

Minor spontaneous hemorrhage, prophylaxis:

Desired levels of factor IX for hemostasis: 15% to 25%

Initial loading dose to achieve desired level: 20-30 int. units/kg

Frequency of dosing: Every 12-24 hours if necessary

Duration of treatment: 1-2 days

Moderate hemorrhage:

Desired levels of factor IX for hemostasis: 25% to 50%

Initial loading dose to achieve desired level: 25-50 int. units/kg

Frequency of dosing: Every 12 -24 hours

Duration of treatment: 2-7 days

Major hemorrhage:

Desired levels of factor IX for hemostasis: >50%

Initial loading dose to achieve desired level: 30-50 int. units/kg

Frequency of dosing: Every 12-24 hours, depending on half-life and measured factor IX levels (after 3-5 days, maintain at least 20% activity)

Duration of treatment: 7-10 days, depending upon nature of insult

Surgery or major trauma:

Desired levels of factor IX for hemostasis: 50% to 100%

Initial loading dose to achieve desired level: 50-100 int. units/kg

Frequency of dosing: Every 12-24 hours or every 18-30 hours, depending on half-life and measured factor IX levels

Duration of treatment: 7-10 days, depending upon nature of insult

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Control bleeding in patients with factor IX deficiency (hemophilia B or Christmas disease):** Dosage is expressed in int. units of factor IX activity; dosing must be individualized based on severity of factor IX deficiency, extent and location of bleeding, and clinical status of patient:

AlphaNine® SD, Mononine®: I.V.: Refer to adult dosing.

BeneFix®: I.V.:

Children <15 years:

Formula for int. units required to raise blood level %:

Number of factor IX int. units required = body weight (in kg) x desired factor IX level increase (int. units/dL or % of normal) x 1.4 int. units/kg

Children ≥15 years: Refer to adult dosing.

Guidelines: As a general rule, the level of factor IX required for treatment of different conditions is listed below:

Minor spontaneous hemorrhage, prophylaxis:

Desired levels of factor IX for hemostasis: 15% to 25%

Initial loading dose to achieve desired level: 20-30 int. units/kg

Frequency of dosing: Every 12-24 hours if necessary

Duration of treatment: 1-2 days

Moderate hemorrhage:

Desired levels of factor IX for hemostasis: 25% to 50%

Initial loading dose to achieve desired level: 25-50 int. units/kg

Frequency of dosing: Every 12 -24 hours

Duration of treatment: 2-7 days

Major hemorrhage:

Desired levels of factor IX for hemostasis: >50%

Initial loading dose to achieve desired level: 30-50 int. units/kg

Frequency of dosing: Every 12-24 hours, depending on half-life and measured factor IX levels (after 3-5 days, maintain at least 20% activity)

Duration of treatment: 7-10 days, depending upon nature of insult

Surgery or major trauma:

Desired levels of factor IX for hemostasis: 50% to 100%

Initial loading dose to achieve desired level: 50-100 int. units/kg

Frequency of dosing: Every 12-24 hours or every 18-30 hours, depending on half-life and measured factor IX levels

Duration of treatment: 7-10 days, depending upon nature of insult

Administration: I.V.Solution should be infused at room temperature

I.V. administration only: Should be infused **slowly**: The rate of administration should be determined by the response and comfort of the patient.

AlphaNine® SD: Administer I.V. at a rate not exceeding 10 mL/minute

BeneFix®: Administer I.V. over several minutes

Mononine®: Administer I.V. at a rate of ~2 mL/minute. Administration rates of up to 225 int. units/minute have been regularly tolerated without incident (when reconstituted as directed to ~100 int. units/mL).

StorageWhen stored at refrigerator temperature, 2°C to 8°C (36°F to 46°F), coagulation factor IX is stable for the period indicated by the expiration date on its label. Avoid freezing which may damage container for the diluent.

AlphaNine® SD: May also be stored at room temperature not to exceed 30°C (86°F) for up to 1 month,

BeneFix®: May also be stored at room temperature not to exceed 25°C (77°F) for up to 6 months. Reconstituted solution at room temperature should be used within 3 hours.

Mononine®: May also be stored at room temperature not to exceed 25°C (77°F) for up to 1 month.

ReconstitutionRefer to instructions for individual products. Diluent and factor IX complex should come to room temperature before combining.

ContraindicationsHypersensitivity to mouse protein (Mononine®) or hamster protein (BeneFix®)

Warnings/Precautions

Concerns related to adverse effects:

- Antibody formation: The development of factor IX antibodies (or inhibitors) has been reported with factor IX therapy; the risk of severe hypersensitivity reactions occurring may be greater in these patients.

- Hypersensitivity reactions: Hypersensitivity and anaphylactic reactions have been reported with use. Delayed reactions (up to 20 days after infusion) in previously untreated patients may also occur. Due to potential for allergic reactions, the initial ~10-20 administrations should be performed under appropriate medical supervision. Hypersensitivity reactions may be associated with factor IX inhibitor development; patients experiencing allergic reactions should be evaluated for factor IX inhibitors.

- Thrombotic events: Observe closely for signs or symptoms of intravascular coagulation or thrombosis; risk is generally associated with the use of factor IX complex concentrates (containing theurapeutic amounts of additional factors); however, potential risk exists with use of factor IX products (containing only factor IX). Use with caution when administering to patients with liver disease, postoperatively, neonates, or patients at risk of thromboembolic phenomena, disseminated intravascular coagulation or patients with signs of fibrinolysis due to the potential risk of thromboembolic complications.

Disease-related concerns:

- Hepatic impairment: Use with extreme caution in patients with hepatic impairment due to the risk of thromboembolic complications.

Dosage form specific issues:

- AlphaNine® SD, Mononine®: Contain **nondetectable levels of factors II, VII, and X** and are, therefore, **NOT INDICATED** for replacement therapy of any of these clotting factors.

- Human plasma (AlphaNine® SD, Mononine®): Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

Other warnings/precautions:

- Appropriate use: Factor IX is NOT INDICATED for the treatment or reversal of coumarin-induced anticoagulation, hemophilia A patients with Factor VIII inhibitors, or patients in a hemorrhagic state caused by reduced production of liver-dependent coagulation factors (eg, hepatitis, cirrhosis).

- Immune tolerance induction: Safety and efficacy have not been established in immune tolerance induction with factor IX products. Nephrotic syndrome has occurred following immune tolerance induction in patients with factor IX inhibitors and a history of allergic reactions to therapy.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Safety and efficacy in pregnant women have not been established. Use during pregnancy only if clearly needed. Parvovirus B19 or hepatitis A, which may be present in plasma-derived products, may affect a pregnant woman more seriously than a nonpregnant woman.

Adverse ReactionsFrequency not defined.

Cardiovascular: Cyanosis, flushing, hypotension, chest tightness, thrombosis

Central nervous system: Chills, dizziness, drowsiness, fever (including transient fever following rapid administration), headache, lethargy, lightheadedness, somnolence

Dermatologic: Angioedema, photosensitivity reaction, rash, urticaria

Gastrointestinal: Abnormal taste, diarrhea, nausea, vomiting

Hematologic: Disseminated intravascular coagulation (DIC)

Hepatic: Alkaline phosphatase increased, ALT increased, AST increased

Local: Injection site reactions: Cellulitis, discomfort, pain, phlebitis, stinging

Neuromuscular & skeletal: Neck tightness, paresthesia, rigors

Ocular: Visual disturbance

Respiratory: Allergic rhinitis, asthma, cough, dyspnea, hypoxia, laryngeal edema, lung disorder

Miscellaneous: Allergic reaction, anaphylaxis, burning sensation in jaw/skull, factor IX inhibitor development, hypersensitivity reaction

Postmarketing and/or case reports: HAV seroconversion, inadequate response/recovery, nephrotic syndrome (associated with immune tolerance induction), parvovirus B19 seroconversion, renal infarction

Drug Interactions

Aminocaproic Acid: May enhance the adverse/toxic effect of Factor IX. Specifically, use of this combination may increase the risk of thrombosis. *Risk X: Avoid combination*

Monitoring ParametersLevels of factors IX, PTT, BP, HR, signs of hypersensitivity reactions

Reference RangeAverage normal factor IX levels are 50% to 150%; patients with severe hemophilia will have levels <1%, often undetectable. Moderate forms of the disease have levels of 1% to 10% while some mild cases may have 11% to 49% of normal factor IX.

Maintain factor IX plasma level at least 20% until hemostasis achieved after acute joint or muscle bleeding.

In preparation for and following surgery:

Level to prevent spontaneous hemorrhage: 5%

Minimum level for hemostasis following trauma and surgery: 30% to 50%

Severe hemorrhage: >50%

Major surgery: ≥50% prior to procedure and for 48 hours after surgery, and 30% to 50% for 10 days thereafter

Monitoring: Lab TestsLevels of factors IX, PTT

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution (**Note:** Exact potency labeled on each vial):

BeneFix® [contains polysorbate 80; sucrose 0.8%; recombinant formulation; supplied with diluent]

Injection, powder for reconstitution [human derived] (**Note:** Exact potency labeled on each vial):

AlphaNine® SD [contains polysorbate 80; solvent detergent treated; virus filtered; contains nondetectable levels of factors II, VII, X; supplied with diluent]

Mononine® [contains polysorbate 80; monoclonal antibody purified; contains nondetectable levels of factors II, VII, X; supplied with diluent]

Generic AvailableNo

Mechanism of ActionReplaces deficient clotting factor IX. Hemophilia B, or Christmas disease, is an X-linked inherited disorder of blood coagulation characterized by insufficient or abnormal synthesis of the clotting protein factor IX. Factor IX is a vitamin K-dependent coagulation factor which is synthesized in the liver. Factor IX is activated by factor XIa in the intrinsic coagulation pathway. Activated factor IX (IXa), in combination with factor VII:C activates factor X to Xa, resulting ultimately in the conversion of prothrombin to thrombin and the formation of a fibrin clot. The infusion of exogenous factor IX to replace the deficiency present in hemophilia B temporarily restores hemostasis.

Pharmacodynamics/KineticsHalf-life elimination: IX component: Adults: 21-31 hours; children: 14-28 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause sedation

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFactor IX Concentrate

References

Shord SS and Lindley CM, “Coagulation Products and Their Uses,” *Am J Health-Syst Pharm*, 2000, 57(15):1403-17.[PubMed 10938981]

Srivastava A, “Dose and Response in Haemophilia-Optimization of Factor Replacement Therapy,” *Br J Haematol*, 2004, 127(1):12-25.[PubMed 15384973]

White GC, Beebe A, and Nielsen B, “Recombinant Factor IX,” *Thromb Haemost*, 1997, 78(1):261-5.[PubMed 9198163]

International Brand NamesBebulin Tim 4 (PL); Berinin P (MX, PL); Immunine (PL); Octanine F (MX, PL)

Factor VIIa (Recombinant)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

NovoSeven® may be confused with Novacet®

Pronunciation(FAK ter SEV en aye ree KOM be nant)

U.S. Brand NamesNovoSeven [DSC]; NovoSeven® RT

Canadian Brand NamesNiastase®

Pharmacologic CategoryAntihemophilic Agent; Blood Product

Use: Labeled IndicationsTreatment of bleeding episodes and prevention of bleeding in surgical interventions in patients with hemophilia A or B with inhibitors to factor VIII or factor IX, acquired hemophilia, and in patients with congenital factor VII deficiency

Use: Unlabeled/InvestigationalReduction of hematoma growth in patients with acute intracerebral hemorrhage, warfarin-related intracerebral hemorrhage

Dosing: Adults Hemophilia A or B with inhibitors: For I.V. administration only:

Bleeding episodes: 90 mcg/kg every 2 hours until hemostasis is achieved or until the treatment is judged ineffective. The dose and interval may be adjusted based upon the severity of bleeding and the degree of hemostasis achieved. For patients experiencing severe bleeds, dosing should be continued at 3- to 6-hour intervals after hemostasis has been achieved and the duration of dosing should be minimized.

Surgical interventions: 90 mcg/kg immediately before surgery; repeat at 2-hour intervals for the duration of surgery. Continue every 2 hours for 48 hours, then every 2-6 hours until healed for minor surgery; continue every 2 hours for 5 days, then every 4 hours until healed for major surgery.

Congenital factor VII deficiency: Bleeding episodes and surgical interventions: 15-30 mcg/kg every 4-6 hours until hemostasis. Doses as low as 10 mcg/kg have been effective.

Acquired hemophilia: 70-90 mcg/kg every 2-3 hours until hemostasis is achieved.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: I.V.I.V. administration only; bolus over 2-5 minutes. Administer within 3 hours after reconstitution.

Administration: I.V. DetailpH: 5.5

Dietary ConsiderationsContains sodium 0.44 mEq/mg rFVIIa

Storage

NovoSeven®: Store under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light. Reconstituted solutions may be stored at room temperature or under refrigeration, but must be infused within 3 hours of reconstitution. Do not freeze reconstituted solutions. Do not store reconstituted solutions in syringes.

NovoSeven® RT: Prior to reconstitution, store under refrigeration or between 2°C to 25°C (36°F to 77°F). Protect from light. Reconstituted solutions may be stored at room temperature or under refrigeration, but must be infused within 3 hours of reconstitution. Do not freeze reconstituted solutions. Do not store reconstituted solutions in syringes.

ReconstitutionPrior to reconstitution, bring vials to room temperature. Add recommended diluent along wall of vial; do not inject directly onto powder. Gently swirl until dissolved.

NovoSeven®: Reconstitute each vial to a final concentration of 0.6 mg/mL as follows:

1.2 mg vial: 2.2 mL sterile water

2.4 mg vial: 4.3 mL sterile water

4.8 mg vial: 8.5 mL sterile water

NovoSeven® RT: Reconstitute each vial to a final concentration of 1 mg/mL using the provided histidine diluent as follows:

1 mg vial: 1.1 mL sterile water

2 mg vial: 2.1 mL sterile water

5 mg vial: 5.2 mL sterile water

ContraindicationsThere are no contraindications listed within the FDA-approved labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Use with caution in patients with known hypersensitivity to mouse, hamster, or bovine proteins, or factor VIIa, or any components of the product.

- Thrombotic events: Patients should be monitored for signs and symptoms of activation of the coagulation system or thrombosis; thrombotic events may be increased in patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, sepsis, crush injury, or concomitant treatment with prothrombin complex concentrates. Decreased dosage or discontinuation is warranted in confirmed DIC.

Other warnings/precautions:

- Long-term use: Efficacy with prolonged infusions and data evaluating this agent's long-term adverse effects are limited.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have demonstrated fetal loss, but no evidence of teratogenic effects. There are no adequate and well-controlled studies in pregnant women. Use only if the potential benefit justifies the potential risk to the fetus.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

1% to 10%:

Cardiovascular: Hypertension

Central nervous system: Fever

Hematologic: Hemorrhage, plasma fibrinogen decreased

Neuromuscular & skeletal: Hemarthrosis

<1%: Abnormal renal function, allergic reactions, arthrosis, bradycardia, coagulation disorder, disseminated intravascular coagulation (DIC), edema, fibrinolysis increased, gastrointestinal bleeding, headache, hypotension, injection site reactions, intracranial hemorrhage, localized phlebitis, pain, pneumonia, prothrombin decreased, pruritus, purpura, rash, splenic hematoma, therapeutic response decreased, thrombosis, vomiting

Postmarketing and/or case reports: Anaphylactic reaction, arterial thrombosis, cerebral infarction and/or ischemia, consumptive coagulopathy, deep vein thrombosis, hypersensitivity, MI, myocardial ischemia, pulmonary embolism, thrombophlebitis

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersMonitor for evidence of hemostasis; although the prothrombin time, aPTT, and factor VII clotting activity have no correlation with achieving hemostasis, these parameters may be useful as adjunct tests to evaluate efficacy and guide dose or interval adjustments

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products the patient may be taking that may affect coagulation or platelet function. Assess results of laboratory tests (eg, prothrombin time and factor VII clotting activity). Patient should be monitored closely during and after therapy (vital signs, cardiac and CNS status, hemolytic status, hypersensitivity). Provide patient education according to patient condition.

Monitoring: Lab TestsAlthough the prothrombin time, aPTT, and factor VII clotting activity have no correlation with achieving hemostasis, these parameters may be useful as adjunct tests to evaluate efficacy and guide dose or interval adjustments

Patient EducationThis medication can only be administered by infusion. Report immediately any swelling, pain, burning, or itching at infusion site. Report acute headache, visual changes, pain in joints or muscles, respiratory difficulty, chills, back pain, dizziness, nausea, or other unusual effects. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution [preservative free]:

NovoSeven®: 1.2 mg, 2.4 mg, 4.8 mg [contains sodium 0.44 mEq/mg rFVIIa, polysorbate 80] [DSC]

NovoSeven® RT:

1 mg [contains polysorbate 80, sodium 0.4 mEq/mg rFVIIa, sucrose 10 mg/vial]

2 mg [contains polysorbate 80, sodium 0.4 mEq/mg rFVIIa, sucrose 20 mg/vial]

5 mg [contains polysorbate 80, sodium 0.4 mEq/mg rFVIIa, sucrose 50 mg/vial]

Generic AvailableNo

ManufacturerNovo Nordisk®

Mechanism of ActionRecombinant factor VIIa, a vitamin K-dependent glycoprotein, promotes hemostasis by activating the extrinsic pathway of the coagulation cascade. It replaces deficient activated coagulation factor VII, which complexes with tissue factor and may activate coagulation factor X to Xa and factor IX to IXa. When complexed with other factors, coagulation factor Xa converts prothrombin to thrombin, a key step in the formation of a fibrin-platelet hemostatic plug.

Pharmacodynamics/Kinetics

Distribution: V_d: 103 mL/kg (78-139)

Half-life elimination: 2.3 hours (1.7-2.7)

Excretion: Clearance: 33 mL/kg/hour (27-49)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other ConsiderationsA number of patient-specific factors may influence the potential efficacy of factor VIIa including hypothermia, thrombocytopenia, acidic arterial pH, and the amount of blood products transfused prior to administration. Factor VIIa exerts its mechanism of action at the site of vascular injury where tissue factor is expressed and activated platelets are found. Factor VIIa binds directly to the surface of activated platelets and activates factor X to Xa and generates thrombin as a result. Adequate platelets may be required for factor VIIa to properly induce coagulation.

Management of Intracerebral Hemorrhage (ICH): Rapid identification of patients experiencing ICH is essential and should be considered a medical emergency due to the progressive deterioration, severe clinical deficits, and high mortality and morbidity. Treatment for ICH has evolved rapidly in recent years. According to the 2007 ACC/AHA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults, patients with ICH should be treated in a balanced and graded approach with therapies that reduce intracranial pressure (ICP) (eg, mannitol, hypertonic saline solutions, barbiturate coma, head of bed elevation) (Class IIa recommendation). Direct monitoring of ICP and central perfusion pressure (CPP) may be necessary if patient is treated more aggressively. Treatment of ICH with recombinant factor VIIa (rFVIIa) within the first 3-4 hours after onset to slow progression of bleeding has shown promise; however, at this time it cannot be routinely recommended in all patients experiencing ICH (Class IIb recommendation).

Management of Warfarin-Related ICH: Overall management of ICH is similar regardless of cause; however, iatrogenic spontaneous ICH may have specific treatments. According to the 2007 ACC/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage, warfarin-related ICH should be treated with I.V. vitamin K at a dose of 10 mg given slowly (not to exceed 1 mg/minute) (Class I recommendation). It is important to also administer fresh frozen plasma (FFP) since vitamin K may take several hours to normalize INR. Other options besides FFP include prothrombin complex concentrate (PCC) which contains high levels of vitamin K-dependent factors (II, VII, and X) and factor IX complex which contains factors II, VII, IX, and X (Class IIb recommendation). Use of rFVIIa has shown promise for this indication. Advantages to rFVIIa include faster onset of action compared to FFP and vitamin K and a 50% lower volume is required compared to FFP. Disadvantages include a short half-life (~2.6 hours) requiring multiple doses to maintain a normalized INR and an increased risk of thromboembolic complications. Dosing of rFVIIa ranges between 15-90 mcg/kg. The use of factor-containing products has a risk of thromboembolism.

Index TermsCoagulation Factor VIIa; Eptacog Alfa (Activated); rFVIIa

References

Broderick J, Connolly S, Feldmann E, et al, "Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults: 2007 Update: A Guideline From the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group," *Stroke*, 2007, 38(6):2001-23. Available at http://stroke.ahajournals.org/cgi/content/short/STROKEAHA.107.183689.[PubMed 17478736]

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Mohr AM, Holcomb JB, Dutton RP, et al, “Recombinant Activated Factor VIIa and Hemostasis in Critical Care: A Focus on Trauma,” *Crit Care*, 2005, 9 (Suppl 5):37-42.[PubMed 15693982]

International Brand NamesNovonordisk (MX); NovoSeven (AR, AT, AU, BE, BG, BR, CH, CN, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, MY, NL, NO, PH, PT, RU, SE, SG, TH, TR, TW); Novoseven (MX)

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Gastric Cancer; Chemotherapy Regimen, Pancreatic Cancer

Regimen Use Gastric cancer; Pancreatic cancer

Regimen NOTE: Multiple variations are listed below

Variation 1:

Fluorouracil: I.V.: 600 mg/m^2/day days 1, 8, 29, and 36

[total dose/cycle = 2400 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2/day days 1 and 29

[total dose/cycle = 60 mg/m^2]

Mitomycin: I.V.: 10 mg/m^2 day 1

[total dose/cycle = 10 mg/m^2]

Repeat cycle every 8 weeks

Variation 2:

Fluorouracil: I.V.: 600 mg/m^2/day days 29 to 32

[total dose/cycle = 2400 mg/m^2]

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Mitomycin: I.V.: 10 mg/m^2 day 3

[total dose/cycle = 10 mg/m^2]

Repeat cycle every 8 weeks

Variation 3:

Fluorouracil: I.V.: 500 mg/m^2/day days 1, 8, 21, and 28

[total dose/cycle = 2000 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2/day days 1 and 21

[total dose/cycle = 60 mg/m^2]

Mitomycin: I.V.: 10 mg/m^2 day 1

[total dose/cycle = 10 mg/m^2]

Repeat cycle every 6 weeks

Variation 4:

Fluorouracil: I.V.: 275 mg/m^2/day days 1 to 5 and 36 to 40

[total dose/cycle = 2750 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2/day days 1 and 36

[total dose/cycle = 60 mg/m^2]

Mitomycin: I.V.: 10 mg/m^2 day 1

[total dose/cycle = 10 mg/m^2]

Repeat cycle every 10 weeks

Variation 5:

Fluorouracil: I.V.: 600 mg/m^2/day days 1, 8, 22, and 29

[total dose/cycle = 2400 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2/day days 1 and 22

[total dose/cycle = 60 mg/m^2]

Mitomycin: I.V.: 10 mg/m^2 day 1

[total dose/cycle = 10 mg/m^2]

Repeat cycle every 6 weeks

References

Variation 1:

Cullinan SA, Moertel CG, Fleming TR, et al, “A Comparison of Three Chemotherapeutic Regimens in the Treatment of Advanced Pancreatic and Gastric Carcinoma. Fluorouracil vs Fluorouracil and Doxorubicin vs Fluorouracil, Doxorubicin, and Mitomycin,” *JAMA*, 1985, 253(14):2061-7. [PubMed 2579257]

Preusser P, Achterrath W, Wilke H, et al, “Chemotherapy of Gastric Cancer,” *Cancer Treat Rev*, 1988, 15(4):257-77.[PubMed 3071419]

Variation 2:

Panettiere FJ, Haas C, McDonald B, et al, “Drug Combinations in the Treatment of Gastric Adenocarcinoma: A Randomized Southwest Oncology Group Study,” *J Clin Oncol*, 1984, 2(5):420-4.[PubMed 6427416]

Variation 3:

Bitran JD, Desser RK, Kozloff MF, et al, “Treatment of Metastatic Pancreatic and Gastric Adenocarcinomas With 5-Fluorouracil, Adriamycin, and Mitomycin C (FAM),” *Cancer Treat Rep*, 1979, 63(11-12):2049-51. [PubMed 393388]

Variation 4:

“A Comparative Clinical Assessment of Combination Chemotherapy in the Management of Advanced Gastric Carcinoma: The Gastrointestinal Tumor Study Group,” *Cancer*, 1982, 49(7):1362-6.[PubMed 7037163]

Variation 5:

Haim N, Epelbaum R, Cohen Y, et al, “Further Studies on the Treatment of Advanced Gastric Cancer by 5-Fluorouracil, Adriamycin (Doxorubicin), and Mitomycin C (Modified FAM),” *Cancer*, 1984, 54(9):1999-2002.[PubMed 6548173]

Famciclovir

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Famvir® may be confused with Femara®

Pronunciation(fam SYE kloe veer)
U.S. Brand NamesFamvir®
Canadian Brand NamesApo-Famciclovir; Famvir®; PMS-Famciclovir; Sandoz-Famciclovir
Pharmacologic CategoryAntiviral Agent
Use: Labeled IndicationsTreatment of acute herpes zoster (shingles); treatment and suppression of recurrent episodes of genital herpes in immunocompetent patients; treatment of herpes labialis (cold sores) in immunocompetent patients; treatment of recurrent mucocutaneous/genital herpes simplex in HIV-infected patients
Use: DentalManagement of acute herpes zoster (shingles); treatment of recurrent herpes labialis in immunocompetent patients
Dosing: Adults

Acute herpes zoster: Oral: 500 mg every 8 hours for 7 days (**Note:** Initiate therapy within 72 hours of rash onset.)

Recurrent genital herpes simplex in immunocompetent patients: Oral:

Initial: 1000 mg twice daily for 1 day (**Note:** initiate therapy within 6 hours of symptoms/lesions.)

Suppressive therapy: 250 mg twice daily for up to 1 year

Recurrent herpes labialis (cold sores): Oral: 1500 mg as a single dose; initiate therapy at first sign or symptom such as tingling, burning, or itching (initiated within 1 hour in clinical studies)

Recurrent mucocutaneous/genital herpes simplex in HIV patients: Oral: 500 mg twice daily for 7 days

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal Impairment

Herpes zoster:

Cl_{cr} 40-59 mL/minute: Administer 500 mg every 12 hours

Cl_{cr} 20-39 mL/minute: Administer 500 mg every 24 hours

Cl_{cr} <20 mL/minute: Administer 250 mg every 24 hours

Hemodialysis: Administer 250 mg after each dialysis session.

Recurrent genital herpes: Treatment (single day regimen):

Cl_{cr} 40-59 mL/minute: Administer 500 mg every 12 hours for 1 day

Cl_{cr} 20-39 mL/minute: Administer 500 mg as a single dose

Cl_{cr} <20 mL/minute: Administer 250 mg as a single dose

Hemodialysis: Administer 250 mg as a single dose after dialysis session.

Recurrent genital herpes: Suppression:

Cl_{cr} 20-39 mL/minute: Administer 125 mg every 12 hours

Cl_{cr} <20 mL/minute: Administer 125 mg every 24 hours

Hemodialysis: Administer 125 mg after each dialysis session.

Recurrent herpes labialis: Treatment (single dose regimen):

Cl_{cr} 40-59 mL/minute: Administer 750 mg as a single dose

Cl_{cr} 20-39 mL/minute: Administer 500 mg as a single dose

Cl_{cr} <20 mL/minute: Administer 250 mg as a single dose

Hemodialysis: Administer 250 mg as a single dose after dialysis session.

Recurrent orolabial or genital herpes in HIV-infected patients:

Cl_{cr} 20-39 mL/minute: Administer 500 mg every 12 hours

Cl_{cr} <20 mL/minute: Administer 250 mg every 24 hours

Hemodialysis: Administer 250 mg after each dialysis session.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsMay be taken with food or on an empty stomach.
StorageStore at controlled room temperature.
ContraindicationsHypersensitivity to famciclovir, penciclovir, or any component of the formulation
Allergy Considerations

- Antiviral Acyclic Guanine Derivative Allergy

Warnings/Precautions

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Lactose: Tablets contain lactose; do not use with galactose intolerance, severe lactase deficiency, or glucose-galactose malabsorption syndromes.

Other warnings/precautions:

- Appropriate use: Has not been established for use in initial episodes of genital herpes, patients with ophthalmic or disseminated zoster, or in immunocompromised patients with herpes zoster.

Geriatric ConsiderationsFor herpes zoster (shingles) infections, famciclovir should be started within 72 hours of the appearance of the rash to be effective. Famciclovir has been shown to accelerate healing, reduce the duration of viral shedding, and resolve posthepatic neuralgia faster than placebo. Comparison trials to acyclovir or valacyclovir are not available. Adjust dose for estimated renal function.
Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use only if benefit outweighs risk. A registry has been established for women exposed to famciclovir during pregnancy (888-669-6682).
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsThere is no specific data describing the excretion of famciclovir in breast milk. If herpes lesions are on breast, breast-feeding should be avoided in order to avoid transmission to infant.
Adverse Reactions

Note: Frequencies vary with dose and duration. Single-dose treatment (herpes labialis) was associated only with headache (10%), diarrhea (2%), fatigue (1%), and dysmenorrhea (1%).

>10%:

Central nervous system: Headache (17% to 39%)

Gastrointestinal: Nausea (7% to 13%)

1% to 10%:

Central nervous system: Fatigue (4% to 6%), migraine (1% to 3%)

Dermatologic: Pruritus (1% to 4%), rash (<1% to 3%)

Endocrine & metabolic: Dysmenorrhea (up to 8%)

Gastrointestinal: Diarrhea (5% to 9%), flatulence (2% to 5%), vomiting (1% to 5%), abdominal pain (1% to 8%)

Hematologic: Neutropenia (3%), leukopenia (1%)

Hepatic: Transaminases increased (2% to 3%), bilirubin increased (2%)

Neuromuscular & skeletal: Paresthesia (1% to 3%)

Postmarketing and/or case reports: Confusion, delirium, disorientation, dizziness, erythema multiforme, hallucinations, jaundice, somnolence, thrombocytopenia, urticaria

Drug Interactions

Zoster Vaccine: Famciclovir may diminish the therapeutic effect of Zoster Vaccine. Management: When possible, discontinue antiviral agents with anti-zoster activity (i.e., acyclovir, valacyclovir, famciclovir) for at least 24 hours prior to and 14 days after receiving a live attenuated zoster vaccine. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: Rate of absorption and/or conversion to penciclovir and peak concentration are reduced with food, but bioavailability is not affected.

Monitoring ParametersPeriodic CBC during long-term therapy

Nursing: Physical Assessment/MonitoringAssess periodic CBC during long-term therapy. Assess potential for interactions with other pharmacological agents the patient may be taking. Assess results of laboratory tests, therapeutic effectiveness according to purpose for use, and adverse response (eg, persistent fatigue, gastrointestinal upset). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPeriodic CBC during long-term therapy

Patient EducationTake for prescribed length of time, even if condition improves. Do not discontinue without consulting prescriber. This is not a cure for genital herpes. May cause mild GI disturbances (eg, nausea, vomiting, constipation, diarrhea), fatigue, headache, or muscle aches and pains. If these are severe, contact prescriber. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 125 mg, 250 mg, 500 mg

Famvir®: 125 mg, 250 mg, 500 mg

Generic AvailableYes

ManufacturerSmithKline Beecham Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Famciclovir)

125 mg (30): $89.99

250 mg (30): $99.99

500 mg (30): $199.98

Tablets (Famvir)

125 mg (30): $153.34

250 mg (30): $165.98

500 mg (30): $304.54

Mechanism of ActionFamciclovir undergoes rapid biotransformation to the active compound, penciclovir, which is phosphorylated by viral thymidine kinase in HSV-1, HSV-2, and VZV-infected cells to a monophosphate form; this is then converted to penciclovir triphosphate and competes with deoxyguanosine triphosphate to inhibit HSV-2 polymerase (eg, herpes viral DNA synthesis/replication is selectively inhibited)

Pharmacodynamics/Kinetics

Absorption: Food decreases maximum peak concentration and delays time to peak; AUC remains the same

Distribution: V_{dss}: 0.91-1.25 L/kg

Protein binding: ≤20%

Metabolism: Rapidly deacetylated and oxidized to penciclovir; not via CYP

Bioavailability: 69% to 85%

Half-life elimination: Penciclovir: 2-3 hours (10, 20, and 7 hours in HSV-1, HSV-2, and VZV-infected cells, respectively); prolonged with renal impairment

Time to peak: 0.9 hours; C_{max} and T_{max} are decreased and prolonged with noncompensated hepatic impairment

Excretion: Urine (73% primarily as penciclovir); feces (27%)

Related Information

- Treatment of Sexually-Transmitted Infections

Pharmacotherapy PearlsMost effective for herpes zoster if therapy is initiated within 48 hours of initial lesion. Resistance may occur by alteration of thymidine kinase, resulting in loss of or reduced penciclovir phosphorylation (cross-resistance occurs between acyclovir and famciclovir). When treatment for herpes labialis is initiated within 1 hour of symptom onset, healing time is reduced by ~2 days.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Alrabiah FA and Sacks SL, “New Antiherpesvirus Agents. Their Targets and Therapeutic Potential,” *Drugs*, 1996, 52(1):17-32. [PubMed 8799682]

Boike SC, Pue MA, and Freed MI, “Pharmacokinetics of Famciclovir in Subjects With Varying Degrees of Renal Impairment,” *Clin Pharmacol Ther*, 1994, 55(4):418-26. [PubMed 8162668]

Boyd MR, Safrin S, and Kern ER, “Penciclovir: A Review of Its Spectrum of Activity, Selectivity, and Cross Resistance Pattern,” *Antivir Chem Chemother*, 1993, 4:3-11.

Daniels S and Schentag JJ, “Drug Interaction Studies and Safety of Famciclovir in Healthy Volunteers: A Review,” *Antivir Chem Chemother*, 1993, 4:57-64.

De Clercq E, “Antivirals for the Treatment of Herpesvirus Infections,” *J Antimicrob Chemother*, 1993, 32(Suppl A):121-32. [PubMed 8407694]

Gill KS and Wood MJ, “The Clinical Pharmacokinetics of Famciclovir,” *Clin Pharmacokinet*, 1996, 31(1):1-8. [PubMed 8827396]

Goffin E, Horsmans Y, Pirson Y, et al, “Acute Necrotico-Hemorrhagic Pancreatitis After Famciclovir Prescription,” *Transplantation*, 1995, 59(8):1218-9. [PubMed 7537399]

Hodge RA, “Famciclovir and Penciclovir: The Mode of Action of Famciclovir Including Its Conversion to Penciclovir,” *Antivir Chem Chemother*, 1993, 4:67-84.

Luber AD and Flaherty JF Jr, “Famciclovir for Treatment of Herpesvirus Infections,” *Ann Pharmacother*, 1996, 30(9):978-85. [PubMed 8876860]

Perry CM and Wagstaff AJ, “Famciclovir. A Review of Its Pharmacological Properties and Therapeutic Efficacy in Herpesvirus Infections,” *Drugs*, 1995, 50(2):396-415. [PubMed 8521764]

Pue MA and Benet LZ, “Pharmacokinetics of Famciclovir in Man,” *Antivir Chem Chemother*, 1993, 4(Suppl 1):47-55.

Sacks SL, “Genital Herpes Simplex Virus and Its Treatment Focus on Famciclovir,” *Semin Dermatol*, 1996, 15(2 Suppl 1):32-6. [PubMed 8840414]

Spruance SL, Bodsworth N, Resnick H, et al, “Single-Dose, Patient-Initiated Famciclovir: A Randomized, Double-Blind, Placebo-Controlled Trial for Episodic Treatment of Herpes Labialis,” *J Am Acad Dermatol*, 2006, 55(1):47-53.[PubMed 16781291]

Tyring SK, Barbarash RA, Nahlik JE, et al, “Famciclovir for the Treatment of Acute Herpes Zoster: Effects on Acute Disease and Postherpetic Neuralgia,” *Ann Intern Med*, 1995, 123(2):89-96. [PubMed 7778840]

Tyring SK, “Efficacy of Famciclovir in the Treatment of Herpes Zoster,” *Semin Dermatol*, 1996, 15(2 Suppl 1):27-31.[PubMed 8840413]

International Brand NamesBencavir (LU); Famicle (KP); Famtrex (IN); Famvics (KP); Famvina (KP); Famvir (AT, AU, BB, BE, BF, BG, BJ, BM, BS, BZ, CH, CI, CZ, DE, DK, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, ID, IE, IL, IT, JM, KE, LR, LU, MA, ML, MR, MU, MW, NE, NG, NL, NO, PK, PT, RU, SC, SD, SE, SL, SN, SR, TH, TN, TR, TT, TW, TZ, UG, ZA, ZM, ZW); Famvir [Tbl.] (PL); Fanle (CL); Oravil (KP); Oravir (FR); Pentavir (AR); Vectavir (LU); Zosfam (KP)

FAMe

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Gastric Cancer]

Regimen UseGastric cancer

Regimen

Fluorouracil: I.V.: 325 mg/m^2/day days 1 to 5 and days 36 to 40

[total dose/cycle = 3250 mg/m^2]

Doxorubicin: I.V.: 40 mg/m^2 day 1 and day 36

[total dose/cycle = 80 mg/m^2]

Lomustine: Oral: 110 mg/m^2 day 1

[total dose/cycle = 110 mg/m^2]

Repeat cycle every 10 weeks

References

Cullinan SA, Moertel CG, Wieand HS, et al, âControlled Evaluation of Three Drug Combination Regimens Versus Fluorouracil Alone for the Therapy of Advanced Gastric Cancer. North Central Cancer Treatment Group,â *J Clin Oncol*, 1994, 12(2):412-6.[PubMed 8113849]

Famotidine, Calcium Carbonate, and Magnesium Hydroxide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(fa MOE ti deen, KAL see um KAR bun ate, & mag NEE zhum hye DROKS ide)

U.S. Brand NamesPepcid® Complete [OTC]

Canadian Brand NamesPepcid® Complete [OTC]

Pharmacologic CategoryAntacid; Histamine H$_2$ Antagonist

Use: Labeled IndicationsRelief of heartburn due to acid indigestion

Dosing: AdultsRelief of heartburn due to acid indigestion: Oral: Pepcid® Complete: 1 tablet as needed; no more than 2 tablets in 24 hours; do **not** swallow whole, chew tablet completely before swallowing; do not use for longer than 14 days (see Additional Information for dosing ranges for individual ingredients)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥12 years: Refer to adult dosing.

StorageStore at 25°C to 30°C (77°F to 86°F). Protect from moisture.

ContraindicationsHypersensitivity to famotidine or other H$_2$ antagonists, calcium carbonate, magnesium hydroxide, or any component of the formulation. See individual agents for additional information.

Allergy Considerations

- Histamine H$_2$ Antagonist Allergy

Warnings/PrecautionsSee individual agents.

Geriatric ConsiderationsUse with caution in the elderly with reduced renal function (Cl$_{cr}$ <30 mL/minute), since accumulation of magnesium and famotidine may occur and potentiate side effects

Adverse ReactionsSee individual agents.

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): H2-Antagonists may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole; Voriconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Atazanavir: H2-Antagonists may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Antacids may decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Cefpodoxime: H2-Antagonists may decrease the absorption of Cefpodoxime. Separate oral doses by at least 2 hours. *Risk C: Monitor therapy*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: H2-Antagonists may decrease the absorption of Cefuroxime. Separate oral doses by at least 2 hours. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Dasatinib: H2-Antagonists may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Erlotinib: H2-Antagonists may decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Estramustine: Calcium Salts may decrease the absorption of Estramustine. *Risk D: Consider therapy modification*

Fexofenadine: Antacids may decrease the serum concentration of Fexofenadine. Management: No specific recommendations concerning the time required between their administration are provided. Separate administration of each agent by as much time as possible to decrease the risk of an interaction. *Risk D: Consider therapy modification*

Fosamprenavir: H2-Antagonists may decrease the serum concentration of Fosamprenavir. Cimetidine may also inhibit the metabolism of the active metabolite amprenavir, making its effects on fosamprenavir/amprenavir concentrations difficult to predict. *Risk C: Monitor therapy*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Iron Salts: H2-Antagonists may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk C: Monitor therapy*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Moxifloxacin. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Saquinavir: H2-Antagonists may increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, chewable: Famotidine 10 mg, calcium carbonate 800 mg, and magnesium hydroxide 165 mg [berry blend and mint flavors]

Generic AvailableNo

Mechanism of Action

Famotidine: H_2 antagonist

Calcium carbonate: Antacid

Magnesium hydroxide: Antacid

Pharmacodynamics/KineticsSee individual agents.

Pharmacotherapy PearlsPresented in dosage field is the specific OTC labeling for the indicated product. Dosing ranges of the individual ingredients include:

Adults:

Famotidine: Duodenal/gastric ulcer: 40 mg/day at bedtime

Calcium carbonate: Antacid: ≤3 g/day of elemental calcium

Magnesium hydroxide: Antacid: Approximately ≤5 g/day of magnesium hydroxide

Healthcare providers should also refer to the individual monographs for more specific information.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness; may rarely cause insomnia

Mental Health: Effects on Psychiatric TreatmentMay cause agranulocytosis; use caution with clozapine and carbamazepine

Index TermsCalcium Carbonate, Magnesium Hydroxide, and Famotidine; Magnesium Hydroxide, Famotidine, and Calcium Carbonate

International Brand NamesMegalex Antiacido (AR); Pepcid Duo (SE); Pepcidduo (FI, FR, NO); Promag Double Action (ID)

Famotidine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(fa MOE ti deen)

U.S. Brand NamesPepcid®; Pepcid® AC Maximum Strength [OTC]; Pepcid® AC [OTC]

Canadian Brand NamesApo-Famotidine®; Apo-Famotidine® Injectable; Famotidine Omega; Gen-Famotidine; Novo-Famotidine; Nu-Famotidine; Pepcid®; Pepcid® AC; Pepcid® I.V.; ratio-Famotidine; Riva-Famotidine; Ulcidine

Pharmacologic CategoryHistamine H_2 Antagonist

Use: Labeled IndicationsMaintenance therapy and treatment of duodenal ulcer; treatment of gastroesophageal reflux, active benign gastric ulcer, and pathological hypersecretory conditions

OTC labeling: Relief of heartburn, acid indigestion, and sour stomach

Use: Unlabeled/InvestigationalPart of a multidrug regimen for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence; stress ulcer prophylaxis in critically-ill patients; symptomatic relief in gastritis

Dosing: Adults

Duodenal ulcer: Oral: Acute therapy: 40 mg/day at bedtime for 4-8 weeks; maintenance therapy: 20 mg/day at bedtime

Gastric ulcer: Oral: Acute therapy: 40 mg/day at bedtime

Hypersecretory conditions: Oral: Initial: 20 mg every 6 hours, may increase in increments up to 160 mg every 6 hours

GERD: Oral: 20 mg twice daily for 6 weeks

Esophagitis and accompanying symptoms due to GERD: Oral: 20 mg or 40 mg twice daily for up to 12 weeks

Peptic ulcer disease: Eradication of*Helicobacter pylori*(unlabeled use): Oral: 40 mg once daily; requires combination therapy with antibiotics

Patients unable to take oral medication: I.V.: 20 mg every 12 hours

Heartburn, indigestion, sour stomach: OTC labeling: Oral: 10-20 mg every 12 hours; dose may be taken 15-60 minutes before eating foods known to cause heartburn

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricTreatment duration and dose should be individualized

Peptic ulcer: 1-16 years:

Oral: 0.5 mg/kg/day at bedtime or divided twice daily (maximum dose: 40 mg/day); doses of up to 1 mg/kg/day have been used in clinical studies

I.V.: 0.25 mg/kg every 12 hours (maximum dose: 40 mg/day); doses of up to 0.5 mg/kg have been used in clinical studies

GERD: Oral:

<3 months: 0.5 mg/kg once daily

3-12 months: 0.5 mg/kg twice daily

1-16 years: 1 mg/kg/day divided twice daily (maximum dose: 40 mg twice daily); doses of up to 2 mg/kg/day have been used in clinical studies

Heartburn, indigestion, sour stomach: OTC labeling: Oral: Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <50 mL/minute: Manufacturer recommendation: Administer 50% of dose **or** increase the dosing interval to every 36-48 hours (to limit potential CNS adverse effects).

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.

I.V. push: Inject over at least 2 minutes.

Solution for infusion: Administer over 15-30 minutes.

Administration: I.V. DetailpH: 5.7-6.4 (premixed solution); 5.0-5.6 (injection)

Administration: Oral

Suspension: Shake vigorously before use. May be taken with or without food.

Tablet: May be taken with or without food.

Storage

Oral:

Powder for oral suspension: Prior to mixing, dry powder should be stored at controlled room temperature of 25°C (77°F). Reconstituted oral suspension is stable for 30 days at room temperature; do not freeze.

Tablet: Store controlled room temperature. Protect from moisture.

I.V.:

Solution for injection: Prior to use, store at 2°C to 8°C (36°F to 46°F). If solution freezes, allow to solubilize at controlled room temperature.

I.V. push: Following preparation, solutions for I.V. push should be used immediately, or may be stored in refrigerator and used within 48 hours.

Infusion: Following preparation, the manufacturer states may be stored for up to 48 hours under refrigeration; however, solutions for infusion have been found to be physically and chemically stable for 7 days at room temperature.

Solution for injection, premixed bags: Store at controlled room temperature of 25°C (77°F). Avoid excessive heat.

Reconstitution

Solution for injection:

I.V. push: Dilute famotidine with NS (or another compatible solution) to a total of 5-10 mL (some centers also administer undiluted).

Infusion: Dilute with D_5W 100 mL or another compatible solution.

Compatibility

Stable in D_5W, $D_{10}W$, LR, fat emulsion 10%, NS, sodium bicarbonate 5%; **variable stability (consult detailed reference)** in TPN.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, aminophylline, ampicillin, ampicillin/sulbactam, amsacrine, atropine, aztreonam, calcium gluconate, cefazolin, cefoperazone, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, chlorpromazine, cisatracurium, cisplatin, cladribine, cyclophosphamide, cytarabine, dexamethasone sodium phosphate, dextran 40, digoxin, diphenhydramine, dobutamine, docetaxel, dopamine, doxorubicin, doxorubicin liposome, droperidol, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, etoposide, filgrastim, fluconazole, fludarabine, folic acid, gatifloxacin, gemcitabine, gentamicin, granisetron, haloperidol, heparin, hydrocortisone, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, imipenem/cilastatin, inamrinone, insulin (regular), isoproterenol, labetalol, lidocaine, linezolid, lorazepam, magnesium sulfate, melphalan, meperidine, methotrexate, methylprednisolone sodium succinate, metoclopramide, midazolam, morphine, nafcillin, nitroglycerin, norepinephrine, ondansetron, oxacillin, paclitaxel, perphenazine, phenylephrine, phenytoin, phytonadione, piperacillin, potassium chloride, potassium phosphates, procainamide, propofol, remifentanil, sargramostim, sodium bicarbonate, sodium nitroprusside, teniposide, theophylline, thiamine, thiotepa, ticarcillin, ticarcillin/clavulanate potassium, tirofiban, verapamil, vinorelbine. **Incompatible:** Amphotericin B cholesteryl sulfate complex, cefepime, piperacillin/tazobactam. **Variable (consult detailed reference):** Furosemide, TPN.

Compatibility when admixed: Compatible: Cefazolin, flumazenil, vancomycin.

Contraindications

Hypersensitivity to famotidine, other H_2 antagonists, or any component of the formulation

Allergy Considerations

- Histamine H_2 Antagonist Allergy

Warnings/Precautions

Concerns related to adverse effects.

- Confusion: Reversible confusional states, usually clearing within 3-4 days after discontinuation, have been linked to use. Increased age (>50 years) and renal or hepatic impairment are thought to be associated.

Disease-related concerns:

- Gastric malignancy: Relief of symptoms does not preclude the presence of a gastric malignancy.

- Renal impairment: Use with caution in patients with moderate-to-severe renal impairment (Cl_{cr} <50 mL/minute); dosage adjustment recommended.

Dosage form specific issues:

- Benzyl alcohol: Multidose vials for injection contain benzyl alcohol which has been associated with "gasping syndrome" in neonates.

Other warnings/precautions:

- OTC labeling: When used for self-medication, patients should be instructed not to use if they have difficulty swallowing, are vomiting blood, or have bloody or black stools. Not for use with other acid reducers.

Geriatric Considerations

H_2 blockers are the preferred drugs for treating PUD in the elderly due to cost and ease of administration. They are no less or more effective than any other therapy. Famotidine is one of the preferred agents (due to side effects, drug interaction profile, and pharmacokinetics). Treatment for PUD in the elderly is recommended for 12 weeks since their lesions are typically larger; therefore, take longer to heal. Always adjust dose based upon creatinine clearance, since slight accumulation may result in CNS side effects, mainly confusion.

Pregnancy Risk FactorB

Pregnancy ConsiderationsCrosses the placenta. There are no adequate and well-controlled studies in pregnant women. Use only if clearly needed.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsFamotidine is concentrated in breast milk, but to a lesser degree than cimetidine or ranitidine; some sources prefer its use if one of these agents is needed.

Adverse Reactions

Note: Agitation and vomiting have been reported in up to 14% of pediatric patients <1 year of age.

1% to 10%:

Central nervous system: Headache (5%), dizziness (1%)

Gastrointestinal: Diarrhea (2%), constipation (1%)

<1% (Limited to important or life-threatening): Abdominal discomfort, acne, agitation, agranulocytosis, allergic reaction, alopecia, anaphylaxis, angioedema, anorexia, anxiety, arrhythmia, arthralgia, AV block, bradycardia, bronchospasm, BUN/creatinine increased, cholestatic jaundice, confusion, decreased libido, depression, drowsiness, facial edema, fatigue, fever, flushing, hallucinations, injection site reactions, insomnia, interstitial pneumonia, jaundice, nausea, leukopenia, liver function tests increased, muscle cramps, palpitation, pancytopenia, paresthesia, proteinuria, pruritus, rash, seizure, somnolence, Stevens-Johnson syndrome, tinnitus, thrombocytopenia, toxic epidermal necrolysis, urticaria, vomiting, weakness, xerostomia

Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): H2-Antagonists may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole; Voriconazole. *Risk D: Consider therapy modification*

Atazanavir: H2-Antagonists may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Cefpodoxime: H2-Antagonists may decrease the absorption of Cefpodoxime. Separate oral doses by at least 2 hours. *Risk C: Monitor therapy*

Cefuroxime: H2-Antagonists may decrease the absorption of Cefuroxime. Separate oral doses by at least 2 hours. *Risk C: Monitor therapy*

Dasatinib: H2-Antagonists may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Erlotinib: H2-Antagonists may decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Fosamprenavir: H2-Antagonists may decrease the serum concentration of Fosamprenavir. Cimetidine may also inhibit the metabolism of the active metabolite amprenavir, making its effects on fosamprenavir/amprenavir concentrations difficult to predict. *Risk C: Monitor therapy*

Iron Salts: H2-Antagonists may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk C: Monitor therapy*

Saquinavir: H2-Antagonists may increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause gastric mucosal irritation).

Food: Famotidine bioavailability may be increased if taken with food.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other medications patient may be taking (eg, anything that may affect neuromuscular transmission). Evaluate patient response on a regular basis throughout therapy. I.V.: See Administration specifics. Teach patient proper use (eg, timing of administration when used concurrently with other medications), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take exactly as directed; do not alter dose or frequency. OTC: Follow package instructions; do not use for more than 14 days unless recommended by prescriber. May cause drowsiness or dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known); constipation (increased exercise, fluids, fruit, or fiber may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report acute headache, unresolved constipation or diarrhea, palpitations, black tarry stools, abdominal pain, rash, worsening of condition being treated, or recurrence of symptoms after therapy is completed. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gelcap:

Pepcid® AC: 10 mg

Infusion [premixed in NS]: 20 mg (50 mL)

Pepcid®: 20 mg (50 mL)

Injection, solution: 10 mg/mL (4 mL, 20 mL, 50 mL)

Pepcid®: 10 mg/mL (20 mL) [contains benzyl alcohol]

Injection, solution [preservative free]: 10 mg/mL (2 mL)

Pepcid®: 10 mg/mL (2 mL)

Powder for oral suspension:

Pepcid®: 40 mg/5 mL (50 mL) [contains sodium benzoate; cherry-banana-mint flavor]

Tablet: 10 mg [OTC], 20 mg, 40 mg

Pepcid®: 20 mg, 40 mg

Pepcid® AC: 10 mg, 20 mg

Pepcid® AC Maximum Strength: 20 mg

Generic Available Yes: Injection, tablet

Manufacturer Merck & Co

Pricing: U.S. (www.drugstore.com)

Suspension (reconstituted) (Pepcid)

40 mg/5 mL (50): $123.88

Tablets (Famotidine)

20 mg (30): $19.99

40 mg (90): $18.00

Tablets (Pepcid)

20 mg (30): $59.99

40 mg (30): $105.99

Tablets (Pepcid AC)

10 mg (6): $8.99

10 mg (12): $7.99

10 mg (18): $7.99

10 mg (30): $9.35

Mechanism of Action Competitive inhibition of histamine at H_2 receptors of the gastric parietal cells, which inhibits gastric acid secretion

Pharmacodynamics/Kinetics

Onset of action: GI: Oral: Within 1-3 hour; I.V.: 30 minutes

Duration: 10-12 hours

Protein binding: 15% to 20%

Bioavailability: Oral: 40% to 45%

Half-life elimination: Injection, oral suspension, tablet: 2.5-3.5 hours; prolonged with renal impairment; Oliguria: >20 hours

Time to peak, serum: Oral: ~1-3 hours

Excretion: Urine (25% to 30% [oral], 65% to 70% [I.V.] as unchanged drug)

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness or drowsiness; may rarely cause insomnia

Mental Health: Effects on Psychiatric Treatment May cause agranulocytosis; use caution with clozapine and carbamazepine

Anesthesia and Critical Care Concerns/Other Considerations The 2008 Surviving Sepsis Campaign guidelines recommend that stress ulcer prophylaxis using an H_2 blocker (Grade 1A) or proton pump inhibitor (Grade 1B) be given to patients with severe sepsis to prevent upper GI bleed. Benefit of prevention of upper GI bleed must be weighed against potential effect of increased stomach pH on development of ventilator-associated pneumonia.

References

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Dellinger RP, Levy MM, Carlet JM, et al, “Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008,” *Intensive Care Med*, 2008, 34(1): 17-60. Available at http://www.survivingsepsis.org/system/files/images/2008_20International_20SSC_20Guidelines_1_.pdf[PubMed 18058085]

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Fish DN, “Safety and Cost of Rapid I.V. Injection of Famotidine in Critically Ill Patients,” *Am J Health Syst Pharm*, 1995, 52(17):1889-94. [PubMed 8528851]

Gottlieb S, Decktor DL, Eckert JM, et al, “Efficacy and Tolerability of Famotidine in Preventing Heartburn and Related Symptoms of Upper Gastrointestinal Discomfort,” *Am J Ther*, 1995, 2:314-9. [PubMed 11850669]

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James LP and Kearns GL, “Pharmacokinetics and Pharmacodynamics of Famotidine in Paediatric Patients,” *Clin Pharmacokinet*, 1996, 31(2):103-10. [PubMed 8853932]

Lipsy RJ and Freeman CD, “Hemodynamic Effects of Intravenous Famotidine in Critically Ill Patients,” *Pharmacotherapy*,1995, 15(1):48-51. [PubMed 7739945]

Simon TJ, Berlin RG, Gardner AH, et al, “Self-Directed Treatment of Intermittent Heartburn: A Randomized, Multicenter, Double-Blind, Placebo-Controlled Evaluation of Antacid and Low Doses of an H_2-Receptor Antagonist (Famotidine),” *Am J Ther*, 1995, 2:304-13. [PubMed 11850668]

Treem WR, Davis PM, and Hyams JS, “Suppression of Gastric Acid Secretion by Intravenous Administration of Famotidine in Children,” *J Pediatr*, 1991, 118(5):812-6.[PubMed 2019939]

International Brand Names Agufam (TH); Androtin (MX); Antidine (ID); Antiflam (UY); Antodine (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Apo-Famo (PL); Apo-Famotidine (NZ); Arfam (AU); Asid (BR); Ausfam (AU); Bestidine (KP); Cepal (GR); Denufam (ID); Durater (MX); Facidex (MX); Fadin (TW); Fadine (AE, BH, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Fadul (DE); Fagastin (PL); Famidyna (PL); Famo (IL); Famoc (SG); Famocid (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Famodar (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Famodil (IT); Famodine (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PK, QA, SA, SY, YE); Famogard (RU); Famogast (PL); Famohexal (AU); Famonerton (DE); Famopsin (MY, TH); Famosan (BG, CZ, EE, HR); Famosia (TH); Famotidine (PL); Famotin (SG); Famowal (IN); Famox (HK, NZ, TW); Fararidin (KP); Farotin (KP); Ferotine (KP); Fibonel (CN); Fudone (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Fuweidin (TW); Gasafe (TW); Gaster (CL, ID, JP, TW); Gastren (PY); Gastridin (IT); Gastro (IL); Gastrodomina (BF, BJ, CI, ET, GH, GM, GN, HU, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Gastrum (CO); H2 Bloc (PH); Hista-Bloc (PH); Ifamul (ID); Logos (ZA); Ludex (MX); Motiax (IT); Motid (PH); Motidine (HK, SG); Novo-Famotidine (PL); Pamacid (AU); Pepcid (BB, BM, BS, BZ, GB, GY, IE, JM, NL, SE, SR, TT); Pepcid AC (CH); Pepcidac (FR); Pepcidin (DK, FI, NL, NO, SE, TR); Pepcidin Rapitab (NO); Pepcidina (PT); Pepcidine (AT, AU, BE, CH, HK, LU, MX, MY, PE, PH, RU); Pepdif (TR); Pepdine (BF, BJ, CI, ET, FR, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Pepfamin (TH); Peptan (GR); Peptifam (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Peptimox (AU); Peptodin (PH); Pepzan (MY, NZ); Promocid (ID); Purifam (ID); Quamatel (HU, PL); Quamtel (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Rogasti (IL); Sedanium-R (GR); Stadin (KP); Stomax (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Tamin (ES); Topcid (IN); Ulcatif (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ulcedine (HK); Ulcefam (PH); Ulcelac (AR); Ulcenol (VE); Ulceran (AE, BG, BH, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SG, SY, YE); Ulcofam (TH); Ulfagel (EC); Ulfam (ID); Ulfamid (HR, HU, PL); Ulmo (ID); Voker (MY); Weimok (TW)

FAMTX

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Gastric Cancer]

Regimen UseGastric cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Methotrexate: I.V.: 1500 mg/m^2 day 1

[total dose/cycle = 1500 mg/m^2]

Fluorouracil: I.V.: 1500 mg/m^2 (1 hour after methotrexate) day 1

[total dose/cycle = 1500 mg/m^2]

Leucovorin: Oral: 15 mg/m^2 every 6 hours for 48 hours (start 24 hours after methotrexate) day 2

[total dose/cycle = 120 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 15

[total dose/cycle = 30 mg/m^2]

Repeat cycle every 28 days

Variation 2:

Methotrexate: I.V.: 1500 mg/m^2 day 1

[total dose/cycle = 1500 mg/m^2]

Fluorouracil: I.V.: 1500 mg/m^2 (1 hour after methotrexate) day 1

[total dose/cycle = 1500 mg/m^2]

Leucovorin: Oral: 30 mg/m^2 every 6 hours for 8 doses (start 24 hours after methotrexate)

[total dose/cycle = 240 mg/m^2]

followed by Oral: 30 mg/m^2 every 6 hours for 8 more doses if 24-hour methotrexate level ≥2.5 mol/L

[total cumulative dose/cycle = 480 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 15

[total dose/cycle = 30 mg/m^2]

Repeat cycle every 28 days

Variation 3:

Methotrexate: I.V.: 1000 mg/m^2 day 1

[total dose/cycle = 1000 mg/m^2]

Fluorouracil: I.V.: 1500 mg/m^2 (1 hour after methotrexate) day 1

[total dose/cycle = 1500 mg/m^2]

Leucovorin: Oral: 15 mg every 6 hours for 8 doses (start 24 hours after methotrexate)

[total dose/cycle = 120 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 15

[total dose/cycle = 30 mg/m^2]

Repeat cycle every 28 days

References

Variation 1:

Kelsen D, Atiq O, Salz L, et al, “FAMTX (Fluorouracil, Methotrexate, Adriamycin®) Is as Effective and Less Toxic Than EAP (Etoposide, Adriamycin®, Cisplatin): A Random Assignment Trial in Gastric Cancer,” *Proc Am Soc Clin Oncol*, 1991, 10:137.

Variation 2:

Wils J, Bleiberg H, Dalesio O, et al, “An EORTC Gastrointestinal Group Evaluation of the Combination of Sequential Methotrexate and 5-Fluorouracil, Combined With Adriamycin in Advanced Measurable Gastric Cancer,” *J Clin Oncol*, 1986, 4(12):1799-803.[PubMed 3783204]

Variation 3:

Murad AM, Santiago FF, Petroianu A, et al, “Modified Therapy With 5-Fluorouracil, Doxorubicin, and Methotrexate in Advanced Gastric Cancer,” *Cancer*, 1993, 72(1):37-41. [PubMed 8508427]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Gastric Cancer

Regimen UseGastric cancer

Regimen

Fluorouracil: I.V.: 300 mg/m^2/day days 1 to 5

[total dose/cycle = 1500 mg/m^2]

Doxorubicin: I.V.: 40 mg/m^2 day 1

[total dose/cycle = 40 mg/m^2]

Cisplatin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 5 weeks

References

Cullinan SA, Moertel CG, Wieand HS, et al, âControlled Evaluation of Three Drug Combination Regimens Versus Fluorouracil Alone for the Therapy of Advanced Gastric Cancer. North Central Cancer Treatment Group,â *J Clin Oncol*, 1994, 12(2):412-6. [PubMed 8113849]

Fat Emulsion

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(fat e MUL shun)

U.S. Brand NamesIntralipid®; Liposyn® II; Liposyn® III

Canadian Brand NamesIntralipid®; Liposyn® II

Pharmacologic CategoryCaloric Agent

Use: Labeled IndicationsSource of calories and essential fatty acids for patients requiring parenteral nutrition of extended duration; prevention and treatment of essential fatty acid deficiency (EFAD)

Use: Unlabeled/InvestigationalLocal anesthetic-induced cardiac arrest unresponsive to conventional resuscitation

Dosing: Adults

Caloric source: I.V.: Initial dose: 1 g/kg/day, increase by 0.5-1 g/kg/day to a maximum of 2.5-3 g/kg/day

Prevention of essential fatty acid deficiency (EFAD): I.V.: Administer 8% to 10% of total caloric intake as fat emulsion (may be higher in stressed patients with EFAD); may be given 2-3 times weekly to meet essential fatty acid requirements

Local anesthetic toxicity (unlabeled use): 20%: 1.5 mL/kg administered over 1 minute, followed immediately by an infusion of 0.25 mL/kg/minute. Continue chest compressions (lipid must circulate). Repeat bolus every 3-5 minutes up to 3 mL/kg total dose until circulation restored. Continue infusion until hemodynamic stability is restored. Increase the infusion rate to 0.5 mL/kg/minute if BP declines. A maximum total dose of 8 mL/kg is recommended.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Caloric source: I.V.:

Premature infants: Initial dose: 0.25-0.5 g/kg/day, increase by 0.25-0.5 g/kg/day to a maximum of 3 g/kg/day depending on needs/nutritional goals; limit to 1 g/kg/day if on phototherapy; should be administered over 24 hours (A.S.P.E.N. guidelines)

Infants and Children: Initial dose: 0.5-1 g/kg/day, increase by 0.5 g/kg/day to a maximum of 3 g/kg/day depending on needs/nutritional goals; may administer over 24 hours (A.S.P.E.N. guidelines)

Note: Monitor triglycerides while receiving intralipids. If serum triglyceride levels >200 mg/dL, stop infusion and restart at 0.5-1g/kg/day. Intravenous heparin (1 unit/mL of parenteral nutrition) may enhance the clearance of lipid emulsions.

Administration: I.VCan be administered in a peripheral line or by central venous infusion. At the onset of therapy, the patient should be observed for any immediate allergic reactions such as dyspnea, cyanosis, and fever.

Children: Infuse for 10-15 minutes at a slower rate. Infuse 10% at ≤0.1 mL/minute; can increase to 1 mL/kg/hour if tolerated. Infuse 20% at ≤0.05 mL/minute; can increase to 0.5 mL/kg/hour if tolerated. **Note:** Premature and/or septic infants may need to reduce infusion rate. Do not exceed 1 g fat/kg in 4 hours in this population.

Adults: Infuse for 15-30 minutes at a slower rate. Infuse 10% at 1 mL/minute. If no untoward effects, can double rate. Infuse 20% at 0.5 mL/minute initially; can double rate if tolerated.

Administration: I.V. DetailCan be administered in a peripheral line or by central venous infusion. At the onset of therapy, the patient should be observed for any immediate allergic reactions such as dyspnea, cyanosis, and fever. Change tubing after each infusion. May be simultaneously infused with amino acid dextrose mixtures by means of Y-connector located near infusion site or administered in total nutrient mixtures (3-in-1) with amino acids, dextrose, and other nutrients. Hang fat emulsion higher than other fluids (has low specific gravity and could run up into other lines). Infuse via pump using either peripheral or central venous line.

Intralipid®, Liposyn® II: Do not use <1.2 micron filter

Liposyn® III: Do not use a filter.

pH: 6-9

Osmolality: 260-292 mOsmol/L

Dietary Considerations

Phosphorus: ~1.5 mMol /100 mL of emulsion

Caloric content: 10% fat emulsion = 1.1 kcal/mL; 20% fat emulsion = 2 kcal/mL; 30% fat emulsion = 3 kcal/mL

Fat emulsion should not exceed 60% of the total daily calories.

StorageDo not freeze. Do not store partly used containers; fat emulsion can support the growth of various organisms. Do not use if emulsion appears to be oiling out.

Intralipid®: Store below 25°C (77°F).

Liposyn®: Store below 30°C (86°F).

ContraindicationsHypersensitivity to fat emulsion or any component of the formulation; severe egg or legume (soybean) allergies; pathologic hyperlipidemia, lipoid nephrosis, acute pancreatitis associated with hyperlipemia

Warnings/Precautions

Boxed warnings:

- Pediatrics: See “Special populations” below.

Disease-related concerns:

- Anemia: Use with caution in patients with anemia.
- Bleeding disorders: Use with caution in patients with bleeding disorders.
- Fat embolism: Use with caution in patients who may be at danger for fat embolism.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Pancreatitis: Use with caution in patients with pancreatitis without hyperlipidemia; ensure triglyceride levels remain <400 mg/dL.
- Respiratory disease: Use with caution in patients with respiratory disease.

Special populations:

- Pediatrics: Premature and small for gestational age infants clear intravenous fat emulsion poorly; serious and sometimes fatal reactions have occurred. **[U.S. Boxed Warning]: Strict adherence to proper infusion rates, dosing, and monitoring are necessary;** infusion rate should not exceed 1g fat/kg in 4 hours; strict monitoring of metabolic tolerance and elimination of infused fat from the circulation must occur. To avoid hyperlipidemia and/or fat deposition, do not exceed recommended daily doses.

Dosage form specific issues:

- Aluminum: Some formulations may contain aluminum which may accumulate following prolonged administration in renally-impaired patients. Due to immature renal function, premature neonates are at higher risk of accumulation/toxicity from aluminum.

Other warnings/precautions:

- Monitoring: Monitor triglyceride levels prior to next dose. Ensure clearance of lipid solution.
- Three-in-one mixtures: Lipid emulsion in a three-in-one mixture may obscure the presence of a precipitate; follow compounding guidelines, especially for calcium and phosphate additions.

Pregnancy Risk FactorC

Pregnancy Considerations

Reproductive studies have not been conducted. The A.S.P.E.N. guidelines for parenteral and enteral nutrition state that intravenous fat emulsion may be used safely in pregnant women to provide calories and prevent essential fatty acid deficiency.

LactationExcretion in breast milk unknown/compatible

Adverse Reactions<1%: Allergic reactions, back pain, brown pigment deposition in the reticuloendothelial system (“intravenous fat pigment”), chest pain, cholestasis, cyanosis, diaphoresis, dizziness, dyspnea, flushing, headache, hepatomegaly, hypercoagulability, hyperlipidemia, infusion site irritation, jaundice, leukopenia, liver function tests increased, nausea, pancreatitis, overloading syndrome (focal seizures, fever, leukocytosis, hepatomegaly, splenomegaly, shock), thrombocytopenia, vomiting

Monitoring ParametersMonitor line site for signs and symptoms of infection.

Monitor liver function tests periodically. Monitor triglycerides before initiation of lipid therapy and at least weekly during therapy; monitor especially closely in premature infants, septic infants, and patients with pancreatitis or liver disease.

Neonates: Frequent (some advise daily) platelet counts should be performed in neonatal patients receiving parenteral lipids.

Nursing: Physical Assessment/MonitoringAssess for allergy to eggs prior to initiating therapy (pruritic urticaria can occur in patients allergic to eggs). Inspect emulsion before administering. Do not administer if oil separation or oiliness is noted. Monitor closely for allergic reactions, fluid overload, thrombosis or sepsis.

Monitoring: Lab TestsMonitor liver function tests periodically. Monitor triglycerides before initiation of lipid therapy and at least weekly during therapy; monitor especially closely in premature infants, septic infants, and patients with pancreatitis or liver disease.

Neonates: Frequent (some advise daily) platelet counts should be performed in neonatal patients receiving parenteral lipids.

Patient EducationReport pain at infusion site, respiratory difficulty, chest pain, calf pain, or excessive sweating. **Pregnancy precaution:** Inform prescriber if you are pregnant

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, emulsion:

Intralipid®: 20% (100 mL, 250 mL, 500 mL, 1000 mL) [contains aluminum, egg yolk phospholipids, and soybean oil]; 30% (500 mL) [contains aluminum, egg yolk phospholipids, and soybean oil]

Liposyn® II: 10% (500 mL) [contains aluminum, egg yolk phospholipids, safflower oil, and soybean oil]; 20% (500 mL) [contains aluminum, egg yolk phospholipids, safflower oil, and soybean oil]

Liposyn® III: 10% (200 mL, 500 mL) [contains aluminum, egg yolk phospholipids, and soybean oil] ; 20% (200 mL, 500 mL) [contains aluminum, egg yolk phospholipids, and soybean oil]; 30% (500 mL) [contains aluminum, egg yolk phospholipids, and soybean oil]

Generic Available No

Mechanism of Action Fat emulsion is metabolized and utilized as an energy source; provides the essential fatty acids, linoleic acid, and alpha linolenic acid necessary for normal structure and function of cell membranes; in local anesthetic toxicity, lipid emulsion probably extracts lipophilic local anesthesia from cardiac muscle

Pharmacodynamics/Kinetics

Metabolism: Undergoes lipolysis to free fatty acids which are utilized by reticuloendothelial cells

Half-life elimination: 0.5-1 hour

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness

Mental Health: Effects on Psychiatric Treatment None reported

Anesthesia and Critical Care Concerns/Other Considerations

Local anesthetic toxicity: Cardiac arrest: Lipid infusion has been used in animal studies and several human cases (Bupivacaine: Rosenblatt, 2006; Levobupivacaine: Foxall, 2007; Ropivacaine: Litz, 2006) where cardiovascular toxicity, unresponsive to conventional resuscitation, resulted. Additional information is available at http://www.lipidrescue.org.

Index Terms Intravenous Fat Emulsion

References

ASPEN Board of Directors and the Clinical Guidelines Task Force, "Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients," *JPEN J Parenter Enteral Nutr*, 2002, 26(1 Suppl):1-138.[PubMed 11841046]

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Foxall G, McCahon R, Lamb J, et al, "Levobupivacaine-Induced Seizures and Cardiovascular Collapse Treated With Intralipid," *Anaesthesia*, 2007, 62(5):516-8.[PubMed 17448066]

Haumont D, Richelle M, Deckelbaum RJ, et al, "Effect of Liposomal Content of Lipid Emulsions of Plasma Lipid Concentrations in Low Birth Weight Infants Receiving Parenteral Nutrition," *J Pediatr*, 1992, 121(5 Pt 1):759-63. [PubMed 1432430]

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Mirtallo J, Canada T, Johnson D, et al, "Safe Practices for Parenteral Nutrition. Task Force for the Revision of Safe Practices for Parenteral Nutrition," *JPEN J Parenter Enteral Nutr*, 2004, 28(6):S39-70.[PubMed 15568296]

Neuzil J, Darlow BA, Inder TE, et al, "Oxidation of Parenteral Lipid Emulsion by Ambient and Phototherapy Lights: Potential Toxicity of Routine Parenteral Feeding," *J Pediatr*, 1995, 126(5 Pt 1):785-90.[PubMed 7752007]

Rosenblatt MA, Abel M, Fischer GW, et al, "Successful Use of a 20% Lipid Emulsion to Resuscitate a Patient After a Presumed Bupivacaine-Related Cardiac Arrest," *Anesthesiology*, 2006, 105(1):217-8.[PubMed 16810015]

Weinberg GL, Ripper R, Murphy P, et al, "Lipid Infusion Accelerates Removal of Bupivacaine and Recovery From Bupivacaine Toxicity in the Isolated Rat Heart," *Reg Anesth Pain Med*, 2006, 31(4):296-303.[PubMed 16857549]

International Brand Names Intrafat (TW); Intralipid (AE, BG, BH, CY, EG, HK, ID, IL, IN, IQ, IR, JO, KW, LB, LY, MY, OM, PH, QA, RU, SA, SY, TH, TR, TW, YE); Intralipos (HK, KP, MY, TH, TW); Lipofundin-S (MY, TW); Liposyn II (MX, PE); Lipovenos (CL, PH, TH)

FEC

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

Regimen

Fluorouracil: I.V.: 500 mg/m^2 day 1

[total dose/cycle = 500 mg/m^2]

Cyclophosphamide: I.V.: 500 mg/m^2 day 1

[total dose/cycle = 500 mg/m^2]

Epirubicin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21 days

References

Bonneterre J, Roché H, Bremond A, et al, “Results of a Randomized Trial of Adjuvant Chemotherapy With FEC 50 vs FEC 100 in High Risk Node-Positive Breast Cancer Patients,” *Proc Am Soc Clin Oncol*, 1998, 17:124a (abstract 473).[PubMed 15837983]

Felbamate

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - February 2008

The U.S. Food and Drug Administration (FDA) is informing healthcare professionals of an increased risk of suicidality (suicidal behavior or ideation) observed from analysis of clinical studies using various antiepileptic medications compared to placebo. The analysis was performed on 199 placebo-controlled studies involving 43,892 patients (27,863 treated patients versus 16,029 placebo patients) aged ≥5 years receiving one of the following 11 drugs: carbamazepine (Carbatrol®, Equetro™, Tegretol®, Tegretol® XR), felbamate (Felbatol®), gabapentin (Neurontin®), lamotrigine (Lamictal®), levetiracetam (Keppra®), oxcarbazepine (Trileptal®), pregabalin (Lyrica®), tiagabine (Gabitril®), topiramate (Topamax®), valproate (Depakote®, Depakote® ER, Depakene®, Depacon®), and zonisamide (Zonegran®). Studies examined medication efficacy in a variety of disorders, including epilepsy, psychiatric disorders (eg, depression, bipolar disorder), and other conditions (eg, migraine, neuropathic pain). According to the FDA, the results revealed a statistically significant increased risk of suicidality in 0.43% treated patients compared to 0.22% placebo patients, or an estimated 2.1 per 1000 (95% CI: 0.7, 4.2) more patients in the treated groups relative to placebo. This increased risk was reported anywhere from 1 week of therapy through 24 weeks. However, most trials were ≤24 weeks duration and the risk of suicide extending beyond 24 weeks is currently unknown. The relative risk of suicidal behavior or ideation in the treated patients was higher for patients with epilepsy (RR=3.6) compared to patients treated for psychiatric (RR=1.6) or other conditions (RR=2.3). Overall, the incidence of suicidal behavior or ideation occurred consistently across all demographic subgroups and with each of the drugs studied. Of note, four patients receiving an antiepileptic committed suicide relative to none in the placebo groups.

Forthcoming product labeling changes are likely to extend to all antiepileptic drugs and not limited to the drugs used in the studies, pending discussions scheduled for the upcoming advisory committee meeting. Healthcare professionals and family members/caregivers are encouraged to monitor patients receiving any antiepileptic medication for signs/symptoms of suicidality (eg, anxiety, depression, behavior changes). Patients should not stop taking their antiepileptic therapy unless advised by a healthcare professional.

Additional information can be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Pronunciation(FEL ba mate)

U.S. Brand NamesFelbatol®

Pharmacologic CategoryAnticonvulsant, Miscellaneous

Use: Labeled IndicationsNot as a first-line antiepileptic treatment; only in those patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use. Patient must be fully advised of risk and provide signed written informed consent. Felbamate can be used as either monotherapy or adjunctive therapy in the treatment of partial seizures (with and without generalization) and in adults with epilepsy. Used as adjunctive therapy in the treatment of partial and generalized seizures associated with Lennox-Gastaut syndrome in children.

Dosing: Adults

Anticonvulsant, monotherapy: Oral:

Initial: 1200 mg/day in divided doses 3 or 4 times/day; titrate previously untreated patients under close clinical supervision, increasing the dosage in 600 mg increments every 2 weeks to 2400 mg/day based on clinical response and thereafter to 3600 mg/day as clinically indicated

Conversion to monotherapy: Initiate at 1200 mg/day in divided doses 3 or 4 times/day, reduce the dosage of the concomitant anticonvulsant(s) by 20% to 33% at the initiation of felbamate therapy; at week 2, increase the felbamate dosage to 2400 mg/day while reducing the dosage of the other anticonvulsant(s) up to an additional 33% of their original dosage; at week 3, increase the felbamate dosage up to 3600 mg/day and continue to reduce the dosage of the other anticonvulsant(s) as clinically indicated

Anticonvulsant, adjunctive therapy: Oral: Initial: 1200 mg/day in divided doses 3 or 4 times/day; may increase once per week by 1200 mg/day increments up to 3600 mg/day in divided doses 3 or 4 times/day.

Note: Dose of concomitant carbamazepine, phenobarbital, phenytoin, or valproic acid should be decreased by 20% to 33% when initiating felbamate therapy. Further dosage reductions may be necessary as dose of felbamate is increased.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Anticonvulsant, monotherapy: Oral: Children >14 years: Refer to adult dosing.

Adjunctive therapy: Oral:

Children 2-14 years with Lennox-Gastaut syndrome: Initial: 15 mg/kg/day in divided doses 3 or 4 times/day; may increase once per week by 15 mg/kg/day increments up to 45 mg/kg/day in divided doses 3 or 4 times/day.

Children >14 years: Refer to adult dosing.

Note: Dose of concomitant carbamazepine, phenobarbital, phenytoin, or valproic acid should be decreased by 20% to 33% when initiating felbamate therapy. Further dosage reductions may be necessary as dose of felbamate is increased.

Dosing: Renal ImpairmentUse caution; reduce initial and maintenance doses by 50% (half-life prolonged by 9-15 hours)

Administration: OralAdminister on an empty stomach for best absorption.

Dietary ConsiderationsMay be taken without regard to meals.

StorageStore in tightly closed container at controlled room temperature of 20°C to 25°C (68°F to 77°F).

RestrictionsA patient “informed consent” form should be completed and signed by the patient and physician. Copies are available from Wallace Pharmaceuticals by calling 800-526-3840 or 609-655-6147.

ContraindicationsHypersensitivity to felbamate any component of the formulation; or known sensitivity to other carbamates; history of any blood dyscrasia; hepatic dysfunction

Warnings/Precautions

Boxed warnings:

- Aplastic anemia: See “Concerns related to adverse effects” below.
- Hepatic failure: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Aplastic anemia: **[U.S. Boxed Warning]: Felbamate is associated with a significant increased risk of aplastic anemia.** Risk may be more than 100 fold greater than in untreated population. Current estimates of fatality are 20% to 30%, but higher rates (up to 70%) have been reported in the past. Aplastic anemia can develop at any point during therapy and for an unknown period of time after discontinuation of therapy. It is not known if dose, duration therapy, or concomitant medication use affects risk. Routine blood monitoring may be helpful in detecting hematologic changes before any clinical onset of signs/symptoms of the disease, however, aplastic anemia often develops without any prior indication or warnings. Discontinue use if any evidence of bone-marrow suppression occurs.

- Hepatic failure: **[U.S. Boxed Warning]: Has been associated with rare cases of hepatic failure (estimated >6 cases per 75,000 patients per year).** Of the cases reported in the literature, 67% have resulted in fatality or liver transplant. Onset may or may not be preceded by prodromal symptoms. It is not known whether dose, duration of therapy, or concomitant medication use affects risk. Monitoring of serum transaminases has not been demonstrated to prevent serious hepatic injury, however, early diagnosis and drug withdrawal may improve the likelihood of recovery. Obtain baseline transaminase levels and periodically thereafter; discontinue use if transaminase levels increase to ≥2 times the upper limit of normal or with signs/symptoms suggesting hepatic failure. Therapy should not be initiated or reintroduced in patients with evidence of hepatic damage or who discontinue use for any reason.

Disease-related concerns:

- Renal impairment: Use with caution in renal impairment; dose adjustment recommended.

Other warnings/precautions:

- Patient education: Patients should be thoroughly educated on the signs/symptoms of aplastic anemia and of hepatic failure prior to starting therapy. The patient or parent/guardian of the patient must provide written informed consent documenting the discussion of risks involved with therapy.

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsClinical studies have not included large numbers of patients >65 years of age. Due to decreased hepatic and renal function, dosing should start at the lower end of the dosage range.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Postmarketing case reports in humans include fetal death, genital malformation, anencephaly, encephalocele, and placental disorder.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsRat studies show a decreased weight and increased death in nursing pups. Felbamate has been detected in human milk. Adverse effects in human infants is unknown.

Adverse Reactions

>10%:

Central nervous system: Somnolence (children 48%; adults 19%), headache (children 7%; adults 7% to 37%), fever (children 23%; adults 3%), dizziness (18%), insomnia (9% to 18%), fatigue (7% to 17%), nervousness (7% to 16%)

Dermatologic: Purpura (children 13%)

Gastrointestinal: Anorexia (children 55%; adults 19%), vomiting (children 39%; adults 9% to 17%), nausea (children 7%; adults 34%), constipation (7% to 13%), dyspepsia (7% to 12%)

Respiratory: Upper respiratory infection (children 45%; adults 5% to 9%)

1% to 10%:

Cardiovascular: Chest pain (3%), facial edema (3%), palpitation (≥1%), tachycardia (≥1%)

Central nervous system: Nervousness (7% to 16%), abnormal thinking (7%), emotional lability (children 7%), ataxia (4% to 7%), depression (5%), anxiety (5%), stupor (3%), malaise ≥1%), agitation (≥1%) psychological disturbances (≥1%), aggressive reaction (≥1%), euphoria (≤1%), hallucination (≤1%), migraine (≤1%), suicide attempt (≤1%)

Dermatologic: Skin rash (children 10%; adults 3% to 4%), acne (3%), pruritus (≥1%), bullous eruption (≤1%), urticaria (≤1%)

Endocrine and metabolic: Hypophosphatemia (≤1% to 3%), intramenstrual bleeding (3%), hypokalemia (≤1%), hyponatremia (≤1%)

Gastrointestinal: Hiccup (children 10%), weight loss (3% to 7%), taste perversion (6%), diarrhea (5%), abdominal pain (5%), xerostomia (3%), weight gain (≥1%), appetite increased (≤1%), esophagitis (≤1%)

Genitourinary: Urinary tract infection (3%)

Hematologic: Leukopenia (1% to 7%), granulocytopenia (≤1%), lymphadenopathy (≤1%), leukocytosis (≤1%), thrombocytopenia (≤1%)

Hepatic: Liver function tests increased (1% to 4%), alkaline phosphatase increased (≤1%)

Neuromuscular & skeletal: Abnormal gait (children 10%; adults 5%), pain (children 7%), tremor (6%), paresthesia (4%), myalgia (3%), weakness (≥1%), dystonia (≤1%)

Ocular: Miosis (7%), diplopia (3% to 6%), abnormal vision (5%)

Otic: Otitis media (children 10%; adults 3%)

Respiratory: Pharyngitis (children 10%; adults 3%), cough (children 7%), rhinitis (7%), sinusitis (4%)

Miscellaneous: Flu-like syndrome (≥1%), lymphadenopathy (≥1%)

<1%, postmarketing, and/or case reports: Acute renal failure, agranulocytosis, allergic reaction, alopecia, anaphylactoid reaction, anemia, apathy, aplastic anemia, asthma exacerbation, atrial arrhythmia, atrial fibrillation, body odor, bradycardia, buccal mucous membrane swelling, cardiac arrest, cardiac failure, cerebrovascular disorder, cerebral edema, choreoathetosis, coagulation disorder, coma, concentration impaired, confusion, CPK increased, delusion, diaphoresis, DIC, dysphagia, dyspnea, dysarthria, dyskinesia, dysuria, embolism, encephalopathy, enteritis, eosinophilia, epistaxis, extrapyramidal disorder, fetal effects (anencephaly, death, encephalocele, genital malformations), flatulence, flushing, gastric ulcer, gastritis, gastroesophageal reflux, GI hemorrhage, gingival bleeding, glossitis, hematemesis, hematuria, hemianopsia, hemolytic anemia, Henoch-Schönlein vasculitis, hepatic failure, hepatitis, hepatorenal syndrome, hyperammonemia, hyper-/hypoglycemia, hyper-/hypotension, hypernatremia, hypocalcemia, hypomagnesemia, hypoxia, ileus, ischemic necrosis, jaundice, leukemia, lichen planus, livedo reticularis, manic reaction, mononeuritis, nephrosis, nystagmus, pancreatitis, pancytopenia, paralysis, paranoid reaction, peripheral ischemia, photosensitivity, platelet disorder, pleural effusion, pneumonitis, psychosis, pulmonary hemorrhage, rectal hemorrhage, renal function abnormal, respiratory depression, rhabdomyolysis, SIADH, Stevens-Johnson syndrome, sudden death, suicidal behavior/ideation, SVT, thrombophlebitis, torsade de pointes, toxic epidermal necrolysis, ulcerative stomatitis, urinary retention, urticaria, vaginal hemorrhage

Metabolism/Transport Effects

Substrate of CYP2E1 (minor), 3A4 (major); **Inhibits** CYP2C19 (weak); **Induces** CYP3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Barbiturates: Felbamate may increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Felbamate may decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Oral Contraceptive (Progestins): Felbamate may decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May increase the metabolism of Felbamate. Felbamate may increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Primidone: Felbamate may increase the serum concentration of Primidone. Specifically, the concentration of its metabolite, phenobarbital. *Risk C: Monitor therapy*

Valproic Acid: Felbamate may increase the serum concentration of Valproic Acid. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Food does not affect absorption.

Herb/Nutraceutical: Avoid evening primrose (seizure threshold decreased).

Monitoring ParametersMonitor serum levels of concomitant anticonvulsant therapy; obtain transaminases (AST, ALT) levels before initiation of therapy and periodically thereafter and bilirubin weekly. Hematologic evaluations before therapy begins, frequently during therapy, and for a significant period after discontinuation.

Reference RangeNot necessary to routinely monitor serum drug levels, since dose should be titrated to clinical response

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness (seizure activity, force, type, duration), laboratory values, and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Assess knowledge/teach patient safety and seizure precautions, appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsMonitor serum levels of concomitant anticonvulsant therapy; obtain transaminases (AST, ALT) levels before initiation of therapy and periodically thereafter and bilirubin weekly. Hematologic evaluations before therapy begins, frequently during therapy, and for a significant period after discontinuation.

Patient EducationTake exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); fever (especially in children), insomnia, fatigue, or nervousness; or nausea, vomiting, loss of appetite, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Wear identification of epileptic status and medications. Report CNS changes, mentation changes, suicide ideation, or changes in cognition; muscle cramping, weakness, tremors, changes in gait; persistent GI symptoms (cramping, constipation, vomiting, anorexia); rash or skin irritations; unusual bruising or bleeding (mouth, urine, stool); cough, runny nose, sore throat, or respiratory difficulty; or worsening of seizure activity or loss of seizure control. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, oral:

Felbatol®: 600 mg/5 mL (240 mL, 960 mL)

Tablet:

Felbatol®: 400 mg; 600 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Suspension (Felbatol)

600 mg/5 mL (237): $276.72

Tablets (Felbatol)

400 mg (90): $205.79

600 mg (90): $239.38

Mechanism of ActionMechanism of action is unknown but has properties in common with other marketed anticonvulsants; has weak inhibitory effects on GABA-receptor binding, benzodiazepine receptor binding, and is devoid of activity at the MK-801 receptor binding site of the NMDA receptor-ionophore complex.

Pharmacodynamics/Kinetics

Absorption: Rapid and almost complete; food has no effect upon the tablet's absorption

Distribution: V_d: 0.7-0.8 L/kg

Protein binding: 22% to 25%, primarily to albumin

Half-life elimination: 20-23 hours (average); prolonged in renal dysfunction

Time to peak, serum: 3-5 hours

Excretion: Urine (40% to 50% as unchanged drug, 40% as inactive metabolites)

Related Information

- Status Epilepticus

Pharmacotherapy PearlsMonotherapy has not been associated with gingival hyperplasia, impaired concentration, weight gain, or abnormal thinking. Because felbamate is the only drug shown effective in Lennox-Gastaut syndrome, it is considered an orphan drug for this indication.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and abnormal taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusAnxiety and dizziness are common; may cause drowsiness, insomnia, or depression

Mental Health: Effects on Psychiatric TreatmentCarbamazepine may decrease effects of felbamate; may increase effects of valproic acid

Anesthesia and Critical Care Concerns/Other ConsiderationsMonotherapy has not been associated with gingival hyperplasia, impaired concentration, weight gain, or abnormal thinking. Because felbamate is the only drug shown effective in Lennox-Gastaut syndrome, it is considered an orphan drug.

References

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Pellock JM, “Felbamate in Epilepsy Therapy: Evaluating the Risks,” *Drug Saf*, 1999, 21(3):225-39.[PubMed 10487399]

Perucca E, “Clinically Relevant Drug Interaction With Antiepileptic Drugs,” *Br J Clin Pharmacol*, 2005, 61(3):246-55.[PubMed 16487217]

International Brand NamesFelbamyl (AR); Taloxa (AT, BE, CH, CZ, DE, ES, FR, HN, HU, IT, LU, NL, NO, PL, PT, SE)

Felodipine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Plendil® may be confused with Isordil®, pindolol, Pletal®, Prilosec®, Prinivil®

Pronunciation (fe LOE di peen)

U.S. Brand Names Plendil®

Canadian Brand Names Plendil®; Renedil®

Pharmacologic Category Calcium Channel Blocker

Use: Labeled Indications Treatment of hypertension

Use: Unlabeled/Investigational Pediatric hypertension

Dosing: Adults Hypertension: Oral: 2.5-10 mg once daily; increase by 5 mg at 2-week intervals, as needed, to a maximum of 20 mg/day; usual dose range (JNC 7): 2.5-20 mg once daily.

Dosing: Elderly Oral: Initial 2.5 mg/day

Dosing: Pediatric Hypertension (unlabeled use): Oral: Initial: 2.5 mg once daily; maximum: 10 mg/day

Dosing: Hepatic Impairment Initial: 2.5 mg/day; monitor blood pressure

Administration: Oral Do not crush or chew extended release tablets; swallow whole.

Dietary Considerations Should be taken without food.

Contraindications Hypersensitivity to felodipine, any component of the formulation, or other calcium channel blocker

Allergy Considerations

- Calcium Channel Blocker, Dihydropyridine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Angina/MI: Increased angina and/or MI has occurred with initiation or dosage titration of dihydropyridine calcium channel blockers; reflex tachycardia may occur resulting in angina and/or MI in patients with obstructive coronary disease especially in the absence of concurrent beta-blockade.
- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition.
- Peripheral edema: The most common side effect is peripheral edema (dose dependent); occurs within 2-3 weeks of starting therapy.

Disease-related concerns:

- Aortic stenosis: Use with extreme caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.
- Heart failure: Use with caution in patients with heart failure. Safety and efficacy have not been established.
- Hepatic impairment: Use with caution in patients with hepatic impairment; may require lower starting dose.
- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

Special populations:

- Elderly: Initiate at a lower dose in the elderly.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Titration: Dosage titration should occur after 14 days on a given dose.

Geriatric Considerations Elderly may experience a greater hypotensive response. Constipation may be more of a problem in the elderly. Calcium channel blockers are no more effective in the elderly than other therapies; however, they do not cause significant CNS effects which is an advantage over some antihypertensive agents.

Pregnancy Risk Factor C

Pregnancy Considerations Potentially, calcium channel blockers may prolong labor. There are no adequate or well-controlled studies in pregnant women.

Lactation Excretion in breast milk unknown/not recommended

Adverse Reactions

>10%: Central nervous system: Headache (11% to 15%)

2% to 10%: Cardiovascular: Peripheral edema (2% to 17%), tachycardia (0.4% to 2.5%), flushing (4% to 7%)

<1% (Limited to important or life-threatening): Abdominal pain, acid regurgitation, anemia, angioedema, angina pectoris, anxiety disorders, arm pain, arrhythmia, arthralgia, back pain, bronchitis, chest pain, CHF, constipation, contusion, CVA, decreased libido, depression, diarrhea, dizziness, dry mouth, dyspnea, dysuria, epistaxis, erythema, facial edema, flatulence, flu-like illness, flushing, foot pain, gingival hyperplasia, gynecomastia, hip pain, hypotension, impotence, influenza, insomnia, irritability, knee pain, leg pain, leukocytoclastic vasculitis, MI, muscle cramps, myalgia, MI, nausea, nervousness, palpitation, paresthesia, pharyngitis, polyuria, premature beats, respiratory infection, sinusitis, somnolence, syncope, urinary frequency, urinary urgency, urticaria, visual disturbances, vomiting

Metabolism/Transport Effects **Substrate** of CYP3A4 (major); **Inhibits** CYP2C8 (moderate), 2C9 (weak), 2D6 (weak), 3A4 (weak)

Drug Interactions

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

CycloSPORINE: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk D: Consider therapy modification*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Increases felodipine's absorption; watch for a greater hypotensive effect.

Food: Increased therapeutic and vasodilator side effects, including severe hypotension and myocardial ischemia, may occur if felodipine is taken with grapefruit juice; avoid concurrent use. High-fat/carbohydrate meals will increase C_{max} by 60%; grapefruit juice will increase C_{max} by twofold.

Herb/Nutraceutical: St John's wort may decrease felodipine levels. Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Nursing: Physical Assessment/MonitoringUse caution in presence of heart failure. Assess potential for interactions with pharmacological agents or herbal products patient may be taking (eg, beta-blockers or other drugs that effect blood pressure). Assess for therapeutic effectiveness and signs/symptoms of adverse reactions at beginning of therapy, when changing dosage, and periodically throughout long-term therapy. When discontinuing, taper gradually (over 2 weeks). Teach patient proper use, possible side effects/interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed, without food. Avoid concurrent grapefruit juice and alcohol (may cause dangerous hypotension). Swallow whole, do not crush or chew. Do not alter dose or stop taking without consulting prescriber. May cause headache (consult prescriber for analgesic); nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased dietary bulk and fluids may help); or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report irregular heartbeat, chest pain or palpitations; persistent headache; vomiting; constipation; peripheral or facial swelling; weight gain >5 lb/week; dyspnea or respiratory changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, extended release: 2.5 mg, 5 mg, 10 mg

Plendil®: 2.5 mg, 5 mg, 10 mg

Generic AvailableYes

ManufacturerAstraZeneca Pharmaceuticals LP

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Felodipine)

2.5 mg (30): $37.99

5 mg (30): $38.99

10 mg (100): $183.98

Tablet, 24-hour (Plendil)

2.5 mg (30): $49.03

5 mg (30): $52.97

10 mg (30): $89.42

Mechanism of ActionInhibits calcium ions from entering the “slow channels” or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary vascular smooth muscle and coronary vasodilation; increases myocardial oxygen delivery in patients with vasospastic angina

Pharmacodynamics/Kinetics

Onset of action: Antihypertensive: 2-5 hours

Duration of antihypertensive effect: 24 hours

Absorption: 100%; Absolute: 20% due to first-pass effect

Protein binding: >99%

Metabolism: Hepatic; CYP3A4 substrate (major); extensive first-pass effect

Half-life elimination: Immediate release: 11-16 hours

Excretion: Urine (70% as metabolites); feces 10%

Related Information

- Calcium Channel Blockers

Pharmacotherapy PearlsFelodipine maintains renal and mesenteric blood flow during hemorrhagic shock in animals.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Gingival hyperplasia (fewer reports than other CCBs, resolves upon discontinuation, consultation with physician is suggested).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness; rarely may cause nervousness, insomnia, or depression

Mental Health: Effects on Psychiatric TreatmentCarbamazepine may decrease felodipine effect

Cardiovascular Considerations

Heart Failure: The V-HeFT III trial randomly assigned 450 male patients with chronic heart failure (on ACE Inhibitor and diuretic) to felodipine (5 mg twice daily) or placebo for an average of 18 months. After 3 month follow-up, the felodipine patients initially had an improvement in their LVEF and atrial natriuretic peptide, but those improvements did not persist. Felodipine prevented worsening of exercise tolerance and quality of life, but it was not significantly different from placebo until about 27 months into therapy. Mortality and hospitalization rates were similar between the groups. Peripheral edema occurred more frequently in the felodipine group. There is a general lack of benefit from use of felodipine in the treatment of chronic heart failure. The ACC/AHA 2005 Heart Failure Guidelines do not recommend the use of calcium channel blockers for chronic heart failure.

Hypertension: Felodipine alone or in combination with other agents is effective in the management of hypertension.

References

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Cohn JN, Ziesche S, Smith R, et al, “Effect of the Calcium Antagonist Felodipine as Supplementary Vasodilator Therapy in Patients With Chronic Heart Failure Treated With Enalapril: V-HeFT III. Vasodilator-Heart Failure Trial (V-HeFT) Study Group,” *Circulation*, 1997, 96(3):856-63. [PubMed 9264493]

Hunt SA, Abraham WT, Chin MH , et al, "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure)," available at http://www.acc.org/qualityandscience/clinical/guidelines/failure/update/index.pdf.

National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, “The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents,” *Pediatrics*, 2004, 114(2 Suppl):555-76.[PubMed 15286277]

Steele RM, Schuna AA, and Schreiber RT, “Calcium Antagonist-Induced Gingival Hyperplasia,” *Ann Intern Med*, 1994, 120(8):663-4.[PubMed 8135450]

International Brand NamesAGON SR (NZ); Decreapin SR (KP); Dilahex (PH); Dilofen ER (PH); Dilopin (KP); Fedil (TW); Feldin ER (KP); Felim (PH); Felo ER (NZ); Felocor (DE); Felocor Retardtab (DE); Feloday (IT); Felodur ER (AU); Felogamma Retard (DE); Felogard (HK, IN); Felopine-SR (TW); Feloten (TH); Felpin (TW); Fenodipine ER (KP); Fensel (ES); Flodil LP (FR); Hydac (FI, SE); Keydipin ER (KP); Lodil (KP); Lodipin ER (KP); Lodistad MR (PH); Modip (DE); Munobal (DE, MX, PH, VE); Munobal Retard (AT, DE); Nirmadil (ID); Penedil (IL); Perfudal (ES); Phelop (TW); Plendil (AE, AR, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CL, CR, CY, CZ, DK, DO, EC, EE, EG, ES, ET, FI, GB, GH, GM, GN, GR, GT, GY, HK, HN, HU, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, OM, PA, PE, PH, PK, PL, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SV, SY, TH, TN, TR, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Plendil Depottab (NO); Plendil ER (AU, PH); Plendil Retard (AT); Preslow (ES, PT); Prevex (IT); Renedil (BE, LU); Selepine (KP); Splendil (BR, CN, JP); Splendil ER (KP); Stapin ER (KP); Versant XR (PH)

Fenofibrate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

TriCor® may be confused with Tracleer®

Pronunciation(fen oh FYE brate)

U.S. Brand NamesAntara™; Fenoglide™; Lipofen™; Lofibra®; TriCor®; Triglide™

Canadian Brand NamesApo-Feno-Micro®; Apo-Fenofibrate®; Dom-Fenofibrate Supra; Gen-Fenofibrate Micro; Lipidil EZ®; Lipidil Micro®; Lipidil Supra®; Novo-Fenofibrate; Novo-Fenofibrate-S; Nu-Fenofibrate; PHL-Fenofibrate Supra; PMS-Fenofibrate Micro; PMS-Fenofibrate Supra; ratio-Fenofibrate MC; Sandoz Fenofibrate S; TriCor®

Pharmacologic CategoryAntilipemic Agent, Fibric Acid

Use: Labeled IndicationsAdjunct to dietary therapy for the treatment of adults with elevations of serum triglyceride levels (types IV and V hyperlipidemia); adjunct to dietary therapy for the reduction of low density lipoprotein cholesterol (LDL-C), total cholesterol (total-C), triglycerides, and apolipoprotein B (apo B) in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson types IIa and IIb)

Dosing: Adults

Hypertriglyceridemia: Oral Initial:

Antara™ (micronized): 43-130 mg/day; maximum dose: 130 mg/day

Fenoglide™: 40-120 mg/day; maximum dose: 120 mg/day

Lipofen™: 50-150 mg/day; maximum dose: 150 mg/day

Lofibra® (micronized): 67-200 mg/day with meals; maximum dose: 200 mg/day

Lofibra® (tablets): 54-160 mg/day; maximum dose: 160 mg/day

TriCor®: 48-145 mg/day; maximum dose: 145 mg/day

Triglide™: 50-160 mg/day; maximum dose: 160 mg/day

Hypercholesterolemia or mixed hyperlipidemia: Oral:

Antara™ (micronized): 130 mg/day

Fenoglide™: 120 mg/day

Lipofen™: 150 mg/day

Lofibra® (micronized): 200 mg/day

Lofibra® (tablets): 160 mg/day

TriCor®: 145 mg/day

Triglide™: 160 mg/day

Dosing: ElderlyOral: Initial:

Antara™ (micronized): 43 mg/day

Fenoglide™: Adjust dosage based on creatinine clearance

Lipofen™: 50 mg/day

Lofibra® (micronized): 67 mg/day

Lofibra® (tablets): 54 mg/day

TriCor®: Adjust dosage based on creatinine clearance

Triglide™: 50 mg/day

Dosing: Renal ImpairmentMonitor renal function and lipid panel before adjusting. Decrease dose or increase dosing interval for patients with renal failure: Initial:

Antara™ (micronized): 43 mg/day

Fenoglide™:

Cl_{cr} 31-80 mL/minute: 40 mg/day

Cl_{cr} ≤30 mL/minute: **Contraindicated**

Lipofen™: 50 mg/day

Lofibra® (micronized): 67 mg/day

Lofibra® (tablets): 54 mg/day

TriCor®:

Cl_{cr} 31-80 mL/minute: 48 mg/day

Cl_{cr} ≤30 mL/minute: **Contraindicated**

Triglide™: 50 mg/day

Calculations

- Creatinine Clearance: Adults

Administration: Oral6-8 weeks of therapy is required to determine efficacy.

Fenoglide™, Lofibra® (capsules [micronized] and tablets), Lipofen™: Administer with meals.

Antara™, TriCor®: May be administered with or without food.

Triglide™: Do not consume chipped or broken tablets. May be administered with or without food.

Dietary Considerations

Fenoglide™, Lofibra® (capsules [micronized] and tablets), Lipofen™: Take with meals.

Antara™, TriCor®, Triglide™: May be taken with or without food.

StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light and moisture. Store tablets in moisture-protective container.

ContraindicationsHypersensitivity to fenofibrate or any component of the formulation; hepatic dysfunction including primary biliary cirrhosis and unexplained persistent liver function abnormalities; severe renal dysfunction; pre-existing gallbladder disease; breast-feeding (only Fenoglide™)

Allergy Considerations

- Fibric Acid Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cholelithiasis: May cause cholelithiasis.
- Hemogloblin/hematocrit/WBC effects: May cause mild to moderate decreases in hemoglobin, hematocrit and WBC upon initiation of therapy which usually stabilizes with long-term therapy.
- Hepatic effects: Hepatic transaminases can become significantly elevated (dose-related); hepatocellular, chronic active, and cholestatic hepatitis have been reported. Regular monitoring of liver function tests is required.
- Hypersensitivity reactions: Rarely hypersensitivity reactions (eg, severe skin rash, Stevens-Johnson syndrome, toxic epidermal necrolysis) may occur.
- Myopathy/rhabdomyolysis: Has been associated with rare myositis or rhabdomyolysis; patients should be monitored closely. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine.
- Renal effects: Increases in serum creatinine (>2 mg/dL) have been observed with use; monitor renal function in patients with renal impairment and consider monitoring patients with increased risk for developing renal impairment.
- Venous thromboembolism (VTE): Use has been associated with pulmonary embolism (PE) and deep vein thrombosis (DVT). Use with caution in patients with risk factors for VTE.

Disease-related concerns:

- Renal impairment: Use with caution in patients with mild-to-moderate renal impairment; dosage adjustment required. Contraindicated with severe renal impairment (Cl_{cr} ≤30 mL/minute).

Concurrent drug therapy issues:

- HMG-CoA reductase inhibitors: Use caution with HMG-CoA reductase inhibitors; may lead to myopathy, rhabdomyolysis. In combination with HMG-CoA reductase inhibitors, fenofibrate is generally regarded as safer than gemfibrozil due to limited pharmacokinetic interaction with statins.

- Warfarin: Use with caution in patient taking warfarin; adjustments in warfarin therapy may be required.

Special populations:

- Elderly: Due to a higher incidence of renal impairment, use with caution in the elderly; dosage adjustment required.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

- Optimal response: Therapy should be withdrawn if an adequate response is not obtained after 2 months of therapy at the maximal daily dose. The occurrence of pancreatitis may represent a failure of efficacy in patients with severely elevated triglycerides.

Geriatric ConsiderationsThe definition of and, therefore, when to treat hyperlipidemia in the elderly is a controversial issue. The National Cholesterol Education Program recommends that all adults maintain a plasma cholesterol <160 mg/dL. Older adults with one additional risk factor, goal LDL would be <130 mg/dL. It is the authors' belief that pharmacologic treatment be reserved for those who are unable to obtain a desirable plasma cholesterol concentration by diet alone and for whom the benefits of treatment are believed to outweigh the potential adverse effects, drug interactions, and cost of treatment.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have shown embryocidal and teratogenic effect. There are no adequate and well-controlled studies in pregnant women. Use should be avoided, if possible, in pregnant women since the neonatal glucuronide conjugation pathways are immature.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsTumor formation was observed in animal studies; nursing is not recommended if the medication cannot be discontinued.

Adverse Reactions

>10%: Hepatic: ALT increased (dose related; 3% to 13%), AST increased (dose related; 3% to 13%)

1% to 10%:

Central nervous system: Headache (3%)

Gastrointestinal: Abdominal pain (5%), constipation (2%)

Neuromuscular & skeletal: Back pain (3%)

Respiratory: Respiratory disorder (6%), rhinitis (2%)

Postmarketing and/or case reports (limited to important or life-threatening): Abnormal vision, acne, agranulocytosis, allergic reaction, alopecia, amblyopia, anemia, angina pectoris, anorexia, anxiety, appetite increased, arrhythmia, arthralgia, arthritis, arthrosis, asthma, atrial fibrillation, bronchitis, bruising, bursitis, cardiovascular disorder, cataract, chest pain, cholecystitis, cholelithiasis, cholestatic hepatitis, cirrhosis, colitis, conjunctivitis, contact dermatitis, coronary artery disorder, cough increased, creatine phosphokinase increased, creatinine increased, cyst, cystitis, deep venous thrombosis, depression, diabetes mellitus, diaphoresis, diarrhea, dizziness, dry mouth, duodenal ulcer, dyspepsia, dyspnea, dysuria, ear pain, eczema, edema, electrocardiogram abnormality, eosinophilia, eructation, esophagitis, extrasystoles, eye disorder, fatty liver deposits, fever, flatulence, fungal dermatitis, gastritis, gastroenteritis, gastrointestinal disorder, gout, gynecomastia, hepatitis, hernia, herpes simplex, herpes zoster, hyper-/hypotension, hypersensitivity reaction, hypertonia, hyperuricemia, hypoglycemia, infection, insomnia, joint disorder, kidney function abnormality, laryngitis, leg cramps, leukopenia, libido decreased, lymphadenopathy, maculopapular rash, malaise, MI, muscle pain, myalgia, myasthenia, myopathy, myositis, nail disorder, nausea, nervousness, neuralgia, otitis media, pain, palpitation, pancreatitis, paresthesia, peptic ulcer, peripheral edema, peripheral vascular disorder, pharyngitis, phlebitis, photosensitivity reaction, pneumonia, pregnancy (unintended), prostatic disorder, pruritus, pulmonary embolus, rectal disorder, rectal hemorrhage, refraction disorder, rhabdomyolysis, sinusitis, skin ulcer, somnolence, Stevens-Johnson syndrome, tachycardia, tenderness, tenosynovitis, thrombocytopenia, tooth disorder, toxic epidermal necrolysis, urinary frequency, urolithiasis, urticaria, vaginal moniliasis, varicose veins, vasodilatation, vertigo, vomiting, weakness, weight gain/loss

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor); **Inhibits** CYP2A6 (weak), 2C8 (weak), 2C9 (weak), 2C19 (weak)

Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Fibric Acid Derivatives. **Exceptions:** Colesevelam. *Risk D: Consider therapy modification*

Ezetimibe: Fibric Acid Derivatives may increase the serum concentration of Ezetimibe. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Fenofibrate may enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Sulfonylureas: Fibric Acid Derivatives may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Fibric Acid Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Warfarin: Fenofibrate may enhance the anticoagulant effect of Warfarin. Fenofibrate may increase the serum concentration of Warfarin. *Risk D: Consider therapy modification*

Monitoring ParametersPeriodic blood counts during first year of therapy. Total cholesterol, LDL-C, triglycerides, and HDL-C should be measured periodically; If only marginal changes are noted in 6-8 weeks, the drug should be discontinued. Monitor LFTs regularly and discontinue therapy if levels remain >3 times normal limits.

Nursing: Physical Assessment/MonitoringUse caution and monitor closely in presence of hepatic or renal dysfunction, gallbladder disease, and advanced age. Assess potential for interactions with other pharmacological agents the patient may be taking (eg, increased risk of myopathy and rhabdomyolysis). Assess results of laboratory tests and patient response (eg, arrhythmias, gastrointestinal upset, CNS changes, hypoglycemia, myalgia) on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsTotal serum cholesterol and triglyceride concentration and CLDL, LDL, and HDL levels should be measured periodically; if only marginal changes are noted in 6-8 weeks, the drug should be discontinued. Serum transaminases should be measured every 3 months; if ALT values increase >100 units/L, therapy should be discontinued. Monitor LFTs prior to initiation, at 6 and 12 weeks after initiation or first dose, then periodically thereafter.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take exactly as directed. Do not change dosage, dosage form, or frequency without consulting prescriber. Maintain diet and exercise program as prescribed. If you are a diabetic taking a sulfonylurea, monitor blood sugars closely; this medication may alter the effects of your antidiabetic medication. You may experience mild GI disturbances (eg, gas, diarrhea, constipation, nausea); inform prescriber if these are severe. Report immediately unusual muscle pain or weakness; skin rash or irritation; insomnia; persistent dizziness; chest pain or palpitations; difficult respirations; pain, swelling, redness, or heat in extremities; or any other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

- Lipofen™: 50 mg; 100 mg [DSC]; 150 mg

Capsule [micronized]: 67 mg, 134 mg, 200 mg

- Antara™: 43 mg, 130 mg
- Lofibra®: 67 mg, 134 mg, 200 mg

Tablet: 54 mg, 160 mg

- Fenoglide™: 40 mg, 120 mg
- Lofibra®: 54 mg, 160 mg
- TriCor®: 48 mg, 145 mg
- Triglide™: 50 mg, 160 mg

Generic AvailableYes: Micronized capsule and tablet

Pricing: U.S. (www.drugstore.com)

Capsules (Antara)

- 43 mg (30): $45.99
- 130 mg (30): $124.79

Capsules (Fenofibrate)

- 134 mg (100): $139.98
- 200 mg (30): $65.99

Capsules (Lofibra)

- 67 mg (30): $34.64
- 134 mg (30): $55.90
- 200 mg (30): $85.07

Tablets (Fenofibrate)

- 54 mg (90): $64.99
- 160 mg (30): $67.99

Tablets (Lofibra)

- 160 mg (30): $83.99

Tablets (Tricor)

- 48 mg (30): $46.74
- 145 mg (30): $123.15

Tablets (Triglide)

- 160 mg (30): $129.59

Mechanism of ActionFenofibric acid, an agonist for the nuclear transcription factor peroxisome proliferator-activated receptor-alpha (PPAR-alpha), downregulates apoprotein C-III (an inhibitor of lipoprotein lipase) and upregulates the synthesis of apolipoprotein A-I, fatty acid transport protein, and lipoprotein lipase resulting in an increase in VLDL catabolism, fatty acid oxidation, and elimination of triglyceride-rich particles; as a result of a decrease in VLDL levels, total plasma triglycerides are reduced by 30% to 60%; modest increase in HDL occurs in some hypertriglyceridemic patients.

Pharmacodynamics/Kinetics

Absorption: Increased when taken with meals

Distribution: Widely to most tissues

Protein binding: >99%

Metabolism: Tissue and plasma via esterases to active form, fenofibric acid; undergoes inactivation by glucuronidation hepatically or renally

Half-life elimination: Fenofibric acid: Mean: 20 hours (range: 10-35 hours)

Time to peak: 3-8 hours

Excretion: Urine (60% as metabolites); feces (25%); hemodialysis has no effect on removal of fenofibric acid from plasma

Related Information

- Hyperlipidemia Management
- Lipid-Lowering Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dry mouth and tooth disorder.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay rarely cause drowsiness or insomnia
Mental Health: Effects on Psychiatric TreatmentNone reported
Cardiovascular ConsiderationsFibric acids decrease triglycerides (TGs) by 20% to 50%, and increase HDL-cholesterol (HDL-C) by 10% to 20%. They decrease LDL-cholesterol (LDL-C) by 5% to 20%, however, LDL-C actually may increase by 10% to 30% when fibrates are initiated in patients with high TGs (>400 mg/dL). Although combination therapy with statins has been used in patients with resistant hyperlipidemias, keep vigilant for signs and symptoms of myopathy.

The combination of ezetimibe and fenofibrate is FDA approved for treatment of mixed hyperlipidemia. Dosing regimen approved: Ezetimibe 10 mg and fenofibrate 160 mg once daily.

Index TermsProcetofene; Proctofene

References

de Lorgeril M, Salen O, Paillard F, et al, “Lipid-Lowering Drugs and Homocyst(e)ine,” *Lancet*, 1999, 353(9148):209-10.

“Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III),” *JAMA*, 2001, 285(19):2486-97. [PubMed 11368702]

Farnier M, Bonnefous F, Debbas N, et al, “Comparative Efficacy and Safety of Micronized Fenofibrate and Simvastatin in Patients With Primary Type IIa or IIb Hyperlipidemia,” *Arch Intern Med*, 1994, 154(4):441-9. [PubMed 8117177]

Mahley RW and Bersot TP, “Drug Therapy for Hypercholesterolemia and Dyslipidemia,” *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th ed, Hardman JE and Limbird LE, eds, New York, NY: McGraw-Hill, 2001, 993-5.

Sitori CR, Montanari G, Gianfranceschi G, et al, “Correlation Between Plasma Levels of Fenofibrate and Lipoprotein Changes in Hyperlipidaemic Patients,” *Eur J Clin Pharmacol*, 1985, 28(6):619-24.[PubMed 3840743]

International Brand NamesApo-Feno (PL); Apo-Feno-Micro (MY); Aterolis (UY); Climage (GR); Controlip (MX); Durafenat (DE); Durafenat Micro (DE); Evothyl (ID); Febrate (TH); Fegenor (FR, HK); Felosma (ID); Fenobrate (AR); Fenofanton (DE); Fenofibrat-ratiopharm (LU); Fenogal (PH); Fenogal Lidose (SG); Fenohexal (TH); Fenomed (TH); Fenopidil (KP); Fenoratio (PL); Fenox (TH); Fibrafen (PH); Grofibrat (PL); Hyperchol (ID); Katalip (HR); Lexemin (HK, SG, TH); Lexemin-M (HK); Lipanthyl (BE, BG, CH, CL, CZ, DE, EE, FI, FR, GR, HK, HN, HU, ID, IT, LU, PH, PL, RU, SE, TH, TW); Lipanthyl Supra (PL); Lipantil (GB, PT); Lipidax (IT); Lipidil (AU, BR, CN, DE, HU); Lipidil Supra (KP); Lipiduce (PH); Lipilfen (KP, PH); Lipofen (PT); Lipofibrat (PL); Lipolin (TW); Lipsin (AT); Lo-Lip (TW); Naftilan (CL); Nofibal (HU); Normolip (CO, CR, DO, GT, NI, PA, SV); Nubrex (PH); Qualipantyl (HK); Redose (KP); Secalip (FR); Secalip Supra (ES); Trichol (ID); Trolip (HK, ID, PH); Versamid (CY); Zerlubron (GR); Zumafib (ID)

Fenofibric Acid

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Special Alerts

TriLipix™ (Fenofibric Acid) Product Availability

TriLipix™ was approved by the U.S. Food and Drug Administration (FDA) in December 2008. It is expected to be available in January of 2009. No specific release date has been announced.

Medication Safety Issues

Sound-alike/look-alike issues:

TriLipix™ may be confused with Trileptal®, TriLyte®

Pronunciation(fen oh FYE brik AS id)

U.S. Brand NamesTriLipix™

Pharmacologic CategoryAntilipemic Agent, Fibric Acid

Use: Labeled IndicationsAdjunct to dietary therapy for the treatment of severely elevated serum triglyceride levels; adjunct to dietary therapy for the reduction of low density lipoprotein cholesterol (LDL-C), total cholesterol (total-C), triglycerides, and apolipoprotein B (apo B) and to increase high density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia or mixed dyslipidemia; adjunct to dietary therapy concomitantly with a statin to reduce triglyceride levels and increase HDL-C levels in patients with mixed dyslipidemia and coronary heart disease (CHD) or at risk for CHD

Dosing: Adults

Mixed dyslipidemia (coadministered with a statin): Oral: 135 mg once daily (maximum: 135 mg/day)

Hypertriglyceridemia: Oral: Initial: 45-135 mg once daily; Maintenance: Individualize according to patient response (maximum: 135 mg/day)

Primary hypercholesterolemia or mixed dyslipidemia: Oral: 135 mg once daily (maximum: 135 mg/day)

Dosing: ElderlyOral: Dosage based on renal function

Dosing: Renal Impairment

Mild-to-moderate impairment (Cl_{cr} 30-80 mL/minute): Initial: 45 mg once daily; only increase once effects on lipids and renal function evaluated

Severe impairment(Cl_{cr} <30 mL/minute; with or without dialysis): Contraindicated

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken with or without food. Patients should follow appropriate lipid-lowering diet.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light and moisture.

RestrictionsAn FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to fenofibric acid, choline fenofibrate, fenofibrate, or any component of the formulation; hepatic dysfunction including primary biliary cirrhosis and unexplained persistent liver function abnormalities; severe renal dysfunction (including patients on dialysis); pre-existing gallbladder disease; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

- Cholelithiasis: May cause cholelithiasis; discontinue if gallstones found upon gallbladder studies.
- Hemogloblin/hematocrit/WBC effects: May cause mild-to-moderate decreases in hemoglobin, hematocrit and WBC upon initiation of therapy which usually stabilizes with long-term therapy. Agranulocytosis and thrombocytopenia have rarely been reported.
- Hepatic effects: Hepatic transaminases can become significantly elevated (dose-related); hepatocellular, chronic active, and cholestatic hepatitis have been reported. Regular monitoring of liver function tests is required.
- Hypersensitivity reactions: Rarely hypersensitivity reactions (eg, severe skin rash, Stevens-Johnson syndrome, toxic epidermal necrolysis) may occur.
- Myopathy/rhabdomyolysis: Has been associated with rare myositis or rhabdomyolysis; patients should be monitored closely. Risk increased in the elderly, patients with diabetes mellitus, renal failure, or hypothyroidism. Patients should be instructed to report

unexplained muscle pain, tenderness, weakness, or brown urine.

- Renal effects: Increases in serum creatinine (>2 mg/dL) have been observed with use; monitor renal function in patients with renal impairment and consider monitoring patients with increased risk for developing renal impairment.

- Venous thromboembolism (VTE): Use has been associated with pulmonary embolism (PE) and deep vein thrombosis (DVT). Use with caution in patients with risk factors for VTE.

Disease-related concerns:

- Renal impairment: Use with caution in patients with mild-to-moderate renal impairment; dosage adjustment required. Contraindicated with severe renal impairment.

Concurrent drug therapy issues:

- Anticoagulants: Use with caution in patient taking oral anticoagulants (eg, warfarin); adjustments in therapy may be required.

- HMG-CoA reductase inhibitors: Use caution with HMG-CoA reductase inhibitors; may lead to myopathy, rhabdomyolysis. In combination with HMG-CoA reductase inhibitors, fenofibric acid derivatives are generally regarded as safer than gemfibrozil due to limited pharmacokinetic interaction with statins.

Special populations:

- Elderly: Due to a higher incidence of renal impairment, use with caution in the elderly; dosage adjustment based on renal function may be required.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

- Optimal response: Therapy should be withdrawn if an adequate response is not obtained after 2-3 months of therapy at the maximal daily dose. In patients with severe hypertriglyceridemia, the occurrence of pancreatitis may represent a failure of efficacy.

Pregnancy Risk FactorC
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use only if benefits outweigh the risks.
LactationExcretion in breast milk unknown/contraindicated
Adverse ReactionsAdverse reactions and frequency reported as observed during monotherapy and concurrent administration with a statin.

>10%: Central nervous system: Headache (12% to 13%)

1% to 10%:

Central nervous system: Dizziness (3% to 4%), pain (1% to 4%), fatigue (2% to 3%)

Gastrointestinal: Nausea (4% to 6%), dyspepsia (3% to 5%), diarrhea (3% to 4%), constipation (3%)

Hepatic: ALT increased (monotherapy: 1%; coadministered with statin: 3%)

Neuromuscular & skeletal: Back pain (4% to 6%), pain in extremities (3% to 5%), arthralgia (4%), myalgia (3% to 4%), muscle spasm (2% to 3%)

Respiratory: Nasopharyngitis (4% to 5%), upper respiratory infection (4% to 5%), sinusitis (3% to 4%)

Additional adverse reactions when fenofibric acid coadministered with a statin (frequency not defined): AST increased, bronchitis, cough, CPK increased, hepatic enzymes increased, hypertension, influenza, insomnia, musculoskeletal pain, pharyngolaryngeal pain, urinary tract infection

Postmarketing (seen with fenofibrate): Abdominal pain, anemia, AST increased, cirrhosis, CPK increased, hepatitis, pancreatitis, renal failure, rhabdomyolysis, weakness

Monitoring ParametersPeriodic blood counts during first year of therapy; total cholesterol, LDL-C, triglycerides, and HDL-C should be measured periodically; monitor LFTs (including ALT) regularly and discontinue therapy if levels remain >3 times normal limits; serum creatinine (in patients with or at risk for renal impairment)
Monitoring: Lab TestsPeriodic blood counts during first year of therapy; total cholesterol, LDL-C, triglycerides, and HDL-C should be measured periodically; monitor LFTs (including ALT) regularly and discontinue therapy if levels remain >3 times normal limits; serum creatinine (in patients with or at risk for renal impairment)
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, delayed release:

TriLipix™: 45 mg, 135 mg

Generic AvailableNo
Mechanism of ActionFenofibric acid, an agonist for the nuclear transcription factor peroxisome proliferator-activated receptor-alpha (PPAR-alpha), downregulates apoprotein C-III (an inhibitor of lipoprotein lipase) and upregulates the synthesis of apolipoprotein A-I, fatty acid transport protein, and lipoprotein lipase resulting in an increase in VLDL catabolism, fatty acid oxidation, and elimination of triglyceride-rich particles; as a result of a decrease in VLDL levels, total plasma triglycerides are reduced by 30% to 60%; modest increased in HDL occurs in some hypertriglyceridemia patients.
Pharmacodynamics/Kinetics

Absorption: Well absorbed

Protein binding: ~99%

Metabolism: Fenofibric acid (active form) undergoes inactivation by glucuronidation. The choline salt dissociates in the GI tract to form fenofibric acid (free acid)

Bioavailability: ~81%

Half-life elimination: ~20 hours

Time to peak, plasma: 4-5 hours

Excretion: Urine (as fenofibric acid and fenofibric acid glucuronide)

Index Terms ABT-335; Choline Fenofibrate

References

Mohiuddin SM, Pepine CJ, Kelly MT, et al, “Efficacy and Safety of ABT-335 (Fenofibric Acid) in Combination With Simvastatin In Patients With Mixed Dyslipidemia: A Phase 3, Randomized, Controlled Study,” *Am Heart J*, 2009, 157(1):195-203.[PubMed 19081418]

Fenoldopam

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Pronunciation(fe NOL doe pam)
U.S. Brand NamesCorlopam®
Canadian Brand NamesCorlopam®
Pharmacologic CategoryDopamine Agonist
Use: Labeled IndicationsTreatment of severe hypertension (up to 48 hours in adults), including in patients with renal compromise; short-term (up to 4 hours) blood pressure reduction in pediatric patients
Dosing: AdultsHypertension, severe: I.V.: Initial: 0.1-0.3 mcg/kg/minute (lower initial doses may be associated with less reflex tachycardia); may be increased in increments of 0.05-0.1 mcg/kg/minute every 15 minutes until target blood pressure is reached; the maximal infusion rate reported in clinical studies was 1.6 mcg/kg/minute
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricHypertension, severe: I.V.: Initial: 0.2 mcg/kg/minute; may be increased to dosages of 0.3-0.5 mcg/kg/minute every 20-30 minutes (maximum dose: 0.8 mcg/kg/minute); limited to short-term (4 hours) use
Dosing: Renal ImpairmentNo guidelines are available.
Administration: I.V.For I.V. infusion using an infusion pump.
StorageStore at 2°C to 30°C (35°F to 86°F). Following dilution, store at room temperature and use solution within 24 hours.
ReconstitutionMust be diluted prior to infusion. Final dilution for children is 60 mcg/mL and for adults is 40 mcg/mL.
CompatibilityStable with NS or D_5W.
ContraindicationsHypersensitivity of fenoldopam or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Tachycardia: A dose-related tachycardia can occur, especially at infusion rates >0.1 mcg/kg/minute.

Disease-related concerns:

- Angina: Use with caution in patients with angina patients; can increase myocardial oxygen demand with tachycardia.
- Glaucoma: Use with caution in patients with open-angle glaucoma or intraocular hypertension.
- Increased intracranial pressure: Use with caution in patients with increased intracranial pressure; use has not been studied in this population.

Dosage form specific issues:

- Sulfites: Contains sulfites; may cause allergic reaction in susceptible individuals.

Other warnings/precautions:

- Administration: For continuous infusion only (no bolus doses).
- Hemodialysis: The effects of hemodialysis on the pharmacokinetics of fenoldopam have not been evaluated.
- Monitoring: Close monitoring of blood pressure is necessary; hypotension can occur. Monitor for hypokalemia at 6-hour intervals during infusion.

Pregnancy Risk FactorB
Pregnancy ConsiderationsFetal harm was not observed in animal studies; however, safety and efficacy have not been established for use during pregnancy. Use during pregnancy only if clearly needed. Fetal heart rate monitoring is recommended.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not always defined.

Cardiovascular: Angina, asymptomatic T wave flattening on ECG, chest pain, edema, facial flushing (>5%), fibrillation (atrial), flutter (atrial), hypotension (>5%), tachycardia

Central nervous system: Dizziness, headache (>5%)

Endocrine & metabolic: Hypokalemia

Gastrointestinal: Abdominal pain/fullness, diarrhea, nausea (>5%), vomiting, xerostomia

Local: Injection site reactions

Ocular: Intraocular pressure (increased), blurred vision

Hepatic: Increases in portal pressure in cirrhotic patients

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersBlood pressure, heart rate, ECG, renal/hepatic function tests

Reference RangeMean plasma fenoldopam levels after a 2 hour infusion (at 0.5 mcg/kg/minute) and a 100 mg dose is approximately 13 ng/mL and 50 ng/mL

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 10 mg/mL (1 mL, 2 mL) [contains sodium metabisulfite and propylene glycol]

Generic AvailableYes

Mechanism of ActionA selective postsynaptic dopamine agonist (D_1-receptors) which exerts hypotensive effects by decreasing peripheral vasculature resistance with increased renal blood flow, diuresis, and natriuresis; 6 times as potent as dopamine in producing renal vasodilitation; has minimal adrenergic effects

Pharmacodynamics/Kinetics

Onset of action: I.V.: 10 minutes

Duration: I.V.: 1 hour

Distribution: V_d: 0.6 L/kg

Half-life elimination: I.V.: Children: 3-5 minutes; Adults: ~5 minutes

Metabolism: Hepatic via methylation, glucuronidation, and sulfation; the 8-sulfate metabolite may have some activity; extensive first-pass effect

Excretion: Urine (90%); feces (10%)

Pharmacotherapy PearlsSuitable for use in patients whose condition is unstable or rapidly changing because the effects of the drug are predictable and easily reversible; it has been found to safely control blood pressure in patients with a variety of pre-existing conditions including kidney disease, liver disease, and heart failure. (Clinical benefit other than blood pressure reduction has not been established.) In none of these situations does the dose need to be adjusted, minimizing the risk of drug overdose in patients with these conditions. The drug is quickly metabolized into inactive substances before it is excreted; therefore, there are no toxic chemicals derived from the drug. Unlike the situation with some other intravenous antihypertensives, the adult patient does not need an arterial line for blood pressure monitoring; a blood pressure cuff is sufficient to monitor blood pressure lowering. Since the drug induces natriuresis, diuresis, and increased creatinine clearance, it may have an advantage over nitroprusside, especially in patients with severe renal insufficiency and in volume overloaded patients.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentCauses hypotension; caution with low potency antipsychotics and TCAs

Cardiovascular Considerations

Contrast Nephropathy: Fenoldopam is ineffective in the prevention of contrast-induced nephropathy. A prospective, randomized trial (Allaqaband, 2002) compared the efficacy of acetylcysteine (600 mg twice daily for 48 hours) plus saline 0.45% to fenoldopam (0.1 mcg/kg/minute) plus saline 0.45% to saline alone (0.45% at 1 mL/kg/hour for 12 hours before procedure, during procedure, and 12 hours afterwards) in preventing radiocontrast-induced nephropathy. Patients were high-risk (serum creatinine >1.6 mg/dL or Cl_{cr} <60 mL/minute) and undergoing cardiovascular procedures using low-osmolality, nonionic contrast. Authors concluded that there was no benefit in either acetylcysteine or fenoldopam over saline in preventing radiocontrast-induced nephropathy.

In a more recent trial (CONTRAST), the efficacy of fenoldopam was evaluated to prevent contrast nephropathy after invasive cardiovascular procedures (Stone G, 2003). This was a prospective, placebo-controlled, double-blind, multicenter trial. Eligible patients were hydrated with 0.45% saline (1-1.5 mL/kg/hour for 2-12 hours prior to procedure) and randomized to fenoldopam (0.05 mcg/kg/minute; titrated to 0.1 mcg/kg/minute) or matching placebo, starting 1 hour before angiography and continuing for 12 hours. Contrast nephropathy was defined as a ≥25% increase in serum creatinine within 96 hours of procedure. One hundred and fifty seven patients received fenoldopam and 158 received placebo. Demographics were similar between the groups. Approximately 49% of patients were patients with diabetes. The average creatinine clearance was 29 mL/minute and 157 mL of contrast (low osmolar, 90% received nonionic) was administered. About half the patients in each group received acetylcysteine. Contrast-induced nephropathy occurred in 33.6% of fenoldopam patients and 30.1% of placebo patients (p: 0.61).

Anesthesia and Critical Care Concerns/Other ConsiderationsSuitable for use in patients whose condition is unstable or rapidly changing because the effects of the drug are predictable and easily reversible; it has been found to safely control blood pressure in patients with a variety of pre-existing conditions including kidney disease, liver disease, and heart failure. (Clinical benefit other than blood pressure reduction has not been established.) Dosage adjustment is not required in any of these situations. The drug is quickly metabolized into inactive substances before it is excreted. Unlike the situation with some other intravenous antihypertensives, the patient does not need an arterial line for blood pressure monitoring; a blood pressure cuff is sufficient. Since the drug induces natriuresis, diuresis, and increased creatinine clearance, it may have an advantage over nitroprusside, especially in patients with severe renal insufficiency and in volume-overloaded patients.

Contrast Nephropathy: Fenoldopam is ineffective in the prevention of contrast-induced nephropathy.

Index TermsFenoldopam Mesylate

References

Allaqaband S, Tumuluri R, Malik AM, et al, “Prospective Randomized Study of N-acetylcysteine, Fenoldopam, and Saline for Prevention of Radiocontrast-Induced Nephropathy,” *Catheter Cardiovasc Interv*, 2002, 57(3):279-83. [PubMed 12410497]

Erstad BL and Barletta JF, “Treatment of Hypertension in the Perioperative Patient,” *Ann Pharmacother*, 2000, 34(1):66-79. [PubMed 10669188]

Stone GW, McCullough PA, Tumlin JA, et al, “Fenoldopam Mesylate for the Prevention of Contrast-Induced Nephropathy: A Randomized Controlled Trial,” *JAMA*, 2003, 290(17):2284-91.[PubMed 14600187]

International Brand NamesCorlopam (CA)

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Fenoprofen may be confused with flurbiprofen

Nalfon® may be confused with Naldecon®

Pronunciation(fen oh PROE fen)

U.S. Brand NamesNalfon®

Canadian Brand NamesNalfon®

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsSymptomatic treatment of acute and chronic rheumatoid arthritis and osteoarthritis; relief of mild to moderate pain

Dosing: Adults

Rheumatoid arthritis, osteoarthritis: Oral: 300-600 mg 3-4 times/day; maximum dose: 3.2 g/day

Mild-to-moderate pain: Oral: 200 mg every 4-6 hours as needed; maximum dose: 3.2 g/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot recommended in patients with advanced renal disease.

Administration: OralDo not crush tablets. Swallow whole with a full glass of water. Take with food to minimize stomach upset.

Dietary ConsiderationsMay be taken with food to decrease GI distress.

StorageStore at controlled room temperature of 20°C to 25°C (67°F to 77°F).

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to fenoprofen, aspirin, or other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery; significant renal dysfunction

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.
- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high-dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (3rd trimester)

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Use of NSAIDs late in pregnancy may cause premature closure of the ductus arteriosis and may inhibit uterine contractions.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsVery low levels of fenoprofen are found in breast milk.

Adverse Reactions

1% to 10%:

Cardiovascular: Peripheral edema (5%), palpitation (3%)

Central nervous system: Headache (9%), somnolence (9%), dizziness (7%), nervousness (6%), fatigue (2%), confusion (1%)

Dermatologic: Itching (4%), rash (4%)

Gastrointestinal: Dyspepsia (10%), nausea (8%), constipation (7%), abdominal pain (2%), vomiting (3%)

Neuromuscular & skeletal: Weakness (5%), tremor (2%)

Ocular: Blurred vision (2%)

Otic: Tinnitus (5%), hearing decreased (2%)

Respiratory: Dyspnea (3%), nasopharyngitis (1%)

Miscellaneous: Diaphoresis (5%)

<1%, postmarketing, and/or case reports: Agranulocytosis, alkaline phosphatase increased, alopecia, anaphylaxis, angioedema (angioneurotic edema), anemia, anorexia, anuria, aphthous ulcerations, aplastic anemia, AST increased, atrial fibrillation, azotemia, blood in stool, bruising, burning tongue, cholestatic hepatitis, cystitis, depression, diplopia, disorientation, dysuria, exfoliative dermatitis, ECG changes, fever, flatulence, gastritis, gastrointestinal hemorrhage, gastrointestinal perforation, gastrointestinal ulcer, hematuria, hemolytic anemia, hemorrhage, hypertension, insomnia, interstitial nephritis, jaundice, LDH increased, lymphadenopathy, malaise, mastodynia, nephrosis, oliguria, optic neuritis, pancreatitis, pancytopenia, peptic ulcer, pulmonary edema, purpura, renal failure, renal papillary necrosis, seizure, Stevens-Johnson syndrome, supraventricular tachycardia, tachycardia, taste perversion, thrombocytopenia, toxic epidermal necrolysis, trigeminal neuralgia, urticaria, xerostomia

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor

Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Fenoprofen peak serum levels may be decreased if taken with food; total amount absorbed is not affected.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Test InteractionsFenoprofen may interfere with Amerlex-M kit assay values; falsely elevated values of total and free triiodothyronine have been reported.

Monitoring ParametersMonitor CBC, liver enzymes; monitor urine output and BUN/serum creatinine in patients receiving diuretics; monitor blood pressure in patients receiving antihypertensives; audiogram (in patients with baseline hearing impairment)

Reference RangeTherapeutic: 20-65 mcg/mL (SI: 82-268 µmol/L)

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess effectiveness and interactions of other medications patient may be taking. Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically throughout therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC, liver enzymes; urine output and BUN/serum creatinine in patients receiving diuretics

Patient EducationTake this medication exactly as directed; do not increase dose without consulting prescriber. Do not crush tablets or break capsules. Take with food or milk to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol, aspirin or aspirin-containing medication, or any other anti-inflammatory medications without consulting prescriber. You may experience drowsiness, dizziness, nervousness, or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); anorexia, nausea, vomiting, or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or fluid retention (weigh yourself weekly and report unusual [3-5 pounds/week] weight gain). GI bleeding, ulceration, or perforation can occur with or without pain; discontinue medication and contact prescriber if persistent abdominal pain or cramping, or blood in stool occurs. Report breathlessness, respiratory difficulty, or unusual cough; chest pain, rapid heartbeat, palpitations; unusual bruising/bleeding; blood in urine, stool, mouth, or vomitus; swollen extremities; skin rash or itching; acute fatigue; weakness in one side or part of body; slurred speech; persistent nausea; yellowing of skin or eyes; abdominal pain; or hearing changes (ringing in ears). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as calcium:

Nalfon®: 200 mg

Tablet, as calcium: 600 mg

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Capsules (Nalfon)

200 mg (100): $69.99

Tablets (Fenoprofen Calcium)

600 mg (30): $21.99

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: A few days; full benefit: up to 2-3 weeks

Absorption: Rapid, 80%

Protein binding: 99%; to albumin

Metabolism: Extensively hepatic

Half-life elimination: 2.5-3 hours

Time to peak, serum: ~2 hours

Excretion: Urine (2% to 5% as unchanged drug); feces (small amounts)

Related Information

- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness; rarely may cause insomnia, confusion, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentMay rarely cause may agranulocytosis; use caution with clozapine and carbamazepine; may decrease the clearance of lithium resulting in elevated serum levels and potential toxicity; monitor serum lithium levels; use acetaminophen, if possible, for pain

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A meta-analysis (Pope, 1993) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 chronic heart failure guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin’s inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. May precipitate renal failure in dehydrated patients.

Index TermsFenoprofen Calcium

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International Brand NamesFenopron (GB, HK, IE, KP); Fepron (TW); Nalfon (AT, BB, BM, BS, BZ, GY, JM, MX, NL, RU, SR, TT); Nalgesic (FR); Progesic (GB)

Fenoterol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(fen oh TER ole)

Canadian Brand NamesBerotec®

Pharmacologic CategoryBeta$_2$ Agonist

Use: Labeled IndicationsTreatment and prevention of symptoms of reversible obstructive pulmonary disease (including asthma and acute bronchospasm), chronic bronchitis, emphysema

Dosing: Adults

Bronchospasm: Inhalation:

Metered dose inhaler (MDI):

Acute treatment: 1 puff initially; may repeat in 5 minutes; if relief is not evident, additional doses and/or other therapy may be necessary

Intermittent/long-term treatment: 1-2 puffs 3-4 times/day (maximum of 8 puffs/24 hours)

Inhalation solution: 0.5-1 mg (up to maximum of 2.5 mg)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥12 years of age: Refer to adult dosing

Administration: Inhalation

MDI: Shake well before use; prime prior to first use, and whenever inhaler has not been used for >2 weeks, by releasing 4 test sprays into the air (away from face)

Solution: Appropriate dose may be diluted with sterile, preservative-free 0.9% sodium chloride to allow nebulization.

Storage

Aerosol: Store at 15°C to 30°C (59°F to 86°F).

Solution:

Unopened unit-dose vial: Store at room temperature of ~25°C (77°F). Protect from light.

Undiluted, opened (original glass amber bottle, recapped): May be stored at room temperature of ~25°C (77°F) for 30 days.

Diluted with preservative-free normal saline: May be stored at room temperature of ~25°C (77°F) for 24 hours.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to fenoterol or any component of the formulation; tachyarrhythmias; hypertrophic obstructive cardiomyopathy

Warnings/Precautions

Concerns related to adverse effects:

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.
- Hypersensitivity reactions: Immediate hypersensitivity reactions (urticaria, angioedema, rash, bronchospasm) have been reported.
- Serious effects/fatalities: Do not exceed recommended dose; serious adverse events, including fatalities, have been associated with excessive use of inhaled sympathomimetics.

Disease-related concerns:

- Asthma: Appropriate use: Optimize anti-inflammatory treatment before initiating maintenance treatment with fenoterol. Do not use as a component of chronic therapy without an anti-inflammatory agent. Only the mildest forms of asthma (Step 1 and/or exercise-induced) would not require concurrent use based upon asthma guidelines.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (arrhythmia or hypertension or HF); beta-agonists may cause elevation in blood pressure, heart rate and result in CNS stimulation/excitation. Beta$_2$-agonists may also increase risk of arrhythmias.
- Diabetes: Use with caution in patients with diabetes mellitus; beta$_2$-agonists may increase serum glucose.
- Glaucoma: Use with caution in patients with glaucoma; may elevate intraocular pressure.

- Hyperthyroidism: Use with caution in hyperthyroidism; may stimulate thyroid activity.
- Hypokalemia: Use with caution in patients with hypokalemia; beta$_2$ agonists may decrease serum potassium.
- Seizures: Use with caution in patients with seizure disorders; beta-agonists may result in CNS stimulation/excitation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Patient information: Patients must be instructed to seek medical attention in cases where acute symptoms are not relieved or a previous level of response is diminished. The need to increase frequency of use may indicate deterioration of asthma, and treatment must not be delayed. All patients should utilize a spacer device when using a metered-dose inhaler.

Pregnancy Risk FactorNot available; similar agents rated C

Pregnancy ConsiderationsSafety and efficacy have not been established in pregnant women. Because of a potential for beta$_2$-agonists to interfere with uterine contractility, use should be restricted to cases where the benefit clearly outweighs the potential risks.

LactationEnters breast milk/not recommended

Adverse Reactions**Note:** Frequency of most effects may be dose related, approximate frequencies noted below. In the treatment of acute bronchospasm (high-dose nebulization), symptoms of headache (up to 12%), tremor (32%), and tachycardia (up to 21%) are frequently noted.

>10%: Endocrine & metabolic: Serum glucose increased, serum potassium decreased

1% to 10%:

Cardiovascular: Palpitation, tachycardia

Central nervous system: Headache, dizziness, nervousness

Neuromuscular & skeletal: Tremor, muscle cramps

Respiratory: Pharyngeal irritation, cough

<1%: Agitation, allergic reaction, arrhythmia, bronchospasm (paradoxical), hyperglycemia, hypertension, nausea, pruritus, rash, restlessness, sleep disorder, tachycardia, urticaria, vomiting

Postmarketing and/or case reports: Hypokalemia

Drug Interactions

Alpha-/Beta-Blockers: May diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Atomoxetine: May enhance the tachycardic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Betahistine: May diminish the therapeutic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Avoid or limit caffeine (may cause CNS stimulation).

Herb/Nutraceutical: Avoid ephedra, yohimbe (may cause CNS stimulation).

Monitoring ParametersFEV$_1$, peak flow, and/or other pulmonary function tests; blood pressure, heart rate; CNS stimulation; serum glucose, serum potassium; asthma symptoms; arterial or capillary blood gases (if patients condition warrants)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking (see Drug Interactions). See Contraindications and Warnings/Precautions for use cautions. Monitor vital signs, effectiveness of therapy, and adverse reactions (see Adverse Reactions) at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report (see Patient Education). **Pregnancy risk factor C** - benefits of use should outweigh possible risks. Breast-feeding is not recommended.

Monitoring: Lab TestsArterial or capillary blood gases (if patient's condition warrants); FEV$_1$, peak flow, and/or other pulmonary function tests; serum potassium, serum glucose (in selected patients)

Patient EducationUse exactly as directed. Do not use more often than recommended. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience nervousness, dizziness, or fatigue (use caution when driving or engaging in hazardous activities until response to drug is known); dry mouth, unpleasant taste, stomach upset (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or difficulty urinating (always void before treatment). Report unresolved GI upset, dizziness or fatigue, vision changes, chest pain or palpitations, persistent inability to void, nervousness or insomnia, muscle cramping or tremor, or unusual cough. If usual dose does not provide relief or if relief does not last at least 3 hours, medical advice should be sought immediately. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Self-administered inhalation: Do not freeze. Shake canister before using. Sit when using medication. Close eyes when administering fenoterol to avoid spray getting into eyes. Exhale slowly and completely through nose; inhale deeply through mouth while administering aerosol. Hold breath for 10 seconds after inhalation. Wait at least 1 full minute between inhalations. Wash mouthpiece between use. If more than one inhalation medication is used, use fenoterol first and wait 5 minutes between medications. Prime inhaler prior to first use, and whenever the inhaler has not been used for more than 2 weeks, by releasing 4 test sprays into the air (away from face). Discard inhaler after labeled number of doses are used, even if the canister does not feel empty. Store with mouthpiece down. Do not allow metal canister to become wet.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Aerosol for inhalation, as hydrobromide: MDI:

Berotec® [CAN]: 100 mcg/dose [200 doses]

Solution for inhalation, as hydrobromide:

Berotec® [CAN] 0.625 mg/mL (2 mL); 0.25 mg/mL (2 mL) [not available in the U.S.]

ManufacturerBoehringer Ingelheim (Canada)

Mechanism of ActionRelaxes bronchial smooth muscle by action on beta$_2$-receptors with little effect on heart rate.

Pharmacodynamics/Kinetics

Onset of action: 5 minutes

Peak effect: 30-60 minutes

Duration: 3-4 hours (up to 6-8 hours)

Pharmacotherapy PearlsNot available in U.S.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness, dizziness, or fatigue

Mental Health: Effects on Psychiatric TreatmentUse caution with TCAs and MAO inhibitors; concomitant use with fenoterol may increase the adverse effects of fenoterol.

Index TermsFenoterol Hydrobromide

References

Expert Panel Report 3, “Guidelines for the Diagnosis and Management of Asthma,” *Clinical Practice Guidelines*, National Institutes of Health, National Heart, Lung, and Blood Institute, NIH Publication No. 08-4051, prepublication 2007. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

International Brand NamesBerotec (AR, AT, AU, BE, BR, CH, CZ, DE, DK, ES, FI, FR, GB, HR, HU, IE, LU, NL, NO, PL, PT, SE); Berotec N (PL); Dosberotec (DE, IT); Fenostad (AT); Fenoterol (PL); Fensol (ZA); Partusisten (CH, CZ, DE, HU, NL, PL); Partusisten intrapartal (PL)

FentaNYL

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Fentanyl Transdermal System Patches: Leakage of Active Gel - Revised August 2008

Various manufacturers of fentanyl transdermal system patches have instituted recalls of fentanyl transdermal patch products due to manufacturing defects resulting in fentanyl gel leakage from the patch. Leakage of active drug out of the patch renders the transdermal system less effective and could potentially expose patients, caregivers, and/or healthcare practitioners handling the products to fentanyl gel. Patients and healthcare professionals should check the drug packaging for affected lots and are advised against directly handling any defective patches. Recommended guidance for product returns and/or disposal should be followed. Anyone exposed to the gel should immediately rinse exposed skin with large amounts of water without using soap or detergents.

For further information regarding specific strengths and lot numbers affected it the U.S. recalls, refer to the following FDA websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Fentanyl

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Duragesic

For information regarding defective patches sold in Canada by Janssen-Ortho, Inc or Ranbaxy see:

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_29_e.html

Medication Safety Issues

Sound-alike/look-alike issues:

FentaNYL may be confused with alfentanil, SUFentanil

Dosing of transdermal fentanyl patches may be confusing. Transdermal fentanyl patches should always be prescribed in mcg/hour, not size. Patch dosage form of Duragesic®-12 actually delivers 12.5 mcg/hour of fentanyl. Use caution, as orders may be written as “Duragesic 12.5” which can be erroneously interpreted as a 125 mcg dose.

Fentora® and Actiq® are not interchangeable; do not substitute doses on a mcg-per-mcg basis.

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Fentanyl transdermal system patches: Leakage of fentanyl gel from the patch has been reported; patch may be less effective; do not use. Thoroughly wash any skin surfaces coming into direct contact with gel with water (do not use soap).

Transdermal patch (eg, Duragesic®) does not contain any metal-based compounds; however, the printed ink used to indicate strength on the outer surface of the patch does contain titanium dioxide, but the amount is minimal.

Pronunciation(FEN ta nil)

U.S. Brand NamesActiq®; Duragesic®; Fentora®; Sublimaze®

Canadian Brand NamesActiq®; Duragesic®; Fentanyl Citrate Injection, USP; RAN™-Fentanyl Transdermal System; ratio-Fentanyl

Pharmacologic CategoryAnalgesic, Opioid; Anilidopiperidine Opioid; General Anesthetic

Use: Labeled Indications

Injection: Sedation, relief of pain, preoperative medication, adjunct to general or regional anesthesia

Transdermal patch (eg, Duragesic®): Management of persistent moderate-to-severe chronic pain

Transmucosal lozenge (eg, Actiq®), buccal tablet (Fentora®): Management of breakthrough cancer pain in opioid-tolerant patients

Use: DentalAdjunct in preoperative intravenous conscious sedation in patients undergoing dental surgery

Dosing: Adults**Note:** These are guidelines and do not represent the maximum doses that may be required in all patients. Doses and dosage intervals should be titrated to pain relief/prevention. Monitor vital signs routinely. Single I.M. doses have a duration of 1-2 hours, single I.V. doses last 0.5-1 hour.

Surgery:

Premedication: I.M., slow I.V.: 50-100 mcg/dose 30-60 minutes prior to surgery

Adjunct to regional anesthesia: Slow I.V.: 25-100 mcg/dose over 1-2 minutes. **Note:** An I.V. should be in place with regional anesthesia so the I.M. route is rarely used but still maintained as an option in the package labeling.

Adjunct to general anesthesia: Slow I.V.:

Low dose: 0.5-2 mcg/kg/dose depending on the indication.

Moderate dose: Initial: 2-20 mcg/kg/dose; Maintenance (bolus or infusion): 1-2 mcg/kg/hour. Discontinuing fentanyl infusion 30-60 minutes prior to the end of surgery will usually allow adequate ventilation upon emergence from anesthesia. For "fast-tracking" and early extubation following major surgery, total fentanyl doses are limited to 10-15 mcg/kg.

High-dose: 20-50 mcg/kg/dose; **Note:** Fentanyl is rarely used, but is still maintained in the package labeling.

Pain management: Adults:

I.V. (unlabeled use): Bolus at start of infusion: 1-2 mcg/kg **or** 25-100 mcg/dose; continuous infusion rate: 1-2 mcg/kg/hour **or** 25-200 mcg/hour

Severe (unlabeled use): I.M, I.V.: 50-100 mcg/dose every 1-2 hours as needed; patients with prior opiate exposure may tolerate higher initial doses

Patient-controlled analgesia (PCA) (unlabeled use): I.V.: Usual concentration: 10 mcg/mL

Basal rate: ≤50 mcg/hour

Demand dose: Usual: 10 mcg; range: 10-50 mcg

Lockout interval: 5-10 minutes

Critically-ill patients (unlabeled dose): Slow I.V.: 25-100 mcg (based on ~70 kg patient) **or** 0.35-1.5 mcg/kg every 30-60 minutes as needed. **Note:** More frequent dosing may be needed (eg, mechanically-ventilated patients).

Continuous infusion: 50-700 mcg/hour (based on ~70 kg patient) **or** 0.7-10 mcg/kg/hour

Breakthrough cancer pain: For patients who are tolerant to and currently receiving opioid therapy for persistent cancer pain; dosing should be individually titrated to provide adequate analgesia with minimal side effects. Dose titration should be done if patient requires more than 1 dose/breakthrough pain episode for several consecutive episodes. Patients experiencing >4 breakthrough pain episodes/day should have the dose of their long-term opioid re-evaluated.

Lozenge: Initial dose: 200 mcg; the second dose may be started 15 minutes after completion of the first dose. Consumption should be limited to ≤4 units/day. Additional requirements suggest need for improved baseline therapy.

Buccal tablet (Fentora®): Initial dose: 100 mcg; a second 100 mcg dose, if needed, may be started 30 minutes after the start of the first dose. **Note:** For patients previously using the transmucosal lozenge (Actiq®), the initial dose should be selected using the conversions listed below (maximum: 2 doses per breakthrough pain episode every 4 hours).

Dose titration, if required, should be done using multiples of the 100 mcg tablets. Patient can take two 100 mcg tablets (one on each side of mouth). If that dose is not successful, can use four 100 mcg tablets (two on each side of mouth). If titration requires >400 mcg/dose, then use 200 mcg tablets.

Conversion from lozenge to buccal tablet (Fentora®):

Lozenge dose 200-400 mcg, then buccal tablet 100 mcg

Lozenge dose 600-800 mcg, then buccal tablet 200 mcg

Lozenge dose 1200-1600 mcg, then buccal tablet 400 mcg

Note: Four 100 mcg buccal tablets deliver approximately 12% and 13% higher values of C_{max} and AUC, respectively, compared to one 400 mcg buccal tablet. To prevent confusion, patient should only have one strength available at a time. Using more than four buccal tablets at a time has not been studied.

Chronic pain management: Children ≥2 years and Adults (opioid-tolerant patients): Transdermal patch (eg, Duragesic®):

Initial: To convert patients from oral or parenteral opioids to transdermal patch, a 24-hour analgesic requirement should be calculated (based on prior opiate use). Using the tables, the appropriate initial dose can be determined. The initial fentanyl dosage may be approximated from the 24-hour morphine dosage equivalent and titrated to minimize adverse effects and provide analgesia. With the initial application, the absorption of transdermal fentanyl requires several hours to reach plateau; therefore transdermal fentanyl is inappropriate for management of acute pain. Change patch every 72 hours.

Conversion from continuous infusion of fentanyl: In patients who have adequate pain relief with a fentanyl infusion, fentanyl may be converted to transdermal dosing at a rate equivalent to the intravenous rate. A two-step taper of the infusion to be completed over 12 hours has been recommended (Kornick, 2001) after the patch is applied. The infusion is decreased to 50% of the original rate six hours after the application of the first patch, and subsequently discontinued twelve hours after application.

Titration: Short-acting agents may be required until analgesic efficacy is established and/or as supplements for "breakthrough" pain. The amount of supplemental doses should be closely monitored. Appropriate dosage increases may be based on daily supplemental dosage using the ratio of 45 mg/24 hours of oral morphine to a 12.5 mcg/hour increase in fentanyl dosage.

Frequency of adjustment: The dosage should not be titrated more frequently than every 3 days after the initial dose or every 6 days thereafter. Patients should wear a consistent fentanyl dosage through two applications (6 days) before dosage increase based on supplemental opiate dosages can be estimated. **Note:** Upon discontinuation, ~17 hours are required for a 50% decrease in fentanyl levels.

Frequency of application: The majority of patients may be controlled on every 72-hour administration; however, a small number of patients require every 48-hour administration.

Dose conversion guidelines for transdermal fentanyl[1] (see tables).

Recommended Initial Duragesic® Dose Based Upon Daily Oral Morphine Dose[1]

Oral 24-Hour Morphine (mg/d)	**Duragesic® Dose (mcg/h)**
60-134[2]	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300
[1]The table should NOT be used to convert from transdermal fentanyl (eg, Duragesic®) to other opioid analgesics. Rather, following removal of the patch, titrate the dose of the new opioid until adequate analgesia is achieved.	
[2]Pediatric patients initiating therapy on a 25 mcg/hour Duragesic® system should be opioid-tolerant and receiving at least 60 mg oral morphine equivalents per day.	

Dosing Conversion Guidelines[1,2]

Current Analgesic	**Daily Dosage (mg/day)**			
Morphine (I.M./I.V.)	10-22	23-37	38-52	53-67
Oxycodone (oral)	30-67	67.5-112	112.5-157	157.5-202
Oxycodone (I.M./I.V.)	15-33	33.1-56	56.1-78	78.1-101

Codeine (oral)	150-447	448-747	748-1047	1048-1347
Hydromorphone (oral)	8-17	17.1-28	28.1-39	39.1-51
Hydromorphone (I.V.)	1.5-3.4	3.5-5.6	5.7-7.9	8-10
Meperidine (I.M.)	75-165	166-278	279-390	391-503
Methadone (oral)	20-44	45-74	75-104	105-134
Methadone (I.M.)	10-22	23-37	38-52	53-67
Fentanyl transdermal recommended dose (mcg/h)	**25 mcg/h**	**50 mcg/h**	**75 mcg/h**	**100 mcg/h**

[1] The table should NOT be used to convert from transdermal fentanyl (eg, Duragesic®) to other opioid analgesics. Rather, following removal of the patch, titrate the dose of the new opioid until adequate analgesia is achieved.

[2] Duragesic® product insert, Janssen Pharmaceutica, Feb 2008.

Opioid Analgesics Initial Oral Dosing Commonly Used for Severe Pain

Drug	**Equianalgesic Dose (mg)**		**Initial Oral Dose**	
	Oral[1]	**Parenteral[2]**	**Children (mg/kg)**	**Adults (mg)**
Buprenorphine	—	0.4	—	—
Butorphanol	—	2	—	—
Hydromorphone	7.5	1.5	0.06	4-8
Levorphanol	Acute: 4 Chronic: 1	Acute: 2 Chronic: 1	0.04	2-4
Meperidine	300	75	Not recommended	
Methadone	10	5	0.2	5-10
Morphine	30	10	0.3	15-30
Nalbuphine	—	10	—	—
Pentazocine	50	30	—	—
Oxycodone	20	—	0.3	10-20
Oxymorphone	—	1	—	—

From “Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain,” *Am*

Pain Soc, Fifth Ed.
[1] Elderly: Starting dose should be lower for this population group
[2] Standard parenteral doses for acute pain in adults; can be used to doses for I.V. infusions and repeated small I.V. boluses. Single I.V. boluses, use half the I.M. dose. Children >6 months: I.V. dose = parenteral equianalgesic dose x weight (kg)/100

Dosing: ElderlyElderly have been found to be twice as sensitive as younger patients to the effects of fentanyl. A wide range of doses may be used. When choosing a dose, take into consideration the following patient factors: age, weight, physical status, underlying disease states, other drugs used, type of anesthesia used, and the surgical procedure to be performed.

Transmucosal lozenge (eg, Actiq®): In clinical trials, patients who were >65 years of age were titrated to a mean dose that was 200 mcg less than that of younger patients.

Dosing: Pediatric**Note:** These are guidelines and do not represent the maximum doses that may be required in all patients. Doses and dosage intervals should be titrated to pain relief/prevention. Monitor vital signs routinely. Single I.M. doses have a duration of 1-2 hours, single I.V. doses last 0.5-1 hour.

Adjunct to anesthesia (induction and maintenance): Children ≥2 years: I.V.: 2-3 mcg/kg/dose every 1-2 hours as needed

Pain management (unlabeled use): I.V.: 0.5-2 mcg/kg/dose given every 1-2 hours as needed; continuous infusion: 0.5-2 mcg/kg/hour; titrate to desired effects

Chronic pain management: Children ≥2 years (opioid-tolerant patients): Transdermal patch: Refer to adult dosing.

Minor procedures/analgesia (unlabeled use): I.V.:

Children 1-12 years: 0.5-2 mcg/kg/dose given 3 minutes prior to procedure; may repeat every 1-2 hours

Children >12 years: 0.5-2 mcg/kg/dose (maximum 50 mcg/dose) given 3 minutes prior to procedure; may repeat in 5 minutes if necessary; if more than 2 doses are needed, repeat with a maximum of 25 mcg/dose up to 5 times

Continuous sedation/analgesia: 0.5-2 mcg/kg/hour; titrate to desired effect

Breakthrough cancer pain: Children ≥16 years: Transmucosal lozenge: Refer to adult dosing.

Dosing: Hepatic ImpairmentFentanyl kinetics may be altered in hepatic disease.

Calculations

- Fentanyl
- Fentanyl Transdermal Conversion
- Opioid Agonist Conversion

Administration: I.V.Administer as slow I.V. infusion over 1-2 minutes. May also be administered as continuous infusion or PCA (unlabeled use) routes. Muscular rigidity may occur with rapid I.V. administration.

Administration: I.V. DetailpH: 4.0-7.5

Administration: Oral

Lozenge: Foil overwrap should be removed just prior to administration. Place the unit in mouth and allow it to dissolve. Do not chew. Lozenge may be moved from one side of the mouth to the other. The unit should be consumed over a period of 15 minutes. Handle should be removed after it is consumed or if patient has achieved an adequate response and/or shows signs of respiratory depression.

Buccal tablet: Patient should not open blister until ready to administer. The blister backing should be peeled back to expose the tablet; tablet should not be pushed out through the blister. Immediately use tablet once removed from blister. Place entire tablet in the buccal cavity (above a rear molar, between the upper cheek and gum). Tablet should not be broken, sucked, chewed, or swallowed. Should dissolve in about 14-25 minutes when left between the cheek and the gum. If remnants remain they may be swallowed with water.

Administration: TopicalTransdermal patch (eg, Duragesic®): Apply to nonirritated and nonirradiated skin, such as chest, back, flank, or upper arm. Do not shave skin; hair at application site should be clipped. Prior to application, clean site with clear water and allow to dry completely. Do not use damaged, cut or leaking patches; patch may be less effective. Skin exposure from fentanyl gel leaking from patch may lead to serious adverse effects; thoroughly wash affected skin surfaces with water (do not use soap). Firmly press in place and hold for 30 seconds. Change patch every 72 hours. Do **not** use soap, alcohol, or other solvents to remove transdermal gel if it accidentally touches skin; use copious amounts of water. Avoid exposing application site to external heat sources (eg, heating pad, electric blanket, heat lamp, hot tub).

Dietary ConsiderationsTransmucosal lozenge contains 2 g sugar per unit.

Storage

Injection formulation: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light.

Transdermal patch: Do not store above 25°C (77°F).

Transmucosal (buccal tablets, lozenge): Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from freezing and moisture.

CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Alatrofloxacin, amphotericin B cholesteryl sulfate complex, atracurium, cisatracurium, diltiazem, dobutamine, dopamine, enalaprilat, epinephrine, esmolol, etomidate, furosemide, gatifloxacin, heparin, hydrocortisone sodium succinate, hydromorphone, labetalol, levofloxacin, linezolid, lorazepam, midazolam, milrinone, morphine, nafcillin, nicardipine, nitroglycerin, norepinephrine, pancuronium, potassium chloride, propofol, ranitidine, remifentanil, sargramostim, thiopental, vecuronium, vitamin B complex with C.

Compatibility in syringe: Compatible: Atracurium, atropine, bupivacaine with ketamine, butorphanol, chlorpromazine, cimetidine, clonidine with lidocaine, dimenhydrinate, diphenhydramine, droperidol, heparin, hydromorphone, hydroxyzine, meperidine, metoclopramide, midazolam, morphine, ondansetron, pentazocine, perphenazine, prochlorperazine edisylate, promazine, promethazine, ranitidine, scopolamine. **Incompatible:** Pentobarbital.

Compatibility when admixed: Compatible: Bupivacaine. **Incompatible:** Fluorouracil, methohexital, pentobarbital, thiopental.

Restrictions C-II

An FDA-approved medication guide for buccal tablet (Fentora®), transmucosal lozenge (eg, Actiq®), and transdermal patch (eg, Duragesic®) must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

Contraindications Hypersensitivity to fentanyl or any component of the formulation

Transdermal system: Severe respiratory disease or depression including acute asthma (unless patient is mechanically ventilated); paralytic ileus; patients requiring short-term therapy, management of intermittent pain

Transmucosal buccal tablets (Fentora®), lozenges (eg, Actiq®), and/or transdermal patches (eg, Duragesic®): Contraindicated in the management of acute or postoperative pain and in patients who are not opioid tolerant

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Abuse/misuse/diversion: See “Other warnings/precautions” below.
- Transmucosal: See “Dosage form specific issues” and "Concurrent drug therapy issues" below.
- Transdermal patches: See “Special populations" and "Dosage form specific issues” below.

Concerns related to adverse effects:

- Opioid agonist toxicities: Shares the toxic potentials of opiate agonists, and precautions of opiate agonist therapy should be observed.
- Opioid-nontolerant patients should not receive some formulations/strengths of fentanyl, including buccal tablets (Fentora®), lozenges (Actiq®), or transdermal patches. Patients are considered opioid-tolerant if they have been receiving at least:

  60 mg of oral morphine/day, **or**

  25 mcg of transdermal fentanyl/hour, **or**

  30 mg of oxycodone/day, **or**

  8 mg oral hydromorphone/day, **or**

  Equianalgesic dose of another opioid for at least 1 week.
- Respiratory depression: **[U.S. Boxed Warning] Actiq®, Duragesic®, Fentora®: May cause potentially life-threatening hypoventilation, respiratory depression, and/or death;** Actiq®, Duragesic®, Fentora® should only be prescribed for opioid-tolerant patients. Risk of respiratory depression increased in elderly patients, debilitated patients, and patients with conditions associated with hypoxia or hypercapnia; usually occurs after administration of initial dose in nontolerant patients or when given with other drugs that depress respiratory function.

Disease-related concerns:

- Bradycardia: Use with caution when administering to patients with bradycardia or bradyarrhythmias.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur. Opioids may obscure the clinical course of head injury.
- Hepatic impairment: Use with caution in patients with hepatic dysfunction.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

Concurrent drug therapy issues:

- CNS depressants: When using with other CNS depressants, reduce dose of one or both agents.
- CYP3A4 inhibitors: **[U.S. Boxed Warning]: Use with strong or moderate CYP3A4 inhibitors; may result in increased effects and potential respiratory depression.**

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.
- Pediatrics: Safety and efficacy have not been established in children <16 years of age for the lozenge and <18 years of age for the buccal tablet. **[U.S. Boxed Warning]: Safety and efficacy of the transdermal patch have been limited to children ≥2 years of age who are opioid-tolerant.**

Dosage form specific issues:

- Injection: May cause muscle rigidity; usually occurs following high doses; respiratory depression may persist beyond analgesic effect; monitor closely.
- Transmucosal: Lozenge (eg, Actiq®), buccal tablet (Fentora®): **[U.S. Boxed Warning]: Should be used only for the care of opioid-tolerant cancer patients with breakthrough pain and is intended for use by specialists who are knowledgeable in treating cancer pain.** Not approved for use in management of acute or postoperative pain. **[U.S. Boxed Warning]: Buccal tablet and lozenge preparations contain an amount of medication that can be fatal to children. Keep all units out of the reach of children and discard any open units properly. Patients and caregivers should be counseled on the dangers to children including the risk of exposure to partially-consumed units.**
- Transmucosal: Buccal tablet (Fentora®): **[U.S. Boxed Warning]: Due to the higher bioavailability of fentanyl in Fentora®, when converting patients from oral transmucosal fentanyl citrate (OTFC, Actiq®) to Fentora®, do not substitute Fentora® on a mcg-per-mcg basis for any other fentanyl product. [U.S. Boxed Warning]: Fentora® is contraindicated in the management of acute or postoperative pain, including headache/migraine. Serious adverse events, including death, have been reported when used inappropriately (improper dose or patient selection). [U.S. Boxed Warning]: Patients using Fentora® who experience breakthrough pain may only take one additional dose using the same strength and must wait four hours before taking another dose.**
- Transdermal patch: **[U.S. Boxed Warning]: Indicated for the management of persistent moderate-to-severe pain when around the clock pain control is needed for an extended time period. Should only be used in patients who are already receiving opioid therapy, are opioid tolerant, and who require a total daily dose equivalent to 25 mcg/hour transdermal patch. Contraindicated in patients who are not opioid tolerant, in the management of short-term analgesia, or in the management of postoperative pain. Should be applied only to intact skin. Use of a patch that has been cut, damaged, or altered in any way may result in overdosage.** Serum fentanyl concentrations may increase approximately one-third for patients with a body temperature of 40°C secondary to a temperature-dependent increase in fentanyl release from the patch and increased skin permeability. **[U.S. Boxed Warning]: Avoid exposure of application site and surrounding area to direct external heat sources.** Patients who experience fever or increase in core temperature should be monitored closely. Patients who experience adverse reactions should be monitored for at least 24 hours after removal of the patch. Transdermal patch does not contain any metal-based compounds; the printed ink used to indicate strength on the outer surface of the patch does contain titanium dioxide, but the amount is minimal; adverse events have not been reported while wearing during an MRI.

Other warnings/precautions:

- Abuse/misuse/diversion: **[U.S. Boxed Warning]: Healthcare provider should be alert to problems of abuse, misuse, and diversion.**
- Optimal regimen: An opioid-containing analgesic regimen should be tailored to each patient's needs and based upon the type of pain being treated (acute versus chronic), the route of administration, degree of tolerance for opioids (naive versus chronic user), age, weight, and medical condition. The optimal analgesic dose varies widely among patients; doses should be titrated to pain relief/prevention.
- Rapid infusion: Inject slowly over 3-5 minutes; rapid I.V. infusion may result in skeletal muscle and chest wall rigidity, impaired ventilation, or respiratory distress/arrest; nondepolarizing skeletal muscle relaxant may be required.
- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsThe elderly may be particularly susceptible to the CNS depressant and constipating effects of narcotics; therefore, use with caution. The effect of age on the pharmacokinetics of Fentora® (oral transmucosal buccal tablets) has not been studied.

Pregnancy Risk FactorC/D (prolonged use or high doses at term)

Pregnancy ConsiderationsFentanyl crosses the placenta and has been used safely during labor. Chronic use during pregnancy has shown detectable serum levels in the newborn with mild opioid withdrawal (case report). Transdermal patch, transmucosal lozenge, and buccal tablet (Fentora®) are not recommended for analgesia during labor and delivery.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsFentanyl is excreted in low concentrations into breast milk. Breast-feeding is considered acceptable following single doses to the mother; however, no information is available when used long-term. **Note:** Transdermal patch, transmucosal lozenge, and buccal tablet (Fentora®) are not recommended in nursing women due to potential for sedation and/or respiratory depression.

Adverse Reactions

>10%:

Cardiovascular: Bradycardia, edema

Central nervous system: CNS depression, confusion, dizziness, drowsiness, headache, sedation

Gastrointestinal: Nausea, vomiting, constipation, xerostomia

Local: Application-site reaction erythema

Neuromuscular & skeletal: Chest wall rigidity (high dose I.V.), muscle rigidity, weakness

Ocular: Miosis

Respiratory: Dyspnea, respiratory depression

Miscellaneous: Diaphoresis

1% to 10%:

Cardiovascular: Cardiac arrhythmia, chest pain, flushing, hyper-/hypotension, orthostatic hypotension, pallor, palpitation, peripheral edema, syncope, tachycardia, vasodilation

Central nervous system: Abnormal dreams, abnormal thinking, agitation, amnesia, anxiety, chills, depression, euphoria, fatigue, fever, hallucinations, hypoesthesia, insomnia, lethargy, migraine, nervousness, paranoid reaction, stupor, vertigo

Dermatologic: Alopecia, bruising, cellulitis, erythema, hyperhidrosis, papules, pruritus, rash

Endocrine & metabolic: Breast pain, dehydration, hyper-/hypocalcemia, hyper-/hypoglycemia, hypoalbuminemia, hypokalemia, hypomagnesemia

Gastrointestinal: Abdominal pain, abnormal taste, anorexia, biliary tract spasm, diarrhea, dyspepsia, dysphagia (buccal tablet), flatulence, GI hemorrhage, gingival pain (buccal tablet), gingivitis (lozenge), glossitis (lozenge), ileus, periodontal abscess (lozenge/buccal tablet), stomatitis (lozenge/buccal tablet), weight loss

Genitourinary: Dysuria, urinary incontinence, urinary retention, vaginitis, vaginal hemorrhage

Hematologic: Anemia, leukopenia, neutropenia, thrombocytopenia

Hepatic: Ascites, jaundice

Local: Application site pain, application site irritation

Neuromuscular & skeletal: Abnormal coordination, abnormal gait, arthralgia, back pain, myalgia, neuropathy, paresthesia, rigors, tremor

Renal: Renal failure

Respiratory: Apnea, asthma, bronchitis, cough, epistaxis, hemoptysis, hypoventilation, hypoxia, nasopharyngitis, pharyngolaryngeal pain, pharyngitis, pneumonia, rhinitis, sinusitis, upper respiratory infection, wheezing

Miscellaneous: Hiccups, flu-like syndrome, lymphadenopathy, speech disorder

<1%, postmarketing, and/or case reports: Abdominal distention, amblyopia, allergic reaction, anaphylaxis, angina, anorgasmia, aphasia, bladder pain, blurred vision, bronchospasm, CNS excitation or delirium, cold/clammy skin, dental caries (lozenge), depersonalization, DVT, dysesthesia, ejaculatory difficulty, emotional lability, eructation, esophageal stenosis, exfoliative dermatitis, fecal impaction, flank pain, gum line erosion (lozenge), gum hemorrhage (lozenge), hematuria, hostility, hyper-/hypotonia, laryngospasm, libido decreased, moniliasis (lozenge/buccal tablet), mouth ulceration (lozenge/buccal tablet), myasthenia, nocturia, oliguria, pancytopenia, paradoxical dizziness, physical and psychological dependence with prolonged use, pleural effusion, polyuria, pustules, speech disorder, stertorous breathing, seizure, sputum increased, tooth loss (lozenge), urinary tract spasm, urticaria, vertigo

Oncology: VesicantNo

Metabolism/Transport Effects **Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Beta-Blockers: Anilidopiperidine Opioids may enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): Anilidopiperidine Opioids may enhance the bradycardic effect of Calcium Channel Blockers (Nondihydropyridine). Anilidopiperidine Opioids may enhance the hypotensive effect of Calcium Channel Blockers (Nondihydropyridine). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

MAO Inhibitors: Anilidopiperidine Opioids may enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. *Risk D: Consider therapy modification*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of FentaNYL. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of FentaNYL. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: St John's wort may decrease fentanyl levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersRespiratory and cardiovascular status, blood pressure, heart rate; signs of misuse, abuse, or addiction

Transdermal patch: Monitor for 24 hours after application of first dose

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for additive or adverse interactions. Monitor therapeutic effectiveness and signs of adverse or overdose reactions. Monitor blood pressure, CNS and respiratory status, and degree of sedation at beginning of therapy and at regular intervals with long-term use. Monitor closely for 24 hours after transdermal product is removed. Order safety precautions for inpatient use. May cause physical and/or psychological dependence. Assess knowledge/teach patient appropriate use (if self-administered), adverse reactions to report, and appropriate interventions to reduce side effects.

Patient EducationTake exactly as prescribed. Do not use more often or increase dosage, and do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. If using oral transmucosal lozenge, you may be at risk for dental carries due to the sugar content. Maintain good oral hygiene. If using patch, avoid exposing application site to external heat sources (eg, heating pad, electric blanket, hot tub, heat lamp). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause hypotension, dizziness, drowsiness, impaired coordination, or blurred vision (use caution when driving, climbing stairs, or changing position - rising from sitting or lying to standing, or when engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help; if unresolved, consult prescriber about use of stool softeners). Report acute dizziness, chest pain, slow or rapid heartbeat, acute headache; confusion or changes in mentation; changes in voiding frequency or amount; swelling of extremities or unusual weight gain; temperature >102°F; shortness of breath or respiratory difficulty; or vision changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Transdermal patch: Apply to clean, dry skin, immediately after removing from package. Firmly press in place and hold for 30 seconds.

Transmucosal lozenge (eg, Actiq®): Contains an amount of medication that can be fatal to children. Keep all units out of the reach of children and discard any open units properly. Actiq® Welcome Kits are available which contain educational materials, safe storage, and disposal instructions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: Strengths expressed as base.

Injection, solution, as citrate [preservative free]: 0.05 mg/mL (2 mL, 5 mL, 10 mL, 20 mL; 30 mL [DSC]; 50 mL)

Sublimaze®: 0.05 mg/mL (2 mL, 5 mL, 10 mL [DSC], 20 mL)

Lozenge, oral, as citrate [transmucosal]: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg

Actiq®: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg [contains sugar 2 g/lozenge; berry flavor]

Powder, for prescription compounding, as citrate: USP (1 g)

Tablet, for buccal application, as citrate:

Fentora®: 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, 800 mcg

Transdermal system, topical, as base: 12 (5s) [delivers 12.5 mcg/hour; 3.13 cm^2]; 12 (5s) [delivers 12.5 mcg/hour; 5 cm^2]; 25 (5s) [delivers 25 mcg/hour; 10 cm^2]; 25 (5s) [delivers 25 mcg/hour; 6.25 cm^2]; 50 (5s) [delivers 50 mcg/hour; 12.5 cm^2]; 50 (5s) [delivers 50 mcg/hour; 20 cm^2]; 75 (5s) [delivers 75 mcg/hour; 18.75 cm^2]; 75 (5s) [delivers 75 mcg/hour; 30 cm^2]; 100 (5s) [delivers 100 mcg/hour; 25 cm^2]; 100 (5s) [delivers 100 mcg/hour; 40 cm^2]

Duragesic®: 12 (5s) [delivers 12.5 mcg/hour; 5 cm^2; contains ethanol 0.1 mL/10 cm^2]; 25 (5s) [delivers 25 mcg/hour; 10 cm^2; contains ethanol 0.1 mL/10 cm^2]; 50 (5s) [delivers 50 mcg/hour; 20 cm^2; contains ethanol 0.1 mL/10 cm^2]; 75 (5s) [delivers 75 mcg/hour; 30 cm^2; contains ethanol 0.1 mL/10 cm^2]; 100 (5s) [delivers 100 mcg/hour; 40 cm^2; contains ethanol 0.1 mL/10 cm^2]

Generic AvailableYes: Excludes buccal tablet

Pricing: U.S. (www.drugstore.com)

Lozenge (Actiq)

200 mcg (20): $696.07

400 mcg (20): $888.28

600 mcg (20): $1076.77

800 mcg (20): $1255.99

1200 mcg (10): $708.23

1600 mcg (20): $1973.95

Lozenge (Fentanyl Citrate)

400 mcg (20): $399.95

Patch, 72-hour (Duragesic-100)

100 mcg/hr (20): $1497.98

Patch, 72-hour (Duragesic-12)

12.5 mcg/hr (20): $344.54

Patch, 72-hour (Duragesic-25)

25 mcg/hr (20): $416.43

Patch, 72-hour (Duragesic-50)

50 mcg/hr (20): $748.96

Patch, 72-hour (Duragesic-75)

75 mcg/hr (20): $1160.84

Patch, 72-hour (Fentanyl)

12 (12.5) mcg/hr (5): $67.99

25 mcg/hr (20): $266.65

50 mcg/hr (20): $526.62

75 mcg/hr (20): $633.31

100 mcg/hr (20): $839.99

Tablets (Fentora)

200 mcg (20): $412.65

Mechanism of ActionBinds with stereospecific receptors at many sites within the CNS, increases pain threshold, alters pain reception, inhibits ascending pain pathways

Pharmacodynamics/Kinetics

Onset of action: Analgesic: I.M.: 7-8 minutes; I.V.: Almost immediate; Transmucosal: 5-15 minutes

Peak effect: Transmucosal: Analgesic: 15-30 minutes

Duration: I.M.: 1-2 hours; I.V.: 0.5-1 hour; Transmucosal: Related to blood level; respiratory depressant effect may last longer than analgesic effect

Absorption:

Transdermal: Initial application: Gradually absorbed for the first 12-24 hours, followed by a constant absorption for the remainder of the dosing interval

Transmucosal, buccal tablet: Rapid, ~50% from the buccal mucosa; remaining 50% swallowed with saliva and slowly absorbed from GI tract.

Transmucosal, lozenge: Rapid, ~25% from the buccal mucosa; 75% swallowed with saliva and slowly absorbed from GI tract

Distribution: 4-6 L/kg; Highly lipophilic, redistributes into muscle and fat

Protein binding: 80% to 85%

Metabolism: Hepatic, primarily via CYP3A4

Bioavailability: Total (transmucosal and GI absorption): Buccal: 65% (range: 45% to 85%); Lozenge: 47% (range: 37% to 57%)

Half-life elimination:

I.V.: 2-4 hours

Transdermal patch: 17 hours (13-22 hours, half-life is influenced by absorption rate)

Transmucosal: Lozenge: 7 hours; Buccal tablet: 100-200 mcg: 3-4 hours, 400-800 mcg: 11-12 hours

Time to peak: Buccal tablet: 20-240 minutes (median: 47 minutes); Lozenge: 20-480 minutes (median: 20-40 minutes); Transdermal patch: 24-72 hours, after several sequential 72-hour applications, steady state serum concentrations are reached

Excretion: Urine 75% (primarily as metabolites, <7% to 10% as unchanged drug); feces ~9%

Pharmacotherapy PearlsFentanyl is 50-100 times as potent as morphine; morphine 10 mg I.M. is equivalent to fentanyl 0.1-0.2 mg I.M.; fentanyl has less hypotensive effects than morphine due to lack of histamine release. However, fentanyl may cause rigidity with high doses. If the patient has required high-dose analgesia or has used for a prolonged period (~7 days), taper dose to prevent withdrawal; monitor for signs and symptoms of withdrawal.

Transmucosal (oral lozenge): Disposal of lozenge units: After consumption of a complete unit, the handle may be disposed of in a trash container that is out of the reach of children. For a partially-consumed unit, or a unit that still has any drug matrix remaining on the handle, the handle should be placed under hot running tap water until the drug matrix has dissolved. Special child-resistant containers are available to temporarily store partially consumed units that cannot be disposed of immediately.

Transdermal patch (Duragesic®): Upon removal of the patch, ~17 hours are required before serum concentrations fall to 50% of their original values. Opioid withdrawal symptoms are possible. Gradual downward titration (potentially by the sequential use of lower-dose patches) is recommended. Keep transdermal patch (both used and unused) out of the reach of children. Do **not** use soap, alcohol, or other solvents to remove transdermal gel if it accidentally touches skin as they may increase transdermal absorption, use copious amounts of water. Avoid exposure of direct external heat sources (eg, heating pads, electric blankets, heat lamps, saunas, hot tubs, heated water beds) to application site.

Dental Health Professional ConsiderationsTransdermal fentanyl should not be used as a pain reliever in dentistry due to danger of hypoventilation

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia, changes in salivation (normal salivary flow resumes upon discontinuation), and orthostatic hypotension. Actiq® may contribute to dental carries due to sugar content of oral lozenge; advise patients to maintain good oral hygiene. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness, sedation, and depression are common; may rarely cause paradoxical CNS excitement or delirium

Mental Health: Effects on Psychiatric TreatmentConcurrent use with low potency antipsychotics and TCAs may produce additive hypotension

Cardiovascular ConsiderationsMay precipitate bradycardia, hypotension, and peripheral vasodilation. These properties necessitate close hemodynamic monitoring.

Anesthesia and Critical Care Concerns/Other ConsiderationsWhen developing a therapeutic plan for pain control, scheduled, intermittent opioid dosing or continuous infusion is preferred over the "as needed" regimen. The 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) recommend fentanyl in patients who need immediate pain relief because of its rapid onset of action. Repeated doses or a continuous infusion of fentanyl may cause accumulation. Fentanyl or hydromorphone is preferred in patients who are hypotensive or have renal dysfunction. Morphine or hydromorphone is recommended for intermittent, scheduled therapy. Both have a longer duration of action requiring less frequent administration. Fentanyl is great to prevent pain during a procedure and can be dosed intermittently for such an application. Prolonged analgesia requires an infusion.

Fentanyl has less hypotensive effects than morphine due to lack of histamine release; however, fentanyl may cause rigidity with high doses. If the patient has required high-dose analgesia or has used for a prolonged period (~7 days), taper dose to prevent withdrawal; monitor for signs and symptoms of withdrawal.

Index TermsFentanyl Citrate; Fentanyl Hydrochloride; OTFC (Oral Transmucosal Fentanyl Citrate)

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International Brand NamesActiq (AU, CH, DE, DK, ES, FI, FR, GB, IE, NO, SE); Durogesic (CL, KP, MX, PL, SG); Fenta (IL); Fentabbott (BR); Fentanest (IT, MX); Fentanyl (CR, DO, GT, HN, NI, PA, PL, SV); Fentanyl Janssen (PL); Fentas (KP); Ionsys (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Leptanal (NO, SE); Matrifen (DK, GB); Sublimax (PH); Sublimaze (AR, AU, GB, IE, PH, ZA); Tanyl (IL); Trofentyl (IN)

Ferric Gluconate

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Ferrlecit® may be confused with Ferralet®

Pronunciation(FER ik GLOO koe nate)

U.S. Brand NamesFerrlecit®

Canadian Brand NamesFerrlecit®

Pharmacologic CategoryIron Salt

Use: Labeled IndicationsRepletion of total body iron content in patients with iron-deficiency anemia who are undergoing hemodialysis in conjunction with erythropoietin therapy

Dosing: AdultsRepletion of iron in hemodialysis patients: I.V.: 125 mg elemental iron per 10 mL (either by I.V. infusion or slow I.V. injection). Most patients will require a cumulative dose of 1 g elemental iron over approximately 8 sequential dialysis treatments to achieve a favorable response.

Note: A test dose of 2 mL diluted in NS 50 mL administered over 60 minutes was previously recommended (not in current manufacturer labeling). Doses >125 mg are associated with increased adverse events.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRepletion of iron in hemodialysis patients: I.V.: Children ≥6 years: 1.5 mg/kg of elemental iron (maximum: 125 mg/dose) diluted in NS 25 mL, administered over 60 minutes at 8 sequential dialysis sessions

Administration: I.V.I.V.: Adults: May be diluted prior to administration; avoid rapid administration. Solutions diluted for infusion should be infused over 1 hour. If administered undiluted, infuse slowly at a rate of up to 12.5 mg/minute.

StorageStore at 20°C to 25°C (68°F to 77°F). Do not freeze.

ReconstitutionFor I.V. infusion, dilute 10 mL ferric gluconate in 0.9% sodium chloride (children: 25 mL NS, adults: 100 mL NS); use immediately after dilution.

CompatibilityStable with 0.9% sodium chloride; do not mix with parenteral nutrition solutions or other medications.

ContraindicationsHypersensitivity to ferric gluconate or any component of the formulation; use in any anemia not caused by iron deficiency; iron overload

Warnings/Precautions

Concerns related to adverse effects:

- Flushing/hypotension: Flushing and transient hypotension may occur. May augment hemodialysis-induced hypotension.
- Hypersensitivity reactions: Potentially serious hypersensitivity reactions may occur; fatal immediate hypersensitivity reactions have occurred with other iron carbohydrate complexes. Avoid rapid administration.

Special populations:

- Elderly: Use with caution in the elderly.
- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Dosage form specific issues:

- Benzyl alcohol: Contains benzyl alcohol which has been associated with "gasping syndrome" in neonates.

Other warnings/precautions:

- Appropriate use: Use only in patients with documented iron deficiency; caution with hemoglobinopathies or other refractory anemias as iron overload may occur.

Geriatric ConsiderationsStudies in the elderly have not been done, nor were there sufficient numbers of the elderly in premarketing studies to identify any differences in the elderly using this drug. Monitor dose closely so as to avoid iron overload.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events were not observed in animal reproduction studies. There are no well-controlled studies available in pregnant women. It is recommended that pregnant women meet the dietary requirements of iron with diet and/or supplements in order to prevent adverse events associated with iron deficiency anemia in pregnancy. Treatment of iron deficiency anemia in pregnant women is the same as in nonpregnant women and in most cases, oral iron preparations may be used. Except in severe cases of maternal anemia, the fetus achieves normal iron stores regardless of maternal concentrations.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIron is normally found in breast milk. Breast milk or iron fortified formulas generally provide enough iron to meet the recommended dietary requirements of infants. The amount of iron in breast milk is generally not influenced by maternal iron status.

Adverse ReactionsFrequency not defined.

Cardiovascular: Angina, bradycardia, chest pain, edema, hyper-/hypotension, hypervolemia, MI, pulmonary edema, syncope, tachycardia, thrombosis, vasodilation

Central nervous system: Agitation, chills, dizziness, fatigue, fever, headache, insomnia, malaise, pain, somnolence

Dermatologic: Pruritus, rash

Endocrine & metabolic: Hyper-/hypokalemia, hypoglycemia

Gastrointestinal: Abdominal pain, anorexia, diarrhea, dyspepsia, epigastric pain, eructation, flatulence, melena, nausea, vomiting

Genitourinary: Urinary tract infection

Hematologic: Abnormal erythrocytes, leukocytosis, lymphadenopathy

Local: Injection site reactions, injection site pain

Neuromuscular & skeletal: Arthralgia, back pain, cramps, groin pain, leg cramps, myalgia, paresthesia, rigors, weakness

Ocular: Blurred vision, conjunctivitis

Respiratory: Cough, dyspnea, pneumonia, rhinitis, upper respiratory infection

Miscellaneous: Carcinoma, diaphoresis increased, flu-like syndrome, hypersensitivity reactions, infection, sepsis

Postmarketing and/or case reports: Dry mouth, dysgeusia, hemorrhage, hypertonia, hypoesthesia, loss of consciousness, nervousness, pallor, phlebitis, seizure, shock, skin discoloration

Drug Interactions

ACE Inhibitors: May enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Cefdinir: Iron Salts may decrease the serum concentration of Cefdinir. Red-appearing, non-bloody stools may also develop due to the formation of an insoluble iron-cefdinir complex. Management: Avoid concurrent cefdinir and iron when possible. Separating doses by several hours may minimize interaction. Iron-containing infant formulas do not appear to interact with cefdinir. *Risk D: Consider therapy modification*

Dimercaprol: May enhance the nephrotoxic effect of Iron Salts. *Risk X: Avoid combination*

Phosphate Supplements: Iron Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Iron Salts. Iron Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Test InteractionsSerum or transferrin bound iron levels may be falsely elevated if assessed within 24 hours of ferric gluconate administration. Serum ferritin levels may be falsely elevated for 5 days after ferric gluconate administration.

Monitoring ParametersHemoglobin and hematocrit, serum ferritin, iron saturation; vital signs

NKF K/DOQI guidelines recommend that iron status should be monitored monthly during initiation through the percent transferrin saturation (TSAT) and serum ferritin.

Reference RangeCKD patients should have sufficient iron to achieve and maintain hemoglobin of 11-12 g/dL. To achieve and maintain this target Hgb, sufficient iron should be administered to maintain a TSAT of 20%, and a serum ferritin level >100 ng/mL (nondialysis chronic kidney disease and peritoneal dialysis chronic kidney disease) or serum ferritin level >200 ng/mL (hemodialysis chronic kidney disease).

Nursing: Physical Assessment/MonitoringAssess results of test dose, infusion rate, effectiveness of therapy (laboratory results), and adverse reactions at beginning of therapy and periodically during therapy. Monitor blood pressure during infusion. Hypotension can occur. Be alert to the potential for hypersensitivity reactions. Assess knowledge/teach patient adverse symptoms to report.

Monitoring: Lab TestsHemoglobin and hematocrit, serum ferritin, iron saturation

NKF K/DOQI guidelines recommend that iron status should be monitored monthly during initiation through the percent transferrin saturation (TSAT) and serum ferritin.

Patient EducationThis medication will be administered by I.V. in conjunction with your dialysis treatment. Report chest pain, rapid heartbeat, or palpitations; respiratory difficulty; headache, dizziness, agitation, or inability to sleep; nausea, vomiting, abdominal or flank pain; or skin rash, itching, or redness. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Ferrlecit®: Elemental iron 12.5 mg/mL (5 mL) [contains benzyl alcohol and sucrose 20%]

Generic AvailableNo

ManufacturerWatson Pharma, Inc

Mechanism of ActionSupplies a source to elemental iron necessary to the function of hemoglobin, myoglobin and specific enzyme systems; allows transport of oxygen via hemoglobin

Pharmacodynamics/KineticsHalf-life elimination: Bound: 1 hour

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Do not prescribe tetracyclines simultaneously with iron since GI tract absorption of both tetracycline and iron may be inhibited.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, insomnia, agitation

Mental Health: Effects on Psychiatric TreatmentMay cause hypotension; caution with low potency antipsychotics

Index TermsSodium Ferric Gluconate

References

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“Routine Iron Supplementation During Pregnancy. Review Article. US Preventive Services Task Force,” *JAMA*, 1993, 270(23):2848-54.[PubMed 8133626]

International Brand NamesFerrlecit (CA)

Ferric Hexacyanoferrate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(FER ik hex a SYE an oh fer ate)

U.S. Brand NamesRadiogardase®

Pharmacologic CategoryAntidote

Use: Labeled IndicationsTreatment of known or suspected internal contamination with radioactive cesium and/or radioactive or nonradioactive thallium

Dosing: Adults

Internal contamination with radioactive cesium and/or radioactive or nonradioactive thallium: Oral: 3 g 3 times/day; treatment should begin as soon as possible following exposure, but is also effective if therapy is delayed

Note: Cesium exposure: Once internal radioactivity is substantially decreased, dosage may be reduced to 1-2 g 3 times/day to improve gastrointestinal tolerance

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricInternal contamination with radioactive cesium and/or radioactive or nonradioactive thallium: Oral: Children:

2-12 years: 1 g 3 times/day; treatment should begin as soon as possible following exposure, but is also effective if therapy is delayed

>12 years: Refer to adult dosing.

Dosing: Renal ImpairmentStudies have not been conducted; however, ferric hexacyanoferrate is not renally eliminated.

Dosing: Hepatic ImpairmentStudies have not been conducted; however, effectiveness may be decreased due to decreased bile excretion of cesium and thallium.

Administration: OralCapsules may be opened and mixed with bland food or liquid (instruct patients that mouth and teeth may become blue). Administer with food to stimulate excretion of cesium or thallium. Increase dietary fiber or take with fiber laxative to decrease constipation.

Dietary ConsiderationsTake with food to stimulate excretion of cesium or thallium. A high-fiber diet or fiber laxative is recommended to avoid constipation.

StorageStore in the dark at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsNone known

Allergy Considerations

- Iron Salt Allergy

Warnings/Precautions

Disease-related concerns:

- Cardiac arrhythmias: Use with caution in patients with pre-existing cardiac arrhythmias.
- Electrolyte imbalances: Use with caution in patients with electrolyte imbalances.
- Gastric immotility: Use with caution in patients with decreased gastric motility; constipation should be avoided to prevent increased radiation absorption from the gastrointestinal tract.

Other warnings/precautions:

- Patient information: Patients should be instructed to minimize radiation exposure to others.
- Radiation toxicity: Appropriate use: Ferric hexacyanoferrate increases the rate of elimination of thallium and cesium; it does not treat complications of radiation exposure. Supportive treatment for radiation toxicity should be given concomitantly. Additional decontamination and/or treatment may be needed if exposure to other radioactive isotopes is known or suspected.

Pregnancy Risk FactorC

Pregnancy ConsiderationsFerric hexacyanoferrate is not absorbed from the gastrointestinal tract and reproduction studies have not been conducted. Cesium-137 crosses the placenta; in one case, reported levels were equal in the mother and the neonate. Thallium also crosses the placenta; fetal death, failure to thrive, and alopecia in the neonate have been reported. Toxicity from exposure to thallium or radioactive cesium is expected to be greater than the risk of toxicity to ferric hexacyanoferrate. Oligospermia or azoospermia has been reported following whole body radiation in doses >1 Gy of cesium-137.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsExcretion of ferric hexacyanoferrate in breast milk is not known, but would not be expected. Cesium and thallium are excreted in breast milk; internally contaminated mothers should not breast-feed.

Adverse Reactions

>10%: Gastrointestinal: Constipation (24%)

1% to 10%: Endocrine & metabolic: Hypokalemia (7%)

Frequency not defined: Gastrointestinal: Gastric distress, fecal discoloration (blue)

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsFood: May increase effectiveness by stimulating bile secretion and thereby increasing the amount of cesium or thallium available to bind with ferric hexacyanoferrate. May bind with essential nutrients.

Monitoring Parameters

Bowel movements; CBC and electrolytes weekly

Baseline cesium and/or thallium exposure (whole body counting and/or bioassay, feces or urine sample); urine and fecal cesium and/or thallium weekly during therapy; residual whole body radioactivity after 30 days of treatment

Monitoring: Lab TestsCBC and electrolytes weekly; baseline cesium and/or thallium exposure (whole body counting and/or bioassay, feces or urine sample); urine and fecal cesium and/or thallium weekly during therapy; residual whole body radioactivity after 30 days of treatment

Patient Education

You may experience constipation (increasing exercise, fluids, and fruit/fiber may help).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 0.5 g

Generic AvailableNo

ManufacturerDistributed by HEYL Chemisch-pharmazeutische Fabrik GmbH & Co KG

Mechanism of ActionBinds to cesium and thallium isotopes in the gastrointestinal tract following their ingestion or excretion in the bile; reduces their gastrointestinal reabsorption (enterohepatic circulation)

Pharmacodynamics/Kinetics

Absorption: Ferric hexacyanoferrate: Oral: None

Half-life elimination:

Cesium-137: Effective: Adults: 80 days, decreased by 69% with ferric hexacyanoferrate; adolescents: 62 days, decreased by 46% with ferric hexacyanoferrate; children: 42 days, decreased by 43% with ferric hexacyanoferrate

Nonradioactive thallium: Biological: 8-10 days; with ferric hexacyanoferrate: 3 days

Excretion:

Cesium-137: Without ferric hexacyanoferrate: Urine (~80%); feces (~20%)

Thallium: Without ferric hexacyanoferrate: Fecal to urine excretion ration: 2:1

Ferric hexacyanoferrate: Feces (99%, unchanged)

Pharmacotherapy PearlsDetailed treatment information should be reported to the manufacturer; contact the manufacturer or the complete prescribing information for data collection forms. In case of thallium intoxication, elimination of thallium may also be increased by: Induced emesis followed by intubation and lavage; forced diuresis if urinary excretion is <1 mg/24 hours; charcoal hemoperfusion during the first 48 hours following ingestion; hemodialysis

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentConstipation is common; concurrent use with anticholinergic psychotropics (eg, clozapine or chlorpromazine) may produce additive effects. May cause hypokalemia; monitor potassium in patients receiving ziprasidone.

Index TermsFerric (III) Hexacyanoferrate (II); Insoluble Prussian Blue; Prussian Blue

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Ferrous Fumarate

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English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Feostat® may be confused with Feosol®

Pronunciation(FER us FYOO ma rate)

U.S. Brand NamesFemiron® [OTC]; Feostat® [OTC] [DSC]; Ferretts [OTC]; Ferro-Sequels® [OTC]; Hemocyte® [OTC]; Ircon® [OTC]; Nephro-Fer® [OTC]

Canadian Brand NamesPalafer®

Pharmacologic CategoryIron Salt

Use: Labeled IndicationsPrevention and treatment of iron-deficiency anemias

Dosing: Adults

Dietary Reference Intake: Dose is RDA presented as elemental iron unless otherwise noted:

19-50 years: Male: 8 mg/day; Female: 18 mg/day; Pregnant female: 27 mg/day; Lactating female: 9 mg/day

≥50 years: 8 mg/day

Doses expressed in terms of elemental iron; elemental iron content of ferrous fumarate is 33%.

Treatment of iron deficiency: Oral: Usual range: 150-200 mg elemental iron/day in divided doses; 60-100 mg elemental iron twice daily, up to 60 mg elemental iron 4 times/day

Prophylaxis of iron deficiency: Oral: 60-100 mg elemental iron/day

Note: To avoid GI upset, start with a single daily dose and increase by 1 tablet/day each week or as tolerated until desired daily dose is achieved

Dosing: Elderly200 mg elemental iron 3-4 times/day

Dosing: Pediatric

Dietary Reference Intake: Dose is RDA presented as elemental iron unless otherwise noted:

0-6 months: 0.27 mg/day (adequate intake)

7-12 months: 11 mg/day

1-3 years: 7 mg/day

4-8 years: 10 mg/day

9-13 years: 8 mg/day

14-18 years: Male: 11 mg/day; Female: 15 mg/day; Pregnant female: 27 mg/day; Lactating female: 10 mg/day

Doses expressed in terms of elemental iron; elemental iron content of ferrous fumarate is 33%.

Treatment of severe iron-deficiency anemia: Oral: 4-6 mg elemental iron/kg/day in 3 divided doses

Treatment of mild-to-moderate iron-deficiency anemia: Oral: 3 mg elemental iron/kg/day in 1-2 divided doses

Prophylaxis of iron deficiency: Oral: 1-2 mg elemental iron/kg/day

Administration: OralAdminister 2 hours prior to or 4 hours after antacids.

Dietary ConsiderationsShould be taken with water or juice on an empty stomach; may be administered with food to prevent irritation; however, not with cereals, dietary fiber, tea, coffee, eggs, or milk.

Elemental iron content of ferrous fumarate: 33%

Dietary sources of iron include beans, cereal (enriched), clams, beef, lentils, liver, oysters, shrimp, and turkey. Foods that enhance dietary absorption of iron include broccoli, grapefruit, orange juice, peppers and strawberries. Foods that decrease dietary absorption of iron include coffee, dairy products, soy products, spinach, and tea.

StorageIron is a leading cause of fatal poisoning in children. Store out of children's reach and in child-resistant containers.

ContraindicationsHypersensitivity to iron salts or any component of the formulation; hemochromatosis, hemolytic anemia

Allergy Considerations

- Iron Salt Allergy

Warnings/Precautions

Boxed warnings:

- Iron toxicity: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Iron toxicity: **[U.S. Boxed Warning]: Severe iron toxicity may occur in overdose, particularly when ingested by children; iron is a leading cause of fatal poisoning in children; store out of children's reach and in child-resistant containers.**

Disease-related concerns:

- Gastrointestinal disease: Avoid in patients with peptic ulcer, enteritis, or ulcerative colitis.

Special populations:

- Blood transfusion recipients: Avoid in patients receiving frequent blood transfusions.

- Elderly: Anemia in the elderly is often caused by “anemia of chronic disease” or associated with inflammation rather than blood loss. Iron stores are usually normal or increased, with a serum ferritin >50 ng/mL and a decreased total iron binding capacity. Hence, the “anemia of chronic disease” is not secondary to iron deficiency but the inability of the reticuloendothelial system to reclaim available iron stores.

- Premature infants: Avoid use in premature infants until the vitamin E stores, deficient at birth, are replenished.

Other warnings/precautions:

- Duration of therapy: Administration of iron for >6 months should be avoided except in patients with continuous bleeding or menorrhagia.

Geriatric ConsiderationsAnemia in the elderly is often caused by “anemia of chronic disease”, a result of aging changes in the bone marrow, or associated with inflammation rather than blood loss. Iron stores are usually normal or increased, with a serum ferritin >50 ng/mL and a decreased total iron binding capacity. Hence, the anemia is not secondary to iron deficiency but the inability of the reticuloendothelial system to use available iron stores. Timed release iron preparations should be avoided due to their erratic absorption. Products combined with a laxative or stool softener should not be used unless the need for the combination is demonstrated.

Pregnancy ConsiderationsIt is recommended that pregnant women meet the dietary requirements of iron with diet and/or supplements in order to prevent adverse events associated with iron deficiency anemia in pregnancy. Treatment of iron deficiency anemia in pregnant women is the same as in nonpregnant women and in most cases, oral iron preparations may be used. Except in severe cases of maternal anemia, the fetus achieves normal iron stores regardless of maternal concentrations.

LactationEnters breast milk

Breast-Feeding ConsiderationsIron is normally found in breast milk. Breast milk or iron-fortified formulas generally provide enough iron to meet the recommended dietary requirements of infants. The amount of iron in breast milk is generally not influenced by maternal iron status.

Adverse Reactions

>10%: Gastrointestinal: Stomach cramping, constipation, nausea, vomiting, dark stools

1% to 10%:

Gastrointestinal: Heartburn, diarrhea, staining of teeth

Genitourinary: Discoloration of urine

<1%: Contact irritation

Drug Interactions

Antacids: May decrease the absorption of Iron Salts. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Iron Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral iron salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Cefdinir: Iron Salts may decrease the serum concentration of Cefdinir. Red-appearing, non-bloody stools may also develop due to the formation of an insoluble iron-cefdinir complex. Management: Avoid concurrent cefdinir and iron when possible. Separating doses by several hours may minimize interaction. Iron-containing infant formulas do not appear to interact with cefdinir. *Risk D: Consider therapy modification*

Dimercaprol: May enhance the nephrotoxic effect of Iron Salts. *Risk X: Avoid combination*

H2-Antagonists: May decrease the absorption of Iron Salts. *Risk C: Monitor therapy*

Levodopa: Iron Salts may decrease the absorption of Levodopa. Only applies to oral iron preparations. *Risk D: Consider therapy modification*

Methyldopa: Iron Salts may decrease the absorption of Methyldopa. Only oral iron salts are of concern. *Risk D: Consider therapy modification*

Penicillamine: Iron Salts may decrease the absorption of Penicillamine. Only oral iron salts are a concern. *Risk D: Consider therapy modification*

Phosphate Supplements: Iron Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May decrease the absorption of Iron Salts. *Risk C: Monitor therapy*

Quinolone Antibiotics: Iron Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Iron Salts may decrease the absorption of Tetracycline Derivatives. Only a concern with orally administered products. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Iron Salts. Iron Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions Food: Cereals, dietary fiber, tea, coffee, eggs, and milk may decrease absorption.

Reference Range

Serum iron:

Male: 75-175 mcg/dL (SI: 13.4-31.3 µmol/L)

Female: 65-165 mcg/dL (SI: 11.6-29.5 µmol/L)

Total iron binding capacity: 230-430 mcg/dL

Transferrin: 204-360 mg/dL

Percent transferrin saturation: 20% to 50%

Iron levels >300 mcg/dL can be considered toxic, should be treated as an overdose

Patient Education May color stool black. Take between meals for maximum absorption; take with food if GI upset occurs. Do not take with milk or antacids. Keep out of reach of children.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: 324 mg [elemental iron 106 mg]

Femiron®: 63 mg [elemental iron 20 mg]

Ferretts: 325 mg [elemental iron 106 mg]

Hemocyte®: 324 mg [elemental iron 106 mg]

Ircon®: 200 mg [elemental iron 66 mg]

Nephro-Fer®: 350 mg [elemental iron 115 mg; contains tartrazine]

Tablet, chewable (Feostat®): 100 mg [elemental iron 33 mg; chocolate flavor] [DSC]

Tablet, timed release (Ferro-Sequels®): 150 mg [elemental iron 50 mg; contains docusate sodium and sodium benzoate]

Generic Available Yes: Tablet

Mechanism of Action Replaces iron found in hemoglobin, myoglobin, and enzymes; allows the transportation of oxygen via hemoglobin

Pharmacodynamics/Kinetics

Onset of action: Hematologic response: Oral, parenteral iron salts: ~3-10 days

Peak effect: Reticulocytosis: 5-10 days; hemoglobin values increase within 2-4 weeks

Absorption: Iron is absorbed in the duodenum and upper jejunum; in persons with normal serum iron stores, 10% of an oral dose is absorbed, this is increased to 20% to 30% in persons with inadequate iron stores. Food and achlorhydria will decrease absorption.

Protein binding: To serum transferrin

Excretion: Urine, sweat, sloughing of intestinal mucosa, and menses

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Staining of teeth. Do not prescribe tetracyclines simultaneously with iron since GI tract absorption of both tetracycline and iron may be inhibited.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment Constipation is common; concurrent use with psychotropic agents may increase the risk

Index Terms Iron Fumarate

References

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Swain RA, Kaplan B, and Montgomery E, “Iron Deficiency Anemia,” *Postgrad Med*, 1996, 100(5):181-93.[PubMed 8917332]

International Brand Names Ercofer (SE); Ferraton (EC); Ferrobet (AT); Ferrokapsul (DE); Ferroklinge (BR); Ferrolina (AT); Ferronat (BG, CZ); Ferrum Hausmann (BE, CH, DE, LU); Fersaday (GB, IE); Ferumat (BE, LU, NL); Ferval (MX); Fumafer (FR, PT, VE); Fumiron (DE); Heferol (HR); Hemoferrol (AR); Hierro Lafedar (AR); Neo-Fer (NO); Rulofer N (DE)

Ferrous Gluconate

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English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(FER us GLOO koe nate)

U.S. Brand NamesFergon® [OTC]

Canadian Brand NamesApo-Ferrous Gluconate®; Novo-Ferrogluc

Pharmacologic CategoryIron Salt

Use: Labeled IndicationsPrevention and treatment of iron-deficiency anemias

Dosing: Adults

Dietary Reference Intake: Dose is RDA presented as elemental iron unless otherwise noted:

19-50 years: Male: 8 mg/day; Female: 18 mg/day; Pregnant female: 27 mg/day; Lactating female: 9 mg/day

≥50 years: 8 mg/day

Dose expressed in terms of elemental iron:

Treatment of iron deficiency anemia: Oral: 60 mg twice daily up to 60 mg 4 times/day

Prophylaxis of iron deficiency: Oral: 60 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Dietary Reference Intake: Dose is RDA presented as elemental iron unless otherwise noted:

0-6 months: 0.27 mg/day (adequate intake)

7-12 months: 11 mg/day

1-3 years: 7 mg/day

4-8 years: 10 mg/day

9-13 years: 8 mg/day

14-18 years: Male: 11 mg/day; Female: 15 mg/day; Pregnant female: 27 mg/day; Lactating female: 10 mg/day

Dose expressed in terms of elemental iron:

Treatment of severe iron-deficiency anemia: Oral: 4-6 mg Fe/kg/day in 3 divided doses

Treatment of mild-to-moderate iron-deficiency anemia: Oral: 3 mg Fe/kg/day in 1-2 divided doses

Prophylaxis: Oral: 1-2 mg Fe/kg/day

Administration: OralAdminister 2 hours before or 4 hours after antacids. Administration of iron preparations to premature infants with vitamin E deficiency may cause increased red cell hemolysis and hemolytic anemia, therefore, vitamin E deficiency should be corrected if possible.

Dietary ConsiderationsShould be taken with water or juice on an empty stomach; may be administered with food to prevent irritation; however, not with cereals, dietary fiber, tea, coffee, eggs, or milk.

Elemental iron content of ferrous gluconate: 12%

Dietary sources of iron include beans, cereal (enriched), clams, beef, lentils, liver, oysters, shrimp, and turkey. Foods that enhance dietary absorption of iron include broccoli, grapefruit, orange juice, peppers and strawberries. Foods that decrease dietary absorption of iron include coffee, dairy products, soy products, spinach, and tea.

StorageIron is a leading cause of fatal poisoning in children. Store out of children's reach and in child-resistant containers.

ContraindicationsHypersensitivity to iron salts or any component of the formulation; hemochromatosis, hemolytic anemia

Allergy Considerations

- Iron Salt Allergy

Warnings/Precautions

Boxed warnings:

- Iron toxicity: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Iron toxicity: **[U.S. Boxed Warning]: Severe iron toxicity may occur in overdose, particularly when ingested by children; iron is a leading cause of fatal poisoning in children; store out of children's reach and in child-resistant containers.**

Disease-related concerns:

- Gastrointestinal disease: Avoid in patients with peptic ulcer, enteritis, or ulcerative colitis.

Special populations:

- Blood transfusion recipients: Avoid in patients receiving frequent blood transfusions.

- Elderly: Anemia in the elderly is often caused by “anemia of chronic disease” or associated with inflammation rather than blood loss. Iron stores are usually normal or increased, with a serum ferritin >50 ng/mL and a decreased total iron binding capacity. Hence, the “anemia of chronic disease” is not secondary to iron deficiency but the inability of the reticuloendothelial system to reclaim available iron stores.

- Premature infants: Avoid use in premature infants until the vitamin E stores, deficient at birth, are replenished.

Other warnings/precautions:

- Duration of therapy: Administration of iron for >6 months should be avoided except in patients with continuous bleeding or menorrhagia.

Geriatric ConsiderationsAnemia in the elderly is often caused by “anemia of chronic disease”, a result of aging changes in the bone marrow, or associated with inflammation rather than blood loss. Iron stores are usually normal or increased, with a serum ferritin >50 ng/mL and a decreased total iron binding capacity. Hence, the anemia is not secondary to iron deficiency but the inability of the reticuloendothelial system to use available iron stores. Timed release iron preparations should be avoided due to their erratic absorption. Products combined with a laxative or stool softener should not be used unless the need for the combination is demonstrated.

Pregnancy ConsiderationsIt is recommended that pregnant women meet the dietary requirements of iron with diet and/or supplements in order to prevent adverse events associated with iron deficiency anemia in pregnancy. Treatment of iron deficiency anemia in pregnant women is the same as in nonpregnant women and in most cases, oral iron preparations may be used. Except in severe cases of maternal anemia, the fetus achieves normal iron stores regardless of maternal concentrations.

LactationEnters breast milk

Breast-Feeding ConsiderationsIron is normally found in breast milk. Breast milk or iron fortified formulas generally provide enough iron to meet the recommended dietary requirements of infants. The amount of iron in breast milk is generally not influenced by maternal iron status.

Adverse Reactions

>10%: Gastrointestinal: Stomach cramping, constipation, nausea, vomiting, dark stools

1% to 10%:

Gastrointestinal: Heartburn, diarrhea, staining of teeth

Genitourinary: Discoloration of urine

<1%: Contact irritation

Drug Interactions

Antacids: May decrease the absorption of Iron Salts. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Iron Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral iron salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Cefdinir: Iron Salts may decrease the serum concentration of Cefdinir. Red-appearing, non-bloody stools may also develop due to the formation of an insoluble iron-cefdinir complex. Management: Avoid concurrent cefdinir and iron when possible. Separating doses by several hours may minimize interaction. Iron-containing infant formulas do not appear to interact with cefdinir. *Risk D: Consider therapy modification*

Dimercaprol: May enhance the nephrotoxic effect of Iron Salts. *Risk X: Avoid combination*

H2-Antagonists: May decrease the absorption of Iron Salts. *Risk C: Monitor therapy*

Levodopa: Iron Salts may decrease the absorption of Levodopa. Only applies to oral iron preparations. *Risk D: Consider therapy modification*

Methyldopa: Iron Salts may decrease the absorption of Methyldopa. Only oral iron salts are of concern. *Risk D: Consider therapy modification*

Penicillamine: Iron Salts may decrease the absorption of Penicillamine. Only oral iron salts are a concern. *Risk D: Consider therapy modification*

Phosphate Supplements: Iron Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May decrease the absorption of Iron Salts. *Risk C: Monitor therapy*

Quinolone Antibiotics: Iron Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Iron Salts may decrease the absorption of Tetracycline Derivatives. Only a concern with orally administered products. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Iron Salts. Iron Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Cereals, dietary fiber, tea, coffee, eggs, and milk may decrease absorption.

Test InteractionsFalse-positive for blood in stool by the guaiac test

Monitoring ParametersSerum iron, total iron binding capacity, reticulocyte count, hemoglobin

Reference RangeTherapeutic: Male: 75-175 mcg/dL (SI: 13.4-31.3 µmol/L); Female: 65-165 mcg/dL (SI: 11.6-29.5 µmol/L); serum iron level >300 mcg/dL usually requires treatment of overdose due to severe toxicity

Monitoring: Lab TestsSerum iron, total iron binding capacity, reticulocyte count, hemoglobin

Patient EducationMay color stool black. Take between meals for maximum absorption; take with food if GI upset occurs. Do not take with milk or antacids. Keep out of reach of children.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: 246 mg [elemental iron 28 mg]; 300 mg [elemental iron 34 mg] [DSC]; 325 mg [elemental iron 36 mg]

Fergon®: 240 mg [elemental iron 27 mg]

Generic AvailableYes

Mechanism of ActionReplaces iron found in hemoglobin, myoglobin, and enzymes; allows the transportation of oxygen via hemoglobin

Pharmacodynamics/KineticsOnset of action: Hematologic response: Oral: 3-10 days; peak reticulocytosis occurs in 5-10 days, and hemoglobin values increase in ~2-4 weeks

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Staining of teeth. Do not prescribe tetracyclines simultaneously with iron since GI tract absorption of both tetracycline and iron may be inhibited.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentConstipation is common; concurrent use with psychotropic agents may increase the risk

Index TermsIron Gluconate

References

American College of Obstetricians and Gynecologists, “ACOG Practice Bulletin No. 95: Anemia in Pregnancy,” *Obstet Gynecol*, 2008, 112(1):201-7.[PubMed 18591330]

Baker WF Jr, “Iron Deficiency in Pregnancy, Obstetrics, and Gynecology,” *Hematol Oncol Clin North Am*, 2000, 14(5):1061-77.[PubMed 11005034]

“Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.” Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, Washington, DC: National Academy Press, 2000. Available at http://www.nap.edu.

Lipschitz DA, “The Anemia of Chronic Disease,” *J Am Geriatr Soc*, 1990, 38(11):1258-64. [PubMed 2123218]

Marx JJM, “Normal Iron Absorption and Decreased Red Cell Iron Uptake in the Aged,” *Blood*, 1979, 53:204-11.[PubMed 760850]

“Nutrition During Lactation.” Subcommittee on Nutrition During Lactation, Committee on Nutritional Status During Pregnancy and Lactation, Food and Nutrition Board Institute of Medicine, National Academy of Sciences Washington, DC: National Academy Press, 1991. Available at http://www.nap.edu.

“Recommendations to Prevent and Control Iron Deficiency in the United States. Centers for Disease Control and Prevention,” *MMWR Recomm Rep*, 1998, 47(RR-3):1-29.[PubMed 9563847]

“Routine Iron Supplementation During Pregnancy. Review Article. US Preventive Services Task Force,” *JAMA*, 1993, 270(23):2848-54.[PubMed 8133626]

International Brand NamesAdditiva Ferrum (PL); Ascofer (PL); Biogam Fe (BE); Cromatonferro (IT); Elixir Ferrous Gluconate (ZA); Emoferrina (IT); Fergon (AU, GB, IE); Fernore (BE); Ferrematos (IT); Ferrlecit (DE, HU); Ferro-Agepha (AT); Ferro-Gradumet (BG); Ferrogluconaat FNA (NL); ferrominerase (DE); Ferronal (IL); Ferrum Verla (DE); Glucoferro (IT); Hemototal (PT); Imperon (ES); Ironax (IT); Losferon (FR); Losferron (DE, IT, LU, NL); Lotanax (CZ); Oligostim Fe (BE); Rulofer G (DE); Sustemial (IT); Vitaferro Brause (DE)

Ferrous Sulfate and Ascorbic Acid

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(FER us SUL fate & a SKOR bik AS id)

U.S. Brand NamesFero-Grad 500® [OTC]; Vitelle™ Irospan® [OTC] [DSC]

Pharmacologic CategoryIron Salt; Vitamin

Use: Labeled IndicationsTreatment of iron deficiency in nonpregnant adults; treatment and prevention of iron deficiency in pregnant adults

Dosing: AdultsIron deficiency: Oral: 1 tablet daily

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsShould be taken with water or juice on an empty stomach; may be administered with food to prevent irritation; however, not with cereals, dietary fiber, tea, coffee, eggs, or milk.

StorageIron is a leading cause of fatal poisoning in children Store out of children's reach and in child-resistant containers.

ContraindicationsBased on **ferrous sulfate** component: Hypersensitivity to iron salts or any component of the formulation; hemochromatosis, hemolytic anemia

Allergy Considerations

- Iron Salt Allergy

Warnings/Precautions

Boxed warnings:

- Iron toxicity: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Iron toxicity: **[U.S. Boxed Warning]: Severe iron toxicity may occur in overdose, particularly when ingested by children; iron is a leading cause of fatal poisoning in children; store out of children's reach and in child-resistant containers.**

Disease-related concerns:

- Gastrointestinal disease: Avoid ferrous sulfate in patients with peptic ulcer, enteritis, or ulcerative colitis.

Special populations:

- Blood transfusion recipients: Avoid in patients receiving frequent blood transfusions.

- Elderly: Anemia in the elderly is often caused by “anemia of chronic disease” or associated with inflammation rather than blood loss. Iron stores are usually normal or increased, with a serum ferritin >50 ng/mL and a decreased total iron binding capacity. Hence, the “anemia of chronic disease” is not secondary to iron deficiency but the inability of the reticuloendothelial system to reclaim available iron stores.

- Premature infants: Avoid use in premature infants until the vitamin E stores, deficient at birth, are replenished.

Other warnings/precautions:

- Duration of therapy: Administration of iron for >6 months should be avoided except in patients with continuous bleeding or menorrhagia.

Pregnancy ConsiderationsSee individual agents.

Breast-Feeding ConsiderationsSee individual agents.

Adverse ReactionsBased on **ferrous sulfate** component:

>10%: Gastrointestinal: GI irritation, epigastric pain, nausea, dark stools, vomiting, stomach cramping, constipation

1% to 10%:

Gastrointestinal: Heartburn, diarrhea

Genitourinary: Discoloration of urine

Miscellaneous: Liquid preparations may temporarily stain the teeth

<1%: Contact irritation

Drug Interactions

Aluminum Hydroxide: Ascorbic Acid may increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Amphetamines: Gastrointestinal Acidifying Agents may decrease the serum concentration of Amphetamines. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Iron Salts. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Iron Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral iron salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Cefdinir: Iron Salts may decrease the serum concentration of Cefdinir. Red-appearing, non-bloody stools may also develop due to the formation of an insoluble iron-cefdinir complex. Management: Avoid concurrent cefdinir and iron when possible. Separating doses by several hours may minimize interaction. Iron-containing infant formulas do not appear to interact with cefdinir. *Risk D: Consider therapy modification*

Deferoxamine: Ascorbic Acid may enhance the adverse/toxic effect of Deferoxamine. Left ventricular dysfunction is of particular concern. *Risk D: Consider therapy modification*

Dimercaprol: May enhance the nephrotoxic effect of Iron Salts. *Risk X: Avoid combination*

H2-Antagonists: May decrease the absorption of Iron Salts. *Risk C: Monitor therapy*

Levodopa: Iron Salts may decrease the absorption of Levodopa. Only applies to oral iron preparations. *Risk D: Consider therapy modification*

Levothyroxine: Ferrous Sulfate may decrease the serum concentration of Levothyroxine. *Risk D: Consider therapy modification*

Methyldopa: Iron Salts may decrease the absorption of Methyldopa. Only oral iron salts are of concern. *Risk D: Consider therapy modification*

Penicillamine: Iron Salts may decrease the absorption of Penicillamine. Only oral iron salts are a concern. *Risk D: Consider therapy modification*

Phosphate Supplements: Iron Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May decrease the absorption of Iron Salts. *Risk C: Monitor therapy*

Quinolone Antibiotics: Iron Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Iron Salts may decrease the absorption of Tetracycline Derivatives. Only a concern with orally administered products. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Iron Salts. Iron Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Cereals, dietary fiber, tea, coffee, eggs, and milk may decrease absorption.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, extended release (Vitelle™ Irospan®): Ferrous sulfate [elemental iron 65 mg] and ascorbic acid 150 mg [DSC]

Tablet, controlled release (Fero-Grad 500®): Ferrous sulfate 525 mg [elemental iron 105 mg] and ascorbic acid 500 mg

Tablet, extended release (Vitelle™ Irospan®): Ferrous sulfate [elemental iron 65 mg] and ascorbic acid 150 mg [DSC]

Generic AvailableNo
Pharmacodynamics/KineticsSee individual agents.
Dental Health: Effects on Dental TreatmentDo not prescribe tetracyclines simultaneously with iron since GI tract absorption of both tetracycline and iron may be inhibited. Liquid preparations may temporarily stain the teeth.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentConstipation is common; concurrent use with psychotropic agents may increase the risk
Index TermsAscorbic Acid and Ferrous Sulfate; Iron Sulfate and Vitamin C
References

American College of Obstetricians and Gynecologists, “ACOG Practice Bulletin No. 95: Anemia in Pregnancy,” *Obstet Gynecol*, 2008, 112(1):201-7.[PubMed 18591330]

Baker WF Jr, “Iron Deficiency in Pregnancy, Obstetrics, and Gynecology,” *Hematol Oncol Clin North Am*, 2000, 14(5):1061-77.[PubMed 11005034]

“Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.” Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, Washington, DC: National Academy Press, 2000. Available at http://www.nap.edu.

“Nutrition During Lactation.” Subcommittee on Nutrition During Lactation, Committee on Nutritional Status During Pregnancy and Lactation, Food and Nutrition Board Institute of Medicine, National Academy of Sciences Washington, DC: National Academy Press, 1991. Available at http://www.nap.edu.

“Recommendations to Prevent and Control Iron Deficiency in the United States. Centers for Disease Control and Prevention,” *MMWR Recomm Rep*, 1998, 47(RR-3):1-29.[PubMed 9563847]

“Routine Iron Supplementation During Pregnancy. Review Article. US Preventive Services Task Force,” *JAMA*, 1993, 270(23):2848-54.[PubMed 8133626]

Ferrous Sulfate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Medication Safety Issue: Change in Concentration/Dosage of Fer-In-Sol® Pediatric Oral Iron Drops - November 2008

Mead Johnson Nutritionals, the maker of Enfamil® oral liquid iron supplement drops Fer-In-Sol®, has recently changed the concentration, and therefore, the dosing of its product. The new labeling indicates that the dose needed to deliver 15 mg of elemental iron has changed from 0.6 mL to 1 mL. Prior to this change, 0.6 mL of Fer-In-Sol® provided 15 mg of elemental iron. The markings on the provided dropper have changed to 0.5 mL and 1 mL instead of 0.3 mL and 0.6 mL to reflect the dosing change. Ferrous sulfate drops made by other manufacturers are still available as the 15 mg/0.6 mL concentration. Due to the concern for potential medication errors, healthcare providers need to be aware of this change and verify the concentration of iron in the actual product being dispensed (generics or unused inventory of Fer-In-Sol® manufactured prior to the change) to ensure the correct volume needed to provide the dose intended. It is recommended that prescribers write prescriptions using dose required, rather than mL needed, and pharmacists should clarify dose if a prescription is written as volume.

Medication Safety Issues

Sound-alike/look-alike issues:

Feosol® may be confused with Feostat®, Fer-In-Sol®

Fer-In-Sol® may be confused with Feosol®

Slow FE® may be confused with Slow-K®

Pronunciation(FER us SUL fate)

U.S. Brand NamesFeosol® [OTC]; Fer-Gen-Sol [OTC]; Fer-In-Sol® [OTC]; Fer-Iron® [OTC]; Feratab® [OTC]; MyKidz Iron 10™; Slow FE® [OTC]

Canadian Brand NamesApo-Ferrous Sulfate®; Fer-In-Sol®; Ferodan™

Pharmacologic CategoryIron Salt

Use: Labeled IndicationsPrevention and treatment of iron-deficiency anemias

Dosing: Adults

Dietary Reference Intake: Dose is RDA presented as elemental iron unless otherwise noted:

19-50 years: Male: 8 mg/day; Female: 18 mg/day; Pregnant female: 27 mg/day; Lactating female: 9 mg/day

≥50 years: 8 mg/day

Dose expressed in terms of ferrous sulfate:

Treatment of iron deficiency anemia: Oral: 300 mg twice daily up to 300 mg 4 times/day or 250 mg (extended release) 1-2 times/day

Prophylaxis of iron deficiency: Oral: 300 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Dietary Reference Intake: Dose is RDA presented as elemental iron unless otherwise noted:

0-6 months: 0.27 mg/day (adequate intake)

7-12 months: 11 mg/day

1-3 years: 7 mg/day

4-8 years: 10 mg/day

9-13 years: 8 mg/day

14-18 years: Male: 11 mg/day; Female: 15 mg/day; Pregnant female: 27 mg/day; Lactating female: 10 mg/day

Dosage expressed in terms of elemental iron:

Treatment of severe iron-deficiency anemia: Oral: 4-6 mg Fe/kg/day in 3 divided doses

Treatment of mild-to-moderate iron-deficiency anemia: Oral: 3 mg Fe/kg/day in 1-2 divided doses

Prophylaxis: Oral: 1-2 mg Fe/kg/day up to a maximum of 15 mg/day

Dietary ConsiderationsShould be taken with water or juice on an empty stomach; may be administered with food to prevent irritation; however, not with cereals, dietary fiber, tea, coffee, eggs, or milk.

Elemental iron content of iron salts in ferrous sulfate is 20% (ie, 300 mg ferrous sulfate is equivalent to 60 mg ferrous iron)

Dietary sources of iron include beans, cereal (enriched), clams, beef, lentils, liver, oysters, shrimp, and turkey. Foods that enhance dietary absorption of iron include broccoli, grapefruit, orange juice, peppers and strawberries. Foods that decrease dietary absorption of iron include coffee, dairy products, soy products, spinach, and tea.

StorageIron is a leading cause of fatal poisoning in children. Store out of children's reach and in child-resistant containers.

ContraindicationsHypersensitivity to iron salts or any component of the formulation; hemochromatosis, hemolytic anemia

Allergy Considerations

- Iron Salt Allergy

Warnings/Precautions

Boxed warnings:

- Iron toxicity: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Iron toxicity: **[U.S. Boxed Warning]: Severe iron toxicity may occur in overdose, particularly when ingested by children; iron is a leading cause of fatal poisoning in children; store out of children's reach and in child-resistant containers.**

Disease-related concerns:

- Gastrointestinal disease: Avoid in patients with peptic ulcer, enteritis, or ulcerative colitis.

Special populations:

- Blood transfusion recipients: Avoid in patients receiving frequent blood transfusions.
- Elderly: Anemia in the elderly is often caused by “anemia of chronic disease” or associated with inflammation rather than blood loss. Iron stores are usually normal or increased, with a serum ferritin >50 ng/mL and a decreased total iron binding capacity. Hence, the “anemia of chronic disease” is not secondary to iron deficiency but the inability of the reticuloendothelial system to reclaim available iron stores.
- Premature infants: Avoid use in premature infants until the vitamin E stores, deficient at birth, are replenished.

Other warnings/precautions:

- Duration of therapy: Administration of iron for >6 months should be avoided except in patients with continuous bleeding or menorrhagia.

Geriatric ConsiderationsAnemia in the elderly is often caused by “anemia of chronic disease”, a result of aging changes in the bone marrow, or associated with inflammation rather than blood loss. Iron stores are usually normal or increased, with a serum ferritin >50 ng/mL and a decreased total iron binding capacity. Hence, the anemia is not secondary to iron deficiency but the inability of the reticuloendothelial system to use available iron stores. Timed release iron preparations should be avoided due to their erratic absorption. Products combined with a laxative or stool softener should not be used unless the need for the combination is demonstrated.

Pregnancy ConsiderationsIt is recommended that pregnant women meet the dietary requirements of iron with diet and/or supplements in order to prevent adverse events associated with iron deficiency anemia in pregnancy. Treatment of iron deficiency anemia in pregnant women is the same as in nonpregnant women and in most cases, oral iron preparations may be used. Except in severe cases of maternal anemia, the fetus achieves normal iron stores regardless of maternal concentrations.

LactationEnters breast milk

Breast-Feeding ConsiderationsIron is normally found in breast milk. Breast milk or iron fortified formulas generally provide enough iron to meet the recommended dietary requirements of infants. The amount of iron in breast milk is generally not influenced by maternal iron status.

Adverse Reactions

>10%: Gastrointestinal: GI irritation, epigastric pain, nausea, dark stools, vomiting, stomach cramping, constipation

1% to 10%:

Gastrointestinal: Heartburn, diarrhea

Genitourinary: Discoloration of urine

Miscellaneous: Liquid preparations may temporarily stain the teeth

<1%: Contact irritation

Drug Interactions

Antacids: May decrease the absorption of Iron Salts. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Iron Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral iron salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Cefdinir: Iron Salts may decrease the serum concentration of Cefdinir. Red-appearing, non-bloody stools may also develop due to the formation of an insoluble iron-cefdinir complex. Management: Avoid concurrent cefdinir and iron when possible. Separating doses by several hours may minimize interaction. Iron-containing infant formulas do not appear to interact with cefdinir. *Risk D: Consider therapy modification*

Dimercaprol: May enhance the nephrotoxic effect of Iron Salts. *Risk X: Avoid combination*

H2-Antagonists: May decrease the absorption of Iron Salts. *Risk C: Monitor therapy*

Levodopa: Iron Salts may decrease the absorption of Levodopa. Only applies to oral iron preparations. *Risk D: Consider therapy modification*

Levothyroxine: Ferrous Sulfate may decrease the serum concentration of Levothyroxine. *Risk D: Consider therapy modification*

Methyldopa: Iron Salts may decrease the absorption of Methyldopa. Only oral iron salts are of concern. *Risk D: Consider therapy modification*

Penicillamine: Iron Salts may decrease the absorption of Penicillamine. Only oral iron salts are a concern. *Risk D: Consider therapy modification*

Phosphate Supplements: Iron Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May decrease the absorption of Iron Salts. *Risk C: Monitor therapy*

Quinolone Antibiotics: Iron Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Iron Salts may decrease the absorption of Tetracycline Derivatives. Only a concern with orally administered products. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Iron Salts. Iron Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Cereals, dietary fiber, tea, coffee, eggs, and milk may decrease absorption.

Test InteractionsFalse-positive for blood in stool by the guaiac test

Monitoring ParametersSerum iron, total iron binding capacity, reticulocyte count, hemoglobin

Reference Range

Serum iron:

Male: 75-175 mcg/dL (SI: 13.4-31.3 µmol/L)

Female: 65-165 mcg/dL (SI: 11.6-29.5 µmol/L)

Total iron binding capacity: 230-430 mcg/dL

Transferrin: 204-360 mg/dL

Percent transferrin saturation: 20% to 50%

Nursing: Physical Assessment/MonitoringAssess therapeutic response and adverse effects. May cause GI irritation. Monitor GI function (observe for epigastric pain, nausea, dark stools, vomiting, stomach cramping, constipation).

Monitoring: Lab TestsSerum iron, total iron binding capacity, reticulocyte count, hemoglobin

Patient EducationMay color stool black. Take between meals for maximum absorption; take with food if GI upset occurs. Do not take with milk or antacids. You may experience constipation; increasing exercise, fluids, fruit/fiber may help. Keep out of reach of children.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Elixir: 220 mg/5 mL (480 mL) [elemental iron 44 mg/5 mL; contains alcohol]

Liquid, oral drops: 75 mg/0.6 mL (50 mL) [elemental iron 15 mg/0.6 mL]

Fer-Gen-Sol: 75 mg/0.6 mL (50 mL) [elemental iron 15 mg/0.6 mL]

Fer-In-Sol®: 75 mg/1 mL (50 mL) [elemental iron 15 mg/1 mL; contains alcohol 0.2% and sodium bisulfite]

Fer-Iron®: 75 mg/0.6 mL (50 mL) [elemental iron 15 mg/0.6 mL]

Suspension, oral [drops]:

MyKidz Iron 10™: 75 mg/1.5 mL [elemental iron 15 mg/1.5 mL] (118 mL) [contains propylene glycol; ethanol free, dye free; strawberry-banana flavor]

Tablet: 324 mg [elemental iron 65 mg]; 325 mg [elemental iron 65 mg]

Feratab®: 300 mg [elemental iron 60 mg]

Tablet, exsiccated (Feosol®): 200 mg [elemental iron 65 mg]

Tablet, exsiccated, timed release (Slow FE®): 160 mg [elemental iron 50 mg]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Elixir (Ferrous Sulfate)

220 (44 Fe) mg/5 mL (473): $12.99

Solution (Fer-In-Sol)

75 (15 Fe) mg/0.6 mL (50): $18.99

Tablets (Ferrous Sulfate)

325 (65 Fe) mg (100): $8.99

325 (65 Fe) mg (1000): $30.00

Mechanism of ActionReplaces iron, found in hemoglobin, myoglobin, and other enzymes; allows the transportation of oxygen via hemoglobin

Pharmacodynamics/Kinetics

Onset of action: Hematologic response: Oral: ~3-10 days

Peak effect: Reticulocytosis: 5-10 days; hemoglobin increases within 2-4 weeks

Absorption: Iron is absorbed in the duodenum and upper jejunum; in persons with normal serum iron stores, 10% of an oral dose is absorbed; this is increased to 20% to 30% in persons with inadequate iron stores. Food and achlorhydria will decrease absorption

Protein binding: To transferrin

Excretion: Urine, sweat, sloughing of the intestinal mucosa, and menses

Dental Health: Effects on Dental TreatmentDo not prescribe tetracyclines simultaneously with iron since GI tract absorption of both tetracycline and iron may be inhibited. Liquid preparations may temporarily stain the teeth.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with SSRIs, carbamazepine, valproic acid, and lithium may produce additive effects

Index Terms$FeSO_4$; Iron Sulfate

References

American College of Obstetricians and Gynecologists, “ACOG Practice Bulletin No. 95: Anemia in Pregnancy,” *Obstet Gynecol*, 2008, 112(1):201-7.[PubMed 18591330]

Baker WF Jr, “Iron Deficiency in Pregnancy, Obstetrics, and Gynecology,” *Hematol Oncol Clin North Am*, 2000, 14(5):1061-77.[PubMed 11005034]

“Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.” Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, Washington, DC: National Academy Press, 2000. Available at http://www.nap.edu.

Lipschitz DA, “The Anemia of Chronic Disease,” *J Am Geriatr Soc*, 1990, 38(11):1258-64. [PubMed 2123218]

Marx JJM, “Normal Iron Absorption and Decreased Red Cell Iron Uptake in the Aged,” *Blood*, 1979, 53:204-11.[PubMed 760850]

“Nutrition During Lactation.” Subcommittee on Nutrition During Lactation, Committee on Nutritional Status During Pregnancy and Lactation, Food and Nutrition Board Institute of Medicine, National Academy of Sciences Washington, DC: National Academy Press, 1991. Available at http://www.nap.edu.

“Recommendations to Prevent and Control Iron Deficiency in the United States. Centers for Disease Control and Prevention,” *MMWR Recomm Rep*, 1998, 47(RR-3):1-29.[PubMed 9563847]

“Routine Iron Supplementation During Pregnancy. Review Article. US Preventive Services Task Force,” *JAMA*, 1993, 270(23):2848-54.[PubMed 8133626]

International Brand NamesAktiferrin (CH, HU); Brofesol (PH); Com-Femic (PH); Conferon (HU); Duroferon (FI, NO, SE); Eisendragees-ratiopharm (PL); Femas (JP); Feosol (PH); Feospan (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, HK, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Fer-In-Sol (AR, BR, CN, CZ, GR, HK, PE, PH, TH); Ferlea (AR); Fero-Gradumet (BE, ES, LU, NL); Ferro Duretter (DK); Ferro-grad (IT); Ferro-Gradumet (AE, AT, AU, BG, BH, CH, CY, EG, HU, ID, IL, IQ, IR, JO, KW, LB, LY, OM, PL, PT, QA, SA, SY, YE); Ferro-Liquid (AU); Ferrogamma (DE); Ferrograd (GB, IE); Ferronemia (PE); Ferrophor (DE); Ferroplex ”Era” (DK); Ferrostatin (JP); Fespan (TW); Haemoprotect (DE); Hemobion (MX); Hemofer Prolongatum (PL); Infa-Tardyferon (CH); Liquifer (NL); Microfer (GR); Mol-Iron (CO); Plastufer (DE); Plexafer (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Resoferon (CH, PL); Retafer (BG, FI, HR); Slow-Fe (AE, BB, BH, BM, BS, BZ, CY, EG, GY, IL, IQ, IR, JM, JO, KW, LB, LY, NL, OM, QA, SA, SR, SY, TT, YE); Tardyferon (CH, ES, FR, HU, LU, PL); Venofer (DK)

Ferumoxides

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Feridex I.V.® may be confused with Fertinex®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(fer yoo MOX ides)

U.S. Brand NamesFeridex I.V.®

Pharmacologic CategoryRadiological/Contrast Media (Nonionic, Low Osmolality); Radiological/Contrast Media, Paramagnetic Agent

Use: Labeled IndicationsFor I.V. administration as an adjunct to MRI (in adult patients) to enhance the T2 weighted images used in the detection and evaluation of lesions of the liver

Dosing: AdultsAdjunct to MRI: I.V.: 0.56 mg of iron (0.05 mL Feridex I.V.®)/kg body weight diluted in 100 mL of 5% dextrose and infused over 30 minutes; a 5-micron filter is recommended; do not administer undiluted

Dosing: ElderlyRefer to adult dosing.

StorageStore at 2°C to 30°C; do not freeze. If there are indications that package has been frozen, do not use.

ContraindicationsHypersensitivity to parenteral iron, parenteral dextran, parenteral iron dextran, parenteral iron-polysaccharide preparations, or any component of the formulation

Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity
- Iron Salt Allergy

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were observed in animal studies.

LactationExcretion in breast milk unknown/not recommended

Drug Interactions

Aldesleukin: Contrast Media (Non-ionic) may enhance the potential for allergic or hypersensitivity reactions to Aldesleukin. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: Iron 11.2 mg/mL (5 mL) [contains mannitol 61.3 mg/mL]

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesEndorem (AT, CH, DE, ES, FI, FR, IT, NO); Feridex (AR); Lumirem (IT)

Jump To Field (Select Field Name)

Special Alerts

Toviaz™ (Fesoterodine) Product Availability

Toviaz™ was approved by the U.S. Food and Drug Administration (FDA) in November 2008. It is expected to be available in the first half of 2009. No specific release date has been announced.

Medication Safety Issues

Sound-alike/look-alike issues:

Fesoterodine may be confused with fexofenadine, tolterodine

Pronunciation(fes oh TER oh deen)
U.S. Brand NamesToviaz™
Pharmacologic CategoryAnticholinergic Agent
Use: Labeled IndicationsTreatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.
Dosing: Adults**Overactive bladder:** Oral: 4 mg once daily; dose may be increased to 8 mg once daily based on individual response and tolerability

Dosing adjustment for concomitant CYP3A4 inhibitors: Maximum dose: 4 mg/day when administered concomitantly with potent CYP3A4 inhibitors including (but not limited to) ketoconazole, itraconazole, and clarithromycin. Concurrent therapy of weak or moderate CYP3A4 inhibitors and fesoterodine should be limited to 4 mg/day and increased to 8 mg/day after assessing tolerability.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal Impairment
Mild-to-moderate renal impairment (Cl_{cr} 30-80 mL/minute): No dose adjustment is recommended.

Severe renal impairment (Cl_{cr} <30 mL/minute): Maximum dose: 4 mg.

Dosing: Hepatic Impairment

Moderate hepatic impairment (Child-Pugh class B): No dose adjustment is recommended.

Severe hepatic impairment (Child-Pugh class C): Use is not recommended; not studied in severe impairment.

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered with or without food. Swallow whole; do not chew, crush, or divide.
Dietary ConsiderationsMay be taken with or without food.
StorageStore at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Protect from moisture.
ContraindicationsHypersensitivity to fesoterodine or any component of the formulation; urinary retention; gastric retention; uncontrolled narrow-angle glaucoma
Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Anticholinergics may cause drowsiness and/or blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Heat prostration: May occur in the presence of increased environmental temperature; use caution in hot weather and/or exercise.

Disease-related concerns:

- Bladder flow obstruction: Use with caution in patients with bladder flow obstruction; may increase the risk of urinary retention.

- Gastrointestinal obstructive disorders: Use with caution in patients with decreased GI motility or gastrointestinal obstructive disorders (ie, pyloric stenosis); may increase the risk of gastric retention.

- Glaucoma: Use with caution in patients with controlled (treated) narrow-angle glaucoma.

- Hepatic impairment: No dosing adjustments recommended for patients with mild or moderate hepatic impairment. No studies have been performed in patients with severe hepatic impairment (Child-Pugh class C); use is not recommended in this population.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis.

- Renal impairment: Use with caution in patients with renal impairment. Dose adjustment recommended in patients with severe renal impairment (Cl_{cr} <30 mL/minute). There are no dosing adjustments for patients with mild-to-moderate renal impairment.

Concurrent drug therapy issues:

- High potential for interactions: Doses >4 mg are not recommended in patients receiving potent CYP3A4 inhibitors. Concurrent therapy of weak or moderate CYP3A4 inhibitors and fesoterodine should be limited to 4 mg and increased to 8 mg after assessing tolerability.

Special populations:

- Elderly: Use caution in elderly patients (>75 years of age); risk of adverse effects may be increased.

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were observed in some animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%: Gastrointestinal: Xerostomia (19% to 35%; dose related)

1% to 10%:

Central nervous system: Insomnia (1%)

Dermatological: Rash (1%)

Gastrointestinal: Constipation (4% to 6%), dyspepsia (2%), nausea (1% to 2%), abdominal pain (1%)

Genitourinary: Urinary tract infection (3% to 4%), dysuria (1% to 2%), urinary retention (1%)

Hepatic: ALT increased (1%), GGT increased (1%)

Neuromuscular & skeletal: Back pain (1% to 2%)

Ocular: Dry eyes (1% to 4%)

Respiratory: Upper respiratory tract infection (2% to 3%), cough (1% to 2%), dry throat (1% to 2%)

Miscellaneous: Peripheral edema (1%)

<1%: Angina, blurred vision, chest pain, diverticulitis, gastroenteritis, heart rate increased (dose related), heat prostration, irritable bowel syndrome, QT_c prolongation

Drug Interactions

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Adverse effects may be potentiated

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, extended release:

Toviaz™: 4 mg, 8 mg

Generic AvailableNo

ManufacturerSchwarz Pharma

Mechanism of ActionFesoterodine acts as a prodrug and is converted to an active metabolite, 5-hydroxymethyl tolterodine (5-HMT); 5-HMT is responsible for fesoterodine’s antimuscarinic activity and acts as a competitive antagonist of muscarinic receptors.

Urinary bladder contractions are mediated by muscarinic receptors; fesoterodine inhibits the receptors in the bladder preventing symptoms of urgency and frequency.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: I.V.: 5-HMT: V_d: 169 L

Protein binding: 5-HMT: ~50% (primarily to albumin and alpha$_1$-acid glycoprotein)

Metabolism: Fesoterodine is rapidly and extensively metabolized to its active metabolite (5-hydroxymethyl tolterodine; 5-HMT) by nonspecific esterases; 5-HMT is further metabolized via CYP2D6 and CYP3A4 to inactive metabolites.

Bioavailability: 5-HMT: 52%

Half-life elimination: ~7 hours

Time to peak, plasma: 5-HMT: ~5 hours; C_{max} higher in poor CYP2D6 metabolizers

Excretion: Urine (~70%; 16% as 5-HMT, ~53% as inactive metabolites); feces (7%)

Index Terms FESO; Fesoterodine Fumarate

References

Chapple C, Van Kerrebroeck P, Tubaro A, et al, “Clinical Efficacy, Safety, and Tolerability of Once-Daily Fesoterodine in Subjects With Overactive Bladder,” *Eur Urol*, 2007, 52(4):1204-12.[PubMed 17651893]

Khullar V, Rovner ES, Dmochowski R, et al, “Fesoterodine Dose Response in Subjects With Overactive Bladder Syndrome,” *Urology*, 2008, 71(5):839-43.[PubMed 18342923]

Michel M, “Fesoterodine: A Novel Muscarinic Receptor Antagonist for the Treatment of Overactive Bladder Syndrome,” *Expert Opin Pharmacother*, 2008, 9(10):1787-96.[PubMed 18570610]

Nitti VW, Dmochowski R, Sand PK, et al, “Efficacy, Safety and Tolerability of Fesoterodine for Overactive Bladder Syndrome,” *J Urol*, 2007, 178(5):2488-94.[PubMed 17937959]

Fexofenadine and Pseudoephedrine

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Allegra-D® may be confused with Viagra®

Pronunciation(feks oh FEN a deen & soo doe e FED rin)

U.S. Brand NamesAllegra-D® 12 Hour; Allegra-D® 24 Hour

Canadian Brand NamesAllegra-D®

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation

Use: Labeled IndicationsRelief of symptoms associated with seasonal allergic rhinitis in adults and children ≥12 years of age

Dosing: AdultsAllergic symptoms and nasal congestion: Oral:

Allegra-D® 12 Hour: One tablet twice daily

Allegra-D® 24 Hour: One tablet once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥12 years: Refer to adult dosing.

Dosing: Renal Impairment

Allegra-D® 12 Hour: Cl_{cr} <80 mL/minute (based on fexofenadine component): One tablet once daily.

Allegra-D® 24 Hour: Avoid use.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralTablets should be swallowed whole; do not crush or chew. Administer with water.

ContraindicationsHypersensitivity to fexofenadine, pseudoephedrine, or any component of the formulation; narrow-angle glaucoma; urinary retention; during or within 14 days of MAO inhibitor therapy; severe hypertension or coronary heart disease

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Renal impairment: Use with caution in patients with renal impairment.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies using this combination showed reduced fetal weight, delayed ossification, and decreased survival. Also refer to individual monographs.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsPseudoephedrine is excreted in breast milk; excretion of fexofenadine is not known. Also refer to individual monographs. The AAP considers both agents to be usually “compatible” with breast-feeding.

Adverse ReactionsSee individual agents.

Metabolism/Transport EffectsFexofenadine: **Substrate** of CYP3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of Fexofenadine. Management: No specific recommendations concerning the time required between their administration are provided. Separate administration of each agent by as much time as possible to decrease the risk of an interaction. **Exceptions:** Calcium Carbonate; Magaldrate; Sodium Bicarbonate. *Risk D: Consider therapy modification*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the tachycardic effect of Alpha-/Beta-Agonists. Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor) may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Erythromycin: May increase the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Ketoconazole: May increase the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Rifampin: May decrease the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Verapamil: May increase the bioavailability of Fexofenadine. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, extended release:

Allegra-D® 12 Hour: Fexofenadine hydrochloride 60 mg [immediate release] and pseudoephedrine hydrochloride 120 mg [extended release]

Allegra-D® 24 Hour: Fexofenadine hydrochloride 180 mg [immediate release] and pseudoephedrine hydrochloride 240 mg [extended release]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablet, 12-hour (Allegra-D 12 Hour)

60-120 mg (30): $68.66

Tablet, 24-hour (Allegra-D 24 Hour)

180-240 mg (30): $126.43

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Fexofenadine
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness, nervousness, and insomnia; may rarely cause hallucinations

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors

Index TermsPseudoephedrine and Fexofenadine

International Brand NamesAlerfedine D (AR); Allegra-D (BB, BM, BR, BS, BZ, CN, CR, DO, EC, GT, GY, HN, JM, KP, MX, NI, NL, PA, PE, PY, SR, SV, TT, UY, VE); Altiva-D (MY); Telfast (PH); Telfast BD 60 (ID); Telfast Decongestant (AU); Telfast HD 180 (ID); Telfast OD 120 (ID); Telfast Plus (ID); Telfast-D (HK, MY, SG)

Fexofenadine

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Medication Safety Issues

Sound-alike/look-alike issues:

Fexofenadine may be confused with fesoterodine

Allegra® may be confused with Viagra®

International issues:

Allegra® may be confused with Allegro® which is a brand name for frovatriptan in Germany; a brand name for fluticasone in Israel

Pronunciation(feks oh FEN a deen)

U.S. Brand NamesAllegra®; Allegra® ODT

Canadian Brand NamesAllegra®

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation

Use: Labeled IndicationsRelief of symptoms associated with seasonal allergic rhinitis; treatment of chronic idiopathic urticaria

Dosing: Adults

Allergic rhinitis, idiopathic urticaria: Oral: 60 mg twice daily **or** 180 mg once daily

Dosing: ElderlyChronic idiopathic urticaria, seasonal allergic rhinitis: Starting dose: 60 mg once daily; adjust for renal impairment.

Dosing: Pediatric

Chronic idiopathic urticaria: Oral:

Children 6 months to <2 years: 15 mg twice daily

Children 2-11 years: 30 mg twice daily

Children ≥12 years: Refer to adult dosing.

Allergic rhinitis: Oral:

Children 2-11 years: Oral: 30 mg twice daily

Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <80 mL/minute:

Children 6 months to <2 years: Initial: 15 mg once daily

Children 2-11 years: Initial: 30 mg once daily

Children ≥12 years and Adults: Initial: 60 mg once daily

Not effectively removed by hemodialysis

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: Oral

Suspension, tablet: Administer with water only; do not administer with fruit juices. Shake suspension well before use.

Orally disintegrating tablet: Take on an empty stomach. Do not remove from blister pack until administered. Using dry hands, place immediately on tongue. Tablet will dissolve within seconds, and may be swallowed with or without liquid. Do not split or chew.

Dietary Considerations Allegra® ODT 30 mg contains phenylalanine 5.3 mg/tablet.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from excessive moisture.

ContraindicationsHypersensitivity to fexofenadine or any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 months of age; orally disintegrating tablet not recommended for use in children <6 years of age.

Dosage form specific issues:

- Orally disintegrating tablet: Contains phenylalanine.

Geriatric ConsiderationsPlasma levels in the elderly are generally higher than those observed in other age groups. Once daily dosing is recommended when starting therapy in elderly patients or patients with decreased renal function.
Pregnancy Risk FactorC
Pregnancy ConsiderationsDecreased fetal weight gain and survival were observed in animal studies. There are no adequate and well-controlled studies in pregnant women; use during pregnancy only if potential benefit to mother outweighs possible risk to fetus.
LactationExcretion in breast milk unknown/use caution (AAP rates “compatible”)
Adverse Reactions

>10%:

Central nervous system: Headache (5% to 11%)

Gastrointestinal: Vomiting (children 6 months to 5 years: 4% to 12%)

1% to 10%:

Central nervous system: Fatigue (1% to 3%), somnolence (1% to 3%), dizziness (2%), fever (2%), pain (2%), drowsiness (1%)

Endocrine & metabolic: Dysmenorrhea (2%)

Gastrointestinal: Dyspepsia (1% to 2%), diarrhea (3% to 4%), nausea (2%)

Neuromuscular & skeletal: Myalgia (3%), back pain (2% to 3%), pain in extremities (2%)

Otic: Otitis media (2% to 4%)

Respiratory: Upper respiratory tract infection (3% to 4%), cough (2% to 4%), rhinorrhea (1% to 2%)

Miscellaneous: Viral infection (3%)

<1%, postmarketing, and/or case reports: Hypersensitivity reactions (anaphylaxis, angioedema, chest tightness, dyspnea, flushing, pruritus, rash, urticaria); insomnia, nervousness, sleep disorders, paroniria

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor); **Inhibits** CYP2D6 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of Fexofenadine. Management: No specific recommendations concerning the time required between their administration are provided. Separate administration of each agent by as much time as possible to decrease the risk of an interaction. **Exceptions:** Calcium Carbonate; Magaldrate; Sodium Bicarbonate. *Risk D: Consider therapy modification*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Erythromycin: May increase the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

Ketoconazole: May increase the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Rifampin: May decrease the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

Verapamil: May increase the bioavailability of Fexofenadine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (although limited with fexofenadine, may increase risk of sedation).

Food: Fruit juice (apple, grapefruit, orange) may decrease bioavailability of fexofenadine by ~36%.

Herb/Nutraceutical: St John's wort may decrease fexofenadine levels.

Monitoring ParametersRelief of symptoms

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake as directed; do not exceed recommended dose. Store at room temperature in a dry place. If taking antacids, separate administration of antacid and this medication. Avoid use of other depressants, alcohol, or sleep-inducing medications unless approved by prescriber. You may experience mild drowsiness or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea (small frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help). Report persistent sedation or drowsiness, menstrual irregularities, or lack of improvement or worsening or condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Suspension, oral, as hydrochloride:

Allegra®: 6 mg/mL (30 mL [DSC], 300 mL) [contains propylene glycol; raspberry cream]

Tablet, oral, as hydrochloride: 30 mg, 60 mg, 180 mg

Allegra®: 30 mg [DSC], 60 mg, 180 mg

Tablet, orally disintegrating, oral, as hydrochloride:

Allegra® ODT: 30 mg [contains phenylalanine 5.3 mg/tablet; orange cream flavor]

Generic AvailableYes: Excludes orally disintegrating tablet and suspension

Pricing: U.S. (www.drugstore.com)

Suspension (Allegra)

30 mg/5 mL (300): $68.67

Tablet, orally-disintegrating (Allegra ODT)

30 mg (60): $109.99

Tablets (Allegra)

30 mg (60): $51.99

60 mg (60): $99.00

180 mg (30): $79.99

Mechanism of ActionFexofenadine is an active metabolite of terfenadine and like terfenadine it competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels and respiratory tract; it appears that fexofenadine does not cross the blood brain barrier to any appreciable degree, resulting in a reduced potential for sedation

Pharmacodynamics/Kinetics

Onset of action: 60 minutes

Duration: Antihistaminic effect: ≥12 hours

Protein binding: 60% to 70%, primarily albumin and alpha_1-acid glycoprotein

Metabolism: Minimal (~5%)

Half-life elimination: 14.4 hours (31% to 72% longer in renal impairment)

Time to peak, serum: ODT: 2 hours (4 hours with high-fat meal); Tablet: ~2.6 hours; Suspension: ~1 hour

Excretion: Feces (~80%) and urine (~11%) as unchanged drug

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFexofenadine Hydrochloride

References

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Day JH, et al, "Onset of Action, Efficacy and Safety of a Single Dose of 60 mg and 120 mg Fexofenadine HCl for Ragweed Allergy Using Controlled Antigen Exposure in an Environmental Exposure Unit," *J Allergy Clin Immunol*, 1996, 97(1 Pt 3):1007.

"Fexofenadine," *Med Lett Drugs Ther*, 1996, 38(986):95-6. [PubMed 8906132]

Simons FE, Bergman JN, Watson WT, et al, "The Clinical Pharmacology of Fexofenadine in Children," *J Allergy Clin Immunol*, 1996, 98(6 Pt 1):1062-4.[PubMed 8977506]

International Brand NamesAlerfedine (AR); Allegra (BB, BM, BR, BS, BZ, CO, CR, DO, EC, GT, GY, HN, IN, JM, KP, MX, NI, NL, PA, PE, PY, SR, SV, TT, TW, UY, VE); Allegra 180 (CN); Altiva (HN); Bosnum (TH); Fenafex (PH, TH); Fexon (KP); Fexotabs (AU); Fexotene (TH); Raltiva (CL); Sizzle (PK); Tefodine (AU); Telfast (AT, AU, BE, BF, BG, BJ, CH, CI, CZ, DE, DK, EE, ES, ET, FI, FR, GB, GH, GM, GN, HK, IE, IL, IT, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, PL, PT, SC, SD, SE, SG, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Telfast BD (ID); Xergic (AU)

Fibrin Sealant Kit

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Pronunciation(FI brin SEEL ent kit)
U.S. Brand NamesEvicel™; Tisseel® VH
Canadian Brand NamesTisseel® VH
Pharmacologic CategoryHemostatic Agent
Use: Labeled Indications

Evicel™: Adjunct to hemostasis in surgery when control of bleeding by conventional surgical techniques is ineffective or impractical

Tisseel® VH: Adjunct to hemostasis in cardiopulmonary bypass surgery and splenic injury (due to blunt or penetrating trauma to the abdomen) when the control of bleeding by conventional surgical techniques is ineffective or impractical; adjunctive sealant for closure of colostomies; hemostatic agent in heparinized patients undergoing cardiopulmonary bypass

Dosing: AdultsAdjunct to hemostasis: Apply topically in an even, thin layer (do not inject directly into circulatory system); actual dose is based on size of surface to be covered:

Evicel™: Spray or drop onto surface of bleeding tissue in short bursts (0.1-0.2 mL); if hemostatic effect is not complete, apply a second layer. To cover a layer of 1 mm thickness:

Maximum area to be sealed: 20 cm^2

Required size of Evicel™ kit: 2 mL

Maximum area to be sealed: 40 cm^2

Required size of Evicel™ kit: 4 mL

Maximum area to be sealed: 100 cm^2

Required size of Evicel™ kit: 10 mL

Tisseel® VH: Adults: Apply in thin layers to avoid excess formation of granulation tissue and slow absorption of the sealant. Following application, hold the sealed parts in the desired position for 3-5 minutes. To prevent sealant from adhering to gloves or surgical instruments, wet them with saline prior to contact.

Maximum area to be sealed: 8 cm^2

Required package size of Tisseel® VH: 2 mL

Maximum area to be sealed: 16 cm^2

Required package size of Tisseel® VH: 4 mL

Maximum area to be sealed: 40 cm^2

Required package size of Tisseel® VH: 10 mL

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricAdjunct to hemostasis: Topical (Evicel™): Refer to adult dosing.
Administration: Topical

Evicel™: Solution should be sprayed or dripped on the tissue to produce an even, thin layer. Application with provided device allows for the simultaneous application of both solutions. Apply spray with provided air tube; distance between nozzle and tissue surface should be 10-15 cm. Apply drops keeping applicator close to, but not touching tissue surface; do not inject directly into circulatory system.

Tisseel® VH: Apply in thin layers to avoid excess formation of granulation tissue and slow absorption of the sealant. Following application, hold the sealed parts in the desired position for 3-5 minutes. To prevent sealant from adhering to gloves or surgical instruments, wet them with saline prior to contact.

Storage

Evicel™: Store frozen at or below -18°C; unopened vials may be stored at 2°C to 8°C (35°F to 46°F) for up to 30 days or up to 24 hours at room temperature. Vials should be thawed prior to use; do not refreeze; if thawed at room temperature, do not re-refrigerate; do not exceed 10 minutes at 37°F.

Tisseel® VH, freeze dried: Store at 2°C to 25°C (35°F to 77°F); do not freeze.

Tisseel® VH, prefilled syringe: Store frozen at or below -20°C. Unopened pouches may be stored for up to 48 hours at room temperature. Do not expose to temperatures >37°C. Do not microwave. Do not refrigerate or refreeze.

Reconstitution

Evicel™: Thaws within 1 day under refrigeration at 2°C to 8°C (35°F to 46°F); within 1 hour at room temperature (20°C to 25°C) or within 10 minutes at 37°F (do not exceed 37°F; do not exceed 10 minutes at 37°F). Draw up equal volumes of each vial into application device.

Tisseel® VH, freeze dried: Solution may be prepared by reconstituting the freeze-dried sealer protein concentrate using the Fibrinotherm® (preferred method), a water bath, or an incubator. The thrombin solution is prepared separately. The two solutions are then transferred to the sterile field and applied to the affected area using the Duploject® syringe system. Application must be done within 4 hours of preparing the solution. Total reconstitution time may take up to 40 minutes.

To reconstitute the sealer protein: Fibrinotherm® method: The Fibrinotherm® is a combined heating and stirring device that can be obtained from the manufacturer. After removing the caps from the sealer concentrate and the fibrinolysis inhibitor solution, disinfect with a germicidal solution that does **not** contain iodine. Turn on the stirring switch of the Fibrinotherm® and insert each vial into the appropriate openings. Turn on the heating switch. The vials will automatically preheat at 37°C for 10 minutes. Transfer the fibrinolysis inhibitor solution into the vial of sealer protein concentrate. Use the adapter to insert the vial into the largest opening of the Fibrinotherm®. Stir contents for 8-10 minutes. If total dissolution has not occurred within 20 minutes, discard and prepare a fresh kit. If not used promptly, keep the solution at 37°C. Stir again shortly before drawing up solution.

Preparation of thrombin solution: After removing the caps from the calcium chloride and thrombin vials, disinfect with a germicidal solution that does **not** contain iodine. Add the calcium chloride to the thrombin vial. Swirl briefly. Keep the prepared solution at 37°C until use.

Note: Prior to application, the sealer protein solution and the thrombin solution should be transferred to a sterile field. To do this, the scrub nurse should withdraw the solution into the provided syringes, while the circulating nurse holds the vials. Withdraw solutions slowly to reduce the possible formation of large air bubbles.

Preparation of the final solution: The two resulting solutions are then placed into the Duploject® system, comprised of two identical disposable syringes, provided in the kit. The syringes have a common plunger, which allows equal volumes of both solutions to be fed through a joining piece, mixed, and ejected through a common application needle. Both syringes should contain equal volumes of solution. Do not expel any air bubbles (may clog). If the application process is interrupted, immediately prior to resuming application, replace the needle with one of the three spare needles provided in the kit. Discard any remaining solution.

Tisseel® VH, prefilled syringe: Thaw in water bath or incubator, following manufacturer guidelines; do not remove protective syringe cap until fully thawed and warmed. Application must be completed within 4 hours of preparing the solution.

Contraindications

Evicel™: Anaphylactic or severe systemic reaction to human blood products; severe or brisk arterial bleeding

Tisseel® VH: Hypersensitivity to bovine protein or aprotinin; direct injection into blood vessels

Warnings/Precautions

Dosage form specific issues:

- Human plasma: Components of the kit made from human plasma may potentially transmit disease. Any infection suspected of being transmitted by this product should be reported to the manufacturer.
- Tisseel® VH: Do not apply to wound surface containing alcohol, iodine, or heavy-metal ions. Do not use with oxycellulose-containing preparations. May contain bovine source fibrinolysis inhibitor solution (aprotinin). Use caution when applying with pressurized gas, may cause air embolism, tissue rupture or gas entrapment with compression. Safety and efficacy in neurologic procedures (or other procedures within a confined space) have not been established. Safety and efficacy in pediatric patients have not been established.

Other warnings/precautions:

- Administration: For topical use only; do not inject into a vessel or tissue; intravascular administration may result in serious or life-threatening thromboembolic or allergic/anaphylactoid reaction.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. There are no adequate and well-controlled studies in pregnant women.

Adverse ReactionsMay be related to aprotinin contained in some products. Frequency may vary by product.

Cardiovascular: Bradycardia (≤10%)

<1%, postmarketing and/or case reports: Hypersensitivity including anaphylactoid or anaphylactic reactions (0.5/100,000 exposures), dyspnea, flushing, hypotension, nausea, paralysis, pruritus, shock, thromboembolic complications, urticaria

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Kit:

Evicel™ [preservative free; each 2 mL kit contains]:

Solution, topical: Fibrinogen 55-85 mg/mL (1 mL) [human derived]

Solution, topical: Thrombin 800-1200 int. units/mL [human derived] and calcium chloride 5.6-6.2 mg/mL (1 mL) [contains albumin]

[each kit also contains a spray application device]

Evicel™ [preservative free; each 4 mL kit contains]:

Solution, topical: Fibrinogen 55-85 mg/mL (2 mL) [human derived]

Solution, topical: Thrombin 800-1200 int. units/mL [human derived] and calcium chloride 5.6-6.2 mg/mL (2 mL) [contains albumin]

[each kit also contains a spray application device]

Evicel™ [preservative free; each 10 mL kit contains]:

Solution, topical: Fibrinogen 55-85 mg/mL (5 mL) [human derived]

Solution, topical: Thrombin 800-1200 int. units/mL [human derived] and calcium chloride 5.6-6.2 mg/mL (5 mL) [contains albumin]

[each kit also contains a spray application device]

Tisseel VH [each 2 mL, 4 mL, or 10 mL kit contains]:

Powder, for solution, topical: Fibrinogen 67-106 mg/mL [human derived; contains polysorbate 80]

Powder, for solution, topical: Thrombin 400-625 int. units/mL [human derived]

Solution, topical: Calcium chloride 36-44 µmol/mL [for thrombin reconstitution]

Solution, topical: Aprotinin 2250-3750 KIU/mL [fibrinolysis inhibitor; synthetic or bovine derived; for fibrinogen reconstitution]

[packaged with Duploject system or Duploject Easyprep]

Tisseel VH [each dual-chamber 2 mL, 4 mL, or 10 mL prefilled syringe contains]:

Solution, topical:

Sealer protein chamber: Fibrinogen 67-106 mg/mL [human derived; contains polysorbate 80] and aprotinin 2250-3750 KIU/mL [fibrinolysis inhibitor; synthetic or bovine derived]

Thrombin chamber: Thrombin 400-625 int. units/mL [human derived] and calcium chloride 36-44 µmol/mL

[packaged with accessory devices]

Generic AvailableNo

Mechanism of ActionFormation of a biodegradable adhesive is done by duplicating the last step of the coagulation cascade, the formation of fibrin from fibrinogen. Fibrinogen is the main component of the sealant solution. The solution also contains thrombin, which transforms fibrinogen from the sealer protein solution into fibrin, and fibrinolysis inhibitor (aprotinin), which prevents the premature degradation of fibrin. When mixed as directed, a viscous solution forms that sets into an elastic coagulum.

Pharmacodynamics/KineticsOnset of action: Tisseel® VH: Time to hemostasis: 5 minutes (65% of patients); Final prepared sealant: 70% strength: ~10 minutes; Full strength: ~2 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFibrin Sealant (Human); FS

References

Beierlein W, Scheule AM, Antoniadis G, et al, “An Immediate, Allergic Skin Reaction to Aprotinin After Reexposure to Fibrin Sealant,” *Transfusion*, 2000, 40 (3):302-5.[PubMed 10738030]

Shirai T, Shimota H, Chida K, et al, “Anaphylaxis to Aprotinin in Fibrin Sealant,” *Intern Med*, 2005, 44(10): 1088-9.

International Brand NamesTisseel Duo 500 (AU)

Fibrinogen Concentrate (Human)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(fi BRIN o gin KON suhn trate HYU man)

U.S. Brand NamesRiaSTAP™

Pharmacologic CategoryBlood Product Derivative

Use: Labeled IndicationsTreatment of acute bleeding episodes in patients with congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia)

Dosing: Adults**Congenital fibrinogen deficiency:** I.V.: **Note:** Adjust dose based on laboratory values and condition of patient. Maintain a target fibrinogen level of 100 mg/dL until hemostasis is achieved.

> When baseline fibrinogen level is known:
>
> > Dose (mg/kg) = [Target level (mg/dL) - measured level (mg/dL)] **divided by** 1.7 (mg/dL per mg/kg body weight)
>
> When baseline fibrinogen level is not known: 70 mg/kg

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Congenital fibrinogen deficiency:** I.V.: Refer to adult dosing.

Administration: I.V.For I.V. administration only; infuse at ≤5 mL/minute

StorageStore at 2°C to 25°C (36°F to 77°F) in original carton; do not freeze. Protect from light. Stable for 24 hours after reconstitution when stored at 20°C to 25°C (68°F to 77°F). Discard partially used vials.

ReconstitutionTransfer sterile water for injection 50 mL into vial. Gently swirl until dissolved; do not shake.

ContraindicationsSevere hypersensitivity reactions to fibrinogen concentrate or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity: Hypersensitivity reactions (eg, urticaria, hives, wheezing, hypotension, anaphylaxis) may occur. In the event of hypersensitivity reactions, treatment should be discontinued immediately.

- Thrombotic events: Thrombosis may occur in patients with congenital fibrinogen deficiency with or without fibrinogen replacement therapy. Consider potential risk of thrombosis with use.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

Other warnings/precautions:

- Appropriate use: Dysfibrinogenemia: Not for the treatment of dysfibrinogenemia.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Increased pregnancy loss is associated with untreated congenital fibrinogen disorders.

Breast-Feeding ConsiderationsThe use of fibrinogen concentrate has not been studied in nursing women with congenital fibrinogen deficiency.

Adverse Reactions

>1%: Central nervous system: Fever, headache

Postmarketing and/or case reports: Allergic reactions, anaphylaxis, arterial thrombosis, chills, DVT, dyspnea, MI, nausea, pulmonary embolism, rash, thromboembolism, vomiting

Drug Interactions

Antifibrinolytic Agents: May enhance the adverse/toxic effect of Fibrinogen Concentrate (Human). Specifically, the risk for thrombosis may be increased. Fibrinogen Concentrate (Human) may enhance the adverse/toxic effect of Antifibrinolytic Agents. Specifically, the risk for thrombosis may be increased. *Risk C: Monitor therapy*

Monitoring ParametersSigns and symptoms of hypersensitivity, thrombosis; fibrinogen level

Reference RangeA target fibrinogen level of 100 mg/dL should be maintained until hemostasis occurs and wound healing is complete.

Normal fibrinogen levels: 200-450 mg/dL

Monitoring: Lab TestsFibrinogen level

Product AvailabilityRiaSTAP™: FDA approved January 2009; availability currently undetermined

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution:

RiaSTAP™: 900-1300 mg [contains albumin (human); exact potency labeled on vial]

Generic AvailableNo

ManufacturerCSL Behring

Mechanism of ActionFibrinogen (coagulation factor I), a protein found in normal plasma, is required to clot blood. Fibrinogen concentrate made from pooled human plasma replaces this protein which is missing or reduced in patients with a congenital fibrinogen deficiency.

Pharmacodynamics/Kinetics

Distribution: V_d: 45-60 mL/kg (range 36-68 mL/kg)

Half-life elimination: 61-97 hours (range 56-117 hours); may be decreased in children <16 years of age

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCoagulation Factor I

References

Acharya SS and Dimichele DM, “Rare Inherited Disorders of Fibrinogen,” *Haemophilia*, 2008, 14(6):1151-8.[PubMed 19141154]

Kreuz W, Meili E, Peter-Salonen K, et al. “Efficacy and Tolerability of a Pasteurised Human Fibrinogen Concentrate in Patients With Congenital Fibrinogen Deficiency,” *Transfus Apher Sci*, 2005, 32(3):247-53.[PubMed 15919240]

Filgrastim

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Neupogen® may be confused with Epogen®, Neumega®, Neupro®, Nutramigen®

Pronunciation(fil GRA stim)
U.S. Brand NamesNeupogen®
Canadian Brand NamesNeupogen®
Pharmacologic Category[Colony Stimulating Factor]
Use: Labeled IndicationsStimulation of granulocyte production in chemotherapy-induced neutropenia (nonmyeloid malignancies, acute myeloid leukemia, and bone marrow transplantation); severe chronic neutropenia (SCN); moblilization of hematopoietic progenitor cells in patients undergoing peripheral blood progenitor cell (PBPC) collection
Use: Unlabeled/InvestigationalTreatment of anemia in myelodysplastic syndrome; treatment of drug-induced (nonchemotherapy) agranulocytosis in the elderly
Dosing: AdultsDetails concerning dosing in combination regimens and institution protocols should also be consulted.

Note: Dosing should be based on actual body weight (even in morbidly obese patients). Rounding doses to the nearest vial size often enhances patient convenience and reduces costs without compromising clinical response.

Chemotherapy-induced neutropenia I.V., SubQ: 5 mcg/kg/day; doses may be increased by 5 mcg/kg according to the duration and severity of the neutropenia; continue for up to 14 days or until the ANC reaches 10,000/mm^3

Bone marrow transplantation: I.V., SubQ: 10 mcg/kg/day; adjust the dose according to the duration and severity of neutropenia; recommended steps based on neutrophil response:

When ANC >1000/mm^3 for 3 consecutive days: Reduce filgrastim dose to 5 mcg/kg/day.

If ANC remains >1000/mm^3 for 3 more consecutive days: Discontinue filgrastim.

If ANC decreases to <1000/mm^3: Resume at 5 mcg/kg/day.

If ANC decreases <1000/mm^3 during the 5 mcg/kg/day dose: Increase filgrastim to 10 mcg/kg/day and follow the above steps.

Peripheral blood progenitor cell (PBPC) collection: SubQ: 10 mcg/kg daily in donors, usually for 6-7 days. Begin at least 4 days before the first leukopheresis and continue until the last leukopheresis; consider dose adjustment for WBC >100,000/mm^3

Hematopoietic stem cell mobilization (in combination with plerixafor, for autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma): SubQ: 10 mcg/kg once daily; begin 4 days before initiation of plerixafor; continue G-CSF on each day prior to apheresis

Severe chronic neutropenia: SubQ:

Congenital: 6 mcg/kg twice daily; adjust the dose based on ANC and clinical response

Idiopathic/cyclic: 5 mcg/kg/day; adjust the dose based on ANC and clinical response

Anemia in myelodysplastic syndrome (unlabeled use - in combination with epoetin): SubQ: 0.3-3 mcg/kg daily **or** 30-150 mcg daily **or** 1-2 mcg/kg 2-3 times weekly

Dosing: ElderlyRefer to adult dosing.

Drug-induced agranulocytosis (nonchemotherapy) in the elderly (unlabeled use): SubQ: 300 mcg daily until ANC >1500/mm^3

Dosing: PediatricChildren: Refer to adult dosing.
Dosing: Combination Regimens

Breast cancer: AC/Paclitaxel (Sequential)

Leukemia, acute myeloid:

FLAG

FLAG-IDA

Lymphoma, non-Hodgkin's:

CODOX-M/IVAC

ICE (Lymphoma, non-Hodgkin's)

RICE

Lymphoma, non-Hodgkin's (Burkitt's): CODOX-M/IVAC

Prostate cancer: Cyclophosphamide + Doxorubicin

Sarcoma, soft tissue: AI

Oncology: Bone Marrow - High Dose5-10 mcg/kg/day
Calculations

- ANC: Absolute Neutrophil Count

Administration: I.V.May be administered by I.V. bolus over 15-30 minutes in D_5W, or by continuous SubQ or I.V. infusion. Do not administer earlier than 24 hours after or in the 24 hours prior to cytotoxic chemotherapy.
Administration: I.V. DetailpH: 4
Administration: OtherMay be administered SubQ.
Dietary ConsiderationsSolution for injection contains sodium 0.035 mg/mL and sorbitol.
StorageIntact vials and prefilled syringes should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from direct sunlight. Filgrastim should be protected from freezing and temperatures >30°C to avoid aggregation. If inadvertently frozen, thaw in a refrigerator and use within 24 hours; do not use if frozen >24 hours or frozen more than once. Do not shake.

Filgrastim vials and prefilled syringes are stable for 24 hours at 9°C to 30°C (47°F to 86°F).

Undiluted filgrastim is stable for 24 hours at 15°C to 30°C (59°F to 86°F) and for up to 14 days at 2°C to 8°C (36°F to 46°F) (data on file, Amgen Medical Information) in BD tuberculin syringes; however, sterility has only been assessed and maintained for up to 7 days when prepared under strict aseptic conditions (Singh, 1994; Jacobson, 1996). The manufacturer recommends using syringes within 24 hours due to the potential for bacterial contamination.

Filgrastim diluted with D_5W or D_5W with albumin for I.V. infusion (5-15 mcg/mL) is stable for 7 days at 2°C to 8°C (36°F to 46°F), however, should be used within 24 hours due to the possibility for bacterial contamination.

Reconstitution**Do not dilute with saline at any time; product may precipitate.** Filgrastim may be diluted with D_5W or with D_5W with albumin to a concentration of 5-15 mcg/mL for I.V. infusion administration (minimum concentration: 5 mcg/mL). Dilution to <5 mcg/mL is not recommended. Concentrations 5-15 mcg/mL require addition of albumin (final concentration of 2 mg/mL) to prevent adsorption to plastics.
CompatibilityStable in D_5W; **incompatible** with NS.

Y-site administration: Compatible: Acyclovir, allopurinol, amikacin, aminophylline, ampicillin, ampicillin/sulbactam, aztreonam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, carmustine, cefazolin, cefotetan, ceftazidime, chlorpromazine, cimetidine, cisplatin, co-trimoxazole, cyclophosphamide, cytarabine, dacarbazine, daunorubicin HCl, dexamethasone sodium phosphate, diphenhydramine, doxorubicin HCl, doxycycline, droperidol, enalaprilat, famotidine, floxuridine, fluconazole, fludarabine, gallium nitrate, ganciclovir, granisetron, haloperidol lactate, hydrocortisone sodium succinate, hydromorphone, hydroxyzine HCl, idarubicin, ifosfamide, leucovorin calcium, lorazepam, mechlorethamine, melphalan, meperidine, mesna, methotrexate, metoclopramide, mitoxantrone, morphine, nalbuphine, ondansetron, potassium chloride, promethazine, ranitidine, sodium bicarbonate, streptozocin, ticarcillin/clavulanate, tobramycin, vancomycin, vinblastine, vincristine, vinorelbine, zidovudine. **Incompatible:** Amphotericin B, cefepime, cefotaxime, cefoxitin, ceftizoxime, ceftriaxone, cefuroxime, clindamycin, dactinomycin, etoposide, fluorouracil, furosemide, heparin, mannitol, methylprednisolone sodium succinate, metronidazole, mitomycin, piperacillin, prochlorperazine edisylate, thiotepa. **Variable (consult detailed reference):** Gentamicin, imipenem/cilastatin.

ContraindicationsHypersensitivity to filgrastim, *E. coli*-derived proteins, or any component of the formulation
Warnings/Precautions

Concerns related to adverse reactions:

- Allergic reactions: Rash, urticaria, wheezing, dyspnea, tachycardia, and/or hypotension have occurred with first or later doses. Reactions tended to occur more frequently with intravenous administration and within 30 minutes of administration.

- Alveolar hemorrhage: Reports of alveolar hemorrhage, manifested as pulmonary infiltrates and hemoptysis, have occurred in healthy donors undergoing PBPC collection (not FDA approved for use in healthy donors); hemoptysis resolved upon discontinuation.

- Cutaneous vasculitis: Has been reported, generally occurring in SCN patients on long-term therapy; dose reductions may improve symptoms to allow for continued therapy.

- Respiratory distress syndrome: Rare cases of acute respiratory distress syndrome have been reported; patients must be instructed to report respiratory distress.

- Splenic rupture: Rare cases of splenic rupture have been reported; patients must be instructed to report left upper quadrant pain or shoulder tip pain.

Disease-related concerns:

- Sickle cell disease: May precipitate sickle cell crises in patients with sickle cell disease; carefully evaluate potential risks and benefits.

Concurrent drug therapy issues:

- Cytotoxic chemotherapy: Do not use filgrastim in the period 24 hours before to 24 hours after administration of cytotoxic chemotherapy because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy.

- Plerixafor: Increases circulating leukocytes when used in conjunction with plerixafor for stem cell mobilization; monitor WBC; use with caution in patients with neutrophil count >50,000/mm^3. May also release tumor cells from marrow which could be collected in leukapheresis product; potential effect of tumor cell re-infusion is unknown.

Special populations:

- Myelosuppressing chemotherapy recipients: Safety and efficacy have not been established with patients receiving chemotherapy associated with delayed myelosuppression (eg, nitrosoureas, mitomycin C).

- Radiation therapy recipients: Safety and efficacy have not been established with patients receiving radiation therapy.

- Severe congenital neutropenia: Cytogenetic abnormalities, transformation to AML and MDS have been observed in patients treated with filgrastim for congenital neutropenia; a longer duration of treatment and poorer ANC response appear to increase the risk.

Dosage form specific issues:

- Latex: The packaging of some dosage forms may contain latex.

Other warnings/precautions:

- Tumor growth factor: May potentially act as a growth factor for any tumor type, particularly myeloid malignancies; precaution should be exercised when using in any malignancy with myeloid characteristics.

Geriatric ConsiderationsNo specific data available for the elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies have demonstrated adverse effects and fetal loss. Filgrastim has been shown to cross the placenta in humans. There are no adequate and well-controlled studies in pregnant women. Use only if potential benefit to mother justifies risk to the fetus.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%:

Central nervous system: Fever (12%)

Dermatologic: Petechiae (17%), rash (12%)

Gastrointestinal: Splenomegaly (severe chronic neutropenia: 30%; rare in other patients)

Hepatic: Alkaline phosphatase increased (21%)

Neuromuscular & skeletal: Bone pain (22% to 33%), commonly in the lower back, posterior iliac crest, and sternum

Respiratory: Epistaxis (9% to 15%)

1% to 10%:

Cardiovascular: Hyper-/hypotension (4%), S-T segment depression (3%), myocardial infarction/arrhythmias (3%)

Central nervous system: Headache (7%)

Gastrointestinal: Nausea (10%), vomiting (7%), peritonitis (2%)

Hematologic: Leukocytosis (2%)

Miscellaneous: Transfusion reaction (10%)

<1%, postmarketing, and/or case reports: Acute respiratory distress syndrome, allergic reactions, alopecia, alveolar hemorrhage, arthralgia, capillary leak syndrome, cerebral hemorrhage, cutaneous vasculitis, dyspnea, edema (facial), erythema nodosum, hematuria, hemoptysis, hepatomegaly, hypersensitivity reaction, injection site reaction, osteoporosis, pericarditis, proteinuria, psoriasis exacerbation, pulmonary infiltrates, renal insufficiency, sickle cell crisis, splenic rupture, Sweet's syndrome (acute febrile dermatosis), tachycardia, thrombocytopenia (in PBPC mobilization), thrombophlebitis, transient supraventricular arrhythmia, urticaria, wheezing

Oncology: VesicantNo
Oncology: Emetic PotentialLow (10% to 30%)
Drug Interactions

Topotecan: Filgrastim may enhance the adverse/toxic effect of Topotecan. *Risk D: Consider therapy modification*

Test InteractionsMay interfere with bone imaging studies; increased hematopoietic activity of the bone marrow may appear as transient positive bone imaging changes
Monitoring ParametersCBC with differential prior to treatment and twice weekly during filgrastim treatment for chemotherapy-induced neutropenia (3 times a week following marrow transplantation). For severe chronic neutropenia, monitor CBC with differential twice weekly during the first month of therapy and for 2 weeks following dose adjustments; monthly thereafter. In PBPC mobilization, monitor platelets.
Reference RangeNo clinical benefit seen with ANC >10,000/mm^3
Nursing: Physical Assessment/MonitoringAssess for hypersensitivity to *E. coli* products prior to beginning therapy. Assess potential for

interactions with pharmacological agents the patient may be taking that may potentiate the release of neutrophils. Assess results of laboratory tests prior to therapy and as indicated in Laboratory Monitoring. Monitor therapeutic effectiveness and signs/symptoms of adverse reactions at beginning of therapy and periodically throughout therapy (eg, allergic-type reactions have occurred in patients receiving G-CSF with first or later doses). If self-administered, teach patient (or caregiver) proper storage, administration, and syringe/needle disposal. Teach patient (or caregiver) possible side effects/appropriate interventions and adverse symptoms to report (including upper quadrant pain, shoulder tip pain, or respiratory distress - splenic rupture and adult respiratory distress have been reported).

Monitoring: Lab TestsCBC with differential prior to treatment and twice weekly during filgrastim treatment for chemotherapy-induced neutropenia (3 times a week following marrow transplantation). For severe chronic neutropenia, monitor CBC with differential twice weekly during the first month of therapy and for 2 weeks following dose adjustments; monthly thereafter. In PBPC mobilization, monitor platelets.

Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. If self-administered, follow directions for proper storage and administration of SubQ medication. Never reuse syringes or needles. May cause bone pain (request analgesic); nausea or vomiting (small, frequent meals may help); hair loss (reversible); or sore mouth (frequent mouth care with soft toothbrush or cotton swab may help). Report immediately any respiratory difficulty or pain in left shoulder, chest, or back. Report unusual fever or chills; unhealed sores; severe bone pain; pain, redness, or swelling at injection site; unusual swelling of extremities; or chest pain and palpitations. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Neupogen®: 300 mcg/mL (1 mL, 1.6 mL) [vial; contains sodium 0.035 mg/mL and sorbitol]

Injection, solution [preservative free]:

Neupogen®: 600 mcg/mL (0.5 mL, 0.8 mL) [prefilled Singleject® syringe; contains sodium 0.035 mg/mL and sorbitol; needle cover contains latex]

Generic AvailableNo

ManufacturerAmgen Inc

Pricing: U.S. (www.drugstore.com)

Solution (Neupogen)

300 mcg/0.5 mL (5): $2653.63

300 mcg/mL (1): $234.62

480 mcg/0.8 mL (8): $4364.06

480 mcg/1.6 mL (16): $3547.96

Mechanism of ActionStimulates the production, maturation, and activation of neutrophils; filgrastim activates neutrophils to increase both their migration and cytotoxicity.

Pharmacodynamics/Kinetics

Onset of action: ~24 hours; plateaus in 3-5 days

Duration: ANC decreases by 50% within 2 days after discontinuing filgrastim; white counts return to the normal range in 4-7 days; peak plasma levels can be maintained for up to 12 hours

Absorption: SubQ: 100%

Distribution: V_d: 150 mL/kg; no evidence of drug accumulation over a 11- to 20-day period

Metabolism: Systemically degraded

Half-life elimination: 1.8-3.5 hours

Time to peak, serum: SubQ: 2-8 hours

Related Information

- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy Pearls

Reimbursement Hotline: 1-800-272-9376

Professional Services [Amgen]: 1-800-77-AMGEN

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay be used to treat clozapine-induced agranulocytosis; lithium may potentiate the release of neutrophils; use with caution

Index TermsG-CSF; Granulocyte Colony Stimulating Factor; NSC-614629

References

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Flomenberg N, Devine SM, DiPersio JF, et al, “The Use of AMD3100 Plus G-CSF for Autologous Hematopoietic Progenitor Cell Mobilization is Superior to G-CSF Alone,” *Blood*, 2005, 106(5): 1867-74.[PubMed 15890685]

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National Comprehensive Cancer Network (NCCN), “Clinical Practice Guidelines in Oncology™: Myeloid Growth Factors,” Version 1, 2008. Available at http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf.

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Smith TJ, Khatcheressian J, Lyman GH, et al, “2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline,” *J Clin Oncol*, 2006, 24(19):3187-205. [PubMed 16682719]

International Brand NamesBiocilin (MX); Biofigran (CO); Biofilgran (MX); Filatil (CR, DO, GT, HN, MX, NI, PA, SV); Filgen (EC, TH); Gran (JP, SG, TH); Granulokine (BR, PH); Grimatin (JP); Inmunef (MX); Jilifen (TH); Jisaixin (CL); Leucokain (KP); Leucostim (KP); Macroleuco (PH); Neupogen (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CN, CO, CY, CZ, DE, DK, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, OM, PE, PK, PL, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TR, TT, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Neutromax (PE); White-C (PH)

Finasteride

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Proscar® may be confused with ProSom®, Prozac®, Psorcon®

Pronunciation(fi NAS teer ide)

U.S. Brand NamesPropecia®; Proscar®

Canadian Brand NamesPropecia®; Proscar®

Pharmacologic Category5 Alpha-Reductase Inhibitor

Use: Labeled Indications

Propecia®: Treatment of male pattern hair loss in **men only**. Safety and efficacy were demonstrated in men between 18-41 years of age.

Proscar®: Treatment of symptomatic benign prostatic hyperplasia (BPH); can be used in combination with an alpha-blocker, doxazosin

Use: Unlabeled/InvestigationalAdjuvant monotherapy after radical prostatectomy in the treatment of prostatic cancer; female hirsutism

Dosing: Adults

Benign prostatic hyperplasia (Proscar®): Oral: 5 mg/day as a single dose; clinical responses occur within 12 weeks to 6 months of initiation of therapy; long-term administration is recommended for maximal response

Male pattern baldness (Propecia®): Oral: 1 mg daily

Female hirsutism (unlabeled use): Oral: 5 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentUse with caution in patients with liver function abnormalities because finasteride is metabolized extensively in the liver

Administration: OralAdministration with food may delay the rate and reduce the extent of oral absorption. Women of childbearing age should not touch or handle broken tablets.

StorageStore below 30°C (86°F). Protect from light.

ContraindicationsHypersensitivity to finasteride or any component of the formulation; pregnancy; not for use in children

Allergy Considerations

- Dutasteride Allergy
- Finasteride Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.
- Women/pregnancy: Women can absorb the active ingredient through the skin and should always use caution whenever handling. Pregnant women or women trying to conceive should not handle the product; finasteride may negatively impact fetal development.

Disease-related concerns:

- Diminished urinary flow: Carefully monitor patients with a large residual urinary volume or severely diminished urinary flow for obstructive uropathy; these patients may not be candidates for finasteride therapy.
- Hepatic impairment: Use with caution in patients with hepatic impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Other urological diseases including cancer should be ruled out before initiating.
- Duration of therapy: A minimum of 6 months of treatment may be necessary to determine whether an individual will respond to finasteride.
- PSA monitoring: Reduces prostate specific antigen (PSA) by 50%; in patients treated for ≥6 months the PSA should be doubled when comparing to normal ranges in untreated patients.

Geriatric ConsiderationsClearance of finasteride is decreased in the elderly, but no dosage reductions are necessary.
Pregnancy Risk FactorX
Pregnancy ConsiderationsAbnormalities of external male genitalia were reported in animal studies. Pregnant women are advised to avoid contact with crushed or broken tablets.
LactationExcretion in breast milk unknown/contraindicated
Breast-Feeding ConsiderationsNot indicated for use in women.
Adverse Reactions**Note:** “Combination therapy” refers to finasteride and doxazosin.

>10%:

Endocrine & metabolic: Impotence (19%; combination therapy 23%), libido decreased (10%; combination therapy 12%)

Neuromuscular & skeletal: Weakness (5%; combination therapy 17%)

1% to 10%:

Cardiovascular: Postural hypotension (9%; combination therapy 18%), edema (1%; combination therapy 3%)

Central nervous system: Dizziness (7%; combination therapy 23%), somnolence (2%; combination therapy 3%)

Genitourinary: Ejaculation disturbances (7%; combination therapy 14%), decreased volume of ejaculate

Endocrine & metabolic: Gynecomastia (2%)

Respiratory: Dyspnea (1%; combination therapy 2%), rhinitis (1%; combination therapy 2%)

<1%, postmarketing, and/or case reports: Hypersensitivity (pruritus, rash, urticaria, swelling of face/lips); breast tenderness, breast enlargement, breast cancer (males), prostate cancer (high grade), testicular pain

Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)
Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb Interactions

Herb/Nutraceutical: St John's wort may decrease finasteride levels. Avoid saw palmetto (concurrent use has not been adequately studied).

Monitoring ParametersObjective and subjective signs of relief of benign prostatic hyperplasia, including improvement in urinary flow, reduction in symptoms of urgency, and relief of difficulty in micturition
Nursing: Physical Assessment/MonitoringAssess potential for interactions with pharmacological agents or herbal products patient may be taking. Assess urinary pattern prior to therapy and periodically during therapy (obstructive uropathy). Assess therapeutic effectiveness and signs/symptoms of adverse reactions. Teach patient proper use (eg, a minimum of 6 months of treatment may be necessary to evaluate response), possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X** - instruct patient on absolute need for barrier contraceptives. Women of childbearing age should not touch or handle broken tablets.
Monitoring: Lab TestsFinasteride does not interfere with free PSA levels.
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Results of therapy may take several months. Take with or without meals. May cause decreased libido or impotence during therapy. Report any changes in urinary pattern (significant increase or decrease in volume or voiding patterns). Report changes in breast condition (pain, lumps, or nipple discharge) in male and female patients. **Pregnancy precautions:** This drug will cause fetal abnormalities - use barrier contraceptives and do not allow women of childbearing age to touch or handle broken or crushed tablets.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 5 mg

Propecia®: 1 mg

Proscar®: 5 mg

Generic AvailableYes
ManufacturerMerck & Co
Pricing: U.S. (www.drugstore.com)

Tablets (Proscar)

5 mg (30): $95.99

Mechanism of ActionFinasteride is a competitive inhibitor of both tissue and hepatic 5-alpha reductase. This results in inhibition of the conversion of testosterone to dihydrotestosterone and markedly suppresses serum dihydrotestosterone levels
Pharmacodynamics/Kinetics

Onset of action: 3-6 months of ongoing therapy

Duration:

After a single oral dose as small as 0.5 mg: 65% depression of plasma dihydrotestosterone levels persists 5-7 days

After 6 months of treatment with 5 mg/day: Circulating dihydrotestosterone levels are reduced to castrate levels without significant effects on circulating testosterone; levels return to normal within 14 days of discontinuation of treatment

Distribution: V_{dss}: 76 L

Protein binding: 90%

Metabolism: Hepatic via CYP3A4; two active metabolites (<20% activity of finasteride)

Bioavailability: Mean: 63%

Half-life elimination, serum: Elderly: 8 hours; Adults: 6 hours (3-16)

Time to peak, serum: 2-6 hours

Excretion: Feces (57%) and urine (39%) as metabolites

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other ConsiderationsFinasteride may be useful in men with moderately symptomatic BPH who either refuse prostatectomy or are poor surgical candidates. Currently, there is no way to predict which men will respond to finasteride. Treatment with finasteride does not alter the ratio of free to total PSA, which is used to detect prostatic cancer.

References

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McConnell JD, Roehrborn CG, Bautista OM, et al, “The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia. Medical Therapy of Prostatic Symptoms (MTOPS) Research Group,” *N Engl J Med*, 2003, 349(25):2387-98. [PubMed 14681504]

Pole M and Koren G, “Finasteride. Does It Affect Spermatogenesis and Pregnancy,” *Can Fam Physician*, 2001, 47:2469-70. [PubMed 11785276]

Thompson IM, Goodman PJ, Tangen CM, et al, “The Influence of Finasteride on the Development of Prostate Cancer,” *N Engl J Med*, 2003, Jul 349(3):215-24.[PubMed 12824459]

International Brand NamesBearfina (KP); Chibro-Proscar (FR); Finastar (KP); Finastid (HR); Finaxal (ID); Fincar (IN); Finpro (ID); Firide (TH); Fistrin (CO); Fynasid (TW); Harifin (TH); Nasterol (CO); Panascar (KP); Penester (PL); Pro-Cure (IL); Propecia (AR, AU, BR, CL, CO, CR, EC, ES, GT, HK, HN, IL, KP, MY, NI, PA, PE, PH, PL, SE, SG, SV, TH, TW); Propeshia (MX); Proscar (AR, AT, AU, BB, BE, BG, BM, BO, BR, BS, BZ, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, GY, HK, HN, HR, HU, ID, IE, IT, JM, KP, LU, MX, MY, NI, NL, NO, PA, PE, PH, PK, PL, PR, PT, PY, RU, SE, SR, SV, TH, TR, TT, TW, UY, VE); Prosmol (KP); Prostacom (ID); Prosterid (HU); Prostop (UY); Reprostom (ID); Sxarex (KP); Tensen (TW); Uromedin (PY)

FIS-HAM

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Lymphocytic; Chemotherapy Regimen, Leukemia, Acute Myeloid
Regimen UseLeukemia, acute lymphocytic; Leukemia, acute myeloid
Regimen

Fludarabine: I.V.: 15 mg/m^2/day every 12 hours days 1, 2, 8, and 9

[total dose/cycle = 120 mg/m^2]

Cytarabine: I.V.: 750 mg/m^2/day every 3 hours days 1, 2, 8, and 9

[total dose/cycle = 24,000 mg/m^2]

Mitoxantrone: I.V.: 10 mg/m^2/day days 3, 4, 10, and 11

[total dose/cycle = 40 mg/m^2]

References

Kern W, Schleyer E, Braess J, et al, âEfficacy of Fludarabine, Intermittent Sequential High-Dose Cytosine Arabinoside, and Mitoxantrone (FIS-HAM) Salvage Therapy in Highly Resistant Acute Leukemias,â *Ann Hematol*, 2001, 80(6):334-9.[PubMed 11475146]

FL

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Prostate Cancer]

Regimen Use Prostate cancer

Index Terms Flutamide + Leuprolide

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Flutamide: Oral: 250 mg every 8 hours

[total dose/cycle = 21,000 mg]

Leuprolide acetate: SubQ: 1 mg/day

[total dose/cycle = 28 mg]

Repeat cycle every 28 days

Variation 2:

Flutamide: Oral: 250 mg every 8 hours

[total dose/cycle = 67,500 mg]

Leuprolide acetate depot: I.M.: 22.5 mg day 1

[total dose/cycle = 22.5 mg]

Repeat cycle every 3 months

References

Variation 1: Crawford ED, Eisenberger MA, McLeod DG, et al, “A Controlled Trial of Leuprolide With and Without Flutamide in Prostatic Carcinoma,” *N Engl J Med*, 1989, 17:321(7):419-24. [PubMed 2503724]

Variation 2: McLeod DG, Schellhammer PF, Vogelzang NJ, et al, “Exploratory Analysis on the Effect of Race on Clinical Outcome in Patients With Advanced Prostate Cancer Receiving Bicalutamide or Flutamide, Each in Combination With LHRH Analogues. The Casodex Combination Study Group.” *Prostate*, 1999, 1:40(4):218-24.[PubMed 10420149]

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid

Regimen UseLeukemia, acute myeloid

Regimen

Fludarabine: I.V.: 30 mg/m^2/day days 1 to 5

[total dose/cycle = 150 mg/m^2]

Cytarabine: I.V.: 2 g/m^2/day days 1 to 5

[total dose/cycle = 10 g/m^2]

Idarubicin: I.V.: 10 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 30 mg/m^2]

Filgrastim: 5 mcg/kg from day 6 until neutrophil recovery

Administer one cycle only

References

Pastore D, Specchia G, Carluccio P, et al, âFLAG-IDA in the Treatment of Refractory/Relapsed Acute Myeloid Leukemia: Single-Center Experience,â *Ann Hematol*, 2003, 82(4):231-5. [PubMed 12707726]

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Leukemia, Acute Myeloid]

Regimen UseLeukemia, acute myeloid

Regimen

Fludarabine: I.V.: 30 mg/m^2/day days 1 to 5

[total dose/cycle = 150 mg/m^2]

Cytarabine: I.V.: 2 g/m^2/day days 1 to 5 (3.5 hours after end of fludarabine infusion)

[total dose/cycle = 10 g/m^2]

Filgrastim: SubQ: 5 mcg/kg day 1

followed by SubQ: 300 mcg daily until ANC >500-1000 cells/mcL postnadir

[total dose/cycle = 40-7800 mcg/kg]

Repeat cycle every 3-4 weeks

References

Clavio M, Carrara P, Miglino M, et al, âHigh Efficacy of Fludarabine-Containing Therapy (FLAG-FLANG) in Poor Risk Acute Myeloid Leukemia,â *Haematologica*, 1996, 81(6):513-20.[PubMed 9009438]

Flavocoxid

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(fla vo KOKS id)
U.S. Brand NamesLimbrel™
Pharmacologic CategoryAnti-inflammatory Agent
Use: Labeled IndicationsClinical dietary management of osteoarthritis, including associated inflammation
Dosing: Adults**Management of osteoarthritis:** Oral: 250 mg every 8-12 hours
Dosing: ElderlyRefer to adult dosing.
Dietary ConsiderationsTake on an empty stomach at least 1 hour before or after meals.
StorageStore at 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to flavocoxid or any component of the formulation.
Warnings/Precautions

Disease-related concerns:

- Gastrointestinal disease: Use with caution in patients with a history of gastrointestinal disorders; may cause gastrointestinal bleeding or ulceration.

Concurrent drug therapy issues:

- NSAIDs: Avoid concomitant use with NSAIDs.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Experienced physician: Should only be used under the close supervision of a healthcare provider.

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions≥2%:

Cardiovascular: Hypertension, varicose veins

Dermatologic: Psoriasis

Gastrointestinal: Occult stools (statistically similar to placebo)

Neuromuscular & skeletal: Fluid on the knee

Metabolism/Transport Effects **Inhibits** CYP1A2 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 3A4 (weak)
Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringEvaluate for history of gastrointestinal disorders prior to prescribing. Teach patient proper use and potential side effects/appropriate interventions, and adverse symptoms to report.
Patient EducationTake on an empty stomach 1 hour before or after meals. Do not take other medications (especially aspirin or other nonsteroidal anti-inflammatory medications) without consulting prescriber. Report change in color of stools (black or tarry) blood in vomitus, or persistent abdominal pain.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Limbrel™: 250 mg, 500 mg [gluten free]

Generic AvailableNo
ManufacturerPharmaFab®
Pricing: U.S. (www.drugstore.com)

Capsules (Limbrel)

250 mg (60): $85.99

500 mg (60): $99.97

Mechanism of ActionExerts anti-inflammatory properties through nonspecific inhibition of cyclooxygenase (COX) and lipoxygenase (5-LOX) pathways; may also possess general analgesic and antioxidant/anticytokine properties
Pharmacodynamics/Kinetics

Onset of action: 1-2 hours

Metabolism: Primarily via glucuronidation and sulfation

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported. May enhance risk of bleeding associated with NSAIDs.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentLithium concentrations may be increased with flavocoxid via decreased renal lithium clearance; dose adjustment may be needed

Index TermsFlavan; Flavonoid

Flavoxate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Flavoxate may be confused with fluvoxamine

Urispas® may be confused with Urised®

Pronunciation(fla VOKS ate)

U.S. Brand NamesUrispas®

Canadian Brand NamesApo-Flavoxate®; Urispas®

Pharmacologic CategoryAntispasmodic Agent, Urinary

Use: Labeled IndicationsAntispasmodic to provide symptomatic relief of dysuria, nocturia, suprapubic pain, urgency, and incontinence due to detrusor instability and hyper-reflexia in elderly with cystitis, urethritis, urethrocystitis, urethrotrigonitis, and prostatitis

Dosing: AdultsUrinary spasms: Oral: 100-200 mg 3-4 times/day; reduce the dose when symptoms improve.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren >12 years: Refer to adult dosing.

Administration: OralShould be administered with water on an empty stomach.

Dietary ConsiderationsShould be taken with water on an empty stomach.

ContraindicationsHypersensitivity to flavoxate; pyloric or duodenal obstruction; GI hemorrhage; GI obstruction; ileus; achalasia; obstructive uropathies of lower urinary tract (BPH)

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Ocular disturbances: May cause ocular disturbances; patients must be advised of potential effects.
- Vertigo: May cause vertigo; patients must be advised of potential effects.

Disease-related concerns:

- Glaucoma: Use with caution in patients with suspected glaucoma.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Geriatric ConsiderationsCaution should be used in the elderly due to anticholinergic activity (eg, confusion, constipation, blurred vision, and tachycardia).

Pregnancy Risk FactorB

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined.

Cardiovascular: Tachycardia, palpitation

Central nervous system: Drowsiness, confusion (especially in the elderly), nervousness, fatigue, vertigo, headache, hyperpyrexia

Dermatologic: Rash. urticaria

Gastrointestinal: Constipation, nausea, vomiting, xerostomia, dry throat

Genitourinary: Dysuria

Hematologic: Leukopenia

Ocular: Increased intraocular pressure, blurred vision

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersMonitor I & O closely

Nursing: Physical Assessment/MonitoringAssess kidney function, voiding pattern, incontinent episodes, frequency, urgency/retention, and ophthalmic assessment for glaucoma prior to starting therapy and periodically with long-term therapy. Assess knowledge/teach patient appropriate use, possible side effects/interventions, and adverse symptoms to report.

Patient EducationTake exactly as directed, with water, preferably on an empty stomach, 1 hour before or 2 hours after meals. Do not use alcohol or OTC medications without consulting prescriber. You may experience mild drowsiness, nervousness, or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, dry mouth (small frequent meals, frequent oral care, chewing gum, or sucking hard candy may help); decreased ability to perspire (avoid extremes of heat); or constipation (increased exercise, fluids, fruit, or fiber may help). Report vision changes (blurred vision); rapid heartbeat; or unresolved nausea, vomiting, or constipation.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 100 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Urispas)

100 mg (28): $51.99

Mechanism of ActionSynthetic antispasmotic with similar actions to that of propantheline; it exerts a direct relaxant effect on smooth muscles via phosphodiesterase inhibition, providing relief to a variety of smooth muscle spasms; it is especially useful for the treatment of bladder spasticity, whereby it produces an increase in urinary capacity

Pharmacodynamics/Kinetics

Onset of action: 55-60 minutes

Metabolism: To methyl; flavone carboxylic acid active

Excretion: Urine (10% to 30%) within 6 hours

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), and dry throat.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause nervousness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFlavoxate Hydrochloride

International Brand NamesBaduson (TW); Bladderon (JP); Bladuril (AR, CO); Cleanxate (MY, SG); Flavate (IN); Flavo-Spa (TH); Flavorin (TH); Foxate (TW); Fucotin (TW); Genurin (CL, IT, TW); Genurin S (BR); Harnin (JP); Patricin (JP); Spagerin (KP); Spasdic (TH); Spasuret (DE); Spasuri (TH); Tonlin (TW); Uripax (MY); Urispadol (DK); Urispas (200 mg) (NL); Urispas (AE, AT, BE, BF, BG, BH, BJ, CH, CI, CY, EG, ET, FR, GB, GH, GM, GN, HK, IE, IL, IN, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, PT, QA, RU, SA, SC, SD, SL, SN, SY, TN, TR, TZ, UG, YE, ZA, ZM, ZW); Urivox (PK); Uronid (ES); Uropyrine (LU); Uroxal (ID); Uroxate (TH, TW); Voxate (TH); Yungken (TW)

Flecainide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Flecainide may be confused with fluconazole

Tambocor™ may be confused with tamoxifen

Pronunciation(fle KAY nide)

U.S. Brand NamesTambocor™

Canadian Brand NamesApo-Flecainide®; Tambocor™

Pharmacologic CategoryAntiarrhythmic Agent, Class Ic

Use: Labeled IndicationsPrevention and suppression of documented life-threatening ventricular arrhythmias (eg, sustained ventricular tachycardia); controlling symptomatic, disabling supraventricular tachycardias in patients without structural heart disease in whom other agents fail

Dosing: Adults

Life-threatening ventricular arrhythmias: Oral:

Initial: 100 mg every 12 hours; increase by 50-100 mg/day (given in 2 doses/day) every 4 days; maximum: 400 mg/day

For patients receiving 400 mg/day who are not controlled and have trough concentrations <0.6 mcg/mL, dosage may be increased to 600 mg/day.

Prevention of paroxysmal supraventricular arrhythmias: Oral: (**Note:** In patients with disabling symptoms but no structural heart disease): Initial: 50 mg every 12 hours; increase by 50 mg twice daily at 4-day intervals; maximum: 300 mg/day

Paroxysmal atrial fibrillation: Outpatient: "Pill-in-the-pocket" dose (unlabeled dose): Oral: 200 mg (weight <70 kg), 300 mg (weight ≥70 kg). May not repeat in ≤24 hours. **Note:** An initial inpatient conversion trial should have been successful before sending patient home on this approach. Patient must be taking an AV nodal-blocking agent (eg, beta-blocker, nondihydropyridine calcium channel blocker) prior to initiation of antiarrhythmic.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Life-threatening ventricular arrhythmias: Oral: Children:

Initial: 3 mg/kg/day or 50-100 mg/m^2/day in 3 divided doses

Usual maintenance: 3-6 mg/kg/day or 100-150 mg/m^2/day in 3 divided doses; up to 11 mg/kg/day or 200 mg/m^2/day for uncontrolled patients with subtherapeutic levels

Dosing: Renal ImpairmentGFR ≤50 mL/minute: Decrease dose by 50%; dose increases should be made cautiously at intervals >4 days and serum levels monitored frequently.

Hemodialysis: No supplemental dose recommended.

Peritoneal dialysis: No supplemental dose recommended.

Dosing: Hepatic ImpairmentMonitoring of plasma levels is recommended because half-life is significantly increased. When transferring from another antiarrhythmic agent, allow for 2-4 half-lives of the agent to pass before initiating flecainide therapy.

Calculations

- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels.

Extemporaneously PreparedA 5 mg/mL suspension compounded from tablets and an oral flavored commercially available diluent (Roxane®) was stable for up to 45 days when stored at 5°C or 25°C in amber glass bottles. Flecainide 20 mg/mL was found stable for up to 60 days at 5°C and 25°C in a 1:1 preparation of Ora-Sweet® and Ora-Plus®, in Ora-Sweet® SF and Ora-Plus® and in cherry syrup

Allen LV and Erickson III MA, "Stability of Baclofen, Captopril, Diltiazem, Hydrochloride, Dipyridamole, and Flecainide Acetate in Extemporaneously Compounded Oral Liquids," *Am J Health Syst Pharm*, 53:2179-84.

Wiest DB, Garner SS, and Pagacz LR, “Stability of Flecainide Acetate in an Extemporaneously Compounded Oral Suspension,” *Am J Hosp Pharm*, 1992, 49(6):1467-70.

ContraindicationsHypersensitivity to flecainide or any component of the formulation; pre-existing second- or third-degree AV block or with right bundle branch block when associated with a left hemiblock (bifascicular block) (except in patients with a functioning artificial pacemaker); cardiogenic shock; coronary artery disease (based on CAST study results); concurrent use of ritonavir or amprenavir

Warnings/Precautions

Boxed warnings:

- Atrial flutter: Appropriate use: See “Disease-related concerns” below.
- CAST trial: See “Other warnings/precautions” below.
- Proarrhythmic effects: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Proarrhythmic effects: **[U.S. Boxed Warning]: Watch for proarrhythmic effects;** monitor and adjust dose to prevent QT_c prolongation. Not recommended for patients with chronic atrial fibrillation.

Disease-related concerns:

- Atrial flutter: Appropriate use: **[U.S. Boxed Warning]: When treating atrial flutter, 1:1 atrioventricular conduction may occur; pre-emptive negative chronotropic therapy (eg, digoxin, beta-blockers) may lower the risk.**
- Conduction disturbances: Use with caution in patients with sick sinus syndrome; dose-related increases in PR and QRS intervals occur.
- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.
- Heart failure (HF): Use with caution in patients with HF; may precipitate or exacerbate condition.
- Hepatic impairment: Use with caution in patients with significant hepatic impairment.

Other warnings/precautions:

- CAST trial: **[U.S. Boxed Warning]: In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, non-life-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide.** An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. The risks of class 1C agents and the lack of improved survival make use in patients without life-threatening arrhythmias generally unacceptable.
- Pacemakers: Use with caution in patients with permanent pacemakers or temporary pacing wires; can increase endocardial pacing thresholds.

Geriatric ConsiderationsDecreased clearance and, therefore, prolonged half-life is possible; however, studies have shown no difference in response to usual doses in the elderly despite slight decrease in clearance; calculate or measure GFR since elderly patients may have GFR ≤50 mL/minute.

Pregnancy Risk FactorC

LactationEnters breast milk/compatible

Adverse Reactions

>10%:

Central nervous system: Dizziness (19% to 30%)

Ocular: Visual disturbances (16%)

Respiratory: Dyspnea (~10%)

1% to 10%:

Cardiovascular: Palpitation (6%), chest pain (5%), edema (3.5%), tachycardia (1% to 3%), proarrhythmic (4% to 12%), sinus node dysfunction (1.2%), syncope

Central nervous system: Headache (4% to 10%), fatigue (8%), nervousness (5%) additional symptoms occurring at a frequency between 1% and 3%: fever, malaise, hypoesthesia, paresis, ataxia, vertigo, somnolence, tinnitus, anxiety, insomnia, depression

Dermatologic: Rash (1% to 3%)

Gastrointestinal: Nausea (9%), constipation (1%), abdominal pain (3%), anorexia (1% to 3%), diarrhea (0.7% to 3%)

Neuromuscular & skeletal: Tremor (5%), weakness (5%), paresthesia (1%)

Ocular: Diplopia (1% to 3%), blurred vision

<1% (Limited to important or life-threatening): Bradycardia, paradoxical increase in ventricular rate in atrial fibrillation/flutter, heart block, increased P-R, QRS duration, ventricular arrhythmia, CHF, flushing, AV block, angina, hyper-/hypotension, amnesia, confusion, decreased libido, depersonalization, euphoria, apathy, nervousness, twitching, neuropathy, weakness, taste disturbance, urticaria, exfoliative dermatitis, pruritus, alopecia, flatulence, xerostomia, blood dyscrasias, possible hepatic dysfunction, paresthesia, eye pain,

photophobia, bronchospasm, pneumonitis, swollen lips/tongue/mouth, arthralgia, myalgia, polyuria, urinary retention, leukopenia, granulocytopenia, thrombocytopenia, metallic taste, alters pacing threshold

Postmarketing and/or case reports: Tardive dyskinesia, corneal deposits

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2D6 (major); **Inhibits** CYP2D6 (weak)
Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amiodarone: May decrease the metabolism of Flecainide. *Risk D: Consider therapy modification*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Flecainide. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Ritonavir: May decrease the metabolism of Flecainide. *Risk X: Avoid combination*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Tipranavir: May increase the serum concentration of Flecainide. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: Clearance may be decreased in patients following strict vegetarian diets due to urinary pH ≥8. Dairy products (milk, infant formula, yogurt) may interfere with the absorption of flecainide in infants; there is one case report of a neonate (GA 34 weeks PNA >6 days) who required extremely large doses of oral flecainide when administered every 8 hours with feedings (“milk feeds”); changing the feedings from “milk feeds” to 5% glucose feeds alone resulted in a doubling of the flecainide serum concentration and toxicity.
Monitoring ParametersECG, blood pressure, pulse, periodic serum concentrations, especially in patients with renal or hepatic impairment
Reference RangeTherapeutic: 0.2-1 mcg/mL; pediatric patients may respond at the lower end of the recommended therapeutic range
Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor cardiac status. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions when beginning therapy, when titrating dosage, and periodically during long-term therapy. **Note:** Flecainide has a low toxic:therapeutic ratio and overdose may easily produce severe and life-threatening reactions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Monitoring: Lab TestsPeriodic serum concentrations, especially in patients with renal or hepatic impairment
Patient EducationTake exactly as directed, around-the-clock. Do not discontinue without consulting prescriber. You will require frequent monitoring while taking this medication. You may experience lightheadedness, nervousness, dizziness, visual disturbances (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea, vomiting, or loss of appetite (small frequent meals may help). Report palpitations, chest pain, excessively slow or rapid heartbeat; acute nervousness, headache, or fatigue; unusual weight gain; unusual cough; respiratory difficulty; swelling of hands or ankles; or muscle tremor, numbness, or weakness. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as acetate: 50 mg, 100 mg, 150 mg

Generic AvailableYes
Manufacturer3M Pharmaceuticals
Pricing: U.S. (www.drugstore.com)

Tablets (Flecainide Acetate)

50 mg (60): $57.99

100 mg (60): $83.98

150 mg (60): $114.98

Tablets (Tambocor)

50 mg (60): $146.26

100 mg (60): $229.24

150 mg (60): $324.83

Mechanism of ActionClass Ic antiarrhythmic; slows conduction in cardiac tissue by altering transport of ions across cell membranes; causes slight prolongation of refractory periods; decreases the rate of rise of the action potential without affecting its duration; increases electrical stimulation threshold of ventricle, His-Purkinje system; possesses local anesthetic and moderate negative inotropic effects

Pharmacodynamics/Kinetics

Absorption: Oral: Rapid

Distribution: Adults: V_d: 5-13.4 L/kg

Protein binding: Alpha$_1$ glycoprotein: 40% to 50%

Metabolism: Hepatic

Bioavailability: 85% to 90%

Half-life elimination: Infants: 11-12 hours; Children: 8 hours; Adults: 7-22 hours, increased with congestive heart failure or renal dysfunction; End-stage renal disease: 19-26 hours

Time to peak, serum: ~1.5-3 hours

Excretion: Urine (80% to 90%, 10% to 50% as unchanged drug and metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsFlecainide is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusDizziness is common; may cause sedation; may rarely cause nervousness

Mental Health: Effects on Psychiatric TreatmentUse beta-blockers with caution; may produce additive negative inotropic effect; use caution with TCAs; may affect cardiac conduction; CYP2D6 substrate; use caution with the SSRIs

Cardiovascular ConsiderationsFlecainide is a Class Ic antiarrhythmic with a very narrow therapeutic index and with considerable proarrhythmic properties. The CAST trial, evaluating flecainide in the treatment of asymptomatic ventricular extrasystoles after myocardial infarction, showed a significant increase in mortality. In lower doses, flecainide has sometimes been used for maintenance of sinus rhythm in patients with severe refractory atrial fibrillation, without structural heart disease.

"Pill-in-the Pocket" administration approach: Patients with a history of palpitations with an abrupt onset, were hemodynamically stable, and had 1-12 episodes of atrial fibrillation within the previous year (and no other cardiac symptoms) were candidates for a clinical trial evaluating flecainide or propafenone for conversion of their rhythm (Alboni P, 2004). Patients had to have minimal, if any, heart disease. Only 12% of all patients evaluated for this trial were eligible for inclusion, thus this type of treatment is only for select patients meeting both inclusion and exclusion criteria. However, patients who had met inclusion criteria and were given either flecainide or propafenone in the hospital phase of the trial and converted to normal sinus rhythm were then enrolled into the ambulatory phase of the trial. Patients in this outpatient trial were to take either flecainide or propafenone at the first onset of palpitations. The doses were as follows: Flecainide 300 mg for patients ≥70 kg and 200 mg for patients <70 kg; propafenone 600 mg for patients ≥70 kg and 450 mg for patients <70 kg. Patients were instructed to sit or lie down after taking either drug until palpitations had stopped or for at least 4 hours. If palpitations had not subsided after 6–8 hours, then the patients were instructed to go to the emergency room. They were not to take more than one dose in a 24-hour period. This treatment regimen demonstrated that 94% of episodes in the 165 patients studied were successfully treated with a mean time to symptom resolution of 113 minutes. Adverse events were reported in 12 patients. One patient developed atrial flutter with a rapid ventricular response that required an emergency room visit. The other 11 patients complained of noncardiac side effects (eg, nausea, weakness, and vertigo). This therapy demonstrated a significant reduction in emergency room visits and hospitalization.

Selected patients with infrequent paroxysmal atrial fibrillation may be candidates for the “Pill-in-the-Pocket” regimen. Many patients may not be appropriate candidates for this regimen, based on previous clinical studies – CAST, CAST 2, CASH; a number of exclusion criteria define the potential harm of these agents.

Anesthesia and Critical Care Concerns/Other ConsiderationsBased on adverse outcomes noted with flecainide in the CAST trial, the FDA recommends that use of flecainide be limited to patients with life-threatening ventricular arrhythmias.

Index TermsFlecainide Acetate

References

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Fuster V, Ryden LE, Cannom DS, et al, “ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation-Executrive Summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients

With Atrial Fibrillation). Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society," *J Am Coll Cardiol*, 2006, 48(4):854-906.[PubMed 16904574]

International Brand NamesAlmarytm (IT); Apocard (ES, PT); Aristocor (AT); Flecadura (DE); Flecaine (FR); Flecaine LP (FR); Flecatab (AU); Tambocor (AE, AR, AU, BE, BF, BH, BJ, CH, CI, CN, CY, DE, DK, EE, EG, ET, FI, GB, GH, GM, GN, HK, IE, IL, IQ, IR, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PH, QA, SA, SC, SD, SE, SL, SN, SY, TH, TN, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Tambocor CR (NZ)

Floctafenine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(flok ta FEN een)
Canadian Brand NamesApo-Floctafenine®
Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral
Use: Labeled IndicationsShort-term management of acute, mild-to-moderate pain
Dosing: AdultsPain management: Oral: 200-400 mg every 6-8 hours as needed, up to a maximum of 1200 mg/day
Dosing: ElderlyElderly/debilitated: Initiate therapy with lower than usual adult starting dose; adjust dose when necessary under close observation
Dosing: PediatricDosage not established; use not recommended
Dosing: Renal ImpairmentAlthough no specific recommendations are given, initial doses should be lower than usual adult starting doses; individual adjustments to dose should be made when necessary and under close supervision.
Dosing: Hepatic ImpairmentUse with caution and under close supervision.
Administration: OralAdminister after food or meal with glass of water.
Dietary ConsiderationsShould be taken with food.
StorageStore at room temperature. Protect from light.
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to floctafenine, aspirin, other NSAIDS, or any component of the formulation; active peptic ulcer or a history of ulcerative disease; inflammatory gastrointestinal disease; severe cardiac insufficiency or ischemic cardiomyopathy; significant hepatic impairment or active liver disease; severely impaired (Cl_{cr} <30 mL/minute) or deteriorating renal function; concurrent use with other NSAIDS; severe heart failure, coronary heart disease; concurrent use with beta-blockers; nasal polyp syndrome (complete or partial); patients who experience “aspirin triad” (bronchial asthma, rhinitis complicated by polyps, aspirin intolerance) with aspirin or NSAID therapy
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.

- Aseptic meningitis: Symptoms of aseptic meningitis have been observed with NSAID therapy; patients with autoimmune disorders may be more predisposed.

- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.

- Cardiovascular events: NSAIDs are associated with an increased risk of adverse cardiovascular events, including MI, stroke, and new onset or worsening of pre-existing hypertension. Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk. Use is contraindicated with severe cardiac insufficiency.

- Gastrointestinal events: NSAIDs may increase risk of gastrointestinal irritation, inlammation, ulceration, bleeding, and perforation. These events can sometimes be severe and occasionally fatal and may occur at any time during therapy and without warning. Use caution with concurrent aspirin, anticoagulant and/or corticosteroid therapy, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk. Use is contraindicated in patients with active peptic ulcer, history of ulcer disease, or inflammatory GI disease.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: Use of NSAIDs is not recommended for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function; contraindicated in patients with severe or active impairment. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Contraindicated in patients with deteriorating function or severe impairment (Cl_{cr} <30 mL/minute). Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Pregnancy Risk FactorRisk factor not assigned. Floctafenic acid (active metabolite) crosses the placenta; therefore, the benefits of use must be weighed against risk to mother and fetus.

Pregnancy ConsiderationsIn late pregnancy, NSAIDs may cause premature closure of the ductus arteriosus.

LactationEnters breast milk/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Edema, flushing, tachycardia

Central nervous system: Depression, dizziness, drowsiness, fatigue, headache, insomnia, irritability, malaise, nervousness, vertigo

Dermatologic: Angioedema, pruritus, rash, urticaria

Endocrine & metabolic: Fluid retention, hyperkalemia

Gastrointestinal: Abdominal pain, bitter taste, constipation, diarrhea, dyspepsia, flatulence, gastrointestinal bleeding, gastrointestinal ulcer, gross bleeding with perforation, heartburn, nausea, vomiting, xerostomia

Hematologic: Agranulocytosis, aplastic anemia, bleeding, leukopenia, neutropenia, thrombocytopenia

Hepatic: Hepatotoxicity, liver enzymes increased

Ocular: Blurred and/or diminished vision

Otic: Tinnitus

Renal: Burning micturition, cystitis, dysuria, hematuria, interstitial nephritis, polyuria, reversible acute renal insufficiency with or without oliguria/anuria, strong smelling urine, urethritis

Respiratory: Asthmatic-type dyspnea

Miscellaneous: Anaphylaxis, diaphoresis, thirst

Drug Interactions

ACE inhibitors: Antihypertensive effects may be decreased by concurrent therapy with NSAIDs; monitor blood pressure. Concomitant use may increase risk of renal dysfunction.

Aminoglycosides: Gentamicin and amikacin serum concentrations may be increased by indomethacin in premature infants. Results may apply to other aminoglycosides and NSAIDs.

Angiotensin II receptor blockers: Antihypertensive effects may be decreased by concurrent therapy with NSAIDs; monitor blood pressure. Concomitant use may increase risk of renal dysfunction.

Anticoagulants (warfarin, heparin, LMWHs): In combination with NSAIDs, may increase the risk of bleeding.

Antidepressants, tricyclic, tertiary amine (amitriptyline, clomipramine, doxepin, imipramine, trimipramine): May enhance the antiplatelet effect of non selective NSAIDs.

Antiplatelet drugs (eg, clopidogrel, dipyridamole, eptifibatide): May increase the risk of bleeding.

Beta-blockers: NSAIDs may decrease the antihypertensive effect of beta-blockers; monitor.

Bile acid sequestrants (cholestyramine, colestipol): May decrease the absorption of NSAIDs. Separate administration by at least 2 hours.

Bisphosphonate derivatives (eg, alendronate): NSAIDs (nonselective) may enhance the adverse/toxic effect of bisphosphonate derivatives, an increased incidence of gastrointestinal ulceration is of concern.

Corticosteroids (systemic): May increase the risk of GI ulceration.

Cyclosporine: NSAIDs may enhance the nephrotoxic effect of cyclosporine and may increase the levels/effects of cyclosporine; monitor cyclosporine levels and renal function carefully.

Hydralazine: NSAIDs may diminish the antihypertensive effect of hydralazine.

Lithium: NSAIDs may increase the levels/effects of lithium; avoid concurrent use if possible or monitor lithium levels and adjust dose. Sulindac may have the least effect. When NSAID is stopped, lithium will need adjustment again.

Loop diuretics (eg, bumetanide, furosemide): NSAIDs may diminish the diuretic effect of loop diuretics; patients with heart failure may be more sensitive to alterations in fluid balance, consider avoiding the concomitant use of NSAIDs and loop diuretics; cirrhotic patients with ascites may also be at increased risk.

Methotrexate: NSAIDs may increase the levels/effects of methotrexate. Severe bone marrow suppression, aplastic anemia, and GI toxicity have been reported with concomitant NSAID therapy. Avoid use during moderate or high-dose methotrexate (increased and prolonged methotrexate levels). NSAID use during low-dose treatment of rheumatoid arthritis has not been fully evaluated; extreme caution is warranted.

Pemetrexed: NSAIDs may increase the levels/effects of pemetrexed. In patients with decreased renal function, avoid floctafenine use for 2-5 days before, the day of, and 2 days following a dose of pemetrexed.

Probenecid: May increase levels/effects of NSAIDs.

Quinolone antibiotics: NSAIDs may enhance the neuroexcitatory and/or seizure-potentiating effect of quinolone antibiotics.

Salicylates: NSAIDs (nonselective) may diminish the cardioprotective effect of acetylated salicylates. Avoid regular use of NSAIDs if possible; consider alternatives (eg, acetaminophen). If ibuprofen is used occasionally, give 30 minutes to 2 hours after aspirin. NSAIDs (nonselective) may enhance the antiplatelet effect of salicylates. Salicylates may decrease the levels/effects of NSAID (nonselective).

Selective serotonin reuptake inhibitors (SSRIs): May enhance the antiplatelet effect of NSAID (nonselective).

Thiazide diuretics: NSAIDs may diminish the antihypertensive effect of thiazide diuretics.

Treprostinil: May enhance the adverse/toxic effect of NSAIDs; bleeding may occur.

Vancomycin: NSAIDs may increase the levels/effects of vancomycin.

Warfarin: NSAIDs (nonselective) may enhance the anticoagulant effect of coumarin derivatives; monitor INR closely.

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Monitoring ParametersCBC, liver function tests, renal function (including bun and creatinine); edema; GI effects (eg, abdominal pain, dyspepsia, bleeding); vision

Monitoring: Lab TestsCBC, liver function tests, renal function (bun and creatinine)

Patient EducationIf self-administered, take exactly as directed; do not increase dose or frequency. Take with food or milk to avoid GI irritation. Maintain adequate hydration (2-3 L/day of fluid) unless instructed to restrict fluid intake. Do not use alcohol, aspirin, or aspirin-containing medication without consulting prescriber. You may experience drowsiness or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known), nausea, vomiting, gastric discomfort (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). GI bleeding, ulceration, and perforation can occur with or without pain. Stop taking medication and report occurrence immediately. Report ringing in ears, changes in hearing or vision, unresolved nausea or vomiting, difficulty breathing or shortness of breath, cramping or stomach pain, unusual bruising or bleeding (blood in urine, stool, mouth, or vomitus), unusual swelling of extremities or weight gain (>3-5 pounds/week), chest pain, rapid heartbeat, or skin rash. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet:

Apo-Floctafenine® [CAN]: 200 mg, 400 mg [not available in the U.S.]

Generic AvailableYes

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Duration: 6-8 hours

Absorption: Rapid, well absorbed

Metabolism: Hepatic

Half-life elimination: Initial phase (distribution): 1 hour; second phase (elimination): 8 hours

Time to peak, plasma: 1-2 hours

Excretion: Feces and bile (60%); urine (40%)

Pharmacotherapy PearlsNo interactions have been noted with concomitant administration of antacids.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), bitter taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression, dizziness, drowsiness, insomnia, irritability, malaise, or nervousness

Mental Health: Effects on Psychiatric TreatmentMay decrease the clearance of lithium resulting in elevated serum levels and potential toxicity; monitor serum lithium levels. Concomitant use with SSRIs may increase the risk of bleeding; monitor.

Index Terms Floctafenina; Floctafeninum

International Brand Names Idalon (JP); Idarac (FR, PK, TH)

FLOX (Nordic FLOX)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Colorectal Cancer

Regimen Use Colorectal cancer

Index Terms Flox

Regimen

Oxaliplatin: I.V.: 85 mg/m^2 day 1

[total dose/cycle = 85 mg/m^2]

Fluorouracil: I.V.: 500 mg/m^2/day days 1 and 2

[total dose/cycle = 1000 mg/m^2]

Leucovorin: I.V.: 60 mg/m^2/day days 1 and 2

[total dose/cycle = 120 mg/m^2]

Repeat cycle every 2 weeks

References

Sorbye H and Dahl O, “Nordic 5-Fluorouracil/Leucovorin Bolus Schedule Combined With Oxaliplatin (Nordic FLOX) as First-Line Treatment of Metastatic Colorectal Cancer,” *Acta Oncol*, 2003, 42(8):827-31.[PubMed 14968943]

Floxuridine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Floxuridine may be confused with Fludara®, fludarabine

FUDR® may be confused with Fludara®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(floks YOOR i deen)

U.S. Brand NamesFUDR®

Canadian Brand NamesFUDR®

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite (Pyrimidine Analog)

Use: Labeled IndicationsManagement of hepatic metastases of colorectal and gastric cancers

Dosing: AdultsRefer to individual protocols.

Colorectal or gastric metastases:

Intra-arterial: Primarily by an implantable pump: 0.1-0.6 mg/kg/day continuous intra-arterial administration for 14 days then heparinized saline is given for 14 days; toxicity requires dose reduction.

I.V.: (unlabeled use) Many regimens in use, examples:

0.15 mg/kg/day for 7-14 days

0.5-1 mg/kg/day for 6-15 days

30 mg/kg/day for 5 days, then 15 mg/kg/day every other day, up to 11 days

Dosing: ElderlyAdjust dose since elderly patients are prone to toxicity.

Dosing: Renal ImpairmentThe FDA-approved labeling does not contain dosing adjustment guidelines; use with extreme caution.

Dosing: Hepatic ImpairmentThe FDA-approved labeling does not contain dosing adjustment guidelines; use with extreme caution. The following guidelines have been used by some clinicians (Floyd, 2006):

Serum bilirubin 1.2 times ULN or alkaline phosphatase 1.2 times ULN: Administer 80% of dose

Serum bilirubin 1.5 times ULN; ALT/AST 3 times baseline or alkaline phosphatase 1.5 times ULN: Administer 50% of dose

Serum bilirubin 2 times ULN; ALT/AST >3 times baseline or alkaline phosphatase 2 times ULN: No recommendation is available

Administration: I.V.Continuous intra-arterial or I.V. infusion (unlabeled use)

Administration: I.V. DetailpH: 4.0-5.5

StorageStore intact vials at room temperature of 15°C to 30°C (59°F to 86°F). Reconstituted vials are stable for up to 2 weeks under refrigeration at 2°C to 8°C (36°C to 46°C). Further dilution in 500-1000 mL D_5W or NS is stable for 2 weeks at room temperature. Solutions in 0.9% sodium chloride are stable in some ambulatory infusion pumps for up to 21 days.

ReconstitutionReconstitute with 5 mL SWI for a final concentration of 100 mg/mL. Further dilute in 500-1000 mL D_5W or NS for I.V. infusion.

CompatibilityStable in D_5W, NS, sterile water for injection.

Y-site administration: Compatible: Amifostine, aztreonam, etoposide phosphate, filgrastim, fludarabine, gemcitabine, granisetron, melphalan, ondansetron, paclitaxel, piperacillin/tazobactam, sargramostim, teniposide, thiotepa, vinorelbine. **Incompatible:** Allopurinol, cefepime.

Compatibility when admixed: Compatible: Carboplatin, cisplatin, cisplatin with etoposide, cisplatin with leucovorin, etoposide, fluorouracil, leucovorin.

ContraindicationsHypersensitivity to floxuridine, fluorouracil, or any component of the formulation; pregnancy

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.
- Initiation of therapy: See “Other warnings/precautions” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Toxicity: Discontinue if intractable vomiting, diarrhea, precipitous fall in leukocyte or platelet counts, myocardial ischemia, hemorrhage, gastrointestinal ulcer, or stomatitis occur.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with depressed (leukocyte count <5000/mm^3 or platelet count <100,000/mm^3) bone marrow function.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Infection: Use with caution in patients with potentially serious infections.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Alkylating agents: Use with caution in patients who have had previous use of alkylating agents.

Special populations:

- Pelvic radiation recipients: Use with caution in patients who have had high-dose pelvic radiation.
- Poor nutritional status: Use with caution in patients with poor nutritional status.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**
- Initiation of therapy: **[U.S. Boxed Warning]: Patients should be hospitalized for initiation of the first course of therapy due to the risk for severe toxic reactions.**

Pregnancy Risk FactorD
LactationExcretion in breast milk unknown/contraindicated
Adverse Reactions

>10%:

Gastrointestinal: Stomatitis, diarrhea; may be dose limiting

Hematologic: Myelosuppression, may be dose limiting; leukopenia, thrombocytopenia, anemia

Onset: 4-7 days

Nadir: 5-9 days

Recovery: 21 days

1% to 10%:

Dermatologic: Alopecia, photosensitivity, hyperpigmentation of the skin, localized erythema, dermatitis

Gastrointestinal: Anorexia

Hepatic: Biliary sclerosis, cholecystitis, jaundice

<1%: Nausea, vomiting, intrahepatic abscess

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Phenytoin: Floxuridine may increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to GI irritation).

Nursing: Physical Assessment/MonitoringUse caution with impaired liver or kidney function. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking. See Administration for infusion specifics. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, CNS changes, acute gastrointestinal reactions [intractable vomiting or diarrhea may be dose limiting]) on a regular basis throughout therapy. Teach patient (caregiver) use and care of implantable pump, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC, platelet count, liver function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug can only be administered by infusion. Follow instructions of prescriber for care of implantable pump. Avoid alcohol. It is important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition (small, frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); loss of hair (reversible); diarrhea (buttermilk, boiled milk, or yogurt may help reduce diarrhea); mouth sores (use a soft toothbrush or cotton swabs for oral care); or sterility. Increased emotional or physical stress will adversely affect the response to this medication. Notify prescriber if you are experiencing unusual or elevated levels of stress. Report extreme fatigue; pain or numbness in extremities; severe GI upset or diarrhea; bleeding or bruising; fever, chills, or sore throat; vaginal discharge; or signs of fluid retention (eg, swelling extremities, respiratory difficulty, unusual weight gain). **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication and for 1 month following therapy. Consult prescriber for appropriate barrier contraceptives. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 500 mg

Generic AvailableYes

Mechanism of ActionMechanism of action and pharmacokinetics are very similar to fluorouracil; floxuridine is the deoxyribonucleotide of fluorouracil. Floxuridine is a fluorinated pyrimidine antagonist which inhibits DNA and RNA synthesis and methylation of deoxyuridylic acid to thymidylic acid.

Pharmacodynamics/Kinetics

Metabolism: Hepatic; Active metabolites: Floxuridine monophosphate (FUDR-MP) and fluorouracil; Inactive metabolites: Urea, CO_2, α-fluoro-β-alanine, α-fluoro-β-guanidopropionic acid, α-fluoro-β-ureidopropionic acid, and dihydrofluorouracil

Excretion: Urine: Fluorouracil, urea, α-fluoro-β-alanine, α-fluoro-β-guanidopropionic acid, α-fluoro-β-ureidopropionic acid, and dihydrofluorouracil; exhaled gases (CO_2)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine

Index Terms5-FUDR; Fluorodeoxyuridine; FUDR; NSC-27640

References

Davidson BS, Izzo F, Chase JL, et al, “Alternating Floxuridine and 5-Fluorouracil Hepatic Arterial Chemotherapy for Colorectal Liver Metastases Minimizes Biliary Toxicity,” *Am J Surg*, 1996, 172(3):244-7. [PubMed 8862076]

DeConti RC, Kaplan SR, Papac RJ, et al, “Continuous Infusions of 5-Fluoro-2-Deoxyuridine in the Treatment of Solid Tumors,” *Cancer*, 1973, 31(4):894-8. [PubMed 4267531]

de Takats PG, Kerr DJ, Poole CJ, et al, “Hepatic Arterial Chemotherapy for Metastatic Colorectal Carcinoma,” *Br J Cancer*, 1994, 69(2):372-8. [PubMed 8297738]

Floyd J, Mirza I, Sachs B, et al, "Hepatotoxicity of Chemotherapy," *Semin Oncol*, 2006, 33(1):50-67.[PubMed 16473644]

Hrushesky WJ, von Roemeling R, Lanning RM, et al, “Circadian-Shaped Infusions of Floxuridine for Progressive Metastatic Renal Cell Carcinoma,” *J Clin Oncol*, 1990, 8(9):1504-13. [PubMed 2144018]

Kemeny N, Seiter K, Conti JA, et al, Hepatic Arterial Floxuridine and Leucovorin for Unresectable Liver Metastases From Colorectal Carcinoma. New Dose Schedules and Survival Update,” *Cancer*, 1994, 73(4):1134-42.

International Brand NamesFUDR (CA)

Fluconazole

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Fluconazole may be confused with flecainide

Diflucan® may be confused with diclofenac, Diprivan®, disulfiram

International issues:

Canesten® [Great Britain]: Brand name for clotrimazole in multiple international markets

Pronunciation(floo KOE na zole)

U.S. Brand NamesDiflucan®

Canadian Brand NamesApo-Fluconazole®; Co-Fluconazole; Diflucan®; Dom-Fluconazole; Fluconazole Injection; Fluconazole Omega; Gen-Fluconazole; GMD-Fluconazole; Novo-Fluconazole; PHL-Fluconazole; PMS-Fluconazole; Pro-Fluconazole; Riva-Fluconazole; Taro-Fluconazole; Zym-Fluconazole

Pharmacologic CategoryAntifungal Agent, Oral; Antifungal Agent, Parenteral

Use: Labeled IndicationsTreatment of candidiasis (vaginal, oropharyngeal, esophageal, urinary tract infections, peritonitis, pneumonia, and systemic infections); cryptococcal meningitis; antifungal prophylaxis in allogeneic bone marrow transplant recipients

Use: DentalTreatment of susceptible fungal infections in the oral cavity including candidiasis, oral thrush, and chronic mucocutaneous candidiasis treatment of esophageal and oropharyngeal candidiasis caused by *Candida* species; treatment of severe, chronic mucocutaneous candidiasis caused by *Candida* species

Dosing: AdultsThe daily dose of fluconazole is the same for both oral and I.V. administration

Usual dosage range: 200-800 mg daily; duration and dosage depends on severity of infection

Indication-specific dosing:

Candidiasis:

Candidemia (neutropenic and non-neutropenic): 400-800 mg/day for 14 days after last positive blood culture and resolution of signs/symptoms

Chronic, disseminated: 400-800 mg/day for 3-6 months

Oropharyngeal (long-term suppression): 200 mg/day; chronic therapy is recommended in immunocompromised patients with history of oropharyngeal candidiasis (OPC)

Osteomyelitis: 400-800 mg/day for 6-12 months

Esophageal: 200 mg on day 1, then 100-200 mg/day for 2-3 weeks after clinical improvement

Prophylaxis in bone marrow transplant: 400 mg/day; begin 3 days before onset of neutropenia and continue for 7 days after neutrophils >1000 cells/mm^3

Urinary: 200 mg/day for 1-2 weeks

Vaginal: 150 mg as a single dose

Coccidiomycosis (unlabeled use, IDSA guideline): 400 mg/day; doses of 800-1000 mg/day have been used for meningeal disease; usual duration of therapy ranges from 3-6 months for primary uncomplicated infections and up to 1 year for pulmonary (chronic and diffuse) infection

Endocarditis, prosthetic valve, early (unlabeled use, IDSA guideline): 400-800 mg/day for 6 weeks after valve replacement; long-term suppression in absence of valve replacement: 200-400 mg/day

Endophthalmitis: 400-800 mg/day for 6-12 weeks after surgical intervention.

Meningitis, cryptococcal: Amphotericin 0.7-1 mg/kg +/- 5-FC for 2 weeks then fluconazole 400 mg/day for at least 10 weeks (consider life-long in HIV-positive); maintenance (HIV-positive): 200-400 mg/day life-long

Pneumonia, cryptococcal (mild-to-moderate) (unlabeled use, IDSA guideline): 200-400 mg/day for 6-12 months (consider life-long in HIV-positive patients)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricThe daily dose of fluconazole is the same for oral and I.V. administration

Usual dosage ranges:

Neonates: First 2 weeks of life, especially premature neonates: Same dose as older children every 72 hours

Children: Loading dose: 6-12 mg/kg; maintenance: 3-12 mg/kg/day; duration and dosage depends on severity of infection

Indication-specific dosing:

Candidiasis:

Oropharyngeal: Loading dose: 6 mg/kg; maintenance: 3 mg/kg/day for 2 weeks

Esophageal: Loading dose: 6 mg/kg; maintenance: 3-12 mg/kg/day for 21 days and at least 2 weeks following resolution of symptoms

Systemic infection: 6 mg/kg every 12 hours for 28 days

Meningitis, cryptococcal: Loading dose: 12 mg/kg; maintenance: 6-12 mg/kg/day for 10-12 weeks following negative CSF culture; relapse suppression (HIV-positive): 6 mg/kg/day

Dosing: Renal Impairment

No adjustment for vaginal candidiasis single-dose therapy

For multiple dosing, administer usual load then adjust daily doses as follows:

Cl_{cr} ≤50 mL/minute (no dialysis): Administer 50% of recommended dose or administer every 48 hours.

Hemodialysis: 50% is removed by hemodialysis; administer 100% of daily dose (according to indication) after each dialysis treatment.

Continuous renal replacement therapy (CRRT): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH: 200-400 mg every 24 hours

CVVHD/CVVHDF: 400-800 mg every 24 hours

Note: Higher daily doses of 400 mg (CVVH) and 800 mg (CVVHD/CVVHDF) should be considered when treating resistant organisms and/or when employing combined ultrafiltration and dialysis flow rates of ≥2 L/hour for CVVHD/CVVHDF (Trotman, 2005).

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.For I.V. only; do not administer I.M. or SubQ

Administration: I.V.Infuse over approximately 1-2 hours.

Administration: I.V. DetailDo not use if cloudy or precipitated. Do not exceed 200 mg/hour when administering by I.V. infusion.

pH: 4-8 (sodium chloride diluent); 3.5-6.5 (dextrose)

Administration: OralMay be administered with or without food.

Dietary ConsiderationsTake with or without regard to food.

Storage

Powder for oral suspension: Store dry powder at ≤30°C (86°F). Following reconstitution, store at 5°C to 30°C (41°F to 86°F). Discard unused portion after 2 weeks. Do not freeze.

Injection: Store injection in glass at 5°C to 30°C (41°F to 86°F). Store injection in Viaflex® at 5°C to 25°C (41°F to 77°F). Do not freeze. Do not unwrap unit until ready for use.

CompatibilityStable in D_5W, LR, NS.

Y-site administration: Compatible: Acyclovir, aldesleukin, allopurinol, amifostine, amikacin, aminophylline, ampicillin/sulbactam, aztreonam, benztropine, cefazolin, cefepime, cefotetan, cefoxitin, cefpirome, chlorpromazine, cimetidine, cisatracurium, dexamethasone sodium phosphate, diltiazem, diphenhydramine, dobutamine, docetaxel, dopamine, doxorubicin liposome, droperidol, etoposide phosphate, famotidine, filgrastim, fludarabine, foscarnet, ganciclovir, gatifloxacin, gemcitabine, gentamicin, granisetron, heparin, hydrocortisone sodium phosphate, immune globulin intravenous, leucovorin, linezolid, lorazepam, melphalan, meperidine, meropenem, metoclopramide, metronidazole, midazolam, morphine, nafcillin, nitroglycerin, ondansetron, oxacillin, paclitaxel, pancuronium, penicillin G potassium, phenytoin, piperacillin/tazobactam, prochlorperazine edisylate, promethazine, propofol, ranitidine, remifentanil, sargramostim, tacrolimus, teniposide, theophylline, thiotepa, ticarcillin/clavulanate, tobramycin, vancomycin, vecuronium, vinorelbine, zidovudine. **Incompatible:** Amphotericin B, amphotericin B cholesteryl sulfate complex, ampicillin, calcium gluconate, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, chloramphenicol, clindamycin, co-trimoxazole, diazepam, digoxin, erythromycin lactobionate, furosemide, haloperidol, hydroxyzine, imipenem/cilastatin, pentamidine, piperacillin, ticarcillin.

Compatibility when admixed: Compatible: Acyclovir, amikacin, amphotericin B, cefazolin, ceftazidime, clindamycin, gentamicin, heparin, meropenem, metronidazole, morphine, piperacillin, potassium chloride, ranitidine with ondansetron, theophylline. **Incompatible:** Co-trimoxazole.

ContraindicationsHypersensitivity to fluconazole, other azoles, or any component of the formulation; concomitant administration with cisapride

Allergy Considerations

- Azole Antifungal Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Skin reactions: Rare exfoliative skin disorders have been observed; monitor closely if rash develops.

Disease-related concerns:

- Arrhythmias: The manufacturer reports rare cases of QT_c prolongation and TdP associated with fluconazole use and advises caution in patients with concomitant medications or conditions which are arrhythmogenic. However, given the limited number of cases and the presence of multiple confounding variables, the likelihood that fluconazole causes conduction abnormalities appears remote.

- Hepatic impairment: Serious (and rarely fatal) hepatic toxicity (eg, hepatitis, cholestasis, fulminant failure) has been observed with azole therapy. Use with caution in patients with pre-existing hepatic impairment; monitor liver function closely and dosage adjustment may be warranted; discontinue if symptoms consistent with liver disease develop.

- Renal impairment: Use with caution in patients with renal impairment.

Geriatric ConsiderationsHas not been specifically studied in the elderly.

Pregnancy Risk FactorC

Pregnancy ConsiderationsWhen used in high doses, fluconazole is teratogenic in animal studies. Following exposure during the first trimester, case reports have noted similar malformations in humans when used in higher doses (400 mg/day) over extended periods of time. Use of lower doses (150 mg as a single dose or 200 mg/day) may have less risk; however, additional data is needed. Use during pregnancy only if the potential benefit to the mother outweighs any potential risk to the fetus.

LactationEnters breast/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsFluconazole is found in breast milk at concentration similar to plasma.

Adverse ReactionsFrequency not always defined.

Cardiovascular: Angioedema, pallor, QT prolongation (rare, case reports), torsade de pointes (rare, case reports)

Central nervous system: Headache (2% to 13%), seizure, dizziness

Dermatologic: Rash (2%), alopecia, toxic epidermal necrolysis, Stevens-Johnson syndrome

Endocrine & metabolic: Hypercholesterolemia, hypertriglyceridemia, hypokalemia

Gastrointestinal: Nausea (4% to 7%), vomiting (2%), abdominal pain (2% to 6%), diarrhea (2% to 3%), taste perversion, dyspepsia

Hematologic: Agranulocytosis, leukopenia, neutropenia, thrombocytopenia

Hepatic: Alkaline phosphatase increased, ALT increased, AST increased, cholestasis, hepatic failure (rare), hepatitis, jaundice

Respiratory: Dyspnea

Miscellaneous: Anaphylactic reactions (rare)

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Metabolism/Transport Effects**Inhibits** CYP1A2 (weak), 2C9 (strong), 2C19 (strong), 3A4 (moderate)

Drug Interactions

Alfentanil: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfentanil: Fluconazole may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Aprepitant: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Aprepitant. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Quazepam. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Fluconazole may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Bosentan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Bosentan. *Risk C: Monitor therapy*

BusPIRone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Busulfan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Busulfan. *Risk C: Monitor therapy*

Calcium Channel Blockers: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Fluconazole may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk C: Monitor therapy*

CarBAMazepine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CarBAMazepine. *Risk C: Monitor therapy*

CarBAMazepine: Fluconazole may decrease the metabolism of CarBAMazepine. *Risk C: Monitor therapy*

Cardiac Glycosides: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Cilostazol: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Cinacalcet: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Cinacalcet. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Cisapride: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Cisapride. *Risk X: Avoid combination*

Conivaptan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Conivaptan. *Risk X: Avoid combination*

Corticosteroids (Orally Inhaled): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticosteroids (Systemic): Fluconazole may decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CycloSPORINE: Fluconazole may decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Didanosine: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). Enteric coated didanosine capsules are not expected to affect these antifungals. *Risk D: Consider therapy modification*

Docetaxel: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Docetaxel. *Risk D: Consider therapy modification*

Dofetilide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Dofetilide. *Risk X: Avoid combination*

Eletriptan: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Eletriptan. *Risk D: Consider therapy modification*

Eletriptan: Fluconazole may decrease the metabolism of Eletriptan. *Risk C: Monitor therapy*

Eplerenone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eplerenone. *Risk D: Consider therapy modification*

Eplerenone: Fluconazole may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Erlotinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Erlotinib. *Risk C: Monitor therapy*

Eszopiclone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eszopiclone. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fosaprepitant: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Fosaprepitant. Specifically, concentrations of aprepitant are likely to be increased. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Gefitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Gefitinib. *Risk C: Monitor therapy*

Grapefruit Juice: May increase the metabolism of Antifungal Agents (Azole Derivatives, Systemic). This specifically applies to oral antifungal administration. *Risk D: Consider therapy modification*

H2-Antagonists: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Rosuvastatin. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: Fluconazole may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Pravastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Imatinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Imatinib. *Risk C: Monitor therapy*

Irbesartan: Fluconazole may decrease the metabolism of Irbesartan. *Risk C: Monitor therapy*

Irinotecan: Antifungal Agents (Azole Derivatives, Systemic) may enhance the adverse/toxic effect of Irinotecan. *Risk D: Consider therapy modification*

Losartan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Losartan. *Risk C: Monitor therapy*

Losartan: Fluconazole may decrease the metabolism of Losartan. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Antifungal Agents (Azole Derivatives, Systemic). Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Macrolide Antibiotics. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Methadone. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Phenytoin: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Phenytoin. Phenytoin may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Phenytoin: Fluconazole may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Phosphodiesterase 5 Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Protease Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of QuiNIDine. Management: Itraconazole, voriconazole, and posaconazole are specifically contraindicated with quinidine. Use of quinidine with any azole antifungal may require quinidine dose adjustment and should be done with caution and close monitoring. *Risk X: Avoid combination*

QuiNIDine: Fluconazole may decrease the metabolism of QuiNIDine. *Risk C: Monitor therapy*

Ramelteon: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ramelteon: Fluconazole may decrease the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ranolazine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Repaglinide. Management: Concurrent use of an azole antifungal with both repaglinide and gemfibrozil should be avoided. *Risk C: Monitor therapy*

Rifamycin Derivatives: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Rifamycin Derivatives. Only rifabutin appears to be affected. Rifamycin Derivatives may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Rifamycin Derivatives: Fluconazole may decrease the metabolism of Rifamycin Derivatives. This appears only affect rifabutin. Rifamycin Derivatives may increase the metabolism of Fluconazole. *Risk C: Monitor therapy*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Sirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Sirolimus. Management: Sirolimus dose reductions of up to 50-90% may be necessary when starting an azole antifungal. Use of sirolimus with the azole antifungals voriconazole and posaconazole is contraindicated. *Risk D: Consider therapy modification*

Solifenacin: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Solifenacin. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk C: Monitor therapy*

Sulfonylureas: Fluconazole may increase the serum concentration of Sulfonylureas. *Risk C: Monitor therapy*

Sunitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Tacrolimus: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Tacrolimus: Fluconazole may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Temsirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Temsirolimus. Concentrations of the active metabolite, sirolimus, are likely to be increased more substantially than those of the parent temsirolimus. *Risk D: Consider therapy*

modification

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Tolterodine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Tolterodine. This is likely only of concern in CYP2D6-deficient patients (ie, "poor metabolizers") *Risk D: Consider therapy modification*

Tolterodine: Fluconazole may decrease the metabolism of Tolterodine. This is likely only of concern in CYP2D6-deficient patients (ie, "poor metabolizers") *Risk C: Monitor therapy*

VinCRIStine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of VinCRIStine. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Fluconazole may decrease the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Zidovudine: Fluconazole may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Ziprasidone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ziprasidone. *Risk C: Monitor therapy*

Zolpidem: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Zolpidem. *Risk D: Consider therapy modification*

Monitoring ParametersPeriodic liver function tests (AST, ALT, alkaline phosphatase) and renal function tests, potassium

Nursing: Physical Assessment/MonitoringAssess results of cultures/sensitivity and patient's allergy history prior to beginning therapy. Assess potential for interactions with other pharmacological agents patient may be taking (eg, potential for toxicities). See Administration specifics for I.V. use. Assess results of laboratory tests (renal and hepatic function), therapeutic effectiveness (resolution of fungal infection), and adverse response (eg, hepatotoxicity [jaundice], skin disorders, abdominal pain) on a regular basis throughout therapy. Teach patient use (full course of therapy may require weeks or months after symptoms resolve), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCulture prior to beginning therapy, periodic liver function (AST, ALT, alkaline phosphatase) and renal function, potassium

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, around-the-clock. Take full course of medication as ordered. Take with or without food. Follow good hygiene measures to prevent reinfection. Frequent blood tests may be required. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause headache, dizziness, drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known); or nausea, vomiting, or diarrhea (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report skin rash, redness, or irritation; persistent GI upset; urinary pattern changes; excessively dry eyes or mouth; or changes in color of stool or urine. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed in sodium chloride or dextrose]: 200 mg (100 mL); 400 mg (200 mL)

Diflucan® [premixed in sodium chloride or dextrose]: 200 mg (100 mL); 400 mg (200 mL)

Powder for oral suspension: 10 mg/mL (35 mL); 40 mg/mL (35 mL)

Diflucan®: 10 mg/mL (35 mL); 40 mg/mL (35 mL) [contains sodium benzoate; orange flavor]

Tablet: 50 mg, 100 mg, 150 mg, 200 mg

Diflucan®: 50 mg, 100 mg, 150 mg, 200 mg

Generic AvailableYes

ManufacturerPfizer U.S. Pharmaceuticals Group

Pricing: U.S. (www.drugstore.com)

Suspension (reconstituted) (Diflucan)

10 mg/mL (35): $45.53

40 mg/mL (35): $157.16

Suspension (reconstituted) (Fluconazole)

10 mg/mL (35): $25.99

40 mg/mL (35): $109.98

Tablets (Diflucan)

50 mg (15): $109.99

100 mg (15): $171.86

150 mg (1): $25.99

200 mg (4): $76.37

Tablets (Fluconazole)

100 mg (15): $54.99

150 mg (12): $167.19

200 mg (4): $39.77

Mechanism of ActionInterferes with fungal cytochrome P450 activity (lanosterol 14-α-demethylase), decreasing ergosterol synthesis (principal sterol in fungal cell membrane) and inhibiting cell membrane formation

Pharmacodynamics/Kinetics

Distribution: Widely throughout body with good penetration into CSF, eye, peritoneal fluid, sputum, skin, and urine

Relative diffusion blood into CSF: Adequate with or without inflammation (exceeds usual MICs)

CSF:blood level ratio: Normal meninges: 70% to 80%; Inflamed meninges: >70% to 80%

Protein binding, plasma: 11% to 12%

Bioavailability: Oral: >90%

Half-life elimination: Normal renal function: ~30 hours

Time to peak, serum: Oral: 1-2 hours

Excretion: Urine (80% as unchanged drug)

Related Information

- Antifungal Agents
- Treatment of Sexually-Transmitted Infections
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Abnormal taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness and seizures

Mental Health: Effects on Psychiatric TreatmentNone reported; CYP3A4 inhibitor; use caution with triazolam, alprazolam, and midazolam

Cardiovascular ConsiderationsFluconazole is contraindicated in patients taking cisapride due to increased risk for significant cardiotoxicity, particularly proarrhythmia.

Anesthesia and Critical Care Concerns/Other ConsiderationsDo not use if cloudy or precipitated. If administered by I.V. infusion, give over 1-2 hours.

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International Brand NamesAfungil (MX); Biozole (MY); Cancid (ID); Candizol (ID); Candizole (BE); Canesoral (AU); Diflu (KP); Diflucan (AE, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SR, SV, SY, TH, TN, TR, TT, TW, TZ, UG, YE, ZA, ZM, ZW); DiflucanOne (AU); Difnazol (KP); Dimycon (HR); Dizole One (AU); EFAC (CR, DO, GT, HN, NI, PA, SV); Flocan (KP); Flozole (KP); Flucand (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Flucanol (IL); Flucazol (AE, BH, BR, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Flucess (ID); Flucona (KP); Fluconazol (PL); Fluconazole (PL); Flucoral (ID, PH); Flucoric (HK, MY); Flucoxan (MX); Flucozal (BR, HK, PK); Fludicon (HK); Fludizol (TH); Flumax (KP); Flumycon (PL); Flunco (TH); Flunizol (PE); Fluzole (AU); Fluzone (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Forcan (IN); Fukole (MY); Fulkor (PH); Fumay (TW); Funazol (KP); Funex (CO); Fungata (AT, DE); Funzela (PH); Govazol (ID); Kyrin (TH); Lucon (HK); Medoflucon (CL, SG); Mutum (AR, PE, VE); Mycocyst (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Mycomax (PL); Mycorest (SG); Mycosyst (HU, PL); Neoconal (KP); Nobzol-1 (CO); Nobzol-2 (CO); Omastin (SG); Oneflu (KP); Oxifungol (MX); Oxole (AU); Plunazol (KP); Sixanol (PY, UY); Stalene (HK, SG, TH); Syscan (IN); Tavor (CO, EC); Tinazole (KP); Treflucan (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Triflucan (FR, IL, TR); Uzol (TW); Zelstan (MY); Zoldicam (MX); Zucon (PL)

Flucytosine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Flucytosine may be confused with fluorouracil

Ancobon® may be confused with Oncovin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(floo SYE toe seen)

U.S. Brand NamesAncobon®

Canadian Brand NamesAncobon®

Pharmacologic CategoryAntifungal Agent, Oral

Use: Labeled IndicationsAdjunctive treatment of systemic fungal infections (eg, septicemia, endocarditis, UTI, meningitis, or pulmonary) caused by susceptible strains of *Candida* or *Cryptococcus*

Dosing: Adults

Endocarditis: Oral: 25-37.5 mg/kg every 6 hours (with amphotericin B) for at least 6 weeks after valve replacement

Meningoencephalitis, cryptococcal: Induction: Oral: 25 mg/kg/dose (with amphotericin B) every 6 hours for 2 weeks; if clinical improvement, may discontinue both amphotericin and flucytosine and follow with an extended course of fluconazole (400 mg/day); alternatively, may continue flucytosine for 6-10 weeks (with amphotericin B) without conversion to fluconazole treatment

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricUnlabeled use. Refer to adult dosing.

Dosing: Renal ImpairmentUse lower initial dose:

Cl_{cr} 20-40 mL/minute: Administer 37.5 mg/kg every 12 hours

Cl_{cr} 10-20 mL/minute: Administer 37.5 mg/kg every 24 hours

Cl_{cr} <10 mL/minute: Administer 37.5 mg/kg every 24-48 hours, but monitor drug concentrations frequently

Hemodialysis: Dialyzable (50% to 100%); administer dose posthemodialysis

Peritoneal dialysis: Adults: Administer 0.5-1 g every 24 hours

Continuous arteriovenous or venovenous hemodiafiltration effects: Change dosing frequency to every 12-24 hours (monitor serum concentrations and adjust)

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels. To avoid nausea and vomiting, administer a few capsules at a time over 15 minutes until full dose is taken.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

Extemporaneously PreparedFlucytosine oral liquid has been prepared by using the contents of ten 500 mg capsules triturated in a mortar and pestle with a small amount of distilled water; the mixture was transferred to a 500 mL volumetric flask; the mortar was rinsed several times with a small amount of distilled water and the fluid added to the flask; sufficient distilled water was added to make a total volume of 500 mL of a 10 mg/mL liquid; oral liquid was stable for 70 days when stored in glass or plastic prescription bottles at 4°C or for up to 14 days at room temperature.

Wintermeyer SM and Nahata MC, “Stability of Flucytosine in an Extemporaneously Compounded Oral Liquid,” *Am J Health Syst Pharm*, 1996, 53:407-9.

ContraindicationsHypersensitivity to flucytosine or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Monitoring: See “Other warnings/precautions” below.

- Renal impairment: See “Disease-related concerns” below.

Disease-related concerns:

- Hematologic disease: Use with caution in patients with bone marrow depression, hematologic disease or who have been treated with radiation or drugs that suppress the bone marrow; bone marrow toxicity can be irreversible.

- Hepatic impairment: Use with caution in patients with hepatic impairment; hepatotoxicity may occur.

- Renal impairment: **[U.S. Boxed Warning]: Use with extreme caution in patients with renal dysfunction;** dosage adjustment required.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Monitoring: **[U.S. Boxed Warning]: Closely monitor hematologic, renal, and hepatic status.** Hepatotoxicity and bone marrow toxicity appear to be dose related; monitor levels closely and adjust dose accordingly.

- Monotherapy: Avoid use as monotherapy; resistance rapidly develops.

Geriatric ConsiderationsAdjust for renal function.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic in some animal studies, however, there are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiac arrest, myocardial toxicity, ventricular dysfunction, chest pain

Central nervous system: Ataxia, confusion, dizziness, drowsiness, fatigue, hallucinations, headache, parkinsonism, psychosis, pyrexia, sedation, seizure, vertigo

Dermatologic: Rash, photosensitivity, pruritus, toxic epidermal necrolysis, urticaria

Endocrine & metabolic: Hypoglycemia, hypokalemia

Gastrointestinal: Abdominal pain, diarrhea, dry mouth, duodenal ulcer, hemorrhage, loss of appetite, nausea, ulcerative colitis, vomiting

Hematologic: Agranulocytosis, anemia, aplastic anemia, eosinophilia, leukopenia, pancytopenia, thrombocytopenia

Hepatic: Acute hepatic injury, bilirubin increased, hepatic dysfunction, jaundice, liver enzymes increased

Neuromuscular & skeletal: Paresthesia, peripheral neuropathy, weakness

Otic: Hearing loss

Renal: Azotemia, BUN increased, crystalluria, renal failure, serum creatinine increased

Respiratory: Dyspnea, respiratory arrest

Miscellaneous: Allergic reaction

Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

Cytarabine: May diminish the therapeutic effect of Flucytosine. *Risk D: Consider therapy modification*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Food decreases the rate, but not the extent of absorption.
Test InteractionsFlucytosine causes markedly false elevations in serum creatinine values when the Ektachem® analyzer is used. The Jaffé reaction is recommended for determining serum creatinine.
Monitoring Parameters

Pretreatment: Electrolytes (especially potassium), CBC with differential, BUN, renal function, blood culture

During treatment: CBC with differential, and LFTs (eg, alkaline phosphatase, AST/ALT) frequently, serum flucytosine concentration, renal function

Reference Range

Therapeutic: Trough: 25–50 mcg/mL; peak: 50–100 mcg/mL; peak levels should not exceed 100 mcg/mL to avoid toxic bone marrow depressive and hepatic effects

Trough: Draw just prior to dose administration

Peak: Draw 2 hours after an oral dose administration

Nursing: Physical Assessment/MonitoringSee Warnings/Precautions for use cautions (eg, renal dysfunction, bone marrow depression, hematologic disease). Assess potential for interactions with other pharmacological agents patient may be taking (see Drug Interactions). Assess results of laboratory tests prior to and during treatment. Hematologic, renal, and hepatic status must be closely monitored; dose adjustments may be necessary. Assess therapeutic effectiveness (resolution of fungal infection) and adverse response (eg, cardiac incidents, CNS changes, bone marrow suppression, jaundice, skin reactions, hearing loss) on a regular basis throughout therapy. Teach patient use (full course of therapy may require some time after symptoms resolve), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab Tests

Pretreatment: Electrolytes (especially potassium), CBC with differential, BUN, renal function, blood culture

During treatment: CBC with differential, and LFTs (eg, alkaline phosphatase, AST/ALT) frequently, serum flucytosine concentration, renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take capsules one at a time over a few minutes with food to reduce GI upset. Take full course of medication as ordered. Do not discontinue without consulting prescriber. Practice good hygiene measures to prevent reinfection. Frequent blood tests may be required. May cause nausea and vomiting (small, frequent meals may help). Report rash; respiratory difficulty; CNS changes (eg, confusion, hallucinations, ataxia, acute headache); yellowing of skin or eyes; changes in color or frequency of stool or urine; unresolved diarrhea or anorexia; or unusual bleeding, fatigue, or weakness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 250 mg, 500 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Ancobon)

250 mg (100): $1018.66

500 mg (30): $668.84

Mechanism of ActionPenetrates fungal cells and is converted to fluorouracil which competes with uracil interfering with fungal RNA and protein synthesis

Pharmacodynamics/Kinetics

Absorption: 76% to 89%

Distribution: Into CSF, aqueous humor, joints, peritoneal fluid, and bronchial secretions; V_d: 0.6 L/kg

Protein binding: 3% to 4%

Metabolism: Minimally hepatic; deaminated, possibly via gut bacteria, to 5-fluorouracil

Half-life elimination:

Normal renal function: 2-5 hours

Anuria: 85 hours (range: 30-250)

End stage renal disease: 75-200 hours

Time to peak, serum: ~1-2 hours

Excretion: Urine (>90% as unchanged drug)

Related Information

- Antifungal Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause drowsiness, confusion, or hallucinations

Mental Health: Effects on Psychiatric TreatmentMay cause bone marrow suppression; use caution with clozapine and carbamazepine

Index Terms5-FC; 5-Fluorocytosine; 5-Flurocytosine

References

Aronoff GR, Berns JS, Brier ME, et al, “Drug Prescribing in Renal Failure: Dosing Guidelines for Adults,” 4th ed. Philadelphia, PA: American College of Physicians; 1999.

Lau AH and Kronfol NO, “Elimination of Flucytosine by Continuous Hemofiltration,” *Am J Nephrol*, 1995, 15(4):327-31. [PubMed 7573192]

Lyman CA and Walsh TJ, “Systemically Administered Antifungal Agents. A Review of Their Clinical Pharmacology and Therapeutic Applications,” *Drugs*, 1992, 44(1):9-35. [PubMed 1379913]

Mofenson LM, Oleske J, Serchuck L, et al, “Treating Opportunistic Infections Among HIV-Exposed and Infected Children: Recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America,” *MMWR Recomm Rep*, 2004, 53(RR-14):1-92. Available at http://www.cdc.gov/MMWR/preview/MMWRhtml/rr5314a1.htm

Patel R, “Antifungal Agents. Part I. Amphotericin B Preparations and Flucytosine,” *Mayo Clin Proc*, 1998, 73(12):1205-25. [PubMed 9868423]

Saag MS, Graybill RJ, Larsen RA, et al, “Practice Guidelines for the Management of Cryptococcal Disease. Infectious Diseases Society of America,” *Clin Infect Dis*, 2000, 30(4):710-8.[PubMed 10770733]

Vermes A, Guchelaar H, and Dankert J, “Flucytosine: A Review of its Pharmacology, Clinical Indications, Pharmacokinetics, Toxicity and Drug Interactions,” *J Antimicrob Chemother*, 2000, 46(2):171-9.[PubMed 10933638]

International Brand NamesAlcobon (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, NZ, OM, QA, SA, SY, YE); Ancotil (AE, AT, AU, BG, BH, BR, CH, CY, CZ, DE, DK, EG, FR, GB, HK, HR, IE, IL, IQ, IR, IT, JO, KW, LB, LY, NL, NO, OM, PL, QA, SA, SE, SY, YE); Cocol (JP)

Fludarabine-Cyclophosphamide (FC)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Chronic Lymphocytic

Regimen UseLeukemia, chronic lymphocytic

Index TermsCyclophosphamide-Fludarabine; FC

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Fludarabine: I.V.: 25 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Cyclophosphamide: I.V.: 250 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 750 mg/m^2]

Repeat cycle every 4 weeks for up to 6 cycles

Variation 2:

Fludarabine: I.V.: 30 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 90 mg/m^2]

Cyclophosphamide: I.V.: 250 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 750 mg/m^2]

Repeat cycle every 4 weeks for up to 6 cycles

Variation 3:

Cyclophosphamide: I.V.: 600 mg/m^2 day 1 only

[total dose/cycle = 600 mg/m^2]

Fludarabine: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 4 weeks for up to 6 cycles

Variation 4:

Fludarabine: I.V.: 30 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 90 mg/m^2]

Cyclophosphamide: I.V.: 300 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 900 mg/m^2]

Repeat cycle every 4 weeks for up to 6 cycles

Variation 5:

Fludarabine: I.V.: 30 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 90 mg/m^2]

Cyclophosphamide: I.V.: 300 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 900 mg/m^2]

Repeat cycle every 4-6 weeks for up to 6 cycles

References

Variation 1:

Catovsky D, Richards S, Matutes E, et al, "Assessment of Fludarabine Plus Cyclophosphamide for Patients With Chronic Lymphocytic Leukaemia (The LRF CLL4 Trial): A Randomised Controlled Trial," *Lancet*, 2007, 370(9583):230-9.[PubMed 17658394]

O'Brien S, Moore JO, Boyd TE, et al, "Randomized Phase III Trial of Fludarabine Plus Cyclophosphamide With or Without Oblimersen Sodium (Bcl-2 Antisense) in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia," *J Clin Oncol*, 2007, 25(9):1114-20.[PubMed 17296974]

Variation 2:

Eichhorst BF, Busch R, Obwandner T, et al, "Health-Related Quality of Life in Younger Patients With Chronic Lymphocytic Leukemia Treated With Fludarabine Plus Cyclophosphamide or Fludarabine Alone for First-Line Therapy: A Study by the German CLL Study Group," *J Clin Oncol*, 2007, 25(13):1722-31.[PubMed 17389338]

Variation 3:

Flinn IW, Neuberg DS, Grever MR, et al, "Phase III Trial of Fludarabine Plus Cyclophosphamide Compared With Fludarabine for Patients With Previously Untreated Chronic Lymphocytic Leukemia: US Intergroup Trial E2997," *J Clin Oncol*, 2007, 25(7):793-8.[PubMed 17283364]

Variation 4:

Wierda W, O'Brien S, Faderl S, et al, "A Retrospective Comparison of Three Sequential Groups of Patients With Recurrent/Refractory Chronic Lymphocytic Leukemia Treated With Fludarabine-Based Regimens," *Cancer*, 2006, 106(2):337-45.[PubMed 16353201]

Variation 5:

O'Brien SM, Kantarjian HM, Cortes J, et al, "Results of the Fludarabine and Cyclophosphamide Combination Regimen in Chronic Lymphocytic Leukemia," *J Clin Oncol*, 2001, 19(5):1414-20.[PubMed 11230486]

Fludarabine-Cyclophosphamide (NHL-Mantle Cell)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's (Mantle cell lymphoma)

Index TermsCF (NHL-Mantle Cell); Cyclophosphamide-Fludarabine (NHL-Mantle Cell); FC (NHL-Mantle Cell)

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Fludarabine: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Cyclophosphamide: I.V.: 800 mg/m^2/dose day 1

[total dose/cycle = 800 mg/m^2]

Repeat cycle every 3-4 weeks for up to a total of 5 cycles

Variation 2:

Fludarabine: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Cyclophosphamide: I.V.: 1000 mg/m^2/dose day 1

[total dose/cycle = 1000 mg/m^2]

Repeat cycle every 3-4 weeks for up to a total of 5 cycles

Variation 3:

Fludarabine: I.V.: 25 mg/m^2/day days 1 to 4

[total dose/cycle = 100 mg/m^2]

Cyclophosphamide: I.V.: 1000 mg/m^2/dose day 1

[total dose/cycle = 1000 mg/m^2]

Repeat cycle every 3-4 weeks for up to a total of 5 cycles

References

Variations 1-3:

Cohen BJ, Moskowitz C, Straus D, et al, "Cyclophosphamide/Fludarabine (CF) is Active in the Treatment of Mantle Cell Lymphoma," *Leuk Lymphoma*, 2001, 42(5):1015-22.[PubMed 11697618]

Fludarabine-Cyclophosphamide-Mitoxantrone-Rituximab

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Lymphoma, non-Hodgkin's]

Regimen UseLymphoma, non-Hodgkin's

Index TermsFCMR (NHL); R-FCM (NHL); Rituximab-Fludarabine-Cyclophosphamide-Mitoxantrone

RegimenNOTE: Multiple variations are listed below.

Consider pretherapy cytoreduction with cyclophosphamide 200 mg/m^2/day for 3-5 days for patients with high tumor burden and/or lymphocytes >20,000/mm^3

Variation 1:

Rituximab: I.V.: 375 mg/m^2/dose day 1

[total dose/cycle = 375 mg/m^2]

Fludarabine: I.V.: 25 mg/m^2/day days 2, 3, and 4

[total dose/cycle = 75 mg/m^2]

Cyclophosphamide: I.V.: 200 mg/m^2/day days 2, 3, and 4

[total dose/cycle = 600 mg/m^2]

Mitoxantrone: I.V.: 8 mg/m^2/dose day 2

[total dose/cycle = 8 mg/m^2]

Repeat cycle every 28 days for total of 4 cycles

Variation 2 (with maintenance rituximab):

Rituximab: I.V.: 375 mg/m^2/dose day 1

[total dose/cycle = 375 mg/m^2]

Fludarabine: I.V.: 25 mg/m^2/day days 2, 3, and 4

[total dose/cycle = 75 mg/m^2]

Cyclophosphamide: I.V.: 200 mg/m^2/day days 2, 3, and 4

[total dose/cycle = 600 mg/m^2]

Mitoxantrone: I.V.: 8 mg/m^2/dose day 2

[total dose/cycle = 8 mg/m^2]

Repeat cycle every 28 days for total of 4 cycles

followed by:

Maintenance rituximab (begin 3 months after completion of cycle 4):

Rituximab: I.V.: 375 mg/m^2/dose day 1, 8, 15, and 22

[total dose/cycle = 1500 mg/m^2]

Repeat maintenance cycle (once) in 6 months

References

Variation 1:

Forstpointner R, Dreyling M, Repp R, et al, "The Addition of Rituximab to a Combination of Fludarabine, Cyclophosphamide, Mitoxantrone (FCM) Significantly Increases the Response Rate and Prolongs Survival as Compared With FCM Alone in Patients With Relapsed and Refractory Follicular and Mantle Cell Lymphomas: Results of a Prospective Randomized Study of the German Low-Grade Lymphoma Study Group," *Blood*, 2004, 104(10):3064-71.[PubMed 15284112]

Variation 2:

Forstpointner R, Unterhalt M, Dreyling M, et al, "Maintenance Therapy With Rituximab Leads to a Significant Prolongation of Response Duration After Salvage Therapy With a Combination of Rituximab, Fludarabine, Cyclophosphamide, and Mitoxantrone (R-FCM) in Patients With Recurring and Refractory Follicular and Mantle Cell Lymphomas: Results of a Prospective Randomized Study of the German Low Grade Lymphoma Study Group (GLSG)," *Blood*, 2006, 108(13):4003-8.[PubMed 16946304]

Fludarabine-Cyclophosphamide-Rituximab (CLL)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Chronic Lymphocytic

Regimen UseLeukemia, chronic lymphocytic

Index TermsRituximab-Fludarabine-Cyclophosphamide (CLL)

Regimen

Cycle 1:

Rituximab: I.V.: 375 mg/m^2 day 1

[total dose/cycle = 375 mg/m^2]

Fludarabine: I.V.: 25 mg/m^2/day days 2, 3, and 4

[total dose/cycle = 75 mg/m^2]

Cyclophosphamide: I.V.: 250 mg/m^2/day days 2, 3, and 4

[total dose/cycle = 750 mg/m^2]

Treatment cycle is 4 weeks

Cycles 2-6:

Rituximab: I.V.: 500 mg/m^2 day 1

[total dose/cycle = 500 mg/m^2]

Fludarabine: I.V.: 25 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Cyclophosphamide: I.V.: 250 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 750 mg/m^2]

Repeat cycle every 4 weeks

References

Keating MJ, O'Brien S, Albitar M, et al, âEarly Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab as Initial Therapy for Chronic Lymphocytic Leukemia,â *J Clin Oncol*, 2005, 23(18):4079-88.[PubMed 15767648]

Fludarabine-Cyclophosphamide-Rituximab (NHL)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen Use Lymphoma, non-Hodgkin's (Follicular lymphoma)

Index Terms Rituximab-Fludarabine-Cyclophosphamide (NHL)

Regimen

Cycle 1:

Rituximab: I.V.: 375 mg/m^2 day 15

[total dose/cycle = 375 mg/m^2]

Fludarabine: I.V.: 25 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Cyclophosphamide: I.V.: 300 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 900 mg/m^2]

Treatment cycle is 3 weeks

Cycles 2-4:

Rituximab: I.V.: 375 mg/m^2 day 1

[total dose/cycle = 375 mg/m^2]

Fludarabine: I.V.: 25 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Cyclophosphamide: I.V.: 300 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 900 mg/m^2]

Each treatment cycle is 3 weeks

References

Sacchi S, Pozzi S, Marcheselli R, et al, "Rituximab in Combination With Fludarabine and Cyclophosphamide in the Treatment of Patients With Recurrent Follicular Lymphoma," *Cancer*, 2007, 110(1):121-8.[PubMed 17503433]

Fludarabine-Mitoxantrone-Dexamethasone-Rituximab

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's
Regimen UseLymphoma, non-Hodgkin's
Index TermsFNDR (NHL); Rituximab-Fludarabine-Mitoxantrone-Dexamethasone
Regimen

Cycle 1:

Rituximab: I.V.: 375 mg/m^2/day days 1 and 8

[total dose/cycle = 750 mg/m^2]

Fludarabine: I.V.: 25 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Mitoxantrone: I.V.: 10 mg/m^2/dose day 1

[total dose/cycle = 10 mg/m^2]

Dexamethasone: I.V. or Oral: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Treatment cycle is 28 days

Cycles 2-5:

Rituximab: I.V.: 375 mg/m^2 day 1

[total dose/cycle = 375 mg/m^2]

Fludarabine: I.V.: 25 mg/m^2/day days 2, 3, and 4

[total dose/cycle = 75 mg/m^2]

Mitoxantrone: I.V.: 10 mg/m^2/dose day 2

[total dose/cycle = 10 mg/m^2]

Dexamethasone: I.V. or Oral: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 28 days

Cycles 6-8:

Fludarabine: I.V.: 25 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Mitoxantrone: I.V.: 10 mg/m^2/dose day 1

[total dose/cycle = 10 mg/m^2]

Dexamethasone: I.V. or Oral: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 28 days

followed by:

Interferon maintenance:

Interferon alfa-2b: SubQ: 3 million units/m^2 days 1 to 14

[total dose/cycle = 42 million units/m^2]

Dexamethasone: Oral: 8 mg/day days 1, 2, and 3

[total dose/cycle = 24 mg]

Repeat cycle every month for 1 year

References

McLaughlin P, Hagemeister FB, Rodriguez MA, et al, "Safety of Fludarabine, Mitoxantrone, and Dexamethasone Combined With Rituximab in the Treatment of Stage IV Indolent Lymphoma," *Semin Oncol*, 2000, 27(6 Suppl 12):37-41.[PubMed 11225999]

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Lymphoma, non-Hodgkin's]

Regimen UseLymphoma, non-Hodgkin's

Index TermsFND (NHL)

Regimen

Fludarabine: I.V.: 25 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Mitoxantrone: I.V.: 10 mg/m^2/dose day 1

[total dose/cycle = 10 mg/m^2]

Dexamethasone: I.V. or Oral: 20 mg/day days 1 to 5

[total dose/cycle = 100 mg]

Repeat cycle every 28 days for up to a total of 8 cycles

References

McLaughlin P, Hagemeister FB, Romaguera JE, et al, "Fludarabine, Mitoxantrone, and Dexamethasone: An Effective New Regimen for Indolent Lymphoma," *J Clin Oncol*, 1996, 14(4):1262-8.[PubMed 8648382]

Tsimberidou AM, McLaughlin P, Younes A, et al, "Fludarabine, Mitoxantrone, Dexamethasone (FND) Compared With an Alternating Triple Therapy (ATT) Regimen in Patients With Stage IV Indolent Lymphoma," *Blood*, 2002, 100(13):4351-7.[PubMed 12393618]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's
Regimen UseLymphoma, non-Hodgkin's
Index TermsFMR (NHL); RFM (NHL); Rituximab-Fludarabine-Mitoxantrone
Regimen

Fludarabine: I.V.: 25 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Mitoxantrone: I.V.: 10 mg/m^2/dose day 1

[total dose/cycle = 10 mg/m^2]

Repeat cycle every 21 days for total of 6 cycles

followed by:

Sequential rituximab (after completion of cycle 6):

Rituximab: I.V.: 375 mg/m^2/dose weekly for 4 doses

[total dose/4 weeks = 1500 mg/m^2]

References

Zinzani PL, Pulsoni A, Perrotti A, et al, "Fludarabine Plus Mitoxantrone With and Without Rituximab Versus CHOP With and Without Rituximab as Front-Line Treatment for Patients With Follicular Lymphoma," *J Clin Oncol*, 2004, 22(13):2654-61.[PubMed 15159414]

Fludarabine-Mitoxantrone

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen Use Lymphoma, non-Hodgkin's

Index Terms FM (NHL)

Regimen

Fludarabine: I.V.: 25 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Mitoxantrone: I.V.: 10 mg/m^2/dose day 1

[total dose/cycle = 10 mg/m^2]

Repeat cycle every 21 days for total of 6 cycles

References

Zinzani PL, Pulsoni A, Perrotti A, et al, "Fludarabine Plus Mitoxantrone With and Without Rituximab Versus CHOP With and Without Rituximab as Front-Line Treatment for Patients With Follicular Lymphoma," *J Clin Oncol*, 2004, 22(13):2654-61.[PubMed 15159414]

Fludarabine-Rituximab

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Leukemia, Chronic Lymphocytic]

Regimen UseLeukemia, chronic lymphocytic

Regimen

Rituximab: I.V.: 375 mg/m^2/day days 1 and 4 (cycle 1); day 1 (cycles 2 to 6)

Fludarabine: I.V.: 25 mg/m^2/day days 1 to 5

Repeat cycle every 4 weeks

References

Byrd JC, Peterson BL, Morrison VA, et al, âRandomized Phase 2 Study of Fludarabine With Concurrent vs Sequential Treatment With Rituximab in Symptomatic, Untreated Patients With B-Cell Chronic Lymphocytic Leukemia: Results From Cancer and Leukemia Group B 9712 (CALGB 9712),â *Blood*, 2003, 101(1):6-14.[PubMed 12393429]

Fludarabine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Fludarabine may be confused with floxuridine, Flumadine®

Fludara® may be confused with FUDR®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(floo DARE a been)

U.S. Brand NamesFludara®

Canadian Brand NamesBeneflur®; Fludara®

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite (Purine Antagonist)

Use: Labeled Indications

U.S. labeling: I.V.: Treatment of chronic lymphocytic leukemia (CLL) (including refractory CLL)

Canadian labeling:

I.V.: Treatment of chronic lymphocytic leukemia (CLL) (including refractory CLL); treatment of low-grade, refractory non-Hodgkin’s lymphoma (NHL)

Oral (formulation not available in U.S.): Treatment of CLL

Use: Unlabeled/InvestigationalTreatment of non-Hodgkin's lymphoma (NHL); refractory acute leukemias and solid tumors (in pediatric patients); Waldenström's macroglobulinemia (WM); reduced-intensity conditioning regimens prior to allogeneic hematopoietic stem cell transplantation (generally administered in combination with busulfan and antithymocyte globulin or lymphocyte immune globulin, or in combination with melphalan and alemtuzumab)

Dosing: Adults

Chronic lymphocytic leukemia (CLL):

I.V.: 25 mg/m^2/day for 5 days every 28 days

Oral: **Note:** Formulation available in Canada; not available in U.S.: 40 mg/m^2 once daily for 5 days every 28 days

Non-Hodgkin's lymphoma, WM (unlabeled uses): I.V.: 25 mg/m^2 for 5 days every 28 days

Reduced-intensity conditioning regimens prior to allogeneic hematopoietic stem cell transplantation (unlabeled use): I.V.: 120-150 mg/m^2 administered in divided doses over 4-5 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Refractory acute leukemia (unlabeled use): I.V.: 10 mg/m^2 bolus over 15 minutes followed by continuous infusion of 30.5 mg/m^2/day for 5 days **or**

10.5 mg/m^2 bolus over 15 minutes followed by 30.5 mg/m^2/day for 48 hours

Refractory solid tumors (unlabeled use): I.V.: 7 mg/m^2 bolus followed by 20 mg/m^2/day continuous infusion for 5 days

Dosing: Renal Impairment

FDA-approved labeling contains the following adjustment recommendations:

Cl_{cr} 30-70 mL/minute: Administer 80% of dose.

Cl_{cr} <30 mL/minute: Avoid use.

Canadian labeling contains the following adjustment recommendations:

Cl_{cr} 30-70 mL/minute: Administer 50% of dose.

Cl_{cr} <30 mL/minute: Use is contraindicated.

The following guidelines have been used by some clinicians:

Aronoff, 2007:

Children:

Cl_{cr} 30-50 mL/minute: Administer 80% of dose.

Cl_{cr} <30 mL/minute: Not recommended.

Hemodialysis: Administer 25% of dose

Continuous ambulatory peritoneal dialysis (CAPD): Not recommended.

Continuous renal replacement therapy (CRRT): Administer 80% of dose.

Adults:

Cl_{cr} 10-50 mL/minute: Administer 75% of dose.

Cl_{cr} <10 mL/minute: Administer 50% of dose.

Hemodialysis: Administer after dialysis

Continuous ambulatory peritoneal dialysis (CAPD): Administer 50% of dose.

Continuous renal replacement therapy (CRRT): Administer 75% of dose.

Kintzel, 1995:

Cl_{cr} 46-60 mL/minute: Administer 80% of dose.

Cl_{cr} 31-45 mL/minute: Administer 75% of dose.

Cl_{cr} <30 mL/minute: Administer 65% of dose.

Dosing: Combination Regimens

Leukemia, acute lymphocytic: FIS-HAM

Leukemia, acute myeloid:

FIS-HAM

FLAG

FLAG-IDA

Leukemia, chronic lymphocytic:

Fludarabine-Cyclophosphamide (FC)

Fludarabine-Cyclophosphamide-Rituximab (CLL)

Fludarabine-Rituximab

Lymphoma, non-Hodgkin's: Fludarabine-Cyclophosphamide-Rituximab (NHL)

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Administer I.V. over 30 minutes or continuous infusion.

Administration: I.V. DetailpH: 7.2-8.2

Administration: OralTablet (formulation not available in U.S.) may be administered with or without food; should be swallowed whole; do not chew, break, or crush.

Storage

I.V.: Store intact vials under refrigeration at 2°C to 8°C (36°F to 46°F). Reconstituted vials are stable for 16 days at room temperature of 15°C to 30°C (59°F to 86°F) or refrigerated, although the manufacturer recommends use within 8 hours. Solutions diluted in saline or dextrose are stable for 48 hours at room temperature or under refrigeration.

Tablet (formulation not available in U.S.): Store between 15°C to 30°C (59°F to 86°F); should be kept within packaging until use.

ReconstitutionReconstitute vials with SWI, NS, or D_5W to a concentration of 10-25 mg/mL. Standard I.V. dilution: 100-125 mL D_5W or NS.

CompatibilityStable in D_5W, NS, sterile water for injection.

Y-site administration: Compatible: Allopurinol, amifostine, amikacin, aminophylline, ampicillin, ampicillin/sulbactam, amsacrine, aztreonam, bleomycin, butorphanol, carboplatin, carmustine, cefazolin, cefepime, cefoperazone, cefotaxime, cefotetan, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cimetidine, cisplatin, clindamycin, co-trimoxazole, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dexamethasone sodium phosphate, diphenhydramine, doxorubicin, doxycycline, droperidol, etoposide, etoposide phosphate, famotidine, filgrastim, floxuridine, fluconazole, fluorouracil, furosemide, gemcitabine, gentamicin, granisetron, haloperidol, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, ifosfamide, imipenem/cilastatin, lorazepam, magnesium sulfate, mannitol, mechlorethamine, melphalan, meperidine, mesna, methotrexate, methylprednisolone sodium succinate, metoclopramide, minocycline, mitoxantrone, morphine, multivitamins, nalbuphine, netilmicin, ondansetron, pentostatin, piperacillin, piperacillin/tazobactam, potassium chloride, promethazine, ranitidine, sodium bicarbonate, teniposide, thiotepa, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, vinblastine, vincristine, vinorelbine, zidovudine. **Incompatible:** Acyclovir, amphotericin B, chlorpromazine, daunorubicin, ganciclovir, hydroxyzine, prochlorperazine edisylate.

Contraindications

Hypersensitivity of fludarabine or any component of the formulation

Canadian labeling: Additional contraindications (not in U.S. labeling): Severe renal impairment (Cl_{cr} <30 mL/minute); decompensated hemolytic anemia; pregnancy; women who are breast-feeding; concurrent use with pentostatin

Warnings/Precautions

Boxed warnings:

- Autoimmune effects: See “Concerns related to adverse effects” below.
- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Experienced physician: See “Concerns related to adverse effects” below.
- Neurologic toxicity: See “Concerns related to adverse effects” below.
- Pentostatin: See “Concurrent drug therapy issues” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Autoimmune effects: **[U.S. Boxed Warning]: Life-threatening (and sometimes fatal) autoimmune effects, including hemolytic anemia, autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evans syndrome, and acquired hemophilia have occurred;** monitor closely for hemolysis. The hemolytic effects usually recur with fludarabine rechallenge.
- Bone marrow suppression: **[U.S. Boxed Warning]: Severe bone marrow suppression (anemia, thrombocytopenia, and neutropenia) may occur;** severe myelosuppression (trilineage bone marrow hypoplasia/aplasia) has been reported (rare); the duration of significant cytopenias in these cases may be prolonged (up to 1 year).
- Neurologic toxicity: **[U.S. Boxed Warning]: Higher than recommended doses (up to 96 mg/m^2/day for 5-7 days) are associated with severe neurologic toxicity (blindness, coma, death);** similar toxicity was reported rarely at recommended doses.
- Progressive multifocal leukoencephalopathy (PML): PML (usually fatal) due to JC virus has been reported with use; most cases were in patients who had received prior and/or other concurrent chemotherapy. Onset may be a few weeks or may be delayed up to 1 year. Evaluate any neurological change promptly.
- Tumor lysis syndrome: May cause tumor lysis syndrome; risk is increased in patients with large tumor burden prior to treatment.

Disease-related concerns:

- CNS disorders: Use with caution in patients with pre-existing central nervous system disorder (epilepsy), spasticity, or peripheral neuropathy.
- Hematologic disorders: Use with caution in patients with pre-existing hematological disorders (particularly granulocytopenia).
- Infection: Use with caution in patients with documented infection or fever. Prophylactic anti-infectives should be considered for patients with an increased risk for developing opportunistic infections.
- Renal impairment: Use with caution in patients with renal impairment; dosage reductions may be recommended; avoid use with Cl_{cr} <30 mL/minute.

Concurrent drug therapy issues:

- Pentostatin: **[U.S. Boxed Warning]: Do not use in combination with pentostatin; may lead to severe, even fatal pulmonary toxicity.** Concomitant use is contraindicated in the Canadian labeling.

Other warnings/precautions:

- Blood products: Patients receiving blood products should only receive irradiated blood products due to the potential for transfusion related GVHD.
- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**
- Live vaccines: Avoid vaccination with live vaccines during and after fludarabine treatment.

Pregnancy Risk Factor

D

Pregnancy ConsiderationsTeratogenic effects were observed in animal studies. Effective contraception is recommended during and for 6 months after treatment for women and men of reproductive potential. The manufacturer recommends pregnant staff should not handle fludarabine.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

>10%:

Cardiovascular: Edema (8% to 19%)

Central nervous system: Fever (60% to 69%), fatigue (10% to 38%), pain (20% to 22%), chills (11% to 19%)

Dermatologic: Rash (15%)

Gastrointestinal: Nausea/vomiting (mild: 31% to 36%), anorexia (7% to 34%), diarrhea (13% to 15%), gastrointestinal bleeding (3% to 13%)

Genitourinary: Urinary tract infection (2% to 15%)

Hematologic: Myelosuppression (nadir: 10-14 days; recovery: 5-7 weeks; dose-limiting toxicity), anemia (60%), neutropenia (grade 4: 59%; nadir: ~13 days), thrombocytopenia (50% to 55%; nadir: ~16 days)

Neuromuscular & skeletal: Weakness (9% to 65%), myalgia (4% to 16%), paresthesia (4% to 12%)

Ocular: Visual disturbance (3% to 15%)

Respiratory: Cough (10% to 44%), pneumonia (16% to 22%), dyspnea (9% to 22%), upper respiratory infection (2% to 16%)

Miscellaneous: Infection (33% to 44%), diaphoresis (1% to 13%)

1% to 10%:

Cardiovascular: Angina (≤6%), CHF (≤3%), arrhythmia (≤3%), cerebrovascular accident (≤3%), MI (≤3%), supraventricular tachycardia (≤3%), deep vein thrombosis (1% to 3%), phlebitis (1% to 3%), aneurysm (≤1%), transient ischemic attack (≤1%)

Central nervous system: Malaise (6% to 8%), headache (≤3%), sleep disorder (1% to 3%), cerebellar syndrome (≤1%), depression (≤1%), mentation impaired (≤1%)

Dermatologic: Alopecia (≤3%), pruritus (1% to 3%), seborrhea (≤1%)

Endocrine & metabolic: Hyperglycemia (1% to 6%), dehydration (≤1%)

Gastrointestinal: Stomatitis (≤9%), esophagitis (≤3%), constipation (1% to 3%), mucositis (≤2%), dysphagia (≤1%)

Genitourinary: Dysuria (3% to 4%), hesitancy (≤3%)

Hematologic: Hemorrhage (≤1%)

Hepatic: Cholelithiasis (≤3%), liver function tests abnormal (1% to 3%), liver failure (≤1%)

Neuromuscular & skeletal: Osteoporosis (≤2%), arthralgia (≤1%)

Otic: Hearing loss (2% to 6%)

Renal: Hematuria (2% to 3%), renal failure (≤1%), renal function test abnormal (≤1%), proteinuria (≤1%)

Respiratory: Pharyngitis (≤9%), allergic pneumonitis (≤6%), hemoptysis (1% to 6%), sinusitis (≤5%), bronchitis (≤1%), epistaxis (≤1%), hypoxia (≤1%)

Miscellaneous: Anaphylaxis (≤1%), tumor lysis syndrome (1%)

<1%, postmarketing, and/or case reports: Agitation, ARDS, blindness, blurred vision, bone marrow fibrosis, coma, confusion, diplopia, eosinophilia, Epstein-Barr virus (EBV) associated lymphoproliferation, EBV reactivation, erythema multiforme, Evans syndrome, flank pain, hemolytic anemia (autoimmune), hemophilia (acquired), hemorrhagic cystitis, herpes zoster reactivation, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, interstitial pneumonitis, metabolic acidosis, opportunistic infection, optic neuritis, optic neuropathy, pancytopenia, pemphigus, pericardial effusion, peripheral neuropathy, photophobia (primarily with high doses), progressive multifocal leukoencephalopathy (PML), pulmonary fibrosis, pulmonary hemorrhage, pulmonary infiltrate, respiratory failure, skin cancer (new onset or exacerbation), Stevens-Johnson syndrome, thrombocytopenia (autoimmune), thrombocytopenic purpura (autoimmune), toxic epidermal necrolysis, trilineage bone marrow aplasia, trilineage bone marrow hypoplasia, urate crystalluria, wrist drop

Also observed: Neurologic syndrome characterized by cortical blindness, coma, and paralysis [36% at doses >96 mg/m^2 for 5-7 days; <0.2% at doses <125 mg/m^2/cycle (onset of neurologic symptoms may be delayed for 3-4 weeks)]

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Pentostatin: Fludarabine may enhance the adverse/toxic effect of Pentostatin. Pulmonary toxicity is of specific concern. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to GI irritation).

Monitoring ParametersCBC with differential, platelet count, AST, ALT, serum creatinine, serum albumin, uric acid

Nursing: Physical Assessment/MonitoringTo be administered under the supervision of an experienced cancer chemotherapy physician. Use caution in the presence of renal insufficiency, fever, infection, hematological disorders, central nervous system disorders, or peripheral neuropathy. See Administration for infusion specifics. Evaluate results of laboratory tests prior to each treatment and on a regular basis throughout therapy. Assess therapeutic effect and adverse reactions closely, especially CNS, hematological, and neuromuscular effects. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, platelet count, AST, ALT, serum creatinine, serum albumin, uric acid

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. This drug is administered by infusion; report any burning, pain, redness, or swelling at infusion site. It is important to maintain adequate hydration (2-3 L/day of fluids unless instructed to restrict fluid intake) and nutrition (small, frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause fatigue, weakness, visual disturbances (use caution when driving or engaged in potentially hazardous tasks until response to drug in known); nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); loss of hair (reversible); diarrhea (buttermilk, boiled milk, or yogurt may help); or mouth sores (use soft toothbrush or cotton swabs for oral care). Report extreme fatigue; fever; pain or numbness in extremities; severe GI upset or diarrhea; any unusual bleeding or bruising; chills; sore throat; vaginal discharge; difficulty or pain on urination; muscle pain or weakness; unusual cough or respiratory difficulty; changes in vision; or other unusual side effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication or for 1 month following therapy. Consult prescriber for appropriate contraceptives. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, powder for reconstitution, as phosphate: 50 mg

Fludara®: 50 mg [contains mannitol 50 mg/vial]

Tablet, as phosphate:

Fludara® [CAN]: 10 mg [not available in U.S.]

Generic AvailableYes

Mechanism of ActionFludarabine inhibits DNA synthesis by inhibition of DNA polymerase, ribonucleotide reductase and DNA primase.

Pharmacodynamics/Kinetics

Distribution: V_d: 38-96 L/m^2; widely with extensive tissue binding

Protein binding: 19% to 29%

Metabolism: I.V.: Fludarabine phosphate is rapidly dephosphorylated to 2-fluoro-ara-A, which subsequently enters tumor cells and is phosphorylated by deoxycytidine kinase to the active triphosphate derivative; rapidly dephosphorylated in the serum

Bioavailability: 75%

Half-life elimination: 2-fluoro-ara-A: ~20 hours

Excretion: Urine (60%, 23% as 2-fluoro-ara-A) within 24 hours

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause agitation, confusion, coma

Mental Health: Effects on Psychiatric TreatmentMyelosuppression is common; use caution with clozapine and carbamazepine; concurrent use with low potency antipsychotics and TCAs may produce additive sedation. May cause nausea, vomiting, diarrhea, and GI bleeding; concomitant use with SSRIs may produce additive risk (use caution).

Index TermsFludarabine Phosphate; NSC-312887

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International Brand NamesBeneflur (ES, MX); Fludara (AR, AT, AU, BE, BG, BR, CH, CL, CN, CZ, DE, DK, EE, FI, FR, GB, GR, HK, HN, HU, ID, IE, IL, IN, IT, LU, MY, NL, NO, PE, PH, PL, PY, RU, SE, SG, TH, TR, TW, UY, VE, ZA)

Fludrocortisone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Florinef® may be confused with Fioricet®, Fiorinal®

Pronunciation(floo droe KOR ti sone)

U.S. Brand NamesFlorinef® [DSC]

Canadian Brand NamesFlorinef®

Pharmacologic CategoryCorticosteroid, Systemic

Use: Labeled IndicationsPartial replacement therapy for primary and secondary adrenocortical insufficiency in Addison's disease; treatment of salt-losing adrenogenital syndrome

Dosing: AdultsMineralocorticoid deficiency: Oral: 0.05-0.2 mg/day with ranges of 0.1 mg 3 times/week to 0.2 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricMineralocorticoid deficiency: Oral: Infants and Children: 0.05-0.1 mg/day

Administration: OralAdministration in conjunction with a glucocorticoid is preferable.

Dietary ConsiderationsSystemic use of mineralocorticoids/corticosteroids may require a diet with increased potassium, vitamins A, B_6, C, D, folate, calcium, zinc, and phosphorus, and decreased sodium. With fludrocortisone, a decrease in dietary sodium is often not required as the increased retention of sodium is usually the desired therapeutic effect.

ContraindicationsHypersensitivity to fludrocortisone or any component of the formulation; systemic fungal infections

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Fludrocortisone is primarily a mineralocorticoid agonist, but may also inhibit the HPA axis.

- Immunosuppression: May increase risk of infection and/or limit response to vaccinations; close observation is required in patients with latent tuberculosis and/or TB reactivity. Restrict use in active TB (only in conjunction with antituberculosis treatment).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with HF; use may be associated with fluid retention, edema, weight gain and hypertension.

- Electrolyte disturbances: Use with caution in patients with sodium retention and potassium loss. Monitor electrolytes periodically; sodium restriction and/or potassium supplementation may be required.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.

- Myocardial infarction (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur.

Special populations:

- Elderly: Because of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly in the smallest possible effective dose for the shortest duration.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Discontinuation of therapy: Withdraw therapy with gradual tapering of dose.

Geriatric ConsiderationsThe most common use of fludrocortisone in the elderly is orthostatic hypotension that is unresponsive to more conservative measures. Attempt nonpharmacologic measures (hydration, support stockings etc) before starting drug therapy.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with fludrocortisone; adverse events have been observed with corticosteroids in animal reproduction studies. Some studies have shown an association between first trimester systemic corticosteroid use and oral clefts; adverse events in the fetus/neonate have been noted in case reports following large doses of systemic corticosteroids during pregnancy.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsCorticosteroids are excreted in human milk; information specific to fludrocortisone has not been located.

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypertension, edema, CHF

Central nervous system: Convulsions, headache, dizziness

Dermatologic: Acne, rash, bruising

Endocrine & metabolic: Hypokalemic alkalosis, suppression of growth, hyperglycemia, HPA suppression

Gastrointestinal: Peptic ulcer

Neuromuscular & skeletal: Muscle weakness

Ocular: Cataracts

Miscellaneous: Diaphoresis, anaphylaxis (generalized)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Monitoring ParametersMonitor blood pressure and signs of edema when patient is on chronic therapy; very potent mineralocorticoid with high glucocorticoid activity; monitor serum electrolytes, serum renin activity, and blood pressure; monitor for evidence of infection; stop treatment if a significant increase in weight or blood pressure, edema, or cardiac enlargement occurs

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor for effectiveness of therapy and adverse reactions according to dose and length of therapy. Assess knowledge/teach patient appropriate use, possible side effects/interventions, and adverse symptoms to report (eg, opportunistic infection, adrenal suppression). Instruct patients with diabetes to monitor serum glucose levels closely; corticosteroids can alter glycemic response. Dose may need to be increased if patient is experiencing higher than normal levels of stress. When discontinuing, taper dose and frequency slowly.

Monitoring: Lab TestsSerum electrolytes, serum renin activity

Patient EducationTake exactly as directed. Do not take more than prescribed dose and do not discontinue abruptly; consult prescriber. Take with or after meals. Take once-a-day dose with food in the morning. Limit intake of caffeine or stimulants. Maintain adequate nutrition; consult prescriber for possibility of special dietary recommendations. If you have diabetes, monitor serum glucose closely and notify prescriber of changes; this medication can alter glycemic response. Notify prescriber if you are experiencing higher than normal levels of stress; medication may need adjustment. Periodic ophthalmic examinations will be necessary with long-term use. You will be susceptible to infection (avoid crowds and exposure to infection). You may experience insomnia or nervousness; use caution when driving or engaging in tasks requiring alertness until response to drug is known. Report weakness, change in menstrual pattern, vision changes, signs of hyperglycemia, signs of infection (eg, fever, chills, mouth sores, perianal itching, vaginal discharge), other persistent side effects, or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, as acetate: 0.1 mg

Florinef®: 0.1 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Fludrocortisone Acetate)

0.1 mg (30): $25.99

Mechanism of ActionPromotes increased reabsorption of sodium and loss of potassium from renal distal tubules

Pharmacodynamics/Kinetics

Absorption: Rapid and complete

Protein binding: 42%

Metabolism: Hepatic

Half-life elimination, plasma: 30-35 minutes; Biological: 18-36 hours

Time to peak, serum: ~1.7 hours

Related Information

- Corticosteroids

Pharmacotherapy PearlsIn patients with salt-losing forms of congenital adrenogenital syndrome, use along with cortisone or hydrocortisone. Fludrocortisone 0.1 mg has sodium retention activity equal to DOCA® 1 mg.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may decrease corticosteroid effects; useful in the management of psychotropic-induced hypotension

Cardiovascular ConsiderationsLong-term steroid therapy is associated with fluid retention and hypertension. This agent has some mineralocorticoid activity with consequent hemodynamic effects. Fludrocortisone has been used to treat severe orthostatic hypotension. Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. In discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia.

Anesthesia and Critical Care Concerns/Other ConsiderationsIn patients with salt-losing forms of congenital adrenogenital syndrome, use along with cortisone or hydrocortisone. Fludrocortisone 0.1 mg has sodium retention activity equal to DOCA® 1 mg.

Adrenal Insufficiency: Patients on long-term steroid supplementation will require higher corticosteroid doses when subject to stress (ie, trauma, surgery, severe infection). This agent has significant mineralocorticoid activity with consequent hemodynamic effects. Fludrocortisone has been used to treat severe orthostatic hypotension. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia. A recent randomized, double-blind, placebo controlled trial assessed whether low dose corticosteroid administration could improve 28-day survival in patients with septic shock and acquired adrenal insufficiency. A lack of adrenal reserves is defined by an increase in serum cortisol of ≤9 mcg/dL in response to corticotropin administration. Cortisol levels were drawn immediately before corticotropin administration and 30 to 60 minutes afterwards. Three hundred adult septic shock patients requiring mechanical ventilation and vasopressor support were randomized to either hydrocortisone (50 mg IVP every 6 hours) and fludrocortisone (50 mcg tablet daily via nasogastric tube) or matching placebos for 7 days. Patients included had severe sepsis requiring vasopressor support and mechanical ventilation. In patients who did not appropriately respond to corticotropin (nonresponders), there were significantly fewer deaths in the active treatment group. Vasopressor therapy was withdrawn more frequently in this subset of the active treatment group. Adverse events were similar in both groups. Patients who lack adrenal reserve and thus have acquired adrenal insufficiency during the stress of septic shock may benefit from physiologic steroid replacement. Further study is required to better characterize the patient populations who may benefit.

The 2008 Surviving Sepsis Campaign guidelines recommend doses of corticosteroids comparable to >300 mg hydrocortisone daily **not** be used in severe sepsis or septic shock for the purpose of treating septic shock (Grade 1A). They also recommend corticosteroids **not** be administered for the treatment of sepsis in the absence of shock. There is, however, no contraindication to continuing maintenance steroid therapy or to using stress dose steroids if the patient's endocrine or corticosteroid administration history warrants (Grade 1D).

Index Terms9α-Fluorohydrocortisone Acetate; Fludrocortisone Acetate; Fluohydrisone Acetate; Fluohydrocortisone Acetate

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International Brand NamesAstonin (ES); Astonin H (AT, CO, CZ, DE, HN); Astonin-H (HR, HU, LU); Cortineff (BG, PL); Floricot (IN); Florinef (AU, CH, CN, DK, FI, GB, GR, HK, IE, KP, MY, NL, NO, RU, SE, TH, TW, ZA); Florinefe (BR, UY, VE); Lonikan (AR)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(FLOO may ze nil)

U.S. Brand NamesRomazicon®

Canadian Brand NamesAnexate®; Flumazenil Injection; Flumazenil Injection, USP; Romazicon®

Pharmacologic CategoryAntidote

Use: Labeled IndicationsBenzodiazepine antagonist; reverses sedative effects of benzodiazepines used in conscious sedation and general anesthesia; treatment of benzodiazepine overdose

Dosing: AdultsSee table.

Flumazenil

Adult dosage for **reversal of conscious sedation and general anesthesia:**	
Initial dose	0.2 mg intravenously over 15 seconds
Repeat doses (maximum: 4 doses)	If desired level of consciousness is not obtained, 0.2 mg may be repeated at 1-minute intervals.
Maximum total cumulative dose	1 mg (usual dose: 0.6-1 mg) **In the event of resedation:** Repeat doses may be given at 20-minute intervals with maximum of 1 mg/dose and 3 mg/hour.
Adult dosage for **suspected benzodiazepine overdose:**	
Initial dose	0.2 mg intravenously over 30 seconds; if the desired level of consciousness is not obtained, 0.3 mg can be given over 30 seconds
Repeat doses	0.5 mg over 30 seconds repeated at 1-minute intervals
Maximum total cumulative dose	3 mg (usual dose: 1-3 mg) Patients with a partial response at 3 mg may require additional titration up to a total dose of 5 mg. If a patient has not responded 5 minutes after cumulative dose of 5 mg, the major cause of sedation is not likely due to benzodiazepines. **In the event of resedation:** May repeat doses at 20-minute intervals with maximum of 1 mg/dose and 3 mg/hour.

Resedation: Repeated doses may be given at 20-minute intervals as needed; repeat treatment doses of 1 mg (at a rate of 0.5 mg/minute) should be given at any time and no more than 3 mg should be given in any hour. After intoxication with high doses of benzodiazepines, the duration of a single dose of flumazenil is not expected to exceed 1 hour; if desired, the period of wakefulness may be prolonged with repeated low intravenous doses of flumazenil, or by an infusion of 0.1-0.4 mg/hour. Most patients with benzodiazepine overdose will respond to a cumulative dose of 1-3 mg and doses >3 mg do not reliably produce additional effects. Rarely, patients with a partial response at 3 mg may require additional titration up to a total dose of 5 mg. **If a patient has not responded 5 minutes after receiving a cumulative dose of 5 mg, the major cause of sedation is not likely to be due to benzodiazepines.**

Dosing: ElderlyRefer to adult dosing. No differences in safety or efficacy have been reported; however, increased sensitivity may occur in some elderly patients.

Dosing: Pediatric

Reversal of benzodiazepine when used in conscious sedation or general anesthesia: I.V.: Initial dose: 0.01 mg/kg (maximum dose: 0.2 mg) given over 15 seconds; may repeat 0.01 mg/kg (maximum dose: 0.2 mg) after 45 seconds, and then every minute (maximum: 4 doses) to a maximum of total cumulative dose of 0.05 mg/kg or 1 mg, whichever is lower; usual total dose: 0.08-1 mg (mean: 0.65 mg).

Dosing: Renal ImpairmentNot significantly affected by renal failure (Cl_{cr} <10 mL/minute) or hemodialysis beginning 1 hour after drug administration.

Dosing: Hepatic ImpairmentUse caution with initial and/or repeat doses in patients with liver disease.

Administration: I.V.Administer in freely-running I.V. into large vein. Inject over 15 seconds for conscious sedation and general anesthesia and over 30 seconds for overdose.

Administration: I.V. DetailpH: 4 (injection)

StorageStore at 15°C to 30°C (59°F to 86°F).

ReconstitutionFor I.V. use only. Once drawn up in the syringe or mixed with solution use within 24 hours. Discard any unused solution after 24 hours.

CompatibilityStable in D_5W, LR, NS.

Compatibility when admixed: Compatible: Aminophylline, cimetidine, dobutamine, dopamine, famotidine, heparin, lidocaine, procainamide, ranitidine.

ContraindicationsHypersensitivity to flumazenil, benzodiazepines, or any component of the formulation; patients given benzodiazepines for control of potentially life-threatening conditions (eg, control of intracranial pressure or status epilepticus); patients who are showing signs of serious cyclic-antidepressant overdosage

Warnings/Precautions

Boxed warnings:

- Seizures: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Amnesia: Does not consistently reverse amnesia; patient may not recall verbal instructions after procedure.
- Resedation: Occurs more frequently in patients where a large single dose or cumulative dose of a benzodiazepine has been administered along with a neuromuscular-blocking agent and multiple anesthetic agents.
- Respiratory depression: Should not rely upon to reverse respiratory depression/hypoventilation. Flumazenil is not a substitute for evaluation of oxygenation. Establishing an airway and assisting ventilation, as necessary, is always the initial step in overdose management.
- Seizures: **[U.S. Boxed Warning]: Benzodiazepine reversal may result in seizures in some patients.** Patients who may develop seizures include patients on benzodiazepines for long-term sedation, tricyclic antidepressant overdose patients, concurrent major sedative-hypnotic drug withdrawal, recent therapy with repeated doses of parenteral benzodiazepines, myoclonic jerking or seizure activity prior to flumazenil administration. Use with caution in patients relying on a benzodiazepine for seizure control.

Disease-related concerns:

- Head injury: Use with caution in patients with a head injury.
- Hepatic impairment: Use with caution in patients with hepatic dysfunction
- Panic disorder: Use with caution in patients with a history of panic disorder; may provoke panic attacks.

Special populations:

- Drug/alcohol dependence: Use caution in drug and ethanol-dependent patients; these patients may also be dependent on benzodiazepines.
- Intensive care patients: Should be used with caution in the intensive care unit because of increased risk of unrecognized benzodiazepine dependence in such settings.
- Pediatrics: Safety and efficacy have not been established in children <1 year of age.

Other warnings/precautions:

- Appropriate use: Should not be used to diagnose benzodiazepine-induced sedation. Reverse neuromuscular blockade before considering use. Flumazenil does not antagonize the CNS effects of other GABA agonists (such as ethanol, barbiturates, or general anesthetics); nor does it reverse narcotics. Not recommended for treatment of benzodiazepine dependence.
- Overdose use: Use with caution in patients with mixed drug overdoses; toxic effects of other drugs taken may emerge once benzodiazepine effects are reversed.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not seen in animal studies. Embryocidal effects were seen at large doses. There are no adequate or well-controlled studies in pregnant women. Use only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Gastrointestinal: Vomiting, nausea

1% to 10%:

Cardiovascular: Vasodilation (1% to 3%), palpitation

Central nervous system: Headache (1% to 3%), agitation (3% to 9%), dizziness (10%), emotional lability (1% to 3%), fatigue (1% to 3%)

Gastrointestinal: Xerostomia

Local: Pain at injection site (3% to 9%)

Neuromuscular & skeletal: Tremor, weakness, paresthesia (1% to 3%)

Ocular: Abnormal vision, blurred vision (3% to 9%)

Respiratory: Dyspnea, hyperventilation (3% to 9%)

Miscellaneous: Diaphoresis

<1%: Abnormal hearing, altered blood pressure (increases and decreases), confusion, sensation of coldness, bradycardia, chest pain, generalized seizure, hiccups, hypertension, junctional tachycardia, shivering, somnolence, tachycardia, thick tongue, ventricular tachycardia, withdrawal syndrome

Postmarketing and/or case reports: Fear, panic attacks

Drug Interactions

Hypnotics (Nonbenzodiazepine): Flumazenil may diminish the sedative effect of Hypnotics (Nonbenzodiazepine). **Exceptions:** Ramelteon. *Risk C: Monitor therapy*

Monitoring Parameters Monitor patients for return of sedation or respiratory depression

Nursing: Physical Assessment/Monitoring Assess level of consciousness frequently. Monitor vital signs and airway closely. ECG monitoring and oxygenation via pulse oximetry is highly recommended. Observe continually for resedation, respiratory depression, preseizure activity, or other residual benzodiazepine effects. May require pain medication sooner after reversal. Assess for nausea and vomiting.

Patient Education Flumazenil does not consistently reverse amnesia. Do not engage in activities requiring alertness for 18-24 hours after discharge. Avoid alcohol or OTC medications for 24 hours after receiving this medication, unless approved by prescriber. Resedation may occur in patients on long-acting benzodiazepines (such as diazepam). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 0.1 mg/mL (5 mL, 10 mL)

Romazicon®: 0.1 mg/mL (5 mL, 10 mL) [contains edetate disodium]

Generic Available Yes

Manufacturer Roche Laboratories Inc

Mechanism of Action Competitively inhibits the activity at the benzodiazepine receptor site on the GABA/benzodiazepine receptor complex. Flumazenil does not antagonize the CNS effect of drugs affecting GABA-ergic neurons by means other than the benzodiazepine receptor (ethanol, barbiturates, general anesthetics) and does not reverse the effects of opioids

Pharmacodynamics/Kinetics

Onset of action: 1-3 minutes; 80% response within 3 minutes

Peak effect: 6-10 minutes

Duration: Resedation: ~1 hour; duration related to dose given and benzodiazepine plasma concentrations; reversal effects of flumazenil may wear off before effects of benzodiazepine

Distribution: Initial V_d: 0.5 L/kg; V_{dss} 0.77-1.6 L/kg

Protein binding: 40% to 50%

Metabolism: Hepatic; dependent upon hepatic blood flow

Half-life elimination: Adults: Alpha: 7-15 minutes; Terminal: 41-79 minutes; Moderate hepatic dysfunction: 1.3 hours; severe hepatic impairment: 2.4 hours

Excretion: Feces; urine (0.2% as unchanged drug)

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Anesthesia and Critical Care Concerns/Other Considerations Flumazenil does **not** antagonize the CNS effects of other GABA agonists (such as ethanol, barbiturates, or general anesthetics), nor does it reverse narcotics.

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International Brand NamesAnexate (AE, AT, AU, BE, BF, BG, BH, BJ, CH, CI, CY, CZ, DE, EE, EG, ES, ET, FR, GB, GH, GM, GN, GR, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JO, JP, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, NO, OM, PK, PL, PT, QA, SA, SC, SD, SL, SN, SY, TH, TN, TR, TW, TZ, UG, YE, ZA, ZM, ZW); Lanexat (AR, BB, BM, BR, BS, BZ, CN, CO, DK, EC, FI, GY, JM, MX, NL, PE, PY, SE, SR, TT, UY, VE)

Flunarizine

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English

Jump To Field (Select Field Name)

Pronunciation(floo NAR i zeen)
Canadian Brand NamesApo-Flunarizine®; Novo-Flunarizine; Sibelium®
Pharmacologic CategoryCalcium Channel Antagonist
Use: Labeled IndicationsProphylaxis of classic (with aura) or common (without aura) migraine; symptomatic treatment of vestibular vertigo (due to a diagnosed functional disorder of the vestibular system)
Storage

Store at room temperature. Protect from light and moisture.

RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to flunarizine, any component of the formulation, or other calcium channel antagonist; depression; Parkinson's disease, or other extrapyramidal disorders
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). Monitor for fatique symptoms.

- Depression: May precipitate depression; greater risk in younger patients. Monitor for depressive symptoms.

- Extrapyramidal symptoms: May produce extrapyramidal symptoms in individuals with no prior history of neurological deficits; risk is increased in elderly patients. Monitor for symptoms.

Disease-related concerns:

- Acute migraines: Not indicated for treatment of acute migraine attacks.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Do not exceed recommended dose; discontinue use if therapeutic effects diminish during treatment.

Pregnancy ConsiderationsNo data to support use during pregnancy; weigh benefits versus potential risks
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Central nervous system: Anxiety, dizziness, drowsiness, fatigue, insomnia, vertigo

Dermatologic: Rash

Endocrine & metabolic: Galactorrhea, prolactin levels increased

Gastrointestinal: Appetite increased, epigastric pain, heartburn, nausea, vomiting, weight gain, xerostomia

Neuromuscular & skeletal: Asthenia/weakness, muscle ache

Metabolism/Transport Effects**Substrate** of CYP2D6
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CarBAMazepine: May decrease the serum concentration of Flunarizine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Phenytoin: May decrease the serum concentration of Flunarizine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Concurrent use may result in excessive sedation.
Monitoring ParametersMonitor for extrapyramidal, depressive, and/or fatigue symptoms and discontinue therapy with flunarizine if observed.
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking. Assess effectiveness (according to purpose for use) and adverse response (extrapyramidal symptoms, CNS changes, gastrointestinal disturbance). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by

prescriber. This medication is not to be used for acute migraine attacks; it may help prevent migraine headaches. Take exactly as directed; take several weeks for effects to be noticed. May cause drowsiness, dizziness, anxiety, or fatigue (use caution when driving or engaging in tasks requiring alertness until response to drug in known); nausea, vomiting, heartburn, dry mouth (small, frequent meals, frequent mouth care may help, chewing gum, or sucking lozenges may help). Report rash; muscle aches, weakness, or tremors; unusual anxiety or confusion; rapid heartbeat, or other persistent adverse effects. **Breast-feeding precaution**: Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Capsule:

Apo-Flunarizine® [CAN], Novo-Flunarizine [CAN], Sibelium® [CAN]: 5 mg [not available in the U.S.]

Generic AvailableYes

Mechanism of ActionFlunarizine is a selective calcium channel antagonist that prevents cellular calcium overload by reducing transmembrane calcium influx; also has antihistamine properties.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: V_d: Mean: 43.2 L/kg

Protein binding: 99%

Metabolism: Hepatic: N-oxidation, aromatic hydroxylation

Half-life elimination: ~19 days

Time to peak, plasma: 2-4 hours

Excretion: Urine (minimal)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, drowsiness, dizziness, or insomnia

Mental Health: Effects on Psychiatric TreatmentContraindicated in patients with depression, Parkinson's disease, or other extrapyramidal disorders (increases prolactin). Concomitant use with psychotropics may produce additive sedative effects. Fluoxetine and paroxetine may increase the effects of flunarizine.

Index TermsFlunarizine Hydrochloride

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International Brand NamesAxilin (MX); Bedriol (UY); Dinegal (CO); Flaryzil (PY); Floxin (TH); Fludan (HK, MY); Fludil (VE); Flumig (PH); Flunatop (BE); Flunavert (DE); Fluzina (DO, GT, NI, PA, SV); Forknow (MY, SG); Frego (ID); Gradient (IT); Irrigor (CN); Lunar (PK); MGR (IN); Migon (IN); Natil-N (DE); Sibelium (AR, BE, BG, BR, CH, CL, CN, CO, CZ, DK, EC, ES, FR, GR, HN, ID, IE, IN, IT, KP, MX, MY, NL, PH, PK, PY, TH, TW, UY, VE, ZA); Suzin (TW); Xepalium (ID); Zinasen (PE)

Flunisolide

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English English

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Special Alerts

Aerospan™" Product Availability: August 2008

Aerospan™ was approved by the Food and Drug Administration (FDA) in January 2006. A product launch date has not been determined.

Medication Safety Issues

Sound-alike/look-alike issues:

Flunisolide may be confused with Flumadine®, fluocinonide

Nasarel® may be confused with Nizoral®

Pronunciation(floo NISS oh lide)
U.S. Brand NamesAeroBid®; AeroBid®-M; Nasarel®
Canadian Brand NamesAlti-Flunisolide; Apo-Flunisolide®; Nasalide®; PMS-Flunisolide; Rhinalar®
Pharmacologic CategoryCorticosteroid, Inhalant (Oral); Corticosteroid, Nasal
Use: Labeled IndicationsSteroid-dependent asthma; nasal solution is used for seasonal or perennial rhinitis
Dosing: Adults**Note:** AeroBid® and Aerospan™ are not interchangeable; dosing changes when switching from one to the other.

Asthma: Oral Inhalation:

AeroBid®: 2 inhalations twice daily (morning and evening); up to 8 inhalations/day maximum

NIH Asthma Guidelines (NIH, 2007) (administer in divided doses twice daily):

"Low" dose: 500-1000 mcg/day

"Medium" dose: >1000-2000 mcg/day

"High" dose: >2000 mcg/day

Aerospan™: 2 inhalations twice daily; up to 8 inhalations/day

NIH Asthma Guidelines (NIH, 2007) (administer in divided doses twice daily):

"Low" dose: 320 mcg/day

"Medium" dose: >320-640 mcg/day

"High" dose: >640 mcg/day

Seasonal allergic rhinitis: Intranasal: 2 sprays each nostril twice daily (morning and evening); may increase to 2 sprays 3 times daily; maximum dose: 8 sprays/day in each nostril (400 mcg/day)

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Note:** AeroBid® and Aerospan™ are not interchangeable; dosing changes when switching from one to the other.

Asthma: Oral Inhalation:

AeroBid®:

Children 6-15 years: 2 inhalations twice daily (morning and evening); up to 4 inhalations/day

Children ≥16 years: Refer to adult dosing.

NIH Asthma Guidelines (NIH, 2007) (administer in divided doses twice daily):

Children 5-11 years:

"Low" dose: 500-750 mcg/day

"Medium" dose: 1000-1250 mcg/day

"High" dose: >1250 mcg/day

Children ≥12 years: Refer to adult dosing.

Aerospan™:

Children 6-11 years: 1 inhalation twice daily; up to 4 inhalations/day

Children ≥12 years: Refer to adult dosing.

NIH Asthma Guidelines (NIH, 2007) (administer in divided doses twice daily):

Children 5-11 years:

"Low" dose: 160 mcg/day

"Medium" dose: 320 mcg/day

"High" dose: ≥640 mcg/day

Children ≥12 years: Refer to adult dosing.

Seasonal allergic rhinitis: Intranasal:

Children 6-14 years: 1 spray each nostril 3 times daily **or** 2 sprays in each nostril twice daily; not to exceed 4 sprays/day in each nostril (200 mcg/day)

Children ≥15 years: Refer to adult dosing.

Administration: InhalationShake well before using. Rinse mouth following use of oral inhalers.

Aerospan™: Has a self-contained spacer; do not use with another spacer. Prime inhaler prior to first use. Begin inhalation immediately prior to actuation; a delay may reduce dose by ≥75%.

Storage

Aerospan™: Store at 15°C to 30°C (59°F to 86°F). Do not store near heat or flame. Protect from freezing and sunlight.

AeroBid®: Store below 49°C (below 120°F).

ContraindicationsHypersensitivity to flunisolide or any component of the formulation; acute status asthmaticus; viral, tuberculosis, fungal, or bacterial respiratory infections; infections of the nasal mucosa

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections. Do not use this product to transfer patients from oral corticosteroid therapy.

- Bronchospasm: May occur with wheezing after inhalation; if this occurs stop steroid and treat with a fast-acting bronchodilator.

- Delayed wound healing: Avoid nasal corticosteroid use in patients with recent nasal septal ulcers, nasal surgery or nasal trauma until healing has occurred.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox should be avoided; corticosteroids should not be used to treat ocular herpes simplex. Corticosteroids should not be used for cerebral malaria. Close observation is required in patients with latent tuberculosis and/or TB reactivity; restrict use in active TB (only in conjunction with antituberculosis treatment).

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

Disease-related concerns:

- Asthma: Supplemental steroids (oral or parenteral) may be needed during stress or severe asthma attacks. Not to be used in status asthmaticus or for the relief of acute bronchospasm.

- Cardiovascular disease: Use with caution in patients with HF; long-term use has been associated with fluid retention and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.

- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids.

- Myocardial infarct (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Consider routine eye exams in chronic users.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Pediatrics: Orally-inhaled and intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients (~1 centimeter per year [range 0.3-1.8 cm per year] and related to dose and duration of exposure). To minimize the systemic effects of orally-inhaled and intranasal corticosteroids, each patient should be titrated to the lowest effective dose. Growth should be routinely monitored in pediatric patients.

Other warnings/precautions:

- Discontinuation of therapy: Withdraw systemic therapy with gradual tapering of dose. There have been reports of systemic corticosteroid withdrawal symptoms (eg, joint/muscle pain, lassitude, depression) when withdrawing oral inhalation therapy.

Geriatric ConsiderationsMany elderly patients have difficulty using metered dose inhalers, which can limit their effectiveness. Assess technique in all older patients. A spacer device may be beneficial for the oral inhaler. Aerospan™ has its own spacer device attached to the unit and may be easier to use for elderly patients.

Pregnancy Risk FactorC

Pregnancy ConsiderationsNo data on crossing the placenta or effects on the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Headache (intranasal <5%; oral 9% to 25%)

Gastrointestinal: Aftertaste (10% to 17%)

Respiratory: Nasal burning (intranasal 45%), pharyngitis (14% to 20%), rhinitis (<15%), nasal irritation (>1% to 13%)

1% to 10%:

Cardiovascular: Chest pain (1% to 3%), edema (1% to 3%), chest tightness, hypertension, palpitation, tachycardia

Central nervous system: Fever (1% to 9%), dizziness (1% to 3%), insomnia (1% to 3%), migraine (1% to 3%), chills, malaise, irritability, shakiness, anxiety, depression, faintness, fatigue, moodiness, vertigo

Dermatologic: Erythema multiform (1% to 3%), acne, eczema, pruritus, urticaria

Endocrine & metabolic: Dysmenorrhea (1% to 3%)

Gastrointestinal: Dyspepsia (2% to 4%), abdominal pain (1% to 3%), diarrhea (1% to 10%), gastroenteritis (1% to 3%), nausea (Aerospan™: 1% to 3%), oral candidiasis (1% to 3%), taste perversion (1% to 3%), abdominal fullness, constipation, gas, heartburn, sore throat, dry throat, mouth discomfort, throat irritation

Genitourinary: Vaginitis (1% to 3%), urinary tract infection (1% to 4%)

Neuromuscular & skeletal: Myalgia (1% to 3%), neck pain (1% to 3%), numbness, weakness

Ocular: Conjunctivitis (1% to 3%), blurred vision

Renal: Laryngitis (1% to 3%)

Respiratory: Sinusitis (<9%), epistaxia (<3%), bronchospasm, cough increased, dyspnea, hoarseness, nasal ulcer, sneezing, wheezing

Miscellaneous: Allergy (4% to 5%), infection (3% to 9%), loss of smell, voice alteration (1% to 3%), flu-like syndrome, diaphoresis

<1%: Adrenal suppression

Metabolism/Transport Effects

Substrate of CYP3A4 (major)

Drug Interactions

Amphotericin B: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antidiabetic Agents: Corticosteroids (Orally Inhaled) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringNot to be used to treat status asthmaticus or fungal infections of nasal passages. Monitor therapeutic effectiveness and adverse reactions. When changing from systemic steroids to inhalational steroid, taper reduction of systemic medication slowly. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationThis medication is not intended to treat an acute asthma attack. Full benefit of regular use may not be seen for 2-4 weeks. Use as directed; do not use nasal preparations for oral inhalation. Do not increase dosage or discontinue abruptly without consulting prescriber. Review use of inhaler or spray with prescriber or follow package insert for directions. Keep oral inhaler clean and unobstructed. Always rinse mouth and throat after use of inhaler to prevent opportunistic infection. If you are also using an inhaled bronchodilator, wait 10 minutes before using this steroid aerosol. You may be susceptible to infections. Avoid measles and chickenpox. You may experience dizziness, anxiety, or blurred vision (rise slowly from sitting or lying position and use caution when driving or engaging in tasks requiring alertness until response to drug is known); or taste disturbance or aftertaste (frequent mouth care and mouth rinses may help). Report pounding heartbeat or chest pain; acute nervousness or inability to sleep; severe sneezing or nosebleed; respiratory difficulty, sore throat, hoarseness, or bronchitis; respiratory difficulty or bronchospasms; disturbed menstrual pattern; vision changes; loss of taste or smell perception; or worsening of condition or lack of improvement. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Inhaler: Sit when using. Take deep breaths for 3-5 minutes, and clear nasal passages before administration (use decongestant as needed). Hold breath for 5-10 seconds after use, and wait 1-3 minutes between inhalations. Follow package insert instructions for use. Do not exceed maximum dosage. If also using inhaled bronchodilator, use before flunisolide. Rinse mouth and throat after use to reduce aftertaste and prevent candidiasis.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol for oral inhalation:

AeroBid®: 250 mcg/actuation (7 g) [100 metered inhalations; contains chlorofluorocarbon]

AeroBid®-M: 250 mcg/actuation (7 g) [100 metered inhalations; contains chlorofluorocarbon; menthol flavor]

Solution, intranasal [spray]: 25 mcg/actuation (25 mL); 29 mcg/actuation (25 mL) [200 sprays]

Nasarel®: 29 mcg/actuation (25 mL) [200 sprays; contains benzalkonium chloride]

Generic AvailableYes: Nasal spray

Pricing: U.S. (www.drugstore.com)

Aerosol solution (Aerobid)

250 mcg/ACT (7): $88.38

Aerosol solution (Aerobid-M)

250 mcg/ACT (7): $84.99

Solution (Flunisolide)

0.025% (25): $39.99

29 mcg/ACT (25): $45.99

Solution (Nasarel)

29 mcg/ACT (25): $59.99

Mechanism of ActionDecreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability; does not depress hypothalamus

Pharmacodynamics/Kinetics

Absorption: Nasal inhalation: ~50%

Metabolism: Rapidly hepatic to active metabolites

Bioavailability: 40% to 50%

Half-life elimination: 1.8 hours

Excretion: Urine and feces (equal amounts)

Related Information

- Asthma
- Inhalant Agents
- Status Epilepticus

Pharmacotherapy PearlsAerospan™and AeroBid® doses are not interchangeable because of differences in delivery characteristics.

Effects of inhaled/intranasal steroids on growth have been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally-inhaled and intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: *Candida* infections of the nose or pharynx, atrophic rhinitis, sore throat, bitter taste, palpitations, dizziness, headache, nervousness, GI irritation, sneezing, coughing, upper respiratory tract infection, bronchitis, nasal congestion, nasal dryness and burning, increased susceptibility to infections, xerostomia (normal salivary flow resumes upon discontinuation), dry throat, loss of taste, epistaxis, and diaphoresis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and nervousness are common; may cause insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other Considerations

Surgery: For patients who have received oral systemic corticosteroids during the past 6 months and for selected patients on long-term, high-dose, inhaled corticosteroid (ICS), give stress doses of hydrocortisone intravenously during the surgical period and reduce the dose rapidly within 24 hours after surgery (Expert Panel Report 3, 2007). Clinically important adrenal suppression has been reported in patients receiving high doses of an ICS, particularly children.

References

Expert Panel Report 3, “Guidelines for the Diagnosis and Management of Asthma,” *Clinical Practice Guidelines*, National Institutes of Health, National Heart, Lung, and Blood Institute, NIH Publication No. 08-4051, prepublication 2007. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

Todd GR, Acerini CL, Buck JJ, et al, "Acute Adrenal Crisis in Asthmatics Treated With High-Dose Fluticasone Propionate," *Eur Respir J*, 2002, 19(6):1207-9.[PubMed 12108877]

Todd GR, Acerini CL, Ross-Russell R, et al, "Survey of Adrenal Crisis Associated With Inhaled Corticosteroids in the United Kingdom," *Arch Dis Child*, 2002, 87(6):457-61.[PubMed 12456538]

International Brand NamesBronalide (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Broncort (CH, LU); Bronilide (FR, PL); Flunitec (AR, BR); Gibiflu (IT); Inhacort (DE); Locasyn Nasal (DK); Lokilan (NO); Lunibron-A (IT); Nasalide (FR); Nasarel (IN); Syntaris (AT, BB, BE, BH, BM, BS, BZ, CH, CZ, DE, GB, GY, IE, IT, JM, KW, LU, NL, PL, PR, SR, TT); Syntaris Nasal Spray (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Tarisin (PK)

Fluocinolone, Hydroquinone, and Tretinoin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(floo oh SIN oh lone, HYE droe kwin one, & TRET i noyn)

U.S. Brand NamesTri-Luma™

Pharmacologic CategoryCorticosteroid, Topical; Depigmenting Agent; Retinoic Acid Derivative

Use: Labeled IndicationsShort-term treatment of moderate to severe melasma of the face

Dosing: AdultsMelasma: Topical: Apply a thin film once daily to hyperpigmented areas of melasma (including $^1/_2$ inch of normal-appearing surrounding skin). Apply 30 minutes prior to bedtime; not indicated for use beyond 8 weeks. Do not use occlusive dressings.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment required.

Administration: TopicalApply 30 minutes before bedtime. Wash face with mild cleanser; rinse and pat dry. Apply to lesion and $^1/_2$ inch of normal-appearing skin surrounding each lesion. Rub lightly and uniformly into the skin. Do not use occlusive dressings.

StorageStore at 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to fluocinolone, hydroquinone, tretinoin, or any component of the formulation; TB of skin, herpes (including varicella); sulfite allergy

Allergy Considerations

- Corticosteroid Allergy
- Retinoid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.

- Dermatitis: Cutaneous hypersensitivity/contact dermatitis to individual ingredients has been reported; instruct patients to seek medical attention.

- Exogenous ochronosis: Hydroquinone may produce exogenous ochronosis (gradual blue/black darkening of skin); discontinuation is recommended.

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Concurrent drug therapy issues:

- Hormonal contraceptives: Consider changing to nonhormonal contraceptive measures in patients who may be receiving hormonal contraceptives.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Sodium metabisulfate: Contains sodium metabisulfite; may cause hypersensitivity reactions, including anaphylaxis, in individuals with sulfite allergy.

Other warnings/precautions:

- Darker skin types: Has not been evaluated in skin types V and VI; excessive bleaching may occur in individuals with darker skin.

- Patient information: Instruct patients to avoid UV exposure, including sunlight (protective clothing and sunscreen recommended). Local irritation, dryness, and pruritus may be expected following application. Avoid contact with abraded skin, mucous membranes, eyes, mouth, angles of the nose.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Tretinoin appears to have a low risk of teratogenicity when used topically since it is rapidly metabolized by the skin; however, there are rare reports of fetal defects. Risk may be greatest in 1st trimester. Use topically only if benefit to mother outweighs potential risk to fetus. In general, the use of topical corticosteroids during pregnancy is not considered to have significant risk, however, intrauterine growth retardation in the infant has been reported (rare). The use of large amounts or for prolonged periods of time should be avoided. Consider delaying treatment until after delivery.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding Considerations Avoid contact between nursing infant and cream.

Adverse Reactions

>10%:

Dermatologic: Erythema (41%), desquamation (38%), burning (18%), dry skin (14%), pruritus (11%)

1% to 10%:

Cardiovascular: Telangiectasia (3%)

Central nervous system: Paresthesia (3%), hyperesthesia (2%)

Dermatologic: Acne (5%), pigmentation change (2%), irritation (2%), papules (1%), rash (1%), rosacea (1%), vesicles (1%)

Gastrointestinal: Xerostomia (1%)

<1%: Other reactions reported with one or more components: Acneiform eruptions, allergic contact dermatitis, burning, Cushing's syndrome, folliculitis, HPA axis suppression, hypertrichosis, hypopigmentation, irritation, itching, miliaria, ochronosis (exogenous), perioral dermatitis, secondary infection, skin atrophy, striae

Metabolism/Transport Effects Tretinoin: **Substrate** (minor) of CYP2A6, 2B6, 2C8/9; **Inhibits** CYP2C8/9 (weak); **Induces** CYP2E1 (weak)

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Avoid excessive intake of vitamin A (cod liver oil, halibut fish oil).

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization). Avoid excessive amounts of vitamin A supplements.

Monitoring Parameters Signs/symptoms of HPA axis suppression

Nursing: Physical Assessment/Monitoring See individual agents.

Patient Education See individual agents.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical: Hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01% (30 g) [contains sodium metabisulfite]

Generic Available No

Manufacturer Galderma

Pricing: U.S. (www.drugstore.com)

Cream (Tri-Luma)

0.01-4-0.05% (30): $190.91

Mechanism of Action Not clearly defined. Hydroquinone may interrupt melanin synthesis (tyrosine-tyrosinase pathway); reduces hyperpigmentation.

Pharmacodynamics/Kinetics

Absorption: Minimal

Metabolism: Hepatic for the small amount absorbed

Excretion: Urine and feces

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment Avoid use with drugs possessing photosensitizing effects (psychotropics, especially phenothiazines). Avoid dong quai and St John's wort (may cause photosensitization).

Index Terms Hydroquinone, Fluocinolone Acetonide, and Tretinoin; Tretinoin, Fluocinolone Acetonide, and Hydroquinone

References

Goedert JJ, Vitale F, Lauria C, et al, "Risk Factors for Classical Kaposi's Sarcoma," *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

International Brand Names Tri-Luma (AR, BR, CN, CO, HK, MX, MY, PE, PH, SG, TH, VE); Triluma (UY); Trimelasin (PK)

Fluocinolone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Fluocinolone may be confused with fluocinonide

Pronunciation(floo oh SIN oh lone)
U.S. Brand NamesCapex®; Derma-Smoothe/FS®; DermOtic® ; Retisert®; Synalar® [DSC]
Canadian Brand NamesCapex®; Derma-Smoothe/FS®; Synalar®
Pharmacologic CategoryCorticosteroid, Ophthalmic; Corticosteroid, Topical
Use: Labeled IndicationsRelief of susceptible inflammatory dermatosis [low, medium corticosteroid]; dermatitis or psoriasis of the scalp; atopic dermatitis in adults and children ≥3 months of age

Ocular implant (Retisert®): Treatment of chronic, noninfectious uveitis affecting the posterior segment of the eye

Otic (DermOtic® Oil): Relief of chronic eczematous external otitis in adults and children ≥2 years of age.

Use: DentalRelief of inflammatory and pruritic manifestations (low, medium, high potency topical corticosteroid)
Dosing: Adults

Atopic dermatitis (Derma-Smoothe/FS® body oil): Apply thin film to affected area 3 times/day

Chronic eczematous external otitis: Otic: 5 drops into the affected ear twice daily for 1-2 weeks

Chronic uveitis: Ocular implant: One silicone-encased tablet (0.59 mg) surgically implanted into the posterior segment of the eye is designed to initially release 0.6 mcg/day, decreasing over 30 days to a steady-state release rate of 0.3-0.4 mcg/day for 30 months. Recurrence of uveitis denotes depletion of tablet, requiring reimplantation.

Corticosteroid-responsive dermatoses: Topical: Cream, ointment, solution: Apply a thin layer to affected area 2-4 times/day; may use occlusive dressings to manage psoriasis or recalcitrant conditions

Inflammatory and pruritic manifestations (dental use): Topical: Apply to oral lesion 4 times/day, after meals and at bedtime

Scalp psoriasis (Derma-Smoothe/FS® scalp oil): Topical: Massage thoroughly into wet or dampened hair/scalp; cover with shower cap. Leave on overnight (or for at least 4 hours). Remove by washing hair with shampoo and rinsing thoroughly.

Seborrheic dermatitis of the scalp (Capex®): Topical: Apply no more than 1 ounce to scalp once daily; work into lather and allow to remain on scalp for ~5 minutes. Remove from hair and scalp by rinsing thoroughly with water.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Atopic dermatitis: Topical: Children ≥3 months (Derma-Smoothe/FS® body oil): Moisten skin; apply a thin filn to affected area twice daily; do not use for longer than 4 weeks

Chronic eczematous external otitis: Otic: Children ≥2 years: Refer to adult dosing.

Chronic uveitis: Ocular implant: Children ≥12 years: Refer to adult dosing.

Corticosteroid-responsive dermatoses: Topical: Refer to adult dosing.

Administration: TopicalApply thin film to affected area; avoid eyes.
Administration: Other

Ocular implant: Handle only by suture tab to avoid damaging the tablet integrity and adversely affecting release characteristics. Maintain strict adherence to aseptic handling of product; do not resterilize.

Storage

Topical: Store at controlled room temperature in tightly-closed container.

Capex®: Store at 15°C to 35°C (59°F to 86°F).

Ocular implant (Retisert®): Store in original container at controlled room temperature of 15°C to 25°C (59°F to 77°F). Do not freeze.

Otic: Store a controlled room temperature of 20°C to 25°C (68°F to 77°F).

ReconstitutionCapex®: Prior to dispensing, the contents of the capsule should be emptied into the liquid shampoo; shake well. Discard after 3 months.

Contraindications Hypersensitivity to fluocinolone or any component of the formulation; TB of skin, herpes (including varicella)

Ocular implant: Additional contraindications include ocular infections of viral, bacterial, or fungal origin; hypersensitivity to other corticosteroids

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections.

- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.

- Infection: Steroids may mask infection or enhance existing ocular infection; prolonged use may result in secondary infections due to immunosuppression.

- Ocular effects: Prolonged use may result in glaucoma and injury to the optic nerve. Visual defects in acuity and field of vision may occur (lasting 1-4 weeks postoperatively). Use with caution in presence of glaucoma (steroids increase intraocular pressure). Perforation may occur with topical steroids in diseases which thin the cornea or sclera. Steroid use may delay healing after cataract surgery. Intraocular pressure should be monitored if this product is used >10 days.

- Systemic effects: Adverse systemic effects may occur when used on large areas of the body, denuded areas, for prolonged periods of time, or with an occlusive dressing. Infants and children may be more susceptible to systemic toxicity from equivalent doses due to larger skin surface to body mass ratio.

Special populations:

- Pediatrics: Safety and efficacy of Derma-Smoothe/FS® body oil have not been established in children <3 months of age. Safety and efficacy of the ocular implant have not been established in children <12 years of age. Safety and efficacy of otic drops have not been established in children <2 years of age.

Dosage form specific issues:

- Ocular implant: May require IOP-lowering treatments within 2 years postimplantation. Recommend unilateral implantation only to minimize risk of postoperative infections developing in both eyes. Due to the potential for separation of the silicone cup reservoir from the suture tab, implant integrity should be monitored during eye exams.

- Peanut oil: Derma-Smoothe/FS® and DermOtic® Oil contain peanut oil; use caution in peanut-sensitive individuals.

Topical: Not for oral, ophthalmic or intravaginal use; do not apply to the face, axillae, groin, or diaper area unless directed by healthcare provider. Discontinue use if irritation occurs.

Geriatric Considerations Due to age-related changes in skin, limit use of topical glucocorticosteroids.

Pregnancy Risk Factor C

Pregnancy Considerations There are no adequate and well-controlled studies in pregnant women. In general, the use of topical corticosteroids during pregnancy is not considered to have significant risk, however, intrauterine growth retardation in the infant has been reported (rare). The use of large amounts or for prolonged periods of time should be avoided.

Lactation Excretion in breast milk unknown/use caution

Breast-Feeding Considerations Systemic corticosteroids are excreted in human milk. It is not known if sufficient quantities of fluocinolone are absorbed following topical or ocular administration to produce detectable amounts in breast milk. Hypertension in the nursing infant has been reported following corticosteroid ointment applied to the nipples. Use with caution.

Adverse Reactions **Topical:** Frequency not defined.

Cardiovascular: Intracranial hypertension (rare)

Central nervous system: Telangiectasia

Dermatologic: Acneiform eruptions, allergic contact dermatitis, atopic dermatitis (secondary), burning, dryness, erythema, folliculitis, irritation, itching, hypertrichosis, hypopigmentation, keratosis pilaris, miliaria, papules, perioral dermatitis, pustules, shiny skin, skin atrophy, striae

Endocrine & metabolic: Cushing's syndrome, HPA axis suppression

Otic: Ear infection

Miscellaneous: Herpes simplex, secondary infection

Ocular implant:

>50%: Ocular: Cataract, intraocular pressure increased, eye pain; procedural complications (eg, cataract fragments, implant migration,

wound complications)

10% to 35%:

Central nervous system: Headache (31%), dizziness (5% to 15%), pain (5% to 15%), fever (5% to 15%)

Dermatologic: Rash (5% to 15%)

Gastrointestinal (5% to 15%): Nausea, vomiting

Neuromuscular & skeletal (5% to 15%): Arthralgia, back pain, limb pain

Ocular: Abnormal sensation, blurred vision, conjunctival hemorrhage, conjunctival hyperemia, dry eye, eye irritation/inflammation, eyelid edema, glaucoma, hypotony, maculopathy, pruritus, ptosis, tearing, visual acuity decrease, vitreous floaters, vitreous hemorrhage

Respiratory (5% to 15%): Cough, influenza, nasopharyngitis, sinusitis, upper respiratory infection

5% to 9%: Ocular: Blepharitis, choroidal detachment, conjunctival edema/chemosis, corneal edema, eye discharge, eye swelling, macular edema, photophobia, photopsia, retinal hemorrhage, visual disturbance, vitreous opacitites

Frequency not specified: Miscellaneous: Secondary infection (bacterial, viral, or fungal)

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Monitoring ParametersHPA axis suppression (ACTH stimulation test, AM plasma cortisol test, urinary free cortisol test); signs of bacterial or fungal infection

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess patient response. Teach patient proper use (according to formulation), side effects/appropriate interventions, and symptoms to report. **Ocular implant:** Regular monitoring of intraocular pressure required. Assess for change in vision.

Patient EducationTopical: For external use only. Inform prescriber if you are allergic to peanuts. Do not use for eyes, mucous membranes, or open wounds. Use exactly as directed and for no longer than the period prescribed. Before using, wash and dry area gently. Apply in a thin layer (may rub in lightly). Apply light dressing (if necessary) to area being treated. Do not use occlusive dressing unless so advised by prescriber. Avoid prolonged or excessive use around sensitive tissues, genital, or rectal areas. Avoid exposing treated area to direct sunlight. Inform prescriber if condition worsens (redness, swelling, irritation, signs of infection, or open sores) or fails to improve after 2 weeks.

Ocular implant: A temporary decrease in visual acuity is expected for 1-4 weeks. Discuss changes in vision with prescriber.

Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, as acetonide: 0.01% (15 g, 60 g); 0.025% (15 g, 60 g)

Synalar®: 0.025% (15 g, 60 g) [DSC]

Implant, intravitreal, as acetonide:

Retisert®: 0.59 mg [enclosed in silicone elastomer]

Oil, as acetonide:

Derma-Smoothe/FS® [body oil]: 0.01% (120 mL) [contains peanut oil]

Derma-Smoothe/FS® [scalp oil]: 0.01% (120 mL) [contains peanut oil; packaged with shower caps]

DermaOtic® [otic drops]: 0.01% (20 mL) [contains peanut oil; packaged with dropper]

Ointment, as acetonide: 0.025% (15 g, 60 g)

Synalar®: 0.025% (15 g, 60 g) [DSC]

Shampoo, as acetonide:

Capex®: 0.01% (120 mL)

Solution, as acetonide: 0.01% (60 mL)

Synalar®: 0.01% (20 mL, 60 mL) [DSC]

Generic AvailableYes: Excludes ocular implant, oil, otic, shampoo

Pricing: U.S. (www.drugstore.com)

Cream (Fluocinolone Acetonide)

0.01% (15): $10.99

0.01% (60): $14.99

0.025% (15): $12.99

0.025% (60): $16.99

Cream (Synalar)

0.025% (60): $91.99

Oil (Derma-Smoothe/FS Body)

0.01% (118.28): $44.84

Oil (DermOtic)

0.01% (20): $37.99

Ointment (Fluocinolone Acetonide)

0.025% (15): $11.99

0.025% (60): $18.99

Ointment (Synalar)

0.025% (60): $94.99

Shampoo (Capex)

0.01% (120): $143.92

Solution (Fluocinolone Acetonide)

0.01% (60): $14.99

Solution (Synalar)

0.01% (60): $96.99

Mechanism of ActionA synthetic fluorinated corticosteroid of low to moderate potency. The mechanism of action for all topical corticosteroids is not well defined, however, is believed to be a combination of anti-inflammatory, antipruritic, and vasoconstrictive properties.

Pharmacodynamics/Kinetics

Absorption:

Topical: Dependent on strength of preparation, amount applied, nature of skin at application site, vehicle, and use of occlusive dressing; increased in areas of skin damage, inflammation, or occlusion

Ocular implant: Systemic absorption is negligible

Duration: Ocular implant: Releases fluocinolone acetonide at an initial rate of 0.6 mcg/day, decreasing over 30 days to a steady-state release rate of 0.3-0.4 mcg/day for 30 months

Distribution:

Topical: Throughout local skin; absorbed drug is distributed rapidly into muscle, liver, skin, intestines, and kidneys

Ocular implant: Aqueous and vitreous humor

Metabolism: Primarily in skin; small amount absorbed into systemic circulation is primarily hepatic to inactive compounds

Excretion: Urine (primarily as glucuronide and sulfate, also as unconjugated products); feces (small amounts)

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFluocinolone Acetonide

References

Reed, BR, “Dermatologic Drugs, Pregnancy, and Lactation. A Conservative Guide,” *Arch Dermatol*, 1997, 133(7):894-8.[PubMed 9236528]

International Brand NamesAdermina (CN); Alvadermo Fuerte (ES); Aplosyn (PH); Cervicum (TH); Cinolon (ID); Coriphate (JP); Cynozet (PH); Dermalar (IL); Dermasolon Gel (ID); Dermoflam (PE); Esacinone (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Fluacet (HR); Flucinar (HU, PL); Flucort (IN, TW); Flulone (AR); Flunolone-V (SG); Fluoderm (ZA); Fluonid (MY); Flupollon (JP); Fluquinol (VE); Flusonlen (TW); Fluvean (JP); Fluzon (JP); Inoderm (ID); Jellin (DE); Localyn (IT); Luci (IN); Radiocin (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Supralan (TH); Synalar (AE, AT, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HN, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, NO, NZ, OM, PK, PT, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TR, TT, TZ, UG, YE, ZA, ZM, ZW); Synalar 25 (PH); Synalar Gamma (LU); Synalar Simple (MX, PE, UY); Syntopic (PH); Tefunote (JP)

Fluocinonide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Fluocinonide may be confused with flunisolide, fluocinolone

Lidex® may be confused with Lasix®, Videx®, Wydase®

Pronunciation(floo oh SIN oh nide)

U.S. Brand NamesLidex-E® [DSC]; Lidex® [DSC]; Vanos™

Canadian Brand NamesLidemol®; Lidex®; Lyderm®; Tiamol®; Topsyn®

Pharmacologic CategoryCorticosteroid, Topical

Use: Labeled IndicationsAnti-inflammatory, antipruritic; treatment of plaque-type psoriasis (up to 10% of body surface area) [high-potency topical corticosteroid]

Use: DentalRelief of inflammatory and pruritic manifestations (high potency topical corticosteroid)

Dosing: Adults

Pruritus and inflammation: Topical (0.05% cream): Apply thin layer to affected area 2-4 times/day depending on the severity of the condition. Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.

Plaque-type psoriasis (Vanos™): Topical (0.1% cream): Apply a thin layer once or twice daily to affected areas (limited to <10% of body surface area). **Note:** Not recommended for use >2 consecutive weeks or >60 g/week total exposure. Discontinue when control is achieved.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Pruritus and inflammation: Refer to adult dosing.

Plaque-type psoriasis: Children ≥12 years: Refer to adult dosing.

ContraindicationsHypersensitivity to fluocinonide or any component of the formulation; viral, fungal, or tubercular skin lesions, herpes simplex

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.

- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Special populations:

- Pediatrics: Use of the 0.1% cream in children <12 years of age is not recommended. Chronic use of corticosteroids in children may interfere with growth and development.

Other warnings/precautions:

- Application site: Lower-strength cream (0.05%) may be used cautiously on face or opposing skin surfaces that may rub or touch (eg, skin folds of the groin, axilla, and breasts); higher-strength (0.1%) should not be used on the face, groin, or axillae.

- Duration of therapy: Use of the 0.1% cream for >2 weeks is not recommended.

Geriatric ConsiderationsDue to age-related changes in skin, limit use of topical glucocorticosteroids.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Cardiovascular: Intracranial hypertension

Dermatologic: Acne, allergic dermatitis, contact dermatitis, dry skin, folliculitis, hypertrichosis, hypopigmentation, maceration of the skin, miliaria, perioral dermatitis, pruritus, skin atrophy, striae, telangiectasia

Endocrine & metabolic: Cushing's syndrome, growth retardation, HPA suppression, hyperglycemia

Local: Burning, irritation

Renal: Glycosuria

Miscellaneous: Secondary infection

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess patient response. Teach patient proper use (according to formulation), side effects/appropriate interventions, and symptoms to report.

Patient EducationFor external use only. Do not use for eyes, mucous membranes, or open wounds. Use exactly as directed and for no longer than the period prescribed. Before using, wash and dry area gently. Apply in a thin layer (may rub in lightly). Apply light dressing (if necessary) to area being treated. Do not use occlusive dressing unless so advised by prescriber. Avoid prolonged or excessive use around sensitive tissues, genital, or rectal areas. Avoid exposing treated area to direct sunlight. Inform prescriber if condition worsens (redness, swelling, irritation, signs of infection, or open sores) or fails to improve. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, anhydrous, emollient: 0.05% (15 g, 30 g, 60 g, 120 g)

Lidex®: 0.05% (15 g, 30 g, 60 g) [DSC]

Cream, aqueous, emollient: 0.05% (15 g, 30 g, 60 g)

Lidex-E®: 0.05% (15 g, 30 g, 60 g) [DSC]

Cream:

Vanos™: 0.1% (30 g, 60 g)

Gel: 0.05% (15 g, 30 g, 60 g)

Lidex®: 0.05% (15 g, 30 g, 60 g) [DSC]

Ointment: 0.05% (15 g, 30 g, 60 g)

Lidex®: 0.05% (15 g, 30 g, 60 g) [DSC]

Solution: 0.05% (20 mL, 60 mL)

Lidex®: 0.05% (60 mL) [contains alcohol 35%] [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Cream (Fluocinonide)

0.05% (15): $11.99

0.05% (30): $12.99

0.05% (60): $14.99

Cream (Fluocinonide-E)

0.05% (15): $13.99

0.05% (30): $15.99

0.05% (60): $17.99

Cream (Vanos)

0.1% (30): $113.37

0.1% (60): $203.14

Gel (Fluocinonide)

0.05% (15): $16.99

0.05% (30): $23.99

0.05% (60): $35.99

Ointment (Fluocinonide)

0.05% (15): $19.99

0.05% (30): $23.99

0.05% (60): $33.99

Solution (Fluocinonide)

0.05% (20): $19.99

0.05% (60): $22.99

Mechanism of ActionFluorinated topical corticosteroid considered to be of high potency. The mechanism of action for all topical corticosteroids is not well defined, however, is felt to be a combination of three important properties: anti-inflammatory activity, immunosuppressive properties, and antiproliferative actions.

Pharmacodynamics/Kinetics

Absorption: Dependent on strength of product, amount applied, and nature of skin at application site; ranges from ~1% in areas of thick stratum corneum (palms, soles, elbows, etc) to 36% in areas of thin stratum corneum (face, eyelids, etc); increased in areas of skin damage, inflammation, or occlusion

Distribution: Throughout local skin; absorbed drug into muscle, liver, skin, intestines, and kidneys

Metabolism: Primarily in skin; small amount absorbed into systemic circulation is primarily hepatic to inactive compounds

Excretion: Urine (primarily as glucuronide and sulfate, also as unconjugated products); feces (small amounts as metabolites)

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

International Brand NamesAcderma (JP); Biscosal (JP); Delipo (JP); Etonalin F (JP); Floremet (PH); Flu-21 (IT); Flubiol (JP); Glycobase (JP); Hakelon (JP); KC-F (JP); Klariderm (ES); Lidemol (PH); Lidex (BE, GR, LU, PH); Medrexim (JP); Metosyn (BB, BF, BJ, BM, BS, BZ, CI, CZ, DK, ET, GB, GH, GM, GN, GY, IE, JM, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, PR, SC, SD, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Murukos F (JP); Novoter (MY); Rauracid (JP); Rufull (JP); Simaron (JP); Solunim (JP); Tohsino (JP); Topsym (AE, AT, BH, CH, CY, DE, EC, EG, IL, IQ, IR, JO, JP, KW, LB, LY, OM, PE, PT, QA, SA, SY, TW, YE); Topsym F (AT); Topsym Polyol (PY); Topsyn (IT, MX); Topsyne (FR, NL); Trappen (JP)

Fluorescein and Benoxinate

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(FLURE e seen & ben OX i nate)
U.S. Brand NamesEyeFlur; Fluress®; Flurox™
Pharmacologic CategoryAnesthetic, Topical; Diagnostic Agent; Ophthalmic Agent
Use: Labeled IndicationsFor use in ophthalmic procedures when a topical disclosing agent is needed along with an anesthetic
Dosing: Adults

Removal of foreign bodies, sutures, or tonometry: Ophthalmic: Instill 1 or 2 drops (single instillations) into each eye before operating

Deep ophthalmic anesthesia: Ophthalmic: Instill 2 drops into each eye every 90 seconds up to 3 doses

Administration: OtherUse of an eye patch is recommended following application.
StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light. May store at room temperature for up to 1 month.
ContraindicationsHypersensitivity to fluorescein, benoxinate, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- CNS stimulation/depression: Rarely, CNS stimulation followed by depression may occur following topical application of local anesthetics.

Disease-related concerns:

- Allergies/asthma: Use with caution in patients with history of hypersensitivity, allergies, or asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: For ophthalmic use only.
- Prolonged use: Delayed wound healing and/or permanent corneal opacification with vision loss may occur with prolonged use (not recommended).

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted. Refer to Fluorescein monograph.
Breast-Feeding ConsiderationsRefer to Fluorescein monograph.
Adverse ReactionsFrequency not defined.

Dermatologic: Contact dermatitis, drying/fissuring of fingertips

Ocular: Conjunctival redness, burning, stinging

> Hyperallergic corneal reaction has also been reported and includes acute, intense and diffuse epithelial keratitis; gray ground glass appearance; sloughing or large areas of necrotic epithelium; corneal filaments; iritis with descemetitis

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic: Fluorescein sodium 0.25% and benoxinate hydrochloride 0.4% (5 mL)

> EyeFlur, Fluress®, Flurox™: Fluorescein sodium 0.25% and benoxinate hydrochloride 0.4% (5 mL)

Generic AvailableYes
Mechanism of ActionFluorescein is a diagnostic dye; benoxinate is a rapid acting anesthetic with short duration.
Related Information

- Fluorescein

Index TermsBenoxinate Hydrochloride and Fluorescein Sodium

Fluorescein

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(FLURE e seen)

U.S. Brand NamesAK-Fluor®; Angiofluor™; Angiofluor™ Lite; Fluorescite®; Fluorets®; Ful-Glo®

Canadian Brand NamesFluorescite®

Pharmacologic CategoryDiagnostic Agent

Use: Labeled Indications

Injection: Diagnostic aid in ophthalmic angiography and angioscopy

Topical: To stain the anterior segment of the eye for procedures (such as fitting contact lenses), disclosing corneal injury, and in applanation tonometry

Dosing: Adults

Diagnostic aid:*Ophthalmic: Strips:* Moisten strip with sterile water, saline or ophthalmic fluid. Touch conjunctiva or fornix with tip of strip until adequately stained. For best results, patient should blink several times after application.

Angiography:*Injection:* 500-750 mg injected rapidly into antecubital vein

> **Note:** Prior to use, an intradermal test dose of 0.05 mL may be used if an allergy is suspected. Evaluate 30-60 minutes following intradermal injection.
>
> *Oral:* 1 g of injection solution has been administered orally in patients with inaccessible veins and when early phases of an angiogram are not needed.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Diagnostic aid: Ophthalmic: Refer to adult dosing.

Angiography: I.V.: 3.5 mg/lb (7.7 mg/kg) injected rapidly into antecubital vein

> **Note:** Prior to use, an intradermal test dose of 0.05 mL may be used if an allergy is suspected. Evaluate 30-60 minutes following intradermal injection.

Dosing: Renal ImpairmentInjection: Dialysis patients: Decrease dose by 50%

Administration: I.V.

Luminescence appears in the eye in 7-30 seconds following injection. A scalp (butterfly) needle attached to a small syringe is suggested for administration. Prior to turning off room light, steps should be taken to ensure the needle has not extravasated. Immediate treatment for anaphylaxis (including epinephrine 1:1000) should be available and premedication or a test dose may be advised in some patients. Maintain venous access following procedure in the event treatment is needed for anaphylaxis. Inject at a rate of 1 mL/second.

Administration: I.V. DetailpH: 8-9.8

Administration: OralThe injection has been administered orally in patients with inaccessible veins. Four grams of sugar or 1 teaspoonful of artificial sweetener may be added to decrease the bitterness of the solution. Luminescence appears in 10-15 minutes.

Storage

Injection: Store at controlled room temperature; protect from freezing. Protect from light.

Ophthalmic strips: Store at controlled room temperature.

ContraindicationsHypersensitivity to fluorescein or any other component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions can occur following injection; immediate treatment (including epinephrine 1:1000) should be available. Premedicating some patients (eg, antihistamines, corticosteroids) may be advisable. An intradermal skin test may be performed prior to use when allergy is suspected.

- Skin/urine discoloration: Following use of the injection, skin may temporarily turn a yellow color and should fade in 6-12 hours. Urine may appear bright yellow for 24-36 hours.

Disease-related concerns:

- Allergies/asthma: Use with caution in patients with history of hypersensitivity, allergies, or asthma.

Special populations:

- Contact lens wearers: Should not be used in patients with soft contact lenses, will cause them to discolor. Flush eyes with saline following use and wait at least 1hour prior to replacing contact lenses.

Dosage form specific issues:

- Injection: For administration via antecubital vein only; not for intrathecal or arterial injection. Avoid extravasation; severe local tissue damage may result.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. Some manufacturers suggest avoiding angiography during the 1st trimester of pregnancy.

LactationExcreted in breast milk/use caution

Breast-Feeding ConsiderationsMilk discoloration may occur following fluorescein injection.

Adverse Reactions

Injection: Frequency not always defined.

Cardiovascular: Cardiac arrest, basilar artery ischemia, hypotension, MI, shock, syncope

Central nervous system: Convulsions, dizziness, headache, pyrexia

Dermatologic: Angioneurotic edema, eczematous dermatitis (delayed), hives, itching, urticaria, pruritus

Gastrointestinal: GI distress, nausea (1% to 15%), taste disturbance, vomiting

Local: Injection site: Dermatitis, thrombophlebitis

Following extravasation: Intense pain at site, dull aching pain in arm of injection, skin sloughing, subcutaneous granuloma, superficial phlebitis, toxic neuritis

Respiratory: Bronchospasm, dyspnea (transient)

Miscellaneous: Anaphylaxis, hypersensitivity reactions

Postmarketing and/or case reports: Hemolytic anemia, localized nerve palsy, pulmonary edema (acute), respiratory arrest, sickle crisis

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersInjection: Monitor for hypersensitivity reactions during procedure and for 30 minutes after.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sodium: 10% (5 mL); 25% (2 mL)

AK-Fluor, Angiofluor™, Angiofluor™ Lite, Fluorescite®: 10% (5 mL); 25% (2 mL)

Strip, ophthalmic, as sodium: 1 mg

Fluorets®: 1 mg (100)

Ful-Glo®: 0.6 mg (300); 1 mg (300)

Generic AvailableYes

Mechanism of ActionYellow, water soluble, dibasic acid xanthine dye which penetrates any break in epithelial barrier to permit rapid penetration

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFluorescein Sodium; Sodium Fluorescein; Soluble Fluorescein

References

Hara T, Inami M, and Hara T. "Efficacy and Safety of Fluorescein Angiography With Orally Administered Sodium Fluorescein," *Am J Ophthalmol*, 1998, 126(4):560-4.[PubMed 9780101]

Kwan AS, Barry C, McAllister IL, et al, "Fluorescein Angiography and Adverse Drug ReactionsRevisited: The Lions Eye Experience," *Clin Experiment Ophthalmol*, 2006, 34(1):33-8.[PubMed 16451256]

International Brand NamesCendo Fluorescein (ID); Colircusi Fluoresceina (ES); Colirio Ocul Fluorescein (ES); Fluocyne (FR); Fluoftal (AT); Fluor-I-Strip (NL); Fluoralfa (IT); Fluore Stain Strips (IN); Fluorecite (NO); Fluorescein (DE, HR); Fluoresceina (BR); Fluoresceina Oculos (ES); Fluoresceine (IL, LU, PL); Fluoresceine Ophtadose (BE); Fluoresceine SDU Faure (CH); Fluoresceinnatrium (SE); Fluorescite (AE, AR, AU, BF, BH, BJ, CI, CY, CZ, EC, EE, EG, ET, GH, GM, GN, HK, HN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PL, QA, SA, SC, SD, SL, SN, SY, TH, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Fluorets (GB, HK, IE, MY); Ful-Glo (AU); Minims Fluorescein Sodium (FI, GB); Minims Fluoresceine (BE); Ophthfluorstrip (PK); Optifluor Diba (MX)

Fluoride

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Luride® may be confused with Lortab®

Phos-Flur® may be confused with PhosLo®

Thera-Flur-N® may be confused with Thera-Flu®

International issues:

Fluorex® [France] may be confused with Flarex® which is a brand name for fluorometholone in the U.S.

Pronunciation(FLOR ide)

U.S. Brand NamesACT® Plus [OTC]; ACT® x2™ [OTC]; ACT® [OTC]; CaviRinse™; ControlRx®; Denta 5000 Plus; DentaGel; EtheDent™; Fluor-A-Day; Fluorigard® [OTC]; Fluorinse®; Flura-Drops®; Gel-Kam® Rinse; Gel-Kam® [OTC]; Just for Kids™ [OTC]; Lozi-Flur™; Luride® Lozi-Tab®; Luride® [DSC]; NeutraCare®; NeutraGard® Advanced; NeutraGard® Plus; NeutraGard® [OTC]; Omnii Gel™ [OTC]; PerioMed™; Pharmaflur® 1.1 [DSC]; Pharmaflur® [DSC]; Phos-Flur®; Phos-Flur® Rinse [OTC]; PreviDent®; PreviDent® 5000 Plus™; StanGard®; StanGard® Perio; Stop®; Thera-Flur-N® [DSC]

Canadian Brand NamesFluor-A-Day

Pharmacologic Category[Nutritional Supplement]

Use: Labeled IndicationsPrevention of dental caries

Use: DentalPrevention of dental caries

Dosing: AdultsPrevention of dental caries: Oral:

The recommended daily dose of oral fluoride supplement (mg), based on fluoride ion content (ppm) in drinking water (2.2 mg of sodium fluoride is equivalent to 1 mg of fluoride ion): See table.

Fluoride Ion

Fluoride Content of Drinking Water	**Daily Dose, Oral (mg)**
<0.3 ppm	
Birth - 6 mo	None
6 mo - 3 y	0.25
3-6 y	0.5
6-16 y	1
0.3-0.6 ppm	
Birth - 6 mo	None
6 mo - 3 y	None
3-6 y	0.25
6-16 y	0.5
Table from: Recommended dosage schedule of The American Dental Association, The American Academy of Pediatric Dentistry, and The American Academy of	

Pediatrics

Cream: Brush teeth with cream once daily regardless of fluoride content of drinking water.

Dental rinse or gel: 10 mL rinse or apply to teeth daily and spit after brushing

Product-specific dosing:

PreviDent® rinse: Once weekly, rinse 10 mL vigorously around and between teeth for 1 minute, then spit; this should be done preferably at bedtime, after thoroughly brushing teeth; for maximum benefit, do not eat, drink, or rinse mouth for at least 30 minutes after treatment; do not swallow

Fluorinse®: Once weekly, vigorously swish 5-10 mL in mouth for 1 minute, then spit

Lozenge (Lozi-Flur™): One lozenge daily regardless of fluoride content of drinking water

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricPrevention of dental caries: Oral:

Cream: Children ≥6 years: Refer to adult dosing.

Dental rinse or gel: Children 6-12 years: 5-10 mL rinse or apply to teeth and spit daily after brushing

Fluorinse®, PreviDent® rinse: Children >6 years: Refer to adult dosing.

Dietary ConsiderationsDo not administer with milk; do **not** allow eating or drinking for 30 minutes after use.
StorageStore in tight plastic containers (not glass).
ContraindicationsHypersensitivity to fluoride, tartrazine, or any component of the formulation; when fluoride content of drinking water exceeds 0.7 ppm; low sodium or sodium-free diets; do not use 1 mg tablets in children <3 years of age or when drinking water fluoride content is ≥0.3 ppm; do not use 1 mg/5 mL rinse (as supplement) in children <6 years of age
Warnings/Precautions

Concerns related to adverse effects:

- Dental fluorosis/osseous: Prolonged ingestion with excessive doses may result in dental fluorosis and osseous changes; do **not** exceed recommended dosage.

Dosage form specific issues:

- Tartrazine: Some products contain tartrazine.

Geriatric ConsiderationsPostmenopausal women taking high doses of sodium fluoride have increased their bone density in the lumbar spine by 35% with a smaller increase in the femoral neck. In spite of these increases, the overall rate of vertebral fracture did not decline significantly while the rate of hip fracture increased. The results of a randomized, placebo-controlled trial using an investigational slow-release fluoride formulation at a lower dose (50 mg/day) are encouraging. Patients who received fluoride for 1 year or more had a lower vertebral fracture rate and substantial increase in L2-L4 bone mass and femoral neck bone density compared to placebo. Both groups took calcium. At the present time, restricted to investigational protocols.
Pregnancy Risk FactorC
Adverse Reactions<1%: Rash, nausea, vomiting; products containing stannous fluoride may stain the teeth
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, oral, as sodium [toothpaste]: 1.1% (51 g) [fluoride 2.5 mg/dose]

Denta 5000 Plus: 1.1% (51 g) [fluoride 2.5 mg/dose; spearmint flavor]

EtheDent™: 1.1% (51 g) [fluoride 2.5 mg/dose]

Gel-drops, as sodium fluoride:

Thera-Flur-N®: 1.1% (24 mL) [fluoride 0.5%; neutral pH; no artificial color or flavor] [DSC]

Gel, topical, as acidulated phosphate fluoride:

Phos-Flur®: 1.1% (60 g) [fluoride 0.5%; cherry and mint flavors]

Gel, topical, as sodium fluoride: 1.1% (56 g) [fluoride 2 mg/dose]

DentaGel, EtheDent™: 1.1% (56 g) [fluoride 2 mg/dose; fresh mint flavor]

NeutraCare®: 1.1% (60 g) [neutral pH; grape and mint flavors]

NeutraGard® Advanced: 1.1% (60 g) [cinnamon and mint flavors]

PreviDent®: 1.1% (60 g) [fluoride 2 mg/dose; berry and mint flavors]

Gel, topical, as stannous fluoride:

Gel-Kam®: 0.4% (129 g) [cinnamon, fruit/berry, and mint flavors]

- Just for Kids™: 0.4% (122 g) [bubble gum, fruit punch, and grapey grape flavors]
- Omnii Gel™: 0.4% (122 g) [cinnamon, grape, natural, mint, and raspberry flavors]
- StanGard®: 0.4% (122 g) [bubble gum, cherry, mint, and raspberry flavors]
- Stop®: 0.4% (120 g) [bubble gum, cinnamon, grape, and mint flavors]

Lozenge, as sodium:

- Lozi-Flur™: 2.21 mg [fluoride 1 mg; cherry flavor]

Paste, oral, as sodium [toothpaste]:

- ControlRx®: 1.1% (56 g) [vanilla mint flavor]

Solution, oral drops, as sodium: 1.1 mg/mL (50 mL) [fluoride 0.5 mg/mL]

- Flura-Drops®: 0.55 mg/drop (24 mL) [fluoride 0.25 mg/drop; dye free, sugar free]
- Luride®: 1.1 mg/mL (50 mL) [fluoride 0.5 mg/mL; sugar free] [DSC]

Solution, oral rinse, as sodium:

- ACT®: 0.05% (530 mL) [fluoride 0.02%; bubble gum, cinnamon (contains tartrazine), and mint flavors]
- ACT® Plus: 0.05% (530 mL) [fluoride 0.02%; alcohol free; icy cool mint flavor]
- ACT® x2™: 0.5% (530 mL) [fluoride 0.02%; contains alcohol 11%; icy cool mint and spearmint flavors]
- CaviRinse™: 0.2% (240 mL) [mint flavor]
- Fluorigard®: 0.05% (480 mL) [alcohol free, sugar free; contains sodium benzoate and tartrazine; mint flavor]
- Fluorinse®: 0.2% (480 mL) [alcohol free; cinnamon and mint flavors]
- NeutraGard®: 0.05% (480 mL) [neutral pH; mint and tropical blast flavors]
- NeutraGard® Plus: 0.2% (480 mL) [neutral pH; mint and tropical blast flavors]
- Phos-Flur®: 0.44% (500 mL) [bubble gum, cherry, grape, and mint flavors]
- PreviDent®: 0.2% (250 mL) [contains alcohol; mint flavor]

Solution, oral rinse concentrate, as stannous fluoride:

- Gel-Kam®: 0.63% (300 mL) [fluoride 0.1%/dose; cinnamon and mint flavors]
- PerioMed™: 0.63% (284 mL) [fluoride 7 mg/30 mL; alcohol free; cinnamon, mint and tropical fruit flavors]
- StanGard® Perio: 0.63% (284 mL) [mint flavor]

Tablet, chewable, as sodium: 0.5 mg [fluoride 0.25 mg]; 1.1 mg [fluoride 0.5 mg]; 2.2 mg [fluoride 1 mg]

- EtheDent™:
  - 0.55 mg [fluoride 0.25 mg; sugar free; contains aspartame; vanilla flavor]
  - 1.1 mg [fluoride 0.5 mg; sugar free; contains aspartame; grape flavor]
  - 2.2 mg [fluoride 1 mg; sugar free; contains aspartame; cherry flavor]
- Fluor-A-Day:
  - 0.56 mg [fluoride 0.25 mg; raspberry flavor]
  - 1.1 mg [fluoride 0.5 mg; raspberry flavor]
  - 2.21 mg [fluoride 1 mg; raspberry flavor]
- Luride® Lozi-Tab®:
  - 0.55 mg [fluoride 0.25 mg; sugar free; vanilla flavor]
  - 1.1 mg [fluoride 0.5 mg; sugar free; grape flavor]
  - 2.2 mg [fluoride 1 mg; sugar free; cherry flavor] [DSC]
- Pharmaflur®: 2.2 mg [fluoride 1 mg; dye free, sugar free; cherry flavor] [DSC]
- Pharmaflur® 1.1: 1.1 mg [fluoride 0.5 mg; dye free, sugar free; grape flavor] [DSC]

Generic AvailableYes: Excludes lozenge, gel drops

Pricing: U.S. (www.drugstore.com)

Chewable (EtheDent)

- 0.55 (0.25 F) mg (120): $13.99
- 1.1 (0.5 F) mg (100): $12.99
- 2.2 (1 F) mg (100): $12.99

Chewable (Fluor-a-day)

- 0.55 (0.25 F) mg (30): $11.99
- 2.2 (1 F) mg (100): $14.99

Chewable (Fluoride)

- 1.1 (0.5 F) mg (30): $11.99
- 2.2 (1 F) mg (100): $14.99

Chewable (Luride)

- 0.55 (0.25 F) mg (30): $12.99
- 1.1 (0.5 F) mg (120): $17.86
- 2.2 (1 F) mg (100): $15.99

Chewable (Sodium Fluoride)

- 2.2 (1 F) mg (100): $15.99

Concentrate (Gel-Kam Oral Care Rinse)

- 0.63% (283): $25.99

Cream (PreviDent 5000 Plus)

- 1.1% (51): $25.99

Cream (SF 5000 Plus)

- 1.1% (51): $14.99

Gel (Gel-Kam)

- 0.4% (122): $24.99

Gel (Phos-Flur)

- 1.1% (51): $19.99

Gel (PreviDent)

- 1.1% (56): $19.99

Solution (Flura-Drops)

- 0.55 (0.25 F) mg/drop (24): $12.99

Solution (Pediaflor)

- 1.1 (0.5 F) mg/mL (50): $17.99

Solution (PreviDent)

- 0.2% (473): $20.01

Solution (Sodium Fluoride)

- 1.1 (0.5 F) mg/mL (50): $15.99

Mechanism of ActionPromotes remineralization of decalcified enamel; inhibits the cariogenic microbial process in dental plaque; increases tooth resistance to acid dissolution

Pharmacodynamics/Kinetics

Absorption: Oral: Rapid and complete; sodium fluoride; other soluble fluoride salts; calcium, iron, or magnesium may delay absorption

Distribution: 50% of fluoride is deposited in teeth and bone after ingestion; topical application works superficially on enamel and plaque; crosses placenta; enters breast milk

Excretion: Urine and feces

Dental Health Professional ConsiderationsNeutral pH fluoride preparations are preferred in patients with oral mucositis to reduce tissue irritation; long-term use of acidulated fluorides has been associated with enamel demineralization and damage to porcelain crowns

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Products containing stannous fluoride may stain teeth. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAcidulated Phosphate Fluoride; Sodium Fluoride; Stannous Fluoride

References

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Cummings CC and McIvor ME, “Fluoride-Induced Hyperkalemia: The Role of Ca(2+)-Dependent K^+ Channels,” *Am J Emerg Med*, 1988, 6(1):1-3. [PubMed 2446637]

Fisher K, Picciotti M, Henretig F, et al, “Fluoride (F1) Toxicity From a Topical Dental Care Product (TDCP),” *Vet Hum Toxicol*, 1991, 33:365.

McIvor ME, “Acute Fluoride Toxicity. Pathophysiology and Management,” *Drug Saf*, 1990, 5(2):79-85. [PubMed 2182050]

Pak CYS, Sakhaee K, Adams-Huet B, et al, “Treatment of Postmenopausal Osteoporosis With Slow-Release Sodium Fluoride: Final Report of a Randomized Controlled Trial,” *Ann Intern Med*, 1995, 123(6):401-8. [PubMed 7639438]

Pitt P and Berry H, “Fluoride Treatment in Osteoporosis,” *Postgrad Med J*, 1991, 67(786):323-6. [PubMed 2068022]

Riggs BL, Hodgson SF, O'Fallon WM, et al, “Effect of Fluoride Treatment on the Fracture Rate in Postmenopausal Women With Osteoporosis,” *N Engl J Med*, 1990, 322(12):802-9. [PubMed 2407957]

Schuman AJ, “How Much Fluoride Is Too Much? The New Guidelines,” *Contemp Pediatr*, 1995, 12(6):65-74. [PubMed 10161198]

U.S. Department of Health and Human Services, “Toxicological Profile for Fluorides, Hydrogen Fluoride, and Fluorine (F) TP-91/17,” Agency for Toxic Substances and Diseases Registry, 1993.

International Brand NamesAFI-Fluor (NO); Arthrofluor (HU); Biogam F (BE, CH); Bobrusie (PL); Carident (NO); Dentalfluoro (IT); Dentan (SE); Dentocar (HU); Duraphat (AT, DE, DK, FI, NO, PL, SE); Endekay (GB); Endekay Fluotabs (GB); F-Tabs (GB); Floam (PL); Floran (AU); Fluden (IL); Fludent (FI, NO, SE); Fluocaril (CH); Fluodel (BR); Fluodont (AT); Fluodontyl (BE, ES, FR, LU); Fluogum (FR, PL); Fluonatril (HR); Fluoplexe (FR); Fluor (BE); Fluor Crinex (FR); Fluor Kin (ES); Fluor Lacer (ES); Fluor Microsol (FR); Fluor Oligosol (FR); Fluor Unicophar (BE); Fluor-a-Day (GB); Fluor-Retard (NO); Fluor-S.M.B. (BE); Fluordent (AR); Fluorette (DK, FI, NO, SE); Fluoretten (DE); Fluorex (FR); Fluorid Gel DENTSPLY DeTrey (DE); Fluorigard (GB); Fluorilette (FI); Fluorogel (AR); Fluoros (DE); Fluortabletjes (NL); Fluorvitin (IT); Fluossen (CZ, PL); Fluotrat (BR); Flura (AU); Flurexal (CH); Fluvium (IL); Flux (NO); Gammadyn F (BE); Koreberon (CZ, DE, HU); Leodent (AR); Les-CAV (GB); Medusit (PT); NAF (AR, HR); Nafluor (AR); NaFril (DE); Natrium Fluoratum (PL); Natriumfluorid Baer (AT, DE, LU); Odontocromil (ES); Oligogranul Fluor (FR); Oligosol F (BE, CH); Oligostim Fluor (FR); Oratol F (PT); Ospur F (DE); Ossin (CH, CZ, DE); Ossofluor (CH); Osteofluor (AT, FR); Osteopor-F (CH); Otofluor (IN); Pharma-Fluor (NL); Procal (BE, LU, NL); Protectfluor (NL); Rumafluor (FR); Sanogyl (FR); Sensifluor (IT); Sodio Fluoruro (IT); Vitamon Fluor (BE); Zymafluor (AT, BE, CH, DE, ES, FR, HU, IT, LU, NL, PL)

Fluorometholone

Lexi-Drugs Online

English

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Medication Safety Issues

International issues:

Flarex® may be confused with Flurets® which is a brand name for sodium fluoride in Australia

Flarex® may be confused with Fluarix® which is a brand name for influenza virus vaccine in the U.S. and in numerous international markets

Flarex® may be confused with Fluorex® which is a brand name for sodium fluoride in France

Fluor-Op® may be confused with Fluoron® which is a brand name for fluorine in Canada

Pronunciation(flure oh METH oh lone)

U.S. Brand NamesFlarex®; FML®; FML® Forte

Canadian Brand NamesFlarex®; FML Forte®; FML®; PMS-Fluorometholone

Pharmacologic CategoryCorticosteroid, Ophthalmic

Use: Labeled IndicationsTreatment of steroid-responsive inflammatory conditions of the eye

Dosing: AdultsOcular inflammation: Ophthalmic:

Ointment (FML®): Apply small amount (~$^{1}/_{2}$ inch ribbon) to conjunctival sac 1-3 times/day; may increase application to every 4 hours during the initial 24-48 hours

Suspension:

FML®: Instill 1 drop into conjunctival sac 2-4 times/day; may instill 1 drop every 4 hours during initial 24-48 hours

FML® Forte: Instill 1 drop into conjunctival sac 2-4 times/day

Flarex®: Instill 1-2 drops into conjunctival sac 4 times/day; may increase application to 2 drops every 2 hours during initial 24-48 hours. Consult prescriber if no improvement after 14 days.

Note: Re-evaluate therapy if improvement is not seen within 2 days; use care not to discontinue prematurely; in chronic conditions, gradually decrease dosing frequency prior to discontinuing treatment.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren >2 years: Refer to adult dosing.

Administration: OtherContact lenses should be removed before instillation. Shake suspension well before use.

Storage

Suspension:

Flarex®, FML®: Store at room temperature of 2°C to 25°C (36°F to 77°F); do not freeze.

FML® Forte: Store at ≤25°C (77°F); do not freeze.

Ointment: FML®: Store at ≤25°C (77°F).

ContraindicationsHypersensitivity to fluorometholone or any component of the formulation; viral diseases of the cornea and conjunctiva (including epithelial herpes simplex keratitis, vaccinia, and varicella); mycobacterial or fungal infections of the eye; untreated eye infections which may be masked/enhanced by a steroid

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Exacerbation of viral infections: May exacerbate severity of viral infections. Use caution in patients with history of herpes simplex. Re-evaluate after 2 days if symptoms have not improved.
- Ocular effects: Prolonged use may result in glaucoma and injury to the optic nerve and lead to or mask secondary ocular infections (eg, bacterial, viral, fungal). Visual defects in acuity and field of vision may occur. Posterior subcapsular cataracts may form after long-term use. Use with caution in presence of glaucoma (steroids increase intraocular pressure). Perforation may occur with topical steroids in diseases which thin the cornea or sclera. Steroid use may delay healing after cataract surgery. Intraocular pressure should be monitored if this product is used >10 days.

Special populations:

- Contact lens wearers: Some products contain benzalkonium chloride which may be adsorbed by contact lenses; remove contacts prior to administration and wait 15 minutes before reinserting.

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Pregnancy Risk FactorC
Pregnancy ConsiderationsThe extent of systemic absorption is not known. Use with caution in pregnant women.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Gastrointestinal: Taste perversion

Ocular: Anterior uveitis, bleb formation increased, blurred vision, burning, cataract formation, conjunctival hyperemia, conjunctivitis, corneal ulcers, delayed wound healing, glaucoma, glaucoma with optic nerve damage, intraocular pressure increased, irritation, keratitis, mydriasis, perforation of the globe, ptosis, secondary ocular infection (bacterial, fungal, viral), stinging, visual acuity and field defects

Miscellaneous: Allergic reaction, systemic hypercorticoidism (rare)

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Monitoring ParametersIntraocular pressure in patients with glaucoma or when used for ≥10 days; presence of secondary infections (including the development of fungal infections and exacerbation of viral infections)
Nursing: Physical Assessment/MonitoringMonitor intraocular pressure in patients with glaucoma or when used for ≥10 days; monitor for presence of secondary infections (including the development of fungal infections and exacerbation of viral infections). Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Patient EducationFor ophthalmic use only. Apply prescribed amount as often as directed. Wash hands before using. Wipe away excess from skin around eye. Do not use any other eye preparation for at least 10 minutes. Do not touch tip of applicator to eye or any other surface. Do not share medication with anyone else. May cause sensitivity to bright light (dark glasses may help); temporary stinging or blurred vision may occur. Do not wear contacts during administration and for 15 minutes after. Inform prescriber if you experience eye pain, redness, burning, watering, dryness, double vision, puffiness around eye, vision changes, or other adverse eye response; worsening of condition or lack of improvement. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Ointment: Gently squeeze the tube to apply to inside of lower lid. Close eye for 1-2 minutes and roll eyeball in all directions.

Suspension: Shake well before using. Tilt head back and look upward. Gently pull down lower lid and put drop(s) in inner corner of eye. Close eye and roll eyeball in all directions. Do not blink for 30 seconds. Apply gentle pressure to inner corner of eye for 30 seconds.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Ointment, ophthalmic, as base:

FML®: 0.1% (3.5 g)

Suspension, ophthalmic, as base: 0.1% (5 mL, 10 mL, 15 mL)

FML®: 0.1% (5 mL, 10 mL, 15 mL) [contains benzalkonium chloride]

FML® Forte: 0.25% (2 mL, 5 mL, 10 mL, 15 mL) [contains benzalkonium chloride]

Suspension, ophthalmic, as acetate:

Flarex®: 0.1% (5 mL) [contains benzalkonium chloride]

Generic AvailableYes: Suspension (as base)
Pricing: U.S. (www.drugstore.com)

Ointment (FML S.O.P.)

0.1% (3.5): $39.99

Suspension (Flarex)

0.1% (5): $40.99

Suspension (FML Forte)

0.25% (5): $25.99

0.25% (10): $41.99

0.25% (15): $56.99

Suspension (FML Liquifilm)

0.1% (5): $35.99

0.1% (10): $51.99

0.1% (15): $70.99

Mechanism of Action Decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability

Pharmacodynamics/Kinetics Absorption: Into aqueous humor with slight systemic absorption

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

International Brand Names Aflarex (CN, CO, EC, PE, VE); Efflumidex (BG, CZ, DE, HN, HR, HU, RU); F.M.L. (PE, UY); Flarex (AR, AT, BF, BG, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, PL, PY, SC, SD, SL, SN, TN, TZ, UG, ZM, ZW); Florom (PK); Flosef (IN); Flu-Base (JP); Fluaton (IT); Flucon (AU, BE, CH, CZ, FR, GR, HN, HU, KP, LU, PL, PT, TH, TW); Flulon (PH); Flumetholon (HK, JP, TW); Flumetol NF Ofteno (MX); Flumex (CO, EC, PA, SV); Flumexo (BR); FluOph (TH); Fluoron (KP); Flurolon (DK, NO); FML (AE, AR, BH, CL, CR, CY, EG, ES, GB, GR, GT, HK, IE, IL, IQ, IR, JO, KW, LB, LY, MY, OM, PH, QA, SA, SY, TH, YE, ZA); FML Damla (TR); FML Forte (KP); FML Liquifilm (CH, FI, LU, NL); Fuluson (KP); Fumelon (KP); Isopto Flucon (ES); Okilon (JP); Ursnon (JP)

Fluorouracil + Carboplatin

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Head and Neck Cancer]

Regimen UseHead and neck cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Fluorouracil: I.V.: 600 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 2400 mg/m^2]

Carboplatin: I.V.: 70 mg/m^2/day days 1 to 4

[total dose/cycle = 280 mg/m^2]

Repeat cycle every 3 weeks for 3 cycles

Variation 2:

Carboplatin: I.V.: 400 mg/m^2 day 1

[total dose/cycle = 400 mg/m^2]

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 4000 mg/m^2]

Repeat cycle every 28 days

References

Variation 1:

Denis F, Garaud P, Bardet E, et al, “Final Results of the 94-01 French Head and Neck Oncology and Radiotherapy Group Randomized Trial Comparing Radiotherapy Alone With Concomitant Radiochemotherapy in Advanced-Stage Oropharynx Carcinoma,” *J Clin Oncol*, 2004, 22(1):69-76. [PubMed 14657228]

Variation 2:

Gregoire V, Beauduin M, Humblet Y, et al, “A Phase I-II Trial of Induction Chemotherapy With Carboplatin and Fluorouracil in Locally Advanced Head and Neck Squamous Cell Carcinoma: A Report From the UCL-Oncology Group, Belgium,” *J Clin Oncol*, 1991, 9(8):1385-92. [PubMed 2072142]

Fluorouracil-Leucovorin-Irinotecan (Saltz Regimen)

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Colorectal Cancer

Regimen UseColorectal cancer

Index TermsFU-LV-CPT-11 (Saltz Regimen); Irinotecan-Fluorouracil-Leucovorin (Saltz Regimen); Saltz Regimen

Regimen

Fluorouracil: I.V.: 500 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 2000 mg/m^2]

Leucovorin: I.V.: 20 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 80 mg/m^2]

Irinotecan: I.V.: 125 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 500 mg/m^2]

Repeat cycle every 42 days

References

Saltz LB, Cox JV, Blanke C, et al, âIrinotecan Plus Fluorouracil and Leucovorin for Metastatic Colorectal Cancer, Irinotecan Study Group,â *N Engl J Med*, 2000, 343(13):905-14.[PubMed 11006366]

Fluorouracil-Leucovorin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Colorectal Cancer

Regimen UseColorectal cancer

Index TermsF-CL; FU-LV; FU/Leucovorin

RegimenNOTE: Multiple variations are listed below.

Variation 1 (Mayo Regimen):

Fluorouracil: I.V.: 425 mg/m^2/day days 1 to 5

[total dose/cycle = 2125 mg/m^2]

Leucovorin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 28 days

Variation 2:

Fluorouracil: I.V.: 400 mg/m^2/day days 1 to 5

[total dose/cycle = 2000 mg/m^2]

Leucovorin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 28 days

Variation 3:

Fluorouracil: I.V.: 500 mg/m^2 day 1

[total dose/cycle = 500 mg/m^2]

Leucovorin: I.V.: 20 mg/m^2 (2-hour infusion) day 1

[total dose/cycle = 20 mg/m^2]

or 500 mg/m^2 (2-hour infusion) day 1

[total dose/cycle = 500 mg/m^2]

Repeat cycle weekly

Variation 4:

Fluorouracil: I.V.: 600 mg/m^2 weekly for 6 weeks

[total dose/cycle = 3600 mg/m^2]

Leucovorin: I.V.: 500 mg/m^2 (3-hour infusion) weekly for 6 weeks

[total dose/cycle = 3000 mg/m^2]

Repeat cycle every 8 weeks

Variation 5:

Fluorouracil: I.V.: 600 mg/m^2 weekly for 6 weeks

[total dose/cycle = 3600 mg/m^2]

Leucovorin: I.V.: 500 mg/m^2 weekly for 6 weeks

[total dose/cycle = 3000 mg/m^2]

Repeat cycle every 8 weeks

Variation 6:

Fluorouracil: I.V.: 600 mg/m^2 weekly

[total dose/cycle = 600 mg/m^2]

Leucovorin: I.V.: 500 mg/m^2 (2-hour infusion) weekly

[total dose/cycle = 500 mg/m^2]

Repeat cycle weekly

Variation 7:

Fluorouracil: I.V.: 2600 mg/m^2 continuous infusion day 1

[total dose/cycle = 2600 mg/m^2]

Leucovorin: I.V.: 500 mg/m^2 continuous infusion day 1

[total dose/cycle = 500 mg/m^2]

Repeat cycle weekly

Variation 8:

Fluorouracil: I.V.: 2600 mg/m^2 continuous infusion day 1

[total dose/cycle = 2600 mg/m^2]

Leucovorin: I.V.: 300 mg/m^2 (maximum 500 mg) continuous infusion day 1

[total dose/cycle = 300 mg/m^2; maximum 500 mg]

Repeat cycle weekly

Variation 9:

Fluorouracil: I.V.: 2600 mg/m^2 continuous infusion once weekly for 6 weeks

[total dose/cycle = 15,600 mg/m^2]

Leucovorin: I.V.: 500 mg/m^2 weekly for 6 weeks

[total dose/cycle = 3000 mg/m^2]

Repeat cycle every 8 weeks

Variation 10:

Fluorouracil: I.V.: 2300 mg/m^2 continuous infusion day 1

[total dose/cycle = 2300 mg/m^2]

Leucovorin: I.V.: 50 mg/m^2 continuous infusion day 1

[total dose/cycle = 50 mg/m^2]

Repeat cycle weekly

Variation 11:

Fluorouracil: I.V.: 200 mg/m^2/day continuous infusion days 1 to 14

[total dose/cycle = 2800 mg/m^2]

Leucovorin: I.V.: 5 mg/m^2/day continuous infusion days 1 to 14

[total dose/cycle = 70 mg/m^2]

Repeat cycle every 28 days

Variation 12:

Cycle 1:

Fluorouracil: I.V.: 200 mg/m^2/day continuous infusion for 4 weeks

[total dose/cycle = 5600 mg/m^2]

Leucovorin: I.V.: 20 mg/m^2/day days 1, 8, 15, 22

[total dose/cycle = 80 mg/m^2]

Treatment cycle is 6 weeks

Subsequent cycles (starting week 7):

Fluorouracil: 200 mg/m^2 continuous infusion days 1 to 21

[total dose/cycle = 4200 mg/m^2]

Leucovorin: I.V.: 20 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 4 weeks

References

Variation 1:

Poon MA, O'Connell MJ, Moertel CG, et al, "Biochemical Modulation of Fluorouracil: Evidence of Significant Improvement of Survival and Quality of Life in Patients With Advanced Colorectal Carcinoma," *J Clin Oncol*, 1989, 7(10):1407-18. [PubMed 2476530]

Variation 2:

Borner MM, Castiglione M, Bacchi M, et al "The Impact of Adding Low-Dose Leucovorin to Monthly 5-Fluorouracil in Advanced Colorectal Carcinoma: Results of a Phase III Trial. Swiss Group for Clinical Cancer Research (SAKK)," *Ann Oncol*, 1998, 9(5):535-41. [PubMed 9653495]

Variation 3:

Jager E, Heike M, Bernhard H, et al, "Weekly High-Dose Leucovorin Versus Low-Dose Leucovorin Combined With Fluorouracil in Advanced Colorectal Cancer: Results of a Randomized Multicenter Trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1," *J Clin Oncol*, 1996, 14(8):2274-9. [PubMed 8708717]

Variation 4:

Leichman CG, Fleming TR, Muggia FM, et al, "Phase II Study of Fluorouracil and Its Modulation in Advanced Colorectal Cancer: A Southwest Oncology Group Study," *J Clin Oncol*, 1995, 13(6):1303-11. [PubMed 7751875]

Variation 5:

Buroker TR, O'Connell MJ, Wieand HS, et al, "Randomized Comparison of Two Schedules of Fluorouracil and Leucovorin in the Treatment of Advanced Colorectal Cancer," *J Clin Oncol*, 1994, 12(1):14-20. [PubMed 7677801]

Variation 6:

Nobile MT, Rosso R, Sertoli MR, et al, "Randomised Comparison of Weekly Bolus 5-Fluorouracil With or Without Leucovorin in Metastatic Colorectal Carcinoma," *Eur J Cancer*, 1992, 28A(11):1823-7. [PubMed 1389519]

Variation 7:

Ardalan B, Chua L, Tian EM, et al, "A Phase II Study of Weekly 24-Hour Infusion With High-Dose Fluorouracil With Leucovorin in Colorectal Carcinoma," *J Clin Oncol*, 1991, 9(4):625-30. [PubMed 2066758]

Variation 8:

Yeh KH, Cheng AL, Lin MT, et al, "A Phase II Study of Weekly 24-Hour Infusion of High-Dose 5-Fluorouracil and Leucovorin (HDFL) in the Treatment of Recurrent or Metastatic Colorectal Cancers," *Anticancer Res*, 1997, 17(5B):3867-72. [PubMed 9427794]

Variation 9:

Kohne CH, Schoffski P, Wilke H, et al, "Effective Biomodulation by Leucovorin of High-Dose Infusion Fluorouracil Given as a Weekly 24-Hour Infusion: Results of a Randomized Trial in Patients With Advanced Colorectal Cancer," *J Clin Oncol*, 1998, 16(2):418-26. [PubMed 9469324]

Variation 10:

Haas NB, Schilder RJ, Nash S, et al, "A Phase II Trial of Weekly Infusional 5-Fluorouracil in Combination With Low-Dose Leucovorin in Patients With Advanced Colorectal Cancer," *Invest New Drugs*, 1995, 13(3):229-33. [PubMed 8729951]

Variation 11:

Falcone A, Allegrini G, Lencioni M, et al, "Protracted Continuous Infusion of 5-Fluorouracil and Low-Dose Leucovorin in Patients With Metastatic Colorectal Cancer Resistant to 5-Fluorouracil Bolus-Based Chemotherapy: A Phase II Study," *Cancer Chemother Pharmacol*, 1999, 44(2):159-63. [PubMed 10412951]

Variation 12:

Leichman CG, Leichman L, Spears CP, et al, "Prolonged Continuous Infusion of Fluorouracil With Weekly Bolus Leucovorin: A Phase II Study in Patients With Disseminated Colorectal Cancer," *J Natl Cancer Inst*, 1993, 85(1):41-4.[PubMed 8416255]

Fluorouracil

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Carac® may be confused with Kuric™

Fluorouracil may be confused with flucytosine

Efudex® may be confused with Efidac (Efidac 24®), Eurax®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

International issues:

Carac® may be confused with Carace® which is a brand name for lisinopril in Ireland and Great Britain

Pronunciation(flure oh YOOR a sil)

U.S. Brand NamesAdrucil®; Carac®; Efudex®; Fluoroplex®; Fluorouracil®

Canadian Brand NamesEfudex®

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite (Pyrimidine Analog)

Use: Labeled IndicationsTreatment of carcinomas of the breast, colon, head and neck, pancreas, rectum, or stomach; topically for the management of actinic or solar keratoses and superficial basal cell carcinomas

Dosing: Adults

Refer to individual protocols.

I.V. bolus: 500-600 mg/m^2 every 3-4 weeks **or**

425 mg/m^2 on days 1-5 every 4 weeks

Continuous I.V. infusion: 1000 mg/m^2/day for 4-5 days every 3-4 weeks **or**

2300-2600 mg/m^2 on day 1 every week **or**

300-400 mg/m^2/day **or**

225 mg/m^2/day for 5-8 weeks (with radiation therapy)

Actinic keratoses: Topical:

Carac™: Apply thin film to lesions once daily for up to 4 weeks, as tolerated

Efudex®: Apply to lesions twice daily for 2-4 weeks; complete healing may not be evident for 1-2 months following treatment

Fluoroplex®: Apply to lesions twice daily for 2-6 weeks

Superficial basal cell carcinoma: Topical: Efudex® 5%: Apply to affected lesions twice daily for 3-6 weeks; treatment may be continued for up to 10-12 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Dosing: Renal ImpairmentThe FDA-approved labeling does not contain specific dosing adjustment guidelines; however, it is stated that extreme caution should be used in patients with renal impairment.

Hemodialysis: Administer dose following hemodialysis.

Aronoff (2007): Recommends that dosage adjustment is not needed in adult patients with Cl_{cr} <50 mL/minute and patients receiving hemodialysis should be administered 50% of dose.

Dosing: Hepatic ImpairmentThe FDA-approved labeling does not contain specific dosing adjustment guidelines; however, it is stated that extreme caution should be used in patients with hepatic impairment. The following guidelines have been used by some clinicians:

Floyd, 2006: Bilirubin >5 mg/dL: Avoid use.

Koren, 1992: Hepatic impairment (degree not specified): Administer <50% of dose, then increase if toxicity does not occur.

Dosing: Combination Regimens

Breast cancer:

- CAF
- CEF
- CFP
- CMF
- CMF-IV
- CMFP
- CMFVP (Cooper Regimen, VPCMF)
- CNF
- Docetaxel-FEC
- Docetaxel-Trastuzumab-FEC
- Dox-CMF (Sequential)
- FAC
- FEC
- MF
- NFL
- Vinorelbine-FEC
- Vinorelbine-Trastuzumab-FEC

Cervical cancer: Cisplatin-Fluorouracil (Cervical Cancer)

Colorectal cancer:

- Bevacizumab-Fluorouracil-Leucovorin
- Bevacizumab-Irinotecan-Fluorouracil-Leucovorin
- Bevacizumab-Oxaliplatin-Fluorouracil-Leucovorin
- Cetuximab-FOLFOX4
- FLOX (Nordic FLOX)
- Fluorouracil-Leucovorin
- Fluorouracil-Leucovorin-Irinotecan (Saltz Regimen)
- FOIL
- FOLFOX 2
- FOLFOX 3
- FOLFOX 4
- FOLFOX 7
- FU-LV-CPT-11
- PFL (Colorectal Cancer)

Esophageal cancer: TCF

Gastric cancer:

- Docetaxel-Cisplatin-Fluorouracil (Gastric Cancer)
- ECF
- EFP
- ELF

FAM

FAMe

FAP

FAMTX

FUP

Head and neck cancer:

Cetuximab-Carboplatin-Fluorouracil

Cetuximab-Cisplatin-Fluorouracil

CF

Docetaxel-Cisplatin-Fluorouracil (Head and Neck Cancer)

Fluorouracil + Carboplatin

FU HURT

PFL (Head and Neck Cancer)

PFL + IFN

Neuroblastoma: N4SE Protocol

Pancreatic cancer: FAM

Calculations

- Body Surface Area: Adults

Administration: I.V.Irritant. Direct I.V. push injection (50 mg/mL solution needs no further dilution) or by I.V. infusion. Doses >1000 mg/m^2 are usually administered as a 24-hour infusion. Toxicity may be reduced by giving the drug as a constant infusion. Bolus doses may be administered by slow IVP or IVPB.

Administration: I.V. DetailAfter vial has been entered, any unused portion should be discarded within 1 hour. Continuous infusions may be administered in D_5W or NS. Solution should be protected from direct sunlight. Fluorouracil may also be administered intra-arterially or intrahepatically (refer to specific protocols).

pH: 9.2 (adjusted)

Administration: OralI.V. formulation may be given orally mixed in water, grape juice, or carbonated beverage. It is generally best to drink undiluted solution, then rinse the mouth. Coca Cola® has been recommended as the “best chaser” for oral fluorouracil.

Administration: TopicalTopical: Apply 10 minutes after washing, rinsing, and drying the affected area. Apply using fingertip (wash hands immediately after application) or nonmetal applicator. Do not cover area with an occlusive dressing. Wash hands immediately after topical application of the 5% cream. Topical preparations are for external use only; not for ophthalmic, oral, or intravaginal use

Dietary ConsiderationsIncrease dietary intake of thiamine.

Storage

Injection: Store intact vials at room temperature and protect from light; slight discoloration does not usually denote decomposition. If exposed to cold, a precipitate may form; **gentle** heating to 60°C will dissolve the precipitate without impairing the potency. Solutions in 50-1000 mL NS or D_5W, or undiluted solutions in syringes are stable for 72 hours at room temperature.

Topical: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ReconstitutionDilute in 50-1000 mL NS, D_5W, or bacteriostatic NS for infusion.

CompatibilityStable in D_5LR, D_5W, NS, bacteriostatic NS; **incompatible** with concentrations >25 mg/mL of fluorouracil and >2 mg/mL of leucovorin (precipitation occurs).

Y-site administration: Compatible: Allopurinol, amifostine, aztreonam, bleomycin, cefepime, cisplatin, cyclophosphamide, doxorubicin, doxorubicin liposome, etoposide phosphate, fludarabine, furosemide, gatifloxacin, gemcitabine, granisetron, heparin, hydrocortisone sodium succinate, leucovorin, linezolid, mannitol, melphalan, methotrexate, metoclopramide, mitomycin, paclitaxel, piperacillin/tazobactam, potassium chloride, propofol, sargramostim, teniposide, thiotepa, vinblastine, vincristine, vitamin B complex with C. **Incompatible:** Amphotericin B cholesteryl sulfate complex, droperidol, filgrastim, ondansetron, topotecan, vinorelbine.

Compatibility in syringe: Compatible: Bleomycin, cisplatin, cyclophosphamide, furosemide, heparin, leucovorin, methotrexate, metoclopramide, mitomycin, vinblastine, vincristine. **Incompatible:** Droperidol, epirubicin. **Variable (consult detailed reference):** Doxorubicin.

Compatibility when admixed: Compatible: Bleomycin, cyclophosphamide, cyclophosphamide with methotrexate, etoposide, floxuridine, hydromorphone, ifosfamide, methotrexate, mitoxantrone, vincristine. **Incompatible:** Carboplatin, cisplatin, cytarabine, diazepam, doxorubicin, fentanyl, leucovorin, metoclopramide, morphine.

ContraindicationsHypersensitivity to fluorouracil or any component of the formulation; dihydropyrimidine dehydrogenase (DPD) enzyme deficiency; pregnancy

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Hand-foot syndrome: Palmar-plantar erythrodysesthesia (hand-foot) syndrome has been associated with use.
- Toxicity: Discontinue if intractable vomiting, diarrhea, precipitous fall in leukocyte or platelet counts, myocardial ischemia, hemorrhage, or stomatitis occur.

Disease-related concerns:

- Dihydropyrimidine dehydrogenase deficiency (DPD): Administration to patients with genetic DPD has been associated with increased toxicity following administration (diarrhea, neutropenia, and neurotoxicity). Systemic toxicity normally associated with parenteral administration has also been associated with topical use, particularly in patients with DPD; discontinue if symptoms of DPD occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Alkylating agents: Use with caution in patients who have had previous use of alkylating agents.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pelvic radiation recipients: Use with caution in patients who have had high-dose pelvic radiation.

Dosage form specific issues:

- Topical: Avoid topical application to mucous membranes due to potential for local inflammation and ulceration. The use of occlusive dressings with topical preparations may increase the severity of inflammation in nearby skin areas. Avoid exposure to ultraviolet rays during and immediately following therapy.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD (injection); X (topical)

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women, however, fetal defects and miscarriages have been reported following use of topical and intravenous products. Use is contraindicated during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsToxicity depends on route and duration of treatment

I.V.:

Cardiovascular: Angina, myocardial ischemia, nail changes

Central nervous system: Acute cerebellar syndrome, confusion, disorientation, euphoria, headache, nystagmus

Dermatologic: Alopecia, dermatitis, dry skin, fissuring, palmar-plantar erythrodysesthesia syndrome, pruritic maculopapular rash, photosensitivity, vein pigmentations

Gastrointestinal: Anorexia, bleeding, diarrhea, esophagopharyngitis, nausea, sloughing, stomatitis, ulceration, vomiting

Hematologic: Agranulocytosis, anemia, leukopenia, pancytopenia, thrombocytopenia

Myelosuppression:

Onset: 7-10 days

Nadir: 9-14 days

Recovery: 21-28 days

Local: Thrombophlebitis

Ocular: Lacrimation, lacrimal duct stenosis, photophobia, visual changes

Respiratory: Epistaxis

Miscellaneous: Anaphylaxis, generalized allergic reactions, nail loss

Topical:Note: Systemic toxicity normally associated with parenteral administration (including neutropenia, neurotoxicity, and gastrointestinal toxicity) has been associated with topical use particularly in patients with a genetic deficiency of dihydropyrimidine dehydrogenase

(DPD).

Central nervous system: Headache, insomnia, irritability

Dermatologic: Alopecia, photosensitivity, pruritus, rash, scarring, telangiectasia

Gastrointestinal: Medicinal taste, stomatitis

Hematologic: Leukocytosis, thrombocytopenia

Local: Application site reactions: Allergic contact dermatitis, burning, crusting, dryness, edema, erosion, erythema, hyperpigmentation, irritation, pain, soreness, ulceration

Ocular: Eye irritation (burning, watering, sensitivity, stinging, itching)

Miscellaneous: Birth defects, herpes simplex, miscarriage

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Gemcitabine: May increase the serum concentration of Fluorouracil. *Risk C: Monitor therapy*

Leucovorin-Levoleucovorin: May enhance the adverse/toxic effect of Fluorouracil. This effect is associated with the ability of leucovorin or levoleucovorin to enhance the anticancer effects of fluorouracil. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Phenytoin: Fluorouracil may increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Sorafenib: May decrease the serum concentration of Fluorouracil. Sorafenib may increase the serum concentration of Fluorouracil. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Fluorouracil may increase the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (due to GI irritation).

Herb/Nutraceutical: Avoid black cohosh, dong quai in estrogen-dependent tumors.

Monitoring ParametersCBC with differential and platelet count, renal function tests, liver function tests

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking. Assess results of laboratory tests prior to each infusion and regularly with all formulations, including topical use. Assess patient response (eg, cardiovascular, respiratory, and renal function) prior to each infusion and on a regular basis throughout therapy. **Note:** Inform prescriber if intractable vomiting or diarrhea, precipitous fall in leukocyte or platelet counts, or myocardial ischemia occurs (drug may be discontinued). Teach patient proper use (topical application [avoid application to mucous membranes]; oral solution [rinse mouth thoroughly]), possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report. **Pregnancy risk factor D/X:** Determine that patient is not pregnant before starting therapy. Do not give to females of childbearing age unless patient is capable of complying with contraceptive use. Male/female: Advise patient about contraceptive measures as appropriate.

Monitoring: Lab TestsCBC with differential, platelet count, renal and liver function

Patient EducationDo not take any new medication during therapy without consulting prescriber. Follow exact directions for use (oral solution or topical application). Avoid excessive alcohol (may increase gastrointestinal irritation). Maintain adequate nutrition and hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause sensitivity to sunlight (use sunblock, wear protective clothing, and avoid direct sunlight); susceptibility to infection (avoid crowds and exposure to infection); nausea, vomiting, diarrhea, or loss of appetite (small frequent meals may help; request medication); weakness, lethargy, dizziness, decreased vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or headache (request medication). Report signs and symptoms of infection (eg, fever, chills, sore throat, burning urination, vaginal itching or discharge, fatigue, mouth sores); bleeding (eg, black or tarry stools, easy bruising, unusual bleeding); vision changes; unremitting nausea, vomiting, or abdominal pain; CNS changes; respiratory difficulty; chest pain or palpitations; severe skin reactions to topical application; or any other adverse reactions.

Topical: Use as directed; do not overuse. Wash hands thoroughly before and after applying medication. Avoid contact with eyes, nostrils, and mouth. Avoid occlusive dressings; use a porous dressing. May cause local reaction (pain, burning, or swelling); if severe, contact prescriber.

Oral solution: May be mixed in water, grape juice, or carbonated beverage. It is generally best to drink undiluted solution, then rinse mouth thoroughly. CocaCola® has been recommended as the best rinse following oral fluorouracil.

Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Male: Do not cause a pregnancy. Male/female: Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical:

Carac™: 0.5% (30 g)

Efudex®: 5% (40 g)

Fluoroplex®: 1% (30 g) [contains benzyl alcohol]

Injection, solution: 50 mg/mL (10 mL, 20 mL, 50 mL, 100 mL)

Adrucil®: 50 mg/mL (10 mL, 50 mL, 100 mL)

Solution, topical: 2% (10 mL); 5% (10 mL)

Efudex®: 2% (10 mL); 5% (10 mL)

Fluorouracil®: 5% (10 mL)

Generic AvailableYes: Injection, topical solution

Pricing: U.S. (www.drugstore.com)

Cream (Carac)

0.5% (30): $163.48

Cream (Fluoroplex)

1% (30): $158.72

Solution (Efudex)

2% (10): $87.07

5% (10): $125.83

Solution (Fluorouracil)

5% (10): $101.99

50 mg/mL (50): $25.99

Mechanism of ActionA pyrimidine antimetabolite that interferes with DNA synthesis by blocking the methylation of deoxyuridylic acid; fluorouracil inhibits thymidylate synthetase (TS), or is incorporated into RNA. The reduced folate cofactor is required for tight binding to occur between the 5-FdUMP and TS.

Pharmacodynamics/Kinetics

Duration: ~3 weeks

Distribution: V_d: ~22% of total body water; penetrates extracellular fluid, CSF, and third space fluids (eg, pleural effusions and ascitic fluid)

Metabolism: Hepatic (90%); via a dehydrogenase enzyme; FU must be metabolized to be active

Bioavailability: <75%, erratic and undependable

Half-life elimination: Biphasic: Initial: 6-20 minutes; two metabolites, FdUMP and FUTP, have prolonged half-lives depending on the type of tissue

Excretion: Lung (large amounts as CO_2); urine (5% as unchanged drug) in 6 hours

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentMyelosuppression is common; use caution with clozapine and carbamazepine

Index Terms5-Fluorouracil; 5-FU; FU

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International Brand Names5-Fluorouracil-biosyn (DE); 5-Fluorouracil-Ebewe (PL); 5-Fluouracyl-Knoll (PL); 5-FU (JP); 5-FU Hexal (DE); 5-FU Lederle (DE); 5-FU medac (DE); Actino-Hermal (DE); Efudix (AE, AR, AU, BB, BE, BG, BH, BM, BS, BZ, CH, CR, CY, CZ, DE, DO, EG, ES, FR, GB, GH, GT, GY, HK, HN, HR, HU, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LU, LY, MX, NI, NL, NO, OM, PA, PE, PL, PR, QA, SA, SG, SR, SV, SY, TT, TW, TZ, UG, UY, YE, ZA, ZM); Efurix (BR); Fivefluro (IN); Fivoflu (PH); Fluoro-uracil (DK); Fluoro-Uracil (PL); Fluoro-Uracil Roche (HU, PT); Fluoro-Uracile Roche (LU); Fluorouracil Cehasol (AT); Fluorouracil Ebewe (AT); Fluorouracil Faulding (SE); Fluorouracil Lederle (FI); Fluorouracil Medac (PL); Fluorouracil Roche (AT); Fluorouracil Therabel (PL); Fluorouracil ”Faulding” (DK); Fluorouracil-GRY (DE); Fluorouracil-Losung (DE); Fluorouracile Teva (HU); Fluorouracilo Dakota Farma (PT); Flurablastin (DK, FI, SE); Fluracedyl (MY, SE); Fluracil (IN); Fluroblastin (DE, PL); Fluroblastine (LU); Gefente (CL); Kecimeton (JP); Neofluor (DE); O-fluor (DE); Oncofu (AR); Ribofluor (DE); Tecflu (MX); Utoral (PH); Verrumal (DE)

FLUoxetine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

FLUoxetine may be confused with DULoxetine, fluvastatin, fluvoxamine, PARoxetine

Prozac® may be confused with Prilosec®, Prograf®, Proscar®, ProSom®, ProStep®

Sarafem® may be confused with Serophene®

International issues:

Fluoxin® [Czech Republic and Romania] may be confused with Floxin® which is a brand name for ofloxacin in the U.S.

Prozac® may be confused with Prazac® a brand of prazosin in Denmark

Reneuron® [Spain] may be confused with Remeron® a brand of mirtazapine in the U.S.

Pronunciation(floo OKS e teen)

U.S. Brand NamesProzac®; Prozac® Weekly™; Sarafem®; Selfemra™

Canadian Brand NamesApo-Fluoxetine®; BCI-Fluoxetine; CO Fluoxetine; Dom-Fluoxetine; Fluoxetine; FXT; Gen-Fluoxetine; Novo-Fluoxetine; Nu-Fluoxetine; PHL-Fluoxetine; PMS-Fluoxetine; Prozac®; ratio-Fluoxetine; Rhoxal-Fluoxetine; Riva-Fluoxetine; Sandoz-Fluoxetine

Pharmacologic CategoryAntidepressant, Selective Serotonin Reuptake Inhibitor

Use: Labeled IndicationsTreatment of major depressive disorder (MDD); treatment of binge-eating and vomiting in patients with moderate-to-severe bulimia nervosa; obsessive-compulsive disorder (OCD); premenstrual dysphoric disorder (PMDD); panic disorder with or without agoraphobia

Use: Unlabeled/InvestigationalSelective mutism; treatment of mild dementia-associated agitation in nonpsychotic patients

Dosing: Adults

Depression, obsessive-compulsive disorder, premenstrual dysphoric disorder, bulimia: 20 mg/day in the morning; may increase after several weeks by 20 mg/day increments; maximum: 80 mg/day; doses >20 mg may be given once daily or divided twice daily. **Note:** Lower doses of 5-10 mg/day have been used for initial treatment.

Usual dosage range:

Depression: 20-40 mg/day; patients maintained on Prozac® 20 mg/day may be changed to Prozac® Weekly™ 90 mg/week, starting dose 7 days after the last 20 mg/day dose

Obsessive compulsive disorder: 40-80 mg/day

Premenstrual dysphoric disorder (Sarafem™): 20 mg/day continuously, **or** 20 mg/day starting 14 days prior to menstruation and through first full day of menses (repeat with each cycle)

Bulimia nervosa: 60-80 mg/day

Panic disorder: Initial: 10 mg/day; after 1 week, increase to 20 mg/day; may increase after several weeks; doses >60 mg/day have not been evaluated

Note: Upon discontinuation of fluoxetine therapy, gradually taper dose. If intolerable symptoms occur following a dose reduction, consider resuming the previously prescribed dose and/or decrease dose at a more gradual rate.

Dosing: ElderlyOral: Some patients may require an initial dose of 10 mg/day with dosage increases of 10 mg and 20 mg every several weeks as tolerated; should not be taken at night unless patient experiences sedation.

Dosing: Pediatric

Depression: Oral: 8-18 years: 10-20 mg/day; lower-weight children can be started at 10 mg/day, may increase to 20 mg/day after 1 week if needed

Obsessive-compulsive disorder: Oral: 7-18 years: Initial: 10 mg/day; in adolescents and higher-weight children, dose may be increased to 20 mg/day after 2 weeks. Range: 10-60 mg/day.

Selective mutism (unlabeled use): Oral:

<5 years: No dosing information available

5-18 years: Initial: 5-10 mg/day; titrate upwards as needed (usual maximum dose: 60 mg/day)

Note: Upon discontinuation of fluoxetine therapy, gradually taper dose. If intolerable symptoms occur following a dose reduction, consider resuming the previously prescribed dose and/or decrease dose at a more gradual rate.

Dosing: Renal Impairment

Single dose studies: Pharmacokinetics of fluoxetine and norfluoxetine were similar among subjects with all levels of impaired renal function, including anephric patients on chronic hemodialysis.

Chronic administration: Additional accumulation of fluoxetine or norfluoxetine may occur in patients with severely impaired renal function.

Not removed by hemodialysis; use of lower dose or less frequent dosing is not usually necessary.

Dosing: Hepatic ImpairmentElimination half-life of fluoxetine is prolonged in patients with hepatic impairment. A lower dose or less frequent dosing of fluoxetine should be used in these patients.
Cirrhosis patient: Administer a lower dose or less frequent dosing interval.

Compensated cirrhosis without ascites: Administer 50% of normal dose.

Dietary ConsiderationsMay be taken with or without food.

StorageAll dosage forms should be stored at controlled room temperature of 15°C to 30°C (50°F to 86°F). Oral liquid should be dispensed in a light-resistant container.

Extemporaneously PreparedA 20 mg capsule may be mixed with 4 oz of water, apple juice, or Gatorade® to provide a solution that is stable for 14 days under refrigeration.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to fluoxetine or any component of the formulation; patients currently receiving MAO inhibitors, pimozide, or thioridazine

Note: MAO inhibitor therapy must be stopped for 14 days before fluoxetine is initiated. Treatment with MAO inhibitors, thioridazine, or mesoridazine should not be initiated until 5 weeks after the discontinuation of fluoxetine.

Allergy Considerations

- Selective Serotonin Reuptake Inhibitor (SSRI) Allergy

Warnings/Precautions

Boxed Warnings:

- Suicidal thinking/behavior: See "Major psychiatric warnings" below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Fluoxetine is FDA approved for the treatment of OCD in children ≥7 years of age and MDD in children ≥8 years of age.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Fluoxetine is not FDA approved for the treatment of bipolar depression.** Safety and efficacy in children <8 years of age (major depressive disorder) and <7 years of age (OCD) have not been established.

Concerns related to adverse effects:

- Allergic events and rash: Fluoxetine use has been associated with occurrences of significant rash and allergic events, including vasculitis, lupus-like syndrome, laryngospasm, anaphylactoid reactions, and pulmonary inflammatory disease. Discontinue if underlying cause of rash cannot be identified.

- Anticholinergic effects: Relatively devoid of these side effects

- Bleeding risk: May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin, NSAIDs, warfarin or other anticoagulants. Bleeding related to SSRI use has been reported to range from relatively minor bruising and epistaxis to life-threatening hemorrhage.

- CNS depression: Has a low potential to impair cognitive or motor performance; caution operating hazardous machinery or driving.

- CNS effects: May cause insomnia, anxiety, nervousness, or anorexia.

- Sexual dysfunction: May cause or exacerbate sexual dysfunction.

- SIADH and hyponatremia: SSRIs and SNRIs have been associated with the development of SIADH; hyponatremia has been reported rarely (including severe cases with serum sodium <110 mmol/L), predominately in the elderly. Volume depletion and/or concurrent use of diuretics likely increases risk.

- Weight loss: May cause weight loss. Use caution in patients where weight loss is undesirable.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of MI or unstable heart disease; use in these patients is limited.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glycemic control.

- Hepatic impairment: Use with caution in patients with hepatic impairment; clearance is decreased and plasma concentrations are increased; a lower dosage may be needed.

- Renal impairment: Use with caution in patients with renal impairment; clearance is decreased and plasma concentrations are increased; a lower dosage may be needed.

- Seizure disorders: Use with caution in patients with a previous seizure disorder or conditions predisposing to seizures such as brain damage or alcoholism.

Concurrent drug therapy issues:

- Agents which lower seizure threshold: Use caution with concurrent therapy.

- Anticoagulants/Antiplatelets: Use caution with concomitant use of NSAIDs, ASA, or other drugs that affect coagulation; the risk of bleeding may be potentiated.

- CNS depressants: Use caution with concomitant therapy.

- MAO inhibitors: Potential for severe reaction when used with MAO inhibitors; autonomic instability, coma, death, delirium, diaphoresis, hyperthermia, mental status changes/agitation, muscular rigidity, myoclonus, neuroleptic malignant syndrome features, and seizures may occur.

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce fluoxetine's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

- Thioridazine: Fluoxetine may elevate plasma levels of thioridazine; increasing risk of QTc interval prolongation; this may lead to serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. **Concurrent use is contraindicated.**

Special populations:

- Elderly: Use caution in elderly patients; risk of hyponatremia and other adverse events may be increased.

Other warnings/precautions:

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

- Long half-life: Due to the long half-life of fluoxetine and its metabolites, the effects and interactions noted may persist for prolonged periods following discontinuation.

- Withdrawal syndrome: May cause dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Upon discontinuation of fluoxetine therapy, gradually taper dose. If intolerable symptoms occur following a decrease in dosage or upon discontinuation of therapy, then resuming the previous dose with a more gradual taper should be considered.

Geriatric ConsiderationsFluoxetine's favorable side effect profile makes it a useful alternative to the traditional tricyclic antidepressants. Its potential stimulating and anorexic effects may be bothersome to some patients and has not been shown to be superior in efficacy to the traditional tricyclic antidepressants or other SSRIs. The long half-life in the elderly makes it less attractive compared to other SSRIs. Data from a clinical trial comparing fluoxetine to tricyclics suggest that fluoxetine is significantly less effective than nortriptyline in hospitalized elderly patients with unipolar major affective disorder, especially those with melancholia and concurrent cardiovascular diseases. The elderly are more prone to SSRI/SNRI-induced hyponatremia.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDue to adverse effects observed in animal studies, fluoxetine is classified as pregnancy category C. Fluoxetine and its metabolite cross the human placenta. Nonteratogenic effects in the newborn following SSRIs exposure late in the third trimester include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypo- or hypertonia, hyper-reflexia, jitteriness, irritability, constant crying, and tremor. An increased risk of low birth weight, lower APGAR scores, and blunted behavioral response to pain for a prolonged period after delivery have also been reported. Exposure to SSRIs after the twentieth week of gestation has been associated with persistent pulmonary hypertension of the newborn (PPHN). Adverse effects may be due to toxic effects of the SSRI or drug withdrawal without a taper. The long term effects of *in utero* SSRI exposure on infant development and behavior are not known.

Due to pregnancy-induced physiologic changes, women who are pregnant may require increased doses of fluoxetine to achieve euthymia.

Women treated for major depression and who are euthymic prior to pregnancy are more likely to experience a relapse when medication is discontinued as compared to pregnant women who continue taking antidepressant medications. The ACOG recommends that therapy with SSRIs or SNRIs during pregnancy be individualized; treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary healthcare provider, and pediatrician. If treatment during pregnancy is required, consider tapering therapy during the third trimester in order to prevent withdrawal symptoms in the infant. If this is done and the woman is considered to be at risk of relapse from her major depressive disorder, the medication can be restarted following delivery, although the dose should be readjusted to that required before pregnancy.

LactationEnters breast milk/not recommended (AAP rates “of concern”)

Breast-Feeding ConsiderationsFluoxetine and its metabolite are excreted into breast milk and can be detected in the serum of breast-feeding infants. Concentrations in breast milk are variable. Colic, irritability, slow weight gain, and feeding and sleep disorders have been reported in nursing infants. The AAP considers fluoxetine to be a "drug for which the effect on the nursing infant is unknown but may be of concern." Breast-feeding is not recommended by the manufacturer.

Because the long-term effects on development and behavior have not been studied and adverse effects have been noted in some infants exposed, one should prescribe fluoxetine to a mother who is breast-feeding only when the benefits outweigh the potential risks.

Pregnancy & Lactation, In-Depth

- FLUoxetine

Adverse ReactionsPercentages listed for adverse effects as reported in placebo-controlled trials and were generally similar in adults and children; actual frequency may be dependent upon diagnosis and in some cases the range presented may be lower than or equal to placebo for a particular disorder.

>10%:

Central nervous system: Insomnia (10% to 33%), headache (21%), anxiety (6% to 15%), nervousness (8% to 14%), somnolence (5% to 17%)

Endocrine & metabolic: Libido decreased (1% to 11%)

Gastrointestinal: Nausea (12% to 29%), diarrhea (8% to 18%), anorexia (4% to 11%), xerostomia (4% to 12%)

Neuromuscular & skeletal: Weakness (7% to 21%), tremor (3% to 13%)

Respiratory: Pharyngitis (3% to 11%), yawn (<1% to 11%)

1% to 10%:

Cardiovascular: Vasodilation (1% to 5%), fever (2%), chest pain, hemorrhage, hypertension, palpitation

Central nervous system: Dizziness (9%), dream abnormality (1% to 5%), thinking abnormality (2%), agitation, amnesia, chills, confusion, emotional lability, sleep disorder

Dermatologic: Rash (2% to 6%), pruritus (4%)

Endocrine & metabolic: Ejaculation abnormal (<1% to 7%), impotence (<1% to 7%)

Gastrointestinal: Dyspepsia (6% to 10%), constipation (5%), flatulence (3%), vomiting (3%), weight loss (2%), appetite increased, taste perversion, weight gain

Genitourinary: Urinary frequency

Ocular: Vision abnormal (2%)

Otic: Ear pain, tinnitus

Respiratory: Sinusitis (1% to 6%)

Miscellaneous: Flu-like syndrome (3% to 10%), diaphoresis (2% to 8%)

<1%, postmarketing and/or case reports: Acne, albuminuria, allergies, alopecia, amenorrhea, anaphylactoid reactions, anemia, angina, aphthous stomatitis, arrhythmia, arthritis, asthma, bone pain, bruising, bursitis, cataract, CHF, cholelithiasis, cholestatic jaundice, colitis, dehydration, dyskinesia, dysphagia, ecchymosis, edema, eosinophilic pneumonia, epistaxis, erythema multiforme, erythema nodosum, esophagitis, euphoria, exfoliative dermatitis, extrapyramidal symptoms (rare), gastritis, glossitis, gout, gynecomastia, hallucinations, hepatic failure/necrosis, hemorrhage, hiccup, hostility, hypercholesteremia, hyperprolactinemia, hyperventilation, hypoglycemia, hypokalemia, hyponatremia (possibly in association with SIADH), hypotension, hypothyroidism, immune-related hemolytic anemia, kidney failure, laryngospasm, leg cramps, liver function test abnormalities, lupus-like syndrome, malaise, migraine, misuse/abuse, MI, neuroleptic malignant syndrome (NMS), optic neuritis, pancreatitis, pancytopenia, photosensitivity reaction, postural hypotension, priapism, pulmonary embolism, pulmonary fibrosis, pulmonary hypertension, QT prolongation, serotonin syndrome, Stevens-Johnson syndrome, suicidal ideation, syncope, tachycardia, tinnitus, thrombocytopenia, thrombocytopenic purpura, vasculitis, ventricular tachycardia (including torsade de pointes)

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2B6 (minor), 2C9 (major), 2C19 (minor), 2D6 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP1A2 (moderate), 2B6 (weak), 2C9 (weak), 2C19 (moderate), 2D6 (strong), 3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alpha-/Beta-Blockers: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Alpha-/Beta-Blockers. *Risk C: Monitor therapy*

Analgesics (Opioid): May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin Reuptake Inhibitor/Antagonist): Selective Serotonin Reuptake Inhibitors may enhance the serotonergic effect of Antidepressants (Serotonin Reuptake Inhibitor/Antagonist). This may cause serotonin syndrome. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Aspirin: Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Beta-Blockers: Selective Serotonin Reuptake Inhibitors may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Acebutolol; Atenolol; Carteolol; Esmolol; Levobunolol; Metipranolol; Nadolol; Penbutolol. *Risk C: Monitor therapy*

BusPIRone: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. Selective Serotonin Reuptake Inhibitors may decrease the metabolism of BusPIRone. *Risk C: Monitor therapy*

CarBAMazepine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of CarBAMazepine. Specifically those SSRIs that inhibit CYP3A4 isoenzymes. CarBAMazepine may increase the metabolism of Selective Serotonin Reuptake Inhibitors. Specifically those agents metabolized via CYP1A2, 2C, and/or 3A4 isoenzymes. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Selective Serotonin Reuptake Inhibitors. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Clozapine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Strong) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk D: Consider therapy modification*

Cyproheptadine: May diminish the therapeutic effect of Selective Serotonin Reuptake Inhibitors. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Desmopressin: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dextromethorphan: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Dextromethorphan. *Risk D: Consider therapy modification*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Galantamine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Galantamine. *Risk C: Monitor therapy*

Haloperidol: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Haloperidol. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Iobenguane I 123: Selective Serotonin Reuptake Inhibitors may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Selective Serotonin Reuptake Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methadone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Methadone. Fluvoxamine appears to be the only interacting SSRI. *Risk D: Consider therapy modification*

Mexiletine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Mexiletine. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

NSAID (COX-2 Inhibitor): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk D: Consider therapy modification*

NSAID (Nonselective): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Phenytoin: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Pimozide: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Pimozide. *Risk X: Avoid combination*

Propafenone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Propafenone. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of QuiNIDine. Fluvoxamine appears to be the only SSRI of concern. *Risk D: Consider therapy modification*

Risperidone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Risperidone. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tamoxifen: CYP2D6 Inhibitors (Strong) may decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Tetrabenazine: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Tetrabenazine. Specifically, concentrations of the active alpha- and beta-dihydrotetrabenazine metabolites may be increased. Management: Tetrabenazine dose should be reduced by 50% when starting a strong CYP2D6 inhibitor. Maximum tetrabenazine dose is 50mg/day when used with a strong CYP2D6 inhibitor. *Risk D: Consider therapy modification*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

TraMADol: Selective Serotonin Reuptake Inhibitors may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. TraMADol may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tryptophan: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Selective Serotonin Reuptake Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression). Depressed patients should avoid/limit intake.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersMental status for depression, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased), anxiety, social functioning, mania, panic attacks; akathisia, sleep
Reference RangeTherapeutic levels have not been well established

Therapeutic: Fluoxetine: 100-800 ng/mL (SI: 289-2314 nmol/L); Norfluoxetine: 100-600 ng/mL (SI: 289-1735 nmol/L)

Toxic: Fluoxetine plus norfluoxetine: >2000 ng/mL

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Assess mental status for depression, suicidal ideation, anxiety, social functioning, mania, or panic attack. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Monitoring: Lab TestsBaseline liver and renal function before beginning drug therapy
Patient EducationTake exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results. Take once-a-day dose in the morning to reduce incidence of insomnia. Avoid alcohol, caffeine, and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); constipation (increased exercise, fluids, fruit, or fiber may help); anorexia (maintain regular dietary intake to avoid excessive weight loss); or postural hypotension (use caution when climbing stairs or changing position from lying or sitting to standing). If you have diabetes, monitor serum glucose closely (may cause hypoglycemia). Report persistent CNS effects (nervousness, restlessness, insomnia, anxiety, excitation, suicide ideation, headache, sedation); thoughts of suicide; rash or skin irritation; muscle cramping, tremors, or change in gait; respiratory depression or respiratory difficulty; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. **Note:** Strength expressed as base unless otherwise noted. [DSC] = Discontinued product

Capsule: 10 mg, 20 mg, 40 mg

Prozac®: 10 mg, 20 mg, 40 mg

Sarafem®: 10 mg, 20 mg [DSC]

Selfemra™: 10 mg, 20 mg [contains soya lecithin]

Capsule, delayed release, enteric coated pellets:

Prozac® Weekly™: 90 mg

Solution, oral: 20 mg/5 mL (5 mL, 120 mL) [contains ethanol 0.23% and benzoic acid; mint flavor]

Prozac®: 20 mg/5 mL (120 mL) [contains ethanol 0.23% and benzoic acid; mint flavor]

Tablet: 10 mg, 20 mg

Prozac® [scored]: 10 mg [DSC]

Sarafem®: 10 mg, 20 mg

Generic AvailableYes: Excludes delayed release capsule
ManufacturerEli Lilly and Co
Pricing: U.S. (www.drugstore.com)

Capsule, delayed release (Prozac Weekly)

90 mg (4): $121.81

Capsules (Fluoxetine HCl)

10 mg (30): $24.99

20 mg (30): $14.99

40 mg (30): $40.99

Capsules (Prozac)

10 mg (30): $166.26

20 mg (30): $151.93

40 mg (30): $325.23

Capsules (Selfemra)

10 mg (28): $25.00

20 mg (28): $27.99

Solution (Fluoxetine HCl)

20 mg/5 mL (120): $72.98

Solution (Prozac)

20 mg/5 mL (120): $252.64

Tablets (Fluoxetine HCl)

10 mg (30): $13.99

20 mg (30): $25.99

Tablets (Prozac)

10 mg (30): $122.17

Tablets (Sarafem)

10 mg (7): $49.99

20 mg (7): $49.99

Mechanism of ActionInhibits CNS neuron serotonin reuptake; minimal or no effect on reuptake of norepinephrine or dopamine; does not significantly bind to alpha-adrenergic, histamine, or cholinergic receptors

Pharmacodynamics/Kinetics

Onset of action: Depression: The onset of action is within a week, however, individual response varies greatly and full response may not be seen until 8-12 weeks after initiation of treatment.

Absorption: Well absorbed; delayed 1-2 hours with weekly formulation

Distribution: V_d: 12-43 L/kg

Protein binding: 95% to albumin and alpha$_1$ glycoprotein

Metabolism: Hepatic, via CYP2C19 and 2D6, to norfluoxetine (activity equal to fluoxetine)

Half-life elimination: Adults:

Parent drug: 1-3 days (acute), 4-6 days (chronic), 7.6 days (cirrhosis)

Metabolite (norfluoxetine): 9.3 days (range: 4-16 days), 12 days (cirrhosis)

Time to peak, serum: 6-8 hours

Excretion: Urine (10% as norfluoxetine, 2.5% to 5% as fluoxetine)

Note: Weekly formulation results in greater fluctuations between peak and trough concentrations of fluoxetine and norfluoxetine compared to once-daily dosing (24% daily/164% weekly; 17% daily/43% weekly, respectively). Trough concentrations are 76% lower for fluoxetine and 47% lower for norfluoxetine than the concentrations maintained by 20 mg once-daily dosing. Steady-state fluoxetine concentrations are ~50% lower following the once-weekly regimen compared to 20 mg once daily. Average steady-state concentrations of once-daily dosing were highest in children ages 6 to <13 (fluoxetine 171 ng/mL; norfluoxetine 195 ng/mL), followed by adolescents ages 13 to <18 (fluoxetine 86 ng/mL; norfluoxetine 113 ng/mL); concentrations were considered to be within the ranges reported in adults (fluoxetine 91-302 ng/mL; norfluoxetine 72-258 ng/mL).

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Selective Serotonin Reuptake Inhibitors (SSRIs) CYP Profile
- Selective Serotonin Reuptake Inhibitors (SSRIs) FDA-Approved Indications
- Selective Serotonin Reuptake Inhibitors (SSRIs) Pharmacokinetics
- Selective Serotonin Reuptake Inhibitors (SSRIs) Receptor Profile
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsECG may reveal S-T segment depression. Not shown to be teratogenic in rodents; 15-60 mg/day, buspirone and cyproheptadine, may be useful in treatment of sexual dysfunction during treatment with a selective serotonin reuptake inhibitor.

Weekly capsules are a delayed release formulation containing enteric-coated pellets of fluoxetine hydrochloride, equivalent to 90 mg fluoxetine. Therapeutic equivalence of weekly formulation with daily formulation for delaying time to relapse has not been established.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and taste perversion. Problems with SSRI-induced bruxism have been reported and may preclude their use. Clinicians attempting to evaluate any patient with bruxism or involuntary muscle movement, who is simultaneously being treated with an SSRI drug, should be aware of this potential association.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAlthough caution should be used in patients taking tricyclic antidepressants, no interactions have been reported with vasoconstrictors and fluoxetine, a nontricyclic antidepressant which acts to increase serotonin; no precautions appear to be needed. Fluoxetine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health: Child/Adolescent ConsiderationsA study in children 8-15 years of age with obsessive compulsive disorder (n=14) used a fixed dose of 20 mg/day (Riddle, 1992). A study of children 10-18 years of age with obsessive compulsive symptoms and Tourette's syndrome (n=5) used 20-40 mg/day (Kurlan, 1993). Six children 6-12 years of age with selective mutism were treated with initial doses of 0.2 mg/kg/day for 1 week, then 0.4 mg/kg/day for 1 week, then 0.6 mg/kg/day for 10 weeks (Black, 1994). Twenty-one children (mean age: 8.2 years) with selective mutism received a mean end dose of 28.1 mg (10-60 mg) in a 9 week open trial (Dummit, 1996). Ninety-six outpatients 7-17 years of age with nonpsychotic major depression received 20 mg/day (Emslie, 1997); further studies are needed.

Numerous studies show a modest effect, at best, for selective serotonin reuptake inhibitors in the treatment of pediatric depression. However, data from these studies has suggested that fluoxetine may be more effective than other SSRIs, particularly in adolescents (Hetrick, 2007; Tsapakis, 2008; Usala, 2008). However, concerns remain for the risk of increased suicidal thinking/behaviors in children and adolescents.

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Usala T, Clavenna A, Zuddas A, et al, “Randomised Controlled Trials of Selective Serotonin Reuptake Inhibitors in Treating Depression in Children and Adolescents: A Systematic Review and Meta-Analysis,” *Eur Neuropsychopharmacol*, 2008, 18(1):62-73.

Mental Health CommentThe SSRIs as a class are generally considered to be safe and equally effective. Allow sufficient dose-response time (6-12 weeks). Differences lie in approved indications, receptor profiles, pharmacokinetics, and cytochrome P450 activity profile. Subtle differences exist in adverse effect profiles. All SSRIs have the potential to cause sexual dysfunction. Among the SSRIs, fluoxetine is felt to be the most activating. The once-weekly dosing formulation may be appropriate for psychiatric populations that are noncompliant with daily administration.

Cardiovascular ConsiderationsSSRIs alone are relatively safe compared to other antidepressants in patients with cardiovascular disease. SSRIs may increase the risk of QT prolongation/torsade de pointes associated with other drugs administered concurrently. Fluoxetine is being evaluated in experimental studies for vasovagal syncope. Fluoxetine may decrease the metabolism of thioridazine possibly predisposing to thioridazine-induced QT interval prolongation. Thioridazine should not be used in combination with fluoxetine and should be dosed at least 5 weeks after fluoxetine is discontinued.

Anesthesia and Critical Care Concerns/Other ConsiderationsSSRIs are relatively safe compared to other antidepressants in patients with cardiovascular disease.

Index TermsFluoxetine Hydrochloride

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International Brand NamesActan (CN); Adepssir (PH); Adofen (ES); Alzac 20 (GT); Andep (IN); Andepin (PL); Ansi (ID); Ansilan (CO); Antiprestin (ID); Apo-Flox (PL); Auscap (AU); Bioxetin (PL); Biozac (BG); Captaton (AR); Daforin (BR); Dawnex (TH); Depren (KP); Deprenon (PL); Deprexetin (PL); Deprexin (BB, BM, BS, BZ, GY, HU, JM, KP, NL, SR, TT); Deprizac (PH); Deproxin (TH); Elizac (ID); Floxet (HU, UY); Fluctin (DE); Fluctine (AT, CH); Fludac (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Fluketin (SG); Flunil (IN); Fluohexal (AU); Fluoksetyna (PL); Fluox (NZ); Fluox-Puren (DE); Fluoxebell (AU); Fluoxeren (IT); Fluoxetin (PL); Fluoxil (DO); Fluran (MY); Fluronin (TW); Flusac (TH); Flutine (TH); Fluxet (DE); Fluxetin (HK, SG); Fluxil (AE, BH, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SG, SY, YE); Fluxin (PL); Fontex (DK, FI, NO, SE); Foxetin (KP); Foxine (AU); Foxtin (SG); Fropine (KP); Fuloren (KP); Huma-Fluoxetin (HU); Lanclic (KP); Lorien (ZA); Lovan (AU); Margrilan (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SG, SY, TH, YE); Neupax (CR, DO, EC, GT, HN, NI, PA, PE, SV); Neuxetin (PH); Nopres (ID); Nuzak (ZA); Nycoflox (EE); Oxedep (CL); Plinzene (NZ); Portal (HR, HU); Praxin (HU); Prizma (IL); Proctin (KP); Prodep (IN); Prozac (AR, AU, BE, BF, BJ, BR, CI, CL, CN, CO, CR, CZ, DO, ES, ET, FR, GB, GH, GM, GN, GT, HK, HN, HR, HU, IE, IL, IT, KE, KP, LR, LU, MA, ML, MR, MU, MW, NE, NG, NI, NL, PA, PE, PK, PL, PT, PY, RU, SC, SD, SL, SN, SV, TH, TN, TR, TZ, UG, VE, ZA, ZM, ZW); Prozac 20 (KP, MY, PH, TW); Prozac Dispersible (KP); Qualisac (HK); Rowexetina (CR, DO, GT, HN, NI, PA, SV); Salipax (BB, BM, BS, BZ, GY, JM, MY, NL, SR, TT); Seronil (FI, PL); Symbyax (MX); Xetin (TH); Xetiran (PL); ZAC (ID); Zactin (AU, ID, SG, TW)

Fluoxymesterone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

> Halotestin® may be confused with Haldol®, haloperidol, halothane

Pronunciation(floo oks i MES te rone)

U.S. Brand NamesAndroxy™

Pharmacologic CategoryAndrogen

Use: Labeled IndicationsReplacement of endogenous testicular hormone; in females, palliative treatment of breast cancer

Use: Unlabeled/InvestigationalStimulation of erythropoiesis, angioneurotic edema

Dosing: Adults

Hypogonadism (Males): Oral: 5-20 mg/day

Delayed puberty (Males): Oral: 2.5-20 mg/day for 4-6 months

Inoperable breast carcinoma (Females): Oral: 10-40 mg/day in divided doses for 1-3 months

Dosing: ElderlyRefer to adult dosing.

Dosing: Combination Regimens

Breast cancer: VATH

StorageProtect from light.

RestrictionsC-III

ContraindicationsHypersensitivity to fluoxymesterone or any component of the formulation; serious cardiac disease; liver or kidney disease; pregnancy

Allergy Considerations

- Androgen Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hepatic effects: Prolonged use and/or high doses may cause peliosis hepatis or liver cell tumors which may not be apparent until liver failure or intra-abdominal hemorrhage develops. Discontinue in case of cholestatic hepatitis with jaundice or abnormal liver function tests.

Disease-related concerns:

- Breast cancer: Use with caution in patients with breast cancer; may cause hypercalcemia by stimulating osteolysis.

- Diabetes: Use with caution in patients with diabetes mellitus; monitor carefully.

- Edematous conditions: Use with caution in patients with conditions influenced by edema (eg, cardiovascular disease, migraine, seizure disorder, renal impairment); may cause fluid retention.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

Special populations:

- Elderly: Use with caution in elderly patients; they may be at greater risk for prostatic hyperplasia, fluid retention, and transaminase elevations.

- Pediatrics: May accelerate bone maturation without producing compensatory gain in linear growth in children. In prepubertal children, perform radiographic examination of the hand and wrist every 6 months to determine the rate of bone maturation and to assess the effect of treatment on the epiphyseal centers.

- Women: Discontinue with evidence of mild virilization in women.

Dosage form specific issues:

- Tartrazine: Product may contain tartrazine.

Pregnancy Risk FactorX

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions

>10%:

Male: Priapism

Female: Menstrual problems (amenorrhea), virilism, breast soreness

Cardiovascular: Edema

Dermatologic: Acne

1% to 10%:

Male: Prostatic carcinoma, hirsutism (increase in pubic hair growth), impotence, testicular atrophy

Cardiovascular: Edema

Gastrointestinal: GI irritation, nausea, vomiting

Genitourinary: Prostatic hyperplasia

Hepatic: Hepatic dysfunction

<1%:

Male: Gynecomastia

Female: Amenorrhea

Hypercalcemia, leukopenia, polycythemia, hepatic necrosis, cholestatic hepatitis, hypersensitivity reactions

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

CycloSPORINE: Androgens may enhance the hepatotoxic effect of CycloSPORINE. Androgens may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Androgens may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Test InteractionsDecreased levels of thyroxine-binding globulin; decreased total T_4 serum levels; increased resin uptake of T_3 and T_4

Monitoring ParametersIn prepubertal children, perform radiographic examination of the hand and wrist every 6 months

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Instruct patients of childbearing age on appropriate contraceptive measures during therapy and for 1 month following therapy. Breast-feeding is contraindicated.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. Take as directed; do not discontinue without consulting prescriber. If you have diabetes, monitor serum glucose closely and notify prescriber of changes; this medication can alter hypoglycemic requirements. May cause acne, growth of body hair, loss of libido, impotence, or menstrual irregularity (usually reversible); or nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report changes in menstrual pattern; deepening of voice or unusual growth of body hair; fluid retention (swelling of ankles, feet, or hands, respiratory difficulty, or sudden weight gain); change in color of urine or stool; yellowing of eyes or skin; unusual bruising or bleeding; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant and do not get pregnant during or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 10 mg

Androxy™: 10 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Androxy)

10 mg (30): $84.98

Mechanism of ActionSynthetic androgenic anabolic hormone responsible for the normal growth and development of male sex hormones and development of male sex organs and maintenance of secondary sex characteristics; synthetic testosterone derivative with significant androgen activity; stimulates RNA polymerase activity resulting in an increase in protein production; increases bone development; halogenated derivative of testosterone with up to 5 times the activity of methyltestosterone

Pharmacodynamics/Kinetics

Absorption: Rapid

Protein binding: 98%

Metabolism: Hepatic; enterohepatic recirculation

Half-life elimination: 10-100 minutes

Excretion: Urine (90%)

Dental Health: Effects on Dental Treatment No significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions
Mental Health: Effects on Mental Status None reported
Mental Health: Effects on Psychiatric Treatment May cause leukopenia; use caution with clozapine and carbamazepine
International Brand Names Afluteston (AT); Halotestin (AU, FR, HU, IT, NL, NO); Oralsterone (IT); Stenox (MX)

Flupenthixol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(floo pen THIKS ol)

Canadian Brand NamesFluanxol®

Pharmacologic CategoryAntipsychotic Agent, Typical

Use: Labeled IndicationsMaintenance therapy of chronic schizophrenic patients whose main manifestations do **not** include excitement, agitation, or hyperactivity

Dosing: Adults

Psychotic symptoms:

I.M.: **Note:** Flupenthixol is administered by deep I.M. injection, preferably in the gluteus maximus, **not for I.V. use**; maintenance dosages are given at 2- to 3-week intervals

Test dose: Patients not previously treated with long-acting depot neuroleptics should be given an initial test dose of 5-20 mg. An initial dose of 20 mg is usually well tolerated; however, a 5 mg test dose is recommended in elderly, frail, and cachectic patients, and in patients whose individual or family history suggests a predisposition to extrapyramidal reactions. In the subsequent 5-10 days, the therapeutic response and the appearance of extrapyramidal symptoms should be carefully monitored. Oral neuroleptic drugs may be continued, but dosage should be reduced during this overlapping period and eventually discontinued.

Oral: Initial: 1 mg 3 times/day; dose must be individualized. May be increased by 1 mg every 2-3 days based on tolerance and control of symptoms. Usual maintenance dosage: 3-6 mg/day in divided doses (doses ≥12 mg/day used in some patients).

Dosing: ElderlyRefer to adult dosing.

Administration: I.M.Administer by deep I.M. injection, preferably in the gluteus maximus.

Administration: I.V.Not for I.V. use

StorageSolution: Store at room temperature. Protect from light.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to flupenthixol, phenothiazines, thioxanthenes, or any component of the formulation; acute intoxication (ethanol, barbiturate, or opioid); severe CNS depression; coma; severely-agitated patients; suspected or established subcortical brain damage; cerebrovascular or renal insufficiency; severe cardiovascular disease/circulatory collapse; blood dyscrasias; pheochromocytoma

Allergy Considerations

- Thioxanthene Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics. Avoid use in patients with underlying QT prolongation, in those taking medicines that prolong the QT interval, or cause polymorphic ventricular tachycardia; monitor ECG closely for dose-related QT effects. Adverse effects of decanoate may be prolonged.

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to other neuroleptics, flupenthixol has a low potency of cholinergic blockade.

- Blood dyscrasias: Myelosuppression (eg, leukopenia, agranulocytosis) has been observed with antipsychotic use; check blood counts periodically and discontinue at first signs of blood dyscrasias; use is contraindicated in patients with bone marrow suppression.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is high relative to other neuroleptics). Risk of dystonia (and possibly other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Pigmentary retinopathy: May be associated with pigmentary retinopathy.

- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Dementia: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo. An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Flupenthixol is not approved for this indication.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC (based on similar agents)
LactationEnters breast milk/not recommended
Adverse ReactionsFrequency not defined.

Central nervous system: Extrapyramidal effects (up to 30%; including akathisia, dystonia, pseudoparkinsonism, tardive dyskinesia), anxiety/nervousness, insomnia, headache, dizziness, depression, fatigue

Dermatologic: Contact dermatitis, exfoliative dermatitis, pruritus, rash

Endocrine & metabolic: Galactorrhea, glycosuria, gynecomastia, hyperglycemia, libido decreased, weight gain

Gastrointestinal: Nausea, salivation increased, vomiting, xerostomia

Genitourinary: Micturition disorder

Neuromuscular & skeletal: Hypertonia, tremor, weakness

Ocular: Abnormal accommodation, abnormal vision

Miscellaneous: Diaphoresis increased

Additional adverse events associated with antipsychotics include arrhythmias, angioedema, hematologic adverse effects (agranulocytosis, hemolytic anemia, pancytopenia, thrombocytopenia), neuroleptic malignant syndrome (NMS), photosensitivity, seizure

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Monitoring ParametersVital signs; lipid profile, fasting blood glucose/Hgb A_{1c}; BMI; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms (EPS)

Monitoring: Lab TestsLipid profile, fasting blood glucose/Hgb A_{1c}; BMI

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as decanoate [depot]: 20 mg/mL (10 mL); 100 mg/mL (2 mL)

Tablet, as dihydrochloride: 0.5 mg, 3 mg

Generic AvailableNo

Mechanism of ActionFlupenthixol is a thioxanthene antipsychotic which blocks postsynaptic dopamine receptors in the CNS, resulting in inhibition of dopamine-mediated effects

Pharmacodynamics/Kinetics

Onset: I.M. depot: 24-72 hours following injection

Duration: I.M. depot: 2-4 weeks

Metabolism: Hepatic

Time to peak:

I.M. depot: 4-7 days

Oral: 3-8 hours

Excretion: Feces (as metabolites); urine (small amounts)

Related Information

- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsNot available in U.S.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsFlupenthixol is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health CommentPrimarily used as a long-acting injectable antipsychotic for patients who are nonadherent to oral medication treatment.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Index TermsFlupenthixol Decanoate; Flupenthixol Dihydrochloride

International Brand NamesDepixol (GB); Fluanxol (AT, BE, BG, CH, CL, CN, CZ, DE, DK, EE, FI, GB, HK, IL, IN, MY, NL, NO, NZ, PE, PH, PK, PT, SE, SG, TH, TW); Fluanxol Depot (AT, AU, BG, CH, CL, CZ, DE, DK, EE, FI, HK, HN, IL, IN, MY, NO, PE, PH, SE, SG, TH, TW, ZA); Psytixol (NZ)

Fluphenazine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

Gill SS, Bronskill SE, Normand SL, et al, “Antipsychotic Drug Use and Mortality in Older Adults With Dementia,” *Ann Intern Med*, 2007, 146(11):775-86.[PubMed 17548409]

Schneeweiss S, Setoguchi S, Brookhart A, et al, “Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients,” *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Medication Safety Issues

Sound-alike/look-alike issues:

Prolixin® may be confused with Proloprim®

International issues:

Prolixin® may be confused with Prolixan® which is a brand name for azapropazone in multiple international markets

Pronunciation(floo FEN a zeen)

Canadian Brand NamesApo-Fluphenazine Decanoate®; Apo-Fluphenazine®; Modecate®; Modecate® Concentrate; PMS-Fluphenazine Decanoate

Pharmacologic CategoryAntipsychotic Agent, Typical, Phenothiazine

Use: Labeled IndicationsManagement of manifestations of psychotic disorders and schizophrenia; depot formulation may offer improved outcome in individuals with psychosis who are nonadherent with oral antipsychotics

Use: Unlabeled/InvestigationalPervasive developmental disorder; nonpsychotic patient, dementia behavior in the elderly; psychosis/agitation related to Alzheimer's dementia

Dosing: Adults

Psychosis:

Oral: 0.5-10 mg/day in divided doses at 6- to 8-hour intervals; some patients may require up to 40 mg/day

I.M.: 2.5-10 mg/day in divided doses at 6- to 8-hour intervals (parenteral dose is $^{1}/_{3}$ to $^{1}/_{2}$ the oral dose for the hydrochloride salts)

Long-acting maintenance injections (Depot):

I.M. (decanoate): 12.5-37.5 mg every 2 weeks

Conversion from hydrochloride to decanoate I.M.: 0.5 mL (12.5 mg) decanoate every 3 weeks is approximately equivalent to 10 mg hydrochloride/day; **Note:** Clinically, an every-2-week interval is frequently utilized

Dosing: ElderlyNonpsychotic patient, dementia behavior (unlabeled use): Oral: 1-2.5 mg/day; increase dose at 4- to 7-day intervals by 1-2.5 mg/day. Increase dosing intervals (bid, tid) as necessary to control response or side effects. Maximum daily dose: 20 mg; gradual increases (titration) may prevent some side effects or decrease their severity.

Dosing: PediatricChildhood-onset pervasive developmental disorder (unlabeled use): Oral: 0.04 mg/kg/day

Dosing: Renal ImpairmentUse with caution; not dialyzable (0% to 5%).

Dosing: Hepatic ImpairmentUse with caution.

Administration: I.M.Watch for hypotension when administering I.M.

Administration: I.V. DetailpH: 4.8-5.2

Administration: OralAvoid contact of oral solution or injection with skin (contact dermatitis). Oral liquid should be diluted in the following **only**: Water, saline, homogenized milk, carbonated orange beverages, pineapple, apricot, prune, orange, tomato, and grapefruit juices. Do **not** dilute in beverages containing caffeine, tannics, or pectinate.

StorageAvoid freezing. Protect all dosage forms from light. Clear or slightly yellow solutions may be used. Should be dispensed in amber or opaque vials/bottles. Solutions may be diluted or mixed with fruit juices or other liquids, but must be administered immediately after mixing. Do not prepare bulk dilutions or store bulk dilutions.

Compatibility**Compatibility in syringe: Compatible:** Benztropine, diphenhydramine, hydroxyzine.

ContraindicationsHypersensitivity to fluphenazine or any component of the formulation (cross-reactivity between phenothiazines may occur); severe CNS depression; coma; subcortical brain damage; blood dyscrasias; hepatic disease

Allergy Considerations

- Phenothiazine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines).

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to other antipsychotics, fluphenazine has a low potency of cholinergic blockade.

- Blood dyscrasias: Check blood counts periodically and discontinue at first signs of blood dyscrasias; use is contraindicated in patients with bone marrow suppression.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).

- Extrapyramidal symptoms: May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is high relative to other neuroleptics).

- Hypotension: May occur, particularly with I.M. administration.

- Neuroleptic malignant syndrome (NMS): May be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Pigmentary retinopathy: May be associated with pigmentary retinopathy.

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for developing tardive dyskinesia.

Dosage form specific issues:

- Depot: Adverse effects of depot injections may be prolonged.

Geriatric ConsiderationsAny changes in disease status in any organ system can result in behavior changes.

Many elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior. Before initiating antipsychotic medication, the clinician should investigate any possible reversible cause; any stress or stress from any disease can cause acute “confusion” or worsening of baseline nonpsychotic behavior. Most commonly, acute changes in behavior are due to increases in drug dose or addition of a new drug to regimen, fluid electrolyte loss, infections, and changes in environment.

In the treatment of agitated, demented, and elderly patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly, neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control.

Pregnancy Risk FactorC
LactationEnters breast milk/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Tachycardia, fluctuations in blood pressure, hyper-/hypotension, arrhythmia, edema

Central nervous system: Parkinsonian symptoms, akathisia, dystonias, tardive dyskinesia, dizziness, hyper-reflexia, headache, cerebral edema, drowsiness, lethargy, restlessness, excitement, bizarre dreams, EEG changes, depression, seizure, NMS, altered central temperature regulation

Dermatologic: Dermatitis, eczema, erythema, itching, photosensitivity, rash, seborrhea, skin pigmentation, urticaria

Endocrine & metabolic: Menstrual cycle changes, breast pain, amenorrhea, galactorrhea, gynecomastia, libido changes, prolactin increased, SIADH

Gastrointestinal: Weight gain, appetite loss, salivation, xerostomia, constipation, paralytic ileus, laryngeal edema

Genitourinary: Ejaculatory disturbances, impotence, polyuria, bladder paralysis, enuresis

Hematologic: Agranulocytosis, leukopenia, thrombocytopenia, nonthrombocytopenic purpura, eosinophilia, pancytopenia

Hepatic: Cholestatic jaundice, hepatotoxicity

Neuromuscular & skeletal: Trembling of fingers, SLE, facial hemispasm

Ocular: Pigmentary retinopathy, cornea and lens changes, blurred vision, glaucoma

Respiratory: Nasal congestion, asthma

Metabolism/Transport Effects**Substrate** of CYP2D6 (major); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2D6 (weak), 2E1 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Analgesics (Opioid): Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antimalarial Agents: May increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Beta-Blockers: Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization). Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Monitoring ParametersVital signs; lipid profile, fasting blood glucose/Hgb A_{1c}; BMI; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms (EPS)

Reference RangeTherapeutic: 0.3-3 ng/mL (SI: 0.6-6.0 nmol/L); correlation of serum concentrations and efficacy is controversial; most often dosed to best response

Nursing: Physical Assessment/MonitoringAssess other medications patient is taking for effectiveness and interactions. Review ophthalmic screening and assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. With I.M. or SubQ use, monitor closely for hypotension. Initiate at lower doses and taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC prior to and regularly during therapy, lipid profile, liver and kidney function, fasting blood glucose/Hgb A_{1c}; BMI

Patient EducationUse exactly as directed; do not increase dose or frequency. Do not discontinue without consulting prescriber. Dilute with water, milk, orange or grapefruit juice; do not dilute with beverages containing caffeine, tannin, or pectinate (eg, coffee, colas, tea, or apple juice). Do not take within 2 hours of any antacid. Avoid alcohol or caffeine and other prescription or OTC medications not approved by prescriber. Avoid skin contact with medication; may cause contact dermatitis (wash immediately with warm, soapy water). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience excess drowsiness, lightheadedness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); dry mouth, upset stomach, nausea, vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruits, or fiber may help); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); urinary retention (void before taking medication); ejaculatory dysfunction (reversible); decreased perspiration (avoid strenuous exercise in hot environments); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report persistent CNS effects (eg, trembling fingers, altered gait or balance, excessive sedation, seizures, unusual movements, anxiety, abnormal thoughts, confusion, personality changes); chest pain, palpitations, rapid heartbeat, severe dizziness; unresolved urinary retention or changes in urinary pattern; altered menstrual pattern, change in libido, swelling or pain in breasts (male or female); vision changes; skin rash or irritation or yellowing of skin; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Elixir, as hydrochloride: 2.5 mg/5 mL (60 mL) [contains alcohol 14% and sodium benzoate] [DSC]

Injection, oil, as decanoate: 25 mg/mL (5 mL) [may contain benzyl alcohol, sesame oil]

Injection, solution, as hydrochloride: 2.5 mg/mL (10 mL)

Solution, oral concentrate, as hydrochloride: 5 mg/mL (120 mL) [contains alcohol 14%]

Tablet, as hydrochloride: 1 mg, 2.5 mg, 5 mg, 10 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Fluphenazine Decanoate)

25 mg/mL (5): $29.99

Tablets (Fluphenazine HCl)

1 mg (90): $18.00

2.5 mg (60): $15.99

5 mg (60): $18.99

10 mg (60): $24.99

Mechanism of ActionFluphenazine is a piperazine phenothiazine antipsychotic which blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors in the brain; depresses the release of hypothalamic and hypophyseal hormones; believed to depress the reticular activating system, thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis

Pharmacodynamics/Kinetics

Onset of action: I.M., SubQ (derivative dependent): Hydrochloride salt: ~1 hour

Peak effect: Neuroleptic: Decanoate: 48-96 hours

Duration: Hydrochloride salt: 6-8 hours; Decanoate: 24-72 hours

Absorption: Oral: Erratic and variable

Distribution: Crosses placenta; enters breast milk

Protein binding: 91% and 99%

Metabolism: Hepatic

Half-life elimination (derivative dependent): Hydrochloride: 33 hours; Decanoate: 163-232 hours

Excretion: Urine (as metabolites)

Related Information

- Antipsychotic Agents
- CMS: Long-Term Care Facility Thresholds
- Liquid Compatibility

Pharmacotherapy PearlsLess sedative and hypotensive effects than chlorpromazine.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and increased salivation (normal salivary flow resumes upon discontinuation). Orthostatic hypotension and nasal congestion are possible and since the drug is a dopamine antagonist, extrapyramidal symptoms of the TMJ are a possibility.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsMost pharmacology textbooks state that in presence of phenothiazines, systemic doses of epinephrine paradoxically decrease the blood pressure. This is the so called “epinephrine reversal” phenomenon. This has never been observed when epinephrine is given by infiltration as part of the anesthesia procedure.

Mental Health: Child/Adolescent ConsiderationsTwelve hospitalized children 7-11 years of age with childhood-onset pervasive developmental disorder received haloperidol or fluphenazine at an average dose of 0.04 mg/kg/day (Joshi, 1988).

Joshi PT, Capozzoli JA, and Coyle JT, “Low-Dose Neuroleptic Therapy for Children With Childhood-Onset Pervasive Developmental Disorder,” *Am J Psychiatry*, 1988, 145(3):335-8.

Mental Health CommentFluphenazine is a high-potency antipsychotic. Older antipsychotic medications (chlorpromazine, haloperidol), which do not meet specific criteria for “atypical” antipsychotics, are often referred to as typical antipsychotics. They are associated with the troubling side effect, EPS. However, it is commonly believed that in order for a drug to treat psychosis, it must block dopamine is some manner.

Common side effects include sedation and neuroleptic effect (reduced initiative, interest in the environment, and display of emotion or affect). All **typical** antipsychotics are considered to be equally effective if given in equipotent doses. An inverse relationship exists between intrinsic antimuscarinic activity and propensity to cause extrapyramidal side effects. If dystonia or pseudoparkinsonism occurs, antiparkinsonian agents should be considered. If akathisia occurs, beta-blockers (eg, propranolol), benzodiazepines, or antiparkinsonian agents should be considered. Tardive dyskinesia (TD) secondary to typical antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. After this time period, the incidence is estimated to be 2% to 3% per year. Prevalence rates are ~15% to 20%. Female gender and age constitute risk factors for TD. Indeed, prevalence rates have been reported to be as high as 70% in elderly females. No specific treatment exists for TD, however, patients are often initiated on/switched to an atypical antipsychotic because of their lower incidence to cause TD and hopes of suppression.

Typical antipsychotics are usually only indicated for schizophrenia, but are generally effective for mania and psychosis and/or behavioral syndromes secondary to other mental conditions. Nonpsychiatric uses include Tourette's syndrome, Huntington's disease, and occasionally, intractable hiccups, pruritus, nausea, and vomiting.

These drugs are thought to exert their antipsychotic activity by blocking dopamine D_2 receptors in the mesolimbic dopaminergic pathway. Side effects are often related to their ability to antagonize dopamine receptors in the nigrostriatal and tuberoinfundibular pathways.

Long-acting dosage form is useful in patients nonadherent to treatment.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Anesthesia and Critical Care Concerns/Other ConsiderationsLess sedative and hypotensive effects than chlorpromazine

Index TermsFluphenazine Decanoate

References

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Saltz BL, Woerner MG, Kane JM, et al, “Prospective Study of Tardive Dyskinesia Incidence in the Elderly,” *JAMA*, 1991, 266(17):2402-6. [PubMed 1681122]

Seifert RD, “Therapeutic Drug Monitoring: Psychotropic Drugs,” *J Pharm Pract*, 1984, 6:403-16.

International Brand NamesAnatensol (BE, IN, NL, PE); Cenilene (PT); Dapatum D25 (DE); Dapotum D (CH, HN); Dapotum d (HN); Dapotum Depot (AT); Deca (CL, MY, TH); Flucan (TW); Fludecasine (JP); Fludecate (CN, IL); Fludecate Multidose (ZA); Flufenan (BR); Fluxim (PH); Mirenil (PL); Mirenil prolongatum (PL); Modecate (AU, BB, BF, BJ, BM, BS, BZ, CI, ES, ET, FR, GB, GH, GM, GN, GY, HK, ID, IE, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, PK, PR, SC, SD, SG, SL, SN, SR, TN, TT, TZ, UG, UY, ZA, ZM, ZW); Modezine (PH); Moditen (AE, BH, CZ, IQ, KW, OM, QA, SA, VE, YE); Moditen Depot (HN); Phenazine (TH); Prolixin-D (CO); Siqualone (DK, FI, NO, SE)

Flurandrenolide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cordran® may be confused with Cardura®, codeine, Cordarone®

Pronunciation(flure an DREN oh lide)

U.S. Brand NamesCordran®; Cordran® SP

Canadian Brand NamesCordran®

Pharmacologic CategoryCorticosteroid, Topical

Use: Labeled IndicationsInflammation of corticosteroid-responsive dermatoses [medium potency topical corticosteroid]

Dosing: Adults**Note:** Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.

Steroid-responsive dermatosis: Topical (cream, lotion): Apply sparingly 2-3 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.

Steroid responsive dermatosis: Topical:

Cream: Apply sparingly 1-2 times/day

Tape: Apply once daily

ContraindicationsHypersensitivity to flurandrenolide or any component of the formulation; viral, fungal, or tubercular skin lesions

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible), particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Contact dermatitis: Allergic contact dermatitis can occur. It is usually diagnosed by failure to heal rather than clinical exacerbation.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Special populations:

- Pediatrics: Chronic use of corticosteroids in children may interfere with growth and development.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Cardiovascular: Intracranial hypertension

Dermatologic: Acne, acneiform eruptions, allergic contact dermatitis, dry skin, folliculitis, hyperpigmentation, hypertrichosis, itching, maceration of the skin, miliaria, perioral dermatitis, skin atrophy, striae

Endocrine & metabolic: Cushing's syndrome, growth retardation, HPA suppression

Local: Burning, irritation

Miscellaneous: Secondary infection

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Patient EducationA thin film is effective; do not overuse. Do not use tight-fitting diapers or plastic pants on children being treated in the diaper area. Use only as prescribed, and for no longer than the period prescribed. Apply sparingly in a light film and rub in lightly. Avoid contact with eyes. Notify prescriber if condition being treated persists or worsens. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, emulsified, as base (Cordran® SP): 0.05% (15 g, 30 g, 60 g)

Lotion (Cordran®): 0.05% (15 mL, 60 mL)

Tape, topical [roll] (Cordran®): 4 mcg/cm^2 (24 inch, 80 inch)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tape (Cordran)

4 mcg/cm^2 (1): $38.84

4 mcg/cm^2 (1): $79.55

Mechanism of ActionDecreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability

Pharmacodynamics/Kinetics

Absorption: Adequate with intact skin; repeated applications lead to depot effects on skin, potentially resulting in enhanced percutaneous absorption

Metabolism: Hepatic

Excretion: Urine; feces (small amounts)

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFlurandrenolone

References

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

International Brand NamesDrenison (BR); Haelan (GB)

Flurazepam

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Flurazepam may be confused with temazepam

Dalmane® may be confused with Demulen®, Dialume®

Pronunciation(flure AZ e pam)

U.S. Brand NamesDalmane®

Canadian Brand NamesApo-Flurazepam®; Dalmane® ; Som Pam

Pharmacologic CategoryBenzodiazepine

Use: Labeled IndicationsShort-term treatment of insomnia

Dosing: AdultsInsomnia (short-term treatment): Oral: 15-30 mg at bedtime

Dosing: ElderlyOral: 15 mg at bedtime. Avoid use if possible.

Dosing: PediatricHypnotic: Oral:

<15 years: Dose not established

≥15 years: 15 mg at bedtime

Administration: OralGive 30 minutes to 1 hour before bedtime on an empty stomach with full glass of water. May be taken with food if GI distress occurs.

StorageStore at 15°C to 30°C (59°F to 86°F).

RestrictionsC-IV

ContraindicationsHypersensitivity to flurazepam or any component of the formulation (cross-sensitivity with other benzodiazepines may exist); narrow-angle glaucoma; pregnancy

Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypersensitivity reactions: Postmarketing studies have indicated that the use of hypnotic/sedative agents for sleep has been associated with hypersensitivity reactions including anaphylaxis as well as angioedema.
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.
- Sleep-related activities: An increased risk for hazardous sleep-related activities such as sleep-driving; cooking and eating food, and making phone calls while asleep have also been noted.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use (generally >10 days).
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; active metabolites with extended half-lives may lead to delayed accumulation and adverse effects.

- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury. Active metabolites with extended half-lives may lead to delayed accumulation and adverse effects.

- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.

- Pediatrics: Safety and efficacy have not been established in children <15 years of age.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.

- Hypnotic: Appropriate use: As a hypnotic, should be used only after evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric or medical illness. A worsening of insomnia or the emergence of new abnormalities of thought or behavior may represent unrecognized psychiatric or medical illness and requires immediate and careful evaluation.

- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsDue to its long-acting metabolite, flurazepam is not considered a drug of choice in the elderly. Long-acting benzodiazepines have been associated with falls in the elderly. Interpretive guidelines from the Centers for Medicare and Medicaid Services (CMS) discourage the use of this agent in residents of long-term care facilities.

Pregnancy Risk FactorX

Pregnancy ConsiderationsAn increased risk of fetal malformations has been associated with maternal use of other benzodiazepines during the 1st trimester of pregnancy. Neonatal depression has been observed, specifically following exposure to flurazepam when used maternally for 10 consecutive days prior to delivery. Serum levels of N-desalkylflurazepam were measurable in the infant during the first 4 days of life. Use of flurazepam during pregnancy is contraindicated.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Chest pain, flushing, hypotension, palpitation

Central nervous system: Apprehension, ataxia, confusion, depression, dizziness, drowsiness, euphoria, faintness, falling, hallucinations, hangover effect, headache, irritability, lightheadedness, memory impairment, nervousness, paradoxical reactions, restlessness, slurred speech, staggering, talkativeness

Dermatologic: Pruritus, rash

Gastrointestinal: Appetite increased/decreased, bitter taste, constipation, diarrhea, GI pain, heartburn, nausea, salivation increased/excessive, upset stomach, vomiting, weight gain/loss, xerostomia

Hematologic: Granulocytopenia, leukopenia

Hepatic: Alkaline phosphatase increased, ALT increased, AST increased, cholestatic jaundice, total bilirubin increased

Neuromuscular & skeletal: Body/joint pain, dysarthria, reflex slowing, weakness

Ocular: Blurred vision, burning eyes, difficulty focusing

Respiratory: Apnea, dyspnea

Miscellaneous: Diaphoresis, drug dependence

Postmarketing and/or case reports: Anaphylaxis, angioedema, complex sleep-related behavior (sleep-driving, cooking or eating food, making phone calls)

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP2E1 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Serum levels and response to flurazepam may be increased by grapefruit juice, but unlikely because of flurazepam's high oral bioavailability.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersRespiratory and cardiovascular status

Reference RangeTherapeutic: 0-4 ng/mL (SI: 0-9 nmol/L); Metabolite N-desalkylflurazepam: 20-110 ng/mL (SI: 43-240 nmol/L); Toxic: >0.12 mcg/mL

Nursing: Physical Assessment/MonitoringFor short-term use. Assess effectiveness and interactions of other medications patient may be taking. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance. Be alert to possibility of anaphylaxis any time during therapy. Evaluate periodically for need for continued use. Monitor for CNS changes. After long-term use, taper dosage slowly when discontinuing. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to sexually-active female patients unless capable of complying with contraceptive use.

Patient EducationUse exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. Drug may cause physical and/or psychological dependence. May take with food to decrease GI upset. While using this medication, do not use alcohol or other prescription or OTC medications (especially, pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, lightheadedness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); dry mouth, nausea, or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); difficulty urinating (void before taking medication); or altered libido (resolves when medication is discontinued). Report CNS changes (confusion, depression, increased sedation, excitation, headache, abnormal thinking, insomnia, or nightmares, memory impairment, impaired coordination); muscle pain or weakness; respiratory difficulty; persistent dizziness, chest pain, or palpitations; unusual swelling, especially on face or neck; alterations in normal gait; vision changes; ringing in ears; or ineffectiveness of medication. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 15 mg, 30 mg

Dalmane®: 15 mg, 30 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Dalmane)

30 mg (30): $61.99

Capsules (Flurazepam HCl)

15 mg (30): $12.99

30 mg (30): $11.99

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Onset of action: Hypnotic: 15-20 minutes

Peak effect: 3-6 hours

Duration: 7-8 hours

Metabolism: Hepatic to N-desalkylflurazepam (active) and N-hydroxyethylflurazepam

Half-life elimination:

Flurazepam: 2.3 hours

N-desalkylflurazepam:

Adults: Single dose: 74-90 hours; Multiple doses: 111-113 hours

Elderly (61-85 years): Single dose: 120-160 hours; Multiple doses: 126-158 hours

Excretion: Urine: N-hydroxyethylflurazepam (22% to 55%); N-desalkylflurazepam (<1%)

Related Information

- Benzodiazepines
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), and bitter taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Flurazepam is a long half-life benzodiazepine. Duration of action after a single dose is determined by redistribution rather than metabolism. Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle-relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include personal or family history of substance abuse and personality disorder.

Anesthesia and Critical Care Concerns/Other ConsiderationsChronic use of this agent may increase the perioperative benzodiazepine dose needed to achieve desired effect. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

Index TermsFlurazepam Hydrochloride

References

Maletta G, Mattox KM, and Dysken M, “Guidelines for Prescribing Psychoactive Drugs in the Elderly: Part 1,” *Geriatrics*, 1991, 46(9):40-7. [PubMed 1889756]

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

Reidenberg MM, Levy M, Warner H, et al, “Relationship Between Diazepam Dose, Plasma Level, Age, and Central Nervous System Depression,” *Clin Pharmacol Ther*, 1978, 23(4):371-4. [PubMed 630787]

Ruff RL, Kutt H, and Hafler D, “Prolonged Benzodiazepine Coma,” *N Y State J Med*, 1981, 81(5):776-7. [PubMed 6111773]

Stringer MD, “Adult Respiratory Distress Syndrome Associated With Flurazepam Overdose,” *J R Soc Med*, 1985, 78(1)1:74-5.

International Brand NamesDalmadorm (BR, CH, GH, GT, HK, ID, KE, NL, NO, PT, TW, TZ, UG, ZM); Dalmane (GB, GH, IE, KE, TZ, UG, ZM); Dormodor (ES, ZA); Flunox (IT); Fluralema (VE); Fluraz (IN); Fluzepam (HR); Fordrim (AR); Insumin (JP); Manlsum (TW); Nergart (JP); Noctosom (IL); Somlan (AR); Staurodorm (AT, BE, DE, LU)

Flurbiprofen

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Flurbiprofen may be confused with fenoprofen

Ansaid® may be confused with Asacol®, Axid®

Ocufen® may be confused with Ocuflox®, Ocupress®

Pronunciation(flure BI proe fen)

U.S. Brand NamesOcufen®

Canadian Brand NamesAlti-Flurbiprofen; Ansaid®; Apo-Flurbiprofen®; Froben-SR®; Froben®; Novo-Flurprofen; Nu-Flurprofen; Ocufen®

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Ophthalmic; Nonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled Indications

Oral: Treatment of rheumatoid arthritis and osteoarthritis

Ophthalmic: Inhibition of intraoperative miosis

Use: DentalOral: Management of postoperative pain

Dosing: Adults

Rheumatoid arthritis and osteoarthritis: Oral: 200-300 mg/day in 2, 3, or 4 divided doses; do not administer more than 100 mg for any single dose; maximum: 300 mg/day

Management of postoperative dental pain: 100 mg every 12 hours

Ophthalmic anti-inflammatory/surgical aid: Ophthalmic: Instill 1 drop every 30 minutes, beginning 2 hours prior to surgery (total of 4 drops in each affected eye)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot recommended in patients with advanced renal disease.

Administration: OralTake with a full glass of water.

Dietary ConsiderationsTablet may be taken with food, milk, or antacid to decrease GI effects.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to flurbiprofen, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure, anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including**

MI, stroke, and new onset or worsening of pre-existing hypertension. Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin's cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.

- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly, or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs, even at low doses.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of the elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers, omeprazole, and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function, especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects, such as confusion, agitation, and hallucinations, are generally seen in overdose or high-dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (3rd trimester)

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies, however, adequate and well-controlled studies have not been conducted in pregnant women. Exposure late in pregnancy may lead to premature closure of the ductus arteriosus.

LactationEnters breast milk/not recommended

Adverse Reactions

Ophthalmic: Frequency not defined: Ocular: Slowing of corneal wound healing, mild ocular stinging, itching and burning, ocular irritation, fibrosis, miosis, mydriasis, bleeding tendency increased

Oral:

>1%:

Cardiovascular: Edema

Central nervous system: Amnesia, anxiety, depression, dizziness, headache, insomnia, malaise, nervousness, somnolence, vertigo

Dermatologic: Rash

Gastrointestinal: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, GI bleeding, nausea, vomiting, weight changes

Hepatic: Liver enzymes increased

Neuromuscular & skeletal: Reflexes increased, tremor, weakness

Ocular: Vision changes

Otic: Tinnitus

Respiratory: Rhinitis

<1% (Limited to important or life-threatening): Anaphylactic reaction, anemia, angioedema, asthma, bruising, cerebrovascular ischemia, CHF, confusion, eczema, eosinophilia, epistaxis, exfoliative dermatitis, fever, gastric/peptic ulcer, hematocrit decreased, hematuria, hemoglobin decreased, hepatitis, hypertension, hyperuricemia, interstitial nephritis, jaundice, leukopenia, paresthesia, parosmia, photosensitivity, pruritus, purpura, renal failure, stomatitis, thrombocytopenia, toxic epidermal necrolysis, urticaria, vasodilation

Metabolism/Transport Effects **Substrate** of CYP2C9 (minor); **Inhibits** CYP2C9 (strong)

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Latanoprost: NSAID (Ophthalmic) may diminish the therapeutic effect of Latanoprost. *Risk C: Monitor therapy*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Food may decrease the rate but not the extent of absorption.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. **Assess for allergic reaction to salicylate or other NSAIDs**. Assess effectiveness and interactions of other medications patient may be taking. Monitor blood pressure at the beginning of therapy and periodically during use. Monitor therapeutic response and adverse reactions at beginning of therapy and periodically throughout therapy. Assess knowledge/teach patient proper use, appropriate interventions to reduce side effects, and adverse symptoms to report.

Patient EducationOral: Take this medication exactly as directed; do not increase dose without consulting prescriber. Do not crush tablets. Take with food or milk to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol, aspirin or aspirin-containing medication, or any other anti-inflammatory medications without consulting prescriber. You may experience drowsiness, dizziness, nervousness, or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); anorexia, nausea, vomiting, or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or fluid retention (weigh yourself weekly and report unusual (3-5 lb/week) weight gain). GI bleeding, ulceration, or perforation can occur with or without pain; discontinue medication and contact prescriber if persistent abdominal pain or cramping, or blood in stool occurs. Report breathlessness, respiratory difficulty, or unusual cough; chest pain, rapid heartbeat, palpitations; unusual bruising/bleeding; blood in urine, stool, mouth, or vomitus; swollen extremities; skin rash or itching; acute fatigue; or hearing changes (ringing in ears). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy. Breast-feeding is not recommended.

Ophthalmic: Wash hands before instilling. Sit or lie down to instill. Open eye, look at ceiling, and instill prescribed amount of medication. Close eye and roll eye in all directions, and apply gentle pressure to inner corner of eye. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Use protective dark eyewear until healed; avoid direct sunlight. Temporary stinging or burning may occur. Report persistent pain, burning, redness, vision changes, swelling, itching, or worsening of condition.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic, as sodium: 0.03% (2.5 mL)

Ocufen®: 0.03% (2.5 mL)

Tablet: 50 mg, 100 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Flurbiprofen Sodium)

0.03% (2.5): $15.99

Solution (Ocufen)

0.03% (2.5): $20.99

Tablets (Ansaid)

100 mg (60): $156.79

Tablets (Flurbiprofen)

50 mg (60): $18.99

100 mg (60): $21.99

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: ~1-2 hours

Distribution: V_d: 0.12 L/kg

Protein binding: 99%, primarily albumin

Metabolism: Hepatic via CYP2C9; forms metabolites such as 4-hydroxy-flurbiprofen (inactive)

Half-life elimination: 5.7 hours

Time to peak: 1.5 hours

Excretion: Urine (primarily as metabolites)

Related Information

- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness; may rarely cause drowsiness, confusion, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease the clearance of lithium resulting in elevated serum levels and potential toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A meta-analysis (Pope, 1993) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 chronic heart failure guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin's inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function, and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

Index TermsFlurbiprofen Sodium

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International Brand Names Anflupin (TW); Ansaid (BB, BM, BS, BZ, CN, CR, CZ, DO, EC, GT, GY, HN, JM, MX, NI, NL, PA, PE, PL, SR, SV, TT); Bifen Cataplasma (KP); Cebutid (FR); Clinadol Forte (AR); Flugalin (PL); Flur Di Fen (TW); Flurofen (GR); Flurofen Retard (DK); Flurozin (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Froben (AE, AT, BE, BH, CH, CY, EG, GB, IL, IN, IQ, IR, JO, KW, LB, LY, MY, NL, OM, PK, PT, QA, SA, SY, YE, ZA); Lapole (JP); Lefenine (TW); Ocufen (AE, AU, BH, BR, CN, CO, CY, DK, EC, EG, FR, GB, IE, IL, IQ, IR, IT, JO, KP, KW, LB, LY, MX, OM, PE, PH, QA, SA, SY, TH, TW, VE, YE, ZA); Ocuflur (AT, BE, BG, CH, CZ, DE, ES, GR, HN, IN, PL, PT, RU); Strepfen (AU, PL); Strepsils Dolointensive (PL); Tolerane (AR, PY)

Flutamide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Flutamide may be confused with Flumadine®, thalidomide

Eulexin® may be confused with Edecrin®, Eurax®

Pronunciation(FLOO ta mide)

U.S. Brand NamesEulexin®

Canadian Brand NamesApo-Flutamide®; Euflex®; Eulexin®; Novo-Flutamide

Pharmacologic CategoryAntineoplastic Agent, Antiandrogen

Use: Labeled IndicationsTreatment of metastatic prostatic carcinoma in combination therapy with LHRH agonist analogues

Use: Unlabeled/InvestigationalFemale hirsutism

Dosing: AdultsRefer to individual protocols.

Prostate carcinoma: Oral: 250 mg 3 times/day; alternatively, once-daily doses of 0.5-1.5 g have been used (unlabeled dosing)

Female hirsutism (unlabeled use): Oral: 250 mg daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Combination Regimens

Prostate cancer:

FL

FZ

Administration: OralUsually administered orally in 3 divided doses. Contents of capsule may be opened and mixed with applesauce, pudding, or other soft foods. Mixing with a beverage is not recommended.

StorageStore at room temperature.

ContraindicationsHypersensitivity to flutamide or any component of the formulation; severe hepatic impairment; pregnancy

Allergy Considerations

- Flutamide Allergy

Warnings/Precautions

Boxed warnings:

- Liver failure: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Liver failure: **[U.S. Boxed Warning]: Hospitalization and, rarely, death due to liver failure have been reported in patients taking flutamide.** Elevated serum transaminase levels, jaundice, hepatic encephalopathy, and acute hepatic failure have been reported. In some patients, the toxicity reverses after discontinuation of therapy. About 50% of the cases occur within the first 3 months of treatment. Serum transaminase levels should be measured prior to starting treatment, monthly for 4 months, and periodically thereafter. Liver function tests should be obtained at the first suggestion of liver dysfunction (nausea, vomiting, abdominal pain, fatigue, anorexia, “flu-like” symptoms, hyperbilirubinuria, jaundice, or right upper quadrant tenderness). Should be immediately discontinued any time a patient has jaundice, and/or an ALT level greater than twice the upper limit of normal. Should not be used in patients whose ALT values are greater than twice the upper limit of normal.

Disease-related concerns:

- Hemoglobin M disease: Patients with hemoglobin M disease are at risk of toxicities associated with aniline exposure, including methemoglobinemia, hemolytic anemia, and cholestatic jaundice; monitor methemoglobin levels.

Special populations:

- Glucose-6 phosphate dehydrogenase deficiency: Patients with glucose-6 phosphate dehydrogenase deficiency are at risk of toxicities associated with aniline exposure, including methemoglobinemia, hemolytic anemia, and cholestatic jaundice; monitor methemoglobin levels.

- Smokers: Patients who smoke are at risk of toxicities associated with aniline exposure, including methemoglobinemia, hemolytic anemia, and cholestatic jaundice; monitor methemoglobin levels.
- Women: Product labeling states it is not for use in women, particularly for non-life-threatening conditions.

Geriatric ConsiderationsA study has shown that the addition of flutamide to leuprolide therapy in patients with advanced prostatic cancer increased median actuarial survival time to 34.9 months versus 27.9 months with leuprolide alone. No specific dose alterations are necessary in the elderly.

Pregnancy Risk FactorD

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Endocrine & metabolic: Breast tenderness, galactorrhea (9% to 42%), gynecomastia, hot flashes, impotence, libido decreased, tumor flare

Gastrointestinal: Nausea, vomiting (11% to 12%)

Hepatic: AST and LDH levels increased, transient, mild

1% to 10%:

Cardiovascular: Edema, hypertension (1%)

Central nervous system: Anxiety, confusion, depression, dizziness, drowsiness, headache, insomnia, nervousness

Dermatologic: Pruritus, ecchymosis, photosensitivity

Gastrointestinal: Anorexia, appetite increased, constipation, diarrhea, indigestion, upset stomach (4% to 6%)

Hematologic: Anemia (6%), leukopenia (3%), thrombocytopenia (1%)

Neuromuscular & skeletal: Weakness (1%)

Miscellaneous: Herpes zoster

<1%: Discoloration of urine (yellow), hepatic failure, hepatitis, hypersensitivity pneumonitis, jaundice, malignant breast neoplasm (male), MI, pulmonary embolism, sulfhemoglobinemia, thrombophlebitis

Oncology: Emetic PotentialLow (10% to 30%)

Metabolism/Transport Effects**Substrate** (major) of CYP1A2, 3A4; **Inhibits** CYP1A2 (weak)

Drug Interactions

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: No effect on bioavailability of flutamide.

Herb/Nutraceutical: St John's wort may decrease flutamide levels.

Monitoring ParametersSerum transaminase levels should be measured prior to starting treatment and should be repeated monthly for the first 4 months of therapy, and periodically thereafter. LFTs should be checked at the first sign or symptom of liver dysfunction (eg, nausea, vomiting, abdominal pain, fatigue, anorexia, flu-like symptoms, hyperbilirubinuria, jaundice, or right upper quadrant tenderness). Other parameters include tumor reduction, testosterone/estrogen, and phosphatase serum levels.

Nursing: Physical Assessment/MonitoringCarefully assess need for caution. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (risk for increased or decreased levels/effects of flutamide). Assess results of laboratory tests prior to and periodically during therapy (eg, serum transaminase levels). Therapeutic effectiveness (eg, reduction of tumor) and adverse response should be assessed on a regular basis throughout therapy (eg, galactorrhea, CNS changes, ataxia, anorexia, vomiting, lacrimation, anemia, liver function). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, chest pain, respiratory difficulty, abdominal pain, signs of liver dysfunction).

Monitoring: Lab TestsSerum transaminase levels should be obtained at baseline and repeated monthly for the first 4 months of therapy, and periodically thereafter. LFTs should be checked at the first sign or symptom of liver dysfunction. Other parameters include tumor reduction, testosterone/estrogen, prostate specific antigen, and phosphatase serum levels.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication will be prescribed in conjunction with another medication; take both exactly as directed; do not discontinue without consulting prescriber. May cause decreased libido, impotence, swelling of breasts, hot flashes, decreased appetite (small, frequent meals may help), or diarrhea (boiled milk, yogurt, or buttermilk may help). Report chest pain or palpitation; acute abdominal pain; pain, tingling, or numbness of extremities; swelling of extremities or unusual weight gain; respiratory difficulty; yellowing of skin or sclera, dark urine, pale stool, unusual fatigue; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant and do not get pregnant during or for 1 month following therapy. Consult prescriber for instruction on appropriate barrier contraceptive measures. This drug may cause severe fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 125 mg

Generic AvailableYes

ManufacturerSchering-Plough Corp

Pricing: U.S. (www.drugstore.com)

Capsules (Eulexin)

125 mg (180): $393.97

Mechanism of ActionNonsteroidal antiandrogen that inhibits androgen uptake or inhibits binding of androgen in target tissues

Pharmacodynamics/Kinetics

Absorption: Oral: Rapid and complete

Protein binding: Parent drug: 94% to 96%; 2-hydroxyflutamide: 92% to 94%

Metabolism: Extensively hepatic to more than 10 metabolites, primarily 2-hydroxyflutamide (active)

Half-life elimination: 5-6 hours (2-hydroxyflutamide)

Excretion: Primarily urine (as metabolites)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause nervousness or confusion

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms4′-Nitro-3′-Trifluoromethylisobutyrantide; Niftolid; NSC-147834; SCH 13521

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International Brand NamesAndraxan (PL); Apo-Flutam (PL); Bedozane (LU); Cytomid-250 (IN); Drogenil (GB, IE); Etaconil (CN, PE); Eulexin (AE, AR, BE, BH, BR, CO, CY, DK, EG, FI, IR, IT, KE, KP, KW, LU, LY, MX, NL, NO, NZ, OM, PE, PK, PT, QA, SA, SE, SY, TR, VE); Eulexine (FR); Flucinom (CH, CZ, GR, RU); Flucinome (HR); Fludinom (HN); Flugerel (TW); Fluken (MX); Flulem (MX, TH); Fluta-Cell (TH); Flutacan (LU, PL); Flutam (HU); Flutamex (DE); Flutamid (PL); Flutamid Abbott (HU); Flutamin (AU); Flutan (BG, TH); Flutaplex (MY, TH); Flutaratio (PL); Flutax (AR); Flutrax (EC); Fluxus (PY); Fugerel (AT, AU, HK, HN, HU, ID, PH, PL, TH); Fuprostatel (TW); Prostacur (ES); Prostandril (PL); Prostica (DE); Tafenil (MX)

Fluticasone and Salmeterol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Advair may be confused with Advicor®

Pronunciation(floo TIK a sone & sal ME te role)

U.S. Brand NamesAdvair Diskus®; Advair® HFA

Canadian Brand NamesAdvair Diskus®; Advair®

Pharmacologic CategoryBeta$_2$ Agonist; Beta$_2$-Adrenergic Agonist, Long-Acting; Corticosteroid, Inhalant (Oral)

Use: Labeled IndicationsMaintenance treatment of asthma; maintenance treatment of COPD

Dosing: Adults Do not use to transfer patients from systemic corticosteroid therapy.

COPD: Oral Inhalation:

Advair Diskus®: Fluticasone 250 mcg/salmeterol 50 mcg twice daily, 12 hours apart. **Note:** This is the maximum dose.

Advair Diskus® [Canadian labeling; not in approved U.S. labeling]: Fluticasone 250 mcg/salmeterol 50 mcg **or** fluticasone 500 mcg/salmeterol 50 mcg twice daily, 12 hours apart.

Maximum dose: Fluticasone 500 mcg/salmeterol 50 mcg per inhalation (2 inhalations/day)

Asthma (maintenance): Oral inhalation:

Advair Diskus®: One inhalation twice daily, morning and evening, 12 hours apart

Maximum dose: Fluticasone 500 mcg/salmeterol 50 mcg per inhalation (2 inhalations/day)

Advair® HFA: Two inhalations twice daily, morning and evening, 12 hours apart

Maximum dose: Fluticasone 230 mcg/salmeterol 21 mcg per inhalation (4 inhalations/day)

Advair® 125 or Advair® 250 [Canadian labeling; not in approved U.S. labeling]: Two inhalations twice daily, morning and evening, 12 hours apart

Maximum dose: Fluticasone 250 mcg/salmeterol 25 mcg per inhalation (4 inhalations/day)

Note: Initial dose prescribed should be based upon previous dose of inhaled-steroid asthma therapy. Dose should be increased after 2 weeks if adequate response is not achieved. Patients should be titrated to lowest effective dose once stable. Each suggestion below specifies the product strength to use; remember to **use 1 inhalation for Diskus® and 2 inhalations for HFA.**

Patients not currently on inhaled corticosteroids:

Advair Diskus®: Fluticasone 100 mcg/salmeterol 50 mcg **or** fluticasone 250 mcg/salmeterol 50 mcg

Advair® HFA: Fluticasone 45 mcg/salmeterol 21 mcg **or** fluticasone 115 mcg/salmeterol 21 mcg

Patients currently using inhaled beclomethasone dipropionate:

≤160 mcg/day: Fluticasone 100 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 45 mcg/salmeterol 21 mcg

320 mcg/day: Fluticasone 250 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 115 mcg/salmeterol 21 mcg

640 mcg/day: Fluticasone 500 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 230 mcg/salmeterol 21 mcg

Patients currently using inhaled budesonide:

≤400 mcg/day: Fluticasone 100 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 45 mcg/salmeterol 21 mcg

800-1200 mcg/day: Fluticasone 250 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 115 mcg/salmeterol 21mcg

1600 mcg/day: Fluticasone 500 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 230 mcg/salmeterol 21 mcg

Patients currently using inhaled flunisolide CFC aerosol:

≤1000 mcg/day: Fluticasone 100 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 45 mcg/salmeterol 21 mcg

1250-2000 mcg/day: Fluticasone 250 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 115 mcg/salmeterol 21 mcg

Patients currently using inhaled flunisolide HFA inhalation aerosol:

≤320 mcg/day: Fluticasone 100 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 45 mcg/salmeterol 21 mcg

640 mcg/day: Fluticasone 250 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 115 mcg/salmeterol 21 mcg

Patients currently using inhaled fluticasone HFA aerosol:

≤176 mcg/day: Fluticasone 100 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 45 mcg/salmeterol 21 mcg

440 mcg/day: Fluticasone 250 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 115 mcg/salmeterol 21 mcg

660-880 mcg/day: Fluticasone 500 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 230 mcg/salmeterol 21 mcg

Patients currently using inhaled fluticasone propionate powder:

≤200 mcg/day: Fluticasone 100 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 45 mcg/salmeterol 21 mcg

500 mcg/day: Fluticasone 250 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 115 mcg/salmeterol 21 mcg

1000 mcg/day: Fluticasone 500 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 230 mcg/salmeterol 21 mcg

Patients currently using inhaled mometasone furoate powder:

220 mcg/day: Fluticasone 100 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 45 mcg/salmeterol 21 mcg

440 mcg/day: Fluticasone 250 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 115 mcg/salmeterol 21 mcg

880 mcg/day: Fluticasone 500 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 230 mcg/salmeterol 21 mcg

Patients currently using inhaled triamcinolone acetonide:

≤1000 mcg/day: Fluticasone 100 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 45 mcg/salmeterol 21 mcg

1100-1600 mcg/day: Fluticasone 250 mcg/salmeterol 50 mcg **or** Advair® HFA: Fluticasone 115 mcg/salmeterol 21 mcg

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAsthma: Oral inhalation:

Children 4-11 years: Advair Diskus®: Fluticasone 100 mcg/salmeterol 50 mcg twice daily, 12 hours apart. **Note:** This is the maximum dose.

Children ≥12 years: Refer to adult dosing.

Dosing: Hepatic ImpairmentNo dosage adjustment reacquired; manufacturer suggests close monitoring of patients with hepatic impairment.

Administration: Inhalation

Advair Diskus®: After removing from box and foil pouch, write the “Pouch opened” and “Use by” dates on the label on top of the Diskus®. The “Use by” date is 1 month from date of opening the pouch. Every time the lever is pushed back, a dose is ready to be inhaled. Do not close or tilt the Diskus® after the lever is pushed back. Do not play with the lever or move the lever more than once. The dose indicator tells you how many doses are left. When the numbers 5 to 0 appear in red, only a few doses remain. Discard device 1 month after you remove it from the foil pouch or when the dose counter reads “0” (whichever comes first). Rinse mouth with water after use to reduce risk of oral candidiasis.

Advair® HFA: Shake well for 5 seconds before each spray. Prime with 4 test sprays (into air and away from face) before using for the first time. If canister is dropped or not used for >4 weeks, prime with 2 sprays. Patient should contact pharmacy for refill when the dose counter reads “020”. Discard device when the dose counter reads “000”. Do not spray in eyes. Rinse mouth with water after use to reduce risk of oral candidiasis.

Dietary ConsiderationsAdvair Diskus® powder for oral inhalation contains lactose; very rare anaphylactic reactions have been reported in patients with severe milk protein allergy.

Storage

Advair Diskus®: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Store in a dry place out of direct heat or sunlight. Diskus® device should be discarded 1 month after removal from foil pouch, or when dosing indicator reads “0” (whichever comes first); device is not reusable.

Advair® HFA: Store at controlled room temperature of 25°C (77°F). Store with mouthpiece down. Discard after 120 inhalations. Discard device when the dose counter reads “000”. Device is not reusable.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to fluticasone, salmeterol, or any component of the formulation; status asthmaticus; acute episodes of asthma or COPD

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Boxed warnings:

- Asthma-related deaths: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Adrenal suppression: Fluticasone may cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving ≥20 mg per day of prednisone (or equivalent) may be most susceptible. Concurrent use of ritonavir (and potentially other strong inhibitors of CYP3A4) may increase fluticasone levels and effects on HPA suppression. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do not provide the systemic steroid needed to treat patients having trauma, surgery, or infections. Do not use this product to transfer patients from oral corticosteroid therapy.

- Asthma-related deaths: **[U.S. Boxed Warning]: Long-acting beta$_2$-agonists may increase the risk of asthma-related deaths.** In a large, randomized clinical trial (SMART, 2006), salmeterol was associated with a small, but statistically significant increase in asthma-related deaths (when added to usual asthma therapy); risk may be greater in African-American patients versus Caucasians. Salmeterol should only be used as adjuvant therapy in patients not adequately controlled on inhaled corticosteroids or whose disease requires two maintenance therapies.

- Bone density: Long-term use may affect bone mineral density in adults.

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.

- Hypersensitivity reactions: Immediate hypersensitivity reactions (urticaria, angioedema, rash, bronchospasm) have been reported.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox or measles should be avoided; corticosteroids should not be used to treat ocular herpes simplex. Corticosteroids should not be used for cerebral malaria. Close observation is required in patients with latent tuberculosis and/or TB reactivity; restrict use in active TB (only in conjunction with antituberculosis treatment). With oral inhalation, local yeast infections (eg, oral pharyngeal candidiasis) may occur; patient should rinse mouth and spit after each use to reduce incidence. Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD using the oral inhalation with an even higher incidence in the elderly.

- Psychiatric manifestations: Corticosteroid use may cause psychiatric manifestations, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

- Serious effects/fatalities: Do not exceed recommended dose; serious adverse events, including fatalities, have been associated with excessive use of inhaled sympathomimetics.

- Upper airway symptoms: There have been reports of laryngeal spasm, irritation, and swelling (stridor, choking) with use.

- Vasculitis: Rare cases of vasculitis (Churg-Strauss syndrome) have been reported with fluticasone use.

Disease-related concerns:

- Asthma: Appropriate use: Do **not** use for acute asthmatic symptoms. Short-acting beta$_2$-agonist (eg, albuterol) should be used for acute symptoms and symptoms occurring between treatments. Do **not** initiate in patients with significantly worsening or acutely deteriorating asthma; reports of severe (sometimes fatal) respiratory events have been reported when salmeterol has been initiated in this situation. Fluticasone/salmeterol should only be used as adjuvant therapy in patients not adequately controlled on inhaled corticosteroids or whose disease requires two maintenance therapies. Corticosteroids should not be stopped or reduced when initiated. Fluticasone/salmeterol is not a substitute for systemic corticosteroids. During initiation watch for signs of worsening asthma.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (arrhythmia, hypertension, or HF); beta-agonists may cause elevation in blood pressure, heart rate, and result in CNS stimulation/excitation. Beta$_2$-agonists may also increase risk of arrhythmias.

- Diabetes: Use with caution in patients with diabetes mellitus; beta$_2$ agonists may increase serum glucose.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Hypokalemia: Use with caution in patients with hypokalemia; beta$_2$ agonists may decrease serum potassium.

- Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged fluticasone use. Consider routine eye exams in chronic users.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Seizure disorders: Use with caution in patients with seizure disorders; beta-agonists may result in CNS stimulation/excitation.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in patients with hyperthyroidism and decreases in hypothyroidism.

Special populations:

- Pediatrics: Orally-inhaled and intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients (~1 centimeter per year [range 0.3-1.8 cm per year] and related to dose and duration of exposure). To minimize the systemic effects of orally-inhaled and intranasal corticosteroids, each patient should be titrated to the lowest effective dose. Growth should be routinely monitored in pediatric patients. Safety and efficacy have not been established in children <4 years of age (Advair Diskus®) and children <12 years of age (Advair® HFA).

Dosage form specific issues:

- Lactose: Powder for oral inhalation (Advair Diskus®) contains lactose; very rare anaphylactic reactions have been reported in patients with severe milk protein allergy.

Other warnings/precautions:

- Discontinuation of therapy: There have been reports of systemic corticosteroid withdrawal symptoms (eg, joint/muscle pain, lassitude, depression) when withdrawing oral inhalation therapy.

- Patient information: Patients must be instructed to use short-acting beta$_2$-agonist (eg, albuterol) for acute asthmatic or COPD symptoms and to seek medical attention in cases where acute symptoms are not relieved or a previous level of response is diminished. The need to increase frequency of use of inhaled short-acting beta$_2$-agonist may indicate deterioration of asthma, and treatment must not be delayed. Salmeterol should not be used more than twice daily; do not use with other long-acting beta$_2$ agonists.

Geriatric ConsiderationsNo differences in safety or effectiveness have been seen in studies of patients ≥65 years of age. However, increased sensitivity may be seen in the elderly. Use with caution in patients with concomitant cardiovascular disease.
Pregnancy Risk FactorC
Pregnancy ConsiderationsSee individual agents.
Lactation

Fluticasone: Excretion in breast milk unknown/use caution

Salmeterol: Enters breast milk/use caution

Adverse ReactionsPercentages reported in patients with asthma; also see individual agents:

>10%:

Central nervous system: Headache (12% to 21%)

Respiratory: Upper respiratory tract infection (16% to 27%), pharyngitis (9% to 13%)

>3% to 10%:

Central nervous system: Dizziness (1% to 4%)

Endocrine & metabolic: Menstruation symptoms (3% to 5%)

Gastrointestinal: Nausea/vomiting (3% to 6%), diarrhea (2% to 4%), pain/discomfort (1% to 4%), oral candidiasis (1% to 4%), gastrointestinal infections (including viral, ≤4%)

Neuromuscular & skeletal: Musculoskeletal pain (2% to 7%), muscle pain (≤4%)

Respiratory: Throat irritation (7% to 9%), bronchitis (2% to 8%), upper respiratory tract inflammation (4% to 7%), lower respiratory tract infections/pneumonia (1% to 7%; COPD diagnosis and age >65 years increase risk), cough (3% to 6%), sinusitis (4% to 5%), hoarseness/dysphonia (1% to 5%), viral respiratory tract infection (3% to 5%)

1% to 3%:

Cardiovascular: Arrhythmia, chest symptoms, fluid retention, MI, palpitation, syncope, tachycardia

Central nervous system: Compressed nerve syndromes, hypnagogic effects, migraine, pain, sleep disorders, tremor

Dermatologic: Dermatitis, dermatosis, eczema, hives, skin flakiness, urticaria, viral skin infection

Endocrine & metabolic: Hypothyroidism

Gastrointestinal: Constipation, dental discomfort/pain, gastrointestinal infection, hemorrhoids, oral discomfort/pain, oral erythema/rash, oral ulcerations, unusual taste, weight gain

Genitourinary: Urinary tract infection

Hematologic: Contusions/hematomas

Hepatic: Abnormal liver function tests

Neuromuscular & skeletal: Arthralgia, articular rheumatism, bone/cartilage disorders, bone pain, cramps, fractures, muscle injuries (≤3%), muscle spasm, muscle stiffness, tightness/rigidity

Ocular: Conjunctivitis, edema, eye redness, keratitis, xerophthalmia

Respiratory: Blood in nasal mucosa, congestion, ear/nose/throat infection, epistaxis, laryngitis, lower respiratory hemorrhage, nasal irritation, rhinitis, rhinorrhea/postnasal drip, sneezing

Miscellaneous: Allergies/allergic reactions, bacterial infection, burns, candidiasis (≤3%), diaphoresis, sweat/sebum disorders, viral infection, wounds and lacerations

Postmarketing and/or case reports: Asthma exacerbation (serious and some fatal), abdominal pain, agitation, aggression, anaphylactic reaction (Diskus®: some in patients with severe milk allergy), angioedema, aphonia, atrial fibrillation, bronchospasm, cataracts, chest congestion, chest tightness, choking, contact dermatitis, Cushing syndrome, Cushingoid features, depression, dysmenorrhea, dyspepsia, dyspnea, earache, ecchymoses, edema (facial, oropharyngeal), eosinophilic conditions, glaucoma, growth velocity reduction in children/adolescents, hypercorticism, hyperglycemia, hypersensitivity reaction (immediate and delayed), hypertension, hypokalemia, hypothyroidism, influenza, intraocular pressure increased, laryngeal spasm/irritation, irregular menstruation, myositis, osteoporosis, pallor, paresthesia, paradoxical tracheitis, paranasal sinus pain, photodermatitis, PID, rash, restlessness, stridor, supraventricular tachycardia, syncope, vaginal candidiasis, vaginitis, vulvovaginitis, rare cases of vasculitis (Churg-Strauss syndrome), ventricular tachycardia, wheezing, xerostomia

Metabolism/Transport EffectsFluticasone: **Substrate** of CYP3A4 (major); Salmeterol: **Substrate** of CYP3A4 (major)

Drug Interactions

Alpha-/Beta-Blockers: May diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Amphotericin B: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antidiabetic Agents: Corticosteroids (Orally Inhaled) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Orally Inhaled). *Risk C: Monitor therapy*

Atomoxetine: May enhance the tachycardic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Betahistine: May diminish the therapeutic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Loop Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Corticosteroids (Orally Inhaled). *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Monitoring ParametersFEV_1, peak flow, and/or other pulmonary function tests; blood pressure, heart rate; CNS stimulation. Monitor for increased use of short-acting beta$_2$-agonist inhalers; may be marker of a deteriorating asthma condition. The growth of pediatric patients receiving inhaled corticosteroids should be monitored routinely (eg, via stadiometry).

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsFEV_1, peak flow, and/or other pulmonary function tests

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product; [CAN] = Canadian brand name/formulation

Aerosol, for oral inhalation:

Advair® HFA:

45/21: Fluticasone propionate 45 mcg and salmeterol 21 mcg (12 g) [120 metered inhalations]

115/21: Fluticasone propionate 115 mcg and salmeterol 21 mcg (12 g) [120 metered inhalations]

230/21: Fluticasone propionate 230 mcg and salmeterol 21 mcg (12 g) [120 metered inhalations]

Advair® [CAN]:

125/25: Fluticasone propionate 125 mcg and salmeterol 25 mcg (12 g) [120 metered inhalations] [not available in the U.S.]

250/25: Fluticasone propionate 250 mcg and salmeterol 25 mcg (12 g) [120 metered inhalations] [not available in the U.S.]

Powder, for oral inhalation:

Advair Diskus®:

100/50: Fluticasone propionate 100 mcg and salmeterol 50 mcg (14s, 28s [DSC], 60s) [contains lactose; chlorofluorocarbon free]

250/50: Fluticasone propionate 250 mcg and salmeterol 50 mcg (14s [DSC], 60s) [contains lactose; chlorofluorocarbon free]

500/50: Fluticasone propionate 500 mcg and salmeterol 50 mcg (14s [DSC], 60s) [contains lactose; chlorofluorocarbon free]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Aerosol (Advair HFA)

45-21 mcg/ACT (12): $178.76

115-21 mcg/ACT (12): $198.42

230-21 mcg/ACT (12): $269.91

Misc (Advair Diskus)

100-50 mcg/dose (60): $173.35

250-50 mcg/dose (60): $204.70

500-50 mcg/dose (28): $189.90

500-50 mcg/dose (60): $269.91

Mechanism of ActionCombination of fluticasone (corticosteroid) and salmeterol (long-acting beta$_2$-agonist) designed to improve pulmonary function and control over what is produced by either agent when used alone. Because fluticasone and salmeterol act locally in the lung, plasma levels do not predict therapeutic effect.

Fluticasone: The mechanism of action for all topical corticosteroids is believed to be a combination of three important properties: Anti-inflammatory activity, immunosuppressive properties, and antiproliferative actions. Fluticasone has extremely potent vasoconstrictive and anti-inflammatory activity.

Salmeterol: Relaxes bronchial smooth muscle by selective action on beta$_2$-receptors with little effect on heart rate

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Fluticasone
- Salmeterol

Pharmacotherapy PearlsEffects of inhaled/intranasal steroids on growth have been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally-inhaled and intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied.

Advair® HFA: Salmeterol (base) 21 mcg is equivalent to 30.45 mcg of salmeterol xinafoate.

Dental Health: Effects on Dental TreatmentLocalized infections with *Candida albicans* or *Aspergillus niger* have occurred frequently in the mouth and pharynx with repetitive use of oral inhaler of corticosteroids. These infections may require treatment with appropriate antifungal therapy or discontinuance of treatment with corticosteroid inhaler.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause headache, nervousness, dizziness, fatigue, or sleep disorders

Mental Health: Effects on Psychiatric TreatmentPropranolol may decrease the effects of salmeterol and cause bronchospasm in asthmatics. Combined use with MAO inhibitors and TCAs may increase the risk of cardiovascular toxicity (avoid concurrent use and within 14 days after discontinuing this agents).

Cardiovascular ConsiderationsCombination therapy for the treatment of asthma should be individualized for each patient. Inhaled steroid therapy, usually used for chronic obstructive lung disease, has the important advantage of having minimal systemic effects. Inhaled beta-agonists may increase heart rate. This should be considered in patients with disease states that may require heart rate control (eg, atrial fibrillation) since frequent use may counteract pharmacologic interventions directed at rate control.

Because of the frequent coexistence of chronic obstructive lung disease and coronary artery disease, many patients may require concurrent therapy with beta-agonists and beta-blockade. Selectivity for the beta-1 receptor varies among the available beta blockers. Cardioselective beta blockade (eg, atenolol, esmolol, metoprolol) with careful titration is preferred when this situation exists (Anderson, 2007). When an inhaled beta-agonist becomes necessary, monitor heart rate closely.

Anesthesia and Critical Care Concerns/Other ConsiderationsInhaled steroid therapy, usually used for chronic obstructive lung disease; has the important advantage of having minimal systemic effects. Beta-agonists may induce increases in heart rate. This should be considered in patients with resting tachycardia. Frequent use of inhaled beta-agonists when used in patients with atrial fibrillation may counteract pharmacologic interventions directed at ventricular rate control. It may take ≥1 week to see full benefits from treatment. This agent is not to be used for the relief of acute attacks.

Index Terms Fluticasone Propionate and Salmeterol Xinafoate; Salmeterol and Fluticasone

References

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Nelson HS, Weiss ST, Bleecker ER, et al, “The Salmeterol Multicenter Asthma Research Trial: A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy Plus Salmeterol,” *Chest*, 2006, 129(1):15-26.[PubMed 16424409]

International Brand Names Seretaide (PT); Seretide (AR, AT, BB, BE, BM, BR, BS, BZ, CH, CL, CN, CO, CR, DK, DO, EE, ES, FI, FR, GB, GT, GY, HK, HN, ID, IE, IL, IN, IT, JM, KP, MX, MY, NI, NL, NZ, PA, PE, PH, PY, SE, SG, SR, SV, TH, TT, VE); Seretide Accuhaler (AU); Serflu (UY)

Fluticasone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cutivate® may be confused with Ultravate®

International issues:

Allegro® [Israel] may be confused with Allegra® which is a brand name for fexofenadine in the U.S.

Allegro®: Brand name for frovatriptan in Germany

Flovent® may be confused with Flogen® which is a brand name for naproxen in Mexico

Pronunciation(floo TIK a sone)

U.S. Brand NamesCutivate®; Flonase®; Flovent® Diskus®; Flovent® HFA; Veramyst™

Canadian Brand NamesApo-Fluticasone; Avamys™; Cutivate™; Flonase®; Flovent® Diskus®; Flovent® HFA; ratio-Fluticasone

Pharmacologic CategoryCorticosteroid, Inhalant (Oral); Corticosteroid, Nasal; Corticosteroid, Topical

Use: Labeled Indications

Oral inhalation: Maintenance treatment of asthma as prophylactic therapy; also indicated for patients requiring oral corticosteroid therapy for asthma to assist in total discontinuation or reduction of total oral dose

Intranasal:

Flonase®: Management of seasonal and perennial allergic rhinitis and nonallergic rhinitis

Veramyst™: Management of seasonal and perennial allergic rhinitis

Avamys™ [CAN]: Management of seasonal allergic rhinitis

Topical: Relief of inflammation and pruritus associated with corticosteroid-responsive dermatoses; atopic dermatitis

Dosing: Adults

Asthma: Inhalation, oral: **Note:** Titrate to the lowest effective dose once asthma stability is achieved

Flovent® HFA: Manufacturers labeling: Dosing based on previous therapy

Bronchodilator alone: Recommended starting dose: 88 mcg twice daily; highest recommended dose: 440 mcg twice daily

Inhaled corticosteroids: Recommended starting dose: 88-220 mcg twice daily; highest recommended dose: 440 mcg twice daily; a higher starting dose may be considered in patients previously requiring higher doses of inhaled corticosteroids

Oral corticosteroids:

Recommended starting dose: 440 mcg twice daily

Highest recommended dose: 880 mcg twice daily; starting dose is patient dependent. In patients on chronic oral corticosteroids therapy, reduce prednisone dose no faster than 2.5-5 mg/day on a weekly basis; begin taper after 1 week of fluticasone therapy.

NIH Asthma Guidelines (NIH, 2007) (administer in divided doses twice daily):

“Low” dose: 88-264 mcg/day

“Medium” dose: 264-440 mcg/day

“High” dose: >440 mcg/day

Flovent® Diskus® *(U.S. labeling)*: **Note:** May increase dose after 2 weeks of therapy in patients not adequately controlled. Higher starting doses may be considered in patients with poorer asthma control or those requiring high ranges of inhaled corticosteroids. Titrate to the lowest effective dose once asthma stability is achieved.

Bronchodilator alone: Recommended starting dose: 100 mcg twice daily; maximum recommended dose: 500 mcg twice daily

Inhaled corticosteroids: Recommended starting dose: 100-250 mcg twice daily; maximum recommended dose: 500 mcg twice daily

Oral corticosteroids: Recommended starting dose: 500-1000 mcg twice daily; maximum recommended dose: 1000 mcg twice daily.

Starting dose is patient dependent. In patients on chronic oral corticosteroids therapy, reduce prednisone dose no faster than 2.5 mg/day on a weekly basis; begin taper after 1 week of fluticasone therapy.

Flovent® Diskus® *(Canadian labeling)*:

Mild asthma: 100-250 mcg twice daily

Moderate asthma: 250-500 mcg twice daily

Severe asthma: 500 mcg twice daily; may increase to 1000 mcg twice daily in very severe patients requiring high doses of corticosteroids

Corticosteroid-responsive dermatoses: Topical: Cream, lotion, ointment: Apply sparingly to affected area twice daily. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Atopic dermatitis: Topical: Cream, lotion: Apply sparingly to affected area once or twice daily. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Rhinitis: Intranasal:

Flonase® (fluticasone propionate): Initial: 2 sprays (50 mcg/spray) per nostril once daily; may also be divided into 100 mcg twice a day. After the first few days, dosage may be reduced to 1 spray per nostril once daily for maintenance therapy.

Veramyst™ (fluticasone furoate): Initial: 2 sprays (27.5 mcg/spray) per nostril once daily (110 mcg/day). Once symptoms are controlled, may reduce dosage to 1 spray per nostril once daily (55 mcg/day) for maintenance therapy.

Avamys™ [CAN] (fluticasone furoate): 2 sprays (27.5 mcg/spray) in each nostril once daily (110 mcg/day). Total daily dosage should not exceed 2 sprays in each nostril (110 mcg)/day.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Asthma: Inhalation, oral:

Flovent® HFA:

Children 4-11 years: 88 mcg twice daily

Children ≥12 years: Refer to adult dosing.

NIH Asthma Guidelines (NIH, 2007) (administer in divided doses twice daily):

"Low" dose:

0-4 years: 176 mcg/day

5-11 years: 88-176 mcg/day

≥12 years: 88-264 mcg/day

"Medium" dose:

0-4 years: >176-352 mcg/day

5-11 years: >176-352 mcg/day

≥12 years: >264-440 mcg/day

"High" dose:

0-4 years: >352 mcg/day

5-11 years: >352 mcg/day

≥12 years: >440 mcg/day

Flovent® Diskus® *(U.S. labeling)*:

Children 4-11 years: Usual starting dose: 50 mcg twice daily; may increase to 100 mcg twice daily in patients not adequately controlled after 2 weeks of therapy. Higher starting doses may be considered in patients with poorer asthma control or those requiring high ranges of inhaled corticosteroids. Titrate to the lowest effective dose once asthma stability is achieved (maximum dose: 100 mcg twice daily)

Children >11 years: Refer to adult dosing.

Flovent® Diskus® *(Canadian labeling)*:

Children 4-16 years: Usual starting dose: 50-100 mcg twice daily; may increase to 200 mcg twice daily in patients not adequately controlled; titrate to the lowest effective dose once asthma stability is achieved

Children ≥16 years: Refer to adult dosing.

Corticosteroid-responsive dermatoses: Topical: Children ≥3 months: Cream: Apply sparingly to affected area twice daily. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary. **Note:** Safety and efficacy of treatment >4 weeks duration have not been established.

Atopic dermatitis: Topical:

Children ≥3 months: Cream: Apply sparingly to affected area 1-2 times/day. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

Children ≥1 year: Lotion: Apply sparingly to affected area once daily.

Note: Safety and efficacy of treatment >4 weeks duration have not been established.

Rhinitis: Intranasal:

Flonase® (fluticasone propionate): Children ≥4 years and Adolescents: Initial: 1 spray (50 mcg/spray) per nostril once daily; patients not adequately responding or patients with more severe symptoms may use 2 sprays (100 mcg) per nostril. Depending on response, dosage may be reduced to 100 mcg daily. Total daily dosage should not exceed 2 sprays in each nostril (200 mcg)/day. Dosing should be at regular intervals.

Veramyst™ (fluticasone furoate):

Children 2-11 years: Initial: 1 spray (27.5 mcg/spray) per nostril once daily (55 mcg/day); patients not adequately responding may use 2 sprays per nostril once daily (110 mcg/day). Once symptoms are controlled, dosage may be reduced to 55 mcg once daily. Total daily dosage should not exceed 2 sprays in each nostril (110 mcg)/day.

Children ≥12 years and Adolescents: Initial: 2 sprays (27.5 mcg/spray) per nostril once daily (110 mcg/day). Once symptoms are controlled, dosage may be reduced to 1 spray per nostril once daily (55 mcg/day). Total daily dosage should not exceed 2 sprays in each nostril (110 mcg)/day.

Avamys™ (fluticasone furoate) [CAN]:Children ≥12 years: 2 sprays (27.5 mcg/spray) in each nostril once daily (110 mcg/day). Total daily dosage should not exceed 2 sprays in each nostril (110mcg)/day.

Dosing: Hepatic ImpairmentFluticasone is primarily cleared in the liver. Fluticasone plasma levels may be increased in patients with hepatic impairment, use with caution; monitor.

Administration: Inhalation

Aerosol inhalation: Flovent® HFA: Shake container thoroughly before using. Take 3-5 deep breaths. Use inhaler on inspiration. Allow 1 full minute between inhalations. Rinse mouth with water after use to reduce aftertaste and incidence of candidiasis; do not swallow. Flovent® HFA inhaler must be primed before first use, when not used for 7 days, or if dropped. To prime the first time, release 4 sprays into air; shake well before each spray and spray away from face. If dropped or not used for 7 days, prime by releasing a single test spray. Patient should contact pharmacy for refill when the dose counter reads “020”. Discard device when the dose counter reads “000”. Do not use “float” test to determine contents.

Nasal spray: Administer at regular intervals. Shake bottle gently before using. Blow nose to clear nostrils. Insert applicator into nostril, keeping bottle upright, and close off the other nostril. Breathe in through nose. While inhaling, press pump to release spray. Discard after labeled number of doses has been used, even if bottle is not completely empty.

Flonase®: Prime pump (press 6 times until fine spray appears) prior to first use or if spray unused for ≥7 days. Once weekly, nasal applicator may be removed and rinsed with warm water to clean.

Veramyst™, Avamys™ [CAN]: Prime pump (press 6 times until fine spray appears) prior to first use, if spray unused for ≥30 days, or if cap left off bottle for ≥5 days. After each use, nozzle should be wiped with a clean, dry tissue. Once weekly, inside of cap should be cleaned with a clean, dry tissue.

Powder for oral inhalation: Flovent® Diskus®: Do not use with a spacer device. Do not exhale into Diskus®. Do not wash or take apart. Use in horizontal position. Mouth should be rinsed with water after use (do not swallow). Discard after 6 weeks once removed from protective pouch or when the dose counter reads “0”, whichever comes first (device is not reusable).

Administration: TopicalCream, lotion, ointment: Apply sparingly in a thin film. Rub in lightly. Unless otherwise directed by healthcare professional, do not use with occlusive dressing; do not use on children’s skin covered by diapers or plastic pants.

Dietary ConsiderationsFlovent® Diskus® contains lactose; very rare anaphylactic reactions have been reported in patients with severe milk protein allergy.

Storage

Nasal spray:

Flonase®: Store between 4°C to 30°C (39°F to 86°F).

Veramyst™: Store between 15°C to 30°C (59°F to 86°F); do not refrigerate or freeze. Store in upright position with cap on.

Avamys™ [CAN]: Store between 4°C to 30°C (39°F to 86°F); do not refrigerate or freeze. Store in upright position with cap on.

Oral inhalation:

Flovent® HFA: Store at 15°C to 30°C (59°F to 86°F). Discard device when the dose counter reads “000”. Store with mouthpiece down.

Flovent® Diskus®: Store at 20°C to 25°C (68°F to 77°F) in a dry place away from direct heat or sunlight. Discard after 6 weeks from removal from protective foil pouch or when the dose counter reads “0” (whichever comes first); device is not reusable.

Topical, cream: Store at 15°C to 30°C (59°F to 86°F).

Cutivate® lotion: Store at 15°C to 30°C (59°F to 86°F). do not refrigerate.

Cutivate® cream, ointment: Store at 2°C to 30°C (36°F to 86°F).

ContraindicationsHypersensitivity to fluticasone or any component of the formulation; primary treatment of status asthmaticus or acute bronchospasm

Topical: Do not use if infection is present at treatment site, in the presence of skin atrophy, or for the treatment of rosacea or perioral dermatitis

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Topical application may also cause suppression of HPA axis, especially when used on large areas of the body, denuded areas, for prolonged periods of time, or with an occlusive dressing. Pediatric patients may be more susceptible to systemic toxicity. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving ≥20 mg per day of prednisone (or equivalent) may be most susceptible. Concurrent use of ritonavir (and potentially other strong inhibitors of CYP3A4) may increase fluticasone levels and effects on HPA suppression. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections.

- Bronchospasm: May occur with wheezing after inhalation; if this occurs, stop steroid and treat with a fast-acting bronchodilator.

- Delayed wound healing: Avoid nasal corticosteroid use in patients with recent nasal septal ulcers, nasal surgery, or nasal trauma until healing has occurred.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox should be avoided; corticosteroids should not be used to treat ocular herpes simplex. Corticosteroids should not be used for cerebral malaria. Close observation is required in patients with latent tuberculosis (TB) and/or TB reactivity; restrict use in active TB (only in conjunction with antituberculosis treatment). With oral inhalation, local yeast infections (eg, oral pharyngeal candidiasis) may occur; patient should rinse mouth and spit after each use to reduce incidence. Lower respiratory tract infections, including pneumonia, have been reported in patients with COPD using the oral inhalation with an even higher incidence in the elderly.

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

- Vasculitis: Rare cases of vasculitis (Churg-Strauss syndrome) or other eosinophilic conditions can occur.

Disease-related concerns:

- Asthma: Supplemental steroids (oral or parenteral) may be needed during stress or severe asthma attacks. Not to be used in status asthmaticus or for the relief of acute bronchospasm.

- Cardiovascular disease: Use with caution in patients with HF; long-term use has been associated with fluid retention and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.

- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred, especially during initial treatment with corticosteroids.

- Myocardial infarct (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Consider routine eye exams in chronic users.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Pediatrics: Orally-inhaled and intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients (~1 centimeter per year [range 0.3-1.8 cm per year] and related to dose and duration of exposure). To minimize the systemic effects of orally-inhaled and intranasal corticosteroids, each patient should be titrated to the lowest effective dose. Growth should be routinely monitored in pediatric patients. Safety and efficacy have not been established in children <4 years of age.

Dosage form specific issues:

- Flovent® Diskus®: Contains lactose; very rare anaphylactic reactions have been reported in patients with severe milk protein allergy.

Other warnings/precautions:

- Discontinuation of therapy: Withdraw systemic therapy with gradual tapering of dose. There have been reports of systemic corticosteroid withdrawal symptoms (eg, joint/muscle pain, lassitude, depression) when withdrawing oral inhalation therapy.

Geriatric ConsiderationsNo specific geriatric information is available. No differences in safety have been observed in the elderly when compared to younger patients. Based on current data, no dosage adjustment is needed based on age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic events have been observed in some, but not all, animal studies. There are no adequate and well-controlled studies using inhaled fluticasone in pregnant women. Oral corticosteroid use has shown animals to be more prone to teratogenic effects than humans. Due to the natural increase in corticosteroid production during pregnancy, most women may require a lower steroid dose; use with caution.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsSystemic corticosteroids are excreted in human milk. The extent of topical absorption is variable. Use with caution while breast-feeding; do not apply to nipples.

Adverse Reactions

Oral inhalation (includes reactions from Flovent® HFA and Flovent® Diskus® trials):

>10%:

Central nervous system: Headache (2% to 14%)

Respiratory: Upper respiratory tract infection (14% to 21%), throat irritation (3% to 22%)

3% to 10%:

Central nervous system: Fever (1% to 7%)

Gastrointestinal: Oral candidiasis (≤9%), nausea/vomiting (1% to 8%), gastrointestinal infection (including viral; 1% to 5%), gastrointestinal discomfort/pain (1% to 4%)

Neuromuscular & skeletal: Musculoskeletal pain (2% to 5%), muscle injury (1% to 5%)

Respiratory: Sinusitis/sinus infection (4% to 10%), lower respiratory tract infections/pneumonia (1% to 7%; COPD diagnosis and age >65 years increase risk), cough (1% to 6%), bronchitis (≤8%), hoarseness/dysphonia (2% to 6%), upper respiratory tract inflammation (≤5%), viral respiratory infection (1% to 5%), rhinitis (1% to 4%)

Miscellaneous: Viral infection (≤5%)

1% to 3%:

Cardiovascular: Chest symptoms, edema, palpitation

Central nervous system: Cranial nerve paralysis, dizziness, fatigue, malaise, migraine, mood disorders, pain, sleep disorder

Dermatologic: Acne, dermatitis/dermatosis, eczema, folliculitis, photodermatitis, infection (fungal, viral), pruritus, rash, urticaria

Endocrine metabolic: Fluid disturbance, goiter, uric acid metabolism disturbance

Gastrointestinal: Abdominal discomfort/pain, appetite changes, dental discomfort/pain, diarrhea, dyspepsia, gastroenteritis, hyposalivation, oral discomfort/pain, oral erythema/rash, oral ulcerations, oropharyngeal plaques, tooth decay, weight gain

Genitourinary: Reproductive organ infections (bacterial), urinary tract infection

Hematologic: Hematoma

Hepatic: Cholecystitis

Neuromuscular & skeletal: Arthralgia, articular rheumatism, muscle cramps/spasms, muscle pain, muscle stiffness/tightness/rigidity, musculoskeletal inflammation

Ocular: Blepharoconjunctivitis, conjunctivitis, keratitis

Otic: Otitis

Respiratory: Epistaxis, hoarseness/dysphonia, laryngitis, nasal sinus disorder, pharyngitis/throat infection, rhinorrhea/postnasal drip, throat constriction

Miscellaneous: Infection (bacterial, fungal); injuries (including muscle, soft tissue); polyps (ear, nose, throat); tonsillitis

Postmarketing and/or case reports: Aggression, agitation, anaphylactic reaction (rare; Diskus®: some patients with severe milk allergy), angioedema, anxiety, aphonia, asthma exacerbation, behavioral changes (eg, hyperactivity and irritability in children; rare), bronchospasm (immediate and delayed), cataracts, chest tightness, Churg-Strauss syndrome, contusion, Cushingoid features, cutaneous hypersensitivity, depression, dyspnea, ecchymoses, eosinophilia, facial edema, growth velocity reduction in children/adolescents, HPA axis suppression, hyperglycemia, hypersensitivity reactions (immediate and delayed), oropharyngeal edema, osteoporosis, paradoxical bronchospasm, restlessness, throat soreness, vasculitis, wheeze

Nasal inhalation (includes reactions from Flonase®, Veramyst™, and Avamys™ [CAN] trials):

>10%: Central nervous system: Headache (7% to 16%)

1% to 10%:

Central nervous system: Dizziness (1% to 3%), fever (1% to 5%)

Gastrointestinal: Nausea/vomiting (3% to 5%), abdominal pain (1% to 3%), diarrhea (1% to 3%)

Neuromuscular & skeletal: Back pain (1%)

Respiratory: Pharyngitis (6% to 8%), epistaxis (4% to 7%), asthma symptoms (3% to 7%), cough (3% to 4%), pharyngolaryngeal pain (2% to 4%), blood in nasal mucous (1% to 3%), bronchitis (1% to 3%), runny nose (1% to 3%), nasal ulcer (1%)

Miscellaneous: Aches and pains (1% to 3%), flu-like syndrome (1% to 3%)

<1% and postmarketing reports: Alteration or loss of sense of taste and/or smell, anaphylaxis/anaphylactoid reactions, angioedema, AST increased, AV block (second degree), blurred vision, bronchospasm, cataracts, conjunctivitis, dry/irritated eyes, dry throat, dyspnea, edema (face and tongue), glaucoma, hoarseness, hypersensitivity reactions, increased intraocular pressure, nasal candidiasis, nasal septal perforation (rare), palpitations, pruritus, psychomotor hyperactivity, sinus congestion, skin rash, sore throat, throat irritation, tremor, urticaria, vaginal candidiasis, voice changes, wheezing

Topical: Pruritus (3%), skin irritation (3%), exacerbation of eczema (2%), dryness (1%), numbness of fingers (1%)

Reported with other topical corticosteroids (in decreasing order of occurrence): Irritation, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, miliaria, pustular psoriasis from chronic plaque psoriasis

Metabolism/Transport Effects **Substrate** of CYP3A4 (major)

Drug Interactions

Amphotericin B: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antidiabetic Agents: Corticosteroids (Orally Inhaled) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Orally Inhaled). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Corticosteroids (Orally Inhaled). *Risk D: Consider therapy modification*

Thiazide Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions Herb/Nutraceutical: In theory, St John's wort may decrease serum levels of fluticasone by inducing CYP3A4 isoenzymes.

Monitoring Parameters Growth (adolescents and children); signs/symptoms of HPA axis suppression/adrenal insufficiency; possible eosinophilic conditions (including Churg-Strauss syndrome); FEV_1, peak flow, and/or other pulmonary function tests; asthma symptoms

Nursing: Physical Assessment/Monitoring Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. May take as long as 2 weeks before full benefit of medication is known. Encourage regular eye exams with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. Monitor for possible eosinophilic conditions (including Churg-Strauss syndrome); growth (adolescents and children); and signs/symptoms of HPA axis suppression/adrenal insufficiency.

Patient Education Use as directed; do not overuse and use only for length of time prescribed. Although you may see improvement within a few hours of use, the full benefit of the medication may not be achieved for several days. Do not change the prescribed dosage without consulting prescriber. Avoid exposure to chickenpox or measles. If exposed, inform your prescriber as soon as possible. May cause headache. Report signs of infection or change in vision to prescriber. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Metered-dose inhalation: Sit when using. Take deep breaths for 3-5 minutes, and clear nasal passages before administration (use decongestant as needed). Hold breath for 5-10 seconds after use, and wait 1-3 minutes between inhalations. Follow package insert instructions for use. Do not exceed maximum dosage. If also using inhaled bronchodilator, use before fluticasone. Rinse mouth and throat after use to reduce aftertaste and prevent candidiasis.

Nasal spray: Shake gently before use. Use at regular intervals, no more frequently than directed. Report unusual cough or spasm; persistent nasal bleeding, burning, or irritation; or worsening of condition.

Powder for oral inhalation: Flovent® Diskus®: Do not attempt to take device apart. Do not use with a spacer device. Do not exhale into the Diskus®; use in a level horizontal position. Do not wash the mouthpiece.

Topical: For external use only. Apply thin film to affected area only; rub in lightly. Do not apply occlusive covering unless advised by prescriber. Wash hand thoroughly after use; avoid contact with eyes. Notify prescriber if skin condition persists or worsens. Do not use for treatment of diaper dermatitis or under diapers or plastic pants.

⇧ Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Aerosol for oral inhalation, as propionate [CFC free]:

- Flovent® HFA: 44 mcg/inhalation (10.6 g) [120 metered actuations]
- Flovent® HFA: 110 mcg/inhalation (12 g) [120 metered actuations]
- Flovent® HFA: 220 mcg/inhalation (12 g) [120 metered actuations]

Cream, as propionate: 0.05% (15 g, 30 g, 60 g)

- Cutivate®: 0.05% (30 g, 60 g)

Lotion, as propionate:

- Cutivate®: 0.05% (120 mL)

Ointment, as propionate: 0.005% (15 g, 30 g, 60 g)

- Cutivate®: 0.005% (30 g, 60 g)

Powder for oral inhalation, as propionate:

- Flovent® Diskus® [U.S.]: 50 mcg (60s) [contains lactose; prefilled blister pack]
- Flovent® Diskus® [CAN]: 50 mcg (28s, 60s) [contains lactose; prefilled blister pack] [not available in the U.S.]
- Flovent® Diskus® [CAN]: 100 mcg (28s, 60s) [contains lactose; prefilled blister pack] [not available in the U.S.]
- Flovent® Diskus® [CAN]: 250 mcg (28s, 60s) [contains lactose; prefilled blister pack] [not available in the U.S.]
- Flovent® Diskus® [CAN]: 500 mcg (28s, 60s) [contains lactose; prefilled blister pack] [not available in the U.S.]

Suspension, intranasal, as furoate [spray]:

- Avamys™ [CAN]: 27.5 mcg/inhalation (4.5 g) [30 metered actuations; contains benzalkonium chloride]; (10 g) [120 metered actuations; contains benzalkonium chloride] [not available in the U.S.]
- Veramyst™: 27.5 mcg/inhalation (10 g) [120 metered actuations; contains benzalkonium chloride]

Suspension, intranasal, as propionate [spray]: 50 mcg/inhalation (16 g) [120 metered actuations]

- Flonase®: 50 mcg/inhalation (16 g) [120 metered actuations; contains benzalkonium chloride]

⇧ Generic AvailableYes: Cream, nasal spray, ointment
⇧ Pricing: U.S. (www.drugstore.com)

Aerosol (Flovent HFA)

- 44 mcg/ACT (10.6): $95.95
- 110 mcg/ACT (12): $125.46
- 220 mcg/ACT (12): $204.04

Cream (Cutivate)

- 0.05% (15): $25.99
- 0.05% (30): $37.99
- 0.05% (60): $85.99

Cream (Fluticasone Propionate)

- 0.05% (15): $14.99
- 0.05% (30): $18.99
- 0.05% (60): $27.99

Lotion (Cutivate)

0.05% (60): $114.99

0.05% (120): $229.98

Ointment (Cutivate)

0.005% (15): $25.99

0.005% (30): $37.99

0.005% (60): $89.99

Ointment (Fluticasone Propionate)

0.005% (15): $14.99

0.005% (30): $23.99

0.005% (60): $28.99

Suspension (Flonase)

50 mcg/ACT (16): $85.99

Suspension (Fluticasone Propionate)

50 mcg/ACT (16): $59.99

Suspension (Veramyst)

27.5 mcg/spray (10): $85.99

Mechanism of ActionFluticasone belongs to a group of corticosteroids which utilizes a fluorocarbothioate ester linkage at the 17 carbon position; extremely potent vasoconstrictive and anti-inflammatory activity; has a weak HPA inhibitory potency when applied topically, which gives the drug a high therapeutic index. The effectiveness of inhaled fluticasone is due to its direct local effect. The mechanism of action for all topical corticosteroids is believed to be a combination of three important properties: anti-inflammatory activity, immunosuppressive properties, and antiproliferative actions.

Pharmacodynamics/Kinetics

Onset of action: Intranasal: Maximal benefit may take several days

Flovent® HFA, Flovent® Diskus®: Maximal benefit may take 1-2 weeks or longer

Absorption:

Topical cream: 5% (increased with inflammation)

Oral inhalation: Absorbed systemically (Flovent® Diskus®: ~18%) primarily via lungs, minimal GI absorption (<1%) due to presystemic metabolism

Distribution: Propionate: 4.2 L/kg

Protein binding: 91% to 99%

Metabolism: Hepatic via CYP3A4 to 17β-carboxylic acid (negligible activity)

Bioavailability: Nasal: ≤2%; Oral inhalation: (~18% to 21%)

Excretion: Feces (as parent drug and metabolites); urine (<5% as metabolites)

Related Information

- Asthma
- Corticosteroids
- Inhalant Agents
- Status Epilepticus

Pharmacotherapy PearlsEffects of inhaled/intranasal steroids on growth have been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally-inhaled and intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied. The product labeling notes that intranasal administration was not associated with a statistically-significant reduction in growth velocity (based on a small study conducted over 1 year).

In the United States, dosage for the metered dose inhaler (Flovent® HFA) is expressed as the amount of drug which leaves the actuater and is delivered to the patient. This differs from other countries, which express the dosage as the amount of drug which leaves the valve.

Dental Health: Effects on Dental TreatmentLocalized infections with *Candida albicans* or *Aspergillus niger* have occurred frequently in the mouth and pharynx with repetitive use of oral inhaler of corticosteroids. These infections may require treatment with appropriate antifungal therapy or discontinuance of treatment with corticosteroid inhaler.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause agitation, aggression, anxiety, depression, hyperactivity, irritability, and restlessness

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other Considerations

Surgery: For patients who have received oral systemic corticosteroids during the past 6 months and for selected patients on long-term, high-dose, inhaled corticosteroid (ICS), give stress doses of hydrocortisone intravenously during the surgical period and reduce the dose rapidly within 24 hours after surgery (Expert Panel Report 3, 2007). Clinically important adrenal suppression has been reported in patients receiving high doses of an ICS, particularly children.

Index TermsFluticasone Furoate; Fluticasone Propionate

References

Expert Panel Report 3, “Guidelines for the Diagnosis and Management of Asthma,” *Clinical Practice Guidelines*, National Institutes of Health, National Heart, Lung, and Blood Institute, NIH Publication No. 08-4051, prepublication 2007. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

Todd GR, Acerini CL, Buck JJ, et al, "Acute Adrenal Crisis in Asthmatics Treated With High-Dose Fluticasone Propionate," *Eur Respir J*, 2002, 19(6):1207-9.[PubMed 12108877]

Todd GR, Acerini CL, Ross-Russell R, et al, "Survey of Adrenal Crisis Associated With Inhaled Corticosteroids in the United Kingdom," *Arch Dis Child*, 2002, 87(6):457-61.[PubMed 12456538]

International Brand NamesAllegro (IL); Atemur Mite (DE); Axotide (CH); Beconase Allergy 24 Hour (AU); Beconase Hayfever (AU); Cutivat (DK); Cutivate (AE, AR, AT, BB, BE, BG, BH, BM, BS, BZ, CH, CL, CO, CR, CY, CZ, DO, EC, EG, GB, GT, GY, HK, HN, HR, HU, ID, IL, IQ, IR, JM, JO, KP, KW, LB, LU, LY, MX, NI, NL, OM, PA, PE, PH, PK, PL, PT, PY, QA, SA, SG, SR, SV, SY, TT, TW, UY, VE, YE); Dalman AQ (HK); Flixonas (PK); Flixonase (AR, AT, BB, BE, BG, BM, BR, BS, BZ, CL, CN, CO, CR, CZ, DK, DO, EC, EE, ES, FI, FR, GT, GY, HK, HN, HR, HU, ID, IL, IT, JM, KP, LU, MX, MY, NI, NL, PA, PE, PL, PY, RU, SG, SR, SV, TH, TR, TT, TW, UY, VE); Flixonase Nasal Spray (NZ); Flixonase nasule (PL); Flixotaide (PT); Flixotide (AE, AT, BB, BE, BH, BM, BS, BZ, CL, CR, CY, CZ, DK, DO, EE, EG, ES, FI, FR, GB, GT, GY, HK, HN, HR, HU, ID, IE, IL, IQ, IR, JM, JO, KP, KW, LB, LU, LY, MX, MY, NI, NL, OM, PA, PE, PH, PL, QA, RU, SA, SE, SG, SR, SV, SY, TH, TT, TW, YE); Flixotide Disk (NZ); Flixotide Disks (AU); Flixotide Diskus (LU); Flixotide Dysk (PL); Flixotide Inhaler (AU); Flixotide Rotadisk (PL); Flixovate (FR); Fluinol (ES); Flusonal (ES); Flutide (DE, NO, SE); Flutivate (BR, CN, DE, NO); Inalacor (ES); Medicort (ID); Rinosone (ES); Trialona (ES); Zoflut (IN)

Fluvastatin

Lexi-Drugs Online

English English

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Special Alerts

HMG-CoA Reductase Inhibitors: Evidence Does Not Suggest Increased Incidence of Amyotrophic Lateral Sclerosis (ALS) - Results of FDA Analysis - September 30, 2008

The U.S. Food and Drug Administration's (FDA) review of 41 long-term controlled clinical trials of HMG-CoA reductase inhibitors finds no evidence of an increased incidence of ALS (also known as Lou Gehrig's disease) related to these medications. This analysis occurred after the FDA had received notice of numerous adverse events of which 109 of these reports mentioned ALS, Lou Gehrig's disease, or motor neurone disease. The clinical trials included in the analysis had a median duration of treatment of 3.3 years (range of duration: 6 months to 5 years) and involved 120,964 patients. The analysis identified a total of 19 cases of ALS – 9 cases per 64,602 patients (0.014%) with statin therapy and 10 cases per 56,362 patients (0.017%) with placebo. The incidence rates, based on approximately 400,000 person-years, were 4.2 per 100,000 person-years in the statin-treated group and 5 per 100,000 person-years in the placebo-treated group.

The FDA recommends that health care providers continue to prescribe, and patients continue to use these products as described within their labeling.

For more information, healthcare professionals may refer to the following:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Statin

Colman E, Szarfman A, Wyeth J, et al, "An Evaluation of a Data Mining Signal for Amyotrophic Lateral Sclerosis and Statins Detected in FDA's Spontaneous Adverse Event Reporting System," *Pharmacoepidemiol Drug Saf*, 2008 (epub ahead of print)

Medication Safety Issues

Sound-alike/look-alike issues:

Fluvastatin may be confused with fluoxetine

Pronunciation(FLOO va sta tin)

U.S. Brand NamesLescol®; Lescol® XL

Canadian Brand NamesLescol®; Lescol® XL

Pharmacologic CategoryAntilipemic Agent, HMG-CoA Reductase Inhibitor

Use: Labeled IndicationsTo be used as a component of multiple risk factor intervention in patients at risk for atherosclerosis vascular disease due to hypercholesterolemia

Adjunct to dietary therapy to reduce elevated total cholesterol (total-C), LDL-C, triglyceride, and apolipoprotein B (apo-B) levels and to increase HDL-C in primary hypercholesterolemia and mixed dyslipidemia (Fredrickson types IIa and IIb); to slow the progression of coronary atherosclerosis in patients with coronary heart disease; reduce risk of coronary revascularization procedures in patients with coronary heart disease

Dosing: Adults

Dyslipidemia (also delay in progression of CAD): Oral:

Patients requiring ≥25% decrease in LDL-C: 40 mg capsule once daily in the evening, 80 mg extended release tablet once daily (anytime), or 40 mg capsule twice daily

Patients requiring <25% decrease in LDL-C: Initial: 20 mg capsule once daily in the evening; may increase based on tolerability and response to a maximum recommended dose of 80 mg/day, given in 2 divided doses (immediate release capsule) or as a single daily dose (extended release tablet)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Heterozygous familial hypercholesterolemia: Adolescents 10-16 years: Oral: Initial: 20 mg once daily; may increase every 6 weeks based on tolerability and response to a maximum recommended dose of 80 mg/day, given in 2 divided doses (immediate release capsule) or as a single daily dose (extended release tablet)

Note: Indicated only for adjunctive therapy when diet alone cannot reduce LDL-C below 190 mg/dL, or 160 mg/dL (with cardiovascular risk factors). Female patients must be 1 year postmenarche.

Dosing: Renal ImpairmentLess than 6% is excreted renally. No dosage adjustment needed with mild-to-moderate renal impairment; use with caution in severe impairment.

Dosing: Hepatic ImpairmentLevels may accumulate in patients with liver disease (increased AUC and C_{max}). Use caution with severe hepatic impairment or heavy ethanol ingestion. Contraindicated in active liver disease or unexplained transaminase elevations. Decrease dose and monitor effects carefully in patients with hepatic insufficiency.

Administration: OralPatient should be placed on a standard cholesterol-lowering diet before and during treatment. Fluvastatin may be taken without regard to meals. Adjust dosage as needed in response to periodic lipid determinations during the first 4 weeks after a dosage change; lipid-lowering effects are additive when fluvastatin is combined with a bile-acid binding resin or niacin, however, it must be administered at least 2 hours following these drugs. Do not break, chew, or crush extended release tablets; do not open capsules.

Dietary ConsiderationsGenerally, patients should be placed on a standard cholesterol-lowering diet and other lifestyle modifications for 3-6 months prior to the initiation of drug therapy. The diet should be continued during drug therapy. However, for patients with advanced risk factors (eg, known coronary heart disease), drug therapy may be initiated concurrently with diet modification. May be taken without regard to meals. Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.

StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light.

ContraindicationsHypersensitivity to fluvastatin or any component of the formulation; active liver disease; unexplained persistent elevations of serum transaminases; pregnancy; breast-feeding

Allergy Considerations

- HMG-CoA Reductase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Myopathy/rhabdomyolysis: Patients receiving HMG-CoA reductase inhibitors have developed rhabdomyolysis with acute renal failure and/or myopathy; patients should be monitored closely. This risk is dose related and is increased with concurrent use of other lipid-lowering medications. Temporarily discontinue for elective major surgery, acute medical or surgical conditions, or in any patient experiencing an acute or serious condition predisposing to renal failure (eg, sepsis, hypotension, trauma, uncontrolled seizures). Based upon current evidence, HMG-CoA reductase inhibitor therapy should be continued in the perioperative period unless risk outweighs cardioprotective benefit. Use caution in patients with renal impairment, inadequately treated hypothyroidism, and those taking other drugs associated with myopathy (eg, colchicine); these patients are predisposed to myopathy. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine.

Disease-related concerns:

- Diseases reducing steroidogenesis: Use caution in patients with conditions or on medications that reduce steroidogenesis.

- Hepatic impairment and/or ethanol use: Use with caution in patients who consume large amounts of ethanol or have a history of liver disease.

Special populations:

- Elderly: Use with caution in patients with advanced age; these patients are predisposed to myopathy.

- Pediatrics: Treatment in patients <18 years of age is not recommended.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

- Liver function tests: Must be monitored by periodic laboratory assessment.

Geriatric ConsiderationsThe definition of and, therefore, when to treat hyperlipidemia in the elderly is a controversial issue. The National Cholesterol Education Program recommends that all adults maintain a plasma cholesterol <160 mg/dL. In elderly patients with one additional risk factor, goal LDL would decrease to <130 mg/dL. Pharmacologic treatment should be reserved for those who are unable to obtain a desirable plasma cholesterol concentration by diet alone and for whom the benefits of treatment are believed to outweigh the potential adverse effects, drug interactions, and cost of treatment.

Pregnancy Risk FactorX

Pregnancy ConsiderationsCholesterol biosynthesis may be important in fetal development. Contraindicated in pregnancy. Administer to women of childbearing potential only when conception is highly unlikely and patients have been informed of potential hazards.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsFluvastatin is excreted in human breast milk (milk plasma ratio 2:1); do not use in breast-feeding women.

Adverse ReactionsAs reported with fluvastatin capsules; in general, adverse reactions reported with fluvastatin extended release tablet were similar, but the incidence was less.

1% to 10%:

Central nervous system: Headache (9%), fatigue (3%), insomnia (3%)

Gastrointestinal: Dyspepsia (8%), diarrhea (5%), abdominal pain (5%), nausea (3%)

Genitourinary: Urinary tract infection (2%)

Neuromuscular & skeletal: Myalgia (5%)

Respiratory: Sinusitis (3%), bronchitis (2%)

<1% including additional class-related events (not necessarily reported with fluvastatin therapy) and postmarketing case reports: Alkaline phosphatase increased, alopecia, anaphylaxis, angioedema, anorexia, anxiety, arthralgia, arthritis, blurred vision, cataracts, chills, cholestatic jaundice, cirrhosis, CPK increased (>10x normal), depression, dermatomyositis, dizziness, dryness of skin/mucous membranes,

dyspnea, eosinophilia, erectile dysfunction, erythema multiforme, ESR increased, extraocular muscle movement impaired, facial paresis, fatty liver, fever, flushing, fulminant hepatic necrosis, GGT increased, gynecomastia, hemolytic anemia, hepatitis, hepatoma, hyperbilirubinemia, hypersensitivity reaction, impotence, leukopenia, libido decreased, malaise, memory loss, muscle cramps, myopathy, nail changes, nodules, ophthalmoplegia, pancreatitis, paresthesia, peripheral nerve palsy, peripheral neuropathy, photosensitivity, polymyalgia, positive ANA, pruritus, psychic disturbance, purpura, rash, renal failure (secondary to rhabdomyolysis), rhabdomyolysis, rheumatica, skin discoloration, Stevens-Johnson syndrome, systemic lupus erythematosus-like syndrome, taste alteration, thrombocytopenia, thyroid dysfunction, toxic epidermal necrolysis, transaminases increased, tremor, urticaria, vasculitis, vertigo, vomiting

Metabolism/Transport Effects**Substrate** of CYP2C9 (major), 2C8 (minor), 2D6 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2C8 (weak), 2C9 (moderate), 2D6 (weak), 3A4 (weak)

Drug Interactions

Amiodarone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. Management: Dose of HMG-CoA reductase inhibitor may need to be reduced (e.g., simvastatin prescribing information recommends not exceeding 20 mg/day during concurrent therapy). *Risk D: Consider therapy modification*

Colchicine: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

DAPTOmycin: HMG-CoA Reductase Inhibitors may enhance the adverse/toxic effect of DAPTOmycin. Specifically, the risk of skeletal muscle toxicity may be increased. Management: Consider temporarily stopping HMG-CoA reductase inhibitor therapy prior to daptomycin. If used together, regular (i.e., at least weekly) monitoring of CPK concentrations is recommended. *Risk D: Consider therapy modification*

Etravirine: May decrease the serum concentration of HMG-CoA Reductase Inhibitors. This applies to atorvastatin, lovastatin and simvastatin. Conversely, levels of fluvastatin may be increased. Management: Dose adjustment of the HMG-CoA reductase inhibitor may be warranted. No interaction is expected with rosuvastatin or pravastatin. *Risk C: Monitor therapy*

Fenofibrate: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Niacin: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Niacinamide: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): HMG-CoA Reductase Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid excessive ethanol consumption (due to potential hepatic effects).

Food: Reduces rate but not the extent of absorption. Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.

Monitoring ParametersObtain baseline LFTs and total cholesterol profile; repeat tests at 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter. Monitor LDL-C at intervals no less than 4 weeks.

Nursing: Physical Assessment/MonitoringEvaluate/rule out secondary causes of hyperlipidemia prior to beginning therapy. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, increased risk of rhabdomyolysis, acute renal failure). Assess results of laboratory tests (eg, LFTs and cholesterol profile) at baseline, when changing dosage and periodically thereafter. Monitor therapeutic effectiveness (reduced hyperlipemia) and adverse response (eg, myalgia, gastrointestinal disturbances; see Adverse Reactions) on a regular basis throughout therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to sexually-active female patients unless capable of complying with effective contraceptive use. Instruct patient in appropriate contraceptive measures. Breast-feeding is contraindicated.

Monitoring: Lab TestsObtain baseline LFTs and total cholesterol profile. Repeat tests at 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter. Monitor LDL-C at intervals no less than 4 weeks.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take as directed, with or without food. If also taking other chloesterol-lowering medication, check with prescriber for appropriate timing. Do not chew, crush, or dissolve extended release tablets; swallow whole. Follow diet and exercise regimen as prescribed. You will need periodic laboratory tests to evaluate response. You may experience nausea or dyspepsia (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or headache (consult prescriber for approved analgesic). Report muscle pain or cramping; tremor; CNS changes (eg, memory loss, depression, personality changes; numbness, weakness, tingling, pain in extremities); or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule (Lescol®): 20 mg, 40 mg

Tablet, extended release (Lescol® XL): 80 mg

Generic AvailableNo

ManufacturerNovartis Pharmaceuticals Corp

Pricing: U.S. (www.drugstore.com)

Capsules (Lescol)

20 mg (30): $85.99

40 mg (30): $83.51

Tablet, 24-hour (Lescol XL)

80 mg (30): $105.49

Mechanism of ActionActs by competitively inhibiting 3-hydroxyl-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the reduction of HMG-CoA to mevalonate; this is an early rate-limiting step in cholesterol biosynthesis. HDL is increased while total, LDL, and VLDL cholesterols; apolipoprotein B; and plasma triglycerides are decreased.

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Maximal LDL-C reductions achieved within 4 weeks

Distribution: V_d: 0.35 L/kg

Protein binding: >98%

Metabolism: To inactive and active metabolites (oxidative metabolism via CYP2C9 [75%], 2C8 [~5%], and 3A4 [~20%] isoenzymes); active forms do not circulate systemically; extensive (saturable) first-pass hepatic extraction

Bioavailability: Absolute: Capsule: 24%; Extended release tablet: 29%

Half-life elimination: Capsule: <3 hours; Extended release tablet: 9 hours

Time to peak: Capsule: 1 hour; Extended release tablet: 3 hours

Excretion: Feces (90%): urine (5%)

Related Information

- Hyperlipidemia Management
- Lipid-Lowering Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, insomnia, or drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular Considerations

HMG-CoA reductase inhibitors are effective in primary and secondary prevention of cardiovascular events in patients with hyperlipidemia. For primary prevention, a patient's major risk factors (cigarette smoking, hypertension or currently taking antihypertensives, low HDL-C, family history, age, gender) should be evaluated. Patients with multiple risk factors (≥2) require more intensive therapy guided by the calculation of a 10-year absolute CHD risk (eg, the percent probability of having a CHD event in next 10 years). An individual's 10-year absolute CHD risk can be calculated at www.med-decisions.com/cvtool/phys/phys.html. LDL cholesterol goals, therapeutic lifestyle changes, and drug therapy are determined based upon a patient's risk factor profile.

Primary prevention trials show that cholesterol-lowering drugs reduce the risk of major coronary events, coronary death, and cerebrovascular events even in the first 6-12 months of use. The WOSCOP trial suggested a trend towards enhanced survival using pravastatin in their patients (mean LDL-cholesterol of 192 mg/dL and no history of MI). In a recent trial (Sever, 2003), patients with HTN and at least three other risk factors were randomized to 10 mg daily of atorvastatin or placebo. These patients had a total nonfasting cholesterol <250 mg/dL before treatment. LDL-C levels were 132 mg/dL before treatment and fell to an average of 90 mg/dL in the atorvastatin-treated group. There was a significant reduction in stroke, cardiovascular events, and coronary events in the atorvastatin-treated group as compared to the placebo group. There was no difference in mortality between the groups.

Secondary prevention trials indicate that “statin” therapy reduces mortality, major coronary events, coronary artery procedures, and stroke. The Heart Protection Study proved that lowering serum cholesterol levels reduces the rate of major vascular events among high-risk individuals with documented vascular disease (CHD, cerebrovascular, peripheral vascular) or diabetes regardless of initial cholesterol concentrations. PROVE IT is a randomized, double-blind trial evaluating hospitalized patients with acute coronary syndrome to determine the effects of intense LDL-C lowering therapy. Four thousand patients with an LDL-C levels of 106 mg/dL were randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily. After 2 years, the combined cardiovascular endpoint (death, MI, unstable angina requiring hospitalization, revascularization and stroke) was ~26% in the pravastatin patients (median LDL-C 95 mg/dL) and ~22% in the atorvastatin treated patients (median LDL-C 62 mg/dL).

LaRosa and colleagues assessed the efficacy and safety of lowering LDL cholesterol <100 mg/dL in patients with stable coronary heart disease (LaRosa, 2005). Ten thousand and one patients with baseline LDL levels <130 mg/dL were randomized to atorvastatin 10 mg or 80 mg daily and followed for a median of 4.9 years. The primary endpoint was the occurrence of the first major cardiovascular event (death from CVD, MI, resuscitation after cardiac arrest, or stroke). A primary event occurred in 434 patients (8.7%) receiving 80 mg daily (mean LDL 77 mg/dL) and 548 patients (10.9%) receiving 10 mg dose (mean LDL 101 mg/dL) (95% CI, 0.69-0.89; p <0.001). There was no mortality difference between the two treatment groups.

HMG-CoA reductase inhibitors decrease levels of high-sensitivity C-reactive protein (hs-CRP). They also possess pleiotropic properties including improved endothelial function, reduced inflammation at the site of the coronary plaque, inhibition of platelet aggregation, and anticoagulant effects. These nonlipid effects may be beneficial when HMG-CoA reductase inhibitors are introduced early in the management of acute coronary syndromes (de Denus, 2002).

Myopathy: Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years of age), women more frequently than men, small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, drug interactions (use with caution or avoid). The combination of a HMG-CoA reductase inhibitor plus nicotinic acid seems to carry a lower risk of myopathy than does a HMG-CoA reductase inhibitor plus a fibrate. Other medications, when used concurrently, may enhance the risk of myopathy associated with statins; these include drugs that inhibit CYP3A4 isoenzymes (lovastatin, simvastatin, atorvastatin) or CYP2C9 isoenzymes (fluvastatin). HMG-CoA reductase inhibitors may exacerbate exercise-induced skeletal muscle injury. Many experts favor getting a baseline creatine kinase (CK) measurement before initiating therapy (asymptomatic CK elevations are common). Obtain a CK measurement if patient complains of muscle soreness, tenderness, or pain.

Anesthesia and Critical Care Concerns/Other Considerations**Myopathy:** Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years), gender (occurs in women more frequently than men), small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, and drug interactions (use with caution or avoid).

Based on current research, HMG-CoA reductase inhibitors should be continued in the perioperative period. Postoperative discontinuation of statin therapy is associated with an increased risk of cardiac morbidity and mortality.

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International Brand NamesCranoc (DE); Digaril (ES); Fractal (FR); Fractal LP (FR); Lescol (AE, AR, AT, AU, BB, BE, BG, BH, BM, BR, BS, BZ, CH, CL, CO, CY, CZ, DK, EE, EG, FI, FR, GB, GY, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JM, JO, KP, KW, LB, LY, MX, MY, NL, NO, NZ, OM, PE, PH, PL, PT, QA, RU, SA, SE, SG, SR, SY, TH, TR, TT, TW, VE, YE); Lescol LP (FR); Lescol XL (AU, EC, GB, ID, KP, MX, MY, PE, PH, PL, SG, TH, TW); Leucol (CN); Lochol (JP); Locol (DE); Lymetel (ES); Vastin (AU); Xilep XL ER (KP)

Fluvoxamine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Fluvoxamine may be confused with flavoxate, fluoxetine

Luvox may be confused with Lasix®, Levoxyl®, Lovenox®

Pronunciation(floo VOKS a meen)

U.S. Brand NamesLuvox® CR

Canadian Brand NamesAlti-Fluvoxamine; Apo-Fluvoxamine®; Luvox®; Novo-Fluvoxamine; Nu-Fluvoxamine; PMS-Fluvoxamine; Rhoxal-Fluvoxamine; Riva-Fluvoxamine; Sandoz-Fluvoxamine

Pharmacologic CategoryAntidepressant, Selective Serotonin Reuptake Inhibitor

Use: Labeled IndicationsTreatment of obsessive-compulsive disorder (OCD); treatment of social anxiety disorder

Use: Unlabeled/InvestigationalTreatment of major depression; panic disorder; anxiety disorders in children; treatment of mild dementia-associated agitation in nonpsychotic patients

Dosing: Adults

Obsessive-compulsive disorder: Oral:

Immediate release: Initial: 50 mg once daily at bedtime; may be increased in 50 mg increments at 4- to 7-day intervals, as tolerated; usual dose range: 100-300 mg/day; maximum dose: 300 mg/day. **Note:** When total daily dose exceeds 100 mg, the dose should be given in 2 divided doses with larger portion administered at bedtime.

Extended release: Initial: 100 mg once daily at bedtime; may be increased in 50 mg increments at intervals of at least 1 week; usual dosage range: 100-300 mg/day; maximum dose: 300 mg/day

Social anxiety disorder: Extended release: Initial: 100 mg once daily at bedtime; may be increased in 50 mg increments at intervals of at least 1 week; usual dosage range: 100-300 mg/day; maximum dose: 300 mg/day

Dosing: ElderlyReduce dose; titrate slowly. See Geriatric Considerations.

Dosing: Pediatric**Obsessive-compulsive disorder:** Oral:

Children 8-17 years: Immediate release: Initial: 25 mg once daily at bedtime; may be increased in 25 mg increments at 4- to 7-day intervals, as tolerated, to maximum therapeutic benefit; usual dose range: 50-200 mg/day. **Note:** When total daily dose of immediate release exceeds 50 mg, the dose should be given in 2 divided doses with larger portion administered at bedtime.

Maximum dose: Children: 8-11 years: 200 mg/day; Adolescents: 300 mg/day; lower doses may be effective in female versus male patients

Dosing: Hepatic ImpairmentReduce dose; titrate slowly.

Administration: OralMay be administered with or without food. Do not crush, open, or chew extended release capsules.

Dietary ConsiderationsMay be taken with or without food.

StorageProtect from high humidity and store at controlled room temperature 25°C (77°F).

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to fluvoxamine or any component of the formulation; concurrent use with alosetron, pimozide, thioridazine, or tizanidine; use with or within 14 days of MAO inhibitors

Allergy Considerations

- Selective Serotonin Reuptake Inhibitor (SSRI) Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Fluvoxamine is FDA approved for the treatment of OCD in children ≥8 years of age; extended release capsules are not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Fluvoxamine is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: Relatively devoid of these side effects.

- Bleeding risk: May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin, NSAIDs, warfarin or other anticoagulants. Bleeding related to SSRI use has been reported to range from relatively minor bruising and epistaxis to life-threatening hemorrhage.

- CNS depression: Has a low potential to impair cognitive or motor performance; caution operating hazardous machinery or driving.

- Neuroleptic malignant syndrome (NMS): Use with or without concomitant antipsychotic therapy has been rarely associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Sexual dysfunction: May cause or exacerbate sexual dysfunction.

- SIADH and hyponatremia: SSRIs and SNRIs have been associated with the development of SIADH; hyponatremia has been reported rarely (including severe cases with serum sodium <110 mmol/L), predominately in the elderly. Volume depletion and/or concurrent use of diuretics likely increases risk.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; fluvoxamine has not been systemically evaluated in patients with a recent history of MI or unstable heart disease.

- Hepatic impairment: Use with caution in patients with hepatic impairment; clearance is decreased and plasma concentrations are increased; a lower dosage may be needed.

- Seizure disorder: Use with caution in patients with a previous seizure disorder or condition predisposing to seizures such as brain damage or alcoholism.

Concurrent drug therapy issues:

- Agents which lower seizure threshold: Use caution with concurrent use of drugs which lower the seizure threshold.

- Alosetron: Fluvoxamine may significantly increase alosetron concentrations; concurrent use **contraindicated.**

- Anticoagulants/Antiplatelets: Use caution with concomitant use of NSAIDs, ASA, or other drugs that affect coagulation; the risk of bleeding may be potentiated.

- CNS depressants: Use caution with concomitant therapy.

- MAO inhibitors: Potential for severe reaction when used with MAO inhibitors; autonomic instability, coma, death, delirium, diaphoresis, hyperthermia, mental status changes/agitation, muscular rigidity, myoclonus, neuroleptic malignant syndrome features, and seizures may occur.

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce fluvoxamine's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

- Thioridazine and pimozide: Potential for QT_c prolongation and arrhythmia; concurrent use of fluvoxamine with either of these agents is **contraindicated.**

- Tizanidine: Concomitant use may cause a significant decrease in blood pressure and increase in drowsiness; concurrent use is **contraindicated.**

Special populations:

- Elderly: Use caution in elderly patients; clearance may be decreased and half-life may be increased compared to younger adults. Risk of hyponatremia and other adverse events may be increased.

- Smokers: Fluvoxamine levels may be lower in patients who smoke.

Other warnings/precautions:

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.
- Withdrawal syndrome: May cause dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Upon discontinuation of fluvoxamine therapy, gradually taper dose. If intolerable symptoms occur following a decrease in dosage or upon discontinuation of therapy, then resuming the previous dose with a more gradual taper should be considered.

Geriatric Considerations Given fluvoxamine's approved indication (OCD), the number of drug interactions, and the limited information available on its use in the elderly, it may be best to select a different agent when treating depression. The elderly are more prone to SSRI/SNRI-induced hyponatremia.

Pregnancy Risk Factor C

Pregnancy Considerations Due to adverse effects observed in animal studies, fluvoxamine is classified as pregnancy category C. Fluvoxamine crosses the human placenta. Nonteratogenic effects in the newborn following SSRI exposure late in the third trimester include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypo- or hypertonia, hyperreflexia, jitteriness, irritability, constant crying, and tremor. An increased risk of low birth weight and low APGAR scores has also been reported. Exposure to SSRIs after the twentieth week of gestation has been associated with persistent pulmonary hypertension of the newborn (PPHN). Adverse effects may be due to toxic effects of the SSRI or drug withdrawal due to discontinuation. The long-term effects of *in utero* SSRI exposure on infant development and behavior are not known.

Women treated for major depression and who are euthymic prior to pregnancy are more likely to experience a relapse when medication is discontinued as compared to pregnant women who continue taking antidepressant medications. The ACOG recommends that therapy with SSRIs or SNRIs during pregnancy be individualized; treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary healthcare provider, and pediatrician (ACOG, 2007). If treatment during pregnancy is required, consider tapering therapy during the third trimester in order to prevent withdrawal symptoms in the infant. If this is done and the woman is considered to be at risk from her major depressive disorder, the medication can be restarted following delivery, although the dose should be readjusted to that required before pregnancy.

Lactation Enters breast milk/consider risk:benefit (AAP rates “of concern”)

Breast-Feeding Considerations Fluvoxamine is excreted in breast milk. Based on case reports, the dose the infant receives is relatively small and adverse events have not been observed. According to the manufacturer, the decision to continue or discontinue breast-feeding during therapy should take into account the risk of exposure to the infant and the benefits of treatment to the mother. The AAP considers fluvoxamine to be a "drug for which the effect on the nursing infant is unknown, but may be of concern."

The long-term effects on development and behavior have not been studied; therefore, fluvoxamine should be prescribed to a mother who is breast-feeding only when the benefits outweigh the potential risks.

Adverse Reactions Frequency varies by dosage form and indication. Adverse reactions reported as a composite of all indications.

>10%:

Central nervous system: Headache (22% to 35%), insomnia (21% to 35%), somnolence (22% to 27%), dizziness (11% to 15%), nervousness (10% to 12%)

Gastrointestinal: Nausea (34% to 40%), diarrhea (11% to 18%), xerostomia (10% to 14%), anorexia (6% to 14%)

Genitourinary: Ejaculation abnormal (8% to 11%)

Neuromuscular & skeletal: Weakness (14% to 26%)

1% to 10%:

Cardiovascular: Chest pain (3%), palpitation (3%), vasodilation (2% to 3%), hypertension (1% to 2%), edema (≤1%), hypotension (≤1%), syncope (≤1%), tachycardia (≤1%)

Central nervous system: Pain (10%), anxiety (5% to 8%), abnormal dreams (3%), abnormal thinking (3%), agitation (2% to 3%), apathy (≥1% to 3%), chills (2%), CNS stimulation (2%), depression (2%), neurosis (2%), amnesia, malaise, manic reaction, psychotic reaction

Dermatologic: Bruising (4%), acne (2%)

Endocrine & metabolic: Libido decreased (2% to 10%; incidence higher in males), anorgasmia (2% to 5%), sexual function abnormal (2% to 4%), menorrhagia (3%)

Gastrointestinal: Dyspepsia (8% to 10%), constipation (4% to 10%), vomiting (4% to 6%), abdominal pain (5%), flatulence (4%), taste perversion (2% to 3%), tooth disorder (2% to 3%), dysphagia (2%), gingivitis (2%), weight loss (≤1% to 2%), weight gain

Genitourinary: Polyuria (2% to 3%), impotence (2%), urinary tract infection (2%), urinary retention (1%)

Hepatic: Liver function tests abnormal (≥1% to 2%)

Neuromuscular & skeletal: Tremor (5% to 8%), myalgia (5%), paresthesia (3%), hypertonia (2%), twitching (2%), hyper-/hypokinesia, myoclonus

Ocular: Amblyopia (2% to 3%)

Respiratory: Upper respiratory infection (9%), pharyngitis (6%), yawn (2% to 5%), laryngitis (3%), bronchitis (2%), dyspnea (2%), epistaxis

(2%), cough increased, sinusitis

Miscellaneous: Diaphoresis (6% to 7%), flu-like syndrome (3%), viral infection (2%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Acute renal failure, agranulocytosis, akinesia, allergic reaction, amenorrhea, anaphylactic reaction, anemia, angina, angioedema, anuria, aplastic anemia, apnea, asthma, ataxia, AV block, bradycardia, bullous eruption, cardiomyopathy, cerebrovascular accident, cholecystitis, cholelithiasis, colitis, conduction delay, coronary artery disease, deafness, delirium, diplopia, dyskinesia, dystonia, extrapyramidal syndrome, embolus, GI bleeding, goiter, hallucinations, heart failure, hematemesis, hematuria, Henoch-Schönlein purpura, hepatitis, hemoptysis, hypercholesterolemia, hyper-/hypoglycemia, hypokalemia, hyponatremia, hypothyroidism, ileus, intestinal obstruction, jaundice, laryngismus, leukopenia, leukocytosis, lymphadenopathy, melena, MI, myasthenia, myopathy, neuralgia, neuroleptic malignant syndrome, neuropathy, pancreatitis, paralysis, pericarditis, porphyria, priapism, purpura, retinal detachment, serotonin syndrome, ST segment changes, seizure, Stevens-Johnson syndrome, suicidal tendencies, supraventricular extrasystoles, tardive dyskinesia, thrombocytopenia, toxic epidermal necrolysis, vasculitis, ventricular tachycardia (including torsade de pointes)

Metabolism/Transport Effects **Substrate** (major) of CYP1A2, 2D6; **Inhibits** CYP1A2 (strong), 2B6 (weak), 2C9 (weak), 2C19 (strong), 2D6 (weak), 3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alosetron: Fluvoxamine may decrease the metabolism of Alosetron. *Risk X: Avoid combination*

Analgesics (Opioid): May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin Reuptake Inhibitor/Antagonist): Selective Serotonin Reuptake Inhibitors may enhance the serotonergic effect of Antidepressants (Serotonin Reuptake Inhibitor/Antagonist). This may cause serotonin syndrome. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Aspirin: Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

BusPIRone: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. Selective Serotonin Reuptake Inhibitors may decrease the metabolism of BusPIRone. *Risk C: Monitor therapy*

CarBAMazepine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of CarBAMazepine. Specifically those SSRIs that inhibit CYP3A4 isoenzymes. CarBAMazepine may increase the metabolism of Selective Serotonin Reuptake Inhibitors. Specifically those agents metabolized via CYP1A2, 2C, and/or 3A4 isoenzymes. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Selective Serotonin Reuptake Inhibitors. *Risk D: Consider therapy modification*

Clozapine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inhibitors (Strong) may decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Cyproheptadine: May diminish the therapeutic effect of Selective Serotonin Reuptake Inhibitors. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Desmopressin: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

DULoxetine: Fluvoxamine may decrease the metabolism of DULoxetine. *Risk C: Monitor therapy*

Haloperidol: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Haloperidol. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Iobenguane I 123: Selective Serotonin Reuptake Inhibitors may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methadone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Methadone. Fluvoxamine appears to be the only interacting SSRI. *Risk D: Consider therapy modification*

Mexiletine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Mexiletine. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk D: Consider therapy modification*

NSAID (Nonselective): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

OLANZapine: Fluvoxamine may decrease the metabolism of OLANZapine. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Phenytoin: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Pimozide: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Pimozide. *Risk X: Avoid combination*

Propranolol: Fluvoxamine may increase the serum concentration of Propranolol. Management: Use a lower initial propranolol dose and be cautious with propranolol dose titration. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

QuiNIDine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of QuiNIDine. Fluvoxamine appears to be the only SSRI of concern. *Risk D: Consider therapy modification*

Ramelteon: Fluvoxamine may decrease the metabolism of Ramelteon. *Risk X: Avoid combination*

Ropivacaine: Fluvoxamine may decrease the metabolism of Ropivacaine. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tacrine: Fluvoxamine may decrease the metabolism of Tacrine. *Risk D: Consider therapy modification*

Theophylline Derivatives: Fluvoxamine may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Thioridazine: Fluvoxamine may increase the serum concentration of Thioridazine. *Risk X: Avoid combination*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

TiZANidine: Fluvoxamine may decrease the metabolism of TiZANidine. *Risk X: Avoid combination*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

TraMADol: Selective Serotonin Reuptake Inhibitors may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. TraMADol may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tryptophan: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Selective Serotonin Reuptake Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol. Patients with depression should avoid/limit intake.

Food: The bioavailability of melatonin has been reported to be increased by fluvoxamine.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava (may increase risk of serotonin syndrome and/or excessive sedation). Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American), ginseng (Panax), ginseng (Siberian), grape seed, green tea, guggul, horse chestnuts, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Monitoring ParametersMental status for depression, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased), anxiety, social functioning, mania, panic attacks; akathisia, weight gain or loss, nutritional intake, sleep; liver function assessment prior to beginning drug therapy

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing (allow 3-4 weeks between discontinuing Luvox® and starting another antidepressant). Assess mental status for depression, suicidal ideation, anxiety, social functioning, mania, or panic attack. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsLiver function assessment prior to beginning drug therapy

Patient EducationTake exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results. Avoid alcohol, caffeine, and other prescription or OTC medications unless approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, weakness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, dry mouth, or anorexia (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruits, or fiber may help); diarrhea (buttermilk, yogurt, or boiled milk may help); postural hypotension (use caution when climbing stairs or changing position from lying or sitting to standing); or decreased sexual function or libido (reversible). Report persistent CNS effects (nervousness, restlessness, insomnia, anxiety, excitation, suicide ideation, headache, sedation, seizures, mania, abnormal thinking); rash or skin irritation; muscle cramping, tremors, or change in gait; chest pain or palpitations; change in urinary pattern; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as maleate: 25 mg, 50 mg, 100 mg

Capsule, extended release, as maleate:

Luvox® CR: 100 mg, 150 mg [gluten free]

Generic AvailableYes: Excludes extended release capsule

ManufacturerSolvay Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Fluvoxamine Maleate)

25 mg (30): $53.99

100 mg (50): $103.99

Mechanism of ActionInhibits CNS neuron serotonin uptake; minimal or no effect on reuptake of norepinephrine or dopamine; does not significantly bind to alpha-adrenergic, histamine or cholinergic receptors

Pharmacodynamics/Kinetics

Onset of action: Depression: The onset of action is within a week, however, individual response varies greatly and full response may not be seen until 8-12 weeks after initiation of treatment.

Absorption: Steady-state plasma concentrations have been noted to be 2-3 times higher in children than those in adolescents; female children demonstrated a significantly higher AUC than males

Distribution: V_d: ~25 L/kg

Protein binding: ~80%, primarily to albumin

Metabolism: Extensively hepatic via oxidative demethylation and deamination

Bioavailability: Immediate release: 53%; not significantly affected by food

Half-life elimination: 15-16 hours; 17-26 hours in the elderly

Time to peak, plasma: 3-8 hours

Excretion: Urine (~85% as metabolites; ~2% as unchanged drug)

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Selective Serotonin Reuptake Inhibitors (SSRIs) CYP Profile
- Selective Serotonin Reuptake Inhibitors (SSRIs) FDA-Approved Indications
- Selective Serotonin Reuptake Inhibitors (SSRIs) Pharmacokinetics
- Selective Serotonin Reuptake Inhibitors (SSRIs) Receptor Profile

- Teratogenic Risks of Psychotropic Medications

Dental Health Professional ConsiderationsProblems with SSRI-induced bruxism have been reported and may preclude their use. Clinicians attempting to evaluate any patient with bruxism or involuntary muscle movement, who is simultaneously being treated with an SSRI drug, should be aware of the potential association.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and abnormal taste. Problems with SSRI-induced bruxism have been reported and may preclude their use; clinicians attempting to evaluate any patient with bruxism or involuntary muscle movement, who is simultaneously being treated with an SSRI drug, should be aware of the potential association. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAlthough caution should be used in patients taking tricyclic antidepressants, no interactions have been reported with vasoconstrictors and fluvoxamine, a nontricyclic antidepressant which acts to increase serotonin; no precautions appear to be needed

Mental Health: Child/Adolescent ConsiderationsChildren 8-17 years of age with obsessive-compulsive disorder (OCD) received 50-200 mg/day for 10 weeks (Riddle, 2001). One hundred twenty-eight children 6-17 years of age with social phobia, separation anxiety disorder, or generalized anxiety disorder, who had received psychological treatment for 3 weeks without improvement, received fluvoxamine up to 300 mg/day for 8 weeks (Research Unit, 2001).

“Fluvoxamine for the Treatment of Anxiety Disorders in Children and Adolescents. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group,” *N Engl J Med*, 2001, 344(17):1279-85.

Riddle MA, Reeve EA, Yaryura-Tobias JA, et al, “Fluvoxamine for Children and Adolescents With Obsessive-Compulsive Disorder: A Randomized, Controlled, Multicenter Trial,” *J Am Acad Child Adolesc Psychiatry*, 2001, 40(2):222-9.

Mental Health CommentThe SSRIs as a class are generally considered to be safe and equally effective. Allow sufficient dose-response time (6-12 weeks). Differences lie in approved indications, receptor profiles, pharmacokinetics, and cytochrome P450 activity profile. Subtle differences exist in adverse effect profiles. All SSRIs have the potential to cause sexual dysfunction. Fluvoxamine is only approved in U.S. for obsessive-compulsive disorder (OCD), offers no advantage over other SSRIs, and is associated with significant CYP inhibitory properties.

Index TermsLuvox

References

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“Fluvoxamine for the Treatment of Anxiety Disorders in Children and Adolescents. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group,” *N Engl J Med*, 2001, 344(17):1279-85. [PubMed 11323729]

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Riddle MA, Reeve EA, Yaryura-Tobias JA, et al, “Fluvoxamine for Children and Adolescents With Obsessive-Compulsive Disorder: A Randomized, Controlled, Multicenter Trial,” *J Am Acad Child Adolesc Psychiatry*, 2001, 40(2):222-9. [PubMed 11211371]

Roose SP, Glassman AH, Attia E, et al, “Comparative Efficacy of Selective Serotonin Reuptake Inhibitors and Tricyclics in the Treatment of Melancholia,” *Am J Psychiatry*, 1994, 151(12):1735-9. [PubMed 7977878]

Wynn RL, “New Antidepressant Medications,” *Gen Dent*, 1997, 45(1):24-8.[PubMed 9171475]

International Brand NamesAnwu (TW); Avoxin (HR); Dumirox (ES, KP, UY); Dumyrox (GR, PT); Faverin (AE, AU, BH, CY, EG, GB, HK, IE, IL, IQ, IR, JO, KW, LB, LY, OM, PH, PK, QA, SA, SY, TH, TR, YE); Favoxil (IL); Fevalax (PY); Fevarin (BG, CZ, DK, EE, FI, HN, HR, HU, IT, NL, NO, PL, RU, SE); Floxyfral (AT, BE, CH, FR, LU); Fluvohexal (DE); Fluvoxin (IN, TH); Luvox (AR, AU, BR, CL, CN, EC, ID, MX, MY, PE, TW, VE, ZA); Movox (AU); Voxam (AU); Voxamin (CO); Vuminix (MX)

FOIL

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Colorectal Cancer]

Regimen Use Colorectal cancer

Regimen

Irinotecan: I.V.: 175 mg/m^2 day 1

[total dose/cycle = 175 mg/m^2]

Oxaliplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Leucovorin: I.V.: 200 mg/m^2 day 1

[total dose/cycle = 200 mg/m^2]

Fluorouracil: I.V.: 3800 mg/m^2/day continuous infusion days 1 and 2

[total dose/cycle = 7600 mg/m^2]

Repeat cycle every 14 days

References

Falcone A, Masi G, Allegrini G, et al, âBiweekly Chemotherapy With Oxaliplatin, Irinotecan, Infusional Fluorouracil, and Leucovorin: A Pilot Study in Patients With Metastatic Colorectal Cancer,â *J Clin Oncol*, 2002, 20(19):4006-14.[PubMed 12351598]

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Colorectal Cancer

Regimen UseColorectal cancer

Regimen

Oxaliplatin: I.V.: 130 mg/m^2 day 1 (every other cycle)

[total dose/cycle = 130 mg/m^2]

Leucovorin: I.V.: 500 mg/m^2/day days 1 and 2

[total dose/cycle = 1000 mg/m^2]

Fluorouracil: I.V.: 1.5-2 g/m^2/day continuous infusion days 1 and 2

[total dose/cycle = 3-4 g/m^2]

Repeat cycle every 14 days

References

de Gramont A, Tournigand C, Louvet C, et al, âOxaliplatin, Folinic Acid, and 5-Fluorouracil (Folfox) in Pretreated Patients With Metastatic Advanced Cancer, The GERCOD,â *Rev Med Interne*, 1997, 18(10):769-75.[PubMed 9500010]

FOLFOX 2

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Colorectal Cancer

Regimen UseColorectal cancer

Regimen

Oxaliplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Leucovorin: I.V.: 500 mg/m^2/day days 1 and 2

[total dose/cycle = 1000 mg/m^2]

Fluorouracil: I.V.: 1.5-2 g/m^2/day continuous infusion days 1 and 2

[total dose/cycle = 3-4 g/m^2]

Repeat cycle every 14 days

References

de Gramont A, Vignoud J, Tournigand C, et al, âOxaliplatin With High-Dose Leucovorin and 5-Fluorouracil 48-Hour Continuous Infusion in Pretreated Metastatic Colorectal Cancer,â *Eur J Cancer*, 1997, 33(2):214-9.[PubMed 9135491]

FOLFOX 3

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Colorectal Cancer

Regimen UseColorectal cancer

Regimen

Oxaliplatin: I.V.: 85 mg/m^2 day 1

[total dose/cycle = 85 mg/m^2]

Leucovorin: I.V.: 500 mg/m^2/day days 1 and 2

[total dose/cycle = 1000 mg/m^2]

Fluorouracil: I.V.: 1.5-2 g/m^2/day continuous infusion days 1 and 2

[total dose/cycle = 3-4 g/m^2]

Repeat cycle every 14 days

References

de Gramont A, Tournigand C, Louvet C, et al, âOxaliplatin, Folinic Acid, and 5-Fluorouracil (Folfox) in Pretreated Patients With Metastatic Advanced Cancer, The GERCOD,â *Rev Med Interne*, 1997, 18(10):769-75.[PubMed 9500010]

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Colorectal Cancer

Regimen UseColorectal cancer

Regimen

Oxaliplatin: I.V.: 85 mg/m^2 day 1

[total dose/cycle = 85 mg/m^2]

Leucovorin: I.V.: 200 mg/m^2/day days 1 and 2

[total dose/cycle = 400 mg/m^2]

Fluorouracil: I.V. bolus: 400 mg/m^2/day days 1 and 2

[total dose/cycle = 800 mg/m^2]

followed by I.V.: 600 mg/m^2 continuous infusion (over 22 hours) days 1 and 2

[total dose/cycle = 1200 mg/m^2]

Note: Bolus fluorouracil and continuous infusion are both given on each day.

Repeat cycle every 14 days

References

André T, Bensmaine MA, Louvet C, et al, “Multicenter Phase II Study of Bimonthly High-Dose Leucovorin, Fluorouracil Infusion, and Oxaliplatin for Metastatic Colorectal Cancer Resistant to the Same Leucovorin and Fluorouracil Regimen,” *J Clin Oncol*, 1999, 17(11):3560-8.[PubMed 10550155]

FOLFOX 6

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Colorectal Cancer

Regimen UseColorectal cancer

Regimen

Oxaliplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Leucovorin: I.V.: 400 mg/m^2 day 1

[total dose/cycle = 400 mg/m^2]

Fluorouracil: I.V. bolus: 400 mg/m^2 day 1

[total dose/cycle = 400 mg/m^2]

followed by I.V.: 2.4-3 g/m^2 continuous infusion (46 hours) extending over days 1 and 2

[total dose/cycle = 2.4-3 g/m^2]

Repeat cycle every 14 days

References

Maindrault-Goebel F, Louvet C, Andre T, et al, âOxaliplatin Added to the Simplified Bimonthly Leucovorin and 5-Fluorouracil Regimen as Second-Line Therapy for Metastatic Colorectal Cancer (FOLFOX6), GERCOR,â *Eur J Cancer*, 1999, 35(9):1338-42.[PubMed 10658524]

FOLFOX 7

Lexi-Drugs Online

Pharmacologic CategoryChemotherapy Regimen, Colorectal Cancer

Regimen UseColorectal cancer

Regimen

Oxaliplatin: I.V.: 130 mg/m^2 day 1

[total dose/cycle = 130 mg/m^2]

Leucovorin: I.V.: 400 mg/m^2 day 1

[total dose/cycle = 400 mg/m^2]

Fluorouracil: I.V. bolus: 400 mg/m^2 day 1

[total dose/cycle = 400 mg/m^2]

followed by I.V.: 2.4 g/m^2 continuous infusion (46 hours) extending over days 1 and 2

[total dose/cycle = 2.4 g/m^2]

Repeat cycle every 14 days

References

Maindrault-Goebel F, de Gramont A, Louvet C, et al, âHigh-Dose Intensity Oxaliplatin Added to the Simplified Bimonthly Leucovorin and 5-Fluorouracil Regimen as Second-Line Therapy for Metastatic Colorectal Cancer (FOLFOX 7),â *Eur J Cancer*, 2001, 37(8):1000-5.[PubMed 11334725]

Folic Acid, Cyanocobalamin, and Pyridoxine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(FOE lik AS id, sye an oh koe BAL a min, & peer i DOKS een)

U.S. Brand NamesAllanFol RX [DSC]; ComBgen™; Folamin™; Folbee; Folgard® RX; Folgard® [OTC]; Foltx®; Tricardio B

Pharmacologic CategoryVitamin

Use: Labeled IndicationsNutritional supplement in end-stage renal failure, dialysis, hyperhomocysteinemia, homocystinuria, malabsorption syndromes, dietary deficiencies

Dosing: AdultsDietary supplement: Oral: One tablet daily

Dosing: ElderlyRefer to adult dosing.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 96°F).

ContraindicationsHypersensitivity to folic acid, cyanocobalamin, pyridoxine, or any component of the formulation

Warnings/PrecautionsSee individual agents.

Adverse ReactionsSee individual agents.

Drug Interactions

Altretamine: Pyridoxine may diminish the therapeutic effect of Altretamine. Specifically when altretamine is used in combination with Cisplatin the response duration may be diminished. *Risk D: Consider therapy modification*

Barbiturates: Pyridoxine may increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

Chloramphenicol: May diminish the therapeutic effect of Cyanocobalamin. The expected hematologic response for the treatment of anemia may be opposed. *Risk D: Consider therapy modification*

Levodopa: Pyridoxine may diminish the therapeutic effect of Levodopa. *Risk D: Consider therapy modification*

PHENobarbital: Folic Acid may decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Phenytoin: Folic Acid may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Phenytoin: Pyridoxine may increase the metabolism of Phenytoin. This is most apparent in high pyridoxine doses (eg, 80 mg to 200 mg daily) *Risk C: Monitor therapy*

Primidone: Folic Acid may decrease the serum concentration of Primidone. Additionally, folic acid may decrease concentrations of active metabolites of primidone (e.g., phenobarbital). *Risk C: Monitor therapy*

Raltitrexed: Folic Acid may diminish the therapeutic effect of Raltitrexed. *Risk X: Avoid combination*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: Folic acid 0.8 mg, cyanocobalamin 1000 mcg, and pyridoxine hydrochloride 50 mg

AllanFol RX: Folic acid 2.2 mg, cyanocobalamin 1000 mcg, and pyridoxine hydrochloride 25 mg [DSC]

ComBgen™: Folic acid 2.2 mg, cyanocobalamin 500 mcg, and pyridoxine hydrochloride 25 mg

Folamin™: Folic acid 2.5 mg, cyanocobalamin 2000 mcg, and pyridoxine hydrochloride 25 mg

Folbee: Folic acid 2.5 mg, cyanocobalamin 1000 mcg, and pyridoxine hydrochloride 25 mg [dye free, lactose free, and sugar free]

Folgard®: Folic acid 0.8 mg, cyanocobalamin 115 mcg, and pyridoxine hydrochloride 10 mg

Folgard® RX: Folic acid 2.2 mg, cyanocobalamin 1000 mcg, and pyridoxine hydrochloride 25 mg

Foltx®: Folic acid 2.5 mg, cyanocobalamin 2000 mcg, and pyridoxine hydrochloride 25 mg

Tricardio B: Folic acid 0.4 mg, cyanocobalamin 250 mcg, and pyridoxine hydrochloride 25 mg

Generic AvailableYes

ManufacturerPamlab

Pricing: U.S. (www.drugstore.com)

Tablets (ComBgen)

2.2-25-0.5 mg (100): $39.99

Tablets (Folbee)

2.5-25-1 mg (30): $14.99

Tablets (Folgard RX)

2.2-25-1 mg (30): $20.99

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Cardiovascular Considerations Epidemiological evidence suggests that total plasma homocysteine level may be an independent cardiovascular risk factor. Plasma homocysteine levels are strongly influenced by genetics and diet (folic acid, pyridoxine/vitamin B_6, and cyanocobalamine/vitamin B_{12}). These vitamins help to break down homocysteine in the body.

Schnyder, et al, studied the effects of homocysteine-lowering therapy (folic acid 1 mg/day, vitamin B_6 10 mg/day, vitamin B_{12} 0.4 mg/day) in patients with coronary artery disease after successful angioplasty in the Swiss Heart Study. This randomized, double-blind, placebo-controlled trial looked at a composite endpoint (death, nonfatal MI, repeat revascularization) 6 months and 1 year after angioplasty. Homocysteine-lowering therapy significantly decreased the incidence of major adverse events, primarily due to a reduced rate of target lesion revascularization. Investigators in the Folate After Coronary Intervention Trial randomized patients who underwent successful coronary stenting procedures to placebo or folic acid (1.2 mg/day), vitamin B_6 (4.8 mg/day), and vitamin B_{12} (0.06 mg/day). Vitamin supplementation was associated with increased restenosis in these PCI patients.

Liem and colleagues randomized 593 patients with stable coronary artery disease to either folic acid supplementation (0.5 mg/day) or none in an open-label study. All patients were being treated with an HMG-CoA reductase inhibitor. The primary endpoint was a composite of vascular events and all cause mortality. Patients were followed up for 2 years. Patients treated with folic acid had a significant reduction in plasma homocysteine levels but the primary endpoint was encountered by a similar number of patients in both groups. The authors concluded that folic acid does not seem to reduce clinical endpoints in patients with stable coronary artery disease. Further investigation is required to sort out the discrepancies in these trials.

Index Terms Cyanocobalamin, Folic Acid, and Pyridoxine; Folacin, Vitamin B_{12}, and Vitamin B_6; Pyridoxine, Folic Acid, and Cyanocobalamin

References

Liem A, Reynierse-Buitenwerf GH, Zwinderman AH, et al, “Secondary Prevention With Folic Acid: Effects on Clinical Outcomes,” *J Am Coll Cardiol*, 2003, 41(12):2105-13. [PubMed 12821232]

Schnyder G, Roffi M, Flammer Y, et al, “Effect of Homocysteine-Lowering Therapy With Folic Acid, Vitamin B_{12}, and Vitamin B_6 on Clinical Outcome After Percutaneous Coronary Intervention: The Swiss Heart Study: A Randomized Controlled Trial,” *JAMA*, 2002, 288(8):973-9.[PubMed 12190367]

International Brand Names Bedoyecta Pediátrica (MX); Kiddi Pharmaton (MX); Vitaverán Fólico (MX); Vytral (MX)

Folic Acid

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Folic acid may be confused with folinic acid

Pronunciation(FOE lik AS id)
U.S. Brand NamesFolacin-800 [OTC]
Canadian Brand NamesApo-Folic®
Pharmacologic CategoryVitamin, Water Soluble
Use: Labeled IndicationsTreatment of megaloblastic and macrocytic anemias due to folate deficiency; dietary supplement to prevent neural tube defects
Use: Unlabeled/InvestigationalAdjunctive cofactor therapy in methanol toxicity (alternative to leucovorin)
Dosing: Adults

Anemia: Oral, I.M., I.V., SubQ: 0.4 mg/day

Pregnant and lactating women: 0.8 mg/day

RDA: Expressed as dietary folate equivalents: 400 mcg/day

Prevention of neural tube defects: Oral:

Females of childbearing potential: 400 mcg/day

Females at high risk or with family history of neural tube defects: 4 mg/day

Dosing: ElderlyRefer to adult dosing. Vitamin B_{12} deficiency must be ruled out before initiating folate therapy due to frequency of combined nutritional deficiencies: RDA requirements (1999): 400 mcg/day (0.4 mg) minimum.
Dosing: Pediatric

Anemia: Oral, I.M., I.V., SubQ:

Infants: 0.1 mg/day

Children <4 years: Up to 0.3 mg/day

Children >4 years and Adults: Refer to adult dosing.

RDA: Expressed as dietary folate equivalents: Oral: Children:

1-3 years: 150 mcg/day

4-8 years: 200 mcg/day

9-13 years: 300 mcg/day

≥14 years: Refer to adult dosing.

Administration: I.M.May also be administered by deep I.M. injection.
Administration: I.V. DetailpH: 8-11
Dietary ConsiderationsAs of January 1998, the FDA has required manufacturers of enriched flour, bread, corn meal, pasta, rice, and other grain products to add folic acid to their products. The intent is to help decrease the risk of neural tube defects by increasing folic acid intake. Other foods which contain folic acid include dark green leafy vegetables, citrus fruits and juices, and lentils.
CompatibilityStable in D_5W, $D_{20}W$, NS, fat emulsion 10%; **incompatible** with $D_{40}W$, $D_{50}W$. Do not use with oxidizing and reducing agents or heavy metal ions.

Y-site administration: Compatible: Famotidine.

Compatibility in syringe: Incompatible: Doxapram.

Compatibility when admixed: Incompatible: Calcium gluconate.

Extemporaneously PreparedA 1 mg/mL folic acid solution may be prepared by crushing fifty 1 mg tablets. Dissolve in a small amount of distilled water, then add sufficient distilled water to make a final volume of 50 mL. Adjust the pH to 8 with sodium hydroxide. It is stable for 42 days at room temperature.

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, Harvey Whitney Books Company, 1992.

ContraindicationsHypersensitivity to folic acid or any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Anemia: Monotherapy: Not appropriate for monotherapy with pernicious, aplastic, or normocytic anemias when anemia is present with vitamin B_{12} deficiency.

- Pernicious anemia: Doses >0.1 mg/day may obscure pernicious anemia with continuing irreversible nerve damage progression.

Dosage form specific issues:

- Benzyl alcohol: Injection contains benzyl alcohol (1.5%) as preservative which has been associated with "gasping syndrome" in neonates.

Other warnings/precautions:

- Resistance to treatment: May occur with depressed hematopoiesis, alcoholism, and deficiencies of other vitamins.

Geriatric ConsiderationsElderly frequently have combined nutritional deficiencies. Must rule out vitamin B_{12} deficiency before initiating folate therapy. Elderly, due to decreased nutrient intake, may benefit from daily intake of a multiple vitamin with minerals.

Pregnancy Risk FactorA

Pregnancy ConsiderationsFolic acid requirements are increased during pregnancy; a deficiency may result in fetal harm.

LactationEnters breast milk/compatible

Adverse ReactionsFrequency not defined.

Allergic reaction, bronchospasm, flushing (slight), malaise (general), pruritus, rash

Drug Interactions

PHENobarbital: Folic Acid may decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Phenytoin: Folic Acid may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Primidone: Folic Acid may decrease the serum concentration of Primidone. Additionally, folic acid may decrease concentrations of active metabolites of primidone (e.g., phenobarbital). *Risk C: Monitor therapy*

Raltitrexed: Folic Acid may diminish the therapeutic effect of Raltitrexed. *Risk X: Avoid combination*

Test InteractionsFalsely low serum concentrations may occur with the *Lactobacillus casei* assay method in patients on anti-infectives (eg, tetracycline)

Reference RangeTherapeutic: 0.005-0.015 mcg/mL

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic effectiveness and adverse response on a regular basis throughout therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as prescribed. Toxicity can occur from elevated doses. Increased intake of foods high in folic acid (eg, dried beans, nuts, bran, vegetables, fruits) may be recommended by prescriber. Excessive use of alcohol increases requirement for folic acid. May turn urine more intensely yellow. Report skin rash. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sodium folate: 5 mg/mL (10 mL) [contains benzyl alcohol, edetate disodium]

Tablet: 0.4 mg, 0.8 mg, 1 mg

Folacin-800: 0.8 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Folic Acid)

1 mg (100): $14.99

400 mcg (250): $12.99

Mechanism of ActionFolic acid is necessary for formation of a number of coenzymes in many metabolic systems, particularly for purine and pyrimidine synthesis; required for nucleoprotein synthesis and maintenance in erythropoiesis; stimulates WBC and platelet production in folate deficiency anemia. Folic acid enhances the elimination of formic acid, the toxic metabolite of methanol (unlabeled use).

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Oral: 0.5-1 hour

Absorption: Proximal part of small intestine

Pharmacotherapy PearlsThe RDA for folic acid is presented as dietary folate equivalents (DFE). DFE adjusts for the difference in bioavailability of folic acid from food as compared to dietary supplements.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental Status May cause drowsiness

Mental Health: Effects on Psychiatric Treatment None reported

Cardiovascular Considerations Epidemiological evidence suggests that total plasma homocysteine level may be an independent cardiovascular risk factor. Plasma homocysteine levels are strongly influenced by genetics and diet (folic acid, pyridoxine/vitamin B_6, and cyanocobalamine/vitamin B_{12}). These vitamins help to break down homocysteine in the body.

Schnyder, et al, studied the effects of homocysteine-lowering therapy (folic acid 1 mg/day, vitamin B_6 10 mg/day, vitamin B_{12} 0.4 mg/day) in patients with coronary artery disease after successful angioplasty in the Swiss Heart Study. This randomized, double-blind, placebo-controlled trial looked at a composite endpoint (death, nonfatal MI, repeat revascularization) 6 months and 1 year after angioplasty. Homocysteine-lowering therapy significantly decreased the incidence of major adverse events, primarily due to a reduced rate of target lesion revascularization. Investigators in the Folate After Coronary Intervention Trial randomized patients who underwent successful coronary stenting procedures to placebo or folic acid (1.2 mg/day), vitamin B_6 (4.8 mg/day), and vitamin B_{12} (0.06 mg/day). Vitamin supplementation was associated with increased restenosis in these PCI patients.

Liem and colleagues randomized 593 patients with stable coronary artery disease to either folic acid supplementation (0.5 mg/day) or none in an open-label study. All patients were being treated with an HMG-CoA reductase inhibitor. The primary endpoint was a composite of vascular events and all cause mortality. Patients were followed up for 2 years. Patients treated with folic acid had a significant reduction in plasma homocysteine levels but the primary endpoint was encountered by a similar number of patients in both groups. The authors concluded that folic acid does not seem to reduce clinical endpoints in patients with stable coronary artery disease. Further investigation is required to sort out the discrepancies in these trials. Recent data suggests increased rates of restenosis with chronic folic acid treatment.

Index Terms Folacin; Folate; Pteroylglutamic Acid

References

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International Brand NamesA.F. Valdecasas (MX); Acfol (ES, PT); Acide Folique CCD (FR); Acido Folico (AR, CO, EC); Acido Folico Fada (AR); Acidum Folicum (PL); Acifol (AR); Acifolik (PL); Apo-Folic (NZ); Bio-Folic (BE); Conacid (AR); Elvefocal (AR); Endofolin (BR); Filicine (GR); Folacid (PL); Folacin (HR, NO, SE, TW); Folart (PH); Folavit (BE); Foliamin (HK, JP, TH); Folic Acid DHA (MY); Folic Acid Pharm Ecologist (AR); Folicid (KP); Folicil (PT); Folifem (PL); Folifort (PL); Folik (PL); Folimet (DK); Folimin (PL); Folin (BR); Folina (IT); Folinsyre ”Dak” (DK); Foliphar (BE); Folivit (TH); Folivital (MX); Folovit (PL); Folsan (AT, HN, HR); Folsyre (NO); Folverlan (DE); Folvite (AE, BB, BH, BM, BS, BZ, CH, CY, EG, FI, GY, IL, IQ, IR, JM, JO, KW, LB, LY, NL, OM, QA, SA, SR, SY, TT, YE); Gravi-Fol (DE); Gravida (BE); Huma-Folacid (HU); Ingafol (IN); Kwas foliowy (PL); Lexpec (GB, IE); Megafol (AU); Mithra Folic (BE); Prinac AC (MX); RubieFol (DE); Tecnovorin (BR); Tifol (PL); Travital Folic Acid (BE); Vifolin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE)

Follitropin Alfa

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English

Jump To Field (Select Field Name)

Pronunciation(foe li TRO pin AL fa)

U.S. Brand NamesGonal-f® ; Gonal-f® RFF

Canadian Brand NamesGonal-f® ; Gonal-f® Pen

Pharmacologic CategoryGonadotropin; Ovulation Stimulator

Use: Labeled Indications

Gonal-f®: Ovulation induction in patients in whom the cause of infertility is functional and not caused by primary ovarian failure; development of multiple follicles with Assisted Reproductive Technology (ART); spermatogenesis induction

Gonal-f® RFF: Ovulation induction in patients in whom the cause of infertility is functional and not caused by primary ovarian failure; development of multiple follicles with ART

Dosing: Adults **Note:** Dose should be individualized. Use the lowest dose consistent with the expectation of good results. Over the course of treatment, doses may vary depending on individual patient response.

Ovulation induction: *Gonal-f®, Gonal-f® RFF:* Females: SubQ: Initial: 75 int. units/day; incremental dose adjustments of up to 37.5 int. units may be considered after 14 days; further dose increases of the same magnitude can be made, if necessary, every 7 days (maximum dose: 300 int. units/day). If response to follitropin is appropriate, hCG is given 1 day following the last dose. Withhold hCG if serum estradiol is >2000 pg/mL, if the ovaries are abnormally enlarged, or if abdominal pain occurs. In general, therapy should not exceed 35 days.

ART: *Gonal-f®, Gonal-f® RFF:* Females: SubQ: Initiate therapy with follitropin alfa in the early follicular phase (cycle day 2 or day 3) at a dose of 150 int. units/day, until sufficient follicular development is attained. In most cases, therapy should not exceed 10 days. In patients ≥35 years whose endogenous gonadotropin levels are suppressed, initiate follitropin alfa at a dose of 225 int. units/day. Continue treatment until adequate follicular development is indicated as determined by ultrasound in combination with measurement of serum estradiol levels. Consider adjustments to dose after 5 days based on the patient's response; adjust subsequent dosage every 3-5 days by ≤75-150 int. units additionally at each adjustment. Doses >450 int. units/day are not recommended. Once adequate follicular development is evident, administer hCG to induce final follicular maturation in preparation for oocyte. Withhold hCG if the ovaries are abnormally enlarged.

Spermatogenesis induction: *Gonal-f®:* Males: SubQ: Therapy should begin with hCG pretreatment until serum testosterone is in normal range, then 150 int. units 3 times/week with hCG 3 times/week; continue with lowest dose needed to induce spermatogenesis (maximum dose: 300 int. units 3 times/week); may be given for up to 18 months

Dosing: ElderlyRefer to adult dosing. Clinical studies did not include patients >65 years.

Administration: OtherGonal-f®, Gonal-f® RFF: Administer SubQ. Contents of multidose vials should be administered using the calibrated syringes provided by the manufacturer. Do not shake solution; allow any bubbles to settle prior to administration.

Storage

Gonal-f®: Store powder refrigerated or at room temperature of 2°C to 25°C (36°F to 77°F). Protect from light. Following reconstitution, multidose vials may be stored under refrigeration or at room temperature for up to 28 days. Protect from light.

Gonal-f® RFF:

Powder: Store at room temperature or under refrigeration of 2°C to 25°C (36°F to 77°F). Protect from light.

Solution: Prior to dispensing, store under refrigeration at 2°C to 8°C (36°F to 46°F). Upon dispensing, patient may store under refrigeration until product expiration date or at room temperature of 20°C to 25°C (68°F to 77°F) for up to 3 months. Do not freeze. Protect from light. After first use, discard unused portion after 28 days.

Reconstitution

Gonal-f®: Dissolve the contents of vial by slowly injecting provided diluent; do not shake. If bubbles appear, allow to settle prior to use. Final concentration: 600 int. units/mL.

Gonal-f® RFF: Powder: Dissolve contents of one or more vials using diluent provided in prefilled syringe. (Total concentration should not exceed 450 int. units/mL.) Slowly inject diluent into vial, and gently rotate vial until powder is dissolved; do not shake vial. If bubbles appear, allow to settle prior to use. Use immediately after reconstitution.

ContraindicationsHypersensitivity to follitropins or any component of the formulation; high levels of FSH indicating primary gonadal failure (ovarian or testicular); uncontrolled thyroid or adrenal dysfunction; tumor of the ovary, breast, uterus, hypothalamus, testis, or pituitary gland; abnormal vaginal bleeding of undetermined origin; ovarian cysts or enlargement not due to polycystic ovary syndrome; pregnancy

Warnings/Precautions

Concerns related to adverse effects:

- Ovarian enlargement: May be accompanied by abdominal distention or abdominal pain, occurs in ~20% of those treated with urofollitropin and hCG, and generally regresses without treatment within 2-3 weeks. If ovaries are abnormally enlarged on the last day of treatment, withhold hCG to reduce the risk of ovarian hyperstimulation syndrome (OHSS).

- Ovarian hyperstimulation syndrome (OHSS): Reported in about 7% of patients; it is characterized by severe ovarian enlargement, abdominal pain/distention, nausea, vomiting, diarrhea, dyspnea, and oliguria, and may be accompanied by ascites, pleural effusion, hypovolemia, electrolyte imbalance, hemoperitoneum, and thromboembolic events. If hyperstimulation occurs, stop treatment and hospitalize patient. This syndrome develops rapidly within 24 hours to several days and generally occurs during the 7-10 days immediately following treatment. Hemoconcentration associated with fluid loss into the abdominal cavity has occurred and should be assessed by fluid intake and output, weight, hematocrit, serum and urinary electrolytes, urine specific gravity, BUN and creatinine, and abdominal girth. Determinations should be performed daily or more often if the need arises. Treatment is primarily symptomatic and consists of bedrest, fluid and electrolyte replacement, and analgesics. The ascitic, pleural, and pericardial fluids should not be removed unless needed to relieve symptoms of cardiopulmonary distress.

- Pulmonary effects: Serious pulmonary conditions (atelectasis, acute respiratory distress syndrome, and exacerbation of asthma) have been reported.

- Thromboembolic events: In association with and separate from ovarian hyperstimulation syndrome (OHSS), thromboembolic events have been reported.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: To minimize risks, use only at the lowest effective dose. Monitor ovarian response with serum estradiol and vaginal ultrasound on a regular basis.

- Experienced physician: These medications should only be used by physicians who are thoroughly familiar with infertility problems and their management.

- Multiple births: May result from the use of these medications; advise patient of the potential risk of multiple births before starting the treatment.

Pregnancy Risk FactorX

Pregnancy ConsiderationsEctopic pregnancy, congenital abnormalities, spontaneous abortion, and multiple births have been reported. The incidence of congenital abnormality may be slightly higher after ART than with spontaneous conception; higher incidence may be related to parenteral characteristics (maternal age, sperm characteristics).

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsPercentage may vary by indication, product formulation

>10%:

Central nervous system: Headache

Endocrine & metabolic: Ovarian cyst

Gastrointestinal: Abdomen enlarged, abdominal pain, nausea

Miscellaneous: Upper respiratory infection

1% to 10%:

Central nervous system: Dizziness, emotional lability, fever, malaise, migraine, pain

Dermatologic: Acne

Endocrine & metabolic: Breast pain, cervix lesion, hot flashes, intermenstrual bleeding, menstrual disorder, ovarian disorder, ovarian hyperstimulation

Gastrointestinal: Constipation, diarrhea, dyspepsia, flatulence, pelvic pain, stomatitis (ulcerative), toothache, vomiting, weight gain

Genitourinary: Cystitis, leukorrhea, micturition frequency, urinary tract infection, uterine hemorrhage, vaginal hemorrhage

Local: Injection site bruising, edema, inflammation, pain, reaction

Neuromuscular & skeletal: Back pain

Respiratory: Cough, flu-like symptoms, pharyngitis, rhinitis, sinusitis

Miscellaneous: Infection, moniliasis

Postmarketing, case reports, or events reported with gonadotropins: Adnexal torsion, anaphylactoid reactions, hemoperitoneum, hypersensitivity reactions, ovarian enlargement, pulmonary complications, vascular complications

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersMonitor sufficient follicular maturation. This may be directly estimated by sonographic visualization of the ovaries and endometrial lining or measuring serum estradiol levels. The combination of both ultrasonography and measurement of estradiol levels is useful for monitoring for the growth and development of follicles and timing hCG administration.

The clinical evaluation of estrogenic activity (changes in vaginal cytology and changes in appearance and volume of cervical mucus) provides an indirect estimate of the estrogenic effect upon the target organs and, therefore, it should only be used adjunctively with more direct estimates of follicular development (ultrasonography and serum estradiol determinations).

The clinical confirmation of ovulation is obtained by direct and indirect indices of progesterone production. The indices most generally used are: rise in basal body temperature, increase in serum progesterone, and menstruation following the shift in basal body temperature.

Monitor for signs and symptoms of OHSS for at least 2 weeks following hCG administration.

Spermatogenesis: Monitor serum testosterone levels, sperm count

Nursing: Physical Assessment/MonitoringThis medication should only be prescribed by a fertility specialist. Assess results of laboratory tests and therapeutic effectiveness on a regular basis. Assess knowledge/teach patient appropriate use (injection technique and syringe disposal), interventions to reduce side effects, and adverse symptoms to report. **Pregnancy risk factor X:** Pregnancy must be excluded before starting medication.

Monitoring: Lab TestsMonitor sufficient follicular maturation. This may be directly estimated by sonographic visualization of the ovaries and endometrial lining or measuring serum estradiol levels. The combination of both ultrasonography and measurement of estradiol levels is useful for monitoring for the growth and development of follicles and timing hCG administration.

Spermatogenesis: Monitor serum testosterone levels, sperm count.

Patient EducationThis medication can only be administered by injection. If you are using this medication at home, follow exact instructions for administering injections and disposal of syringes. Administer exact amount as instructed; do not alter dosage or miss a dose. If dose is missed, notify prescriber. Frequent laboratory tests will be required while you are on this therapy; do not miss appointments for laboratory tests or ultrasound. You may experience headache, dizziness, or fever (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea or vomiting (small frequent meals, frequent oral care, sucking lozenges, or chewing gum may help). Report immediately abdominal pain/distension, bloating, persistent nausea, vomiting, diarrhea; dyspnea, respiratory difficulty, exacerbation of asthma; swelling, pain, or redness of extremities; itching or burning on urination; menstrual irregularity, acute backache; rash, pain, or inflammation at injection site; or other adverse response. **Pregnancy/breast-feeding precautions:** Pregnancy must be ruled out prior to initiating this medication. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [rDNA origin]:

Gonal-f®: 450 int. units [contains sucrose 30 mg; packaged with diluent and calibrated syringes; diluent contains benzyl alcohol]

Gonal-f® RFF: 75 int. units [contains sucrose 30 mg; packaged with diluent in prefilled syringe]

Injection, solution [rDNA origin]:

Gonal-f® RFF: 300 int. units/0.5 mL (0.5 mL) [contains sucrose 60 mg/mL]; 450 int. units/0.75 mL (0.75 mL) [contains sucrose 60 mg/mL]; 900 int. units/1.5 mL (1.5 mL) [contains sucrose 60 mg/mL]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Gonal-f)

450 unit (1): $592.68

Solution (reconstituted) (Gonal-f RFF)

75 unit (1): $99.99

Mechanism of ActionFollitropin alfa is a human FSH preparation of recombinant DNA origin. Follitropins stimulate ovarian follicular growth in women who do not have primary ovarian failure, and stimulate spermatogenesis in men with hypogonadotrophic hypogonadism. FSH is required for normal follicular growth, maturation, gonadal steroid production, and spermatogenesis.

Pharmacodynamics/Kinetics

Onset of action: Peak effect:

Spermatogenesis, median: 6.8-12.4 months (range 2.7-15.7 months)

Follicle development: Within cycle

Absorption: I.M., SubQ: Absorption rate is slower than the elimination rate

Distribution: Mean V_d: 10 L with *in vitro* fertilization/embryo transfer patients

Bioavailability: ~66% to 76% in healthy female volunteers

Half-life elimination:

I.M.: 50 hours in healthy female volunteers

SubQ: 24 hours in healthy female volunteers; 32 hours with *in vitro* fertilization/embryo transfer patients; 32-41 hours in healthy male volunteers

Time to peak: In healthy volunteers:

Females: SubQ: 8-16 hours; I.M.: 25 hours

Males: SubQ: 11-20 hours

Excretion: Clearance: I.V.: 0.6 L/hour in healthy female volunteers

Pharmacotherapy PearlsThe currently available recombinant follitropin products are structurally identical to native follicle-stimulating hormone. The “alpha” and “beta” nomenclature refers to their differences in purification and order of marketing. Follitropin alpha was marketed first, followed by follitropin beta. RFF for the Gonal-f® product signifies “revised formula female.”

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis and toothache.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFollicle Stimulating Hormone, Recombinant; FSH; rFSH-alpha; rhFSH-alpha

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International Brand NamesGonal-F (AR, AT, AU, BE, BG, BR, CH, CN, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IN, IT, KP, MX, MY, NL, NO, PE, PH, PK, PT, RU, SE, SG, TR); Gonalef (VE)

Follitropin Beta

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(foe li TRO pin BAY ta)

U.S. Brand NamesFollistim® AQ; Follistim® AQ Cartridge

Canadian Brand NamesPuregon®

Pharmacologic CategoryGonadotropin; Ovulation Stimulator

Use: Labeled IndicationsOvulation induction in patients in whom the cause of infertility is functional and not caused by primary ovarian failure; development of multiple follicles with Assisted Reproductive Technology (ART)

Dosing: Adults**Note:** Dose should be individualized. Use the lowest dose consistent with the expectation of good results. Over the course of treatment, doses may vary depending on individual patient response.

Ovulation induction: Females:

Follistim® AQ: I.M., SubQ: Stepwise approach: Initiate therapy with 75 int. units/day for up to 14 days. Increase by 37.5 int. units at weekly intervals until follicular growth or serum estradiol levels indicate an adequate response. The maximum (individualized) daily dose that has been safely used for ovulation induction in patients during clinical trials is 300 int. units. If response to follitropin is appropriate, hCG is given 1 day following the last dose. Withhold hCG if the ovaries are abnormally enlarged, or if abdominal pain occurs.

Follistim® AQ Cartridge: SubQ: Stepwise approach: Initiate therapy with 75 int. units/day for up to 7 days. Increase by 25 or 50 int. units at weekly intervals until follicular growth or serum estradiol levels indicate an adequate response. The maximum (individualized) daily dose that has been safely used for ovulation induction in patients during clinical trials is 175 int. units. If response to follitropin is appropriate, hCG is given 1 day following the last dose. Withhold hCG if the ovaries are abnormally enlarged, or if abdominal pain occurs. See **"Note"** for dosage adjustment for this product.

ART: Females:

Follistim® AQ: I.M., SubQ: A starting dose of 150-225 int. units is recommended for at least the first 4 days of treatment. The dose may be adjusted for the individual patient based upon their ovarian response. The usual maintenance dose was 75-300 int. units for 6-12 days; 375-600 int. units in patients who were poor responders. The maximum daily dose used in clinical studies is 600 int. units. When a sufficient number of follicles of adequate size are present, the final maturation of the follicles is induced by administering hCG. Oocyte retrieval is performed 34-36 hours later. Withhold hCG in cases where the ovaries are abnormally enlarged on the last day of follitropin beta therapy.

Follistim® AQ Cartridge: SubQ: A starting dose of 150-225 int. units is recommended for at least the first 5 days of treatment. The dose may be adjusted for the individual patient based upon their ovarian response. The maximum daily dose used in clinical studies is 450 int. units. When a sufficient number of follicles of adequate size are present, the final maturation of the follicles is induced by administering hCG. Oocyte retrieval is performed 34-36 hours later. Withhold hCG in cases where the ovaries are abnormally enlarged on the last day of follitropin beta therapy. See **"Note"** for dosage adjustment for this product.

Note: Dose adjustment for Follistim® AQ Cartridge: When administered using the Follistim Pen®, the Follistim® AQ Cartridge delivers 18% more follitropin beta when compared to dissolved lyophilized follitropin beta administered by a conventional syringe. If the above starting doses were previously used when administering a recombinant lyophilized gonadotropin product via a conventional syringe, lower starting and maintenance doses should be considered when switching to Follistim® AQ Cartridge. The following dose conversion may be used:

Follistim® AQ Dosing Conversion

Dose Administered Using Powder for Solution/Conventional Syringe	Follistim® AQ Dose Administered Using Follistim Pen®
75 int. units	50 int. units
150 int. units	125 int. units
225 int. units	175 int. units
300 int. units	250 int. units
375 int. units	300 int. units
450 int. units	375 int. units

Administration: I.M.Follistim® AQ may be administered by I.M. or SubQ injection.
Administration: Other

Follistim® AQ may be administered by I.M. or SubQ injection. Follistim® AQ cartridge may be administered only by SubQ injection using the Follistim Pen® which can be set to deliver the appropriate dose.

StoragePrior to dispensing, store refrigerated at 2°C to 8°C (36°F to 46°F). After dispensed, may be stored under refrigeration or ≤25°C (77°F) for up to 3 months. Once cartridge is pierced, must be stored in refrigerator and used within 28 days. Do not freeze. Protect from light.
ContraindicationsHypersensitivity to follitropins or any component of the formulation; high levels of FSH indicating primary ovarian failure; uncontrolled thyroid or adrenal dysfunction; tumor of the ovary, breast, uterus, hypothalamus, or pituitary gland; abnormal vaginal bleeding of undetermined origin; ovarian cysts or enlargement not due to polycystic ovary syndrome; pregnancy
Warnings/Precautions

Concerns related to adverse effects:

- Ovarian enlargement: May be accompanied by abdominal distention or abdominal pain, occurs in ~20% of those treated with urofollitropin and hCG, and generally regresses without treatment within 2-3 weeks. If ovaries are abnormally enlarged on the last day of treatment, withhold hCG to reduce the risk of ovarian hyperstimulation syndrome (OHSS).

- Ovarian hyperstimulation syndrome (OHSS): OHSS is characterized by severe ovarian enlargement, abdominal pain/distention, nausea, vomiting, diarrhea, dyspnea, and oliguria, and may be accompanied by ascites, pleural effusion, hypovolemia, electrolyte imbalance, hemoperitoneum, and thromboembolic events. If hyperstimulation occurs, stop treatment and hospitalize patient. This syndrome develops rapidly within 24 hours to several days and generally occurs during the 7-10 days immediately following treatment. Hemoconcentration associated with fluid loss into the abdominal cavity has occurred and should be assessed by fluid intake and output, weight, hematocrit, serum and urinary electrolytes, urine specific gravity, BUN and creatinine, and abdominal girth. Determinations should be performed daily or more often if the need arises. Treatment is primarily symptomatic and consists of bedrest, fluid and electrolyte replacement, and analgesics. The ascitic, pleural, and pericardial fluids should not be removed unless needed to relieve symptoms of cardiopulmonary distress.

- Pulmonary effects: Serious pulmonary conditions (atelectasis, acute respiratory distress syndrome, and exacerbation of asthma) have been reported.

- Thromboembolic events: In association with and separate from ovarian hyperstimulation syndrome, thromboembolic events have been reported.

Special populations:

- Elderly: Safety and efficacy have not been established in the elderly.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Neomycin: May contain trace amounts of neomycin.

- Streptomycin: May contain trace amounts of streptomycin.

Other warnings/precautions:

- Appropriate use: To minimize risks, use only at the lowest effective dose. Monitor ovarian response with serum estradiol and vaginal ultrasound on a regular basis.

- Experienced physician: These medications should only be used by physicians who are thoroughly familiar with infertility problems and their management.

- Multiple births: May result from the use of these medications; advise patient of the potential risk of multiple births before starting the treatment.

Pregnancy Risk FactorX
Pregnancy ConsiderationsEctopic pregnancy, congenital abnormalities, and multiple births have been reported. The incidence of congenital abnormality may be slightly higher after ART than with spontaneous conception; higher incidence may be related to parenteral characteristics (maternal age, sperm characteristics).
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsPercentage may vary by indication, product formulation

>10%:

Endocrine & metabolic: Breast pain

Gastrointestinal: Abdominal pain, flatulence, nausea

Miscellaneous: Miscarriage

1% to 10%:

Central nervous system: Headache

Endocrine & metabolic: Ovarian hyperstimulation syndrome, ovarian pain

Gastrointestinal: Abdomen enlarged, constipation

Local: Injection site reaction

Neuromuscular & skeletal: Back pain

Respiratory: Sinusitis, upper respiratory tract infection

Postmarketing, case reports, or events reported with gonadotropins: Acute respiratory distress syndrome, adnexal torsion, arterial occlusions, atelectasis, breast tenderness, chills, dizziness, dry skin, dyspnea, erythema, febrile reaction, fever, flu-like syndrome, hair loss, cerebral vascular occlusion, hemoperitoneum, hives, joint pain, malaise, musculoskeletal ache, ovarian neoplasm, pulmonary embolism, rash, tachycardia, tachypnea

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersMonitor sufficient follicular maturation. This may be directly estimated by sonographic visualization of the ovaries and endometrial lining or measuring serum estradiol levels. The combination of both ultrasonography and measurement of estradiol levels is useful for monitoring for the growth and development of follicles and timing hCG administration.

The clinical evaluation of estrogenic activity (changes in vaginal cytology and changes in appearance and volume of cervical mucus) provides an indirect estimate of the estrogenic effect upon the target organs and, therefore, it should only be used adjunctively with more direct estimates of follicular development (ultrasonography and serum estradiol determinations).

The clinical confirmation of ovulation is obtained by direct and indirect indices of progesterone production. The indices most generally used are: rise in basal body temperature, increase in serum progesterone, and menstruation following the shift in basal body temperature.

Monitor for signs and symptoms of OHSS for at least 2 weeks following hCG administration.

Nursing: Physical Assessment/MonitoringThis medication should only be prescribed by a fertility specialist. Assess results of laboratory tests and therapeutic effectiveness on a regular basis. Assess knowledge/teach patient appropriate use (injection technique and syringe disposal), interventions to reduce side effects, and adverse symptoms to report. **Pregnancy risk factor X:** Pregnancy must be excluded before starting medication.

Monitoring: Lab TestsMonitor sufficient follicular maturation. This may be directly estimated by sonographic visualization of the ovaries and endometrial lining or measuring serum estradiol levels. The combination of both ultrasonography and measurement of estradiol levels is useful for monitoring for the growth and development of follicles and timing hCG administration.

Patient EducationThis medication can only be administered by injection. If you are using this medication at home, follow exact instruction for administering injections and disposal of syringes. Administer exact amount as instructed; do not alter dosage or miss a dose. If dose is missed, notify prescriber. Frequent laboratory tests will be required while you are on this therapy; do not miss appointments for laboratory tests or ultrasound. You may experience headache, dizziness, or fever (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea or vomiting (small frequent meals, frequent oral care, sucking lozenges, or chewing gum may help). Report immediately abdominal pain/distension, bloating, persistent nausea, vomiting, diarrhea; dyspnea, respiratory difficulty, exacerbation of asthma; swelling, pain, or redness of extremities; itching or burning on urination; menstrual irregularity, acute backache; rash, pain, or inflammation at injection site; or other adverse response. **Pregnancy/breast-feeding precautions:** Pregnancy must be ruled out prior to initiating this medication. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [rDNA origin]:

Follistim® AQ Cartridge:

175 int. units/0.21 mL (0.21 mL) [delivers 150 int. units; contains benzyl alcohol and sucrose; may contain trace amounts of neomycin or streptomycin]

350 int. units/0.42 mL (0.42 mL) [delivers 300 int. units; contains benzyl alcohol and sucrose; may contain trace amounts of neomycin or streptomycin]

650 int. units/0.78 mL (0.78 mL) [delivers 600 int. units; contains benzyl alcohol and sucrose; may contain trace amounts of neomycin or streptomycin]

975 int. units/1.17 mL (1.17 mL) [delivers 900 int. units; contains benzyl alcohol and sucrose; may contain trace amounts of neomycin or streptomycin]

Injection, solution [rDNA origin; single-dose]:

Follistim® AQ:

75 int. units/0.5 mL (0.5mL) [contains sucrose; may contain trace amounts of neomycin or streptomycin]

150 int. units/0.5 mL (0.5 mL) [contains sucrose; may contain trace amounts of neomycin or streptomycin]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Follistim AQ)

300 units/0.36 mL (0.525): $483.83

600 units (0.885): $888.96

900 units/1.08 mL (1.17): $1167.14

Mechanism of ActionFollitropin beta is a human FSH preparation of recombinant DNA origin. Follitropins stimulate ovarian follicular growth in women who do not have primary ovarian failure. FSH is required for normal follicular growth, maturation, gonadal steroid production, and spermatogenesis.

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Follicle development: Within cycle

Absorption: I.M.: 76%; SubQ: 78%

Distribution: 8 L

Half-life elimination: I.M.: 44 hours (single dose), 27-30 hours (multiple doses); SubQ: 33 hours (single dose)

Time to peak: SubQ: 13 hours

Pharmacotherapy PearlsThe currently available recombinant follitropin products are structurally identical to native follicle-stimulating hormone. The “alpha” and “beta” nomenclature refers to their differences in purification and order of marketing. Follitropin alpha was marketed first, followed by follitropin beta.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFollicle Stimulating Hormone, Recombinant; FSH; rFSH-beta; rhFSH-beta

References

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International Brand NamesPuregon (MX)

Jump To Field (Select Field Name)

Pronunciation(foe ME pi zole)

U.S. Brand NamesAntizol®

Pharmacologic CategoryAntidote

Use: Labeled IndicationsTreatment of methanol or ethylene glycol poisoning alone or in combination with hemodialysis

Use: Unlabeled/InvestigationalTreatment of propylene glycol toxicity

Dosing: Adults**Note:** Fomepizole therapy should begin immediately upon suspicion of ethylene glycol or methanol ingestion.

Ethylene glycol and methanol toxicity: I.V.: Loading dose of 15 mg/kg should be administered, followed by doses of 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours thereafter until ethylene glycol levels have been reduced <20 mg/dL and patient is asymptomatic with normal pH.

Dosing: ElderlySpecific studies have not been conducted in elderly patients.

Dosing: PediatricSafety and efficacy have not been established in pediatric patients.

Dosing: Renal ImpairmentThe manufacturer provides the following dosage recommendations:

Dose at the beginning of hemodialysis:

If <6 hours since last fomepizole dose: Do not administer dose

If ≥6 hours since last fomepizole dose: Administer next scheduled dose

Dosing during hemodialysis: Dose every 4 hours

Dosing at the time hemodialysis is complete, based on time between last dose and the end of hemodialysis:

<1 hour: Do not administer dose at the end of hemodialysis

1-3 hours: Administer $^{1}/_{2}$ of next scheduled dose

>3 hours: Administer next scheduled dose

Maintenance dose when off hemodialysis: Give next scheduled dose 12 hours from last dose administered.

Alternatively, a loading dose of 10-20 mg/kg followed by 1-1.5 mg/kg/hour continuous infusion during hemodialysis has been described in case reports (Jobard, 1996).

Dosing: Hepatic ImpairmentFomepizole is metabolized in the liver. Specific dosage adjustments have not been determined in patients with hepatic impairment.

Administration: I.V.All doses should be administered as a slow intravenous infusion (IVPB) over 30 minutes

Administration: I.V. DetailAll doses should be administered as a slow intravenous infusion (IVPB) over 30 minutes

StorageStore at controlled room temperature, 20°C to 25°C (68°F to 77°F); fomepizole solidifies at temperatures <25°C (77°F). If solution becomes solid in the vial, it be should be carefully warmed by running the vial under warm water or by holding in the hand. Solidification does not affect the efficacy, safety, or stability of the drug.

ReconstitutionPrior to administration, dilute in at least 100 mL 0.9% sodium chloride or dextrose 5% water for injection. Diluted solution should be used within 24 hours and may be stored at room temperature or under refrigeration. Although, it is chemically and physically stable when diluted as recommended, sterile precautions should be observed because diluents generally do not contain preservatives.

ContraindicationsHypersensitivity to fomepizole, other pyrazoles, or any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; metabolized in the liver.
- Renal impairment: Use with caution in patients with renal impairment; excreted in the urine; dialysis should be considered in addition to fomepizole in the case of renal failure, significant or worsening metabolic acidosis, or ethylene glycol/methanol levels ≥50 mg/dL.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Administration: Should not be given undiluted or by bolus injection.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted; use in pregnant women only if the benefits clearly outweigh the risks.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Central nervous system: Headache (14%)

Gastrointestinal: Nausea (11%)

1% to 10% (≤3% unless otherwise noted):

Cardiovascular: Bradycardia, facial flush, hypotension, shock, tachycardia

Central nervous system: Dizziness (6%), drowsiness increased (6%), agitation, anxiety, lightheadedness, seizure, vertigo

Dermatologic: Rash

Gastrointestinal: Bad/metallic taste (6%), abdominal pain, appetite decreased, diarrhea, heartburn, vomiting

Hematologic: Anemia, disseminated intravascular coagulation (DIC), eosinophilia, lymphangitis

Hepatic: Liver function tests increased

Local: Application site reaction, injection site inflammation, pain during injection, phlebitis

Neuromuscular & skeletal: Backache

Ocular: Nystagmus, transient blurred vision, visual disturbances

Renal: Anuria

Respiratory: Abnormal smell, hiccups, pharyngitis

Miscellaneous: Multiorgan failure, speech disturbances

Postmarketing and/or case reports: Mild allergic reactions (mild rash, eosinophilia)

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsEthanol: Ethanol decreases the rate of fomepizole elimination by ~50%; conversely, fomepizole decreases the rate of elimination of ethanol by ~40%.

Monitoring ParametersFomepizole plasma levels should be monitored; response to fomepizole; monitor plasma/urinary ethylene glycol or methanol levels, urinary oxalate (ethylene glycol), plasma/urinary osmolality, renal/hepatic function, serum electrolytes, arterial blood gases; anion and osmolar gaps, resolution of clinical signs and symptoms of ethylene glycol or methanol intoxication

Reference RangeThe manufacturer recommends concentrations 100-300 µmol/L (8.2-24.6 mg/L) to achieve enzyme inhibition of alcohol dehydrogenase; according to practice guidelines, serum fomepizole concentrations of ≥0.8 mg/L provide constant inhibition of alcohol dehydrogenase

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 1 g/mL (1.5 mL)

Antizol®: 1 g/mL (1.5 mL)

Generic AvailableYes

ManufacturerOrphan Medical, Inc

Mechanism of ActionFomepizole competitively inhibits alcohol dehydrogenase, an enzyme which catalyzes the metabolism of ethanol, ethylene glycol, and methanol to their toxic metabolites. Ethylene glycol is metabolized to glycoaldehyde, then oxidized to glycolate, glyoxylate, and oxalate. Glycolate and oxalate are responsible for metabolic acidosis and renal damage. Methanol is metabolized to formaldehyde, then oxidized to formic acid. Formic acid is responsible for metabolic acidosis and visual disturbances.

Pharmacodynamics/Kinetics

Onset of effect: Peak effect: Maximum: 1.5-2 hours

Absorption: Oral: Readily absorbed

Distribution: V_d: 0.6-1.02 L/kg; rapidly into total body water

Protein binding: Negligible

Metabolism: Hepatic to 4-carboxypyrazole (80% to 85% of dose), 4-hydroxymethylpyrazole, and their N-glucuronide conjugates; following multiple doses, induces its own metabolism via CYP oxidases after 30-40 hours

Half-life elimination: Has not been calculated; varies with dose

Excretion: Urine (1% to 3.5% as unchanged drug and metabolites)

Pharmacotherapy PearlsAlternate therapies, including ethanol and hemodialysis, are difficult to use in children. Fomepizole's affinity for alcohol dehydrogenase is 8000 times greater than ethanol.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Bad/metallic taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other Considerations Alternate therapies, including ethanol and hemodialysis, are difficult to use in children. Fomepizole's affinity for alcohol dehydrogenase is 8000 times greater than ethanol.

Index Terms 4-Methylpyrazole; 4-MP

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International Brand Names Antizol (GB); Fomepizole AP-HP (FR)

Fomivirsen

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(foe MI vir sen)
U.S. Brand NamesVitravene™ [DSC]
Pharmacologic CategoryAntiviral Agent, Ophthalmic
Use: Labeled IndicationsLocal treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome who are intolerant or insufficiently responsive to other treatments for CMV retinitis or when other treatments for CMV retinitis are contraindicated
Dosing: AdultsCMV retinitis: Intravitreal injection: Induction: 330 mcg (0.05 mL) every other week for 2 doses, followed by maintenance dose of 330 mcg (0.05 mL) every 4 weeks

Note: If progression occurs during maintenance, a repeat of the induction regimen may be attempted to establish resumed control. Unacceptable inflammation during therapy may be managed by temporary interruption, provided response has been established. Topical corticosteroids have been used to reduce inflammation.

Dosing: ElderlyRefer to adult dosing.
StorageStore between 2°C to 25°C (35°F to 77°F). Protect from excessive heat or light.
ContraindicationsHypersensitivity to fomivirsen or any component
Warnings/Precautions

Concerns related to adverse effects:

- Increased intraocular pressure: Commonly increases intraocular pressure; monitoring is recommended.

- Uveitis: Occurs frequently, particularly during induction dosing.

Concurrent drug therapy issues:

- Cidofovir: Do not use in patients who have received intravenous or intravitreal cidofovir within 2-4 weeks; risk of exaggerated inflammation is increased.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: For ophthalmic use via intravitreal injection only. Patients should be monitored for CMV disease in the contralateral eye and/or extraocular disease.

Pregnancy ConsiderationsStudies have not been conducted in pregnant women. Should be used in pregnancy only when potential benefit to the mother outweighs the potential risk to the fetus.
LactationExcretion in breast milk unknown/contraindicated
Adverse Reactions

5% to 10%:

Central nervous system: Fever, headache

Gastrointestinal: Abdominal pain, diarrhea, nausea, vomiting

Hematologic: Anemia

Neuromuscular & skeletal: Asthenia

Ocular: Uveitis, abnormal vision, anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, visual acuity decreased, color vision loss, eye pain, intraocular pressure increased, photophobia, retinal detachment, retinal edema, retinal hemorrhage, retinal pigment changes, vitreitis

Respiratory: Pneumonia, sinusitis

Miscellaneous: Systemic CMV, sepsis, infection

2% to 5%:

Cardiovascular: Chest pain

Central nervous system: Confusion, depression, dizziness, neuropathy, pain

Endocrine & metabolic: Dehydration

Gastrointestinal: Abnormal LFTs, pancreatitis, anorexia, weight loss

Hematologic: Thrombocytopenia, lymphoma

Neuromuscular & skeletal: Back pain, cachexia

Ocular: Application site reaction, conjunctival hyperemia, conjunctivitis, corneal edema, decreased peripheral vision, eye irritation, keratic precipitates, optic neuritis, photopsia, retinal vascular disease, visual field defect, vitreous hemorrhage, vitreous opacity

Renal: Kidney failure

Respiratory: Bronchitis, dyspnea, cough

Miscellaneous: Allergic reaction, flu-like syndrome, diaphoresis increased

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersImmediately after injection, light perception and optic nerve head perfusion should be monitored. Anterior chamber paracentesis may be necessary if perfusion is not complete within 7-10 minutes after injection. Subsequent patient evaluation should include monitoring for contralateral CMV infection or extraocular CMV disease, and intraocular pressure prior to each injection.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution, intravitreal, as sodium: 6.6 mg/mL (0.25 mL) [DSC]

Generic AvailableNo

Mechanism of ActionInhibits synthesis of viral protein by binding to mRNA which blocks replication of cytomegalovirus through an antisense mechanism

Pharmacodynamics/KineticsPharmacokinetic studies have not been conducted in humans. In animal models, the drug is cleared from the eye after 7-10 days. It is metabolized by sequential nucleotide removal, with a small amount of the radioactivity from a dose appearing in the urine.

Pharmacotherapy PearlsBecause the mechanism of action of fomivirsen is different than other antiviral agents active against CMV, fomivirsen may be active against isolates resistant to ganciclovir, foscarnet, or cidofovir. The converse may also be true.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause confusion, depression, or dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFomivirsen Sodium

References

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International Brand NamesVitravene (CH, DE, DK, SE)

Fondaparinux

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(fon da PARE i nuks)

U.S. Brand NamesArixtra®

Canadian Brand NamesArixtra®

Pharmacologic CategoryFactor Xa Inhibitor

Use: Labeled IndicationsProphylaxis of deep vein thrombosis (DVT) in patients undergoing surgery for hip replacement, knee replacement, hip fracture (including extended prophylaxis following hip fracture surgery), or abdominal surgery (in patients at risk for thromboembolic complications); treatment of acute pulmonary embolism (PE); treatment of acute DVT without PE

Note: Additional Canadian approvals (not approved in U.S.): Unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) for the prevention of death and subsequent MI; ST segment elevation MI (STEMI) for the prevention of death and myocardial reinfarction

Use: Unlabeled/InvestigationalProphylaxis of DVT in patients with a history of heparin-induced thrombocytopenia (HIT)

Dosing: Adults

DVT prophylaxis: SubQ: Adults ≥50 kg: 2.5 mg once daily.

DVT prophylaxis with history of HIT (unlabeled use): 2.5 mg once daily.

Note: Initiate dose after hemostasis has been established, 6-8 hours postoperatively.

Usual duration: 5-9 days (up to 10 days following abdominal surgery or up to 11 days following hip replacement or knee replacement).

Extended prophylaxis is recommended following hip fracture surgery (has been tolerated for up to 32 days).

Acute DVT/PE treatment: SubQ: **Note:** Concomitant treatment with warfarin sodium should be initiated as soon as possible, usually within 72 hours:

<50 kg: 5 mg once daily

50-100 kg: 7.5 mg once daily

>100 kg: 10 mg once daily

Usual duration: 5-9 days (has been administered up to 26 days)

Canadian labeling only: Adults:

UA/NSTEMI: SubQ: 2.5 mg once daily; initiate as soon as possible after diagnosis; treat for up to 8 days or until hospital discharge.

STEMI: I.V.: 2.5 mg once; subsequent doses: SubQ: 2.5 mg once daily; treat for up to 8 days or until hospital discharge

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 30-50 mL/minute: Use caution

Cl_{cr} <30 mL/minute: Contraindicated

Calculations

- Creatinine Clearance: Adults

Administration: I.M.Do not administer I.M.

Administration: I.V.**Canadian labeling only:** STEMI patients: I.V. push or mixed in 25-50 mL of NS and infused over 1-2 minutes. Flush tubing with NS after infusion to ensure complete administration of fondaparinux. Infusion bag should not be mixed with other agents.

Administration: OtherFor SubQ administration only. Do not mix with other injections or infusions. Do not expel air bubble from syringe before injection. Administer according to recommended regimen; early initiation (before 6 hours after surgery) has been associated with increased bleeding.

StorageStore at 15°C to 30°C (59°F to 86°F).

Canadian labeling: For I.V. administration: Manufacturer recommends immediate use once diluted in NS, but is stable for up to 24 hours at 15°C to 30°C (59°F to 86°F).

ReconstitutionCanadian labeling: For I.V. administration: May mix with 25 mL or 50 mL NS
Compatibility

Do not mix with other injections or infusions.

Canadian labeling: Stable in NS

ContraindicationsHypersensitivity to fondaparinux or any component of the formulation; severe renal impairment (Cl_{cr} <30 mL/minute); body weight <50 kg (prophylaxis); active major bleeding; bacterial endocarditis; thrombocytopenia associated with a positive *in vitro* test for antiplatelet antibody in the presence of fondaparinux
Allergy Considerations

- Fondaparinux Allergy

Warnings/Precautions

Boxed warnings:

- Neuraxial anesthesia: See "Other warnings/precautions" below.

Concerns related to adverse effects:

- Bleeding: Monitor patient closely for signs or symptoms of bleeding. Certain patients are at increased risk of bleeding. Risk factors include bacterial endocarditis; congenital or acquired bleeding disorders; active ulcerative or angiodysplastic GI diseases; severe uncontrolled hypertension; hemorrhagic stroke; or use shortly after brain, spinal, or ophthalmology surgery; in patient treated concomitantly with platelet inhibitors; recent GI bleeding; thrombocytopenia or platelet defects; severe liver disease; hypertensive or diabetic retinopathy; or in patients undergoing invasive procedures. Risk of major bleeding may be increased if initial dose is administered earlier then recommended (initiation recommended at 6-8 hours following surgery). Discontinue if bleeding occurs.

Disease-related concerns:

- Renal impairment: Use with caution in patients with moderate renal dysfunction (Cl_{cr} 30-50 mL/minute). Patients with serum creatinine >2 mg/dL were excluded from clinical trials. Periodically monitor renal function; discontinue if severe dysfunction or labile function develops.

Special populations:

- Elderly: Use with caution in the elderly.

- Patients <50 kg: Use with caution in patients <50 kg who are being treated for DVT/PE; fondaparinux clearance may be decreased. Dosage reduction recommended.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- **Canadian labeling warnings/precautions:** The administration of fondaparinux is not recommended prior to and during primary percutaneous coronary intervention (PCI) for reperfusion in STEMI patients, due to an increased risk for guiding catheter thrombosis. UA/NSTEMI and STEMI patients undergoing any PCI should not receive fondaparinux as a sole anticoagulant agent. Use of an antithrombin regimen (eg, unfractionated heparin) is recommended as adjunctive therapy to PCI. Following sheath removal, fondaparinux therapy should not resume for at least 2 hours in UA/NSTEMI patients and 3 hours in STEMI patients. Use caution in UA/NSTEMI/STEMI patients <50 kg. Avoid administration 24 hours before and 48 hours after coronary artery bypass graft (CABG) surgery.

- Neuraxial anesthesia: **[U.S. Boxed Warning]: Patients with recent or anticipated neuraxial anesthesia (epidural or spinal anesthesia) are at risk of spinal or epidural hematoma and subsequent paralysis.** Consider risk versus benefit prior to neuraxial anesthesia; risk is increased by concomitant agents which may alter hemostasis, as well as traumatic or repeated epidural or spinal puncture. Patient should be observed closely for bleeding and signs and symptoms of neurological impairment if therapy is administered during or immediately following diagnostic lumbar puncture, epidural anesthesia, or spinal anesthesia.

Geriatric ConsiderationsPatients studied for DVT prophylaxis following elective knee or hip fracture surgery averaged 67.5 and 77 years of age, respectively. Use with caution in patients with estimated or actual creatinine clearance between 30-50 mL/minute. Contraindicated in patients with Cl_{cr} <30 mL/minute.
Pregnancy Risk FactorB
Pregnancy ConsiderationsReproductive animal studies have not shown fetal harm. Based on case reports, small amounts of fondaparinux have been detected in the umbilical cord following multiple doses during pregnancy. There are no adequate and well-controlled studies in pregnant women; use only if clearly needed.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsAs with all anticoagulants, bleeding is the major adverse effect. Hemorrhage may occur at any site. Risk appears increased by a number of factors including renal dysfunction, age (>75 years), and weight (<50 kg).

>10%:

Central nervous system: Fever (4% to 14%)

Gastrointestinal: Nausea (11%)

Hematologic: Anemia (20%)

1% to 10%:

- Cardiovascular: Edema (9%), hypotension (4%), thrombosis PCI catheter (without heparin 1%)
- Central nervous system: Insomnia (5%), dizziness (4%), headache (2% to 5%), confusion (3%), pain (2%)
- Dermatologic: Rash (8%), purpura (4%), bullous eruption (3%)
- Endocrine & metabolic: Hypokalemia (1% to 4%)
- Gastrointestinal: Constipation (5% to 9%), nausea (3%), vomiting (6%), diarrhea (3%), dyspepsia (2%)
- Genitourinary: Urinary tract infection (4%), urinary retention (3%)
- Hematologic: Moderate thrombocytopenia (50,000-100,000/mm^3: 3%), major bleeding (1% to 3%), minor bleeding (2% to 4%), hematoma (3%); risk of major bleeding increased as high as 5% in patients receiving initial dose <6 hours following surgery
- Hepatic: ALT increased (3%), AST increased (2%)
- Local: Injection site reaction (bleeding, rash, pruritus)
- Miscellaneous: Wound drainage increased (5%)

<1%: Heparin-induced thrombocytopenia (1 case report), hepatic enzymes increased, severe thrombocytopenia (<50,000/mm^3)

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Drotrecogin Alfa: May enhance the adverse/toxic effect of Fondaparinux. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, coleus, cordyceps, dong quai, evening primrose oil, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American/Panax/Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, sweet clover, turmeric, white willow (all possess anticoagulant or antiplatelet activity and as such, may enhance the anticoagulant effects of fondaparinux).

Test InteractionsInternational standards of heparin or LMWH are not the appropriate calibrators for antifactor Xa activity of fondaparinux.

Monitoring ParametersPeriodic monitoring of CBC, serum creatinine, occult blood testing of stools recommended. Antifactor Xa activity of fondaparinux can be measured by the assay if fondaparinux is used as the calibrator. PT and aPTT are insensitive measures of fondaparinux activity.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (especially anything that will affect coagulation or platelet function). Assess closely for bleeding; bleeding precautions should be observed. Assess results of laboratory tests, therapeutic effectiveness, and adverse response regularly during therapy. Teach appropriate use, including appropriate injection technique and syringe/needle disposal. Teach patient possible side effects/appropriate interventions (eg, bleeding precautions) and adverse symptoms to report.

Monitoring: Lab TestsCBC, platelet count, serum creatinine; stool occult blood tests

Patient EducationDo not take any new medication during therapy without consulting prescriber. This drug can only be administered by injection. Report pain, burning, redness, or swelling at injection site. You may have a tendency to bleed easily while taking this drug (brush teeth with soft brush, floss with waxed floss, use electric razor, avoid scissors or sharp knives, and avoid potentially harmful activities). May cause nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or dizziness, headache, insomnia (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report unusual bleeding or bruising (bleeding gums, nosebleed, blood in urine, dark stool); pain in joints or back; CNS changes (fever, severe headache, confusion); unusual fever; persistent nausea or GI upset; changes in urinary pattern; or other persistent adverse response. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sodium [preservative free]: 2.5 mg/0.5 mL (0.5 mL); 5 mg/0.4 mL (0.4 mL); 7.5 mg/0.6 mL (0.6 mL); 10 mg/0.8 mL (0.8 mL) [prefilled syringe]

Generic AvailableNo

ManufacturerOrganon/Sanofi-Synthelabo LLC

Pricing: U.S. (www.drugstore.com)

Solution (Arixtra)

2.5 mg/0.5 mL (5): $537.88

7.5 mg/0.6 mL (0.6): $127.06

Mechanism of ActionFondaparinux is a synthetic pentasaccharide that causes an antithrombin III-mediated selective inhibition of factor Xa. Neutralization of factor Xa interrupts the blood coagulation cascade and inhibits thrombin formation and thrombus development.

Pharmacodynamics/Kinetics

Absorption: SubQ: Rapid and complete

Distribution: V_d: 7-11 L; mainly in blood

Protein binding: ≥94% to antithrombin III

Bioavailability: SubQ: 100%

Half-life elimination: 17-21 hours; prolonged with worsening renal impairment

Time to peak: SubQ: 2-3 hours

Excretion: Urine (as unchanged drug); decreased clearance in patients <50 kg

Related Information

- Anticoagulants, Injectable

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Hemorrhage may occur at any site; risk increased in renal dysfunction, patients >75 years and/or <50 kg; major bleeding increased as high as 5% in patients receiving initial dose <6 hours postsurgery.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or insomnia

Mental Health: Effects on Psychiatric TreatmentMay cause thrombocytopenia; use caution with valproic acid

Cardiovascular ConsiderationsThe OASIS-5 trial is an international, randomized, double-blind trial in patients with non-ST segment elevation acute coronary syndrome who were randomized to fondaparinux (2.5 mg SubQ once daily) versus enoxaparin (1 mg/kg SubQ twice daily). If patients in the fondaparinux arm had PCI, then route and dose were adjusted. If PCI <6 hours and GPIIb/IIIa **was not** used, fondaparinux 2.5 mg I.V. was administered. If PCI <6 hours and GPIIb/IIIa **was** used, no fondaparinux was administered. If PCI >6 hours, fondaparinux was adjusted based on concurrent GPIIb/IIIa use. If a GPIIb/IIIa was used, fondaparinux was administered at 2.5 mg I.V., while fondaparinux 5 mg was administered in patients without concurrent GP IIb/IIIa. In the enoxaparin arm, if PCI <6 hours, then no additional unfractionated heparin (UFH) was used. If PCI >6 hours, I.V. UFH was used (doses varied depending on use of GPIIb/IIIa). The primary outcome was a composite of death, MI, refractory ischemia, and major bleeds at 9 days. Patients were also evaluated at 1 month and 6 months for these endpoints. Over 20,000 patients were enrolled. Patients were excluded if they had any contraindications to enoxaparin, had a hemorrhagic stroke <12 months ago, or serum creatinine >3 mg/dL. The primary efficacy outcome (death, MI, refractory ischemia) at day 9 was similar for both treatment arms. Major bleeding at day 9 was significantly less for fondaparinux (2.1%) than enoxaparin (4%). At one month and at 6 months, there is a significant reduction in mortality with fondaparinux.

Index TermsFondaparinux Sodium

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International Brand NamesArixtra (AR, AT, AU, BE, BG, BR, CH, CO, CR, CZ, DE, DK, DO, FI, FR, GB, GR, GT, HN, IE, IT, MX, MY, NI, NL, NO, PA, PH, PT, RU, SE, SG, SV, TH, TR); Quixidar (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Formoterol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Public Health Advisory: Formoterol and Tiotropium Capsules for Inhalation - February 2008

The U.S. Food and Drug Administration (FDA) has issued a Public Health Advisory emphasizing the correct administration of formoterol (Foradil®) capsules and tiotropium (Spiriva®) capsules. The capsules for both medications contain powder intended for inhalation via their respective inhalation devices: Aerolizer™ (Foradil®) and HandiHaler® (Spiriva®). There have been numerous reports of patients *swallowing* the capsule, including some reports of patients experiencing side effects from the swallowed capsules. The FDA is reminding healthcare professionals to discuss with patients the correct administration of the capsules via the inhalation device and **not** to swallow the capsules.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Spiriva

Medication Safety Issues

Sound-alike/look-alike issues:

Foradil® may be confused with Toradol®

Foradil® capsules for inhalation are for administration via Aerolizer™ inhaler and are **not** for oral use.

International issues:

Foradil® may be confused with Theradol® which is a brand name for tramadol in the Netherlands.

Pronunciation(for MOH te rol)

U.S. Brand NamesForadil® Aerolizer®; Perforomist™

Canadian Brand NamesForadil®; Oxeze® Turbuhaler®

Pharmacologic CategoryBeta$_2$ Agonist

Use: Labeled IndicationsMaintenance treatment of asthma and prevention of bronchospasm in patients ≥5 years of age with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting beta$_2$-agonists; maintenance treatment of bronchoconstriction in patients with COPD; prevention of exercise-induced bronchospasm in patients ≥5 years of age

Note:

Oxeze® is also approved in Canada for acute relief of symptoms ("on demand" treatment) in patients ≥6 years of age.

Perforomist™ is only indicated for maintenance treatment of bronchoconstriction in patients with COPD.

Dosing: Adults

Asthma, maintenance: Inhalation:

Foradil®: 12 mcg capsule inhaled every 12 hours via Aerolizer™ device

Oxeze® (CAN): **Note:** Not labeled for use in the U.S.: Inhalation: 6 mcg or 12 mcg every 12 hours. Maximum dose: Children: 24 mcg/day; Adults: 48 mcg/day

Exercise-induced bronchospasm: Inhalation:

Foradil®: 12 mcg capsule inhaled via Aerolizer™ device at least 15 minutes before exercise on an "as needed" basis; additional doses should not be used for another 12 hours. **Note:** If already using for asthma maintenance then should not use additional doses for exercise-induced bronchospasm.

Oxeze® (CAN): **Note:** Not labeled for use in the U.S.: Children ≥6 years and Adults: Inhalation: 6 mcg or 12 mcg at least 15 minutes before exercise.

COPD (maintenance): Inhalation:

Foradil®: 12 mcg capsule inhaled every 12 hours via Aerolizer™ device

Perforomist™: 20 mcg twice daily (maximum dose: 40 mcg/day)

Acute ("on demand") relief of bronchoconstriction: *Indication for Oxeze® approved in Canada:* 6 mcg or 12 mcg as a single dose (maximum dose: 72 mcg in any 24-hour period). The prolonged use of high dosages (48 mcg/day for ≥3 consecutive days) may be a sign of suboptimal control, and should prompt the re-evaluation of therapy.

Dosing: Elderly

Refer to adult dosing.

Dosing: Pediatric

Asthma maintenance (Foradil®): Inhalation: Children ≥5 years: Refer to adult dosing.

Exercise-induced bronchospasm (Foradil®): Inhalation: Children ≥5 years: Refer to adult dosing.

Acute "on demand" treatment of bronchospasm (Oxeze® [CAN]): Inhalation: Refer to adult dosing.

Dosing: Renal Impairment

Not studied

Administration: Inhalation

Foradil®: Remove capsule from foil blister **immediately** before use. Place capsule in the capsule-chamber in the base of the Aerolizer™ Inhaler. Must only use the Aerolizer™ Inhaler. Press both buttons **once only** and then release. Keep inhaler in a level, horizontal position. Exhale fully. Do not exhale into inhaler. Tilt head slightly back and inhale (rapidly, steadily, and deeply). Hold breath as long as possible. If any powder remains in capsule, exhale and inhale again. Repeat until capsule is empty. Throw away empty capsule; do not leave in inhaler. Do not use a spacer with the Aerolizer™ Inhaler. Always keep capsules and inhaler dry.

Perforomist™: Remove unit-dose vial from foil pouch **immediately** before use. Solution does not require dilution prior to administration; do not mix other medications with formoterol solution. Place contents of unit-dose vial into the reservoir of a standard jet nebulizer connected to an air compressor; assemble nebulizer based on the manufacturer's instructions and turn nebulizer on; breathe deeply and evenly until all of the medication has been inhaled. Discard any unused medication immediately; do not ingest contents of vial. Clean nebulizer after use.

Storage

Foradil®: Prior to dispensing, store in refrigerator at 2°C to 8°C (36°F to 46°F). After dispensing, store at room temperature at 20°C to 25°C (68°F to 77°F). Protect from heat and moisture. Capsules should always be stored in the blister and only removed immediately before use. Always check expiration date. Use within 4 months of purchase date or product expiration date, whichever comes first.

Perforomist™: Prior to dispensing, store in refrigerator at 2°C to 8°C (36°F to 46°F). After dispensing, store at 2°C to 25°C (36°F to 77°F) for up to 3 months. Protect from heat. Unit-dose vials should always be stored in the foil pouch and only removed immediately before use.

Restrictions

An FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

Contraindications

Foradil®: Hypersensitivity to formoterol, or any component of the formulation

Oxeze®: Hypersensitivity to formoterol, inhaled lactose, or any component of the formulation; presence of tachyarrhythmias

Perforomist™: No contraindications listed in the product labeling

Warnings/Precautions

Boxed warnings:

- Asthma-related deaths: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Asthma-related deaths: **[U.S. Boxed Warning]: Long-acting beta$_2$-agonists may increase the risk of asthma-related deaths.** In a large, randomized clinical trial (SMART, 2006), salmeterol was associated with a small, but statistically significant, increase in asthma-related deaths (when added to usual asthma therapy); risk may be greater in African-American patients versus Caucasians.

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.

- Hypersensitivity reactions: Immediate hypersensitivity reactions (urticaria, angioedema, rash, bronchospasm) have been reported.

- Serious effects/fatalities: Do not exceed recommended dose or frequency; serious adverse events, including fatalities, have been associated with excessive use of inhaled sympathomimetics.

Disease-related concerns:

- Asthma: Appropriate use:

  Foradil®: Should only be used as adjuvant therapy in patients not adequately controlled on other asthma medications (eg, low-to-medium dose inhaled corticosteroids) or whose disease warrants initiation of two maintenance therapies. Optimize anti-inflammatory treatment before initiating maintenance treatment with formoterol. Do not use as a component of chronic therapy without an anti-inflammatory agent. Corticosteroids should not be stopped or reduced at formoterol initiation. Acute episodes should be treated with a rapid-onset beta$_2$-agonist.

  Perforomist™: The safety and efficacy of Perforomist™ in the treatment of asthma have not been established.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (arrhythmia, coronary insufficiency, hypertension, or

HF); beta-agonists may cause elevation in blood pressure and heart rate and result in CNS stimulation/excitation. Beta$_2$-agonists may also increase risk of arrhythmias and prolong QT$_c$ interval.

- Chronic obstructive pulmonary disease (COPD), acute: Formoterol should not be used for the treatment of rapidly deteriorating COPD or for acute symptomatic COPD; increased use and/or ineffectiveness of short-acting beta$_2$-agonists may indicate rapidly deteriorating disease and should prompt re-evaluation of the patient's condition.

- Diabetes: Use with caution in patients with diabetes mellitus; beta$_2$-agonists may increase serum glucose.

- Glaucoma: Use with caution in patients with glaucoma; may elevate intraocular pressure.

- Hyperthyroidism: Use with caution in hyperthyroidism; may stimulate thyroid activity.

- Hypokalemia: Use with caution in patients with hypokalemia; beta$_2$-agonists may decrease serum potassium.

- Seizures: Use with caution in patients with seizure disorders; beta-agonists may result in CNS stimulation/excitation.

Special populations:

- Pediatrics:

  Foradil®: Safety and efficacy have not been established in children <5 years of age.

  Perforomist™: Safety and efficacy have not been established in children <18 years of age.

Dosage form specific issues:

- Foradil®: The contents of the capsules are for inhalation via the Aerolizer™ device. There have been reports of incorrect administration (swallowing of the capsules).

- Lactose: Powder for oral inhalation contains lactose; very rare anaphylactic reactions have been reported in patients with severe milk protein allergy.

- Oxeze®: Oxeze® is a formulation of formoterol (available outside the U.S. [eg, Canada]) approved for acute treatment of asthmatic symptoms. The labelings for U.S. approved formulations (Foradil®, Perforomist™) state that formoterol is not meant to relieve acute asthmatic symptoms.

Other warnings/precautions:

- Patient information: Patients using inhaled, short-acting beta$_2$-agonists should be instructed to discontinue routine use of these medications prior to beginning treatment; short-acting agents should still be provided to patients; however, use should be reserved for symptomatic relief of acute symptoms. Patients must be instructed to seek medical attention in cases where acute symptoms are not relieved or a previous level of response is diminished. The need to increase frequency of use may indicate deterioration of asthma or COPD, and treatment must not be delayed.

Geriatric ConsiderationsElderly patients should be specifically counseled about the proper use of this inhaler/spacing of doses and/or the proper use of a nebulizer system. No significant difference in both safety and effectiveness was seen between elderly and younger patients.

Pregnancy Risk FactorC

Pregnancy ConsiderationsWhen given orally to rats throughout organogenesis, formoterol caused delayed ossification and decreased fetal weight, but no malformations. There were no adverse events when given to pregnant rats in late pregnancy. Doses used were ≥70 times the recommended daily inhalation dose in humans. There are no adequate and well-controlled studies in pregnant women. Use only if benefit outweighs risk to the fetus. Beta-agonists interfere with uterine contractility so use during labor only if benefit outweighs risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Cardiovascular: Chest pain (2%), palpitation

Central nervous system: Anxiety (2%), dizziness (2%), fever (2%), insomnia (2%), dysphonia (1%), headache

Dermatologic: Rash (1%)

Gastrointestinal: Diarrhea (5%), nausea (5%), xerostomia (1% to 3%), vomiting (2%), abdominal pain, dyspepsia, gastroenteritis

Neuromuscular & skeletal: Tremor

Respiratory: Asthma exacerbation (age 5-12 years: 5% to 6%; age >12 years: <4%), bronchitis (5%), infection (3% to 7%), pharyngitis (3% to 4%), sinusitis (3%), dyspnea (2%), tonsillitis (1%)

<1%: Acute asthma deterioration, anaphylactic reactions (severe hypotension/angioedema), agitation, angina, arrhythmia, bronchospasm (paradoxical), fatigue, hyperglycemia, hypertension, hypokalemia, glucose intolerance, malaise, metabolic acidosis, muscle cramps, nervousness, tachycardia

Metabolism/Transport Effects**Substrate** (minor) of CYP2A6, 2C9, 2C19, 2D6

Drug Interactions

Alpha-/Beta-Blockers: May diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Atomoxetine: May enhance the tachycardic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Betahistine: May diminish the therapeutic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Monitoring ParametersFEV$_1$, peak flow, and/or other pulmonary function tests; blood pressure, heart rate; CNS stimulation; serum glucose, serum potassium

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically throughout period of therapy. Assess knowledge/teach appropriate use of medication, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsFEV$_1$, peak flow, and/or other pulmonary function tests; serum potassium, serum glucose (in selected patients)

Patient EducationDo not swallow capsules; this medication can only be used in the Aerolizer™ Inhaler. Use exactly as directed and do not use more often than recommended. Store capsules in blister and do not remove from blister until ready for treatment. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. It is recommended that you wear identification (Med-Alert bracelet) if you have an asthmatic condition. You may experience nervousness, dizziness, or insomnia (use caution when driving or engaging in hazardous activities until response to medication is known); dry mouth, nausea, or GI discomfort (small frequent meals, good mouth care, sucking lozenges, or chewing gum may help); or difficulty voiding (always void before treatment). Report any unresolved GI upset, nervousness or dizziness, muscle cramping, chest pain or palpitations, skin rash, signs of infection, unusual cough, or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Administration: Follow directions for use and storage of inhaler exactly. Wash hands prior to treatment and sit in comfortable position for treatment. Remove capsule from foil blister immediately before treatment and place capsule in the capsule-chamber in the base of the Aerolizer™ Inhaler. Press both buttons once only and then release. Hold inhaler in a level, horizontal position, exhale fully (do not exhale into inhaler). Tilt head slightly back and inhale from inhaler rapidly, steadily, and deeply. Hold breath as long as possible. If any powder remains in capsule, exhale and inhale again. Repeat until capsule is empty. Throw away empty capsule. Do not use a spacer with Aerolizer™. Do not wash inhaler; store in dry place.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Powder for oral inhalation, as fumarate:

Foradil® Aerolizer™ [capsule]: 12 mcg (12s, 60s) [contains lactose 25 mg]

Oxeze® Turbuhaler® [CAN]: 6 mcg/inhalation [delivers 60 metered doses; contains lactose 600 mcg/dose]; 12 mcg/inhalation [delivers 60 metered doses; contains lactose 600 mcg/dose] [not available in the U.S.]

Solution for nebulization, as fumarate dihydrate:

Perforomist™: 20 mcg/2 mL (2 mL)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Foradil Aerolizer)

12 mcg (60): $148.72

Mechanism of ActionRelaxes bronchial smooth muscle by selective action on beta$_2$ receptors with little effect on heart rate. Formoterol has a long-acting effect.

Pharmacodynamics/Kinetics

Onset of action: Within 3 minutes

Peak effect: 80% of peak effect within 15 minutes

Duration: Improvement in FEV$_1$ observed for 12 hours in most patients

Absorption: Rapidly into plasma

Protein binding: 61% to 64% *in vitro* at higher concentrations than achieved with usual dosing

Metabolism: Hepatic via direct glucuronidation and O-demethylation; CYP2D6, CYP2C8/9, CYP2C19, CYP2A6 involved in O-demethylation

Half-life elimination: Powder: ~10-14 hours; Nebulized solution: ~7 hours

Time to peak: Maximum improvement in FEV$_1$ in 1-3 hours

Excretion:

Children 5-12 years: Urine (7% to 9% as direct glucuronide metabolites, 6% as unchanged drug)

Adults: Urine (15% to 18% as direct glucuronide metabolites, 2% to 10% as unchanged drug)

Related Information

- Inhalant Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or insomnia

Mental Health: Effects on Psychiatric TreatmentConcurrent use with MAO inhibitors, TCAs, thioridazine, or mesoridazine may potentiate cardiovascular effects

Index TermsFormoterol Fumarate; Formoterol Fumarate Dihydrate

References

Cazzola M, Centanni S, Regorda C, et al, “Onset of Action of Single Doses of Formoterol Administered Via Turbuhaler in Patients With Stable COPD,” *Pulm Pharmacol Ther*, 2001, 14:41-45. [PubMed 11162418]

Cazzola M and Donner CF, “Long-Acting Beta$_2$-Agonists in the Management of Stable Chronic Obstructive Pulmonary Disease,” *Drugs*, 2000, 60:307-20. [PubMed 10983735]

Expert Panel Report 3, “Guidelines for the Diagnosis and Management of Asthma,” *Clinical Practice Guidelines*, National Institutes of Health, National Heart, Lung, and Blood Institute, NIH Publication No. 08-4051, prepublication 2007. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

International Brand NamesAcarol Dry Syrup (KP); Asmelor Novolizer (FR); Atimos Modulite (GB); Atock (CL, JP, PH, TW); Broncoral (ES); Foradil (AT, BB, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CO, CZ, DK, EE, ET, FI, FR, GH, GM, GN, GR, GY, HK, HN, IE, IL, IT, JM, KE, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, NZ, PE, PH, PL, PT, RU, SC, SD, SE, SG, SL, SN, SR, TN, TR, TT, TZ, UG, UY, VE, ZA, ZM, ZW); Foradil Aerolizer (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, NZ, OM, QA, SA, SY, YE); Foradil P (DE); Foradile (AU); Fordilen (AR); Formoair (FR); Lexoma (KP); Oxis (AU, BB, BF, BJ, BM, BS, BZ, CH, CI, CR, DE, DO, ET, GH, GM, GN, GT, GY, HN, HU, IE, IL, JM, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, PA, PH, SC, SD, SE, SG, SL, SN, SR, SV, TN, TT, TZ, UG, ZA, ZM, ZW); Oxis Turbuhaler (MX); Oxis turbuhaler (PL); Sortel (KP); Tempus (PY); Zafiron (PL)

Fosamprenavir

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Lexiva® may be confused with Levitra®

Pronunciation(FOS am pren a veer)

U.S. Brand NamesLexiva®

Canadian Brand NamesTelzir®

Pharmacologic CategoryAntiretroviral Agent, Protease Inhibitor

Use: Labeled IndicationsTreatment of HIV infections in combination with at least two other antiretroviral agents

Dosing: Adults

HIV infection: Oral:

Antiretroviral therapy-naive patients:

Unboosted regimen: 1400 mg twice daily (without ritonavir)

Ritonavir-boosted regimens:

- Once-daily regimen: Fosamprenavir 1400 mg plus ritonavir 100-200 mg once daily
- Twice-daily regimen: Fosamprenavir 700 mg plus ritonavir 100 mg twice daily

Protease inhibitor-experienced patients: Fosamprenavir 700 mg plus ritonavir 100 mg twice daily. **Note:** Once-daily administration is not recommended in protease inhibitor-experienced patients.

Combination therapy with efavirenz (ritonavir-boosted regimen):

Once-daily regimen: Fosamprenavir 1400 mg daily plus ritonavir 300 mg once daily

Twice-daily regimen: No dosage adjustment recommended for twice-daily regimen

Combination therapy with nevirapine (ritonavir-boosted regimen): Fosamprenavir 700 mg plus ritonavir 100 mg twice daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

HIV infection: Oral:

Antiretroviral therapy-naive patients:

Children 2-5 years of age: Fosamprenavir 30 mg/kg twice daily (not to exceed adult dosage of 1400 mg twice daily)

Children ≥6 years of age:

- Unboosted regimen: Fosamprenavir 30 mg/kg twice daily (not to exceed adult dosage of 1400 mg twice daily)
- Ritonavir-boosted regimen: Fosamprenavir 18 mg/kg twice daily plus ritonavir 3 mg/kg twice daily (not to exceed the adult dose of 700 mg plus ritonavir 100 mg twice daily)

Protease inhibitor-experienced patients: Children ≥6 years: Fosamprenavir 18 mg/kg plus ritonavir 3 mg/kg twice daily (not to exceed the adult dose of 700 mg plus ritonavir 100 mg twice daily)

Notes: The adult regimen of 1400 mg twice daily may be used for pediatric patients who weigh ≥47 kg. When combined with ritonavir, fosamprenavir tablets may be administered to children who weigh ≥39 kg while ritonavir capsules may be used for pediatric patients who weigh ≥33 kg.

Dosing: Renal ImpairmentNo dosage adjustment required.

Dosing: Hepatic Impairment

Mild impairment (Child-Pugh score 5-6): Reduce dosage of fosamprenavir to 700 mg twice daily without concurrent ritonavir (therapy naive) or fosamprenavir 700 mg twice daily plus ritonavir 100 mg once daily (therapy naive or PI experienced)

Moderate impairment (Child-Pugh score 7-9): Reduce dosage of fosamprenavir to 700 mg twice daily without concurrent ritonavir (therapy naive) or fosamprenavir 450 mg twice daily plus ritonavir 100 mg once daily (therapy naive or PI experienced)

Severe impairment (Child-Pugh score 10-12): Reduce dosage of fosamprenavir to 350 mg twice daily without concurrent ritonavir (therapy naive).

No data concerning the use of fosamprenavir plus ritonavir are available in severe hepatic impairment.

Administration: Oral

Oral suspension: Administer **without** food to adults; administer **with** food to pediatric patients. Shake suspension vigorously prior to use.

Tablet: May be taken with or without food.

Dietary ConsiderationsTablets may be taken with or without food. Adults should take oral suspension without food, however, children should take oral suspension with food.

Storage

Lexiva®: Store tablets at controlled room temperature of 25°C (77°F). Store oral suspension at 5°C to 30°C (41°F to 86°F). Do not freeze.

Telzir®: Store tablets 2°C to 30°C; do not freeze and discard 25 days after opening.

ContraindicationsClinically-significant hypersensitivity (eg, Stevens-Johnson syndrome) to fosamprenavir, amprenavir, or any component of the formulation; concurrent therapy with CYP3A4 substrates with a narrow therapeutic window; concomitant use with cisapride, delavirdine, ergot derivatives, lovastatin, midazolam, pimozide, rifampin, simvastatin, St John's wort, and triazolam; use of flecainide and propafenone with concomitant ritonavir therapy

The Canadian product labeling of fosamprenavir (Telzir®) indicates that this product is contraindicated in severe hepatic impairment; in addition, concurrent therapy with potent inducers of CYP3A4 including rifampin is specifically contraindicated

Allergy Considerations

- Amprenavir Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Hemolytic anemia: Acute hemolytic anemia has been reported in association with amprenavir use.
- Hypersensitivity reactions: Protease inhibitors have been associated with a variety of hypersensitivity events (some severe), including rash, anaphylaxis (rare), angioedema, bronchospasm, erythema multiforme, and/or Stevens-Johnson syndrome (rare). It is generally recommended to discontinue treatment if severe rash or moderate symptoms accompanied by other systemic symptoms occur.
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Increased cholesterol: Increases in total cholesterol and triglycerides have been reported; screening should be done prior to therapy and periodically throughout treatment.
- Sulfonamide allergy: Use with caution in patients with sulfonamide allergy. In clinical trials, the incidence of rash did not differ appreciably in patients with or without past history of sulfonamide allergy.

Disease-related concerns:

- Diabetes: Changes in glucose tolerance, hyperglycemia, exacerbation of diabetes, DKA, and new-onset diabetes mellitus have been reported in patients receiving protease inhibitors.
- Hemophilia A or B: Use with caution in patients with hemophilia A or B; increased bleeding during protease inhibitor therapy has been reported.
- Hepatic impairment: May cause transaminase elevations, hepatitis, and/or exacerbate pre-existing hepatic dysfunction; use with caution in patients with underlying hepatic disease, such as hepatitis B or C or cirrhosis. Dosage adjustment required in hepatic impairment.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers, and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.
- Contraceptive failure: Do not use with hormonal contraceptives (eg, ethinyl estradiol/norethindrone). Estrogen/progestin levels may be reduced with concomitant use; nonhormonal contraception is recommended.
- Toxicity: Use with hormonal contraceptives (eg, ethinyl estradiol/norethindrone) in combination with ritonavir may increase the risk of transaminase elevations; avoid use.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal data showed some abortifacient and minor skeletal abnormalities with amprenavir. It is not known if amprenavir crosses the human placenta. There are no adequate and well-controlled studies in pregnant women. Pregnancy and protease inhibitors are both associated with an increased risk of hyperglycemia. Glucose levels should be closely monitored. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse ReactionsFrequency not defined: Fat redistribution, immune reconstitution syndrome have been associated with protease inhibitor therapy.

>10%:

Dermatologic: Rash (up to 19%; onset ~11 days; duration ~13 days)

Endocrine & metabolic: Hypertriglyceridemia (>750 mg/dL: up to 11%)

Gastrointestinal: Diarrhea (moderate-to-severe; 5% to 13%)

1% to 10%:

Central nervous system: Headache (moderate-to-severe; 2% to 4%), fatigue (moderate-to-severe; 2% to 4%)

Dermatologic: Pruritus (7% to 8%)

Endocrine & metabolic: Hyperglycemia (>251 mg/dL: <1% to 2%)

Gastrointestinal: Serum lipase increased (>2 times ULN: 5% to 8%), nausea (moderate-to-severe; 3% to 7%, vomiting (moderate-to-severe; 2% to 6%), abdominal pain (moderate-to-severe; 1% to 2%)

Hematologic: Neutropenia (<750 cells/mm^3: 3%)

Hepatic: Transaminases increased (>5 times ULN: 4% to 8%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Angioedema, Stevens-Johnson syndrome

Note: Spontaneous bleeding has been reported in patients with hemophilia A or B following treatment with protease inhibitors. Acute hemolytic anemia has been reported in association with amprenavir use.

Metabolism/Transport EffectsAs amprenavir: **Substrate** of CYP2C9 (minor), 3A4 (major); **Inhibits** CYP2C19 (weak), 3A4 (strong)

Drug Interactions

Abacavir: Protease Inhibitors may decrease the serum concentration of Abacavir. *Risk C: Monitor therapy*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amiodarone: Protease Inhibitors may decrease the metabolism of Amiodarone. *Risk X: Avoid combination*

Antacids: May decrease the absorption of Protease Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Protease Inhibitors may decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Dihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Protease Inhibitors. Protease Inhibitors may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cisapride: Protease Inhibitors may decrease the metabolism of Cisapride. The resultant increase in serum cisapride concentrations may result in QTc prolongation and malignant cardiac arrhythmias. *Risk X: Avoid combination*

Clarithromycin: Protease Inhibitors may diminish the therapeutic effect of Clarithromycin. Specifically, certain protease inhibitors may decrease formation of the active 14-hydroxy-clarithromycin metabolite, which may negatively impact clarithromycin effectiveness vs. H. influenzae and other non-MAC infections. Protease Inhibitors may increase the serum concentration of Clarithromycin. Clarithromycin dose adjustment in renally impaired patients may be needed. Clarithromycin may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): Protease Inhibitors may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk D: Consider therapy modification*

CycloSPORINE: Protease Inhibitors may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Delavirdine: Fosamprenavir may decrease the serum concentration of Delavirdine. The active metabolite amprenavir is likely responsible for this effect. Delavirdine may increase the serum concentration of Fosamprenavir. Specifically, delavirdine may increase concentrations of the active metabolite amprenavir. *Risk X: Avoid combination*

Digoxin: Protease Inhibitors may increase the serum concentration of Digoxin. Increased serum concentrations of digoxin may increase risk of AV nodal blockade. *Risk C: Monitor therapy*

Efavirenz: May increase the metabolism of Protease Inhibitors. This specifically includes amprenavir, indinavir, and saquinavir. Efavirenz may increase the serum concentration of Protease Inhibitors. This specifically includes nelfinavir and ritonavir. *Risk D: Consider therapy modification*

Enfuvirtide: Protease Inhibitors may increase the serum concentration of Enfuvirtide. Enfuvirtide may increase the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

Eplerenone: Protease Inhibitors may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Protease Inhibitors may decrease the metabolism of Ergot Derivatives. **Exceptions:** Cabergoline. *Risk X: Avoid combination*

Etravirine: May increase the serum concentration of Fosamprenavir. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

FentaNYL: Protease Inhibitors may decrease the metabolism of FentaNYL. *Risk C: Monitor therapy*

Fusidic Acid: Protease Inhibitors may decrease the metabolism of Fusidic Acid. Fusidic Acid may decrease the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Garlic: May decrease the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

H2-Antagonists: May decrease the serum concentration of Fosamprenavir. Cimetidine may also inhibit the metabolism of the active metabolite amprenavir, making its effects on fosamprenavir/amprenavir concentrations difficult to predict. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Protease Inhibitors may increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. **Exceptions:** Fluvastatin. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Meperidine: Protease Inhibitors may enhance the adverse/toxic effect of Meperidine. Protease Inhibitors may decrease the serum concentration of Meperidine. Concentrations of the toxic Normeperidine metabolite may be increased. *Risk D: Consider therapy modification*

Methadone: Protease Inhibitors may decrease the metabolism of Methadone. *Risk C: Monitor therapy*

Nefazodone: Protease Inhibitors may decrease the metabolism of Nefazodone. *Risk C: Monitor therapy*

Nevirapine: May increase the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): May diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

PARoxetine: Fosamprenavir may decrease the serum concentration of PARoxetine. The active metabolite amprenavir is likely responsible for this effect. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Fosamprenavir may decrease the serum concentration of Phenytoin. The active amprenavir metabolite is likely responsible for this effect. Phenytoin may increase the serum concentration of Fosamprenavir. Specifically, phenytoin may increase the concentration of the active metabolite amprenavir. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: Protease Inhibitors may decrease the metabolism of Phosphodiesterase 5 Inhibitors. Management: Dose restrictions for tadalafil, and/or sildenafil and vardenafil are recommended in combination with ritonavir, atazanavir, indinavir, darunavir and saquinavir. Consult specific prescribing information for detailed recommendations. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Protease Inhibitors may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Protease Inhibitors: May increase the serum concentration of other Protease Inhibitors. Management: Atazanavir--indinavir combination contraindicated. Amprenavir oral solution not recommended with ritonavir oral solution; tipranavir/ritonavir or atazanavir/ritonavir not recommended with other protease inhibitors. Other combos may require dose changes. *Risk D: Consider therapy modification*

QuiNIDine: Protease Inhibitors may decrease the metabolism of QuiNIDine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: Protease Inhibitors may decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Sirolimus: Protease Inhibitors may increase the serum concentration of Sirolimus. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Protease Inhibitors. *Risk X: Avoid combination*

Tacrolimus: Protease Inhibitors may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Temsirolimus: Protease Inhibitors may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tenofovir: May decrease the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Tenofovir. *Risk C: Monitor therapy*

TraZODone: Protease Inhibitors may increase the serum concentration of TraZODone. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Protease Inhibitors may increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Valproic Acid: Protease Inhibitors may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Zidovudine: Protease Inhibitors may decrease the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Amprenavir serum concentration may be decreased by St John's wort; concurrent use contraindicated.

Monitoring ParametersMonitor viral load, CD4 count, triglycerides, cholesterol, glucose

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions or toxicity (multiple liver enzyme interactions may increase or decrease levels/effects drugs and increase potential for severe toxicity or loss of effectiveness); dosing adjustments may be necessary. A list of medications that should not be used is available in each bottle and patients should be provided with this information. Assess therapeutic response (CD4 count, hepatic function) and adverse reactions at regular intervals during therapy (eg, gastrointestinal disturbance [nausea, vomiting, diarrhea] that can lead to dehydration and weight loss, hyperlipidemia and redistribution of body fat, rash, CNS effects [malaise, insomnia, abnormal thinking], electrolyte imbalance). Caution patients to monitor glucose levels closely; protease inhibitors may cause hyperglycemia or new-onset diabetes. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions (eg, glucose testing: protease inhibitors may cause hyperglycemia, exacerbation, or new-onset diabetes; use of nonhormonal contraceptives: protease inhibitors may decrease effectiveness of oral contraceptives), and adverse symptoms to report.

Monitoring: Lab TestsMonitor viral load, CD4 count, triglycerides, cholesterol, glucose

Patient EducationYou will be provided with a list of specific medications that should not be used during therapy; do not take any new prescription or OTC medications or herbal products during therapy - even if they are not on the list - without consulting prescriber. This is not a cure for HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. Take as directed: Adults take tablets with or without food, take suspension without food; children take suspension with food. Maintain adequate hydration (2-3 L/day of fluids unless instructed to restrict fluid intake). You may be susceptible to infection (avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber). This medication will be prescribed with a combination of other medications; time these medications as directed by prescriber. You may be advised to check your glucose levels; this drug can cause hyperglycemia. Frequent blood tests may be required with prolonged therapy. May cause body changes due to redistribution of body fat, facial atrophy, or breast enlargement (normal effects of drug); headache, dizziness, or fatigue (use caution when driving or engaged in potentially hazardous tasks until response to drug is known); nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea (buttermilk, boiled milk, or yogurt may help); back pain; or arthralgia (consult prescriber for approved analgesic). Inform prescriber immediately if you experience unusual skin rash or reaction. Report muscle numbness or tingling; unresolved persistent vomiting, diarrhea, or abdominal pain; respiratory difficulty or chest pain; change in color of stool or urine; or any persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber for appropriate contraceptives.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet, as calcium:

Lexiva®: 700 mg [equivalent to amprenavir ~600 mg)

Telzir® [CAN]: 700 mg [not available in the U.S.]

Suspension, oral, as calcium:

Lexiva®: 50 mg/mL (225 mL) [equivalent to amprenavir ~43 mg/mL; contains propylene glycol; grape-bubblegum-peppermint flavored]

Telzir® [CAN]: 50 mg/mL (225 mL) [not available in the U.S.]

Generic AvailableNo
ManufacturerGlaxoSmithKline
Pricing: U.S. (www.drugstore.com)

Tablets (Lexiva)

700 mg (30): $358.90

Mechanism of ActionFosamprenavir is rapidly and almost completely converted to amprenavir by cellular phosphatases *in vivo*. Amprenavir binds to the active site of HIV protease activity and inhibits cleavage of viral polyprotein precursors (eg, Gag and Gag-Pol) into individual functional proteins found in infectious HIV. Inhibition prevents cleavage of these polyproteins, resulting in the formation of immature, noninfectious viral particles.
Pharmacodynamics/Kinetics

Absorption: 63%

Protein-binding: >90% (to alpha$_1$-acid glycoprotein)

Metabolism: Fosamprenavir is rapidly and almost completely converted to amprenavir by cellular phosphatases in gut epithelium; amprenavir is hepatically metabolized via CYP isoenzymes (primarily CYP3A4)

Bioavailability: Not established; food does not have a significant effect on absorption of tablets. Administration of oral suspension with food reduced C_{max} by 46% and AUC by 28%.

Half-life elimination: ~7.7 hours (amprenavir)

Time to peak, plasma: 1.5-4 hours (median: 2.5 hours)

Excretion: Feces (75% as metabolites, <1% as unchanged drug); urine (14% as metabolites, <1% as unchanged drug)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusFatigue is common; may cause depression
Mental Health: Effects on Psychiatric TreatmentContraindicated in patients receiving midazolam, pimozide, and triazolam; concurrent use with other benzodiazepines may produce additive effects. Oral solution contraindicated with disulfiram. Do not use fosamprenavir with St John's wort; may lead to loss of response. Rash is common; consider in differential in patients receiving lamotrigine. GI side effects are common; concurrent use with SSRIs may produce additive GI effects. May produce hypertriglyceridemia; monitor with atypical antipsychotics. May produce neutropenia; use caution with clozapine and carbamazepine. Effects of methadone may be diminished with maintenance therapy; consider an alternative antiretroviral. Amprenavir may increase serum concentration/toxicity of sildenafil, tricyclic antidepressants, and vardenafil.
Index TermsFosamprenavir Calcium; GW433908G
References

Falcoz C, Jenkins JM, Bye C, et al, “Pharmacokinetics of GW433908, A Prodrug of Amprenavir, in Healthy Male Volunteers,” *Clin Pharmacol*, 2002, 42(8):887-98.

“Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection,” January 29, 2008. Available at http://www.aidsinfo.nih.gov

Kodoth S, Bakshi S, Scimeca P, et al, “Possible Linkage of Amprenavir With Intracranial Bleeding in an HIV-Infected Hemophiliac,” *AIDS Patient Care STDS*, 2001, 15(7):347-52.[PubMed 11483161]

“Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,” July 8, 2008. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” July 29, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesLexiva (IL); Telzer (MX); Telzir (AR, AT, AU, BE, BG, CH, CO, CR, CZ, DE, DK, DO, ES, FI, FR, GB, GR, GT, HN, IE, IT, NI, NL, NO, PA, PT, RU, SE, SV, TR, UY)

Fosaprepitant

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Fosaprepitant may be confused with aprepitant, fosamprenavir

Emend® for injection (fosaprepitant) may be confused with Emend® (aprepitant) which is an oral capsule formulation.

Pronunciation(fos a PRE pi tant)

U.S. Brand NamesEmend® for Injection

Pharmacologic CategoryAntiemetic; Substance P/Neurokinin 1 Receptor antagonist

Use: Labeled IndicationsPrevention of acute and delayed nausea and vomiting associated with moderately- and highly-emetogenic chemotherapy (in combination with other antiemetics)

Dosing: AdultsPrevention of chemotherapy-induced nausea/vomiting: I.V.: 115 mg 30 minutes prior to chemotherapy on day 1 (followed by aprepitant 80 mg orally on days 2 and 3) in combination with other antiemetics

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Mild, moderate, or severe impairment: No adjustment required.

Dialysis-dependent end-stage renal disease (ESRD): No adjustment required.

Dosing: Hepatic Impairment

Child-Pugh class A and B: No adjustment required.

Child-Pugh class C: Has not been evaluated.

Administration: I.V.Infuse over 15 minutes

StorageStore intact vials at 2°C to 8°C (36°F to 46°F). Solutions diluted for infusion are stable for 24 hours at room temperature of ≤25°C (≤77°F).

ReconstitutionReconstitute with 5 mL of sodium chloride 0.9%, directing diluent down side of vial to avoid foaming. Add reconstituted contents of vial to 110 mL sodium chloride 0.9%, resulting in a final concentration of 1 mg/mL; gently invert bag to mix.

CompatibilityStable in sodium chloride 0.9%

Incompatible with solutions containing calcium (eg, lactated Ringer's solution, Hartmann's solution) or magnesium.

ContraindicationsHypersensitivity to fosaprepitant, aprepitant, polysorbate 80, or any component of the formulation; concurrent use with pimozide or cisapride

Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; has not been studied in patients with severe hepatic impairment (Child-Pugh class C).
- Nausea/vomiting: Appropriate use: Not intended for treatment of existing nausea and vomiting or for chronic continuous therapy.

Concurrent drug therapy issues:

- High potential for interactions: Fosaprepitant is rapidly converted to aprepitant, which has a high potential for drug interactions. Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions. The effect of aprepitant on orally-administered CYP3A4 substrates is greater than those administered intravenously. Aprepitant concentrations may be elevated with concomitant use of another strong CYP3A4 inhibitor.

Geriatric ConsiderationsPrior studies with aprepitant by the manufacturer were demonstrated in a total of 544 patients, 31% were >65 years of age, while 5% were >75 years. No differences in safety and efficacy were noted between elderly subjects and younger adults. No dosing adjustment is necessary.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women; use only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsAdverse reactions reported with aprepitant and fosaprepitant (as part of a combination chemotherapy regimen) occurring at a higher frequency than standard therapy:

>10%:

Central nervous system: Fatigue (≤18%)

Gastrointestinal: Nausea (≤13%)

Neuromuscular & skeletal: Weakness (≤18%)

Miscellaneous: Hiccups (11%)

1% to 10%:

Central nervous system: Dizziness (≤7%), headache (≤3%)

Endocrine & metabolic: Dehydration (6%), hot flushing (3%)

Gastrointestinal: Diarrhea (≤10%), dyspepsia (≤8%), abdominal pain (5%), stomatitis (≤5%), epigastric discomfort (4%), gastritis (4%), throat pain (≤3%)

Hematologic: Neutropenia (≤9%)

Hepatic: ALT increased (≤6%), AST increased (≤3%)

Local: Injection site pain (8%), injection site induration (2%)

Renal: BUN increased (≤5%), proteinuria (≤7%)

>0.5%: Acid reflux, acne, alkaline phosphatase increased, anemia, anxiety, appetite decreased, arthralgia, back pain, candidiasis, confusion, conjunctivitis, cough, depression, diabetes mellitus, diaphoresis, DVT, dysphagia, dyspnea, dysuria, edema, eructation, erythrocyturia, flatulence, herpes simplex, hyper-/hypotension, hypokalemia, hyponatremia, leukocytes increased, leukocyturia, malaise, MI, muscle weakness, musculoskeletal pain, myalgia, nasal secretion, obstipation, palpitation, pelvic pain, peripheral neuropathy, pharyngitis, pneumonitis, pulmonary embolism, rash, renal insufficiency, respiratory infection, respiratory insufficiency, rigors, salivation increased, sensory neuropathy, septic shock, swallowing disorder, tachycardia, taste disturbance, tremor, urinary tract infection, vocal disturbance, weight loss, xerostomia

Postmarketing and/or case reports (with fosaprepitant or aprepitant): Albumin decreased, angioedema, bilirubin increased, bradycardia, disorientation, duodenal ulcer (perforating), dysarthria, enterocolitis, fever, glycosuria, hematoma, hyperglycemia, hypoesthesia, hypothermia, hypovolemia, hypoxia, miosis, neutropenic sepsis, pneumonia, pruritus, sensory disturbance, sinus tachycardia, Stevens-Johnson syndrome, subileus, syncope, urticaria, visual acuity decreased, wheezing

Metabolism/Transport Effects **Substrate** of CYP1A2 (minor), 2C19 (minor), 3A4 (major); **Inhibits** CYP2C9 (weak), 2C19 (weak), 3A4 (moderate); **Induces** CYP2C9 (weak), 3A4 (weak)

Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Fosaprepitant. Specifically, concentrations of aprepitant are likely to be increased. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Fosaprepitant may increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Cisapride: Fosaprepitant may increase the serum concentration of Cisapride. The active metabolite aprepitant is likely responsible for this effect. *Risk X: Avoid combination*

Contraceptive (Progestins): Fosaprepitant may decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Fosaprepitant may increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diltiazem: Fosaprepitant may increase the serum concentration of Diltiazem. The active metabolite aprepitant is likely responsible for this effect. Diltiazem may increase the serum concentration of Fosaprepitant. Specifically, diltiazem may increase the concentration of the active metabolite aprepitant. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Fosaprepitant may decrease the serum concentration of Oral Contraceptive (Estrogens). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Fosaprepitant may increase the serum concentration of Pimozide. The active metabolite aprepitant is likely responsible for this effect. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Rifampin: May decrease the serum concentration of Fosaprepitant. More specifically, rifampin may decrease concentrations of the active metabolite aprepitant. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Warfarin: Fosaprepitant may decrease the serum concentration of Warfarin. The active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Aprepitant serum concentration may be increased when taken with grapefruit juice; avoid concurrent use.

Herb/Nutraceutical: Avoid St John's wort (may decrease aprepitant levels).

Nursing: Physical Assessment/MonitoringSee Aprepitant for Assessment/Monitoring and Patient Education. I.V.: See Administration specifics.

Patient EducationSee Aprepitant for Assessment/Monitoring and Patient Education.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Emend® for Injection: 115 mg [contains edetate disodium; lactose; polysorbate 80]

Generic AvailableNo

ManufacturerMerck and Co, Inc

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Emend)

115 mg (1): $195.98

Mechanism of ActionFosaprepitant is a prodrug of aprepitant, which prevents acute and delayed vomiting by inhibiting the substance P/neurokinin 1 (NK1) receptor; augments the antiemetic activity of the 5-HT$_3$ receptor antagonist and corticosteroid activity and inhibits chemotherapy-induced emesis.

Pharmacodynamics/Kinetics

Distribution: Fosaprepitant: ~5 L; Aprepitant: V$_d$: ~70 L; crosses the blood brain barrier

Protein binding: Aprepitant: >95%

Metabolism:

Fosaprepitant: Hepatic and extrahepatic; rapidly converted to aprepitant (nearly complete conversion)

Aprepitant: Hepatic via CYP3A4 (major); CYP1A2 and CYP2C19 (minor); forms 7 weakly-active metabolites

Bioavailability: Fosaprepitant 115 mg I.V. is bioequivalent to aprepitant 125 mg orally.

Half-life elimination: Half-life elimination: Fosaprepitant: ~2 minutes; Aprepitant: ~9-13 hours

Time to peak, plasma: Fosaprepitant is converted to aprepitant within 30 minutes after the end of infusion

Excretion: Urine (57%); feces (45%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, taste disturbances, xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusFatigue is common; may cause dizziness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with pimozide is contraindicated; avoid combination. GI side effects are common; concurrent use with SSRIs, carbamazepine, lithium, and valproic acid may produce additive effects. May produce neutropenia; use caution with clozapine and carbamazepine. A potential for numerous drug-drug interactions exists. Aprepitant may increase the serum concentration of benzodiazepines including alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, midazolam, quazepam, and triazolam (metabolized by oxidation). CYP3A4 inducers (eg, carbamazepine, phenobarbital, and phenytoin) may decrease levels/effects of aprepitant. CYP3A4 inhibitors (eg, nefazodone and verapamil) may increase levels/effects of aprepitant. Aprepitant may increase the levels/effects of CYP3A4 substrates (eg, benzodiazepines, calcium channel blockers, ergot derivatives, mirtazapine, nefazodone, and venlafaxine. Avoid St John's wort (may decrease aprepitant levels).

Index Terms Aprepitant Injection; Fosaprepitant Dimeglumine; L-758,298; MK 0517

References

Cocquyt V, Van Belle S, Reinhardt RR, et al, “Comparison of L-758,298, a Prodrug for the Selective Neurokinin-1 Antagonist, L-754,030, With Ondansetron for the Prevention of Cisplatin-Induced Emesis,” *Eur J Cancer*, 2001, 37(7):835-42.[PubMed 11313170]

Lasseter KC, Gambelle J, Jin B, et al, “Tolerability of Fosaprepitant and Bioequivalency to Aprepitant in Healthy Subjects,” *J Clin Pharmacol*, 2007,47(7):834-40.[PubMed 117525168]

Van Belle S, Lichinitser SR, Navari RM, et al,” Prevention of Cisplatin-Induced Acute and Delayed Emesis by the Selective Neurokinin-1 Antagonists, L-758,298 and MK-869,” *Cancer*, 2002, 94(11):3032-41.[PubMed 12115394]

Foscarnet

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(fos KAR net)

U.S. Brand NamesFoscavir®

Canadian Brand NamesFoscavir®

Pharmacologic CategoryAntiviral Agent

Use: Labeled IndicationsTreatment of acyclovir-resistant mucocutaneous herpes simplex virus (HSV) infections in immunocompromised persons (eg, with advanced AIDS); treatment of CMV retinitis in persons with HIV

Use: Unlabeled/InvestigationalOther CMV infections (eg, colitis, esophagitis, neurological disease); CMV prophylaxis for cancer patients receiving alemtuzumab therapy or allogeneic stem cell transplant

Use: DentalTreatment of acyclovir-resistant mucocutaneous herpes simplex virus (HSV) infections in immunocompromised persons (eg, with advanced AIDS); treatment of CMV retinitis in persons with HIV

Dosing: Adults

CMV retinitis: I.V.:

Induction treatment: 60 mg/kg/dose every 8 hours for 14-21 days **or** 90 mg/kg every 12 hours for 14-21 days

Maintenance therapy: 90-120 mg/kg/day as a single daily infusion

Acyclovir-resistant HSV induction treatment: I.V.: 40 mg/kg/dose every 8-12 hours for 14-21 days

Therapy of CMV infection in cancer patients (unlabeled use): I.V.:

Prophylaxis: 60 mg/kg every 8-12 hours for 7 days, followed by 90-120 mg/kg daily until day 100 after HSCT

Pre-emptive treatment: 60 mg/kg every 12 hours for 14 days; if CMV still detectable, continue with 90 mg/kg daily for 5 days/week for 2 additional weeks

Treatment: 90 mg/kg every 12 hours for 2 weeks, followed by 120 mg/kg daily for ≥2 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAdolescents: Refer to adult dosing.

Dosing: Renal ImpairmentSee tables.

Induction Dosing of Foscarnet in Patients With Abnormal Renal Function

Cl_{cr} (mL/min/kg)	**HSV**	**HSV**	**CMV**	**CMV**
	Equivalent to 40 mg/kg q12h	**Equivalent to 40 mg/kg q8h**	**Equivalent to 60 mg/kg q8h**	**Equivalent to 90 mg/kg q12h**
<0.4	Not recommended	Not recommended	Not recommended	Not recommended
≥0.4-0.5	20 mg/kg every 24 hours	35 mg/kg every 24 hours	50 mg/kg every 24 hours	50 mg/kg every 24 hours
>0.5-0.6	25 mg/kg every 24 hours	40 mg/kg every 24 hours	60 mg/kg every 24 hours	60 mg/kg every 24 hours
>0.6-0.8	35 mg/kg every 24 hours	25 mg/kg every 12 hours	40 mg/kg every 12 hours	80 mg/kg every 24 hours
>0.8-1.0	20 mg/kg every 12 hours	35 mg/kg every 12 hours	50 mg/kg every 12 hours	50 mg/kg every 12 hours
>1.0-1.4	30 mg/kg every 12 hours	30 mg/kg every 8 hours	45 mg/kg every 8 hours	70 mg/kg every 12 hours
	40 mg/kg every 12	40 mg/kg every 8	60 mg/kg every 8	90 mg/kg every 12

>1.4	hours	hours	hours	hours

Maintenance Dosing of Foscarnet in Patients With Abnormal Renal Function

Cl_{cr} (mL/min/kg)	**CMV**	**CMV**
	Equivalent to 90 mg/kg q24h	**Equivalent to 120 mg/kg q24h**
<0.4	Not recommended	Not recommended
≥0.4-0.5	50 mg/kg every 48 hours	65 mg/kg every 48 hours
>0.5-0.6	60 mg/kg every 48 hours	80 mg/kg every 48 hours
>0.6-0.8	80 mg/kg every 48 hours	105 mg/kg every 48 hours
>0.8-1.0	50 mg/kg every 24 hours	65 mg/kg every 24 hours
>1.0-1.4	70 mg/kg every 24 hours	90 mg/kg every 24 hours
>1.4	90 mg/kg every 24 hours	120 mg/kg every 24 hours

Hemodialysis:

Foscarnet is highly removed by hemodialysis (up to ~38% in 2.5 hours HD with high-flux membrane)

Doses of 50 mg/kg/dose posthemodialysis have been found to produce similar serum concentrations as doses of 90 mg/kg twice daily in patients with normal renal function

Doses of 60-90 mg/kg/dose loading dose (posthemodialysis) followed by 45-60 mg/kg/dose posthemodialysis (3 times/week) with the monitoring of weekly plasma concentrations to maintain peak plasma concentrations in the range of 400-800 µMolar have been recommended by some clinicians

Continuous arteriovenous or venovenous hemodiafiltration effects: Dose as for Cl_{cr} 10-50 mL/minute

Administration: I.V.Use an infusion pump, at a rate not exceeding 1 mg/kg/minute. Adult induction doses of 60 mg/kg are administered over 1 hour. Adult maintenance doses of 90-120 mg/kg are infused over 2 hours. The manufacturer recommends 750-1000 mL of NS or D_5W be administered prior to first infusion to establish diuresis. With subsequent infusions of 90-120 mg/kg, this volume would be repeated. If the dose were 40-60 mg/kg, then the volume could be reduced to 500 mL. After the first dose, the hydration fluid should be administered concurrently with foscarnet.

Administration: I.V. DetailUndiluted (24 mg/mL) solution can be administered without further dilution when using a central venous catheter for infusion. For peripheral vein administration, the solution **must** be diluted to a final concentration **not to exceed** 12 mg/mL. The recommended dosage, frequency, and rate of infusion should not be exceeded.

pH: 7.4 (adjusted)

StorageFoscarnet injection is a clear, colorless solution. Store intact bottles at room temperature of 15°C to 30°C (59°F to 86°F) and protect from temperatures >40°C and from freezing. Diluted solution is stable for 24 hours at room temperature or under refrigeration.

ReconstitutionFoscarnet should be diluted in D_5W or NS. For peripheral line administration, foscarnet **must** be diluted to ≤12 mg/mL with D_5W or NS. For central line administration, foscarnet may be administered undiluted.

CompatibilityStable in D_5W, NS; **incompatible** with dextrose 30%, LR, TPN, and I.V. solutions containing calcium, magnesium, vancomycin.

Y-site administration: Compatible: Aldesleukin, amikacin, aminophylline, ampicillin, aztreonam, cefazolin, cefoperazone, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, chloramphenicol, cimetidine, clindamycin, dexamethasone sodium phosphate, dopamine, erythromycin lactobionate, fluconazole, flucytosine, furosemide, gentamicin, heparin, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, imipenem/cilastatin, metoclopramide, metronidazole, morphine, nafcillin, oxacillin, penicillin G potassium, phenytoin, piperacillin, ranitidine, ticarcillin/clavulanate, tobramycin. **Incompatible:** Acyclovir, amphotericin B, diazepam, digoxin, diphenhydramine, dobutamine, droperidol, ganciclovir, haloperidol, leucovorin, midazolam, pentamidine, prochlorperazine edisylate, promethazine. **Variable (consult detailed reference):** Co-trimoxazole, lorazepam, vancomycin.

Compatibility when admixed: Compatible: Potassium chloride.

ContraindicationsHypersensitivity to foscarnet or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Approved indications: See “Other warnings/precautions” below.
- Renal impairment: See “Concerns related to adverse effects” below.

- Seizures: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Dental effects: Foscarnet is deposited in teeth and bone of young, growing animals; it has adversely affected tooth enamel development in rats.

- Electrolyte imbalance: Imbalance of serum electrolytes or minerals occurs in at least 15% of patients (hypocalcemia, low ionized calcium, hyper/hypophosphatemia, hypomagnesemia, or hypokalemia); reducing infusion rate may decrease/prevent symptoms. Patients with low ionized calcium may experience perioral tingling, numbness, paresthesias, tetany, and seizures. Correct electrolytes before initiating therapy; use caution in patients who have any underlying electrolyte imbalances, those with neurologic or cardiac abnormalities, and those receiving medications that are influenced by calcium levels. Use caution when administering other medications that cause electrolyte imbalances. Patients who experience signs or symptoms of an electrolyte imbalance should be assessed immediately.

- Hematologic effects: May cause anemia and granulocytopenia.

- Renal impairment: **[U.S. Boxed Warning]: Renal impairment occurs to some degree in the majority of patients treated with foscarnet;** renal impairment may occur at any time (though typically during second week of induction therapy) and is usually reversible within 1 week following dose adjustment or discontinuation of therapy, however, several patients have died with renal failure within 4 weeks of stopping foscarnet; therefore, renal function should be closely monitored during both induction and maintenance therapy. To reduce the risk of nephrotoxicity and the potential to administer a relative overdose, always calculate the Cl_{cr} even if serum creatinine is within the normal range. Dosage adjustments are recommended for renal dysfunction; safety and efficacy in patients with a baseline S_{cr} >2.8 mg/dL or Cl_{cr} <50 mL/minute are limited. Use in patients with Cl_{cr} <0.4 mL/kg/minute is not recommended. Adequate hydration may reduce the risk of nephrotoxicity; the manufacturer makes specific recommendations regarding this (see Administration).

- Seizures: **[U.S. Boxed Warning]: Seizures related to plasma electrolyte/mineral imbalance may occur;** incidence has been reported in up to 10% of HIV patients. Risk factors for seizures include impaired baseline renal function, low total serum calcium, and underlying CNS condition. Some patients who have experienced seizures have been able to continue or resume foscarnet treatment after their mineral or electrolyte abnormality has been corrected, their underlying disease state treated, or their dose decreased.

- Vascular irritant: Administer only into vein with adequate blood flow to prevent tissue irritation/ulceration. Genital vascular tissue damage has been reported; adequate hydration recommended.

Other warnings/precautions:

- Approved indications: **[U.S. Boxed Warning]: Indicated only for immunocompromised patients with CMV retinitis and mucocutaneous acyclovir-resistant HSV infection.**

Geriatric ConsiderationsInformation on the use of foscarnet is lacking in the elderly. Dose adjustments and proper monitoring must be performed because of the decreased renal function common in older patients.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAssociated with an increase in skeletal anomalies in animal studies at approximately the equivalent of 13% to 33% of the maximal daily human dose. There are no adequate and well controlled studies in pregnant women. A single case report of use during the third trimester with normal infant outcome was observed. Monitoring of amniotic fluid volumes by ultrasound is recommended weekly after 20 weeks of gestation to detect oligohydramnios.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsThe CDC recommends **not** to breast-feed if diagnosed with HIV to avoid postnatal transmission of the virus.

Adverse Reactions

>10%:

Central nervous system: Fever (65%), headache (26%)

Endocrine & metabolic: Hypokalemia (16% to 48%), hypocalcemia (15% to 30%), hypomagnesemia (15% to 30%), hypophosphatemia (8% to 26%)

Gastrointestinal: Nausea (47%), diarrhea (30%), vomiting (26%)

Hematologic: Anemia (33%), granulocytopenia (17%)

Renal: Abnormal renal function/decreased creatinine clearance (12%; without adequate hydration 33%)

1% to 10%:

Cardiovascular: Chest pain (1% to 5%), edema (1% to 5%), facial edema (1% to 5%), flushing (1% to 5%), hyper-/hypotension (1% to 5%), palpitation (1% to 5%), ECG changes (1% to 5%)

Central nervous system: Seizure (includes grand mal; 8%), anxiety (≥5%), confusion (≥5%), depression (≥5%), dizziness (≥5%), fatigue (≥5%), hypoesthesia (≥5%), malaise (≥5%), pain (≥5%), aggressiveness (1% to 5%), agitation (1% to 5%), amnesia (1% to 5%), aphasia (1% to 5%), ataxia (1% to 5%), coordination abnormal (1% to 5%), dementia (1% to 5%), EEG abnormal (1% to 5%), hallucination (1% to 5%), insomnia (1% to 5%), meningitis (1% to 5%), nervousness (1% to 5%), somnolence (1% to 5%), stupor (1% to 5%)

Dermatologic: Rash (≥5%), erythematous rash (1% to 5%), maculopapular rash (1% to 5%), pruritus (1% to 5%), seborrhea (1% to 5%), skin discoloration (1% to 5%), skin ulceration (1% to 5%)

Endocrine & metabolic: Hyperphosphatemia (6%), acidosis (1% to 5%), hyponatremia (1% to 5%)

Gastrointestinal: Abdominal pain (≥5%), anorexia (≥5%), constipation (1% to 5%), dyspepsia (1% to 5%), dysphasia (1% to 5%), flatulence (1% to 5%), melena (1% to 5%), pancreatitis (1% to 5%), rectal hemorrhage (1% to 5%), taste perversion (1% to 5%), ulcerative stomatitis (1% to 5%), weight loss (1% to 5%), xerostomia (1% to 5%)

Genitourinary: Dysuria (1% to 5%), nocturia (1% to 5%), urinary retention (1% to 5%)

Hematologic: Leukopenia (≥5%), lymphadenopathy (1% to 5%), thrombocytopenia (1% to 5%), thrombosis (1% to 5%)

Hepatic: Alkaline phosphatase increased (1% to 5%), ALT increased (1% to 5%), AST increased (1% to 5%), hepatic function abnormal (1% to 5%), LDH increased (1% to 5%)

Local: Injection site pain/inflammation (1% to 5%)

Neuromuscular & skeletal: Paresthesia (≥5%), involuntary muscle contractions (≥5%), rigors (≥5%), neuropathy (peripheral; ≥5%), weakness (≥5%), arthralgia (1% to 5%), back pain (1% to 5%), leg cramps (1% to 5%), myalgia (1% to 5%), tremor (1% to 5%)

Ocular: Vision abnormalities (≥5%), conjunctivitis (1% to 5%), eye pain (1% to 5%)

Renal: Acute renal failure (1% to 5%), albuminuria (1% to 5%), BUN increased (1% to 5%), polyuria (1% to 5%), urinary tract infection (1% to 5%)

Respiratory: Cough (≥5%), dyspnea (≥5%), bronchospasm (1% to 5%), hemoptysis (1% to 5%), pharyngitis (1% to 5%), pneumonia (1% to 5%), pneumothorax (1% to 5%), rhinitis (1% to 5%), sinusitis (1% to 5%), stridor (1% to 5%)

Miscellaneous: Diaphoresis (≥5%), sepsis (≥5%), infection (includes bacterial and fungal; ≥5%), flu-like syndrome (1% to 5%), malignancies (lymphoma/sarcoma 1% to 5%), thirst (1% to 5%)

<1%, postmarketing, and/or case reports: Amylase increased, cardiac arrest, coma, creatinine phosphokinase increased, dehydration, diabetes insipidus (usually nephrogenic), erythema multiforme, GGT increased muscle weakness, hematuria, hypoproteinemia, myopathy, myositis, neutropenia, pancytopenia, QT_c prolongation, renal calculus, rhabdomyolysis, Stevens-Johnson syndrome, syndrome of inappropriate antidiuretic hormone (SIADH), toxic epidermal necrolysis, ventricular arrhythmia, vesiculobullous eruptions

Oncology: VesicantNo
Oncology: Emetic PotentialModerate (30% to 60%)
Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Monitoring Parameters24-hour creatinine clearance at baseline and periodically thereafter. During induction therapy: Obtain complete blood counts, and electrolytes (including serum creatinine, calcium, magnesium, potassium and phosphorus) twice weekly and then one weekly during maintenance therapy. More frequent monitoring may be required in some patients. Check hydration status before and after infusion.
Nursing: Physical Assessment/MonitoringEvaluate electrolytes, renal status, and dental status prior to beginning therapy. Assess potential for interactions with other pharmacological agents patient may be taking (eg, increased risk of seizures, renal failure, electrolyte imbalance). See Administration for infusion specifics. Assess results of laboratory tests (electrolytes) and renal function, therapeutic effectiveness (resolution of viral infection), and adverse response (eg, nephrotoxicity, electrolyte imbalance, seizures). Teach patient possible side effects/appropriate interventions (eg, need for regular dental evaluations) and adverse symptoms to report.
Monitoring: Lab TestsRenal function, CBC, electrolytes, calcium, magnesium
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Foscarnet is not a cure for the disease; progression may occur during or following therapy. While on therapy, it is important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition (small, frequent meals may help). Regular dental check-ups are recommended. May cause dizziness or confusion (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea and vomiting (small, frequent meals, frequent mouth care, chewing gum or sucking lozenges may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report any change in sensorium or seizures; unresolved diarrhea or vomiting; unusual fever, chills, sore throat, unhealed sores, swollen lymph glands; or malaise. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Barrier contraceptives are recommended to reduce transmission of disease. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sodium [preservative-free]: 24 mg/mL (250 mL, 500 mL)

Foscavir®: 24 mg/mL (500 mL)

Generic AvailableYes
ManufacturerAstraZeneca Pharmaceuticals LP
Mechanism of ActionPyrophosphate analogue which acts as a noncompetitive inhibitor of many viral RNA and DNA polymerases as well as HIV reverse transcriptase. Similar to ganciclovir, foscarnet is a virostatic agent. Foscarnet does not require activation by thymidine kinase.

Pharmacodynamics/Kinetics

Distribution: V_d: ~0.5 L/kg; up to 28% of cumulative I.V. dose may be deposited in bone

Protein binding: 14% to 17%

Metabolism: Biotransformation does not occur

Half-life elimination: Elimination: ~3-4 hours; terminal: ~88 hours (due to bone deposition)

Excretion: Urine (≤28% as unchanged drug)

Pharmacotherapy PearlsCMV retinitis maintenance treatment may be discontinued if immune reconstitution occurs as a result of ART.

Dental Health Professional Considerations Foscarnet is known to prolong the QT interval. The QT interval is measured as the time and distance between the Q point of the QRS complex and the end of the T wave in the ECG tracing. After adjustment for heart rate, the QT interval is defined as prolonged if it is more than 450 msec in men and 460 msec in women. A long QT syndrome was first described in the 1950s and 60s as a congenital syndrome involving QT interval prolongation and syncope and sudden death. Some of the congenital long QT syndromes were characterized by a peculiar electrocardiographic appearance of the QRS complex involving a premature atria beat followed by a pause, then a subsequent sinus beat showing marked QT prolongation and deformity. This type of cardiac arrhythmia was originally termed “torsade de pointes” (translated from the French as “twisting of the points”).

Prolongation of the QT interval is thought to result from delayed ventricular repolarization. The repolarization process within the myocardial cell is due to the efflux of intracellular potassium. The channels associated with this current can be blocked by many drugs and predispose the electrical propagation cycle to torsade de pointes.

Foscarnet is considered as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. It is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), taste perversion, and ulcerative stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Foscarnet is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution. See Dental Comment.

Mental Health: Effects on Mental Status Dizziness, anxiety, confusion, and depression are common; may rarely produce abnormal crying

Mental Health: Effects on Psychiatric Treatment Leukopenia is common; use caution with clozapine and carbamazepine

Index TermsPFA; Phosphonoformate; Phosphonoformic Acid

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International Brand NamesFoscarnet Elea (AR); Foscarnet Filaxis (AR); Foscarnet Richmond (AR); Foscavir (AR, AT, AU, BE, BR, CH, CZ, DE, ES, FI, FR, GB, GR, HN, HU, IL, IT, JP, LU, NL, NO, PT, SE); Terap (AR); Triapten (DE, PL)

Fosfomycin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Monurol® may be confused with Monopril®

Pronunciation(fos foe MYE sin)

U.S. Brand NamesMonurol®

Canadian Brand NamesMonurol®

Pharmacologic CategoryAntibiotic, Miscellaneous

Use: Labeled IndicationsSingle oral dose in the treatment of uncomplicated urinary tract infections in women due to susceptible strains of *E. coli* and *Enterococcus faecalis*

Use: Unlabeled/InvestigationalMultiple doses have been investigated for complicated urinary tract infections in men

Dosing: Adults

Urinary tract infections, uncomplicated: Oral: Females: Single dose of 3 g in 3-4 oz (90-120 mL) of water

Complicated UTI (unlabeled): Males: Oral: 3 g every 2-3 days for 3 doses

Prostatitis (unlabeled): Males: Oral: 3 g every 3 days for a total of 21 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic ImpairmentNo dosage decrease needed.

Administration: OralAlways mix with cool water before ingesting; do not administer in its dry form. Pour contents of envelope into 3-4 oz (90-120 mL) of water (not hot), stir to dissolve, and take immediately.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to fosfomycin or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children ≤12 years of age.

Pregnancy Risk FactorB

Pregnancy ConsiderationsFollowing I.M. administration to animals at doses 9 times the human dose, fosfomycin crossed the placental barrier, but did not produce teratogenic effects. Some fetotoxicities were observed in rabbits; however, these toxicities were considered to be due to the changes in intestinal microflora. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

1% to 10%:

Central nervous system: Headache (4% to 10%), pain (2%), dizziness (1% to 2%)

Dermatologic: Rash (1%)

Endocrine and metabolic: Dysmenorrhea (3%)

Gastrointestinal: Diarrhea (9% to 10%), nausea (4% to 5%), abdominal pain (2%), dyspepsia (1% to 2%)

Genitourinary: Vaginitis (6% to 8%)

Neuromuscular & skeletal: Back pain (3%), weakness (1% to 2%)

Respiratory: Rhinitis (5%), pharyngitis (3%)

<1%: Anorexia, constipation, drowsiness, dysuria, ear disorder, fatigue, fever, flatulence, flu-like syndrome, hematuria, insomnia, lymphadenopathy, menstrual disorder, migraine, myalgia, nervousness, paresthesia, pruritus, SGPT increased, skin disorder, somnolence, stools abnormal, vomiting, xerostomia

Postmarketing and/or case reports: Anaphylaxis, angioedema, aplastic anemia, asthma (exacerbation), cholestatic jaundice, hearing loss, hepatic necrosis, optic neuritis, toxic megacolon

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Monitoring ParametersSigns and symptoms of urinary tract infection; urine culture plus sensitivity

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for solution:

Monurol®: 3 g/sachet (3s) [orange flavor]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Pack (Monurol)

3 g (1): $44.99

Mechanism of ActionAs a phosphoric acid derivative, fosfomycin inhibits bacterial wall synthesis (bactericidal) by inactivating the enzyme, pyruvyl transferase, which is critical in the synthesis of cell walls by bacteria

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: V_d: 90-180 L; high concentrations in urine; well into other tissues; crosses maximally into CSF with inflamed meninges

Protein binding: None

Bioavailability: Fasting: 37%; With food: 30%

Half-life elimination: 4-8 hours; Cl_{cr} <54 mL/minute: 50 hours

Time to peak, serum: 2 hours; within 4 hours with high-fat meal

Excretion: Urine (38% as unchanged drug); high urinary levels (100 mcg/mL) persist for >48 hours; feces (18% as unchanged drug)

Related Information

- Antimicrobial Drugs of Choice

Pharmacotherapy Pearls

May have an advantage over other agents since it maintains high concentration in the urine for up to 48 hours.

Many gram-positive and gram-negative organisms, such as staphylococci, pneumococci, *E. coli*, *Salmonella*, *Shigella*, *H. influenzae*, *Neisseria* spp, and some strains of *P. aeruginosa*, indole-negative *Proteus*, and *Providencia*, are inhibited. *B. fragilis* and anaerobic gram-negative cocci are resistant.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFosfomycin Tromethamine

References

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Shrestha N, Amuh D, Goldman MP, et al, “Treatment of a Complicated Vancomycin-Resistant Enterococcal Urinary Tract Infection With Fosfomycin,” *Infectious Diseases in Clinical Practice*, 2000, 9:368-71.

International Brand NamesFosfocina (EC); Fosfurol (PY, UY); Fosmicin-S (JP); Fosmidex (ID); Fu An Xin (CL); Monural (HU); Monuril (BR, CH, CO, DE, FR, ID, IE, LU, PT); Monurol (AR, AT, BE, CN, ES, FI, GR, HK, HN, IL, IT, MX, MY, NL, PE, PH, PK, SE, TH, TW); Uridoz (FR); Veramina (AR); Veramina[inj.] (AR)

Fosinopril and Hydrochlorothiazide

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Monopril® may be confused with Accupril®, minoxidil, moexipril, Monoket®, Monurol™, ramipril

Pronunciation(foe SIN oh pril & hye droe klor oh THYE a zide)

U.S. Brand NamesMonopril-HCT®

Canadian Brand NamesMonopril-HCT®

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension; not indicated for first-line treatment

Dosing: AdultsHypertension: Oral: Fosinopril 10-80 mg per day, hydrochlorothiazide 12.5-50 mg per day

Note: A patient whose blood pressure is not adequately controlled with fosinopril or hydrochlorothiazide monotherapy may be switched to combination therapy.

Dosing: ElderlyNo dosage adjustment needed

Dosing: PediatricSafety and efficacy have not been established in pediatric patients

Dosing: Renal Impairment

Cl_{cr} ≥30 mL/minute: No dosage adjustment needed

Cl_{cr} <30 mL/minute or serum creatinine ≥3 mg/dL: Use is not recommended

Dosing: Hepatic ImpairmentUse caution in patients with impaired hepatic function from progressive liver disease. Metabolism of fosinopril to its active metabolite, fosinoprilat, will be reduced as will clearance of fosinoprilat.

Calculations

- Creatinine Clearance: Adults

StorageStore at 15°C to 30°C (59°F to 86°F). Protect from moisture.

ContraindicationsHypersensitivity to fosinopril, any other ACE inhibitor, hydrochlorothiazide, sulfonamide-derived drugs, or any component of the formulation; anuria

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See "Special populations" below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose), angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema or previous angioedema associated with ACE inhibitor therapy may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Electrolyte disturbances: Hyperkalemia may occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE Inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use enalapril with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity. Hydrochlorothiazide can cause systemic lupus erythematosus (SLE) exacerbation or activation.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use fosinopril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use ACE inhibitors with caution in pre-existing renal insufficiency; not recommended for use in patients with Cl_{cr} <30 mL/minute or serum creatinine ≥3 mg/dL. Avoid rapid dosage escalation which may lead to further renal impairment. Contraindicated in anuric patients.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimester)

Pregnancy Considerations **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.** See individual agents.

LactationEnters breast milk/contraindicated

Adverse Reactions

2% to 10%:

Central nervous system: Headache (7%, less than placebo), fatigue (4%), dizziness (3%), orthostatic hypotension (2%)

Neuromuscular & skeletal: Musculoskeletal pain (2%)

Respiratory: Cough (6%), upper respiratory infection (2%, less than placebo)

<2%: Abdominal pain, angioedema, breast mass, BUN elevation (similar to placebo), chest pain, creatinine elevation (similar to placebo), depression, diarrhea, dyspepsia, dysuria, edema, eosinophilia, esophagitis, fever, flushing, gastritis, gout, heartburn, hepatic necrosis, leukopenia, libido change, liver function test elevations (transaminases, LDH, alkaline phosphatase, serum bilirubin), muscle cramps, myalgia, nausea, neutropenia, numbness, paresthesia, pharyngitis, pruritus, rash, rhinitis, sexual dysfunction, sinus congestion, somnolence, syncope, tinnitus, urinary frequency, urinary tract infection, viral infection, vomiting, weakness

Other adverse events reported with **ACE inhibitors**: Aplastic anemia, bullous pemphigus, cardiac arrest, cholestatic jaundice, exfoliative dermatitis, hemolytic anemia, hyperkalemia, pancreatitis, pancytopenia, photosensitivity; syndrome that may include one or more of arthralgia/arthritis, vasculitis, serositis, myalgia, fever, rash or other dermopathy, positive ANA titer, leukocytosis, eosinophilia, and elevated ESR; thrombocytopenia

Other adverse events reported with **hydrochlorothiazide**: Agranulocytosis, anaphylactic reactions, anorexia, blurred vision (transient), constipation, cramping, glucosuria, hemolytic anemia, hypercalcemia, hyperglycemia, hyperuricemia, hypokalemia, jaundice (intrahepatic cholestatic), lightheadedness, muscle spasm, necrotizing angiitis, pancreatitis, photosensitivity, pneumonitis, pulmonary edema, purpura, respiratory distress, restlessness, sialadenitis, SLE, Stevens-Johnson syndrome, urticaria, vertigo, xanthopsia

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Hydrochlorothiazide peak serum levels may be decreased if taken with food.

Herb/Nutraceutical: Avoid dong quai (has estrogenic activity, may also cause photosensitization). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Test InteractionsDiscontinue prior to parathyroid function test; digoxin levels if using Digi-Tab RIA kit

Monitoring ParametersBlood pressure; BUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Monitoring: Lab TestsBUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 10/12.5: Fosinopril sodium 10 mg and hydrochlorothiazide 12.5 mg; 20/12.5: Fosinopril sodium 20 mg and hydrochlorothiazide 12.5 mg

Monopril-HCT® 10/12.5: Fosinopril sodium 10 mg and hydrochlorothiazide 12.5 mg

Monopril-HCT® 20/12.5: Fosinopril sodium 20 mg and hydrochlorothiazide 12.5 mg

Generic AvailableYes

ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)

Pricing: U.S. (www.drugstore.com)

Tablets (Fosinopril Sodium-Hydrochlorothiazide)

10-12.5 mg (60): $54.99

20-12.5 mg (60): $54.99

Tablets (Monopril HCT)

10-12.5 mg (60): $86.09

20-12.5 mg (60): $86.09

Mechanism of ActionFosinopril is a competitive inhibitor of angiotensin-converting enzyme (ACE); prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor; results in lower levels of angiotensin II which causes an increase in plasma renin activity and a reduction in aldosterone secretion; a CNS mechanism may also be involved in hypotensive effect as angiotensin II increases adrenergic outflow from CNS; vasoactive kallikreins may be decreased in conversion to active hormones by ACE inhibitors, thus reducing blood pressure. Hydrochlorothiazide inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions.

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness; may rarely cause depression

Mental Health: Effects on Psychiatric TreatmentNeutropenia and agranulocytosis may rarely occur; use caution with clozapine and carbamazepine. Thiazide diuretics may decrease the renal clearance of lithium increasing the risk for toxicity; monitor. May cause photosensitivity; concomitant use with psychotropics may further the risk. Use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight.

Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for fosinopril and hydrochlorothiazide combination therapy may include improved compliance and synergistic reductions in blood pressure with an accompanying reduction in side effects. ACE inhibitors and thiazides are also standard therapy for left ventricular systolic dysfunction.

Index Terms Hydrochlorothiazide and Fosinopril

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International Brand Names Dynacil (DE); Elidiur (IT); Fosicomp (CH); Fosinorm (DE); Fositen Plus (PT); Foziretic (FR); Monoplus (AU, BR); Monopril Plus (CO); Monozide (BG, EE, ZA)

Fosinopril

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Fosinopril may be confused with lisinopril

Monopril® may be confused with Accupril®, minoxidil, moexipril, Monoket®, Monurol™, ramipril

Pronunciation(foe SIN oh pril)

U.S. Brand NamesMonopril®

Canadian Brand NamesApo-Fosinopril®; Gen-Fosinopril; Lin-Fosinopril; Monopril®; Novo-Fosinopril; PMS-Fosinopril; RAN-Fosinopril; ratio-Fosinopril; Riva-Fosinopril

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor

Use: Labeled IndicationsTreatment of hypertension, either alone or in combination with other antihypertensive agents; treatment of heart failure (HF)

Dosing: Adults

Hypertension: Oral: Initial: 10 mg/day; increase to a maximum dose of 80 mg/day. Most patients are maintained on 20-40 mg/day. May need to divide the dose into two if trough effect is inadequate. Discontinue the diuretic, if possible 2-3 days before initiation of therapy. Resume diuretic therapy carefully, if needed.

Heart failure: Oral: Initial: 10 mg/day (5 mg if renal dysfunction present) and increase, as needed, to a maximum of 40 mg once daily over several weeks. Usual dose: 20-40 mg/day. If hypotension, orthostasis, or azotemia occurs during titration, consider decreasing concomitant diuretic dose, if any.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricHypertension: Children ≥6 years and >50 kg: Oral: Initial: 5-10 mg once daily (maximum: 40 mg/day)

Dosing: Renal ImpairmentNone needed since hepatobiliary elimination compensates adequately diminished renal elimination.

Hemodialysis: Moderately dialyzable (20% to 50%)

Dosing: Hepatic ImpairmentDecrease dose and monitor effects

Dietary ConsiderationsShould not take a potassium salt supplement without the advice of healthcare provider.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture by keeping bottle tightly closed.

ContraindicationsHypersensitivity to fosinopril, any other ACE inhibitor, or any component of the formulation; angioedema related to previous treatment with an ACE inhibitor

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose), angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE Inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsDue to frequent decreases in glomerular filtration (also creatinine clearance) with aging, elderly patients may have exaggerated responses to ACE inhibitors. Differences in clinical response due to hepatic changes are not observed. ACE inhibitors may be preferred agents in elderly patients with congestive heart failure and diabetes mellitus. Diabetic proteinuria is reduced and insulin sensitivity is enhanced. In general, the side effect profile is favorable in the elderly and causes little or no CNS confusion; use lowest dose recommendations initially. Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.

Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)

Pregnancy ConsiderationsDue to adverse events observed in some animal studies, fosinopril is considered pregnancy category C during the first trimester. Based on human data, fosinopril is considered pregnancy category D if used during the second and third trimesters (per the manufacturer; however, one study suggests that fetal injury may occur at anytime during pregnancy). First trimester exposure to ACE inhibitors may cause major congenital malformations. An increased risk of cardiovascular and/or central nervous system malformations was observed in one study; however, an increased risk of teratogenic events was not observed in other studies. Second and third trimester use of an ACE inhibitor is associated with oligohydramnios. Oligohydramnios due to decreased fetal renal function may lead to fetal limb contractures, craniofacial deformation, and hypoplastic lung development. The use of ACE inhibitors during the second and third trimesters is also associated with anuria, hypotension, renal failure (reversible or irreversible), skull hypoplasia, and death in the fetus/neonate. Chronic maternal hypertension itself is also associated with adverse events in the fetus/infant. ACE inhibitors are not recommended during pregnancy to treat maternal hypertension or heart failure. Those who are planning a pregnancy should be considered for other medication options if an ACE inhibitor is currently prescribed or the ACE inhibitor should be discontinued as soon as possible once pregnancy is detected. The exposed fetus should be monitored for fetal growth, amniotic fluid volume, and organ formation. Infants exposed to an ACE inhibitor *in utero*, especially during the second and third trimester, should be monitored for hyperkalemia, hypotension, and oliguria.

[U.S. Boxed Warning]: Based on human data, ACE inhibitors can cause injury and death to the developing fetus when used in the second and third trimesters. ACE inhibitors should be discontinued as soon as possible once pregnancy is detected.

Lactation Enters breast milk/not recommended

Breast-Feeding Considerations Fosinoprilat is excreted in breast milk. Breast-feeding is not recommended by the manufacturer.

Pregnancy & Lactation, In-Depth

- Fosinopril in Pregnancy & Lactation

Adverse Reactions **Note:** Frequency ranges include data from hypertension and heart failure trials. Higher rates of adverse reactions have generally been noted in patients with CHF. However, the frequency of adverse effects associated with placebo is also increased in this population.

>10%: Central nervous system: Dizziness (2% to 12%)

1% to 10%:

Cardiovascular: Orthostatic hypotension (1% to 2%), palpitation (1%)

Central nervous system: Dizziness (1% to 2%; up to 12% in CHF patients), headache (3%), fatigue (1% to 2%)

Endocrine & metabolic: Hyperkalemia (2.6%)

Gastrointestinal: Diarrhea (2%), nausea/vomiting (1.2% to 2.2%)

Hepatic: Transaminases increased

Neuromuscular & skeletal: Musculoskeletal pain (<1% to 3%), noncardiac chest pain (<1% to 2%), weakness (1%),

Renal: Serum creatinine increased, renal function worsening (in patients with bilateral renal artery stenosis or hypovolemia)

Respiratory: Cough (2% to 10%)

Miscellaneous: Upper respiratory infection (2%)

>1% but ≤ frequency in patients receiving placebo: Sexual dysfunction, fever, flu-like syndrome, dyspnea, rash, headache, insomnia

<1% (Limited to important or life-threatening): Abdominal distension, anaphylactoid reaction, angina, angioedema, arthralgia, behavioral change, bradycardia, bronchospasm, , cerebral infarction, cerebrovascular accident, claudication, confusion, constipation, decreased libido, drowsiness, drowsiness, dysphagia, edema, epistaxis, eye irritation, flatulence, flushing, gout, heartburn, hepatitis, hepatomegaly, hyperhidrosis, hypertension, hypertensive crisis, hypotension, insomnia, laryngitis, lower extremity edema, lymphadenopathy, memory disturbance, MI, mood change, myalgia, numbness, pancreatitis, paresthesia, pharyngitis, photosensitivity, pleuritic chest pain, pruritus, rash, renal insufficiency, shock, sinus abnormality, sleep disturbance, sudden death, syncope, tachycardia, taste disturbance, TIA, tinnitus, tracheobronchitis, tremor, urinary frequency, urticaria, vertigo, vision disturbance, weight gain, xerostomia. In a small number of patients, a symptom complex of cough, bronchospasm, and eosinophilia has been observed with fosinopril.

Other events reported with ACE inhibitors: Acute renal failure, agranulocytosis, anemia, aplastic anemia, bullous pemphigus, cardiac arrest, eosinophilic pneumonitis, exfoliative dermatitis, gynecomastia, hemolytic anemia, hepatic failure, jaundice, neutropenia, pancytopenia, Stevens-Johnson syndrome, symptomatic hyponatremia, thrombocytopenia. In addition, a syndrome which may include fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash, eosinophilia and positive ANA, and elevated ESR has been reported for other ACE inhibitors.

Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, california poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Test InteractionsPositive Coombs' [direct]; may cause false-positive results in urine acetone determinations using sodium nitroprusside reagent

Monitoring ParametersBlood pressure; serum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringUse with caution in presence of renal impairment, hypovolemia, aortic stenosis, and postanesthesia. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (especially anything that may impact fluid balance or cardiac status). Assess results of laboratory tests, therapeutic effectiveness according to purpose for use, and adverse response on a regular basis during therapy (eg, anaphylactic reactions, hypovolemia, angioedema, postural hypotension). Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. Do not use potassium supplement or salt substitutes without consulting prescriber. Take exactly as directed; do not discontinue without consulting prescriber. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); or nausea, vomiting, abdominal pain, dry mouth, or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help) - report if these persist. Report chest pain or palpitations; mouth sores; fever or chills; swelling of extremities, face, mouth, or tongue; skin rash; numbness, tingling, or pain in muscles; respiratory difficulty; unusual cough; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as sodium: 10 mg, 20 mg, 40 mg

Monopril®: 10 mg, 20 mg, 40 mg

Generic AvailableYes

ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)

Pricing: U.S. (www.drugstore.com)

Tablets (Fosinopril Sodium)

10 mg (60): $59.99

20 mg (60): $59.99

40 mg (30): $30.99

Tablets (Monopril)

10 mg (60): $85.99

20 mg (60): $89.99

40 mg (60): $88.93

Mechanism of ActionCompetitive inhibitor of angiotensin-converting enzyme (ACE); prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor; results in lower levels of angiotensin II which causes an increase in plasma renin activity and a reduction in aldosterone secretion; a CNS mechanism may also be involved in hypotensive effect as angiotensin II increases adrenergic outflow from CNS; vasoactive kallikreins may be decreased in conversion to active hormones by ACE inhibitors, thus reducing blood pressure

Pharmacodynamics/Kinetics

Onset of action: 1 hour

Duration: 24 hours

Absorption: 36%

Protein binding: 95%

Metabolism: Prodrug, hydrolyzed to its active metabolite fosinoprilat by intestinal wall and hepatic esterases

Bioavailability: 36%

Half-life elimination, serum (fosinoprilat): 12 hours

Time to peak, serum: ~3 hours

Excretion: Urine and feces (as fosinoprilat and other metabolites in roughly equal proportions, 45% to 50%)

Related Information

- Angiotensin Agents
- Heart Failure (Systolic)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness; may rarely cause insomnia

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Congestive Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines recommend that ACE inhibitors be used in patients with a reduced EF (with or without heart failure symptoms) unless contraindicated. ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. In this situation, they decrease hospitalizations for, and retard progression to, congestive heart failure. When used in patients with heart failure, the target dose should be achieved, if possible. Lower daily doses of ACE inhibitors have demonstrated the same mortality effects as high doses, but have not decreased hospitalizations to the extent that high-dose ACE inhibitors have, as demonstrated in the ATLAS study (Packer M, 1999).

Hypertension: The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) can be beneficial in patients with hypertension and LVH without symptoms of heart failure. JNC 7 suggests that patients can benefit from treatment with an ACE inhibitor if they have hypertension **and** heart failure, acute myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, a history of stroke.

Vascular Disease: The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors can be useful in preventing heart failure in patients who have a history of atherosclerotic vascular disease, diabetes, or hypertension with associated cardiovascular risk factors. The HOPE trial (Heart Outcomes Prevention Evaluation Study Investigators, 2000) investigated the value of an ACE inhibitor (ramipril 5-10 mg daily) versus placebo in patients who had evidence of vascular disease or diabetes (one other cardiovascular risk factor) and were at least 55 years of age. Patients were excluded if they had a low ejection fraction, heart failure, or were on an ACE inhibitor. The primary outcome was a composite of death from cardiovascular cause, myocardial infarction, or stroke; 9297 patients were enrolled and randomized. Ramipril significantly reduced the risk of death from CV causes, MI, or stroke over placebo. New cases of diabetes were also reduced in the ramipril group. In the EUROPA trial, patients with stable coronary artery disease (at low risk for cardiovascular events) received perindopril or placebo and were evaluated for incidence of cardiovascular events after four years of treatment. In this randomized, placebo-controlled, prospective study, 12,218 patients received either perindopril (8 mg/day, n=6110) or placebo (n=6108) and were assessed for the primary endpoint of a cardiovascular event, defined as cardiovascular death, myocardial infarction, or cardiac arrest. The study population was well balanced with respect to baseline demographics and concomitant medication use (including beta-blockers, platelet inhibitors, antihyperlipidemics, calcium channel blockers, nitrates, and diuretics). Intent-to-treat analysis revealed that 603 (10%) of placebo patients experienced the primary endpoint of a cardiovascular event compared to 488 (8%) of perindopril-receiving patients, for a 20% relative risk reduction (p=0.0003). This result was not influenced by presence of other comorbidities (eg, diabetes, hypertension) or concomitant beta-blocker, calcium channel blocker, or lipid-lowering therapies. Withdrawal from the study (postrandomization) due to adverse reactions was similar between treatment groups. Number needed to treat analysis suggests that treatment of 50 patients over a 4-year period will prevent one major cardiovascular event.

Acute Coronary Syndromes: In the treatment of unstable angina/non-ST-segment elevation MI, ACE inhibitors are recommended when hypertension persists despite treatment with nitroglycerin and a beta-blocker in patients with LV systolic dysfunction or CHF and in ischemic patients with diabetes (Class I). ACE inhibitors are also recommended for all post-ACS individuals (Class IIa). According to 2004 ACC/AHA STEMI guidelines, an ACE inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF <0.4, in the absence of hypotension or known contraindications to this class of medicines. In the emergency management of complicated STEMI, a short-acting ACEI (eg, captopril 1-6.25 mg) may be added once the patient's systolic blood pressure is >100 mm Hg and not <30 mm Hg below baseline. The VALIANT trial evaluated the effects of valsartan (target dose: 160 mg twice daily), captopril (target dose: 50 mg twice daily), and the combination (target doses: valsartan 80 mg twice daily and captopril 150 mg once daily) in a randomized, double-blind trial of patients with acute MI (0.5-10 days post-MI) complicated by left ventricular systolic dysfunction, heart failure, or both. Enrollment in the study numbered 14,703 patients and followed for a median of 24.7 months. There was no difference in the primary endpoint (all cause mortality) among the 3 groups. There was no difference in incidence of CV death, recurrent MI, or hospitalization for heart failure either. Hypotension and renal dysfunction occurred significantly more often in the valsartan group than captopril alone. Cough, rash, and taste disturbances occurred more often in the captopril group. The authors (Pfeffer MA, 2003) concluded that valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after MI. Combining valsartan with captopril increased the rate of adverse events without improving survival.

Potential Adverse Events: ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. In those patients experiencing cough on an ACE inhibitor, the ACE inhibitor may be discontinued and, if necessary, ARB therapy instituted. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Drug Interactions: Concomitant indomethacin therapy may blunt the reduction in sitting and 24-hour ambulatory diastolic blood pressure. Use of NSAIDs should be avoided or limited, with monitoring of blood pressure control in this setting. In patients with heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

Anesthesia and Critical Care Concerns/Other ConsiderationsACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. ACE inhibitors are also indicated in patients postmyocardial infarction in whom left ventricular ejection fraction is <40%. ACE inhibitors have renal protective effects in patients with proteinuria and possibly cardioprotective effects in high-risk patients.

Index TermsFosinopril Sodium

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International Brand NamesAcenor-M (ID); BPNorm (PH); Dynacil (DE); Fosavis (SE); Fosinil (BE, ES, LU); Fosinorm (DE); Fosipres (IT); Fosipril (AU); Fosiril (KP); Fositen (CH, PT); Fositens (AE, AT, BH, CY, EG, ES, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Fovas (IN); Fozitec (FR); Hiperlex (ES); Monace (AU); Monopril (AU, BB, BG, BM, BR, BS, BZ, CL, CN, CO, CZ, DK, EE, GR, GY, HK, HN, HU, JM, KP, MX, MY, NL, NO, PE, PK, PL, RU, SE, SR, TH, TR, TT, TW, VE, ZA); Newace (NL); Sapril (PH); Staril (GB); Tenso Stop (ES); Tensocardil (ES)

Fosphenytoin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Phenytoin and Fosphenytoin: Genetic Susceptibility to Serious Skin Reactions - November 2008

The U.S. Food and Drug Administration (FDA) is notifying healthcare professionals of preliminary information concerning the potential for serious skin reactions in susceptible patients treated with phenytoin (or fosphenytoin). Data suggests that patients testing positive for the human leukocyte antigen (HLA) allele *HLA-B*1502* have an increased risk of developing Stevens-Johnson syndrome (SJS) and/or toxic epidermal necrolysis (TEN). The risk appears to be highest in the early months of therapy initiation. The presence of this genetic variant exists in up to 15% of people of Asian descent in China, Thailand, Malaysia, Indonesia, Taiwan, and the Philippines, and may vary from <1% in Japanese and Koreans, to 2% to 4% of South Asians and Indians. This variant is virtually absent in those of Caucasian, African-American, Hispanic, or European ancestry. Of note, carbamazepine, another antiepileptic with a chemical structure similar to phenytoin, updated its prescribing information (December 2007) to include a warning of an increased risk of SJS and TEN in patients carrying the *HLA-B*1502* allele and a recommendation to screen patients of Asian descent for the allele prior to initiating therapy. In contrast to carbamazepine, the FDA is not recommending testing for the presence of *HLA-B*1502* prior to initiating phenytoin therapy until more information is available. In the interim, the FDA is advising that prescribers avoid phenytoin or fosphenytoin as alternatives to carbamazepine therapy in patients positive for *HLA-B*1502*.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Phenytoin

Medication Safety Issues

Sound-alike/look-alike issues:

> Cerebyx® may be confused with Celebrex®, Celexa™, Cerezyme®

Overdoses have occurred due to confusion between the **mg per mL concentration** of fosphenytoin (50 mg PE/mL) and **total drug content per vial** (either 100 mg PE/2 mL vial or 500 mg PE/10 mL vial). ISMP recommends that the total drug content per container is identified instead of the concentration in mg per mL to avoid confusion and potential overdosages. Additionally, since most errors have occurred with overdoses in children, they recommend that pediatric hospitals should consider stocking only the 2 mL vial.

Pronunciation(FOS fen i toyn)

U.S. Brand NamesCerebyx®

Canadian Brand NamesCerebyx®

Pharmacologic CategoryAnticonvulsant, Hydantoin

Use: Labeled IndicationsUsed for the control of generalized convulsive status epilepticus and prevention and treatment of seizures occurring during neurosurgery; indicated for short-term parenteral administration when other means of phenytoin administration are unavailable, inappropriate, or deemed less advantageous (the safety and effectiveness of fosphenytoin in this use has not been systematically evaluated for more than 5 days)

Dosing: Adults

The dose, concentration in solutions, and infusion rates for fosphenytoin are expressed as phenytoin sodium equivalents (PE); fosphenytoin should always be prescribed and dispensed in phenytoin sodium equivalents (PE)

Status epilepticus: I.V.: Loading dose: 15-20 mg PE/kg I.V. administered at 100-150 mg PE/minute

Nonemergent loading and maintenance dosing: I.V. or I.M.:

> *Loading dose:* 10-20 mg PE/kg I.V. or I.M. (maximum I.V. rate: 150 mg PE/minute)
>
> *Initial daily maintenance dose:* 4-6 mg PE/kg/day I.V. or I.M.

Substitution for oral phenytoin therapy: I.M. or I.V.: May be substituted for oral phenytoin sodium at the same total daily dose; however, Dilantin® capsules are ~90% bioavailable by the oral route; phenytoin, supplied as fosphenytoin, is 100% bioavailable by both the I.M. and I.V. routes; for this reason, plasma phenytoin concentrations may increase when I.M. or I.V. fosphenytoin is substituted for oral phenytoin sodium therapy; in clinical trials, I.M. fosphenytoin was administered as a single daily dose utilizing either 1 or 2 injection sites; some patients may require more frequent dosing

Dosing: ElderlyPhenytoin clearance is decreased in geriatric patients; lower doses may be required. In addition, older adults may have lower serum albumin which may increase the free fraction and, therefore, pharmacologic response. Refer to adult dosing.

Dosing: Pediatric

Note: The dose, concentration in solutions, and infusion rates for fosphenytoin are expressed as phenytoin sodium equivalents (PE); fosphenytoin should

always be prescribed and dispensed in phenytoin sodium equivalents (PE).

Infants and Children (unlabeled use): I.V.:

Loading dose: 10-20 mg PE/kg for the treatment of generalized convulsive status epilepticus.

Maintenance dosing: Phenytoin dosing guidelines in pediatric patients are used when dosing fosphenytoin using doses in PE equal to the phenytoin doses (ie, phenytoin 1 mg = fosphenytoin 1 PE); maintenance doses may be started 8-12 hours after a loading dose

Dosing: Renal ImpairmentFree phenytoin levels should be monitored closely in patients with renal disease or in those with hypoalbuminemia; furthermore, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance in these patients leading to increase frequency and severity of adverse events.

Dosing: Hepatic ImpairmentPhenytoin clearance may be substantially reduced in cirrhosis and plasma level monitoring with dose adjustment advisable. Free phenytoin levels should be monitored closely in patients with hepatic disease or in those with hypoalbuminemia; furthermore, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance in these patients leading to increased frequency and severity of adverse events.

Administration: I.M.I.M. may be administered as a single daily dose using either 1 or 2 injection sites.

Administration: I.V.Rates of infusion:

Children: 1-3 mg PE/kg/minute

Adults: Should not exceed 150 mg PE/minute

Dietary ConsiderationsProvides phosphate 0.0037 mmol/mg PE fosphenytoin

StorageRefrigerate at 2°C to 8°C (36°F to 46°F). Do not store at room temperature for more than 48 hours. Do not use vials that develop particulate matter.

ReconstitutionMust be diluted to concentrations of 1.5-25 mg PE/mL, in normal saline or D_5W, for I.V. infusion.

CompatibilityStable in D_5LR, $D_5{}^1/_2NS$, D_5W, $D_{10}W$, hetastarch 6% in NS, mannitol 20%, LR, NS.

Y-site administration: Compatible: Lorazepam. **Incompatible:** Midazolam.

Compatibility when admixed: Compatible: Potassium chloride.

ContraindicationsHypersensitivity to phenytoin, other hydantoins, or any component of the formulation; patients with sinus bradycardia, sinoatrial block, second- and third-degree AV block, or Adams-Stokes syndrome; occurrence of rash during treatment (should not be resumed if rash is exfoliative, purpuric, or bullous); treatment of absence seizures

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Arrhythmias: Administration of phenytoin has been associated with atrial and ventricular conduction depression and ventricular fibrillation; careful cardiac monitoring is needed when administering I.V. loading doses of fosphenytoin.
- Blood dyscrasias: A spectrum of hematologic effects have been reported with use (eg, neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias); patients with a previous history of adverse hematologic reaction to any drug may be at increased risk. Early detection of hematologic change is important; advise patients of early signs and symptoms including fever, sore throat, mouth ulcers, infections, easy bruising, petechial or purpuric hemorrhage.
- Dermatologic reactions: Severe reactions, including toxic epidermal necrolysis and Stevens-Johnson syndromes, although rarely reported, have resulted in fatalities; drug should be discontinued if there are any signs of rash. Data suggests a genetic susceptibility for serious skin reactions in patients of Asian descent (see "Special populations" below).
- Hypersensitivity syndrome: Acute hepatotoxicity associated with a hypersensitivity syndrome characterized by fever, skin eruptions, and lymphadenopathy has been reported to occur within the first 2 months of treatment; discontinue if skin rash or lymphadenopathy occurs.
- Hypotension: May occur, especially after I.V. administration at high doses and high rates of administration.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with hypotension and/or severe myocardial insufficiency.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Fever: Use with caution in patients with fever.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hypoalbuminemia: Use with caution in patients with hypoalbuminemia.
- Hypothyroidism: Use with caution in patients with hypothyroidism.
- Porphyria: Use with caution in patients with porphyria.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Asian ancestry: Asian patients with the variant *HLA-B*1502* may be at an increased risk of developing Stevens-Johnson syndrome and/or toxic epidermal necrolysis.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Phenytoin sodium equivalent (PE): Doses of fosphenytoin are expressed as their phenytoin sodium equivalent (PE).

Other warnings/precautions:

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsNo significant changes in fosphenytoin pharmacokinetics with age have been noted. Phenytoin clearance is decreased in the elderly and lower doses may be needed. Elderly may have reduced hepatic clearance due to age decline in Phase I metabolism. Elderly may have low albumin which will increase free fraction and, therefore, pharmacologic response. Monitor closely in those who are hypoalbuminemic. Free fraction measurements advised, also elderly may display a higher incidence of adverse effects (cardiovascular) when using the I.V. loading regimen; therefore, it is recommended to decrease loading I.V. dose to 25 mg/minute.

Pregnancy Risk FactorD

Pregnancy ConsiderationsFosphenytoin is the prodrug of phenytoin. Refer to Phenytoin for additional information.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsFosphenytoin is the prodrug of phenytoin. It is not known if fosphenytoin is excreted in breast milk prior to conversion to phenytoin. Refer to Phenytoin monograph for additional information.

Adverse ReactionsThe more important adverse clinical events caused by the I.V. use of fosphenytoin or phenytoin are cardiovascular collapse and/or central nervous system depression. Hypotension can occur when either drug is administered rapidly by the I.V. route. Do not exceed a rate of 150 mg phenytoin equivalent/minute when administering fosphenytoin.

The adverse clinical events most commonly observed with the use of fosphenytoin in clinical trials were nystagmus, dizziness, pruritus, paresthesia, headache, somnolence, and ataxia. Paresthesia and pruritus were seen more often following fosphenytoin (versus phenytoin) administration and occurred more often with I.V. fosphenytoin than with I.M. administration. These events were dose and rate related (doses ≥15 mg/kg at a rate of 150 mg/minute). These sensations, generally described as itching, burning, or tingling are usually not at the infusion site. The location of the discomfort varied with the groin mentioned most frequently. The paresthesia and pruritus were transient events that occurred within several minutes of the start of infusion and generally resolved within 10 minutes after completion of infusion.

Transient pruritus, tinnitus, nystagmus, somnolence, and ataxia occurred 2-3 times more often at doses ≥15 mg/kg and rates ≥150 mg/minute.

I.V. administration (maximum dose/rate):

>10%:

Central nervous system: Nystagmus, dizziness, somnolence, ataxia

Dermatologic: Pruritus

1% to 10%:

Cardiovascular: Hypotension, vasodilation, tachycardia

Central nervous system: Stupor, incoordination, paresthesia, extrapyramidal syndrome, tremor, agitation, hypoesthesia, dysarthria, vertigo, brain edema, headache

Gastrointestinal: Nausea, tongue disorder, dry mouth, vomiting

Neuromuscular & skeletal: Pelvic pain, muscle weakness, back pain

Ocular: Diplopia, amblyopia

Otic: Tinnitus, deafness

Miscellaneous: Taste perversion

I.M. administration (substitute for oral phenytoin):

1% to 10%:

Central nervous system: Nystagmus, tremor, ataxia, headache, incoordination, somnolence, dizziness, paresthesia, reflexes decreased

Dermatologic: Pruritus

Gastrointestinal: Nausea, vomiting

Hematologic/lymphatic: Ecchymosis

Neuromuscular & skeletal: Muscle weakness

<1% (Limited to important or life-threatening): Acidosis, acute hepatic failure, acute hepatotoxicity, alkalosis, anemia, atrial flutter, bundle branch block, cardiac arrest, cardiomegaly, cerebral hemorrhage, cerebral infarct, CHF, cyanosis, dehydration, hyperglycemia, hyperkalemia, hypertension, hypochromic anemia, hypokalemia, hypophosphatemia, ketosis, leukocytosis, leukopenia, lymphadenopathy, palpitation, postural hypotension, pulmonary embolus, QT interval prolongation, sinus bradycardia, syncope, Stevens-Johnson syndrome, thrombocytopenia, thrombophlebitis, toxic epidermal necrolysis, ventricular extrasystoles

Metabolism/Transport EffectsAs phenytoin: **Substrate** of CYP2C9 (major), 2C19 (major), 3A4 (minor); **Induces** CYP2B6 (strong), 2C8 (strong), 2C9 (strong), 2C19 (strong), 3A4 (strong)

Drug Interactions

Acetaminophen: Anticonvulsants (Hydantoin) may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May enhance the adverse/toxic effect of Anticonvulsants (Hydantoin). Specifically, osteomalacia and rickets. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Anticonvulsants (Hydantoin). Anticonvulsants (Hydantoin) may decrease the serum concentration of Chloramphenicol. Increased chloramphenicol concentrations have also been seen. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Anticonvulsants (Hydantoin). *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inducers (Strong) may increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C19 Substrates: CYP2C19 Inducers (Strong) may increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inducers (Highly Effective) may increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inducers (Highly Effective) may increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol:

Acute use: Avoid or limit ethanol (inhibits metabolism of phenytoin); watch for sedation.

Chronic use: Avoid or limit ethanol (stimulates metabolism of phenytoin).

Test InteractionsIncreased glucose, alkaline phosphatase (S); decreased thyroxine (S), calcium (S); serum sodium increased in overdose setting

Monitoring ParametersContinuous blood pressure, ECG, and respiratory function monitoring with loading dose and for 10-20 minutes following infusion; vital signs, CBC, liver function tests, plasma level monitoring (plasma levels should not be measured until conversion to phenytoin is complete, ~2 hours after an I.V. infusion or ~4 hours after an I.M. injection)

Reference Range

Therapeutic: 10-20 mcg/mL (SI: 40-79 µmol/L); toxicity is measured clinically, and some patients require levels outside the suggested therapeutic range

Toxic: 30-50 mcg/mL (SI: 120-200 µmol/L)

Lethal: >100 mcg/mL (SI: >400 µmol/L)

Manifestations of toxicity:

Nystagmus: 20 mcg/mL (SI: 79 µmol/L)

Ataxia: 30 mcg/mL (SI: 118.9 µmol/L)

Decreased mental status: 40 mcg/mL (SI: 159 µmol/L)

Coma: 50 mcg/mL (SI: 200 µmol/L)

Peak serum phenytoin level after a 375 mg I.M. fosphenytoin dose in healthy males: 5.7 mcg/mL

Peak serum fosphenytoin levels and phenytoin levels after a 1.2 g infusion (I.V.) in healthy subjects over 30 minutes were 129 mcg/mL and 17.2 mcg/mL, respectively

Nursing: Physical Assessment/MonitoringAssess all other medications patient may be taking. Continuous monitoring is essential during infusion and for 30 minutes following infusion. Monitor closely for adverse or overdose reactions during and following infusion.

Monitoring: Lab TestsSerum phenytoin, renal function, albumin

Patient EducationPatients may not be in a position to evaluate their response. If conscious or alert, advise patient to report signs or symptoms of palpitations, racing or falling heartbeat, respiratory difficulty, acute faintness, or CNS disturbances (eg, somnolence, ataxia), and visual disturbances. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sodium: 75 mg/mL (2 mL, 10 mL) [equivalent to phenytoin sodium 50 mg/mL]

Cerebyx®: 75 mg/mL (2 mL, 10 mL) [equivalent to phenytoin sodium 50 mg/mL]

Generic AvailableYes

ManufacturerPfizer Inc (Cerebyx®, Dilantin®)

Mechanism of ActionDiphosphate ester salt of phenytoin which acts as a water soluble prodrug of phenytoin; after administration, plasma esterases convert fosphenytoin to phosphate, formaldehyde, and phenytoin as the active moiety; phenytoin works by stabilizing neuronal membranes and decreasing seizure activity by increasing efflux or decreasing influx of sodium ions across cell membranes in the motor cortex during generation of nerve impulses

Pharmacodynamics/KineticsAlso refer to Phenytoin monograph for additional information.

Protein binding: Fosphenytoin: 95% to 99% to albumin; can displace phenytoin and increase free fraction (up to 30% unbound) during the period required for conversion of fosphenytoin to phenytoin

Metabolism: Fosphenytoin is rapidly converted via hydrolysis to phenytoin; phenytoin is metabolized in the liver and forms metabolites

Bioavailability: I.M.: Fosphenytoin: 100%

Half-life elimination:

Fosphenytoin: 15 minutes

Phenytoin: Variable (mean: 12-29 hours); kinetics of phenytoin are saturable

Time to peak: Conversion to phenytoin: Following I.V. administration (maximum rate of administration): 15 minutes; following I.M. administration, peak phenytoin levels are reached in 3 hours

Excretion: Phenytoin: Urine (as inactive metabolites)

Related Information

- Fosphenytoin and Phenytoin

Pharmacotherapy Pearls1.5 mg fosphenytoin is approximately equivalent to 1 mg phenytoin. Equimolar fosphenytoin dose is 375 mg (75 mg/mL solution) to phenytoin 250 mg (50 mg/mL).

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tongue disorder and dry mouth.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, or visual hallucinations

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine

Cardiovascular ConsiderationsAs with phenytoin, fosphenytoin, when given I.V., can cause marked and dramatic hypotension and reflex tachycardia. Avoid rapid I.V. infusion of fosphenytoin (infusion rates >150 mg of phenytoin equivalent per minute).

Anesthesia and Critical Care Concerns/Other ConsiderationsFosphenytoin 1.5 mg is approximately equivalent to phenytoin 1 mg.

Fosphenytoin is compatible with all diluents; does not require propylene glycol or ethanol for solubility. Since there is no precipitation problem with fosphenytoin, no I.V. filter is required. Formaldehyde production is not expected to be clinically consequential (about 200 mg) if used for 1 week. As with phenytoin, fosphenytoin, when given I.V., can cause marked and dramatic hypotension and reflex tachycardia. Fosphenytoin administration is safer, in that the risk of hypotension may be somewhat less, and there are no adverse effects of extravasation. Avoid rapid I.V. infusion of fosphenytoin (infusion rates >150 mg of phenytoin equivalent per minute). Pruritus can be severe, requiring discontinuation of infusion.

Index Terms Fosphenytoin Sodium

References

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International Brand Names Pro-Epanutin (AT, AU, DK, FI, GB, IE, NO, SE); Prodilantin (FR)

Fospropofol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Product availability: FDA approved December 2008; availability anticipated in April 2009

Sound-alike/look-alike issues:

Fospropofol may be confused with fosaprepitant, fosphenytoin, propofol

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Onset of action: The onset of action will be delayed due to need for conversion to the active metabolite, propofol. If supplemental doses are administered before full effect occurs, the risk of dose-stacking may be elevated resulting in deeper sedation than intended.

Pronunciation

(fos PROE po fole)

U.S. Brand NamesLusedra™

Pharmacologic CategorySedative

Use: Labeled IndicationsMonitored anesthesia care (MAC) sedation in patients undergoing diagnostic or therapeutic procedures

Dosing: Adults**Note: Onset of effect is delayed as compared to propofol-emulsion due to need for conversion to active component.** If <60 kg, base dosing on 60 kg; however, lower doses may be used to achieve lower levels of sedation. If >90 kg, base dosing on 90 kg.

Monitored anesthesia care sedation: I.V.:

Healthy adults <65 years or with mild systemic disease (ASA-PS1 or -PS2): *Standard dosing regimen:* Initial: 6.5 mg/kg (maximum initial dose: 577.5 mg or 16.5 mL), followed by supplemental doses of 1.6 mg/kg (maximum supplemental dose: 140 mg or 4 mL) no more frequently than every 4 minutes as needed to achieve desired level of sedation.

Patients with severe systemic disease (ASA-PS3 or -PS4): *Modified dosing regimen:* Initial: 4.9 mg/kg (maximum initial dose: 437.5 mg or 12.5 mL), followed by supplemental doses of 1.2 mg/kg (maximum supplemental dose: 105 mg or 3 mL) no more frequently than every 4 minutes as needed to achieve desired level of sedation.

Dosing: Elderly**Note: Onset of effect is delayed as compared to propofol-emulsion due to need for conversion to active component.** If <60 kg, base dosing on 60 kg; however, lower doses may be used to achieve lower levels of sedation. If >90 kg, base dosing on 90 kg.

Monitored anesthesia care sedation: I.V.: Patients ≥65 years:*Modified dosing regimen:* Initial: 4.9 mg/kg (maximum initial dose: 437.5 mg or 12.5 mL), followed by supplemental doses of 1.2 mg/kg (maximum supplemental dose: 105 mg or 3 mL) no more frequently than every 4 minutes as needed to achieve desired level of sedation.

Dosing: Renal ImpairmentNo dosage adjustment recommended. Use with caution in patients with severe renal impairment (Cl_{cr} <30 mL/minute); limited safety and efficacy data available in these patients.

Dosing: Hepatic ImpairmentNo dosage adjustment recommended. Use with caution in patients with hepatic impairment; has not been adequately studied in this population.

Administration: I.V.Administer as an I.V. bolus (no recommendations on rate of administration provided by manufacturer) via a peripheral I.V. line. Flush I.V. line with NS before and after administration. Strict aseptic technique must be maintained in handling. Discard any unused portion at the end of the procedure. Do not filter.

Administration: I.V. DetailpH: 8.2-9.0

StorageStore at controlled room temperature of 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

ReconstitutionSingle-use vials do not need to be diluted prior to administration. Draw into sterile syringes immediately after opening vials. Discard any unused portion at the end of procedure.

CompatibilityDo not mix with other therapeutic agents prior to administration.

Y-site administration: Compatible: $D5_{1/4}NS$, $D5_{1/2}NS$, $D5_{1/2}NS$ with 20 mEq KCl, D_5W, D_5LR, LR, $^1/_2NS$, NS. **Incompatible:** Meperidine, midazolam.

Restrictions**Pending information:** Per the manufacturer, it is likely that fospropofol will be labeled as a C-II

ContraindicationsThere are no contraindications in the manufacturer's FDA approved labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Hypotension: The major cardiovascular effect is hypotension. Use with caution in patients who are hemodynamically unstable, hypovolemic, or have abnormally low vascular tone (eg, sepsis), or compromised myocardial function (eg, heart failure).

- Respiratory depression: May cause loss of spontaneous respiration and/or hypoxemia; supplemental oxygen is recommended for all patients receiving fospropofol; monitor patient closely. The risk of these effects may be increased with the concomitant use of opioids and/or other sedatives.

- Unresponsiveness: May cause patients to become unresponsive or minimally responsive to vigorous tactile or painful stimuli.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; has not been adequately studied in this population.

- Renal impairment: Use with caution in patients with severe renal impairment (Cl_{cr} <30 mL/minute); limited safety and efficacy data available in these patients.

- Respiratory disease: Use with caution in patients with respiratory disease; risk of cardiorespiratory depression may be increased.

- Seizure disorder: Use with caution in patients with a history of epilepsy or seizures; seizure may occur during recovery phase.

Concurrent drug therapy issues:

- Opiates/sedative-hypnotics: Concomitant use may lead to increased sedative or respiratory depressant effects of fospropofol, more pronounced decreases in systolic, diastolic, and mean arterial pressures, heart rate, and cardiac output.

Special populations:

- ASA-PS (American Society of Anesthesiologists - Physical Status) 3/4 patients: Use lower doses in ASA-PS 3/4 patients to reduce the incidence of unwanted cardiorespiratory and neurologic depressive events.

- Elderly: Use lower doses in patients ≥65 years to reduce the incidence of unwanted cardiorespiratory and neurologic depressive events.

- Pediatrics: Safety and efficacy have not been established in patients <18 years of age.

- Pregnancy: Fospropofol should only be used in pregnancy if clearly needed. Not recommended for use in obstetrics, including cesarean section deliveries.

Other warnings/precautions:

- Analgesic supplementation: Fospropofol lacks analgesic properties; pain management requires specific use of analgesic agents.

- Appropriate use: Use only for sedation during procedures as an I.V. bolus with supplemental doses as needed; not recommended for use as a continuous infusion (safety has not been established).

- Experienced personnel: Use requires careful patient monitoring, **should only be used by experienced personnel** who are not actively engaged in the diagnostic or therapeutic procedure. Sedated patients should be continuously monitored, and facilities for maintenance of a patent airway, providing artificial ventilation, administering supplemental oxygen, and instituting cardiovascular resuscitation must be immediately available. Patients should be continuously monitored during sedation and through the recovery process for early signs of hypotension, apnea, airway obstruction, and/or oxygen desaturation. Use to induce moderate (conscious) sedation in patients warrants monitoring equivalent to that seen with general anesthesia.

- Onset of action: The **onset of action will be delayed** due to need for conversion to the active metabolite, propofol. If supplemental doses are administered before full effect occurs, the risk of dose-stacking may be elevated resulting in deeper sedation than intended.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events were not observed in animal reproduction studies; however, fospropofol should only be used in pregnancy if clearly needed. Fospropofol is not recommended for obstetrics, including cesarean section deliveries. It is not known if fospropofol crosses the placenta. However, propofol crosses the placenta, and therefore, may be associated with neonatal CNS and respiratory depression.

LactationPropofol (the active metabolite of fospropofol) enters breast milk/not recommended

Adverse Reactions

>10%:

Dermatologic: Pruritus (see "Note" below; 8% to 28%)

Neuromuscular & skeletal: Paresthesia (see "Note" below; 52% to 74%)

Respiratory: Hypoxemia (1% to 11%)

1% to 10%:

Cardiovascular: Hypotension (2% to 7%)

Central nervous system: Headache (1% to 2%)

Gastrointestinal: Nausea (≤4%), vomiting (≤3%)

Miscellaneous: Procedural pain (≤2%)

<1%, postmarketing, and/or case reports: Apnea, myoclonus, systolic blood pressure increased, heart rate increased

Note: Paresthesias (including perineal discomfort or burning sensation) and pruritus (including genital, perineal, and generalized pruritus) generally occur within 5 minutes of administration and usually described as mild-moderate in intensity. No pretreatments are helpful in reducing the incidence of these adverse effects.

Metabolism/Transport Effects **Substrate** of CYP1A2 (minor), 2A6 (minor), 2B6 (major), 2C9 (major), 2C19 (minor), 2D6 (minor), 2E1 (minor), 3A4 (minor); **Inhibits** CYP1A2 (moderate), 2C9 (weak), 2C19 (moderate), 2D6 (weak), 2E1 (weak), 3A4 (strong)

Drug Interactions

Alfentanil: May enhance the adverse/toxic effect of Fospropofol. Specifically, the development of opisthotonus (severe hyperextension and spasticity resulting in arching or bridging position) and/or grand mal seizures. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Strong): May decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

Ropivacaine: Fospropofol may increase the serum concentration of Ropivacaine. Specifically, propofol (the active metabolite of fospropofol) is the entity with the potential to interact with ropivacaine. *Risk C: Monitor therapy*

Monitoring Parameters Cardiac monitor, blood pressure, oxygen saturation; patient responsiveness; respiration

Product Availability Lusedra™: FDA approved December 2008; availability anticipated in April 2009

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection [preservative-free]:

Lusedra ™: 35 mg/mL (30 mL)

Generic Available No

Manufacturer Eisai Incorporated

Mechanism of Action Fospropofol disodium is a prodrug of propofol. Propofol interacts with the GABAA receptor, which is the presumed mechanism of action whereby it produces a sedative/hypnotic effect. Propofol is an alkyl-phenolic compound with intravenous general anesthetic properties. The drug is unrelated to any of the currently used barbiturate, opioid, benzodiazepine, arylcyclohexylamine, or imidazole intravenous anesthetic agents.

Pharmacodynamics/Kinetics

Onset of action: Bolus (dose dependent): Attainment of adequate sedation was achieved between 2-28 minutes (median: 8 minutes)

Duration of sedation: Time to fully alert: ≤1 hour (median: 5 minutes)

Distribution:

Fospropofol: V_d: 0.26-0.4 L/kg

Propofol: V_d: ~6 L/kg; decreased in the elderly

Protein binding: Fospropofol: ~98% to albumin; does not affect protein binding of propofol (also ~98% bound to albumin)

Metabolism: Fospropofol is completely metabolized by plasma alkaline phosphatases to propofol, formaldehyde (rapidly converted to formate), and phosphate. Propofol is further metabolized hepatically to water-soluble sulfate and glucuronide conjugates (~50%).

Half-life elimination:

Fospropofol: 0.8-0.96 hours

Propofol: 0.85-1.41 hours

Time to peak: Propofol (from fospropofol): ~12 minutes

Excretion:

Fospropofol: Urine (<0.02% unchanged)

Propofol: Urine (~88% as metabolites, 40% as glucuronide metabolite); feces (<2%)

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment May produce hypotension and respiratory depression; concomitant use with sedative hypnotics or opiates may produce additive effects.

Index Terms Aquavan; Fospropofol Disodium; GPI 15715

References

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Frovatriptan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

International issues:

Allegro® [Germany] may be confused with Allegra® which is a brand name for fexofenadine in the U.S.

Allegro®: Brand name for fluticasone in Israel

Pronunciation(froe va TRIP tan)
U.S. Brand NamesFrova®
Canadian Brand NamesFrova®
Pharmacologic CategoryAntimigraine Agent; Serotonin 5-HT$_{1B, 1D}$ Receptor Agonist
Use: Labeled IndicationsAcute treatment of migraine with or without aura in adults
Dosing: Adults**Migraine:** Oral:

U.S. labeling: 2.5 mg; if headache recurs, a second dose may be given if first dose provided relief and at least 2 hours have elapsed since the first dose (maximum daily dose: 7.5 mg)

Canadian labeling: 2.5 mg; if headache recurs, a second dose may be given if first dose provided relief and at least 4 hours have elapsed since the first dose (maximum daily dose: 5 mg)

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo adjustment necessary.
Dosing: Hepatic ImpairmentNo adjustment necessary in mild-to-moderate hepatic impairment; use with caution in severe impairment (has not been studied in severe impairment).

Canadian labeling (not in U.S. labeling): Use is contraindicated in severe hepatic impairment.

Administration: OralAdminister with fluids.
StorageStore at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture and light.
ContraindicationsHypersensitivity to frovatriptan or any component of the formulation; patients with ischemic heart disease or signs or symptoms of ischemic heart disease (including Prinzmetal's angina, angina pectoris, myocardial infarction, silent myocardial ischemia); cerebrovascular syndromes (including strokes, transient ischemic attacks); peripheral vascular syndromes (including ischemic bowel disease); uncontrolled hypertension; use within 24 hours of ergotamine derivatives; use within 24 hours of another 5-HT$_1$ agonist; management of hemiplegic or basilar migraine; prophylactic treatment of migraine

Canadian labeling: Additional contraindications (not in U.S. labeling): Cardiac arrhythmias, valvular heart disease, congenital heart disease, atherosclerotic disease; management of ophthalmoplegic migraine; severe hepatic impairment

Allergy Considerations

- Serotonin 5-HT$_{1B,1D}$ Receptor Agonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac events: Coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia/fibrillation, cardiac arrest, and death have been reported with 5-HT$_1$ agonist administration. Patients who experience sensations of chest pain/pressure/tightness or symptoms suggestive of angina following dosing should be evaluated for coronary artery disease or Prinzmetal's angina before receiving additional doses.

- Cerebrovascular events: Cerebral/subarachnoid hemorrhage and stroke have been reported with 5-HT$_1$ agonist administration.

- Elevated blood pressure: Significant elevation in blood pressure, including hypertensive crisis, has also been reported on rare occasions in patients with and without a history of hypertension.

- Vasospasm-related events: Peripheral vascular ischemia and colonic ischemia have been reported with 5-HT$_1$ agonist.

Disease-related concerns:

- Coronary artery disease: Should not be given to patients who have risk factors for CAD (eg, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, menopause, male >40 years of age) without adequate cardiac evaluation. Patients with suspected CAD should have cardiovascular evaluation to rule out CAD before considering use; if cardiovascular evaluation “is satisfactory”, first dose should be given in the healthcare provider's office. Periodic evaluation of cardiovascular status should be done in all patients.

- Neurologic disease: Use with caution in patients with epilepsy and structural brain lesions; may lower seizure threshold.

Concurrent drug therapy issues:

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (eg, SSRIs/SNRIs or triptans) or agents which reduce frovatriptan's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

Other warnings/precautions:

- Appropriate use: Only indicated for treatment of acute migraine; if a patient does not respond to the first dose, the diagnosis of migraine should be reconsidered; rule out underlying neurologic disease in patients with atypical headache, migraine (with no prior history of migraine) or inadequate clinical response to initial dosing.

Geriatric ConsiderationsSince elderly often have cardiovascular disease, careful evaluation of the use of 5-HT agonists is needed to avoid complications with the use of these agents. The pharmacokinetic disposition of these agents is similar to that seen in younger adults.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies using frovatriptan in pregnant women. Use only if potential benefit to the mother outweighs the potential risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Cardiovascular: Chest pain (2%), flushing (4%), palpitation (1%)

Central nervous system: Dizziness (8%), fatigue (5%), headache (4%), hot or cold sensation (3%), anxiety (1%), dysesthesia (1%), hypoesthesia (1%), insomnia (1%), pain (1%)

Gastrointestinal: Xerostomia (3%), dyspepsia (2%), abdominal pain (1%), diarrhea (1%), vomiting (1%)

Neuromuscular & skeletal: Paresthesia (4%), skeletal pain (3%)

Ocular: Vision abnormal (1%)

Otic: Tinnitus (1%)

Respiratory: Rhinitis (1%), sinusitis (1%)

Miscellaneous: Diaphoresis (1%)

<1%, postmarketing, and/or case reports: Abnormal dreaming, abnormal gait, abnormal lacrimation, abnormal reflexes, abnormal urine, agitation, amnesia, arthralgia, arthrosis, ataxia, back pain, bradycardia, bullous eruption, cheilitis, concentration impaired, confusion, conjunctivitis, constipation, dehydration, depersonalization, depression, dysphagia, dyspnea, earache, ECG changes, emotional lability, epistaxis, eructation, esophagospasm, euphoria, eye pain, fever, gastroesophageal reflux, hiccup, hot flushes, hyperacusis, hyperesthesia, hypertonia, hyperventilation, hypocalcemia, hypoglycemia, hypotonia, involuntary muscle contractions, laryngitis, leg cramps, malaise, micturition, muscle weakness, myalgia, nervousness, nocturia, peptic ulcer, personality disorder, pharyngitis, polyuria, pruritus, purpura, renal pain, rigors, saliva increased, salivary gland pain, seizure, speech disorder, stomatitis, syncope, tachycardia, taste perversion, thirst, tongue paralysis, toothache, tremor, unspecified pain, urinary frequency, vertigo, weakness

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor)

Drug Interactions

Ergot Derivatives: May enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: Food does not affect frovatriptan bioavailability.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, ergot derivatives). Cardiovascular status should be evaluated prior to initiating medication and periodically thereafter. Assess effectiveness and adverse response. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis drug is to be used to reduce your migraine, not to prevent or reduce the number of attacks. Follow exact instructions for use. Do not take within 24 hours of any other migraine medication without first consulting prescriber. If first dose brings relief, a second dose may be taken anytime after 2 hours if migraine returns. Do not take more than three tablets (7.5 mg) in 24 hours without consulting prescriber. May cause dizziness, fatigue, insomnia, or drowsiness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); dry mouth (frequent mouth care and sucking on lozenges may help); skin flushing or hot flashes (cool clothes or a cool environment may help); or mild abdominal discomfort or vomiting (small frequent meals, good mouth care, chewing gum, or sucking lozenges may help). Report immediately any chest pain, palpitations, or irregular heartbeat; severe dizziness, acute headache, stiff or painful neck, facial swelling, muscle weakness or pain, changes in mental acuity, blurred vision, eye pain, or ringing in ears; changes in urinary pattern; respiratory difficulty; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as base: 2.5 mg

Generic AvailableNo
ManufacturerEndo Pharmaceuticals
Pricing: U.S. (www.drugstore.com)

Tablets (Frova)

2.5 mg (9): $142.98

Mechanism of ActionSelective agonist for serotonin (5-HT_{1B} and 5-HT_{1D} receptor) in cranial arteries to cause vasoconstriction and reduces sterile inflammation associated with antidromic neuronal transmission correlating with relief of migraine.
Pharmacodynamics/Kinetics

Distribution: Male: 4.2 L/kg; Female: 3.0 L/kg

Protein binding: 15%

Metabolism: Primarily hepatic via CYP1A2

Bioavailability: 20% to 30%

Half-life elimination: 26 hours

Time to peak: 2-4 hours

Excretion: Feces (62%); urine (32%)

Related Information

- Antimigraine Drugs: 5-HT1 Receptor Agonists

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Cardiovascular ConsiderationsCoronary vasospasm has been associated with 5-$HT_{1B/1D}$ agonists. These agents are contraindicated in patients with documented ischemic or vasospastic coronary artery disease. Patients with risk factors for CAD may receive these agents, provided a cardiovascular evaluation yields satisfactory evidence that the patient is free of cardiovascular disease. In patients with risk factors for CAD, administration of the initial dose in a medically staffed/equipped facility (ie, physician's office) is recommended. In addition, ECG monitoring after the initial dose should be considered. Patients who acquire risk factors for CAD, or long-term users of agents from this class of medications, should undergo periodic cardiovascular evaluation.
Index TermsFrovatriptan Succinate
References

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Rapoport A, Ryan R, Goldstein J, et al, “Dose Range-Finding Studies With Frovatriptan in the Acute Treatment of Migraine,” *Headache*, 2002, 42(Suppl 2):74-83.[PubMed 12028323]

Ryan R, Geraud G, Goldstein J, et al, “Clinical Efficacy of Frovatriptan: Placebo-Controlled Studies,” *Headache*, 2002, 42(Suppl 2):84-92.[PubMed 12028324]

International Brand NamesAllegro (DE); Auradol (IT); Forvey (ES); Fromirex (NL); Frovex (IE); Menamig (CH); Menatriptan (CR, DO, GT, HN, NI, PA, SV); Migard (DK, EE, FI, GB, HN, NO, SE); Relieva (BG); Tigreat (FR, NO)

Fructose, Dextrose, and Phosphoric Acid

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Emetrol® may be confused with emetine

Pronunciation(FRUK tose, DEKS trose, & foss FOR ik AS id)
U.S. Brand NamesEmetrol® [OTC]; Especol® [OTC]; Formula EM [OTC]; Kalmz [OTC]; Nausea Relief [OTC]; Nausetrol® [OTC]
Pharmacologic CategoryAntiemetic
Use: Labeled IndicationsRelief of nausea associated with upset stomach that occurs with intestinal or stomach flu, and food indiscretions
Dosing: Adults**Nausea:** Oral: 15-30 mL; repeat dose every 15 minutes until distress subsides; do not take for more than 1 hour (5 doses)
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Nausea:** Oral

Children 2-12 years: 5-10 mL; repeat dose every 15 minutes until distress subsides; do not take for more than 1 hour (5 doses)

Children ≥12 years: Refer to adult dosing.

Administration: OralMay chill or drink after pouring over ice to improve taste. Should not be diluted or followed with other fluids immediately before or after administration.
ContraindicationsHypersensitivity to any component of the formulation; hereditary fructose intolerance
Warnings/Precautions

Disease-related concerns:

- Diabetes: Not for self-medication (OTC use) in patients with diabetes.

Other warnings/precautions:

- Lack of improvement: Contact healthcare provider if nausea continues or recurs frequently.

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, oral: Fructose 1.87 g, dextrose 1.87 g, and phosphoric acid 21.5 mg per 5 mL (120 mL)

Emetrol®: Fructose 1.87 g, dextrose 1.87 g, and phosphoric acid 21.5 mg per 5 mL (120 mL, 240 mL) [cherry and lemon mint flavors]

Especol®: Fructose 1.87 g, dextrose 1.87 g, and phosphoric acid 21.5 mg per 5 mL (120 mL) [cherry and lemon-lime flavors]

Formula EM, Nausea Relief: Fructose 1.87 g, dextrose 1.87 g, and phosphoric acid 21.5 mg per 5 mL (120 mL)

Kalmz, Nausetrol®: Fructose 1.87 g, dextrose 1.87 g, and phosphoric acid 21.5 mg per 5 mL (120 mL) [cherry flavor]

Generic AvailableYes
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsDextrose, Levulose, and Phosphoric Acid; Levulose, Dextrose, and Phosphoric Acid; Phosphorated Carbohydrate Solution; Phosphoric Acid, Levulose, and Dextrose

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FU HURT

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Head and Neck Cancer](#)

Regimen UseHead and neck cancer

Regimen

Hydroxyurea: Oral: 1000 mg every 12 hours for 11 doses days 0 to 5

Fluorouracil: I.V.: 800 mg/m^2/day continuous infusion (start AM after admission) days 1 to 5

Paclitaxel: I.V.: 5-25 mg/m^2/day continuous infusion days 1 to 5

Filgrastim: SubQ: 5 mcg/kg/day days 6 to 12 (start ≥12 hours after completion of fluorouracil infusion)

5-7 cycles may be administered

References

"Induction Chemotherapy Plus Radiation Compared With Surgery Plus Radiation in Patients With Advanced Laryngeal Cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group," *N Engl J Med*, 1991, 324(24):1685-90.[PubMed 2034244]

FU-LV-CPT-11

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Colorectal Cancer]

Regimen UseColorectal cancer

Index TermsFluorouracil-Leucovorin-Irinotecan; Irinotecan-Fluorouracil-Leucovorin

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Irinotecan: I.V.: 350 mg/m^2 day 1

[total dose/cycle = 350 mg/m^2]

Leucovorin: I.V.: 20 mg/m^2/day days 22 to 26

[total dose/cycle = 100 mg/m^2]

Fluorouracil: I.V.: 425 mg/m^2/day days 22 to 26

[total dose/cycle = 2125 mg/m^2]

Repeat cycle every 6 weeks

Variation 2:

Irinotecan: I.V.: 80 mg/m^2 day 1

[total dose/cycle = 80 mg/m^2]

Fluorouracil: I.V.: 2300 mg/m^2 continuous infusion day 1

[total dose/cycle = 2300 mg/m^2]

Leucovorin: I.V.: 500 mg/m^2 day 1

[total dose/cycle = 500 mg/m^2]

Repeat cycle weekly

or

Irinotecan: I.V.: 180 mg/m^2 day 1

[total dose/cycle = 180 mg/m^2]

Leucovorin: I.V.: 200 mg/m^2/day days 1 and 2

[total dose/cycle = 400 mg/m^2]

Fluorouracil: I.V.: 400 mg/m^2/day days 1 and 2

[total dose/cycle = 800 mg/m^2]

followed by I.V.: 600 mg/m^2/day continuous infusion days 1 and 2

[total dose/cycle = 1200 mg/m^2]

Repeat cycle every 2 weeks

Variation 3:

Irinotecan: I.V.: 175 mg/m^2 day 1

[total dose/cycle = 175 mg/m^2]

Leucovorin: I.V.: 250 mg/m^2 day 2

[total dose/cycle = 250 mg/m^2]

Fluorouracil: I.V.: 950 mg/m^2 day 2

[total dose/cycle = 950 mg/m^2]

or

Irinotecan: I.V.: 200 mg/m^2 day 1

[total dose/cycle = 200 mg/m^2]

Leucovorin: I.V.: 250 mg/m^2 day 2

[total dose/cycle = 250 mg/m^2]

Fluorouracil: I.V.: 850 mg/m^2 day 2

[total dose/cycle = 850 mg/m^2]

Repeat cycle every other week

References

Variation 1:

Van Cutsem E, Pozzo C, Starkhammar H, et al, “A Phase II Study of Irinotecan Alternated With Five Days Bolus of 5-Fluorouracil and Leucovorin in First-Line Chemotherapy of Metastatic Colorectal Cancer,” *Ann Oncol*, 1998, 9(11):1199-204. [PubMed 9862050]

Variation 2:

Douillard JY, Cunningham D, Roth AD, et al, “Irinotecan Combined With Fluorouracil Compared With Fluorouracil Alone as First-Line Treatment for Metastatic Colorectal Cancer: A Multicentre Randomised Trial,” *Lancet*, 2000, 355(9209):1041-7. [PubMed 10744089]

Variation 3:

Comella P, Casaretti F, De Vita F, et al, “Concurrent Irinotecan and 5-Fluorouracil Plus Levo-Folinic Acid Given Every Other Week in the First-Line Management of Advanced Colorectal Carcinoma: A Phase I Study of the Southern Italy Cooperative Oncology Group,” *Ann Oncol*, 1999, 10(8):915-21.[PubMed 10509152]

Fulvestrant

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(fool VES trant)
U.S. Brand NamesFaslodex®
Pharmacologic Category[Antineoplastic Agent, Estrogen Receptor Antagonist]
Use: Labeled IndicationsTreatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy
Use: Unlabeled/InvestigationalEndometriosis; uterine bleeding
Dosing: AdultsMetastatic breast cancer (postmenopausal women): I.M.: 250 mg at 1-month intervals
Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo dosage adjustment required.
Dosing: Hepatic ImpairmentUse in moderate-to-severe hepatic impairment has not been evaluated; use caution
Administration: I.M.I.M. injection into a relatively large muscle (ie, buttock); do not administer I.V., SubQ, or intra-arterially. May be administered as a single 5 mL injection or two concurrent 2.5 mL injections.
StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F).
ContraindicationsHypersensitivity to fulvestrant or any component of the formulation; contraindications to I.M. injections (bleeding diatheses, thrombocytopenia, or therapeutic anticoagulation); pregnancy
Allergy Considerations

- Furantoin Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; safety and efficacy have not been established in moderate-to-severe impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorD
Pregnancy ConsiderationsAntiestrogenic compounds have been associated with embryotoxicity, abnormalities in fetal development, and failure to maintain pregnancy in animal models. Approved for use only in postmenopausal women.
LactationExcretion in breast milk unknown/contraindicated
Breast-Feeding ConsiderationsApproved for use only in postmenopausal women.
Adverse Reactions

>10%:

Cardiovascular: Vasodilation (18%)

Central nervous system: Pain (19%), headache (15%)

Endocrine & metabolic: Hot flushes (19% to 24%)

Gastrointestinal: Nausea (26%), vomiting (13%), constipation (13%), diarrhea (12%), abdominal pain (12%)

Local: Injection site reaction (11%)

Neuromuscular & skeletal: Weakness (23%), bone pain (16%), back pain (14%)

Respiratory: Pharyngitis (16%), dyspnea (15%)

1% to 10%:

Cardiovascular: Edema (9%), chest pain (7%)

Central nervous system: Dizziness (7%), insomnia (7%), paresthesia (6%), fever (6%), depression (6%), anxiety (5%)

Dermatologic: Rash (7%)

Gastrointestinal: Anorexia (9%), weight gain (1% to 2%)

Genitourinary: Pelvic pain (10%), urinary tract infection (6%), vaginitis (2% to 3%)

Hematologic: Anemia (5%)

Neuromuscular & skeletal: Arthritis (3%)

Respiratory: Cough (10%)

Miscellaneous: Diaphoresis increased (5%)

<1%: Angioedema, hypersensitivity reactions, leukopenia, myalgia, thrombosis, urticaria, vaginal bleeding, vertigo

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringSee Administration for injection specifics. Assess therapeutic effectiveness and adverse response (eg, vasodilation, edema, gastrointestinal disturbances, dyspnea, pain) on a regular basis throughout therapy. Teach patient use (if self-administered - injection technique and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. If self-administered, follow directions for injection and syringe/needle disposal. You may experience bone pain, back pain, or headache (consult prescriber for approved analgesic); nausea, vomiting, or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or increased perspiration. Report persistent pain; chest pain or palpitations; swelling of extremities or unusual weight gain (>5 lb/week); cough of respiratory difficulty; burning on urination or changes in urinary pattern; or other persistent, unrelieved adverse effects. **Pregnancy/breast-feeding precautions**: Approved only for postmenopausal women. Severe fetal damage can occur with this drug. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Faslodex®: 50 mg/mL (2.5 mL, 5 mL) [contains alcohol, benzyl alcohol, benzyl stearate, castor oil]

Generic AvailableNo

ManufacturerAstraZeneca (distributor); Vetter Pharma-Fertigung GMBH & Co (manufacturer)

Mechanism of ActionSteroidal compound which competitively binds to estrogen receptors on tumors and other tissue targets, producing a nuclear complex that decreases DNA synthesis and inhibits estrogen effects. Fulvestrant has no estrogen-receptor agonist activity. Causes down-regulation of estrogen receptors and inhibits tumor growth.

Pharmacodynamics/Kinetics

Duration: I.M.: Plasma levels maintained for at least 1 month

Distribution: V_d: 3-5 L/kg

Protein binding: 99%

Metabolism: Hepatic via multiple pathways (CYP3A4 substrate, relative contribution to metabolism unknown)

Bioavailability: Oral: Poor

Half-life elimination: ~40 days

Time to peak, plasma: I.M.: 7-9 days

Excretion: Feces (>90%); urine (<1%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression, anxiety, insomnia, or dizziness

Mental Health: Effects on Psychiatric TreatmentGastrointestinal side effects are common, these effects may be additive with concurrent use of SSRIs, lithium, or valproate; rare reports of leukopenia; use caution with clozapine and carbamazepine; fluoxetine, fluvoxamine, and nefazodone may increase the serum levels and/or toxicity of fulvestrant; barbiturates and carbamazepine may decrease the therapeutic effect via increased metabolism

Index TermsICI-182,780; Zeneca 182,780; ZM-182,780

References

Bundred N and Howell A, “Fulvestrant (Faslodex): Current Status in the Therapy of Breast Cancer,” *Expert Rev Anticancer Ther*, 2002, 2(2):151-60. [PubMed 12113237]

Curran M and Wiseman L, “Fulvestrant,” *Drugs*, 2001, 61(6):807-13. [PubMed 11398912]

Wardley AM, “Fulvestrant: A Review of Its Development, Preclinical and Clinical Data,” *Int J Clin Pract*, 2002, 56(4):305-9.[PubMed 12074216]

International Brand NamesFaslodex (AR, AT, BE, BG, CH, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, MX, NL, NO, NZ, PT, RU, SE, SG, TR, TW, VE)

FUP

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Gastric Cancer

Regimen UseGastric cancer

Regimen

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 5000 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 2

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 28 days

References

Vanhoefer U, Rougier P, Wilke H, et al, âFinal Results of a Randomized Phase III Trial of Sequential High-Dose Methotrexate, Fluorouracil, and Doxorubicin Versus Etoposide, Leucovorin, and Fluorouracil Versus Infusional Fluorouracil and Cisplatin in Advanced Gastric Cancer: A Trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group,â *J Clin Oncol*, 2000, 18(14):2648-57.[PubMed 10894863]

Furazolidone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(fyoor a ZOE li done)

Canadian Brand NamesFuroxone®

Pharmacologic CategoryAntiprotozoal

Use: Labeled IndicationsTreatment of bacterial or protozoal diarrhea and enteritis caused by susceptible organisms *Giardia lamblia* and *Vibrio cholerae*

Dosing: AdultsDiarrhea/enteritis: Oral: 100 mg 4 times/day; not more than 8.8 mg/kg/day; treatment duration: 7 days

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDiarrhea/enteritis: Oral: Children >1 month: 5-8 mg/kg/day in 4 divided doses for 7 days, not to exceed 400 mg/day or 8.8 mg/kg/day

Dietary ConsiderationsAvoid tyramine-containing foods/beverages. Some examples include aged or matured cheese, air-dried or cured meats (including sausages and salamis), fava or broad bean pods, tap/draft beers, Marmite concentrate, sauerkraut, and soy sauce and other soybean condiments.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to furazolidone or any component of the formulation; concurrent use of ethanol; infants <1 month of age because of the possibility of producing hemolytic anemia; foods high in tyramine content

Allergy Considerations

- Furantoin Allergy

Warnings/Precautions

Special populations:

• G6PD deficiency: Use with caution in patients with G6PD deficiency when administering large doses for prolonged periods.

Other warnings/precautions:

• Monoamine oxidase: Inhibits monoamine oxidase.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown

Adverse Reactions

>10%: Genitourinary: Discoloration of urine (dark yellow to brown)

1% to 10%:

Central nervous system: Headache

Gastrointestinal: Abdominal pain, diarrhea, nausea, vomiting

<1%: Agranulocytosis, arthralgia, disulfiram-like reaction after ethanol ingestion, dizziness, drowsiness, fever, hemolysis in patients with G6PD deficiency, hypoglycemia, leukopenia, malaise, orthostatic hypotension, rash

Drug Interactions

Alcohol (Ethyl): Furazolidone may enhance the adverse/toxic effect of Alcohol (Ethyl). A disulfiram-like reaction may occur. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): MAO Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists (Indirect-Acting): MAO Inhibitors may enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Alpha1-Agonists: MAO Inhibitors may enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Alpha2-Agonists (Ophthalmic): MAO Inhibitors may enhance the hypertensive effect of Alpha2-Agonists (Ophthalmic). *Risk X: Avoid combination*

Altretamine: May enhance the orthostatic effect of MAO Inhibitors. *Risk C: Monitor therapy*

Amphetamines: MAO Inhibitors may enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Anilidopiperidine Opioids: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. *Risk D: Consider therapy modification*

Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor): MAO Inhibitors may enhance the serotonergic effect of Antidepressants (Serotonin/Norepinephrine Reuptake Inhibitor). This may cause serotonin syndrome. *Risk X: Avoid combination*

Atomoxetine: MAO Inhibitors may enhance the neurotoxic (central) effect of Atomoxetine. *Risk X: Avoid combination*

Beta2-Agonists: MAO Inhibitors may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: MAO Inhibitors may enhance the neurotoxic (central) effect of BuPROPion. *Risk X: Avoid combination*

BusPIRone: May enhance the adverse/toxic effect of MAO Inhibitors. Elevated blood pressure has been reported. *Risk X: Avoid combination*

COMT Inhibitors: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Cyclobenzaprine: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

Dexmethylphenidate: MAO Inhibitors may enhance the hypertensive effect of Dexmethylphenidate. *Risk X: Avoid combination*

Dextromethorphan: MAO Inhibitors may enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

Levodopa: May enhance the adverse/toxic effect of MAO Inhibitors. Of particular concern is the development of hypertensive reactions when levodopa is used with nonselective MAOI. *Risk D: Consider therapy modification*

Linezolid: MAO Inhibitors may enhance the adverse/toxic effect of Linezolid. *Risk X: Avoid combination*

Lithium: MAO Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Maprotiline: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

Meperidine: MAO Inhibitors may enhance the serotonergic effect of Meperidine. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methyldopa: MAO Inhibitors may enhance the adverse/toxic effect of Methyldopa. *Risk X: Avoid combination*

Methylphenidate: MAO Inhibitors may enhance the hypertensive effect of Methylphenidate. *Risk X: Avoid combination*

Mirtazapine: MAO Inhibitors may enhance the neurotoxic (central) effect of Mirtazapine. *Risk X: Avoid combination*

Propoxyphene: May enhance the adverse/toxic effect of MAO Inhibitors. Specifically, the risk of serotonin syndrome or other serotonergic adverse events may be increased. *Risk X: Avoid combination*

Rauwolfia Alkaloids: MAO Inhibitors may enhance the adverse/toxic effect of Rauwolfia Alkaloids. Existing MAOI therapy can result in paradoxical effects of added rauwolfia alkaloids (eg, excitation, hypertension). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: MAO Inhibitors may decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. **Exceptions:** Eletriptan; Frovatriptan; Naratriptan. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tetrabenazine: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

TraMADol: May enhance the neuroexcitatory and/or seizure-potentiating effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: MAO Inhibitors may enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (a disulfiram-like reaction may occur).

Food: Concurrent ingestion of foods rich in tyramine may cause sudden and severe high blood pressure (hypertensive crisis). Avoid tyramine-containing foods with MAO-Is. Food's freshness is also an important concern; improperly stored or spoiled food can create an environment where tyramine concentrations may increase.

Herb/Nutraceuticals: Avoid supplements containing caffeine, tyrosine, tryptophan, or phenylalanine. Ingestion of large quantities may increase the risk of severe side effects (eg, hypertensive reactions, serotonin syndrome).

Test InteractionsFalse-positive results for urine glucose with Clinitest®

Monitoring ParametersCBC

Nursing: Physical Assessment/MonitoringMonitor other medications patient may be taking for effectiveness and interactions. Avoid use of Clinitest® for patients with diabetes. Monitor for adequate hydration. Assess/teach patient the importance of appropriate diet. Patient should be cautioned against eating foods high in tyramine. See Tyramine Content of Foods list.

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy.

Patient EducationTake as directed. Avoid tyramine-containing foods and beverages during and for 4 days following therapy. Do not take any other prescription or OTC medications without consulting prescriber. Your urine may turn dark brown or yellow (normal). If you have diabetes, use something other than Clinitest® for urine glucose testing. Report acute GI pain, unresolved diarrhea, unresolved nausea or vomiting, fever, dizziness, or unusual joint pain. Consult prescriber if condition is not resolved at the end of therapy. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Liquid:

Furoxone® [CAN]: 50 mg/15 mL [not available in the U.S.]

Tablet:

Furoxone® [CAN]: 100 mg [not available in the U.S.]

Generic AvailableNo

ManufacturerRoberts Pharmaceuticals

Mechanism of ActionInhibits several vital enzymatic reactions causing antibacterial and antiprotozoal action

Pharmacodynamics/Kinetics

Absorption: Poor

Excretion: Urine (33% as active drug and metabolites)

Related Information

- Tyramine Content of Foods

Pharmacotherapy PearlsNot available in U.S.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; furazolidone inhibits MAO; caution with alcohol, anorexiants, antidepressants, meperidine, sympathomimetics, dopamine agonists, and tyramine-containing foods

Index TermsFuroxone

References

“Drugs for Parasitic Infections,” *Med Lett Drugs Ther*, 1993, 35(911):111-22. [PubMed 8246830]

Murphy TV and Nelson JD, “Five vs Ten Days' Therapy With Furazolidone for Giardiasis,” *Am J Dis Child*, 1983, 137(3):267-70. [PubMed 6823925]

Shulman KI and Walker SE, “A Reevaluation of Dietary Restrictions for Irreversible Monoamine Oxidase Inhibitors,” *Psychiatr Ann*, 2001, 31(6):378-84.

Shulman KI and Walker SE, “Refining the MAOI Diet: Tyramine Content of Pizzas and Soy Products,” *J Clin Psychiatry*, 1999, 60(3):191-3.[PubMed 10192596]

Turner JA, “Giardiasis and Infections With Dientamoeba Fragilis,” *Pediatr Clin North Am*, 1985, 32(4):865-80.[PubMed 3927250]

Walker SE, Shulman KI, Tailor SA, et al, “Tyramine Content of Previously Restricted Foods in Monoamine Oxidase Inhibitor Diets,” *J Clin Psychopharmacol*, 1996, 16(5):383-8.[PubMed 8889911]

International Brand NamesEnterar (IT); Enterocodil (BR); Enteroxon (IT); Furapill (EC); Furazolidon (PL); Furazon (JP); Furion (TH); Furoxane (FR); Furoxona (CN, CO, MX, PE, VE); Furoxone (DE, IN, IT, PH, PK); Giardil (AR); Giarlam (PT); Intefuran (IT); Neo Prodiar (ID); Nifulidone (IL); Nifuran (DE); Tanoton (AT)

Furosemide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Furosemide may be confused with torsemide

Lasix® may be confused with Esidrix®, Lanoxin®, Lidex®, Lomotil®, Luvox®, Luxiq®

International issues:

Urex® [Australia] may be confused with Eurax® which is a brand name for crotamiton in the U.S.

Urex® [Australia]: Brand name for methenamine in the U.S.

Pronunciation(fyoor OH se mide)

U.S. Brand NamesLasix®

Canadian Brand NamesApo-Furosemide®; Dom-Furosemide; Furosemide Injection, USP; Furosemide Special; Lasix®; Lasix® Special; Novo-Semide; Nu-Furosemide; PMS-Furosemide

Pharmacologic CategoryDiuretic, Loop

Use: Labeled IndicationsManagement of edema associated with congestive heart failure and hepatic or renal disease; alone or in combination with antihypertensives in treatment of hypertension

Dosing: Adults

Edema, CHF, or hypertension (diuresis):

Oral: 20-80 mg/dose initially increased in increments of 20-40 mg/dose at intervals of 6-8 hours; usual maintenance dose interval is twice daily or every day

Usual dosage range for hypertension (JNC 7): 20-80 mg/day in 2 divided doses

I.M., I.V.: 20-40 mg/dose, may be repeated in 1-2 hours as needed and increased by 20 mg/dose with each succeeding dose up to 1000 mg/day; usual dosing interval: 6-12 hours. **Note:** ACC/AHA 2005 guidelines for chronic congestive heart failure recommend a maximum single dose of 160-200 mg.

Continuous I.V. infusion: Initial I.V. bolus dose 20-40 mg, followed by continuous I.V. infusion doses of 10-40 mg/hour. If urine output is <1 mL/kg/hour, double as necessary to a maximum of 80-160 mg/hour. The risk associated with higher infusion rates (80-160 mg/hour) must be weighed against alternative strategies. **Note:** ACC/AHA 2005 guidelines for chronic congestive heart failure recommend 40 mg I.V. load, then 10-40 mg/hour infusion.

Refractory heart failure: Oral, I.V.: Doses up to 8 g/day have been used.

Dosing: ElderlyOral, I.M., I.V.: Initial: 20 mg/day; increase slowly to desired response.

Dosing: Pediatric

Edema, CHF, or hypertension (diuresis): Infants and Children:

Oral: 0.5-2 mg/kg/dose increased in increments of 1 mg/kg/dose with each succeeding dose until a satisfactory effect is achieved to a maximum of 6 mg/kg/dose no more frequently than 6 hours

I.M., I.V.: 1 mg/kg/dose, increasing by each succeeding dose at 1 mg/kg/dose at intervals of 6-12 hours until a satisfactory response up to 6 mg/kg/dose

Dosing: Renal Impairment

Acute renal failure: Doses up to 1-3 g/day may be necessary to initiate desired response; avoid use in oliguric states.

Not removed by hemo- or peritoneal dialysis; supplemental dose is not necessary.

Dosing: Hepatic ImpairmentDiminished natriuretic effect with increased sensitivity to hypokalemia and volume depletion in cirrhosis. Monitor effects, particularly with high doses.

Administration: I.V.I.V. injections should be given slowly. In adults, undiluted direct I.V. injections may be administered at a rate of 40 mg over 1-2 minutes; maximum rate of administration for IVPB or continuous infusion: 4 mg/minute. In children, a maximum rate of 0.5 mg/kg/minute has been recommended.

Administration: I.V. DetailAs a general guideline, I.V. bolus doses may be infused at a rate <20 mg/minute.

pH: 8-9.3

Administration: OralMay be taken with or without food.

Dietary ConsiderationsMay cause a potassium loss; potassium supplement or dietary changes may be required. Administer on an empty stomach. May be administered with food or milk if GI distress occurs. Do not mix with acidic solutions.

StorageFurosemide injection should be stored at controlled room temperature and protected from light. Exposure to light may cause discoloration. Do not use furosemide solutions if they have a yellow color. Refrigeration may result in precipitation or crystallization, however, resolubilization at room temperature or warming may be performed without affecting the drugs stability. I.V. infusion solution mixed in NS or D_5W solution is stable for 24 hours at room temperature.

ReconstitutionI.V. infusion solution may also be diluted for infusion 1-2 mg/mL (maximum: 10 mg/mL) over 10-15 minutes (following infusion rate parameters).

CompatibilityStable in D_5LR, D_5NS, D_5W, $D_{10}W$, $D_{20}W$, mannitol 20%, LR, NS.

Y-site administration: Compatible: Allopurinol, amifostine, amikacin, amphotericin B cholesteryl sulfate complex, aztreonam, bleomycin, cefepime, cisplatin, cladribine, cyclophosphamide, cytarabine, docetaxel, doxorubicin liposome, epinephrine, etoposide phosphate, fentanyl, fludarabine, fluorouracil, foscarnet, granisetron, heparin, hydrocortisone sodium succinate, hydromorphone, indomethacin, kanamycin, leucovorin, linezolid, lorazepam, melphalan, meropenem, methotrexate, mitomycin, nitroglycerin, norepinephrine, paclitaxel, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, sargramostim, tacrolimus, teniposide, thiotepa, tobramycin, tolazoline, vitamin B complex with C. **Incompatible:** Alatrofloxacin, amsacrine, chlorpromazine, ciprofloxacin, clarithromycin, diltiazem, droperidol, esmolol, filgrastim, fluconazole, gatifloxacin, gemcitabine, gentamicin, hydralazine, idarubicin, levofloxacin, metoclopramide, midazolam, milrinone, netilmicin, nicardipine, ondansetron, quinidine gluconate, thiopental, vecuronium, vinblastine, vincristine, vinorelbine. **Variable (consult detailed reference):** Cisatracurium, dobutamine, dopamine, doxorubicin, famotidine, labetalol, meperidine, morphine.

Compatibility in syringe: Compatible: Bleomycin, cisplatin, cyclophosphamide, fluorouracil, heparin, leucovorin, methotrexate, mitomycin. **Incompatible:** Doxapram, doxorubicin, droperidol, metoclopramide, milrinone, vinblastine, vincristine.

Compatibility when admixed: Compatible: Amikacin, aminophylline, ampicillin, atropine, bumetanide, calcium gluconate, cefamandole, cefoperazone, cefuroxime, cimetidine, dexamethasone sodium phosphate, diamorphine, digoxin, epinephrine, heparin, isosorbide, kanamycin, lidocaine, meropenem, morphine, nitroglycerin, penicillin G, potassium chloride, ranitidine, scopolamine, sodium bicarbonate, sulfadimidine, theophylline, tobramycin. **Incompatible:** Buprenorphine, chlorpromazine, diazepam, dobutamine, erythromycin lactobionate, isoproterenol, meperidine, metoclopramide, netilmicin, prochlorperazine edisylate, promethazine. **Variable (consult detailed reference):** Amiodarone, gentamicin, hydrocortisone sodium succinate, verapamil.

ContraindicationsHypersensitivity to furosemide, any component, or sulfonylureas; anuria; patients with hepatic coma or in states of severe electrolyte depletion until the condition improves or is corrected

Allergy Considerations

- Loop Diuretic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Fluid/electrolyte loss: Loop diuretics are potent diuretics; excess amounts can lead to profound diuresis with fluid and electrolyte loss; close medical supervision and dose evaluation are required. Watch for and correct electrolyte disturbances; adjust dose to avoid dehydration.
- Hyperuricemia: Asymptomatic hyperuricemia has been reported with use.
- Nephrotoxicity: Monitor fluid status and renal function in an attempt to prevent oliguria, azotemia, and reversible increases in BUN and creatinine; close medical supervision of aggressive diuresis required.
- Ototoxicity: Rapid I.V. administration, renal impairment, excessive doses, and concurrent use of other ototoxins is associated with ototoxicity.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonylurea allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Cirrhosis: In cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

Concurrent drug therapy issues:

- Antihypertensives: Coadministration of antihypertensives may increase the risk of hypotension.

Geriatric ConsiderationsLoop diuretics are potent diuretics; excess amounts can lead to profound diuresis with fluid and electrolyte loss; close medical supervision and dose evaluation is required, particularly in the elderly. Severe loss of sodium and/or increase in BUN can cause confusion. For any change in mental status in patients on furosemide, monitor electrolytes and renal function.

Pregnancy Risk FactorC

Pregnancy ConsiderationsCrosses the placenta. Increased fetal urine production, electrolyte disturbances reported. Generally, use of diuretics during pregnancy is avoided due to risk of decreased placental perfusion.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsCrosses into breast milk; may suppress lactation. AAP has NO RECOMMENDATION.

Adverse ReactionsFrequency not defined.

Cardiovascular: Acute hypotension, chronic aortitis, necrotizing angiitis, orthostatic hypotension, thrombophlebitis, sudden death from cardiac arrest (with I.V. or I.M. administration)

Central nervous system: Blurred vision, dizziness, fever, headache, lightheadedness, restlessness, vertigo, xanthopsia

Dermatologic: Cutaneous vasculitis, erythema multiforme, exfoliative dermatitis, photosensitivity, pruritus, purpura, rash, urticaria

Endocrine & metabolic: Gout, hyperglycemia, hyperuricemia, hypocalcemia, hypochloremia, hypokalemia, hypomagnesemia, hyponatremia, metabolic alkalosis

Gastrointestinal: Anorexia, constipation, cramping, diarrhea, intrahepatic cholestatic jaundice, ischemia hepatitis, nausea, oral and gastric irritation, pancreatitis, vomiting

Genitourinary: Urinary bladder spasm, urinary frequency

Hematological: Agranulocytosis (rare), anemia, aplastic anemia (rare), hemolytic anemia, leukopenia, purpura, thrombocytopenia

Neuromuscular & skeletal: Muscle spasm, paresthesia, weakness

Otic: Hearing impairment (reversible or permanent with rapid I.V. or I.M. administration), reversible deafness (with rapid I.V. or I.M. administration), tinnitus

Renal: Allergic interstitial nephritis, fall in glomerular filtration rate and renal blood flow (due to overdiuresis), glycosuria, transient rise in BUN, vasculitis

Miscellaneous: Anaphylaxis (rare), exacerbate or activate systemic lupus erythematosus

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

ACE Inhibitors: Loop Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aliskiren: May decrease the serum concentration of Furosemide. *Risk C: Monitor therapy*

Allopurinol: Loop Diuretics may enhance the adverse/toxic effect of Allopurinol. Loop Diuretics may increase the serum concentration of Allopurinol. Specifically, Loop Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoglycosides: Loop Diuretics may enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Loop Diuretics. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dofetilide: Loop Diuretics may enhance the QTc-prolonging effect of Dofetilide. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Loop Diuretics may diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Loop Diuretics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Phenytoin: May diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Furosemide serum levels may be decreased if taken with food.

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, and ginseng (may worsen hypertension). Limit intake of natural licorice. Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersMonitor weight and I & O daily; blood pressure, orthostasis, serum electrolytes, renal function; in high doses, monitor hearing
Nursing: Physical Assessment/MonitoringAssess for allergy to sulfonylurea before beginning therapy. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (especially anything that may impact fluid balance, electrolyte balance, or increase potential for ototoxicity or hypotension). For intravenous use, see Administration specifics. Assess results of laboratory

tests (electrolytes), therapeutic effectiveness, and adverse response on a regular basis during therapy (eg, dehydration, electrolyte imbalance, postural hypotension). Caution patients with diabetes about closely monitoring glucose levels (glucose tolerance may be decreased). Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum electrolytes, renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed with food or milk (to reduce GI distress) early in the day (daily), or if twice daily, take last dose in late afternoon in order to avoid sleep disturbance and achieve maximum therapeutic effect. Keep medication in original container, away from light; do not use discolored medication. Follow dietary advice of prescriber; include bananas or orange juice or other potassium-rich foods in daily diet. Do not take potassium supplements without advice of prescriber. If you have diabetes, monitor glucose levels closely (this medication may alter glucose tolerance requiring an adjustment in the dose of hypoglycemic agent). Weigh yourself each day, at the same time, in the same clothes when beginning therapy and weekly on long-term therapy. Report unusual or unanticipated weight gain or loss. May cause dizziness, blurred vision, or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from lying or sitting position or when climbing stairs); or sensitivity to sunlight (use sunblock or wear protective clothing and sunglasses). Report signs of edema (eg, weight gains; swollen ankles, feet, or hands), trembling, numbness or fatigue, cramping or muscle weakness, palpitations, unresolved nausea or vomiting, or change in hearing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 10 mg/mL (2 mL, 4 mL, 10 mL)

Injection, solution [preservative free]: 10 mg/mL (2 mL, 4 mL, 10 mL)

Solution, oral: 10 mg/mL (60 mL, 120 mL) [orange flavor]; 40 mg/5 mL (5 mL, 500 mL) [pineapple-peach flavor]

Tablet: 20 mg, 40 mg, 80 mg

Lasix®: 20 mg

Lasix®: 40 mg, 80 mg [scored]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Furosemide)

10 mg/mL (60): $16.99

10 mg/mL (120): $15.98

Tablets (Furosemide)

20 mg (100): $13.99

40 mg (100): $13.99

80 mg (30): $12.99

Tablets (Lasix)

20 mg (30): $20.60

40 mg (30): $23.86

80 mg (30): $30.37

Mechanism of ActionInhibits reabsorption of sodium and chloride in the ascending loop of Henle and distal renal tubule, interfering with the chloride-binding cotransport system, thus causing increased excretion of water, sodium, chloride, magnesium, and calcium

Pharmacodynamics/Kinetics

Onset of action: Diuresis: Oral: 30-60 minutes; I.M.: 30 minutes; I.V.: ~5 minutes

Peak effect: Oral: 1-2 hours

Duration: Oral: 6-8 hours; I.V.: 2 hours

Absorption: Oral: 60% to 67%

Protein binding: >98%

Metabolism: Minimally hepatic

Half-life elimination: Normal renal function: 0.5-1.1 hours; End-stage renal disease: 9 hours

Excretion: Urine (Oral: 50%, I.V.: 80%) within 24 hours; feces (as unchanged drug); nonrenal clearance prolonged in renal impairment

Related Information

- Heart Failure (Systolic)
- Hemodynamic Support, Intravenous
- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common

Mental Health: Effects on Psychiatric TreatmentOrthostatic hypotension is common; use caution with low potency antipsychotics and TCAs; may rarely cause agranulocytosis; caution with clozapine and carbamazepine; may decrease renal clearance of lithium resulting in elevated serum levels and risk for toxicity; more common with thiazide diuretics; monitor lithium levels

Cardiovascular ConsiderationsIt is important that patients be closely followed for hypokalemia, hypomagnesemia, and volume depletion because of significant diuresis.

Anesthesia and Critical Care Concerns/Other ConsiderationsIt is important that patients be closely followed for hypokalemia, hypomagnesemia, and volume depletion because of significant diuresis. If given the morning of surgery, it may render the patient volume depleted and blood pressure may be labile during general anesthesia.

Index TermsFrusemide

References

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Schuller D, Lynch JP, and Fine D, “Protocol-Guided Diuretic Management: Comparison of Furosemide by Continuous Infusion and Intermittent Bolus,” *Crit Care Med*, 1997, 25(12):1969-75.[PubMed 9403744]

International Brand NamesA-Basedock (JP); Accent (JP); Anfuramide (JP); Aquarid (ZA); Arasemide (JP); Cetasix (ID); Classic (ID); Daiteren F (JP); Depix (JP); Dirine (MY); Diural (DK, NO, SE); Diurefo (ID); Diuresal (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Diurin (NZ); Diusemide (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Diuspec (PH); Dryptal (IE); Edemid (HR); Errolon (AR); Femide 500 (TH); Foliront (JP); Fretic (PH); Frumid (MY); Frusebeta (AU); Frusedan (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Frusehexal (AU); Frusid (AU, HK, NZ); Fulsix (JP); Fuluvamide (JP); Furanthril (CZ); Furanturil (BG); Furesin (BR); Furetic (TH); Furide (TW); Furix (NO, SE); Furo-Puren (DE); Furomen (FI); Furomex (CZ); Furomin (FI); Furon (HU); Furorese (DE, LU); Furoscan (PH); Furosedon (JP); Furosemid (HR, HU); Furosemid Pharmavit (HU); Furosemid-ratiopharm (LU); Furosemide-Eurogenerics (LU); Furosemidum (PL); Furosemix (LU); Furosix (ID); Fursemid (HR); Fursemid[inj.] (HR); Furusemide (JP); Fusid (DE, IL); Hissuflux (CO); Impugan (DK, ID, SE); Jufurix (DE); Katlex (JP); Kofuzon (TW); Kutrix (JP); Lasiletten (NL); Lasilix (FR, MA); Lasix (AE, AT, AU, BB, BE, BF, BH, BJ, BM, BR, BS, BZ, CH, CI, CN, CR, CY, CZ, DE, DK, DO, EC, EG, ET, FI, GB, GH, GM, GN, GR, GT, GY, HK, HN, HR, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PK, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SV, SY, TH, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Lasix Retard (DK, EE, NL, NO, PT, SE); Lasix[inj.] (HR); Lowpston (JP); Luseck (JP); Maoread (JP); Naclex (ID); Nadis (TW); Naqua (HK); Nephron (AR); Odemase (DE); Odemex (CR, DO, EC, GT, HN, NI, PA, SV); Oedemex (AE, BH, CH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Pharmix (PH); Promedes (JP); Radisemide (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Radouna (JP); Rasitol (MY); Retep (AR); Seguril (ES); Suopinchon (MY); Synephron (JP); Trofurit (HU); Uremide (AU); Uresix (ID); Urex (HK, JP); Urex Forte (HK); Urex-M (AU)

Fusidic Acid

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(fyoo SI dik AS id)

Canadian Brand NamesFucidin®; Fucithalmic®

Pharmacologic CategoryAntibiotic, Miscellaneous

Use: Labeled Indications

Systemic: Treatment of skin and soft tissue infections, or osteomyelitis, caused by susceptible organisms, including *Staphylococcus aureus* (penicillinase-producing or nonpenicillinase strains); may be used in the treatment of pneumonia, septicemia, endocarditis, burns, and cystic fibrosis caused by susceptible organisms when other antibiotics have failed

Topical: Treatment of primary and secondary skin infections caused by susceptible organisms

Ophthalmic: Treatment of superficial infections of the eye and conjunctiva caused by susceptible organisms

Dosing: Adults

Susceptible infections: Oral, I.V.: 500 mg 3 times/day. (**Note:** Oral dosage may be increased to 1000 mg 3 times/day in fulminating infections.)

Superficial dermatologic infections: Topical: Apply to affected area 3-4 times/day until favorable results are achieved. If a gauze dressing is used, frequency of application may be reduced to 1-2 times/day.

Ophthalmic infections/conjunctivitis: Ophthalmic: Instill 1 drop in each eye every 12 hours for 7 days.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Susceptible infections: Children ≤12 years: I.V.: 20 mg/kg/day in 3 divided doses

Superficial dermatologic infections: Topical: Refer to adult dosing.

Ophthalmic infections/conjunctivitis: Ophthalmic: Children ≥2 years: Refer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment required.

Dosing: Hepatic ImpairmentOral, I.V.: Use with extreme caution in patients with hepatic impairment, and monitor liver function periodically during therapy.

Administration: I.V.Should not be administered I.M. or SubQ. Intravenous administration should be via a large bore vein with good blood flow. Administer over 2 hours or more. Do not administer with whole blood or amino acid solutions.

Dietary ConsiderationsMay take tablets with food to minimize gastrointestinal upset.

Storage

Cream: Store below 25°C.

Injection, powder for reconstitution: Store below 25°C.

Ointment: Store below 30°C.

Ophthalmic suspension: Store at 2°C to 25°C. Discard multidose vials 1 month after opening.

ReconstitutionInjection, powder for reconstitution: Reconstitute 500 mg vial of powder for injection by adding 10 mL of supplied diluent containing phosphate/citrate buffer. Reconstituted solution may be further diluted with NS or D_5W; should be used within 24 hours. Add to NS or D_5W to produce a final concentration of 1-2 mg/mL. For patients weighing <50 kg, reconstituted drug should be diluted at least 10-fold in a compatible solution. Discard solution if opalescence is observed.

CompatibilityStable in NS, D_5W, or LR.

Incompatible with whole blood or amino acid solutions.

Compatibility when admixed: Incompatible with calcium solutions, carbenicillin, gentamicin, kanamycin.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to fusidic acid or any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with extreme caution in hepatic impairment; monitor liver function regularly during treatment.

Dosage form specific issues:

- Phosphate/citrate buffer: Intravenous formulation contains phosphate/citrate buffer; excessive amounts may lead to hypocalcemia. Use with extreme caution in patients with pre-existing hypocalcemia.

Other warnings/precautions:

- Administration: Should not be administered I.M. or SubQ; local tissue injury may occur.

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Fusidic acid crosses the placenta. Use only when potential benefit exceeds possible risk to the fetus. Excreted in breast milk; safety in breast-feeding women has not been established. May displace bilirubin from albumin in neonates or preterm babies.

LactationEnters breast milk/use caution

Adverse Reactions

Cardiovascular: Edema (leg), thrombophlebitis, venospasm

Central nervous system: Dizziness, headache, psychic disturbance

Dermatologic: Pruritus, rash

Gastrointestinal: Anorexia, dyspepsia, diarrhea, epigastric distress, nausea, vomiting

Hepatic: Jaundice

Local: Injection site reaction (redness, irritation)

Ocular: Blurred vision

Ophthalmic suspension: Ocular: Transient stinging, tearing, eyelid edema, temporary blurred vision

Drug Interactions

Penicillins: Fusidic Acid may diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Fusidic Acid. Fusidic Acid may decrease the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Monitoring ParametersMonitor liver function tests, including bilirubin periodically during systemic therapy

Monitoring: Lab TestsMonitor liver function tests, including bilirubin periodically during systemic therapy

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Cream, as fusidic acid:

Fucidin®: 2% (15 g, 30 g)

Injection, powder for reconstitution, as sodium fusidate:

Fucidin®: 500 mg [packaged with 10 mL diluent/buffer solution]

Ointment, topical, as sodium fusidate:

Fucidin®: 2% (15 g, 30 g) [contains lanolin]

Suspension, ophthalmic, as fusidic acid:

Fucithalmic®: 10 mg/g [1%] (0.2 g) [unit-dose, without preservative]; (3 g, 5 g) [multidose, contains benzalkonium chloride]

Tablet, as sodium fusidate:

Fucidin®: 250 mg

Generic AvailableNo

ManufacturerLeo Pharma (Canada)

Mechanism of ActionInhibits protein synthesis by blocking aminoacyl-sRNA transfer to protein in susceptible bacteria.

Pharmacodynamics/Kinetics

Protein binding: 97%

Metabolism: Hepatic, to multiple metabolites

Half-life elimination: 5-6 hours

Time to peak, serum: Oral: 2-4 hours

Excretion: Feces (~100%, via bile)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsSodium Fusidate

International Brand NamesDifusin (TH); Foban (HK); Fucidin (AT, AU, BE, BG, CH, CL, CN, CO, CR, CZ, DK, DO, EE, FI, GB, GR, GT, HK, HN, ID, IE, IL, IN, IT, LU, MX, MY, NL, NO, PA, PE, PH, PK, PY, SE, SG, SV, TH, TW, UY, ZA); Fucidin [crème] (PL); Fucidine (DE, ES, FR); Fucithalmic (AT, BE, BG, CH, CL, CN, CO, CZ, DE, DK, EE, ES, FI, FR, GB, HK, HN, ID, IE, IL, IT, LU, MY, NL, NO, NZ, PH, PK, PT, SE, SG, TH, UY, ZA); Fumacin (KP); Fusimed (AR); Iretein (PE, PY); Parason (KP); Verutex (BR)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer
Regimen UseProstate cancer
Index TermsFlutamide + Goserelin
RegimenNOTE: Multiple variations are listed below.

Variation 1:

Flutamide: Oral: 250 mg every 8 hours

[total dose/cycle = 21,000 mg]

Goserelin acetate: SubQ: 3.6 mg day 1

[total dose/cycle = 3.6 mg]

Repeat cycle every 28 days

Variation 2:

Flutamide: Oral: 250 mg every 8 hours

[total dose/cycle = 67,500 mg]

Goserelin acetate: SubQ: 10.8 mg day 1

[total dose/cycle = 10.8 mg]

Repeat cycle every 3 months

References

McLeod DG, Schellhammer PF, Vogelzang NJ, et al, âExploratory Analysis on the Effect of Race on Clinical Outcome in Patients With Advanced Prostate Cancer Receiving Bicalutamide or Flutamide, Each in Combination With LHRH Analogues. The Casodex Combination Study Group,â *Prostate*, 1999, 40(4):218-24.[PubMed 10420149]

Gabapentin

Lexi-Drugs Online

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Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - February, 2008

The U.S. Food and Drug Administration (FDA) is informing healthcare professionals of an increased risk of suicidality (suicidal behavior or ideation) observed from analysis of clinical studies using various antiepileptic medications compared to placebo. The analysis was performed on 199 placebo-controlled studies involving 43,892 patients (27,863 treated patients versus 16,029 placebo patients) aged ≥5 years receiving one of the following 11 drugs: carbamazepine (Carbatrol®, Equetro™, Tegretol®, Tegretol® XR), felbamate (Felbatol®), gabapentin (Neurontin®), lamotrigine (Lamictal®), levetiracetam (Keppra®), oxcarbazepine (Trileptal®), pregabalin (Lyrica®), tiagabine (Gabitril®), topiramate (Topamax®), valproate (Depakote®, Depakote® ER, Depakene®, Depacon®), and zonisamide (Zonegran®). Studies examined medication efficacy in a variety of disorders, including epilepsy, psychiatric disorders (eg, depression, bipolar disorder), and other conditions (eg, migraine, neuropathic pain). According to the FDA, the results revealed a statistically significant increased risk of suicidality in 0.43% treated patients compared to 0.22% placebo patients, or an estimated 2.1 per 1000 (95% CI: 0.7, 4.2) more patients in the treated groups relative to placebo. This increased risk was reported anywhere from 1 week of therapy through 24 weeks. However, most trials were ≤24 weeks duration and the risk of suicide extending beyond 24 weeks is currently unknown. The relative risk of suicidal behavior or ideation in the treated patients was higher for patients with epilepsy (RR=3.6) compared to patients treated for psychiatric (RR=1.6) or other conditions (RR=2.3). Overall, the incidence of suicidal behavior or ideation occurred consistently across all demographic subgroups and with each of the drugs studied. Of note, four patients receiving an antiepileptic committed suicide relative to none in the placebo groups.

Forthcoming product labeling changes are likely to extend to all antiepileptic drugs and not limited to the drugs used in the studies, pending discussions scheduled for the upcoming advisory committee meeting. Healthcare professionals and family members/caregivers are encouraged to monitor patients receiving any antiepileptic medication for signs/symptoms of suicidality (eg, anxiety, depression, behavior changes). Patients should not stop taking their antiepileptic therapy unless advised by a healthcare professional.

Additional information can be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

Neurontin® may be confused with Neoral®, Noroxin®

Pronunciation(GA ba pen tin)
U.S. Brand NamesNeurontin®
Canadian Brand NamesApo-Gabapentin®; BCI-Gabapentin; Gen-Gabapentin; Neurontin®; Novo-Gabapentin; Nu-Gabapentin; PMS-Gabapentin
Pharmacologic CategoryAnticonvulsant, Miscellaneous
Use: Labeled IndicationsAdjunct for treatment of partial seizures with and without secondary generalized seizures in patients >12 years of age with epilepsy; adjunct for treatment of partial seizures in pediatric patients 3-12 years of age; management of postherpetic neuralgia (PHN) in adults
Use: Unlabeled/InvestigationalSocial phobia; chronic pain
Use: DentalNeuropathic pain (consult with physician)
Dosing: Adults

Anticonvulsant: Oral:

Initial: 300 mg 3 times/day, if necessary the dose may be increased up to 1800 mg/day

Maintenance: 900-1800 mg/day administered in 3 divided doses; doses of up to 2400 mg/day have been tolerated in long-term clinical studies; up to 3600 mg/day has been tolerated in short-term studies

Note: If gabapentin is discontinued or if another anticonvulsant is added to therapy, it should be done slowly over a minimum of 1 week.

Chronic pain (unlabeled use): Oral: 300-1800 mg/day given in 3 divided doses has been the most common dosage range

Postoperative pain (unlabeled use): 300-1200 mg 1-2 hours before surgery

Postherpetic neuralgia: Day 1: 300 mg, Day 2: 300 mg twice daily, Day 3: 300 mg 3 times/day; dose may be titrated as needed for pain relief (range: 1800-3600 mg/day, daily doses >1800 mg do not generally show greater benefit)

Dosing: ElderlyStudies in elderly patients have shown a decrease in clearance as age increases. This is most likely due to age-related decreases in renal function; dose reductions may be needed.

Dosing: Pediatric

Anticonvulsant: Oral

Children 3-12 years: Initial: 10-15 mg/kg/day in 3 divided doses; titrate to effective dose over ~3 days; dosages of up to 50 mg/kg/day have been tolerated in clinical studies

Children 3-4 years: Effective dose: 40 mg/kg/day in 3 divided doses

Children 5-12 years: Effective dose: 25-35 mg/kg/day in 3 divided doses

Children >12 years: Refer to adult dosing.

Note: If gabapentin is discontinued or if another anticonvulsant is added to therapy, it should be done slowly over a minimum of 1 week

Dosing: Renal ImpairmentChildren ≥12 years and Adults: See table.

Hemodialysis: Dialyzable

Gabapentin Dosing Adjustments in Renal Impairment

Creatinine Clearance (mL/min)	**Daily Dose Range**
≥60	300-1200 mg tid
>30-59	200-700 mg bid
>15-29	200-700 mg daily
15[1]	100-300 mg daily
Hemodialysis[2]	125-350 mg
[1] Cl_{cr}<15 mL/minute: Reduce daily dose in proportion to creatinine clearance.	
[2] Single supplemental dose administered after each 4 hours of hemodialysis	

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister first dose on first day at bedtime to avoid somnolence and dizziness. Dosage must be adjusted for renal function; when given 3 times daily, the maximum time between doses should not exceed 12 hours.

Dietary ConsiderationsMay be taken without regard to meals.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Extemporaneously PreparedA 100 mg/mL suspension was stable for 91 days when refrigerated or 56 days when kept at room temperature when compounded as follows:

Triturate sixty-seven 300 mg tablets in a mortar, reduce to a fine powder, then add a small amount of one of the following vehicles to make a paste; then add the remaining vehicle in small quantities while mixing:

Vehicle 1. Methylcellulose 1% (100 mL) and Simple Syrup N.F. (100 mL) mixed together in a graduate, **or**

Vehicle 2. Ora-Sweet® (100 mL) and Ora-Plus® (100 mL) mixed together in a graduate

Shake well before using and keep in refrigerator

Nahata MC, Morosco RS, and Hipple TF, *Stability of Gabapentin in Extemporaneously Prepared Suspensions at Two Temperatures*, American Society of Health System Pharmacists Midyear Meeting, December 7-11, 1997.

ContraindicationsHypersensitivity to gabapentin or any component of the formulation

Allergy Considerations

- Gabapentin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Renal impairment: Use with caution in patients with severe renal impairment; dose adjustment required.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <3 years of age. Children 3-12 years of age have shown increased incidence of CNS-related adverse effects, including emotional lability, hostility, thought disorder, and hyperkinesia.

Other warnings/precautions:

- Tumorigenic potential: Male rat studies demonstrated an association with pancreatic adenocarcinoma (clinical implication unknown).

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsStudies in the elderly have shown a decrease in clearance as age increases. This is most likely due to age-related decreases in renal function; calculations of Cl_{cr} recommended since dose reductions may be needed.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have documented teratogenic effects. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsGabapentin is excreted in human breast milk. A nursed infant could be exposed to ~1 mg/kg/day of gabapentin; the effect on the child is not known. Use in breast-feeding women only if the benefits to the mother outweigh the potential risk to the infant.

Adverse ReactionsAs reported in patients >12 years of age, unless otherwise noted in children (3-12 years)

>10%:

Central nervous system: Dizziness (17% to 28%; children 3%), somnolence (20%; children 8%), ataxia (13%), fatigue (11%)

Miscellaneous: Viral infection (children 11%)

1% to 10%:

Cardiovascular: Peripheral edema (2% to 8%), vasodilatation (1%)

Central nervous system: Fever (children 10%), hostility (children 8%), emotional lability (children 4%), fatigue (children 3%), headache (3%), ataxia (3%), abnormal thinking (2% to 3%; children 2%), amnesia (2%), depression (2%), dysarthria (2%), nervousness (2%), abnormal coordination (1% to 2%), twitching (1%), hyperesthesia (1%)

Dermatologic: Pruritus (1%), rash (1%)

Endocrine & metabolic: Hyperglycemia (1%)

Gastrointestinal: Diarrhea (6%), nausea/vomiting (3% to 4%; children 8%), abdominal pain (3%), weight gain (adults and children 2% to 3%), dyspepsia (2%), flatulence (2%), dry throat (2%), xerostomia (2% to 5%), constipation (2% to 4%), dental abnormalities (2%), appetite stimulation (1%)

Genitourinary: Impotence (2%)

Hematologic: Leukopenia (1%), WBC decreased (1%)

Neuromuscular & skeletal: Tremor (7%), weakness (6%), hyperkinesia (children 3%), abnormal gait (2%), back pain (2%), myalgia (2%), fracture (1%)

Ocular: Nystagmus (8%), diplopia (1% to 6%), blurred vision (3% to 4%), conjunctivitis (1%)

Otic: Otitis media (1%)

Respiratory: Rhinitis (4%), bronchitis (children 3%), respiratory infection (children 3%), pharyngitis (1% to 3%), cough (2%)

Miscellaneous: Infection (5%)

Postmarketing and additional clinical reports (limited to important or life-threatening): Acute renal failure, anemia, angina, angioedema, aphasia, arrhythmias (various), aspiration pneumonia, blindness, bradycardia, bronchospasm, cerebrovascular accident, CNS tumors, coagulation defect, colitis, Cushingoid appearance, dyspnea, encephalopathy, facial paralysis, fecal incontinence, glaucoma, glycosuria, heart block, hearing loss, hematemesis, hematuria, hemiplegia, hemorrhage, hepatitis, hepatomegaly, hyper-/hypotension, hyperlipidemia, hyper-/hypothyroidism, hyper-/hypoventilation, gastroenteritis, heart failure, leukocytosis, liver function tests increased, local myoclonus, lymphadenopathy, lymphocytosis, meningismus, MI, migraine, nephrosis, nerve palsy, non-Hodgkin's lymphoma, ovarian failure, pulmonary thrombosis, pericardial rub, pulmonary embolus, pericardial effusion, pericarditis, pancreatitis, peptic ulcer, purpura, paresthesia, palpitation, peripheral vascular disorder, pneumonia, psychosis, renal stone, retinopathy, skin necrosis, status epilepticus, subdural hematoma, suicidal behavior/ideation, syncope, tachycardia, thrombocytopenia, thrombophlebitis

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Does not change rate or extent of absorption.

Herb/Nutraceutical: Avoid evening primrose (seizure threshold decreased). Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsFalse positives have been reported with the Ames N-Multistix SG® dipstick test for urine protein

Monitoring ParametersMonitor serum levels of concomitant anticonvulsant therapy

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness, laboratory values, and adverse reactions at beginning of therapy and periodically with long-term use. Assess for CNS depression. Taper dosage slowly when discontinuing. Assess knowledge/teach patient safety and seizure precautions, appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsMonitor serum levels of concomitant anticonvulsant therapy. Routine monitoring of gabapentin levels is not mandatory.

Patient EducationTake exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results; may cause physical and/or psychological dependence. If prescribed once-a-day, take dose at bedtime. If taking antacids, take at least 2 hours after antacids. Do not stop medication abruptly, may lead to increased seizure activity. Avoid alcohol, caffeine, and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or anorexia (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); diarrhea (buttermilk, yogurt, or boiled milk may help); postural hypotension (use caution when climbing stairs or changing position from lying or sitting to standing); or decreased sexual function or libido (reversible). Report persistent CNS effects (nervousness, restlessness, insomnia, anxiety, excitation, headache, sedation, seizures, mania, abnormal thinking); suicidal ideation or depression; rash or skin irritation; muscle cramping, tremors, or change in gait; chest pain or palpitations; change in urinary pattern; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 100 mg, 300 mg, 400 mg

Neurontin®: 100 mg, 300 mg, 400 mg

Solution, oral:

Neurontin®: 250 mg/5 mL (480 mL) [cool strawberry anise flavor]

Tablet: 100 mg, 300 mg, 400 mg, 600 mg, 800 mg

Neurontin®: 600 mg, 800 mg

Generic AvailableYes: Capsule, tablet

ManufacturerPfizer Inc

Pricing: U.S. (www.drugstore.com)

Capsules (Gabapentin)

100 mg (90): $25.99

300 mg (90): $59.99

400 mg (90): $74.99

Capsules (Neurontin)

100 mg (100): $74.99

300 mg (30): $55.64

400 mg (30): $66.14

Solution (Neurontin)

250 mg/5 mL (470): $136.58

Tablets (Neurontin)

600 mg (90): $299.23

800 mg (90): $363.26

Mechanism of ActionGabapentin is structurally related to GABA. However, it does not bind to GABA_A or GABA_B receptors, and it does not appear to influence synthesis or uptake of GABA. High affinity gabapentin binding sites have been located throughout the brain; these sites correspond to the presence of voltage-gated calcium channels specifically possessing the alpha-2-delta-1 subunit. This channel appears to be located presynaptically, and may modulate the release of excitatory neurotransmitters which participate in epileptogenesis and nociception.

Pharmacodynamics/Kinetics

Absorption: 50% to 60% from proximal small bowel by L-amino transport system

Distribution: V_d: 0.6-0.8 L/kg

Protein binding: <3%

Bioavailability: Inversely proportional to dose due to saturable absorption:

900 mg/day: 60%

1200 mg/day: 47%

2400 mg/day: 34%

3600 mg/day: 33%

4800 mg/day: 27%

Half-life elimination: 5-7 hours; anuria 132 hours; during dialysis 3.8 hours

Excretion: Proportional to renal function; urine (as unchanged drug)

Related Information

- Anticonvulsants by Seizure Type
- Status Epilepticus

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), dry throat, and dental abnormalities.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentDouble-blind studies have failed to differentiate this drug from placebo when used as an adjunctive treatment for bipolar disorder. Gabapentin may be useful for some of the anxiety disorders.

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International Brand NamesBapex (MX); Blugat (MX); Dineurin (CN); Engaba (PK); Epiven (ID); Epleptin (ZA); Gaba-Act (KP); Gabadin (PY); Gabahexal (AU); Gabalep (KP); Gabantin (MX); Gabapenin (KP); Gabatin (CH, KP); Gabatine (AU); Gabax (PL); Gabexol (ID); Gabietal (EC); Ganin (ID); Gantin (AU); Gapridol (MX); Kaptin (CO); Nepatic (ID); Neuril (DK); Neurontin (AE, AR, AT, AU, BE, BG, BH, BO, BR, CH, CN, CO, CR, CY, CZ, DE, DO, EC, EE, EG, ES, FI, FR, GB, GR, GT, HK, HN, HU, ID, IE, IL, IN, IQ, IR, IT, JO, KE, KP, KW, LB, LY, MX, MY, NI, NL, NO, OM, PA, PE, PH, PL, PR, PT, PY, QA, SA, SE, SG, SV, SY, TH, TW, UY, VE, YE, ZA); Nopatic (MX); Nupentin (AU); Pendine (AU); Pengatine (KP)

Gadobenate Dimeglumine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(gad oh BEN ate dye MEG loo meen)

U.S. Brand NamesMultihance®; Multihance® Multipack™

Pharmacologic CategoryGadolinium-Containing Contrast Agent; Radiological/Contrast Media (Nonionic, High Osmolality); Radiological/Contrast Media, Paramagnetic Agent

Use: Labeled IndicationsContrast medium for magnetic resonance imaging (MRI) to visualize CNS lesions with abnormal vascularity in the brain, spine, and associated tissues

Dosing: Adults

CNS lesions: I.V.: 0.1 mmol/kg (0.2 mL/kg)

Dosing: ElderlyRefer to adult dosing. Monitor renal function.

Dosing: Renal ImpairmentUse caution; elimination half-life increases with decreased renal function, however, dose adjustment is not recommended.

Mild-to-moderate renal dysfunction: Use caution; extent of risk for NSF development is unknown

Severe renal dysfunction (GFR <30 mL/minute/1.73 m^2): Not recommended; consider alternatives to use

Hemodialysis: If administered to patients already receiving hemodialysis, consider prompt hemodialysis following exposure. Data has shown hemodialysis enhances gadolinium elimination with average gadolinium excretory rates of 78%, 96%, and 99% in the first, second, and third hemodialysis sessions, respectively.

Peritoneal dialysis: Likely to be less efficient at clearing gadolinium.

Dosing: Hepatic Impairment

Child-Pugh class B or C: Pharmacokinetics were not significantly altered.

Perioperative liver transplantation period or hepato-renal syndrome (with concomitant acute renal insufficiency, of any severity): Not recommended; consider alternatives to use.

Administration: I.V.Administer as rapid bolus injection. Flush line with NS 5 mL to ensure complete injection of medium.

Administration: I.V. DetailOsmolality: 1970 mOsmol/kg; ~7 times plasma osmolality (285 mOsmol/kg)

pH 6.5-7.5

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F); do not freeze. Once open, discard pharmacy bulk package after 8 hours.

ContraindicationsHypersensitivity to gadobenate dimeglumine, gadolinium, or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Nephrogenic systemic fibrosis (NSF): See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Arrhythmias: AV conduction changes and atrial/ventricular arrhythmias have been observed rarely with use; use with caution in patients with predisposing proarrhythmic conditions (metabolic or cardiac abnormalities, or concurrent drug therapy).
- Hypersensitivity reactions: Anaphylactic reactions have occurred rarely; monitor patients closely during and after infusion.
- Nephrogenic systemic fibrosis (NSF): **[U.S. Boxed Warning]: Gadolinium-based contrast agents (GBCAs) exposure may increase the risk for NSF** development in patients with acute or chronic severe renal insufficiency (GFR <30 mL/minute/1.73 m^2) or acute renal insufficiency, of any severity, due to hepatorenal syndrome or in patients during the perioperative liver transplantation period. Avoid use in those high risk patients unless use of GBCA enhanced imaging is essential for diagnostic purposes. NSF, a potentially fatal disease, affects the skin, muscle, and internal organs and can occur days to months after exposure. The potential risk of NSF development, if any, in patients with mild-to-moderate renal insufficiency or normal function is unknown; all patients should be screened for renal dysfunction prior to administration. Additional risk factors may include repeated exposure and exceeding dosage recommendations.

Disease-related concerns:

- Asthma/allergies: Use with caution in patients with history of asthma, allergy, drug reactions, or hypersensitivity disorders.

- Hemolytic/sickle cell anemia: Use in patients with sickle cell anemia, other hemoglobinopathies, or other hemolytic anemias has not been studied. Sickling, possibly leading to vaso-occlusive crisis, in sickle cell patients has been reported (rare, case reports) with use of hyperosmolar contrast solution; vaso-occlusion is believed to result form red blood cell dehydration following hyperosmolar contrast administration.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Metabolic disorders: Use with caution in patients with metabolic disorders such as Dubin Johnson syndrome.

- Renal impairment: Use with caution in patients with renal impairment; avoid use in severe impairment. Dose-dependent worsening of renal function or acute renal failure has occurred in patients with renal insufficiency, generally within 48 hours following adminstration.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Magnetic resonance angiography (MRA): Safety and efficacy have not been established for use in MRA.

- Scan interpretation: Use caution when interpreting a contrast-enhanced scan in the absence of a companion unenhanced noncontrast MRI.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects and increased intrauterine deaths were observed in some but not all animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsThe manufacturer recommends discontinuing breast-feeding for 24 hours following administration.

Adverse Reactions

1% to 10%:

Central nervous system: Headache (2% to 6%), dizziness (4%)

Gastrointestinal: Taste perversion (3%), nausea (2%)

<1%: Abdominal pain, albuminuria, alkaline phosphatase increased, anaphylactic reaction, anemia, aphasia, arrhythmia, ALT increased, AST increased, atrial fibrillation, back pain, basophilia, bilirubinemia, bradycardia, chest pain, chills, cold feeling, constipation, cough, diaphoresis, dyspepsia, dyspnea, ear pain, ECG abnormality, eye disorder, facial edema, fecal incontinence, fever, GGT increased, glycosuria, hematuria, hemiplegia, hemolysis, hyper-/hypoglycemia, hyperkalemia, hyperlipemia, hypertonia, hyperventilation, hypocalcemia, hypoesthesia, hyponatremia, hypoproteinemia, hypotension, infection, injection site inflammation, injection site pain, laryngismus, LDH increased, leukocytosis, leukopenia, lung edema, malaise, myalgia, myocardial ischemia, myositis, necrotizing pancreatitis (acute), pain, palpitation, paralysis, parosmia, peripheral edema, pruritus, pulmonary edema (acute), pulmonary embolus, rhinitis, salivation increased, seizure, serum iron increased, stupor, supraventricular extrasystoles, syncope, thirst, tinnitus, tremor, urinary frequency/urgency, urinary incontinence, urinary tract infection, urticaria, ventricular arrhythmia, ventricular extrasystoles, vision abnormal, weakness, xerostomia

Postmarketing and/or case reports: Anaphylactic shock, loss of consciousness, nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD; reported with another gadolinium-containing contrast agent)

Drug Interactions

Aldesleukin: Contrast Media (Non-ionic) may enhance the potential for allergic or hypersensitivity reactions to Aldesleukin. *Risk C: Monitor therapy*

Test InteractionsMay cause transient increase in serum ferritin, urine zinc (with renal disease), or bilirubin (with hepatic metabolic disorders)

Monitoring ParametersSigns of hypersensitivity (during and for several hours after procedure); renal function (prior to administration); short- and long-term monitoring of signs and symptoms of NSF (eg, burning, itching, swelling, hardening and/or tightening of skin, joint stiffness, deep hip or rib bone pain, muscle weakness, limited range of motion, and/or yellowed/raised spots on whites of eye)

Nursing: Physical Assessment/MonitoringEvaluate patient for contraindications prior to treatment (high risk of nephrogenic systemic fibrosis in patients with acute or chronic renal insufficiency). Assess other pharmacological or herbal products patient may be taking for potential interactions. See specific Administration instructions. Teach possible side effects/appropriate interventions and adverse symptoms to report.

Patient EducationThis product may only be administered by intravenous infusion. You may experience unusual taste, mild nausea, dizziness or headache. Report immediately any burning, pain, or swelling at infusion site or any acute headache or gastrointestinal effects, swelling, burning, itching or discoloration of skin, or unusual bone pain or pain in joints.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Multihance®: 529 mg/mL (5 mL, 10 mL, 15 mL, 20 mL)

Multihance® Multipack™: 529 mg/mL (50 mL, 100 mL) [pharmacy bulk package]

Generic AvailableNo

ManufacturerBracco Diagnostics

Mechanism of ActionGadobenate dimeglumine is a gadolinium-containing paramagnetic agent. Exposure to an external magnetic field induces a large local magnetic field in exposed tissues. This local magnetism disrupts water protons in the vicinity, resulting in a change in proton density and spin characteristics, which can be detected by the imaging device.

Pharmacodynamics/Kinetics

Distribution: V_d: 0.15-0.36 L/kg; does not cross intact blood brain barrier; distribution half-life: 0.072-0.68 hours

Half-life elimination:

Normal renal function: 0.9-2.6 hours

Cl_{cr} 30-60 mL/minute: 3-9 hours

Cl_{cr} 10-30 mL/minute: 6-12 hours

End-stage renal disease (without dialysis): 18-67 hours

Excretion: Urine (78% to 96%); feces

Pharmacotherapy PearlsContrast agents are generally classified as high-osmolar (≥1400 mOsm/kg), low-osmolar (780-800 mOsm/kg), or iso-osmolar (~300 mOsm/kg) relative to plasma osmolarity (~285 mOsmol/kg).

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsGadolinum-BOPTA; Gd-BOPTA

References

Centers for Disease Control, “Nephrogenic Fibrosing Dermopathy Associated with Exposure to Gadolinium-Containing Contrast Agents: St. Louis, Missouri,” *MMWR Weekly Rep*, 2007, 56(07):137-141

Grobner T, “Gadolinium - A Specific Trigger for the Development of Nephrogenic Fibrosing Dermopathy and Nephrogenic Systemic Fibrosis,” *Nephrol Dial Transplant*, 2006, 21(4):1104-8.[PubMed 16431890]

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Okada S, Katagiri K, Kumazaki T, et al, “Safety of Gadolinium Contrast Agent in Hemodialysis Patients,” *Acta Radiol*, 2001, 42(3):339-41.[PubMed 11350296]

Wanko SO, Telen MJ, “Transfusion Management in Sickle Cell Disease,” *Hematol Oncol Clin N Am*, 2005, 19(5):803-26.

Widmark JM, “Imaging-related Medications: A Class Overview,” *Proc(Bayl Univ Med Cent)*, 2007, 20(4):408-17.

International Brand NamesMultihance (BE, CH, CZ, DK, FI, IL, NO, NZ, SE)

Gadobutrol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Gadovist® may be confused with Magnevist®, Vasovist™

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(gad oh BYOO trol)

Canadian Brand NamesGadovist®

Pharmacologic CategoryGadolinium-Containing Contrast Agent; Radiological/Contrast Media (Nonionic, High Osmolality); Radiological/Contrast Media, Paramagnetic Agent

Use: Labeled IndicationsContrast medium for magnetic resonance imaging (MRI) of CNS lesions (brain, spine, and associated tissues); perfusion studies to diagnose stroke, or to detect focal cerebral ischemia or tumor perfusion; contrast-enhanced magnetic resonance angiography (CE-MRA)

Dosing: Adults

General CNS imaging: I.V.: 0.1 mmol/kg (0.1 mL/kg); if needed, a second dose of 0.1-0.2 mmol/kg (0.1-0.2 mL/kg) may be repeated once within 30 minutes of the first dose

Exclusion of metastatic or recurrent tumors: I.V.: 0. 3 mmol/kg (0.3 mL/kg)

Perfusion studies: I.V.: 0. 3 mmol/kg (0.3 mL/kg)

CE-MRA: I.V.:

- Imaging of a single field of view (FOV):
  - Patient weight <75 kg: 7.5 mL
  - Patient weight ≥75 kg: 10 mL
- Imaging >1 FOV:
  - Patient weight <75 kg: 15 mL
  - Patient weight ≥75 kg: 20 mL

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentUse caution; reduce dosing with renal impairment; no specific guideline available from manufacturer. With severe renal impairment, manufacturer recommends at least 3 hemodialysis sessions within 5 days of the administration of gadobutrol.

Dosing: Hepatic ImpairmentNo specific guideline available from manufacturer; however, based on exclusive renal excretion of gadobutrol, dose adjustment in hepatic impairment is likely unnecessary.

Administration: I.V.Administer as intravenous bolus injection only. Extravascular administration may result in tissue damage and pain. Flush line with NS to ensure complete injection of medium. Imaging should be completed within 45 minutes of injection.

Administration: I.V. DetailOsmolality: 1603 mOsmol/kg water

pH: 6.6-8

StorageStore at 15°C to 30°C (59°F to 86°F); protect from freezing.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to gadobutrol, gadolinium, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Hypersensitivity, including anaphylactic reactions (rare), may occur; appropriate equipment (eg, ventilator) and emergency medications (eg, epinephrine) should be available during use. Delayed reactions may also occur (hours-to-days following administration of contrast media). Patients with a history of allergic reactions and/or bronchial asthma may be at an increased risk for developing hypersensitivity reactions; use caution in these patients.

- Nephrogenic systemic fibrosis (NSF): Gadolinium-based contrast agent (GBCA) exposure may increase the risk for NSF development in patients with acute or chronic severe renal insufficiency (GFR <30 mL/minute/1.73 m^2) or acute renal insufficiency, of any severity, due to hepatorenal syndrome or in patients during the perioperative liver transplantation period. Avoid use in those high risk patients unless use of GBCA enhanced imaging is essential for diagnostic purposes. NSF, a potentially fatal disease, affects the skin, muscle, and internal organs and can occur days to months after exposure. The potential risk of NSF development, if any, in patients with mild-to-moderate renal insufficiency or normal function is unknown; all patients should be screened for renal dysfunction prior to administration. Additional risk factors may include repeated exposure and exceeding dosage recommendations.

- QT prolongation: Gadobutrol may prolong the QT interval. Females may be more susceptible than males. Use caution in patients with prior history of QT prolongation, current proarrhythmic states, hypokalemia, and those receiving Class Ia (eg, quinidine) or Class III (eg, amiodarone) antiarrhythmics. Patients at risk for QT prolongation should be monitored for at least one hour after administration of gadobutrol.

Disease-related concerns:

- Seizure disorder: Use with caution in patients with a history of seizure disorder; may lower seizure threshold. Injectable anticonvulsant agents should be readily available.

- Sickle cell anemia: In *in vitro* studies, deoxygenated sickle erythrocytes align perpendicular to a magnetic field; the enhancement of magnetic moment by contrast agents may potentiate this alignment possibly resulting in vaso-occlusive complications *in vivo*. Use in patients with sickle cell anemia or other hemoglobinopathies has not been studied.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsThe manufacturer recommends discontinuing breast-feeding for 24 hours following administration and discarding milk for that period.

Adverse Reactions

1% to 10%:

Cardiovascular: Vasodilation (1%)

Central nervous system: Headache (1%), dizziness (up to 1%)

Gastrointestinal: Nausea (1%), diarrhea (up to 1%), dysgeusia (1%), vomiting (up to 1%)

Neuromuscular & skeletal: Paresthesia (up to 3%)

<1% and/or frequency not defined: Abdominal pain, allergic reaction, apathy, aphasia, convulsion, diaphoresis, dyspnea, fever, hot flashes, hypoesthesia, infection, injection site pain, insomnia, palpitation, parosmia, postural hypotension, rash, urinary urgency, vertigo, vision abnormal, xerostomia

Drug Interactions

Aldesleukin: Contrast Media (Non-ionic) may enhance the potential for allergic or hypersensitivity reactions to Aldesleukin. *Risk C: Monitor therapy*

QTc-Prolonging Agents: Gadobutrol may enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Monitoring ParametersRenal function; signs of hypersensitivity (during and for several hours after procedure); short- and long-term monitoring of signs and symptoms of NSF/NFD (eg, burning, itching, swelling, hardening and/or tightening of skin, joint stiffness, deep hip or rib bone pain, muscle weakness, limited range of motion, and/or yellowed/raised spots on whites of eye); EKG (if concerns of prior history of QT_c interval changes)

Nursing: Physical Assessment/MonitoringUse caution in the presence of renal impairment (dose reduction may be necessary), proarrhythmic states, history of QT prolongation, hypokalemia, sickle cell anemia, or history of seizures. Assess potential for interactions with other pharmacological agents patient may be taking (eg, drugs known to cause prolonged QT interval). Teach patient possible side effects and adverse symptoms to report.

Monitoring: Lab TestsRenal function

Patient EducationThis medication can only be administered by infusion; you will be closely monitored during treatment. Report immediately unusual pain, headache, nausea, vomiting, or other unusual reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant or breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, solution [preservative free]:

Gadovist® [CAN]: 604.72 mg/mL (15 mL) [contains calcium sodium butrol 0.513 mg/mL and trometamol 1.211 mg/mL; not available in U.S.]

Generic AvailableNo

Manufacturer

Berlex Canada, Inc

Mechanism of ActionGadobutrol is a gadolinium-containing, nonionic paramagnetic agent. Exposure to an external magnetic field induces a large local magnetic field in exposed tissues. This local magnetism disrupts water protons in the vicinity, resulting in a change in proton density and spin characteristics, which can be detected by the imaging device.

Pharmacodynamics/Kinetics

Onset of action: ~15 minutes

Duration: ~45 minutes

Distribution: Rapid into extracellular space

Half-life elimination: Normal renal function: ~1.5 hours; severe renal dysfunction (Cl_{cr} <30 mL/minute: ~18-20 hours

Urine: (as unchanged drug); feces (negligible)

Index Terms Gadovist 1.0

References

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Goyen M, Lauenstein TC, Herborn CU, et al, “0.5 M Gd Chelate (Magnevist®) Versus 1.0 M Gd Chelate (Gadovist®): Dose-Independent Effect on Image Quality of Pelvic Three-Dimensional MR-Angiography,” *J Magn Res Imag*, 2001, 14(5):602-07.[PubMed 11747013]

Grobner T, “Gadolinium - A Specific Trigger for the Development of Nephrogenic Fibrosing Dermopathy and Nephrogenic Systemic Fibrosis,” *Nephrol Dial Transplant*, 2006, 21(4):1104-8.[PubMed 16431890]

Tomach B, Bremer C, Reimer P, et al, “Pharmacokinetics of 1M Gadobutrol in Patients With Chronic Renal Failure,” *Invest Radiol*, 2000, 35(1):35-40.[PubMed 10639034]

International Brand Names Gadovist (BE, BG, CZ, DK, EE, FI, IE, KP, NO, NZ, SE, ZA)

Gadodiamide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(gad oh DYE a mide)

U.S. Brand NamesOmniscan™

Pharmacologic CategoryGadolinium-Containing Contrast Agent; Radiological/Contrast Media (Nonionic, Low Osmolality); Radiological/Contrast Media, Paramagnetic Agent

Use: Labeled IndicationsContrast medium for magnetic resonance imaging (MRI) to visualize CNS lesions with abnormal vascularity in the brain, spine, and associated tissues, and to visualize body lesions with abnormal vascularity within the thoracic (noncardiac), abdominal, pelvic cavities, and retroperitoneal space

Dosing: Adults

Body imaging: I.V.:

Kidney: 0.05 mmol/kg (0.1 mL/kg); the safety of additional doses has not been studied

Intrathoracic (noncardiac), intra-abdominal, pelvic cavities: 0.1 mmol/kg (0.2 mL/kg); the safety of additional doses has not been studied

CNS imaging: 0.1 mmol/kg (0.2 mL/kg); if needed, a second dose of 0.2 mmol/kg (0.4 mL/kg) may be repeated once within 20 minutes of the first dose

Dosing: Elderly

Refer to adult dosing. Monitor renal function.

Dosing: Pediatric

Body imaging: Children ≥2 years: I.V.

Kidney: 0.05 mmol/kg (0.1 mL/kg); the safety of additional doses has not been studied

Intrathoracic (noncardiac), intra-abdominal, pelvic cavities: 0.1 mmol/kg (0.2 mL/kg)

CNS imaging: Children ≥2 years: I.V.: 0.1 mmol/kg (0.2 mL/kg); the safety of additional doses has not been studied

Dosing: Renal ImpairmentUse with caution; safety and efficacy have not been studied.

Mild-to-moderate renal dysfunction: Use caution; extent of risk for NSF development is unknown.

Severe renal dysfunction (GFR <30 mL/minute/1.73 m^2): Not recommended; consider alternatives to use.

Hemodialysis: If administered to patients already receiving hemodialysis, consider prompt hemodialysis following exposure. Data has been shown hemodialysis enhances gadolinium elimination with average gadolinium excretory rates of 78%, 96%, and 99% in the first, second, and third hemodialysis sessions, respectively.

Peritoneal dialysis: Likely to be less efficient at clearing gadolinium.

Dosing: Hepatic ImpairmentUse with caution; safety and efficacy have not been studied.

Perioperative liver transplantation period or hepatorenal syndrome (with concomitant acute renal insufficiency, of any severity): Not recommended; consider alternatives to use.

Administration: I.V.**For I.V. use only; not for intrathecal use.**Administer as bolus injection. Flush line with NS 5 mL to ensure complete injection of medium. Imaging should be completed within 60 minutes of injection.

Administration: I.V. DetailOsmolality: 789 mOsmol/kg water; ~3 times plasma osmolality (285 mOsmol/kg)

pH: 5.5-7

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F); protect from light. Do not freeze; do not use if inadvertently frozen.

ContraindicationsThere are no contraindications listed in manufacturer's labeling.

Warnings/Precautions

Boxed warnings:

- Nephrogenic systemic fibrosis (NSF): See “Concerns related to adverse effects” below.
- Not for intrathecal use: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Hypersensitivity reactions: Anaphylactic reactions have occurred rarely; monitor patients closely during and after infusion.
- Nephrogenic systemic fibrosis (NSF): **[U.S. Boxed Warning]: Gadolinium-based contrast agents (GBCAs) exposure may increase the risk for NSF** development in patients with acute or chronic severe renal insufficiency (GFR <30 mL/minute/1.73 m^2) or acute renal insufficiency, of any severity, due to hepatorenal syndrome or in patients during the perioperative liver transplantation period. Avoid use in those high risk patients unless use of GBCA enhanced imaging is essential for diagnostic purposes. NSF, a potentially fatal disease, affects the skin, muscle, and internal organs and can occur days to months after exposure. The potential risk of NSF development, if any, in patients with mild-to-moderate renal insufficiency or normal function is unknown; all patients should be screened for renal dysfunction prior to administration. Additional risk factors may include repeated exposure and exceeding dosage recommendations.

Disease-related concerns:

- Asthma/allergies: Use with caution in patients with history of asthma, allergy, drug reactions, or hypersensitivity disorders.
- Hemolytic/sickle cell anemia: Use in patients with sickle cell anemia, other hemoglobinopathies, or other hemolytic anemias has not been studied. Sickling, possibly leading to vaso-occlusive crisis, in sickle cell patients has been reported (rare, case reports) with use of hyperosmolar contrast solution; vaso-occlusion is believed to result form red blood cell dehydration following hyperosmolar contrast administration.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment; avoid use in severe impairment. Dose-dependent worsening of renal function or acute renal failure has occurred in patients with renal insufficiency, generally within 48 hours following adminstration.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Other warnings/precautions:

- Magnetic resonance angiography (MRA): Safety and efficacy have not been established for use in MRA.
- Not for intrathecal use: For I.V. use only. **[U.S. Boxed Warning]: Convulsions, coma, and sensory/motor neurologic deficits have occurred with inadvertent intrathecal administration.**
- Repeat dosing: Safety of repeat dosing has only been studied in adults for CNS studies. If repeat dosing is needed in children or non-CNS adult studies, and patient has normal renal function, an interval of at least 7 hours is suggested to allow normal clearance of drug from the body.
- Scan interpretation: Use caution when interpreting a contrast-enhanced scan in the absence of a companion unenhanced noncontrast MRI.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were observed in some but not all animal studies and may partially be due to maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Central nervous system: Dizziness (≤3%), headache (≤3%)

Gastrointestinal: Nausea (≤3%)

<1%: Abdominal pain, anaphylactoid reactions, anorexia, anxiety, arrhythmias, arthralgia, ataxia, cardiac failure, chest pain, coordination abnormal, diaphoresis, diarrhea, dyspnea, eructation, erythematous rash, fatigue, fever, flushing, hepatic dysfunction, hot flushes, injection site reaction, malaise, melena, MI, migraine, MS (aggravated), myalgia, pain, paresthesia, personality disorder, pruritus, rash, renal dysfunction (acute/reversible), rhinitis, rigors, seizure, skin discoloration, somnolence, syncope, taste loss, taste perversion, thrombophlebitis, tinnitus, tremor, urticaria, vasodilation, vision abnormal, vomiting, weakness, xerostomia

Postmarketing and/or case reports: Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD)

Drug Interactions

Aldesleukin: Contrast Media (Non-ionic) may enhance the potential for allergic or hypersensitivity reactions to Aldesleukin. *Risk C: Monitor therapy*

Test InteractionsTransitory changes in serum iron have been observed. May interfere with colorimetric tests for serum calcium (apparent decrease); alternate testing method is recommended for 12-24 hours after administration.

Monitoring ParametersSigns of hypersensitivity (during and for several hours after procedure); renal function (prior to administration); short- and long-term monitoring of signs and symptoms of NSF (eg, burning, itching, swelling, hardening and/or tightening of skin, joint stiffness, deep hip or rib bone pain, muscle weakness, limited range of motion, and/or yellowed/raised spots on whites of eye)

Nursing: Physical Assessment/MonitoringSee specific Administration instructions. Teach possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis product may only be administered by intravenous infusion. You may experience mild nausea, dizziness, or headache. Report immediately any burning, pain, or swelling at infusion site or any acute headache or gastrointestinal effects, swelling, burning, itching or discoloration of skin, or unusual bone pain or pain in joints.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Omniscan™: 287 mg/mL (5 mL, 10 mL, 15 mL, 20 mL, 50 mL) [contains caldiamide sodium 12 mg/mL; some packaging may contain natural latex/natural rubber]

Generic AvailableNo

ManufacturerAmersham Health

Mechanism of ActionGadodiamide is a gadolinium-containing paramagnetic agent. Exposure to an external magnetic field induces a large local magnetic field in exposed tissues. This local magnetism disrupts water protons in the vicinity, resulting in a change in proton density and spin characteristics, which can be detected by the imaging device.

Pharmacodynamics/Kinetics

Distribution: V_d: 139-261 mL/kg; does not cross intact blood-brain barrier; distribution half-life: 1-6 minutes

Half-life elimination: 62-94 minutes

Excretion: Urine (~95%)

Pharmacotherapy PearlsContrast agents are generally classified as high-osmolar (≥1400 mOsm/kg), low-osmolar (780-800 mOsm/kg), or iso-osmolar (~300 mOsm/kg) relative to plasma osmolarity (~285 mOsmol/kg).

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsGadolinium-DTPA-BMA; Gd-DTPA-BMA

References

Centers for Disease Control, "Nephrogenic Fibrosing Dermopathy Associated with Exposure to Gadolinium-Containing Contrast Agents: St. Louis, Missouri," *MMWR Weekly Rep*, 2007, 56(07):137-141.

Emerson J and Kost G, "Spurious Hypocalcemia After Omniscan- or Optimark-Enhanced Magnetic Resonance Imaging: An Algorithm for Minimizing a False-Positive Laboratory Value," *Arch Pathol Lab Med* , 2004, 128(10):1151-6.[PubMed 15387706]

Grobner T, "Gadolinium - A Specific Trigger for the Development of Nephrogenic Fibrosing Dermopathy and Nephrogenic Systemic Fibrosis," *Nephrol Dial Transplant*, 2006, 21(4):1104-8.[PubMed 16431890]

Okada S, Katagiri K, Kumazaki T, et al, "Safety of Gadolinium Contrast Agent in Hemodialysis Patients," *Acta Radiol*, 2001, 42(3):339-41.[PubMed 11350296]

Wanko SO, Telen MJ, "Transfusion Management in Sickle Cell Disease," *Hematol Oncol Clin N Am*, 2005, 19(5):803-26.

Widmark JM, "Imaging-related Medications: A Class Overview," *Proc(Bayl Univ Med Cent)*, 2007, 20(4):408-17.

International Brand NamesOmniscan (AU, BE, BG, BR, CH, CN, CO, CZ, DK, EE, FI, FR, HN, IL, IT, NL, NO, PL, PY, SE, UY, VE)

Gadofosveset

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Vasovist® may be confused with Magnevist®, Gadovist®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(gad oh FOS ve set)

Canadian Brand NamesVasovist®

Pharmacologic CategoryGadolinium-Containing Contrast Agent; Radiological/Contrast Media (Nonionic, Low Osmolality); Radiological/Contrast Media, Paramagnetic Agent

Use: Labeled IndicationsContrast medium used to enhance visualization of abdominal or limb vasculature in magnetic resonance angiography (MRA)

Dosing: Adults

MRA: I.V.: 0.03 mmol/kg (0.12 mL/kg); doses >0.03 mmol/kg are not recommended

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentManufacturer suggests use with caution in renal impairment, however no dosage adjustment is recommended.

Dosing: Hepatic ImpairmentNo dosage adjustment necessary for Child-Pugh class A and B. Use caution for Child-Pugh class C; no dosing recommendations provided with approved labeling.

Administration: I.V.Administer as an intravenous bolus injection at a rate not exceeding 1.5 mL/sec through a dedicated I.V. line separate from other medications. Flush line with 25-30 mL NS after administration to ensure complete injection of medium. Imaging should be completed within 1 hour of injection.

Administration: I.V. DetailOsmolality: 825 mOsmol/kg water

pH: 5.4-6.9

StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to gadofosveset, gadolinium, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Hypersensitivity, including anaphylactic reactions (rare), may occur; appropriate equipment (eg, ventilator) and emergency medications (eg, epinephrine) should be available during use. Delayed reactions may also occur (hours-to-days following administration of contrast media). Patients with a history of allergic reactions and/or bronchial asthma may be at an increased risk for developing hypersensitivity reactions; use caution in these patients.

- Nephrogenic systemic fibrosis (NSF): Gadolinium-based contrast agent (GBCA) exposure may increase the risk for NSF development in patients with acute or chronic severe renal insufficiency (GFR <30 mL/minute/1.73 m^2) or acute renal insufficiency, of any severity, due to hepatorenal syndrome or in patients during the perioperative liver transplantation period. Avoid use in those high risk patients unless use of GBCA enhanced imaging is essential for diagnostic purposes. NSF, a potentially fatal disease, affects the skin, muscle, and internal organs and can occur days to months after exposure. The potential risk of NSF development, if any, in patients with mild-to-moderate renal insufficiency or normal function is unknown; all patients should be screened for renal dysfunction prior to administration. Additional risk factors may include repeated exposure and exceeding dosage recommendations.

- QT_c prolongation: Rare cases of QT_c prolongation have been observed with gadofosveset use. Prolongation of the QT interval can increase the risk of torsade de pointes. Female and elderly patients may be more susceptible to torsade de pointes. Manufacturer states to use caution in patients with prior history of QT_c prolongation, current proarrhythmic states, electrolyte imbalances, and those receiving drugs whose use may be associated with QT_c interval prolongation. However, data from pooled safety studies demonstrated that the administration of gadofosveset resulted in minimal changes to the QT_c interval as compared to placebo (means of 2.8 msec and 3.2 msec respectively). Patients should be monitored for at least 1 hour after the administration of gadofosveset.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment.

- Hypoalbuminemia: Elimination of gadofosveset may be quicker in patients with decreased levels of serum albumin.

Concurrent drug therapy issues:

- Contrast agents: Safety and efficacy have not been studied for the use of gadofosveset in conjunction with other contrast agents (eg, iodine-containing, gadolinium based). Use caution in patients who have received iodine-containing agents within 72 hours or other gadolinium-based agents within 24 hours prior to gadofosveset administration.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsThe manufacturer recommends discontinuing breast-feeding for 24 hours following administration and discarding milk for that period.

Adverse Reactions

1% to 10% (observed with 0.03 mmol/kg dose):

Cardiovascular: QT_c prolongation (up to 7%; placebo up to 9%), vasodilatation (3%)

Central nervous system: Headache (2%)

Dermatologic: Pruritus (4%)

Gastrointestinal: Nausea (4%), taste disturbance (2%)

Neuromuscular & skeletal: Paresthesia (3%)

Miscellaneous: Burning sensation (2%), cold feeling (1%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening; observed in clinical studies using doses 0.005-0.10 mmol/kg): Anaphylactoid reaction, anemia, anxiety, arteriosclerosis, atrial fibrillation, AV block (first degree), bradycardia, chest pain, creatine phosphokinase increased, diaphoresis, diarrhea, dizziness, dyspnea, erythema, extravasation, glycosuria, hallucination, hematocrit decreased, hematuria, hemoglobin decreased, hyperglycemia, hypersensitivity, hyper-/hypotension, hypoalbuminemia, hypocalcemia, injection site pain, injection site thrombosis, lactate dehydrogenase increased, leukocytosis, microalbuminuria, muscle cramps, muscle spasms, myocardial ischemia, palpitation, phlebitis, polyuria, pyrexia, QT_c prolongation (>60 msec), respiratory depression, rigors, serum creatinine increased, tachycardia, thrombocytopenia, TIBC decreased, transaminases increased, tremor, urticaria, vomiting, weakness, xerostomia

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Monitoring ParametersBaseline ECG if risk factors for QT_c prolongation/torsade de pointes; baseline electrolytes (including potassium, calcium and magnesium); renal function; signs of hypersensitivity (during and for several hours after procedure); short- and long-term monitoring of signs and symptoms of NSF/NFD (eg, burning, itching, swelling, hardening and/or tightening of skin, joint stiffness, deep hip or rib bone pain, muscle weakness, limited range of motion, and/or yellowed/raised spots on whites of eye); patients should be monitored for at least 1 hour after administration of gadofosveset.

Nursing: Physical Assessment/MonitoringUse caution in the presence of severe renal impairment (dose reduction may be necessary), history of QT prolongation, hypersensitivity disorders, or asthma. Assess potential for interactions with other pharmacological or biological agents patient may be taking (eg, drugs known to cause prolonged QT interval). Teach patient possible side effects and adverse symptoms to report.

Monitoring: Lab TestsBaseline electrolytes (including potassium, calcium and magnesium), renal function

Patient EducationThis medication can only be administered by infusion; you will be closely monitored during treatment. Report immediately unusual pain, headache, nausea or vomiting, or other unusual reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant or breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, solution [preservative free]:

Vasovist® [CAN]: 0.25 mmoL/mL (10 mL, 15 mL, 20 mL) [not available in U.S.]

Generic AvailableNo

ManufacturerBayer Canada Inc

Mechanism of ActionGadofosveset is a gadolinium-containing paramagnetic agent that reversibly binds to albumin in the plasma. Exposure to an external magnetic field induces a large local magnetic field in exposed blood vessels. This local magnetism disrupts water protons in the vicinity, resulting in a change in proton density and spin characteristics, which can be detected by the imaging device. The binding of gadofosveset to albumin prolongs the period of time gadofosveset resides intravascularly, enhances T1 relaxivity up to 10 times greater than nonprotein bound gadolinium chelates and provides a longer imaging window.

Pharmacodynamics/Kinetics

Onset of action: ~15 minutes

Duration: ~1 hour

Distribution: V_{dss}: 0.132-0.164 L/kg

Protein binding: 75% to 96% to albumin

Metabolism: Negligible

Half-life elimination: ~16 hours; increases with moderate-to-severe renal impairment (Cl_{cr} <50 mL/minute)

Excretion: Urine (84% as unchanged drug); feces (~5%)

Index TermsGadofosveset Trisodium

References

Caravan P, Cloutier NJ, Greenfield MT, et al, “The Interaction of MS-325 With Human Serum Albumin and Its Effect on Proton Relaxation Rates,” *J Am Chem Soc*, 2002, 124(12): 3152-62.[PubMed 11902904]

Lauffer RB, Parmelee DJ, Dunham SU, et al, “MS-325: Albumin-Targeted Contrast Agent for MR Angiography,” *Radiology*, 1998, 207(2): 529-38.[PubMed 9577506]

Perreault P, Edelman MA, Baum RA, et al, “MR Angiography with Gadofosveset Trisodium for Peripheral Vascular Disease: Phase II Trial,” *Radiology*, 2003, 229(3):811-20.[PubMed 14593194]

Shamsi K, Yucel EK, and Chamberlin P, “A Summary of Safety of Gadofosveset (MS-325) at 0.03 mmol/kg Body Weight Dose,” *Invest Radiol*, 2006, 41(11): 822-30.[PubMed 17035873]

International Brand NamesVasovist (CH, CZ, DK, IE, SE)

Gadopentetate Dimeglumine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(gad oh PEN te tate dye MEG loo meen)

U.S. Brand NamesMagnevist®

Canadian Brand NamesMagnevist®

Pharmacologic CategoryGadolinium-Containing Contrast Agent; Radiological/Contrast Media (Ionic, High Osmolality); Radiological/Contrast Media, Paramagnetic Agent

Use: Labeled IndicationsContrast medium for magnetic resonance imaging (MRI) to visualize lesions with abnormal vascularity in the brain, spine and associated tissues, head and neck, and body (excluding the heart)

Dosing: AdultsMRI: I.V.: 0.1 mmol/kg (0.2 mL/kg)

Note: Dosing for patients >130 kg (286 pounds) has not been studied.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricMRI: I.V.: Children ≥2 years: Refer to adult dosing.

Dosing: Renal ImpairmentUse with caution.

Mild-to-moderate renal dysfunction: Use caution; extent of risk for NSF development is unknown.

Severe renal dysfunction (GFR <30 mL/minute/1.73 m^2): Not recommended; consider alternatives to use.

Hemodialysis: If administered to patients already receiving hemodialysis, consider prompt hemodialysis following exposure. Data has been shown hemodialysis enhances gadolinium elimination with average gadolinium excretory rates of 78%, 96%, and 99% in the first, second, and third hemodialysis sessions, respectively.

Peritoneal dialysis: Likely to be less efficient at clearing gadolinium.

Dosing: Hepatic ImpairmentUse with caution.

Perioperative liver transplantation period or hepatorenal syndrome (with concomitant acute renal insufficiency, of any severity): Not recommended; consider alternatives to use.

Administration: I.V.Dose should be administered at a rate not to exceed 10 mL per 15 seconds. Complete imaging procedure within 1 hour of injection. Following administration, flush line with NS 5 mL.

Administration: I.V. DetailOsmolality: 1960 mOsmol/kg water; ~7 times plasma osmolality (285 mOsmol/kg)

pH: 6.5-8.0

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F); do not freeze. Protect from light. If freezing does occur in the vial, place at room temperature for a minimum of 90 minutes. Ensure return to clear particulate-free solution prior to use.

ContraindicationsThere are no contraindications listed in manufacturer's labeling.

Warnings/Precautions

Boxed warnings:

- Nephrogenic systemic fibrosis (NSF): See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Hypersensitivity reactions: Anaphylactic reactions have occurred rarely; monitor patients closely during and after infusion.

- Nephrogenic systemic fibrosis (NSF): **[U.S. Boxed Warning]: Gadolinium-based contrast agents (GBCAs) exposure may increase the risk for NSF** development in patients with acute or chronic severe renal insufficiency (GFR <30 mL/minute/1.73 m^2) or acute renal insufficiency, of any severity, due to hepatorenal syndrome or in patients during the perioperative liver transplantation period. Avoid use in those high risk patients unless use of GBCA enhanced imaging is essential for diagnostic purposes. NSF, a potentially fatal disease, affects the skin, muscle, and internal organs and can occur days to months after exposure. The potential risk of NSF development, if any, in patients with mild-to-moderate renal insufficiency or normal function is unknown; all patients should be screened for renal dysfunction prior to administration. Additional risk factors may include repeated exposure and exceeding dosage recommendations.

Disease-related concerns:

- Asthma/allergies: Use with caution in patients with history of asthma, allergy, drug reactions, or hypersensitivity disorders.

- Hemolytic/sickle cell anemia: Use in patients with sickle cell anemia, other hemoglobinopathies, or other hemolytic anemias has not been studied. Sickling, possibly leading to vaso-occlusive crisis, in sickle cell patients has been reported (rare, case reports) with use of hyperosmolar contrast solution; vaso-occlusion is believed to result form red blood cell dehydration following hyperosmolar contrast administration.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment; avoid use in severe impairment. Dose-dependent worsening of renal function or acute renal failure has occurred in patients with renal insufficiency, generally within 48 hours following adminstration.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Other warnings/precautions:

- Injection site reactions: Site of contrast injection or limb may develop thrombosis with fasciitis, skin and soft tissue necrosis, and/or compartment syndrome requiring surgical intervention (rare); assess line patency prior to administration.

- Magnetic resonance angiography (MRA): Safety and efficacy have not been established for use in MRA.

- Repeat doses: Safety of repeat doses has not been studied.

- Scan interpretation: Use caution when interpreting a contrast-enhanced scan in the absence of a companion unenhanced noncontrast MRI.

Pregnancy Risk FactorC
Pregnancy ConsiderationsRetarded fetal development was noted in animal studies; congenital anomalies in animals have not been reported. There are no adequate and well-controlled studies in pregnant women.
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsFollowing administration of gadopentetate dimeglumine 0.1 mmol/kg, <0.04% gadolinium was excreted in breast milk within 24 hours. In an average 70 kg woman, this would be equivalent to <3 micromol of gadolinium transferred to a breast-feeding infant. The duration of excretion into breast milk and the possible effects to the infant are not known.
Adverse Reactions

1% to 10%:

Central nervous system: Headache (5%), dizziness (1%)

Gastrointestinal: Nausea (3%)

Local: Injection site coldness/localized coldness (2%)

<1%: Abdominal pain, agitation, anaphylactoid reaction, angina, anorexia, anxiety, arrhythmia, back pain, chest tightness, coldness (generalized), compartment syndrome, conjunctivitis, constipation, convulsions, cough, deep vein thrombophlebitis, diaphoresis, diarrhea, diplopia, drowsiness, dyspnea, ear pain, ECG changes (nonspecific), edema (local), epidermal necrolysis, erythema multiforme, eye irritation, eye pain, facial edema, fever, gastrointestinal distress, hypertension, hypotension; injection site reactions (burning, localized warmth, pain); lacrimation disorder, laryngismus, lymphangitis (regional), MI, migraine; nystagmus, pallor, paresthesia, pelvic pain, phlebitis, pruritus, pustules, rash, respiratory complaints, rhinorrhea, salivation increased, shivering, sneezing, stomach pain, stupor, substernal chest pain, syncope, tachycardia, taste abnormality, teeth pain, tension in extremities, thirst, throat irritation, thrombophlebitis, tinnitus, tiredness, trembling, urticaria, vasodilation, visual field defect, vomiting, warmth (generalized), weakness, wheezing, xerostomia

Postmarketing and/or case reports: Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD)

Drug InteractionsThere are no known significant interactions.
Test InteractionsTransitory changes in serum iron, bilirubin, and transaminase levels have been observed
Monitoring ParametersPatient and injection site should be monitored for signs of hypersensitivity for several hours following injection; renal function (prior to administration); short- and long-term monitoring of signs and symptoms of NSF (eg, burning, itching, swelling, hardening and/or tightening of skin, joint stiffness, deep hip or rib bone pain, muscle weakness, limited range of motion, and/or yellowed/raised spots on whites of eye)
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Magnevist®: Gadopentetate dimeglumine 469.01 mg/mL (5 mL, 10 mL, 15 mL, 20 mL, 50 mL, 100 mL)

Generic AvailableNo
ManufacturerBerlex Imaging
Mechanism of ActionExposure to an external magnetic field induces a large local magnetic field in gadopentetate exposed tissues. This local magnetism disrupts water protons in the vicinity, resulting in a change in proton density and spin characteristics, which can be detected by the imaging device.
Pharmacodynamics/Kinetics

Distribution: V_d: 223-309 mL/kg; does not cross intact blood-brain barrier; distribution half-life: 4-20 minutes

Half-life elimination: 1.5-1.7 hours

Excretion: Urine (~91% as gadopentetate)

Pharmacotherapy Pearls Contrast agents are generally classified as high-osmolar (≥1400 mOsm/kg), low-osmolar (780-800 mOsm/kg), or iso-osmolar (~300 mOsm/kg) relative to plasma osmolarity (~285 mOsmol/kg).

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness; may rarely cause agitation, anxiety, or sedation

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Gadolinium-DTPA; Gd-DTPA

References

Centers for Disease Control, “Nephrogenic Fibrosing Dermopathy Associated with Exposure to Gadolinium-Containing Contrast Agents: St. Louis, Missouri,” *MMWR Weekly Rep*, 2007, 56(07):137-141.

Grobner T, “Gadolinium - A Specific Trigger for the Development of Nephrogenic Fibrosing Dermopathy and Nephrogenic Systemic Fibrosis,” *Nephrol Dial Transplant*, 2006, 21(4):1104-8.[PubMed 16431890]

Okada S, Katagiri K, Kumazaki T, et al, “Safety of Gadolinium Contrast Agent in Hemodialysis Patients,” *Acta Radiol*, 2001, 42(3):339-41.[PubMed 11350296]

Wanko SO, Telen MJ, “Transfusion Management in Sickle Cell Disease,” *Hematol Oncol Clin N Am*, 2005, 19(5):803-26.

Widmark JM, “Imaging-related Medications: A Class Overview,” *Proc(Bayl Univ Med Cent)*, 2007, 20(4):408-17.

International Brand Names Magnetol (IL); Magnevist (BE, BG, CO, CZ, DK, EE, FI, HN, IN, NL, NO, NZ, PE, SE, UY, ZA); Magnevistan (BR, CN, VE); Megaray (KP); Viewgam (PY)

Gadoteridol

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(gad oh TER i dol)

U.S. Brand NamesProHance®

Pharmacologic CategoryGadolinium-Containing Contrast Agent; Radiological/Contrast Media (Nonionic, Low Osmolality); Radiological/Contrast Media, Paramagnetic Agent

Use: Labeled IndicationsContrast medium for magnetic resonance imaging (MRI) to visualize CNS lesions with abnormal vascularity in the brain, spine, and associated tissues and to visualize extracranial/extraspinal tissues in the head and neck

Dosing: Adults

CNS imaging: I.V.: 0.1 mmol/kg (0.2 mL/kg); if needed, a second dose of 0.2 mmol/kg (0.4 mL/kg) may be repeated once within 30 minutes of the first dose

Extracranial/extraspinal tissue: I.V.: 0.1 mmol/kg (0.2 mL/kg)

Dosing: PediatricCNS imaging: I.V.: Children ≥2 years: 0.1 mmol/kg (0.2 mL/kg); the safety of additional doses has not been studied

Dosing: Renal ImpairmentUse with caution; safety and efficacy have not been studied.

Mild-to-moderate renal dysfunction: Use caution; extent of risk for NSF development is unknown.

Severe renal dysfunction (GFR <30 mL/minute/1.73 m^2): Not recommended; consider alternatives to use.

Hemodialysis: If administered to patients already receiving hemodialysis, consider prompt hemodialysis following exposure. Data has been shown hemodialysis enhances gadolinium elimination with average gadolinium excretory rates of 78%, 96%, and 99% in the first, second, and third hemodialysis sessions, respectively.

Peritoneal dialysis: Likely to be less efficient at clearing gadolinium.

Dosing: Hepatic ImpairmentUse with caution; safety and efficacy have not been studied.

Perioperative liver transplantation period or hepatorenal syndrome (with concomitant acute renal insufficiency, of any severity): Not recommended; consider alternatives to use.

Administration: I.V.Administer as a rapid infusion (10-60 mL/minute) or as a bolus (>60 mL/minute). Flush line with NS 5 mL to ensure complete injection of medium. Imaging should be completed within 60 minutes of injection.

Administration: I.V. DetailOsmolality: 630 mOsmol/kg water; ~2 times plasma osmolality (285 mOsmol/kg)

pH: 6.5-8

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F); protect from light, do not freeze. If frozen, bring to room temperature for ≥60 minutes before use. Solution should be clear and colorless or slightly yellow. Discard any syringes that freeze; discard vials containing solids that do not redissolve. Once open, discard pharmacy bulk package after 8 hours.

ContraindicationsThere are no contraindications listed in manufacturer's labeling.

Warnings/Precautions

Boxed warnings:

- Nephrogenic systemic fibrosis (NSF): See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Hypersensitivity reactions: Anaphylactic reactions have occurred rarely; monitor patients closely during and after infusion.

- Nephrogenic systemic fibrosis (NSF): **[U.S. Boxed Warning]: Gadolinium-based contrast agents (GBCAs) exposure may increase the risk for NSF** development in patients with acute or chronic severe renal insufficiency (GFR <30 mL/minute/1.73 m^2) or acute renal insufficiency, of any severity, due to hepatorenal syndrome or in patients during the perioperative liver transplantation period. Avoid use in those high risk patients unless use of GBCA enhanced imaging is essential for diagnostic purposes. NSF, a potentially fatal disease, affects the skin, muscle, and internal organs and can occur days to months after exposure. The potential risk of NSF development, if any, in patients with mild-to-moderate renal insufficiency or normal function is unknown; all patients should be screened for renal dysfunction prior to administration. Additional risk factors may include repeated exposure and exceeding dosage recommendations.

Disease-related concerns:

- Asthma/allergies: Use with caution in patients with history of asthma, allergy, drug reactions, or hypersensitivity disorders.

- Hemolytic/sickle cell anemia: Use in patients with sickle cell anemia, other hemoglobinopathies, or other hemolytic anemias has not been studied. Sickling, possibly leading to vaso-occlusive crisis, in sickle cell patients has been reported (rare, case reports) with use of hyperosmolar contrast solution; vaso-occlusion is believed to result form red blood cell dehydration following hyperosmolar contrast administration.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment; avoid use in severe impairment. Dose-dependent worsening of renal function or acute renal failure has occurred in patients with renal insufficiency, generally within 48 hours following adminstration.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Other warnings/precautions:

- Magnetic resonance angiography (MRA): Safety and efficacy have not been established for use in MRA.

- Repeat doses: Repeated procedures have not been studied; safety of sequential doses has only been studied in adults in central nervous system during the same diagnostic session.

Pregnancy Risk FactorC
Pregnancy ConsiderationsPostimplantation loss was observed in animal studies; use during pregnancy only if clearly needed
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

1% to 10%: Gastrointestinal: Nausea (1%), taste perversion (1%)

<1%: Abdominal cramps, anaphylactoid reaction, anxiety, apnea, A-V nodal rhythm, bradycardia, cardiac arrest, chest pain, coordination loss, cough, cyanosis, deafness (transient), diaphoresis, diarrhea, dizziness, dysphagia, dyspnea, edema, facial edema, fever, flushing, gingivitis, headache, heart rate increased, hives, hyper/ hypotension, injection site pain/reactions, itching, laryngeal edema, laryngismus, loss of consciousness, macular papular rash, malaise, mental status decline, neck rigidity, pain, paresthesia, P-R interval prolonged, pruritus, rash, rhinitis, salivation increased, seizure, staring episode, stupor, syncope, tingling sensations, tinnitus, tongue edema/itching, tremor, urinary incontinence, urticaria, vasovagal reaction, voice alteration, vomiting, watery eyes, wheezing, xerostomia

Postmarketing and/or case reports: Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD; reported with another gadolinium-containing contrast agent)

Drug Interactions

Aldesleukin: Contrast Media (Non-ionic) may enhance the potential for allergic or hypersensitivity reactions to Aldesleukin. *Risk C: Monitor therapy*

Monitoring ParametersSigns of hypersensitivity (during and for several hours after procedure); renal function (prior to administration); short- and long-term monitoring of signs and symptoms of NSF (eg, burning, itching, swelling, hardening and/or tightening of skin, joint stiffness, deep hip or rib bone pain, muscle weakness, limited range of motion, and/or yellowed/raised spots on whites of eye)
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

ProHance®: 279.3 mg/mL (5 mL, 10 mL, 15 mL, 17 mL, 20 mL, 50 mL) [contains calteridol calcium 0.23 mg/mL and tromethamine 1.21 mg/mL; packaging may contain natural rubber/natural latex]

ProHance® Multipack™: 279.3 mg/mL (50 mL) [contains calteridol calcium 0.23 mg/mL and tromethamine 1.21 mg/mL; pharmacy bulk package]

Generic AvailableNo
ManufacturerBracco Diagnostics
Mechanism of ActionGadoteridol is a gadolinium-containing paramagnetic agent. Exposure to an external magnetic field induces a large local magnetic field in exposed tissues. This local magnetism disrupts water protons in the vicinity, resulting in a change in proton density and spin characteristics, which can be detected by the imaging device.
Pharmacodynamics/Kinetics

Distribution: V_d: 146-262 mL/kg; does not cross intact blood brain barrier; distribution half-life: ~0.2 hours

Half-life elimination: 1.49-1.65 hours

Excretion: Urine (~94%)

Pharmacotherapy PearlsContrast agents are generally classified as high-osmolar (≥1400 mOsm/kg), low-osmolar (780-800 mOsm/kg), or iso-osmolar (~300 mOsm/kg) relative to plasma osmolarity (~285 mOsmol/kg).
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms Gadolinium-HP-DO3A; Gd-HP-DO3A

References

Centers for Disease Control, “Nephrogenic Fibrosing Dermopathy Associated with Exposure to Gadolinium-Containing Contrast Agents: St. Louis, Missouri,” *MMWR Weekly Rep*, 2007, 56(07):137-141.

Grobner T, “Gadolinium - A Specific Trigger for the Development of Nephrogenic Fibrosing Dermopathy and Nephrogenic Systemic Fibrosis,” *Nephrol Dial Transplant*, 2006, 21(4):1104-8.[PubMed 16431890]

Okada S, Katagiri K, Kumazaki T, et al, “Safety of Gadolinium Contrast Agent in Hemodialysis Patients,” *Acta Radiol*, 2001, 42(3):339-41.[PubMed 11350296]

Wanko SO, Telen MJ, “Transfusion Management in Sickle Cell Disease,” *Hematol Oncol Clin N Am*, 2005, 19(5):803-26.

Widmark JM, “Imaging-related Medications: A Class Overview,” *Proc(Bayl Univ Med Cent)*, 2007, 20(4):408-17.

International Brand Names ProHance (AU, BE, CH, CZ, DK, FI, FR, IT, NL, NO, PL, SE)

Gadoversetamide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(gad oh ver SET a mide)

U.S. Brand NamesOptiMARK®

Pharmacologic CategoryGadolinium-Containing Contrast Agent; Radiological/Contrast Media (Nonionic, High Osmolality); Radiological/Contrast Media, Paramagnetic Agent

Use: Labeled IndicationsContrast medium for magnetic resonance imaging (MRI) to visualize lesions with abnormal vascularity in the liver or CNS (brain, spine, and associated tissues)

Dosing: Adults**CNS or liver lesions**: I.V.: 0.1 mmol/kg (0.2 mL/kg)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentUse with caution; elimination half-life increases with decreased renal function.

Mild-to-moderate renal dysfunction: Use caution; extent of risk for NSF development is unknown.

Severe renal dysfunction (GFR <30 mL/minute/1.73 m^2): Not recommended; consider alternatives to use.

Hemodialysis: If administered to patients already receiving hemodialysis, consider prompt hemodialysis following exposure. Data has been shown hemodialysis enhances gadolinium elimination with average gadolinium excretory rates of 78%, 96%, and 99% in the first, second, and third hemodialysis sessions, respectively.

Peritoneal dialysis: Likely to be less efficient at clearing gadolinium.

Dosing: Hepatic ImpairmentPharmacokinetics were not significantly altered.

Perioperative liver transplantation period or hepatorenal syndrome (with concomitant acute renal insufficiency, of any severity): Not recommended; consider alternatives to use.

Administration: I.V.Administer as rapid bolus injection over 1-2 mL/second. Flush line with NS 5 mL to ensure complete injection of medium. Imaging should be completed within 60 minutes of injection.

Administration: I.V. DetailOsmolality: 1110 mOsmol/kg water; ~4 times plasma osmolality (285 mOsmol/kg)

pH: 5.5-7.5

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F); protect from light; do not freeze. Once open, discard pharmacy bulk package after 4 hours.

ContraindicationsHypersensitivity to gadolinium, versetamide, or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Nephrogenic systemic fibrosis (NSF): See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Hypersensitivity reactions: Anaphylactic reactions have occurred rarely; monitor patients closely during and after infusion.
- Nephrogenic systemic fibrosis (NSF): **[U.S. Boxed Warning]: Gadolinium-based contrast agents (GBCAs) exposure may increase the risk for NSF** development in patients with acute or chronic severe renal insufficiency (GFR <30 mL/minute/1.73 m^2) or acute renal insufficiency, of any severity, due to hepatorenal syndrome or in patients during the perioperative liver transplantation period. Avoid use in those high risk patients unless use of GBCA enhanced imaging is essential for diagnostic purposes. NSF, a potentially fatal disease, affects the skin, muscle, and internal organs and can occur days to months after exposure. The potential risk of NSF development, if any, in patients with mild-to-moderate renal insufficiency or normal function is unknown; all patients should be screened for renal dysfunction prior to administration. Additional risk factors may include repeated exposure and exceeding dosage recommendations.

Disease-related concerns:

- Asthma/allergies: Use with caution in patients with history of asthma, allergy, drug reactions, or hypersensitivity disorders.
- Hemolytic/sickle cell anemia: Use in patients with sickle cell anemia, other hemoglobinopathies, or other hemolytic anemias has not been studied. Sickling, possibly leading to vaso-occlusive crisis, in sickle cell patients has been reported (rare, case reports) with use of hyperosmolar contrast solution; vaso-occlusion is believed to result form red blood cell dehydration following hyperosmolar contrast administration.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment; avoid use in severe impairment. Dose-dependent worsening of renal function or acute renal failure has occurred in patients with renal insufficiency, generally within 48 hours following adminstration.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Magnetic resonance angiography (MRA): Safety and efficacy have not been established for use in MRA.

- Repeat doses: Safety of repeat doses has not been studied.

- Scan interpretation: Use caution when interpreting a contrast-enhanced scan in the absence of a companion unenhanced noncontrast MRI.

Pregnancy Risk FactorC
Pregnancy ConsiderationsDecreased neonatal weight and cardiac abnormalities were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsThe manufacturer recommends discontinuing breast-feeding and discard breast milk for 72 hours following administration.
Adverse Reactions

1% to 10%:

Cardiovascular: Vasodilation (6%), QT_c prolongation (≥61 msec, 3%)

Central nervous system: Headache (9%), dizziness (4%), pain (1%)

Gastrointestinal: Taste perversion (6%), nausea (3%), abdominal pain (2%), diarrhea (2%), dyspepsia (1%)

Local: Injection site reaction (2%)

Neuromuscular & skeletal: Paresthesia (2%), weakness (2%), back pain (1%)

Respiratory: Rhinitis (2%)

<1%: Agitation, allergic reaction, amblyopia, anorexia, anxiety, appetite increased, arrhythmia, arthralgia, asthma, chest pain, confusion, conjunctivitis, constipation, cough, creatinine increased, depersonalization, diaphoresis, diplopia, dry skin, dysphagia, dyspnea, dystonia, dysuria, edema, epistaxis, eructation, erythema multiforme, facial edema, fever, flatulence, flu-like syndrome, hallucinations, hemoptysis, hyperacusis, hypercalcemia, hyper-/hypoglycemia, hyper-/hypotension, hypertonia, hypoesthesia, hyponatremia, injection site edema, injection site reactions, laryngismus, leg cramps, malaise, mucous membrane discharge, myalgia, myasthenia, neck pain, neck rigidity, nervousness, oliguria, palpitation, pallor, parosmia, pelvic pain, pharyngitis, pruritus, rash (maculopapular and vesiculous bullous), salivation increased, sinusitis, somnolence, spasm, syncope, tachycardia, thirst, thrombocytopenia, thrombophlebitis, tinnitus, tremor, urinary frequency, urticaria, vasospasm, vertigo, voice alteration, vomiting, xerostomia

Postmarketing and/or case reports: Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD), seizure

Drug Interactions

Aldesleukin: Contrast Media (Non-ionic) may enhance the potential for allergic or hypersensitivity reactions to Aldesleukin. *Risk C: Monitor therapy*

Test InteractionsMay cause transient changes in serum iron, copper or zinc. May interfere with colorimetric tests for serum calcium (apparent decrease); alternate testing method is recommended for 12-24 hours after administration.
Monitoring ParametersSigns of hypersensitivity (during and for several hours after procedure); renal function (prior to administration); short- and long-term monitoring of signs and symptoms of NSF (eg, burning, itching, swelling, hardening and/or tightening of skin, joint stiffness, deep hip or rib bone pain, muscle weakness, limited range of motion, and/or yellowed/raised spots on whites of eye)
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

OptiMARK®: 330.9 mg/mL (5 mL, 10 mL, 15 mL, 20 mL, 30 mL, 50 mL) [contains versetamide sodium 28.4 mg/mL and calcium chloride dihydrate 0.7 mg/mL]

Generic AvailableNo
ManufacturerMallinckrodt
Mechanism of ActionGadoversetamide is a paramagnetic agent formed by the chelation of gadolinium and versetamide. Exposure to an external magnetic field induces a large local magnetic field in exposed tissues. This local magnetism disrupts water protons in the vicinity, resulting in a change in proton density and spin characteristics, which can be detected by the imaging device.
Pharmacodynamics/Kinetics

Distribution: V_d: 137-187 mL/kg; does not cross intact blood brain barrier; distribution half-life: 6.5-20 minutes

Half-life elimination: 84-123 minutes

Excretion: Urine (~96%)

Pharmacotherapy Pearls Contrast agents are generally classified as high-osmolar (≥1400 mOsm/kg), low-osmolar (780-800 mOsm/kg), or iso-osmolar (~300 mOsm/kg) relative to plasma osmolarity (~285 mOsmol/kg).

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Gadolinium-DTPA-BMEA; Gd-DTPA-BMEA

References

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Emerson J and Kost G, "Spurious Hypocalcemia After Omniscan- or Optimark-Enhanced Magnetic Resonance Imaging: An Algorithm for Minimizing a False-Positive Laboratory Value," *Arch Pathol Lab Med* , 2004, 128(10):1151-6.[PubMed 15387706]

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Wanko SO, Telen MJ, "Transfusion Management in Sickle Cell Disease," *Hematol Oncol Clin N Am*, 2005, 19(5):803-26.

Widmark JM, "Imaging-related Medications: A Class Overview," *Proc(Bayl Univ Med Cent)*, 2007, 20(4):408-17.

International Brand Names OptiMARK (AR, PE, PY, UY)

Galantamine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Razedyne™ may be confused with Rozerem™

Reminyl® may be confused with Amaryl®

Due to patient safety concerns regarding prescribing and dispensing errors between Reminyl® and Amaryl®, Reminyl® (galantamine) is being renamed to Razadyne™ (immediate-release) and Razadyne™ ER (extended-release). The brand name Reminyl® was discontinued with the July, 2005 distribution of Razadyne™.

Pronunciation(ga LAN ta meen)

U.S. Brand NamesRazadyne™; Razadyne™ ER; Reminyl® [DSC]

Canadian Brand NamesReminyl®; Reminyl® ER

Pharmacologic CategoryAcetylcholinesterase Inhibitor (Central)

Use: Labeled IndicationsTreatment of mild-to-moderate dementia of Alzheimer's disease

Use: Unlabeled/InvestigationalSevere dementia associated with Alzheimer's disease; mild-to-moderate dementia associated with Parkinson's disease; Lewy body dementia

Dosing: Adults

Alzheimer's dementia (mild-to-moderate): Oral:

Immediate release tablet or solution: Mild-to-moderate dementia of Alzheimer's: Initial: 4 mg twice a day for 4 weeks; if tolerated, increase to 8 mg twice daily for ≥4 weeks; if tolerated, increase to 12 mg twice daily

Range: 16-24 mg/day in 2 divided doses

Extended-release capsule: Initial: 8 mg once daily for 4 weeks; if tolerated, increase to 16 mg once daily for ≥4 weeks; if tolerated, increase to 24 mg once daily

Range: 16-24 mg once daily

Note: Oral solution and tablet should be taken with breakfast and dinner; capsule should be taken with breakfast. If therapy is interrupted for ≥3 days, restart at the lowest dose and increase to current dose.

Conversion to galantamine from other cholinesterase inhibitors: Patients experiencing poor tolerability with donepezil or rivastigmine should wait until side effects subside or allow a 7-day washout period prior to beginning galantamine. Patients not experiencing side effects with donepezil or rivastigmine may begin galantamine therapy the day immediately following discontinuation of previous therapy (Morris, 2001).

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Moderate renal impairment: Maximum dose: 16 mg/day.

Severe renal dysfunction (Cl_{cr} <9 mL/minute): Use is not recommended

Dosing: Hepatic Impairment

Moderate liver dysfunction (Child-Pugh score 7-9): Maximum dose: 16 mg/day

Severe liver dysfunction (Child-Pugh score 10-15): Use is not recommended

Calculations

- Creatinine Clearance: Adults

Administration: OralAdminister oral solution or tablet with breakfast and dinner; administer extended release capsule with breakfast. If therapy is interrupted for ≥3 days, restart at the lowest dose and increase to current dose. If using oral solution, mix dose with 3-4 ounces of any nonalcoholic beverage; mix well and drink immediately.

Dietary Considerations

Administration with food is preferred, but not required; should be taken with breakfast and dinner (tablet or solution) or with breakfast (capsule).

StorageStore at 15°C to 30°C (59°F to 86°F). Do not freeze oral solution; protect from light.

ContraindicationsHypersensitivity to galantamine or any component of the formulation; severe liver dysfunction (Child-Pugh score 10-15); severe renal dysfunction (Cl_{cr} <9 mL/minute)

Warnings/Precautions

Concerns related to adverse effects:

- Anorexia/weight loss: May cause anorexia and/or weight loss.
- Diarrhea: May cause diarrhea.
- Nausea/vomiting: May cause nausea and/or vomiting.
- Vagotonic effects: Cholinesterase inhibitors may have vagotonic effects which may cause bradycardia and/or heart block with or without a history of cardiac disease.

Disease-related concerns:

- Cardiac conduction abnormalities: Use with caution in patients with sick-sinus syndrome, bradycardia, or conduction abnormalities. Alzheimer's treatment guidelines consider bradycardia to be a relative contraindication for use of centrally-active cholinesterase inhibitors.
- Hepatic impairment: Use with caution in patients with mild to moderate liver impairment; not recommended in severe impairment.
- Peptic ulcer disease: Use with caution in patients at risk of ulcer disease (eg, previous history or NSAID use); may increase gastric acid secretion. Monitor for symptoms of bleeding.
- Renal impairment: Use with caution in patients with moderate renal impairment; not recommended in severe impairment (Cl_{cr} <9 mL/minute).
- Respiratory disease: Use with caution in patients with COPD and/or asthma.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.
- Urinary tract obstruction: Use with caution in patients with bladder outlet obstruction or prostatic hyperplasia; cholinomimetics may cause or worsen outflow obstructions, including possible exacerbation of BPH symptoms.

Concurrent drug therapy issues:

- Depolarizing neuromuscular-blocking agents: May exaggerate neuromuscular blockade effects of depolarizing neuromuscular-blocking agents like succinylcholine.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo dosage adjustment needed.

Pregnancy Risk FactorB

Pregnancy ConsiderationsIn animal studies, there was a slight increased in the incident of skeletal variations when given during organogenesis. Adequate, well-controlled studies in pregnant women do not exist. Should be used in pregnancy only if benefit outweighs potential risk to the fetus.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%: Gastrointestinal: Nausea (6% to 24%), vomiting (4% to 13%), diarrhea (6% to 12%)

1% to 10%:

Cardiovascular: Bradycardia (2% to 3%), syncope (0.4% to 2.2%: dose related), chest pain (≥1%)

Central nervous system: Dizziness (9%), headache (8%), depression (7%), fatigue (5%), insomnia (5%), somnolence (4%)

Gastrointestinal: Anorexia (7% to 9%), weight loss (5% to 7%), abdominal pain (5%), dyspepsia (5%), flatulence (≥1%)

Genitourinary: Urinary tract infection (8%), hematuria (<1% to 3%), incontinence (≥1%)

Hematologic: Anemia (3%)

Neuromuscular & skeletal: Tremor (3%)

Respiratory: Rhinitis (4%)

<1%: Alkaline phosphatase increase, apathy, aphasia, apraxia, ataxia, atrial fibrillation, AV block, bundle branch block, convulsions, cystitis, delirium, dependent edema, diverticulitis, dysphagia, epistaxis, esophageal perforation, fever, gastritis, gastroenteritis, heart failure, hiccups, hyperglycemia, hyper-/hypokinesia, hypertonia, hypotension, involuntary muscle contractions, libido increase, malaise, melena, MI, micturition frequency increased, muscle weakness, nocturia, palpitation, paranoid reaction, paresthesia, paroniria, postural hypotension, purpura, QT prolongation, rectal hemorrhage, renal calculi, saliva increased, stroke, suicide, supraventricular tachycardia, T-wave inversion, thrombocytopenia, TIA, urinary retention, ventricular tachycardia, vertigo, weakness, xerostomia

Postmarketing and/or case reports: Aggression, dehydration, gastrointestinal bleeding, hypokalemia, renal failure (due to dehydration)

Metabolism/Transport Effects**Substrate** (minor) of CYP2D6, 3A4

Drug Interactions

Anticholinergics: May diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotics: Acetylcholinesterase Inhibitors (Central) may enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Beta-Blockers: Acetylcholinesterase Inhibitors may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Cholinergic Agonists: Acetylcholinesterase Inhibitors may enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Ginkgo Biloba: May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): Acetylcholinesterase Inhibitors may diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). Acetylcholinesterase Inhibitors may decrease the metabolism of Neuromuscular-Blocking Agents (Nondepolarizing). This is only true for mivacurium in which case the neuromuscular blocking effects might be prolonged. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Galantamine. **Exceptions:** Citalopram; Escitalopram; Fluvoxamine. *Risk C: Monitor therapy*

Succinylcholine: Acetylcholinesterase Inhibitors may enhance the neuromuscular-blocking effect of Succinylcholine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS adverse events).

Herb/Nutraceutical: St John's wort may decrease galantamine serum levels; avoid concurrent use.

Monitoring ParametersMental status

Nursing: Physical Assessment/MonitoringAssess bladder and sphincter adequacy prior to starting therapy. Assess other medications patient may be taking for effectiveness and interactions (especially those dependent on cytochrome P450 metabolism). Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically throughout therapy (eg, cholinergic crisis). Assess knowledge/teach appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationThis medication will not cure Alzheimer's disease, but may help reduce symptoms. Use exactly as directed; do not increase dose or discontinue without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause dizziness, sedation, hypotension, or tremor (use caution when driving or engaging in hazardous tasks, rise slowly from sitting or lying position, and use caution when climbing stairs until response to drug is known); diarrhea (boiled milk, yogurt, or buttermilk may help); or nausea or vomiting (small frequent meals, good mouth care, sucking lozenges, or chewing gum may help). Report persistent GI disturbances; significantly increased salivation, sweating, or tearing; excessive fatigue, insomnia, dizziness, or depression; increased muscle, joint, or body pain or spasms; vision changes; respiratory changes, wheezing, or signs of dyspnea; chest pain or palpitations; or other adverse reactions. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release, oral, as hydrobromide:

Razadyne™ ER: 8 mg, 16 mg, 24 mg [contains gelatin]

Solution, oral, as hydrobromide:

Razadyne™: 4 mg/mL (100 mL) [with calibrated pipette]

Tablet, as hydrobromide: 4 mg, 8 mg, 12 mg

Razadyne™: 4 mg, 8 mg, 12 mg

Generic AvailableYes: Tablet

ManufacturerJanssen Pharmaceutica Products, LP

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Razadyne ER)

8 mg (30): $195.48

16 mg (30): $196.03

24 mg (30): $195.99

Tablets (Razadyne)

4 mg (30): $93.37

8 mg (30): $93.37

12 mg (30): $93.37

Mechanism of ActionCentrally-acting cholinesterase inhibitor (competitive and reversible). It elevates acetylcholine in cerebral cortex by slowing the degradation of acetylcholine. Modulates nicotinic acetylcholine receptor to increase acetylcholine from surviving presynaptic nerve terminals. May increase glutamate and serotonin levels.

Pharmacodynamics/Kinetics

Duration: 3 hours; maximum inhibition of erythrocyte acetylcholinesterase ~40% at 1 hour post 8 mg oral dose; levels return to baseline at 30 hours

Absorption: Rapid and complete

Distribution: 175 L; levels in the brain are 2-3 times higher than in plasma

Protein binding: 18%

Metabolism: Hepatic; linear, CYP2D6 and 3A4; metabolized to epigalanthaminone and galanthaminone both of which have acetylcholinesterase inhibitory activity 130 times less than galantamine

Bioavailability: ~90%

Half-life elimination: 7 hours

Time to peak: Immediate release: 1 hour (2.5 hours with food); extended release: 4.5-5 hours

Excretion: Urine (25%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index TermsGalantamine Hydrobromide

References

Morris JC, Farlow MR, Ferris SH, et al, "Therapeutic Continuity in Alzheimer's Disease: Switching Patients to Galantamine. Panel Discussion: Recommendations for Prescribers," *Clin Ther*, 2001, 23 (Suppl A):31-9.

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International Brand NamesNivalin (AT, BG, DE, HN, HU, PL, RU); Proneurax (VE); Reminyl (AR, AU, BE, BR, CH, CO, CZ, DE, DK, EE, ES, FI, FR, GB, HK, ID, IE, IL, IT, KP, MX, MY, NL, NO, PE, PH, PL, PT, SE, SG, TH, TW, UY); Reminyl ER (CN, EC); Reminyl LP (FR); Reminyl PR (KP); Reminyl PRC (IL); Reminyl XL (GB, IE)

Gallium Nitrate

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(GAL ee um NYE trate)

U.S. Brand NamesGanite™

Pharmacologic CategoryCalcium-Lowering Agent

Use: Labeled IndicationsTreatment of symptomatic cancer-related hypercalcemia

Dosing: Adults **Note:** Initiate I.V. hydration prior to treatment; maintain throughout treatment.

Hypercalcemia: I.V.: 200 mg/m^2/day for 5 days; duration may be shortened during a course if normocalcemia is achieved. If hypercalcemia is mild and with very few symptoms, 100 mg/m^2/day may be used.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Serum creatinine >2.5 mg/dL: Contraindicated

Serum creatinine 2 to ≤2.5 mg/dL: No guidelines exist; frequent monitoring is recommended.

Calculations

- Body Surface Area: Adults

Administration: I.V.The manufacturer recommends continuous I.V. infusion over 24 hours.

Administration: I.V. DetailpH: 6-7

StorageStore unopened vials (25 mg/mL) at room temperature of 20°C to 25°C (68°F to 77°F); not light sensitive. Solutions in 0.9% NaCl or D$_5$W are stable for 48 hours at room temperature or for 7 days under refrigeration at 2°C to 8°C (36°F to 46°F).

ReconstitutionDilute in 1000 mL NS (preferred) or D$_5$W for infusion.

CompatibilityStable in NS, D$_5$W.

ContraindicationsHypersensitivity to gallium nitrate or any component of the formulation; severe renal dysfunction (serum creatinine >2.5 mg/dL)

Warnings/Precautions

Boxed warnings:

- Renal toxicity: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Hypocalcemia: Therapy may result in mild-to-moderate hypocalcemia.
- Renal toxicity: BUN and serum creatinine elevations have been observed with gallium nitrate use; monitor closely; discontinue with serum creatinine >2.5 mg/dL. **[U.S. Boxed Warning]: Concurrent administration with other nephrotoxic drugs (eg, aminoglycosides, amphotericin B) may increase the risk for renal insufficiency; discontinue gallium nitrate during treatment with nephrotoxic drugs.** Establish and maintain adequate hydration with normal saline. Urinary output ≥2 L/day should be established prior to treatment initiation.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients where aggressive hydration may be poorly tolerated, such as in cardiovascular disease (HF or hypertension) and pulmonary disease.

Concurrent drug therapy issues:

- Nephrotoxicity: Discontinue gallium nitrate during treatment with nephrotoxic drugs.

Special populations:

- Pediatrics: Safety and efficacy in children have not been established.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for adverse reactions in the nursing infant, it is recommended to discontinue nursing during treatment or discontinue gallium nitrate.

Adverse ReactionsNot all frequencies defined.

Cardiovascular: Edema (lower extremity), hypotension, tachycardia

Central nervous system: Coma, confusion, dreams, encephalopathy, fever, hallucinations, hypothermia, lethargy

Dermatologic: Rash

Endocrine & metabolic: Hypophosphatemia (up to 79%), serum bicarbonate decreased (40% to 50%), hypocalcemia (38%), respiratory alkalosis (mild)

Hematologic: Anemia, leukopenia

Gastrointestinal: Constipation, diarrhea, nausea, vomiting

Neuromuscular & skeletal: Paresthesia, positive Cvostek's sign

Ocular: Optic neuritis

Otic: Auditory acuity decreased (<1%), hearing decreased, tinnitus (<1%)

Renal: BUN increased (13%), creatinine increased (13%), acute renal failure

Respiratory: Dyspnea, pleural effusion, pulmonary infiltrates, rales, rhonchi

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

Aminoglycosides: May enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Amphotericin B: May enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Vancomycin: May enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Monitoring ParametersRenal function (BUN, serum creatinine); serum calcium (baseline, then daily); serum phosphorus (baseline, then twice weekly); fluid intake, urine output

Nursing: Physical Assessment/MonitoringUse with caution in presence of renal impairment. Assess potential for interactions with other pharmacological agents patient may be taking (eg, other nephrotoxic drugs). Assess results of laboratory tests and renal function, therapeutic effectiveness (calcium levels), and adverse response (eg, hypotension, tachycardia, gastrointestinal upset, central nervous system changes, hypocalcemia, renal impairment) on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsRenal function (BUN, serum creatinine); serum calcium (baseline, then daily); serum phosphorus (baseline, then twice weekly)

Patient EducationThis medication is given only by intravenous infusion: Report immediately any redness, swelling, or pain at infusion site. Inform prescriber if you experience chest pain, palpitations, or swelling of extremities; difficulty breathing; rash; CNS changes (confusion, dreams, hallucinations); numbness, pain, or tingling in extremities; unusual and persistent fatigue or lethargy; changes in urinary pattern or output; persistent gastrointestinal upset (diarrhea, nausea, vomiting, or constipation); or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Ganite™: 25 mg/mL (20 mL)

Generic AvailableNo

ManufacturerGenta Pharmaceuticals

Mechanism of ActionInhibits bone resorption by inhibiting osteoclast function. Gallium nitrate appears to be effective in parathyroid hormone-related protein (PTHrP) and non-PTHrP-associated hypercalcemia.

Pharmacodynamics/Kinetics

Onset of calcium lowering: Seen within 24-48 hours of beginning therapy, with normocalcemia achieved within 4-7 days of beginning therapy

Duration: Normocalcemia: 7-10 days

Bioavailability: Oral: 5%

Distribution: Tissue concentrations were determined postmortem in one patient and concentrations were higher in liver and kidney than in lung, skin, muscle, heart, and cervix tumor; in dogs, tissue gallium concentrations were higher in renal cortex, bone, bone marrow, small intestine, and liver than in skeletal muscle and brain

Half-life elimination: Alpha: 1.25 hours; Beta: ~24 hours

Elimination half-life varies with method of administration (72-115 hours with prolonged intravenous infusion versus 24 hours with bolus administration); long elimination half-life may be related to slow release from tissue such as bone

Excretion: Primarily renal with no prior metabolism in the liver or kidney

Pharmacotherapy PearlsIn addition to the hypocalcemic effect, gallium nitrate has also been studied for its antitumor effects. Gallium nitrate was studied at higher doses infused over 30 minutes every 2 weeks in bladder cancer and lymphoma (Einhorn, 2003; Straus, 2003).

Rapid infusion rates and higher doses are associated with an increased risk of toxicity, including nephrotoxicity and gastrointestinal toxicity.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNausea is common; risk may be increased with concomitant SSRI use

Index TermsNSC-15200

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Galsulfase

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(gal SUL fase)
U.S. Brand NamesNaglazyme™
Pharmacologic CategoryEnzyme
Use: Labeled IndicationsReplacement therapy in mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy Syndrome) for improvement of walking and stair-climbing capacity
Dosing: Adults**Note:** Premedicate with antihistamines with/without antipyretics 30-60 minutes prior to infusion.

MPS VI: I.V.: 1 mg/kg once weekly

Dosing: Pediatric**Note:** Premedicate with antihistamines with/without antipyretics 30-60 minutes prior to infusion.

MPS VI: Children >5 years: I.V.: 1 mg/kg once weekly

Administration: I.V.Administer using infusion pump and PVC infusion set with in-line low protein-binding 0.2 micrometer filter. Pretreatment with antihistamines with or without antipyretics is recommended 30-60 minutes prior to infusion. Infuse a 250 mL solution at 6 mL/hour for the first hour. If well-tolerated, increase to 80 mL/hour for the remaining 3 hours. Doses prepared in 100 mL should also be infused over at least 4 hours. In case of infusion-related reactions, decrease infusion rate or temporarily discontinue. Infusion time can be extended up to 20 hours if infusion reactions occur. Discontinue immediately if severe reaction occurs. Patients requiring supplemental oxygen or CPAP during sleep should have these treatments readily available in case of infusion-related or antihistamine-induced reaction.
StoragePrior to use, store vials under refrigeration, 2° to 8°C (36°F to 46°F). Do not freeze or shake. Following dilution, use immediately. May store under refrigeration if used within 48 hours from the time of preparation to the completion of infusion. Do not store solution for infusion at room temperature. Allow vials to reach room temperature prior to dilution. Do not keep vials at room temperature >24 hours prior to dilution. Do not heat or microwave vials.
ReconstitutionAfter calculating dose, round to the nearest whole vial to prepare infusion (do not use partial vials). Dilute in NS to a final volume of 250 mL (including volume of galsulfase). Slowly add galsulfase to infusion bag (compatibility in glass containers has not been studied). Gently rotate to distribute. Do not shake or agitate, do not use filter needle. In patients <20 kg or in those who are susceptible to volume overload, dose may be diluted into a 100 mL NS.
Compatibility

Stable in NS.

Contraindications

Hypersensitivity to galsulfase or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Infusion reactions: Infusion-related reactions have been reported; may be severe; reactions may occur as late as week 55 of treatment. Patients should be premedicated with antihistamines and/or antipyretics prior to infusion; evaluate airway prior to therapy (due to possible effects of antihistamine use). In case of reaction, decrease the rate of infusion, temporarily discontinue the infusion, and/or administer additional antipyretics/antihistamines and possibly corticosteroids.

Disease-related concerns:

- Acute febrile/respiratory illness: Consider delaying treatment in patients with an acute febrile or respiratory illness.

Special populations:

- Adults: Studies did not include patients >29 years of age.

- Pediatrics: Studies did not include children <5 years of age.

Dosage form specific issues:

- Preparation: Excess agitation of solution prior to or after dilution may denature galsulfase rendering it inactive.

Other warnings/precautions:

- Registry: A Clinical Surveillance Program has been created to monitor therapeutic response, progression of disease and adverse effects during long-term treatment; patients should be encouraged to register. Registry information may be obtained at www.MPSVI.com or by calling 866-906-6100.

Pregnancy Risk FactorB
Pregnancy ConsiderationsFetal harm was not reported in animal studies. There are no studies in pregnant women. Pregnant women are encouraged to enroll in the Clinical Surveillance Program.

Lactation

Excretion in breast milk unknown/use caution

Breast-Feeding Considerations

Breast-feeding women are encouraged to enroll in the Clinical Surveillance Program.

Adverse Reactions

Note: Percentages reported are from a placebo-controlled study (39 patients, 19 on galsulfase); also included are adverse effects noted during other clinical studies.

Cardiovascular: Chest pain (16%), facial edema (11%), hypertension (11%)

Central nervous system: Pain (26%), malaise (11%), fever, headache

Gastrointestinal: Abdominal pain (53%), gastroenteritis (11%), diarrhea, nausea, vomiting

Neuromuscular & skeletal: Rigors (21%), areflexia (11%), arthralgia

Ocular: Conjunctivitis (21%), corneal opacification increased (11%)

Otic: Ear pain (42%), otitis media

Respiratory: Dyspnea (21%), pharyngitis (16%), nasal congestion (11%), cough, upper respiratory tract infections

Miscellaneous: Antigalsulfase antibodies (98%), umbilical hernia (11%)

Infusion-related reactions: Angioedema, apnea, bronchospasm, chills, facial and neck urticaria, hypotension, rash, respiratory distress

Drug Interactions There are no known significant interactions.

Monitoring Parameters Monitor for infusion reactions. In clinical studies, tests of mobility and physical function were monitored at baseline and every 6 weeks.

Nursing: Physical Assessment/Monitoring Airway and respiratory status should be evaluated prior to treatment. Premedicate with antihistamines (with or without antipyretics) prior to each administration. See Administration for specific infusion and dosing directions. Patient must be monitored closely with each infusion; infusion reactions may occur as late as week 55 of treatment. Emergency equipment should be at hand during each treatment. If infusion reaction occurs, rate should be decreased or discontinued. Instruct patient/caregiver about participation in the Clinical Surveillance Program. Teach patient and caregiver interventions to reduce side effects and adverse symptoms to report.

Patient Education This medication can only be administered by intravenous infusion. You will be closely monitored during treatment. Report immediately any swelling of face, tongue or lips, difficulty swallowing, difficulty breathing, chills, or rash that occurs during infusion, or any redness, burning, or swelling at infusion site. Inform prescriber if you experience nausea, vomiting, or diarrhea; headache, pain in joints or muscles; ear pain, cough, or other adverse reactions between infusions.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Naglazyme™: 5 mg/5 mL (5 mL) [contains polysorbate 80]

Generic Available

No

Manufacturer

BioMarin

Mechanism of Action Galsulfase is a recombinant form of N-acetylgalactosamine 4-sulfatase, produced in Chinese hamster cells. A deficiency of this enzyme leads to accumulation of the glycosaminoglycan dermatan sulfate in various tissues, causing progressive disease which includes decreased growth, skeletal deformities, upper airway obstruction, clouding of the cornea, heart disease, and coarse facial features. Replacement of this enzyme has been shown to improve mobility and physical function (measured by walking and stair-climbing).

Pharmacodynamics/Kinetics

Distribution: V_d: Week 1: 56-323 mL/kg; Week 24: 59-2799 mL/kg

Half-life elimination: Week 1: Median 9 hours (range: 6-21 hours); Week 24: Median 26 hours (range: 8-40 hours)

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause sedation

Mental Health: Effects on Psychiatric Treatment Concomitant administration with psychotropic agents may produce additive sedation; monitor

Index Terms Recombinant N-Acetylgalactosamine 4-Sulfatase; rhASB

References

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International Brand Names Naglazyme (CZ, DE, DK, EE, ES, SE)

Ganciclovir

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Cytovene® may be confused with Cytosar®, Cytosar-U®

Pronunciation(gan SYE kloe veer)

U.S. Brand NamesCytovene®; Vitrasert®

Canadian Brand NamesCytovene®; Vitrasert®

Pharmacologic CategoryAntiviral Agent

Use: Labeled Indications

Parenteral: Treatment of CMV retinitis in immunocompromised individuals, including patients with acquired immunodeficiency syndrome; prophylaxis of CMV infection in transplant patients

Oral: Alternative to the I.V. formulation for maintenance treatment of CMV retinitis in immunocompromised patients, including patients with AIDS, in whom retinitis is stable following appropriate induction therapy and for whom the risk of more rapid progression is balanced by the benefit associated with avoiding daily I.V. infusions.

Implant: Treatment of CMV retinitis

Use: Unlabeled/InvestigationalMay be given in combination with foscarnet in patients who relapse after monotherapy with either drug

Dosing: AdultsDosing is based on total body weight.

CMV retinitis:

I.V. (slow infusion):

Induction therapy: 5 mg/kg/dose every 12 hours for 14-21 days followed by maintenance therapy

Maintenance therapy: 5 mg/kg/day as a single daily dose for 7 days/week or 6 mg/kg/day for 5 days/week

Oral: 1000 mg 3 times/day with food **or** 500 mg 6 times/day with food

Ocular implant: Intravitreally: One implant for 5- to 8-month period; following depletion of ganciclovir, as evidenced by progression of retinitis, implant may be removed and replaced

Prevention of CMV disease in patients with advanced HIV infection and normal renal function: Oral: 1000 mg 3 times/day with food

Prevention of CMV disease in transplant patients: Same initial and maintenance dose as CMV retinitis except duration of initial course is 7-14 days, duration of maintenance therapy is dependent on clinical condition and degree of immunosuppression

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricCMV retinitis: Children >3 months: Refer to adult dosing.

Dosing: Renal Impairment

I.V. (Induction):

Cl_{cr} 50-69 mL/minute: Administer 2.5 mg/kg/dose every 12 hours.

Cl_{cr} 25-49 mL/minute: Administer 2.5 mg/kg/dose every 24 hours.

Cl_{cr} 10-24 mL/minute: Administer 1.25 mg/kg/dose every 24 hours.

Cl_{cr} <10 mL/minute: Administer 1.25 mg/kg/dose 3 times/week following hemodialysis.

I.V. (Maintenance):

Cl_{cr} 50-69 mL/minute: Administer 2.5 mg/kg/dose every 24 hours.

Cl_{cr} 25-49 mL/minute: Administer 1.25 mg/kg/dose every 24 hours.

Cl_{cr} 10-24 mL/minute: Administer 0.625 mg/kg/dose every 24 hours

Cl_{cr} <10 mL/minute: Administer 0.625 mg/kg/dose 3 times/week following hemodialysis.

Oral:

Cl_{cr} 50-69 mL/minute: Administer 1500 mg/day or 500 mg 3 times/day.

Cl_{cr} 25-49 mL/minute: Administer 1000 mg/day or 500 mg twice daily.

Cl_{cr} 10-24 mL/minute: Administer 500 mg/day.

Cl_{cr} <10 mL/minute: Administer 500 mg 3 times/week following hemodialysis.

Hemodialysis effects: Dialyzable (50%) following hemodialysis; administer dose postdialysis. During peritoneal dialysis, dose as for Cl_{cr} <10 mL/minute. During continuous arteriovenous or venovenous hemofiltration, administer 2.5 mg/kg/dose every 24 hours.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Should not be administered by I.M., SubQ, or rapid IVP. Administer by slow I.V. infusion over at least 1 hour. Too rapid infusion can cause increased toxicity and excessive plasma levels.
Administration: I.V. DetailFlush line well with NS before and after administration.

pH: 11

Administration: OralShould be administered with food.
Dietary ConsiderationsSodium content of 500 mg vial: 46 mg
StorageIntact vials should be stored at room temperature and protected from temperatures >40°C. Reconstituted solution is stable for 12 hours at room temperature, however, conflicting data indicates that reconstituted solution is stable for 60 days under refrigeration (4°C). Stability of parenteral admixture at room temperature (25°C) and at refrigeration temperature (4°C) is 5 days.
ReconstitutionReconstitute powder with unpreserved sterile water not bacteriostatic water because parabens may cause precipitation. Dilute in 250-1000 mL D_5W or NS to a concentration ≤10 mg/mL for infusion.
CompatibilityStable in D_5W, LR, NS; **incompatible** with paraben preserved bacteriostatic water for injection (may cause precipitation).

Y-site administration: Compatible: Allopurinol, amphotericin B cholesteryl sulfate complex, cisplatin, cyclophosphamide, docetaxel, doxorubicin liposome, enalaprilat, etoposide phosphate, filgrastim, fluconazole, gatifloxacin, granisetron, linezolid, melphalan, methotrexate, paclitaxel, propofol, remifentanil, tacrolimus, teniposide, thiotepa. **Incompatible:** Aldesleukin, amifostine, amsacrine, aztreonam, cefepime, cytarabine, doxorubicin, fludarabine, foscarnet, gemcitabine, ondansetron, piperacillin/tazobactam, sargramostim, vinorelbine. **Variable (consult detailed reference):** Cisatracurium.

ContraindicationsHypersensitivity to ganciclovir, acyclovir, or any component of the formulation; absolute neutrophil count <500/mm^3; platelet count <25,000/mm^3
Allergy Considerations

- Antiviral Acyclic Guanine Derivative Allergy

Warnings/Precautions

Boxed warnings:

- Appropriate use: See “Other warnings/precautions” below.

- Carcinogenic/teratogenic/fertility effects: See “Concerns related to adverse effects” below.

- Blood dyscrasias: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Blood dyscrasias: **[U.S. Boxed Warning]: Granulocytopenia (neutropenia), anemia, and thrombocytopenia may occur.** Dosage adjustment or interruption of therapy may be necessary in patients with neutropenia and/or thrombocytopenia.

- Carcinogenic/teratogenic/fertility effects: **[U.S. Boxed Warning]: Animal studies have demonstrated carcinogenic and teratogenic effects, and inhibition of spermatogenesis;** contraceptive precautions for female and male patients need to be followed during and for at least 90 days after therapy with the drug.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment or interruption of therapy may be necessary.

Other warnings/precautions:

- Administration: Take care to administer only into veins with good blood flow.

- Appropriate use: **[U.S. Boxed Warning]: Indicated only for treatment of CMV retinitis in the immunocompromised patient and CMV prevention in transplant patients at risk.**

Geriatric ConsiderationsAdjust dose based upon renal function.

Pregnancy Risk FactorC

Pregnancy Considerations **[U.S. Boxed Warning]: Animal studies have demonstrated carcinogenic and teratogenic effects, and inhibition of spermatogenesis;** contraceptive precautions for female and male patients need to be followed during and for at least 90 days after therapy.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsThe CDC recommends **not** to breast-feed if diagnosed with HIV to avoid postnatal transmission of the virus.

Adverse Reactions

>10%:

Central nervous system: Fever (38% to 48%)

Dermatologic: Rash (15% oral, 10% I.V.)

Gastrointestinal: Abdominal pain (17% to 19%), diarrhea (40%), nausea (25%), anorexia (15%), vomiting (13%)

Hematologic: Anemia (20% to 25%), leukopenia (30% to 40%)

1% to 10%:

Central nervous system: Confusion, neuropathy (8% to 9%), headache (4%)

Dermatologic: Pruritus (5%)

Hematologic: Thrombocytopenia (6%), neutropenia with ANC <500/mm^3 (5% oral, 14% I.V.)

Neuromuscular & skeletal: Paresthesia (6% to 10%), weakness (6%)

Ocular: Retinal detachment (8% oral, 11% I.V.; relationship to ganciclovir not established)

Miscellaneous: Sepsis (4% oral, 15% I.V.)

<1% (Limited to important or life-threatening): Alopecia, arrhythmia, ataxia, bronchospasm, coma, dyspnea, encephalopathy, exfoliative dermatitis, extrapyramidal symptoms, nervousness, pancytopenia, psychosis, seizure, alopecia, urticaria, eosinophilia, hemorrhage, Stevens-Johnson syndrome, torsade de pointes, renal failure, SIADH, visual loss

Oncology: VesicantNo

Drug Interactions

Imipenem: Ganciclovir may enhance the adverse/toxic effect of Imipenem. May increase risk of seizures. *Risk X: Avoid combination*

Mycophenolate: May increase the serum concentration of Ganciclovir-Valganciclovir. Ganciclovir-Valganciclovir may increase the serum concentration of Mycophenolate. *Risk C: Monitor therapy*

Reverse Transcriptase Inhibitors (Nucleoside): Ganciclovir-Valganciclovir may enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. **Exceptions:** Stavudine; Zalcitabine. *Risk D: Consider therapy modification*

Tenofovir: Ganciclovir-Valganciclovir may decrease the excretion of Tenofovir. *Risk C: Monitor therapy*

Monitoring ParametersCBC with differential and platelet count, serum creatinine, ophthalmologic exams

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking that may result in increased risk for neutropenia, hematologic toxicity, or nephrotoxicity. **I.V.:** See Administration for infusion specifics. Assess results of laboratory tests prior to therapy and on a regular basis during therapy. Evaluate therapeutic effectiveness and adverse response (eg, paresthesia, neutropenia, anemia, nephrotoxicity, retinal detachment) throughout therapy. Teach proper use (according to formulation), possible side effects/appropriate interventions (importance of contraceptive precautions during and for 90 days following therapy), and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelet count, serum creatinine before beginning therapy and on a regular basis thereafter; liver function tests

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Ganciclovir is not a cure for CMV retinitis. For oral administration, take as directed and maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will need frequent blood tests and regular ophthalmic exams while taking this drug. You may experience increased susceptibility to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). You may experience confusion or headache (use cautions when driving or engaging in potentially hazardous tasks until response to drug is known); nausea, vomiting, or anorexia (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report rash, infection (fever, chills, unusual bleeding or bruising, or unhealed sores or white plaques in mouth); abdominal pain; tingling, weakness, or pain in extremities; any vision changes; or pain, redness, swelling at injection site. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Males and females should use appropriate barrier contraceptive measures during and for 60-90 days following end of therapy. Consult prescriber for appropriate barrier contraceptive measures if necessary or if you suspect you might be pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 250 mg, 500 mg

Implant, intravitreal:

Vitrasert®: 4.5 mg [released gradually over 5-8 months]

Injection, powder for reconstitution, as sodium:

Cytovene®: 500 mg

Generic AvailableYes: Capsule
ManufacturerRoche Laboratories Inc
Pricing: U.S. (www.drugstore.com)

Capsules (Cytovene)

250 mg (60): $279.14

500 mg (60): $549.47

Capsules (Ganciclovir)

250 mg (30): $133.67

Mechanism of ActionGanciclovir is phosphorylated to a substrate which competitively inhibits the binding of deoxyguanosine triphosphate to DNA polymerase resulting in inhibition of viral DNA synthesis
Pharmacodynamics/Kinetics

Distribution: V_d: 15.26 L/1.73 m^2; widely to all tissues including CSF and ocular tissue

Protein binding: 1% to 2%

Bioavailability: Oral: Fasting: 5%; Following food: 6% to 9%; Following fatty meal: 28% to 31%

Half-life elimination: 1.7-5.8 hours; prolonged with renal impairment; End-stage renal disease: 5-28 hours

Excretion: Urine (80% to 99% as unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause confusion; may rarely cause nervousness, psychosis, hallucinations, or disorientation
Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; use caution with clozapine and carbamazepine
Index TermsDHPG Sodium; GCV Sodium; Nordeoxyguanosine
References

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Paul S and Dummer S, “Topics in Clinical Pharmacology, Ganciclovir,” *Am J Med Sci*, 1992, 304(4):272-7. [PubMed 1329509]

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Whitley RJ, Jacobson MA, Friedberg DN, et al, “Guidelines for the Treatment of Cytomegalovirus Diseases in Patients With AIDS in the Era of Potent Antiretroviral Therapy: Recommendations of an International Panel. International AIDS Society-USA,” *Arch Intern Med*, 1998, 158(9):957-69.[PubMed 9588429]

International Brand NamesCymevan (FR); Cymeven (DE); Cymevene (AE, AR, AT, AU, BB, BD, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PH, PK, PL, PR, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Virgan (FR, GB, PH); Vitrasert Implant (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Ganirelix

Lexi-Drugs Online

English

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Medication Safety Issues
International issues:

Antagon® (former U.S. brand name for ganirelix): Brand name for astemizole in Mexico; brand name for ranitidine in Brazil

Pronunciation(ga ni REL ix)
Canadian Brand NamesOrgalutran®
Pharmacologic CategoryGonadotropin Releasing Hormone Antagonist
Use: Labeled IndicationsInhibits premature luteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation
Dosing: AdultsAdjunct to controlled ovarian hyperstimulation: SubQ: 250 mcg/day during the mid-to-late phase after initiating follicle-stimulating hormone on day 2 or 3 of cycle. Treatment should be continued daily until the day of chorionic gonadotropin administration.
Dosing: ElderlyRefer to adult dosing.
Administration: OtherAdminister SubQ in abdomen (around upper navel) or upper thigh; rotate injection site.
StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.
ContraindicationsHypersensitivity to ganirelix or any component of the formulation; hypersensitivity to gonadotropin-releasing hormone (GnRH) or any other GnRH analog; known or suspected pregnancy
Allergy Considerations

- GnRH Antagonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

• Hypersensitivity: Hypersensitivity reactions, including anaphylactoid reactions, have been reported; may occur with the first dose.

Special populations:

• Pregnancy: Exclude pregnancy before beginning treatment.

Dosage form specific issues:

• Latex: The packaging contains natural rubber latex.

Other warnings/precautions:

• Experienced specialists: Should only be prescribed by fertility specialists.

Pregnancy Risk FactorX
Pregnancy ConsiderationsFetal resorption occurred in pregnant rats and rabbits. These effects are results of hormonal alterations and could result in fetal loss in humans. The drug should not be used in pregnant women.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

1% to 10%:

Central nervous system: Headache (3%)

Endocrine & metabolic: Ovarian hyperstimulation syndrome (2%)

Gastrointestinal: Abdominal pain (1%), nausea (1%)

Genitourinary: Pelvic pain (5%), vaginal bleeding (2%)

Local: Injection site reaction (1%)

<1%, postmarketing, and/or case reports: Anaphylactoid reaction, hypersensitivity

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersUltrasound to assess follicle size
Nursing: Physical Assessment/MonitoringThis medication should only be prescribed by a fertility specialist. Assess/teach patient use (demonstrate injection procedures, syringe disposal), interventions to reduce side-effects, and adverse reactions to report. **Pregnancy risk factor X:** Pregnancy must be excluded before starting medication.
Monitoring: Lab TestsUltrasound to assess follicle size
Patient EducationThis drug can only be given by injection as demonstrated. Use this and any other medications as directed by prescriber; do not skip any doses. You must keep all scheduled ultrasound appointments. You may experience headache (use of mild analgesic may help); or nausea (small frequent meals, good mouth care, chewing gum, or sucking hard candy may help). Report immediately any sudden or acute

abdominal pain; vaginal bleeding; or pain, itching, or signs of infection at injection site. **Note:** Packaging contains natural rubber latex; if you have a known latex allergy, advise prescriber. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this drug. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as acetate: 250 mcg/0.5 mL [prefilled glass syringe with 27-gauge x $^1/_2$ inch needle]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Ganirelix Acetate)

250 mcg/0.5 mL (0.5): $114.87

Mechanism of ActionCompetitively blocks the gonadotropin-release hormone receptors on the pituitary gonadotroph and transduction pathway. This suppresses gonadotropin secretion and luteinizing hormone secretion preventing ovulation until the follicles are of adequate size.

Pharmacodynamics/Kinetics

Duration: <48 hours

Absorption: SubQ: Rapid

Distribution: Mean V_d: Single dose: 43.7 L; Multiple dosing: 76.5 L

Protein binding: 81.9%

Metabolism: Hepatic to two primary metabolites (1-4 and 1-6 peptide)

Bioavailability: SubQ: 91.1%

Half-life elimination: Single dose : 12.8 hours; Multiple dosing: 16.2 hours

Time to peak: 1.1 hours

Excretion: Feces (75%) within 288 hours; urine (22%) within 24 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAntagon; Ganirelix Acetate

International Brand NamesOrgalutran (AE, AR, AT, AU, BE, BG, BH, BR, CH, CN, CO, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, HK, HN, IE, IL, IQ, IR, IT, JO, KW, LB, LY, MX, MY, NL, NO, OM, PE, PK, PL, PT, QA, RU, SA, SE, SG, SY, TH, TR, TW, VE, YE)

Gatifloxacin

Lexi-Drugs Online

English

English

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Pronunciation(gat i FLOKS a sin)

U.S. Brand NamesZymar®

Canadian Brand NamesZymar®

Pharmacologic CategoryAntibiotic, Ophthalmic; Antibiotic, Quinolone

Use: Labeled IndicationsTreatment of bacterial conjunctivitis

Dosing: Adults

Bacterial conjunctivitis: Ophthalmic:

> *Days 1 and 2:* Instill 1 drop into affected eye(s) every 2 hours while awake (maximum: 8 times/day)
>
> *Days 3-7:* Instill 1 drop into affected eye(s) up to 4 times/day while awake

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricBacterial conjunctivitis: Children ≥1 year: Ophthalmic: Refer to adult dosing.

StorageStore between 15°C to 25°C (59°F to 77°F); do not freeze.

ContraindicationsHypersensitivity to gatifloxacin, other quinolone antibiotics, or any component of the formulation

Allergy Considerations

- Fluoroquinolone Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Severe hypersensitivity reactions, including anaphylaxis, have occurred with systemic quinolone therapy. The spectrum of these reactions can vary widely; reactions may present as typical allergic symptoms (eg, itching, urticaria, rash, edema) after a single dose, or may manifest as severe idiosyncratic dermatologic (eg, Stevens-Johnson, toxic epidermal necrolysis), vascular (eg, vasculitis), pulmonary (eg, pneumonitis), renal (eg, nephritis), hepatic (eg, hepatic failure or necrosis), and/or hematologic (eg, anemia, cytopenias) events, usually after multiple doses. Prompt discontinuation of drug should occur if skin rash or other symptoms arise.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection.

Special populations:

- Contact lens wearers: Contact lenses should not be worn during treatment of ophthalmic infections.

- Pediatrics: Safety and efficacy have not been established in children <1 year of age.

Dosage form specific issues:

- Ophthalmic solution: Do not inject ophthalmic solution subconjunctivally or introduce directly into the anterior chamber of the eye.

Geriatric ConsiderationsEvaluate the patient's ability to self-administer the ophthalmic product.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReports of arthropathy (observed in immature animals and reported rarely in humans) have limited the use of fluoroquinolones during pregnancy. Gatifloxacin has been show to be fetotoxic in animal studies. There are no adequate and well-controlled studies in pregnant women. Based on limited data, quinolones are not expected to be a major human teratogen. Although quinolone antibiotics should not be used as first-line agents during pregnancy, when considering treatment for life-threatening infection and/or prolonged duration of therapy, the potential risk to the fetus must be balanced against the severity of the potential illness.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsOther quinolones are known to be excreted in breast milk. The manufacturer recommends using caution if gatifloxacin is administered while nursing.

Adverse Reactions

5% to 10%: Ocular: Conjunctival irritation, keratitis, lacrimation increased, papillary conjunctivitis

1% to 4%:

> Central nervous system: Headache
>
> Gastrointestinal: Taste disturbance
>
> Ocular: Chemosis, conjunctival hemorrhage, discharge, dry eye, edema, irritation, pain, visual acuity decreased

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. **Exceptions:** Sodium Bicarbonate. *Risk D: Consider therapy modification*

Calcium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Calcium Chloride. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Quinolone Antibiotics may enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Didanosine: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents (excludes enteric coated formulation of didanosine). *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Insulin: May enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Mycophenolate: Quinolone Antibiotics may decrease the serum concentration of Mycophenolate. Specifically, quinolones may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nonsteroidal Anti-Inflammatory Agents: May enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Probenecid: May increase the serum concentration of Quinolone Antibiotics. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Quinapril: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sevelamer: May decrease the absorption of Quinolone Antibiotics. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sulfonylureas: Quinolone Antibiotics may enhance the hyperglycemic effect of Sulfonylureas. Quinolone Antibiotics may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Quinolone Antibiotics may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zinc Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Monitoring ParametersSigns of infection

Nursing: Physical Assessment/MonitoringAssess allergy history and previous exposure to quinolone antibiotics before initiating therapy. Evaluate therapeutic effectiveness (resolution of infection) and adverse effects (eg, hypersensitivity) regularly during therapy. Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Use as directed: Tilt head back and instill prescribed number of drops in affected eye as often as directed for length of time prescribed. Do not allow dropper to touch any surface, including the eyes or hands. Apply light pressure to the inside corner of the eye (near the nose) after each drop. Avoid wearing contact lenses during treatment. May cause headache or dizziness (use caution when driving or engaging in tasks requiring alertness until response is known). May cause temporary stinging, burning, itching, redness, or tearing; eyelid swelling or itching; or a bad taste in mouth after instillation. Report persistent adverse reactions, visual disturbances, or if condition worsens. If you experience signs of allergic reaction (eg, itching, rash, respiratory difficulty, facial edema, difficulty swallowing), discontinue use immediately and report to prescriber.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to be pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic:

Zymar®: 0.3% (5 mL) [contains benzalkonium chloride]

Generic AvailableNo
ManufacturerAllergan
Pricing: U.S. (www.drugstore.com)

Solution (Zymar)

0.3% (5): $74.19

Tablets (Tequin)

200 mg (30): $269.98

Mechanism of ActionGatifloxacin is a DNA gyrase inhibitor, and also inhibits topoisomerase IV. DNA gyrase (topoisomerase II) is an essential bacterial enzyme that maintains the superhelical structure of DNA. DNA gyrase is required for DNA replication and transcription, DNA repair, recombination, and transposition; inhibition is bactericidal.
Pharmacodynamics/KineticsAbsorption: Ophthalmic: Not measurable
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste disturbance.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsGatifloxacin is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.
Mental Health: Effects on Mental StatusGatifloxacin may cause dizziness, insomnia; may rarely produce abnormal thinking, agitation, anorexia, anxiety, asthenia, ataxia, confusion, depersonalization, depression, euphoria, hallucination, hostility, nervousness, panic attacks, paranoia, psychosis, somnolence, or stress
Mental Health: Effects on Psychiatric TreatmentMay have potential to prolong QT interval; should avoid in patients with uncorrected hypokalemia, or concurrent administration of other medications known to prolong the QT interval (antipsychotics, tricyclic antidepressants, ziprasidone)
Cardiovascular ConsiderationsGatifloxacin causes a dose-dependent QT prolongation. Coadministration of gatifloxacin with other drugs that also prolong the QT interval or induce bradycardia (eg, beta-blockers, amiodarone) should be avoided. Careful consideration should be given in the use of gatifloxacin in patients with cardiovascular disease, particularly in those with conduction abnormalities.
Anesthesia and Critical Care Concerns/Other ConsiderationsGatifloxacin causes a dose-dependent QT prolongation. Coadministration of gatifloxacin with other drugs that also prolong the QT interval or induce bradycardia (eg, beta-blockers, amiodarone) should be done cautiously. Careful consideration should be given in the use of gatifloxacin in patients with cardiovascular disease, particularly in those with conduction abnormalities.
International Brand NamesBonoq (DE); Bonoq-Uro (DE); Fudixing (CL); Gaticin (ID); Gatiflo (JP, KP); Gatilox (PY); Gatimax (ID); Starox (CN); Tequin (AU, BR, MX, MY, ZA); Zequin (PK); Zymar (IL, MY, PH, SG, TH); Zymaran (AR, CO, EC, PE); Zyquin (IN)

Gefitinib

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Gefitinib may be confused with erlotinib

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ge FI tye nib)

U.S. Brand NamesIRESSA®

Pharmacologic CategoryAntineoplastic Agent, Tyrosine Kinase Inhibitor

Use: Labeled Indications

U.S. labeling: Treatment of locally advanced or metastatic nonsmall cell lung cancer after failure of platinum-based and docetaxel therapies. Treatment is limited to patients who are benefiting or have benefited from treatment with gefitinib.

Note: Due to the lack of improved survival data from clinical trials of gefitinib, and in response to positive survival data with another EGFR inhibitor, physicians are advised to use other treatment options in advanced nonsmall cell lung cancer patients following one or two prior chemotherapy regimens when they are refractory/intolerant to their most recent regimen.

Canada labeling: Approved indication is limited to NSCLC patients with epidermal growth factor receptor (EGFR) expression status positive or unknown.

Dosing: Adults**Note:** In response to the lack of improved survival data from the ISEL trial, AstraZeneca has temporarily suspended promotion of this drug.

Nonsmall cell lung cancer: Oral: 250 mg/day; consider 500 mg/day in patients receiving effective CYP3A4 inducers (eg, rifampin, phenytoin)

Dosing: ElderlyNo adjustment necessary. Refer to adult dosing.

Dosing: Renal ImpairmentNo adjustment necessary.

Dosing: Hepatic ImpairmentNo adjustment necessary.

Dosing: Adjustment for ToxicityConsider interruption of therapy in any patient with evidence of pulmonary decompensation or severe hepatic injury; discontinuation may be required if toxicity is confirmed. Poorly tolerated diarrhea or adverse skin reactions may be managed by a brief interruption of therapy (up to 14 days), followed by reinitiation of therapy at 250 mg/day. Eye pain should be promptly evaluated and therapy may be interrupted based on appropriate medical evaluation; may be reinitiated following resolution of symptoms and eye changes.

Administration: OralMay administer with or without food.

For patients unable to swallow tablets or for administration via NG tube: Tablets may be dispersed in noncarbonated drinking water. Drop whole tablet (do not crush) into $^1/_2$ glass of water; stir until tablet is dispersed (~10 minutes). Drink immediately. Rinse with $^1/_2$ glass of water and drink.

Dietary ConsiderationsFood does not affect gefitinib absorption.

StorageStore tablets at controlled room temperature of 20°C to 25°C (68°F to 77°F).

RestrictionsAs of September 15, 2005, distribution will be limited to patients enrolled in the Iressa Access Program. Under this program, access to gefitinib will be limited to the following groups:

Patients who are currently receiving and benefitting from gefitinib (IRESSA®)

Patients who have previously received and benefited from gefitinib (IRESSA®)

Previously-enrolled patients or new patients in non-Investigational New Drug (IND) clinical trials involving gefitinib (IRESSA®) if these protocols were approved by an IRB prior to June 17, 2005

New patients may also receive Iressa if the manufacturer (AstraZeneca) decides to make it available under IND, and the patients meet the criteria for enrollment under the IND

Additional information on the IRESSA® Access Program, including enrollment forms, may be obtained by calling AstraZeneca at 1-800-601-8933 or via the web at www.Iressa-access.com

ContraindicationsHypersensitivity to gefitinib or any component of the formulation; pregnancy

Allergy Considerations

- Gefitinib Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Diarrhea: Interruption of therapy may be required in patients with poorly tolerated diarrhea.

- Eye pain: Promptly evaluate eye pain. Therapy may be interrupted based on appropriate medical evaluation; may be reinitiated following resolution of symptoms and eye changes.

- Pulmonary toxicity: Rare, sometimes fatal, pulmonary toxicity (eg, alveolitis, interstitial pneumonia, pneumonitis) has occurred. Therapy should be interrupted in patients with acute onset or worsening pulmonary symptoms; discontinue if interstitial pneumonitis is confirmed.

- Skin reactions: Interruption of therapy may be required in patients with adverse skin reactions.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; may cause hepatic injury and elevation of transaminases; discontinue if elevations/changes are severe.

- Renal impairment: Use with caution in patients with severe renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorD
Pregnancy ConsiderationsAnimal studies have demonstrated fetal harm; there are no well-controlled studies in pregnant women. The risk of fetal harm should be carefully weighed. Women of childbearing potential should be advised to avoid pregnancy.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%:

Dermatologic: Rash (43% to 54%), acne (25% to 33%), dry skin (13% to 26%)

Gastrointestinal: Diarrhea (48% to 76%), nausea (13% to 18%), vomiting (9% to 12%)

1% to 10%:

Cardiovascular: Peripheral edema (2%)

Dermatologic: Pruritus (8% to 9%)

Gastrointestinal: Anorexia (7% to 10%), weight loss (3% to 5%), mouth ulceration (1%)

Neuromuscular & skeletal: Weakness (4% to 6%)

Ocular: Amblyopia (2%), conjunctivitis (1%)

Respiratory: Dyspnea (2%), interstitial lung disease (1% to 2%)

<1%: Aberrant eyelash growth, angioedema, corneal erosion and membrane sloughing, epistaxis, erythema multiforme, eye pain, hematuria, hemorrhage, ocular hemorrhaging, ocular ischemia, pancreatitis, toxic epidermal necrolysis, urticaria

Postmarketing and/or case reports: CNS hemorrhage and death were reported in clinical trials of pediatric patients with primary CNS tumors

Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP2C19 (weak), 2D6 (weak)
Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Gefitinib. *Risk C: Monitor therapy*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be

increased. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Gefitinib. *Risk D: Consider therapy modification*

Topotecan: BCRP/ABCG2 Inhibitors may increase the serum concentration of Topotecan. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Gefitinib may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Grapefruit juice may increase serum gefitinib concentrations; St John's wort may decrease serum gefitinib concentrations.

Monitoring ParametersPeriodic liver function tests (asymptomatic increases in liver enzymes have occurred)

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, increased or decreased levels/effects of gefitinib). Assess results of liver function tests on a regular basis. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPeriodic liver function tests (asymptomatic increases in liver enzymes have occurred)

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take exactly as directed with or without food. Do not take with grapefruit juice and do not take antacids 2 hours before or 2 hours after taking this mediation. You will need periodic laboratory tests while taking this medication. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience loss of appetite, nausea and vomiting (small, frequent meals and frequent mouth care may help), or diarrhea (buttermilk, boiled milk, or yogurt may help). Report immediately persistent diarrhea; skin rash; unusual or persistent respiratory difficulty or wheezing; chest pain or cough; any change in vision, eye pain, or signs of eye infection; unusual weakness or joint pain; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant. Consult prescriber for appropriate contraceptive measures while on this medication. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 250 mg

Generic AvailableNo

ManufacturerAstraZeneca

Pricing: U.S. (www.drugstore.com)

Tablets (Iressa)

250 mg (30): $1805.91

Mechanism of ActionThe mechanism of antineoplastic action is not fully understood. Gefitinib inhibits tyrosine kinases (TK) associated with transmembrane cell surface receptors found on both normal and cancer cells. One such receptor is epidermal growth factor receptor. TK activity appears to be vitally important to cell proliferation and survival.

Pharmacodynamics/Kinetics

Absorption: Oral: slow

Distribution: I.V.: 1400 L

Protein binding: 90%, albumin and alpha$_1$-acid glycoprotein

Metabolism: Hepatic, primarily via CYP3A4; forms metabolites

Bioavailability: 60%

Half-life elimination: I.V.: 48 hours

Time to peak, plasma: Oral: 3-7 hours

Excretion: Feces (86%); urine (<4%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mouth ulceration.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; use caution with SSRIs. Carbamazepine may decrease gefitinib concentrations, while nefazodone and fluvoxamine may increase its concentrations.

Index TermsNSC-715055; ZD1839

References

Cohen EE, Rosen F, Stadler WM, et al, “Phase II Trial of ZD1839 in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck,” *J Clin Oncol*, 2003, 21(10):1980-7. [PubMed 12743152]

Culy CR and Faulds D, “Gefitinib,” *Drugs*, 2002, 62(15):2237-48. [PubMed 12381224]

Fukuoka M, Yano S, Giaccone G, et al, “Multi-Institutional Randomized Phase II Trial of Gefitinib for Previously Treated Patients With Advanced

Non-Small-Cell Lung Cancer," *J Clin Oncol*, 2003, 21(12):2237-46.[PubMed 12748244]

International Brand Names Iresa (KP); Iressa (AR, AU, CH, CL, CN, CR, DO, GT, HK, HN, ID, IL, MY, NI, PA, PE, PH, SG, SV, TH, TW, VE)

Jump To Field (Select Field Name)

Pronunciation(JEL a tin, ab SORB a ble)
U.S. Brand NamesGelfilm®; Gelfoam®
Pharmacologic CategoryHemostatic Agent
Use: Labeled IndicationsAdjunct to provide hemostasis in surgery; open prostatic surgery
Use: DentalAdjunct to provide hemostasis in oral and dental surgery
Dosing: AdultsHemostasis: Local: Apply packs or sponges dry or saturated with sodium chloride. When applied dry, hold in place with moderate pressure. When applied wet, squeeze to remove air bubbles. The powder is applied as a paste prepared by adding approximately 4 mL of sterile saline solution to the powder.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
StorageTo ensure sterility, use immediately after withdrawal from envelope.
ContraindicationsShould not be used in closure of skin incisions since they may interfere with the healing of skin edges
Warnings/Precautions

Disease-related concerns:

- Infection: Do not use in the presence of infection; if signs or symptoms of infection or abscess develop in an area where placed, reoperation may be necessary to remove material and allow drainage.

- Postpartum bleeding/menorrhagia: Do not use to control postpartum bleeding or menorrhagia.

Other warnings/precautions:

- Appropriate use: Do not overpack, product expands by absorbing fluid.

- Sterilization: Do not sterilize by heat.

Pregnancy Risk FactorNo data reported
Adverse Reactions1% to 10%: Local: Infection and abscess formation
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Film, ophthalmic (Gelfilm®): 25 mm x 50 mm (6s)

Film, topical (Gelfilm®): 100 mm x 125 mm (1s)

Powder, topical (Gelfoam®): 1 g

Sponge, dental (Gelfoam®): Size 4 (12s)

Sponge, topical (Gelfoam®):

Size 50 (4s)

Size 100 (6s)

Size 200 (6s)

Size 2 cm (1s)

Size 6 cm (6s)

Size 12-7 mm (12s)

Generic AvailableNo
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Local infection and abscess formation.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsAbsorbable Gelatin Sponge

Jump To Field (Select Field Name)

Pronunciation(JEL a tin, PEK tin, & meth il SEL yoo lose)

Pharmacologic CategoryTopical Skin Product

Use: Labeled IndicationsTemporary relief from minor oral irritations

Dosing: AdultsOral irritation: Topical: Press small dabs into place until the involved area is coated with a thin film; do not try to spread onto area; may be used as often as needed

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Dental Health: Effects on Dental TreatmentNo effects or complications reported

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMethylcellulose, Gelatin, and Pectin; Pectin, Gelatin, and Methylcellulose

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Gemcitabine-Capecitabine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Gastrointestinal Cancer; Chemotherapy Regimen, Pancreatic Cancer

Regimen Use Biliary adenocarcinoma; Pancreatic cancer

Regimen

Gemcitabine: I.V.: 1000 mg/m^2/day days 1 and 8

[total dose/cycle = 2000 mg/m^2]

Capecitabine: Oral: 650 mg/m^2 twice daily days 1 to 14

[total dose/cycle = 18,200 mg/m^2]

Repeat cycle every 21 days

References

Hess V, Salzberg M, Borner M, et al, “Combining Capecitabine and Gemcitabine in Patients With Advanced Pancreatic Carcinoma: A Phase I/II Trial,” *J Clin Oncol*, 2003, 21(1):66-8.[PubMed 12506172]

Knox JJ, Hedley D, Oza A, et al, “Combining Gemcitabine and Capecitabine in Patients With Advanced Biliary Cancer: A Phase II Trial,” *J Clin Oncol*, 2005, 23(10):2332-8.[PubMed 15800324]

Gemcitabine-Carboplatin (Bladder Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Bladder Cancer

Regimen UseBladder cancer

Regimen

Gemcitabine: I.V.: 1000 mg/m^2/day days 1 and 8

[total dose/cycle = 2000 mg/m^2]

Carboplatin: I.V.: AUC 5 day 1

[total dose/cycle = AUC = 5]

Repeat cycle every 21 days for up to 6 cycles

References

Bamias A, Moulopoulos LA, Koutras A, et al, âThe Combination of Gemcitabine and Carboplatin as First-Line Treatment in Patients With Advanced Urothelial Carcinoma. A Phase II Study of the Hellenic Cooperative Oncology Group,â *Cancer*, 2006, 106(2):297-303. [PubMed 16342065]

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Nonsmall Cell)

Regimen UseLung cancer, nonsmall cell

Index TermsCarboplatin-Gemcitabine (NSCLC)

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Gemcitabine: I.V.: 1000 mg/m^2/dose days 1, 8, and 15

[total dose/cycle = 3000 mg/m^2]

Carboplatin: I.V.: AUC 5 day 1

[total dose/cycle = AUC = 5]

Repeat cycle every 28 days for up to 4 cycles

Variation 2:

Gemcitabine: I.V.: 1000 or 1100 mg/m^2/day days 1 and 8

[total dose/cycle = 2000 or 2200 mg/m^2]

Carboplatin: I.V.: AUC 5 day 8

[total dose/cycle = AUC = 5]

Repeat cycle every 28 days

References

Variation 1:

Danson S, Middleton MR, O'Byrne KJ, et al, “Phase III Trial of Gemcitabine and Carboplatin Versus Mitomycin, Ifosfamide, and Cisplatin or Mitomycin, Vinblastine, and Cisplatin in Patients With Advanced Nonsmall Cell Lung Carcinoma,” *Cancer*, 2003, 98(3):542-53.[PubMed 12879472]

Variation 2:

Iaffaioli RV, Tortoriello A, Facchini G, et al, “Phase I-II Study of Gemcitabine and Carboplatin in Stage IIIB-IV Nonsmall-Cell Lung Cancer,” *J Clin Oncol*, 1999, 17(3):921-6.[PubMed 10071285]

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Ovarian Cancer

Regimen UseOvarian cancer

Regimen

Gemcitabine: I.V.: 1000 mg/m^2/day days 1 and 8

[total dose/cycle = 2000 mg/m^2]

Carboplatin: I.V.: AUC 4 day 1

[total dose/cycle = AUC = 4]

Repeat cycle every 21 days for 6-10 cycles

References

Pfisterer J, Plante M, Vergote I, et al, "Gemcitabine Plus Carboplatin Compared With Carboplatin in Patients With Platinum-Sensitive Recurrent Ovarian Cancer: An Intergroup Trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG," *J Clin Oncol*, 2006, 24(29):4699-707.[PubMed 16966687]

Gemcitabine-Cisplatin (Bladder Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Bladder Cancer

Regimen UseBladder cancer

Regimen

Gemcitabine: I.V.: 1000 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 3000 mg/m^2]

Cisplatin: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Repeat cycle every 28 days for 6 cycles

References

von der Maase H, Hansen SW, Roberts JT, et al, âGemcitabine and Cisplatin Versus Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in Advanced or Metastatic Bladder Cancer: Results of a Large, Randomized, Multinational, Multicenter, Phase III Study,â *J Clin Oncol*, 2000, 18(17):3068-77.[PubMed 11001674]

Gemcitabine-Cisplatin (Cervical Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Cervical Cancer

Regimen Use Cervical cancer

Index Terms Cisplatin-Gemcitabine (Cervical Cancer)

Regimen

Gemcitabine: I.V.: 1250 mg/m^2/day days 1 and 8

[total dose/cycle = 2500 mg/m^2]

Cisplatin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Repeat cycle every 21 days

References

Burnett AF, Roman LD, Garcia AA, "A Phase II Study of Gemcitabine and Cisplatin in Patients With Advanced, Persistent, or Recurrent Squamous Cell Carcinoma of the Cervix," *Gynecol Oncol*, 2000, 76(1):63-6.[PubMed 10620443]

Gemcitabine-Cisplatin (NSCLC)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Nonsmall Cell)
Regimen UseLung cancer, nonsmall cell
Index TermsCisplatin-Gemcitabine (NSCLC)
RegimenNOTE: Multiple variations are listed below.

Variation 1:

Gemcitabine: I.V.: 1000 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 3000 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 28 days

Variation 2:

Gemcitabine: I.V.: 1250 mg/m^2/day days 1 and 8

[total dose/cycle = 2500 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21 days

Variation 3:

Gemcitabine: I.V.: 1000 mg/m^2/day days 1 and 8

[total dose/cycle = 2000 mg/m^2]

Cisplatin: I.V.: 80 mg/m^2 day 1

[total dose/cycle = 80 mg/m^2]

Repeat cycle every 21 days

Variation 4:

Gemcitabine: I.V.: 1250 mg/m^2/day days 1 and 8

[total dose/cycle = 2500 mg/m^2]

Cisplatin: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 21 days for up to 6 cycles

Variation 5:

Gemcitabine: I.V.: 1000 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 3000 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 15

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 28 days

Variation 6:

Gemcitabine: I.V.: 1000 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 3000 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 2

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 28 days for 5 cycles

Variation 7:

Gemcitabine: I.V.: 1200 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 3600 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 15

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 28 days for up to 6 cycles

Variation 8 (patients ≥70 years of age):

Gemcitabine: I.V.: 1000 mg/m^2/day days 1 and 8

[total dose/cycle = 2000 mg/m^2]

Cisplatin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 21 days for up to 6 cycles

References

Variation 1:

Comella P, Frasci G, Panza N, et al, "Randomized Trial Comparing Cisplatin, Gemcitabine, and Vinorelbine With Either Cisplatin and Gemcitabine or Cisplatin and Vinorelbine in Advanced Non-Small-Cell Lung Cancer: Interim Analysis of a Phase III Trial of the Southern Italy Cooperative Oncology Group," *J Clin Oncol*, 2000, 18(7):1451-7.[PubMed 10735892]

Sandler AB, Nemunaitis J, Denham C, et al, "Phase III Trial of Gemcitabine Plus Cisplatin Versus Cisplatin Alone in Patients With Locally Advanced or Metastatic Nonsmall-Cell Lung Cancer," *J Clin Oncol*, 2000, 18(1):122-30.[PubMed 10623702]

Schiller JH, Harrington D, Belani CP, et al, "Comparison of Four Chemotherapy Regimens for Advanced Non-Small-Cell Lung Cancer," *N Engl J Med*, 2002, 346(2):92-8.[PubMed 11784875]

Variation 2:

Cardenal F, López-Cabrerizo MP, Antón A, et al, "Randomized Phase III Study of Gemcitabine-Cisplatin Versus Etoposide-Cisplatin in the Treatment of Locally Advanced or Metastatic Non-Small-Cell Lung Cancer," *J Clin Oncol*, 1999, 17(1):12-8.[PubMed 10458212]

Variation 3:

Ohe Y, Ohashi Y, Kubota K, et al, "Randomized Phase III Study of Cisplatin Plus Irinotecan Versus Carboplatin Plus Paclitaxel, Cisplatin Plus Gemcitabine, and Cisplatin Plus Vinorelbine for Advanced Non-Small-Cell Lung Cancer: Four-Arm Cooperative Study in Japan," *Ann Oncol*, 2007, 18(2):317-23. [PubMed 17079694]

Variation 4:

Scagliotti GV, Parikh P, von Pawel J, et al, "Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non-Small-Cell Lung Cancer," *J Clin Oncol*, 2008, 26(21):3543-51.[PubMed 18506025]

Variation 5:

Abratt RP, Bezwoda WR, Goedhals L, et al, "Weekly Gemcitabine With Monthly Cisplatin: Effective Chemotherapy for Advanced Nonsmall-Cell Lung Cancer," *J Clin Oncol*, 1997, 15(2):744-9. [PubMed 9053500]

Variation 6:

Crino L, Scagliotti G, Marangolo M, et al, "Cisplatin-Gemcitabine Combination in Advanced Nonsmall-Cell Lung Cancer: A Phase II Study," *J Clin Oncol*, 1997, 15(1):297-303. [PubMed 8996156]

Variation 7:

Anton A, Diaz-Fernandez N, Gonzalez Larriba JL, et al, "Phase II Trial Assessing the Combination of Gemcitabine and Cisplatin in Advanced Non-Small Cell Lung Cancer (NSCLC)," *Lung Cancer*, 1998, 22(2):139-48.[PubMed 10022221]

Variation 8:

Gridelli C, Maione P, Illiano A, et al, "Cisplatin Plus Gemcitabine or Vinorelbine for Elderly Patients With Advanced Non Small-Cell Lung Cancer: The MILES-2P Studies," *J Clin Oncol*, 2007, 25(29):4663-9.[PubMed 17925563]

Gemcitabine-Docetaxel (Bladder Cancer)

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Bladder Cancer

Regimen UseBladder cancer

Regimen

Docetaxel: I.V.: 40 mg/m^2/day days 1 and 8

[total dose/cycle = 80 mg/m^2]

Gemcitabine: 800 mg/m^2/day days 1 and 8

[total dose/cycle = 1600 mg/m^2]

Repeat cycle every 21 days for up to 6 cycles

References

Dreicer R, Manola J, Schneider DJ, et al, âPhase II Trial of Gemcitabine and Docetaxel in Patients With Advanced Carcinoma of the Urothelium: A Trial of the Eastern Cooperative Oncology Group,â *Cancer*, 2003, 97(11):2743-7.[PubMed 12767086]

Gemcitabine-Docetaxel (Sarcoma)

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Sarcoma](); [Chemotherapy Regimen, Soft Tissue Sarcoma]()

Regimen UseOsteosarcoma; Soft tissue sarcoma

Regimen

Gemcitabine: I.V.: 675 mg/m^2/day days 1 and 8

[total dose/cycle = 1350 mg/m^2]

Docetaxel: I.V.: 100 mg/m^2 day 8

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21 days

References

Leu KM, Ostruszka LJ, Shewach D, et al, âLaboratory and Clinical Evidence of Synergistic Cytotoxicity of Sequential Treatment With Gemcitabine Followed by Docetaxel in the Treatment of Sarcoma,â *J Clin Oncol*, 2004, 22(9):1706-12.[PubMed 15117993]

Gemcitabine-Erlotinib

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Gastrointestinal Cancer](); [Chemotherapy Regimen, Pancreatic Cancer]()

Regimen UsePancreatic cancer

Index TermsErlotinib-Gemcitabine

Regimen

Cycle 1:

Gemcitabine: I.V.: 1000 mg/m^2/day days 1, 8, 15, 22, 29, 36, and 43 (cycle 1 only)

[total dose/cycle 1 = 7000 mg/m^2]

Erlotinib: Oral: 100 mg once daily days 1 to 56

[total dose/cycle 1 = 5600 mg]

Treatment cycle is 56 days

Subsequent cycles:

Gemcitabine: I.V.: 1000 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 3000 mg/m^2]

Erlotinib: Oral: 100 mg once daily days 1 to 28

[total dose/cycle = 2800 mg]

Repeat cycle every 28 days

References

Moore MJ, Goldstein D, Hamm J, et al, "Erlotinib Plus Gemcitabine Compared With Gemcitabine Alone in Patients With Advanced Pancreatic Cancer: A Phase III Trial of the National Cancer Institute of Canada Clinical Trials Group," *J Clin Oncol*, 2007, 25(15):1960-6.[PubMed 17452677]

Gemcitabine-Irinotecan

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Pancreatic Cancer

Regimen UsePancreatic cancer

Index TermsIrinotecan-Gemcitabine

Regimen

Gemcitabine: I.V.: 1000 mg/m^2/day days 1 and 8

[total dose/cycle = 2000 mg/m^2]

Irinotecan: I.V.: 100 mg/m^2/day days 1 and 8

[total dose/cycle = 200 mg/m^2]

Repeat cycle 21 days

References

Rocha Lima CM, Savarese D, Bruckner H, et al, âIrinotecan Plus Gemcitabine Induces Both Radiographic and CA 19-9 Tumor Marker Responses in Patients With Previously Untreated Advanced Pancreatic Cancer,â *J Clin Oncol*, 2002, 20(5):1182-91.[PubMed 11870159]

Gemcitabine-Oxaliplatin

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Pancreatic Cancer

Regimen Use Pancreatic cancer

Index Terms Oxaliplatin-Gemcitabine

Regimen

Gemcitabine: I.V.: 1000 mg/m^2/day (infused at 10 mg/m^2/minute) day 1

[total dose/cycle = 1000 mg/m^2]

Oxaliplatin: I.V.: 100 mg/m^2/day (over 2 hours) day 2

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 14 days

References

Louvet C, Labianca R, Hammel P, et al, "Gemcitabine in Combination With Oxaliplatin Compared With Gemcitabine Alone in Locally Advanced or Metastatic Pancreatic Cancer: Results of a GERCOR and GISCAD Phase III Trial," *J Clin Oncol*, 2005, 23(15):3509-16.[PubMed 15908661]

Gemcitabine-Paclitaxel

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Ovarian Cancer

Regimen UseOvarian cancer

Regimen

Paclitaxel: I.V.: 80 mg/m^2 infused over 60 minutes days 1, 8, and 15

[total dose/cycle = 240 mg/m^2]

Gemcitabine: I.V.: 1000 mg/m^2/day (start at end of paclitaxel infusion) days 1, 8, and 15

[total dose/cycle = 3000 mg/m^2]

Repeat cycle every 4 weeks

References

Garcia AA, O'Meara A, Bahador A, et al, âPhase II Study of Gemcitabine and Weekly Paclitaxel in Recurrent Platinum-Resistant Ovarian Cancer,â *Gynecol Oncol*, 2004, 93(2):493-8.[PubMed 15099968]

Gemcitabine-Vinorelbine-Doxorubicin (Liposomal)

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, Hodgkin's Disease

Regimen UseLymphoma, Hodgkin's disease

Index TermsGVD; Vinorelbine-Gemcitabine-Doxorubicin (Liposomal)

RegimenNOTE: Multiple variations are listed below.

Variation 1 (for transplant naive patients):

Vinorelbine: I.V.: 20 mg/m^2/day days 1 and 8

[total dose/cycle = 40 mg/m^2]

Gemcitabine: I.V.: 1000 mg/m^2/day days 1 and 8

[total dose/cycle = 2000 mg/m^2]

Doxorubicin liposomal: I.V.: 15 mg/m^2/day days 1 and 8

[total dose/cycle = 30 mg/m^2]

Repeat cycle every 21 days for 2-6 cycles

Variation 2 (for patients with prior transplant):

Vinorelbine: I.V.: 15 mg/m^2/day days 1 and 8

[total dose/cycle = 30 mg/m^2]

Gemcitabine: I.V.: 800 mg/m^2/day days 1 and 8

[total dose/cycle = 1600 mg/m^2]

Doxorubicin liposomal: I.V.: 10 mg/m^2/day days 1 and 8

[total dose/cycle = 20 mg/m^2]

Repeat cycle every 21 days for 2-6 cycles

References

Variations 1 and 2:

Bartlett NL, Niedzwiecki D, Johnson JL, et al, "Gemcitabine, Vinorelbine, and Pegylated Liposomal Doxorubicin (GVD), a Salvage Regimen in Relapsed Hodgkin's Lymphoma: CALGB 59804," *Ann Oncol*, 2007, 18(6):1071-9.[PubMed 17426059]

Gemcitabine-Vinorelbine

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Lung Cancer (Nonsmall Cell)]

Regimen UseLung cancer, nonsmall cell

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Gemcitabine: I.V.: 1200 mg/m^2/day days 1 and 8

[total dose/cycle = 2400 mg/m^2]

Vinorelbine: I.V.: 30 mg/m^2/day days 1 and 8

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 21 days for 6 cycles

Variation 2:

Gemcitabine: I.V.: 1000 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 3000 mg/m^2]

Vinorelbine: I.V.: 20 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 28 days for 6 cycles

References

Variation 1 and 2:

Frasci G, Lorusso V, Panza N, et al, “Gemcitabine Plus Vinorelbine vs Vinorelbine Alone in Elderly Patients With Advanced Nonsmall Cell Lung Cancer,” *J Clin Oncol*, 2000, 18(13):2529-36. [PubMed 10893283]

Hainsworth JD, Burris HA 3rd, Litchy S, et al, “Gemcitabine and Vinorelbine in the Second-Line Treatment of Nonsmall Cell Lung Carcinoma Patients: A Minnie Pearl Cancer Research Network Phase II Trial,” *Cancer*, 2000, 88(6):1353-8.[PubMed 10717616]

Gemcitabine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Gemcitabine may be confused with gemtuzumab

Gemzar® may be confused with Zinecard®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(jem SITE a been)
U.S. Brand NamesGemzar®
Canadian Brand NamesGemzar®
Pharmacologic CategoryAntineoplastic Agent, Antimetabolite (Pyrimidine Analog)
Use: Labeled IndicationsTreatment of metastatic breast cancer; locally-advanced or metastatic nonsmall cell lung cancer (NSCLC) or pancreatic cancer; advanced, relapsed ovarian cancer
Use: Unlabeled/InvestigationalTreatment of bladder cancer, acute leukemia
Dosing: AdultsRefer to individual protocols. **Note**: Prolongation of the infusion time >60 minutes and administration more frequently than once weekly have been shown to increase toxicity. I.V.:

Pancreatic cancer: Initial: 1000 mg/m^2 weekly for up to 7 weeks followed by 1 week rest; then weekly for 3 weeks out of every 4 weeks.

Dose adjustment: Patients who complete an entire cycle of therapy may have the dose in subsequent cycles increased by 25% as long as the absolute granulocyte count (AGC) nadir is >1500 x 10^6/L, platelet nadir is >100,000 x 10^6/L, and nonhematologic toxicity is less than WHO Grade 1. If the increased dose is tolerated (with the same parameters) the dose in subsequent cycles may again be increased by 20%.

Nonsmall cell lung cancer:

1000 mg/m^2 days 1, 8, and 15; repeat cycle every 28 days

or

1250 mg/m^2 days 1 and 8; repeat cycle every 21 days

Breast cancer: 1250 mg/m^2 days 1 and 8; repeat cycle every 21 days

Ovarian cancer: 1000 mg/m^2 days 1 and 8; repeat cycle every 21 days

Bladder cancer (unlabeled use):

I.V.: 1000 mg/m^2 once weekly for 3 weeks; repeat cycle every 4 weeks

Intravesicular instillation: 2000 mg (in 100 mL NS; retain for 1 hour) twice weekly for 3 weeks; repeat cycle every 4 weeks (for at least 2 cycles)

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentThe FDA-approved labeling does not contain dosing adjustment guidelines; use caution. Gemcitabine has not been studied in patients with significant renal dysfunction.
Dosing: Hepatic ImpairmentThe FDA-approved labeling does not contain dosing adjustment guidelines; use caution. Gemcitabine has not been studied in patients with significant hepatic dysfunction. The following guidelines have been used by some clinicians (Floyd, 2006):
Serum bilirubin >1.6 mg/dL: Use starting dose of 800 mg/m^2
Dosing: Adjustment for Toxicity

Pancreatic cancer: Hematologic toxicity:

AGC ≥1000 x 10^6/L and platelet count ≥100,000 x 10^6/L: Administer 100% of full dose

AGC 500-999 x 10^6/L or platelet count 50,000-90,000 x 10^6/L: Administer 75% of full dose

AGC <500 x 10^6/L or platelet count <50,000 x 10^6/L: Hold dose

Nonsmall cell lung cancer:

Hematologic toxicity: Refer to guidelines for pancreatic cancer. Cisplatin dosage may also need adjusted.

Severe (grades 3 or 4) nonhematologic toxicity (except alopecia, nausea and vomiting): Hold or decrease dose by 50%.

Breast cancer:

Hematologic toxicity: Adjustments based on granulocyte and platelet counts on day 8:

AGC ≥1200 x 10^6/L and platelet count >75,000 x 10^6/L: Administer 100% of full dose

AGC 1000-1199 x 10^6/L or platelet count 50,000-75,000 x 10^6/L: Administer 75% of full dose

AGC 700-999 x 10^6/L and platelet count ≥50,000 x 10^6/L: Administer 50% of full dose

AGC <700 x 10^6/L or platelet count <50,000 x 10^6/L: Hold dose

Severe (grades 3 or 4) nonhematologic toxicity (except alopecia, nausea, and vomiting): Hold or decrease dose by 50%. Paclitaxel dose may also need adjusted.

Ovarian cancer:

Hematologic toxicity: Adjustments based on granulocyte and platelet counts on day 8:

AGC ≥1500 x 10^6/L and platelet count ≥100,000 x 10^6/L: Administer 100% of full dose

AGC 1000-1499 x 10^6/L and/or platelet count 75,000-99,999 x 10^6/L: Administer 50% of full dose

AGC <1000 x 10^6/L and/or platelet count <75,000 x 10^6/L: Hold dose

Severe (grades 3 or 4) nonhematologic toxicity (except nausea and vomiting): Hold or decrease dose by 50%. Carboplatin dose may also need adjusted.

Dose adjustment for subsequent cycles:

AGC < 500 x 10^6/L for >5 days, AGC <100 x 10^6/L for >3 days, febrile neutropenia, platelet count <25,000 x 10^6/L, cycle delay >1 week due to toxicity: Reduce gemcitabine to 800 mg/m2 on days 1 and 8.

For recurrence of any of the above toxicities after initial dose reduction: Administer gemcitabine 800 mg/m^2 on day 1 only for the subsequent cycle

Dosing: Combination Regimens

Biliary adenocarcinoma:

Gemcitabine-Capecitabine

GEMOX

Bladder cancer:

Gemcitabine-Carboplatin (Bladder Cancer)

Gemcitabine-Cisplatin (Bladder Cancer)

Gemcitabine-Docetaxel (Bladder Cancer)

Paclitaxel-Carboplatin-Gemcitabine

Paclitaxel-Gemcitabine

Cervical cancer: Gemcitabine-Cisplatin (Cervical Cancer)

Leukemia, acute lymphocytic: TVTG

Leukemia, acute myeloid: TVTG

Lung cancer (nonsmall cell):

Bevacizumab-Cisplatin-Gemcitabine

Gemcitabine-Carboplatin (NSCLC)

Gemcitabine-Cisplatin (NSCLC)

Gemcitabine-Vinorelbine

Vinorelbine-Gemcitabine

Lymphoma, Hodgkin's: Gemcitabine-Vinorelbine-Doxorubicin (Liposomal)

Osteosarcoma: Gemcitabine-Docetaxel (Sarcoma)

Ovarian cancer: Gemcitabine-Carboplatin (Ovarian Cancer)

Pancreatic cancer:

Gemcitabine-Capecitabine

Gemcitabine-Erlotinib

Gemcitabine-Irinotecan

Gemcitabine-Oxaliplatin

Soft tissue sarcoma: Gemcitabine-Docetaxel (Sarcoma)

Calculations

- Body Surface Area: Adults

Administration: I.V.Infuse over 30 minutes. **Note**: Prolongation of the infusion time >60 minutes has been shown to increase toxicity. Gemcitabine is being investigated in clinical trials for fixed dose rate (FDR) infusion administration at doses from 1000 mg/m^2 to 2200 mg/m^2 at a rate of 10 mg/m^2/minute. Prolonged infusion times increase the accumulation of the active metabolite, gemcitabine triphosphate. Patients who receive gemcitabine FDR experience more grade 3/4 hematologic toxicity.

Administration: I.V. DetailpH: 2.7-3.3

StorageStore intact vials at room temperature of 20°C to 25°C (68°F to 77°F). Reconstituted vials are stable for up to 35 days and infusion solutions diluted in 0.9% sodium chloride are stable up to 7 days at 23°C when protected from light ; however, the manufacturer recommends use within 24 hours for both reconstituted vials and infusion solutions. Do not refrigerate.

ReconstitutionReconstitute the 200 mg vial with preservative free 0.9% NaCl 5 mL or the 1000 mg vial with preservative free 0.9% NaCl 25 mL. Resulting solution is 38 mg/mL. Dilute with 50-500 mL 0.9% sodium chloride injection or D_5W to concentrations as low as 0.1 mg/mL.

CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Amifostine, amikacin, aminophylline, ampicillin, ampicillin/sulbactam, aztreonam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, carmustine, cefazolin, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, chlorpromazine, cimetidine, ciprofloxacin, cisplatin, clindamycin, co-trimoxazole, cyclophosphamide, cytarabine, dactinomycin, daunorubicin, dexamethasone sodium phosphate, dexrazoxane, diphenhydramine, dobutamine, docetaxel, dopamine, doxorubicin, doxycycline, droperidol, enalaprilat, etoposide, etoposide phosphate, famotidine, floxuridine, fluconazole, fludarabine, fluorouracil, gatifloxacin, gentamicin, granisetron, haloperidol, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, idarubicin, ifosfamide, leucovorin, linezolid, lorazepam, mannitol, meperidine, mesna, metoclopramide, metronidazole, minocycline, mitoxantrone, morphine, nalbuphine, netilmicin, ofloxacin, ondansetron, paclitaxel, plicamycin, potassium chloride, promethazine, ranitidine, sodium bicarbonate, streptozocin, teniposide, thiotepa, ticarcillin, ticarcillin/clavulanate, tobramycin, topotecan, vancomycin, vinblastine, vincristine, vinorelbine, zidovudine. **Incompatible:** Acyclovir, amphotericin B, cefoperazone, cefotaxime, furosemide, ganciclovir, imipenem/cilastatin, irinotecan, methotrexate, methylprednisolone sodium succinate, mitomycin, piperacillin, piperacillin/tazobactam, prochlorperazine edisylate.

ContraindicationsHypersensitivity to gemcitabine or any component of the formulation; pregnancy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: May cause bone marrow suppression (leukopenia, thrombocytopenia, and anemia); myelosuppression is usually the dose-limiting toxicity.
- Fever: May cause fever in the absence of clinical infection.
- Hemolytic uremic syndrome: With use, hemolytic uremic syndrome has been reported; monitor for evidence of microangiopathic hemolysis (elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or renal failure).
- Hepatotoxicity: Serious hepatotoxicity has been reported; use caution with hepatic impairment (history of cirrhosis, hepatitis, or alcoholism) or in patients with hepatic metastases; may lead to exacerbation of hepatic impairment.
- Pulmonary toxicity: With use, pulmonary toxicity has occurred; discontinue if severe.

Disease-related concerns:

- Renal impairment: Use with caution in patients with pre-existing renal impairment.

Special populations:

- Elderly: Use with caution in the elderly; clearance is affected by age.
- Pediatrics: Efficacy has not been established in children.
- Radiation therapy recipients: Use with caution with concurrent radiation therapy; radiation toxicity has been reported with concurrent and nonconcurrent administration; may have radiosensitizing activity when gemcitabine and radiation therapy are given ≤7 days apart; optimum regimen for combination therapy has not been determined for all tumor types.

Other warnings/precautions:

- Administration: Prolongation of the infusion time >60 minutes and more frequent than weekly dosing have been shown to increase toxicity.

Geriatric ConsiderationsClearance is affected by age. There is no evidence; however, that unusual dose adjustment is necessary in patients older than 65 years of age. In general, adverse reaction rates were similar to patients older and younger than 65 years. Grade 3/4 thrombocytopenia was more common in the elderly. Older women were more likely to experience grade 3/4 neutropenia and thrombocytopenia.

Pregnancy Risk FactorD

Pregnancy ConsiderationsEmbryotoxicity and fetal malformations (cleft palate, incomplete ossification, fused pulmonary artery, absence of gallbladder) have been reported in animal studies. There are no adequate and well-controlled studies in pregnant women. If patient becomes pregnant, she should be informed of risks.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Cardiovascular: Peripheral edema (20%), edema (13%)

Central nervous system: Pain (10% to 48%), fever (30% to 41%), somnolence (5% to 11%)

Dermatologic: Rash (24% to 30%), alopecia (15% to 18%), pruritus (13%)

Gastrointestinal: Nausea/vomiting (64% to 71%; grades 3/4: 1% to 13%), constipation (10% to 31%), diarrhea (19% to 30%), stomatitis (10% to 14%)

Hematologic: Anemia (65% to 73%; grade 4: 1% to 3%), leukopenia (62% to 71%; grade 4: ≤1%), neutropenia (61% to 63%; grade 4: 6% to 7%), thrombocytopenia (24% to 47%; grade 4: ≤1%), hemorrhage (4% to 17%; grades 3/4: <1% to 2%); myelosuppression is the dose-limiting toxicity

Hepatic: Transaminases increased (67% to 78%; grades 3/4: 1% to 12%), alkaline phosphatase increased (55% to 77%; grades 3/4: 2% to 16%), bilirubin increased (13% to 26%; grades 3/4: <1% to 6%)

Renal: Proteinuria (10% to 45%; grades 3/4: <1%), hematuria (13% to 35%; grades 3/4: <1%), BUN increased (8% to 16%; grades 3/4: 0%)

Respiratory: Dyspnea (6% to 23%)

Miscellaneous: Flu-like syndrome (19%), infection (8% to 16%; grades 3/4: <1% to 2%)

1% to 10%:

Local: Injection site reactions (4%)

Neuromuscular & skeletal: Paresthesia (2% to 10%)

Renal: Creatinine increased (2% to 8%)

Respiratory: Bronchospasm (<2%)

<1%, postmarketing, and/or case reports (reported with single-agent use or with combination therapy, all reported rarely): Adult respiratory distress syndrome, anaphylactoid reaction, anorexia, arrhythmias, bullous skin eruptions, cellulitis, cerebrovascular accident, CHF, chills, cough, desquamation, diaphoresis, gangrene, GGT increased, headache, hemolytic uremic syndrome (HUS), hepatotoxic reaction (rare), hypertension, insomnia, interstitial pneumonitis, liver failure, malaise, MI, peripheral vasculitis, petechiae, pulmonary edema, pulmonary fibrosis, radiation recall, renal failure, respiratory failure, rhinitis, sepsis, supraventricular arrhythmia, weakness

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

Bleomycin: Gemcitabine may enhance the adverse/toxic effect of Bleomycin. The risk of pulmonary toxicity may be increased. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fluorouracil: Gemcitabine may increase the serum concentration of Fluorouracil. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to GI irritation).

Monitoring ParametersCBC with differential and platelet count (prior to each dose); hepatic and renal function (prior to initiation of therapy and periodically, thereafter); monitor electrolytes, including potassium, magnesium, and calcium (when in combination therapy with cisplatin)

Nursing: Physical Assessment/MonitoringSee specific Administration directions (adverse reactions increase when infused over >60 minutes). Assess results of laboratory tests (eg, CBC with differential and platelet count), prior to each dose. Monitor patient response (symptom relief) and adverse reactions (eg, CNS changes, rash, gastrointestinal upset, anemia, myelosuppression, dyspnea) prior to each treatment and on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelet count (prior to each dose); hepatic and renal function (prior to initiation of therapy and periodically, thereafter); monitor electrolytes, including potassium, magnesium, and calcium (when in combination therapy with cisplatin)

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug can only be administered by infusion; report any redness, pain, or swelling at infusion site. During therapy, do not use alcohol. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition (small, frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). You may experience fatigue, lethargy, somnolence (use caution when driving or engaging in potentially hazardous tasks until response to drug is known); nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); loss of hair (reversible); mouth sores (frequent mouth care and use of a soft toothbrush or cotton swabs may help); or diarrhea (buttermilk, boiled milk, or yogurt may help reduce diarrhea). This drug may cause sterility. Report extreme fatigue; severe GI upset or diarrhea; bleeding or bruising; fever, chills, sore throat; vaginal discharge; signs of fluid retention (swelling extremities, respiratory difficulty, unusual weight gain); yellowing of skin or eyes; change in color of urine or stool; muscle or skeletal pain or weakness; or other persistent adverse effects. **Pregnancy/breast-feeding precautions**: Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate barrier contraceptive measures. This drug may cause severe fetal birth defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Gemzar®: 200 mg, 1 g

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Gemzar)

1 g (1): $771.17

200 mg (1): $154.75

Mechanism of ActionA pyrimidine antimetabolite that inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase, specific for the S-phase of the cycle. Gemcitabine is phosphorylated intracellularly by deoxycytidine kinase to gemcitabine monophosphate, which is further phosphorylated to active metabolites gemcitabine diphosphate and gemcitabine triphosphate. Gemcitabine diphosphate inhibits DNA synthesis by inhibiting ribonucleotide reductase; gemcitabine triphosphate incorporates into DNA and inhibits DNA polymerase.

Pharmacodynamics/Kinetics

Distribution: Infusions <70 minutes: 50 L/m^2; Long infusion times: 370 L/m^2

Protein binding: Low

Metabolism: Metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleoside metabolites

Half-life elimination:

Gemcitabine: Infusion time ≤1 hour: 42-94 minutes; infusion time 3-4 hours: 4-10.5 hours

Metabolite (gemcitabine triphosphate), terminal phase: 1.7-19.4 hours

Time to peak, plasma: 30 minutes after completion of infusion

Excretion: Urine (92% to 98%; primarily as inactive uracil metabolite); feces (<1%)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; use caution with clozapine and carbamazepine

Index TermsGemcitabine Hydrochloride; NSC-613327

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Noble S and Goa KL, "Gemcitabine. A Review of its Pharmacology and Clinical Potential in Nonsmall Cell Lung Cancer and Pancreatic Cancer," *Drugs*, 1997, 54(3):447-72. [PubMed 9279506]

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International Brand NamesAbine (AR); Gembine (KP); Gemcibine (KP); Gemcite (IN); Gemmis (TW); Gemtan (KP); Gemtro (AR); Gemzar (AR, AT, AU, BE, BF, BG, BJ, BO, BR, CH, CI, CL, CN, CO, CR, CZ, DE, DK, DO, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, HK, HN, HR, HU, ID, IE, IL, IT, KE, KP, LR, LU, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, PA, PE, PH, PK, PL, PR, PT, PY, RU, SC, SD, SE, SG, SL, SN, SV, TH, TN, TR, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Geroam (KP); Zefei (PH)

Gemfibrozil

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English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Lopid® may be confused with Levbid®, Lodine®, Lorabid®, Slo-bid™

Pronunciation(jem FI broe zil)

U.S. Brand NamesLopid®

Canadian Brand NamesApo-Gemfibrozil®; Gen-Gemfibrozil; GMD-Gemfibrozil; Lopid®; Novo-Gemfibrozil; Nu-Gemfibrozil; PMS-Gemfibrozil

Pharmacologic CategoryAntilipemic Agent, Fibric Acid

Use: Labeled IndicationsTreatment of hypertriglyceridemia in types IV and V hyperlipidemia for patients who are at greater risk for pancreatitis and who have not responded to dietary intervention

Dosing: AdultsHyperlipidemia/hypertriglyceridemia: Oral: 1200 mg/day in 2 divided doses, 30 minutes before breakfast and dinner

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentHemodialysis effects: Not removed by hemodialysis; supplemental dose is not necessary.

Dietary ConsiderationsBefore initiation of therapy, patients should be placed on a standard cholesterol-lowering diet for 3-6 months and the diet should be continued during drug therapy.

ContraindicationsHypersensitivity to gemfibrozil or any component of the formulation; significant hepatic or renal dysfunction; primary biliary cirrhosis; pre-existing gallbladder disease

Allergy Considerations

- Fibric Acid Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anemia/leukopenia: Have been reported.
- Cholelithiasis: May increase risk of cholelithiasis.
- Elevated transaminases: Elevations in serum transaminases can be seen.
- Malignancy: Possible increased risk of malignancy.
- Myopathy/rhabdomyolysis: Has been associated with rare myositis or rhabdomyolysis; patients should be monitored closely. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; deterioration has been seen when used in patients with a serum creatinine >2.0 mg/dL.

Concurrent drug therapy issues:

- HMG-CoA reductase inhibitors: Use caution with HMG-CoA reductase inhibitors; may lead to myopathy, rhabdomyolysis.
- Warfarin: Use with caution in patient taking warfarin; adjustments in warfarin therapy may be required.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Be careful in patient selection, this is not a first- or second-line choice; other agents may be more suitable. Discontinue if lipid response not seen.
- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.
- Mortality benefit: The use of gemfibrozil has not demonstrated a reduction in cardiovascular mortality.

Geriatric ConsiderationsGemfibrozil is the drug of choice for the treatment of hypertriglyceridemia and hypoalphaproteinemia in the elderly; it is usually well tolerated; myositis may be more common in patients with poor renal function. The definition of and, therefore, when to treat hyperlipidemia in the elderly is a controversial issue. The National Cholesterol Education Program recommends that all adults maintain a plasma cholesterol <160 mg/dL. Older adults with one additional risk factor, goal LDL would be <130 mg/dL. It is the authors' belief that pharmacologic treatment be reserved for those who are unable to obtain a desirable plasma cholesterol concentration by diet alone and for whom the benefits of treatment are believed to outweigh the potential adverse effects, drug interactions, and cost of treatment.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/contraindicated
Adverse Reactions

>10%: Gastrointestinal: Dyspepsia (20%)

1% to 10%:

Central nervous system: Fatigue (4%), vertigo (2%), headache (1%)

Dermatologic: Eczema (2%), rash (2%)

Gastrointestinal: Abdominal pain (10%), diarrhea (7%), nausea/vomiting (3%), constipation (1%)

<1% or case reports with probable causation (limited to important or life-threatening): Alkaline phosphatase increased, anemia, angioedema, arthralgia, bilirubin increased, blurred vision, bone marrow hypoplasia, cataracts, cholelithiasis, cholecystitis, cholestatic jaundice, creatine phosphokinase increased, depression, dermatitis, dermatomyositis/polymyositis, dizziness, eosinophilia, exfoliative dermatitis, headache, hypoesthesia, hypokalemia, impotence, intracranial hemorrhage, laryngeal edema, leukopenia, libido decreased, myalgia, myasthenia, myopathy, nephrotoxicity, paresthesia, peripheral neuritis, peripheral vascular disease, pruritus, rash, Raynaud's phenomenon, rhabdomyolysis, somnolence, synovitis, taste perversion, transaminases increased, urticaria, vasculitis

Reports where causal relationship has not been established: Weight loss, extrasystoles, pancreatitis, hepatoma, colitis, confusion, seizure, syncope, retinal edema, decreased fertility (male), renal dysfunction, positive ANA, drug-induced lupus-like syndrome, thrombocytopenia, anaphylaxis, vasculitis, alopecia, photosensitivity

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor); **Inhibits** CYP1A2 (moderate), 2C8 (strong), 2C9 (strong), 2C19 (strong)
Drug Interactions

Antidiabetic Agents (Thiazolidinedione): Gemfibrozil may decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Fibric Acid Derivatives. **Exceptions:** Colesevelam. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Strong) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Ezetimibe: Fibric Acid Derivatives may increase the serum concentration of Ezetimibe. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Gemfibrozil may enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Gemfibrozil may increase the serum concentration of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin. *Risk D: Consider therapy modification*

Repaglinide: Gemfibrozil may increase the serum concentration of Repaglinide. The addition of itraconazole may augment the effect of gemfibrozil on repaglinide. Management: Consider alternative therapy combinations to avoid this potentially significant interaction. Avoid concurrent use when also used with a CYP3A4 inhibitor. *Risk D: Consider therapy modification*

Sulfonylureas: Fibric Acid Derivatives may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Fibric Acid Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol to decrease triglycerides.
Monitoring ParametersSerum cholesterol, LFTs
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking (eg, increased risk of myopathy, rhabdomyolysis, hypoglycemia, and toxicity). Assess results of laboratory tests (serum cholesterol and LFTs), therapeutic effectiveness (decreased lipid levels), and adverse reactions (eg, gastrointestinal disturbances) periodically during therapy. Teach proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsSerum cholesterol, LFTs
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Should be taken 30 minutes before meals. Take with milk or meals if GI upset occurs. Avoid alcohol. Follow dietary recommendations of prescriber. You will need check-ups and blood work to assess effectiveness of therapy. You may experience loss of appetite and flatulence (small, frequent meals may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report severe stomach pain, nausea, vomiting; headache; persistent diarrhea; or vision changes. **Pregnancy/breast-feeding precautions**: Inform prescriber if you are or intend to become pregnant. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, oral: 600 mg

Lopid®: 600 mg [scored]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Gemfibrozil)

600 mg (60): $15.99

Tablets (Lopid)

600 mg (60): $135.43

Mechanism of ActionThe exact mechanism of action of gemfibrozil is unknown, however, several theories exist regarding the VLDL effect; it can inhibit lipolysis and decrease subsequent hepatic fatty acid uptake as well as inhibit hepatic secretion of VLDL; together these actions decrease serum VLDL levels; increases HDL-cholesterol; the mechanism behind HDL elevation is currently unknown

Pharmacodynamics/Kinetics

Onset of action: May require several days

Absorption: Well absorbed

Protein binding: 99%

Metabolism: Hepatic via oxidation to two inactive metabolites; undergoes enterohepatic recycling

Half-life elimination: 1.4 hours

Time to peak, serum: 1-2 hours

Excretion: Urine (70% primarily as conjugated drug); feces (6%)

Related Information

- Hyperlipidemia Management
- Lipid-Lowering Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause sedation or depression

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsFibric acids decrease triglycerides (TGs) by 20% to 50%, and increase HDL-cholesterol (HDL-C) by 10% to 20%. They decrease LDL-cholesterol (LDL-C) by 5% to 20%, however, LDL-C actually may increase by 10% to 30% when fibrates are initiated in patients with high TGs (>400 mg/dL). Although combination therapy with statins has been used in patients with resistant hyperlipidemias, keep vigilant for signs and symptoms of myopathy.

A recent study (VA-HIT) showed that gemfibrozil therapy resulted in a significant reduction in the risk of major cardiovascular events in patients with CHD and isolated low HDL-C ≤40 mg/dL (average: 32 mg/dL) with LDL-C ≤140 mg/dL (average: 111 mg/dL) and TGs ≤300 mg/dL (average: 161 mg/dL) (Rubins, 1999). These findings suggest that the rate of coronary events is reduced by raising HDL-cholesterol levels in patients with isolated low HDL-C levels. The treatment of isolated low HDL-C in the general population is usually reserved for patients at high risk for developing CAD with therapy focused on addressing the other risk factors. At present, minimal if any, data are available on how to use medications in patients with low HDL-C and no risk factors.

Anesthesia and Critical Care Concerns/Other ConsiderationsGemfibrozil increases HDL, decreases total cholesterol and triglycerides. A recent study (HIT), showed that gemfibrozil therapy resulted in a significant reduction in the risk of major cardiovascular events in patients with low HDL-cholesterol. These findings suggest that the rate of coronary events is reduced by raising HDL-cholesterol levels and lowering triglyceride levels. The treatment of low HDL in the general population, is not established.

Index TermsCI-719

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Tal A, Rajeshawari M, and Isley W, “Rhabdomyolysis Associated With Simvastatin/Gemfibrozil Therapy,” *South Med J*, 1997, 90(5):546-7.[PubMed 9160078]

International Brand NamesAfibrozil (PL); Apo-Gemfibrozil (NZ); Ausgem (AU); Bisil (TH); Brozil (MY, SG); Cholespid (PH); Detrichol (ID); Elmogan (HK, HR, PL); Fetinor (ID); Fibralip (ID); Fibrocit (IT); Gedum (AR); Gemd (SG, TW); Gemfi (DE); Gemfibral (PL); Gemfibril (TH); Gemizol

(NZ); Gemlipid (IT, TR); Gemnpid (TW); Gevilon (AT, BG, CH, CZ, DE, FI, HN, HR, HU, PL); Gozid (TH); Grifogemzilo (PE); Hidil (SG, TH); Hipolixan (PY); Innogem (HU); Ipolipid (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, HK, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, QA, SA, SC, SD, SG, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Jezil (AU); Lifibron (ID); Lipazil (AU); Lipidys (TH); Lipigem (PH, PL); Lipira (ID); Lipison (HK); Lipistorol (HK); Lipizile (PH); Lipofor (HK, SG); Lipolo (TH); Lipozil (PL); Lipur (FR); Lopid (AE, AR, AU, BE, BH, BR, CN, CO, CR, CY, DK, EC, EG, FI, GB, GR, GT, HK, HN, ID, IE, IL, IQ, IR, IT, JO, KW, LB, LU, LY, MX, NI, NL, NO, OM, PA, PE, PH, PK, PT, QA, SA, SE, SV, SY, TH, TR, TW, UY, VE, YE, ZA); Low-Lip (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Manobrozil (TH); Marbrozil (HK); Mersikol (ID); Minilip (HU); Normolip (IN); Polyxit (TH); Progemzal (ID); Qualipid (HK); Recozil (SG); Reducel (PH); Regulip (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Synbrozil (HK); Trialmin (ES); Triglizil (CO); Weijiangzhi (CL); Zilop (CO)

Gemifloxacin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(je mi FLOKS a sin)

U.S. Brand NamesFactive®

Canadian Brand NamesFactive®

Pharmacologic Category[Antibiotic, Quinolone](); [Respiratory Fluoroquinolone]()

Use: Labeled IndicationsTreatment of acute exacerbation of chronic bronchitis; treatment of community-acquired pneumonia (CAP), including pneumonia caused by multidrug-resistant strains of *S. pneumoniae* (MDRSP)

Use: Unlabeled/InvestigationalAcute sinusitis

Dosing: Adults

Susceptible infections: Oral: 320 mg once daily

Acute exacerbations of chronic bronchitis: Oral: 320 mg once daily for 5 days

Community-acquired pneumonia (mild to moderate): Oral: 320 mg once daily for 5 or 7 days (decision to use 5- or 7-day regimen should be guided by initial sputum culture; 7 days are recommended for MDRSP, *Klebsiella*, or *M. catarrhalis* infection)

Sinusitis (unlabeled use): Oral: 320 mg once daily for 10 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} >40 mL/minute: No adjustment required.

Cl_{cr} ≤40 mL/minute (or patients on hemodialysis/CAPD): 160 mg once daily (administer dose following hemodialysis).

Dosing: Hepatic ImpairmentNo adjustment required.

Calculations

- [Creatinine Clearance: Adults]()

Administration: OralMay be administered with or without food, milk, or calcium supplements. Gemifloxacin should be taken 3 hours before or 2 hours after supplements (including multivitamins) containing iron, zinc, or magnesium.

Dietary ConsiderationsMay take tablets with or without food, milk, or calcium supplements. Gemifloxacin should be taken 3 hours before or 2 hours after supplements (including multivitamins) containing iron, zinc, or magnesium.

StorageStore at 25°C (77°F). Protect from light.

RestrictionsAn FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to gemifloxacin, other fluoroquinolones, or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Tendon inflammation/rupture: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Altered cardiac conduction: Fluoroquinolones may prolong QT_c interval; avoid use in patients with a history of QT_c prolongation, uncorrected hypokalemia, hypomagnesemia, or concurrent administration of other medications known to prolong the QT interval (including Class Ia and Class III antiarrhythmics, cisapride, erythromycin, antipsychotics, and tricyclic antidepressants).

- CNS stimulation: Tremor, restlessness, confusion, and very rarely hallucinations or seizures may occur; use with caution in patients with known or suspected CNS disorder. Discontinue in patients who experience significant CNS adverse effects (eg, dizziness, hallucinations, suicidal ideations or actions).

- Glucose regulation: Fluoroquinolones have been associated with the development of serious, and sometimes fatal, hypoglycemia. These events have occurred most often in elderly patients with diabetes, but have also been reported in patients without a prior history of diabetes. Prompt identification and treatment of hypoglycemia is essential. Individual quinolones may differ in their potential to cause this effect. It was most evident with gatifloxacin (no longer marketed as s systemic formulation). Hyperglycemia has also been associated with the use of fluoroquinolones. Patients should be monitored closely for signs/symptoms of disordered glucose regulation.

- Hypersensitivity reactions: Severe hypersensitivity reactions, including anaphylaxis, have occurred with quinolone therapy. The spectrum of these reactions can vary widely; reactions may present as typical allergic symptoms (eg, itching, urticaria, rash, edema) after a single dose, or may manifest as severe idiosyncratic dermatologic (eg, Stevens-Johnson, toxic epidermal necrolysis), vascular (eg, vasculitis), pulmonary (eg, pneumonitis), renal (eg, nephritis), hepatic (eg, hepatic failure or necrosis), and/or hematologic (eg, anemia, cytopenias) events, usually after multiple doses. May cause maculopapular rash, usually 8-10 days after treatment initiation; risk factors may include age <40 years, female gender (including postmenopausal women on HRT), and treatment duration >7 days. Prompt discontinuation of drug should occur if skin rash or other symptoms arise.

- Peripheral neuropathy: The use of quinolones has been linked to peripheral neuropathy (rare); discontinue if symptoms of sensory or sensorimotor neuropathy occur.
- Phototoxicity: Avoid excessive sunlight and take precautions to limit exposure (eg, loose fitting clothing, sunscreen); may cause moderate-to-severe phototoxicity reactions. Discontinue use if photosensitivity occurs.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.
- Tendon inflammation/rupture: **[U.S. Boxed Warning]: There have been reports of tendon inflammation and/or rupture with quinolone antibiotics; risk may be increased with concurrent corticosteroids, organ transplant recipients, and in patients >60 years of age.** Rupture of the Achilles tendon sometimes requiring surgical repair has been reported most frequently; but other tendon sites (eg, rotator cuff, biceps) have also been reported. Strenuous physical activity may be an independent risk factor for tendonitis. Discontinue at first sign of tendon inflammation or pain. May occur even after discontinuation of therapy.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with significant bradycardia or acute myocardial ischemia.
- Myasthenia gravis: Some quinolones may exacerbate myasthenia gravis, use with caution (rare, potentially life-threatening weakness of respiratory muscles may occur).
- Renal impairment: Use with caution in renal impairment; dosage adjustment required for Cl_{cr} ≤40 mL/minute. May increase risk of tendon rupture.
- Rheumatoid arthritis: Use with caution in patients with rheumatoid arthritis; may increase risk of tendon rupture.
- Seizures: Use with caution in individuals at risk of seizures (CNS disorders or concurrent therapy with medications which may lower seizure threshold). Potential for seizures, although very rare, may be increased with concomitant NSAID therapy.

Special populations:

- Elderly: Adverse effects (eg, tendon rupture, QT changes) may be increased in the elderly.
- G6PD deficiency: Hemolytic reactions may (rarely) occur with quinolone use in patients with latent or actual G6PD deficiency.
- Pediatrics: Safety and effectiveness have not been established in children.

Geriatric ConsiderationsThe risk of torsade de pointes and tendon inflammation and/or rupture associated with the concomitant use of corticosteroids and quinolones is increased in the elderly population. See Warnings/Precautions regarding tendon rupture in patients >60 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in some animal studies; therefore, the manufacturer classifies gemifloxacin as pregnancy category C. Quinolone exposure during human pregnancy has been reported with other agents (see Ciprofloxacin, Ofloxacin, and Norfloxacin monographs). To date, no specific teratogenic effect or increased pregnancy risk has been identified; however, because of concerns of cartilage damage in immature animals exposed to quinolones and the limited gemifloxacin specific data, gemifloxacin should only be used during pregnancy if a safer option is not available.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if gemifloxacin is excreted in breast milk. Breast-feeding is not recommended by the manufacturer. Although there is no information on the use of gemifloxacin during breast-feeding, other quinolones are generally considered compatible. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Gemifloxacin in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Central nervous system: Headache (4%), dizziness (2%)

Dermatologic: Rash (4%)

Gastrointestinal: Diarrhea (5%), nausea (4%), abdominal pain (2%), vomiting (2%)

Hematologic: Neutropenia/neutrophilia (1%), platelets increased (1%), thrombocythemia (1%),

Hepatic: Transaminases increased (1% to 4%), GGT increased (1%)

Neuromuscular & skeletal: CPK increased (1%)

<1%, postmarketing and/or case reports: Acute renal failure, alkaline phosphatase increased, anaphylactic reaction, anemia, anorexia, arthralgia, back pain, bilirubin increased, BUN increased, constipation, cramps (leg), dermatitis, dyspepsia, dyspnea, eczema, eosinophilia, erythema multiforme, facial edema, fatigue, flatulence, flushing, fungal infection, gastritis, gastroenteritis, genital moniliasis, granulocytopenia, hematocrit decreased/increased, hemoglobin decreased/increased, hemorrhage, hot flashes,

hyperglycemia, hyper-/hypocalcemia, hyper-/hypokalemia, hyper-/hyponatremia, hypoalbuminemia, INR increased, insomnia, leukopenia, moniliasis, myalgia, nervousness, pain, pharyngitis, photosensitivity, pneumonia, pruritus, pseudomembranous colitis, QT_c prolongation, retinal hemorrhage, serum creatinine increased, skin exfoliation, somnolence, supraventricular tachycardia, syncope, taste perversion, tendonitis, tendon rupture, thrombocytopenia, TIA, tremor, urticaria, vaginitis, vertigo, vision abnormal, weakness, xerostomia

Important adverse effects reported with other agents in this drug class include (not reported for gemifloxacin): Allergic reactions, CNS stimulation, hepatic necrosis/failure, hepatitis, hypersensitivity, jaundice, pancytopenia, peripheral neuropathy, pneumonitis (eosinophilic), seizure, sensorimotor-axonal neuropathy (paresthesia, hypoesthesias, dysesthesias, weakness), serum sickness, severe dermatologic reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome), thrombotic thrombocytopenia purpura, torsade de pointes, vasculitis

Drug Interactions

Antacids: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. **Exceptions:** Sodium Bicarbonate. *Risk D: Consider therapy modification*

Calcium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Calcium Chloride. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Quinolone Antibiotics may enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Didanosine: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents (excludes enteric coated formulation of didanosine). *Risk D: Consider therapy modification*

Insulin: May enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Mycophenolate: Quinolone Antibiotics may decrease the serum concentration of Mycophenolate. Specifically, quinolones may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Probenecid: May decrease the excretion of Gemifloxacin. *Risk C: Monitor therapy*

Probenecid: May increase the serum concentration of Quinolone Antibiotics. *Risk C: Monitor therapy*

Quinapril: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sevelamer: May decrease the absorption of Quinolone Antibiotics. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sulfonylureas: Quinolone Antibiotics may enhance the hyperglycemic effect of Sulfonylureas. Quinolone Antibiotics may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Quinolone Antibiotics may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zinc Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization).

Monitoring ParametersWBC, signs/symptoms of infection, renal function

Nursing: Physical Assessment/MonitoringAssess allergy history before initiating therapy. Use caution in presence of bradycardia, CNS disorders, renal dysfunction, or colitis. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, increased risk of tendon rupture or arrhythmias). Evaluate results of laboratory tests, therapeutic effectiveness (resolution of infection), and adverse effects regularly during therapy. Teach patient proper use (timing of meals, supplements, or other medications), possible side effects/appropriate interventions, and adverse symptoms to report (eg, allergic reaction, tendon pain, opportunistic infection).

Monitoring: Lab TestsWBC, renal function

Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy without consulting prescriber. Take exactly as directed (with or without food). Should be taken at least 3 hours before or 2 hours after antacids or other products containing aluminum, iron, magnesium, or zinc (including multivitamins). Take entire prescription, even if feeling better. Maintain adequate hydration (2-3 L/day of fluids, unless instructed to restrict fluid intake). May cause headache or dizziness (use caution when driving or engaging in hazardous tasks until response to drug is known); nausea, vomiting, or abdominal discomfort (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea (buttermilk, boiled milk, or yogurt may reduce diarrhea). Discontinue use immediately and report to prescriber if signs of inflammation or tendon pain occur or if you experience signs of allergic reaction (eg, itching, rash, respiratory difficulty, facial edema, difficulty swallowing). Report CNS changes (eg, hallucinations, suicidal ideation, seizures) or signs of opportunistic infection (unusual fever or chills; vaginal itching or foul-smelling vaginal discharge; easy bruising or bleeding). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Factive®: 320 mg

Generic AvailableNo

ManufacturerGeneSoft

Pricing: U.S. (www.drugstore.com)

Tablets (Factive)

320 mg (5): $119.99

Mechanism of ActionGemifloxacin is a DNA gyrase inhibitor and also inhibits topoisomerase IV. DNA gyrase (topoisomerase IV) is an essential bacterial enzyme that maintains the superhelical structure of DNA. DNA gyrase is required for DNA replication and transcription, DNA repair, recombination, and transposition; bactericidal

Pharmacodynamics/Kinetics

Absorption: Well absorbed from the GI tract

Distribution: V_{dss}: 4.2 L/kg

Bioavailability: ~71%

Metabolism: Hepatic (minor); forms metabolites (CYP isoenzymes are not involved)

Time to peak, plasma: 0.5-2 hours

Protein binding: ~60% to 70%

Half-life elimination: 7 hours (range 4-12 hours)

Excretion: Feces (61%); urine (36%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, hallucinations, and suicidal ideation

Mental Health: Effects on Psychiatric TreatmentContraindicated with ziprasidone. May lower seizure threshold; use caution with clozapine. Gemifloxacin may prolong QT interval; avoid use with antipsychotics and TCAs.

Cardiovascular ConsiderationsGemifloxacin causes a dose-dependent QT prolongation. Coadministration of gemifloxacin with other drugs that also prolong the QT interval or induce bradycardia (eg, beta-blockers, amiodarone) should be avoided. Careful consideration should be given in the use of gemifloxacin in patients with cardiovascular disease, particularly in those with conduction abnormalities.

Index TermsDW286; Gemifloxacin Mesylate; LA 20304a; SB-265805

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International Brand NamesFactive (CL, KP, ZA)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Gastrointestinal Cancer

Regimen UseBiliary adenocarcinoma

Regimen

Gemcitabine: I.V.: 1000 mg/m^2 day 1

[total dose/cycle = 1000 mg/m^2]

Oxaliplatin: I.V.: 100 mg/m^2 day 2

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 2 weeks

References

Andre T, Tournigand C, Rosmorduc O, et al, âGemcitabine Combined With Oxaliplatin (GEMOX) in Advanced Biliary Tract Adenocarcinoma: A GERCOR Study,â *Ann Oncol*, 2004, 15(9):1339-43. [PubMed 15319238]

Gemtuzumab Ozogamicin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Gemtuzumab may be confused with gemcitabine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(gem TOO zoo mab oh zog a MY sin)

U.S. Brand NamesMylotarg®

Canadian Brand NamesMylotarg®

Pharmacologic CategoryAntineoplastic Agent, Monoclonal Antibody

Use: Labeled IndicationsTreatment of relapsed CD33 positive acute myeloid leukemia (AML) in patients ≥60 years of age who are not candidates for cytotoxic chemotherapy

Use: Unlabeled/InvestigationalSalvage therapy for acute promyelocytic leukemia (APL), relapsed/ refractory CD33 positive acute myeloid leukemia in children and adults <60 years

Dosing: AdultsRefer to individual protocols. **Note:** Patients should receive diphenhydramine 50 mg orally and acetaminophen 650-1000 mg orally 1 hour prior to administration of each dose. Acetaminophen dosage should be repeated as needed every 4 hours for 2 additional doses. Pretreatment with methylprednisolone may ameliorate infusion-related symptoms.

AML: I.V.:

≥60 years: 9 mg/m^2 infused over 2 hours. A full treatment course is a total of 2 doses administered with 14 days between doses. Full hematologic recovery is not necessary for administration of the second dose. There has been only limited experience with repeat courses of gemtuzumab ozogamicin.

<60 years (unlabeled use): 9 mg/m^2 infused over 2 hours. A full treatment course is a total of 2 doses administered with 14 days between doses.

APL (unlabeled use): I.V.: 6 mg/m^2 infused over 2 hours. A full treatment course is a total of 2 doses administered with 15 days between doses.

Dosage adjustment with recent hematopoietic stem cell transplant (HSCT): Gemtuzumab use within 3-4 months of HSCT is associated with an increased risk of hepatic veno-occlusive disease, the National Comprehensive Cancer Network (NCCN) guidelines (AML, v.1.2009) recommend a 30% to 50% dosage reduction in this situation.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Patients should receive diphenhydramine (1 mg/kg) 1 hour prior to infusion and acetaminophen 15 mg/kg 1 hour prior to infusion and every 4 hours for 2 additional doses.

AML (unlabeled use): I.V.: 4-9 mg/m^2 infused over 2 hours every 2 weeks for a total of 1-3 doses per treatment course. Patients received the second and third doses and/or dose escalation if no dose-limiting toxicities were observed. (**Note:** Higher incidences of liver toxicities were observed in children at the 9 mg/m^2 dose level.)

or

Children <3 years: 0.2 mg/kg infused over 2 hours every 2 weeks for a total of 2 doses

Children ≥3 years: 6 mg/m^2 infused over 2 hours every 2 weeks for a total of 2 doses

Dosing: Renal ImpairmentNo recommendation (not studied).

Dosing: Hepatic ImpairmentUse extra caution; has not been studied in patients with bilirubin >2 mg/dL.

Dosing: Adjustment for Toxicity

Dyspnea or significant hypotension: Interrupt infusion; monitor

Anaphylaxis, pulmonary edema, acute respiratory distress syndrome: Strongly consider discontinuing treatment

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Do not administer as I.V. push or bolus. Administer via I.V. infusion, over at least 2 hours through a low protein-binding

(0.2-1.2 micron) in-line filter. Protect from light during infusion. Premedicate with acetaminophen and diphenhydramine prior to each infusion.

StorageLight sensitive; protect from light (including direct and indirect sunlight, and unshielded fluorescent light). The infusion container should be placed in a UV protectant bag immediately after preparation. Store intact vials under refrigeration at 2°C to 8°C (36°F to 46°F). Reconstituted solutions may be stored for up to 2 hours at room temperature or under refrigeration. Following dilution for infusion, solutions are stable for up to 16 hours at room temperature. Administration requires 2 hours; therefore, the maximum elapsed time from initial reconstitution to completion of infusion should be 20 hours.

ReconstitutionProtect from light during preparation (and administration). Prepare in biologic safety hood with shielded fluorescent light; (some institutions prepare in a darkened room with the lights in the biologic safety cabinet turned off). Allow to warm to room temperature prior to reconstitution. Reconstitute vial with sterile water for injection to a concentration of 1 mg/mL. Dilute in 100 mL of 0.9% sodium chloride injection. Hazardous agent - use appropriate precautions for handling and disposal.

CompatibilityStable in NS. **Incompatible** in D_5W and electrolyte-containing solutions. Infuse via a separate line.

ContraindicationsHypersensitivity to gemtuzumab ozogamicin, calicheamicin derivatives, or any component of the formulation; patients with anti-CD33 antibody

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Combination chemotherapy: See “Concurrent drug therapy issues” below.
- Experienced physician: See “Other warnings/precautions” below.
- Hepatotoxicity: See “Concerns related to adverse effects” below.
- Hypersensitivity/infusion reaction: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: Severe myelosuppression occurs in all patients at recommended dosages.**
- Hepatotoxicity: **[U.S. Boxed Warning]: Has been associated with hepatotoxicity, including severe hepatic veno-occlusive disease (VOD).** Symptoms of VOD include right upper quadrant pain, rapid weight gain, ascites, hepatomegaly, and bilirubin/transaminase elevations. Risk may be increased by combination chemotherapy, underlying hepatic disease, or hematopoietic stem cell transplant.
- Hypersensitivity/infusion reaction: **[U.S. Boxed Warning]: Severe hypersensitivity reactions (including anaphylaxis) and other infusion-related reactions may occur.** Infusion-related events are common, generally reported to occur with the first dose after the end of the 2-hour intravenous infusion. These symptoms usually resolved after 2-4 hours with a supportive therapy of acetaminophen, diphenhydramine, and intravenous fluids. Other severe and potentially fatal infusion related pulmonary events (including dyspnea and hypoxia) have been reported infrequently. High peripheral blast counts may increase the risk of severe reactions (consider leukoreduction with hydroxyurea or leukapheresis to lower WBC to <30,000 cells/mm^3 prior to therapy initiation). Fewer infusion-related events were observed after the second dose. Postinfusion reactions (may include fever, chills, hypotension, or dyspnea) may occur during the first 24 hours after administration. Consider discontinuation in patients who develop severe infusion-related reactions.
- Pulmonary events: In addition to infusion-related pulmonary events, gemtuzumab therapy is also associated with acute respiratory distress syndrome, pulmonary infiltrates, pleural effusion, noncardiogenic pulmonary edema, and pulmonary insufficiency. Risk for pulmonary events may be increased with WBC ≥30,000 cells/mm^3. Symptomatic intrinsic lung disease may increase the risk for severe pulmonary reactions.
- Tumor lysis syndrome: May occur as a consequence of leukemia treatment, adequate hydration and prophylactic allopurinol must be instituted prior to use. Other methods to lower WBC <30,000 cells/mm^3 may be considered (hydroxyurea or leukapheresis) to minimize the risk of tumor lysis syndrome.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; has not been studied in patients with serum bilirubin >2 mg/dL.
- Renal impairment: Use with caution in patients with renal impairment; has not been studied.

Concurrent drug therapy issues

- Combination chemotherapy: **[U.S. Boxed Warning]: Safety and efficacy have not been established in combination with other chemotherapy agents.**

Special populations:

- Pediatrics: Not FDA-approved for use in children.
- Poor performance status: Safety and efficacy have not been established in patients with poor performance status.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician. Should only be administered in facilities equipped to monitor and treat patients with leukemia.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenic effects, fetal loss, and maternal toxicity. There are no adequate and well-controlled studies in pregnant women. May cause fetal harm when administered to a pregnant woman. Women of childbearing potential should avoid becoming pregnant while receiving treatment.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse ReactionsAdverse reactions reported for adults of all ages. **Note:** A postinfusion symptom complex (fever, chills, less commonly hypertension, and/or dyspnea) may occur within 24 hours of administration; the incidence of infusion-related events decreases with repeat administration.

>10%:

Cardiovascular: Hypotension (20%), hypertension (16%), peripheral edema (14%)

Central nervous system: Fever (82%), chills (66%), headache (37%), pain (18%), dizziness (12%), insomnia (12%)

Dermatologic: Petechiae (19%), rash (18%)

Endocrine & metabolic: Hypokalemia (26%)

Gastrointestinal: Nausea (68%), vomiting (58%), abdominal pain (32%), diarrhea (32%), anorexia (25%), mucositis/stomatitis (25%), constipation (23%)

Hematologic: Thrombocytopenia (grades 3/4: 49% to 99%; median recovery 36-51 days), neutropenia (grades 3/4: 98%; median recovery 40-51 days), leukopenia (grades 3/4: 46% to 96%), lymphopenia (grades 3/4: 94%), anemia/hemoglobin decreased (grades 3/4: 14% to 52%), neutropenic fever (17%), hemorrhage (11% to 13%)

Hepatic: Hyperbilirubinemia (grades 3/4: 29%), veno-occlusive disease (1% to 20%; higher frequency in patients with prior history of or subsequent hematopoietic stem cell transplant), AST increased (grades 3/4: 18%), LDH increased (16%)

Local: Local reaction (22%)

Neuromuscular & skeletal: Weakness (36%), back pain (14%)

Respiratory: Epistaxis (28%; grade 3/4: 3%), dyspnea (26%), cough (17%), pneumonia (13%; grades 3/4: 8%), pharyngitis (12%)

Miscellaneous: Infection (grades 3/4: 30%), sepsis (26%; grades 3/4: 17%), cutaneous herpes simplex (21%)

1% to 10%:

Cardiovascular: Tachycardia (10%), cerebral hemorrhage (2%)

Central nervous system: Depression (9%), anxiety (8%), intracranial hemorrhage (1%)

Dermatologic: Bruising (10%), pruritus (6%)

Endocrine & metabolic: Hyperglycemia (10%), hypocalcemia (10%), hypophosphatemia (8%) hypomagnesemia (6%)

Gastrointestinal: Dyspepsia (10%), gingival hemorrhage (9%), melena (1%)

Genitourinary: Vaginal hemorrhage (4%), vaginal bleeding (3%), hematuria (grade 3/4: 1%)

Hematologic: Disseminated intravascular coagulation (DIC) (1%)

Hepatic: ALT increased (grades 3/4: 9%), prothrombin time increased (grades 3/4: 9%), alkaline phosphatase increased (8%; grades 3/4: 4%), ascites (3%), PTT increased (grades 3/4: 2%)

Neuromuscular & skeletal: Arthralgia (10%), myalgia (6%)

Renal: Creatinine increased (2%)

Respiratory: Rhinitis (8%), hypoxia (5%)

<1%, postmarketing, and/or case reports: Acute respiratory distress syndrome, anaphylaxis, bradycardia, Budd-Chiari syndrome, gastrointestinal hemorrhage, hepatic failure, hepatosplenomegaly, hypersensitivity reactions, jaundice, neutropenic sepsis, noncardiogenic pulmonary edema, portal vain thrombosis, pulmonary hemorrhage, renal impairment, renal failure (including renal failure secondary to tumor lysis syndrome)

Oncology: VesicantNo

Oncology: Emetic PotentialModerate (30% to 60%)

Drug Interactions

Abciximab: May enhance the potential for allergic or hypersensitivity reactions to Monoclonal Antibodies. Also may cause thrombocytopenia or diminished therapeutic effects. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to GI irritation).

Test InteractionsNone known

Monitoring ParametersMonitor vital signs during the infusion and for 4 hours following the infusion. Monitor for signs/symptoms of postinfusion reaction. Monitor electrolytes, liver function, CBC with differential and platelets frequently. Monitor for signs and symptoms of hepatic veno-occlusssive disease (weight gain, right upper quadrant abdominal pain, hepatomegaly, ascites).

Nursing: Physical Assessment/MonitoringInfusion reactions can be severe; premedication with acetaminophen and diphenhydramine should be administered prior to each infusion and acetaminophen as needed following each infusion. See Administration for specific infusion directions. Patient must be monitored closely during and for 4 hours following treatment for infusion-related reactions (eg, anaphylaxis, pulmonary edema, or ARDS). Assess results of laboratory tests, patient response, and adverse reactions for immediate 24 hours following infusion (eg, postinfusion symptom complex) and regularly between infusions (eg, tachycardia, hyper- or hypotension, CNS changes, gastrointestinal disturbance, hepatic reaction). Teach patient purpose for use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsMonitor electrolytes, liver function, CBC with differential, and platelet counts frequently.

Patient EducationThis medication can only be administered intravenously. During and immediately following infusion, you will be closely monitored; report immediately any burning, pain, or swelling at infusion site; difficulty breathing or swallowing; chest pain, chills, or sudden headache. You will need frequent laboratory tests during course of therapy. Do not use alcohol, aspirin-containing medications, any prescription or OTC medications between treatments without consulting your prescriber. It is important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake and nutrition (small frequent meals will help). You will be susceptible to infection (avoid crowds and exposure to infection). You may experience nausea or vomiting (small frequent meals, good mouth care, sucking lozenges or chewing gum may help); contact prescriber if nausea and vomiting persists. Frequent mouth care with a soft toothbrush or soft swabs and avoidance of spicy or salty foods may reduce mouth sores. Report immediately any difficulty breathing, unusual cough, nosebleed, fever, or chills; unusual bleeding or bruising; signs of infection (eg, sore throat, cough, white plaques in mouth or perianal area, burning on urination); chest pain or palpitations; yellowing of the eyes or skin; swelling of extremities; rapid weight gain; right upper quadrant pain; rash; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication; may cause fetal damage. Consult prescriber for appropriate contraceptives. Do not breast-feed

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Mylotarg®: 5 mg

Generic AvailableNo

ManufacturerWyeth Pharmaceuticals, Inc

Mechanism of ActionAntibody to CD33 antigen, which is expressed on leukemic blasts in 80% of AML patients. Binds to the CD33 antigen, resulting in internalization of the antibody-antigen complex. Following internalization, the calicheamicin derivative is released inside the myeloid cell. The calicheamicin derivative binds to DNA resulting in double strand breaks and cell death. Pluripotent stem cells and nonhematopoietic cells are not affected.

Pharmacodynamics/Kinetics

Distribution: V_{ss}: Adults: Initial dose: 21 L; Repeat dose: 10 L

Half-life elimination: Total calicheamicin: Initial: 41-45 hours, Repeat dose: 60-64 hours; Unconjugated: 100-143 hours (no change noted in repeat dosing)

Time to peak, plasma: Immediate; higher concentrations observed after repeat dose

Pharmacotherapy Pearls**Oncology Comment:** In addition to the FDA-approved indication, the National Comprehensive Cancer Network (NCCN) Acute Myeloid Leukemia Guidelines (AML, v.1.2009) recommend gemtuzumab ozogamicin as salvage and/or post remission therapy for the treatment of acute promyelocytic leukemia (APL). Gemtuzumab has activity (single agent) in patients with persistent disease following postremission arsenic trioxide therapy in APL patients who are not candidates for allogeneic transplantation.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, gingival hemorrhage, and mucositis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness, insomnia, and depression are common

Mental Health: Effects on Psychiatric TreatmentHypotension is common; caution with low potency antipsychotics and TCAs; nausea and vomiting are common, use caution with the SSRIs. Neutropenia is common, use caution with carbamazepine and clozapine.

Index TermsCMA-676; NSC-720568

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International Brand Names Mylotarg (CO)

Gentamicin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Garamycin® may be confused with kanamycin, Terramycin®

Gentamicin may be confused with gentian violet, kanamycin, vancomycin

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (intrathecal administration) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(jen ta MYE sin)

U.S. Brand NamesGentak®; Gentasol™

Canadian Brand NamesAlcomicin®; Diogent®; Garamycin®; Gentamicin Injection, USP; SAB-Gentamicin

Pharmacologic CategoryAntibiotic, Aminoglycoside; Antibiotic, Ophthalmic; Antibiotic, Topical

Use: Labeled IndicationsTreatment of susceptible bacterial infections, normally gram-negative organisms including *Pseudomonas*, *Proteus*, *Serratia*, and gram-positive *Staphylococcus*; treatment of bone infections, respiratory tract infections, skin and soft tissue infections, as well as abdominal and urinary tract infections, and septicemia; treatment of infective endocarditis; used topically to treat superficial infections of the skin or ophthalmic infections caused by susceptible bacteria

Dosing: AdultsIndividualization is **critical** because of the low therapeutic index.

Use of ideal body weight (IBW) for determining the mg/kg/dose appears to be more accurate than dosing on the basis of total body weight (TBW). In morbid obesity, dosage requirement may best be estimated using a dosing weight of IBW + 0.4 (TBW - IBW).

Initial and periodic plasma drug levels (eg, peak and trough with conventional dosing) should be determined, particularly in critically-ill patients with serious infections or in disease states known to significantly alter aminoglycoside pharmacokinetics (eg, cystic fibrosis, burns, or major surgery).

Usual dosage ranges:

I.M., I.V.:

Conventional: 1-2.5 mg/kg/dose every 8-12 hours; to ensure adequate peak concentrations early in therapy, higher initial dosage may be considered in selected patients when extracellular water is increased (edema, septic shock, postsurgical, or trauma)

Once daily: 4-7 mg/kg/dose once daily; some clinicians recommend this approach for all patients with normal renal function; this dose is at least as efficacious with similar, if not less, toxicity than conventional dosing

Intrathecal: 4-8 mg/day

Ophthalmic:

Ointment: Instill 1/2” (1.25 cm) 2-3 times/day to every 3-4 hours

Solution: Instill 1-2 drops every 2-4 hours, up to 2 drops every hour for severe infections

Topical: Apply 3-4 times/day to affected area

Indication-specific dosing: I.M., I.V.:

Brucellosis: 240 mg (I.M.) daily or 5 mg/kg (I.V.) daily for 7 days; either regimen recommended in combination with doxycycline

Cholangitis: 4-6 mg/kg once daily with ampicillin

Diverticulitis (complicated): 1.5-2 mg/kg every 8 hours (with ampicillin and metronidazole)

Endocarditis: Treatment: 3 mg/kg/day in 1-3 divided doses

Meningitis*(Enterococcus*sp or*Pseudomonas aeruginosa)*: I.V.: Loading dose 2 mg/kg, then 1.7 mg/kg/dose every 8 hours (administered with another bacteriocidal drug)

Pelvic inflammatory disease: Loading dose: 2 mg/kg, then 1.5 mg/kg every 8 hours

Alternate therapy: 4.5 mg/kg once daily

Plague (*Yersinia pestis*): Treatment: 5 mg/kg/day, followed by postexposure prophylaxis with doxycycline

Pneumonia, hospital- or ventilator-associated: 7 mg/kg/day (with antipseudomonal beta-lactam or carbapenem)

Synergy (for gram-positive infections): 3 mg/kg/day in 1-3 divided doses (with ampicillin)

Tularemia: 5 mg/kg/day divided every 8 hours for 1-2 weeks

Urinary tract infection: 1.5 mg/kg/dose every 8 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricIndividualization is **critical** because of the low therapeutic index.

Use of ideal body weight (IBW) for determining the mg/kg/dose appears to be more accurate than dosing on the basis of total body weight (TBW). In morbid obesity, dosage requirement may best be estimated using a dosing weight of IBW + 0.4 (TBW - IBW).

Initial and periodic plasma drug levels (eg, peak and trough with conventional dosing) should be determined, particularly in critically-ill patients with serious infections or in disease states known to significantly alter aminoglycoside pharmacokinetics (eg, cystic fibrosis, burns, or major surgery).

Usual dosage ranges: I.M., I.V.:

Infants and Children <5 years: 2.5 mg/kg/dose every 8 hours*

Children ≥5 years: 2-2.5 mg/kg/dose every 8 hours*

*__Note:__ Higher individual doses and/or more frequent intervals (eg, every 6 hours) may be required in selected clinical situations (cystic fibrosis) or serum levels document the need

Ophthalmic, Dermatologic infections: Children: Refer to adult dosing.

Indication-specific dosing:

Meningitis: Neonates: I.V.:

0-7 days of age: <2000 g: 2.5 mg/kg every 18-24 hours; >2000 g: 2.5 mg/kg every 12 hours

8-28 days of age: <2000 g: 2.5 mg/kg every 8-12 hours; >2000 g: 2.5 mg/kg every 8 hours

Dosing: Renal Impairment

Conventional dosing:

Cl_{cr} ≥60 mL/minute: Administer every 8 hours

Cl_{cr} 40-60 mL/minute: Administer every 12 hours

Cl_{cr} 20-40 mL/minute: Administer every 24 hours

Cl_{cr} <20 mL/minute: Loading dose, then monitor levels

High-dose therapy: Interval may be extended (eg, every 48 hours) in patients with moderate renal impairment (Cl_{cr} 30-59 mL/minute) and/or adjusted based on serum level determinations.

Hemodialysis: Dialyzable; removal by hemodialysis: 30% removal of aminoglycosides occurs during 4 hours of HD; administer dose after dialysis and follow levels

Removal by continuous ambulatory peritoneal dialysis (CAPD):

Administration via CAPD fluid:

Gram-negative infection: 4-8 mg/L (4-8 mcg/mL) of CAPD fluid

Gram-positive infection (eg, synergy): 3-4 mg/L (3-4 mcg/mL) of CAPD fluid

Administration via I.V., I.M. route during CAPD: Dose as for Cl_{cr} <10 mL/minute and follow levels

Removal via continuous arteriovenous or venovenous hemofiltration: Dose as for Cl_{cr} 10-40 mL/minute and follow levels

Dosing: Hepatic ImpairmentMonitor plasma concentrations.

Calculations

- Adjusted Body Weight
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Ideal Body Weight: Adults
- Ideal Body Weight: Pediatrics

Administration: I.M.Administer by deep I.M. route if possible. Slower absorption and lower peak concentrations, probably due to poor circulation in the atrophic muscle, may occur following I.M. injection; in paralyzed patients, suggest I.V. route.

Administration: I.V. Some penicillins (eg, carbenicillin, ticarcillin, and piperacillin) have been shown to inactivate aminoglycosides *in* *vitro*. This has been observed to a greater extent with tobramycin and gentamicin, while amikacin has shown greater stability against inactivation. Concurrent use of these agents may pose a risk of reduced antibacterial efficacy *in vivo*, particularly in the setting of profound renal impairment. However, definitive clinical evidence is lacking. If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered.

Administration: I.V. DetailpH: 3.0-5.5 (I.V./I.M. injection); ph: 4 (premixed infusion in sodium chloride)

Administration: OtherAdminister any other ophthalmics 10 minutes before or after gentamicin preparations.

Dietary ConsiderationsCalcium, magnesium, potassium: Renal wasting may cause hypocalcemia, hypomagnesemia, and/or hypokalemia.

StorageGentamicin is a colorless to slightly yellow solution which should be stored between 2°C to 30°C, but refrigeration is not recommended. I.V. infusion solutions mixed in NS or D_5W solution are stable for 24 hours at room temperature and refrigeration. Premixed bag: Manufacturer expiration date; remove from overwrap stability: 30 days.

CompatibilityStable in dextran 40, D_5W, $D_{10}W$, mannitol 20%, LR, NS; **incompatible** with fat emulsion 10%; **variable stability (consult detailed reference)** in peritoneal dialysis solution.

Y-site administration: Compatible: Acyclovir, alatrofloxacin, amifostine, amiodarone, amsacrine, atracurium, aztreonam, cefpirome, ciprofloxacin, cisatracurium, clarithromycin, cyclophosphamide, cytarabine, diltiazem, docetaxel, doxorubicin liposome, enalaprilat, esmolol, etoposide phosphate, famotidine, fluconazole, fludarabine, foscarnet, gatifloxacin, gemcitabine, granisetron, hydromorphone, IL-2, insulin (regular), labetalol, levofloxacin, linezolid, lorazepam, magnesium sulfate, melphalan, meperidine, meropenem, midazolam, morphine, multivitamins, ondansetron, paclitaxel, pancuronium, perphenazine, remifentanil, sargramostim, tacrolimus, teniposide, theophylline, thiotepa, tolazoline, vecuronium, vinorelbine, vitamin B complex with C, zidovudine. **Incompatible:** Allopurinol, amphotericin B cholesteryl sulfate complex, cefamandole, furosemide, heparin, hetastarch, idarubicin, indomethacin, iodipamide meglumine, phenytoin, propofol, warfarin. **Variable (consult detailed reference):** Filgrastim.

Compatibility in syringe: Compatible: Clindamycin, diatrizoate meglumine 52% and diatrizoate sodium 8%, diatrizoate sodium 60%, iohexol, iopamidol, iothalamate meglumine 60%, penicillin G sodium. **Incompatible:** Ampicillin, cefamandole, heparin. **Variable (consult detailed reference):** Ioxaglate meglumine 39.3% and ioxaglate sodium 19.6%.

Compatibility when admixed: Compatible: Atracurium, aztreonam, bleomycin, cefoxitin, cimetidine, chloroprocaine, ciprofloxacin, fluconazole, hexylcaine, lidocaine, lidocaine with epinephrine, mepivacaine, meropenem, metronidazole, metronidazole with sodium bicarbonate, ofloxacin, penicillin G sodium, piperocaine, procaine, ranitidine, verapamil. **Incompatible:** Amphotericin B, ampicillin, cefamandole, cefazolin with clindamycin, cefepime, heparin, nafcillin, ticarcillin. **Variable (consult detailed reference):** Cefotaxime, cefotetan, cefuroxime, clindamycin, cytarabine, dopamine, floxacillin, furosemide.

ContraindicationsHypersensitivity to gentamicin or other aminoglycosides

Warnings/Precautions

Boxed Warnings:

- Nephrotoxicity: See “Concerns related to adverse effects” below.
- Neurotoxicity: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Nephrotoxicity: **[U.S. Boxed Warning]: May cause nephrotoxicity;** usual risk factors include pre-existing renal impairment, concomitant nephrotoxic medications, advanced age and dehydration. Discontinue treatment if signs of nephrotoxicity occur; renal damage is usually reversible.
- Neuromuscular blockade and respiratory paralysis: May cause neuromuscular blockade and respiratory paralysis; especially when given soon after anesthesia or muscle relaxants.
- Neurotoxicity: **[U.S. Boxed Warning]: May cause neurotoxicity;** usual risk factors include pre-existing renal impairment, concomitant neuro-/nephrotoxic medications, advanced age and dehydration. Ototoxicity is proportional to the amount of drug given and the duration of treatment. Tinnitus or vertigo may be indications of vestibular injury and impending bilateral irreversible damage. Discontinue treatment if signs of ototoxicity occur.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hearing impairment: Use with caution in patients with pre-existing vertigo, tinnitus, or hearing loss.
- Hypocalcemia: Use with caution in patients with hypocalcemia.
- Neuromuscular disorders: Use with caution in patients with neuromuscular disorders, including myasthenia gravis.
- Renal impairment: Use with caution in patients with pre-existing renal insufficiency; dosage modification required.

Other warnings/precautions:

- Long-term use: Not intended for long-term therapy due to toxic hazards associated with extended administration.

Geriatric ConsiderationsThe aminoglycosides are important therapeutic interventions for infections due to susceptible organisms and as empiric therapy in seriously ill patients. Their use is not without risk of toxicity, however, these risks can be minimized if initial dosing is adjusted for estimated renal function and appropriate monitoring performed. High dose, once daily aminoglycosides have been advocated as an alternative to traditional dosing regimens. Once daily or extended interval dosing is as effective and may be safer than traditional dosing. The interval must be adjusted for renal function.

Pregnancy Risk FactorC (ophthalmic, topical); D (injection)

Pregnancy ConsiderationsGentamicin crosses the placenta and produces detectable serum levels in the fetus. Because of several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy, manufacturers classify gentamicin as pregnancy risk factor D. Renal toxicity has been observed in animals. Other than a single case report of renal cystic dysplasia, reports of fetal toxicity in humans have not been located. Adequate and well-controlled studies have not been conducted in pregnant women and it is not known whether gentamicin can cause fetal harm. Although manufacturers consider systemic gentamicin pregnancy risk factor D, gentamicin-specific clinical data would suggest a pregnancy risk factor C.

Due to pregnancy induced physiologic changes, some pharmacokinetic parameters of gentamicin may be altered. Pregnant women have an average-to-larger volume of distribution which may result in lower serum peak levels than for the same dose in nonpregnant women. Serum half-life is also shorter.

LactationEnters breast milk (small amounts)/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsGentamicin is excreted into breast milk; however, it is not well absorbed when taken orally. This limited oral absorption may minimize exposure to the nursing infant. Nondose-related effects could include modification of bowel flora. The AAP considers gentamicin to be “usually compatible with breast-feeding.”

Pregnancy & Lactation, In-Depth

- Gentamicin in Pregnancy & Lactation

Adverse Reactions

>10%:

Central nervous system: Neurotoxicity (vertigo, ataxia)

Neuromuscular & skeletal: Gait instability

Otic: Ototoxicity (auditory), ototoxicity (vestibular)

Renal: Nephrotoxicity, decreased creatinine clearance

1% to 10%:

Cardiovascular: Edema

Dermatologic: Skin itching, reddening of skin, rash

<1%: Drowsiness, headache, pseudomotor cerebri, photosensitivity, allergic reaction, erythema, anorexia, nausea, vomiting, weight loss, increased salivation, enterocolitis, granulocytopenia, agranulocytosis, thrombocytopenia, elevated LFTs, burning, stinging, tremor, muscle cramps, weakness, dyspnea

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Test Interactions

Some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*, leading to a potential underestimation of aminoglycoside serum concentration.

Monitoring ParametersUrinalysis, urine output, BUN, serum creatinine; hearing should be tested before, during, and after treatment; particularly in those at risk for ototoxicity or who will be receiving prolonged therapy (>2 weeks)

Some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*. This may be clinically-significant for certain penicillin (ticarcillin, piperacillin, carbenicillin) and aminoglycoside (gentamicin, tobramycin) combination therapy in patients with significant renal impairment. Close monitoring of aminoglycoside levels is warranted.

Reference Range

Timing of serum samples: Draw peak 30 minutes after 30-minute infusion has been completed or 1 hour after I.M. injection; draw trough immediately before next dose

Sample size: 0.5-2 mL blood (red top tube) or 0.1-1 mL serum (separated)

Therapeutic levels:

- Peak:
  - Serious infections: 6-8 mcg/mL (12-17 µmol/L)
  - Life-threatening infections: 8-10 mcg/mL (17-21 µmol/L)
  - Urinary tract infections: 4-6 mcg/mL
  - Synergy against gram-positive organisms: 3-5 mcg/mL
- Trough:
  - Serious infections: 0.5-1 mcg/mL
  - Life-threatening infections: 1-2 mcg/mL
  - The American Thoracic Society (ATS) recommends trough levels of <1 mcg/mL for patients with hospital-acquired pneumonia.

Obtain drug levels after the third dose unless renal dysfunction/toxicity suspected

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess kidney function and hearing before, during, and following therapy. **Note:** This medication has a very low TI. Monitor for decreased renal function, ototoxicity, and neurotoxicity. Perform hearing tests prior to initiating treatment and periodically during therapy (>2 weeks) if at high risk. Monitor therapeutic effectiveness, laboratory values and adverse reactions at beginning of therapy and periodically throughout therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsUrinalysis, BUN, serum creatinine, plasma gentamicin levels (as appropriate to dosing method). Peak levels are drawn 30 minutes after the end of a 30-minute infusion or 1 hour after initiation of infusion or I.M. injection. The trough is drawn just before the next dose. Levels are typically obtained after the third dose in conventional dosing. Perform culture and sensitivity studies prior to initiating therapy to determine the causative organism and its susceptibility to gentamicin. Some penicillin derivatives may accelerate the degradation of aminoglycosides.

Patient EducationTake exactly as directed and when prescribed. Drink adequate amounts of water (2-3 L/day) unless instructed to restrict fluid intake. You may experience headaches, ringing in ears, dizziness, blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); GI upset, loss of appetite (small frequent meals and frequent mouth care may help); or photosensitivity (use sunscreen wear protective clothing and eyewear, and avoid direct sunlight). Report severe headache, changes in hearing acuity, ringing in ears, change in balance, changes in urine pattern, persistent diarrhea, respiratory difficulty, rash, fever, unhealed sores, sores in mouth, vaginal drainage, muscle or bone pain, change in gait, or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Ophthalmic: Wash hands before instilling. Sit or lie down to instill. Open eye, look at ceiling, and instill prescribed amount of solution; for ointment, pull lower lid down gently, instill thin ribbon of ointment inside lid. Close eye and roll eye in all directions, and apply gentle pressure to inner corner of eye. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Temporary stinging or blurred vision may occur. Report persistent pain, burning, vision changes, swelling, itching, or worsening of condition.

Topical: Apply thin film of ointment to affected area as often as recommended. May apply porous dressing. Report persistent burning, swelling, itching, worsening of condition, or lack of response to therapy.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, topical, as sulfate: 0.1% (15 g, 30 g)

Infusion, as sulfate [premixed in NS]: 40 mg (50 mL); 60 mg (50 mL, 100 mL); 70 mg (50 mL); 80 mg (50 mL, 100 mL); 90 mg (100 mL); 100 mg (50 mL, 100 mL); 120 mg (100 mL)

Injection, solution, as sulfate: 10 mg/mL (6 mL, 8 mL, 10 mL)

Injection, solution, as sulfate: 40 mg/mL (2 mL, 20 mL)

Injection, solution [pediatric], as sulfate: 10 mg/mL (2 mL)

Injection, solution [pediatric], as sulfate [preservative free]: 10 mg/mL (2 mL)

Ointment, ophthalmic, as sulfate (Gentak®): 0.3% [3 mg/g] (3.5 g)

Ointment, topical, as sulfate: 0.1% (15 g, 30 g)

Solution, ophthalmic, as sulfate: 0.3% (5 mL, 15 mL) [contains benzalkonium chloride]

Gentak®: 0.3% (5 mL; 15 mL [DSC]) [contains benzalkonium chloride]

Gentasol™: 0.3% (5 mL) [contains benzalkonium chloride]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Cream (Gentamicin Sulfate)

0.1% (15): $12.99

Ointment (Gentamicin Sulfate)

0.1% (15): $9.99

Solution (Genoptic)

0.3% (1): $8.99

Solution (Gentamicin Sulfate)

0.3% (5): $9.99

10 mg/mL (50): $125.00

Mechanism of ActionInterferes with bacterial protein synthesis by binding to 30S and 50S ribosomal subunits resulting in a defective bacterial cell membrane

Pharmacodynamics/Kinetics

Absorption:

Intramuscular: Rapid and complete

Oral: None

Distribution: Primarily into extracellular fluid (highly hydrophilic); high concentration in the renal cortex; minimal penetration to ocular tissues via I.V. route

V_d: Increased by edema, ascites, fluid overload; decreased with dehydration

Neonates: 0.4-0.6 L/kg

Children: 0.3-0.35 L/kg

Adults: 0.2-0.3 L/kg

Relative diffusion from blood into CSF: Minimal even with inflammation

CSF:blood level ratio: Normal meninges: Nil; Inflamed meninges: 10% to 30%

Protein binding: <30%

Half-life elimination:

Infants: <1 week: 3-11.5 hours; 1 week to 6 months: 3-3.5 hours

Adults: 1.5-3 hours; End-stage renal disease: 36-70 hours

Time to peak, serum: I.M.: 30-90 minutes; I.V.: 30 minutes after 30-minute infusion

Excretion: Urine (as unchanged drug)

Clearance: Directly related to renal function

Related Information

- Antibiotic Treatment of Adults With Infective Endocarditis
- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Prevention of Infective Endocarditis
- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause drowsiness

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine

Cardiovascular ConsiderationsLoop diuretics may enhance the toxic effects (ototoxicity, nephrotoxicity). This is probably of most concern if the diuretic is administered in high doses for extended periods of time.

Anesthesia and Critical Care Concerns/Other ConsiderationsGentamicin is the only aminoglycoside that is commercially available in a preservative-free solution for injection.

Index TermsGentamicin Sulfate

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International Brand NamesAlcomicin (AE, BE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TH, TN, TZ, UG, YE, ZA, ZM, ZW); Apigent (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Azupel (PY); Bactiderm (PH); Biogaracin (IN); Biogen (ES); Cidomycin (AE, BB, BH, BM, BS, BZ, CY, EG, GB, GY, IE, IL, IQ, IR, JM, JO, KW, LB, LY, MY, NL, OM, PR, QA, SA, SR, SY, TT, YE, ZA); Colircusi Gentamicina (ES); Colirio Ocul Gentamicina (ES); Coliriocilina Gentamicina (ES); Danigen (ID); Dermogen (MY); Dexa-Gentamicin (LU); Diakarmon (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, GR, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Dispagent (UY); Duracoll (LU); Epigent (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Espectrocina (ES); Ethigent (ID); G-Mycin (KP); Garabiotic (ID); Garalone (PT); Garamicin (TH); Garamicina (BR, CO, CR, DO, EC, GT, HN, MX, NI, PA, SV); Garamicina Cream (CO); Garamicina Crema (EC); Garamicina Oftalmica (CO, CR, DO, EC, GT, HN, NI, PA, SV); Garamsa (MX); Garamycin (AE, AU, BB, BG, BH, BM, BS, BZ, CH, CY, CZ, DK, EG, GR, GY, HK, HN, HR, HU, ID, IL, IN, IQ, IR, JM, JO, KW, LB, LY, MY, NL, NO, OM, PH, PL, QA, RU, SA, SE, SR, SY, TR, TT, TW, YE); Garbilocin (GR); Genacin (PK); Genkova (MX); Genoptic (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, NZ, OM, QA, SA, SY, TW, YE); Genrex (MX); Gensumycin (DK, FI, NO, SE); Genta Gobens (ES); Gentabiotic (PE); Gentabiox (PE); Gentac (TW); Gentacin (HK); Gentacyl (ID);

Gentagram (PE); Gentallenas (ES); Gentalline (FR); Gentallorens (ES); Gentalodina (ES); Gentalyn (CN, IT, PE, VE); Gentalyn Oftalmico-Otico (PE); Gentame (MY); Gentamedical (ES); Gentamen (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Gentamerck (ID); Gentamicin (PL); Gentamicin Biochemie (HU); Gentamicin Hexal (LU); Gentamicin-ratiopharm (LU); Gentamicin-Ratiopharm I.M. (PL); Gentamicin-Ratiopharm I.V. (PL); Gentamicina Braun (ES); Gentamicina CEPA (ES); Gentamicina Harkley (ES); Gentamicina Juste (ES); Gentamicina Llorente (ES); Gentamicine (PL); Gentamil (MX); Gentamina (AR, PY, UY); Gentamival (ES); Gentamycin (HU, PL); Gentamytrex (DE, HN, LU, NL, PL); Gentarad (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Gentaroger (ES); Gentasil (PE); Gentasporin (IN); Gentatrim (IL); Gentazol (MX); Genticin (AE, BF, BH, BJ, CI, CY, EG, ET, GB, GH, GM, GN, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Genticina (ES); Gentiderm (ID); Gentralay (ES); Geomycine (BE, LU); Gevramycin (ES); Grammicin (TH); Hexamycin (DK); Hosbogen (ES); Konigen (ID); Lacromycin (IL); Lantogent (ES); Lisagent (TW); Metrorrigen (ES); Migenta (UY); Migentax (TW); Miragenta (CO); Miramycin (HK, MY, SG, TH); Misinex (MX); Nichogencin (ID); Nuclogen (ES); Obogen (PH); Ocugenta (KP); Oft Cusi Gentamicina (ES); Oftagen (PE); Ophtagram (BE, CH, DE, HU, LU); Opthagen (PH); Opti-Genta (IL); Optigen (MY); Optimycin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Ottogenta (ID); Palacos (LU); Refobacin (AT, DE, LU); Rexgenta (ES); Rigaminol (PE); Rocy Gen (PH); Rovixida (AR); Rupegen (AR); Sagestam Eye Drops (ID); Septopal (HR, HU, LU); Septopal 10 Minikette (PL); Servigenta (MX, MY); Skinfect (TH); Sulmycin (DE); Supragenta (ES); Tamadit (ES); Tangyn (PH); Tondex (MX); Versigen (TH); Yectamicina (MX)

Gentian Violet

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Gentian violet may be confused with gentamicin

Pronunciation(JEN shun VYE oh let)

Pharmacologic CategoryAntibiotic, Topical; Antifungal Agent, Topical

Use: Labeled IndicationsTreatment of cutaneous or mucocutaneous infections caused by *Candida albicans* and other superficial skin infections; external treatment of minor abrasions or cuts

Dosing: Adults**Superficial skin or mucocutaneous infection:** Topical: Apply to affected area once or twice daily. Solutions diluted to 0.25% to 0.5% may be less irritating. Solutions diluted to 0.01% have been recommended for use in closed cavities.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Superficial skin or mucocutaneous infection:** Refer to adult dosing.

Administration: TopicalApply with cotton-tipped applicator directly to affected area. Do not cover with bandage. If applied to mucous membranes inside mouth, do not allow to be swallowed. Do not use in the eyes.

ContraindicationsHypersensitivity to gentian violet or any component of the formulation; ulcerated areas

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue if sensitivity or irritation occur, or if condition worsens.
- Staining: Will stain skin and clothing. Application to ulcerative lesions may result in tattooing.

Other warnings/precautions:

- Appropriate use: For topical use only; avoid contact with eyes. Not for self-medication (OTC use) for serious burns or deep puncture wounds

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Dermatologic: Necrotic skin reactions, staining, vesicle formation

Gastrointestinal: Esophagitis, gastrointestinal irritation, ulceration of mucous membranes

Genitourinary: Hemorrhagic cystitis

Local: Burning, irritation

Ocular: Keratoconjunctivitis

Respiratory: Epistaxis, laryngitis, laryngeal obstruction, tracheitis

Miscellaneous: Allergic contact dermatitis, sensitivity reactions

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, topical: 1% (59 mL); 2% (60 mL)

Generic AvailableYes

Mechanism of ActionTopical antiseptic/germicide effective against some vegetative gram-positive bacteria, particularly *Staphylococcus* sp, and some yeast; it is much less effective against gram-negative bacteria and is ineffective against acid-fast bacteria

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Ulceration of mucous membranes.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCrystal Violet; Methylrosaniline Chloride

References

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Glatiramer Acetate

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Copaxone® may be confused with Compazine®

Pronunciation(gla TIR a mer AS e tate)
U.S. Brand NamesCopaxone®
Canadian Brand NamesCopaxone®
Pharmacologic Category[Biological, Miscellaneous]
Use: Labeled IndicationsManagement of relapsing-remitting type multiple sclerosis
Dosing: AdultsMultiple sclerosis (relapsing-remitting): SubQ: 20 mg daily
Dosing: ElderlyRefer to adult dosing.
Administration: OtherFor SubQ administration in the arms, abdomen, hips, or thighs; rotate injection sites to prevent lipoatrophy. Bring to room temperature prior to use. Visually inspect the solution; discard if solution is cloudy or contains any particulate matter.
StorageStore in refrigerator at 2°C to 8°C (36°F to 46°F); excursions to room temperature for up to 1 month do not have a negative impact on potency. Avoid heat; protect from intense light.
ContraindicationsHypersensitivity to glatiramer acetate, mannitol, or any component of the formulation
Allergy Considerations

- Mannitol Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Systemic reactions: Immediate postinjection systemic reactions occur in a substantial percentage of patients (~10% in premarketing studies); symptoms may begin within minutes of injection and usually spontaneously resolve within 30 minutes. Most patients only have one reaction despite repeated administration.

Disease-related concerns:

- Renal impairment: Safety and efficacy has not been established in patients with renal impairment.

Special populations:

- Elderly: Safety and efficacy has not been established in the elderly.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Administration: For SubQ use only, **not for I.V. administration.**

- Antigenic: Glatiramer acetate is antigenic, and may possibly lead to the induction of untoward host responses.

Pregnancy Risk FactorB
Pregnancy ConsiderationsAdverse events were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use in pregnancy only if clearly necessary.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions
>10%:

Cardiovascular: Vasodilation (27%), chest pain (21%), palpitation (17%)

Central nervous system: Pain (28%), anxiety (23%)

Dermatologic: Pruritus (18%), rash (18%)

Gastrointestinal: Nausea (22%), diarrhea (12%)

Local: Injection site reactions: Pain (73%), erythema (66%), inflammation (49%), pruritus (40%), mass (27%), induration (13%), welt (11%)

Neuromuscular & skeletal: Weakness (41%), arthralgia (24%), hypertonia (22%), back pain (16%)

Respiratory: Dyspnea (19%), rhinitis (14%)

Miscellaneous: Infection (50%), flu-like syndrome (19%), diaphoresis (15%), lymphadenopathy (12%)

1% to 10%:

Cardiovascular: Peripheral edema (7%), facial edema (6%), syncope (5%), tachycardia (5%), edema (3%), hypertension (1%)

Central nervous system: Fever (8%), vertigo (6%), migraine (5%), agitation (4%), chills (4%), confusion (2%), nervousness (2%), speech disorder (2%)

Dermatologic: Bruising (8%), erythema (4%), urticaria (4%), skin nodule (2%), eczema (1%), pustular rash (1%), skin atrophy (1%)

Endocrine & metabolic: Dysmenorrhea (6%)

Gastrointestinal: Anorexia (8%), vomiting (6%), gastrointestinal disorder (5%), gastroenteritis (3%), weight gain (3%), oral moniliasis (1%), salivary gland enlargement (1%), ulcerative stomatitis (1%)

Genitourinary: Urinary urgency (10%), vaginal moniliasis (8%), hematuria (1%)

Local: Injection site reactions: Hemorrhage (5%), urticaria (5%), edema (1%), atrophy (1%), abscess (1%), hypersensitivity (1%)

Neuromuscular & skeletal: Neck pain (8%), tremor (7%), foot drop (3%)

Ocular: Eye disorder (4%), nystagmus (2%)

Otic: Ear pain (7%)

Respiratory: Bronchitis (9%), laryngismus (5%)

Miscellaneous: Bacterial infection (5%), herpes simplex (4%), cyst (2%), herpes zoster (1%)

<1% (Limited to important or life-threatening): Angioedema, aphasia, atrial fibrillation, cholecystitis, coma, corneal ulcer, esophageal ulcer, esophagitis, ethanol intolerance, gastrointestinal hemorrhage, GI carcinoma, gout, hallucination, hematemesis, hepatomegaly, hypotension, injection site abscess, injection site fibrosis, leukopenia, manic reaction, optic neuritis, pancreatitis, pancytopenia, paraplegia, photosensitivity reaction, postural hypotension, priapism, rash, seizure, serum sickness, splenomegaly, stomatitis

Postmarketing and/or case reports (limited to important or life-threatening): Allergic reaction, anaphylactoid reaction, angina, arrhythmia, blindness, carcinoma (breast, bladder, lung), cardiomyopathy, CHF, cholelithiasis, cirrhosis, CNS neoplasm, glaucoma, hepatitis, lupus erythematosus, meningitis, MI, neuralgia, pericardial, effusion, pulmonary embolism, renal failure, rheumatoid arthritis, sepsis, stroke, thrombocytopenia, thrombosis

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess effectiveness and adverse response (eg, postinjection reactions - self-resolving flushing, chest tightness, dyspnea, palpitations). Teach patient proper use (reconstitution, injection technique, and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis drug will not cure MS, but may help relieve the severity and frequency of attacks. This drug can only be given by subcutaneous injection; your prescriber will instruct you in how to prepare the medication, proper injection technique, and syringe/needle disposal. If using prefilled glass syringe, use **only** the auto*ject*® 2 *for glass syringe* device (not the original Copaxone® autoject). Do not stop or change doses without consulting your prescriber. May cause a transient reaction after injection, including flushing, chest tightness, dyspnea, or palpitations (usually last 30 minutes or less). May cause weakness, dizziness, confusion, nervousness, or anxiety (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea or vomiting (frequent mouth care and sucking on lozenges may help). Report chest pain or pounding heartbeat; persistent diarrhea or GI upset; infection (vaginal itching or drainage, sores in mouth, unusual fever or chills) or flu-like symptoms (swollen glands, chills, excessive sweating); bruising, rash, or skin irritation; joint pain or neck pain; swelling of puffiness of face; vision changes or ear pain; unusual cough or respiratory difficulty; alterations in menstrual pattern; skin depression, hard lump, redness, pain, or swelling at injection site; or any other persistent adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Copaxone®: 20 mg/mL (1 mL) [prefilled syringe; contains mannitol; packaged with alcohol pads]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Kit (Copaxone)

20 mg/mL (1): $2563.84

Mechanism of ActionGlatiramer is a mixture of random polymers of four amino acids; L-alanine, L-glutamic acid, L-lysine and L-tyrosine, the resulting mixture is antigenically similar to myelin basic protein, which is an important component of the myelin sheath of nerves; glatiramer is thought to induce and activate T-lymphocyte suppressor cells specific for a myelin antigen, it is also proposed that glatiramer interferes with the antigen-presenting function of certain immune cells opposing pathogenic T-cell function

Pharmacodynamics/Kinetics

Distribution: Small amounts of intact and partial hydrolyzed drug enter lymphatic circulation

Metabolism: SubQ: Large percentage hydrolyzed locally

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Ulcerative stomatitis, salivary gland enlargement, and oral moniliasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety or depression

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCopolymer-1

References

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Comi G, Filippi M, Wolinsky JS, et al, “European/Canadian Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Effects of Glatiramer Acetate on Magnetic Resonance Imaging-Measured Disease Activity and Burden in Patients With Relapsing Multiple Sclerosis,” *Ann Neurol*, 2001, 49(3):290-7.[PubMed 11261502]

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Noseworthy JH, Lucchinetti C, Rodriguez M, and Weinshenker BG, “Multiple Sclerosis,” *N Engl J Med*, 2000, 343(13):938-52.[PubMed 11006371]

International Brand NamesCopaxone (AR, AU, BE, BG, BR, CH, DE, DK, EE, ES, FI, FR, GB, HN, HU, IE, IL, IT, NL, PE, PL, PY, SE, TW, UY)

Gliclazide

Lexi-Drugs Online

English

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(GLYE kla zide)

Canadian Brand NamesApo-Gliclazide®; Diamicron®; Diamicron® MR; Gen-Gliclazide; Gliclazide-80; Novo-Gliclazide; PMS-Gliclazide; Sandoz-Gliclazide

Pharmacologic CategoryAntidiabetic Agent, Sulfonylurea

Use: Labeled IndicationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM)

Dosing: AdultsType 2 diabetes: Oral:

Immediate release tablet: Initial: 80-160 mg/day; dose range 80-320 mg/day; dosage of ≥160 mg should be divided into 2 equal parts for twice-daily administration; maximum dose: 320 mg/day. Should be taken with meals.

Sustained release tablet: 30-120 mg once daily

Note: There is no fixed dosage regimen for the management of diabetes mellitus with gliclazide or any other hypoglycemic agent. Dose must be individualized based on frequent determinations of blood glucose during dose titration and throughout maintenance.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentContraindicated in severe impairment.

Dosing: Hepatic ImpairmentContraindicated in severe impairment.

Administration: OralPatients who are anorexic or NPO, may need to have their dose held to avoid hypoglycemia. Should be administered with meals.

Dietary ConsiderationsShould be taken with meals. Dietary modification based on ADA recommendations is a part of therapy. Decreases blood glucose concentration. Hypoglycemia may occur. Must be able to recognize symptoms of hypoglycemia (palpitations, sweaty palms, lightheadedness).

StorageStore at 20°C to 30°C (68°F to 86°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to gliclazide, sulfonylureas, or any component of the formulation; type 1 diabetes mellitus (insulin dependent, IDDM), diabetic ketoacidosis with or without coma; renal or hepatic impairment; pregnancy (per manufacturer); breast-feeding

Allergy Considerations

- Sulfonylurea Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiovascular mortality: Product labeling of sulfonylureas (in U.S.) states oral hypoglycemic drugs may be associated with an increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS), have not supported an association.

- Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when ethanol is ingested, or when more than one glucose-lowering drug is used. It is also more likely in elderly patients, malnourished patients and in patients with impaired renal or hepatic function; use with caution.

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Disease-related concerns:

- Stress-related states: It may be necessary to discontinue therapy and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsAge, hepatic impairment, and renal impairment are independent risk factors for hypoglycemia; conservative initial dosing and slow titration are required to avoid hypoglycemic reactions; dosage titration should be made at weekly intervals. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorNot available (similar agents rated C); manufacturer contraindicates use

Pregnancy ConsiderationsClinical effects on the fetus: Crosses the placenta. Hypoglycemia; ear defects reported with sulfonylureas; other malformations reported but may have been secondary to poor maternal glucose control/diabetes. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsPotential for neonatal hypoglycemia contraindicates use.

Adverse ReactionsFrequency not defined.

Central nervous system: Headache, nervousness, dizziness

Dermatologic: Rash, erythema, pruritus, urticaria. Sulfonylureas have also been associated with rare photosensitivity and porphyria cutanea tarda

Endocrine & metabolic: Hypoglycemia (dose dependent), hyponatremia (rare)

Gastrointestinal: Nausea, vomiting, diarrhea, epigastric fullness, gastritis

Hematologic: Agranulocytosis, leukopenia, thrombocytopenia, anemia

Hepatic: Jaundice, LDH increased, transaminases increased

Miscellaneous: Disulfiram reaction (very low potential)

Drug Interactions

Alcohol (Ethyl): Sulfonylureas may enhance the adverse/toxic effect of Alcohol (Ethyl). A flushing reaction may occur. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Cyclic Antidepressants: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonylureas may increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Fibric Acid Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Fluconazole: May increase the serum concentration of Sulfonylureas. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Salicylates: May enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. **Exceptions:** Sulfacetamide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause hypoglycemia and/or rare disulfiram reactions).

Herb/Nutraceutical: Avoid chromium, garlic, gymnema (may cause hypoglycemia).

Monitoring ParametersSigns and symptoms of hypoglycemia, fasting blood glucose, hemoglobin A_{1c}

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Monitoring: Lab Tests Fasting blood glucose, hemoglobin A_{1c}

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet: 80 mg [not available in the U.S.]

Diamicron® [CAN]: 80 mg [not available in the U.S.]

Tablet, sustained release:

Diamicron® MR [CAN]: 30 mg [not available in the U.S.]

Generic Available Yes: 80 mg tablet

ManufacturerServier (Canada)

Mechanism of Action Stimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; lowers plasma glucose concentrations. Gliclazide has also been shown to decrease platelet aggregation at therapeutic doses.

Pharmacodynamics/Kinetics

Absorption: Rapid

Protein binding: 94%

Metabolism: Hepatic, to inactive metabolites

Half-life elimination: 10 hours

Time to peak: 4-6 hours

Excretion: Urine (60% to 70%) and feces (10% to 20%) as metabolites

Pharmacotherapy Pearls Not available in U.S.

Dental Health: Effects on Dental Treatment Gliclazide-dependent patients with diabetes (noninsulin dependent, type 2) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause nervousness and dizziness

Mental Health: Effects on Psychiatric Treatment May cause leukopenia, thrombocytopenia, and agranulocytosis; use caution with clozapine, carbamazepine, and valproic acid

Cardiovascular Considerations The possibility of higher doses of sulfonylureas eliciting an increase in cardiovascular events, because of their effects on blocking potassium sensitive ATP channels, has been raised. However, there are presently only limited data to support this premise, particularly with newer generation agents. An early study suggested poor cardiovascular outcomes in patients with diabetes treated with tolbutamide. Retrospective studies evaluating cardiovascular outcomes following angioplasty and acute myocardial infarction in patients with diabetes receiving newer sulfonylureas are inconsistent. Longer-term prospective trials of sulfonylurea therapy, such as the UKPDS, do not reveal any increased cardiovascular mortality.

References

Canadian Diabetes Association, Clinical Practice Guildelines, http://www.diabetes.ca/cpg2003/chapters.aspx

International Brand Names Azide (PK); Azukon (IN); Azukon MR (IN); Beclazide MR (TH); Cadicon (TH); Clizid (PH); D-Verin (KP); Diabezidum (PL); Diabrezide (PL); Diacose (TH); Diaklat (PL); Diamicron (AR, AT, AU, BE, BR, CH, CN, CO, CZ, DE, DK, ES, FR, GB, GR, HK, IE, IN, IT, KP, LU, MX, MY, NL, PE, PH, PK, PT, TH, TW, UY, VE, ZA); Diamicron MR (AR, BB, BM, BR, BS, BZ, CH, CL, CN, CO, CR, DO, GB, GT, GY, HK, HN, ID, JM, KP, MY, NI, NL, NZ, PA, PE, PH, PY, SR, SV, TH, TT, TW, UY, VE); Dianorm (AU); Diaprel (BG, EE, HN, HR, HU, PL); Diazidan (PL); Dimetus (TH); Gliclazide (PL); Glikamel (ID); Gliklazyd (PL); Glimicron (HK, JP); Glinormax (PL); Glizide (KP, SG); Glubitor-OD (PH); Gluctam (BG, EE, HU, PL); Glyade (AU, TW); Linodiab (ID); Mellihexal (AU); Nidem (AU); Norsulin (PL); Pedab (ID); Reclide (VE); Sunglizide (HK); Unava (PY); Zebet (PH); Ziclin (ZA)

Glimepiride

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Glimepiride may be confused with glipiZIDE

Amaryl® may be confused with Altace®, Amerge®, Reminyl®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(GLYE me pye ride)

U.S. Brand NamesAmaryl®

Canadian Brand NamesAmaryl®; Apo-Glimepiride; CO Glimepiride; Novo-Glimepiride; PMS-Glimepiride; ratio-Glimepiride; Rhoxal-glimepiride; Sandoz-Glimepiride

Pharmacologic CategoryAntidiabetic Agent, Sulfonylurea

Use: Labeled IndicationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as an adjunct to diet and exercise to lower blood glucose; may be used in combination with metformin or insulin in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with a single oral hypoglycemic agent

Dosing: Adults

Type 2 diabetes: Oral:

Initial: 1-2 mg once daily, administered with breakfast or the first main meal

Adjustment: Allow several days between dose titrations: usual maintenance dose: 1-4 mg once daily; after a dose of 2 mg once daily, increase in increments of 2 mg at 1- to 2-week intervals based upon the patient's blood glucose response to a maximum of 8 mg once daily. If inadequate response to maximal dose, combination therapy with metformin may be considered.

Combination with insulin therapy:

Note: Fasting glucose level for instituting combination therapy is in the range of >150 mg/dL in plasma or serum depending on the patient)

Initial: 8 mg once daily with the first main meal

Adjustment: After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose. Once stable, combination-therapy patients should monitor their capillary blood glucose on an ongoing basis, preferably daily.

Conversion from therapy with long half-life agents: Observe patient carefully for 1-2 weeks when converting from a longer half-life agent (eg, chlorpropamide) to glimepiride due to overlapping hypoglycemic effects.

Dosing: ElderlyInitial: 1 mg/day; dose titration and maintenance dosing should be conservative to avoid hypoglycemia

Dosing: Pediatric**Type 2 diabetes:** Oral: Children 10-18 years (unlabeled use): Initial: 1 mg once daily; maintenance: 1-4 mg once daily

Dosing: Renal ImpairmentCl_{cr} <22 mL/minute: Initial starting dose should be 1 mg and dosage increments should be based on fasting blood glucose levels.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister once daily with breakfast or first main meal of the day. Patients who are NPO may need to have their dose held to avoid hypoglycemia.

Dietary ConsiderationsAdminister with breakfast or the first main meal of the day. Dietary modification based on ADA recommendations is a part of therapy. Decreases blood glucose concentration. Hypoglycemia may occur. Must be able to recognize symptoms of hypoglycemia (palpitations, sweaty palms, lightheadedness).

ContraindicationsHypersensitivity to glimepiride, any component of the formulation, or sulfonamides; diabetic ketoacidosis (with or without coma)

Allergy Considerations

- Sulfonylurea Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS) have not supported an association.

- Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when ethanol is ingested, or when more than one glucose-lowering drug is used. It is also more likely in elderly patients, malnourished patients and in patients with impaired renal or hepatic function; use with caution.

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Disease-related concerns:

- Stress-related states: It may be necessary to discontinue therapy and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsRapid and prolonged hypoglycemia (>12 hours) despite hypertonic glucose injections have been reported with glimepiride. Age, hepatic impairment, and renal impairment are independent risk factors for hypoglycemia; dosage titration should be made at weekly intervals. How “tightly” a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar of <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well they recognize hypoglycemic or hyperglycemic symptoms, and how to respond to them and their other disease states. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy Considerations

Adverse events have been observed in animal studies; therefore, glimepiride is classified as pregnancy category C. Severe hypoglycemia lasting 4-10 days has been noted in infants born to mothers taking a sulfonylurea at the time of delivery. The manufacturer recommends that patients be switched to insulin during pregnancy. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if glimepiride is excreted in breast milk. Breast-feeding is not recommended by the manufacturer. Potentially, hypoglycemia may occur in a nursing infant exposed to a sulfonylurea via breast milk.

Pregnancy & Lactation, In-Depth

- Glimepiride in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Central nervous system: Dizziness (2%), headache (2%)

Endocrine & metabolic: Hypoglycemia (1% to 2%)

Gastrointestinal: Nausea (1%)

Neuromuscular & skeletal: Weakness (2%)

<1% or frequency not defined: Agranulocytosis, anorexia, aplastic anemia, cholestatic jaundice, constipation, diarrhea, disulfiram-like reaction, diuretic effect, edema, epigastric fullness, gastrointestinal pain, erythema, heartburn, hemolytic anemia, hepatitis, hypoglycemia, hyponatremia, leukopenia, liver function tests abnormal, nausea, pancytopenia, photosensitivity, porphyria cutanea tarda, pruritus, rash (morbilliform or maculopapular), SIADH, thrombocytopenia, urticaria, vasculitis (allergic), visual accommodation changes (early treatment), vomiting

Metabolism/Transport Effects**Substrate** of CYP2C9 (major)

Drug Interactions

Alcohol (Ethyl): Sulfonylureas may enhance the adverse/toxic effect of Alcohol (Ethyl). A flushing reaction may occur. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Cyclic Antidepressants: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonylureas may increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Fibric Acid Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Fluconazole: May increase the serum concentration of Sulfonylureas. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Salicylates: May enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. **Exceptions:** Sulfacetamide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Caution with ethanol (may cause hypoglycemia).

Herb/Nutraceutical: Caution with chromium, garlic, gymnema (may cause hypoglycemia).

Monitoring ParametersUrine for glucose and ketones; monitor for signs and symptoms of hypoglycemia (fatigue, excessive hunger, profuse sweating, numbness of extremities), fasting blood glucose, hemoglobin A_{1c}, fructosamine

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringAssess any allergies prior to beginning therapy. Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response at regular intervals during therapy. Teach patient proper use (or refer patient to diabetic educator for instruction), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsUrine for glucose and ketones, fasting blood glucose, hemoglobin A_{1c}, fructosamine

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is used to control diabetes; it is not a cure. Monitor glucose as recommended by prescriber. Other important components of treatment plan may include prescribed diet and exercise regimen (consult prescriber or diabetic educator). Always carry quick source of sugar with you. Take exactly as directed with breakfast or the first main meal of the day. Do not change dose or discontinue without consulting prescriber. Avoid alcohol while taking this medication; could cause severe reaction. Do not take other medication within 2 hours of this medication unless advised by prescriber. If you experience hypoglycemic reaction, contact prescriber immediately. You may experience side effects during first weeks of therapy (eg, headache, nausea); consult prescriber if these persist. Report severe or persistent side effects (eg, hypoglycemia: palpitations, sweaty palms, lightheadedness; extended vomiting or flu-like symptoms; skin rash; easy bruising or bleeding; or change in color of urine or stool). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 1 mg, 2 mg, 4 mg

Amaryl®: 1 mg, 2 mg, 4 mg

Generic AvailableYes

ManufacturerHoechst-Marion Roussel

Pricing: U.S. (www.drugstore.com)

Tablets (Amaryl)

1 mg (30): $28.20

2 mg (30): $36.89

4 mg (30): $52.99

Tablets (Glimepiride)

1 mg (30): $12.99

2 mg (90): $18.99

4 mg (30): $14.99

Mechanism of ActionStimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Blood glucose reductions: 2-3 hours

Duration: 24 hours

Absorption: 100%; delayed when given with food

Distribution: V_d: 8.8 L

Protein binding: >99.5%

Metabolism: Hepatic oxidation via CYP2C9 to M1 metabolite (~33% activity of parent compound); further oxidative metabolism to inactive M2 metabolite

Half-life elimination: 5-9 hours

Time to peak, plasma: 2-3 hours

Excretion: Urine (60%, 80% to 90% as M1 and M2); feces (40%, 70% as M1 and M2)

Related Information

- Diabetes Mellitus Management, Adults
- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentGlimepiride-dependent patients with diabetes (noninsulin dependent, type 2) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; phenothiazines and TCAs may antagonize glimepiride hypoglycemic effects; MAO inhibitors and TCAs may enhance hypoglycemic effects

Cardiovascular ConsiderationsThe possibility of higher doses of sulfonylureas eliciting an increase in cardiovascular events, because of their effects on blocking potassium sensitive ATP channels, has been raised. However, there are presently only limited data to support this premise, particularly with newer generation agents. An early study suggested poor cardiovascular outcomes in patients with diabetes treated with tolbutamide. Retrospective studies evaluating cardiovascular outcomes following angioplasty and acute myocardial infarction in patients with diabetes receiving newer sulfonylureas are inconsistent. Longer-term prospective trials of sulfonylurea therapy, such as the UKPDS, do not reveal any increased cardiovascular mortality.

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O'Keefe JH, Blackstone EH, Sergeant P, et al, “The Optimal Mode of Coronary Revascularization for Diabetics. A Risk-Adjusted Long-Term Study Comparing Coronary Angioplasty and Coronary Bypass Surgery,” *Eur Heart J*, 1998, 19(11):1696-703. [PubMed 9857923]

International Brand NamesAcotryl (PH); Amadiab (ID); Amarel (FR); Amaryl (AR, AT, AU, BB, BF, BG, BJ, BM, BO, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CZ, DE, DK, DO, EC, EE, EG, ES, ET, FI, GB, GH, GM, GN, GT, GY, HK, HN, HR, ID, IE, IL, IN, IT, JM, KE, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, PA, PE, PK, PL, PR, PY, SC, SD, SE, SL, SN, SR, SV, TH, TN, TT, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Amarylle (BE); Ameride (MY); Amerine (TW); Aramyl (KP); Arya (PH); Aylide (AU); Azulix (PH); Diaglime (ID); Diapride (AU, HK, MY, SG); Dimirel (AU); Endial (AR); Euglex (KP); Euglim (IN); Getryl (PH); Glidiamid (PL); Glimaryl (TW); Glimep (KP); Glimepid (KP); Glimerid (CO); Glimexal (ID); Glimpid (MY); Glimulin (MY); Glipirin (KP); Gludine (KP); Gluvas (ID); Glymil (KP); Imerid (PH); Mapryl (ID); Metrix (ID); Miaryl (KP, MY); Neomaryl (KP); Norizec (PH); Paride (ID); Relide (ID); Solosa (PH); Sulfast (PH)

Glipizide and Metformin

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(GLIP i zide & met FOR min)

U.S. Brand NamesMetaglip™

Pharmacologic CategoryAntidiabetic Agent, Biguanide; Antidiabetic Agent, Sulfonylurea

Use: Labeled IndicationsIndicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (noninsulin dependent, NIDDM)

Dosing: Adults**Type 2 diabetes:**

Patients inadequately controlled on diet and exercise alone: Initial dose: Glipizide 2.5 mg/metformin 250 mg once daily with a meal. In patients with fasting plasma glucose (FPG) 280-320 mg/dL, initiate therapy with glipizide 2.5 mg/metformin 500 mg twice daily.

Note: Increase dose by 1 tablet/day every 2 weeks (maximum daily dose: glipizide 10 mg/metformin 2000 mg in divided doses)

Patients inadequately controlled on a sulfonylurea and/or metformin: Initial dose: Glipizide 2.5 mg/metformin 500 mg or glipizide 5 mg/metformin 500 mg twice daily with morning and evening meals; starting dose should not exceed current daily dose of glipizide (or sulfonylurea equivalent) and/or metformin.

Note: Increase dose in increments of no more than glipizide 5 mg/metformin 500 mg (maximum daily dose: glipizide 20 mg/metformin 2000 mg)

Dosing: ElderlyConservative doses are recommended in the elderly due to potentially decreased renal function; **do not titrate to maximum dose**; should not be used in patients ≥80 years unless renal function is verified as normal

Dosing: Renal ImpairmentContraindicated in the presence of renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL [males], ≥1.4 mg/dL [females], or abnormal creatinine clearance).

Dosing: Hepatic ImpairmentAvoid use in patients with impaired liver function.

Administration: OralAll doses should be administered with a meal. Twice-daily dosing should be administered with the morning and evening meals. Dietary modification based on ADA recommendations is a part of therapy. Patients that are NPO or require decreased caloric intake may need doses held to avoid hypoglycemia.

Dietary ConsiderationsMay cause GI upset; should be taken with food to decrease GI upset. Dietary modification based on ADA recommendations is a part of therapy. Decreases blood glucose concentration; hypoglycemia may occur. Must be able to recognize symptoms of hypoglycemia (palpitations, sweaty palms, lightheadedness). Monitor for signs and symptoms of vitamin B_{12} and folic acid deficiency; supplementation may be required.

StorageStore at room temperature of 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to glipizide, metformin, or any component of the formulation; renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females, or abnormal creatinine clearance which may also result from conditions such as cardiovascular collapse, acute myocardial infarction, and septicemia); acute or chronic metabolic acidosis with or without coma (including diabetic ketoacidosis)

Note: Temporarily discontinue in patients undergoing radiologic studies in which intravascular iodinated contrast materials are utilized.

Allergy Considerations

- Biguanide Allergy
- Sulfonylurea Allergy

Warnings/Precautions

Boxed warnings:

- Lactic acidosis: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS) have not supported an association.

- Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when ethanol is ingested, or when more than one glucose-lowering drug is used. It is also more likely in elderly patients, malnourished patients and in patients with impaired renal, hepatic, adrenal and/or pituitary function; use with caution.

- Lactic acidosis: **[U.S. Boxed Warning]: Lactic acidosis is a rare, but potentially severe consequence of therapy with metformin.** Lactic acidosis should be suspected in any patient with diabetes receiving metformin with evidence of acidosis but without evidence of ketoacidosis. Discontinue metformin in clinical situations predisposing to hypoxemia, including conditions such as cardiovascular collapse, respiratory failure, acute myocardial infarction, acute congestive heart failure, and septicemia. The risk of accumulation and lactic acidosis increases with the degree of impairment of renal function and patient age.

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is not specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Disease-related concerns:

- Heart failure: Use metformin with caution in patients with congestive heart failure requiring pharmacologic management, particularly in patients with unstable or acute heart failure; risk of lactic acidosis may be increased secondary to hypoperfusion.

- Hepatic impairment: Avoid metformin use in patients with impaired liver function due to potential for lactic acidosis; use glipizide with caution in patients with severe hepatic disease.

- Renal impairment: Metformin is substantially excreted by the kidney; patients with renal function below the limit of normal for their age should not receive therapy. Use of concomitant medications that may affect renal function (ie, affect tubular secretion) may also affect metformin disposition. Metformin should be withheld in patients with dehydration and/or prerenal azotemia.

- Stress-related states: It may be necessary to discontinue metformin and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Special populations:

- Elderly: Metformin should not be initiated in patients ≥80 years of age unless normal renal function is confirmed. Risk of lactic acidosis increases with age.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism and increase risk of hypoglycemia.

- Iodinated contrast: Metformin therapy should be temporarily discontinued prior to or at the time of intravascular administration of iodinated contrast media (potential for acute alteration in renal function). Metformin should be withheld for 48 hours after the radiologic study and restarted only after renal function has been confirmed as normal.

- Surgical procedures: Metformin therapy should be suspended for any surgical procedures (resume only after oral intake resumed and normal renal function is verified).

Geriatric ConsiderationsIntensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies were not conducted with this combination; therefore, glipizide/metformin is classified as pregnancy category C. Refer to individual agents.

Lactation

Glipizide: Excretion in breast milk unknown/not recommended

Metformin: Enters breast milk/not recommended

Breast-Feeding ConsiderationsRefer to individual agents.

Pregnancy & Lactation, In-Depth

- GlipiZIDE in Pregnancy & Lactation
- MetFORMIN in Pregnancy & Lactation

Adverse ReactionsAlso see individual agents.

>10%:

Central nervous system: Headache (13%)

Endocrine & metabolic: Hypoglycemia (8% to 13%)

Gastrointestinal: Diarrhea (2% to 18%)

1% to 10%:

Cardiovascular: Hypertension (3% to 4%)

Central nervous system: Dizziness (2% to 5%)

Gastrointestinal: Nausea/vomiting (<1% to 8%), abdominal pain (6%)

Neuromuscular & skeletal: Musculoskeletal pain (8%)

Renal: Urinary tract infection (1%)

Respiratory: Upper respiratory tract infection (8% to 10%)

Metabolism/Transport EffectsGlipizide: **Substrate** of 2C8/9 (major)
Drug Interactions

Alcohol (Ethyl): Sulfonylureas may enhance the adverse/toxic effect of Alcohol (Ethyl). A flushing reaction may occur. *Risk C: Monitor therapy*

Cephalexin: May increase the serum concentration of MetFORMIN. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Cimetidine: May decrease the excretion of MetFORMIN. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Cyclic Antidepressants: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonylureas may increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Fibric Acid Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Fluconazole: May increase the serum concentration of Sulfonylureas. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Iodinated Contrast Agents: May enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Salicylates: May enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. **Exceptions:** Sulfacetamide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsSee individual agents.
Monitoring ParametersSigns and symptoms of hypoglycemia, urine (glucose and ketones), FPG, Hb A_{1c}, and fructosamine. Initial and periodic monitoring of hematologic parameters (eg, hemoglobin/hematocrit and red blood cell indices) and renal function should be performed; monitor at least annually once patient is on maintenance therapy. While megaloblastic anemia has been rarely seen with metformin, if suspected, vitamin B_{12} deficiency should be excluded.
Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringSee individual agents.
Monitoring: Lab TestsSee individual agents.

Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 2.5/250: Glipizide 2.5 mg and metformin hydrochloride 250 mg; 2.5/500: Glipizide 2.5 mg and metformin hydrochloride 500 mg; 5/500: Glipizide 5 mg and metformin hydrochloride 500 mg

Metaglip™ 2.5/250: Glipizide 2.5 mg and metformin hydrochloride 250 mg

Metaglip™ 2.5/500: Glipizide 2.5 mg and metformin hydrochloride 500 mg

Metaglip™ 5/500: Glipizide 5 mg and metformin hydrochloride 500 mg

Generic AvailableYes
ManufacturerBristol-Myers Squibb Company
Pricing: U.S. (www.drugstore.com)

Tablets (GlipiZIDE-MetFORMIN HCl)

2.5-500 mg (60): $74.99

Tablets (GlipiZIDE-Metformin HCl)

5-500 mg (60): $63.99

Tablets (Metaglip)

2.5-250 mg (30): $38.51

Mechanism of ActionThe combination of glipizide and metformin is used to improve glycemic control in patients with type 2 diabetes mellitus (noninsulin dependent, NIDDM) by using two different, but complementary, mechanisms of action:

Glipizide: Stimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites

Metformin: Decreases hepatic glucose production, decreasing intestinal absorption of glucose and improves insulin sensitivity (increases peripheral glucose uptake and utilization)

Pharmacodynamics/KineticsSee individual agents.
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Upper respiratory tract infection (8% to 10%). Dependent patients with diabetes (noninsulin dependent, type 2) should be appointed for dental treatment in the morning in order to minimize chance of stress-induced hypoglycemia.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness
Mental Health: Effects on Psychiatric TreatmentDiarrhea is common; use caution with SSRIs. May rarely cause agranulocytosis; use caution with clozapine and carbamazepine. Phenothiazines and TCAs may antagonize glipizide hypoglycemic effects; MAO inhibitors and TCAs may enhance hypoglycemic effects.
Index TermsGlipizide and Metformin Hydrochloride; Metformin and Glipizide
References

American Diabetes Association, “Standards of Medical Care in Diabetes Mellitus -- 2009,” *Diabetes Care*, 2009, 32(Suppl 1):13-61.[PubMed 19118286]

“Effect of Intensive Blood-Glucose Control With Metformin on Complications in Overweight Patients With Type 2 Diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group,” *Lancet*, 1998, 352(9131):854-65.[PubMed 9742977]

GlipiZIDE

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

GlipiZIDE may be confused with glimepiride, glyBURIDE

Glucotrol® may be confused with Glucophage®, Glucotrol® XL, glyBURIDE

Glucotrol® XL may be confused with Glucotrol®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(GLIP i zide)

U.S. Brand NamesGlucotrol XL®; Glucotrol®

Pharmacologic Category[Antidiabetic Agent, Sulfonylurea]

Use: Labeled IndicationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM)

Dosing: Adults

Type 2 diabetes: Oral (allow several days between dose titrations): Initial: 5 mg/day; adjust dosage at 2.5-5 mg daily increments as determined by blood glucose response at intervals of several days.

Immediate release tablet: Maximum recommended once-daily dose: 15 mg; maximum recommended total daily dose: 40 mg. Doses >15 mg/day should be administered in divided doses.

Extended release tablet (Glucotrol XL®): Maximum recommended dose: 20 mg

When transferring from insulin to glipizide:

Current insulin requirement ≤20 units: Discontinue insulin and initiate glipizide at usual dose

Current insulin requirement >20 units: Decrease insulin by 50% and initiate glipizide at usual dose; gradually decrease insulin dose based on patient response. Several days should elapse between dosage changes.

Dosing: ElderlyInitial: 2.5 mg/day; increase by 2.5-5 mg/day at 1- to 2-week intervals.

Dosing: Renal ImpairmentCl_{cr} <10 mL/minute: Some investigators recommend not using.

Dosing: Hepatic ImpairmentInitial dosage should be 2.5 mg/day.

Administration: OralAdminister immediate release tablets 30 minutes before a meal to achieve greatest reduction in postprandial hyperglycemia. Extended release tablets should be given with breakfast. Patients who are NPO may need to have their dose held to avoid hypoglycemia.

Dietary ConsiderationsTake immediate release tablets 30 minutes before meals; extended release tablets should be taken with breakfast. Dietary modification based on ADA recommendations is a part of therapy. Decreases blood glucose concentration. Hypoglycemia may occur. Must be able to recognize symptoms of hypoglycemia (palpitations, sweaty palms, lightheadedness).

ContraindicationsHypersensitivity to glipizide or any component of the formulation, other sulfonamides; type 1 diabetes mellitus (insulin dependent, IDDM); diabetic ketoacidosis

Allergy Considerations

- Sulfonylurea Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS) have not supported an association.

- Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when ethanol is ingested, or when more than one glucose-lowering drug is used. It is also more likely in elderly patients, malnourished patients and in patients with impaired renal or hepatic function; use with caution.

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with severe hepatic disease.
- Stress-related states: It may be necessary to discontinue therapy and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- GI tract stricture/narrowing: The extended release formulation consists of drug within a nondeformable matrix; following drug release/absorption, the matrix/shell is expelled in the stool. The use of nondeformable products in patients with known stricture/narrowing of the GI tract has been associated with symptoms of obstruction. Avoid use of extended release tablets (Glucotrol® XL) in patients with severe gastrointestinal narrowing or esophageal dysmotility.

Geriatric ConsiderationsGlipizide is a useful agent since there are few drug-to-drug interactions and elimination of the active drug is not dependent upon renal function. How “tightly” a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well they recognize hypoglycemic or hyperglycemic symptoms, and how to respond to them and their other disease states. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in animal studies; therefore, glipizide is classified as pregnancy category C. Glipizide crosses the placenta. Severe hypoglycemia lasting 4-10 days has been noted in infants born to mothers taking a sulfonylurea at the time of delivery. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. The manufacturer recommends if glipizide is used during pregnancy it should be discontinued at least 1 month before the expected delivery date. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsData from initial studies note that glipizide was not detected in breast milk. Breast-feeding is not recommended by the manufacturer. Potentially, hypoglycemia may occur in a nursing infant exposed to a sulfonylurea via breast milk.

Pregnancy & Lactation, In-Depth

- GlipiZIDE in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Cardiovascular: Edema, syncope

Central nervous system: Anxiety, depression, dizziness, drowsiness, headache, hypoesthesia, insomnia, nervousness, pain

Dermatologic: Eczema, erythema, maculopapular eruptions, morbilliform eruptions, photosensitivity, pruritus, rash, urticaria

Endocrine & metabolic: Disulfiram-like reaction, hypoglycemia, hyponatremia, SIADH (rare)

Gastrointestinal: Anorexia, constipation, diarrhea, epigastric fullness, flatulence, gastralgia, heartburn, nausea, vomiting

Hematologic: Agranulocytopenia, aplastic anemia, blood dyscrasias, hemolytic anemia, leukopenia, pancytopenia, porphyria cutanea tarda, thrombocytopenia

Hepatic: Cholestatic jaundice, hepatic porphyria

Neuromuscular & skeletal: Arthralgia, leg cramps, myalgia, paresthesia, tremor

Ocular: Blurred vision

Renal: Diuretic effect (minor)

Respiratory: Rhinitis

Miscellaneous: Diaphoresis

Postmarketing and/or case reports: Abdominal pain

Metabolism/Transport Effects**Substrate** of 2C9 (major)

Drug Interactions

Alcohol (Ethyl): Sulfonylureas may enhance the adverse/toxic effect of Alcohol (Ethyl). A flushing reaction may occur. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Cyclic Antidepressants: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonylureas may increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Fibric Acid Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Fluconazole: May increase the serum concentration of Sulfonylureas. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Salicylates: May enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. **Exceptions:** Sulfacetamide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Caution with ethanol (may cause hypoglycemia or rare disulfiram reaction).

Food: A delayed release of insulin may occur if glipizide is taken with food. Immediate release tablets should be administered 30 minutes before meals to avoid erratic absorption.

Herb/Nutraceutical: Herbs with hypoglycemic properties may enhance the hypoglycemic effect of glipizide. This includes alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, stinging nettle

Monitoring ParametersSigns and symptoms of hypoglycemia (fatigue, excessive hunger, profuse sweating, numbness of extremities), blood glucose, hemoglobin A_{1c}

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking, and any allergies they may have. Assess results of laboratory tests, therapeutic effects, and adverse response (eg, hypoglycemia) at regular intervals during therapy. Teach patient proper use (or refer patient to diabetic educator for instruction), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsBlood glucose, hemoglobin A_{1c}

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is used to control diabetes; it is not a cure. Monitor glucose as recommended by prescriber. Other important components of treatment plan may include prescribed diet and exercise regimen (consult prescriber or diabetic educator). Always carry quick source of sugar with you. Take exactly as directed. Immediate release tablets should be taken 30 minutes before meals, at the same time each day. Extended release tablets should be taken with breakfast. Do not chew or crush extended release tablets. Do not change dose or discontinue without consulting prescriber. Avoid alcohol while taking this medication; could cause severe reaction. Do not take other medication within 2 hours of this medication unless advised by prescriber. If you experience hypoglycemic reaction, contact prescriber immediately. You may experience more sensitivity to sunlight (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); or headache or nausea (consult prescriber if these persist). Report severe or persistent side effects (eg, hypoglycemia: palpitations, sweaty palms, lightheadedness; extended vomiting; diarrhea or constipation; flu-like symptoms; skin rash; easy bruising or bleeding; or change in color of urine or stool). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 5 mg, 10 mg

Glucotrol®: 5 mg, 10 mg

Tablet, extended release: 2.5 mg, 5 mg, 10 mg

Glucotrol XL®: 2.5 mg, 5 mg, 10 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (GlipiZIDE XL)

2.5 mg (30): $18.99

5 mg (30): $14.99

10 mg (30): $19.99

Tablet, 24-hour (Glucotrol XL)

2.5 mg (30): $27.29

5 mg (30): $27.29

10 mg (30): $41.99

Tablets (GlipiZIDE)

5 mg (100): $19.98

10 mg (90): $19.49

Tablets (Glucotrol)

5 mg (60): $44.09

10 mg (60): $72.44

Mechanism of ActionStimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites

Pharmacodynamics/Kinetics

Duration: 12-24 hours

Absorption: Rapid and complete; delayed with food

Distribution: 10-11 L

Protein binding: 98% to 99%; primarily to albumin

Bioavailability: 90% to 100%

Metabolism: Hepatic via CYP2C9; forms metabolites (inactive)

Half-life elimination: 2-5 hours

Time to peak: 1-3 hours; extended release tablets: 6-12 hours

Excretion: Urine (60% to 80%, 91% to 97% as metabolites); feces (11%)

Related Information

- Diabetes Mellitus Management, Adults
- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentGlipizide-dependent patients with diabetes (noninsulin dependent, type 2) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; phenothiazines and TCAs may antagonize glipizide hypoglycemic effects; MAO inhibitors and TCAs may enhance hypoglycemic effects

Cardiovascular ConsiderationsThe possibility of higher doses of sulfonylureas eliciting an increase in cardiovascular events, because of their effects on blocking potassium sensitive ATP channels, has been raised. However, there are presently only limited data to support this premise, particularly with newer generation agents. An early study suggested poor cardiovascular outcomes in patients with diabetes treated with tolbutamide. Retrospective studies evaluating cardiovascular outcomes following angioplasty and acute myocardial infarction in patients with diabetes receiving newer sulfonylureas are inconsistent. Longer-term prospective trials of sulfonylurea therapy, such as the UKPDS, do not reveal any increased cardiovascular mortality.

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: The possibility of higher doses of sulfonylureas eliciting an increase in cardiovascular events, because of their effects on blocking potassium-sensitive ATP channels, has been raised. Longer-term prospective trials of sulfonylurea therapy, such as the UKPDS and

ADVANCE, do not reveal any increased cardiovascular mortality.

Index Terms Glydiazinamide

References

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International Brand Names Aldiab (ID); Antidiab (HR, PL); Apamid (SE); Brilizid (PH); Diabes (TW); Diasef (HK, SG); Dibizide (MY); Digrin (KP); Dipazide (TH); Flumedil (MX); Gabaz (MX); Gipzide (TH); Glibenese (AE, AT, BE, BF, BH, BJ, CH, CI, CY, DE, DK, EG, ET, FI, FR, GH, GM, GN, GR, IL, IQ, IR, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PL, QA, RU, SA, SC, SD, SE, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Glibenese GITS (PL); Glibetin (TW); Glican (SV); Glidiab (TW); Glipid (NZ); Glipimed (TH); Glipizide (PL); Glipizide BP (PL); Glix (MY); Glizide (TH); Gluco-Rite (IL); Glucodiab (TH); Glucolip (IN); Gluconil (PH); Glucotrol XL (BB, BM, BS, BZ, CL, GY, HK, ID, JM, SR, TT); Glucozide (TW); Glupizide (TW); Glygen (TH); Glynase (IN, SG); Glyzip (IN); Luditec (MX); Melizid (FI); Melizide (AU, SG); Mindiab (DK, EE, FI, HK, NO, PK, RU, SE); Minidiab (AE, AT, AU, BE, BF, BG, BH, BJ, BR, CI, CN, CY, CZ, EG, ET, FR, GH, GM, GN, HK, HN, HU, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, PH, PL, PT, QA, SA, SC, SD, SL, SN, SY, TH, TN, TR, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Minodiab (AR, CR, ES, GB, GR, GT, IE, MX, NI, PA); Napizide (TW); Ozidia (FR); Pezide (TH); Singloben (MX); Sucrazide (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Sunglucon (HK); Topizide (TH); Xeltic (TH)

Glucagon

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Glucagon may be confused with Glaucon®

Pronunciation(GLOO ka gon)
U.S. Brand NamesGlucaGen®; GlucaGen® Diagnostic Kit; GlucaGen® HypoKit™; Glucagon Emergency Kit
Pharmacologic CategoryAntidote; Diagnostic Agent
Use: Labeled IndicationsManagement of hypoglycemia; diagnostic aid in radiologic examinations to temporarily inhibit GI tract movement
Use: Unlabeled/InvestigationalUsed with some success as a cardiac stimulant in management of severe cases of beta-adrenergic blocking agent overdosage; treatment of myocardial depression due to calcium channel blocker overdose
Dosing: Adults

Hypoglycemia or insulin shock therapy: I.M., I.V., SubQ: 1 mg; may repeat in 20 minutes as needed

Note: I.V. dextrose should be administered as soon as it is available; if patient fails to respond to glucagon, I.V. dextrose must be given.

Beta-blocker overdose, calcium channel blocker overdose (unlabeled use): I.V.: 5-10 mg over 1 minutes followed by an infusion of 1-10 mg/hour. The following has also been reported for beta-blocker overdose: 3-10 mg or initially 0.5-5 mg bolus followed by continuous infusion 1-5 mg/hour

Diagnostic aid: I.M., I.V.: 0.25-2 mg 10 minutes prior to procedure

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Hypoglycemia or insulin shock therapy: I.M., I.V., SubQ:

Children <20 kg: 0.5 mg or 20-30 mcg/kg/dose; repeated in 20 minutes as needed

Children ≥20 kg: Refer to adult dosing.

Note: I.V. dextrose should be administered as soon as it is available; if patient fails to respond to glucagon, I.V. dextrose must be given.

Administration: I.V.Bolus may be associated with nausea and vomiting. Continuous infusions may be used in beta-blocker overdose/toxicity.
Dietary ConsiderationsAdminister carbohydrates to patient as soon as possible after response to treatment.
StoragePrior to reconstitution, store at controlled room temperature of 20°C to 25° (69°F to 77°F); do not freeze. Use reconstituted solution immediately. May be kept at 5°C for up to 48 hours if necessary.
ReconstitutionReconstitute powder for injection by adding 1 mL of sterile diluent to a vial containing 1 unit of the drug, to provide solutions containing 1 mg of glucagon/mL. Gently roll vial to dissolve. If dose to be administered is <2 mg of the drug, then use only the diluent provided by the manufacturer. If >2 mg, use sterile water for injection.
ContraindicationsHypersensitivity to glucagon or any component of the formulation; insulinoma; pheochromocytoma
Warnings/Precautions

Disease-related concerns:

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency; levels of glucose stores in liver may be decreased.
- Chronic hypoglycemia: Use with caution in patients with chronic hypoglycemia; levels of glucose stores in liver may be decreased.
- Insulinoma: Exogenous glucagon may cause an initial rise in blood glucose followed by rebound hypoglycemia. The use of glucagon is contraindicated in patients with this condition.
- Pheochromocytoma: Exogenous glucagon may cause the release of catecholamines, resulting in an increase in blood pressure. The use of glucagon is contraindicated in patients with this condition.
- Starvation/fasting: Use caution with prolonged fasting and/or starvation; levels of glucose stores in liver may be decreased.

Dosage form specific issues:

- Lactose: May contain lactose; avoid administration in hereditary galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

Other warnings/precautions:

- Monitoring: Monitor blood glucose levels closely.

- Secondary hypoglycemia: Supplemental carbohydrates should be given to patients who respond to glucagon for severe hypoglycemia to prevent secondary hypoglycemia.

Geriatric ConsiderationsNo specific recommendations needed.
Pregnancy Risk FactorB
LactationExcretion in breast milk unknown/compatible
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension (up to 2 hours after GI procedures), hypertension, tachycardia

Gastrointestinal: Nausea, vomiting (high incidence with rapid administration of high doses)

Miscellaneous: Hypersensitivity reactions, anaphylaxis

Drug Interactions

Vitamin K Antagonists (eg, warfarin): Glucagon may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsGlucagon depletes glycogen stores.
Monitoring ParametersBlood pressure, blood glucose, ECG, heart rate, mentation
Nursing: Physical Assessment/MonitoringArouse patient from hypoglycemic or insulin shock as soon as possible and administer carbohydrates. Evaluate insulin dosage and patient's ability to administer appropriate dose. Instruct patient (or significant other) in appropriate administration procedures for emergency use of glucagon. If home glucose monitoring device is available, check blood sugar as soon as possible.
Monitoring: Lab TestsBlood glucose
Patient EducationIdentify appropriate support person to administer glucagon if necessary. Follow prescribers instructions for administering glucagon. Review diet, insulin administration, and testing procedures with prescriber or diabetic educator.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as hydrochloride:

GlucaGen®: 1 mg [equivalent to 1 unit; contains lactose 107 mg]

GlucaGen® Diagnostic Kit: 1 mg [equivalent to 1 unit; contains lactose 107 mg; packaged with sterile water]

GlucaGen® HypoKit™: 1 mg [equivalent to 1 unit; contains lactose 107 mg; packaged with prefilled syringe containing sterile water]

Glucagon Emergency Kit: 1 mg [equivalent to 1 unit; contains lactose 49 mg; packaged with diluent syringe containing glycerin 12 mg/mL and water for injection]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Kit (Glucagon Emergency)

1 mg (1): $108.01

Solution (reconstituted) (GlucaGen HypoKit)

1 mg (1): $107.01

Mechanism of ActionStimulates adenylate cyclase to produce increased cyclic AMP, which promotes hepatic glycogenolysis and gluconeogenesis, causing a raise in blood glucose levels
Pharmacodynamics/Kinetics

Onset of action: Peak effect: Blood glucose levels: Parenteral:

I.V.: 5-20 minutes

I.M.: 30 minutes

SubQ: 30-45 minutes

Duration: Glucose elevation:

SubQ: 60-90 minutes

I.V.: 30 minutes

Metabolism: Primarily hepatic; some inactivation occurring renally and in plasma

Half-life elimination, plasma: 8-18 minutes

Pharmacotherapy Pearls1 unit = 1 mg
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsGlucagon Hydrochloride
References

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International Brand NamesGlucaGen (AT, AU, BE, CH, DE, DK, FI, FR, GB, HR, HU, IT, LU, NL, PT); Glucagen (PL); Glucagon (PL); Glucagon Novo Nordisk (SE); R-Glucagon Lilly (MX)

Glucose Polymers

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(GLOO kose POL i merz)
U.S. Brand NamesModucal® [OTC]; Polycose® [OTC]
Pharmacologic CategoryNutritional Supplement
Use: Labeled IndicationsSupplies calories for those persons not able to meet the caloric requirement with usual food intake
Dosing: AdultsCaloric supplement: Oral: Add to foods or beverages or mix in water
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid (Polycose®): 43% (126 mL)

Powder:

Moducal®: 368 g

Polycose®: 350 g

Generic AvailableNo
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported

Glutamic Acid

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(gloo TAM ik AS id)

Pharmacologic Category[Gastrointestinal Agent, Miscellaneous]

Use: Labeled IndicationsTreatment of hypochlorhydria and achlorhydria

Dosing: AdultsHypochlorhydria or achlorhydria: Oral: 500-1000 mg/day before meals or food

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsShould be taken before meals or food.

Pregnancy Risk FactorC

Adverse ReactionsSystemic acidosis may occur with massive overdosage

Drug Interactions

Amphetamines: Gastrointestinal Acidifying Agents may decrease the serum concentration of Amphetamines. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 500 mg

Generic AvailableYes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsGlutamic Acid Hydrochloride

International Brand NamesGlutacid (NO); Glutamin-Verla (DE); Glutaneurol (IN); Glutestere (IT); Gluti-Agil (DE); Hypochylin (FI, SE); Magnesium Biomed (CH); Magnesium Verla (DE); Muripsin (GB); Neuroglutamin (AT); Orisediv (ES); Pepsaletten (DE); Psico-Soma (ES)

Glutamine

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English

Jump To Field (Select Field Name)

Pronunciation(GLOO ta meen)

U.S. Brand NamesEnterex® Glutapak-10® [OTC]; NutreStore™; Resource® GlutaSolve® [OTC]; Sympt-X G.I. [OTC]; Sympt-X [OTC]

Pharmacologic CategoryAmino Acid

Use: Labeled IndicationsTreatment of short bowel syndrome when used in combination with nutritional support and growth hormone therapy; a medical food used to promote GI tract healing and nutritional supplementation with GI disorders, HIV/AIDS, cancer, and other critical illnesses

Dosing: Adults

Nutritional supplement (Enterex® Glutapak-10®, Resource® GlutaSolve®, Sympt-X, Sympt-X G.I.): Oral: Average dose: 10 g 3 times/day; dosing range: 5-30 g/day

Short bowel syndrome (NutreStore™): Oral: 30 g/day administered as 5 g 6 times/day (every 2-3 hours while awake) for up to 16 weeks; to be used in combination with growth hormone and nutritional support

Dosing: ElderlyRefer to adult dosing.

Administration: Oral

Enterex® Glutapak-10®: Prior to use, mix with clear liquids or semisolid food. If administering via feeding tube, mix each 10 g packet with ≥60 mL water. Use immediately after preparation. May also be added directly to enteral formula if used within 24 hours.

Resource® GlutaSolve®: Mix each 15 g packet with 120-240 mL of water. May also be mixed in hot or cold beverages, applesauce, or pudding. If administering via feeding tube, mix with 60-120 mL water. Use immediately after preparation.

NutreStore™: Mix each packet (5 g) with ~240 mL of water prior to administration. May be given with meals or snacks

Sympt-X, Sympt-X G.I.: Mix dose with 6-8 ounces of juice or another beverage, may also be mixed with applesauce or pudding. Administer with meals. If administering via feeding tube, mix with ≥60 mL water; do not add directly to feeding bag. Use immediately after preparation.

Dietary ConsiderationsNutreStore™: To be used in combination with a specialized diet. May be taken with food or a snack.

StorageStore at controlled room temperature.

Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.

Dosage form specific issues:

- NutreStore™: Should be used with nutritional support based on individual patient requirements.

Other warnings/precautions:

- Appropriate use: Medical foods are intended to be used under the direction of a healthcare provider.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsThe amount of total protein and free amino acids found in breast milk varies during lactation. Effects of the suggested oral dose of glutamine are unknown.

Adverse ReactionsFrequency not defined.

Cardiovascular: Facial edema, peripheral edema

Central nervous system: Dizziness, fever, headache, pain

Dermatologic: Pruritus, rash

Gastrointestinal: Abdominal pain, flatulence, nausea, pancreatitis, tenesmus, vomiting

Neuromuscular & skeletal: Arthralgia, back pain, hypoesthesia

Otic: Ear or hearing symptoms

Respiratory: Rhinitis

Miscellaneous: Flu-like syndrome, infection, sepsis

Monitoring ParametersBUN; body weight, nutritional status

Nursing: Physical Assessment/MonitoringAssess therapeutic effectiveness according to purpose for use and adverse response (see Adverse Reactions). Teach patient proper use (reconstitution and storage), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsBUN

Patient EducationPrepare, store, and use exactly as directed. Do not exceed recommended dosage. May cause increased flatulence, nausea or vomiting, or abdominal pain; if persistent or severe contact prescriber. Report facial or peripheral swelling, rash; unusual back pain; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for oral solution:

Enterex® Glutapak-10®: 10 g/packet (50s)

NutreStore™: 5 g/packet

Resource® GlutaSolve®: 15 g/packet (56s)

Sympt-X, Sympt-X G.I.: 10 g/packet (60s)

Mechanism of ActionGlutamine regulates gastrointestinal cell growth, function, and regeneration. Considered a “conditionally essential” amino acid during metabolic stress and injury.

Pharmacodynamics/KineticsAs reported in healthy adults; parameters may vary following oral administration in patients with short bowel syndrome.

Distribution: I.V.: V_d: 200 mL/kg

Metabolism: Via splanchnic tissue, lymphocytes, kidney, and liver to glutamate and ammonia

Half-life elimination: I.V.: 1 hour

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsGln; L-Glutamine

Glyburide and Metformin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Glucovance may be confused with Vyvanse™

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(GLYE byoor ide & met FOR min)

U.S. Brand NamesGlucovance®

Pharmacologic CategoryAntidiabetic Agent, Biguanide; Antidiabetic Agent, Sulfonylurea

Use: Labeled IndicationsAdjunct to diet and exercise for the management of type 2 diabetes mellitus (noninsulin dependent, NIDDM)

Dosing: Adults**Note:** Dose must be individualized. All doses should be taken with a meal. Twice daily dosage should be taken with the morning and evening meals. Dosages expressed as glyburide/metformin components.

Type 2 diabetes: Oral:

No prior treatment with sulfonylurea or metformin: Initial: 1.25 mg/250 mg once daily with a meal; patients with Hb A_{1c} >9% or fasting plasma glucose (FPG) >200 mg/dL may start with 1.25 mg/250 mg twice daily with meals. Adjustment: Dosage may be increased in increments of 1.25 mg/250 mg, at intervals of not less than 2 weeks; maximum daily dose: 10 mg/2000 mg (limited experience with higher doses); **Note:** Doses of 5 mg /500 mg should not be used as initial therapy, due to risk of hypoglycemia.

Previously treated with a sulfonylurea or metformin alone: Initial: 2.5 mg/500 mg or 5 mg/500 mg twice daily with meals; increase in increments no greater than 5 mg/500 mg; maximum daily dose: 20 mg/2000 mg

Note: When switching patients previously on a sulfonylurea and metformin together, do not exceed the daily dose of glyburide (or glyburide equivalent) or metformin. When adding thiazolidinedione, continue glyburide and metformin at current dose and initiate thiazolidinedione at recommended starting dose.

Combination with thiazolidinedione: May be combined with a thiazolidinedione in patients with an inadequate response to glyburide/metformin therapy, however the risk of hypoglycemia may be increased.

Dosing: ElderlyRefer to adult dosing. Adjust carefully to renal function. Should not be used in patients ≥80 years of age unless renal function is verified as normal. Do not titrate to maximum dose.

Administration: OralAll doses should be administered with a meal. Twice-daily dosing should be administered with the morning and evening meals. Patients who are anorexic or NPO may need to have their dose held to avoid hypoglycemia.

Dietary ConsiderationsMay cause GI upset; take with food to decrease GI upset. Dietary modification based on ADA recommendations is a part of therapy. Decreases blood glucose concentration. Hypoglycemia may occur. Must be able to recognize symptoms of hypoglycemia (palpitations, sweaty palms, lightheadedness). Monitor for signs and symptoms of vitamin B_{12} deficiency. Monitor for signs and symptoms of folic acid deficiency.

StorageStore at ≤25°C (≤77°F). Protect from light.

ContraindicationsHypersensitivity to glyburide, metformin, or any component of the formulation; renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females, or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse, acute myocardial infarction, and septicemia; acute or chronic metabolic acidosis with or without coma (including diabetic ketoacidosis)

Note: Temporarily discontinue in patients undergoing radiologic studies in which intravascular iodinated contrast materials are utilized. Temporarily discontinue for surgical procedures.

Allergy Considerations

- Biguanide Allergy
- Sulfonylurea Allergy

Warnings/Precautions

Boxed warnings:

- Lactic acidosis: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS) have not supported an association. Metformin does not appear to share this risk.

- Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when ethanol is ingested, or when more than one glucose-lowering drug is used. It is also more likely in elderly patients, malnourished patients and in patients with impaired renal, hepatic, adrenal and/or pituitary function; use with caution.

- Lactic acidosis: **[U.S. Boxed Warning]: Lactic acidosis is a rare, but potentially fatal and severe consequence of therapy with metformin.** Lactic acidosis should be suspected in any patient with diabetes receiving metformin with evidence of acidosis but without evidence of ketoacidosis. Discontinue metformin in clinical situations predisposing to hypoxemia, including conditions such as cardiovascular collapse, respiratory failure, acute myocardial infarction, acute congestive heart failure, and septicemia. The risk of accumulation and lactic acidosis increases with the degree of impairment of renal function.

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is not specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Disease-related concerns:

- Heart failure: Use metformin with caution in patients with heart failure requiring pharmacologic management, particularly in patients with unstable or acutely decompensated heart failure; risk of lactic acidosis may be increased secondary to hypoperfusion.

- Hepatic impairment: Avoid metformin use in patients with impaired liver function due to potential for lactic acidosis.

- Renal impairment: Metformin is substantially excreted by the kidney; patients with renal function below the limit of normal for their age should not receive therapy. Use of concomitant medications that may affect renal function (ie, affect tubular secretion) may also affect metformin disposition. Metformin should be withheld in patients with dehydration and/or prerenal azotemia.

- Stress-related states: It may be necessary to discontinue therapy and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Concurrent drug therapy issues:

- Thiazolidinediones: Concurrent use with a thiazolidinedione may increase risk of hypoglycemia and/or weight gain. Liver function tests should be monitored periodically with concurrent use.

Special populations:

- Elderly: Rapid and prolonged hypoglycemia (>12 hours) despite hypertonic glucose injections have been reported; age and hepatic and renal impairment are independent risk factors for hypoglycemia; dosage titration should be made at weekly intervals. Metformin should not be initiated in patients ≥80 years of age unless normal renal function is confirmed.

Other warnings/precautions:

- Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism.

- Iodinated contrast: Metformin therapy should be temporarily discontinued prior to or at the time of intravascular administration of iodinated contrast media (potential for acute alteration in renal function). Metformin should be withheld for 48 hours after the radiologic study and restarted only after renal function has been confirmed as normal.

- Surgical procedures: Metformin therapy should be suspended for any surgical procedures requiring food or fluid restriction (resume only after normal intake resumed and normal renal function is verified).

Geriatric ConsiderationsConservative doses are recommended in the elderly due to potentially decreased renal function. **Do not titrate to maximum dose**. Should not be used in patients ≥80 years of age unless renal function is verified as normal. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAnimal reproduction studies were not conducted with this combination. Adverse events were not observed in animal studies of the individual agents; therefore, glyburide/metformin is classified as pregnancy category B. Refer to individual agents.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsRefer to individual agents.

Pregnancy & Lactation, In-Depth

- GlyBURIDE in Pregnancy & Lactation
- MetFORMIN in Pregnancy & Lactation

Adverse ReactionsAlso see individual agents.

>10%:

Endocrine & metabolic: Hypoglycemia (11% to 38%, effects higher when increased doses were used as initial therapy)

Gastrointestinal: Diarrhea (17%)

Respiratory: Upper respiratory infection (17%)

1% to 10%:

Central nervous system: Headache (9%), dizziness (6%)

Gastrointestinal: Nausea (8%), vomiting (8%), abdominal pain (7%) (combined GI effects increased to 38% in patients taking high doses as initial therapy)

<1%: Disulfiram-like reactions (rare) reported in patients taking glyburide

Drug Interactions

Alcohol (Ethyl): Sulfonylureas may enhance the adverse/toxic effect of Alcohol (Ethyl). A flushing reaction may occur. *Risk C: Monitor therapy*

Bosentan: GlyBURIDE may enhance the hepatotoxic effect of Bosentan. GlyBURIDE may increase the metabolism of Bosentan. Bosentan may increase the metabolism of GlyBURIDE. *Risk X: Avoid combination*

Cephalexin: May increase the serum concentration of MetFORMIN. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Cimetidine: May decrease the excretion of MetFORMIN. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Colesevelam: May decrease the serum concentration of GlyBURIDE. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Cyclic Antidepressants: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonylureas may increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Fibric Acid Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Fluconazole: May increase the serum concentration of Sulfonylureas. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Iodinated Contrast Agents: May enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Salicylates: May enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. **Exceptions:** Sulfacetamide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: May cause hypoglycemia; incidence of lactic acidosis may be increased; a disulfiram-like reaction characterized by flushing, headache, nausea, vomiting, sweating, or tachycardia has been reported with sulfonylureas; avoid or limit use.

Food: Metformin decreases absorption of vitamin B_{12}. Metformin decreases absorption of folic acid.

Monitoring ParametersSigns and symptoms of hypoglycemia, urine for glucose and ketones, FPG, Hb A_{1c}, and fructosamine. Initial and periodic monitoring of hematologic parameters (eg, hemoglobin/hematocrit and red blood cell indices) and renal function should be performed; monitor at least annually once patient is on maintenance therapy. While megaloblastic anemia has been rarely seen with metformin, if suspected, vitamin B_{12} deficiency should be excluded.

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 1.25 mg/250 mg: Glyburide 1.25 mg and metformin hydrochloride 250 mg; 2.5 mg/500 mg: Glyburide 2.5 mg and metformin hydrochloride 500 mg; 5 mg/500 mg: Glyburide 5 mg and metformin hydrochloride 500 mg

Glucovance®: 1.25 mg/250 mg: Glyburide 1.25 mg and metformin hydrochloride 250 mg

Glucovance®: 2.5 mg/500 mg: Glyburide 2.5 mg and metformin hydrochloride 500 mg

Glucovance®: 5 mg/500 mg: Glyburide 5 mg and metformin hydrochloride 500 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Glucovance)

1.25-250 mg (60): $55.99

2.5-500 mg (60): $85.99

5-500 mg (60): $92.00

Tablets (Glyburide-Metformin)

1.25-250 mg (60): $39.99

2.5-500 mg (60): $45.99

5-500 mg (100): $83.99

Mechanism of ActionThe combination of glyburide and metformin is used to improve glycemic control in patients with type 2 diabetes mellitus by using two different, but complementary, mechanisms of action:

Glyburide: Stimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites

Metformin: Decreases hepatic glucose production, decreasing intestinal absorption of glucose and improves insulin sensitivity (increases peripheral glucose uptake and utilization)

Pharmacodynamics/Kinetics

Glucovance®:

Bioavailability: 18% with 2.5 mg glyburide/500 mg metformin dose; 7% with 5 mg glyburide/500 mg metformin dose; bioavailability is greater than that of Micronase® brand of glyburide and therefore not bioequivalent

Time to peak: 2.75 hours when taken with food

Glyburide: See Glyburide monograph.

Metformin: This component of Glucovance® is bioequivalent to metformin coadministration with glyburide.

Related Information

- GlyBURIDE
- MetFORMIN

Dental Health: Effects on Dental TreatmentGlyburide-dependent patients with diabetes (noninsulin dependent, type 2) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia. Metformin-dependent patients with diabetes (noninsulin dependent, type 2) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDizziness is common; may cause sedation
Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; phenothiazines and TCAs may antagonize glyburide's hypoglycemic effects; MAO inhibitors and TCAs may enhance hypoglycemic effects; concurrent use with psychotropics may produce additive sedation
Cardiovascular ConsiderationsCombination therapy for the treatment of diabetes should be individualized for each patient.

Glyburide: The possibility of higher doses of sulfonylureas eliciting an increase in cardiovascular events, because of their effects on blocking potassium sensitive ATP channels, has been raised. However, there are presently only limited data to support this premise, particularly with newer generation agents. An early study suggested poor cardiovascular outcomes in patients with diabetes treated with tolbutamide. Retrospective studies evaluating cardiovascular outcomes following angioplasty and acute myocardial infarction in patients with diabetes receiving newer sulfonylureas are inconsistent. Longer-term prospective trials of sulfonylurea therapy, such as the UKPDS, do not reveal any increased cardiovascular mortality.

Metformin: Metformin, alone or in combination with other agents (sulfonylurea), is effective in the management of diabetes. Lactic acidosis is an uncommon side effect in patients without renal or respiratory insufficiency, hepatic failure, or conditions that predispose to hypoxemia. As heart failure may affect renal and pulmonary function, metformin should be avoided or used with caution in patients with diabetes and heart failure.

Index Terms Glyburide and Metformin Hydrochloride; Metformin and Glyburide

References

American Diabetes Association, “Standards of Medical Care in Diabetes Mellitus -- 2009,” *Diabetes Care*, 2009, 32(Suppl 1):13-61.[PubMed 19118286]

International Brand Names Benclamet (IN); Bi-Euglucon (CO, IT, VE); Bi-Euglucon M "5" (MX); Bi-Euglucon M (EC, UY); Diavance (AU); Euglo Plus (PH); Glibomet (CR, DO, GT, HN, IT, KP, NI, PA, SV); Glucovance (AU, BR, CH, CN, EC, FR, HK, ID, KP, MY, PE, PH, PK, SG, TH, TW); Glurid (KP); Glymet (MY); Marglucon (HK)

GlyBURIDE

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

GlyBURIDE may be confused with glipiZIDE, Glucotrol®

Diaβeta® may be confused with Diabinese®, Zebeta®

Micronase® may be confused with microK®, miconazole, Micronor®, Microzide™

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(GLYE byoor ide)

U.S. Brand NamesDiaβeta®; Glynase® PresTab®; Micronase®

Canadian Brand NamesAlbert® Glyburide; Apo-Glyburide®; Diaβeta®; Euglucon®; Gen-Glybe; Novo-Glyburide; Nu-Glyburide; PMS-Glyburide; ratio-Glyburide; Sandoz-Glyburide

Pharmacologic CategoryAntidiabetic Agent, Sulfonylurea

Use: Labeled IndicationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM)

Use: Unlabeled/InvestigationalAlternative to insulin in women for the treatment of gestational diabetes mellitus (GDM) (11-33 weeks gestation)

Dosing: Adults

Type 2 diabetes: Oral:

Note: Regular tablets cannot be used interchangeably with micronized tablet formulations

Regular tablets (Diaβeta®, Micronase®):

Initial: 2.5-5 mg/day, administered with breakfast or the first main meal of the day. In patients who are more sensitive to hypoglycemic drugs, start at 1.25 mg/day.

Adjustment: Increase in increments of no more than 2.5 mg/day at weekly intervals based on the patient's blood glucose response

Maintenance: 1.25-20 mg/day given as single or divided doses; maximum: 20 mg/day

Micronized tablets (Glynase® PresTab®):

Initial: 1.5-3 mg/day, administered with breakfast or the first main meal of the day in patients who are more sensitive to hypoglycemic drugs, start at 0.75 mg/day. Increase in increments of no more than 1.5 mg/day in weekly intervals based on the patient's blood glucose response.

Maintenance: 0.75-12 mg/day given as a single dose or in divided doses. Some patients (especially those receiving >6 mg/day) may have a more satisfactory response with twice-daily dosing. Maximum: 12 mg/day

Dosing: ElderlyRegular tablets (Diaβeta®, Micronase®): Oral: Initial: 1.25-2.5 mg/day, increase by 1.25-2.5 mg/day every 1-3 weeks. Refer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <50 mL/minute: Not recommended

Dosing: Hepatic ImpairmentUse conservative initial and maintenance doses and avoid use in severe disease.

Calculations

- Creatinine Clearance: Adults

Administration: OralAdminister with meals at the same time each day. Patients who are anorexic or NPO may need to have their dose held to avoid hypoglycemia.

Dietary ConsiderationsShould be taken with meals at the same time each day. Dietary modification based on ADA recommendations is a part of therapy. Decreases blood glucose concentration. Hypoglycemia may occur. Must be able to recognize symptoms of hypoglycemia (palpitations, sweaty palms, lightheadedness).

ContraindicationsHypersensitivity to glyburide, any component of the formulation, or other sulfonamides; type 1 diabetes mellitus (insulin dependent, IDDM), diabetic ketoacidosis; concurrent use with bosentan

Allergy Considerations

- Sulfonylurea Allergy

Warnings/Precautions

Concerns related to adverse reactions:

- Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS) have not supported an association.

- Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when ethanol is ingested, or when more than one glucose-lowering drug is used. It is also more likely in elderly patients, malnourished patients and in patients with impaired renal, hepatic, adrenal and/or pituitary function; use with caution.

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Disease-related concerns:

- Stress-related states: It may be necessary to discontinue therapy and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Special populations:

- Elderly: Rapid and prolonged hypoglycemia (>12 hours) despite hypertonic glucose injections have been reported; age and hepatic and renal impairment are independent risk factors for hypoglycemia; dosage titration should be made at weekly intervals.

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsRapid and prolonged hypoglycemia (>12 hours) despite hypertonic glucose injections has been reported; age, hepatic, and renal impairment are independent risk factors for hypoglycemia; dosage titration should be made at weekly intervals. How “tightly” a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well they recognize hypoglycemic or hyperglycemic symptoms, and how to respond to them and their other disease states. Use with caution in the elderly with renal insufficiency.

Pregnancy Risk FactorB/C (manufacturer dependent)

Pregnancy ConsiderationsReproduction studies differ by manufacturer labeling. Because adverse events were not observed in animal reproduction studies, one manufacturer classifies glyburide as pregnancy category B. Because adverse events were noted in animal studies during the period of lactation, another manufacturer classifies glyburide as pregnancy category C.

Glyburide was not found to significantly cross the placenta *in vitro* and was not found in the cord serum infants of mothers taking glyburide for gestational diabetes mellitus (GDM). Nonteratogenic effects such as hypoglycemia in the neonate have been associated with maternal glyburide use. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. The manufacturer recommends that if glyburide is used during pregnancy, it should be discontinued at least 2 weeks before the expected delivery date. Although studies have shown positive outcomes using glyburide for the treatment of GDM, use may not be appropriate for all women. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of type 2 diabetes mellitus during pregnancy. Insulin is considered the drug of choice for the control of diabetes mellitus during pregnancy.

LactationDoes not enter breast milk/use caution

Breast-Feeding ConsiderationsData from initial studies note that glyburide was not detected in breast milk. Breast-feeding is not recommended by the manufacturer. Potentially, hypoglycemia may occur in a nursing infant exposed to a sulfonylurea via breast milk.

Pregnancy & Lactation, In-Depth

- GlyBURIDE in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Cardiovascular: Vasculitis

Central nervous system: Dizziness, headache

Dermatologic: Erythema, maculopapular eruptions, morbilliform eruptions, pruritus, purpura, rash, urticaria, photosensitivity reaction

Endocrine & metabolic: Disulfiram-like reaction, hypoglycemia, hyponatremia (SIADH reported with other sulfonylureas)

Gastrointestinal: Anorexia, constipation, diarrhea, epigastric fullness, heartburn, nausea

Genitourinary: Nocturia

Hematologic: Leukopenia, thrombocytopenia, hemolytic anemia, agranulocytosis, aplastic anemia, pancytopenia, porphyria cutanea tarda

Hepatic: Cholestatic jaundice, hepatitis, transaminase increased

Neuromuscular & skeletal: Arthralgia, myalgia, paresthesia

Ocular: Blurred vision

Renal: Diuretic effect (minor)

Miscellaneous: Allergic reaction

Metabolism/Transport Effects**Inhibits** CYP2C8 (weak), 3A4 (weak)

Drug Interactions

Alcohol (Ethyl): Sulfonylureas may enhance the adverse/toxic effect of Alcohol (Ethyl). A flushing reaction may occur. *Risk C: Monitor therapy*

Bosentan: GlyBURIDE may enhance the hepatotoxic effect of Bosentan. GlyBURIDE may increase the metabolism of Bosentan. Bosentan may increase the metabolism of GlyBURIDE. *Risk X: Avoid combination*

Chloramphenicol: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Colesevelam: May decrease the serum concentration of GlyBURIDE. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Cyclic Antidepressants: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonylureas may increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Fibric Acid Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Fluconazole: May increase the serum concentration of Sulfonylureas. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Salicylates: May enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. **Exceptions:** Sulfacetamide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Caution with ethanol (may cause hypoglycemia).

Herb/Nutraceutical: Herbs with hypoglycemic properties may enhance the hypoglycemic effect of glyburide. This includes alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, stinging nettle

Monitoring ParametersSigns and symptoms of hypoglycemia, fasting blood glucose, hemoglobin A_{1c}

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringAssess allergy history prior to beginning therapy. Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, hypoglycemia) at regular intervals during therapy. Teach patient proper use (or refer patient to diabetic educator) for instruction, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsFasting blood glucose, hemoglobin A_{1c}, fructosamine

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is used to control diabetes; it is not a cure. Monitor glucose as recommended by prescriber. Other important components of treatment plan may include prescribed diet and exercise regimen (consult prescriber or diabetic educator). If you experience hypoglycemic reaction, contact prescriber immediately. Always carry quick source of sugar with you. Take exactly as directed, 30 minutes before meal(s) at the same time each day. Do not change dose or discontinue without consulting prescriber. Avoid alcohol while taking this medication; could cause severe reaction. Do not take other medication within 2 hours of this medication unless advised by prescriber. You may experience more sensitivity to sunlight (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); headache; or nausea (consult prescriber if these persist). Report severe or persistent side effects; hypoglycemia (palpitations, sweaty palms, lightheadedness); extended vomiting, diarrhea, or constipation; flu-like symptoms; skin rash; easy bruising or bleeding; or change in color of urine or stool. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: 1.25 mg, 2.5 mg, 5 mg

- Diaβeta®: 1.25 mg, 2.5 mg, 5 mg
- Micronase®: 1.25 mg, 2.5 mg [DSC], 5 mg

Tablet, micronized: 1.5 mg, 3 mg, 6 mg

- Glynase® PresTab®: 1.5 mg, 3 mg, 6 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Diabeta)

- 1.25 mg (50): $27.11
- 2.5 mg (30): $28.20
- 5 mg (30): $35.99

Tablets (GlyBURIDE)

- 1.25 mg (30): $12.99
- 2.5 mg (30): $12.99
- 5 mg (30): $11.99

Tablets (GlyBURIDE Micronized)

- 1.5 mg (90): $26.00
- 3 mg (90): $15.00
- 6 mg (90): $17.00

Tablets (Glynase)

- 1.5 mg (60): $50.07
- 3 mg (60): $73.64
- 6 mg (60): $114.89

Tablets (Micronase)

- 1.25 mg (30): $17.39
- 2.5 mg (30): $28.10
- 5 mg (30): $44.99

Mechanism of ActionStimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites

Pharmacodynamics/Kinetics

Onset of action: Serum insulin levels begin to increase 15-60 minutes after a single dose

Duration: ≤24 hours

Absorption: Significant within 1 hour

Distribution: 9-10 L

Protein binding, plasma: >99% primarily to albumin

Metabolism: Hepatic; forms metabolites (weakly active)

Half-life elimination: Diabeta®, Micronase®: 10 hours; Glynase® PresTab®: ~4 hours; may be prolonged with renal or hepatic impairment

Time to peak, serum: Adults: 2-4 hours

Excretion: Feces (50%) and urine (50%) as metabolites

Related Information

- Diabetes Mellitus Management, Adults
- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentGlyburide-dependent patients with diabetes (noninsulin dependent, type 2) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; phenothiazines and TCAs may antagonize glimepiride hypoglycemic effects; MAO inhibitors and TCAs may enhance hypoglycemic effects

Cardiovascular ConsiderationsThe possibility of higher doses of sulfonylureas eliciting an increase in cardiovascular events, because of their effects on blocking potassium sensitive ATP channels, has been raised. However, there are presently only limited data to support this premise, particularly with newer generation agents. An early study suggested poor cardiovascular outcomes in patients with diabetes treated with tolbutamide. Retrospective studies evaluating cardiovascular outcomes following angioplasty and acute myocardial infarction in patients with diabetes receiving newer sulfonylureas are inconsistent. Longer-term prospective trials of sulfonylurea therapy, such as the UKPDS, do not reveal any increased cardiovascular mortality.

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: The possibility of higher doses of sulfonylureas eliciting an increase in cardiovascular events, because of their effects on blocking potassium-sensitive ATP channels, has been raised. Longer-term prospective trials of sulfonylurea therapy, such as the UKPDS and ADVANCE, do not reveal any increased cardiovascular mortality.

Index TermsDiabeta; Glibenclamide; Glybenclamide; Glybenzcyclamide

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International Brand NamesAmecladin (PH); Apo-Glibenclamide (NZ); Benclamin (TH); Betanase (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Betanese 5 (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Bevoren (LU); Calabren (CZ); Clamide (HK); Daonil (AE, AR, AU, BB, BD, BE, BF, BH, BJ, BM, BO, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CY, DK, DO, EC, EG, ET, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HR, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, NZ, OM, PA, PE, PH, PK, PR, PT, PY, QA, RU, SA, SC, SD, SG, SL, SN, SR, SV, SY, TH, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Daono (TH); Debtan (TH); Diaben (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Diabitor (PH); Dibelet (MY, TH); Euclamin (PL); Euglotab (PH); Euglucan (FR); Euglucon (AE, AR, AT, AU, BD, BE, BF, BH, BJ, BO, BR, CH, CI, CL, CN, CO, CR, CY, CZ, DE, DO, EC, EG, ES, ET, FI, GH, GM, GN, GR, GT, HK, HN, HR, ID, IL, IN, IQ, IR, IT, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, OM, PA, PE, PH, PK, PR, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SV, SY, TH, TN, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Euglusid (CN); Gilemal (AT, BG, HN, HU); Gliban (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Glibedal (HR); Gliben (IT, NZ); Glibenclamid (HR); Glibenclamid Pharmavit (HU); Glibenclamid-ratiopharm (LU); Glibenhexal (LU); Glibesyn (MY, SG); Glibet (IN); Glibetic (IL); Glibil (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Gliboral (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Glidiabet (PE); Glimel (AU, HK); Glimide (MY); Glisulin (KP); Glitisol (HK); Gluben (IL); Glucal (MX); Glucobene (HU); Glucomid (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Gluconic (ID); Glulo (ID); Glycomin (ZA); Hemi-Daonil (AR, FR, MA, NL); Insol (PH); Lodulce (PH); Maninil (EE, PL); Manoglucon (TH); Melix (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Miglucan (FR); Norboral (MX); Norglicem (ES); Orabetic (PH); Pira (AR); Renabetic (ID); Semi-Daonil (AE, AR, AU, BH, CH, CY, EG, GB, HK, ID, IE, IL, IQ, IR, JO, KW, LB, LY, MA, NZ, OM, PT, QA, SA, SY, YE); Semi-Euglucon (AR, AT, AU, NL, PH, TH); Sugril (TH); Tiabet (ID); Trodeb (ID); Unil-5 (TH); Xeltic (HK)

Glycerin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(GLIS er in)

U.S. Brand NamesBausch & Lomb® Computer Eye Drops [OTC]; Colace® Adult/Children Suppositories [OTC]; Colace® Infant/Children Suppositories [OTC]; Fleet® Babylax® [OTC]; Fleet® Glycerin Suppositories Maximum Strength [OTC]; Fleet® Glycerin Suppositories [OTC]; Fleet® Liquid Glycerin Suppositories [OTC]; Osmoglyn® [DSC]; Sani-Supp® [OTC]

Pharmacologic CategoryLaxative, Osmotic; Ophthalmic Agent, Miscellaneous

Use: Labeled IndicationsConstipation; reduction of intraocular pressure; reduction of corneal edema; glycerin has been administered orally to reduce intracranial pressure

Dosing: Adults

Constipation: Rectal: 1 adult suppository 1-2 times/day as needed or 5-15 mL as an enema

Reduction of intracranial pressure: Oral: 1.5 g/kg/day divided every 4 hours; 1 g/kg/dose every 6 hours has also been used

Reduction of corneal edema: Ophthalmic solution: Instill 1-2 drops in eye(s) prior to examination OR for lubricant effect, instill 1-2 drops in eye(s) every 3-4 hours

Reduction of intraocular pressure: Oral: 1-1.8 g/kg 1-1$^{1}/_{2}$ hours preoperatively; additional doses may be administered at 5-hour intervals

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Constipation: Rectal:

Children <6 years: 1 infant suppository 1-2 times/day as needed or 2-5 mL as an enema

Children >6 years: Refer to adult dosing.

Reduction of intraocular pressure: Refer to adult dosing.

Reduction of intracranial pressure: Refer to adult dosing.

Reduction of corneal edema: Refer to adult dosing.

Storage

Refrigerate suppositories; avoid freezing. Protect from heat.

Ophthalmic: Store at room temperature. Keep bottle tightly closed. Discard 6 months after dropper is first placed in the solution.

Geriatric ConsiderationsThe primary use of glycerin in the elderly is as a laxative, although it is not recommended as a first-line treatment

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias

Central nervous system: Headache, confusion, dizziness, hyperosmolar nonketotic coma

Endocrine: Polydipsia, hyperglycemia, dehydration

Gastrointestinal: Nausea, vomiting, tenesmus, rectal irritation, cramping pain, diarrhea, dry mouth

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, ophthalmic, sterile (Bausch & Lomb® Computer Eye Drops): 1% (15 mL) [contains benzalkonium chloride]

Solution, oral (Osmoglyn®): 50% (220 mL) [lime flavor] [DSC]

Solution, rectal:

Fleet® Babylax®: 2.3 g/2.3 mL (4 mL) [6 units per box]

Fleet® Liquid Glycerin Suppositories: 5.6 g/5.5 mL (7.5 mL) [4 units per box]

Suppository, rectal: 82.5% (12s, 25s) [pediatric size]; 82.5% (12s, 24s, 25s, 50s, 100s) [adult size]

Colace® Adult/Children: 2.1 g (12s, 24s, 48s, 100s)

Colace® Infant/Children: 1.2 g (12s, 24s)

Fleet® Glycerin Suppositories: 1 g (12s) [pediatric size]; 2g (12s, 24s, 50s) [adult size]

Fleet® Glycerin Suppositories Maximum Strength: 3g (18s) [adult size]

Sani-Supp®: 82.5% (10s, 25s) [pediatric size]; 82.5% (10s, 25s, 50s) [adult size]

Generic Available Yes: Suppositories

Mechanism of Action Osmotic dehydrating agent which increases osmotic pressure; draws fluid into colon and thus stimulates evacuation

Pharmacodynamics/Kinetics

Onset of action:

- Decrease in intraocular pressure: Oral: 10-30 minutes
- Reduction of intracranial pressure: Oral: 10-60 minutes
- Constipation: Suppository: 15-30 minutes
- Peak effect:
  - Decrease in intraocular pressure: Oral: 60-90 minutes
  - Reduction of intracranial pressure: Oral: 60-90 minutes

Duration:

- Decrease in intraocular pressure: Oral: 4-8 hours
- Reduction of intracranial pressure: Oral: ~2-3 hours

Absorption: Oral: Well absorbed; Rectal: Poorly absorbed

Half-life elimination, serum: 30-45 minutes

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause confusion or dizziness

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Glycerol

International Brand Names Babylax (AT, DE, IL); Bebegel (FR, PT); Bulboid (CH); Cristal (CH); Czopki Glicerolowe (PL); Czopki Glicerynowe (PL); Farmino (AR); Formula Liquida Limpieza (AR); Gely (ES); Glicerina (ES, IT); Glicerina Cinfa (ES); Glicerina Quimpe (ES); Glicerine (BE); Glicerol Vilardell (ES); Glicerolo (IT); Glicerolo Dynacren (IT); Glicerolo Sofar (IT); Glicerolo supposte (IT); Glicerotens (ES); Glycerin Suppositories (AU); Glycerinzapfchen Sanova (AT); Glycerinzapfchen Sokosi (CH); Glycerol Suppositories BP (AU); Glycerol "Oba" (DK); Glycerotone (BE, FR, LU); Glycilax (CY, DE); Glyzerinzapfchen Rosch (AT); Jabon de glicerina (ES); Jabon Dermic (AR); Kimos (ES); Luxoral (IT); Micronema (AR); Milax (DE); Miniderm (SE); Nene-Lax (DE); Neotomic (IN); Neutrobar (MX); Obifax (ES); Practomil (CH); Q.V. Wash Soap Free Cleansing Liquid (AU); RubieLax (DE); Supo Glicerina Brota (ES); Supo Glicerina Cinfa (ES); Supo Glicerina Cuve (ES); Supo Glicerina Orravan (ES); Supo Glicerina Orto (ES); Supo Glicerina Rovi (ES); Supo Glicerina Torrent (ES); Supo Glicerina Vilardell (ES); Supo Glicerina Viviar (ES); Supo Gliz (ES); Supo Kristal (ES); Supos Glicerina Mandri (ES); Supositorios de Glicerina Fecofar (AR); Supositorios de Glicerina Parke-Davis (AR); Suppositoria Glycerini (PL); Supposte Glicerina Carlo Erba (IT); Supposte Glicerina S.Pellegrino (IT); Supposte Glicerolo AD-BB Sofar (IT); Verolax (ES, IT); Vitrosups (ES); Zetalax (IT)

English

English

Jump To Field (Select Field Name)

Pronunciation(glye koe PYE roe late)

U.S. Brand NamesRobinul®; Robinul® Forte

Canadian Brand NamesGlycopyrrolate Injection, USP

Pharmacologic CategoryAnticholinergic Agent

Use: Labeled IndicationsInhibit salivation and excessive secretions of the respiratory tract preoperatively; reversal of neuromuscular blockade; control of upper airway secretions; adjunct in treatment of peptic ulcer

Dosing: Adults

Reduction of secretions: I.M.:

Preoperative: I.M.: 4 mcg/kg 30-60 minutes before procedure

Intraoperative: I.V.: 0.1 mg repeated as needed at 2- to 3-minute intervals

Reversal of neuromuscular blockade: I.V.: 0.2 mg for each 1 mg of neostigmine or 5 mg of pyridostigmine administered or 5-15 mcg/kg glycopyrrolate with 25-70 mcg/kg of neostigmine or 0.1-0.3 mg/kg of pyridostigmine (agents usually administered simultaneously, but glycopyrrolate may be administered first if bradycardia is present)

Peptic ulcer:

Oral: 1-2 mg 2-3 times/day

I.M., I.V.: 0.1-0.2 mg 3-4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Reduction of secretions:

Preoperative: I.M.:

<2 years: 4-9 mcg/kg 30-60 minutes before procedure

>2 years: 4 mcg/kg 30-60 minutes before procedure

Intraoperative: I.V.: 4 mcg/kg not to exceed 0.1 mg; repeat at 2- to 3-minute intervals as needed.

Chronic:

Oral: 40-100 mcg/kg/dose 3-4 times/day

I.M., I.V.: 4-10 mcg/kg/dose every 3-4 hours; maximum: 0.2 mg/dose or 0.8 mg/24 hours

Reversal of neuromuscular blockade: Refer to adult dosing.

Administration: I.V.Administer at a rate of 0.2 mg over 1-2 minutes.

Administration: I.V. DetailFor I.V. administration, glycopyrrolate may be administered by I.M. or I.V. without dilution. May also be administered via the tubing of a running I.V. infusion of a compatible solution. May be administered in the same syringe with neostigmine or pyridostigmine.

pH: 2-3

StorageStore at 20°C to 25°C (68°F to 77°F).

CompatibilityStable in $D_5{}^1/_2NS$, D_5W, $D_{10}W$, LR, NS.

Y-site administration: Compatible: Propofol.

Compatibility in syringe: Compatible: Atropine, butorphanol, chlorpromazine, cimetidine, codeine, diphenhydramine, droperidol, droperidol and fentanyl, hydromorphone, hydroxyzine, levorphanol, lidocaine, meperidine, meperidine and promethazine, midazolam, morphine, nalbuphine, neostigmine, ondansetron, oxymorphone, physostigmine, procaine, prochlorperazine edisylate, promazine, promethazine, propiomazine, pyridostigmine, ranitidine, scopolamine, triflupromazine, trimethobenzamide. **Incompatible:** Chloramphenicol, dexamethasone sodium phosphate, diazepam, dimenhydrinate, methohexital, pentazocine, pentobarbital, secobarbital, sodium bicarbonate, thiopental.

Compatibility when admixed: Compatible: Buprenorphine. **Incompatible:** Methylprednisolone sodium succinate.

ContraindicationsHypersensitivity to glycopyrrolate or any component of the formulation; severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, paralytic ileus, obstructive disease of GI tract, intestinal atony in the elderly or debilitated patient; unstable cardiovascular status in acute hemorrhage; narrow-angle glaucoma; acute hemorrhage; tachycardia; obstructive uropathy; myasthenia gravis

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause drowsiness and/or blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Diarrhea: May be a sign of incomplete intestinal obstruction, treatment should be discontinued if this occurs.
- Heat prostration: May occur in the presence of increased environmental temperature; use caution in hot weather and/or exercise.
- Pigment effects: Caution should be used in individuals demonstrating decreased pigmentation (skin and iris coloration, dark versus light) since there has been some evidence that these individuals have an enhanced sensitivity to the anticholinergic response.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease, tachyarrhythmias, heart failure, or hypertension; evaluate tachycardia prior to administration.
- Gastric ulcer treatment: Use of anticholinergics in gastric ulcer treatment may cause a delay in gastric emptying due to antral statis.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hiatal hernia: Use with caution in patients with hiatal hernia with reflux.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Neuropathy: Use with caution in patients with autonomic neuropathy.
- Prostatic hyperplasia: Use with caution in patients with prostatic hyperplasia.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.
- Ulcerative colitis: Use with caution in patients with ulcerative colitis; may precipitate/aggravate toxic megacolon.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for anticholinergic effects, confusion, and hallucinations.
- Pediatrics: Infants, patients with Down syndrome, and children with spastic paralysis or brain damage may be hypersensitive to antimuscarine effects. Not recommended for use in children <12 years of age for the management of peptic ulcer or <16 years for preanesthetic use.

Dosage form specific issues:

- Benzyl alcohol: Injection contains benzyl alcohol which has been associated with "gasping syndrome" in neonates.

Geriatric ConsiderationsAnticholinergic agents are generally not well tolerated in the elderly and their use should be avoided when possible.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Small amounts of glycopyrrolate cross the human placenta.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsMay suppress lactation

Adverse ReactionsFrequency not defined. **Note:** Includes adverse effects which may occur as an extension of the pharmacologic action of anticholinergics (including glycopyrrolate) and adverse effects reported postmarketing with glycopyrrolate.

Cardiovascular: Arrhythmias, cardiac arrest, heart block, hyper-/hypotension, malignant hyperthermia, palpitation, QT_c interval prolongation, tachycardia

Central nervous system: Confusion, dizziness, drowsiness, excitement, headache, insomnia, nervousness, seizure

Dermatologic: Dry skin, pruritus, sensitivity to light increased

Endocrine & metabolic: Lactation suppression

Gastrointestinal: Bloated feeling, constipation, loss of taste, nausea, vomiting, xerostomia

Genitourinary: Impotence, urinary hesitancy, urinary retention

Local: Irritation at injection site

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision, cycloplegia, mydriasis, ocular tension increased, photophobia, sensitivity to light increased

Respiratory: Respiratory depression

Miscellaneous: Anaphylactoid reactions, diaphoresis decreased, hypersensitivity reactions

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Monitoring ParametersHeart rate; anticholinergic effects; bowel sounds

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, anything that may add to anticholinergic effects). Assess therapeutic effectiveness and adverse response (eg, excessive dryness of eyes, nose, mouth, throat). Teach patient proper use (self-administered), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed before meals; do not increase dose and do not discontinue without consulting prescriber. Void before taking medication. You may experience dizziness or blurred vision (use caution when driving or engaging in tasks that require alertness until response to drug is known); dry mouth (sucking on lozenges may help); photosensitivity (wear dark glasses in bright sunlight); decreased ability to sweat (use caution in hot weather or hot rooms or engaging in strenuous activity); or impotence (temporary). Report excessive and persistent anticholinergic effects (blurred vision, headache, flushing, tachycardia, nervousness, constipation, dizziness, insomnia, mental confusion or excitement, dry mouth, altered taste perception, dysphagia, palpitations, bradycardia, urinary hesitancy or retention, impotence, decreased sweating). **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution: 0.2 mg/mL (1 mL, 2 mL, 5 mL, 20 mL)

Robinul®: 0.2 mg/mL (1 mL, 2 mL, 5 mL; 20 mL [DSC]) [contains benzyl alcohol]

Tablet: 1 mg, 2 mg

Robinul®: 1 mg

Robinul® Forte: 2 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Glycopyrrolate)

1 mg (100): $104.99

2 mg (90): $134.02

Tablets (Robinul)

1 mg (90): $309.09

Tablets (Robinul-Forte)

2 mg (60): $300.72

Mechanism of ActionBlocks the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands, and the CNS

Pharmacodynamics/Kinetics

Onset of action: Oral: 50 minutes; I.M.: 15-30 minutes; I.V.: ~1 minute

Peak effect: Oral: ~1 hour; I.M.: 30-45 minutes

Duration: Vagal effect: 2-3 hours; Inhibition of salivation: Up to 7 hours; Anticholinergic: Oral: 8-12 hours

Absorption: Oral: Poor and erratic

Distribution: V_d: 0.2-0.62 L/kg

Metabolism: Hepatic (minimal)

Bioavailability: ~10%

Half-life elimination: Infants: 22-130 minutes; Children 19-99 minutes; Adults: ~30-75 minutes

Excretion: Urine (as unchanged drug, I.M.: 80%, I.V.: 85%); bile (as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause drowsiness, confusion, amnesia

Mental Health: Effects on Psychiatric TreatmentConcurrent use with other psychotropics may produce additive sedation and dry mouth

Index TermsGlycopyrronium Bromide

References

Friedl KE, Hannan CJ, Mader TH, et al, “Effect of Eye Color on Heart Rate Response to Intramuscular Administration of Atropine,” *J Auton Nerv Syst*, 1988, 24(1-2):51-6.[PubMed 3209800]

International Brand NamesAcpan (AR); Gastrodyn (FI); Robinul (AT, AU, BE, CH, DE, DK, FI, GB, JP, NL, NO, SE)

Gold Sodium Thiomalate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(gold SOW dee um thye oh MAL ate)

U.S. Brand NamesMyochrysine®

Canadian Brand NamesMyochrysine®

Pharmacologic CategoryGold Compound

Use: Labeled IndicationsTreatment of progressive rheumatoid arthritis

Dosing: AdultsRheumatoid arthritis: I.M.: 10 mg first week; 25 mg second week; then 25-50 mg/week until 1 g cumulative dose has been given; if improvement occurs without adverse reactions, administer 25-50 mg every 2-3 weeks for 2-20 weeks, then every 3-4 weeks indefinitely

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRheumatoid arthritis: I.M.: Initial: Test dose of 10 mg is recommended, followed by 1 mg/kg/week for 20 weeks; maintenance: 1 mg/kg/dose at 2- to 4-week intervals thereafter for as long as therapy is clinically beneficial and toxicity does not develop. Administration for 2-4 months is usually required before clinical improvement is observed.

Dosing: Renal Impairment

Cl_{cr} 50-80 mL/minute: Administer 50% of normal dose.

Cl_{cr} <50 mL/minute: Avoid use.

Dosing: Adjustment for ToxicityIf toxicity develops, gold sodium thiomalate should be discontinued immediately and symptomatic treatment may be given as required. Severe reactions are a contraindication to further gold therapy. If the reaction to gold therapy is not severe, therapy may be resumed, generally 2-3 weeks following resolution of the toxic reaction. A challenge dose of 5-10 mg of gold may be administered; if the "challenge dose" is tolerated, dosage may be cautiously increased by 5-10 mg in subsequent injections until usual dosage is achieved (25-50 mg).

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Deep I.M. injection into the upper outer quadrant of the gluteal region; addition of 0.1 mL of 1% lidocaine to each injection may reduce the discomfort associated with I.M. administration. Patient should remain in recumbent position for approximately 10 minutes following administration.

StorageShould not be used if solution is darker than pale yellow.

ContraindicationsHypersensitivity to gold compounds or any component of the formulation; systemic lupus erythematosus; history of blood dyscrasias; congestive heart failure, exfoliative dermatitis, colitis

Allergy Considerations

- Gold Salt Allergy

Warnings/Precautions

Boxed warnings:

- Gold toxicity: **[U.S. Boxed Warning]: May be associated with significant toxicity involving dermatologic, gastrointestinal, hematologic, pulmonary, renal, and hepatic systems (see below); patient eduction is required.**

Concerns related to adverse effects:

- Dermatologic reactions: Dermatitis and lesions of the mucous membranes are common and may be serious; pruritus may precede the early development of a skin reaction. Consider alternative therapy in patients with dermatitis (urticaria or eczema; relative contraindication); may increase risk and/or symptoms of gold toxicity may be more difficult to detect.

- Gastrointestinal effects: Signs of toxicity include persistent diarrhea, stomatitis, and enterocolitis; avoid use in patients with prior inflammatory bowel disease.

- Hematologic effects: Signs of toxicity include hematologic depression (depressed hemoglobin, eosinophilia >5%, leukocytes, granulocytes, or platelets). Avoid use in patients with a history of blood dyscrasias (anemia, agranulocytosis), hemorrhagic diathesis, or drug induced granulocytopenia. Symptoms of gold toxicity may be difficult to detect in patients with prior abnormalities; consider alternative therapy. Therapy should be discontinued if platelet count falls to <100,000/mm^3, WBC <4000, granulocytes <1500/mm^3.

- Hepatic effects: May be associated with the development of cholestatic jaundice. Consider alternative therapy in patients with hepatic impairment (relative contraindication); may increase risk and/or symptoms of gold toxicity may be more difficult to detect.

- Hypersensitivity reactions: Rare hypersensitivity reactions, including anaphylactic shock, syncope, bradycardia, thickening of the tongue, difficulty in swallowing and breathing, and angioedema have been reported in association with injections of sodium aurothiomalate; treatment should be discontinued if occur. In addition, a vasomotor (nitritoid) reaction characterized by acute flushing and tachycardia may occur within minutes of injection; this reaction should be differentiated from anaphylaxis and therapy may be continued, but a careful evaluation of risk vs. benefit should be undertaken and extreme caution should be exercised before resuming therapy, particularly in patient with cardiovascular disease.

- Pulmonary toxicity: May be associated with interstitial fibrosis; monitor closely.
- Renal effects: Renal toxicity ranges from mild proteinuria to nephrotic syndrome. Consider alternative therapy in patients with renal impairment; may increase risk and/or symptoms of gold toxicity may be more difficult to detect.

Disease-related concerns:

- Cardiovascular disease: Use caution in patients with HF, hypertension, or cerebrovascular disease.
- Systemic lupus erythematosus (SLE): Consider alternative therapy is patients with SLE (relative contraindication); may increase risk and/or symptoms of gold toxicity may be more difficult to detect.

Concurrent drug therapy issues:

- ACE inhibitors: Concurrent use with ACE inhibitors may increase the risk of nitritoid reactions.
- Corticosteroids: In general, corticosteroids may be discontinued after initiation of therapy (corticosteroid tapering may be required).
- NSAIDs: May be discontinued after initiation of therapy.

Other warnings/precautions:

- Administration: Must not be injected I.V.
- Monitoring: Frequent monitoring of patients for signs and symptoms of toxicity will prevent serious adverse reactions.

Geriatric ConsiderationsTolerance to gold decreases with advanced age; use cautiously only after traditional therapy and other disease-modifying antirheumatic drugs (DMARDs) have been attempted. Since elderly frequently have Cl_{cr} <50 mL/minute, it is advisable to measure or calculate creatinine clearance before use.

Pregnancy Risk FactorC

LactationEnters breast milk/not recommended

Adverse ReactionsFrequency not defined.

Dermatologic: Alopecia, angioedema, pruritus, rash, urticaria

Gastrointestinal: Stomatitis, gingivitis, glossitis, dysphagia, taste disturbance (metallic), nausea, GI hemorrhage, diarrhea, enterocolitis (ulcerative)

Hematologic: Agranulocytosis, aplastic anemia, eosinophilia, leukopenia, thrombocytopenia

Hepatic: Cholestasis, hepatitis, hepatotoxicity, jaundice

Neuromuscular & skeletal: Peripheral neuropathy

Ocular: Conjunctivitis

Respiratory: Gold bronchitis, interstitial pneumonitis

Renal: Hematuria, proteinuria

Miscellaneous: Anaphylactoid reaction, anaphylaxis, nitritoid reaction

Drug Interactions

ACE Inhibitors: May enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Monitoring ParametersPatients should have a CBC with differential, platelet count, hemoglobin determination and urinalysis for protein, white cells, red cells and casts; at baseline and prior to each injection. Skin and oral mucosa should be inspected for skin rash, bruising or oral ulceration/stomatitis. Specific questioning for symptoms such as pruritus, rash, stomatitis or metallic taste should be included. Dosing should be withheld in patients with significant gastrointestinal, renal, dermatologic, or hematologic effects (platelet count falls to <100,000/mm^3, WBC <4000, granulocytes <1500/mm^3

Reference RangeGold: Normal: 0-0.1 mcg/mL (SI: 0-0.0064 µmol/L); Therapeutic: 1-3 mcg/mL (SI: 0.06-0.18 µmol/L); Urine: <0.1 mcg/24 hour

Monitoring: Lab TestsPatients should have a CBC with differential, platelet count, hemoglobin determination and urinalysis for protein, white cells, red cells and casts; at baseline and prior to each infection. Dosing should be withheld in patients with significant gastrointestinal, renal, dermatologic, or hematologic effects (platelet count falls to <100,000/mm^3, WBC <4000, granulocytes <1500/mm^3

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Myochrysine®: 50 mg/mL (1 mL, 10 mL)

Generic AvailableNo

Mechanism of ActionUnknown, may decrease prostaglandin synthesis or may alter cellular mechanisms by inhibiting sulfhydryl systems

Pharmacodynamics/Kinetics

Onset of action: Delayed; may require up to 3 months

Half-life elimination: 5 days; may be prolonged with multiple doses

Time to peak, serum: 4-6 hours

Excretion: Urine (60% to 90%); feces (10% to 40%)

Pharmacotherapy PearlsApproximately 50% gold
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, gingivitis, and glossitis.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine
Index TermsSodium Aurothiomalate
International Brand NamesAllochrysine (BE); Auromyose (NL); Aurothio (KP); Miocrin (CO, SG); Myocrisin (AE, AU, BB, BH, BM, BS, BZ, CY, DK, EG, FI, GB, GY, HK, HN, IE, IL, IQ, IR, JM, JO, KW, LB, LY, NL, NO, OM, PR, QA, SA, SE, SR, SY, TH, TT, YE); Tauredon (AT, CH, CZ, HN, PT, RU)

Gonadorelin

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Medication Safety Issues

Sound-alike/look-alike issues:

Gonadorelin may be confused with gonadotropin, guanadrel

Factrel® may be confused with Sectral®

Gonadotropin may be confused with gonadorelin

Pronunciation(goe nad oh RELL in)
U.S. Brand NamesFactrel®
Canadian Brand NamesLutrepulse™
Pharmacologic CategoryDiagnostic Agent; Gonadotropin
Use: Labeled IndicationsEvaluation of functional capacity and response of gonadotrophic hormones; evaluate abnormal gonadotropin regulation as in precocious puberty and delayed puberty.

Orphan drug: Lutrepulse®: Induction of ovulation in females with hypothalamic amenorrhea

Dosing: Adults

Diagnostic test: I.V., SubQ (hydrochloride salt): 100 mcg administered in women during early phase of menstrual cycle (day 1-7)

Primary hypothalamic amenorrhea: I.V. (acetate): 5 mcg every 90 minutes via Lutrepulse® pump kit at treatment intervals of 21 days (pump will pulsate every 90 minutes for 7 days)

Dosing: PediatricDiagnostic test: Children >12 years: Refer to adult dosing.
Administration: I.V.

Factrel®: Give I.V. push over 30 seconds.

Lutrepulse®: A presterilized reservoir bag with the infusion catheter set supplied with the kit should be filled with the reconstituted solution and administered I.V. using the Lutrepulse® pump. Set the pump to deliver 25-50 mL of solution, based upon the dose, over a pulse period of 1 minute and at a pulse frequency of 90 minutes.

Administration: I.V. DetailFactrel®: Dilute in 3 mL of normal saline.
Storage

Factrel®: After reconstitution, store at room temperature and use within 1 day. Discard unused portion.

Lutrepulse®: Store at room temperature.

Reconstitution

Factrel®: Prepare immediately prior to use.

Lutrepulse®: Reconstitute with diluent immediately prior to use and transfer to plastic reservoir. The solution will supply 90-minute pulsatile doses for 7 consecutive days (Lutrepulse® pump).

ContraindicationsHypersensitivity to gonadorelin or any component of the formulation; women with any condition that could be exacerbated by pregnancy; patients who have ovarian cysts or causes of anovulation other than those of hypothalamic origin; any condition that may worsened by reproductive hormones
Allergy Considerations

- GH-RH Analog Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity/anaphylactic reactions: Hypersensitivity and anaphylactic reactions have occurred following multiple-dose administration.

Disease-related concerns:

- Pituitary prolactinemia: Use with caution in women in whom pregnancy could worsen pre-existing conditions (eg, pituitary prolactinemia).

Other warnings/precautions:

- Multiple pregnancy: Alert patients that multiple pregnancy is a possibility.

Pregnancy Risk FactorB
LactationExcretion in breast milk unknown
Adverse Reactions

1% to 10%: Local: Pain at injection site

<1%: Flushing, lightheadedness, headache, rash, nausea, abdominal discomfort

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersLH, FSH
Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. When used for induction of ovulation, assess results of laboratory tests and therapeutic effectiveness. Assess knowledge/teach patient appropriate use (use of pulsating pump if applicable), interventions to reduce side effects, and adverse symptoms to report.
Monitoring: Lab TestsLH, FSH
Patient EducationIf receiving this drug via pulsating pump, check all procedures with prescriber, and use exactly as prescribed. Report any rash, pain, or inflammation at injection site, and any change in respiratory status. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as hydrochloride: 100 mcg [diluent contains benzyl alcohol]

Generic AvailableNo
Mechanism of ActionStimulates the release of luteinizing hormone (LH) from the anterior pituitary gland
Pharmacodynamics/Kinetics

Onset of action: Peak effect: Maximal LH release: ~20 minutes

Duration: 3-5 hours

Half-life elimination: 4 minutes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentAntipsychotics may decrease the effects of gonadorelin
Index TermsGnRH; Gonadorelin Acetate; Gonadorelin Hydrochloride; Gonadotropin Releasing Hormone; LHRH; LRH; Luteinizing Hormone Releasing Hormone
References

Pescovitz OH, Comite F, Hench K, et al, “The NIH Experience With Precocious Puberty: Diagnostic Subgroups and Response to Short-Term Luteinizing Hormone-Releasing Hormone Analogue Therapy,” *J Pediatr*, 1986, 108(1):47-54.[PubMed 3080571]

International Brand NamesCryptocur (GR, NL); Gonadorelin (PL); HRF (BE, GB, IE, LU); Kryptocur (BE, CH, CZ, DE, HN, HR, IT, LU); LH-RH Tanabe (TW); Luforan (BE, ES); Lutamin (JP); Lutrelef (BE, CH, FR, HU, PL, SE); Relefact (CZ, GR, IE); Relefact LH-RH (AT, NL); Relisorm L (BR, HU, PL); Wyeth-Ayerst HRF (AU); Zyklomat (MY); Zyklomat Pulse Set (PL)

English

Jump To Field (Select Field Name)

Pronunciation(GOE se rel in)

U.S. Brand NamesZoladex®

Canadian Brand NamesZoladex®; Zoladex® LA

Pharmacologic CategoryAntineoplastic Agent, Gonadotropin-Releasing Hormone Agonist; Gonadotropin Releasing Hormone Agonist

Use: Labeled IndicationsPalliative treatment of advanced breast cancer and carcinoma of the prostate; treatment of endometriosis, including pain relief and reduction of endometriotic lesions; endometrial thinning agent as part of treatment for dysfunctional uterine bleeding

Dosing: Adults

Prostate cancer: SubQ:

Monthly implant: 3.6 mg injected into upper abdomen every 28 days

3-month implant: 10.8 mg injected into the upper abdominal wall every 12 weeks

Breast cancer, endometriosis, endometrial thinning: SubQ: Monthly implant: 3.6 mg injected into upper abdomen every 28 days

Note: For breast cancer, treatment may continue indefinitely; for endometriosis, it is recommended that duration of treatment not exceed 6 months. Only 1-2 doses are recommended for endometrial thinning.

Dosing: ElderlyRefer to adult dosing.

Dosing: Combination Regimens

Prostate cancer:

Bicalutamide + LHRH-A

FZ

Administration: OtherSubcutaneous implant: Insert the hypodermic needle into the subcutaneous fat. Do not try to aspirate with the goserelin syringe. If the needle is in a large vessel, blood will immediately appear in the syringe chamber. Change the direction of the needle so it parallels the abdominal wall. Push the needle in until the barrel hub touches the patient's skin. Fully depress the plunger to discharge. Withdraw needle and bandage the site. Confirm discharge by ensuring tip of the plunger is visible within the tip of the needle.

StorageZoladex® should be stored at room temperature not to exceed 25°C (77°F). Protect from light. Should be dispensed in a lightproof bag.

ContraindicationsHypersensitivity to goserelin, LHRH, LHRH agonist analogues, or any component of the formulation; pregnancy (or potential to become pregnant); breast-feeding

Allergy Considerations

- GnRH Agonist Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Decreased bone density: Has been reported in women and may be irreversible; use caution if other risk factors are present; evaluate and institute preventative treatment if necessary.

- Hypercalcemia: Has been reported in prostate and breast cancer patients with bone metastases.

- Pituitary apoplexy: Rare cases of pituitary apoplexy (frequently secondary to pituitary adenoma) have been observed with leuprolide administration (onset from 1 hour to usually <2 weeks); may present as sudden headache, vomiting, visual or mental status changes, and infrequently cardiovascular collapse; immediate medical attention required.

- Spinal cord suppression: Has been reported when used for prostate cancer; closely observe patients for weakness and paresthesias in first few weeks of therapy.

- Tumor flare: Transient worsening of signs and symptoms (tumor flare) may develop during the first few weeks of treatment.

- Urinary tract obstruction: Has been reported when used for prostate cancer; closely observe patients for urinary tract obstruction in first few weeks of therapy.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo dosage adjustments are needed in the elderly. Monitoring for bone density changes, serum lipid and serum calcium changes is recommended.
Pregnancy Risk FactorX (endometriosis, endometrial thinning); D (advanced breast cancer)
Pregnancy ConsiderationsGoserelin has been found to be teratogenic and increases pregnancy loss in animal studies. Women of childbearing potential should avoid pregnancy. Pregnancy must be ruled out prior to treatment. Use of nonhormonal contraception should be used during therapy and following discontinuation until the return of menses (or for at least 12 weeks).
LactationEnters breast milk/contraindicated
Adverse ReactionsPercentages reported in males with prostatic carcinoma and females with endometriosis using the 1-month implant:

>10%:

Central nervous system: Headache (female 75%, male 1% to 5%), emotional lability (female 60%), depression (female 54%, male 1% to 5%), pain (female 17%, male 8%), insomnia (female 11%, male 5%)

Endocrine & metabolic: Hot flashes (female 96%, male 62%), sexual dysfunction (21%), erections decreased (18%), libido decreased (female 61%), breast enlargement (female 18%)

Genitourinary: Lower urinary symptoms (male 13%), vaginitis (75%), dyspareunia (female 14%)

Miscellaneous: Diaphoresis (female 45%, male 6%); infection (female 13%)

1% to 10%:

Cardiovascular: CHF (male 5%), arrhythmia, cerebrovascular accident, hypertension, MI, peripheral vascular disorder, chest pain, palpitation, tachycardia, edema

Central nervous system: Lethargy (male 8%), dizziness (female 6%, male 5%), abnormal thinking, anxiety, chills, fever, malaise, migraine, somnolence

Dermatologic: Rash (female >1%, male 6%), alopecia, bruising, dry skin, skin discoloration

Endocrine & metabolic: Breast pain (female 7%), breast swelling/tenderness (male 1% to 5%), dysmenorrhea, gout, hyperglycemia

Gastrointestinal: Anorexia (female >1%, male 5%), nausea (male 5%), constipation, diarrhea, flatulence, dyspepsia, ulcer, vomiting, weight increased, xerostomia

Genitourinary: Renal insufficiency, urinary frequency, urinary obstruction, urinary tract infection, vaginal hemorrhage

Hematologic: Anemia, hemorrhage

Neuromuscular & skeletal: Arthralgia, bone mineral density decreased (female; ~4% decrease in 6 months), joint disorder, paresthesia

Ocular: Amblyopia, dry eyes

Respiratory: Upper respiratory tract infection (male 7%), COPD (male 5%), pharyngitis (female 5%), bronchitis, cough, epistaxis, rhinitis, sinusitis

Miscellaneous: Allergic reaction

Postmarketing and/or case reports: Pituitary apoplexy

Oncology: VesicantNo
Oncology: Emetic PotentialLow (10% to 30%)
Drug Interactions

Antidiabetic Agents: Luteinizing Hormone-Releasing Hormone Analogs may diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Test InteractionsSerum alkaline phosphatase, serum acid phosphatase, serum testosterone, serum LH and FSH, serum estradiol
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic effectiveness and adverse response periodically during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Do not give to women of childbearing age unless female is capable of complying with contraceptive measures 1 month prior to therapy, during therapy, and at least 12 weeks following therapy. Instruct patient in appropriate contraceptive measures.
Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug must be implanted under the skin of your abdomen every 28 days; it is important to maintain appointment schedule. Males or females, you may experience systemic hot flashes (layered, cool clothes may help); headache (consult prescriber for approved analgesic); constipation (increased bulk and water in diet or stool softener may help); sexual dysfunction (decreased libido, males: decreased erection, females: vaginal dryness); or bone pain (consult prescriber for approved analgesic). Symptoms may worsen temporarily during first weeks of therapy. Report chest pain, palpitations, or respiratory difficulty; swelling of extremities; unusual persistent nausea, vomiting, or constipation; chest pain or respiratory difficulty; unresolved dizziness; or skin rash. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant; do not get pregnant 1 month before, during, or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not donate blood during or for 1 month following therapy. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Implant, subcutaneous:

Zoladex®:

3.6 mg [1-month implant packaged with 16-gauge hypodermic needle]

10.8 mg [3-month implant packaged with 14-gauge hypodermic needle]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Implant (Zoladex)

10.8 mg (1): $1339.48

Mechanism of ActionGoserelin is a synthetic analog of luteinizing-hormone-releasing hormone (LHRH). Following an initial increase in luteinizing hormone (LH) and follicle stimulating hormone (FSH), chronic administration of goserelin results in a sustained suppression of pituitary gonadotropins. Serum testosterone falls to levels comparable to surgical castration. The exact mechanism of this effect is unknown, but may be related to changes in the control of LH or down-regulation of LH receptors.
Pharmacodynamics/Kinetics**Note:** Data reported using the 1-month implant.

Absorption: SubQ: Rapid and can be detected in serum in 10 minutes

Distribution: V_d: Male: 44.1 L; Female: 20.3 L

Time to peak, serum: SubQ: Male: 12-15 days, Female: 8-22 days

Half-life elimination: SubQ: Male: ~4 hours, Female: ~2 hours; Renal impairment: Male: 12 hours

Excretion: Urine (90%)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and taste disturbances.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause sedation or insomnia
Mental Health: Effects on Psychiatric TreatmentSexual dysfunction is common; concurrent use with SSRIs may produce additive dysfunction
Index TermsD-Ser(Bu^t)^6,Azgly^{10}-LHRH; Goserelin Acetate; ICI-118630; NSC-606864
References

Ahmann FR, Citrin DL, deHaan HA, et al, “Zoladex: A Sustained-Release, Monthly Luteinizing Hormone-Releasing Hormone Analog for the Treatment of Advanced Prostate Cancer,” *J Clin Oncol*, 1987, 5(6):912-7. [PubMed 2953870]

Brogden RN and Faulds D, “Goserelin. A Review of Its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Efficacy in Prostate Cancer,” *Drugs Aging*, 1995, 6(4);324-43.

Goldspiel BR and Kohler DR, “Goserelin Acetate Implant: A Depot Luteinizing Hormone-Releasing Hormone Analog for Advanced Prostate Cancer,” *DICP*, 1991, 25(7-8):796-804. [PubMed 1835221]

International Brand NamesZoladex (AE, AR, AT, BB, BD, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CR, CY, CZ, DE, DK, DO, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PK, PL, PT, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SV, SY, TH, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Zoladex Depot (KP); Zoladex Implant (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Zoladex Inj. (NZ); Zoladex LA (AR, BR, ID, IL, MY, PH, PL, SG)

Granisetron

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Granisetron may be confused with dolasetron, ondansetron, palonosetron

Pronunciation(gra NI se tron)

U.S. Brand NamesGranisol™; Kytril®; Sancuso®

Canadian Brand NamesKytril®

Pharmacologic CategoryAntiemetic; Selective 5-HT_3 Receptor Antagonist

Use: Labeled IndicationsProphylaxis of nausea and vomiting associated with emetogenic chemotherapy and radiation therapy, (including total body irradiation and fractionated abdominal radiation); prophylaxis and treatment of postoperative nausea and vomiting (PONV)

Transdermal patch: Prophylaxis of nausea and vomiting associated with moderate-to-high emetogenic chemotherapy regimens ≤5 days consecutive duration

Generally **not** recommended for treatment of existing chemotherapy-induced emesis (CIE) or for prophylaxis of nausea from agents with a low emetogenic potential.

Dosing: Adults

Prophylaxis of chemotherapy-related emesis:

Oral: 2 mg once daily up to 1 hour before chemotherapy or 1 mg twice daily; the first 1 mg dose should be given up to 1 hour before chemotherapy.

I.V.:

Within U.S.: 10 mcg/kg/dose (maximum: 1 mg/dose) given 30 minutes prior to chemotherapy; for some drugs (eg, carboplatin, cyclophosphamide) with a later onset of emetic action, 10 mcg/kg every 12 hours may be necessary.

Outside U.S.: 40 mcg/kg/dose (or 3 mg/dose); maximum: 9 mg/24 hours

Breakthrough: Granisetron has not been shown to be effective in terminating nausea or vomiting once it occurs and should not be used for this purpose.

Transdermal patch: Prophylaxis of chemotherapy-related emesis: Apply 1 patch at least 24 hours prior to chemotherapy; do not apply ≥48 hours before chemotherapy. Remove patch a minimum of 24 hours after chemotherapy completion. Maximum duration: Patch may be worn up to 7 days, depending on chemotherapy regimen duration.

Prophylaxis of radiation therapy-associated emesis: Oral: 2 mg once daily given 1 hour before radiation therapy.

Postoperative nausea and vomiting (PONV): I.V.:

Prevention: 1 mg given undiluted over 30 seconds; administer before induction of anesthesia or immediately before reversal of anesthesia

Treatment: 1 mg given undiluted over 30 seconds

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricProphylaxis associated with cancer chemotherapy: Children >2 years: Refer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment required.

Dosing: Hepatic ImpairmentKinetic studies in patients with hepatic impairment showed that total clearance was approximately halved; however, standard doses were very well tolerated, and dose adjustments are not necessary.

Administration: I.V.Administer I.V. push over 30 seconds or as a 5-10 minute-infusion

Prevention of PONV: Administer before induction of anesthesia or immediately before reversal of anesthesia.

Treatment of PONV: Administer undiluted over 30 seconds.

Administration: I.V. DetailpH: 4.7-7.3

Administration: OralDoses should be given up to 1 hour prior to initiation of chemotherapy/radiation

Administration: TopicalTransdermal (Sancuso®): Apply patch to clean, dry, intact skin on upper outer arm. Do not use on red, irritated or damaged skin. Remove patch from pouch immediately before application. Do not cut patch.

Storage

I.V.: Store at 15°C to 30°C (59°F to 86°F). Protect from light. Do not freeze vials. Stable when mixed in NS or D_5W for 7 days under refrigeration and for 3 days at room temperature.

Oral: Store tablet or oral solution at 15°C to 30°C (59°F to 86°F). Protect from light.

Transdermal patch: Store at 20°C to 25°C (68°F to 77°F). Keep patch in original packaging until immediately prior to use.

CompatibilityStable in $D_5{}^{1}/{}_{2}NS$, D_5NS, D_5W, NS, bacteriostatic water.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, amikacin, aminophylline, amphotericin B cholesteryl sulfate complex, ampicillin, ampicillin/sulbactam, amsacrine, aztreonam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, carmustine, cefazolin, cefepime, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, chlorpromazine, cimetidine, ciprofloxacin, cisplatin, cladribine, clindamycin, co-trimoxazole, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, dexamethasone sodium phosphate, dexmedetomidine, diphenhydramine, dobutamine, docetaxel, dopamine, doxorubicin, doxorubicin liposome, doxycycline, droperidol, enalaprilat, etoposide, etoposide phosphate, famotidine, fenoldopam mesylate, filgrastim, floxuridine, fluconazole, fludarabine, fluorouracil, furosemide, gallium nitrate, ganciclovir, gatifloxacin, gemcitabine, gentamicin, haloperidol, heparin, hetastarch in lactated electrolytes, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, idarubicin, ifosfamide, imipenem/cilastatin, leucovorin calcium, levoleucovorin, linezolid, lorazepam, magnesium sulfate, mechlorethamine, melphalan, meperidine, mesna, methotrexate, methylprednisolone sodium succinate, metoclopramide, metronidazole, mitomycin, mitoxantrone, morphine, nalbuphine, netilmicin, ofloxacin, paclitaxel, pemetrexed, piperacillin, piperacillin/tazobactam, potassium chloride, prochlorperazine edisylate, promethazine, propofol, ranitidine, sargramostim, sodium bicarbonate, streptozocin, teniposide, thiotepa, ticarcillin, ticarcillin/clavulanate, tobramycin, topotecan, vancomycin, vinblastine, vincristine, vinorelbine, zidovudine. **Incompatible:** Amphotericin B.

Compatibility in syringe: Compatible: Dexamethasone sodium phosphate, methylprednisolone sodium succinate.

Compatibility when admixed: Compatible: Dexamethasone sodium phosphate, methylprednisolone sodium succinate.

ContraindicationsHypersensitivity to granisetron or any component of the formulation

Allergy Considerations

- Serotonin 5-HT$_3$ Antagonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Allergic reactions: Use with caution in patients allergic to other 5-HT$_3$ receptor antagonists; cross-reactivity has been reported.

- ECG effects: Selective 5-HT$_3$ antagonists, including granisetron, have been associated with a number of dose-dependent increases in ECG intervals (eg, PR, QRS duration, QT/QT$_c$, JT), usually occurring 1-2 hours after I.V. administration. In general, these changes are not clinically relevant, however, when used in conjunction with other agents that prolong these intervals, arrhythmia may occur. When used with agents that prolong the QT interval (eg, Class I and III antiarrhythmics), clinically relevant QT interval prolongation may occur resulting in torsade de pointes. A number of trials have shown that 5-HT$_3$ antagonists produce QT interval prolongation to variable degrees. Use with caution in patients at risk of QT prolongation and/or ventricular arrhythmia. Reduction in heart rate may also occur with the 5-HT$_3$ antagonists. I.V. formulations of 5-HT$_3$ antagonists have more association with ECG interval changes, compared to oral formulations.

Disease-related concerns:

- Long QT syndrome: Use with caution in patients with congenital long QT syndrome or other risk factors for QT prolongation (eg, medications known to prolong QT interval, electrolyte abnormalities [hypokalemia or hypomagnesemia], and cumulative high-dose anthracycline therapy).

Dosage form specific issues:

- Benzyl alcohol: Injection contains benzyl alcohol (1 mg/mL) which has been associated with "gasping syndrome" in neonates.

- Transdermal patch: Application site reactions, generally mild, have occurred with use; if skin reaction is severe or generalized, remove patch. Cover patch application site with clothing to protect from natural or artificial sunlight exposure while patch is applied and for 10 days following removal; granisetron may potentially be affected by natural or artificial sunlight. Do not apply to red, irritated or damaged skin.

Other warnings/precautions:

- Chemotherapy-related emesis: **For chemotherapy, should be used on a scheduled basis, not on an “as needed” (PRN) basis,** since data support the use of this drug only in the prevention of nausea and vomiting (due to antineoplastic therapy) and not in the rescue of nausea and vomiting. Should only be used in the first 24-48 hours of chemotherapy. Data does not support any increased efficacy in delayed nausea and vomiting.

- Ileus or gastric distention: Does not stimulate gastric or intestinal peristalsis; may mask progressive ileus and/or gastric distension.

- Postoperative nausea/vomiting use: Routine prophylaxis for PONV is not recommended in patients where there is little expectation of nausea and vomiting postoperatively. In patients where nausea and vomiting must be avoided postoperatively, administer to all patients even when expected incidence of nausea and vomiting is low.

Geriatric ConsiderationsClinical trials with patients older than 65 years of age are limited; however, the data indicates that safety and efficacy are similar to that observed in younger adults. No adjustment in dose necessary for elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsThere are no adequate or well-controlled studies in pregnant women. Teratogenic effects were not observed in animal studies. Injection (1 mg/mL strength) contains benzyl alcohol which may cross the placenta. Use only if benefit exceeds the risk.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Headache (3% to 21%; transdermal patch: 1%)

Gastrointestinal: Constipation (3% to 18%)

Neuromuscular & skeletal: Weakness (5% to 18%)

1% to 10%:

Cardiovascular: QT_c prolongation (1% to 3%), hypertension (1% to 2%)

Central nervous system: Pain (10%), fever (3% to 9%), dizziness (4% to 5%), insomnia (<2% to 5%), somnolence (1% to 4%), anxiety (2%), agitation (<2%), CNS stimulation (<2%)

Dermatologic: Rash (1%)

Gastrointestinal: Diarrhea (3% to 9%), abdominal pain (4% to 6%), dyspepsia (3% to 6%), taste perversion (2%)

Hepatic: Liver enzymes increased (5% to 6%)

Renal: Oliguria (2%)

Respiratory: Cough (2%)

Miscellaneous: Infection (3%)

<1%, postmarketing, and/or case reports: Agitation, allergic reactions; anaphylaxis (including hypotension, dyspnea, urticaria); angina, application site reactions (transdermal patch), arrhythmias, atrial fibrillation, extrapyramidal syndrome, hot flashes, hypotension, hypersensitivity, syncope

Oncology: VesicantNo

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)

Drug Interactions

Apomorphine: Antiemetics (5HT3 Antagonists) may enhance the hypotensive effect of Apomorphine. *Risk X: Avoid combination*

Nursing: Physical Assessment/MonitoringAssess allergy history (selective $5\text{-}HT_3$ receptor antagonists) prior to administering. Use with caution in presence of, or potential for, cardiac conduction abnormalities (eg, QT prolongation, medication known to prolong QT interval, electrolyte abnormalities). I.V.: Follow infusion specifics. **Note:** Oral and I.V. doses have different schedules and should not be administered on PRN basis. Assess therapeutic effectiveness and adverse reactions on a regular basis. Teach patient possible side effects and adverse symptoms to report.

Patient EducationThis drug is given to reduce the incidence of nausea and vomiting. Do not take any other medication for nausea and vomiting with this medication unless approved by prescriber. If this medication is given by intravenous infusion you will be monitored during infusion. Report immediately any chest pain, respiratory difficulty, pain or itching at infusion site. Self-administered oral doses must be taken exactly as directed. You may experience headache, drowsiness, or dizziness (request assistance when getting up or changing position and do not perform activities requiring alertness (including driving) until response to drug is known). Report chest pain or palpitations; persistent headache; excessive drowsiness; fever; or changes in elimination patterns (constipation or diarrhea) or other adverse effects. **Breast-feeding precaution:** Consult prescriber if you are or intend to breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution: 1 mg/mL (1 mL, 4 mL)

Kytril®: 1 mg/mL (1 mL, 4 mL) [contains benzyl alcohol]

Injection, solution [preservative free]: 0.1 mg/mL (1 mL); 1 mg/mL (1 mL)

Kytril®: 0.1 mg/mL (1 mL)

Solution, oral:

Granisol™: 2 mg/10 mL (30 mL) [contains sodium benzoate; orange flavor]

Kytril®: 2 mg/10 mL (30 mL) [contains sodium benzoate; orange flavor] [DSC]

Tablet: 1 mg

Kytril®: 1 mg

Transdermal system, topical:

Sancuso®: 3.1 mg/24 hours (1s) [52 cm^2, total granisetron 34.3 mg]

Generic AvailableYes

ManufacturerRoche Laboratories Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Granisetron HCl)

1 mg (2): $45.99

Tablets (Kytril)

1 mg (2): $131.99

Mechanism of ActionSelective 5-HT$_3$-receptor antagonist, blocking serotonin, both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone

Pharmacodynamics/Kinetics

Duration: Oral, I.V.: Generally up to 24 hours

Absorption: Oral: Tablets and oral solution are bioequivalent; Transdermal patch: ~66% over 7 days

Distribution: V$_d$: 2-4 L/kg; widely throughout body

Protein binding: 65%

Metabolism: Hepatic via N-demethylation, oxidation, and conjugation; some metabolites may have 5-HT$_3$ antagonist activity

Half-life elimination: Oral: 6 hours; I.V.: 9 hours

Time to peak, plasma: Transdermal patch: Maximum systemic concentrations: ~48 hours after application (range: 24-168 hours)

Excretion: Urine (12% as unchanged drug, 48% to 49% as metabolites); feces (34% to 38% as metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety or insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBRL 43694

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Yarker YE and McTavish D, “Granisetron. An Update of Its Therapeutic Use in Nausea and Vomiting Induced by Antineoplastic Therapy,” *Drugs*, 1994, 48(5):761-93.[PubMed 7530631]

International Brand NamesGranicip (IN); Grantron (TW); Kanitron (KP); Kevatril (DE); Kytril (AE, AR, AT, AU, BE, BF, BG, BH, BJ, CH, CI, CN, CO, CY, CZ, DE, DK, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, OM, PE, PH, PK, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SY, TH, TN, TR, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Neosetron (BR); Setron (IL); Sulingqiong (CL)

Griseofulvin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

International issues: Fulvicin® (brand name used in international markets) may be confused with Furacin®

Pronunciation(gri see oh FUL vin)
U.S. Brand NamesGrifulvin® V; Gris-PEG®
Pharmacologic CategoryAntifungal Agent, Oral
Use: Labeled IndicationsTreatment of susceptible tinea infections of the skin, hair, and nails
Dosing: Adults

Tinea infections: Oral:

Microsize: 500-1000 mg/day in single or divided doses

Ultramicrosize: 375 mg/day in single or divided doses; doses up to 750 mg/day have been used for infections more difficult to eradicate such as tinea unguium and tinea pedis.

Note: Duration of therapy depends on the site of infection:

Tinea corporis: 2-4 weeks

Tinea capitis: 4-6 weeks or longer (up to 8-12 weeks)

Tinea pedis: 4-8 weeks

Tinea unguium: 4-6 months

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Tinea infections: Oral: Children >2 years:

Microsize: 10-20 mg/kg/day in single or divided doses. In the treatment of tinea capitis, higher dosages (20-25 mg/kg/day for 8-12 weeks) have been recommended by some authors (unlabeled).

Ultramicrosize: Usual: 7.3 mg/kg/day in single dose or 2 divided doses; range: 5-15 mg/kg/day in single dose or 2 divided doses (maximum: 750 mg/day)

Administration: OralAdminister with a fatty meal (peanuts or ice cream) to increase absorption, or with food or milk to avoid GI upset

Gris-PEG® tablets: May be swallowed whole or crushed and sprinkled onto 1 tablespoonful of applesauce and swallowed immediately without chewing.

ContraindicationsHypersensitivity to griseofulvin or any component of the formulation; severe liver disease; porphyria (interferes with porphyrin metabolism); pregnancy
Warnings/Precautions

Concerns related to adverse effects:

- Penicillin allergy: Hypersensitivity cross reaction between penicillins and griseofulvin is possible.
- Photosensitivity: Avoid exposure to intense sunlight to prevent photosensitivity reactions.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children ≤2 years of age.
- Pregnancy: May cause fetal harm when administered to pregnant women.

Other warnings/precautions:

- Monitoring: During long-term therapy, periodic assessment of hepatic, renal, and hematopoietic functions should be performed.

Geriatric ConsiderationsNo specific changes in dosing are needed.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies have shown decreased spermatogenesis, as well as embryotoxic and teratogenic effects with

griseofulvin. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy is contraindicated.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Central nervous system: Dizziness, fatigue, headache, insomnia, mental confusion

Dermatologic: Angioneurotic edema (rare), erythema multiforme-like drug reaction, photosensitivity, rash (most common), urticaria (most common),

Gastrointestinal: Nausea, vomiting, epigastric distress, diarrhea, GI bleeding

Genitourinary: Menstrual irregularities (rare)

Hematologic: Granulocytopenia, leukopenia

Hepatic: Hepatotoxicity

Neuromuscular & skeletal: Paresthesia (rare)

Renal: Nephrosis, proteinuria

Miscellaneous: Drug-induced lupus-like syndrome (rare), oral thrush

Metabolism/Transport Effects**Induces** CYP1A2 (weak), 2C8 (weak), 2C9 (weak), 3A4 (weak)

Drug Interactions

Alcohol (Ethyl): Griseofulvin may enhance the adverse/toxic effect of Alcohol (Ethyl). A disulfiram-like reaction may occur. *Risk C: Monitor therapy*

Barbiturates: May decrease the absorption of Griseofulvin. **Exceptions:** Methohexital; Thiopental. *Risk D: Consider therapy modification*

Contraceptive (Progestins): Griseofulvin may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

CycloSPORINE: Griseofulvin may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Griseofulvin may increase the metabolism of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Griseofulvin may increase the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression). Concomitant use with ethanol will cause “disulfiram”-type reaction consisting of tachycardia, flushing, headache, nausea, and in some patients, vomiting and chest and/or abdominal pain.

Food: Griseofulvin concentrations may be increased if taken with food, especially with high-fat meals.

Test InteractionsFalse-positive urinary VMA levels

Monitoring ParametersPeriodic renal, hepatic, and hematopoietic function tests

Nursing: Physical Assessment/MonitoringAssess allergic history prior to beginning treatment (cross reaction with penicillin is possible). Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, decreased effectiveness of oral contraceptives). Assess results of laboratory tests, renal function, and hepatic function with long-term use, therapeutic effectiveness (resolution of viral infection), and adverse response (eg, CNS changes, gastrointestinal upset, rash, opportunistic infection) periodically during therapy. Teach patient proper use, possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsPeriodic renal, hepatic, and hematopoietic function especially with long-term use

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, around-the-clock with food. Take full course of medication; do not discontinue without consulting prescriber. Avoid alcohol while taking this drug (disulfiram reactions). Practice good hygiene measures to prevent reinfection. Frequent blood tests may be required with prolonged therapy. You may experience confusion, dizziness, drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea, vomiting, or diarrhea (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or increased sensitivity to sun (use sunscreen, wear protective clothing and eyewear, and avoid excessive exposure to direct sunlight). Report skin rash; respiratory difficulty; CNS changes (confusion, dizziness, acute headache); changes in color of stool or urine; white plaques in mouth; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, oral [microsize]: 125 mg/5mL (120 mL)

Grifulvin® V: 125 mg/5 mL (120 mL) [contains alcohol 0.2%]

Tablet, oral [microsize]:

Grifulvin® V: 500 mg

Tablet, oral [ultramicrosize]:

Gris-PEG®: 125 mg, 250 mg

Generic AvailableYes: Suspension, ultramicrosized product

Pricing: U.S. (www.drugstore.com)

Suspension (Grifulvin V)

125 mg/5 mL (120): $68.14

Suspension (Griseofulvin Microsize)

125 mg/5 mL (120): $43.00

Tablets (Gris-PEG)

125 mg (90): $162.41

Mechanism of ActionInhibits fungal cell mitosis at metaphase; binds to human keratin making it resistant to fungal invasion

Pharmacodynamics/Kinetics

Absorption: Ultramicrosize griseofulvin absorption is almost complete; absorption of microsize griseofulvin is variable (25% to 70% of an oral dose); enhanced by ingestion of a fatty meal (GI absorption of ultramicrosize is ~1.5 times that of microsize)

Distribution: Crosses placenta

Metabolism: Extensively hepatic

Half-life elimination: 9-22 hours

Excretion: Urine (<1% as unchanged drug); feces; perspiration

Related Information

- Antifungal Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: May cause soreness or irritation of mouth or tongue. May cause oral thrush.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, confusion, or insomnia

Mental Health: Effects on Psychiatric TreatmentMay rarely cause leukopenia; use caution with clozapine and carbamazepine; barbiturates may decrease levels of griseofulvin

Index TermsGriseofulvin Microsize; Griseofulvin Ultramicrosize

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International Brand NamesBiogrisin (PL); Delmofulvina (IT); Fulcin (BR, ES, FI, GB, IT, NO, PT); Fulcin Forte (MX); Fulcin S (DE); Fulvicina (ES); Fungin (TH); Fungivin (NO); Greosin (ES); Gricin (CZ, DE, HU, PL); Grifulin Forte (IL); Gris O.D. (IN); Grisefuline (FR); Grisenova (GR); griseo von ct (DE); Griseofort (ID); Griseofulvin (HN, IE, PL); Griseofulvin Leo (LU); Griseofulvina (IT); Griseomed (AT); Griseostatin (TW); Grisflavin (TH); Grisol (CH); Grisomicon (PT); Grisovin (AE, AT, AU, BH, CO, CY, CZ, EG, GB, IL, IQ, IR, JO, KW, LB, LY, MX, OM, PE, PT, QA, SA, SY, VE, YE); Grisovin-FP (AR, MY, UY); Grisovina FP (IT); Grisuvin (MY); Grivin (MY); Krisovin (MY, SG); Likuden (DE); Microcidal (ZA); Myconil (MY); Ponzyr V (KP); Sporostatin U F (PH); Sulvina (ES)

Guaifenesin and Codeine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(gwye FEN e sin & KOE deen)

U.S. Brand NamesBrontex®; Cheracol®; Diabetic Tussin C®; Gani-Tuss® NR; Guaifenesin AC; Guaituss AC; Kolephrin® #1; Mytussin® AC; Robafen® AC; Romilar® AC; Tussi-Organidin® NR; Tussi-Organidin® S-NR; Tusso-C™

Pharmacologic CategoryAntitussive; Cough Preparation; Expectorant

Use: Labeled IndicationsTemporary control of cough due to minor throat and bronchial irritation

Dosing: Adults**Cough (antitussive/expectorant):** Oral:

Brontex® tablets: 1 tablet every 4 hours; maximum 6 tablets/24 hours

Diabetic Tussin C®, Kolephrin® #1, Romilar® AC, Tussi-Organidin® NR liquid: 10 mL every 4 hours; maximum 60 mL/24 hours

Note: Also refer to specific product labeling.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Cough (antitussive/expectorant):** Oral:

Children:

2-6 years (Diabetic Tussin C® liquid, Tussi-Organidin® NR): Codeine 1 mg/kg/day in 4 divided doses

6-12 years (Diabetic Tussin C®, Kolephrin® #1, Romilar® AC, Tussi-Organidin® NR liquid): 5 mL every 4 hours; maximum 30 mL/24 hours

≥12 years: Refer to adult dosing.

Note: Also refer to specific product labeling.

Dietary ConsiderationsRomilar® AC contains phenylalanine. Diabetic Tussin C® contains phenylalanine 0.03 mcg/5 mL. Kolephrin® #1 contains sodium 1.1 mg/5 mL. Tusso-C™ contains phenylalanine 0.03 mcg/5 mL

RestrictionsC-V

ContraindicationsHypersensitivity to guaifenesin, codeine, or any component of the formulation; asthma

Allergy Considerations

- GuaiFENesin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension.
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Fever: Use with caution in patients with fever.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Renal impairment: Use with caution in patients with severe renal impairment.
- Respiratory disease: Use with caution in patients with pulmonary disease or decrease ventilatory function; dose-related respiratory

depression occurs.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.
- Ulcerative colitis: Use with caution in patients with ulcerative colitis.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Safety and efficacy of this combination have not been established in children <2 years of age.
- Surgery: Use with caution in patients with recent GI or urinary tract surgery.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing. Dose should not be increased if cough does not respond; reevaluate within 5 days for possible underlying pathology.

Geriatric ConsiderationsElderly may be more sensitive to the CNS depressant effects of codeine; monitor closely for excessive sedation.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Also see individual agents.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsCodeine is excreted in breast milk. Excretion of guaifenesin is not known. Also refer to Codeine monograph.
Adverse ReactionsFrequency not defined; also see individual agents.

Cardiovascular: Bradycardia, circulatory depression, flushing, orthostatic hypotension, palpitation, syncope, tachycardia

Central nervous system: Convulsions, CNS depression, disorientation, dizziness, dysphoria, euphoria, faintness, hallucinations (transient), headache, lightheadedness, sedation

Dermatologic: Angioneurotic edema, pruritus, urticaria

Gastrointestinal: Biliary tract spasm, colonic motility increase (with chronic ulcerative colitis), constipation, nausea, stomach pain, toxic dilation (with acute ulcerative colitis), vomiting

Genitourinary: Oliguria, urinary retention

Neuromuscular & skeletal: Weakness

Ocular: Visual disturbances

Respiratory: Laryngeal edema, respiratory depression

Miscellaneous: Anaphylaxis, diaphoresis

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid or limit ethanol (may increase CNS depression). Watch for sedation.
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid: Guaifenesin 300 mg and codeine phosphate 10 mg per 5 mL (120 mL, 480 mL)

Brontex®: Guaifenesin 75 mg and codeine phosphate 2.5 mg per 5 mL (480 mL) [alcohol free; strawberry mint flavor]

Diabetic Tussin C®: Guaifenesin 200 mg and codeine phosphate 10 mg per 5 mL (480 mL) [contains phenylalanine 0.03 mcg/5 mL; cherry vanilla flavor]

Gani-Tuss® NR: Guaifenesin 100 mg and codeine phosphate 10 mg per 5 mL (480 mL) [raspberry flavor]

Guaifenesin AC: Guaifenesin 100 mg and codeine phosphate 10 mg per 5 mL (120 mL, 480 mL) [alcohol free, sugar free; raspberry flavor]

Kolephrin® #1: Guaifenesin 100 mg and codeine phosphate 10 mg per 5 mL (120 mL) [contains sodium 1.1 mg/5 mL and sodium benzoate]

Tussi-Organidin® NR: Guaifenesin 300 mg and codeine phosphate 10 mg per 5 mL (480 mL) [alcohol free, sugar free; contains sodium benzoate; raspberry flavor]

Tussi-Organidin® S-NR: Guaifenesin 300 mg and codeine phosphate 10 mg per 5 mL (120 mL) [alcohol free, sugar free; contains sodium benzoate; raspberry flavor]

Syrup:

Cheracol®: Guaifenesin 100 mg and codeine phosphate 10 mg per 5 mL (120 mL) [contains alcohol 4.75% and benzoic acid]

Guaituss AC: Guaifenesin 100 mg and codeine phosphate 10 mg per 5 mL (120 mL, 480 mL) [contains alcohol; sugar free; fruit-mint flavor]

Mytussin® AC: Guaifenesin 100 mg and codeine phosphate 10 mg per 5 mL (120 mL, 480 mL) [contains alcohol; sugar free; fruit flavor]

Robafen® AC: Guaifenesin 100 mg and codeine phosphate 10 mg per 5 mL (120 mL, 480 mL)

Romilar® AC: Guaifenesin 100 mg and codeine phosphate 10 mg per 5 mL (480 mL) [alcohol free, sugar free, dye free; contains benzoic acid and phenylalanine; grape flavor]

Tusso-C™: Guaifenesin 200 mg and codeine phosphate 10 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; contains phenylalanine 0.03 mcg/5 mL; cherry vanilla flavor]

Tablet: Guaifenesin 300 mg and codeine phosphate 10 mg

Brontex®: Guaifenesin 300 mg and codeine phosphate 10 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Liquid (Brontex)

10-300 mg/20 mL (120): $32.99

Liquid (Tussi-Organidin NR)

300-10 mg/5 mL (473): $184.38

Syrup (Cheratussin AC)

100-10 mg/5 mL (118): $11.99

100-10 mg/5 mL (480): $15.98

Tablets (Brontex)

10-300 mg (30): $97.99

Tablets (Guaifenesin-Codeine)

300-10 mg (30): $13.99

Mechanism of Action

Guaifenesin may act as an expectorant by irritating the gastric mucosa and stimulating respiratory tract secretions, thereby increasing respiratory fluid volumes and decreasing phlegm viscosity

Codeine is an antitussive that controls cough by depressing the medullary cough center

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Codeine
- GuaiFENesin

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause confusion, headache, dizziness, lightheadedness, false feeling of well being, restlessness, paradoxical CNS stimulation, or malaise; may rarely cause hallucinations, mental depression, nightmares, or insomnia

Mental Health: Effects on Psychiatric TreatmentConstipation and drowsiness are common, this effect may be additive when used concurrently with psychotropics

Index TermsCodeine and Guaifenesin

Guaifenesin and Dextromethorphan

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Benylin® may be confused with Benadryl®, Ventolin®

Pronunciation(gwye FEN e sin & deks troe meth OR fan)

U.S. Brand NamesAllfen-DM; Altarussin DM [OTC]; Cheracol® D [OTC]; Cheracol® Plus [OTC]; Coricidin HBP® Chest Congestion and Cough [OTC]; Diabetic Tussin® DM Maximum Strength [OTC]; Diabetic Tussin® DM [OTC]; Double Tussin DM [OTC]; Duratuss® DM; Fenesin DM IR; Gani-Tuss DM NR; Genatuss DM® [OTC]; Guaicon DM [OTC]; Guaicon DMS [OTC]; Guaifenex® DM [DSC]; Guia-D; Guiatuss-DM® [OTC]; Hydro-Tussin™ DM [DSC]; Kolephrin® GG/DM [OTC]; Mintab DM; Mucinex® Children's Cough [OTC]; Mucinex® DM Maximum Strength [OTC]; Mucinex® DM [OTC]; Phanatuss® DM [OTC]; Phlemex; Refenesen™ DM [OTC]; Respa-DM®; Robafen DM Clear [OTC]; Robafen DM [OTC]; Robitussin® Cough and Congestion [OTC]; Robitussin® DM Infant [OTC] [DSC]; Robitussin® DM [OTC]; Robitussin® Sugar Free Cough [OTC]; Safe Tussin® DM [OTC]; Scot-Tussin® Senior [OTC]; Silexin [OTC]; Siltussin DM DAS [OTC]; Siltussin DM [OTC]; Simuc-DM; Su-Tuss DM; Touro® DM; Tussi-Organidin® DM NR; Tussi-Organidin® DM-S NR; Vicks® 44E [OTC]; Vicks® Pediatric Formula 44E [OTC]; Z-Cof LA™

Canadian Brand NamesBalminil DM E; Benylin® DM-E; Koffex DM-Expectorant; Robitussin® DM

Pharmacologic CategoryAntitussive; Cough Preparation; Expectorant

Use: Labeled IndicationsTemporary control of cough due to minor throat and bronchial irritation

Dosing: Adults**Cough (antitussive/expectorant):** Oral:

General dosing guidelines: Guaifenesin 200-400 mg and dextromethorphan 10-20 mg every 4 hours (maximum dose: Guaifenesin 2400 mg and dextromethorphan 120 mg per day)

Product-specific labeling:

Guaifenex® DM, Mucinex® DM, Touro® DM: 1-2 tablets every 12 hours (maximum: 4 tablets/24 hours)

Robitussin® DM, Robitussin® Sugar Free Cough: 10 mL every 4 hours (maximum: 6 doses/24 hours)

Vicks® 44E: 15 mL every 4 hours (maximum: 6 doses/24 hours)

Vicks® Pediatric Formula 44E: 30 mL every 4 hours (maximum: 6 doses/24 hours)

Z-Cof LA™: 1 tablet every 12 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Cough (antitussive/expectorant):** Oral: Children:

2-6 years:

General dosing guidelines: Guaifenesin 50-100 mg and dextromethorphan 2.5-5 mg every 4 hours (maximum dose: Guaifenesin 600 mg and dextromethorphan 30 mg per day)

Product-specific labeling:

Guaifenex® DM, Touro® DM: $^{1}/_{2}$ tablet every 12 hours (maximum: 1 tablet/24 hour)

Robitussin® DM, Robitussin® Sugar Free Cough: 2.5 mL every 4 hours (maximum: 6 doses/24 hours)

Vicks® Pediatric Formula 44E: 7.5 mL every 4 hours (maximum: 6 doses/24 hours)

6-12 years:

General dosing guidelines: Guaifenesin 100-200 mg and dextromethorphan 5-10 mg every 4 hours (maximum dose: Guaifenesin 1200 mg and dextromethorphan 60 mg per day)

Product-specific labeling:

Guaifenex® DM, Touro® DM: 1 tablet every 12 hours (maximum: 2 tablets/24 hours)

Robitussin® DM, Robitussin® Sugar Free Cough: 5 mL every 4 hours (maximum: 6 doses/24 hours)

Vicks® 44E: 7.5 mL every 4 hours (maximum: 6 doses/24 hours)

Vicks® Pediatric Formula 44E: 15 mL every 4 hours (maximum: 6 doses/24 hours)

Z-Cof LA™: $^{1}/_{2}$ tablet very 12 hours

≥12 years: Refer to adult dosing.

Administration: OralTake with water. Do not crush or chew extended release or long acting formulations.

Dietary ConsiderationsSafe Tussin® DM contains phenylalanine 4.2 mg/5 mL. Diabetic Tussin® DM and Diabetic Tussin® DM Maximum Strength contain phenylalanine 8.4 mg/5 mL. Vicks® 44E contains sodium 31 mg/15 mL; Vicks® Pediatric Formula 44E contains sodium 30 mg/15 mL. Mucinex® Children's Cough contains sodium 3 mg/5 mL

StorageStore at room temperature.

ContraindicationsHypersensitivity to guaifenesin, dextromethorphan, or any component of the formulation; use with or within 14 days of MAO inhibitor therapy

Allergy Considerations

- GuaiFENesin Allergy

Warnings/Precautions

Special populations:

- Debilitated patients: Use with caution in patients who are sedated, debilitated or confined to a supine position.

- Pediatrics: Use with caution in atopic children. Not for OTC use in children <2 years of age.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

- Self-medication (OTC use): When used for self medication (OTC), notify healthcare provider if symptoms do not improve within 7 days, or are accompanied by fever, rash, or persistent headache.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Refer to individual agents.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsDextromethorphan: **Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2D6 (weak)
Drug Interactions

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet:

Fenesin DM IR: Guaifenesin 400 mg and dextromethorphan hydrobromide 15 mg

Refenesen™ DM: Guaifenesin 400 mg and dextromethorphan hydrobromide 20 mg

Capsule, softgel:

Coricidin HBP® Chest Congestion and Cough: Guaifenesin 200 mg and dextromethorphan hydrobromide 10 mg

Elixir:

Duratuss DM®: Guaifenesin 225 mg and dextromethorphan hydrobromide 25 mg per 5 mL (480 mL) [contains sodium benzoate; grape flavor]

Simuc-DM: Guaifenesin 225 mg and dextromethorphan hydrobromide 25 mg per 5 mL (480 mL) [grape flavor]

Su-Tuss DM: Guaifenesin 200 mg and dextromethorphan hydrobromide 20 mg per 5 mL (480 mL) [fruit flavor]

Liquid: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (480 mL); guaifenesin 300 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL, 480 mL)

Diabetic Tussin® DM: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL) [alcohol free, sugar free, dye free; contains phenylalanine 8.4 mg/5 mL]

Diabetic Tussin® DM Maximum Strength: Guaifenesin 200 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL) [alcohol free, sugar free, dye free; contains phenylalanine 8.4 mg/5 mL]

Double Tussin DM: Guaifenesin 300 mg and dextromethorphan hydrobromide 200 mg per 5 mL (120 mL, 480 mL) [alcohol free, dye free, sugar free]

Gani-Tuss® DM NR: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (480 mL) [raspberry flavor]

Hydro-Tussin™ DM: Guaifenesin 200 mg and dextromethorphan hydrobromide 20 mg per 5 mL (480 mL) [alcohol free, sugar free; contains sodium benzoate] [DSC]

Kolephrin® GG/DM: Guaifenesin 150 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL) [alcohol free; cherry flavor]

Mucinex® Children’s Cough: Guaifenesin 100 mg and dextromethorphan hydrobromide 5 mg per 5 mL (120 mL) [contains sodium 3 mg/5 mL;

cherry flavor]

Safe Tussin® DM: Guaifenesin 100 mg and dextromethorphan hydrobromide 15 mg per 5 mL (120 mL) [contains phenylalanine 4.2 mg/5 mL, benzoic acid, and propylene glycol; orange and mint flavors]

Scot-Tussin® Senior: Guaifenesin 200 mg and dextromethorphan hydrobromide 15 mg per 5 mL (120 mL) [alcohol free, sodium free, sugar free]

Tussi-Organidin® DM NR: Guaifenesin 300 mg and dextromethorphan hydrobromide 10 mg per 5 mL (480 mL) [alcohol free, sugar free; contains sodium benzoate; grape flavor]

Tussi-Organidin® DM-S NR: Guaifenesin 300 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL) [alcohol free, sugar free; contains sodium benzoate; grape flavor]

Vicks® 44E: Guaifenesin 200 mg and dextromethorphan hydrobromide 20 mg per 15 mL (120 mL, 235 mL) [contains sodium 31 mg/15 mL, alcohol, sodium benzoate]

Vicks® Pediatric Formula 44E: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 15 mL (120 mL) [alcohol free; contains sodium 30 mg/15 mL, sodium benzoate; cherry flavor]

Liquid, oral [drops]:

Robitussin® DM Infant: Guaifenesin 100 mg and dextromethorphan hydrobromide 5 mg per 2.5 mL (30 mL) [alcohol free; contains sodium benzoate; fruit punch flavor] [DSC]

Syrup: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL, 480 mL)

Altarussin DM: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL, 240 mL, 480 mL, 3840 mL)

Cheracol® D: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL, 180 mL) [contains alcohol 4.75%, benzoic acid]

Cheracol® Plus: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL) [contains alcohol 4.75%, benzoic acid]

Genatuss DM®: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL)

Guiatuss® DM: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL, 480 mL, 3840 mL) [alcohol free; contains sodium benzoate]

Guaicon DM®: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (10 mL) [alcohol free]

Guaicon DMS®: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (10 mL) [alcohol free, sugar free]

Mintab DM: Guaifenesin 200 mg and dextromethorphan hydrobromide 10 mg per 5 mL (480 mL) [alcohol free, dye free; cherry vanilla flavor]

Phanatuss® DM: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL) [alcohol free, sugar free]

Robafen® DM: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL, 240 mL, 480 mL) [cherry flavor]

Robafen® DM Clear: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL)

Robitussin® Cough and Congestion: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL) [alcohol free; contains sodium benzoate]

Robitussin®-DM: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (5 mL, 120 mL, 340 mL, 360 mL) [alcohol free; contains sodium benzoate]

Robitussin® Sugar Free Cough: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL) [alcohol free, sugar free; contains sodium benzoate]

Silexin: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (45 mL) [alcohol free, sugar free)]

Siltussin DM: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL, 240 mL, 480 mL) [strawberry flavor]

Siltussin DM DAS: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL) [alcohol free, dye free, sugar free; strawberry flavor]

Tablet: Guaifenesin 1000 mg and dextromethorphan hydrobromide 60 mg; guaifenesin 1200 mg and dextromethorphan hydrobromide 60 mg

Silexin: Guaifenesin 100 mg and dextromethorphan hydrobromide 10 mg

Tablet, extended release: 800/30: Guaifenesin 800 mg and dextromethorphan hydrobromide 30 mg; 1200/20: Guaifenesin 1200 mg and dextromethorphan hydrobromide 20 mg

Guaifenex® DM: Guaifenesin 600 mg and dextromethorphan hydrobromide 30 mg [DSC]

Mucinex® DM, Respa-DM®: Guaifenesin 600 mg and dextromethorphan hydrobromide 30 mg

Mucophen® DM: Guaifenesin 1000 mg and dextromethorphan hydrobromide 60 mg

Mucinex® DM Maximum Strength: Guaifenesin 1200 mg and dextromethorphan hydrobromide 60 mg

Phlemex: Guaifenesin 1200 mg and dextromethorphan hydrobromide 20 mg

Touro® DM: Guaifenesin 575 mg and dextromethorphan hydrobromide 30 mg

Tablet, long-acting: Guaifenesin 1000 mg and dextromethorphan hydrobromide 60 mg

Z-Cof LA [scored]: Guaifenesin 650 mg and dextromethorphan hydrobromide 30 mg

Tablet, sustained release:

Allfen-DM: Guaifenesin 1000 mg and dextromethorphan hydrobromide 55 mg

Relacon LAX: Guaifenesin 835 mg and dextromethorphan hydrobromide 30 mg

Tussi-Bid®: Guaifenesin 1200 mg and dextromethorphan hydrobromide 60 mg

Tablet, timed release [scored]: Guaifenesin 1200 mg and dextromethorphan hydrobromide 60 mg

Guia-D: Guaifenesin 1000 mg and dextromethorphan hydrobromide 60 mg [dye free]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Elixir (Duratuss DM)

25-225 mg/5 mL (473): $145.78

Liquid (Guaifenesin-DM)

100-10 mg/5 mL (240): $17.26

Liquid (Tussi-Organidin DM-S NR)

100-10 mg/5 mL (120): $29.99

Tablet, 12-hour (Amibid DM)

30-600 mg (100): $19.99

Tablet, 12-hour (Bidex-DM)

30-800 mg (30): $29.99

Tablet, 12-hour (GFN 1200/DM 60)

1200-60 mg (30): $24.99

Tablet, 12-hour (Muco-Fen DM)

60-1000 mg (30): $35.83

Tablet, 12-hour (Touro DM)

30-575 mg (100): $115.99

Mechanism of Action

Guaifenesin is thought to act as an expectorant by irritating the gastric mucosa and stimulating respiratory tract secretions, thereby increasing respiratory fluid volumes and decreasing phlegm viscosity

Dextromethorphan is a chemical relative of morphine lacking narcotic properties except in overdose; controls cough by depressing the medullary cough center

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Dextromethorphan
- GuaiFENesin

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation

Index TermsDextromethorphan and Guaifenesin

International Brand NamesBre-A-Col (MX); Cheracol D (MX); Debequin C (MX); Dequin (MX); Dexometorfano-Guaifenesina (MX); Dimacol (MX); Exiadol (MX); Megal (MX); Robitussin DM (MX); Tukol D (MX)

Guaifenesin and Phenylephrine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Endal® may be confused with Depen®, Intal®

Entex® may be confused with Tenex®

Entex® LA brand name represents a different product in the U.S. than it does in Canada. In the U.S., Entex® LA contains guaifenesin and phenylephrine, while in Canada the product bearing this brand name contains guaifenesin and pseudoephedrine.

Pronunciation(gwye FEN e sin & fen il EF rin)

U.S. Brand NamesAldex™; Crantex LA; D-Phen 1000; Deconsal® II; Donatussin Drops; Duomax; Duratuss GP®; Duratuss®; ExeFen-PD; ExeTuss [DSC]; ExeTuss-GP; Fenesin PE IR; Genexa™ LA [DSC]; Gentex LA [DSC]; Gilphex TR®; Guaifed-PD®; Guaifed®; Guaiphen-D; Guaiphen-D 1200; Guaiphen-PD; Liquibid-D®; MyDex; Nasex-G; Nexphen PD; norel® EX; Pendex; PhenaVent™ D [DSC]; PhenaVent™ LA [DSC]; PhenaVent™ Ped [DSC]; PhenaVent™ [DSC]; Prolex®-D [DSC]; Prolex®-PD [DSC]; Refenesen™ PE [OTC]; Rescon GG [OTC]; Respa® PE [DSC]; Sil-Tex; Simuc [DSC]; Sina-12X; SINUvent® PE; XPECT-PE™ [DSC]

Pharmacologic CategoryDecongestant; Expectorant

Use: Labeled IndicationsTemporary relief of nasal congestion, sinusitis, rhinitis, and hay fever; temporary relief of cough associated with upper respiratory tract conditions, especially when associated with dry, nonproductive cough

Dosing: AdultsExpectorant/decongestant: Oral:

Aldex™, Crantex LA, Duomax, ExeTuss, ExeTuss-GP, Gentex LA, XPECT-PE™, Liquibid-D®, PhenaVent™ D: One tablet every 12 hours

Deconsal® II: 1-2 capsules every 12 hours; maximum: 3 capsules/24 hours

Sil-Tex: 5-10 mL every 4-6 hours; maximum: 40 mL/24 hours

Guaifed-PD®, PhenaVent™ Ped: 1-2 capsules every 12 hours

Guaifed®, PhenaVent™, PhenaVent™ LA: One capsule every 12 hours; maximum: 2 capsules/24 hours

ExeFen PD, Prolex®-D, Prolex®-PD: 1-2 tablets every 12 hours

SINUvent® PE: Two tablets every 12 hours

Rescon GG: 10 mL every 4-6 hours; maximum: 40 mL/24 hours

Sina-12X suspension: 5-10 mL every 12 hours

Sina-12X tablet: 1-2 tablets every 12 hours; maximum: 4 tablets/24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricExpectorant/decongestant: Oral:

Children 3-6 months (Donatussin): 0.3-0.6 mL; may repeat every 4-6 hours as needed; maximum 4 doses/24 hours

Children 6 months to 1 year (Donatussin): 0.6-1 mL; may repeat every 4-6 hours as needed; maximum: 4 doses/24 hours

Children 1-2 years (Donatussin): 1-2 mL; may repeat every 4-6 hours as needed; maximum: 4 doses/24 hours

Children 2-6 years:

Rescon GG, Sil-Tex: 2.5 mL every 4-6 hours; maximum 10 mL/24 hours

Sina-12X suspension: 2.5-5 mL every 12 hours

Children 6-12 years:

Aldex™, Crantex LA, Duomax, ExeTuss, Gentex LA, Liquibid-D®, PhenaVent™ D, Sina-12X tablet: One-half tablet every 12 hours; maximum: 1 tablet/24 hours

Deconsal® II: One capsule daily

Rescon GG: 5 mL every 4-6 hours; maximum: 20 mL/24 hours

ExeFen PD, Prolex®-D, Prolex®-PD: One-half to 1 tablet every 12 hours

Guaifed-PD®, PhenaVent™ Ped: One capsule every 12 hours

SINUvent® PE: One tablet every 12 hours; maximum: 2 tablets/24 hours

Sina-12X suspension: Refer to adult dosing.

Children ≥12 years:

Aldex™, Crantex LA, Deconsal® II, Duomax, ExeFen PD, ExeTuss, ExeTuss-GP, Gentex LA, Guaifed®, Guaifed-PD®, Liquibid-D®, PhenaVent™, PhenaVent™ D, PhenaVent™ LA, PhenaVent™ Ped, Prolex®-D, Prolex®-PD, Rescon GG, Sil-Tex, Sina-12X, SINUvent® PE: Refer to adult dosing

Administration: OralTablets and capsules should not be crushed or chewed. Capsules should not be opened.

Dietary ConsiderationsMay be taken with or without food. Taking with food, water or milk may help decrease gastric irritation.

ContraindicationsHypersensitivity to guaifenesin, phenylephrine, sympathomimetic amines, or any component of the formulation; severe hypertension; severe cardiovascular disease; use with or within 2 weeks of discontinuing MAO inhibitor

Allergy Considerations

- GuaiFENesin Allergy

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

Dosage form specific issues:

- Tartrazine: Some products may contain tartrazine.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination. See individual agents.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsPhenylephrine is excreted in breast milk; excretion of guaifenesin is unknown. See individual agents.

Adverse ReactionsSee individual agents.

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet:

Fenesin PE IR, Refenesen™ PE: Guaifenesin 400 mg and phenylephrine hydrochloride 10 mg

Capsule:

Nexphen PD: Guaifenesin 200 mg and phenylephrine hydrochloride 7 mg

Capsule, variable release:

Deconsal® II: Guaifenesin 375 mg [immediate release] and phenylephrine hydrochloride 20 mg [extended release] [contains tartrazine]

Genexa™ LA [DSC], PhenaVent™ LA [DSC]: Guaifenesin 400 mg [immediate release] and phenylephrine hydrochloride 30 mg [extended release]

Guaifed®, PhenaVent™ [DSC]: Guaifenesin 400 mg [immediate release] and phenylephrine hydrochloride 15 mg [extended release]

  - Guaifed-PD®, PhenaVent™ Ped [DSC]: Guaifenesin 200 mg [immediate release] and phenylephrine hydrochloride 7.5 mg [extended release]
- Liquid: Guaifenesin 100 mg and phenylephrine hydrochloride 7.5 mg per 5 mL (480 mL)
  - Sil-Tex: Guaifenesin 100 mg and phenylephrine hydrochloride 7.5 mg per 5 mL (480 mL) [alcohol free, dye-free, sugar free; punch flavor]
  - Rescon GG: Guaifenesin 100 mg and phenylephrine hydrochloride 5 mg per 5 mL (120 mL, 480 mL) [cherry orange-pineapple flavor]
- Liquid [drops]:
  - Donatussin: Guaifenesin 20 mg and phenylephrine hydrochloride 1.5 mg (30 mL) [raspberry flavor]
- Suspension:
  - Sina-12X: Guaifenesin 100 mg and phenylephrine tannate 5 mg per 5 mL (120 mL) [contains benzoic acid; grape flavor]
- Tablet: Guaifenesin 900 mg and phenylephrine hydrochloride 30 mg
  - Sina-12X: Guaifenesin 200 mg and phenylephrine tannate 25 mg
- Tablet, extended release: Guaifenesin 600 mg and phenylephrine hydrochloride 20 mg; guaifenesin 600 mg and phenylephrine hydrochloride 40 mg; guaifenesin 1200 mg and phenylephrine hydrochloride 40 mg
  - Aldex™: Guaifenesin 650 mg and phenylephrine hydrochloride 25 mg
  - D-Phen: Guaifenesin 1000 mg and phenylephrine hydrochloride 30 mg
  - Duomax: Guaifenesin 1200 mg and phenylephrine hydrochloride 40 mg [Duomatrix release]
  - ExeFen-PD: Guaifenesin 600 mg and phenylephrine hydrochloride 10 mg
  - Gentex LA: Guaifenesin 650 mg and phenylephrine hydrochloride 23.75 mg [DSC]
  - PhenaVent™ D: Guaifenesin 1200 mg and phenylephrine hydrochloride 40 mg [DSC]
  - Simuc: Guaifenesin 900 mg and phenylephrine hydrochloride 25 mg [DSC]
  - SINUvent® PE: Guaifenesin 600 mg and phenylephrine hydrochloride 15 mg
- Tablet, long acting: Guaifenesin 900 mg and phenylephrine hydrochloride 25 mg; guaifenesin 1200 mg and phenylephrine hydrochloride 25 mg
- Tablet, prolonged release: Guaifenesin 600 mg and phenylephrine hydrochloride 15 mg
  - Respa® PE: Guaifenesin 600 mg and phenylephrine hydrochloride 18 mg [DSC]
- Tablet, sustained release: Guaifenesin 600 mg and phenylephrine hydrochloride 30 mg; guaifenesin 1200 mg and phenylephrine hydrochloride 30 mg
  - Crantex LA: Guaifenesin 600 mg and phenylephrine hydrochloride 30 mg [dye-free]
  - Duratuss®, ExeTuss [DSC]: Guaifenesin 900 mg and phenylephrine hydrochloride 25 mg
  - Duratuss GP®, ExeTuss-GP: Guaifenesin 1200 mg and phenylephrine hydrochloride 25 mg
  - MyDex: Guaifenesin 900 mg and phenylephrine hydrochloride 30 mg
  - Nasex-G: Guaifenesin 835 mg and phenylephrine hydrochloride 25 mg
  - Pendex, Prolex®-PD: Guaifenesin 600 mg and phenylephrine hydrochloride 10 mg
  - Prolex™-D: Guaifenesin 600 mg and phenylephrine hydrochloride 20 mg [dye-free] [DSC]
  - XPECT-PE™: Guaifenesin 1200 mg and phenylephrine hydrochloride 25 mg [DSC]
- Tablet, timed release:
  - Gilphex TR®: Guaifenesin 600 mg and phenylephrine hydrochloride 25 mg [sugar free, dye free; scored]
  - Guaiphen-D: Guaifenesin 600 mg and phenylephrine hydrochloride 40 mg
  - Guaiphen-D 1200: Guaifenesin 1200 mg and phenylephrine hydrochloride 40 mg
  - Guaiphen-PD: Guaifenesin 275 mg and phenylephrine hydrochloride 25 mg
- Tablet, variable release:
  - Liquibid-D®: Guaifenesin 400 mg and phenylephrine 10 mg [immediate release] and guaifenesin 800 mg and phenylephrine hydrochloride 30 mg [sustained release]
  - norel® EX: Guaifenesin 400 mg [immediate release] and guaifenesin 400 mg and phenylephrine hydrochloride 40 mg [extended release]

Generic AvailableYes: Excludes suspension

Pricing: U.S. (www.drugstore.com)

Capsule, 12-hour (Deconsal II)

20-375 mg (30): $57.58

Tablet, 12-hour (Duratuss GP)

25-1200 mg (30): $59.99

Tablet, 12-hour (GFN 600/Phenylephrine 20)

600-20 mg (30): $15.99

Tablet, 12-hour (Liquibid-D)

40-600 mg (30): $22.99

Tablet, 12-hour (Liquibid-PD)

25-275 mg (60): $39.67

Tablets (Sina-12X)

25-200 mg (30): $74.06

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Guaifenesin: No significant effects or complications reported

Phenylephrine: Up to 10% of patients could experience tachycardia, palpitations, and xerostomia (normal salivary flow resumes upon discontinuation); use vasoconstrictor with caution

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusGuaifenesin may cause drowsiness; phenylephrine may cause anxiety or restlessness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation or lessen the effects of anxiolytics depending on whether the effects of guaifenesin or phenylephrine predominate; concurrent use with MAO inhibitors may result in hypertensive crisis; avoid combination

Index TermsGuaifenesin and Phenylephrine Tannate; Phenylephrine Hydrochloride and Guaifenesin

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Guaifenesin and Pseudoephedrine

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Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Entex® may be confused with Tenex®

Entex® LA brand name represents a different product in the U.S. than it does in Canada. In the U.S., Entex® LA contains guaifenesin and phenylephrine, while in Canada the product bearing this brand name contains guaifenesin and pseudoephedrine.

Profen II® may be confused with Profen II DM®, Profen Forte®, Profen Forte™ DM

Profen Forte® may be confused with Profen II®, Profen II DM®, Profen Forte™ DM

Pronunciation(gwye FEN e sin & soo doe e FED rin)
U.S. Brand NamesAmbifed-G; Congestac® [OTC]; Dynex [DSC]; Entex® PSE; Eudal®-SR; ExeFen; Guaifenex® GP [DSC]; Guaifenex® PSE [DSC]; Guaimax-D®; Levall G; Maxifed-G®; Maxifed®; Medent LD; Mucinex® D Maximum Strength [OTC]; Mucinex®-D [OTC]; Nasatab® LA; Profen II® [DSC]; Pseudo GG TR; Pseudo Max; Pseudovent™ 400 [DSC]; Pseudovent™ [DSC]; Pseudovent™-Ped [DSC]; Refenesen Plus [OTC]; Respaire®-120 SR [DSC]; Respaire®-60 SR [DSC]; Respa®-1st; Rutuss Jr; Sinutab® Non-Drying [OTC]; SudaTex-G; Touro LA®
Canadian Brand NamesContac® Cold-Chest Congestion, Non Drowsy, Regular Strength; Entex® LA; Novahistex® Expectorant with Decongestant
Pharmacologic CategoryAlpha/Beta Agonist; Expectorant
Use: Labeled IndicationsTemporary relief of nasal congestion and to help loosen phlegm and thin bronchial secretions in the treatment of cough
Dosing: Adults**Expectorant/decongestant:** Oral:

Ambifed-G, Dynex, Entex® PSE, Eudal®-SR, Guaifenex® GP, Guaifenex® PSE 120, Guaimax-D®, Levall G, Mucinex®-D 1200/120, Nasatab® LA, Pseudovent™, Respaire®-120 SR, Touro LA: One tablet or capsule every 12 hours (maximum: 2 tablets or capsules in 24 hours)

Congestac®: One caplet every 4-6 hours (maximum: 4 caplets in 24 hours)

Guaifenex® PSE 60, Maxifed-G®, Mucinex®-D 600/60, Pseudovent™-Ped, Respaire®-60 SR: 1-2 tablets or capsules every 12 hours (maximum: 4 tablets or capsules/24 hours)

Guaifenex® PSE 80, PanMist®-LA: One tablet every twelve hours (maximum: 3 tablets/24 hours)

Guaifenex™ RX: 1-2 of the AM tablets every morning and 1-2 of the PM tablets 12 hours following morning dose

Maxifed®: One to $1^{1}/_{2}$ tablets every 12 hours (maximum: 3 tablets/24 hours)

Dosing: ElderlyRefer to adult dosing; use with caution.
Dosing: Pediatric**Expectorant/decongestant:** Oral:

Children 2-6 years:

Guaifenex® PSE 60: One-half tablet every 12 hours (maximum: 1 tablet/12 hours)

Maxifed-G®: One-third to $^{1}/_{2}$ tablet every 12 hours (maximum: 1 tablet/12 hours)

Children 6-12 years:

Ambifed-G, Dynex, Eudal-SR®, Guaimax-D®, Guaifenex® PSE 80, Guaifenex® PSE 120, Maxifed®, Nasatab® LA: One-half caplet or tablet every 12 hours (maximum: 1 tablet/24 hours)

Congestac®: One-half caplet every 4-6 hours (maximum: 2 caplets/24 hours)

Guaifenex® PSE 60, Pseudovent™-Ped, Respaire®-60 SR: One tablet or capsule every 12 hours (maximum: 2 tablets or capsules every 24 hours)

Levall G: One capsule every 24 hours

Maxifed-G®: One-half to 1 tablet every 12 hours (maximum: 2 tablets/24 hours)

>12 years: Refer to adult dosing.

Administration: OralOral: Do not open variable release capsules. Long acting formulations should not be crushed or chewed. May interfere with sleep; administering some products a few hours before bedtime may help minimize insomnia. Take with full glass of water.
ContraindicationsHypersensitivity to guaifenesin, pseudoephedrine, sympathomimetic amines, or any component of the formulation; use with or within 14 days of MAO inhibitor; severe hypertension or cardiovascular disease
Allergy Considerations

- GuaiFENesin Allergy

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.
- Self-medication (OTC use): When used for self-medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever, rash, or persistent headache. Discontinue and contact healthcare provider if nervousness, dizziness, or sleeplessness occur.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination. Refer to individual monographs.
LactationEnters breast milk/contraindicated (by some manufacturers)
Breast-Feeding ConsiderationsExcretion of guaifenesin into breast milk is unknown. Pseudoephedrine is excreted in breast milk. The use of this combination while breast-feeding is contraindicated by some manufacturers. Also refer to individual monographs.
Adverse ReactionsSee individual agents.
Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet:

Congestac®, Refenesen Plus: Guaifenesin 400 mg and pseudoephedrine hydrochloride 60 mg

Caplet, long acting:

Touro LA®: Guaifenesin 500 mg and pseudoephedrine hydrochloride 120 mg

Caplet, prolonged release:

Ambifed-G: Guaifenesin 1000 mg and pseudoephedrine hydrochloride 60 mg

Capsule, extended release:

Respaire®-60 SR: Guaifenesin 200 mg and pseudoephedrine hydrochloride 60 mg [DSC]

Respaire®-120 SR: Guaifenesin 250 mg and pseudoephedrine hydrochloride 120 mg [DSC]

Capsule, liquicap:

Sinutab® Non-Drying: Guaifenesin 200 mg and pseudoephedrine hydrochloride 30 mg

Capsule, variable release:

Entex® PSE: Guaifenesin 400 mg [immediate release] and pseudoephedrine hydrochloride 120 mg [extended release]

Levall G: Guaifenesin 400 mg [immediate release] and pseudoephedrine hydrochloride 90 mg [extended release]

Pseudovent™: Guaifenesin 250 mg [immediate release] and pseudoephedrine hydrochloride 120 mg [prolonged release] [DSC]

Pseudovent™-Ped: Guaifenesin 300 mg [immediate release] and pseudoephedrine hydrochloride 60 mg [prolonged release] [DSC]

Pseudovent™ 400: Guaifenesin 400 mg [immediate release] and pseudoephedrine hydrochloride 120 mg [extended release] [DSC]

Syrup: Guaifenesin 200 mg and pseudoephedrine hydrochloride 40 mg per 5 mL (480 mL)

Tablet:

ExeFen: Guaifenesin 780 mg and pseudoephedrine hydrochloride 80 mg

Rutuss Jr: 600/45: Guaifenesin 600 mg and pseudoephedrine hydrochloride 45 mg

Tablet, extended release:

Guaifenesin 550 mg and pseudoephedrine hydrochloride 60 mg

Guaifenesin 595 mg and pseudoephedrine hydrochloride 48 mg

Guaifenesin 600 mg and pseudoephedrine hydrochloride 120 mg

Guaifenesin 1200 mg and pseudoephedrine hydrochloride 50 mg

Guaifenesin 1200 mg and pseudoephedrine hydrochloride 75 mg

Guaifenesin 1200 mg and pseudoephedrine hydrochloride 120 mg

Guaifenex® GP: Guaifenesin 1200 mg and pseudoephedrine hydrochloride 120 mg [dye free] [DSC]

Guaifenex® PSE 60: Guaifenesin 600 mg and pseudoephedrine hydrochloride 60 mg [DSC]

Guaifenex® PSE 80: Guaifenesin 800 mg and pseudoephedrine hydrochloride 80 mg [DSC]

Guaifenex® PSE 85: Guaifenesin 795 mg and pseudoephedrine hydrochloride 85 mg [DSC]

Guaifenex® PSE 120: Guaifenesin 600 mg and pseudoephedrine hydrochloride 120 mg [dye free] [DSC]

Guaimax-D®: Guaifenesin 600 mg and pseudoephedrine hydrochloride 120 mg

Maxifed®: Guaifenesin 780 mg and pseudoephedrine hydrochloride 80 mg

Maxifed-G®: Guaifenesin 580 mg and pseudoephedrine hydrochloride 60 mg

Mucinex®-D 600/60: Guaifenesin 600 mg and pseudoephedrine hydrochloride 60 mg

Mucinex® D Maximum Strength [OTC]: Guaifenesin 1200 mg and pseudoephedrine hydrochloride 120 mg

Profen II®: Guaifenesin 800 mg and pseudoephedrine hydrochloride 45 mg [DSC]

Pseudo Max: Guaifenesin 700 mg and pseudoephedrine hydrochloride 80 mg

Tablet, long acting:

Dynex: Guaifenesin 1200 mg and pseudoephedrine hydrochloride 90 mg [DSC]

Medent LD: Guaifenesin 800 mg and pseudoephedrine hydrochloride 60 mg [dye free; scored]

Tablet, sustained release:

Nasatab® LA: Guaifenesin 500 mg and pseudoephedrine hydrochloride 120 mg

Respa®-1st: Guaifenesin 600 mg and pseudoephedrine hydrochloride 58 mg

SudaTex-G: Guaifenesin 580 mg and pseudoephedrine hydrochloride 60 mg [dye free; scored]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsule, 12-hour (Pseudovent 400)

120-400 mg (30): $37.99

Capsule, controlled release (PSE-GG CR)

120-250 mg (20): $18.99

Capsule, controlled release (Pseudovent Ped)

300-60 mg (30): $14.99

Tablet, 12-hour (Medent LD)

60-800 mg (30): $26.99

Tablet, 12-hour (Mucinex D)

120-1200 mg (24): $28.21

Tablet, 12-hour (Profen II)

45-800 mg (30): $19.81

Tablet, 12-hour (Pseudoephedrine-Guaifenesin)

90-800 mg (30): $19.99

Tablet, 12-hour (Ru-Tuss Jr)

45-600 mg (30): $18.04

Tablets (Zephrex)

60-400 mg (30): $25.99

Pharmacodynamics/KineticsSee individual agents.

Related Information

- GuaiFENesin
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Guaifenesin: No significant effects or complications reported

Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusGuaifenesin may cause drowsiness; pseudoephedrine may cause anxiety or restlessness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation or lessen the effects of anxiolytics depending on whether the effects of guaifenesin or pseudoephedrine predominate; concurrent use with MAO inhibitors may result in hypertensive crisis; avoid combination

Index TermsPseudoephedrine and Guaifenesin

International Brand NamesActifed Chesty Syrup (NZ); Contac Cold-Chest Congestion, Non Drowsy, Regular Strength (CA); Entex LA (CA); Guaifenex PSE 60 (HK); Novahistex Expectorant with Decongestant (CA)

Guaifenesin, Dextromethorphan, and Phenylephrine

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English

English

Jump To Field (Select Field Name)

Pronunciation(gwye FEN e sin, deks troe meth OR fan, & fen il EF rin)

U.S. Brand NamesAnextuss; Certuss-D®; Dacex-DM; Dexcon-PE; Duraphen™ DM [DSC]; Duraphen™ Forte; Duraphen™ II DM; Dynatuss-EX; ExeCof; ExeTuss-DM; Giltuss Pediatric®; Giltuss TR®; Giltuss®; Guaifen™ DM [DSC]; Maxiphen DM; Robitussin® Cold and Cough CF [OTC]; Robitussin® Pediatric Cold and Cough CF [OTC]; SINUtuss® DM; TriTuss®; TriTuss® ER; Tusso™-DMR

Pharmacologic Category[Antitussive](); [Decongestant]()

Use: Labeled IndicationsSymptomatic relief of dry nonproductive coughs and upper respiratory symptoms associated with hay fever, colds, or the flu

Dosing: Adults

Also refer to specific product labeling.

Oral:

Certuss-D®, Duraphen™ DM, Duraphen™ Forte, Maxiphen DM: One tablet every 12 hours, not to exceed 2 tablets/24 hours

Duraphen™ II DM: 1-$1^{1}/_{2}$ tablets twice daily, not to exceed 3 tablets/24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Also refer to specific product labeling.

Children 6-12 years: Oral: Certuss-D®, Duraphen™ DM, Duraphen™ Forte, Duraphen™ II DM, Maxiphen DM: One-half tablet every 12 hours, not to exceed 1 tablet/24 hours

Children ≥12 years: Refer to adult dosing.

Administration: OralLong-acting tablet formulations may be broken in half, but should not be crushed or chewed. Administer with a full glass of water.

Dietary ConsiderationsGiltuss® Liquid contains phenylalanine 3.75 mg/5 mL

StorageRefer to individual product labeling.

Certuss-D, Duraphen™ DM, Duraphen™ Forte, Duraphen™ II DM, Maxiphen DM: Store at room temperature.

ContraindicationsHypersensitivity to guaifenesin, dextromethorphan, phenylephrine, sympathetic amines, or any component of the formulation; severe hypertension; coronary disease; prostatic hypertrophy; breast-feeding; use with or within 14 days of MAO inhibitors

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- Debilitated patients: Use with caution in debilitated, sedated and/or patients confined to the supine position.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Use with caution in atopic children.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing. Re-evaluate if cough persists >7 days.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. See individual agents.

LactationEnters breast milk/ not recommended

Breast-Feeding ConsiderationsPhenylephrine is excreted in breast milk. See individual agents. Use of some products is contraindicated by manufacturers.

Adverse Reactions Reactions which follow have been reported with the combination product; see individual drug monographs for additional adverse reactions that may be expected from each agent.

Cardiovascular: Cardiovascular collapse, palpitation, tachycardia

Central nervous system: Anxiety, CNS depression, convulsions, dizziness, drowsiness, excitability increased, fear, hallucinations, headache, insomnia, irritability increased, lightheadedness, nervousness

Gastrointestinal: Nausea, vomiting

Neuromuscular & skeletal: Tremor, weakness

Respiratory: Respiratory difficulties

Metabolism/Transport EffectsDextromethorphan: **Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Test InteractionsGuaifenesin: Possible color interference with determination of 5-HIAA and VMA; discontinue for 48 hours prior to test

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet:

Dexcon-PE: Guaifenesin 550 mg, dextromethorphan hydrobromide 25 mg, and phenylephrine hydrochloride 20 mg

Caplet, extended release:

TriTuss®-ER: Guaifenesin 600 mg, dextromethorphan hydrobromide 30 mg, and phenylephrine hydrochloride 10 mg

Capsule:

Tusso™-DMR: Guaifenesin 288 mg, dextromethorphan hydrobromide 14 mg, and phenylephrine hydrochloride 7 mg [gluten free, sodium free, sugar free]

Liquid:

Giltuss®: Guaifenesin 300 mg, dextromethorphan hydrobromide 15 mg, and phenylephrine hydrochloride 10 mg per 5 mL (237 mL) [alcohol free, sugar free; contains phenylalanine 3.75 mg per 5 mL; natural grape flavor]

Giltuss Pediatric®: Guaifenesin 50 mg, dextromethorphan hydrobromide 5 mg, and phenylephrine hydrochloride 2.5 mg per mL (60 mL) [alcohol free, dye free, sugar free; grape flavor]

Liquid, oral [drops]: Guaifenesin 50 mg, dextromethorphan hydrobromide 5 mg, and phenylephrine 2.5 mg per mL (30 mL) [alcohol free; cherry flavor]

Robitussin® Pediatric Cold and Cough CF: Guaifenesin 100 mg, dextromethorphan hydrobromide 5 mg, and phenylephrine hydrochloride 2.5 mg per 2.5 mL (30 mL) [alcohol free; contains propylene glycol and sodium benzoate; fruit punch flavor]

Syrup: Guaifenesin 200 mg, dextromethorphan hydrobromide 30 mg, and phenylephrine hydrochloride 10 mg (473 mL) [cherry flavor]

Dacex-DM: Guaifenesin 175 mg, dextromethorphan hydrobromide 25 mg, and phenylephrine hydrochloride 12.5 mg per 5 mL (480 mL) [strawberry flavor]

Dynatuss-Ex: Guaifenesin 200 mg, dextromethorphan hydrobromide 30 mg, and phenylephrine hydrochloride 10 mg (473 mL) [alcohol free; cherry vanilla flavor]

Robitussin® Cold and Cough CF: Guaifenesin 100 mg, dextromethorphan hydrobromide 10 mg, and phenylephrine hydrochloride 5 mg per 5 mL (120 mL, 240 mL, 355 mL) [alcohol free; contains sodium benzoate and propylene glycol]

TriTuss®: Guaifenesin 175 mg, dextromethorphan hydrobromide 25 mg, and phenylephrine hydrochloride 12.5 mg per 5 mL (480 mL) [alcohol free, sugar free]

Tablet [scored]:

SINUtuss™ DM: Guaifenesin 600 mg, dextromethorphan hydrobromide 30 mg, and phenylephrine hydrochloride 15 mg

Tablet, extended release [scored]:

Duraphen™ II DM: Guaifenesin 800 mg, dextromethorphan hydrobromide 20 mg, and phenylephrine hydrochloride 20 mg [dye free]

Duraphen™ Forte: Guaifenesin 1200 mg, dextromethorphan hydrobromide 30 mg, and phenylephrine hydrochloride 30 mg [dye free, sugar free]

Tablet, prolonged release [scored]:

Maxiphen DM: Guaifenesin 1000 mg, dextromethorphan hydrobromide 60 mg, and phenylephrine hydrochloride 40 mg [dye free]

Tablet, sustained release: Guaifenesin 600 mg, dextromethorphan hydrobromide 60 mg, and phenylephrine hydrochloride 40 mg

Anextuss: Guaifenesin 600 mg, dextromethorphan hydrobromide 60 mg, and phenylephrine hydrochloride 40 mg

Certuss-D® [scored]: Guaifenesin 600 mg, dextromethorphan hydrobromide 60 mg, and phenylephrine hydrochloride 40 mg

Duraphen™ DM [scored]: Guaifenesin 1200 mg, dextromethorphan hydrobromide 20 mg, and phenylephrine hydrochloride 40 mg [dye free] [DSC]

ExeCof: Guaifenesin 100 mg, dextromethorphan hydrobromide 60 mg, and phenylephrine hydrochloride 40 mg [dye free; scored]

ExeTuss-DM: Guaifenesin 600 mg, dextromethorphan hydrobromide 25 mg, and phenylephrine hydrochloride 20 mg

Guaifen™ DM [scored]: Guaifenesin 1200 mg, dextromethorphan hydrobromide 20 mg, and phenylephrine hydrochloride 40 mg [dye free] [DSC]

Tablet, timed release [scored]:

Giltuss TR®: Guaifenesin 600 mg, dextromethorphan hydrobromide 30 mg, and phenylephrine hydrochloride 20 mg [dye free, sugar free]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, 12-hour (Duraphen Forte)

30-30-1200 mg (100): $132.57

Tablet, 12-hour (Duraphen II DM)

20-20-800 mg (30): $41.76

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Dextromethorphan
- GuaiFENesin
- Phenylephrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Dextromethorphan: No significant effects or complications reported

Guaifenesin: No significant effects or complications reported

Phenylephrine: Up to 10% of patients could experience tachycardia, palpitations, and xerostomia (normal salivary flow resumes upon discontinuation); use vasoconstrictor with caution

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause anxiety, dizziness, drowsiness, hallucinations, insomnia, irritability, or nervousness

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment. Concurrent use with psychotropic agents may produce additive CNS depression.

Index TermsGuaifenesin, Dextromethorphan Hydrobromide, and Phenylephrine Hydrochloride; Phenylephrine Hydrochloride, Guaifenesin, and Dextromethorphan Hydrobromide

Guaifenesin, Pseudoephedrine, and Codeine

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Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(gwye FEN e sin, soo doe e FED rin, & KOE deen)

U.S. Brand NamesGuiatuss DAC; Mytussin® DAC; Nucofed® Expectorant [DSC]; Nucofed® Pediatric Expectorant [DSC]

Canadian Brand NamesBenylin® 3.3 mg-D-E; Calmylin with Codeine

Pharmacologic CategoryAntitussive/Decongestant/Expectorant

Use: Labeled IndicationsTemporarily relieves nasal congestion and controls cough associated with upper respiratory infections and related conditions (common cold, sinusitis, bronchitis, influenza)

Dosing: Adults **Expectorant/decongestant/cough suppressant:** Oral:

Guaituss DAC: 10 mL every 4 hours (maximum 40 mL/24 hours)

Nucofed® Pediatric: 10 mL every 6 hours (maximum 40 mL/24 hours)

Nucofed®: 5 mL every 6 hours (maximum 20 mL/24 hours)

Dosing: Elderly Refer to adult dosing; use with caution.

Dosing: Pediatric **Expectorant/decongestant/cough suppressant:** Oral:

Children 2-6 years:

Nucofed® Pediatric: 2.5 mL every 6 hours (maximum 10 mL/24 hours)

Nucofed®: 1.25 mL every 6 hours (maximum 5 mL/24 hours)

Children 6-12 years:

Guaituss DAC: 5 mL every 4 hours (maximum 20 mL/24 hours)

Nucofed® Pediatric: 5 mL every 6 hours (maximum 20 mL/24 hours)

Nucofed®: 2.5 mL every 6 hours (maximum 10 mL/24hours)

Children >12 years: Refer to adult dosing.

Restrictions C-III; C-V

Contraindications Hypersensitivity to guaifenesin, pseudoephedrine, codeine, or any component of the formulation; use with or within 14 days of MAO inhibitor therapy

Allergy Considerations

- GuaiFENesin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).

- Diabetes: Use with caution in patients with diabetes mellitus.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with pulmonary disease or decrease ventilatory function; dose-related respiratory depression occurs.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

- Ulcerative colitis: Use with caution in patients with chronic ulcerative colitis.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Safety and efficacy of this combination have not been established in children <2 years of age.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing. Use caution with persistent cough or chronic cough (as with smoking, asthma, chronic bronchitis, emphysema) or cough accompanied by excessive phlegm. Re-evaluate if cough persists >7 days.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. See individual agents
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsPseudoephedrine and codeine are excreted in breast milk. Excretion of guaifenesin is not known. Also see individual agents.
Adverse ReactionsSee individual agents.
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Test InteractionsSee individual agents.
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Syrup:

Guiatuss DAC: Guaifenesin 100 mg, pseudoephedrine hydrochloride 30 mg, and codeine phosphate 10 mg per 5 mL (480 mL)

Mytussin® DAC: Guaifenesin 100 mg, pseudoephedrine hydrochloride 30 mg, and codeine phosphate 10 mg per 5 mL (120 mL, 480 mL) [sugar free; contains alcohol 1.7%; strawberry-raspberry flavor]

Nucofed® Expectorant: Guaifenesin 200 mg, pseudoephedrine hydrochloride 60 mg, and codeine phosphate 20 mg per 5 mL (480 mL) [contains alcohol 12.5%; cherry flavor] [DSC]

Nucofed® Pediatric Expectorant: Guaifenesin 100 mg, pseudoephedrine hydrochloride 30 mg, and codeine phosphate 10 mg per 5 mL (480 mL) [contains alcohol 6%; strawberry flavor] [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Mytussin DAC)

30-10-100 mg/5 mL (120): $10.07

Solution (Nucofed Pediatric Expectorant)

30-10-100 mg/5 mL (120): $19.00

Syrup (Nucofed Expectorant)

60-20-200 mg/5 mL (120): $25.99

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Codeine
- GuaiFENesin
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Codeine: Xerostomia (normal salivary flow resumes upon discontinuation).

Guaifenesin: No significant effects or complications reported

Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusGuaifenesin may cause drowsiness or dizziness; pseudoephedrine may cause anxiety or restlessness; codeine may cause drowsiness; may cause euphoria, confusion, insomnia, hallucinations, or depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation or lessen the effects of anxiolytics depending on whether the effects of guaifenesin/codeine or pseudoephedrine predominate; concurrent use with MAO inhibitors may result in hypertensive crisis; avoid combination

Index TermsCodeine, Guaifenesin, and Pseudoephedrine; Pseudoephedrine, Guaifenesin, and Codeine

International Brand NamesBenylin 3.3 mg-D-E (CA); Calmylin with Codeine (CA)

Guaifenesin, Pseudoephedrine, and Dextromethorphan

Lexi-Drugs Online

English

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Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

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Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

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It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Profen II DM® may be confused with Profen II®, Profen Forte®, Profen Forte™ DM

Profen Forte™ DM may be confused with Profen II®, Profen II DM®, Profen Forte®

Pronunciation(gwye FEN e sin, soo doe e FED rin, & deks troe meth OR fan)

U.S. Brand NamesAmbifed-G DM; Coldmist DM [DSC]; ExeFen-DMX; Maxifed DM; Maxifed DMX; Medent-DM; Profen Forte™ DM; Profen II DM®; Pseudo Max DMX; Pseudovent™ DM [DSC]; Relacon-DM NR; Robitussin® Cough and Cold CF [OTC]; Robitussin® Cough and Cold Infant CF [OTC]; Robitussin® Cough and Cold [OTC]; Ru-Tuss DM; SudaTex-DM; Touro® CC; Touro® CC-LD; Tri-Vent™ DM [DSC]; Trikof-D® [DSC]; Tusnel Liquid®; Tusnel Pediatric®; Tusnel-DM Pediatric®; Z-Cof™ 12DM

Canadian Brand NamesBalminil DM + Decongestant + Expectorant; Benylin® DM-D-E; Koffex DM + Decongestant + Expectorant; Novahistex® DM Decongestant Expectorant; Novahistine® DM Decongestant Expectorant; Robitussin® Cough & Cold®

Pharmacologic CategoryAntitussive/Decongestant/Expectorant

Use: Labeled IndicationsTemporarily relieves nasal congestion and controls cough due to minor throat and bronchial irritation; helps loosen phlegm and thin bronchial secretions to make coughs more productive

Dosing: AdultsExpectorant/decongestant/cough suppressant: Oral:

Ambifed-G DM, Aquatab® C, Profen Forte™ DM: 1 tablet every 12 hours not to exceed 2 tablets/24 hours

Maxifed DM, Touro® CC, Pseudovent™ DM: 1-2 tablets every 12 hours, not to exceed 4 tablets/24 hours

Tri-Vent™ DM: Up to 10 mL 3-4 times/day, not to exceed pseudoephedrine 240 mg/24 hours

Profen II DM (tablet): 1 to $1^{1}/_{2}$ tablets every 12 hours, not to exceed 3 tablets/24 hours

Profen II DM (syrup): 5-10 mL every 4 hours, not to exceed 60 mL/24 hours

Z-Cof™ DM: 10 mL 2-3 times/day, not to exceed 30 mL/24 hours

Note: Also refer to specific product labeling.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricExpectorant/decongestant/cough suppressant: Oral:

Children 2-6 years:

Maxifed DM: $^{1}/_{3}$ to $^{1}/_{2}$ tablet every 12 hours, not to exceed 1 tablet/24 hours

Tri-Vent™ DM: 2.5 mL up to 3-4 times/day, not to exceed pseudoephedrine 4 mg/kg/day

Profen II DM (syrup): 1.25-2.5 mL every 4 hours, not to exceed 15 mL/24 hours

Touro® CC: $^{1}/_{2}$ tablet every 12 hour, not to exceed 1 tablet/24 hours

Z-Cof™ DM: 2.5 mL 2-3 times/day, not to exceed 7.5 mL/24 hours

Children 6-12 years:

Ambifed-G DM, Profen Forte™ DM, Profen II DM®: $^{1}/_{2}$ tablet every 12 hours not to exceed 1 tablet/24 hours

Maxifed DM: $^{1}/_{2}$ to 1 tablet every 12 hours, not to exceed 2 tablets/24 hours

Tri-Vent™ DM: 5 mL up to 3-4 times/day, not to exceed pseudoephedrine 4 mg/kg/day

Touro® CC, Pseudovent™ DM: 1 tablet every 12 hours, not to exceed 2 tablets/24 hours

Profen II DM (syrup): 2.5-5 mL every 4 hours, not to exceed 30 mL/24 hours

Z-Cof™ DM: 5 mL 2-3 times/day, not to exceed 15 mL/24 hours

Children ≥12 years: Refer to adult dosing.

Note: Also refer to specific product labeling.

Administration: OralLong-acting formulations should not be crushed or chewed. Take with a full glass of water.

ContraindicationsHypersensitivity to guaifenesin, pseudoephedrine, sympathomimetic amines, dextromethorphan, or any component of the formulation; use with or within 14 days of MAO inhibitors; severe hypertension or cardiovascular disease

Allergy Considerations

- GuaiFENesin Allergy

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- Debilitated patients: Use with caution in debilitated, sedated and/or patients confined to the supine position.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Use with caution in atopic children. Not for OTC use in children <2 years of age.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination. Also see individual agents monographs. The use of this product during pregnancy is contraindicated by some manufacturers.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsSee individual agents. The use of this combination while breast-feeding is contraindicated by some manufacturers.

Adverse ReactionsSee individual agents.

Metabolism/Transport EffectsDextromethorphan: **Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet, prolonged release:

Ambifed-G DM: Guaifenesin 1000 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg

Caplet, sustained release [scored]:

Touro® CC: Guaifenesin 575 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg [dye free]

Touro® CC-LD: Guaifenesin 575 mg, pseudoephedrine hydrochloride 25 mg, and dextromethorphan hydrobromide 30 mg

Capsule, softgel:

Robitussin® Cough and Cold: Guaifenesin 200 mg, pseudoephedrine hydrochloride 30 mg, and dextromethorphan hydrobromide 10 mg

Liquid: Guaifenesin 100 mg, pseudoephedrine hydrochloride 30 mg, and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL)

Profen II DM®: Guaifenesin 200 mg, pseudoephedrine hydrochloride 15 mg, and dextromethorphan hydrobromide 10 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; cherry flavor]

Relacon-DM NR: Guaifenesin 200 mg, pseudoephedrine hydrochloride 32 mg, and dextromethorphan hydrobromide 15 mg (480 mL) [alcohol free, sugar free; grape flavor]

Tusnel Liquid®: Guaifenesin 200 mg, pseudoephedrine hydrochloride 30 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (180 mL) [alcohol free, dye free, sugar free]

Tusnel Pediatric®: Guaifenesin 50 mg, pseudoephedrine hydrochloride 15 mg, and dextromethorphan hydrobromide 5 mg per 5 mL (120 mL) [alcohol free]

Liquid, oral [drops]:

Robitussin® Cough and Cold Infant CF: Guaifenesin 100 mg, pseudoephedrine hydrochloride 15 mg, and dextromethorphan hydrobromide 5 mg per 2.5 mL (30 mL) [alcohol free; contains sodium benzoate]

Tusnel-DM Pediatric®: Guaifenesin 25 mg, pseudoephedrine hydrochloride 5 mg, and dextromethorphan hydrobromide 5 mg per 1 mL (60 mL)

Suspension:

Z-Cof™ 12DM: Guaifenesin 175 mg, pseudoephedrine tannate (equivalent to pseudoephedrine hydrochloride 30 mg), and dextromethorphan tannate (equivalent to dextromethorphan hydrobromide 15 mg) per 5 mL (480 mL) [alcohol free; contains phenylalanine 25.26 mg/5 mL and sodium benzoate; grape flavor]

Syrup: Guaifenesin 100 mg, pseudoephedrine hydrochloride 45 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL)

Robitussin® Cough and Cold CF: Guaifenesin 100 mg, pseudoephedrine hydrochloride 30 mg, and dextromethorphan hydrobromide 10 mg per 5 mL (120 mL, 240 mL, 360 mL) [alcohol free; contains sodium benzoate]

Ru-Tuss DM: Guaifenesin 100 mg, pseudoephedrine hydrochloride 45 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; strawberry flavor]

Tri-Vent™ DM: Guaifenesin 100 mg, pseudoephedrine hydrochloride 40 mg, and dextromethorphan hydrobromide 15 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; strawberry flavor] [DSC]

Tablet, extended release: Guaifenesin 100 mg, pseudoephedrine hydrochloride 30 mg, and dextromethorphan hydrobromide 10 mg; guaifenesin 800 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg; guaifenesin 1200 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 60 mg; guaifenesin 1200 mg, pseudoephedrine hydrochloride 120 mg, and dextromethorphan hydrobromide 60 mg; guaifenesin 800 mg, pseudoephedrine hydrochloride 90 mg, and dextromethorphan hydrobromide 60 mg; guaifenesin 550 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg; guaifenesin 595 mg, pseudoephedrine hydrochloride 48 mg, and dextromethorphan hydrobromide 32 mg; guaifenesin 600 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg

Coldmist DM: Guaifenesin 595 mg, pseudoephedrine hydrochloride 48 mg, and dextromethorphan hydrobromide 32 mg [DSC]

Profen Forte™ DM: Guaifenesin 800 mg, pseudoephedrine hydrochloride 90 mg, and dextromethorphan hydrobromide 60 mg

Profen II DM®: Guaifenesin 800 mg, pseudoephedrine hydrochloride 45 mg, and dextromethorphan hydrobromide 30 mg

Pseudovent™ DM: Guaifenesin 595 mg, pseudoephedrine hydrochloride 48 mg, and dextromethorphan hydrobromide 32 mg [DSC]

Tablet, long acting [scored]: Guaifenesin 800 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg

Medent-DM: Guaifenesin 800 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg [dye free]

Tablet, sustained release:

ExeFen-DMX: Guaifenesin 780 mg, pseudoephedrine hydrochloride 80 mg, and dextromethorphan hydrobromide 40 mg [dye free]

Maxifed DM, SudaTex-DM: Guaifenesin 580 mg, pseudoephedrine hydrochloride 60 mg, and dextromethorphan hydrobromide 30 mg [dye free; scored]

Maxifed DM: Guaifenesin 780 mg, pseudoephedrine hydrochloride 80 mg, and dextromethorphan hydrobromide 40 mg [dye free; scored]

Pseudo Max DMX: Guaifenesin 700 mg, pseudoephedrine hydrochloride 80 mg, and dextromethorphan hydrobromide 40 mg

Trikof-D®: Guaifenesin 600 mg, pseudoephedrine hydrochloride 50 mg, and dextromethorphan hydrobromide 30 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, 12-hour (PanMist DM)

48-32-595 mg (30): $16.83

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Dextromethorphan: No significant effects or complications reported

Guaifenesin: No significant effects or complications reported

Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Use with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental Status Guaifenesin may cause drowsiness or dizziness; pseudoephedrine may cause anxiety or restlessness; dextromethorphan may cause drowsiness

Mental Health: Effects on Psychiatric Treatment Concurrent use with psychotropics may produce additive sedation or lessen the effects of anxiolytics depending on whether the effects of guaifenesin/dextromethorphan or pseudoephedrine predominate; concurrent use with MAO inhibitors may result in hypertensive crisis; avoid combination

Index Terms Dextromethorphan, Guaifenesin, and Pseudoephedrine; Pseudoephedrine, Dextromethorphan, and Guaifenesin

International Brand Names Balminil DM + Decongestant + Expectorant (CA); Benylin DM-D-E (CA); DextroPlus (HK); Koffex DM + Decongestant + Expectorant (CA); Novahistex DM Decongestant Expectorant (CA); Novahistine DM Decongestant Expectorant (CA); Robitussin Cough & Cold (CA); Thymicol (KR)

GuaiFENesin

Lexi-Drugs Online

English English

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Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

GuaiFENesin may be confused with guanFACINE

Mucinex® may be confused with Mucomyst®

Naldecon® may be confused with Nalfon®

International issues:

Mucolex® [Hong Kong] may be confused with Mycelex® which is a brand name for clotrimazole in the U.S.

Pronunciation(gwye FEN e sin)

U.S. Brand NamesAllfen Jr; Diabetic Tussin® EX [OTC]; Fenesin IR; Ganidin NR; Guiatuss™ [OTC]; Mucinex® Maximum Strength [OTC]; Mucinex® [OTC]; Mucinex®, Children's Mini-Melts™ [OTC]; Mucinex®, Children's [OTC]; Mucinex®, Junior Mini-Melts™ [OTC]; Organidin® NR; Phanasin® Diabetic Choice [OTC]; Phanasin® [OTC]; Refenesen™ 400 [OTC]; Refenesen™ [OTC]; Robitussin® [OTC]; Scot-Tussin® Expectorant [OTC]; Siltussin DAS [OTC]; Siltussin SA [OTC]; Vicks® Casero™ Chest Congestion Relief [OTC]; XPECT™ [OTC]

Canadian Brand NamesBalminil Expectorant; Benylin® E Extra Strength; Koffex Expectorant; Robitussin®

Pharmacologic CategoryExpectorant

Use: Labeled IndicationsHelp loosen phlegm and thin bronchial secretions to make coughs more productive

Dosing: Adults

Cough (expectorant): Oral: 200-400 mg every 4 hours to a maximum of 2.4 g/day

Extended release tablet: 600-1200 mg every 12 hours, not to exceed 2.4 g/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Cough (expectorant): Oral: Children:

6 months to 2 years: 25-50 mg every 4 hours, not to exceed 300 mg/day

2-5 years: 50-100 mg every 4 hours, not to exceed 600 mg/day

6-11 years: 100-200 mg every 4 hours, not to exceed 1.2 g/day

>12 years: Refer to adult dosing.

Administration: OralDo not crush, chew, or break extended release tablets. Administer with a full glass of water.

Dietary Considerations

Diabetic Tussin® EX contains phenylalanine 8.4 mg/5 mL.

Mucinex® Children's Mini-Melts™ 50 mg/packet contains phenylalanine 0.6 mg/packet; Mucinex® Junior Mini-Melts™ 100 mg/packet contains phenylalanine 1 mg/packet

Vicks® Casero™ contains phenylalanine 5.5 mg/12.5 mL and sodium 32 mg/12.5 mL.

ContraindicationsHypersensitivity to guaifenesin or any component of the formulation

Allergy Considerations

- GuaiFENesin Allergy

Warnings/Precautions

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Other warnings/precautions:

- Self-medication (OTC use): When used for self medication (OTC) notify healthcare provider if symptoms do not improve within 7 days, or are accompanied by fever, rash or persistent headache. Do not use for persistent or chronic cough (as with smoking, asthma, chronic bronchitis, emphysema) or if cough is accompanied b excessive phlegm unless directed to do so by healthcare provider. Not for OTC use in children <2 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Central nervous system: Dizziness, drowsiness, headache

Dermatologic: Rash

Endocrine & metabolic: Uric acid levels decreased

Gastrointestinal: Nausea, vomiting, stomach pain

Postmarketing and/or case reports: Kidney stone formation (with consumption of large quantities)

Drug InteractionsThere are no known significant interactions.

Test InteractionsPossible color interference with determination of 5-HIAA and VMA; discontinue for 48 hours prior to test

Nursing: Physical Assessment/MonitoringAssess effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take as prescribed; do not exceed prescribed dose or frequency. Do not chew or crush extended release tablet; take with a full glass of water. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience some drowsiness (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Report excessive drowsiness, respiratory difficulty, lack of improvement, or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet:

Fenesin IR, Refenesen™ 400: 400 mg

Granules, oral:

Mucinex® Children's Mini-Melts™: 50 mg/packet (12s) [contains phenylalanine 0.6 mg/packet and magnesium 6 mg/packet; grape flavor]

Mucinex® Junior Mini-Melts™: 100 mg/packet (12s) [contains phenylalanine 1 mg/packet and magnesium 10 mg/packet; bubble gum flavor]

Liquid: 100 mg/5 mL (120 mL, 480 mL)

Diabetic Tussin EX®: 100 mg/5 mL (120 mL) [alcohol free, sugar free, dye free; contains phenylalanine 8.4 mg/5 mL]

Ganidin NR: 100 mg/5 mL (480 mL) [raspberry flavor]

Mucinex® Children's: 100 mg/5 mL (120 mL) [alcohol free; grape flavor]

Organidin® NR: 100 mg/5 mL (480 mL) [contains sodium benzoate; raspberry flavor]

Siltussin DAS: 100 mg/5 mL (120 mL) [alcohol free, dye free, sugar free; strawberry flavor]

Syrup: 100 mg/5 mL (120 mL, 480 mL)

Guiatuss™: 100 mg/5 mL (120 mL, 480 mL) [alcohol free; fruit-mint flavor]

Phanasin®: 100 mg/5 mL (120 mL, 240 mL) [alcohol free, sugar free; mint flavor]

Phanasin® Diabetic Choice: 100 mg/5 mL (120 mL) [alcohol free, sugar free; mint flavor]

Robitussin®: 100 mg/5 mL (5 mL, 10 mL, 15 mL, 30 mL, 120 mL, 240 mL, 480 mL) [alcohol free; contains sodium benzoate]

Scot-Tussin® Expectorant: 100 mg/5 mL (120 mL) [alcohol free, dye free, sugar free; contains benzoic acid; grape flavor]

Siltussin SA: 100 mg/5 mL (120 mL, 240 mL, 480 mL) [alcohol free, sugar free; strawberry flavor]

Vicks® Casero™ Chest Congestion Relief: 100 mg/6.25 mL (120 mL, 240 mL) [contains phenylalanine 5.5 mg/12.5 mL, sodium 32 mg/12.5 mL, and sodium benzoate; honey menthol flavor]

Tablet: 200 mg

Allfen Jr: 400 mg [dye free]

Organidin® NR: 200 mg

Refenesen™: 200 mg

XPECT™: 400 mg

Tablet, extended release:

Mucinex®: 600 mg

Mucinex® Maximum Strength: 1200 mg

Generic AvailableYes: Excludes extended release and granules

Pricing: U.S. (www.drugstore.com)

Liquid (Organidin NR)

100 mg/5 mL (120): $52.42

Syrup (Guiatuss)

100 mg/5 mL (473): $11.99

Tablet, 12-hour (Mucinex)

600 mg (20): $18.80

Tablets (Guaifenesin)

200 mg (90): $18.00

Tablets (Organidin NR)

200 mg (30): $25.67

Mechanism of ActionThought to act as an expectorant by irritating the gastric mucosa and stimulating respiratory tract secretions, thereby increasing respiratory fluid volumes and decreasing mucous viscosity

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Half-life elimination: ~1 hour

Excretion: Urine (as unchanged drug and metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsGG; Glycerol Guaiacolate

References

Kuhn JJ, Hendley JO, Adams DF, et al, “Antitussive Effect of Guaifenesin in Young Adults With Natural Colds,” *Chest*, 1982, 6:713-8.

International Brand NamesBronchol (CH); Broncovanil (IT); Chamberlain`s Cough Remedy (ZA); Coldrex Broncho (PL); Deflenol (MX); Desbly (FR); Fagusan (DE); Fluidin (ES); Formulaexpec (ES); Guafen (AT); Guaiatussin (PL); Guajacuran (CZ); Guajasyl (CH); Guajazyl (PL); Gufen N (DE); Gwajafen (PL); Idropulmina (IT); Lactocol (ES); Myoscain (AT); Negatos (AR); Nephulon (DE); Omega Bronquial (AR); Plenum Duncan (AR); Relaxil-G (HU); Respenyl (GB); Resyl (AT, CH, IT, SE); Robitussin (AR, AU, ES, FI, IE, LU, MX, PL); Tintus (FI); Vicks Cough Syrup (AU); Vicks expectorant adulte (FR); Vicks Hustensirup mit Guaifenesin (CH); Vicks Tosse Fluidificante (IT); Vicks Vaposyrup (BE); VicksFormel 44 Expectin (CH); Wick Formel 44 Husten-Loser (AT, DE); Wick Formula 44 Plus L (PL)

Guanabenz

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Guanabenz may be confused with guanadrel, guanfacine

Pronunciation(GWAHN a benz)
Canadian Brand NamesWytensin®
Pharmacologic CategoryAlpha$_2$-Adrenergic Agonist
Use: Labeled IndicationsManagement of hypertension
Dosing: AdultsHypertension: Oral: Initial: 4 mg twice daily; increase in increments of 4-8 mg/day every 1-2 weeks to a maximum of 32 mg twice daily.
Dosing: ElderlyInitial: 4 mg once daily, increase every 1-2 weeks
Dosing: Hepatic ImpairmentDosage adjustment is probably necessary; however, no specific guidelines are available.
StorageProtect from light.
ContraindicationsHypersensitivity to guanabenz or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause sedation and drowsiness; avoid use in CNS disease.
- Orthostasis: May cause significant orthostasis.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe coronary insufficiency or recent MI.
- Cerebrovascular disease: Use with caution in patients with cerebrovascular disease.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Renal impairment: Use with caution in patients with severe renal impairment.

Concurrent drug therapy issues:

- CNS depressants: Avoid use with other CNS depressants; effects may be potentiated.

Special populations:

- Elderly: Avoid use in the elderly.
- Pediatrics: Safety and efficacy have not been established for use in children <12 years of age.

Other warnings/precautions:

- Abrupt withdrawal: Abrupt discontinuation can result in nervousness, anxiety and rarely, rebound hypertension (occurs 2-4 days after withdrawal).

Geriatric ConsiderationsBecause of its CNS adverse effects, guanabenz is not considered a drug of choice for the treatment of hypertension in the elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were observed in animal studies. There are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsHigher rates with larger doses

>5% (at doses of 16 mg/day):

Cardiovascular: Orthostasis

Central nervous system: Drowsiness or sedation (39%), dizziness (12% to 17%), headache (5%)

Gastrointestinal: Xerostomia (28% to 38%)

Neuromuscular & skeletal: Weakness (~10%)

≤3% (may be similar to placebo):

Cardiovascular: Arrhythmias, chest pain, edema, palpitation

Central nervous system: Anxiety, ataxia, depression, sleep disturbances

Dermatologic: Pruritus, rash

Endocrine & metabolic: Disturbances of sexual function, gynecomastia, decreased sexual function

Gastrointestinal: Constipation, diarrhea, nausea, vomiting

Genitourinary: Polyuria

Neuromuscular & skeletal: Myalgia

Ocular: Blurring of vision

Respiratory: Dyspnea, nasal congestion

Miscellaneous: Taste disorders

Metabolism/Transport Effects **Substrate** of CYP1A2 (major)

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antidepressants (Alpha2-Antagonist): May diminish the hypotensive effect of Alpha2-Agonists. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Iobenguane I 123: Alpha2-Agonists may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May diminish the antihypertensive effect of Alpha2-Agonists. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May diminish the antihypertensive effect of Alpha2-Agonists. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring Parameters Monitor blood pressure, standing and sitting/supine

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 4 mg, 8 mg

Generic Available Yes

Pricing: U.S. (www.drugstore.com)

Tablets (Guanabenz Acetate)

8 mg (60): $93.99

Mechanism of Action Stimulates alpha$_2$-adrenoreceptors in the brain stem, thus activating an inhibitory neuron, resulting in reduced sympathetic outflow, producing a decrease in vasomotor tone and heart rate

Pharmacodynamics/Kinetics

Onset of action: Antihypertensive: ~1 hour

Absorption: ~75%

Half-life elimination, serum: 7-10 hours

Pharmacotherapy Pearls Considered an alternate to clonidine; it causes less sodium retention than clonidine or methyldopa.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Taste disorder, nasal congestion, dyspnea, significant xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and dizziness are common; may cause anxiety or depression

Mental Health: Effects on Psychiatric TreatmentHas been used to treat ADHD; concurrent use with psychotropics may produce additive sedation and dry mouth; TCAs may decrease the hypotensive effect of guanabenz

Cardiovascular ConsiderationsNot routinely used in clinical practice because of significant and marked orthostatic hypotension.

Anesthesia and Critical Care Concerns/Other ConsiderationsGuanabenz is not routinely used in clinical practice because of significant and marked orthostatic hypotension.

Index TermsGuanabenz Acetate

References

Chobanian AV, Bakris GL, Black HR, et al, “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report,” *JAMA*, 2003, 289(19):2560-71.[PubMed 12748199]

International Brand NamesLisapres (BR); Rexitene (AT, IT); Tenelid (BR); Wytensin (AT)

English

English

Jump To Field (Select Field Name)

Special Alerts

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) has issued a statement in April 2008 recommending that all children diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the recommendations due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: Methylphenidate, amphetamine, dextroamphetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children's Healthcare Quality.

For more information, refer to:

http://americanheart.mediaroom.com/index.php?s=43&item=422

http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1

http://americanheart.mediaroom.com/index.php?s=43&item=398

http://www.fda.gov/medwatch/safety/2007/safety07.htm

http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html

Nissen SE, "ADHD Drugs and Cardiovascular Risk," *N Engl J Med*, 2006, 354(14):1445-48.

"Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder," *J Am Acad Child Adolesc Psychiatry*, 2007, 46(7):894-921.

Vetter VL, Elia J, Erickson CH, et al, "Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing," *Circulation*, 2008, 117:2407-23.

Wilens TE, Prince JB, Spencer TJ, et al, "Stimulants and Sudden Death: What is a Physician to do?" *Pediatrics*, 2006, 118(3):1215-19.

Medication Safety Issues

Sound-alike/look-alike issues:

GuanFACINE may be confused with guaiFENesin, guanabenz, guanidine

Tenex® may be confused with Entex®, Ten-K®, Xanax®

International issues:

Tenex® may be confused with Kinex® which is a brand name for biperiden in Mexico

Pronunciation(GWAHN fa seen)
U.S. Brand NamesTenex®
Canadian Brand NamesTenex®
Pharmacologic CategoryAlpha$_2$-Adrenergic Agonist
Use: Labeled IndicationsManagement of hypertension
Use: Unlabeled/InvestigationalADHD, tic disorder, aggression
Dosing: Adults

Hypertension: Oral: 1 mg usually at bedtime, may increase if needed at 3- to 4-week intervals; usual dose range (JNC 7): 0.5-2 mg once daily

ADHD, tic disorder, aggression (unlabeled uses): Oral: Initial: 0.5 mg at bedtime; increase as tolerated (every 3-14 days) to usual dose range (1.5-3 mg/day) given in 3 divided doses (maximum: 4 mg/day)

Dosing: ElderlyRefer to adult dosing.
ContraindicationsHypersensitivity to guanfacine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause sedation and drowsiness; avoid use in CNS disease.
- Orthostasis: May cause orthostasis.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe coronary insufficiency or recent MI.
- Cerebrovascular disease: Use with caution in patients with cerebrovascular disease.
- Diabetes: Use with caution in patients with diabetes mellitus; may mask signs of hypoglycemia.
- Hepatic impairment: Use with caution in patients with chronic hepatic impairment.
- Renal impairment: Use with caution in patients with chronic renal impairment.

Concurrent drug therapy issues:

- CNS depressants: Avoid use with other CNS depressants; effects may be potentiated.

Special populations:

- Elderly: Avoid use in the elderly.
- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Abrupt withdrawal: Abrupt discontinuation can result in nervousness, anxiety and rarely, rebound hypertension (occurs 2-4 days after withdrawal).

Geriatric ConsiderationsBecause of adverse effects such as CNS depression, dry mouth, and constipation, guanfacine may not be considered a drug of choice in the elderly.
Pregnancy Risk FactorB
Adverse Reactions

>10%:

Central nervous system: Somnolence (5% to 40%), headache (3% to 13%), dizziness (2% to 15%)

Gastrointestinal: Xerostomia (10% to 54%), constipation (2% to 15%)

1% to 10%:

Central nervous system: Fatigue (2% to 10%)

Endocrine & metabolic: Impotence (up to 7%)

<1% (Limited to important or life-threatening): Agitation, alopecia, amnesia, blurred vision, bradycardia, chest pain, confusion, depression, dermatitis, diaphoresis, dysphagia, dyspnea, edema, exfoliative dermatitis, hypokinesia, hypotension, insomnia, leg cramps, malaise, nervousness, orthostasis, palpitation, paresthesia, pruritus, rash, rebound hypertension, syncope, tinnitus, urinary incontinence, vertigo; **Note:** Mania and aggressive behavior have been reported in pediatric patients with ADHD who received guanfacine.

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antidepressants (Alpha2-Antagonist): May diminish the hypotensive effect of Alpha2-Agonists. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Iobenguane I 123: Alpha2-Agonists may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May diminish the antihypertensive effect of Alpha2-Agonists. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May diminish the antihypertensive effect of Alpha2-Agonists. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring ParametersHeart rate, blood pressure
When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure (when started and weaned), and consider obtaining ECG prior to initiation (Vetter, 2008).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 1 mg, 2 mg

Tenex®: 1 mg, 2 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Guanfacine HCl)

1 mg (30): $20.99

2 mg (30): $25.99

Mechanism of ActionStimulates alpha$_2$-adrenoreceptors in the brain stem, thus activating an inhibitory neuron, resulting in reduced sympathetic outflow, producing a decrease in vasomotor tone and heart rate
Pharmacodynamics/Kinetics

Onset of action: Peak effect: 8-11 hours

Duration: 24 hours following single dose

Half-life elimination, serum: 17 hours

Time to peak, serum: 1-4 hours

Pharmacotherapy PearlsMore selective alpha$_2$ agonist than clonidine; withdrawal effects rarely occur due to its long half-life.
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDrowsiness is common; may cause insomnia or dizziness, may rarely cause confusion or depression
Mental Health: Effects on Psychiatric TreatmentHas been used to treat ADHD; concurrent use with psychotropics may produce additive sedation and dry mouth; TCAs may decrease the hypotensive effect of guanfacine
Cardiovascular ConsiderationsNot routinely used in clinical practice because of significant and marked hypotension.

Anesthesia and Critical Care Concerns/Other Considerations Guanfacine is not routinely used in clinical practice because of significant and marked hypotension.

Index Terms Guanfacine Hydrochloride

References

Bassarath L, "Medication Strategies in Childhood Aggression: A Review," *Can J Psychiatry*, 2003, 48(6):367-73.[PubMed 12894610]

Chappell PB, Riddle MA, Scahill L, et al, Guanfacine Treatment of Comorbid Attention-Deficit Hyperactivity Disorder and Tourette's Syndrome: Preliminary Clinical Experience," *J Am Acad Child Adolesc Psychiatry*, 1995, 34(9):1140-6.

Chobanian AV, Bakris GL, Black HR, et al, "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report," *JAMA*, 2003, 289(19):2560-71. [PubMed 12748199]

"Consensus Recommendations for the Management of Chronic Heart Failure. On Behalf of the Membership of the Advisory Council to Improve Outcomes Nationwide in Heart Failure," *Am J Cardiol*, 1999, 83(2A):1A-38A. [PubMed 10072251]

Cummings DD, Singer HS, Krieger M, et al, " Neuropsychiatric Effects of Guanfacine in Children With Mild Tourette Syndrome: A Pilot Study," *Clin Neuropharmacol*, 2002, 25(6):325-32.[PubMed 12469007]

Hunt RD, Arnsten AF, and Asbell MD, "An Open Trial of Guanfacine in the Treatment of Attention-Deficit Hyperactivity Disorder," *J Am Acad Child Adolesc Psychiatry*, 1995, 34(1):50-4.[PubMed 7860456]

Kaplan NM and Sever PS, "Combination Therapy: A Key to Comprehensive Patient Care," *Am J Hypertens*, 1997, 10(7 Pt 2):127S. [PubMed 9231887]

Moser M and Black HR, "The Role of Combination Therapy in the Treatment of Hypertension," *Am J Hypertens*, 1998, 11(6 Pt 2):73S-8S, 95S-100S.[PubMed 9655566]

Olfson M, "New Options in the Pharmacological Management of Attention-Deficit/Hyperactivity Disorder," *Am J Manag Care*, 2004, 10 (Suppl 4): 117-24.[PubMed 15623264]

Scahill L, Chappell PB, Kim YS, et al, "A Placebo-Controlled Study of Guanfacine in the Treatment of Children With Tic Disorders and Attention Deficit Hyperactivity Disorder," *Am J Psychiatry*, 2001, 158(7):1067-74.[PubMed 11431228]

Vetter VL, Elia J, Erickson CH, et al, "Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing," *Circulation*, 2008, 117:2407-23.[PubMed 18427125]

International Brand Names Akfen (IE); Dipresan (HR); Estulic (BE, BF, BJ, CH, CI, CZ, DE, ET, FR, GH, GM, GN, HN, HU, ID, JP, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, PH, PL, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Hipertensal (AR)

Guanidine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Guanidine may be confused with guanfacine, guanethidine

Pronunciation(GWAHN i deen)

Pharmacologic CategoryCholinergic Agonist

Use: Labeled IndicationsReduction of the symptoms of muscle weakness associated with the myasthenic syndrome of Eaton-Lambert, not for myasthenia gravis

Dosing: AdultsEaton-Lambert syndrome: Oral: Initial: 10-15 mg/kg/day in 3-4 divided doses, gradually increase to 35 mg/kg/day, or up to development of side effects

Dosing: ElderlyRefer to adult dosing.

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 125 mg

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsGuanidine Hydrochloride

Haemophilus b Conjugate and Hepatitis B Vaccine'; return;">

Haemophilus b Conjugate and Hepatitis B Vaccine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Comvax® may be confused with Recombivax [Recombivax HB®]

Pronunciation(he MOF i lus bee KON joo gate & hep a TYE tis bee vak SEEN)

U.S. Brand NamesComvax®

Pharmacologic CategoryVaccine, Inactivated (Bacterial); Vaccine, Inactivated (Viral)

Use: Labeled Indications

Immunization against invasive disease caused by *H. influenzae* type b and against infection caused by all known subtypes of hepatitis B virus in infants 6 weeks to 15 months of age born of hepatitis B surface antigen (HB$_S$Ag) negative mothers

Infants born of HB$_S$Ag-positive mothers or mothers of unknown HB$_S$Ag status should receive hepatitis B immune globulin and hepatitis B vaccine (recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule

Dosing: Pediatric

Immunization: Infants: I.M.: 0.5 mL at 2, 4, and 12-15 months of age (total of 3 doses). **Note:** If the recommended schedule cannot be followed, the interval between the first two doses should be at least 6 weeks and the interval between the second and third dose should be as close as possible to 8-11 months. Minimum age for first dose is 6 weeks.

Modified Schedule: Children who receive one dose of hepatitis B vaccine at or shortly after birth may receive Comvax® on a schedule of 2, 4, and 12-15 months of age

Administration: I.M.Shake well prior to use. Administer 0.5 mL I.M. into anterolateral thigh [data suggests that injections given in the buttocks frequently are given into fatty tissue instead of into muscle to result in lower seroconversion rates]; **do not administer intravenously, intradermally, or subcutaneously.**

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

Administration with other vaccines:

Haemophilus b conjugate and Hepatitis B vaccine with live vaccines: May be given simultaneously or at any interval between doses.

Haemophilus b conjugate and Hepatitis B vaccine with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Vaccine administration with antibody-containing products:*Haemophilus* b conjugate and Hepatitis B vaccine may be given simultaneously at different sites or at any interval between doses. Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products

StorageStore at 2°C to 8°C (36°F to 48°F); do not freeze.

ContraindicationsHypersensitivity to *Haemophilus* b vaccine, hepatitis B vaccine, yeast, or to any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Acute illness: The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and the etiology of the disease. Immunization should be delayed during the course of an acute febrile illness.

- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination. May be used in patients with HIV infection.

Dosage form specific issues:

- Latex: Packaging contains natural latex rubber.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. This product is not indicated for use in women of childbearing age.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

>10%:

Central nervous system: Irritability (32% to 57%), somnolence (21% to 50%), fever (101°F to 102.9°F: 11% to 14%), crying (unusual/high pitched: 3% to 11%)

Local: Injection site reactions: Pain/soreness (24% to 35%), swelling/induration (<1 inch: 27% to 30%), erythema (<1 inch: 22% to 27%)

1% to 10%:

Central nervous system: Fever (≥103°F: <1% to 3%), crying (<1% to 2%)

Dermatologic: Rash (≤1%)

Gastrointestinal: Anorexia (<1% to 4%), vomiting (1% to 3%), diarrhea (<1% to 2%), oral candidiasis (≤1%)

Local: Injection site reactions: Erythema (>1 inch: 1% to 3%), swelling/induration (>1 inch: 3% to 4%)

Otic: Otitis media (<1% to 3%)

Respiratory: cough (≤1%), respiratory congestion (≤1%), rhinorrhea (≤1%), upper respiratory tract infection (≤1%)

Postmarketing and/or case reports: Anaphylaxis, angioedema, erythema multiforme, febrile seizure, seizure, thrombocytopenia, urticaria

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension [preservative free]:

Comvax®: *Haemophilus* b capsular polysaccharide 7.5 mcg (bound to *Neisseria meningitides* OMPC 125 mcg) and hepatitis B surface antigen 5 mcg per 0.5 mL (0.5 mL) [contains aluminum; contains natural rubber/natural latex in packaging]

Generic AvailableNo

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Hepatitis B Vaccine (Recombinant)
- Immunization Recommendations

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause irritability or lethargy

Mental Health: Effects on Psychiatric TreatmentMay lessen or potentiate the effects of anxiolytics or mood stabilizers

Index Terms*Haemophilus* b (meningococcal protein conjugate) Conjugate Vaccine; Hepatitis B Vaccine (Recombinant); Hib Conjugate Vaccine

References

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.[PubMed 17136024]

International Brand NamesComvax (MX); Procomvax (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Haemophilus b Conjugate Vaccine'; return;">

Haemophilus b Conjugate Vaccine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

International issues:

Hiberix is also a brand name for influenza virus vaccine in multiple international markets

Pronunciation(he MOF fi lus bee KON joo gate vak SEEN)

U.S. Brand NamesActHIB®; PedvaxHIB®

Canadian Brand NamesActHIB®; PedvaxHIB®

Pharmacologic CategoryVaccine, Inactivated (Bacterial)

Use: Labeled IndicationsRoutine immunization of children against invasive disease caused by *H. influenzae* type b

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of all children through age 59 months. Efficacy data is not available for use in older children and adults with chronic conditions associated with an increased risk of Hib disease. However, a single dose may also be considered for older children, adolescents, and adults who did not receive the childhood series and who have had splenectomies or who have sickle cell disease, leukemia or HIV infection.

Dosing: PediatricImmunization: I.M.: 0.5 mL as a single dose should be administered to previously unvaccinated children according to one of the following “brand-specific” schedules; number of doses in series is dependent upon age at first dose

ActHIB®:*Age at first dose:*

2 months of age: Immunization consists of 3 doses (0.5 mL/dose) administered at 2-, 4- and 6 months of age (may reconstitute with provided diluent or DTP vaccine). A booster dose is given at 15-18 months of age (may reconstitute with provided diluent or Tripedia® vaccine).

7-11 months of age: Two doses (0.5 mL/dose) administered 8 months apart, with a booster dose at 15-18 months of age

12-14 months of age: One dose (0.5 mL) followed by a booster dose 2 months later

PedvaxHIB®:*Age at first dose:*

2-10 months of age: Two doses (0.5 mL/dose) administered 2 months apart; booster dose at 12-15 months of age

11-14 months of age: Two doses (0.5 mL/dose) administered 1 months apart

15-71 months of age: One 0.5 mL dose

Administration: I.M.For I.M. administration; do not inject I.V.

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

Administration with other vaccines:

Haemophilus b conjugate vaccine with live vaccines: May be given simultaneously or at any interval between doses.

Haemophilus b conjugate vaccine with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Vaccine administration with antibody-containing products:*Haemophilus* b conjugate vaccine may ay be given simultaneously at different sites or at any interval between doses. Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products

StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze.

ActHIB®: Use within 24 hours following reconstitution with saline. Use within 30 minutes following reconstitution with Tripedia®.

ContraindicationsHypersensitivity to *Haemophilus* b polysaccharide vaccine or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Acute illness: The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and the etiology of the disease. Immunization should be delayed during the course of an acute febrile illness.

- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination. May be used in patients with HIV infection.

- Children in whom DTP or DT vaccination is deferred: The carrier proteins used in PRP-T (but not PRP-OMP) are chemically and immunologically related to toxoids contained in DTP vaccine. Earlier or simultaneous vaccination with diphtheria or tetanus toxoids may be required to elicit an optimal anti-PRP antibody response. In contrast, the immunogenicity of PRP-OMP is not affected by vaccination with DTP. In infants in whom DTP or DT vaccination is deferred, PRP-OMP may be advantageous for *Haemophilus influenzae* type b vaccination.

Dosage form specific issues:

- Latex: Packaging may contain natural latex rubber.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.** Frequency not defined:

Central nervous system: Crying (unusual, high pitched, prolonged), fever, irritability, pain, sleepiness

Dermatologic: Rash

Gastrointestinal: Anorexia, diarrhea, vomiting

Local: Injection site: Erythema, induration, pain, soreness, swelling, warmth

Otic: Otitis media

Respiratory: Upper respiratory tract infection

Postmarketing and/or case reports: Anaphylactoid reactions, angioedema, erythema multiforme, facial edema, febrile seizure, Guillain-Barré syndrome, headache, hypersensitivity, hyporesponsive episodes, hypotonia, inflammation, injection site abscess (sterile), lethargy, lymphadenopathy, malaise, mass, seizure, shock, skin discoloration, urticaria

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Test InteractionsMay interfere with interpretation of antigen detection tests; antigenuria may occur up to 2 weeks following immunization

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

ActHIB® *Haemophilus* b capsular polysaccharide 10 mcg (bound to tetanus toxoid 24 mcg) per 0.5 mL [contains sucrose; may be reconstituted with provided diluent (forms solution; contains natural rubber/natural latex in packaging) or Tripedia® (forms suspension)]

Injection, suspension:

PedvaxHIB®: *Haemophilus* b capsular polysaccharide 7.5 mcg [bound to *Neisseria meningitidis* OMPC 125 mcg] per 0.5 mL (0.5 mL) [contains aluminum]

Generic AvailableNo

Mechanism of ActionStimulates production of anticapsular antibodies and provides active immunity to *Haemophilus influenzae* type b

Pharmacodynamics/KineticsSeroconversion following one dose of Hib vaccine for children 18 months or 24 months of age or older is 75% to 90%, respectively.

Onset of action: Serum antibody response: 1-2 weeks

Duration: Immunity: 1.5 years

Related Information

- Immunization Recommendations

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

The two conjugate vaccines currently available consist of *Haemophilus influenzae* type b (Hib) capsular polysaccharide (also referred to as PRP) linked to a carrier protein. PedvaxHIB® (PRP-OMP) is linked to the outer membrane protein complex from *Neisseria meningitidis*. ActHIB® (PRP-T) uses tetanus toxoid conjugate as the carrier protein.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause irritability or lethargy
Mental Health: Effects on Psychiatric TreatmentMay lessen or potentiate the effects of anxiolytics or mood stabilizers
Index Terms*Haemophilus* b Oligosaccharide Conjugate Vaccine; *Haemophilus* b Polysaccharide Vaccine; Diphtheria Toxoid Conjugate; HbCV; Hib Conjugate Vaccine; Hib Polysaccharide Conjugate; PRP-OMP; PRP-T
References

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.[PubMed 17136024]

International Brand NamesAct-HIB (BE, BG, BR, CL, CN, DK, EE, FR, GR, IL, KP, PE, PK, PY, SE, UY); Hiberix (SI); HIBest (FR, IN); HibTITER (AE, AT, BH, CY, DE, EG, FI, GB, HN, IL, IQ, IR, IT, JO, KW, LB, LY, NZ, OM, QA, SA, SY, YE); Pedvax HIB (BR)

Halcinonide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Halcinonide may be confused with Halcion®

Halog® may be confused with Haldol®, Mycolog®

Pronunciation(hal SIN oh nide)

U.S. Brand NamesHalog®

Canadian Brand NamesHalog®

Pharmacologic CategoryCorticosteroid, Topical

Use: Labeled IndicationsInflammation of corticosteroid-responsive dermatoses [high potency topical corticosteroid]

Dosing: AdultsSteroid-responsive dermatoses: Topical: Apply sparingly 1-3 times/day, occlusive dressing may be used for severe or resistant dermatoses; a thin film is effective; do not overuse. Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

ContraindicationsHypersensitivity to halcinonide or any component of the formulation; viral, fungal, or tubercular skin lesions

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Special populations:

- Pediatrics: Chronic use of corticosteroids in children may interfere with growth and development.

Geriatric ConsiderationsDue to age-related changes in skin, limit use of topical glucocorticosteroids.

Pregnancy Risk FactorC

Adverse Reactions

Frequency not defined.

Dermatologic: Acneiform eruptions, allergic contact dermatitis, dry skin, folliculitis, hypertrichosis, itching, miliaria, perioral dermatitis, skin atrophy, skin maceration, striae

Local: Burning, itching

Miscellaneous: Secondary infection

Reported with other topical corticosteroids, may occur more frequently with occlusive dressings: Cushing’s syndrome, glucosuria, growth retardation (children), HPA axis suppression, hyperglycemia, intracranial hypertension (children)

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess patient response. Teach patient proper use (according to formulation), side effects/appropriate interventions, and symptoms to report.

Patient EducationFor external use only. Do not use for eyes, mucous membranes, or open wounds. Use exactly as directed and for no longer than the period prescribed. Before using, wash and dry area gently. Apply in a thin layer (may rub in lightly). Apply light dressing (if necessary) to area being treated. Do not use occlusive dressing unless so advised by prescriber. Avoid prolonged or excessive use around sensitive tissues, genital, or rectal areas. Avoid exposing treated area to direct sunlight. Inform prescriber if condition worsens (redness, swelling, irritation, signs of infection, or open sores) or fails to improve. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream (Halog®): 0.1% (30 g, 60 g)

Ointment (Halog®): 0.1% (30 g, 60 g)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Cream (Halog)

0.1% (15): $28.99

0.1% (30): $57.59

0.1% (60): $102.38

0.1% (240): $198.98

Ointment (Halog)

0.1% (15): $30.99

0.1% (30): $57.59

0.1% (60): $102.38

0.1% (240): $198.98

Solution (Halog)

0.1% (20): $33.99

0.1% (60): $68.99

Mechanism of ActionDecreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability

Pharmacodynamics/Kinetics

Absorption: Percutaneous absorption varies by location of topical application and use of occlusive dressings

Metabolism: Primarily hepatic

Excretion: Urine

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

International Brand NamesBerodan (KP); Betacorton Solution (EE); Cortilate (IN); Halciderm (AU, CH, GB, IE, IT, NL); Halciderm Crema Al (CR, DO, GT, HN, NI, PA, SV); Halciderme (PE); Halog (AT, BR, CL, DE, DK, ES, FR, ID, NO, VE); Volog (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PK, QA, SA, SC, SD, SL, SN, SY, TN, TR, TZ, UG, YE, ZA, ZM, ZW)

Halobetasol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Ultravate® may be confused with Cutivate®

Pronunciation(hal oh BAY ta sol)

U.S. Brand NamesUltravate®

Canadian Brand NamesUltravate®

Pharmacologic CategoryCorticosteroid, Topical

Use: Labeled IndicationsRelief of inflammatory and pruritic manifestations of corticosteroid-response dermatoses [super high potency topical corticosteroid]

Use: DentalRelief of inflammatory and pruritic manifestations (super high potency topical corticosteroid)

Dosing: Adults**Inflammatory and pruritic manifestations (dental use):** Cream: Apply sparingly to lesion twice daily. Treatment should not exceed 2 consecutive weeks and total dosage should not exceed 50 g/week. Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.**Steroid-responsive dermatoses:** Topical: Apply sparingly to skin twice daily, rub in gently and completely; treatment should not exceed 2 consecutive weeks and total dosage should not exceed 50 g/week. Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥12 years: Refer to adult dosing.

Administration: TopicalUse of occlusive dressings is not recommended. Do not apply to the face, groin, or axillae. Apply thin film to affected area and rub in completely.

ContraindicationsHypersensitivity to halobetasol or any component of the formulation; viral, fungal, or tubercular skin lesions

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Disease-related concerns:

- Periorbital dermatitis: Should not be used for the treatment of perioral dermatitis.
- Rosacea: Should not be used for the treatment of rosacea.

Special populations:

- Pediatrics: Safety and efficacy have not been established in pediatric patients; use in children <12 years of age is not recommended.

Other warnings/precautions:

- Application site: Not for ophthalmic use. Not recommended for application to the face, groin, or axillae.

Geriatric ConsiderationsDue to age-related changes in skin, limit use of topical glucocorticosteroids.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women, however, halobetasol is teratogenic in animals; use during pregnancy with caution. Increased incidence of cleft palate, neonatal adrenal suppression, low birth weight, and cataracts in the infant have been reported following corticosteroid use during pregnancy. In general, the use of large amounts, or prolonged use, of topical corticosteroids during pregnancy should be avoided.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsSystemically administered corticosteroids appear in human milk and may cause adverse effects in a nursing infant. It is not known if the systemic absorption of topical halobetasol results in detectable quantities in human milk.

Adverse Reactions

1% to 4%: Dermatologic: Burning, itching, stinging

<1%: Acneiform eruptions, allergic contact dermatitis, dry skin, erythema, HPA axis suppression, hypopigmentation, leukoderma, miliaria, perioral dermatitis, pustulation, rash, secondary infection, skin atrophy, striae, vesicles

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Patient Education

A thin film of cream or ointment is effective; do not overuse. Use only as prescribed, and for no longer than the period prescribed. Apply sparingly in a light film and rub in lightly. Avoid contact with eyes. Notify prescriber if condition being treated persists or worsens. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, as propionate: 0.05% (15 g, 50 g)

Ointment, as propionate: 0.05% (15 g, 50 g)

Generic Available

Yes

Pricing: U.S. (www.drugstore.com)

Cream (Halobetasol Propionate)

0.05% (15): $25.99

0.05% (50): $49.99

Cream (Ultravate)

0.05% (15): $52.64

0.05% (50): $116.08

Ointment (Halobetasol Propionate)

0.05% (15): $25.99

0.05% (50): $46.99

Ointment (Ultravate)

0.05% (15): $53.99

0.05% (50): $143.08

Mechanism of Action

Corticosteroids inhibit the initial manifestations of the inflammatory process (ie, capillary dilation and edema, fibrin deposition, and migration and diapedesis of leukocytes into the inflamed site) as well as later sequelae (angiogenesis, fibroblast proliferation)

Pharmacodynamics/Kinetics

Absorption: Percutaneous absorption varies by location of topical application; ~6% of a topically applied dose of ointment enters circulation within 96 hours

Metabolism: Primarily hepatic

Excretion: Urine

Related Information

- Corticosteroids

Dental Health: Effects on Dental Treatment

No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions

No information available to require special precautions

Mental Health: Effects on Mental Status

None reported

Mental Health: Effects on Psychiatric Treatment

None noted

Index Terms

Halobetasol Propionate

References

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

Reed BR, “Dermatologic Drugs, Pregnancy, and Lactation. A Conservative Guide,” *Arch Dermatol*, 1997, 133(7):894-8.[PubMed 9236528]

Haloperidol

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

Gill SS, Bronskill SE, Normand SL, et al, “Antipsychotic Drug Use and Mortality in Older Adults With Dementia,” *Ann Intern Med*, 2007, 146(11):775-86.[PubMed 17548409]

Schneeweiss S, Setoguchi S, Brookhart A, et al, “Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients,” *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Medication Safety Issues

Sound-alike/look-alike issues:

Haloperidol may be confused Halotestin®

Haldol® may be confused with Halcion®, Halenol®, Halog®, Halotestin®, Stadol®

Pronunciation(ha loe PER i dole)

U.S. Brand NamesHaldol®; Haldol® Decanoate

Canadian Brand NamesApo-Haloperidol LA®; Apo-Haloperidol®; Haloperidol Injection, USP; Haloperidol Long Acting; Haloperidol-LA; Haloperidol-LA Omega; Novo-Peridol; Peridol; PMS-Haloperidol LA

Pharmacologic CategoryAntipsychotic Agent, Typical

Use: Labeled IndicationsManagement of schizophrenia; control of tics and vocal utterances of Tourette's disorder in children and adults; severe behavioral problems in children

Use: Unlabeled/InvestigationalTreatment of non-schizophrenia psychosis; may be used for the emergency sedation of severely-agitated or delirious patients; adjunctive treatment of ethanol dependence; antiemetic; psychosis/agitation related to Alzheimer's dementia

Dosing: Adults

Psychosis:

Oral: 0.5-5 mg 2-3 times/day; usual maximum: 30 mg/day

I.M. (as lactate): 2-5 mg every 4-8 hours as needed

I.M. (as decanoate): Initial: 10-20 times the daily oral dose administered at 4-week intervals. Maintenance dose: 10-15 times initial oral dose; used to stabilize psychiatric symptoms

Delirium in the intensive care unit (unlabeled use, unlabeled route):

I.V.: 2-10 mg; may repeat bolus doses every 20-30 minutes until calm achieved then administer 25% of the maximum dose every 6 hours; monitor ECG and QT_c interval

Intermittent I.V.: 0.03-0.15 mg/kg every 30 minutes to 6 hours

Oral: Agitation: 5-10 mg

Continuous I.V. infusion (100 mg/100 mL D_5W): Rates of 3-25 mg/hour have been used

Rapid tranquilization of severely-agitated patient (unlabeled use; administer every 30-60 minutes):

Oral: 5-10 mg

I.M. (as lactate): 5 mg

Average total dose (oral or I.M.) for tranquilization: 10-20 mg

Dosing: ElderlyNonpsychotic patient, dementia behavior (unlabeled use): Initial: Oral: 0.25-0.5 mg 1-2 times/day; increase dose at 4- to 7-day intervals by 0.25-0.5 mg/day. Increase dosing intervals (twice daily, 3 times/day, etc) as necessary to control response or side effects.

Dosing: Pediatric

Sedation/psychotic disorders: Oral:

Children 3-12 years (15-40 kg): Initial: 0.05 mg/kg/day or 0.25-0.5 mg/day given in 2-3 divided doses; increase by 0.25-0.5 mg every 5-7 days; maximum: 0.15 mg/kg/day

Usual maintenance:

Agitation or hyperkinesia: 0.01-0.03 mg/kg/day once daily

Nonpsychotic disorders: 0.05-0.075 mg/kg/day in 2-3 divided doses

Psychotic disorders: 0.05-0.15 mg/kg/day in 2-3 divided doses

Children 6-12 years: Sedation/psychotic disorders: I.M. (as lactate): 1-3 mg/dose every 4-8 hours to a maximum of 0.15 mg/kg/day; change over to oral therapy as soon as able.

Dosing: Renal ImpairmentHemodialysis/peritoneal dialysis: Supplemental dose is not necessary.

Administration: I.M.The decanoate injectable formulation should be administered I.M. only; **do not give decanoate I.V.**

Administration: I.V.

Decanoate: Do **not** administer I.V.

Lactate: Although not an FDA-approved route of administration, Haldol® has been administered by this route in many acute care settings.

Administration: I.V. DetailThe response to I.V. Haldol® may be delayed by several minutes.

pH: 3.0-3.6

Administration: OralDilute the oral concentrate with water or juice before administration. **Note:** Avoid skin contact with oral medication; may cause contact dermatitis.

StorageProtect oral dosage forms from light. Haloperidol lactate injection should be stored at controlled room temperature; do not freeze or expose to temperatures >40°C. Protect from light; exposure to light may cause discoloration and the development of a grayish-red precipitate over several weeks. Stability of standardized solutions is 38 days at room temperature (24°C).

ReconstitutionHaloperidol lactate may be administered IVPB or I.V. infusion in D_5W solutions. NS solutions should not be used due to reports of decreased stability and incompatibility.

Standardized dose: 0.5-100 mg/50-100 mL D_5W.

CompatibilityStable in D_5W; **variable stability (consult detailed reference)** in $D_5{}^1/_4$NS, LR, ${}^1/_2$NS, NS.

Y-site administration: Compatible: Amifostine, amsacrine, aztreonam, cimetidine, cisatracurium, cladribine, dobutamine, docetaxel, dopamine, doxorubicin liposome, etoposide phosphate, famotidine, filgrastim, fludarabine, gatifloxacin, gemcitabine, granisetron, lidocaine, linezolid, lorazepam, melphalan, midazolam, nitroglycerin, norepinephrine ondansetron, paclitaxel, phenylephrine, propofol, remifentanil, sufentanil, tacrolimus, teniposide, theophylline, thiotepa, vinorelbine. **Incompatible:** Allopurinol, amphotericin B cholesteryl sulfate complex, cefepime, fluconazole, foscarnet, heparin, piperacillin/tazobactam, sargramostim. **Variable (consult detailed reference):** Sodium nitroprusside.

Compatibility in syringe: Compatible: Hydromorphone, sufentanil. **Incompatible:** Diphenhydramine, heparin, hydroxyzine, ketorolac. **Variable (consult detailed reference):** Benztropine, cyclizine, diamorphine, morphine.

ContraindicationsHypersensitivity to haloperidol or any component of the formulation; Parkinson's disease; severe CNS depression; bone marrow suppression; severe cardiac or hepatic disease; coma

Allergy Considerations

- Butyrophenone Allergy

Warnings/Precautions

Boxed warnings:

- Dementia: See "Disease-related concerns" below.

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction and prolong QT interval; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics, but risk may be increased with doses exceeding recommendations and/or intravenous administration (unlabeled route). Use with caution or avoid use in patients with electrolyte abnormalities (eg, hypokalemia, hypomagnesemia), hypothyroidism, familial long QT syndrome, concomitant medications which may augment QT prolongation, or any underlying cardiac abnormality which may also potentiate risk. Monitor ECG closely for dose-related QT effects. Adverse effects of decanoate may be prolonged.

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to other neuroleptics, haloperidol has a low potency of cholinergic blockade.

- Blood dyscrasias: Myelosuppression (eg, leukopenia, agranulocytosis) has been observed with antipsychotic use; check blood counts periodically and discontinue at first signs of blood dyscrasias; use is contraindicated in patients with bone marrow suppression.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is high relative to other neuroleptics). Risk of dystonia (and possibly other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Pigmentary retinopathy: May be associated with pigmentary retinopathy.

- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Dementia: **[U.S. Boxed Warning]: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo.** An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Haloperidol is not approved for this indication.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

- Thyroid dysfunction: Avoid in thyrotoxicosis.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

Dosage form specific issues:

- Tartrazine: Some tablets contain tartrazine.

Other warnings/precautions:

- Parenteral administration: Hypotension may occur, particularly with parenteral administration. Risk of QT prolongation, torsade de pointes, and sudden death appear to be increased with intravenous administration, particularly at higher doses. Although the short-acting form (lactate) is used clinically intravenously, the I.V. use of the injection is not an FDA-approved route of administration; the decanoate form should never be administered intravenously.

Geriatric ConsiderationsMany elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior. Before initiating antipsychotic medication, the clinician should investigate any possible reversible cause; any stress or stress from any disease can cause acute “confusion” or worsening of baseline nonpsychotic behavior. Most commonly acute changes in behavior are due to increases in drug dose or addition of new drug to regimen; fluid electrolyte loss; infections; and changes in environment.

Any changes in disease status in any organ system can result in behavior changes.

In the treatment of agitated, demented, elderly patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control.

Clinical studies of haloperidol did not include sufficient numbers of subjects ≥65 years of age to determine whether they respond differently from younger subjects. Other reported clinical experience has not consistently identified differences between the elderly and younger patients. However, the prevalence of tardive dyskinesia appears to be highest among the elderly, especially elderly women. Also, the pharmacokinetics of haloperidol in geriatric patients generally warrants the use of lower doses.

Pregnancy Risk FactorC
LactationEnters breast milk/not recommended (AAP rates “of concern”)
Breast-Feeding ConsiderationsDecline in developmental scores may be seen in nursing infants.
Adverse ReactionsFrequency not defined.

Cardiovascular: Abnormal T waves with prolonged ventricular repolarization, arrhythmia, hyper-/hypotension, QT prolongation, sudden death, tachycardia, torsade de pointes

Central nervous system: Agitation, akathisia, altered central temperature regulation, anxiety, confusion, depression, drowsiness, dystonic reactions, euphoria, extrapyramidal reactions, headache, insomnia, lethargy, neuroleptic malignant syndrome (NMS), pseudoparkinsonian signs and symptoms, restlessness, seizure, tardive dyskinesia, tardive dystonia, vertigo

Dermatologic: Alopecia, contact dermatitis, hyperpigmentation, photosensitivity (rare), pruritus, rash

Endocrine & metabolic: Amenorrhea, breast engorgement, galactorrhea, gynecomastia, hyper-/hypoglycemia, hyponatremia, lactation, mastalgia, menstrual irregularities, sexual dysfunction

Gastrointestinal: Anorexia, constipation, diarrhea, dyspepsia, hypersalivation, nausea, vomiting, xerostomia

Genitourinary: Priapism, urinary retention

Hematologic: Cholestatic jaundice, obstructive jaundice

Ocular: Blurred vision

Respiratory: Bronchospasm, laryngospasm

Miscellaneous: Diaphoresis, heat stroke

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2D6 (major), 3A4 (major); **Inhibits** CYP2D6 (moderate), 3A4 (moderate)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Haloperidol. *Risk D: Consider therapy modification*

ChlorproMAZINE: Haloperidol may enhance the QTc-prolonging effect of ChlorproMAZINE. ChlorproMAZINE may decrease the metabolism of Haloperidol. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: May increase the serum concentration of Haloperidol. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Haloperidol. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersVital signs; lipid profile, fasting blood glucose/Hgb A_{1c}; BMI; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms (EPS); ECG (with off-label intravenous administration)

Reference Range

Therapeutic: 5-20 ng/mL (SI: 10-40 nmol/L) (psychotic disorders - less for Tourette's and mania)

Toxic: >42 ng/mL (SI: >84 nmol/L)

Nursing: Physical Assessment/MonitoringAssess other medications patient is taking for effectiveness and interactions (especially drugs metabolized by P450 enzymes). Review ophthalmic screening. Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. With I.M. or I.V. use, monitor for hypotension and cardiac irregularities. Initiate at lower doses and taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsLipid profile, fasting blood glucose/Hgb A_{1c}; BMI

Patient EducationUse exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results; do not discontinue without consulting prescriber. Dilute oral concentration with water or juice. Do not take within 2 hours of any antacid. Store away from light. Avoid alcohol or caffeine and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid skin contact with medication; may cause contact dermatitis (wash immediately with warm, soapy water). You may experience excess drowsiness, restlessness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); urinary retention (void before taking medication); or decreased perspiration (avoid strenuous exercise in hot environments). Report persistent CNS effects (eg, trembling fingers, altered gait or balance, excessive sedation, seizures, unusual movements, anxiety, abnormal thoughts, confusion, personality changes); chest pain, palpitations, rapid heartbeat, severe dizziness; unresolved urinary retention or changes in urinary pattern; vision changes; skin rash or yellowing of skin; respiratory difficulty; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Note: Strength expressed as base.

Injection, oil, as decanoate: 50 mg/mL (1 mL, 5 mL); 100 mg/mL (1 mL, 5 mL)

Haldol® Decanoate: 50 mg/mL (1 mL; 5 mL [DSC]); 100 mg/mL (1 mL; 5 mL [DSC]) [contains benzyl alcohol, sesame oil]

Injection, solution, as lactate: 5 mg/mL (1 mL, 10 mL)

Haldol®: 5 mg/mL (1 mL)

Solution, oral concentrate, as lactate: 2 mg/mL (15 mL, 120 mL)

Tablet: 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg, 20 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Haldol Decanoate)

100 mg/mL (5): $378.99

Solution (Haloperidol Decanoate)

100 mg/mL (5): $184.99

Tablets (Haloperidol)

0.5 mg (90): $17.00

1 mg (90): $19.99

2 mg (90): $18.99

5 mg (90): $25.99

10 mg (60): $72.26

20 mg (60): $124.07

Mechanism of ActionHaloperidol is a butyrophenone antipsychotic which blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors in the brain; depresses the release of hypothalamic and hypophyseal hormones; believed to depress the reticular activating system thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis

Pharmacodynamics/Kinetics

Onset of action: Sedation: I.M., I.V.: 30-60 minutes

Duration: Decanoate: 2-4 weeks

Distribution: V_d: 8-18 L/kg; crosses placenta; enters breast milk

Protein binding: 90%

Metabolism: Hepatic to inactive compounds

Bioavailability: Oral: 60%

Half-life elimination: 18 hours; Decanoate: ~1 day

Time to peak, serum: Oral: 2-6 hours; I.M.: 20 minutes; Decanoate: 7 days

Excretion: Urine (33% to 40% as metabolites) within 5 days; feces (15%)

Clearance: 550 ± 133 mL/minute

Related Information

- Antipsychotic Agents
- Antipsychotic Receptor Profile
- CMS: Long-Term Care Facility Thresholds
- Depression
- Discontinuation of Psychotropic Drugs
- Liquid Compatibility
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Orthostatic hypotension, and nasal congestion are possible; since the drug is a dopamine antagonist, extrapyramidal symptoms of the TMJ are a possibility.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsManufacturer's information states that haloperidol may block vasopressor activity of epinephrine. This has not been observed during use of epinephrine as a vasoconstrictor in local anesthesia. Haloperidol is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health CommentHaloperidol is a high-potency antipsychotic. Older antipsychotic medications (chlorpromazine, haloperidol), which do not meet specific criteria for “atypical” antipsychotics, are often referred to as typical antipsychotics. They are associated with the troubling side effect, EPS. However, it is commonly believed that in order for a drug to treat psychosis, it must block dopamine is some manner.

Common side effects include sedation and neuroleptic effect (reduced initiative, interest in the environment, and display of emotion or affect). All **typical** antipsychotics are considered to be equally effective if given in equipotent doses. An inverse relationship exists between intrinsic antimuscarinic activity and propensity to cause extrapyramidal side effects. If dystonia or pseudoparkinsonism occurs, antiparkinsonian agents should be considered. If akathisia occurs, beta-blockers (eg, propranolol), benzodiazepines, or antiparkinsonian agents should be considered. Tardive dyskinesia (TD) secondary to typical antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. After this time period, the incidence is estimated to be 2% to 3% per year. Prevalence rates are ~15% to 20%. Female gender and age constitute risk factors for TD. Indeed, prevalence rates have been reported to be as high as 70% in elderly females. No specific treatment exists for TD, however, patients are often initiated on/switched to an atypical antipsychotic because of their lower incidence to cause TD and hopes of suppression.

Typical antipsychotics are usually only indicated for schizophrenia, but are generally effective for mania and psychosis and/or behavioral syndromes secondary to other mental conditions. Nonpsychiatric uses include Tourette's syndrome, Huntington's disease, and occasionally, intractable hiccups, pruritus, nausea, and vomiting.

These drugs are thought to exert their antipsychotic activity by blocking dopamine D_2 receptors in the mesolimbic dopaminergic pathway. Side effects are often related to their ability to antagonize dopamine receptors in the nigrostriatal and tuberoinfundibular pathways.

Long-acting dosage form is useful in patients nonadherent to treatment.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Cardiovascular ConsiderationsHypotension may occur, particularly with parenteral administration. Tachycardic arrhythmias and QT interval prolongation may also occur. When used at recommended doses, cardiac arrhythmias have occurred.

Anesthesia and Critical Care Concerns/Other Considerations

Delirium in the ICU Patient: Set goals for control of delirium. Haloperidol has not been studied in well-controlled trials enrolling ICU patients with acute delirium or agitation. The FDA and Johnson and Johnson have recently (September, 2007) informed healthcare providers about an increased risk of QT prolongation, torsade de pointes (TdP), and sudden death associated with haloperidol use, particularly high dose, intravenous administration (unlabeled use). Case-control studies indicate a dose-response between intravenous haloperidol and TdP. Even when used at recommended doses, cardiac arrhythmias have occurred. Caution or avoidance of haloperidol is advised in patients with predisposing risk factors including electrolyte abnormalities (eg, hypokalemia, hypomagnesemia), hypothyroidism, familial long QT syndrome, concomitant medications which may augment QT prolongation, or any underlying cardiac abnormality which may also potentiate risk. In addition, ECG monitoring is recommended with off-label intravenous use of haloperidol.

Haloperidol may cause extrapyramidal symptoms. It is the most frequently implicated antipsychotic associated with neuroleptic malignant syndrome.

Index Terms Haloperidol Decanoate; Haloperidol Lactate

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International Brand NamesAloperidin (GR); Apo-Haloperidol (MY, PL); Decaldol (PL); Haldecan (TW); Haldol (EC, HR, LU, MX, NI, NO, NZ, PA, PK, PL, PT, VE); Haldol Decanoaat (NL); Haldol Decanoas (AE, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CR, CY, CZ, DO, EG, ET, FR, GH, GM, GN, GT, GY, HK, HN, ID, IL, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PE, PR, PY, QA, SA, SC, SD, SL, SN, SR, SV, SY, TH, TN, TT, TZ, UG, UY, YE, ZA, ZM, ZW); Haldol decanoas (LU); Haldol Decanoat (AT, DE); Haldol Decanoate (AU, GB, IE); Haldol Decanoato (BR, CN); Haldol depo (HR); Haldol Depot (SE); Haloper (RU); Haloperidol (PL); Haloperidol Decanoat (HU, PL); Haloperidol Esteve (ES); Haloperidol Prodes (ES); Haloperidol-ratiopharm (LU); Haloperil (MX); Halopidol decanoato (AR, CO); Haridol Decanoate (TH); Haridol-D (CL); Motivan (MY); Pericate (IL); Senorm L.A. (IN, TH); Seredol Deca (PH); Serenace (BD, CL, JP, MY, PK, SG); Serenase (FI); Serenase Dekanoat (DK); Serenelfi (PT)

Halothane

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Halothane may be confused with Halotestin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(HA loe thane)

Pharmacologic CategoryGeneral Anesthetic, Inhalation

Use: Labeled IndicationsInduction and maintenance of general anesthesia

Dosing: AdultsAnesthesia: Inhalation: Minimum alveolar concentration (MAC), the concentration at which 50% of patients do not respond to surgical incision, is 0.74% for halothane. The concentration at which amnesia and loss of awareness occur (MAC - awake) is 0.41%. Surgical levels of anesthesia are maintained with concentrations between 0.5% to 2%; inspired concentrations of up to 3% required for induction of anesthesia. MAC is reduced in the elderly.

Dosing: ElderlyMAC is reduced in the elderly.

Administration: InhalationVia halothane-specific calibrated vaporizer

StorageHalothane mixed with oxygen or air is not flammable or explosive.

ContraindicationsHypersensitivity to halothane or any component of the formulation; known or suspected history of malignant hyperthermia; history of hepatitis after a previous anesthetic

Warnings/Precautions

Concerns related to adverse effects:

- Cardiovascular effects: Decrease in blood pressure is dose dependent, due to myocardial depression and blunting of the baroreceptor mediated tachycardic response to hypotension. Sinus bradycardia, wandering pacemaker, and junctional rhythm are not uncommon.
- Decreased blood flow: May cause decrease in hepatic, renal and splenic blood flow.
- Hepatitis: Induces hepatic microsomal enzymes function. Incidence of halothane-induced hepatitis is 1/10,000 to 1/30,000 anesthetics (less in children); it most often occurs following repeat administration (etiology is likely immune-mediated, mortality is 50%).
- Hyperkalemia: Use of other inhaled anesthetics has been associated with rare cases of perioperative hyperkalemia; concomitant use of succinylcholine was associated with many of the reported cases, but not all. Risk of hyperkalemia is increased in pediatric patients with underlying neuromuscular disease (eg, Duchenne muscular dystrophy). Other abnormalities may include elevation in CPK and myoglobinuria. Monitor closely for arrhythmias. Aggressively identify and treat hyperkalemia.
- Increased intracranial pressure: Dilates the cerebral vasculature and may, in certain conditions, increase intracranial pressure.
- Malignant hyperthermia: May trigger malignant hyperthermia; avoid use in patients susceptible to malignant hyperthermia.
- Respiratory depression: Respiration is depressed (increase $PaCO_2$ at 1 MAC to 45 mm Hg with spontaneous ventilation). Hypoxic pulmonary vasoconstriction is depressed which may lead to increased pulmonary shunt. Hypoxemia-induced increase in ventilation is abolished at low halothane concentration. Can produce elevated carbon monoxide levels in the presence of a dry carbon dioxide absorbent within the circle breathing system of an anesthetic machine.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, hypotension, myocardial depression, reflex tachycardia, ventricular or supraventricular arrhythmias

Central nervous system: Agitation, restlessness

Gastrointestinal: Nausea, vomiting

Respiratory: Hypoxemia, respiratory depression/arrest

Miscellaneous: Shivering

Metabolism/Transport Effects**Substrate** of CYP2A6 (minor), 2B6 (minor), 2C9 (minor), 2D6 (minor), 2E1 (major), 3A4 (minor)

Drug Interactions

CYP2E1 Inhibitors (Moderate): May decrease the metabolism of CYP2E1 Substrates. *Risk C: Monitor therapy*

CYP2E1 Inhibitors (Strong): May decrease the metabolism of CYP2E1 Substrates. *Risk D: Consider therapy modification*

EPINEPHrine: Inhalational Anesthetics may enhance the arrhythmogenic effect of EPINEPHrine. *Risk D: Consider therapy modification*

Methylphenidate: May enhance the hypertensive effect of Inhalational Anesthetics. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): Inhalational Anesthetics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure, heart rate and rhythm, temperature, oxygen saturation, end-tidal CO_2 and end-tidal halothane concentrations should be monitored prior to and throughout anesthesia.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Liquid: 125 mL [DSC], 250 mL [DSC]

Generic AvailableYes

Pharmacodynamics/Kinetics

Onset of action: 1.5-3 minutes

Duration: Emergence time: Depends on blood concentration when halothane is discontinued

Metabolism: Hepatic (20% to 50%) via CYP, both oxidatively and reductively

Excretion: Exhaled gases within 24 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause agitation or restlessness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with benzodiazepines decrease the minimum alveolar concentration of halothane. Disulfiram may increase levels of halothane via enzyme inhibition.

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International Brand NamesAnestane (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Fluothane (AE, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CN, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HN, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, NZ, OM, PE, PK, PT, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TN, TR, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Halan (PL); Ineltano (AR, PY); Narcotan (BG, CZ, HN, HU, PL)

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Pharmacologic Category[Chemotherapy Regimen, Osteosarcoma]

Regimen UseOsteosarcoma

Regimen

Methotrexate: I.V.: 12 g/m^2/week for 2-12 weeks

[total dose/cycle = 24-144 g/m^2]

Leucovorin calcium rescue: Oral, I.V.: 15 mg/m^2 every 6 hours (beginning 30 hours after the beginning of the 4-hour methotrexate infusion) for 10 doses; **serum methotrexate levels must be monitored**

[total dose/cycle = 150 mg/m^2]

References

Camitta BM and Holcenberg JS, "Safety of Delayed Leucovorin "Rescue" Following High-Dose Methotrexate in Children," *Med Pediatr Oncol*, 1978, 5(1):55-9.[PubMed 370536]

Hemin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(HEE min)

U.S. Brand NamesPanhematin®

Pharmacologic CategoryBlood Modifiers

Use: Labeled IndicationsTreatment of recurrent attacks of acute intermittent porphyria (AIP)

Dosing: AdultsPorphyria (AIP): I.V.: 1-4 mg/kg/day administered over 10-15 minutes for 3-14 days; may be repeated no earlier than every 12 hours; not to exceed 6 mg/kg in any 24-hour period

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Porphyria (AIP): Children ≥16 years: I.V.: Refer to adult dosing.

Administration: I.V.Infuse over 10-15 minutes using a 0.45 micron or smaller filter. Administer through a large vein or central line to prevent phlebitis.

StorageUndergoes rapid chemical decomposition in solution; prepare immediately before administration. Prior to reconstitution, store vials at 2°C to 8°C (36°F to 46°F).

ReconstitutionImmediately before use, reconstitute each vial with 43 mL sterile water for injection, resulting in a final concentration of 7 mg/mL. Shake well for 2-3 minutes to dissolve.

ContraindicationsHypersensitivity to hemin or any component of the formulation; porphyria cutanea tarda

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.
- Porphyria: Appropriate use: See “Disease-related concerns” below.

Disease-related concerns:

- Porphyria: Appropriate use: **[U.S. Boxed Warning]: Should only be used after an appropriate period of alternate therapy (carbohydrate loading) has been tried.** Intended to prevent porphyria attacks from becoming critical; not intended to repair neuronal damage resulting from attacks.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <16 years of age.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to Ovation Pharmaceuticals at 1-800-455-1141.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of a physician experienced in the management of porphyrias.**

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit out weighs the potential risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Central nervous system: Pyrexia

Hematologic: Leukocytosis

Local: Phlebitis

Postmarketing and/or case reports: Coagulopathy, fibrin split products increased, hematocrit decreased, hypofibrogenemia, prothrombin time increased, partial thromboplastin time increased, thrombocytopenia

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersUrinary levels of delta-aminolevulinic acid (ALA), uroporphyrinogen (UPG), porphobilinogen (PBG), coproporphyrin

Monitoring: Lab TestsUrinary levels of delta-aminolevulinic acid (ALA), uroporphyrinogen (UPG), porphobilinogen (PBG), coproporphyrin
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Panhematin®: 313 mg [provides 7 mg/mL when reconstituted]

Generic AvailableNo
ManufacturerOvation Pharmaceuticals Inc
Mechanism of ActionInhibits the hepatic and/or marrow synthesis of ALA synthase, the enzyme that regulates the porphyrin/heme pathway
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentAvoid concurrent use with barbiturates
Index TermsHematin
References

Anderson KE, Bloomer JR, Bonkovsky HL, et al, "Recommendations for the diagnosis and Treatment of the Acute Porphyrias," *Ann Intern Med*, 2005, 142(6):439-50.[PubMed 15767622]

International Brand NamesHuman Hemin Orphan Europe (PL); Normosang (CH, CZ, DK, EE, FI, GB, SE); Panhematin (AU)

Heparin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Heparin Sodium Recall Updated - April 3, 2008

The U.S. Food and Drug Administration (FDA) is alerting healthcare professionals that Covidien (formerly Tyco Healthcare), has initiated a voluntary recall of heparin sodium prefilled syringes from the U.S. market. This recall follows notification from the manufacturer's supplier, Scientific Protein Laboratories LLC (SPL) that a heparin-like contaminant (previously identified as oversulfated chondroitin sulfate) was present in two lots of heparin sodium USP acquired by Covidien. This announcement follows previously announced recalls of heparin sodium products by Baxter Healthcare and the FDA (single-use and multidose vials, lock flush solutions) from U.S. markets, and by B. Braun Medical Inc, along with the FDA and Health Canada (premixed heparin sodium solutions) from U.S. and Canadian markets, respectively. In each case, all recalled heparin sodium products were supplied by SPL.

Serious adverse events have been reported to Baxter Healthcare and include hypersensitivity reactions (eg, severe hypotension, oral swelling, shortness of breath, nausea, and vomiting) that generally occur within minutes after administering intravenous bolus doses of heparin sodium largely associated with the multiple-dose vials. However, reactions have also been associated with use of single-dose vials. No adverse events have been reported to Covidien or B. Braun Medical Inc.

Patients receiving medically necessary intravenous bolus doses of heparin should be monitored closely for adverse events, especially signs of hypersensitivity. Equipment for resuscitation and trained personnel experienced in handling emergencies should always be immediately available. Whenever possible, infusions of heparin should be instituted without a bolus or the lowest possible bolus dose should be used. Use of pretreatment corticosteroids or antihistamines before heparin has not been determined to be of benefit at this time. Use of other anticoagulants (eg, direct thrombin inhibitors, low molecular weight heparins) should be used only if heparin is unavailable and the indication is appropriate.

For more information, refer to the following:

U.S.:

http://www.fda.gov/oc/po/firmrecalls/covidien03_08.html

http://www.fda.gov/oc/po/firmrecalls/bbraun03_08.html

http://www.fda.gov/medwatch/safety/2008/safety08.htm#HeparinInj2

http://www.baxter.com/about_baxter/news_room/news_releases/2008/01-25-08-heparin_multi.htm

Canada:

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_49_e.html

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_52_e.html

Medication Safety Issues

Sound-alike/look-alike issues:

Heparin may be confused with Hespan®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Heparin sodium injection 10,000 units/mL and Hep-Lock U/P 10 units/mL have been confused with each other. Fatal medication errors have occurred between the two whose labels are both blue. **Never rely on color as a sole indicator to differentiate product identity.**

Heparin lock flush solution is intended only to maintain patency of I.V. devices and is **not** to be used for anticoagulant therapy.

Note: The 100 unit/mL concentration should not be used in neonates or infants <10 kg. The 10 unit/mL concentration may cause systemic anticoagulation in infants <1 kg who receive frequent flushes.

2009 National Patient Safety Goals: The Joint Commission on Accreditation of Healthcare Organizations requires healthcare organizations that provide anticoagulant therapy to have a process in place to reduce the risk of anticoagulant-associated patient harm. Patients receiving anticoagulants should receive individualized care through a defined process that includes standardized ordering, dispensing, administration, monitoring and education. This does not apply to routine short-term use of anticoagulants for prevention of venous thromboembolism when the expectation is that the patient's laboratory values will remain within or close to normal values (NPSG.03.05.01).

Pronunciation(HEP a rin)

U.S. Brand NamesHep-Lock U/P; Hep-Lock®; HepFlush®-10

Canadian Brand NamesHepalean®; Hepalean® Leo; Hepalean®-LOK

Pharmacologic CategoryAnticoagulant

Use: Labeled IndicationsProphylaxis and treatment of thromboembolic disorders; as an anticoagulant for extracorporeal and dialysis procedures

Note: Heparin lock flush solution is intended only to maintain patency of I.V. devices and is **not** to be used for anticoagulant therapy.

Use: Unlabeled/InvestigationalST-elevation myocardial infarction (STEMI) - combination regimen of heparin (unlabeled dose), tenecteplase (half dose), and abciximab (full dose)

Dosing: Adults**Note:** Many concentrations of heparin are available ranging from 1 unit/mL to 20,000 units/mL. Carefully examine each prefilled syringe or vial prior to use ensuring that the correct concentration is chosen. Heparin lock flush solution is intended only to maintain patency of I.V. devices and is not to be used for anticoagulant therapy.

DVT Prophylaxis (low-dose heparin): SubQ: 5000 units every 8-12 hours

Systemic anticoagulation: I.V. infusion (weight-based dosing per institutional nomogram recommended):

Acute coronary syndromes: I.V. infusion:

Percutaneous coronary intervention:

If no concurrent GPIIb/IIIa inhibitor: Initial bolus of 60-100 units/kg (target ACT 250-350 seconds)

or

If receiving GPIIb/IIIa inhibitor: Initial bolus of 50-70 units/kg (target ACT 200-250 seconds)

STEMI: Fibrinolytic therapy:

Full-dose alteplase, reteplase, or tenecteplase with dosing as follows: Concurrent bolus of 60 units/kg (maximum: 4000 units), then 12 units/kg/hour (maximum: 1000 units/hour) as continuous infusion. Check aPTT every 4-6 hours; adjust to target of 1.5-2 times the upper limit of control (50-70 seconds in clinical trials); usual range 10-30 units/kg/hour. Duration of heparin therapy depends on concurrent therapy and the specific patient risks for systemic or venous thromboembolism.

Combination regimen (unlabeled): Half-dose tenecteplase (15-25 mg based on weight) and abciximab 0.25 mg/kg bolus then 0.125 mcg/kg/minute (maximum 10 mcg/minute) for 12 hours with heparin dosing as follows: Concurrent bolus of 40 units/kg (maximum 3000 units), then 7 units/kg/hour (maximum: 800 units/hour) as continuous infusion. Adjust to a aPTT target of 50-70 seconds.

Unstable angina/Non-ST-elevation myocardial infarction (NSTEMI): Initial bolus of 60 units/kg (maximum: 4000 units), followed by an initial infusion of 12 units/kg/hour (maximum: 1000 units/hour). The American College of Chest Physicians consensus conference has recommended dosage adjustments to correspond to a therapeutic range equivalent to heparin levels of 0.3-0.7 units/mL by antifactor Xa determinations.

Treatment of venous thromboembolism:

DVT/PE: I.V.: 80 units/kg (or 5000 units) I.V. push followed by continuous infusion of 18 units/kg/hour (or 1300 units/hour). The American College of Chest Physicians consensus conference has recommended dosage adjustments to correspond to a therapeutic range equivalent to heparin levels of 0.3-0.7 units/mL by antifactor Xa determinations.

DVT/PE: SubQ:

Monitored dosing regimen: Initial: 17,500 units or 250 units/kg then 250 units/kg every 12 hours. The American College of Chest Physicians consensus conference has recommended dosage adjustments to correspond to a therapeutic range equivalent to heparin levels of 0.3-0.7 units/mL by antifactor Xa determinations.

Unmonitored dosing regimen: Initial: 333 units/kg then 250 units/kg every 12 hours

Intermittent I.V. Anticoagulation: Intermittent I.V.: Initial: 10,000 units, then 50-70 units/kg (5000-10,000 units) every 4-6 hours

Maintenance of line patency (line flushing): When using daily flushes of heparin to maintain patency of single and double lumen central catheters, 10 units/mL is commonly used for younger infants (eg, <10 kg) while 100 units/mL is used for older infants, children, and adults. Capped PVC catheters and peripheral heparin locks require flushing more frequently (eg, every 6-8 hours). Volume of heparin flush is usually similar to volume of catheter (or slightly greater). Additional flushes should be given when stagnant blood is observed in catheter, after catheter is used for drug or blood administration, and after blood withdrawal from catheter.

Parenteral nutrition: Addition of heparin (0.5-3 unit/mL) to peripheral and central parenteral nutrition has not been shown to decrease catheter-related thrombosis. The final concentration of heparin used for TPN solutions may need to be decreased to 0.5 units/mL in small infants receiving larger amounts of volume in order to avoid approaching therapeutic amounts. Arterial lines are heparinized with a final concentration of 1 unit/mL.

Dosing: ElderlyPatients >60 years of age may have higher serum levels and clinical response (longer aPTTs) as compared to younger patients receiving similar dosages. Lower dosages may be required.
Dosing: Pediatric**Note:** Many concentrations of heparin are available ranging from 1 unit/mL to 20,000 units/mL. Carefully examine each prefilled syringe or vial prior to use ensuring that the correct concentration is chosen. Heparin lock flush solution is intended only to maintain patency of I.V. devices and is not to be used for anticoagulant therapy.

Prophylaxis for cardiac catheterization (arterial approach): I.V.: Bolus: 100-150 units/kg (Monagle, 2008)

Systemic heparinization:

Intermittent I.V.: Initial: 50-100 units/kg, then 50-100 units/kg every 4 hours (**Note:** Continuous I.V. infusion is preferred)

I.V. infusion: Initial loading dose: 75 units/kg given over 10 minutes, then initial maintenance dose: 20 units/kg/hour; adjust dose to maintain aPTT of 60-85 seconds (assuming this reflects an antifactor Xa level of 0.35-0.7 units/mL); see table.

Pediatric Protocol For Systemic Heparin Adjustment

To be used after initial loading dose and maintenance I.V. infusion dose (see usual dosage listed above) to maintain aPTT of 60-85 seconds (assuming this reflects antifactor Xa level of 0.35-0.7 units/mL).

Obtain blood for aPTT 4 hours after heparin loading dose and 4 hours after every infusion rate change.

Obtain daily CBC and aPTT after aPTT is therapeutic.

aPTT (seconds)	**Dosage Adjustment**	**Time to Repeat aPTT**
<50	Give 50 units/kg bolus and increase infusion rate by 10%	4 h after rate change
50-59	Increase infusion rate by 10%	4 h after rate change
60-85	Keep rate the same	Next day
86-95	Decrease infusion rate by 10%	4 h after rate change
96-120	Hold infusion for 30 minutes and decrease infusion rate by 10%	4 h after rate change
>120	Hold infusion for 60 minutes and decrease infusion rate by 15%	4 h after rate change
Modified from Monagle P, Chalmers E, Chan A, et al, “Antithrombotic Therapy in Neonates and Children,” *Chest*, 2008, 133(6 Suppl):887-968.		

Note: Refer to adult dosing for notes on line flushing and TPN.

Calculations

- Heparin Maintenance Infusion

Administration: I.M.Do not administer I.M. due to pain, irritation, and hematoma formation.
Administration: I.V.

Continuous infusion: Infuse via infusion pump.

Heparin lock: Inject via injection cap using positive pressure flushing technique. Heparin lock flush solution is intended only to maintain patency of I.V. devices and is **not** to be used for anticoagulant therapy.

Administration: OtherSubQ: Inject in subcutaneous tissue only (not muscle tissue). Injection sites should be rotated (usually left and right portions of the abdomen, above iliac crest).
StorageHeparin solutions are colorless to slightly yellow. Minor color variations do not affect therapeutic efficacy. Heparin should be stored at controlled room temperature. Protect from freezing and temperatures >40°C.

Stability at room temperature and refrigeration:

Prepared bag: 24 hours.

Premixed bag: After seal is broken. 4 days.

Out of overwrap stability: 30 days.

Reconstitution

Standard concentration/diluent: 25,000 units/500 mL D_5W (premixed). If preparing solution, mix thoroughly prior to administration.

Minimum volume: 250 mL D_5W.

Compatibility

Stable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, $D_{25}W$, fat emulsion 10%, ${}^1/_2NS$, NS, Ringer's injection; **variable stability (consult detailed reference)** in D_5NS, D_5W, $D_{10}W$, LR, peritoneal dialysis solutions, TPN.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, aminophylline, ampicillin, ampicillin/sulbactam, anidulafungin, atracurium, atropine, aztreonam, bleomycin, calcium gluconate, cefazolin, cefotetan, ceftazidime, ceftriaxone, chlordiazepoxide, chlorpromazine, cimetidine, cisplatin, cladribine, clindamycin, cyanocobalamin, cyclophosphamide, cytarabine, daptomycin, dexmedetomidine, dexamethasone sodium phosphate, digoxin, diphenhydramine, docetaxel, dopamine, doxapram, doxorubicin liposome, edrophonium, enalaprilat, epinephrine, ertapenem, erythromycin lactobionate, esmolol, estrogens (conjugated), ethacrynate, etoposide phosphate, famotidine, fenoldopam, fentanyl, fluconazole, fludarabine, fluorouracil, foscarnet, furosemide, gemcitabine, granisetron, hetastarch in lactated electrolyte injection, hydralazine, hydrocortisone sodium succinate, hydromorphone, insulin (regular), isoproterenol, kanamycin, leucovorin calcium, lidocaine, linezolid, lorazepam, magnesium sulfate, melphalan, menadiol sodium diphosphate, meperidine, meropenem, methotrexate, methoxamine, methyldopate, methylergonovine, metoclopramide, metronidazole, micafungin, midazolam, milrinone, minocycline, mitomycin, morphine, nafcillin, neostigmine, nitroglycerin, norepinephrine, ondansetron, oxacillin, oxytocin, paclitaxel, pancuronium, pemetrexed, penicillin G potassium, pentazocine, phytonadione, piperacillin, piperacillin/tazobactam, potassium chloride, procainamide, prochlorperazine edisylate, propofol, propranolol, pyridostigmine, ranitidine, remifentanil, sargramostim, scopolamine, sodium bicarbonate, sodium nitroprusside, streptokinase, succinylcholine, tacrolimus, theophylline, thiopental, thiotepa, ticarcillin/clavulanate potassium, tigecycline, tirofiban, trimethobenzamide, trimethaphan camsylate, vasopressin, vecuronium, vinblastine, vincristine, warfarin, zidovudine. **Incompatible:** Alteplase, amiodarone, amphotericin B cholesteryl sulfate complex, amsacrine, ciprofloxacin, clarithromycin, diazepam, doxycycline, ergotamine, filgrastim, gatifloxacin, gentamicin, haloperidol lactate, idarubicin, isosorbide dinitrate, levofloxacin, methotrimeprazine, nesiritide, phenytoin, tobramycin, triflupromazine. **Variable (consult detailed reference):** Aldesleukin, antithymocyte globulin (rabbit), cisatracurium, dacarbazine, diltiazem, dobutamine, doxorubicin HCl, droperidol, drotrecogin alfa, fentanyl, labetalol, methylprednisolone sodium succinate, nicardipine, promethazine, quinidine gluconate, TPN, vancomycin, vinorelbine.

Compatibility in syringe: Compatible: Aminophylline, amphotericin B, ampicillin, atropine, bleomycin, buprenorphine, caffeine citrate, cefazolin, cefotaxime, cefoxitin, chloramphenicol, cisplatin, clindamycin, clonazepam, clonidine, cyclophosphamide, diatrizoate meglumine 52%, diatrizoate sodium 8%, diatrizoate sodium 60%, diazoxide, digoxin, dobutamine, dopamine, epinephrine, etomidate, fentanyl, floxacillin, fluorouracil, fosfomycin, furosemide, iohexol, iopamidol, iothalamate meglumine 60%, ioxaglate meglumine 39.3%, ioxaglate sodium 19.6%, leucovorin calcium, lidocaine, lincomycin, methotrexate, metoclopramide, mitomycin, nafcillin, naloxone, neostigmine, nitroglycerin, norepinephrine, pancuronium, penicillin G, pentoxifylline, phenobarbital, piperacillin, ranitidine, sodium nitroprusside, succinylcholine, tramadol, trimethoprim/sulfamethoxazole, verapamil, vincristine. **Incompatible:** Amikacin, amiodarone, chlorpromazine, diazepam, doxorubicin hydrochloride, droperidol, erythromycin, erythromycin lactobionate, gentamicin, haloperidol lactate, hydromorphone, kanamycin, meperidine, methotrimeprazine, midazolam, pantoprazole, pentazocine, promethazine, streptomycin, tobramycin, triflupromazine, vancomycin, warfarin. **Variable (consult detailed reference):** Cimetidine, dimenhydrinate, morphine, vinblastine.

Compatibility when admixed: Compatible: Aminophylline, amphotericin B, amphotericin B with hydrocortisone sodium succinate, ascorbic acid injection, bleomycin, calcium gluconate, cefepime, chloramphenicol, clindamycin, colistimethate, dimenhydrinate, dopamine, enalaprilat, esmolol, floxacillin, fluconazole, flumazenil, furosemide, hydromorphone, isoproterenol, lidocaine, lincomycin, magnesium sulfate, meropenem, methyldopate, methylprednisolone sodium succinate, nafcillin, norepinephrine, octreotide, potassium chloride, promazine, ranitidine, sodium bicarbonate, teicoplanin, verapamil, vitamin B complex, vitamin B complex with C. **Incompatible:** Alteplase, amikacin, atracurium, ciprofloxacin, cytarabine, daunorubicin hydrochloride, erythromycin lactobionate, gentamicin, hyaluronidase, kanamycin, levorphanol, meperidine, morphine, polymyxin B sulfate, promethazine, streptomycin. **Variable (consult detailed reference):** Ampicillin, antithymocyte globulin (rabbit), dobutamine, hydrocortisone sodium succinate, mitomycin, penicillin G potassium, penicillin G sodium, vancomycin.

Contraindications

Hypersensitivity to heparin or any component of the formulation (unless a life-threatening situation necessitates use and use of an alternative anticoagulant is not possible); severe thrombocytopenia; uncontrolled active bleeding except when due to disseminated intravascular coagulation (DIC); suspected intracranial hemorrhage; not for I.M. use; not for use when appropriate blood coagulation tests cannot be obtained at appropriate intervals (applies to full-dose heparin only)

Allergy Considerations

- Heparin (Unfractionated) Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: Monitor patient closely for signs or symptoms of bleeding. Certain patients are at increased risk of bleeding; risk factors include subacute bacterial endocarditis; congenital or acquired bleeding disorders; active ulcerative or angiodysplastic GI diseases; continuous GI tube drainage; severe uncontrolled hypertension; history of hemorrhagic stroke; or use shortly after brain, spinal, or ophthalmologic surgery or other invasive procedures including spinal tap or spinal anesthesia; concomitant treatment with platelet inhibitors; recent GI bleeding; thrombocytopenia or platelet defects; severe liver disease; hypertensive or diabetic retinopathy; or in patients (especially women) >60 years of age. Discontinue if bleeding occurs; severe hemorrhage or overdosage may require protamine.

- Heparin-induced thrombocytopenia (HIT): May cause thrombocytopenia; monitor platelet count closely. Patients who develop HIT may be at risk of developing a new thrombus (heparin-induced thrombocytopenia and thrombosis [HITT]). Discontinue therapy and consider alternatives if platelets are <100,000/mm^3 and/or thrombosis develops. HIT or HITT may be delayed and can occur up to several weeks after discontinuation of heparin.

- Heparin resistance: Dose requirements >35,000 units/24 hours to maintain a therapeutic aPTT may occur in patients with antithrombin deficiency, increased heparin clearance, elevations in heparin-binding proteins, elevations in factor VIII and/or fibrinogen; frequently encountered in patients with fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, MI, cancer, and in postsurgical patients; measurement of anticoagulant effects using antifactor Xa levels may be of benefit.

- Hyperkalemia: Monitor for hyperkalemia; can cause hyperkalemia by suppressing aldosterone production.

- Hypersensitivity reactions: May occur; only in life-threatening situations when use of an alternative anticoagulant is not possible should heparin be cautiously used in patients with a documented hypersensitivity reaction.

- Osteoporosis: May occur with prolonged use (>6 months) due to a reduction in bone mineral density.

Special populations:

- Elderly: Use with caution in patients >60 years of age, particularly women; they are also more sensitive to the dose and a higher incidence of bleeding has been reported in these patients. May require lower doses.

Dosage form specific issues:

- Benzyl alcohol: Some preparations contain benzyl alcohol as a preservative. In neonates, large amounts of benzyl alcohol (>100 mg/kg/day) have been associated with fatal toxicity (gasping syndrome). The use of preservative-free heparin is, therefore, recommended in neonates.

- Sulfites: Some preparations contain sulfite which may cause allergic reactions.

Other warnings/precautions:

- Fatal medications errors: Many concentrations of heparin are available ranging from 1 unit/mL to 20,000 units/mL. Clinicians **must** carefully examine each prefilled syringe or vial prior to use ensuring that the correct concentration is chosen; fatal hemorrhages have occurred related to heparin overdose especially in pediatric patients.

Geriatric ConsiderationsIn the clinical setting, age has not been shown to be a reliable predictor of a patient's anticoagulant response to heparin. However, it is common for the elderly to have a "standard" response for the first 24-48 hours after a loading dose (5000 units) and a maintenance infusion of 800-1000 units/hour. After this period, they then have an exaggerated response (ie, elevated PTT), requiring a lower infusion rate. Hence, monitor closely during this period of therapy. Elderly women are more likely to have bleeding complications and osteoporosis may be a problem when used >3 months or total daily dose exceeds 30,000 units.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Heparin does not cross the placenta.

LactationDoes not enter breast milk/compatible

Adverse ReactionsFrequency not defined.

Cardiovascular: Allergic vasospastic reaction (possibly related to thrombosis), chest pain, hemorrhagic shock, shock, thrombosis

Central nervous system: Chills, fever, headache

Dermatologic: Alopecia (delayed, transient), bruising (unexplained), cutaneous necrosis, dysesthesia pedis, erythematous plaques (case reports), eczema, urticaria, purpura,

Endocrine & metabolic: Adrenal hemorrhage, hyperkalemia (suppression of aldosterone synthesis), ovarian hemorrhage, rebound hyperlipidemia on discontinuation

Gastrointestinal: Constipation, hematemesis, nausea, tarry stools, vomiting

Genitourinary: Frequent or persistent erection

Hematologic: Bleeding from gums, epistaxis, hemorrhage, ovarian hemorrhage, retroperitoneal hemorrhage, thrombocytopenia (see note)

Hepatic: Liver enzymes increased

Local: Irritation, erythema, pain, hematoma, and ulceration have been rarely reported with deep SubQ injections; I.M. injection (not recommended) is associated with a high incidence of these effects

Neuromuscular & skeletal: Peripheral neuropathy, osteoporosis (chronic therapy effect)

Ocular: Conjunctivitis (allergic reaction), lacrimation

Renal: Hematuria

Respiratory: Asthma, bronchospasm (case reports), hemoptysis, pulmonary hemorrhage, rhinitis

Miscellaneous: Allergic reactions, anaphylactoid reactions, heparin resistance, hypersensitivity (including chills, fever, and urticaria)

Note: Thrombocytopenia has been reported to occur at an incidence between 0% and 30%. It is often of no clinical significance. However, immunologically mediated heparin-induced thrombocytopenia (HIT) has been estimated to occur in 1% to 2% of patients, and is marked by a progressive fall in platelet counts and, in some cases, thromboembolic complications (skin necrosis, pulmonary embolism, gangrene of the extremities, stroke or MI). For recommendations regarding platelet monitoring during heparin therapy, see Monitoring Parameters.

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Aspirin: May enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Corticorelin: Heparin may enhance the adverse/toxic effect of Corticorelin. Significant hypotension and bradycardia have been previously attributed to this combination. *Risk X: Avoid combination*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Drotrecogin Alfa: Heparin may enhance the adverse/toxic effect of Drotrecogin Alfa. This is of concern with therapeutic dosages of heparin. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nitroglycerin: May diminish the anticoagulant effect of Heparin. Nitroglycerin may decrease the serum concentration of Heparin. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid cat's claw, dong quai, evening primrose, feverfew, red clover, horse chestnut, garlic, green tea, ginseng, ginkgo (all have additional antiplatelet activity).

Test InteractionsIncreased thyroxine (competitive protein binding methods); increased PT

Aprotinin significantly increases aPTT and celite Activated Clotting Time (ACT) which may not reflect the actual degree of anticoagulation by heparin. Kaolin-based ACTs are not affected by aprotinin to the same degree as celite ACTs. While institutional protocols may vary, a minimal celite ACT of 750 seconds or kaolin-ACT of 480 seconds is recommended in the presence of aprotinin. Consult the manufacturer's information on specific ACT test interpretation in the presence of aprotinin.

Monitoring ParametersHemoglobin, hematocrit, signs of bleeding; fecal occult blood test; aPTT (or antifactor Xa activity levels) or ACT depending upon indication

Platelet counts should be routinely monitored when the risk of HIT is >0.1% (eg, receiving therapeutic dose heparin, postoperative antithrombotic prophylaxis), if the patient has received heparin or low molecular weight heparin (eg, enoxaparin) within the past 100 days, if preexposure history is uncertain, or if anaphylactoid reaction to heparin occurs. When the risk of HIT is <0.1% (eg, medical/obstetrical patients receiving heparin flushes), routine platelet count monitoring is not recommended (Hirsh, 2008).

For intermittent I.V. injections, aPTT is measured 3.5-4 hours after I.V. injection.

For SubQ injections, when used for treatment (eg, monitored dosing regimen), aPTT is measured 6 hours after injection.

Note: Continuous I.V. infusion is preferred over I.V. intermittent injections. For full-dose heparin (ie, nonlow-dose), the dose should be titrated according to aPTT results. For anticoagulation, an aPTT 1.5-2.5 times normal is usually desired. Because of variation among hospitals in the control aPTT values, nomograms should be established at each institution, designed to achieve aPTT values in the target range (eg, for a control aPTT of 30 seconds, the target range [1.5-2.5 times control] would be 45-75 seconds). Measurements should be made prior to heparin therapy, 6 hours (pediatric: 4 hours) after initiation, and 6 hours (pediatric: 4 hours) after any dosage change, and should be used to adjust the heparin infusion until the aPTT exhibits a therapeutic level. When two consecutive aPTT values are therapeutic, subsequent measurements may be made every 24 hours, and if necessary, dose adjustment carried out. In addition, a significant change in the patient's clinical condition (eg, recurrent ischemia, bleeding, hypotension) should prompt an immediate aPTT determination, followed by dose adjustment if necessary. In general, may increase or decrease infusion by 2-4 units/kg/hour dependent upon aPTT.

Heparin infusion dose adjustment: A number of dose-adjustment nomograms have been developed which target an aPTT range of 1.5-2.5 times control (Cruickshank, 1991; Flaker, 1994; Hull, 1992; Raschke, 1993). However, institution-specific and indication-specific nomograms should be consulted for dose adjustment. **Note:** aPTT values vary throughout the day with maximum values occurring during the night (Decousus, 1985).

Reference RangeHeparin: 0.3-0.7 unit/mL (by anti-Xa chromogenic assay) or 0.2-0.4 unit/mL (by protamine titration); aPTT: 1.5-2.5 times **the patient's baseline**

Nursing: Physical Assessment/MonitoringAssess for risk factors for increased bleeding prior to starting therapy. Assess potential for interactions with other pharmacologic agents or herbal products patient may be taking (especially anything that will affect coagulation or platelet function). Note specific infusion directions in Administration. Bleeding precautions should be observed at all times during heparin therapy. Evaluate results of laboratory tests regularly for necessary dosing adjustments and therapeutic effectiveness. Assess therapeutic response and adverse response on a regular basis throughout therapy (eg, hypersensitivity reaction, bleeding, chest pain, hyperkalemia, peripheral neuropathy). For I.V. bolus administration, emergency treatment for hypersensitivity reactions should be immediately available. Teach patient possible side effects/appropriate interventions (eg, bleeding precautions) and adverse symptoms to report.

Monitoring: Lab TestsHemoglobin, hematocrit; fecal occult blood test; aPTT (or antifactor Xa activity levels) or ACT depending upon indication

Platelet counts should be routinely monitored when the risk of HIT is >0.1% (eg, receiving therapeutic dose heparin, postoperative antithrombotic prophylaxis), if the patient has received heparin or low molecular weight heparin (eg, enoxaparin) within the past 100 days, if preexposure history is uncertain, or if anaphylactoid reaction to heparin occurs. When the risk of HIT is <0.1% (eg, medical/obstetrical patients receiving heparin flushes), routine platelet count monitoring is not recommended (Hirsh, 2008).

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Patient EducationDo not take any new medication, including over-the-counter and biological products, during therapy unless approved by prescriber. This drug can only be administered by infusion or injection. You may have a tendency to bleed easily while taking this drug (brush teeth with soft brush, floss with waxed floss, use electric razor, avoid scissors or sharp knives, and potentially harmful activities). Report immediately any chest pain; difficulty breathing or unusual cough; bleeding or bruising (bleeding gums, nosebleed, blood in urine, dark stool); pain in joints or back; CNS changes (fever, confusion); unusual fever; persistent nausea or GI upset; change in vision, or swelling, pain, or redness at injection site. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion, as sodium [premixed in NaCl 0.45%; porcine intestinal mucosa source]: 12,500 units (250 mL); 25,000 units (250 mL, 500 mL)

Infusion, as sodium [preservative free; premixed in D_5W; porcine intestinal mucosa source]: 10,000 units (100 mL) [contains sodium metabisulfite]; 12,500 units (250 mL) [contains sodium metabisulfite]; 20,000 units (500 mL) [contains sodium metabisulfite]; 25,000 units (250 mL, 500 mL) [contains sodium metabisulfite]

Infusion, as sodium [preservative free; premixed in NaCl 0.9%; porcine intestinal mucosa source]: 1000 units (500 mL); 2000 units (1000 mL)

Injection, solution, as sodium [lock flush preparation; porcine intestinal mucosa source; multidose vial]: 10 units/mL (1 mL, 10 mL, 30 mL) [contains parabens]; 100 units/mL (1 mL, 5 mL) [contains parabens]

Injection, solution, as sodium [lock flush preparation; porcine intestinal mucosa source; multidose vial]: 10 units/mL (10 mL, 30 mL); 100 units/mL (10 mL, 30 mL) [contains benzyl alcohol]

Hep-Lock®: 10 units/mL (1 mL, 2 mL, 10 mL, 30 mL); 100 units/mL (1 mL, 2 mL, 10 mL, 30 mL) [contains benzyl alcohol]

Injection, solution, as sodium [lock flush preparation; porcine intestinal mucosa source; prefilled syringe]: 10 units/mL (1 mL, 2 mL, 3 mL, 5 mL); 100 units/mL (1 mL, 2 mL, 3 mL, 5 mL) [contains benzyl alcohol]

Injection, solution, as sodium [preservative free; lock flush preparation; porcine intestinal mucosa source; prefilled syringe]: 1 unit/mL (2 mL, 3 mL, 5 mL); 2 units/mL (3 mL); 10 units/mL (2.5 mL, 3 mL, 5 mL, 10 mL); 100 units/mL (3 mL, 5 mL, 10 mL)

Injection, solution, as sodium [preservative free; lock flush preparation; porcine intestinal mucosa source; vial]:

HepFlush®-10: 10 units/mL (10 mL)

Hep-Lock U/P: 10 units/mL (1 mL); 100 units/mL (1 mL)

Injection, solution, as sodium [porcine intestinal mucosa source; multidose vial]: 1000 units/mL (1 mL, 10 mL, 30 mL) [contains benzyl alcohol]; 1000 units/mL (1 mL, 10 mL, 30 mL) [contains methylparabens]; 5000 units/mL (1 mL, 10 mL) [contains benzyl alcohol]; 5000 units/mL (1 mL) [contains methylparabens]; 10,000 units/mL (1 mL, 4 mL) [contains benzyl alcohol]; 10,000 units/mL (1 mL, 5 mL) [contains methylparabens]; 20,000 units/mL (1 mL) [contains methylparabens]

Injection, solution, as sodium [porcine intestinal mucosa source; prefilled syringe]: 5000 units/mL (1 mL) [contains benzyl alcohol]

Injection, solution, as sodium [preservative free; porcine intestinal mucosa source; prefilled syringe]: 10,000 units/mL (0.5 mL)

Injection, solution, as sodium [preservative free; porcine intestinal mucosa source; vial]: 1000 units/mL (2 mL); 2000 units/mL (5 mL); 2500 units/mL (10 mL)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Heparin Sodium (Porcine))

1000 units/mL (10): $188.99

10000 units/mL (25): $259.20

10000 units/mL (125): $660.64

Mechanism of ActionPotentiates the action of antithrombin III and thereby inactivates thrombin (as well as activated coagulation factors IX, X, XI, XII, and plasmin) and prevents the conversion of fibrinogen to fibrin; heparin also stimulates release of lipoprotein lipase (lipoprotein lipase hydrolyzes triglycerides to glycerol and free fatty acids)

Pharmacodynamics/Kinetics

Onset of action: Anticoagulation: I.V.: Immediate; SubQ: ~20-30 minutes

Absorption: Oral, rectal: Erratic at best from these routes of administration; SubQ absorption is also erratic, but considered acceptable for prophylactic use

Distribution: Does not cross placenta; does not enter breast milk

Metabolism: Hepatic; may be partially metabolized in the reticuloendothelial system

Half-life elimination: Mean: 1.5 hours; Range: 1-2 hours; affected by obesity, renal function, hepatic function, malignancy, presence of pulmonary embolism, and infections

Excretion: Urine (small amounts as unchanged drug)

Related Information

- Anticoagulants, Injectable

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Bleeding from the gums.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular Considerations

Heparin-Induced Thrombocytopenia: There are many misconceptions regarding the treatment of patient's with suspected or actual heparin-induced thrombocytopenia (HIT). It is well known that the diagnosis of HIT is based on clinical context and aided by serologic testing. In the right context, development of thrombocytopenia in patients receiving heparin therapy leads one to consider the diagnosis of HIT. A standardized patient evaluation should be adopted to optimally treat patients. Patients should be evaluated for heparin exposure and all forms of heparin discontinued. Next, initiation of an appropriate alternative form of anticoagulation is essential to prevent morbidity and mortality related to HIT. Finally, issues regarding long-term anticoagulation need to be considered.

The development of HIT can occur with the administration of either unfractionated or low molecular weight heparin and is not necessarily dependent on the dose administered. An evaluation for HIT should occur when the platelet count falls by ≥50% and/or a thrombotic event occurs between 5 and 14 days after heparin is initiated or received. Of note, patients who undergo cardiac surgery are at high risk of developing anti-PF4/heparin antibodies due to the amount of heparin exposure. HIT/HITT may even occur several weeks after heparin has been discontinued. It is important to recognize and evaluate patients for all sources of heparin they may be receiving. This includes subcutaneous heparin product administration, heparin flushes, heparin in admixtures such as parenteral nutrition, heparin use during dialysis, flushes for central and peripheral catheters, and implanted devices that may have heparin impregnated on the surface (heparin-coated pulmonary artery catheters). All forms of heparin must be discontinued and an appropriate alternate form of anticoagulation be initiated in patients with HIT regardless of documented thrombosis. Also, patients with suspected HIT or definite HIT should have this documented as an allergy in their medical record and signs indicating "No Heparin" should be placed above the patient's bed and documented in the pharmacy system.

Alternative anticoagulants such as direct thrombin inhibitors (argatroban, lepirudin, and bivalirudin) are the best approach in the United States (Greinacher, 1999; Greinacher, 1999; Greinacher, 2000). In Canada and other countries, one could also consider the initiation of full dose danaparoid. Alternative anticoagulation is necessary in order to treat and/or prevent new thromboembolic complications. During the subsequent days following the cessation of heparin in patients with isolated HIT, there is a high degree of thrombin generation increasing the likelihood of the development of thrombosis.

Low-molecular weight heparins should be avoided in the treatment of HIT because of the high degree of antibody cross reactivity (Warkentin, 1999). Also, in patients with isolated HIT or HIT with thrombosis (HITT), the use of vitamin K antagonists may lead to the development of venous limb gangrene when initiated as the treatment of HIT or if initiated without adequate anticoagulation from an appropriate alternative anticoagulant. Initiation of warfarin (maximum dose of 5 mg) or other vitamin K antagonists should be postponed until the platelet count has reached >150,000 x 10^9 cells/L. The patient should remain on the appropriate alternative anticoagulant, in the therapeutic range, while warfarin is being initiated. Since the effects of coumarin anticoagulants are delayed upon initiation, anticoagulation with an alternative anticoagulant should be continued for five days and the patient should have a therapeutic INR for at least two consecutive days before the alternative anticoagulant is discontinued (Hirsh, 2008).

Finally, there has been increasing interest in the use of specific factor Xa inhibitors, such as fondaparinux, for the treatment of HIT. Currently there is limited data for using fondaparinux for treating patients with HIT. Recent laboratory data suggests that fondaparinux is not reactive with HIT antibody positive serum (Savi, 2005). As more data becomes available, these agents may be suitable alternatives in the treatment of HIT.

ST-Elevation Myocardial Infarction (STEMI): In patients with STEMI, the use of I.V. unfractionated heparin (UFH) or LMWH should be used when patients are at high risk for systemic emboli (eg, large or anterior MI, atrial fibrillation, previous embolus, known LV thrombus, or cardiogenic shock) (Class I indication).

Unlike earlier nonspecific thrombolytics (eg, streptokinase, urokinase), fibrin-specific thrombolytics (eg, alteplase, reteplase, or tenecteplase) do not decrease levels of coagulation factors (eg, factors V and VIII) instead they increase thrombin generation which may propagate further thrombus formation. Therefore, the concomitant use of weight-adjusted unfractionated heparin or enoxaparin (if renal function is preserved) is recommended (Class I indication).

Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI): In patients with UA/NSTEMI, the 2007 ACC/AHA Guidelines recommend anticoagulation with subcutaneous LMWH or intravenous UFH be added to antiplatelet therapy with aspirin and/or clopidogrel as soon as possible after presentation in patients undergoing an invasive or a conservative strategy (Class I recommendation; level of evidence: A).

Clinical trials have indicated that UFH should be weight-adjusted which would provide a more predictable response. The ACC/AHA UA/STEMI and STEMI Guidelines recommend an initial dose of 60 units/kg and an initial infusion of 12 units/kg/hour with a goal to maintain activated partial thromboplastin time (aPTT) between 50-70 seconds (approximately 1.5-2 times control). Monitor aPTT at baseline and every 4-6 hours. Daily platelet counts may help in early identification of heparin-induced thrombocytopenia (HIT).

Anesthesia and Critical Care Concerns/Other Considerations

Evidence-Based Information:

Management of Intracerebral Hemorrhage (ICH) Due to Unfractionated Heparin (UFH): Overall management of ICH is similar regardless of cause; however, iatrogenic spontaneous ICH may have specific treatments. According to the 2007 ACC/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage, UFH-related ICH should be treated with I.V. protamine given by slow I.V. injection (not to exceed 5 mg/minute) with a maximum dose of 50 mg (Class I recommendation). Faster infusions of protamine can result in cardiovascular collapse. The use of protamine for reversal of low molecular weight heparins (eg, enoxaparin) is significantly less effective.

Thrombocytopenia: Heparin-associated thrombocytopenia (HAT) commonly occurs within 48-72 hours of initiation. Platelet counts usually fall below 100,000 cells/mm^3 and return to normal within 4 days with continued heparin therapy. Heparin-induced thrombocytopenia (HIT) is a serious, immunoglobulin-mediated reaction with a high risk for thromboembolic events. In HIT, thrombocytopenia usually begins 5-10 days following heparin initiation; HIT can begin within ~10 hours in patients who have received heparin within the previous 100 days (Warkentin, 2001). It can also occur up to several weeks after heparin has been discontinued. Thrombocytopenia can be severe; heparin of all forms must be stopped including flushes and heparin-coated indwelling catheters.

Index TermsHeparin Calcium; Heparin Lock Flush; Heparin Sodium

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International Brand NamesAgglutek (TW); Calciparine (PL); Caprin (IN); Depot-Heparin (PL); Hemastat (PH); Hepacutan (PL); Hepaflex (FI, NO); Heparin (AT, BF, BG, BJ, CH, CI, CZ, DE, ET, FI, GB, GH, GM, GN, GR, HN, IL, KE, LR, MA, ML, MR, MU, MW, NE, NG, NO, PL, SC, SD, SE, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Heparin Biochemie (PL); Heparin Injection B.P. (AU); Heparin Leo (DK, HK, ID, MY, PH, TW); Heparin Natrium-Braun (PL); Heparin Novo (TW); Heparin Sodium B Braun (ID, MY); Heparin-Calcium-Richter (PL); Heparine (BE, NL); Heparine Choay (FR); Heparine Novo (BE, NL); Heparinum (PL); Heparyl (PL); Heptin (PH); Inviclot (ID); Lioton (PL); Liquemin (DE, IT); Liquemine (BE, BR, UY, VE); Lumbolin (PL); Multiparin (NZ, PK); Natrium Heparin (PL); Parinix (AR); Proparin (MX); Thrombophob (DE); Thromboreduct (DE)

Hepatitis A and Hepatitis B Recombinant Vaccine

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Pronunciation(hep a TYE tis aye & hep a TYE tis bee ree KOM be nant vak SEEN)

U.S. Brand NamesTwinrix®

Canadian Brand NamesTwinrix®

Pharmacologic CategoryVaccine, Inactivated (Viral)

Use: Labeled IndicationsActive immunization against disease caused by hepatitis A virus and hepatitis B virus (all known subtypes) in populations desiring protection against or at high risk of exposure to these viruses.

Populations include travelers to areas of intermediate/high endemicity for **both** HAV and HBV; those at increased risk of HBV infection due to behavioral or occupational factors; patients with chronic liver disease; laboratory workers who handle live HAV and HBV; healthcare workers, police, and other personnel who render first-aid or medical assistance; workers who come in contact with sewage; employees of day care centers and correctional facilities; patients/staff of hemodialysis units; male homosexuals; patients frequently receiving blood products; military personnel; users of injectable illicit drugs; close household contacts of patients with hepatitis A and hepatitis B infection; residents of drug and alcohol treatment centers

Dosing: AdultsPrimary immunization: I.M.: Three doses (1 mL each) given on a 0-, 1-, and 6-month schedule

Alternative regimen: Accelerated regimen: Four doses (1 mL each) on day 0, 7, and 21-30, followed by a booster at 12 months

Dosing: ElderlyRefer to adult dosing.

Administration: I.M.Shake well prior to use. Do not dilute prior to administration. Administer in the deltoid region; do not administer in the gluteal region (may give suboptimal response). Do not administer at the same site, or using the same syringe, as additional vaccines or immunoglobulins.

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

Administration with other vaccines:

Hepatitis A and Hepatitis B vaccine with live vaccines: May be given simultaneously or at any interval between doses.

Hepatitis A and Hepatitis B vaccine with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Vaccine administration with antibody-containing products: Hepatitis A and Hepatitis B vaccine may be given simultaneously at different sites or at any interval between doses. Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StorageStore in refrigerator at 2°C to 8°C (36°F to 46°F); do not freeze (discard if frozen).

ContraindicationsHypersensitivity to hepatitis A vaccine; hepatitis B vaccine, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).
- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.
- Cardiopulmonary disease: Use hepatitis B vaccine with caution in patients with decreased cardiopulmonary function.
- Hepatitis B infection: Unrecognized hepatitis B infection may be present; immunization may not prevent infection in these patients.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination.

- Elderly: Patients >65 years may have lower response rates to hepatitis B vaccine.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Latex: Packaging may contain natural latex rubber.

- Yeast, neomycin, aluminum: Contains aluminum, yeast and trace amounts of neomycin.

Geriatric ConsiderationsNo adjustment for age is necessary. Some studies with HBV demonstrate a lower antibody titer in the elderly as compared to younger adults.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Healthcare providers are encouraged to call the manufacturer of Twinrix® to register any patients who may have received this vaccine during pregnancy (888-825-5249).

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Incidence of adverse effects of the combination product were similar to those occurring after administration of hepatitis A vaccine and hepatitis B vaccine alone. (Incidence reported is not versus placebo.)

>10%:

Central nervous system: Headache (13% to 22%), fatigue (11% to 14%)

Local: Injection site reaction: Soreness (37% to 41%), redness (8% to 11%)

1% to 10%:

Central nervous system: Fever (2% to 4%)

Gastrointestinal: Diarrhea (4% to 6%), nausea (2% to 4%), vomiting (≤1%)

Local: Injection site reaction: Swelling (4% to 6%), induration

Respiratory: Upper respiratory tract infection

<1%: Abdominal pain, agitation, anorexia, arthralgia, back pain, bruising at the injection site, diaphoresis, dizziness, erythema, flu-like syndrome, flushing, insomnia, irritability, migraine, myalgia, paresthesia, petechiae, pruritus at the injection site, rash, respiratory tract illness, somnolence, syncope, urticaria, vertigo, weakness

Postmarketing and/or case reports (as reported with hepatitis A vaccine and hepatitis B vaccine; also see individual agents): Allergic reactions, alopecia, anaphylactoid reactions, anaphylaxis, angioedema, arthritis, asthma-like symptoms, Bell's palsy, bronchospasm, conjunctivitis, convulsions, dyspepsia, dyspnea, earache, eczema, encephalopathy, erythema multiforme, erythema nodosum, Guillain-Barré syndrome, hepatitis, herpes zoster, hyperhidrosis, jaundice, liver function tests abnormal, MS, myelitis, neuropathy, optic neuritis, palpitations, paresis, serum-sickness like syndrome (days to weeks after vaccination), tachycardia, thrombocytopenia, tinnitus, transverse myelitis, visual disturbances

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, suspension [preservative free]:

Twinrix®: Hepatitis A virus antigen 720 ELISA units and hepatitis B surface antigen 20 mcg per mL (1 mL) [contains aluminum, yeast protein, and trace amounts of neomycin; prefilled syringe contains natural rubber/natural latex]

Generic AvailableNo

ManufacturerGlaxoSmithKline

Mechanism of Action

Hepatitis A vaccine, an inactivated virus vaccine, offers active immunization against hepatitis A virus infection at an effective immune response rate in up to 99% of subjects.

Recombinant hepatitis B vaccine is a noninfectious subunit viral vaccine. The vaccine is derived from hepatitis B surface antigen (HB_sAg) produced through recombinant DNA techniques from yeast cells. The portion of the hepatitis B gene which codes for HB_sAg is cloned into yeast which is then cultured to produce hepatitis B vaccine.

In immunocompetent people, Twinrix® provides active immunization against hepatitis A virus infection (at an effective immune response rate >99% of subjects) and against hepatitis B virus infection (at an effective immune response rate of 93% to 97%) 30 days after completion of the 3-dose series. This is comparable to using hepatitis A vaccine and hepatitis B vaccine concomitantly.

Pharmacodynamics/Kinetics

Onset of action: Seroconversion for antibodies against HAV and HBV were detected 1 month after completion of the 3-dose series.

Duration: Patients remained seropositive for at least 4 years during clinical studies.

Pharmacotherapy Pearls Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Flu-like syndrome and upper respiratory tract infection.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Fatigue is common

Mental Health: Effects on Psychiatric Treatment May cause GI side effects; concomitant use with SSRIs, lithium, and valproic acid may produce additive effects. May cause flu-like syndrome; differentiate from antidepressant withdrawal symptoms.

Index Terms Engerix-B® and Havrix®; Havrix® and Engerix-B®; Hepatitis B and Hepatitis A Vaccine

References

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.

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International Brand Names Ambirix (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Twinrix (AR, AT, BB, BE, BG, BM, BO, BR, BS, BZ, CH, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, GY, HN, ID, IE, IL, IT, JM, MX, NI, NL, NO, NZ, PA, PE, PH, PR, PT, PY, RU, SE, SR, SV, TR, TT, TW, UY, VE)

Hepatitis A Vaccine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(hep a TYE tis aye vak SEEN)
U.S. Brand NamesHAVRIX®; VAQTA®
Canadian Brand NamesAvaxim®; Avaxim®-Pediatric; HAVRIX®; VAQTA®
Pharmacologic CategoryVaccine, Inactivated (Viral)
Use: Labeled Indications

Active immunization against disease caused by hepatitis A virus (HAV)

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for:

- All children ≥12 months of age
- Travelers to countries with intermediate to high endemicity of HAV (a list of countries is available at http://wwwn.cdc.gov/travel/contentdiseases.aspx)
- Men who have sex with men
- Illegal drug users
- Patients with chronic liver disease
- Patients who receive clotting-factor concentrates
- Persons who work with HAV-infected primates or with HAV in a research laboratory setting

Dosing: AdultsImmunization: I.M.: **Note:** When used for primary immunization, the vaccine should be given at least 2 weeks prior to expected HAV exposure. When used for post-exposure prophylaxis, the vaccine should be given as soon as possible.

HAVRIX®: 1440 ELISA units (1 mL) with a booster dose of 1440 ELISA units to be given 6-12 months following primary immunization

VAQTA®: 50 units (1 mL) with 50 units (1 mL) booster dose of 50 units to be given 6-18 months after primary immunization (6-12 months if initial dose was with HAVRIX®)

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricImmunization: I.M.: **Note:** When used for primary immunization, the vaccine should be given at least 2 weeks prior to expected HAV exposure. When used for post-exposure prophylaxis, the vaccine should be given as soon as possible.

HAVRIX®: Children 12 months to 18 years: 720 ELISA units (0.5 mL) with a booster dose of 720 ELISA units to be given 6-12 months following primary immunization

VAQTA®: Children 12 months to 18 years: 25 units (0.5 mL) with 25 units (0.5 mL) booster to be given 6-18 months after primary immunization (6-12 months if initial dose was with HAVRIX®)

Administration: I.M.The deltoid muscle is the preferred site for injection; gluteal administration may decrease efficacy. Do not administer intravenously, intradermally, or subcutaneously. Shake well prior to use; discard if the suspension is discolored or does not appear homogenous after shaking. When used for primary immunization, the vaccine should be given at least 2 weeks prior to expected HAV exposure. When used for post-exposure prophylaxis, the vaccine should be given as soon as possible. For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

Administration with other vaccines:

Hepatitis A vaccine with live vaccines: May be given simultaneously or at any interval between doses.

Hepatitis A vaccine with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Vaccine administration with antibody-containing products: Hepatitis A vaccine may be given simultaneously at different sites or at any interval between doses. Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StorageStore under refrigeration at 2˚C to 8˚C (36°F to 46˚F); do not freeze.
ContraindicationsHypersensitivity to hepatitis A vaccine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).

- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination.

- Pediatrics: Safety and efficacy have not been established in children <12 months of age

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Dosage form specific issues:

- Latex: Packaging may contain natural latex rubber.

- Neomycin: Some products may contain neomycin.

Geriatric ConsiderationsThere is no specific data to suggest dosing is different than it is for younger adults.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted. The safety of vaccination during pregnancy has not been determined, however, the theoretical risk to the infant is expected to be low.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS)) at 1-800-822-7967 or online at https://secure.vaers.org.**

Frequency dependent upon age, product used, and concomitant vaccine administration. In general, injection site reactions were less common in younger children.

>10%:

Central nervous system: Irritability (11% to 36%), drowsiness (15% to 17%), headache (≤1% to 16%), fever ≥100.4°F (9% to 11%)

Gastrointestinal: Anorexia (1% to 19%)

Local: Injection site: Pain, soreness, tenderness (3% to 56%), erythema (1% to 22%), warmth (<1% to 17%), swelling (1% to 14%)

1% to 10%:

Central nervous system: Fever ≥102°F (3%)

Dermatologic: Rash (≤1% to 5%)

Endocrine & metabolic: Menstrual disorder (1%)

Gastrointestinal: Diarrhea (<1% to 6%), vomiting (<1% to 4%), nausea (2%), abdominal pain (<1% to 2%)

Local: Injection site bruising (1% to 2%), induration

Neuromuscular & skeletal: Weakness/fatigue (4%), myalgia (<1% to 2%), arm pain (1%), back pain (1%), stiffness (1%)

Ocular: Conjunctivitis (1%)

Otic: Otitis media (8%), otitis (2%)

Respiratory: Upper respiratory tract infection (<1% to 10%), rhinorrhea (6%), cough (1% to 5%), pharyngitis (<1% to 3%), respiratory congestion (2%), nasal congestion (1%), laryngotracheobronchitis (1%)

Miscellaneous: Crying (2%), viral exanthema (1%)

<1%, postmarketing, and/or case reports: Allergic reaction, anaphylaxis, angioedema, arthralgia, asthma, bronchial constriction, bronchiolitis, cerebellar ataxia, CK increased, dehydration, dermatitis, diabetes mellitus, dizziness, dyspnea, encephalitis, erythema multiforme, eosinophilia, eye irritation, gastroenteritis, Guillain-Barré syndrome, hepatitis, hyperhidrosis, hypertonic episode, injection site hematoma, injection site itching, injection site rash, insomnia, jaundice, Kawasaki's disease, liver function tests increased, lymphadenopathy, multiple sclerosis, myelitis, neuropathy, paresthesia, photophobia, pneumonia, pruritus, seizure, somnolence, syncope, taste disturbance, thrombocytopenia, urine protein increased, urticaria, vertigo, wheezing

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Monitoring ParametersLiver function tests

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension [adult formulation; preservative free]:

HAVRIX®: Hepatitis A virus antigen 1440 ELISA units/mL (1 mL) [contains aluminum, trace amounts of neomycin; prefilled syringe contains natural rubber/natural latex]

VAQTA®: Hepatitis A virus antigen 50 units/mL (1 mL) [contains aluminum, natural rubber/natural latex in packaging]

Injection, suspension [pediatric formulation; preservative free]:

HAVRIX®: Hepatitis A virus antigen 720 ELISA units/0.5 mL (0.5 mL) [contains aluminum, trace amounts of neomycin; prefilled syringe contains natural rubber/natural latex]

Injection, suspension [pediatric/adolescent formulation; preservative free]:

VAQTA®: Hepatitis A virus antigen 25 units/0.5 mL (0.5 mL) [contains aluminum, natural rubber/natural latex in packaging]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Injection (Vaqta)

25 units/0.5 mL (0.5): $32.73

50 units/mL (1): $75.99

Suspension (Havrix)

720 Elisa units/0.5 mL (0.5): $39.99

1440 Elisa units/mL (1): $64.73

1440 Elisa units/mL (1): $72.88

Mechanism of ActionAs an inactivated virus vaccine, hepatitis A vaccine offers active immunization against hepatitis A virus infection at an effective immune response rate in up to 99% of subjects

Pharmacodynamics/Kinetics

Onset of action (protection): 2-4 weeks after a single dose; 2 weeks after vaccine administration, 54% to 62% of patients develop neutralizing antibodies; this percentage increases to 94% to 100% at 1 month postvaccination (CDC, 2006)

Duration: Neutralizing antibodies have persisted for up to 8 years; based on kinetic models, antibodies may be present ≥14-20 years in children and ≥25 years in adults who receive the complete vaccination series (CDC, 2006; Van Damme, 2003).

Related Information

- Immunization Recommendations
- Prophylaxis for Patients Exposed to Common Communicable Diseases
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsThe ACIP currently recommends that older adults, the immunocompormised, or persons with underlying medical conditions (including chronic liver disease) that are vaccinated <2 weeks from departure to an area with a high risk of hepatitis A infection also receive immune globulin.

Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title and address be entered into the patient's permanent medical record.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusIrritability and drowsiness are common; may cause weakness and fatigue

Mental Health: Effects on Psychiatric TreatmentNone reported

References

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American Academy of Pediatrics Committee on Infectious Diseases, “Hepatitis A Vaccine Recommendations,” *Pediatrics*, 2007, 120(1):189-99.[PubMed 17606579]

Bancroft WH, “Hepatitis A Vaccine,” *N Engl J Med*, 1992, 327(7):453-7. [PubMed 1320740]

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Centers for Disease Control and Prevention, “Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP),” *MMWR Recomm Rep*, 2006, 55(RR-7):1-23.[PubMed 16708058]

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 2006, 55(RR-15):1. [PubMed 17136024]

Committee on Infectious Diseases, “Hepatitis A Vaccine Recommendations,” *Pediatrics*, 2007, 120(1):189-99.[PubMed 17606579]

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Lemon SM, “Inactivated Hepatitis A Vaccines,” *JAMA*, 1994, 271(17):1363-4. [PubMed 8158824]

Niu MT, Salive M, Krueger C, et al, “Two-Year Review of Hepatitis A Vaccine Safety: Data From the Vaccine Adverse Event Reporting System (VAERS),” *Clin Infect Dis*, 1998, 26(6):1475-6.[PubMed 9636890]

Usonis V, Meriste S, Bakasenas V, et al, “Immunogenicity and Safety of a Combined Hepatitis A and B Vaccine Administered Concomitantly With Either a Measles-Mumps-Rubella or a Diphtheria-Tetanus-Acellular Pertussis-Inactivated Poliomyelitis Vaccine Mixed With a *Haemophilus influenza* type b Conjugate Vaccine in Infants Aged 12-18 Months,” *Vaccine*, 2005, 23(20):2602-6. [PubMed 15780442]

Van Damme P, Banatvala J, Fay O, et al, “Hepatitis A Booster Vaccination: Is There a Need?,” *Lancet*, 2003, 362(9389):1065-71.[PubMed 14522539]

International Brand NamesAvaxim (AR, AU, BG, BR, CO, GB, HK, IE, IL, KP, PL, TH); Epaxal (GB, IE, IL, NZ, PE); HAVpur (DE); Havrix (AT, BE, CH, CN, CR, CZ, DK, DO, EC, EE, FI, FR, GB, GT, HN, IE, IL, IT, KP, NI, NL, NO, NZ, PA, PE, PK, PT, PY, SE, SG, SV, TW, UY, VE); Havrix 1440 (AU, BB, BM, BS, BZ, GY, HK, IN, JM, MX, NL, SR, TT); Havrix 720 Junior (PL); Havrix Adult (PL); Havrix Junior (AU, BB, BM, BS, BZ, GY, HK, IN, JM, MX, NL, SR, TT); Havrix Monodose (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Havrix Pediatric (PL); Vaqta (AU, CL, DE, GB, IE, MX, PL, SG, TW)

Hepatitis B Immune Globulin (Human)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

HBIG may be confused with BabyBIG

Pronunciation(hep a TYE tis bee i MYUN GLOB yoo lin YU man)

U.S. Brand NamesHepaGam B™; HyperHEP B™ S/D; Nabi-HB®

Canadian Brand NamesHepaGam B™; HyperHep B®

Pharmacologic CategoryImmune Globulin

Use: Labeled Indications

Passive prophylactic immunity to hepatitis B following: Acute exposure to blood containing hepatitis B surface antigen (HBsAg); perinatal exposure of infants born to HBsAg-positive mothers; sexual exposure to HBsAg-positive persons; household exposure to persons with acute HBV infection

Prevention of hepatitis B virus recurrence after liver transplantation in HBsAg-positive transplant patients

Note: Hepatitis B immune globulin is not indicated for treatment of active hepatitis B infection and is ineffective in the treatment of chronic active hepatitis B infection.

Dosing: Adults

Postexposure prophylaxis: I.M.: 0.06 mL/kg as soon as possible after exposure (ie, within 24 hours of needlestick, ocular, or mucosal exposure or within 14 days of sexual exposure); usual dose: 3-5 mL; repeat at 28-30 days after exposure in nonresponders to hepatitis B vaccine or in patients who refuse vaccination

Note: HBIG may be administered at the same time (but at a different site) or up to 1 month preceding hepatitis B vaccination without impairing the active immune response

Prevention of hepatitis B virus recurrence after liver transplantation (HepaGam B™): I.V.: 20,000 int. units/dose according to the following schedule:

Anhepatic phase (Initial dose): One dose given with the liver transplant

Week 1 postop: One dose daily for 7 days (days 1-7)

Weeks 2-12 postop: One dose every 2 weeks starting day 14

Month 4 onward: One dose monthly starting on month 4

Dose adjustment: Adjust dose to reach anti-HBs levels of 500 int. units/L within the first week after transplantation. In patients with surgical bleeding, abdominal fluid drainage >500 mL or those undergoing plasmapheresis, administer 10,000 int. units/dose every 6 hours until target anti-HBs levels are reached.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Perinatal exposure of infants born to HBsAg-positive mothers: Newborns: I.M.: 0.5 mL as soon after birth as possible (within 12 hours); active vaccination with hepatitis B vaccine may begin at the same time in a different site (if not contraindicated). If first dose of hepatitis B vaccine is delayed for as long as 3 months, dose may be repeated. If hepatitis B vaccine is refused, dose may be repeated at 3 and 6 months.

Household exposure prophylaxis in infants <12 months: I.M.: 0.5 mL (to be administered if mother or primary caregiver has acute HBV infection).

Postexposure prophylaxis: I.M.: Children ≥12 months: Refer to adult dosing.

Note: HBIG may be administered at the same time (but at a different site) or up to 1 month preceding hepatitis B vaccination without impairing the active immune response

Administration: I.M.Postexposure prophylaxis: I.M. injection only in anterolateral aspect of upper thigh and deltoid muscle of upper arm; to prevent injury from injection, care should be taken when giving to patients with thrombocytopenia or bleeding disorders

Administration: I.V.

HepaGam B™: Liver transplant: Administer at 2 mL/minute. Decrease infusion to ≤1 mL/minute for patient discomfort or infusion-related adverse events. Actual volume of infusion is dependant upon potency labeled on each individual vial.

Nabi-HB®: Although not an FDA-approved for this purpose, Nabi-HB® has been administered intravenously in hepatitis B-positive liver transplant patients

StorageRefrigerate at 2°C to 8°C (36°F to 46°F); do not freeze. Use within 6 hours of entering vial. Do not shake vial; avoid foaming.
ContraindicationsHypersensitivity to hepatitis B immune globulin or any component of the formulation; severe allergy to gamma globulin or anti-immunoglobulin therapies
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1:1000) should be available. Use with caution in patients with isolated immunoglobulin A deficiency or a history of systemic hypersensitivity to human immunoglobulins.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with thrombocytopenia or coagulation disorders; I.M. injections may be contraindicated.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

- Maltose: Some products may contain maltose, which may result in falsely-elevated blood glucose readings.

Geriatric ConsiderationsNo data available to suggest different dosing in the elderly than in younger adults.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsInfants born to HBsAg-positive mothers may be breast fed.
Adverse ReactionsReported with postexposure prophylaxis; frequency not defined. Adverse events reported in liver transplant patients included tremor and hypotension, were associated with a single infusion during the first week of treatment, and did not recur with additional infusions.

Central nervous system: Fainting, headache, lightheadedness, malaise

Dermatologic: Angioedema, bruising, urticaria

Gastrointestinal: Nausea, vomiting

Hematologic: WBC decreased

Hepatic: Alkaline phosphatase increased, AST increased

Local: Ache, erythema, pain, and/or tenderness at injection site

Neuromuscular & skeletal: Arthralgia, joint stiffness, myalgia

Renal: Creatinine increased

Respiratory: Cold symptoms

Miscellaneous: Anaphylaxis, flu-like syndrome

Drug Interactions

Vaccines (Live): Immune Globulins may diminish the therapeutic effect of Vaccines (Live). **Exceptions:** Influenza Virus Vaccine; Yellow Fever Vaccine. *Risk D: Consider therapy modification*

Test Interactions

Glucose testing: HepaGam B™ contains maltose. Falsely-elevated blood glucose levels may occur when glucose monitoring devices and test strips utilizing the glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) based methods are used.

Serological testing: Antibodies transferred following administration of immune globulins may provide misleading positive test results (eg, Coombs' test)

Monitoring ParametersLiver transplant: Serum HBsAg; infusion-related adverse events
Monitoring: Lab TestsLiver transplant: Serum HBsAg
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: Potency expressed in international units (as compared to the WHO standard) is noted by individual lot on the vial label.

Injection, solution [preservative free]:

HyperHEP B™ S/D: Anti-HBs ≥220 int. units/mL (0.5 mL, 1 mL, 5 mL)

Nabi-HB®: Anti-HBs >312 int. units/mL (1 mL, 5 mL) [contains polysorbate 80]

HepaGam B™: Anti-HBs 312 int. units/mL (1 mL, 5 mL) [contains maltose and polysorbate 80]

Generic AvailableNo

Mechanism of ActionHepatitis B immune globulin (HBIG) is a nonpyrogenic sterile solution containing immunoglobulin G (IgG) specific to hepatitis B surface antigen (HB_sAg). HBIG differs from immune globulin in the amount of anti-HB_s. Immune globulin is prepared from plasma that is not preselected for anti-HB_s content. HBIG is prepared from plasma preselected for high titer anti-HB_s. In the U.S., HBIG has an anti-HB_s high titer >1:100,000 by IRA.

Pharmacodynamics/Kinetics

Duration: Postexposure prophylaxis: 3-6 months

Absorption: I.M.: Slow

Half-life: 17-25 days

Distribution: V_d: 7-15 L

Time to peak, serum: I.M.: 2-10 days

Related Information

- Immunization Recommendations

Pharmacotherapy PearlsEach vial contains anti-HB_s antibody equivalent to or exceeding the potency of anti-HB_s in a U.S. reference standard hepatitis B immune globulin (FDA). The U.S. reference standard has been tested against the WHO standard hepatitis B immune globulin with listed values between 207 int. units/mL and 220 int. units/mL (included in individual product information).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness

Mental Health: Effects on Psychiatric TreatmentSedative effects may be additive with concurrent psychotropic use

Anesthesia and Critical Care Concerns/Other ConsiderationsHepatitis B immune globulin has been administered intravenously in hepatitis B-positive liver transplant patients.

Index TermsHBIG

References

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International Brand NamesAunativ (DK); Euvax-B (KP, TH); Gamma Anty HBs (PL); Hebagam IM (ZA); Hepatect (AT, CZ, DE, EE, HN, PL, TW); Hepatect CP (PL); Hepatitis B Immunoglobulin-VF (AU); HepBQuin (NL); Hepuman (BE); Hepuman Berna (PE); HyperHEP B (IL, NZ, TW); Igantibe (TH); IVheBex (FR)

Hepatitis B Vaccine (Recombinant)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Recombivax HB® may be confused with Comvax®

Pronunciation(hep a TYE tis bee vak SEEN ree KOM be nant)

U.S. Brand NamesEngerix-B®; Recombivax HB®

Canadian Brand NamesEngerix-B®; Recombivax HB®

Pharmacologic CategoryVaccine, Inactivated (Viral)

Use: Labeled IndicationsImmunization against infection caused by all known subtypes of hepatitis B virus (HBV), in individuals seeking protection from HBV infection and/or in the following individuals considered at high risk of potential exposure to hepatitis B virus or HBsAg-positive materials:

Workplace Exposure:

- Healthcare workers[1] (including students, custodial staff, lab personnel, etc)
- Police and fire personnel
- Military personnel
- Morticians and embalmers
- Clients/staff of institutions for the developmentally disabled

Lifestyle Factors:

- Homosexual men
- Heterosexually-active persons with multiple partners in a 6-month period or those with recently acquired sexually-transmitted disease
- Intravenous drug users

Specific Patient Groups:

- Those on hemodialysis[2], receiving transfusions[3], or in hematology/oncology units
- Adolescents
- Infants born of HBsAG-positive mothers
- Individuals with chronic liver disease
- Individual with HIV infection

Others:

- Prison inmates and staff of correctional facilities
- Household and sexual contacts of HBV carriers
- Residents, immigrants, adoptees, and refugees from areas with endemic HBV infection (eg, Alaskan Eskimos, Pacific Islanders, Indochinese, and Haitian descent)
- International travelers to areas of endemic HBV
- Children born after 11/21/1991

[1] The risk of hepatitis B virus (HBV) infection for healthcare workers varies both between hospitals and within hospitals. Hepatitis B vaccination is recommended for all healthcare workers with blood exposure.

[2] Hemodialysis patients often respond poorly to hepatitis B vaccination; higher vaccine doses or increased number of doses are required. A special formulation of one vaccine is now available for such persons (Recombivax HB®, 40 mcg/mL). The anti-HB$_s$ (antibody to hepatitis B

surface antigen) response of such persons should be tested after they are vaccinated, and those who have not responded should be revaccinated with 1-3 additional doses. Patients with chronic renal disease should be vaccinated as early as possible, ideally before they require hemodialysis. In addition, their anti-HB^{s} levels should be monitored at 6- to 12-month intervals to assess the need for revaccination.

[3] Patients with hemophilia should be immunized subcutaneously, not intramuscularly.

In addition, the Advisory Committee on Immunization Practices (ACIP) recommends vaccination for any persons who are wounded in bombings or similar mass casualty events who have penetrating injuries or nonintact skin exposure, or who have contact with mucous membranes (exception - superficial contact with intact skin), and who cannot confirm receipt of a hepatitis B vaccination.

Dosing: Adults

Immunization regimen:

Note: Regimen consists of 3 doses (0, 1, and 6 months): First dose given on the elected date, second dose given 1 month later, third dose given 6 months after the first dose; see table.

When used for immediate prophylactic intervention (eg, administration to persons who are wounded in bombings or similar mass casualty events), vaccination should begin within 24 hours and no later than 7 days following the event

Routine Immunization Regimen of Three I.M. Hepatitis B Vaccine Doses

Age	Initial		1 mo		2 mo	6 mo[1]	
	Recombivax HB® (mL)	**Engerix-B® (mL)**	**Recombivax HB® (mL)**	**Engerix-B® (mL)**	**Engerix-B® (mL)**	**Recombivax HB® (mL)**	**Engerix-B® (mL)**
Birth[2] to 19 y	0.5[3]	0.5[4]	0.5[3]	0.5[4]	--	0.5[3]	0.5[4]
≥20 y[5]	1[6]	1[7]	1[6]	1[7]	--	1[6]	1[7]
Dialysis or immunocompromised patients[8]	1[9]	2[10]	1[9]	2[10]	2[10]	1[9]	2[10]
[1] Final dose in series should not be administered before age of 24 weeks.							
[2] Infants born of HBsAg **negative** mothers.							
[3] 5 mcg/0.5 mL pediatric/adolescent formulation.							
[4] 10 mcg/0.5 mL formulation.							
[5] Alternately, doses may be administered at 0, 1, and 4 months **or** at 0, 2, and 4 months.							
[6] 10 mcg/mL adult formulation.							
[7] 20 mcg/mL formulation.							
[8] Revaccinate if anti-HBs <10 mIU/mL ≥1-2 months after third dose.							
[9] 40 mcg/mL dialysis formulation.							
[10] Two 1 mL doses given at different sites using the 20 mcg/mL formulation.							

Alternative dosing schedule for ***Recombivax HB®:*** Adults ≥20 years: Doses may be administered at 0, 1, and 4 months **or** at 0, 2, and 4 months

Alternative dosing schedules for ***Engerix-B®:*** Adults ≥20 years:

Doses may be administered at 0, 1, and 4 months **or** at 0, 2, and 4 months

High-risk adults (20 mcg/mL formulation): 1 mL at 0, 1, 2, and 12 months. If booster dose is needed, revaccinate with 1 mL.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Immunization regimen: I.M.: Regimen consists of 3 doses (0, 1, and 6 months): First dose given on the elected date, second dose given 1 month later, third dose given 6 months after the first dose; see table.

Note: When used for immediate prophylactic intervention (eg, administration to persons who are wounded in bombings or similar mass casualty events), vaccination should begin within 24 hours and no later than 7 days following the event.

Alternative dosing schedule for Recombivax HB®: Children 11-15 years (10 mcg/mL adult formulation): First dose of 1 mL given on the elected date, second dose given 4-6 months later

Alternative dosing schedules for Engerix-B®:

Children ≤10 years (10 mcg/0.5 mL formulation): High-risk children: 0.5 mL at 0, 1, 2, and 12 months; lower-risk children ages 5-10 who are candidates for an extended administration schedule may receive an alternative regimen of 0.5 mL at 0, 12, and 24 months. If booster dose is needed, revaccinate with 0.5 mL.

Adolescents 11-19 years (20 mcg/mL formulation): 1 mL at 0, 1, and 6 months. High-risk adolescents: 1 mL at 0, 1, 2, and 12 months; lower-risk adolescents 11-16 years who are candidates for an extended administration schedule may receive an alternative regimen of 0.5 mL (using the 10 mcg/0.5 mL) formulation at 0, 12, and 24 months. If booster dose is needed, revaccinate with 20 mcg.

Postexposure prophylaxis: Note: High-risk individuals may include children born of hepatitis B-infected mothers, those who have been or might be exposed or those who have traveled to high-risk areas. See table.

Postexposure Prophylaxis Recommended Dosage for Infants Born to HBsAg-Positive Mothers

Treatment	**Birth ≤12 h**	**1 mo**	**6 mo**
Engerix-B® (pediatric formulation 10 mcg/0.5 mL)[1]	0.5 mL[2]	0.5 mL	0.5 mL
Recombivax HB® (pediatric/adolescent formulation 5 mcg/0.5 mL)	0.5 mL[2]	0.5 mL	0.5 mL
Hepatitis B immune globulin	0.5 mL[2]	—	—
[1] An alternate regimen is administration of the vaccine at birth, and 1, 2, and 12 months later.			
[2] The first dose of vaccine may be given at birth at the same time as HBIG, but give in the opposite anterolateral thigh. This may better ensure vaccine absorption. HBIG should be given immediately if mother is determined to be HBsAg-positive within 7 days of birth.			

Administration: I.M.It is possible to interchange the vaccines for completion of a series or for booster doses; the antibody produced in response to each type of vaccine is comparable, however, the quantity of the vaccine will vary

I.M. injection only; in adults, the deltoid muscle is the preferred site; the anterolateral thigh is the recommended site in infants and young children. Not for gluteal administration. Shake well prior to withdrawal and use.

For patients at risk of hemorrhage following intramuscular injection, hepatitis B vaccine may be administered subcutaneously although lower titers and/or increased incidence of local reactions may result. The ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

Administration with other vaccines:

Hepatitis B vaccine with live vaccines: May be given simultaneously or at any interval between doses.

Hepatitis B vaccine with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Vaccine administration with antibody-containing products: Hepatitis B vaccine may be given simultaneously at different sites or at any interval between doses. Examples of antibody containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products

Vaccination at the time of HBsAg testing: For persons in whom vaccination is recommended, the first dose of hepatitis B vaccine can be given after blood is drawn to test for HBsAg.

StorageRefrigerate at 2°C to 8°C (36°F to 46°F); do not freeze.
ContraindicationsHypersensitivity to yeast, hepatitis B vaccine, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Acute illness: The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and the etiology of the disease. Immunization should be delayed during the course of an acute febrile illness.

- Cardiopulmonary disease: Use with caution in patients with decreased cardiopulmonary function.

- Hepatitis B infection: Unrecognized hepatitis B infection may be present, immunization may not prevent infection in these patients.

- Multiple sclerosis: Use with caution in patients with multiple sclerosis; rare exacerbations of symptoms have been observed.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination.

- Elderly: Patients >65 years may have lower response rates.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Dosage form specific issues:

- Latex: Packaging may contain natural latex rubber.

Geriatric ConsiderationsNo dose adjustments required based on age. Some studies demonstrate a lower antibody titer in the elderly as compared to young adults.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted. The ACIP recommends HBsAg testing for all pregnant women. Based on limited data, there is no apparent risk to the fetus when the hepatitis B vaccine is administered during pregnancy. Pregnancy itself is not a contraindication to vaccination; vaccination should be considered if otherwise indicated.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsStudies suggest that infants born to HBsAg-positive mothers do not incur an increased risk of HBV infection through breast-feeding.
Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Frequency not defined. The most common adverse effects reported with both products included injection site reactions (>10%).

Cardiovascular: Flushing, hypotension

Central nervous system: Agitation, chills, dizziness, fatigue, fever (≥37.5°C / 100°F), headache, insomnia, irritability, lightheadedness, malaise, somnolence, vertigo

Dermatologic: Angioedema, petechiae, pruritus, rash, urticaria

Gastrointestinal: Abdominal pain, appetite decreased, constipation, cramps, diarrhea, dyspepsia, nausea, vomiting

Genitourinary: Dysuria

Local: Injection site reactions: Ecchymosis, erythema, induration, pain, nodule formation, soreness, swelling, tenderness, warmth

Neuromuscular & skeletal: Achiness, arthralgia, back pain, myalgia, neck pain, neck stiffness, paresthesia, shoulder pain, tingling, weakness

Otic: Earache

Respiratory: Cough, pharyngitis, rhinitis, upper respiratory tract infection

Miscellaneous: Diaphoresis, lymphadenopathy, flu-like syndrome

Postmarketing and/or case reports: Alopecia, anaphylaxis, arthritis, Bell's palsy, bronchospasm, conjunctivitis, eczema, encephalitis, erythema nodosum, erythema multiforme, erythrocyte sedimentation rate increased, febrile seizure, Guillain-Barré syndrome, herpes zoster, hypoesthesia, keratitis, liver enzymes increased, lupus-like syndrome, migraine, multiple sclerosis, muscle weakness, neuropathy, optic neuritis, palpitation, paresis, paresthesia, polyarteritis nodosa, purpura, seizure, serum-sickness like syndrome (may be delayed days to weeks), Stevens-Johnson syndrome, SLE, syncope, tachycardia, thrombocytopenia, tinnitus, transverse myelitis, vasculitis, visual disturbances, vertigo

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension [adult; preservative free]:

Engerix-B®: Hepatitis B surface antigen 20 mcg/mL (1 mL) [contains aluminum, trace amounts of thimerosal; prefilled syringes contain natural rubber/natural latex]

Recombivax HB®: Hepatitis B surface antigen 10 mcg/mL (1 mL, 3 mL) [contains aluminum and yeast protein]

Injection, suspension [pediatric/adolescent; preservative free]:

Engerix-B®: Hepatitis B surface antigen 10 mcg/0.5 mL (0.5 mL) [contains aluminum, trace amounts of thimerosal; prefilled syringes contain natural rubber/natural latex]

Recombivax HB®: Hepatitis B surface antigen 5 mcg/0.5 mL (0.5 mL) [contains aluminum and yeast protein]

Injection, suspension [dialysis formulation; preservative free]:

Recombivax HB®: Hepatitis B surface antigen 40 mcg/mL (1 mL) [contains aluminum and yeast protein]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Suspension (Recombivax HB)

10 mcg/mL (1): $73.99

Mechanism of ActionRecombinant hepatitis B vaccine is a noninfectious subunit viral vaccine, which confers active immunity via formation of antihepatitis B antibodies. The vaccine is derived from hepatitis B surface antigen (HBsAg) produced through recombinant DNA techniques from yeast cells. The portion of the hepatitis B gene which codes for HBsAg is cloned into yeast which is then cultured to produce hepatitis B vaccine.

Pharmacodynamics/KineticsDuration: Following a 3-dose series in children, up to 50% of patients will have low or undetectable anti-HB antibody 5-15 years postvaccination. However, anamnestic increases in anti-HB have been shown up to 23 years later suggesting a lifelong immune memory response.

Related Information

- Immunization Recommendations
- Prophylaxis for Patients Exposed to Common Communicable Diseases
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Dental Health Professional ConsiderationsImmunization is recommended for dentists, oral surgeons, dental hygienists, dental nurses, and dental students

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMalaise and fatigue are common; may rarely cause lightheadedness, somnolence, insomnia, irritability, agitation, anorexia

Mental Health: Effects on Psychiatric TreatmentSedative effects may be additive with concurrent psychotropic use

Index TermsHepatitis B Inactivated Virus Vaccine (recombinant DNA)

References

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Centers for Disease Control, “Hepatitis B Virus: A Comprehensive Strategy for Eliminating Transmission in the United States Through Universal Childhood Vaccination: Recommendations of the Immunization Practices Advisory Committee (ACIP),” *MMWR Recomm Rep*, 1991, 40(RR-13):23.

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.

Chapman LE, Sullivent EE, Grohskopf LA, et al, “Recommendations for Postexposure Interventions to Prevent Infection With Hepatitis B Virus, Hepatitis C Virus, or Human Immunodeficiency Virus, and Tetanus in Persons Wounded During Bombings and Other Mass-Casualty Events -- United States, 2008: Recommendations of the Centers for Disease Control and Prevention (CDC),” *MMWR Recomm Rep*, 2008, 57(RR-6):1-21.[PubMed 18668022]

Gardner P and Schaffner W, “Immunization of Adults,” *N Engl J Med*, 1993, 328(17):1252-8.[PubMed 8464436]

Weinbaum CM, Williams I, Mast EE, et al, “Recommendations for Identification and Public Health Management of Persons With Chronic Hepatitis B Virus Infection,” *MMWR Recomm Rep*, 2008, 57(RR-8):1-20.[PubMed 18802412]

International Brand NamesBio-Hep-B (IL); Engerix-B (AR, AT, AU, BB, BE, BG, BM, BR, BS, BZ, CH, CN, CR, CZ, DE, DK, DO, EC, FI, FR, GB, GR, GT, GY, HN, IE, IN, IT, JM, MX, NI, NL, NO, PA, PE, PK, PL, PT, PY, RU, SE, SR, SV, TR, TT, TW, UY, VE, ZA); Euvax B (PL); Fendrix (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Gen H-B-Vax (PL); Gen Hevac B Pasteur (PL); H-B-Vax II (AT, AU, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PL, PT, RU, SE, TR, TW); HBvaxPRO (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, NZ, PT, RU, SE, TR); Hbvaxpro (PL); Hepavax Gene (CO); Hepavax-Gene (PL); Shanvac-B (TW); Temrevac-HB (PH)

Hetastarch

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Hespan® may be confused with heparin

Pronunciation(HET a starch)

U.S. Brand NamesHespan®; Hextend®; Voluven®

Canadian Brand NamesHextend®; Voluven®

Pharmacologic CategoryPlasma Volume Expander, Colloid

Use: Labeled IndicationsBlood volume expander used in treatment of hypovolemia; prevention of hypovolemia (Voluven®); adjunct in leukapheresis to improve harvesting and increase the yield of granulocytes by centrifugation (Hespan®)

Use: Unlabeled/InvestigationalHextend®: Priming fluid in pump oxygenators during cardiopulmonary bypass; plasma volume expansion during cardiopulmonary bypass

Dosing: Adults

Volume expansion: 500-1000 mL (up to 1500 mL/day) or 20 mL/kg/day (up to 1500 mL/day); larger volumes (15,000 mL/24 hours) have been used safely in small numbers of patients

Voluven®: Up to 50 mL/kg/day

Leukapheresis (Hextend®): 250-700 mL; **Note:** Citrate anticoagulant is added before use.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricPlasma volume expansion: I.V. infusion (requires an infusion pump):

Children <2 years: Voluven®: Average dose: 7-25 mL/kg; titrate to individual colloid needs, hemodynamic and hydration status

Children 2-12 years: Not studied

Children >12 years: Voluven®: Up to 50 mL/kg/day

Dosing: Renal ImpairmentCl_{cr} <10 mL/minute: Initial dose is the same but subsequent doses should be reduced by 20% to 50% of normal.

Administration: I.V.Administer I.V. only; infusion pump is required. May administer up to 1.2 g/kg/hour (20 mL/kg/hour). Change I.V. tubing or flush copiously with normal saline before administering blood through the same line. Change I.V. tubing at least every 24 hours. Do not administer Hextend® with blood through the same administration set. Anaphylactoid reactions can occur, have epinephrine and resuscitative equipment available.

Administration: I.V. DetailDo not use if crystalline precipitate forms or is turbid deep brown.

pH: 3.5-7

Administration: OtherLeukapheresis: Mix Hespan® and citrate well. Administer to the input line of the centrifuge apparatus at a ration of 1:8 to 1:13 to venous whole blood.

StorageStore at room temperature; do not freeze. Do not use if crystalline precipitate forms or is turbid deep brown. In leukapheresis, admixtures of 500-560 mL of Hespan® with citrate concentrations up to 2.5% are compatible for 24 hours.

CompatibilityStable in NS.

Hespan®:

Y-site administration: Compatible: Cimetidine, diltiazem, doxycycline, enalaprilat, ertapenem, nicardipine. **Incompatible:** Amikacin, cefamandole, cefoperazone, cefotaxime, cefoxitin, gentamicin, ranitidine, theophylline, tobramycin. **Variable (consult detailed reference):** Ampicillin, cefazolin.

Compatibility when admixed: Compatible: Fosphenytoin, citrate.

Hextend®:

Y-site administration: Compatible: Alfentanil, amikacin, aminophylline, amiodarone, ampicillin, ampicillin-sulbactam, atracurium, azithromycin, aztreonam, bumetanide, butorphanol, calcium gluconate, cefazolin, cefepime, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, chlorpromazine, cimetidine, ciprofloxacin, cisatracurium, clindamycin, dexamethasone, digoxin, diltiazem, diphenhydramine, dobutamine, dolasetron, dopamine, doxycycline, droperidol, enalaprilat, ephedrine, epinephrine, erythromycin, esmolol, famotidine, fenoldopam, fentanyl, fluconazole, furosemide, gentamicin, granisetron, haloperidol, heparin, hydrocortisone, hydromorphone, hydroxyzine, inamrinone, isoproterenol, ketorolac, labetalol, levofloxacin, lidocaine, lorazepam, magnesium, mannitol, meperidine, methylprednisolone, metoclopramide, metronidazole, midazolam, milrinone, mivacurium, morphine, nalbuphine, nitroglycerin, norepinephrine, ofloxacin, ondansetron, pancuronium, phenylephrine, piperacillin, piperacillin-tazobactam, potassium chloride, procainamide, prochlorperazine, promethazine, ranitidine, rocuronium, sodium nitroprusside, succinylcholine, sufentanil, theophylline, thiopental, ticarcillin, ticarcillin-clavulanate, tobramycin, trimethoprim-sulfamethoxazole, vancomycin, vecuronium, verapamil. **Incompatible:** Amphotericin B, diazepam, sodium bicarbonate.

ContraindicationsHypersensitivity to hydroxyethyl starch or any component of the formulation; renal failure with oliguria or anuria (not related to hypovolemia); any fluid overload condition (eg, pulmonary edema, congestive heart failure)

Hespan ® is also contraindicated in patients with pre-existing coagulation or bleeding disorders

Hextend® is also contraindicated with bleeding disorders; in the treatment of lactic acidosis and in leukapheresis

Voluven® is also contraindicated in patients receiving dialysis; severe hypernatremia; severe hyperchloremia; patients with intracranial bleeding

Allergy Considerations

- Hetastarch Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid reactions: Have occurred; use caution in patients allergic to corn (may have cross allergy to hetastarch).
- Decreased hemoglobin: Large volume may cause drops in hemoglobin concentrations.
- Impaired platelet function: Volumes >1500 mL may interfere with platelet function and prolong PT and PTT times.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with severe hepatic impairment; may result in further reduction of coagulation factors, increasing the risk of bleeding.
- Patients at risk for fluid overload: Use with caution in patients at risk from overexpansion of blood volume, including the very young or aged patients, those with HF.
- Renal impairment: The risk of adverse reactions may be increased in patients with renal impairment; monitor fluid status, urine output, and infusion rate. Larger hetastarch molecules may leak into urine in patients with glomerular damage; may elevate urine specific gravity.
- Thrombocytopenia: Use with caution in patients with thrombocytopenia; may interfere with platelet function.

Dosage form specific issues:

- Hextend®: Contains calcium, lactate and potassium; use with caution in situations where electrolyte and/or acid-base disturbances may be exacerbated (renal impairment, respiratory alkalosis).

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, circulatory overload, heart failure, peripheral edema, tachycardia

Central nervous system: Chills, fever, headache, intracranial bleeding

Dermatologic: Itching, pruritus (dose dependant; may be delayed), rash

Endocrine & metabolic: Metabolic acidosis, parotid gland enlargement

Gastrointestinal: Amylase levels increased, vomiting

Hematologic: Anemia, bleeding, bleeding time prolonged, clotting time prolonged, dilutional coagulopathy, disseminated intravascular coagulopathy (rare), factor VIII:C plasma levels decreased, hemolysis (rare), plasma aggregation decreased, PT prolonged, PTT prolonged, thrombocytopenia, von Willebrand factor decreased, wound hemorrhage

Hepatic: Bilirubin increased (indirect)

Neuromuscular & skeletal: Myalgia

Respiratory: Bronchospasm, pulmonary edema (noncardiac)

Miscellaneous: Anaphylactoid reactions, flu-like syndrome (mild), hypersensitivity

Postmarketing and/or case reports: Hypotension, urticaria

Drug InteractionsThere are no known significant interactions.
Test Interactions

Serum amylase levels may be temporarily elevated following administration; could interfere with the diagnosis of pancreatitis.

Large hetastarch volumes may result in decreased coagulation factors, plasma proteins, and /or hematocrit due to dilutional effect.

Monitoring ParametersVolume expansion: Blood pressure, heart rate, capillary refill time, CVP, RAP, MAP, urine output; if pulmonary artery catheter in place, monitor PCWP, SVR, and PVR; hemoglobin, hematocrit, serum electrolytes, renal function, acid-base balance, coagulation parameters, cardiac index

Leukapheresis: CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, PT, PTT

Nursing: Physical Assessment/MonitoringAssess patient's allergy history prior to therapy (patients allergic to corn may have a cross allergy to hetastarch). Evaluate appropriateness for treatment (eg, contraindicated with coagulation or bleeding disorder, intracranial bleeding, dialysis, renal failure, severe hepatic disease, fluid overload condition). Note specific directions for compatibility and administration. Patient must be monitored closely for hypersensitivity (anaphylactic reaction) and other major adverse reactions (eg, circulatory overload, cranial bleed, pulmonary edema). Vital signs, CVP, and urine output should be monitored frequently (every 5-15 minutes) during first hour and at regular intervals thereafter. Evaluate results of laboratory test during and after treatment. Patient teaching should be appropriate to patient condition.

Monitoring: Lab TestsVolume expansion: Hemoglobin, hematocrit, serum electrolytes, renal function, acid-base balance, coagulation parameters

Leukapheresis: CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, PT, PTT

Patient EducationReport immediately any chest pain or palpitations, respiratory difficulty, acute headache, muscle pain, abdominal cramping, chills, itching, or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant or breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed in lactated electrolyte injection]:

Hextend®: 6% (500 mL)

Infusion, solution [premixed in NaCl 0.9%]: 6% (500 mL)

Hespan®, Voluven®: 6% (500 mL)

Generic AvailableYes: Sodium chloride infusion

Mechanism of ActionProduces plasma volume expansion by virtue of its highly colloidal starch structure, similar to albumin

Pharmacodynamics/Kinetics

Onset of action: Volume expansion: I.V.: ~30 minutes

Duration: 6-36 hours

Distribution: Voluven®: 5.9 L

Metabolism: Molecules >50,000 daltons require enzymatic degradation by the reticuloendothelial system or amylases in the blood

Half-life elimination: Voluven®: 12 hours

Excretion: Urine (33% to 40% within 24 hours; ~62% within 72 hours); smaller molecular weight molecules readily excreted

Pharmacotherapy PearlsHetastarch is a synthetic polymer derived from a waxy starch composed of amylopectin.

Hespan®: 6% hetastarch in 0.9% sodium chloride

Molecular weight: 600,000

Sodium: 154 mEq/L

Chloride: 154 mEq/L

Osmolarity: ~309 mOsm/L

Hextend®: 6% hetastarch in lactated electrolyte injection

Molecular weight: ~670,000

Sodium: 143 mEq/L

Chloride: 124 mEq/L

Calcium: 5 mEq/L

Potassium: 3 mEq/L

Magnesium: 0.9 mEq/L

Lactate: 28 mEq/L

Dextrose: 0.99 g/L

Osmolarity: ~307 mOsm/L

Voluven®: 6% hetastarch (130/0.4) in 0.9% sodium chloride

Molecular weight: ~130,000

Sodium: 154 mEq/L

Chloride: 154 mEq/L

Osmolarity: 308 mOsm/L

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Hetastarch is a synthetic polymer derived from a waxy starch composed of amylopectin.

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Chloride: 124 mEq/L

Calcium: 5 mEq/L

Potassium: 3 mEq/L

Magnesium: 0.9 mEq/L

Lactate: 28 mEq/L

Dextrose: 0.99 g/L

Osmolarity: ~307 mOsm/L

Voluven®: 6% hetastarch (130/0.4) in 0.9% sodium chloride

Molecular weight: ~130,000

Sodium: 154 mEq/L

Chloride: 154 mEq/L

Osmolarity: 308 mOsm/L

Hextend®, Hespan®, and Voluven® will expand the intravascular volume the same as an equal volume of 5% albumin. Hetastarch will increase the intravascular volume up to 6-36 hours depending on the formulation. Hetastarch does not have oxygen-carrying capacity and is not a substitute for blood or plasma. Large volumes of Hespan®, Hextend®, or Voluven® may interfere with platelet function, prolong PT and PTT times, and cause hemodilution; however, clinically Hextend® has not been associated with coagulation abnormalities in doses >20 mL/kg up to a total of 5000 mL. Voluven®, because of its low molecular weight and reduced molar substitution, also has a low potential for affecting coagulation.

Hextend®: Formulated with near physiologic levels of sodium, chloride, calcium, potassium, magnesium; may be associated with less electrolyte abnormalities than Hespan®; not to be used for the treatment of lactic acidosis; should not be administered through the same line as blood products; use with caution in patients with heart failure.

Hespan®: Intraoperative use in patients undergoing cardiac surgery with cardiopulmonary bypass may increase bleeding; each 500 mL provides 77 mEq sodium chloride and may cause hyperchloremic metabolic acidosis in large volumes; critically-ill patients receiving hetastarch infusions (goal: PCWP 12-18 mm Hg) had an increase in cardiac index, oxygen delivery, and consumption.

Voluven®: Up to 50 mL/kg/day (or 3500 mL/day in a 70 kg patient) may be used without significant effects on coagulation parameters. Eliminated more rapidly resulting in a shorter duration of action (4-6 hours) compared to other HES products. Because of minimal accumulation, tissue storage is reduced and may result in a lower rate of delayed-onset pruritus seen with other HES products.

Hextend®, Hespan®, and Voluven®: May increase serum amylase temporarily without an association with pancreatitis; not eliminated by hemodialysis.

Index TermsHES; Hydroxyethyl Starch
References

Bick RL, "Evaluation of a New Hydroxyethyl Starch Preparation (Hextend™) on Selected Coagulation Parameters," *Clin Appl Thrombosis/Hemostasis*, 1995, 1(3):215-29.

Boldt J, Heesen M, Müller M, et al, "The Effects of Albumin Versus Hydroxyethyl Starch Solution on Cardiorespiratory and Circulatory Variables in Critically Ill Patients," *Anesth Analg*, 1996, 83(2):254-61. [PubMed 8694302]

Brutocao D, Bratton SL, Thomas JR, et al, "Comparison of Hetastarch With Albumin for Postoperative Volume Expansion in Children After Cardiopulmonary Bypass," *J Cardiothorac Vasc Anesth*, 1996, 10(3):348-51. [PubMed 8725415]

Gan TJ, Bennett-Guerrero E, Phillips-Bute B, et al "Hextend®, a Physiologically Balanced Plasma Expander for Large Volume Use in Major Surgery: A Randomized Phase III Clinical Trial," *Anesth Analg*, 1999, 88(5):992-8. [PubMed 10320157]

Gan TJ, Wright D, Robertson C, et al, "Randomized Comparison of the Coagulation Profile When Hextend® or 5% Albumin is Used for Intraoperative Fluid Resuscitation," *Anesthesiology*, 2001, 95:A193.

Knutson JE, Deering JA, Hall FW, et al, "Does Intraoperative Hetastarch Administration Increase Blood Loss and Transfusion Requirements After Cardiac Surgery?" *Anesth Analg*, 2000, 90(4):801-7. [PubMed 10735779]

University Health System Consortium. *Technology Assessment: Albumin, Nonprotein Colloid, and Crystalloid Solutions*, May 2000.

Wilkes NJ, Woolf RL, Powanda MC, et al, "Hydroxyethyl Starch in Balanced Electrolyte Solution (Hextend®) - Pharmacokinetic and Pharmacodynamic Profiles in Healthy Volunteers," *Anesth Analg*, 2002, 94(3):538-44.[PubMed 11867371]

International Brand NamesElo Hes (ES); Elohaes (HR, NL); Elohaest (AT); Elohast (CH); Elohes (FR); Expafusin (ES); Expahes (CH); Haes Esteril (ES); HAES-steril (AR, BE, CH, CZ, DK, FI, HR, LU, NL, PL, SE); Haes-Steril (BG, DE, GB, HN, PH, RU); Heafusine (FR); Hemohes (CH, CL, LU, NL, SE, TW); Hespander (JP); Hesteril (ES, FR); Hydroksyetyloskrobia (PL); Infukoll HES (PL); Isohes (CH); Lomol (FR); Plasmafusin (FI); Plasmasteril (BE, CH, PL, TR); StarQuin (NZ); Varihes (CH); Voluven (DK)

Hexachlorophene

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

pHisoHex® may be confused with Fostex®, pHisoDerm®

Pronunciation(heks a KLOR oh feen)
U.S. Brand NamespHisoHex®
Canadian Brand NamespHisoHex®
Pharmacologic CategoryAntibiotic, Topical
Use: Labeled IndicationsSurgical scrub and as a bacteriostatic skin cleanser; control an outbreak of gram-positive infection when other procedures have been unsuccessful
Dosing: AdultsAntiseptic (Children and Adults): Topical: Apply 5 mL cleanser and water to area to be cleansed; lather and rinse thoroughly under running water
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
StorageStore in nonmetallic container. Prolonged direct exposure to strong light may cause brownish surface discoloration, but this does not affect its action.
Compatibility**Incompatible** with many metals.
ContraindicationsHypersensitivity to halogenated phenol derivatives or hexachlorophene; use in premature infants; use on burned or denuded skin; occlusive dressing; application to mucous membranes
Warnings/Precautions

Concerns related to adverse effects:

- Cerebral irritability: Discontinue use if signs of cerebral irritability occur.

Special populations:

- Burn patients: Exposure to patients with extensive burns has been associated with apnea, convulsions, agitation and coma.
- Pediatrics: Exposure to preterm infants has been associated with apnea, convulsions, agitation and coma; particularly susceptible to hexachlorophene topical absorption. Do not use for bathing infants.

Other warnings/precautions:

- Appropriate use: For external use only; avoid exposure to eyes.

Pregnancy Risk FactorC
Adverse Reactions<1%: CNS injury, seizure, irritability, photosensitivity, dermatitis, redness, dry skin
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, topical: 3% (150 mL, 500 mL, 3840 mL)

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Liquid (Phisohex)

3% (148): $32.55

3% (473): $54.25

Mechanism of ActionBacteriostatic polychlorinated biphenyl which inhibits membrane-bound enzymes and disrupts the cell membrane
Pharmacodynamics/Kinetics

Absorption: Percutaneously through inflamed, excoriated, and intact skin

Distribution: Crosses placenta

Half-life elimination: Infants: 6.1-44.2 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Halling H, “Suspected Link Between Exposure to Hexachlorophene and Malformed Infants,” *Ann N Y Acad Sci*, 1979, 320:426-35. [PubMed 287398]

Lester RS, “Topical Formulary for the Pediatrician,” *Pediatr Clin North Am*, 1983, 30(4):749-65. [PubMed 6225068]

Lockhart JD, “How Toxic is Hexachlorophene?” *Pediatrics*, 1972, 50(2):229-35. [PubMed 4625618]

Marquardt ED, “Hexachlorophene Toxicity in a Pediatric Burn Patient,” *Drug Intell Clin Pharm*, 1986, 20(7-8):624.

Nagy L and Orosz M, “Occupational Asthma Due to Hexachlorophene,” *Thorax*, 1984, 39(8):630-1.[PubMed 6474393]

International Brand NamesAknefug-simplex (DE); Dermisan (ID); Jabon Antiseptico (ES); Phisohex (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Ritosept (HU)

Hexylresorcinol

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(heks il re ZOR si nole)
U.S. Brand NamesS.T. 37® [OTC]; Sucrets® Original [OTC]
Pharmacologic CategoryAntiseptic, Topical; Local Anesthetic
Use: Labeled IndicationsMinor antiseptic and local anesthetic for sore throat; topical antiseptic for minor cuts or abrasions
Dosing: Adults

Antiseptic: Topical: Solution: Apply to affected area 1-3 times/day

Sore throat: Oral:

Lozenge: May be used as needed, allow to dissolve slowly in mouth (maximum: 10 lozenges/day)

Solution: Gargle or swish in mouth up to 4 times/day

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Antiseptic: Topical: Children ≥2 years: Refer to adult dosing.

Sore throat: Oral: Children ≥2 years: Refer to adult dosing.

ContraindicationsHypersensitivity to hexylresorcinol or any component of the formulation
Warnings/Precautions

Dosage form specific issues:

- Sore throat (self-medication, OTC use): When self-medicating, patients should be instructed to contact healthcare provider if the medication is used for sore throat lasting >7 days; if accompanied by fever, rash, nausea, or vomiting; or if symptoms worsen

- Topical antiseptic: Not for use over large areas of body, around eyes, deep or puncture wounds, animal bites, or serious burns. When used for self-medication (OTC use), not for use for >7 days. Contains sodium bisulfite which may cause allergic reactions in some individuals.

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Lozenge (Sucrets® Original): 2.4 mg [mint flavor]

Solution (S.T. 37®): 0.1% (480 mL) [contains sodium bisulfite]

Generic AvailableNo
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesNyal Medithroat Anaesthetic Lozenges (AU); Oxana (IT)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Neuroblastoma

Regimen UseNeuroblastoma

Regimen

Cisplatin: I.V.: 40 mg/m^2/day days 1 to 5

[total dose/cycle = 200 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Ifosfamide: I.V.: 3 g/m^2/day days 21 to 23

[total dose/cycle = 9 g/m^2]

Mesna: I.V.: 3 g/m^2/day continuous infusion days 21 to 23

[total dose/cycle = 9 g/m^2]

Vincristine: I.V.: 1.5 mg/m^2 day 21

[total dose/cycle = 1.5 mg/m^2]

Doxorubicin: I.V.: 60 mg/m^2 day 23

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 28 days

References

Pinkerton CR, Zucker JM, Hartmann O, et al, âShort Duration, High Dose, Alternating Chemotherapy in Metastatic Neuroblastoma. (ENSG 3C Induction Regimen). The European Neuroblastoma Study Group,â *Br J Cancer*, 1990, 62(2):319-23.[PubMed 2386751]

Histrelin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(his TREL in)

U.S. Brand NamesSupprelin® LA; Vantas™

Canadian Brand NamesVantas™

Pharmacologic CategoryGonadotropin Releasing Hormone Agonist

Use: Labeled IndicationsPalliative treatment of advanced prostate cancer; treatment of children with central precocious puberty (CPP)

Dosing: AdultsPalliative treatment of advanced prostate cancer: SubQ (Vantas™): 50 mg implant surgically inserted every 12 months

Dosing: ElderlySee adult dosing.

Dosing: PediatricCPP: SubQ (Supprelin® LA): Children ≥2 years: 50 mg implant surgically inserted every 12 months. Discontinue at the appropriate time for the onset of puberty.

Dosing: Renal ImpairmentCl_{cr}: 15-60 mL/minute: Adjustment not needed.

Administration: OtherSubQ: Surgical implantation into the inner portion of the upper arm requires the use of the implantation device provided. Use the patient's nondominant arm for placement. Removal must occur after 12 months; a replacement implant may be required. Palpate area of incision to locate implant for removal. If not readily palpated, ultrasound, CT or MRI may be used to locate implant; plain films are not recommended because the implant is not radiopaque.

StorageSupprelin® LA, Vantas™: Upon delivery, separate contents of implant carton. Store implant under refrigeration at 2°C to 8°C (36°F to 46°F), wrapped in the amber pouch for protection from light. Do not freeze. The implantation kit does not require refrigeration.

ContraindicationsHypersensitivity to histrelin acetate, GnRH, GnRH-agonist analogs, or any component of the formulation; pregnancy

Allergy Considerations

- GnRH Agonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hormonal effects: Transient increases in estradiol serum levels (female) or testosterone levels (female and male) may occur during the first week of use for CPP. Transient increases in testosterone serum levels occur during the first week of use for prostate cancer (initial flare).
- Pituitary apoplexy: Rare cases of pituitary apoplexy (frequently secondary to pituitary adenoma) have been observed with leuprolide administration (onset from 1 hour to usually <2 weeks); may present as sudden headache, vomiting, visual or mental status changes, and infrequently cardiovascular collapse; immediate medical attention required.
- Spinal cord compression: Has been reported, may contribute to paralysis when used for prostate cancer; closely observe patients with metastatic vertebral lesions for weakness and paresthesias in first few weeks of therapy.
- Urinary tract obstruction: Ureteral obstruction, may contribute to paralysis when used for prostate cancer; closely observe patients for urinary tract obstruction or poor urine output in first few weeks of therapy.
- Worsening of symptoms: May occur when using for CPP, however, manifestations of puberty should decrease within 4 weeks. Worsening symptoms such as bone pain, hematuria, neuropathy, ureteral or bladder outlet obstruction, and spinal cord compression have been reported when using for prostate cancer.

Disease-related concerns:

- Hepatic impairment: Safety and efficacy have not been established in prostate cancer patients with hepatic dysfunction.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age when using for CPP.

Pregnancy Risk FactorX

Pregnancy ConsiderationsFetal harm and an increase in fetal mortalities have been noted in animal studies. Histrelin is contraindicated for use during pregnancy or in women who may become pregnant.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding Considerations

Products are not indicated for use in postpubertal women.

Adverse Reactions

CPP:

>10%: Local: Insertion site reaction (51%; includes bruising, discomfort, itching, pain, protrusion of implant area, soreness, swelling, tingling)

>2% to 10%:

Endocrine & metabolic: Metrorrhagia (4%)

Local: Keloid scar (6%), scar (6%), suture-related complication (6%), pain at the application site (4%), post procedural pain (4%)

≤2%: Amblyopia, breast tenderness, cold feeling, disease progression, dysmenorrhea, epistaxis, erythema, flu-like syndrome, gynecomastia, headache, infection at the implant site, menorrhagia, migraine, mood swings, pituitary adenoma, pruritus, weight increase

Prostate cancer:

>10%:

Endocrine & metabolic: Hot flashes (66%)

Local: Implant site reaction (6% to 14%; includes bruising, erythema, pain, soreness, swelling, tenderness)

2% to 10%:

Central nervous system: Fatigue (10%), headache (3%), insomnia (3%)

Endocrine & metabolic: Gynecomastia (4%), sexual dysfunction (4%), libido decreased (2%)

Gastrointestinal: Constipation (4%), weight gain (2%)

Genitourinary: Expected pharmacological consequence of testosterone suppression: Testicular atrophy (5%)

Renal: Renal impairment (5%)

<2%: Abdominal discomfort, alopecia, anemia, appetite increased, arthralgia, AST increased, back pain, bone density decreased, bone pain, breast pain, breast tenderness, cold feeling, contusion, craving food, creatinine increased, depression, diaphoresis, dizziness, dyspnea (exertional), dysuria, fluid retention, flushing, genital pruritus, hematoma, hematuria, hypercalcemia, hypercholesterolemia, hyperglycemia, irritability, LDH increased, lethargy, limb pain, liver disorder, malaise, muscle twitching, myalgia, nausea, neck pain, night sweats, palpitation, peripheral edema, prostatic acid phosphatase increased, pruritus, renal calculi, renal failure, stent occlusion, testosterone increased, tremor, urinary frequency, urinary retention, ventricular asystoles, weakness, weight loss

Drug Interactions

Antidiabetic Agents: Luteinizing Hormone-Releasing Hormone Analogs may diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Test InteractionsResults of diagnostic test of pituitary gonadotropic and gonadal functions may be affected during and after therapy

Monitoring Parameters

CPP: LH, FSH, estradiol or testosterone (after 1 month then every 6 months); height, bone age (every 6-12 months); tanner staging

Prostate cancer: LH and FSH levels, serum testosterone levels, prostate specific antigen (PSA), bone mineral density; weakness, paresthesias, and urinary tract obstruction (especially during first few weeks of therapy)

Reference RangeProstate cancer:

Testosterone level: Expected to rise during the first few days and decline to below initiation level by week 2 before reaching ≤50 ng/dL (castrate level)

PSA: Expected to decrease to normal levels after 6 months of therapy

Note: Lack of response (testosterone and PSA decreases) should prompt suspicion that the implant has been expelled.

Nursing: Physical Assessment/MonitoringEvaluate results of laboratory tests after insertion and then periodically thereafter. Teach patient proper care of insertion site, possible side effects/appropriate interventions, and adverse symptoms to report (according to purpose for use). **Pregnancy risk factor X:** Not for use with postpubertal females.

Monitoring: Lab Tests

CPP: LH, FSH, estradiol or testosterone (after 1 month then every 6 months)

Prostate cancer: LH and FSH levels, serum testosterone levels, prostate specific antigen (PSA)

Patient EducationFollow directions for care of insertion site: Wait 24 hours before allowing moisture or water to touch the arm and 7 days before participating in strenuous activity or heavy lifting. Report immediately any redness, swelling, pain, drainage, or tingling at insertion site. You may experience increased or worsened symptoms (increased bone pain) during first week following insertion; these should subside. May cause hot flashes (cool cloths or a cool environment may help); dizziness, headache, insomnia, irritability (use caution when driving or engaging in tasks that require alertness until response to medication is known); enlarged or painful breasts, decreased libido, or sexual dysfunction; constipation (increased fluids and exercise may help); weight gain; or loss of hair. Report any persistent difficulty urinating; shortness of breath; muscle pain, twitching, or weakness; persistent dizziness, confusion, depression, or mood swings; or other persistent adverse reactions. **Pregnancy/breast-feeding precaution:** Not for use with postpubertal females.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Implant, subcutaneous:

Supprelin® LA: 50 mg (1) [releases ~65 mcg/day over 12 months; packaged with implantation kit]

Vantas™: 50 mg (1) [releases 50-60 mcg/day over 12 months; packaged with implantation kit]

Generic AvailableNo

ManufacturerIndevus Pharmaceuticals

Mechanism of ActionPotent inhibitor of gonadotropin secretion; continuous administration results in, after an initiation phase, the suppression of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and a subsequent decrease in testosterone (females and males) and estrogen (premenopausal females). Additionally, in patients with CPP, linear growth velocity is slowed (improves chance of attaining predicted adult height).

Pharmacodynamics/Kinetics

Onset of action: Prostate cancer: Chemical castration: 2-4 weeks; CPP: progression of sexual development stops and growth is decreased in ~1 month

Duration: 1 year

Distribution: Adults: V_d: ~58 L

Protein binding: Adults: 70% ± 9%

Metabolism: Hepatic via C-terminal dealkylation and hydrolysis

Bioavailability: Adults: 92%

Half-life elimination: Adults: Terminal: ~4 hours

Time to peak, serum: Adults: 12 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue and insomnia; may rarely cause depression, dizziness, irritability, lethargy, or malaise

Mental Health: Effects on Psychiatric TreatmentMay cause sexual dysfunction; concomitant use with psychotropic agents (especially SSRIs) may produce additive effects. May cause renal dysfunction; monitor serum levels in patients receiving lithium.

Index TermsGnRH Agonist; Histrelin Acetate; LH-RH Agonist

References

Dineen MK, Tierney DS, Kuzma P, et al, “An Evaluation of the Pharmacokinetics and Pharmacodynamics of the Histrelin Implant for the Palliative Treatment of Prostate Cancer,” *J Clin Pharmacol*, 2005, 45(11):1245-9.[PubMed 16239357]

Schlegel PN, Histrelin Study Group, “Efficacy and Safety of Histrelin Subdermal Implant in Patients With Advanced Prostate Cancer,” *J Urol*, 2006, 175(4):1353-8.[PubMed 16515997]

International Brand NamesVantas (MY, SG, TH)

Homatropine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(hoe MA troe peen)

U.S. Brand NamesIsopto® Homatropine

Pharmacologic CategoryAnticholinergic Agent, Ophthalmic; Ophthalmic Agent, Mydriatic

Use: Labeled IndicationsProducing cycloplegia and mydriasis for refraction; treatment of acute inflammatory conditions of the uveal tract; optical aid in axial lens opacities

Dosing: Adults

Mydriasis and cycloplegia for refraction: Ophthalmic: Instill 1-2 drops of 2% solution or 1 drop of 5% solution before the procedure; repeat at 5- to 10-minute intervals as needed; maximum of 3 doses for refraction

Uveitis: Ophthalmic: Instill 1-2 drops of 2% or 5% 2-3 times/day up to every 3-4 hours as needed

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Mydriasis and cycloplegia for refraction: Ophthalmic: Instill 1 drop of 2% solution immediately before the procedure; repeat at 10-minute intervals as needed

Uveitis: Ophthalmic: Instill 1 drop of 2% solution 2-3 times/day

Administration: OtherOphthalmic instillation: Finger pressure should be applied to lacrimal sac for 1-2 minutes after instillation to decrease risk of absorption and systemic reactions

StorageStore at 8°C to 24°C (46°F to 75°F). Protect from light.

ContraindicationsHypersensitivity to homatropine or any component of the formulation; primary glaucoma or predisposition to glaucoma (eg, narrow-angle glaucoma)

Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Excessive use may cause CNS disturbances, including confusion, delirium, agitation, and coma (rare). May occur with any age group, although children and the elderly are more susceptible.
- Increased intraocular pressure: May cause an increase in intraocular pressure.
- Light sensitivity (ocular): May cause sensitivity to light; appropriate eye protection should be used.

Disease-related concerns:

- Down syndrome: Patients with Down syndrome are predisposed to angle-closure glaucoma; use with caution.
- Keratoconus: May result in fixed pupil dilation in patients with keratoconus; use with caution.

Special populations:

- Elderly: Use with caution in the elderly due to susceptibility to systemic effects.
- Pediatrics: Safety and efficacy have not been established in infants and young children, therefore, use with extreme caution due to susceptibility of systemic effects.

Dosage form specific issues:

- Contact lens wearers: Some strengths may contain benzalkonium chloride which may be adsorbed by contact lenses; remove contacts prior to administration and wait 15 minutes before reinserting.

Other warnings and precautions:

- Appropriate use: To minimize systemic absorption, apply pressure over the nasolacrimal sac for 2-3 minutes after instillation. To avoid contamination, do not touch dropper tip to any surface. For topical ophthalmic use only.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Ocular: Blurred vision, photophobia

1% to 10%:

Local: Stinging, local irritation

Ocular: Increased intraocular pressure

Respiratory: Congestion

<1%: Vascular congestion, edema, drowsiness, exudate, eczematoid dermatitis, follicular conjunctivitis

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic, as hydrobromide:

Isopto® Homatropine: 2% (5 mL); 5% (5 mL, 15 mL) [contains benzalkonium chloride]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Isopto Homatropine)

2% (5): $30.99

5% (5): $38.82

5% (15): $34.99

Mechanism of ActionBlocks response of iris sphincter muscle and the accommodative muscle of the ciliary body to cholinergic stimulation resulting in dilation and loss of accommodation

Pharmacodynamics/Kinetics

Onset of action: Accommodation and pupil effect: Ophthalmic:

Maximum mydriatic effect: Within 10-30 minutes

Maximum cycloplegic effect: Within 30-90 minutes

Duration:

Mydriasis: 6 hours to 4 days

Cycloplegia: 10-48 hours

Related Information

- Cycloplegic Mydriatics

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Nasal congestion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsHomatropine Hydrobromide

References

Barker DB and Solomon DA, “The Potential for Mental Status Changes Associated With Systemic Absorption of Anticholinergic Ophthalmic Medications: Concerns in the Elderly,” *DICP Ann Pharmacother*, 1990, 24(9):847-50.

International Brand NamesBromhydrate d'homatropine-Chauvin (LU); Homa (MY); Homarin Forte (IN); Homatropin (HR, NO); Homatropin-POS (DE); Homatropine (AU, BE, NL); Homatropine Faure (FR); Isopto Homatropine (AE, AU, BF, BH, BJ, CI, CY, EG, ET, FR, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Isopto-Homatropine (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Minims Homatropine (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Minims Homatropine HBr (HK); Minims Homatropine Hydrobromide (GB, IE); Minims-Homatropinhydrobromid (AT);

Hyaluronate and Derivatives

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Synvisc® may be confused with Synagis®

Pronunciation(hye al yoor ON ate & dah RIV ah tives)
U.S. Brand NamesBiolon™ [DSC]; Bionect®; Euflexxa™; Healon GV®; Healon®; Healon®5; Hyalgan®; Hylaform®; Hylaform® Plus; Hylira™; IPM Wound Gel™ [OTC]; Juvederm™ 24HV; Juvederm™ 30; Juvederm™ 30HV; Orthovisc®; Perlane®; Provisc®; Restylane®; Supartz™; Synvisc®; Vitrax®
Canadian Brand NamesCystistat®; Durolane®; Eyestil; Healon GV®; Healon®; OrthoVisc®; Suplasyn®
Pharmacologic CategoryAntirheumatic, Miscellaneous; Ophthalmic Agent, Viscoelastic; Skin and Mucous Membrane Agent, Miscellaneous
Use: Labeled Indications

Intra-articular injection: Treatment of pain in osteoarthritis in knee in patients who have failed nonpharmacologic treatment and simple analgesics

Intradermal: Correction of moderate-to-severe facial wrinkles or folds

Ophthalmic: Surgical aid in cataract extraction, intraocular implantation, corneal transplant, glaucoma filtration, and retinal attachment surgery

Topical cream, gel, spray: Management of skin ulcers and wounds

Topical lotion: Treatment of xerosis (dry, scaly skin)

Use: Unlabeled/InvestigationalTreatment of refractory interstitial cystitis
Dosing: Adults

Surgical aid: Ophthalmic (Biolon™, Healon®, Provisc®, Vitrax®): Depends upon procedure (slowly introduce a sufficient quantity into eye)

Osteoarthritis of the knee: Intra-articular:

Eulexxa™: Inject 20 mg (2 mL) once weekly for 3 weeks

Hyalgan®: Inject 20 mg (2 mL) once weekly for 5 weeks; some patients may benefit with a total of 3 injections

Orthovisc®: Inject 30 mg (2 mL) once weekly for 3-4 weeks

Supartz™: Inject 25 mg (2.5 mL) once weekly for 5 weeks

Synvisc®: Inject 16 mg (2 mL) once weekly for 3 weeks (total of 3 injections)

Facial wrinkles: Intradermal

Note: Formulations differ in terms of recommended injection depth: Juvederm™, Hylaform®, and Restylane® are intended for mid to deep intradermal injection; Perlane® is intended for injection into the deep dermis to superficial subcutis

Hylaform®, Hylaform® Plus: Inject as required for cosmetic result; typical treatment regimen requires <2 mL; limit injection to ≤1.5 mL per injection site; maximum: 20 mL/60 kg/year

Perlane®: Inject as required into deep dermis/superficial subcutis for cosmetic result; typical treatment regimen requires 1.9-4.6 mL; maximum 6 mL per treatment

Juvederm™ (all formulations): Inject as required for cosmetic result; typical treatment regimen requires <2 mL; limit injection to 1.6 mL per injection site; maximum: 20 mL/60 kg/year

Restylane®): Inject as required for cosmetic result; typical treatment regimen requires <2 mL; limit injection to ≤1.5 mL per injection site

Skin ulcers and wounds:

Bionect® cream, gel, and spray: Topical: Apply a thin layer to clean and disinfected wound or ulcer 2-3 times/day, and cover with sterile gauze pad. If needed, cover with elastic or compressive bandage.

IPM Wound Gel™: Topical: Apply to clean dry ulcer or wound, and cover with nonstick dressing; repeat daily. Discontinue if wound size increase after 3-4 applications.

Xerosis (dry, scaly skin): Hylira™ lotion: Topical: Apply to affected area and rub in thoroughly 2-3 times daily. Discontinue if condition worsens.

Interstitial cystitis, refractory (unlabeled use): Intravesical (unlabeled route): 40 mg in 50 mL saline intravesically (retain in bladder for at least 30 minutes) once weekly for 4 weeks, then monthly for up to 1 year in patients showing an initial response

Dosing: ElderlyRefer to adult dosing.

Administration: Topical

Bionect® products: Clean and disinfect wound prior to use (do not use quaternary ammonium salts), and debride if necessary; apply a thin layer to wound or ulcer without extensive rubbing.

IPM Wound Gel™: Clean wound with normal saline; remove excess moisture with dry gauze; apply gel liberally to wound

Hylira™ lotion: Apply and rub in thoroughly into affected area. Avoid eyes, lips and mucous membranes.

Administration: Other

Intra-articular: Inject directly into the knee joint. Do not use disinfectants containing quaternary salts for skin cleansing prior to injection. Remove effusion, if present, prior to injection. If used for bilateral treatment, use a separate syringe for each injection site.

Intradermal: Do not inject into a blood vessel. May apply ice pack to injection site for a short period immediately after administration if treatment area swollen.

Juvederm™, Hylaform®, and Restylane® are intended for mid to deep intradermal injection

Perlane® is intended for injection into the deep dermis to superficial subcutis

Ophthalmic: Drug may become cloudy or form a slight precipitate after administration; clinical significance unknown, but cloudy or precipitated material should be removed by irrigation or aspiration

Storage

Bionect® products: Store at room temperature. Cream and gel may be stored up to 24 months; spray may be stored up to 36 months.

Euflexxa™: Store under refrigeration at 2°C to 8°C (36°F to 46°F) or at room temperature up to 25°C (77°F); do not freeze. Protect from light. If refrigerated, remove from refrigeration at least 20-30 minutes before use.

Healon® products, Provisc®: Store under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light.

Hylaform®, Hylaform® Plus: Store at room temperature of 2°C to 30°C; do not freeze. Do not use if gel separates or becomes cloudy.

Hyalgan®, Orthovisc®: Store below 25°C (77°F); do not freeze.

Hylira™ Lotion: Store at room temperature of 15°C to 30°C; do not freeze.

IPM Wound Gel™: Store below 35°C (95°F); do not freeze.

Juvederm™ (all formulations), Perlane®, Restylane®: Store at up to 25°C (77°F); do not freeze. Protect from light. Do not use if gel separates or becomes cloudy.

Synvisc®: Store at room temperature below 30°C (86°F); do not freeze. Protect from light.

Compatibility**Incompatible:** Disinfectants containing quaternary ammonium salts may precipitate hyaluronic acid. Detergents and benzalkonium chloride may cause solution to have a milky appearance.

ContraindicationsHypersensitivity to hyaluronate or any component of the formulation

Intradermal:

Hylaform®, Hylaform® Plus: Additional contraindications include hypersensitivity to avian proteins (egg products, feathers)

Juvederm™, Perlane®, Restylane®: Additional contraindications include history of or presence of multiple severe allergies; bleeding disorders; sensitivity to gram-positive bacterial proteins

Intra-articular: Knee joint infections, infections or skin diseases at the site of injection

Orthovisc®: Additional contraindications include hypersensitivity to avian proteins (egg products, feathers)

Warnings/Precautions

Dosage form specific issues:

- Injection (gel): Intradermal: Treatment may result in bruising/bleeding; use caution in patients receiving or recently exposed (≤3 weeks) to thrombolytics, anticoagulants, or platelet inhibitors. Do not inject into site of active inflammation or infection. Injection into a blood vessel may lead to localized superficial necrosis. Use in patients susceptible to keloid formation, hypertrophic scarring, or pigmentation disorders has not been studied; use cautiously. Use caution with immunosuppressive treatment. Use in patients with prior herpetic eruption may result in reactivation. Delayed inflammatory papules may result from injections, necessitating evaluation and treatment as soft tissue infection. Laser treatment or chemical peeling may cause acute inflammatory reaction. Patient must avoid exposure to ultraviolet rays (sun and UV lamp) or severe cold until swelling and redness is resolved. Treatment site reactions usually improve in <1 week. Strenuous exercise and ethanol consumption should be avoided for 24 hours following use. Supplemental “touch up” treatments may be required. Use in lip augmentation has not been established. Safety and efficacy in patients <18 years of age have not been established.

- Injection (solution): Intra-articular: Not for use in infected joints; do not use disinfectants containing quaternary salts for skin preparation (may cause precipitation of hyaluronate). Remove effusion, if present, prior to injection. Use with caution if venous or lymphatic stasis is present in the leg. Avoid strenuous activities for 48 hours after injection. Safety and efficacy have not been established in children.

- Ophthalmic: Do not overfill the anterior chamber; carefully monitor intraocular pressure.

- Topical: Bionect® products (cream, gel, spray): Do not use disinfectants containing quaternary ammonium salts for skin preparation (may cause precipitation of hyaluronate). IPM™ wound gel: Cleansing agents other than normal saline are not recommended. Hylira™ lotion: Avoid contact with eyes, lips, mucous membranes; discontinue if condition worsens.

Other warnings/precautions:

- Not for I.V. injection. Do not inject into blood vessels; may cause occlusion, infarction, embolism, or other systemic adverse events.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequencies and/or type of local reaction may vary by formulation and site of application/injection.

>10%:

Local: Injection site (intradermal): Bruising (47% to 61%), erythema (58% to 93%), lumps/bumps (79% to 83%), pain (57% to 90%), swelling (81% to 89%); pruritus (28% to 36%), skin discoloration (31% to 34%)

Respiratory: Infection (12%)

1% to 10%:

Cardiovascular: Blood pressure increased (2% to 4%)

Central nervous system: Fatigue (1%)

Gastrointestinal: Nausea (≤2%)

Local: Dry skin (intradermal >1%), peeling (intradermal >1%)

Neuromuscular & skeletal: Back pain (<1% to 6%), tendonitis (2%), parasthesia (1%)

Respiratory: Rhinitis (3%)

Frequency not defined:

Cardiovascular: Edema, flushing, hypotension, tachycardia

Central nervous system: Dizziness, headache

Dermatologic: Rash, hyperpigmentation, exfoliation

Local: Injection site: Arthralgia, nodule

Neuromuscular & skeletal: Hypokinesia (knee)

Ocular (with ophthalmic formulation): Postoperative inflammatory reactions (iritis, hypopyon), corneal edema, corneal decompensation, transient postoperative increase in IOP

Miscellaneous: Abscess formation, allergic reactions, anaphylaxis, respiratory difficulties

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersIntraocular pressure; intradermally administered products, signs and symptoms of excess local inflammation or infection

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Hylan B: Injection, gel:

Hylaform® [500 micron particle]: 5.5 mg/mL (0.75 mL) [prefilled syringe; derived from avian source]

Hylaform® Plus [700 micron particle]: 5.5 mg/mL (0.75 mL) [prefilled syringe; derived from avian source]

Hylan polymers A and B (Hylan G-F 20): Injection, solution, intra-articular (Synvisc®): 8 mg/mL (2 mL) [prefilled syringe; contains trace amounts of *Streptococcus*]

Sodium hyaluronate:

Cream, topical:

Bionect®: 0.2% (25 g)

Gel, topical:

Bionect®: 0.2% (30 g, 60 g)

IPM Wound Gel™: 2.5% (10 g)

Lotion, topical: 0.1% (340 g, 1000 g)

Hylira™: 0.1% (340 g, 1000 g)

Injection, gel, intradermal:

Juvederm™ 24HV, Juvederm™ 30, Juvederm™ 30HV: 24 mg/mL [prefilled syringe]

Perlane®: 20 mg/mL (1mL) [prefilled syringe]

Restylane®: 20 mg/mL [prefilled syringe]

Injection, solution, intra-articular:

Euflexxa™: 10 mg/mL (2 mL) [prefilled syringe; syringe contains latex]

Hyalgan®: 10 mg/mL (2 mL)

Orthovisc®: 15 mg/mL (2 mL) [prefilled syringe; derived from avian source]

Supartz™: 10 mg/mL (2.5 mL) [derived from avian source]

Synvisc®: 8 mg/mL (2 mL) [prefilled syringe; derived from avian source]

Injection, solution, intraocular:

Biolon™: 10 mg/mL (0.5 mL, 1 mL) [DSC]

Healon®: 10 mg/mL (0.4 mL, 0.55 mL, 0.85 mL, 2 mL)

Healon®5: 23 mg/mL

Healon GV®: 14 mg/mL (0.55 mL, 0.85 mL)

Provisc®: 10 mg/mL (0.4 mL, 0.55 mL, 0.8 mL) [prefilled syringe; contains lactose]

Vitrax®: 30 mg/mL (0.65 mL)

Solution, topical [spray]:

Bionect®: 0.2% (20 mL) [DSC]

Generic AvailableYes: Lotion
Pricing: U.S. (www.drugstore.com)

Cream (Bionect)

0.2% (25): $66.59

Gel (Bionect)

0.2% (30): $65.53

Solution (Bionect)

0.2% (20): $59.59

Solution (Euflexxa)

10 mg/mL (6): $459.99

Solution (Hyalgan)

20 mg/2 mL (2): $138.31

Solution (OrthoVisc)

15 mg/mL (2): $256.50

Mechanism of ActionSodium hyaluronate is a polysaccharide which is distributed widely in the extracellular matrix of connective tissue in man (vitreous and aqueous humor of the eye, synovial fluid, skin, and umbilical cord). Sodium hyaluronate and its derivatives form a viscoelastic solution in water (at physiological pH and ionic strength) which makes it suitable for aqueous and vitreous humor in ophthalmic surgery, and functions as a tissue and/or joint lubricant which plays an important role in modulating the interactions between adjacent tissues. Intradermal injection may decrease the depth of facial wrinkles.
Pharmacodynamics/Kinetics

Distribution: Intravitreous injection: Diffusion occurs slowly

Excretion: Ophthalmic: Via Canal of Schlemm

Pharmacotherapy PearlsJuvederm™ 24HV provides more versatility in contouring and volumizing of facial wrinkles. Juvederm™ 30 provides subtle correction for facial folds and wrinkles. Juvederm™ 30HV provides greater volumizing for correction of deeper folds and wrinkles. Perlane® differs from Restylane® in the size of its hyaluronate particles within the gel, allowing its use in deeper injections relative to other dermal fillers.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsHyaluronan; Hyaluronic Acid; Hylan Polymers; Sodium Hyaluronate

References

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International Brand NamesAdant Dispo (ID); Amo Vitrax (AU, TH); Amvisc (NL); Aragan (KP); Artz (CL); Atri (KP); Biolon (IL, KP); Curiosin (HU); Durolane (ID); Eyecon (IL); Fermathron (AU); Go-On (PH); Healon (CO, HU, IN, LU, PK, ZA); Healon GV (AU, ZA); Healon5 (AU); Healonid (AT, FR); Hialid (ID, PH, TH); Hyal Forte (KP); Hyalein (JP); Hyalgan (BE, BG, CZ, DK, ES, FI, FR, HN, IT, PL); Hyaludrop (KP); Hylo-Comod (DE); Hyruan (KP, TH); Hyruan III (TH); IAL (ID, TH); Iolvisc (LU); Lacure (KP); Lagricel Ofteno (CR, DO, GT, HN, NI, PA, SV); Laservis (DE); Lghyal (IN); Osflex (ID); Provisc (AU, LU, PL, ZA); Suplasyn (DE, ID); Synvisc (AR, BR, CH, CN, EC, GB, HK, IE, MX, MY, NZ, PE, PL, PY, SE, SG, TW, UY, VE); Synvisc One (MY); Viscoseal (DE)

Hyaluronidase

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Medication Safety Issues

Sound-alike/look-alike issues:

Wydase may be confused with Lidex®, Wyamine®

Pronunciation(hye al yoor ON i dase)

U.S. Brand NamesAmphadase™; Hydase™; Hylenex™; Vitrase®

Pharmacologic CategoryEnzyme

Use: Labeled IndicationsIncrease the dispersion and absorption of other drugs; increase rate of absorption of parenteral fluids given by hypodermoclysis; adjunct in subcutaneous urography for improving resorption of radiopaque agents

Use: Unlabeled/InvestigationalManagement of drug extravasations

Dosing: Adults**Note:** A preliminary skin test for hypersensitivity can be performed. ACTH, antihistamines, corticosteroids, estrogens, and salicylates, when used in large doses, may cause tissues to be partly resistant to hyaluronidase. May require larger doses of hyaluronidase for the same effect.

Skin test: Intradermal: 0.02 mL (3 units) of a 150 units/mL solution. Positive reaction consists of a wheal with pseudopods appearing within 5 minutes and persisting for 20-30 minutes with localized itching.

Hypodermoclysis: SubQ: 15 units is added to each 100 mL of I.V. fluid to be administered; 150 units facilitates absorption of >1000 mL of solution; rate and volume of a single clysis should not exceed those used for infusion of I.V. fluids

Urography: SubQ: 75 units over each scapula followed by injection of contrast medium at the same site; patient should be in the prone position.

Extravasation (unlabeled use): SubQ: Inject 1 mL of a 150 unit/mL solution (as 5-10 injections of 0.1-0.2 mL) into affected area; doses of 15-250 units have been reported. **Note:** Do not use for extravasation of pressor agents (eg, dopamine, norepinephrine).

Dosing: ElderlyRefer to adult dosing. Adjust dose carefully to individual patient.

Dosing: Pediatric

Skin test: See "Note" in adult dosing: Intradermal: 0.02 mL (3 units) of a 150 units/mL solution. Positive reaction consists of a wheal with pseudopods appearing within 5 minutes and persisting for 20-30 minutes with localized itching.

Hypodermoclysis: SubQ: 15 units is added to each 100 mL of I.V. fluid to be administered; 150 units facilitates absorption of >1000 mL of solution

Premature Infants and Neonates: Volume of a single clysis should not exceed 25 mL/kg and the rate of administration should not exceed 2 mL/minute

Children <3 years: Volume of a single clysis should not exceed 200 mL

Children ≥3 years: Refer to adult dosing.

Urography: Refer to adult dosing.

Administration: I.V.Do **not** administer I.V.

Storage

Amphadase™, Hydase™, Hylenex™: Store in refrigerator at 2°C to 8°C (35°F to 46°F); do not freeze.

Vitrase®: Store unopened vial in refrigerator at 2°C to 8°C (35°F to 46°F). After reconstitution, store at 20°C to 25°C (68°F to 77°F) and use within 6 hours.

ReconstitutionVitrase®: Add 6.2 mL of NaCl to vial (1000 units/mL). Further dilute with NaCl before administration.

For 50 units/mL, draw up 0.05 mL of hyaluronidase reconstituted solution (1000 units/mL) and add 0.95 mL of NaCl.

For 75 units/mL, draw up 0.075 mL of hyaluronidase reconstituted solution and add 0.925 mL of NaCl.

For 150 units/mL, draw up 0.15 mL of hyaluronidase reconstituted solution and add 0.85 mL of NaCl.

For 300 units/mL, draw up 0.3 mL of hyaluronidase reconstituted solution and add 0.7 mL of NaCl.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, ${}^1/_2NS$, NS.

Compatibility in syringe: Compatible: Diatrizoate meglumine 34.3%, diatrizoate sodium 35%, iothalamate meglumine 60%, iothalamate sodium 80%, pentobarbital, thiopental. **Incompatible:** Hydromorphone. **Variable (consult detailed reference):** Diatrizoate meglumine 52%, diatrizoate sodium 8%, diatrizoate sodium 75%, iodipamide meglumine 52%.

Compatibility when admixed: Compatible: Amikacin, sodium bicarbonate. **Incompatible:** Benzodiazepines, epinephrine, furosemide, heparin, phenytoin.

ContraindicationsHypersensitivity to hyaluronidase or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Sensitization: Discontinue if sensitization occurs.

Other warnings/precautions:

- Administration: Do not administer intravenously; do not inject in or around infected or inflamed areas; may spread localized infection. Do not apply directly to the cornea.

- Appropriate use: Should not be used for extravasation management of dopamine or alpha agonists or to reduce swelling of bites or stings.

Geriatric ConsiderationsThe most common use of hyaluronidase in the elderly is in hypodermoclysis. Hypodermoclysis is very useful in dehydrated patients in whom oral intake is minimal and I.V. access is a problem.
Pregnancy Risk FactorC
Pregnancy ConsiderationsThere are no adequate or well-controlled studies in pregnant women; use only if clearly needed. Administration during labor did not cause any increase in blood loss or differences in cervical trauma. It is not known whether it affects the fetus if used during labor.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

Frequency not defined:

Cardiovascular: Edema

Local: Injection site reactions

<1%: Allergic reactions, anaphylactic-like reactions (retrobulbar block or I.V. injections), angioedema, urticaria

Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringResults of skin test should be assessed prior to administering. Should not be administered in or around infected or inflamed areas (see Warnings/Precautions). Teach patient possible side effects/interventions, and adverse symptoms to report (see Patient Education). **Pregnancy risk factor C** - benefits of use should outweigh possible risks. Note breast-feeding caution.
Patient EducationInform prescriber of any allergies you may have. This drug can only be administered by injection. Report immediately any unusual skin rash, pain, redness, or swelling at or around injection site, swelling of mouth or lips, difficulty breathing, or onset of sudden dizziness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Vitrase®: 6200 units [ovine derived; contains lactose]

Injection, solution:

Amphadase™: 150 units/mL (1 mL) [bovine derived; contains edetate disodium 1 mg, thimerosal ≤0.1 mg]

Injection, solution [preservative free]:

Hydase™: 150 units/mL (1 mL) [bovine derived; contains edetate disodium 1 mg]

Hylenex™: 150 units/mL (1 mL, 2 mL) [recombinant; contains human albumin and edetate disodium]

Vitrase®: 200 units/mL (2 mL) [ovine derived; contains lactose]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Solution (Vitrase)

200 units/mL (7.2): $234.35

Mechanism of ActionModifies the permeability of connective tissue through hydrolysis of hyaluronic acid, one of the chief components of tissue cement which offers resistance to diffusion of liquids through tissues; hyaluronidase increases both the distribution and absorption of locally injected substances.
Pharmacodynamics/Kinetics

Onset of action: SubQ: Immediate

Duration: 24-48 hours

Pharmacotherapy Pearls

Amphadase™ pH: 6.8

Hydase™: pH: 6.9, osmolality: 275-305 mOsm

Hylenex™: pH: 7.4, osmolality: 290-350 mOsm

Vitrase® pH: ~6.7

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness
Mental Health: Effects on Psychiatric TreatmentNone reported
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Zenk KE, “Treating I.V. Extravasations With Hyaluronidase,” *ASHP Signal*, 1986, 10:25,29.

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International Brand NamesHyalase (AU, BB, BM, BS, BZ, GB, GY, IE, IL, JM, NL, PR, SR, TT, ZA); Hyalasedessau (KP); Hyalozima (BR); Hyaluronidase (AT); Hyaluronidase Choay (FR); Hyasa Sevac (CZ); Hyase (HN); Hyason (NL); Hylase (BG, DE, PL); Hynidase (IN); Jaluran (IT); Lasonil (PT); Neopermease (AT); Penetrase (DK); Permease (AT, CH); Sprase (JP); Unidasa (AR)

Hydralazine and Hydrochlorothiazide

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Pronunciation(hye DRAL a zeen & hye droe klor oh THYE a zide)

Pharmacologic CategoryDiuretic, Thiazide; Vasodilator, Direct-Acting

Use: Labeled IndicationsManagement of moderate to severe hypertension and treatment of congestive heart failure

Dosing: AdultsHypertension: Oral: Hydralazine 25-100 mg/day and hydrochlorothiazide 25-50 mg/day in 2 divided doses (maximum: Hydrochlorothiazide: 50 mg/day)

Dosing: ElderlyRefer to dosing in individual monographs.

Contraindications

Based on **hydralazine** component: Hypersensitivity to hydralazine or any component of the formulation; mitral valve rheumatic heart disease

Based on **hydrochlorothiazide** component: Hypersensitivity to hydrochlorothiazide or any component of the formulation, thiazides, or sulfonamide-derived drugs; anuria; renal decompensation; pregnancy

Allergy Considerations

- HydrALAZINE Allergy
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Drug-induced lupus-like syndrome: Hydralazine may cause a drug-induced lupus-like syndrome (more likely on larger doses, longer duration).
- Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, and hyponatremia can occur with hydrochlorothiazide.
- Photosensitivity: Photosensitization may occur.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Cardiovascular disease: Use hydralazine with caution in patients with coronary artery disease (CAD); increase in tachycardia may increase myocardial oxygen demand.
- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.
- Hepatic impairment: Use hydrochlorothiazide with caution in patients with severe hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.
- Hypokalemia: Use hydrochlorothiazide with caution in patients with hypokalemia; correct before initiating.
- Pulmonary hypertension: Use hydralazine with caution in pulmonary hypertension; may cause hypotension.
- Renal impairment: Use hydralazine with caution in patients with severe renal impairment; dosage adjustment recommended; avoid hydrochlorothiazide in severe renal disease (ineffective).
- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsSee individual agents.

LactationEnters breast milk/compatible

Adverse ReactionsSee individual agents.

Metabolism/Transport EffectsHydralazine: **Inhibits** CYP3A4 (weak)

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

25/25: Hydralazine hydrochloride 25 mg and hydrochlorothiazide 25 mg

50/50: Hydralazine hydrochloride 50 mg and hydrochlorothiazide 50 mg

100/50: Hydralazine hydrochloride 100 mg and hydrochlorothiazide 50 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsules (Hydralazine-HCTZ)

25-25 mg (30): $22.69

50-50 mg (30): $33.60

100-50 mg (30): $15.99

Pharmacodynamics/KineticsSee individual agents.
Related Information

- HydrALAZINE
- Hydrochlorothiazide

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness or depression
Mental Health: Effects on Psychiatric TreatmentConcurrent use with MAO inhibitors may result in significant decrease in blood pressure, use cautiously; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for hydralazine and hydrochlorothiazide combination therapy may include improved compliance and synergistic reductions in blood pressure with an accompanied reduction in side effects. Thiazide therapy improves cardiovascular outcomes in patients with hypertension. Hydralazine, in combination with isosorbide dinitrate, and hydrochlorothiazide are also used in management of heart failure. See Cardiovascular Considerations for individual agents.

Index TermsApresazide [DSC]; Hydrochlorothiazide and Hydralazine

References

Chobanian AV, Bakris GL, Black HR, et al, “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report,” *JAMA*, 2003, 289(19):2560-71. [PubMed 12748199]

Kaplan NM and Sever PS, “Combination Therapy: A Key to Comprehensive Patient Care,” *Am J Hypertens*, 1997, 10(7 Pt 2):127S. [PubMed 9231887]

Moser M and Black HR, “The Role of Combination Therapy in the Treatment of Hypertension,” *Am J Hypertens*, 1998, 11(6 Pt 2):73S-8S, 95S-100S.[PubMed 9655566]

HydrALAZINE

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English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

HydrALAZINE may be confused with hydrOXYzine

Pronunciation(hye DRAL a zeen)

Canadian Brand NamesApo-Hydralazine®; Apresoline®; Novo-Hylazin; Nu-Hydral

Pharmacologic CategoryVasodilator

Use: Labeled IndicationsManagement of moderate to severe hypertension, congestive heart failure, hypertension secondary to pre-eclampsia/eclampsia; treatment of primary pulmonary hypertension

Dosing: Adults

Hypertension: Oral:

Initial: 10 mg 4 times/day; increase by 10-25 mg/dose every 2-5 days (maximum: 300 mg/day); usual dose range (JNC 7): 25-100 mg/day in 2 divided doses

Acute hypertension: I.M., I.V.: Initial: 10-20 mg/dose every 4-6 hours as needed, may increase to 40 mg/dose; change to oral therapy as soon as possible.

Pre-eclampsia/eclampsia: I.M., I.V.: 5 mg/dose then 5-10 mg every 20-30 minutes as needed

Congestive heart failure: Oral:

Initial dose: 10-25 mg 3-4 times/day

Adjustment: Dosage must be adjusted based on individual response

Target dose: 225-300 mg/day in divided doses; use in combination with isosorbide dinitrate

Dosing: ElderlyOral: Initial: 10 mg 2-3 times/day; increase by 10-25 mg/day every 2-5 days.

Dosing: Pediatric

Hypertension: Oral: Initial: 0.75-1 mg/kg/day in 2-4 divided doses; increase over 3-4 weeks to maximum of 7.5 mg/kg/day in 2-4 divided doses; maximum daily dose: 200 mg/day

Acute hypertension: I.M., I.V.: 0.1-0.2 mg/kg/dose (not to exceed 20 mg) every 4-6 hours as needed, up to 1.7-3.5 mg/kg/day in 4-6 divided doses

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer every 8 hours.

Cl_{cr} <10 mL/minute: Administer every 8-16 hours in fast acetylators and every 12-24 hours in slow acetylators.

Hemodialysis effects: Supplemental dose is not necessary.

Peritoneal dialysis effects: Supplemental dose is not necessary.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Inject over 1 minute. Hypotensive effect may be delayed and unpredictable in some patients.

Administration: I.V. DetailpH: 3.4-4.0

Dietary ConsiderationsAdminister with meals.

StorageIntact ampuls/vials of hydralazine should not be stored under refrigeration because of possible precipitation or crystallization.

ReconstitutionHydralazine should be diluted in NS for IVPB administration due to decreased stability in D_5W. Stability of IVPB solution in NS is 4 days at room temperature.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, $D_{10}W$, LR, $^1/_2NS$, NS; **incompatible** with D_5W.

Y-site administration: Compatible: Heparin, hydrocortisone sodium succinate, potassium chloride, verapamil, vitamin B complex with C. **Incompatible:** Aminophylline, ampicillin, diazoxide, furosemide. **Variable (consult detailed reference):** Nitroglycerin.

Compatibility when admixed: Compatible: Dobutamine. **Incompatible:** Aminophylline, ampicillin, chlorothiazide, edetate calcium disodium, ethacrynate, hydrocortisone sodium succinate, mephentermine, methohexital, nitroglycerin, phenobarbital, verapamil.

Extemporaneously PreparedAn oral solution (20 mg/5 mL) has been made from 20 mL of the hydralazine injection (20 mg/mL), 8 mL of propylene glycol and purified water USP qs ad 100 mL; expected stability: 30 days if refrigerated

A flavored syrup (1.25 mg/mL) has been made using seventy-five hydralazine hydrochloride 50 mg tablets, dissolved in 250 mL of distilled water with 2250 g of Lycasin® (75% w/w maltitol syrup vehicle); edetate disodium 3 g and sodium saccharin 3 g dissolved in 50 mL distilled water was added; solution was preserved with 30 mL of a solution containing methylparaben 10% (w/v) and propylparaben 2% (w/v) in propylene glycol; flavored with 3 mL orange flavoring; qs ad to 3 L with distilled water and then pH adjusted to pH of 3.7 using glacial acetic acid; measured stability was 5 days at room temperature (25°C); less than 2% loss of hydralazine occurred at 2 weeks when syrup was stored at 5°C

Alexander KS, Pudipeddi M, and Parker GA, "Stability of Hydralazine Hydrochloride Syrup Compounded From Tablets," *Am J Hosp Pharm*, 1993, 50(4):683-6.

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, 2nd ed, Cincinnati, OH: Harvey Whitney Books Co, 1992.

ContraindicationsHypersensitivity to hydralazine or any component of the formulation; mitral valve rheumatic heart disease

Warnings/Precautions

Concerns related to adverse effects:

- Drug-induced lupus-like syndrome: May cause a drug-induced lupus-like syndrome (more likely on larger doses, longer duration).
- Fluid/sodium retention: Hydralazine-induced fluid and sodium retention may require addition or increased dosage of a diuretics.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease (CAD); increase in tachycardia may increase myocardial oxygen demand.
- Pulmonary hypertension: Use with caution in pulmonary hypertension; may cause hypotension.
- Renal impairment: Use with caution in patients with severe renal impairment; dosage adjustment recommended.

Other warnings/precautions:

- I.V. administration: Monitor blood pressure closely following I.V. administration. Response may be delayed and unpredictable in some patients; titrate cautiously to response.
- Patient compliance: Patients may be poorly compliant because of frequent dosing.

Pregnancy Risk FactorC

Pregnancy ConsiderationsCrosses the placenta. One report of fetal arrhythmia; transient neonatal thrombocytopenia and fetal distress reported following late 3rd trimester use. A large amount of clinical experience with the use of this drug for management of hypertension during pregnancy is available. Available evidence suggests safe use during pregnancy.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsCrosses into breast milk in extremely small amounts. Available evidence suggests safe use during breast-feeding. AAP considers **compatible** with breast-feeding.

Adverse ReactionsFrequency not defined.

Cardiovascular: Tachycardia, angina pectoris, orthostatic hypotension (rare), dizziness (rare), paradoxical hypertension, peripheral edema, vascular collapse (rare), flushing

Central nervous system: Increased intracranial pressure (I.V., in patient with pre-existing increased intracranial pressure), fever (rare), chills (rare), anxiety*, disorientation*, depression*, coma*

Dermatologic: Rash (rare), urticaria (rare), pruritus (rare)

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, constipation, adynamic ileus

Genitourinary: Difficulty in micturition, impotence

Hematologic: Hemolytic anemia (rare), eosinophilia (rare), decreased hemoglobin concentration (rare), reduced erythrocyte count (rare), leukopenia (rare), agranulocytosis (rare), thrombocytopenia (rare)

Neuromuscular & skeletal: Rheumatoid arthritis, muscle cramps, weakness, tremor, peripheral neuritis (rare)

Ocular: Lacrimation, conjunctivitis

Respiratory: Nasal congestion, dyspnea

Miscellaneous: Drug-induced lupus-like syndrome (dose related; fever, arthralgia, splenomegaly, lymphadenopathy, asthenia, myalgia, malaise, pleuritic chest pain, edema, positive ANA, positive LE cells, maculopapular facial rash, positive direct Coombs' test, pericarditis, pericardial tamponade), diaphoresis

*Seen in uremic patients and severe hypertension where rapidly escalating doses may have caused hypotension leading to these effects.

Metabolism/Transport Effects**Inhibits** CYP3A4 (weak)

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Food enhances bioavailability of hydralazine.

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure (monitor closely with I.V. use), standing and sitting/supine, heart rate, ANA titer

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (especially anything that may impact blood pressure). For infusion see Administration specifics. Orthostatic precautions should be observed and patient monitored closely during and following infusion. Assess results of laboratory tests, therapeutic effectiveness (decreased blood pressure), and adverse response (eg, hypotension, fluid retention) periodically during therapy. Teach patient proper use (oral), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsANA titer

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, with meals. Avoid alcohol. This medication does not replace other antihypertensive interventions; follow prescriber's instructions for diet and lifestyle changes. Weigh daily at the same time, in the same clothes for the first 2 weeks and weekly thereafter. Report weight gain >5 lb/week or swelling of feet or ankles. May cause postural hypotension, dizziness, or weakness (change position slowly when rising from sitting or lying position, climbing stairs, and avoid driving or activities requiring alertness until response to drug is known); nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); impotence (reversible); diarrhea (boiled milk, buttermilk, or yogurt may help); or constipation (increased exercise, fluids, fruit, or fiber may help). Report chest pain, rapid heartbeat, or palpitations; flu-like symptoms; respiratory difficulty; skin rash; numbness and tingling of extremities; muscle cramps, weakness, or tremors; persistent GI problems; or other adverse reactions. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride: 20 mg/mL (1 mL)

Tablet, as hydrochloride: 10 mg, 25 mg, 50 mg, 100 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (HydrALAZINE HCl)

10 mg (30): $13.99

25 mg (100): $25.99

50 mg (30): $13.99

100 mg (30): $20.00

Mechanism of ActionDirect vasodilation of arterioles (with little effect on veins) with decreased systemic resistance

Pharmacodynamics/Kinetics

Onset of action: Oral: 20-30 minutes; I.V.: 5-20 minutes

Duration: Oral: Up to 8 hours; I.V.: 1-4 hours; **Note:** May vary depending on acetylator status of patient

Distribution: Crosses placenta; enters breast milk

Protein binding: 85% to 90%

Metabolism: Hepatically acetylated; extensive first-pass effect (oral)

Bioavailability: 30% to 50%; increased with food

Half-life elimination: Normal renal function: 2-8 hours; End-stage renal disease: 7-16 hours

Excretion: Urine (14% as unchanged drug)

Related Information

- Depression

- Heart Failure (Systolic)
- Hypertension

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness
Mental Health: Effects on Psychiatric TreatmentConcurrent use with MAO inhibitors may result in significant decrease in blood pressure; use cautiously
Cardiovascular Considerations

Heart Failure: May be combined with isosorbide dinitrate for the treatment of heart failure. This combination has shown to decrease cardiovascular morbidity and mortality in patients with heart failure (Cohn JN, 1986). The ACC/AHA 2005 Heart Failure Guidelines suggest that the addition of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already on an ACE inhibitor and a beta-blocker for symptomatic heart failure and who have persistent symptoms or in patients who cannot tolerate an ACE inhibitor or ARB (intolerance, hypotension, renal insufficiency).

Ethnic Considerations: Isosorbide dinitrate and hydralazine may be added to a medical regimen for heart failure (ACE inhibitors and beta-blockers) in black patients with NYHA functional Class III or IV (Taylor AL, 2004).

Hypertension: For the management of hypertension, hydralazine may be used alone or in combination with other agents. It is considered to be safe for the management of blood pressure during pregnancy.

Anesthesia and Critical Care Concerns/Other ConsiderationsMay be combined with isosorbide dinitrate for the treatment of heart failure. It is considered to be safe for the management of blood pressure during pregnancy.
Index TermsApresoline [DSC]; Hydralazine Hydrochloride
References

Chobanian AV, Bakris GL, Black HR, et al, “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report,” *JAMA*, 2003, 289(19):2560-71. [PubMed 12748199]

Cohn JN, Archibald DG, Ziesche S, et al, "Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure. Results of a Veterans Administration Cooperative Study," *N Engl J Med*, 1986, 314(24):1547-52.[PubMed 3520315]

Cohn JN, Johnson G, Ziesche S, et al, "A Comparison of Enalapril With Hydralazine-Isosorbide Dinitrate in the Treatment of Chronic Congestive Heart Failure," *N Engl J Med*, 1991, 325(5):303-10.[PubMed 2057035]

Erstad BL and Barletta JF, “Treatment of Hypertension in the Perioperative Patient,” *Ann Pharmacother*, 2000, 34(1):66-79. [PubMed 10669188]

Hunt SA, Abraham WT, Chin MH , et al, "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure)," available at http://www.acc.org/qualityandscience/clinical/guidelines/failure/update/index.pdf.

Taylor AL, Ziesche S, Yancy C, et al, "Combination of Isosorbide Dinitrate and Hydralazine in Blacks With Heart Failure," *N Engl J Med*, 2004, 351(20):2049-57.[PubMed 15533851]

International Brand NamesAlphapress (AU); Aprelazine (TW); Apresol (IN); Apresolin (NO, SE, TR); Apresolina (MX, PT, UY, VE); Apresoline (AU, BB, BF, BJ, BM, BS, BZ, CI, ET, GB, GH, GM, GN, GY, IE, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, PH, SC, SD, SL, SN, SR, TH, TN, TT, TW, TZ, UG, ZA, ZM, ZW); Aprezin (TW); Cesoline-W (TH); Clorana (BR); Hidral (AR); Hydrapres (AR, ES); Hyperphen (ZA); Slow-Apresoline (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PR, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW)

Hydrochlorothiazide and Reserpine

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English

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Pronunciation(hye droe klor oh THYE a zide & re SER peen)

Pharmacologic CategoryCentral Monoamine-Depleting Agent; Diuretic, Thiazide; Rauwolfia Alkaloid

Use: Labeled IndicationsManagement of mild to moderate hypertension; treatment of edema in congestive heart failure and nephrotic syndrome

Dosing: AdultsHypertension: Oral: Hydrochlorothiazide 25-50 mg/day and reserpine 0.125-0.25 mg/day in 1-2 divided doses; not to exceed 50 mg hydrochlorothiazide per day

Dosing: ElderlyRefer to dosing in individual monographs.

RestrictionsNot available in U.S.

Contraindications

Based on **hydrochlorothiazide** component: Hypersensitivity to hydrochlorothiazide or any component of the formulation, thiazides, or sulfonamide-derived drugs; anuria; renal decompensation

Based on **reserpine** component: Hypersensitivity to reserpine or any component of the formulation; active peptic ulcer disease, ulcerative colitis, history of mental depression (especially with suicidal tendencies); MAO inhibitors

Allergy Considerations

- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: With high doses of reserpine, significant mental depression, anxiety, or psychosis may occur (uncommon at dosages <0.25 mg/day).
- Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, and hyponatremia can occur with hydrochlorothiazide.
- Orthostatic hypotension: Reserpine may cause orthostatic hypotension; use with caution in patients at risk of hypotension or in patients where transient hypotensive episodes would be poorly tolerated (cardiovascular disease or cerebrovascular disease).
- Photosensitivity: Photosensitization may occur.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Asthma: Use reserpine with caution in patients with asthma.
- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Gallstones: Use reserpine with caution in patients with gallstones.
- Gastrointestinal disease: Use reserpine with caution in patients with inflammatory bowel disease or history of peptic ulcer disease.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.
- Hepatic impairment: Use hydrochlorothiazide with caution in patients with severe hepatic dysfunction. In cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.
- Hypokalemia: Use hydrochlorothiazide with caution in patients with hypokalemia; correct before initiating therapy.
- Parkinson's disease: Use reserpine with caution in patients with Parkinson’s disease.
- Renal impairment: Use reserpine with caution in patients with impaired renal function; avoid hydrochlorothiazide in severe renal disease (ineffective).
- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Special populations:

- Elderly: Use with caution in the elderly.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Electroshock therapy: Discontinue reserpine 7 days before electroshock therapy.

Pregnancy Risk FactorC
Pregnancy ConsiderationsRefer to Hydrochlorothiazide monograph.
LactationEnters breast milk/compatible
Adverse ReactionsSee individual agents.
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amphetamines: Gastrointestinal Acidifying Agents may decrease the serum concentration of Amphetamines. *Risk C: Monitor therapy*

Beta-Blockers: Reserpine may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Iobenguane I 123: Reserpine may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

MAO Inhibitors: May enhance the adverse/toxic effect of Rauwolfia Alkaloids. Existing MAOI therapy can result in paradoxical effects of added rauwolfia alkaloids (eg, excitation, hypertension). *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Tetrabenazine: Reserpine may enhance the adverse/toxic effect of Tetrabenazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

25: Hydrochlorothiazide 25 mg and reserpine 0.125 mg

50: Hydrochlorothiazide 50 mg and reserpine 0.125 mg

Generic AvailableYes

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Hydrochlorothiazide
- Reserpine

Pharmacotherapy PearlsNot available in U.S.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, depression, dizziness, headache, nightmares, nervousness, fatigue, dull sensorium, paradoxical anxiety

Mental Health: Effects on Psychiatric TreatmentConcurrent use with MAO inhibitors may result in hypertensive crisis, avoid use; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity, monitor serum lithium levels. Use caution in patients with depression, as reserpine may worsen it or lessen the effect of the antidepressant.

Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for hydrochlorothiazide and reserpine combination therapy may include improved compliance and synergistic reductions in blood pressure with an accompanied reduction in side effects. Thiazide therapy improves cardiovascular outcomes in patients with hypertension. Reserpine is infrequently used as monotherapy for the treatment of hypertension due to side effects. See Cardiovascular Considerations for individual agents.

Index TermsReserpine and Hydrochlorothiazide

References

Chobanian AV, Bakris GL, Black HR, et al, “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report,” *JAMA*, 2003, 289(19):2560-71. [PubMed 12748199]

Kaplan NM and Sever PS, “Combination Therapy: A Key to Comprehensive Patient Care,” *Am J Hypertens*, 1997, 10(7 Pt 2):127S. [PubMed 9231887]

Moser M and Black HR, “The Role of Combination Therapy in the Treatment of Hypertension,” *Am J Hypertens*, 1998, 11(6 Pt 2):73S-8S, 95S-100S.[PubMed 9655566]

Hydrochlorothiazide and Spironolactone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Aldactazide® may be confused with Aldactone®

Pronunciation(hye droe klor oh THYE a zide & speer on oh LAK tone)

U.S. Brand NamesAldactazide®

Canadian Brand NamesAldactazide 25®; Aldactazide 50®; Novo-Spirozine

Pharmacologic CategoryDiuretic, Thiazide; Selective Aldosterone Blocker

Use: Labeled IndicationsManagement of mild-to-moderate hypertension; treatment of edema in congestive heart failure and nephrotic syndrome, and cirrhosis of the liver accompanied by edema and/or ascites

Dosing: AdultsHypertension, edema: Oral: Hydrochlorothiazide 12.5-50 mg/day and spironolactone 12.5-50 mg/day; manufacturer labeling states hydrochlorothiazide maximum 200 mg/day, however, usual dose in JNC-7 is 12.5-50 mg/day

Dosing: ElderlyOral: Initial: 1 tablet/day; increase as necessary.

Dosing: PediatricEdema: Oral: 1.5-3 mg/kg/day in 2-4 divided doses (maximum: 200 mg/day)

Dosing: Renal ImpairmentEfficacy of hydrochlorothiazide is limited in patients with Cl_{cr} <30 mL/minute.

ContraindicationsHypersensitivity to spironolactone, hydrochlorothiazide or any component of the formulation, thiazides, or sulfonamide-derived drugs; anuria; renal decompensation; hyperkalemia

Allergy Considerations

- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Fixed-dose combination drugs: See “Appropriate use” below
- Tumorigenic: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Electrolyte disturbances: Hyperkalemia may occur with spironolactone; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.
- Gynecomastia: Related to dose and duration of spironolactone therapy.
- Photosensitivity: Photosensitization may occur.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.
- Tumorigenic: **[U.S. Boxed Warning]: Spironolactone shown to be a tumorigen in chronic toxicity animal studies. Avoid unnecessary use.**

Disease-related concerns:

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.
- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.
- Renal impairment: Avoid hydrochlorothiazide in severe renal disease (ineffective). Spironolactone may cause hyperkalemia in patients with renal impairment.

- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Appropriate use:

- Fixed-dose combination drugs: **[U.S. Boxed Warning] should not be used in the initial therapy for edema or hypertension.** These conditions require individual dose titration.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsThe efficacy of hydrochlorothiazide is limited in patients with a Cl_{cr} <30 mL/minute; monitor serum potassium.
Pregnancy Risk FactorC
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/use caution
Adverse ReactionsSee individual agents.
Drug Interactions

ACE Inhibitors: Potassium-Sparing Diuretics may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Ammonium Chloride: Potassium-Sparing Diuretics may enhance the adverse/toxic effect of Ammonium Chloride. Specifically the risk of systemic acidosis. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Cardiac Glycosides: Potassium-Sparing Diuretics may diminish the therapeutic effect of Cardiac Glycosides. Specifically, the inotropic effects. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Drospirenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Mitotane: Potassium-Sparing Diuretics may diminish the therapeutic effect of Mitotane. High dose diuretics (eg, Cushings syndrome) may present significantly higher risk than low doses (eg, CHF). *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: Potassium-Sparing Diuretics may diminish the therapeutic effect of QuiNIDine. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Avoid food with high potassium content and potassium-containing salt substitutes.

Herb/Nutraceutical: Avoid natural licorice (causes sodium and water retention and increases potassium loss).

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Hydrochlorothiazide 25 mg and spironolactone 25 mg

- Aldactazide®:
  - 25/25: Hydrochlorothiazide 25 mg and spironolactone 25 mg
  - 50/50: Hydrochlorothiazide 50 mg and spironolactone 50 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Aldactazide)

25-25 mg (30): $37.79

50-50 mg (30): $57.74

Tablets (Spironolactone-HCTZ)

25-25 mg (30): $16.99

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Hydrochlorothiazide
- Spironolactone

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause lethargy or anorexia

Mental Health: Effects on Psychiatric TreatmentMay decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for hydrochlorothiazide and spironolactone combination therapy may include improved compliance and synergistic reductions in blood pressure with an accompanied reduction in side effects (eg, hypokalemia). Thiazide and spironolactone also are effective in the management of heart failure. See Cardiovascular Considerations for individual agents.

Index TermsSpironolactone and Hydrochlorothiazide

References

Chobanian AV, Bakris GL, Black HR, et al, "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report," *JAMA*, 2003, 289(19):2560-71. [PubMed 12748199]

"Consensus Recommendations for the Management of Chronic Heart Failure. On Behalf of the Membership of the Advisory Council to Improve Outcomes Nationwide in Heart Failure," *Am J Cardiol*, 1999, 83(2A):1A-38A. [PubMed 10072251]

Kaplan NM and Sever PS, "Combination Therapy: A Key to Comprehensive Patient Care," *Am J Hypertens*, 1997, 10(7 Pt 2):127S. [PubMed 9231887]

Moser M and Black HR, "The Role of Combination Therapy in the Treatment of Hypertension," *Am J Hypertens*, 1998, 11(6 Pt 2):73S-8S, 95S-100S. [PubMed 9655566]

Pitt B, Zannad F, Remme WJ, et al, "The Effect of Spironolactone on Morbidity and Mortality in Patients With Severe Heart Failure. Randomized Aldactone Evaluation Study Investigators," *N Engl J Med*, 1999, 341(10):709-17.[PubMed 10471456]

International Brand NamesAdactazida (VE); Aldactazide (IT, PK); Aldazida (BR); Docspirochlor (BE); Slosat (TW); Spironothiazid (SE); Spirozide (KP)

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Dyazide® may be confused with diazoxide, Dynacin®

Maxzide® may be confused with Maxidex®, Microzide®

Pronunciation(hye droe klor oh THYE a zide & trye AM ter een)

U.S. Brand NamesDyazide®; Maxzide®; Maxzide®-25

Canadian Brand NamesApo-Triazide®; Novo-Triamzide; Nu-Triazide; Penta-Triamterene HCTZ; Riva-Zide

Pharmacologic CategoryDiuretic, Potassium Sparing; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension or edema (not recommended for initial treatment) when hypokalemia has developed on hydrochlorothiazide alone or when the development of hypokalemia must be avoided

Dosing: AdultsHypertension, edema: Oral:

Hydrochlorothiazide 25 mg and triamterene 37.5 mg: 1-2 tablets/capsules once daily

Hydrochlorothiazide 50 mg and triamterene 75 mg: $^1/_2$-1 tablet daily

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsShould be taken after meals.

Storage

Store at 20°C to 25°C (68°F to 77°F). Protect from light.

ContraindicationsHypersensitivity to hydrochlorothiazide, triamterene, any component of the formulation, or sulfonamide-derived drugs; anuria; acute and chronic renal insufficiency or significant renal impairment; patients receiving other potassium-sparing diuretics, potassium-containing salt substitutes, or potassium supplements (except in severe cases of hypokalemia); preexisting hyperkalemia

Allergy Considerations

- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Hyperkalemia: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, and hyponatremia can occur with hydrochlorothiazide.
- Hyperkalemia: **[U.S. Boxed Warning]: Hyperkalemia can occur with triamterene; patients at risk include those with renal dysfunction, diabetes mellitus, the elderly, and the severely ill. Serum potassium levels must be monitored at frequent intervals especially when dosages are changed or with any illness that may cause renal dysfunction.** Avoid potassium supplements (except in severe cases of hypokalemia), potassium-containing salt substitutes, a diet rich in potassium, or other drugs that can cause hyperkalemia. Discontinue if hyperkalemia develops.
- Photosensitivity: Photosensitization may occur.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Diabetes: Use with caution in patients with prediabetes or diabetes mellitus; may alter glycemic control.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.
- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Kidney stones: Use triamterene with caution in patients with kidney stones.

- Parathyroid disease: With prolonged use, hydrochlorothiazide may produce pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia. Thiazides should be discontinued prior to tests for parathyroid function.

- Renal impairment: Avoid hydrochlorothiazide in severe renal disease (ineffective). Triamterene may cause hyperkalemia in patients with renal impairment.

- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsThe efficacy of hydrochlorothiazide is limited in patients with a Cl_{cr} <30 mL/minute; monitor serum potassium.
Pregnancy Risk FactorC
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsAlso see individual agents. Frequency not defined.

Cardiovascular: Angina, arrhythmia, postural hypotension, tachycardia

Central nervous system: Anxiety, dizziness, depression, fatigue, headache, insomnia, restlessness, vertigo

Dermatologic: Photosensitivity, purpura, rash, subacute cutaneous lupus erythematosus-like reactions, urticaria

Endocrine & metabolic: Acidosis, diabetes mellitus, hypercalcemia, hyperglycemia, hyper-/hypokalemia, hyperuricemia, hypochloremia, hypomagnesemia, hyponatremia

Gastrointestinal: Abdominal pain, anorexia, burning of tongue, constipation, diarrhea, loss of appetite, nausea, pancreatitis, sialadenitis, stomach cramps, taste alteration, tongue discoloration (bright orange), upset stomach, vomiting, xerostomia

Genitourinary: Impotence

Hematologic: Aplastic anemia, agranulocytosis, hemolytic anemia, leukopenia, thrombocytopenia, megaloblastic anemia

Hepatic: Jaundice, liver function tests (abnormal)

Neuromuscular & skeletal: Muscle cramping, parasthesia, weakness

Ocular: Xanthopsia, blurred vision (transient)

Renal: Acute renal failure, BUN increased, glycosuria, interstitial nephritis, necrotizing vasculitis, renal stone formation, serum creatinine increased, urinary sediment abnormal, urine discoloration

Respiratory: Allergic pneumonitis, dyspnea, pulmonary edema, respiratory distress

Miscellaneous: Anaphylaxis, systemic lupus erythematosus (SLE) exacerbation

Drug Interactions

ACE Inhibitors: Potassium-Sparing Diuretics may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Ammonium Chloride: Potassium-Sparing Diuretics may enhance the adverse/toxic effect of Ammonium Chloride. Specifically the risk of systemic acidosis. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Cardiac Glycosides: Potassium-Sparing Diuretics may diminish the therapeutic effect of Cardiac Glycosides. Specifically, the inotropic effects.

Risk C: Monitor therapy

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Drospirenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Indomethacin: May enhance the nephrotoxic effect of Triamterene. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Mitotane: Potassium-Sparing Diuretics may diminish the therapeutic effect of Mitotane. High dose diuretics (eg, Cushings syndrome) may present significantly higher risk than low doses (eg, CHF). *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: Potassium-Sparing Diuretics may diminish the therapeutic effect of QuiNIDine. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Avoid food with high potassium content and potassium-containing salt substitutes.
Monitoring ParametersMonitor blood pressure, serum electrolytes, BUN, creatinine, liver function tests, signs of hyperkalemia
Nursing: Physical Assessment/MonitoringSee individual agent for Hydrochlorothiazide.
Monitoring: Lab TestsSerum electrolytes, BUN, creatinine, liver function tests
Patient EducationSee individual agent for Hydrochlorothiazide.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, oral: Hydrochlorothiazide 25 mg and triamterene 37.5 mg; hydrochlorothiazide 25 mg and triamterene 50 mg

Dyazide®: Hydrochlorothiazide 25 mg and triamterene 37.5 mg

Tablet: Hydrochlorothiazide 25 mg and triamterene 37.5 mg; hydrochlorothiazide 50 mg and triamterene 75 mg

Maxzide®: Hydrochlorothiazide 50 mg and triamterene 75 mg [scored]

Maxzide®-25: Hydrochlorothiazide 25 mg and triamterene 37.5 mg [scored]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsules (Dyazide)

37.5-25 mg (30): $40.99

Capsules (Triamterene-HCTZ)

37.5-25 mg (100): $15.99

50-25 mg (100): $49.99

Tablets (Maxzide)

75-50 mg (30): $61.59

Tablets (Maxzide-25)

37.5-25 mg (30): $34.09

Tablets (Triamterene-HCTZ)

37.5-25 mg (100): $29.99

75-50 mg (100): $17.99

Mechanism of Action

Based on **triamterene** component: Interferes with potassium/sodium exchange (active transport) in the distal tubule, cortical collecting tubule and collecting duct by inhibiting sodium, potassium-ATPase; decreases calcium excretion; increases magnesium loss

Based on **hydrochlorothiazide** component: Inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions

Pharmacodynamics/Kinetics See individual agents.

Related Information

- Hydrochlorothiazide
- Triamterene

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause lethargy or anorexia

Mental Health: Effects on Psychiatric Treatment May decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations Thiazide diuretics are effective first-line therapeutic agents in the management of hypertension and have proven to be of benefit in terms of cardiovascular outcome. The initial concern about thiazide diuretic-induced hypokalemia, glucose intolerance, and lipid profiles does not appear to be of substantial clinical consequence in the treatment of hypertension. The benefits of this class of agents in the treatment of hypertension is established and compares well with other first-line therapeutic agents. The combination of hydrochlorothiazide and triamterene may reduce the incidence of hypokalemia.

Diuretics are standard therapy for the management of edema in patients with heart failure.

Index Terms Triamterene and Hydrochlorothiazide

References

Chobanian AV, Bakris GL, Black HR, et al, “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report,” *JAMA*, 2003, 289(19):2560-71.[PubMed 12748199]

Hunt SA, Abraham WT, Chin MH , et al, “ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure).” Available at http://content.onlinejacc.org/cgi/reprint/46/6/e1.[PubMed 16168273]

International Brand Names Anjal (TW); Dazid (TW); Dinazide (TH); Diuracet-K (PE); Dyazide (AE, BB, BF, BH, BJ, BM, BS, BZ, CH, CI, CY, EG, ET, GB, GH, GM, GN, GY, HK, IE, IL, IQ, IR, JM, JO, JP, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, OM, PH, QA, SA, SC, SD, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Dyberzide (GR); Dytenzide (BE, NL); Dytide H (AT, DE); Hidronol T (CN); Hydrene (AU); Kaldrene (DO); Maxzide (HK); Renezide (ZA); Triamizide (NZ, TW); Triampur Compositum (BG, EE); Triazide (TW); Trizid (NZ); Turfa (DE)

Hydrochlorothiazide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Esidrix may be confused with Lasix®

HCTZ is an error-prone abbreviation (mistaken as hydrocortisone)

Hydrochlorothiazide may be confused with hydrocortisone, hydroflumethiazide

Microzide™ may be confused with Maxzide®, Micronase®

International issues:

Microzide™ may be confused with Nitrobide® which is a brand name for isosorbide dinitrate in Japan

Microzide™ may be confused with Mikrozid® which is a brand name for ethanol/propanol combination in Great Britain

Pronunciation(hye droe klor oh THYE a zide)

U.S. Brand NamesMicrozide®

Canadian Brand NamesApo-Hydro®; Novo-Hydrazide; PMS-Hydrochlorothiazide

Pharmacologic CategoryDiuretic, Thiazide

Use: Labeled IndicationsManagement of mild to moderate hypertension; treatment of edema in congestive heart failure and nephrotic syndrome

Use: Unlabeled/InvestigationalTreatment of lithium-induced diabetes insipidus

Dosing: Adults

Edema (diuresis): Oral: 25-100 mg/day in 1-2 doses; maximum: 200 mg/day

Hypertension: Oral: 12.5-50 mg/day; minimal increase in response and more electrolyte disturbances are seen with doses >50 mg/day

Dosing: ElderlyOral: 12.5-25 mg once daily; minimal increase in response and more electrolyte disturbances are seen with doses >50 mg/day (see Special Geriatric Considerations).

Dosing: PediatricHypertension, edema (diuretic): Oral (effect of drug may be decreased when used every day):

<6 months: 1-3 mg/kg/day in 2 divided doses

>6 months to 2 years: 1-3 mg/kg/day in 2 divided doses; maximum: 37.5 mg/day

>2-17 years: Initial: 1 mg/kg/day; maximum: 3 mg/kg/day (50 mg/day)

Note: In pediatric patients, chlorothiazide may be preferred over hydrochlorothiazide as there are more dosage formulations (eg, suspension) available.

Dosing: Renal ImpairmentCl_{cr} <10 mL/minute: Avoid use. Usually ineffective with GFR <30 mL/minute. Effective at lower GFR in combination with a loop diuretic.

Administration: OralMay be taken with food or milk. Take early in day to avoid nocturia. Take the last dose of multiple doses no later than 6 PM unless instructed otherwise.

ContraindicationsHypersensitivity to hydrochlorothiazide or any component of the formulation, thiazides, or sulfonamide-derived drugs; anuria; renal decompensation; pregnancy

Allergy Considerations

- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, and hyponatremia can occur.
- Photosensitivity: Photosensitization may occur.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Diabetes: Use with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated.
- Hepatic impairment: Use with caution in patients with severe hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations.
- Hypokalemia: Use with caution in patients with hypokalemia; correct before initiating therapy.
- Renal impairment: Avoid in severe renal disease (ineffective).
- Systemic lupus erythematosus (SLE): Can cause SLE exacerbation or activation.

Geriatric ConsiderationsHydrochlorothiazide is not effective in patients with a Cl_{cr} <30 mL/minute, therefore, it may not be a useful agent in many elderly patients.
Pregnancy Risk FactorB (manufacturer); D (expert analysis)
Pregnancy ConsiderationsAlthough there are no adequate and well-controlled studies using hydrochlorothiazide in pregnancy, thiazide diuretics may cause an increased risk of congenital defects. Hypoglycemia, hypokalemia, hyponatremia, jaundice, and thrombocytopenia are also reported as possible complications to the fetus or newborn.
LactationEnters breast milk/use caution (AAP rates “compatible”)
Adverse Reactions

1% to 10%:

Cardiovascular: Orthostatic hypotension, hypotension

Dermatologic: Photosensitivity

Endocrine & metabolic: Hypokalemia

Gastrointestinal: Anorexia, epigastric distress

<1% (Limited to important or life-threatening): Agranulocytosis, allergic myocarditis, allergic reactions (possibly with life-threatening anaphylactic shock), alopecia, aplastic anemia, eosinophilic pneumonitis, erythema multiforme, exfoliative dermatitis, hemolytic anemia, hepatic function impairment, hypercalcemia, interstitial nephritis, leukopenia, pancreatitis, renal failure, respiratory distress, Stevens-Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Hydrochlorothiazide peak serum levels may be decreased if taken with food. This product may deplete potassium, sodium, and magnesium.

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Dong quai may also cause photosensitization. Avoid ephedra, ginseng, yohimbe (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Test InteractionsIncreased creatine phosphokinase [CPK] (S), ammonia (B), amylase (S), calcium (S), chloride (S), cholesterol (S), glucose, increased acid (S), decreased chloride (S), magnesium, potassium (S), sodium (S); Tyramine and phentolamine tests, histamine tests for pheochromocytoma

Monitoring ParametersAssess weight, I & O reports daily to determine fluid loss; blood pressure, serum electrolytes, BUN, creatinine

Nursing: Physical Assessment/MonitoringAssess allergy history prior to beginning therapy (sulfonamides). Assess potential for interactions with other pharmacological or herbal products patient may be taking (altered affect of oral hypoglycemics, increased risk of hypotension, or toxicity). Assess results of laboratory tests (electrolytes, BUN, creatinine), therapeutic effectiveness (according to purpose for use), and adverse response (eg, hypotension, hypokalemia, confusion) regularly during therapy. Caution patients with diabetes to monitor glucose levels closely; may alter glucose control. Teach proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum electrolytes, BUN, creatinine

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication does not replace other antihypertensive interventions; follow prescriber's instructions for diet and lifestyle changes. Take as directed, with meals, early in the day to avoid nocturia. Your prescriber may prescribe a potassium supplement or recommend that you eat foods high in potassium (include bananas and/or orange juice in daily diet). Do not change your diet on your own while taking this medication, especially if you are taking potassium supplements or medications to reduce potassium loss; too much potassium can be as harmful as too little. If you have diabetes, monitor serum glucose closely; this medication may increase serum glucose levels. May cause dizziness or postural hypotension (use caution when rising from sitting or lying position, when driving, climbing stairs, or engaging in tasks that require alertness until response to drug is known); nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); impotence (reversible); constipation (increased exercise, fluids, fruit, or fiber may help); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report persistent flu-like symptoms, chest pain, palpitations, muscle cramping, respiratory difficulty, skin rash or itching, unusual bruising or easy bleeding, or excessive fatigue. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 12.5 mg

Microzide®: 12.5 mg

Tablet: 25 mg, 50 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Microzide)

12.5 mg (30): $30.99

Tablets (Hydrochlorothiazide)

25 mg (100): $12.99

50 mg (100): $15.99

Mechanism of ActionInhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions

Pharmacodynamics/Kinetics

Onset of action: Diuresis: ~2 hours

Peak effect: 4-6 hours

Duration: 6-12 hours

Absorption: ~50% to 80%

Distribution: 3.6-7.8 L/kg

Protein binding: 68%

Metabolism: Not metabolized

Bioavailability: 50% to 80%

Half-life elimination: 5.6-14.8 hours

Time to peak: 1-2.5 hours

Excretion: Urine (as unchanged drug)

Related Information

- Sulfonamide Derivatives

Pharmacotherapy PearlsIf given the morning of surgery it may render the patient volume depleted and blood pressure may be labile during general anesthesia. Effect of drug may be decreased when used every day.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension and hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentUsed to treat lithium-induced diabetes insipidus; monitor for hypokalemia; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Hypertension: Thiazide diuretics are effective first-line therapeutic agents in the management of hypertension and have proven to be of benefit in terms of cardiovascular outcome. They may act synergistically to lower blood pressure when combined with an ACE inhibitor or beta-blocker. The initial concern about thiazide diuretic-induced hypokalemia, glucose intolerance, and lipid profiles does not appear to be of substantial clinical consequence in the treatment of hypertension. The benefits of this class of agents in the treatment of hypertension is established and compares well with other first-line therapeutic agents. The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The JNC 7 recommends diuretics for the treatment of hypertension with concurrent heart failure where diuresis is also required (loop diuretics may more frequently be required), high coronary disease risk (as in the ALLHAT trial), diabetes (beneficial in reducing CVD and stroke incidence), and recurrent stroke prevention (in combination with an ACE inhibitor). Thiazides are useful in slowing demineralization in osteoporosis, but need to be used cautiously in gout and in patients with significant history of hyponatremia.

Diuretics are standard therapy for the management of edema in patients with heart failure. However, it is important to ensure that edema is not secondary to pericardial effusion. Marked reduction in intravascular volume with consequent decreased cardiac filling pressures may precipitate significant hypotension in these circumstances.

Anesthesia and Critical Care Concerns/Other ConsiderationsIf given the morning of surgery it may render the patient volume depleted and blood pressure may be labile during general anesthesia.

Thiazide diuretics are effective first-line therapeutic agents in the management of hypertension and have proven to be of benefit in terms of cardiovascular outcome. They may act synergistically to lower blood pressure when combined with an ACE inhibitor or beta-blocker.

Index TermsHCTZ (error-prone abbreviation)

References

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National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, “The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents,” *Pediatrics*, 2004, 114(2 Suppl):555-76.[PubMed 15286277]

International Brand NamesAcortiz (MX); Apo-Hydro (MY); BPzide (IN); Chlothia (JP); Cotrazid (PH); Di-Ertride (SG); Di-Eudrin (VE); Dichlothiazide (RU); Dichlotride (BE, DK, HK, LU, NL, PH, PT, TH); Dichlozid (KP); Didralin (MY, TH); Disalunil (BG, PL); Disothiazide (IL); Dithiazide (AU); Diurace (PE); Diuret-P (TH); Diurex (AR); Diurix (BR); Diursan (PY); Diuzid (PH); Diuzide (PH); Esidrex (AE, AT, BB, BE, BF, BH, BJ, BM, BS, BZ, CH, CI, CY, EG, ET, FR, GH, GM, GN, GY, IL, IN, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, NO, OM, QA, SA, SC, SD, SE, SL, SN, SR, SY, TN, TT, TZ, UG, UY, YE, ZA, ZM, ZW); Esidrix (DE); H.C.T. (ID); HCT (EC); Hidroronol (CN); Hidrosaluretil (ES); Hychlozide (TH); Hydrex (FI); Hydrex-semi (FI); Hydro-Saluric (GB, IE); Hydrochlorothiazidum (PL); Hydrochlorzide (MY); Hydrozide (HK, TH); Hypothiazid (HN, HU); Hytaz (PH); Lonpra (CO); Maschitt (JP); Newtolide (JP); Pantemon (JP); Ridaq (ZA); Rofucal (MX); Tandiur (AR); Unazid (HR)

Hydrocodone and Acetaminophen

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Lorcet® may be confused with Fioricet®

Lortab® may be confused with Cortef®, Lorabid®, Luride®

Vicodin® may be confused with Hycodan®, Hycomine®, Indocin®, Uridon®

Zydone® may be confused with Vytone®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(hye droe KOE done & a seet a MIN oh fen)

U.S. Brand NamesCo-Gesic® [DSC]; hycet™; Lorcet® 10/650; Lorcet® Plus; Lortab®; Margesic® H; Maxidone®; Norco®; Stagesic™; Vicodin®; Vicodin® ES; Vicodin® HP; Xodol® 10/300; Xodol® 5/300; Xodol® 7.5/300; Zamicet®; Zydone®

Pharmacologic CategoryAnalgesic Combination (Opioid)

Use: Labeled IndicationsRelief of moderate to severe pain

Use: DentalTreatment of postoperative pain

Dosing: Adults

Pain management (analgesic): Oral (doses should be titrated to appropriate analgesic effect): Average starting dose in opioid naive patients: Hydrocodone 5-10 mg 4 times/day; the dosage of acetaminophen should be limited to ≤4 g/day (and possibly less in patients with hepatic impairment or ethanol use).

Dosage ranges (based on specific product labeling): Hydrocodone 2.5-10 mg every 4-6 hours; maximum: 60 mg hydrocodone/day (maximum dose of hydrocodone may be limited by the acetaminophen content of specific product)

Dosing: ElderlyDoses should be titrated to appropriate analgesic effect; 2.5-5 mg of the hydrocodone component every 4-6 hours. Do not exceed 4 g/day of acetaminophen.

Dosing: Pediatric

Pain management (analgesic): Oral (doses should be titrated to appropriate analgesic effect):

Children 2-13 years or <50 kg: Hydrocodone 0.1-0.2 mg/kg/dose every 4-6 hours; do not exceed 6 doses/day or the maximum recommended dose of acetaminophen

Children ≥50 kg: Refer to adult dosing.

Dosing: Hepatic ImpairmentUse with caution. Limited, low-dose therapy usually well tolerated in hepatic disease/cirrhosis; however, cases of hepatotoxicity at daily acetaminophen dosages <4 g/day have been reported. Avoid chronic use in hepatic impairment.

RestrictionsC-III

ContraindicationsHypersensitivity to hydrocodone, acetaminophen, or any component of the formulation; CNS depression; severe respiratory depression

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hepatotoxicity: May cause severe hepatic toxicity on acute overdose; in addition, chronic daily dosing in adults has resulted in liver damage in some patients.
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: Hydrocodone may obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Adrenocortical insufficiency: Use with caution in patients with adrenocortical insufficiency, including Addison's disease.

- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.

- Drug abuse: Use hydrocodone with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.

- G6PD deficiency: Use with caution in patients with known G6PD deficiency.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Obesity: Use with caution in patients who are morbidly obese.

- Prostatic hyperplasia/urinary stricture: Use hydrocodone with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Psychosis: Use with caution in patients with toxic psychosis.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use hydrocodone with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages. May suppress cough reflex; use with caution postoperatively and in patients with pulmonary disease.

- Seizures: Use with caution in patients with a history of seizure disorders.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

Other warnings/precautions:

- Dosage limit: Limit acetaminophen dose to <4 g/day.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsElderly may be particularly susceptible to the CNS depressant action (sedation, confusion) and constipating effects of narcotics. If 1 tablet/dose is used, it may be useful to add an additional 325 mg of acetaminophen to maximize analgesic effect.
Pregnancy Risk FactorC/D (prolonged use or high doses near term)
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination product. Opioid analgesics are considered FDA risk category D if used for prolonged periods or in large doses near term. Withdrawal symptoms may be observed in babies born to mothers taking opioids regularly during pregnancy. Respiratory depression may be observed in the newborn if opioids are given close to delivery. Also refer to Acetaminophen monograph.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsAcetaminophen and hydrocodone are excreted in breast milk. The manufacturers recommend discontinuing the medication or to discontinue nursing during therapy. Also refer to Acetaminophen monograph.
Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, cardiac arrest, circulatory collapse, coma, hypotension

Central nervous system: anxiety, dizziness, drowsiness, dysphoria, euphoria, fear, lethargy, lightheadedness, malaise, mental clouding, mental impairment, mood changes, physiological dependence, sedation, somnolence, stupor

Dermatologic: Pruritus, rash

Endocrine & metabolic: Hypoglycemic coma

Gastrointestinal: Abdominal pain, constipation, gastric distress, heartburn, nausea, peptic ulcer, vomiting, xerostomia

Genitourinary: Ureteral spasm, urinary retention, vesical sphincter spasm

Hematologic: Agranulocytosis, bleeding time prolonged, hemolytic anemia, iron deficiency anemia, occult blood loss, thrombocytopenia

Hepatic: Hepatic necrosis, hepatitis

Neuromuscular & skeletal: Skeletal muscle rigidity

Otic: Hearing impairment or loss (chronic overdose)

Renal: Renal toxicity, renal tubular necrosis

Respiratory: Acute airway obstruction, apnea, dyspnea, respiratory depression (dose related)

Miscellaneous: Allergic reactions, clamminess, diaphoresis

Metabolism/Transport Effects

Hydrocodone: **Substrate** (minor) of CYP2D6, 3A

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

QuiNIDine: May diminish the analgesic effect of Hydrocodone. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression); consuming ≥3 alcoholic drinks/day may increase the risk of liver damage

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava (may increase risk of excessive sedation).

Monitoring ParametersPain relief, respiratory and mental status, blood pressure

Nursing: Physical Assessment/MonitoringSee individual agent for Acetaminophen.

Patient EducationSee individual agent for Acetaminophen. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

- Margesic® H, Stagesic™: Hydrocodone bitartrate 5 mg and acetaminophen 500 mg

Elixir: Hydrocodone bitartrate 7.5 mg and acetaminophen 500 mg per 15 mL (480 mL)

- Lortab®: Hydrocodone bitartrate 7.5 mg and acetaminophen 500 mg per 15 mL (480 mL) [contains ethanol 7%, propylene glycol; tropical fruit punch flavor]

Solution, oral: Hydrocodone bitartrate 7.5 mg and acetaminophen 500 mg per 15 mL (5 mL, 10 mL, 15 mL, 118 mL, 473 mL)

- hycet™: Hydrocodone bitartrate 7.5 mg and acetaminophen 325 mg per 15 mL (473 mL) [contains ethanol 6.7%, propylene glycol; fruit flavor]
- Zamicet™: Hydrocodone bitartrate 10 mg and acetaminophen 325 mg per 15 mL (473 mL) [contains ethanol 6.7%, propylene glycol; fruit flavor]

Tablet:

- Hydrocodone bitartrate 2.5 mg and acetaminophen 500 mg
- Hydrocodone bitartrate 5 mg and acetaminophen 325 mg
- Hydrocodone bitartrate 5 mg and acetaminophen 500 mg
- Hydrocodone bitartrate 7.5 mg and acetaminophen 325 mg
- Hydrocodone bitartrate 7.5 mg and acetaminophen 500 mg
- Hydrocodone bitartrate 7.5 mg and acetaminophen 650 mg
- Hydrocodone bitartrate 7.5 mg and acetaminophen 750 mg
- Hydrocodone bitartrate 10 mg and acetaminophen 325 mg
- Hydrocodone bitartrate 10 mg and acetaminophen 500 mg
- Hydrocodone bitartrate 10 mg and acetaminophen 650 mg
- Hydrocodone bitartrate 10 mg and acetaminophen 660 mg
- Hydrocodone bitartrate 10 mg and acetaminophen 750 mg
- Co-Gesic® 5/500: Hydrocodone bitartrate 5 mg and acetaminophen 500 mg
- Lorcet® 10/650: Hydrocodone bitartrate 10 mg and acetaminophen 650 mg
- Lorcet® Plus: Hydrocodone bitartrate 7.5 mg and acetaminophen 650 mg
- Lortab®:
  - 5/500: Hydrocodone bitartrate 5 mg and acetaminophen 500 mg
  - 7.5/500: Hydrocodone bitartrate 7.5 mg and acetaminophen 500 mg
  - 10/500: Hydrocodone bitartrate 10 mg and acetaminophen 500 mg
- Maxidone™: Hydrocodone bitartrate 10 mg and acetaminophen 750 mg
- Norco®:
  - Hydrocodone bitartrate 5 mg and acetaminophen 325 mg
  - Hydrocodone bitartrate 7.5 mg and acetaminophen 325 mg
  - Hydrocodone bitartrate 10 mg and acetaminophen 325 mg
- Vicodin®: Hydrocodone bitartrate 5 mg and acetaminophen 500 mg
- Vicodin® ES: Hydrocodone bitartrate 7.5 mg and acetaminophen 750 mg
- Vicodin® HP: Hydrocodone bitartrate 10 mg and acetaminophen 660 mg
- Xodol®:
  - 10/300: Hydrocodone bitartrate 10 mg and acetaminophen 300 mg
  - 5/300: Hydrocodone bitartrate 5 mg and acetaminophen 300 mg
  - 7/300: Hydrocodone bitartrate 7 mg and acetaminophen 300 mg
- Zydone®:
  - Hydrocodone bitartrate 5 mg and acetaminophen 400 mg
  - Hydrocodone bitartrate 7.5 mg and acetaminophen 400 mg

Hydrocodone bitartrate 10 mg and acetaminophen 400 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Bancap-HC)

5-500 mg (30): $42.99

Capsules (Stagesic)

5-500 mg (30): $18.99

Elixir (Lortab)

7.5-500 mg/15 mL (120): $36.44

Solution (Hydrocodone-Acetaminophen)

7.5-500 mg/15 mL (473): $60.97

Tablets (Anexsia)

5-500 mg (28): $18.99

Tablets (Hydrocodone-Acetaminophen)

2.5-500 mg (30): $12.99

5-325 mg (30): $16.99

5-500 mg (30): $11.99

7.5-325 mg (30): $18.99

7.5-500 mg (30): $12.99

7.5-750 mg (30): $12.99

10-325 mg (30): $16.99

10-500 mg (30): $14.99

10-650 mg (30): $13.99

10-660 mg (30): $15.99

10-750 mg (30): $32.99

Tablets (Lorcet 10/650)

10-650 mg (30): $59.27

Tablets (Lorcet Plus)

7.5-650 mg (30): $45.74

Tablets (Lortab 10)

10-500 mg (30): $50.56

Tablets (Lortab 2.5)

2.5-500 mg (30): $28.99

Tablets (Lortab 5)

5-500 mg (30): $43.86

Tablets (Lortab 7.5)

7.5-500 mg (30): $49.16

Tablets (Norco)

5-325 mg (30): $43.19

7.5-325 mg (30): $48.59

10-325 mg (30): $58.31

Tablets (Vicodin)

5-500 mg (30): $48.25

Tablets (Vicodin ES)

7.5-750 mg (30): $46.63

Tablets (Vicodin HP)

10-660 mg (30): $51.27

Tablets (Xodol)

10-300 mg (100): $216.22

Tablets (Zydone)

5-400 mg (30): $21.99

7.5-400 mg (30): $29.99

10-400 mg (30): $31.99

Mechanism of ActionHydrocodone, as with other narcotic (opiate) analgesics, blocks pain perception in the cerebral cortex by binding to specific receptor molecules (opiate receptors) within the neuronal membranes of synapses. This binding results in a decreased synaptic chemical transmission throughout the CNS thus inhibiting the flow of pain sensations into the higher centers. Mu and kappa are the two subtypes of the opiate receptor which hydrocodone binds to cause analgesia.

Acetaminophen inhibits the synthesis of prostaglandins in the CNS and peripherally blocks pain impulse generation; produces antipyresis from inhibition of hypothalamic heat-regulating center.

Pharmacodynamics/Kinetics

Acetaminophen: See Acetaminophen monograph.

Hydrocodone:

Onset of action: Narcotic analgesic: 10-20 minutes

Duration: 4-8 hours

Distribution: Crosses placenta

Metabolism: Hepatic; O-demethylation; N-demethylation and 6-ketosteroid reduction

Half-life elimination: 3.3-4.4 hours

Excretion: Urine

Related Information

- Acetaminophen
- Narcotic / Opioid Analgesics

Dental Health Professional ConsiderationsNeither hydrocodone nor acetaminophen elicit anti-inflammatory effects. Because of addiction liability of opiate analgesics, the use of hydrocodone should be limited to 2-3 days postoperatively for treatment of dental pain. Nausea is the most common adverse effect seen after use in dental patients; sedation and constipation are second. Nausea elicited by narcotic analgesics is centrally mediated and the presence or absence of food will not affect the degree nor incidence of nausea.

Acetaminophen:

A study by Hylek, et al, suggested that the combination of acetaminophen with warfarin (Coumadin®) may cause enhanced anticoagulation. The following recommendations have been made by Hylek, et al, and supported by an editorial in *JAMA* by Bell.

Dose and duration of acetaminophen should be as low as possible, individualized and monitored

The study by Hylek reported the following:

For patients who reported taking the equivalent of at least 4 regular strength (325 mg) tablets for longer than a week, the odds of having an INR >6.0 were increased 10-fold above those not taking acetaminophen. Risk decreased with lower intakes of acetaminophen reaching a background level of risk at a dose of 6 or fewer 325 mg tablets per week.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause confusion; may rarely cause hallucinations

Mental Health: Effects on Psychiatric TreatmentMay result in loss of pain control when used in combination with SSRIs (especially paroxetine and fluoxetine); concurrent use with psychotropics may produce additive sedation

Cardiovascular ConsiderationsMay cause constipation which may be problematic in patients with unstable angina, and patients after myocardial infarction. The hemodynamic responses to valsalva-like maneuvers due to straining may have adverse cardiovascular consequences in patients with critical coronary artery disease.

Anesthesia and Critical Care Concerns/Other ConsiderationsDoses of agent must be individualized according to degree of pain; commonly used in place of Tylenol® with Codeine; patients on this drug chronically should have liver function monitored secondary to acetaminophen in the product. Keep acetaminophen dose ≤4 g/day. Patients with chronic alcoholism, liver disease, or those who are fasting can develop severe hepatic disease even at therapeutic doses.

Index TermsAcetaminophen and Hydrocodone

References

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Hydrocodone and Chlorpheniramine

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Special Alerts

Tussionex® Pennkinetic® Extended-Release Suspension Associated With Life-Threatening Adverse Events - March 2008

The Food and Drug Administration (FDA) has issued a public health advisory to highlight safe and appropriate use of Tussionex® Pennkinetic® Extended-Release Suspension (Tussionex®). The FDA has received reports of life-threatening adverse events and death in pediatric and adult patients receiving Tussionex® due to inappropriate prescribing and/or use. Tussionex®, a long-acting combination product containing hydrocodone and chlorpheniramine, is indicated for use in patients ≥6 years of age. It is not to be given more frequently than every 12 hours. Tussionex® is contraindicated in children <6 years of age due to increased susceptibility to life-threatening and fatal respiratory depression. Reports received by the FDA indicate this product is being inappropriately prescribed in children <6 years, dosed more frequently than every 12 hours, and is being administered using inappropriate dosing devices. Healthcare providers are urged to review dosing recommendations prior to prescribing or dispensing Tussionex®. Healthcare providers, patients, and caregivers should be alerted to the signs/symptoms of hydrocodone overdose, including difficulty breathing, slow or shallow breathing, slow heart beat, severe sleepiness, cold, clammy skin, trouble walking or talking, feeling faint, dizzy, or confused. Patients and caregivers should also be instructed on the use of proper measuring devices (calibrated oral syringes are most accurate) and be warned against using household teaspoons or tablespoons.

For more information, refer to:

http://www.fda.gov/cder/drug/infopage/hydrocodone/default.htm

Medication Safety Issues

Sound-alike/look-alike issues:

> Tussionex® represents a different product in the U.S. than it does in Canada. In the U.S., Tussionex® contains hydrocodone and chlorpheniramine, while in Canada the product bearing this name contains hydrocodone and phenyltoloxamine.

Pronunciation(hye droe KOE done & klor fen IR a meen)
U.S. Brand NamesTussiCaps™; Tussionex®
Pharmacologic CategoryAnalgesic, Opioid; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation
Use: Labeled IndicationsSymptomatic relief of cough and upper respiratory symptoms associated with cold and allergy
Dosing: AdultsAntitussive/antihistamine: Oral:

TussiCaps™ 10 mg/8 mg: One capsule every 12 hours (maximum: 2 capsules/24 hours)

Tussionex®: 5 mL every 12 hours; do not exceed 10 mL/24 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricAntitussive/antihistamine: Oral:

Children 6-12 year:

> TussiCaps™: 5 mg/4 mg: One capsule every 12 hours (maximum: 2 capsules/24 hours)
>
> Tussionex®: 2.5 mL every 12 hours; do not exceed 5 mL/24 hours

Children >12 years: Refer to adult dosing.

Administration: Oral

Capsule: Administer with or without food. Do not dilute with fluid or mix with other medications. Do not give more frequently than every 12 hours.

Suspension: Shake well before using. Use calibrated oral syringe to measure doses. Do not give more frequently than every 12 hours.
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).
RestrictionsC-III
ContraindicationsHypersensitivity to hydrocodone, chlorpheniramine, or any component of the formulation; children <6 years of age
Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydromorphone, levorphanol, morphine, oxycodone, oxymorphone).

- Respiratory depression: May cause dose-related respiratory depression, risk increased in children, elderly, patients with pulmonary disease, and when used postoperatively.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.

- Obstructive bowel disease: Use with caution in patients with obstructive bowel disease.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.

- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use with caution in patients with pulmonary disease or decrease ventilatory function; dose-related respiratory depression occurs.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Use with caution in children ≥6 years of age; may be more sensitive to adverse effects. Contraindicated in children <6 years of age.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

- Frequency of dosing: Appropriate use: Should not be given any more frequently than every 12 hours.

- Measuring device: Appropriate use: Accurate measuring devices should be used to measure suspension doses. Calibrated oral syringes are most accurate. Household teaspoons and tablespoons are not recommended for measurement.

Pregnancy Risk FactorC
Pregnancy ConsiderationsHydrocodone is teratogenic in animal studies. Opioid analgesics are considered FDA risk category D if used for prolonged periods or in large doses near term. Withdrawal symptoms may be observed in babies born to mothers taking opioids regularly during pregnancy. Respiratory depression may be observed in the newborn if opioids are given close to delivery.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsHydrocodone is excreted in breast milk; information for chlorpheniramine is not available. The manufacturers recommend discontinuing the medication or to discontinue nursing during therapy.
Adverse ReactionsAlso refer to Chlorpheniramine monograph. Frequency not defined.

Cardiovascular: Chest tightness

Central nervous system: Anxiety, dizziness, drowsiness, dysphoria, euphoria, fear, lethargy, mental impairment, mood changes, sedation

Dermatologic: Pruritus, rash

Gastrointestinal: Constipation, nausea, vomiting

Genitourinary: Ureteral spasm, urinary retention, vesicle sphincter spasm

Respiratory: Dryness of pharynx, respiratory depression

Miscellaneous: Psychological dependence

Metabolism/Transport Effects

Hydrocodone: **Substrate** (minor) of CYP2D6, 3A

Chlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May diminish the analgesic effect of Hydrocodone. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol (may increase CNS depression). Watch for sedation.

Patient Education

Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release:

TussiCaps™ 5 mg/4 mg: Hydrocodone polistirex [equivalent to hydrocodone bitartrate 5 mg] and chlorpheniramine polistirex [equivalent to chlorpheniramine maleate 4 mg]

TussiCaps™ 10 mg/8 mg: Hydrocodone polistirex [equivalent to hydrocodone bitartrate 10 mg] and chlorpheniramine polistirex [equivalent to chlorpheniramine maleate 8 mg]

Suspension, extended release:

Tussionex®: Hydrocodone polistirex [equivalent to hydrocodone bitartrate 10 mg] and chlorpheniramine polistirex [equivalent to chlorpheniramine maleate 8 mg] per 5 mL (480 mL)

Generic Available

No

Pricing: U.S. (www.drugstore.com)

Liquid, controlled release (Tussionex Pennkinetic ER)

8-10 mg/5 mL (60): $50.36

Mechanism of Action

Hydrocodone binds to opiate receptors in the CNS, altering the perception of and response to pain; suppresses cough in medullary center; produces generalized CNS depression

Chlorpheniramine competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract

Pharmacodynamics/Kinetics

Chlorpheniramine: See Chlorpheniramine monograph.

Hydrocodone:

Duration: 4-8 hours

Metabolism: Hepatic; O-demethylation; N-demethylation and 6-ketosteroid reduction

Half-life elimination: 3.3-4.4 hours

Excretion: Urine

Related Information

- Chlorpheniramine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Prolonged use will cause significant xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause confusion, dizziness, excitability, nervousness, fatigue, or depression; may rarely cause hallucinations

Mental Health: Effects on Psychiatric TreatmentMay result in loss of pain control when used in combination with SSRIs (especially paroxetine and fluoxetine); concurrent use with psychotropics may produce additive sedation or dry mouth

Index TermsChlorpheniramine Maleate and Hydrocodone Bitartrate ; Hydrocodone Polistirex and Chlorpheniramine Polistirex

References

Anderson PO, Sauberan JB, Lane JR, et al, “Hydrocodone Excretion Into Breast Milk: The First Two Reported Cases,” *Breastfeed Med*, 2007, 2(1):10-4.[PubMed 17661614]

Rathmell JP, Viscomi CM, and Ashburn MA, “Management of Nonobstetric Pain During Pregnancy and Lactation,” *Anesth Analg*, 1997, 85(5):1074-87. [PubMed 9356103]

Hydrocodone and Guaifenesin

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Pronunciation(hye droe KOE done & gwye FEN e sin)

U.S. Brand NamesAtuss® HX [DSC]; Codiclear® DH [DSC]; EndaCof [DSC]; EndaCof-XP [DSC]; ExeClear [DSC]; ExeCof-XP [DSC]; Extendryl® HC [DSC]; Hycotuss® [DSC]; Kwelcof® [DSC]; Maxi-Tuss HCG [DSC]; Pancof-XP [DSC]; Phanatuss® HC [DSC]; Pneumotussin® [DSC]; Touro® HC [DSC]; Tusso-DF® [DSC]; Vitussin [DSC]; Xpect-HC™ [DSC]; Ztuss™ ZT [DSC]

Pharmacologic CategoryAntitussive/Expectorant

Use: Labeled IndicationsSymptomatic relief of nonproductive coughs associated with upper and lower respiratory tract congestion

Dosing: Adults**Expectorant/antitussive:** Oral:

Atuss® HX: 1-2 capsules every 8 hours

Codiclear® DH, Kwelcof®, ExeClear, Hycotuss®: 5-15 mL every 4 hours, after meals and at bedtime (maximum: 30 mL/24 hours)

Maxi-Tuss HCG: 5-10 mL every 4 hours, after meals and at bedtime

Pneumotussin®: 1-2 tablets or 10 mL every 4-6 hours (maximum: 4 doses/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Expectorant/antitussive:** Oral: Children:

<6 years (unlabeled): Hydrocodone 0.3 mg/kg/day in 4 divided doses

6-12 years:

Atuss® Hx: 1 capsule every 8 hours

Codiclear® DH, ExeClear, Hycotuss®, Kwelcof®, Maxi-Tuss HCG: 2.5-5 mL every 4 hours, after meals and at bedtime

Pneumotussin®: One tablet or 5 mL every 4-6 hours (maximum: 4 doses/24 hours)

>12 years:

Codiclear® DH, ExeClear, Hycotuss®, Kwelcof®, Maxi-Tuss HCG: 5-10 mL every 4 hours, after meals and at bedtime

Pneumotussin®: 1-2 tablets or 10 mL every 4-6 hours (maximum: 4 doses/24 hours)

≥12 years (Atuss® Hx): Refer to adult dosing.

Dietary ConsiderationsShould be taken after meals. EndaCof-XP contains phenylalanine.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).

RestrictionsC-III

ContraindicationsHypersensitivity to hydrocodone, guaifenesin, or any component of the formulation; increased intracranial pressure; depressed ventilation

Allergy Considerations

- GuaiFENesin Allergy
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydromorphone, levorphanol, morphine, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.

- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use with caution in patients with pulmonary disease or decrease ventilatory function; dose-related respiratory depression occurs.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Use with caution in children; may be more sensitive to adverse effects.

- Post-op patients: Use with caution postoperatively; causes respiratory depression.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Opioid analgesics are considered FDA risk category D if used for prolonged periods or in large doses near term. Withdrawal symptoms may be observed in babies born to mothers taking opioids regularly during pregnancy. Respiratory depression may be observed in the newborn if opioids are given close to delivery.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsHydrocodone is excreted in breast milk; information for guaifenesin is not available. The manufacturers recommend discontinuing the medication or to discontinue nursing during therapy.
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypertension, postural hypotension, palpitation

Central nervous system: Drowsiness, sedation, mental clouding, mental and physical impairment, anxiety, fear, dysphoria, dizziness, psychotic dependence, mood changes

Gastrointestinal: Nausea, vomiting, constipation with prolonged use, xerostomia

Genitourinary: Ureteral spasm, urinary retention

Ocular: Blurred vision

Respiratory: Respiratory depression (dose related)

Metabolism/Transport EffectsHydrocodone: **Substrate** (minor) of CYP2D6, 3A
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

QuiNIDine: May diminish the analgesic effect of Hydrocodone. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid or limit ethanol (may increase CNS depression). Watch for sedation.

Test InteractionsGuaifenesin: Possible color interference with determination of 5-HIAA and VMA

Nursing: Physical Assessment/MonitoringSee individual agent for Guaifenesin.

Patient EducationSee individual agent for Guaifenesin. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet:

Ztuss™ ZT: Hydrocodone bitartrate 5 mg and guaifenesin 300 mg [DSC]

Capsule, variable release:

Atuss® HX: Hydrocodone bitartrate 5 mg [immediate release] and guaifenesin 100 mg [sustained release] [DSC]

Liquid: Hydrocodone bitartrate 5 mg and guaifenesin 100 mg per 5 mL (480 mL, 960 mL) [DSC]

ExeCof-XP: Hydrocodone bitartrate 3 mg and guaifenesin 90 mg per 5 mL (3840 mL) [contains benzoic acid] [DSC]

Kwelcof®: Hydrocodone bitartrate 5 mg and guaifenesin 100 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; contains benzoic acid; apricot-pineapple flavor] [DSC]

Pancof-XP: Hydrocodone bitartrate 3 mg and guaifenesin 90 mg per 5 mL (3840 mL) [contains benzoic acid] [DSC]

Phanatuss® HC: Hydrocodone bitartrate 5 mg and guaifenesin 100 mg per 5 mL (480 mL) [alcohol free, sugar free; mint flavor] [DSC]

Vitussin: Hydrocodone bitartrate 5 mg and guaifenesin 100 mg per 5 mL (480 mL) [alcohol free, sugar free, dye free; cherry flavor] [DSC]

Syrup: Hydrocodone bitartrate 3.5 mg and guaifenesin 100 mg per 5 mL (120 mL, 480 mL); hydrocodone bitartrate 3.5 mg and guaifenesin 300 mg per 5 mL (120 mL, 480 mL); hydrocodone bitartrate 5 mg and guaifenesin 100 mg per 5 mL (480 mL) [DSC]

Codiclear® DH: Hydrocodone bitartrate 3.5 mg and guaifenesin 300 mg per 5 mL (120 mL, 480 mL) [alcohol free, dye free, sugar free; contains sodium benzoate; grape flavor] [DSC]

EndaCof-XP: Hydrocodone bitartrate 2.5 mg and guaifenesin 200 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; contains phenylalanine; cherry punch flavor] [DSC]

ExeClear: Hydrocodone bitartrate 3.5 mg and guaifenesin 100 mg per 5 mL (480 mL) [DSC]

Hycotuss®: Hydrocodone bitartrate 5 mg and guaifenesin 100 mg per 5 mL (480 mL) [contains alcohol 10%; butterscotch flavor] [DSC]

Maxi-Tuss HCG: Hydrocodone bitartrate 6 mg and guaifenesin 200 mg per 5 mL (480 mL) [alcohol free, sugar free; contains aspartame; butterscotch flavor] [DSC]

Pneumotussin®: Hydrocodone bitartrate 2.5 mg and guaifenesin 200 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; cherry punch flavor] [DSC]

Tusso-DF®: Hydrocodone bitartrate 2.5 mg and guaifenesin 100 mg per 5 mL (480 mL) [cherry flavor] [DSC]

Tablet:

EndaCof: Hydrocodone bitartrate 2.5 mg and guaifenesin 300 mg [DSC]

Touro® HC: Hydrocodone bitartrate 5 mg and guaifenesin 575 mg [DSC]

Tablet, sustained release:

Extendryl® HC: Hydrocodone bitartrate 10 mg and guaifenesin 1000 mg [DSC]

Xpect-HC™: Hydrocodone bitartrate 5 mg and guaifenesin 600 mg [DSC]

Generic AvailableYes: Liquid, syrup

Pricing: U.S. (www.drugstore.com)

Syrup (Hycotuss Expectorant)

5-100 mg/5 mL (120): $25.46

Mechanism of Action

Hydrocodone binds to opiate receptors in the CNS, altering the perception of and response to pain; suppresses cough in medullary center; produces generalized CNS depression

Guaifenesin is thought to act as an expectorant by irritating the gastric mucosa and stimulating respiratory tract secretions, thereby increasing respiratory fluid volumes and decreasing phlegm viscosity

Pharmacodynamics/Kinetics

Guaifenesin: See Guaifenesin monograph.

Hydrocodone:

Onset of action: Narcotic analgesic: 10-20 minutes

Duration: 4-8 hours

Distribution: Crosses placenta

Metabolism: Hepatic; O-demethylation; N-demethylation and 6-ketosteroid reduction

Half-life elimination: 3.3-4.4 hours

Excretion: Urine

Related Information

- GuaiFENesin

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, sedation, mental clouding, mental impairment, anxiety, fear, dysphoria, dizziness, psychotic dependence, mood changes

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation

Index TermsGuaifenesin and Hydrocodone

References

Anderson PO, Sauberan JB, Lane JR, et al, “Hydrocodone Excretion Into Breast Milk: The First Two Reported Cases,” *Breastfeed Med*, 2007, 2(1):10-4.[PubMed 17661614]

Rathmell JP, Viscomi CM, and Ashburn MA, “Management of Nonobstetric Pain During Pregnancy and Lactation,” *Anesth Analg*, 1997, 85(5):1074-87. [PubMed 9356103]

Hydrocodone and Homatropine

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Medication Safety Issues

Sound-alike/look-alike issues:

Hycodan® may be confused with Hycomine®, Vicodin®

Pronunciation(hye droe KOE done & hoe MA troe peen)

U.S. Brand NamesHycodan® [DSC]; Hydromet®; Tussigon®

Pharmacologic CategoryAntitussive

Use: Labeled IndicationsSymptomatic relief of cough

Dosing: Adults**Antitussive:** Oral: 1 tablet or 5 mL every 4-6 hours as needed (maximum: 6 tablets/24 hours or 30 mL/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Antitussive:** Oral:

Children 6-12 years: $^1/_2$ tablet or 2.5 mL every 4-6 hours as needed (maximum: 3 tablets or 15 mL/24 hours)

Children ≥12 years: Refer to adult dosing.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).

RestrictionsC-III

ContraindicationsHypersensitivity to hydrocodone, homatropine, or any component of the formulation

Allergy Considerations

- Belladonna Alkaloid Allergy
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydromorphone, levorphanol, morphine, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.

- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use with caution in patients with pulmonary disease or decrease ventilatory function; dose-related respiratory depression occurs.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Use with caution in children; may be more sensitive to adverse effects. Safety and efficacy of this combination have not been established in children <6 years of age.
- Post-op patients: Use with caution postoperatively; causes respiratory depression.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Opioid analgesics are considered FDA risk category D if used for prolonged periods or in large doses near term. Withdrawal symptoms may be observed in babies born to mothers taking opioids regularly during pregnancy. Respiratory depression may be observed in the newborn if opioids are given close to delivery.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsHydrocodone is excreted in breast milk; information for homatropine is not available. The manufacturers recommend discontinuing the medication or to discontinue nursing during therapy.

Adverse ReactionsFrequency not defined.

Central nervous system: Anxiety, dizziness, drowsiness, dysphoria, fear, lethargy, mental clouding, mental impairment, mood changes, sedation

Dermatologic: Pruritus, rash

Gastrointestinal: Constipation, nausea, vomiting, xerostomia

Genitourinary: Urinary retention, urinary tract spasm

Respiratory: Respiratory depression

Miscellaneous: Physical and psychological dependence with prolonged use

Metabolism/Transport EffectsHydrocodone: **Substrate** (minor) of CYP2D6, 3A

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May diminish the analgesic effect of Hydrocodone. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid or limit ethanol (may increase CNS depression).

Test InteractionsIncreased ALT, AST

Patient Education**Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] =

Discontinued product

Syrup: Hydrocodone bitartrate 5 mg and homatropine methylbromide 1.5 mg per 5 mL (473 mL)

Hycodan® [DSC], Hydromet®: Hydrocodone bitartrate 5 mg and homatropine methylbromide 1.5 mg per 5 mL (480 mL) [cherry flavor]

Tablet: Hydrocodone bitartrate 5 mg and homatropine methylbromide 1.5 mg [DSC]

Hycodan® [DSC], Tussigon®: Hydrocodone bitartrate 5 mg and homatropine methylbromide 1.5 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Syrup (Hydrocodone-Homatropine)

5-1.5 mg/5 mL (473): $29.99

Syrup (Hydromet)

5-1.5 mg/5 mL (120): $25.99

Tablets (Tussigon)

5-1.5 mg (100): $61.03

Mechanism of Action

Hydrocodone binds to opiate receptors in the CNS, altering the perception of and response to pain; suppresses cough in medullary center; produces generalized CNS depression.

Homatropine is an anticholinergic agent, present in a subtherapeutic amount to discourage deliberate overdose.

Related Information

- Homatropine
- Narcotic / Opioid Analgesics

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusLightheadedness, dizziness, sedation, drowsiness, and fatigue are common; may cause confusion; may rarely cause hallucinations

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation

Index TermsHomatropine and Hydrocodone

References

Anderson PO, Sauberan JB, Lane JR, et al, “Hydrocodone Excretion Into Breast Milk: The First Two Reported Cases,” *Breastfeed Med*, 2007, 2(1):10-4.[PubMed 17661614]

Rathmell JP, Viscomi CM, and Ashburn MA, “Management of Nonobstetric Pain During Pregnancy and Lactation,” *Anesth Analg*, 1997, 85(5):1074-87. [PubMed 9356103]

International Brand NamesHydromet (MX)

Hydrocodone and Ibuprofen

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(hye droe KOE done & eye byoo PROE fen)

U.S. Brand NamesIbudone™; Reprexain®; Vicoprofen®

Canadian Brand NamesVicoprofen®

Pharmacologic CategoryAnalgesic, Opioid; Nonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsShort-term (generally <10 days) management of moderate to severe acute pain; is not indicated for treatment of such conditions as osteoarthritis or rheumatoid arthritis

Use: DentalShort-term management (generally <10 days) of moderate-to-severe acute postoperative dental pain where an anti-inflammatory effect is desired

Dosing: AdultsAnalgesic: Oral: 1 tablet every 4-6 hours as needed for pain; maximum: 5 tablets/day. **Note:** Short-term use is recommended (<10 days).

Dosing: ElderlyUse with caution; consider reduced doses. Refer to dosing in individual monographs.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.

RestrictionsC-III; An FDA-approved medication guide for NSAIDs must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to hydrocodone, ibuprofen, or any component of the formulation; patients who have experienced asthma, urticaria, or allergic-type reactions to aspirin or other NSAIDs; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings (related to ibuprofen):

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Aseptic meningitis: May increase the risk of aseptic meningitis, especially in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydromorphone, levorphanol, oxycodone, oxymorphone).

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Abdominal conditions: Hydrocodone may obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Adrenocortical insufficiency: Use with caution in patients with adrenocortical insufficiency, including Addison's disease.

- Asthma: Do not administer NSAIDs to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Biliary tract impairment: Use hydrocodone with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use of NSAIDs is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Drug abuse: Use hydrocodone with caution in patients with a potential for or a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Obesity: Use with caution in patients who are morbidly obese.

- Prostatic hyperplasia/urinary stricture: Use hydrocodone with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Psychosis: Use with caution in patients with toxic psychosis.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

- Respiratory disease: Use hydrocodone with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages. May suppress cough reflex; use with caution postoperatively and in patients with pulmonary disease.

- Seizures: Use with caution in patients with a history of seizure disorders.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Safety and efficacy have not been established in children <16 years of age.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsThe elderly are at increased risk for adverse effects from NSAIDs. As many as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high-dose situations; however, elderly patients may demonstrate these adverse effects at lower doses than younger adults. The elderly are also at increased risk of renal toxicity.

Pregnancy Risk FactorC/D (3rd trimester)

Pregnancy ConsiderationsAs with other NSAID-containing products, this agent should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus. Opioid analgesics are considered FDA risk category D if used for prolonged periods or in large doses near term. Withdrawal symptoms may be observed in babies born to mothers taking opioids regularly during pregnancy. Respiratory depression may be observed in the newborn if opioids are given close to delivery. Also refer to Ibuprofen monograph.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsHydrocodone and ibuprofen are excreted in breast milk. The manufacturers recommend discontinuing the medication or to discontinue nursing during therapy. Also refer to Ibuprofen monograph.

Adverse Reactions

>10%:

Central nervous system: Headache (27%), somnolence (22%), dizziness (14%)

Gastrointestinal: Constipation (22%), nausea (21%), dyspepsia (12%)

1% to 10%:

Cardiovascular: Edema (3% to 9%), palpitation (<3%), vasodilation (<3%)

Central nervous system: Anxiety (3% to 9%), insomnia (3% to 9%), nervousness (3% to 9%), confusion (<3%), fever (<3%), pain (<3%), thought abnormalities (<3%)

Dermatologic: Pruritus (3% to 9%)

Gastrointestinal: Abdominal pain (3% to 9%), diarrhea (3% to 9%), flatulence (3% to 9%), vomiting (3% to 9%), xerostomia (3% to 9%), anorexia (<3%), gastritis (<3%), melena (<3%), mouth ulcers (<3%)

Genitourinary: Polyuria (<3%)

Neuromuscular & skeletal: Weakness (3% to 9%), hypertonia (<3%), paresthesia (<3%)

Otic: Tinnitus (<3%)

Respiratory: Dyspnea (<3%), pharyngitis (<3%), rhinitis (<3%)

Miscellaneous: Diaphoresis (3% to 9%), infection (3% to 9%), flu-like syndrome (<3%), hiccups (<3%), thirst (<3%)

<1%, postmarketing, and/or case reports: Abnormal dreams, agitation, allergic reaction, arrhythmia, arthralgia, asthma, bronchitis, chalky stool, clenching teeth, cough, cystitis, depression, dry eyes, dysphagia, esophageal spasm, esophagitis, euphoria, exfoliative dermatitis, gastroenteritis, GI bleeding, GI inflammation, GI perforation, glossitis, glycosuria, hoarseness, hyper/hypotension, impotence, libido decreased, liver enzymes increased, mood changes, myalgia, neuralgia, pneumonia, physical/psychological dependence (with prolonged use), pulmonary congestion, rash, respiratory depression, sinusitis, slurred speech, Stevens-Johnson syndrome, tachycardia, taste (unpleasant), tremor, toxic epidermal necrolysis, ulcer, urinary incontinence, urinary retention, urticaria, vertigo, vision change, weight loss

Metabolism/Transport Effects

Hydrocodone: **Substrate** (minor) of CYP2D6, 3A

Ibuprofen: **Substrate** (minor) of CYP2C9, 2C19; **Inhibits** CYP2C9 (strong)

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

QuiNIDine: May diminish the analgesic effect of Hydrocodone. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Based on **hydrocodone** component: Ethanol: Avoid or limit ethanol (may increase CNS depression). Watch for sedation.

Based on **ibuprofen** component:

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Ibuprofen peak serum levels may be decreased if taken with food.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Monitoring ParametersSigns/symptoms of bleeding; periodic CBC and chemistry profile with long-term use; blood pressure

Nursing: Physical Assessment/MonitoringSee individual agent for Ibuprofen.

Monitoring: Lab TestsPeriodic CBC and chemistry profile with long-term use

Patient EducationSee individual agent for Ibuprofen. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Hydrocodone bitartrate 5 mg and ibuprofen 200 mg; hydrocodone bitartrate 7.5 mg and ibuprofen 200 mg

Ibudone™:

5/200: Hydrocodone bitartrate 5 mg and ibuprofen 200 mg

10/200: Hydrocodone bitartrate 10 mg and ibuprofen 200 mg

Reprexain®: Hydrocodone bitartrate 5 mg and ibuprofen 200 mg; hydrocodone bitartrate 7.5 mg and ibuprofen 200 mg

Vicoprofen®: Hydrocodone bitartrate 7.5 mg and ibuprofen 200 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Hydrocodone-Ibuprofen)

7.5-200 mg (30): $29.99

Tablets (Reprexain)

5-200 mg (30): $39.99

Tablets (Vicoprofen)

7.5-200 mg (30): $74.78

Mechanism of Action

Hydrocodone: Binds to opiate receptors in the CNS, altering the perception of and response to pain; suppresses cough in medullary center; produces generalized CNS depression

Ibuprofen: Reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Ibuprofen: See Ibuprofen monograph.

Hydrocodone:

Onset of action: Narcotic analgesic: 10-20 minutes

Duration: 4-8 hours

Distribution: Crosses placenta

Protein binding: 19% to 45%

Metabolism: Hepatic via CYP2D6 and 3A4; O-demethylation; N-demethylation and 6-ketosteroid reduction

Half-life elimination: 4.5 hours

Time to peak: 1.7 hours

Excretion: Urine

Related Information

- Ibuprofen
- Narcotic / Opioid Analgesics

Pharmacotherapy PearlsThe antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation, drowsiness, and fatigue are common; may cause nervousness or confusion; may rarely cause hallucinations, depression, or insomnia

Mental Health: Effects on Psychiatric TreatmentHypotension is common and may be potentiated by low potency antipsychotics and other psychotropics. May rarely cause agranulocytosis, caution with clozapine and carbamazepine. Sedation may be additive with psychotropics. Ibuprofen may inhibit the clearance of lithium resulting in elevated serum lithium levels; may need to adjust dosage downward.

Index TermsHydrocodone Bitartrate and Ibuprofen; Ibuprofen and Hydrocodone

References

"American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk," *Pediatrics*, 2001, 108(3):776-89. [PubMed 11533352]

Anderson PO, Sauberan JB, Lane JR, et al, "Hydrocodone Excretion Into Breast Milk: The First Two Reported Cases," *Breastfeed Med*, 2007, 2(1):10-4.[PubMed 17661614]

Mokhlesi B, Leikin JB, Murray P, et al, "Adult Toxicology in Critical Care: Part II: Specific Poisonings," *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

Rathmell JP, Viscomi CM, and Ashburn MA, "Management of Nonobstetric Pain During Pregnancy and Lactation," *Anesth Analg*, 1997, 85(5):1074-87. [PubMed 9356103]

Sunshine A, Olson NZ, O'Neill E, et al, "Analgesic Efficacy of a Hydrocodone With Ibuprofen Combination Compared With Ibuprofen Alone for the Treatment of Acute Postoperative Pain," *J Clin Pharmacol*, 1997, 37:908-15.[PubMed 9505982]

International Brand Names Vicoprofen (CA)

Hydrocodone and Pseudoephedrine

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English

English

Jump To Field (Select Field Name)

Pronunciation(hye droe KOE done & soo doe e FED rin)

U.S. Brand NamesCoughcold HCM [DSC]; P-V Tussin Tablet [DSC]; SymTan™ [DSC]

Pharmacologic CategoryAntitussive/Decongestant

Use: Labeled IndicationsSymptomatic relief of cough and nasal congestion

Dosing: AdultsAntitussive/nasal decongestant: Oral:

Coldcough HCM: 5-10 mL 4 times/day as needed

SymTan™: 5 mL every 12 hours (maximum: 10 mL/day)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAntitussive/nasal decongestant: Oral:

Children 2-6 years: Coldcough HCM: 1.25-2.5 mL 4 times/day a needed

Children 6-12 years:

Coldcough HCM: 2.5-5 mL 4 times/day as needed

SymTan™: 2.5 mL every 12 hours (maximum: 5 mL/day)

Children >12 years: Refer to adult dosing.

Dietary ConsiderationsSymTan™ solution contains aspartame.

RestrictionsC-III

ContraindicationsHypersensitivity to hydrocodone, pseudoephedrine or any component of the formulation; severe hypertension or coronary artery disease; MAO inhibitor therapy; increased intracranial pressure; depressed ventilatory function; diarrhea associated with pseudomembranous colitis or poisoning; infants; breast-feeding

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Overdosage: May cause hallucinations, seizures, CNS depression, and death with overdosage.
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydromorphone, levorphanol, morphine, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use with caution in patients with pulmonary disease or decreased ventilatory function; dose-related respiratory depression occurs.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Safety and efficacy of this combination have not been established in children <2 years of age.

- Postop patients: Use with caution postoperatively; suppresses the cough reflex.

Dosage forms specific issues:

- Aspartame: Some products may contain aspartame.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Opioid analgesics are considered FDA risk category D if used for prolonged periods or in large doses near term. Withdrawal symptoms may be observed in babies born to mothers taking opioids regularly during pregnancy. Respiratory depression may be observed in the newborn if opioids are given close to delivery.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsHydrocodone and pseudoephedrine are excreted in breast milk. Use of this combination is contraindicated by some manufacturers while breast-feeding. Also refer to Pseudoephedrine monograph.

Metabolism/Transport EffectsHydrocodone: **Substrate** (minor) of CYP2D6, 3A

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

QuiNIDine: May diminish the analgesic effect of Hydrocodone. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Hydrocodone may enhance the CNS depressant effect of alcohol (ethyl).

Nursing: Physical Assessment/MonitoringSee individual agent for Pseudoephedrine.

Patient EducationSee individual agent for Pseudoephedrine. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution:

SymTan™: Hydrocodone tannate 10 mg and pseudoephedrine tannate 45 mg per 5 mL (480 mL) [contains aspartame, propylene glycol; cherry mint flavor] [DSC]

Syrup:

Coldcough HCM: Hydrocodone bitartrate 3 mg and pseudoephedrine hydrochloride 15 mg per 5 mL (480 mL) [alcohol, dye and sugar free; contains propylene glycol; grape flavor] [DSC]

Tablet:

P-V Tussin: Hydrocodone bitartrate 5 mg and pseudoephedrine hydrochloride 60 mg [DSC]

Generic AvailableNo

Mechanism of Action

Hydrocodone binds to opiate receptors in the CNS, altering the perception of and response to pain; suppresses cough in medullary center; produces generalized CNS depression.

Pseudoephedrine directly stimulates alpha-adrenergic receptors of respiratory mucosa causing vasoconstriction; directly stimulates beta-adrenergic receptors causing bronchial relaxation, increased heart rate and contractility.

Pharmacodynamics/Kinetics

Pseudoephedrine: See Pseudoephedrine monograph.

Hydrocodone:

Onset of action: Narcotic analgesic: 10-20 minutes

Duration: 4-8 hours

Metabolism: Hepatic; O-demethylation; N-demethylation and 6-ketosteroid reduction

Half-life elimination: 3.3-4.4 hours

Excretion: Urine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause sedation, drowsiness, mental clouding, lethargy, impairment of mental performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors

Index TermsHydrocodone Tannate and Pseudoephedrine Tannate; Pseudoephedrine Hydrochloride and Hydrocodone Bitartrate

References

“American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk,” *Pediatrics*, 2001, 108(3):776-89. [PubMed 11533352]

Anderson PO, Sauberan JB, Lane JR, et al, “Hydrocodone Excretion Into Breast Milk: The First Two Reported Cases,” *Breastfeed Med*, 2007, 2(1):10-4.[PubMed 17661614]

Rathmell JP, Viscomi CM, and Ashburn MA, “Management of Nonobstetric Pain During Pregnancy and Lactation,” *Anesth Analg*, 1997, 85(5):1074-87. [PubMed 9356103]

Hydrocodone, Carbinoxamine, and Pseudoephedrine

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Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(hye droe KOE done, kar bi NOKS a meen, & soo doe e FED rin)

U.S. Brand NamesTri-Vent™ HC [DSC]

Pharmacologic CategoryAlpha/Beta Agonist; Analgesic, Opioid; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of cough, congestion, and rhinorrhea associated with the common cold, influenza, bronchitis, or sinusitis

Dosing: AdultsRelief of cough, congestion, and runny nose: Oral: 5-10 mL every 4-6 hours; maximum dose: 30 mL/24 hours
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRelief of cough, congestion, and runny nose: Oral:

Children *2-10 years:* Dosing based on hydrocodone content: 0.6 mg/kg/day given in 4 divided doses. Alternately, the following dosing may be used based on age:

2-4 years: 1.25 mL every 4-6 hours; maximum dose: 7.5 mL/24 hours

4-10 years: 2.5 mL every 4-6 hours; maximum dose: 15 mL/24 hours

Children >10 years: Refer to adult dosing.

Administration: OralDoses should be administered every 4-6 hours, up to 4 times/day.
StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).
RestrictionsC-III
ContraindicationsHypersensitivity to hydrocodone, carbinoxamine, pseudoephedrine or any component of the formulation; use with or within 14 days of MAO inhibitors; narrow-angle glaucoma; urinary retention; peptic ulcer; severe hypertension or cardiovascular disease; intracranial lesion associated with elevated intracranial pressure; acute asthmatic attack
Allergy Considerations

- Belladonna Alkaloid Allergy
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydromorphone, levorphanol, morphine, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Asthma: Use with caution in patients with a history of asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Diabetes: Use with caution in patients with diabetes mellitus.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia: Use with caution in patients with prostatic hyperplasia.
- Renal impairment: Use with caution in patients with renal impairment.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- Elderly: Use with caution in patients >60 years of age.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination product. Opioid analgesics are considered FDA risk category D if used for prolonged periods or in large doses near term. Withdrawal symptoms may be observed in babies born to mothers taking opioids regularly during pregnancy. Respiratory depression may be observed in the newborn if opioids are given close to delivery.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsIt is not known if carbinoxamine is found in breast milk. Hydrocodone and pseudoephedrine are excreted in breast milk. Also refer to the individual Pseudoephedrine and Carbinoxamine monographs.
Adverse ReactionsSee individual agents.
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May diminish the analgesic effect of Hydrocodone. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid or limit ethanol (may increase CNS depression).

Nursing: Physical Assessment/MonitoringSee individual agent for Pseudoephedrine.

Patient EducationSee individual agent for Pseudoephedrine. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Liquid:

Tri-Vent™ HC: Hydrocodone bitartrate 5 mg, carbinoxamine maleate 2 mg, and pseudoephedrine hydrochloride 30 mg per 5 mL (480 mL) [alcohol free, sugar free; peach flavor] [DSC]

Generic AvailableNo

Mechanism of Action

Hydrocodone binds to opiate receptors in the CNS, altering the perception of and response to pain; suppresses cough in medullary center; produces generalized CNS depression.

Carbinoxamine competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract.

Pseudoephedrine is a sympathomimetic amine and isomer of ephedrine; acts as a decongestant in respiratory tract mucous membranes with less vasoconstrictor action than ephedrine in normotensive individuals.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Carbinoxamine
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause anxiety, dizziness, insomnia, restlessness, hallucinations, or depression

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment; may cause tremor which may be mistaken for EPS; may cause tachycardia; tachycardia is also common with clozapine; monitor vital signs; may cause sedation (concurrent use with psychotropics may produce additive sedative effects)

Index Terms Carbinoxamine, Pseudoephedrine, and Hydrocodone; Hydrocodone Bitartrate, Carbinoxamine Maleate, and Pseudoephedrine Hydrochloride; Pseudoephedrine, Hydrocodone, and Carbinoxamine

References

“American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk,” *Pediatrics*, 2001, 108(3):776-89. [PubMed 11533352]

Anderson PO, Sauberan JB, Lane JR, et al, “Hydrocodone Excretion Into Breast Milk: The First Two Reported Cases,” *Breastfeed Med*, 2007, 2(1):10-4.[PubMed 17661614]

Rathmell JP, Viscomi CM, and Ashburn MA, “Management of Nonobstetric Pain During Pregnancy and Lactation,” *Anesth Analg*, 1997, 85(5):1074-87. [PubMed 9356103]

Hydrocodone, Phenylephrine, and Diphenhydramine

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Endal® may be confused with Depen®, Intal®

Pronunciation(hye droe KOE done, fen il EF rin, & dye fen HYE dra meen)

U.S. Brand NamesD-Tann HC [DSC]; Gentuss-HC; Hydro DP; Rindal HPD [DSC]; TussiNate™ [DSC]

Pharmacologic CategoryAlpha/Beta Agonist; Analgesic, Opioid; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of cough and congestion associated with the common cold, sinusitis, or acute upper respiratory tract infections

Dosing: AdultsRelief of cough, congestion: Oral:

D-Tann HC: 5-10 mL every 12 hours

Rindal HPD, TussiNate™: 10 mL every 4 hours (maximum: 40 mL/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRelief of cough, congestion: Oral:

D-Tann HC:

Children 6 to <12 years: 2.5-5 mL every 12 hours

Children ≥12 years: Refer to adult dosing.

Rindal HPD, TussiNate™:

Children 6-12 years: 5 mL every 4 hours (maximum: 20 mL/24 hours)

Children >12 years: Refer to adult dosing.

Dietary Considerations

D-Tann HC contains phenylalanine.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

RestrictionsC-III

ContraindicationsHypersensitivity to codeine, hydrocodone, phenylephrine, diphenhydramine, sympathomimetic amines, antihistamines, or any component of the formulation; asthma; severe hypertension or cardiovascular disease; use with or within 14 days of an MAO inhibitor; glaucoma; urinary retention; peptic ulcer; breast-feeding; infants

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydromorphone, levorphanol, morphine, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists.

Tolerance, psychological and physical dependence may occur with prolonged use.

- Head trauma: May produce adverse reactions which may obscure the clinical course of patients with head injuries.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Renal impairment: Use with caution in patients with severe renal impairment.
- Respiratory disease: Use with caution in patients with pulmonary disease or decrease ventilatory function; dose-related respiratory depression occurs.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children. Safety and efficacy have not been established in children <6 years of age.

Other warnings/precautions:

- Appropriate use: Do not use with other products containing diphenhydramine, even ones used on the skin.
- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Opioid analgesics are considered FDA risk category D if used for prolonged periods or in large doses near term. Withdrawal symptoms may be observed in babies born to mothers taking opioids regularly during pregnancy. Respiratory depression may be observed in the newborn if opioids are given close to delivery. Also refer to Diphenhydramine monograph.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsIt is not known if phenylephrine is found in breast milk. Hydrocodone and diphenhydramine are excreted in breast milk. Use of this combination is contraindicated by the manufacturers while breast-feeding. Also refer to Diphenhydramine monograph.

Adverse ReactionsSee individual agents.

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May diminish the analgesic effect of Hydrocodone. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid or limit ethanol (may increase CNS depression).
Nursing: Physical Assessment/MonitoringSee individual agents for Phenylephrine and Diphenhydramine.
Patient EducationSee individual agents for Phenylephrine and Diphenhydramine. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Suspension:

D-Tann HC: Hydrocodone tannate 3.5 mg, phenylephrine tannate 7.5 mg, and diphenhydramine tannate 25 mg per 5 mL (120 mL) [alcohol free, sugar free; contains phenylalanine; grape flavor] [DSC]

Syrup:

Gestuss-HC: Hydrocodone bitartrate 3 mg, phenylephrine hydrochloride 5 mg, and diphenhydramine hydrochloride 12.5 mg per 5 mL (480 mL) [black raspberry flavor]

Hydro DP: Hydrocodone bitartrate 2 mg, phenylephrine hydrochloride 7.5 mg, and diphenhydramine hydrochloride 12.5 mg per 5 mL (480 mL) [cherry flavor]

Rindal HPD: Hydrocodone bitartrate 2 mg, phenylephrine hydrochloride 7.5 mg, and diphenhydramine hydrochloride 12.5 mg per 5 mL (480 mL) [alcohol free, sugar free; black raspberry flavor] [DSC]

TussiNate™: Hydrocodone bitartrate 3.5 mg, phenylephrine hydrochloride 5 mg, and diphenhydramine hydrochloride 12.5 mg per 5 mL (480 mL) [alcohol free; contains sodium benzoate; black raspberry flavor] [DSC]

Generic AvailableYes: Syrup
Pricing: U.S. (www.drugstore.com)

Syrup (Hydro-DP)

7.5-12.5-2 mg/5 mL (473): $32.97

Mechanism of Action

Hydrocodone binds to opiate receptors in the CNS; suppresses cough in medullary center.

Phenylephrine is a potent, direct-acting alpha-adrenergic stimulator.

Diphenhydramine is an H_1-receptor antagonist.

Pharmacodynamics/KineticsSee individual agents.
Related Information

- DiphenhydrAMINE
- Phenylephrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response
Mental Health: Effects on Mental StatusDiphenhydramine may cause paradoxical excitation in pediatric patients and can result in hallucinations, coma, and death in overdose. Sedation is common; may cause dizziness, fatigue, nervousness, insomnia, euphoria, or

confusion; may rarely cause hallucinations.

Mental Health: Effects on Psychiatric Treatment Contraindicated with MAO inhibitors. Rare reports of agranulocytosis and thrombocytopenia; use caution with clozapine, carbamazepine, valproic acid, and mirtazapine. Therapeutic effects of cholinergic agents (donepezil, rivastigmine, and galantamine) may be antagonized. Concurrent use with psychotropic agents may result in additive sedative and anticholinergic effects; monitor.

Index Terms Diphenhydramine, Hydrocodone, and Phenylephrine; Hydrocodone Bitartrate, Phenylephrine Hydrochloride, and Diphenhydramine Hydrochloride; Hydrocodone Tannate, Phenylephrine Tannate, and Diphenhydramine Tannate; Phenylephrine, Diphenhydramine, and Hydrocodone

References

Anderson PO, Sauberan JB, Lane JR, et al, “Hydrocodone Excretion Into Breast Milk: The First Two Reported Cases,” *Breastfeed Med*, 2007, 2(1):10-4.[PubMed 17661614]

Rathmell JP, Viscomi CM, and Ashburn MA, “Management of Nonobstetric Pain During Pregnancy and Lactation,” *Anesth Analg*, 1997, 85(5):1074-87. [PubMed 9356103]

Hydrocodone, Phenylephrine, and Guaifenesin

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English

English

Jump To Field (Select Field Name)

Pronunciation(hye droe KOE done, fen il EF rin, & gwye FEN e sin)

U.S. Brand NamesCrantex HC [DSC]; De-Chlor G [DSC]; Donatussin DC [DSC]; Duratuss® HD [DSC]; ExeTuss HC [DSC]; Gentex HC [DSC]; Giltuss HC® [DSC]; Guiaplex™ HC [DSC]; Hydro-GP [DSC]; HydroFed [DSC]; Levall 5.0 [DSC]; Mintuss G [DSC]; Tussafed® HC [DSC]; Tussafed® HCG [DSC]

Pharmacologic CategoryAntitussive/Decongestant/Expectorant

Use: Labeled IndicationsTemporary relief of cough, congestion, and other symptoms associated with colds or allergies

Dosing: Adults**Cough/congestion:** Oral:

Crantex HC: 5-10 mL every 4-6 hours (maximum: 40 mL/24 hours)

Giltuss HC®: 5 mL every 6 hours (maximum: 6 doses/24 hours)

Tussafed® HC: 10 mL every 4-6 hours as needed (maximum: 6 doses/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Cough/congestion:** Oral: Children:

2-6 years (Crantex HC): 2.5 mL every 4-6 hours (maximum: 10 mL/24 hours)

3-6 years:

Giltuss HC®: 1.25 mL every 6 hours (maximum: 6 doses/24 hours)

Tussafed® HC: 2.5 mL every 4-6 hours as needed (maximum: 6 doses/24 hours)

6-12 years:

Crantex HC: 5 mL every 4-6 hours (maximum: 4 doses/24 hours)

Giltuss HC®: 2.5 mL every 6 hours (maximum: 6 doses/24 hours)

Tussafed® HC: 5 mL every 4-6 hours as needed (maximum: 6 doses/24 hours)

≥12 years: Refer to adult dosing.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).

RestrictionsC-III

ContraindicationsHypersensitivity to hydrocodone, phenylephrine, guaifenesin, or any component of the formulation; severe hypertension, severe cardiac disease; use with or within 14 days of MAO inhibitors; urinary retention; peptic ulcer

Allergy Considerations

- GuaiFENesin Allergy
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydromorphone, levorphanol, morphine, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.

- Diabetes: Use with caution in patients with diabetes mellitus.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.

- Respiratory disease: Use with caution in patients with pulmonary disease or decrease ventilatory function; dose-related respiratory depression occurs.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Use with caution in children; may be more sensitive to adverse effects.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Geriatric ConsiderationsElderly may be particularly susceptible to CNS depression and confusion, as well as the constipating effects of narcotics. Elderly are more predisposed to adverse effects of sympathomimetics since they frequently have cardiovascular disease and diabetes, as well as multiple drug therapies.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Opioid analgesics are considered FDA risk category D if used for prolonged periods or in large doses near term. Withdrawal symptoms may be observed in babies born to mothers taking opioids regularly during pregnancy. Respiratory depression may be observed in the newborn if opioids are given close to delivery.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsHydrocodone is excreted in breast milk; information for guaifenesin and phenylephrine is not available.
Adverse ReactionsFrequency not defined.

Central nervous system: Drowsiness, giddiness, lassitude

Gastrointestinal: Constipation, GI upset, nausea

Metabolism/Transport EffectsHydrocodone: **Substrate** (minor) of CYP2D6, 3A
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

QuiNIDine: May diminish the analgesic effect of Hydrocodone. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Test InteractionsRefer to individual Guaifenesin monograph.
Nursing: Physical Assessment/MonitoringSee individual agents for Phenylephrine and Guaifenesin.
Patient EducationSee individual agents for Phenylephrine and Guaifenesin. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Elixir:

Duratuss® HD: Hydrocodone bitartrate 2.5 mg, phenylephrine hydrochloride 10 mg, and guaifenesin 225 mg per 5 mL (480 mL) [contains sodium benzoate; cherry flavor] [DSC]

Liquid:

Crantex HC: Hydrocodone bitartrate 5 mg, phenylephrine hydrochloride 7.5 mg, and guaifenesin 100 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; black cherry flavor] [DSC]

De-Chlor G: Hydrocodone bitartrate 2 mg, phenylephrine hydrochloride 10 mg, and guaifenesin 100 mg per 5 mL (480 mL) [grape-menthol mint flavor] [DSC]

ExeTuss HC: Hydrocodone bitartrate 2.5 mg, phenylephrine hydrochloride 10 mg, and guaifenesin 225 mg per 5 mL (480 mL) [alcohol free, sugar free; cherry flavor] [DSC]

Gentex HC: Hydrocodone bitartrate 2.5 mg, phenylephrine hydrochloride 7.5 mg, and guaifenesin 100 mg per 5 mL (480 mL) [cherry flavor] [DSC]

Giltuss HC®: Hydrocodone bitartrate 5 mg, phenylephrine hydrochloride 10 mg, and guaifenesin 300 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; strawberry banana flavor] [DSC]

Guiaplex™ HC: Hydrocodone bitartrate 5 mg, phenylephrine hydrochloride 15 mg, and guaifenesin 100 mg per 5 mL (480 mL) [alcohol free, sugar free; contains sodium benzoate; grape flavor] [DSC]

Hydro-GP: Hydrocodone bitartrate 2.5 mg, phenylephrine hydrochloride 7.5 mg, and guaifenesin 50 mg per 5 mL (480 mL) [cherry flavor] [DSC]

Levall 5.0: Hydrocodone bitartrate 5 mg, phenylephrine hydrochloride 15 mg, and guaifenesin 100 mg per 5 mL (480 mL) [grape flavor] [DSC]

Mintuss G: Hydrocodone bitartrate 2 mg, phenylephrine hydrochloride 10 mg, and guaifenesin 100 mg per 5 mL (480 mL) [alcohol free; contains sodium benzoate; grape flavor] [DSC]

Syrup:

Donatussin DC: Hydrocodone bitartrate 2.5 mg, phenylephrine hydrochloride 6 mg, and guaifenesin 120 mg per 5 mL (480 mL) [cherry flavor] [DSC]

HydroFed: Hydrocodone bitartrate 2.5 mg, phenylephrine hydrochloride 6 mg, and guaifenesin 150 mg per 5 mL (480 mL) [alcohol free, sugar free; contains propylene glycol; cherry flavor] [DSC]

Tussafed® HC: Hydrocodone bitartrate 2.5 mg, phenylephrine hydrochloride 7.5 mg, and guaifenesin 50 mg per 5 mL (480 mL) [alcohol free] [DSC]

Tussafed® HCG: Hydrocodone bitartrate 2.5 mg, phenylephrine hydrochloride 6 mg, and guaifenesin 150 mg per 5 mL (480 mL) [alcohol free, sugar free; cherry flavor] [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Syrup (Tussafed HC)

7.5-2.5-50 mg/5 mL (473): $133.10

Mechanism of Action

Hydrocodone binds to opiate receptors in the CNS, altering the perception of and response to pain; suppresses cough in medullary center; produces generalized CNS depression.

Phenylephrine is a direct-acting alpha-adrenergic stimulator with weak beta-adrenergic activity; causes vasoconstriction of the arterioles of the nasal mucosa and conjunctiva; activates the dilator muscle of the pupil to cause contraction; produces vasoconstriction of arterioles in the body; produces systemic arterial vasoconstriction.

Guaifenesin is thought to act as an expectorant by irritating the gastric mucosa and stimulating respiratory tract secretions, thereby increasing respiratory fluid volumes and decreasing phlegm viscosity.

Related Information

- GuaiFENesin
- Phenylephrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tachycardia, palpitations, and xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDrowsiness and giddiness are common; may cause CNS depression; concomitant use with psychotropic agents may produce additive effects

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor use; CNS depressants, MAO inhibitors, and tricyclic antidepressants may potentiate the effects of opiate agonists. Dextroamphetamine may enhance the analgesic effect of opiate agonists. Chlorpromazine, fluoxetine, paroxetine, pergolide, and ropinirole may decrease the effects of hydrocodone.

Index TermsGuaifenesin, Hydrocodone Bitartrate, and Phenylephrine Hydrochloride; Phenylephrine, Guaifenesin, and Hydrocodone

References

Anderson PO, Sauberan JB, Lane JR, et al, “Hydrocodone Excretion Into Breast Milk: The First Two Reported Cases,” *Breastfeed Med*, 2007, 2(1):10-

4.[PubMed 17661614]

Rathmell JP, Viscomi CM, and Ashburn MA, “Management of Nonobstetric Pain During Pregnancy and Lactation,” *Anesth Analg*, 1997, 85(5):1074-87. [PubMed 9356103]

Hydrocodone, Pseudoephedrine, and Guaifenesin

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English English

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Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(hye droe KOE done, soo doe e FED rin & gwye FEN e sin)

U.S. Brand NamesEntex® HC [DSC]; Hydro-Tussin™ HD [DSC]; Hydro-Tussin™ XP [DSC]; Su-Tuss®-HD [DSC]; Ztuss™ Tablet [DSC]

Pharmacologic CategoryAntitussive/Decongestant/Expectorant

Use: Labeled IndicationsSymptomatic relief of irritating, nonproductive cough associated with upper respiratory conditions and allergies

Dosing: Adults**Cough/congestion:** Oral:

Hydro-Tussin™ XP: 5-10 mL 4 times/day as needed

Hydro-Tussin™ HD: 10 mL every 4-6 hours as needed

Ztuss™: 1-1$^{1}/_{2}$ tablets every 4-6 hours (maximum: 8 tablets/24 hours)

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Cough/congestion:** Oral: Children:

2-6 years: Hydro-Tussin™ XP: 1.25-2.5 mL 4 times/day as needed

6-12 years:

Hydro-Tussin™ XP: 2.5-5 mL 4 times/day as needed

Hydro-Tussin™ HD: 5 mL every 4-6 hours as needed

Ztuss™: One-half to 1 tablet every 4-6 hours (maximum: 6 tablets/24 hours)

≥12 years: Refer to adult dosing.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).
RestrictionsC-III
ContraindicationsHypersensitivity to hydrocodone, pseudoephedrine, guaifenesin, or any component of the formulation; severe hypertension; severe cardiac disease; use with or within 14 days of MAO inhibitors; increased intracranial pressure; pregnancy; breast-feeding
Allergy Considerations

- GuaiFENesin Allergy
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydromorphone, levorphanol, morphine, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.

- Diabetes: Use with caution in patients with diabetes mellitus.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.

- Respiratory disease: Use with caution in patients with pulmonary disease or decrease ventilatory function; dose-related respiratory depression occurs.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Use with caution in children; may be more sensitive to adverse effects.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Opioid analgesics are considered FDA risk category D if used for prolonged periods or in large doses near term. Withdrawal symptoms may be observed in babies born to mothers taking opioids regularly during pregnancy. Respiratory depression may be observed in the newborn if opioids are given close to delivery. Use during

pregnancy is contraindicated by some manufacturers.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsHydrocodone and pseudoephedrine are excreted in breast milk; information for guaifenesin is not available. Use while breast-feeding is contraindicated by some manufacturers. Also refer to Pseudoephedrine monograph.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, tachycardia, hypertension

Central nervous system: Drowsiness, fear, anxiety, tenseness, restlessness, pallor, insomnia, hallucinations, CNS depression

Gastrointestinal: GI upset, nausea, constipation with prolonged use

Genitourinary: Dysuria

Hepatic: Transaminases increased (slight)

Neuromuscular & skeletal: Weakness, tremor

Respiratory: Respiratory difficulty

Patients hyper-reactive to pseudoephedrine may display ephedrine-like reactions such as tachycardia, palpitation, headache, dizziness, or nausea; patient idiosyncrasy to adrenergic agents may be manifested by insomnia, dizziness, weakness, tremor, or arrhythmia.

Metabolism/Transport EffectsHydrocodone: **Substrate** (minor) of CYP2D6, 3A

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

QuiNIDine: May diminish the analgesic effect of Hydrocodone. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Test InteractionsRefer to individual monographs for Pseudoephedrine and Guaifenesin.

Nursing: Physical Assessment/MonitoringSee individual agents for Pseudoephedrine and Guaifenesin.

Patient EducationSee individual agents for Pseudoephedrine and Guaifenesin. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Elixir:

Su-Tuss®-HD: Hydrocodone bitartrate 2.5 mg, pseudoephedrine hydrochloride 30 mg, and guaifenesin 100 mg per 5 mL (480 mL) [contains alcohol; fruit punch flavor] [DSC]

Liquid:

Entex® HC: Hydrocodone bitartrate 3.75 mg, pseudoephedrine hydrochloride 22.5 mg, and guaifenesin 50 mg per 5 mL (480 mL) [alcohol free, sugar free; contains propylene glycol; tropical fruit punch flavor] [DSC]

Hydro-Tussin™ HD: Hydrocodone bitartrate 2.5 mg, pseudoephedrine hydrochloride 30 mg, and guaifenesin 100 mg per 5 mL (480 mL) [alcohol free; contains sodium benzoate] [DSC]

Hydro-Tussin® XP: Hydrocodone bitartrate 3 mg, pseudoephedrine hydrochloride 15 mg, and guaifenesin 100 mg per 5 mL (480 mL) [alcohol free, dye free] [DSC]

Tablet:

Ztuss™: Hydrocodone bitartrate 5 mg, pseudoephedrine hydrochloride 30 mg, and guaifenesin 300 mg [sugar free] [DSC]

Generic AvailableYes: Excludes tablet

Pricing: U.S. (www.drugstore.com)

Elixir (Drituss HD)

30-2.5-100 mg/5 mL (120): $16.00

Solution (Tussend Expectorant)

30-2.5-100 mg/5 mL (120): $23.99

Mechanism of Action

Hydrocodone binds to opiate receptors in the CNS, altering the perception of and response to pain; suppresses cough in medullary center; produces generalized CNS depression.

Pseudoephedrine directly stimulates alpha-adrenergic receptors of respiratory mucosa causing vasoconstriction; directly stimulates beta-adrenergic receptors causing bronchial relaxation, increased heart rate and contractility.

Guaifenesin is thought to act as an expectorant by irritating the gastric mucosa and stimulating respiratory tract secretions, thereby increasing respiratory fluid volumes and decreasing phlegm viscosity.

Pharmacodynamics/Kinetics

See Guaifenesin and Pseudoephedrine monographs.

Hydrocodone:

Onset of action: Narcotic analgesic: 10-20 minutes

Duration: 4-8 hours

Distribution: Crosses placenta

Metabolism: Hepatic; O-demethylation; N-demethylation and 6-ketosteroid reduction

Half-life elimination: 3.3-4.4 hours

Excretion: Urine

Related Information

- GuaiFENesin
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Guaifenesin: No significant effects or complications reported

Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause drowsiness, fear, anxiety, tenseness, restlessness, insomnia, hallucinations, CNS depression

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors

Index TermsGuaifenesin, Hydrocodone, and Pseudoephedrine; Pseudoephedrine, Hydrocodone, and Guaifenesin

References

Anderson PO, Sauberan JB, Lane JR, et al, “Hydrocodone Excretion Into Breast Milk: The First Two Reported Cases,” *Breastfeed Med*, 2007, 2(1):10-4.[PubMed 17661614]

Rathmell JP, Viscomi CM, and Ashburn MA, “Management of Nonobstetric Pain During Pregnancy and Lactation,” *Anesth Analg*, 1997, 85(5):1074-87. [PubMed 9356103]

International Brand NamesThyrogen (AU, BE, CH, CZ, DK, EE, FR, HK, IL, KP, NO, SE, SG, TH)

Hydrocortisone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Hydrocortisone may be confused with hydrocodone, hydroxychloroquine, hydrochlorothiazide

Anusol® may be confused with Anusol-HC®, Aplisol®, Aquasol®

Anusol-HC® may be confused with Anusol®

Cortef® may be confused with Coreg®, Lortab®

Cortizone® may be confused with cortisone

HCT (occasional abbreviation for hydrocortisone) is an error-prone abbreviation (mistaken as hydrochlorothiazide)

Hytone® may be confused with Vytone®

Proctocort® may be confused with ProctoCream®

ProctoCream® may be confused with Proctocort®

Solu-Cortef® may be confused with Solu-Medrol®

International issues:

Hytone® may be confused with Hysone® [Australia]

Nutracort® may be confused with Nitrocor® which is a brand name of nitroglycerin in Chile and Italy

Pronunciation(hye droe KOR ti sone)

U.S. Brand NamesAnucort-HC®; Anusol-HC®; Anusol® HC-1 [OTC]; Aquanil™ HC [OTC]; Beta-HC®; Caldecort® [OTC]; Cetacort® [DSC]; Colocort®; Cortaid® Intensive Therapy [OTC]; Cortaid® Maximum Strength [OTC]; Cortaid® Sensitive Skin [OTC]; Cortef®; Cortenema®; Corticool® [OTC]; Cortifoam®; Cortizone®-10 Maximum Strength [OTC]; Cortizone®-10 Plus Maximum Strength [OTC]; Cortizone®-10 Quick Shot [OTC]; Dermarest Dricort® [OTC]; Dermtex® HC [OTC]; EarSol® HC; Encort™; Hemril®-30; Hydro-Rx; HydroZone Plus [OTC]; Hytone®; IvySoothe® [OTC]; Locoid Lipocream®; Locoid®; Nupercainal® Hydrocortisone Cream [OTC]; Nutracort®; Pandel®; Post Peel Healing Balm [OTC]; Preparation H® Hydrocortisone [OTC]; Procto-Kit™; Procto-Pak™; Proctocort®; ProctoCream® HC; Proctosert; Proctosol-HC®; Proctozone-HC™; Sarnol®-HC [OTC]; Solu-Cortef®; Summer's Eve® SpecialCare™ Medicated Anti-Itch Cream [OTC] [DSC]; Texacort®; Tucks® Anti-Itch [OTC]; Westcort®

Canadian Brand NamesAquacort®; Cortamed®; Cortef®; Cortenema®; Cortifoam™; Emo-Cort®; Hycort™; Hyderm; HydroVal®; Locoid®; Prevex® HC; Sarna® HC; Solu-Cortef®; Westcort®

Pharmacologic CategoryCorticosteroid, Rectal; Corticosteroid, Systemic; Corticosteroid, Topical

Use: Labeled IndicationsManagement of adrenocortical insufficiency; relief of inflammation of corticosteroid-responsive dermatoses (low and medium potency topical corticosteroid); adjunctive treatment of ulcerative colitis

Use: Unlabeled/InvestigationalManagement of septic shock when blood pressure is poorly responsive to fluid resuscitation and vasopressor therapy

Use: DentalTreatment of a variety of oral diseases of allergic, inflammatory, or autoimmune origin

Dosing: AdultsDose should be based on severity of disease and patient response.

Adrenal hyperplasia (congenital): Oral: Initial: 10-20 mg/m^2/day in 3 divided doses; a variety of dosing schedules have been used. **Note:** Inconsistencies have occurred with liquid formulations; tablets may provide more reliable levels. Doses must be individualized by monitoring growth, bone age, and hormonal levels. Mineralocorticoid and sodium supplementation may be required based upon electrolyte regulation and plasma renin activity.

Adrenal insufficiency (acute): I.M., I.V.: Succinate: 100 mg I.V. bolus, then 300 mg/day in divided doses every 8 hours or as a continuous infusion for 48 hours. Once patient is stable change to oral, 50 mg every 8 hours for 6 doses, then taper to 30-50 mg/day in divided doses.

Adrenal insufficiency (chronic)/physiologic replacement: Oral: 20-30 mg/day

Anti-inflammatory or immunosuppressive: Oral, I.M., I.V.: Succinate: 15-240 mg every 12 hours

Dermatosis: Topical: Apply to affected area 2-4 times/day.

Septic shock (unlabeled use): I.V.: 50 mg every 6 hours (or 200-300 mg total daily dose) (Marik, 2008). Taper slowly (for total of 11 days) and do not stop abruptly. **Note:** Fludrocortisone is optional with use of hydrocortisone.

Shock: I.M., I.V.: Succinate: 500 mg to 2 g every 2-6 hours

Status asthmaticus: I.V.: Succinate: 1-2 mg/kg/dose every 6 hours for 24 hours, then maintenance of 0.5-1 mg/kg every 6 hours

Stress dosing (surgery) in patients known to be adrenally-suppressed or on chronic systemic steroids: I.V.:

Minor stress (ie, inguinal herniorrhaphy): 25 mg/day for 1 day

Moderate stress (ie, joint replacement, cholecystectomy): 50-75 mg/day (25 mg every 8-12 hours) for 1-2 days

Major stress (pancreatoduodenectomy, esophagogastrectomy, cardiac surgery): 100-150 mg/day (50 mg every 8-12 hours) for 2-3 days

Rheumatic diseases:

Intralesional, intra-articular, soft tissue injection: Acetate:

Large joints: 25 mg (up to 37.5 mg)

Small joints: 10-25 mg

Tendon sheaths: 5-12.5 mg

Soft tissue infiltration: 25-50 mg (up to 75 mg)

Bursae: 25-37.5 mg

Ganglia: 12.5-25 mg

Ulcerative colitis: Rectal: 10-100 mg 1-2 times/day for 2-3 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDose should be based on severity of disease and patient response.

Adrenal hyperplasia (congenital): Oral: Initial: 10-20 mg/m^2/day in 3 divided doses; a variety of dosing schedules have been used. **Note:** Inconsistencies have occurred with liquid formulations; tablets may provide more reliable levels. Doses must be individualized by monitoring growth, bone age, and hormonal levels. Mineralocorticoid and sodium supplementation may be required based upon electrolyte regulation and plasma renin activity

Adrenal insufficiency (acute): I.M., I.V.:

Infants and young Children: Succinate: 1-2 mg/kg/dose bolus, then 25-150 mg/day in divided doses every 6-8 hours

Older Children: Succinate: 1-2 mg/kg bolus then 150-250 mg/day in divided doses every 6-8 hours

Anti-inflammatory or immunosuppressive:

Infants and Children:

Oral: 2.5-10 mg/kg/day **or** 75-300 mg/m^2/day every 6-8 hours

I.M., I.V.: Succinate: 1-5 mg/kg/day **or** 30-150 mg/m^2/day divided every 12-24 hours

Adolescents: Oral, I.M., I.V.: Succinate: 15-240 mg every 12 hours

Physiologic replacement: Children:

Oral: 0.5-0.75 mg/kg/day **or** 20-25 mg/m^2/day every 8 hours

I.M.: Succinate: 0.25-0.35 mg/kg/day **or** 12-15 mg/m^2/day once daily

Shock: I.M., I.V.: Succinate:

Children: Initial: 50 mg/kg, then repeated in 4 hours and/or every 24 hours as needed

Adolescents: 500 mg to 2 g every 2-6 hours

Status asthmaticus: Children: I.V.: Succinate: 1-2 mg/kg/dose every 6 hours for 24 hours, then maintenance of 0.5-1 mg/kg every 6 hours.

Dermatosis: Topical: Children >2 years: Apply to affected area 2-4 times/day (Buteprate: Apply once or twice daily).

Dosing: Combination Regimens

Prostate cancer:

Estramustine + Docetaxel + Hydrocortisone

Mitoxantrone + Hydrocortisone

Calculations

- Corticosteroid Conversion

Administration: I.V.

Parenteral: Hydrocortisone sodium succinate may be administered by I.M. or I.V. routes.

I.V. bolus: Dilute to 50 mg/mL and administer over 30 seconds or over 10 minutes for doses ≥500 mg

I.V. intermittent infusion: Dilute to 1 mg/mL and give over 20-30 minutes.

Note: Should be administered in a 0.1-1 mg/mL concentration due to stability problems.

Administration: I.V. Detail

pH: Hydrocortisone sodium succinate: 7-8

Administration: OralAdminister with food or milk to decrease GI upset.
Administration: TopicalApply a thin film sparingly to clean, dry skin and rub in gently.
Dietary ConsiderationsSystemic use of corticosteroids may require a diet with increased potassium, vitamins A, B_6, C, D, folate, calcium, zinc, phosphorus, and decreased sodium. Sodium content of 1 g (sodium succinate injection): 47.5 mg (2.07 mEq)
StorageStore at controlled room temperature 20°C to 25°C (68°F to 77°F). Protect from light. Hydrocortisone sodium phosphate and hydrocortisone sodium succinate are clear, light yellow solutions which are heat labile.

Sodium succinate: After initial reconstitution, hydrocortisone sodium succinate solutions are stable for 3 days at room temperature or under refrigeration when protected from light. Stability of parenteral admixture (Solu-Cortef®) at room temperature (25°C) and at refrigeration temperature (4°C) is concentration-dependent:

Stability of concentration 1 mg/mL: 24 hours.

Stability of concentration 2 mg/mL to 60 mg/mL: At least 4 hours.

Reconstitution

Sodium succinate: Reconstitute 100 mg vials with bacteriostatic water (not >2 mL). Act-O-Vial (self-contained powder for injection plus diluent) may be reconstituted by pressing the activator to force diluent into the powder compartment. Following gentle agitation, solution may be withdrawn via syringe through a needle inserted into the center of the stopper. May be administered (I.V. or I.M.) without further dilution.

Solutions for I.V. infusion: Reconstituted solutions may be added to an appropriate volume of compatible solution for infusion. Concentration should generally not exceed 1 mg/mL. However, in cases where administration of a small volume of fluid is desirable, 100-3000 mg may be added to 50 mL of D_5W or NS (stability limited to 4 hours).

Compatibility

Hydrocortisone sodium phosphate: Stable in D_5W, NS, fat emulsion 10%.

Y-site administration: Compatible: Allopurinol, amifostine, aztreonam, cefepime, cladribine, clarithromycin, docetaxel, etoposide, famotidine, filgrastim, fluconazole, fludarabine, gemcitabine, granisetron, melphalan, ondansetron, paclitaxel, piperacillin/tazobactam, teniposide, thiotepa, vinorelbine. **Incompatible:** Sargramostim.

Compatibility in syringe: Compatible: Metoclopramide. **Incompatible:** Doxapram.

Compatibility when admixed: Compatible: Amikacin, amphotericin B, amphotericin B with heparin, bleomycin, dacarbazine, metaraminol, sodium bicarbonate, verapamil. **Variable (consult detailed reference):** Mitoxantrone.

Hydrocortisone sodium succinate: Stable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, $D_{20}W$, LR, ${}^1/_2NS$, NS, fat emulsion 10%.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, aminophylline, amphotericin B cholesteryl sulfate complex, ampicillin, amsacrine, argatroban, atracurium, atropine, aztreonam, betamethasone sodium phosphate, bivalirudin, calcium gluconate, cefepime, chlordiazepoxide, chlorpromazine, cisatracurium, cladribine, cyanocobalamin, cytarabine, dexamethasone sodium phosphate, digoxin, diphenhydramine, docetaxel, dopamine, doxorubicin liposome, droperidol, droperidol and fentanyl, edrophonium, enalaprilat, epinephrine, esmolol, estrogens (conjugated), ethacrynate sodium, etoposide, famotidine, fentanyl, filgrastim, fludarabine, fluorouracil, foscarnet, furosemide, gatifloxacin, gemcitabine, granisetron, heparin, hydralazine, inamrinone, insulin (regular), isoproterenol, kanamycin, lidocaine, linezolid, lorazepam, magnesium sulfate, melphalan, menadiol sodium diphosphate, meperidine, methoxamine, methylergonovine, minocycline, morphine, neostigmine, nicardipine, norepinephrine, ondansetron, oxacillin, oxytocin, paclitaxel, pancuronium, penicillin G potassium, pentazocine, phytonadione, piperacillin/tazobactam, procainamide, prochlorperazine edisylate, propofol, propranolol, pyridostigmine, remifentanil, scopolamine, sodium bicarbonate, succinylcholine, tacrolimus, teniposide, theophylline, thiotepa, trimethaphan camsylate, trimethobenzamide, vecuronium, vinorelbine. **Incompatible:** Ciprofloxacin, diazepam, ergotamine, idarubicin, midazolam, phenytoin, sargramostim. **Variable (consult detailed reference):** Diltiazem, methylprednisolone sodium succinate, promethazine.

Compatibility in syringe: Compatible: Diatrizoate meglumine 52%, diatrizoate sodium 8%, diatrizoate sodium 60%, iohexol, iopamidol, iothalamate meglumine 60%, ioxaglate meglumine 39.3%, ioxaglate sodium 19.6%, metoclopramide, thiopental. **Incompatible:** Doxapram.

Compatibility when admixed: Compatible: Amikacin, aminophylline, amphotericin B, calcium chloride, calcium gluconate, chloramphenicol, clindamycin, corticotropin, daunorubicin, diphenhydramine, dopamine, erythromycin lactobionate, floxacillin, lidocaine, magnesium sulfate, mephentermine, metronidazole, metronidazole with sodium bicarbonate, mitomycin, mitoxantrone, norepinephrine, penicillin G potassium, penicillin G sodium, piperacillin, polymyxin B sulfate, potassium chloride, procaine, sodium bicarbonate, theophylline, thiopental, vancomycin, verapamil, vitamin B complex with C. **Incompatible:** Aminophylline with cephalothin, bleomycin, colistimethate, ephedrine, hydralazine, nafcillin, pentobarbital, phenobarbital, prochlorperazine edisylate, promethazine. **Variable (consult detailed reference):** Amobarbital, ampicillin, cytarabine, dimenhydrinate, furosemide, heparin, kanamycin, metaraminol.

ContraindicationsHypersensitivity to hydrocortisone or any component of the formulation; serious infections, except septic shock or tuberculous meningitis; viral, fungal, or tubercular skin lesions; I.M. administration contraindicated in idiopathic thrombocytopenia purpura

Rectal suspension: Systemic fungal infections; ileocolostomy during the immediate or early postoperative period

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox should be avoided; corticosteroids should not be used to treat ocular herpes simplex. Corticosteroids should not be used for cerebral malaria or viral hepatitis. Close observation is required in patients with latent tuberculosis and/or TB reactivity; restrict use in active TB (only in conjunction with antituberculosis treatment).

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Myopathy: Acute myopathy has been reported with high dose corticosteroids, usually in patients with neuromuscular transmission disorders; may involve ocular and/or respiratory muscles; monitor creatine kinase; recovery may be delayed.

- Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with HF or hypertension; long-term use has been associated with fluid retention and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.

- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.

- Head injury: Increased mortality was observed in patients receiving high-dose I.V. methylprednisolone; high-dose corticosteroids should not be used for the management of head injury.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids.

- Myocardial infarct (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Consider routine eye exams in chronic users.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Elderly: Because of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly in the smallest possible effective dose for the shortest duration.

- Pediatrics: May affect growth velocity; growth should be routinely monitored in pediatric patients.

Dosage form specific issues:

- Topical preparations: Avoid use of topical preparations with occlusive dressings or on weeping or exudative lesions.

Other warnings/precautions:

- Discontinuation of therapy: Withdraw therapy with gradual tapering of dose.

Geriatric ConsiderationsBecause of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly, in the smallest possible dose, and for the shortest possible time.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed with corticosteroids in animal reproduction studies. Hydrocortisone crosses the placenta. Some studies have shown an association between first trimester systemic corticosteroid use and oral clefts; adverse events in the fetus/neonate have been noted in case reports following large doses of systemic corticosteroids during pregnancy. Topical products are not recommended for extensive use, in large quantities, or for long periods of time in pregnant women.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsCorticosteroids are excreted in breast milk and endogenous hydrocortisone is also found in human milk; the effect of maternal hydrocortisone intake is not known.

Adverse Reactions

Systemic:

Frequency not defined:

Cardiovascular: Edema, hypertension

Central nervous system: Delirium, euphoria, hallucinations, headache, insomnia, nervousness, pseudotumor cerebri, psychoses, seizure, vertigo

Dermatologic: Bruising, hyperpigmentation, skin atrophy

Endocrine & metabolic: Adrenal suppression, alkalosis, amenorrhea, Cushing's syndrome, diabetes mellitus, glucose intolerance, growth suppression, hyperglycemia, hyperlipidemia, hypokalemia, pituitary-adrenal axis suppression, sodium and water retention

Gastrointestinal: Abdominal distention, appetite increased, indigestion, nausea, pancreatitis, peptic ulcer, ulcerative esophagitis, vomiting

Hematologic: Leukocytosis (transient)

Neuromuscular & skeletal: Arthralgia, fractures, muscle weakness, osteoporosis

Ocular: Cataracts, glaucoma

Miscellaneous: Avascular necrosis, hypersensitivity reactions, infection, secondary malignancy

Topical:

>10%: Dermatologic: Eczema (12.5%)

1% to 10%: Dermatologic: Pruritus (6%), stinging (2%), dry skin (2%)

<1%: Allergic contact dermatitis, burning, dermal atrophy, folliculitis, HPA axis suppression, hypopigmentation; metabolic effects (hyperglycemia, hypokalemia); striae

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor); **Induces** CYP3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Hydrocortisone interferes with calcium absorption.

Herb/Nutraceutical: St John's wort may decrease hydrocortisone levels. Avoid cat's claw, echinacea (have immunostimulant properties).

Monitoring ParametersBlood pressure, weight, serum glucose, and electrolytes

Reference RangeTherapeutic: AM: 5-25 mcg/dL (SI: 138-690 nmol/L), PM: 2-9 mcg/dL (SI: 55-248 nmol/L) depending on test, assay

Nursing: Physical Assessment/MonitoringMonitor laboratory results, effects and interactions of other medications patient may be taking, response to therapy and adverse effects according to diagnosis, formulation of hydrocortisone, dosage, and extent of time used. Systemic administration and long-term use will require close and frequent monitoring, especially for Cushing's syndrome. Assess for signs of fluid retention. Taper dosage when discontinuing. Assess/teach patient appropriate use, interventions for possible adverse reactions, and symptoms to report. Topical absorption may be minimal.

Monitoring: Lab TestsSerum glucose, electrolytes

Patient EducationSystemic: Take as directed; do not increase doses and do not stop abruptly without consulting prescribed. Dosage of systemic hydrocortisone is usually tapered off gradually. Take oral dose with food to reduce GI upset. Avoid alcohol. Hydrocortisone may cause immunosuppression and mask symptoms of infection; avoid exposure to contagion and notify prescriber of any signs of infection (eg, fever, chills, sore throat, injury) and notify dentist or surgeon (if necessary) that you are taking this medication. You may experience increased appetite, indigestion, or increased nervousness. Report any sudden weight gain (>5 lb/week), swelling of extremities or respiratory difficulty, abdominal pain, severe vomiting, black or tarry stools, fatigue, anorexia, weakness, or unusual mood swings. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Topical: Before applying, wash area gently and thoroughly. Apply a thin film to cleansed area and rub in gently until medication vanishes. Avoid use of occlusive dressings over topical application unless directed by a prescriber. Avoid use on weeping or exudative lesions. Avoid exposing affected area to sunlight; you will be more sensitive and severe sunburn may occur. Consult prescriber if breast-feeding.

Rectal: Gently insert suppository as high as possible with gloved finger while lying down. Avoid injury with long or sharp fingernails. Remain in resting position for 10 minutes after insertion.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol, rectal, as acetate (Cortifoam®): 10% (15 g) [90 mg/applicator]

Cream, rectal, as acetate (Nupercainal® Hydrocortisone Cream): 1% (30 g) [strength expressed as base]

Cream, rectal, as base:

Cortizone®-10: 1% (30 g) [contains aloe]

Preparation H® Hydrocortisone: 1% (27 g)

Cream, topical, as acetate: 0.5% (9 g, 30 g, 60 g) [available with aloe]; 1% (30 g, 454 g) [available with aloe]

Cream, topical, as base: 0.5% (30 g); 1% (1.5 g, 30 g, 114 g, 454 g); 2.5% (20 g, 30 g, 454 g)

Anusol-HC®: 2.5% (30 g) [contains benzyl alcohol]

Caldecort®: 1% (30 g) [contains aloe vera gel]

Cortaid® Intensive Therapy: 1% (60 g)

Cortaid® Maximum Strength: 1% (15 g, 30 g, 40 g, 60 g) [contains aloe vera gel and benzyl alcohol]

Cortaid® Sensitive Skin: 0.5% (15 g) [contains aloe vera gel]

Cortizone®-10 Maximum Strength: 1% (15 g, 30 g, 60 g) [contains aloe]

Cortizone®-10 Plus Maximum Strength: 1% (30 g, 60 g) [contains vitamins A, D, E and aloe]

Dermarest® Dricort®: 1% (15 g, 30 g)

HydroZone Plus, Proctocort®, Procto-Pak™: 1% (30 g)

Hytone®: 2.5% (30 g, 60 g)

IvySoothe®: 1% (30 g) [contains aloe]

Post Peel Healing Balm: 1% (23 g)

ProctoCream® HC: 2.5% (30 g) [contains benzyl alcohol]

Procto-Kit™: 1% (30 g) [packaged with applicator tips and finger cots]; 2.5% (30 g) [packaged with applicator tips and finger cots]

Proctosol-HC®, Proctozone-HC™: 2.5% (30 g)

Summer's Eve® SpecialCare™ Medicated Anti-Itch Cream: 1% (30 g) [DSC]

Cream, topical, as butyrate (Locoid®, Locoid Lipocream®): 0.1% (15 g, 45 g)

Cream, topical, as probutate (Pandel®): 0.1% (15 g, 45 g, 80 g)

Cream, topical, as valerate (Westcort®): 0.2% (15 g, 45 g, 60 g)

Gel, topical, as base (Corticool®): 1% (45 g)

Injection, powder for reconstitution, as sodium succinate:

A-Hydrocort®: 100 mg [contains monobasic sodium phosphate 0.8 mg, anhydrous dibasic sodium phosphate 8.73 mg; strength expressed as base]

Solu-Cortef®: 100 mg, 250 mg, 500 mg, 1 g [diluent contains benzyl alcohol; strength expressed as base]

Lotion, topical, as base: 1% (120 mL); 2.5% (60 mL)

Aquanil™ HC: 1% (120 mL)

Beta-HC®, Cetacort® [DSC], Sarnol®-HC: 1% (60 mL)

HydroZone Plus: 1% (120 mL)

Hytone®: 2.5% (60 mL)

Nutracort®: 1% (60 mL, 120 mL); 2.5% (60 mL, 120 mL)

Lotion, topical, as butyrate:

Locoid®: 0.1% (60 mL)

Ointment, topical, as acetate: 1% (30 g) [strength expressed as base; available with aloe]

Anusol® HC-1: 1% (21 g) [strength expressed as base]

Cortaid® Maximum Strength: 1% (15 g, 30 g) [strength expressed as base]

Ointment, topical, as base: 0.5% (30 g); 1% (30 g, 454 g); 2.5% (20 g, 30 g, 454 g)

Cortizone®-10 Maximum Strength: 1% (30 g, 60 g)

Hytone®: 2.5% (30 g) [DSC]

Ointment, topical, as butyrate (Locoid®): 0.1% (15 g, 45 g)

Ointment, topical, as valerate (Westcort®): 0.2% (15 g, 45 g, 60 g)

Powder, for prescription compounding [micronized]:

Hydro-Rx: USP (10 g, 25 g, 50 g, 100 g)

Powder, for prescription compounding, as acetate [micronized]: USP (10 g, 25 g, 50 g)

Solution, otic, as base (EarSol® HC): 1% (30 mL) [contains alcohol 44%, benzyl benzoate, yerba santa]

Solution, topical, as base (Texacort®): 2.5% (30 mL) [contains ethanol 48%]

Solution, topical, as butyrate (Locoid®): 0.1% (20 mL, 60 mL) [contains alcohol 50%]

Solution, topical spray, as base:

Cortaid® Intensive Therapy: 1% (60 mL) [contains alcohol]

Cortizone®-10 Quick Shot: 1% (44 mL) [contains benzyl alcohol]

Dermtex® HC: 1% (52 mL) [contains menthol 1%]

Suppository, rectal, as acetate: 25 mg (12s, 24s, 100s)

Anucort-HC®, Tucks® Anti-Itch: 25 mg (12s, 24s, 100s) [strength expressed as base; Anucort-HC® *renamed* Tucks® Anti-Itch]

Anusol-HC®, Proctosol-HC®: 25 mg (12s, 24s)

Encort™, Proctocort®: 30 mg (12s)

Hemril®-30, Proctosert: 30 mg (12s, 24s)

Suspension, rectal, as base: 100 mg/60 mL (7s)

Colocort®, Cortenema®: 100 mg/60 mL (1s, 7s)

Tablet, as base: 20 mg

Cortef®: 5 mg, 10 mg, 20 mg

Generic AvailableYes: Excludes acetate foam, butyrate cream and ointment, gel as base, otic drops as base, probutate cream, sodium succinate injection

Pricing: U.S. (www.drugstore.com)

Cream (Anusol-HC)

2.5% (30): $80.49

Cream (Hydrocortisone)

0.5% (28.35): $4.99

1% (15): $8.99

1% (28): $11.99

2.5% (30): $13.67

Cream (Hydrocortisone Butyrate)

0.1% (45): $42.99

Cream (Hydrocortisone Valerate)

0.2% (15): $19.99

0.2% (45): $33.99

0.2% (60): $44.99

Cream (Locoid)

0.1% (15): $67.49

0.1% (45): $172.71

Cream (Locoid Lipocream)

0.1% (15): $60.94

0.1% (45): $176.35

0.1% (60): $223.10

Cream (Pandel)

0.1% (15): $111.99

Cream (Proctocort)

1% (28.35): $96.41

Cream (ProctoCream-HC)

2.5% (30): $59.40

Cream (Proctozone-HC)

2.5% (30): $22.99

Cream (Westcort)

0.2% (15): $21.99

Enema (Colocort)

100 mg/60 mL (420): $71.99

Enema (Hydrocortisone)

100 mg/60 mL (420): $70.01

Foam (Cortifoam)

90 mg (15): $119.84

Lotion (Hydrocortisone)

1% (118): $15.99

2.5% (59): $39.99

2.5% (60): $33.99

Lotion (Hytone)

2.5% (60): $63.99

Ointment (Hydrocortisone)

2.5% (28.35): $13.68

Ointment (Hydrocortisone Acetate)

1-1% (30): $11.99

Ointment (Hydrocortisone Valerate)

0.2% (15): $24.18

0.2% (45): $26.47

0.2% (60): $44.90

Ointment (Hytone)

2.5% (30): $42.99

Ointment (Locoid)

0.1% (15): $62.04

0.1% (45): $164.29

Ointment (Tucks Anti-Itch)

1% (19.8): $4.99

Ointment (Westcort)

0.2% (15): $25.20

0.2% (45): $46.97

0.2% (60): $55.00

Solution (Locoid)

0.1% (20): $79.28

0.1% (60): $219.43

Solution (Texacort)

2.5% (30): $65.08

Suppository (Anucort-HC)

25 mg (24): $12.99

Suppository (Hydrocortisone Acetate)

25 mg (12): $14.99

Suppository (Proctosert HC)

30 mg (12): $44.99

Tablets (Cortef)

5 mg (50): $27.31

10 mg (30): $27.29

20 mg (30): $38.49

Tablets (Hydrocortisone)

20 mg (30): $12.99

Mechanism of ActionDecreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability

Pharmacodynamics/Kinetics

Onset of action:

Hydrocortisone acetate: Slow

Hydrocortisone sodium succinate (water soluble): Rapid

Duration: Hydrocortisone acetate: Long

Absorption: Rapid by all routes, except rectally

Metabolism: Hepatic

Half-life elimination: Biologic: 8-12 hours

Excretion: Urine (primarily as 17-hydroxysteroids and 17-ketosteroids)

Related Information

- Corticosteroids
- Management of Drug Extravasations

Pharmacotherapy PearlsHydrocortisone base topical cream, lotion, and ointments in concentrations of 0.25%, 0.5%, and 1% may be OTC or prescription depending on the product labeling.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia and nervousness are common; rare reports of delirium, euphoria, hallucinations, and mood swings

Mental Health: Effects on Psychiatric TreatmentBarbiturates may increase the metabolism of hydrocortisone; lithium has been used to treat mood swings associated with hydrocortisone

Cardiovascular ConsiderationsLong-term steroid therapy is associated with a fluid retention and hypertension. Glucocorticoid agents have some mineralocorticoid activity with consequent hemodynamic effects. Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. In discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia.

Oral and intravenous steroid therapy in patients with heart failure should be administered cautiously with special attention given to signs and symptoms of fluid retention.

Although glucocorticoids can provide relief from pericarditis postmyocardial infarctions, these drugs may cause thinning of the developing scar and myocardial rupture.

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Hydrocortisone is a long-acting corticosteroid with minimal sodium-retaining potential.

Evidence-Based Information:

Neuromuscular Effects: ICU-acquired paresis was recently studied in 5 ICUs (3 medical and 2 surgical ICUs) at 4 French hospitals. All ICU patients without pre-existing neuromuscular disease admitted from March 1999 through June 2000 were evaluated (De Jonghe, 2002). Each patient had to be mechanically ventilated for ≥7 days and was screened daily for awakening. The first day the patient was considered awake was Study Day 1. Patients with severe muscle weakness on Study Day 7 were considered to have ICU-acquired paresis. Among the 95 patients who were evaluated, about 25% developed ICU-acquired paresis. Independent predictors included: female gender, the number of days with ≥2 organ dysfunction, and administration of corticosteroids. Further studies may be required to verify and characterize the association between the development of ICU-acquired paresis and use of corticosteroids. Concurrent use of a corticosteroid and muscle relaxant appears to increase the risk of certain ICU myopathies; avoid or administer the corticosteroid at the lowest dose possible.

Adrenal Insufficiency: Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. When discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that the steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia. Patients on long-term steroid supplementation will require higher corticosteroid doses when subject to stress (eg, trauma, surgery, severe infection). Guidelines for glucocorticoid replacement during various surgical procedures have been published (Coursin, 2002; Salem, 1994).

Septic Shock: Annane, et al (2002) randomized 300 septic shock patients to either hydrocortisone (50 mg I.V. push every 6 hours) and fludrocortisone (50 mcg tablet daily via nasogastric tube) or matching placebos for 7 days. The mean Simplified Acute Physiology Score II (SAPS II) was 57 ± 19 in the placebo group and 60 ± 19 in the active treatment group. The Logistic Organ Dysfunction score was 9 ± 3 in the placebo group and 9 ± 3 in the active treatment group. In patients who did not appropriately respond to corticotropin (nonresponders), there were significantly fewer deaths in the active treatment group. Vasopressor therapy was withdrawn more frequently in this subset of the active treatment group. Adverse events were similar in both groups.

In the CORTICUS trial (Sprung, 2008), 484 septic shock patients were randomized within 72 hours of onset to receive either hydrocortisone (50 mg I.V. push every 6 hours) or placebo for 5 days followed by a 6-day taper. The primary endpoint was 28 day mortality in patients who did not respond to corticotropin. The SAPS II score in the treatment group was 49.5 ± 17.8 and 48.6 ± 16.7 in the placebo group. The Sequential Organ Failure Assessment scores were 10.6 ± 3.4 in the treatment group and 10.6 ± 3.2 in the placebo group. Different than the Annane study, in the patients who did not respond to corticotropin, there was no mortality difference at 28 days; 39.2% (95% CI: 30.5-47.9) mortality in the hydrocortisone group and 36.1 % (95% CI: 26.9-45.3, P=0.69) mortality in the placebo group. A trend towards increased incidence of superinfection was noted in hydrocortisone patients. New septic shock episodes, hyperglycemia, and hypernatremia were more frequent in the hydrocortisone group. Hydrocortisone did not improve survival in this population of septic shock patients regardless of corticotropin response.

The 2008 Surviving Sepsis Campaign Guidelines suggest the following: Intravenous hydrocortisone be given only to adult septic shock patients after blood pressure is identified to be poorly responsive to fluid resuscitation and vasopressor therapy (Grade 2C); ACTH stimulation test not be used to identify the subset of adults with septic shock who should receive hydrocortisone (Grade 2B); patients with septic shock should not receive dexamethasone if hydrocortisone is available (Grade 2B); the addition of fludrocortisone if hydrocortisone is not available and the steroid that is substituted does not have significant mineralocorticoid activity (Grade 2C); doses of corticosteroids comparable to >300 mg hydrocortisone daily not be used in severe sepsis or septic shock for the purpose of treating septic shock (Grade 1A). They also recommend corticosteroids not be administered for the treatment of sepsis in the absence of shock. There is, however, no contraindication to continuing maintenance steroid therapy or to using stress dose steroids if the patient's endocrine or corticosteroid administration history warrants (Grade 1D).

The 2008 Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients suggest a diagnosis of critical illness related corticosteroid insufficiency can be made by a delta cortisol level (after 250 mcg cosyntropin) of <9 mcg/dL or a random cortisol <10 mcg/dL (Grade 2B). However, they recommend **against** the use of ACTH stimulation test to determine if septic shock or ARDS patients should receive steroid therapy (Grade 2B). They recommend to consider using hydrocortisone in septic shock patients who have responded poorly to resuscitation and vasopressors (Grade 2B) and glucocorticoid treatment should be tapered slowly and not stopped abruptly (Grade 2B). Dexamethasone is **not** recommended for the treatment of septic shock or ARDS (Grade 1B). Fludrocortisone therapy is considered optional (Grade 2B).

Index Terms A-hydroCort; Compound F; Cortisol; Hemorrhoidal HC; Hydrocortisone Acetate; Hydrocortisone Butyrate; Hydrocortisone Probutate; Hydrocortisone Sodium Succinate; Hydrocortisone Valerate

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International Brand NamesAlfacort (AR, PY); Alphaderm (LU); Aphilan (FR); Aphilan Dermangeaisons (FR); Apocort (FI); Aquanil HC (MX); Berlison (BR); Biocort (ZA); Calacort (ID); Colifoam (AT, AU, DE, DK, FI, GB, GR, IE, IT, PT, SE); Colofoam (FR); Coripen (UY); Cort Dome (CO, EC); Cort-Dome (CR, DO, GT, HN, NI, PA, SV); Cortef (AE, BH, CY, EG, HN, HR, HU, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Cortef Cream (AU); Cortema (TW); Cortic-DS (AU); Cortifoam (IL, NO); Cortril (LU, TW); Dermacrin HC Lotion (KP); DHAcort (HK, MY); Dilucort (ZA); Eczacort (PH); Efcortelan (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZM, ZW); Efficort Lipo (MX); Ekzemsalbe (AT); Eldecort (AE, BH, CY, EG, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Enkacort (ID); Entofoam (IN); Ficortril (DE, SE); Flebocortid (MX); Flkeboconadrol (MX); Harond (KP); Hidrotex (EC); Hidrotisona (AR); Hipoge (CN); Hovicor (PH); Hycortisone (PK); Hydrocort (SG); Hydrocortison (HN, HU); Hydrocortison Dispersa (LU); Hydrocortison Streuli (CH); Hydrocortison-POS N (DE); Hydrocortisone Roussel (LU); Hydrocortisonum (NL, PL); Hydrocortisyl (AE, BH, CY, EG, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Hydrocutan (DE); Hydrokortison (EE); Hydrosone (HK); Hydrotopic (PH); Hyproderm HC (LU); Hysone (KP); Hytisone (TH); Lacticare HC (PH, TW); Lactisona (ES); Lanacort (IL); Laticort (PL); Laticort (BG); Lexacorton (ID); Locoid (PL, TR); Medrocil (AR); Microsona (MX, UY); Mylocort (ZA); Nositrol (MX); Nutracort (CR, DO, FI, GT, HN, MX, NI, PA, PE, SV, VE); Ophticor H (PL); Pannocort (BE); Paxosit (MX); Procortin (PL); Proctocort (FR); Sigmacort (AU, HK); Siquent Hycor Eye Ointment (AU); Skincalm (NZ); Solhidrol (MX); Solu Cortef (BD, CL, CZ, JP, RU); Solu-Cortef (BB, BM, BS, BZ, GY, JM, LU, SR, TT); Squibb-HC (AU); Steroderm (ID); Wycort (IN)

Hydroflumethiazide and Reserpine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(hye droe floo meth EYE a zide & re SER peen)

Canadian Brand NamesSalutensin®

Pharmacologic CategoryCentral Monoamine-Depleting Agent; Diuretic, Thiazide

Use: Labeled IndicationsManagement of hypertension

Dosing: AdultsHypertension: Oral: 1 tablet once or twice daily (as determined by individual titration)

Dosing: ElderlyRefer to adult dosing.

RestrictionsNot available in U.S.

Contraindications

Based on **hydroflumethiazide** component: Hypersensitivity to hydroflumethiazide or any component of the formulation, thiazides, or sulfonamide-derived drugs; anuria; renal decompensation

Based on **reserpine** component: Hypersensitivity to reserpine or any component of the formulation; active peptic ulcer disease, ulcerative colitis, history of mental depression (especially with suicidal tendencies); MAO inhibitors

Allergy Considerations

- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: With high doses of reserpine, significant mental depression, anxiety, or psychosis may occur (uncommon at dosages <0.25 mg/day).
- Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, and hyponatremia can occur with hydroflumethiazide.
- Orthostatic hypotension: Reserpine may cause orthostatic hypotension; use with caution in patients at risk of hypotension or in patients where transient hypotensive episodes would be poorly tolerated (cardiovascular disease or cerebrovascular disease).
- Photosensitivity: Photosensitization may occur.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Asthma: Use reserpine with caution in patients with asthma.
- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Gallstones: Use reserpine with caution in patients with gallstones.
- Gastrointestinal disease: Use reserpine with caution in patients with inflammatory bowel disease or history of peptic ulcer disease.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydroflumethiazide.
- Hepatic impairment: Use hydroflumethiazide with caution in patients with severe hepatic dysfunction. In cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.
- Hypokalemia: Use hydroflumethiazide with caution in patients with hypokalemia; correct before initiating therapy.
- Renal impairment: Use reserpine with caution in patients with impaired renal function; avoid hydroflumethiazide in severe renal disease (ineffective).
- Systemic lupus erythematosus (SLE): Hydroflumethiazide can cause SLE exacerbation or activation.

Special populations:

- Elderly: Use with caution in the elderly.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Electroshock therapy: Discontinue reserpine 7 days before electroshock therapy.

Pregnancy Risk FactorC

Adverse ReactionsSee individual agents.

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amphetamines: Gastrointestinal Acidifying Agents may decrease the serum concentration of Amphetamines. *Risk C: Monitor therapy*

Beta-Blockers: Reserpine may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Iobenguane I 123: Reserpine may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

MAO Inhibitors: May enhance the adverse/toxic effect of Rauwolfia Alkaloids. Existing MAOI therapy can result in paradoxical effects of added rauwolfia alkaloids (eg, excitation, hypertension). *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Tetrabenazine: Reserpine may enhance the adverse/toxic effect of Tetrabenazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Salutensin®: Hydroflumethiazide 50 mg and reserpine 0.125 mg

Salutensin-Demi®: Hydroflumethiazide 25 mg and reserpine 0.125 mg

Generic AvailableYes

Pharmacodynamics/KineticsSee individual agents.

Pharmacotherapy PearlsNot available in U.S.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, nightmares, nervousness, drowsiness, fatigue, mental depression, parkinsonism, dull sensorium, syncope, paradoxical anxiety

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity, monitor serum lithium levels; contraindicated in those with depression or undergoing ECT; avoid concurrent use with MAO inhibitors

Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for hydroflumethiazide and reserpine combination therapy may include improved compliance and synergistic reductions in blood pressure with an accompanied reduction in side effects. Thiazide therapy improves cardiovascular outcomes in patients with hypertension. Reserpine is infrequently used alone for the treatment of hypertension due to possible side effects. See Cardiovascular Considerations for individual agents.

Index TermsReserpine and Hydroflumethiazide

References

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Moser M and Black HR, “The Role of Combination Therapy in the Treatment of Hypertension,” *Am J Hypertens*, 1998, 11(6 Pt 2):73S-8S, 95S-100S.[PubMed 9655566]

International Brand NamesSalutensin (CA)

HYDROmorphone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Hydromorphone Tablets: Recall Due to Potential for Oversized Tablets – December 2008

Ethex Corporation, in conjunction with the Federal Drug Administration (FDA), is notifying practitioners of a voluntary nationwide recall of a single lot of hydromorphone 2 mg tablets. The tablets are being recalled due to the potential for oversized tablets which may contain increased amounts of the active ingredient. In addition, as a precaution, KV Pharmaceutical (the parent company of Ethex Corporation) is voluntarily suspending shipments of all FDA-approved drug products in a tablet form so the company may address manufacturing issues that have come to management's attention.

For additional information, please refer to the MedWatch Alert at: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Hydromorphone

Medication Safety Issues

Sound-alike/look-alike issues:

Dilaudid® may be confused with Demerol®, Dilantin®

HYDROmorphone may be confused with morphine; significant overdoses have occurred when hydromorphone products have been inadvertently administered instead of morphine sulfate. Commercially available prefilled syringes of both products looks similar and are often stored in close proximity to each other. **Note:** Hydromorphone 1 mg oral is approximately equal to morphine 4 mg oral; hydromorphone 1 mg I.V. is approximately equal to morphine 5 mg I.V.

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Dilaudid®, Dilaudid-HP®: Extreme caution should be taken to avoid confusing the highly-concentrated (Dilaudid-HP®) injection with the less-concentrated (Dilaudid®) injectable product.

Significant differences exist between oral and I.V. dosing. Use caution when converting from one route of administration to another.

Pronunciation(hye droe MOR fone)

U.S. Brand NamesDilaudid-HP®; Dilaudid®

Canadian Brand NamesDilaudid-HP-Plus®; Dilaudid-HP®; Dilaudid-XP®; Dilaudid®; Dilaudid® Sterile Powder; Hydromorph Contin®; Hydromorph-IR®; Hydromorphone HP; Hydromorphone HP® 10; Hydromorphone HP® 20; Hydromorphone HP® 50; Hydromorphone HP® Forte; Hydromorphone Hydrochloride Injection, USP; PMS-Hydromorphone

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled IndicationsManagement of moderate-to-severe pain

Use: Unlabeled/InvestigationalAntitussive

Dosing: Adults

Antitussive (unlabeled use): Oral: 1 mg every 3-4 hours as needed

Acute pain (moderate to severe):Note: These are guidelines and do not represent the maximum doses that may be required in all patients. Doses should be titrated to pain relief/prevention. Doses should be titrated to appropriate analgesic effects; when changing routes of administration, note that oral doses are <50% as effective as parenteral doses (may be only one-fifth as effective).

Oral:

Initial: Opiate-naive: 2-4 mg every 3-6 hours as needed; elderly/debilitated patients may require lower doses; patients with prior opiate exposure may require higher initial doses

Usual dosage range: 2-8 mg every 3-4 hours as needed

I.V.: Initial: Opiate-naive: 0.2-0.6 mg every 2-3 hours as needed; patients with prior opiate exposure may tolerate higher initial doses

Critically-ill patients (unlabeled dose): 0.7-2 mg (based on 70 kg patient) every 1-2 hours as needed. **Note:** More frequent dosing may be needed (eg, mechanically-ventilated patients).

Continuous infusion: Usual dosage range: 0.5-1 mg/hour (based on 70 kg patient) or 7-15 mcg/kg/hour

Patient-controlled analgesia (PCA): (Opiate-naive: Consider lower end of dosing range)

Usual concentration: 0.2 mg/mL

Demand dose: Usual: 0.1-0.2 mg; range: 0.05-0.5 mg

Lockout interval: 5-15 minutes

4-hour limit: 4-6 mg

Epidural:

Bolus dose: 1-1.5 mg

Infusion concentration: 0.05-0.075 mg/mL

Infusion rate: 0.04-0.4 mg/hour

Demand dose: 0.15 mg

Lockout interval: 30 minutes

I.M., SubQ: **Note:** I.M. use may result in variable absorption and a lag time to peak effect.

Initial: Opiate-naive: 0.8-1 mg every 4-6 hours as needed; patients with prior opiate exposure may require higher initial doses

Usual dosage range: 1-2 mg every 3-6 hours as needed

Rectal: 3 mg every 4-8 hours as needed

Chronic pain: **Note:** Patients taking opioids chronically may become tolerant and require doses higher than the usual dosage range to maintain the desired effect. Tolerance can be managed by appropriate dose titration. There is no optimal or maximal dose for hydromorphone in chronic pain. The appropriate dose is one that relieves pain throughout its dosing interval without causing unmanageable side effects.

Controlled release formulation (Hydromorph Contin®, not available in U.S.): Oral: 3-30 mg every 12 hours. **Note:** A patient's hydromorphone requirement should be established using prompt release formulations; conversion to long acting products may be considered when chronic, continuous treatment is required. Higher dosages should be reserved for use only in opioid-tolerant patients.

Dosing: ElderlyDoses should be titrated to appropriate analgesic effects. When changing routes of administration, note that oral doses are less than half as effective as parenteral doses (may be only 20% as effective).

Pain: Oral: 1-2 mg every 4-6 hours

Antitussive: Refer to adult dosing.

Dosing: Pediatric

Acute pain (moderate to severe): **Note:** These are guidelines and do not represent the maximum doses that may be required in all patients. Doses should be titrated to pain relief/prevention.

Children ≥6 months and <50 kg:

Oral: 0.03-0.08 mg/kg/dose every 3-4 hours as needed

I.V.: 0.015 mg/kg/dose every 3-6 hours as needed

Children >50 kg: Refer to adult dosing.

Antitussive (unlabeled use): Oral:

Children 6-12 years: 0.5 mg every 3-4 hours as needed

Children >12 years: 1 mg every 3-4 hours as needed

Dosing: Hepatic ImpairmentDose adjustment should be considered.

Calculations

- Fentanyl Transdermal Conversion
- Opioid Agonist Conversion

Administration: I.M.May be given SubQ or I.M.; vial stopper contains latex

Administration: I.V.For IVP, must be given slowly over 2-3 minutes (rapid IVP has been associated with an increase in side effects, especially respiratory depression and hypotension)

Administration: I.V. DetailpH: 4.0-5.5

Administration: OralHydromorph Contin®: Capsule should be swallowed whole; do not crush or chew; contents may be sprinkled on soft food and swallowed

Administration: OtherMay be given SubQ or I.M.

StorageStore injection and oral dosage forms at 15°C to 30°C (59°F to 86°F). Protect tablets from light. A slightly yellowish discoloration has not been associated with a loss of potency.

CompatibilityStable in D_5LR, D_5W, $D_5{}^1/_2NS$, D_5NS, LR, ${}^1/_2NS$, NS.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, amikacin, amsacrine, aztreonam, cefamandole, cefepime, cefoperazone, cefotaxime, cefoxitin, ceftazidime, ceftizoxime, cefuroxime, chloramphenicol, cisatracurium, cisplatin, cladribine, clindamycin, cyclophosphamide, cytarabine, diltiazem, dobutamine, docetaxel, dopamine, doxorubicin, doxorubicin liposome, doxycycline, epinephrine, erythromycin lactobionate, etoposide, famotidine, fentanyl, filgrastim, fludarabine, foscarnet, furosemide, gatifloxacin, gemcitabine, gentamicin, granisetron, heparin, kanamycin, labetalol, linezolid, lorazepam, magnesium sulfate, melphalan, methotrexate, metronidazole, midazolam, milrinone, morphine, nafcillin, nicardipine, nitroglycerin, norepinephrine, ondansetron, oxacillin, paclitaxel, penicillin G potassium, piperacillin, piperacillin/tazobactam, propofol, ranitidine, remifentanil, tacrolimus, teniposide, thiotepa, ticarcillin, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, vecuronium, vinorelbine. **Incompatible:** Amphotericin B cholesteryl sulfate complex, diazepam, minocycline, phenobarbital, phenytoin, sargramostim, tetracycline, thiopental. **Variable (consult detailed reference):** Ampicillin, cefazolin.

Compatibility in syringe: Compatible: Albuterol, atropine, bupivacaine, ceftazidime, chlorpromazine, cimetidine, dimenhydrinate, diphenhydramine, fentanyl, glycopyrrolate, haloperidol, hydroxyzine, lorazepam, midazolam, pentazocine, pentobarbital, prochlorperazine mesylate, promethazine, ranitidine, scopolamine, thiethylperazine, trimethobenzamide. **Incompatible:** Ampicillin, diazepam, hyaluronidase, phenobarbital, phenytoin. **Variable (consult detailed reference):** Cefazolin, dexamethasone sodium phosphate, ketorolac, prochlorperazine edisylate.

Compatibility when admixed: Compatible: Bupivacaine, fluorouracil, midazolam, ondansetron, promethazine, verapamil. **Incompatible:** Sodium bicarbonate, thiopental. **Variable (consult detailed reference):** Tetracaine.

RestrictionsC-II

ContraindicationsHypersensitivity to hydromorphone, any component of the formulation; acute or severe asthma, severe respiratory depression (in absence of resuscitative equipment or ventilatory support); severe CNS depression; pregnancy (prolonged use or high doses at term); obstetrical analgesia

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Abuse/misuse/diversion: See "Other warnings/precautions" below.
- Injection: See "Dosage form specific issues" below.

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydrocodone, levorphanol, oxycodone, oxymorphone).
- Seizures: Myoclonus and seizures have been reported with high doses.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Obesity: Use with caution in patients who are morbidly obese.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Psychoses: Use with caution in patients with toxic psychoses.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

Dosage form specific issues:

- Controlled release capsules: Should only be used when continuous analgesia is required over an extended period of time. Controlled release products are not to be used on an "as needed" (PRN) basis.

- Injection: **[U.S. Boxed Warning]: Extreme caution should be taken to avoid confusing the highly-concentrated (Dilaudid-HP®) injection with the less-concentrated (Dilaudid®) injectable product.** Dilaudid-HP® should only be used in patients who are opioid-tolerant.

- Sodium metabisulfite: Some dosage forms contain trace amounts of sodium metabisulfite which may cause allergic reactions in susceptible individuals.

Other warnings/precautions:

- Abuse/misuse/diversion: **[U.S. Boxed Warning]: Hydromorphone has a high potential for abuse;** healthcare provider should be alert to problems of abuse, misuse, and diversion.

- I.M. administration: Variable absorption and a lag time to peak effect may result from I.M. use.

- Optimal regimen: An opioid-containing analgesic regimen should be tailored to each patient's needs and based upon the type of pain being treated (acute versus chronic), the route of administration, degree of tolerance for opioids (naive versus chronic user), age, weight, and medical condition. The optimal analgesic dose varies widely among patients; doses should be titrated to pain relief/prevention.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsElderly may be particularly susceptible to the CNS depressant and constipating effects of narcotics.
Pregnancy Risk FactorC/D (prolonged use or high doses at term)
Pregnancy ConsiderationsHydromorphone was teratogenic in some, but not all, animal studies; however, maternal toxicity was also reported. Hydromorphone crosses the placenta. Chronic opioid use during pregnancy may lead to a withdrawal syndrome in the neonate. Symptoms include irritability, hyperactivity, loss of sleep pattern, abnormal crying, tremor, vomiting, diarrhea, weight loss, or failure to gain weight.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsOther opioid analgesics can be found in breast milk; specific data for hydromorphone is not available. The possibility of sedation or respiratory depression in the nursing infant should be considered.
Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, flushing of face, hyper-/hypotension, palpitation, peripheral vasodilation, syncope, tachycardia

Central nervous system: Agitation, chills, CNS depression, dizziness, drowsiness, dysphoria, euphoria, fatigue, hallucinations, headache, increased intracranial pressure, insomnia, lightheadedness, mental depression, nervousness, restlessness, sedation, seizure

Dermatologic: Pruritus, rash, urticaria

Endocrine & metabolic: Antidiuretic hormone release

Gastrointestinal: Anorexia, biliary tract spasm, constipation, diarrhea, nausea, paralytic ileus, stomach cramps, taste perversion, vomiting, xerostomia

Genitourinary: Ureteral spasm, urinary retention, urinary tract spasm, urination decreased

Hepatic: LFTs increased

Local: Pain at injection site (I.M.), wheal/flare over vein (I.V.)

Neuromuscular & skeletal: Myoclonus, paresthesia, trembling, tremor, weakness

Ocular: Blurred vision, diplopia, miosis, nystagmus

Respiratory: Apnea, bronchospasm, dyspnea, laryngospasm, respiratory depression

Miscellaneous: Diaphoresis, histamine release, physical and psychological dependence

Oncology: VesicantNo
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic

doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsSome quinolones may produce a false-positive urine screening result for opiates using commercially-available immunoassay kits. This has been demonstrated most consistently for levofloxacin and ofloxacin, but other quinolones have shown cross-reactivity in certain assay kits. Confirmation of positive opiate screens by more specific methods should be considered.

Monitoring ParametersPain relief, respiratory and mental status, blood pressure

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for additive or adverse interactions. Monitor for effectiveness of pain relief, adverse reactions, and signs of overdose at beginning of therapy and periodically during long-term use. May cause physical and/or psychological dependence. Monitor blood pressure, CNS and respiratory status, and degree of sedation at beginning of therapy and at regular intervals with long-term use. For inpatients, implement safety measures. Assess knowledge/teach patient appropriate use (if self-administered). Teach patient to monitor for adverse reactions, adverse reactions to report, and appropriate interventions to reduce side effects. Discontinue slowly after prolonged use.

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause dizziness, drowsiness, impaired coordination, or blurred vision (use caution when driving, climbing stairs, or changing position - rising from sitting or lying to standing, or when engaging in tasks requiring alertness until response to drug is known); loss of appetite, nausea, or vomiting (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help; if unresolved, consult prescriber about use of stool softeners). Report chest pain, slow or rapid heartbeat, acute dizziness, or persistent headache; swelling of extremities or unusual weight gain; changes in urinary elimination; acute headache; back or flank pain or spasms; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Capsule, controlled release:

Hydromorph Contin® [CAN]: 3 mg, 6 mg, 12 mg, 18 mg, 24 mg, 30 mg [not available in U.S.]

Injection, powder for reconstitution, as hydrochloride:

Dilaudid-HP®: 250 mg [may contain trace amounts of sodium bisulfite]

Injection, solution, as hydrochloride: 1 mg/mL (1 mL); 2 mg/mL (1 mL, 20 mL); 4 mg/mL (1 mL)

Dilaudid®: 1 mg/mL (1 mL); 2 mg/mL (1 mL, 20 mL) [20 mL size contains edetate sodium; vial stopper contains latex]; 4 mg/mL (1 mL)

Injection, solution, as hydrochloride [preservative free]: 10 mg/mL (1 mL, 5 mL, 50 mL)

Dilaudid-HP®: 10 mg/mL (1 mL, 5 mL) [contains sodium metabisulfate]

Dilaudid-HP®: 10 mg/mL (50 mL) [contains natural rubber/natural latex in packaging, sodium metabisulfate]

Liquid, oral, as hydrochloride:

Dilaudid®: 1 mg/mL (480 mL) [may contain trace amounts of sodium bisulfite]

Powder, for prescription compounding: 100% (15 grain)

Suppository, rectal, as hydrochloride: 3 mg

Dilaudid®: 3 mg (6s)

Tablet, as hydrochloride: 2 mg, 4 mg, 8 mg

Dilaudid®: 2 mg, 4 mg, 8 mg (8 mg tablets may contain trace amounts of sodium bisulfite)

Generic AvailableYes: Excludes capsule, liquid, powder for injection

Pricing: U.S. (www.drugstore.com)

Solution (Hydromorphone HCl)

4 mg/mL (20): $33.33

Suppository (Hydromorphone HCl)

3 mg (20): $159.17

Tablets (Dilaudid)

2 mg (20): $23.99

4 mg (20): $29.99

8 mg (100): $197.41

Tablets (Hydromorphone HCl)

2 mg (20): $15.33

4 mg (20): $15.99

8 mg (20): $27.99

Mechanism of Action Binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; causes cough supression by direct central action in the medulla; produces generalized CNS depression

Pharmacodynamics/Kinetics

Onset of action: Analgesic: Immediate release formulations:

Oral: 15-30 minutes

Peak effect: Oral: 30-60 minutes

Duration: Immediate release formulations: 4-5 hours

Absorption: I.M.: Variable and delayed

Distribution: V_d: 4 L/kg

Protein binding: ~8% to 19%

Metabolism: Hepatic via glucuronidation; to inactive metabolites

Bioavailability: 62%

Half-life elimination: Immediate release formulations: 1-3 hours

Excretion: Urine (primarily as glucuronide conjugates)

Related Information

- Narcotic / Opioid Analgesics

Pharmacotherapy Pearls Equianalgesic doses: Morphine 10 mg I.M. = hydromorphone 1.5 mg I.M.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Drowsiness and dizziness are common; may cause nervousness or restlessness; may rarely cause hallucinations or depression

Mental Health: Effects on Psychiatric Treatment Concurrent use with psychotropics may produce additive sedation

Anesthesia and Critical Care Concerns/Other Considerations When developing a therapeutic plan for pain control, scheduled, intermittent opioid dosing or continuous infusion is preferred over the “as needed” regimen. The 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) recommend fentanyl in patients who need immediate pain relief because of its rapid onset of action; fentanyl or hydromorphone is preferred in patients who are hypotensive or have renal dysfunction. Morphine or hydromorphone is recommended for intermittent, scheduled therapy. Both have a longer duration of action requiring less frequent administration. Hydromorphone does not have any active metabolites, has less protein binding than other opiates and does not cause histamine release. If the patient has required high-dose analgesia or has used for a prolonged period (~7 days), taper dose to prevent withdrawal; monitor for signs and symptoms of withdrawal.

Index Terms Dihydromorphinone; Hydromorphone Hydrochloride

References

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International Brand NamesDilaudid (AT, AU); Dilaudid-HP (AU); Dilid (KP); Dolonovag (AR); Jurnista (DE, DK, EE, ES); Liberaxim (MX); Palladon Retardkaps (DE); Palladon (CH, DK, FI, NL, NO, SE); Palladon OD (SE); Palladon Retard (CH); Palladone (BE, EE, ES, GB, HN, IE, IL); Palladone SR (GB, IE); Sophidone (FR)

Hydroquinone

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English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Eldopaque® may be confused with Eldoquin®

Eldoquin® may be confused with Eldopaque®

Eldopaque Forte® may be confused with Eldoquin Forte®

Eldoquin Forte® may be confused with Eldopaque Forte®

Pronunciation(HYE droe kwin one)
U.S. Brand NamesAclaro PD™; Alphaquin HP®; Claripel™ [DSC]; Dermarest® Skin Correction Cream Plus [OTC]; Eldopaque Forte®; Eldopaque® [OTC]; Eldoquin Forte®; Eldoquin® [OTC]; EpiQuin™ Micro; Esoterica® Regular [OTC]; Glyquin-XM™; Glyquin®; Lustra-AF™; Lustra®; Melanex®; Melpaque HP®; Melquin HP®; Melquin-3®; NeoStrata® AHA [OTC]; Nuquin HP®; Palmer's® Skin Success Eventone® Fade Cream [OTC]; Solaquin Forte®; Solaquin® [OTC]
Canadian Brand NamesEldopaque®; Eldoquin®; Glyquin® XM; Lustra®; NeoStrata® HQ; Solaquin Forte®; Solaquin®; Ultraquin™
Pharmacologic CategoryDepigmenting Agent
Use: Labeled IndicationsGradual bleaching of hyperpigmented skin conditions
Dosing: AdultsBleaching: Topical: Apply a thin layer and rub in twice daily.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Administration: TopicalFor external use only; avoid contact with eyes
ContraindicationsHypersensitivity to hydroquinone or any component of the formulation; sunburn, depilatory usage
Warnings/Precautions

Other warnings/precautions:

- Appropriate use: Limit application to area no larger than face and neck or hands and arms.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown
Adverse ReactionsFrequency not defined.

Dermatologic: Dermatitis, dryness, erythema, stinging, inflammatory reaction, sensitization

Local: Irritation

Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringSee application directions above. When applied to large areas or for extensive periods of time, monitor for adverse reactions. Assess knowledge/teach patient appropriate application and use and adverse symptoms to report.
Patient EducationUse exactly as directed; do not overuse. Therapeutic effect may take several weeks. Test response by applying to small area of unbroken skin and check in 24 hours; if irritation or blistering occurs do not use. Avoid contact with eyes. Do not apply to open wounds or weeping areas. Before using, wash and dry area gently. Apply a thin film to affected area and rub in gently. Avoid direct sunlight or use sunblock or protective clothing to prevent repigmentation. Report swelling, redness, rash, itching, signs of infection, worsening of condition, or lack of healing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, topical: 4% (30 g) [may contain sodium metabisulfite]

Alphaquin HP®: 4% (30 g, 60 g)

Eldoquin®: 2% (15 g, 30 g)

Eldoquin Forte®: 4% (30 g) [contains sodium metabisulfite]

EpiQuin™ Micro: 4% (30 g) [contains benzyl alcohol and sodium metabisulfite]

Esoterica® Regular: 2% (85 g) [contains sodium bisulfite]

Lustra®: 4% (30 g) [contains sodium metabisulfite]

Melquin HP®: 4% (15 g, 30 g) [contains sodium metabisulfite]

Cream, topical [with sunscreen]: 4% (30 g) [may contain sodium metabisulfite]

- Claripel™: 4% (30 g, 45 g) [contains sodium metabisulfite] [DSC]
- Dermarest® Skin Correcting Cream Plus: 2% (85 g) [contains aloe vera, sodium bisulfite]
- Eldopaque®: 2% (15 g, 30 g)
- Eldopaque Forte®: 4% (30 g) [contains sodium metabisulfite]
- Glyquin®: 4% (30 g)
- Glyquin-XM™: 4% (30 g)
- Lustra-AF™: 4% (30 g, 60 g) [contains sodium metabisulfite]
- Melpaque HP®: 4% (15 g, 30 g) [contains sodium metabisulfite; sunblocking cream base]
- Nuquin HP®: 4% (15 g, 30 g, 60 g) [contains sodium metabisulfite]
- Palmer's® Skin Success Eventone® Fade Cream: 2% (81 g, 132 g) [contains sodium sulfite; available in regular, oily skin, and dry skin formulas]
- Solaquin®: 2% (30 g)
- Solaquin Forte®: 4% (30 g) [contains sodium metabisulfite]

Emulsion, topical:

- Aclaro PD™: 4% (42.5 g) [contains benzyl alcohol; with sunscreen]

Gel, topical:

- NeoStrata® AHA: 2% (45 g) [contains glycolic acid 10%, sodium bisulfite, and sodium sulfite]

Gel, topical [with sunscreen]: 4% (30 g)

- Nuquin HP: 4% (15 g, 30 g) [contains sodium bisulfite]
- Solaquin Forte®: 4% (30 g) [contains sodium metabisulfite]

Solution, topical: 3% (30 mL) [DSC]

- Melanex®, Melquin-3®: 3% (30 mL) [contains alcohol]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Cream (Alphaquin HP)

- 4-5-7.5% (28.4): $42.99

Cream (Claripel)

- 4% (28): $96.93

Cream (Eldopaque Forte)

- 4% (28.35): $61.99

Cream (EpiQuin Micro)

- 4% (30): $110.99

Cream (Glyquin)

- 4% (28): $69.69

Cream (Glyquin XM)

- 4% (28): $72.96

Cream (Lustra)

- 4% (56.8): $130.53

Cream (Lustra-AF)

- 4% (56.8): $139.99

Cream (Melpaque HP)

- 4% (28.35): $33.99

Cream (Melquin HP)

4% (30): $35.99

Cream (Nuquin HP)

4% (30): $31.99

Cream (Solaquin Forte)

4% (28.35): $55.50

Emulsion (Aclaro)

4% (48.2): $137.82

Emulsion (Aclaro PD)

4% (42.5): $104.99

Gel (Hydroquinone-Sunscreens)

4% (28.35): $39.99

Solution (Melquin 3)

3% (30): $17.99

Mechanism of ActionProduces reversible depigmentation of the skin by suppression of melanocyte metabolic processes, in particular the inhibition of the enzymatic oxidation of tyrosine to DOPA (3,4-dihydroxyphenylalanine); sun exposure reverses this effect and will cause repigmentation.

Pharmacodynamics/KineticsOnset and duration of depigmentation produced by hydroquinone varies among individuals

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsHydroquinol; Quinol

International Brand NamesAldoquin 2 (CO); Clariderm (TH); Clariderm DS (TH); Claripel (AR); Clasifel (PY, UY); Crema Blanca Bustillos (MX); Delanin (TH); Eldopaque (AE, BH, CY, EG, GR, HK, IL, IQ, IR, JO, KW, LB, LY, OM, PH, QA, SA, SY, YE); Eldopaque Forte (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, MY, OM, PH, QA, SA, SY, TW, YE); Eldoquin (AE, BH, CR, CY, EG, GT, HK, HN, IL, IQ, IR, JO, KW, LB, LY, MX, NI, OM, PA, PH, PK, PT, QA, SA, SV, SY, YE); Eldoquin Cream (NZ); Eldoquin Forte (AE, BH, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, MY, OM, PH, QA, SA, SY, YE); Equinon (ID); Equinon Forte (ID); Eslite (IN); Esomed (IL); Etnoderm (CN); Gentleclean (TW); Ginomi (KP); Melanox (ID); Melquin HP (KP); Melquine (TW); Pharquinon (VE); Pigmentasa (ES); Polyquin Forte (SG); Skinox (ID); Solaquin (AE, BH, BR, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, MY, OM, QA, SA, SY, YE); Solaquin Forte (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, MY, OM, QA, SA, SY, YE); Zumae (TW)

Hydroxocobalamin

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English

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Pronunciation(hye droks oh koe BAL a min)

U.S. Brand NamesCyanokit®

Pharmacologic CategoryAntidote; Vitamin, Water Soluble

Use: Labeled IndicationsTreatment of pernicious anemia, vitamin B_{12} deficiency due to dietary deficiencies or malabsorption diseases, inadequate secretion of intrinsic factor, and inadequate utilization of B_{12} (eg, during neoplastic treatment); diagnostic agent for Schilling test

Cyanokit®: Treatment of cyanide poisoning (known or suspected)

Use: Unlabeled/InvestigationalNeuropathies

Dosing: Adults

Vitamin B_{12} deficiency: I.M.: 30 mcg/day for 5-10 days, followed by 100-200 mcg/month

Note: Larger doses may be required in critically-ill patients or if patient has neurologic disease, an infectious disease, or hyperthyroidism.

Schilling test: I.M.: 1000 mcg

Cyanide toxicity (Cyanokit®): I.V.: Initial: 5 g as single infusion; may repeat a second 5 g dose depending on severity of poisoning and clinical response. Maximum cumulative dose: 10 g. **Note:** If suspected, antidotal therapy must be given immediately.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricVitamin B_{12} deficiency: I.M.: 100 mcg once daily for 2 or more weeks (total dose: 1-5 mg); maintenance: 30-50 mcg/month

Administration: I.M.Solution for I.M. injection: Administer 1000 mcg/mL solution I.M. only

Administration: I.V.Cyanokit®: Administer by I.V. infusion over 15 minutes; if repeat dose needed, administer second dose over 15 minutes to 2 hours

Storage

Solution for I.M. injection: Store at 20°C to 25°C (68°F to 77°F). Protect from light.

I.V. infusion (Cyanokit®): Prior to reconstitution, store at 15°C to 30°C (59°F to 86°F).

Temperature variation exposure allowed for transport of lyophilized form:

Usual transport: ≤15 days at 5°C to 40°C (41°F to 104°F)

Desert transport: ≤4 days at 5°C to 60°C (41°F to 140°F)

Freezing/defrosting cycles: ≤15 days at -20°C to 40°C (-4°F to 104°F)

Following reconstitution, store up to 6 hours at ≤40°C (104°F); do not freeze. Discard any remaining solution after 6 hours.

ReconstitutionI.V. infusion (Cyanokit®): Reconstitute each 2.5 g vial with 100 mL of NS using provided sterile transfer spike. If NS unavailable, may use LR or D_5W. Invert or rock each vial for at least 30 seconds prior to infusion; do not shake. Do not use if solution is **not** dark red.

CompatibilityStable in NS (preferred), LR, D_5W

Y-site administration: Incompatible with ascorbic acid, blood products, sodium nitrite, sodium thiosulfate.

Compatibility when admixed: Incompatible with diazepam, dopamine, dobutamine, fentanyl, nitroglycerin, pentobarbital, propofol, thiopental.

ContraindicationsHypersensitivity to hydroxocobalamin, cyanocobalamin, cobalt, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Hypertension: Cyanide poisoning: Increased blood pressure (≥180 mm Hg systolic or ≥110 mm Hg diastolic) is associated with infusion; elevations usually noted at beginning of infusion, peak toward the end of infusion and return to baseline within 4 hours of infusion.
- Photosensitivity: May cause photosensitivity; avoid direct sunlight while skin remains discolored.

Disease-related concerns:

- Anemia: Appropriate use: Neurologic manifestations of vitamin B_{12} deficiency will not be prevented with folic acid unless vitamin B_{12} is also given; spinal cord degeneration might also occur when folic acid is used as a substitute for vitamin B_{12} in anemia prevention.
- Polycythemia vera: Vitamin B_{12} deficiency masks signs of polycythemia vera; vitamin B_{12} administration may unmask this condition.

Dosage form specific concerns:

- Cyanokit®: Use caution or consider alternatives in patients with known allergic reactions, including anaphylaxis to hydroxocobalamin or cyanocobalamin. Collection of pretreatment blood cyanide concentrations does not preclude administration and should not delay administration in the emergency management of highly suspected or confirmed cyanide toxicity. Pretreatment levels may be useful as post infusion levels may be inaccurate. Treatment of cyanide poisoning should include decontamination and supportive therapy. Safety and efficacy have not been established in children.

- Solution for I.M. injection: Treatment of severe vitamin B_{12} megaloblastic anemia may result in thrombocytosis and severe hypokalemia, sometimes fatal, due to intracellular potassium shift upon anemia resolution. Use caution in folic acid deficient megaloblastic anemia; administration of vitamin B_{12} alone is not a substitute for folic acid and might mask true diagnosis. Blunted therapeutic response to vitamin B_{12} may occur in certain conditions (eg, infection, uremia, concurrent iron or folic acid deficiency) or in patients on medications with bone marrow suppressant properties (eg, chloramphenicol). Approved for use as I.M. injection only.

Geriatric ConsiderationsEvidence exists that people, particularly elderly, whose serum cobalamin concentrations are <500 pg/mL, should receive replacement parenteral therapy. This recommendation is based upon neuropsychiatric disorders and cardiovascular disorders associated with lower sodium cobalamin concentrations.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies are insufficient to determine the effect, if any, on pregnancy or fetal development. There are no adequate and well-controlled studies in pregnant women. Data on the use of hydroxocobalamin in pregnancy for the treatment of cyanide poisoning and cobalamin defects are limited.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

I.M. injection: Frequency not defined:

Dermatologic: Exanthema (transient), itching

Gastrointestinal: Diarrhea (mild, transient)

Local: Injection site pain

Miscellaneous: Anaphylaxis

I.V. infusion (Cyanokit®):

>10%:

Cardiovascular: Blood pressure increased (18% to 28%; systolic ≥180 mm Hg or diastolic ≥110 mm Hg)

Central nervous system: Headache (6% to 33%)

Dermatologic: Erythema (94% to 100%; may last up to 2 weeks), rash (predominantly acneiform; 20% to 44%; can appear 7-28 days after administration and usually resolves within a few weeks)

Gastrointestinal: Nausea (6% to 11%)

Genitourinary: Chromaturia (100%; may last up to 5 weeks after administration)

Hematologic: Lymphocytes decreased (8% to 17%)

Local: Infusion site reaction (6% to 39%)

Frequency not defined:

Cardiovascular: Chest discomfort, heart rate increased/decreased, hot flashes, peripheral edema

Central nervous system: Dizziness, memory impairment, restlessness

Dermatologic: Pruritus, urticaria

Gastrointestinal: Abdominal discomfort, diarrhea, dyspepsia, dysphagia, hematochezia, vomiting

Ocular: Irritation, redness, swelling

Respiratory: Dry throat, dyspnea, throat tightness

Miscellaneous: Allergic reaction (including anaphylaxis)

Postmarketing and/or case reports: Angioneurotic edema

Drug InteractionsThere are no known significant interactions.
Test InteractionsThe following values may be affected, *in vitro*, following hydroxocobalamin 5 g dose. Interference following hydroxocobalamin 10 g dose can be expected to last up to an additional 24 hours. **Note:** Extent and duration of interference dependant on analyzer used and patient variability.

Falsely elevated:

Basophils, hemoglobin, MCH, and MCHC [duration: 12-16 hours]

Albumin, alkaline phosphatase, cholesterol, creatinine, glucose, total protein, and triglycerides [duration: 24 hours]

Bilirubin [duration: up to 4 days]

Urinalysis: Glucose, protein, erythrocytes, leukocytes, ketones, bilirubin, urobilinogen, nitrite [duration: 2-8 days]

Falsely decreased: ALT and amylase [duration: 24 hours]

Unpredictable:

AST, CK, CKMB, LDH, phosphate, and uric acid [duration: 24 hours]

PT (quick or INR) and aPTT [duration: 24-48 hours]

Urine pH [duration: 2-8 days]

May also interfere with colorimetric tests

Monitoring ParametersVitamin B_{12}, hematocrit, hemoglobin, reticulocyte count, red blood cell counts, folate and iron levels should be obtained prior to treatment and periodically during treatment.

Cyanide toxicity: Blood pressure and heart rate during and after infusion, serum lactate levels, venous-arterial PO_2 gradient. Pretreatment levels may be useful as post infusion levels may be inaccurate.

Megaloblastic anemia: In addition to normal hematological parameters, serum potassium and platelet counts should be monitored during therapy, particularly in the first 48 hours of treatment.

Reference RangeBlood cyanide levels may be used for diagnosis confirmation; however, reliable levels require prompt testing and proper storage conditions.

Cyanide level:

Tachycardia/flushing: 0.5-1 mg/L

Obtundation: 1-2.5 mg/L

Coma: 2.5-3 mg/L

Death: >3 mg/L

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests at beginning of therapy and periodically with long-term therapy. Assess knowledge/teach patient appropriate administration (injection technique and needle disposal), appropriate nutrition, and adverse symptoms to report. Cyanide toxicity: Monitor blood pressure and heart rate during infusion.

Monitoring: Lab TestsVitamin B_{12}, hematocrit, hemoglobin, reticulocyte count, red blood cell counts, folate and iron levels should be obtained prior to treatment and periodically during treatment.

Cyanide toxicity: Blood pressure and heart rate during and after infusion, serum lactate levels, venous-arterial PO_2 gradient. Pretreatment levels may be useful as post infusion levels may be inaccurate.

Megaloblastic anemia: In addition to normal hematological parameters, serum potassium and platelet counts should be monitored during therapy, particularly in the first 48 hours of treatment.

Patient EducationUse exactly as directed. Pernicious anemia may require monthly injections for life. Report skin rash; swelling, pain, or redness in extremities; or acute persistent diarrhea. Cyanokit®: May cause headache, redness of skin (can last up to 2 weeks; avoid exposure to sun while skin is red), skin lesions (can appear 7-28 days after infusion), and red urine (can last for 5 weeks). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 1000 mcg/mL (30 mL)

Injection, powder for reconstitution:

Cyanokit®: 2.5 g (2 vials) [provided in a kit which also contains one I.V. infusion set]

Generic AvailableYes: Excludes powder for injection

Mechanism of ActionHydroxocobalamin (vitamin B_{12a}) is a precursor to cyanocobalamin (vitamin B_{12}). Cyanocobalamin acts as a coenzyme for various metabolic functions, including fat and carbohydrate metabolism and protein synthesis, used in cell replication and hematopoiesis. In the presence of cyanide, each hydroxocobalamin molecule can bind one cyanide ion by displacing it for the hydroxo ligand linked to the trivalent cobalt ion, forming cyanocobalamin.

Pharmacodynamics/KineticsFollowing I.V. administration of Cyanokit®:

Protein binding: Significant; forms various cobalamin-(III) complexes

Half-life elimination: 26-31 hours

Excretion: Urine (50% to 60% within initial 72 hours)

Pharmacotherapy PearlsExpert advice from a regional poison control center for appropriate use may be obtained (1-800-222-1222). Cyanide is a clear colorless gas or liquid with a faint bitter almond odor. Cyanide reacts with trivalent ions in cytochrome oxidase in the mitochondria leading to histotoxic hypoxia and lactic acidosis. Signs and symptoms of cyanide toxicity include headache, altered mental status, dyspnea, mydriasis, chest tightness, nausea, vomiting, tachycardia/hypertension (initially), bradycardia/hypotension (later), seizures, cardiovascular collapse, or coma.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsVitamin B_{12a}

References

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International Brand NamesAquo-Cytobion (DE); B!1!2-Depot-Vicotrat (DE); B12 Depot-Rotexmedica (DE); B12-Depot-Hevert (DE); B12-Depot-Vicotrat (DE); Behepan (SE); Benzoral (AR); Berubi-long (DE); Bradirubra (IT); Cobalin-H (GB); Cobalparen (DE); Cobalvit (IT); Cohemin Depot (FI); Cyanokit (FR); Dodecavit (FR); Doleven (JP); Dosixbe (AR); Forta B 5.000 (BE); Forta B12 (BE, LU); Hepavit (AT); Hidroxuber (ES); Hydrocobamine (NL); Hydroxo 5.000 (FR, LU); Idroxocobalamina (IT); Lisoneurin (AR); Lophakomp-B 12 Depot (DE); Megamilbedoce (ES); Neo-Cytamen (AU, GB, IE, IT, NZ); Novidroxin (DE); Novobedouze (BE, LU); OH B12 (IT); OHB12 (PT); Rasedon 500 (JP); Rubranova (BR); Twelvmin-s (JP); Vibeden (DK); Vitamin B!1!2-Depot-Injektopas (DE); Vitamin B12 Depot (NO); Vitarubin-Depot (CH); Westhidroxo (MX)

Hydroxyamphetamine and Tropicamide

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(hye droks ee am FET a meen & troe PIK a mide)
U.S. Brand NamesParemyd®
Pharmacologic CategoryAdrenergic Agonist Agent, Ophthalmic
Use: Labeled IndicationsShort-term pupil dilation for diagnostic procedures and exams
Dosing: AdultsMydriasis/cycloplegia: Ophthalmic: Instill 1-2 drops into conjunctival sac(s)
Dosing: ElderlyRefer to adult dosing.
StorageStore at 15°C to 25°C (59°F to 77°F). Protect from light.
ContraindicationsHypersensitivity to hydroxyamphetamine, tropicamide, or any component of the formulation; angle-closure glaucoma or those with narrow angles where dilation of the pupil may precipitate angle-closure glaucoma
Allergy Considerations

- Amphetamine Allergy

Warnings/Precautions

Disease-related concerns:

- Glaucoma: Use with caution in patients with glaucoma; increased ocular pressure may occur following administration.

Special populations:

- Elderly: Use with caution in the elderly; monitor closely for increased intraocular pressure following use.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: For ophthalmic use only.

- Monitoring: Patients with hypertension, hyperthyroidism, diabetes, or cardiac disease should be monitored after instillation.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined (as reported with Paremyd® or similar medications):

Cardiovascular: Hypotension, MI, pallor, tachycardia, ventricular fibrillation

Central nervous system: Behavioral disturbances, headache, psychotic reactions

Gastrointestinal: Dry mouth, nausea, vomiting

Neuromuscular & skeletal: Muscle rigidity

Ocular: Blurred vision, intraocular pressure increased, photophobia, transient stinging

Miscellaneous: Allergic reaction, cardiorespiratory collapse, vasomotor collapse

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic: Hydroxyamphetamine hydrobromide 1% and tropicamide 0.25% (15 mL) [contains benzalkonium chloride]

Generic AvailableNo
ManufacturerAkorn, Inc
Mechanism of ActionHydroxyamphetamine hydrobromide is an indirect acting sympathomimetic agent which causes the release of norepinephrine from adrenergic nerve terminals, resulting in mydriasis. Tropicamide is a parasympatholytic agent which produces mydriasis and paralysis by blocking the sphincter muscle in the iris and the ciliary muscle.
Pharmacodynamics/Kinetics

Onset of action: 15 minutes

Duration: 3 hours; complete recovery usually occurs in 6-8 hours, but may take up to 24 hours

Time to peak: 60 minutes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsHydroxyamphetamine Hydrobromide and Tropicamide; Tropicamide and Hydroxyamphetamine

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Hydroxychloroquine

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English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

> Hydroxychloroquine may be confused with hydrocortisone
>
> Plaquenil® may be confused with Platinol®

Pronunciation(hye droks ee KLOR oh kwin)

U.S. Brand NamesPlaquenil®

Canadian Brand NamesApo-Hydroxyquine®; Gen-Hydroxychloroquine; Plaquenil®; Pro-Hydroxyquine

Pharmacologic CategoryAminoquinoline (Antimalarial)

Use: Labeled IndicationsSuppression and treatment of acute attacks of malaria; treatment of systemic lupus erythematosus (SLE) and rheumatoid arthritis

Use: Unlabeled/InvestigationalPorphyria cutanea tarda, polymorphous light eruptions

Dosing: Adults

Note: Hydroxychloroquine sulfate 200 mg is equivalent to 155 mg hydroxychloroquine base and 250 mg chloroquine phosphate. Second-line alternative treatment (chloroquine is preferred).

Chemoprophylaxis of malaria: 310 mg (base) weekly on same day each week; begin 2 weeks before exposure. Continue for 4 weeks (per CDC guidelines) after leaving endemic area; if suppressive therapy is not begun prior to the exposure, double the initial dose and give in 2 doses, 6 hours apart for 8 weeks.

Malaria, acute attack: 620 mg (base) initially, followed by 310 mg (base) at 6, 24, and 48 hours

Rheumatoid arthritis: Initial: 310-465 mg/day (base) taken with food or milk; increase dose gradually until optimum response level is reached; usually after 4-12 weeks dose should be reduced by $^1/_2$ to a maintenance dose of 155-310 mg/day (base)

Lupus erythematosus: 310 mg (base) every day or twice daily for several weeks-months depending on response; 155-310 mg/day (base) for prolonged maintenance therapy

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Note: Hydroxychloroquine sulfate 200 mg is equivalent to 155 mg hydroxychloroquine base and 250 mg chloroquine phosphate.

Chemoprophylaxis of malaria: Oral: 5 mg/kg (base) once weekly; should not exceed the recommended adult dose. Begin 2 weeks before exposure and continue for 4-6 weeks after leaving endemic area. If suppressive therapy is not begun prior to the exposure, double the initial dose and give in 2 doses, 6 hours apart for 8 weeks.

Malaria, acute attack: Oral: 10 mg/kg (base) initially, followed by 5 mg/kg (base) at 6, 24, and 48 hours.

Juvenile rheumatoid arthritis (JRA) or SLE (unlabeled use): Oral: 3-5 mg/kg/day (base) divided 1-2 times/day; avoid exceeding 7 mg/kg/day.

Dosing: Hepatic ImpairmentUse with caution; dosage adjustment may be necessary.

Administration: OralTake with food or milk.

Dietary ConsiderationsMay be taken with food or milk.

Extemporaneously PreparedA 25 mg/mL hydroxychloroquine sulfate suspension is made by removing the coating off of fifteen 200 mg hydroxychloroquine sulfate tablets with a towel moistened with alcohol; tablets are ground to a fine powder and levigated to a paste with 15 mL of Ora-Plus® suspending agent; add an additional 45 mL of suspending agent and levigate until a uniform mixture is obtained; qs ad to 120 mL with sterile water for irrigation; a 30 day expiration date is recommended, although stability testing has not been performed

> Pesko LJ, “Compounding: Hydroxychloroquine,” *Am Druggist*, 1993, 207:57.

ContraindicationsHypersensitivity to hydroxychloroquine, 4-aminoquinoline derivatives, or any component of the formulation; retinal or visual field changes attributable to 4-aminoquinolines; long-term use in children

Allergy Considerations

- QuiNIDine/QuiNINE Derivative Allergy

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Cardiovascular: Rare cardiomyopathy has been associated with long-term use of hydroxychloroquine.

- Hematologic: Aminoquinolines have been associated with rare hematologic reactions, including agranulocytosis, aplastic anemia, and thrombocytopenia; monitoring (CBC) is recommended in prolonged therapy.

- Neuromuscular: Myopathy, neuromyopathy, and progressive weakness have been associated with aminoquinoline derivatives; muscle strength (especially proximal muscles) should be assessed periodically during prolonged therapy.

- Ophthalmic effects: Hydroxychloroquine has been associated with important adverse effects on vision, including loss of visual acuity, macular pigmentary changes, and loss of foveal reflex. Monitoring is recommended in long-term therapy.

Disease-related concerns:

- G6PD deficiency: Use with caution in patients with known G6PD; use of 4-aminoquinolines such as chloroquine has been associated with hemolysis and renal impairment in this population.

- Hepatic impairment: Use with caution in patients with hepatic impairment, alcoholism, or concurrent therapy with hepatotoxic agents.

- Porphyria: Use with caution in patients with porphyria; may exacerbate disease.

- Psoriasis: Use with caution in patients with psoriasis; may exacerbate disease.

Special populations:

- Pediatrics: Use caution due to increased sensitivity to aminoquinolones; long-term use in children is contraindicated.

Other warnings/precautions:

- Appropriate use: Malaria: Hydroxychloroquine is not effective against chloroquine-resistant strains of *P. falciparum*.

- Experienced physician: **[U.S. Boxed Warning]: Should be prescribed by physicians familiar with its use.**

Geriatric ConsiderationsNo specific recommendations for dosing.

Pregnancy ConsiderationsMalaria infection in pregnant women may be more severe than in nonpregnant women. Therefore, pregnant women and women who are likely to become pregnant are advised to avoid travel to malaria-risk areas. Hydroxychloroquine is recommended as an alternative treatment of pregnant women for uncomplicated malaria in chloroquine-sensitive regions. Women exposed to hydroxychloroquine for the treatment of rheumatoid arthritis or systemic lupus erythematosus during pregnancy may be enrolled in the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases Study pregnancy registry (877-311-8972).

LactationEnters breast milk (AAP considers “compatible”)

Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiomyopathy (rare, relationship to hydroxychloroquine unclear)

Central nervous system: Ataxia, dizziness, emotional changes, headache, irritability, lassitude, nervousness, nightmares, psychosis, seizure, vertigo

Dermatologic: Alopecia, angioedema, bleaching of hair, pigmentation changes (skin and mucosal; black-blue color), rash (acute generalized exanthematous pustulosis, erythema annulare centrifugum, exfoliative dermatitis, lichenoid, maculopapular, morbilliform, purpuric, Stevens-Johnson syndrome, urticarial), urticaria

Endocrine & metabolic: Weight loss

Gastrointestinal: Abdominal cramping, anorexia, diarrhea, nausea, vomiting

Hematologic: Agranulocytosis, aplastic anemia, hemolysis (in patients with glucose-6-phosphate deficiency), leukopenia, thrombocytopenia

Hepatic: Abnormal liver function/hepatic failure (isolated cases)

Neuromuscular & skeletal: Myopathy, palsy, or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups (may be associated with mild sensory changes, loss of deep tendon reflexes, and abnormal nerve conduction)

Ocular: Abnormal color vision, abnormal retinal pigmentation, atrophy, attenuation of retinal arterioles, decreased visual acuity, disturbance in accommodation, keratopathy, corneal changes/deposits (visual disturbances, blurred vision, photophobia [reversible on discontinuation]), macular edema, nystagmus, optic disc pallor/atrophy, pigmentary retinopathy, retinopathy (early changes reversible [may progress despite discontinuation if advanced]), scotoma

Otic: Deafness, tinnitus

Miscellaneous: Exacerbation of porphyria and nonlight sensitive psoriasis

Respiratory: Bronchospasm, respiratory failure (myopathy-related)

Drug Interactions

Anthelmintics: Aminoquinolines (Antimalarial) may decrease the serum concentration of Anthelmintics. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): Antimalarial Agents may increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Beta-Blockers: Aminoquinolines (Antimalarial) may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Carteolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Cardiac Glycosides: Aminoquinolines (Antimalarial) may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Mefloquine: Aminoquinolines (Antimalarial) may enhance the adverse/toxic effect of Mefloquine. Specifically, the risk for QTc-prolongation and the risk for convulsions may be increased. Mefloquine may increase the serum concentration of Aminoquinolines (Antimalarial). Management: Avoid concurrent use, and delay administration of mefloquine until at least 12 hours after the last dose of an aminoquinoline antimalarial when possible. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to GI irritation).

Monitoring ParametersOphthalmologic exam at baseline and every 3 months during prolonged therapy (including visual acuity, slit-lamp, fundoscopic, and visual field exam); CBC at baseline and periodically; muscle strength (especially proximal, as a symptom of neuromyopathy) during long-term therapy

Nursing: Physical Assessment/MonitoringEvaluate need for cautions prior to beginning therapy. Assess potential for interactions with other pharmacological agents patient may be taking. Assess results of periodic CBC and liver function tests, therapeutic effectiveness (according to purpose for therapy), and adverse response (eg, deep tendon reflexes, muscle weakness). Teach patient appropriate use, possible side effects/interventions (necessity for periodic ophthalmic examinations with long-term therapy), and adverse symptoms to report.

Monitoring: Lab TestsCBC, liver function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. It is important to complete full course of therapy, which may take up to 6 months for full effect. May be taken with meals to decrease GI upset and bitter aftertaste. Avoid alcohol. You should have regular ophthalmic exams (every 4-6 months) if using this medication over extended periods. You may experience skin discoloration (blue/black), hair bleaching, or skin rash. If you have psoriasis, you may experience exacerbation. You may experience dizziness, headache, nervousness, abnormal color vision, or lightheadedness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or increased sensitivity to sunlight (wear dark glasses and protective clothing, use sunblock, and avoid direct exposure to sunlight). Report weakness, numbness, tingling or tremors in muscles; vision changes; rash or itching; persistent diarrhea or GI disturbances; change in hearing acuity or ringing in the ears; chest pain or palpitation; CNS changes; unusual fatigue; easy bruising or bleeding, or any other persistent adverse reactions. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as sulfate: 200 mg [equivalent to 155 mg base]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Plaquenil)

200 mg (60): $173.58

Mechanism of ActionInterferes with digestive vacuole function within sensitive malarial parasites by increasing the pH and interfering with lysosomal degradation of hemoglobin; inhibits locomotion of neutrophils and chemotaxis of eosinophils; impairs complement-dependent antigen-antibody reactions

Pharmacodynamics/Kinetics

Onset of action: Rheumatic disease: May require 4-6 weeks to respond

Absorption: Rapid and complete

Protein binding: 55%

Metabolism: Hepatic

Half-life elimination: 32-50 days

Time to peak: Rheumatic disease: Several months

Excretion: Urine (as metabolites and unchanged drug); may be enhanced by urinary acidification

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or nervousness

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine

Index TermsHydroxychloroquine Sulfate

References

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Seguin P, Camus C, Leroy JP, et al, “Respiratory Failure Associated With Hydroxychloroquine Neuromyopathy,” *Eur Neurol*, 1995, 35(4):236-7. [PubMed 7671986]

Wang R, “Hydroxychloroquine Cardiotoxicity,” *Clin Toxicol*, 1995, 33(5):548.

White NJ, “The Treatment of Malaria,” *N Engl J Med*, 1996, 335(11):800-6.[PubMed 8703186]

International Brand NamesDimard (CO); Dolquine (ES); Duroc (KP); Ercoquin (DK, NO); Evoquin (AR, UY); Geniquin (TW); HCQS (TH); Hydroquin (TH); Oxiklorin (FI, KP); Plaquenil (LU, MX); Plaquenil Sulfate (AR, AT, AU, BB, BE, BF, BG, BJ, BM, BS, BZ, CH, CI, CZ, DE, DK, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, IE, IL, IT, JM, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, PH, PT, RU, SC, SD, SE, SL, SN, SR, TH, TN, TR, TT, TW, TZ, UG, ZA, ZM, ZW); Plaquinol (BR, CN, CR, DO, EC, GT, HN, NI, PA, PE, PT, PY, SV, VE); Quensyl (DE)

Hydroxypropyl Cellulose

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(hye droks ee PROE pil SEL yoo lose)
U.S. Brand NamesLacrisert速
Canadian Brand NamesLacrisert速
Pharmacologic CategoryOphthalmic Agent, Miscellaneous
Use: Labeled IndicationsDry eyes (moderate to severe)
Dosing: AdultsOcular lubricant: Ophthalmic: Apply once daily into the inferior cul-de-sac beneath the base of tarsus, not in apposition to the cornea nor beneath the eyelid at the level of the tarsal plate
Dosing: ElderlyRefer to adult dosing.
Adverse ReactionsFrequency not defined: Ocular: Local irritation, blurred vision, edema of the eyelids
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Insert, ophthalmic [preservative free]: 5 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

INST (Lacrisert)

5 mg (60): $222.59

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesLacrisert (AU, FI, FR, NL, SE, TW); Tears Naturale (TW)

Hydroxypropyl Methylcellulose

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Isopto® Tears may be confused with Isoptin®

Pronunciation(hye droks ee PROE pil meth il SEL yoo lose)
U.S. Brand NamesCellugel®; GenTeal® Mild [OTC]; GenTeal® [OTC]; Gonak™ [OTC]; Goniosoft™; Goniosol® [OTC] [DSC]; Isopto® Tears [OTC]; Tearisol® [OTC]; Tears Again® MC [OTC]
Canadian Brand NamesGenteal®; Isopto® Tears
Pharmacologic CategoryDiagnostic Agent, Ophthalmic; Lubricant, Ocular
Use: Labeled IndicationsRelief of burning and minor irritation due to dry eyes; diagnostic agent in gonioscopic examination
Dosing: AdultsDry eyes: Ophthalmic: Instill 1-2 drops in affected eye(s) as needed
Dosing: ElderlyRefer to adult dosing.
ContraindicationsHypersensitivity to hydroxypropyl methylcellulose or any component of the formulation
Warnings/Precautions

Other warnings/precautions:

- Appropriate use: Remove contact lenses prior to use. Not labeled for OTC use for >72 hours. Do not use if solution changes color or becomes cloudy.

Pregnancy Risk FactorC
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Gel, ophthalmic (GenTeal®): 0.3% (10 mL)

Solution, ophthalmic: 0.4% (15 mL)

GenTeal®: 0.3% (15 mL, 25 mL)

GenTeal® Mild: 0.2% (15 mL, 25 mL)

Gonak™: 2.5% (15 mL)

Goniosoft™: 2.5% (15 mL)

Goniosol®: 2.5% (15 mL) [contains benzalkonium chloride] [DSC]

Isopto® Tears: 0.5% (15 mL) [contains benzalkonium chloride]

Tearisol®: 0.5% (15 mL) [contains benzalkonium chloride]

Tears Again® MC: 0.3% (15 mL)

Solution, ophthalmic [for injection] (Cellugel®): 2% (1 mL)

Generic AvailableYes: Solution
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsGonioscopic Ophthalmic Solution; Hypromellose
International Brand NamesArtelac (AE, AT, BE, BG, BH, CY, DK, EG, FR, HU, IL, IQ, IR, JO, KW, LB, LU, LY, OM, PH, PL, QA, SA, SE, SY, YE); Artific (ES); Bion Tears (AU); Celulose Grin (MX); Genteal (AR, ID, IL, IN, KP, SG, TH); Humalac B (HU); Hypromellose (NL); Ilube (PH); Isopto Alkaline (FI); Isopto Plain (AE, BH, CY, EG, FI, GB, IE, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SE, SY, YE); Isopto Tears (AU, BF, BJ, CH, CI, ET, GH, GM, GN, HK, HR, KE, LR, LU, MA, ML, MR, MU, MW, NE, NG, PL, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Lac-Oph (HK); Lacrisic (DE); Lacrystat (LU); Methocel (PL, SG, TW); Methopt Eye Drops (AU, PH, TW); Meticel (CR, DO, GT, HN, NI, PA, SV); Metilcellulosa (IT); Naturalag (MX); Nicotears (PE); Occucoat (LU); Ocucoat (KP); Ocucort (KP); Okuzell (AT); Opsil Tears (TH); OQ-Coat (CO); Prosicca (AT); Tears Natural II (IL); Tears Naturale (KP); Ultra Tears (CH)

Hydroxyurea

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Hydroxyurea may be confused with hydrOXYzine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

International issues:

Hydrea® may be confused with Hydra® which is a brand name for isoniazid in Japan

Pronunciation(hye droks ee yoor EE a)

U.S. Brand NamesDroxia®; Hydrea®; Mylocel™

Canadian Brand NamesApo-Hydroxyurea®; Gen-Hydroxyurea; Hydrea®

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite

Use: Labeled IndicationsTreatment of melanoma, refractory chronic myelocytic leukemia (CML), relapsed and refractory metastatic ovarian cancer; radiosensitizing agent in the treatment of squamous cell head and neck cancer (excluding lip cancer); adjunct in the management of sickle cell patients who have had at least three painful crises in the previous 12 months (to reduce frequency of these crises and the need for blood transfusions)

Use: Unlabeled/InvestigationalTreatment of HIV; treatment of psoriasis, treatment of hematologic conditions such as essential thrombocythemia, polycythemia vera, hypereosinophilia, and hyperleukocytosis due to acute leukemia; treatment of uterine, cervix and nonsmall cell lung cancers; radiosensitizing agent in the treatment of primary brain tumors; has shown activity against renal cell cancer and prostate cancer

Dosing: AdultsRefer to individual protocols.

Note: Dose should always be titrated to patient response and WBC counts; usual oral doses range from 10-30 mg/kg/day or 500-3000 mg/day; if WBC count falls to <2500 cells/mm^3, or the platelet count to <100,000/mm^3, therapy should be stopped for at least 3 days and resumed when values rise toward normal.

Solid tumors: Oral:

Intermittent therapy: 80 mg/kg as a single dose every third day

Continuous therapy: 20-30 mg/kg/day given as a single dose/day

Concomitant therapy with irradiation: 80 mg/kg as a single dose every third day starting at least 7 days before initiation of irradiation

Resistant chronic myelocytic leukemia: Oral: Continuous therapy: 20-30 mg/kg once daily

HIV (unlabeled use; in combination with antiretroviral agents): 1000-1500 mg daily in single or divided doses

Psoriasis: 1000-1500 mg daily in single or divided doses

Sickle cell anemia (moderate/severe disease): Initial: 15 mg/kg/day, increased by 5 mg/kg every 12 weeks if blood counts are in an acceptable range until the maximum tolerated dose of 35 mg/kg/day is achieved or the dose that does not produce toxic effects

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols. All doses should be based on ideal or actual body weight, whichever is less: Children (unlabeled use):

Note: No FDA-approved dosage regimens have been established; dosages of 1500-3000 mg/m^2 as a single dose in combination with other agents every 4-6 weeks have been used in the treatment of pediatric astrocytoma, medulloblastoma, and primitive neuroectodermal tumors

CML: Oral: Initial: 10-20 mg/kg/day once daily; adjust dose according to hematologic response

Dosing: Renal Impairment

The FDA-approved labeling recommends the following adjustment:

Sickle cell anemia: Cl$_{cr}$ <60 mL/minute or ESRD: Reduce initial dose to 7.5 mg/kg; titrate to response/avoidance of toxicity (refer to usual dosing).

Other indications: It is recommended to reduce the initial dose; however, no specific guidelines are available.

The following guidelines have been used by some clinicians:

Aronoff, 2007: Adults:

Cl_{cr} 10-50 mL/minute: Administer 50% of dose

Cl_{cr} <10 mL/minute: Administer 20% of dose

Hemodialysis: Administer dose after dialysis on dialysis days; supplemental dose is not necessary. Hydroxyurea is a low molecular weight compound with high aqueous solubility that may be freely dialyzable, however, clinical studies confirming this hypothesis have not been performed.

Continuous renal replacement therapy (CRRT): Administer 50% of dose

Kintzel, 1995:

Cl_{cr} 46-60 mL/minute: Administer 85% of dose

Cl_{cr} 31-45 mL/minute: Administer 80% of dose

Cl_{cr} <30 mL/minute: Administer 75% of dose

Dosing: Hepatic ImpairmentSpecific guidelines are not available for dosage adjustment in hepatic impairment. The FDA-approved labeling recommends closely monitoring for bone marrow toxicity in patients with hepatic impairment.

Dosing: Adjustment for Toxicity

Acceptable range:

Neutrophils ≥2500 cells/mm^3

Platelets ≥95,000/mm^3

Hemoglobin >5.3 g/dL, and

Reticulocytes ≥95,000/mm^3 if the hemoglobin concentration is <9 g/dL

Toxic range:

Neutrophils <2000 cells/mm^3

Platelets <80,000/mm^3

Hemoglobin <4.5 g/dL

Reticulocytes <80,000/mm^3 if the hemoglobin concentration is <9 g/dL

Monitor for toxicity every 2 weeks; if toxicity occurs, stop treatment until the bone marrow recovers; restart at 2.5 mg/kg/day less than the dose at which toxicity occurs; if no toxicity occurs over the next 12 weeks, then the subsequent dose should be increased by 2.5 mg/kg/day; reduced dosage of hydroxyurea alternating with erythropoietin may decrease myelotoxicity and increase levels of fetal hemoglobin in patients who have not been helped by hydroxyurea alone

Dosing: Combination Regimens

Brain tumors: 8 in 1 (Brain Tumors)

Gestational trophoblastic tumor:

CHAMOCA (Modified Bagshawe Regimen)

CHAMOMA (Bagshawe Regimen)

Head and neck cancer: FU HURT

Neuroblastoma: N4SE Protocol

Retinoblastoma: 8 in 1 (Retinoblastoma)

Calculations

- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralCapsules may be opened and emptied into water (will not dissolve completely); observe proper handling procedures

Dietary ConsiderationsIn sickle cell patients, supplemental administration of folic acid is recommended; hydroxyurea may mask development of folic acid deficiency.

StorageStore at room temperature between 15°C and 30°C (59°F and 86°F).

ContraindicationsHypersensitivity to hydroxyurea or any component of the formulation; severe anemia; severe bone marrow suppression;

WBC <2500/mm^3 or platelet count <100,000/mm^3 (neutrophils <2000/mm^3, platelets <80,000/mm^3, and hemoglobin <4.5 g/dL for sickle cell anemia); pregnancy

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.
- Leukemia (secondary): See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: May occur, but more likely in patients with a history of prior cytotoxic chemotherapy and radiation therapy
- Cutaneous vasculitic toxicities (vasculitic ulceration and gangrene): Have been reported with hydroxyurea treatment, most often in patients with a history of or receiving concurrent interferon therapy; discontinue hydroxyurea and consider alternate cytoreductive therapy if cutaneous vasculitic toxicity develops.
- Leukemia (secondary): **[U.S. Boxed Warning]: Hydroxyurea is mutagenic and clastogenic. Treatment of myeloproliferative disorders (polycythemia vera and thrombocythemia) with long-term hydroxyurea is associated with secondary leukemia**; it is unknown if this is drug-related or disease-related.
- Megaloblastic erythropoiesis: May be seen early in treatment; plasma iron clearance may be delayed and the rate of utilization of iron by erythrocytes may be delayed.

Disease-related issues:

- Renal impairment: Use with caution in patients with renal impairment; may require dose reductions.

Special populations:

- HIV-infected patients: When treated with hydroxyurea and antiretroviral agents (including didanosine) HIV-infected patients are at higher risk for potentially fatal pancreatitis, hepatotoxicity, hepatic failure, and severe peripheral neuropathy; discontinue immediately if signs of these develop.
- Radiation therapy recipients: Patients with a history of radiation therapy are also at risk for exacerbation of post irradiation erythema.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of a physician experienced in cancer chemotherapy or in the treatment of sickle cell anemia.**

Geriatric ConsiderationsElderly may be more sensitive to the effects of this drug and may require a lower dosage regimen; advance dose slowly and adjust dose for renal function with careful monitoring.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenicity and embryotoxicity. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid pregnancy.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions, breast-feeding is not recommended.

Adverse ReactionsFrequency not defined.

Cardiovascular: Edema

Central nervous system: Chills, disorientation, dizziness, drowsiness (dose-related), fever, hallucinations, headache, malaise, seizure

Dermatologic: Alopecia (rare), cutaneous vasculitic toxicities, dermatomyositis-like skin changes, dry skin, facial erythema, gangrene, hyperpigmentation, maculopapular rash, nail atrophy, nail pigmentation, peripheral erythema, scaling, skin atrophy, skin cancer, skin ulcer, vasculitis ulcerations, violet papules

Endocrine & metabolic: Hyperuricemia

Gastrointestinal: Anorexia, constipation, diarrhea, gastrointestinal irritation and mucositis, (potentiated with radiation therapy), nausea, pancreatitis, stomatitis, vomiting

Genitourinary: Dysuria (rare)

Hematologic: Myelosuppression (primarily leukopenia; onset: 24-48 hours; nadir: 10 days; recovery: 7 days after stopping drug; reversal of WBC count occurs rapidly but the platelet count may take 7-10 days to recover); thrombocytopenia and anemia, megaloblastic erythropoiesis, macrocytosis, hemolysis, serum iron decreased, persistent cytopenias, secondary leukemias (long-term use)

Hepatic: Hepatic enzymes increased, hepatotoxicity

Neuromuscular & skeletal: Peripheral neuropathy, weakness

Renal: BUN increased, creatinine increased

Respiratory: Acute diffuse pulmonary infiltrates (rare), dyspnea, pulmonary fibrosis (rare)

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Didanosine: May enhance the adverse/toxic effect of Hydroxyurea. An increased risk of pancreatitis, hepatotoxicity and/or neuropathy may exist. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersCBC with differential and platelets, renal function and liver function tests, serum uric acid

Sickle cell disease: Monitor for toxicity every 2 weeks. If toxicity occurs, stop treatment until the bone marrow recovers; restart at 2.5 mg/kg/day less than the dose at which toxicity occurs. If no toxicity occurs over the next 12 weeks, then the subsequent dose should be increased by 2.5 mg/kg/day. Reduced dosage of hydroxyurea alternating with erythropoietin may decrease myelotoxicity and increase levels of fetal hemoglobin in patients who have not been helped by hydroxyurea alone.

Acceptable range: Neutrophils ≥2500 cells/mm^3, platelets ≥95,000/mm^3, hemoglobin >5.3 g/dL, and reticulocytes ≥95,000/mm^3 if the hemoglobin concentration is <9 g/dL

Toxic range: Neutrophils <2000 cells/mm^3, platelets <80,000/mm^3, hemoglobin <4.5 g/dL, and reticulocytes <80,000/mm^3 if the hemoglobin concentration is <9 g/dL

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking (eg, potential for increased neurotoxicity or hepatotoxicity). Hydroxyurea therapy requires close supervision to assess results of laboratory tests (eg, CBC, renal function and LFTs), therapeutic effectiveness, and adverse response (eg, CNS changes, gastrointestinal upset. hepatotoxicity, peripheral neuropathy). Teach proper use and need for frequent monitoring, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelets, renal function and liver function tests, serum uric acid

Sickle cell disease: Monitor for toxicity every 2 weeks. If toxicity occurs, stop treatment until the bone marrow recovers; restart at 2.5 mg/kg/day less than the dose at which toxicity occurs. If no toxicity occurs over the next 12 weeks, then the subsequent dose should be increased by 2.5 mg/kg/day. Reduced dosage of hydroxyurea alternating with erythropoietin may decrease myelotoxicity and increase levels of fetal hemoglobin in patients who have not been helped by hydroxyurea alone.

Acceptable range: Neutrophils ≥2500 cells/mm^3, platelets ≥95,000/mm^3, hemoglobin >5.3 g/dL, and reticulocytes ≥95,000/mm^3 if the hemoglobin concentration is <9 g/dL

Toxic range: Neutrophils <2000 cells/mm^3, platelets <80,000/mm^3, hemoglobin <4.5 g/dL, and reticulocytes <80,000/mm^3 if the hemoglobin concentration is <9 g/dL

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take capsules exactly as directed by prescriber (dosage and timing will be specific to purpose of therapy). Contents of capsule may be emptied into a glass of water and taken immediately. You will require frequent monitoring and blood tests while taking this medication to assess effectiveness and monitor adverse reactions. You will be susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea, vomiting, or loss of appetite (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); constipation (increased exercise, fluid, fruit, or fiber may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or mouth sores (frequent mouth care will help). Report persistent vomiting, diarrhea, constipation, stomach pain, or mouth sores; skin rash, redness, irritation, or sores; painful or difficult urination; anemia (unusual fatigue, lethargy), CNS changes (increased confusion, depression, hallucinations, or seizures); opportunistic infection (persistent fever or chills, white plaques in mouth, vaginal discharge, or unhealed sores); unusual lassitude, muscle tremors or weakness; easy bruising/bleeding; or blood in vomitus, stool, or urine. **Note:** People not taking hydroxyurea should not be exposed to it. If powder from capsule is spilled, wipe up with damp, disposable towel immediately, and discard the towel in a closed container, such as a plastic bag. Wash hands thoroughly. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate barrier contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 500 mg

Droxia®: 200 mg, 300 mg, 400 mg

Hydrea®: 500 mg

Tablet:

Mylocel™: 1000 mg

Generic AvailableYes: Capsule

Pricing: U.S. (www.drugstore.com)

Capsules (Droxia)

300 mg (30): $28.99

Capsules (Hydrea)

500 mg (100): $139.09

Capsules (Hydroxyurea)

500 mg (100): $89.99

Mechanism of ActionThought to interfere (unsubstantiated hypothesis) with synthesis of DNA, during the S phase of cell division, without interfering with RNA synthesis; inhibits ribonucleoside diphosphate reductase, preventing conversion of ribonucleotides to deoxyribonucleotides; cell-cycle specific for the S phase and may hold other cells in the G_1 phase of the cell cycle. In sickle cell anemia, hydroxyurea increases red blood cell (RBC) hemoglobin F levels, RBC water content, deformability of sickled cells, and alters adhesion of RBCs to endothelium.

Pharmacodynamics/Kinetics

Absorption: Readily (≥80%)

Distribution: Readily crosses blood-brain barrier; distributes into intestine, brain, lung, kidney tissues, effusions and ascites

Metabolism: 60% via hepatic and GI tract

Half-life elimination: 3-4 hours

Time to peak: 1-4 hours

Excretion: Urine (80%, 50% as unchanged drug, 30% as urea); exhaled gases (as CO_2)

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsAlthough I.V. use is reported, no parenteral product is commercially available in the U.S.

If WBC decreases to $<2500/mm^3$ or platelet count to $<100,000/mm^3$ (neutrophils $<2000/mm^3$ and platelets $<80,000/mm^3$ for patients with sickle cell anemia), interrupt therapy until values rise significantly toward normal. Treat anemia with whole blood replacement; do not interrupt therapy (for sickle cell anemia patients, withhold treatment for hemoglobin <4.5 g/dL until recovery to >5.3 g/dL). Adequate trial period to determine the antineoplastic effectiveness is 6 weeks. Almost all patients receiving hydroxyurea in clinical trials needed to have their medication stopped for a time to allow their low blood count to return to acceptable levels.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may rarely cause disorientation and hallucinations

Mental Health: Effects on Psychiatric TreatmentMyelosuppression is common; use caution with clozapine and carbamazepine

Index TermsHydroxycarbamide

References

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International Brand NamesBiosupressin (HU); Durea (PE); Hydab (PH); Hydrea (AR, AU, BE, BG, BR, CL, CN, CO, DK, EE, ES, FI, GB, GR, HK, ID, IE, JP, KP, LU, MX, NL, PK, RU, SE, SG, TH, TW, UY, ZA); Hydrox (PH); Hydroxycarbamid (PL); Hydroxyurea medac (PL, SE); Litalir (AT, CH, CZ, HN, HR, HU, PH); Neodrea (IN); Onco-Carbide (IT); Siklos (FR); Syrea (DE)

HydrOXYzine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

HydrOXYzine may be confused with hydrALAZINE, hydroxyurea

Atarax® may be confused with amoxicillin, Ativan®

Vistaril® may be confused with Restoril®, Versed, Zestril®

International issues:

Vistaril® may be confused with Vastarel® which is a brand name for trimetazidine in multiple international markets

Pronunciation(hye DROKS i zeen)
U.S. Brand NamesVistaril®
Canadian Brand NamesApo-Hydroxyzine®; Atarax®; Hydroxyzine Hydrochloride Injection, USP; Novo-Hydroxyzin; PMS-Hydroxyzine; Vistaril®
Pharmacologic CategoryAntiemetic; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation
Use: Labeled IndicationsTreatment of anxiety; preoperative sedative; antipruritic
Use: Unlabeled/InvestigationalAntiemetic; ethanol withdrawal symptoms
Use: DentalTreatment of anxiety, as a preoperative sedative in pediatric dentistry
Dosing: Adults

Antiemetic (unlabeled use): I.M.: 25-100 mg/dose every 4-6 hours as needed

Anxiety: Oral, I.M.: 50-100 mg 4 times/day

Preoperative sedation:

Oral: 50-100 mg

I.M.: 25-100 mg

Pruritus: Oral, I.M.: 25 mg 3-4 times/day

Dosing: ElderlyManagement of pruritus: 10 mg 3-4 times/day; increase to 25 mg 3-4 times/day if necessary.
Dosing: Pediatric

Preoperative sedation:

Oral: 0.6 mg/kg/dose

I.M.: 0.5-1 mg/kg/dose

Pruritus, anxiety: Oral:

<6 years: 50 mg daily in divided doses

≥6 years: 50-100 mg daily in divided doses

Dosing: Hepatic ImpairmentChange dosing interval to every 24 hours in patients with primary biliary cirrhosis.
Administration: I.M.Do not administer SubQ or intra-arterially. Administer I.M. deep in large muscle.
Administration: I.V.Extravasation can result in sterile abscess and marked tissue induration.
Administration: I.V. DetailpH: 3.5-6.0
StorageInjection: Store at 15°C to 30°C. Protect from light.
Compatibility**Compatibility in syringe: Compatible:** Atropine, atropine with meperidine, butorphanol, chlorpromazine, cimetidine, codeine, diphenhydramine, doxapram, droperidol, fentanyl, fluphenazine, glycopyrrolate, hydromorphone, lidocaine, meperidine, methotrimeprazine, metoclopramide, midazolam, morphine, nalbuphine, oxymorphone, pentazocine, perphenazine, procaine, prochlorperazine edisylate, promazine, promethazine, scopolamine, sufentanil. **Incompatible:** Dimenhydrinate, haloperidol, ketorolac, pentobarbital, ranitidine.
ContraindicationsHypersensitivity to hydroxyzine or any component of the formulation; early pregnancy; SubQ, intra-arterial, or I.V. administration of injection
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Respiratory disease: Use with caution in patients with asthma or COPD.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Anticholinergic effects are not well tolerated in the elderly; may be useful as a short-term antipruritic, but it is not recommended for use as a sedative or anxiolytic in the this population.

Other warnings/precautions:

- Appropriate administration: I.V., SubQ, and intra-arterial administration are contraindicated since tissue damage, intravascular hemolysis, thrombosis, and digital gangrene can occur.

Geriatric ConsiderationsAnticholinergic effects are not well tolerated in the elderly and frequently result in bowel, bladder, and mental status changes (ie, constipation, confusion, and urinary retention). Hydroxyzine may be useful as a short-term antipruritic, but it is not recommended for use as a sedative or anxiolytic in the elderly.

Pregnancy Risk FactorC

Pregnancy ConsiderationsHydroxyzine-induced fetal abnormalities at high dosages in animal studies. Neonatal withdrawal symptoms have been reported following long-term maternal use or the use of large doses near term. Use in early pregnancy is contraindicated by the manufacturer.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Central nervous system: Dizziness, drowsiness, fatigue, hallucination, headache, nervousness, seizure

Dermatologic: Pruritus, rash, urticaria

Gastrointestinal: Xerostomia

Neuromuscular & skeletal: Involuntary movements, paresthesia, tremor

Ocular: Blurred vision

Respiratory: Thickening of bronchial secretions

Miscellaneous: Allergic reaction

Oncology: Emetic PotentialVery low (<10%)

Metabolism/Transport Effects**Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersRelief of symptoms, mental status, blood pressure

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and possible interactions. **Systemic:** Monitor therapeutic effectiveness and adverse reactions; ensure patient safety (institute safety precautions), have patient void prior to administration; and ensure adequate hydration and environmental temperature control. **Oral:** Monitor therapeutic effectiveness according to purpose for use and adverse reactions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationWill cause drowsiness. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. Use caution when driving or engaging in activities requiring alertness until response to drug is known. Report hallucinations, seizure activity, tremors or involuntary movements, or loss of sensation. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is contraindicated.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, as pamoate: 25 mg, 50 mg, 100 mg

Vistaril®: 25 mg, 50 mg

Injection, solution, as hydrochloride: 25 mg/mL (1 mL); 50 mg/mL (1 mL, 2 mL, 10 mL)

Suspension, oral, as pamoate:

Vistaril®: 25 mg/5 mL (120 mL, 480 mL) [lemon flavor] [DSC]

Syrup, as hydrochloride: 10 mg/5 mL (120 mL, 480 mL)

Tablet, as hydrochloride: 10 mg, 25 mg, 50 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (HydrOXYzine Pamoate)

25 mg (60): $14.98

50 mg (90): $19.00

100 mg (30): $19.99

Capsules (Vistaril)

25 mg (30): $48.29

50 mg (30): $59.84

Solution (HydrOXYzine HCl)

50 mg/mL (25): $44.38

Suspension (Vistaril)

25 mg/5 mL (240): $102.98

Tablets (HydrOXYzine HCl)

10 mg (30): $17.99

50 mg (30): $30.99

Mechanism of ActionCompetes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract. Possesses skeletal muscle relaxing, bronchodilator, antihistamine, antiemetic, and analgesic properties.

Pharmacodynamics/Kinetics

Onset of action: Oral: 15-30 minutes

Duration: 4-6 hours

Absorption: Oral: Rapid

Metabolism: Forms metabolites

Half-life elimination: 3-7 hours

Time to peak: ~2 hours

Excretion: Urine

Related Information

- CMS: Long-Term Care Facility Thresholds
- Nonbenzodiazepine Anxiolytics and Hypnotics

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentCommonly used as an anxiolytic, especially in individuals with a history of or active substance use. Postmarketing experience revealed cases of headache and hallucinations.

Index TermsHydroxyzine Hydrochloride; Hydroxyzine Pamoate

References

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Simons KJ, Watson WT, Chen XY, et al, “Pharmacokinetic and Pharmacodynamic Studies of the H_1-Receptor Antagonist Hydroxyzine in the Elderly,” *Clin Pharmacol Ther*, 1989, 45(1):9-14. [PubMed 2562944]

International Brand NamesAbacus (TH); Antizine (TH); Atarax (AT, AU, BB, BE, BG, BM, BS, BZ, CH, CZ, DE, DK, ES, FI, FR, GB, GR, GY, HK, HN, HU, IE, IN, IT, JM, LU, MX, MY, NL, NO, PE, PL, PT, RU, SE, SR, TH, TR, TT, TW); Atarax Uce (PK); Ataraxone (AR, UY); Aterax (ZA); Bestalin (ID); Cedar (CO); Centilax (KP); Cerax (TH); Disron-P (JP); Dormirex (GT); Drazine (TH); Hiderax (CO); Histan (TH); Hizin (SG, TH); Hydroksyzyna (PL); Hydroxyzinum (PL); Iremofar (GR); Iterax (ID, PH); Nirax (TW); Otarex (IL); Paxistil (BE); Postarax (TH); Prurid (PY); Qualidrozine (HK); R-Rax (TH); Serecid (NZ); Trandozine (TH); Ucerax (IE, KP); Unamine (TH); Vistaril (KE, SE, TR, TW); Warazix (JP)

Hyoscyamine, Atropine, Scopolamine, and Phenobarbital

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Donnatal® may be confused with Donnagel®

Pronunciation(hye oh SYE a meen, A troe peen, skoe POL a meen, & fee noe BAR bi tal)

U.S. Brand NamesDonnatal Extentabs®; Donnatal®

Pharmacologic CategoryAnticholinergic Agent; Antispasmodic Agent, Gastrointestinal

Use: Labeled IndicationsAdjunct in treatment of irritable bowel syndrome, acute enterocolitis, duodenal ulcer

Dosing: AdultsSpasmolytic: Oral:

Donnatal®: 1-2 tablets or 5-10 mL of elixir 3-4 times/day

Donnatal Extentabs®: 1 tablet every 12 hours; may increase to 1 tablet every 8 hours if needed

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricOral: Donnatal® elixir: To be given every 4-6 hours; initial dose based on weight:

4.5 kg: 0.5 mL every 4 hours **or** 0.75 mL every 6 hours

10 kg: 1 mL every 4 hours **or** 1.5 mL every 6 hours

14 kg: 1.5 mL every 4 hours **or** 2 mL every 6 hours

23 kg: 2.5 mL every 4 hours **or** 3.8 mL every 6 hours

34 kg: 3.8 mL every 4 hours **or** 5 mL every 6 hours

≥45 kg: 5 mL every 4 hours **or** 7.5 mL every 6 hours

Administration: OralDo not crush extended release tablets.

Dietary ConsiderationsShould be taken 30-60 minutes before meals unless otherwise directed.

ContraindicationsHypersensitivity to hyoscyamine, atropine, scopolamine, phenobarbital, or any component of the formulation; narrow-angle glaucoma; tachycardia; GI and GU obstruction; myasthenia gravis; paralytic ileus; intestinal atony; unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; hiatal hernia associated with reflux esophagitis; acute intermittent porphyria

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity
- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause drowsiness and/or blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Diarrhea: May be a sign of incomplete intestinal obstruction, treatment should be discontinued if this occurs.
- Heat prostration: May occur in the presence of increased environmental temperature; use caution in hot weather and/or exercise.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease, tachyarrhythmias, heart failure, or hypertension; evaluate tachycardia prior to administration.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Gastric ulcer treatment: Use of anticholinergics in gastric ulcer treatment may cause a delay in gastric emptying due to antral statis.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Neuropathy: Use with caution in patients with autonomic neuropathy.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Elderly: Use with caution in the elderly; may be more susceptible to adverse effects.

Other warnings/precautions:

- Withdrawal: Due to the phenobarbital component should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsBecause of the anticholinergic effects of this product, it is not recommended for use in the elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies with this combination have not been done; refer to individual components.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation, tachycardia

Central nervous system: Dizziness, drowsiness, headache, insomnia, nervousness

Dermatologic: Urticaria

Gastrointestinal: Bloating, constipation, nausea, taste loss, vomiting, xerostomia

Genitourinary: Impotence, urinary hesitancy, urinary retention

Neuromuscular & skeletal: Musculoskeletal pain, weakness

Ocular: Blurred vision, cycloplegia, mydriasis, ocular tension increased

Miscellaneous: Allergic reaction (may be severe), anaphylaxis, lactation suppressed, diaphoresis decreased

Metabolism/Transport EffectsPhenobarbital: **Substrate** (minor) of CYP2C8/9, 2C19, 2E1; **Induces** CYP1A2 (strong), 2A6 (strong), 2B6 (strong), 2C8/9 (strong), 3A4 (strong)
Drug Interactions

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Aminocamptothecin: PHENobarbital may decrease the serum concentration of Aminocamptothecin. *Risk C: Monitor therapy*

Amphetamines: May decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inducers (Strong) may decrease the serum concentration of Bendamustine. Concentrations of active metabolites may be increased. *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May enhance the adverse/toxic effect of Anticonvulsants (Barbiturate). Specifically, osteomalacia and rickets. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inducers (Strong) may increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2A6 Substrates: CYP2A6 Inducers (Strong) may increase the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inducers (Strong) may increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inducers (Highly Effective) may increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inducers (Highly Effective) may increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Darunavir: PHENobarbital may decrease the serum concentration of Darunavir. *Risk X: Avoid combination*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Etravirine: PHENobarbital may decrease the serum concentration of Etravirine. Management: The manufacturer of etravirine states these drugs should not be used in combination *Risk X: Avoid combination*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

Folic Acid: May decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Griseofulvin: Barbiturates may decrease the absorption of Griseofulvin. *Risk D: Consider therapy modification*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Lacosamide: PHENobarbital may decrease the serum concentration of Lacosamide. *Risk C: Monitor therapy*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Leucovorin-Levoleucovorin: May decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Methylfolate: May decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

OXcarbazepine: PHENobarbital may decrease the serum concentration of OXcarbazepine. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Rufinamide: May increase the serum concentration of PHENobarbital. PHENobarbital may decrease the serum concentration of Rufinamide. *Risk C: Monitor therapy*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tipranavir: PHENobarbital may decrease the serum concentration of Tipranavir. Tipranavir may decrease the serum concentration of PHENobarbital. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Voriconazole: Barbiturates may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Elixir:

Donnatal®: Hyoscyamine sulfate 0.1037 mg, atropine sulfate 0.0194 mg, scopolamine hydrobromide 0.0065 mg, and phenobarbital 16.2 mg per 5 mL (120 mL, 480 mL) [contains alcohol 95%; grape flavor]

Tablet: Hyoscyamine sulfate 0.1037 mg, atropine sulfate 0.0194 mg, scopolamine hydrobromide 0.0065 mg, and phenobarbital 16.2 mg

Donnatal®: Hyoscyamine sulfate 0.1037 mg, atropine sulfate 0.0194 mg, scopolamine hydrobromide 0.0065 mg, and phenobarbital 16.2 mg

Tablet, extended release:

Donnatal Extentabs®: Hyoscyamine sulfate 0.3111 mg, atropine sulfate 0.0582 mg, scopolamine hydrobromide 0.0195 mg, and phenobarbital 48.6 mg

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Elixir (Belladonna Alk-Phenobarbital)

16 mg/5 mL (473): $56.00

Elixir (Donnatal)

16.2 mg/5 mL (120): $34.99

Tablet, controlled release (Donnatal Extentabs)

(30): $49.21

Tablets (Belladonna Alk-Phenobarbital)

16.2 mg (60): $12.99

Tablets (Donnatal)

(60): $38.51

Mechanism of ActionA fixed combination of belladonna alkaloids and phenobarbital which provides anticholinergic/antispasmodic action and mild sedation.

Related Information

- Atropine
- Hyoscyamine
- PHENobarbital
- Scopolamine Derivatives

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause confusion, drowsiness, headache, loss of memory, fatigue, ataxia

Mental Health: Effects on Psychiatric TreatmentAnticholinergic effects are common and may be increased with concurrent psychotropic use

Index TermsAtropine, Hyoscyamine, Scopolamine, and Phenobarbital; Belladonna Alkaloids With Phenobarbital; Phenobarbital, Hyoscyamine, Atropine, and Scopolamine; Scopolamine, Hyoscyamine, Atropine, and Phenobarbital

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Hyoscyamine

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Anaspaz® may be confused with Anaprox®, Antispas®

Levbid® may be confused with Lithobid®, Lopid®, Lorabid®

Levsinex® may be confused with Lanoxin®

Levsin/SL® maybe confused with Levaquin®

Pronunciation(hye oh SYE a meen)
U.S. Brand NamesAnaspaz®; Cystospaz®; Hyosyne; Levbid®; Levsin®; Levsin®/SL; NuLev™ [DSC]; Spacol T/S [DSC]; Spacol [DSC]; Symax SL; Symax SR
Canadian Brand NamesCystospaz®; Levsin®
Pharmacologic CategoryAnticholinergic Agent
Use: Labeled Indications

Oral: Adjunctive therapy for peptic ulcers, irritable bowel, neurogenic bladder/bowel; treatment of infant colic, GI tract disorders caused by spasm; to reduce rigidity, tremors, sialorrhea, and hyperhidrosis associated with parkinsonism; as a drying agent in acute rhinitis

Injection: Preoperative antimuscarinic to reduce secretions and block cardiac vagal inhibitory reflexes; to improve radiologic visibility of the kidneys; symptomatic relief of biliary and renal colic; reduce GI motility to facilitate diagnostic procedures (ie, endoscopy, hypotonic duodenography); reduce pain and hypersecretion in pancreatitis, certain cases of partial heart block associated with vagal activity; reversal of neuromuscular blockade

Dosing: Adults

Gastrointestinal spasms:

Oral or S.L.: 0.125-0.25 mg every 4 hours or as needed (before meals or food); maximum: 1.5 mg/24 hours

Product-specific dosing: Cystospaz®: 0.15-0.3 mg up to 4 times/day

Oral, timed release: 0.375-0.75 mg every 12 hours; maximum: 1.5 mg/24 hours

I.M., I.V., SubQ: 0.25-0.5 mg; may repeat as needed up to 4 times/day, at 4-hour intervals

Diagnostic procedures: I.V.: 0.25-0.5 mg given 5-10 minutes prior to procedure

Preanesthesia: I.V.: 5 mcg/kg given 30-60 minutes prior to induction of anesthesia or at the time preoperative narcotics or sedatives are administered

To reduce drug-induced bradycardia during surgery: I.V.: 0.125 mg; repeat as needed

Reverse neuromuscular blockade: I.V.: 0.2 mg for every 1 mg neostigmine (or the physostigmine/pyridostigmine equivalent)

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Gastrointestinal disorders:

Children <2 years: Oral: Dose as listed, based on age and weight (kg) using the 0.125 mg/mL drops. Repeat dose every 4 hours as needed:

3.4 kg: 4 drops; maximum: 24 drops/24 hours

5 kg: 5 drops; maximum: 30 drops/24 hours

7 kg: 6 drops; maximum: 36 drops/24 hours

10 kg: 8 drops; maximum: 48 drops/24 hours

Children 2-12 years: Oral or S.L.: Dose as listed, based on age and weight (kg); repeat dose every 4 hours as needed:

10 kg: 0.031-0.033 mg; maximum: 0.75 mg/24 hours

20 kg: 0.0625 mg; maximum: 0.75 mg/24 hours

40 kg: 0.0938 mg; maximum: 0.75 mg/24 hours

50 kg: 0.125 mg; maximum: 0.75 mg/24 hours

Preanesthesia: Children >2 years: I.V.: Refer to adult dosing.

Administration: I.M.May be administered without dilution.
Administration: I.V.Inject over at least 1 minute. May be administered without dilution.
Administration: I.V. DetailMay be administered undiluted.
Administration: OralOral: Tablets should be administered before meals or food.

Levbid®: Tablets are scored and may be broken in half for dose titration; do not crush or chew.

Levsin/SL®: Tablets may be used sublingually, chewed, or swallowed whole.

NuLev™: Tablet is placed on tongue and allowed to disintegrate before swallowing; may take with or without water.

Symax SL: Tablets may be used sublingually or swallowed whole.

Dietary ConsiderationsShould be taken before meals or food; NuLev™ contains phenylalanine
StorageStore at controlled room temperature. Protect NuLev™ from moisture.
ContraindicationsHypersensitivity to belladonna alkaloids or any component of the formulation; glaucoma; obstructive uropathy; myasthenia gravis; obstructive GI tract disease, paralytic ileus, intestinal atony of elderly or debilitated patients, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis; unstable cardiovascular status in acute hemorrhage, myocardial ischemia
Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effect:

- CNS effects: May cause drowsiness and/or blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Diarrhea: May be a sign of incomplete intestinal obstruction, treatment should be discontinued if this occurs.
- Heat prostration: May occur in the presence of increased environmental temperature; use caution in hot weather and/or exercise.
- Psychosis: Has been reported in patients with an extreme sensitivity to anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease, tachyarrhythmias, heart failure, or hypertension; evaluate tachycardia prior to administration.
- Hiatal hernia: Use with caution in patients with hiatal hernia with reflux esophagitis.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Neuropathy: Use with caution in patients with autonomic neuropathy.
- Prostatic hyperplasia: Use with caution in patients with prostatic hyperplasia.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Elderly: Use with caution in the elderly; may be more susceptible to adverse effects. May precipitate undiagnosed glaucoma and/or severely impair memory function (especially in those patients with previous memory problems).
- Pediatrics: Use with caution in children with spastic paralysis.

Dosage form specific issues:

- Phenylalanine: NuLev™ contains phenylalanine.

Geriatric ConsiderationsAvoid long-term use; the potential for toxic reactions is higher than the potential benefit, elderly are particularly prone to CNS side effects of anticholinergics (eg, confusion, delirium, hallucinations). Side effects often occur before clinical response is obtained.
Pregnancy Risk FactorC
Pregnancy ConsiderationsCrosses the placenta, effects to the fetus not known; use during pregnancy only if clearly needed.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsExcreted in breast milk in trace amounts. May also suppress lactation. Breast-feeding is not recommended.
Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation, tachycardia

Central nervous system: Ataxia, dizziness, drowsiness, headache, insomnia, mental confusion/excitement, nervousness, speech disorder

Dermatologic: Urticaria

Endocrine & metabolic: Lactation suppression

Gastrointestinal: Bloating, constipation, dry mouth, loss of taste, nausea, vomiting

Genitourinary: Impotence, urinary hesitancy, urinary retention

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision, cycloplegia, increased ocular tension, mydriasis

Miscellaneous: Allergic reactions, sweating decreased

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, anything that may add to anticholinergic effects). **I.V./I.M.:** Have patient void before administration. Assess therapeutic effectiveness and adverse response (eg, excessive dryness of eyes, nose, mouth, or throat). Teach patient proper use (according to formulations prescribed), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed before meals; do not increase dose and do not discontinue without consulting prescriber. Void immediately before taking medication. Do not crush or chew (swallow whole) extended release form. Levbid® and Levsinex® may not completely disintegrate and may be excreted. You may experience dizziness or blurred vision (use caution when driving or engaging in tasks that require alertness until response to drug is known); dry mouth (sucking on lozenges may help); photosensitivity (wear dark glasses in bright sunlight); decreased ability to sweat (use caution in hot weather or hot rooms or when engaging in strenuous activity); or impotence (temporary). Report excessive and persistent anticholinergic effects (blurred vision, headache, flushing, tachycardia, nervousness, constipation, dizziness, insomnia, mental confusion or excitement, dry mouth, altered taste perception, dysphagia, palpitations, bradycardia, urinary hesitancy or retention, impotence, decreased sweating). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Sublingual tablets: Place tablet under tongue and allow to dissolve.

Orally-disintegrating tablet: Place tablet on tongue and allow to disintegrate before swallowing. Take with or without food.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, timed release, as sulfate: 0.375 mg

Elixir, as sulfate: 0.125 mg/5 mL (480 mL)

Hyosyne: 0.125 mg/5 mL (480 mL) [contains ethanol 20% and sodium benzoate; orange flavor]

Levsin®: 0.125 mg/5 mL (480 mL) [contains ethanol 20%; orange flavor]

Injection, solution, as sulfate: 0.5 mg/mL (1 mL)

Levsin®: 0.5 mg/mL (1 mL)

Solution, oral, as sulfate [drops]: 0.125 mg/mL (15 mL)

Hyosyne: 0.125 mg/mL (15 mL) [contains ethanol 5% and sodium benzoate; orange flavor]

Levsin®: 0.125 mg/mL (15 mL) [contains ethanol 5%; orange flavor]

Tablet:

Cystospaz®: 0.15 mg [DSC]

Tablet, as sulfate: 0.125 mg

Anaspaz®: 0.125 mg

Levsin®: 0.125 mg

Tablet, extended release, as sulfate: 0.375 mg

Levbid®: 0.375 mg

Symax SR: 0.375 mg

Tablet, orally disintegrating, as sulfate: 0.125 mg

NuLev™: 0.125 mg [contains phenylalanine 1.7 mg/tablet, mint flavor] [DSC]

Tablet, sublingual, as sulfate: 0.125 mg

Levsin®/SL: 0.125 mg

Symax SL: 0.125 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsule, 12-hour (Hyoscyamine Sulfate CR)

0.375 mg (100): $85.99

Elixir (Levsin)

0.125 mg/5 mL (150): $42.99

Solution (Levsin)

0.125 mg/mL (15): $44.09

Sublingual (Levsin/SL)

0.125 mg (100): $107.79

Sublingual (Symax-SL)

0.125 mg (30): $75.92

Tablet, 12-hour (Hyoscyamine Sulfate CR)

0.375 mg (30): $29.99

Tablet, 12-hour (Levbid)

0.375 mg (30): $54.99

Tablets (Anaspaz)

0.125 mg (100): $29.99

Tablets (Hyoscyamine Sulfate)

0.125 mg (90): $49.99

Mechanism of ActionBlocks the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands and the CNS; increases cardiac output, dries secretions, antagonizes histamine and serotonin
Pharmacodynamics/Kinetics

Onset of action: 2-3 minutes

Duration: 4-6 hours

Absorption: Well absorbed

Distribution: Crosses placenta; small amounts enter breast milk

Protein binding: 50%

Metabolism: Hepatic

Half-life elimination: 3-5 hours

Excretion: Urine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness; may rarely cause restlessness, amnesia, or delirium
Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation and dry mouth
Index Terms/-Hyoscyamine Sulfate; Hyoscyamine Sulfate
References

Boyson SJ, "Bethanechol for Anticholinergic Side Effects," *Ann Neurol*, 1988, 23(4):422-3. [PubMed 3382184]

Shutt LE and Bowes JB, "Atropine and Hyoscine," *Anaesthesia*, 1979, 34(5):476-90.[PubMed 382907]

International Brand Names Duboisine (FR); Egacene (NL); Egazil Duretter (DK, FI, NO, SE); Eyosin (PH); Levsin SL (HK); Neo-Allospasmin (BG); Nuspas (TW)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Lymphocytic

Regimen UseLeukemia, acute lymphocytic

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cycle A: (Cycles 1, 3, 5, and 7)

Cyclophosphamide: I.V.: 300 mg/m^2 every 12 hours, for 6 doses, days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Mesna: I.V.: 1200 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 3600 mg/m^2]

Vincristine: I.V.: 2 mg/day days 4 and 11

[total dose/cycle = 4 mg]

Doxorubicin: I.V.: 50 mg/m^2 day 4

[total dose/cycle = 50 mg/m^2]

Dexamethasone: (route not specified): 40 mg/day days 1, 2, 3, 4, 11, 12, 13, and 14

[total dose/cycle = 320 mg]

Cycle B: (Cycles 2, 4, 6, and 8)

Methotrexate: I.V.: 1 g/m^2 continuous infusion day 1

[total dose/cycle = 1g/m^2]

Leucovorin: (route not specified): 15 mg every 6 hours, for 8 doses (start 12 hours after end of methotrexate infusion)

[total dose/cycle = 120 mg]

Cytarabine: I.V.: 3 g/m^2 every 12 hours, for 4 doses, days 2 and 3

[total dose/cycle = 12 g/m^2]

Methylprednisolone: I.V.: 50 mg twice daily, for 6 doses, days 1, 2, and 3

[total dose/cycle = 300 mg/m^2]

Repeat every 6 weeks in the following sequence: ABABABAB

CNS Prophylaxis

Methotrexate: I.T.: 12 mg/day day 2

[total dose/cycle = 12 mg]

or 6 mg/day into Ommaya day 2

[total dose/cycle = 6 mg]

Cytarabine: I.T: 100 mg day 8

[total dose/cycle = 100 mg]

Repeat cycle every 3 weeks

Maintenance (POMP)

Mercaptopurine: Oral: 50 mg 3 times/day

[total dose/cycle = 4200-4650 mg]

Vincristine: I.V.: 2 mg day 1

[total dose/cycle = 2 mg]

Methotrexate: Oral: 20 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 80 mg/m^2]

Prednisone: Oral: 200 mg/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

or

Mercaptopurine: I.V.: 1 g/m^2/day days 1 to 5

[total dose/cycle = 5 g/m^2]

Vincristine: I.V.: 2 mg day 1

[total dose/cycle = 2 mg]

Methotrexate: I.V.: 10 mg/m^2/day days 1 to 5

[total dose/cycle = 50 mg/m^2]

Prednisone: Oral: 200 mg/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

Repeat cycles every month for 2 years

Variation 2:

Cycle A: (Cycles 1, 3, 5, and 7)

Cyclophosphamide: I.V.: 300 mg/m^2 every 12 hours, for 6 doses, days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Mesna: I.V.: 600 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Vincristine: I.V.: 2 mg/day days 4 and 11

[total dose/cycle = 4 mg]

Doxorubicin: I.V.: 50 mg/m^2 day 4

[total dose/cycle = 50 mg/m^2]

Dexamethasone: Oral, I.V.: 40 mg/day days 1, 2, 3, 4, 11, 12, 13, and 14

[total dose/cycle = 320 mg]

Cycle B: (Cycles 2, 4, 6, and 8)

Methotrexate: I.V.: 1 g/m^2 continuous infusion day 1

[total dose/cycle = 1 g/m^2]

Leucovorin: I.V.: 50 mg (start 12 hours after end of methotrexate infusion)

followed by I.V.: 15 mg every 6 hours, for 8 doses

[total dose/cycle = 170 mg]

Cytarabine: I.V.: 3 g/m^2 every 12 hours, for 4 doses, days 2 and 3

[total dose/cycle = 12 g/m^2]

Repeat every 6 weeks in the following sequence: ABABABAB

CNS Prophylaxis

Methotrexate: I.T.: 12 mg day 2

[total dose/cycle = 12 mg]

or 6 mg into Ommaya day 2

[total dose/cycle = 6 mg]

Cytarabine: I.T.: 100 mg day 7

[total dose/cycle = 100 mg]

Repeat cycle every 3 weeks

Variation 3:

Cycle A: (Cycles 1, 3, 5, and 7)

Cyclophosphamide: I.V.: 300 mg/m^2 every 12 hours, for 6 doses, days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Mesna: I.V.: 600 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Vincristine: I.V.: 2 mg/day days 4 and 11

[total dose/cycle = 4 mg]

Doxorubicin: I.V.: 50 mg/m^2 continuous infusion day 4

[total dose/cycle = 50 mg/m^2]

Dexamethasone: Oral, I.V.: 40 mg/day days 1, 2, 3, 4, 11, 12, 13, and 14

[total dose/cycle = 320 mg]

Cycle B: (Cycles 2, 4, 6, and 8)

Methotrexate: I.V.: 200 mg/m^2 day 1

followed by I.V.: 800 mg/m^2 continuous infusion day 1

[total dose/cycle = 1 g/m^2]

Leucovorin: I.V.: 50 mg (start 12 hours after end of methotrexate infusion)

followed by I.V.: 15 mg every 6 hours, for 8 doses

[total dose/cycle = 170 mg/m^2]

Cytarabine: I.V.: 3 g/m^2 every 12 hours, for 4 doses, days 2 and 3

[total dose/cycle = 12 g/m^2]

Repeat every 6 weeks in the following sequence: ABABABAB

CNS Prophylaxis

Methotrexate: I.T.: 12 mg day 2

[total dose/cycle = 12 mg]

or 6 mg into Ommaya day 2

[total dose/cycle = 6 mg]

Cytarabine: I.T.: 100 mg day 7 **or** 8

[total dose/cycle = 100 mg]

Repeat cycles every 3 weeks for 6 or 8 cycles

Maintenance (POMP)

Mercaptopurine: Oral: 50 mg 3 times/day

[total dose/cycle = 4200-4650 mg]

Vincristine: I.V.: 2 mg day 1

[total dose/cycle = 2 mg]

Methotrexate: Oral, I V: 20 mg/m^2/ day days 1, 8, 15, and 22

[total dose/cycle = 80 mg/m^2]

Prednisone: Oral: 200 mg/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

or

Mercaptopurine: I.V.: 1 g/m^2/day days 1 to 5

[total dose/cycle = 5 g/m^2]

Vincristine: I.V.: 2 mg day 1

[total dose/cycle = 2 mg]

Methotrexate: I.V.: 10 mg/m^2 /day days 1 to 5

[total dose/cycle = 50 mg/m^2]

Prednisone: Oral: 200 mg/day days 1 to 5

[total dose/cycle = 1000 mg]

Repeat cycles every month (except months 7 and 11 or 9 and 12) for 2 years

Intensification

Etoposide: I.V.: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Pegaspargase: I.V.: 2500 units/m^2 day 1

[total dose/cycle = 2500 units/m^2]

Given during months 9 and 12 of maintenance

or

Methotrexate: I.V.: 100 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 400 mg/m^2]

Asparaginase: I.V.: 20,000 units/day days 2, 9, 16, and 23

[total dose/cycle = 80,000 units]

Given during months 7 and 11 of maintenance

Variation 4:

Cycle A: (Cycles 1, 3, 5, and 7)

Cyclophosphamide: I.V.: 300 mg/m^2 every 12 hours, for 6 doses, days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Mesna: I.V.: 600 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Vincristine: I.V.: 2 mg/day days 4 and 11

[total dose/cycle = 4 mg]

Doxorubicin: I.V.: 50 mg/m^2day 4

[total dose/cycle = 50 mg/m^2]

Dexamethasone: (route not specified): 40 mg/day days 1, 2, 3, 4, 11, 12, 13, and 14

[total dose/cycle = 320 mg]

Cycle B: (Cycles 2, 4, 6, and 8)

Methotrexate: I.V.: 200 mg/m^2 day 1

followed by I.V.: 800 mg/m^2 continuous infusion day 1

[total dose/cycle = 1 g/m^2]

Leucovorin: (route not specified): 15 mg every 6 hours, for 8 doses (start 24 hours after end of methotrexate infusion)

[total dose/cycle = 120 mg]

Cytarabine: I.V.: 3 g/m^2 every 12 hours, for 4 doses, days 2 and 3

[total dose/cycle = 12 g/m^2]

Repeat every 6 weeks in the following sequence: ABABABAB

CNS Prophylaxis

Methotrexate: I.T.: 12 mg day 2

[total dose/cycle = 12 mg]

Cytarabine: I.T.: 100 mg day 8

[total dose/cycle = 100 mg]

Repeat cycle every 3 weeks for 4 or 8 cycles

Maintenance (POMP)

Mercaptopurine: Oral: 50 mg 3 times/day

[total dose/cycle = 4200-4650 mg]

Vincristine: I.V.: 2 mg day 1

[total dose/cycle = 2 mg]

Methotrexate: Oral: 20 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 80 mg/m^2]

Prednisone: Oral: 200 mg/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

or

Mercaptopurine: I.V.: 1 g/m^2/day days 1 to 5

[total dose/cycle = 5 g/m^2]

Vincristine: I.V.: 2 mg day 1

[total dose/cycle = 2 mg]

Methotrexate: I.V.: 10 mg/m^2/day days 1 to 5

[total dose/cycle = 50 mg/m^2]

Prednisone: Oral: 200 mg/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

or

Interferon alfa: SubQ: 5 million units/m^2 daily

[total dose/cycle = 140-155 million units/m^2]

Cytarabine: SubQ: 10 mg daily

[total dose/cycle = 280-310 mg]

Repeat cycles every month for 2 years

Variation 5:

Cycle A: (Cycles 1, 4, 6, and 8)

Cyclophosphamide: I.V.: 300 mg/m^2 every 12 hours, for 6 doses, days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Mesna: I.V.: 600 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Vincristine: I.V.: 2 mg/day days 4 and 11

[total dose/cycle = 4 mg]

Doxorubicin: I.V.: 50 mg/m^2 continuous infusion day 4

[total dose/cycle = 50 mg/m^2]

Dexamethasone: Oral, I.V.: 40 mg/day days 1, 2, 3, 4, 11, 12, 13, and 14

[total dose/cycle = 320 mg]

Cycle B: (Cycles 3, 5, 7, and 9)

Methotrexate: I.V.: 200 mg/m^2 day 1

followed by I.V.: 800 mg/m^2/day continuous infusion day 1

[total dose/cycle = 1 g/m^2]

Leucovorin: I.V.: 50 mg (start 12 hours after end of methotrexate infusion)

followed by I.V.: 15 mg every 6 hours, for 8 doses

[total dose/cycle = 170 mg]

Cytarabine: I.V.: 3 g/m ^{2} every 12 hours, for 4 doses, days 2 and 3

[total dose/cycle = 12 g/m^2]

Cycle C: Liposomal Daunorubicin/cytarabine (Cycle 2):

Daunorubicin, liposomal: I.V.: 150 mg/m^2/day days 1 and 2

[total dose/cycle = 300 mg/m^2]

Cytarabine: I.V.: 1.5 g/m^2/day continuous infusion days 1 and 2

[total dose/cycle = 3 g/m^2]

Prednisone: Oral: 200 mg/day days 1 to 5

[total dose/cycle = 1000 mg]

Administer in the following sequence: ACBABABA (Cycle C does not repeat)

CNS Prophylaxis

Methotrexate: I.T.: 12 mg day 2

[total dose/cycle = 12 mg]

or 6 mg into Ommaya day 2

[total dose/cycle = 6 mg]

Cytarabine: I.T.: 100 mg days 7 **or** 8

[total dose/cycle = 100 mg]

Repeat cycle every 3 weeks for 6 or 8 cycles

Maintenance (POMP)

Mercaptopurine: I.V.: 1 g/m^2/day days 1 to 5

[total dose/cycle = 5 g/m^2]

Vincristine: I.V.: 2 mg day 1

[total dose/cycle = 2 mg]

Methotrexate: I.V.: 10 mg/m^2/day days 1 to 5

[total dose/cycle = 50 mg/m^2]

Prednisone: Oral: 200 mg/day days 1 to 5

[total dose/cycle = 1000 mg]

Repeat cycles monthly, except months 6, 7, 18, and 19 for 3 years

Intensification

Methotrexate: I.V.: 100 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 400 mg/m^2]

Asparaginase: I.V.: 20,000 units/day days 2, 9, 16, and 23

[total dose/cycle = 80,000 units]

Given during months 6 and 18 of maintenance

Cyclophosphamide: I.V.: 300 mg/m^2 every 12 hours, for 6 doses, days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Mesna: I.V.: 600 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Vincristine: I.V.: 2 mg/day days 4 and 11

[total dose/cycle = 4 mg]

Doxorubicin: I.V.: 50 mg/m^2/day continuous infusion day 4

[total dose/cycle = 50 mg/m^2]

Dexamethasone: Oral, I.V.: 40 mg/day days 1, 2, 3, 4, 11, 12, 13, and 14

[total dose/cycle = 320 mg]

Given during months 7 and 19 of maintenance

References

Variation 1:

Kantarjian H, Thomas D, O'Brien S, et al, “Long-Term Follow-Up Results of Hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone (Hyper-CVAD), A Dose-Intensive Regimen, in Adult Acute Lymphocytic Leukemia,” *Cancer*, 2004, 101(12):2788-2801.[PubMed 15481055]

Variation 2:

Thomas DA, Cortes J, O'Brien S, et al, “Hyper-CVAD Program in Burkitt's-Type Adult Acute Lymphoblastic Leukemia,” *J Clin Oncol*, 1999, 17(8):2461-70. [PubMed 10561310]

Variation 3:

Thomas DA, O'Brien S, Cortes J, et al, “Outcome With the Hyper-CVAD Regimens in Lymphoblastic Lymphoma,” *Blood*, 2004, 104(6):1624-30. [PubMed 15178574]

Variation 4:

Kantarjian HM, O'Brien S, Smith TL, et al, “Results of Treatment With Hyper-CVAD, A Dose-Intensive Regimen, in Adult Acute Lymphocytic Leukemia,” *J Clin Oncol*, 2000, 18(3): 547-61.[PubMed 10653870]

Variation 5:

Thomas DA, O'Brien S, Cortes J, et al, “Outcome With the Hyper-CVAD Regimens in Lymphoblastic Lymphoma,” *Blood*, 2004, 104(6):1624-30. [PubMed 15178574]

Hyper-CVAD (Lymphoma, non-Hodgkin's)

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's
Regimen UseLymphoma, non-Hodgkin's
Regimen

Cycle A: (Cycles 1, 3, 5, and 7)

Cyclophosphamide: I.V.: 300 mg/m^2 every 12 hours, for 6 doses, days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Vincristine: I.V.: 2 mg/day days 4 and 11

[total dose/cycle = 4 mg]

Doxorubicin: I.V.: 25 mg/m^2/day continuous infusion days 4 and 5

[total dose/cycle = 50 mg/m^2]

Dexamethasone: Oral, I.V.: 40 mg/day days 1, 2, 3, 4, 11, 12, 13, and 14

[total dose/cycle = 320 mg]

Cycle B: (Cycles 2, 4, 6, and 8)

Methotrexate: I.V.: 200 mg/m^2 day 1

followed by I.V.: 800 mg/m^2 continuous infusion day 1

[total dose/cycle = 1 g/m^2]

Leucovorin: Oral: 50 mg

followed by Oral: 15 mg every 6 hours, for 8 doses (start 24 hours after end of methotrexate infusion)

[total dose/cycle = 170 mg]

Cytarabine: I.V.: 3 g/m^2 every 12 hours, for 4 doses, days 2 and 3

[total dose/cycle = 12 g/m^2]

Repeat every 6 weeks in the following sequence: ABABABAB

References

Khouri IF, Romaguera J, Kantarjian H, et al, âHyper-CVAD and High-Dose Methotrexate/Cytarabine Followed by Stem-Cell Transplantation: An Active Regimen for Aggressive Mantle-Cell Lymphoma,â *J Clin Oncol*, 1998, 16(12):3803-9.[PubMed 9850025]

Hyper-CVAD (Multiple Myeloma)

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Multiple Myeloma]

Regimen UseMultiple myeloma

Related Information

- POMP

Regimen

Cyclophosphamide: I.V.: 300 mg/m^2 every 12 hours, for 6 doses, days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Mesna: I.V.: 600 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Doxorubicin: I.V.: 25 mg/m^2/day continuous infusion days 4 and 5

[total dose/cycle = 50 mg/m^2]

Vincristine: I.V.: 1 mg/day continuous infusion days 4 and 5

followed by I.V.: 2 mg day 11

[total dose/cycle = 4 mg]

Dexamethasone: Oral, I.V.: 20 mg/m^2/day days 1 to 5 and 11 to 14

[total dose/cycle = 180 mg/m^2]

Repeat cycle once if ≥50% reduction in myeloma protein

Maintenance

Cyclophosphamide: Oral: 125 mg/m^2 every 12 hours, for 10 doses, days 1 to 5

[total dose/cycle = 1250 mg/m^2]

Dexamethasone: Oral: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat maintenance cycle every 5 weeks

References

Dimopoulos MA, Weber D, Kantarjian H, et al, “HyperCVAD for VAD-Resistant Multiple Myeloma,” *Am J Hematol*, 1996, 52(2):77-81. [PubMed 8638645]

Hyper-CVAD + Imatinib

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Leukemia, Acute Lymphocytic]()
Regimen UseLeukemia, acute lymphocytic
Regimen

Cycle A: (Cycles 1, 3, 5, and 7)

Imatinib: Oral: 400 mg/day days 1 to 14

[total dose/cycle = 5600 mg]

Cyclophosphamide: I.V.: 300 mg/m^2 every 12 hours, for 6 doses, days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Mesna: I.V. 600 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Vincristine: I.V.: 2 mg/day days 4 and 11

[total dose/cycle = 4 mg]

Doxorubicin: I.V.: 50 mg/m^2/day continuous infusion day 4

[total dose/cycle = 50 mg/m^2]

Dexamethasone: Oral, I.V.: 40 mg/day days 1, 2, 3, 4, 11, 12, 13, and 14

[total dose/cycle = 320 mg]

Cycle B: (Cycles 2, 4, 6, and 8)

Imatinib: Oral: 400 mg/day days 1 to 14

[total dose/cycle = 5600 mg]

Methotrexate: I.V.: 1 g/m^2/day continuous infusion day 1

[total dose/cycle = 1 g/m^2]

Leucovorin: I.V.: 50 mg then 15 mg every 6 hours, for 8 doses (start 12 hours after the end of the methotrexate infusion)

[total dose/cycle = 170 mg]

Cytarabine: I.V.: 3 g/m^2 every 12 hours for 4 doses, days 2 and 3

[total dose/cycle = 12 g/m^2]

Repeat every 6 weeks in the following sequence: ABABABAB

CNS Prophylaxis

Methotrexate: I.T.: 12 mg/day day 2

[total dose/cycle = 12 mg/day]

or 6 mg into Ommaya day 2

[total dose/cycle = 6 mg/day]

Cytarabine: I.T.: 100 mg/day day 7 or 8

[total dose/cycle = 100 mg/day]

Repeat cycle every 3 weeks for 3 or 4 cycles

Maintenance (POMP)

Imatinib: Oral: 600 mg/day

[total dose/cycle = 18,000 mg]

Vincristine: I.V.: 2 mg/day day 1

[total dose/cycle = 2 mg]

Prednisone: Oral: 200 mg/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

Repeat cycle every month (except months 6 and 13) for 13 months

Intensification

Imatinib: Oral: 400 mg/day days 1 to 14

[total dose/cycle = 5600 mg]

Cyclophosphamide: I.V.: 300 mg/m^2 every 12 hours, for 6 doses, days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Mesna: I.V.: 600 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Vincristine: I.V.: 2 mg/day days 4 and 11

[total dose/cycle = 4 mg]

Doxorubicin: 50 mg/m^2/day continuous infusion day 4

[total dose/cycle = 50 mg/m^2]

Dexamethasone: I.V. or Oral: 40 mg/day days 1, 2, 3, 4, 11, 12, 13, and 14

[total dose/cycle = 320 mg]

Cycle is given in months 6 and 13 during maintenance

References

Thomas DA, Faderl S, Cortes J, et al, âTreatment of Philadelphia Chromosome-Positive Acute Lymphocytic Leukemia With Hyper-CVAD and Imatinib Mesylate,â *Blood,* 2004, 103(12):4396-407.[PubMed 14551133]

Hyper-CVAD + Rituximab

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphona, non-Hodgkin's (Mantle cell)

Regimen

Cycle A: (Cycles 1, 3, 5 [and 7, if needed])

Rituximab: I.V.: 375 mg/m^2 day 1

[total dose/cycle = 375 mg/m^2]

Cyclophosphamide: I.V.: 300 mg/m^2 every 12 hours, for 6 doses, days 2, 3, and 4

[total dose/cycle = 1800 mg/m^2]

Mesna: I.V.: 600 mg/m^2 continuous infusion days 2, 3, and 4

[total dose/cycle = 1800 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 (maximum 2 mg) days 5 and 12

[total dose/cycle = 2.8 mg/m^2; maximum 4 mg]

Doxorubicin: I.V.: 16.7 mg/m^2 continuous infusion days 5, 6, and 7

[total dose/cycle = 50.1 mg/m^2]

Dexamethasone: Oral, I.V.: 40 mg/day days 2, 3, 4, 5, 12, 13, 14, and 15

[total dose/cycle = 320 mg]

Cycle B: (Cycles 2, 4, 6 [and 8, if needed])

Rituximab: I.V.: 375 mg/m^2 day 1

[total dose/cycle = 375 mg/m^2]

Methotrexate: I.V.: 200 mg/m^2 day 2

followed by I.V.: 800 mg/m^2continuous infusion day 2

[total dose/cycle = 1000 mg/m^2]

Leucovorin: Oral: 50 mg (start 12 hours after the end of the methotrexate infusion)

followed by Oral: 15 mg every 6 hours, for 8 doses

[total dose/cycle = 170 mg]

Cytarabine: I.V.: 3 g/m^2 every 12 hours, for 4 doses, day 3 and 4

[total dose/cycle = 12 g/m^2]

Repeat every 6 weeks in the following sequence: ABABABAB

References

Romaguera JE, Fayad L, Rodriguez MA, et al, âHigh Rate of Durable Remissions After Treatment of Newly Diagnosed Aggressive Mantle-Cell Lymphoma With Rituximab Plus Hyper-CVAD Alternating With Rituximab Plus High-Dose Methotrexate and Cytarabine,â *J Clin Oncol*, 2005, 23(28):7013-23. [PubMed 16145068]

Ibandronate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Bisphosphonates: Safety Update Regarding Possible Association With Atrial Fibrillation - November 2008

The Food and Drug Administration (FDA) has been reviewing placebo-controlled trials of the 7 bisphosphonates currently marketed in the US. This review is in response to study results associating an increased incidence of atrial fibrillation (AF) with alendronate or zoledronic acid use in women (65-89 years of age) with osteoporosis.

The FDA reviewed all the submitted data (19,687 bisphosphonate-treated patients and 18,358 placebo-treated patients) from these studies. Overall, the occurrence of AF was rare in each study with an absolute difference in event rates between each of the bisphosphonate and placebo arms of 0-3 per 1000. A zoledronic acid study showed a statistically significant increase in the rate of AF in the active treatment arm. However, no clear association between bisphosphonate use and AF could be established. In this study, AF events were diagnosed more than 30 days after receiving zoledronic acid in 47 of the 50 patients diagnosed with AF. According to the FDA, healthcare providers should not alter their prescribing patterns for bisphosphonates and patients should not stop taking their medication.

The FDA will continue monitoring the safety of bisphosphonates through postmarketing reports and is assessing the need for additional epidemiologic studies.

Further information is available at http://www.fda.gov/cder/drug/early_comm/bisphosphonates_update_200811.htm

Pronunciation(eye BAN droh nate)

U.S. Brand NamesBoniva®

Canadian Brand NamesBondronat®

Pharmacologic CategoryBisphosphonate Derivative

Use: Labeled IndicationsTreatment and prevention of osteoporosis in postmenopausal females

Use: Unlabeled/InvestigationalHypercalcemia of malignancy; corticosteroid-induced osteoporosis; Paget's disease; reduce bone pain and skeletal complications from metastatic bone disease

Dosing: Adults

Treatment of postmenopausal osteoporosis:

Oral: 2.5 mg once daily **or** 150 mg once a month

I.V.: 3 mg every 3 months

Prevention of postmenopausal osteoporosis: Oral: 2.5 mg once daily **or** 150 mg once a month

Hypercalcemia of malignancy (unlabeled use): I.V.: 2-4 mg over 2 hours

Metastatic bone disease (unlabeled use):

Oral: 50 mg once daily

I.V.: 6 mg over 1 hour every 3-4 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Mild or moderate impairment: Dosing adjustment not needed.

Severe impairment (Cl_{cr} <30 mL/minute): Use not recommended.

Dosage adjustment in renal impairment for oncologic uses (unlabeled): Severe impairment (Cl_{cr} <30 mL/minute):

Oral: 50 mg once weekly

I.V.: 2 mg over 1 hour every 3-4 weeks

Dosing: Hepatic ImpairmentDosing adjustment not needed.

Calculations

- Creatinine Clearance: Adults

Administration: I.V.Administer as a 15-30 second bolus. Do not mix with calcium-containing solutions or other drugs. For osteoporosis, do not administer more frequently than every 3 months. Infuse over 1 hour for metastatic bone disease and over 2 hours for hypercalcemia of malignancy.

Administration: OralShould be administered 60 minutes before the first food or drink of the day (other than water) and prior to taking any oral medications or supplements (eg, calcium, antacids, vitamins). Ibandronate should be taken in an upright position with a full glass (6-8 oz) of plain water and the patient should avoid lying down for 60 minutes to minimize the possibility of GI side effects. Mineral water with a high calcium content should be avoided. The tablet should be swallowed whole; do not chew or suck. Do not eat or drink anything (except water) for 60 minutes following administration of ibandronate.

Once-monthly dosing: The 150 mg tablet should be taken on the same date each month. In case of a missed dose, do not take two 150 mg tablets within the same week. If the next scheduled dose is 1-7 days away, wait until the next scheduled dose to take the tablet. If the next scheduled dose is >7 days away, take the dose the morning it is remembered, and then resume taking the once-monthly dose on the originally scheduled day.

Dietary ConsiderationsSupplemental calcium or vitamin D may be required if dietary intake is not adequate; women >50 years of age should consume 1200-1500 mg/day of elemental calcium and 800-1000 int. units/day of vitamin D. Ibandronate tablet should be taken with a full glass (6-8 oz) of plain water, at least 60 minutes prior to any food, beverages, or medications. Mineral water with a high calcium content should be avoided.

StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to ibandronate or any component of the formulation; hypocalcemia; oral tablets are also contraindicated in patients unable to stand or sit upright for at least 60 minutes

Warnings/Precautions

Concerns related to adverse effects:

- Bone/joint/muscle pain: Infrequently, severe (and occasionally debilitating) bone, joint, and/or muscle pain have been reported during bisphosphonate treatment. The onset of pain ranged from a single day to several months. Consider discontinuing therapy in patients who experience severe symptoms; symptoms usually resolve upon discontinuation. Some patients experienced recurrence when rechallenged with same drug or another bisphosphonate; avoid use in patients with a history of these symptoms in association with bisphosphonate therapy.

- Gastrointestinal mucosa irritation: May cause irritation to upper gastrointestinal mucosa. Esophagitis, dysphagia, esophageal ulcers, esophageal erosions, and esophageal stricture (rare) have been reported with oral bisphosphonates; risk increases in patients unable to comply with dosing instructions. Use with caution in patients with dysphagia, esophageal disease, gastritis, duodenitis, or ulcers (may worsen underlying condition). Discontinue use if new or worsening symptoms develop.

- Hypocalcemia: Hypocalcemia has been reported with the use of bisphosphonates. Prior to therapy initiation, hypocalcemia must be corrected; ensure adequate calcium and vitamin D intake.

- Osteonecrosis of the jaw: Bisphosphonate therapy has been associated with osteonecrosis, primarily of the jaw; this has been observed mostly in cancer patients, but also in patients with postmenopausal osteoporosis and other diagnoses. Risk factors include a diagnosis of cancer, with concomitant chemotherapy, radiotherapy, or corticosteroids; anemia, coagulopathy, infection, or pre-existing dental disease. Most reported cases occurred after I.V. bisphosphonate therapy; however, cases have been reported following oral therapy. Symptoms included nonhealing extraction socket or an exposed jawbone. There are no data addressing whether discontinuation of therapy reduces the risk of developing osteonecrosis; however, as a precautionary measure, dental exams and preventative dentistry should be performed prior to placing patients with risk factors on chronic bisphosphonate therapy. Invasive dental procedures should be avoided during treatment.

Disease-related concerns:

- Renal impairment: Use not recommended with severe renal impairment (Cl_{cr} <30 mL/minute).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Injection: Intravenous bisphosphonates may cause transient decreases in serum calcium and have also been associated with renal toxicity.

Geriatric ConsiderationsStudies with elderly found no difference between younger adults and the elderly. No special dosage changes are necessary.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse effects were demonstrated in animal studies. There are no adequate and well-controlled studies in pregnant women. Bisphosphonates are incorporated into the bone matrix and are gradually released over time. Theoretically, there may be a risk of fetal harm when pregnancy follows the completion of therapy. Based on limited case reports with pamidronate, serum calcium levels in the newborn may be altered if administered during pregnancy.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsPercentages vary based on frequency of administration (daily vs monthly). Unless specified, percentages are reported with oral use.

>10%:

Gastrointestinal: Dyspepsia (6% to 12%)

Neuromuscular & skeletal: Back pain (4% to 14%)

1% to 10%:

Cardiovascular: Hypertension (6% to 7%)

Central nervous system: Headache (3% to 7%), dizziness (1% to 4%), insomnia (1% to 2%)

Dermatologic: Rash (1% to 2%)

Endocrine & metabolic: Hypercholesterolemia (5%)

Gastrointestinal: Abdominal pain (5% to 8%), diarrhea (4% to 7%), nausea (5%), tooth disorder (4%), constipation (3% to 4%), vomiting (3%)

Genitourinary: Urinary tract infection (2% to 6%)

Hepatic: Alkaline phosphatase decreased (frequency not defined)

Local: Injection site reaction (<2%)

Neuromuscular & skeletal: Pain in extremity (1% to 8%), arthralgia (4% to 6%), myalgia (1% to 6%), joint disorder (4%), weakness (4%), muscle cramp (2%)

Respiratory: Bronchitis (3% to 10%), pneumonia (6%), pharyngitis/nasopharyngitis (3% to 4%), upper respiratory infection (2%)

Miscellaneous: Acute phase reaction (I.V. 10%; oral 3% to 9%), infection (4%), flu-like syndrome (1% to 4%), allergic reaction (3%)

Postmarketing and/or case reports: Anaphylaxis; angioedema; bronchospasm; hypocalcemia; incapacitating bone, joint or muscle pain; iritis; ocular inflammation; osteonecrosis of the jaw; scleritis; uveitis

Drug Interactions

Aminoglycosides: May enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Magaldrate; Sodium Bicarbonate. *Risk D: Consider therapy modification*

Calcium Salts: May decrease the absorption of Bisphosphonate Derivatives. *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral iron salts are of concern. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Phosphate Supplements: Bisphosphonate Derivatives may enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase risk of osteoporosis).

Food: May reduce absorption; mean oral bioavailability is decreased up to 90% when given with food.

Test InteractionsBisphosphonates may interfere with diagnostic imaging agents such as technetium-99m-diphosphonate in bone scans.

Monitoring ParametersBone mineral density as measured by central dual-energy x-ray absorptiometry (DXA) of the hip or spine (at least every 2 years); serum creatinine prior to each I.V. dose

Nursing: Physical Assessment/MonitoringAssess history for any previous adverse response to bisphosphonates and ability to comply with administration instructions. Use caution with renal impairment. Correct any hypocalcemia prior to beginning treatment. Patients at risk for osteonecrosis (eg, chemotherapy, corticosteroids, poor oral hygiene) should have dental exams and necessary preventive dentistry should be done before beginning bisphosphonate therapy. I.V.: See infusion specifics. Assess results of periodic laboratory tests, therapeutic effectiveness, and adverse reactions (eg, immediate or long-term musculoskeletal pain). Teach appropriate use and specific administration directions (oral), lifestyle and dietary changes according to purpose for use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum creatinine prior to each I.V. dose

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Oral: Take as directed, with a full glass of water first thing in the morning and at least 60 minutes before the first food or beverage of the day. Wait at least 60 minutes after taking Ibandronate before taking anything else. Stay in sitting or standing position for 60 minutes following administration and until after the first food of the day to reduce potential for esophageal irritation. Consult prescriber to determine necessity of lifestyle changes (eg, decreased smoking, decreased alcohol intake, dietary supplements of calcium or vitamin D). Certain dental procedures should be avoided if possible while you are taking this medication; consult prescriber. You may experience temporary flatulence, bloating, nausea, or acid regurgitation (small, frequent meals may help) or temporary bone pain (consult prescriber for analgesic). Report persistent muscle or bone pain; leg cramps; acute headache; persistent gastric pain or unresolved GI upset; unusual fever; chills; rash; or pain in mouth. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 1 mg/mL (3 mL) [prefilled syringe]

Tablet: 2.5 mg [once-daily formulation]; 150 mg [once-monthly formulation]

Generic AvailableNo

ManufacturerRoche Laboratories, Inc

Pricing: U.S. (www.drugstore.com)

Kit (Boniva)

3 mg/3 mL (1): $465.09

Tablets (Boniva)

150 mg (3): $306.59

Mechanism of ActionA bisphosphonate which inhibits bone resorption via actions on osteoclasts or on osteoclast precursors; decreases the rate of bone resorption, leading to an indirect increase in bone mineral density.

Pharmacodynamics/Kinetics

Distribution: Terminal V_d: 90 L; 40% to 50% of circulating ibandronate binds to bone

Protein binding: 85.7% to 99.5%

Metabolism: Not metabolized

Bioavailability: Oral: Reduced by 90% following standard breakfast

Half-life elimination:

Oral: 150 mg dose: Terminal: 37-157 hours

I.V.: Terminal: ~5-25 hours

Time to peak, plasma: Oral: 0.5-2 hours

Excretion: Urine (50% to 60% of absorbed dose, excreted as unchanged drug); feces (unabsorbed drug)

Dental Health Professional ConsiderationsCases of oral bisphosphonate-associated ONJ have been reported. A report by the Council of Scientific Affairs of the American Dental Association (accessed at: http://www.ada.org/prof/resources/topics/osteonecrosis.asp) as of July 2006 gave an estimated incidence of 0.7 cases for every 100,000 person-years of exposure to alendronate (Fosamax®). This translates to one case for every 142,857 person-years exposure. This figure from the ADA report was based on information received from Merck & Co citing 170 worldwide cases for alendronate (Fosamax®). In addition, Procter & Gamble Pharmaceuticals has cited 20 cases for risedronate (Actonel®) and Roche Laboratories has cited one case for ibandronate (Boniva®).

Consumer Reports On Health stated that the risk of jaw bone osteoporosis due to alendronate (Fosamax®), risedronate (Actonel®), or ibandronate (Boniva®) taken to prevent osteoporosis is very low and is estimated to be one out of every 20,000 users. That report mentioned that tooth extraction or implants increase the risk of developing osteonecrosis in patients taking any of these drugs for osteoporosis. The report also recommended that patients should stop taking any of these oral drugs 1-2 months before and after such dental treatment. No evidence was presented to support this statement.

In terms of length of exposure to oral bisphosphonates prior to onset of ONJ, data from large population studies or controlled studies is lacking. A report by Marx et al, observed that of three cases of ONJ associated with Fosamax® exposure, one patient had been taking 10 mg/day by mouth for 6 years and the other two patients 10 mg/day by mouth for 3 and 2 years respectively. In contrast, they observed that in cancer patients receiving intravenous bisphosphonates, the time period between the first doses of the bisphosphonate to first recognition of exposed bone either by the patients or by the clinician, was 9.4 months for zoledronate (Zometa®), 14.3 months for pamidronate (Aredia®), and 12.1 months for pamidronate then to zoledronate.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tooth disorder.

Osteonecrosis of the jaw (ONJ), generally associated with local infection and/or tooth extraction and often with delayed healing, has been reported in patients taking bisphosphonates. Symptoms included nonhealing extraction socket or an exposed jawbone. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates. However, some have occurred in patients with postmenopausal osteoporosis taking oral bisphosphonates. Dental surgery may exacerbate ONJ. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Patients who develop ONJ while on bisphosphonate therapy should receive care by an oral surgeon. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsIbandronate Sodium; Ibandronic Acid

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International Brand Names Bandrobon (AR); Bonat (IL); Bondronat (BE, BG, CH, CL, CN, CZ, DE, DK, EC, EE, GR, ID, IE, MX, NO, PE, SE, TH, TW); Bondronat IV (PH); Bonviva (AT, BE, BG, BR, CH, CN, CO, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, ID, IE, IT, KP, MX, NL, NO, PE, PH, PT, RU, SE, SG, TH, TR, TW, UY); Tefal (PY)

Ibritumomab

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Dosage maximum: Do not exceed the Y-90 Ibritumomab maximum allowable dose of 32 mCi, regardless of the patient’s body weight.

Pronunciation(ib ri TYOO mo mab)

U.S. Brand NamesZevalin®

Canadian Brand NamesZevalin®

Pharmacologic CategoryAntineoplastic Agent, Monoclonal Antibody; Radiopharmaceutical

Use: Labeled IndicationsTreatment of relapsed or refractory low-grade or follicular B-cell non-Hodgkin's lymphoma

Dosing: Adults**Note:** Premedication with acetaminophen and diphenhydramine is recommended for rituximab infusions.

Non-Hodgkin's lymphoma, B-cell (relapsed or refractory low-grade, follicular, or transformed): I.V.: Ibritumomab is administered **only** as part of the Zevalin® therapeutic regimen (a combined treatment regimen with rituximab). The regimen consists of two steps:

Day 1:

Rituximab infusion: 250 mg/m^2 at an initial rate of 50 mg/hour. If hypersensitivity or infusion-related events do not occur, increase infusion in increments of 50 mg/hour every 30 minutes, to a maximum of 400 mg/hour. Discontinue for severe infusion reaction. For less severe infusion reactions, temporarily slow or interrupt; the infusion may be resumed at one-half the previous rate upon improvement of symptoms.

In-111 ibritumomab infusion: Within 4 hours of the completion of rituximab infusion, inject 5 mCi (1.6 mg total antibody dose) over 10 minutes.

Note: Biodistribution of In-111 ibritumomab should be assessed by imaging at 48-72 hours postinjection. Optional additional imaging may be performed to resolve ambiguities. If biodistribution is not acceptable, the patient should not proceed to Step 2.

Day 7, 8, or 9:

Rituximab infusion: 250 mg/m^2 at an initial rate of 100 mg/hour (50 mg/hour if infusion-related events occurred with the first infusion). If hypersensitivity or infusion-related events do not occur, increase infusion in increments of 100 mg/hour every 30 minutes, to a maximum of 400 mg/hour, as tolerated.

Y-90 ibritumomab infusion: Within 4 hours of the completion of rituximab infusion:

Platelet count ≥150,000 cells/mm^3: Inject 0.4 mCi/kg (14.8 MBq/kg actual body weight) over 10 minutes; maximum dose: 32 mCi (1184 MBq)

Platelet count between 100,000-149,000 cells/mm^3: Inject 0.3 mCi/kg (11.1 MBq/kg actual body weight) over 10 minutes; maximum dose: 32 mCi (1184 MBq)

Platelet count <100,000 cells/mm^3: Do **not** administer

Maximum dose: The prescribed, measured, and administered dose of Y-90 ibritumomab must not exceed 32 mCi (1184 MBq), regardless of the patient's body weight

Dosing: ElderlyRefer to adult dosing.

Calculations

- Body Surface Area: Adults

Administration: I.V.

Rituximab: Administer the first infusion of rituximab at an initial rate of 50 mg/hour. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. Immediately stop infusion for severe infusion reaction (discontinue ibritumomab regimen); less severe reactions may be managed by slowing or interrupting infusion. For less severe reactions, infusion may continue at one-half the previous rate upon improvement of patient symptoms. Subsequent rituximab infusion can be administered at an initial rate of 100 mg/hour and increased in 100 mg/hour increments at 30-minute intervals, to a maximum of 400 mg/hour as tolerated.

In-111 and Y-90 ibritumomab: Inject slowly, over 10 minutes through a 0.22 micron low protein binding in-line filter. After injection, flush line with at least 10 mL normal saline. Y-90 ibritumomab: establish free-flowing I.V. line prior to administration; avoid extravasation.

StorageStore at 2°C to 8°C (36°F to 46°F); do not freeze. Kit is not radioactive.
ReconstitutionTo prepare radiolabeled injection, follow detailed preparation guidelines provided by manufacturer.
ContraindicationsThere are no contraindications listed within the manufacturer's labeling.
Warnings/Precautions

Boxed warnings:

- Cutaneous/mucocutaneous reactions: See "Concerns related to adverse effects" below.
- Cytopenias: See "Concerns related to adverse effects" below.
- Infusion reactions: See "Concerns related to adverse effects" below.
- Maximum dose: See "Other warnings/precautions" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Cutaneous/mucocutaneous reactions: **[U.S. Boxed Warning]: Severe cutaneous and mucocutaneous skin reactions have been reported (with fatalities) in postmarketing experience.** These include erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis. Onset may occur within days to 3-4 months following infusion. Patients experiencing severe cutaneous or mucocutaneous skin reactions should not receive any further component of the ibritumomab regimen.
- Cytopenias: **[U.S. Boxed Warning]: Delayed, prolonged, and severe cytopenias (thrombocytopenia and neutropenia) are common. Do not administer to patients with ≥25% lymphoma marrow involvement, patients with impaired bone marrow reserve** (eg, prior myeloablative treatment, platelet count <100,000/mm^3, neutrophil count <1500/mm^3, hypocellular marrow), or to patients with prior stem cell collection failure. Hemorrhage may occur due to thrombocytopenia; use caution with patients taking anticoagulants or medications interfering with platelet function. Closely monitor patients for complications of cytopenias (eg, febrile neutropenia, hemorrhage) for up to 3 months after administration.
- Infusion reactions: **[U.S. Boxed Warning]: Severe and potentially fatal infusion reactions (angioedema, bronchospasm, hypotension, hypoxia) have been reported, typically with the first rituximab infusion** (during infusion or within 30-120 minutes of infusion). Severe reactions have also included acute respiratory distress syndrome, pulmonary infiltrates, urticaria, cardiogenic shock, MI, and ventricular fibrillation. Immediately stop infusion for severe infusion reaction; less severe reactions may be managed by slowing or interrupting infusion. Medications for the treatment of hypersensitivity reactions should be available for immediate use.
- Radiation injury: Delayed (up to 1 month) radiation injury has occurred in or near areas of lymphomatous involvement.
- Secondary malignancies: Secondary malignancies (acute myelogenous leukemia and/or myelodysplastic syndrome) have been reported; the median time to secondary malignancy diagnosis following ibritumomab treatment was 1.9 years (range: 0.4-6.3 years).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Albumin: Product contains albumin, which confers a theoretical risk of transmission of viral disease or Creutzfeldt-Jakob disease.

Other warnings/precautions:

- Experienced professionals: Use should be reserved to physicians and other professionals qualified and experienced in the safe handling of radiopharmaceuticals, and in monitoring and emergency treatment of infusion reactions.
- Extravasation/radiation necrosis: Infusion site erythema and ulceration have been reported following extravasation; monitor infusion site; promptly terminate infusion with symptoms/signs of extravasation (restart in another limb). There is a case report of (delayed) erythema and ulceration, which is described as radiation necrosis following yttrium-90-ibritumomab extravasation (Williams, 2006).
- Immunizations: Do not administer live viral vaccines to patients who have recently received ibritumomab treatment. The safety of immunization with live vaccines following ibritumomab therapy has not been studied; the ability to generate a response to any vaccine after receiving treatment has not been studied.
- Maximum dose: **[U.S. Boxed Warning]: Do not exceed the Y-90 Ibritumomab maximum allowable dose of 32 mCi; do not administer to patients with altered biodistribution.** To be used as part of the Zevalin® therapeutic regimen (in combination with rituximab). Safety and efficacy of repeated courses of the therapeutic regimen have not been established.
- Radioactivity: The contents of the kit are not radioactive until radiolabeling occurs. During and after radiolabeling, adequate shielding should be used with this product, in accordance with institutional radiation safety practices.

Pregnancy Risk FactorD
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Y-90 ibritumomab may cause fetal harm. Women of childbearing potential should avoid becoming pregnant during treatment with ibritumomab. Both males and females should use effective contraception for 12 months following treatment. The effect on future fertility is unknown.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsIt is not known whether ibritumomab is excreted in breast milk; women are advised to discontinue breast-feeding and substitute with formula feedings.

Adverse ReactionsSevere, potentially life-threatening allergic reactions have occurred in association with infusions. Also refer to Rituximab monograph.

>10%:

Central nervous system: Chills (24%), fever (17%), pain (13%), headache (12%)

Gastrointestinal: Nausea (31%), abdominal pain (16%), vomiting (12%)

Hematologic: Thrombocytopenia (95%; grades 3/4: 63%; nadir: 53 days), neutropenia (77%; grades 3/4: 60%; nadir: 62 days), anemia (61%; grades 3/4: 17%; nadir: 68 days), myelosuppression (nadir: 7-9 weeks; duration: 22-35 days)

Neuromuscular & skeletal: Weakness (43%)

Respiratory: Dyspnea (14%)

Miscellaneous: Infection (29%)

1% to 10%:

Cardiovascular: Peripheral edema (8%), flushing (6%), hypotension (6%)

Central nervous system: Dizziness (10%), insomnia (5%), anxiety (4%)

Dermatologic: Pruritus (9%), rash (8%), bruising (7%), angioedema (5%; grades 3/4: <1%), urticaria (4%), petechiae (3%)

Gastrointestinal: Diarrhea (9%), anorexia (8%), abdominal distension (5%), constipation (5%), dyspepsia (4%), melena (2%; life threatening in 1%), gastrointestinal hemorrhage (severe: 1%)

Hematologic: Pancytopenia (severe: 2%), secondary malignancies (2% to 6%; includes acute myelogenous leukemia and myelodysplastic syndrome)

Neuromuscular & skeletal: Back pain (8%), arthralgia (7%), myalgia (7%)

Respiratory: Cough (10%), throat irritation (10%), rhinitis (6%), bronchospasm (5%), epistaxis (3%), apnea (severe: 1%)

Miscellaneous: Diaphoresis (4%), HAMA antibody formation (4%), allergic reaction (2%), infusion reaction (severe: 1%), tumor pain (severe: 1%)

<1%: Anaphylactic reactions, arthritis, cerebral hemorrhage, cytogenetic abnormalities, encephalopathy, hematemesis, hemorrhage, hypersensitivity, meningioma (benign), pulmonary edema, pulmonary embolism, stroke (hemorrhagic), subdural hematoma, tachycardia, vaginal hemorrhage

Postmarketing and/or case reports: Cutaneous and mucocutaneous reactions (eg, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis and exfoliative dermatitis); infusion site erythema/ulceration (following extravasation), radiation injury/complications (delayed; in tissues in or near areas of lymphomatous involvement); radiation necrosis (following yttrium-90-ibritumomab extravasation)

Oncology: VesicantThere is an isolated case report of (delayed) erythema and ulceration, which is described as radiation necrosis following yttrium-90-ibritumomab extravasation (Williams, 2006).

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

Anticoagulants: May enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid echinacea (may diminish therapeutic effect). Avoid cat's claw, dong quai, evening primrose, feverfew, garlic, ginger, ginkgo, red clover, horse chestnut, green tea, ginseng (all have antiplatelet activity).

Monitoring ParametersPatients must be monitored for infusion-related allergic reactions (typically within 30-120 minutes of administration). Obtain CBC with differential and platelet counts weekly. Platelet count must be obtained prior to Day 7, 8,or 9. Monitor for up to 3 months after use.

Biodistribution of In-111 ibritumomab should be assessed by imaging at 48-72 hours post injection. Optional additional imaging may be performed to resolve ambiguities. If biodistribution is not acceptable, the patient should not proceed to Day 7, 8, or 9.

Monitoring: Lab TestsObtain CBC with differential and platelet counts weekly. Platelet count must be obtained prior to Day 7, 8, or 9. Monitor for up to 3 months after use.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Each kit contains 4 vials for preparation of either In-111 or Y-90 conjugate (as indicated on container label)

Injection, solution:

Zevalin®: 1.6 mg/mL (2 mL) [supplied with sodium acetate solution, formulation buffer vial (includes albumin 750 mg), and an empty reaction vial]

Generic AvailableNo

ManufacturerIDEC Pharmaceuticals

Mechanism of ActionIbritumomab is a monoclonal antibody directed against the CD20 antigen found on B lymphocytes (normal and malignant). Ibritumomab binding induces apoptosis in B lymphocytes *in vitro*. It is combined with the chelator tiuxetan, which acts as a specific chelation site for either Indium-111 (In-111) or Yttrium-90 (Y-90). The monoclonal antibody acts as a delivery system to direct the radioactive isotope to the targeted cells, however, binding has been observed in lymphoid cells throughout the body and in lymphoid nodules in organs such as the large and small intestines. Indium-111 is a gamma-emitter used to assess biodistribution of ibritumomab, while Y-90 emits beta particles. Beta-emission induces cellular damage through the formation of free radicals (in both target cells and surrounding cells).

Pharmacodynamics/Kinetics

Duration: Beta cell recovery begins in ~12 weeks; generally in normal range within 9 months

Distribution: To lymphoid cells throughout the body and in lymphoid nodules in organs such as the large and small intestines, spleen, testes, and liver

Metabolism: Has not been characterized; the product of yttrium-90 radioactive decay is zirconium-90 (nonradioactive); Indium-111 decays to cadmium-111 (nonradioactive)

Half-life elimination: Y-90 ibritumomab: 30 hours; Indium-111 decays with a physical half-life of 67 hours; Yttrium-90 decays with a physical half-life of 64 hours

Excretion: A median of 7.2% of the radiolabeled activity was excreted in urine over 7 days

Pharmacotherapy PearlsIbritumomab tiuxetan is produced in Chinese hamster ovary cell cultures. Kit is not radioactive. Radiolabeling of ibritumomab with Yttrium-90 and Indium-111 (not included in kit) must be performed by appropriate personnel in a specialized facility.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Hypotension, cough, throat irritation, rhinitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, insomnia, or anxiety

Mental Health: Effects on Psychiatric TreatmentGastrointestinal side effects are common; use caution with SSRIs, lithium, and valproic acid. Hematologic side effects are common; use caution with clozapine, carbamazepine, and valproic acid.

Index TermsIbritumomab Tiuxetan; IDEC-Y2B8; In-111 Ibritumomab; In-111 Zevalin; Y-90 Ibritumomab; Y-90 Zevalin

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Witzig TE, White CA, Gordon LI, et al, “Safety of Yttrium-90 Ibritumomab Tiuxetan Radioimmunotherapy for Relapsed Low-Grade, Follicular, or Transformed Non-Hodgkin’s Lymphoma,” *J Clin Oncol*, 2003, 21(7):1263-70.[PubMed 12663713]

Witzig TE, White CA, Wiseman GA, et al, “Phase I/II Trial of IDEC-Y2B8 Radioimmunotherapy for Treatment of Relapsed or Refractory CD20(+) B-Cell Non-Hodgkin's Lymphoma,” *J Clin Oncol*, 1999, 17(12):3793-803.[PubMed 10577851]

International Brand NamesZevalin (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, NL, NO, NZ, PT, RU, SE, TH, TR); Zevamab (CO, UY)

Ibuprofen, Pseudoephedrine, and Chlorpheniramine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation

(eye byoo PROE fen, soo doe e FED rin, & klor fen IR a meen)

U.S. Brand NamesAdvil® Allergy Sinus; Advil® Multi-Symptom Cold

Canadian Brand NamesAdvil® Cold and Sinus Plus

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation; Nonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsTemporary relief of symptoms associated with the common cold, hay fever, or other respiratory allergies

Dosing: Adults**Common cold, hay fever, respiratory allergies:** Oral: One caplet every 4-6 hours while symptoms persist (maximum: 6 caplets/24 hours); treatment for >10 days is not recommended unless directed by healthcare provider

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Common cold, hay fever, respiratory allergies**: Oral: Children ≥12 years: Refer to adult dosing.

Administration: OralMay be administered with food or milk if stomach upset occurs.

Dietary ConsiderationsMay be taken with food or milk if stomach upset occurs.

StorageStore at 20°C to 25ºC (68°F to 77°F); avoid excessive heat.

ContraindicationsHypersensitivity to ibuprofen, pseudoephedrine, chlorpheniramine, or any component of the formulation; use with or within 2 weeks of an MAO inhibitor (MAO-I); immediately prior to or after coronary bypass graft (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Aseptic meningitis: May increase the risk of aseptic meningitis, especially in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: NSAIDs are associated with an increased risk of adverse cardiovascular events, including MI, stroke, and new onset or worsening of pre-existing hypertension. Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Gastrointestinal events: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation. These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.
- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.
- Coronary artery bypass graft surgery: Use is contraindicated when used immediately prior to or after coronary artery bypass graft (CABG) surgery. Risk of MI and stroke may be increased with use following CABG surgery.
- Diabetes: Use with caution in patients with diabetes mellitus.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or angle-closure glaucoma.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or urinary obstruction.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

- Thyroid disease: Use with caution in patients with thyroid disease.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Not for self-medication (OTC use) in children <12 years of age.

Other warnings/precautions:

- Self-medication (OTC use): Prior to self-medication, patients should contact healthcare provider if they have had recurring stomach pain or upset, ulcers, bleeding problems, asthma, emphysema, chronic bronchitis, high blood pressure, heart or kidney disease, thyroid disease, diabetes, glaucoma, enlarged prostate, other serious medical problems, are currently taking a diuretic, aspirin, anticoagulant, sedative or tranquilizer, or are ≥60 years of age. Recommended dosages should not be exceeded, due to an increased risk of GI bleeding. Stop use and consult a healthcare provider if symptoms get worse, newly appear, or continue; if an allergic reaction occurs; if nervousness, dizziness, or sleeplessness occurs; or if fever lasts for >3 days, congestion lasts for >7 days, or pain >10 days. Consuming ≥3 alcoholic beverages/day or taking longer than recommended may increase the risk of GI bleeding.

Pregnancy ConsiderationsSee individual agents.
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsSee individual agents.
Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression and/or enhance gastric mucosal irritation).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet:

Advil® Allergy Sinus, Advil® Multi-Symptom Cold: Ibuprofen 200 mg, pseudoephedrine hydrochloride 30 mg, and chlorpheniramine maleate 2 mg

Generic AvailableNo

Manufacturer

Wyeth

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Chlorpheniramine
- Ibuprofen
- Pseudoephedrine

Mental Health: Effects on Mental StatusMay cause dizziness, sedation, nervousness, or insomnia; may rarely cause confusion, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor therapy. Ibuprofen component may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels. Concurrent use with psychotropic agents may produce worsening dry mouth.

Index TermsChlorpheniramine Maleate, Ibuprofen, and Pseudoephedrine; Ibuprofen, Pseudoephedrine, and Chlorpheniramine Maleate; Pseudoephedrine, Chlorpheniramine, and Ibuprofen

International Brand NamesAdvil Cold and Sinus Plus (CA)

Ibuprofen

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Haltran® may be confused with Halfprin®

Pronunciation(eye byoo PROE fen)

U.S. Brand NamesAddaprin [OTC]; Advil® Children's [OTC]; Advil® Infants' [OTC]; Advil® Junior [OTC] [DSC]; Advil® Migraine [OTC]; Advil® [OTC]; Genpril® [OTC] [DSC]; I-Prin [OTC]; Ibu-200 [OTC]; Ibu®; Midol® Cramp and Body Aches [OTC]; Motrin® Children's [OTC]; Motrin® IB [OTC]; Motrin® Infants' [OTC]; Motrin® Junior [OTC]; Motrin® [DSC]; NeoProfen®; Proprinal [OTC]; Ultraprin [OTC]

Canadian Brand NamesAdvil®; Apo-Ibuprofen®; Motrin® (Children's); Motrin® IB; Novo-Profen; Nu-Ibuprofen

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral; Nonsteroidal Anti-inflammatory Drug (NSAID), Parenteral

Use: Labeled Indications

Oral: Inflammatory diseases and rheumatoid disorders including juvenile rheumatoid arthritis, mild-to-moderate pain, fever, dysmenorrhea

Injection: Ibuprofen lysine is for use in premature infants weighing between 500-1500 g and who are ≤32 weeks gestational age (GA) to induce closure of a clinically-significant patent ductus arteriosus (PDA) when usual treatments are ineffective

Use: Unlabeled/InvestigationalCystic fibrosis, gout, ankylosing spondylitis, acute migraine headache

Use: DentalManagement of pain and swelling

Dosing: Adults

Inflammatory disease: Oral: 400-800 mg/dose 3-4 times/day (maximum: 3.2 g/day)

Analgesia/pain/fever/dysmenorrhea: Oral: 200-400 mg/dose every 4-6 hours (maximum daily dose: 1.2 g, unless directed by physician; under physician supervision daily doses ≤2.4 g may be used)

OTC labeling (analgesic, antipyretic): Oral: 200 mg every 4-6 hours as needed (maximum: 1200 mg/24 hours); treatment for >10 days is not recommended unless directed by healthcare provider.

Migraine: 2 capsules at onset of symptoms (maximum: 400 mg/24 hours unless directed by healthcare provider)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Antipyretic: Oral: 6 months to 12 years: Temperature <102.5°F (39°C): 5 mg/kg/dose; temperature >102.5°F: 10 mg/kg/dose given every 6-8 hours; maximum daily dose: 40 mg/kg/day

Juvenile rheumatoid arthritis: Oral: 30-50 mg/kg/24 hours divided every 8 hours; start at lower end of dosing range and titrate upward (maximum: 2.4 g/day)

Analgesic: Oral: 4-10 mg/kg/dose every 6-8 hours

Cystic fibrosis (unlabeled use): Oral: Chronic (>4 years) twice daily dosing adjusted to maintain serum levels of 50-100 mcg/mL has been associated with slowing of disease progression in younger patients with mild lung disease

Patent ductus arteriosus: I.V.: Infants between 500-1500 g and ≤32 weeks GA: Initial dose: Ibuprofen 10 mg/kg, followed by two doses of 5 mg/kg at 24 and 48 hours. Dose should be based on birth weight.

OTC labeling (analgesic, antipyretic): Oral: **Note:** Treatment for >10 days is not recommended unless directed by healthcare provider.

Children 6 months to 11 years: See table; use of weight to select dose is preferred; doses may be repeated every 6-8 hours (maximum: 4 doses/day)

Children ≥12 years: Refer to adult dosing.

Ibuprofen Dosing

Weight (lb)	**Age**	**Dosage (mg)**
12-17	6-11 mo	50

18-23	12-23 mo	75
24-35	2-3 y	100
36-47	4-5 y	150
48-59	6-8 y	200
60-71	9-10 y	250
72-95	11 y	300

Dosing: Renal ImpairmentIf anuria or oliguria evident, hold dose until renal function returns to normal.

Dosing: Hepatic ImpairmentAvoid use in severe hepatic impairment.

Administration: I.V.For I.V. administration only; administration via umbilical arterial line has not been evaluated. Infuse over 15 minutes through port closest to insertion site. Avoid extravasation. Do not administer simultaneously via same line with TPN. If needed, interrupt TPN for 15 minutes prior to and after ibuprofen administration, keeping line open with dextrose or saline.

Administration: OralAdminister with food.

Dietary ConsiderationsShould be taken with food. Chewable tablets may contain phenylalanine; amount varies by product, consult manufacturers labeling.

Storage

Injection: Store at room temperature of 20°C to 25°C (68°F to 77°F). Protect from light. Following dilution, administer within 30 minutes of preparation.

Suspension, tablet: Store at room temperature of 20°C to 25°C (68°F to 77°F).

ReconstitutionInjection: Dilute with dextrose or saline to an appropriate volume.

CompatibilityStable in dextrose, saline; **incompatible** with TPN solution.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to ibuprofen, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Ibuprofen lysine is contraindicated in preterm infants with untreated proven or suspected infection; congenital heart disease where patency of the PDA is necessary for pulmonary or systemic blood flow; bleeding (especially with active intracranial hemorrhage or GI bleed); thrombocytopenia; coagulation defects; proven or suspected necrotizing enterocolitis (NEC); significant renal dysfunction

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Aseptic meningitis: May increase the risk of aseptic meningitis, especially in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and**

perforation. These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

Dosage form specific issues:

- Injection: Hold second or third doses if urinary output is <0.6 mL/kg/hour. May alter signs of infection. May inhibit platelet aggregation; monitor for signs of bleeding. May displace bilirubin; use caution when total bilirubin is elevated. Long-term evaluations of neurodevelopment, growth, or diseases associated with prematurity following treatment have not been conducted. A second course of treatment, alternative pharmacologic therapy or surgery may be needed if the ductus arteriosus fails to close or reopens following the initial course of therapy. Avoid extravasation.

- Phenylalanine: Some products may contain phenylalanine.

Other warnings/precautions:

- Self medication (OTC use): Prior to self-medication, patients should contact healthcare provider if they have had recurring stomach pain or upset, ulcers, bleeding problems, high blood pressure, heart or kidney disease, other serious medical problems, are currently taking a diuretic, aspirin, anticoagulant, or are ≥60 years of age. If patients are using for migraines, they should also contact healthcare provider if they have not had a migraine diagnosis by healthcare provider, a headache that is different from usual migraine, worst headache of life, fever and neck stiffness, headache from head injury or coughing, first headache at ≥50 years of age, daily headache, or migraine requiring bed rest. Recommended dosages should not be exceeded, due to an increased risk of GI bleeding. Stop use and consult a healthcare provider if symptoms get worse, newly appear, fever lasts for >3 days or pain lasts >3 days (children) and >10 days (adults). Do not give for >10 days unless instructed by healthcare provider. Consuming ≥3 alcoholic beverages/day or taking longer than recommended may increase the risk of GI bleeding.

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but the elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (3rd trimester)

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsLimited data suggests minimal excretion in breast milk.

Adverse Reactions

Oral:

1% to 10%:

Cardiovascular: Edema (1% to 3%)

Central nervous system: Dizziness (3% to 9%), headache (1% to 3%), nervousness (1% to 3%)

Dermatologic: Rash (3% to 9%), itching (1% to 3%)

Endocrine & metabolic: Fluid retention (1% to 3%)

Gastrointestinal: Epigastric pain (3% to 9%), heartburn (3% to 9%), nausea (3% to 9%), abdominal pain/cramps/distress (1% to 3%), appetite decreased (1% to 3%), constipation (1% to 3%), diarrhea (1% to 3%), dyspepsia (1% to 3%), flatulence (1% to 3%), vomiting (1% to 3%)

Otic: Tinnitus (3% to 9%)

<1%: Acute renal failure, agranulocytosis, allergic rhinitis, alopecia, amblyopia, anaphylaxis, arrhythmia, aplastic anemia, aseptic meningitis, azotemia, blurred vision, bone marrow suppression, bronchospasm, CHF, confusion, conjunctivitis, creatinine clearance decreased, cystitis, depression, drowsiness, dry eyes, duodenal ulcer, edema, emotional lability, eosinophilia, epistaxis, erythema multiforme, gastric ulcer, gastritis, GI bleed, GI hemorrhage, GI ulceration, hallucinations, hearing decreased, hematuria, hematocrit decreased, hemoglobin decreased, hemolytic anemia, hepatitis, hypertension, inhibition of platelet aggregation, insomnia, jaundice, liver function tests abnormal, leukopenia, melena, neutropenia, palpitation, pancreatitis, peripheral neuropathy, photosensitivity, polydipsia, polyuria, Stevens-Johnson syndrome, tachycardia, thrombocytopenia, toxic amblyopia, toxic epidermal necrolysis, urticaria, vesiculobullous eruptions, vision changes

Injection:

>10%:

Cardiovascular: Intraventricular hemorrhage (29%; grade 3/4: 15%)

Dermatologic: Skin irritation (16%)

Endocrine & metabolic: Hypocalcemia (12%), hypoglycemia (12%)

Gastrointestinal: GI disorders, non NEC (22%)

Hematologic: Anemia (32%)

Respiratory: Apnea (28%), respiratory infection (19%)

Miscellaneous: Sepsis (43%)

1% to 10%:

Cardiovascular: Edema (4%)

Endocrine & metabolic: Adrenal insufficiency (7%), hypernatremia (7%)

Genitourinary: Urinary tract infection (9%)

Renal: Urea increased (7%), renal impairment (6%), creatinine increased (3%), urine output decreased (3%; small decrease reported on days 2-6 with compensatory increase in output on day 9), renal failure (1%)

Respiratory: Respiratory failure (10%), atelectasis (4%)

Frequency not defined: Abdominal distension, cholestasis, feeding problems, gastritis, GI reflux, heart failure, hyperglycemia, hypotension, ileus, infection, inguinal hernia, injection site reaction, jaundice, neutropenia, seizure, tachycardia, thrombocytopenia

Postmarketing and/or case reports: GI perforation, necrotizing enterocolitis

Metabolism/Transport Effects **Substrate** (minor) of CYP2C9, 2C19; **Inhibits** CYP2C9 (strong)

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Ibuprofen peak serum levels may be decreased if taken with food.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Monitoring ParametersCBC; occult blood loss and periodic liver function tests; monitor response (pain, range of motion, grip strength, mobility, ADL function), inflammation; observe for weight gain, edema; monitor renal function (urine output, serum BUN and creatinine); observe for bleeding, bruising; evaluate gastrointestinal effects (abdominal pain, bleeding, dyspepsia); mental confusion, disorientation; with long-term therapy, periodic ophthalmic exams

Injection: Renal function, signs of infection or bleeding, ECG

Reference RangePlasma concentrations >200 mcg/mL may be associated with severe toxicity

PDA: Minimum effective level: 10-12 mg/L

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess patient for allergic reaction to salicylates or other NSAIDs. Assess other medications patient may be taking for additive or adverse interactions. Monitor blood pressure at the beginning of therapy and periodically during use. Monitor therapeutic effectiveness and signs of adverse reactions or overdose at beginning of therapy and periodically during long-term therapy. With long-term therapy, periodic ophthalmic exams are recommended. Assess knowledge/teach patient appropriate use. Teach patient to monitor for adverse reactions, adverse reactions to report, and appropriate interventions to reduce side effects.

Monitoring: Lab TestsCBC, periodic liver function, renal function (serum BUN and creatinine)

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Adverse reactions can occur with overuse. Consult your prescriber before use if you have hypertension or heart failure. Do not take longer than 3 days for fever, or 10 days for pain without consulting medical advisor. Take with food or milk. While using this medication, do not use alcohol, excessive amounts of vitamin C, or salicylate-containing foods (curry powder, prunes, raisins, tea, or licorice), other prescription or OTC medications containing aspirin or salicylate, or other NSAIDs without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience nausea, vomiting, gastric discomfort (frequent mouth care, small frequent meals, chewing gum, sucking lozenges may help). GI bleeding, ulceration, or perforation can occur with or without pain. Stop taking medication and report ringing in ears; persistent cramping or stomach pain; unresolved nausea or vomiting; respiratory difficulty or shortness of breath; unusual bruising or bleeding (mouth, urine, stool); skin rash; unusual swelling of extremities; chest pain; or palpitations. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet: 200 mg [OTC]

Advil®: 200 mg [contains sodium benzoate]

Ibu-200, Motrin® IB: 200 mg

Motrin® Junior: 100 mg [scored]

Capsule, liquid-filled:

Advil®: 200 mg [solubilized ibuprofen; contains potassium 20 mg]

Advil® Migraine: 200 mg [solubilized ibuprofen; contains potassium 20 mg]

Gelcap:

Advil®: 200 mg [contains coconut oil]

Injection, solution, as lysine [preservative free]:

NeoProfen®: 17.1 mg/mL (2 mL) [equivalent to ibuprofen 10 mg/mL]

Suspension, oral: 100 mg/5 mL (5 mL, 10 mL, 120 mL, 240 mL, 480 mL)

Advil® Children's: 100 mg/5 mL (120 mL) [contains sodium benzoate, sodium, propylene glycol; blue raspberry, fruit, and grape flavors]

Motrin® Children's: 100 mg/5 mL (60 mL, 120 mL) [contains sodium benzoate; berry, dye free berry, bubble gum, and grape flavors]

Suspension, oral [concentrate, drops]: 40 mg/mL (15 mL)

Advil® Infants': 40 mg/mL (15 mL) [contains sodium benzoate; fruit, grape, and white grape flavors]

Motrin® Infants': 40 mg/mL (15 mL) [contains sodium benzoate; ethanol free; berry and dye-free berry flavors]

Tablet: 200 mg [OTC], 400 mg, 600 mg, 800 mg

Addaprin: 200 mg

Advil®: 200 mg [contains sodium benzoate]

Advil® Junior: 100 mg [contains sodium benzoate; coated tablets] [DSC]

Genpril® [DSC], I-Prin, Midol® Cramp and Body Aches, Motrin® IB, Proprinal, Ultraprin: 200 mg

Ibu®: 400 mg, 600 mg, 800 mg

Ibu-200: 200 mg

Motrin®: 400 mg, 600 mg, 800 mg [DSC]

Proprinal: 200 mg [contains sodium benzoate]

Ultraprin: 200 mg [sugar free]

Tablet, chewable:

Advil® Children's: 50 mg [contains phenylalanine 2.1 mg; grape flavors]

Advil® Junior: 100 mg [contains phenylalanine 4.2 mg; grape flavors] [DSC]

Motrin® Junior: 100 mg [contains phenylalanine 2.1 mg; grape and orange flavors]

Generic AvailableYes: Caplet, suspension, tablet

Pricing: U.S. (www.drugstore.com)

Suspension (Ibuprofen)

100 mg/5 mL (473): $24.27

Tablets (Advil)

200 mg (100): $18.99

Tablets (Ibuprofen)

400 mg (30): $11.99

600 mg (90): $14.99

Tablets (Motrin)

600 mg (30): $17.99

Mechanism of Action Reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: Analgesic: 30-60 minutes; Anti-inflammatory: ≤7 days

Peak effect: 1-2 weeks

Duration: 4-6 hours

Absorption: Oral: Rapid (85%)

Distribution: Premature infants with ductal closure (highly variable between studies):

Day 3: 145-349 mL/kg

Day 5: 72-222 mL/kg

Protein binding: 90% to 99%

Metabolism: Hepatic via oxidation

Half-life elimination:

Premature infants (highly variable between studies):

Day 3: 35-51 hours

Day 5: 20-33 hours

Children 3 months to 10 years: 1.6 ± 0.7 hours

Adults: 2-4 hours; End-stage renal disease: Unchanged

Time to peak: ~1-2 hours

Excretion: Urine (80% as metabolites; 1% as unchanged drug); some feces

Related Information

- Nonsteroidal Anti-inflammatory Agents

Dental Health Professional Considerations Preoperative use of ibuprofen at a dose of 400-600 mg every 6 hours 24 hours before the appointment decreases postoperative edema and hastens healing time.

New information from the FDA states that ibuprofen can interfere with the antiplatelet effect of low-dose aspirin (81 mg/day), potentially rendering aspirin less effective when used for cardioprotection and stroke protection. In situations where these drugs could be used concomitantly, the FDA has provided the following information.

Patients who use immediate release aspirin (not enteric-coated aspirin) and take a single dose or chronic doses of ibuprofen 400 mg, should dose the ibuprofen at least **30 minutes or longer after aspirin ingestion or more than 8 hours before aspirin ingestion** to avoid attenuation of aspirin's effect.

At this time, recommendations about the timing of ibuprofen 400 mg in patients taking enteric-coated low-dose aspirin cannot be made based on available data. One study however, showed that the antiplatelet effect of enteric-coated low-dose aspirin was attenuated when ibuprofen 400 mg was dosed 2, 7, and 12 hours after aspirin (Catella-Lawson, 2001).

With occasional use of ibuprofen, there is likely to be minimal risk from any attenuation of the antiplatelet effect of low-dose aspirin, because of a long-lasting effect of aspirin on platelets.

Other over-the-counter (OTC) NSAIDs (ie, naproxen sodium and ketoprofen) should be viewed as having the potential to interfere with the antiplatelet effect of low-dose aspirin until proven otherwise. However, the FDA is unaware of any studies that have looked at the same type of interference by ketoprofen with low-dose aspirin. One study of naproxen and low-dose aspirin has suggested that naproxen may interfere with aspirin's antiplatelet activity when they are coadministered (Steinhubl, 2005). However, naproxen 500 mg administered 2 hours before or after aspirin 100 mg, did not interfere with aspirin's antiplatelet effect. The FDA stated that there is no data looking at doses of naproxen <500 mg. Naproxen OTC strength is 220 mg tablets.

Dental Health: Effects on Dental Treatment In a statement released on September 8, 2006, the FDA notified consumers and healthcare professionals that the administration of ibuprofen for pain relief to patients taking aspirin for cardioprotection may interfere with aspirin's cardiovascular benefits. The FDA states that ibuprofen can interfere with the antiplatelet effect of low-dose aspirin (81 mg/day). This could result in diminished effectiveness of aspirin as used for cardioprotection and stroke prevention. The FDA adds that although ibuprofen and aspirin can be taken together, it is recommended that consumers talk with their healthcare providers for additional information. For more information, including how to advise aspirin patients requiring ibuprofen for pain relief, see Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and dizziness are common; may cause nervousness; may rarely cause insomnia, confusion, hallucinations, or depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A meta-analysis (Pope, 1993) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 Heart Failure Guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin's inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take 1/2 -2 hours after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. May precipitate renal failure in dehydrated patients.

Index Terms*p*-Isobutylhydratropic Acid; Ibuprofen Lysine

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International Brand Names Actron (PY, UY); Adex 200 (IL); Adex Liqui-Gels (IL); Advil (AU, BR, CO, CR, DO, EC, EE, ES, FR, GT, HN, IL, MX, NI, PA, PL, SV, VE, ZA); Aktren (PL); Algofen (IT); Am-Fam 400 (IN); Anafen (ID); Anco (DE); Antarene (FR); Balkaprofen (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Bestafen (MX); Bifen (HK, SG); Bolinet (PL); Brufen (AE, AT, AU, BD, BE, BG, BH, CH, CL, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IN, IQ, IR, IT, JO, JP, KP, KW, LB, LY, MY, NL, NO, NZ, OM, PH, PK, PT, QA, RU, SA, SE, SG, SY, TH, TR, TW, YE, ZA); Brufen 400 (IL); Brufen Retard (NZ); Brufort (IT); Bufect (ID); Bufect Forte (ID); Burana (FI); Carol (KP); Cenbufen (TH); Codral Period Pain (AU); Cuprofen (TH); Degiton (TW); Diffutab SR 600 (KP); Diverin (PL); Dolan FP (PH); Dolgit (AE, BH, CY, DE, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE); Dolocyl (CH); Dolofen-F (ID); Dolomax (PE); Dolormin (DE); Drin (GR); Druisel (AR); Easifon (TW); Expanfen (FR); Febratic (MX); Fenbid (AE, BF, BH, BJ, CI, CY, EG, ET, GB, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Fenpaed (NZ); Focus (IT); Gesica (TH); Gyno-neuralgin (DE); Ibufac (MY); Ibufen (IL, PL); Ibuflam (MX); Ibufug (DE); Ibugesic (IN); Ibulgan (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Ibum (PL); Ibumetin (DK, FI, NL, NO, PL, SE); Ibupar forte (PL); Ibupirac (AR, CN); Ibuprofen (HK, PL); Ibuprom (PL); Ibuprox (ES); Ibusal (FI); Ibusan (PL); Ibutop (PL); Idyl SR (PH); Infacalm (HK); Ipren (DK, RU, SE); Iprox (ID); Ipufen (TW); Irfen (AE, BH, CH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Liptan (AE, BH, CY, EG, IL, IQ, IR, JO, JP, KW, LB, LY, OM, QA, SA, SY, YE); Medicol (PH); Mensoton (DE); Mofen (ID); Motrin (AE, BH, CO, CR, CY, EC, EG, GT, HN, IL, IQ, IR, JO, KW, LB, LY, MX, NI, OM, PA, PE, QA, SA, SV, SY, TW, YE); Noritis (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Novogent (DE); Nurofen (AT, BE, BF, BG, BJ, CI, CZ, DK, ET, FR, GB, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, NL, PL, SC, SD, SE, SG, SL, SN, TN, TR, TZ, UG, ZA, ZM, ZW); Nurofen for Children (TH); Nurofen Gel (IL, MY, SG); Nurofen Pro san sucre (FR); Optifen (CH); Opturem (DE); Ostarin (ID); Panafen IB (AU); Pedea (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Perfen (TW); Perofen (BB, BM, BS, BZ, GY, JM, MY, SR, TT); Profen (HK, ID); Proris (ID); Prosinal (ID); Proven (AU); Provon (PE); Quadrax (MX); Rafen (AU); Ranofen (ZA); Rhelafen (ID); Rhelafen Forte (ID); Rupan (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, TH, YE); Solpaflex (PL); Spedifen (FR); Speedifen (TH); Spifen (FR); Syntofene (FR); Tabalon 400 (MX); Taskine (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Tofen (TH); Upfen (FR); Uprofen (TW); Urem (DE); Zofen (MY)

Ibutilide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(i BYOO ti lide)

U.S. Brand NamesCorvert®

Pharmacologic CategoryAntiarrhythmic Agent, Class III

Use: Labeled IndicationsAcute termination of atrial fibrillation or flutter of recent onset; the effectiveness of ibutilide has not been determined in patients with arrhythmias >90 days in duration

Dosing: Adults

Atrial fibrillation/flutter: I.V.:

<60 kg: 0.01 mg/kg over 10 minutes

≥60 kg: 1 mg over 10 minutes

If the arrhythmia does not terminate within 10 minutes after the end of the initial infusion, a second infusion of equal strength may be infused over a 10-minute period.

Dosing: ElderlyRefer to adult dosing. Dose selection should be cautious, usually starting at the lower end of the dosing range.

Administration: I.V.May be administered undiluted or diluted in 50 mL diluent (0.9% NS or D_5W). Infuse over 10 minutes.

Administration: I.V. DetailObserve patient with continuous ECG monitoring for at least 4 hours following infusion or until QT_c has returned to baseline. Skilled personnel and proper equipment should be available during administration of ibutilide and subsequent monitoring of the patient.

StorageAdmixtures are chemically and physically stable for 24 hours at room temperature and for 48 hours at refrigerated temperatures.

ReconstitutionMay be administered undiluted or diluted in 50 mL diluent (0.9% NS or D_5W).

ContraindicationsHypersensitivity to ibutilide or any component of the formulation; QT_c >440 msec

Allergy Considerations

- Ibutilide Allergy

Warnings/Precautions

Boxed warnings:

- Chronic atrial fibrillation: See “Disease-related concerns” below.
- Proarrhythmic effects: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Conduction disturbances: Monitor for heart block.
- Proarrhythmic effects: **[U.S. Boxed Warning]: Potentially fatal arrhythmias (eg, polymorphic ventricular tachycardia) can occur with ibutilide, usually in association with torsade de pointes (QT prolongation).** Studies indicate a 1.7% incidence of arrhythmias in treated patients.

Disease-related concerns:

- Arrhythmias: Appropriate use: The drug should be given in a setting of continuous ECG monitoring and by personnel trained in treating arrhythmias particularly polymorphic ventricular tachycardia.
- Chronic atrial fibrillation: **[U.S. Boxed Warning]: Patients with chronic atrial fibrillation may not be the best candidates for ibutilide since they often revert after conversion and the risks of treatment may not be justified when compared to alternative management.**
- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.
- Hepatic impairment: Dosing adjustments are not required in patients with hepatic impairment.
- Renal impairment: Dosing adjustments are not required in patients with renal impairment.

Concurrent drug therapy issues:

- Drugs with QT prolongation potential: Avoid concurrent use with any drug that can prolong QT interval.

Special populations:

- Elderly: Use with caution in the elderly.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- CAST trial: In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, non-life-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide. An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. Antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic and embryocidal in rats; avoid use in pregnancy
LactationEnters breast milk/contraindicated
Adverse Reactions

1% to 10%:

Cardiovascular: Ventricular extrasystoles (5.1%), nonsustained monomorphic ventricular tachycardia (4.9%), nonsustained polymorphic ventricular tachycardia (2.7%), tachycardia/supraventricular tachycardia (2.7%), hypotension (2%), bundle branch block (1.9%), sustained polymorphic ventricular tachycardia (eg, torsade de pointes) (1.7%, often requiring cardioversion), AV block (1.5%), bradycardia (1.2%), QT segment prolongation, hypertension (1.2%), palpitation (1%)

Central nervous system: Headache (3.6%)

Gastrointestinal: Nausea (>1%)

<1% (Limited to important or life-threatening): Supraventricular extrasystoles (0.9%), nodal arrhythmia (0.7%), CHF (0.5%), syncope (0.3%, not > placebo), idioventricular rhythm (0.2%), sustained monomorphic ventricular tachycardia (0.2%), renal failure (0.3%)

Postmarketing and/or case reports: Erythematous bullous lesions

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Monitoring ParametersObserve patient with continuous ECG monitoring for at least 4 hours following infusion or until QT_c has returned to baseline; skilled personnel and proper equipment should be available during administration of ibutilide and subsequent monitoring of the patient
Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Requires infusion pump and continuous cardiac and hemodynamic monitoring during and for 4 hours following infusion. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions. Teach patient adverse symptoms to report.
Monitoring: Lab TestsElectrolytes
Patient EducationThis drug is only given I.V. and you will be on continuous cardiac monitoring during and for several hours following administration. You may experience headache or irregular heartbeat during infusion. Report chest pain or respiratory difficulty immediately. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as fumarate: 0.1 mg/mL (10 mL)

Generic AvailableNo
ManufacturerPharmacia & Upjohn
Mechanism of ActionExact mechanism of action is unknown; prolongs the action potential in cardiac tissue
Pharmacodynamics/Kinetics

Onset of action: ~90 minutes after start of infusion ($^1/_2$ of conversions to sinus rhythm occur during infusion)

Distribution: V_d: 11 L/kg

Protein binding: 40%

Metabolism: Extensively hepatic; oxidation

Half-life elimination: 2-12 hours (average: 6 hours)

Excretion: Urine (82%, 7% as unchanged drug and metabolites); feces (19%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsIbutilide is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentConcurrent use with phenothiazine and antidepressants may produce prolongation of the QT interval; use combination with caution; consider a nonphenothiazine antipsychotic

Cardiovascular ConsiderationsIbutilide may be used for pharmacologic cardioversion of atrial fibrillation or flutter. Ibutilide may lower the energy requirement for DC cardioversion in atrial fibrillation. However, a significant problem associated with therapy is torsade de pointes. It is important that the administration of ibutilide be carried out under closely monitored conditions and that facilities for cardiopulmonary resuscitation be at the bedside. It is also important that all precautionary measures for standard electrical cardioversion (eg, electrolytes, thromboembolic precautions) be maintained.

Anesthesia and Critical Care Concerns/Other ConsiderationsIbutilide may lower the energy requirement for direct current cardioversion in atrial fibrillation; effective for termination of postsurgical atrial fibrillation or atrial flutter, but at the risk of precipitating ventricular arrhythmias.

Index TermsIbutilide Fumarate

International Brand NamesCorvert (AT, CH, FI, FR, IT, NL, NO, SE)

ICE (Lymphoma, non-Hodgkin's)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's
Regimen UseLymphoma, non-Hodgkin's
Regimen

Etoposide: I.V.: 100 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 300 mg/m^2]

Carboplatin: I.V.: AUC 5 (maximum 800 mg) day 2

[total dose/cycle = AUC = 5]

Ifosfamide: I.V.: 5000 mg/m^2 continuous infusion day 2

[total dose/cycle = 5000 mg/m^2]

Mesna: I.V.: 5000 mg/m^2 continuous infusion day 2

[total dose/cycle = 5000 mg/m^2]

Filgrastim: SubQ: 5 mcg/kg/day days 5-12 (cycles 1 and 2 only)

[total dose/cycle = 40 mcg/kg]

followed by SubQ: 10 mcg/kg/day day 5 through completion of leukapheresis (cycle 3 only)

Repeat cycle every 2 weeks for 3 cycles

References

Moskowitz CH, Bertino JR, Glassman JR, et al, âIfosfamide, Carboplatin, and Etoposide: A Highly Effective Cytoreduction and Peripheral-Blood Progenitor-Cell Mobilization Regimen for Transplant-Eligible Patients With Non-Hodgkin's Lymphoma,â *J Clin Oncol*, 1999, 17(12):3776-85.[PubMed 10577849]

ICE (Sarcoma)

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Osteosarcoma](); [Chemotherapy Regimen, Soft Tissue Sarcoma]()

Regimen UseOsteosarcoma; Soft tissue sarcoma

Regimen

Ifosfamide: I.V.: 1500 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 4500 mg/m^2]

Carboplatin: I.V.: 300-635 mg/m^2 day 3

[total dose/cycle = 300-635 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 300 mg/m^2]

Mesna: I.V.: 500 mg/m^2 prior to each ifosfamide, and every 3 hours for 2 more doses/day days 1, 2, and 3

[total dose/cycle = 4500 mg/m^2]

Repeat cycle every 21-28 days

References

Kung FH, Desai SJ, Dickerman JD, et al, âIfosfamide/Carboplatin/Etoposide (ICE) for Recurrent Malignant Solid Tumors of Childhood: A Pediatric Oncology Group Phase I/II Study,â *J Pediatr Hematol Oncol*, 1995, 17(3):265-9.[PubMed 7620926]()

ICE-T

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Soft Tissue Sarcoma

Regimen Use Breast cancer; Soft tissue sarcoma

Regimen

Ifosfamide: I.V.: 1250 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 3750 mg/m^2]

Carboplatin: I.V.: 300 mg/m^2 day 1

[total dose/cycle = 300 mg/m^2]

Etoposide: I.V.: 80 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 240 mg/m^2]

Paclitaxel: I.V.: 175 mg/m^2 day 4

[total dose/cycle = 175 mg/m^2]

Mesna: I.V.: 250 mg prior to ifosfamide days 1, 2, and 3

followed by: Oral: 500 mg at 4 and 8 hours after ifosfamide days 1, 2, and 3

[total dose/cycle = I.V. 750 mg; Oral: 3000 mg]

or

Mesna: I.V.: 1250 mg/m^2/day over 6 hours, days 1, 2, and 3

[total dose/cycle = 3750 mg/m^2]

Repeat cycle every 28 days

References

Chang AY, Boros L, Garrow GC, et al, âIfosfamide, Carboplatin, Etoposide, and Paclitaxel Chemotherapy: A Dose-Escalation Study,â *Semin Oncol*, 1996, 23(3 Suppl 6):74-7.[PubMed 8677454]

Icodextrin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Special care is warranted in patients with diabetes: Due to potential interference by maltose, careful attention must be given to glucose monitoring; only glucose monitors and test strips which employ the glucose-specific method should be used. Innacurate methods (GDH-PQ or glucose-dye-oxidoreductase methods) can result in falsely-elevated readings. Inaccurate readings may mask recognition of true hypoglycemia, or may prompt the administration of insulin, potentially leading to life-threatening consequences.

Pronunciation(eye KOE dex trin)

U.S. Brand NamesAdept®; Extraneal®

Pharmacologic CategoryAdhesiolytic; Peritoneal Dialysate, Osmotic

Use: Labeled Indications

Adept®: Reduction of postsurgical adhesions in gynecologic laparoscopic procedures

Extraneal®: Daily exchange for the long dwell (8- to 16-hour) during continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) for the management of end-stage renal disease (ESRD); improvement of long-dwell ultrafiltration and clearance of creatinine and urea nitrogen (compared to 4.25% dextrose) in patients with high/average or greater transport characteristics as measured by peritoneal equilibration test (PET)

Dosing: Adults

CAPD or APD (Extraneal®): Intraperitoneal: Given as a single daily exchange in CAPD or APD; dwell time of 8-16 hours is suggested

Laparoscopic gynecologic surgery (Adept®): Intraperitoneal: Irrigate with at least 100 mL every 30 minutes during surgery; aspirate remaining fluid after surgery is completed, then instill 1 L into the cavity

Dosing: ElderlyRefer to adult dosing.

Administration: I.V.Not for I.V. injection.

Administration: OtherIntraperitoneal administration only; not for I.V. injection.

Adept®: Warm to body temperature prior to use

Osmolarity: 278 mOsm/L

Extraneal®: If using manual method, infuse into intraperitoneal cavity over 10-20 minutes. For increased comfort, dry heat (such as that derived from a heating pad) may be used to warm the solution in the over pouch to 37°C (98.6°F) prior to administration. Neither warm water nor the microwave should be used for warming.

Osmolarity: 282-286 mOsm/L

pH: 5.0-6.0.

Dietary ConsiderationsCAPD or APD: Monitor fluid intake; avoid over-/under hydration

Storage

Adept®: Store between 4°C and 30°C (39°F to 86°F); do not refrigerate or freeze. May be stored for up to 14 days in a warming device, as long as it is not removed and replaced back into the device.

Extraneal®: Store at controlled room temperature of 15°C to 30°C (68°F to 86°F) in moisture barrier overwrap in carton; do not freeze. Potassium chloride may be added up to a concentration of 4 mEq/L.

Compatibility**Compatible when admixed:** Extraneal®: Potassium chloride. Potassium chloride may be added up to a concentration of 4 mEq/L.

ContraindicationsHypersensitivity to icodextrin, cornstarch, or any component of the formulation; patients with glycogen storage disease

Adept® is also contraindicated with infection of the abdominopelvic cavity; procedures with laparotomy incision; bowel resection or repair; appendectomy; maltose or isomaltose intolerance

Warnings/Precautions

Dosage form specific issues:

- Adept®: Safety and efficacy have not been established for use in pregnancy, volumes left in peritoneal cavity >1 L, hepatic or renal dysfunction, or with a breach in the vaginal epithelium. Effectiveness has not been established for long-term clinical outcomes following surgery (eg, pregnancy, pain). Serious postoperative complications (dehiscence, cutaneous fistula formation) have been associated with laparotomy incision; anastomotic failure, ileus and peritonitis have been reported following bowel resection or repair, or appendectomy; use is contraindicated with these procedures. Postoperative leaking may occur through laparoscopic port site and may be associated with wound complications; meticulous closure of the fascia may help reduce complications. Use may be associated with vulvar swelling, most cases resolving within 1 week.

- Extraneal®: Use with caution with a history of abdominal surgery (within 30 days), abdominal fistulae, tumors, open wounds, hernia or other conditions which compromise the integrity of the abdominal wall, abdominal surface, or intra-abdominal cavity. Caution should be used in patients who are malnourished, have decreased respiratory function, decreased potassium, or increased calcium levels.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Glucose monitoring: Due to potential interference by maltose, careful attention must be given to glucose monitoring; only glucose monitors and test strips which employ the glucose-specific method should be used. Inaccurate methods (GDH-PQ or glucose-dye-oxidoreductase methods) can result in falsely-elevated readings. Inaccurate readings may mask recognition of true hypoglycemia, or may prompt the administration of insulin, potentially leading to life-threatening consequences.

- I.V. administration: Do not administer intravenously.

Pregnancy Risk FactorC

Pregnancy ConsiderationsComplete reproduction studies have not been conducted.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

CAPD or APD (Extraneal®):

>10%:

Cardiovascular: Hypertension (13%)

Respiratory: Upper respiratory infection (15%)

Miscellaneous: Peritonitis (26% vs 25% in controls)

5% to 10%:

Cardiovascular: Edema (up to 6%), chest pain (5%), hypervolemia, hypotension

Central nervous system: Headache (9%), dizziness

Dermatological: Rash (10%), pruritus, skin disorder

Endocrine & metabolic: Hyperglycemia (5%), hyperphosphatemia, hypokalemia, hypoproteinemia

Gastrointestinal: Abdominal pain (8%), nausea (7%), dyspepsia (5%), diarrhea, vomiting

Hematologic: Anemia

Neuromuscular & skeletal: Arthralgia, pain, weakness

Respiratory: Cough increased (7%), dyspnea

Miscellaneous: Accidental injury (6%), flu syndrome (7%), infection

<5%:

Cardiovascular: Postural hypotension, CHF

Central nervous system: Confusion

Dermatologic: Exfoliative dermatitis, erythema multiforme, eczema, maculopapular rash, vesicobullous rash

Endocrine & metabolic: Hypercalcemia, hypochloremia, hypoglycemia, hyponatremia, alkaline phosphatase increased

Gastrointestinal: Abdominal enlargement, cramps

Hepatic: ALT increased, AST increased

Local: Infusion pain

Miscellaneous: Cloudy effluent

Laparoscopic surgery (Adept®):

>10%:

Central nervous system: Headache (35%)

Endocrine & metabolic: Dysmenorrhea (13%)

Gastrointestinal: Nausea (6% to 17%), constipation (11%)

1% to 10%:

Central nervous system: Pyrexia (6%), insomnia (5%)

Gastrointestinal: Flatulence (8%), abdominal pain (7%), abdominal distention (6%), vomiting (6%), diarrhea (1%)

Genitourinary: Dysuria (7%), urinary tract infection (7%); labial, vulvar, or vaginal swelling (6%); vaginal bleeding (6%)

Neuromuscular & skeletal: Arthralgia (9%), back pain (8%)

Respiratory: Nasopharyngitis (7%), cough (4%)

Postmarketing and/or case reports: Sterile peritonitis

Drug InteractionsThere are no known significant interactions.

Test InteractionsFalsely-elevated blood glucose levels may occur when glucose monitoring devices and test strips utilizing the glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ or glucose-dye-oxidoreductase) based methods are used. Glucose monitoring devices and test strips which utilize the glucose-specific methodologies are recommended.

Inaccurate serum amylase levels may be reported. Icodextrin and the metabolites may interfere with enzymatic-based amylase assays.

Monitoring ParametersCAPD or APD: Serum electrolytes (chloride and sodium may be decreased); fluid balance

Nursing: Physical Assessment/MonitoringSee specific Administration instructions (intraperitoneal administration only, not for I.V. infusion). Assess results of laboratory reports, blood pressure, nutritional status, and hydration status on regular basis. **Note:** When used for patients with diabetes, glucose levels should be monitored closely using only glucose-specific methods (see Lab Interactions) to reduce potential for inaccurate readings. Teach possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCAPD or APD: Serum electrolytes

Patient EducationYou will be monitored closely during peritoneal dialyses. Report immediately any burning or pain; dizziness or acute headache; swelling of extremities; gastrointestinal upset (nausea, vomiting, or diarrhea); swelling of abdomen or abdominal pain; flu symptoms or signs of respiratory infection (cough or difficulty breathing); unusual weakness or fatigue; or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, intraperitoneal:

Adept®: 4% (1.5 L) [for laparoscopic surgery; contains sodium chloride 5.4 g/L, sodium lactate 4.5 g/L, calcium chloride 257 mg/L, magnesium chloride 51 mg/L]

Extraneal: 7.5% (1.5 L, 2 L, 2.5 L) [for peritoneal dialysis; contains sodium 132 mEq/L, calcium 3.5 mEq/L, magnesium 0.5 mEq/L, chloride 96 mEq/L, and lactate 40 mEq/L]

Generic AvailableNo

Mechanism of ActionWhen used for dialysis, icodextrin exerts osmotic pressure across small intercellular pores resulting in transcapillary ultrafiltration throughout the dwell while providing electrolytes and lactate for the maintenance of both the electrolyte and acid-base balance. When used for laparoscopic surgery, the colloidal osmotic action allows the fluid to be retained in the peritoneal cavity for 3-4 days, physically providing a temporary separation of peritoneal surfaces and minimizing adhesion formation.

Pharmacodynamics/Kinetics

Absorption: 40% during 12-hour dwell (CAPD); slowly transferred into systemic circulation via peritoneal lymphatic drainage

Metabolism: Primarily by alpha-amylase into maltose (DP2), maltotriose (DP3), maltotetraose (DP4), and other glucose polymers with a lower degree of polymerization

Time to peak, plasma: 13 hours

Excretion: Renal (amount proportional to residual renal function); diasylate

Pharmacotherapy PearlsFor a list of glucose monitor and test strip manufacturers for verification, the Baxter Renal Clinical Help Line at 1-888-Renal-Help may be called.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness and confusion

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Frampton JE and Plosker GL, “Icodextrin: a review of its use in peritoneal dialysis,” *Drugs*, 2003, 63(19):2079-105.[PubMed 12962523]

Sutton C, Minelli L, Garcia E, et al, “Use of Icodextrin 4% Solution in the Reduction of Adhesion Formation After Gynaecological Surgery,” *Gynecol Surg*, 2005, 2(4): 287-296.

International Brand NamesExtraneal Dialysis Solution (CH, DK, FI, IL, NZ, SE)

Idarubicin, Cytarabine, Etoposide (ICE Protocol)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid
Regimen UseLeukemia, acute myeloid
Index TermsICE (Leukemia)
Regimen

Idarubicin: I.V.: 6 mg/m^2/day days 1 to 5

[total dose/cycle = 30 mg/m^2]

Cytarabine: I.V.: 600 mg/m^2/day days 1 to 5

[total dose/cycle = 3000 mg/m^2]

Etoposide: I.V.: 150 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 450 mg/m^2]

Administer one cycle only

References

Carella AM, Carlier P, Pungolino E, et al, âIdarubicin in Combination With Intermediate-Dose Cytarabine and VP-16 in the Treatment of Refractory or Rapidly Relapsed Patients With Acute Myeloid Leukemia,â *Leukemia*, 1993, 7(2):196-9.[PubMed 8426473]

Idarubicin, Cytarabine, Etoposide (IDA-Based BF12)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid

Regimen UseLeukemia, acute myeloid

RegimenInduction:

Idarubicin: I.V.: 5 mg/m^2/day days 1 to 5

[total dose/cycle = 25 mg/m^2]

Cytarabine: I.V.: 2000 mg/m^2 every 12 hours days 1 to 5 (10 doses)

[total dose/cycle = 20,000 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Second cycle may be given based on individual response; time between cycles not specified

References

Mehta J, Powles R, Singhal S, et al, âIdarubicin, High-Dose Cytarabine, and Etoposide for Induction of Remission in Acute Leukemia,â *Semin Hematol*, 1996, 33(4 Suppl 3):18-23.[PubMed 12290624]

IDArubicin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

IDArubicin may be confused with DOXOrubicin, DAUNOrubicin, epirubicin

Idamycin PFS® may be confused with Adriamycin

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye da ROO bi sin)

U.S. Brand NamesIdamycin PFS®

Canadian Brand NamesIdamycin®

Pharmacologic CategoryAntineoplastic Agent, Anthracycline; Antineoplastic Agent, Antibiotic

Use: Labeled IndicationsTreatment of acute leukemias (AML, ANLL, ALL), accelerated phase or blast crisis of chronic myelogenous leukemia (CML), breast cancer

Use: Unlabeled/InvestigationalAutologous hematopoietic stem cell transplantation

Dosing: AdultsRefer to individual protocols.

Leukemia: I.V.:

Induction: 12 mg/m^2/day for 3 days

Consolidation: 10-12 mg/m^2/day for 2 days

Stem cell transplantation (unlabeled use): 20 mg/m^2/24 hours continuous I.V. infusion **or** 21 mg/m^2/24 hours continuous infusion for 48 hours (both with high-dose oral busulfan)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Leukemia: I.V.: 10-12 mg/m^2 once daily for 3 days every 3 weeks.

Solid tumors: I.V.: 5 mg/m^2 once daily for 3 days every 3 weeks.

Dosing: Renal ImpairmentThe FDA-approved labeling does not contain specific dosing adjustment guidelines; however, it does reccomend that dosage reductions be made. Patients with S_{cr}: ≥2 mg/dL did not receive treatment in many clinical trials. The following guidelines have been used by some clinicians (Aronoff, 2007):

Children:

Cl_{cr} <50 mL/minute: Administer 75% of dose.

Hemodialysis: Administer 75% of dose.

Continuous ambulatory peritoneal dialysis (CAPD): Administer 75% of dose.

Continuous renal replacement therapy (CRRT): Administer 75% of dose.

Adults:

Cl_{cr} 10-50 mL/minute: Administer 75% of dose.

Cl_{cr} <10 mL/minute: Administer 50% of dose.

Hemodialysis: Supplemental dose not needed.

Continuous ambulatory peritoneal dialysis (CAPD): Supplemental dose not needed.

Dosing: Hepatic Impairment

Bilirubin 2.6-5 mg/dL: Administer 50% of dose

Bilirubin >5 mg/dL: Avoid use

Dosing: Combination Regimens

Leukemia, acute myeloid:

7 + 3 (Idarubicin)

Idarubicin, Cytarabine, Etoposide (ICE Protocol)

Idarubicin, Cytarabine, Etoposide (IDA-Based BF12)

FLAG-IDA

Leukemia, acute promyelocytic: Tretinoin-Idarubicin

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Do not administer I.M. or SubQ; administer as slow push over 3-5 minutes, preferably into the side of a freely-running saline or dextrose infusion **or** as intermittent infusion over 10-15 minutes into a free-flowing I.V. solution of NS or D_5W; also occasionally administered as a bladder lavage.

Administration: I.V. DetailAdminister into a free-flowing I.V. solution of NS or D_5W. Avoid extravasation - potent vesicant. Local erythematous streaking along the vein may indicate rapid administration. Unless specific data is available, do not mix with other drugs.

Extravasation management: Topical cooling may be achieved using ice packs or cooling pad with circulating ice water. Cooling of site for 24 hours as tolerated by the patient. Elevate and rest extremity 24-48 hours, then resume normal activity as tolerated. Application of cold inhibits vesicant's cytotoxicity. **Application of heat can be harmful and is contraindicated.** If pain, erythema, and/or swelling persist beyond 48 hours, refer patient immediately to plastic surgeon for consultation and possible debridement.

pH: 5-7

StorageStore intact vials of solution under refrigeration (2°C to 8°C/36°F to 46°F). Protect from light. Solutions diluted in D_5W or NS for infusion are stable for 4 weeks at room temperature, protected from light. Syringe and IVPB solutions are stable for 72 hours at room temperature and 7 days under refrigeration.

CompatibilityStable in D_5NS, D_5W, LR, NS, sterile water for injection, **incompatible** with bacteriostatic water.

Y-site administration: Compatible: Amifostine, amikacin, aztreonam, cimetidine, cladribine, cyclophosphamide, cytarabine, diphenhydramine, droperidol, erythromycin lactobionate, etoposide phosphate, filgrastim, gemcitabine, granisetron, imipenem/cilastatin, magnesium sulfate, mannitol, melphalan, metoclopramide, potassium chloride, ranitidine, sargramostim, thiotepa, vinorelbine. **Incompatible:** Acyclovir, allopurinol, ampicillin/sulbactam, cefazolin, cefepime, ceftazidime, clindamycin, dexamethasone sodium phosphate, etoposide, fluorouracil, furosemide, gentamicin, heparin, hydrocortisone sodium succinate, lorazepam, meperidine, methotrexate, piperacillin/tazobactam, sodium bicarbonate, teniposide, vancomycin, vincristine.

Compatibility when admixed: Incompatible: Heparin.

ContraindicationsHypersensitivity to idarubicin, other anthracyclines, or any component of the formulation; bilirubin >5 mg/dL; pregnancy

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.
- Hepatic impairment: See “Disease-related concerns” below.
- Myocardial toxicity: See “Concerns related to adverse effects” below.
- Renal impairment: See “Disease-related concerns” below.
- Skin irritation/extravasation: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: May cause severe myelosuppression.**
- Hyperuricemia: Rapid lysis of leukemic cells may lead to hyperuricemia.
- Myocardial toxicity: **[U.S. Boxed Warning]: May cause myocardial toxicity (HF, arrhythmias or cardiomyopathies) and is more common in patients who have previously received anthracyclines or have pre-existing cardiac disease.** The risk of myocardial toxicity is also increased in patients with concomitant or prior mediastinal/pericardial irradiation, patients with anemia, bone marrow depression, infections, leukemic pericarditis or myocarditis. Monitor cardiac function during treatment.

- Skin irritation/extravasation: **[U.S. Boxed Warning] For I.V. administration only; may cause severe local tissue damage and necrosis if extravasation occurs.**

Disease-related concerns:

- Bone marrow suppression: Use with extreme caution in patients with pre-existing bone marrow suppression from prior treatment or radiation; use only if benefits warrants risks.

- Cardiovascular disease: Use with caution in patients with pre-existing cardiac disease; may increase risk of cardiotoxicity.

- Hepatic impairment: **[U.S. Boxed Warning] Use with caution in patients with hepatic impairment; may require dosage reductions.**

- Infections: Systemic infections should be managed prior to initiation of treatment.

- Renal impairment: **[U.S. Boxed Warning] Use with caution in patients with renal impairment; may require dosage reductions.**

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Geriatric ConsiderationsDuring induction therapy, patients >60 years of age experience CHF, arrhythmias, MI, and decline in LVEF more frequently than younger populations.
Pregnancy Risk FactorD
LactationExcretion in breast milk unknown
Adverse Reactions

>10%:

Cardiovascular: Transient ECG abnormalities (supraventricular tachycardia, S-T wave changes, atrial or ventricular extrasystoles); generally asymptomatic and self-limiting. CHF, dose related. The relative cardiotoxicity of idarubicin compared to doxorubicin is unclear. Some investigators report no increase in cardiac toxicity at cumulative oral idarubicin doses up to 540 mg/m^2; other reports suggest a maximum cumulative intravenous dose of 150 mg/m^2.

Central nervous system: Headache

Dermatologic: Alopecia (25% to 30%), radiation recall, skin rash (11%), urticaria

Gastrointestinal: Nausea, vomiting (30% to 60%); diarrhea (9% to 22%); stomatitis (11%); GI hemorrhage (30%)

Genitourinary: Discoloration of urine (darker yellow)

Hematologic: Myelosuppression, primarily leukopenia; thrombocytopenia and anemia. Effects are generally less severe with oral dosing.

Nadir: 10-15 days

Recovery: 21-28 days

Hepatic: Bilirubin and transaminases increased (44%)

1% to 10%:

Central nervous system: Seizure

Neuromuscular & skeletal: Peripheral neuropathy

<1%: Hyperuricemia

Oncology: VesicantYes; see Management of Drug Extravasations.
Oncology: Emetic PotentialModerate (30% to 60%)
Drug Interactions

Bevacizumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk C: Monitor therapy*

Cardiac Glycosides: May diminish the cardiotoxic effect of Antineoplastic Agents (Anthracycline). Antineoplastic Agents (Anthracycline) may decrease the serum concentration of Cardiac Glycosides. The effects of liposomal formulations may be unique from those of the free drug, as liposomal formulation have unique drug disposition and toxicity profiles, and liposomes themselves may alter digoxin absorption/distribution. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Taxane Derivatives: May enhance the adverse/toxic effect of Antineoplastic Agents (Anthracycline). Taxane Derivatives may increase the serum concentration of Antineoplastic Agents (Anthracycline). Taxane Derivatives may also increase the formation of toxic anthracycline metabolites in heart tissue. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersCBC with differential, platelet count, cardiac function, serum electrolytes, creatinine, uric acid, ALT, AST, bilirubin, signs of extravasation

Nursing: Physical Assessment/MonitoringSee Administration for specific infusion directions. Infusion site must be closely monitored; extravasation can cause severe cellulitis or tissue necrosis (eg, do not apply heat). Assess results of laboratory tests prior to each infusion and on a regular basis throughout therapy. Monitor therapeutic effectiveness (symptom relief) and adverse response (eg, cardiac toxicity, myelosuppression, peripheral neuropathy) frequently for full course of therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, platelet count, cardiac function, serum electrolytes, creatinine, uric acid, ALT, AST, bilirubin

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is only administered by intravenous infusion; report immediately any swelling, pain, burning, redness at infusion site or sudden onset of chest pain, breathing or swallowing difficulty or chills. It is important to maintain adequate hydration (2-3 L/day of fluids unless instructed to restrict fluid intake), and nutrition. You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). You may experience nausea or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or loss of hair (reversible). Urine may turn darker (normal). Report immediately chest pain, swelling of extremities, respiratory difficulty, palpitations, or rapid heartbeat. Report unresolved nausea, vomiting, or diarrhea; alterations in urinary pattern (increased or decreased); opportunistic infection (eg, fever, chills, unusual bruising or bleeding, signs of infection fatigue, purulent vaginal discharge, unhealed mouth sores); abdominal pain or blood in stools; excessive fatigue; yellowing of eyes or skin; swelling of extremities; respiratory difficulty; or unresolved diarrhea. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for use appropriate contraceptive measures. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride [preservative free] (Idamycin PFS®): 1 mg/mL (5 mL, 10 mL, 20 mL)

Generic AvailableYes

Mechanism of ActionSimilar to doxorubicin and daunorubicin; inhibition of DNA and RNA synthesis by intercalation between DNA base pairs

Pharmacodynamics/Kinetics

Absorption: Oral: Variable (4% to 77%; mean: ~30%)

Distribution: V_d: 64 L/kg (some reports indicate 2250 L); extensive tissue binding; CSF

Protein binding: 94% to 97%

Metabolism: Hepatic to idarubicinol (pharmacologically active)

Half-life elimination: Oral: 14-35 hours; I.V.: 12-27 hours

Time to peak, serum: 1-5 hours

Excretion:

Oral: Urine (~5% of dose; 0.5% to 0.7% as unchanged drug, 4% as idarubicinol); hepatic (8%)

I.V.: Urine (13% as idarubicinol, 3% as unchanged drug); hepatic (17%)

Related Information

- Management of Drug Extravasations
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; use caution with clozapine and carbamazepine

Index Terms4-Demethoxydaunorubicin; 4-DMDR; Idarubicin Hydrochloride; IDR; IMI 30; NSC-256439; SC 33428

References

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Aronoff GR, Bennett WM, Berns JS, et al, *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*, 5th ed. Philadelphia, PA: American College of Physicians; 2007, p 100, 172.

Berman E, "A Review of Idarubicin in Acute Leukemia," *Oncology*, 1993, 7(10):91-8, 104. [PubMed 8251309]

Blijlevens NM, Donnelly JP, and de Pauw BE, "Prospective Evaluation of Gut Mucosal Barrier Injury Following Various Myeloablative Regimens for Haematopoietic Stem Cell Transplant," *Bone Marrow Transplant*, 2005, 35:707-11.[PubMed 15785771]

Borchmann P, Hubel K, Schnell R, et al, “Idarubicin: A Brief Overview on Pharmacology and Clinical Use,” *Int J Clin Pharmacol Ther*, 1997, 35(2):80-3.[PubMed 9147715]

Buckley MM and Lamb HM, "Oral Idarubicin. A Review of its Pharmacological Properties and Clinical Efficacy in the Treatment of Haematological Malignancies and Advanced Breast Cancer," *Drugs Aging*, 1997, 11(1):61-86.[PubMed 9237041]

Ferrara F, Palmieri S, Annunziata M, et al, “Continuous Infusion Idarubicin and Oral Busulfan as Conditioning for Patients With Acute Myeloid Leukemia Aged Over 60 Years Undergoing Autologous Stem Cell Transplantation,” *Bone Marrow Transplant*, 2004, 34(7):73-576.

Fields SM and Koeller JM, “Idarubicin: A Second Generation Anthracycline,” *DICP*, 1991, 25(5):505-17. [PubMed 2068836]

Goebel M, "Oral Idarubicin--An Anthracycline Derivative With Unique Properties," *Ann Hematol*, 1993, 66(1):33-43.[PubMed 8431520]

Hollingshead LM and Faulds D, “Idarubicin: A Review of Its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential in the Chemotherapy of Cancer,” *Drugs*, 1991, 42(4):690-719.[PubMed 1723369]

Mengarelli A, Iori AP, Guglielmi C, et al, "Idarubicin Intensified BUCY2 Regimen in Allogeneic Unmanipulated Transplant for High-Risk Hematological Malignancies," *Leukemia*, 2000, 14(12):2052-8.[PubMed 11187892]

Robert J, "Clinical Pharmacokinetics of Edarubicin," *Clin Pharmacokinet*, 1993, 24(4):275-88.[PubMed 8491056]

International Brand NamesIdamycin (MX); Idaralem (TH); Zavedos (AE, AR, AT, AU, BE, BG, BH, BR, CH, CL, CN, CO, CY, CZ, DE, DK, EC, EG, ES, FI, FR, GB, GR, HK, HN, HR, HU, IE, IL, IN, IQ, IR, IT, JO, KP, KW, LB, LU, LY, MY, NL, NO, OM, PE, PH, PK, PL, PT, QA, RU, SA, SE, SG, SY, TH, TR, TW, UY, VE, YE, ZA); Zavedos CS (SG)

Idursulfase

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Elaprase™ may be confused with Elspar®

Pronunciation(eye dur SUL fase)

U.S. Brand NamesElaprase™

Canadian Brand NamesElaprase™

Pharmacologic CategoryEnzyme

Use: Labeled IndicationsReplacement therapy in mucopolysaccharidosis II (MPS II, Hunter syndrome) for improvement of walking capacity

Dosing: AdultsRefer to pediatric dosing.

Dosing: ElderlyStudies did not include patients ≥65 years.

Dosing: PediatricMPS II: I.V.: Children ≥5 years: 0.5 mg/kg once weekly

Administration: I.V.Administer using an infusion set containing a 0.2 micron filter. Infuse at an initial rate of 8 mL/hour for the first 15 minutes. If tolerated, may increase rate by 8 mL/hour increments every 15 minutes; maximum infusion rate 100 mL/hour. Solution should be infused over 1-3 hours, but rate may be decreased, temporarily stopped, or discontinued based on patient response. Total infusion time should not exceed 8 hours.

Administration: I.V. DetailpH: 6

StorageStore vials under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light, do not freeze or shake. Should be used immediately after dilution. However, solution for infusion may be stored under refrigeration for up to 48 hours; administer within 8 hours if stored at room temperature.

ReconstitutionPrior to infusion, dilute total dose in NS 100 mL. Mix gently, do not shake.

CompatibilityStable in NS.

ContraindicationsThere are no contraindications listed in the manufacturer's labeling.

Warnings/Precautions

Boxed warnings:

- Anaphylactic reactions: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Anaphylactic reactions: **[U.S. Boxed Warning]: Serious and sometimes fatal anaphylactic reactions, as well as delayed reactions (24 hours after initial reaction), have occurred. Use with caution in patients with compromised respiratory function or acute respiratory disease; risk of complications may be increased and additional monitoring may be required. Appropriate medical support should be readily available.** Antihistamines, corticosteroids and/or decreased infusion rates may be used to manage subsequent infusions.

- Antibody formation: Development of anti-idursulfase IgG antibodies has been reported in ~50% of patients; may increase incidence of infusion-related reaction.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <5 years of age.

Other warnings/precautions:

- Registry: Patients and healthcare providers are encouraged to participate in the Hunter Outcome Survey, intended to monitor disease progression, patient outcomes. and long-term effects of therapy. For more information, refer to www.elaprase.com or call OnePath^{sm} at 1-866-888-0660.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Cardiovascular: Hypertension (25%), atrial abnormality (13%)

Central nervous system: Pyrexia (63%), headache (59%), malaise (22%), anxiety (13%), irritability (13%)

Dermatologic: Pruritus (28%), urticaria (16%), pruritic rash (13%), skin disorder (13%)

Gastrointestinal: Dyspepsia (13%)

Local: Abscess (16%), infusion-site edema (13%)

Neuromuscular & skeletal: Arthralgia (31%), limb pain (28%), chest wall musculoskeletal pain (16%), musculoskeletal dysfunction (16%)

Ocular: Visual disturbance (22%)

Respiratory: Wheezing (19%)

Miscellaneous: Antibody development (51%), infusion reactions (15%), superficial injury (13%)

<1: Anaphylaxis, angioedema, cardiac arrhythmia, cyanosis, hypotension, infection, loss of consciousness, pulmonary embolism, respiratory distress, respiratory failure, seizure

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersMonitor for infusion-related and hypersensitivity reactions; pulmonary function, oxygen saturation; blood pressure

Nursing: Physical Assessment/MonitoringMeasure patient weight accurately prior to each infusion dosage determined by weight. Assess respiratory status closely prior to and during infusion; risk of complication may be increased in presence of acute disease or compromised respiratory function. Patient should be monitored closely during and following infusion for anaphylactic reaction (can be fatal) and appropriate emergency rescue support should be readily available. Antihistamines, corticosteroids and/or decreased infusion rates may be used to reduce reactions. Assess effectiveness of therapy (relief of symptoms) and adverse reactions at beginning of therapy and periodically with long-term use. Teach patient/caregiver appropriate use, possible side effects, and interventions to reduce side effects, and adverse symptoms to report. Inform patient/caregiver about participation in the voluntary Hunter Outcome Survey.

Patient EducationThis medication will not cure Hunter syndrome, but may reduce symptoms. It can only be given by infusion. You will be monitored closely during infusion. Report immediately and difficulty breathing, abdominal cramping, acute headache or dizziness, chest pain, difficulty swallowing. Between infusions, report abdominal cramping, pain, bleeding, headache, or anxiety, dizziness, palpitations, difficulty breathing, skin rash or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to be pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Elaprase™: 2 mg/mL (5 mL) [extractable volume: 3 mL]

Generic AvailableNo

ManufacturerShire

Mechanism of ActionIdursulfase is a recombinant form of iduronate-2-sulfatase, an enzyme needed to hydrolyze the mucopolysaccharides dermatan sulfate and heparan sulfate in various cells. Accumulation of these polysaccharides can lead to various manifestations of disease, including physical changes, CNS involvement, cardiac, respiratory, and mobility dysfunction. Replacement of this enzyme has been shown to improve walking capacity in patients with a deficiency.

Pharmacodynamics/KineticsHalf-life elimination: 44-48 minutes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause malaise, anxiety, or irritability

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesElaprase (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Soft Tissue Sarcoma

Regimen UseSoft tissue sarcoma

Regimen

Etoposide: I.V.: 100 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 300 mg/m^2]

Ifosfamide: I.V.: 2500 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 7500 mg/m^2]

Mesna: I.V.: 500 mg/m^2 prior to ifosfamide, after ifosfamide, and every 4 hours for 3 more doses (total of 5 doses/day) days 1, 2, and 3

[total dose/cycle = 7500 mg/m^2]

Repeat cycle every 28 days

References

Edmonson JH, Buckner JC, Long HJ, et al, âPhase II Study of Ifosfamide-Etoposide-Mesna in Adults With Advanced Nonosseous Sarcomas,â *J Natl Cancer Inst*, 1989, 81(11):863-6.[PubMed 2498525]

Ifosfamide

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English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Ifosfamide may be confused with cyclophosphamide

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye FOSS fa mide)

U.S. Brand NamesIfex®

Canadian Brand NamesIfex®

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent; Antineoplastic Agent, Alkylating Agent (Nitrogen Mustard)

Use: Labeled IndicationsTreatment of testicular cancer

Use: Unlabeled/InvestigationalTreatment of bladder, breast, cervical, ovarian, pancreatic, and lung cancers; Hodgkin's and non-Hodgkin's lymphoma; acute lymphocytic leukemia; Ewing’s sarcoma, osteosarcoma, and soft tissue sarcomas

Dosing: AdultsRefer to individual protocols.

Antineoplastic: I.V.:

Testicular cancer: 1200 mg/m^2/day for 5 days every 3 weeks

Dose ranges used in other cancers (unlabeled uses):

4000-5000 mg/m^2/day for 1 day every 14-28 days **or**

1000-3000 mg/m^2/day for 2-5 days every 21-28 days

Note: To prevent bladder toxicity, ifosfamide should be given with extensive hydration consisting of at least 2 L of oral or I.V. fluid per day. The dose-limiting toxicity is hemorrhagic cystitis and, therefore, ifosfamide should be used in conjunction with a uroprotective agent, such as mesna.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols.

Antineoplastic (unlabeled use): I.V.:

1200-1800 mg/m^2/day for 3-5 days every 21-28 days **or**

5 g/m^2 once every 21-28 days **or**

3 g/m^2/day for 2 days every 21-28 days

See “Note” in adult dosing.

Dosing: Renal ImpairmentThe FDA-approved labeling does not contain dosage adjustment guidelines (has not been studied). The following guidelines have been used by some clinicians:

Aronoff, 2007:

Cl_{cr} <10 mL/minute: Children and Adults: Administer 75% of dose

Hemodialysis:

Children: 1 g/m^2 followed by hemodialysis 6-8 hours later

Adults: No supplemental dose needed

Kintzel, 1995:

Cl_{cr} 46-60 mL/minute: Administer 80% of dose

Cl_{cr} 31-45 mL/minute: Administer 75% of dose

Cl_{cr} <30 mL/minute: Administer 70% of dose

Dosing: Hepatic ImpairmentThe FDA-approved labeling does not contain dosage adjustment guidelines (has not been studied). The following guidelines have been used by some clinicians (Floyd, 2006): Bilirubin >3 mg/dL: Administer 25% of dose

Dosing: Combination Regimens

Breast cancer: ICE-T

Cervical cancer: BIP

Esophageal cancer: TIP

Head and neck cancer: TIP

Hepatoblastoma: IPA

Lung cancer (small cell): VIP (Small Cell Lung Cancer)

Lymphoma, non-Hodgkin's:

CODOX-M/IVAC

ICE (Lymphoma, non-Hodgkin's)

IMVP-16

MINE

MINE-ESHAP

RICE

Lymphoma, non-Hodgkin's (Burkitt's): CODOX-M/IVAC

Neuroblastoma:

CI (Neuroblastoma)

HIPE-IVAD

Osteosarcoma: ICE (Sarcoma)

Sarcoma: VAC Alternating With IE (Ewing's Sarcoma)

Sarcoma, soft tissue:

AI

ICE (Sarcoma)

ICE-T

IE

MAID

Testicular cancer:

Paclitaxel-Ifosfamide-Cisplatin

VIP (Etoposide) (Testicular Cancer)

VIP (Vinblastine) (Testicular Cancer)

Oncology: Bone Marrow - High DoseI.V.: 7.5-16 g/m^2 in divided doses over several days; generally combined with other high-dose chemotherapy

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Administer I.V. over 30 minutes to several hours or continuous intravenous infusion over 5 days.

Administration: I.V. DetailAdequate hydration (at least 2 L/day) of the patient before and for 72 hours after therapy is recommended to minimize the risk of hemorrhagic cystitis.

pH: 6

StorageStore intact vials of powder for injection at room temperature of 20°C to 25°C (68°F to 77°F). Store intact vials of solution under refrigeration at 2°C to 8°C (36°F to 46°F). Reconstituted solutions may be stored under refrigeration for up to 21 days. Solutions diluted for administration are stable for 7 days at room temperature and for 6 weeks under refrigeration.

ReconstitutionDilute powder with SWFI or bacteriostatic SWFI to a concentration of 50 mg/mL. Further dilution in 50-1000 mL D_5W or NS (to a final concentration of 0.6-20 mg/mL) is recommended for I.V. infusion.

CompatibilityStable in D_5LR, D_5NS, D_5W, LR, $^1/_2$NS, NS.

Y-site administration: Compatible: Allopurinol, amifostine, amphotericin B cholesteryl sulfate complex, aztreonam, doxorubicin liposome, etoposide phosphate, filgrastim, fludarabine, gatifloxacin, gemcitabine, granisetron, linezolid, melphalan, ondansetron, paclitaxel, piperacillin/tazobactam, propofol, sargramostim, sodium bicarbonate, teniposide, thiotepa, topotecan, vinorelbine. **Incompatible:** Cefepime, methotrexate.

Compatibility in syringe: Compatible: Epirubicin, mesna. **Incompatible:** Mesna with epirubicin.

Compatibility when admixed: Compatible: Carboplatin, carboplatin with etoposide, cisplatin, cisplatin with etoposide, epirubicin, etoposide, fluorouracil, mesna. **Incompatible:** Mesna with epirubicin.

ContraindicationsHypersensitivity to ifosfamide or any component of the formulation; patients with severely depressed bone marrow function

Allergy Considerations

- Nitrogen Mustard Allergy

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- CNS toxicity: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.
- Hemorrhagic cystitis: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: Severe bone marrow suppression may occur (dose-limiting toxicity)**; use with caution in patients with compromised bone marrow reserve; use is contraindicated in patients with severely depressed bone marrow function.
- CNS toxicity: **[U.S. Boxed Warning]: May cause CNS toxicity, including confusion and coma**; usually reversible upon discontinuation of treatment. Encephalopathy (ranging from mild somnolence to hallucinations and/or coma) may occur; risk factors may include hypoalbuminemia, renal dysfunction, and prior history of ifosfamide -induced encephalopathy.
- Hemorrhagic cystitis: **[U.S. Boxed Warning]: Urotoxic side effects, primarily hemorrhagic cystitis, may occur (dose-limiting toxicity)**; hydration (at least 2 L/day) and/or mesna administration will protect against hemorrhagic cystitis.
- Wound healing: May interfere with wound healing.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsIncreased resorptions and embryotoxic effects have been observed in animal studies.

LactationEnters breast milk/not recommended

Adverse Reactions

>10%:

Central nervous system: CNS toxicity or encephalopathy (10% to 30%; includes somnolence, agitation, confusion, delirium, hallucinations, depressive psychosis, incontinence, palsy, diplopia, aphasia, or coma)

Dermatologic: Alopecia (83%)

Endocrine & metabolic: Metabolic acidosis (31%)

Gastrointestinal: Nausea/vomiting (58%), may be more common with higher doses or bolus infusion

Hematologic: Myelosuppression (onset: 7-14 days; nadir: 21-28 days; recovery: 21-28 days), leukopenia (50% to ≤100%; grade 4: ≤50%), thrombocytopenia (20%; grades 3/4: 8%)

Renal: Hematuria (6% to 92%; grade 2 [gross hematuria]: 8% to 12%)

1% to 10%:

Central nervous system: Fever

Hepatic: Bilirubin increased (3%), liver dysfunction (3%), transaminases increased (3%)

Local: Phlebitis (2%)

Renal: Renal impairment (6%)

Miscellaneous: Infection (8%)

<1%, postmarketing, and/or case reports: Acidosis, acute renal failure, acute tubular necrosis, allergic reaction, anemia, anorexia, BUN increased, cardiotoxicity, chronic renal failure, coagulopathy, constipation, creatinine increased, dermatitis, diarrhea, Fanconi syndrome, fatigue, hyper-/hypotension, hyperpigmentation, malaise, nail banding/ridging, nonconvulsive status epilepticus, polyneuropathy, proteinuria, pulmonary fibrosis, renal rickets, renal tubular acidosis, salivation, SIADH, sterility, stomatitis

Oncology: VesicantNo

Oncology: Emetic PotentialModerate (30% to 60%)

Metabolism/Transport Effects**Substrate** of CYP2A6 (major), 2B6 (minor), 2C8 (minor), 2C9 (minor), 2C19 (major), 3A4 (major); **Inhibits** CYP3A4 (weak); **Induces** CYP2C8 (weak), 2C9 (weak)

Drug Interactions

CYP2A6 Inducers (Strong): May increase the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2A6 Inhibitors (Moderate): May decrease the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2A6 Inhibitors (Strong): May decrease the metabolism of CYP2A6 Substrates. *Risk D: Consider therapy modification*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Ifosfamide may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease ifosfamide levels.

Monitoring ParametersCBC with differential, hemoglobin, and platelet count, urine output, urinalysis (prior to each dose), liver function, and renal function tests

Nursing: Physical Assessment/MonitoringUse caution in presence of impaired renal function or compromised bone marrow reserve. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, increased or decreased levels/effects of ifosfamide). See Administration for infusion specifics. To prevent bladder toxicity, maintain adequate hydration for 72 hours prior to infusion to minimize risk of hemorrhagic cystitis (2-3 L/day). Premedicate with antiemetic may be advisable prior to each infusion. Assess vital signs and results of laboratory tests prior to each infusion and regularly during therapy. Monitor therapeutic effectiveness (according to purpose for use) and adverse response (eg, CNS depression or psychoses, hematuria [hemorrhagic cystitis], myelosuppression [anemia]) throughout therapy. Teach patient (or caregiver) possible side effects/appropriate interventions (eg, importance of adequate hydration) and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, platelet count, urinalysis (prior to each dose), liver and renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug can only be administered by infusion. Report immediately any swelling, redness, or pain at infusion site. Maintain adequate hydration (3-4 L/day of fluids unless instructed to restrict fluid intake) for at least 3 days prior to infusion and each day of therapy. You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause loss of hair (reversible, although regrowth hair may be different color or texture); fertility or amenorrhea; nausea or vomiting (small, frequent meals, good mouth care, chewing gum, or sucking lozenges may help - if persistent consult prescriber for antiemetic); headache (consult prescriber for analgesic); or mouth sores (use soft toothbrush or cotton swab for oral care). Report any difficulty or pain with urination; chest pain, rapid heartbeat, or palpitations; CNS changes (eg, hallucinations, confusion, somnolence); unusual rash; persistent nausea or vomiting; swelling of extremities; respiratory difficulty; unusual fatigue; or opportunistic infection (eg, fever, chills, easy bruising or unusual bleeding). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Male: Do not cause a female to become pregnant. Male/female: Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 1 g

Ifex®: 1 g, 3 g

Injection, solution: 50 mg/mL (20 mL, 60 mL)

Generic AvailableYes

Mechanism of ActionCauses cross-linking of strands of DNA by binding with nucleic acids and other intracellular structures; inhibits protein synthesis and DNA synthesis

Pharmacodynamics/KineticsPharmacokinetics are dose dependent

Distribution: V_d: 5.7-49 L; does penetrate CNS, but not in therapeutic levels

Protein binding: Negligible

Metabolism: Hepatic to active metabolites isofosforamide mustard, 4-hydroxy-ifosfamide, acrolein, and inactive dichloroethylated and carboxy metabolites; acrolein is the agent implicated in development of hemorrhagic cystitis

Half-life elimination:

High dose (3800-5000 mg/m^2): ~15 hours

Lower dose (1600-2400 mg/m^2): ~7 hours

Excretion:

High dose (5000 mg/m^2): Urine (70% to 86%; 61% as unchanged drug)

Lower dose (1600-2400 mg/m^2): Urine (12% to 18% as unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation, confusion, and hallucinations are common

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine; barbiturates and chloral hydrate may increase the metabolism of ifosfamide

Index TermsIsophosphamide; NSC-109724; Z4942

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International Brand NamesCuantil (AR, PY); Farmamide (DE); Holoxan (AE, AT, AU, BD, BE, BG, BH, CH, CL, CN, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JO, JP, KP, KW, LB, LU, LY, MY, NL, NO, OM, PH, PK, PL, PT, QA, RU, SA, SE, SG, SY, TH, TR, TW, UY, YE); Holoxane (BR); Ifadex (MX); IFO-cell (TH); Ifolem (MX, TH); Ifomida (MX); Ifomide (JP); Ifos (PE); Ipamide (IN); Macdafen (PL); Mitoxana (GB); Tolcamin (CO)

Iloprost

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English

Jump To Field (Select Field Name)

Pronunciation(EYE loe prost)

U.S. Brand NamesVentavis®

Pharmacologic Category[Prostacyclin](); [Prostaglandin](); [Vasodilator]()

Use: Labeled IndicationsTreatment of idiopathic pulmonary arterial hypertension in patients with NYHA Class III or IV symptoms

Dosing: AdultsInhalation: Initial: 2.5 mcg/dose; if tolerated, increase to 5 mcg/dose. Administer 6-9 times daily (dosing at intervals ≥2 hours while awake according to individual need and tolerability). Maintenance dose: 2.5-5 mcg/dose; maximum daily dose: 45 mcg

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentAdjustments are not necessary. Use caution in dialysis patients; may be more susceptible to hypotension.

Dosing: Hepatic ImpairmentUse caution.

Administration: InhalationDo not mix with other medications. For inhalation only via the I-neb™ AAD® System or Prodose® AAD® System. Transfer entire contents of ampul into the medication chamber. Only use 1 mL ampul with I-neb™ AAD® System. After use, discard remainder of the medicine; not for reuse.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsThere are no contraindications listed within the FDA-approved labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Pulmonary edema: If pulmonary edema occurs during administration, discontinue therapy immediately.
- Syncope: Dosage or therapy adjustment may be required if exertional syncope occurs. Use caution with concurrent conditions or medications that may increase risk of syncope.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with active bleeding or at increased risk of bleeding (eg, concomitant anticoagulation); mild inhibitor of platelet aggregation when administered as an aerosol.
- Hepatic impairment: Use with caution in patients with Child-Pugh classes B and C hepatic impairment; inhaled iloprost has not been evaluated in this population. Studies of I.V. administered iloprost in Child-Pugh class B patients have demonstrated an approximate 50% reduction in iloprost clearance.
- Hypotension: Avoid use in patients with hypotension (systolic BP <85 mm Hg).
- Renal impairment: Use with caution in patients on dialysis; inhaled iloprost has not been evaluated in this population. Studies of I.V. administered iloprost in patients on dialysis demonstrated an approximate fivefold increase in iloprost AUC when compared to healthy individuals.
- Respiratory disease: Safety and efficacy have not been established in patients with other concurrent pulmonary diseases (eg, COPD, severe asthma, or acute pulmonary infections); may induce bronchospasm in patients with hyper-reactive airways.

Special populations:

- Pediatrics: Not FDA labeled for use in children.

Other warnings/precautions:

- Administration: Intended for inhalation administration using only the I-neb™ AAD® System or Prodose® AAD® System. Solution should not come in contact with skin or eyes. Monitor vital signs during initiation.

Pregnancy Risk FactorC

Pregnancy ConsiderationsIloprost was shown to be embryolethal or teratogenic in some, but not all, animal studies. There are no adequate or well-controlled studies in pregnant women; use only if clearly needed. Women with pulmonary hypertension are urged to avoid pregnancy.

LactationExcretion in breast milk unknown/ not recommended

Adverse Reactions

>10%:

Cardiovascular: Flushing (27%), hypotension (11%)

Central nervous system: Headache (30%)

Gastrointestinal: Nausea (13%)

Neuromuscular & skeletal: Trismus (12%), jaw pain (12%)

Respiratory: Cough increased (39%)

Miscellaneous: Flu-like syndrome (14%)

≥3% to 10%:

Cardiovascular: Syncope (8%), palpitation (7%)

Central nervous system: Insomnia (8%)

Gastrointestinal: Vomiting (7%), tongue pain (4%)

Hepatic: Alkaline phosphatase increased (6%), GGT increased (6%)

Neuromuscular & skeletal: Back pain (7%), muscle cramps (6%)

Respiratory: Hemoptysis (5%), pneumonia (4%)

<3%: Chest pain, CHF, dizziness, dyspnea, kidney failure, paradoxical reaction (increased PVR), peripheral edema, supraventricular tachycardia

Postmarketing and/or case reports: Bronchospasm, diarrhea, epistaxis, gingival bleeding, wheezing

Drug Interactions

Anticoagulants: Prostacyclin Analogues may enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Antihypertensives: Prostacyclin Analogues may enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Antiplatelet Agents: Prostacyclin Analogues may enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Monitoring Parameters Heart rate, blood pressure, and respiratory rate at baseline, with initiation and dosage adjustments. Monitor for improvements in pulmonary function, improved exercise tolerance, NYHA Class improvement; side effects

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution for oral inhalation [preservative-free]:

Ventavis®: 10 mcg/mL (1 mL, 2 mL) [ampul]

Generic Available No

Manufacturer Actelion Pharmaceuticals US, Inc

Mechanism of Action Acutely, iloprost dilates systemic and pulmonary arterial vascular beds. With longer-term use, alters pulmonary vascular resistance and suppresses vascular smooth muscle proliferation. In addition, it is a mild endogenous inhibitor of platelet aggregation when aerosolized (Beghetti, 2002).

Pharmacodynamics/Kinetics

Duration: 30-60 minutes

Distribution: V_d: 0.7-0.8 L/kg

Protein binding: ~60%, primarily to albumin

Metabolism: Hepatic via beta oxidation of the carboxyl side chain; main metabolite, tetranor-iloprost (inactive in animal studies)

Half-life elimination: 20-30 minutes (effect), 7-9 minutes (elimination)

Time to peak, serum: Within 5 minutes after inhalation

Excretion: Urine (68% as metabolite); feces (12%)

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Jaw pain (reported in >10% of patients).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause insomnia

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Iloprost Tromethamine; Prostacyclin PGI_2

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12151469]

International Brand Names Ilomedin (CH, GR, IL, NZ, PL, SE, TH, TW); Ventavis (AR, AT, AU, BE, BG, CH, CL, CN, CO, CZ, DE, DK, FI, FR, GB, GR, HK, HN, ID, IE, IL, IT, MY, NL, NO, PE, PT, RU, SE, SG, TH, TR, TW, UY); Ventavis RES (KP)

Imatinib

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye MAT eh nib)
U.S. Brand NamesGleevec®
Canadian Brand NamesGleevec®
Pharmacologic CategoryAntineoplastic Agent, Tyrosine Kinase Inhibitor
Use: Labeled IndicationsTreatment of:

Gastrointestinal stromal tumors (GIST) kit-positive (CD117) unresectable and/or metastatic malignant

Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (newly-diagnosed)

Ph+ CML in chronic phase in pediatric patients recurring following stem cell transplant or who are resistant to interferon-alpha therapy (**not** an approved use in Canada)

Ph+ CML in blast crisis, accelerated phase, or chronic phase after failure of interferon therapy

Ph+ acute lymphoblastic leukemia (ALL) (relapsed or refractory)

Aggressive systemic mastocytosis (ASM) without D816V c-Kit mutation (or c-Kit mutation status unknown)

Dermatofibrosarcoma protuberans (DFSP) (unresectable, recurrent and/or metastatic)

Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL)

Myelodysplastic/myeloproliferative disease (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements

Note: The following use is approved in Canada (not an approved indication in the U.S.):

Ph+ ALL induction therapy (newly diagnosed)

Use: Unlabeled/InvestigationalTreatment of desmoid tumors (soft tissue sarcoma)
Dosing: Adults**Note:** For concurrent use with a strong CYP3A4 enzyme-inducing agent (eg, rifampin, phenytoin), imatinib dosage should be increased by at least 50%.

Ph+ CML: Oral:

Chronic phase: 400 mg once daily; may be increased to 600 mg/day, if tolerated, for disease progression, lack of hematologic response after 3 months, lack of cytogenetic response after 6-12 months, or loss of previous hematologic or cytogenetic response

Canadian labeling and NCCN CML guidelines (v.2.2009): Includes range up to 800 mg/day (400 mg twice daily)

Accelerated phase or blast crisis: 600 mg once daily; may be increased to 800 mg/day (400 mg twice daily), if tolerated, for disease progression, lack of hematologic response after 3 months, lack of cytogenetic response after 6-12 months, or loss of previous hematologic or cytogenetic response

Ph+ ALL (relapsed or refractory): Oral: 600 mg once daily

GIST: Oral: 400 mg once daily; may be increased up to 800 mg/day (400 mg twice daily), if tolerated, for disease progression

ASM with eosinophilia: Oral: Initiate at 100 mg once daily; titrate up to a maximum of 400 mg once daily (if tolerated) for insufficient response to lower dose

ASM without D816V c-Kit mutation or c-Kit mutation status unknown: Oral: 400 mg once daily

DFSP: Oral: 400 mg twice daily

HES/CEL: Oral: 400 mg once daily

HES/CEL with FIP1L1-PDGFRα fusion kinase: Oral: Initiate at 100 mg once daily; titrate up to a maximum of 400 mg once daily (if tolerated) if insufficient response to lower dose

MDS/MPD: Oral: 400 mg once daily

Ph+ ALL (induction, newly diagnosed):*Canadian labeling (not an approved use in the U.S.):* Oral: 600 mg once daily

Dosage adjustment with concomitant strong CYP3A4 inducers: Avoid concomitant use of strong CYP3A4 inducers (eg, dexamethasone, carbamazepine, phenobarbital, phenytoin, rifampin); if concomitant use can not be avoided, increase imatinib dose by at least 50% with careful monitoring.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Notes:** May be administered once daily or in 2 divided doses. Dosage should be increased by at least 50% when used concurrently with a potent CYP3A4 enzyme-inducing agent (ie, rifampin, phenytoin).

Ph+ CML: Children ≥2 years: Oral:

Chronic phase, recurrent or resistant: 260 mg/m^2/day

Chronic phase, newly diagnosed: 340 mg/m^2/day; maximum: 600 mg /day

Dosage adjustment for hepatotoxicity or other nonhematologic adverse reactions: Refer to “Hepatic Impairment” dosing.

Dosage adjustment for hematologic adverse reactions: Refer to dosing adjustment for toxicity.

Dosing: Renal Impairment

Recommendation in the FDA-approved labeling:

Mild impairment (Cl_{cr} 40-59 mL/minute): Maximum recommended dose: 600 mg

Moderate impairment (Cl_{cr} 20-39 mL/minute): Decrease recommended starting dose by 50%; dose may be increased as tolerated; maximum recommended dose: 400 mg

Severe impairment (Cl_{cr} <20 mL/minute): Use caution; a dose of 100 mg/day has been tolerated in severe impairment (case reports)

Canadian labeling recommendation:

Mild impairment (Cl_{cr} 40-59 mL/minute): Use caution; usual minimum recommended effective dose: 400 mg once daily; titrate to efficacy and tolerability

Moderate impairment (Cl_{cr} 20-39 mL/minute): Use caution; usual minimum recommended effective dose: 400 mg once daily; titrate to efficacy and tolerability; the use of 800 mg dose is not recommended

Severe impairment (Cl_{cr} <20 mL/minute): Use is not recommended

Dosing: Hepatic Impairment
Mild-to-moderate impairment: No adjustment necessary

Canadian labeling: GIST: Minimum effective dose: 400 mg once daily

Severe impairment: Reduce dose by 25%

Canadian labeling: GIST: 200 mg dose once daily with titration to 300 mg once daily in the absence of severe toxicity

Hepatotoxicity (during therapy) or other nonhematologic adverse reactions: Withhold treatment until toxicity resolves; may resume if appropriate (depending on initial severity of adverse event)

If elevations of bilirubin >3 times upper limit of normal (ULN) or transaminases (ALT/AST) >5 times ULN occur, withhold treatment until bilirubin <1.5 times ULN or transaminases <2.5 times ULN. Resume treatment at a reduced dose as follows:

Children ≥2 years:

If current dose 260 mg/m^2/day, reduce dose to 200 mg/m^2/day

If current dose 340 mg/m^2/day, reduce dose to 260 mg/m^2/day

Adults:

If current dose 400 mg, reduce dose to 300 mg

If current dose 600 mg, reduce dose to 400 mg

If current dose 800 mg, reduce dose to 600 mg

Dosing: Adjustment for Toxicity
Dosage adjustment for hematologic adverse reactions:

Chronic phase CML (initial dose 400 mg/day in adults or 260-340 mg/m^2/day in children), ASM, MDS/MPD, and HES/CEL (initial dose 400 mg/day), or GIST (initial dose 400 mg or 600 mg): If ANC <1 x 10^9/L and/or platelets <50 x 10^9/L: Withhold until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L; resume treatment at original starting dose. For recurrent neutropenia or thrombocytopenia, withhold until recovery, and reinstitute treatment at a reduced dose as follows:

Children ≥2 years:

If initial dose 260 mg/m^2/day, reduce dose to 200 mg/m^2/day

If initial dose 340 mg/m^2/day, reduce dose to 260 mg/m^2/day

Adults:

If initial dose 400 mg, reduce dose to 300 mg

If initial dose 600 mg, reduce dose to 400 mg

CML (accelerated phase or blast crisis) and PH+ ALL: Adults (initial dose 600 mg): If ANC <0.5 x 10^9/L and/or platelets <10 x 10^9/L, establish whether cytopenia is related to leukemia (bone marrow aspirate or biopsy). If unrelated to leukemia, reduce dose to 400 mg. If cytopenia persists for an additional 2 weeks, further reduce dose to 300 mg. If cytopenia persists for 4 weeks and is still unrelated to leukemia, withhold treatment until ANC ≥1 x 10^9/L and platelets ≥20 x 10^9/L, then resume treatment at 300 mg.

ASM associated with eosinophilia and HES/CEL with FIP1L1-PDGFRα fusion kinase (starting dose 100 mg/day): If ANC <1 x 10^9/L and/or platelets <50 x 10^9/L: Withhold until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L; resume treatment at previous dose.

DFSP (initial dose 800 mg/day): If ANC <1 x 10^9/L and/or platelets <50 x 10^9/L , withhold until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L; resume treatment at reduced dose of 600 mg/day. If depression in neutrophils or platelets recurs, withhold until recovery, and reinstitute treatment with a further dose reduction to 400 mg/day.

Dosing: Combination Regimens

Leukemia, acute lymphocytic: Hyper-CVAD + Imatinib

Calculations

- ANC: Absolute Neutrophil Count
- Body Surface Area: Pediatrics

Administration: OralShould be administered with food and a large glass of water. Tablets may be dispersed in water or apple juice (using ~50 mL for 100 mg tablet, ~200 mL for 400 mg tablet); stir until dissolved and use immediately. For daily dosing ≥800 mg, the 400 mg tablets should be used in order to reduce iron exposure.

Dietary ConsiderationsShould be taken with food and a large glass of water to decrease gastrointestinal irritation.

StorageStore at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Protect from moisture.

ContraindicationsThere are no contraindications listed within the FDA-approved manufacturer's labeling.

Canadian labeling: Hypersensitivity to imatinib or any component of the formulation

Allergy Considerations

- Imatinib Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: May cause bone marrow suppression (anemia, neutropenia, and thrombocytopenia). Median duration of neutropenia is 2-3 weeks; median duration of thrombocytopenia is 3-4 weeks.

- Cardiovascular effects: Severe HF and left ventricular dysfunction (LVD) have been reported (rarely), usually in patients with comorbidities and/or risk factors; carefully monitor patients with preexisting cardiac disease or risk factors for heart failure. With initiation of imatinib treatment, cardiogenic shock and/or LVD have been reported in patients with hypereosinophilic syndrome and cardiac involvement (reversible with systemic steroids, circulatory support and temporary cessation of imatinib). Patients with high eosinophil levels and an abnormal echocardiogram or abnormal serum troponin level may benefit from prophylactic systemic steroids with the initiation of imatinib.

- Dermatologic reactions: Severe bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported; reintroduction has been attempted following resolution. Successful resumption at a lower dose (with corticosteroids and/or antihistamine) has been described; however, some patients may experience recurrent reactions.

- Fluid retention/edema: Often associated with fluid retention, weight gain, and edema (probability increases with higher doses and age >65 years); occasionally leading to significant complications, including pleural effusion, pericardial effusion, pulmonary edema, and ascites. Use with caution in patients where fluid accumulation may be poorly tolerated, such as in cardiovascular disease (HF or hypertension) and pulmonary disease.

- GI irritation: May cause GI irritation; take with food and water to minimize irritation. There have been rare reports (including fatalities) of GI perforation.

- Hemorrhage: Severe hemorrhage (grades 3 and 4) has been reported with use, including gastrointestinal hemorrhage and/or tumor hemorrhage. The incidence of hemorrhage is higher in patients with GIST.

- Hepatotoxicity: Hepatotoxicity may occur (may be severe); monitor; therapy interruption or dose reduction may be necessary. Acute liver failure has also been reported.

- Opportunistic infections: Has been associated with development of opportunistic infections.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with bone marrow suppression.
- Hepatic impairment: Use with caution in patients with hepatic impairment; may require dosage adjustment.
- Renal impairment: Use with caution in patients with renal impairment; may require dosage adjustment.
- Thyroid disease: Hypothyroidism has been reported in thyroidectomy patients (receiving thyroid hormone replacement therapy) during imatinib therapy; monitor.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients receiving concurrent therapy which alters CYP2D6 and/or CYP3A4 activity; may require dosage adjustments.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Geriatric ConsiderationsIncidence of edema and edema-related adverse effects is increased in elderly patients.
Pregnancy Risk FactorD
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Animal studies have demonstrated teratogenic effects and fetal loss. Women of childbearing potential are advised not to become pregnant (female patients and female partners of male patients). Adequate contraception is recommended. Case reports of pregnancies while on therapy (both males and females) include reports of spontaneous abortion, minor abnormalities (hypospadias, pyloric stenosis, and small intestine rotation) at or shortly after birth, and other congenital abnormalities including skeletal malformations, hypoplastic lungs, exomphalos, kidney abnormalities, hydrocephalus, cerebellar hypoplasia, and cardiac defects.

Retrospective case reports of women with CML in complete hematologic response (CHR) with cytogenic response (partial or complete) who interrupted imatinib therapy due to pregnancy, demonstrated a loss of response in some patients while off treatment. At 18 months after treatment reinitiation following delivery, CHR was again achieved in all patients and cytogenic response was achieved in some patients. Cytogenetic response rates may not be at as high as compared to patients with 18 months of uninterrupted therapy (Ault, 2006; Pye, 2008).

LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.
Adverse Reactions

>10%:

Cardiovascular: Edema/fluid retention (33% to 86%; grades 3/4: 3% to 13%; includes aggravated edema, anasarca, pericardial effusion, peripheral edema, pulmonary edema and superficial edema); facial edema (DFSP 17%), chest pain (CML 7% to 11%)

Central nervous system: Fatigue (29% to 75%), fever (13% to 41%), headache (20% to 37%), dizziness (10% to 19%), insomnia (10% to 19%), depression (≤15%), anxiety (7% to 12%), chills (≤11%)

Dermatologic: Rash (25% to 50%; grades 3/4: 3% to 9%), pruritus (8% to 19%), alopecia (GIST 12% to 15%)

Endocrine & metabolic: Hypokalemia (CML 6% to 13%)

Gastrointestinal: Nausea (42% to 73%), diarrhea (25% to 58%), vomiting (23% to 58%), abdominal pain (30% to 57%), anorexia (≤36%), weight gain (5% to 32%), dyspepsia (11% to 27%), constipation (9% to 16%), taste disturbance (GIST 3% to 15%), loose stools (GIST 10% to 12%)

Hematologic: Hemorrhage (12% to 53%; grades 3/4: 2% to 19%), neutropenia (grade 3: 7% to 27%; grade 4: 3% to 48%), thrombocytopenia (grade 3: 1% to 31%; grade 4: <1% to 33%), anemia (grade 3: 3% to 42%; grade 4: 1% to 11%), leukopenia (GIST 17% to 20%)

Hepatic: Ascites/pleural effusion (GIST 12% to 15%), hepatotoxicity (6% to 12%; grades 3/4: 3% to 8%)

Neuromuscular & skeletal: Muscle cramps (28% to 62%), musculoskeletal pain (adults 30% to 49%; children 21%), arthralgia (≤40%), joint pain (11% to 31%), myalgia (9% to 32%), back pain (GIST 23% to 26%), weakness (≤21%), rigors (10% to 12%), bone pain (≤11%)

Ocular: Periorbital edema (DFSP 33%; MPD 29%), lacrimation increased (DFSP 25%; GIST 16% to 18%)

Renal: Serum creatinine increased (≤11%; grade 3: ≤3%; DFSP: grade 4: 8%)

Respiratory: Nasopharyngitis (10% to 31%), cough (14% to 27%), dyspnea (≤21%), upper respiratory tract infection (3% to 21%), pharyngolaryngeal pain (7% to 18%), rhinitis (DFSP 17%), pharyngitis (CML 10% to 15%), pneumonia (CML 4% to 13%), sinusitis (4% to 11%)

Miscellaneous: Night sweats (CML 13% to 17%), infection without neutropenia (GIST 16% to 17%), influenza (1% to 14%), diaphoresis (GIST 9% to 13%)

1% to 10%:

Cardiovascular: Flushing

Central nervous system: CNS/cerebral hemorrhage (≤9%), hypoesthesia

Dermatologic: Dry skin, erythema, photosensitivity reaction

Endocrine & metabolic: Albumin decreased (grade 3: ≤4%)

Gastrointestinal: Flatulence (≤10%), stomatitis/mucositis (≤10%), gastrointestinal hemorrhage (2% to 8%), abdominal distension, gastritis, gastroesophageal reflux, mouth ulceration, weight loss, xerostomia

Hematologic: Lymphopenia (GIST 6% to 10%), neutropenic fever, pancytopenia

Hepatic: Alkaline phosphatase increased (grade 3: ≤6%; grade 4: <1%), ALT increased (grade 3: 2% to 7%; grade 4: <1%), AST increased (grade 3: 2% to 4%; grade 4: ≤3%), bilirubin increased (grade 3: 1% to 4%; grade 4: ≤3%)

Neuromuscular & skeletal: Joint swelling, paresthesia

Ocular: Blurred vision, conjunctival hemorrhage, conjunctivitis, dry eyes, eyelid edema

Respiratory: Epistaxis

Miscellaneous: Tumor hemorrhage (GIST 1% to 4%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Acute febrile neutropenic dermatosis (Sweet’s syndrome), amylase increased, anaphylactic shock, angina, angioedema, aplastic anemia, arrhythmia, ascites, atrial fibrillation, avascular necrosis, blepharitis, breast enlargement, bullous eruption, cardiac arrest, cardiac failure, cardiac tamponade, cardiogenic shock, cataract, cellulitis, cerebral edema, cheilitis, CHF (severe), colitis, confusion, CPK increased, dehydration, diverticulitis, dysphagia, embolism, eosinophilia, erythema multiforme, esophagitis, exanthematous pustulosis (acute generalized), exfoliative dermatitis, fungal infection, gastric ulcer, gastroenteritis, gastrointestinal obstruction, gastrointestinal perforation, glaucoma, gout, hearing loss, hematoma, hematemesis, hematuria, hemolytic anemia, hepatic failure, hepatic necrosis, hepatitis, herpes simplex, herpes zoster, hip osteonecrosis, hypercalcemia, hyperglycemia, hyperkalemia, hyperuricemia, hyper-/hypotension, hypomagnesemia, hyponatremia, hypophosphatemia, ileus, inflammatory bowel disease, interstitial lung disease, interstitial pneumonitis, intracranial pressure increased, jaundice, LDH increased, left ventricular dysfunction, leukocytoclastic vasculitis, libido decreased, lichen planus, lichenoid keratosis, lymphadenopathy, macular edema, melena, memory impairment, menorrhagia, MI, migraine, optic neuritis, palpitation, pancreatitis, papilledema, pericarditis, peripheral neuropathy, petechiae, pleural effusion, pleuritic pain, pulmonary fibrosis, pulmonary hemorrhage, pulmonary hypertension, purpura, pustular rash, Raynaud's phenomenon, renal failure, respiratory failure, respiratory tract (lower) infection, retinal hemorrhage, sciatica, scleral hemorrhage, seizure, sepsis, sexual dysfunction, skin pigment changes, somnolence, Stevens-Johnson syndrome, syncope, tachycardia, thrombocythemia, thrombosis, tinnitus, toxic epidermal necrolysis, tremor, tumor necrosis, urinary tract infection, urticaria, vertigo, vesicular rash, vitreous hemorrhage

Oncology: Emetic PotentialModerate (30% to 60%)

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2D6 (minor), 2C9 (minor), 2C19 (minor), 3A4 (major), **Inhibits** CYP2C9 (weak), 2D6 (moderate), 3A4 (strong)

Drug Interactions

Acetaminophen: Imatinib may increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Imatinib. *Risk C: Monitor therapy*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CycloSPORINE: Imatinib may increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Lansoprazole: May enhance the dermatologic adverse effect of Imatinib. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Imatinib. *Risk D: Consider therapy modification*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Simvastatin: Imatinib may decrease the metabolism of Simvastatin. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Imatinib. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Topotecan: BCRP/ABCG2 Inhibitors may increase the serum concentration of Topotecan. *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Warfarin: Imatinib may enhance the anticoagulant effect of Warfarin. Imatinib may decrease the metabolism of Warfarin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol.

Food: Food may reduce gastrointestinal irritation. Avoid grapefruit juice (may increase imatinib plasma concentration).

Herb/Nutraceutical: Avoid St John's wort (may increase metabolism and decrease imatinib plasma concentration).

Monitoring ParametersCBC (weekly for first month, biweekly for second month, then periodically thereafter), liver function tests (at baseline and monthly or as clinically indicated), renal function, serum electrolytes (including calcium, phosphorus, potassium and sodium levels); thyroid function tests (in thyroidectomy patients); fatigue, weight, and edema/fluid status; consider echocardiogram and serum troponin levels in patients with HES/CEL, and in patients with MDS/MPD or ASM with high eosinophil levels; in pediatric patients, also monitor serum glucose and albumin

Monitor for signs/symptoms of CHF in patients with at risk for cardiac failure or patients with pre-existing cardiac disease. In Canada, a baseline evaluation of left ventricular ejection fraction is recommended prior to initiation of imatinib therapy in all patients with known underlying heart disease or in elderly patients.

Nursing: Physical Assessment/MonitoringUse caution when fluid accumulation may be poorly tolerated (CHF, hypertension), cardiac or pulmonary disease, or renal or hepatic impairment. Assess closely any other pharmacological agents or herbal products patient may be taking for effectiveness and possible interactions prior to beginning therapy (especially those drugs affected by cytochrome P450 actions). Assess results of laboratory tests on a regular basis (eg, CBC, LFTs, renal and thyroid function tests, calcium and phosphorus levels). Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and regularly during therapy (eg, weight and fluid status, hemorrhage, paresthesia, respiratory or CNS changes). Teach appropriate use, interventions to reduce side effects, and symptoms to report.

Monitoring: Lab TestsCBC (weekly for first month, biweekly for second month, then periodically thereafter), liver function tests (at baseline and monthly or as clinically indicated), renal function, serum electrolytes (including calcium, phosphorus, potassium and sodium levels); thyroid function tests (in thyroidectomy patients); consider echocardiogram and serum troponin levels in patients with HES/CEL, and in patients with MDS/MPD or ASM with high eosinophil levels; in pediatric patients, also monitor serum glucose and albumin

In Canada, a baseline evaluation of left ventricular ejection fraction is recommended prior to initiation of imatinib therapy in all patients with known underlying heart disease or in elderly patients.

Patient EducationDo not take any new prescription or OTC medications, or herbal products during therapy without consulting prescriber. Take exactly as directed with food or a large glass of water. If you have difficulty swallowing tablets, tablet(s) may be dispersed in water or apple juice (using 50 mL of fluid for 100 mg tablet; 200 mL fluid for 400 mg tablet), stir until dissolved and use immediately. Avoid alcohol and chronic use of acetaminophen or aspirin unless approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will be required to have regularly scheduled laboratory tests while on this medication. You will be more susceptible to infection (avoid crowds and exposure to infection and do not receive any vaccination unless approved by prescriber). You may experience headache or fatigue (use caution when driving or engaging in tasks requiring alertness until response to drug in known); loss of appetite, nausea, vomiting, or mouth sores (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); or diarrhea (buttermilk, boiled milk, or yogurt may reduce diarrhea). Report immediately any chest pain, palpitations, or swelling of extremities; unusual cough, respiratory difficulty, or wheezing; weight gain >5 lb; skin rash; muscle or bone pain, tremors, or cramping; persistent fatigue or weakness; easy bruising or unusual bleeding (eg, tarry stools, blood in vomitus, stool, urine, or mouth); persistent GI problems or pain; or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant (female) or cause a pregnancy (male) while taking this medication. Consult prescriber for appropriate contraception. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Gleevec®: 100 mg; 400 mg

Generic AvailableNo

ManufacturerNovartis Pharmaceuticals Corp

Pricing: U.S. (www.drugstore.com)

Tablets (Gleevec)

100 mg (30): $906.27

400 mg (30): $3984.06

Mechanism of ActionInhibits Bcr-Abl tyrosine kinase, the constitutive abnormal gene product of the Philadelphia chromosome in chronic myeloid leukemia (CML). Inhibition of this enzyme blocks proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as in fresh leukemic cells in Philadelphia chromosome positive CML. Also inhibits tyrosine kinase for platelet-derived growth factor (PDGF), stem cell factor (SCF), c-Kit, and cellular events mediated by PDGF and SCF.

Pharmacodynamics/Kinetics

Absorption: Rapid

Protein binding: Parent drug and metabolite: ~95% to albumin and alpha$_1$-acid glycoprotein

Metabolism: Hepatic via CYP3A4 (minor metabolism via CYP1A2, CYP2D6, CYP2C9, CYP2C19); primary metabolite (active): N-demethylated piperazine derivative (CGP74588); severe hepatic impairment (bilirubin >3-10 times ULN) increases AUC by 45% to 55% for imatinib and its active metabolite, respectively

Bioavailability: 98%

Half-life elimination: Adults: Parent drug: ~18 hours; N-desmethyl metabolite: ~40 hours; Children: Parent drug: ~15 hours

Time to peak: 2-4 hours

Excretion: Feces (68% primarily as metabolites, 20% as unchanged drug); urine (13% primarily as metabolites, 5% as unchanged drug)

Related Information

- Management of Nausea and Vomiting
- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsPatients with HES/CEL, MDS/MPD or ASM with an abnormal echocardiogram or abnormal serum troponin level may benefit from prophylactic systemic steroids (1-2 mg/kg for 1-2 weeks) with the initiation of imatinib.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mouth ulceration and taste disturbance.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may infrequently cause depression, anxiety, insomnia, somnolence, migraine, and memory impairment; may rarely cause confusion and convulsions

Mental Health: Effects on Psychiatric TreatmentGastrointestinal irritation is common; use caution with lithium, valproic acid, and SSRIs. May cause hepatotoxicity; use caution with valproic acid and olanzapine. May cause neutropenia or thrombocytopenia; use caution with clozapine, carbamazepine, and valproic acid. Imatinib may inhibit the metabolism of alprazolam, carbamazepine, clozapine, diazepam, fluoxetine, haloperidol, nefazodone, phenothiazines (avoid thioridazine and mesoridazine), sertraline, TCAs, trazodone, and triazolam resulting in elevated serum levels. Fluoxetine and nefazodone may inhibit the metabolism of imatinib. Carbamazepine, St John's wort, and phenobarbital may increase the metabolism of imatinib.

Index TermsCGP-57148B; Glivec; Imatinib Mesylate; NSC-716051; STI-571

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International Brand NamesGleevec (JP); Glivec (AR, AT, AU, BE, BG, BR, CH, CL, CN, CO, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IT, KP, MX, MY, NL, NO, PE, PH, PK, PL, PT, PY, RU, SE, SG, TH, TR, UY, VE); Glivic (NZ)

Imiglucerase

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cerezyme® may be confused with Cerebyx®, Ceredase®

Pronunciation(i mi GLOO ser ace)
U.S. Brand NamesCerezyme®
Canadian Brand NamesCerezyme®
Pharmacologic CategoryEnzyme
Use: Labeled IndicationsLong-term enzyme replacement therapy for patients with Type 1 Gaucher's disease
Dosing: AdultsGaucher's disease: I.V.: Initial: 30-60 units/kg every 2 weeks; dosing is individualized based on disease severity. Dosing range: 2.5 units/kg 3 times/week up to as much as 60 units/kg administered as frequently as once a week or as infrequently as every 4 weeks. Average dose: 60 units/kg administered every 2 weeks.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren ≥2 years: Refer to adult dosing.
Administration: I.V.I.V.: Infuse over 1-2 hours; may use an in-line, low protein-binding 0.2 micron filter during infusion
StoragePrior to reconstitution, store at 2°C to 8°C (36°F to 46°F). Reconstituted solution is stable for 12 hours at 25°C and at 2°C to 8°C (36°F to 46°F). Do not use if discolored or contains particles. Solution for infusion further diluted in NS is stable for up to 24 hours when stored at 2°C to 8°C (36°F to 46°F).
ReconstitutionVials should be reconstituted with SWFI. Solution for infusion should be further diluted in NS.
ContraindicationsHypersensitivity to imiglucerase or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactic reactions: Have been reported (<1%). Most patients have continued treatment with pretreatment (antihistamines and/or corticosteroids) and a slower rate of infusion. Use caution in patients with previous hypersensitivity to or who have developed antibodies to alglucerase.

- Antibody formation: Development of IgG antibodies has been reported in ~15% of patients; may increase risk of hypersensitivity reactions.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age (limited experience).

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

1% to 10%: Miscellaneous: Hypersensitivity reaction (7%; symptoms may include pruritus, flushing, urticaria, angioedema, bronchospasm)

Individual frequency not defined, but <1.5%:

Cardiovascular: Tachycardia

Central nervous system: Headache, dizziness, fatigue, fever

Dermatologic: Rash, pruritus

Gastrointestinal: Nausea, abdominal discomfort, vomiting, diarrhea

Local: Injection site burning, swelling, or sterile abscess (<1%)

Neuromuscular & skeletal: Backache

Miscellaneous: Anaphylactoid reactions (<1%)

Postmarketing and/or case reports: Dyspnea, peripheral edema, pulmonary hypertension

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersCBC, platelets, liver function tests, IgG antibody formation, acid phosphatase (AP); MRI or CT of liver and spleen, skeletal x-rays, physical exam every 6-12 months
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Cerezyme®: 200 units, 400 units [derived from Chinese hamster cells; contains mannitol and polysorbate 80]

Generic AvailableNo

Mechanism of ActionImiglucerase is an analogue of glucocerebrosidase; it is produced by recombinant DNA technology using mammalian cell culture. Glucocerebrosidase is an enzyme deficient in Gaucher's disease. It is needed to catalyze the hydrolysis of glucocerebroside to glucose and ceramide.

Pharmacodynamics/Kinetics

Distribution: V_d: 0.09-0.15 L/kg

Half-life elimination: 3.6-10.4 minutes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

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International Brand NamesCerezym (HK); Cerezyme (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, KP, NL, NO, PL, PT, RU, SE, TR, TW)

Imipenem and Cilastatin

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Medication Safety Issues

Sound-alike/look-alike issues:

Imipenem may be confused with ertapenem, meropenem

Primaxin® may be confused with Premarin®, Primacor®

Pronunciation(i mi PEN em & sye la STAT in)
U.S. Brand NamesPrimaxin®
Canadian Brand NamesPrimaxin®; Primaxin® I.V.
Pharmacologic CategoryAntibiotic, Carbapenem
Use: Labeled IndicationsTreatment of lower respiratory tract, urinary tract, intra-abdominal, gynecologic, bone and joint, skin and skin structure, and polymicrobic infections as well as bacterial septicemia and endocarditis. Antibacterial activity includes resistant gram-negative bacilli (*Pseudomonas aeruginosa* and *Enterobacter* sp), gram-positive bacteria (methicillin-sensitive *Staphylococcus aureus* and *Streptococcus* sp) and anaerobes.
Use: Unlabeled/InvestigationalHepatic abscess; neutropenic fever; melioidosis
Dosing: AdultsDoses based on **imipenem** content. **Note:** I.M. administration is not intended for severe or life-threatening infections (eg, septicemia, endocarditis, shock), UTI, bone/joint or polymicrobic infections. For adults weighing <70 kg, refer to Dosing Adjustment in Renal Impairment:

Burkholderia mallei (melioidosis) (unlabeled use): I.V.: 20 mg/kg (up to 1 g) every 6-8 hours for 10 days

Intra-abdominal infections:

I.V.: Mild infection: 250-500 mg every 6 hours; severe: 500 mg every 6 hours

I.M.: Mild-to-moderate infection: 750 mg every 12 hours

Liver abscess (unlabeled use): I.V.: 500 mg every 6 hours for 2-3 weeks, then appropriate oral therapy for a total of 4-6 weeks

Lower respiratory tract, skin/skin structure, gynecologic infections: I.M.: Mild/moderate: 500-750 mg every 12 hours

Moderate infections:

I.M.: 750 mg every 12 hours

I.V.:

Fully-susceptible organisms: 500 mg every 6-8 hours

Moderately-susceptible organisms: 500 mg every 6 hours or 1 g every 8 hours

Neutropenic fever (unlabeled use): I.V.: 500 mg every 6 hours

***Pseudomonas* infections:** I.V.: 500 mg every 6 hours; **Note:** Higher doses may be required based on organism sensitivity.

Severe infections: I.V.: **Note:** I.M. administration is not intended for severe or life-threatening infections (eg, septicemia, endocarditis, shock):

Fully-susceptible organisms: 500 mg every 6 hours

Moderately-susceptible organisms: 1 g every 6-8 hours

Maximum daily dose should not exceed 50 mg/kg or 4 g/day, whichever is lower

Urinary tract infection, uncomplicated: I.V.: 250 mg every 6 hours

Urinary tract infection, complicated: I.V.: 500 mg every 6 hours

Mild infections:Note: Rarely a suitable option in mild infections; normally reserved for moderate-severe cases:

I.M.: 500 mg every 12 hours

I.V.:

Fully-susceptible organisms: 250 mg every 6 hours

Moderately-susceptible organisms: 500 mg every 6 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDosage based on **imipenem** content:

Non-CNS infections: I.V.:

Neonates ≤3 months and weight ≥1500 g:

<1 week: 25 mg/kg every 12 hours

1-4 weeks: 25 mg/kg every 8 hours

4 weeks to 3 months: 25 mg/kg every 6 hours

Children: >3 months: 15-25 mg/kg every 6 hours

Maximum dosage: Susceptible infections: 2 g/day; moderately-susceptible organisms: 4 g/day

Burkholderia mallei (melioidosis) (unlabeled use): 20 mg/kg every 8 hours for 10 days

Cystic fibrosis: Doses up to 90 mg/kg/day have been used

Dosing: Renal ImpairmentI.V.: **Note:** Adjustments have not been established for I.M. dosing:

Patients with a Cl_{cr} ≤5 mL/minute/1.73 m^2 should not receive imipenem/cilastatin unless hemodialysis is instituted within 48 hours.

Patients weighing <30 kg with impaired renal function should not receive imipenem/cilastatin.

Hemodialysis: Use the dosing recommendation for patients with a Cl_{cr} 6-20 mL/minute; administer dose after dialysis session and every 12 hours thereafter

Peritoneal dialysis: Dose as for Cl_{cr} 6-20 mL/minute.

Continuous renal replacement therapy (CRRT): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH: 250 mg every 6 hours or 500 mg every 8 hours

CVVHD/CVVHDF: 250 mg every 6 hours or 500 mg every 6-8 hours

Note: Data suggest that 500 mg every 12 hours may provide sufficient T>MIC to cover organisms with MIC values ≤2 mg/L; however, a higher dose of 500 mg every 6 hours is recommended for resistant organisms (particularly *Pseudomonas*) with MIC ≥4 mg/L (Fish, 2005).

See table.

Imipenem and Cilastatin Dosage in Renal Impairment

Reduced I.V. Dosage Regimen Based on **Creatinine Clearance (mL/minute/1.73 m^2) and/or Body Weight <70 kg**					
	Body Weight (kg)				
	≥70	**60**	**50**	**40**	**30**
Total daily dose for normal renal function: 1 g/day					
Cl_{cr} ≥71	250 mg q6h	250 mg q8h	125 mg q6h	125 mg q6h	125 mg q8h
Cl_{cr} 41-70	250 mg q8h	125 mg q6h	125 mg q6h	125 mg q8h	125 mg q8h
Cl_{cr} 21-40	250 mg q12h	250 mg q12h	125 mg q8h	125 mg q12h	125 mg q12h
Cl_{cr} 6-20	250 mg q12h	125 mg q12h	125 mg q12h	125 mg q12h	125 mg q12h
Total daily dose for normal renal function: 1.5 g/day					
Cl_{cr} ≥71	500 mg q8h	250 mg q6h	250 mg q6h	250 mg q8h	125 mg q6h

Cl cr 41-70	250 mg q6h	250 mg q8h	250 mg q8h	125 mg q6h	125 mg q8h
Cl cr 21-40	250 mg q8h	250 mg q8h	250 mg q12h	125 mg q8h	125 mg q8h
Cl cr 6-20	250 mg q12h	250 mg q12h	250 mg q12h	125 mg q12h	125 mg q12h
Total daily dose for normal renal function: 2 g/day					
Cl cr ≥71	500 mg q6h	500 mg q8h	250 mg q6h	250 mg q6h	250 mg q8h
Cl cr 41-70	500 mg q8h	250 mg q6h	250 mg q6h	250 mg q8h	125 mg q6h
Cl cr 21-40	250 mg q6h	250 mg q8h	250 mg q8h	250 mg q12h	125 mg q8h
Cl cr 6-20	250 mg q12h	250 mg q12h	250 mg q12h	250 mg q12h	125 mg q12h
Total daily dose for normal renal function: 3 g/day					
Cl cr ≥71	1000 mg q8h	750 mg q8h	500 mg q6h	500 mg q8h	250 mg q6h
Cl cr 41-70	500 mg q6h	500 mg q8h	500 mg q8h	250 mg q6h	250 mg q8h
Cl cr 21-40	500 mg q8h	500 mg q8h	250 mg q6h	250 mg q8h	250 mg q8h
Cl cr 6-20	500 mg q12h	500 mg q12h	250 mg q12h	250 mg q12h	250 mg q12h
Total daily dose for normal renal function: 4 g/day					
Cl cr ≥71	1000 mg q6h	1000 mg q8h	750 mg q8h	500 mg q6h	500 mg q8h
Cl cr 41-70	750 mg q8h	750 mg q8h	500 mg q6h	500 mg q8h	250 mg q6h
Cl cr 21-40	500 mg q6h	500 mg q8h	500 mg q8h	250 mg q6h	250 mg q8h
Cl cr 6-20	500 mg q12h	500 mg q12h	500 mg q12h	250 mg q12h	250 mg q12h

Dosing: Hepatic ImpairmentHepatic dysfunction may further impair cilastatin clearance; consider decreasing the dosing frequency.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.**Note:** I.M. administration is not intended for severe or life-threatening infections (eg, septicemia, endocarditis, shock). Administer by deep injection into a large muscle (gluteal or lateral thigh). **Only the I.M. formulation can be used for I.M. administration.**

Administration: I.V.I.V.: Do not administer I.V. push. Infuse doses ≤500 mg over 20-30 minutes; infuse doses ≥750 mg over 40-60 minutes. **Only the I.V. formulation can be used for I.V. administration.**

Administration: I.V. DetailVial contents must be transferred to 100 mL of infusion solution. If nausea and/or vomiting occur during administration, decrease the rate of I.V. infusion. Do not mix with or physically add to other antibiotics; however, may administer concomitantly.

pH: 6.5-8.5 (buffered)

Dietary ConsiderationsSodium content of 500 mg injection:

I.M.: 32 mg (1.4 mEq)

I.V.: 37.5 mg (1.6 mEq)

StorageImipenem/cilastatin powder for injection should be stored at <25°C (77°F).
I.M.: The I.M. suspension should be used within 1 hour of reconstitution.

I.V.: Reconstituted I.V. solutions are stable for 4 hours at room temperature and 24 hours when refrigerated. Do not freeze.

Reconstitution

I.M.: Prepare 500 mg vial with 2 mL 1% lidocaine (do not use lidocaine with epinephrine). The I.V. formulation does not form a stable suspension in lidocaine and cannot be used to prepare an I.M dose.

I.V.: Prior to use, dilute dose into 100-250 mL of an appropriate solution. Imipenem is inactivated at acidic or alkaline pH. Final concentration should not exceed 5 mg/mL. The I.M. formulation is not buffered and cannot be used to prepare I.V. solutions.

Compatibility**I.V. formulation:**

Variable stability (consult detailed reference) in D_5W, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, $D_{10}W$, mannitol 2.5%, mannitol 5%, mannitol 10%, NS, TPN.

Y-site administration: Compatible: Acyclovir, amifostine, aztreonam, cefepime, cisatracurium, diltiazem, docetaxel, famotidine, fludarabine, foscarnet, gatifloxacin, granisetron, idarubicin, insulin (regular), linezolid, melphalan, methotrexate, ondansetron, propofol, remifentanil, tacrolimus, teniposide, thiotepa, vinorelbine, zidovudine. **Incompatible:** Allopurinol, amphotericin B cholesteryl sulfate complex, etoposide phosphate, fluconazole, gemcitabine, lorazepam, meperidine, midazolam, sargramostim, sodium bicarbonate. **Variable (consult detailed reference):** Filgrastim, TPN.

ContraindicationsHypersensitivity to imipenem/cilastatin or any component of the formulation

I.M. formulation (due to lidocaine diluent) additional contraindications: Hypersensitivity to amide-type anesthetics; severe shock or heart block

Allergy Considerations

- Carbapenem Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Serious hypersensitivity reactions, including anaphylaxis, have been reported (some without a history of previous allergic reactions to beta-lactams).
- CNS effects: Has been associated with CNS adverse effects, including confusional states and seizures (myoclonic); use caution with CNS disorders (eg, brain lesions, history of seizures, or renal impairment). Incidence of seizures may be higher than with other carbapenems.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required in patients with moderate-to-severe renal dysfunction. Increased seizure risk and thrombocytopenia have been reported in patients with significant renal dysfunction.

Special populations:

- Elderly: Lower doses (based upon renal function) are often required in the elderly.
- Pediatrics: Not recommended in pediatric CNS infections due to seizure potential. Safety and efficacy of I.M. administration have not been established in children <12 years of age.

Dosage form specific issues:

- I.M./I.V. preparations: Two different products are available; due to differences in formulation, the I.V. and I.M. preparations **cannot** be interchanged.

Other warnings/precautions:

- I.M. administration: Doses for I.M. administration are mixed with lidocaine; consult Lidocaine information for associated Warnings/Precautions.

Geriatric ConsiderationsImipenem/cilastatin's role is limited to the treatment of infections caused by susceptible multiresistant organism(s) and in patients whose bacterial infection(s) have failed to respond to other appropriate antimicrobials; many of the seizures attributed to imipenem/cilastatin were in elderly patients; dose must be adjusted for creatinine clearance and body weight.

Pregnancy Risk FactorC

Pregnancy ConsiderationsWith the exception of slightly decreased fetal weights at the highest doses in rats and an increase in embryonic loss in cynomolgus monkeys, most animal studies have not shown an increased fetal risk or teratogenic effects. However, due to the adverse events observed in some animal studies, imipenem/cilastatin is classified as pregnancy category C. No adequate and well-controlled studies have been conducted in pregnant women and it is not known whether imipenem can cause fetal harm. Due to pregnancy induced physiologic changes, some pharmacokinetic parameters of imipenem/cilastatin may be altered. Pregnant women have a larger volume of distribution resulting in lower serum peak levels than for the same dose in nonpregnant women. Clearance is also increased.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsImipenem is excreted in human milk. The low concentrations and low oral bioavailability suggest minimal exposure risk to the infant. The manufacturer recommends that caution be exercised when administering imipenem/cilastatin to nursing women, however, most penicillins and carbapenems are safe for use in breast-feeding. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Imipenem and Cilastatin in Pregnancy & Lactation

Adverse ReactionsAdverse reactions reported with use for both I.V. and I.M. formulations in adults, except where noted.

1% to 10%:

Cardiovascular: Tachycardia (infants 2%; adults <1%)

Central nervous system: Seizure (infants 6%; adults <1%)

Dermatologic: Rash (≤1%, children 2%)

Gastrointestinal: Nausea (1% to 2%), diarrhea (children 3% to 4%; adults 1% to 2%), vomiting (≤2%)

Genitourinary: Oliguria/anuria (infants 2%; adults <1%)

Local: Phlebitis/thrombophlebitis (3%), pain at I.M. injection site (1.2%)

<1%, postmarketing and/or case reports: Abdominal pain, abnormal urinalysis, acute renal failure, alkaline phosphatase increased, anaphylaxis, anemia, angioneurotic edema, asthenia, bilirubin increased, bone marrow depression, BUN/creatinine increased, candidiasis, confusion, cyanosis, dizziness, drug fever, dyspnea, encephalopathy, eosinophilia, erythema multiforme, fever, flushing, gastroenteritis, glossitis, hallucinations, headache, hearing loss, hematocrit decreased, hemoglobin decreased, hemolytic anemia, hemorrhagic colitis, hepatitis (including fulminant onset), hepatic failure, hyperchloremia, hyperhidrosis, hyperkalemia, hypersensitivity, hyperventilation, hyponatremia, hypotension, injection site erythema, jaundice, lactate dehydrogenase increased, leukocytosis, leukopenia, myoclonus, neutropenia (including agranulocytosis), palpitation, pancytopenia, paresthesia, pharyngeal pain, polyarthralgia, polyuria, positive Coombs' test, prothrombin time increased, pruritus, pruritus vulvae, pseudomembranous colitis, psychic disturbances, rash, resistant *P. aeruginosa*, salivation increased, somnolence, staining of teeth, Stevens-Johnson syndrome, taste perversion, thoracic spine pain, thrombocythemia, thrombocytopenia, tinnitus, tongue/tooth discoloration, tongue papillar hypertrophy, toxic epidermal necrolysis, transaminases increased, tremor, urine discoloration, urticaria, vertigo

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Ganciclovir: May enhance the adverse/toxic effect of Imipenem. May increase risk of seizures. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Carbapenems. Management: Avoid concomitant use of doripenem and probenecid. *Risk C: Monitor therapy*

Valproic Acid: Carbapenems may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Test InteractionsInterferes with urinary glucose determination using Clinitest®

Monitoring ParametersPeriodic renal, hepatic, and hematologic function tests; monitor for signs of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's allergy history prior to beginning therapy. Note Administration for I.M. and I.V. specifics. Assess results of laboratory tests, therapeutic effectiveness (resolution of infection), and adverse response periodically during therapy. Advise patients with diabetes about use of Clinitest®. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating therapy. Periodically monitor renal, hepatic, and hematologic function.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by injection or infusion. Report immediately any warmth, swelling, pain, or redness at infusion or injection site. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition (small, frequent meals). May cause false test results with Clinitest®; use of another type of glucose testing is preferable. Report immediately any CNS changes (dizziness, hallucinations, anxiety, visual disturbances); swelling of throat, tongue, lips, or face; chills or fever; persistent diarrhea; or unusual discharge or foul-smelling urine.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [I.M.]:

Primaxin®: Imipenem 500 mg and cilastatin 500 mg [contains sodium 32 mg (1.4 mEq)]

Injection, powder for reconstitution [I.V.]:

Primaxin®: Imipenem 250 mg and cilastatin 250 mg [contains sodium 18.8 mg (0.8 mEq)]; imipenem 500 mg and cilastatin 500 mg [contains sodium 37.5 mg (1.6 mEq)]

Generic AvailableNo

ManufacturerMerck & Co

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs); which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested. Cilastatin prevents renal metabolism of imipenem by competitive inhibition of dehydropeptidase along the brush border of the renal tubules.

Pharmacodynamics/Kinetics

Absorption: I.M.: Imipenem: 60% to 75%; cilastatin: 95% to 100%

Distribution: Rapidly and widely to most tissues and fluids including sputum, pleural fluid, peritoneal fluid, interstitial fluid, bile, aqueous humor, and bone; highest concentrations in pleural fluid, interstitial fluid, and peritoneal fluid; low concentrations in CSF

Protein binding: Imipenem: 20%; cilastatin: 40%

Metabolism: Imipenem is metabolized in the kidney by dehydropeptidase I; cilastatin prevents imipenem metabolism by this enzyme; cilastatin is partially metabolized renally

Half-life elimination: I.V.: Both drugs: 60 minutes; prolonged with renal impairment; I.M.: Imipenem: 2-3 hours

Time to peak: I.M.: 3.5 hours

Excretion: Both drugs: Urine (~70% as unchanged drug)

Related Information

- Antimicrobial Drugs of Choice

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusReports of encephalopathy

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine

Index TermsImipemide

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International Brand NamesAnipen (PH); Arzobema (MX); Bacqure (MY, TH); Iminen (MX); Newpenem (KP); Pelastin IV (ID); Prepenem (HK, KP, TH); Primaxin (AU, GB, GR); Primaxin IV (BB, BM, BS, BZ, GY, JM, SR, TT); Tenacid (IT); Tienam (AT, BD, BE, BG, BR, CH, CL, CN, CO, CR, CZ, DE, DK, EC, EG, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IL, IN, IT, JP, KP, MX, MY, NI, NL, NO, PA, PE, PH, PK, PT, RU, SE, SG, SV, TH, TR, TW); Tipem (KP); Zienam (AR, AT, DE, PY, UY, VE)

Imipramine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) has issued a statement in April 2008 recommending that all children diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the recommendations due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: Methylphenidate, amphetamine, dextroamphetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children's Healthcare Quality.

For more information, refer to:

- http://americanheart.mediaroom.com/index.php?s=43&item=422
- http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1
- http://americanheart.mediaroom.com/index.php?s=43&item=398
- http://www.fda.gov/medwatch/safety/2007/safety07.htm
- http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html

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Medication Safety Issues

Sound-alike/look-alike issues:

Imipramine may be confused with amitriptyline, desipramine, Norpramin®

Pronunciation(im IP ra meen)

U.S. Brand NamesTofranil-PM®; Tofranil®

Canadian Brand NamesApo-Imipramine®; Novo-Pramine; Tofranil®

Pharmacologic CategoryAntidepressant, Tricyclic (Tertiary Amine)

Use: Labeled IndicationsTreatment of depression; treatment of nocturnal enuresis in children

Use: Unlabeled/InvestigationalAnalgesic for certain chronic and neuropathic pain; panic disorder; attention-deficit/hyperactivity disorder (ADHD)

Dosing: Adults**Depression:**

Outpatients: Initial: 75 mg/day; may increase gradually to 150 mg/day. May be given in divided doses or as a single bedtime dose; maximum: 200 mg/day

Inpatients: Initial: 100-150 mg/day; may increase gradually to 200 mg/day; if no response after 2 weeks, may further increase to 250-300 mg/day. May be given in divided doses or as a single bedtime dose; maximum: 300 mg/day.

Note: Maximum antidepressant effect may not be seen for 2 or more weeks after initiation of therapy.

Dosing: Elderly

Depression: Initial: 25-50 mg at bedtime; may increase every 3 days for inpatients and weekly for outpatients if tolerated to a recommended maximum of 100 mg/day.

Dosing: Pediatric

Depression: Oral:

Children (unlabeled use): 1.5 mg/kg/day with dosage increments of 1 mg/kg every 3-4 days to a maximum dose of 5 mg/kg/day in 1-4 divided doses; monitor carefully especially with doses ≥3.5 mg/kg/day.

Adolescents: Initial: 30-40 mg/day; increase gradually; maximum: 100 mg/day in single or divided doses.

Enuresis: Oral: Children ≥6 years: Initial: 25 mg at bedtime, if inadequate response still seen after 1 week of therapy, increase by 25 mg/day; dose should not exceed 2.5 mg/kg/day or 50 mg at bedtime if 6-12 years of age or 75 mg at bedtime if ≥12 years of age.

Adjunct in the treatment of cancer pain (unlabeled use): Oral: Children: Initial: 0.2-0.4 mg/kg at bedtime; dose may be increased by 50% every 2-3 days up to 1-3 mg/kg/dose at bedtime.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to imipramine (cross-reactivity with other dibenzodiazepines may occur) or any component of the formulation; concurrent use of MAO inhibitors (within 14 days); in a patient during acute recovery phase of MI; pregnancy

Allergy Considerations

- Tricyclic Antidepressant and Related Compounds Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Imipramine is FDA approved for the treatment of nocturnal enuresis in children ≥6 years of age.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Imipramine is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. The degree of anticholinergic blockade produced by this agent is high relative to other antidepressants.

- Hematologic effects: TCAs may rarely cause bone marrow suppression; monitor for any signs of infection and obtain CBC if symptoms (eg, fever, sore throat) evident.

- Orthostatic hypotension: May cause orthostatic hypotension (risk is very high relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Photosensitization: Has been associated with photosensitization; avoid excessive exposure to sunlight.

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is high relative to other antidepressants.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk of conduction abnormalities with this agent is high relative to other antidepressants.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose regulation.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

- Thyroid dysfunction: Use with caution in patients with hyperthyroidism or those receiving thyroid supplementation due to concerns of pro-arrhythmogenesis.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Discontinuation of therapy: Recommended to discontinue prior to elective surgery requiring general anesthesia. Therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods.

- ECG monitoring: Baseline and periodic assessment recommended with use of higher dosages; should also be considered in elderly patients and/or patients with pre-existing cardiovascular disease.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

Geriatric ConsiderationsOrthostatic hypotension is a concern with this agent, especially in patients taking other medications that may affect blood pressure. May precipitate arrhythmias in predisposed patients; may aggravate seizures. A less anticholinergic antidepressant may be a better choice. Data from a clinical trial comparing fluoxetine to tricyclics suggests that fluoxetine is significantly less effective than nortriptyline in hospitalized elderly patients with unipolar major affective disorder, especially those with melancholia and concurrent cardiovascular diseases.
Pregnancy Risk FactorD
LactationEnters breast milk/not recommended (AAP rates “of concern”)
Adverse ReactionsReported for tricyclic antidepressants in general. Frequency not defined.

Cardiovascular: Arrhythmia, CHF, ECG changes, heart block, hypertension, MI, orthostatic hypotension, palpitation, stroke, tachycardia

Central nervous system: Agitation, anxiety, confusion, delusions, disorientation, dizziness, drowsiness, fatigue, hallucination, headache, hypomania, insomnia, nightmares, psychosis, restlessness, seizure

Dermatologic: Alopecia, itching, petechiae, photosensitivity, purpura, rash, urticaria

Endocrine & metabolic: Breast enlargement, galactorrhea, gynecomastia, increase or decrease in blood sugar, increase or decrease in libido, SIADH

Gastrointestinal: Abdominal cramps, anorexia, black tongue, constipation, diarrhea, epigastric disorders, ileus, nausea, stomatitis, taste disturbance, vomiting, weight gain/loss, xerostomia

Genitourinary: Impotence, testicular swelling, urinary retention

Hematologic: Agranulocytosis, eosinophilia, thrombocytopenia

Hepatic: Cholestatic jaundice, transaminases increased

Neuromuscular & skeletal: Ataxia, extrapyramidal symptoms, incoordination, numbness, paresthesia, peripheral neuropathy, tingling, tremor, weakness

Ocular: Blurred vision, disturbances of accommodation, mydriasis

Otic: Tinnitus

Miscellaneous: Diaphoresis, falling, hypersensitivity (eg, drug fever, edema)

Metabolism/Transport Effects **Substrate** of CYP1A2 (minor), 2B6 (minor), 2C19 (major), 2D6 (major), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2C19 (weak), 2D6 (moderate), 2E1 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Tricyclic Antidepressants may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Agonists: Tricyclic Antidepressants may enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Alpha2-Agonists: Tricyclic Antidepressants may diminish the antihypertensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Altretamine: May enhance the orthostatic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Amphetamines: Tricyclic Antidepressants may enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Aspirin: Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Beta2-Agonists: Tricyclic Antidepressants may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cinacalcet: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Desmopressin: Tricyclic Antidepressants may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dexmethylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

DULoxetine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Iobenguane I 123: Tricyclic Antidepressants may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May enhance the neurotoxic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

NSAID (COX-2 Inhibitor): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Tricyclic Antidepressants may enhance the QTc-prolonging effect of QuiNIDine. QuiNIDine may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

St Johns Wort: May increase the metabolism of Tricyclic Antidepressants. The risk of serotonin syndrome may theoretically be increased. *Risk D: Consider therapy modification*

Sulfonylureas: Cyclic Antidepressants may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Terbinafine: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: Tricyclic Antidepressants may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. *Risk C: Monitor therapy*

Valproic Acid: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Tricyclic Antidepressants may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Yohimbine: Tricyclic Antidepressants may increase the serum concentration of Yohimbine. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: St John's wort may decrease imipramine levels. Avoid valerian, St John's wort, SAMe, kava kava (may increase risk of serotonin syndrome and/or excessive sedation).

Monitoring ParametersMonitor blood pressure and pulse rate prior to and during initial therapy; ECG in older adults, with high doses, and/or in patients with pre-existing cardiovascular disease; evaluate mental status, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased); blood levels are useful for therapeutic monitoring

When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure, and consider obtaining ECG prior to initiation (Vetter, 2008); ensure PR interval ≤200 ms, QRS duration ≤120 ms, and QT_c ≤460 ms.

Reference RangeTherapeutic: Imipramine and desipramine: 150-250 ng/mL (SI: 530-890 nmol/L); desipramine: 150-300 ng/mL (SI: 560-1125 nmol/L); Toxic: >500 ng/mL (SI: 446-893 nmol/L); utility of serum level monitoring controversial

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Perform careful cardiovascular assessment prior to initiating therapy. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. Assess CNS status and clinical worsening, and be alert for suicidal ideation. Taper dosage slowly when discontinuing (allow 3-4 weeks between discontinuing and starting another antidepressant), if possible. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsECG, CBC

Patient EducationTake exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results. Take in the evening. Avoid alcohol, caffeine, and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, altered taste, dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); diarrhea (buttermilk, yogurt, or boiled milk may help); postural hypotension (use caution when climbing stairs or changing position from lying or sitting to standing); or urinary retention (void before taking medication). Report persistent insomnia; muscle cramping or tremors; chest pain, palpitations, rapid heartbeat, swelling of extremities, or severe dizziness; unresolved urinary retention; rash or skin irritation; yellowing of eyes or skin; pale stools/dark urine; worsening of condition; and suicide ideation. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as pamoate: 75 mg, 100 mg, 125 mg, 150 mg

Tofranil-PM®: 75 mg, 100 mg, 125 mg, 150 mg

Tablet, as hydrochloride: 10 mg, 25 mg, 50 mg

Tofranil®): 10 mg, 25 mg, 50 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Imipramine Pamoate)

75 mg (30): $402.57

Capsules (Tofranil-PM)

75 mg (30): $482.98

100 mg (30): $447.27

125 mg (30): $503.56

150 mg (30): $496.73

Tablets (Imipramine HCl)

10 mg (30): $13.99

50 mg (30): $17.64

Tablets (Tofranil)

25 mg (30): $155.99

50 mg (30): $167.88

Mechanism of ActionTraditionally believed to increase the synaptic concentration of serotonin and/or norepinephrine in the central nervous system by inhibition of their reuptake by the presynaptic neuronal membrane. However, additional receptor effects have been found including desensitization of adenyl cyclase, down regulation of beta-adrenergic receptors, and down regulation of serotonin receptors.

Pharmacodynamics/Kinetics

Onset of action: Peak antidepressant effect: Usually after ≥2 weeks

Absorption: Well absorbed

Distribution: Crosses placenta

Metabolism: Hepatic, primarily via CYP2D6 to desipramine (active) and other metabolites; significant first-pass effect

Half-life elimination: 6-18 hours

Excretion: Urine (as metabolites)

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation). Long-term treatment with TCAs, such as imipramine, increases the risk of caries by reducing salivation and salivary buffer capacity. In a study by Rundergren, et al, pathological alterations were observed in the oral mucosa of 72% of 58 patients; 55% had new carious lesions after taking TCAs for a median of $5^1/_2$ years. Current research is investigating the use of the salivary stimulant pilocarpine to overcome the xerostomia from imipramine.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Use with caution; epinephrine and levonordefrin have been shown to have an increased pressor response in combination with TCAs. Imipramine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health Comment Tricyclic antidepressants may be classified as tertiary (amitriptyline, doxepin, clomipramine, imipramine, trimipramine) or secondary amines (nortriptyline, desipramine, protriptyline). The tertiary amines are not recommended to treat depression in the elderly. If a TCA is used in the elderly, it should be a secondary amine. The tertiary amines are commonly used in low dosages for various conditions associated with pain. Toxicity is generally dose dependent. Relatively small overdoses (1-week supply) can be potentially fatal.

Plasma concentrations correlate with clinical response. A linear relationship exists.

Index Terms Imipramine Hydrochloride; Imipramine Pamoate

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International Brand Names Antidep (IN); Chrytemin (JP); Depsol (IN); Depsonil (IN); Ethipramine (ZA); Eupramin (HR); Feinalmin (JP); Fronil (TW); Imidol (JP); Imilanyle (JP); Imimine (TW); Imine (TW); Imipramin (PL); Melipramin (CZ, HN, HU, PL); Meripramin (JP); Primonil (IL); Pryleugan (DE); Sermonil (TH); Talpramin (MX); Tofranil (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CN, CO, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PH, PK, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Tofranil-PM (AR, CO); Tolerade (AU)

Imiquimod

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Medication Safety Issues

Sound-alike/look-alike issues:

Aldara™ may be confused with Alora®, Lialda™

Pronunciation(i mi KWI mod)

U.S. Brand NamesAldara®

Canadian Brand NamesAldara®

Pharmacologic CategorySkin and Mucous Membrane Agent; Topical Skin Product

Use: Labeled IndicationsTreatment of external genital and perianal warts/condyloma acuminata; nonhyperkeratotic, nonhypertrophic actinic keratosis on face or scalp; superficial basal cell carcinoma (sBCC) with a maximum tumor diameter of 2 cm located on the trunk, neck, or extremities (excluding hands or feet)

Use: Unlabeled/InvestigationalTreatment of common warts

Dosing: Adults**Note:** A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. Treatment may resume once the reaction subsides.

Perianal warts/condyloma acuminata: Topical: Apply a thin layer 3 times/week on alternative days prior to bedtime and leave on skin for 6-10 hours. Remove by washing with mild soap and water. Continue imiquimod treatment until there is total clearance of the genital/perianal warts for ≤16 weeks.

Actinic keratosis: Topical: Apply twice weekly for 16 weeks to a treatment area on face or scalp (but not both concurrently); apply prior to bedtime and leave on skin for 8 hours. Remove with mild soap and water.

Common warts (unlabeled use): Topical: Apply once daily prior to bedtime.

Superficial basal cell carcinoma: Topical: Apply once daily prior to bedtime, 5 days/week for 6 weeks. Treatment area should include a 1 cm margin of skin around the tumor. Leave on skin for 8 hours. Remove with mild soap and water.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricPerianal warts/condyloma acuminata: Topical: Children ≥12 years: Refer to adult dosing.

Note: A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. Treatment may resume once the reaction subsides.

Administration: Topical

Actinic keratosis: Treatment area should be a single contiguous area (approximately 25 cm^2) on the face or scalp. Both areas should not be treated concurrently. Apply a thin layer to the wart area and rub in until the cream is no longer visible. Avoid contact with the eyes, lips, and nostrils. Do not occlude the application site. Wash hands before and following application. No more than one packet should be applied at each application and no more than 36 packets should be used per 16-week treatment period.

External genital warts: Nonocclusive dressings such as cotton gauze or cotton underwear may be used in the management of skin reactions. Handwashing before and after cream application is recommended. Imiquimod is packaged in single-use packets that contain sufficient cream to cover a wart area of up to 20 cm^2; avoid use of excessive amounts of cream. Instruct patients to apply imiquimod to external or perianal warts; not for vaginal use. Apply a thin layer to the wart area and rub in until the cream is no longer visible. Do not occlude the application site.

Superficial basal cell carcinoma: Treatment area should have a maximum diameter no more than 2 cm on the trunk, neck, or extremities (excluding the hands, feet, and anogenital skin). Treatment area should include a 1 cm margin around the tumor. Apply a thin layer to the wart area (and margin) and rub in until the cream is no longer visible. Avoid contact with the eyes, lips, and nostrils. Do not occlude the application site. Wash hands before and following application. No more than 36 packets should be used during the 6-week treatment period.

StorageStore at 4°C to 25°C (39°F to 77°F); do not freeze.

Warnings/Precautions

Concerns related to adverse effects:

- Inflammatory reactions: Intense inflammatory reactions may occur, and may be accompanied by systemic symptoms (fever, malaise, myalgia); interruption of therapy should be considered.
- Photosensitivity: May increase sunburn susceptibility; patients should protect themselves from the sun and artificial forms of sunlight.

Disease related concerns:

- Actinic keratosis: Appropriate use: Treatment should be limited to areas ≤25 cm^2. Safety and efficacy of repeated use in the same 25 cm^2

area has not been established.

- Basal cell carcinoma: Appropriate use: Should be limited to superficial carcinomas with a maximum diameter of 2 cm. Safety and efficacy in treatment of sBCC lesions of the face, head, and anogenital area, or other subtypes of basal cell carcinoma (including nodular and morpheaform), have not been established.

- Basal cell nevus syndrome: Safety and efficacy have not been established for basal cell nevus syndrome.

- External genital warts: Appropriate use: Has not been evaluated for the treatment of urethral, intravaginal, cervical, rectal, or intra-anal human papilloma viral disease and is not recommended for these conditions.

- Skin inflammatory conditions: Has the potential to exacerbate inflammatory conditions of the skin.

- Xeroderma pigmentosum: Safety and efficacy have not been established for xeroderma pigmentosum.

Special populations:

- Immunocompromised patients: Safety and efficacy have not been established in immunosuppressed patients.

- Pediatrics: Safety and efficacy have not been established in children <12 years of age. Efficacy was not established for molluscum contagiosum in children 2-12 years of age.

Other warnings/precautions:

- Administration: Not intended for oral, intravaginal, or ophthalmic use. Administration is not recommended until tissue is healed from any previous drug or surgical treatment.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were noted in some animal studies following oral administration. Safety and efficacy have not been established in pregnant women. A registry has been established for women exposed to imiquimod during pregnancy (800-670-6126).

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Local: Application site reactions are common. Frequency of reactions vary, and are related to the degree of inflammation associated with the treated disease, number of weekly applications, and individual sensitivity.

Edema, erosion/ulceration, erythema, excoriation, flaking, induration, itching, scabbing/crusting, scaling/dryness, vesicles, weeping/exudate

Respiratory: Upper respiratory infection (3% to 15%)

1% to 10%:

Cardiovascular: Chest pain (1%)

Central nervous system: Headache (4% to 8%), fatigue (2%), fever (1% to 2%), anxiety (1%), dizziness (1%)

Dermatologic: Eczema (2%), alopecia (1%)

Gastrointestinal: Diarrhea (3%), dyspepsia (2% to 3%), nausea (1%), vomiting (1%)

Genitourinary: Urinary tract infection (1%)

Local: Bleeding, burning, hypopigmentation, infection, irritation, pain, papule, rash, sensitivity, soreness, stinging, tenderness

Neuromuscular & skeletal: Myalgia (1%), back pain (4%), rigors (1%)

Respiratory: Sinusitis (2% to 7%), rhinitis (3%), pharyngitis (1%), coughing (2%)

Miscellaneous: Squamous cell carcinoma (4%), influenza-like syndrome (1% to 3%), lymphadenopathy (3%)

Postmarketing and/or case reports (limited to important and/or life-threatening): Agitation, anemia, angioedema, arrhythmias, capillary leak syndrome, cardiac failure, cardiomyopathy, cerebrovascular accident, depression, dyspnea, erythema multiforme, exfoliative dermatitis, Henoch-Schönlein purpura syndrome, idiopathic thrombocytopenia purpura, insomnia, ischemia, leukopenia, liver function abnormal, lymphoma, MI, multiple sclerosis aggravated, paresis, proteinuria, pulmonary edema, seizure, syncope, thrombocytopenia, thyroiditis

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 3A4

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersReduction in wart size is indicative of a therapeutic response; patients should be monitored for signs and symptoms of hypersensitivity to imiquimod

Nursing: Physical Assessment/MonitoringMonitor effectiveness of treatment and adverse reactions experienced at the beginning and periodically during therapy. Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis medication will not eliminate nor prevent the transmission of the virus. For external use only; avoid contact with eyes, mouth, nostrils, or vagina. Use only as frequently as directed and apply as instructed. Exposure to sun should be avoided or minimized. Use sunscreen or wear protective clothing if sun exposure is unavoidable. Sexual contact (vaginal, anal, or oral) should be avoided while cream is on skin. May cause pain, itching, redness, burning, flaking, swelling, or scabbing in treated area. If these effects persist or become severe or open sores develop, stop treatment and notify prescriber. Report fever, malaise, myalgia, or flu-like symptoms. Prescriber may recommend a rest period of several days before resuming treatment. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This medication may weaken condoms or vaginal diaphragms; consult prescriber for appropriate forms of protection.

Consult prescriber if breast-feeding.

Apply treatment just prior to sleeping and leave on 6-10 hours. Wash hands thoroughly before and after application. Wash and dry area to be treated before applying cream. After treatment period, remove cream with mild soap and water. Apply a thin layer to external warts and rub in until cream is no longer visible. Avoid use of excessive cream. May cover area with light gauze dressing or cotton underwear; do not apply occlusive dressing.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream:

Aldara®: 5% (12s, 24s) [contains benzyl alcohol; single-dose packets]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Cream (Aldara)

5% (24): $524.97

Mechanism of ActionMechanism of action is unknown; however, induces cytokines, including interferon-alpha and others

Pharmacodynamics/Kinetics

Absorption: Minimal; systemic absorption more dependant upon surface area of application as opposed to dose

Excretion: Urine (≤2% of applied dose as imiquimod and metabolites)

Dental Health Professional ConsiderationsImiquimod 5% has been used for actinic cheilitis or keratosis; however, oral ulcerations have been reported as well as other serious side effects associated with its use. Imiquimod use in the treatment of oral papilloma virus remains inadequately studied.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

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International Brand NamesAldara (AR, AT, AU, BE, BG, BR, CH, CL, CN, CR, CZ, DE, DK, ES, FI, FR, GB, GR, GT, HK, HN, IE, IL, IT, KP, MX, MY, NL, NO, PA, PH, PL, PT, RU, SE, SG, SV, TH, TR, TW); Arsilon (UY); Imimore (PE)

Immune Globulin (Intramuscular)

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Pronunciation(i MYUN GLOB yoo lin, IN tra MUS kyoo ler)

U.S. Brand NamesGamaSTAN™ S/D

Canadian Brand NamesBayGam®

Pharmacologic CategoryImmune Globulin

Use: Labeled IndicationsTo provide passive immunity in susceptible individuals under the following circumstances:

Hepatitis A: Within 14 days of exposure and prior to manifestation of disease

Measles: For use within 6 days of exposure in an unvaccinated person, who has not previously had measles

Varicella: When Varicella Zoster Immune Globulin is not available

Rubella: Postexposure prophylaxis (within 72 hours) to reduce the risk of infection in exposed pregnant women who will not consider therapeutic abortion

Immunoglobulin deficiency: To help prevent serious infections

Dosing: Adults

Hepatitis A: I.M.:

Pre-exposure prophylaxis upon travel into endemic areas (hepatitis A vaccine preferred):

0.02 mL/kg for anticipated risk of exposure <3 months

0.06 mL/kg for anticipated risk of exposure ≥3 months

Repeat approximate dose every 5 months if exposure continues

Postexposure prophylaxis: 0.02 mL/kg given within 14 days of exposure. IG is not needed if at least 1 dose of hepatitis A vaccine was given at ≥1 month before exposure

Measles: I.M.:

Prophylaxis, immunocompetent: 0.25 mL/kg/dose (maximum dose: 15 mL) given within 6 days of exposure followed by live attenuated measles vaccine in 5-6 months when indicated

Prophylaxis, immunocompromised: 0.5 mL/kg (maximum dose: 15 mL) immediately following exposure

Rubella: I.M.: Prophylaxis during pregnancy: 0.55 mL/kg/dose within 72 hours of exposure

Varicella: I.M.: Prophylaxis: 0.6-1.2 mL/kg (varicella zoster immune globulin preferred) within 72 hours of exposure

IgG deficiency: I.M.: 0.66 mL/kg/dose every 3-4 weeks. A double dose may be given at onset of therapy; some patients may require more frequent injections.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: I.M.

Not for I.V. administration. Administer I.M. in the anterolateral aspects of the upper thigh or deltoid muscle of the upper arm. Avoid gluteal region due to risk of injury to sciatic nerve; use upper outer quadrant only. Divide doses >10 mL.

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

Administration: I.V.Not for I.V. administration

StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F).

ContraindicationsHypersensitivity to immune globulin or any component of the formulation; IgA deficiency; severe thrombocytopenia or coagulation disorders where I.M. injections are contraindicated

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1:1000) should be available.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

Other warnings/precautions:

- Administration: Not for I.V. administration.

- Skin testing: Skin testing should not be performed as local irritation can occur and be misinterpreted as a positive reaction.

Geriatric ConsiderationsNo special recommendations are made for the elderly, doses are same as recommended for younger adults.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this product. Immune globulins cross the placenta in increased amounts after 30 weeks gestation.
Adverse ReactionsFrequency not defined.

Cardiovascular: Flushing, angioedema

Central nervous system: Chills, lethargy, fever

Dermatologic: Urticaria, erythema

Gastrointestinal: Nausea, vomiting

Local: Pain, tenderness, muscle stiffness at I.M. site

Neuromuscular & skeletal: Myalgia

Miscellaneous: Hypersensitivity reactions

Drug Interactions

Vaccines (Live): Immune Globulins may diminish the therapeutic effect of Vaccines (Live). **Exceptions:** Influenza Virus Vaccine; Yellow Fever Vaccine. *Risk D: Consider therapy modification*

Test InteractionsSkin tests should **not** be done
Reference RangeImmunoglobulin deficiency: Maintain circulating IgG levels ~200 mg/100 mL plasma to prevent serious infection
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free; solvent detergent-treated]:

GamaSTAN™ S/D: 15% to 18% (2 mL, 10 mL)

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Injection (BayGam)

(2): $32.99

(10): $127.99

Mechanism of ActionProvides passive immunity by increasing the antibody titer and antigen-antibody reaction potential
Pharmacodynamics/Kinetics

Duration: Immune effect: Usually 3-4 weeks

Half-life elimination: 23 days

Time to peak, serum: I.M.: ~48 hours

Related Information

- Immunization Recommendations
- Prophylaxis for Patients Exposed to Common Communicable Diseases

Pharmacotherapy PearlsWhen administering IG for hepatitis A prophylaxis, use should be considered for the following close contacts of persons with confirmed hepatitis A: unvaccinated household and sexual contacts, persons who have shared illicit drugs, regular babysitters, staff and attendees of child care centers, food handlers within the same establishment.

For travelers, IG is not an alternative to careful selection of foods and water; immune globulin can interfere with the antibody response to parenterally administered live virus vaccines. Frequent travelers should be tested for hepatitis A antibody, immune hemolytic anemia, and neutropenia (with ITP, I.V. route is usually used).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsGamma Globulin; IG; IGIM; Immune Serum Globulin; ISG

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Immune Globulin (Intravenous)

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Gamimune® N may be confused with CytoGam®

Immune globulin (intravenous) may be confused with hepatitis B immune globulin

Pronunciation(i MYUN GLOB yoo lin, IN tra VEE nus)

U.S. Brand NamesCarimune® NF; Flebogamma®; Gammagard Liquid; Gammagard S/D; Gammar®-P I.V. [DSC]; Gamunex®; Octagam®; Panglobulin® NF [DSC]; Polygam® S/D [DSC]; Privigen™

Canadian Brand NamesGamimune® N; Gammagard Liquid; Gammagard S/D; Gamunex®

Pharmacologic CategoryImmune Globulin

Use: Labeled Indications

Treatment of primary immunodeficiency syndromes (congenital agammaglobulinemia, severe combined immunodeficiency syndromes [SCIDS], common variable immunodeficiency, X-linked immunodeficiency, Wiskott-Aldrich syndrome) (Carimune® NF, Flebogamma®, Gammagard Liquid, Gammagard S/D, Gammar®-P I.V., Gamunex®, Octagam®, Panglobulin® NF, Polygam® S/D, Privigen™)

Treatment of immune (idiopathic) thrombocytopenic purpura (ITP) (Carimune® NF, Gammagard S/D, Gamunex®, Panglobulin® NF, Polygam® S/D, Privigen™)

Prevention of coronary artery aneurysms associated with Kawasaki disease (in combination with aspirin) (Gammagard S/D, Polygam® S/D)

Prevention of bacterial infection in B-cell chronic lymphocytic leukemia (CLL) (Gammagard S/D, Polygam® S/D)

Treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) (Gamunex®)

Use: Unlabeled/InvestigationalPrevention of serious bacterial infections among HIV-infected children with hypogammaglobulinemia (IgG <400 mg/dL) (CDC guidelines); hematopoietic stem cell transplantation (HSCT), to prevent bacterial infections among allogeneic recipients with severe hypogammaglobulinemia (IgG <400 mg/dL) at <100 days post transplant (CDC guidelines); fetal-neonatal alloimmune thrombocytopenia; pregnancy-associated ITP; prevention of gastroenteritis in children; multiple sclerosis (relapsing, remitting when other therapies cannot be used); hemolytic disease of the newborn; HIV-associated thrombocytopenia; acquired hypogammaglobulinemia secondary to malignancy; myasthenia gravis; refractory dermatomyositis/polymyositis

Dosing: AdultsApproved doses and regimens may vary between brands; check manufacturer guidelines. **Note:** Some clinicians dose IVIG on ideal body weight or an adjusted ideal body weight in morbidly obese patients.

Primary immunodeficiency disorders: Adjust dose/frequency based desired IgG levels and clinical response: General dosing range: 200-800 mg/kg per month

Carimune® NF, Panglobulin® NF: 200 mg/kg every 4 weeks. May increase dose to 300 mg/kg every 4 weeks or may increase frequency based on patient response.

Flebogamma®, Gammagard Liquid, Gammagard S/D, Gamunex®, Octagam®, Polygam® S/D: 300-600 mg/kg every 3-4 weeks; adjusted based on dosage and interval in conjunction with monitored serum IgG concentrations

Gamma®-P I.V.: 200-400 mg/kg every 3-4 weeks

Privigen™: 200-800 mg/kg every 3-4 weeks; adjusted based on dosage and interval in conjunction with monitored serum IgG concentrations

B-cell chronic lymphocytic leukemia (CLL) (Gammagard S/D, Polygam® S/D): 400 mg/kg/dose every 3-4 weeks

Chronic inflammatory demyelinating polyneuropathy (CIDP) (Gamunex®): Loading dose: 2000 mg/kg divided over 2-4 consecutive days; Maintenance: 1000 mg/kg/day for 1 day every 3 weeks **or** 500 mg/kg/day for 2 consecutive days every 3 weeks

Immune (idiopathic) thrombocytopenic purpura (ITP):

Carimune® NF, Panglobulin® NF:

Acute: 400 mg/kg/day for 2-5 days

Chronic: 400 mg/kg as needed to maintain platelet count ≥30,000/mm^3 or to control significant bleeding; may increase dose if needed (range: 800-1000 mg/kg)

Gammagard S/D, Polygam® S/D: 1000 mg/kg; adjust additional doses based on patient response or platelet count. Up to 3 separate doses may be administered on alternate days if required.

Gamunex®: 1000 mg/kg/day for 1-2 days, **or** 400 mg/kg/day for 5 days

Privigen™: 1000 mg/kg/day for 2 consecutive days

Kawasaki disease: Initiate IVIG therapy within 10 days of disease onset: Must be used in combination with aspirin: 80-100 mg/kg/day in 4 divided doses for 14 days; when fever subsides, dose aspirin at 3-5 mg/kg once daily for ≥6-8 weeks

AHA guidelines: 2000 mg/kg as a single dose

Gammagard S/D, Polygam® S/D: 1000 mg/kg as a single dose administered over 10 hours, **or** 400 mg/kg/day for 4 days. Begin within 7 days of onset of fever.

Hematopoietic stem cell transplantation with hypogammaglobulinemia (CDC guidelines): 500 mg/kg/week

Unlabeled uses:

Acquired hypogammaglobulinemia secondary to malignancy (unlabeled use): 400 mg/kg/dose every 3 weeks; reevaluate every 4-6 months

Guillain-Barré syndrome (unlabeled use): Various regimens have been used, including:

400 mg/kg/day for 5 days

or

2000 mg/kg in divided doses administered over 2 days

HIV-associated thrombocytopenia (unlabeled use): 1000 mg/kg/day for 2 days

Multiple sclerosis (relapsing-remitting, when other therapies cannot be used) (unlabeled use): 1000 mg/kg per month, with or without an induction of 400 mg/kg/day for 5 days

Myasthenia gravis (severe exacerbation) (unlabeled use): Total dose of 2000 mg/kg over 2-5 days

Refractory dermatomyositis (unlabeled use): 2000 mg/kg per month administered over 2-5 days

Refractory polymyositis (unlabeled use): 2000 mg/kg per course administered over 2-5 days

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricApproved doses and regimens may vary between brands; check manufacturer guidelines. **Note:** Some clinicians dose IVIG on ideal body weight or an adjusted ideal body weight in morbidly obese patients.

Pediatric HIV, prevention of infection (CDC guidelines): I.V.: 400 mg/kg every 2-4 weeks

Primary immunodeficiency disorders: Adjust dose/frequency based desired IgG levels and clinical response: General dosing range: 200-800 mg/kg per month: Children and Adolescents:

Carimune® NF, Panglobulin® NF: 200 mg/kg every 4 weeks. May increase dose to 300 mg/kg every 4 weeks or may increase frequency based on patient response.

Flebogamma®, Gammagard Liquid, Gammagard S/D, Gamunex®, Octagam®, Polygam® S/D: 300-600 mg/kg every 3-4 weeks; adjusted based on dosage and interval in conjunction with monitored serum IgG concentrations

Gamma®-P I.V.: Children and Adolescents: Initial dose: 200 mg/kg every 3-4 weeks

Privigen™: 200-800 mg/kg every 3-4 weeks; adjusted based on dosage and interval in conjunction with monitored serum IgG concentrations

Hematopoietic stem cell transplantation with hypogammaglobulinemia (CDC guidelines):

Children: 400 mg/kg per month; increase dose or frequency to maintain IgG levels >400 mg/dL

Adolescents : Refer to adult dosing.

B-cell chronic lymphocytic leukemia (CLL): Refer to adult dosing.

Guillain-Barré syndrome (unlabeled use): Refer to adult dosing.

Immune (idiopathic) thrombocytopenic purpura (ITP): Refer to adult dosing.

Kawasaki disease: Refer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <10 mL/minute: Avoid use; in patients at risk of renal dysfunction, consider infusion at a rate less than maximum.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.For I.V. use only; for initial treatment, a lower concentration and/or a slower rate of infusion should be used. Refrigerated product should be warmed to room temperature prior to infusion. Some products require filtration; refer to individual product labeling. Antecubital veins should be used, especially with concentrations ≥10% to prevent injection site discomfort.

Administration: I.V. DetailInfuse over 2-24 hours; administer in separate infusion line from other medications; if using primary line, flush with saline prior administration. Decrease dose, rate and/or concentration of infusion in patients who may be at risk of renal failure. Decreasing the rate or stopping the infusion may help relieve some adverse effects (flushing, changes in pulse rate, changes in blood pressure). Epinephrine should be available during administration.

Carimune® NF, Panglobulin® NF: pH 6.4-6.8

Flebogamma®: pH 5-6

Gammagard Liquid: pH 4.6-5.1

Gammagard S/D 5%, Gammar®-P I.V., Polygam® S/D: pH 6.4-7.2

Gamunex®: pH 4.0-4.5

Octagam®: pH 5.1-6.0

Privigen™: pH 4.6-5

Dietary ConsiderationsOctagam® contains sodium 30 mmol/L

StorageStability is dependent upon the manufacturer and brand. Do not freeze.

Carimune® NF, Panglobulin® NF: Prior to reconstitution, store at or below 30°C (86°F). Following reconstitution, store under refrigeration. Begin infusion within 24 hours.

Flebogamma®: Store at 2°C to 25°C (36°F to 77°F).

Gammagard Liquid: Prior to use, store at 2°C to 8°C (36°F to 46°F) for up to 36 months. May store at room temperature of 25°C (77°F) within the first 24 months of manufacturing. Storage time at room temperature varies with length of time previously refrigerated; refer to product labeling for details.

Gammagard S/D, Polygam® S/D: Store at ≤25°C (≤77°F).

Gammar®-P I.V.: Store at ≤25°C (≤77°F).

Gamunex®: May be stored for up to 36 months at 2°C to 8°C (36°F to 46°F); may be stored at ≤25°C (≤77°F) for up to 6 months.

Octagam®: Store at 2°C to 25°C (36°F to 77°F).

Privigen™: Store at ≤25°C (≤77°F); do not freeze (do not use if previously frozen). Protect from light.

ReconstitutionDilution is dependent upon the manufacturer and brand. Gently swirl; do not shake; avoid foaming. Do not mix products from different manufacturers together. Discard unused portion of vials.

Carimune® NF, Panglobulin® NF: Reconstitute with NS, D_5W, or SWFI.

Flebogamma®: Dilution is not recommended.

Gammagard Liquid: May dilute in D_5W only.

Gammagard S/D, Gammar®-P I.V., Polygam® S/D: Reconstitute with SWFI.

Gamunex®:Dilute in D_5W only.

Privigen™: If necessary to further dilute, D_5W may be used.

CompatibilityStable (variable/product dependent) in D_5W, $D_{15}W$, $D_5{}^1/_4NS$; **variable stability (consult detailed reference)** in TPN.

Y-site administration: Compatible: Fluconazole, sargramostim.

ContraindicationsHypersensitivity to immune globulin or any component of the formulation; selective IgA deficiency; hyperprolinemia (Privigen™)

Warnings/Precautions

Boxed warnings:

- Renal impairment: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1:1000) should be available.
- Aseptic meningitis: Aseptic meningitis syndrome (AMS) has been reported with intravenous immune globulin administration (rare); may occur with high doses (≥2 g/kg). Syndrome usually appears within several hours to 2 days following treatment; usually resolves within several days after IVIG is discontinued. Patients with a migraine history may be at higher risk for AMS.
- Hemolysis: Intravenous immune globulin has been associated with antiglobulin hemolysis; monitor for signs of hemolytic anemia.

- Hyperproteinemia: Hyperproteinemia, increased serum viscosity, and hyponatremia may occur; distinguish hyponatremia from pseudohyponatremia to prevent volume depletion and further increase in serum viscosity.

- Infusion reactions: Patients should be monitored for adverse events during and after the infusion. Stop administration with signs of infusion reaction (fever, chills, nausea, vomiting, and rarely shock). Risk may be increased with initial treatment, when switching brands of immune globulin, and with treatment interruptions of >8 weeks.

- Pulmonary edema: Monitor for transfusion-related acute lung injury (TRALI); noncardiogenic pulmonary edema has been reported with intravenous immune globulin use. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, and fever in the presence of normal left ventricular function. Usually occurs within 1-6 hours after infusion.

- Renal impairment: **[U.S. Boxed Warning]: Acute renal dysfunction (increased serum creatinine, oliguria, acute renal failure, osmotic nephrosis) can rarely occur; usually within 7 days of use (more likely with products stabilized with sucrose). Use with caution in the elderly, patients with renal disease, diabetes mellitus, volume depletion, sepsis, paraproteinemia, and nephrotoxic medications due to risk of renal dysfunction.** In patients at risk of renal dysfunction, the rate of infusion and concentration of solution should be minimized. Discontinue if renal function deteriorates.

- Thrombotic events: Thrombotic events have been reported with administration of intravenous immune globulin; use with caution in patients with a history of atherosclerosis or cardiovascular and/or thrombotic risk factors or patients with known/suspected hyperviscosity. Consider a baseline assessment of blood viscosity in patients at risk for hyperviscosity.

Disease-related concerns:

- Fluid overload: High-dose regimens (1000 mg/kg for 1-2 days) are not recommended for individuals with fluid overload or where fluid volume may be of concern.

- Hypovolemia: Patients should not be volume depleted prior to initiation of therapy.

Special populations:

- Elderly: Use with caution in the elderly; may be at increased risk for renal dysfunction.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

- Latex: Packaging of some products may contain natural latex/natural rubber.

- L-proline: Privigen™ contains the stabilizer L-proline and is contraindicated in patients with hyperprolinemia.

- Maltose: Some products may contain maltose, which may result in falsely-elevated blood glucose readings.

- Sorbitol: Some products may contain sorbitol; do not use in patients with fructose intolerance.

- Sucrose: Some products may contain sucrose.

Other warnings/precautions:

- Administration: For intravenous administration only; patients should be adequately hydrated prior to therapy.

- Vaccinations: Response to live vaccinations may be impaired.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted. Immune globulins cross the placenta in increased amounts after 30 weeks gestation. Intravenous immune globulin has been recommended for use in fetal-neonatal alloimmune thrombocytopenia and pregnancy-associated ITP.
LactationExcretion in breast milk unknown
Adverse ReactionsFrequency not defined.

Cardiovascular: Chest tightness, edema, flushing of the face, hyper-/hypotension, palpitation, tachycardia

Central nervous system: Anxiety, aseptic meningitis syndrome, chills, dizziness, drowsiness, fatigue, fever, headache, irritability, lethargy, lightheadedness, malaise, migraine, pain

Dermatologic: Bruising, petechiae, pruritus, purpura, rash, urticaria

Gastrointestinal: Abdominal cramps, abdominal pain, diarrhea, discomfort, dyspepsia, nausea, sore throat, vomiting

Hematologic: Anemia, autoimmune hemolytic anemia, hematocrit decreased, hemolysis (mild), hemorrhage, thrombocytopenia

Hepatic: Bilirubin increased, LDH increased, liver function test increased

Local: Pain or irritation at the infusion site

Neuromuscular & skeletal: Arthralgia, back or hip pain, leg cramps, muscle cramps, myalgia, neck pain, weakness

Otic: Ear pain

Renal: Acute renal failure, acute tubular necrosis, anuria, BUN increased, creatinine increased, oliguria, proximal tubular nephropathy, osmotic nephrosis

Respiratory: Asthma aggravated, bronchitis, cough, dyspnea, epistaxis, nasal congestion, pharyngeal pain, pharyngitis, rhinitis, rhinorrhea, sinus headache, sinusitis, upper respiratory infection, wheezing

Miscellaneous: Anaphylaxis, diaphoresis, flu-like syndrome, hypersensitivity reactions, infusion reaction

Postmarketing and/or case reports: Apnea, ARDS, autoimmune pure red cell aplasia (PRCA) exacerbation, bronchopneumonia, bronchospasm, bullous dermatitis, cardiac arrest, chest pain, coma, Coombs' test positive, cyanosis, epidermolysis, erythema multiforme, hepatic dysfunction, hypoxemia, leukopenia, loss of consciousness, pancytopenia, papular rash, pulmonary edema, pulmonary embolism, rigors, seizure, Stevens-Johnson syndrome, thromboembolism, transfusion-related acute lung injury (TRALI), tremor, vascular collapse

Oncology: VesicantNo
Oncology: Emetic PotentialLow
Drug Interactions

Vaccines (Live): Immune Globulins may diminish the therapeutic effect of Vaccines (Live). **Exceptions:** Influenza Virus Vaccine; Yellow Fever Vaccine. *Risk D: Consider therapy modification*

Test InteractionsOctagam® contains maltose. Falsely-elevated blood glucose levels may occur when glucose monitoring devices and test strips utilizing the glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) based methods are used. Glucose monitoring devices and test strips which utilize the glucose-specific method are recommended. Passively-transferred antibodies may yield false-positive serologic testing results; may yield false-positive direct and indirect Coombs' test.
Monitoring ParametersRenal function, urine output, hemoglobin and hematocrit, platelets (in patients with ITP); infusion-related adverse reactions, anaphylaxis, signs and symptoms of hemolysis; blood viscosity (in patients at risk for hyperviscosity); presence of antineutrophil antibodies (if TRALI is suspected)
Nursing: Physical Assessment/MonitoringAssess for history of previous allergic reactions. Patient should be monitored during infusion for vital sign changes and adverse or allergic reactions. Teach patient adverse symptoms to report.
Monitoring: Lab TestsRenal function, hemoglobin and hematocrit, platelets (in patients with ITP); signs and symptoms of hemolysis; blood viscosity (in patients at risk for hyperviscosity); presence of antineutrophil antibodies (if TRALI is suspected)
Patient EducationThis medication can only be administered by infusion. You will be monitored closely during the infusion. If you experience nausea ask for assistance, do not get up alone. Do not have any vaccinations for the next 3 months without consulting prescriber. Immediately report chills; chest pain, tightness, or rapid heartbeat; acute back pain; or respiratory difficulty during infusion. Also report decrease in urine output, swelling of extremities, unexplained weight gain of >3-5 lb/week; fever and other signs of infection; trouble breathing; increased heart rate, yellowing of skin or eyes, dark urine; stiff neck, severe headache, unexplained drowsiness, or sensitivity to light. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution [preservative free]:

Gammar®-P I.V.: 5 g, 10 g [stabilized with human albumin and sucrose] [DSC]

Injection, powder for reconstitution [preservative free, nanofiltered]:

Carimune® NF: 3 g, 6 g, 12 g [contains sucrose]

Panglobulin® NF: 6 g, 12 g [contains sucrose] [DSC]

Injection, powder for reconstitution [preservative free, solvent detergent-treated]:

Gammagard S/D: 2.5 g, 5 g, 10 g [stabilized with human albumin, glycine, glucose, and polyethylene glycol; packaging may contain natural latex/natural rubber]

Polygam® S/D: 5 g, 10 g [stabilized with human albumin, glycine, glucose, and polyethylene glycol] [DSC]

Injection, solution [preservative free; solvent detergent-treated]:

Gammagard Liquid: 10% (10 mL, 25 mL, 50 mL, 100 mL, 200 mL) [latex free, sucrose free; stabilized with glycine]

Octagam®: 5% (20 mL, 50 mL, 100 mL, 200 mL) [sucrose free; contains sodium 30 mmol/L and maltose]

Injection, solution [preservative free]

Flebogamma®: 5% (10 mL, 50 mL, 100 mL, 200 mL) [contains polyethylene glycol and sorbitol]

Gamunex®: 10% (10 mL, 25 mL, 50 mL, 100 mL, 200 mL) [caprylate/chromatography purified]

Privigen™: 10% (50 mL, 100 mL, 200 mL) [sucrose free]

Generic AvailableNo
Mechanism of ActionReplacement therapy for primary and secondary immunodeficiencies; interference with F_c receptors on the cells of the reticuloendothelial system for autoimmune cytopenias and ITP; possible role of contained antiviral-type antibodies
Pharmacodynamics/Kinetics

Onset of action: I.V.: Provides immediate antibody levels

Duration: Immune effect: 3-4 weeks (variable)

Distribution: V_d: 0.09-0.13 L/kg

Intravascular portion (primarily): Healthy subjects: 41% to 57%; Patients with congenital humoral immunodeficiencies: ~70%

Half-life elimination: IgG (variable among patients): Healthy subjects: 14-24 days; Patients with congenital humoral immunodeficiencies: 26-40 days; hypermetabolism associated with fever and infection have coincided with a shortened half-life

Related Information

- Immunization Recommendations
- Intravenous Immune Globulin

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsIGIV; IV Immune Globulin; IVIG

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International Brand NamesOctagam (MX); Pentaglobin (MX); Sandoglobulina (MX); Vigam (MX)

Immune Globulin (Subcutaneous)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(i MYUN GLOB yoo lin sub kyoo TAY nee us)

U.S. Brand NamesVivaglobin®

Pharmacologic CategoryImmune Globulin

Use: Labeled IndicationsTreatment of primary immune deficiency (PID)

Dosing: Adults**Note:** Consider premedicating with acetaminophen and diphenhydramine.

Primary immune deficiency: SubQ infusion: 100-200 mg/kg weekly (maximum rate: 20 mL/hour; doses >15 mL should be divided between sites); adjust the dose over time to achieve desired clinical response or target IgG levels

Conversion from I.V. to SubQ: Multiply previous I.V. dose by 1.37, then divide into a weekly regimen by dividing by the previous I.V. dosing interval (eg, if the dosing interval was every 3 weeks, divide by 3); adjust the dose over time to achieve desired clinical response or target IgG levels. SubQ infusion administration should begin 1 week after the last I.V. dose.

Dosing: Elderly Refer to adult dosing.

Dosing: Pediatric

Children ≥2 years: Refer to adult dosing.

Administration: I.V. DetailpH: 6.4-7.2

Administration: OtherSubcutaneous: Initial dose should be administered in a healthcare setting capable of providing monitoring and treatment in the event of hypersensitivity. Using aseptic technique, follow the infusion device manufacturer's instructions for filling the reservoir and preparing the pump. Remove air from administration set and needle by priming. Inject via infusion pump into the abdomen, thigh, upper arm, and/or lateral hip. The maximum rate is 20 mL/hour and maximum volume per injection site is 15 mL (doses >15 mL should be divided and infused into several sites). Select the number of required infusion sites; multiple concurrent injection sites may be achieved with the use of Y-site connection tubing; injection sites must be at least 2 inches apart. After the sites are clean and dry, insert subcutaneous needle and prime administration set. Attach sterile needle to administration set, gently pull back on the syringe to assure a blood vessel has not been inadvertently accessed. Repeat for each injection site; infuse following instructions for the infusion device. Rotate the site(s) weekly. Treatment may be transitioned to the home/home care setting in the absence of adverse reactions.

StorageStore at 2°C to 8°C (36°F to 46°F); do not freeze. Do not shake. Store in original box until ready to use. Allow vial(s) to reach room temperature prior to use. The appearance of immune globulin (subcutaneous) may vary from colorless to light brown; do not use if cloudy or contains precipitate.

CompatibilityDo not mix with other products.

ContraindicationsHypersensitivity to immune globulin or any component of the formulation; history of anaphylactic or severe systemic reaction to immune globulin preparations; selective IgA deficiency with known antibody against IgA

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1:1000) should be available.

- Infusion reactions: Patients should be monitored for adverse events during and after the infusion. Stop administration with signs of infusion reaction (fever, chills, nausea, vomiting, and rarely shock). Risk may be increased with initial treatment, when switching brands of immune globulin, and with treatment interruptions of >8 weeks.

Special populations:

- Pediatrics: Safety and efficacy have not been established for children <2 years of age.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

Other warnings/precautions:

- Administration: For subcutaneous administration only; not for I.V. use.

Geriatric ConsiderationsNo clinical data specific to elderly at this time. Use caution and monitor closely.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have not been conducted. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsAdverse reactions can be expected to be similar to those experienced with other immune globulin products; percentages are reported as adverse events per patient; injection site reactions decreased with subsequent infusions

>10%:

Central nervous system: Headache (32% to 48%), fever (3% to 25%)

Dermatologic: Rash (6% to 17%)

Gastrointestinal: Gastrointestinal disorder (5% to 37%), nausea (11% to 18%), sore throat (17%)

Local: Injection site reactions (swelling, redness, itching; 92%)

Miscellaneous: Allergic reaction (11%)

1% to 10%:

Cardiovascular: Tachycardia (3%)

Central nervous system: Pain (10%)

Dermatologic: Skin disorder (3%)

Gastrointestinal: Diarrhea (10%)

Genitourinary: Urine abnormality (3%)

Neuromuscular & skeletal: Weakness (5%)

Respiratory: Cough (10%)

<1%: Abdominal pain, dyspnea, nervousness

Drug Interactions

Vaccines (Live): Immune Globulins may diminish the therapeutic effect of Vaccines (Live). **Exceptions:** Influenza Virus Vaccine; Yellow Fever Vaccine. *Risk D: Consider therapy modification*

Test InteractionsPassively-transferred antibodies may yield false-positive serologic testing results; may yield false-positive direct and indirect Coombs' test

Monitoring ParametersInfusion-related adverse reactions, anaphylaxis, IgG levels, clinical response

Reference RangeAlthough the trough serum concentration of IgG has not been established, clinical experience has led to the use of 500 mg/dL as a guideline.

Nursing: Physical Assessment/MonitoringThis medication can only be administered via SubQ infusion. Assess for history of previous allergic reaction. Monitor for an allergic reaction during infusion; have anaphylaxis kit available. Assess infusion site periodically during infusion. Observe for redness, swelling, or itching. Teach patient adverse symptoms to report. Teach patient appropriate infusion technique if patient is to self administer.

Monitoring: Lab TestsIgG levels

Patient EducationDo not have any vaccinations for at least 3 months unless approved by prescriber. You may experience headache, fever, rash, nausea, diarrhea, cough, or sore throat. Stop infusion and report signs of infusion reaction (fever, chills, nausea, vomiting, and rarely, shock) immediately. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: IgG 160 mg/mL (3 mL, 10 mL, 20 mL)

Generic AvailableNo

ManufacturerZLB Behring GmbH

Mechanism of ActionImmune globulin replacement therapy of IgG antibodies against bacteria and viral agents.

Pharmacodynamics/Kinetics

Bioavailability: 73% (compared to I.V.)

Time to peak, plasma: 2.5 days

Pharmacotherapy PearlsSerum IgG levels may be drawn at any time. Subcutaneous weekly treatments provide more constant levels rather than the more pronounced peak and trough patterns observed with I.V. monthly immune globulin treatments.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusHeadache is very common

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with SSRIs, lithium, valproic acid, and carbamazepine may produce additive effects

Index TermsImmune Globulin Subcutaneous (Human); SCIG

References

Chapel HM, Spickett GP, Ericson D, et al, "The Comparison of the Efficacy and Safety of Intravenous Versus Subcutaneous Immunoglobulin Replacement Therapy," *J Clin Immunol*, 2000, 20(2):94-100.[PubMed 10821460]

Gardulf A, Hammerstrom L, and Smith CI, "Home Treatment of Hypogammaglobulinaemia With Subcutaneous Gammaglobulin by Rapid Infusion," *Lancet*, 1991, 338(8760):162-6.[PubMed 1712881]

Stiehm ER, Casillas AM, Finkelstein JZ, et al, "Slow Subcutaneous Human Intravenous Immunoglobulin in the Treatment of Antibody Immunodeficiency: Use of an Old Method With a New Product," *J Allergy Clin Immunol*, 1998, 101(6):848-9.[PubMed 9648714]

IMVP-16

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's

Regimen

Ifosfamide: I.V.: 4 g/m^2 continuous infusion over 24 hours day 1

[total dose/cycle = 4 g/m^2]

Mesna: I.V.: 800 mg/m^2 bolus prior to ifosfamide, then 4 g/m^2 continuous infusion over 12 hours concurrent with ifosfamide, then 2.4 g/m^2 continuous infusion over 12 hours after ifosfamide infusion day 1

[total dose/cycle = 7.2 g/m^2]

Methotrexate: I.V.: 30 mg/m^2/day days 3 and 10

[total dose/cycle = 60 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 300 mg/m^2]

Repeat cycle every 21-28 days

References

Cabanillas F, Hagemeister FB, Bodey GP, et al, âIMVP-16: An Effective Regimen for Patients With Lymphoma Who Have Relapsed After Initial Combination Chemotherapy,â *Blood*, 1982, 60(3):693-7.[PubMed 7104493]

Inamrinone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Amrinone may be confused with aMILoride, amiodarone

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye NAM ri none)

Pharmacologic CategoryPhosphodiesterase Enzyme Inhibitor

Use: Labeled IndicationsShort-term therapy in patients with intractable heart failure

Dosing: AdultsDosage is based on clinical response (**Note:** Dose should not exceed 10 mg/kg/24 hours).

Heart failure: 0.75 mg/kg I.V. bolus over 2-3 minutes followed by maintenance infusion of 5-10 mcg/kg/minute; I.V. bolus may need to be repeated in 30 minutes.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricHeart failure: Infants and Children (unlabeled populations): Refer to adult dosing.

Dosing: Renal Impairment

Infants and Children:

Cl_{cr} 30-50 mL/minute: Administer 100% of dose

Cl_{cr} 10-29 mL/minute: Administer 50% of dose

Cl_{cr} <10 mL/minute: Administer 25% of dose

Intermittent hemodialysis or peritoneal dialysis: Administer 25% of dose

Adults:

Cl_{cr} ≥10 mL/minute: Administer 100% of dose

Cl_{cr} <10 mL/minute: Administer 50% to 75% of dose

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.

May be administered undiluted for I.V. bolus doses. Dilute for use as continuous infusion.

StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light. Store in carton until ready for use.

ReconstitutionFor continuous infusion, dilute with 0.45% or 0.9% sodium chloride to final concentration of 1-3 mg/mL. Use within 24 hours. Do not directly dilute with dextrose-containing solutions; chemical interaction occurs. May be administered I.V. into running dextrose infusions.

CompatibilityStable in NS, $^1/_2$NS; **incompatible** in D_5W.

Y-site administration: Compatible: Aminophylline, atropine, bretylium, calcium chloride, cimetidine, cisatracurium, digoxin, dobutamine, dopamine, epinephrine, famotidine, hydrocortisone sodium succinate, isoproterenol, lidocaine, metaraminol, methylprednisolone sodium succinate, nitroglycerin, nitroprusside, norepinephrine, phenylephrine, potassium chloride, propofol, propranolol, remifentanil, verapamil. **Incompatible:** Furosemide, sodium bicarbonate. **Variable (consult detailed reference):** Procainamide.

Compatibility in syringe: Compatible: Propranolol, verapamil.

Compatibility when admixed: Compatible: Propafenone. **Incompatible:** Furosemide.

ContraindicationsHypersensitivity to inamrinone, any component of the formulation, or bisulfites (contains sodium metabisulfite); patients with severe aortic or pulmonic valvular disease

Warnings/Precautions

Concerns related to adverse effects:

- Arrhythmias: Observe for arrhythmias in this very high-risk patient population. Ventricular or atrial arrhythmias may persist even after discontinuation of inamrinone, especially in patients with renal dysfunction. Ensure that ventricular rate is controlled in atrial fibrillation/flutter before initiating therapy; may increase ventricular response rate. In heart transplant candidates, institute appropriate measures to protect patient against risks of sudden cardiac death.

- Hepatic effects: Discontinue therapy if dose-related changes in LFTs and clinical symptoms of hepatotoxicity occur; monitor liver function.

- Hypotension: Monitor blood pressure and heart rate closely. Infusion may require reduction or temporary discontinuation if hypotension occurs. Hypotension may be prolonged especially in patients with renal dysfunction. Vigorous diuresis may contribute to hypotension; cautious administration of fluids may be required to prevent hypotension.

- Thrombocytopenia: Can cause thrombocytopenia (due to decreased platelet survival time). If platelet count falls below 150,000/mm^3, may maintain therapy, decrease daily dose, or discontinue therapy based upon risk versus benefit. Monitor closely.

Disease-related concerns:

- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to initiation of and throughout therapy.

- Idiopathic hypertrophic subaortic stenosis (IHSS)/hypertrophic obstructive cardiomyopathy (HOCM): May aggravate this condition.

- Myocardial infarction (MI): Not recommended in acute MI treatment.

Other warnings/precautions:

- Long-term therapy: According to the ACC/AHA chronic heart failure 2005 guidelines, long-term, regularly-scheduled intermittent infusions are strongly discouraged.

- Monitoring: Monitor fluid status closely; patients may require adjustment of diuretic and electrolyte replacement therapy.

Geriatric ConsiderationsWhile inamrinone is not specifically arrhythmogenic, the elderly may be at high risk for ventricular and particularly atrial arrhythmias due to high incidence of arrhythmias in this population. Also, the elderly are often hypovolemic due to dehydration; therefore, monitor fluid status carefully (CVP line) in order to have effective falling pressure for maximal response. Found to be as effective as dobutamine in the elderly with heart failure in one study despite the decline in beta-adrenergic response with age.

Pregnancy Risk FactorC

Adverse Reactions

1% to 10%:

Cardiovascular: Arrhythmias (3%; especially in high-risk patients), hypotension (1% to 2%; dose related)

Gastrointestinal: Nausea (1% to 2%), vomiting (1%)

Hematologic: Thrombocytopenia (~2%; dose related)

<1% (Limited to important or life-threatening): Abdominal pain, anorexia, chest pain, fever, hepatotoxicity, hyperbilirubinemia, hypersensitivity, injection site reactions, jaundice, liver enzymes increased

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersPlatelet count, CBC, electrolytes (especially potassium and magnesium), liver function and renal function tests; ECG, CVP, SBP, DBP, heart rate; infusion site

If pulmonary artery catheter is in place, monitor cardiac index, stroke volume, systemic vascular resistance, pulmonary capillary wedge pressure and pulmonary vascular resistance.

Monitoring: Lab Tests

Platelet count, CBC, electrolytes (especially potassium and magnesium), liver function and renal function tests

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as lactate: 5 mg/mL (20 mL) [contains sodium metabisulfite]

Generic AvailableYes

Mechanism of ActionInhibits myocardial cyclic adenosine monophosphate (cAMP) phosphodiesterase activity and increases cellular levels of cAMP resulting in a positive inotropic effect and increased cardiac output; also possesses systemic and pulmonary vasodilator effects resulting in pre- and afterload reduction; slightly increases atrioventricular conduction

Pharmacodynamics/Kinetics

Onset of action: I.V.: 2-5 minutes

Peak effect: ~10 minutes

Duration (dose dependent): Low dose: ~30 minutes; Higher doses: ~2 hours

Half-life elimination, serum: Adults: Healthy volunteers: 3.6 hours, Congestive heart failure: 5.8 hours

Excretion: Urine (10% to 40% as parent drug)

Related Information

- Hemodynamic Support, Intravenous

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause hypotension which may be exacerbated by psychotropics

Cardiovascular ConsiderationsAlthough the phosphodiesterase inhibitor drugs may induce short-term improvement in clinical status in patients with intractable heart failure, longer-term studies of these drugs in heart failure have suggested that there is a net increase in mortality.

Index TermsAmrinone Lactate

References

Adams KF, Lindenfeld J, Arnold JMO, et al, “HFSA 2006 Comprehensive Heart Failure Practice Guideline,” *J Card Fail*, 2006, 12(1):e1–122. Available at http://www.heartfailureguideline.org[PubMed 16500560]

Aronoff GR, Bennett WM, Berns JS, et al, *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*, 5th ed. Philadelphia, PA: American College of Physicians; 2007, p 45, 145.

Feldman AM, Bristow MR, Parmley WW, et al, “Effects of Vesnarinone on Morbidity and Mortality in Patients With Heart Failure. Vesnarinone Study Group,” *N Engl J Med*, 1993, 329(3):149-55. [PubMed 8515787]

Hunt SA, Abraham WT, Chin MH , et al, “ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure).” Available at http://www.acc.org/qualityandscience/clinical/guidelines/failure/index.pdf.[PubMed 16160202]

Packer M, Carver JR, Rodeheffer RJ, et al, “Effect of Oral Milrinone on Mortality in Severe Chronic Heart Failure. The PROMISE Study Research Group,” *N Engl J Med*, 1991, 325(21):1468-75. [PubMed 1944425]

Packer M, Medina N, and Yushak M, “Hemodynamic and Clinical Limitations of Long-Term Inotropic Therapy With Amrinone in Patients With Severe Chronic Heart Failure,” *Circulation*, 1984, 70(6):1038-47.[PubMed 6388899]

International Brand NamesInocor (BE, IT)

Indapamide

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Indapamide may be confused with Iopidine®

International issues:

Pretanix® [Hungary] may be confused with Protonix® which is a brand name for pantoprazole in the U.S.

Pronunciation(in DAP a mide)

Canadian Brand NamesApo-Indapamide®; Dom-Indapamide; Gen-Indapamide; Lozide®; Lozol®; Novo-Indapamide; Nu-Indapamide; PHL-Indapamide; PMS-Indapamide; Pro-Indapamide; Riva-Indapamide

Pharmacologic CategoryDiuretic, Thiazide-Related

Use: Labeled IndicationsManagement of mild to moderate hypertension; treatment of edema in congestive heart failure and nephrotic syndrome

Dosing: Adults

Edema (diuretic): Oral: 2.5-5 mg/day. **Note:** There is little therapeutic benefit to increasing the dose >5 mg/day; there is, however, an increased risk of electrolyte disturbances.

Hypertension: Oral: 1.25 mg in the morning, may increase to 5 mg/day by increments of 1.25-2.5 mg; consider adding another antihypertensive and decreasing the dose if response is not adequate.

Dosing: ElderlyRefer to adult dosing.

Administration: OralMay be taken with food or milk. Take early in day to avoid nocturia. Take the last dose of multiple doses no later than 6 PM unless instructed otherwise.

Dietary ConsiderationsMay be taken with food or milk to decrease GI adverse effects.

ContraindicationsHypersensitivity to indapamide or any component of the formulation, thiazides, or sulfonamide-derived drugs; anuria; renal decompensation; pregnancy (based on expert analysis)

Allergy Considerations

- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, and hyponatremia can occur.
- Photosensitivity: Photosensitization may occur.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with thiazide or sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Diabetes: Use with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated.
- Hepatic impairment: Use with caution in patients with severe hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations.
- Hypokalemia: Use with caution in patients with hypokalemia; correct before initiating therapy.
- Renal impairment: Avoid in severe renal disease (ineffective).
- Systemic lupus erythematosus (SLE): Can cause SLE exacerbation or activation.

Other warnings/precautions:

- I.V. use: Generally not recommended, but is available.

Geriatric ConsiderationsThiazide diuretics lose efficacy when Cl_{cr} is <30-35 mL/minute. Many elderly may have Cl_{cr} below this limit. Calculate Cl_{cr} for elderly before initiating therapy. Indapamide has the advantage over thiazide diuretics in that it is effective when Cl_{cr} is <30 mL/minute.

Pregnancy Risk FactorB (manufacturer); D (expert analysis)

LactationExcretion in breast milk unknown

Adverse Reactions

1% to 10%:

Cardiovascular: Orthostatic hypotension, palpitation (<5%), flushing

Central nervous system: Dizziness (<5%), lightheadedness (<5%), vertigo (<5%), headache (≥5%), restlessness (<5%), drowsiness (<5%), fatigue, lethargy, malaise, lassitude, anxiety, agitation, depression, nervousness (≥5%)

Dermatologic: Rash (<5%), pruritus (<5%), hives (<5%)

Endocrine & metabolic: Hyperglycemia (<5%), hyperuricemia (<5%)

Gastrointestinal: Anorexia, gastric irritation, nausea, vomiting, abdominal pain, cramping, bloating, diarrhea, constipation, dry mouth, weight loss

Genitourinary: Nocturia, frequent urination, polyuria, impotence (<5%), reduced libido (<5%), glycosuria (<5%)

Neuromuscular & skeletal: Muscle cramps, spasm, weakness (≥5%)

Ocular: Blurred vision (<5%)

Renal: Necrotizing angiitis, vasculitis, cutaneous vasculitis (<5%)

Respiratory: Rhinorrhea (<5%)

<1% (Limited to important or life-threatening symptoms, and/or postmarketing reports): Hepatitis, hypercalcemia, jaundice, liver function test abnormality, pancreatitis, purpura

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure (both standing and sitting/supine), serum electrolytes, renal function, assess weight, I & O reports daily to determine fluid loss

Nursing: Physical Assessment/MonitoringAssess allergy history prior to beginning therapy (sulfonamides, thiazides). Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, altered effect of oral hypoglycemics, increased risk of hypotension or toxicity). Assess results of laboratory tests, therapeutic effectiveness (according to purpose for use), and adverse response (hypotension, hypokalemia, confusion) at regular intervals during therapy. Instruct patients with diabetes to monitor glucose levels closely; may interfere with oral hypoglycemic medications. Teach patient proper use, possible side effects (eg, orthostatic hypotension, photosensitivity) and appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum electrolytes, renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, early in the day. Do not exceed recommended dosage. This medication does not replace other antihypertensive interventions; follow prescriber's instructions for diet and lifestyle changes. If you have diabetes, monitor serum glucose closely (medication may decrease effect of oral hypoglycemics). Monitor weight on a regular basis. Report sudden or excessive weight gain (>5 lb/week), swelling of ankles or hands, or respiratory difficulty. You may experience dizziness, weakness, or drowsiness (use caution when rising from sitting or lying position, when climbing stairs and when driving or engaging in tasks that require alertness until response to drug is known); sensitivity to sunlight (use sunblock, wear protective clothing or sunglasses); impotence (reversible); or dry mouth or thirst (frequent mouth care, chewing gum, or sucking lozenges may help). Report any changes in visual acuity; unusual bleeding; chest pain or palpitations; or numbness, tingling, cramping of muscles. **Pregnancy/breast-feeding precaution:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 1.25 mg, 2.5 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Indapamide)

1.25 mg (90): $15.00

2.5 mg (30): $13.99

Tablets (Lozol)

1.25 mg (30): $34.85

Mechanism of ActionDiuretic effect is localized at the proximal segment of the distal tubule of the nephron; it does not appear to have significant effect on glomerular filtration rate nor renal blood flow; like other diuretics, it enhances sodium, chloride, and water excretion by interfering with the transport of sodium ions across the renal tubular epithelium

Pharmacodynamics/Kinetics

Onset of action: 1-2 hours

Duration: ≤36 hours

Absorption: Complete

Protein binding, plasma: 71% to 79%

Metabolism: Extensively hepatic

Half-life elimination: 14-18 hours

Time to peak: 2-2.5 hours

Excretion: Urine (~60%) within 48 hours; feces (~16% to 23%)

Related Information

- Depression
- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension, palpitations, flushing, xerostomia (normal salivary flow resumes upon discontinuation), and rhinorrhea.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsIndapamide is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay rarely cause mood changes

Mental Health: Effects on Psychiatric TreatmentMay decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular ConsiderationsIndapamide may be used to treat hypertension but offers no compelling advantages over thiazide diuretics in this setting.

International Brand NamesAmoron (HR); Apo-Indap (PL); Arifon (PL); Damide (IT); Dapa (MY); Dapa-tabs (AU); Dapamax (TZ, UG, ZA, ZM, ZW); Depermide (TW); Diuresin SR (PL); Dixamid (GR); Extur (ES); Fludex (AT, BE, CH, DK, FR, GR, LU, NL, PT, TR); Fludex SR (KP); Frumeron (TH); Indahexal (AU); Indalix (HK, ZA); Indapam (KP); Indapamid Anpharm (PL); Indapamide-Eurogenerics (LU); Indapamide-Generics (LU); Indapen (PL); Indapres (PL); Indapress (CN); Indapsan (PL); Indicontin Continus (HK); Inpamide (TH); Insig (AU); Intril SR (TH); Ipamix (IT); Lorvas (IN); Magniton-R (GR); Millibar (CL, TW); Napamide (MY, NZ, SG, TH); Natrilix (AE, AR, AU, BF, BH, BJ, BR, CI, CY, DE, EG, ET, FI, GB, GH, GM, GN, HK, ID, IL, IN, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NZ, OM, PE, PK, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Natrilix Retard (SE); Natrilix SR (AU, BB, BM, BS, BZ, CL, CO, CR, DE, DO, GT, GY, HN, IE, IN, JM, NI, NL, PA, PH, PY, SG, SR, SV, TT, UY); Natrix SR (KP); Pamid (IL); Pretanix (HU); Rinalix (SG); Sicco (DE); Tandix (PT); Tertensif (BG, CZ, EE, ES, FI, HR, PL); Vazamide SR (PH)

Indinavir

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Indinavir may be confused with Denavir™

Pronunciation(in DIN a veer)

U.S. Brand NamesCrixivan®

Canadian Brand NamesCrixivan®

Pharmacologic CategoryAntiretroviral Agent, Protease Inhibitor

Use: Labeled IndicationsTreatment of HIV infection; should always be used as part of a multidrug regimen (at least three antiretroviral agents)

Dosing: Adults**HIV infection:** Oral:

Unboosted regimen: 800 mg every 8 hours

Ritonavir-boosted regimens:

Ritonavir 100-200 mg twice daily plus indinavir 800 mg twice daily **or**

Ritonavir 400 mg twice daily plus indinavir 400 mg twice daily

Dosage adjustments for indinavir when administered in combination therapy:

Delavirdine, itraconazole, or ketoconazole: Reduce indinavir dose to 600 mg every 8 hours

Efavirenz: Increase indinavir dose to 1000 mg every 8 hours

Lopinavir and ritonavir (Kaletra™): Indinavir 600 mg twice daily

Nelfinavir: Increase indinavir dose to 1200 mg twice daily

Nevirapine: Increase indinavir dose to 1000 mg every 8 hours

Rifabutin: Reduce rifabutin to $^1/_2$ the standard dose plus increase indinavir to 1000 mg every 8 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricHIV: Children 4-15 years (investigational): 500 mg/m^2 every 8 hours

Dosing: Hepatic Impairment600 mg every 8 hours with mild/medium impairment due to cirrhosis

Administration: OralDrink at least 48 oz of water daily. Administer with water, 1 hour before or 2 hours after a meal. May also be administered with other liquids (eg, skim milk, juice, coffee, tea) or a light meal (eg, toast, corn flakes). Administer around-the-clock to avoid significant fluctuation in serum levels. May be taken with food when administered in combination with ritonavir.

Dietary ConsiderationsShould be taken without food but with water 1 hour before or 2 hours after a meal. Administration with lighter meals (eg, dry toast, skim milk, corn flakes) resulted in little/no change in indinavir concentration. If taking with ritonavir, may take with food. Patient should drink at least 48 oz of water daily.

StorageMedication should be stored at 15°C to 30°C (59°F to 86°F), and used in the original container and the desiccant should remain in the bottle. Capsules are sensitive to moisture.

ContraindicationsHypersensitivity to indinavir or any component of the formulation; concurrent use of alprazolam, amiodarone, cisapride, triazolam, midazolam (oral), pimozide, or ergot alkaloids

Allergy Considerations

- Indinavir Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Hemolytic anemia: Has been associated with hemolytic anemia; discontinue if diagnosed.
- Hyperbilirubinemia: Has been observed frequently. Do not use concurrently with atazanavir.
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.

- Nephrolithiasis/urolithiasis: May cause nephrolithiasis/urolithiasis; discontinue if signs and symptoms occur. Adequate hydration is recommended. Risk is substantially higher in pediatric patients versus adults. Symptoms may require temporary interruption of therapy (1-3 days) or discontinuation.

- Tubulointerstitial nephritis: May cause tubulointerstitial nephritis (rare); severe asymptomatic leukocyturia may warrant evaluation.

Disease-related concerns:

- Diabetes: Changes in glucose tolerance, hyperglycemia, exacerbation of diabetes, DKA, and new-onset diabetes mellitus have been reported in patients receiving protease inhibitors.

- Hemophilia A or B: Use with caution in patients with hemophilia A or B; increased bleeding during protease inhibitor therapy has been reported.

- Hepatic impairment: May cause hepatitis and/or exacerbate pre-existing hepatic dysfunction; use with caution in patients with underlying hepatic disease, such as hepatitis B or C or cirrhosis.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

Pregnancy Risk FactorC

Pregnancy ConsiderationsPlasma levels of indinavir were 74% lower at weeks 30-32 of gestation when compared to the same women at 14-28 weeks of gestation. Plasma levels were not measurable in some patients 8 hours post dose. It is not known if indinavir will exacerbate hyperbilirubinemia in neonates. Pregnancy and protease inhibitors are both associated with an increased risk of hyperglycemia. Glucose levels should be closely monitored. Until optimal dosing during pregnancy has been established, the manufacturer does not recommend indinavir use in pregnant patients. The AIDSinfo guidelines consider indinavir an alternative agent if lopinavir/ritonavir cannot be used, however, indinavir should be used in combination with low-dose ritonavir during pregnancy (optimal dosing is not known). Healthcare professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsIndinavir is minimally excreted in breast milk. HIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse Reactions

>10%:

Gastrointestinal: Abdominal pain (17%), nausea (12%)

Hepatic: Hyperbilirubinemia (14%; dose dependent)

Renal: Nephrolithiasis/urolithiasis, including flank pain with/without hematuria (29%, pediatric patients; 12% adult patients; dose dependent)

1% to 10%:

Central nervous system: Headache (5%), dizziness (3%), somnolence (2%), fever (2%), malaise (2%), fatigue (2%)

Dermatologic: Pruritus (4%), rash (1%)

Endocrine & metabolic: Hyperglycemia (1%)

Gastrointestinal: Vomiting (8%), diarrhea (3%), taste perversion (3%), acid reflux (3%), anorexia (3%), appetite increased (2%), dyspepsia (2%), serum amylase increased (2%)

Hematologic: Neutropenia (2%), anemia (1%), thrombocytopenia (1%)

Hepatic: Transaminases increased (4% to 5%), jaundice (2%)

Neuromuscular & skeletal: Back pain (8%), weakness (2%)

Renal: Dysuria (2%)

Respiratory: Cough (2%)

<1%, postmarketing, and/or case reports: Abdominal distention, acute renal failure, alopecia, anaphylactoid reactions, angina, arthralgia, bleeding (spontaneous in patients with hemophilia A or B), cerebrovascular disorder, cholesterol increased, crystalluria, depression, dry skin, erythema multiforme, fat redistribution, hemolytic anemia, hepatic failure, hepatitis, hydronephrosis, hyperpigmentation, immune reconstitution syndrome, interstitial nephritis (with medullary calcification and cortical atrophy), leukocyturia (severe and asymptomatic), MI, new-onset diabetes, pancreatitis, paresthesia (oral), paronychia, pharyngitis, pyelonephritis, renal insufficiency, renal failure, Stevens-Johnson syndrome, triglycerides increased, upper respiratory infection, urticaria, vasculitis

Metabolism/Transport Effects**Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2C9 (weak), 2C19 (weak), 2D6 (weak), 3A4 (strong)

Drug Interactions

Abacavir: Protease Inhibitors may decrease the serum concentration of Abacavir. *Risk C: Monitor therapy*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amiodarone: Protease Inhibitors may decrease the metabolism of Amiodarone. *Risk X: Avoid combination*

Antacids: May decrease the absorption of Protease Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Atovaquone: May decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Protease Inhibitors may decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Dihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Protease Inhibitors. Protease Inhibitors may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cisapride: Protease Inhibitors may decrease the metabolism of Cisapride. The resultant increase in serum cisapride concentrations may result in QTc prolongation and malignant cardiac arrhythmias. *Risk X: Avoid combination*

Clarithromycin: Protease Inhibitors may diminish the therapeutic effect of Clarithromycin. Specifically, certain protease inhibitors may decrease formation of the active 14-hydroxy-clarithromycin metabolite, which may negatively impact clarithromycin effectiveness vs. H. influenzae and other non-MAC infections. Protease Inhibitors may increase the serum concentration of Clarithromycin. Clarithromycin dose adjustment in renally impaired patients may be needed. Clarithromycin may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): Protease Inhibitors may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk D: Consider therapy modification*

CycloSPORINE: Protease Inhibitors may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Delavirdine: Protease Inhibitors may decrease the serum concentration of Delavirdine. Delavirdine may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Didanosine: May decrease the serum concentration of Indinavir. Management: Indinavir should be administered on an empty stomach at least 1 hour apart from administration of buffer-containing formulations of didanosine. *Risk D: Consider therapy modification*

Digoxin: Protease Inhibitors may increase the serum concentration of Digoxin. Increased serum concentrations of digoxin may increase risk of AV nodal blockade. *Risk C: Monitor therapy*

Efavirenz: May increase the metabolism of Protease Inhibitors. This specifically includes amprenavir, indinavir, and saquinavir. Efavirenz may increase the serum concentration of Protease Inhibitors. This specifically includes nelfinavir and ritonavir. *Risk D: Consider therapy modification*

Enfuvirtide: Protease Inhibitors may increase the serum concentration of Enfuvirtide. Enfuvirtide may increase the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

Eplerenone: Protease Inhibitors may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Protease Inhibitors may decrease the metabolism of Ergot Derivatives. **Exceptions:** Cabergoline. *Risk X: Avoid combination*

Etravirine: Protease Inhibitors may decrease the serum concentration of Etravirine. This effect is anticipated with darunavir & saquinavir (with low-dose ritonavir). Etravirine may increase the serum concentration of Protease Inhibitors. This effect is anticipated with nelfinavir. Protease Inhibitors may increase the serum concentration of Etravirine. This is expected with lopinavir/ritonavir. Management: Low-dose ritonavir boosting MUST be used when these protease inhibitors are used with etravirine. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

FentaNYL: Protease Inhibitors may decrease the metabolism of FentaNYL. *Risk C: Monitor therapy*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fusidic Acid: Protease Inhibitors may decrease the metabolism of Fusidic Acid. Fusidic Acid may decrease the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Garlic: May decrease the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

H2-Antagonists: May decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Protease Inhibitors may increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. **Exceptions:** Fluvastatin. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Meperidine: Protease Inhibitors may enhance the adverse/toxic effect of Meperidine. Protease Inhibitors may decrease the serum concentration of Meperidine. Concentrations of the toxic Normeperidine metabolite may be increased. *Risk D: Consider therapy modification*

Nefazodone: Protease Inhibitors may decrease the metabolism of Nefazodone. *Risk C: Monitor therapy*

Nevirapine: May increase the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): May diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: Protease Inhibitors may decrease the metabolism of Phosphodiesterase 5 Inhibitors. Management: Dose restrictions for tadalafil, and/or sildenafil and vardenafil are recommended in combination with ritonavir, atazanavir, indinavir, darunavir and saquinavir. Consult specific prescribing information for detailed recommendations. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Protease Inhibitors may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Protease Inhibitors: May increase the serum concentration of other Protease Inhibitors. Management: Atazanavir--indinavir combination contraindicated. Amprenavir oral solution not recommended with ritonavir oral solution; tipranavir/ritonavir or atazanavir/ritonavir not recommended with other protease inhibitors. Other combos may require dose changes. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

QuiNIDine: Protease Inhibitors may decrease the metabolism of QuiNIDine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: Protease Inhibitors may decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Protease Inhibitors may increase the serum concentration of Sirolimus. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Protease Inhibitors. *Risk X: Avoid combination*

Tacrolimus: Protease Inhibitors may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Temsirolimus: Protease Inhibitors may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tenofovir: May decrease the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Tenofovir. *Risk C: Monitor therapy*

Theophylline Derivatives: Protease Inhibitors may decrease the serum concentration of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C:*

Monitor therapy

TraZODone: Protease Inhibitors may increase the serum concentration of TraZODone. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Protease Inhibitors may increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Valproic Acid: Protease Inhibitors may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Venlafaxine: May decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Zidovudine: Protease Inhibitors may decrease the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Indinavir bioavailability may be decreased if taken with food. Meals high in calories, fat, and protein result in a significant decrease in drug levels. Indinavir serum concentrations may be decreased by grapefruit juice.

Herb/Nutraceutical: Garlic may decrease the levels/effects of protease inhibitors. St John's wort *(Hypericum)* appears to induce CYP3A enzymes and has lead to 57% reductions in indinavir AUCs and 81% reductions in trough serum concentrations, which may lead to treatment failures; should not be used concurrently with indinavir.

Monitoring ParametersMonitor viral load, CD4 count, triglycerides, cholesterol, glucose, liver function tests, CBC, urinalysis (severe leukocyturia should be monitored frequently).

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions or toxicity (multiple liver enzyme interactions may increase or decrease levels/effects of drugs and increase potential for severe toxicity or loss of effectiveness); dosing adjustments may be necessary. A list of medications that should not be used is available in each bottle and patients should be provided with this information. Assess therapeutic response (CD4 count, hepatic function) and adverse reactions (eg, gastrointestinal disturbance [nausea, vomiting, diarrhea] that can lead to dehydration and weight loss; hyperlipidemia and redistribution of body fat; rash; CNS effects [malaise, insomnia, abnormal thinking]; electrolyte imbalance) at regular intervals during therapy. Caution patients to monitor glucose levels closely; protease inhibitors may cause hyperglycemia or new-onset diabetes. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions (eg, glucose testing; use of barrier contraceptives; protease inhibitors may decrease effectiveness of oral contraceptives), and adverse symptoms to report.

Monitoring: Lab TestsMonitor viral load, CD4 count, triglycerides, cholesterol, glucose, liver function tests, CBC, urinalysis (severe leukocyturia should be monitored frequently).

Patient EducationYou will be provided with a list of specific medications that should not be used during therapy; do not take any new prescriptions, over-the-counter medications, or herbal products (even if they are not on the list) without consulting prescriber. This is not a cure for HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. Take as directed with meals. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. This medication will be prescribed with a combination of other medications; time these medications as directed by prescriber. You may be advised to check your glucose levels; this class of drug can cause hyperglycemia. Frequent blood tests may be required with prolonged therapy. You may be susceptible to infection; avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber. May cause body changes due to redistribution of body fat, facial atrophy, or breast enlargement (normal effects of drug); headache, dizziness, or fatigue (use caution when driving or engaged in potentially hazardous tasks until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea (buttermilk, boiled milk, or yogurt may help); back pain, or arthralgia (consult prescriber for approved analgesic). Inform prescriber if you experience muscle numbness or tingling; unresolved persistent vomiting, diarrhea, or abdominal pain; respiratory difficulty or chest pain; unusual skin rash; change in color of stool or urine; or any persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Effectiveness of oral contraceptives may be decreased, use of alternative (nonhormonal) forms of contraception is recommended; consult prescriber for appropriate contraceptives. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Crixivan®: 100 mg, 200 mg, 333 mg, 400 mg

Generic AvailableNo

ManufacturerMerck & Co

Pricing: U.S. (www.drugstore.com)

Capsules (Crixivan)

200 mg (360): $475.09

400 mg (90): $240.00

Mechanism of ActionIndinavir is a human immunodeficiency virus protease inhibitor, binding to the protease activity site and inhibiting the activity of this enzyme. HIV protease is an enzyme required for the cleavage of viral polyprotein precursors into individual functional proteins found in infectious HIV. Inhibition prevents cleavage of these polyproteins resulting in the formation of immature noninfectious viral particles.

Pharmacodynamics/Kinetics

Absorption: Administration with a high fat, high calorie diet resulted in a reduction in AUC and in maximum serum concentration (77% and 84% respectively); lighter meal resulted in little or no change in these parameters.

Protein binding, plasma: 60%

Metabolism: Hepatic via CYP3A4; seven metabolites of indinavir identified

Bioavailability: Good

Half-life elimination: 1.8 ± 0.4 hour; hepatic insufficiency: 2.8 ± 0.5 hour

Time to peak: 0.8 ± 0.3 hour

Excretion: Feces (83%; 19% as unchanged drug); urine (19%; 9% as unchanged drug)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV
- Perinatal HIV Guidelines

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Abnormal taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia; may rarely cause dizziness or drowsiness

Mental Health: Effects on Psychiatric TreatmentContraindicated with midazolam and triazolam; use caution with other benzodiazepines; may produce additive sedation and respiratory depression. Concomitant use of indinavir and St John's wort is not recommended. Coadministration of protease inhibitors (indinavir) with St John's wort is expected to substantially decrease protease inhibitor serum concentrations leading to a loss of virologic response and possible resistance to indinavir or to the class of protease inhibitors.

Index TermsIndinavir Sulfate

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International Brand NamesAviran (MX); Crixivan (AR, AT, AU, BB, BE, BG, BM, BO, BR, BS, BZ, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, HK, HN, HR, IE, IL, IT, JM, KP, LU, MX, MY, NI, NL, NO, PA, PE, PH, PL, PR, PT, PY, RU, SE, SG, SV, TH, TR, TT, TW, UY, VE); Elvenavir (AR); Indilan (MX); Indivan (PY); Indivir (IN); Virxit (CO)

Indocyanine Green

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(in doe SYE a neen green)
U.S. Brand NamesIC-Green™
Pharmacologic CategoryDiagnostic Agent
Use: Labeled IndicationsDetermining hepatic function, cardiac output, and liver blood flow; ophthalmic angiography
Dosing: Adults

Ophthalmic angiography: Use doses of up to 40 mg of dye in 2 mL of aqueous solvent, in some patients, half the volume (1 mL) has been found to produce angiograms of comparable resolution; immediately following the bolus dose of dye, a bolus of sodium chloride 0.9% 5 mL is given; this regimen will deliver a spatially limited dye bolus of optimal concentration to the choroidal vasculature following I.V. injection into the antecubital vein.

Cardiac output determination: Dye is injected as rapidly as possible through a cardiac catheter; the usual dose is 1.25 mg for infants, 2.5 mg for children, and 5 mg for adults; total dose should not exceed 2 mg/kg; the dye should be flushed from the catheter with sodium chloride 0.9% to prevent hemolysis

Hepatic function studies: 0.5 mg/kg injected as rapidly as possible into the lumen of an arm vein; patient should be in a fasting basal state

Dosing: ElderlyRefer to adult dosing.
Administration: I.V. DetailpH: 6.5
StorageStore at room temperature of 15°C to 25°C (59°F to 77˚F). Use within 6 hours of dilution. Discard if precipitate is present.
ReconstitutionReconstitute only with aqueous solvent supplied by manufacturer.
ContraindicationsHypersensitivity to indocyanine green, iodides, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis: Immediate treatment for anaphylactic reactions should be available.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been done.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Central nervous system: Headache

Dermatologic: Pruritus, urticaria

Gastrointestinal: Feces discoloration (green)

Miscellaneous: Diaphoresis, anaphylactoid reactions

Drug InteractionsThere are no known significant interactions.
Test InteractionsDo not perform radioactive iodine tests for at least 1 week following indocyanine green administration. Heparin solutions containing sodium bisulfate should not be used as an anticoagulant when collecting blood samples for analysis (reduces absorption peak).
Reference RangeNormal percentage disappearance rate is 18% to 24% per minute
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 25 mg

IC-Green™: 25 mg [contains sodium iodide ≤5%]

Generic AvailableYes
Pharmacodynamics/Kinetics

Protein binding: 95% to albumin

Half-life elimination: 2.5-3 minutes

Excretion: Bile

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Indomethacin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Indocin® may be confused with Imodium®, Lincocin®, Minocin®, Vicodin®

International issues:

Flexin® [Great Britain] may be confused with Floxin® which is a brand name for ofloxacin in the U.S.

Flexin® [Great Britain]: Brand name for orphenadrine in Israel

Pronunciation(in doe METH a sin)

U.S. Brand NamesIndocin®; Indocin® I.V.

Canadian Brand NamesApo-Indomethacin®; Indo-Lemmon; Indocid® P.D.A.; Indocin®; Indotec; Novo-Methacin; Nu-Indo; Rhodacine®

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral; Nonsteroidal Anti-inflammatory Drug (NSAID), Parenteral

Use: Labeled IndicationsAcute gouty arthritis, acute bursitis/tendonitis, moderate to severe osteoarthritis, rheumatoid arthritis, ankylosing spondylitis; I.V. form used as alternative to surgery for closure of patent ductus arteriosus in neonates

Dosing: Adults

Inflammatory/rheumatoid disorders (use lowest effective dose): Oral: 25-50 mg/dose 2-3 times/day; maximum dose: 200 mg/day; extended release capsule should be given on a 1-2 times/day schedule (maximum dose for extended release: 150 mg/day). In patients with arthritis and persistent night pain and/or morning stiffness, may give the larger portion (up to 100 mg) of the total daily dose at bedtime.

Bursitis/tendonitis: Oral: Initial dose: 75-150 mg/day in 3-4 divided doses **or** 1-2 divided doses for extended release; usual treatment is 7-14 days

Acute gouty arthritis: Oral: 50 mg 3 times daily until pain is tolerable then reduce dose; usual treatment <3-5 days

Dosing: ElderlyRefer to adult dosing. Use lowest recommended dose and frequency in elderly to initiate therapy for indications listed in adult dosing.

Dosing: Pediatric

Patent ductus arteriosus:

Neonates: I.V.: Initial: 0.2 mg/kg, followed by 2 doses depending on postnatal age (PNA):

PNA at time of FIRST dose <48 hours: 0.1 mg/kg at 12- to 24-hour intervals

PNA at time of FIRST dose 2-7 days: 0.2 mg/kg at 12- to 24-hour intervals

PNA at time of FIRST dose >7 days: 0.25 mg/kg at 12- to 24-hour intervals

Note: In general, may use 12-hour dosing interval if urine output >1 mL/kg/hour after prior dose; use 24-hour dosing interval if urine output is <1 mL/kg/hour but >0.6 mL/kg/hour; doses should be withheld if patient has oliguria (urine output <0.6 mL/kg/hour) or anuria

Inflammatory/rheumatoid disorders: Children ≥2 years: Oral: 1-2 mg/kg/day in 2-4 divided doses; maximum dose: 4 mg/kg/day; not to exceed 150-200 mg/day

Dosing: Renal ImpairmentNot recommended with advanced renal disease.

Administration: I.V.Administer over 20-30 minutes. Reconstitute I.V. formulation just prior to administration; discard any unused portion; avoid I.V. bolus administration or infusion via an umbilical catheter into vessels near the superior mesenteric artery as these may cause vasoconstriction and can compromise blood flow to the intestines. Do not administer intra-arterially.

Administration: I.V. DetailpH: 6.0-7.5

Administration: OralAdminister with food, milk, or antacids to decrease GI adverse effects. Extended release capsules must be swallowed whole; do not crush.

Dietary ConsiderationsMay cause GI upset; take with food or milk to minimize

StorageI.V.: Store below 30°C (86°F). Protect from light.

ReconstitutionReconstitute with 1-2 mL preservative free NS or SWFI just prior to administration. Discard any unused portion. Do not use preservative-containing diluents for reconstitution.

CompatibilityStable in NS.

Y-site administration: Compatible: Furosemide, insulin (regular), potassium chloride, sodium bicarbonate, sodium nitroprusside. **Incompatible:** Amino acid injection, calcium gluconate, cimetidine, dobutamine, dopamine, gentamicin, levofloxacin, tobramycin, tolazoline. **Variable (consult detailed reference):** Dextrose injection.

Restrictions An FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

Contraindications Hypersensitivity to indomethacin, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery; patients with a history of proctitis or recent rectal bleeding (suppositories)

Neonates: Necrotizing enterocolitis; impaired renal function; active bleeding (including intracranial hemorrhage and gastrointestinal bleeding), thrombocytopenia, coagulation defects; untreated infection; congenital heart disease where patent ductus arteriosus is necessary

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See“Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.
- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.
- Visual disturbances: Prolonged use may cause corneal deposits and retinal disturbances; discontinue if visual changes are observed.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.
- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.
- Depression: Use caution with depression; use may aggravate depression or other psychiatric disorders.
- Epilepsy: Use caution with epilepsy; use may aggravate this condition.
- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.
- Parkinsonism: Use caution with Parkinson’s disease; use may aggravate this condition.
- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.
- Pediatrics: Oral: Safety and efficacy have not been established in children <14 years of age. Hepatotoxicity has been reported in younger children treated for JRA. Closely monitor if needed in children ≥2 years of age.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but the elderly may demonstrate these adverse effects at lower doses than younger adults. Indomethacin frequently causes confusion at recommended doses in the elderly.

Pregnancy Risk FactorC/D (3rd trimester)

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Adverse Reactions

>10%: Central nervous system: Headache (12%)

1% to 10%:

Central nervous system: Dizziness (3% to 9%), fatigue (<3%), vertigo (<3%), depression (<3%), malaise (<3%), somnolence (<3%)

Gastrointestinal: Nausea (3% to 9%), epigastric pain (3% to 9%), abdominal pain/cramps/distress (<3%), heartburn (3% to 9%), indigestion (3% to 9%), constipation (<3%), diarrhea (<3%), dyspepsia (3% to 9%), rectal irritation (suppository), tenesmus (suppository), vomiting

Otic: Tinnitus (<3%)

<1%: Acute respiratory distress, agranulocytosis, allergic reactions, allergic rhinitis, anaphylaxis, anemia, angiitis, angioedema, anorexia, anxiety, aplastic anemia, arrhythmia, aseptic meningitis, asthma, bloating, BUN increased, blurred vision, bone marrow suppression, breast enlargement, breast tenderness, bronchospasm, chest pain, cholestatic jaundice, coma, confusion, CHF, conjunctivitis, corneal opacities, cystitis, deafness, depersonalization, depression, diplopia, disseminated intravascular coagulation (DIC), drowsiness, dry eyes, dysarthria, dyspnea, ecchymosis, edema, epistaxis, erythema multiforme, erythema nodosum, exfoliative dermatitis, fatigue, fever, flatulence, fluid retention, flushing, hair loss, gastric perforation (rare), gastritis, GI bleeding, GI ulceration, glucosuria, gynecomastia, hearing decreased, hematuria, hemolytic anemia, hepatitis (including fatal cases), hot flashes, hyperglycemia, hyperkalemia, hypersensitivity reactions, hyper-/hypotension, insomnia, interstitial nephritis, intestinal strictures, itching, involuntary muscle movements, leukopenia, lightheadedness, necrotizing fasciitis, nephrotic syndrome, nervousness, oliguria, palpitation, paresthesia, parkinson’s exacerbation, peptic ulcer, peripheral neuropathy, petechiae, polydipsia, polyuria, proctitis, proteinuria, pruritus, psychic disturbances, psychosis, pulmonary edema, purpura, rash, rectal bleeding, renal insufficiency, renal failure, retinal/macular disturbances, seizure exacerbation, shock, somnolence, Stevens-Johnson syndrome, stomatitis, sweating, syncope, tachycardia, thrombocytopenia, thrombocytopenic purpura, thrombophlebitis, toxic amblyopia, toxic epidermal necrolysis, ulcerative stomatitis, urinary frequency, urticaria, vaginal bleeding, weakness, weight gain

Metabolism/Transport Effects**Substrate** (minor) of CYP2C9, 2C19; **Inhibits** CYP2C9 (strong), 2C19 (weak)

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Indomethacin may increase the bioavailability of Tiludronate. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Triamterene: Indomethacin may enhance the nephrotoxic effect of Triamterene. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Food may decrease the rate but not the extent of absorption. Indomethacin peak serum levels may be delayed if taken with food.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Test InteractionsFalse-negative dexamethasone suppression test

Monitoring ParametersMonitor response (pain, range of motion, grip strength, mobility, ADL function), inflammation; observe for weight gain, edema; monitor renal function (serum creatinine, BUN); observe for bleeding, bruising; evaluate gastrointestinal effects (abdominal pain, bleeding, dyspepsia); mental confusion, disorientation, CBC, liver function tests (particularly with pediatric use); ophthalmologic exams with prolonged therapy

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests, therapeutic effectiveness (according to rationale for use), and adverse response when beginning therapy and at regular intervals during treatment. Teach patient proper use, side effects/appropriate interventions (regular ophthalmic evaluations with long-term use), and adverse symptoms to report.

Monitoring: Lab TestsRenal function (serum creatinine and BUN), CBC, liver function (particularly with pediatric use)

Patient EducationDo not take any new medication during therapy without consulting prescriber. Use exactly as directed; do not increase dose without consulting prescriber. Do not crush, break, or chew capsules. Take with food or milk to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause drowsiness, dizziness, nervousness, or headache (use caution when driving or engaging in tasks that require alertness until response to drug is known); anorexia, nausea, vomiting, or heartburn (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help): fluid retention (weigh yourself weekly and report unusual weight gain >3-5 lb/week); or may turn urine green (normal). GI bleeding, ulceration, or perforation can occur with or without pain; discontinue medication and contact prescriber if persistent abdominal pain or cramping or blood in stool occurs. Report difficult breathing or unusual cough; chest pain, rapid heartbeat, or palpitations; unusual bruising or bleeding; blood in urine, gums, or vomitus; swollen extremities; skin rash, irritation, or itching; acute persistent fatigue; or vision changes or ringing in ears. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 25 mg, 50 mg

Capsule, extended release, oral: 75 mg

Injection, powder for reconstitution:

Indocin® I.V: 1 mg

Suppository, rectal: 50 mg (30s)

Suspension, oral:

Indocin®: 25 mg/5 mL (237 mL) [contains alcohol 1%; pineapple-coconut-mint flavor]

Generic AvailableYes: Excludes injection, oral suspension

Pricing: U.S. (www.drugstore.com)

Capsule, controlled release (Indomethacin CR)

75 mg (30): $82.15

Capsules (Indomethacin)

25 mg (30): $14.99

50 mg (30): $12.99

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: ~30 minutes

Duration: 4-6 hours

Absorption: Oral: Immediate release: Prompt and extensive; Extended release: 90% over 12 hours

Distribution: V_d: 0.34-1.57 L/kg; crosses blood brain barrier and placenta; enters breast milk

Protein binding: 99%

Metabolism: Hepatic; significant enterohepatic recirculation

Bioavailability: 100%

Half-life elimination: 4.5 hours; prolonged in neonates

Time to peak: Oral: Immediate release: 2 hours

Excretion: Urine (60%, primarily as glucuronide conjugates); feces (33%, primarily as metabolites)

Related Information

- Antacid Drug Interactions
- Depression
- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness; may rarely cause sedation, confusion, depression, and hallucinations

Mental Health: Effects on Psychiatric TreatmentMay cause bone marrow suppression; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A recent meta-analysis (see References) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 chronic heart failure guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin's inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other Considerations The 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

Index Terms Indometacin; Indomethacin Sodium Trihydrate

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International Brand NamesAgilex (AR); Amuno Retard (DE); Antalgin (MX); Areumatin (ID); Argilex (AR); Arthrexin (AU, ZA); Artrilona S (UY); Asimet (MY); Catlep (JP); Chrono-Indocid (FR); Confortid (AE, BH, CY, DK, EG, FI, IL, IQ, IR, JO, KW, LB, LY, NO, OM, QA, SA, SE, SY, YE); Docin (TH); Dolazal (NL); Dometin (NL); Elmego Spray (TH); Elmetacin (EC, PL); Flamaret (ZA); IDC (TH); Idicin (IN); IM-75 (AR); Imet (BF, BJ, CI, ET, GH, GM, GN, IT, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Indacin (PK); Indaflex (MX); Indalgin (TW); Indanet (MX); Indecin (TW); Indo (MY); Indocap (IN); Indocap S.R. (IN); Indocid (AE, AT, AU, BB, BE, BF, BH, BJ, BR, BS, BZ, CH, CI, CY, EG, ET, FR, GH, GM, GN, GR, HK, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, OM, PE, PH, PL, QA, SA, SC, SD, SL, SN, SY, TN, TT, TZ, UG, VE, YE, ZA, ZM, ZW); Indocid-R (NZ); Indocin I.V. (IL); Indocolir (DE); Indocollyre (FR, HK, PL); Indocontin (CL); Indogesic (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Indolag (AE, BF, BH, BJ, BM, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PR, QA, SA, SC, SD, SL, SN, SR, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Indolgina (CR, DO, GT, HN, NI, PA, SV); Indomecin (CO); Indomed (IL); Indomed F (TH); Indomee (SE); Indomelan (AT); Indomen (SG); Indomet (EE); Indometin (FI); Indomin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Indono (TH); Indorem (BM, GY, PR, SR); Indosan (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Indosima (PY); Indovis (IL); Indoxen (HK); Indoy (TW); Indrenin (CZ); Indylon (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Malival (MX); Metacen (IT); Methacin (MY); Metindol (CZ, PL); Metindol Retard (PL); Reumacid (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Rheumacid (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Rheumacin (NZ); Rheumacin SR (NZ); Stratasin (MX); Vi-Gel (PH)

InFLIXimab

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Tumor Necrosis Factor: Alpha Blockers Associated with Unrecognized Invasive Fungal Infections - September 4, 2008

The U.S. Food and Drug Administration (FDA) is alerting healthcare professionals of an increased risk for opportunistic fungal infections in patients treated with antitumor necrosis factor (anti-TNF) agents adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), and infliximab (Remicade®). The FDA has received reports of pulmonary and disseminated cases of histoplasmosis, coccidioidomycosis, blastomycosis, and other fungal infections associated with use of these agents. In some cases, the symptoms of fungal infection (eg, fever, cough, malaise, dyspnea, fatigue) were unrecognized and precluded prompt antifungal treatment, resulting in 12 deaths. In response, the FDA is requiring manufacturers of these agents to strengthen the boxed warning statement in the labeling to further emphasize the risk of invasive fungal infection. Patients should be monitored closely for signs and symptoms suggestive of fungal infection, evidence of which should result in prompt discontinuation of the medication and appropriate diagnostic evaluation. Symptomatic patients should be questioned about their residence in or travel from areas of endemic mycoses, which should prompt consideration of empiric antifungal therapy.

Additional information can be found at: http://www.fda.gov/medwatch/safety/2008/safety08.htm#TNF2

Tumor Necrosis Factor (TNF) Blockers and Malignancy Risk - June 5, 2008

The U.S. Food and Drug Administration (FDA) issued an Early Communication to healthcare professionals regarding a possible association between TNF blocker (adalimumab, certolizumb pegol, etanercept, and infliximab) use and the development of malignancies in children and young adults. Over the last 10 years, the FDA has received ~30 reports of cancer in children or young adults who had been treated with TNF blockers prior to the age of 18 years. TNF blockers were given for the treatment of Juvenile Idiopathic Arthritis (JIA [formerly termed Juvenile Rheumatoid Arthritis]), Crohn's disease, or other indications in combination with other immunosuppressive medications (eg, azathioprine, 6-mercaptopurine or methotrexate). Approximately half of the reported cancers were lymphomas (Hodgkin's and non-Hodgkin's), which are cancers involving the cells of the immune system.

TNF blockers work by suppressing the immune system. The prescribing information for each TNF blocker contains warnings regarding the possible association of malignancy development with use. Malignancies may not be detected in short-term studies; long-term studies are necessary to identify the impact of TNF blocker therapy on malignancy development. The manufacturers of the four TNF blockers available in the U.S. are being asked by the FDA to provide information regarding all cases of cancer reported in children taking TNF blockers. The FDA is expected to report its findings in approximately 6 months, after completing a safety review and evaluation.

Additional information is available at http://www.fda.gov/medwatch/safety/2008/safety08.htm#TNF

Medication Safety Issues

Sound-alike/look-alike issues:

Remicade® may be confused with Renacidin®, Rituxan®

InFLIXimab may be confused with riTUXimab

Pronunciation(in FLIKS e mab)

U.S. Brand NamesRemicade®

Canadian Brand NamesRemicade®

Pharmacologic CategoryAntirheumatic, Disease Modifying; Gastrointestinal Agent, Miscellaneous; Monoclonal Antibody; Tumor Necrosis Factor (TNF) Blocking Agent

Use: Labeled IndicationsTreatment of rheumatoid arthritis (moderate-to-severe, with methotrexate); treatment of Crohn's disease (moderate-to-severe with inadequate response to conventional therapy) for induction and maintenance of remission, and/or to reduce the number of draining enterocutaneous and rectovaginal fistulas, and to maintain fistula closure; treatment of psoriatic arthritis; treatment of plaque psoriasis (chronic severe); treatment of ankylosing spondylitis; treatment of and maintenance of healing of ulcerative colitis (moderately- to severely-active with inadequate response to conventional therapy)

Use: Unlabeled/InvestigationalAcute graft-versus-host disease (GVHD), juvenile rheumatoid arthritis (JRA)

Dosing: Adults**Note:** Premedication with antihistamines (anti-H_1 and/or anti-H_2), acetaminophen and/or corticosteroids may be considered to prevent and/or manage infusion-related reactions.

Crohn's disease: I.V.:

Induction regimen: 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks; dose may be increased to 10 mg/kg in patients who respond but then lose their response. If no response by week 14, consider discontinuing therapy.

Psoriatic arthritis (with or without methotrexate): 5 mg/kg at 0,2, and 6 weeks, then every 8 weeks

Rheumatoid arthritis: I.V. (in combination with methotrexate therapy): 3 mg/kg at 0, 2, and 6 weeks then every 8 weeks thereafter; doses have ranged from 3-10 mg/kg intravenous infusion repeated at 4- to 8-week intervals

Ankylosing spondylitis: I.V.: 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg every 6 weeks thereafter

Plaque psoriasis: I.V.: 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks thereafter

Ulcerative colitis: I.V.: 5 mg/kg at 0, 2, and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter

Acute GVHD (unlabeled use): 10 mg/kg weekly for up to 8 weeks (median 4 weeks of treatment)

Dosage adjustment with CHF: Weigh risk versus benefits for individual patient:

NYHA Class III or IV: ≤5 mg/kg

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Premedication with antihistamines (anti-H_1 and/or anti-H_2), acetaminophen and/or corticosteroids may be considered to prevent and/or manage infusion-related reactions.

Crohn's disease: Children: U.S. labeling ≥6 years, Canadian labeling ≥9 years: 5 mg/kg at 0, 2, and 6 weeks, followed by a maintenance dose of 5 mg/kg every 8 weeks; if no response by week 14, consider discontinuing therapy

Juvenile rheumatoid arthritis (unlabeled use): 3-4 mg/kg at 0, 2, and 6 weeks, and then every 8 weeks thereafter

Dosing: Renal ImpairmentNo adjustment is recommended.

Dosing: Hepatic ImpairmentNo adjustment necessary.

Administration: I.V.Infuse over at least 2 hours; do not infuse with other agents; use in-line low protein binding filter (≤1.2 micron). Temporarily discontinue or decrease infusion rate with infusion-related reactions. Antihistamines (anti-H_1 and/or anti-H_2), acetaminophen and/or corticosteroids may be used to manage reactions. Infusion may be reinitiated at a lower rate upon resolution of mild-to-moderate symptoms.

Canadian labeling (not approved in U.S. labeling): Infusion of doses ≤6 mg/kg over not less than 1 hour may be considered in patients treated for rheumatoid arthritis who have initially tolerated 3 infusions each over 2 hours. Safety of shortened infusion has not been studied with doses >6 mg/kg.

Guidelines for the treatment and prophylaxis of infusion reactions: (**Note:** Limited to dosages used in Crohn's; prospective information on other indications/dosing such as in GVHD are not available).

Treatment of infusion reactions: Medications for the treatment of hypersensitivity reactions should be available for immediate use. A protocol for the treatment of acute infusion reactions, as well a prophylactic therapy for repeat infusions, has been published (Cheifetz, 2003). Decreasing the rate of infusion to 10 mL/hour (for mild-to-moderate reactions) or a 20-minute interruption of the infusion (moderate to severe reactions) is recommended. Monitor vital signs every 10 minutes until normal. Administration of appropriate symptomatic treatment (acetaminophen and diphenhydramine, as well as hydrocortisone and epinephrine for severe reactions) should be instituted (consult institutional policies, if available). Following initial treatment, the infusion may be reinstituted at 10 mL/hour; then increased at 15-minute intervals, as tolerated (first to 20 mL/hour, then 40 mL/hour, then 80 mL/hour to completion).

Prophylaxis of infusion reactions: Premedication with acetaminophen and diphenhydramine 90 minutes prior to infusion may be considered in all patients with prior infusion reactions, and in patients with severe reactions corticosteroid administration is recommended (Cheifetz, 2003). Steroid dosing may be oral (prednisone 50 mg orally for 3 doses over a 24-hour period prior to infusion) or intravenous (a single dose of hydrocortisone 100 mg or methylprednisolone 20-240 mg administered 20 minutes prior to the infusion) (Cheifetz, 2003). On initiation of the infusion, a test dose (infusion at 10 mL/hour for 15 minutes may be considered. If tolerated, for patients with mild reactions, the infusion may be completed over 3 hours. For patients with prior moderate-to-severe reactions, the infusion may be increased at 15-minute intervals, as tolerated, to completion (first to 20 mL/hour, then 40 mL/hour, then 100 mL/hour, and finally 125 mL/hour to completion). A maximum rate of 100 mL/hour is recommended in patients who experienced prior severe reactions. In patients with cutaneous flushing, aspirin may be considered (Becker, 2004).

Administration: I.V. DetailDo not infuse with other agents. Use in-line low protein binding filter (≤ 1.2 micron).

pH ~7.2

StorageStore vials at 2°C to 8°C (36°F to 46°F); do not freeze.

ReconstitutionReconstitute vials with 10 mL sterile water for injection. Swirl vial gently to dissolve powder; do not shake. Allow solution to stand for 5 minutes. Total dose of reconstituted product should be further diluted to 250 mL of 0.9% sodium chloride injection to a final concentration of 0.4-4 mg/mL. Infusion of dose should begin within 3 hours of preparation.

CompatibilityDo not infuse with other agents.

RestrictionsAn FDA-approved medication guide is available at www.fda.gov/cder/Offices/ODS/labeling.htm; distribute to each patient to whom this medication is dispensed.

ContraindicationsHypersensitivity to infliximab, murine proteins or any component of the formulation; doses >5 mg/kg in patients with moderate or severe congestive heart failure (NYHA Class III/IV)

Canadian labeling: Additional contraindications (not in U.S. labeling): Severe infections (eg, sepsis, abscesses, tuberculosis, and opportunistic infections)

Allergy Considerations

- InFLIXimab Allergy

Warnings/Precautions

Boxed warnings:

- Fatal infections: See “Concerns related to adverse effects” below.
- Malignancy: See “Concerns related to adverse effects” below.
- Tuberculosis: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Autoimmune disorder: Positive antinuclear antibody titers have been detected in patients (with negative baselines). Rare cases of autoimmune disorder, including lupus-like syndrome, have been reported; monitor and discontinue if symptoms develop.
- Fatal infections: **[U.S. Boxed Warning]: Serious and potentially fatal infections (including sepsis, pneumonia, and invasive fungal and other opportunist infections) have been reported in patients receiving TNF-blocking agents.** Cases of unrecognized invasive fungal infections (eg, histoplasmosis, blastomycosis, coccidioidomycosis) have also been reported with anti-TNF agent use. Many of the serious infections in patients treated have occurred in patients on concomitant immunosuppressive therapy. Other opportunistic infections (eg, listeriosis, *Pneumocystis*) have occurred during therapy. Caution should be exercised when considering the use in patients with a history of new/recurrent infections, with conditions that predispose them to infections (eg, diabetes or residence/travel from areas of endemic mycoses), or with chronic, latent, or localized infections. Do not give with clinically important active infection. Patients who develop a new infection while undergoing treatment should be monitored closely. If a patient develops a serious infection, therapy should be discontinued.
- Hepatic reactions: Severe hepatic reactions (including hepatitis, jaundice, acute hepatic failure, and cholestasis) have have been reported during treatment; discontinue with jaundice or marked increase in liver enzymes (≥5 times ULN).
- Hepatitis B: Rare reactivation of hepatitis B virus (HBV) has occurred in chronic virus carriers. Use with caution; evaluate prior to initiation and during treatment.
- Hypersensitivity reactions: Acute infusion reactions may occur. Hypersensitivity reaction may occur within 2 hours of infusion. Medication and equipment for management should be available for immediate use. Interruptions and/or reinstitution at a slower rate may be required (consult protocols). Pretreatment may be considered, and may be warranted in all patients with prior infusion reactions. Serum sickness-like reactions have occurred; may be associated with a decreased response to treatment.
- Malignancy: **[U.S. Boxed Warning]: Hepatosplenic T-cell lymphoma has been reported (rarely) in adolescent and young adults with Crohn’s disease treated with infliximab and azathioprine or 6-mercaptopurine.** The impact of infliximab on the development and course of malignancies is not fully defined, but may be dose dependent. As compared to the general population, an increased risk of lymphoma has been noted in clinical trials; however, rheumatoid arthritis alone has been previously associated with an increased rate of lymphoma. Use caution in patients with a history of COPD, higher rates of malignancy were reported in COPD patients treated with infliximab. Psoriasis patients with a history of phototherapy had a higher incidence of nonmelanoma skin cancers.
- Tuberculosis: **[U.S. Boxed Warning]: Reactivation of latent infections have been associated with infliximab therapy.** Tuberculosis (disseminated or extrapulmonary) has been reactivated in patients previously exposed to TB while on therapy. Most cases have been reported within the first 3-6 months of treatment. Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test prior to starting therapy. Treatment of latent tuberculosis should be initiated before therapy is used. The risk/benefit ratio should be weighed in patients who have resided in regions where histoplasmosis is endemic.

Disease-related concerns:

- Demyelinating CNS disease: Use with caution in patients with pre-existing or recent onset CNS demyelinating disorders; rare cases of optic neuritis and demyelinating disease have been reported; consider discontinuation of therapy if patient develops significant CNS reactions.
- Heart failure (HF): Use with caution in patients with mild HF (NYHA Class I, II) or decreased left ventricular function; worsening and new-onset HF has been reported; doses >5 mg/kg should not be administered in patients with moderate-to-severe heart failure; discontinue therapy with onset of new or worsening symptoms.
- Hematologic disorders: Use with caution in patients with history of hematologic abnormalities; hematologic toxicities (eg, leukopenia, neutropenia, thrombocytopenia, pancytopenia) have been reported. Patients must be advised to seek medical attention if they develop signs and symptoms suggestive of blood dyscrasias; discontinue if significant hematologic abnormalities are confirmed.
- Seizure disorders: Use with caution in patients with a history of seizures; discontinue if significant CNS adverse reactions develop.

Concurrent drug therapy issues:

- Anakinra: Serious infections were reported when anakinra was used with another TNF-blocking agent (etanercept); therefore, concurrent use of infliximab and anakinra is not recommended.

Special populations:

- Pediatrics: Safety and efficacy for use in juvenile rheumatoid arthritis, pediatric plaque psoriasis, or pediatric ulcerative colitis have not been established in children. **Note:** For use in Crohn’s disease: Safety and efficacy have not been established in children <6 years of age (U.S. labeling); safety and efficacy have not been established in children <9 years of age (Canadian labeling).

Other warnings/precautions:

- Immunizations: Patients should be brought up to date with all immunizations before initiating therapy. Live vaccines should not be given concurrently; there is no data available concerning secondary transmission of live vaccines in patients receiving therapy.

Pregnancy Risk FactorB

Pregnancy ConsiderationsReproduction studies have not been conducted. Use during pregnancy only if clearly needed. A Rheumatoid Arthritis and Pregnancy Registry has been established for women exposed to infliximab during pregnancy (Organization of Teratology Information Services, 877-311-8972).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known whether infliximab is secreted in human milk. Because many immunoglobulins are secreted in milk and the potential for serious adverse reactions exists, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Adverse Reactions**Although profile is similar, frequency of adverse effects may vary with disease state. Except where noted, percentages reported in adults with rheumatoid arthritis:**

>10%:

Central nervous system: Headache (18%)

Gastrointestinal: Nausea (21%), diarrhea (12%), abdominal pain (12%, Crohn’s 26%)

Hepatic: ALT increased (risk increased with concomitant methotrexate)

Respiratory: Upper respiratory tract infection (32%), sinusitis (14%), cough (12%), pharyngitis (12%)

Miscellaneous: Development of antinuclear antibodies (~50%), infection (36%), development of antibodies to double-stranded DNA (17%), infusion reactions (20%; severe <1%); Crohn's patients with fistulizing disease: Development of new abscess (15%)

5% to 10%:

Cardiovascular: Hypertension (7%)

Central nervous system: Fatigue (9%), pain (8%), fever (7%)

Dermatologic: Rash (1% to 10%), pruritus (7%)

Gastrointestinal: Dyspepsia (10%)

Genitourinary: Urinary tract infection (8%)

Neuromuscular & skeletal: Arthralgia (1% to 8%), back pain (8%)

Respiratory: Bronchitis (10%), rhinitis (8%), dyspnea (6%)

Miscellaneous: Moniliasis (5%)

<5%: Abscess, adult respiratory distress syndrome, allergic reaction, anemia, arrhythmia, basal cell carcinoma, biliary pain, bradycardia, brain infarction, breast cancer, cardiac arrest, cellulitis, cholecystitis, cholelithiasis, circulatory failure, confusion, constipation, dehydration, delayed hypersensitivity (plaque psoriasis), diaphoresis increased, dizziness, edema, gastrointestinal hemorrhage, heart failure, hemolytic anemia, hepatitis, hypersensitivity reactions, hypotension, ileus, intervertebral disk herniation, intestinal obstruction, intestinal perforation, intestinal stenosis, leukopenia, lupus-like syndrome, lymphadenopathy, lymphoma, malignancies, meningitis, menstrual irregularity, MI, myalgia, neuritis, pancreatitis, pancytopenia, peripheral neuropathy, peritonitis, pleural effusion, pleurisy, proctalgia, pulmonary edema, pulmonary embolism, renal calculus, renal failure, respiratory insufficiency, seizure, sepsis, serum sickness, suicide attempt, syncope, tachycardia, tendon disorder, thrombocytopenia, thrombophlebitis (deep), ulceration

The following adverse events were reported in children with Crohn’s disease and were found more frequently in children than adults:

>10%:

Hepatic: Liver enzymes increased (18%; ≥5 times ULN: 1%)

Hematologic: Anemia (11%)

Miscellaneous: Infections (56%; more common with every 8-week versus every 12-week infusions)

1% to 10%:

Central nervous system: Flushing (9%)

Gastrointestinal: Blood in stool (10%)

Hematologic: Leukopenia (9%), neutropenia (7%)

Neuromuscular & skeletal: Bone fracture (7%)

Respiratory: Respiratory tract allergic reaction (6%)

Miscellaneous: Viral infection (8%), bacterial infection (6%), antibodies to infliximab (3%)

Postmarketing and/or case reports (adults or children): Agranulocytosis, anaphylactic reactions, anaphylactic shock, angina, angioedema, autoimmune hepatitis, bronchospasm, cholestasis, demyelinating disorders (eg, multiple sclerosis, optic neuritis); drug-induced lupus-like syndrome, erythema multiforme, Guillain-Barré syndrome, heart failure (worsening), hepatitis B reactivation, hepatocellular damage, hepatosplenic T-cell lymphoma (HSTCL), Hodgkin's disease, idiopathic thrombocytopenia purpura, interstitial fibrosis, interstitial pneumonitis, jaundice, laryngeal/pharyngeal edema, latent tuberculosis reactivation, liver failure, liver function tests increased, neuropathy, numbness, opportunistic infection, pericardial effusion, pneumonia, psoriasis, seizure, Stevens-Johnson syndrome, thrombotic thrombocytopenia purpura, taste abnormal, tingling, toxic epidermal necrolysis, transverse myelitis, tuberculosis, urticaria, vasculitis (systemic and cutaneous)

Drug Interactions

Abatacept: Anti-TNF Agents may enhance the adverse/toxic effect of Abatacept. An increased risk of serious infection during concomitant use has been reported. *Risk D: Consider therapy modification*

Abciximab: May enhance the potential for allergic or hypersensitivity reactions to Monoclonal Antibodies. Also may cause thrombocytopenia or diminished therapeutic effects. *Risk C: Monitor therapy*

Anakinra: Anti-TNF Agents may enhance the adverse/toxic effect of Anakinra. An increased risk of serious infection during concomitant use has been reported. *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Rilonacept: Anti-TNF Agents may enhance the adverse/toxic effect of Rilonacept. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid echinacea (may diminish the therapeutic effect of infliximab).

Monitoring ParametersDuring infusion, if reaction is noted, monitor vital signs every 10 minutes until normal. Follow-up monitoring includes monitoring for improvement of symptoms; signs of infection; LFTs (discontinue if >5 times ULN); place and read PPD before initiation. Psoriasis patients with history of phototherapy should be monitored for nonmelanoma skin cancer.

Nursing: Physical Assessment/MonitoringMonitor therapeutic effectiveness and adverse reactions. Place and read PPD before initiation of therapy. Treatment of latent TB infection should be initiated prior to treatment with infliximab. Monitor for signs or symptoms of infection. Assess for signs of liver dysfunction (eg, unusual fatigue, easy bruising or bleeding, jaundice). Teach patient appropriate interventions to reduce side effects and adverse symptoms to report.

Patient EducationThis drug can only be administered by infusion. Avoid receiving immunizations unless approved by prescriber. You will be more prone to infection. Avoid crowds and wash your hands frequently. Report headache or unusual fatigue; increased nausea or abdominal pain; bruising or bleeding easily; cough, runny nose, respiratory difficulty; chest pain or persistent dizziness; fatigue, muscle pain or weakness, back pain; fever or chills; mouth sores; vaginal itching or discharge; sore throat; unhealed sores; or frequent infections. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Remicade®: 100 mg [contains sucrose 500 mg and polysorbate 80]

Generic AvailableNo

ManufacturerCentocor, Inc

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Remicade)

100 mg (1): $646.61

Mechanism of ActionInfliximab is a chimeric monoclonal antibody that binds to human tumor necrosis factor alpha (TNFα), thereby interfering with endogenous TNFα activity. Biological activities of TNFα include the induction of proinflammatory cytokines (interleukins), enhancement of leukocyte migration, activation of neutrophils and eosinophils, and the induction of acute phase reactants and tissue degrading enzymes. Animal models have shown TNFα expression causes polyarthritis, and infliximab can prevent disease as well as allow diseased joints to heal.

Pharmacodynamics/Kinetics

Onset of action: Crohn's disease: ~2 weeks

Distribution: V_d: 3-6 L

Half-life elimination: 7-12 days

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusFatigue is common; may cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsInfliximab, Recombinant; NSC-728729

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International Brand NamesRemicade (AR, AT, AU, BE, BG, BR, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IT, KP, MX, MY, NI, NL, NO, PA, PE, PH, PL, PT, RU, SE, SG, SV, TH, TR, UY, VE)

Influenza Virus Vaccine (H5N1)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Influenza virus vaccine (H5N1) may be confused with the nonavian strain of influenza virus vaccine

Pronunciation(in floo EN za VYE rus vak SEEN H5N1)

Pharmacologic CategoryVaccine

Use: Labeled IndicationsActive immunization of adults at increased risk of exposure to the H5N1 viral subtype of influenza

Dosing: AdultsImmunization: Adults 18-64 years: I.M.: 1 mL, followed by second 1 mL dose given 28 days later (acceptable range: 21-35 days)

Administration: I.M.For I.M. administration only. Inspect for particulate matter and discoloration prior to administration. Vaccinate in the deltoid muscle using a ≥1 inch needle length. Suspension should be shaken well prior to use. **Note:** For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

StorageStore between 2°C to 8°C (36°F to 46°F). Potency is destroyed by freezing; do not use if product has been frozen. Protect from light.

RestrictionsCommercial distribution is not planned. The vaccine will be included as part of the U.S. Strategic National Stockpile. It will be distributed by public health officials if needed.

ContraindicationsManufacturer states no contraindications

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

- Hypersensitivity: Small quantities of egg protein may be present; may cause severe reactions in patients with egg allergies. Administration to patients with known hypersensitivity to previous influenza virus vaccination, or any component of the formulation, should be carefully weighed against the risk of not vaccinating.

Disease-related concerns:

- Guillain-Barré (GBS): Use with caution in patients with a history of GBS; these patients may have a greater likelihood of developing GBS. Relationship to this influenza vaccine formulation is not known; in patients with recent GBS (≤6 weeks), decision to administer vaccine should entail careful consideration of risk:benefit.

Special populations:

- Elderly: Safety and efficacy have not been established in adults >64 years of age.

- Immunosuppressed patients: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy [including high-dose corticosteroids]); may have a reduced response to vaccination.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Formulation components: Vaccine contains thimerosal, chicken protein, and egg protein.

Geriatric ConsiderationsNo clinical studies in elderly have been done to date. Differences in immune response may be different than the titer response seen in younger adults.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. Vaccine should be given only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

>10%:

Central nervous system: Headache (3% to 36%), malaise (22%)

Local: Pain (74%), tenderness (70%), erythema/redness (20%), induration/swelling (15%)

Neuromuscular & skeletal: Myalgia (16%)

1% to 10%:

Central nervous system: Fever (up to 7%)

Gastrointestinal: Nausea (10%), diarrhea (6%)

Respiratory: Nasopharyngitis (2%), upper respiratory infection (2%), nasal congestion (1%)

Additional reactions observed with other influenza vaccine formulations: Allergic reaction, anaphylaxis, angioedema, asthma, encephalopathy, facial paralysis, hives, GBS, neuropathy, optic neuritis, vasculitis

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringCarefully evaluate patient for contraindications and prior immunization history for possible adverse events. Treatment for anaphylactic/anaphylactoid reaction should be immediately available during vaccine use. See specific administration directions. **Note:** All serious adverse reactions must be reported to the U.S. DHHS. Date of administration, name of manufacturer, lot number, and administering person's name, title, and address should be recorded in patient's permanent medical record. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Patient Education

Notify prescriber immediately of any acute reaction to vaccination (eg, difficulty breathing, chest pain, acute headache, rash, difficulty swallowing). May cause mild headache, fever, muscle pain, or some redness, pain, or swelling at injection site; consult prescriber if excessive or persisting. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsInjection, suspension [monovalent]: Hemagglutinin (H5N1 strain) 90 mcg/1 mL (5 mL) [contains thimerosal, and chicken, porcine, and egg proteins]

Generic AvailableNo

Mechanism of ActionA monovalent, split virus (inactivated) preparation of the H5N1 avian strain of influenza virus (A/Vietnam/1203/2004) which promotes active immunity to avian influenza.

Pharmacodynamics/KineticsOnset of action: Four-fold increase in antibody titers occurred in up to 58% of patients 28 days after second dose.

Related Information

- Immunization Recommendations
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

The 2-dose regimen prompted antibody response consistent with a protective titer in up to 58% of patients. However, there are no clinical data evaluating whether vaccination protects patients against development of infection. Therefore, protection against a pandemic avian flu strain cannot be assured.

Healthcare workers involved in the care of patients with known or suspected H5N1 viral subtype influenza infection should be vaccinated with the most recent seasonal human influenza vaccine in order to reduce the risk of co-infection of human influenza A viruses.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMalaise is common

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAvian Influenza Virus Vaccine; Bird Flu Vaccine; H5N1 Influenza Vaccine; Influenza Virus Vaccine (Monovalent)

References

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Influenza Virus Vaccine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Fluarix® may be confused with Flarex®

Influenza virus vaccine may be confused with tetanus toxoid and tuberculin products. Medication errors have occurred when tuberculin skin tests (PPD) have been inadvertently administered instead of tetanus toxoid products and influenza virus vaccine. These products are refrigerated and often stored in close proximity to each other.

Influenza virus vaccine (human strain) may be confused with the avian strain (H5N1) of influenza virus vaccine

International issues:

Hiberix is also a brand name for *Haemophilus* b conjugate vaccine in Slovenia

Pronunciation(in floo EN za VYE rus vak SEEN)

U.S. Brand NamesAfluria®; Fluarix®; FluLaval™; FluMist®; Fluvirin®; Fluzone®

Canadian Brand NamesFluviral S/F®; Vaxigrip®

Pharmacologic CategoryVaccine, Inactivated (Viral); Vaccine, Live (Viral)

Use: Labeled IndicationsProvide active immunity to influenza virus strains contained in the vaccine

Advisory Committee on Immunization Practices (ACIP) recommends annual vaccination for all children (6 months to 18 years) and adults. Target groups for vaccination (those at higher risk of complications from influenza infection and their close contacts) include the following:

- Persons ≥50 years of age
- Residents of nursing homes and other chronic-care facilities that house persons of any age with chronic medical conditions
- Adults and children with chronic disorders of the pulmonary or cardiovascular systems (except hypertension), including asthma
- Adults and children who have chronic metabolic diseases (including diabetes mellitus), hepatic disease, renal dysfunction, hematologic disorders, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or HIV)
- Adults and children with conditions which may compromise respiratory function, the handling of respiratory secretions, or that can increase the risk of aspiration (eg, cognitive dysfunction, spinal; cord injuries, seizure disorders, other neuromuscular disorders)
- Children and adolescents (6 months to 18 years of age) who are receiving long-term aspirin therapy and therefore, may be at risk for developing Reye's syndrome after influenza
- Women who will be pregnant during the influenza season
- Children 6-59 months of age
- Healthcare personnel
- Household contacts and caregivers of children <5 years (particularly children <6 months) and adults ≥50 years
- Household contacts and caregivers of persons with medical conditions which put them at high risk of complications from influenza infection

Dosing: AdultsOptimal time to receive vaccine is October-November, prior to exposure to influenza; however, vaccination should continue into December and throughout the influenza season as long as vaccine is available.

Immunization:

Afluria®, Fluarix®, FluLaval™: I.M.: 0.5 mL/dose (1 dose per season)

Fluzone®, Fluvirin®: I.M.: 0.5 mL/dose (1 dose per season)

FluMist®: Intranasal: Adults ≤49 years: 0.2 mL/dose (1 dose per season)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricOptimal time to receive vaccine is October-November, prior to exposure to influenza; however, vaccination should continue into December and throughout the influenza season as long as vaccine is available.

Note: Children <9 years who are not previously vaccinated or who received only 1 dose of vaccine during the previous season should receive 2 doses, in order to achieve satisfactory antibody response. Although products are licensed for use in specific ages, if a particular vaccine is inadvertently administered to a child in a nonapproved age group, it does not need to be repeated.

Immunization:

Fluzone®: I.M.:

Children 6-35 months: 0.25 mL/dose (1 or 2 doses per season; see **Note**)

Children 3-8 years: 0.5 mL/dose (1 or 2 doses per season; see **Note**)

Children ≥9 years: Refer to adult dosing.

Fluvirin®: I.M.:

Children 4-8 years: 0.5 mL/dose (1 or 2 doses per season; see **Note**)

Children ≥9 years: Refer to adult dosing.

FluMist®: Intranasal:

Children 2-8 years, previously **not vaccinated** with influenza vaccine: Initial season: Two 0.2 mL doses separated by at least 4 weeks

Children 2-8 years, previously **vaccinated** with influenza vaccine: 0.2 mL/dose (1 or 2 doses separated by at least 4 weeks; see **Note**)

Children ≥9 years: Refer to adult dosing.

Administration: I.M.TIV: For I.M. administration only. Inspect for particulate matter and discoloration prior to administration. Adults and older children should be vaccinated in the deltoid muscle using a ≥1 inch needle length. Infants and young children <12 months of age should be vaccinated in the anterolateral aspect of the thigh using a $^{7}/_{8}$ inch to 1 inch needle length. Young children with adequate deltoid muscle mass should be vaccinated using a $^{7}/_{8}$ inch to 1.25 inch needle. Suspensions should be shaken well prior to use.

Note: For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends "it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection."

Administration with other vaccines:

Influenza virus vaccine (inactivated; TIV) with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Influenza virus vaccine (inactivated; TIV) with live vaccines: May be given simultaneously or at any interval between doses

Influenza virus vaccine (live; LAIV) with other live vaccines:

Intranasal or injectable: If not given simultaneously, wait at least 4 weeks between administration

Oral: May be given simultaneously or at any interval between doses of live or inactivated injectable vaccines

Vaccine administration with antibody-containing products*:

Antibody-containing products and influenza virus vaccine (inactivated; TIV): May be given simultaneously at different sites or at any interval between doses

Antibody-containing products and influenza virus vaccine (live; LAIV): Influenza virus vaccine (live; LAIV) may be given at any time before, after or simultaneously with an antibody-containing product.

*Examples of antibody containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products

Administration: OtherLAIV: Intranasal: Half the dose (0.1 mL) is administered to each nostril; patient should be in upright position. A dose divider clip is provided. Severely-immunocompromised persons should not administer the live vaccine. If recipient sneezes following administration, the dose should not be repeated. Also refer to Administration I.M. for use with other vaccines.

Storage

Injection: Store between 2°C to 8°C (36°F to 46°F). Potency is destroyed by freezing; do not use if product has been frozen.

Afluria®, FluLaval™: Discard 28 days after initial entry. Protect from light.

Fluarix®: Protect from light.

Fluzone®: Between uses, the multiple dose vial should be stored at 2°C to 8°C (36°F to 46°F).

Nasal spray: Store in refrigerator at 2°C to 8°C (36°F to 46°F). **Do not freeze.**

ContraindicationsHypersensitivity to influenza virus vaccine, or any component of the formulation; presence of acute respiratory disease or other active infections or febrile illnesses; active neurological disorder (immunization should be delayed)

In addition, for nasal spray: Children 2-17 years of age receiving aspirin therapy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Guillain-Barré syndrome: Use with caution in patients with history of Guillain-Barré syndrome (GBS); patients with history of GBS have a greater likelihood of developing GBS than those without. May consider avoiding vaccination in patients with a history of GBS and who are at low risk for severe influenza complications, and in patients known to have experienced GBS within 6 weeks following previous vaccination (consider influenza antiviral chemoprophylaxis in these patients).

- HIV: Antigenic response may not be as great as expected in HIV-infected persons with CD4 cells <100/mm^3 and with viral copies of HIV type 1 >30,000/mL.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Adults: Safety and efficacy of the nasal spray have not been established in adults ≥50 years of age.

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination. Data on the use of the nasal spray in immunocompromised patients is limited.

- Pediatrics: Safety and efficacy of the injection have not been established in children <6 months of age. Safety and efficacy of the nasal spray have not been established in children <2 years of age.

Dosage form specific issues:

- Arginine: Some products are manufactured using arginine.

- Chicken egg protein: Some products are manufactured with chicken egg protein.

- Gelatin: Some products are manufactured using gelatin

- Gentamicin: Some products are manufactured with gentamicin.

- Injection (inactivated, split virus, TIV): Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration. May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever). Inactivated vaccine is preferred over live virus vaccine for household members, healthcare workers and others coming in close contact with severely-immunosuppressed persons requiring care in a protected environment.

- Latex: Packaging may contain natural latex rubber.

- Nasal spray (live, attenuated virus; LAIV): For intranasal use only. **Avoid contact with severely immunocompromised individuals for at least 7 days following vaccination.** Use the nasal spray with caution in patients with asthma or children <5 years of age with recurrent wheezing; risk of wheezing following vaccination is increased. Patients with severe asthma or active wheezing were not included in clinical trials and use in these patients is not recommended. Children <24 months of age had increased wheezing and hospitalizations following administration in clinical trials; use of the nasal spray is not approved in this age group. Defer immunization if nasal congestion is present which may impede delivery of vaccine. Because safety and efficacy information is limited, the ACIP does not recommend the use of LAIV in patients with the following conditions: chronic metabolic diseases (including diabetes mellitus), hepatic disease, renal dysfunction, hematologic disorders, hemoglobinopathies, history of GBS, immunosuppression, chronic disorders of the pulmonary or cardiovascular systems (including asthma), pregnant women, or children and adolescents receiving long-term aspirin therapy

- Neomycin: Some products are manufactured with neomycin.

- Polymyxin: Some products are manufactured with polymyxin.

- Thimerosal: Some products contain thimerosal; hypersensitivity reactions may occur.

Other warnings/precautions:

- Previous season vaccines: Influenza vaccines from previous seasons must not be used.

Geriatric ConsiderationsLimited data on the elderly exists due to ethical considerations precluding use of placebo and differences in studies and vaccines; 80% develop a 1:40 HA titer, 70% are completely protected, 90% protected from death.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. Case reports and limited studies suggest pregnancy may increase the risk of serious medical complications from influenza infection. Vaccination is recommended regardless of stage of pregnancy. Vaccination with the injection during the third trimester of pregnancy has been shown to decrease the incidence of laboratory confirmed influenza and respiratory illness with fever in infants ≤6 months. The safety and efficacy of the nasal spray have not been studied in pregnant pregnant women; however, pregnant women do not need to avoid contact with persons recently vaccinated with LAIV.

Breast-Feeding ConsiderationsUse of influenza vaccine has not been shown to affect the safety of breast-feeding mothers or their infants. The use of the nasal spray (live virus vaccine) should be used with caution (per manufacturer) due to the possibility of viral shedding from mother to infant. The ACIP recommends use of either TIV or LAIV in breast-feeding women unless contraindicated due to other medical conditions.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Injection:

Frequency not defined.

Cardiovascular: Chest tightness, facial edema

Central nervous system: Chills, fatigue, fever, headache, irritability, insomnia, and malaise (may start within 6-12 hours and last 1-2 days; incidence equal to placebo in adults; occurs more frequently than placebo in children); Guillain-Barré syndrome (GBS)

Dermatologic: Angioedema, bruising, rash, urticaria

Gastrointestinal: Sore throat

Local: Tenderness, redness, sweling, or induration at the site of injection (10% to 64%; may last up to 2 days); injection site pain

Neuromuscular & skeletal: Arthralgia, myalgia (may start within 6-12 hours and last 1-2 days; incidence equal to placebo in adults; occurs more frequently than placebo in children)

Ocular: Red eyes

Respiratory: Cough, nasopharyngitis

Miscellaneous: Allergic or anaphylactoid reactions (most likely to residual egg protein; includes allergic asthma, angioedema, hives, systemic anaphylaxis)

Postmarketing and/or case reports: Angioneurotic edema, arthritis, brachial neuritis, bronchospasm, cellulites, conjunctivitis, diaphoresis, dizziness, dysphagia, dysphonia, dyspnea, encephalopathy, eye pain, facial palsy (Bell’s palsy), flushing, Henoch-Schönlein purpura, hypoesthesia, hypokinesia, limb paralysis, microscopic polyangiitis (vasculitis), paresthesia, laryngitis, lymphadenopathy, neuralgia, neuropathy, optic neuritis, pallor, pharyngitis, photophobia, periorbital edema, pruritus, rhinitis, seizure (rare; majority associated with fever), serum sickness, somnolence, Stevens-Johnson syndrome, syncope, tachycardia, throat tightness, transient thrombocytopenia, transverse myelitis, tremor, vasodilation, vasculitis (with transient renal involvement), vertigo, vomiting, weakness

Nasal spray: Frequency of events reported within 10 days

>10%:

Central nervous system: Headache (children 3% to 9%; adults 40%), irritability (children 12% to 21%), lethargy (children 6% to 14%)

Gastrointestinal: Appetite decreased (children 13% to 21%)

Neuromuscular & skeletal: Tiredness/weakness (adults 26%), muscle aches (children 2% to 6%; adults 17%)

Respiratory: Cough (adults 14%), nasal congestion/ runny nose (children 51% to 58%; adults 9% to 44%), sore throat (children 5% to 11%; adults 28%)

1% to 10%:

Central nervous system: Chills (children 2% to 4%, adults 9%), fever (100°F to 101°F: children 6% to 9%; >101°F: children 1% to 4%)

Gastrointestinal: Abdominal pain (children 2% to 12%)

Otic: Otitis media (children 3%)

Respiratory: Sinusitis (adults 4%), sneezing (children 2%), wheezing (children 6-23 months 6%; children 24-59 months 2%)

Postmarketing and/or case reports: Anaphylactic reactions, asthma exacerbations, Bell's palsy, diarrhea, epistaxis, facial edema, Guillain-Barré syndrome, hypersensitivity reaction, mitochondrial encephalomyopathy (Leigh syndrome) exacerbation, nausea, rash, urticaria, vomiting

Drug Interactions

Antiviral Agents (Influenza A and B): May diminish the therapeutic effect of Influenza Virus Vaccine. This only pertains to live, attentuated influenza virus vaccine. *Risk D: Consider therapy modification*

Immunosuppressants: May enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Tuberculin Tests: Vaccines (Live) may diminish the diagnostic effect of Tuberculin Tests. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringEvaluate patient’s prior immunization history, allergy to eggs, and appropriateness for vaccination prior to therapy. See administration directions according to formulation. **Note:** All serious adverse reactions must be reported to the U.S. DHHS. Date of administration, name of manufacturer, lot number, and administering person’s name, title, and address should be recorded in patient’s permanent medical record. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Patient EducationNotify prescriber immediately of any acute reaction to vaccination (eg, difficulty breathing or swallowing, chest pain, palpitations, acute headache, rash, seizures, high fever). Follow directions for care of injection site. May cause mild headache, chills, fever, or muscle pain; if these persist beyond 1-2 days or become severe, consult prescriber. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension [purified split-virus]:

Afluria®: 5 mL [TIV; contains chicken egg protein, thimerosal, neomycin (trace amounts), and polymyxin (trace amounts)]

FluLaval™: 5 mL [TIV; contains chicken egg protein and thimerosal]

Fluvirin®: 5 mL [TIV; contains chicken egg protein, thimerosal, neomycin (trace amounts), and polymyxin (trace amounts)]

Fluzone®: 5 mL [TIV; contains chicken egg protein and thimerosal]

Injection, suspension [purified split-virus; preservative free]:

Afluria®: 0.5 mL [TIV; contains chicken egg protein, neomycin (trace amounts), and polymyxin (trace amounts)]

Fluarix®: 0.5 mL [TIV; contains chicken egg protein, gentamicin (trace amounts), natural rubber/natural latex in packaging, polysorbate 80, and thimerosal (trace amounts)]

Fluvirin®: 0.5 mL [TIV; contains chicken egg protein, thimerosal (trace amounts), neomycin (trace amounts), and polymyxin (trace amounts)]

Fluzone®: 0.25 mL, 0.5 mL [TIV; contains chicken egg protein]

Solution, intranasal [preservative free; spray]:

FluMist®: 0.2 mL [trivalent, LAIV; contains arginine, chicken egg protein, gelatin, and gentamicin]

Generic AvailableNo

Mechanism of ActionPromotes immunity to influenza virus by inducing specific antibody production. Each year the formulation is standardized according to the U.S. Public Health Service. Preparations from previous seasons must not be used.

Pharmacodynamics/Kinetics

Onset of action: Protective antibody titers achieved ~2 weeks after vaccination

Duration: Protective antibody titers persist approximately ≥6 months. Elderly: Protective antibody titers may fall ≤4 months after vaccination.

Related Information

- Immunization Recommendations
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsPharmacies will stock the formulations(s) standardized according to the USPHS requirements for the season. Influenza vaccines from previous seasons must not be used. Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

The optimal time to receive vaccine is October-November, prior to exposure to influenza; however, vaccination should continue into December and later as long as vaccine is available. To avoid missed opportunities for vaccination, patients at risk for complications can be offered the vaccine during routine healthcare visits as early as September if vaccine is available. Avoid vaccination before October in older persons in nursing homes or similar housing facilities because antibody levels can decline more rapidly following vaccination. When vaccine is available, children aged 6 months to <9 years of age who have not been previously vaccinated, should receive their first dose in September so that both doses can be administered prior to the onset of influenza activity.

When vaccine supply is not limited, either TIV or LAIV can be used in healthy, nonpregnant persons aged 2-49 years of age.

When vaccine supply is limited, administration should focus on the ACIP target groups. When TIV vaccine is in short supply, administering LAIV to eligible persons is encouraged to increase available TIV to those patients in whom LAIV cannot be used. During periods of inactivated influenza vaccine (TIV) shortage, the CDC and ACIP have recommended vaccination be prioritized based on the following three tiers. The grouping is based on influenza associated mortality and hospitalization rates. Those listed in group 1 should be vaccinated first, followed by persons in group 2, and then group 3. If the vaccine supply is extremely limited, group 1 has also been subdivided in three tiers, where those in group 1A should be vaccinated first, followed by 1B, then 1C.

Priority groups for vaccination with inactivated influenza vaccine during periods of vaccine shortage:

Tier 1A:

Persons ≥65 years with comorbid conditions

Residents of long-term-care facilities

Tier 1B:

Persons 2-64 years with comorbid conditions

Persons ≥65 years without comorbid conditions

Children 6-23 months

        - Pregnant women

    - Tier 1C:

        - Healthcare personnel

        - Household contacts and out-of-home caregivers of children <6 months

    - Tier 2:

        - Household contacts of children and adults at increased risk of influenza associated complications

        - Healthy persons 50-64 years

    - Tier 3:

        - Persons 2-49 years without high-risk conditions

Further information available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5430a4.htm

Dental Health: Effects on Dental Treatment No significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions
Mental Health: Effects on Mental Status May cause fatigue, irritability, insomnia, and malaise
Mental Health: Effects on Psychiatric Treatment None reported
Index Terms Influenza Virus Vaccine (Purified Surface Antigen); Influenza Virus Vaccine (Split-Virus); Influenza Virus Vaccine (Trivalent, Live); Live Attenuated Influenza Vaccine (LAIV); Trivalent Inactivated Influenza Vaccine (TIV)
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International Brand Names Agrippal (FR, GB, IE, IT, PH, ZA); Agrippal S1 (HK, IL, KP); Alorbat (DE); Begrivac (AT, DE); Begrivac F (IL); Fluad (AU); Fluarix (AR, AU, BB, BM, BR, BS, BZ, CN, GY, HK, IL, JM, KP, MX, NL, SR, TT, TW); Fluvax (AU); Fluvirin (AE, BF, BH, BJ, CI, CY, EG, ET, GB, GH, GM, GN, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Fluvirine (FR); Fluzone (BF, BJ, CI, ET, GB, GH, GM, GN, IE, KE, LR, MA, ML, MR, MU, MW, MX, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Hiberix (CR, GT, HN, NI, PA, PE, SV); Inflexal (AT, ES, IT); Inflexal Berna (PH); Inflexal Berna Polyvalent Vaccine (MY); Inflexal V (CH, MY); Influvac (AE, AU, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TH, TN, TZ, UG, YE, ZA, ZM, ZW); Mutagrip (BE, DE, ES, FR, NL); Sandovac (AT); Vaxigrip (AT, BE, BG, CL, CO, DK, EC, FR, GR, HK, ID, IL, IN, NL, NO, NZ, PH, PK, PY, TH, TW, UY); Viroflu (GB, IE); X-Flu (ZA)

Insulin Aspart Protamine and Insulin Aspart

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

NovoLog® Mix 70/30 may be confused with Novolin® 70/30

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error. ***Due to the number of insulin preparations, it is essential to identify/clarify the type of insulin to be used.***

Cross-contamination may occur if insulin pens are shared among multiple patients. Steps should be taken to prohibit sharing of insulin pens.

Pronunciation(IN soo lin AS part PROE ta meen & IN soo lin AS part)

U.S. Brand NamesNovoLog® Mix 70/30

Canadian Brand NamesNovoMix® 30

Pharmacologic CategoryInsulin, Combination

Use: Labeled IndicationsTreatment of type 1 diabetes mellitus (insulin dependent, IDDM) and type 2 diabetes mellitus (noninsulin dependent, NIDDM) to improve glycemic control

Dosing: AdultsRefer to Insulin Regular. Fixed ratio insulins (such as insulin aspart protamine and insulin aspart combination) are normally administered in 2 daily doses.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentInsulin requirements are reduced due to changes in insulin clearance or metabolism.

Administration: OtherAspart protamine human suspension and aspart human solution (NovoLog® Mix 70/30): SubQ administration only. Cold injections should be avoided. Should be administered within 15 minutes before a meal. Normally administered twice daily (before breakfast and supper). SubQ administration is usually made into the thighs, arms, buttocks, or abdomen, with sites rotated. Resuspend immediately prior to use. Gently roll vial or pen in the palms of the hands to resuspend before using. Do not mix or dilute with other insulins.

StorageNovoLog® Mix 70/30: Store unopened container in refrigerator. Do not use if frozen. If refrigeration is not possible, vial (in use) may be stored at room temperature for up to 28 days. The pen in use should **not** be refrigerated, store below 30°C (86°F) away from direct heat or light; discard after 14 days. If refrigeration is not available, opened vials may be stored unrefrigerated in cool place away from heat and sunlight.

CompatibilityDo not mix or dilute with other insulins.

ContraindicationsHypersensitivity to any component of the formulation; during episodes of hypoglycemia

Allergy Considerations

- Insulin Preparations Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypoglycemia: The most common adverse effects of insulin is hypoglycemia. The timing of hypoglycemia differs among various insulin formulations. Hypoglycemia may result from increased work or exercise without eating; use of long-acting insulin preparations (insulin detemir, insulin glargine) may delay recovery from hypoglycemia. Profound and prolonged episodes of hypoglycemia may result in convulsions, unconsciousness, temporary or permanent brain damage or even death. Insulin requirements may be altered during illness, emotional disturbances or other stresses.

- Hypokalemia: Insulin causes a shift of potassium from the extracellular space to the intracellular space, possibly producing hypokalemia which, if left untreated, may result in respiratory paralysis, ventricular arrhythmia and even death. Use with caution in patients at risk for hypokalemia (eg, loop diuretic use). Monitor serum potassium and supplement potassium when necessary.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment. Dosage requirements may be reduced.

- Renal impairment: Use with caution in patients with renal impairment. Dosage requirements may be reduced.

Special populations:

- Pediatrics: Safety and efficacy of this insulin product have not been established in children.

Dosage form specific issues:

- Product variation: Human insulin differs from animal-source insulin. Any change of insulin should be made cautiously; changing manufacturers, type, and/or method of manufacture may result in the need for a change of dosage.

Other warnings/precautions:

- Appropriate use: The general objective of exogenous insulin therapy is to approximate the physiologic pattern of insulin secretion which is characterized by two distinct phases. Phase 1 insulin secretion suppresses hepatic glucose production and phase 2 insulin secretion occurs in response to carbohydrate ingestion; therefore, exogenous insulin therapy may consist of basal insulin (eg, intermediate- or long-acting insulin or continuous insulin infusion administered via an external SubQ insulin infusion pump) and/or preprandial insulin (eg, short- or rapid-acting insulin) (see Related Information: Insulin Products). Patients with type 1 diabetes do not produce endogenous insulin; therefore, these patients require both basal and preprandial insulin administration. Patients with type 2 diabetes retain some beta-cell function in the early stages of their disease; however, as the disease progresses, phase 1 insulin secretion may become completely impaired and phase 2 insulin secretion becomes delayed and/or inadequate in response to meals. Therefore, patients with type 2 diabetes may be treated with oral antidiabetic agents, basal insulin, and/or preprandial insulin depending on the stage of disease and current glycemic control. Since treatment regimens often consist of multiple agents, dosage adjustments must address the specific phase of insulin release that is primarily contributing to the patient’s impaired glycemic control. Treatment and monitoring regimens must be individualized.

- I.V. administration: Regular insulin is the only insulin to be used intravenously. Insulin aspart may also be administered I.V. in selected clinical situations to control hyperglycemia; close medical supervision is required.

- Patient education: Diabetic education and nutritional counseling are essential to maximize the effectiveness of therapy.

Geriatric ConsiderationsHow “tightly” a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well he/she recognizes hypoglycemic or hyperglycemic symptoms, and how to respond to them and any other disease states. Patients who are unable to accurately draw up their dose will need assistance such as prefilled syringes. Initial doses may require considerations for renal function in the elderly with dosing adjusted subsequently based on blood glucose monitoring. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination; see Insulin Aspart monograph

LactationSee Insulin Aspart monograph.

Breast-Feeding ConsiderationsSee Insulin Aspart monograph.

Pregnancy & Lactation, In-Depth

- Insulin Aspart in Pregnancy & Lactation

Adverse ReactionsRefer to Insulin Regular.

Drug Interactions

Antidiabetic Agents (Thiazolidinedione): Insulin may enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Beta-Blockers: May enhance the hypoglycemic effect of Insulin. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Edetate CALCIUM Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Edetate Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Insulin may enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/Monitoring

See individual agent for Insulin Aspart.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension:

NovoLog® Mix 70/30: Insulin aspart protamine suspension 70% [intermediate acting] and insulin aspart solution 30% [rapid acting]: 100 units/mL (3 mL) [FlexPen® prefilled syringe]; (10 mL) [vial]

Generic AvailableNo

Manufacturer

NovoNordisk

Pricing: U.S. (www.drugstore.com)

Suspension (NovoLOG Mix 70/30)

70-30% (10): $102.62

Suspension (NovoLOG Mix 70/30 FlexPen)

70-30% (15): $192.42

Mechanism of ActionRefer to Insulin Regular. Insulin aspart protamine and insulin aspart is a combination insulin product with intermediate-acting characteristics. Normally administered twice daily.

Pharmacodynamics/Kinetics**Note:** Rate of absorption, onset, and duration of activity may be affected by site of injection, exercise, presence of lipodystrophy, local blood supply, and/or temperature.

Onset of action: 0.2 hours

Peak effect: 1-4 hours

Duration: 18-24 hours

Half-life: 8-9 hours

Time to peak, plasma: 1-1.5 hours

Excretion: Urine

Related Information

- Insulin Aspart
- Insulin Products
- Insulin Regular

Pharmacotherapy PearlsRefer to Insulin Regular for additional details on adverse effects, drug interactions, warnings, and dosing of insulin products.

Dental Health: Effects on Dental TreatmentPatients with type 1 diabetes (insulin dependent) should be appointed for dental treatment in the morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or confusion

Mental Health: Effects on Psychiatric TreatmentMAO inhibitors may enhance the hypoglycemic effects of insulin; TCAs may antagonize the effects of insulin

Index TermsInsulin Aspart and Insulin Aspart Protamine

International Brand NamesNovomix 30 (CN, ES, IL, MY, TW, UY); Novomix 70 (SE)

Insulin Aspart

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

NovoLog® may be confused with Novolin®

NovoLog® Mix 70/30 may be confused with NovoLog®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error. ***Due to the number of insulin preparations, it is essential to identify/clarify the type of insulin to be used.***

Cross-contamination may occur if insulin pens are shared among multiple patients. Steps should be taken to prohibit sharing of insulin pens.

Pronunciation(IN soo lin AS part)

U.S. Brand NamesNovoLog®

Canadian Brand NamesNovoRapid®

Pharmacologic CategoryInsulin, Rapid-Acting

Use: Labeled IndicationsTreatment of type 1 diabetes mellitus (insulin dependent, IDDM) and type 2 diabetes mellitus (noninsulin dependent, NIDDM) to improve glycemic control

Dosing: AdultsRefer to Insulin Regular. Insulin aspart is a rapid-acting insulin analog which is normally administered as a premeal component of the insulin regimen. It is normally used along with a long-acting (basal) form of insulin or continuous basal administration of insulin via a SubQ infusion pump.

I.V.: Insulin aspart may be administered I.V. in selected clinical situations to control hyperglycemia. Appropriate medical supervision is required.

SubQ: When used in a meal-related treatment regimen, 50% to 70% of total daily insulin requirement may be provided by insulin aspart as divided premeal boluses and the remainder provided by an intermediate or long-acting insulin or continuous basal administration of insulin via a SubQ infusion pump. Due to rapid onset and short duration, some patients may require more basal insulin to prevent premeal hyperglycemia when using insulin aspart as opposed to regular insulin.

SubQ infusion pump: Initial programming of the pump may be based upon the total daily dose of insulin (TDD) given in the previous regimen with ~50% of the TDD given as divided premeal boluses and ~50% of TDD given as a basal infusion; adjust dose as necessary.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing. Also refer to Insulin Regular.

Dosing: Renal ImpairmentInsulin requirements are reduced due to changes in insulin clearance or metabolism. Close monitoring of blood glucose and adjustment of therapy is required in renal impairment.

Dosing: Hepatic ImpairmentInsulin requirements may be reduced. Close monitoring of blood glucose and adjustment of therapy is required in hepatic impairment.

Administration: I.V.Do not use if solution is viscous or cloudy; use only if clear and colorless. Insulin aspart may be administered I.V. in selected clinical situations to control hyperglycemia. Appropriate medical supervision is required. **Do not administer insulin mixtures intravenously.**

Administration: I.V. DetailBecause of adsorption, the actual amount of insulin aspart being administered via I.V. infusion could be substantially less than the apparent amount. Therefore, adjustment of the insulin aspart I.V. infusion rate should be based on effect and not solely on the apparent insulin aspart dose. The apparent dose may be used as a starting point for determining the subsequent SubQ dosing regimen (Schmeltz, 2006); however, frequent monitoring of blood glucose and adjustment of therapy is required. Infusion requires continuous medical supervision.

Administration: OtherDo not use if solution is viscous or cloudy; use only if clear and colorless.

SubQ: Should be administered immediately before a meal (within 5-10 minutes of the start of a meal). Cold injections should be avoided. SubQ administration is usually made into the thighs, arms, buttocks, or abdomen, with sites rotated. If mixed with human NPH insulin, insulin aspart should be drawn into syringe first. Can be infused SubQ by external insulin pump; however, when used in an external pump, should not be diluted with other insulins. **Do not administer insulin mixtures intravenously.**

SubQ infusion pump: When used in an external SubQ infusion pump, insulin aspart should not be diluted or mixed with other insulins. The reservoir, infusion sets, and infusion set insertion site must be changed at least every 48 hours.

Dietary ConsiderationsDietary modification based on ADA recommendations is a key component of therapy.

StorageInsulin aspart (NovoLog®): Store unopened vials, cartridges, and syringes in refrigerator between 2°C and 8°C (36°F to 46°F); do not use if frozen. If stored at room temperature of <30°C (<86°F), use within 28 days and protect from heat and light. Once punctured (in use), vials may be stored for up to 28 days at temperatures of <30°C (<86°F); do not freeze. Cartridges that are punctured (in use) should be stored at temperatures <30°C (<86°F) and used within 28 days; do not freeze or refrigerate. For insulin pumps, the insulin aspart in the reservoir should be replaced every 48 hours. Discard if exposed to temperatures ≥37°C (98.6°F).

For SubQ administration: Should be stored at temperatures <30°C (<86°F) and used within 28 days; do not freeze or refrigerate.

For I.V. infusion. Stable for 24 hours at room temperature of <30°C (<86°F).

Reconstitution

For SubQ administration: May be diluted with insulin-diluting medium to a concentration of 10 units/mL (U-10) or 50 units/mL (U-50).

For I.V. infusion; May be diluted in NS, D_5W, or $D_{10}W$ with 40 mEq/L potassium chloride at concentrations from 0.05 units/mL to 1 unit/mL using polypropylene infusion bags.

CompatibilityDo not mix with Lantus®. May mix with human NPH insulin; draw NovoLog® into the syringe first and use immediately after mixing. When used in an external pump, should not be diluted with other insulins.

ContraindicationsHypersensitivity to insulin aspart or any component of the formulation; during episodes of hypoglycemia

Warnings/Precautions

Concerns related to adverse effects:

- Hypoglycemia: The most common adverse effect of insulin is hypoglycemia. The timing of hypoglycemia differs among various insulin formulations. Hypoglycemia may result from increased work or exercise without eating; use of long-acting insulin preparations (insulin detemir, insulin glargine) may delay recovery from hypoglycemia. Profound and prolonged episodes of hypoglycemia may result in convulsions, unconsciousness, temporary or permanent brain damage, or even death. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

- Hypokalemia: Insulin (especially I.V. insulin) causes a shift of potassium from the extracellular space to the intracellular space, possibly producing hypokalemia which, if left untreated, may result in respiratory paralysis, ventricular arrhythmia and even death. Use with caution in patients at risk for hypokalemia (eg, loop diuretic use). Monitor serum potassium frequently with I.V. use and supplement potassium when necessary.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment. Dosage requirements may be reduced.

- Renal impairment: Use with caution in patients with renal impairment. Dosage requirements may be reduced.

Dosage form specific issues:

- Product variation: Human insulin differs from animal-source insulin. Any change of insulin should be made cautiously; changing manufacturers, type, and/or method of manufacture may result in the need for a change of dosage.

Other warnings/precautions:

- Appropriate use: The general objective of exogenous insulin therapy is to approximate the physiologic pattern of insulin secretion which is characterized by two distinct phases. Phase 1 insulin secretion suppresses hepatic glucose production and phase 2 insulin secretion occurs in response to carbohydrate ingestion; therefore, exogenous insulin therapy may consist of basal insulin (eg, intermediate- or long-acting insulin or continuous insulin infusion administered via an external SubQ insulin infusion pump) and/or preprandial insulin (eg, short- or rapid-acting insulin) (see Related Information: Insulin Products). Patients with type 1 diabetes do not produce endogenous insulin; therefore, these patients require both basal and preprandial insulin administration. Patients with type 2 diabetes retain some beta-cell function in the early stages of their disease; however, as the disease progresses, phase 1 insulin secretion may become completely impaired and phase 2 insulin secretion becomes delayed and/or inadequate in response to meals. Therefore, patients with type 2 diabetes may be treated with oral antidiabetic agents, basal insulin, and/or preprandial insulin depending on the stage of disease and current glycemic control. Since treatment regimens often consist of multiple agents, dosage adjustments must address the specific phase of insulin release that is primarily contributing to the patient's impaired glycemic control. Treatment and monitoring regimens must be individualized.

  Due to short duration of action, a longer acting insulin or continuous basal administration of insulin via a SubQ infusion pump is needed to maintain adequate glucose control in type 1 diabetes mellitus (insulin dependent, IDDM). In type 2 diabetes mellitus (noninsulin dependent, NIDDM), insulin aspart may be used without a long-acting insulin or continuous basal administration of insulin via a SubQ infusion pump when used in combination with a sulfonylurea. Preprandial administration should be immediately followed by a meal within 5-10 minutes. Insulin aspart may be administered I.V. in selected clinical situations to control hyperglycemia.

- I.V. administration: Insulin aspart may be administered I.V. in selected clinical situations to control hyperglycemia; close medical supervision is required.

- Patient education: Diabetic education and nutritional counseling are essential to maximize the effectiveness of therapy.

Geriatric ConsiderationsHow "tightly" a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well he/she recognizes hypoglycemic or hyperglycemic symptoms, and how to respond to them and any other disease states. Patients who are unable to accurately draw up their dose will need assistance such as prefilled syringes. Initial doses may require considerations for renal function in the elderly with dosing adjusted subsequently based on blood glucose monitoring. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have generally not been observed in animal reproduction studies; therefore, the manufacturer classifies insulin aspart as pregnancy category B. When compared to regular insulin, the use of insulin aspart during pregnancy has not been found to increase the risk of adverse events to the fetus. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range.

Insulin requirements tend to fall during the first trimester of pregnancy and increase in the later trimesters, peaking at 28-32 weeks of gestation. Following delivery, insulin requirements decrease rapidly. Diabetes can be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the fetus and the mother. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy. Insulin aspart has been demonstrated to be as safe and effective as regular human insulin when used during pregnancy and may have advantages over regular insulin during pregnancy.

LactationExcretion in breast milk unknown/compatible

Breast-Feeding ConsiderationsIt is not known if insulin aspart is found in breast milk. Endogenous insulin can be found in breast milk. Plasma glucose concentrations in the mother affect glucose concentrations in breast milk. The gastrointestinal tract destroys insulin when administered orally; therefore, insulin is not expected to be absorbed intact by the breast-feeding infant. All types of insulin are safe for use while breast-feeding. Due to increased calorie expenditure, women with diabetes may require less insulin while nursing.

Pregnancy & Lactation, In-Depth

- Insulin Aspart in Pregnancy & Lactation

Adverse ReactionsRefer to Insulin Regular.

Drug Interactions

Antidiabetic Agents (Thiazolidinedione): Insulin may enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Beta-Blockers: May enhance the hypoglycemic effect of Insulin. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Edetate CALCIUM Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Edetate Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Insulin may enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsRefer to Insulin Regular.

Monitoring ParametersSerum glucose, electrolytes, Hb A_{1c}

Reference RangeRefer to Insulin Regular.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, hypoglycemia) at regular intervals during therapy. Teach patient proper use, including appropriate injection technique and syringe/needle disposal and monitoring requirements (or refer to diabetic educator), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum glucose, electrolytes, Hb A_{1c}

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is used to control diabetes; it is not a cure. It is imperative to follow other components of prescribed treatment (eg, diet and exercise regimen). Take exactly as directed. Do not change dose or discontinue unless advised by prescriber. With insulin aspart (NovoLog®), you must start eating within 5-10 minutes after injection. If you experience hypoglycemic reaction, contact prescriber immediately. Always carry quick source of sugar with you. Monitor glucose levels as directed by prescriber. Report adverse side effects, including chest pain or palpitations; persistent fatigue, confusion, headache; skin rash or redness; numbness of mouth, lips, or tongue; muscle weakness or tremors; vision changes; respiratory difficulty; or nausea, vomiting, or flu-like symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

NovoLog®: 100 units/mL (3 mL) [FlexPen® prefilled syringe or PenFill® prefilled cartridge]; (10 mL) [vial]

Generic AvailableNo

Manufacturer

NovoNordisk

Pricing: U.S. (www.drugstore.com)

Solution (NovoLog)

100 units/mL (10): $102.62

Solution (NovoLog Flexpen)

100 units/mL (15): $205.12

Solution (NovoLOG PenFill)

100 units/mL (15): $188.07

Mechanism of ActionRefer to Insulin Regular. Insulin aspart is a rapid-acting insulin analog.

Pharmacodynamics/Kinetics**Note:** Rate of absorption, onset, and duration of activity may be affected by site of injection, exercise, presence of lipodystrophy, local blood supply, and/or temperature.

Onset of action: 0.2-0.5 hours

Peak effect: 1-3 hours

Duration: 3-5 hours

Protein binding: <10%

Half-life elimination: 81 minutes

Time to peak, plasma: 40-50 minutes

Excretion: Urine

Related Information

- Insulin Products
- Insulin Regular

Dental Health: Effects on Dental TreatmentPatients with type 1 diabetes (insulin dependent) should be appointed for dental treatment in the morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or confusion

Mental Health: Effects on Psychiatric TreatmentMAO inhibitors may enhance the hypoglycemic effects of insulin; TCAs may antagonize the effects of insulin

Index TermsAspart Insulin

References

Schmeltz LR, DeSantis AJ, Schmidt K, et al, "Conversion of Intravenous Insulin Infusions to Subcutaneously Administered Insulin Glargine in Patients With Hyperglycemia," *Endocr Pract*, 2006, 12(6):641-50.[PubMed 17229660]

International Brand NamesInsulina Novorapid (AR, UY); NovoMix 30 (AT, AU, BE, BG, CH, CL, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, ID, IE, IT, MY, NL, NO, PT, RU, SE, TR); Novomix 30 (MX); Novomix 50 (FR); Novomix 70 (FR); NovoMix [30% sol./70% isoph.] (PL); NovoRapid (PL); Novorapid (AT, AU, BE, BG, BR, CH, CN, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HN, ID, IE, IL, IT, NL, NO, NZ, PT, RU, SE, TR); Novorapid Flexpen (PH); NovoRapid FlexPen (PL); NovoRapid NovoLet (PL); NovoRapid Penfill (PL)

Insulin Detemir

Lexi-Drugs Online

English English

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error. ***Due to the number of insulin preparations, it is essential to identify/clarify the type of insulin to be used.***

Note: Insulin detemir is a clear solution, but it is NOT intended for I.V. or I.M. administration.

Cross-contamination may occur if insulin pens are shared among multiple patients. Steps should be taken to prohibit sharing of insulin pens.

Pronunciation(IN soo lin DE te mir)

U.S. Brand NamesLevemir®

Canadian Brand NamesLevemir®

Pharmacologic CategoryInsulin, Intermediate- to Long-Acting

Use: Labeled IndicationsTreatment of type 1 diabetes mellitus (insulin dependent, IDDM) and type 2 diabetes mellitus (noninsulin dependent, NIDDM) to improve glycemic control

Dosing: AdultsAlso refer to Insulin Regular.

Note: Duration is dose-dependent. Dosage must be carefully titrated (adjustment of dose and timing. Adjustment of concomitant antidiabetic treatment (short-acting insulins or oral antidiabetic agents) may be required.

Type 1 or type 2 diabetes: Basal insulin or basal-bolus: May be substituted on a unit-per-unit basis. Adjust dose to achieve glycemic targets.

Insulin-naive patients (type 2 diabetes only): 0.1-0.2 units/kg once daily in the evening or 10 units once or twice daily. Adjust dose to achieve glycemic targets. Note: Canadian labeling recommends 10 units once daily (twice daily dosing is not included).

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥ 6 years: Refer to adult dosing. Note: In Canada, insulin detemir is not approved for use in children.

Dosing: Renal ImpairmentInsulin requirements are reduced due to changes in insulin clearance or metabolism.

Administration: I.M.Not for I.M. administration.

Administration: I.V.Insulin detemir is a clear solution but it is NOT intended for I.V. administration.

Administration: Other Insulin detemir (Levemir®): SubQ administration: Cold injections should be avoided. SubQ administration is usually made into the thighs, arms, buttocks, or abdomen, with sites rotated. Not for infusion pumps. Cannot be diluted or mixed with other insulins.

Once daily: Administer with evening meal or at bedtime.

Twice daily: Administer evening dose with evening meal, at bedtime, or 12 hours following morning dose.

Dietary ConsiderationsDietary modification based on ADA recommendations is a key component of therapy.

StorageInsulin detemir (Levemir®): Store unopened container in refrigerator; do not use if it has been frozen. Once opened (in use), vials may be stored in refrigerator or for up to 42 days at room temperature (below 30°C). Cartridges and prefilled syringes that are in use should be stored at room temperature and used within 42 days; do not refrigerate. Do not store with needle in place. All opened (in-use) vials should be stored away from direct heat and sunlight.

CompatibilityDo not dilute or mix with other insulins.

ContraindicationsHypersensitivity to any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Hypoglycemia: The most common adverse effects of insulin is hypoglycemia. The timing of hypoglycemia differs among various insulin formulations. Hypoglycemia may result from increased work or exercise without eating; use of long-acting insulin preparations (insulin detemir, insulin glargine) may delay recovery from hypoglycemia. Profound and prolonged episodes of hypoglycemia may result in convulsions, unconsciousness, temporary or permanent brain damage or even death. Insulin requirements may be altered during illness, emotional disturbances or other stresses.

- Hypokalemia: Insulin causes a shift of potassium from the extracellular space to the intracellular space, possibly producing hypokalemia which, if left untreated, may result in respiratory paralysis, ventricular arrhythmia and even death. Use with caution in patients at risk for hypokalemia (eg, loop diuretic use). Monitor serum potassium and supplement potassium when necessary.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment. Dosage requirements may be reduced.

- Renal impairment: Use with caution in patients with renal impairment. Dosage requirements may be reduced.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Dosage form specific issues:

- Product variation: Human insulin differs from animal-source insulin. Any change of insulin should be made cautiously; changing manufacturers, type, and/or method of manufacture may result in the need for a change of dosage.

Other warnings/precautions:

- Appropriate use: The general objective of exogenous insulin therapy is to approximate the physiologic pattern of insulin secretion which is characterized by two distinct phases. Phase 1 insulin secretion suppresses hepatic glucose production and phase 2 insulin secretion occurs in response to carbohydrate ingestion; therefore, exogenous insulin therapy may consist of basal insulin (eg, intermediate- or long-acting insulin or continuous insulin infusion administered via an external SubQ insulin infusion pump) and/or preprandial insulin (eg, short- or rapid-acting insulin) (see Related Information: Insulin Products). Patients with type 1 diabetes do not produce endogenous insulin; therefore, these patients require both basal and preprandial insulin administration. Patients with type 2 diabetes retain some beta-cell function in the early stages of their disease; however, as the disease progresses, phase 1 insulin secretion may become completely impaired and phase 2 insulin secretion becomes delayed and/or inadequate in response to meals. Therefore, patients with type 2 diabetes may be treated with oral antidiabetic agents, basal insulin, and/or preprandial insulin depending on the stage of disease and current glycemic control. Since treatment regimens often consist of multiple agents, dosage adjustments must address the specific phase of insulin release that is primarily contributing to the patient's impaired glycemic control. Treatment and monitoring regimens must be individualized.

- Dosage adjustments: Careful adjustment of dosage and timing is required to achieve glycemic targets. Adjustment of other antidiabetic therapy (short-acting or oral antidiabetic agents) may be required. The duration of of action of insulin detemir is dose-dependent and this factor must be considered during dosage adjustment and titration.

- Not intended for I.V. administration: Insulin detemir is a clear solution but it is NOT intended for I.V. or I.M. administration. Regular insulin and/or insulin aspart may be administered I.V. in selected clinical situations to control hyperglycemia; close medical supervision is required.

- Patient education: Diabetic education and nutritional counseling are essential to maximize the effectiveness of therapy.

Geriatric Considerations How “tightly” a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well he/she recognizes hypoglycemic or hyperglycemic symptoms, and how to respond to them and any other disease states. Patients who are unable to accurately draw up their dose will need assistance such as prefilled syringes. Initial doses may require considerations for renal function in the elderly with dosing adjusted subsequently based on blood glucose monitoring. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk Factor C

Pregnancy Considerations Adverse events were observed in animal reproduction studies; therefore, the manufacturer classifies insulin detemir as pregnancy category C. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Insulin requirements tend to fall during the first trimester of pregnancy and increase in the later trimesters, peaking at 28-32 weeks of gestation. Following delivery, insulin requirements decrease rapidly. Diabetes can be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the fetus and the mother. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy. Pregnant women using insulin detemir should be switched to NPH insulin pending additional safety information with this agent.

Lactation Excretion in breast milk unknown/compatible

Breast-Feeding Considerations It is not known if insulin detemir is found in breast milk. Endogenous insulin can be found in breast milk. Plasma glucose concentrations in the mother affect glucose concentrations in breast milk. The gastrointestinal tract destroys insulin when administered orally; therefore, insulin is not expected to be absorbed intact by the breast-feeding infant. All types of insulin are safe for use while breast-feeding. Due to increased calorie expenditure, women with diabetes may require less insulin while nursing.

Pregnancy & Lactation, In-Depth

- Insulin Detemir in Pregnancy & Lactation

Adverse Reactions Refer to Insulin Regular.

Metabolism/Transport Effects Refer to Insulin Regular.

Drug Interactions

Antidiabetic Agents (Thiazolidinedione): Insulin may enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Beta-Blockers: May enhance the hypoglycemic effect of Insulin. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Edetate CALCIUM Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Edetate Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Insulin may enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsRefer to Insulin Regular.

Monitoring ParametersUrine sugar and acetone, serum glucose, electrolytes, Hb A_{1c}, lipid profile

Reference RangeRefer to Insulin Regular.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, hypoglycemia) at regular intervals during therapy. Teach patient proper use, including appropriate injection technique and syringe/needle disposal and monitoring requirements (or refer to diabetic educator), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsUrine sugar and acetone, serum glucose, electrolytes, Hb A_{1c}, lipid profile

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is used to control diabetes; it is not a cure. It is imperative to follow other components of prescribed treatment (eg, diet and exercise regimen). Take exactly as directed. Do not change dose or discontinue unless advised by prescriber. If you experience hypoglycemic reaction, contact prescriber immediately. Always carry quick source of sugar with you. Monitor glucose levels as directed by prescriber. Report adverse side effects, including chest pain or palpitations; persistent fatigue, confusion, headache; skin rash or redness; numbness of mouth, lips, or tongue; muscle weakness or tremors; vision changes; respiratory difficulty; or nausea, vomiting, or flu-like symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Levemir®: 100 units/mL (3 mL) [FlexPen® prefilled syringe]; (10 mL) [vial]

Generic AvailableNo

Manufacturer

NovoNordisk

Pricing: U.S. (www.drugstore.com)

Solution (Levemir)

100 units/mL (10): $95.30

Solution (Levemir Flexpen)

100 units/mL (15): $181.72

Mechanism of ActionRefer to Insulin Regular. Insulin detemir differs from human insulin by a single amino acid omission (threonine at B30) and the addition of a 14-carbon fatty acid chain attached at the B29 position. On injection, the fatty acid chain facilitates self-association between the molecules as well as binding to albumin. The delayed release of insulin from the injection site and albumin binding sites result in more prolonged action and limits variability in the amount of free insulin at steady-state. Insulin detemir has a duration of action which is dose-dependent. The FDA-approved product labeling identifies this product as a long-acting insulin analog; however, at lower dosages (<0.6 units/kg) published data regarding its duration of action is consistent with an intermediate insulin form (12-20 hours). In clinical trials it has been compared primarily with NPH insulin and dosed in a similar manner. In some patients, or at higher dosages, it may have a duration of action up to 24 hours, which is consistent with a long-acting insulin.

Pharmacodynamics/Kinetics**Note:** Rate of absorption, onset, and duration of activity may be affected by site of injection, exercise, presence of lipodystrophy, local blood supply, and/or temperature.

Onset of action: 3-4 hours

Peak effect: 3-14 hours

Duration: Dose dependent: 6-23 hours; **Note:** Duration is dose-dependent. At lower dosages (0.1-0.2 units/kg), mean duration is variable (5.7-12.1 hours). At 0.6 units/kg, the mean duration was 19.9 hours. At high dosages (>0.6 units/kg) the duration is longer and less variable (mean of 22-23 hours).

Bioavailability: 60%

Half-life: 5-7 hours (dose dependent)

Protein binding: >98% (albumin)

Distribution: V_d: 0.1 L/kg

Time to peak, plasma: 6-8 hours

Excretion: Urine

Related Information

- Insulin Products
- Insulin Regular

Pharmacotherapy PearlsThe product labeling identifies this product as a long-acting form of insulin; however, at lower dosages (≤0.6 units/kg) its pharmacodynamic characteristics and dosing are consistent with intermediate insulin forms such as NPH.

Dental Health: Effects on Dental TreatmentPatients with type 1 diabetes (insulin dependent) should be appointed for dental treatment in the morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or confusion

Mental Health: Effects on Psychiatric TreatmentMAO inhibitors may enhance the hypoglycemic effects of insulin; TCAs may antagonize the effects of insulin

Index TermsDetemir Insulin

References

Plank J, Bodenlenz M, Sinner F, et al, “A Double-Blind, Randomized, Dose-Response Study Investigating the Pharmacodynamic and Pharmacokinetic Properties of the Long-Acting Insulin Analog Detemir,” *Diabetes Care*, 2005, 28(5):1107-12.[PubMed 15855574]

International Brand NamesInsulina Levemir (AR); Levemir (AT, AU, BE, BG, BR, CH, CN, CZ, DE, DK, FI, FR, GB, GR, HN, ID, IE, IL, IT, KP, MX, MY, NL, NO, PH, PT, RU, SE, SG, TH, TR, TW, UY)

Insulin Glargine

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Insulin glargine may be confused with insulin glulisine

Lantus® may be confused with Lente®

Lente® may be confused with Lantus®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error. ***Due to the number of insulin preparations, it is essential to identify/clarify the type of insulin to be used.***

Pronunciation(IN soo lin GLAR jeen)

U.S. Brand NamesLantus®

Canadian Brand NamesLantus®; Lantus® OptiSet®

Pharmacologic CategoryInsulin, Long-Acting

Use: Labeled IndicationsTreatment of type 1 diabetes mellitus (insulin dependent, IDDM) and type 2 diabetes mellitus (noninsulin dependent, NIDDM) requiring basal (long-acting) insulin to improve glycemic control

Dosing: AdultsSubQ:

Type 1 diabetes: As a basal component of combination insulin regimen, normally 50% to 75% of daily insulin requirement is administered as a long-acting form. More rapid acting forms are usually used in association with meals. Refer to Insulin Regular.

Type 2 diabetes:

Patient not already on insulin: 10 units once daily, adjusted according to patient response (range in clinical study: 2-100 units/day)

Patient already receiving insulin: In clinical studies, when changing to insulin glargine from once-daily NPH or Ultralente® insulin, the initial dose was not changed; when changing from twice-daily NPH to once-daily insulin glargine, the total daily dose was reduced by 20% and adjusted according to patient response

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Type 1 or type 2 diabetes:** Children ≥6 years: Refer to adult dosing.

Dosing: Renal ImpairmentInsulin requirements may be reduced due to changes in insulin clearance or metabolism.

Dosing: Hepatic ImpairmentInsulin requirements may be reduced due to changes in glucose production and insulin metabolism.

Administration: OtherInsulin glargine (Lantus®): SubQ administration: Should be administered once daily, at any time of day, but should be administered at the same time each day. Cold injections should be avoided. SubQ administration is usually made into the thighs, arms, buttocks, or abdomen, with sites rotated. Cannot be diluted or mixed with any other insulin or solution. Solution should be clear and colorless with no visible particles; inspect solution prior to administration.

StorageInsulin glargine (Lantus®): Store unopened vials, cartridges, and disposable insulin devices in refrigerator; do not use if it has been frozen. If not refrigerated, use within 28 days and protect from heat and light. Once opened (in use), vials may be stored in refrigerator or for up to 28 days at room temperature. Opened cartridge systems (OptiClik®) and disposable insulin devices (SoloStar®) (in use) should be stored at room temperature and used within 28 days; do not refrigerate.

CompatibilityDo not dilute or mix with any other insulin or solution.

ContraindicationsHypersensitivity to insulin glargine or any component of the formulation

Allergy Considerations

- Insulin Preparations Allergy

Warnings/Precautions

Concerns related to adverse effects:

• Hypoglycemia: The most common adverse effect of insulin is hypoglycemia. The timing of hypoglycemia differs among various insulin formulations. Hypoglycemia may result from increased work or exercise without eating; use of long-acting insulin preparations (insulin detemir, insulin glargine) may delay recovery from hypoglycemia. Profound and prolonged episodes of hypoglycemia may result in convulsions, unconsciousness, temporary or permanent brain damage, or even death. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

• Hypokalemia: Insulin causes a shift of potassium from the extracellular space to the intracellular space, possibly producing hypokalemia which, if left untreated, may result in respiratory paralysis, ventricular arrhythmia and even death. Use with caution in patients at risk for hypokalemia (eg, loop diuretic use). Monitor serum potassium and supplement potassium when necessary.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment. Dosage requirements may be reduced.

- Renal impairment: Use with caution in patients with renal impairment. Dosage requirements may be reduced.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Dosage form specific issues:

- Product variation: Human insulin differs from animal-source insulin. Any change of insulin should be made cautiously; changing manufacturers, type, and/or method of manufacture may result in the need for a change of dosage.

Other warnings/precautions:

- Appropriate use: The general objective of exogenous insulin therapy is to approximate the physiologic pattern of insulin secretion which is characterized by two distinct phases. Phase 1 insulin secretion suppresses hepatic glucose production and phase 2 insulin secretion occurs in response to carbohydrate ingestion; therefore, exogenous insulin therapy may consist of basal insulin (eg, intermediate- or long-acting insulin or continuous insulin infusion administered via an external SubQ insulin infusion pump) and/or preprandial insulin (eg, short- or rapid-acting insulin) (see Related Information: Insulin Products). Patients with type 1 diabetes do not produce endogenous insulin; therefore, these patients require both basal and preprandial insulin administration. Patients with type 2 diabetes retain some beta-cell function in the early stages of their disease; however, as the disease progresses, phase 1 insulin secretion may become completely impaired and phase 2 insulin secretion becomes delayed and/or inadequate in response to meals. Therefore, patients with type 2 diabetes may be treated with oral antidiabetic agents, basal insulin, and/or preprandial insulin depending on the stage of disease and current glycemic control. Since treatment regimens often consist of multiple agents, dosage adjustments must address the specific phase of insulin release that is primarily contributing to the patient’s impaired glycemic control. Treatment and monitoring regimens must be individualized.

- Not intended for I.V. administration: Insulin glargine is a clear solution, but it is **NOT** intended for I.V. or I.M. administration. Regular insulin and/or insulin aspart may be administered I.V. in selected clinical situations to control hyperglycemia; close medical supervision is required.

- Patient education: Diabetic education and nutritional counseling are essential to maximize the effectiveness of therapy.

Geriatric ConsiderationsIntensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been shown in some animal studies; therefore, the manufacturer classifies insulin glargine as pregnancy category C. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when Hb A_{1c} is above the normal range.

Insulin requirements tend to fall during the first trimester of pregnancy and increase in the later trimesters, peaking at 28-32 weeks of gestation. Following delivery, insulin requirements decrease rapidly. Diabetes can be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the fetus and the mother. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy. Pregnancy outcome information following the use of insulin glargine is available from case reports and small studies. Current reports indicate that insulin glargine is effective when used during pregnancy and may be an option for pregnant women with significantly uncontrolled diabetes; however, pregnant women using insulin glargine should be switched to NPH insulin pending additional safety information with this agent.

LactationExcretion in breast milk unknown/compatible

Breast-Feeding ConsiderationsIt is not known if significant amounts of insulin glargine are found in breast milk. Endogenous insulin can be found in breast milk. Plasma glucose concentrations in the mother affect glucose concentrations in breast milk. The gastrointestinal tract destroys insulin when administered orally; therefore, insulin is not expected to be absorbed intact by the breast-feeding infant. All types of insulin are safe for use while breast-feeding. Due to increased calorie expenditure, women with diabetes may require less insulin while nursing.

Pregnancy & Lactation, In-Depth

- Insulin Glargine in Pregnancy & Lactation

Adverse ReactionsRefer to Insulin Regular.

Metabolism/Transport EffectsRefer to Insulin Regular.

Drug Interactions

Antidiabetic Agents (Thiazolidinedione): Insulin may enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Beta-Blockers: May enhance the hypoglycemic effect of Insulin. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Edetate CALCIUM Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Edetate Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Insulin may enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsRefer to Insulin Regular.

Monitoring ParametersUrine sugar and acetone, serum glucose, electrolytes, Hb A_{1c}

Reference RangeRefer to Insulin Regular.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, hypoglycemia) at regular intervals during therapy. Teach patient proper use, including appropriate injection technique and syringe/needle disposal and monitoring requirements (or refer to diabetic educator), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsUrine sugar and acetone, serum glucose, electrolytes, Hb A_{1c}

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is used to control diabetes; it is not a cure. It is imperative to follow other components of prescribed treatment (eg, diet and exercise regimen). Take exactly as directed. Do not change dose or discontinue unless advised by prescriber. If you experience hypoglycemic reaction, contact prescriber immediately. Always carry quick source of sugar with you. Monitor glucose levels as directed by prescriber. Report adverse side effects, including chest pain or palpitations; persistent fatigue, confusion, headache; skin rash or redness; numbness of mouth, lips, or tongue; muscle weakness or tremors; vision changes; respiratory difficulty; or nausea, vomiting, or flu-like symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Lantus®: 100 units/mL (3 mL) [OptiClik® prefilled cartridge or SoloStar® disposable insulin device]; (10 mL) [vial]

Generic AvailableNo

Manufacturer

Aventis Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Solution (Lantus)

100 units/mL (10): $103.59

Solution (Lantus for OptiClik)

100 units/mL (15): $190.75

Solution (Lantus SoloStar)

100 units/mL (15): $187.61

Mechanism of ActionRefer to Insulin Regular. Insulin glargine is a long-acting insulin analog.

Pharmacodynamics/Kinetics**Note:** Rate of absorption, onset, and duration of activity may be affected by site of injection, exercise, presence of lipodystrophy, local blood supply, and/or temperature.

Onset of action: 3-4 hours

Peak effect: No pronounced peak

Duration: Generally 24 hours or longer; reported range: 10.8 to >24 hours (up to 32 hours documented in some studies)

Absorption: Slow; upon injection into the subcutaneous tissue, microprecipitates form which allow small amounts of insulin glargine to release over time

Metabolism: Partially metabolized in the skin to form two active metabolites

Time to peak, plasma: No pronounced peak

Excretion: Urine

Related Information

- Insulin Products
- Insulin Regular

Pharmacotherapy PearlsThe duration of action of insulin glargine is generally 24 hours or longer with a relatively flat action profile throughout this interval. Many pharmacokinetic and pharmacodynamic studies were terminated at 24 hours despite the fact that insulin glargine continued to exhibit hypoglycemic activity beyond 24 hours; therefore, it is difficult to determine the absolute duration of action.

Clinicians should be aware that, in rare cases, patients may exhibit hypoglycemic activity beyond 24 hours and that accumulation of insulin glargine is possible. Adequate monitoring and subsequent dosage adjustments should be made in patients who are requiring less insulin to maintain euglycemia after several days of therapy.

On the other hand, insulin glargine has a reported duration of action that ranges from 10.8 to >24 hours. On rare occasions, patients may require twice-daily injections of insulin glargine to deliver adequate basal insulin coverage over 24 hours. Some clinicians may also switch to twice-daily dosing in patients who require >100 units of insulin glargine per day to allow for complete absorption. Dosing insulin glargine 3 times daily is not recommended.

Dental Health: Effects on Dental TreatmentPatients with type 1 diabetes (insulin dependent) should be appointed for dental treatment in the morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or confusion

Mental Health: Effects on Psychiatric TreatmentMAO inhibitors may enhance the hypoglycemic effects of insulin; TCAs may antagonize the effects of insulin

Index TermsGlargine Insulin

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International Brand NamesLantus (AR, AT, AU, BB, BE, BG, BM, BR, BS, BZ, CH, CL, CN, CR, CZ, DE, DK, DO, EC, FI, FR, GB, GR, GT, GY, HN, IE, IL, IN, IT, JM, KP, MX, NI, NL, NO, PA, PE, PK, PL, PT, PY, RU, SE, SR, SV, TR, TT, UY, VE); Optisulin (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Insulin Glulisine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Insulin glulisine may be confused with insulin glargine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error. ***Due to the number of insulin preparations, it is essential to identify/clarify the type of insulin to be used.***

Pronunciation(IN soo lin gloo LIS een)
U.S. Brand NamesApidra®
Canadian Brand NamesApidra®
Pharmacologic CategoryInsulin, Rapid-Acting
Use: Labeled IndicationsTreatment of type 1 diabetes mellitus (insulin dependent, IDDM) and type 2 diabetes mellitus (noninsulin dependent, NIDDM) to improve glycemic control
Dosing: AdultsRefer to Insulin Regular. Insulin glulisine is equipotent to insulin regular, but has a more rapid onset. Insulin glulisine is normally administered as a premeal component of the insulin regimen. It is normally used along with a long-acting (basal) form of insulin or continuous basal administration of insulin via a SubQ infusion pump.

SubQ: When used in a meal-related treatment regimen, 50% to 70% of total daily insulin requirement may be provided by insulin glulisine (in divided doses) and the remainder provided by an intermediate or long-acting insulin. Insulin glulisine may also be administered by external subcutaneous infusion pumps.

I.V.: Under close medical supervision, insulin glulisine may be administered by infusion.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to Insulin Regular. Insulin glulisine is equipotent to insulin regular, but has a more rapid onset.
Dosing: Renal ImpairmentInsulin requirements are reduced due to changes in insulin clearance or metabolism. Close monitoring of blood glucose and adjustment of therapy is required in renal impairment.
Administration: I.V.

Insulin glulisine may be administered by the I.V. route only in a carefully controlled clinical setting with medical supervision and close monitoring of blood glucose as well as serum potassium.

Administration: I.V. DetailA dedicated infusion line should be used. **Do not administer insulin mixtures intravenously.** The recommended infusion concentration is 0.05-1 unit/mL in NS using PVC bags.
Administration: OtherInsulin glulisine (Apidra®): SubQ administration: Cold injections should be avoided. SubQ administration is usually made into the thighs, arms, buttocks, or abdomen, with sites rotated. Insulin glulisine should be administered within 15 minutes before or within 20 minutes after start of a meal. Can be infused SubQ into the abdominal wall by external insulin pump; however, when used in an external pump, should not be diluted or mixed with other insulins. Rotate infusion site.
StorageInsulin glulisine (Apidra®): Store unopened vials in refrigerator at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Once opened, may store under refrigeration or at room temperature ≤25°C (77°F); use within 28 days. Stable in infusion pump for up to 48 hours. Discard if exposed to temperatures >37°C (98.6°F). Open, in-use cartridges inserted in the Opti-Clik® system should not be refrigerated; keep at room temperature ≤25°C (77°F); use within 28 days.

For I.V. infusion in a controlled clinical setting: Store at room temperature. Stable for 48 hours.

ReconstitutionFor I.V. infusion in a controlled clinical setting: The recommended infusion concentration is 0.05-1 unit/mL in NS using PVC bags.
Compatibility

For SubQ administration by injection (not via pump), insulin glulisine (Apidra®) may be mixed with NPH insulin; Apidra® should be drawn into the syringe first. When used in an external pump, insulin glulisine should not be diluted or mixed with other insulins.

For I.V. infusion, may be mixed with NS.

ContraindicationsHypersensitivity to insulin glulisine or any component of the formulation; during episodes of hypoglycemia
Allergy Considerations

- Insulin Preparations Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypoglycemia: The most common adverse effect of insulin is hypoglycemia. The timing of hypoglycemia differs among various insulin formulations. Hypoglycemia may result from increased work or exercise without eating; use of long-acting insulin preparations (insulin detemir, insulin glargine) may delay recovery from hypoglycemia. Profound and prolonged episodes of hypoglycemia may result in convulsions, unconsciousness, temporary or permanent brain damage or even death. Insulin requirements may be altered during illness, emotional disturbances or other stresses.

- Hypokalemia: Insulin (especially I.V. insulin) causes a shift of potassium from the extracellular space to the intracellular space, possibly producing hypokalemia which, if left untreated, may result in respiratory paralysis, ventricular arrhythmia and even death. Use with caution in patients at risk for hypokalemia (eg, loop diuretic use). Monitor serum potassium frequently with I.V. use and supplement potassium when necessary.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment. Dosage requirements may be reduced.

- Renal impairment: Use with caution in patients with renal impairment. Dosage requirements may be reduced.

Dosage form specific issues:

- Product variation: Human insulin differs from animal-source insulin. Any change of insulin should be made cautiously; changing manufacturers, type, and/or method of manufacture may result in the need for a change of dosage.

Other warnings/precautions:

- Appropriate use: The general objective of exogenous insulin therapy is to approximate the physiologic pattern of insulin secretion which is characterized by two distinct phases. Phase 1 insulin secretion suppresses hepatic glucose production and phase 2 insulin secretion occurs in response to carbohydrate ingestion; therefore, exogenous insulin therapy may consist of basal insulin (eg, intermediate- or long-acting insulin or continuous insulin infusion administered via an external SubQ insulin infusion pump) and/or preprandial insulin (eg, short- or rapid-acting insulin) (see Related Information: Insulin Products). Patients with type 1 diabetes do not produce endogenous insulin; therefore, these patients require both basal and preprandial insulin administration. Patients with type 2 diabetes retain some beta-cell function in the early stages of their disease; however, as the disease progresses, phase 1 insulin secretion may become completely impaired and phase 2 insulin secretion becomes delayed and/or inadequate in response to meals. Therefore, patients with type 2 diabetes may be treated with oral antidiabetic agents, basal insulin, and/or preprandial insulin depending on the stage of disease and current glycemic control. Since treatment regimens often consist of multiple agents, dosage adjustments must address the specific phase of insulin release that is primarily contributing to the patient's impaired glycemic control. Treatment and monitoring regimens must be individualized.

  Due to short duration of action, a longer acting insulin or continuous basal administration of insulin via a SubQ infusion pump is needed to maintain adequate glucose control in type 1 diabetes mellitus (insulin dependent, IDDM). In type 2 diabetes mellitus (noninsulin dependent, NIDDM), insulin glulisine may be used without a long-acting insulin or continuous basal administration of insulin via a SubQ infusion pump when used in combination with a sulfonylurea. Preprandial administration should be immediately followed by a meal within 5-10 minutes.

- I.V. administration: May be administered by the I.V. route only in a carefully controlled clinical setting with medical supervision and close monitoring of blood glucose as well as serum potassium.

- Patient education: Diabetic education and nutritional counseling are essential to maximize the effectiveness of therapy.

Geriatric ConsiderationsHow "tightly" a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well he/she recognizes hypoglycemic or hyperglycemic symptoms, and how to respond to them and any other disease states. Patients who are unable to accurately draw up their dose will need assistance such as prefilled syringes. Initial doses may require considerations for renal function in the elderly with dosing adjusted subsequently based on blood glucose monitoring. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events were observed in some animal reproduction studies; therefore, the manufacturer classifies insulin glulisine as pregnancy category C. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range.

Insulin requirements tend to fall during the first trimester of pregnancy and increase in the later trimesters, peaking at 28-32 weeks of gestation. Following delivery, insulin requirements decrease rapidly. Diabetes can be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the fetus and mother. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy. Due to lack of clinical studies with insulin glulisine in pregnant women, the manufacturer recommends use during pregnancy only if the potential benefit to the mother justifies any potential risk to the fetus.

LactationExcretion in breast milk unknown/compatible

Breast-Feeding ConsiderationsIt is not known if insulin glulisine is found in breast milk. Endogenous insulin can be found in breast milk. Plasma glucose concentrations in the mother affect glucose concentrations in breast milk. The gastrointestinal tract destroys insulin when administered orally; therefore, insulin is not expected to be absorbed intact by the breast-feeding infant. All types of insulin are safe for use while breast-feeding. Due to increased calorie expenditure, women with diabetes may require less insulin while nursing.

Pregnancy & Lactation, In-Depth

- Insulin Glulisine in Pregnancy & Lactation

Adverse ReactionsRefer to Insulin Regular.

Drug Interactions

Antidiabetic Agents (Thiazolidinedione): Insulin may enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Beta-Blockers: May enhance the hypoglycemic effect of Insulin. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Edetate CALCIUM Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Edetate Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Insulin may enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsRefer to Insulin Regular.

Monitoring ParametersUrine sugar and acetone, serum glucose, electrolytes, Hb A_{1c}, lipid profile

Blood glucose and serum potassium should be closely monitored during I.V. infusion.

Reference RangeRefer to Insulin Regular.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, hypoglycemia) at regular intervals during therapy. Teach patient proper use, including appropriate injection technique and syringe/needle disposal and monitoring requirements (or refer to diabetic educator), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsUrine sugar and acetone, serum glucose, electrolytes, Hb A_{1c}, lipid profile

Blood glucose and serum potassium should be closely monitored during I.V. infusion.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is used to control diabetes; it is not a cure. It is imperative to follow other components of prescribed treatment (eg, diet and exercise regimen). Take exactly as directed. Do not change dose or discontinue unless advised by prescriber. Insulin glulisine (Apidra®) should be administered within 15 minutes before or within 20 minutes after start of a meal. If you experience hypoglycemic reaction, contact prescriber immediately. Always carry quick source of sugar with you. Monitor glucose levels as directed by prescriber. Report adverse side effects, including chest pain or palpitations; persistent fatigue, confusion, headache; skin rash or redness; numbness of mouth, lips, or tongue; muscle weakness or tremors; vision changes; respiratory difficulty; or nausea, vomiting, or flu-like symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Apidra®: 100 units/mL (3 mL [cartridge], 10 mL [vial])

Generic AvailableNo

ManufacturerSanofi-Aventis Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Solution (Apidra)

100 units/mL (10): $101.88

Solution (Apidra OptiClik)

100 units/mL (15): $195.82

Mechanism of ActionRefer to Insulin Regular. Insulin glulisine is a rapid-acting insulin analog. Insulin glulisine differs from human insulin by the replacement of two amino acids on the B-chain (positions B3 and B29).

Pharmacodynamics/Kinetics**Note:** Rate of absorption, onset, and duration of activity may be affected by site of injection, exercise, presence of lipodystrophy, local blood supply, and/or temperature.

Onset of action: 0.2-0.5 hours

Peak effect: 1.6-2.8 hours

Duration: 3-4 hours

Distribution: I.V.: 13 L

Bioavailability: SubQ: ~70%

Half-life

I.V.: 13 minutes

SubQ: 42 minutes

Time to peak, plasma: 0.6-2 hours

Excretion: Urine

Related Information

- Insulin Products
- Insulin Regular

Dental Health: Effects on Dental Treatment Patients with type 1 diabetes (insulin dependent) should be appointed for dental treatment in the morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause drowsiness or confusion

Mental Health: Effects on Psychiatric TreatmentMAO inhibitors may enhance the hypoglycemic effects of insulin; TCAs may antagonize the effects of insulin

Index Terms Glulisine Insulin

International Brand Names Apidra (AR, AT, BE, BG, CH, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HN, ID, IE, IL, IT, KP, NL, NO, PT, RU, SE, TR, UY)

Insulin Lispro Protamine and Insulin Lispro

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

> Humalog® Mix 75/25™ may be confused with Humulin® 70/30.

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error. ***Due to the number of insulin preparations, it is essential to identify/clarify the type of insulin to be used.***

Cross-contamination may occur if insulin pens are shared among multiple patients. Steps should be taken to prohibit sharing of insulin pens.

Pronunciation(IN soo lin LYE sproe PROE ta meen & IN soo lin LYE sproe)
U.S. Brand NamesHumalog® Mix 50/50™; Humalog® Mix 75/25™
Canadian Brand NamesHumalog® Mix 25
Pharmacologic CategoryInsulin, Combination
Use: Labeled IndicationsTreatment of type 1 diabetes mellitus (insulin dependent, IDDM) and type 2 diabetes mellitus (noninsulin dependent, NIDDM) to improve glycemic control
Dosing: AdultsRefer to Insulin Regular. Fixed ratio insulins (such as insulin lispro protamine and insulin lispro) are normally administered in 2 daily doses.
Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentInsulin requirements are reduced due to changes in insulin clearance or metabolism.
Administration: OtherInsulin lispro protamine and insulin lispro (Humalog® Mix 75/25™): SubQ administration only. Should be administered within 15 minutes before or after a meal. Normally administered twice daily (breakfast and supper). Cold injections should be avoided. SubQ administration is usually made into the thighs, arms, buttocks, or abdomen, with sites rotated. Resuspend immediately prior to use. Gently roll vial or pen in the palms of the hands to resuspend before using. Do not mix or dilute with other insulins.
Dietary ConsiderationsDietary modification based on ADA recommendations is a key component of therapy.
StorageInsulin lispro protamine and insulin lispro (Humalog® Mix): Store unopened container in refrigerator; do not use if it has been frozen. Once opened (in use), vials may be stored in refrigerator or for up to 28 days at room temperature. Pens should be stored at room temperature and used within 10 days. Do not expose to temperatures >37°C (98.6°F).
CompatibilityDo not mix or dilute with other insulins.
ContraindicationsHypersensitivity to any component of the formulation; during episodes of hypoglycemia
Allergy Considerations

- Insulin Preparations Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypoglycemia: The most common adverse effects of insulin is hypoglycemia. The timing of hypoglycemia differs among various insulin formulations. Hypoglycemia may result from increased work or exercise without eating; use of long-acting insulin preparations (insulin detemir, insulin glargine) may delay recovery from hypoglycemia. Profound and prolonged episodes of hypoglycemia may result in convulsions, unconsciousness, temporary or permanent brain damage, or even death. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

- Hypokalemia: Insulin causes a shift of potassium from the extracellular space to the intracellular space, possibly producing hypokalemia which, if left untreated, may result in respiratory paralysis, ventricular arrhythmia and even death. Use with caution in patients at risk for hypokalemia (eg, loop diuretic use). Monitor serum potassium and supplement potassium when necessary.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment. Dosage requirements may be reduced.

- Renal impairment: Use with caution in patients with renal impairment. Dosage requirements may be reduced.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Product variation: Human insulin differs from animal-source insulin. Any change of insulin should be made cautiously; changing manufacturers, type, and/or method of manufacture may result in the need for a change of dosage.

Other warnings/precautions:

- Appropriate use: The general objective of exogenous insulin therapy is to approximate the physiologic pattern of insulin secretion which is characterized by two distinct phases. Phase 1 insulin secretion suppresses hepatic glucose production and phase 2 insulin secretion occurs in response to carbohydrate ingestion; therefore, exogenous insulin therapy may consist of basal insulin (eg, intermediate- or long-acting insulin or continuous insulin infusion administered via an external SubQ insulin infusion pump) and/or preprandial insulin (eg, short- or rapid-acting insulin) (see Related Information: Insulin Products). Patients with type 1 diabetes do not produce endogenous insulin; therefore, these patients require both basal and preprandial insulin administration. Patients with type 2 diabetes retain some beta-cell function in the early stages of their disease; however, as the disease progresses, phase 1 insulin secretion may become completely impaired and phase 2 insulin secretion becomes delayed and/or inadequate in response to meals. Therefore, patients with type 2 diabetes may be treated with oral antidiabetic agents, basal insulin, and/or preprandial insulin depending on the stage of disease and current glycemic control. Since treatment regimens often consist of multiple agents, dosage adjustments must address the specific phase of insulin release that is primarily contributing to the patient's impaired glycemic control. Treatment and monitoring regimens must be individualized.

- Patient education: Diabetic education and nutritional counseling are essential to maximize the effectiveness of therapy.

Geriatric ConsiderationsIntensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorB

Pregnancy ConsiderationsSee Insulin Lispro monograph.

LactationSee Insulin Lispro monograph.

Breast-Feeding ConsiderationsSee Insulin Lispro monograph.

Pregnancy & Lactation, In-Depth

- Insulin Lispro in Pregnancy & Lactation

Adverse ReactionsRefer to Insulin Regular.

Drug Interactions

Antidiabetic Agents (Thiazolidinedione): Insulin may enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Beta-Blockers: May enhance the hypoglycemic effect of Insulin. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Edetate CALCIUM Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Edetate Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Insulin may enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsRefer to Insulin Regular.

Reference RangeRefer to Insulin Regular.

Nursing: Physical Assessment/MonitoringSee individual agent for Insulin Lispro.

Patient EducationSee individual agent for Insulin Lispro.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension:

Humalog® Mix 50/50™: Insulin lispro protamine suspension 50% [intermediate acting] and insulin lispro solution 50% [rapid acting]: 100 units/mL (3 mL) [disposable pen]

Humalog® Mix 75/25™: Insulin lispro protamine suspension 75% [intermediate acting] and insulin lispro solution 25% [rapid acting]: 100 units/mL (3 mL) [disposable pen]; (10 mL) [vial]

Generic AvailableNo

ManufacturerEli Lilly & Co

Pricing: U.S. (www.drugstore.com)

Suspension (Humalog Mix 75/25)

75-25% (10): $102.74

Suspension (Humalog Mix 75/25 Pen)

75-25% (15): $173.98

Mechanism of ActionRefer to Insulin Regular. Insulin lispro protamine and insulin lispro is a combination product with a rapid onset, and a duration of action which is similar to intermediate-acting insulin products.

Pharmacodynamics/Kinetics**Note:** Rate of absorption, onset, and duration of activity may be affected by site of injection, exercise, presence of lipodystrophy, local blood supply, and/or temperature.

Onset of action: 0.2-0.5 hours

Peak effect: 2-4 hours

Duration: 18-24 hours

Time to peak, plasma: 0.5-4 hours

Excretion: Urine

Related Information

- Insulin Lispro
- Insulin Products
- Insulin Regular

Pharmacotherapy PearlsRefer to Insulin Regular for additional details on adverse effects, drug interactions, warnings, and dosing of insulin products.

Dental Health: Effects on Dental TreatmentPatients with type 1 diabetes (insulin-dependent) should be appointed for dental treatment in the morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or confusion

Mental Health: Effects on Psychiatric TreatmentMAO inhibitors may enhance the hypoglycemic effects of insulin; TCAs may antagonize the effects of insulin

Index TermsInsulin Lispro and Insulin Lispro Protamine

International Brand NamesHumalog Mix (AT, DE, DK, EE, ES, FR, GB, IL, SE, TW); Humalog Mix 25 (BB, BM, BR, BS, BZ, CN, CO, CR, DO, GT, GY, HK, HN, ID, JM, KP, MX, MY, NI, NL, NZ, PA, PE, PH, SR, SV, TT, VE); Humalog Mix 50 (AU); Humalog NPL (IL)

Insulin Lispro

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Humalog® may be confused with Humulin®, Humira®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error. ***Due to the number of insulin preparations, it is essential to identify/clarify the type of insulin to be used.***

Cross-contamination may occur if insulin pens are shared among multiple patients. Steps should be taken to prohibit sharing of insulin pens.

Pronunciation(IN soo lin LYE sproe)

U.S. Brand NamesHumalog®

Canadian Brand NamesHumalog®

Pharmacologic CategoryInsulin, Rapid-Acting

Use: Labeled IndicationsTreatment of type 1 diabetes mellitus (insulin dependent, IDDM) and type 2 diabetes mellitus (noninsulin dependent, NIDDM) to improve glycemic control

Dosing: AdultsRefer to Insulin Regular. Insulin lispro is equipotent to insulin regular, but has a more rapid onset.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to Insulin Regular. Insulin lispro is equipotent to insulin regular, but has a more rapid onset.

Dosing: Renal ImpairmentInsulin requirements are reduced due to changes in insulin clearance or metabolism. Close monitoring of blood glucose and adjustment of therapy is required in renal impairment.

Administration: OtherInsulin lispro (Humalog®): SubQ administration: May be administered within 15 minutes before or immediately after a meal. Cold injections should be avoided. SubQ administration is usually made into the thighs, arms, buttocks, or abdomen, with sites rotated. Can be infused SubQ by external insulin pump; however, when used in an external pump, should not be diluted or mixed with other insulins.

Note: May be mixed in the same syringe as Humulin® N or Humulin® U, but Humalog® should be drawn into the syringe first.

Dietary ConsiderationsDietary modification based on ADA recommendations is a key component of therapy.

StorageInsulin lispro (Humalog®): Store unopened container in refrigerator; do not use if it has been frozen. If not refrigerated, use within 28 days and protect from heat and light. Once opened (in use), vials may be stored in refrigerator or for up to 28 days at room temperature. Cartridges/pens should be stored at room temperature and used within 28 days. When used in an external pump, replace insulin in reservoir within 48 hours and cartridges within 7 days; do not expose to temperatures >37°C (98.6°F). If diluted with sterile diluent (available from manufacturer), 1:10 dilutions are stable for 28 days stored at 5°C (41°F) or 14 days stored at 30°C (86°F).

CompatibilityA sterile diluent is available from the manufacturer for preparing dilutions of Humalog®.

Insulin lispro (Humalog®): May be mixed in the same syringe as Humulin® N or Humulin® U, but Humalog® should be drawn into the syringe first. When used in an external pump, should not be diluted or mixed with other insulins.

ContraindicationsHypersensitivity to any component of the formulation

Allergy Considerations

- Insulin Preparations Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypoglycemia: The most common adverse effects of insulin is hypoglycemia. The timing of hypoglycemia differs among various insulin formulations. Hypoglycemia may result from increased work or exercise without eating; use of long-acting insulin preparations (insulin detemir, insulin glargine) may delay recovery from hypoglycemia. Profound and prolonged episodes of hypoglycemia may result in convulsions, unconsciousness, temporary or permanent brain damage or even death. Insulin requirements may be altered during illness, emotional disturbances or other stresses.

- Hypokalemia: Insulin (especially I.V. insulin) causes a shift of potassium from the extracellular space to the intracellular space, possibly producing hypokalemia which, if left untreated, may result in respiratory paralysis, ventricular arrhythmia and even death. Use with caution in patients at risk for hypokalemia (eg, loop diuretic use). Monitor serum potassium frequently with I.V. use and supplement potassium when necessary.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment. Dosage requirements may be reduced.

- Renal impairment: Use with caution in patients with renal impairment. Dosage requirements may be reduced.

Dosage form specific issues:

- Product variation: Human insulin differs from animal-source insulin. Any change of insulin should be made cautiously; changing manufacturers, type, and/or method of manufacture may result in the need for a change of dosage.

Other warnings/precautions:

- Appropriate use: The general objective of exogenous insulin therapy is to approximate the physiologic pattern of insulin secretion which is characterized by two distinct phases. Phase 1 insulin secretion suppresses hepatic glucose production and phase 2 insulin secretion occurs in response to carbohydrate ingestion; therefore, exogenous insulin therapy may consist of basal insulin (eg, intermediate- or long-acting insulin or continuous insulin infusion administered via an external SubQ insulin infusion pump) and/or preprandial insulin (eg, short- or rapid-acting insulin) (see Related Information: Insulin Products). Patients with type 1 diabetes do not produce endogenous insulin; therefore, these patients require both basal and preprandial insulin administration. Patients with type 2 diabetes retain some beta-cell function in the early stages of their disease; however, as the disease progresses, phase 1 insulin secretion may become completely impaired and phase 2 insulin secretion becomes delayed and/or inadequate in response to meals. Therefore, patients with type 2 diabetes may be treated with oral antidiabetic agents, basal insulin, and/or preprandial insulin depending on the stage of disease and current glycemic control. Since treatment regimens often consist of multiple agents, dosage adjustments must address the specific phase of insulin release that is primarily contributing to the patient's impaired glycemic control. Treatment and monitoring regimens must be individualized.

  Due to short duration of action, a longer acting insulin or continuous basal administration of insulin via a SubQ infusion pump is needed to maintain adequate glucose control in type 1 diabetes mellitus (insulin dependent, IDDM). In type 2 diabetes mellitus (noninsulin dependent, NIDDM), insulin lispro may be used without a long-acting insulin or continuous basal administration of insulin via a SubQ infusion pump when used in combination with a sulfonylurea. Preprandial administration should be immediately followed by a meal within 5-10 minutes.

- I.V. administration: May be administered via I.V. route only in a carefully controlled clinical setting with medical supervision and close monitoring of blood glucose as well as serum potassium.

- Patient education: Diabetic education and nutritional counseling are essential to maximize the effectiveness of therapy.

Geriatric ConsiderationsHow “tightly” a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well he/she recognizes hypoglycemic or hyperglycemic symptoms, and how to respond to them and any other disease states. Patients who are unable to accurately draw up their dose will need assistance such as prefilled syringes. Initial doses may require considerations for renal function in the elderly with dosing adjusted subsequently based on blood glucose monitoring. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal reproduction studies; therefore, the manufacturer classifies insulin lispro as pregnancy category B. Insulin lispro has not been shown to cross the placenta at standard clinical doses. Although congenital anomalies have been noted in case reports, when compared to regular insulin, insulin lispro has not been found to increase the risk of adverse events to the fetus in larger studies. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when Hb A_{1c} is above the normal range.

Insulin requirements tend to fall during the first trimester of pregnancy and increase in the later trimesters, peaking at 28-32 weeks of gestation. Following delivery, insulin requirements decrease rapidly. Diabetes can be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the fetus and mother. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy. The use of insulin lispro has been shown to be as effective as regular insulin to treat diabetes in pregnancy and may have advantages over regular insulin during pregnancy.

LactationExcretion in breast milk unknown/compatible

Breast-Feeding ConsiderationsIt is not known if significant amounts of insulin lispro are found in breast milk. Endogenous insulin can be found in breast milk. Plasma glucose concentrations in the mother affect glucose concentrations in breast milk. The gastrointestinal tract destroys insulin when administered orally; therefore, insulin is not expected to be absorbed intact by the breast-feeding infant. All types of insulin are safe for use while breast-feeding. Due to increased calorie expenditure, women with diabetes may require less insulin while nursing.

Pregnancy & Lactation, In-Depth

- Insulin Lispro in Pregnancy & Lactation

Adverse ReactionsRefer to Insulin Regular.

Metabolism/Transport EffectsRefer to Insulin Regular.

Drug Interactions

Antidiabetic Agents (Thiazolidinedione): Insulin may enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Beta-Blockers: May enhance the hypoglycemic effect of Insulin. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Edetate CALCIUM Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Edetate Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Insulin may enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsRefer to Insulin Regular.

Monitoring ParametersUrine sugar and acetone, serum glucose, electrolytes, Hb A_{1c}, lipid profile

Reference RangeRefer to Insulin Regular.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, hypoglycemia) at regular intervals during therapy. Teach patient proper use, including appropriate injection technique and syringe/needle disposal and monitoring requirements (or refer to diabetic educator), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsUrine sugar and acetone, serum glucose, electrolytes, Hb A_{1c}, lipid profile

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is used to control diabetes; it is not a cure. It is imperative to follow other components of prescribed treatment (eg, diet and exercise regimen). Take exactly as directed. Do not change dose or discontinue unless advised by prescriber. If you experience hypoglycemic reaction, contact prescriber immediately. Always carry quick source of sugar with you. Monitor glucose levels as directed by prescriber. Report adverse side effects, including chest pain or palpitations; persistent fatigue, confusion, headache; skin rash or redness; numbness of mouth, lips, or tongue; muscle weakness or tremors; vision changes; respiratory difficulty; or nausea, vomiting, or flu-like symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Humalog®: 100 units/mL (3 mL) [prefilled cartridge or prefilled disposable pen]; (10 mL) [vial]

Generic AvailableNo

ManufacturerEli Lilly and Co

Pricing: U.S. (www.drugstore.com)

Solution (Humalog)

100 units/mL (3): $43.46

100 units/mL (10): $95.99

Solution (Humalog KwikPen)

100 units/mL (15): $183.36

Solution (Humalog Pen)

100 units/mL (15): $193.16

Mechanism of ActionRefer to Insulin Regular. Insulin lispro is a rapid-acting form of insulin.

Pharmacodynamics/Kinetics**Note:** Rate of absorption, onset, and duration of activity may be affected by site of injection, exercise, presence of lipodystrophy, local blood supply, and/or temperature.

Onset of action: 0.2-0.5 hours

Peak effect: 1.5-2.5 hours

Duration: 3-4 hours

Distribution: 0.26-0.36 L/kg

Bioavailability: 55% to 77%

Time to peak, plasma: 0.5-1.5 hours

Excretion: Urine

Related Information

- Insulin Products
- Insulin Regular

Dental Health: Effects on Dental Treatment Patients with type 1 diabetes (insulin dependent) should be appointed for dental treatment in the morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause drowsiness or confusion

Mental Health: Effects on Psychiatric TreatmentMAO inhibitors may enhance the hypoglycemic effects of insulin; TCAs may antagonize the effects of insulin

Index Terms Lispro Insulin

International Brand Names Humalog (AT, AU, BB, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CZ, DE, DK, ET, FI, FR, GB, GH, GM, GN, GR, GY, HN, ID, IE, IN, IT, JM, KE, LR, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, PK, PT, PY, RU, SC, SD, SE, SL, SN, SR, TH, TN, TR, TT, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Humalog Lispro (CR, GT, HN, IL, KP, NI, PA, PE, SV); Humalog Mix NPL (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Insulin Humalog (PL); Insuline Lispro Humalog (FR); Liprolog (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Insulin NPH and Insulin Regular

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Humulin® 70/30 may be confused with Humalog® Mix 75/25

Novolin® 70/30 may be confused with NovoLog® Mix 70/30

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error. ***Due to the number of insulin preparations, it is essential to identify/clarify the type of insulin to be used.***

Cross-contamination may occur if insulin pens are shared among multiple patients. Steps should be taken to prohibit sharing of insulin pens.

Pronunciation(IN soo lin N P H & IN soo lin REG yoo ler)

U.S. Brand NamesHumulin® 50/50; Humulin® 70/30; Novolin® 70/30

Canadian Brand NamesHumulin® 20/80; Humulin® 70/30; Novolin® ge 30/70; Novolin® ge 40/60; Novolin® ge 50/50

Pharmacologic CategoryInsulin, Combination

Use: Labeled IndicationsTreatment of type 1 diabetes mellitus (insulin dependent, IDDM) and type 2 diabetes mellitus (noninsulin dependent, NIDDM) to improve glycemic control

Dosing: Adults

Refer to Insulin Regular. Fixed ratio insulins are normally administered in 1-2 daily doses.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Refer to Insulin Regular. Fixed ratio insulins are normally administered in 1-2 daily doses.

Administration: OtherSubQ administration only. Should be administered ~30 minutes before a meal. Normally administered once or twice daily (before breakfast and supper). Cold injections should be avoided. SubQ administration is usually made into the thighs, arms, buttocks, or abdomen, with sites rotated. Resuspend immediately prior to use. Gently roll vial or pen in the palms of the hands to resuspend before using.

StorageStore unopened container in refrigerator. Do not use if it has been frozen. The pen in use should not be refrigerated; store below 30°C (86°F) away from direct heat or light; discard after 10 days. If refrigeration is not available, opened vials may be stored unrefrigerated in cool place away from heat and sunlight.

CompatibilityDo not mix or dilute with other insulins.

ContraindicationsHypersensitivity to any component of the formulation; during episodes of hypoglycemia

Allergy Considerations

- Insulin Preparations Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypoglycemia: The most common adverse effects of insulin is hypoglycemia. The timing of hypoglycemia differs among various insulin formulations. Hypoglycemia may result from increased work or exercise without eating; use of long-acting insulin preparations (insulin detemir, insulin glargine) may delay recovery from hypoglycemia. Profound and prolonged episodes of hypoglycemia may result in convulsions, unconsciousness, temporary or permanent brain damage, or even death. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

- Hypokalemia: Insulin causes a shift of potassium from the extracellular space to the intracellular space, possibly producing hypokalemia which, if left untreated, may result in respiratory paralysis, ventricular arrhythmia and even death. Use with caution in patients at risk for hypokalemia (eg, loop diuretic use). Monitor serum potassium and supplement potassium when necessary.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment. Dosage requirements may be reduced.

- Renal impairment: Use with caution in patients with renal impairment. Dosage requirements may be reduced.

Dosage form specific issues:

- Product variation: Human insulin differs from animal-source insulin. Any change of insulin should be made cautiously; changing manufacturers, type, and/or method of manufacture may result in the need for a change of dosage.

Other warnings/precautions:

- Appropriate use: The general objective of exogenous insulin therapy is to approximate the physiologic pattern of insulin secretion which is characterized by two distinct phases. Phase 1 insulin secretion suppresses hepatic glucose production and phase 2 insulin secretion occurs in response to carbohydrate ingestion; therefore, exogenous insulin therapy may consist of basal insulin (eg, intermediate- or long-acting insulin or continuous insulin infusion administered via an external SubQ insulin infusion pump) and/or preprandial insulin (eg, short- or rapid-acting insulin) (see Related Information: Insulin Products). Patients with type 1 diabetes do not produce endogenous insulin; therefore, these patients require both basal and preprandial insulin administration. Patients with type 2 diabetes retain some beta-cell function in the early stages of their disease; however, as the disease progresses, phase 1 insulin secretion may become completely impaired and phase 2 insulin secretion becomes delayed and/or inadequate in response to meals. Therefore, patients with type 2 diabetes may be treated with oral antidiabetic agents, basal insulin, and/or preprandial insulin depending on the stage of disease and current glycemic control. Since treatment regimens often consist of multiple agents, dosage adjustments must address the specific phase of insulin release that is primarily contributing to the patient's impaired glycemic control. Treatment and monitoring regimens must be individualized.

- Patient education: Diabetic education and nutritional counseling are essential to maximize the effectiveness of therapy.

Geriatric ConsiderationsIntensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy ConsiderationsSee individual agents.

Breast-Feeding ConsiderationsSee individual agents.

Pregnancy & Lactation, In-Depth

- Insulin NPH in Pregnancy & Lactation
- Insulin Regular in Pregnancy & Lactation

Drug Interactions

Antidiabetic Agents (Thiazolidinedione): Insulin may enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Beta-Blockers: May enhance the hypoglycemic effect of Insulin. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Edetate CALCIUM Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Edetate Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Insulin may enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Reference RangeRefer to Insulin Regular.

Nursing: Physical Assessment/Monitoring

See individual agents.

Patient Education

See individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension:

Humulin® 50/50: Insulin NPH suspension 50% [intermediate acting] and insulin regular solution 50% [short acting]: 100 units/mL (10 mL) [vial]

Humulin® 70/30: Insulin NPH suspension 70% [intermediate acting] and insulin regular solution 30% [short acting]: 100 units/mL (3 mL) [disposable pen]; (10 mL) [vial]

Novolin® 70/30: Insulin NPH suspension 70% [intermediate acting] and insulin regular solution 30% [short acting]: 100 units/mL (3 mL) [InnoLet® prefilled syringe or PenFill® prefilled cartridge]; (10 mL) [vial]

Additional formulations available in Canada: Injection, suspension:

Humulin® 20/80: Insulin regular solution 20% [short acting] and insulin NPH suspension 80% [intermediate acting]: 100 units/mL (3 mL) [PenFill® prefilled cartridge]

Novolin® ge 30/70: Insulin regular solution 30% [short acting] and insulin NPH suspension 70% [intermediate acting]: 100 units/mL (3 mL) [prefilled syringe or PenFill® prefilled cartridge]; (10 mL) [vial]

Novolin® ge 40/60: Insulin regular solution 40% [short acting] and insulin NPH suspension 60% [intermediate acting]: 100 units/mL (3 mL) [PenFill® prefilled cartridge]

Novolin® ge 50/50: Insulin regular solution 50% [short acting] and insulin NPH suspension 50% [intermediate acting]: 100 units/mL (3 mL) [PenFill® prefilled cartridge]

Generic AvailableNo
ManufacturerEli Lilly & Co
Pricing: U.S. (www.drugstore.com)

Suspension (Humulin 50/50)

50-50% (10): $54.00

Suspension (Humulin 70/30)

70-30% (10): $54.00

Suspension (Humulin 70/30 Pen)

70-30% (30): $274.36

Suspension (Novolin 70/30)

70-30% (10): $52.59

Suspension (Novolin 70/30 Innolet)

70-30% (15): $94.67

Suspension (Novolin 70/30 PenFill)

70-30% (15): $136.75

Mechanism of ActionRefer to Insulin Regular. Insulin NPH and insulin regular is a combination insulin product with intermediate-acting characteristics. It may be administered once or twice daily.
Pharmacodynamics/Kinetics**Note:** Rate of absorption, onset, and duration of activity may be affected by site of injection, exercise, presence of lipodystrophy, local blood supply, and/or temperature.

Onset of action: 0.5 hours

Peak effect: 2-12 hours

Duration: 18-24 hours

Time to peak, plasma: 0.8-2 hours

Excretion: Urine

Related Information

- Insulin NPH
- Insulin Products
- Insulin Regular

Pharmacotherapy PearlsRefer to Insulin Regular and Insulin NPH for additional details on adverse effects, drug interactions, warnings, and dosing of insulin products.
Dental Health: Effects on Dental TreatmentPatients with type 1 diabetes (insulin dependent) should be appointed for dental treatment in the morning in order to minimize chance of stress-induced hypoglycemia.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness or confusion
Mental Health: Effects on Psychiatric TreatmentMAO inhibitors may enhance the hypoglycemic effects of insulin; TCAs may antagonize the effects of insulin
Index TermsInsulin Regular and Insulin NPH; Isophane Insulin and Regular Insulin; NPH Insulin and Regular Insulin
International Brand NamesActraphane HM (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, PH, SC, SD, SL, SN, TH, TN, TW, TZ, UG, ZA, ZM, ZW); Berlinsulin H 10 90 (DE); Berlinsulin H 20 80 (DE); Berlinsulin H 30 70 (DE); Berlinsulin H 40 60 (DE); Gensulin M30 (TH); Huminsulin "Lilly" Long (AT); Huminsulin Profil I (CH, DE); Huminsulin Profil II (CH, DE); Huminsulin Profil III (CH, DE); Huminsulin Profil IV (CH, DE); Humulin 10 90 (IT, MY); Humulin 20 80 (AU, IT, MY); Humulin 30 70 (AU, CR, DO, GT, HN, IT, MX, MY, NI, PA, SE, SV); Humulin 40 60 (IT, MY); Humulin 50/50 (AU); Humulin 60 40 (KP, TH); Humulin 70/30 (BB, BM, BS, BZ, CL, CO, GY, JM, NL, NZ, PE, SR, TT, VE); Humulin 70N/30R (BR); Humulin 80 20 (TH); Humulin M1 (GB); Humulin M2 (GB); Humulin M3 (GB); Humulin M4 (GB); Humulina 30 70 (ES); Humuline 20 80 (BE); Humuline 30 70 (BE); Humuline 40 60 (BE); Insulin "Novo Nordisk" Mixtard HM 15 85 (AT); Insulin "Novo Nordisk" Mixtard HM 30 70 (AT); Insulin "Novo Nordisk" Mixtard HM 50 50 (AT); Insulin Actraphan HM (CH); Insulin Actraphane HM (HN); Insulin Actraphane HM 10 90 (DE); Insulin Actraphane HM 20 80 (DE); Insulin Actraphane HM 30 70 (DE); Insulin Actraphane HM 40 60 (DE); Insulin Actraphane HM 50 50 (DE); Insulin Hoechst-Komb 15 U-100

(CH); Insulin Hoechst-Komb 25 U-100 (CH); Insulin Hoechst-Komb 50 U-100 (CH); Insulin Mixtard 10 HM (CH); Insulin Mixtard 15 85 Human (IL); Insulin Mixtard 20 HM (CH); Insulin Mixtard 30 70 Human (DE); Insulin Mixtard 30 HM (CH, IL); Insulin Mixtard 40 HM (CH); Insulin Mixtard 50 50 HM (IL); Insulin Mixtard 50 50 Human (DE); Insulin Mixtard 50 HM (CH); Insulina Humulin 70/30 (AR, CN); Insuline Humaan (NL); Insuline Humuline 10 90 (NL); Insuline Humuline 20 80 (NL); Insuline Humuline 30 70 (NL); Insuline Humuline 40 60 (NL); Insuman 25 (DE); Insuman 50 (DE); Insuman Comb 15 (DE); Mixtard 15 85 (AU); Mixtard 30 70 (AU); Mixtard 30 HM (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, HK, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Mixtard 30 Human (ID); Mixtard 50 50 (AU); Mixtard Human (KP); Mixtard Innolet (FR); Novolin 70/30 (MX); Orgasuline 30/70 (FR); Ransilun 30/70 (PH); Scilin M30 (HK, PH); Umuline Profil 10 (FR); Umuline Profil 20 (FR); Umuline Profil 30 (FR); Umuline Profil 40 (FR); Wosulin 30/70 (PH)

Insulin NPH

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Humulin® may be confused with Humalog®, Humira®

Novolin® may be confused with NovoLog®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error. ***Due to the number of insulin preparations, it is essential to identify/clarify the type of insulin to be used.***

Cross-contamination may occur if insulin pens are shared among multiple patients. Steps should be taken to prohibit sharing of insulin pens.

Pronunciation(IN soo lin N P H)

U.S. Brand NamesHumulin® N; Novolin® N

Canadian Brand NamesHumulin® N; Novolin® ge NPH

Pharmacologic CategoryInsulin, Intermediate-Acting

Use: Labeled IndicationsTreatment of type 1 diabetes mellitus (insulin dependent, IDDM) and type 2 diabetes mellitus (noninsulin dependent, NIDDM) to improve glycemic control

Dosing: AdultsRefer to Insulin Regular. Insulin NPH is usually administered 1-2 times daily.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to Insulin Regular. Insulin NPH is usually administered 1-2 times daily.

Dosing: Renal ImpairmentInsulin requirements are reduced due to changes in insulin clearance or metabolism.

Administration: OtherInsulin NPH (intermediate-acting insulin): SubQ administration: May be administered 1-2 times/day. Cold injections should be avoided. SubQ administration is usually made into the thighs, arms, buttocks, or abdomen, with sites rotated. When mixing regular insulin with other preparations of insulin, regular insulin should be drawn into syringe first. Gently roll vial or pen in the palms of the hands to resuspend before using. Insulin lispro (Humalog®) may be mixed in the same syringe as Humulin® N, but Humalog® should be drawn into the syringe first.

Dietary ConsiderationsDietary modification based on ADA recommendations is a key component of therapy.

StorageInsulin NPH (Humulin® N, Novolin® N): Store unopened container in refrigerator at 2°C to 8°C (36°F to 46°F); do not freeze. Vial in use may be stored under refrigeration or at room temperature. Humulin® N Pen in use should not be refrigerated; store below 30°C (86°F) away from direct heat or light. Discard after 2 weeks.

CompatibilityInsulin lispro (Humalog®) may be mixed in the same syringe as Humulin® N, but Humalog® should be drawn into the syringe first. A sterile diluent is available from the manufacturer for preparing dilutions of Humulin® N.

ContraindicationsHypersensitivity to any component of the formulation

Allergy Considerations

- Insulin Preparations Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypoglycemia: The most common adverse effects of insulin is hypoglycemia. The timing of hypoglycemia differs among various insulin formulations. Hypoglycemia may result from increased work or exercise without eating; use of long-acting insulin preparations (insulin detemir, insulin glargine) may delay recovery from hypoglycemia. Profound and prolonged episodes of hypoglycemia may result in convulsions, unconsciousness, temporary or permanent brain damage or even death. Insulin requirements may be altered during illness, emotional disturbances or other stresses.

- Hypokalemia: Insulin causes a shift of potassium from the extracellular space to the intracellular space, possibly producing hypokalemia which, if left untreated, may result in respiratory paralysis, ventricular arrhythmia and even death. Use with caution in patients at risk for hypokalemia (eg, loop diuretic use). Monitor serum potassium and supplement potassium when necessary.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment. Dosage requirements may be reduced.

- Renal impairment: Use with caution in patients with renal impairment. Dosage requirements may be reduced.

Dosage form specific issues:

- Product variation: Human insulin differs from animal-source insulin. Any change of insulin should be made cautiously; changing manufacturers, type, and/or method of manufacture may result in the need for a change of dosage.

Other warnings/precautions:

- Appropriate use: The general objective of exogenous insulin therapy is to approximate the physiologic pattern of insulin secretion which is characterized by two distinct phases. Phase 1 insulin secretion suppresses hepatic glucose production and phase 2 insulin secretion occurs in response to carbohydrate ingestion; therefore, exogenous insulin therapy may consist of basal insulin (eg, intermediate- or long-acting insulin or continuous insulin infusion administered via an external SubQ insulin infusion pump) and/or preprandial insulin (eg, short- or rapid-acting insulin) (see Related Information: Insulin Products). Patients with type 1 diabetes do not produce endogenous insulin; therefore, these patients require both basal and preprandial insulin administration. Patients with type 2 diabetes retain some beta-cell function in the early stages of their disease; however, as the disease progresses, phase 1 insulin secretion may become completely impaired and phase 2 insulin secretion becomes delayed and/or inadequate in response to meals. Therefore, patients with type 2 diabetes may be treated with oral antidiabetic agents, basal insulin, and/or preprandial insulin depending on the stage of disease and current glycemic control. Since treatment regimens often consist of multiple agents, dosage adjustments must address the specific phase of insulin release that is primarily contributing to the patient's impaired glycemic control. Treatment and monitoring regimens must be individualized.

- Patient education: Diabetic education and nutritional counseling are essential to maximize the effectiveness of therapy.

Geriatric ConsiderationsHow “tightly” a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well he/she recognizes hypoglycemic or hyperglycemic symptoms, and how to respond to them and any other disease states. Patients who are unable to accurately draw up their dose will need assistance such as prefilled syringes. Initial doses may require considerations for renal function in the elderly with dosing adjusted subsequently based on blood glucose monitoring. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy ConsiderationsMaternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Insulin requirements tend to fall during the first trimester of pregnancy and increase in the later trimesters, peaking at 28-32 weeks of gestation. Following delivery, insulin requirements decrease rapidly. Diabetes can be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the fetus and the mother. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy. NPH insulin is preferred over other intermediate-acting insulin products during pregnancy.

LactationExcretion in breast milk unknown/compatible

Breast-Feeding ConsiderationsEndogenous insulin can be found in breast milk. Plasma glucose concentrations in the mother affect glucose concentrations in breast milk. The gastrointestinal tract destroys insulin when administered orally; therefore, insulin is not expected to be absorbed intact by the breast-feeding infant. All types of insulin are safe for use while breast-feeding. Due to increased calorie expenditure, women with diabetes may require less insulin while nursing.

Pregnancy & Lactation, In-Depth

- Insulin NPH in Pregnancy & Lactation

Adverse ReactionsRefer to Insulin Regular.

Metabolism/Transport EffectsRefer to Insulin Regular.

Drug Interactions

Antidiabetic Agents (Thiazolidinedione): Insulin may enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Beta-Blockers: May enhance the hypoglycemic effect of Insulin. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Edetate CALCIUM Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Edetate Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Insulin may enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsRefer to Insulin Regular.

Monitoring ParametersUrine sugar and acetone, serum glucose, electrolytes, Hb A_{1c}, lipid profile

Reference RangeRefer to Insulin Regular.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, hypoglycemia) at regular intervals during therapy. Teach patient proper use, including appropriate injection technique and syringe/needle disposal and monitoring requirements (or refer to diabetic educator), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsUrine sugar and acetone, serum glucose, electrolytes, Hb A_{1c}, lipid profile

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is used to control diabetes; it is not a cure. It is imperative to follow other components of prescribed treatment (eg, diet and exercise regimen). Take exactly as directed. Do not change dose or discontinue unless advised by prescriber. If you experience hypoglycemic reaction, contact prescriber immediately. Always carry quick source of sugar with you. Monitor glucose levels as directed by prescriber. Report adverse side effects, including chest pain or palpitations; persistent fatigue, confusion, headache; skin rash or redness; numbness of mouth, lips, or tongue; muscle weakness or tremors; vision changes; respiratory difficulty; or nausea, vomiting, or flu-like symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, suspension:

Humulin® N: 100 units/mL (3 mL) [disposable pen]; (10 mL) [vial]

Novolin® ge NPH [CAN]: 100 units/mL (3 mL) [NovolinSet® prefilled syringe or PenFill® prefilled cartridge]; 10 mL [vial]

Novolin® N: 100 units/mL (3 mL) [InnoLet® prefilled syringe or PenFill® prefilled cartridge]; (10 mL) [vial]

Generic AvailableNo

ManufacturerEli Lilly & Co

Pricing: U.S. (www.drugstore.com)

Suspension (Humulin N)

100 units/mL (10): $54.00

Suspension (Humulin N Pen)

100 units/mL (15): $145.32

Suspension (Novolin N)

100 units/mL (10): $52.59

Suspension (Novolin N Innolet)

100 units/mL (15): $91.77

Suspension (Novolin N PenFill)

100 units/mL (15): $121.27

Mechanism of ActionRefer to Insulin Regular. Insulin NPH is an intermediate-acting form of insulin.

Pharmacodynamics/Kinetics**Note:** Rate of absorption, onset, and duration of activity may be affected by site of injection, exercise, presence of lipodystrophy, local blood supply, and/or temperature.

Onset of action: 1-2 hours

Peak effect: 4-12 hours

Duration: 18-24 hours

Time to peak, plasma: 6-12 hours

Excretion: Urine

Related Information

- Insulin Products
- Insulin Regular

Dental Health: Effects on Dental TreatmentPatients with type 1 diabetes (insulin dependent) should be appointed for dental treatment in the morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or confusion

Mental Health: Effects on Psychiatric TreatmentMAO inhibitors may enhance the hypoglycemic effects of insulin; TCAs may antagonize the effects of insulin

Index TermsIsophane Insulin; NPH Insulin

International Brand NamesBasal-H-Insulin (DE); Biohulin NPH (KP); Gensulin N (TH); Human Insulatard (IN); Human Protaphane (GB, IE); Huminsulin "Lilly" Basal (NPH) (AT); Huminsulin Basal (NPH) (CH, DE); Humulin I (IT); Humulin N (AE, AU, BB, BF, BG, BH, BJ, BM, BR, BS, BZ, CI, CO, CR, CY, DO, EE, EG, ET, GH, GM, GN, GT, GY, HK, HN, IL, IQ, IR, JM, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, OM, PA, PE, PK, PY, QA, SA, SC, SD, SL, SN, SR, SV, SY, TH, TN, TT, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Humulin NPH (DK, GR, PH, SE, TW); Humulina (ES); Humuline NPH (BE); Insulatard (DK); Insulatard HM (AE, BE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Insulatard Innolet (FR); Insulin "Novo Nordisk" Insulatard HM (AT); Insulin Insulatard Human (DE, TH); Insulin Protaphane HM (DE); Insulina Humulin (AR, CN); Insuline Humuline NPH (NL); Insuline Insulatard (NL); Insuline Isuhuman Basal (NL); Insuman (EC); Insuman Basal (DE); Novolet N (KP); Novolin N (CL, KP, MX); Protaphane HM (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, HK, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, PH, QA, SA, SC, SD, SL, SN, SY, TH, TN, TZ, UG, YE, ZA, ZM, ZW); Ranisulin-N (PH); Scilin N (HK, PH); Umuline NPH (FR); Umuline Protamine Isophane (FR); Wosulin-N (PH)

Insulin Regular

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Humulin® may be confused with Humalog®, Humira®

Novolin® may be confused with NovoLog®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error. ***Due to the number of insulin preparations, it is essential to identify/clarify the type of insulin to be used.***

Concentrated solutions (eg, U-500) should not be available in patient care areas.

Cross-contamination may occur if insulin pens are shared among multiple patients. Steps should be taken to prohibit sharing of insulin pens.

Pronunciation(IN soo lin REG yoo ler)

U.S. Brand NamesHumulin® R; Humulin® R U-500; Novolin® R

Canadian Brand NamesHumulin® R; Novolin® ge Toronto

Pharmacologic CategoryAntidote; Insulin, Short-Acting

Use: Labeled IndicationsTreatment of type 1 diabetes mellitus (insulin dependent, IDDM); type 2 diabetes mellitus (noninsulin dependent, NIDDM) unresponsive to treatment with diet and/or oral hypoglycemics, to improve glycemic control; adjunct to parenteral nutrition; diabetic ketoacidosis (DKA)

Use: Unlabeled/InvestigationalHyperkalemia (regular insulin only; use with glucose to shift potassium into cells to lower serum potassium levels)

Dosing: AdultsSubQ (regular insulin may also be administered I.V.): The number and size of daily doses, time of administration, and diet and exercise require continuous medical supervision. In addition, specific formulations may require distinct administration procedures (see Administration).

Type 1 Diabetes Mellitus:Note: Multiple daily doses guided by blood glucose monitoring are the standard of diabetes care. Combinations of insulin are commonly used.

Initial dose: 0.2-0.6 unit/kg/day in divided doses. Conservative initial doses of 0.2-0.4 units/kg/day are often recommended to avoid the potential for hypoglycemia.

Division of daily insulin requirement: Generally, 50% to 75% of the daily insulin dose is given as an intermediate- or long-acting form of insulin (in 1-2 daily injections). The remaining portion of the 24-hour insulin requirement is divided and administered as a rapid-acting or short-acting form of insulin. These may be given with meals (before or at the time of meals depending on the form of insulin) or at the same time as injections of intermediate forms (some premixed combinations are intended for this purpose).

Adjustment of dose: Dosage must be titrated to achieve glucose control and avoid hypoglycemia. Adjust dose to maintain premeal and bedtime glucose of 80-140 mg/dL (children <5 years: 100-200 mg/dL). Since combinations of agents are frequently used, dosage adjustment must address the individual component of the insulin regimen which most directly influences the blood glucose value in question, based on the known onset and duration of the insulin component. Also see Additional Information or Pharmacotherapy Pearls.

Usual maintenance range: 0.5-1.2 units/kg/day in divided doses. An estimate of anticipated needs may be based on body weight and/or activity factors as follows:

Adolescents: May require ≤1.5 units/kg/day during growth spurts

Nonobese: 0.4-0.6 units/kg/day

Obese: 0.8-1.2 units/kg/day

Renal failure: Due to alterations in pharmacokinetics of insulin, may require <0.2 units/kg/day

Type 2 Diabetes Mellitus:

Augmentation therapy: Dosage must be carefully adjusted.

Insulins other than glargine: Initial dosage of 0.15-0.2 units/kg/day have been recommended

Insulin glargine: Initial dose: 10 units/day

Note: Administered when residual beta-cell function is present, as a supplemental agent when oral hypoglycemics have not achieved goal glucose control. Twice daily NPH, or an evening dose of NPH, lente, or glargine insulin may be added to oral therapy with metformin or a sulfonylurea. Augmentation to control postprandial glucose may be accomplished with regular, glulisine, aspart, or lispro insulin.

Monotherapy: Initial dose: Highly variable: See Augmentation therapy dosing.

Note: An empirically-defined scheme for dosage estimation based on fasting plasma glucose and degree of obesity has been published with recommended doses ranging from 6-77 units/day (Holman, 1995). In the setting of glucose toxicity (loss of beta-cell sensitivity to glucose concentrations), insulin therapy may be used for short-term management to restore sensitivity of beta-cells; in these cases, the dose may need to be rapidly reduced/withdrawn when sensitivity is re-established.

Hyperkalemia (unlabeled use): I.V.: Administer dextrose at 0.5-1 mL/kg and regular insulin 1 unit for every 4-5 g dextrose given

Diabetic ketoacidosis:

I.V.: Regular insulin 0.15 units/kg initially followed by an infusion of 0.1 units/kg/hour

SubQ, I.M.: Regular insulin 0.4 units/kg given half as I.V. bolus and half as SubQ or I.M., followed by 0.1 units/kg/hour SubQ or I.M.

If serum glucose does not fall by 50-70 mg/dL in the first hour, double insulin dose hourly until glucose falls at an hourly rate of 50-70 mg/dL. Decrease dose to 0.05-0.1 units/kg/hour once serum glucose reaches 250 mg/dL.

Note: Newly-diagnosed patients with IDDM presenting in DKA and patients with blood sugars <800 mg/dL may be relatively “sensitive” to insulin and should receive loading and initial maintenance doses ~50% of those indicated.

Infusion should continue until reversal of acid-base derangement/ketonemia. Serum glucose is not a direct indicator of these abnormalities, and may decrease more rapidly than correction of the range of metabolic abnormalities.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Diabetes mellitus:** Refer to adult dosing. Adolescents (growth spurts): Maintenance range: May require ≤1.5 units/kg/day in divided doses.

Diabetic ketoacidosis: Children <20 years:

I.V.: Regular insulin infused at 0.1 units/kg/hour; continue until acidosis clears, then decrease to 0.05 units/kg/hour until SubQ replacement dosing can be initiated

SubQ, I.M.: If no I.V. infusion access, regular insulin 0.1 units/kg I.M. bolus followed by 0.1 units/kg/hour SubQ or I.M.; continue until acidosis clears, then decrease to 0.05 units/kg/hour until SubQ replacement dosing can be initiated

If serum glucose does not fall by 50-70 mg/dL in the first hour, double insulin dose hourly until glucose falls at an hourly rate of 50-70 mg/dL. Decrease dose to 0.05-0.1 units/kg/hour once serum glucose reaches 250 mg/dL.

Note: Newly-diagnosed patients with IDDM presenting in DKA and patients with blood sugars <800 mg/dL may be relatively “sensitive” to insulin and should receive loading and initial maintenance doses ~50% of those indicated.

Hyperkalemia (unlabeled use): Refer to adult dosing.

Dosing: Renal ImpairmentInsulin requirements are reduced due to changes in insulin clearance or metabolism. Close monitoring of blood glucose and adjustment of therapy is required in renal impairment.

Cl_{cr} 10-50 mL/minute: Administer 75% of normal dose.

Cl_{cr} <10 mL/minute: Administer 25% to 50% of normal dose and monitor glucose closely.

Hemodialysis: Because of a large molecular weight (6000 daltons), insulin is not significantly removed by either peritoneal or hemodialysis.

Supplemental dose is not necessary.

Peritoneal dialysis: Supplemental dose is not necessary.

Continuous arteriovenous or venovenous hemofiltration effects: Supplemental dose is not necessary.

Administration: I.V.Regular insulin may be administered by SubQ, I.M., or I.V. routes.

I.V. administration (requires use of an infusion pump): May be administered I.V. with close monitoring of blood glucose and serum potassium.

Administration: I.V. DetailI.V. administration (requires use of an infusion pump): **Only regular insulin** may be administered I.V.

I.V. infusions: To minimize adsorption problems to I.V. solution bag:

If new tubing is **not** needed: Wait a minimum of 30 minutes between the preparation of the solution and the initiation of the infusion.

If new tubing is needed: After receiving the insulin drip solution, the administration set should be attached to the I.V. container and the line should be flushed with the insulin solution. The nurse should wait 30 minutes, then flush the line again with the insulin solution prior to initiating the infusion.

If insulin is required prior to the availability of the insulin drip, regular insulin should be administered by I.V. push injection.

Because of adsorption, the actual amount of insulin being administered could be substantially less than the apparent amount. Therefore, adjustment of the insulin drip rate should be based on effect and not solely on the apparent insulin dose. Furthermore, the apparent dose should not be used as the basis for determining the subsequent insulin dose upon discontinuing the insulin drip. Dose requires continuous medical supervision.

pH: Regular insulin: 7.0-7.8

Administration: OtherSubQ administration: Cold injections should be avoided. SubQ administration is usually made into the thighs, arms, buttocks, or abdomen, with sites rotated. When mixing regular insulin with other preparations of insulin, regular insulin should be drawn into syringe first. Except for rapid-acting, short-acting, or insulin detemir or glargine, gently roll vial or pen in the palms of the hands to resuspend before using. When rapid-acting insulin is mixed with an intermediate or long-acting insulin, it should be administered within 15 minutes before a meal.

Human regular insulin: Should be administered within 30-60 minutes before a meal; may be administered by SubQ, I.M., or I.V. routes

Dietary ConsiderationsDietary modification based on ADA recommendations is a part of therapy.

StorageInsulin, regular (Humulin® R, Novolin® R): Store unopened containers in refrigerator at 2°C to 8°C (36°F to 46°F); do not freeze. Vial in use may be stored under refrigeration or at room temperature; store below 30°C (86°F) away from direct heat or light. Regular insulin should only be used if clear.

ReconstitutionStandard diluent for regular insulin: 100 units/100 mL NS; **Note:** All bags should be prepared fresh; tubing should be flushed 30 minutes prior to administration to allow adsorption as time permits. Can be given as a more diluted solution (eg, 100 units/250 mL 0.45% NS).

CompatibilityA sterile diluent is available from the manufacturer for preparing dilutions of Humalog®, Humulin® N, Humulin® R, Humulin® 70/30, or Humulin® R U-500.

ContraindicationsHypersensitivity to any component of the formulation

Allergy Considerations

- Insulin Preparations Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypoglycemia: The most common adverse effects of insulin is hypoglycemia. The timing of hypoglycemia differs among various insulin formulations. Hypoglycemia may result from increased work or exercise without eating; use of long-acting insulin preparations (insulin detemir, insulin glargine) may delay recovery from hypoglycemia. Profound and prolonged episodes of hypoglycemia may result in convulsions, unconsciousness, temporary or permanent brain damage, or even death. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

- Hypokalemia: Insulin (especially I.V. insulin) causes a shift of potassium from the extracellular space to the intracellular space, possibly producing hypokalemia which, if left untreated, may result in respiratory paralysis, ventricular arrhythmia and even death. Use with caution in patients at risk for hypokalemia (eg, loop diuretic use). Monitor serum potassium frequently with I.V. use and supplement potassium when necessary.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment. Dosage requirements may be reduced.

- Renal impairment: Use with caution in patients with renal impairment. Dosage requirements may be reduced.

Dosage form specific issues:

- Product variation: Human insulin differs from animal-source insulin. Any change of insulin should be made cautiously; changing manufacturers, type, and/or method of manufacture may result in the need for a change of dosage.

Other warnings/precautions:

- Appropriate use: The general objective of exogenous insulin therapy is to approximate the physiologic pattern of insulin secretion which is characterized by two distinct phases. Phase 1 insulin secretion suppresses hepatic glucose production and phase 2 insulin secretion occurs in response to carbohydrate ingestion; therefore, exogenous insulin therapy may consist of basal insulin (eg, intermediate- or long-acting insulin or continuous insulin infusion administered via an external SubQ insulin infusion pump) and/or preprandial insulin (eg, short- or rapid-acting insulin) (see Related Information: Insulin Products). Patients with type 1 diabetes do not produce endogenous insulin; therefore, these patients require both basal and preprandial insulin administration. Patients with type 2 diabetes retain some beta-cell function in the early stages of their disease; however, as the disease progresses, phase 1 insulin secretion may become completely impaired and phase 2 insulin secretion becomes delayed and/or inadequate in response to meals. Therefore, patients with type 2 diabetes may be treated with oral antidiabetic agents, basal insulin, and/or preprandial insulin depending on the stage of disease and current glycemic control. Since treatment regimens often consist of multiple agents, dosage adjustments must address the specific phase of insulin release that is primarily contributing to the patient's impaired glycemic control. Treatment and monitoring regimens must be individualized.

- I.V. administration: Regular insulin may be administered I.V. in selected clinical situations to control hyperglycemia; close medical supervision is required.

- Patient education: Diabetic education and nutritional counseling are essential to maximize the effectiveness of therapy.

Geriatric ConsiderationsHow "tightly" a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well he/she recognizes hypoglycemic or hyperglycemic symptoms, and how to respond to them and any other disease states. Patients who are unable to accurately draw up their dose will need assistance such as prefilled syringes. Initial doses may require considerations for renal function in the elderly with dosing adjusted subsequently based on blood glucose monitoring. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorB

Pregnancy ConsiderationsInsulin has not been found to cross the placenta, but insulin bound to anti-insulin antibodies has been detected in cord blood. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Insulin requirements tend to fall during the first trimester of pregnancy and increase in the later trimesters, peaking at 28-32 weeks of gestation. Following delivery, insulin requirements decrease rapidly. Diabetes can be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the fetus and the mother. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

LactationExcretion in breast milk unknown/compatible

Breast-Feeding ConsiderationsEndogenous insulin can be found in breast milk. Plasma glucose concentrations in the mother affect glucose concentrations in breast milk. The gastrointestinal tract destroys insulin when administered orally; therefore, insulin is not expected to be absorbed intact by the breast-feeding infant. All types of insulin are safe for use while breast-feeding. Due to increased calorie expenditure, women with diabetes may require less insulin while nursing.

Pregnancy & Lactation, In-Depth

- Insulin Regular in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation, pallor, tachycardia

Central nervous system: Fatigue, headache, hypothermia, loss of consciousness, mental confusion

Dermatologic: Urticaria, redness

Endocrine & metabolic: Hypoglycemia, hypokalemia

Gastrointestinal: Hunger, nausea, numbness of mouth, weight gain

Local: Atrophy or hypertrophy of SubQ fat tissue; edema, itching, pain or warmth at injection site; stinging

Neuromuscular & skeletal: Muscle weakness, paresthesia, tremor

Ocular: Transient presbyopia or blurred vision

Miscellaneous: Anaphylaxis, antibodies to insulin (no change in efficacy), diaphoresis, local allergy, systemic allergic symptoms

Metabolism/Transport Effects**Induces** CYP1A2 (weak)

Drug Interactions

Antidiabetic Agents (Thiazolidinedione): Insulin may enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Beta-Blockers: May enhance the hypoglycemic effect of Insulin. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Edetate CALCIUM Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Edetate Disodium: May enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Insulin may enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Caution with ethanol (may increase hypoglycemia).

Food: Insulin shifts potassium from extracellular to intracellular space. Decreases potassium serum concentration.

Herb/Nutraceutical: Use caution with chromium, garlic, gymnema (may increase hypoglycemia).

Monitoring ParametersUrine sugar and acetone, serum glucose, electrolytes, Hb A_{1c}, lipid profile

DKA: Arterial blood gases, CBC with differential, urinalysis, serum glucose (baseline and every hour until reaches 250 mg/dL), BUN, creatinine, electrolytes, anion gap

Hyperkalemia: Serum potassium and glucose must be closely monitored to avoid hypoglycemia and/or hypokalemia.

Reference Range

Therapeutic, serum insulin (fasting): 5-20 µIU/mL (SI: 35-145 pmol/L)

Glucose, fasting:

Newborns: 60-110 mg/dL

Adults: 60-110 mg/dL

Elderly: 100-180 mg/dL

Recommendations for glycemic control, adults with type 1 diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Criteria for diagnosis of DKA:

Serum glucose: >250 mg/dL

Arterial pH: <7.3

Bicarbonate: <15 mEq/L

Moderate ketonuria or ketonemia

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, hypoglycemia) at regular intervals during therapy. Teach patient proper use, including appropriate injection technique and syringe/needle disposal and monitoring requirements (or refer to diabetic educator), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsUrine sugar and acetone, serum glucose, electrolytes, Hb A_{1c}, lipid profile

DKA: Arterial blood gases, CBC with differential, urinalysis, serum glucose (baseline and every hour until reaches 250 mg/dL), BUN, creatinine, electrolytes, anion gap

Hyperkalemia: Serum potassium and glucose must be closely monitored to avoid hypoglycemia and/or hypokalemia.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is used to control diabetes; it is not a cure. It is imperative to follow other components of prescribed treatment (eg, diet and exercise regimen). Take exactly as directed. Do not change dose or discontinue unless advised by prescriber. With insulin aspart (NovoLog®), you must start eating within 5-10 minutes after injection. Insulin glulisine (Apidra™) should be administered within 15 minutes before or within 20 minutes after start of meal. If you experience hypoglycemic reaction, contact prescriber immediately. Always carry quick source of sugar with you. Monitor glucose levels as directed by prescriber. Report adverse side effects, including chest pain or palpitations; persistent fatigue, confusion, headache; skin rash or redness; numbness of mouth, lips, or tongue; muscle weakness or tremors; vision changes; respiratory difficulty; or nausea, vomiting, or flu-like symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Humulin® R: 100 units/mL (10 mL)

Novolin® R: 100 units/mL (3 mL) [InnoLet® prefilled syringe or PenFill® prefilled cartridge]; (10 mL) [vial]

Injection, solution [concentrate]:

Humulin® R U-500: 500 units/mL (20 mL vial)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Humulin R)

100 units/mL (10): $54.00

Solution (HumuLIN R U-500 (Concentrated))

500 units/mL (20): $235.02

Solution (Novolin R)

100 units/mL (10): $52.59

Solution (Novolin R InnoLet)

100 units/mL (3): $21.99

Solution (Novolin R PenFill)

100 units/mL (15): $121.27

Mechanism of Action

Insulin acts via specific membrane-bound receptors on target tissues to regulate metabolism of carbohydrate, protein, and fats. Insulin facilitates entry of glucose into muscle, adipose, and other tissues via hexose transporters, including GLUT4. Insulin stimulates the cellular uptake of amino acids and increases cellular permeability to several ions, including potassium, magnesium, and phosphate. By activating sodium-potassium ATPases, insulin promotes the intracellular movement of potassium.

Target organs for insulin include the liver, skeletal muscle, and adipose tissue. Within the liver, insulin stimulates hepatic glycogen synthesis through the activation of the enzymes hexokinase, phosphofructokinase, and glycogen synthase as well as the inhibition of glucose-6 phosphatase. Insulin promotes hepatic synthesis of fatty acids, which are released into the circulation as lipoproteins. Skeletal muscle effects of insulin include increased protein synthesis and increased glycogen synthesis. Within adipose tissue, insulin stimulates the processing of circulating lipoproteins to provide free fatty acids, facilitating triglyceride synthesis and storage by adipocytes. Insulin also directly inhibits the hydrolysis of triglycerides.

Normally secreted by the pancreas, insulin products are manufactured for pharmacologic use through recombinant DNA technology using either *E. coli* or *Saccharomyces cerevisiae*. Insulins are categorized based on promptness and duration of effect, including rapid-, short-, intermediate-, and long-acting insulins.

Pharmacodynamics/Kinetics

Note: Rate of absorption, onset, and duration of activity may be affected by site of injection, exercise, presence of lipodystrophy, local blood supply, and/or temperature.

Onset of action: 0.5 hours

Peak effect: 2.5-5 hours

Duration: 4-12 hours (may increase with dose)

Time to peak, plasma: 0.8-2 hours

Excretion: Urine

Related Information

- Desensitization Protocols
- Diabetes Mellitus Management, Adults
- Insulin Aspart
- Insulin Aspart Protamine and Insulin Aspart
- Insulin Detemir
- Insulin Glargine
- Insulin Glulisine
- Insulin Lispro
- Insulin Lispro Protamine and Insulin Lispro
- Insulin NPH
- Insulin NPH and Insulin Regular
- Insulin Products

Pharmacotherapy Pearls

Split-mixed or basal-bolus regimens: Combination regimens which exploit differences in the onset and duration of different insulin products are commonly used to approximate physiologic secretion. In split-mixed regimens, an intermediate-acting insulin (such as NPH insulin) is administered once or twice daily and supplemented by short-acting (regular) or rapid-acting (lispro, aspart, or glulisine) insulin. Blood glucose measurements are completed several times daily. Dosages are adjusted emphasizing the individual component of the regimen which most directly influences the blood sugar in question (either the intermediate-acting component or the shorter-acting component). Fixed-ratio formulations (eg, 70/30 mix) may be used as twice daily injections in this scenario; however, the ability to titrate the dosage of an individual component is limited. A example of a “split-mixed” regimen would be 21 units of NPH plus 9 units of regular insulin in the morning and an evening meal dose consisting of 14 units of NPH plus 6 units of regular insulin.

Basal-bolus regimens are designed to more closely mimic physiologic secretion. These employ a long-acting insulin (eg, glargine) to simulate basal insulin secretion. The basal component is frequently administered at bedtime or in the early morning. This is supplemented by multiple daily injections of very rapid-acting products (lispro or aspart) immediately prior to a meal, which provides insulin at the time when nutrients are absorbed. An example of a basal-bolus regimen would be 30 units of glargine at bedtime and 12 units of lispro insulin prior to each meal.

Estimation of the effect per unit: A “Rule of 1500” has been frequently used as a means to estimate the change in blood sugar relative to each unit of insulin administered. In fact, the recommended values used in these calculations may vary from 1500-2200 (a value of 1500 is generally recommended for regular insulin while 1800 is recommended for "rapid-acting insulins"). The higher values lead to more conservative estimates of the effect per unit of insulin, and therefore lead to more cautious adjustments. The effect per unit of insulin is approximated by dividing the selected numerical value (eg, 1500-2200) by the number of units/day received by the patient. This may be used as a crude approximation of the patient’s insulin sensitivity as adjustments to individual components of the regimen are made. Each additional unit of insulin added to the corresponding insulin dose may be expected to lower the blood glucose by this amount.

To illustrate, in the “basal-bolus” regimen example presented above, the rule of 1800 would indicate an expected change of 27 mg/dL per unit of lispro insulin (the total daily insulin dose is 66 units; using the formula: 1800/66 = 27). A patient may be instructed to add additional insulin if the preprandial glucose is >125 mg/dL. For a prelunch glucose of 195 mg/dL, this would mean the patient would administer the scheduled 12 units of lispro along with an additional “correctional” 3 units for a total of 15 units prior to the meal. If correctional doses are required on a consistent basis, an adjustment of the patients diet and/or scheduled insulin dose may be necessary.

Dental Health: Effects on Dental TreatmentPatients with type 1 diabetes (insulin dependent) should be appointed for dental treatment in the morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or confusion

Mental Health: Effects on Psychiatric TreatmentMAO inhibitors may enhance the hypoglycemic effects of insulin; TCAs may antagonize the effects of insulin

Cardiovascular Considerations**Acute coronary syndromes (ACS):** Numerous studies have shown that hyperglycemia is associated with increase mortality in ACS. Although the 2004 ACC/AHA STEMI guidelines (Antman, 2004) recommend an insulin infusion to normalize blood glucose in patients with STEMI and complicated courses, no study has shown whether treatment of hyperglycemia has benefit in patients with ACS. According to a recent AHA statement, in patients admitted to an ICU with ACS, glucose should be monitored closely and it is reasonable to consider intensive insulin therapy using an insulin infusion in those patients with a serum glucose >180 mg/dL regardless of diabetes history. For patients with milder degrees of hyperglycemia, optimization of glucose may be considered. However, the precise target glucose range has not been established. Until this range is established, a serum glucose level between 90-140 mg/dL seems reasonable. Episodes of hypoglycemia should be avoided especially since hypoglycemia in ACS has been associated with high mortality (Deedwania, 2008).

Anesthesia and Critical Care Concerns/Other Considerations

Evidence-Based Information:

Surgical Patients: Van den Berghe and colleagues (2001) performed a single-center, prospective, randomized, controlled study in 1548 surgical intensive care patients (~63% cardiac surgery patients). Authors compared “conventional” control of blood glucose (180-200 mg/dL) versus “intensive” control of blood glucose (80-110 mg/dL). Primary outcome was ICU mortality. The authors showed an absolute ICu mortality reduction of 3.4% (8.0% vs 4.6%; p<0.04) in the intensive insulin therapy arm. Intensive insulin therapy also reduced bloodstream infections (7.8% vs 4.2%; p=0.003), acute renal failure requiring hemodialysis (8.2 vs 4.8%; p=0.007), and critical-illness polyneuropathy (51.9% vs 28.7%; p<0.001). Greatest ICU mortality reduction appeared in patients with an ICU stay >5 days, reducing mortality by 9.6% (20.2% vs 10.6%; p=0.005). Other authors have shown intensive insulin therapy to reduce morbidity and mortality after myocardial infarction and coronary bypass.

Medical Patients: Following the study conducted in surgical patients, a similar study (Van den Berghe, 2006) was done in adults admitted to the medical intensive care unit who were assumed to require at least 3 days of ICU care. The goal blood glucose was the same as the previous Van den Berghe study. The primary outcome was hospital mortality. Mortality in the ICU, 90-day mortality, days to wean from mechanical ventilation, days in ICU and hospital, new kidney injury were some of the secondary outcome measurements evaluated. A subgroup analysis was planned for patients staying in the ICU for >3 days. Twelve hundred patients were randomized to conventional versus intensive blood glucose control. Intensive insulin therapy did not significantly reduce in-hospital mortality (40% conventional treatment group vs 37.3% intensive treatment group, p=0.33). Morbidity was significantly reduced in the intensive group by the prevention of newly acquired kidney injury, accelerated weaning from mechanical ventilation and shortened stay in the ICU/hospital. For patients who stayed in the ICU for <3 days, mortality was greater in those receiving intensive insulin therapy. A subset of patients who remained in the ICU for 3 or more days was evaluated and in-hospital mortality was significantly reduced (52.5% vs 43%; p=0.009) in those who received intensive insulin therapy.

An additional study evaluated intensive insulin therapy in 537 medical ICU patients with severe sepsis. In this multicenter, two-by-two factorial design study, patients were randomized to intensive insulin therapy to maintain euglycemia (80-110 mg/dL) or conventional insulin therapy to maintain blood glucose levels between 180-200 mg/dL. For fluid resuscitation, patients were also randomized to 10% pentastarch, a low-molecular weight hydroxyethyl starch (HES), or Ringer’s lactate. The coprimary endpoints of the trial were mortality at 28 days and morbidity as measured by the Sequential Organ Failure Assessment (SOFA) score. Of note, previous studies evaluated mortality as a single primary endpoint. Some of the secondary endpoints included rate of acute renal failure, mean SOFA subscores, mechanical ventilation duration, ICU length of stay, and 90 day mortality. Severe hypoglycemia was defined as a serum glucose ≤40 mg/dL. The trial was stopped early due to an increased number of hypoglycemic events with intensive insulin therapy compared to conventional insulin therapy (17% vs 4.1%, respectively, p<0.001). In addition, there was no significant difference in the rates of mortality or mean SOFA scores. Patients receiving conventional insulin therapy were continued on the randomized resuscitation fluid (HES or Ringer’s lactate). Patients who received HES had a higher rate of renal failure and trended toward a higher rate of mortality at 90 days (Brunkhorst, 2008).

Guidelines: The American College of Endocrinology recommends patients in an intensive care setting maintain serum glucose levels ≤110 mg/dL. In other inpatient units, patients may have preprandial glucoses ≤110 mg/dL and maximal glucose ≤180 mg/dL. The 2008 Surviving Sepsis Campaign guidelines suggest targeting blood glucose levels <150 mg/dL by using a validated protocol for insulin adjustments (Grade 2C). The guidelines recommend that all patients receiving I.V. insulin should receive a glucose calorie source. Concurrently blood glucose values should be monitored every 1-2 hours until glucose values and insulin infusion rates are stable, then monitored every 4 hours thereafter (Grade 1C).

Index TermsRegular Insulin

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International Brand NamesActraphane (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Actrapid (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, NL, NO, PT, RU, SE, TR); Actrapid HM (AE, BF, BH, BJ, CI, CY, DE, EG, ET, GH, GM, GN, HK, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, PH, QA, SA, SC, SD, SL, SN, SY, TH, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Actrapid Human (ID, JP); Berlinsulin Actrapid Normal U-40 (DE); Berlinsulin H Basal U-40 (DE); Biohulin (KP); Gensulin R (TH); Human Actrapid (IE, IN); Human Nordisulin (IN); Huminsulin "Lilly" Normal (AT); Huminsulin Normal (CH, DE); Humulin (Regular) (GR); Humulin R (AE, AU, BB, BF, BG, BH, BJ, BM, BS, BZ, CI, CL, CO, CR, CY, CZ, DO, EE, EG, ET, GH, GM, GN, GT, GY, HK, HN, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, OM, PA, PE, PH, PK, PY, QA, SA, SC, SD, SL, SN, SR, SV, SY, TH, TN, TT, TZ, UG, VE, YE, ZA, ZM, ZW); Humulin Regular (DK, FI, NO, PT, SE, TW); Humulina Regular (ES); Insulin "Novo Nordisk" Actrapid HM (AT); Insulin "Novo Nordisk" Velosulin HM (AT); Insulin Actrapid HM (BG); Insulin Hoechst-Rapid U-100 (CH); Insulin Human Actrapid (GB); Insulina (ES); Insulina Actrapid HM (ES); Insulina Humulin R (AR); Insulina Velosulin HM (ES); Insuline (NL); Insuline Actrapid (NL); Insuline Humuline Regular (NL); Insuline Velosulin Humaan (NL); Insuman (AT, BE, BG, BR, CH, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Insuman Basal (DE); Insuman Infusat (DE); Insuman R (EC); Insuman Rapid (DE); Novolet R (KP); Novolin R (CL, EC, KP, PE); Orgasulin Rapid (FR); Ransulin-R (PH); Scilin R (HK, PH); Velosulin (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Velosulin HM (AT); Velosuline Humaine (FR); Wosulin-R (PH)

Interferon Alfa-2a

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Interferon alfa-2a may be confused with interferon alfa-2b, interferon alfa-n3, pegylated interferon alfa-2b

Roferon-A® may be confused with Rocephin®

International issues:

Interferon alfa-2a may be confused with interferon alpha multi-subtype which is available in international markets

Pronunciation(in ter FEER on AL fa too aye)

U.S. Brand NamesRoferon®-A [DSC]

Canadian Brand NamesRoferon®-A

Pharmacologic CategoryInterferon

Use: Labeled Indications

Patients >18 years of age: Treatment of hairy cell leukemia, chronic hepatitis C

Children and Adults: Treatment of Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) in chronic phase, within 1 year of diagnosis (limited experience in children)

Use: Unlabeled/InvestigationalAdjuvant therapy for malignant melanoma; treatment of AIDS-related Kaposi's sarcoma, carcinoid tumors; bladder, cervical, and ovarian cancers; hemangioma; chronic hepatitis D; low-grade non-Hodgkin's lymphoma; multiple myeloma; renal cell carcinoma; basal and squamous cell skin cancer; cutaneous T-cell lymphoma

Dosing: AdultsRefer to individual protocols.

Hairy cell leukemia: SubQ: 3 million units/day for 16-24 weeks, then 3 million units 3 times/week for up to 6-24 months

Ph+ chronic myelogenous leukemia (CML): SubQ: 9 million units/day, continue treatment until disease progression **or** 3 million units/day for 3 days, followed by 6 million units/day for 3 days, followed by 9 million units daily until disease progression

AIDS-related Kaposi's sarcoma (unlabeled use): SubQ, I.M.: 36 million units/day for 10-12 weeks, then 36 million units 3 times/week; to minimize adverse reactions, can use escalating dose (3-, 9-, then 18 million units each day for 3 days, then 36 million units daily thereafter).

Chronic hepatitis C: SubQ: 3 million units 3 times/week for 12 months **or** 6 million units 3 times/week for 12 weeks followed by 3 million units 3 times/week for 36 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols. Children (limited data):

Ph+ chronic myelogenous leukemia (CML): I.M.: 2.5-5 million units/m^2/day. **Note:** In juveniles, higher dosages (30 million units/m^2/day) have been associated with severe adverse events, including death.

Dosing: Renal ImpairmentNot removed by hemodialysis

Dosing: Combination Regimens

Leukemia, acute lymphocytic: Hyper-CVAD (Leukemia, Acute Lymphocytic)

Renal cell cancer:

Bevacizumab-Interferon Alfa-2a

Interleukin 2-Interferon Alfa-2

Melanoma: CVD-Interleukin-Interferon (Melanoma)

Calculations

- Body Surface Area: Pediatrics

Administration: I.M.May also be administered I.M. (unlabeled route).

Administration: OtherFor SubQ administration, rotate SubQ injection site

StorageRefrigerate (2°C to 8°C/36°F to 46°F); do not freeze. Protect from light. Do not shake.

CompatibilityStable in LR, NS; **incompatible** with D_5W.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to interferon alfa or any component of the formulation; autoimmune hepatitis; hepatic decompensation (Child-Pugh class B or C)

Allergy Considerations

- Interferon Allergy

Warnings/Precautions

Boxed warnings:

- Autoimmune disease: See "Disease-related concerns" below.
- Infectious disorders: See "Disease-related concerns" below.
- Ischemic disorders: See "Disease-related concerns" below.
- Neuropsychiatric disorders: See "Concerns related to adverse effects" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Causes bone marrow suppression, including potentially severe cytopenias, and very rarely, aplastic anemia. Use caution in patients with pre-existing myelosuppression and/or with concomitant medications which cause myelosuppression.
- Flu-like symptoms: Commonly associated with flu-like symptoms, including fever; rule out other causes/infection with persistent or high fever.
- Gastrointestinal effects: Gastrointestinal hemorrhage, ulcerative and hemorrhagic/ischemic colitis have been observed with interferon alfa treatment; may be severe and/or life-threatening; discontinue if symptoms (eg, abdominal pain, bloody diarrhea, and/or fever) develop.
- Hepatic effects: Transient liver abnormalities may occur when treating chronic hepatitis C with interferon alfa-2a; increased ascites, hepatic failure, and death may occur with poorly-compensated liver disease.
- Hypersensitivity: Acute hypersensitivity reactions have been reported (rarely) with alfa interferons.
- Hypertriglyceridemia: Has been reported (discontinue if severe, particularly if combined with symptoms of pancreatitis).
- Infections: Serious and severe infections (bacterial, viral and fungal) have been reported with treatment; evaluate and treat promptly; consider discontinuing interferon.
- Nephrotoxicity: Renal toxicities, some requiring dialysis, have been reported with interferon alfa (alone or in combination with interleukin-2); monitor closely for signs/symptoms of toxicity.
- Neuropsychiatric disorders: **[U.S. Boxed Warning]: May cause severe psychiatric adverse events (eg, depression, psychosis, mania, suicidal behavior/ideation) in patients with and without previous psychiatric symptoms;** use with extreme caution in patients with a history of depression. Careful neuropsychiatric monitoring is required during therapy. Patients developing severe depression may require discontinuation of treatment. Although dose reduction or discontinuation may resolve symptoms, depression may persist; suicides have been reported after therapy has been discontinued. Use with caution in patients with seizure disorders, brain metastases, or compromised CNS function. Higher doses in the elderly or in malignancies other than hairy cell leukemia may result in severe obtundation.
- Ocular effects: Decreased/loss of vision, retinopathy (including macular edema), retinal artery or vein thrombosis, retinal hemorrhages, cotton wool spots, optic neuritis and papilledema have occurred in patients receiving interferon alfa. Use caution in patients with pre-existing ophthalmic disorders; monitor closely and discontinue with new or worsening ophthalmic symptoms.
- Pancreatitis: Has been observed (occasionally fatal); hypertriglyceridemia increases the risk for pancreatitis; consider discontinuing treatment in patients with pancreatitis.
- Pulmonary effects: Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonia, and sarcoidosis, resulting in potential fatal respiratory failure may occur with interferon alfa treatment. Discontinue with unexplained pulmonary infiltrates or evidence of impaired pulmonary function. Use caution in patients with a history of pulmonary disease.

Disease-related concerns:

- Autoimmune disease: **[U.S. Boxed Warning]: Avoid use in patients with history of autoimmune disorders.** Development or exacerbation of autoimmune disorders (thrombocytopenic purpura, vasculitis, Raynaud's disease, rheumatoid arthritis, interstitial nephritis, thyroiditis, lupus erythematosus, and rhabdomyolysis) has been associated with interferon alfa. Monitor closely and consider discontinuing if autoimmune disease develops.
- Cardiovascular disease: Use with caution and monitor closely in patients with history of cardiovascular disease; acute toxicities may exacerbate pre-existing cardiac conditions. MI has been observed (rarely) in patients receiving interferon alfa-2a; cardiomyopathy has been reported (rarely) in patients receiving interferon alfa.
- Diabetes: Use with caution in patients with diabetes mellitus; hyperglycemia has been reported which may require adjustments in

medications.

- Infectious disorders: **[U.S. Boxed Warning]: May cause or aggravate fatal or life-threatening infectious disorders;** discontinue treatment for persistent severe or worsening symptoms.
- Ischemic disorders: **[U.S. Boxed Warning]: May cause or aggravate fatal or life-threatening ischemic disorders;** discontinue treatment for persistent severe or worsening symptoms.
- Renal impairment: Use with caution in patients with renal impairment (Cl_{cr} <50 mL/minute).
- Thyroid disorders: Use with caution in patients with pre-existing thyroid disease; thyroid disorders (hyper- or hypothyroidism) have been reported.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <18 years for uses other than Ph+ CML.
- Transplant recipients: Safety and efficacy have not been established in organ transplant recipients.

Dosage form specific issues:

- Benzyl alcohol: Injection solution contains benzyl alcohol which has been associated with "gasping syndrome" in neonates.
- Product variability: **Due to differences in dosage, patients should not change brands of interferons without the concurrence of their healthcare provider.**

Geriatric ConsiderationsNo specific data is available for the elderly; however, pay close attention to Warnings/Precautions since the elderly often have reduced Cl_{cr} (<50 mL/minute), diabetes, and hyper-/hypothyroidism.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have demonstrated abortifacient effects in large doses. Disruption of the normal menstrual cycle was also observed in animal studies; therefore, the manufacturer recommends that reliable contraception is used in women of childbearing potential. Alfa interferon is endogenous to normal amniotic fluid. *In vitro* administration studies have reported that when administered to the mother, it does not cross the placenta. Case reports of use in pregnant women are limited. The Perinatal HIV Guidelines Working Group does not recommend that interferon-alfa be used during pregnancy. Interferon alfa-2a should only be used in pregnancy when the potential benefit to the mother justifies the possible risk to the fetus.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsBreast milk samples obtained from a lactating mother prior to and after administration of interferon alfa-2b showed that interferon alfa is present in breast milk and administration of the medication did not significantly affect endogenous levels. The AAP considers interferon alfa to be “usually compatible with breast-feeding.” Breast-feeding is not linked to the spread of hepatitis C virus; however, if nipples are cracked or bleeding, breast-feeding is not recommended. Mothers coinfected with HIV are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse Reactions**Note:** A flu-like syndrome (fever, chills, tachycardia, malaise, myalgia, arthralgia, headache) occurs within 1-2 hours of administration; may last up to 24 hours and may be dose limiting.

>10%:

Cardiovascular: Chest pain (<4% to 11%), edema (1% to 11%), hypertension (11%)

Central nervous system: Fever (28% to 92%), fatigue (58% to 88%), headache (44% to 64%), chills (23% to 64%), depression (16% to 28%), pain (24%), dizziness (11% to 21%), mental status decreased (10% to 16%), irritability (15%), insomnia (14%), sleep disturbances (10% to 11%)

Dermatologic: Rash (8% to 44%), alopecia (17% to 19%), pruritus (7% to 13%), dry skin (7% to 17%)

Endocrine & metabolic: Hypocalcemia (28%), hypophosphatemia (22%)

Gastrointestinal: Anorexia (14% to 48%), nausea (33% to 39%), vomiting (33% to 39%), diarrhea (20% to 37%), weight loss (33%), throat irritation (21%), abdominal pain (12%)

Hematologic (often due to underlying disease): Myelosuppression (onset: 7-10 days; nadir 14 days [may be delayed 20-40 days in hairy cell leukemia], recovery: 21 days), neutropenia (≤68%; dose dependant); thrombocytopenia (5% to 62%), leukopenia (2% to 45%), anemia (≤31%)

Hepatic: Alkaline phosphatase increased (≤50%), transaminases increased (≤50%)

Local: Injection site reaction (29%)

Neuromuscular & skeletal: Weakness (6% to 88%) myalgia (51% to 71%), arthralgia (47% to 51%), bone pain (25% to 47%), joint pain (25%), back pain (16%), numbness (12%), paresthesia (7% to 12%)

Respiratory: Cough (1% to 19%), rhinorrhea/rhinitis (3% to 12%), dyspnea (1% to 12%), pneumonia (11%), sinusitis (11%)

Miscellaneous: Flu-like syndrome (16% to 33%), diaphoresis (1% to 22%)

1% to 10%:

Cardiovascular: Dysrhythmia (7%), hypotension (<5%), syncope (<5%), murmur (<5%), thrombophlebitis (<5%), palpitations (<3%), vasculitis (<3%), arrhythmia (1%)

Central nervous system: Confusion (<4% to 7%), anxiety (5% to 6%), lethargy (1% to 6%), nervousness (<5%), vertigo (<5%), concentration impaired (4%), memory loss (<4%), seizure (<4%), behavior disturbances (3%), malaise (1%)

Dermatologic: Bruising (<4%), skin lesions (1% to 3%)

Endocrine & metabolic: Hyperphosphatemia (9%), diabetes (<5%), hyper-/hypothyroidism (<5%), hypertriglyceridemia (<4%), libido changes (<4%), sexual dysfunction (1% to 3%), menstrual irregularity (2%)

Gastrointestinal: Colitis (<5%), gastrointestinal hemorrhage (<5%), pancreatitis (<5%), flatulence (3%), taste change (3% to <4%), stomatitis (1% to <5%), constipation (<3%), digestion impaired (2%), gingival bleeding (≤2%)

Genitourinary: Impotence (<4%), urinary tract infection (1% to 3%)

Hematologic: Coagulopathy (<4%), hemolytic anemia (<3%), hematoma (1%)

Hepatic: Liver pain (3%)

Neuromuscular & skeletal: Involuntary movements (7%), arthritis (≤5%), polyarthritis (5%), gait disturbance (<5%), leg cramps (3%), muscle cramps (1% to 3%)

Ocular: Visual disturbance (6%), conjunctivitis (4%), eye pain (1% to 3%)

Otic: Hearing alteration (<4%)

Renal: Proteinuria (≤10%)

Respiratory: Oropharynx dryness/inflammation (6%), pneumonitis (<5%), epistaxis (≤4%), bronchospasm (<4%), chest congestion (<3%)

Miscellaneous: Herpes virus reactivation (1% to 3%), lupus erythematosus syndrome (<3%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Anaphylactic reaction, anaphylaxis, angioedema, aplastic anemia, ascites, autoimmune reaction with worsening of liver disease, bronchiolitis obliterans, BUN/creatinine increased, cardiomyopathy, coma, CHF, cutaneous eruptions, cyanosis, dysphasia, EEG abnormalities, encephalopathy, hallucinations, hearing loss, hemolytic anemia (Coombs' positive), hemorrhagic colitis, hepatic failure, hepatitis, hyperglycemia, hyperlipidemia, hypersensitivity, hyponatremia (SIADH), inflammation (injection site), macular edema, mania, idiopathic thrombocytopenia purpura, interstitial nephritis, interstitial pneumonitis, ischemic colitis, ischemic retinopathy, LDH increased, MI, myositis, nephrotic syndrome, obtundation, optic neuritis, petechiae, pneumonia, pneumonitis, presenile dementia, proteinuria, psoriasis, psychomotor retardation, psychotic episodes, pulmonary edema, pulmonary infiltrates, Raynaud's phenomenon, renal failure (acute), retinopathy, rhabdomyolysis, sarcoidosis, seizure, serum creatinine increased, somnolence, stroke, suicidal behavior/ideation, syncope, tachypnea, transient ischemic attacks, ulcerative colitis, uric acid increased, urticaria (injection site), vasculitis, visual acuity decreased

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Inhibits** CYP1A2 (weak)
Drug Interactions

Aldesleukin: Interferons (Alfa) may enhance the adverse/toxic effect of Aldesleukin. In particular, risks of myocardial and renal toxicity may be increased by this combination. *Risk D: Consider therapy modification*

Ribavirin: Interferons (Alfa) may enhance the adverse/toxic effect of Ribavirin. Hemolytic anemia has been observed. *Risk C: Monitor therapy*

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Monitoring ParametersCBC with differential and platelets, liver function, electrolytes, triglycerides. Baseline chest x-ray and ECG. Baseline ophthalmologic exam should be performed in all patients, with periodic reassessment in patients with impairment. Patients with thyroid dysfunction should be monitored by TSH levels at baseline and every 3 months during therapy.

Chronic hepatitis C: Monitor ALT (at baseline, after 2 weeks, and monthly thereafter) and HCV-RNA (particularly in first 3 months of therapy)

CML/hairy cell leukemia: Hematologic monitoring should be performed monthly

Nursing: Physical Assessment/MonitoringAssess laboratory results on a regular basis. Monitor for effectiveness of therapy and possible adverse reactions. Monitor for neuropsychiatric changes. Monitor for signs of depression or suicidal ideation. Perform eye exam prior to initiating therapy and periodically during treatment. Monitor weight periodically. Patients with pre-existing cardiac abnormalities or advanced stages of cancer should have ECG before and during treatment. Assess knowledge/instruct patient/caregiver on appropriate reconstitution, injection and needle disposal, possible side effects, and symptoms to report.
Monitoring: Lab TestsBaseline chest x-ray, ECG, CBC with differential and platelets, liver function, electrolytes, triglycerides, TSH (if pre-existing thyroid dysfunction)
Patient EducationUse as directed; do not change dosage, brand, or schedule of administration without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience flu-like syndrome (acetaminophen may help); nausea, vomiting, dry mouth, or metallic taste (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or drowsiness, dizziness, agitation, abnormal thinking (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Inform prescriber **immediately** if you feel depressed or have any thoughts of suicide. Report unusual bruising or bleeding; persistent abdominal disturbances; unusual fatigue; muscle pain or tremors; chest pain or palpitation; swelling of extremities or unusual weight gain; respiratory difficulty; pain, swelling, or redness at injection site; change in vision; or other unusual symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution:

Roferon®-A: 3 million units/0.5 mL (0.5 mL) [contains benzyl alcohol and polysorbate 80] [DSC]; 6 million units/0.5 mL (0.5 mL) [contains benzyl alcohol and polysorbate 80] [DSC]; 9 million units/0.5 mL (0.5 mL) [contains benzyl alcohol and polysorbate 80] [DSC]

Generic AvailableNo
ManufacturerRoche Laboratories Inc
Pricing: U.S. (www.drugstore.com)

Kit (Roferon-A)

9000000 units/0.5 mL (1): $131.99

Mechanism of ActionFollowing activation, multiple effects can be detected including induction of gene transcription. Inhibits cellular growth, alters the state of cellular differentiation, interferes with oncogene expression, alters cell surface antigen expression, increases phagocytic activity of macrophages, and augments cytotoxicity of lymphocytes for target cells

Pharmacodynamics/Kinetics

Distribution: V_d: 0.223-0.748 L/kg

Metabolism: Primarily renal; filtered through glomeruli and undergoes rapid proteolytic degradation during tubular reabsorption

Bioavailability: I.M.: 83%; SubQ: 90%

Half-life elimination: I.V.: 3.7-8.5 hours (mean ~5 hours)

Time to peak, serum: I.M., SubQ: ~4-7 hours

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation), metallic taste, taste change, loss of taste, cough, irritation of oropharynx, dry throat, and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSevere psychiatric disorders including depression, suicidal behavior, ideation, attempts, and suicides have been reported with alfa interferons in patients with and without a previous psychiatric history. Extreme caution should be used in individuals who report a history of depression and patients should be informed of these potential side effects and how to respond if they occur. Careful neuropsychiatric monitoring for depressive symptoms is recommended. Dizziness and drowsiness are common. May cause memory impairment, agitation, manic behavior, and psychotic reactions; may rarely cause delirium.

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation and dry mouth

Anesthesia and Critical Care Concerns/Other ConsiderationsIndications and dosage regimens are specific for a particular brand of interferon; other brands have different indications and dosage guidelines.

Index TermsIFLrA; Interferon Alpha-2a; NSC-367982; rIFN-A

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International Brand NamesMultiferon (MX); Roceron (NO); Roceron-A (DK, FI); Roferon A (AT, BB, BE, BG, BM, BS, BZ, GY, HN, JM, NL, PR, PT, SR, TT); Roferon-A (AE, AR, BF, BH, BJ, BR, CH, CI, CL, CN, CY, CZ, DE, EE, EG, ET, FR, GB, GH, GM, GN, GR, IL, IN, IQ, IR, IT, JO, JP, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NZ, OM, PE, PH, PK, PY, QA, RU, SA, SC, SD, SE, SL, SN, SY, TN, TR, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Roquiferon (MX)

Interferon Alfa-2b and Ribavirin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(in ter FEER on AL fa too bee & rye ba VYE rin)

U.S. Brand NamesRebetron®

Pharmacologic CategoryAntiviral Agent; Interferon

Use: Labeled IndicationsCombination therapy for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with alpha interferon or who have relapsed after alpha interferon therapy

Dosing: Adults

Chronic hepatitis C: Recommended dosage of combination therapy:

- *Intron® A:* SubQ: 3 million int. units 3 times/week **and**
- *Rebetol® capsule:* Oral:
  - ≤75 kg (165 pounds): 1000 mg/day (two 200 mg capsules in the morning and three 200 mg capsules in the evening)
  - >75 kg: 1200 mg/day (three 200 mg capsules in the morning and three 200 mg capsules in the evening)
- **Note:** Treatment duration may vary. Consult current guidelines and literature.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Chronic hepatitis C:**

Children ≥3 years: **Note:** Treatment duration may vary. Consult current guidelines and literature. Combination therapy:

- *Intron® A:* SubQ:
  - 25-61 kg: 3 million int. units/m^2 3 times/week
  - >61 kg: Refer to adult dosing
- *Rebetol®:* Oral: **Note:** Oral solution should be used in children 3-5 years of age, children ≤25 kg, or those unable to swallow capsules.
  - Capsule/solution: 15 mg/kg/day in 2 divided doses (morning and evening)
  - Capsule dosing recommendations:
    - 26-36 kg: 400 mg/day (200 mg morning and evening)
    - 37-49 kg: 600 mg/day (200 mg in the morning and two 200 mg capsules in the evening)
    - 50-61 kg: 800 mg/day (two 200 mg capsules morning and evening)
    - >61 kg: Refer to adult dosing.

Dosing: Renal ImpairmentPatients with Cl_{cr} <50 mL/minutes should not receive ribavirin.

Dosing: Adjustment for Toxicity**Note:** Recommendations (per manufacturer labeling):

Anemia (RBC depression):

- Patient **without** cardiac history:
  - Hemoglobin <10 g/dL:
    - Children: Decrease dose by $^1/_2$
    - Adults: Decrease dose to 600 mg/day
  - Hemoglobin <8.5 g/dL: Permanently discontinue treatment
- Patient **with** cardiac history:
  - Hemoglobin has ≥2 g/dL decrease during any 4-week period of treatment:
    - Children: Decrease ribavirin dose by $^1/_2$**and** decrease interferon alfa-2b to 1.5 million int. units 3 times/week
    - Adults: Decrease dose to ribavirin to 600 mg/day **and** decrease interferon-alfa 2b dose to 1.5 million int. units 3 times/week.

Hemoglobin <12 g/dL after 4 weeks of reduced dose: Permanently discontinue treatment

WBC, neutrophil, or platelet depression:

WBC <1500 cells/mm^3, neutrophils <750 cells/mm^3, or platelet count <50,000 cells/ mm^3 (<80,000 cells/mm^3 in children): Reduce interferon alfa-2b dose to 1.5 million int. units 3 times/week (50% reduction)

WBC <1000 cells/mm^3, neutrophils <500 cells/mm^3, or platelet count <25,000 cells/mm^3 (<50,000 cells/mm^3 in children): Permanently discontinue therapy

Calculations

- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralCapsule should not be opened, crushed, chewed, or broken. Capsules are not for use in children <5 years of age. Use oral solution for children 3-5 years, those ≤25 kg, or those who cannot swallow capsules.

Administration: OtherSee individual agents.

Dietary ConsiderationsTake oral formulation without regard to food, but always in a consistent manner with respect to food intake (ie, always take with food or always take on an empty stomach).

StorageStore the Rebetol® capsules plus Intron® A injection combination package refrigerated between 2°C and 8°C (36°F and 46°F).

When separated, the individual carton of Rebetol® capsules should be stored refrigerated between 2°C and 8°C (36°F and 46°F) or at 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F).

When separated, the individual carton or vial of Intron® A injection and the Intron® A multidose pen should be stored refrigerated between 2°C and 8°C (36°F and 46°F).

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) for treatment of hepatitis C where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to interferon alfa-2b, ribavirin, or any component of the formulation; autoimmune hepatitis; males with a pregnant female partner; pregnancy

Allergy Considerations

- Interferon Allergy

Warnings/Precautions

Boxed warnings:

- Autoimmune disease: See "Disease-related concerns" below.
- Hepatic impairment: See "Disease-related concerns" below.
- Hemolytic anemia: See "Concerns related to adverse effects" below.
- Infectious disorders: See "Disease-related concerns" below.
- Ischemic disorders: See "Disease-related concerns" below.
- Neuropsychiatric disorders: See "Concerns related to adverse effects" below.
- Pregnancy: See "Special populations" below.
- Pulmonary symptoms: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Bone marrow suppression: Intron® A may cause bone marrow suppression, including very rarely, aplastic anemia. Anemia has been observed in patients receiving the interferon/ribavirin combination. Use with caution in patients with myelosuppression.
- CNS toxicity: Higher doses of interferon alfa-2b in diseases other than hairy cell leukemia, may result in increased CNS toxicity.
- Dental/periodontal disorders: Have been reported with ribavirin and interferon therapy; patients should be instructed to brush teeth twice daily and have regular dental exams.
- Hemolytic anemia: **[U.S. Boxed Warning]: Hemolytic anemia is a significant toxicity of ribavirin; usually occurring within 1-2 weeks.** Assess cardiac disease before initiation. Anemia may worsen underlying cardiac disease; use caution. If any deterioration in cardiovascular status occurs, discontinue therapy. Patients with renal dysfunction and/or those >50 years of age should be carefully assessed for development of anemia. Hemolytic anemia (hemoglobin <10 g/dL) was observed in up to 10% of treated patients in clinical trials when interferon alfa-2b was combined with ribavirin.
- Hypertriglyceridemia: Has been reported with interferon alfa-2b; discontinue if severe.
- Neuropsychiatric disorders: **[U.S. Boxed Warning]: Interferon alfa-2b may cause severe psychiatric adverse events (psychosis, mania, depression, suicidal behavior/ideation) in patients with and without previous psychiatric symptoms, avoid use in severe psychiatric disorders or in patients with a history of depression;** careful neuropsychiatric monitoring is required during therapy. Suicidal ideation or attempts may occur more frequently in pediatric patients when compared to adults. Severe psychiatric events have also occurred with ribavirin.

- Ocular effects: Ophthalmologic disorders (including retinal hemorrhages, cotton wool spots and retinal artery or vein obstruction) have occurred in patients receiving alpha interferons.

- Pancreatitis: Discontinue ribavirin therapy in suspected/confirmed pancreatitis.

- Pulmonary symptoms: **[U.S. Boxed Warning]: Interferon alfa-2b treatment should be discontinued in patients who develop severe pulmonary symptoms with chest x-ray changes;** use the combination with caution in patients with pulmonary disease; pulmonary symptoms have been associated with administration.

Disease-related concerns:

- Autoimmune disease: **[U.S. Boxed Warning]: Interferon alfa-2b treatment should be discontinued in patients who develop severe autoimmune disorders.** Avoid use in patients with autoimmune disorders; worsening of psoriasis and/or development of autoimmune disorders has been associated with alpha interferons.

- Bleeding disorders: Use interferon alfa-2b with caution in patients with a history of coagulopathy.

- Cardiovascular disease: Use interferon alfa-2b with caution in patients with cardiac disease (ischemic or thromboembolic), hypertension or arrhythmias.

- CNS disorders: Use interferon alfa-2b with caution in patients with a history of seizures, brain metastases, or multiple sclerosis.

- Diabetes: Use interferon alfa-2b with caution in patients with a history of diabetes mellitus (particularly if prone to DKA).

- Hepatic impairment: **[U.S. Boxed Warning]: Interferon alfa-2b treatment should be discontinued in patients who develop worsening of hepatic function;** use with caution in patients with hepatic impairment. Safety and efficacy of ribavirin have not been established in patients with decompensated liver disease.

- Hepatitis: Safety and efficacy of ribavirin have not been established in patients with concurrent hepatitis B virus. A transient increase in AST (>2x baseline) is common in patients treated with interferon alfa-2b for chronic hepatitis. Therapy generally may continue, however, functional indicators (albumin, prothrombin time, bilirubin) should be monitored at 2-week intervals.

- HIV: Safety and efficacy of ribavirin have not been established in patients with HIV exposure. Do use interferon alfa-2b to treat patients with visceral AIDS-related Kaposi's sarcoma associated with rapidly-progressing or life-threatening disease.

- Infectious disorders: **[U.S. Boxed Warning]: Interferon alfa-2b treatment should be discontinued in patients with worsening or persistently severe signs/symptoms of infectious disorders.**

- Ischemic disorders: **[U.S. Boxed Warning]: Interferon alfa-2b treatment should be discontinued in patients with worsening or persistently severe signs/symptoms of ischemic disorders.**

- Renal impairment: Use interferon alfa-2b with caution in patients with renal impairment; use is not recommended if Cl_{cr}<50 mL/minute.

- Sarcoidosis: Use ribavirin with caution in patients with sarcoidosis (exacerbation reported).

- Thyroid disease: Use interferon alfa-2b with caution in patients with a history of thyroid disease; monitor closely.

Concurrent drug therapy issues:

- Medications causing lactic acidosis: Use with caution in patient receiving medications which may cause lactic acidosis (eg, nucleoside analogues).

Special populations:

- Elderly: Use ribavirin with caution in elderly patients; higher frequency of anemia; take renal function into consideration before initiating. Use higher doses of interferon alfa-2b with caution in the elderly; may cause CNS toxicity.

- Organ transplant recipients: Safety and efficacy of ribavirin have not been established in organ transplant patients.

- Pediatrics: Safety and efficacy have not been established in children <3 years.

- Pregnancy: **[U.S. Boxed Warning]: Avoid pregnancy in female patients and female partners of patients during ribavirin therapy.** Negative pregnancy test is required before initiation and monthly thereafter.

Dosage form specific issues:

- Product variability: **Due to differences in dosage, patients should not change brands of interferons.**

Pregnancy Risk FactorX

Pregnancy ConsiderationsAbortifacient and teratogenic effects have been reported with ribavirin. Negative pregnancy test is required before initiation and monthly thereafter. Avoid pregnancy in female patients and female partners of patients during therapy by using two effective forms of contraception; continue contraceptive measures for at least 6 months after completion of therapy. If patient or female partner becomes pregnant during treatment, she should be counseled about potential risks of exposure. Pregnancies that occur during use, or within 6 months after treatment, should be reported to the manufacturer (800-593-2214).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsWomen with hepatitis C should be instructed that there is a theoretical risk the virus may be transmitted in breast milk.

Adverse Reactions**Note:** Adverse reactions listed are specific to combination regimen in previously untreated hepatitis patients. See individual agents for additional adverse reactions reported with each agent during therapy for other diseases.

>10%:

Central nervous system: Fatigue (children 61%; adults 68%), headache (63%), insomnia (children 14%; adults 39%), fever (children 61%; adults 37%), depression (children 13%; adults 32% to 36%), irritability (children 10%; adults 23% to 32%), dizziness (17% to 23%), emotional lability (children 16%; adults 7% to 11%), impaired concentration (5% to 14%)

Dermatologic: Alopecia (23% to 32%), pruritus (children 12%; adults 19% to 21%), rash (17% to 28%)

Gastrointestinal: Nausea (33% to 46%), anorexia (children 51%; adults 25% to 27%), dyspepsia (children <1%; adults 14% to 16%), vomiting (children 42%; adults 9% to 11%)

Hematologic: Leukopenia, neutropenia (usually recovers within 4 weeks of treatment discontinuation), anemia

Hepatic: Hyperbilirubinemia (27%; only 0.9% to 2% >3.0-6 mg/dL)

Local: Injection site inflammation (13%)

Neuromuscular & skeletal: Myalgia (children 32%; adults 61% to 64%), rigors (40%), arthralgia (children 15%; adults 30% to 33%), musculoskeletal pain (20% to 28%)

Respiratory: Dyspnea (children 5%; adults 18% to 19%)

Miscellaneous: Flu-like syndrome (children 31%; adults 14% to 18%)

1% to 10%:

Cardiovascular: Chest pain (5% to 9%)

Central nervous system: Nervousness (3% to 4%)

Endocrine & metabolic: Thyroid abnormalities (hyper- or hypothyroidism), serum uric acid increased, hyperglycemia

Gastrointestinal: Taste perversion (children <1%; adults 7% to 8%)

Hematologic: Hemolytic anemia (10%), thrombocytopenia

Local: Injection site reaction (7%)

Neuromuscular & skeletal: Weakness (5% to 9%)

Respiratory: Sinusitis (children <1%; adults 9% to 10%)

<1%: Acute hypersensitivity reactions, anaphylaxis, angioedema, aplastic anemia (very rare), arrhythmia, bronchoconstriction, cardiomyopathy, cotton wool spots, diabetes, hearing loss, hepatotoxic reactions, hypotension, MI, pneumonia, pneumonitis, retinal hemorrhages, retinal artery or vein obstruction, severe psychiatric reactions, suicidal behavior, suicidal ideation, tinnitus, urticaria; rare cases of autoimmune diseases including vasculitis, polyarteritis reaction, rheumatoid arthritis, lupus erythematosus, and Raynaud's phenomenon

Postmarketing and/or case reports: Dental disorders, hypertriglyceridemia, nephrotic syndrome, pancreatitis, periodontal disorders, hallucinations, renal failure, sarcoidosis (including exacerbations of sarcoidosis)

Metabolism/Transport EffectsInterferon Alfa-2b: **Inhibits** CYP1A2 (weak)

Drug Interactions

Aldesleukin: Interferons (Alfa) may enhance the adverse/toxic effect of Aldesleukin. In particular, risks of myocardial and renal toxicity may be increased by this combination. *Risk D: Consider therapy modification*

Influenza Virus Vaccine: Antiviral Agents (Influenza A and B) may diminish the therapeutic effect of Influenza Virus Vaccine. This only pertains to live, attentuated influenza virus vaccine. *Risk D: Consider therapy modification*

Interferons (Alfa): May enhance the adverse/toxic effect of Ribavirin. Hemolytic anemia has been observed. *Risk C: Monitor therapy*

Reverse Transcriptase Inhibitors (Nucleoside): Ribavirin may enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Ribavirin: Interferons (Alfa) may enhance the adverse/toxic effect of Ribavirin. Hemolytic anemia has been observed. *Risk C: Monitor therapy*

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Monitoring ParametersObtain pretreatment CBC, liver function tests, TSH, and electrolytes and monitor routinely throughout therapy (at 2 weeks and 4 weeks, more frequently if indicated); discontinue if WBC <1.0 x 10^9/L, neutrophils <0.5 x 10^9/L, platelets <25 x 10^9/L, or if hemoglobin <8.5 g/dL (in cardiac patients, discontinue if hemoglobin <12 g/dL after 4 weeks of dosage reduction). Pretreatment and monthly pregnancy test for women of childbearing age. Baseline chest x-ray, ECG, weight; patients with pre-existing cardiac abnormalities, or in advanced stages of cancer should have ECGs taken before and during treatment; reticulocyte count, serum HCV RNA levels; I & O; dental exams

Reference RangePeak serum level after I.V. infusion of 10 million units: 546 units/mL

Early viral response (EVR): >2 log decrease in HCV RNA after 12 weeks of treatment

End of treatment response (ETR): Absence of detectable HCV RNA at end of the recommended treatment period

Sustained treatment response (STR): Absence of HCV RNA in the serum 6 months following completion of full treatment course

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsObtain pretreatment CBC, liver function tests, TSH, and electrolytes and monitor routinely throughout therapy (at 2 weeks and 4 weeks, more frequently if indicated); discontinue if WBC <1.0 x 10^9/L, neutrophils <0.5 x 10^9/L, platelets <25 x 10^9/L, or if hemoglobin <8.5 g/dL (in cardiac patients, discontinue if hemoglobin <12 g/dL after 4 weeks of dosage reduction). Pretreatment and monthly pregnancy test for women of childbearing age. Reticulocyte count, serum HCV RNA levels

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Combination package:

For patients ≤75 kg [contains single-dose vials]:

Injection, solution: Interferon alfa-2b (Intron® A): 3 million int. units/0.5 mL (0.5 mL) [6 vials (3 million int. units/vial), 6 syringes, and alcohol swabs]

Capsule: Ribavirin (Rebetol®): 200 mg (70s)

For patients ≤75 kg [contains multidose vials]:

Injection, solution: Interferon alfa-2b (Intron® A): 3 million int. units/0.5 mL (3.8 mL) [1 multidose vial (18 million int. units/vial), 6 syringes, and alcohol swabs]

Capsule: Ribavirin (Rebetol®): 200 mg (70s)

For patients ≤75 kg [contains multidose pen]:

Injection, solution: Interferon alfa-2b (Intron® A): 3 million int. units/0.2 mL (1.5 mL) [1 multidose pen (18 million int. units/pen), 6 needles, and alcohol swabs]

Capsule: Ribavirin (Rebetol®): 200 mg (70s)

For patients >75 kg [contains single-dose vials]:

Injection, solution: Interferon alfa-2b (Intron® A): 3 million int. units/0.5 mL (0.5 mL) [6 vials (3 million int. units/vial), 6 syringes, and alcohol swabs]

Capsule: Ribavirin (Rebetol®): 200 mg (84s)

For patients >75 kg [contains multidose vials]:

Injection, solution: Interferon alfa-2b (Intron® A): 3 million int. units/0.5 mL (3.8 mL) [1 multidose vial (18 million int. units/vial), 6 syringes, and alcohol swabs]

Capsule: Ribavirin (Rebetol®): 200 mg (84s)

For patients >75 kg [contains multidose pen]:

Injection, solution: Interferon alfa-2b (Intron® A): 3 million int. units/0.2 mL (1.5 mL) [1 multidose pen (18 million int. units/pen), 6 needles, and alcohol swabs]

Capsule: Ribavirin (Rebetol®): 200 mg (84s)

For Rebetol® dose reduction [contains single-dose vials]:

Injection, solution: Interferon alfa-2b (Intron® A): 3 million int. units/0.5 mL (0.5 mL) [6 vials (3 million int. units/vial), 6 syringes, and alcohol swabs]

Capsule: Ribavirin (Rebetol®): 200 mg (42s)

For Rebetol® dose reduction [contains multidose vials]:

Injection, solution: Interferon alfa-2b (Intron® A): 3 million int. units/0.5 mL (3.8 mL) [1 multidose vial (18 million int. units/vial), 6 syringes, and alcohol swabs]

Capsule: Ribavirin (Rebetol®): 200 mg (42s)

For Rebetol® dose reduction [contains multidose pen]:

Injection, solution: Interferon alfa-2b (Intron® A): 3 million int. units/0.2 mL (1.5 mL) [1 multidose pen (18 million int. units/pen), 6 needles, and alcohol swabs]

Capsule: Ribavirin (Rebetol®): 200 mg (42s)

Generic AvailableNo

ManufacturerSchering-Plough Corp

Pricing: U.S. (www.drugstore.com)

Kit (Rebetron 1000/3 MU Pen)

(1): $690.99

Kit (Rebetron 1200/3 MU Pen)

(1): $772.96

Kit (Rebetron 600/3 MU Pen)

(1): $573.99

Mechanism of Action

Interferon Alfa-2b: Alpha interferons are a family of proteins, produced by nucleated cells, that have antiviral, antiproliferative, and immune-regulating activity. There are 16 known subtypes of alpha interferons. Interferons interact with cells through high affinity cell surface receptors. Following activation, multiple effects can be detected including induction of gene transcription. Inhibits cellular growth, alters the state of cellular differentiation, interferes with oncogene expression, alters cell surface antigen expression, increases phagocytic activity of macrophages, and augments cytotoxicity of lymphocytes for target cells

Ribavirin: Inhibits replication of RNA and DNA viruses; inhibits influenza virus RNA polymerase activity and inhibits the initiation and elongation of RNA fragments resulting in inhibition of viral protein synthesis

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), metallic taste, and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSevere psychiatric disorders, including depression and suicidal behavior, have been associated with interferon use. Careful neuropsychiatric monitoring is recommended.

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsInterferon Alfa-2b and Ribavirin Combination Pack; Ribavirin and Interferon Alfa-2b Combination Pack

References

Dienstag JL and McHutchinson JG, “American Gastroenterological Association Medical Position Statement on the Management of Hepatitis C,” *Gastroenterology*, 2006, 130(1):225-30.[PubMed 16401485]

Hoofnagle JH and Seeff LB,”Peginterferon and Ribavirin for Chronic Hepatitis C,” *N Engl J Med*, 2006, 355(23):2444-51.[PubMed 17151366]

Scottish Intercollegiate Guideline Network (SIGN), “Management of Hepatitis C. A National Clinical Guideline,” Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN), 2006, Dec 49 p. (SIGN publication no. 92).

Strader DB, Wright T, and Thomas DL, et al, “Diagnosis, Management And Treatment Of Hepatitis. American Association for the Study of Liver Diseases,” *Hepatology*, 2004, 39(4):1147-71.[PubMed 15057920]

International Brand NamesHepatron C (MX); Rebetron (AR, HK); Rebetron Combination (NZ)

Interferon Alfa-2b

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Interferon alfa-2b may be confused with interferon alfa-2a, interferon alfa-n3, pegylated interferon alfa-2b

Intron® A may be confused with PEG-Intron®

International issues:

Interferon alfa-2b may be confused with interferon alpha multi-subtype which is available in international markets

Pronunciation(in ter FEER on AL fa too bee)

U.S. Brand NamesIntron® A

Canadian Brand NamesIntron® A

Pharmacologic CategoryInterferon

Use: Labeled Indications

Patients ≥1 year of age: Chronic hepatitis B

Patients ≥3 years of age: Chronic hepatitis C (in combination with ribavirin)

Patients ≥18 years of age: Condyloma acuminata, chronic hepatitis B, chronic hepatitis C, hairy cell leukemia, malignant melanoma, AIDS-related Kaposi's sarcoma, follicular non-Hodgkin's lymphoma

Use: Unlabeled/InvestigationalAIDS-related thrombocytopenia, cutaneous ulcerations of Behçet's disease, neuroendocrine tumors (including carcinoid syndrome and islet cell tumor), cutaneous T-cell lymphoma, desmoid tumor, lymphomatoid granulomatosis, hepatitis D, chronic myelogenous leukemia (CML), non-Hodgkin's lymphomas (other than follicular lymphoma, see approved use), multiple myeloma, renal cell carcinoma, basal and squamous cell skin cancers, West Nile virus

Dosing: AdultsDetails concerning dosing in combination regimens should also be consulted. **Note:** Withhold treatment for ANC <500/mm^3 or platelets <25,000/mm^3. Consider premedication with acetaminophen prior to administration to reduce the incidence of some adverse reactions. Not all dosage forms and strengths are appropriate for all indications; refer to product labeling for details.

Hairy cell leukemia: I.M., SubQ: 2 million units/m^2 3 times/week for up to 6 months (may continue treatment with continued treatment response)

Lymphoma (follicular): SubQ: 5 million units 3 times/week for up to 18 months

Malignant melanoma: Induction: 20 million units/m^2 I.V. for 5 consecutive days per week for 4 weeks, followed by maintenance dosing of 10 million units/m^2 SubQ 3 times/week for 48 weeks

AIDS-related Kaposi's sarcoma: I.M., SubQ: 30 million units/m^2 3 times/week

Chronic hepatitis B: I.M., SubQ: 5 million units/day or 10 million units 3 times/week for 16 weeks

Chronic hepatitis C: I.M., SubQ: 3 million units 3 times/week for 16 weeks. In patients with normalization of ALT at 16 weeks, continue treatment for 18-24 months; consider discontinuation if normalization does not occur at 16 weeks. **Note:** May be used in combination therapy with ribavirin in previously untreated patients or in patients who relapse following alpha interferon therapy.

Condyloma acuminata: Intralesionally: 1 million units/lesion (maximum: 5 lesions/treatment) 3 times/week (on alternate days) for 3 weeks. May administer a second course at 12-16 weeks.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDetails concerning dosing in combination regimens should also be consulted.

Chronic hepatitis B: SubQ: Children 1-17 years: 3 million units/m^2 3 times/week for 1 week; then 6 million units/m^2 3 times/week; maximum: 10 million units 3 times/week; total duration of therapy 16-24 weeks

Dosing: Renal ImpairmentCombination therapy with ribavirin (hepatitis C) should not be used in patients with reduced renal function (Cl$_{cr}$ <50 mL/minute).

Dosing: Adjustment for Toxicity Manufacturer-recommended adjustments, listed according to indication:

Lymphoma (follicular):

Neutrophils >1000/mm^3 to <1500/mm^3: Reduce dose by 50%; may re-escalate to starting dose when neutrophils return to >1500/mm^3

Severe toxicity (neutrophils <1000/mm^3 or platelets <50,000/mm^3): Temporarily withhold

AST >5 times ULN or serum creatinine >2 mg/dL: Permanently discontinue

Hairy cell leukemia, chronic hepatitis C: Severe toxicity: Reduce dose by 50% or temporarily withhold and resume with 50% dose reduction; permanently discontinue if persistent or recurrent severe toxicity is noted

Chronic hepatitis B:

WBC <1500/mm^3, granulocytes <750/mm^3, or platelet count <50,000/mm^3, or other laboratory abnormality or severe adverse reaction: Reduce dose by 50%; may re-escalate to starting dose upon resolution of hematologic toxicity. Discontinue for persistent intolerance.

WBC <1000/mm^3, granulocytes <500/mm^3, or platelet count <25,000/mm^3: Permanently discontinue

Kaposi sarcoma: Severe toxicity: Reduce dose by 50% or temporarily withhold; may resume at reduced dose with toxicity resolution; permanently discontinue for persistent/recurrent toxicities

Malignant melanoma:

Severe toxicity (neutrophils >250/mm^3 to <500/mm^3 or ALT/AST >5-10 times ULN): Temporarily withhold; resume with a 50% dose reduction when adverse reaction abates

Neutrophils <250/mm^3, ALT/AST >10 times ULN, or severe/persistent adverse reactions: Permanently discontinue

Dosing: Combination Regimens

Head and neck cancer: PFL + IFN

Leukemia, acute lymphocytic: Hyper-CVAD (Leukemia, Acute Lymphocytic)

Lymphoma, non-Hodgkin's: Fludarabine-Mitoxantrone-Dexamethasone-Rituximab

Melanoma:

BOLD + Interferon

Cisplatin-Dacarbazine-Interferon Alfa-2b-Aldesleukin

CVD-Interleukin-Interferon (Melanoma)

Renal cell cancer:

Interleukin 2 (Low Dose)-Interferon Alfa 2b

Interleukin 2-Interferon Alfa-2

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Administer in evening (if possible)

Administration: I.V.Infuse over ~20 minutes

Administration: I.V. DetailpH: 6.9-7.5

Administration: OtherSubQ administration is suggested for those who are at risk for bleeding or are thrombocytopenic. Rotate SubQ injection site. Administer in evening (if possible). Patient should be well hydrated. Reconstitute with recommended amount of SWFI and agitate gently; do not shake. **Note:** Different vial strengths require different amounts of diluent. Not every dosage form is appropriate for every indication; refer to manufacturer's labeling.

StorageStore powder and solution for injection (vials and pens) under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze.

Powder for injection: Following reconstitution, should be used immediately, but may be stored under refrigeration for up to 24 hours.

Prefilled pens: After first use, discard unused portion after 4 weeks.

ReconstitutionThe manufacturer recommends reconstituting vial with the diluent provided (SWFI). To prepare solution for infusion, further dilute appropriate dose in NS 100 mL. Final concentration should be ≥10 million units/100 mL.

CompatibilityStable in LR, NS; **incompatible** with D$_5$W.

RestrictionsAn FDA-approved medication guide is available at http://www.fda.gov/cder/Offices/ODS/labeling.htm; distribute to each patient to whom this medication is dispensed.

ContraindicationsHypersensitivity to interferon alfa or any component of the formulation; decompensated liver disease; autoimmune hepatitis

Warnings/Precautions

Boxed warnings:

- Autoimmune disease: See “Disease-related concerns” below.

- Infectious disorders: See "Disease-related concerns" below.

- Ischemic disorders: See "Disease-related concerns" below.

- Neuropsychiatric disorders: See "Concerns related to adverse effects" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Causes bone marrow suppression, including potentially severe cytopenias, and very rarely, aplastic anemia. Discontinue treatment for severe neutropenia (ANC <500/mm^3) or thrombocytopenia (platelets <25,000/mm^3). Hemolytic anemia (hemoglobin <10 g/dL) was observed in up to 10% of treated patients in clinical trials when combined with ribavirin; anemia occurred within 1-2 weeks of initiation of therapy. Use caution in patients with pre-existing myelosuppression and in patients with concomitant medications which cause myelosuppression.

- Cerebrovascular events: Hemorrhagic cerebrovascular events have been observed.

- Flu-like symptoms: Commonly associated with fever and flu-like symptoms; rule out other causes/infections with persistent fever. Use with caution in patients with debilitating conditions.

- Hepatic effects: May cause hepatotoxicity; monitor closely if abnormal liver function tests develop. A transient increase in ALT (≥2 times baseline) may occur in patients treated with interferon alfa-2b for chronic hepatitis B. Therapy generally may continue, however, functional indicators (eg, albumin, prothrombin time, bilirubin) should be monitored frequently. Worsening and potentially fatal liver disease, including jaundice, hepatic encephalopathy, and hepatic failure have been reported in patients receiving interferon alfa for chronic hepatitis B and C with decompensated liver disease, autoimmune hepatitis, history of autoimmune disease, and immunosuppressed transplant recipients; avoid interferon treatment (if appropriate) in these patients. Discontinue treatment in any patient developing signs or symptoms of liver failure.

- Hypersensitivity: Acute hypersensitivity reactions have been reported (rarely) with alfa interferons.

- Hypertriglyceridemia: Has been reported (discontinue if severe, particularly if combined with symptoms of pancreatitis).

- Neuropsychiatric disorders: **[U.S. Boxed Warning]: May cause severe psychiatric adverse events (eg, depression, psychosis, mania, suicidal behavior/ideation) in patients with and without previous psychiatric symptoms;** avoid use in patients with pre-existing psychiatric condition, severe psychiatric disorder or history of severe depression; careful neuropsychiatric monitoring is required during and for 6 months after therapy. Suicidal ideation or attempts may occur more frequently in pediatric patients when compared to adults. Discontinue in patients developing severe depression or psychiatric disorders. Higher doses in elderly patients, or diseases other than hairy cell leukemia, may result in increased CNS toxicity.

- Ocular effects: Decreased/loss of vision, macular edema, optic neuritis, retinal hemorrhages, cotton wool spots, papilledema, and retinal artery or vein thrombosis have occurred (or been aggravated) in patients receiving alpha interferons. Use caution in patients with pre-existing eye disorders; monitor closely; discontinue with new or worsening ophthalmic disorders.

- Pulmonary effects: Pulmonary infiltrates, pneumonitis and pneumonia have been reported with interferon alfa therapy; occurs more frequently in patients being treated for chronic hepatitis C. Patients with fever, cough, dyspnea or other respiratory symptoms should be evaluated with a chest x-ray; monitor closely and consider discontinuing treatment with evidence of impaired pulmonary function. Use with caution in patients with a history of pulmonary disease.

Disease-related concerns:

- AIDS-related Kaposi's sarcoma: Do not treat patients with visceral AIDS-related Kaposi's sarcoma associated with rapidly-progressing or life-threatening disease.

- Autoimmune disease: **[U.S. Boxed Warning]: Avoid use in patients with history of autoimmune disorders;** development of autoimmune disorders (thrombocytopenia, vasculitis, Raynaud's disease, rheumatoid arthritis, lupus erythematosus and rhabdomyolysis) has been associated with alfa interferons. Monitor closely if autoimmune disease develops; consider discontinuing. Worsening of psoriasis and sarcoidosis (and the development of new sarcoidosis) have been reported; use caution in patients with these conditions.

- Cardiovascular disease: Use with caution and monitor closely in patients patients with cardiovascular disease (ischemic or thromboembolic), arrhythmias, hypertension, and in patients with a history of MI or prior therapy with cardiotoxic drugs. Patients with pre-existing cardiac disease and/or advanced cancer should have baseline and periodic ECGs. May cause hypotension (during administration or delayed), arrhythmia, tachycardia, cardiomyopathy (~2% in AIDS-related Kaposi's Sarcoma patients) and/or MI.

- Chronic hepatitis: Patients being treated for chronic hepatitis B or C with a history of autoimmune disease or who are immunosuppressed transplant recipients should not receive interferon alfa-2b.

- Coagulation disorders: Use with caution and monitor closely in patients with coagulation disorders.

- Diabetes: Has been reported; discontinue if diabetes cannot be effectively managed with medication. Use caution in patients with a history of diabetes mellitus, particularly if prone to DKA.

- Infectious disorders: **[U.S. Boxed Warning]: May cause or aggravate fatal or life-threatening infectious disorders;** discontinue treatment for persistent severe or worsening symptoms.

- Ischemic disorders: **[U.S. Boxed Warning]: May cause or aggravate fatal or life-threatening ischemic disorders;** discontinue treatment for persistent severe or worsening symptoms.

- Thyroid disorders: Use with caution in patients with pre-existing thyroid disease; thyroid disorders (hyper- or hypothyroidism) have been reported. Some have been irreversible upon discontinuation of treatment. Discontinue use in patients with thyroid disease who cannot maintain normal ranges with thyroid medication.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <1 year of age.

Dosage form specific issues:

- Albumin: Some formulations contain albumin, which may carry a remote risk of viral transmission, including a theoretical risk of Creutzfeldt-Jakob disease transmission.

- Product variability: **Due to differences in dosage, patients should not change brands of interferons without the concurrence of their healthcare provider.**

Pregnancy Risk FactorC / X in combination with ribavirin

Pregnancy ConsiderationsAnimal studies have demonstrated abortifacient effects. Disruption of the normal menstrual cycle was also observed in animal studies; therefore, the manufacturer recommends that reliable contraception is used in women of childbearing potential. Alfa interferon is endogenous to normal amniotic fluid. *In vitro* administration studies have reported that when administered to the mother, it does not cross the placenta. Case reports of use in pregnant women are limited. The Perinatal HIV Guidelines Working Group does not recommend that interferon-alfa be used during pregnancy. Interferon alfa-2b monotherapy should only be used in pregnancy when the potential benefit to the mother justifies the possible risk to the fetus. Combination therapy with ribavirin is contraindicated in pregnancy (refer to Ribavirin monograph); a pregnancy registry has been established for women inadvertently exposed to ribavirin while pregnant (800-593-2214).

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsBreast milk samples obtained from a lactating mother prior to and after administration of interferon alfa-2b showed that interferon alfa is present in breast milk and administration of the medication did not significantly affect endogenous levels. The AAP considers interferon alfa to be “usually compatible with breast-feeding.” Breast-feeding is not linked to the spread of hepatitis C virus; however, if nipples are cracked or bleeding, breast-feeding is not recommended. Mothers coinfected with HIV are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse Reactions**Note:** In a majority of patients, a flu-like syndrome (fever, chills, tachycardia, malaise, myalgia, headache), occurs within 1-2 hours of administration; may last up to 24 hours and may be dose limiting.

>10%:

Cardiovascular: Chest pain (≤28%)

Central nervous system: Fatigue (8% to 96%), fever (34% to 94%), headache (21% to 62%), chills (≤54%), depression (3% to 40%; grades 3/4: 2%), somnolence (≤33%), dizziness (≤24%), irritability (≤22%), pain (≤18%), amnesia (≤14%), concentration impaired (≤14%), malaise (≤14%), confusion (≤12%), insomnia (≤12%)

Dermatologic: Alopecia (≤38%), rash (≤25%), pruritus (≤11%)

Endocrine & metabolic: Amenorrhea (≤12%)

Gastrointestinal: Anorexia (1% to 69%), nausea, (17% to 66%), diarrhea (2% to 45%), vomiting (2% to 32%), xerostomia (≤28%), taste alteration (≤24%), abdominal pain (1% to 23%), constipation (≤14%), gingivitis (≤14%), weight loss (<1% to 13%)

Hematologic: Neutropenia (≤92%; grade 4: 1% to 4%), leukopenia (≤68%), anemia (≤32%), thrombocytopenia (≤15%)

Hepatic: AST increased (≤63%; grades 3/4: 14%), ALT increased (≤15%), pain (upper right quadrant: up to 15%); alkaline phosphatase increased (≤13%)

Local: Injection site reaction (≤20%)

Neuromuscular & skeletal: Myalgia (28% to 75%), weakness (≤63%), rigors (≤42%), paresthesia (1% to 21%), skeletal pain (≤21%), arthralgia (≤19%), back pain (≤19%)

Renal: BUN increased (≤12%)

Respiratory: Dyspnea (≤34%), cough (≤31%), pharyngitis (≤31%), sinusitis (≤21%)

Miscellaneous: Flu-like syndrome (≤79%), diaphoresis (1% to 21%), moniliasis (≤17%)

5% to 10%:

Cardiovascular: Edema (≤10%), hypertension (≤9%)

Central nervous system: Hypoesthesia (≤10%), anxiety (≤9%), vertigo (≤8%), agitation (≤7%)

Dermatologic: Dry skin (≤10%), dermatitis (≤8%), purpura (≤5%)

Endocrine & metabolic: Libido decreased (≤5%)

Gastrointestinal: Loose stools (≤10%), dyspepsia (≤8%)

Genitourinary: Urinary tract infection (≤5%)

Renal: Polyuria (≤10%), serum creatinine increased (≤6%)

Respiratory: Bronchitis (≤10%), nasal congestion (≤10%), epistaxis (≤7%)

Miscellaneous: Infection (≤7%), herpes virus infections (≤5%)

<5%, postmarketing, and/or case reports (limited to important or life-threatening):

Cardiovascular: Angina, arrhythmia, arteritis, atrial fibrillation, bradycardia, cardiac failure, cardiomegaly, cardiomyopathy, coronary artery disorder, ejection fraction decreased, extrasystoles, flushing, heart valve disorder, hypotension, MI, palpitation, peripheral ischemia, polyarteritis, Raynaud's disease, syncope, tachycardia, thrombosis, vasculitis

Central nervous system: Nervousness (≤3%), aggression, alcohol intolerance, aphasia, ataxia, Bell’s palsy, coma, extrapyramidal disorder, hallucination, hypothermia, mania, migraine, neurosis, paranoia, psychosis, stroke, suicidal attempt/ideation, seizure

Dermatologic: Angioedema, cellulitis, dermatitis lichenoides, eczema, epidermal necrolysis, erythema, erythema multiforme, erythematous rash, folliculitis, hirsutism, lipoma, maculopapular rash, photosensitivity, psoriasis, psoriasis exacerbation, sebaceous cyst, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Endocrine & metabolic: Dehydration, diabetes mellitus, goiter, hot flashes, hypercalcemia, hyperglycemia, hyper-/hypothyroidism, hypertriglyceridemia, mastitis, menorrhagia, sexual dysfunction

Gastrointestinal: Colitis, dysphasia, esophagitis, gastritis, gastrointestinal hemorrhage, mucositis, pancreatitis, rectal bleeding/hemorrhage, stomatitis, ulcerative stomatitis

Genitourinary: Cystitis, dysuria, incontinence, impotence, leukorrhea, nocturia, pelvic pain, uterine bleeding

Hematologic: Aplastic anemia (rarely), granulocytopenia, hemolytic anemia, hypochromic anemia, lymphopenia, lymphadenitis, lymphadenopathy, lymphocytosis, pure red cell aplasia, thrombocytopenia purpura (idiopathic and thrombotic)

Hepatic: Ascites, biliary pain, bilirubinemia, hepatic encephalopathy, hepatic failure, hepatitis, hepatotoxicity, jaundice, lactate dehydrogenase increased (up to 1%), liver function test abnormal

Local: Injection site necrosis

Neuromuscular & skeletal: Arthritis, carpal tunnel syndrome, hyporeflexia, leg cramps, muscle atrophy, myositis, neuralgia, neuropathy, rhabdomyolysis, rheumatoid arthritis, spondylitis, tendonitis, tremor

Ocular: Blurred vision, conjunctivitis, cotton wool spots, macular edema, nystagmus, optic neuritis, papilledema, photophobia, retinal artery thrombosis, retinal vein thrombosis

Otic: Hearing impairment, hearing loss

Renal: Albuminuria, hematuria, nephrotic syndrome, proteinuria, renal failure, renal insufficiency

Respiratory: Asthma, bronchoconstriction, bronchospasm, cyanosis, hemoptysis, hypoventilation, pleural effusion, pneumonitis, pneumothorax, pulmonary embolism, pulmonary fibrosis, respiratory insufficiency, upper respiratory tract infection, wheezing

Miscellaneous: Abscess, acute hypersensitivity reaction, allergic reactions, anaphylaxis, fungal infection, lupus erythematosus, sarcoidosis, sarcoidosis exacerbation, sepsis

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Metabolism/Transport Effects**Inhibits** CYP1A2 (weak)

Drug Interactions

Aldesleukin: Interferons (Alfa) may enhance the adverse/toxic effect of Aldesleukin. In particular, risks of myocardial and renal toxicity may be increased by this combination. *Risk D: Consider therapy modification*

Ribavirin: Interferons (Alfa) may enhance the adverse/toxic effect of Ribavirin. Hemolytic anemia has been observed. *Risk C: Monitor therapy*

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Monitoring ParametersBaseline chest x-ray, ECG; CBC with differential and platelets (baseline and routinely during treatment), liver function tests, serum creatinine, electrolytes, triglycerides, thyroid function tests (baseline and periodically during treatment); weight; ophthalmic exam (baseline and periodic, or with new ocular symptoms); patients with pre-existing cardiac abnormalities or in advanced stages of cancer should have ECGs taken before and during treatment

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests on a regular basis, therapeutic effectiveness, and adverse reactions. Patients with pre-existing cardiac abnormalities, or in advanced stages of cancer should have ECGs taken before and during treatment. Monitor for neuropsychiatric changes. Assess knowledge/instruct patient/caregiver on appropriate reconstitution, injection and needle disposal, possible side effects, and symptoms to report.

Monitoring: Lab TestsCBC with differential and platelets (baseline and routinely during treatment), liver function tests, serum creatinine, electrolytes, triglycerides, thyroid function tests (baseline and periodically during treatment)

Patient EducationUse as directed; do not change dosage or schedule of administration without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience flu-like syndrome (acetaminophen may help); nausea, vomiting, dry mouth, or metallic taste (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); fatigue, drowsiness, insomnia, dizziness, agitation, abnormal thinking (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Inform prescriber **immediately** if you feel depressed or have any thoughts of suicide. Report unusual bruising or bleeding; persistent abdominal disturbances; unusual fatigue; muscle pain or tremors; fever; chest pain or palpitation; swelling of extremities or unusual weight gain; respiratory difficulty; pain, swelling, or redness at injection site; decreased vision; or other unusual symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] =

Discontinued product

Injection, powder for reconstitution [preservative free]:

Intron® A: 10 million units; 18 million units; 50 million units [contains human albumin]

Injection, solution [multidose prefilled pen]:

Intron® A:

Delivers 3 million units/0.2 mL (1.5 mL) [delivers 6 doses; 18 million units; contains polysorbate 80; edetate disodium]

Delivers 5 million units/0.2 mL (1.5 mL) [delivers 6 doses; 30 million units; contains polysorbate 80; edetate disodium]

Delivers 10 million units/0.2 mL (1.5 mL) [delivers 6 doses; 60 million units; contains polysorbate 80; edetate disodium]

Injection, solution [multidose vial]:

Intron® A: 6 million units/mL (3 mL); 10 million units/mL (2.5 mL) [contains polysorbate 80; edetate disodium]

Injection, solution [single-dose vial]:

Intron® A: 10 million units/ mL (1 mL) [DSC] [contains polysorbate 80; edetate disodium]

See also Interferon Alfa-2b and Ribavirin Combination Pack monograph.

Generic AvailableNo

ManufacturerSchering-Plough Corp

Pricing: U.S. (www.drugstore.com)

Kit (Intron-A)

5000000 units/0.2 mL (1): $616.73

10000000 units/0.2 mL (1): $1008.58

Mechanism of ActionFollowing activation, multiple effects can be detected including induction of gene transcription. Inhibits cellular growth, alters the state of cellular differentiation, interferes with oncogene expression, alters cell surface antigen expression, increases phagocytic activity of macrophages, and augments cytotoxicity of lymphocytes for target cells

Pharmacodynamics/Kinetics

Distribution: V_d: 31 L; but has been noted to be much greater (370-720 L) in leukemia patients receiving continuous infusion IFN; IFN does not penetrate the CSF

Metabolism: Primarily renal

Bioavailability: I.M.: 83%; SubQ: 90%

Half-life elimination: I.V.: ~2 hours; I.M., SubQ: ~2-3 hours

Time to peak, serum: I.M., SubQ: ~3-12 hours

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), metallic taste, taste alteration, and gingivitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and drowsiness are common; may rarely cause delirium. Severe psychiatric disorders, including depression and suicidal behavior, have been associated with some interferons. Careful neuropsychiatric monitoring is recommended.

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation and dry mouth

Anesthesia and Critical Care Concerns/Other ConsiderationsIndications and dosage regimens are specific for a particular brand of interferon; other brands have different indications and dosage guidelines.

Index TermsINF-alpha 2; Interferon Alpha-2b; NSC-377523; rLFN-α2; α-2-interferon

References

ACOG Practice Bulletin No. 86: "Viral Hepatitis in Pregnancy," *Obstet Gynecol*, 2007, 110(4):941-56.[PubMed 17906043]

"American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk," *Pediatrics*, 2001, 108(3):776-89. [PubMed 11533352]

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Wills RJ, “Clinical Pharmacokinetics of Interferons,” *Clin Pharmacokinet*, 1990, 19(5):390-9. [PubMed 1702693]

International Brand NamesBioferon (PY, TH, UY); FNI 2B (MX); Intron A (AR, AT, AU, BE, BG, BR, CH, CL, CN, CO, CR, CZ, DE, DK, DO, ES, FI, FR, GB, GR, GT, HK, HN, IE, IL, IT, JP, KE, NI, NL, NO, PA, PE, PK, PT, RU, SE, SV, TR, TW, VE); Intron-A (GR, ID, MY, SG); Introna (AT, DK, FI, FR, NO, SE); Kalferon (ID); Peg-Intron (HK, KP); Realfa (IN); Shanferon (PH); Uniferon (PH); Viraferon (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Interferon Alfa-n3

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Alferon® may be confused with Alkeran®

Pronunciation(in ter FEER on AL fa en three)

U.S. Brand NamesAlferon® N

Canadian Brand NamesAlferon® N

Pharmacologic CategoryInterferon

Use: Labeled IndicationsPatients ≥18 years of age: Intralesional treatment of refractory or recurring genital or venereal warts (condylomata acuminata)

Dosing: AdultsCondylomata acuminata: Intralesional: Inject 250,000 units (0.05 mL) in each wart twice weekly for a maximum of 8 weeks; therapy should not be repeated for at least 3 months after the initial 8-week course of therapy

Dosing: ElderlyRefer to adult dosing.

StorageStore solution at 2°C to 8°C (36°F to 46°F); do not freeze or shake solution.

ContraindicationsHypersensitivity to alpha interferon or any component of the formulation; anaphylactic sensitivity to mouse immunoglobulin, egg protein, or neomycin

Allergy Considerations

- Interferon Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Flu-like symptoms: Flu-like symptoms are common; may aggravate debilitating conditions.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with severe myelosuppression.
- Cardiovascular disease: Use with caution in patients with pre-existing cardiac disease, including unstable angina, uncontrolled HF, or arrhythmias.
- Coagulation disorders: Use with caution in patients with coagulation disorders (such as thrombophlebitis, pulmonary embolism, hemophilia).
- Diabetes: Use with caution in patients with diabetes with ketoacidosis.
- Pulmonary disease: Use with caution in patients with severe pulmonary disease.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Special populations:

- Pediatrics: Safety and efficacy have not been not established in children.

Dosage form specific issues:

- Albumin: Contains albumin, which may carry a remote risk of transmitting Creutzfeldt-Jakob or other viral diseases.
- Product variability: **Due to differences in dosage, patients should not change brands of interferons.**

Pregnancy Risk FactorC

Pregnancy ConsiderationsSafety and efficacy for use during pregnancy have not been established. Interferon alpha has been shown to decrease serum estradiol and progesterone levels in humans. Menstrual irregularities and abortion have been reported in animals. Effective contraception is recommended during treatment.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions**Note:** Adverse reaction incidence noted below is specific to intralesional administration in patients with condylomata acuminata. Flu-like reactions, consisting of headache, fever, and/or myalgia, were reported in 30% of patients, and abated with repeated dosing.

>10%:

Central nervous system: Fever (40%), headache (31%), chills (14%), fatigue (14%)

Hematologic: Decreased WBC (11%)

Neuromuscular & skeletal: Myalgia (45%)

Miscellaneous: Flu-like syndrome (30%)

1% to 10%:

Central nervous system: Malaise (9%), dizziness (9%), depression (2%), insomnia (2%), thirst (1%)

Dermatologic: Pruritus (2%)

Gastrointestinal: Nausea (45), vomiting (3%), dyspepsia (3%), diarrhea (2%), tongue hyperesthesia (1%), taste disturbance (1%)

Genitourinary: Groin lymph node swelling (1%)

Neuromuscular & skeletal: Arthralgia (5%), back pain (4%), cramps (1%), paresthesia (1%)

Ocular: Visual disturbance (1%)

Respiratory: Rhinitis (2%), pharyngitis (1%), nosebleed (1%)

Miscellaneous: Diaphoresis increased (2%), vasovagal reaction (2%)

<1%: Dysuria, hot flashes, impaired concentration, nervousness, photosensitivity. Rare adverse reactions reported with other alfa-interferons include depression, suicide, autoimmune disorders, ophthalmic disorders.

Drug Interactions

Aldesleukin: Interferons (Alfa) may enhance the adverse/toxic effect of Aldesleukin. In particular, risks of myocardial and renal toxicity may be increased by this combination. *Risk D: Consider therapy modification*

Ribavirin: Interferons (Alfa) may enhance the adverse/toxic effect of Ribavirin. Hemolytic anemia has been observed. *Risk C: Monitor therapy*

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 5 million int. units (1 mL) [contains albumin]

Generic AvailableNo

Mechanism of ActionInterferons interact with cells through high affinity cell surface receptors. Following activation, multiple effects can be detected including induction of gene transcription. Inhibits cellular growth, alters the state of cellular differentiation, interferes with oncogene expression, alters cell surface antigen expression, increases phagocytic activity of macrophages, and augments cytotoxicity of lymphocytes for target cells

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), metallic taste, tongue hyperesthesia, abnormal taste, thirst, rhinitis, pharyngitis, nosebleed, increased diaphoresis, taste disturbance, and gingivitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and drowsiness are common; may cause delirium or neurotoxicity. Severe psychiatric disorders, including depression and suicidal behavior, have been associated with some interferons. Careful neuropsychiatric monitoring is recommended.

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation and dry mouth

Anesthesia and Critical Care Concerns/Other ConsiderationsIndications and dosage regimens are specific for a particular brand of interferon; other brands have different indications and dosage guidelines.

References

Vial T and Descotes J, “Clinical Toxicity of the Interferons,” *Drug Saf*, 1994, 10(2):115-50.[PubMed 7516663]

International Brand NamesAlferon N (CA)

Interferon Alfacon-1

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Interferon alfacon-1 may be confused with interferon alfa-2a, interferon alfa-2b, interferon alfa-n3, peginterferon alfa-2b

International issues:

Interferon alfacon-1 may be confused with interferon alpha multi-subtype which is available in international markets

Pronunciation(in ter FEER on AL fa con one)

U.S. Brand NamesInfergen®

Pharmacologic CategoryInterferon

Use: Labeled IndicationsTreatment of chronic hepatitis C virus (HCV) infection in patients ≥18 years of age with compensated liver disease and anti-HCV serum antibodies or HCV RNA.

Dosing: AdultsChronic HCV infection: SubQ: 9 mcg 3 times/week for 24 weeks; allow 48 hours between doses.

Patients who have previously tolerated interferon therapy but did not respond or relapsed: SubQ: 15 mcg 3 times/week week for up to 48 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricNot indicated for patients <18 years of age.

Dosing: Hepatic ImpairmentUse in decompensated hepatic disease is contraindicated.

Dosing: Adjustment for ToxicityDose should be held in patients who experience a severe adverse reaction, and treatment should be stopped or decreased if the reaction does not become tolerable.

Doses were reduced from 9 mcg to 7.5 mcg in the pivotal study.

For patients receiving 15 mcg/dose, doses were reduced in 3 mcg decrements. Efficacy is decreased with doses <7.5 mcg.

Administration: OtherInterferon alfacon-1 is given by SubQ injection, 3 times/week, with at least 48 hours between doses. Allow to reach room temperature just prior to administration.

StorageStore in refrigerator 2°C to 8°C (36°F to 46°F); do not freeze. Avoid exposure to direct sunlight. Do not shake vigorously.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to interferon alfacon-1 or any component of the formulation, other alpha interferons, or *E. coli*-derived products; decompensated liver disease; autoimmune hepatitis

Allergy Considerations

- Interferon Allergy

Warnings/Precautions

Boxed warnings:

- Autoimmune disease: See “Disease-related concerns” below.
- Infectious disorders: See “Disease-related concerns” below.
- Ischemic disorders: See “Disease-related concerns” below.
- Neuropsychiatric disorders: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Causes bone marrow suppression, including potentially severe cytopenias; discontinue for ANC <500/mm^{3}and platelets <50,000/mm^3. Use with caution in patients with low peripheral blood counts or myelosuppression, including concurrent use of myelosuppressive therapy.
- Cardiovascular events: Hypertension, palpitations, tachycardia, and tachyarrhythmias have been reported with interferon alfacon-1use.

Alfa interferon treatment has been associated with supraventricular arrhythmias, chest pain and MI. Use with caution in patients with pre-existing cardiac disease.

- Flu-like symptoms: Commonly associated with flu-like symptoms, including fever; rule out other causes/infection with persistent or high fever.

- Gastrointestinal effects: Gastrointestinal hemorrhage, ulcerative and hemorrhagic/ischemic colitis have been observed with interferon alfa treatment, including alfacon-1; may be severe and/or life-threatening; discontinue if symptoms (eg, abdominal pain, bloody diarrhea, and/or fever) develop.

- Hypersensitivity: Acute hypersensitivity reactions have been reported (rarely) with alfa interferons.

- Nephrotoxicity: Increases in serum creatinine and (rarely) renal failure have been reported with use; monitor closely for signs/symptoms of toxicity.

- Neuropsychiatric disorders: **[U.S. Boxed Warning]: May cause severe psychiatric adverse events (eg, depression, psychosis, mania, suicidal behavior/ideation) in patients with and without previous psychiatric symptoms;** use with extreme caution in patients with a history of depression. Careful neuropsychiatric monitoring is required during therapy. Patients developing severe depression may require discontinuation of treatment. Although dose reduction or discontinuation may resolve symptoms, depression may persist; suicides have been reported after therapy with alfa interferons has been discontinued. Use with caution in patients with seizure disorders, brain metastases, or compromised CNS function.

- Ocular effects: Decreased/loss of vision, retinopathy (including macular edema), retinal artery or vein thrombosis, retinal hemorrhages, cotton wool spots, optic neuritis and papilledema have occurred in patients receiving other alpha interferons. Use caution in patients with pre-existing ophthalmic disorders; monitor closely and discontinue with new or worsening ophthalmic symptoms. Visual exams are recommended for patients with diabetes mellitus or hypertensive retinopathy.

- Pancreatitis: Has been observed (occasionally fatal); hypertriglyceridemia increases the risk for pancreatitis; discontinue treatment in patients with confirmed pancreatitis.

- Pulmonary effects: Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonia, and sarcoidosis, resulting in potential fatal respiratory failure may occur with interferon alfa treatment, including interferon alfacon-1. Discontinue with unexplained pulmonary infiltrates or evidence of impaired pulmonary function. Use caution in patients with a history of pulmonary disease.

Disease-related concerns:

- Autoimmune disease: **[U.S. Boxed Warning]: Avoid use in patients with history of autoimmune disorders.** Development or exacerbation of autoimmune disorders (thrombocytopenic purpura, vasculitis, Raynaud’s disease, rheumatoid arthritis, interstitial nephritis, thyroiditis, lupus erythematosus, and rhabdomyolysis) has been associated with interferon alfa. Monitor closely and consider discontinuing if autoimmune disease develops. Use is contraindicated in patients with autoimmune hepatitis.

- Diabetes: Use with caution in patients with diabetes mellitus; hyperglycemia has been reported which may require adjustments in medications. Discontinue interferon alfacon-1 if unable to control blood sugars with medication during treatment.

- Hepatic impairment: Use with caution in patients with hepatic impairment; may be at risk for hepatic decompensation with alfa interferon therapy. Monitor closely; discontinue with signs (eg, jaundice, ascites, coagulopathy, hypoalbuminemia) of hepatic decompensation.

- Infectious disorders: **[U.S. Boxed Warning]: May cause or aggravate fatal or life-threatening infectious disorders;** discontinue treatment for persistent severe or worsening symptoms.

- Ischemic disorders: **[U.S. Boxed Warning]: May cause or aggravate fatal or life-threatening ischemic disorders;** discontinue treatment for persistent severe or worsening symptoms.

- Renal impairment: Use with caution in patients with renal impairment; interferon alfacon-1 has not been studied in these patients. Monitor closely.

- Thyroid disorders: Use with caution in patients with pre-existing thyroid disease; thyroid disorders (hyper- or hypothyroidism) have been reported. Discontinue interferon alfacon-1 if unable to control thyroid disorders with medication during treatment.

Special populations:

- Immunocompromised patients: Use with caution in chronically-immunosuppressed patients, including transplantation recipients.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Product variability: **Due to differences in dosage, patients should not change brands of interferons without the concurrence of their healthcare provider.**

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere have been no well-controlled studies in pregnant women. Animal studies have shown embryolethal or abortifacient effects. Males and females who are being treated with interferon alfacon-1 should use effective contraception.

LactationExcretion in breast milk unknown/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsWomen with hepatitis C should be instructed that there is a theoretical risk the virus may be transmitted in breast milk.

Adverse ReactionsAdverse reactions reported using 9 mcg/dose interferon alfacon-1 3 times/week. Flu-like symptoms (which included headache, fatigue, fever, myalgia, rigors, arthralgia, and increased diaphoresis) were the most commonly reported adverse reaction; this was reported separately from flu-like syndrome.

>10%:

Cardiovascular: Chest pain (13%)

Central nervous system: Headache (82%), fatigue (69%), fever (61%), insomnia (39%), nervousness (31%), depression (26%), dizziness (22%), anxiety (19%), emotional lability (12%), malaise (11%)

Dermatologic: Alopecia (14%), pruritus (14%), rash (13%)

Endocrine & metabolic: Hot flashes (13%)

Gastrointestinal: Abdominal pain (41%), nausea (40%), diarrhea (29%), anorexia (24%), dyspepsia (21%), vomiting (12%)

Hematologic: Granulocytopenia (23%), thrombocytopenia (3% to 19%), leukopenia (15%)

Local: Injection site erythema (23%)

Neuromuscular & skeletal: Myalgia (58%), rigors (57%), body pain (54%), arthralgia (51%), back pain (42%), limb pain (26%), neck pain (14%), skeletal pain (14%), paresthesia (13%)

Respiratory: Pharyngitis (34%), upper respiratory tract infection (31%), cough (22%), sinusitis (17%), rhinitis (13%), respiratory tract congestion (12%)

Miscellaneous: Flu-like syndrome (15%), diaphoresis increased (12%)

1% to 10%:

Cardiovascular: Peripheral edema (9%), hypertension (5%), tachycardia (4%), palpitation (3%)

Central nervous system: Amnesia (10%), hypoesthesia (10%), abnormal thinking (8%), agitation (6%), confusion (4%), somnolence (4%), apathy (2%), hyperesthesia (1%)

Dermatologic: Bruising (6%), erythema (6%), dry skin (6%), wound (4%)

Endocrine & metabolic: Thyroid test abnormalities (9%), dysmenorrhea (9%), triglycerides increased (6%), menstrual disorder (6%), decreased libido (5%), hypothyroidism (4%), menorrhagia (3%)

Gastrointestinal: Constipation (9%), flatulence (8%), toothache (7%), salivation decreased (6%), hemorrhoids (6%), weight loss (5%), taste perversion (3%), stomatitis (3%), gingivitis (2%)

Genitourinary: Vaginitis (8%), genital moniliasis (2%)

Hematologic: Anemia (1% to 2%)

Hepatic: Liver tenderness (5%), hepatomegaly (3%), prothrombin time increased (3%)

Local: Injection site pain (9%), access pain (8%), injection site bruising (6%)

Neuromuscular & skeletal: Weakness (9%), hypertonia (7%), musculoskeletal disorder (4%)

Ocular: Conjunctivitis (8%), eye pain (5%), vision abnormalities (3%)

Otic: Tinnitus (6%), earache (5%), otitis (2%)

Respiratory: Upper respiratory tract congestion (10%), epistaxis (8%), dyspnea (7%), bronchitis (6%)

Miscellaneous: Allergic reaction (7%), lymphadenopathy (6%), lymphocytosis (5%), infection (3%)

<1%, postmarketing, and/or case reports: Abdominal distension, abnormal gait, arthritis, ascites, ataxia, autoimmune disorders exacerbated, bone pain, cerebrovascular hemorrhage, cerebrovascular ischemia, creatinine increased, dehydration, delusion, diabetes, gastritis, gastrointestinal bleeding, hallucinations, hearing impairment, hearing loss, hemorrhage, hemorrhagic/ischemic colitis, hepatic encephalopathy, hepatic function abnormal, hyperbilirubinemia, hyperglycemia, hypersensitivity, injection site necrosis, injection site ulcer, jaundice, loss of consciousness, memory impairment, pancreatitis, pyoderma gangrenosum, renal failure, rhabdomyolysis, seizure, sepsis, speech disorder, tachyarrhythmias, toxic epidermal necrolysis, transaminases increased, tremor, visual field defect

Drug Interactions

Aldesleukin: Interferons (Alfa) may enhance the adverse/toxic effect of Aldesleukin. In particular, risks of myocardial and renal toxicity may be increased by this combination. *Risk D: Consider therapy modification*

Ribavirin: Interferons (Alfa) may enhance the adverse/toxic effect of Ribavirin. Hemolytic anemia has been observed. *Risk C: Monitor therapy*

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Monitoring Parameters

Hemoglobin and hematocrit; white blood cell count; platelets; triglycerides; thyroid function. Laboratory tests should be taken prior to therapy, 2 weeks after therapy has begun, and periodically during treatment. HCV RNA, ALT to determine success/response to therapy.

The following guidelines were used during the clinical studies as acceptable baseline values:

Platelet count ≥75 x 10^9/L

Hemoglobin ≥100 g/L

ANC ≥1500 x 10^6/L

S_{cr} <180 µmol/L (<2 mg/dL) or Cl_{cr} >0.83 mL/second (>50 mL/minute)

Serum albumin ≥25 g/L

Bilirubin WNL

TSH and T_4 WNL

Patients should also be monitored for signs of depression. Patients with pre-existing diabetes mellitus or hypertensive retinopathy should have a baseline ophthalmic exam and periodic exams during therapy.

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor for signs of depression and suicidal ideation. Assess results of laboratory tests on a regular basis during therapy. Patient with pre-existing diabetes mellitus or hypertension should have an ophthalmic exam prior to beginning treatment. Patient must be monitored closely for adverse reactions. If self-administered, instruct patient in appropriate storage, injection technique, and syringe disposal. Assess knowledge/teach patient purpose for use, adverse reactions and interventions, and adverse reactions to report.

Monitoring: Lab TestsHemoglobin and hematocrit, white blood cell count, platelets, triglycerides, and thyroid function. Laboratory tests should be taken prior to therapy, 2 weeks after therapy has begun, and periodically during treatment. HCV RNA, and ALT to determine success/response to therapy.

The following guidelines were used during the clinical studies as acceptable baseline values:

Platelet count ≥75 x 10^9/L

Hemoglobin ≥100 g/L

ANC ≥1500 x 10^6/L

S_{cr} <180 µmol/L (<2 mg/dL) or Cl_{cr} >0.83 mL/second (>50 mL/minute)

Serum albumin ≥25 g/L

Bilirubin WNL

TSH and T_4 WNL

Patient EducationUse exactly as directed (if self-administered, follow exact instructions for injection and syringe disposal). Do not alter dosage or brand of medication without consulting prescriber. You will need frequent laboratory tests during course of therapy. If you have diabetes or hypertension you should have ophthalmic exam prior to beginning therapy. You may experience headache, dizziness, nervousness, anxiety (use caution when driving or engaging in dangerous tasks until response to medication is known); nausea, vomiting, diarrhea, or loss of appetite (small frequent meals, frequent mouth care, sucking hard candy or chewing gum may help); flu-like symptoms such as headache, fatigue, muscle or joint pain, increased perspiration (mild non-narcotic analgesic may help); or hair loss (will probably grow back when treatment is completed). Promptly report any persistent GI upset; insomnia, depression, suicide ideation, anxiety, nervousness; chest pain or palpitations; muscle, bone, or joint pain; respiratory difficulties or congestion; abdominal pain; unusual bruising or bleeding; yellowing of skin; vision changes; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Infergen®: 30 mcg/mL (0.3 mL, 0.5 mL)

Generic AvailableNo

ManufacturerValeant Pharmaceuticals North America

Pricing: U.S. (www.drugstore.com)

Injection (Infergen)

15 mcg/0.5 mL (0.5): $122.62

Mechanism of ActionInterferon alfacon-1 is a member of the alpha interferon family of proteins, which are produced by nucleated cells, and have antiviral, antiproliferative, and immune-regulating activity. Interferons interact with cells through high affinity cell surface receptors. Following activation, multiple effects can be detected. Interferons induce gene transcription, inhibit cellular growth, alter the state of cellular differentiation, interfere with oncogene expression, alter cell surface antigen expression, increase phagocytic activity of macrophages, and augment cytotoxicity of lymphocytes for target cells. Although all alpha interferons share similar properties, the actual biological effects vary between subtypes.

Pharmacodynamics/KineticsPharmacokinetic studies have not been conducted on patients with chronic hepatitis C.

Time to peak: Healthy volunteers: 24-36 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusUse caution in those patients with depressive disorders. Severe psychiatric adverse effects, including depression, suicidal ideation, and suicide attempt may occur. Fatigue, insomnia, nervousness, depression, anxiety, and emotional lability are common.

Mental Health: Effects on Psychiatric TreatmentGranulocytopenia, thrombocytopenia, and leukopenia are common. Use caution with clozapine, carbamazepine, and valproate.

Anesthesia and Critical Care Concerns/Other ConsiderationsIndications and dosage regimens are specific for a particular brand of interferon; other brands have different indications and dosage guidelines.

References

"American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk," *Pediatrics*, 2001, 108(3):776-89.[PubMed 11533352]

International Brand NamesInfergen (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PL, PT, RU, SE, TR)

Interferon Beta-1a

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Avonex® may be confused with Avelox®

Pronunciation(in ter FEER on BAY ta won aye)

U.S. Brand NamesAvonex®; Rebif®

Canadian Brand NamesAvonex®; Rebif®

Pharmacologic CategoryInterferon

Use: Labeled IndicationsTreatment of relapsing forms of multiple sclerosis (MS)

Dosing: AdultsMultiple sclerosis: **Note:** Analgesics and/or antipyretics may help decrease flu-like symptoms on treatment days:

I.M. (Avonex®): 30 mcg once weekly

SubQ (Rebif®): Doses should be separated by at least 48 hours:

Target dose 44 mcg 3 times/week:

Initial: 8.8 mcg (20 % of final dose) 3 times/week for 2 weeks

Titration: 22 mcg (50% of final dose) 3 times/week for 2 weeks

Final dose: 44 mcg 3 times/week

Target dose 22 mcg 3 times/week:

Initial: 4.4 mcg (20 % of final dose) 3 times/week for 2 weeks

Titration: 11 mcg (50% of final dose) 3 times/week for 2 weeks

Final dose: 22 mcg 3 times/week

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic ImpairmentRebif®: If liver function tests increase or in case of leukopenia: Decrease dose 20% to 50% until toxicity resolves

Administration: I.M.Avonex®: Must be given by I.M. injection.

Administration: OtherRebif®: Administer SubQ at the same time of day on the same 3 days each week (ie, late afternoon/evening Mon, Wed, Fri). Rotate injection sites.

Storage

Avonex®:

Prefilled syringe: Store at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Allow to warm to room temperature prior to use (do not use external heat source). If refrigeration is not available, product may be stored at ≤25°C (77°F) for up to 7 days.

Vial: Store unreconstituted vial at 2°C to 8°C (36°F to 46°F). If refrigeration is not available, may be stored at 25°C (77°F) for up to 30 days; do not freeze. Protect from light. Following reconstitution, use immediately, but may be stored up to 6 hours at 2°C to 8°C (36°F to 46°F); do not freeze.

Rebif®: Store at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. May also be stored ≤25°C (77°F) for up to 30 days if protected from heat and light.

ReconstitutionAvonex®: Reconstitute with 1.1 mL of diluent and swirl gently to dissolve. Do not shake. The reconstituted product contains no preservative and is for single-use only; discard unused portion.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to natural or recombinant interferons, human albumin, or any other component of the formulation

Allergy Considerations

- Interferon Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Allergic reactions, including anaphylaxis, have been reported.

- Autoimmune disorders: Autoimmune disorders including idiopathic thrombocytopenia, hyper- and hypothyroidism and rarely autoimmune hepatitis have been reported.

- Bone marrow suppression: Pancytopenia (rare) and thrombocytopenia have been reported; use with caution in patients with bone marrow suppression.

- Flu-like symptoms: Associated with a high incidence of flu-like adverse effects; use of analgesics and/or antipyretics on treatment days may be helpful.

- Hepatic effects: Rare cases of severe hepatic injury, including hepatic failure, have been reported in patients receiving interferon beta-1a; risk may be increased by ethanol use or concurrent therapy with hepatotoxic drugs. Treatment should be suspended if jaundice or symptoms of hepatic dysfunction occur. Some reports indicate symptoms began after 1-6 months of treatment. Transaminase elevations may be asymptomatic, so monitoring is important.

- Neuropsychiatric disorders: Interferons have been associated with severe psychiatric adverse events (psychosis, mania, depression, suicidal behavior/ideation) in patients with and without previous psychiatric symptoms, avoid use in severe psychiatric disorders and use caution in patients with a history of depression; patients exhibiting symptoms of depression should be closely monitored and discontinuation of therapy should be considered.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with pre-existing cardiovascular disease, including angina, HF, and/or arrythmia. Rare cases of new-onset cardiomyopathy and/or HF have been reported.

- Hepatic impairment: Use with caution in patients with hepatic impairment or in those who abuse alcohol. Dosage adjustment may be necessary.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Special populations:

- Chronic progressive MS: Safety and efficacy have not been established for this use.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Albumin: Some formulations contain albumin, which may carry a remote risk of transmitting Creutzfeldt-Jakob or other viral diseases. Interferon beta-1a is contraindicated in albumin-sensitive patients.

Pregnancy Risk FactorC
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Consideration should be given to discontinue treatment if a woman becomes pregnant, or plans to become pregnant during therapy. A dose-related abortifacient activity was reported in Rhesus monkeys.

Healthcare providers are encouraged to register pregnant women receiving Rebif® during pregnancy online at www.rebifpregnancyregistry.com or by telephone at MS LifeLines 1-877-44-REBIF. A registry has been established for women who become pregnant while receiving Avonex®. Women may be enrolled in the registry by calling 1-800-456-2255.

LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsPotential for serious adverse reactions. Because its use has not been evaluated during lactation, a decision should be made to either discontinue breast-feeding or discontinue the drug.
Adverse Reactions**Note:** Adverse reactions reported as a composite of both commercially-available products. Spectrum and incidence of reactions is generally similar between products, but consult individual product labels for specific incidence.

>10%:

Central nervous system: Headache (58% to 70%), fatigue (33% to 41%), fever (20% to 28%), pain (23%), chills (19%), depression (18% to 25%), dizziness (14%)

Gastrointestinal: Nausea (23%), abdominal pain (8% to 22%)

Genitourinary: Urinary tract infection (17%)

Hematologic: Leukopenia (28% to 36%)

Hepatic: ALT increased (20% to 27%), AST increased (10% to 17%)

Local: Injection site reaction (3% to 92%)

Neuromuscular & skeletal: Myalgia (25% to 29%), back pain (23% to 25%), weakness (24%), skeletal pain (10% to 15%), rigors (6% to 13%)

Ocular: Vision abnormal (7% to 13%)

Respiratory: Sinusitis (14%), upper respiratory tract infection (14%)

Miscellaneous: Flu-like syndrome (49% to 59%), neutralizing antibodies (significance not known; Avonex® 5%; Rebif® 24%), lymphadenopathy (11% to 12%)

1% to 10%:

Cardiovascular: Chest pain (5% to 6%), vasodilation (2%)

Central nervous system: Migraine (5%), somnolence (4% to 5%), malaise (4% to 5%), seizure (1% to 5%)

Dermatologic: Erythematous rash (5% to 7%), maculopapular rash (4% to 5%), alopecia (4%), urticaria

Endocrine & metabolic: Thyroid disorder (4% to 6%)

Gastrointestinal: Xerostomia (1% to 5%), toothache (3%)

Genitourinary: Micturition frequency (2% to 7%), urinary incontinence (2% to 4%)

Hematologic: Thrombocytopenia (2% to 8%), anemia (3% to 5%)

Hepatic: Bilirubinemia (2% to 3%)

Local: Injection site pain (8%), injection site bruising (6%), injection site necrosis (1% to 3%), injection site inflammation

Neuromuscular & skeletal: Arthralgia (9%), hypertonia (6% to 7%), coordination abnormal (4% to 5%)

Ocular: Eye disorder (4%), xerophthalmia (1% to 3%)

Respiratory: Bronchitis (8%)

Miscellaneous: Infection (7%)

<1%, postmarketing, and/or case reports: Anaphylaxis, autoimmune hepatitis, cardiomyopathy, CHF, hepatic failure, hepatitis, hyper-/hypothyroidism, idiopathic thrombocytopenia, injection site abscess/cellulitis, menorrhagia, metrorrhagia, pancytopenia, psychiatric disorders (new or worsening; including suicidal ideation), vesicular rash

Drug Interactions

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Monitoring ParametersThyroid function tests, CBC with differential, transaminase levels, symptoms of autoimmune disorders, signs/symptoms of psychiatric disorder (including depression and/or suicidal ideation), signs/symptoms of new onset/worsening cardiovascular disease

Avonex®: Frequency of monitoring for patients receiving Avonex® has not been specifically defined; in clinical trials, monitoring was at 6-month intervals.

Rebif®: CBC and liver function testing at 1-, 3-, and 6 months, then periodically thereafter. Thyroid function every 6 months (in patients with pre-existing abnormalities and/or clinical indications)

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests on a regular a basis, therapeutic effectiveness, and adverse reactions. Monitor for signs of depression and suicidal ideation. Assess knowledge/instruct patient/caregiver on appropriate reconstitution, injection and needle disposal, possible side effects, and symptoms to report.

Monitoring: Lab TestsThyroid function, transaminase levels, blood chemistries, CBC and differential, BUN, creatinine

Avonex®: Frequency of monitoring has not been specifically defined; in clinical trials, monitoring was at 6-month intervals.

Rebif®: CBC and liver function testing at 1-, 3-, and 6 months, then periodically thereafter; thyroid function every 6 months (in patients with pre-existing abnormalities and/or clinical indications)

Patient EducationThis is not a cure for MS; you will continue to receive regular treatment and follow-up for MS. Use as directed; do not change dosage or schedule of administration without consulting prescriber. If self-injecting and you miss a dose, take it as soon as you remember, but two injections should not be given within 48 hours of each other. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience flu-like syndrome (analgesics and/or antipyretics may help); nausea, vomiting, or loss of appetite (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or drowsiness, sleep disturbances, dizziness, agitation, or abnormal thinking (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Inform prescriber **immediately** if you feel depressed or have any thoughts of suicide. Report unusual bruising or bleeding; persistent abdominal disturbances; unusual fatigue; muscle pain or tremors; chest pain or palpitations; shortness of breath; swelling of extremities; visual disturbances; pain, swelling, or redness at injection site; seizures; or other unusual symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Combination package [preservative free] (Rebif® Titration Pack):

Injection, solution: 8.8 mcg/0.2 mL (0.2 mL) [6 prefilled syringes; contains albumin]

Injection, solution: 22 mcg/0.5 mL (0.5 mL) [6 prefilled syringes; contains albumin]

Injection, powder for reconstitution (Avonex®): 33 mcg [6.6 million units; provides 30 mcg/mL following reconstitution] [contains albumin; packaged with SWFI, alcohol wipes, and access pin and needle]

Injection, solution (Avonex®): 30 mcg/0.5 mL (0.5 mL) [albumin free; prefilled syringe; syringe cap contains latex; packaged with alcohol wipes, gauze pad, and adhesive bandages]

Injection, solution [preservative free] (Rebif®): 22 mcg/0.5 mL (0.5 mL) [prefilled syringe; contains albumin]; 44 mcg/0.5 mL (0.5 mL) [prefilled syringe; contains albumin]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Kit (Avonex)

30 mcg/0.5 mL (4): $2099.99

30 mcg/vial (4): $2178.20

Solution (Rebif)

22 mcg/0.5 mL (0.5): $204.30

44 mcg/0.5 mL (6): $2387.09

Solution (Rebif Titration Pack)

6X8.8 & 6X22 mcg (4.2): $2260.96

Mechanism of ActionInterferon beta differs from naturally occurring human protein by a single amino acid substitution and the lack of carbohydrate side chains; alters the expression and response to surface antigens and can enhance immune cell activities. Properties of interferon beta that modify biologic responses are mediated by cell surface receptor interactions; mechanism in the treatment of MS is unknown.

Pharmacodynamics/Kinetics

Onset of action: Avonex®: 12 hours (based on biological response markers)

Duration: Avonex®: 4 days (based on biological response markers)

Half-life elimination: Avonex®: 10 hours; Rebif®: 69 hours

Time to peak, serum: Avonex® (I.M.): 3-15 hours; Rebif® (SubQ): 16 hours

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), and toothache.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation, anxiety, agitation, or confusion. Severe psychiatric disorders, including depression and suicidal behavior, have been associated with the use of some interferons. Careful neuropsychiatric monitoring is recommended.

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation

Index TermsrIFN beta-1a

References

Jacobs LD, Beck RW, Simon JH, et al, “Intramuscular Interferon Beta-1a Therapy Initiated During a First Demyelinating Event in Multiple Sclerosis. CHAMPS Study Group, *N Engl J Med*, 2000, 343(13):898-904.

Panitch H, Goodin DS, Francis G, et al, “Randomized, Comparative Study of Interferon Beta-1a Treatment Regimens in MS: The EVIDENCE Trial. EVIDENCE Study Group. Evidence of Interferon Dose-Response: European North American Comparative Efficacy; University of British Columbia MS/MRI Research Group,” *Neurology*, 2002, 59(10):1496-506.[PubMed 12451188]

International Brand NamesAvonex (AR, AT, AU, BE, BG, BR, CH, CN, CO, CZ, DE, DK, EC, EE, ES, FI, FR, GB, GR, HN, IE, IL, IT, NL, NO, PE, PT, PY, RU, SE, TR, UY, VE); Betaferon (HU, LU, ZA); Emaxem (CR, DO, EC, GT, HN, NI, PA, SV); Rebif (AR, AU, BG, BR, CH, CL, CZ, DE, DK, EE, ES, FR, GB, HK, HN, HU, IE, IL, IN, MX, MY, NL, PE, PH, SE, SG, TH, TW)

Interferon Beta-1b

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(in ter FEER on BAY ta won bee)
U.S. Brand NamesBetaseron®
Canadian Brand NamesBetaseron®
Pharmacologic CategoryInterferon
Use: Labeled IndicationsTreatment of relapsing forms of multiple sclerosis (MS); treatment of first clinical episode with MRI features consistent with MS
Dosing: Adults**Note:** Gradual dose-titration, analgesics, and/or antipyretics may help decrease flu-like symptoms on treatment days.

Multiple sclerosis (relapsing): SubQ: Initial: 0.0625 mg (2 million units; 0.25 mL) every other day; gradually increase dose by 0.0625 every 2 weeks

Target dose: 0.25 mg (8 million units; 1 mL) every other day

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricNot recommended in children <18 years of age
Administration: OtherSubQ: Withdraw 1 mL of reconstituted solution from the vial into a sterile syringe fitted with a 27-gauge needle and inject the solution subcutaneously. Sites for self-injection include outer surface of the arms, abdomen, hips, and thighs. Rotate SubQ injection site. Patient should be well hydrated.
StorageStore at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). If not used immediately following reconstitution, refrigerate solution at 2°C to 8°C (36°F to 46°F); do not freeze or shake solution.
ReconstitutionTo reconstitute solution, inject 1.2 mL of diluent (provided); gently swirl to dissolve, do not shake. Reconstituted solution provides 0.25 mg/mL (8 million units). Use product within 3 hours of reconstitution.
RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guide is available at http://www.berlex.com/html/products/pi/Betaseron_Medication_Guide.pdf.
ContraindicationsHypersensitivity to *E. coli*-derived products, natural or recombinant interferon beta, albumin human or any other component of the formulation
Allergy Considerations

- Interferon Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis: Has been reported rarely with use.
- Flu-like symptoms: Associated with a high incidence of flu-like adverse effects; use of analgesics and/or antipyretics on treatment days may be helpful.
- Hepatotoxicity: Has been reported with beta interferons, including rare reports of hepatitis (autoimmune) and hepatic failure requiring transplant; use with caution in patients with hepatic impairment.
- Infection: Increased risk of infection.
- Injection site reactions: Severe injection site reactions (necrosis) may occur, which may or may not heal with continued therapy; patient and/or caregiver competency in injection technique should be confirmed and periodically re-evaluated.
- Neuropsychiatric disorders: Interferons have been associated with severe psychiatric adverse events (psychosis, mania, depression, suicidal behavior/ideation) in patients with and without previous psychiatric symptoms, avoid use in severe psychiatric disorders and use caution in patients with a history of depression; patients exhibiting symptoms of depression should be closely monitored and discontinuation of therapy should be considered.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with bone marrow suppression.
- Cardiovascular disease: Use with caution in patients with pre-existing cardiovascular disease.
- Respiratory disease: Use with caution in patients with respiratory disease.
- Renal impairment: Use with caution in patients with renal impairment.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Albumin: Contains albumin, which may carry a remote risk of transmitting Creutzfeldt-Jakob or other viral diseases.

Geriatric ConsiderationsNo specific recommendations necessary for use in the elderly. Monitor for CNS adverse effects which may be significant in the elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsA dose-related abortifacient activity was reported in Rhesus monkeys. There are no adequate and well-controlled studies in pregnant women. Treatment should be discontinued if a woman becomes pregnant, or plans to become pregnant during therapy.
LactationExcretion in breast milk unknown/contraindicated
Breast-Feeding ConsiderationsBecause its use has not been evaluated during lactation, breast-feeding is not recommended
Adverse Reactions**Note:** Flu-like symptoms (including at least two of the following - headache, fever, chills, malaise, diaphoresis, and myalgia) are reported in the majority of patients (60%) and decrease over time (average duration ~1 week).

>10%:

Cardiovascular: Peripheral edema (15%), chest pain (11%)

Central nervous system: Headache (57%), fever (36%), pain (51%), chills (25%), dizziness (24%), insomnia (24%)

Dermatologic: Rash (24%), skin disorder (12%)

Endocrine & metabolic: Metrorrhagia (11%)

Gastrointestinal: Nausea (27%), diarrhea (19%), abdominal pain (19%), constipation (20%), dyspepsia (14%)

Genitourinary: Urinary urgency (13%)

Hematologic: Lymphopenia (88%), neutropenia (14%), leukopenia (14%)

Local: Injection site reaction (85%), inflammation (53%), pain (18%)

Neuromuscular & skeletal: Weakness (61%), myalgia (27%), hypertonia (50%), myasthenia (46%), arthralgia (31%), incoordination (21%)

Miscellaneous: Flu-like syndrome (decreases over treatment course; 60%)

1% to 10%:

Cardiovascular: Palpitation (4%), vasodilation (8%), hypertension (7%), tachycardia (4%), peripheral vascular disorder (6%)

Central nervous system: Anxiety (10%), malaise (8%), nervousness (7%)

Dermatologic: Alopecia (4%)

Endocrine & metabolic: Menorrhagia (8%), dysmenorrhea (7%)

Gastrointestinal: Weight gain (7%)

Genitourinary: Impotence (9%), pelvic pain (6%), cystitis (8%), urinary frequency (7%), prostatic disorder (3%)

Hematologic: Lymphadenopathy (8%)

Hepatic: ALT increased >5x baseline (10%), AST increased >5x baseline (3%)

Local: Injection site necrosis (4% to 5%), edema (3%), mass (2%)

Neuromuscular & skeletal: Leg cramps (4%)

Respiratory: Dyspnea (7%)

Miscellaneous: Diaphoresis (8%), hypersensitivity (3%)

<1% (Limited to important or life-threatening): Anaphylactoid reaction, anemia, apnea, arrhythmia, asthma, blindness, cardiac arrest, cardiomegaly, cardiomyopathy, cerebral hemorrhage, cholecystitis, coma, delirium, depression, diabetes mellitus, diabetes insipidus, erythema nodosum, esophagitis, ethanol intolerance, exfoliative dermatitis, gastrointestinal hemorrhage, hallucinations, heart failure, hematemesis, hepatitis, hepatomegaly, hypercalcemia, hyper-/hypoglycemia, hypothermia, hypothyroidism, manic reaction, MI, nephritic syndrome, pancreatitis, pericardial effusion, photosensitivity, psoriasis, psychosis, pulmonary embolism, rash (maculopapular and vesiculobullous), renal calculus, sepsis, shock, suicidal ideation, syncope, SIADH, thrombocytopenia, tremor, vaginal hemorrhage

Postmarketing and/or case reports: Anorexia, ataxia, bronchospasm, capillary leak syndrome (in patients with pre-existing monoclonal gammopathy), confusion, depersonalization, DVT, emotional lability, gamma GT increase, hepatic failure, hyperthyroidism, hyperuricemia, hypocalcemia, paresthesia, pneumonia, pruritus, seizure, skin discoloration, thyroid dysfunction, triglyceride increased, urinary tract infection, urosepsis, urticaria, vasculitis, vomiting, weight loss

Drug Interactions

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Monitoring ParametersComplete blood chemistries (including platelet count) and liver function tests are recommended at 1, 3, and 6 months following initiation of therapy and periodically thereafter. Thyroid function should be assessed every 6 months in patients with history of thyroid dysfunction.

Nursing: Physical Assessment/MonitoringMonitor laboratory results. Monitor closely for adverse reactions, especially patients with psychiatric or suicidal histories. Monitor injection sites for signs of necrosis. Assess patient/caregiver knowledge and teach proper administration for SubQ injections and disposal of needles if appropriate. Teach the need for adequate hydration. Monitor for opportunistic infection.

Monitoring: Lab TestsHemoglobin, liver function, blood chemistries

Patient EducationThis is not a cure for MS; you will continue to receive regular treatment and follow-up for MS. Use as directed; do not change dosage or schedule of administration without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience flu-like syndrome (acetaminophen may help); nausea, vomiting, or loss of appetite (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea or constipation; or drowsiness, sleep disturbances, dizziness, agitation, headache, or abnormal thinking (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Inform prescriber **immediately** if you feel depressed or have any thoughts of suicide. Report any broken skin or black-blue discoloration around the injection site. Report unusual bruising or bleeding; persistent abdominal disturbances; unusual fatigue; muscle pain or tremors; chest pain or palpitations, swelling of extremities; visual disturbances; pain, swelling, or redness at injection site; or other unusual symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Betaseron®: 0.3 mg [9.6 million units] [contains albumin; packaged with prefilled syringe containing diluent]

Generic AvailableNo

ManufacturerBerlex Laboratories, Inc

Pricing: U.S. (www.drugstore.com)

Kit (Betaseron)

0.3 mg (14): $2217.72

Mechanism of ActionInterferon beta-1b differs from naturally occurring human protein by a single amino acid substitution and the lack of carbohydrate side chains; mechanism in the treatment of MS is unknown; however, immunomodulatory effects attributed to interferon beta-1b include enhancement of suppressor T cell activity, reduction of proinflammatory cytokines, down-regulation of antigen presentation, and reduced trafficking of lymphocytes into the central nervous system. Improves MRI lesions, decreases relapse rate, and disease severity in patients with secondary progressive MS.

Pharmacodynamics/KineticsLimited data due to small doses used

Half-life elimination: 8 minutes to 4.3 hours

Time to peak, serum: 1-8 hours

Pharmacotherapy PearlsAmerican Academy of Neurology and MS Council guidelines suggest that, based upon published data, 6 million units of Avonex® (interferon beta-1a) (30 mcg) is equivalent to approximately 7-9 million units of Betaseron® (220-280 mcg).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation, anxiety, agitation, or confusion. Severe psychiatric disorders, including depression and suicidal behavior, have been associated with use of some interferons. Careful neuropsychiatric monitoring is recommended.

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation

Anesthesia and Critical Care Concerns/Other ConsiderationsIndications and dosage regimens are specific for a particular brand of interferon; other brands have different indications and dosage guidelines.

Index TermsrIFN beta-1b

References

Goodin DS, Frohman EM, Garmany GP, et al, “Disease Modifying Therapies In Multiple Sclerosis: Report Of The Therapeutics And Technology Assessment Subcommittee Of The American Academy Of Neurology And The MS Council For Clinical Practice Guidelines,” *Neurology*, 2002, 58:169-78.[PubMed 11805241]

Sheremata WA, Taylor JR, and Elgart GW, “Severe Necrotizing Cutaneous Lesions Complicating Treatment With Interferon Beta-1b,” *N Engl J Med*, 1995, 332(23):1584. [PubMed 7739724]

International Brand NamesBetaferon (AR, AT, AU, BE, BG, BR, CH, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, MX, MY, NL, NO, PE, PH, PT, RU, SE, SG, TH, TR, TW, UY, ZA); Emaxem (CR, DO, GT, HN, PA, SV); Uribeta (CR, DO, GT, HN, PA, SV)

English

English

Jump To Field (Select Field Name)

Pronunciation(in ter FEER on GAM ah won bee)

U.S. Brand NamesActimmune®

Canadian Brand NamesActimmune®

Pharmacologic CategoryInterferon

Use: Labeled IndicationsReduce frequency and severity of serious infections associated with chronic granulomatous disease; delay time to disease progression in patients with severe, malignant osteopetrosis

Dosing: AdultsIf severe reactions occur, modify dose (50% reduction) or therapy should be discontinued until adverse reactions abate.

Chronic granulomatous disease: SubQ:

BSA ≤0.5 m^2: 1.5 mcg/kg/dose 3 times/week

BSA >0.5 m^2: 50 mcg/m^2 (1 million int. units/m^2) 3 times/week

Note: Previously expressed as 1.5 million units/m^2; 50 mcg is equivalent to 1 million int. units/m^2.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Chronic granulomatous disease: Refer to adult dosing.

Severe, malignant osteopetrosis: SubQ:

BSA ≤0.5 m^2: 1.5 mcg/kg/dose 3 times/week

BSA >0.5 m^2: 50 mcg/m^2 (1 million int. units/m^2) 3 times/week

Dosing: Adjustment for ToxicityIf severe reactions occur, reduce dose by 50% or therapy should be interrupted until adverse reaction abates.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: OtherAdminister by SubQ injection into the right and left deltoid or anterior thigh.

StorageStore in refrigerator at 2°C to 8°C (36°F to 46°F); do not freeze. Do not shake. Discard if left unrefrigerated for >12 hours.

ContraindicationsHypersensitivity to interferon gamma, *E. coli* derived proteins, or any component of the formulation

Allergy Considerations

- Interferon Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bone marrow suppression: Dose-related bone marrow toxicity has been reported; use caution in patients with myelosuppression.
- CNS effects: The development of neurologic disorders have been noted at the higher doses; use with caution in patients with a history of seizure disorder or compromised CNS function.
- Flu-like symptoms: Have been noted at the higher doses and may exacerbate pre-existing cardiovascular disorders (including ischemia, HF, or arrhythmias).
- Hepatotoxicity: May cause hepatotoxicity and the incidence may be increased in children <1 year of age.
- Hypersensitivity reactions/rash: Hypersensitivity reactions have been reported (rarely). Transient cutaneous rashes may occur.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.

Other warnings/precautions:

- Investigational doses: Doses >10 times the weekly recommended dose (used in studies for unlabeled indications) have been associated with a different pattern/frequency of adverse effects.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. A dose-related abortifacient activity was reported in Rhesus monkeys. Safety and efficacy in pregnant women has not been established.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsPotential for serious adverse reactions. Because its use has not been evaluated during lactation, breast-feeding is not recommended

Adverse ReactionsBased on 50 mcg/m^2 dose administered 3 times weekly for chronic granulomatous disease

>10%:

Central nervous system: Fever (52%), headache (33%), chills (14%), fatigue (14%)

Dermatologic: Rash (17%)

Gastrointestinal: Diarrhea (14%), vomiting (13%)

Local: Injection site erythema or tenderness (14%)

1% to 10%:

Central nervous system: Depression (3%)

Gastrointestinal: Nausea (10%), abdominal pain (8%)

Neuromuscular & skeletal: Myalgia (6%), arthralgia (2%), back pain (2%)

Postmarketing and/or case reports: Alkaline phosphatase elevated, atopic dermatitis, granulomatous colitis, hepatomegaly, hypersensitivity reactions, hypokalemia, neutropenia, Stevens-Johnson syndrome

Additional adverse reactions noted at doses >100 mcg/m^2 administered 3 times weekly: ALT increased, AST increased, autoantibodies increased, bronchospasm, chest discomfort, confusion, dermatomyositis exacerbation, disorientation, DVT, gait disturbance, GI bleeding, hallucinations, heart block, heart failure, hepatic insufficiency, hyperglycemia, hypertriglyceridemia, hyponatremia, hypotension, interstitial pneumonitis, lupus-like syndrome, MI, neutropenia, pancreatitis (may be fatal), Parkinsonian symptoms, PE, proteinuria, renal insufficiency (reversible), seizure, syncope, tachyarrhythmia, tachypnea, thrombocytopenia, TIA

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Metabolism/Transport Effects**Inhibits** CYP1A2 (weak), 2E1 (weak)

Drug Interactions

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Monitoring ParametersCBC with differential, platelets, LFTs (monthly in children <1 year), electrolytes, BUN, creatinine, and urinalysis prior to therapy and at 3-month intervals

Nursing: Physical Assessment/MonitoringMonitor closely for effectiveness and/or interactions. Assess results of laboratory tests on a regular basis, therapeutic effectiveness, and adverse reactions. Assess knowledge and instruct patient/caregiver on appropriate reconstitution, injection and needle disposal, possible side effects, and symptoms to report.

Monitoring: Lab TestsCBC with differential, platelets, LFTs (monthly in children <1 year), electrolytes, BUN, creatinine, and urinalysis prior to therapy and at 3-month intervals

Patient EducationUse as directed; do not change the dosage or schedule of administration without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience flu-like syndrome (acetaminophen may help); nausea, vomiting, or loss of appetite (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or drowsiness, dizziness, agitation, or abnormal thinking (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Report unusual bruising or bleeding; persistent abdominal disturbances; unusual fatigue; muscle pain or tremors; chest pain or palpitations; swelling of extremities; visual disturbances; pain, swelling, or redness at injection site; or other unusual symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Actimmune®: 100 mcg [2 million int. units] (0.5 mL)

Generic AvailableNo

Mechanism of ActionInterferon gamma participates in immunoregulation by enhancing the oxidative metabolism of macrophages; it also enhances antibody dependent cellular cytotoxicity, activates natural killer cells and has a role in the expression of Fc receptors and histocompatibility antigens. The exact mechanism of action for the treatment of chronic granulomatous disease or osteopetrosis has not been defined.

Pharmacodynamics/Kinetics

Absorption: I.M., SubQ: >89%

Half-life elimination: I.V.: 38 minutes; I.M.: ~3 hours, SubQ: ~6 hours

Time to peak, plasma: I.M.: 4 hours (1.5 ng/mL); SubQ: 7 hours (0.6 ng/mL)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Sedation is common; may rarely cause depression

Mental Health: Effects on Psychiatric Treatment May cause leukopenia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation

Anesthesia and Critical Care Concerns/Other Considerations Indications and dosage regimens are specific for a particular brand of interferon; other brands have different indications and dosage guidelines.

References

Key LL, Rodriguiz RM, Willi SM, et al, “Long-Term Treatment of Osteopetrosis With Recombinant Human Interferon Gamma,” *N Engl J Med* 1995, 332(24):1594-9.[PubMed 7753137]

Marciano BE, Wesley R, DeCarlo E, et al, “Long-Term Interferon-Gamma Therapy for Patients With Chronic Granulomatous Disease,” *Clin Infect Dis*, 2004, 39(5):692-9.[PubMed 15356785]

Raghu G, Brown KK, Bradford WZ, et al, “A Placebo-Controlled Trial of Interferon Gamma-1b in Patients With Idiopathic Pulmonary Fibrosis,” *N Engl J Med*, 2004 Jan 8;350(2):125-33.[PubMed 14711911]

International Brand Names Immukin (HK); Immukine (BE, NL); Imufor (AR, AT); Imukin (AE, AT, AU, BH, CH, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, IL, IQ, IR, IT, JO, KW, LB, LY, NO, OM, QA, SA, SE, SY, TW, YE); Imukin Inj. (NZ); Intermax gamma (KP); Lizhu Yindefu (CL)

Interleukin 2 (Low Dose)-Interferon Alfa 2b

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Renal Cell Cancer

Regimen UseRenal cell cancer

Index TermsAldesleukin (Low Dose)-Interferon Alfa 2b; IL-2 (Low Dose)-Interferon Alfa 2b

Regimen

Cycle 1:

Week 1:

Aldesleukin: SubQ: 5 million units/m^2 every 8 hours for 3 doses day 1

followed by SubQ: 5 million units/m^2/day days 2 to 5

[total dose/week 1 = 35 million units/m^2]

Interferon alfa-2b: SubQ: 5 million units/m^2 3 times/week

[total dose/week 1 = 15 million units/m^2]

Weeks 2-4:

Aldesleukin: SubQ: 5 million units/m^2/day days 1 to 5

[total dose/weeks 2-4 = 75 million units/m^2]

Interferon alfa-2b: SubQ: 5 million units/m^2 3 times/week

[total dose/weeks 2-4 = 45 million units/m^2]

Treatment cycle is 6 weeks

Cycles 2-6

Weeks 1-4:

Aldesleukin: SubQ: 5 million units/m^2/day days 1 to 5

[total dose/cycle = 100 million units/m^2]

Interferon alfa-2b: SubQ: 5 million units/m^2 3 times/week

[total dose/cycle = 60 million units/m^2]

Repeat cycle every 6 weeks for up to a total of 6 cycles

References

McDermott DF, Regan MM, Clark JI, et al, "Randomized Phase III Trial of High-Dose Interleukin-2 Versus Subcutaneous Interleukin-2 and Interferon in Patients With Metastatic Renal Cell Carcinoma," *J Clin Oncol*, 2005, 23(1):133-41.[PubMed 15625368]

Interleukin 2-Interferon Alfa-2

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Renal Cell Cancer

Regimen Use Renal cell cancer

Index TermsIL-2-Interferon Alfa 2; Interferon Alfa 2-Interleukin

Regimen

Weeks 1 and 4:

Aldesleukin: SubQ: 20 million units/m^2 3 times weekly

[total dose/cycle = 120 million units/m^2]

Interferon Alfa-2: SubQ: 6 million units/m^2 once weekly

[total dose/cycle = 12 million units/m^2]

Weeks 2, 3, 5, and 6:

Aldesleukin: SubQ: 5 million units/m^2 3 times weekly

[total dose/cycle = 60 million units/m^2]

Interferon Alfa-2: SubQ: 6 million units/m^2 3 times weekly

[total dose/cycle = 72 million units/m^2]

Repeat cycle every 56 days

References

Atzpodien J, Kirchner H, Hanninen EL, et al, âEuropean Studies of Interleukin-2 in Metastatic Renal Cell Carcinoma,â *Semin Oncol*, 1993, 20(6 Suppl 9):22-6.[PubMed 8284688]

English

Jump To Field (Select Field Name)

Pronunciation(eye oh BEN gwane eye one TWEN tee three)

U.S. Brand NamesAdreView™

Pharmacologic CategoryRadiopharmaceutical

Use: Labeled IndicationsAs an adjunct to other diagnostic tests, in the detection of primary or metastatic pheochromocytoma or neuroblastoma

Dosing: Adults**Note:** Thyroid protective agents (SSKI, Lugol's solution or potassium iodide), should be given at least 1 hour prior to administration. Perform whole body planar scintigraphy imaging 18-30 hours after Iobenguane I 123 administration.

Radioimaging: I.V.: 10 mCi (370 MBq)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Thyroid protective agents (SSKI, Lugol's solution or potassium iodide), should be given at least 1 hour prior to administration. Perform whole body planar scintigraphy imaging 18-30 hours after Iobenguane I 123 administration.

Radioimaging: I.V.:

Children 1 month to 16 years and <70 kg: Dose according to body weight; see table.

Children <16 years and ≥70 kg: 10 mCi (370 MBq)

Children ≥16 years: Refer to adult dosing

Iobenguane I 123 Pediatric Dosing by Body Weight: (Children 1 Month to 16 Years and <70 kg)

Weight (kg)	mCi Dose	MBq Dose
3	1	37
4	1.4	52
6	1.9	70
8	2.3	85.1
10	2.7	99.9
12	3.2	118.4
14	3.6	133.2
16	4	148
18	4.4	162.8
20	4.6	170.2
22	5	185
24	5.3	196.1
26	5.6	207.2
28	5.8	214.6

30	6.2	229.4
32	6.5	240.5
34	6.8	251.6
36	7.1	262.7
38	7.3	270.1
40	7.6	281.2
42	7.8	288.6
44	8	296
46	8.2	303.4
48	8.5	314.5
50	8.8	325.6
52-54	9	333
56-58	9.2	340.4
60-62	9.6	355.2
64-66	9.8	362.6
68	9.9	366.3

Administration: I.V.Administer intravenously over 1-2 minutes. May flush with NS to ensure full delivery of dose. Prior to administration, a thyroid-protective agent should be started. Ensure adequate hydration before and after treatment.

Administration: I.V. DetailpH: 5-6.5

Dietary ConsiderationsSome dietary sources of iodine include cow's milk and dairy products, fish, seaweed, eggs, chocolate, and iodized salt.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Should be stored in original lead container or adequate radiation shield.

ContraindicationsHypersensitivity to iobenguane or any component of the formulation

Warnings/Precautions

Special handling:

- Radiopharmaceutical: Use appropriate precautions for handling, disposal, and minimizing exposure to patients and healthcare personnel. Use under supervision of experienced personnel.

Concerns related to adverse effects:

- Hypersensitivity reactions: Have been reported. Use extreme caution in patients with iodine or iodine-contrast agent hypersensitivity. Appropriate equipment and emergency medications should be available during use.

Disease-related concerns:

- Hypertension: Use with caution in patients with hypertension; may increase blood pressure and heart rate.

- Renal impairment: Use with caution in patients with severe renal impairment; safety and efficacy have not been established. Patients with severe renal impairment may have delayed elimination, therefore, decreasing quality of images. Not dialyzable.

Concurrent drug therapy issues:

- Norepinephrine uptake inhibitors: If possible, discontinue medications that inhibit norepinephrine uptake prior to iobenguane I 123 administration; allow at least 5 half-lives to elapse. These medications may interfere with the uptake of iobenguane I 123 in neuroendocrine tumors leading to false-negative results.

Special populations:

- Pediatrics: Safety and efficacy have not been established in infants <1 month of age.

Dosage form specific issues:

- Benzyl alcohol: Contains benzyl alcohol which has been associated with "gasping syndrome" in neonates.

Other warnings/precautions:

- Appropriate use: Administer thyroid blocking medications (eg, potassium iodide oral solution, potassium perchlorate) at least 1 hour prior to administration; long-term risk for thyroid neoplasia can occur from failure to block thyroid uptake of iodine 123. Patients should be adequately hydrated prior to dosing; instruct patients to void frequently for 48 hours following administration to decrease radiation exposure.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have not been conducted. There are no adequate and well-controlled studies in pregnant women. Radiopharmaceuticals have the potential to cause fetal harm. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIodine 123 is excreted into human milk, therefore, due to potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended. May consider interrupting breast-feeding for 6 days after administration of iobenguane I 123 to minimize risk to infant.

Adverse Reactions<1%, postmarketing, and/or case reports: Dizziness, flushing, hypersensitivity (rare), injection site hemorrhage, pruritus, rash

Drug Interactions

Alpha2-Agonists: May diminish the therapeutic effect of Iobenguane I 123. **Exceptions:** Apraclonidine; Brimonidine. *Risk X: Avoid combination*

Antidepressants (Selective Norepinephrine Reuptake Inhibitor): May diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Cocaine: May diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Methyldopa: May diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Reserpine: May diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Selective Serotonin Reuptake Inhibitors: May diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Serotonin/Norepinephrine Reuptake Inhibitors: May diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Sympathomimetics: May diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Tricyclic Antidepressants: May diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Monitoring ParametersPulse and blood pressure prior to administration and intermittently for 30 minutes following; monitor for hypersensitivity reaction

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

AdreView™: Iobenguane sulfate 0.08 mg and I 123 74 MBq (2 mCi) per mL (5 mL) [contains benzyl alcohol]

Generic AvailableNo

ManufacturerGE Healthcare

Mechanism of ActionIobenguane is structurally similar to norepinephrine and therefore is taken up and stored in adrenergic tissue such as adrenal medulla, heart, liver, lungs, salivary glands, and spleen. Iobenguane is bound to radioactive iodine in order to obtain organ and tissue images.

Pharmacodynamics/Kinetics

Distribution: Increased in adrenergically innervated tissues (eg, heart, salivary glands, adrenal medulla)

Metabolism: Has not been characterized

Half-life elimination: Iodine 123: 13.2 hours

Excretion: Urine (70 % to 90%) within 4 days (normal renal function); feces <1%

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNorepinephrine reuptake inhibitors (most antidepressants and ziprasidone) may interfere with the uptake of iobenguane I 123 in neuroendocrine tumors leading to false-negative results. If possible taper/discontinue norepinephrine reuptake inhibitor and allow 5 half-lives to elapse prior to administration of iobenguane.

Index Terms123 Meta-Iodobenzlyguanidine Sulfate; 123I-Metaiodobenzylguanidine (MIBG); I-123 MIBG; I^{123} Iobenguane; Iobenguane Sulfate I 123

Iodinated Glycerol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(EYE oh di nay ted GLI ser ole)
Pharmacologic CategoryExpectorant
Use: Labeled IndicationsMucolytic expectorant in adjunctive treatment of bronchitis, bronchial asthma, pulmonary emphysema, cystic fibrosis, or chronic sinusitis
Dosing: AdultsExpectorant: Oral: 60 mg 4 times/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricExpectorant: Oral: Up to 30 mg 4 times/day
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to inorganic iodides, iodinated glycerol, or any component of the formulation; pregnancy, newborns
Warnings/Precautions

Disease-related concerns:

â˘ Renal impairment: Use with caution in patients with renal impairment.

â˘ Thyroid disease: Use with caution in patients with thyroid disease.

Pregnancy Risk FactorX
Adverse ReactionsFrequency not defined.

Central nervous system: Headache

Dermatologic: Acne, dermatitis

Endocrine & metabolic: Acute parotitis, thyroid gland enlargement

Gastrointestinal: Diarrhea, nausea, vomiting, GI irritation

Ocular: Eyelid edema

Respiratory: Pulmonary edema

Miscellaneous: Hypersensitivity

Drug InteractionsThere are no known significant interactions.
Test InteractionsThyroid function tests may be altered
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid: 6.25 mg iodine/mL (50 mL)

Generic AvailableYes
Mechanism of ActionIncreases respiratory tract secretions by decreasing surface tension and thereby decreases the viscosity of mucus, which aids in removal of the mucus
Pharmacodynamics/Kinetics

Distribution: Accumulates in the thyroid gland

Excretion: Urine

Pharmacotherapy PearlsNot available in U.S.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentMay result in increased toxicity when used with disulfiram, MAO inhibitors, CNS depressants, and lithium

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Iodine

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Medication Safety Issues

Sound-alike/look-alike issues:

Iodine may be confused with codeine, Iopidine®, Lodine®

Pronunciation(EYE oh dyne)
U.S. Brand NamesIodex [OTC]; Iodoflex™; Iodosorb®
Pharmacologic CategoryAntiseptic, Topical
Use: Labeled IndicationsUsed topically as an antiseptic in the management of minor, superficial skin wounds and has been used to disinfect the skin preoperatively
Dosing: Adults

Topical:

Cleaning wet ulcers and wounds (Iodosorb®, Iodoflex™): Apply to clean wound; maximum: 50 g/application and 150 g/week. Change dressing ~3 times/week; reduce applications as exudate decreases. Do not use for >3 months; discontinue when wound is free of exudate.

Antiseptic for minor cuts, scrapes, burns: Apply small amount to affected area 1- 3 times/day

RDA: Oral: 150 mcg/day

Pregnancy: 220 mcg/day

Breast-feeding: 290 mcg/day

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**RDA:** Oral:

Children:

1-8 years: 90 mcg/day

9-13 years: 120 mcg/day

≥14 years: Refer to adult dosing

Administration: TopicalIodosorb®: Apply $^{1}/_{8}$" to $^{1}/_{4}$" thickness to dry sterile gauze, then place prepared gauze onto clean wound. Change dressing when gel changes color from brown to yellow/gray (~3 times/week). Remove with sterile water, saline, or wound cleanser; gently blot fluid from surface leaving wound slightly moist before reapplying gel.
Dietary ConsiderationsSome dietary sources of iodine include cow's milk and dairy products, fish, seaweed, eggs, chocolate and iodized salt.
ContraindicationsHypersensitivity to iodine or any component of the formulation

Iodosorb®, Iodoflex™: Hashimoto thyroiditis, history of Grave's disease, or nontoxic nodular goiter; pregnancy; breast-feeding

Warnings/Precautions

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment.

Dosage form specific issues:

- Iodosorb®: For use as topical application to wet wounds only.

Other warnings/precautions:

- Appropriate use: Not for application to large areas of the body or for use with tight or air-excluding bandages.

- OTC labeling: When used for self-medication (OTC), do not use on deep wounds, puncture wounds, animal bites, or serious burns without consulting with healthcare provider. Notify healthcare provider if condition does not improve within 7 days.

Pregnancy ConsiderationsAn adequate amount of iodine intake is essential for thyroid function. Iodine crosses the placenta and requirements are increased during pregnancy. Iodine deficiency in pregnancy can lead to neurologic damage in the newborn; an extreme form, cretinism, is characterized by gross mental retardation, short stature, deaf mutism, and spasticity. Large amounts of iodine during pregnancy can cause fetal goiter or hyperthyroidism. Transient hypothyroidism in the newborn has also been reported following topical or vaginal use prior to delivery.

LactationEnters breast milk/use caution (AAP rates "compatible")

Breast-Feeding ConsiderationsIodine is excreted in breast milk and is a source of iodine for the nursing infant. Actual levels are variable, but have been reported as 113-270 mcg/L in American women. Application of topical iodine antiseptic solutions can be absorbed in amounts which may affect levels in breast milk. Exposure to excess iodine may cause thyrotoxicosis. Skin rash in the nursing infant has been reported with maternal intake of potassium iodide.

Adverse ReactionsReactions reported following topical application: Frequency not defined:

Endocrine & metabolic: TSH increased

Local: Eczema, edema, irritation, pain, redness

Miscellaneous: Allergic reaction

Reactions reported more likely observed following large doses or chronic iodine intoxication; frequency not defined:

Central nervous system: Fever, headache

Dermatologic: Skin rash, angioedema, urticaria, acne

Endocrine & metabolic: Hypothyroidism

Gastrointestinal: Metallic taste, diarrhea

Hematologic: Eosinophilia, hemorrhage (mucosal)

Neuromuscular & skeletal: Arthralgia

Ocular: Swelling of eyelids

Respiratory: Pulmonary edema

Miscellaneous: Ioderma, lymph node enlargement

Drug InteractionsThere are no known significant interactions.

Test InteractionsLarge amounts from excessive absorption may alter thyroid function tests.

Monitoring ParametersThyroid function should be monitored in pregnant women, neonates, and young infants if repeat applications over large areas are needed.

Monitoring: Lab TestsThyroid function should be monitored in pregnant women, neonates, and young infants if repeat applications over large areas are needed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Dressing, topical [gel pad] (Iodoflex™): 0.9% (5 g, 10 g)

Gel, topical (Iodosorb®): 0.9% (40 g)

Ointment, topical (Iodex): 4.7% (30 g, 720 g)

Tincture, topical: 2% (30 mL, 480 mL); 7% (30 mL, 480 mL)

Generic AvailableYes: Tincture

Mechanism of ActionIodine is required for thyroid hormone synthesis. Iodine is also known to be a powerful broad spectrum germicidal agent effective against a wide range of bacteria, viruses, fungi, protozoa, and spores. Iodosorb® and Iodoflex™ contain iodine in hydrophilic beads of cadexomer which allows a slow release of iodine into the wound and absorption of fluid, bacteria, and other substances from the wound

Pharmacodynamics/Kinetics

Absorption: Topical: Amount absorbed systemically depends upon concentration and characteristics of skin

Distribution: Primarily trapped by the thyroid

Bioavailability: Oral: >90%

Excretion: Urine (>90%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

"American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk," *Pediatrics*, 2001, 108(3):776-89. [PubMed 11533352]

"Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc." Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, Washington, DC: National Academy Press, 2000. Available at: http://www.nap.edu.

Dorea JG, "Iodine Nutrition and Breast Feeding," *J Trace Elem Med Biol*, 2002, 16(4):207-20.[PubMed 12530582]

Linder N, Davidovitch N, Reichman B, et al, "Topical Iodine-Containing Antiseptics and Subclinical Hypothyroidism in Preterm Infants," *J Pediatr*, 1997, 131(3):434-9.[PubMed 9329422]

Mestman JH, "Diagnosis and Management of Maternal and Fetal Thyroid Disorders," *Curr Opin Obstet Gynecol*, 1999, 11(2):167-75. [PubMed 10219918]

International Brand NamesKelp (PL)

Iodipamide Meglumine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye oh DI pa mide MEG loo meen)

U.S. Brand NamesCholografin® Meglumine

Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Ionic, High Osmolality)

Use: Labeled IndicationsContrast medium for intravenous cholangiography and cholecystography

Dosing: Adults**Note:** Do not repeat for 24 hours

Cholangiography and cholecystography: I.V.: 20 mL

Dosing: Pediatric**Note:** Do not repeat for 24 hours

Cholangiography and cholecystography: I.V.: Infants and Children: 0.3-0.6 mL/kg (maximum: 20 mL)

Administration: I.V.For intravenous use only; solution should be at body temperature for administration. Administer slowly over 10 minutes. Slow infusion if nausea or flushing occurs.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light and excessive heat. If crystallization occurs, place vial in hot water and shake gently for several minutes until the solids redissolve. Allow solution to cool to body temperature before administering. Discard if cloudiness persists.

Compatibility

Y-site administration: Incompatible: Diphenhydramine

Compatibility when admixed: Incompatible: Diphenhydramine

ContraindicationsHypersensitivity to iodipamide salts or any component of the formulation; use in intrathecal procedures; concomitant severe renal and hepatic dysfunction

Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Intrathecal use: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Allergic reactions: Use extreme caution with history of previous reaction to contrast dye or iodine-based contrast media or asthma. Severe, potentially life-threatening, reactions and delayed reactions may occur. Pretreatment with corticosteroids (eg, prednisone) and antihistamines (eg, diphenhydramine) may be beneficial to decrease the frequency/severity of allergic reactions in “at risk” patients. Equipment for resuscitation and trained personnel experienced in handling emergencies should be immediately available. Monitor closely after injection.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with mild-to-moderate liver disease; visualization may not be achieved. Contraindicated in patients with severe hepatic impairment.

- Hypertension: Use with caution in patients with hypertension.

- Pheochromocytoma: Use with extreme caution in patients with pheochromocytoma; monitor blood pressure closely.

- Renal impairment: Nephrotoxicity has been associated with iodinated contrast agents; therefore, use caution in patients with severe renal impairment or in patients predisposed to contrast-induced nephrotoxicity (eg, diabetes, elderly, concomitant medications such as metformin).

- Sickle cell disease: Contrast agents may exacerbate sickling in sickle cell disease.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.

Other warnings/precautions:

- Intrathecal: **[U.S. Boxed Warning]: Injectable solution should never be used intrathecally; serious adverse reactions have occurred,** including acute renal failure, cardiac arrest, cerebral hemorrhage, coma, death, paralysis, and seizures.

Pregnancy ConsiderationsReproduction studies have not been conducted. In general, iodinated contrast media agents are avoided during pregnancy unless essential for diagnosis.

Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiac reactions (rare), cyanosis (rare), hypotension (rare)

Ocular: Edema of eyelids (rare)

Renal: Renal failure, renal function tests altered

Respiratory: Laryngospasm (rare), respiratory difficulties (rare)

Miscellaneous: Anaphylactoid reaction (rare); hypersensitivity reactions; infusion reactions (generally mild and transient; associated with rapid infusion rates; includes restlessness, sensations of warmth, sneezing, perspiration, salivation, flushing, pressure in the upper abdomen, dizziness, nausea, vomiting, chills, fever, headache, pallor, tremors)

Drug Interactions

MetFORMIN: Iodinated Contrast Agents may enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Cholografin® Meglumine: Iodipamide meglumine 520 mg/mL (20 mL) [provides organically-bound iodine 257 mg/mL; contains edetate disodium, sodium 0.91 mg (0.39 mEq)/mL]

Generic AvailableNo

ManufacturerBracco Diagnostics

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

ACOG Committee on Obstetric Practice, “ACOG Committee Opinion. Guidelines for Diagnostic Imaging During Pregnancy,” *Obstet Gynecol*, 2004, 104(3):647-51.[PubMed 15339791]

Iodixanol

Lexi-Drugs Online

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Not for intrathecal use

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(EYE oh dix an ole)

U.S. Brand NamesVisipaque™

Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Nonionic, Iso-Osmolality)

Use: Labeled Indications

Intra-arterial: Digital subtraction angiography, angiocardiography, peripheral arteriography, visceral arteriography, cerebral arteriography

Intravenous: Contrast enhanced computed tomography imaging, excretory urography, and peripheral venography

Dosing: Adults**Note:** Maximum recommended total dose of iodine: 80 g

Intra-arterial: Iodixanol 320 mg iodine/mL: Dose individualized based on injection site and study type; refer to product labeling

I.V.: Iodixanol 270 mg and 320 mg iodine /mL: concentration and dose vary based on study type; refer to product labeling.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Maximum recommended total dose of iodine: Not been established

Cerebral, cardiac chambers, and related major arteries and visceral studies: Intra-arterial: Children >1 year: Iodixanol 320 mg iodine/mL: 1-2 mL/kg; maximum dose: 4 mL/kg

Contrast-enhanced computer tomography or excretory urography: I.V.: Children >1 year: Iodixanol 270 mg iodine /mL: 1-2 mL/kg; maximum dose: 2 mL/kg

Children >12 years: Refer to adult dosing.

Dosing: Renal ImpairmentNot studied; use caution.

Administration: I.V.Patients should be adequately hydrated prior to and following administration.

Administration: I.V. DetailpH: 7-8

StorageStore in protective foil at room temperature of 15°C to 30°C (59°F to 86°F); do not freeze. Do not use if inadvertently frozen. Protect from light. Vials, glass and polymer bottles (**not** flexible containers) may be stored for up to 1 month at 37°C (98.6°F) in contrast agent warmer.

ContraindicationsHypersensitivity to iodixanol or any component of the formulation; not intended for intrathecal use

In pediatric population: Prolonged fasting or laxative administration prior to iodixanol administration

Refer to product labeling for procedure-specific contraindications.

Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Administration: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Anaphylaxis: May cause serious and potentially fatal anaphylactoid reactions.
- Contrast dye/iodine hypersensitivity: Use with caution in patients with history of previous reaction to contrast dye or iodine.
- Delayed reactions: May cause delayed reaction; monitor patients for 30-60 minutes after injection.
- Thromboembolic events: Serious thromboembolic events have been reported during angiographic procedures with both ionic and nonionic contrast agents. Severe adverse events may occur during and for 30-60 minutes after administration.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Hepatic impairment: Use with caution in patients with hepatic impairment, especially those with concomitant renal dysfunction or when using both oral and IV contrast agents in close proximity.
- Multiple myeloma: Use with caution in patients with multiple myeloma; may worsen renal insufficiency.
- Pheochromocytoma: Use with extreme caution in patients with known or suspected pheochromocytoma. Dose injected should be kept to a minimum to minimize exposure; monitor blood pressure closely.
- Renal impairment: Use with caution in patients with renal impairment; clearance is reduced.
- Sickle cell disease: Use with caution in patients with sickle cell disease; may promote sickling.
- Thyroid dysfunction: Use with caution in patients with thyroid disease; thyroid storm has been reported in patients with history of hyperthyroidism.

Special populations:

- Elderly: Use with caution in elderly patients with age-related renal impairment.
- Pediatrics: Children may have an increased risk of adverse effects, especially patients with asthma, sensitivity to allergens or medications, heart disease, or renal dysfunction.

Other warnings/precautions:

- Administration: For I.V. or intra-arterial use only. **[U.S. Boxed Warning]: May be fatal if given intrathecally.** Avoid extravasation, especially in patients with severe arterial or venous disease.
- *In vitro* clotting: Clotting has been reported when blood remains in contact with syringes containing ioxilan; use of plastic syringes in place of glass syringes has been reported to decrease, but not eliminate, the likelihood of *in vitro* clotting.

Pregnancy Risk FactorB

Pregnancy ConsiderationsFetal harm was not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. In general, iodinated contrast media agents are avoided during pregnancy unless essential for diagnosis.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for adverse reactions, temporary discontinuation of breast-feeding should be considered.

Adverse Reactions

>10%: Local: Injection site reactions (discomfort/pain/warmth 30%)

1% to 10%:

Cardiovascular: Angina/chest pain (2%)

Central nervous system: Headache/migraine (3%), vertigo (2%)

Dermatologic: Nonurticarial rash/erythema (2%), pruritus (2%)

Gastrointestinal: Taste perversion (4%), nausea (3%)

Neuromuscular & skeletal: Paresthesia (1%)

Respiratory: Parosoma (1%)

<1%: Abnormal renal function, abnormal vision, acute renal failure, agitation, amnesia, anxiety, apnea (children only), arrhythmia (children only), asthma, AV block (children only), back pain, bronchitis, bundle branch block (children only), cardiac arrest, cardiac failure (children only), cerebral vascular disorder, confusion, diaphoresis, diarrhea, disseminated intravascular coagulation (children only), dizziness, dyspepsia, dyspnea, edema, fatigue, fever (children only), flushing, hematoma, hematuria, hemorrhage, hypersensitivity, hypertension, hypoesthesia, hypotensive collapse, insomnia, malaise, nervousness, peripheral ischemia, pharyngeal edema, pulmonary edema, rhinitis, scotoma, seizure, sensory disturbance, shock, stupor, syncope, tinnitus, urticaria, vomiting

Postmarketing and/or case reports: Anaphylactoid reaction, anaphylaxis, cortical blindness, dyskinesia, hypoglycemia, polymyalgia, pulmonary embolism, respiratory depression

Drug Interactions

Aldesleukin: Contrast Media (Non-ionic) may enhance the potential for allergic or hypersensitivity reactions to Aldesleukin. *Risk C: Monitor therapy*

MetFORMIN: Iodinated Contrast Agents may enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Test InteractionsThyroid function tests (protein bound and radioactive iodine uptake studies) may be inaccurate for up to 16 days after administration; may cause false positive urine protein test using Multistix®; may affect urine specific gravity

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Visipaque™ 270: 550 mg/mL (50 mL, 100 mL, 125 mL, 150 mL, 200 mL) [provides organically-bound iodine 270 mg/mL; contains tromethamine 1.2 mg/mL, edetate calcium disodium]

Visipaque™ 320: 652 mg/mL (50 mL, 100 mL, 125 mL, 150 mL, 200 mL) [provides organically-bound iodine 320 mg/mL; contains tromethamine 1.2 mg/mL, edetate calcium disodium]

Generic Available No

ManufacturerAmersham Health

Mechanism of Action Opacifies vessels in the path of flow permitting radiographic imaging of internal structures.

Pharmacodynamics/Kinetics

Distribution: V_d: 0.26 L/kg

Protein binding: No

Half-life elimination: Children: 2-4 hours; Adults: 2 hours

Time to peak, plasma: Immediate; peak enhancement at 15-120 seconds; optimum renal contrast at 5-15 minutes; brain contrast at up to 1 hour

Excretion: Urine (97% within 24 hours); feces (<2%)

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause serious thromboembolic events including stroke

Mental Health: Effects on Psychiatric Treatment None reported

References

ACOG Committee on Obstetric Practice, “ACOG Committee Opinion. Guidelines for Diagnostic Imaging During Pregnancy,” *Obstet Gynecol*, 2004, 104(3):647-51.[PubMed 15339791]

International Brand Names Visipaque (AU, BE, BG, CH, CO, CZ, DK, EE, FI, FR, GR, IL, KP, NO, PL, SE, UY)

Iodoquinol and Hydrocortisone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Vytone® may be confused with Hytone®, Zydone®

Pronunciation(eye oh doe KWIN ole & hye droe KOR ti sone)
U.S. Brand NamesAlcortin™; Dermazene®; Vytone®
Pharmacologic CategoryAntifungal Agent, Topical; Corticosteroid, Topical
Use: Labeled IndicationsTreatment of eczema (including impetiginized, nuchal, and nummular); acne urticaria; anogenital pruritus, atopic dermatitis, chronic infectious dermatitis; chronic eczematoid otitis externa; folliculitis, intertrigo; lichen simplex chronicus; moniliasis; mycotic dermatoses; neurodermatitis (localized or systemic); pyoderma, stasis dermatitis
Use: DentalReported to be useful in the treatment of angular cheilitis
Dosing: AdultsDermatoses: Topical: Apply 3-4 times/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren ≥12 years: Topical: Refer to adult dosing.
StorageStore at 15°C to 30°C (59°C to 86°C). Keep tightly closed.
Contraindications

Based on **iodoquinol** component: Hypersensitivity to iodine or iodoquinol or any component of the formulation; hepatic damage; pre-existing optic neuropathy

Based on **hydrocortisone** component: Hypersensitivity to hydrocortisone or any component of the formulation; serious infections, except septic shock or tuberculous meningitis; viral, fungal, or tubercular skin lesions

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Optic atrophy/neuritis: Following prolonged use of iodoquinol, optic neuritis and optic atrophy have occurred; avoid long-term therapy.

- Peripheral neuropathy: Following prolonged use of iodoquinol, peripheral neuropathy has occurred; avoid long-term therapy.

- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Disease-related concerns:

- Thyroid disease: Use with caution in patients with thyroid abnormalities.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

Based on **iodoquinol** component:

Central nervous system: Fever, chills, agitation, retrograde amnesia, headache

Dermatologic: Rash, urticaria, pruritus

Endocrine & metabolic: Thyroid gland enlargement

Gastrointestinal: Diarrhea, nausea, vomiting, stomach pain, abdominal cramps

Neuromuscular & skeletal: Peripheral neuropathy, weakness

Ocular: Optic neuritis, optic atrophy, visual impairment

Miscellaneous: Itching of rectal area

Based on **hydrocortisone** component:

>10%:

Central nervous system: Insomnia, nervousness

Gastrointestinal: Increased appetite, indigestion

1% to 10%:

Dermatologic: Hirsutism

Endocrine & metabolic: Diabetes mellitus

Neuromuscular & skeletal: Arthralgia

Ocular: Cataracts

Respiratory: Epistaxis

<1%: Hypertension, edema, euphoria, headache, delirium, hallucinations, seizure, mood swings, acne, dermatitis, skin atrophy, bruising, hyperpigmentation, hypokalemia, hyperglycemia, Cushing's syndrome, sodium and water retention, bone growth suppression, amenorrhea, peptic ulcer, abdominal distention, ulcerative esophagitis, pancreatitis, muscle wasting, hypersensitivity reactions, immunosuppression

Metabolism/Transport EffectsHydrocortisone: **Substrate** of CYP3A4 (minor); **Induces** CYP3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream: Iodoquinol 1% and hydrocortisone acetate 1% (30 g)

Dermazene®: Iodoquinol 1% and hydrocortisone acetate 1% (30 g, 45 g)

Vytone®: Iodoquinol 1% and hydrocortisone acetate 1% (30 g)

Gel, topical:

Alcortin™: Iodoquinol 1% and hydrocortisone 2% (2 g) [contains benzyl alcohol]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Cream (Hydrocortisone-Iodoquinol)

1-1% (28.35): $34.99

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Hydrocortisone
- Iodoquinol

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsHydrocortisone and Iodoquinol
References

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

Sirois DA, “Oral Manifestations of HIV Disease,” *Mt Sinai J Med*, 1998, 65(5-6):322-32.[PubMed 9844359]

Iodoquinol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(eye oh doe KWIN ole)
U.S. Brand NamesYodoxin®
Canadian Brand NamesDiodoquin®
Pharmacologic CategoryAmebicide
Use: Labeled IndicationsTreatment of acute and chronic intestinal amebiasis; asymptomatic cyst passers; *Blastocystis hominis* infections; ineffective for amebic hepatitis or hepatic abscess
Dosing: AdultsTreatment of susceptible infections: Oral: 650 mg 3 times/day after meals for 20 days; not to exceed 2 g/day
Dosing: ElderlyThis agent is no longer a drug of choice; use only if other therapy is contraindicated or has failed. Due to optic nerve damage, use cautiously in the elderly.
Dosing: PediatricTreatment of susceptible infections: Oral: Children: 30-40 mg/kg/day (maximum: 650 mg/dose) in 3 divided doses for 20 days; not to exceed 1.95 g/day
Administration: OralTablets may be crushed and mixed with applesauce or chocolate syrup. May take with food or milk to reduce stomach upset. Complete full course of therapy.
Dietary ConsiderationsShould be taken after meals.
ContraindicationsHypersensitivity to iodine or iodoquinol or any component of the formulation; hepatic damage; pre-existing optic neuropathy
Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: May occur.
- Optic atrophy/neuritis: Following prolonged use, optic neuritis and optic atrophy have occurred; avoid long-term therapy.

Disease-related concerns:

- Thyroid disease: Use with caution in patients with thyroid abnormalities.

Geriatric ConsiderationsNo special considerations for the elderly, however, this agent is no longer a drug of choice. Use only if other therapy is contraindicated or has failed. Due to optic nerve damage, use cautiously in the elderly.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown
Adverse ReactionsFrequency not defined.

Central nervous system: Fever, chills, agitation, retrograde amnesia, headache

Dermatologic: Rash, urticaria, pruritus

Endocrine & metabolic: Thyroid gland enlargement

Gastrointestinal: Diarrhea, nausea, vomiting, stomach pain, abdominal cramps

Neuromuscular & skeletal: Peripheral neuropathy, weakness

Ocular: Optic neuritis, optic atrophy, visual impairment

Miscellaneous: Itching of rectal area

Drug InteractionsThere are no known significant interactions.
Test InteractionsMay increase protein-bound serum iodine concentrations reflecting a decrease in ^{131}I uptake; false-positive ferric chloride test for phenylketonuria
Monitoring ParametersOphthalmologic exam
Nursing: Physical Assessment/MonitoringCheck allergy history (iodine) prior to beginning therapy. Perform ophthalmological exams with long-term therapy. Teach patient appropriate use, reinfection prevention, possible side effects/interventions, and adverse symptoms to report.
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed; complete full course of therapy. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake and nutrition (small frequent meals may help). You may experience GI upset (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report unresolved or severe nausea or vomiting, skin rash, fever, or fatigue. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 210 mg, 650 mg

Generic AvailableNo

Mechanism of ActionContact amebicide that works in the lumen of the intestine by an unknown mechanism

Pharmacodynamics/Kinetics

Absorption: Poor and erratic

Metabolism: Hepatic

Excretion: Feces (high percentage)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause agitation or amnesia

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDiiodohydroxyquin

References

“Drugs for Parasitic Infections,” *Med Lett Drugs Ther*, 1993, 35(911):111-22.[PubMed 8246830]

International Brand NamesDepofin (MX); Floraquin (TW)

Iohexol

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Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye oh HEX ole)
U.S. Brand NamesOmnipaque™
Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Nonionic, Low Osmolality)
Use: Labeled Indications

Intrathecal: Myelography; contrast enhancement for computerized tomography

Intravascular: Angiocardiography, aortography, digital subtraction angiography, peripheral arteriography, excretory urography; contrast enhancement for computed tomographic imaging

Oral/body cavity: Arthrography, GI tract examination, hysterosalpingography, pancreatography, cholangiopancreatography, herniography, cystourethrography; enhanced computed tomography of the abdomen

StorageSolution for injection: Store at room temperature of 20°C to 25°C (68°F to 77°F). Protect from light.
ContraindicationsHypersensitivity to iohexol or any component of the formulation

Refer to product labeling for procedure-specific contraindications

Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Pregnancy Risk FactorB
Pregnancy ConsiderationsFetal harm was not observed in animal studies. In general, iodinated contrast media agents are avoided during pregnancy unless essential for diagnosis.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsBottle feedings are recommended for 24 hours after administration.
Drug Interactions

Aldesleukin: Contrast Media (Non-ionic) may enhance the potential for allergic or hypersensitivity reactions to Aldesleukin. *Risk C: Monitor therapy*

MetFORMIN: Iodinated Contrast Agents may enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, injection [preservative free]:

140: 302 mg/mL (50 mL) [provides organic iodine 140 mg/mL; contains tromethamine 1.21 mg/mL, edetate calcium disodium]

180: 388 mg/mL (10 mL, 20 mL) [provides organic iodine 180 mg/mL; contains tromethamine 1.21 mg/mL, edetate calcium disodium]

240: 518 mg/mL (10 mL, 20 mL, 100 mL, 150 mL, 200 mL) [provides organic iodine 240 mg/mL; contains tromethamine 1.21 mg/mL, edetate calcium disodium]

300: 647 mg/mL (10 mL, 30 mL, 50 mL, 75 mL, 100 mL, 125 mL, 150 mL, 200 mL) [provides organic iodine 300 mg/mL; contains tromethamine 1.21 mg/mL, edetate calcium disodium]

350: 755 mg/mL (50 mL, 75 mL, 100 mL, 125 mL, 150 mL, 200 mL, 250 mL) [provides organic iodine 350 mg/mL; contains tromethamine 1.21 mg/mL, edetate calcium disodium]

Generic AvailableNo
ManufacturerAmersham Health
Pharmacotherapy PearlsInformation in this monograph is currently limited to the fields presented. Consult product labeling for additional details.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
References

ACOG Committee on Obstetric Practice, “ACOG Committee Opinion. Guidelines for Diagnostic Imaging During Pregnancy,” *Obstet Gynecol*, 2004, 104(3):647-51.[PubMed 15339791]

International Brand NamesIobrix (KP); Omnipaque (AU, BG, CH, CN, CO, CZ, DK, EE, FI, FR, GR, HN, IL, KP, NL, NO, PL, PY, SE, UY, VE); Radiopaque (IN)

Iopamidol

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye oh PA mi dole)

U.S. Brand NamesIsovue Multipack®; Isovue-M®; Isovue®

Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Nonionic, Low Osmolality)

Use: Labeled Indications

Intrathecal (Isovue-M®): Neuroradiology; contrast enhancement of computed tomographic cisternography and ventriculography; thoraco-lumbar myelography

Intravascular (Isovue®, Isovue Multipack®): Angiography, excretory urography; contrast enhancement of computed tomographic imaging; evaluation of certain malignancies; image enhancement of non-neoplastic lesions

StorageStore at 20°C to 25°C (68°F to 77°F). Protect from light.

ContraindicationsHypersensitivity to iopamidol or any component of the formulation

Refer to product labeling for product- and procedure-specific contraindications

Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Pregnancy Risk FactorB

Pregnancy ConsiderationsFetal harm was not observed in animal studies. In general, iodinated contrast media agents are avoided during pregnancy unless essential for diagnosis.

LactationExcretion in breast milk unknown/use caution

Drug Interactions

Aldesleukin: Contrast Media (Non-ionic) may enhance the potential for allergic or hypersensitivity reactions to Aldesleukin. *Risk C: Monitor therapy*

MetFORMIN: Iodinated Contrast Agents may enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Isovue®:

200: 41% (50 mL, 200 mL) [provides organically-bound iodine 200 mg/mL; contains sodium 0.029 mg (0.001 mEq)/mL, tromethamine 1 mg/mL, edetate calcium disodium]

250: 51% (50 mL, 100 mL, 150 mL) [provides organically-bound iodine 250 mg/mL; contains sodium 0.036 mg (0.002 mEq)/mL, tromethamine 1 mg/mL, edetate calcium disodium]

300: 61% (30 mL, 50 mL, 75 mL, 100 mL, 125 mL, 150 mL, 175 mL) [provides organically-bound iodine 300 mg/mL; contains sodium 0.043 mg (0.002 mEq)/mL, tromethamine 1 mg/mL, edetate calcium disodium]

370: 76% (20 mL, 30 mL, 50 mL, 75 mL, 100 mL, 125 mL, 150 mL, 200 mL) [provides organically-bound iodine 370 mg/mL; contains sodium 0.053 mg (0.002 mEq)/mL, tromethamine 1 mg/mL, edetate calcium disodium]

Isovue-M®:

200: 41% (10 mL, 20 mL) [provides organically-bound iodine 200 mg/mL; contains sodium 0.029 mg (0.001 mEq)/mL, tromethamine 1 mg/mL, edetate calcium disodium]

300: 61% (15 mL) [provides organically-bound iodine 300 mg/mL; contains sodium 0.043 mg (0.002 mEq)/mL, tromethamine 1 mg/mL, edetate calcium disodium]

Isovue Multipack® [pharmacy bulk package]:

250: 51% (200 mL) [provides organically-bound iodine 250 mg/mL; contains sodium 0.036 mg (0.002 mEq)/mL, tromethamine 1 mg/mL, edetate calcium disodium]

300: 61% (200 mL, 500 mL) [provides organically-bound iodine 300 mg/mL; contains sodium 0.043 mg (0.002 mEq)/mL, tromethamine 1 mg/mL, edetate calcium disodium]

370: 76% (200 mL, 500 mL) [provides organically-bound iodine 370 mg/mL; contains sodium 0.053 mg (0.002 mEq)/mL, tromethamine 1 mg/mL, edetate calcium disodium]

Generic Available No

Manufacturer Bracco Diagnostics

Pharmacotherapy Pearls Information in this monograph is currently limited to the fields presented. Consult product labeling for additional details.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

References

ACOG Committee on Obstetric Practice, “ACOG Committee Opinion. Guidelines for Diagnostic Imaging During Pregnancy,” *Obstet Gynecol*, 2004, 104(3):647-51.[PubMed 15339791]

International Brand Names Iopamiro (BG, CH, EE, GR, HN, IL, IT, KP, PL, SE); Iopamiron (AR, BR, CO, FR, PE, PY, UY, VE); Isovue (AU); Radiomiron (CN)

Iopromide

Lexi-Drugs Online

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye oh PROE mide)

U.S. Brand NamesUltravist®

Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Nonionic, Low Osmolality)

Use: Labeled IndicationsEnhance imaging in cerebral arteriography and peripheral arteriography; coronary arteriography and left ventriculography, visceral angiography and aortography; contrast-enhanced computed tomographic imaging of the head and body, excretory urography, intra-arterial digital subtraction angiography, peripheral venography

Dosing: Adults**Note:** Maximum recommended total dose of iodine is 86 g. Individualize dose based upon patient's age, body weight, size of the vessel, and the rate of blood flow within the vessel.

Aortography and visceral angiography: Intravascular (370 mg iodine/mL): Volume and rate of administration based on blood flow and specific characteristics of vessels being studied; maximum dose for procedure: 225 mL

Cerebral arteriography: Intravascular (300 mg iodine/mL): Maximum dose for procedure: 150 mL

Carotid artery visualization: 3-12 mL

Vertebral artery visualization: 4-12 mL

Aortic arch injection: 20-50 mL

Coronary arteriography and left ventriculography: Intravascular (370 mg iodine/mL): Maximum dose for procedure: 225 mL

Left coronary: 3-14 mL

Right coronary: 3-14 mL

Left ventricle: 30-60 mL

Intra-arterial digital subtraction angiography: Intravascular (150 mg iodine/mL): Maximum dose for procedure: 250 mL

Carotid arteries: 6-10 mL

Vertebral: 4-8 mL

Aorta: 20-50 mL

Major branches of the abdominal aorta: 2-20 mL

Peripheral arteriography: Intravascular (300 mg iodine/mL): Maximum dose for procedure: 250 mL. **Note:** The artery needs a pulse to be injected.

Subclavian or femoral artery: 5-40 mL

Aortic bifurcation for distal runoff 25-50 mL

Contrast-enhanced CT: I.V. (300 mg iodine/mL):

Head: 50-200 mL; maximum dose for procedure: 200 mL

Body: 50-200 mL (usual dose for infusion is 100-200 mL); **Note:** Can be given by bolus injection, by rapid infusion, or both; maximum dose for procedure: 200 mL

Excretory urography (normal renal function): I.V. (300 mg iodine/mL): 1 mL/kg; maximum dose for procedure: 100 mL

Peripheral venography: I.V. (240 mg iodine/mL): Minimum amount to clearly visualize the structure under examination; maximum dose for procedure: 250 mL

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Cardiac chambers and related arteries: Children >2 years: I.V. (370 mg iodine/mL): 1-2 mL/kg; maximum dose for procedure: 4 mL/kg

Contrast-enhanced CT: Children >2 years: I.V. (300 mg iodine/mL): 1-2 mL/kg; maximum dose for procedure: 3 mL/kg

Administration: OtherSolutions for intra-arterial injections should be as close to body temperature as possible. Injection rates should be about equal to the flow rate in the vessel being injected. Allow sufficient time between each large injection. Visually inspect prior to use; do not use if discolored, if particulate matter is present, or if containers are defective.

StorageStore at 25°C (77°F). Protect from light.

CompatibilityShould not be mixed with or injected into any lines containing other drugs or solutions.

ContraindicationsNot indicated for intrathecal use

Pediatrics: Prolonged fasting and laxative use prior to administration of iopromide

Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Administration: See "Other warnings/precautions" below.

Concerns related to adverse effects:

- Anaphylaxis: May cause serious and potentially fatal anaphylactoid reactions
- Blood-brain barrier disruption: In patients with known or suspected blood brain barrier disruption or with normal blood-brain barriers and renal failure, iodinated contrast agents have been associated with blood-brain barrier disruption and accumulation of contrast in the brain; use with caution.
- Contrast media nephropathy: Contrast agents may cause acute renal impairment defined as a serum creatinine rise of 0.5 mg/dL or increase of 50% over baseline. Risk factors include concurrent use of nephrotoxic agents, dehydration, diabetes, heart failure, high-dose contrast, and pre-existing renal impairment. In patients at risk, minimize dose and monitor renal function.
- Delayed reactions: May cause delayed adverse reactions; monitor patients for 30-60 minutes after injection.
- Immune reaction: Risks for an immune reaction include previous reaction to contrast, known sensitivity to iodine and known allergies (asthma, hay fever and food allergies), other hypersensitivities, and underlying immune disorder. Skin testing cannot be relied upon and may be dangerous. Treatment for severe reactions should be immediately available.
- Thromboembolic events: Serious thromboembolic events have been reported during angiographic procedures with both ionic and nonionic contrast agents.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Diabetes: Use with caution in patients with diabetes mellitus; these patients may have altered renal blood flow, increasing risk of nephrotoxicity.
- Hepatic impairment: Use with caution in patients with hepatic impairment, especially those with concomitant renal dysfunction or when using both oral and I.V. contrast agents in close proximity.
- Multiple myeloma: Use with caution in patients with multiple myeloma; may worsen renal insufficiency.
- Pheochromocytoma: Use with extreme caution in patients with known or suspected pheochromocytoma. Dose injected should be kept to a minimum to minimize exposure; monitor blood pressure closely.
- Renal impairment: Use with caution in patients with renal impairment; clearance is reduced.
- Sickle cell disease: Use with caution in patients with sickle cell disease; may promote sickling.
- Thyroid dysfunction: Use with caution in patients with thyroid disease; thyroid storm has been reported in patients with history of hyperthyroidism.

Concurrent drug therapy issues:

- General anesthesia: Use with caution in patients undergoing general anesthesia while receiving contrast agents; may be an increased risk of adverse events.

Special populations:

- Elderly: Use with caution in elderly patients with age-related renal impairment.
- Pediatrics: Safety and efficacy have not been established in children ≤2 years of age. Pediatric patients may have an increased risk of adverse effects, especially patients with asthma, sensitivity to allergens or medications, heart disease, or renal dysfunction.

Other warnings/precautions:

- Administration: For I.V. or intra-arterial use only. **[U.S. Boxed Warning]: May be fatal if given intrathecally.** Avoid extravasation, especially in patients with severe arterial or venous disease.
- Appropriate use: Adequately hydrate patient prior to and following administration. Delay intravenous contrast agent administration in patients who have recently received a cholecystographic contrast agent. In contrast-enhanced computerized tomography, contrast may obscure some lesions previously seen on unenhanced CT scans.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAnimal studies do not show evidence of direct fetal harm. Embryolethality was observed, but may be related to maternal toxicity. Safety has not been established in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Cardiovascular: Vasodilatation (4%), chest pain (3%), hypertension (1%)

Central nervous system: Headache (6%), pain (2%), dizziness (1%)

Gastrointestinal: Nausea (4%), vomiting (2%), abnormal taste (1%),

Genitourinary: Urinary urgency (3%)

Local: Injection site hematoma (3%), injection site pain (1%)

Neuromuscular & skeletal: Back pain (3%)

Ocular: Abnormal vision (2%)

<1%: Abdominal pain, agitation, anxiety, apnea, arthralgia, asthenia, asthma, AV block (complete), bradycardia, chills, confusion, constipation, cough increased, coronary thrombosis, depression, diaphoresis increased, diarrhea, dry mouth, dysmenorrhea, dyspepsia, dyspnea, dysuria, emotional lability, facial edema, fever, hypertonia, hypoesthesia, hypotension, hypoxemia, hypoxia, incoordination, injection site reactions (edema, erythema, rash, warm feeling), insomnia, kidney pain, malaise, myasthenia, neck pain, neuropathy, paresthesia, pharyngitis, polydypsia, premature ventricular contractions, pruritus, pulmonary hypertension, salivation, seizure, somnolence, sore throat, speech disorder, syncope, tenesmus, tremor, urticaria, urinary retention, vascular anomaly, visual field defect

Postmarketing and/or case reports: Amnesia, anaphylaxis, angioedema (pediatric), aphasia, brain edema (pediatric), bullous eruption (delayed), erythema (delayed), CHF, conjunctivitis (pediatric), diabetes insipidus (pediatric), epistaxis (pediatric), fixed eruptions (pediatric), hematuria, hemopericardium, hypersensitivity, hypotonia, hypovolemic shock, hypoxia (pediatric), joint effusion (pediatric), lacrimation disorder, laryngeal edema, migraine (pediatric), mucosal swelling (pediatric), muscle cramping (pediatric), mydriasis, nephropathy, papular rash (delayed), renal failure, skin discoloration, skin eruption (delayed), sneezing (delayed), tachycardia, thrombosis, tongue paralysis, ventricular fibrillation, vertigo (pediatric), wheals (delayed)

Drug Interactions

Aldesleukin: Contrast Media (Non-ionic) may enhance the potential for allergic or hypersensitivity reactions to Aldesleukin. *Risk C: Monitor therapy*

MetFORMIN: Iodinated Contrast Agents may enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Test InteractionsThyroid function tests (which depend on estimates of iodine) will not accurately assess function for at least 16 days following administration of iodinated contrast agents. Iopromide may affect PTT, calcium thromboplastin time, and thrombin activity. It may activate the complement alternate pathway. No effects on Factor XIIa have been demonstrated.

Monitoring ParametersCoronary arteriography: ECG (coronary arteriography); vital signs; signs and symptoms of hypersensitivity; renal function

Monitoring: Lab TestsRenal function

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution (Ultravist®):

Iodine 150 mg/mL (provides iopromide 311.7 mg/mL) (50 mL) [contains edetate calcium disodium 0.1 mg]

Iodine 240 mg/mL (provides iopromide 498.72 mg/mL) (50 mL, 100 mL, 200 mL) [contains edetate calcium disodium 0.1 mg]

Iodine 300 mg/mL (provides iopromide 623.4 mg/mL) (50 mL, 100 mL, 150 mL, 500 mL) [contains edetate calcium disodium 0.1 mg]

Iodine 370 mg/mL (provides iopromide 768.86 mg/mL) (50 mL, 100 mL, 150 mL, 200 mL, 500 mL) [contains edetate calcium disodium 0.1 mg]

Generic AvailableNo

ManufacturerBayer HealthCare Pharmaceuticals Inc

Mechanism of ActionIopromide opacifies vessels in its path of flow, permitting radiographic visualization of internal structures.

Pharmacodynamics/Kinetics

Distribution: V_d: 16 L

Protein binding: 1%

Half-life elimination: Main phase: 2 hours, terminal phase: 6.2 hours

Time to peak:

Intravascular: Contrast enhancement: 15-120 seconds after bolus injection

Intravenous: Contrast enhancement: Kidneys: 5-15 minutes

Excretion: Urine 97% (as unchanged drug)

Pharmacotherapy PearlsSeafood allergy: There is a concern that an allergy to seafood may increase the risk of hypersensitivity reactions to iodinated contrast agents due to the iodine content in food. The American College of Radiology and The American Academy of Allergy, Asthma, and Immunology both agree that allergy to seafood or shellfish does not pose any increased risk of hypersensitivity over any other food allergies. Patients with food allergies or asthma may have an increased risk of being atopic, which may put them at an increased risk for hypersensitivity reactions over those who do not.

Osmolality:

150 mg iodine/mL: 328

240 mg iodine/mL: 483

300 mg iodine/mL: 607

370 mg iodine/mL: 774

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Abnormal taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause agitation, amnesia, anxiety, confusion, depression, emotional lability, insomnia, malaise, or somnolence.

Mental Health: Effects on Psychiatric TreatmentNone reported

References

“Academy Position Statement: The Risk of Severe Allergic Reactions from the Use of Potassium Iodide for Radiation Emergencies,” Adverse Reactions to Foods Committee and the Adverse Reactions to Drugs and Biologicals Committee, available at http://www.aaaai.org/media/resources/academy_statements/position_statements/potassium_iodide.asp. Accessed October 24, 2007.

American College of Radiology Committee on Drugs and Contrast Media, *Manual on Contrast Media V 5.0* Reston, VA: American College of Radiology. 2004.

Cutronea P, Polimeni G, Curcuruto R, et al, “Adverse Reactions to Contrast Media: An Analysis From Spontaneous Reporting Data,” *Pharmacol Res*, 2007, 56(1):35-41.[PubMed 17482832]

Murphy SW, Barrett BJ, and Parfrey PS, “Contrast Nephropathy,” *J Am Soc Nephrol*, 2000, 11(1):177-82.[PubMed 10616853]

International Brand NamesClarograf (AR); Ultravist (AU, BG, CH, CL, CZ, DK, FI, FR, GR, HN, IE, IL, IN, KP, NL, NO, PL, SE, ZA)

Iothalamate Meglumine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye oh thal A mate MEG loo meen)

U.S. Brand NamesConray®; Conray® 30; Conray® 43; Cysto-Conray® II

Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Ionic, High Osmolality)

Use: Labeled Indications

Solution for injection: Arthrography, cerebral angiography, cranial computerized angiotomography, digital subtraction angiography, direct cholangiography, endoscopic retrograde cholangiopancreatography, excretory urography, peripheral arteriography, urography, venography; contrast enhancement of computed tomographic images

Solution for instillation: Retrograde cystography and cystourethrography

StorageStore below 30°C (86°F). Protect from strong daylight or direct exposure to the sun.

ContraindicationsHypersensitivity to any component of the formulation; intrathecal administration; solution for instillation should not be used intravascularly

Refer to product labeling for product and procedure specific contraindications

Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Pregnancy Risk FactorB/C (product dependent)

Pregnancy ConsiderationsIn general, iodinated contrast media agents are avoided during pregnancy unless essential for diagnosis.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsBottle feedings are recommended for 24 hours after administration.

Drug Interactions

MetFORMIN: Iodinated Contrast Agents may enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Conray®: 60% (30 mL, 50 mL, 100 mL, 150 mL) [provides organically-bound iodine 282 mg/mL; contains edetate calcium disodium]

Conray® 30: 30% (50 mL, 150 mL) [provides organically-bound iodine 141 mg/mL; contains edetate calcium disodium]

Conray® 43: 43% (50 mL, 100 mL, 200 mL, 250 mL) [provides organically-bound iodine 202 mg/mL; contains edetate calcium disodium]

Injection, solution for instillation (Cysto-Conray® II): 17.2% (250 mL, 500 mL) [provides organically-bound iodine 81 mg/mL; contains edetate calcium disodium]

Generic AvailableNo

ManufacturerMallinckrodt

Pharmacotherapy PearlsInformation in this monograph is currently limited to the fields presented. Consult product labeling for additional details.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

ACOG Committee on Obstetric Practice, "ACOG Committee Opinion. Guidelines for Diagnostic Imaging During Pregnancy," *Obstet Gynecol*, 2004, 104(3):647-51.[PubMed 15339791]

International Brand NamesConray (AU)

Iothalamate Sodium

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye oh thal A mate SOW dee um)

U.S. Brand NamesConray® 400

Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Ionic, High Osmolality)

Use: Labeled IndicationsExcretory urography, angiocardiography, aortography; contrast enhancement of computed tomographic brain images

StorageStore below 30°C (86°F). Protect from strong daylight or direct exposure to the sun.

ContraindicationsHypersensitivity to iothalamate or any component of the formulation; myelography; cerebral angiography by direct injection into carotid or vertebral arteries

Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Pregnancy Risk FactorB

Pregnancy ConsiderationsHarm to the fetus was not observed in animal studies. In general, iodinated contrast media agents are avoided during pregnancy unless essential for diagnosis.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsBottle feedings are recommended for 24 hours after administration.

Drug Interactions

MetFORMIN: Iodinated Contrast Agents may enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 66.8% (50 mL) [provides organically-bound iodine 400 mg/mL; contains edetate calcium disodium, sodium 24.2 mg (1.05 mEq)/mL]

Generic AvailableNo

ManufacturerMallinckrodt

Pharmacotherapy PearlsInformation in this monograph is currently limited to the fields presented. Consult product labeling for additional details.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

ACOG Committee on Obstetric Practice, “ACOG Committee Opinion. Guidelines for Diagnostic Imaging During Pregnancy,” *Obstet Gynecol*, 2004, 104(3):647-51.[PubMed 15339791]

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(EYE oh ver sole)
U.S. Brand NamesOptiray®
Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Nonionic, Low Osmolality)
Use: Labeled IndicationsArteriography, angiography, angiocardiography, ventriculography, excretory urography, and venography procedures; contrast enhanced tomographic imaging
StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from strong daylight or direct exposure to the sun.
ContraindicationsHypersensitivity to any component of the formulation; not intended for intrathecal use
Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. In general, iodinated contrast media agents are avoided during pregnancy unless essential for diagnosis.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsTemporary discontinuation of nursing should be considered.
Drug Interactions

Aldesleukin: Contrast Media (Non-ionic) may enhance the potential for allergic or hypersensitivity reactions to Aldesleukin. *Risk C: Monitor therapy*

MetFORMIN: Iodinated Contrast Agents may enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

160: 34% (50 mL) [provides organically-bound iodine 160 mg/mL; contains tromethamine 3.6 mg/mL, edetate calcium disodium]

240: 51% (50 mL, 100 mL, 125 mL, 200 mL, 500 mL) [provides organically-bound iodine 240 mg/mL; contains tromethamine 3.6 mg/mL, edetate calcium disodium]

300: 64% (50 mL, 100 mL, 150 mL, 200 mL) [provides organically-bound iodine 300 mg/mL; contains tromethamine 3.6 mg/mL, edetate calcium disodium]

320: 68% (20 mL, 30 mL, 50 mL, 75 mL, 100 mL, 125 mL, 150 mL, 200 mL, 250 mL) [provides organically-bound iodine 320 mg/mL; contains tromethamine 3.6 mg/mL, edetate calcium disodium]

350: 74% (50 mL, 75 mL, 100 mL, 150 mL, 200 mL, 250 mL, 500 mL) [provides organically-bound iodine 350 mg/mL; contains tromethamine 3.6 mg/mL, edetate calcium disodium]

Generic AvailableNo
ManufacturerMallinckrodt
Pharmacotherapy PearlsInformation in this monograph is currently limited to the fields presented. Consult product labeling for additional details.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
References

ACOG Committee on Obstetric Practice, “ACOG Committee Opinion. Guidelines for Diagnostic Imaging During Pregnancy,” *Obstet Gynecol*, 2004, 104(3):647-51.[PubMed 15339791]

International Brand NamesOptiject (FR); Optiray (AR, AU, CH, CO, CZ, DK, HN, IT, KP, NL, NO, PE, PY, SE)

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye ox AG late MEG loo meen & eye ox AG late SOW dee um)
U.S. Brand NamesHexabrix™
Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Ionic, Low Osmolality)
Use: Labeled IndicationsAngiocardiography, arteriography, aortography, arthrography, angiography, hysterosalpingography, venography, and urography procedures; contrast enhancement of computed tomographic imaging
StorageStore below 30°C (86°F). Protect from strong daylight or direct exposure to the sun.
ContraindicationsHypersensitivity to ioxaglate or any component of the formulation; myelography; hysterosalpingography during the menstrual period, pregnancy, genital tract infection, or cervical conization or curettage within 30 days; arthrography with infection present in or near the joint
Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Pregnancy Risk FactorB
Pregnancy ConsiderationsAnimal reproduction studies did not show fetal harm. In general, iodinated contrast media agents are avoided during pregnancy unless essential for diagnosis.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsBottle feedings are recommended for 24 hours after administration.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: Ioxaglate meglumine 39.3% and ioxaglate sodium 19.6% (20 mL, 50 mL, 100 mL, 150 mL, 200 mL) [provides organically-bound iodine 32% (320 mg/mL); contains edetate calcium disodium, sodium 3.48 mg (0.15 mEq)/mL]

Generic AvailableNo
ManufacturerMallinckrodt
Pharmacotherapy PearlsInformation in this monograph is currently limited to the fields presented. Consult product labeling for additional details.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsIoxaglate Sodium and Ioxaglate Meglumine
References

ACOG Committee on Obstetric Practice, “ACOG Committee Opinion. Guidelines for Diagnostic Imaging During Pregnancy,” *Obstet Gynecol*, 2004, 104(3):647-51.[PubMed 15339791]

International Brand NamesHexabrix (NO, NZ)

Ioxilan

Lexi-Drugs Online

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye OKS ee lan)

U.S. Brand NamesOxilan®

Canadian Brand NamesOxilan® 300; Oxilan® 350

Pharmacologic CategoryIodinated Contrast Media; Radiological/Contrast Media (Nonionic, Low Osmolality)

Use: Labeled Indications

Intra-arterial: Ioxilan 300 mgI/mL is indicated for cerebral arteriography. Ioxilan 350 mgI/mL is indicated for coronary arteriography and left ventriculography, visceral angiography, aortography, and peripheral arteriography

Intravenous: Both products are indicated for excretory urography and contrast-enhanced computed tomographic (CECT) imaging of the head and body

Dosing: Adults

Coronary arteriography and left ventriculography: Intra-arterial: For visualization of coronary arteries and left ventricle, ioxilan injection with a concentration of 350 mg iodine/mL is recommended

Usual injection volumes:

Left and right coronary: 2-10 mL (0.7-3.5 g iodine)

Left ventricle: 25-50 mL (8.75-17.5 g iodine)

Total doses should not exceed 250 mL; the injection rate of ioxilan should approximate the flow rate in the vessel injected

Cerebral arteriography: Intra-arterial: For evaluation of arterial lesions of the brain, a concentration of 300 mg iodine/mL is indicated

Recommended doses: 8-12 mL (2.4-3.6 g iodine)

Total dose should not exceed 150 mL

Dosing: ElderlyRefer to adult dosing.

StorageStore at 15°C to 30°C (59°F to 86°F); do not freeze. Protect from light.

ContraindicationsHypersensitivity to ioxilan or any component of the formulation; ioxilan injection is not indicated for intrathecal use

Allergy Considerations

- Contrast Agent, Iodinated, Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Administration: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Anaphylaxis: May cause serious and potentially fatal anaphylactoid reactions.
- Contrast dye/iodine hypersensitivity: Use with caution in patients with history of previous reaction to contrast dye or iodine.
- Thromboembolic events: Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Hepatic impairment: Use with caution in patients with hepatic impairment, especially those with concomitant renal dysfunction or when using both oral and IV contrast agents in close proximity.

- Multiple myeloma: Use with caution in patients with multiple myeloma; may worsen renal insufficiency.

- Pheochromocytoma: Use with extreme caution in patients with known or suspected pheochromocytoma. Dose injected should be kept to a minimum to minimize exposure; monitor blood pressure closely.

- Renal impairment: Use with caution in patients with renal impairment; clearance is reduced.

- Sickle cell disease: Use with caution in patients with sickle cell disease; may promote sickling.

- Thyroid dysfunction: Use with caution in patients with thyroid disease; thyroid storm has been reported in patients with history of hyperthyroidism.

Special populations:

- Elderly: Use with caution in elderly patients with age-related renal impairment.

Other warnings/precautions:

- Administration: For I.V. or intra-arterial use only. **[U.S. Boxed Warning]: May be fatal if given intrathecally.** Avoid extravasation, especially in patients with severe arterial or venous disease.

- *In vitro* clotting: Clotting has been reported when blood remains in contact with syringes containing ioxilan; use of plastic syringes in place of glass syringes has been reported to decrease, but not eliminate, the likelihood of *in vitro* clotting.

Pregnancy Risk FactorB

Pregnancy ConsiderationsFetal harm was not observed in animal studies. In general, iodinated contrast media agents are avoided during pregnancy unless essential for diagnosis.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Cardiovascular: Angina (1%), hypertension (1%)

Central nervous system: Headache (4%), fever (2%)

Gastrointestinal: Nausea (2%)

<1%: Bradycardia, chills, diarrhea, dizziness, hypotension, injection site hematomas, rash, urticaria, vomiting

Drug Interactions

Aldesleukin: Contrast Media (Non-ionic) may enhance the potential for allergic or hypersensitivity reactions to Aldesleukin. *Risk C: Monitor therapy*

MetFORMIN: Iodinated Contrast Agents may enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Test InteractionsThe results of protein-bound iodine and radioactive iodine uptake studies, which depend on iodine estimations, will not accurately reflect thyroid function for at least 16 days following administration of iodinated contrast media. However, thyroid function tests that do not depend on iodine estimations (eg, T_3 resin uptake and total or free thyroxine (T_4) assays), are not affected.

Monitoring ParametersPrior to and 24-48 hours after intravascular administration: Thyroid function tests, renal function tests, blood counts, serum electrolytes, and urinalysis should be monitored for and blood pressure, heart rate, electrocardiogram, and temperature should be monitored throughout the procedure

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Oxilan® 300: 62% (50 mL, 100 mL, 150 mL, 200 mL) [provides organically-bound iodine 300 mg/mL; contains sodium 0.22 mg (0.01 mEq)/mL, edetate calcium disodium]

Oxilan® 350: 73% (50 mL, 100 mL, 150 mL, 200 mL) [provides organically- bound iodine 350 mg/mL; contains sodium 0.22 mg (0.01 mEq)/mL, edetate calcium disodium]

Generic AvailableNo

Mechanism of ActionIoxilan is a nonionic, water soluble, triiodinated x-ray contrast agent for intravascular injection. Intravascular injection of a radiopaque diagnostic agent opacifies those vessels in the path of flow of the contrast medium, permitting radiographic visualization of the internal structures of the human body until significant hemodilution occurs.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

ACOG Committee on Obstetric Practice, “ACOG Committee Opinion. Guidelines for Diagnostic Imaging During Pregnancy,” *Obstet Gynecol*, 2004, 104(3):647-51.[PubMed 15339791]

International Brand NamesOxilan 300 (CA); Oxilan 350 (CA)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Hepatoblastoma

Regimen UseHepatoblastoma

Regimen

Ifosfamide: I.V.: 500 mg/m^2 day 1

[total dose/cycle = 500 mg/m^2]

followed by I.V.: 1000 mg/m^2/day continuous infusion days 1 to 3

[total dose/cycle = 3000 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 4 to 8

[total dose/cycle = 100 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2/day continuous infusion days 9 and 10

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 21 days

References

von Schweinitz D, Byrd DJ, Hecker H, et al, âEfficiency and Toxicity of Ifosfamide, Cisplatin, and Doxorubicin in the Treatment of Childhood Hepatoblastoma. Study Committee of the Cooperative Paediatric Liver Tumour Study HB89 of the German Society for Paediatric Oncology and Haematology,â *Eur J Cancer*, 1997, 33(8):1243-9.[PubMed 9301450]

Ipecac Syrup

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(IP e kak SIR up)
Pharmacologic CategoryAntidote
Use: Labeled IndicationsTreatment of acute oral drug overdosage and in certain poisonings
Dosing: AdultsEmetic: Oral: 15-30 mL followed by 200-300 mL of water; repeat dose one time if vomiting does not occur within 20 minutes.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricEmetic: Oral:

6-12 months: 5-10 mL followed by 10-20 mL/kg of water; repeat dose one time if vomiting does not occur within 20 minutes.

1-12 years: 15 mL followed by 10-20 mL/kg of water; repeat dose one time if vomiting does not occur within 20 minutes.

Note: If emesis does not occur within 30 minutes after second dose, ipecac must be removed from stomach by gastric lavage.

Administration: OralDo **not** administer to unconscious patients. Patients should be kept active and moving following administration of ipecac. If vomiting does not occur after second dose, gastric lavage may be considered to remove ingested substance.
ContraindicationsHypersensitivity to ipecac or any component of the formulation; do not use in unconscious patients; patients with no gag reflex; following ingestion of strong bases, acids, or volatile oils; when seizures are likely
Warnings/Precautions

Disease-related concerns:

- Bulimia: Use with caution in patients with bulimia.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease.

Other warnings/precautions:

- Product confusion: Do not confuse ipecac syrup with ipecac fluid extract, which is 14 times more potent.

Other warnings/precautions:

- Antiemetic overdose: May not be effective in antiemetic overdose.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiotoxicity

Central nervous system: Lethargy

Gastrointestinal: Protracted vomiting, diarrhea

Neuromuscular & skeletal: Myopathy

Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb InteractionsFood: Milk, carbonated beverages may decrease effectiveness.
Nursing: Physical Assessment/MonitoringThe Poison Control Center should be contacted before administration. Administer only to conscious patients. If vomiting does not occur within 30 minutes, contact the Poison Control Center (or prescriber) again. Assess patient's knowledge for home use.
Patient EducationThe Poison Control Center should be contacted before administration. Take only as directed; do not take more than recommended or more often than recommended. Follow with 8 oz of water. If vomiting does not occur within 30 minutes, contact the Poison Control Center or emergency services again. Do not administer if vomiting. If vomiting occurs after taking, do not eat or drink until vomiting subsides. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Syrup: 70 mg/mL (30 mL) [contains alcohol]

Generic AvailableYes
Mechanism of ActionIrritates the gastric mucosa and stimulates the medullary chemoreceptor trigger zone to induce vomiting
Pharmacodynamics/Kinetics

Onset of action: 15-30 minutes

Duration: 20-25 minutes; 60 minutes in some cases

Absorption: Significant amounts, mainly when it does not produce emesis

Excretion: Urine; emetine (alkaloid component) may be detected in urine 60 days after excess dose or chronic use

Pharmacotherapy PearlsThe benefit of ipecac syrup to treat poisoning in children has been questioned. In November 2003, the American Academy of Pediatrics recommended that syrup of ipecac no longer be used routinely for the management of poisonings in the home. They advised parents to dispose of existing supplies of ipecac to help prevent inappropriate use.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentCombination with chlorpromazine has been associated with dystonic reactions

Index TermsSyrup of Ipecac

References

American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention, “Poison Treatment in the Home,” *Pediatrics*, 2003, 112(5):1182-5. [PubMed 14595067]

Colletti RB and Wasserman RC, “Recurrent Infantile Vomiting Due to Intentional Ipecac Poisoning,” *J Pediatr Gastroenterol Nutr*, 1989, 8(3):394-6. [PubMed 2565382]

Day L, Kelly C, Reed G, et al, “Fatal Cardiomyopathy: Suspected Child Abuse by Chronic Ipecac Administration,” *Vet Hum Toxicol*, 1989, 31(3):225-7. [PubMed 2741309]

Klein-Schwartz W, Gorman RL, Oderda GM, et al, “Ipecac Use in the Elderly: The Unanswered Question,” *Ann Emerg Med*, 1984, 13(12):1152-4. [PubMed 6150669]

Kunkel DB, “The Toxic Toll of Keeping Thin,” *Emerg Med*, 1985, 17:176-80.

Manno BR and Manno JE, “Toxicology of Ipecac: A Review,” *J Toxicol Clin Toxicol*, 1977, 10:221-42.

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

Moran DM, Crouch DC, Finkle BS, et al, “Absorption of Ipecac Alkaloids in Emergency Room Patients,” *Vet Hum Toxicol*, 1983, 25:286.

Ipratropium and Albuterol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Combivent® may be confused with Combivir®, Serevent®

International issues:

DuoNeb® may be confused with DuoTrav™ which is a brand name for travoprost/timolol combination product in Canada

Pronunciation(i pra TROE pee um & al BYOO ter ole)
U.S. Brand NamesCombivent®; DuoNeb®
Canadian Brand NamesCO Ipra-Sal; Combivent®; Gen-Combo Sterinebs; ratio-Ipra Sal UDV
Pharmacologic CategoryBronchodilator
Use: Labeled IndicationsTreatment of COPD in those patients who are currently on a regular bronchodilator who continue to have bronchospasms and require a second bronchodilator
Dosing: Adults

COPD:

Aerosol for inhalation: 2 metered-dose inhalations 4 times/day; may receive additional doses as necessary, but total number of doses in 24 hours should not exceed 12 inhalations.

Solution for nebulization: Initial: 3 mL every 6 hours (maximum: 3 mL every 4 hours)

Dosing: ElderlyRefer to adult dosing.
Administration: InhalationNebulization: Administer via jet nebulizer to an air compressor with an adequate air flow, equipped with a mouthpiece or face mask. MDI: Shake canister vigorously for ≥10 seconds. Prior to first use (or if not used for >24 hours) a test spray of 3 sprays is recommended. Avoid spraying into eyes.
Dietary ConsiderationsSome dosage forms may contain soya lecithin. Do not use in patients allergic to soya lecithin or related food products such as soybean and peanut.
Storage

DuoNeb®: Store at 2°C to 30°C (36°F to 86°F). Protect from light.

Combivent®: Store at 15°C to 30°C (59°F to 86°F). Avoid excessive humidity. Do not store near heat or open flame.

ContraindicationsHypersensitivity to ipratropium, albuterol, atropine (and its derivatives) or any component of the formulation
Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.
- Hypersensitivity reactions: Immediate hypersensitivity reactions (urticaria, angioedema, rash, bronchospasm) have been reported.
- Sympathomimetic amines sensitivity: Use albuterol with caution in patients with a sensitivity to sympathomimetic amines.

Disease-related concerns:

- Asthma: Appropriate use: Ipratropium is not indicated for the initial treatment of acute episodes of bronchospasm.
- Cardiovascular disease: Use albuterol with caution in patients with cardiovascular disease (arrhythmia or hypertension or HF); beta-agonists may cause elevation in blood pressure, heart rate and result in CNS stimulation/excitation. Beta$_2$-agonists may also increase risk of arrhythmias.
- Diabetes: Use albuterol with caution in patients with diabetes mellitus; beta$_2$-agonists may increase serum glucose.
- Glaucoma: Use ipratropium with caution in patients with narrow-angle glaucoma.
- Hyperthyroidism: Use albuterol with caution in hyperthyroidism; may stimulate thyroid activity.

- Prostatic hyperplasia/bladder neck obstruction: Use ipratropium with caution in patients with prostatic hyperplasia or bladder neck obstruction.

- Seizure disorder: Use albuterol with caution in patients with seizure disorders; beta-agonists may result in CNS stimulation/excitation.

Special populations:

- Elderly: Ipratropium has not been specifically studied in the elderly, but it is poorly absorbed from the airways and appears to be safe in this population. Because of its minimal effect on beta$_1$-receptors and its relatively long duration of action, albuterol is a rational choice in the elderly when a beta-agonist is indicated; oral albuterol use should be avoided in the elderly due to adverse effects.

- Pediatrics: Some adverse reactions may occur more frequently in children 2-5 years of age than in adults and older children. Safety and efficacy have not been established in children.

Dosage form specific issues:

- Soya lecithin: Some dosage forms contain soya lecithin; may cause allergic reactions in patients with allergy to soya lecithin or related food products (eg, soybean and peanut)

Other warnings/precautions:

- Appropriate use: Do not exceed recommended dose; serious adverse events, including fatalities, have been associated with excessive use of inhaled sympathomimetics.

- Patient education: A spacer device is recommended when using a metered-dose inhaler.

- Tolerance: Excessive use may result in tolerance.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. See individual agents.
Breast-Feeding ConsiderationsSee individual agents.
Adverse Reactions

Percentages reported with either combination product (not versus placebo). Also see individual agents.

>10%: Respiratory: Bronchitis (2% to 12%), upper respiratory tract infection (11%)

1% to 10%:

Cardiovascular: Chest pain (≤3%), angina (<2%), arrhythmia (<2%), edema (<2%), hypertension (<2%), palpitation (<2%), tachycardia (<2%)

Central nervous system: Headache (6%), pain (1% to 3%), dizziness (<2%), fatigue (<2%), insomnia (<2%), nervousness (<2%), tremor (<2%)

Gastrointestinal: Diarrhea (≤2%), dyspepsia (≤2%), sputum increased (<2%), taste perversion (<2%), vomiting (<2%), xerostomia (<2%), nausea (1% to 2%), dyspepsia (≤1%), constipation

Genitourinary: Urinary tract infection (≤2%)

Neuromuscular & skeletal: Arthralgia (<2%), paresthesia (<2%), leg cramps (1%)

Respiratory: Lung disease (6%), dyspnea (5%), cough (4%), pharyngitis (2% to 4%), respiratory disorder (3%), sinusitis (2%), pneumonia (1%), rhinitis (1%)

Miscellaneous: Dysphonia (<2%), flu-like syndrome (1%)

<1%: Allergic reactions (angioedema of tongue, lips or face; laryngospasm, pruritus, rash, urticaria); anaphylactic reaction, bronchospasm

Metabolism/Transport EffectsAlbuterol: **Substrate** of CYP3A4 (major)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alpha-/Beta-Blockers: May diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Atomoxetine: May enhance the tachycardic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Betahistine: May diminish the therapeutic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Monitoring ParametersSpirometry (FEV, FVC); weight
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol for oral inhalation:

Combivent®: Ipratropium bromide 18 mcg and albuterol sulfate 103 mcg per actuation (14.7 g) [contains chlorofluorocarbon, soya lecithin; 200 metered actuations]

Solution for nebulization: Ipratropium bromide 0.5 mg and albuterol base 2.5 mg per 3 mL (30s, 60s)

DuoNeb®: Ipratropium bromide 0.5 mg and albuterol base 2.5 mg per 3 mL (30s, 60s)

Generic AvailableYes: Solution for nebulization
Pricing: U.S. (www.drugstore.com)

Aerosol (Combivent)

103-18 mcg/ACT (14.7): $116.53

Solution (DuoNeb)

0.5-2.5 (3) mg/3 mL (90): $76.64

0.5-2.5 (3) mg/3 mL (180): $140.53

Solution (Ipratropium-Albuterol)

0.5-2.5 (3) mg/3 mL (90): $40.00

Mechanism of ActionSee individual agents.
Pharmacodynamics/KineticsSee individual agents.
Related Information

- Albuterol
- Inhalant Agents
- Ipratropium

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), dry mucous membrane, and unusual taste.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNervousness, dizziness, fatigue, headache are common; may cause insomnia or anxiety
Mental Health: Effects on Psychiatric TreatmentMay produce additive anticholinergic effects if used concurrently with psychotropics; effect of propranolol may be reduced; cardiovascular effects (tachycardia, palpitations) may be increased with MAO inhibitors, TCAs, and amphetamines
Index TermsAlbuterol and Ipratropium; Salbutamol and Ipratropium
References

Rabe KF, Hurd S, Anzueto A, et al, “Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease,” *Am J Respir Crit Care Med*, 2007, 176(6):532–55.[PubMed 17507545]

International Brand NamesAtrolin (TW); Combipul (PH); Combivent (AE, AR, AT, BB, BE, BF, BH, BJ, BM, BR, BS, BZ, CI, CL, CN, CO, CR, CY, DK, DO, EE, EG, ES, ET, FR, GH, GM, GN, GT, GY, HK, HN, ID, IE, IL, IQ, IR, JM, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NI, NL, OM, PA, PE, PH, PY, QA, SA, SC, SD, SE, SL, SN, SR, SV, SY, TH, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Combivent Aerosol (AU); Combivent UDV (GB, IE); Di-Promal (AT); Dospir (CH); Duavent (PH); Duolin (AU, IN); Duospirel (AT); Ipramol (MY); Zarent (IT)

Ipratropium

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Atrovent® may be confused with Alupent®, Serevent®

Pronunciation(i pra TROE pee um)

U.S. Brand NamesAtrovent®; Atrovent® HFA

Canadian Brand NamesAlti-Ipratropium; Apo-Ipravent®; Atrovent®; Atrovent® HFA; Gen-Ipratropium; Novo-Ipramide; Nu-Ipratropium; PMS-Ipratropium

Pharmacologic CategoryAnticholinergic Agent

Use: Labeled Indications

Oral inhalation: Anticholinergic bronchodilator used in bronchospasm associated with COPD, bronchitis, and emphysema

Nasal spray: Symptomatic relief of rhinorrhea associated with the common cold and allergic and nonallergic rhinitis

Use: Unlabeled/InvestigationalOral inhalation: Adjunct to short-acting beta-adrenergic agonists therapy in moderate-to-severe exacerbations of acute asthma in the emergency room

Dosing: Adults

Asthma exacerbation, acute (*NIH Asthma Guidelines, 2007*):

Nebulization: 500 mcg every 20 minutes for 3 doses, then as needed. **Note:** Should be given in combination with a short-acting beta-adrenergic agonist.

Metered-dose inhaler: 8 inhalations every 20 minutes as needed for up to 3 hours. **Note:** Should be given in combination with a short-acting beta-adrenergic agonist.

Bronchospasm associated with COPD:

Nebulization: 500 mcg (one unit-dose vial) 3-4 times/day with doses 6-8 hours apart

Metered-dose inhaler: 2 inhalations 4 times/day, up to 12 inhalations/24 hours

Colds (symptomatic relief of rhinorrhea): Safety and efficacy of use beyond 4 days not established: *Intranasal:* Nasal spray (0.06%): 2 sprays in each nostril 3-4 times/day

Allergic/nonallergic rhinitis:*Intranasal:* Nasal spray (0.03%): 2 sprays in each nostril 2-3 times/day

Seasonal allergic rhinitis (safety and efficacy of use beyond 3 weeks in patients with seasonal allergic rhinitis has not been established): *Intranasal:* Nasal spray (0.06%): 2 sprays in each nostril 4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Asthma exacerbation, acute (*NIH Asthma Guidelines, 2007*):

Nebulization:

Children ≤12 years: 250-500 mcg every 20 minutes for 3 doses, then as needed. **Note:** Should be given in combination with a short-acting beta-adrenergic agonist.

Children >12 years: Refer to adult dosing.

Metered-dose inhaler:

Children ≤12 years: 4-8 inhalations every 20 minutes as needed for up to 3 hours. **Note:** Should be given in combination with a short-acting beta-adrenergic agonist.

Children >12 years: Refer to adult dosing.

Colds (symptomatic relief of rhinorrhea): Intranasal: Safety and efficacy of use beyond 4 days in patients with the common cold have not been established:

Children 5-11 years: 0.06%: 2 sprays in each nostril 3 times/day

Children ≥12 years and Adults: 0.06%: 2 sprays in each nostril 3-4 times/day

Allergic/nonallergic rhinitis: Intranasal: Children ≥6 years: Refer to adult dosing.

Seasonal allergic rhinitis: Intranasal: Children ≥5 years: Refer to adult dosing.

Administration: Inhalation

Atrovent® HFA: Prior to initial use, prime inhaler by releasing 2 test sprays into the air. If the inhaler has not been used for >3 days, reprime.

Nasal spray: Prior to initial use, prime inhaler by releasing 7 test sprays into the air. If the inhaler has not been used for >24 hours, reprime by releasing 2 test sprays into the air.

Storage

Oral inhalation aerosol and nasal spray: Store at controlled room temperature of 25°C (77°F). Do not store near heat or open flame.

Oral inhalation solution: Store at 15°C to 30°C (59°F to 86°F). Protect from light.

CompatibilityCompatible for 1 hour when mixed with albuterol in a nebulizer.
ContraindicationsHypersensitivity to ipratropium, atropine (and its derivatives), or any component of the formulation
Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.
- Hypersensitivity reactions: Immediate hypersensitivity reactions (urticaria, angioedema, rash, bronchospasm) have been reported.

Disease-related concerns:

- Glaucoma: Use with caution in patients with narrow-angle glaucoma.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis.
- Prostatic hyperplasia/bladder neck obstruction: Use with caution in patients with prostatic hyperplasia or bladder neck obstruction.

Other warnings/precautions:

- Appropriate use: Inhalation/nebulizer not indicated for the initial treatment of acute episodes of bronchospasm where rescue therapy is required for rapid response. Should only be used in acute exacerbations of asthma in conjunction with short-acting beta-adrenergic agonists for acute episodes.

Geriatric ConsiderationsThe elderly may find it difficult to use the metered dose inhaler. A spacer device may be useful. Ipratropium has not been specifically studied in the elderly, but it is poorly absorbed from the airways and appears to be safe in this population.
Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

Inhalation aerosol and inhalation solution:

>10%: Respiratory: Upper respiratory tract infection (9% to 34%), bronchitis (10% to 23%), sinusitis (1% to 11%)

1% to 10%:

Cardiovascular: Chest pain (3%), palpitation

Central nervous system: Headache (6% to 7%), dizziness (2% to 3%)

Gastrointestinal: Dyspepsia (1% to 5%), nausea (4%), xerostomia (2% to 4%)

Genitourinary: Urinary tract infection (2% to 10%)

Neuromuscular & skeletal: Back pain (2% to 7%)

Respiratory: Dyspnea (7% to 10%), rhinitis (2% to 6%), cough (3% to 5%), pharyngitis (4%), bronchospasm (2%), sputum increased (1%)

Miscellaneous: Flu-like syndrome (4% to 8%)

<1%, postmarketing, and/or case reports: Anaphylactic reaction, angioedema, arthritis, atrial fibrillation, bitter taste, constipation, diarrhea, eye pain (acute), glaucoma, hypersensitivity reactions, hypotension, insomnia, laryngospasm, mydriasis, nervousness, pruritus, rash, tachycardia (including supraventricular), tremor, urinary retention, urticaria

Nasal spray:

1% to 10%:Central nervous system: Headache (4% to 10%)

Gastrointestinal: Taste perversion (≤4%), xerostomia (1% to 4%), diarrhea (2%), nausea (2%)

Respiratory: Epistaxis (6% to 9%), pharyngitis (≤8%), upper respiratory tract infection (5% to 10%), nasal dryness (<1% to 5%), nasal irritation (2%), nasal congestion (1%)

<2%, postmarketing, and/or case reports: Anaphylactic reaction, angioedema, blurred vision, conjunctivitis, cough, dizziness, hoarseness, laryngospasm, nasal burning, ocular irritation, palpitation, rash, tachycardia, thirst, tinnitus, urticaria, xerostomia

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (especially anything that may have anticholinergic properties). Assess patient response on a regular basis throughout therapy. Teach patient proper use, possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Use exactly as directed (see below). Use care to avoid direct contact with eyes. Do not use more often than recommended. Store solution away from light. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause sensitivity to heat (avoid extremes in temperature); nervousness, dizziness, or fatigue (use caution when driving or engaging in tasks requiring alertness until response to drug is known); dry mouth, unpleasant taste, stomach upset (small frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help); or difficulty urinating (always void before treatment). Report unresolved GI upset, dizziness or fatigue, vision changes, palpitations, persistent inability to void, nervousness, or insomnia. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Inhaler: Follow instructions for use accompanying the product. Close eyes when administering ipratropium; blurred vision may result if sprayed into eyes. Effects are enhanced by holding breath 10 seconds after inhalation; wait at least 1 full minute between inhalations.

Nebulizer: Wash hands before and after treatment. Wash and dry nebulizer after each treatment. Twist open the top of one unit dose vial and squeeze the contents into the nebulizer reservoir. Connect the nebulizer reservoir to the mouthpiece or face mask. Connect nebulizer to compressor. Sit in a comfortable, upright position. Place mouthpiece in your mouth or put on the face mask and turn on the compressor. If a face mask is used, avoid leakage around the mask (temporary blurring of vision, worsening of narrow-angle glaucoma, or eye pain may occur if mist gets into eyes). Breathe calmly and deeply until no more mist is formed in the nebulizer (about 5 minutes). At this point, treatment is finished.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol for oral inhalation, as bromide:

Atrovent® HFA: 17 mcg/actuation (12.9 g)

Solution for nebulization, as bromide: 0.02% (2.5 mL)

Solution, intranasal, as bromide [spray]:

Atrovent®: 0.03% (30 mL); 0.06% (15 mL)

Generic AvailableYes: Excludes solution for oral inhalation, aerosol for oral inhalation

Pricing: U.S. (www.drugstore.com)

Aerosol solution (Atrovent HFA)

17 mcg/ACT (12.9): $107.91

Solution (Atrovent)

0.03% (30): $84.70

0.06% (15): $76.98

Solution (Ipratropium Bromide)

0.03% (30): $37.95

0.06% (15): $33.95

Mechanism of ActionBlocks the action of acetylcholine at parasympathetic sites in bronchial smooth muscle causing bronchodilation; local application to nasal mucosa inhibits serous and seromucous gland secretions.

Pharmacodynamics/Kinetics

Onset of action: Bronchodilation: Within 15 minutes

Peak effect: 1-2 hours

Duration: 2-5 hours

Absorption: Negligible

Distribution: Inhalation: 15% of dose reaches lower airways

Protein Binding: ≤9%

Half-life elimination: 2 hours

Excretion: Urine

Related Information

- Inhalant Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), and dry mucous membranes.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNervousness, dizziness, and fatigue are common; may cause insomnia

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive anticholinergic effects

Index TermsIpratropium Bromide

References

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Wilkie RA and Bryan MH, “Effect of Bronchodilators on Airway Resistance in Ventilator-dependent Neonates With Chronic Lung Disease,” *J Pediatr*, 1987, 111(2):278-82.[PubMed 2956405]

International Brand NamesAeron (AU); Aerovent (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Apovent (IL); Aproven (AU); Atem (AE, BH, CY, EG, IL, IQ, IR, IT, JO, KW, LB, LY, OM, QA, SA, SY, YE); Atronase (BE, LU); Atrovent (AR, AT, BB, BD, BE, BG, BM, BR, BS, BZ, CH, CL, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, GY, HK, HN, HR, HU, ID, IE, IN, IT, JM, JP, KP, LU, MX, MY, NI, NL, NO, NZ, PA, PE, PH, PK, PL, PT, PY, RU, SE, SG, SR, SV, TH, TR, TT, TW, UY, VE); Atrovent Aerosol (NZ); Atrovent N (MY, SG); Atrovent Nasal (AU, HK, NZ); Ipravent (HK, IN); Itrop (PL); Steri-Neb Ipratropium (PL)

Irbesartan and Hydrochlorothiazide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Avalide® may be confused with Avandia®

Pronunciation(ir be SAR tan & hye droe klor oh THYE a zide)

U.S. Brand NamesAvalide®

Canadian Brand NamesAvalide®

Pharmacologic CategoryAngiotensin II Receptor Blocker; Diuretic, Thiazide

Use: Labeled IndicationsCombination therapy for the management of hypertension; may be used as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals

Note: In Canada, this combination product is approved for initial therapy in severe, essential hypertension (sitting diastolic blood pressure [DBP] ≥110 mm Hg).

Dosing: AdultsOral: Dose must be individualized.

Hypertension:

Add-on therapy: A patient who is not controlled with either agent alone may be switched to the combination product. Mean effect increases with the dose of each component. The lowest dosage available is irbesartan 150 mg/hydrochlorothiazide 12.5 mg. Dose increases should be made not more frequently than every 2-4 weeks.

Initial therapy: Irbesartan 150 mg/hydrochlorothiazide 12.5 mg once daily. If initial response is inadequate, may titrate dose after 2-4 weeks, to a maximum dose of irbesartan 300 mg/hydrochlorothiazide 25 mg once daily.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot recommended in patients with Cl_{cr} ≤30 mL/minute.

Dosing: Hepatic ImpairmentUse with caution.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsMay be taken without regard to meals.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to irbesartan, hydrochlorothiazide, or any component of the formulation; sulfonamide-derived drugs; anuria

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Electrolyte disturbances: Hyperkalemia may occur with angiotensin II receptor antagonists; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first. Combination product not recommended as initial therapy in patients with volume depletion.

- Renal artery stenosis: Use irbesartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use irbesartan with caution with pre-existing renal insufficiency and severe renal impairment. Avoid hydrochlorothiazide in severe renal disease (ineffective); may precipitate azotemia; discontinue or consider withholding if renal impairment occurs. Combination product not recommended in patients with Cl_{cr} ≤30 mL/minute.

- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Pregnancy Risk FactorC/D (2nd and 3rd trimesters)
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/contraindicated
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsIrbesartan: **Substrate** of CYP2C9 (minor); **Inhibits** CYP2C8 (moderate), 2C9 (moderate), 2D6 (weak), 3A4 (weak)
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Irbesartan. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring ParametersAssess weight, I & O reports daily to determine fluid loss; blood pressure, symptomatic hypotension, and tachycardia; serum electrolytes, BUN, creatinine

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsSerum electrolytes, BUN, creatinine

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Irbesartan 150 mg and hydrochlorothiazide 12.5 mg

Irbesartan 300 mg and hydrochlorothiazide 12.5 mg

Irbesartan 300 mg and hydrochlorothiazide 25 mg

Generic AvailableNo

ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)

Pricing: U.S. (www.drugstore.com)

Tablets (Avalide)

150-12.5 mg (30): $85.59

300-12.5 mg (30): $85.99

300-25 mg (30): $99.50

Mechanism of Action

Irbesartan: Irbesartan is an angiotensin receptor antagonist. Angiotensin II acts as a vasoconstrictor. In addition to causing direct vasoconstriction, angiotensin II also stimulates the release of aldosterone. Once aldosterone is released, sodium as well as water are reabsorbed. The end result is an elevation in blood pressure. Irbesartan binds to the AT1 angiotensin II receptor. This binding prevents angiotensin II from binding to the receptor thereby blocking the vasoconstriction and the aldosterone secreting effects of angiotensin II.

Hydrochlorothiazide: Inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Hydrochlorothiazide
- Irbesartan

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, dizziness, nervousness

Mental Health: Effects on Psychiatric TreatmentMay decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Hypertension: According to the 2003 JNC 7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Index TermsAvapro® HCT; Hydrochlorothiazide and Irbesartan

References

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International Brand NamesAprozide (BR); Avalide (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Avapro HCT (AR, AU); Co-Aprovel (HK, MX); CoApprovel (DE); Coaprovel (AR, AT, BE, BG, CH, CL, CN, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, ID, IE, IT, KP, MY, NL, NO, PE, PH, PT, PY, RU, SE, SG, TH, TR, TW, UY, VE); Irbeprex H (CO); Irovel-H (IN); Irtan Plus (ID); Karvezide (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Irbesartan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Avapro® may be confused with Anaprox®

Pronunciation(ir be SAR tan)

U.S. Brand NamesAvapro®

Canadian Brand NamesAvapro®

Pharmacologic CategoryAngiotensin II Receptor Blocker

Use: Labeled IndicationsTreatment of hypertension alone or in combination with other antihypertensives; treatment of diabetic nephropathy in patients with type 2 diabetes mellitus (noninsulin dependent, NIDDM) and hypertension

Use: Unlabeled/InvestigationalTo slow the rate of progression of aortic-root dilation in pediatric patients with Marfan's syndrome

Dosing: Adults

Hypertension: Oral: 150 mg once daily; patients may be titrated to 300 mg once daily. **Note:** Starting dose in volume-depleted patients should be 75 mg.

Nephropathy in patients with type 2 diabetes and hypertension: Oral: Target dose: 300 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Hypertension:** Oral:

<6 years: Safety and efficacy have not been established.

≥6-12 years: Initial: 75 mg once daily; may be titrated to a maximum of 150 mg once daily

13-16 years: Refer to adult dosing.

Aortic-root dilation with Marfan's syndrome (unlabeled use): Children 14 months to 16 years: Initial: 1.4 mg/kg/day; can be increased to a maximum of 2 mg/kg/day (not to exceed adult maximum of 300 mg/day)

Dosing: Renal ImpairmentNo dosage adjustment necessary with mild to severe impairment unless the patient is also volume depleted.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to irbesartan or any component of the formulation

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See "Special populations" below.

Concerns related to adverse effects:

- Hyperkalemia: May occur; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.

- Hypovolemia: Avoid use or use smaller doses in patients who are volume depleted; correct depletion first.

- Renal artery stenosis: Use irbesartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution with pre-existing renal insufficiency, and severe renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.
- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Geriatric ConsiderationsNo dosage adjustment is necessary when initiating angiotensin II receptor antagonists in the elderly. In clinical studies, no differences between younger adults and the elderly were demonstrated. Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.
Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)
Pregnancy ConsiderationsMedications which act on the renin-angiotensin system are reported to have the following fetal/neonatal effects: Hypotension, neonatal skull hypoplasia, anuria, renal failure, and death; oligohydramnios is also reported. These effects are reported to occur with exposure during the second and third trimesters. There are no adequate and well-controlled studies in pregnant women. **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**
LactationExcretion in breast milk unknown/contraindicated
Adverse ReactionsUnless otherwise indicated, percentage of incidence is reported for patients with hypertension.

>10%: Endocrine & metabolic: Hyperkalemia (19%, diabetic nephropathy; rarely seen in HTN)

1% to 10%:

Cardiovascular: Orthostatic hypotension (5%, diabetic nephropathy)

Central nervous system: Fatigue (4%), dizziness (10%, diabetic nephropathy)

Gastrointestinal: Diarrhea (3%), dyspepsia (2%)

Respiratory: Upper respiratory infection (9%), cough (2.8% versus 2.7% in placebo)

>1% but frequency ≤ placebo: Abdominal pain, anxiety, chest pain, edema, headache, influenza, musculoskeletal pain, nausea, nervousness, pharyngitis, rash, rhinitis, sinus abnormality, syncope, tachycardia, urinary tract infection, vertigo, vomiting

<1% (Limited to important or life-threatening): Abdominal distension, abnormal urination, angina, arrhythmia, arthritis, bronchitis, bursitis, cardiopulmonary arrest, cerebrovascular accident, chest pain (noncardiac), chills, congestion, conjunctivitis, constipation, depression, dermatitis, dyspnea, ear infection, ear pain, ecchymosis, epistaxis, erythema, facial edema, fever, flatulence, flushing, gastroenteritis, gout, hearing abnormality, heart failure, hyper-/hypotension, hypertensive crisis, libido decreased, MI, muscle aches, muscle cramps, muscle weakness, numbness, orthostatic hypotension, paresthesia, prostate disorder, pruritus, pulmonary congestion, serum creatinine increased (0.7% versus 0.9% in placebo), sexual dysfunction, sleep disturbance, somnolence, TIA, tremor, upper extremity edema, vision disturbance, wheezing. May be associated with worsening of renal function in patients dependent on renin-angiotensin-aldosterone system.

Postmarketing reports: Angioedema, hepatitis, jaundice, transaminases increased, urticaria; rhabdomyolysis has been reported (rarely) with angiotensin-receptor antagonists

Metabolism/Transport Effects**Substrate** of CYP2C9 (minor); **Inhibits** CYP2C8 (moderate), 2C9 (moderate), 2D6 (weak), 3A4 (weak)
Drug Interactions

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Irbesartan. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Nursing: Physical Assessment/MonitoringUse caution in presence of renal insufficiency or aortic/mitral stenosis. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (risk of hyperkalemia or toxicity). Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, hypotension) at regular intervals during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsElectrolytes, serum creatinine, BUN, urinalysis

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed; do not discontinue without consulting prescriber. May be taken with or without food. Take first dose at bedtime. This medication does not replace other antihypertensive interventions; follow prescriber's instructions for diet and lifestyle changes. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea, vomiting, or abdominal pain (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (buttermilk, boiled milk, yogurt may help). Report chest pain or palpitations, skin rash, fluid retention (swelling of extremities), respiratory difficulty or unusual cough, or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 75 mg, 150 mg, 300 mg

Generic AvailableNo

ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)

Pricing: U.S. (www.drugstore.com)

Tablets (Avapro)

75 mg (30): $70.61

150 mg (30): $75.99

300 mg (30): $79.99

Mechanism of ActionIrbesartan is an angiotensin receptor antagonist. Angiotensin II acts as a vasoconstrictor. In addition to causing direct vasoconstriction, angiotensin II also stimulates the release of aldosterone. Once aldosterone is released, sodium as well as water are reabsorbed. The end result is an elevation in blood pressure. Irbesartan binds to the AT1 angiotensin II receptor. This binding prevents angiotensin II from binding to the receptor thereby blocking the vasoconstriction and the aldosterone secreting effects of angiotensin II.

Pharmacodynamics/Kinetics

Onset of action: Peak effect: 1-2 hours

Duration: >24 hours

Distribution: V_d: 53-93 L

Protein binding, plasma: 90%

Metabolism: Hepatic, primarily CYP2C9

Bioavailability: 60% to 80%

Half-life elimination: Terminal: 11-15 hours

Time to peak, serum: 1.5-2 hours

Excretion: Feces (80%); urine (20%)

Related Information

- Angiotensin Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, dizziness, nervousness

Mental Health: Effects on Psychiatric Treatment

None reported

Cardiovascular Considerations

Hypertension: According to the 2003 JNC 7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Marfan's Syndrome: Marfan's syndrome is a genetic disorder due to a mutation in the gene encoding for fibrillin-1 (FBN-1) and is associated with progressive aortic root dilation and may subsequently result in aortic dissection. The deficiency of FBN-1 leads to an increase in the activity of transforming growth factor β (TGF-β) which is thought to contribute to aortic root dilation and other Marfan's syndrome characteristics. Angiotensin II receptor blockers have been shown to inhibit TGF-β signaling.

Recently, a retrospective study evaluated the use of angiotensin II receptor blockers specifically losartan (1 patient received irbesartan) in a cohort of 18 pediatric patients (age range 14 months to 16 years) with Marfan's syndrome. All patients had evidence of severe aortic root enlargement. Patients who received losartan were initiated with 0.6 mg/kg/day and increased to a maximum dose of 1.4 mg/kg/day. The patient who received irbesartan was initiated with 1.4 mg/kg/day and increased to a maximum dose of 2 mg/kg/day. Patients were followed for a median of 26 months. The mean rate of change in aortic-root diameter prior to initiation of ARB therapy was 3.54 ± 2.87 mm per year. After initiation of ARB therapy, the rate of change decreased to 0.46 ± 0.62 mm per year ($p<0.001$). A similar decline in rate of change was seen in the patient treated with irbesartan. This small cohort study demonstrates that ARB therapy in patients with aortic-root dilation due to Marfan's syndrome may be of benefit. Future randomized controlled clinical trials will be needed to confirm these findings (Brooke, 2008).

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Anesthesia and Critical Care Concerns/Other Considerations

The angiotensin II receptor antagonists appear to have similar indications as the ACE inhibitors. In heart failure, the angiotensin II antagonists are especially useful in providing an alternative therapy in those patients who have intractable cough in response to ACE inhibitor therapy. Candesartan has been studied as an alternative therapy in chronic heart failure patients who cannot tolerate an ACE-I (CHARM-Alternative) and as an added therapy in heart failure patients who are maintained on an ACE-I (CHARM-Added). In both studies, the combined endpoint of cardiovascular death or heart failure hospitalizations was significantly improved over the placebo-treated group. Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

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International Brand NamesApprovel (DE); Aprovel (AR, AT, BE, BG, BO, BR, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IT, MX, MY, NI, NL, NO, PA, PE, PH, PL, PR, PT, PY, RU, SE, SG, SV, TR, TW, UY, VE); Avapro (AR, AU, BB, BM, BR, BS, BZ, GY, JM, MX, SR, TT); Fristens (ID); Irbesel (PE); Irebeprex (CO); Iretensa (ID); Irovel (IN); Irvell (ID); Izart (PH); Karvea (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Esophageal Cancer

Regimen Use Esophageal cancer

Index Terms Cisplatin-Irinotecan (Esophageal Cancer)

Regimen

Cisplatin: I.V.: 30 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 120 mg/m^2]

Irinotecan: I.V.: 65 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 260 mg/m^2]

Repeat cycle every 6 weeks

References

Ilson DH, Saltz L, Enzinger P, et al, âPhase II Trial of Weekly Irinotecan Plus Cisplatin in Advanced Esophageal Cancer,â *J Clin Oncol*, 1999, 17(10):3270-5.[PubMed 10506629]

Irinotecan

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye rye no TEE kan)

U.S. Brand NamesCamptosar®

Canadian Brand NamesCamptosar®; Irinotecan Hydrochloride Trihydrate

Pharmacologic CategoryAntineoplastic Agent, Camptothecin; Antineoplastic Agent, Natural Source (Plant) Derivative

Use: Labeled IndicationsTreatment of metastatic carcinoma of the colon or rectum

Use: Unlabeled/InvestigationalLung cancer (small cell and nonsmall cell), cervical cancer, gastric cancer, pancreatic cancer, leukemia, lymphoma, breast cancer, brain tumors

Dosing: AdultsRefer to individual protocols. **Note:** A reduction in the starting dose by one dose level should be considered for patients ≥65 years of age, prior pelvic/abdominal radiotherapy, performance status of 2, homozygosity for UGT1A1*28 allele, or increased bilirubin (dosing for patients with a bilirubin >2 mg/dL cannot be recommended based on lack of data per manufacturer).

Single-agent therapy:

I.V.: Weekly regimen: 125 mg/m^2 over 90 minutes on days 1, 8, 15, and 22 of a 6-week treatment cycle

Adjusted dose level -1: 100 mg/m^2

Adjusted dose level -2: 75 mg/m^2

I.V.: Once-every-3-week regimen: 350 mg/m^2 over 90 minutes, once every 3 weeks

Adjusted dose level -1: 300 mg/m^2

Adjusted dose level -2: 250 mg/m^2

Depending on the patient's ability to tolerate therapy, doses should be adjusted in increments of 25-50 mg/m^2. Irinotecan doses may range from 50-150 mg/m^2 for the weekly regimen. Patients may be dosed as low as 200 mg/m^2 (in 50 mg/m^2 decrements) for the once-every-3-week regimen.

Combination therapy with fluorouracil and leucovorin: Six-week (42-day) cycle:

Regimen 1: I.V.: 125 mg/m^2 over 90 minutes on days 1, 8, 15, and 22; to be given in combination with bolus leucovorin and fluorouracil (leucovorin administered immediately following irinotecan; fluorouracil immediately following leucovorin)

Adjusted dose level -1: 100 mg/m^2

Adjusted dose level -2: 75 mg/m^2

Regimen 2: 180 mg/m^2 over 90 minutes on days 1, 15, and 29; to be given in combination with infusional leucovorin and bolus/infusion fluorouracil (leucovorin administered immediately following irinotecan; fluorouracil immediately following leucovorin)

Adjusted dose level -1: 150 mg/m^2

Adjusted dose level -2: 120 mg/m^2

Note: For all regimens: It is recommended that new courses begin only after the granulocyte count recovers to ≥1500/mm^3, the platelet count recovers to ≥100,000/mm^3, and treatment-related diarrhea has fully resolved. Treatment should be delayed 1-2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing irinotecan.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentEffects have not been evaluated; not recommended for use in patients on dialysis.

Dosing: Hepatic ImpairmentThe manufacturer recommends that no change in dosage or administration be made for patients with liver metastases and normal hepatic function. Consideration may be given to starting irinotecan at a lower dose (eg, 100 mg/m^2) if bilirubin is 1-2 mg/dL; for total serum bilirubin elevations >2 mg/dL, specific recommendations are not available in the FDA labeling. The following guidelines have been used by some clinicians:

Bilirubin 1.5-3 mg/dL: Administer 75% of dose (Floyd, 2006)

Dosing: Adjustment for ToxicityIt is recommended that new courses begin only after the granulocyte count recovers to ≥1500/mm^3, the platelet counts recover to ≥100,000/mm^3, and treatment-related diarrhea has fully resolved. Depending on the patient's ability to tolerate therapy, doses should be adjusted in increments of 25-50 mg/m^2. Treatment should be delayed 1-2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing irinotecan. See tables.

Single-Agent Schedule: Recommended Dosage Modifications[1]

Toxicity NCI Grade[2] (Value)	**During a Cycle of Therapy**	**At Start of Subsequent Cycles of Therapy (After Adequate Recovery), Compared to Starting Dose in Previous Cycle[1]**	
	Weekly	**Weekly**	**Once Every 3 Weeks**
No toxicity	Maintain dose level	↑ 25 mg/m^2 up to a maximum dose of 150 mg/m^2	Maintain dose level
Neutropenia			
1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	↓ 25 mg/m^2	Maintain dose level	Maintain dose level
3 (500-999/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
4 (<500/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2
Neutropenic Fever (grade 4 neutropenia and ≥ grade 2 fever)	Omit dose until resolved, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2
Other Hematologic Toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
Diarrhea			
1 (2-3 stools/day > pretreatment)	Maintain dose level	Maintain dose level	Maintain dose level
2 (4-6 stools/day > pretreatment)	↓ 25 mg/m^2	Maintain dose level	Maintain dose level
3 (7-9 stools/day > pretreatment)	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
4 (≥10 stools/day > pretreatment)	Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2
Other Nonhematologic Toxicities[3]			
1	Maintain dose level	Maintain dose level	Maintain dose level

2	↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
3	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
4	Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2

[1] All dose modifications should be based on the worst preceding toxicity.

[2] National Cancer Institute Common Toxicity Criteria (version 1.0).

[3] Excludes alopecia, anorexia, asthenia.

Combination Schedules: Recommended Dosage Modifications[1]

Toxicity NCI[2] Grade (Value)	**During a Cycle of Therapy**	**At the Start of Subsequent Cycles of Therapy (After Adequate Recovery), Compared to the Starting Dose in the Previous Cycle[1]**
No toxicity	Maintain dose level	Maintain dose level
Neutropenia		
1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	↓ 1 dose level	Maintain dose level
3 (500-999/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4 (<500/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
Neutropenic Fever (grade 4 neutropenia and ≥ grade 2 fever)	Omit dose until resolved, then ↓ 2 dose levels	
Other Hematologic Toxicities	Dose modifications for leukopenia or thrombocytopenia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea		
1 (2-3 stools/day > pretreatment)	Delay dose until resolved to baseline, then give same dose	Maintain dose level
2 (4-6 stools/day > pretreatment)	Omit dose until resolved to baseline, then ↓ 1 dose level	Maintain dose level
3 (7-9 stools/day > pretreatment)	Omit dose until resolved to baseline, then ↓ by 1 dose level	↓ 1 dose level
4 (≥10 stools/day > pretreatment)	Omit dose until resolved to baseline, then ↓ 2 dose levels	↓ 2 dose levels

Other Nonhematologic Toxicities[3]		
1	Maintain dose level	Maintain dose level
2	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	Maintain dose level
3	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
Mucositis and/or stomatitis	Decrease only 5-FU, not irinotecan	Decrease only 5-FU, not irinotecan
[1] All dose modifications should be based on the worst preceding toxicity.		
[2] National Cancer Institute Common Toxicity Criteria (version 1.0).		
[3] Excludes alopecia, anorexia, asthenia.		

Dosing: Combination Regimens

Brain tumors: Bevacizumab-Irinotecan (Glioblastoma)

Colorectal cancer:

Bevacizumab-Irinotecan-Fluorouracil-Leucovorin

Cetuximab (Biweekly)-Irinotecan

Cetuximab-Irinotecan

Fluorouracil-Leucovorin-Irinotecan (Saltz Regimen)

FOIL

FU-LV-CPT-11

Esophageal cancer: Irinotecan-Cisplatin (Esophageal Cancer)

Lung cancer (small cell): Cisplatin-Irinotecan (Small Cell Lung Cancer)

Pancreatic cancer: Gemcitabine-Irinotecan

Calculations

- Body Surface Area: Adults

Administration: I.VI.V. infusion, usually over 90 minutes.
Administration: I.V. DetailpH: 3-3.8
Dietary ConsiderationsContains sorbitol; do not use in patients with hereditary fructose intolerance.
StorageStore intact vials of injection at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light. Solutions diluted in NS may precipitate if refrigerated. Solutions diluted in D_5W are stable for 24 hours at room temperature or 48 hours under refrigeration at 2°C to 8°C. Do not freeze.
ReconstitutionDilute in 250-500 mL D_5W or NS to a final concentration of 0.12-2.8 mg/mL. Due to the relatively acidic pH, irinotecan appears to be more stable in D_5W than NS.
CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Leucovorin; **Incompatible:** Gemcitabine.

Compatibility when admixed: Incompatible: Methylprednisolone sodium succinate.

ContraindicationsHypersensitivity to irinotecan or any component of the formulation; concurrent use of ketoconazole, St John's wort
Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.

- Diarrhea: See “Concerns related to adverse effects” below.

- Experienced physician: See “Other warnings/precautions” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: May cause severe myelosuppression.** Deaths due to sepsis following severe myelosuppression have been reported. Therapy should be temporarily discontinued if neutropenic fever occurs or if the absolute neutrophil count is <1000/mm^3. The dose of irinotecan should be reduced if there is a clinically significant decrease in the total WBC (<200/mm^3), neutrophil count (<1500/mm^3), hemoglobin (<8 g/dL), or platelet count (<100,000/mm^3). Routine administration of a colony-stimulating factor is generally not necessary, but may be considered for patients experiencing significant neutropenia.

- Colitis: Colitis, complicated by ulceration, bleeding, ileus, and infection has been reported.

- Diarrhea: **[U.S. Boxed Warning]: Severe diarrhea may be dose-limiting and potentially fatal; two severe (life-threatening) forms of diarrhea may occur.** Early diarrhea occurs during or within 24 hours of receiving irinotecan and is characterized by cholinergic symptoms (eg, increased salivation, diaphoresis, abdominal cramping); it is usually responsive to atropine. Late diarrhea occurs more than 24 hours after treatment which may lead to dehydration, electrolyte imbalance, or sepsis; it should be promptly treated with loperamide. Patients with diarrhea should be carefully monitored and treated promptly.

- Hypersensitivity reactions: Severe hypersensitivity reactions have occurred.

- Renal toxicity: Renal impairment and acute renal failure have been reported, possibly due to dehydration secondary to diarrhea.

Disease-related concerns:

- Bowel obstruction: Patients with bowel obstruction should not be treated with irinotecan until resolution of obstruction.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Hyperbilirubinemia: Patients with even modest elevations in total serum bilirubin levels (1-2 mg/dL) have a significantly greater likelihood of experiencing first-course grade 3 or 4 neutropenia than those with bilirubin levels that were <1 mg/dL. Patients with abnormal glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with irinotecan. Use caution when treating patients with known hepatic dysfunction or hyperbilirubinemia; dosage adjustments should be considered.

Special populations:

- Elderly: Use with caution in elderly patients with comorbid conditions, or baseline performance status of 2; close monitoring and dosage adjustments are recommended.

- Patients homozygous/heterozygous for the UGT1A1*28 allele: Patients homozygous for the UGT1A1*28 allele are at increased risk of neutropenia; initial one-level dose reduction should be considered for both single-agent and combination regimens. Heterozygous carriers of the UGT1A1*28 allele may also be at increased risk; however, most patients have tolerated normal starting doses.

- Pelvic/abdominal radiation recipients: Use with caution in patients who have previously received pelvic/abdominal radiation.

Dosage form specific issues:

- Sorbitol: Product contains sorbitol; do not use in patients with hereditary fructose intolerance.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

- Appropriate use: Except as part of a clinical trial, use in combination with the fluorouracil and leucovorin “Mayo Clinic” regimen is not recommended. Increased toxicity has also been noted in patients with a baseline performance status of 2 in other combination regimens containing irinotecan, leucovorin, and fluorouracil.

Pregnancy Risk FactorD
Pregnancy ConsiderationsTeratogenic effects were noted in animal studies. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should avoid becoming pregnant while receiving treatment.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.
Adverse ReactionsFrequency of adverse reactions reported for single-agent use of irinotecan only.

>10%:

Cardiovascular: Vasodilation (9% to 11%)

Central nervous system: Cholinergic toxicity (47% - includes rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing and intestinal hyperperistalsis); fever (44% to 45%), pain (23% to 24%), dizziness (15% to 21%), insomnia (19%), headache (17%), chills (14%)

Dermatologic: Alopecia (46% to 72%), rash (13% to 14%)

Endocrine & metabolic: Dehydration (15%)

Gastrointestinal: Diarrhea, late (83% to 88%; grade 3/4: 6% to 31%), diarrhea, early (43% to 51%; grade 3/4: 6% to 22%), nausea (70% to 86%), abdominal pain (57% to 68%), vomiting (62% to 67%), cramps (57%), anorexia (44% to 55%), constipation (30% to 32%), mucositis (30%), weight loss (30%), flatulence (12%), stomatitis (12%)

Hematologic: Anemia (60% to 97%; grades 3/4: 5% to 22%), leukopenia (63% to 96%, grades 3/4: 14% to 28%), thrombocytopenia (96%, grades 3/4: 1% to 4%), neutropenia (30% to 96%; grades 3/4: 14% to 31%)

Hepatic: Bilirubin increased (84%), alkaline phosphatase increased (13%)

Neuromuscular & skeletal: Weakness (69% to 76%), back pain (14%)

Respiratory: Dyspnea (22%), cough (17% to 20%), rhinitis (16%)

Miscellaneous: Diaphoresis (16%), infection (14%)

1% to 10%:

Cardiovascular: Edema (10%), hypotension (6%), thromboembolic events (5%)

Central nervous system: Somnolence (9%), confusion (3%)

Gastrointestinal: Abdominal fullness (10%), dyspepsia (10%)

Hematologic: Neutropenic fever (grades 3/4: 2% to 6%), hemorrhage (grades 3/4: 1% to 5%), neutropenic infection (grades 3/4: 1% to 2%)

Hepatic: AST increased (10%), ascites and/or jaundice (grades 3/4: 9%)

Respiratory: Pneumonia (4%)

<1%, postmarketing, and/or case reports: ALT increased, amylase increased, anaphylactoid reaction, anaphylaxis, angina, arterial thrombosis, bleeding, bradycardia, cardiac arrest, cerebral infarct, cerebrovascular accident, circulatory failure, colitis, deep thrombophlebitis, dysrhythmia, embolus, gastrointestinal bleeding, gastrointestinal obstruction, hepatomegaly, hiccups, hyperglycemia, hypersensitivity, hyponatremia, ileus, interstitial lung disease, intestinal perforation, ischemic colitis, lipase increased, lymphocytopenia, megacolon, MI, muscle cramps, myocardial ischemia, pancreatitis, paresthesia, peripheral vascular disorder, pulmonary embolus; pulmonary toxicity (dyspnea, fever, reticulonodular infiltrates on chest x-ray); renal failure (acute), renal impairment, syncope, thrombophlebitis, thrombosis, typhlitis, ulceration, ulcerative colitis, vertigo

Note: In limited pediatric experience, dehydration (often associated with severe hypokalemia and hyponatremia) was among the most significant grade 3/4 adverse events, with a frequency up to 29%. In addition, grade 3/4 infection was reported in 24%.

Oncology: VesicantNo

Oncology: Emetic PotentialModerate-to-high (30% to 90%)

Metabolism/Transport Effects**Substrate** (major) of CYP2B6, 3A4

Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): May enhance the adverse/toxic effect of Irinotecan. *Risk D: Consider therapy modification*

Atazanavir: May increase the serum concentration of Irinotecan. The metabolism (via glucuronidation) of the active SN-38 metabolite may be primarily impacted by this interaction. *Risk X: Avoid combination*

Bevacizumab: May enhance the adverse/toxic effect of Irinotecan. *Risk C: Monitor therapy*

CYP2B6 Inducers (Strong): May increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Strong): May decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Irinotecan. *Risk D: Consider therapy modification*

Sorafenib: May increase the serum concentration of Irinotecan. Sorafenib may also increase the concentration of the active metabolite of irinotecan, SN-38. *Risk C: Monitor therapy*

St Johns Wort: May diminish the therapeutic effect of Irinotecan. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid St John's wort (decreases the efficacy of irinotecan).

Monitoring ParametersCBC with differential, platelet count, and hemoglobin with each dose; bilirubin, electrolytes (with severe diarrhea); bowel movements and hydration status; monitor infusion site for signs of inflammation and avoid extravasation

Nursing: Physical Assessment/MonitoringUse caution and closely monitor use for patients with increased risk of neutropenia, previous pelvic or abdominal radiation, elderly patients with comorbid conditions. Assess potential for interactions with other pharmacological agents prescriptions or herbal products patient may be taking (eg, potential for increased or decreased levels/effects of irinotecan). Premedicate with antiemetic (emetic potential moderately high). Infusion site must be monitored to prevent extravasation. Assess results of laboratory tests (CBC with differential and platelet count), therapeutic effectiveness, and adverse response before each infusion and at regular intervals during therapy (eg, neutropenia, immediate or delayed diarrhea [can be fatal], sepsis, mucositis and/or stomatitis). Teach patient possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelet count, bilirubin, electrolytes (with severe diarrhea)

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug can only be administered by infusion. Report immediately any burning, pain, redness, or swelling at infusion site. Maintain adequate hydration (3-4 L/day of fluids) unless instructed to restrict fluid intake during therapy. May cause severe diarrhea; follow instructions for taking antidiarrheal medication (do not use antidiarrheal medication for longer than 48 consecutive hours). Report immediately if diarrhea persists or you experience signs of dehydration (eg, fainting, dizziness, lightheadedness). You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). You may experience nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); hair loss (will regrow after treatment is completed). Report immediately persistent diarrhea; unresolved nausea, or vomiting, alterations in urinary pattern (increased or decreased); opportunistic infection (fever, chills, unusual bruising or bleeding, fatigue, purulent vaginal discharge, unhealed mouth sores), chest pain or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant or cause a pregnancy (males) while taking this medication. Consult prescriber for use appropriate contraceptive measures (may cause severe fetal defects). Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride: 20 mg/mL (2 mL, 5 mL)

Camptosar®: 20 mg/mL (2 mL, 5 mL) [contains sorbitol 45 mg/mL]

Generic AvailableYes

Mechanism of ActionIrinotecan and its active metabolite (SN-38) bind reversibly to topoisomerase I-DNA complex preventing religation of the cleaved DNA strand. This results in the accumulation of cleavable complexes and double-strand DNA breaks. As mammalian cells cannot efficiently repair these breaks, cell death consistent with S-phase cell cycle specificity occurs, leading to termination of cellular replication.

Pharmacodynamics/Kinetics

Distribution: V_d: 33-150 L/m^2

Protein binding, plasma: Predominantly albumin; Parent drug: 30% to 68%, SN-38 (active metabolite): ~95%

Metabolism: Primarily hepatic to SN-38 (active metabolite) by carboxylesterase enzymes; SN-38 undergoes conjugation by UDP- glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. Conversion of irinotecan to SN-38 is decreased and glucuronidation of SN-38 is increased patients who smoke cigarettes, resulting in lower levels of the metabolite and overall decreased systemic exposure. SN-38 is increased by UGT1A1*28 polymorphism (10% of North Americans are homozygous for UGT1A1*28 allele). The lactones of both irinotecan and SN-38 undergo hydrolysis to inactive hydroxy acid forms.

Half-life elimination: SN-38: Mean terminal: 10-20 hours

Time to peak: SN-38: Following 90-minute infusion: ~1 hour

Excretion: Within 24 hours: Urine: Irinotecan (11% to 20%), metabolites (SN-38 <1%, SN-38 glucuronide, 3%)

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsPatients who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia; a decreased dose is recommended. Clinical research of patients who are heterozygous for UGT1A1*28 have been variable for increased neutropenic risk and such patients have tolerated normal starting doses. An FDA-approved test (Invader® Molecular Assay) is available for clinical determination of UGT phenotype.

The recommended regimen to manage late diarrhea is loperamide 4 mg orally at onset of late diarrhea, followed by 2 mg every 2 hours (or 4 mg every 4 hours at night) until 12 hours have passed without a bowel movement. If diarrhea recurs, then repeat administration. Loperamide should not be used for more than 48 consecutive hours.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Increased salivation, mucositis, and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and insomnia are common

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine; concurrent use with prochlorperazine has produced akathisia. Two severe (life-threatening) forms of diarrhea may occur; these effects may be additive with concurrent use of SSRIs, lithium, or valproate; use caution.

Index TermsCamptothecin-11; CPT-11; NSC-616348

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International Brand NamesCampto (AT, BE, BF, BG, BJ, CH, CI, CL, CZ, DE, DK, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, ID, IE, IL, IT, JP, KE, KP, LR, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, PH, PK, PL, PT, RU, SC, SD, SE, SG, SL, SN, TH, TN, TR, TW, TZ, UG, ZA, ZM, ZW); Camptosar (AR, AU, BO, BR, CN, CO, CR, DO, EC, GT, HN, MX, NI, PA, PE, PR, PY, SV, UY, VE); Camtecan (KP); Crabcan (KP); Efixano (PY); Herocan (TW); Indotecan (KP); Irenax (TH); Irican (PH); Irinotel (IN, TH, TW); Irnocam (MY); Linatecan (PE); Litecin (KP); Pipetecan (AR); Terican (MX); Topotecin (JP)

Iron Dextran Complex

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Dexferrum® may be confused with Desferal®

Pronunciation(EYE ern DEKS tran KOM pleks)

U.S. Brand NamesDexferrum®; INFeD®

Canadian Brand NamesDexiron™; Infufer®

Pharmacologic CategoryIron Salt

Use: Labeled IndicationsTreatment of iron deficiency in patients in whom oral administration is infeasible or ineffective

Dosing: Adults

Note: A 0.5 mL test dose should be given prior to starting iron dextran therapy.

Iron-deficiency anemia: I.M. (INFeD®), I.V. (Dexferrum®, INFeD®):

Dose (mL) = 0.0442 (desired Hgb - observed Hgb) x LBW + (0.26 x LBW)

Desired hemoglobin: Usually 14.8 g/dL

LBW = Lean body weight in kg

Iron replacement therapy for blood loss: (INFeD®), I.V. (Dexferrum®, INFeD®): Replacement iron (mg) = blood loss (mL) x Hct

Cancer-associated anemia (NCCN guidelines v.3.2009): I.V.: Test dose: 25 mg slow I.V. slow push, followed 1 hour later by 100 mg over 5 minutes; larger doses (unlabeled), up to total dose infusion (over several hours) may be administered

Maximum daily dosage: Manufacturer's labeling: **Note:** Replacement of larger estimated iron deficits may be achieved by serial administration of smaller incremental dosages. Daily dosages should be limited to 100 mg iron (2 mL)

Total dose infusion (unlabeled): The entire dose (estimated iron deficit) may be diluted and administered as a one-time I.V. infusion.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** A 0.5 mL test dose (0.25 mL in infants) should be given prior to starting iron dextran therapy.

Iron-deficiency anemia: I.M. (INFeD®), I.V. (Dexferrum®, INFeD®):

Children 5-15 kg: Should not normally be given in the first 4 months of life:

Dose (mL) = 0.0442 (desired Hgb - observed Hgb) x W + (0.26 x W)

Desired hemoglobin: Usually 12 g/dL

W = Total body weight in kg

Children >15 kg: Refer to adult dosing.

Iron replacement therapy for blood loss: Refer to adult dosing.

Maximum daily dose:

Children <5 kg: 25 mg iron (0.5 mL)

Children 5-10 kg: 50 mg iron (1 mL)

Children ≥10 kg: Refer to adult dosing.

Calculations

- Iron Dextran

Administration: I.M.**Note:** Test dose: A test dose should be given on the first day of therapy; patient should be observed for 1 hour for hypersensitivity reaction, then the remaining dose (dose minus test dose) should be given. Epinephrine should be available.

I.M. (INFeD®): Use Z-track technique (displacement of the skin laterally prior to injection); injection should be deep into the upper outer quadrant of buttock; alternate buttocks with subsequent injections. Administer test dose at same recommended site using the same technique.

Administration: I.V.Test dose should be given gradually over at least 30 seconds (INFeD®) or 5 minutes (Dexferrum®). Subsequent dose(s) may be administered by I.V. bolus undiluted at a rate not to exceed 50 mg/minute or diluted in 250-1000 mL NS and infused over 1-6 hours (initial 25 mL should be given slowly and patient should be observed for allergic reactions); avoid dilutions with dextrose (increased incidence of local pain and phlebitis)

Administration: I.V. DetailpH: 4.2-7

StorageStore at controlled room temperature.

ReconstitutionSolutions for infusion should be diluted in 250-1000 mL NS.

CompatibilityStable in D_5W, NS; **variable stability (consult detailed reference)** in TPN.

Compatibility when admixed: Compatible: Cyanocobalamin, netilmicin.

ContraindicationsHypersensitivity to iron dextran or any component of the formulation; any anemia not associated with iron deficiency

Allergy Considerations

- Iron Salt Allergy

Warnings/Precautions

Boxed warnings:

- Anaphylactic-type reactions: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactic-type reactions: **[U.S. Boxed Warning]: Deaths associated with parenteral administration following anaphylactic-type reactions have been reported (use only where resuscitative equipment and personnel are available).** Adverse events (including life-threatening) associated with iron dextran usually occur more with the high-molecular-weight formulation (DexFerrum®), compared to low-molecular-weight (INFeD®) (Chertow, 2006).

- Delayed reaction: Delayed (1-2 days) infusion reaction (including arthralgia, back pain, chills, dizziness, and fever) may occur with large doses (eg, total dose infusion) of I.V. iron dextran; usually subsides within 3-4 days. May also occur (less commonly) with I.M. administration; subsiding within 3-7 days.

Disease-related concerns:

- Allergies/asthma: Use with caution in patients with a significant history of allergies or asthma.

- Cancer-associated anemia: In patients with cancer-related anemia (either due to cancer or chemotherapy-induced) requiring iron supplementation, the I.V. route is superior to oral therapy; I.M. administration is not recommended for parenteral iron supplementation.

- Cardiovascular disease: Use with caution in patients with pre-existing cardiovascular disease; iron dextran may exacerbate cardiovascular complications.

- Hepatic impairment: Use with extreme caution in patients with serious hepatic impairment.

- Renal disease/impairment: In patients with chronic kidney disease (CKD) requiring iron supplementation, the I.V. route is preferred for hemodialysis patients; either oral iron or I.V. iron may be used for nondialysis and peritoneal dialysis CKD patients. Avoid use during acute kidney infection.

- Rheumatoid arthritis: Use with caution in patients with rheumatoid arthritis; may exacerbate joint pain and swelling.

Special populations:

- Elderly: Anemia in the elderly is often caused by “anemia of chronic disease” or associated with inflammation rather than blood loss. Iron stores are usually normal or increased, with a serum ferritin >50 ng/mL and a decreased total iron binding capacity. I.V. administration of iron dextran is often preferred over I.M. in the elderly secondary to a decreased muscle mass and the need for daily injections.

- Pediatrics: Not recommended in children <4 months of age. Intramuscular iron dextran use in neonates may be associated with an increased incidence of gram-negative sepsis.

Other warnings/precautions:

- Appropriate use: Use only in patients where the iron deficient state is not amenable to oral iron therapy. Discontinue oral iron prior to initiating parenteral iron therapy.

- Carcinogenicity: Intramuscular injections of iron-carbohydrate complexes may have a risk of delayed injection site tumor development.

- Iron overload: Exogenous hemosiderosis may result from excess iron stores; patients with refractory anemias and/or hemoglobinopathies may be prone to iron overload with unwarranted iron supplementation.

- Test dose: A test dose of 0.5 mL I.V. or I.M. should be given to observe for adverse reactions.

Geriatric ConsiderationsAnemia in the elderly is most often caused by “anemia of chronic disease”, a result of aging effect in bone marrow, or associated with inflammation rather than blood loss. Iron stores are usually normal or increased, with a serum ferritin >50 ng/mL and a decreased total iron binding capacity. Hence, the anemia is not secondary to iron deficiency but the inability of the reticuloendothelial system to use available iron stores. I.V. administration of iron dextran is often preferred over I.M. in the elderly secondary to a decreased muscle mass and the need for daily injections.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in animal reproduction studies. It is not known if iron dextran (as iron dextran) crosses the placenta. It is recommended that pregnant women meet the dietary requirements of iron with diet and/or supplements in order to prevent adverse events associated with iron deficiency anemia in pregnancy. Treatment of iron deficiency anemia in pregnant women is the same as in nonpregnant women and in most cases, oral iron preparations may be used. Except in severe cases of maternal anemia, the fetus achieves normal iron stores regardless of maternal concentrations.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsTrace amounts of iron dextran (as iron dextran) are found in human milk. Iron is normally found in breast milk. Breast milk or iron fortified formulas generally provide enough iron to meet the recommended dietary requirements of infants. The amount of iron in breast milk is generally not influenced by maternal iron status.

Adverse ReactionsFrequency not defined. **Note:** Adverse event risk is reported to be higher with the high-molecular-weight iron dextran formulation.

Cardiovascular: Arrhythmia, bradycardia, cardiac arrest, chest pain, chest tightness, cyanosis, flushing, hyper-/hypotension, shock, syncope, tachycardia

Central nervous system: Chills, disorientation, dizziness, fever, headache, malaise, seizure, unconsciousness, unresponsiveness

Dermatologic: Pruritus, purpura, rash, urticaria

Gastrointestinal: Abdominal pain, diarrhea, nausea, taste alteration, vomiting

Genitourinary: Discoloration of urine

Hematologic: Leukocytosis, lymphadenopathy

Local: Injection site reactions (cellulitis, inflammation, pain, phlebitis, soreness, swelling), muscle atrophy/fibrosis (with I.M. injection), skin/tissue staining (at the site of I.M. injection), sterile abscess

Neuromuscular & skeletal: Arthralgia, arthritis/arthritis exacerbation, back pain, myalgia, paresthesia, weakness

Respiratory: Bronchospasm, dyspnea, respiratory arrest, wheezing

Renal: Hematuria

Miscellaneous: Anaphylactic reactions (sudden respiratory difficulty, cardiovascular collapse), diaphoresis

Postmarketing and/or case reports: Angioedema, tumor formation (at former injection site)

Drug Interactions

Cefdinir: Iron Salts may decrease the serum concentration of Cefdinir. Red-appearing, non-bloody stools may also develop due to the formation of an insoluble iron-cefdinir complex. Management: Avoid concurrent cefdinir and iron when possible. Separating doses by several hours may minimize interaction. Iron-containing infant formulas do not appear to interact with cefdinir. *Risk D: Consider therapy modification*

Dimercaprol: May enhance the nephrotoxic effect of Iron Salts. *Risk X: Avoid combination*

Eltrombopag: Iron Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., iron-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Phosphate Supplements: Iron Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Iron Salts. Iron Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Test InteractionsMay cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium. Residual iron dextran may remain in reticuloendothelial cells; may affect accuracy of examination of bone marrow iron stores. Bone scans with 99m Tc-labeled bone seeking agents may show reduced bony uptake, marked renal activity, and excess blood pooling and soft tissue accumulation following I.V. iron dextran infusion or with high serum ferritin levels. Following I.M. iron dextran, bone scans with 99m Tc-diphosphonate may show dense activity in the buttocks.

Monitoring ParametersHemoglobin, hematocrit, reticulocyte count, serum ferritin, serum iron, TIBC; monitor for anaphylaxis/hypersensitivity reaction

Reference Range

Hemoglobin: Adults:

Males: 13.5-16.5 g/dL

Females: 12.0-15.0 g/dL

Serum iron: 40-160 mcg/dL

Total iron binding capacity: 230-430 mcg/dL

Transferrin: 204-360 mg/dL

Percent transferrin saturation: 20% to 50%

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests regularly and patient for adverse reactions. Note that adverse response may occur some time (1-4 days) after administration. Assess patients with rheumatoid arthritis for exacerbated swelling and joint pain; adjust medications as needed.

Monitoring: Lab TestsHemoglobin, hematocrit, reticulocyte count, serum ferritin

Patient EducationYou will need frequent blood tests while on this therapy. If you have rheumatoid arthritis, you may experience increased swelling or joint pain; consult prescriber for medication adjustment. If you experience dizziness or severe headache, use caution when driving or engaging in tasks that require alertness until response to drug is known. Small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may relieve nausea and metallic taste. You may experience increased sweating. Report acute GI problems, fever, respiratory difficulty, rapid heartbeat, yellowing of skin or eyes, or swelling of hands and feet. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: Strength expressed as elemental iron

Injection, solution:

Dexferrum®: 50 mg/mL (1 mL, 2 mL) [high-molecular-weight iron dextran]

INFeD®: 50 mg/mL (2 mL) [low-molecular-weight iron dextran]

Generic AvailableNo

Mechanism of ActionThe released iron, from the plasma, eventually replenishes the depleted iron stores in the bone marrow where it is incorporated into hemoglobin

Pharmacodynamics/Kinetics

Onset of action: I.V.: Serum ferritin peak: 7-9 days after dose

Absorption:

I.M.: 50% to 90% is promptly absorbed, balance is slowly absorbed over month

I.V.: Uptake of iron by the reticuloendothelial system appears to be constant at about 10-20 mg/hour

Excretion: Urine and feces via reticuloendothelial system

Related Information

- Antacid Drug Interactions

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Metallic taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsHigh-Molecular-Weight Iron Dextran (DexFerrum®); Imferon; Iron Dextran; Low-Molecular-Weight Iron Dextran (INFeD®)

References

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International Brand NamesCosmofer (DE, GB, KP, NL, VE); Desman (TW); Driken (MX); Fexibron (PE); Fexiron (AR, PY); Hibiron (ID); Imferon (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Supral (IN)

Iron Sucrose

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(EYE ern SOO krose)

U.S. Brand NamesVenofer®

Canadian Brand NamesVenofer®

Pharmacologic CategoryIron Salt

Use: Labeled IndicationsTreatment of iron-deficiency anemia in chronic renal failure, including nondialysis-dependent patients (with or without erythropoietin therapy) and dialysis-dependent patients receiving erythropoietin therapy

Dosing: AdultsDoses expressed in mg of **elemental** iron. **Note:** Test dose: Product labeling does not indicate need for a test dose in product-naive patients.

Iron-deficiency anemia in chronic renal disease: I.V.:

Hemodialysis-dependent patient: 100 mg over 2-5 minutes administered 1-3 times/week during dialysis; administer no more than 3 times/week to a cumulative total dose of 1000 mg (10 doses); may continue to administer at lowest dose necessary to maintain target hemoglobin, hematocrit, and iron storage parameters

Peritoneal dialysis-dependent patient: Slow intravenous infusion at the following schedule: Two infusions of 300 mg each over $1^{1}/_{2}$ hours 14 days apart followed by a single 400 mg infusion over $2^{1}/_{2}$ hours 14 days later (total cumulative dose of 1000 mg in 3 divided doses)

Nondialysis-dependent patient: 200 mg slow injection (over 2-5 minutes) on 5 different occasions within a 14-day period. Total cumulative dose: 1000 mg in 14-day period. **Note:** Dosage has also been administered as two infusions of 500 mg in a maximum of 250 mL 0.9% NaCl infused over 3.5-4 hours on day 1 and day 14 (limited experience)

Dosing: ElderlyInsufficient data to identify differences between elderly and other adults; use caution.

Dosing: PediatricDoses expressed in mg of **elemental** iron. **Note:** Test dose: Product labeling does not indicate need for a test dose in product-naive patients.

Iron-deficiency anemia in chronic renal disease (hemodialysis-dependent patients): Children ≥2 years (unlabeled use): I.V.:

Correction: 1 mg/kg/dose per dialysis session (maximum: 100 mg)

Maintenance therapy: 0.3 mg/kg/dose per dialysis session (maximum: 100 mg). **Note:** Dosing based on limited data from a study (Leijn, 2004); study used only 14 patients (2-14 years of age) with ESRD on hemodialysis. Study initially used an iron repletion dose of 3 mg/kg/dose per dialysis session which resulted in possible iron overload (ferritin >400 mcg/L); protocol dose subsequently lowered to 1 mg/kg/dose per dialysis session which resulted in a gradual increase in ferritin levels >100 mcg/L; maintenance therapy resulted in median ferritin levels between 193-250 mcg/L.

Administration: I.V.Not for rapid I.V. injection; inject slowly over 2-5 minutes. Can be administered through dialysis line. Do not mix with other medications or parenteral nutrient solutions.

Slow I.V. injection: May administer undiluted by slow I.V. injection (100 mg over 2-5 minutes in hemodialysis-dependent patients **or** 200 mg over 2-5 minutes in nondialysis-dependent patients)

Infusion: Dilute 100 mg in maximum of 100 mL 0.9% NaCl; infuse over at least 15 minutes; 300 mg/250 mL should be infused over at least $1^{1}/_{2}$ hours; 400 mg/250 mL should be infused over at least $2^{1}/_{2}$ hours; 500 mg/250 mL should be infused over at least $3^{1}/_{2}$ hours.

StorageStore vials at controlled room temperature of 25°C (77°F); do not freeze. Following dilution, solutions are stable for 48 hours at room temperature or under refrigeration.

ReconstitutionMay be administered via the dialysis line as an undiluted solution or by diluting 100 mg (5 mL) in a maximum of 100 mL normal saline. Doses ≥200 mg should be diluted in a maximum of 250 mL normal saline.

CompatibilityDo not mix with other medications.

ContraindicationsHypersensitivity to iron sucrose or any component of the formulation; evidence of iron overload; anemia not caused by iron deficiency

Allergy Considerations

- Iron Salt Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Cases of hypersensitivity reactions, including rare postmarketing anaphylactic and anaphylactoid reactions, have been reported.
- Hypotension: Has been reported frequently in hemodialysis-dependent patients. Has also been reported in peritoneal dialysis and nondialysis patients. Hypotension may be related to total dose or rate of administration (avoid rapid I.V. injection), follow

recommended guidelines.

Special populations:

- Pediatrics: Not FDA-approved for use in children.

Other warnings/precautions:

- Appropriate use: Withhold iron in the presence of tissue iron overload; periodic monitoring of hemoglobin, hematocrit, serum ferritin, and transferrin saturation is recommended.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Based on limited data, iron sucrose may be effective for the treatment of iron-deficiency anemia in pregnancy. It is recommended that pregnant women meet the dietary requirements of iron with diet and/or supplements in order to prevent adverse events associated with iron deficiency anemia in pregnancy. Treatment of iron deficiency anemia in pregnant women is the same as in nonpregnant women and in most cases, oral iron preparations may be used. Except in severe cases of maternal anemia, the fetus achieves normal iron stores regardless of maternal concentrations.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIron is normally found in breast milk. Breast milk or iron fortified formulas generally provide enough iron to meet the recommended dietary requirements of infants. The amount of iron in breast milk is generally not influenced by maternal iron status.

Adverse Reactions

>10%:

Cardiovascular: Hypotension (1% to 7%; 39% in hemodialysis patients; may be related to total dose or rate of administration), peripheral edema (2% to 13%)

Central nervous system: Headache (3% to 13%)

Gastrointestinal: Nausea (1% to 15%)

Neuromuscular & skeletal: Muscle cramps (1% to 3%; 29% in hemodialysis patients)

1% to 10%:

Cardiovascular: Hypertension (6% to 8%), edema (1% to 7%), chest pain (1% to 6%), murmur (<1% to 3%), heart failure

Central nervous system: Dizziness (1% to 10%), fatigue (2% to 5%), fever (1% to 3%)

Dermatologic: Pruritus (1% to 7%), rash (≤1%)

Endocrine & metabolic: Gout (2% to 7%), hypoglycemia (<1% to 4%), hyperglycemia (3% to 4%), fluid overload (1% to 3%)

Gastrointestinal: Diarrhea (1% to 10%), vomiting (3% to 9%), taste perversion (1% to 9%), peritoneal infection (≤8%), constipation (1% to 7%), abdominal pain (1% to 4%), positive fecal occult blood (1% to 3%)

Genitourinary: Urinary tract infection (≤1%)

Local: Injection site reaction (2% to 4%), catheter site infection (≤4%)

Neuromuscular & skeletal: Muscle pain (1% to 7%), extremity pain (3% to 6%), arthralgia (1% to 4%), weakness (1% to 3%), back pain (1% to 3%)

Ocular: Conjunctivitis (<1% to 3%)

Otic: Ear pain (1% to 7%)

Respiratory: Dyspnea (1% to 10%), pharyngitis (<1% to 7%), cough (1% to 7%), sinusitis (1% to 4%), nasopharyngitis (≤3%), upper respiratory infection (1% to 3%), nasal congestion (1%), rhinitis (≤1%)

Miscellaneous: Graft complication (1% to 10%), sepsis

<1%, postmarketing, and/or case reports: Anaphylactoid reactions, anaphylactic shock, bronchospasm (with dyspnea), collapse, facial rash, hypersensitivity (including wheezing), hypoesthesia, loss of consciousness, necrotizing enterocolitis (reported in premature infants, no causal relationship established), seizure, urticaria

Drug Interactions

Cefdinir: Iron Salts may decrease the serum concentration of Cefdinir. Red-appearing, non-bloody stools may also develop due to the formation of an insoluble iron-cefdinir complex. Management: Avoid concurrent cefdinir and iron when possible. Separating doses by several hours may minimize interaction. Iron-containing infant formulas do not appear to interact with cefdinir. *Risk D: Consider therapy modification*

Dimercaprol: May enhance the nephrotoxic effect of Iron Salts. *Risk X: Avoid combination*

Eltrombopag: Iron Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., iron-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Phosphate Supplements: Iron Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Iron Salts. Iron Salts may decrease the serum concentration of Trientine. *Risk D: Consider*

therapy modification

Monitoring ParametersHematocrit, hemoglobin, serum ferritin, transferrin, percent transferrin saturation, TIBC; takes about 4 weeks of treatment to see increased serum iron and ferritin, and decreased TIBC. Serum iron concentrations should be drawn 48 hours after last dose.
Reference Range

Hemoglobin: Adults:

Males: 13.5-16.5 g/dL

Females: 12.0-15.0 g/dL

Serum iron: 40-160 mcg/dL

Total iron binding capacity: 230-430 mcg/dL

Transferrin: 204-360 mg/dL

Percent transferrin saturation: 20% to 50%

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Facilities for cardiopulmonary resuscitation must be available during administration. Monitor blood pressure closely during infusion. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically throughout therapy. Assess knowledge/teach patient appropriate use according to product and purpose (dangers of iron overdosing), interventions to reduce side effects, and adverse symptoms to report.
Monitoring: Lab TestsHematocrit, hemoglobin, serum ferritin, transferrin, percent transferrin saturation, TIBC; takes about 4 weeks of treatment to see increased serum iron and ferritin, and decreased TIBC. Serum iron concentrations should be drawn 48 hours after last dose.
Patient EducationYou will be watched closely during infusion. You will need frequent blood tests while on this therapy. You may experience hypotension (use caution when driving or climbing stairs or engaging in tasks requiring alertness until response to drug is known); black tarry stools (normal), nausea, vomiting (taking with meals will reduce this), constipation (adequate fluids and exercise may help, may need a stool softener); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report immediately severe unresolved GI irritation (cramping, nausea, vomiting, diarrhea, constipation); headache, lethargy, fatigue, dizziness, or other CNS changes; rapid respiration; leg cramps; chest pain or palpations; swelling of extremities or unexplained weight gain; vision changes; choking sensation; loss of consciousness; or convulsions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Venofer®: 20 mg of elemental iron/mL (5 mL, 10 mL)

Generic AvailableNo
Mechanism of ActionIron sucrose is dissociated by the reticuloendothelial system into iron and sucrose. The released iron increases serum iron concentrations and is incorporated into hemoglobin.
Pharmacodynamics/Kinetics

Distribution: V_{dss}: Healthy adults: 7.9 L

Metabolism: Dissociated into iron and sucrose by the reticuloendothelial system

Half-life elimination: Healthy adults: 6 hours

Excretion: Healthy adults: Urine (5%) within 24 hours

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste perversion.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness and malaise
Mental Health: Effects on Psychiatric TreatmentHypotension is common; concurrent use with psychotropic medications may produce additive hypotensive effects; use caution. Nausea and vomiting are common; concurrent use with SSRIs, valproic acid, and lithium may produce additive effects; monitor.
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International Brand NamesVenofer (PL)

Isocarboxazid

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(eye soe kar BOKS a zid)

U.S. Brand NamesMarplan®

Pharmacologic CategoryAntidepressant, Monoamine Oxidase Inhibitor

Use: Labeled IndicationsTreatment of depression

Dosing: AdultsDepression: Oral: Initial: 10 mg 2-4 times/day; may increase by 10 mg/day every 2-4 days to 40 mg/day by the end of the first week (divided into 2-4 doses). After first week, may increase by up to 20 mg/week to a maximum of 60 mg/day. May take 3-6 weeks to see effects. Dose should be reduced once maximum clinical effect is seen. If no response obtained within 6 weeks, additional titration is unlikely to be beneficial. **Note:** Use caution in patients on >40 mg/day; experience is limited.

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsAvoid tyramine-containing foods/beverages. Some examples include aged or matured cheese, air-dried or cured meats (including sausages and salamis), fava or broad bean pods, tap/draft beers, Marmite concentrate, sauerkraut, soy sauce and other soybean condiments.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

Contraindications

Hypersensitivity to isocarboxazid or any component of the formulation; cardiovascular disease (including CHF, or HTN); cerebrovascular disease; history of hepatic disease or abnormal liver function tests; pheochromocytoma; renal disease or severe renal impairment

Concurrent use of sympathomimetics (including amphetamines, cocaine, dopamine, epinephrine, methylphenidate, norepinephrine, or phenylephrine) and related compounds (methyldopa, levodopa, phenylalanine, tryptophan, or tyrosine), as well as ophthalmic alpha$_2$-agonists (apraclonidine, brimonidine); may result in behavioral and neurologic symptoms

CNS depressants, cyclobenzaprine, dextromethorphan, ethanol, meperidine, bupropion, buspirone; may result in delirium, excitation, hyper-/hypotension, hyperpyrexia, seizures, and coma

Isocarboxazid **initiation**: At least 2 weeks should elapse between the discontinuation of serotoninergic agents (including SSRIs and tricyclics) and the initiation of isocarboxazid; at least 5 weeks should elapse between the discontinuation of fluoxetine and the initiation of isocarboxazid; at least 1 week should elapse between the discontinuation of other monoamine oxidase (MAO) inhibitors and the initiation of isocarboxazid (using half the normal starting dose). In all cases, a sufficient amount of time must be allowed for the clearance of the serotoninergic agent and any active metabolites prior to the initiation of isocarboxazid.

Isocarboxazid **discontinuation**: At least 2 weeks should elapse between the discontinuation of isocarboxazid and the initiation of the following agents: Serotoninergic agents (including SSRIs, fluoxetine, and tricyclics), bupropion, and other antidepressants. Two to 3 weeks should elapse between the discontinuation of isocarboxazid and the initiation of meperidine. At least 10 days should elapse between the discontinuation of isocarboxazid and initiation of buspirone. At least 1 week should elapse between the discontinuation of isocarboxazid and the initiation of other MAO inhibitors (see specific agent for details).

Antihypertensive agents (including thiazide diuretics): may result in potentiation of antihypertensive effects.

General anesthesia, spinal anesthesia (hypotension may be exaggerated). Use caution with local anesthetics containing sympathomimetic agents. Discontinue drug 10 days prior to elective surgery.

Foods high in tyramine or dopamine content; foods and/or supplements containing tyrosine, phenylalanine, tryptophan, or caffeine; may result in hypertensive reactions.

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Isocarboxazid is FDA approved for the treatment of depression in children ≥16 years of age.**

  The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Isocarboxazid is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Hypertensive crisis: May occur with foods/supplements high in tyramine, tryptophan, phenylalanine, or tyrosine content. Treatment with phentolamine is recommended for hypertensive crises.

- Orthostatic hypotension: May cause orthostatic hypotension (especially at dosages >30 mg/day); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; sensitization to the effects of insulin may occur, monitor blood glucose closely.

- Glaucoma: Use with caution in patients with glaucoma.

- Hepatic impairment: Should not be used in patients with a history of liver disease or with abnormal liver function tests.

- Renal impairment: Use with caution in patients with renal impairment. Should not be used in patients with severe impairment.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

- Thyroid dysfunction: Use with caution in patients with hyperthyroidism.

Concurrent drug therapy issues:

- High potential for interactions: Do not use with other MAO inhibitors or antidepressants. Avoid products containing sympathomimetic stimulants, dextromethorphan, disulfiram, and meperidine. Concurrent use with antihypertensive agents may lead to exaggeration of hypotensive effects.

Special populations:

- Elderly: The MAO inhibitors are effective and generally well tolerated by older patients. It is the potential interactions with tyramine-containing foods and other drugs, and their effects on blood pressure that have limited their use.

- Pediatrics: Safety and efficacy have not been established in patients <16 years of age. Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents and young adults. (See major psychiatric warnings).

- Hyperactive or agitated patients: Use with caution in patients who are hyperactive and/or hyperexcitable.

Other warnings/precautions:

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

- Isocarboxazid is **not** indicated for initial therapy, but should be reserved for patients who have not responded to other antidepressants.

- Myelography: Discontinue at least 48 hours prior to myelography.

Geriatric ConsiderationsThe MAO inhibitors are effective and generally well tolerated by elderly patients. It is their potential interactions with tyramine-containing foods and other drugs and their effects on blood pressure that have limited their use. The MAO inhibitors are usually reserved for patients who do not tolerate or respond to the traditional "cyclic" or "second generation" antidepressants. The brain activity of monoamine oxidase increases with age and even more so in patients with Alzheimer's disease. Therefore, the MAO inhibitor may have an increased role in patients with Alzheimer's disease who are depressed. Information on the use of isocarboxazid in the elderly is limited.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%: Central nervous system: Dizziness (29%), headache (15%)

1% to 10%:

Cardiovascular: Orthostatic hypotension (4%), syncope (2%), palpitation (2%)

Central nervous system: Sleep disturbance (5%), drowsiness (4%), anxiety (2%), chills (2%), forgetfulness (2%), hyperactivity (2%), lethargy (2%), sedation (2%)

Gastrointestinal: Xerostomia (9%), constipation (7%), nausea (6%), diarrhea (2%)

Genitourinary: Urinary frequency (2%), impotence (2%), urinary hesitancy (1%)

Neuromuscular & skeletal: Tremor (4%), myoclonus (2%), paresthesia (2%)

Miscellaneous: Diaphoresis (2%), heavy feeling (2%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Ataxia, black tongue, coma, hallucination, hematologic changes, hepatitis, SIADH, Parkinsonian syndrome, sexual disturbances, toxic amblyopia

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): MAO Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists (Indirect-Acting): MAO Inhibitors may enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Alpha1-Agonists: MAO Inhibitors may enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Alpha2-Agonists (Ophthalmic): MAO Inhibitors may enhance the hypertensive effect of Alpha2-Agonists (Ophthalmic). *Risk X: Avoid combination*

Altretamine: May enhance the orthostatic effect of MAO Inhibitors. *Risk C: Monitor therapy*

Amphetamines: MAO Inhibitors may enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Anilidopiperidine Opioids: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. *Risk D: Consider therapy modification*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Atomoxetine: MAO Inhibitors may enhance the neurotoxic (central) effect of Atomoxetine. *Risk X: Avoid combination*

Beta2-Agonists: MAO Inhibitors may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: MAO Inhibitors may enhance the neurotoxic (central) effect of BuPROPion. *Risk X: Avoid combination*

BusPIRone: May enhance the adverse/toxic effect of MAO Inhibitors. Elevated blood pressure has been reported. *Risk X: Avoid combination*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

COMT Inhibitors: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Cyclobenzaprine: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

Dexmethylphenidate: MAO Inhibitors may enhance the hypertensive effect of Dexmethylphenidate. *Risk X: Avoid combination*

Dextromethorphan: MAO Inhibitors may enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

Levodopa: May enhance the adverse/toxic effect of MAO Inhibitors. Of particular concern is the development of hypertensive reactions when levodopa is used with nonselective MAOI. *Risk D: Consider therapy modification*

Linezolid: MAO Inhibitors may enhance the adverse/toxic effect of Linezolid. *Risk X: Avoid combination*

Lithium: MAO Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Maprotiline: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

Meperidine: MAO Inhibitors may enhance the serotonergic effect of Meperidine. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methyldopa: MAO Inhibitors may enhance the adverse/toxic effect of Methyldopa. *Risk X: Avoid combination*

Methylphenidate: MAO Inhibitors may enhance the hypertensive effect of Methylphenidate. *Risk X: Avoid combination*

Mirtazapine: MAO Inhibitors may enhance the neurotoxic (central) effect of Mirtazapine. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the adverse/toxic effect of MAO Inhibitors. Specifically, the risk of serotonin syndrome or other serotonergic adverse events may be increased. *Risk X: Avoid combination*

Rauwolfia Alkaloids: MAO Inhibitors may enhance the adverse/toxic effect of Rauwolfia Alkaloids. Existing MAOI therapy can result in paradoxical effects of added rauwolfia alkaloids (eg, excitation, hypertension). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: MAO Inhibitors may decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. **Exceptions:** Eletriptan; Frovatriptan; Naratriptan. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tetrabenazine: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

TraMADol: May enhance the neuroexcitatory and/or seizure-potentiating effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: MAO Inhibitors may enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (based on CNS depressant effects and potential tyramine content)

Food: Concurrent ingestion of foods rich in tyramine may cause sudden and severe high blood pressure (hypertensive crisis). Avoid tyramine-containing foods with MAO inhibitors. Food’s freshness is also an important concern; improperly stored or spoiled food can create an environment where tyramine concentrations may increase.

Herb/Nutraceuticals: Avoid supplements containing caffeine, tyrosine, tryptophan or phenylalanine. Ingestion of large quantities may increase the risk of severe side effects (eg, hypertensive reactions, serotonin syndrome).

Monitoring Parameters

Blood pressure, heart rate; mood, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 10 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Marplan)

10 mg (30): $71.99

Mechanism of ActionThought to act by increasing endogenous concentrations of epinephrine, norepinephrine, dopamine, and serotonin through inhibition of the enzyme (monoamine oxidase) responsible for the breakdown of these neurotransmitters

Related Information

- Antidepressant Agents
- Teratogenic Risks of Psychotropic Medications
- Tyramine Content of Foods

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension, xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAttempts should be made to avoid use of vasoconstrictor due to possibility of hypertensive episodes with monoamine oxidase inhibitors

Mental Health CommentNot commonly used due to a required low tyramine diet and drug-drug interactions. It is estimated that 20 mg of tranylcypromine = 40 mg of isocarboxazid = 45 mg phenelzine. Phenelzine and isocarboxazid are hydrazine MAO inhibitors and tranylcypromine is a nonhydrazine. These drugs produce irreversible inhibition of MAO inhibitors. The half-life for regeneration is 2-3 days. Therefore, a 2-week period is required when switching from an MAO inhibitor to another antidepressant.

While hypertension and hypertensive crisis are risks associated with MAO inhibitor therapy, orthostatic hypotension may also occur. Orthostasis associated with MAO inhibitor therapy is not related to alpha$_1$-adrenergic receptor blockade. The “false transmitter” concept is used to explain this side effect. This concept states that MAO inhibitors promote gradual accumulation in sympathetic nerve ending of amines lacking direct sympathomimetic activity (octopamine) at the expense of the normal synaptic transmitter, norepinephrine. Since octopamine has little ability to activate either alpha- or beta-adrenergic receptors, a functional impairment of sympathetic neurotransmission occurs.

The MAO inhibitors are usually reserved for patients who do not tolerate or respond to other antidepressants. The brain activity of monoamine oxidase increases with age and even more so in patients with Alzheimer's disease. Therefore, the MAO inhibitors may have an increased role in patients with Alzheimer's disease who are depressed. Phenelzine is less stimulating than tranylcypromine.

References

Pass SE and Simpson RW, “Discontinuation and Reinstitution of Medications During the Perioperative Period,” *Am J Health Syst Pharm*, 2004, 61(9):899-912.[PubMed 15156966]

Shulman KI and Walker SE, “A Reevaluation of Dietary Restrictions for Irreversible Monoamine Oxidase Inhibitors,” *Psychiatr Ann*, 2001, 31(6):378-84.

Shulman KI and Walker SE, “Refining the MAOI Diet: Tyramine Content of Pizzas and Soy Products,” *J Clin Psychiatry*, 1999, 60(3):191-3.[PubMed 10192596]

Walker SE, Shulman KI, Tailor SA, et al, “Tyramine Content of Previously Restricted Foods in Monoamine Oxidase Inhibitor Diets,” *J Clin Psychopharmacol*, 1996, 16(5):383-8.[PubMed 8889911]

International Brand Names Marplan (DK, GB)

Isoflurane

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Isoflurane may be confused with enflurane, isoflurophate

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(eye soe FLURE ane)

U.S. Brand NamesForane®; Terrell™

Canadian Brand NamesForane®

Pharmacologic CategoryGeneral Anesthetic, Inhalation

Use: Labeled IndicationsInduction and maintenance of general anesthesia

Dosing: Adults**Anesthesia:** Inhalation: Minimum alveolar concentration (MAC), the concentration at which 50% of patients do not respond to surgical incision, is 1.15% (44 years of age) for isoflurane.

Induction: 1.5% to 3%

Maintenance: In nitrous oxide: 1% to 2.5%; in oxygen: 1.5% to 3.5%

Dosing: ElderlyMAC is reduced in the elderly.

Administration: InhalationVia isoflurane-specific calibrated vaporizer

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to isoflurane or any component of the formulation; known or suspected history of malignant hyperthermia

Warnings/Precautions

Concerns related to adverse effects:

- Cardiovascular effects: Decrease in blood pressure is dose dependent due to peripheral vasodilation primarily in skin and muscle; cardiac output is maintained. May produce cardiac steal (due to coronary vasodilation) in patients with hypertension under certain conditions (eg, unusual coronary artery anatomy). May produce reflex tachycardia, but has less potential to alter atrioventricular conduction or sensitize the myocardium to epinephrine-induced arrhythmias compared to other inhaled anesthetics (eg. halothane, enflurane).

- Decreased blood flow: May cause decrease in hepatic, renal and splenic blood flow.

- Hepatitis: Postoperative hepatic dysfunction and hepatitis have rarely been reported. Postmarketing reports of hepatic failure and necrosis have also been rarely associated with isoflurane.

- Hyperkalemia: Use of other inhaled anesthetics has been associated with rare cases of perioperative hyperkalemia; concomitant use of succinylcholine was associated with many of the reported cases, but not all. Risk of hyperkalemia is increased in pediatric patients with underlying neuromuscular disease (eg, Duchenne muscular dystrophy). Other abnormalities may include elevation in CPK and myoglobinuria. Monitor closely for arrhythmias. Aggressively identify and treat hyperkalemia.

- Increased intracranial pressure: Dilates the cerebral vasculature and may, in certain conditions, increase intracranial pressure.

- Malignant hyperthermia: May trigger malignant hyperthermia; avoid use in patients susceptible to malignant hyperthermia.

- Respiratory depression: Respiration is depressed as is the normal hyperventilatory response to hypoxia. Hypoxic pulmonary vasoconstriction is depressed which may lead to pulmonary shunt. Hypoxemia-induced increase in ventilation is abolished at low concentrations. Can produce elevated carbon monoxide levels in the presence of a dry carbon dioxide absorbent within the circle breathing system of an anesthetic machine.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have demonstrated adverse fetal effects. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsPotential safety issues exist for occupational exposure to inhaled anesthetic gases (primarily nitrous oxide). Although there are no documented adverse effects of chronic occupational exposure to halogenated anesthetic vapors, like isoflurane, some epidemiological studies suggest a link between these anesthetics and increased health problems (particularly spontaneous abortion). No conclusive relationship has been determined, but the National Institute for Occupational Safety and Health Administration (NIOSH) recommends no worker be exposed to >2 ppm (ceiling concentrations) over a period of 1 hour. Precautions (eg, adequate ventilation, scavenging-systems, minimizing leaks/spills) can help to lessen any potential risk.

Frequency not defined.

Cardiovascular: Arrhythmia, hypotension, myocardial depression, tachycardia (transient)

Central nervous system: Mood changes (may persist for ≤6 days after administration), cognitive function decreased (may persist for ≤3 days after administration)

Endocrine & metabolic: Cholesterol decreased, hyperglycemia, hyperkalemia (pediatric patients, perioperative)

Gastrointestinal: Ileus, nausea, vomiting

Hepatic: Hepatic dysfunction (mild to severe; rare), hepatitis (rare), alkaline phosphatase decreased

Renal: BUN decreased, creatinine increased

Respiratory: Respiratory depression/arrest; respiratory irritation (coughing, laryngospasms-related to induction)

Miscellaneous: Malignant hyperthermia, shivering

Postmarketing and/or case reports: Hepatic failure (rare), hepatic necrosis (rare)

Metabolism/Transport Effects **Substrate** of CYP2E1 (major); **Inhibits** CYP2B6 (weak)

Drug Interactions

CYP2E1 Inhibitors (Moderate): May decrease the metabolism of CYP2E1 Substrates. *Risk C: Monitor therapy*

CYP2E1 Inhibitors (Strong): May decrease the metabolism of CYP2E1 Substrates. *Risk D: Consider therapy modification*

EPINEPHrine: Inhalational Anesthetics may enhance the arrhythmogenic effect of EPINEPHrine. *Risk D: Consider therapy modification*

Methylphenidate: May enhance the hypertensive effect of Inhalational Anesthetics. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): Inhalational Anesthetics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure, heart rate and rhythm, serum potassium, oxygen saturation, end-tidal CO_2 and isoflurane concentrations should be monitored prior to and throughout anesthesia

Monitoring: Lab TestsSerum potassium should be monitored prior to and throughout anesthesia

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, for inhalation: >99.9% (100 mL, 250 mL)

Forane®: >99.9% (100 mL, 250 mL) [amber-colored bottle]

Forane®: >99.9% (100 mL, 250 mL) [aluminum bottle]

Terrell™: >99.9% (100 mL, 250 mL) [amber-colored bottle]

Generic AvailableYes

Pharmacodynamics/Kinetics

Onset of action: 7-10 minutes (pungent odor limits inhalation rate)

Duration: Emergence time: Depends on blood concentration when discontinued

Metabolism: Hepatic (0.2%)

Excretion: Exhaled gases

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other ConsiderationsUse of isoflurane for induction of anesthesia is limited by its pungent odor which may cause breath holding or coughing.

References

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Eger EI 2nd, “Isoflurane: A Review,” *Anesthesiology*, 1981, 55(5):559-76. [PubMed 7027831]

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Park KW, “Cardiovascular Effects of Inhalational Anesthetics,” *Int Anesthesiol Clin*, 2002, 40(1):1-14.

Stachnik J, “Inhaled Anesthetic Agents,” *Am J Health-Syst Pharm*, 2006, 63(7):623-34.[PubMed 16554286]

Yasuda N, Lockhart SH, Eger EI 2nd, et al, “Comparison of Kinetics of Sevoflurane and Isoflurane in Humans,” *Anesth Analg*, 1991, 72(3):316-24. [PubMed 1994760]

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International Brand NamesAerane (KP); Aerrane (BE, ES, ID, IL, LU, NL, NZ, PH, PL, TW, ZA); Floran (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Forane (AR, AT, BG, BR, CL, CZ, DE, EE, ES, HK, HN, HR, HU, IE, IL, IT, JP, KP, MY, PE, PH, PK, PL, PY, RU, TH, TR, TW, UY); Forene (BE, CH, DK, FI, LU, NO, SE, VE); Forthane (AU); Isofluran (FI); Isofluran Pharmacia (FI); Isoflurane (FR, NZ); Isoflurano (CN, EC); Isorane (IN, MX); Sofloran (MX); Terrell Soln (ID)

Isoniazid

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

International issues:

Hydra® [Japan] may be confused with Hydrea®

Pronunciation(eye soe NYE a zid)

Canadian Brand NamesIsotamine®; PMS-Isoniazid

Pharmacologic Category[Antitubercular Agent]()

Use: Labeled IndicationsTreatment of susceptible tuberculosis infections; treatment of latent tuberculosis infection (LTBI)

Dosing: AdultsRecommendations often change due to resistant strains and newly-developed information; consult *MMWR* for current CDC recommendations. Intramuscular injection is available for patients who are unable to either take or absorb oral therapy.

Nontuberculous mycobacterium (*M. kansasii*) (unlabeled use): Oral, I.M.: 5 mg/kg/day (maximum: 300 mg/day) for duration to include 12 months of culture-negative sputum; typically used in combination with ethambutol and rifampin

Treatment of latent tuberculosis infection (LTBI): Oral, I.M.: 300 mg/day or 900 mg twice weekly for 6-9 months in patients who do not have HIV infection (9 months is optimal, 6 months may be considered to reduce costs of therapy) and 9 months in patients who have HIV infection. Extend to 12 months of therapy if interruptions in treatment occur.

Treatment of active TB infection (drug susceptible): Oral, I.M.:

Daily therapy: 5 mg/kg/day given daily (usual dose: 300 mg/day)

Twice weekly or 3 times/week directly observed therapy (DOT): 15 mg/kg (maximum: 900 mg). **Note:** CDC guidelines state that once-weekly therapy (15 mg/kg/dose) may be considered, but only after the first 2 months of initial therapy in HIV-negative patients, and only in combination with rifapentine.

Note: Treatment may be defined by the number of doses administered (eg, "six-month" therapy involves 182 doses of INH and rifampin, and 56 doses of pyrazinamide). Six months is the shortest interval of time over which these doses may be administered, assuming no interruption of therapy.

Note: Concomitant administration of 10-50 mg/day pyridoxine is recommended in malnourished patients or those prone to neuropathy (eg, alcoholics, patients with diabetes)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRecommendations often change due to resistant strains and newly-developed information; consult *MMWR* for current CDC recommendations. Intramuscular injection is available for patients who are unable to either take or absorb oral therapy.

Treatment of latent TB infection (LTBI): Infants and Children: Oral, I.M.: 10 mg/kg/day as a singe dose (maximum: 300 mg/day) or 20-30 mg/kg (maximum: 900 mg/dose) twice weekly for 9 months

Treatment of active TB infection: Infants and Children: Oral, I.M.:

Daily therapy: 10-15 mg/kg/day in 1-2 divided doses (maximum: 300 mg/day)

Twice weekly or 3 times/week directly observed therapy (DOT): 20-40 mg/kg (maximum: 900 mg)

Dosing: Renal ImpairmentNo adjustment necessary

Hemodialysis: Dialyzable (50% to 100%); administer dose postdialysis

Dosing: Hepatic ImpairmentNo adjustment required, however, use with caution, may accumulate and additional liver damage may occur in patients with pre-existing liver disease. For ALT or AST >3 times the ULN: discontinue or temporarily withhold treatment. Treatment with isoniazid for latent tuberculosis infection should be deferred in patients with acute hepatic diseases.

Calculations

- [Creatinine Clearance: Adults]()
- [Creatinine Clearance: Pediatrics]()

Administration: OralShould be administered 1 hour before or 2 hours after meals on an empty stomach.

Dietary ConsiderationsShould be taken 1 hour before or 2 hours after meals on an empty stomach; increase dietary intake of folate, niacin, magnesium. Avoid tyramine-containing foods. Avoid histamine-containing foods.

Storage

Tablet: Store at 20°C to 25°C (68°F to 77°F). Protect from light.

Oral solution: Store at 15°C to 30°C (59°F to 86°F). Protect from light.

Extemporaneously PreparedA 10 mg/mL oral suspension was stable for 21 days when refrigerated when compounded as follows:

Triturate ten 100 mg tablets in a mortar, reduce to a fine powder, then add 10 mL of purified water U.S.P. to make a paste; then transfer to a graduate and qs to 100 mL with sorbitol (do not use sugar-based solutions)

Shake well before using and keep in refrigerator

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, 3rd ed, Cincinnati, OH: Harvey Whitney Books Co, 1997.

ContraindicationsHypersensitivity to isoniazid or any component of the formulation; acute liver disease; previous history of hepatic damage during isoniazid therapy; previous severe adverse reaction (drug fever, chills, arthritis) to isoniazid

Allergy Considerations

- Isoniazid Allergy

Warnings/Precautions

Boxed warnings:

- Hepatitis: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Hepatitis: **[U.S. Boxed Warning]: Severe and sometimes fatal hepatitis may occur; usually occurs within the first 3 months of treatment, although may develop even after many months of treatment.** The risk of developing hepatitis is age-related; daily ethanol consumption may also increase the risk. Patients must report any prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea, or vomiting.

- Peripheral neuropathies: Pyridoxine (10-50 mg/day) is recommended in individuals at risk for development of peripheral neuropathies (eg, HIV infection, nutritional deficiency, diabetes, pregnancy).

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment. Treatment with isoniazid for latent tuberculosis infection should be deferred in patients with acute hepatic diseases.

- Renal impairment: Use with caution in patients with severe renal impairment.

Other warnings/precautions:

- Appropriate use: Multidrug regimens should be utilized for the treatment of active tuberculosis to prevent the emergence of drug resistance.

- Ophthalmic exams: Periodic ophthalmic examinations are recommended even when usual symptoms do not occur.

Geriatric ConsiderationsAge has not been shown to affect the pharmacokinetics of INH since acetylation phenotype determines clearance and half-life, acetylation rate does not change significantly with age. Most strains of *M. tuberculosis* found the elderly should be susceptible to INH since most acquired their initial infection prior to INH's introduction.

Pregnancy Risk FactorC

Pregnancy ConsiderationsIsoniazid was found to be embryocidal in animal studies; teratogenic effects were not noted. Isoniazid crosses the human placenta. Due to the risk of tuberculosis to the fetus, treatment is recommended when the probability of maternal disease is moderate to high. The CDC recommends isoniazid as part of the initial treatment regimen (CDC, 2003). Pyridoxine supplementation is recommended (25 mg/day).

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsSmall amounts of isoniazid are excreted in breast milk. However, women with tuberculosis should not be discouraged from breast-feeding. Pyridoxine supplementation is recommended for the mother and infant.

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypertension, palpitation, tachycardia, vasculitis

Central nervous system: Depression, dizziness, encephalopathy, fever, lethargy, memory impairment, psychosis, seizure, slurred speech

Dermatologic: Flushing, rash (morbilliform, maculopapular, pruritic, or exfoliative)

Endocrine & metabolic: Gynecomastia, hyperglycemia, metabolic acidosis, pellagra, pyridoxine deficiency

Gastrointestinal: Anorexia, nausea, stomach pain, vomiting

Hematologic: Agranulocytosis, anemia (sideroblastic, hemolytic, or aplastic), eosinophilia, thrombocytopenia

Hepatic: LFTs mildly increased (10% to 20%); hyperbilirubinemia, bilirubinuria, jaundice, hepatic dysfunction, hepatitis (may involve progressive liver damage; risk increases with age; 2.3% in patients >50 years)

Neuromuscular & skeletal: Arthralgia, hyper-reflexia, peripheral neuropathy (dose-related incidence, 10% to 20% incidence with 10 mg/kg/day), weakness

Ocular: Blurred vision, loss of vision, optic neuritis and atrophy

Miscellaneous: Lupus-like syndrome, lymphadenopathy, rheumatic syndrome

Metabolism/Transport Effects **Substrate** of CYP2E1 (major); **Inhibits** CYP1A2 (weak), 2A6 (moderate), 2C9 (weak), 2C19 (strong), 2D6 (moderate), 2E1 (moderate), 3A4 (strong); **Induces** CYP2E1 (after discontinuation) (weak)

Drug Interactions

Acetaminophen: Isoniazid may enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Isoniazid may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: Isoniazid may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Chlorzoxazone: Isoniazid may decrease the metabolism of Chlorzoxazone. *Risk C: Monitor therapy*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

CycloSERINE: May enhance the CNS depressant effect of Isoniazid. *Risk D: Consider therapy modification*

CYP2A6 Substrates: CYP2A6 Inhibitors (Moderate) may decrease the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP2E1 Substrates: CYP2E1 Inhibitors (Moderate) may decrease the metabolism of CYP2E1 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Phenytoin: Isoniazid may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May enhance the hepatotoxic effect of Isoniazid. Even so, this is a frequently employed combination regimen. *Risk C: Monitor therapy*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Theophylline Derivatives: Isoniazid may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (increases the risk of hepatitis).

Food: Isoniazid should not be taken with food; serum levels may be decreased if taken with food. Has some ability to inhibit tyramine metabolism; several case reports of mild reactions (flushing, palpitations) after ingestion of cheese (with or without wine). Reactions resembling allergic symptoms following ingestion of fish high in histamine content have been reported. Isoniazid decreases folic acid absorption. Isoniazid alters pyridoxine metabolism.

Test InteractionsFalse-positive urinary glucose with Clinitest®

Monitoring ParametersBaseline and periodic (more frequently in patients with higher risk for hepatitis) liver function tests (ALT and AST); sputum cultures monthly (until 2 consecutive negative cultures reported); monitoring for prodromal signs of hepatitis

Reference RangeTherapeutic: 1-7 mcg/mL (SI: 7-51 µmol/L); Toxic: 20-710 mcg/mL (SI: 146-5176 µmol/L)

Nursing: Physical Assessment/MonitoringUse caution with pre-existing renal impairment or hepatic disease. Assess potential for interactions with other pharmacological or herbal agents patient may be taking (eg, risk of toxicity, decreased effects). Evaluate results of laboratory tests, therapeutic effectiveness, and adverse response (eg, nausea, vomiting, peripheral neuropathy, liver damage, CNS changes) at regular intervals during therapy. Advise patients with diabetes about use of Clinitest® (may cause false-positive results). Teach patient proper use, possible side effects/appropriate interventions (eg, diet [see Tyramine Foods List], ophthalmic examinations), and adverse symptoms to report.

Monitoring: Lab TestsBaseline and periodic (more frequently in patients with higher risk for hepatitis) liver function tests (ALT and AST); sputum cultures monthly (until 2 consecutive negative cultures reported)

Patient EducationDo not take any new prescription, OTC medications, or herbal products during therapy unless approved by prescriber. Best if taken on an empty stomach, 1 hour before or 2 hours after meals. Avoid missing any dose and do not discontinue without notifying prescriber. Avoid excessive alcohol and tyramine-containing foods (eg, aged cheese, broad beans, dry sausage, preserved meats or sausages, liver pate, fish, soy bean, protein supplements, wine) and increase dietary intake of folate, niacin, and magnesium. May cause false test results with Clinitest®; use of another type of glucose testing is preferable. You will need to have frequent ophthalmic exams and periodic medical check-ups to evaluate drug effects. You may experience nausea, vomiting, or loss of appetite (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report chest pain, rapid heart beat, or palpitations; tingling, numbness, or loss of sensation in hands or feet; unusual weakness or fatigue; persistent gastrointestinal upset; dark-colored urine or change in urinary pattern; yellowing skin or eyes; change in color of stool; change in vision; skin rash; or other persistent adverse effects. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 100 mg/mL (10 mL)

Oral solution: 50 mg/5 mL (473 mL) [orange flavor]

Tablet: 100 mg, 300 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Syrup (Isoniazid)

50 mg/5 mL (473): $68.73

Tablets (Isoniazid)

100 mg (30): $8.99

300 mg (90): $17.00

Mechanism of ActionUnknown, but may include the inhibition of mycolic acid synthesis resulting in disruption of the bacterial cell wall

Pharmacodynamics/Kinetics

Absorption: Rapid and complete; rate can be slowed with food

Distribution: All body tissues and fluids including CSF; crosses placenta; enters breast milk

Protein binding: 10% to 15%

Metabolism: Hepatic with decay rate determined genetically by acetylation phenotype

Half-life elimination: Fast acetylators: 30-100 minutes; Slow acetylators: 2-5 hours; may be prolonged with hepatic or severe renal impairment

Time to peak, serum: 1-2 hours

Excretion: Urine (75% to 95%); feces; saliva

Related Information

- Antacid Drug Interactions
- Tuberculosis
- Tyramine Content of Foods
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsThe AAP recommends that pyridoxine supplementation (1-2 mg/kg/day) should be administered to malnourished patients, children or adolescents on meat or milk-deficient diets, breast-feeding infants, and those predisposed to neuritis to prevent peripheral neuropathy; administration of isoniazid syrup has been associated with diarrhea

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause drowsiness or dizziness; may rarely cause depression or psychosis; reports of insomnia, restlessness, disorientation, hallucinations, delusions, obsessive-compulsive symptoms, and exacerbation of schizophrenia

Mental Health: Effects on Psychiatric Treatment Isoniazid may impair the metabolism of carbamazepine and oxidatively metabolized benzodiazepines; monitor for adverse effects

Index Terms INH; Isonicotinic Acid Hydrazide

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International Brand NamesAntimic (TH); Cemidon (ES); Curazid Forte (PH); Dardex (ES); Dianicotyl (GR); Diazid (JP); Eutizon (HR); Fimazid (ES); Fluodrazin (BR); Hidrafasa (ES); Hidranison (ES); Hidrasolco (ES); Hidrazida (ES, PT); Hydrazin (TW); INH Agepha (AT); INH Lannacher (AT); INH Waldheim (AT); Iscotin (TW); Iso-Dexter (ES); Isokin (IN); Isonex (ID, IN); Isoniac (AR); Isoniazid (AU); Isoniazid Atlantic (HK); Isoniazid ”Dak” (DK); Isoniazid ”Oba” (DK); Isoniazide Drank FNA (NL); Isoniazidum (PL); Isonicid (HN); Isozid (DE); Kridan Simple (ES); Lefos (ES); Medic Aid Isoniazid (PH); Nicotibine (BE, IL, LU); Nicozid (IT); Nidrazid (CZ); Nydrazide (PK); Pycazide (GB); Pyreazid (ES); Rimicid (BG); Rimifon (CH, ES, FR, GB); Tebilon (AT); Tibinide (SE); Tubilysin (FI); Valifol (MX); Yuhan-Zid (KP)

Isoproterenol

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Medication Safety Issues

Sound-alike/look-alike issues:

Isuprel® may be confused with Disophrol®, Ismelin®, Isordil®

Pronunciation(eye soe proe TER e nole)

U.S. Brand NamesIsuprel®

Pharmacologic CategoryBeta$_1$/Beta$_2$ Agonist

Use: Labeled IndicationsVentricular arrhythmias due to AV nodal block; hemodynamically compromised bradyarrhythmias or atropine- and dopamine-resistant bradyarrhythmias (when transcutaneous/venous pacing is not available); temporary use in third-degree AV block until pacemaker insertion

Use: Unlabeled/InvestigationalPharmacologic overdrive pacing for torsade de pointes; diagnostic aid (vasovagal syncope)

Dosing: AdultsCardiac arrhythmias: I.V.: Initial: 2 mcg/minute; titrate to patient response (2-10 mcg/minute)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricCardiac arrhythmias: I.V.: Start 0.1 mcg/kg/minute (usual effective dose 0.2-2 mcg/kg/minute)

Administration: I.V.I.V. infusion administration requires the use of an infusion pump. To prepare for infusion: 1 mg isoproterenol to 500 mL D_5W, final concentration 2 mcg/mL

Administration: I.V. DetailpH: 2.5-4.5

StorageIsoproterenol solution should be stored at room temperature. It should not be used if a color or precipitate is present. Exposure to air, light, or increased temperature may cause a pink to brownish pink color to develop.

ReconstitutionStability of parenteral admixture at room temperature (25°C) or at refrigeration (4°C) is 24 hours.

Standard diluent: 2 mg/500 mL D_5W; 4 mg/500 mL D_5W.

Minimum volume: 1 mg/100 mL D_5W.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5\,{}^1/_4$ NS, $D_5\,{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, ${}^1/_2NS$, NS; **incompatible** with sodium bicarbonate 5% and alkaline solutions.

Y-site administration: Compatible: Amiodarone, atracurium, bretylium, cisatracurium, famotidine, heparin, hydrocortisone sodium succinate, inamrinone, levofloxacin, milrinone, pancuronium, potassium chloride, propofol, remifentanil, tacrolimus, vecuronium, vitamin B complex with C.

Compatibility in syringe: Compatible: Ranitidine.

Compatibility when admixed: Compatible: Atracurium, calcium chloride, cimetidine, dobutamine, floxacillin, heparin, magnesium sulfate, multivitamins, potassium chloride, ranitidine, succinylcholine, verapamil, vitamin B complex with C. **Incompatible:** Aminophylline, furosemide, sodium bicarbonate.

ContraindicationsHypersensitivity to sulfites or isoproterenol, any component of the formulation, or other sympathomimetic amines; angina, pre-existing cardiac arrhythmias (ventricular); tachycardia or AV block caused by cardiac glycoside intoxication

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Renal impairment: Use with caution in patients with renal impairment.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Appropriate use: Use with extreme caution; not currently a treatment of choice. Excessive or prolonged use may result in decreased effectiveness.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown
Adverse ReactionsFrequency not defined.

Cardiovascular: Premature ventricular beats, bradycardia, hyper-/hypotension, chest pain, palpitation, tachycardia, ventricular arrhythmia, MI size increased

Central nervous system: Headache, nervousness or restlessness

Endocrine & metabolic: Serum glucose increased, serum potassium decreased, hypokalemia

Gastrointestinal: Nausea, vomiting

Respiratory: Dyspnea

Drug Interactions

COMT Inhibitors: May decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid ephedra, yohimbe (may cause CNS stimulation).
Monitoring ParametersECG, heart rate, respiratory rate, arterial blood gas, arterial blood pressure, CVP; serum glucose, serum potassium, serum magnesium
Nursing: Physical Assessment/MonitoringAssess results of laboratory tests, cardiac, respiratory, and hemodynamic status when used in acute or emergency situations. Assess knowledge/teach patient appropriate use and administration procedures and adverse reactions to report.
Monitoring: Lab TestsECG, arterial blood gas, serum magnesium, serum potassium, serum glucose (in selected patients)
Patient EducationYou may experience nervousness, dizziness, or fatigue (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or dry mouth, nausea, or vomiting (small frequent meals may reduce the incidence of nausea or vomiting). If you have diabetes, check blood sugar; blood glucose level may be increased. Report chest pain, rapid heartbeat or palpitations, unresolved/persistent GI upset, dizziness, fatigue, trembling, increased anxiety, sleeplessness, or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride:

Isuprel®: 0.2 mg/mL (1:5000) (1 mL, 5 mL) [contains sodium metabisulfite]

Generic AvailableNo
Mechanism of ActionStimulates beta$_1$- and beta$_2$-receptors resulting in relaxation of bronchial, GI, and uterine smooth muscle, increased heart rate and contractility, vasodilation of peripheral vasculature
Pharmacodynamics/Kinetics

Onset of action: Bronchodilation: I.V.: Immediate

Duration: I.V.: 10-15 minutes

Metabolism: Via conjugation in many tissues including hepatic and pulmonary

Half-life elimination: 2.5-5 minutes

Excretion: Urine (primarily as sulfate conjugates)

Related Information

- Bronchodilators
- Hemodynamic Support, Intravenous
- Inhalant Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsIsoproterenol is selective for beta-adrenergic receptors and not alpha-receptors; therefore, there is no precaution in the use of vasoconstrictor such as epinephrine
Mental Health: Effects on Mental StatusInsomnia and restlessness are common
Mental Health: Effects on Psychiatric TreatmentNone reported
Cardiovascular ConsiderationsIsoproterenol is being increasingly used for provoking vasovagal syncope during tilt table testing. Incremental doses of isoproterenol are used in patients with a history suggestive of vasovagal syncope but in whom upright tilt alone does not induce symptoms. Another important use for isoproterenol is in the intensive care setting in the treatment of torsade de pointes. In patients with recurrent torsade de pointes, treatment consists of correcting underlying cause (eg, electrolyte abnormalities or drug ingestion). Supportive therapy consists of increasing heart rate so as to decrease the QT interval. This can be achieved by either placement of a temporary external pacemaker or by incremental isoproterenol infusion to achieve a resting heart rate of approximately 100 beats per minute or a resting heart rate that is not conducive to the occurrence of torsade de pointes.

Isoproterenol may be used together with atropine as a temporizing measure in treating patients with hemodynamically significant bradycardia.

Study data suggest that elderly healthy or hypertensive patients are less responsive to beta-adrenergic stimulation compared to younger subjects. Use caution in elderly patients; start dosing at the lower end of the dosing range.

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Isoproterenol can be effective in terminating torsade de pointes associated with bradycardia and drug-induced prolonged QT (adult case series; Keren, 1981).

Index Terms Isoproterenol Hydrochloride

References

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Rachelefsky GS and Siegel SC, "Asthma in Infants and Children - Treatment of Childhood Asthma: Part II," *J Allergy Clin Immunol*, 1985, 76(3):409-25.[PubMed 2863296]

International Brand Names Aleudrina (ES); Antasthmin (AT); Asmadren (NO); Bellasthman Medihaler (DE); Dyspnoesan (NL); Erydin (DK); Euspiran (CZ); Ingelan (AT, DE); Isolin (IN); Isomel (IE); Isomenyl (JP); Isoprenalin (NO, SE); Isoprenalin Hydrochlorid (AU); Isoprenalina Cloridrato (IT); Isoprenalinhydrochlorid-Braun (LU); Isuprel (AU, HU, LU); Isuprel HCl (BE, FR, HK, TH); Isuprel Mistometer (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Kattwilon N (DE); Medihaler-Iso (GB, LU, NL, PT); Min-I-Jet Isoprenaline (GB); Novodrin (DE); Proterenal (AR); Proternol L (TW); Saventrine (FI, GB, GR, IE, SG); Sedansol Iso (JP); Sooner (JP)

Isosorbide Dinitrate and Hydralazine

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Pronunciation (eye soe SOR bide dye NYE trate & hye DRAL a zeen)

U.S. Brand Names BiDil®

Pharmacologic Category [Vasodilator]

Use: Labeled Indications Treatment of heart failure, adjunct to standard therapy, in self-identified African-Americans

Dosing: Adults **Heart failure:** Oral: Initial: 1 tablet 3 times/day; titrate to a maximum dose of 2 tablets 3 times/day

Dosing: Elderly Refer to adult dosing.

Dosing: Adjustment for Toxicity If patient experiences persistent headache, adjust dosing to twice daily.

Storage Store at controlled room temperature of 15°C to 30°C (58°F to 86°F). Protect from light.

Contraindications Hypersensitivity to isosorbide dinitrate, hydralazine, or any component of the formulation; hypersensitivity to organic nitrates; concurrent use with phosphodiesterase-5 inhibitors (sildenafil, tadalafil, or vardenafil); angle-closure glaucoma (intraocular pressure may be increased); head trauma or cerebral hemorrhage (increase intracranial pressure); severe anemia; mitral valve rheumatic heart disease

Warnings/Precautions

Concerns related to adverse effects:

- Drug-induced lupus-like syndrome: Hydralazine may cause a drug-induced lupus-like syndrome (more likely on larger doses, longer duration).
- Fluid/sodium retention: Hydralazine-induced fluid and sodium retention may require addition or increased dosage of a diuretics.
- Hypotension/bradycardia: Severe hypotension can occur; paradoxical bradycardia and increased angina pectoris can accompany hypotension. Postural hypotension can also occur. Use with caution in volume depletion, hypotension, and right ventricular infarctions.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease (CAD); increase in tachycardia may increase myocardial oxygen demand.
- Hypertrophic cardiomyopathy: Use with caution in patients with hypertrophic cardiomyopathy; nitrates may reduce preload, exacerbating obstruction and cause hypotension and/or worsening of heart failure.
- Pulmonary hypertension: Use with caution in pulmonary hypertension; may cause hypotension.
- Renal impairment: Use with caution in patients with severe renal impairment; dosage adjustment recommended.

Concurrent drug therapy issues:

- PDE-5 inhibitors: Avoid concurrent use with PDE-5 inhibitors (eg, sildenafil, tadalafil, vardenafil).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Tolerance: Appropriate dosing is needed to minimize tolerance development.

Geriatric Considerations The pharmacokinetics of hydralazine and isosorbide alone or in combination have not been studied. As with all antihypertensives and nitrate products, caution should be used on initiation of therapy, as hypotension may be encountered. Since many elderly are volume depleted, secondary to their blunted thirst reflex and/or use of diuretics, doses used initially should be at lowest recommended dose. The use of nitrates may occasionally promote reflux esophagitis. Monitor for these effects at start of therapy.

Pregnancy Risk Factor C

Pregnancy Considerations See individual agents.

Lactation See individual agents.

Breast-Feeding Considerations See individual agents.

Adverse Reactions The following events were reported in the A-HeFT Study using the combination isosorbide dinitrate/hydralazine product. See individual drug monographs for additional information.

>10%:

Cardiovascular: Chest pain (16%)

Central nervous system: Headache (50%), dizziness (32%)

Neuromuscular & skeletal: Weakness (14%)

1% to 10%:

Cardiovascular: Hypotension (8%), ventricular tachycardia (4%), palpitation (4%), tachycardia (2%)

Dermatologic: Alopecia (1%), angioedema (1%)

Endocrine & metabolic: Hyperglycemia (4%), hyperlipidemia (3%), hypercholesterolemia (1%)

Gastrointestinal: Nausea (10%), vomiting (4%)

Hepatic: Cholecystitis (1%)

Neuromuscular & skeletal: Paresthesia (4%), arthralgia (1%), myalgia (1%), tendon disorder (1%)

Respiratory: Bronchitis (8%), sinusitis (4%), rhinitis (4%)

Miscellaneous: Allergic reaction (1%), diaphoresis (1%)

Metabolism/Transport Effects Hydralazine: **Inhibits** CYP3A4 (weak); Isosorbide dinitrate: **Substrate** of CYP3A4 (major)

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: May enhance the vasodilatory effect of Vasodilators (Organic Nitrates). *Risk X: Avoid combination*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rosiglitazone: Vasodilators (Organic Nitrates) may enhance the adverse/toxic effect of Rosiglitazone. Specifically, a greater risk of myocardial ischemia was reported for users of this combination in a meta-analysis. Management: Consider alternatives to this combination when possible. Rosiglitazone prescribing information states that the combination of rosiglitazone and a nitrate is not recommended. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring Parameters

Blood pressure (standing and sitting/supine), heart rate, ANA titers

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Isosorbide dinitrate 20 mg and hydralazine 37.5 mg

Generic AvailableNo

Manufacturer

NitroMed, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (BiDil)

20-37.5 mg (30): $63.99

Mechanism of Action

Hydralazine: Direct vasodilation of arterioles (with little effect on veins) resulting in decreased systemic resistance

Isosorbide Dinitrate: Nitric oxide release causes stimulation of intracellular guanylyl cyclase leading to increased cyclic GMP. This results in vascular smooth muscle relaxation of both arterial and venous vasculature. Increased venous pooling decreases left ventricular pressure (preload) and arterial dilatation decreases arterial resistance (afterload). Therefore, this reduces cardiac oxygen demand by decreasing left ventricular pressure and systemic vascular resistance by dilating arteries. Additionally, coronary artery dilation improves collateral flow to ischemic regions.

Pharmacodynamics/Kinetics The following values are from administration of isosorbide dinitrate 40 mg and hydralazine 75 mg in healthy adults. Also see individual drug monographs.
Half-life elimination: Hydralazine: 4 hours; Isosorbide dinitrate: 2 hours

Time to peak, plasma: 1 hour (both agents)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness
Mental Health: Effects on Psychiatric TreatmentConcomitant use with MAO inhibitors may result in large decreases in blood pressure; monitor
Index TermsHydralazine and Isosorbide Dinitrate
References

Cohn JN, Archibald DG, Francis GS, et al, "Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure: Results of a Veterans Administration Cooperative Study," *N Engl J Med*, 1986, 314 (24):1547-52.[PubMed 3520315]

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Isosorbide Dinitrate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Isordil® may be confused with Inderal®, Isuprel®

International issues:

Nitrobide® [Japan] may be confused with Microzide® which is a brand name for hydrochlorothiazide in the U.S.

Pronunciation(eye soe SOR bide dye NYE trate)

U.S. Brand NamesDilatrate®-SR; Isochron™; Isordil®

Canadian Brand NamesApo-ISDN®; Cedocard®-SR; Coronex®; Novo-Sorbide; PMS-Isosorbide

Pharmacologic CategoryVasodilator

Use: Labeled IndicationsPrevention and treatment of angina pectoris; for congestive heart failure; to relieve pain, dysphagia, and spasm in esophageal spasm with GE reflux

Use: Unlabeled/InvestigationalEsophageal spastic disorders

Dosing: Adults

Angina:

Oral: 5-40 mg 4 times/day or 40 mg every 8-12 hours in sustained released dosage form

Sublingual: 2.5-5 mg every 5-10 minutes for maximum of 3 doses in 15-30 minutes; may also use prophylactically 15 minutes prior to activities which may provoke an attack

Congestive heart failure:

Initial dose: 20 mg 3-4 times/day

Target dose: 120-160 mg/day in divided doses; use in combination with hydralazine

Esophageal spastic disorders (unlabeled use):

Oral: 5-10 mg before meals

Sublingual: 2.5 mg after meals

Note: Tolerance to nitrate effects develops with chronic exposure. Dose escalation does not overcome this effect. Tolerance can only be overcome by short periods of nitrate absence from the body. Short periods (10-12 hours) of nitrate withdrawal help minimize tolerance. General recommendations are to take the last dose of short-acting agents no later than 7 PM; administer 2-3 times/day rather than 4 times/day. Sustained release preparations could be administered at times to allow a 15- to 17-hour interval between first and last daily dose. Example: Administer sustained release at 8 AM and 2 PM for a twice daily regimen.

Dosing: ElderlyElderly patients should be given lowest recommended adult daily doses initially and titrate upward.

Dosing: Renal ImpairmentHemodialysis: During hemodialysis, administer dose postdialysis or administer supplemental 10-20 mg dose. During peritoneal dialysis, supplemental dose is not necessary.

Administration: OralDo not administer around-the-clock; the first dose of nitrates should be administered in a physician's office to observe for maximal cardiovascular dynamic effects and adverse effects (orthostatic blood pressure drop, headache); when immediate release products are prescribed twice daily (recommend 7 AM and noon); for 3 times/day dosing (recommend 7 AM, noon, and 5 PM); when sustained-release products are indicated, suggest once a day in morning or via twice daily dosing at 8 AM and 2 PM. Do not crush sublingual tablets.

ContraindicationsHypersensitivity to isosorbide dinitrate or any component of the formulation; hypersensitivity to organic nitrates; concurrent use with phosphodiesterase-5 (PDE-5) inhibitors (sildenafil, tadalafil, or vardenafil); angle-closure glaucoma (intraocular pressure may be increased); head trauma or cerebral hemorrhage (increase intracranial pressure); severe anemia

Allergy Considerations

- Nitrate Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypotension/bradycardia: Severe hypotension can occur; paradoxical bradycardia and increased angina pectoris can accompany hypotension. Postural hypotension can also occur. Use with caution in volume depletion, hypotension, and right ventricular infarctions.

Disease-related concerns:

- Hypertrophic cardiomyopathy: Use with caution in patients with hypertrophic cardiomyopathy; nitrates may reduce preload, exacerbating obstruction and cause hypotension and/or worsening of heart failure.

Concurrent drug therapy issues:

- PDE-5 inhibitors: Avoid concurrent use with PDE-5 inhibitors (eg, sildenafil, tadalafil, vardenafil).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Tolerance: Appropriate dosing is needed to minimize tolerance development.

Geriatric ConsiderationsThe first dose of nitrates (sublingual, chewable, oral) should be taken in a physician's office to observe for maximal cardiovascular dynamic effects and adverse effects (eg, orthostatic blood pressure drop, headache). The use of nitrates for angina may occasionally promote reflux esophagitis. This may require dose adjustments or changing therapeutic agents to correct this adverse effect.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension (infrequent), postural hypotension, crescendo angina (uncommon), rebound hypertension (uncommon), pallor, cardiovascular collapse, tachycardia, shock, flushing, peripheral edema, syncope (uncommon)

Central nervous system: Headache (most common), lightheadedness (related to blood pressure changes), dizziness, restlessness

Gastrointestinal: Nausea, vomiting, bowel incontinence, xerostomia

Genitourinary: Urinary incontinence

Hematologic: Methemoglobinemia (rare, overdose)

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision

Miscellaneous: Cold sweat

The incidence of hypotension and adverse cardiovascular events may be increased when used in combination with sildenafil (Viagra®).

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)
Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: May enhance the vasodilatory effect of Vasodilators (Organic Nitrates). *Risk X: Avoid combination*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rosiglitazone: Vasodilators (Organic Nitrates) may enhance the adverse/toxic effect of Rosiglitazone. Specifically, a greater risk of myocardial ischemia was reported for users of this combination in a meta-analysis. Management: Consider alternatives to this combination when possible. Rosiglitazone prescribing information states that the combination of rosiglitazone and a nitrate is not recommended. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Caution with ethanol (may increase risk of hypotension).

Test InteractionsDecreased cholesterol (S)

Monitoring ParametersMonitor for orthostasis

Nursing: Physical Assessment/MonitoringAssess patient closely for cautious use (eg, volume depletion, hypotension, and right ventricular infarctions). Assess potential for interactions with other pharmacological agents patient may be taking (potential for decreased or increased levels/effect of Isosorbide, additive hypotension), Tolerance does develop to nitrates and appropriate dosing is needed to minimize tolerance (10-12 hours of withdrawal). Assess therapeutic effectiveness and adverse response (eg, hypotension, tolerance) at regular intervals during therapy. When discontinuing, reduce dosage gradually. Teach patient proper use, possible side effects/appropriate interventions (eg, importance of maintaining dosing schedule), and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed, at the same time each day with last dose in early evening. Do not chew or swallow sublingual tablets; allow them to dissolve under your tongue. Do not crush or chew sustained release capsules, swallow whole with 8 oz water. Do not change brands without consulting prescriber. Do not discontinue abruptly. Keep medication in original container, tightly closed. Avoid excessive alcohol; combination may cause severe hypotension. May cause postural hypotension (take medication while sitting down and use caution when rising from sitting or lying position or climbing stairs until response to drug is known); headache, dizziness, weakness, or blurred vision (use caution when driving or engaging in hazardous activities until response to drug is known); or nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). If chest pain occurs, seek emergency medical help at once. Report acute headache, rapid heartbeat, unusual restlessness or dizziness, muscular weakness, or blurring vision. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, sustained release (Dilatrate®-SR): 40 mg

Tablet: 5 mg, 10 mg, 20 mg, 30 mg

Isordil®: 5 mg, 10 mg [DSC], 20 mg [DSC], 30 mg [DSC], 40 mg

Tablet, extended release (Isochron™): 40 mg

Tablet, sublingual: 2.5 mg, 5 mg

Isordil®: 2.5 mg, 5 mg, 10 mg [DSC]

Generic AvailableYes: Tablet, sublingual tablet

Pricing: U.S. (www.drugstore.com)

Sublingual (Isosorbide Dinitrate)

2.5 mg (100): $39.16

5 mg (100): $18.99

Tablet, controlled release (Isosorbide Dinitrate CR)

40 mg (60): $43.45

Tablets (Isordil Titradose)

5 mg (100): $64.50

40 mg (60): $97.18

Tablets (Isosorbide Dinitrate)

5 mg (90): $14.00

10 mg (30): $12.99

20 mg (30): $12.99

Mechanism of ActionStimulation of intracellular cyclic-GMP results in vascular smooth muscle relaxation of both arterial and venous vasculature. Increased venous pooling decreases left ventricular pressure (preload) and arterial dilatation decreases arterial resistance (afterload). Therefore, this reduces cardiac oxygen demand by decreasing left ventricular pressure and systemic vascular resistance by dilating arteries. Additionally, coronary artery dilation improves collateral flow to ischemic regions; esophageal smooth muscle is relaxed via the same mechanism.

Pharmacodynamics/Kinetics

Onset of action: Sublingual tablet: 2-10 minutes; Chewable tablet: 3 minutes; Oral tablet: 45-60 minutes

Duration: Sublingual tablet: 1-2 hours; Chewable tablet: 0.5-2 hours; Oral tablet: 4-6 hours

Metabolism: Extensively hepatic to conjugated metabolites, including isosorbide 5-mononitrate (active) and 2-mononitrate (active)

Half-life elimination: Parent drug: 1-4 hours; Metabolite (5-mononitrate): 4 hours

Excretion: Urine and feces

Related Information

- Heart Failure (Systolic)
- Nitrates

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsNitrates improve the balance between myocardial oxygen supply and demand, primarily by decreasing oxygen demand. Nitrates decrease myocardial oxygen demand by reducing preload via dilation of peripheral veins. Nitrates improve myocardial oxygen supply by dilating epicardial coronary arteries and collateral vessels, leaving resistance vessels alone. Nitrates are unlikely to induce a coronary steal syndrome. Nitrates improve exercise tolerance in stable angina patients. An adequate nitroglycerin-free period must be provided with all nitrate products to prevent nitrate tolerance from developing. Caution should be observed if administering nitrates to individuals who are volume depleted or are experiencing a right ventricular infarction. Additionally, nitrates should not be given to an individual who has received a phosphodiesterase-5 (PDE-5) enzyme inhibitor within the past 24 hours.

Anesthesia and Critical Care Concerns/Other ConsiderationsNitrates used in right ventricular infarction may induce acute hypotension. Nitrate use in severe pericardial effusion may reduce cardiac filling pressure and precipitate cardiac tamponade. In the management of heart failure, the combination of isosorbide dinitrate and hydralazine confers beneficial effects on disease progression and cardiac outcomes.

Index TermsISD; ISDN

References

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International Brand NamesAerosonit (PL); Angibid SR (KP); Angitrit (TH); APO-ISDN (MY); Apo-ISDN (PL); Bideren (PH); Cardiosorbid (PL); Cardonit (HU, PL); Cardonit Prolongatum (PL); Cardopax (DK); Carsodil (KP); Carvasin (IT); Cedocard (AT, BE, GB, ID, IE, LU, NL, PH); Cedocard Retard (AT, GB, ID, NL, RU); Cordil (IL); Cordil 40 SR (IL); Cornilat (PL); Coronex (NZ); Diconpin (DE); Flindix (PT); Hartsorb (TH); Huma-Sorbide (HU); Imtack (IE); ISDN (DE); ISDN AL (HU); ISDN-Q (HU); ISDN-ratiopharm (LU); Iso Mack (CH, HU, PL); Iso Mack Retard (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE); Iso-Lacer (ES); Iso-Mack Retard (MY); Iso-Puren (DE); Isobar (PH); Isobide (TW); Isobinate (TH); Isocard (LU); Isocard Retard (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Isocord (BR, CO); Isoday 40 (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Isodin (AU); Isodinit (LU, PL); Isodinit Retard (PL); Isogen (AU); Isoket (AR, BG, CH, CL, CZ, DE, EE, HK, HU, ID, IE, IL, LU, PH, PL, RU, UY, VE); Isoket Retard (BG, CH, CZ, DE, GB, HK, IN, KP, MY, PL); Isoket Salbe (PL); Isoket Spray (KP); Isomack (AT, HU, LU); Isomack Spray (KP); Isomec Retard (KP); Isorbid (MX); Isorbide (PE); Isordil (AE, AR, AU, BH, BR, CY, EG, HN, ID, IE, IL, IN, IQ, IR, JO, KW, LB, LU, LY, NL, OM, PH, PK, PY, QA, SA, SY, TR, YE, ZA); Isorem (TH); Isotonax (LU); Langoran (FR); Langoran LP (FR); Maycor (CZ, DE); Maycor Retard (CZ, ES, PL); Nitrol R (JP); Nitrosid (FI); Nitrosid Retard (FI); Nitrosorbide (BF, BJ, CI, ET, GH, GM, GN, IT, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Nitrosorbon (DE, PH); Novisor (PH); Pensodril (GR); Risordan (FR, GR); Risordan LP (FR); Soni-Slo (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Sorbangil (NO, SE); Sorbid (TR); Sorbidilat (AT, CH); Sorbidilat Retard (AT); Sorbidin (AU); Sorbitrate (FR, IN, LU, MY); Sorbonit (HN, HU, PL); Sorbonit Prolongatum (PL); TD Spray Iso Mack (HU, LU); Tinidil (HR); Vascardin (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, ID, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Vasorbate (PL)

Isosorbide Mononitrate

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English

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Special Alerts

Isosorbide Mononitrate Tablets: Recall Due to Potential for Oversized Tablets - November 2008

Certain lots of generic isosorbide mononitrate tablets have been recalled due to possibility of oversized tablets. Oversized tablets may contain up to twice the amount of the active ingredient which may result in serious or life-threatening effects.

For more information, including lots involved, please refer to the FDA MedWatch alert: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Ethex

Medication Safety Issues

Sound-alike/look-alike issues:

Imdur® may be confused with Imuran®, Inderal LA®, K-Dur®

Monoket® may be confused with Monopril®

International issues:

Nitrex® [Italy] may be confused with Imitrex® which is a brand name for sumatriptan in the U.S.

Pronunciation(eye soe SOR bide mon oh NYE trate)

U.S. Brand NamesImdur®; Ismo®; Monoket®

Canadian Brand NamesApo-ISMN®; Imdur®; PMS-ISMN; Pro-ISMN

Pharmacologic CategoryVasodilator

Use: Labeled IndicationsLong-acting metabolite of the vasodilator isosorbide dinitrate used for the prophylactic treatment of angina pectoris

Dosing: Adults

Angina: Oral:

Regular tablet: 5-20 mg twice daily with the two doses given 7 hours apart (eg, 8 AM and 3 PM) to decrease tolerance development; then titrate to 10 mg twice daily in first 2-3 days.

Extended release tablet: Initial: 30-60 mg given in morning as a single dose; titrate upward as needed, giving at least 3 days between increases; maximum daily single dose: 240 mg

Note: Tolerance to nitrate effects develops with chronic exposure. Dose escalation does not overcome this effect. Tolerance can only be overcome by short periods of nitrate absence from the body. Short periods (10-12 hours) of nitrate withdrawal help minimize tolerance. Recommended dosage regimens incorporate this interval. General recommendations are to take the last dose of short-acting agents no later than 7 PM; administer 2 times/day rather than 4 times/day. Administer sustained release tablet once daily in the morning.

Dosing: ElderlyStart with lowest recommended adult dose.

Dosing: Renal ImpairmentNot necessary for elderly or patients with altered renal or hepatic function. Tolerance to nitrate effects develops with chronic exposure.

Administration: OralDo not administer around-the-clock; Monoket® and Ismo® should be scheduled twice daily with doses 7 hours apart (8 AM and 3 PM); Imdur® may be administered once daily. Extended release tablets should not be chewed or crushed. Should be swallowed with a half-glassful of fluid.

StorageTablets should be stored in a tight container at room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to isosorbide or any component of the formulation; hypersensitivity to organic nitrates; concurrent use with phosphodiesterase-5 (PDE-5) inhibitors (sildenafil, tadalafil, or vardenafil); angle-closure glaucoma (intraocular pressure may be increased); head trauma or cerebral hemorrhage (increase intracranial pressure); severe anemia

Allergy Considerations

- Nitrate Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypotension/bradycardia: Severe hypotension can occur; paradoxical bradycardia and increased angina pectoris can accompany hypotension. Orthostatic hypotension can also occur; ethanol can accentuate this. Use with caution in volume depletion, hypotension, and right ventricular infarctions.

Disease-related concerns:

- Hypertrophic cardiomyopathy: Use with caution in patients with hypertrophic cardiomyopathy; nitrates may reduce preload, exacerbating obstruction and cause hypotension and/or worsening of heart failure.

Concurrent drug therapy issues:

- PDE-5 inhibitors: Avoid concurrent use with PDE-5 inhibitors (eg, sildenafil, tadalafil, vardenafil).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Tolerance: Appropriate dosing is needed to minimize tolerance development.

Geriatric ConsiderationsThe first dose of nitrates (sublingual, chewable, oral) should be taken in a physician's office to observe for maximal cardiovascular dynamic effects and adverse effects (eg, orthostatic blood pressure drop, headache). The use of nitrates for angina may occasionally promote reflux esophagitis. This may require dose adjustments or changing therapeutic agents to correct this adverse effect.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown
Adverse Reactions

>10%: Central nervous system: Headache (19% to 38%)

1% to 10%:

Central nervous system: Dizziness (3% to 5%)

Gastrointestinal: Nausea/vomiting (2% to 4%)

<1% (Limited to important or life-threatening): Angina pectoris, arrhythmia, atrial fibrillation, hypotension, palpitation, postural hypotension, premature ventricular contractions, supraventricular tachycardia, syncope, pruritus, rash, abdominal pain, diarrhea, dyspepsia, tenesmus, tooth disorder, vomiting, dysuria, impotence, urinary frequency, asthenia, blurred vision, cold sweat, diplopia, edema, malaise, neck stiffness, rigors, agitation, anxiety, confusion, dyscoordination, hypoesthesia, nightmares, bronchitis, pneumonia, upper respiratory tract infection, arthralgia, methemoglobinemia (rare, overdose)

The incidence of hypotension and adverse cardiovascular events may be increased when used in combination with sildenafil (Viagra®).

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)
Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: May enhance the vasodilatory effect of Vasodilators (Organic Nitrates). *Risk X: Avoid combination*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rosiglitazone: Vasodilators (Organic Nitrates) may enhance the adverse/toxic effect of Rosiglitazone. Specifically, a greater risk of myocardial ischemia was reported for users of this combination in a meta-analysis. Management: Consider alternatives to this combination when possible. Rosiglitazone prescribing information states that the combination of rosiglitazone and a nitrate is not recommended. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Caution with ethanol (may increase risk of hypotension).

Monitoring ParametersMonitor for orthostasis, increased hypotension

Nursing: Physical Assessment/MonitoringAssess patient closely for cautious use (eg,volume depletion, hypotension, and right ventricular infarctions). Assess potential for interactions with other pharmacological agents patient may be taking (potential for decreased or increased levels/effect of Isosorbide, additive hypotension). Tolerance does develop to nitrates and appropriate dosing is needed to minimize tolerance (10-12 hours of withdrawal). Assess therapeutic effectiveness and adverse response (eg, hypotension, tolerance) at regular intervals during therapy. When discontinuing, reduce dosage gradually. Teach patient proper use, possible side effects/appropriate interventions (eg, importance of maintaining dosing schedule), and adverse symptoms to report.

Monitoring: Lab TestsOrthostasis

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed, at the same time each day with last dose in early evening. Do not chew or swallow sublingual tablets; allow them to dissolve under your tongue. Do not crush or chew sustained release capsules, swallow whole with $^{1}/_{2}$ glass of water. Do not change brands without consulting prescriber. Do not discontinue abruptly. Keep medication in original container, tightly closed. Avoid excessive alcohol; combination may cause severe hypotension. May cause postural hypotension (take medication while sitting down and use caution when rising from sitting or lying position or climbing stairs until response to drug is known); headache, dizziness, weakness, or blurred vision (use caution when driving or engaging in hazardous activities until response to drug is known); or nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). If chest pain occurs, seek emergency medical help at once. Report acute headache, rapid heartbeat, unusual restlessness or dizziness, muscular weakness, or blurring vision. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 10 mg, 20 mg

Ismo®: 20 mg

Monoket®: 10 mg, 20 mg

Tablet, extended release: 30 mg, 60 mg, 120 mg

Imdur®: 30 mg, 60 mg, 120 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Imdur)

120 mg (30): $80.12

Tablet, 24-hour (Isosorbide Mononitrate CR)

60 mg (30): $19.99

120 mg (30): $19.99

Tablets (Ismo)

20 mg (60): $101.99

Tablets (Isosorbide Mononitrate)

10 mg (60): $19.99

20 mg (60): $19.99

Tablets (Monoket)

10 mg (60): $76.92

20 mg (60): $109.99

Mechanism of ActionPrevailing mechanism of action for nitroglycerin (and other nitrates) is systemic venodilation, decreasing preload as measured by pulmonary capillary wedge pressure and left ventricular end diastolic volume and pressure; the average reduction in left ventricular end diastolic volume is 25% at rest, with a corresponding increase in ejection fractions of 50% to 60%. This effect improves congestive symptoms in heart failure and improves the myocardial perfusion gradient in patients with coronary artery disease.

Pharmacodynamics/Kinetics

Onset of action: 30-60 minutes

Absorption: Nearly complete and low intersubject variability in its pharmacokinetic parameters and plasma concentrations

Metabolism: Hepatic

Half-life elimination: Mononitrate: ~4 hours

Excretion: Urine and feces

Related Information

- Nitrates

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness; may rarely cause drowsiness, agitation, anxiety, confusion, nervousness, or insomnia

Mental Health: Effects on Psychiatric Treatment None reported

Cardiovascular Considerations Nitrates improve the balance between myocardial oxygen supply and demand, primarily by decreasing oxygen demand. Nitrates decrease myocardial oxygen demand by reducing preload via dilation of peripheral veins. Nitrates improve myocardial oxygen supply by dilating epicardial coronary arteries and collateral vessels, leaving resistance vessels alone. Nitrates are unlikely to induce a coronary steal syndrome. Nitrates improve exercise tolerance in stable angina patients. An adequate nitroglycerin-free period must be provided with all nitrate products to prevent nitrate tolerance from developing. Caution should be observed if administering nitrates to individuals who are volume depleted or are experiencing a right ventricular infarction. Additionally, nitrates should not be given to an individual who has received a phosphodiesterase-5 (PDE-5) enzyme inhibitor within the past 24 hours.

Anesthesia and Critical Care Concerns/Other Considerations Nitrates used in right ventricular infarction may induce acute hypotension. Nitrate use in severe pericardial effusion may reduce cardiac filling pressure and precipitate cardiac tamponade.

Index Terms ISMN

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International Brand Names Angistad (PH); Angitrate (ZA); Cardismo (ID); Cardisorb (HU); Cincordil (BR); Conpin (CR, DE, DO, GT, HN, NI, PA, SV); Conpin Retard (CR, DO, GT, HN, NI, PA, SV); Corangin (CH, NZ, PL); Corangin SR (TW); Coxime (TW); Coxine SR (TW); Duride (AU, MY, TW); Effox (PL); Elan (IT); Elantan (AT, CZ, DE, EC, GB, HK, IE, LU, MX, MY, PE, PH, PK, TH, VE); Elantan LA (MY); Elantan Long (CL, CZ, DE, HK, MY, PH); Elonton SR (KP); Etimonis (CL, PL); Imdex (HK, TH); Imdex CR (SG); Imdur (BF, BJ, CI, CY, DK, EE, ET, GB, GH, GM, GN, HK, IE, KE, KP, LR, LU, MA, ML, MR, MU, MW, NE, NG, PH, PT, SC, SD, SE, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Imdur 60 (MX, TW); Imdur Durules (AU); Imtrate (AU); Ismexin (FI); ISMN (AT, DE); ISMN AL (HU); ISMN Genericon (HR); ISMN Pharmavit (HU); ISMO (CN, DK, GB, IE, IT, NL, SE); Ismo (LU); Ismo 20 (BB, BM, BS, BZ, GY, IN, JM, MY, NZ, PR, SR, TT, TW, ZA); Ismo-20 (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Ismox (FI); Isobid (KP); Isolan (AR); Isomon (GR); Isomonat (AT, CZ); Isomonit (CL, DE, LU, PL); Isopen-20 (TH); Isoratio (PL); Isosorbide (CY, HR); Isospan SR (HU); Isotrate (PH); Isotril ER (KP); Izonit (PL); Izonit prolongatum (PL); Monicor (FR); Monis (CO); Monit 20 (IN); Mono Corax (DE); Mono Corax Retard (DE); Mono Mack (CY, HU, LU, MX, PL); Mono Mack Depot (PL); Mono-Mack (CZ); Mono-Sanorania (DE); Monobide (EC); Monocard (PL); Monoclair (DE); Monocord 40 (IL); Monocord 50 SR (IL); Monodilate (BG); Monodur Durules (AU); Monoket (IT, NO, PY, SE, UY); Monoket OD (NO, SE); Monoket Retard (AT, IT); Monolong (DE); Monolong 40 (IL); Monolong 60 (IL); Mononit (PL); Mononit 20 (IL); Mononit Retard (PL); Monopront (FI); Monosorbitrate (IN); Monosordil (GR); Monotrate (IN); Nitramin (GR); Olicard (HR, HU, PL); Olicard Retard (PL); Pentacard (BE, ID); Rangin (HU); Solotrate (TH); Sorbimon (HU); Uniket (ES); Vasotrate (IN, PH); Vasotrate-OD (SG)

Isosulfan Blue

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(eye soe SUL fan bloo)
U.S. Brand NamesLymphazurin™
Pharmacologic CategoryContrast Agent
Use: Labeled IndicationsAdjunct to lymphography for visualization of the lymphatic system; sentinel node identification
Dosing: AdultsLymphography: SubQ: Inject 0.5 mL into 3 interdigital spaces of each extremity per study; maximum: 3 mL (30 mg)
Administration: I.V. DetailpH: 6.8-7.4
Administration: OtherSubQ: Single patient use only; do not mix with local anesthetics (in same syringe)
StorageStore at room temperature. Avoid prolonged exposure to elevated temperatures.
Compatibility**Compatibility in syringe: Incompatible:** Local anesthetics (eg, lidocaine)
ContraindicationsHypersensitivity to isosulfan, triphenylmethane, or any component of the formulation
Warnings/Precautions

Concerns related to adverse events:

- Hypersensitivity reactions: Hypersensitivity reactions, including anaphylactic reactions (rare), may occur; appropriate equipment and emergency medications should be available during use. Competent personnel and emergency facilities should be available during and for at least 60 minutes after administration, since severe delayed reactions may occur. Risk likely higher risk in patients with history of asthma, allergies, drug reactions, including previous sensitivity to triphenylmethane dyes.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Methemoglobin: Methemoglobin levels via ABG may be falsely elevated; co-oximetry may be required to accurately assess.

- Oximetry interference: Peripheral oxygenation measurements may be falsely depressed due to discoloration of serum caused by isosulfan blue; (peak interference 30 minutes after administration; minimal effect by 4 hours postdose); direct determination of arterial blood gases (ABG) may be required.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproductive studies have not been conducted. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.
LactationExcretion in breast milk is unknown/use caution
Adverse Reactions

1% to 10%:

Dermatologic: Pruritus (2%; affecting hands, abdomen and neck)

Local: Administration site swelling (2%)

Miscellaneous: Hypersensitivity reactions (2%)

Postmarketing and/or case reports: Anaphylaxis; body fluid discoloration (urine, serum; may lead to falsely low oximetry readings); skin discoloration (including blue urticaria)

Drug InteractionsThere are no known significant interactions.
Test InteractionsPeripheral oxygenation measurements may be falsely depressed (peak interference 30 minutes after administration; minimal effect by 4 hours postdose). Methemoglobin levels via arterial blood gas analyzer may be falsely elevated.
Nursing: Physical Assessment/MonitoringEvaluate history of allergies, asthma, and previous drug reactions prior to administration. Hypersensitivity reactions can occur. Patient must be closely monitored during and for 1 hour following administration (severe reactions may be delayed). Emergency treatment for anaphylactic reactions should be available. For SubQ injection only.
Patient EducationHypersensitivity reactions can occur. Patient must be closely monitored during and for 1 hour following administration (severe reactions may be delayed). Emergency treatment for anaphylactic reactions should be available. For SubQ injection only; see Administration.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative-free]:

Lymphazurin™: 1% (5 mL)

Generic AvailableNo
ManufacturerUnited States Surgical, a division of Tyco Healthcare Group LP
Mechanism of ActionFollowing subcutaneous administration, isosulfan blue binds to interstitial proteins; these proteins/extracellular

fluids are drained by the regional lymphatic system, resulting in concentration of the dye within the lymph. Bright blue coloration imparted by the dye permits delineation of the vessels against the surrounding tissue.

Pharmacodynamics/Kinetics

Absorption: 34% absorbed in 30 minutes; 69% and 100% in 1 and 24 hours, respectively

Protein binding: ~50%

Excretion: Urine (10%; as unchanged drug); feces (~90%; via biliary excretion)

Pharmacotherapy Pearls May cause blue discoloration of urine for 24 hours.

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

References

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Isotretinoin

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Accutane® may be confused with Accolate®, Accupril®

Claravis™ may be confused with Cleviprex™

Isotretinoin may be confused with tretinoin

Pronunciation(eye soe TRET i noyn)

U.S. Brand NamesAccutane®; Amnesteem™; Claravis™; Sotret®

Canadian Brand NamesAccutane®; Clarus™; Isotrex®

Pharmacologic CategoryAcne Products; Retinoic Acid Derivative

Use: Labeled IndicationsTreatment of severe recalcitrant nodular acne unresponsive to conventional therapy

Use: Unlabeled/InvestigationalInvestigational: Treatment of children with metastatic neuroblastoma or leukemia that does not respond to conventional therapy

Dosing: AdultsSevere recalcitrant nodular acne: Oral: 0.5-1 mg/kg/day in 2 divided doses (dosages as low as 0.05 mg/kg/day have been reported to be beneficial) for 15-20 weeks or until the total cyst count decreases by 70%, whichever is sooner. Adults with very severe disease/scarring or primarily involves the trunk may require dosage adjustment up to 2 mg/kg/day. A second course of therapy may be initiated after a period of ≥2 months off therapy.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Neuroblastoma (investigational): Oral: Children: Maintenance therapy for neuroblastoma: 100-250 mg/m^2/day in 2 divided doses

Acne (severe recalcitrant nodular): Oral: Children 12-17 years: 0.5-1 mg/kg/day in 2 divided doses (dosages as low as 0.05 mg/kg/day have been reported to be beneficial) for 15-20 weeks or until the total cyst count decreases by 70%, whichever is sooner. A second course of therapy may be initiated after a period of ≥2 months off therapy.

Dosing: Hepatic ImpairmentEmpiric dose reductions are recommended in patient with hepatitis.

Calculations

- Body Surface Area: Pediatrics

Administration: OralAdminister with food. Capsules should be swallowed whole with a full glass of water. For patients unable to swallow, the Accutane® capsule may be pierced with a large-gauge needle and the contents placed in food (cottage cheese, ice cream, pudding, or oatmeal with butter) for immediate consumption (Accutane® data on file, Roche Pharmaceuticals). Use appropriate precautions for handling teratogenic capsule contents.

Dietary ConsiderationsShould be taken with food. Limit intake of vitamin A; avoid use of other vitamin A products. Some formulations may contain soybean oil.

StorageStore at room temperature. Protect from light.

Extemporaneously Prepared

Alternate method of administration of Accutane® capsules, based on unpublished data (not recommended by manufacturer): An oral suspension using the entire capsule may be prepared by adding one 10 mg capsule to 15 mL warm (~37°C or 97°F) 2% reduced-fat milk (or 20 mg capsule to 30 mL, etc, so that the concentration is maintained). Stir until capsule shell dissolves and capsule contents are dispersed throughout solution (approximately 10-15 minutes). Suspension stable for ≤4 hours at controlled room temperature or under refrigeration. Use appropriate precautions for handling teratogenic capsule contents.

Accutane® data on file, Roche Pharmaceuticals

RestrictionsAll patients (male and female), prescribers, wholesalers, and dispensing pharmacists must register and be active in the iPLEDGE™ risk management program, designed to eliminate fetal exposures to isotretinoin. This program covers all isotretinoin products (brand and generic). The iPLEDGE™ program requires that all patients meet qualification criteria and monthly program requirements. Registration, activation, and additional information are provided at www.ipledgeprogram.com or by calling 866-495-0654.

An FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to isotretinoin or any component of the formulation; sensitivity to parabens, vitamin A, or other retinoids; pregnancy

Allergy Considerations

- Retinoid Allergy

Warnings/Precautions

Boxed warnings:

- Teratogenic effects/iPLEDGE™ program: See "Other warnings/precautions" below.

Concerns related to adverse effects:

- Auditory impairment: Hearing impairment, which can continue after therapy is discontinued, may occur. Discontinue therapy if hearing impairment or tinnitus develops.
- Decreased bone mineral density: May decrease bone mineral density; osteoporosis, osteopenia, and bone fractures have been reported with use. Use caution in patients with a genetic predisposition to bone disorders (eg, osteoporosis, osteomalacia) and with disease states or concomitant medications that can induce bone disorders. Patients may be at risk when participating in activities with repetitive impact (such as sports).
- Growth effects: Skeletal hyperostosis and premature epiphyseal closure have also been reported with the use.
- Hepatic effects: Clinical hepatitis and elevated liver enzymes have been reported with use.
- Inflammatory bowel disease: Has been reported with use; discontinue treatment if abdominal pain, rectal bleeding, or severe diarrhea occurs.
- Ocular effects: Vision impairment, corneal opacities, and decreased night vision have also been reported with use.
- Pseudotumor cerebri: Retinoids have been associated with pseudotumor cerebri (benign intracranial hypertension), especially in children. Concurrent use of other drugs associated with this effect (eg, tetracyclines) may increase risk. Early signs and symptoms include papilledema, headache, nausea, vomiting and visual disturbances; discontinue if papilledema occurs.
- Psychiatric effects: May cause depression, psychosis, aggressive or violent behavior, and changes in mood. Rarely, suicidal thoughts and actions have been reported during isotretinoin usage. All patients should be observed closely for symptoms of depression or suicidal thoughts. Discontinuation of treatment alone may not be sufficient, further evaluation may be necessary. Use with extreme caution in patients with a history of psychiatric disorder.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; impaired glucose control has been reported.
- Hypertriglyceridemia: Use with caution in patients with hypertriglyceridemia; acute pancreatitis and fatal hemorrhagic pancreatitis (rare) have been reported; discontinue therapy if severe hypertriglyceridemia or symptoms of pancreatitis occurs.

Concurrent drug therapy issues:

- Tetracyclines: Pseudotumor cerebri (benign intracranial hypertension) has been reported with use of isotretinoin in combination with tetracyclines; concomitant use should be avoided.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Blood donation: Patients should be instructed not to donate blood during therapy and for 1 month following discontinuation of therapy due to risk of donated blood being given to a pregnant female.
- Experienced physician: This medication should only be prescribed by prescribers competent in treating severe recalcitrant nodular acne, are experienced in the use of systemic retinoids.
- Long-term use: Safety of long-term use is not established and is not recommended.
- Teratogenic effects/iPLEDGE™ program: **[U.S. Boxed Warning]: Because of the high likelihood of teratogenic effects, all patients (male and female), prescribers, wholesalers, and dispensing pharmacists must register and be active in the iPLEDGE™ risk management program; do not prescribe isotretinoin for women who are or who are likely to become pregnant while using the drug (see Additional Information or Pharmacotherapy Pearls for details).** Women of childbearing potential must be capable of complying with effective contraceptive measures. Patients must select and commit to two forms of contraception. Therapy is begun after two negative pregnancy tests; effective contraception must be used for at least 1 month before beginning therapy, during therapy, and for 1 month after discontinuation of therapy. Prescriptions should be written for no more than a 30-day supply, and pregnancy testing and counseling should be repeated monthly.

Pregnancy Risk FactorX

Pregnancy ConsiderationsMajor fetal abnormalities (both internal and external), spontaneous abortion, premature births and low IQ scores in surviving infants have been reported. [**U.S. Boxed Warning]: Because of the high likelihood of teratogenic effects, all patients (male and female), prescribers, wholesalers, and dispensing pharmacists must register and be active in the iPLEDGE™ risk management program; do not prescribe isotretinoin for women who are or who are likely to become pregnant while using the drug.** This medication is contraindicated in females of childbearing potential unless they are able to comply with the guidelines of the iPLEDGE™ pregnancy prevention program. Females of childbearing potential should not become pregnant during therapy or for 1 month following discontinuation of isotretinoin. Upon discontinuation of treatment, females of childbearing potential should have a pregnancy test after their last dose and again one month after their last dose. Two forms of contraception should be continued during this time. Any pregnancies should be reported to the iPLEDGE™ program (www.ipledgeprogram.com or 866-495-0654).

LactationExcretion in breast milk unknown/contraindicated

Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation, tachycardia, vascular thrombotic disease, stroke, chest pain, syncope, flushing

Central nervous system: Edema, fatigue, pseudotumor cerebri, dizziness, drowsiness, headache, insomnia, lethargy, malaise, nervousness, paresthesia, seizure, stroke, suicidal ideation, suicide attempts, suicide, depression, psychosis, aggressive or violent behavior, emotional instability

Dermatologic: Cutaneous allergic reactions, purpura, acne fulminans, alopecia, bruising, cheilitis, dry mouth, dry nose, dry skin, epistaxis, eruptive xanthomas, fragility of skin, hair abnormalities, hirsutism, hyperpigmentation, hypopigmentation, peeling of palms, peeling of soles, photoallergic reactions, photosensitizing reactions, pruritus, rash, dystrophy, paronychia, facial erythema, seborrhea, eczema, increased sunburn susceptibility, urticaria, abnormal wound healing

Endocrine & metabolic: Triglycerides increased (25%), abnormal menses, blood glucose increased, cholesterol increased, HDL decreased

Gastrointestinal: Weight loss, inflammatory bowel disease, regional ileitis, pancreatitis, bleeding and inflammation of the gums, colitis, nausea, nonspecific gastrointestinal symptoms

Genitourinary: Nonspecific urogenital findings

Hematologic: Anemia, thrombocytopenia, neutropenia, agranulocytosis, pyogenic granuloma

Hepatic: Hepatitis

Neuromuscular & skeletal: Skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure, arthralgia, CPK elevations, arthritis, tendonitis, bone abnormalities, weakness, back pain (29% in pediatric patients), rhabdomyolysis (rare), bone mineral density decreased

Ocular: Corneal opacities, decreased night vision, cataracts, color vision disorder, conjunctivitis, dry eyes, eyelid inflammation, keratitis, optic neuritis, photophobia, visual disturbances

Otic: Hearing impairment, tinnitus

Renal: Vasculitis, glomerulonephritis

Respiratory: Bronchospasms, respiratory infection, voice alteration, Wegener's granulomatosis

Miscellaneous: Allergic reactions, anaphylactic reactions, lymphadenopathy, infection, disseminated herpes simplex, diaphoresis

Drug Interactions

Oral Contraceptive (Estrogens): Retinoic Acid Derivatives may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): Retinoic Acid Derivatives may diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. *Risk C: Monitor therapy*

Tetracycline Derivatives: May enhance the adverse/toxic effect of Retinoic Acid Derivatives. The development of pseudotumor cerebri is of particular concern. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol (may increase triglyceride levels if taken in excess).

Food: Isotretinoin bioavailability increased if taken with food or milk.

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization and may decrease the effectiveness of oral contraceptives). Additional vitamin A supplements may lead to vitamin A toxicity (dry skin, irritation, arthralgias, myalgias, abdominal pain, hepatic changes); avoid use.

Monitoring ParametersCBC with differential and platelet count, baseline sedimentation rate, glucose, CPK; signs of depression, mood alteration, psychosis, and agression

Pregnancy test (for all female patients of childbearing potential): Two negative tests with a sensitivity of at least 25 mIU/mL prior to beginning therapy (the second performed at least 19 days after the first test and performed during the first 5 days of the menstrual period immediately preceding the start of therapy); monthly tests to rule out pregnancy prior to refilling prescription.

Lipids: Prior to treatment and at weekly or biweekly intervals until response to treatment is established. Test should not be performed <36 hours after consumption of ethanol.

Liver function tests: Prior to treatment and at weekly or biweekly intervals until response to treatment is established.

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and regularly with long-term use. Monitor patients with diabetes closely. Observe for depression or suicidal thoughts. Assess knowledge/teach patient appropriate use, possible side effects/interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Must have two negative pregnancy tests prior to beginning treatment. Do not give to women of childbearing age unless female is capable of complying with two contraceptive measures 1 month prior to therapy, during therapy, and 1 month following therapy.

Monitoring: Lab TestsCBC with differential and platelet count, baseline sedimentation rate, serum triglycerides, liver enzymes

Must have two negative pregnancy tests prior to beginning therapy (for all female patients of childbearing potential): Two negative tests with a sensitivity of at least 25 mIU/mL prior to beginning therapy (the second performed at least 19 days after the first test and performed during the first 5 days of the menstrual period immediately preceding the start of therapy); monthly tests to rule out pregnancy prior to refilling prescription.

Patient EducationA patient information/consent form must be signed before this medication is prescribed. Do not sign (and do not take this medication) if you do not understand all of the information on the form. Use exactly as directed; do not take more than recommended. Prescriptions will be written for a 1-month supply and must be filled within 7 days; they will not be honored if filled after that time or if they do not have the appropriate yellow qualification sticker attached. Capsule can be chewed and swallowed, swallowed, or opened with a large needle and contents sprinkled on applesauce or ice cream. Whole capsules should be swallowed with a full glass of liquid. Do not take any other vitamin A products, limit vitamin A intake, and increase exercise during therapy. Limit or avoid alcohol intake. Exacerbations of acne may occur during first weeks of therapy. You may experience headache, loss of night vision, muscle aches, lethargy, or visual disturbances (use caution when driving or engaging in tasks requiring alertness until response to drug is known); photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); dry mouth or nausea (small frequent meals, sucking hard candy, or chewing gum may may help); or dryness, redness, or itching of skin, eye irritation, or increased sensitivity to contact lenses (wear regular glasses). Report depression or suicidal thoughts. Discontinue therapy and report acute vision changes, ringing in the ears or changes in hearing, rectal bleeding, abdominal cramping, or unresolved diarrhea. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Do not get pregnant 1 month before, during, or for 1 month following therapy. This drug may cause severe fetal defects. Two forms of contraception and monthly tests to rule out pregnancy are required during therapy. It is important to note that any type of contraception may fail, it is the responsibility of the patient to be compliant with contraceptive therapy. Do not donate blood during or for 1 month following therapy. Consult prescriber if you suspect you might be pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Accutane®: 10 mg, 20 mg, 40 mg [contains soybean oil and parabens]

Amnesteem™: 10 mg, 20 mg, 40 mg [contains soybean oil]

Claravis™: 10 mg, 20 mg, 40 mg

Sotret®: 10 mg, 20 mg, 30 mg, 40 mg [contains soybean oil]

Generic AvailableYes

ManufacturerRoche Laboratories Inc

Mechanism of ActionReduces sebaceous gland size and reduces sebum production; regulates cell proliferation and differentiation

Pharmacodynamics/Kinetics

Distribution: Crosses placenta

Protein binding: 99% to 100%; primarily albumin

Metabolism: Hepatic via CYP2B6, 2C8, 2C9, 2D6, 3A4; forms metabolites; major metabolite: 4-oxo-isotretinoin (active)

Half-life elimination: Terminal: Parent drug: 21 hours; Metabolite: 21-24 hours

Time to peak, serum: 3-5 hours

Excretion: Urine and feces (equal amounts)

Pharmacotherapy PearlsAll patients (male and female), must be registered in the iPLEDGE™ risk management program. Females of childbearing potential must receive oral and written information reviewing the hazards of therapy and the effects that isotretinoin can have on a fetus. Therapy should not begin without two negative pregnancy tests at least 19 days apart. Two forms of contraception (a primary and secondary form as described in the iPLEDGE™ program materials) must be used simultaneously beginning 1 month prior to treatment, during treatment, and for 1 month after therapy is discontinued; limitations to their use must be explained. Prescriptions should be written for no more than a 30-day supply, and pregnancy testing and counseling should be repeated monthly. During therapy, pregnancy tests must be conducted by a CLIA-certified laboratory. Prescriptions must be filled and picked up from the pharmacy within 7 days of specimen collection for pregnancy test for women of childbearing potential. Prescriptions for males and females of non-childbearing potential must be filled and picked up within 30 days of prescribing.

Any cases of accidental pregnancy should be reported to the iPLEDGE™ program or FDA MedWatch. All patients (male and female) must read and sign the informed consent material provided in the pregnancy prevention program.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression, psychosis; may rarely cause suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors

Mental Health: Effects on Psychiatric TreatmentMay increase the clearance of carbamazepine, leading to decreased levels; monitor. Avoid dong quai and St John's wort (may cause photosensitization).

Index Terms13-*cis*-Retinoic Acid

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International Brand NamesA-Cnotren (TH); Accunetan (KP); Acnal SC (KP); Acnetrex (PH); Acnotin (HK, TH); Akinol (KP); Aknenormin (DE); Contracne (FR); Curacne Ge (FR); Curatane (IL); Isoface (DO, GT, MX, PA, PE, SV); Isotane (NZ, TH); Isotinon (KP); Isotren (KP); Isotret-Hexal (DE); Isotrex (AR, AU, BR, CR, DK, GB, IE, LU, MX, NI, PK, PL, TW); Isotrex Gel (AT, CO, DE, FR, HK, IL, IT, MY, NZ, PH, TH); Isotroin (IN); Neotrex (MX); Nimegen (MY, SG); Oratane (AU, MY, SG); Procuta Ge (FR); Reducar (HK); Roaccutan (AR, AT, CO, DK, EC, FI, HU, IT, MX, NO, PT, PY, UY, VE); Roaccutane (AE, AU, BB, BE, BG, BH, BM, BS, BZ, CH, CY, CZ, EE, EG, FR, GB, GH, GR, GY, HK, HR, IE, IL, IQ, IR, JM, JO, KE, KP, KW, LB, LU, LY, NL, OM, PH, PL, PR, QA, SA, SR, SY, TH, TT, TW, TZ, UG, YE, ZM); Roaccuttan (CO); Roacnetan (CN); Roacutan (BR, ES); Roacuttan (HN); Sotret (TH); Sotrexe (MX); Tai Er Si (CL); Tretin (KP)

Isoxsuprine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Vasodilan® may be confused with Vasocidin®

Pronunciation(eye SOKS syoo preen)
U.S. Brand NamesVasodilan® [DSC]
Pharmacologic CategoryVasodilator
Use: Labeled IndicationsTreatment of peripheral vascular diseases, such as arteriosclerosis obliterans and Raynaud's disease
Dosing: AdultsPeripheral vascular disease: Oral: 10-20 mg 3-4 times/day; start with lower dose in elderly due to potential hypotension
Dosing: ElderlyRefer to adult dosing.
ContraindicationsHypersensitivity to isoxsuprine or any component of the formulation; presence of arterial bleeding; do not administer immediately postpartum
Geriatric ConsiderationsVasodilators have been used to treat dementia upon the premise that dementia is secondary to a cerebral blood flow insufficiency. The hypothesis is that if blood flow could be increased, cognitive function would be increased. This hypothesis is no longer valid. The use of vasodilators for cognitive dysfunction is not recommended or proven by appropriate scientific study.
Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension, chest pain, tachycardia

Central nervous system: Dizziness

Dermatologic: Rash

Gastrointestinal: Nausea, vomiting

Neuromuscular & skeletal: Weakness

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 10 mg, 20 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Isoxsuprine HCl)

10 mg (90): $103.10

20 mg (90): $299.48

Tablets (Vasodilan)

20 mg (90): $59.99

Mechanism of ActionIn studies on normal human subjects, isoxsuprine increases muscle blood flow, but skin blood flow is usually unaffected. Rather than increasing muscle blood flow by beta-receptor stimulation, isoxsuprine probably has a direct action on vascular smooth muscle. The generally accepted mechanism of action of isoxsuprine on the uterus is beta-adrenergic stimulation. Isoxsuprine was shown to inhibit prostaglandin synthetase at high serum concentrations, with low concentrations there was an increase in the P-G synthesis.

Pharmacodynamics/Kinetics

Absorption: Nearly complete

Half-life elimination, serum: Mean: 1.25 hours

Time to peak, serum: ~1 hour

Dental Health: Effects on Dental TreatmentMay enhance effects of other vasodilators.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsSince isoxsuprine is frequently used in patients with significant peripheral vascular disease, these patients often have stenoses in the large coronary and cranial blood vessels. Hence, vasodilator effects which decrease perfusion pressure induce hypoperfusion magnified by the vascular stenotic lesions.

Index TermsIsoxsuprine Hydrochloride

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International Brand NamesAngiclan (ES); Dilator (PE); Dilum (PT); Dunaprine (PH); Duvadilan (AE, AR, AU, BE, BH, CY, DE, EG, ES, FR, ID, IE, IL, IN, IQ, IR, JO, KW, LB, LU, LY, NL, OM, PH, QA, SA, SY, VE, YE); Duvadilan Retard (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, NL, OM, QA, SA, SY, YE); Hystolan (ID); Inibina (BR); Isoprin (TW); Isoxilan (PH); Proterine (ID); Synzedrin (JP); Uterine (AR, PY); Vasoplex (DE); Vasosuprina (IT); Xuprin (AT)

Isradipine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

> DynaCirc® may be confused with Dynabac®, Dynacin®

Pronunciation(iz RA di peen)
U.S. Brand NamesDynaCirc® CR
Canadian Brand NamesDynaCirc®
Pharmacologic CategoryCalcium Channel Blocker
Use: Labeled IndicationsTreatment of hypertension
Use: Unlabeled/InvestigationalPediatric hypertension
Dosing: AdultsHypertension: Oral:

Capsule: 2.5 mg twice daily; antihypertensive response occurs in 2-3 hours; maximal response in 2-4 weeks; increase dose at 2- to 4-week intervals at 2.5-5 mg increments; usual dose range (JNC 7): 2.5-10 mg/day in 2 divided doses. **Note:** Most patients show no improvement with doses >10 mg/day except adverse reaction rate increases; therefore, maximal dose in older adults should be 10 mg/day.

Controlled release tablet: 5 mg once daily; antihypertensive response occurs in 2 hours. Adjust dose in increments of 5 mg at 2-4 week intervals. Maximum dose 20 mg/day; adverse events are increased at doses >10 mg/day.

Dosing: Elderly

Capsule: Refer to adult dosing.

Controlled release tablet: Initial dose: 5 mg once daily

Dosing: Pediatric

Hypertension (unlabeled use): Capsule: Oral: Initial: 0.15-0.2 mg/kg/day in 2-3 divided doses; maximum 0.8 mg/kg/day, up to 20 mg/day. **Note:** Controlled release formulation is administered once daily or in 2 divided doses.

Dosing: Renal Impairment
Cl_{cr} 30-80 mL/minute: Bioavailability increased by 45%

Cl_{cr} <10 mL/minute on hemodialysis: Bioavailability decreased by 20% to 50%

Capsule: Refer to adult dosing.

Controlled release tablet: Initial dose: 5 mg once daily

Dosing: Hepatic Impairment

Peak serum concentrations are increased by 32% and bioavailability is increased by 52%.

Capsule: Refer to adult dosing.

Controlled release tablet: Initial dose: 5 mg once daily

Administration: OralControlled release tablets should be swallowed whole; do not divide or chew
Dietary ConsiderationsMay be taken without regard to meals.
Extemporaneously PreparedA 1 mg/mL oral liquid was stable for 35 days when refrigerated when compounded as follows:

Dissolve the contents of ten 5 mg capsules in simple syrup, qs ad 50 mL

Shake well before using and keep in refrigerator

> MacDonald JL, Johnson CE, and Jacobson P, “Stability of Isradipine in Extemporaneously Compounded Oral Liquids,” *Am J Hosp Pharm*, 1994, 51(19):2409-11.

ContraindicationsHypersensitivity to isradipine or any component of the formulation; hypotension (<90 mm Hg systolic)
Allergy Considerations

- Calcium Channel Blocker, Dihydropyridine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Angina/MI: Increased angina and/or MI has occurred with initiation or dosage titration of calcium channel blockers.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition.

- Peripheral edema: The most common side effect is peripheral edema; occurs within 2-3 weeks of starting therapy.

- Reflex tachycardia: May occur with use.

Disease-related concerns:

- Heart failure (HF): Use with caution in patients with HF.

- Hepatic impairment: Use with caution in patients with hepatic impairment; may require lower starting dose.

- Idiopathic hypertrophic subaortic stenosis (IHSS): Use with caution in patients with IHSS.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Controlled release tablets: Use controlled release tablets with caution in patients with severe GI narrowing.

Other warnings/precautions:

- Titration: Adjust doses at 2- to 4-week intervals.

Geriatric ConsiderationsElderly may experience a greater hypotensive response. Constipation may be more of a problem in the elderly. Calcium channel blockers are no more effective in the elderly than other therapies; however, they do not cause significant CNS effects which is an advantage over some antihypertensive agents.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Israpidine crosses the human placenta. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsPercentages reported with capsule formulation.

>10%: Central nervous system: Headache (dose related 2% to 22%)

1% to 10%:

Cardiovascular: Edema (dose related 1% to 9%), palpitation (dose related 1% to 5%), flushing (dose related 1% to 5%), tachycardia (1% to 3%), chest pain (2% to 3%)

Central nervous system: Dizziness (2% to 8%), fatigue (dose related 1% to 9%)

Dermatologic: Rash (2%)

Gastrointestinal: Nausea (1% to 5%), abdominal discomfort (≤3%), vomiting (≤1%), diarrhea (≤3%)

Neuromuscular & skeletal: Weakness (≤1%)

Renal: Urinary frequency (1% to 3%)

Respiratory: Dyspnea (1% to 3%)

<1%: Angioedema, atrial fibrillation, back pain, constipation, cough, cramps of legs and feet, depression, drowsiness, drug fever, dry mouth, dysuria, epistaxis, gingival hyperplasia (incidence unknown), heart failure, hyperhidrosis, hypotension, impotence, insomnia, joint pain, leg pain, lethargy, leukopenia, libido decreased, liver function tests increased, MI, nasal congestion, nervousness, nocturia, numbness, paresthesia,pruritus, stroke, syncope, throat discomfort,transient ischemic attack, urticaria, ventricular fibrillation, visual disturbance, weight gain

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (weak)

Drug Interactions

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

CycloSPORINE: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Calcium Channel Blockers (Dihydropyridine) may decrease the serum concentration of QuiNIDine. *Risk C: Monitor therapy*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Administration with food delays absorption, but does not affect availability

Herb/Nutraceutical: St John's wort may decrease isradipine levels. Avoid dong quai if using for hypertension. Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), gotu kola, licorice (may worsen hypertension) Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure; renal, hepatic dysfunction

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, potential to increase or decrease levels/effects of isradipine). Assess therapeutic effectiveness (normotensive) and adverse response (eg, tachycardia, hypotension, edema, dyspnea) at regular intervals during therapy. When discontinuing, taper dose slowly. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as prescribed, with or without food. Do not stop abruptly without consulting prescriber. Do not crush extended release tablets. This medication does not replace other antihypertensive interventions; follow prescriber's instructions for diet and lifestyle changes. You may experience headache (if unrelieved, consult prescriber for approved analgesic); nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased dietary bulk and fluids may help); or dizziness, fatigue, confusion (use caution when driving or engaging in potentially hazardous tasks until response to drug is known). Report unrelieved headache, vomiting, or constipation; chest pain, palpitations, or rapid heartbeat; swelling of hands or feet or sudden weight gain (>5 lb/week); or unusual cramps in legs or feet. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 2.5 mg, 5 mg

Tablet, controlled release:

DynaCirc® CR: 5 mg, 10 mg

Generic AvailableYes: Capsule

Pricing: U.S. (www.drugstore.com)

Capsules (DynaCirc)

2.5 mg (60): $79.99

5 mg (60): $129.19

Capsules (Isradipine)

2.5 mg (60): $65.99

Tablet, 24-hour (DynaCirc CR)

5 mg (30): $79.99

10 mg (30): $159.73

Mechanism of ActionInhibits calcium ion from entering the “slow channels” or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary vascular smooth muscle and coronary vasodilation; increases myocardial oxygen delivery in patients with vasospastic angina

Pharmacodynamics/Kinetics

Onset of action: Immediate release: 2-3 hours

Duration: Immediate release: >12 hours

Absorption: 90% to 95%

Distribution: V_d: 3 L/kg

Protein binding: 95%

Metabolism: Hepatic; CYP3A4 substrate (major); extensive first-pass effect; forms metabolites (inactive)

Bioavailability: 15% to 24%

Half-life elimination: Terminal: 8 hours

Time to peak, serum: 1-1.5 hours

Excretion: Urine (60% to 65% as metabolites); feces (25% to 30%)

Related Information

- Calcium Channel Blockers

Dental Health: Effects on Dental TreatmentUnlike other calcium channel blockers, information is sparse as to whether isradipine causes gingival hyperplasia. Consultation with physician is suggested if hyperplasia is observed in patients taking isradipine.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsIsradipine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsIsradipine alone or in combination with other agents is effective in the management of hypertension.

In the treatment of unstable angina/non-ST-segment elevation MI, a nondihydropyridine calcium antagonist (diltiazem or verapamil) may be considered in patients with continuing or frequently recurring ischemia when beta-blockers are contraindicated (Class I). Oral long-acting calcium antagonists may also be considered in addition to beta-blockers and nitrates (Class IIa).

References

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Steele RM, Schuna AA, and Schreiber RT, “Calcium Antagonist-Induced Gingival Hyperplasia,” *Ann Intern Med*, 1994, 120(8):663-4.[PubMed 8135450]

International Brand NamesDynaCirc (AR); Dynacirc (BB, BM, BS, BZ, CO, GY, HK, JM, MX, MY, PH, PK, SR, TH, TT, TW, VE); Dynacirc SRO (CN, CO, KP, MX, MY, NZ, TH); Icaz LP (FR); Icaz SRO (PH); Lomir (AE, AT, BE, BF, BH, BJ, BR, CH, CI, CY, CZ, DE, EG, ES, ET, FI, GH, GM, GN, GR, HN, HU, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, NO, OM, PT, QA, SA, SC, SD, SE, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Lomir Retard (DK); Lomir SRO (AT, CH, CZ, FI, HN, IT, NL, NO, PL, PT, SE); Prescal (GB); Tenzipin (HR); Vascal (DE); Vaslan (ES)

Itraconazole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Sporanox® may be confused with Suprax®

Pronunciation(i tra KOE na zole)

U.S. Brand NamesSporanox®

Canadian Brand NamesSporanox®

Pharmacologic CategoryAntifungal Agent, Oral

Use: Labeled IndicationsTreatment of susceptible fungal infections in immunocompromised and immunocompetent patients including blastomycosis and histoplasmosis; indicated for aspergillosis, and onychomycosis of the toenail; treatment of onychomycosis of the fingernail without concomitant toenail infection via a pulse-type dosing regimen; has activity against *Aspergillus*, *Candida*, *Coccidioides*, *Cryptococcus*, *Sporothrix*, tinea unguium

Oral: Useful in superficial mycoses including dermatophytoses (eg, tinea capitis), pityriasis versicolor, sebopsoriasis, vaginal and chronic mucocutaneous candidiases; systemic mycoses including candidiasis, meningeal and disseminated cryptococcal infections, paracoccidioidomycosis, coccidioidomycoses; miscellaneous mycoses such as sporotrichosis, chromomycosis, leishmaniasis, fungal keratitis, alternariosis, zygomycosis

Oral solution: Treatment of oral and esophageal candidiasis

Intravenous solution: Indicated in the treatment of blastomycosis, histoplasmosis (nonmeningeal), and aspergillosis (in patients intolerant or refractory to amphotericin B therapy); empiric therapy of febrile neutropenic fever

Use: DentalTreatment of susceptible fungal infections in immunocompromised and immunocompetent patients including blastomycosis and histoplasmosis; has activity against *Aspergillus, Candida, Coccidioides, Cryptococcus, Sporothrix,* and chromomycosis. Useful in superficial mycoses including dermatophytoses (eg, tinea capitis), pityriasis versicolor, sebopsoriasis, vaginal and chronic mucocutaneous candidiases; systemic mycoses including candidiasis, meningeal and disseminated cryptococcal infections, paracoccidioidomycosis, coccidioidomycoses; miscellaneous mycoses such as sporotrichosis, chromomycosis, leishmaniasis, fungal keratitis, alternariosis, zygomycosis.

Dosing: Adults

Aspergillosis, invasive (salvage therapy): Duration of therapy should be a minimum of 6-12 weeks or throughout period of immunosuppression:

Oral: 200-400 mg/day; **Note:** 2008 IDSA guidelines recommend 600 mg/day for 3 days, followed by 400 mg/day

I.V.: 200 mg twice daily for 4 doses, followed by 200 mg daily

Appropriate use: Itraconazole should **NOT** be used for voriconazole-refractory aspergillosis since the same antifungal and/or resistance mechanism(s) may be shared by both agents. Itraconazole oral solution and capsule formulations are not bioequivalent or interchangeable. Due to variable bioavailability of oral preparations, therapeutic drug monitoring advisable.

Aspergillosis, allergic (ABPA, sinusitis): Oral: 200 mg/day; may be used in conjunction with corticosteroids

Blastomycosis/histoplasmosis:

Oral: 200 mg once daily, if no obvious improvement or there is evidence of progressive fungal disease, increase the dose in 100 mg increments to a maximum of 400 mg/day. Doses >200 mg/day are given in 2 divided doses. Length of therapy varies from 1 day to >6 months depending on the condition and mycological response.

I.V.: 200 mg twice daily for 4 doses, followed by 200 mg daily

Brain abscess: Cerebral phaeohyphomycosis (dematiaceous): Oral: 200 mg twice daily for at least 6 months with amphotericin

Candidiasis:

Oropharyngeal: Oral (solution): 200 mg once daily for 1-2 weeks; in patients unresponsive or refractory to fluconazole: 100 mg twice daily (clinical response expected in 1-2 weeks)

Esophageal: Oral (solution): 100-200 mg once daily for a minimum of 3 weeks; continue dosing for 2 weeks after resolution of symptoms

Coccidioides: Oral: 200 mg twice daily

Infections, Life-threatening:

Oral: Loading dose: 200 mg 3 times/day (600 mg/day) should be given for the first 3 days of therapy.

I.V.: 200 mg twice daily for 4 doses, followed by 200 mg/day

Meningitis: Oral:

Coccidioides: 400-800 mg/day

Cryptococcal: HIV positive (unlabeled use): Induction: 400 mg/day for 10-12 weeks; maintenance: 200 mg twice daily lifelong

Onychomycosis: Oral: 200 mg once daily for 12 consecutive weeks; alternative “pulse-dosing” may be considering for fingernail involvement only: 200 mg twice daily for 1 week; repeat 1-week course after 3 week off-time

Pneumonia:

Coccidioides: Mild to moderate: Oral, I.V.: 200 mg twice daily

Cryptococcal: Mild to moderate (unlabeled use): 200-400 mg/day for 6-12 months (lifelong for HIV positive)

Protothecal infection: 200 mg once daily for 2 months

Sporotrichosis: Oral:

Lymphocutaneous: 100-200 mg/day for 3-6 months

Osteoarticular and pulmonary: 200 mg twice daily for 1-2 years (may use amphotericin B initially for stabilization)

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricEfficacy and safety have not been established; a small number of patients 3-16 years of age have been treated with 100 mg/day for systemic fungal infections with no serious adverse effects reported. A dose of 5 mg/kg once daily was used in a pharmacokinetic study using the oral solution in patients 6 months-12 years; duration of study was 2 weeks.
Dosing: Renal ImpairmentNot necessary. Itraconazole injection is not recommended in patients with a creatinine clearance <30 mL/minute; hydroxypropyl-β-cyclodextrin (the excipient) is eliminated primarily by the kidneys.

Not dialyzable

Dosing: Hepatic ImpairmentMay be necessary, but specific guidelines are not available. Risk-to-benefit evaluation should be undertaken in patients who develop liver function abnormalities during treatment.
Administration: I.V.Infuse 60 mL of the dilute solution (3.33 mg/mL = 200 mg itraconazole, pH ~4.8) over 60 minutes; flush with 15-20 mL of 0.9% sodium chloride over 30 seconds to 15 minutes
Administration: OralDoses >200 mg/day are given in 2 divided doses; do not administer with antacids. Capsule and oral solution formulations are not bioequivalent and thus are not interchangeable. Capsule absorption is best if taken with food, therefore, it is best to administer itraconazole after meals; solution should be taken on an empty stomach. When treating oropharyngeal and esophageal candidiasis, solution should be swished vigorously in mouth, then swallowed.
Dietary Considerations

Capsule: Administer with food.

Solution: Take without food, if possible.

Storage

Capsule: Store at room temperature, 15°C to 25°C (59°F to 77°F). Protect from light and moisture.

Oral solution: Store at ≤25°C (77°F); do not freeze.

Solution for injection: Store at ≤25°C (77°F); do not freeze. Protect from light. Stable for 48 hours at room temperature or under refrigeration.

ReconstitutionDilute solution for injection with 0.9% sodium chloride. A precise mixing ratio is required to maintain stability (3.33:1) and avoid precipitate formation. Add 25 mL (1 ampul) to 50 mL 0.9% sodium chloride. Mix and withdraw 15 mL of solution before infusing.
CompatibilityStable in NS.
ContraindicationsHypersensitivity to itraconazole, any component of the formulation, or to other azoles; concurrent administration with cisapride, dofetilide, ergot derivatives, levomethadyl, lovastatin, midazolam, pimozide, quinidine, simvastatin, or triazolam; treatment of onychomycosis in patients with evidence of left ventricular dysfunction, CHF, or a history of CHF
Allergy Considerations

- Azole Antifungal Allergy

Warnings/Precautions

Boxed warnings:

• High potential for interactions: See “Concurrent drug therapy issues” below.

• Onychomycosis: See “Disease-related concerns” below.

Concerns related to adverse effects:

• Heart failure (HF): Discontinue if signs or symptoms of HF occurs during treatment.

• Neuropathy: Discontinue if signs or symptoms of neuropathy occurs during treatment.

Disease-related concerns:

- Cystic fibrosis: Large differences in itraconazole pharmacokinetic parameters have been observed in cystic fibrosis patients receiving the solution; if a patient with cystic fibrosis does not respond to therapy, alternate therapies should be considered.

- Hepatic impairment: Serious (and rarely fatal) hepatic toxicity (eg, hepatitis, cholestasis, fulminant failure) has been observed with azole therapy. Use with caution in patients with pre-existing hepatic impairment; monitor liver function closely and dosage adjustment may be warranted. Not recommended for use in patients with active liver disease, elevated liver enzymes, or prior hepatotoxic reactions to other drugs.

- Onychomycosis: **[U.S. Boxed Warning]: Not recommended for treatment of onychomycosis in patients with left ventricular dysfunction or a history of CHF.**

Concurrent drug therapy issues:

- High potential for interactions: **[U.S. Boxed Warning]: Rare cases of serious cardiovascular adverse events (including death), ventricular tachycardia, and torsade de pointes have been observed due to increased cisapride, pimozide, quinidine, dofetilide or levomethadyl concentrations induced by itraconazole; concurrent use contraindicated.**

Dosage form specific issues:

- Injectable: Intravenous formulation should be used with caution in renal impairment; consider conversion to oral therapy if renal dysfunction/toxicity is noted.

- Oral solution: Initiation of treatment with oral solution is not recommended in patients at immediate risk for systemic candidiasis (eg, patients with severe neutropenia).

- Product interchangeability: Due to differences in bioavailability, oral capsules and oral solution **cannot be used interchangeably.**

Geriatric ConsiderationsNo specific data for the elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsShould not be used to treat onychomycosis during pregnancy. Effective contraception should be used during treatment and for 2 months following treatment. Congenital abnormalities have been reported during postmarketing surveillance, but a causal relationship has not been established.
LactationEnters breast milk/not recommended
Adverse ReactionsListed incidences are for higher doses appropriate for systemic fungal infection.

>10%: Gastrointestinal: Nausea (11%)

1% to 10%:

Cardiovascular: Edema (4%), hypertension (3%)

Central nervous system: Headache (4%), fatigue (2% to 3%), malaise (1%), fever (3%), dizziness (2%)

Dermatologic: Rash (9%), pruritus (3%)

Endocrine & metabolic: Decreased libido (1%), hypertriglyceridemia, hypokalemia (2%)

Gastrointestinal: Abdominal pain (2%), anorexia (1%), vomiting (5%), diarrhea (3%)

Hepatic: Abnormal LFTs (3%), hepatitis

Renal: Albuminuria (1%)

<1%: Adrenal suppression, constipation, gastritis, gynecomastia, impotence, somnolence, tinnitus

Postmarketing and/or case reports: Allergic reactions (urticaria, angioedema); alopecia, anaphylactoid reactions, anaphylaxis, arrhythmia, CHF, hepatic failure, menstrual disorders, neutropenia, peripheral neuropathy, photosensitivity, pulmonary edema, Stevens-Johnson syndrome

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (strong)
Drug Interactions

Alfentanil: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amphotericin B: Antifungal Agents (Azole Derivatives, Systemic) may diminish the therapeutic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Aprepitant: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Aprepitant. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Quazepam. *Risk D: Consider therapy modification*

Bosentan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Bosentan. *Risk C: Monitor therapy*

BusPIRone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Busulfan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Busulfan. *Risk C: Monitor therapy*

Calcium Channel Blockers: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CarBAMazepine. *Risk C: Monitor therapy*

Cardiac Glycosides: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cilostazol: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Cisapride: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Cisapride. *Risk X: Avoid combination*

Conivaptan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Conivaptan. *Risk X: Avoid combination*

Corticosteroids (Orally Inhaled): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Didanosine: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). Enteric coated didanosine capsules are not expected to affect these antifungals. *Risk D: Consider therapy modification*

Docetaxel: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Docetaxel. *Risk D: Consider therapy modification*

Dofetilide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Dofetilide. *Risk X: Avoid combination*

Efavirenz: May decrease the serum concentration of Itraconazole. *Risk D: Consider therapy modification*

Eletriptan: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Eletriptan. *Risk D: Consider therapy modification*

Eplerenone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eplerenone. *Risk D: Consider therapy modification*

Erlotinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Erlotinib. *Risk C: Monitor therapy*

Eszopiclone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eszopiclone. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fosaprepitant: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Fosaprepitant. Specifically, concentrations of aprepitant are likely to be increased. *Risk C: Monitor therapy*

Gefitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Gefitinib. *Risk C: Monitor therapy*

Grapefruit Juice: May increase the metabolism of Antifungal Agents (Azole Derivatives, Systemic). This specifically applies to oral antifungal administration. *Risk D: Consider therapy modification*

H2-Antagonists: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Imatinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Imatinib. *Risk C: Monitor therapy*

Irinotecan: Antifungal Agents (Azole Derivatives, Systemic) may enhance the adverse/toxic effect of Irinotecan. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Losartan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Losartan. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Antifungal Agents (Azole Derivatives, Systemic). Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Macrolide Antibiotics. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Methadone. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Paliperidone: Itraconazole may decrease the metabolism of Paliperidone. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Phenytoin. Phenytoin may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Phosphodiesterase 5 Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Protease Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May decrease the serum concentration of Itraconazole. *Risk D: Consider therapy modification*

QuiNIDine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of QuiNIDine. Management: Itraconazole, voriconazole, and posaconazole are specifically contraindicated with quinidine. Use of quinidine with any azole antifungal may require quinidine dose adjustment and should be done with caution and close monitoring. *Risk X: Avoid combination*

Ramelteon: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ranolazine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Repaglinide. Management: Concurrent use of an azole antifungal with both repaglinide and gemfibrozil should be avoided. *Risk C: Monitor therapy*

Rifamycin Derivatives: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Rifamycin Derivatives. Only rifabutin appears to be affected. Rifamycin Derivatives may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Sirolimus. Management: Sirolimus dose reductions of up to 50-90% may be necessary when starting an azole antifungal. Use of sirolimus with the azole antifungals voriconazole and posaconazole is contraindicated. *Risk D: Consider therapy modification*

Solifenacin: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Solifenacin. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Sucralfate: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk C: Monitor therapy*

Sunitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Tacrolimus: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Temsirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Temsirolimus. Concentrations of the active metabolite, sirolimus, are likely to be increased more substantially than those of the parent temsirolimus. *Risk D: Consider therapy modification*

Tolterodine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Tolterodine. This is likely only of concern in CYP2D6-deficient patients (ie, "poor metabolizers") *Risk D: Consider therapy modification*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

VinBLAStine: Itraconazole may increase the serum concentration of VinBLAStine. *Risk C: Monitor therapy*

VinCRIStine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of VinCRIStine. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Itraconazole may increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ziprasidone. *Risk C: Monitor therapy*

Zolpidem: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Zolpidem. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food:

Capsules: Enhanced by food and possibly by gastric acidity. Cola drinks have been shown to increase the absorption of the capsules in patients with achlorhydria or those taking H_2-receptor antagonists or other gastric acid suppressors. Avoid grapefruit juice.

Solution: Decreased by food, time to peak concentration prolonged by food.

Herb/Nutraceutical: St John's wort may decrease itraconazole levels.

Monitoring ParametersLiver function in patients with pre-existing hepatic dysfunction, and in all patients being treated for longer than 1 month; serum (trough) concentrations particularly for oral therapy (due to erratic bioavailability with capsule formulation)

Reference RangeTrough serum concentrations may be performed to assure therapeutic levels, especially in the face of oral therapy. Trough concentration of itraconzole plus the metabolite hydroxyitraconazole should be at least 0.5 mcg/mL.

Nursing: Physical Assessment/MonitoringEvaluate hepatic status carefully prior to treatment. Assess potential for interactions with other pharmacological or herbal products patient may be taking (eg, anything that reduces gastric acidity may result in treatment failure of itraconazole). See Administration for capsule, oral solution, and infusion specifics (eg, oral capsules and oral solution cannot be used interchangeably). Assess results of laboratory tests (LFTs), therapeutic effectiveness (resolution of fungal infection), and adverse reactions at regular intervals during therapy. Teach patient proper use (eg, necessity of taking full course of therapy), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsLiver function in patients with pre-existing hepatic dysfunction, and in all patients being treated for longer than 1 monthmonth; serum (trough) concentrations particularly for oral therapy (due to erratic bioavailability with capsule formulation)

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Use exactly as directed. Take full course of medication even if infections appears to be resolved, do not discontinue without consulting prescriber (treatment for some fungal infections may take several weeks or months). Take capsule immediately after meals; take solution on empty stomach, 1 hour before or 2 hours after meals. Do not take antacids of other medications within 1 hour before or 2 hours after itraconazole. Avoid grapefruit juice while taking this medication. Observe good hygiene measures to prevent reinfection. If you have diabetes, test serum glucose regularly (may affect response to oral hypoglycemics). Frequent blood tests may be required with prolonged therapy. May cause dizziness or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea, vomiting, or anorexia (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Stop therapy and report immediately any signs and symptoms that may suggest liver dysfunction (eg, unusual fatigue, anorexia, nausea and/or vomiting, jaundice [yellowing of skin or sclera], dark urine, or pale stool) so that the appropriate laboratory testing can be done. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber about appropriate contraceptive use, efficacy of oral contraceptives may be reduced. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule: 100 mg

Sporanox®: 100 mg

Injection, solution:

Sporanox®: 10 mg/mL (25 mL) [packaged in a kit containing sodium chloride 0.9% (50 mL); filtered infusion set (1)] [DSC]

Solution, oral:

Sporanox®: 100 mg/10 mL (150 mL) [cherry flavor]

Generic AvailableYes: Capsule

ManufacturerJanssen Pharmaceutica Products, LP

Pricing: U.S. (www.drugstore.com)

Capsules (Itraconazole)

100 mg (28): $239.97

100 mg (30): $239.99

Capsules (Sporanox)

100 mg (30): $353.13

Capsules (Sporanox Pulsepak)

100 mg (28): $330.88

Solution (Sporanox)

10 mg/mL (150): $173.85

Mechanism of ActionInterferes with cytochrome P450 activity, decreasing ergosterol synthesis (principal sterol in fungal cell membrane) and inhibiting cell membrane formation

Pharmacodynamics/Kinetics

Absorption: Requires gastric acidity; capsule better absorbed with food, solution better absorbed on empty stomach

Distribution: V_d (average): 796 ± 185 L or 10 L/kg; highly lipophilic and tissue concentrations are higher than plasma concentrations. The highest concentrations: adipose, omentum, endometrium, cervical and vaginal mucus, and skin/nails. Aqueous fluids (eg, CSF and urine) contain negligible amounts.

Protein binding, plasma: 99.9%; metabolite hydroxy-itraconazole: 99.5%

Metabolism: Extensively hepatic via CYP3A4 into >30 metabolites including hydroxy-itraconazole (major metabolite); appears to have *in vitro* antifungal activity. Main metabolic pathway is oxidation; may undergo saturation metabolism with multiple dosing.

Bioavailability: Variable, ~55% (oral solution) in 1 small study; **Note:** Oral solution has a higher degree of bioavailability (149% ± 68%) relative to oral capsules; should not be interchanged

Half-life elimination: Oral: After single 200 mg dose: 21 ± 5 hours; 64 hours at steady-state; I.V.: steady-state: 35 hours; steady-state concentrations are achieved in 13 days with multiple administration of itraconazole 100-400 mg/day.

Excretion: Feces (~3% to 18%); urine (~0.03% as parent drug, 40% as metabolites)

Related Information

- Antifungal Agents
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsDue to potential toxicity, the manufacturer recommends confirmation of diagnosis testing of nail specimens prior to treatment of onychomycosis.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentContraindicated with oral midazolam, pimozide, and triazolam

Cardiovascular ConsiderationsItraconazole has negative inotropic properties and cases of new heart failure or exacerbation of congestive heart failure have been reported. Itraconazole is contraindicated for the treatment of onychomycosis in patients with heart failure. The benefit:risk for therapy in the treatment of other types of fungal infections should be carefully considered in each patient, particularly those with congestive heart failure and in heart transplant recipients. If indicated after cardiac, renal, or liver transplantation, itraconazole can increase cyclosporine levels by up to 50% at high doses. It also increases serum levels of lovastatin by up to 20-fold, as well as other HMG-CoA reductase inhibitors, by inhibiting CYP3A4. This is important since many post-transplantation patients are also hyperlipidemic and on HMG-CoA reductase inhibitors. Itraconazole may also increase levels of dofetilide and quinidine. The simultaneous administration of these medications is contraindicated because of increased risk of cardiotoxicity.

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International Brand NamesAranox (HK); Canadiol (ES); Candistat (IN); Canditral (MY, PE, TH); Forcanox (ID); Fungitrazol (ID); Furolnok (ID); Hitrazole (KP); Icomein (TW); Icona (TH); Inox (HK, MY); Irta (KP); Isox (DO, GT, HN, MX, PA, SV); Itra (TH); Itracon (HK, KP, SG, TH); Itranax (MX); Itranol (IL); Itzol (ID); Konitra (KP); Norspor (TH); Nufatrac (ID); Onikonazole (KP); Orungal (BG, EE, HN, HR, HU, PL); Quali-Itrazole (HK); Sempera (DE); Sinozol (MX); Spazol (TH); Sporacid (ID); Sporal (TH); Sporanox (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CY, CZ, DE, DK, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PH, PK, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Sporanox IV (HK, PH); Spornar (TH); Spyrocon (ID); Trachon (ID); Tracor (ID); Trisporal (NL); Unitrac (SG)

IVAC

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's
Regimen UseLymphoma, non-Hodgkin's
Regimen

Ifosfamide: I.V.: 1500 mg/m^2/day days 1 to 5

[total dose/cycle = 7500 mg/m^2]

Etoposide: I.V.: 60 mg/m^2/day days 1 to 5

[total dose/cycle = 300 mg/m^2]

Cytarabine: I.V.: 2 g/m^2 every 12 hours days 1 and 2

[total dose/cycle = 8 g/m^2]

Mesna: I.V.: 360 mg/m^2 every 3 hours days 1 to 5

[total dose/cycle = 14,400 mg/m^2]

Methotrexate: I.T.: 12 mg day 5

Sargramostim: SubQ: 7.5 mcg/kg day 7 until ANC >1000 cells/mm^3

Repeat when ANC >1000 cells/mm^3

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Ivermectin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(eye ver MEK tin)
U.S. Brand NamesStromectol®
Pharmacologic CategoryAnthelmintic
Use: Labeled IndicationsTreatment of the following infections: Strongyloidiasis of the intestinal tract due to the nematode parasite *Strongyloides stercoralis*. Onchocerciasis due to the nematode parasite *Onchocerca volvulus*. Ivermectin is only active against the immature form of *Onchocerca volvulus*, and the intestinal forms of *Strongyloides stercoralis*.
Use: Unlabeled/InvestigationalHas been used for other parasitic infections including *Ascaris lumbricoides*, Bancroftian filariasis, *Brugia malayi*, scabies, *Enterobius vermicularis*, *Mansonella ozzardi*, *Gnathostomia spingerum*, *Mansonella ozzardi*, *Mansonella streptocera*, pediculosis pubis, *Trichuris trichiura*.
Dosing: Adults

Onchocerciasis: Oral: 150 mcg/kg as a single dose; retreatment may be required every 3-12 months until the adult worms die

Weight-based dosage to provide ~150 mcg/kg:

15-25 kg: 3 mg

26-44 kg: 6 mg

45-64 kg: 9 mg

65-84 kg: 12 mg

≥85 kg: 150 mcg/kg

Strongyloidiasis: Oral: 200 mcg/kg as a single dose; perform follow-up stool examinations; CDC recommendations: 200 mcg/kg/day for 2 days

Weight-based dosage to provide ~200 mcg/kg:

15-24 kg: 3 mg

25-35 kg: 6 mg

36-50 kg: 9 mg

51-65 kg: 12 mg

66-79 kg: 15 mg

≥80 kg: 200 mcg/kg

Ascariasis due to*Ascaris lumbricoides*(unlabeled use): Oral: CDC recommendation: 150-200 mcg/kg as a single dose

Filariasis due to*Mansonella ozzardi*(unlabeled use): Oral: CDC recommendation: 200 mcg/kg as a single dose

Filariasis due to*Mansonella streptocera*(unlabeled use): Oral: CDC recommendation: 150 mcg/kg as a single dose

Gnathostomiasis due to*Gnathostomia spingerum*(unlabeled use): Oral: CDC recommendation: 200 mcg/kg/day for 2 days

Scabies due to *Sarcoptes scabiei*(unlabeled use): Oral: CDC recommendation: 200 mcg/kg as a single dose; repeat in 2 weeks

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricParasitic infections: Oral: Children ≥15 kg: Refer to adult dosing.
Administration: OralAdminister on an empty stomach with water.
Dietary ConsiderationsTake on an empty stomach with water.
StorageStore at <30°C (86°F).
ContraindicationsHypersensitivity to ivermectin or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Cutaneous/systemic reactions: Data have shown that antihelmintic drugs like ivermectin may cause cutaneous and/or systemic reactions (Mazzoti reaction) of varying severity including ophthalmological reactions in patients with onchocerciasis. These reactions are probably due to allergic and inflammatory responses to the death of microfilariae. Patients with hyper-reactive onchodermatitis may be more likely than others to experience severe adverse reactions, especially edema and aggravation of the onchodermatitis.

Disease-related concerns:

- Loiasis: Pretreatment assessment for *Loa loa* infection is recommended in any patient with significant exposure to endemic areas (West and Central Africa); serious and/or fatal encephalopathy has been reported (rarely) during treatment in patients with loiasis.

Special populations:

- Immunocompromised patients: Repeated treatment may be required in immunocompromised patients (eg, HIV); control of extraintestinal strongyloidiasis may necessitate suppressive (once monthly) therapy.

- Pediatrics: Safety and efficacy have not be established in children <15 kg.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects have been observed in animal studies. Safety has not been established in pregnant women. The manufacturer and the Centers for Disease Control and Prevention (CDC) do not recommend use in pregnant women.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsSafety and efficacy for use in children <15 kg have not been established in the U.S.; therefore, ivermectin use is not recommended during lactation.

Adverse Reactions

>10%: Miscellaneous: Mazzotti-type reaction (with onchocerciasis): Pruritus (28%), fever (23%), skin involvement (including edema/urticarial rash [23%]), lymph node tenderness (1% to 14%), lymph node enlargement (3% to 13%), arthralgia/synovitis (9%)

1% to 10%:

Cardiovascular: Tachycardia (4%), peripheral edema (3%), facial edema (1%), orthostatic hypotension (1%)

Central nervous system: Dizziness (3%)

Dermatologic: Pruritus (3%)

Gastrointestinal: Diarrhea (2%), nausea (2%)

Hematologic: Eosinophilia (3%), leukocytes decreased (3%), hemoglobin increased (1%)

Hepatic: ALT increased (2%), AST increased (2%)

Ocular: Limbitis (4% to 6%), punctuate opacity (1% to 2%)

<1%, postmarketing, and/or case reports: Abdominal pain, anemia, anorexia, anterior uveitis, asthma exacerbation, back pain, bilirubin increased, chest discomfort, chorioretinitis, choroiditis, coma, confusion, conjunctival hemorrhage, conjunctivitis, constipation, dyspnea, encephalopathy (rare; associated with loiasis), eyelid edema, eye sensation abnormal, fatigue, fecal incontinence, headache, hypotension, INR increased, keratitis, lethargy, leukopenia, mental status changes, myalgia, neck pain, rash, red eye, seizure, somnolence, standing/walking difficulty, Stevens-Johnson syndrome, stupor, toxic epidermal necrolysis, tremor, urinary incontinence, urticaria, vertigo, vision loss (transient), weakness, vomiting

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)

Drug Interactions

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Ivermectin may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Bioavailability is increased 2.5-fold when administered following a high-fat meal.

Monitoring ParametersSkin and eye microfilarial counts, periodic ophthalmologic exams; follow up stool examinations

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet [scored]:

Stromectol®: 3 mg

Generic AvailableNo

ManufacturerMerck & Co

Pricing: U.S. (www.drugstore.com)

Tablets (Stromectol)

3 mg (20): $103.99

Mechanism of ActionIvermectin is a semisynthetic antihelminthic agent; it binds selectively and with strong affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to increased permeability of cell membranes to chloride ions then hyperpolarization of the nerve or muscle cell, and death of the parasite.

Pharmacodynamics/Kinetics

Onset of action: Peak effect in treatment of onchocerciasis: 3-6 months

Absorption: Well absorbed

Distribution: Does not cross blood-brain barrier

Half-life elimination: ~18 hours

Metabolism: Hepatic (>97%)

Bioavailability: Increased with high-fat meal

Time to peak, serum: ~4 hours

Excretion: Feces; urine (<1%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, or insomnia

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine

References

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Centers for Disease Control and Prevention: “River Blindness Onchoceriasis.” Available at http://www.cdc.gov/ncidod/dpd/parasites/onchocerciasis/factsht_onchocerciasis.pdf; last accessed September 29, 2008.

Centers for Disease Control and Prevention, “Ascariasis (*Ascaris lumbricoides*, roundworm).” Available at http://www.dpd.cdc.gov/DPDx/HTML/PDF_Files/MedLetter/Ascariasis.pdf; last accessed September 29, 2008.

Centers for Disease Control and Prevention, “Filariasis.” Available at http://www.dpd.cdc.gov/dpdx/HTML/PDF_Files/MedLetter/Filariasis.pdf; last accessed September 29, 2008.

Centers for Disease Control and Prevention, “Gnathostomiasis (*Gnathostoma spinigerum*).” Available at http://www.dpd.cdc.gov/dpdx/HTML/PDF_Files/MedLetter/Gnathostomiasis.pdf; last accessed September 29, 2008.

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Centers for Disease Control and Prevention, “Strongyloides (*Strongyloides stercoralis*).” Available at http://www.dpd.cdc.gov/dpdx/HTML/PDF_Files/MedLetter/Strongyloidiasis.pdf; last accessed September 29, 2008.

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Ottesen EA and Campbell WC, “Ivermectin in Human Medicine,” *J Antimicrob Chemother*, 1994, 34(2):195-203.[PubMed 7814280]

International Brand NamesIvenox (CO); Ivermectol (IN); Ivexterm (CR, DO, GT, HN, MX, NI, PA, SV); Ivomec (CH); Mectizan (BF, BJ, CI, ET, FR, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Quanox Gotas (CO, PE); Revectina (BR); Sanifer (UY); Securo (AR); Stromectol (FR, NL, NO, NZ); Vermectin (TH); Vermokill (PY)

Ixabepilone-Capecitabine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer
Regimen Use Breast cancer
Index Terms Capecitabine-Ixabepilone
Regimen

Capecitabine: Oral: 1000 mg/m^2 twice daily days 1 to 14

[total dose/cycle = 28,000 mg/m^2]

Ixabepilone: I.V.: 40 mg/m^2 day 1

[total dose/cycle = 40 mg/m^2]

Repeat cycle every 3 weeks

References

Thomas ES, Gomez HL, Li RK, et al, "Ixabepilone Plus Capecitabine for Metastatic Breast Cancer Progressing After Anthracycline and Taxane Treatment," *J Clin Oncol*, 2007, 25(33):5210-7.[PubMed 17968020]

Vahdat LT, Thomas E, Li R, et al, "Phase III Trial of Ixabepilone Plus Capecitabine Compared to Capecitabine Alone in Patients With Metastatic Breast Cancer (MBC) Previously Treated or Resistant to an Anthracycline and Resistant to Taxanes," *J Clin Onc*, 2007, 25(18S):1006 [abstract from 2007 Proceedings of ASCO Annual Meeting]. [PubMed 17968020]

Ixabepilone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ix ab EP i lone)

U.S. Brand NamesIxempra™

Pharmacologic CategoryAntineoplastic Agent, Antimicrotubular; Antineoplastic Agent, Epothilone B Analog

Use: Labeled IndicationsTreatment of metastatic or locally-advanced breast cancer (refractory or resistant)

Dosing: AdultsMetastatic or locally-advanced breast cancer: 40 mg/m^2 every 3 weeks (maximum dose: 88 mg)

Note: Premedicate with an oral H_1-antagonist (eg, diphenhydramine 50 mg) and an oral H_2-antagonist (eg, ranitidine 150-300 mg) 1 hour prior to infusion. Patients with a history of hypersensitivity should also be premedicated with corticosteroids (orally 1 hour before or I.V. 30 minutes before infusion). Body surface area (BSA) is capped at a maximum of 2.2 m^2.

Dosage adjustment with concurrent strong CYP3A4 inhibitor: If concurrent use can not be avoided, reduce ixabepilone dose to 20 mg/m^2. When a strong CYP3A4 inhibitor is discontinued, allow ~1 week to elapse prior to adjusting ixabepilone dose upward.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentPharmacokinetics (monotherapy) are not affected in patients with mild-to-moderate renal insufficiency (Cl_{cr} >30 mL/minute); monotherapy has not been studied in patients with serum creatinine >1.5 times ULN. Combination therapy with capecitabine has not been studied in patients with Cl_{cr} <50 mL/minute.

Dosing: Hepatic Impairment

Ixabepilone monotherapy (initial cycle; adjust doses for subsequent cycles based on toxicity):

AST and ALT ≤2.5 times ULN and bilirubin ≤1 times ULN: No adjustment necessary

AST or ALT ≤10 times ULN and bilirubin ≤1.5 times ULN: Reduce dose to 32 mg/m^2

AST and ALT ≤10 times ULN and bilirubin >1.5 - ≤3 times ULN: Reduce dose to 20-30 mg/m^2

AST or ALT >10 times ULN or bilirubin >3 times ULN: Use is not recommended

Combination therapy of ixabepilone with capecitabine:

AST and ALT ≤2.5 times ULN and bilirubin ≤1 times ULN: No adjustment necessary

AST or ALT >2.5 times ULN or bilirubin >1 times ULN: Use is contraindicated

Dosing: Adjustment for Toxicity

Hematologic:

Neutrophils <500/mm^3 for ≥7 days: Reduce dose by 20%

Neutropenic fever: Reduce dose by 20%

Platelets <25,000/mm^3 (or <50,000/mm^3 with bleeding): Reduce dose by 20%

Nonhematologic:

Neuropathy:

- Grade 2 (moderate) for ≥7 days: Reduce dose by 20%
- Grade 3 (severe) for <7days: Reduce dose by 20%
- Grade 3 (severe or disabling) for ≥7 days: Discontinue treatment

Grade 3 toxicity (severe; other than neuropathy): Reduce dose by 20%

Grade 3 arthralgia/myalgia or fatigue (transient): Continue at current dose

Grade 3 hand-foot syndrome: Continue at current dose

Grade 4 toxicity (disabling): Discontinue treatment

Note: Adjust dosage at the start of a cycle are based on toxicities (hematologic and nonhematologic) from the previous cycle; delay new cycles until neutrophils have recovered to >1500/mm^3, platelets have recovered to >100,000/mm^3 and nonhematologic toxicities have resolved to at least grade 1. If toxicities persist despite initial dose reduction, reduce dose an additional 20%.

Capecitabine dosage adjustments for combination therapy with ixabepilone:

Hematologic:

Neutrophils <500/mm^3 for ≥7 days or neutropenic fever: Hold for concurrent diarrhea or stomatitis until neutrophils recover to >1000/mm3, then continue at same dose

Platelets <25,000/mm^3 (or <50,000/mm^3 with bleeding): Hold for concurrent diarrhea or stomatitis until platelets recover to >50,000/mm^3, then continue at same dose

Nonhematologic: Refer to Capecitabine monograph.

Dosing: Combination Regimens

Breast cancer: Ixabepilone-Capecitabine

Calculations

- Body Surface Area: Adults

Administration: I.V.Infuse over 3 hours.

Administration: I.V. DetailUse non-DEHP administration set (eg, polyethylene); filter with a 0.2-1.2 micron inline filter.

Dietary ConsiderationsAvoid grapefruit juice.

StorageStore intact vials under refrigeration at 2°C to 8°C (36°F to 46°F); protect from light. Reconstituted solution (in the vial) is stable for 1 hour at room temperature; infusion solution diluted in lactated Ringer's is stable for 6 hours at room temperature.

ReconstitutionAllow to reach room temperature for ~30 minutes prior to reconstitution. Diluent vial may contain a white precipitate which should dissolve upon reaching room temperature. **Reconstitute only with the provided diluent.** Dilute the 15 mg vial with 8 mL and the 45 mg vial with 23.5 mL (using provided diluent) to a concentration of 2 mg/mL (contains overfill). Gently swirl and invert vial until dissolved completely. Prior to administration, further dilute in lactated Ringer's (~250 mL) using a non-DEHP container (eg, glass, polypropylene or polyolefin), to a final concentration of 0.2-0.6 mg/mL.

CompatibilityStable in lactated Ringer's injection.

ContraindicationsHistory of severe hypersensitivity to Cremophor® EL or its derivatives (eg, polyoxyethylated castor oil); neutrophil count <1500/mm^3 or platelet count <100,000mm^3; combination therapy with ixabepilone and capecitabine in patients with AST or ALT >2.5 times ULN or bilirubin >1 times ULN

Warnings/Precautions

Boxed Warnings:

- Hepatic impairment: See "Disease-related concerns" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Dose dependant myelosuppression, particularly neutropenia, may occur with mono- or combination therapy. Neutropenic fever and infection have been reported with use. The risk for neutropenia is increased with hepatic dysfunction, especially when used in combination with capecitabine. Severe neutropenia and/or thrombocytopenia may require dosage adjustment and/or treatment delay.

- Cognitive impairment: Due to the ethanol content in the diluent, may cause cognitive impairment; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Hypersensitivity: Diluent contains Cremophor® EL, which is associated with hypersensitivity reactions; use is contraindicated in patients with a history of severe hypersensitivity to Cremophor® EL. Medications for the treatment of reaction should be available for immediate use; reactions may also be managed by reducing infusion rate. Premedicate with an H_1- and H_2-antagonist 1 hour prior to infusion; patients who experience hypersensitivity (eg, bronchospasm, dyspnea, flushing, rash) should also be premedicated with a corticosteroid for all subsequent cycles if treatment is continued.

- Peripheral neuropathy: Peripheral (sensory and motor) neuropathy occurs commonly; may require dose reductions, treatment delays or discontinuation. Usually occurs during the first 3 cycles. Use with caution in patients with pre-existing neuropathy.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease. The incidence of MI, ventricular dysfunction and supraventricular arrhythmias is higher when ixabepilone is used in combination with capecitabine (as compared to capecitabine alone). Consider discontinuing ixabepilone in patients who develop cardiac ischemia or impaired cardiac function.

- Diabetes: Use with caution; may have an increased risk for severe peripheral neuropathy.

- Hepatic impairment: **[U.S. Boxed Warning]: Combination therapy with capecitabine is contraindicated in patients with AST or ALT >2.5 times ULN or bilirubin >1 times ULN;** the risk of toxicity and neutropenia-related death is increased. Use (as monotherapy) is not recommended if AST or ALT >10 times ULN or bilirubin >3 times ULN; use caution in patients with AST or ALT >5 times ULN; data is limited. In mono- and combination therapy, toxicities and serious adverse reactions are increased with hepatic dysfunction; dosage reductions are necessary.

Special populations:

- Elderly: Use with caution in the elderly; toxicities or serious adverse events with combination therapy may be increased.

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorD

Pregnancy ConsiderationsIn animal studies, ixabepilone caused maternal toxicity and embryo/fetal toxicity at doses ~1/10 the human dose. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to use effective contraception during treatment.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reaction in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

Percentages reported with monotherapy:

>10%:

Central nervous system: Headache (11%)

Dermatologic: Alopecia (48%)

Gastrointestinal: Nausea (42%), vomiting (29%), mucositis/stomatitis (29%), diarrhea (22%), anorexia (19%), constipation (16%), abdominal pain (13%)

Hematologic: Leukopenia (36%; grade 4: 13%), neutropenia (31%; grade 4: 23%)

Neuromuscular & skeletal: Peripheral neuropathy (~75%; grades 3/4: 14%; median onset: cycle 4), sensory neuropathy (62%; grades 3/4: 14%), weakness (56%), myalgia/arthralgia (49%), musculoskeletal pain (20%)

1% to 10%:

Cardiovascular: Edema (9%), hot flush (6%), chest pain (5%)

Central nervous system: Fever (8%), pain (8%), dizziness (7%), insomnia (5%)

Dermatologic: Nail disorder (9%), rash (9%), palmar-plantar erythrodysesthesia/hand-and-foot syndrome (8%), pruritus (6%), skin exfoliation (2%), hyperpigmentation (2%)

Endocrine & metabolic: Dehydration (2%)

Gastrointestinal: Gastroesophageal reflux disease (6%), taste perversion (6%), weight loss (6%)

Hematologic: Anemia (6%; grade 4: 2%), neutropenic fever (3%; grade 3: 3%), thrombocytopenia (5%; grade 4: 2%)

Neuromuscular & skeletal: Motor neuropathy (10%; grade 3: 1%)

Ocular: Lacrimation increased (4%)

Respiratory: Dyspnea (9%), upper respiratory tract infection (6%), cough (2%)

Miscellaneous: Hypersensitivity (5%; grade 3: 1%), infection (5%)

Mono- and combination therapy: <1%, postmarketing, and/or case reports (limited to important or life-threatening): Alkaline phosphatase increased, angina, atrial flutter, autonomic neuropathy, cardiomyopathy, cerebral hemorrhage, coagulopathy, colitis, embolism, dysphagia, enterocolitis, erythema multiforme, gastrointestinal hemorrhage, gastroparesis, GGT increased, hemorrhage, hepatic failure (acute), hypokalemia, hyponatremia, hypotension, hypovolemia, hypovolemic shock, hypoxia, ileus, interstitial pneumonia, jaundice, left ventricular dysfunction, metabolic acidosis, MI, nephrolithiasis, neutropenic infection, orthostatic hypotension, pneumonia, pneumonitis, pulmonary edema (acute), renal failure, respiratory failure, sepsis, septic shock, supraventricular arrhythmia, syncope, thrombosis, transaminases increased, trismus, urinary tract infection, vasculitis

Oncology: Emetic PotentialLow (10% to 30%)

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)

Drug Interactions

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid St John’s wort (may decrease ixabepilone levels).

Monitoring ParametersCBC with differential; hepatic function (ALT, AST, bilirubin); monitor for hypersensitivity

Nursing: Physical Assessment/MonitoringUse caution with hepatic dysfunction, pre-existing neuropathy, or cardiovascular disease. Assess potential for interactions with other pharmacological or herbal agents patient may be taking (eg, risk of toxicity, decreased effects). Premedication prior to administration is recommended. Patient must be monitored closely for hypersensitivity reaction and treatment for reaction should be immediately available. In case of adverse infusion reactions, infusion should be stopped and prescriber notified; reduced infusion rate may be necessary. Teach patient possible side effects/interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential; hepatic function (ALT, AST, bilirubin)

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy unless approved by prescriber. This medication can only be administered by infusion and you will be closely monitored during each infusion. Report immediately unusual chest tightness; difficulty breathing or swallowing; itching or skin rash; back pain or acute headache; or redness, swelling, or pain at infusion site. Maintain adequate nutrition (small, frequent meals) and hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience dizziness, headache, insomnia, or lightheadedness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, or yogurt may reduce diarrhea); constipation (increased dietary fruit, fluids, fiber, or increased exercise may help); tingling, numbness, or loss of sensation in hands or feet; or loss of hair (may regrow when treatment is ended). Report chest pain or palpitations; swelling of extremities; difficulty breathing or unusual cough; persistent or unresolved gastrointestinal disturbance; weakness, numbness, tingling, or tremors in muscles; skin rash or change in pigmentation; unusual fatigue; or any other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Ixempra™: 15 mg, 45 mg [packaged with diluent; diluent contains alcohol and purified polyoxyethylated castor oil (Cremophor® EL)]

Generic AvailableNo

ManufacturerBristol-Myers Squibb Company

Mechanism of ActionEpothilone B analog; binds to the beta-tubulin subunit of the microtubule, stabilizing microtubular function, thus arresting the cell cycle (at the G2/M phase) and inducing apoptosis

Pharmacodynamics/Kinetics

Distribution: >1000 L/m^2

Protein binding: 67% to 77%

Metabolism: Extensively hepatic, via CYP3A4; >30 metabolites (inactive) formed

Half-life elimination: ~52 hours

Time to peak, plasma: At the end of infusion (3 hours)

Excretion: Feces (65%; 2% as unchanged drug); urine (21%; 6% as unchanged drug)

Related Information

- Common Toxicity Criteria
- Management of Nausea and Vomiting
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, mucositis, and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause cognitive impairment, dizziness, and insomnia

Mental Health: Effects on Psychiatric TreatmentIxabepilone causes bone marrow depression; use caution with clozapine, carbamazepine, and valproic acid. GI side effects are common; concomitant use with lithium, SSRIs, valproic acid, and carbamazepine may produce additive effects. Carbamazepine, phenobarbital, and St John's wort may decrease the levels/effects of ixabepilone; avoid concurrent use. Nefazodone may increase the levels/effects of ixabepilone; avoid concurrent use.

Index TermsBMS-247550; NSC-710428

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Japanese Encephalitis Virus Vaccine (Inactivated)

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English

English

Jump To Field (Select Field Name)

Pronunciation(jap a NEESE en sef a LYE tis VYE rus vak SEEN, in ak ti VAY ted)
U.S. Brand NamesJE-VAX®
Canadian Brand NamesJE-VAX®
Pharmacologic CategoryVaccine
Use: Labeled IndicationsActive immunization against Japanese encephalitis
Dosing: Adults

U.S. recommended primary immunization schedule: SubQ: Three 1 mL doses given on days 0, 7, and 30

Booster dose: Give after 2 years, or according to current recommendation

Abbreviated dosing schedule: Three recommended doses, given on days 0, 7, and 14 with the last dose given at least 10 days before travel. Alternately, two doses given 1 week apart provide immunity in ~80% of patients. Abbreviated schedules should be used only when necessary due to time constraints.

Dosing: ElderlyRefer to adult dosing. Elderly may be at increased risk of developing neuroinvasive disease if infected with Japanese encephalitis virus.
Dosing: Pediatric

U.S. recommended primary immunization schedule: SubQ:

Children 1-3 years: Three 0.5 mL doses given on days 0, 7, and 30

Children >3 years: Three 1 mL doses given on days 0, 7, and 30

Booster dose: Give after 2 years, or according to current recommendation

Abbreviated dosing schedule: Three recommended doses, given on days 0, 7, and 14 with the last dose given at least 10 days before travel. Alternately, two doses given 1 week apart provide immunity in ~80% of patients. Abbreviated schedules should be used only when necessary due to time constraints.

Dietary ConsiderationsAvoid alcohol for 48 hours following vaccination.
StoragePrior to and following reconstitution, store under refrigeration at 2°C to 8°C (35°F to 46°F). Discard 8 hours after reconstitution. Do not freeze.
ReconstitutionReconstitute with 1.3 mL of provided diluent. Shake well.
ContraindicationsHypersensitivity to Japanese encephalitis virus vaccine, including serious adverse reaction (generalized urticaria or angioedema) to a prior dose; proven or suspected hypersensitivity to any component of the vaccine including proteins of rodent or neural origin; hypersensitivity to thimerosal
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use. Severe adverse reactions (generalized urticaria or angioedema) may occur within minutes to 17 days following vaccination; most occur within 10 days with the majority occurring within 48 hours. Patients should be observed for 30 minutes after vaccination. Travel should not be started for ≥10 days following vaccination and patients should remain within ready access to medical care for 10 days and seek immediate medical attention at onset of any reaction.

Disease-related concerns:

- Acute illness: The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and the etiology of the disease. Immunization should be delayed during the course of an acute febrile illness.

- Drug allergies: Use with caution in patients with severe allergies to other medications.

- Insect sting urticaria: Use caution with a significant history of urticaria following exposure to insect stings; risk of adverse events may be increased.

Concurrent drug therapy issues:

- Alcohol: Avoid alcohol consumption within 48 hours of vaccination; may increase risk of hypersensitivity reactions.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy [including high dose corticosteroids]); may have a reduced response to vaccination.

- Patients residing/traveling to Asia: Because of the potential for severe adverse reactions, not recommended for all persons traveling to or residing in Asia (also see Additional Information or Pharmacotherapy Pearls).

- Pediatrics: Safety and efficacy have not been established in children <1 year of age.

Other warnings/precautions:

- Other methods to reduce mosquito exposure: Use of vaccine should also include other means to reduce the risk of mosquito exposure (bed nets, insect repellents, protective clothing, avoidance of travel in endemic areas, and avoidance of outdoor activity during twilight and evening periods).

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. Risks of vaccine administration should be carefully considered and in general, pregnant women should only be vaccinated if they are at high risk for exposure. Infection from Japanese encephalitis during the 1st or 2nd trimesters of pregnancy may increase risk of abortion.

Adverse Reactions**Report allergic or unusual adverse reactions to the Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.** Percentage of adverse reactions may depend upon timing of vaccination. In general, adverse reactions occur more frequently following the first dose or when doses are administered closer together (abbreviated dosing schedule). However, reactions have been reported when previous doses were tolerated uneventfully.

>10%:

Central nervous system: Headache (<5% to 15%)

Local: Injection site reaction (<1% to 31%)

1% to 10%:

Central nervous system: Chills (~10%), dizziness (~10%), malaise (~10%), fever (<5% to 10%)

Dermatologic: Rash (≤10%)

Gastrointestinal: Abdominal pain (~10%), nausea (~10%), vomiting (~10%)

Neuromuscular & skeletal: Myalgia (~10%)

Miscellaneous: Flu-like syndrome (<5%)

<1%, frequency not defined, and/or case reports: Angioedema, behavior disorder, Bell’s palsy, cerebellar ataxia, cranial nerve paresis, encephalopathy, erythema multiforme, erythema nodosum, facial swelling, Guillain-Barré syndrome, hepatitis, hives, hypotension, itching, joint swelling, myocarditis, optic neuritis, peripheral neuropathy, renal failure, respiratory distress, respiratory failure, seizure, transverse myelitis, urticaria (generalized), wheezing

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Alcohol consumption within 48 hours of vaccination may increase risk of hypersensitivity reactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

JE-VAX®: [contains mouse serum protein, thimerosal, gelatin, polysorbate 80]

Generic AvailableNo

Related Information

- Immunization Recommendations

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Because of the potential for severe adverse reactions, Japanese encephalitis vaccine is not recommended for all persons traveling to or residing in Asia. Risk of exposure to the Japanese encephalitis virus may vary from year to year for a particular area. In general, use should be limited to persons spending ≥1 month in endemic areas during transmission season. Under specific circumstances, the CDC notes that vaccination may also be considered for persons spending <30 days in endemic areas, such as:

- Travel to areas with epidemic transmission

- Travelers with high risk activities (eg, extensive outdoor activity in rural areas, adventure travelers)

The CDC also recommends vaccination for research laboratory workers who may be exposed to the Japanese encephalitis virus.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or malaise; may rarely cause encephalopathy

Mental Health: Effects on Psychiatric TreatmentNone reported

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International Brand Names CD Jevax (KP, TH)

Kanamycin

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English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Kanamycin may be confused with Garamycin®, gentamicin

Pronunciation(kan a MYE sin)

U.S. Brand NamesKantrex®

Canadian Brand NamesKantrex®

Pharmacologic CategoryAntibiotic, Aminoglycoside

Use: Labeled IndicationsTreatment of serious infections caused by susceptible strains of *E. coli*, *Proteus* species, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Serratia marcescens*, and *Acinetobacter* species; second-line treatment of *Mycobacterium tuberculosis*

Dosing: Adults**Note:** Dosing should be based on ideal body weight

Susceptible systemic infections: I.M., I.V.: 5-7.5 mg/kg/dose in divided doses every 8-12 hours (<15 mg/kg/day)

Following surgical contamination, peritonitis: Intraperitoneal: 500 mg

Irrigating solution: 0.25%; maximum 1.5 g/day (via all administration routes)

Aerosol: 250 mg 2-4 times/day

Dosing: ElderlyI.M., I.V.: Initial dose should be 5-7.5 mg/kg based on ideal body weight (except in obese patients); maintenance dose and interval should be adjusted for estimated renal function; dosing interval in most older patients is every 12-24 hours (see Dosing in Renal Impairment).

Dosing: Pediatric**Note:** Dosing should be based on ideal body weight

Infections: I.M., I.V.: 15 mg/kg/day in divided doses every 8-12 hours

Dosing: Renal Impairment

Cl_{cr} 50-80 mL/minute: Administer 60% to 90% of dose or administer every 8-12 hours.

Cl_{cr} 10-50 mL/minute: Administer 30% to 70% of dose or administer every 12 hours.

Cl_{cr} <10 mL/minute: Administer 20% to 30% of dose or administer every 24-48 hours.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Ideal Body Weight: Adults
- Ideal Body Weight: Pediatrics

Administration: I.M.Administer deeply in upper outer quadrant of the gluteal muscle.

Administration: I.V.Infuse over 30-60 minutes.

Some penicillins (eg, carbenicillin, ticarcillin and piperacillin) have been shown to inactivate aminoglycosides *in vitro*. This has been observed to a greater extent with tobramycin and gentamicin, while amikacin has shown greater stability against inactivation. Concurrent use of these agents may pose a risk of reduced antibacterial efficacy *in vivo*, particularly in the setting of profound renal impairment. However, definitive clinical evidence is lacking. If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered.

StorageStore vial at controlled room temperature. Darkening of vials does not indicate loss of potency.

Reconstitution

I.V.: Must be further diluted prior to I.V. infusion. For adults, dilute 500 mg in 100-200 mL of appropriate solution or 1 g in 200-400 mL. For pediatric patients, use sufficient amount to infuse solution over 30-60 minutes.

Intraperitoneal: Dilute dose in 20 mL sterile distilled water.

Aerosol: Dilute 250 mg in 3 mL normal saline.

CompatibilityStable in D_5NS, D_5W, $D_{10}W$, LR, NS; **variable stability (consult detailed reference)** in TPN.

Y-site administration: Compatible: Cyclophosphamide, furosemide, heparin with hydrocortisone sodium succinate, hydromorphone, magnesium sulfate, meperidine, morphine, perphenazine, potassium chloride, vitamin B complex with C. **Variable (consult detailed reference):** TPN.

Compatibility in syringe: Compatible: Penicillin G sodium. **Incompatible:** Ampicillin, heparin, piperacillin.

Compatibility when admixed: Compatible: Ascorbic acid injection, cefoxitin, chloramphenicol, clindamycin, dopamine, furosemide, penicillin G potassium, penicillin G sodium, polymyxin B sulfate, sodium bicarbonate, vitamin B complex with C. **Incompatible:** Amphotericin B, cefazolin, cefotaxime, cefotetan, chlorpheniramine, colistimethate, heparin, lincomycin, methohexital, phenobarbital, phenytoin, piperacillin. **Variable (consult detailed reference):** Hydrocortisone sodium succinate.

ContraindicationsHypersensitivity to kanamycin, any component of the formulation, or other aminoglycosides; pregnancy
Warnings/Precautions

Boxed warnings:

- Nephrotoxicity: See “Concerns related to adverse effects” below.

- Neurotoxicity: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Nephrotoxicity: **[U.S. Boxed Warning]: May cause nephrotoxicity;** usual risk factors include pre-existing renal impairment, concomitant nephrotoxic medications, advanced age, and dehydration. Discontinue treatment if signs of nephrotoxicity occur; renal damage is usually reversible.

- Neuromuscular blockade and respiratory paralysis: May cause neuromuscular blockade and respiratory paralysis, especially when given soon after anesthesia or muscle relaxants.

- Neurotoxicity: **[U.S. Boxed Warning]: May cause neurotoxicity;** usual risk factors include pre-existing renal impairment, concomitant neuro-/nephrotoxic medications, advanced age, and dehydration. Ototoxicity is proportional to the amount of drug given and the duration of treatment. Tinnitus or vertigo may be indications of vestibular injury and impending bilateral irreversible damage. Discontinue treatment if signs of ototoxicity occur.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hearing impairment: Use with caution in patients with pre-existing vertigo, tinnitus, or hearing loss.

- Hypocalcemia: Use with caution in patients with hypocalcemia.

- Neuromuscular disorders: Use with caution in patients with neuromuscular disorders, including myasthenia gravis.

- Renal impairment: Use with caution in patients with pre-existing renal insufficiency; dosage modification required.

Other warnings/precautions:

- Long-term use: Not intended for long-term therapy due to toxic hazards associated with extended administration.

Geriatric ConsiderationsThis is not a drug of choice since elderly may have increased adverse effects (renal).
Pregnancy Risk FactorD
Pregnancy ConsiderationsKanamycin crosses the placenta and produces detectable serum levels in the fetus. There is one case report of hearing impairment in a child with prenatal exposure to kanamycin. Because of several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy, kanamycin has been classified by the manufacturer as pregnancy risk category D.
LactationEnters breast milk/not recommended (AAP rates “compatible”)
Breast-Feeding ConsiderationsKanamycin is excreted into breast milk in minute amounts; however, it is not well absorbed when taken orally. This limited oral absorption may minimize exposure to the nursing infant. Nondose-related effects could include modification of bowel flora. The AAP considers kanamycin to be “usually compatible with breast-feeding.”
Pregnancy & Lactation, In-Depth

- Kanamycin in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Cardiovascular: Edema

Central nervous system: Neurotoxicity, drowsiness, headache, pseudomotor cerebri

Dermatologic: Skin itching, redness, rash, photosensitivity, erythema

Gastrointestinal: Nausea, vomiting, diarrhea, malabsorption syndrome (with prolonged and high-dose therapy of hepatic coma), anorexia, weight loss, salivation increased, enterocolitis

Hematologic: Granulocytopenia, agranulocytosis, thrombocytopenia

Local: Burning, stinging

Neuromuscular & skeletal: Weakness, tremor, muscle cramps

Otic: Ototoxicity (auditory), ototoxicity (vestibular)

Renal: Nephrotoxicity

Respiratory: Dyspnea

Drug Interactions

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

Cardiac Glycosides: Aminoglycosides may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Test InteractionsSome penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*, leading to a potential underestimation of aminoglycoside serum concentration.

Monitoring ParametersSerum creatinine and BUN every 2-3 days; peak and trough concentrations; hearing

Some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*. This may be clinically-significant for certain penicillin (ticarcillin, piperacillin, carbenicillin) and aminoglycoside (gentamicin, tobramycin) combination therapy in patients with significant renal impairment. Close monitoring of aminoglycoside levels is warranted.

Reference RangeTherapeutic: Peak: 15-30 mcg/mL; Trough: 5-10 mcg/mL; Toxic: Peak: >35 mcg/mL; Trough: >10 mcg/mL

Monitoring: Lab TestsSerum creatinine and BUN every 2-3 days; peak and trough concentrations

Patient EducationReport persistent diarrhea.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sulfate: 1 g/3 mL (3 mL) [contains sodium bisulfate]

Generic AvailableNo

ManufacturerGeneva Pharmaceuticals

Mechanism of ActionInterferes with protein synthesis in bacterial cell by binding to ribosomal subunit

Pharmacodynamics/Kinetics

Absorption:

I.M.: Rapid

Oral: Minimal

Distribution:

Relative diffusion from blood into CSF: Good only with inflammation (exceeds usual MICs)

CSF:blood level ratio: Normal meninges: Nil; Inflamed meninges: 43%

Protein binding: 0%

Half-life elimination: 2-4 hours; Anuria: 80 hours; End-stage renal disease: 40-96 hours

Time to peak, serum: I.M.: 1-2 hours (decreased in burn patients)

Excretion: Urine (as unchanged drug)

Related Information

- Antimicrobial Drugs of Choice
- Tuberculosis

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Salivation increased.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness; case reports of delirium and psychosis with aminoglycosides
Mental Health: Effects on Psychiatric TreatmentMay cause agranulocytosis; use caution with clozapine and carbamazepine
Index TermsKanamycin Sulfate
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International Brand NamesCristalomicina (AR); Kamycine (FR); Kan-Ophtal (DE); Kana-Stulln (DE); Kanacet (IT); Kanacin (KP); Kanacolirio (ES); Kanacyn (BE, LU, PK); Kanafil (IT); Kanafluid (ES); Kanahidro (ES); Kanamicin (HR); Kanamicina Firma (IT); Kanamycin Capsules Meiji (TH); Kanamycin Meiji (HK, PH, TW); Kanamycin Sanbe (ID); Kanamycin-POS (DE); Kanamytrex (DE); Kananovo (ES); Kanapiam Orale (IT); Kanaplus (ES); Kanaqua (ES); Kanarco (ID); Kanasig (AU); Kanatrol (IT); Kancin (IN, MY, PH, TH); Kanescin (ES); Kannasyn (GB, IE); Kano (IT); Kantrex (BF, BJ, CI, ES, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MX, NE, NG, PE, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Keimicina (IT); Visiokan (IT)

Ketamine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Ketalar® may be confused with Kenalog®, ketorolac

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(KEET a meen)
U.S. Brand NamesKetalar®
Canadian Brand NamesKetalar®; Ketamine Hydrochloride Injection, USP
Pharmacologic Category[General Anesthetic]
Use: Labeled IndicationsInduction and maintenance of general anesthesia
Use: Unlabeled/InvestigationalAnalgesia, sedation
Dosing: AdultsMay be used in combination with anticholinergic agents to decrease hypersalivation.

Induction of anesthesia:

I.M.: 6.5-13 mg/kg; usual dose to produce 12-25 minutes of anesthesia: 10 mg/kg

I.V.: 1-4.5 mg/kg; usual dose to produce 5-10 minutes of anesthesia: 2 mg/kg

I.V. infusion: 1-2 mg/kg infuse over 0.5 mg/kg/minute; may administer with diazepam to prevent emergence reactions

Maintenance of anesthesia: Supplemental doses of $^1/_2$ to the full induction dose; may also be maintained with a continuous infusion of 0.1-5 mg/minute

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricMay be used in combination with anticholinergic agents to decrease hypersalivation. **Note:** Titrate dose for desired effect.

Sedation (unlabeled use):

Oral (unlabeled route): 6-10 mg/kg for 1 dose (mixed in 0.2-0.3 mL/kg of cola or other beverage) given 30 minutes before the procedure

Continuous I.V. infusion: 5-20 mcg/kg/minute; titrate to reach desired level of sedation

Sedation/analgesia (unlabeled use):

I.M.: 4-5 mg/kg/dose; doses up to 13 mg/kg have been reported

I.V.: 1-2 mg/kg/dose; titrate repeat doses for desired effect

Children ≥16 years: Refer to adult dosing.

Administration: I.V.Do not exceed 0.5 mg/kg/minute or administer faster than 60 seconds. Solutions for infusion should not exceed final concentration of 2 mg/mL.
Administration: OralUse 100 mg/mL I.V. solution and mix the appropriate dose in 0.2-0.3 mL/kg of cola or other beverage.
StorageStore at 20°C to 25°C (68°F to 77°F). Protect from light.
ReconstitutionThe 50 mg/mL and 100 mg/mL vials may be further diluted in D_5W or NS to a final concentration of 1 mg/mL (or 2 mg/mL in patients with fluid restrictions). The 10 mg/mL vials are not recommended to be further diluted. Do not mix with barbiturates or diazepam (precipitation may occur).
CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Propofol.

Compatibility in syringe: Compatible: Bupivacaine with fentanyl, clonidine with tetracaine, lidocaine with morphine, meperidine, morphine. **Incompatible:** Amobarbital, diazepam, doxapram, methohexital, pentobarbital, phenobarbital, secobarbital, thiopental.

Compatibility when admixed: Compatible: Morphine.

RestrictionsC-III
ContraindicationsHypersensitivity to ketamine or any component of the formulation; conditions in which an increase in blood pressure would be hazardous
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). When used on an outpatient basis, patient should be accompanied by a responsible adult.

- Dependence: May cause dependence (withdrawal symptoms on discontinuation) and tolerance with prolonged use.

- Emergence reactions: Postanesthetic emergence reactions which can manifest as vivid dreams, hallucinations, and/or frank delirium occur; these reactions are less common in patients >65 years of age and when given intramuscularly. Emergence reactions, confusion, or irrational behavior may occur up to 24 hours postoperatively and may be reduced by pretreatment with a benzodiazepine and the use of ketamine at the lower end of the dosing range.

- Respiratory depression: Rapid I.V. administration or overdose may cause respiratory depression, apnea, and enhanced pressor response. Resuscitative equipment should be available during use.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease, catecholamine depletion, hypertension, and tachycardia. Cardiac function should be continuously monitored in patients with increased blood pressure or cardiac decompensation.

- Cerebrospinal fluid (CSF) pressure elevation: Use with caution in patients with CSF pressure elevation; an increase in CSF pressure is associated with use.

- Ethanol use: Use with caution in the chronic alcoholic or acutely alcohol-intoxicated.

Other warnings/precautions:

- Experienced physician: Should be administered under the supervision of a physician experienced in administering general anesthetics.

Pregnancy ConsiderationsAdverse events have not been observed in animal reproduction studies. Ketamine crosses the placenta and can be detected in fetal tissue. Ketamine produces dose dependant increases in uterine contractions; effects may vary by trimester. The plasma clearance of ketamine is reduced during pregnancy. Dose related neonatal depression and decreased APGAR scores have been reported with large doses administered at delivery.

Adverse ReactionsFrequency not always defined.

Cardiovascular: Arrhythmia, bradycardia, hyper-/hypotension, pulse rate increased

Central nervous system: CSF pressure increased

Dermatologic: Erythema (transient), morbilliform rash (transient)

Gastrointestinal: Anorexia, nausea, vomiting

Local: Pain at the injection site, exanthema at the injection site

Neuromuscular & skeletal: Skeletal muscle tone enhanced (tonic-clonic movements)

Ocular: Diplopia, intraocular pressure increased, nystagmus

Respiratory: Airway obstruction, apnea, respiratory depression or stimulation, laryngospasm

Miscellaneous: Anaphylaxis, dependence with prolonged use, emergence reactions (~12%; includes confusion, delirium, dreamlike state, excitement, hallucinations, irrational behavior, vivid imagery)

Metabolism/Transport Effects**Substrate** (major) of CYP2B6, 2C9, 3A4

Drug Interactions

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Strong): May decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Monitoring ParametersHeart rate, blood pressure, respiratory rate, transcutaneous O_2 saturation, emergence reactions; cardiac function should be continuously monitored in patients with increased blood pressure or cardiac decompensation

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effect, and adverse/toxic effects. Keep patient under observation. Monitor cardio/respiratory status and institute patient safety precautions. Monitor effectiveness of therapy and adverse reactions. Monitor respiratory status (for conscious sedation, includes pulse oximetry), cardiovascular status, CNS status (when used for procedures monitor sedation score); cardiac monitor and blood pressure monitor required.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 50 mg/mL (10 mL); 100 mg/mL (5 mL)

Ketalar®: 10 mg/mL (20 mL); 50 mg/mL (10 mL); 100 mg/mL (5 mL)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Ketamine HCl)

50 mg/mL (10): $7.69

Mechanism of ActionProduces a cataleptic-like state in which the patient is dissociated from the surrounding environment by direct action on the cortex and limbic system. Releases endogenous catecholamines (epinephrine, norepinephrine) which maintain blood pressure and heart rate. Reduces polysynaptic spinal reflexes.

Pharmacodynamics/Kinetics

Onset of action:

I.V.: Anesthetic effect: 30 seconds

I.M.: Anesthetic effect: 3-4 minutes

Duration: Anesthetic effect: I.V.: 5-10 minutes; I.M.: 12-25 minutes

Metabolism: Hepatic via hydroxylation and N-demethylation; the metabolite norketamine is 33% as potent as parent compound

Half-life elimination: Alpha: 10-15 minutes; Beta: 2.5 hours

Excretion: Primarily urine

Pharmacotherapy PearlsProduces emergence psychosis including auditory and visual hallucinations, restlessness, disorientation, vivid dreams, and irrational behavior in ~12% of patients; pretreatment with a benzodiazepine reduces incidence of psychosis by >50%. Spontaneous involuntary movements, nystagmus, hypertonus, and vocalizations are also commonly seen.

The analgesia outlasts the general anesthetic component. Bronchodilation is beneficial in asthmatic or COPD patients. Laryngeal reflexes may remain intact or may be obtunded. The direct myocardial depressant action of ketamine can be seen in stressed, catecholamine-deficient patients. Ketamine increases cerebral metabolism and cerebral blood flow while producing a noncompetitive block of the neuronal postsynaptic NMDA receptor. It lowers seizure threshold and stimulates salivary secretions (atropine/scopolamine treatment is recommended).

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Increased salivation.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusVivid dreams and hallucinations common

Mental Health: Effects on Psychiatric TreatmentContraindicated in patients with psychotic disorders; barbiturates and hydroxyzine may increase the effects of ketamine; avoid combination

Cardiovascular ConsiderationsKetamine increases myocardial demand secondary to catecholamine release.

Anesthesia and Critical Care Concerns/Other ConsiderationsProduces emergence psychosis including auditory and visual hallucinations, restlessness, disorientation, vivid dreams, and irrational behavior in ~12% of patients; pretreatment with a benzodiazepine reduces incidence of psychosis by >50%. Spontaneous involuntary movements, nystagmus, hypertonus, and vocalizations are also commonly seen.

The analgesia outlasts the general anesthetic component. Bronchodilation is beneficial in asthmatic or COPD patients. Laryngeal reflexes may remain intact or may be obtunded. The direct myocardial depressant action of ketamine can be seen in stressed, catecholamine-deficient patients. Ketamine increases cerebral metabolism and cerebral blood flow while producing a noncompetitive block of the neuronal postsynaptic NMDA receptor. It lowers seizure threshold and stimulates salivary secretions (atropine/scopolamine treatment is recommended).

Ketamine increases myocardial oxygen demand secondary to catecholamine release.

Index TermsKetamine Hydrochloride

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International Brand NamesAnesket (CO); Brevinaze (ZA); Calypsol (AE, BB, BG, BH, BM, BS, BZ, CY, CZ, EG, GY, HU, IL, IQ, IR, JM, JO, KW, LB, LY, OM, PK, PL, PR, QA, SA, SR, SY, TH, TT, YE); Ivanes (ID); Keiran (VE); Ketalar (AE, AR, AT, AU, BB, BE, BG, BH, BM, BR, BS, BZ, CH, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, GY, HK, HN, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KW, LB, LU, LY, MY, NL, NO, OM, PE, PT, QA, RU, SA, SE, SR, SY, TR, TT, TW, UY, YE); Ketalin (MX); Ketamax (PH); Ketamin-S (+) (PY); Ketanest (HR, PL); Ketava (MY); Ketazol (PH); Ketmin (IN); Ketolar (ES); KTM (ID); Narkamon (DE, PL); Quetanex (PH); Soon-Soon (TW); Tekam (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Velonarcon (PL)

Ketoconazole

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English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Kuric™ may be confused with Carac®

Nizoral® may be confused with Nasarel®, Neoral®, Nitrol®

Pronunciation(kee toe KOE na zole)

U.S. Brand NamesExtina®; Kuric™; Nizoral®; Nizoral® A-D [OTC]; Xolegel™

Canadian Brand NamesApo-Ketoconazole®; Ketoderm®; Novo-Ketoconazole; Xolegel™

Pharmacologic CategoryAntifungal Agent, Oral; Antifungal Agent, Topical

Use: Labeled Indications

Systemic: Treatment of susceptible fungal infections, including candidiasis, oral thrush, blastomycosis, histoplasmosis, paracoccidioidomycosis, coccidioidomycosis, chromomycosis, candiduria, chronic mucocutaneous candidiasis, as well as certain recalcitrant cutaneous dermatophytoses

Topical:

Cream: Treatment of tinea corporis, tinea cruris, tinea versicolor, cutaneous candidiasis, seborrheic dermatitis

Foam, gel: Treatment of seborrheic dermatitis

Shampoo: Treatment of dandruff, seborrheic dermatitis, tinea versicolor

Use: Unlabeled/InvestigationalTablet: Treatment of prostate cancer (androgen synthesis inhibitor)

Use: DentalTreatment of susceptible fungal infections in the oral cavity including candidiasis, oral thrush, and chronic mucocutaneous candidiasis

Dosing: Adults

Fungal infections:

Oral: 200-400 mg/day as a single daily dose

Topical: Tinea infections: Cream: Rub gently into the affected area once daily. Duration of treatment: Tinea corporis, cruris: 2 weeks; tinea pedis: 6 weeks

Shampoo: Tinea versicolor: Apply twice weekly for 4 weeks with at least 3 days between each shampoo

Seborrheic dermatitis:*Topical:*

Cream: Rub gently into the affected area twice daily for 4 weeks or until clinical response is noted.

Foam: Apply to affected area twice daily for 4 weeks

Gel: Rub gently into the affected area once daily for 2 weeks.

Shampoo: Apply twice weekly for 4 weeks with at least 3 days between each shampoo

Prostate cancer (unlabeled use): Oral: Adults: 400 mg 3 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Fungal infections:***Oral:* Children ≥2 years: 3.3-6.6 mg/kg/day as a single dose for 1-2 weeks for candidiasis, for at least 4 weeks in recalcitrant dermatophyte infections, and for up to 6 months for other systemic mycoses

Seborrheic dermatitis:*Topical (cream/foam/gel, shampoo):* Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentNot dialyzable (0% to 5%)

Dosing: Hepatic ImpairmentDose reductions should be considered in patients with severe liver disease.

Dosing: Combination Regimens

Prostate cancer:

Doxorubicin + Ketoconazole

Doxorubicin + Ketoconazole/Estramustine + Vinblastine

Administration: OralAdminister oral tablets 2 hours prior to antacids to prevent decreased absorption due to the high pH of gastric contents.

Administration: TopicalCream, foam, gel, and shampoo are for external use only. Avoid exposure to flame or smoking immediately following application of gel or foam; do not apply directly to hands.

Dietary ConsiderationsTablet: May be taken with food or milk to decrease GI adverse effects.

Storage

Cream: Store at <25°C (<77°F).

Foam: Store at 20°C to 25°C (68°F to 77°F). Do not refrigerate. Do not store in direct sunlight. Contents are flammable.

Gel: Store at 15°C to 30°C (59°F to 86°F).

Shampoo: Store between 2°C to 30°C (35°F to 86°F); protect from freezing. Protect from light.

Tablet: Store at 15°C to 25°C (59°F to 77°F).

Extemporaneously PreparedA 20 mg/mL suspension may be made by pulverizing twelve 200 mg ketoconazole tablets to a fine powder; add 40 mL Ora-Plus® in small portions with thorough mixing; incorporate Ora-Sweet® to make a final volume of 120 mL and mix thoroughly; refrigerate (no stability information is available)

Allen LV, "Ketoconazole Oral Suspension," *US Pharm*, 1993, 18(2):98-9, 101.

ContraindicationsHypersensitivity to ketoconazole or any component of the formulation; CNS fungal infections (due to poor CNS penetration); coadministration with ergot derivatives or cisapride is contraindicated due to risk of potentially fatal cardiac arrhythmias

Allergy Considerations

- Azole Antifungal Allergy

Warnings/Precautions

Boxed warnings:

- Cisapride: See "Concurrent drug therapy issues" below.
- Hepatic impairment: See "Disease-related concerns" below.

Concerns related to adverse effects:

- Adrenal suppression: High doses of ketoconazole may depress adrenocortical function.

Disease-related concerns:

- Hepatic impairment: **[U.S. Boxed Warning]: Ketoconazole has been associated with hepatotoxicity, including some fatalities;** use with caution in patients with pre-existing hepatic impairment; monitor liver function closely and dosage adjustment may be warranted.

Concurrent drug therapy issues:

- Cisapride: **[U.S. Boxed Warning]: Concomitant use with cisapride is contraindicated due to the occurrence of ventricular arrhythmias.**

Dosage form specific issues:

- Foam: Formulation contains alcohol and propane/butane; do not expose to open flame or smoking during or immediately after application. Do not puncture or incinerate container.
- Topical: Formulations may contain sulfites. Avoid exposure of gel to open flames during or immediately after application.

Geriatric ConsiderationsNo specific recommendations.

Pregnancy Risk FactorC

Pregnancy Considerations

Teratogenic effects were noted in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationEnters breast milk/not recommended

Adverse Reactions

Oral:

1% to 10%:

Dermatologic: Pruritus (2%)

Gastrointestinal: Nausea/vomiting (3% to 10%), abdominal pain (1%)

<1%: Bulging fontanelles, chills, depression, diarrhea, dizziness, fever, gynecomastia, headache, hemolytic anemia, hepatotoxicity, impotence, leukopenia, photophobia, somnolence, thrombocytopenia

Topical cream/gel: Allergic reaction, contact dermatitis (possibly related to sulfites or propylene glycol), facial swelling, headache, impetigo, local burning, ocular irritation, paresthesia, pruritus, severe irritation, stinging (~5%)

Topical foam: Application site burning (10%), application site reaction (6%), contact sensitization, dryness, erythema, pruritus, rash

Shampoo: Abnormal hair texture, hair loss increase, irritation (<1%), itching, mild dryness of skin, oiliness/dryness of hair, scalp pustules

Metabolism/Transport Effects **Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (strong), 2A6 (moderate), 2B6 (weak), 2C8 (weak), 2C9 (strong), 2C19 (moderate), 2D6 (moderate), 3A4 (strong)

Drug Interactions

Alfentanil: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Aliskiren: Ketoconazole may increase the serum concentration of Aliskiren. *Risk C: Monitor therapy*

Almotriptan: Ketoconazole may increase the serum concentration of Almotriptan. *Risk C: Monitor therapy*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amphotericin B: Antifungal Agents (Azole Derivatives, Systemic) may diminish the therapeutic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Aprepitant: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Aprepitant. *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Quazepam. *Risk D: Consider therapy modification*

Bosentan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Bosentan. *Risk C: Monitor therapy*

BusPIRone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Busulfan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Busulfan. *Risk C: Monitor therapy*

Calcium Channel Blockers: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CarBAMazepine. *Risk C: Monitor therapy*

Cardiac Glycosides: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cilostazol: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Cinacalcet: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Cinacalcet. *Risk C: Monitor therapy*

Cisapride: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Cisapride. *Risk X: Avoid combination*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

Conivaptan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Conivaptan. *Risk X: Avoid combination*

Corticosteroids (Orally Inhaled): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inhibitors (Strong) may decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2A6 Substrates: CYP2A6 Inhibitors (Moderate) may decrease the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Didanosine: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). Enteric coated didanosine capsules are not expected to affect these antifungals. *Risk D: Consider therapy modification*

Docetaxel: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Docetaxel. *Risk D: Consider therapy modification*

Dofetilide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Dofetilide. *Risk X: Avoid combination*

Eletriptan: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Eletriptan. *Risk D: Consider therapy modification*

Eplerenone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eplerenone. *Risk D: Consider therapy modification*

Erlotinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Erlotinib. *Risk C: Monitor therapy*

Eszopiclone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eszopiclone. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Fexofenadine: Ketoconazole may increase the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

Fosaprepitant: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Fosaprepitant. Specifically, concentrations of aprepitant are likely to be increased. *Risk C: Monitor therapy*

Gefitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Gefitinib. *Risk C: Monitor therapy*

Grapefruit Juice: May increase the metabolism of Antifungal Agents (Azole Derivatives, Systemic). This specifically applies to oral antifungal administration. *Risk D: Consider therapy modification*

H2-Antagonists: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Imatinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Imatinib. *Risk C: Monitor therapy*

Irinotecan: Antifungal Agents (Azole Derivatives, Systemic) may enhance the adverse/toxic effect of Irinotecan. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Losartan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Losartan. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Antifungal Agents (Azole Derivatives, Systemic). Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Macrolide Antibiotics. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Methadone. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Phenytoin. Phenytoin may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Phosphodiesterase 5 Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Praziquantel: Ketoconazole may increase the serum concentration of Praziquantel. Management: Praziquantel dose may need to be reduced when used with ketoconazole. *Risk D: Consider therapy modification*

Protease Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May decrease the serum concentration of Ketoconazole. Ketoconazole may increase the serum concentration of Proton Pump Inhibitors. *Risk D: Consider therapy modification*

QuiNIDine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of QuiNIDine. Management: Itraconazole, voriconazole, and posaconazole are specifically contraindicated with quinidine. Use of quinidine with any azole antifungal may require quinidine dose adjustment and should be done with caution and close monitoring. *Risk X: Avoid combination*

Ramelteon: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ranolazine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Repaglinide. Management: Concurrent use of an azole antifungal with both repaglinide and gemfibrozil should be avoided. *Risk C: Monitor therapy*

Rifamycin Derivatives: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Rifamycin Derivatives. Only rifabutin appears to be affected. Rifamycin Derivatives may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Sirolimus. Management: Sirolimus dose reductions of up to 50-90% may be necessary when starting an azole antifungal. Use of sirolimus with the azole antifungals voriconazole and posaconazole is contraindicated. *Risk D: Consider therapy modification*

Solifenacin: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Solifenacin. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Sucralfate: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk C: Monitor therapy*

Sunitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Tacrolimus: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Temsirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Temsirolimus. Concentrations of the active metabolite, sirolimus, are likely to be increased more substantially than those of the parent temsirolimus. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Tolterodine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Tolterodine. This is likely only of concern in CYP2D6-deficient patients (ie, "poor metabolizers") *Risk D: Consider therapy modification*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

VinCRIStine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of VinCRIStine. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Ketoconazole may increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ziprasidone. *Risk C: Monitor therapy*

Zolpidem: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Zolpidem. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Ketoconazole peak serum levels may be prolonged if taken with food.

Herb/Nutraceutical: St John's wort may decrease ketoconazole levels.

Monitoring ParametersLiver function tests

Nursing: Physical Assessment/MonitoringEvaluate hepatic function prior to beginning therapy. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, anything that reduces gastric acidity may result in treatment failures with ketoconazole, concurrent use of ergot derivatives or cisapride increases the risk of potentially fatal cardiac arrhythmias, oral contraceptive efficacy may be reduced). Assess liver function, therapeutic effect (resolution of viral infection), and adverse reactions on a regular basis. Instruct patients with diabetes to monitor glucose levels closely; may impact effectiveness of oral hypoglycemics. Teach patient proper use (administration or application) and necessity of completing full therapy, possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report.

Monitoring: Lab TestsLiver function

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Oral formulations may be taken with food, at least 2 hours before any antacids. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Cream, foam, gel, and shampoo are for external use only. Use full course of medication as directed; some infections may require long periods of therapy. If you have diabetes, test serum glucose regularly; may impact effectiveness of oral hypoglycemics. May cause nausea and vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report unresolved headache, rash or itching, yellowing of eyes or skin, changes in color of urine or stool, chest pain or palpitations, sense of fullness or ringing in ears, or if condition worsens. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Cream, foam, and gel: Apply exactly as directed. Wash hands thoroughly before and after applying; keep away from eyes or mouth. Keep Extina foam can away from open fire, flame, or direct heat (Extina foam is flammable). You may experience some burning, dryness, irritation, or rash at site of application. Report severe or persistent adverse effects or if condition worsens.

Shampoo: Use as directed. May cause some temporary hair loss, scalp irritation, itching, or change in hair texture. Report severe or persistent adverse effects or if condition worsens.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol, topical [foam]:

Extina®: 2% (50 g, 100 g)

Cream, topical: 2% (15 g, 30 g, 60 g)

Kuric™: 2%: (75 g)

Gel, topical:

Xolegel™: 2% (15 g) [contains dehydrated alcohol 34%]

Shampoo, topical: 1% (120 mL), 2% (120 mL)

Nizoral®: 2% (120 mL)

Nizoral® A-D: 1% (120 mL, 210 mL)

Tablet: 200 mg

Generic AvailableYes: Cream, shampoo, tablet

Pricing: U.S. (www.drugstore.com)

Cream (Kuric)

2% (25): $45.99

2% (75): $97.42

Foam (Extina)

2% (100): $334.85

Gel (Xolegel)

2% (15): $112.73

Shampoo (Ketoconazole)

2% (120): $27.98

Shampoo (Nizoral)

2% (120): $48.35

Tablets (Ketoconazole)

200 mg (14): $30.99

Tablets (Nizoral)

200 mg (14): $64.27

Mechanism of ActionAlters the permeability of the cell wall by blocking fungal cytochrome P450; inhibits biosynthesis of triglycerides and phospholipids by fungi; inhibits several fungal enzymes that results in a build-up of toxic concentrations of hydrogen peroxide; also inhibits androgen synthesis

Pharmacodynamics/Kinetics

Absorption: Oral: Rapid (~75%); Shampoo: None; Gel: Minimal

Distribution: Well into inflamed joint fluid, saliva, bile, urine, breast milk, sebum, cerumen, feces, tendons, skin and soft tissue, and testes; crosses blood-brain barrier poorly; only negligible amounts reach CSF

Protein binding: 93% to 96%

Metabolism: Partially hepatic via CYP3A4 to inactive compounds

Bioavailability: Decreases as gastric pH increases

Half-life elimination: Biphasic: Initial: 2 hours; Terminal: 8 hours

Time to peak, serum: 1-2 hours

Excretion: Feces (57%); urine (13%)

Related Information

- Antacid Drug Interactions
- Antifungal Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, or depression
Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine
Cardiovascular ConsiderationsKetoconazole may increase cyclosporine levels by up to 50% at high doses. It may also potentiate the anticoagulant effect of warfarin and can increase lovastatin and simvastatin levels. Concomitant administration with cisapride is contraindicated.
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International Brand NamesAkorazol (MX); Antanazol (SG); Aquarius (GR); Arcolan (BR); Cetonil (AR); Conazol (MX); DaktaGOLD (AU); Dexazol (ID); Dezor Cream (MY, TH); Dezor Shampoo (MY); Dezoral (SG); Diazon (HK, SG, TH); Dysfungal (ID); Fitonal (AR); Formyco (ID); Funet (ID); Fungarest (ES); Fungaway (TW); Fungazol Tabs (HK, MY, TH); Fungicide (TH); Fungicide Tabs (IN); Fungiderm-K (TH); Funginox Tabs (TH); Fungium (CN, PY); Fungoral (GR, MX, NO, SE); Fungores (PL); Kenazol (TH); Kenazole (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Kenzol (HK); Ketazol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE, ZA); Ketazol Shampoo (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ketoconazol (CR, DO, GT, HN, NI, PA, SV); Ketoderm (FR); Ketokonazol (PL); Ketolium (FR); Ketona (TW); Ketopine (NZ); Ketoprin (CR, GT, PA, SV); Ketovid (PH); Ketozol (PL); Ketozole (IN); Kezon (TH); Kezoral (SG); Konaturil (MX); Kozec (PH); Larry (TH); Lusanoc (ID); Mizoron (TH); Muzoral Cream (ID); Mycofebrin (GR); Nastil (MX); Nazole (KP); Niz Creme (ZA); Niz Shampoo (ZA); Nizoral (AE, AT, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CY, CZ, DE, DK, EE, EG, ET, FI, GH, GM, GN, GY, HK, HN, HU, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, OM, PH, PK, PL, PT, QA, RU, SA, SC, SD, SG, SL, SN, SR, SY, TH, TN, TR, TT, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Nizoral 2% Cream (AU, PH); Nizoral Cream and Tablets (GB, IE, NL); Nizoral Shampoo (AU, DE, PH); Nizoral Tablets (AU, CO, EC, FR, NZ, PE, TW); Oronazol (HR, PL); Oxonazol (PE); Panfungol (ES); Pasalen (TH); Picamic (ID); Pristine (HK); Pristinex (HK); Reduff (PH); Sebizole (AU, MY); Sporaxyl (TH); Sporex (ID); Sporium (CO); Tiniazol (MX); Tinuvin (TW); Yucomy (MY); Ziconal (HK); Zoralin Tabs (ID)

Ketoprofen

Lexi-Drugs Online

English

Arabic

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Ketoprofen may be confused with ketotifen

Oruvail® may be confused with Clinoril®, Elavil®

Pronunciation(kee toe PROE fen)

Canadian Brand NamesApo-Keto SR®; Apo-Keto-E®; Apo-Keto®; Novo-Keto; Novo-Keto-EC; Nu-Ketoprofen; Nu-Ketoprofen-E; Oruvail®; Rhodis SR™; Rhodis-EC™; Rhodis™

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsAcute and long-term treatment of rheumatoid arthritis and osteoarthritis; primary dysmenorrhea; mild-to-moderate pain

Use: DentalManagement of pain and swelling

Dosing: Adults**Note:** The extended release formulation is not recommended for the treatment of acute pain.

Rheumatoid arthritis or osteoarthritis: Oral:

Regular release: 50 mg 4 times/day **or** 75 mg 3 times/day; up to a maximum of 300 mg/day

Extended release: 200 mg once daily

Note: Lower doses may be used in small patients or in the elderly, or debilitated.

Dysmenorrhea, mild-to-moderate pain: Oral: Regular release: 25-50 mg every 6-8 hours up to a maximum of 300 mg/day

Dosing: ElderlyInitial: 25-50 mg 3-4 times/day; increase up to 150-300 mg/day (maximum daily dose: 300 mg)

Dosing: Renal ImpairmentIn general, NSAIDs are not recommended for use in patients with advanced renal disease, but the manufacturer of ketoprofen does provide some guidelines for adjustment in renal dysfunction:

Mild impairment: Maximum dose: 150 mg/day

Severe impairment: Cl_{cr} <25 mL/minute: Maximum dose: 100 mg/day

Dosing: Hepatic ImpairmentHepatic impairment and serum albumin <3.5 g/dL: Maximum dose: 100 mg/day

Calculations

- Creatinine Clearance: Adults

Administration: OralMay take with food to reduce GI upset. Do not crush or break extended release capsules.

Dietary ConsiderationsIn order to minimize gastrointestinal effects, ketoprofen can be prescribed to be taken with food or milk.

StorageStore at room temperature of 25°C (77°F). Protect from light; avoid excessive heat and humidity.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to ketoprofen, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Allergy Considerations

- Fibric Acid Derivative Allergy
- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.

- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.

- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin's cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.

- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs, even at low doses.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of the elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (3rd trimester)

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Embryotoxicity was observed in some, but not all, animal studies. Renal insufficiency and pulmonary hypertension have been noted in premature infants (case reports). Accumulation of the active enantiomer of ketoprofen has also been reported in premature neonates with renal insufficiency. Exposure to NSAIDs late in pregnancy may lead to premature closure of the ductus arteriosus and may inhibit uterine contractions.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Gastrointestinal: Dyspepsia (11%)

Hepatic: Liver function test abnormal (≤15%)

1% to 10%:

Cardiovascular: Peripheral edema (2%)

Central nervous system: Headache (3% to 9%), depression, dizziness (>1%), dreams, insomnia, malaise, nervousness, somnolence

Dermatologic: Rash (>1%)

Gastrointestinal: Abdominal pain (3% to 9%), constipation (3% to 9%), diarrhea (3% to 9%), flatulence (3% to 9%), nausea (3% to 9%), gastrointestinal bleeding (>2%), peptic ulcer (>2%), anorexia (>1%), stomatitis (>1%), vomiting (>1%)

Genitourinary: Urinary tract irritation (>1%)

Ocular: Visual disturbances (>1%)

Otic: Tinnitus (>1%)

Renal: Renal dysfunction (3% to 9%)

<1%, postmarketing, and/or case reports (Limited to important or life-threatening): Agranulocytosis, allergic reaction, allergic rhinitis, alopecia, anaphylaxis, anemia, angioedema, arrhythmia, aseptic meningitis, blurred vision, bone marrow suppression, bronchospasm, buccal necrosis, bullous rash, chills, cholestatic hepatitis, confusion, CHF, conjunctivitis, cystitis, diabetes mellitus (aggravated), drowsiness, dysphoria, dyspnea, eczema, edema, epistaxis, erythema multiforme, exfoliative dermatitis, facial edema, fecal occult blood, fluid retention, gastritis, gastrointestinal perforation, GI ulceration, gynecomastia, hallucinations, hearing decreased, hematemesis, hematuria, hemolytic anemia, hemoptysis, hepatic dysfunction, hepatitis, hot flashes, hypertension, hyponatremia, impotence, infection, interstitial nephritis, intestinal ulceration, jaundice, laryngeal edema, leukopenia, libido disturbance, melena, microvesicular steatosis, migraine, myocardial infarction, nephrotic syndrome, onycholysis, palpitation, pancreatitis, peptic ulcer, peripheral neuropathy, peripheral vascular disease, photosensitivity, polydipsia, polyuria, pruritus, purpura, purpuric rash, renal failure, renal papillary necrosis, retinal hemorrhage, septicemia, shock, Stevens-Johnson syndrome, tachycardia, thrombocytopenia, toxic amblyopia, toxic epidermal necrolysis, tubulopathy, ulcerative colitis, urticaria, vasodilation, xerostomia

Metabolism/Transport Effects **Inhibits** CYP2C9 (weak)

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Ketoprofen. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of

Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (due to GI irritation).

Food: Food slows rate of absorption resulting in delayed and reduced peak serum concentrations; total bioavailability is not affected by food.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, and white willow (all have additional antiplatelet activity).

Monitoring ParametersCBC, chemistry profile, occult blood loss, periodic liver function; renal function (urine output, serum BUN, creatinine)

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess effectiveness and interactions of other medications patient may be taking. Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests, therapeutic effectiveness, and adverse or overdose reactions at beginning of therapy and periodically throughout therapy. Schedule ophthalmic evaluations for patients who develop eye complaints during long-term NSAID therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC, chemistry profile, occult blood loss, periodic liver function; renal function (urine output, serum BUN, creatinine)

Patient EducationTake this medication exactly as directed; do not increase dose without consulting prescriber. Do not crush tablets or break capsules. Take with food or milk to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol, aspirin or aspirin-containing medication, or any other anti-inflammatory medications without consulting prescriber. You may experience drowsiness, dizziness, nervousness, or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); anorexia, nausea, vomiting, or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); fluid retention (weigh yourself weekly and report unusual (3-5 lb/week) weight gain). GI bleeding, ulceration, or perforation can occur with or without pain; discontinue medication and contact prescriber if persistent abdominal pain or cramping, or blood in stool occurs. Report breathlessness, respiratory difficulty, or unusual cough; chest pain, rapid heartbeat, palpitations; unusual bruising/bleeding; blood in urine, stool, mouth, or vomitus; swollen extremities; skin rash or itching; acute fatigue; hearing changes (ringing in ears); jaundice; right upper quadrant tenderness; or flu-like symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, regular release: 50 mg, 75 mg

Capsule, extended release: 200 mg

Generic AvailableYes

ManufacturerWyeth-Ayerst Laboratories

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Ketoprofen CR)

200 mg (30): $84.12

Capsules (Ketoprofen)

50 mg (90): $20.98

75 mg (60): $14.99

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: Regular release: <30 minutes

Duration: Regular release: Up to 6 hours

Absorption: Almost complete

Protein binding: >99%, primarily to albumin; Hepatic impairment: Unbound fraction is approximately doubled

Metabolism: Hepatic via glucuronidation; metabolite can be converted back to parent compound; may have enterohepatic recirculation

Bioavailability: ~90%

Half-life elimination:

Regular release: 2-4 hours; Renal impairment: Mild: 3 hours; moderate-to-severe: 5-9 hours

Extended release: ~3-7.5 hours

Time to peak, serum:

Regular release: 0.5-2 hours

Extended release: 6-7 hours

Excretion: Urine (~80%, primarily as glucuronide conjugates)

Related Information

- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

According to the FDA, the over-the-counter NSAID ketoprofen should be viewed as having the potential to interfere with the antiplatelet effect of low-dose aspirin until proven otherwise. This statement was provided in the same warning from the FDA that ibuprofen can interfere with the antiplatelet effect of low-dose aspirin (81 mg/day), potentially rendering aspirin less effective when used for cardioprotection and stroke protection. In situations where these drugs could be used concomitantly, the FDA has provided the following information: Patients who use immediate release aspirin (not enteric-coated aspirin) and take single doses of ibuprofen 400 mg, should dose the ibuprofen at least 30 minutes or longer after aspirin ingestion or more than 8 hours before aspirin ingestion to avoid attenuation of aspirin's effect. Similar recommendations may hold for concomitant ketoprofen and aspirin use.

At this time, recommendations about the timing of ibuprofen 400 mg or other NSAIDs (such as ketoprofen) in patients taking enteric-coated low-dose aspirin cannot be made based on available data.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness; may rarely cause insomnia, confusion, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A recent meta-analysis (see References) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 chronic heart failure guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin's inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective), if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function, and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

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International Brand NamesArket (CL); Bi-Profenid (FR, PL); Bi-Rofenid (BE); Dolofar (CN); Dolomax (CO); Fastum (CH, CR, DO, GT, HN, IT, NI, PA, PH, PL, SV); Febin (TW); Febrofen (PL); Fetik (ID); Gabrilen (DE); Gabrilen Retard (DE); Helenil (AR); Kaltrofen (ID); Kebanon (KP); Kenhancer (MY); Keotsan (PE); Ketadom (HK); Ketin (TW); Ketofen (IN, TW); Ketoflam (ZA); Ketolgin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ketolgin Gel (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ketolgin SR (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ketomex (FI); Ketonal (PL); Ketoprofen (PL); Ketopronil (PL); Ketores (PL); Ketorin (FI); Ketros (ID); Lantiflam (ID); Lolita (TH); Mohrus (JP); Nazovell (ID); Orudis (AE, AU, BH, CY, DK, EG, ES, FI, GB, HK, IL, IQ, IR, IT, JO, KW, LB, LY, MY, NL, NO, OM, QA, SA, SE, SY, UY, YE); Orudis EC (PH); Orudis R-PR (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Orudis SR (AU); Oruvail (AE, BF, BH, BJ, CI, CY, EG, ET, GB, GH, GM, GN, GR, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NZ, OM, PK, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Oruvail SR (AU); Ovurila (ID); Ovurila E (ID); Profecom (ID); Profenid (AT, BG, CZ, EC, EE, ID, IL, MX, PE, PL, PT, PY, RU, TR, VE); Profenid Prolongatum (PL); Profenil (IT); Profika (ID); Prontoket (PL); Protofen (ID); Rematof (ID); Rhetoflam (ID); Rheuna PAP (KP); Rofenid (BE); Spondylon (DE); Toprec (FR, PL); Udzapen (PH); Vestam Gel (TH)

Ketorolac

Lexi-Drugs Online

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English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Acular® may be confused with Acthar®, Ocular®

Ketorolac may be confused with Ketalar®

Toradol® may be confused with Foradil®, Inderal®, Tegretol®, Torecan®, traMADol, tromethamine

International issues:

Toradol® may be confused with Theradol® which is a brand name for tramadol in the Netherlands

Pronunciation(KEE toe role ak)

U.S. Brand NamesAcular LS™; Acular®; Acular® PF

Canadian Brand NamesAcular LS™; Acular®; Apo-Ketorolac Injectable®; Apo-Ketorolac®; Ketorolac Tromethamine Injection, USP; Novo-Ketorolac; ratio-Ketorolac; Toradol®; Toradol® IM

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Ophthalmic; Nonsteroidal Anti-inflammatory Drug (NSAID), Oral; Nonsteroidal Anti-inflammatory Drug (NSAID), Parenteral

Use: Labeled Indications

Oral, injection: Short-term (≤5 days) management of moderate-to-severe acute pain requiring analgesia at the opioid level

Ophthalmic: Temporary relief of ocular itching due to seasonal allergic conjunctivitis; postoperative inflammation following cataract extraction; reduction of ocular pain and photophobia following incisional refractive surgery; reduction of ocular pain, burning, and stinging following corneal refractive surgery

Use: DentalOral, injection: Short-term (≤5 days) management of moderate-to-severe acute pain requiring analgesia at the opioid level

Dosing: Adults

Pain management (acute; moderately-severe):Note: The maximum combined duration of treatment (for parenteral and oral) is 5 days; do not increase dose or frequency; supplement with low dose opioids if needed for breakthrough pain. For patients <50 kg and/or ≥65 years of age, see Elderly dosing.

I.M.: 60 mg as a single dose or 30 mg every 6 hours (maximum daily dose: 120 mg)

I.V.: 30 mg as a single dose or 30 mg every 6 hours (maximum daily dose: 120 mg)

Oral: 20 mg, followed by 10 mg every 4-6 hours; do not exceed 40 mg/day; oral dosing is intended to be a continuation of I.M. or I.V. therapy only

Ophthalmic uses:

Seasonal allergic conjunctivitis (relief of ocular itching) (Acular®):*Ophthalmic:* Instill 1 drop (0.25 mg) 4 times/day

Inflammation following cataract extraction (Acular®):*Ophthalmic:* Instill 1 drop (0.25 mg) to affected eye(s) 4 times/day beginning 24 hours after surgery; continue for 2 weeks

Pain and photophobia following incisional refractive surgery (Acular® PF):*Ophthalmic:* Instill 1 drop (0.25 mg) 4 times/day to affected eye for up to 3 days

Pain following corneal refractive surgery (Acular LS™):*Ophthalmic:* Instill 1 drop 4 times/day as needed to affected eye for up to 4 days

Dosing: ElderlyDosage adjustments in elderly (≥65 years), renal insufficiency, or low body weight (<50 kg): **Note:** These groups have an increased incidence of GI bleeding, ulceration, and perforation. The maximum combined duration of treatment (for parenteral and oral) is 5 days.

I.M.: 30 mg as a single dose or 15 mg every 6 hours (maximum daily dose: 60 mg)

I.V.: 15 mg as a single dose or 15 mg every 6 hours (maximum daily dose: 60 mg)

Oral: 10 mg, followed by 10 mg every 4-6 hours; do not exceed 40 mg/day; oral dosing is intended to be a continuation of I.M. or I.V. therapy only

Dosing: Pediatric

Pain management (acute; moderately-severe):

Children 2-16 years (unlabeled use): Limited pediatric studies. The maximum combined duration of treatment (for parenteral and oral) is 5 days. **Do not exceed adult doses.Note:** The manufacturer warns that oral ketorolac is not indicated for children.

I.V.: Initial dose: 0.5 mg/kg followed by 0.25-1 mg/kg every 6 hours for up to 48 hours; maximum daily dose: 90 mg

Oral: 0.25 mg/kg every 6 hours

Children ≥16 years and <50 kg: *I.V.:* Refer to elderly dosing.

Children ≥16 years and ≥50 kg: *I.V.:* Refer to adult dosing.

Children ≥17 years and <50 kg: *Oral:* Refer to elderly dosing.

Children ≥17 years and ≥50 kg: *Oral:* Refer to adult dosing.

Ophthalmic uses: Children ≥3 years: Refer to adult dosing.

Dosing: Renal ImpairmentContraindicated in patients with advanced renal impairment. Patients with moderately-elevated serum creatinine should use half the recommended dose, not to exceed 60 mg/day I.M./I.V.

Dosing: Hepatic ImpairmentUse with caution, may cause elevation of liver enzymes; discontinue if clinical signs and symptoms of liver disease develop.

Administration: I.M.Administer slowly and deeply into the muscle. Analgesia begins in 30 minutes and maximum effect within 2 hours.

Administration: I.V.Administer I.V. bolus over a minimum of 15 seconds; onset within 30 minutes; peak analgesia within 2 hours.

Administration: I.V. DetailpH: 6.9-7.9

Administration: OralMay take with food to reduce GI upset.

Administration: OtherOphthalmic solution: Contact lenses should be removed before instillation.

Dietary ConsiderationsAdminister tablet with food or milk to decrease gastrointestinal distress.

Storage

Injection: Store at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light. Injection is clear and has a slight yellow color. Precipitation may occur at relatively low pH values.

Ophthalmic solution: Store at room temperature 15°C to 25°C (59°F to 77°F). Protect from light.

Tablet: Store at room temperature of 15°C to 30°C (59°F to 86°F).

CompatibilityStable in D_5NS, D_5W, LR, NS.

Y-site administration: Compatible: Cisatracurium, dexmedetomidine, fentanyl, hydromorphone, methadone, morphine, remifentanil, sufentanil. **Incompatible:** Azithromycin, fenoldopam.

Compatibility in syringe: Compatible: Diazepam, sufentanil. **Incompatible:** Haloperidol, hydroxyzine, nalbuphine, prochlorperazine edisylate, promethazine, triethylperazine. **Variable (consult detailed reference):** Hydromorphone.

Compatibility when admixed: Incompatible: Hydroxyzine, meperidine, morphine, promethazine.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

Contraindications

Oral, injection: Hypersensitivity to ketorolac, aspirin, other NSAIDs, or any component of the formulation; active or history of peptic ulcer disease; recent or history of GI bleeding or perforation; patients with advanced renal disease or risk of renal failure (due to volume depletion); prophylaxis before major surgery; suspected or confirmed cerebrovascular bleeding; hemorrhagic diathesis, incomplete hemostasis, or high risk of bleeding; concurrent ASA or other NSAIDs; concomitant probenecid or pentoxifylline; epidural or intrathecal administration; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery; labor and delivery; breast-feeding

Ophthalmic: Hypersensitivity to ketorolac or any component of the formulation

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Aspirin/other NSAIDs: See “Concurrent drug therapy issues” below.
- Bleeding/hemostasis: See “Concerns related to adverse effects” below.
- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery/major surgery: See “Disease-related concerns” below.
- Elderly: See “Special populations” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

- Hypersensitivity: See “Concerns related to adverse effects” below.

- Labor and delivery/breast-feeding: See “Special populations” below.

- Low body weight: See “Special populations” below.

- Pediatrics: See “Special populations” below.

- Renal impairment: See “Disease-related concerns” below.

- Systemic preparations: See “Dosage form specific issues” below.

Concerns related to adverse effects:

- Bleeding/hemostasis: **[U.S. Boxed Warning]: May inhibit platelet function; contraindicated in patients with cerebrovascular bleeding (suspected or confirmed), hemorrhagic diathesis, incomplete hemostasis and patients at high risk for bleeding.** Effects on platelet adhesion and aggregation may prolong bleeding time. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.

- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.

- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding, ulcers, inflammatory bowel disease), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly, or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Hypersensitivity: Even in patients without prior exposure, hypersensitivity including bronchospasm and anaphylactic shock, may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy. **[U.S. Boxed Warning]: Ketorolac injection is contraindicated in patients with prior hypersensitivity reaction to aspirin or NSAIDs.**

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery/major surgery: **[U.S. Boxed Warning]: Use is contraindicated as prophylactic analgesic before any major surgery and is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery. Wound bleeding and postoperative hematomas have been associated with ketorolac use in the perioperative setting.

- Hepatic impairment: Use with caution in patients with hepatic impairment or a history of liver disease. Closely monitor patients with any abnormal LFT. Rarely, severe hepatic reactions (eg, fulminant hepatitis, hepatic necrosis, liver failure) have occurred with NSAID use; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: **[U.S. Boxed Warning]: Ketorolac is contraindicated in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion.** NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Use with caution in patients with impaired renal function or history of kidney disease. Dosage adjustment is required in patients with moderate elevation in serum creatinine. Acute renal failure, interstitial nephritis, and nephrotic syndrome have been reported with ketorolac use; papillary necrosis and renal injury have been reported with the use of NSAIDs.

Concurrent drug therapy issues:

- Aspirin/other NSAIDs: **[U.S. Boxed Warning]: Concurrent use of ketorolac with aspirin or other NSAIDs is contraindicated due to the increased risk of adverse reactions.**

Special populations:

- Elderly: **[U.S. Boxed Warning]: Dosage adjustment is required for patients ≥65 years of age.** The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs, even at low doses.

- Labor and delivery/breast-feeding: **[U.S. Boxed Warning]: May inhibit uterine contractions (increasing the risk for uterine hemorrhage) and affect fetal circulation; inhibition of prostaglandin synthesis may adversely affect neonates; use is contraindicated in labor and delivery and breast-feeding women.** Avoid use in late pregnancy.

- Low body weight: **[U.S. Boxed Warning]: Dosage adjustment is required for patients weighing <50 kg (<110 pounds).**

- Pediatrics: **[U.S. Boxed Warning]: Oral ketorolac is not indicated for use in children.** Safety and efficacy for ophthalmic solution have not been established in children <3 years of age.

Dosage form specific issues:

- Ophthalmic solution: May increase bleeding time associated with ocular surgery. Use with caution in patients with known bleeding tendencies or those receiving anticoagulants. Healing time may be slowed or delayed. Corneal thinning, erosion, or ulceration have been reported with topical NSAIDs; discontinue if corneal epithelial breakdown occurs. Use caution with complicated ocular surgery, corneal denervation, corneal epithelial defects, diabetes, rheumatoid arthritis, ocular surface disease, or ocular surgeries repeated within short periods of time; risk of corneal epithelial breakdown may be increased. Use for >24 hours prior to or for >14 days following surgery also increases risk of corneal adverse effects. Do not administer while wearing soft contact lenses.

- Systemic preparations: **[U.S. Boxed Warning]: Oral therapy is only indicated for use as continuation treatment, following parenteral ketorolac and is not indicated for minor or chronic painful conditions. The maximum daily oral dose is 40 mg (adults); doses above 40 mg/day do not improve efficacy but may increase the risk of serious adverse effects. [U.S. Boxed Warning]: Systemic ketorolac is indicated for short term (≤5 days) use in adults for treatment of moderately severe acute pain requiring opioid-level analgesia.** The combined therapy duration (oral and parenteral) should not exceed 5 days. **[U.S. Boxed Warning]: Ketorolac injection is contraindicated for epidural or intrathecal administration.**

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsKetorolac is cleared more slowly in the elderly. It is recommended to use lower doses in the elderly. Elderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute or weight <50 kg. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (3rd trimester)

Pregnancy Considerations**[U.S. Boxed Warning]: Ketorolac is contraindicated during labor and delivery (may inhibit uterine contractions and adversely affect fetal circulation).** Avoid the use of ketorolac (all dosage forms) during late pregnancy.

LactationEnters breast milk/contraindicated

Breast-Feeding Considerations**[U.S. Boxed Warning]: Inhibition of prostaglandin synthesis may adversely affect neonates; use of systemic ketorolac is contraindicated in breast-feeding women.**

Adverse Reactions

Systemic (frequencies noted for parenteral administration):

>10%:

Central nervous system: Headache (17%)

Gastrointestinal: Gastrointestinal pain (13%), dyspepsia (12%), nausea (12%)

>1% to 10%:

Cardiovascular: Edema (4%), hypertension

Central nervous system: Dizziness (7%), drowsiness (6%)

Dermatologic: Pruritus, purpura, rash

Gastrointestinal: Diarrhea (7%), constipation, flatulence, GI bleeding, GI fullness, GI perforation, GI ulcer, heartburn, stomatitis, vomiting

Hematologic: Anemia, bleeding time increased

Hepatic: Liver enzymes increased

Local: Injection site pain (2%)

Otic: Tinnitus

Renal: Renal function abnormal

Miscellaneous: Diaphoresis

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Abnormal thinking, acute pancreatitis, acute renal failure, agranulocytosis, alopecia, anaphylactoid reaction, anaphylaxis, angioedema, anxiety, aplastic anemia, arrhythmia, aseptic meningitis, asthma, azotemia, blurred vision, bradycardia, bronchospasm, bruising, chest pain, CHF, cholestatic jaundice, coma, confusion, conjunctivitis, cough, cystitis, depression, dyspnea, dysuria, eosinophilia, epistaxis, eructation, erythema multiforme, esophagitis, euphoria, excessive thirst, exfoliative dermatitis, extrapyramidal symptoms, fever, flank pain, flushing, gastritis, GI hemorrhage, glossitis, hallucinations, hearing loss, hematemesis, hematuria, hemolytic anemia, hemolytic uremic syndrome, hepatitis, hyperglycemia, hyperkalemia, hyperkinesis, hypersensitivity reactions, hyponatremia, hypotension, inability to concentrate, infection, infertility, inflammatory bowel disease exacerbation, insomnia, interstitial nephritis, jaundice, laryngeal edema, leukopenia, liver failure, Lyell's syndrome, lymphadenopathy, maculopapular rash, melena, MI, nephritis, nervousness, oliguria, pallor, palpitation, pancytopenia, paresthesia, photosensitivity, pneumonia, polyuria, proteinuria, psychosis, pulmonary edema, rectal bleeding, renal failure, respiratory depression, rhinitis, seizure, sepsis, somnolence, Stevens-Johnson syndrome, stomatitis (ulcerative), stupor, syncope, tachycardia, thrombocytopenia, tongue edema, toxic epidermal necrolysis, tremor, urinary frequency increased, urinary retention, urticaria, vasculitis, vertigo, weakness, weight gain, wound hemorrhage (postoperative), xerostomia

Ophthalmic solution:

>10%: Ocular: Transient burning/stinging (Acular®: 40%; Acular® PF: 20%)

>1% to 10%:

Central nervous system: Headache

Ocular: Conjunctival hyperemia, corneal infiltrates, iritis, ocular edema, ocular inflammation, ocular irritation, ocular pain, superficial keratitis, superficial ocular infection

Miscellaneous: Allergic reactions

≤1%: Dry eyes, corneal ulcer, blurred vision

Postmarketing and/or case reports: Corneal erosion, corneal perforation, corneal thinning, epithelial breakdown

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Anticonvulsants: Ketorolac may diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Aspirin: Ketorolac may enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Latanoprost: NSAID (Ophthalmic) may diminish the therapeutic effect of Latanoprost. *Risk C: Monitor therapy*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Ketorolac may enhance the adverse/toxic effect of Neuromuscular-Blocking Agents (Nondepolarizing). Specifically, episodes of apnea have been reported in patients using this combination. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: Ketorolac may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Pentoxifylline: Ketorolac may enhance the adverse/toxic effect of Pentoxifylline. Specifically, the risk of bleeding may be increased with this combination. *Risk X: Avoid combination*

Probenecid: May increase the serum concentration of Ketorolac. *Risk X: Avoid combination*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Oral: High-fat meals may delay time to peak (by ~1 hour) and decrease peak concentrations.

Herb/Nutraceuticals: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, and white willow (all have additional antiplatelet activity).

Monitoring ParametersMonitor response (pain, range of motion, grip strength, mobility, ADL function), inflammation; observe for weight gain, edema; monitor renal function (serum creatinine, BUN, urine output); observe for bleeding, bruising; evaluate gastrointestinal effects (abdominal pain, bleeding, dyspepsia); mental confusion, disorientation, CBC and platelets, liver function tests

Reference RangeSerum concentration: Therapeutic: 0.3-5 mcg/mL; Toxic: >5 mcg/mL

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess allergy history prior to beginning therapy. Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. **I.V./I.M.:** Vital signs should be monitored on a regular basis during infusion or following injection. **Oral:** Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests, therapeutic effectiveness, and adverse response on a regular basis throughout therapy. Teach patient proper use, possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report.

Monitoring: Lab TestsCBC and platelets, liver function, platelets; renal function (serum creatinine, BUN, urine output)

Patient EducationDo not take any new medication during therapy without consulting prescriber (especially aspirin-containing products or any other NSAIDs). Use exactly as directed; do not increase dose or frequency. Adverse reactions can occur with overuse. Oral doses may be taken with food or milk. Avoid alcohol. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause nausea or vomiting (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help). Report blood in vomitus or stool or other signs of unusual bleeding; abdominal pain; weakness; slurring of speech; ringing in ears; unresolved nausea or vomiting; respiratory difficulty or shortness of breath; skin rash; unusual swelling of extremities; unexplained weight gain; chest pain; or palpitations. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary. Consult prescriber if breast-feeding.

Ophthalmic: Instill drops as often as recommended. Wash hands before instilling. Sit or lie down to instill. Open eye, look at ceiling, and instill prescribed amount of solution. Close eye and roll eye in all directions. Apply gentle pressure to inner corner of eye for 1-2 minutes after instillation. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Temporary stinging or blurred vision may occur. Do not wear soft contact lenses. Report persistent pain, burning, double vision, swelling, itching, or worsening of condition.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as tromethamine: 15 mg/mL (1 mL); 30 mg/mL (1 mL, 2 mL, 10 mL) [contains ethanol]

Solution, ophthalmic, as tromethamine:

Acular®: 0.5% (3 mL, 5 mL, 10 mL) [contains benzalkonium chloride]

Acular LS™: 0.4% (5 mL) [contains benzalkonium chloride]

Solution, ophthalmic, as tromethamine [preservative free]:

Acular® P.F.: 0.5% (0.4 mL)

Tablet, as tromethamine: 10 mg

Generic AvailableYes: Injection, tablet

Pricing: U.S. (www.drugstore.com)

Solution (Acular)

0.5% (3): $59.34

0.5% (5): $99.60

0.5% (10): $185.45

Solution (Acular LS)

0.4% (5): $102.79

Solution (Acular PF)

0.5% (12): $80.13

Tablets (Ketorolac Tromethamine)

10 mg (30): $24.99

Tablets (Toradol Oral)

10 mg (30): $41.99

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: Analgesic: I.M.: ~10 minutes

Peak effect: Analgesic: 2-3 hours

Duration: Analgesic: 6-8 hours

Absorption: Oral: Well absorbed (100%)

Distribution: ~13 L; poor penetration into CSF; crosses placenta

Protein binding: 99%

Metabolism: Hepatic

Half-life elimination: 2-6 hours; prolonged 30% to 50% in elderly; up to 19 hours in renal impairment

Time to peak, serum: I.M.: 30-60 minutes

Excretion: Urine (92%, ~60% as unchanged drug); feces ~6%

Related Information

- Nonsteroidal Anti-inflammatory Agents

Pharmacotherapy PearlsFirst parenteral NSAID for analgesia; 30 mg provides the analgesia comparable to 12 mg of morphine or 100 mg of meperidine.

Dental Health Professional ConsiderationsAccording to the manufacturer, ketorolac has been used inappropriately by physicians in the past. The drug had been prescribed to NSAID-sensitive patients, patients with GI bleeding, and for long-term use; a warning has been issued regarding increased incidence and severity of GI complications with increasing doses and duration of use. Labeling now includes the statement that ketorolac inhibits platelet function and is indicated for up to 5 days use only.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and stomatitis.

NSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®). See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness; may rarely produce depression

Mental Health: Effects on Psychiatric TreatmentMay decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A meta-analysis (Pope, 1993) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 chronic heart failure guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin's inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective), if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) recommend that ketorolac therapy be limited to a maximum of 5 days with close attention to gastrointestinal and renal function. The risk of developing renal dysfunction or gastrointestinal bleeding further increases as treatment extends beyond 5 days.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

Ketorolac is contraindicated during labor and delivery (may inhibit uterine contractions and adversely affect fetal circulation). Avoid use of ketorolac ophthalmic solution during late pregnancy.

Index TermsKetorolac Tromethamine

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International Brand NamesAcular (AT, AU, BR, CH, CN, CR, DE, DK, DO, EC, ES, FI, FR, GB, GT, HK, HN, IE, KP, NI, NL, PA, SG, SV, TH, UY, ZA); Acular LS (CO); Aculare (BE); Alidol (MX); Analac (TW); Dolac (BF, BJ, CI, ET, GH, GM, GN, ID, KE, LR, MA, ML, MR, MU, MW, MX, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Dolorex (PE); Dolten (AR, PY); Eleadol (UY); Estopein (MX); Eurolac (PH); Inco (TW); Kelac (IN); Keromin (KP); Ketanov (IN); Keto (HK, ID); Ketomed (PH); Ketoracin (KP); Ketron (CO); Kortezor (PH); Notolac (VE); Painoff (TW); Remopain (ID); Rolesen (EC); Scelto (ID); Supradol (DO, MX, PA, SV); Tabel (KP); Taresin (KP); Teromac (PH); Toloran (MX); Tora-Dol (CH); Toradol (AE, AU, BB, BH, BM, BS, BZ, CY, DK, EG, ES, FI, GB, GY, HK, ID, IL, IQ, IR, IT, JM, JO, KW, LB, LY, NO, OM, PH, PK, PL, QA, RU, SA, SE, SR, SY, TR, TT, YE); Toragesic (BR); Toral (MX); Toramine (ID); Torasic (ID); Torkol (MX); Torpain (ID); Tral (PH)

Ketotifen

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Ketotifen may be confused with ketoprofen

Pronunciation(kee toe TYE fen)

U.S. Brand NamesAlaway™ [OTC]; Zaditor® [OTC]

Canadian Brand NamesNovo-Ketotifen®; Nu-Ketotifen®; Zaditen®; Zaditor®

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation; Mast Cell Stabilizer

Use: Labeled Indications

Ophthalmic: Temporary prevention of eye itching due to allergic conjunctivitis

Oral (Canadian use; not approved in U.S.): Adjunctive therapy in the chronic treatment of pediatric patients ≥6 months of age with mild, atopic asthma

Dosing: Adults**Allergic conjunctivitis:** Ophthalmic: Instill 1 drop into the affected eye(s) twice daily, every 8-12 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Allergic conjunctivitis: Children ≥3 years: Ophthalmic: Refer to adult dosing.

Atopic asthma (**Note:** Not for acute attacks): Oral (not approved in U.S.):

Children 6 months to 3 years: Initial: 0.025 mg/kg once daily or in 2 divided doses for 5 days; Maintenance: 0.05 mg/kg twice daily

Children >3 years: Initial: 0.5 mg once daily or in 2 divided doses for 5 days; Maintenance: 1 mg twice daily

Administration: OralMay administer without regard to meals.

Dietary ConsiderationsNovo-Ketotifen® syrup contains carbohydrate 4 g/5 mL.

Storage

Ophthalmic solution: Store at 25°C (77°F).

Syrup: Store at up to 25°C (up to 77°F).

Tablet: Store at 15°C to 25°C (59°F to 77°F).

RestrictionsOral formulation not available in U.S.

ContraindicationsHypersensitivity to ketotifen or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Sedation (oral use): May cause drowsiness early in therapy; initiate therapy at one-half the recommended daily dose and gradually increase over 5 days to maintenance dose; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Thrombocytopenia: Rare cases of thrombocytopenia have been reported in patients concurrently using oral ketotifen and oral antidiabetic agents.

Concurrent drug therapy issues:

- Antiasthmatic agents: Oral ketotifen should not be used to treat acute asthma attacks. Therapy with agents used for prophylaxis or relief of asthma related symptoms (eg, corticosteroids, $beta_2$-agonists, xanthine derivatives), should be not be interrupted nor should dosing be immediately reduced with the onset of ketotifen therapy. Reduce dosing gradually especially in patients taking corticosteroids or ACTH therapy. Steroid-dependent patients with adrenocortical insufficiency can take up to one year to recover a normal stress related pituitary-adrenal response.

Special populations:

- Contact lens wearers: Ophthalmic solution: Not to treat contact lens-related irritation. After ketotifen use, soft contact lens wearers should wait at least 10 minutes before putting their lenses in. Do not wear contact lenses if eyes are red. Do not contaminate dropper tip or solution when placing drops in eyes.
- Diabetics: Due to the carbohydrate content of the syrup preparation, diabetic patients may need to use alternative dosage form (tablet)

- Pediatrics: Safety and efficacy have not been established in children <3 years of age and of oral preparation in patients <6 months of age have not been established.

Dosage form specific issues:

- Benzoate allergy: Syrup products may contain benzoate compounds.

Other warnings/precautions:

- Delayed clinical response: Therapeutic effects may not be clinically evident until several weeks after the initiation of therapy while full effectiveness is usually not evident until after 10 weeks of therapy. Patients with an inadequate response after a few weeks should be maintained for at least 2-3 months on therapy. Discontinuation of therapy if needed should occur gradually over 2-4 weeks however symptoms of asthma may reoccur with discontinuation.

Geriatric ConsiderationsInstruct the patient on proper instillation of ophthalmic solution.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse fetal effects were found in some but not all animal studies. Topical ocular administration has not been studied.

LactationEnters breast milk/not recommended

Adverse Reactions

Ophthalmic: 1% to 10%:

Ocular: Allergic reactions, burning or stinging, conjunctivitis, discharge, dry eyes, eye pain, eyelid disorder, itching, keratitis, lacrimation disorder, mydriasis, photophobia, rash

Respiratory: Pharyngitis

Miscellaneous: Flu syndrome

Oral:

1% to 10%:

Central nervous system: Sedation (8%; less than placebo), headache (1%), sleep disturbance (1%)

Dermatologic: Rash (4%), urticaria (1%)

Gastrointestinal: Weight gain (5%), abdominal pain (1%), appetite increased (1%)

Respiratory: Respiratory infection (4%), epistaxis (1%)

Miscellaneous: Flu (3%), puffy eyelid (1%)

<1%, postmarketing, and/or case reports: Cystitis, dizziness, erythema multiforme, excitation, insomnia, irritability, nervousness, Stevens-Johnson syndrome, thrombocytopenia, transaminases increased, xerostomia

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Effects may be increased with concomitant use of ketotifen.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic response and adverse effects. Teach patient proper use, side effects/appropriate interventions, and symptoms to report. Taper dosage slowly when discontinuing. Do not discontinue abruptly.

Patient Education

Ophthalmic use: For use in eyes only. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Not to be used to treat contact lens-related irritation. Wait at least 10 minutes before putting soft contact lenses in. Do not wear contact lenses if eyes are red.

Oral: Do not use to treat acute asthmatic attacks. Therapeutic effects may not be clinically evident until several weeks after the initiation of therapy. Do not discontinue abruptly. You may experience drowsiness or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known).

Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant or breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] =

Canadian brand name

Solution, ophthalmic [drops]: 0.025% (5 mL)

Alaway™: 0.025% (10 mL) [contains benzalkonium chloride]

Zaditor®: 0.025% (5 mL) [contains benzalkonium chloride]

Syrup: 1 mg/5 mL (250 mL) [not available in U.S.]

Novo-Ketotifen® [CAN]: 1 mg/5 mL (250 mL) [not available in U.S.; contains alcohol, benzoate compounds; strawberry flavor]

Nu-Ketotifen® [CAN]: 1 mg/5 mL (250 mL) [not available in U.S.]

Zaditen® [CAN]: 1 mg/5 mL (250 mL) [not available in U.S.]

Tablet: 1 mg [not available in U.S.]

Novo-Ketotifen® [CAN]: 1 mg [not available in U.S.]

Zaditen® [CAN]: 1 mg [not available in U.S.]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Zaditor)

0.025% (5): $69.99

Mechanism of ActionExhibits noncompetitive H_1-receptor antagonist and mast cell stabilizer properties. Efficacy in conjunctivitis and asthma likely results from a combination of anti-inflammatory and antihistaminergic actions including interference with chemokine-induced migration of eosinophils into inflamed conjunctiva and airways, inhibition of airway hyper-reactivity due to platelet activating factor (PAF), antagonism of leukotriene-induced bronchoconstriction.

Pharmacodynamics/Kinetics

Ophthalmic:

Onset of action: Minutes

Duration: 8-12 hours

Absorption: Minimally systemic

Oral:

Absorption: Rapid, ≥60%

Protein binding: 75%

Metabolism: Hepatic via N-glucuronidation to inactive metabolite ketotifen-N-glucoronide; N-demethylation to active metabolite nor-ketotifen; and keto-reduction to hydroxyl derivative

Clearance: Increased in children >3 years; decreased in children ≤3 years

Bioavailability: ~50%

Half-life elimination: ~9-9.5 hours

Time to peak, plasma: 2-4 hours

Excretion: Urine (60% to 70% as metabolites, 1% as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pharyngitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause dry eyes which can be exacerbated by anticholinergic agents or psychotropics with significant anticholinergic activity

Index TermsKetotifen Fumarate

References

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Kabra SK, Pandey RM, Singh R, et al, "Ketotifen for Asthma in Children Aged 5 to 15 Years: A Randomized Placebo-Controlled Trial," *Ann Allergy Asthma Immunol*, 2000. 85(1):46-52.[PubMed 10923604]

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International Brand NamesAllerfen (KP); Amitone (HK); Asdron (BR); Asmafen (NZ); Asmalergin (BR); Asmax (BR); Asmen (BR); Asthafen (IN); Asthan (TW); Astifen (HK); Asumalife (MY, SG); Bentifen (SE); Butifeno (MX); Demetofrin (GR); Denerel (MY, TW); Dhatifen (HK, MY); Difen (CO); Dihalar (HR); Edifen (KP); Eucycline (GR); Hyalcrom NF (MX); Kedrop (MX); Ketasma (IN); Ketaxal (MX); Ketifen (HK); Keto (TH); Ketof (LU, PL);

Ketohexal (ZA); Ketokid (AR); Ketomin (TW); Ketosma (TW); Ketotifen (PL); Ketotifen-ratiopharm (LU); Ketotifeno MK (CR, DO, GT, NI, PA, SV); Ketovent (IN); Nazalen (KP); Nemesil (BR); Orpidix (GR); Pozitan (PL); Profilar (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Profilasmin-Ped (BR); Profiten (IL); Santiten (TW); Scanditen (ID); Soother (TW); Sykofen (TH); Totinal (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Zadec (PH); Zadec SRO (PH); Zadin (KP); Zaditen (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CN, CY, CZ, DE, DK, EC, EE, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HN, HU, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PH, PL, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Zaditen Eye Drops (IL); Zaditen SDU (HK); Zaditen SRO (HK, MY, PH, PL); Zatin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Zatofen (PK); Zerosma (IN); Zytofen (TH)

L-Lysine

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Jump To Field (Select Field Name)

Pronunciation(el LYE seen)
U.S. Brand NamesLysinyl [OTC]
Pharmacologic CategoryNutritional Supplement
Use: Labeled IndicationsImproves utilization of vegetable proteins
Use: DentalPrevention of recurrent herpes simplex infection
Dosing: AdultsSupplement: Oral: 334-1500 mg/day
Dosing: ElderlyRefer to adult dosing.
Pregnancy Risk FactorC
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 500 mg

Lysinyl: 500 mg

Powder, oral: 100% (100 g)

Lysinyl: 500 mg/ $^{1}/_{4}$ teaspoon (150 g) [powder equivalent is level $^{1}/_{4}$ teaspoon for each capsule]

Tablet: 500 mg, 1000 mg

Generic AvailableYes
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsL-Lysine Hydrochloride

Labetalol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Labetalol may be confused with betaxolol, Hexadrol®, lamoTRIgine

Trandate® may be confused with traMADol, Trendar®, Trental®, Tridrate®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Significant differences exist between oral and I.V. dosing. Use caution when converting from one route of administration to another.

Pronunciation(la BET a lole)

U.S. Brand NamesTrandate®

Canadian Brand NamesApo-Labetalol®; Labetalol Hydrochloride Injection, USP; Normodyne®; Trandate®

Pharmacologic CategoryBeta Blocker With Alpha-Blocking Activity

Use: Labeled IndicationsTreatment of mild-to-severe hypertension; I.V. for severe hypertension (eg, hypertensive emergencies)

Use: Unlabeled/InvestigationalPediatric hypertension

Dosing: Adults

Hypertension: Oral: Initial: 100 mg twice daily, may increase as needed every 2-3 days by 100 mg twice daily (titration increments not to exceed 200 mg twice daily) until desired response is obtained; usual dose: 200-400 mg twice daily; may require up to 2.4 g/day.

Usual dose range (JNC 7): 200-800 mg/day in 2 divided doses

Acute hypertension (hypertensive urgency/emergency):

I.V. bolus: 20 mg I.V. push over 2 minutes, may give 40-80 mg at 10-minute intervals, up to 300 mg total dose

I.V. infusion (acute loading): Initial: 2 mg/minute; titrate to response up to 300 mg total dose. Administration requires the use of an infusion pump.

Note: Although loading infusions are well described in the product labeling, the labeling is silent in specific clinical situations, such as in the patient who has an initial response to labetalol infusions but cannot be converted to an oral route for subsequent dosing. There is limited documentation of prolonged continuous infusions. In rare clinical situations, higher continuous infusion dosages (up to 6 mg/minute) have been used in the critical care setting (eg, aortic dissection). At the other extreme, continuous infusions at relatively low doses (0.03-0.1 mg/minute) have been used in some settings (following loading infusion in patients who are unable to be converted to oral regimens or in some cases as a continuation of outpatient oral regimens). These prolonged infusions should not be confused with loading infusions. Because of wide variation in the use of infusions, an awareness of institutional policies and practices is extremely important. Careful clarification of orders and specific infusion rates/units is required to avoid confusion. Due to the prolonged duration of action, careful monitoring should be extended for the duration of the infusion and for several hours after the infusion. Excessive administration may result in prolonged hypotension and/or bradycardia.

Dosing: ElderlyInitial dose: Refer to adult dosing. Usual maintenance: 100-200 mg twice daily

Dosing: Pediatric**Note:** Due to limited documentation of its use, labetalol should be initiated cautiously in pediatric patients with careful dosage adjustment and blood pressure monitoring.

Hypertension:

Oral: Hypertension (unlabeled use): Initial: 1-3 mg/kg/day, in 2 divided doses; maximum: 10-12 mg/kg/day, up to 1200 mg/day

I.V.: Intermittent bolus doses of 0.3-1 mg/kg/dose have been reported.

Pediatric hypertensive emergencies: Initial continuous infusions of 0.4-1 mg/kg/hour with a maximum of 3 mg/kg/hour have been used; administration requires the use of an infusion pump.

Dosing: Renal ImpairmentNot removed by hemo- or peritoneal dialysis; supplemental dose is not necessary.

Dosing: Hepatic ImpairmentDosage reduction may be necessary.

Administration: I.V.Bolus dose may be administered I.V. push at a rate of 10 mg/minute; may follow with continuous I.V. infusion

Administration: I.V. DetailpH: 3-4

Storage

Tablets: Store tablets at 2°C to 30°C (36°F to 86°F). Protect from light and excessive moisture.

Vials: Store unopened injectable vials at 20°C to 25°C (68°F to 77°F); do not freeze. Protect from light. The solution is clear to slightly yellow.

Parenteral admixture: Stability of parenteral admixture at room temperature (25°C) and refrigeration temperature (4°C): 3 days.

Reconstitution

Standard concentration: 500 mg/250 mL D_5W.

Minimum volume: 250 mL D_5W.

CompatibilityStable in D_5LR, $D_{2.5}{}^1/{}_2NS$, $D_5{}^1/{}_4NS$, $D_5{}^1/{}_3NS$, D_5NS, D_5W, LR, NS, Ringer's; most stable at pH of 2-4. **Incompatible** with sodium bicarbonate 5% and alkaline solutions.

Y-site administration: Compatible: Amikacin, aminophylline, amiodarone, ampicillin, butorphanol, calcium gluconate, cefazolin, ceftazidime, ceftizoxime, chloramphenicol, cimetidine, clindamycin, diltiazem, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, gatifloxacin, gentamicin, hydromorphone, lidocaine, linezolid, lorazepam, magnesium sulfate, meperidine, metronidazole, midazolam, milrinone, morphine, nicardipine, nitroglycerin, norepinephrine, oxacillin, penicillin G potassium, piperacillin, potassium chloride, potassium phosphates, propofol, ranitidine, sodium acetate, sodium nitroprusside, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, vecuronium. **Incompatible:** Amphotericin B cholesteryl sulfate complex, cefoperazone, ceftriaxone, nafcillin, thiopental, warfarin. **Variable (consult detailed reference):** Furosemide, heparin, insulin (regular).

Compatibility when admixed: Incompatible: Sodium bicarbonate.

Extemporaneously PreparedA 40 mg/mL suspension of labetalol hydrochloride can be made by first crushing sixteen 300 mg labetalol hydrochloride tablets into a fine powder. Using equal amounts of Ora-Sweet® and Ora-Plus® as a vehicle, add a small amount to make a paste; add additional amounts of the vehicle to qs to 120 mL. Suspension is stable for 60 days when stored in the refrigerator. Shake well before using.

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, 4th ed, Cincinnati, OH: Harvey Whitney Books Co, 2000.

ContraindicationsHypersensitivity to labetalol or any component of the formulation; severe bradycardia; heart block greater than first degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; bronchial asthma; uncompensated cardiac failure; conditions associated with severe and prolonged hypotension

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

- Hepatic injury: Severe hepatic injury including some fatalities have also been rarely reported with use; periodically monitor LFTs with prolonged use.

- Hypotension/syncope: Symptomatic hypotension with or without syncope may occur with labetalol; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Initiation with a low dose and gradual up-titration may help to decrease the occurrence of hypotension or syncope. Patients should be advised to avoid driving or other hazardous tasks during initiation of therapy due to the risk of syncope. Orthostatic hypotension may occur with I.V. administration; patient should remain supine during and for up to 3 hours after I.V. administration

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.

- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.

- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms. May also reduce release of insulin in response to hyperglycemia; dosage of antidiabetic agents may need to be adjusted.

- Heart failure (HF): Use with extreme caution in patients with compensated heart failure and monitor for a worsening of the condition.

- Hepatic impairment: Use with caution in patients with hepatic impairment; bioavailability is increased due to decreased first-pass metabolism.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis.

- Peripheral vascular disease (PVD): May precipitate or aggravate symptoms of arterial insufficiency in patients with PVD and Raynaud's disease; use with caution and monitor for progression of arterial obstruction.

- Pheochromocytoma (untreated): If possible, obtain diagnostic tests for pheochromocytoma prior to use. Labetalol has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, some patients have experienced paradoxical hypertensive responses; use with caution in patients with pheochromocytoma. Additional alpha-blockade may be required during use of labetalol.

- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents which decrease myocardial function.
- Calcium channel blockers: Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur. Avoid concurrent I.V. use of both agents.

Special populations:

- Elderly: Elimination of labetalol is reduced in elderly patients; lower maintenance doses may be required.

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.

Geriatric ConsiderationsDue to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (ie, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20% to 50% in elderly populations. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults.

Pregnancy Risk FactorC (manufacturer); D (2nd and 3rd trimesters - expert analysis)

Pregnancy ConsiderationsLabetalol crosses the placenta. Beta-blockers have been associated with persistent bradycardia, hypotension, and IUGR; IUGR is probably related to maternal hypertension. Available evidence suggests beta-blockers are generally safe during pregnancy (JNC 7). Cases of neonatal hypoglycemia have been reported following maternal use of beta-blockers at parturition or during breast-feeding. Monitor breast-fed infant for symptoms of beta-blockade.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsAvailable evidence suggests safe use during breast-feeding. Monitor breast-fed infant for symptoms of beta-blockade.

Adverse Reactions

>10%:

Cardiovascular: Postural hypotension (I.V. use; ≤58%)

Central nervous system: Dizziness (1% to 20%), fatigue (1% to 11%)

Gastrointestinal: Nausea (≤19%)

1% to 10%:

Cardiovascular: Hypotension (1% to 5%), edema (≤2%), flushing (1%), ventricular arrhythmia (I.V. use; 1%)

Central nervous system: Somnolence (3%), headache (2%), vertigo (1% to 2%)

Dermatologic: Scalp tingling (≤7%), pruritus (1%), rash (1%)

Gastrointestinal: Dyspepsia (≤4%), vomiting (≤3%), taste disturbance (1%)

Genitourinary: Ejaculatory failure (≤5%), impotence (1% to 4%)

Hepatic: Transaminases increased (4%)

Neuromuscular & skeletal: Paresthesia (≤5%), weakness (1%)

Ocular: Vision abnormal (1%)

Renal: BUN increased (≤8%)

Respiratory: Nasal congestion (1% to 6%), dyspnea (2%)

Miscellaneous: Diaphoresis (≤4%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Alopecia (reversible), anaphylactoid reaction, ANA positive, angioedema, bradycardia, bronchospasm, cholestatic jaundice, CHF, diabetes insipidus, heart block, hepatic necrosis, hepatitis, hypersensitivity, Peyronie's disease, Raynaud's syndrome, syncope, systemic lupus erythematosus, toxic myopathy, urinary retention, urticaria

Other adverse reactions noted with beta-adrenergic blocking agents include mental depression, catatonia, disorientation, short-term memory loss, emotional lability, clouded sensorium, intensification of pre-existing AV block, laryngospasm, respiratory distress, agranulocytosis, thrombocytopenic purpura, nonthrombocytopenic purpura, mesenteric artery thrombosis, and ischemic colitis.

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Beta2-Agonists: Alpha-/Beta-Blockers may diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Alpha-/Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Labetalol serum concentrations may be increased if taken with food.

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid natural licorice (causes sodium and water retention and increases potassium loss). Avoid garlic (may have increased antihypertensive effect).

Test InteractionsFalse-positive urine catecholamines, vanillylmandelic acid (VMA) if measured by fluorometric or photometric methods; use HPLC or specific catecholamine radioenzymatic technique; false-positive amphetamine if measured by thin-layer chromatography or radioenzymatic assay (gas chromatographic-mass spectrometer technique should be used)

Monitoring ParametersBlood pressure, standing and sitting/supine, pulse, cardiac monitor and blood pressure monitor required for I.V. administration

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (especially anything that will effect blood pressure). Blood pressure and heart rate should be assessed prior to and following first dose and any change in dosage. Caution patients with diabetes to monitor glucose levels closely; beta-blockers may alter glucose tolerance. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, CHF). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, with meals. Do not skip dose or discontinue without consulting prescriber. This medication does not replace other antihypertensive interventions; follow prescriber's instructions for diet and lifestyle changes. If you have diabetes, monitor serum glucose closely and notify prescriber of changes (this medication can alter glycemic response). You may experience drowsiness, dizziness, or impaired judgment (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from sitting or lying position or when climbing stairs); dry mouth, nausea, or loss of appetite (frequent mouth care or sucking lozenges may help); or sexual dysfunction (reversible, may resolve with continued use). Report altered CNS status (eg, fatigue, depression, numbness or tingling of fingers, toes, or skin); palpitations or slowed heartbeat; respiratory difficulty; edema or cold extremities; or other persistent side effects.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride: 5 mg/mL (4 mL, 8 mL, 20 mL, 40 mL)

Trandate®: 5 mg/mL (20 mL, 40 mL) [contains edetate disodium]

Tablet, as hydrochloride: 100 mg, 200 mg, 300 mg

Trandate®: 100 mg, 200 mg [contains sodium benzoate], 300 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Labetalol HCl)

100 mg (60): $20.99

200 mg (60): $28.99

300 mg (60): $38.99

Tablets (Trandate)

200 mg (60): $50.99

Mechanism of ActionBlocks alpha-, beta$_1$-, and beta$_2$-adrenergic receptor sites; elevated renins are reduced. The ratios of alpha- to beta-blockade differ depending on the route of administration: 1:3 (oral) and 1:7 (I.V.).

Pharmacodynamics/Kinetics

Onset of action: Oral: 20 minutes to 2 hours; I.V.: 2-5 minutes

Peak effect: Oral: 1-4 hours; I.V.: 5-15 minutes

Duration: Blood pressure response:

Oral: 8-12 hours (dose dependent)

I.V.: 2-18 hours (dose dependent; based on single and multiple sequential doses of 0.25-0.5 mg/kg with cumulative dosing up to 3.25 mg/kg)

Distribution: V$_d$: Adults: 3-16 L/kg; mean: <9.4 L/kg; moderately lipid soluble, therefore, can enter CNS; crosses placenta; small amounts enter breast milk

Protein binding: 50%

Metabolism: Hepatic, primarily via glucuronide conjugation; extensive first-pass effect

Bioavailability: Oral: 25%; increased with liver disease, elderly, and concurrent cimetidine

Half-life elimination: Oral: 6-8 hours; I.V.: ~5.5 hours

Excretion: Urine (55% to 60% as glucuronide conjugates, <5% as unchanged drug)

Clearance: Possibly decreased in neonates/infants

Related Information

- Beta-Blockers
- Hypertension

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste disorder.

Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution; epinephrine has interacted with nonselective beta-blockers to result in initial hypertensive episode followed by bradycardia

Mental Health: Effects on Mental StatusDizziness is common; may cause sedation

Mental Health: Effects on Psychiatric TreatmentBarbiturates may decrease effects of beta-blockers; low potency antipsychotic and TCAs may potentiate the hypotensive effects of beta-blockers

Cardiovascular Considerations

Hypertension: Beta-blocker therapy in the treatment of hypertension has been associated with improved cardiovascular outcomes. According to the 2003 JNC-VII guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Beta-blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for a beta-blocker include patients with heart failure, postmyocardial infarction, high coronary disease risk, or diabetes. In type 2 diabetic patients, a UK Prospective Diabetes Study Group (UKPDS) trial showed that beta-blocker therapy (atenolol) was as effective as an ACE inhibitor in reducing cardiovascular events and that the benefits of therapy were related more to the degree of antihypertensive efficacy rather than the class of drug used.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia and hypertension.

Anesthesia and Critical Care Concerns/Other ConsiderationsDue to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response in the elderly than seen in younger adults. Despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (eg, exercise).

Index TermsIbidomide Hydrochloride; Labetalol Hydrochloride

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International Brand NamesAlbetol (FI); Amipress (IT); Biascor (AR, PY); Hybloc (NZ); Ipolab (IT); Lamitol (HR); Normadate (IN); Presolol (AU, TW); Pressocard (PL); Salmagne (GR); Trandate (AE, AT, AU, BB, BE, BF, BH, BJ, BM, BS, BZ, CH, CI, CN, CY, CZ, DK, EE, EG, ES, ET, FR, GB, GH, GM, GN, GY, HK, HN, HU, IE, IL, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PT, QA, SA, SC, SD, SE, SG, SL, SN, SR, SY, TN, TR, TT, TW, TZ, UG, VE, YE, ZA, ZM, ZW)

Lacosamide

Lexi-Drugs Online

English

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Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - February 2008

The U.S. Food and Drug Administration (FDA) is informing healthcare professionals of an increased risk of suicidality (suicidal behavior or ideation) observed from analysis of clinical studies using various antiepileptic medications compared to placebo. The analysis was performed on 199 placebo-controlled studies involving 43,892 patients (27,863 treated patients versus 16,029 placebo patients) aged ≥5 years receiving one of the following 11 drugs: carbamazepine (Carbatrol®, Equetro®, Tegretol®, Tegretol® XR), felbamate (Felbatol®), gabapentin (Neurontin®), lamotrigine (Lamictal®), levetiracetam (Keppra®), oxcarbazepine (Trileptal®), pregabalin (Lyrica®), tiagabine (Gabitril®), topiramate (Topamax®), valproate (Depakote®, Depakote® ER, Depakene®, Depacon®), and zonisamide (Zonegran®). Studies examined medication efficacy in a variety of disorders, including epilepsy, psychiatric disorders (eg, depression, bipolar disorder), and other conditions (eg, migraine, neuropathic pain). According to the FDA, the results revealed a statistically significant increased risk of suicidality in 0.43% treated patients compared to 0.22% placebo patients, or an estimated 2.1 per 1000 (95% CI: 0.7, 4.2) more patients in the treated groups relative to placebo. This increased risk was reported anywhere from 1 week of therapy through 24 weeks. However, most trials were ≤24 weeks duration and the risk of suicide extending beyond 24 weeks is currently unknown. The relative risk of suicidal behavior or ideation in the treated patients was higher for patients with epilepsy (RR=3.6) compared to patients treated for psychiatric (RR=1.6) or other conditions (RR=2.3). Overall, the incidence of suicidal behavior or ideation occurred consistently across all demographic subgroups and with each of the drugs studied. Of note, four patients receiving an antiepileptic committed suicide relative to none in the placebo groups.

Forthcoming product labeling changes are likely to extend to all antiepileptic drugs and not limited to the drugs used in the studies, pending discussions scheduled for the upcoming advisory committee meeting. Healthcare professionals and family members/caregivers are encouraged to monitor patients receiving any antiepileptic medication for signs/symptoms of suicidality (eg, anxiety, depression, behavior changes). Patients should not stop taking their antiepileptic therapy unless advised by a healthcare professional.

Additional information can be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

Lacosamide may be confused with zonisamide

Pronunciation(la KOE sa mide)

U.S. Brand NamesVimpat®

Pharmacologic CategoryAnticonvulsant, Miscellaneous

Use: Labeled IndicationsAdjunctive therapy in the treatment of partial-onset seizures

Dosing: Adults**Partial onset seizure:** Oral, I.V.:

Initial: 50 mg twice daily; may be increased at weekly intervals by 100 mg/day

Maintenance dose: 200-400 mg/day

Note: When switching from oral to I.V. formulations, the total daily dose and frequency should be the same; I.V. therapy should only be used temporarily.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAdolescents ≥17 years: Refer to adult dosing.

Dosing: Renal Impairment
Mild-to-moderate renal impairment: No dose adjustment necessary.

Severe renal impairment (Cl_{cr} ≤30 mL/minute): Maximum dose: 300 mg/day.

Hemodialysis: Removed by hemodialysis; after 4-hour HD treatment, a supplemental dose of up to 50% should be considered.

Dosing: Hepatic Impairment
Mild-to-moderate hepatic impairment: Maximum dose: 300 mg/day.

Severe hepatic impairment: Use is not recommended.

Calculations

- Creatinine Clearance: Adults

Administration: I.V.Administer over 30-60 minutes. Twice daily I.V. infusions have been used for up to 5 days.
Administration: I.V. DetailCan be administered without further dilution or may be mixed with compatible diluents (NS, LR, D_5W). Should not be admixed with other solutions. If diluted, stable for ≤24 hours when stored in glass or PVC bags at room temperature. Discard any unused portion.

pH: 3.5-5

Dietary ConsiderationsTablets may be taken with or without food.
Storage

Injection: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Stable when mixed with compatible diluents for ≤24 hours in glass or PVC at room temperature of 15°C to 30°C (59°F to 86°F). Any unused portion should be discarded.

Tablets: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

ReconstitutionInjection solution: Can be administered without further dilution or may be mixed with compatible diluents (NS, LR, D_5W).
CompatibilityStable in NS, LR, D_5W.
RestrictionsAn FDA-approved medication guide is available. Distribute to each patient to whom this medication is dispensed.
ContraindicationsThere are no contraindications listed in manufacturer's labeling.
Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: Lacosamide may prolong PR interval; use caution in patients with conduction problems (eg, first/second degree atrioventricular block and sick sinus syndrome without pacemaker), myocardial ischemia, heart failure, or if concurrent use with other drugs that prolong the PR interval; ECG is recommended prior to initiating therapy and when at steady state.

- CNS effects: Dizziness and ataxia may occur during therapy; patients should be cautioned about performing tasks which require alertness (eg, operating machinery or driving).

- Multiorgan hypersensitivity reactions (drug reaction with eosinophilia and systemic symptoms [DRESS]): Potentially serious (sometimes fatal, possibly delayed) multiorgan hypersensitivity reactions have been reported with some antiepileptic drugs (rare); monitor for signs and symptoms of possible disparate manifestations associated with lymphatic, hepatic, renal, and/or hematologic organ systems; gradual discontinuation and conversion to alternate therapy may be required.

- Suicidal ideation: Monitor all patients for notable changes in behavior that might indicate suicidal thoughts or depression.

Disease-related concerns:

- Hepatic impairment: Not recommended for use in patients with severe hepatic impairment; dose limitation for mild to moderate hepatic impairment.

- Renal impairment: Use caution in patients with renal impairment; dose limitation and supplementation for severe renal impairment (Cl_{cr} ≤30 mL/minute) and hemodialysis, respectively.

Concurrent drug therapy issues:

- Ethanol: Avoid ethanol (may increase CNS depression).

Special populations:

- Pediatrics: Safety and effectiveness have not been established in patients <17 years of age.

Other warnings/precautions:

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually (≥1 week) to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Pregnancy Risk FactorC
Pregnancy ConsiderationsDevelopmental toxicities were observed in animal studies. There are no adequate and well-controlled studies in pregnant women; only use during pregnancy if potential benefit justifies the potential risk to the fetus. Two registries are available for women exposed to lacosamide during pregnancy:

Antiepileptic Drug Pregnancy Registry (888-233-2334 or http://www.aedpregnancyregistry.org)

Vimpat® pregnancy registry (888-537-7734)

Lactation Excretion in breast milk unknown/use caution

Breast-Feeding Considerations It is unknown if lacosamide is excreted in human milk. Use during lactation only if the potential benefits to the mother outweigh the potential risks to the infant.

Adverse Reactions

>10%:

Central nervous system: Dizziness (31%), headache (13%)

Gastrointestinal: Nausea (11%)

Ocular: Diplopia (11%)

1% to 10%:

Cardiovascular: Syncope (1%; dose-related: >400 mg/day)

Central nervous system: Fatigue (9%), ataxia (8%), somnolence (7%), coordination impaired (4%), vertigo (4%), depression (2%), memory impairment (2%)

Dermatologic: Pruritus (2%)

Gastrointestinal: Vomiting (9%), diarrhea (4%)

Local: Contusion (3%), skin laceration (3%), injection site pain/discomfort (2.5%), irritation (1%)

Neuromuscular & skeletal: Tremor (7%), weakness (2%)

Ocular: Blurred vision (8%), nystagmus (5%)

<1%, postmarketing, and/or case reports: ALT increased, anemia, atrial fibrillation/flutter, atrioventricular block, attention disturbance, bradycardia, cerebellar syndrome, cognitive dysfunction, confusion, constipation, depression, dysarthria, dyspepsia, erythema (injection site), falling, fever, hepatitis, hypoesthesia (including oral), inebriation-like feeling, irritability, mood changes, multiorgan hypersensitivity, muscle spasm, nephritis, neutropenia, palpitation, paresthesia, tinnitus, xerostomia

Drug Interactions

CarBAMazepine: May decrease the serum concentration of Lacosamide. *Risk C: Monitor therapy*

PHENobarbital: May decrease the serum concentration of Lacosamide. *Risk C: Monitor therapy*

Phenytoin: May decrease the serum concentration of Lacosamide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions Ethanol: Avoid ethanol (may increase CNS depression).

Monitoring Parameters Patients with conduction problems or severe cardiac disease should have ECG tracing prior to start of therapy and when at steady-state

Monitoring: Lab Tests ECG

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Vimpat®: 200 mg/20 mL

Tablet:

Vimpat®: 50 mg, 100 mg, 150 mg, 200 mg

Generic Available No

Manufacturer UCB Pharmaceuticals, Inc

Mechanism of Action *In vitro* studies have shown that lacosamide stabilizes hyperexcitable neuronal membranes and inhibits repetitive neuronal firing by enhancing the slow inactivation of sodium channels (with no effects on fast inactivation of sodium channels).

Pharmacodynamics/Kinetics

Absorption: Oral: Completely

Distribution: V_d: ~0.6 L/kg

Protein binding: <15%

Metabolism: Hepatic; forms metabolite, O-desmethyl-lacosamide (inactive)

Bioavailability: ~100%

Half-life elimination: 13 hours

Time to peak, plasma: Oral: 1-4 hours postdose

Excretion: Urine (95%; 40% as unchanged drug, 30% as inactive metabolite, 20% as uncharacterized metabolite); feces (<0.5%)

Related Information

- Anticonvulsant Drugs of Choice

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsLacosamide may prolong PR interval resulting in cardiac conduction problems; it is not known what effect vasoconstrictors will have in patients taking medications that could prolong PR interval. It is suggested that the clinician consult with the physician prior to use of vasoconstrictor in suspected patients; use vasoconstrictor with caution.

Mental Health: Effects on Mental StatusMay cause suicidal behavior or ideation, dizziness, fatigue, somnolence, memory impairment, and depression

Mental Health: Effects on Psychiatric TreatmentMay cause GI side effects; concomitant use with lithium, carbamazepine, valproic acid, and SSRIs may produce additive effects

Index TermsADD 234037; Harkoseride; LCM; SPM 927

References

Ben-Menachem E, Biton V, Jatuzis D, et al, “Efficacy and Safety of Oral Lacosamide as Adjunctive Therapy in Adults With Partial-Onset Seizures,” *Epilepsia*, 2007, 48(7):1308-17.[PubMed 17635557]

Beyreuther BK, Freitag J, Heers C, et al, “Lacosamide: A Review of Preclinical Properties,” *CNS Drug Rev*, 2007, 13(1):21-42.[PubMed 17461888]

Biton V, Rosenfeld WE, Whitesides J, et al, “Intravenous Lacosamide as Replacement for Oral Lacosamide in Patients With Partial-Onset Seizures,” *Epilepsia*, 2008, 49(3):418-24.[PubMed 17888078]

Doty P, Rudd GD, Stoehr T, et al, “Lacosamide,” *Neurotherapeutics*, 2007, 4(1):145-8.[PubMed 17199030]

Lactase

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(LAK tase)
U.S. Brand NamesLac-Dose [OTC]; Lactaid® Fast Act [OTC]; Lactaid® Original [OTC]; Lactrase® [OTC]
Canadian Brand NamesDairyaid®
Pharmacologic CategoryEnzyme
Use: Labeled IndicationsHelp digest lactose in milk for patients with lactose intolerance
Dosing: AdultsLactose intolerance: Oral:

Capsule: 1-2 capsules taken with milk or meal; pretreat milk with 1-2 capsules/quart of milk

Liquid: 5-15 drops/quart of milk

Tablet: 1-3 tablets with meals

Dosing: ElderlyRefer to adult dosing.
Dietary ConsiderationsMay be taken with meals.

Lactaid®: Contains sodium 1.67 mg per caplet.

Lactaid® Extra Strength: Contains sodium 2.5 mg per caplet.

Lactaid® Ultra caplet/chewable tablet: Contains sodium 5 mg per caplet/tablet.

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet:

Lactaid® Original: 3000 FCC lactase units [contains sodium 5 mg per 3 caplets]

Lactaid® Fast Act: 9000 FCC lactase units [contains sodium 5 mg/caplet]

Capsule:

Lactrase®: 250 mg standardized enzyme lactase

Tablet, oral, chewable:

Lactaid® Fast Act: 9000 FCC lactase units [contains sodium 5 mg; vanilla twist flavor]

Tablet, oral:

Lac-Dose: 3000 FCC lactase units

Generic AvailableNo
Pharmacotherapy PearlsMay be taken with meals.

Lactaid®: Contains sodium 1.67 mg per caplet.

Lactaid® Extra Strength: Contains sodium 2.5 mg per caplet.

Lactaid® Ultra caplet and chewable tablet: Contains sodium 5 mg per caplet/tablet.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesEnzym laktaza (PL); Lactosanol (PL)

Lactic Acid and Ammonium Hydroxide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(LAK tik AS id & a MOE nee um hye DROKS ide)
U.S. Brand NamesAmLactin® [OTC]; Geri-Hydrolac™ [OTC]; Geri-Hydrolac™-12 [OTC]; Lac-Hydrin®; Lac-Hydrin® Five [OTC]; LAClotion™
Pharmacologic CategoryTopical Skin Product
Use: Labeled IndicationsTreatment of moderate to severe xerosis and ichthyosis vulgaris
Dosing: AdultsDermatologic conditions: Topical: Cream, lotion: Apply twice daily to affected area; rub in well
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricDermatologic conditions: Topical:

Cream: Children ≥2 years: Refer to adult dosing.

Lotion: Refer to adult dosing.

Administration: TopicalFor topical use only; rub in well; shake lotion well before application. Avoid use on eyes, lips, or mucous membranes.
StorageLac-Hydrin® cream/lotion: Store at 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to lactic acid, ammonium hydroxide, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Burning/stinging: May cause burning or stinging upon application to abraded skin.
- Photosensitivity: May cause photosensitivity; minimize exposure to the sun of areas being treated.

Other warnings/precautions:

- Appropriate use: For external use only; not for use on eyes, lips, or mucous membranes; use with caution to facial area (may be more sensitive to irritation).

Pregnancy Risk FactorB
Pregnancy ConsiderationsLactic acid is a normal component in blood and tissues. Topical application in animals has not shown fetal harm.
LactationUse caution
Breast-Feeding ConsiderationsIt is not known how this medication affects normal levels of lactic acid in human milk. Because studies have not been done in nursing women, use with caution when needed.
Adverse Reactions1% to 10%: Dermatologic: Burning/stinging (3% to 15%), rash (including erythema and irritation; 2% to 15%), itching (5%), dry skin (2%)
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical: Lactic acid 12% with ammonium hydroxide (140 g, 280 g, 385 g)

AmLactin®: Lactic acid 12% with ammonium hydroxide (140 g)

Lac-Hydrin®: Lactic acid 12% with ammonium hydroxide (280 g, 385 g)

Lotion, topical:

AmLactin®, Lac-Hydrin®, LAClotion™: Lactic acid 12% with ammonium hydroxide (225 g, 400 g)

Geri-Hydrolac™, Lac-Hydrin® Five: Lactic acid 5% with ammonium hydroxide (120 mL, 240 mL)

Geri-Hydrolac™-12: Lactic acid 12% with ammonium hydroxide (120 mL, 240 mL)

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Cream (AmLactin)

12% (140): $18.99

Cream (Ammonium Lactate)

12% (280): $34.47

12% (385): $46.01

Cream (Lac-Hydrin)

12% (280): $53.48

12% (385): $65.26

Lotion (Ammonium Lactate)

12% (225): $45.00

12% (400): $48.00

Lotion (Lac-Hydrin)

12% (225): $51.35

12% (400): $73.84

Lotion (Lac-Hydrin Five)

5% (113): $8.99

5% (226): $21.40

Mechanism of ActionExact mechanism of action unknown; lactic acid is a normal component in blood and tissues. When applied topically to the skin, acts as a humectant.

Pharmacodynamics/KineticsAbsorption: 6%

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAmmonium Lactate

International Brand NamesLac-Hydrin (SG); Lactrex (AR, MX, PY, VE)

Jump To Field (Select Field Name)

Pronunciation(LAK tik AS id)
U.S. Brand NamesLactiCare® [OTC]; Lactinol-E®; Lactinol®
Pharmacologic CategoryTopical Skin Product
Use: Labeled IndicationsLubricate and moisturize the skin counteracting dryness and itching
Dosing: AdultsLubricant/moisturizer: Topical: Apply twice daily
Dosing: ElderlyRefer to adult dosing.
StorageStore at controlled room temperature.
ContraindicationsHypersensitivity to lactic acid or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Photosensitivity: May cause photosensitivity; minimize exposure to the sun of areas being treated.
- Skin Irritation: Mild burning, stinging, or peeling may occur with use; discontinue if irritation occurs.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: For external use only; not for use near eyes, lips, or mucous membranes.

Adverse ReactionsFrequency not defined.

Dermatologic: Burning, mild stinging, peeling

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream: 10% (120 g) [contains vitamin E]

Lactinol-E®: 10% (120 g) [contains vitamin E]

Lotion: 10% (360 mL)

LactiCare®: 5% (222 mL, 340 mL) [contains sodium PCA]

Lactinol®: 10% (360 mL)

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Cream (Lactic Acid E)

10-3500 (113.4): $25.99

Cream (Lactinol-E)

10-3500 (113.4): $52.97

Lotion (Lactinol)

10% (354.84): $73.84

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsSodium-PCA and Lactic Acid
International Brand NamesAcidum Lacticum (PL)

Lactobacillus

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(lak toe ba SIL us)

U.S. Brand NamesBacid® [OTC]; Culturelle® [OTC]; Dofus [OTC]; Flora-Q™ [OTC]; Kala® [OTC]; Lactinex™ [OTC]; Lacto-Bifidus [OTC]; Lacto-Key [OTC]; Lacto-Pectin [OTC]; Lacto-TriBlend [OTC]; Megadophilus® [OTC]; MoreDophilus® [OTC]; Superdophilus® [OTC]

Canadian Brand NamesBacid®; Fermalac

Pharmacologic CategoryDietary Supplement; Probiotic

Use: Labeled IndicationsPromote normal bacterial flora of the intestinal tract

Use: DentalTreatment of uncomplicated diarrhea, particularly that caused by antibiotic therapy; re-establish normal physiologic and bacterial flora of the intestinal tract

Dosing: AdultsDietary supplement: Oral: Dosing varies by manufacturer; consult product labeling

Bacid®: 2 caplets/day

Culturelle®: 1 capsule daily; may increase to twice daily

Flora-Q™: 1 capsule/day

Lacto-Key 100 or 600: 1-2 capsules/day

Lactinex™: 1 packet or 4 tablets 3-4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDietary supplement: Oral: Dosing varies by manufacturer; consult product labeling

Culturelle®: 1 capsule daily

Administration: Oral

Culturelle®: Capsules may be opened and mixed in a cool beverage or sprinkled onto baby food or applesauce.

Flora-Q™: May be taken with or without food.

Lactinex™: Granules may be added to or administered with cereal, food, or milk.

Megadophilus®, Superdophilus®: Administer on an empty stomach; powder should be mixed in unchilled water.

Dietary ConsiderationsProducts may contain whey, evaporated milk, soy peptone casein and/or beef extract; consult individual product labeling. Lactinex™ contains sodium 5.6 mg/4 tablets

Storage

Bacid®: Store at room temperature.

Flora-Q™: Store at or below room temperature; do not store in bathroom.

Kala®, MoreDophilus®: Refrigeration recommended after opening.

Lactinex™, Dofus: Store in refrigerator.

ContraindicationsHypersensitivity to any component of the formulation

Warnings/Precautions

Other warnings/precautions:

- Appropriate use: *Lactobacillus* species have been studied for various gastrointestinal disorders including diarrhea, inflammatory bowel disease, gastrointestinal infection. Effectiveness may be dependent upon actual species used; studies are ongoing. Currently, there are no FDA-approved disease-prevention or therapeutic indications for these products.

Geriatric ConsiderationsNo specific recommendations due to age; keep in mind that elderly suffer significantly with fluid and electrolyte loss (lethargy, confusion, etc) and diarrhea should be aggressively treated

Adverse ReactionsGastrointestinal: Flatulence

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringTeach patient proper use and adverse symptoms to report (eg, discontinue and notify prescriber if high fever develops).

Patient EducationUse exactly as directed; do not take more than prescribed. Granules in capsules may be added to or taken with cereal, food, milk, fruit juice, or water. You may experience increased flatus while taking this medication. Discontinue and notify prescriber if a high fever develops. Refrigerate Lactinex™ and Bacid®. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Culturelle®: *L. rhamnosus* GG 10 billion colony-forming units [contains casein and whey]

Dofus: *L. acidophilus* and *L. bifidus* 10:1 ratio [beet root powder base]

Flora-Q™: *L. acidophilus* and *L. paracasei* ≥8 billion colony-forming units [also contains *Bifidobacterium* and *S. thermophilus*]

Lacto-Key:

100: *L. acidophilus* 1 billion colony-forming units [milk, soy, and yeast free; rice derived]

600: *L. acidophilus* 6 billion colony-forming units [milk, soy, and yeast free; rice derived]

Lacto-Bifidus:

100: *L. bifidus* 1 billion colony-forming units [milk, soy, and yeast free; rice derived]

600: *L. bifidus* 6 billion colony-forming units [milk, soy, and yeast free; rice derived]

Lacto-Pectin: *L. acidophilus* and *L. casei* ≥5 billion colony-forming units [also contains *Bifidobacterium lactis* and citrus pectin cellulose complex]

Lacto-TriBlend:

100: *L. acidophilus, L. bifidus,* and *L. bulgaricus* 1 billion colony-forming units [milk, soy and yeast free; rice derived]

600: *L. acidophilus, L. bifidus,* and *L. bulgaricus* 6 billion colony-forming units [milk, soy and yeast free; rice derived]

Megadophilus®, Superdophilus®: *L. acidophilus* 2 billion units [available in dairy based or dairy free formulations]

Capsule, softgel: *L. acidophilus* 100 active units

Caplet (Bacid®): *L. acidophilus 80%* and *L. bulgaricus* 10% [also contains *Bifidobacterium biffidum* 5% and *S. thermophilus* 5%]

Granules (Lactinex™): *L. acidophilus* and *L. bulgaricus* 100 million live cells per 1 g packet (12s) [contains whey, evaporated milk, soy peptone, lactose, and beef extract]

Powder:

Lacto-TriBlend: *L. acidophilus, L. bifidus,* and *L. bulgaricus* 10 billion colony-forming units per ¼ teaspoon (60 g) [milk, soy, and yeast free; rice derived]

Megadophilus®, Superdophilus®: *L. acidophilus* 2 billion units per half-teaspoon (49 g, 70 g, 84 g, 126 g) [available in dairy based or dairy free (garbanzo bean) formulations]

MoreDophilus®: *L. acidophilus* 12.4 billion units per teaspoon (30 g, 120 g) [dairy free, yeast free; soy and carrot derived]

Tablet:

Kala®: *L. acidophilus* 200 million units [dairy free, yeast free; soy based]

Lactinex™: *L. acidophilus* and *L. bulgaricus* 1 million live cells [contains whey, evaporated milk, soy peptone, lactose, and beef extract; contains sodium 5.6 mg/4 tablets]

Tablet, chewable: *L. reuteri* 100 million organisms

Wafer: *L. acidophilus* 90 mg and *L. bifidus* 25 mg (100s) [provides 1 billion organisms/wafer at time of manufacture; milk free]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Granules (Lactinex)

1 g (12): $8.99

Mechanism of ActionHelps re-establish normal intestinal flora; suppresses the growth of potentially pathogenic microorganisms by producing lactic acid which favors the establishment of an aciduric flora.

Pharmacodynamics/Kinetics

Absorption: Oral: None

Distribution: Local, primarily colon

Excretion: Feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms *Lactobacillus acidophilus*; *Lactobacillus bifidus*; *Lactobacillus bulgaricus*; *Lactobacillus casei*; *Lactobacillus paracasei*; *Lactobacillus reuteri*; *Lactobacillus rhamnosus* GG

International Brand Names Lacteol Fort (MX)

Lactulose

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Lactulose may be confused with lactose

Pronunciation(LAK tyoo lose)

U.S. Brand NamesConstulose; Enulose; Generlac; Kristalose®

Canadian Brand NamesAcilac; Apo-Lactulose®; Laxilose; PMS-Lactulose

Pharmacologic CategoryAmmonium Detoxicant; Laxative, Osmotic

Use: Labeled IndicationsAdjunct in the prevention and treatment of portal-systemic encephalopathy; treatment of chronic constipation

Dosing: Adults

Note: Diarrhea may indicate overdosage and responds to dose reduction.

Acute portal-systemic encephalopathy (PSE):

Oral: 20-30 g (30-45 mL) every 1-2 hours to induce rapid laxation; adjust dosage daily to produce 2-3 soft stools; doses of 30-45 mL may be given hourly to cause rapid laxation, then reduce to recommended dose; usual daily dose: 60-100 g (90-150 mL) daily

Rectal: 200 g (300 mL) diluted with 700 mL of H_2O or NS; administer rectally via rectal balloon catheter and retain 30-60 minutes every 4-6 hours.

Constipation: Oral: 10-20 g/day (15-30 mL/day) increased to 60 mL/day in 1-2 divided doses if necessary

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDiarrhea may indicate overdosage and responds to dose reduction.

Prevention of portal systemic encephalopathy (PSE): Oral:

Infants: 2.5-10 mL/day divided 3-4 times/day; adjust dosage to produce 2-3 stools/day.

Older Children: Daily dose of 40-90 mL divided 3-4 times/day; if initial dose causes diarrhea, then reduce it immediately; adjust dosage to produce 2-3 stools/day.

Constipation: Oral: 5 g/day (7.5 mL) after breakfast

Administration: OralDilute lactulose in water, usually 60-120 mL, prior to administering through a gastric or feeding tube.

Administration: OtherSyrup formulation has been used in preparation of rectal solution.

Dietary ConsiderationsContraindicated in patients on galactose-restricted diet; may be mixed with fruit juice, milk, water, or citrus-flavored carbonated beverages.

StorageKeep solution at room temperature to reduce viscosity. Discard solution if cloudy or very dark.

ContraindicationsHypersensitivity to lactulose or any component of the formulation; galactosemia (or patients requiring a low galactose diet)

Warnings/Precautions

Concerns related to adverse effects:

- Electrolyte imbalance: Monitor periodically for electrolyte imbalance when lactulose is used >6 months or in patients predisposed to electrolyte abnormalities (eg, elderly).

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; solution contains galactose and lactose.

Concurrent drug therapy issues:

- Anti-infectives (oral): Patients receiving lactulose and an oral anti-infective agent should be monitored for possible inadequate response to lactulose.

Geriatric ConsiderationsElderly are more likely to show CNS signs of dehydration and electrolyte loss than younger adults. Therefore, monitor closely for fluid and electrolyte loss with chronic use. Sorbitol is equally effective as a laxative and less expensive. However, sorbitol **cannot be substituted** in the treatment of hepatic encephalopathy.

Pregnancy Risk FactorB

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined: Gastrointestinal: Flatulence, diarrhea (excessive dose), abdominal discomfort, nausea, vomiting, cramping

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersBlood pressure, standing/supine; serum potassium, bowel movement patterns, fluid status, serum ammonia
Nursing: Physical Assessment/MonitoringAssess results of laboratory tests, therapeutic effectiveness (soft formed stools or resolution of CNS status in PSE), and adverse response (eg, CHF). Monitor frequency/consistency of stools; diarrhea may indicate overdose. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsSerum potassium, serum ammonia
Patient EducationNot for long-term use. Take as directed, alone, or diluted with water, juice or milk, or take with food. Laxative results may not occur for 24-48 hours; do not take more often than recommended or for a longer time than recommended. Do not use any other laxatives while taking lactulose. Increased fiber, fluids, and exercise may also help reduce constipation. Do not use if experiencing abdominal pain, nausea, or vomiting. Diarrhea may indicate overdose. May cause flatulence, belching, or abdominal cramping. Report persistent or severe diarrhea or abdominal cramping. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Crystals for solution, oral:

Kristalose®: 10 g/packet (30s), 20 g/packet (30s)

Solution, oral: 10 g/15 mL (15 mL, 30 mL, 237 mL, 473 mL, 946 mL, 1890 mL)

Constulose: 10 g/15 mL (240 mL, 960 mL)

Enulose: 10 g/15 mL (480 mL)

Generlac: 10 g/15 mL (480 mL, 1920 mL)

Solution, oral/rectal: 10 g/15 mL (473 mL)

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Pack (Kristalose)

10 g (30): $44.50

20 g (30): $65.20

Solution (Enulose)

10 g/15 mL (480): $19.97

Solution (Lactulose)

10 g/15 mL (473): $20.01

Mechanism of ActionThe bacterial degradation of lactulose resulting in an acidic pH inhibits the diffusion of NH_3 into the blood by causing the conversion of NH_3 to NH_4+; also enhances the diffusion of NH_3 from the blood into the gut where conversion to NH_4+ occurs; produces an osmotic effect in the colon with resultant distention promoting peristalsis
Pharmacodynamics/Kinetics

Absorption: Not appreciable

Metabolism: Via colonic flora to lactic acid and acetic acid; requires colonic flora for drug activation

Excretion: Primarily feces and urine (~3%)

Related Information

- Laxatives, Classification and Properties

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentThe therapeutic GI effect of laxation is desired; however, concomitant use with SSRIs, carbamazepine, valproic acid, and lithium may produce additive GI side effects
References

Lederle FA, Busch DL, Mattox KM, et al, “Cost-Effective Treatment of Constipation in the Elderly: A Randomized Double-Blind Comparison of Sorbitol and Lactulose,” *Am J Med*, 1990, 89(5):597-601.[PubMed 2122724]

International Brand NamesActilax (AU); Alpha-Lactulose (NZ); Amivalex (HU); Avilac (IL); Bifiteral (BE, DE, LU); Constipen (ID); Danilax (HK); Dhactulose (MY, SG); Dia-Colon (IT); Dismam L (PE); Duphalac (AE, AT, BE, BG, BH, CL, CN, CY, CZ, EE, EG, ES, FI, FR, GB, GR, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JO, KP, KW, LB, LU, LY, MY, NL, NO, OM, PE, PH, PK, PL, PT, PY, QA, SA, SE, SG, SY, TH, TR, TW, YE, ZA); Farlac (BR); Genlac (AU); Genocolan (AR); Hepalac (TH); Lac-Dol (AU); Lacson (ZA); Lactocur (LU); Lactul (MY, PH, TW); Lactulax (EC, ID, MX, UY); Lactulen (CO); Lactulol (PL); Lactulose-MIP (PL); Lactulose-ratiopharm (LU); Lactulosum (PL); Lactumed (MY); Lactus (SG); Lactuverlan (DE); Laevolac (AT, HK, HN, IL, IT, PT); Laxadilac (ID); Laxette (ZA); Legendal (CH); Levan (PH); Levolac (FI, NO); Lilac (PH); Lipebin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PE, QA, SA, SY, YE); Livo Luk (IN); Martulose (HK); Medilax (DK); Moderan (VE); Monilac (JP); Normalac (PL); Normase (PL); Normolax (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Opilax (ID); Portalak (HR); Pralax (ID); Regulact (MX); Solac (ID); Tenualax (AR); Tulotract (DE)

LamiVUDine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

LamiVUDine may be confused with lamoTRIgine

Epivir® may be confused with Combivir®

Pronunciation(la MI vyoo deen)

U.S. Brand NamesEpivir-HBV®; Epivir®

Canadian Brand Names3TC®; Heptovir®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)

Use: Labeled Indications

Epivir®: Treatment of HIV infection when antiretroviral therapy is warranted; should always be used as part of a multidrug regimen (at least three antiretroviral agents)

Epivir-HBV®: Treatment of chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation

Use: Unlabeled/InvestigationalPostexposure prophylaxis for HIV exposure as part of a multidrug regimen

Dosing: Adults**Note:** The formulation and dosage of Epivir-HBV® are not appropriate for patients infected with both HBV and HIV.

HIV: Oral (use with at least two other antiretroviral agents): 150 mg twice daily **or** 300 mg once daily

<50 kg: 4 mg/kg twice daily (maximum: 150 mg twice daily)

Postexposure prophylaxis for HIV exposure: Oral: 150 mg twice daily (with zidovudine with or without a protease inhibitor, depending on risk)

Prevention of maternal-fetal HIV transmission (AIDSinfo guidelines):Note: Lamivudine may be used in combination with zidovudine and nevirapine in select situations (eg, infants born to mothers with suboptimal viral suppression at delivery, infants born to mothers with only intrapartum therapy or no therapy, or infants born to mothers with known antiretroviral drug-resistant virus). Lamivudine is used in this situation to reduce the development of nevirapine resistant virus:

Mother: 150 mg twice daily starting at onset of labor and continuing through 1 week postpartum

Treatment of hepatitis B (Epivir-HBV®): Oral: 100 mg/day. **Note:** Usual treatment duration is at least 1 year and varies with HBeAg status, consult current guidelines and literature.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** The formulation and dosage of Epivir-HBV® are not appropriate for patients infected with both HBV and HIV.

HIV: Oral (use with at least two other antiretroviral agents)

Neonates <30 days (AIDSinfo guidelines): 2 mg/kg/dose twice daily

Infants 1-3 months (AIDSinfo guidelines): 4 mg/kg/dose twice daily

Infants and Children 3 months to 16 years: 4 mg/kg/dose twice daily (maximum: 150 mg/dose twice daily)

Alternate weight-based dosing using scored 150 mg tablets (AIDSinfo guidelines):

14-21 kg: 75 mg/dose twice daily (150 mg/day)

22-29 kg: 75 mg in the morning, 150 mg in the evening (225 mg/day)

≥30 kg: 150 mg/dose twice daily (300 mg/day)

Children >16 years: Refer to adult dosing.

Prevention of maternal-fetal HIV transmission (AIDSinfo guidelines):Note: Lamivudine may be used in combination with zidovudine and nevirapine in select situations (eg, infants born to mothers with suboptimal viral suppression at delivery, infants born to mothers with only intrapartum therapy or no therapy, or infants born to mothers with known antiretroviral drug-resistant virus). Lamivudine is used in this situation to reduce the development of nevirapine resistant virus:

Neonate: 2 mg/kg/dose twice daily given at birth through 1 week of age

Treatment of hepatitis B: Oral: Children 2-17 years: 3 mg/kg/dose once daily (maximum: 100 mg/day). **Note:** Usual treatment duration is at least 1 year and varies with HBeAg status, consult current guidelines and literature.

Dosing: Renal Impairment

HIV:

Patients ≤16 years: Insufficient data; however, dose reduction should be considered.

Patients >16 years:

Cl_{cr} 30-49 mL/minute: Administer 150 mg once daily

Cl_{cr} 15-29 mL/minute: Administer 150 mg first dose, then 100 mg once daily

Cl_{cr} 5-14 mL/minute: Administer 150 mg first dose, then 50 mg once daily

Cl_{cr} <5 mL/minute: Administer 50 mg first dose, then 25 mg once daily

Treatment of hepatitis B patients: Adults:

Cl_{cr} 30-49 mL/minute: Administer 100 mg first dose, then 50 mg once daily.

Cl_{cr} 15-29 mL/minute: Administer 100 mg first dose, then 25 mg once daily.

Cl_{cr} 5-14 mL/minute: Administer 35 mg first dose, then 15 mg once daily.

Cl_{cr} <5 mL/minute: Administer 35 mg first dose, then 10 mg once daily.

Dialysis: Negligible amounts are removed by 4-hour hemodialysis or peritoneal dialysis. Supplemental dosing is not required.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: Oral May be taken with or without food. Adjust dosage in renal failure.

Dietary Considerations May be taken with or without food. Each 5 mL of oral solution contains 1 g of sucrose.

Storage

Oral solution:

Epivir®: Store at 25°C (77°F) tightly closed.

Epivir-HBV®: Store at 20°C to 25°C (68°F to 77°F) tightly closed.

Tablet: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Contraindications Hypersensitivity to lamivudine or any component of the formulation

Allergy Considerations

- LamiVUDine Allergy

Warnings/Precautions

Boxed warnings:

- Chronic hepatitis B: See “Disease-related concerns” below.
- Epivir-HBV®: See “Dosage form specific issues” below.
- Lactic acidosis/hepatomegaly: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).
- Pancreatitis: Has been reported, particularly in HIV-infected children with a history of nucleoside use.

Disease-related concerns:

- Chronic hepatitis B: **[U.S. Boxed Warning]: Monitor patients closely for several months following discontinuation of therapy for chronic hepatitis B;** clinical exacerbations may occur. Treatment of HBV in patients with unrecognized/untreated HIV may lead to rapid HIV resistance;

- HIV: Appropriate use: Do not use as monotherapy in treatment of HIV. Treatment of HIV in patients with unrecognized/untreated HBV may lead to rapid HBV resistance.

- Renal impairment: Use with caution in patients with renal impairment; dosage reduction recommended.

Concurrent drug therapy issues:

- Interferon alfa: Use with caution in combination with interferon alfa with or without ribavirin in HIV/HBV coinfected patients; monitor closely for hepatic decompensation, anemia, or neutropenia; dose reduction or discontinuation of interferon and/or ribavirin may be required if toxicity evident.

Special populations:

- Pediatrics: Use with extreme caution in children with history of pancreatitis or risk factors for development of pancreatitis.

Dosage form specific issues:

- Epivir-HBV®: **[U.S. Boxed Warning]: Do not use Epivir-HBV® tablets or Epivir-HBV® oral solution for the treatment of HIV.**

Pregnancy Risk FactorC

Pregnancy ConsiderationsLamivudine crosses the placenta. No increased risk of overall birth defects has been observed following 1st trimester exposure according to data collected by the antiretroviral pregnancy registry. The pharmacokinetics of lamivudine during pregnancy are not significantly altered and dosage adjustment is not required. The Perinatal HIV Guidelines Working Group recommends lamivudine for use during pregnancy; the combination of lamivudine with zidovudine is the recommended dual combination NRTI in pregnancy. It may also be used in combination with zidovudine in HIV-infected women who are in labor, but have had no prior antiretroviral therapy, in order to reduce the maternal-fetal transmission of HIV. Cases of lactic acidosis/hepatic steatosis syndrome have been reported in pregnant women receiving nucleoside analogues. It is not known if pregnancy itself potentiates this known side effect; however, pregnant women may be at increased risk of lactic acidosis and liver damage. Hepatic enzymes and electrolytes should be monitored frequently during the 3rd trimester of pregnancy in women receiving nucleoside analogues. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse ReactionsReported for treatment of HIV or HBV in adults. Incidence data includes patients on combination therapy with other antiretroviral agents.

>10%:

Central nervous system: Headache (21% to 35%), fatigue (24% to 27%), insomnia (11%)

Gastrointestinal: Nausea (15% to 33%), diarrhea (14% to 18%), pancreatitis (range: 0.3% to 18%; higher percentage in pediatric patients), abdominal pain (9% to 16%), vomiting (13% to 15%)

Hematologic: Neutropenia (7% to 15%)

Hepatic: Transaminases increased (2% to 11%)

Neuromuscular & skeletal: Myalgia (8% to 14%), neuropathy (12%), musculoskeletal pain (12%)

Respiratory: Nasal signs and symptoms (20%), cough (18%), sore throat (13%)

Miscellaneous: Infections (25%; includes ear, nose, and throat)

1% to 10%:

Central nervous system: Dizziness (10%), depression (9%), fever (7% to 10%), chills (7% to 10%)

Dermatologic: Rash (5% to 9%)

Gastrointestinal: Anorexia (10%), lipase increased (10%), abdominal cramps (6%), dyspepsia (5%), amylase increased (<1% to 4%), heartburn

Hematologic: Thrombocytopenia (1% to 4%), hemoglobinemia (2% to 3%)

Neuromuscular & skeletal: Creatine phosphokinase increased (9%), arthralgia (5% to 7%)

<1%, postmarketing, and/or case reports: Alopecia, anaphylaxis, anemia, body fat redistribution, hepatitis B exacerbation, hepatomegaly, hyperbilirubinemia, hyperglycemia, immune reconstitution syndrome, lactic acidosis, lymphadenopathy, muscle weakness, paresthesia, peripheral neuropathy, pruritus, red cell aplasia, rhabdomyolysis, splenomegaly, steatosis, stomatitis, urticaria, weakness, wheezing

Drug Interactions

Emtricitabine: LamiVUDine may enhance the adverse/toxic effect of Emtricitabine. *Risk X: Avoid combination*

Ganciclovir-Valganciclovir: May enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. *Risk D: Consider therapy modification*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Trimethoprim: May decrease the excretion of LamiVUDine. *Risk C: Monitor therapy*

Zalcitabine: LamiVUDine may diminish the therapeutic effect of Zalcitabine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Food decreases the rate of absorption and C_{max}; however, there is no change in the systemic AUC. Therefore, may be taken with or without food.

Monitoring ParametersAmylase, bilirubin, liver enzymes, hematologic parameters, viral load, and CD4 count; signs and symptoms of pancreatitis

Nursing: Physical Assessment/MonitoringUse caution in presence of impaired hepatic or renal function. Assess potential for interactions with other pharmacological agents patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, nausea/vomiting [dehydration]; peripheral neuropathy; hepatitis B [jaundice, fatigue, anorexia]) on a regular basis throughout therapy. Monitor patients closely for several months following discontinuation of therapy for chronic hepatitis B and clinical exacerbations. Teach patient proper use (eg, timing of multiple medications), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsAmylase, bilirubin, liver enzymes, CBC

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. This is not a cure for HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. This medication may be prescribed with a combination of other medications; time these medications as directed by prescriber. Take with or without food. Do not take antacids within 1 hour of lamivudine. Frequent blood tests may be required with prolonged therapy. You may be susceptible to infection (avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber). May cause nausea, vomiting, or abdominal pain (sucking on lozenges, chewing gum, or small, frequent meals may help); diarrhea (boiled milk, buttermilk, or yogurt may help); dizziness or insomnia (use caution when driving or engaging in tasks that require alertness until response to drug is known); or headache, fever, or muscle pain (an analgesic may be recommended). Report persistent lethargy or unusual fatigue, yellowing of eyes, pale stool and dark urine, acute headache, severe nausea or vomiting, respiratory difficulty, loss of sensation, rash, or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral:

Epivir®: 10 mg/mL (240 mL) [strawberry-banana flavor]

Epivir-HBV®: 5 mg/mL (240 mL) [strawberry-banana flavor]

Tablet:

Epivir®: 150 mg [scored], 300 mg

Epivir-HBV®: 100 mg

Generic AvailableNo

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Solution (Epivir)

10 mg/mL (240): $96.79

Tablets (Epivir)

150 mg (60): $375.34

300 mg (30): $385.88

Tablets (Epivir HBV)

100 mg (60): $678.48

Mechanism of ActionLamivudine is a cytosine analog. After lamivudine is triphosphorylated, the principle mode of action is inhibition of HIV reverse transcription via viral DNA chain termination; inhibits RNA- and DNA-dependent DNA polymerase activities of reverse transcriptase. The monophosphate form of lamivudine is incorporated into the viral DNA by hepatitis B virus polymerase, resulting in DNA chain termination.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: V_d: 1.3 L/kg

Protein binding, plasma: <36%

Metabolism: 4.2% to trans-sulfoxide metabolite

Bioavailability: Absolute; Cp_{max} decreased with food although AUC not significantly affected

Children: 66%

Adults: 86% to 87%

Half-life elimination: Children: 2 hours; Adults: 5-7 hours

Time to peak, plasma: Fed: 3.2 hours; Fasted: 0.9 hours

Excretion: Primarily urine (as unchanged drug)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV
- Perinatal HIV Guidelines

Pharmacotherapy PearlsLamivudine has been well studied in the treatment of chronic hepatitis B infection. Potential compliance problems, frequency of administration, and adverse effects should be discussed with patients before initiating therapy to help prevent the emergence of resistance.

A high rate of early virologic nonresponse was observed when abacavir, lamivudine and tenofovir were used as the initial regimen in treatment-naive patients. A high rate of early virologic nonresponse was also observed when didanosine, lamivudine, and tenofovir were used as the initial regimen in treatment-naive patients. Use of either of these combinations is not recommended; patients currently on either of these regimens should be closely monitored for modification of therapy.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusFatigue and insomnia are common; may cause dizziness or depression
Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine
Index Terms3TC
References

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International Brand Names3TC (AR, BB, BM, BS, BZ, CO, GY, HK, ID, JM, KP, MX, MY, NZ, PL, SR, TT, UY); 3TC-HBV (ID); Epivir (AE, AT, BE, BG, BH, BR, CH, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, HN, HR, IE, IL, IQ, IR, IT, JO, KW, LB, LU, LY, NL, NO, OM, PE, PT, PY, QA, RU, SA, SE, SG, SY, TH, TR, VE, YE); epivir 3TC (CN); Heptodin (CL); Inhavir (CO); Ladiwin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Lamidac (IN); Zeffix (AT, AU, BE, BG, BR, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, KP, MY, NL, NO, PH, PK, PL, PT, RU, SE, SG, TH, TR, TW)

LamoTRIgine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

LamoTRIgine may be confused with labetalol, Lamisil®, lamiVUDine, Lomotil®, ludiomil

Lamictal® may be confused with Lamisil®, Lomotil®, ludiomil

Pronunciation(la MOE tri jeen)

U.S. Brand NamesLamictal®

Canadian Brand NamesApo-Lamotrigine®; Gen-Lamotrigine; Lamictal®; Novo-Lamotrigine; PMS-Lamotrigine; ratio-Lamotrigine

Pharmacologic CategoryAnticonvulsant, Miscellaneous

Use: Labeled IndicationsAdjunctive therapy in the treatment of generalized seizures of Lennox-Gastaut syndrome, primary generalized tonic-clonic seizures, and partial seizures in adults and children ≥2 years of age; conversion to monotherapy in adults with partial seizures who are receiving treatment with valproic acid or a single enzyme-inducing antiepileptic drug (specifically carbamazepine, phenytoin, phenobarbital or primidone); maintenance treatment of bipolar I disorder

Dosing: Adults**Note:** Only whole tablets should be used for dosing, round calculated dose down to the nearest whole tablet. Enzyme-inducing regimens specifically refer to those containing carbamazepine, phenytoin, phenobarbital, or primidone. Oral:

Lennox-Gastaut (adjunctive), primary generalized tonic-clonic seizures (adjunctive) or partial seizures (adjunctive): Initial: 25 mg/day for weeks 1 and 2, then increase to 50 mg/day for weeks 3 and 4; maintenance: titrate dose to effect; after week 4 increase daily dose every 1-2 weeks by 50 mg/day; usual maintenance: 225-375 mg/day in 2 divided doses.

Adjustment for AED regimens **containing** valproic acid (see "Note"): Initial: 25 mg every other day for weeks 1 and 2, then increase to 25 mg every day for weeks 3 and 4. Maintenance: Titrate dose to effect; after week 4 increase daily dose every 1-2 weeks by 25-50 mg/day; usual maintenance: 100-400 mg/day in 1 or 2 divided doses.

Note: For patients taking lamotrigine with valproic acid alone, the usual maintenance dose is 100-200 mg/day.

Adjustment for **enzyme-inducing** AED regimens **without** valproic acid: Initial: 50 mg/day for weeks 1 and 2, then increase to 100 mg/day in 2 divided doses for weeks 3 and 4. Maintenance: Titrate dose to effects; after week 4 increase daily dose every 1-2 weeks by 100 mg/day; usual maintenance: 300-500 mg/day in 2 divided doses. Doses as high as 700 mg/day have been used, though additional benefit has not been established.

Conversion to monotherapy with lamotrigine:

Conversion from adjunctive therapy with valproic acid: Initiate and titrate as per recommendations to a lamotrigine dose of 200 mg/day. Then taper valproic acid dose in decrements of not >500 mg/day at intervals of 1 week (or longer) to a valproic acid dosage of 500 mg/day; this dosage should be maintained for 1 week. The lamotrigine dosage should then be increased to 300 mg/day while valproic acid is decreased to 250 mg/day; this dosage should be maintained for 1 week. Valproic acid may then be discontinued, while the lamotrigine dose is increased by 100 mg/day at weekly intervals to achieve a lamotrigine maintenance dose of 500 mg/day.

Conversion from adjunctive therapy with carbamazepine, phenytoin, phenobarbital, or primidone: Initiate and titrate as per recommendations to a lamotrigine dose of 500 mg/day. Concomitant enzyme-inducing AED should then be withdrawn by 20% decrements each week over a 4-week period. Patients should be monitored for rash.

Conversion from adjunctive therapy with AED other than carbamazepine, phenytoin, phenobarbital, primidone or valproic acid: No specific guidelines available.

Bipolar disorder: Initial: 25 mg/day for weeks 1 and 2, then increase to 50 mg/day for weeks 3 and 4, then increase to 100 mg/day for week 5; Maintenance: Increase dose to 200 mg/day beginning week 6.

Adjustment for regimens **containing** valproic acid: Initial: 25 mg every other day for weeks 1 and 2, then increase to 25 mg every day for weeks 3 and 4, then increase to 50 mg/day for week 5. Maintenance: 100 mg/day beginning week 6.

Adjustment for **enzyme-inducing** regimens **without** valproic acid: Initial: 50 mg/day for weeks 1 and 2, then increase to 100 mg/day in divided doses for weeks 3 and 4, then increase to 200 mg/day in divided doses for week 5, then increase to 300 mg/day in divided dose for week 6. Maintenance: 400 mg/day in divided doses beginning week 7.

Adjustment following discontinuation of psychotropic medication:

Discontinuing valproic acid with current dose of lamotrigine 100 mg/day: 150 mg/day for week 1, then increase to 200 mg/day beginning week 2.

Discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or rifampin with current dose of lamotrigine 400 mg/day: 400 mg/day for week 1, then decrease to 300 mg/day for week 2, then decrease to 200 mg/day beginning week 3.

Discontinuing therapy: Decrease dose by ~50% per week, over at least 2 weeks unless safety concerns require a more rapid withdrawal. Discontinuing carbamazepine, phenytoin, phenobarbital, or primidone should prolong the half-life of lamotrigine; discontinuing valproic acid should shorten the half-life of lamotrigine

Restarting therapy after discontinuation: If lamotrigine has been withheld for >5 half-lives, consider restarting according to initial dosing recommendations.

Dosage adjustment with combination hormonal contraceptives: Follow initial dosing guidelines, maintenance dose should be adjusted as follows: Patients taking carbamazepine, phenytoin, phenobarbital, primidone or rifampin: No dosing adjustment required

Patients **not** taking carbamazepine, phenytoin, phenobarbital, primidone or rifampin: Maintenance dose may need increased by twofold over target dose. If already taking a stable dose of lamotrigine and starting contraceptive, maintenance dose may need increased by twofold. Dose increases should start when contraceptive is started and titrated to clinical response increasing no more rapidly than 50-100 mg/day every week. Gradual increases of lamotrigine plasma levels may occur during the inactive “pill-free” week and will be greater when dose increases are made the week before. If increased adverse events consistently occur during “pill-free” week, overall dose adjustments may be required. When discontinuing combination hormonal contraceptive, dose of lamotrigine may need decreased by as much as 50%; do not decrease by more than 25% of total daily dose over a 2-week period unless clinical response or plasma levels indicate otherwise. Dose adjustments during “pill-free” week are not recommended.

⇧ Dosing: ElderlyRefer to adult dosing.

⇧ Dosing: Pediatric**Note:** Only whole tablets should be used for dosing, round calculated dose down to the nearest whole tablet. Enzyme-inducing regimens specifically refer to those containing carbamazepine, phenytoin, phenobarbital, or primidone.

Lennox-Gastaut (adjunctive), primary generalized tonic-clonic seizures (adjunctive), or partial seizures (adjunctive): Oral: **Note:** Children <30 kg will likely require maintenance doses to be increased as much as 50% based on clinical response regardless of regimen below:

Children 2-12 years: Initial: 0.3 mg/kg/day in 1-2 divided doses for weeks 1 and 2, then increase to 0.6 mg/kg/day in 1-2 divided doses for weeks 3 and 4; maintenance: titrate dose to effect; after week 4, increase daily dose every 1-2 weeks by 0.6 mg/kg/day; usual maintenance: 4.5-7.5 mg/kg/day in 2 divided doses; maximum: 300 mg/day in 2 divided doses.

Adjustment for AED regimens **containing** valproic acid (see "Note"): Initial: 0.15 mg/kg/day in 1-2 divided doses for weeks 1 and 2, then increase to 0.3 mg/kg/day in 1-2 divided doses for weeks 3 and 4; maintenance: titrate dose to effect; after week 4, increase daily dose every 1-2 weeks by 0.3 mg/kg/day; usual maintenance: 1-5 mg/kg/day in 2 divided doses; maximum: 200 mg/day in 1-2 divided doses

Note: For patients >6.7 kg and <14 kg, initial dosing should be 2 mg every other day for first 2 weeks, then increased to 2 mg daily for weeks 3-4. For patients taking lamotrigine with valproic acid alone, the usual maintenance dose is 1-3 mg/kg/day in 2 divided doses

Adjustment for **enzyme-inducing** AED regimens **without** valproic acid: Initial: 0.6 mg/kg/day in 2 divided doses for weeks 1 and 2, then increase to 1.2 mg/kg/day in 2 divided doses for weeks 3 and 4; maintenance: titrate dose to effect; after week 4, increase daily dose every 1-2 weeks by 1.2 mg/kg/day; usual maintenance: 5-15 mg/kg/day in 2 divided doses; maximum: 400 mg/day in 2 divided doses

Children >12 years: Refer to adult dosing.

Conversion from single enzyme-inducing AED regimen to monotherapy: Children ≥16 years: Refer to adult dosing.

Discontinuing therapy: Refer to adult dosing.

Restarting therapy after discontinuation: Refer to adult dosing.

Dosage adjustment with combination hormonal contraceptives: Refer to adult dosing.

⇧ Dosing: Renal ImpairmentDecreased dosage may be effective in patients with significant renal impairment; use with caution.

⇧ Dosing: Hepatic Impairment

Moderate-to-severe impairment without ascites: Decrease initial, escalation, and maintenance doses by ~25%

Moderate-to-severe impairment with ascites: Decrease initial, escalation, and maintenance doses by ~50%

Administration: OralDoses should be rounded down to the nearest whole tablet. Dispersible tablets may be chewed, dispersed in water or diluted fruit juice, or swallowed whole. To disperse tablets, add to a small amount of liquid (just enough to cover tablet); let sit ~1 minute until dispersed; swirl solution and consume immediately. Do not administer partial amounts of liquid. If tablets are chewed, a small amount of water or diluted fruit juice should be used to aid in swallowing.

Dietary ConsiderationsTake without regard to meals; drug may cause GI upset.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.

Extemporaneously PreparedA 1 mg/mL oral suspension may be compounded as follows: Crush one 100 mg tablet and reduce to a fine powder. Add small amount of Ora-Sweet® or Ora-Plus® and mix to uniform paste. Transfer to graduate and qs to 100 mL. Shake well before using and refrigerate. Suspension is stable for 91 days.

Nahata M, Morosco R, Hipple T. "Stability of Lamotrigine in Two Extemporaneously Prepared Oral Suspensions at 4 and 25°C," *Am J Health Syst Pharm*, 1999, 56:240-2.

ContraindicationsHypersensitivity to lamotrigine or any component of the formulation

Allergy Considerations

- LamoTRIgine Allergy

Warnings/Precautions

Boxed warnings:

- Skin rashes: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Blood dyscrasias: A spectrum of hematologic effects have been reported with use (eg, neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias); patients with a previous history of adverse hematologic reaction to any drug may be at increased risk. Early detection of hematologic change is important; advise patients of early signs and symptoms including fever, sore throat, mouth ulcers, infections, easy bruising, petechial or purpuric hemorrhage. May be associated with hypersensitivity syndrome.

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Multiorgan hypersensitivity reactions: Potentially serious, sometimes fatal multiorgan hypersensitivity reactions have been reported with some antiepileptic drugs; monitor for signs and symptoms of possible disparate manifestations associated with lymphatic, hepatic, renal, and/or hematologic organ systems; gradual discontinuation and conversion to alternate therapy may be required.

- Skin rashes: **[U.S. Boxed Warning]: Severe and potentially life-threatening skin rashes requiring hospitalization have been reported; risk may be increased by coadministration with valproic acid, higher than recommended starting doses, and rapid dose titration.** The majority of cases occur in the first 8 weeks; however, isolated cases may occur after prolonged treatment; discontinue at first sign of rash unless rash is clearly not drug related.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with impaired cardiac function.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Hormonal contraceptives: May cause a decrease in lamotrigine levels requiring dose adjustment.

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Other warnings/precautions:

- Bipolar disorder use: Patients treated for bipolar disorder should be monitored closely for clinical worsening or suicidality; prescriptions should be written for the smallest quantity consistent with good patient care.

- Melanin binding: Binds to melanin and may accumulate in the eye and other melanin-rich tissues; the clinical significance of this is not known.

- Monotherapy: Safety and efficacy have not been established for use as initial monotherapy, conversion to monotherapy from antiepileptic drugs (AED) other than carbamazepine, phenytoin, phenobarbital, primidone or valproic acid or conversion to monotherapy from two or more AEDs.

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal. Taper over at least 2 weeks if possible.

Geriatric ConsiderationsNo pharmacokinetic differences noted between young adults and the elderly. Use with caution in the elderly with significant renal decline.

Pregnancy Risk FactorC

Pregnancy ConsiderationsLamotrigine has been found to decrease folate concentrations in animal studies. Teratogenic effects in animals were not observed. Lamotrigine crosses the human placenta and can be measured in the plasma of exposed newborns. Preliminary data from the North American Antiepileptic Drug Pregnancy Registry (NAAED) suggest an increased incidence of cleft lip and/or cleft palate following first trimester exposure. Healthcare providers may enroll patients in the Lamotrigine Pregnancy Registry by calling (800) 336-2176. Patients may enroll themselves in the NAAED registry by calling (888) 233-2334. Dose of lamotrigine may need adjustment during pregnancy to maintain clinical response; lamotrigine serum levels may decrease during pregnancy and return to prepartum levels following delivery. Monitor frequently during pregnancy, following delivery, and when adding or discontinuing combination hormonal contraceptives.

LactationEnters breast milk/not recommended (AAP rates "of concern")

Breast-Feeding ConsiderationsLamotrigine is found in breast milk. In one study, the relative dose to the infant was 9% (range 2% to 20%) of the weight-adjusted maternal dose. Lamotrigine was measurable in the plasma of nursing infants; adverse events were not observed.

Adverse ReactionsPercentages reported in adults on monotherapy for epilepsy or bipolar disorder.

>10%: Gastrointestinal: Nausea (7% to 14%)

1% to 10%:

Cardiovascular: Chest pain (5%), peripheral edema (2% to 5%), edema (1% to 5%)

Central nervous system: Somnolence (9%), fatigue (8%), dizziness (7%), anxiety (5%), insomnia (5% to 10%), pain (5%), ataxia (2% to 5%), irritability (2% to 5%), suicidal ideation (2% to 5%), agitation (1% to 5%), amnesia (1% to 5%), depression (1% to 5%), dream abnormality (1% to 5%), emotional lability (1% to 5%), fever (1% to 5%), hypoesthesia (1% to 5%), migraine (1% to 5%), thought abnormality (1% to 5%), confusion (1%)

Dermatologic: Rash (nonserious: 7%), dermatitis (2% to 5%), dry skin (2% to 5%)

Endocrine & metabolic: Dysmenorrhea (5%), libido increased (2% to 5%)

Gastrointestinal: Vomiting (5% to 9%), dyspepsia (7%), abdominal pain (6%), xerostomia (2% to 6%), constipation (5%), weight loss (5%), anorexia (2% to 5%), peptic ulcer (2% to 5%), rectal hemorrhage (2% to 5%), flatulence (1% to 5%), weight gain (1% to 5%)

Genitourinary: Urinary frequency (1% to 5%)

Neuromuscular & skeletal: Back pain (8%), coordination abnormal (7%), weakness (2% to 5%), arthralgia (1% to 5%), myalgia (1% to 5%), neck pain (1% to 5%), paresthesia (1%)

Ocular: Nystagmus (2% to 5%), vision abnormal (2% to 5%), amblyopia (1%)

Respiratory: Rhinitis (7%), cough (5%), pharyngitis (5%), bronchitis (2% to 5%), dyspnea (2% to 5%), epistaxis (2% to 5%), sinusitis (1% to 5%)

Miscellaneous: Infection (5%), diaphoresis (2% to 5%), reflexes increased/decreased (2% to 5%), dyspraxia (1% to 5%)

<1%: Any indication (limited to important or life-threatening): Accommodation abnormality, acne, alcohol intolerance, allergic reaction, alopecia, anemia, angina, angioedema, aphasia, appetite increased, arthritis, atrial fibrillation, breast pain, bruising, cerebellar syndrome, cerebral sinus thrombosis, cerebrovascular accident, chills, choreoathetosis, CNS depression/stimulation, conjunctivitis, deafness, deep thrombophlebitis, delirium, delusions, dermatitis (exfoliative, fungal), dry eyes, dysphagia, dysphoria, dystonia, ear pain, ECG abnormality, ejaculation abnormal, eructation, euphoria, extrapyramidal syndrome, faintness, flushing, gastritis, gingivitis, goiter, halitosis, hallucinations, hematuria, hemiplegia, hemorrhage, hiccup, hirsutism, hot flashes, hyperalgesia, hyperglycemia, hypertension, hyperventilation, hypokinesia, hypothyroidism, hypotonia, impotence, kidney failure (acute), leg cramps, leukopenia, liver function tests abnormal, maculopapular rash, malaise, menorrhagia, MI, mouth ulceration, movement disorder, muscle spasm, myasthenia, neuralgia, neurosis, palpitation, paralysis, peripheral neuritis, photophobia, polyuria, postural hypotension, salivation increased, skin discoloration, Stevens-Johnson syndrome, suicide, syncope, tachycardia, taste loss/perversion, thrombocytopenia, tinnitus, tongue edema, twitching, urinary incontinence, urticaria, vasodilation, yawn

Also observed: Rash requiring hospitalization: Children <16 years 0.8% (epilepsy adjunctive therapy); Adults 0.3% (epilepsy adjunctive therapy), 0.13% (epilepsy monotherapy), 0.8% (bipolar disorder, monotherapy)

Postmarketing and/or case reports (any indication): Agranulocytosis, aplastic anemia, apnea, disseminated intravascular coagulation, esophagitis, hemolytic anemia, hypersensitivity reactions, lupus-like reaction, multiorgan failure, neutropenia, pancreatitis, pancytopenia, parkinsonian exacerbation, progressive immunosuppression, red cell aplasia, rhabdomyolysis, tic, toxic epidermal necrolysis, vasculitis

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

CarBAMazepine: LamoTRIgine may enhance the adverse/toxic effect of CarBAMazepine. CarBAMazepine may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: LamoTRIgine may enhance the adverse/toxic effect of Desmopressin. LamoTRIgine may enhance the therapeutic effect of Desmopressin. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

OLANZapine: LamoTRIgine may enhance the sedative effect of OLANZapine. *Risk C: Monitor therapy*

Oral Contraceptive (Estrogens): May decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Phenytoin: May increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Primidone: May increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Rifampin: May increase the metabolism of LamoTRIgine. *Risk C: Monitor therapy*

Ritonavir: May decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Valproic Acid: May enhance the adverse/toxic effect of LamoTRIgine. Valproic Acid may increase the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Has no effect on absorption.

Herb/Nutraceutical: Avoid evening primrose (seizure threshold decreased).

Monitoring ParametersSeizure, frequency and duration, serum levels of concurrent anticonvulsants, hypersensitivity reactions, especially rash

Reference RangeA therapeutic serum concentration range has not been established for lamotrigine. Dosing should be based on therapeutic response. Lamotrigine plasma concentrations of 0.25-29.1 mcg/mL have been reported in the literature.

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness, laboratory values, and adverse reactions at beginning of therapy and periodically with long-term use. Monitor for skin rash. Discontinue at the first sign of rash, unless clearly not drug related. Taper dosage slowly when discontinuing. Observe and teach seizure/safety precautions. Use caution in writing and/or interpreting prescriptions/orders. Confusion between Lamictal® (lamotrigine) and Lamisil® (terbinafine) has occurred. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsSerum levels of concurrent anticonvulsants, LFTs, renal function

Patient EducationTake exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. Only whole tablets should be used for dosing, rounded down to the nearest whole tablet. When having the prescription refilled, contact the prescriber if the medicine looks different or the label name has changed. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea, vomiting, loss of appetite, heartburn, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Women who start or stop oral contraceptives should notify their prescriber. Wear identification of epileptic status and medications. Report CNS changes, mentation changes, suicidal ideation, depression, or changes in cognition; persistent GI symptoms (cramping, constipation, vomiting, anorexia); swelling of face, lips, or tongue; easy bruising or bleeding (mouth, urine, stool); vision changes; worsening of seizure activity, or loss of seizure control. A skin rash may indicate a serious medical problem; contact prescriber immediately if rash noted. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 25 mg, 100 mg, 150 mg, 200 mg

Lamictal®: 25 mg, 100 mg, 150 mg, 200 mg

Tablet, combination package [each unit-dose starter kit contains]:

Lamictal® (blue kit; for patients taking valproic acid):

Tablet: Lamotrigine 25 mg (35s)

Lamictal® (green kit; for patients taking carbamazepine, phenytoin, phenobarbital, primidone, or rifampin and **not** taking valproic acid):

Tablet: Lamotrigine 25 mg (84s)

Tablet: Lamotrigine 100 mg (14s)

Lamictal® (orange kit; for patients **not** taking carbamazepine, phenytoin, phenobarbital, primidone, rifampin, or valproic acid):

Tablet: Lamotrigine 25 mg (42s)

Tablet: Lamotrigine 100 mg (7s)

Tablet, dispersible/chewable: 5 mg, 25 mg

Lamictal®: 2 mg, 5 mg, 25 mg [black currant flavor]

Generic AvailableYes

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Tablet, orally-disintegrating (Lamictal)

25 mg (30): $153.19

Tablet, orally-disintegrating (Lamotrigine)

25 mg (30): $89.99

Tablets (Lamictal)

25 mg (60): $279.99

100 mg (60): $319.99

150 mg (60): $349.99

200 mg (60): $389.99

Tablets (Lamotrigine)

25 mg (100): $385.97

100 mg (100): $400.00

150 mg (60): $296.82

200 mg (60): $323.14

Mechanism of ActionA triazine derivative which inhibits release of glutamate (an excitatory amino acid) and inhibits voltage-sensitive sodium channels, which stabilizes neuronal membranes. Lamotrigine has weak inhibitory effect on the 5-HT$_3$ receptor; *in vitro* inhibits dihydrofolate reductase.

Pharmacodynamics/Kinetics

Absorption: Rapid and complete

Distribution: V$_d$: ~1 L/kg

Protein binding: 55%

Metabolism: Hepatic and renal; metabolized by glucuronic acid conjugation to inactive metabolites

Bioavailability: 98%

Half-life elimination: Adults: 25-33 hours

Concomitant valproic acid therapy: 59-70 hours

Concomitant phenytoin or carbamazepine therapy: 13-14 hours

Chronic renal failure: 43 hours

Hemodialysis: 13 hours during dialysis; 57 hours between dialysis

Hepatic impairment: 26-148 hours

Time to peak, plasma: 1-5 hours

Excretion: Urine (94%, ~90% as glucuronide conjugates and ~10% unchanged); feces (2%)

Related Information

- Adverse Effects of Approved Mood Stabilizers / Anticonvulsants
- Agents Approved for Bipolar Disorder
- Anticonvulsant Drugs of Choice

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentValproic acid decreases clearance of lamotrigine; carbamazepine may decrease effects of lamotrigine

Mental Health CommentLamotrigine is useful for the maintenance treatment of bipolar disorder. Best efficacy appears to be in the prophylaxis of depressive episodes. This medication requires a slow titration process. If patient is receiving valproic acid and/or carbamazepine, a dosage adjustment is necessary (see Dosage).

Potentially life-threatening skin rashes have been reported. These appear to be more frequent in pediatric patients and is associated with high serum levels, use of higher than recommended starting dose, and rapid dose titration. The majority of cases occur within the first 8 weeks of treatment. The combination use with valproate may increase this risk. Discontinue if rash develops.

Index TermsBW-430C; LTG

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International Brand NamesElmendos (AU); Labicitin (KP); Lamdra SBK (MX); Lamepil (IN); Lamictal (AE, AR, AT, AU, BB, BD, BE, BG, BH, BM, BO, BR, BS, BZ, CH, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, FI, FR, GB, GR, GT, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KP, KW, LB, LU, LY, MX, MY, NI, NL, NO, OM, PA, PE, PH, PK, PL, PR, PT, PY, QA, RU, SA, SE, SG, SR, SV, SY, TH, TR, TT, TW, UY, VE, YE); Lamidus (AU); Lamitrin (AU, PL); Lamodex (IL); Lamogin (TW); Lamogine (IL); Lamotrix (MY, PL, TW); Lamozine (KP); Latrigine (TW); Logem (AU); Lotrigine (AU); Mogine (NZ); Neurium (BR); Plexxo (PL); Protalgine (MX); Seaze (AU)

Lanolin, Cetyl Alcohol, Glycerin, Petrolatum, and Mineral Oil

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(LAN oh lin, SEE til AL koe hol, GLIS er in, pe troe LAY tum, & MIN er al oyl)
U.S. Brand NamesLubriderm速 Fragrance Free [OTC]; Lubriderm速 [OTC]
Pharmacologic CategoryTopical Skin Product
Use: Labeled IndicationsTreatment of dry skin
Dosing: AdultsDry skin: Topical: Apply to skin as necessary
Dosing: ElderlyRefer to adult dosing.
Pregnancy Risk FactorC
Adverse Reactions1% to 10%: Local irritation
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Lotion, topical [bottle]: 180 mL, 300 mL, 480 mL

Lotion, topical [tube]: 100 mL

Generic AvailableYes
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsMineral Oil, Petrolatum, Lanolin, Cetyl Alcohol, and Glycerin

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Lanreotide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Somatuline® may be confused with somatropin, SUMAtriptan

International issues:

Somatuline® may be confused with Soma® which is a brand name for carisoprodol in the U.S.

Pronunciation(lan REE oh tide)

U.S. Brand NamesSomatuline® Depot

Canadian Brand NamesSomatuline® Autogel®

Pharmacologic CategorySomatostatin Analog

Use: Labeled IndicationsLong-term treatment of acromegaly in patients who are not candidates for or are unresponsive to surgery and/or radiotherapy

Canadian labeling: Also approved in Canada for relief of symptoms of acromegaly

Dosing: AdultsAcromegaly: **Note: Differences in U.S. and Canadian labeled dosing:** SubQ:

U.S. labeling: Adults: 90 mg once every 4 weeks for 3 months; after initial 90 days of therapy, adjust dose based on clinical response of patient, growth hormone (GH) levels, and/or insulin-like growth factor 1 (IGF-1) levels as follows:

GH ≤1 ng/mL, IGF-1 normal, symptoms stable:60 mg once every 4 weeks

GH >1-2.5 ng/mL, IGF-1 normal, symptoms stable: 90 mg once every 4 weeks

GH >2.5 ng/mL, IGF-1 elevated and/or uncontrolled symptoms: 120 mg once every 4 weeks

Canadian labeling: Children ≥16 years and Adults: 90 mg once every 4 weeks for 3 months; after initial 90 days of therapy, adjust dose based on clinical response of patient, growth hormone (GH) levels, and/or insulin-like growth factor 1 (IGF-1) levels as follows:

GH = 1 ng/mL, IGF-1 normal, symptoms stable: 60 mg once every 4 weeks

GH >1-2.5 ng/mL, IGF-1 normal, symptoms stable: 90 mg once every 4 weeks

GH >2.5 ng/mL, IGF-1 elevated and/or uncontrolled symptoms: 120 mg once every 4 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric
Acromegaly: Children ≥16 years (*Canadian labeling*): Refer to adult dosing.

Dosing: Renal Impairment
U.S. labeling: Moderate-to-severe impairment: Recommended starting dose: 60 mg

Canadian labeling: No adjustment is necessary

Dosing: Hepatic Impairment
U.S. labeling: Moderate-to-severe impairment: Recommended starting dose: 60 mg

Canadian labeling: No adjustment is necessary

Administration: OtherSubQ: Administer by deep subcutaneous injection into superior outer quadrant of buttocks. Do not fold skin. Alternate injection sites.

StorageStore under refrigeration 2°C to 8°C (36°F to 46°F). Protect from light. Allow to reach room temperature by removing sealed pouch from refrigerator 30 minutes prior to administration; keep in sealed pouch until just prior to administration.

Contraindications

There are no contraindications listed in the manufacturer’s labeling.

Canadian labeling contraindications: Hypersensitivity to lanreotide, somatostatin (or related peptides), or any component of the formulation; complicated, untreated lithiasis of the bile ducts

Warnings/Precautions

Concerns related to adverse effects:

- Cholelithiasis: May reduce gall bladder motility, leading to gall stone formation (may be dose- or duration-related); monitor. **Note:** In Canada, ultrasonography is recommended with the initiation of therapy and periodically thereafter.
- Hyper-/hypoglycemia: Inhibition of insulin and glucagon secretion may affect glucose regulation, leading to hyper-/hypoglycemia. Carefully monitor blood glucose levels with the initiation of therapy and with dosage alterations. Use with caution in patients with diabetes; may require dosage adjustments in antidiabetic therapy.
- Hypothyroidism: Decreases (slight) in thyroid function have been observed during therapy; may require monitoring of thyroid function tests.

Disease-related concerns:

- Cardiac disorders: Bradycardia, sinus bradycardia, and hypertension have been observed with therapy. Use with caution in patients with preexisting cardiac disease. Patients without preexisting cardiac disease may experience a decrease in heart rate though not to the level of bradycardia.
- Hepatic impairment: Use with caution in patients with hepatic impairment; lower doses are recommended at therapy initiation in patients with moderate-to-severe impairment.
- Renal impairment: Use with caution in patients with renal impairment; lower doses are recommended at therapy initiation in patients with moderate-to-severe impairment.

Concurrent drug therapy issues:

- Cyclosporine: Concurrent use with cyclosporine may result in decreased serum levels of cyclosporine; monitor.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children. **Note:** In Canada, safety and efficacy have not been established in children <16 years of age.

Dosage form specific issues:

- Latex: The packaging (needle cover) may contain latex.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have demonstrated embryocidal and teratogenic effects, as well as transitory growth retardation. Very little data exists from clinical trials and/or postmarketing reports of lanreotide in pregnancy. There are no adequate and well-controlled studies in pregnant women. Use in pregnancy only if benefits outweigh potential risks to fetus.

Lactation

Excretion into breast milk unknown/not recommended

Adverse Reactions

>10%:

Cardiovascular: Bradycardia (5% to 18%)

Gastrointestinal: Diarrhea (26% to 65%; dose related), abdominal pain (7% to 19%; dose related), flatulence (≤14%; dose related), nausea (11%), weight loss (5% to 11%)

Hematologic: Anemia (3% to 14%)

Hepatic: Cholelithiasis/gall bladder sludge (2% to 20%)

Local: Injection site reaction (6% to 22%; induration: 5%; pain: 4%; mass: 2%)

1% to 10%:

Cardiovascular: Hypertension (5%), sinus bradycardia (3%)

Central nervous system: Headache (7%)

Endocrine & metabolic: Hyper-/hypoglycemia/diabetes (7%)

Gastrointestinal: Constipation (8%), vomiting (7%), loose stools (6%)

Neuromuscular & skeletal: Arthralgia (7%)

<1%, postmarketing, and/or case reports: Allergic skin reaction, aortic valve regurgitation, dysautonomia, injection site pruritus, mitral valve regurgitation, steatorrhea

Drug Interactions

Codeine: Somatostatin Analogs may decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

CycloSPORINE: Somatostatin Analogs may decrease the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Pegvisomant: Somatostatin Analogs may enhance the adverse/toxic effect of Pegvisomant. Specifically, this combination may increase the risk for significant elevations of liver enzymes. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions Herb/Nutraceutical: Avoid hypoglycemic herbs, including alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng, gymnema, marshmallow, and stinging nettle (may enhance the hypoglycemic effect of lanreotide).

Monitoring Parameters Serum GH, IGF-1, glucose levels, thyroid function (where clinically indicated); heart rate, gall bladder ultrasonography (prior to initiation and periodically during therapy)

Monitoring: Lab Tests Serum GH, IGF-1, glucose levels, thyroid function (where clinically indicated)

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, solution:

Somatuline® Autogel® [CAN]: 60 mg/ 0.3 mL (0.3 mL); 90 mg/ 0.3 mL (0.3 mL); 120 mg/0.5 mL (0.5 mL) [packaging contains natural rubber/natural latex]

Somatuline® Depot®: 60 mg/~0.4 mL (~0.4 mL); 90 mg/~0.4 mL (~0.4 mL); 120 mg/~0.5 mL (~0.5 mL) [packaging contains natural rubber/natural latex]

ManufacturerIpsen Pharma Biotech [U.S.]; Ipsen Limited [CAN]

Mechanism of Action Synthetic octapeptide analogue of somatostatin which is a peptide inhibitor of multiple endocrine, neuroendocrine, and exocrine mechanisms. Displays a greater affinity for somatostatin type 2 (SSTR2) and type 5 (SSTR5) receptors found in pituitary gland, pancreas, and growth hormone (GH) secreting neoplasms of pituitary gland and a lesser affinity for somatostatin receptors 1, 3, and 4. Reduces GH secretion and also reduces the levels of insulin-like growth factor 1.

Pharmacodynamics/Kinetics

Distribution: V_{ss}: ~0.2 L/kg

Protein binding: 79% to 83%

Metabolism: Extensively within GI tract after biliary excretion

Bioavailability: 69% to 83%

Half-life, elimination: 23-36 days

Time to peak, plasma: Mean: 7-12 hours

Excretion: Urine (<1% to 5% as unchanged drug); feces (<0.5% as unchanged drug)

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Index Terms Lanreotide Acetate

References

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Rasmussen E, Eriksson B, Oberg K, et al, “Selective Effects of Somatostatin Analogs on Human Drug-Metabolizing Enzymes,” *Clin Pharmacol Ther*, 1998, 64(2):150-9.[PubMed 9728895]

Reubi JC, Waser B, Schaer JC, et al, “Somatostatin Receptor sst1-sst5 Expression in Normal and Neoplastic Human Tissues Using Receptor Autoradiography With Subtype-Selective Ligands,” *Eur J Nucl Med*, 2001, 28(7):836-46.[PubMed 11504080]

International Brand Names Ipstyl (DK, IT); Somatulina (ES); Somatuline (BE, CZ, EE, GB, NL); Somatuline Autogel (AR, AU, BG, CH, CO, DE, GB, IE, IL, KP, SE); Somatuline LP (FR); Somatuline P.R. (CZ, FI, HK, IL, SG, TW)

Lansoprazole and Naproxen

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Clopidogrel (Plavix®) and Proton Pump Inhibitors (PPIs): Ongoing Safety Review - January 2009

The U.S. Food and Drug Administration (FDA) is communicating important information regarding an ongoing safety review of clopidogrel and its effectiveness when used with proton pump inhibitors (PPIs).

Clopidogrel is a prodrug requiring hepatic conversion via CYP3A4 and/or CYP2C19 to its active metabolite. Impaired clopidogrel conversion to its active metabolite may be due to either CYP450 polymorphisms or drug-drug interactions resulting in suboptimal antiplatelet activity.

A PPI is often prescribed with the combination of aspirin and clopidogrel to prevent gastrointestinal bleeding. A number of PPIs are available and include esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. Several studies have reported greater clinical event rates (eg, myocardial infarction, death) or greater platelet reactivity associated with concurrent use of clopidogrel and a PPI (Ho, 2008; Pezella, 2008; Gilard, 2006). Similarly, a prospective, randomized, double-blind trial demonstrated a reduction in antiplatelet activity when omeprazole and clopidogrel are used concurrently (Gilard, 2008). Another controlled trial with the PPI lansoprazole also found evidence of a possible interaction resulting in less antiplatelet activity (Small, 2008). This interaction is thought to result from competitive inhibition of the CYP2C19-mediated activation of clopidogrel by omeprazole and other PPIs, which are all metabolized to at least some degree by CYP2C19. In contrast, one study with esomeprazole and pantoprazole did not find evidence of reduced antiplatelet activity when administered with clopidogrel (Siller-Matula, 2009), highlighting the need for additional studies to determine the degree to which individual PPIs may differ in their potential for interacting with clopidogrel.

The manufacturer of Plavix® has agreed to conduct further studies to better understand the effect of other drugs (including PPIs) and genetic factors on the effectiveness of clopidogrel. The FDA is recommending that healthcare providers continue to prescribe clopidogrel while reevaluating the need for prescription or over-the-counter (OTC) PPIs in patients taking clopidogrel. Patients should continue taking clopidogrel as directed. If taking a PPI with clopidogrel, patients should consult with their healthcare provider.

For more information, healthcare professionals may refer to the following FDA website:
http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm

References:

Ho PM, Maddox TM, Wang L, et al, “Proton Pump Inhibitors May Attenuate the Benefits of Clopidogrel Among ACS Patients: Using Registry Data to Address Medication Effectiveness,” United States Department of Veterans Affairs, 2008 QUERI National Meeting Abstract. Available at http://www.hsrd.research.va.gov/meetings/QUERI08/display_abstract.cfm?RecordID=118; accessed October 30, 2008).

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Small DS, Farid NA, Payne CD, et al, “Effects of the Proton Pump Inhibitor Lansoprazole on the Pharmacokinetics and Pharmacodynamics of Prasugrel and Clopidogrel,” *J Clin Pharmacol*, 2008, 48(4):475-84.

Medication Safety Issues

Sound-alike/look-alike issues:

Prevacid® may be confused with Pravachol®, Prevpac®, Prilosec®, Prinivil®

Pronunciation(lan SOE pra zole & na PROKS en)

U.S. Brand NamesPrevacid® NapraPAC®

Pharmacologic Category[Nonsteroidal Anti-inflammatory Drug (NSAID), Oral](Nonsteroidal Anti-inflammatory Drug (NSAID), Oral); Proton Pump Inhibitor

Use: Labeled IndicationsReduction of the risk of NSAID-associated gastric ulcers in patients with history of gastric ulcer who require an

NSAID for the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis

Dosing: AdultsReduce NSAID-associated gastric ulcers during treatment for arthritis: Oral: Lansoprazole 15 mg once daily in the morning; naproxen 500 mg twice daily

Dosing: ElderlyNaproxen: Dosing adjustment should be considered.

Dosing: Renal ImpairmentNaproxen: Cl_{cr} <30 mL/minute: use is not recommended.

Dosing: Hepatic Impairment

Lansoprazole: Severe liver disease: consider dosage adjustment.

Naproxen: Consider dosage adjustment in patients with liver disease.

Administration: OralMorning doses should be taken prior to eating and with a glass of water; evening dose should be taken with a glass of water. Lansoprazole capsules should be swallowed whole; do not crush or chew.

Dietary ConsiderationsMorning doses should be taken prior to eating and with a glass of water; evening dose should be taken with a glass of water

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light and moisture.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to lansoprazole, naproxen, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy
- Proton Pump Inhibitor, Benzimidazole Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Naproxen therapy may cause anaphylactoid reactions, even without prior exposure; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Aseptic meningitis: May increase the risk of aseptic meningitis, especially in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders.
- Atrophic gastritis: Long-term omeprazole therapy has caused atrophic gastritis (by biopsy); this may also occur with lansoprazole.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Carcinoma: No occurrences of enterochromaffin-like (ECL) cell carcinoids, dysplasia, or neoplasia, such as those seen in rodent studies, have been reported in humans.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding, inflammatory bowel disease, ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.
- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.
- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.
- Gastric malignancy: Relief of symptoms does not preclude the presence of a gastric malignancy.

- Gastrointestinal infection (eg, *Salmonella, Campylobacter*): Use of proton pump inhibitors may increase risk of these infections.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Naproxen is not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Safety and efficacy of this combination product have not been established in children.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric Considerations

The elderly are at increased risk for adverse effects from NSAIDs. As many as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high-dose situations; however, elderly patients may demonstrate these adverse effects at lower doses than younger adults. The elderly are also at increased risk of renal toxicity.

Pregnancy Risk FactorC (naproxen: D/third trimester)
Pregnancy ConsiderationsTeratogenic effects were not observed with lansoprazole or naproxen in animal studies. Naproxen use late in pregnancy is associated with persistent pulmonary hypertension, renal dysfunction, and abnormal prostaglandin E levels in preterm infants. Exposure to NSAIDs late in pregnancy may lead to premature closure of the ductus arteriosus and may inhibit uterine contractions. Use of this combination product is not recommended for use during pregnancy unless clearly needed.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsNaproxen is excreted in breast milk; excretion of lansoprazole is unknown. Breast-feeding is not recommended.
Adverse ReactionsSee individual agents.
Metabolism/Transport Effects

Lansoprazole: **Substrate** of CYP2C9 (minor), 2C19 (major), 3A4 (major); **Inhibits** CYP2C9 (weak), 2C19 (moderate), 2D6 (weak), 3A4 (weak); **Induces** CYP1A2 (weak)

Naproxen: **Substrate** (minor) of CYP1A2, 2C9

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Atazanavir: Proton Pump Inhibitors may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Clopidogrel: Proton Pump Inhibitors may diminish the therapeutic effect of Clopidogrel. This appears to be due to reduced formation of the active clopidogrel metabolite. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory

Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: Proton Pump Inhibitors may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Proton Pump Inhibitors may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Erlotinib: Proton Pump Inhibitors may decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Fluconazole: May increase the serum concentration of Proton Pump Inhibitors. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Imatinib: Lansoprazole may enhance the dermatologic adverse effect of Imatinib. *Risk C: Monitor therapy*

Indinavir: Proton Pump Inhibitors may decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Iron Salts: Proton Pump Inhibitors may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk C: Monitor therapy*

Itraconazole: Proton Pump Inhibitors may decrease the serum concentration of Itraconazole. *Risk D: Consider therapy modification*

Ketoconazole: Proton Pump Inhibitors may decrease the serum concentration of Ketoconazole. Ketoconazole may increase the serum concentration of Proton Pump Inhibitors. *Risk D: Consider therapy modification*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Mesalamine: Proton Pump Inhibitors may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids; proton pump inhibitors would be expected to interact in a similar manner. *Risk X: Avoid combination*

Methotrexate: Proton Pump Inhibitors may decrease the excretion of Methotrexate. Antirheumatic doses of methotrexate probably hold minimal risk. *Risk C: Monitor therapy*

Mycophenolate: Proton Pump Inhibitors may decrease the serum concentration of Mycophenolate. Specifically, concentrations of the active mycophenolic acid may be reduced. *Risk C: Monitor therapy*

Nelfinavir: Proton Pump Inhibitors may decrease serum concentrations of the active metabolite(s) of Nelfinavir. Proton Pump Inhibitors may decrease the serum concentration of Nelfinavir. *Risk X: Avoid combination*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Saquinavir: Proton Pump Inhibitors may increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tipranavir: May decrease the serum concentration of Proton Pump Inhibitors. These data are derived from studies with Ritonavir-boosted Tipranavir. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Voriconazole: Proton Pump Inhibitors may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Monitoring ParametersOccult blood loss, periodic liver function test, CBC, BUN, serum creatinine
Nursing: Physical Assessment/MonitoringSee individual agents.
Monitoring: Lab TestsOccult blood loss, periodic liver function test, CBC, BUN, serum creatinine
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Combination package:

Prevacid® NapraPAC® 500 [each administration card contains]:

Capsule, delayed release (Prevacid®): Lansoprazole 15 mg (7 capsules per card)

Tablet (Naprosyn®): Naproxen 500 mg (14 tablets per card)

Generic AvailableNo
ManufacturerTakeda Pharmaceuticals
Pricing: U.S. (www.drugstore.com)

Kit (Prevacid NapraPAC)

15-500 mg (84): $153.28

Mechanism of Action

Lansoprazole: Proton pump inhibitor which decreases acid secretion in gastric parietal cells

Naproxen: Reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/KineticsSee individual agents.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness or sedation; may rarely cause confusion, insomnia, depression, or hallucinations
Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine, carbamazepine, and mirtazapine. May decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels. Combined use with SSRIs may increase bleeding risk.
Index TermsNapraPAC®; Naproxen and Lansoprazole

Lansoprazole, Amoxicillin, and Clarithromycin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

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A PPI is often prescribed with the combination of aspirin and clopidogrel to prevent gastrointestinal bleeding. A number of PPIs are available and include esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. Several studies have reported greater clinical event rates (eg, myocardial infarction, death) or greater platelet reactivity associated with concurrent use of clopidogrel and a PPI (Ho, 2008; Pezella, 2008; Gilard, 2006). Similarly, a prospective, randomized, double-blind trial demonstrated a reduction in antiplatelet activity when omeprazole and clopidogrel are used concurrently (Gilard, 2008). Another controlled trial with the PPI lansoprazole also found evidence of a possible interaction resulting in less antiplatelet activity (Small, 2008). This interaction is thought to result from competitive inhibition of the CYP2C19-mediated activation of clopidogrel by omeprazole and other PPIs, which are all metabolized to at least some degree by CYP2C19. In contrast, one study with esomeprazole and pantoprazole did not find evidence of reduced antiplatelet activity when administered with clopidogrel (Siller-Matula, 2009), highlighting the need for additional studies to determine the degree to which individual PPIs may differ in their potential for interacting with clopidogrel.

The manufacturer of Plavix® has agreed to conduct further studies to better understand the effect of other drugs (including PPIs) and genetic factors on the effectiveness of clopidogrel. The FDA is recommending that healthcare providers continue to prescribe clopidogrel while reevaluating the need for prescription or over-the-counter (OTC) PPIs in patients taking clopidogrel. Patients should continue taking clopidogrel as directed. If taking a PPI with clopidogrel, patients should consult with their healthcare provider.

For more information, healthcare professionals may refer to the following FDA website: http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm

References:

Ho PM, Maddox TM, Wang L, et al, "Proton Pump Inhibitors May Attenuate the Benefits of Clopidogrel Among ACS Patients: Using Registry Data to Address Medication Effectiveness," United States Department of Veterans Affairs, 2008 QUERI National Meeting Abstract. Available at http://www.hsrd.research.va.gov/meetings/QUERI08/display_abstract.cfm?RecordID=118; accessed October 30, 2008).

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Medication Safety Issues

Sound-alike/look-alike issues:

Prevpac® may be confused with Prevacid®

Pronunciation(lan SOE pra zole, a moks i SIL in, & kla RITH roe mye sin)

U.S. Brand NamesPrevpac®

Canadian Brand NamesHp-PAC®; Prevpac®

Pharmacologic CategoryAntibiotic, Macrolide Combination; Antibiotic, Penicillin; Gastrointestinal Agent, Miscellaneous

Use: Labeled IndicationsEradication of *H. pylori* to reduce the risk of recurrent duodenal ulcer

Dosing: Adults*H. pylori* eradication: Oral: Lansoprazole 30 mg, amoxicillin 1 g, and clarithromycin 500 mg taken together twice daily for 10 or

14 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} <30 mL/minute: Use is not recommended.

Calculations

- Creatinine Clearance: Adults

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light and moisture.

ContraindicationsHypersensitivity to lansoprazole, amoxicillin, any penicillin, clarithromycin, any macrolide, or any component of the formulation; concurrent use with pimozide, cisapride, or ergot derivatives (eg, ergotamine, dihydroergotamine)

Allergy Considerations

- Macrolide Allergy
- Penicillin Allergy
- Proton Pump Inhibitor, Benzimidazole Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: Macrolides have been associated with rare QT_c prolongation and ventricular arrhythmias, including torsade de pointes; use with caution in patients at risk of prolonged cardiac repolarization.
- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.
- Atrophic gastritis: Long-term omeprazole therapy has caused atrophic gastritis (by biopsy); this may also occur with lansoprazole.
- Superinfection: Prolonged use of amoxicillin or clarithromycin may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Gastric malignancy: Relief of symptoms does not preclude the presence of a gastric malignancy.
- Gastrointestinal infection (eg, *Salmonella, Campylobacter*): Use of proton pump inhibitors may increase risk of these infections.
- Infectious mononucleosis: A high percentage of patients with infectious mononucleosis have developed rash during amoxicillin therapy; ampicillin-class antibiotics not recommended in these patients.
- Hepatic impairment: Use lansoprazole with caution in patients with severe hepatic impairment; dosage reductions recommended.
- Renal impairment: Use amoxicillin with caution in patients with renal impairment; dosage adjustment recommended. Use clarithromycin with caution in severe renal impairment; dosage adjustment required.

Pregnancy Risk FactorC (clarithromycin)

Pregnancy ConsiderationsSee individual agents.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsSee individual agents.

Adverse Reactions**Note:** Frequencies noted refer to experience with combination therapy. Also see individual agents.

3% to 10%:

Central nervous system: Headache (6%)

Gastrointestinal: Diarrhea (7%), taste perversion (5%)

<3%: Abdominal pain, candidiasis (oral and vaginal), confusion, dark stools, dermatologic reactions, dizziness, dry mouth, glossitis, myalgia, nausea, rectal itching, stomatitis, thirst, tongue discoloration, vaginitis, vomiting

Metabolism/Transport Effects

Lansoprazole: **Substrate** of CYP2C9 (minor), 2C19 (major), 3A4 (major); **Inhibits** CYP2C9 (weak), 2C19 (moderate), 2D6 (weak), 3A4 (weak); **Induces** CYP1A2 (weak)

Clarithromycin: **Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (weak), 3A4 (strong)

Drug Interactions

Alfentanil: Macrolide Antibiotics may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Allopurinol: May enhance the potential for allergic or hypersensitivity reactions to Amoxicillin. *Risk C: Monitor therapy*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Macrolide Antibiotics may decrease the metabolism of Antifungal Agents (Azole Derivatives, Systemic). Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Macrolide Antibiotics. *Risk D: Consider therapy modification*

Atazanavir: Proton Pump Inhibitors may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Macrolide Antibiotics may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

BusPIRone: Macrolide Antibiotics may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Macrolide Antibiotics may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: Macrolide Antibiotics may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Cardiac Glycosides: Macrolide Antibiotics may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cilostazol: Macrolide Antibiotics may decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Cisapride: Macrolide Antibiotics may decrease the metabolism of Cisapride. *Risk X: Avoid combination*

Clopidogrel: Macrolide Antibiotics may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Clopidogrel: Proton Pump Inhibitors may diminish the therapeutic effect of Clopidogrel. This appears to be due to reduced formation of the active clopidogrel metabolite. *Risk C: Monitor therapy*

Clozapine: Macrolide Antibiotics may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

Colchicine: Macrolide Antibiotics may decrease the metabolism of Colchicine. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Macrolide Antibiotics may decrease the metabolism of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

CycloSPORINE: Macrolide Antibiotics may decrease the metabolism of CycloSPORINE. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: Proton Pump Inhibitors may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Proton Pump Inhibitors may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disopyramide: Macrolide Antibiotics may enhance the QTc-prolonging effect of Disopyramide. Macrolide Antibiotics may decrease the metabolism of Disopyramide. *Risk X: Avoid combination*

Eletriptan: Macrolide Antibiotics may decrease the metabolism of Eletriptan. *Risk D: Consider therapy modification*

Eplerenone: Macrolide Antibiotics may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Macrolide Antibiotics may enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Cabergoline. *Risk D: Consider therapy modification*

Erlotinib: Proton Pump Inhibitors may decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Etravirine: May decrease the serum concentration of Macrolide Antibiotics. Clarithromycin AUC is reduced and levels of the active metabolite (14-hydroxy-clarithromycin) are modestly increased. Management: For the treatment of *Mycobacterium avium* complex, consider changing to alternative agent, such as azithromycin. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fluconazole: May increase the serum concentration of Proton Pump Inhibitors. *Risk C: Monitor therapy*

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Macrolide Antibiotics may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Pravastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Imatinib: Lansoprazole may enhance the dermatologic adverse effect of Imatinib. *Risk C: Monitor therapy*

Indinavir: Proton Pump Inhibitors may decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Iron Salts: Proton Pump Inhibitors may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk C: Monitor therapy*

Itraconazole: Proton Pump Inhibitors may decrease the serum concentration of Itraconazole. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Ketoconazole: Proton Pump Inhibitors may decrease the serum concentration of Ketoconazole. Ketoconazole may increase the serum concentration of Proton Pump Inhibitors. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mesalamine: Proton Pump Inhibitors may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids; proton pump inhibitors would be expected to interact in a similar manner. *Risk X: Avoid combination*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Methotrexate: Proton Pump Inhibitors may decrease the excretion of Methotrexate. Antirheumatic doses of methotrexate probably hold minimal risk. *Risk C: Monitor therapy*

Mycophenolate: Proton Pump Inhibitors may decrease the serum concentration of Mycophenolate. Specifically, concentrations of the active mycophenolic acid may be reduced. *Risk C: Monitor therapy*

Nelfinavir: Proton Pump Inhibitors may decrease serum concentrations of the active metabolite(s) of Nelfinavir. Proton Pump Inhibitors may decrease the serum concentration of Nelfinavir. *Risk X: Avoid combination*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: Macrolide Antibiotics may decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Macrolide Antibiotics may decrease the metabolism of Pimozide. QTc prolongation is a risk. *Risk X: Avoid combination*

Protease Inhibitors: May diminish the therapeutic effect of Clarithromycin. Specifically, certain protease inhibitors may decrease formation of the active 14-hydroxy-clarithromycin metabolite, which may negatively impact clarithromycin effectiveness vs. H. influenzae and other non-MAC infections. Protease Inhibitors may increase the serum concentration of Clarithromycin. Clarithromycin dose adjustment in renally impaired patients may be needed. Clarithromycin may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Macrolide Antibiotics may decrease the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Macrolide Antibiotics may increase the serum concentration of Repaglinide. *Risk C: Monitor therapy*

Rifamycin Derivatives: Macrolide Antibiotics may decrease the metabolism of Rifamycin Derivatives. **Exceptions:** Rifapentine. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Saquinavir: Proton Pump Inhibitors may increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Macrolide Antibiotics may decrease the metabolism of Selective Serotonin Reuptake Inhibitors. **Exceptions:** Fluvoxamine; PARoxetine. *Risk C: Monitor therapy*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Macrolide Antibiotics may decrease the metabolism of Sirolimus. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Tacrolimus: Macrolide Antibiotics may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Temsirolimus: Macrolide Antibiotics may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Theophylline Derivatives: Macrolide Antibiotics may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Tipranavir: May decrease the serum concentration of Proton Pump Inhibitors. These data are derived from studies with Ritonavir-boosted Tipranavir. *Risk C: Monitor therapy*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Macrolide Antibiotics may decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Voriconazole: Proton Pump Inhibitors may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Zopiclone: Macrolide Antibiotics may increase the serum concentration of Zopiclone. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Combination package [each administration card contains]:

Prevpac®:

Capsule: Amoxicillin 500 mg (4 capsules/day)

Capsule, delayed release (Prevacid®): Lansoprazole 30 mg (2 capsules/day)

Tablet (Biaxin®): Clarithromycin 500 mg (2 tablets/day)

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Misc (Prevpac)

(14): $347.41

Pharmacodynamics/KineticsSee individual agents.
Related Information

- ***Helicobacter pylori*** Treatment
- Amoxicillin
- Clarithromycin
- Lansoprazole

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste perversion.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness; rarely large doses may produce confusion, hallucinations, and depression; penicillins have been reported to cause apprehension, illusions, agitation, insomnia, depersonalization, and encephalopathy; macrolides have been reported to cause nightmares, confusion, anxiety, and mood lability
Mental Health: Effects on Psychiatric TreatmentDisulfiram may increase amoxicillin levels; macrolides are contraindicated with pimozide and increase carbamazepine and triazolam levels; monitor for signs of toxicity
Index TermsAmoxicillin, Lansoprazole, and Clarithromycin; Clarithromycin, Lansoprazole, and Amoxicillin
International Brand NamesHp-PAC (CA); Prevpac (CA)

Lansoprazole

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Clopidogrel (Plavix®) and Proton Pump Inhibitors (PPIs): Ongoing Safety Review - January 2009

The U.S. Food and Drug Administration (FDA) is communicating important information regarding an ongoing safety review of clopidogrel and its effectiveness when used with proton pump inhibitors (PPIs).

Clopidogrel is a prodrug requiring hepatic conversion via CYP3A4 and/or CYP2C19 to its active metabolite. Impaired clopidogrel conversion to its active metabolite may be due to either CYP450 polymorphisms or drug-drug interactions resulting in suboptimal antiplatelet activity.

A PPI is often prescribed with the combination of aspirin and clopidogrel to prevent gastrointestinal bleeding. A number of PPIs are available and include esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. Several studies have reported greater clinical event rates (eg, myocardial infarction, death) or greater platelet reactivity associated with concurrent use of clopidogrel and a PPI (Ho, 2008; Pezella, 2008; Gilard, 2006). Similarly, a prospective, randomized, double-blind trial demonstrated a reduction in antiplatelet activity when omeprazole and clopidogrel are used concurrently (Gilard, 2008). Another controlled trial with the PPI lansoprazole also found evidence of a possible interaction resulting in less antiplatelet activity (Small, 2008). This interaction is thought to result from competitive inhibition of the CYP2C19-mediated activation of clopidogrel by omeprazole and other PPIs, which are all metabolized to at least some degree by CYP2C19. In contrast, one study with esomeprazole and pantoprazole did not find evidence of reduced antiplatelet activity when administered with clopidogrel (Siller-Matula, 2009), highlighting the need for additional studies to determine the degree to which individual PPIs may differ in their potential for interacting with clopidogrel.

The manufacturer of Plavix® has agreed to conduct further studies to better understand the effect of other drugs (including PPIs) and genetic factors on the effectiveness of clopidogrel. The FDA is recommending that healthcare providers continue to prescribe clopidogrel while reevaluating the need for prescription or over-the-counter (OTC) PPIs in patients taking clopidogrel. Patients should continue taking clopidogrel as directed. If taking a PPI with clopidogrel, patients should consult with their healthcare provider.

For more information, healthcare professionals may refer to the following FDA website: http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm

References:

Ho PM, Maddox TM, Wang L, et al, “Proton Pump Inhibitors May Attenuate the Benefits of Clopidogrel Among ACS Patients: Using Registry Data to Address Medication Effectiveness,” United States Department of Veterans Affairs, 2008 QUERI National Meeting Abstract. Available at http://www.hsrd.research.va.gov/meetings/QUERI08/display_abstract.cfm?RecordID=118; accessed October 30, 2008).

Pezalla E, Day D, and Pulliadath I, “Initial Assessment of Clinical Impact of a Drug Interaction Between Clopidogrel and Proton Pump Inhibitors,” *J Am Coll Cardiol*, 2008, 52(12): 1038-9.

Gilard M, Arnaud B, Le Gal G, et al, “Influence of Omeprazol on the Antiplatelet Action of Clopidogrel Associated to Aspirin,” *J Thromb Haemost*, 2006, 4(11):2508-9.

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Siller-Matula JM, Spiel AO, Lang IM, et al, “Effects of Pantoprazole and Esomeprazole on Platelet Inhibition by Clopidogrel,” *Am Heart J*, 2009, 157(1): 148.e1-5.

Small DS, Farid NA, Payne CD, et al, “Effects of the Proton Pump Inhibitor Lansoprazole on the Pharmacokinetics and Pharmacodynamics of Prasugrel and Clopidogrel,” *J Clin Pharmacol*, 2008, 48(4):475-84.

Medication Safety Issues

Sound-alike/look-alike issues:

Prevacid® may be confused with Pravachol®, Prevpac®, Prilosec®, Prinivil®

Pronunciation(lan SOE pra zole)

U.S. Brand NamesPrevacid®; Prevacid® SoluTab™

Canadian Brand NamesPrevacid®

Pharmacologic CategoryProton Pump Inhibitor; Substituted Benzimidazole

Use: Labeled IndicationsShort-term treatment of active duodenal ulcers; maintenance treatment of healed duodenal ulcers; as part of a multidrug regimen for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence; short-term treatment of active benign gastric ulcer;

treatment of NSAID-associated gastric ulcer; to reduce the risk of NSAID-associated gastric ulcer in patients with a history of gastric ulcer who require an NSAID; short-term treatment of symptomatic GERD; short-term treatment for all grades of erosive esophagitis; to maintain healing of erosive esophagitis; long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome

Dosing: Adults

Symptomatic GERD: Oral: Short-term treatment: 15 mg once daily for up to 8 weeks

Erosive esophagitis: Oral: Short-term treatment: 30 mg once daily for up to 8 weeks; continued treatment for an additional 8 weeks may be considered for recurrence or for patients who do not heal after the first 8 weeks of therapy; maintenance therapy: 15 mg once daily

Hypersecretory conditions: Oral: Initial: 60 mg once daily; adjust dose based upon patient response and to reduce acid secretion to <10 mEq/hour (5 mEq/hour in patients with prior gastric surgery); doses of 90 mg twice daily have been used; administer doses >120 mg/day in divided doses

Duodenal ulcer: Oral: Short-term treatment: 15 mg once daily for 4 weeks; maintenance therapy: 15 mg once daily

Peptic ulcer disease: Eradication of *Helicobacter pylori*: Currently accepted recommendations (may differ from product labeling): Oral: Dose varies with regimen: 30 mg once daily or 60 mg/day in 2 divided doses; requires combination therapy with antibiotics

Gastric ulcer: Oral: Short-term treatment: 30 mg once daily for up to 8 weeks

NSAID-associated gastric ulcer (healing): Oral: 30 mg once daily for 8 weeks; controlled studies did not extend past 8 weeks

NSAID-associated gastric ulcer (to reduce risk): Oral: 15 mg once daily for up to 12 weeks; controlled studies did not extend past 12 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

GERD, erosive esophagitis: Oral: Children 1-11 years:

≤30 kg: 15 mg once daily

>30 kg: 30 mg once daily

Note: Doses were increased in some pediatric patients if still symptomatic after 2 or more weeks of treatment (maximum dose: 30 mg twice daily)

Erosive esophagitis: Children 12-17 years: Oral: 30 mg once daily for up to 8 weeks

Nonerosive GERD: Children 12-17 years: Oral: 15 mg once daily for up to 8 weeks

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentMay require a dose reduction.

Administration: Oral

Administer before food; best if taken before breakfast. The intact granules should not be chewed or crushed; however, several options are available for those patients unable to swallow capsules:

Capsules may be opened and the intact granules sprinkled on 1 tablespoon of applesauce, Ensure® pudding, cottage cheese, yogurt, or strained pears. The granules should then be swallowed immediately.

Capsules may be opened and emptied into ~60 mL orange juice, apple juice, or tomato juice; mix and swallow immediately. Rinse the glass with additional juice and swallow to assure complete delivery of the dose.

Orally-disintegrating tablets: Should not be swallowed whole or chewed. Place tablet on tongue; allow to dissolve (with or without water) until particles can be swallowed. Orally-disintegrating tablets may also be administered via an oral syringe: Place the 15 mg tablet in an oral syringe and draw up ~4 mL water, or place the 30 mg tablet in an oral syringe and draw up ~10 mL water. After tablet has dispersed, administer within 15 minutes. Refill the syringe with water (2 mL for the 15 mg tablet; 4 mL for the 30 mg tablet), shake gently, then administer any remaining contents.

Administration: OtherNasogastric tube administration:

Capsule: Capsule can be opened, the granules mixed (not crushed) with 40 mL of apple juice and then injected through the NG tube into the stomach, then flush tube with additional apple juice. Do not mix with other liquids.

Orally-disintegrating tablet: Nasogastric tube ≥8 French: Place a 15 mg tablet in a syringe and draw up ~4 mL water, or place the 30 mg tablet in a syringe and draw up ~10 mL water. After tablet has dispersed, administer within 15 minutes. Refill the syringe with ~5 mL water, shake gently, and then flush the nasogastric tube.

Dietary ConsiderationsShould be taken before eating; best if taken before breakfast. Prevacid® SoluTab™ contains phenylalanine 2.5 mg per 15 mg tablet; phenylalanine 5.1 mg per 30 mg tablet.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Extemporaneously PreparedA 3 mg/mL lansoprazole oral solution (Simplified Lansoprazole Solution) can be prepared with ten lansoprazole 30 mg capsules and 100 mL 8.4% sodium bicarbonate. Empty capsules into beaker. Add sodium bicarbonate solution. Gently stir (about 15 minutes) until dissolved. Transfer to amber-colored syringe or bottle. Stable for 8 hours at room temperature or for 14 days under refrigeration.

DiGiancinto JL, Olsen KM, Bergman KL, et al, "Stability of Suspension Formulations of Lansoprazole and Omeprazole Stored in Amber-Colored Plastic Oral Syringes," *Ann Pharmacother*, 2000, 34:600-5

Sharma V, "Comparison of 24-hour Intragastric pH Using Four Liquid Formulations of Lansoprazole and Omeprazole," *Am J Health Syst*

Pharm, 1999, 56(Suppl 4):S18-21.

Sharma VK, Vasudeva R, and Howden CW, “Simplified Lansoprazole Suspension - Liquid Formulations of Lansoprazole - Effectively Suppresses Intragastric Acidity When Administered Through a Gastrostomy,” *Am J Gastroenterol*, 1999, 94(7):1813-7.

Contraindications Hypersensitivity to lansoprazole, substituted benzimidazoles (ie, esomeprazole, omeprazole, pantoprazole, rabeprazole), or any component of the formulation

Allergy Considerations

- Proton Pump Inhibitor, Benzimidazole Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Atrophic gastritis: Long-term omeprazole therapy has caused atrophic gastritis (by biopsy); this may also occur with lansoprazole.
- Carcinoma: No reports of enterochromaffin-like (ECL) cell carcinoids, dysplasia, or neoplasia has occurred.

Disease-related concerns:

- Gastric malignancy: Relief of symptoms does not preclude the presence of a gastric malignancy.
- Gastrointestinal infection (eg, *Salmonella, Campylobacter*): Use of proton pump inhibitors may increase risk of these infections.
- Hepatic impairment: Patients with severe liver dysfunction may require dosage reductions.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <1 year of age.

Dosage form specific issues:

- Phenylalanine: Prevacid® SoluTab™ contains phenylalanine.

Geriatric Considerations The clearance of lansoprazole is decreased in the elderly; however, the half-life is only increased by 50% to 100%, resulting in a short half-life and no accumulation in the elderly. No dosage adjustment is required with normal hepatic function. The rate of healing and side effects are similar to younger adults.

Pregnancy Risk Factor B

Pregnancy Considerations Animal studies have not shown teratogenic effects to the fetus. However, there are no adequate and well-controlled studies in pregnant women; use during pregnancy only if clearly needed.

Lactation Excretion in breast milk unknown/not recommended

Adverse Reactions

1% to 10%:

Central nervous system: Headache (children 1-11 years 3%, 12-17 years 7%)

Gastrointestinal: Abdominal pain (children 12-17 years 5%; adults 2%), constipation (children 1-11 years 5%; adults 1%), diarrhea (60 mg/day; adults 7%), nausea (children 12-17 years 3%; adults 1%)

<1%: Abdomen enlarged, abnormal dreams, abnormal menses, abnormal stools, abnormal vision, acne, agitation, albuminuria, allergic reaction, alkaline phosphatase increased, ALT increased, alopecia, amnesia, anemia, angina, anorexia, anxiety, apathy, appetite increased, arrhythmia, AST increased, arthralgia, arthritis, asthma, back pain, bezoar, bilirubinemia, blurred vision, bradycardia, breast enlargement, breast pain, breast tenderness, bronchitis, bone disorder, candidiasis, carcinoma, cardiospasm, cerebrovascular accident, cerebral infarction, chest pain, chills, cholelithiasis, cholesterol increased, cholesterol decreased, colitis, confusion, conjunctivitis, contact dermatitis, convulsion, cough increased, creatinine increased, deafness, dehydration, depersonalization, depression, diabetes mellitus, diplopia, dizziness, dry eyes, dry mouth, dry skin, dyspepsia, dysphagia, dyspnea, dysmenorrhea, dysuria, ear disorder, edema, electrolytes imbalance, emotional lability, enteritis, eosinophilia, epistaxis, eructation, esophageal ulcer, esophagitis, eye pain, fecal discoloration, fever, fixed eruption, flatulence, flu-like syndrome, fundic gland polyps, gastric nodules, gastrin levels increased, gastritis, gastroenteritis, gastrointestinal anomaly, gastrointestinal hemorrhage, GGTP increased, GGTP decreased, glucocorticoid levels increased, globulins increased, glossitis, glycosuria, goiter, gout, gum hemorrhage, gynecomastia, hair disorder, halitosis, hallucinations, hematemesis, hematuria, hemiplegia, hemolysis, hemoptysis, hiccup, hostility aggravated, hyper-/hypoglycemia, hyperkinesia, hyperlipemia, hypertonia, hypoesthesia, hyper-/hypotension, hypothyroidism, impotence, infection, insomnia, joint disorder, kidney calculus, kidney pain, laryngeal neoplasia, LDH increased, leg cramps, leukorrhea, libido decreased, libido increased, liver function test abnormal, lymphadenopathy, maculopapular rash, malaise, melena, menorrhagia, menstrual disorder, migraine, moniliasis (oral), mouth ulceration, musculoskeletal pain, myalgia, myasthenia, MI, nail disorder, neck pain, neck rigidity, nervousness, neurosis, otitis media, pain, palpitation, paresthesia, parosmia, pelvic pain, penis disorder, peripheral edema, pharyngitis, photophobia, platelet abnormalities, pleural disorder, pneumonia, polyuria, pruritus, rash, RBC abnormal, rectal disorder, rectal hemorrhage, respiratory disorder, retinal degeneration, rhinitis, salivation increased, shock, sinusitis, skin carcinoma, sleep disorder, somnolence, stomatitis, stridor, sweating, syncope, synovitis, tachycardia, taste loss, taste perversion, tenesmus, testis disorder, thirst, thinking abnormality, thrombocytopenia, tinnitus, tremor, tongue disorder, ulcerative colitis, ulcerative stomatitis, upper respiratory inflammation, upper respiratory infection, urethral pain, urinary frequency, urination impaired, urticaria, vaginitis, vasodilation, vertigo, visual field defect, vomiting, weakness, WBC abnormal, weight gain/loss

Postmarketing and/or case reports: Agranulocytosis, anaphylactoid reaction, aplastic anemia, erythema multiforme, hemolytic anemia, hepatotoxicity, interstitial nephritis, leukopenia, myositis, neutropenia, pancreatitis, pancytopenia, speech disorder, Stevens-Johnson syndrome, thrombotic thrombocytopenic purpura, toxic epidermal necrolysis, urinary retention

Metabolism/Transport Effects **Substrate** of CYP2C9 (minor), 2C19 (major), 3A4 (major); **Inhibits** CYP2C9 (weak), 2C19 (moderate), 2D6 (weak), 3A4 (weak); **Induces** CYP1A2 (weak)

Drug Interactions

Atazanavir: Proton Pump Inhibitors may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Clopidogrel: Proton Pump Inhibitors may diminish the therapeutic effect of Clopidogrel. This appears to be due to reduced formation of the active clopidogrel metabolite. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: Proton Pump Inhibitors may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Proton Pump Inhibitors may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Erlotinib: Proton Pump Inhibitors may decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Fluconazole: May increase the serum concentration of Proton Pump Inhibitors. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Imatinib: Lansoprazole may enhance the dermatologic adverse effect of Imatinib. *Risk C: Monitor therapy*

Indinavir: Proton Pump Inhibitors may decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Iron Salts: Proton Pump Inhibitors may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk C: Monitor therapy*

Itraconazole: Proton Pump Inhibitors may decrease the serum concentration of Itraconazole. *Risk D: Consider therapy modification*

Ketoconazole: Proton Pump Inhibitors may decrease the serum concentration of Ketoconazole. Ketoconazole may increase the serum concentration of Proton Pump Inhibitors. *Risk D: Consider therapy modification*

Mesalamine: Proton Pump Inhibitors may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids; proton pump inhibitors would be expected to interact in a similar manner. *Risk X: Avoid combination*

Methotrexate: Proton Pump Inhibitors may decrease the excretion of Methotrexate. Antirheumatic doses of methotrexate probably hold minimal risk. *Risk C: Monitor therapy*

Mycophenolate: Proton Pump Inhibitors may decrease the serum concentration of Mycophenolate. Specifically, concentrations of the active mycophenolic acid may be reduced. *Risk C: Monitor therapy*

Nelfinavir: Proton Pump Inhibitors may decrease serum concentrations of the active metabolite(s) of Nelfinavir. Proton Pump Inhibitors may decrease the serum concentration of Nelfinavir. *Risk X: Avoid combination*

Saquinavir: Proton Pump Inhibitors may increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

Tipranavir: May decrease the serum concentration of Proton Pump Inhibitors. These data are derived from studies with Ritonavir-boosted Tipranavir. *Risk C: Monitor therapy*

Voriconazole: Proton Pump Inhibitors may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause gastric mucosal irritation).

Food: Lansoprazole serum concentrations may be decreased if taken with food.

Herb/Nutraceutical: Avoid St John's wort (may decrease the levels/effect of lansoprazole).

Monitoring ParametersPatients with Zollinger-Ellison syndrome should be monitored for gastric acid output, which should be maintained at ≤10 mEq/hour during the last hour before the next lansoprazole dose; lab monitoring should include CBC, liver function, renal function, and serum gastrin levels

Nursing: Physical Assessment/MonitoringAssess periodic laboratory results and assess effectiveness of medications that require an acid medium for absorption (eg, ketoconazole, itraconazole). Monitor effectiveness of ulcer symptom relief.

Monitoring: Lab TestsCBC, liver function, renal function, and serum gastrin levels. Patients with Zollinger-Ellison syndrome should be monitored for gastric acid output, which should be maintained at ≤10 mEq/hour during the last hour before the next lansoprazole dose.

Patient EducationTake as directed, before eating. Do not crush or chew granules. Patients who may have difficulty swallowing capsules may open the delayed-release capsules and sprinkle the contents on applesauce, pudding, cottage cheese, or yogurt. Avoid alcohol. Report unresolved diarrhea. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, delayed release:

Prevacid®: 15 mg, 30 mg

Tablet, delayed release, orally disintegrating:

Prevacid® SoluTab™: 15 mg [contains phenylalanine 2.5 mg; strawberry flavor]; 30 mg [contains phenylalanine 5.1 mg; strawberry flavor]

Generic AvailableNo
ManufacturerTakeda Pharm Inc
Pricing: U.S. (www.drugstore.com)

Capsule, delayed release (Prevacid)

15 mg (30): $168.69

30 mg (30): $167.98

Tablet, orally-disintegrating (Prevacid SoluTab)

15 mg (100): $557.45

30 mg (30): $159.98

Mechanism of ActionDecreases acid secretion in gastric parietal cells through inhibition of (H+, K+)-ATPase enzyme system, blocking the final step in gastric acid production.
Pharmacodynamics/Kinetics

Duration: >1 day

Absorption: Rapid

Distribution: V_d: 14-18 L

Protein binding: 97%

Metabolism: Hepatic via CYP2C19 and 3A4, and in parietal cells to two active metabolites that are not present in systemic circulation

Bioavailability: 80%; decreased 50% to 70% if given 30 minutes after food

Half-life elimination: 1-2 hours; Elderly: 2-3 hours; Hepatic impairment: ≤7 hours

Time to peak, plasma: 1.7 hours

Excretion: Feces (67%); urine (33%)

Related Information

- ***Helicobacter pylori*** Treatment

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness
Mental Health: Effects on Psychiatric TreatmentNone reported
Anesthesia and Critical Care Concerns/Other Considerations

Evidence-Based Information:

Stress ulcer prophylaxis: The 2008 Surviving Sepsis Campaign guidelines recommend that stress ulcer prophylaxis using an H_2 blocker (Grade 1A) or proton pump inhibitor (Grade 1B) be given to patients with severe sepsis to prevent upper GI bleed. Benefit of prevention of upper GI bleed must be weighed against potential effect of increased stomach pH on development of ventilator-associated pneumonia.

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Wolfe MM and Sachs G, “Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome,” *Gastroenterology*, 2000,118(2 Suppl 1):9-31.

International Brand NamesAgopton (AT, CH, DE); Compraz (ID); Dakar (LU); Daxar (BE); Digest (ID); Estomil (ES); Imidex (MX); Inhipraz (ID); Lancid (KP); Lancopen (CO); Lanodizol (MX); Lanpezol (KP); Lanpra (KP); Lanpraz (CO); Lanprol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Lanproton (CO); Lans-OD (MY); Lansal (FI); Lanso (IL); Lansone (HN, HU, PL); Lansopep (CO); Lansozole (KP); Lanster (KP); Lanston (KP); Lanton (IL); Lanximed (CO); Lanzo (DK, NO, SE); Lanzol-30 (IN); Lanzopral (AR, PE, PY, UY, VE); Lanzor (DE, FR); Lanzul (BG, CZ, EE, HR, PL); Lapraz (ID); Laproton (ID); Lasgan (ID); Lasoprol (SG); Laz (ID); Monolitum (CR, DO, ES, GT, HN, NI, PA, SV); Ogast (FR); Ogastro (BB, BM, BR, BS, BZ, CN, CO, CR, EC, FR, GT, GY, HN, JM, MX, NI, NL, PA, PE, SR, SV, TT); Olan (MX); Palatrin (MX); Prevacid (MY, PH, PK, SG); Prevacid FDT (TH); Prezal (NL); Prilosan (MX); Prolanz (ID); Prosogan (ID); Pylison (PH); Safemar (MX); Solox (NZ); Sopra (KP); Sopralan-30 (ID); Sopranix (SE); Sorifran (MX); Takepron (BF, BJ, CI, CL, ET, GH, GM, GN, HK, JP, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TW, TZ, UG, ZA, ZM, ZW); Takepron OD (HK); Taquidine (TW); Uldapril (MX); Ulpax (MX); Zoton (AU, GB, IE, IL, IT); Zoton Fastab (GB, IE)

Lanthanum

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(LAN tha num)
U.S. Brand NamesFosrenol®
Canadian Brand NamesFosrenol®
Pharmacologic CategoryPhosphate Binder
Use: Labeled IndicationsReduction of serum phosphate in patients with stage 5 chronic kidney disease (end-stage renal disease [ESRD]; kidney failure: GFR <15 mL/minute/1.73 m^2 or dialysis)
Dosing: AdultsInitial: Oral: 1500 mg/day divided and taken with meals; typical increases of 750 mg/day every 2-3 weeks are suggested as needed to bring the serum phosphate level <6 mg/dL. Usual dosage range: 1500-3000 mg; doses of up to 3750 mg have been used.
Dosing: ElderlyRefer to adult dosing.
Administration: OralAdminister with or immediately after meals; tablet should be chewed completely prior to swallowing; do not swallow whole. Tablet may be crushed to aid in chewing.
Dietary ConsiderationsTake with or immediately after meals.
StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture.
ContraindicationsThere are no contraindications listed within the manufacturer's labeling.
Warnings/Precautions

Disease-related concerns:

- Gastrointestinal disease: Use with caution in patients with active peptic ulcer, ulcerative colitis, Crohn's disease, or bowel obstruction.

Special populations:

- Pediatrics: Use in children is not recommended; lanthanum deposits into developing bone, including growth plates; the consequences on developing bone are not known.

Other warnings/precautions:

- Abdominal x-rays: May have a radiopaque appearance in patients taking lanthanum.

Geriatric ConsiderationsIn initial studies, no overall clinical differences were noted in those >65 years old compared to younger adults.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were observed in some, but not all, animal studies. The effect on absorption of vitamins and nutrients has not been studied. Lanthanum is not recommended for use during pregnancy.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsReported in short-term (4-6 weeks) trials at frequency > placebo:

>10%:

Gastrointestinal: Nausea (11%), vomiting (9%), abdominal pain (5%)

Miscellaneous: Dialysis graft occlusion (8%)

1% to 10%: Endocrine & metabolic: Hypercalcemia was reported in longer-term trials at frequencies ≤4% (less frequently than with alternate therapy)

Note: Additional adverse effects noted in longer-term trials at rates higher than alternate therapy included constipation, diarrhea, and headache.

Drug InteractionsThere are no known significant interactions.
Test InteractionsAbdominal x-rays may have a radiopaque appearance.
Monitoring ParametersCalcium and phosphate levels
Reference RangeIn patients with stage 5 chronic kidney disease (ESRD) and those on hemodialysis or peritoneal dialysis, the serum phosphorus levels should be maintained between 3.5-5.5 mg/dL (1.13-1.78 mmol/L).
Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and potential interactions (See Drug Interactions). Assess blood pressure periodically. Can cause hypotension. Monitor laboratory tests, adverse reactions, and therapeutic response. **Pregnancy risk factor C:** Benefits of use should outweigh possible risks. Breast-feeding is not recommended
Monitoring: Lab TestsCalcium and phosphate levels
Patient EducationInform prescriber of all prescription medications, OTC medications, or herbal products you are taking. Chew tablets prior to swallowing. Maintain adequate hydration (2-3 L/day unless instructed to restrict intake by prescriber). You may experience dizziness or lightheadedness, (use caution when climbing stairs or changing position), headache, nausea, vomiting, diarrhea, abdominal pain, and constipation (increasing exercise, fluids, fruit/fiber may help). Report persistent dizziness, headache, nausea, vomiting, and diarrhea. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, chewable:

Fosrenol®: 500 mg, 750 mg, 1000 mg

Generic AvailableNo
ManufacturerShire
Pricing: U.S. (www.drugstore.com)

Chewable (Fosrenol)

500 mg (45): $273.23

1000 mg (30): $186.27

Mechanism of ActionDisassociates in the upper gastrointestinal tract to lanthanum ions (La^{3+}) which bind to dietary phosphate resulting in insoluble lanthanum phosphate complexes and a net decrease in serum phosphate and calcium levels.
Pharmacodynamics/Kinetics

Absorption: <0.002%

Protein binding: >99%

Metabolism: Not metabolized

Half-life elimination: Plasma: 53 hours; Bone: 2-3.6 years

Excretion: Feces primarily; urine <2%

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concurrent use with SSRIs, lithium, or valproic acid may produce additive GI effects; may bind with gabapentin; separate administration by at least 2 hours
Index TermsLanthanum Carbonate
References

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"K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Kidney Disease Outcome Quality Initiative," *Am J Kidney Dis*, 2002, 39(2 Suppl 2):1-266. [PubMed 11774095]

International Brand NamesFosrenol (AU, BE, CH, CZ, DE, DK, EE, FI, FR, GB, HK, NO, SE, TW); Foznol (IE)

Lapatinib

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Lapatinib may be confused with dasatinib, erlotinib, imatinib

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(la PA ti nib)

U.S. Brand NamesTykerb®

Pharmacologic CategoryAntineoplastic Agent, Tyrosine Kinase Inhibitor; Epidermal Growth Factor Receptor (EGFR) Inhibitor

Use: Labeled IndicationsTreatment (in combination with capecitabine) of HER2/neu overexpressing advanced or metastatic breast cancer, in patients who have received prior therapy (with an anthracycline, a taxane, and trastuzumab)

Use: Unlabeled/InvestigationalTreatment of head and neck cancers

Dosing: AdultsDetails concerning dosing in combination regimens should also be consulted. **Note:** Dose reductions are likely to be needed when lapatinib is administered concomitantly with a strong CYP3A4 inhibitor (an alternate medication for CYP3A4 enzyme inhibitors should be investigated first).

Breast cancer: 1250 mg once daily (in combination with capecitabine)

Dosage adjustment for concomitant CYP3A4 inhibitors/inducers:

CYP3A4 inhibitors: Dose reductions are likely to be needed when lapatinib is administered concomitantly with a strong CYP3A4 inhibitor (an alternate medication for CYP3A4 enzyme inhibitors should be investigated first); in the event that lapatinib must be administered concomitantly with a potent enzyme inhibitor, consider reducing lapatinib to 500 mg once daily with careful monitoring. (When a strong CYP3A4 inhibitor is discontinued; allow ~1 week to elapse prior to adjusting the lapatinib dose upward.)

CYP3A4 inducers: Concomitant administration with CYP3A4 inducers may require increased lapatinib doses (alternatives to the enzyme-inducing agent should be utilized first); consider titrating gradually up to 4500 mg/day, with careful monitoring. (If the strong CYP3A4 enzyme inducer is discontinued, reduce the lapatinib dose to the indicated dose.)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot studied in renal dysfunction, however, due to the minimal renal elimination (<2%), dosage adjustments for renal dysfunction may not be necessary.

Dosing: Hepatic ImpairmentSevere hepatic impairment (Child-Pugh Class C): Consider a dose reduction to 750 mg once daily.

Dosing: Adjustment for Toxicity

Cardiac toxicity: Discontinue treatment for decreased LVEF ≥ grade 2 or LVEF < LLN; may be restarted after 2 weeks at 1000 mg once daily if LVEF recovers to normal and patient is asymptomatic

Other toxicities: Withhold for any toxicity (other than cardiac) ≥ grade 2 until toxicity resolves to ≤ grade 1; reduce dosage to 1000 mg once daily for persistent toxicity

Dosing: Combination Regimens

Breast cancer: Capecitabine + Lapatinib

Administration: OralAdminister once daily, on an empty stomach, 1 hour before or 1 hour after a meal. Take at the same time each day; dividing doses is not recommended.

Dietary ConsiderationsTake on an empty stomach, 1 hour before or 1 hour after a meal. (**Note:** For combination with capecitabine treatment, capecitabine should be taken with food, or within 30 minutes after a meal.)

StorageStore at room temperature of 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

RestrictionsLapatinib is available **only** at specialty pharmacies through a restricted-access program, Tykerb® CARES. Information is available at www.tykerbcares.com or 1-866-489-5372.

ContraindicationsThere are no contraindications listed within the manufacturer's labeling.

Warnings/Precautions

Boxed warnings:

- Hepatotoxicity: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Diarrhea: Diarrhea is common, may be severe; manage with antidiarrheal agents; severe diarrhea may require hydration, electrolytes, and/or interruption of therapy.

- Hepatotoxicity: **[U.S. Boxed Warning]: Hepatotoxicity (ALT or AST >3 times ULN and total bilirubin >1.5 times ULN) has been reported with lapatinib; may be severe and/or fatal.** Onset may occur within days to several months after treatment initiation. Monitor; discontinue with severe changes in liver function; do not retreat.

- Left ventricular dysfunction: Decreases in left ventricular ejection fraction (LVEF) have been reported; baseline and periodic LVEF evaluations are recommended. Interrupt therapy or decrease dose with decreased LVEF ≥ grade 2 or LVEF < LLN.

- Pulmonary toxicity: Interstitial lung disease (ILD) and pneumonitis have been reported (with lapatinib monotherapy and combination chemotherapy); discontinue therapy for grade 3 (or higher) pulmonary symptoms indicative of ILD or pneumonitis (eg, dyspnea, dry cough).

- QT_c prolongation: QT_c prolongation has been observed; use caution in patients with a history of QT_c prolongation or with medications known to prolong the QT interval; baseline and periodic 12-lead ECG should be considered; correct electrolyte (potassium, calcium, and magnesium) abnormalities prior to and during treatment.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of or predisposed (prior treatment with anthracyclines, chest wall irradiation) to left ventricular dysfunction.

- Hepatic impairment: Use with caution in patients with hepatic dysfunction; dose reductions should be considered in patients with severe (Child-Pugh class C) hepatic impairment.

Concurrent drug therapy issues:

- High potential for interactions: Avoid use with strong CYP3A4 inhibitors or inducers (see Drug Interactions); if concomitant therapy cannot be avoided, lapatinib dosage adjustments should be considered.

- QT_c-prolonging agents: Concurrent use with other drugs which may prolong QT_c interval may increase the risk of potentially-fatal arrhythmias.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo differences in safety or effectiveness were observed between elderly and younger patients.
Pregnancy Risk FactorD
Pregnancy ConsiderationsIncreased pup deaths were demonstrated in animal studies. There are no adequate and well-controlled studies in pregnant women. Lapatinib may cause fetal harm if administered during pregnancy. Women of childbearing potential should be advised to avoid pregnancy during treatment.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.
Adverse Reactions Percentages reported for combination chemotherapy.

>10%:

Central nervous system: Fatigue (10% to 18%)

Dermatologic: Palmar-plantar erythrodysesthesia (hand-and-foot syndrome) (53%; grade 3: 12%), rash (28%)

Gastrointestinal: Diarrhea (65%; grade 3: 13%; grade 4: 1%), nausea (44%), vomiting (26%), abdominal pain (15%), mucosal inflammation (15%), stomatitis (14%), dyspepsia (11%)

Hematologic: Anemia (56%; grade 3: <1%), neutropenia (22%; grade 3: 3%; grade 4: <1%), thrombocytopenia (18%; grade 3: <1%)

Hepatic: AST increased (49%; grade 3: 2%; grade 4: <1%), total bilirubin increased (45%; grade 3: 4%), ALT increased (37%; grade 3: 2%)

Neuromuscular & skeletal: Limb pain (12%), back pain (11%)

Respiratory: Dyspnea (12%)

1% to 10%:

Cardiovascular: LVEF decreased (grade 2: 2%; grade 3: <1%)

Central nervous system: Insomnia (10%)

Dermatologic: Dry skin (10%)

<1%, postmarketing, and/or case reports: Hepatotoxicity, interstitial lung disease, pneumonitis, Prinzmetal's angina, QT_c prolongation

Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Substrate** of CYP2C8 (minor), 3A4 (major), P-glycoprotein (P-gp, ABCB1); **Inhibits** CYP2C8, 3A4
Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Systemic exposure of lapatinib is increased when administered with food (AUC three- to fourfold higher). Avoid grapefruit juice (may increase the levels/effects of lapatinib).

Herb/Nutraceutical: Avoid St John's wort (may increase metabolism and decrease lapatinib concentrations).

Monitoring ParametersLVEF (baseline and periodic), CBC with differential, liver function tests, including transaminases, bilirubin, and alkaline phosphatase (baseline and every 4-6 weeks during treatment); electrolytes including calcium, potassium, magnesium; monitor for fluid retention; ECG monitoring if at risk for QT_c prolongation; symptoms of ILD

Nursing: Physical Assessment/MonitoringUse caution in presence of hepatic or left ventricular dysfunction. Assess all other pharmacological or herbal products patient may be taking for potential adverse interactions (anything that may prolong QT interval or strong

CYP3A4 inducers or inhibitors); dose adjustment may be necessary. Evaluate results of laboratory tests at baseline and on a regular basis (eg, CBC, LFTs, electrolytes, left ventricular ejection fraction). Assess therapeutic effectiveness and adverse reactions periodically during therapy (eg, cardiac changes, gastrointestinal disturbance [diarrhea may become severe], pulmonary status [interstitial lung disease or pneumonitis]). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, liver function tests, including transaminases, bilirubin, and alkaline phosphatase (baseline and every 4-6 weeks during treatment); electrolytes including calcium, potassium, magnesium

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take as directed on an empty stomach 1 hour before or 1 hour after a meal. Avoid grapefruit or grapefruit juice while taking this medication. Maintain adequate hydration (2-3 L/day) unless instructed to restrict fluid intake. You may be required to have regularly scheduled laboratory tests while on this medication. You will be more susceptible to infection (avoid crowds and exposure to infection and do not receive any vaccination unless approved by prescriber). You may experience diarrhea (buttermilk, boiled milk, or yogurt may reduce diarrhea; contact prescriber if persistent or severe); insomnia or fatigue (use caution when driving or engaging in hazardous tasks until response to drug is known); nausea, vomiting, stomach pain, or dyspepsia (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or red, painful hands, feet, limb, or back pain (contact prescriber for appropriate analgesia). Report chest pain or palpitations; any unusual cough, respiratory difficulty, or wheezing; easy bruising or unusual bleeding; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant. Consult prescriber for appropriate contraception while using this medication. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Tykerb®: 250 mg

Generic AvailableNo

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Tablets (Tykerb)

250 mg (150): $3604.11

Mechanism of ActionTyrosine kinase (dual kinase) inhibitor; inhibitor of EGFR (ErbB1) and HER2 (ErbB2) by reversibly binding to tyrosine kinase, blocking phosphorylation and activation of downstream second messengers (Erk1/2 and Akt), regulating cellular proliferation and survival in ErbB- and ErbB2-expressing tumors.

Pharmacodynamics/Kinetics

Absorption: Incomplete and variable

Protein binding: >99% to albumin and alpha$_1$-acid glycoprotein

Metabolism: Hepatic; extensive via CYP3A4 and 3A5, and to a lesser extent via CYP2C19 and 2C8 to oxidized metabolites

Half-life elimination: ~24 hours

Time to peak, plasma: 3-6 hours

Excretion: Feces (27% as unchanged drug; range 3% to 67%); urine (<2%)

Related Information

- Common Toxicity Criteria
- Management of Nausea and Vomiting

Pharmacotherapy Pearls**Oncology Comment:** The National Comprehensive Cancer Network (NCCN) breast cancer guidelines list lapatinib (in combination with capecitabine) as an option for the treatment of HER2-positive breast cancer in patients who are refractory to anthracycline, taxane and trastuzumab treatment. In a randomized phase III study (Geyer, 2006) of lapatinib plus capecitabine versus capecitabine alone in HER2-positive advanced breast cancer, the addition of lapatinib was associated with a 51% reduction in the risk of disease progression in heavily pretreated patients. Lapatinib shows activity in HER2-positive metastatic breast cancer that has progressed after trastuzumab treatment.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsLapatinib is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusFatigue is common; may cause insomnia

Mental Health: Effects on Psychiatric TreatmentDiarrhea is common; concurrent use with SSRIs or lithium may produce additive effects. May prolong QT$_c$ interval; concurrent use with ziprasidone, paliperidone, and thioridazine is not recommended. Hematologic side effects are common; use caution with clozapine, carbamazepine, and valproic acid. Lapatinib is a CYP3A4 substrate and inhibitor. CYP3A4 inducers (St John's wort, carbamazepine, barbiturates) may decrease the levels/effects of lapatinib. The effects/levels of CYP3A4 substrates (benzodiazepines, mirtazapine, venlafaxine, and nefazodone) may be increased by lapatinib. Selected benzodiazepines (midazolam, triazolam), and pimozide are generally contraindicated with strong CYP3A4 inhibitors.

Index TermsGW572016; Lapatinib Ditosylate; NSC-727989

References

Burris HA 3rd, Hurwitz HI, Dees EC, et al, "Phase I Safety, Pharmacokinetics, and Clinical Activity Study of Lapatinib (GW572016), a Reversible Dual Inhibitor of Epidermal Growth Factor Receptor Tyrosine Kinases, in Heavily Pretreated Patients with Metastatic Carcinomas," *J Clin Oncol*, 2005, 23(23):5305-13.[PubMed 15955900]

Geyer CE, Forster J, Lindquist D, et al "Lapatinib Plus Capecitabine for HER2-Positive Advanced Breast Cancer," *N Engl J Med*, 2006, 355(26):2733-43.[PubMed 17192538]

National Comprehensive Cancer Network (NCCN), "Clinical Practice Guidelines in Oncology™: Breast Cancer Version 2.2008." Available at http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf

Nelson MH and Dolder CR, "Lapatinib: A Novel Dual Tyrosine Kinase Inhibitor with Activity in Solid Tumors," *Ann Pharmacother*, 2006, 40(2):261-9.[PubMed 16418322]

Spector NL, Xia W, Burris H 3rd, et al, "Study of the Biologic Effects of Lapatinib, a Reversible Inhibitor of ErbB1 and ErbB2 Tyrosine Kinases, on Tumor Growth and Survival Pathways in Patients with Advanced Malignancies," *J Clin Oncol*, 2005, 23(11):2502-12.[PubMed 15684311]

International Brand NamesTykerb (HK, ID, KP, MY, NZ, PH, SG); Tyverb (CH, CZ, DE, DK, GB, IE, SE)

Laronidase

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(lair OH ni days)

U.S. Brand NamesAldurazyme®

Canadian Brand NamesAldurazyme®

Pharmacologic CategoryEnzyme

Use: Labeled IndicationsTreatment of Hurler and Hurler-Scheie forms of mucopolysaccharidosis I (MPS I); treatment of Scheie form of MPS I in patients with moderate to severe symptoms

Dosing: Adults**Note:** Premedicate with antipyretic and/or antihistamines 1 hour prior to start of infusion.

MPS I (Hurler syndrome, Hurler-Scheie, and Scheie forms): I.V.: 0.58 mg/kg once weekly; dose should be rounded up to the nearest whole vial

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Premedicate with antipyretic and/or antihistamines 1 hour prior to start of infusion.

MPS I (Hurler syndrome, Hurler-Scheie, and Scheie forms): Children ≥5 years: I.V.: 0.58 mg/kg once weekly; dose should be rounded up to the nearest whole vial

Administration: I.V.Administer using PVC container and PVC infusion set with in-line, low protein-binding 0.2 micrometer filter. Antipyretics and/or antihistamines should be administered prior to infusion. Volume and infusion rate are based on body weight. Vital signs should be monitored every 15 minutes, if stable; rate may be increased as follows:

- ≤20 kg: Total infusion volume: 100 mL
  - 2 mL/hour for 15 minutes
  - 4 mL/hour for 15 minutes
  - 8 mL/hour for 15 minutes
  - 16 mL/hour for 15 minutes
  - 32 mL/hour for remainder of infusion
- >20 kg: Total infusion volume: 250 mL
  - 5 mL/hour for 15 minutes
  - 10 mL/hour for 15 minutes
  - 20 mL/hour for 15 minutes
  - 40 mL/hour for 15 minutes
  - 80 mL/hour for remainder of infusion

Note: In case of infusion-related reaction, decrease the rate of infusion, temporarily discontinue the infusion, and/or administer additional antipyretics/antihistamines.

StorageStore vials under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Do not shake. Following dilution, solution for infusion should be used immediately; however, if not used immediately, refrigerate. Infusion of solution should be completed within 36 hours of preparation.

ReconstitutionSolution should be prepared based on body weight and should begin by making a solution of NS and albumin 0.1%.

≤20 kg: Using NS 100 mL PVC bag and albumin (human) [2 mL of albumin 5% or 0.4 mL of albumin 25%]:

Remove and discard a volume of NS equal to the amount of albumin to be added to the infusion bag. Add albumin; the total volume of this solution should equal 100 mL. From this bag, remove and discard an equal volume of the laronidase to be added (based on calculated dose). Slowly withdraw and add laronidase to the NS/albumin 0.1% solution; avoid excessive agitation, do not use filtered syringe. Gently rotate infusion bag to mix (do not shake).

>20 kg: Using NS 250 mL PVC bag and albumin (human) [5 mL of albumin 5% or 1 mL of albumin 25%]:

Remove and discard a volume of NS equal to the amount of albumin to be added to the infusion bag. Add albumin; the total volume of this solution should equal 250 mL. From this bag, remove and discard an equal volume of the laronidase to be added (based on calculated dose). Slowly withdraw and add laronidase to the NS/albumin 0.1% solution; avoid excessive agitation, do not use filtered syringe. Gently rotate infusion bag to mix (do not shake).

CompatibilityStable in NS.

ContraindicationsThere are no contraindications listed within the manufacturer's labeling.

Warnings/Precautions

Boxed warnings:

- Anaphylaxis/infusion reactions: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Anaphylaxis/infusion reactions: **[U.S. Boxed Warning]: Anaphylactic reactions have been observed during infusion, immediate treatment for hypersensitivity reactions should be available during administration. Additional monitoring may be required in patients with compromised respiratory function or acute respiratory disease; may be at increased risk for acute exacerbation of respiratory symptoms due to infusion reaction.** Patients with acute illness may also be at increased risk for infusion reactions. Reactions, which may include airway obstruction, bradycardia, bronchospasm, hypotension, hypoxia, respiratory distress/failure, stridor, tachypnea, and urticaria, may be severe and tend to occur during or within 3 hours after administration. Antipyretics and or antihistamines should be administered prior to infusion to reduce the incidence/severity of headache, fever, and/or flushing. In event of reaction, decrease the rate of infusion, temporarily discontinue the infusion, and/or administer additional antipyretics/antihistamines. Risks and benefits should be carefully considered prior to readministering following a severe hypersensitivity reaction. In the case of anaphylaxis, caution should be used if epinephrine is being considered; many patients with MPS I have pre-existing heart disease.

Disease-related concerns:

- MPS I: Appropriate use: Has not been studied in patients with mild symptoms of the Scheie form of MPS I. Not indicated for the CNS manifestations of the disorder.

Special populations:

- Pediatrics: Studies did not include children <5 years of age.

Dosage form specific issues:

- Albumin: Prepared infusions contain human albumin.

Other warnings/precautions:

- Registry: A patient registry has been established and all patients are encouraged to participate. Registry information may be obtained at www.MPSIregistry.com or by calling 800-745-4447.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; however, there are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed. Patients are encouraged to enroll in the MPS I registry.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsPatients are encouraged to enroll in the MPS I registry.

Adverse Reactions**Note:** Percentages reported are from a placebo-controlled study (45 patients, 22 receiving laronidase).

>10%:

Cardiovascular: Vein disorder (14%)

Dermatologic: Rash (36%)

Local: Injection site reaction (18%)

Neuromuscular & skeletal: Hyper-reflexia (14%), paresthesia (14%)

Respiratory: Upper respiratory tract infection (32%)

Miscellaneous: Antibody development to laronidase (91%); infusion reactions (32%; may be severe; includes flushing [23%], fever, and headache; frequency decreased over time during open-label extension period)

1% to 10%:

Cardiovascular: Chest pain (9%), edema (9%), facial edema (9%), hypotension (9%)

Hematologic: Thrombocytopenia (9%)

Hepatic: Bilirubinemia (9%)

Local: Abscess (9%), injection site pain (9%)

Ocular: Corneal opacity (9%)

Miscellaneous: Allergic reaction (severe/serious: 1%)

<1%, postmarketing, and/or case reports: Abdominal pain, airway obstruction, anaphylaxis, angioedema, arthralgia, bronchospasm, chills, cough, diarrhea, dyspnea, hypersensitivity, hypertension, nausea, oxygen saturation decreased, pruritus, tachycardia, urticaria, vomiting

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersVital signs; injection site reactions, infusion reactions

Nursing: Physical Assessment/MonitoringNote administration and reconstitution specifics. Antipyretics and or antihistamines should be administered prior to infusion to reduce incidence/severity of reaction (headache, fever, flushing). Patient must be closely monitored for infusion reactions during and after every infusion (reactions may be severe and usually occur within 3 hours of infusion). Encourage patient to enroll in patient registry for this medication. Teach possible side effects, appropriate interventions, and adverse symptoms to report.

Patient EducationThis medication will not cure your form of mucopolysaccharidosis, but rather may help reduce the symptoms. This medication can only be administered by intravenous infusion. You will be monitored during and after each infusion. Report immediately any chest pain, throat tightness, difficulty breathing, chills, fever, vomiting, or acute headache at time of infusion. Report any chest pain, upper respiratory infection, infusion site redness or swelling, or other adverse reactions that occur between infusions. **Breast-feeding precaution:** Consult prescriber if you are or intend to breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Aldurazyme®: 2.9 mg/5 mL (5 mL) [contains polysorbate 80; derived from Chinese hamster cells]

Generic AvailableNo

ManufacturerBioMarin Pharmaceutical Inc

Mechanism of ActionLaronidase is a recombinant (replacement) form of α-L-iduronidase derived from Chinese hamster cells. α-L-iduronidase is an enzyme needed to break down endogenous glycosaminoglycans (GAGs) within lysosomes. A deficiency of α-L-iduronidase leads to an accumulation of GAGs, causing cellular, tissue, and organ dysfunction as seen in MPS I. Improved pulmonary function and walking capacity have been demonstrated with the administration of laronidase to patients with Hurler, Hurler-Scheie, or Scheie (with moderate to severe symptoms) forms of MPS.

Pharmacodynamics/Kinetics

Distribution: V_d: 0.24-0.6 L/kg

Half-life elimination: 1.5-3.6 hours

Excretion: Clearance: 1.7 to 2.7 mL/minute/kg; during the first 12 weeks of therapy the clearance of laronidase increases proportionally to the amount of antibodies a given patient develops against the enzyme. However, with long-term use (≥26 weeks) antibody titers have no effect on laronidase clearance.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsRecombinant α-L-Iduronidase (Glycosaminoglycan α-L-Iduronohydrolase)

References

Kakkis ED, Muenzer J, Tiller GE, et al, “Enzyme-Replacement Therapy in Mucopolysaccharidosis I,” *N Engl J Med*, 2001, 18;344(3):182-8.[PubMed 11172140]

Wraith JE, Beck M, Lane R, et al, “Enzyme Replacement Therapy in Patients Who Have Mucopolysaccharidosis I and Are Younger Than 5 Years: Results of a Multinational Study of Recombinant Human {alpha}-L-Iduronidase (Laronidase),” *Pediatrics*, 2007, 120(1):e37-46.[PubMed 17606547]

International Brand NamesAldurazyme (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, NL, NO, NZ, PT, RU, SE, TR, TW)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Lymphocytic

Regimen UseLeukemia, acute lymphocytic

Regimen

Cyclophosphamide: I.V.: 1200 mg/m^2 day 1

[total dose/cycle = 1200 mg/m^2]

Daunorubicin: I.V.: 45 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 135 mg/m^2]

Vincristine: I.V.: 2 mg/day days 1, 8, 15, and 22

[total dose/cycle = 8 mg]

Prednisone: Oral or I.V.: 60 mg/m^2/day days 1 to 21

[total dose/cycle = 1260 mg/m^2]

Asparaginase: SubQ: 6000 units/m^2/day days 5, 8, 11, 15, 18, and 22

[total dose/cycle = 36,000 units/m^2]

Administer one cycle only

References

Larson RA, Dodge RK, Burns CP, et al, âA Five-Drug Remission Induction Regimen With Intensive Consolidation for Adults With Acute Lymphoblastic Leukemia: Cancer and Leukemia Group B Study 8811,â *Blood*, 1995, 85(8):2025-37.[PubMed 7718875]

Latanoprost

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Xalatan® may be confused with Travatan®, Zarontin®

Pronunciation(la TA noe prost)
U.S. Brand NamesXalatan®
Canadian Brand NamesXalatan®
Pharmacologic CategoryOphthalmic Agent, Antiglaucoma; Prostaglandin, Ophthalmic
Use: Labeled IndicationsReduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Dosing: AdultsGlaucoma: Ophthalmic: 1 drop (1.5 mcg) in the affected eye(s) once daily in the evening; do not exceed the once daily dosage because it has been shown that more frequent administration may decrease the IOP lowering effect

Note: A medication delivery device (Xal-Ease™) is available for use with Xalatan®.

Dosing: ElderlyRefer to adult dosing.
Administration: OtherIf more than one topical ophthalmic drug is being used, administer the drugs at least 5 minutes apart. A delivery aid, Xal-Ease™, is available for administering Xalatan®.
StorageStore intact bottles under refrigeration (2°C to 8°C/36°F to 46°F). Protect from light. Once opened, the container may be stored at room temperature up to 25°C (77°F) for 6 weeks.
ContraindicationsHypersensitivity to latanoprost or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Bacterial keratitis: Inadvertent contamination of multiple-dose ophthalmic solutions, has caused bacterial keratitis.
- Ocular effects: May permanently change/increase brown pigmentation of the iris, the eyelid skin, and eyelashes. In addition, may increase the length and/or number of eyelashes (may vary between eyes); changes occur slowly and may not be noticeable for months or years. Long-term consequences and potential injury to eye are not known.

Disease-related concerns:

- Ocular disease: Use with caution in patients with intraocular inflammation, aphakic patients, pseudophakic patients with a torn posterior lens capsule, or patients with risk factors for macular edema. Safety and efficacy have not been determined for use in patients with angle-closure-, inflammatory-, or neovascular glaucoma.

Special populations:

- Contact lens wearers: Contains benzalkonium chloride which may be adsorbed by contact lenses; remove contacts prior to administration and wait 15 minutes before reinserting.

Geriatric ConsiderationsEvaluate patient's ability to self-administer eye drops
Pregnancy Risk FactorC
Adverse Reactions

>10%: Ocular: Blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased pigmentation of the iris, and punctate epithelial keratopathy

1% to 10%:

Cardiovascular: Chest pain, angina pectoris

Dermatologic: Rash, allergic skin reaction

Neuromuscular & skeletal: Myalgia, arthralgia, back pain

Ocular: Dry eye, excessive tearing, eye pain, lid crusting, lid edema, lid erythema, lid discomfort/pain, photophobia

Respiratory: Upper respiratory tract infection, cold, flu

<1%: Conjunctivitis, diplopia, discharge from the eye, retinal artery embolus, retinal detachment, vitreous hemorrhage from diabetic retinopathy

Postmarketing and/or case reports: Asthma, corneal edema, corneal erosion, dyspnea, eyelash change, eyelid skin darkening, herpes keratitis, iritis, keratitis, macular edema, toxic epidermal necrolysis, uveitis

Drug Interactions

Bimatoprost: The concomitant use of Latanoprost and Bimatoprost may result in increased intraocular pressure. *Risk D: Consider therapy modification*

NSAID (Ophthalmic): May diminish the therapeutic effect of Latanoprost. *Risk C: Monitor therapy*

Nursing: Physical Assessment/Monitoring Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic response and adverse effects (eg, blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased pigmentation of the iris, and punctate epithelial keratopathy). Teach patient proper use, side effects/appropriate interventions, and symptoms to report.

Patient Education For use in eyes only. Iris color may change because of an increase of the brown pigment (cosmetically different eye coloration that may occur). Iris pigmentation changes may be more noticeable in patients with green-brown, blue/gray-brown, or yellow-brown irides. If any ocular reaction develops, particularly conjunctivitis and lid reactions, immediately notify prescriber. If more than one topical ophthalmic drug is being used, administer the drugs at least 5 minutes apart. Latanoprost contains benzalkonium chloride, which may be absorbed by contact lenses. Remove contact lenses prior to administration; lenses may be reinserted after 15 minutes. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. A delivery aid, Xal-Ease™, is available for administering Xalatan®. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic: 0.005% (2.5 mL) [contains benzalkonium chloride]

Generic Available No

Pricing: U.S. (www.drugstore.com)

Solution (Xalatan)

0.005% (2.5): $85.86

Mechanism of Action Latanoprost is a prostaglandin F_2-alpha analog believed to reduce intraocular pressure by increasing the outflow of the aqueous humor

Pharmacodynamics/Kinetics

Onset of action: 3-4 hours

Peak effect: Maximum: 8-12 hours

Absorption: Through the cornea where the isopropyl ester prodrug is hydrolyzed by esterases to the biologically active acid. Peak concentration is reached in 2 hours after topical administration in the aqueous humor.

Distribution: V_d: 0.16 L/kg

Metabolism: Primarily hepatic via fatty acid beta-oxidation

Half-life elimination: 17 minutes

Excretion: Urine (as metabolites)

Related Information

- Glaucoma Drug Therapy

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

References

Patel SS and Spencer CM, “Latanoprost: A Review of Its Pharmacological Properties, Clinical Efficacy and Tolerability in the Management of Primary Open-Angle Glaucoma and Ocular Hypertension,” *Drugs Aging*, 1996, 9(5):363-78.[PubMed 8922563]

International Brand Names 9 PM eye drops (IN); Lanoprost (TW); Lanotan (KP); Latanox (CO); Lataro (KP); Louten (AR, CN, PY, UY); Protan (KP); Xalatan (AE, AR, AT, AU, BE, BG, BH, BO, BR, CH, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EE, EG, ES, FI, FR, GB, GT, HK, HN, HU, IE, IL, IN, IQ, IR, IT, JO, KW, LB, LY, MX, MY, NI, NL, NO, OM, PA, PE, PH, PK, PL, PR, PT, PY, QA, SA, SE, SG, SV, SY, TW, UY, VE, YE, ZA)

Leflunomide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(le FLOO noh mide)

U.S. Brand NamesArava®

Canadian Brand NamesApo-Leflunomide®; Arava®; DOM-Leflunomide; GEN-Leflunomide; NOVO-Leflunomide; PHL-Leflunomide; PMS-Leflunomide; SANDOZ-Leflunomide

Pharmacologic CategoryAntirheumatic, Disease Modifying

Use: Labeled IndicationsTreatment of active rheumatoid arthritis; indicated to reduce signs and symptoms, and to retard structural damage and improve physical function

Orphan drug: Prevention of acute and chronic rejection in recipients of solid organ transplants

Use: Unlabeled/InvestigationalTreatment of cytomegalovirus (CMV) disease

Dosing: Adults

Rheumatoid arthritis: Oral: Loading dose: 100 mg/day for 3 days, followed by 20 mg/day; **Note:** May be omitted in patients at increased risk of hepatic or hematologic toxicity (eg, recent concomitant methotrexate). Dosage may be decreased to 10 mg/day in patients who have difficulty tolerating the 20 mg dose. Due to the long half-life of the active metabolite, plasma levels may require a prolonged period to decline after dosage reduction.

CMV (unlabeled): Some authors recommend 200 mg daily for 7 days, followed by 40-60 mg/day targeting blood levels of 100 mcg/mL. Others have utilized the standard arthritis dosing.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo specific dosage adjustment is recommended. There is no clinical experience in the use of leflunomide in patients with renal impairment. The free fraction of MI is doubled in dialysis patients. Patients should be monitored closely for adverse effects requiring dosage adjustment.

Dosing: Hepatic ImpairmentNo specific dosage adjustment is recommended; not recommended for use in patients with significant hepatic impairment. Since the liver is involved in metabolic activation and subsequent metabolism/elimination of leflunomide, patients with hepatic impairment should be monitored closely for adverse effects requiring dosage adjustment.

Dosing adjustment in hepatic toxicity: Guidelines for dosage adjustment or discontinuation based on the severity and persistence of ALT elevation secondary to leflunomide have been developed. If ALT elevations >2 times but ≤3 times ULN are noted, reduce dose to 10 mg/day, and monitor closely. If elevations persist or if elevations >3 times ULN are observed, discontinue leflunomide and initiate protocol to accelerate elimination. Cholestyramine (8 g 3 times/day for 1-3 days) or activated charcoal (50 g every 6 hours for 24 hours) may be administered to decrease leflunomide concentrations rapidly. If elevations >3 times ULN persist additional cholestyramine and/or activated charcoal may be required.

Dosing: Adjustment for ToxicityHepatic toxicity: Guidelines for dosage adjustment or discontinuation based on the severity and persistence of ALT elevation secondary to leflunomide have been developed. If ALT elevations >2 times but ≤3 times ULN are noted, reduce dose to 10 mg/day, and monitor closely. If elevations persist or if elevations >3 times ULN are observed, discontinue leflunomide and initiate protocol to accelerate elimination. Cholestyramine (8 g 3 times/day for 1-3 days) or activated charcoal (50 g every 6 hours for 24 hours) may be administered to decrease leflunomide concentrations rapidly. If elevations >3 times ULN persist additional cholestyramine and/or activated charcoal may be required.

Dietary ConsiderationsAdminister without regard to meals.

StorageStore at 25°C (77°F). Protect from light.

ContraindicationsHypersensitivity to leflunomide or any component of the formulation; pregnancy

Allergy Considerations

- Leflunomide Allergy

Warnings/Precautions

Boxed warnings:

- Women of childbearing potential: See “Special populations” below.

Concerns related to adverse effects:

- Dermatologic reactions: Rare cases of dermatologic reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported; discontinue if evidence or severe dermatologic reaction occurs, and begin procedure to accelerate elimination (cholestyramine or activated charcoal).

- Hepatotoxicity: Use has been associated with rare reports of hepatotoxicity, hepatic failure, and death. Multiple risk factors for hepatotoxicity including hepatic disease (including seropositive hepatitis B or C patients) and/or concurrent exposure to other hepatotoxins may increase the risk of hepatotoxicity. Most severe cases occur within 6 months of initiation; monitoring of hepatic function is required.

- Immunosuppression: May increase susceptibility to infection, including opportunistic pathogens. Severe infections, sepsis, and fatalities have been reported.

- Infections: Caution should be exercised when considering the use in patients with a history of new/recurrent infections, with conditions that predispose them to infections, or with chronic, latent, or localized infections. Patients who develop a new infection while undergoing treatment should be monitored closely. If a patient develops a serious infection, therapy should be discontinued and drug elimination procedures initiated.

- Interstitial lung disease: Use has been associated (rarely) with interstitial lung disease; discontinue in patients who develop new onset or worsening of pulmonary symptoms. Accelerated elimination procedures should be considered if interstitial lung disease occurs; fatal outcomes have been reported.

- Malignancy: Use may affect defenses against malignancies; impact on the development and course of malignancies is not fully defined. As compared to the general population, an increased risk of lymphoma has been noted in clinical trials; however, rheumatoid arthritis has been previously associated with an increased rate of lymphoma.

Disease-related concerns:

- Hematologic disorders: Use with caution in patients with a prior history of significant hematologic abnormalities including bone marrow dysplasia; use has been associated with rare pancytopenia, agranulocytosis, and thrombocytopenia, particularly when given in combination with methotrexate or other immunosuppressive agents. Monitoring of hematologic function is required; discontinue if evidence of bone marrow suppression and begin procedure to accelerate elimination (cholestyramine or activated charcoal).

- Hepatic disease: Due to risk of toxicity, use in patients with hepatic impairment or evidence of hepatitis B or C is not recommended.

- Renal impairment: Use with caution in patients with renal impairment; will increase uric acid excretion.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Women of childbearing potential: **[U.S. Boxed Warning]: Women of childbearing potential should not receive therapy until pregnancy has been excluded, they have been counseled concerning fetal risk and reliable contraceptive measures have been confirmed.**

Other warnings/precautions:

- Immunizations: Patients should be brought up to date with all immunizations before initiating therapy. Live vaccines should not be given concurrently; there is no data available concerning secondary transmission of live vaccines in patients receiving therapy.

Geriatric ConsiderationsIn Phase III studies, no difference in safety and effectiveness were seen between older and younger adults. No dosage reduction necessary based on age alone; monitor in renal and hepatic impairment.

Pregnancy Risk FactorX

Pregnancy ConsiderationsHas been associated with teratogenic and embryolethal effects in animal models at low doses. Leflunomide is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be excluded prior to initiating treatment. **[U.S. Boxed Warning]: Women of childbearing potential should not receive therapy until pregnancy has been excluded, they have been counseled concerning fetal risk, and reliable contraceptive measures have been confirmed.** Following treatment, pregnancy should be avoided until undetectable plasma levels (<0.02 mcg/mL) are verified. This may be accomplished by an extended drug elimination procedure: Administer cholestyramine 8 g 3 times/day for 11 days (the 11 days do not need to be consecutive). Plasma levels <0.02 mg/L should be verified by two separate tests performed at least 14 days apart. If plasma levels are >0.02 mg/L, additional cholestyramine treatment should be considered. Pregnant women exposed to leflunomide should be registered with the pregnancy registry (877-311-8972).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsIt is not known whether leflunomide is secreted in human milk. Because many immunoglobulins are secreted in milk, and the potential for serious adverse reactions exists, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Adverse Reactions

>10%:

Gastrointestinal: Diarrhea (17%)

Respiratory: Respiratory tract infection (15%)

1% to 10%:

Cardiovascular: Hypertension (10%), chest pain (2%), palpitation, tachycardia, vasodilation, varicose vein, edema (peripheral)

Central nervous system: Headache (7%), dizziness (4%), pain (2%), fever, malaise, migraine, anxiety, depression, insomnia, sleep disorder

Dermatologic: Alopecia (10%), rash (10%), pruritus (4%), dry skin (2%), eczema (2%), acne, dermatitis, hair discoloration, hematoma, nail disorder, subcutaneous nodule, skin disorder/discoloration, skin ulcer, bruising

Endocrine & metabolic: Hypokalemia (1%), diabetes mellitus, hyperglycemia, hyperlipidemia, hyperthyroidism, menstrual disorder

Gastrointestinal: Nausea (9%), abdominal pain (5%), dyspepsia (5%), weight loss (4%), anorexia (3%), gastroenteritis (3%), stomatitis (3%), vomiting (3%), cholelithiasis, colitis, constipation, esophagitis, flatulence, gastritis, gingivitis, melena, candidiasis (oral), enlarged salivary gland, tooth disorder, xerostomia, taste disturbance

Genitourinary: Urinary tract infection (5%), albuminuria, cystitis, dysuria, hematuria, vaginal candidiasis, prostate disorder, urinary frequency

Hematologic: Anemia

Hepatic: Abnormal LFTs (5%)

Neuromuscular & skeletal: Back pain (5%), joint disorder (4%), weakness (3%), tenosynovitis (3%), synovitis (2%), paresthesia (2%), arthralgia (1%), muscle cramps (1%), neck pain, pelvic pain, CPK increased, arthrosis, bursitis, myalgia, bone necrosis, bone pain, tendon rupture, neuralgia, neuritis

Ocular: Blurred vision, cataract, conjunctivitis, eye disorder

Respiratory: Bronchitis (7%), cough (3%), pharyngitis (3%), pneumonia (2%), rhinitis (2%), sinusitis (2%), asthma, dyspnea, epistaxis

Miscellaneous: Accidental injury (5%), infection (4%), allergic reactions (2%), diaphoresis, herpes infection

<1%, postmarketing and/or case reports: Agranulocytosis, anaphylaxis, angioedema, cholestasis, cutaneous necrotizing vasculitis, eosinophilia, erythema multiforme; hepatotoxicity (rare, including hepatic necrosis and hepatic failure, some fatalities reported); interstitial lung disease, leukopenia, opportunistic infection, pancreatitis, pancytopenia, peripheral neuropathy, pneumonitis (interstitial), pulmonary fibrosis, sepsis, Stevens-Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis, urticaria, vasculitis

Metabolism/Transport Effects**Inhibits** CYP2C9 (weak)

Drug Interactions

Methotrexate: May enhance the myelosuppressive effect of Leflunomide. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Leflunomide may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: No interactions with food have been noted.

Monitoring ParametersA complete blood count (WBC, hemoglobin, hematocrit, and platelet count), serum phosphate, as well as serum transaminase determinations should be monitored at baseline and monthly during the initial 6 months of treatment; if stable, monitoring frequency may be decreased to every 6-8 weeks thereafter (continue monthly when used in combination with other immunosuppressive agents). In addition, monitor for signs/symptoms of severe infection, abnormalities in hepatic function tests, or symptoms of hepatotoxicity. If coadministered with methotrexate, monthly transaminase and serum albumin levels are recommended.

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions. Do not administer live vaccines. Monitor for signs and symptoms of severe infection, hypertension, or hepatic dysfunction. Monitor for new onset or worsening of pulmonary symptoms. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to sexually-active female patients unless capable of complying with contraceptive use. Breast-feeding is contraindicated.

Monitoring: Lab TestsA complete blood count (WBC, hemoglobin, hematocrit, and platelet count), serum phosphate, as well as serum transaminase determinations, should be monitored at baseline and monthly during the initial 6 months of treatment; if stable, monitoring frequency may be decreased to every 6-8 weeks thereafter (continue monthly when used in combination with other immunosuppressive agents). If coadministered with methotrexate, monthly transaminase and serum albumin levels are recommended.

Patient EducationTake as directed; do not increase dose without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Store medication away from light. Do not receive any vaccinations unless approved by prescriber. You may experience diarrhea (buttermilk, boiled milk, or yogurt may help); nausea, vomiting, loss of appetite, and flatulence (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known). If you have diabetes, monitor blood sugars closely; this medication may alter glucose levels. If you experience symptoms such as nausea, vomiting, stomach pain or swelling, jaundice, dark urine, or unusual tiredness, report these to your prescriber **immediately**. Report chest pain, palpitations, rapid heartbeat, or swelling of extremities; persistent GI problems; skin rash, mucous membrane lesions, redness, irritation, acne, ulcers; frequent, painful, or difficult urination, or genital itching or irritation; depression, acute headache, anxiety, or difficulty sleeping; muscle tremors, cramping or weakness, back pain, or altered gait; cough, cold symptoms, wheezing, or respiratory difficulty; easy bruising/bleeding; blood in vomitus, stool, urine; or other unusual effects related to this medication. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Do not get pregnant or have sex unless using appropriate contraception while on this medication. This drug may cause severe fetal defects. Consult prescriber if you suspect you might be pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet (Arava®): 10 mg, 20 mg

Generic AvailableYes

ManufacturerHoechst-Marion Roussel

Pricing: U.S. (www.drugstore.com)

Tablets (Arava)

10 mg (30): $546.20

20 mg (30): $569.99

Tablets (Leflunomide)

10 mg (30): $64.00

20 mg (30): $40.01

Mechanism of ActionInhibits pyrimidine synthesis, resulting in antiproliferative and anti-inflammatory effects. For CMV, may interfere with virion assembly.

Pharmacodynamics/Kinetics

Distribution: V_d: 0.13 L/kg

Metabolism: Hepatic to A77 1726 (MI) which accounts for nearly all pharmacologic activity; further metabolism to multiple inactive metabolites; undergoes enterohepatic recirculation

Bioavailability: 80%

Half-life elimination: Mean: 14-15 days; enterohepatic recycling appears to contribute to the long half-life of this agent, since activated charcoal and cholestyramine substantially reduce plasma half-life

Time to peak: 6-12 hours

Excretion: Feces (48%); urine (43%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), stomatitis, oral candidiasis, abnormal taste, tooth disorder, enlarged salivary gland, esophagitis, and gingivitis.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness, malaise, anxiety, depression, or insomnia
Mental Health: Effects on Psychiatric TreatmentMay rarely cause leukopenia, caution with clozapine and carbamazepine
References

Avery RK, Bolwell BJ, Yen-Lieberman B, et al, "Use of Leflunomide in an Allogenic Bone Marrow Tranplant Recipient With Refractory Cytomegalovirus Infection," *Bone Marrow Transplant*, 2004, 34(12):1071-5.

Fox RI, “Mechanism of Action of Leflunomide in Rheumatoid Arthritis,” *J Rheumatol*, 1998, 53:20-6.

John GT, Manivannan J, Chandy S, et al, "Leflunomide Therapy for Cytomegalovirus Disease in Renal Allograft Recipients," *Transplantation*, 2004, 77(9):1460-1.[PubMed 15167608]

“New Drugs for Rheumatoid Arthritis,” *Med Lett Drugs Ther*, 1998, 40(1040):110-2. [PubMed 9844625]

Popovic M, Stefanovic D, Pejnovic N, et al, “Comparative Study of the Clinical Efficacy of Four DMARDs (Leflunomide, Methotrexate, Cyclosporine, and Levamisole) in Patients With Rheumatoid Arthritis,” *Transplant Proc*, 1998, 30(8):4135-6. [PubMed 9865325]

Rozman B, “Clinical Experience With Leflunomide in Rheumatoid Arthritis,” *J Rheumatol*, 1998, 53:27-32.

Smolen JS, Kalden JR, Scott DL, et al, “Efficacy and Safety of Leflunomide Compared With Placebo and Sulfasalazine in Active Rheumatoid Arthritis: A Double-Blind, Ramdomised, Multicentre Trial,” *Lancet*, 1999, 353(9149):259-66.[PubMed 9929017]

Williams JW, Mital D, Chong A, et al, "Experiences With Leflunomide in Solid Organ Transplantation," *Transplantation*, 2002, 73(3):358-66.[PubMed 11884931]

International Brand NamesAiruohua (CL); Arabloc (AU); Arava (AR, AT, AU, BD, BE, BG, BO, BR, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, FI, FR, GB, GR, GT, HK, HN, ID, IE, IL, IN, IT, JP, KP, MX, MY, NI, NL, NO, PA, PE, PH, PK, PL, PR, PT, PY, RU, SE, SG, SV, TH, TR, TW, UY, VE); Arheuma (TW)

Lenalidomide-Dexamethasone (Low Dose)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Multiple Myeloma]

Regimen UseMultiple myeloma

Index TermsDexamethasone (Low Dose)-Lenalidomide

Regimen

Lenalidomide: Oral: 25 mg/day days 1 to 21

[total dose/cycle = 525 mg]

Dexamethasone: Oral: 40 mg/day days 1, 8, 15, and 22

[total dose/cycle = 160 mg]

Repeat cycle every 28 days

References

Rajkumar SV, Jacobus S, Callander N, et al, "A Randomized Phase III Trial of Lenalidomide Plus High-Dose Dexamethasone Versus Lenalidomide Plus Low-Dose Dexamethasone in Newly Diagnosed Multiple Myeloma (E4A03): A Trial Coordinated by the Eastern Cooperative Oncology Group," *Blood*, 2006, 108(11), ASH Abstract 799.

Rajkumar SV, Jacobus S, Callander N, et al, "Phase III Trial of Lenalidomide Plus High-Dose Dexamethasone Versus Lenalidomide Plus Low-Dose Dexamethasone in Newly Diagnosed Multiple Myeloma (E4A03): A Trial Coordinated by the Eastern Cooperative Oncology Group, *J Clin Onc*, 2007, 25(18S), ASCO Abstract LBA8025.

Lenalidomide-Dexamethasone

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Multiple Myeloma

Regimen Use Multiple myeloma

Index Terms Dexamethasone-Lenalidomide

Regimen

Lenalidomide: Oral: 25 mg/day days 1 to 21

[total dose/cycle = 525 mg]

Dexamethasone: Oral: 40 mg/day days 1 to 4, 9 to 12, and 17 to 20 (cycles 1, 2, 3, and 4)

[total dose/cycle = 480 mg]

Dexamethasone: Oral 40 mg/day days 1 to 4 (cycle 5 and beyond)

[total dose/cycle = 160 mg]

Repeat cycle every 28 days

References

Dimopoulos M, Spencer A, Attal M, et al, "Lenalidomide Plus Dexamethasone for Relapsed or Refractory Multiple Myeloma," *N Engl J Med*, 2007, 357(21):2123-32.[PubMed 18032762]

Rajkumar SV, Hayman SR, Lacy MQ, et al, "Combination Therapy With Lenalidomide Plus Dexamethasone (Rev/Dex) for Newly Diagnosed Myeloma," *Blood*, 2005, 106(13):4050-3. [PubMed 16118317]

Weber DM, Chen C, Niesvizky R, et al, "Lenalidomide Plus Dexamethasone for Relapsed Multiple Myeloma in North America," *N Engl J Med*, 2007, 357(21):2133-42.[PubMed 18032763]

Lenalidomide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(le na LID oh mide)

U.S. Brand NamesRevlimid®

Canadian Brand NamesRevlimid®

Pharmacologic CategoryAngiogenesis Inhibitor; Antineoplastic Agent; Immunomodulator, Systemic

Use: Labeled IndicationsTreatment of myelodysplastic syndrome (MDS) in patients with deletion 5q (del 5q) cytogenetic abnormality; treatment of multiple myeloma

Use: Unlabeled/InvestigationalTreatment of metastatic malignant melanoma; treatment of myelofibrosis

Dosing: Adults

Myelodysplastic syndrome (MDS): Oral: 10 mg once daily

Multiple myeloma: 25 mg once daily for 21 days of a 28-day treatment cycle (in combination with dexamethasone)

Metastatic malignant melanoma (unlabeled/investigational use): 10-25 mg once daily

Myelofibrosis (unlabeled/investigational use): Oral: 5-10 mg once daily

Dosing: ElderlyRefer to adult dosing. Due to the potential for decreased renal function in the elderly, select dose carefully and closely monitor renal function.

Dosing: Renal ImpairmentSelect dose carefully and closely monitor renal function. The FDA-approved labeling does not contain renal dosing adjustment guidelines. Lenalidomide AUC is increased 56% in multiple myeloma patients with mild renal impairment. Consider dose reductions in patients with renal dysfunction. Lenalidomide use with renal dysfunction has been studied in a limited number of patients with the following initial dosage recommendations (Chen, 2007):

MDS:

- Cl_{cr} 30-49 mL/minute: 5 mg once daily
- Cl_{cr} <30 mL/minute (nondialysis dependent): 5 mg every 48 hours
- Cl_{cr} <30 mL/minute (dialysis dependent): 5 mg 3 times/week (administer following dialysis)

Multiple myeloma:

- Cl_{cr} 30-49 mL/minute: 10 mg once daily (may increase to 15 mg once daily for inadequate treatment response after 2 cycles)
- Cl_{cr} <30 mL/minute (nondialysis dependent): 15 mg every 48 hours
- Cl_{cr} <30 mL/minute (dialysis dependent): 15 mg 3 times/week (administer following dialysis)

Dosing: Adjustment for Toxicity

Adjustment for thrombocytopenia in MDS:

Thrombocytopenia developing within 4 weeks of beginning treatment at 10 mg/day:

- Baseline platelets ≥100,000/mm^3:
  - If platelets <50,000/mm^3: Hold treatment
  - When platelets return to ≥50,000/mm^3: Resume treatment at 5 mg/day
- Baseline platelets <100,000/mm^3:
  - If platelets fall to 50% of baseline: Hold treatment
  - If baseline ≥60,000/mm^3 and platelet level returns to ≥50,000/mm^3: Resume at 5 mg/day
  - If baseline <60,000/mm^3 and platelet level returns to ≥30,000/mm^3: Resume at 5 mg/day

Thrombocytopenia developing after 4 weeks of beginning treatment at 10 mg/day:

Platelets <30,000/mm^3 **or** <50,000/mm^3 with platelet transfusions: Hold treatment

Platelets ≥30,000/mm^3 (without hemostatic failure): Resume at 5 mg/day

Thrombocytopenia developing with treatment at 5 mg/day:

Platelets <30,000/mm^3 **or** <50,000/mm^3 with platelet transfusions: Hold treatment

Platelets ≥30,000/mm^3 (without hemostatic failure): Resume at 5 mg every other day day

Adjustment for neutropenia in MDS:

Neutropenia developing within 4 weeks of beginning treatment at 10 mg/day:

For baseline absolute neutrophil count (ANC) ≥1000/mm^3:

ANC <750/mm^3: Hold treatment

When ANC returns to ≥1000/mm^3: Resume at 5 mg/day

For baseline absolute neutrophil count (ANC) <1000/mm^3:

ANC <500/mm^3: Hold treatment

When ANC returns to ≥500/mm^3: Resume at 5 mg/day

Neutropenia developing after 4 weeks of beginning treatment at 10 mg/day:

ANC <500/mm^3 for ≥7 days or associated with fever: Hold treatment

When ≥500/mm^3: Resume at 5 mg/day

Neutropenia developing with treatment at 5 mg/day:

ANC <500/mm^3 for ≥7 days or associated with fever: Hold treatment

When ≥500/mm^3: Resume at 5 mg every other day

Adjustment for thrombocytopenia in multiple myeloma:

Platelets <30,000/mm^3: Hold treatment, check CBC weekly

When platelets ≥30,000/mm^3: Resume at 15 mg daily

Additional occurrence of platelets <30,000/mm^3: Hold treatment

When platelets ≥30,000/mm^3: Resume treatment at 5 mg below previous dose; do not dose below 5 mg daily

Adjustment for neutropenia in multiple myeloma:

ANC <1000/mm^3: Hold treatment, add G-CSF, check CBC weekly

When ≥1000/mm^3 (with neutropenia as only toxicity): Resume at 25 mg/day

When ≥1000/mm^3 (with additional toxicities): Resume at 15 mg/day

Additional occurrence of ANC <1000/mm^3: Hold treatment

When ≥1000/mm^3: Resume treatment at 5 mg below previous dose; do not dose below 5 mg daily.

Adjustment for other toxicities in multiple myeloma: For additional treatment-related grade 3/4 toxicities, hold treatment and restart at next dose level when toxicity has resolved to ≤ grade 2.

Dosing: Combination Regimens

Multiple myeloma:

Lenalidomide-Dexamethasone

Lenalidomide-Dexamethasone (Low Dose)

Calculations

- ANC: Absolute Neutrophil Count

Administration: OralAdminister with water. Swallow capsule whole; do not break, open, or chew.

StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C and 30°C (59°F and 86°F).

RestrictionsLenalidomide is approved for marketing in the U.S. only under a Food and Drug Administration (FDA) approved, restricted distribution program called RevAssist^{SM} (www.REVLIMID.com or 1-888-423-5436). In Canada, distribution is restricted through RevAid^{SM} (www.RevAid.ca or 1-888-738-2431). Physicians, pharmacies, and patients must be registered; a maximum 28-day supply may be dispensed; a new prescription is required each time it is filled; pregnancy testing is required for females of childbearing potential.

An FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to lenalidomide or any component of the formulation; pregnancy or women capable of becoming pregnant; patients unable to comply with the RevAssist^{SM} program

Canadian labeling: Additional contraindications (not in U.S. labeling): Platelet count <50,000/mm^3; hypersensitivity to thalidomide; breast-feeding women

Warnings/Precautions

Boxed warnings:

- Hematologic toxicity: See “Concerns related to adverse effects” below.
- Pregnancy: See “Special populations” below.
- Thrombosis/embolism: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- CNS effects: May cause dizziness or fatigue; caution patients about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hematologic toxicity: **[U.S. Boxed Warning]: Hematologic toxicity (neutropenia and thrombocytopenia) occurs in a majority of patients (grade 3/4: 80%)** and may require dose reductions and/or delays; the use of blood product support and/or growth factors may be needed.
- Thromboembolic events: **[U.S. Boxed Warning]: Lenalidomide has been associated with a significant increase in risk for thrombosis and embolism in multiple myeloma patients treated with combination therapy. Deep vein thrombosis (DVT) and pulmonary embolism (PE) have occurred;** monitor for signs and symptoms of thromboembolism (shortness of breath, chest pain, or arm or leg swelling) and seek prompt medical attention with development of these symptoms.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; may experience an increased rate of toxicities.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: **[U.S. Boxed Warning]: Lenalidomide is an analogue of thalidomide (a human teratogen) and could potentially cause birth defects in humans.** Distribution is restricted; physicians, pharmacists, and patients must be registered with the RevAssist^{SM} program.

Other warnings/precautions:

- Blood donation: Patients should be advised not to donate blood during therapy and for 4 weeks following completion of therapy.
- Lactose intolerance: Product may contain lactose; avoid use in patients with Lapp lactase deficiency, glucose-galactose malabsorption, or glucose intolerance.

Geriatric Considerations The manufacturer reports that the frequency of serious adverse effects was higher in patients >65 years of age compared to younger patients (54% vs 33%). More older patients withdrew from the clinical studies because of side effects. There was no significant difference in efficacy in older versus younger patients.

Pregnancy Risk FactorX

Pregnancy Considerations**[U.S. Boxed Warning]: Lenalidomide is an analogue of thalidomide (a human teratogen) and could potentially cause birth defects in humans.** Animal studies with lenalidomide are ongoing; there are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be treated only if they are able to comply with the conditions of the RevAssist^{SM} program. Two forms of effective contraception are required beginning 4 weeks prior to, during, and for 4 weeks after therapy and during therapy interruptions. Pregnancy tests (sensitivity of at least 50 mIU/mL) should be performed 10-14 days and 24 hours prior to beginning therapy; weekly for the first 4 weeks and every 4 weeks (every 2 weeks if menstrual cycle irregular) thereafter and during therapy interruptions. Lenalidomide must be immediately discontinued and the patient referred to a reproductive toxicity specialist if pregnancy occurs during treatment. Males (even those vasectomized) should use a latex condom during any sexual contact with women of childbearing age. Risk to the fetus from semen of male patients is unknown. The parent or legal guardian for patients between 12 and 18 years of age must agree to ensure compliance with the required guidelines. Any suspected fetal exposure should be reported to the FDA via the MedWatch program (1-800-FDA-1088) and to Celgene Corporation (1-888-423-5436)

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for adverse reactions in nursing infants, breast-feeding is not recommended.

Adverse Reactions

>10%:

Cardiovascular: Peripheral edema (8% to 21%)

Central nervous system: Fatigue (31% to 38%), insomnia (10% to 32%), pyrexia (21% to 23%), dizziness (20% to 21%), headache (20%)

Dermatologic: Pruritus (42%), rash (16% to 36%), dry skin (14%)

Endocrine & metabolic: Hyperglycemia (15%), hypokalemia (11%)

Gastrointestinal: Diarrhea (29% to 49%), constipation (24% to 39%), nausea (22% to 24%), weight loss (18%), dyspepsia (14%), anorexia (10% to 14%), taste perversion (6% to 13%), abdominal pain (8% to 12%)

Genitourinary: Urinary tract infection (11%)

Hematologic: Thrombocytopenia (17% to 62%; grades 3/4: 10% to 50%), neutropenia (28% to 59%; grades 3/4: 21% to 53%), anemia (12% to 24%; grades 3/4: 6% to 9%); myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction

Neuromuscular & skeletal: Muscle cramp (18% to 30%), weakness (15% to 23%), arthralgia (10% to 22%), back pain (15% to 21%), tremor (20%), paresthesia (12%), limb pain (11%)

Ocular: Blurred vision (15%)

Respiratory: Nasopharyngitis (23%), cough (15% to 20%), dyspnea (7% to 20%), pharyngitis (16%), epistaxis (15%), upper respiratory infection (14% to 15%), pneumonia (11% to 12%)

1% to 10%:

Cardiovascular: Edema (10%), deep vein thrombosis (≤8%; grades 3/4: 7%), hypertension (6%), chest pain (5%), palpitation (5%), atrial fibrillation (grades 3/4: 3%), syncope (grade 3: 2%)

Central nervous system: Hypoesthesia (7%), pain (7%), depression (5%)

Dermatologic: Bruising (5% to 8%), cellulitis (5%), erythema (5%)

Endocrine & metabolic: Hypothyroidism (7%), hypomagnesemia (6%), hypocalcemia (grades 3/4: 4%)

Gastrointestinal: Vomiting (10%), xerostomia (7%), loose stools (6%)

Genitourinary: Dysuria (7%)

Hematologic: Leukopenia (8%; grade 3: 4%), febrile neutropenia (5%), lymphopenia (grade 3: 2%)

Hepatic: ALT increased (8%)

Neuromuscular & skeletal: Myalgia (9%), rigors (6%), neuropathy (peripheral 5%)

Respiratory: Sinusitis (8%), rhinitis (7%), bronchitis (6%), pulmonary embolism (≤3%; grades 3/4: 3%)

Miscellaneous: Night sweats (8%), diaphoresis increased (7%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Acute febrile neutrophilic dermatosis, acute leukemia, acute myeloid leukemia (AML), adrenal insufficiency, angina, angioedema, aortic disorder, aphasia, azotemia, bacteremia, Basedow's disease, biliary obstruction, blindness, bone marrow depression, bradycardia, brain edema, C-reactive protein decreased, cardiac arrest, cardiac failure, cardiogenic shock, cardiomyopathy, cardiopulmonary arrest, cellulitis, cerebellar infarction, cerebral infarction, cerebrovascular accident, CHF, cholecystitis, chondrocalcinosis, chronic obstructive airway disease, circulatory collapse, coagulopathy, colonic polyp, dehydration, delirium, delusion, diabetes mellitus, diabetic ketoacidosis, diverticulitis, dysphagia, encephalitis, erythema multiforme, gait abnormal, gastritis, gastroenteritis, gastrointestinal hemorrhage, gout, hematuria, hemoglobin decreased, hemolysis, hemolytic anemia, hemorrhage, hepatitis, herpesvirus infection, hyperbilirubinemia, hypernatremia, hypersensitivity, hypoglycemia, hypotension, hypoxia, infection, INR increased, interstitial lung disease, intestinal perforation, intracranial hemorrhage, intracranial venous sinus thrombosis, irritable bowel syndrome, ischemia, ischemic colitis, leukoencephalopathy, liver failure, liver function tests abnormal, lung cancer, lung infiltration, lymphoma, melena, MI, migraine, myocardial ischemia, myopathy, neutropenic sepsis, orthostatic hypotension, pancreatitis, pancytopenia, performance status decreased, peripheral ischemia, phlebitis, post procedural hemorrhage, pseudomembraneous colitis, pulmonary edema, rectal hemorrhage, refractory anemia, renal calculus, renal failure, renal mass, renal tubular necrosis, respiratory failure, septic shock, sepsis, serum creatinine increased, skin desquamation, small bowel obstruction, somnolence, spinal cord compression, splenic infarction, Stevens-Johnson syndrome, stomatitis, subarachnoid hemorrhage, supraventricular arrhythmia, tachyarrhythmia, thrombophlebitis, thrombosis, toxic epidermal necrolysis, transient ischemic attack, troponin I increased, urinary retention, urosepsis, urticaria, ventricular dysfunction, wheezing

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

Abatacept: Anti-TNF Agents may enhance the adverse/toxic effect of Abatacept. An increased risk of serious infection during concomitant use has been reported. *Risk D: Consider therapy modification*

Anakinra: Anti-TNF Agents may enhance the adverse/toxic effect of Anakinra. An increased risk of serious infection during concomitant use has been reported. *Risk X: Avoid combination*

Dexamethasone: May enhance the thrombogenic effect of Lenalidomide. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be

increased. *Risk X: Avoid combination*

Rilonacept: Anti-TNF Agents may enhance the adverse/toxic effect of Rilonacept. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid echinacea (has immunostimulant properties; consider therapy modifications).

Monitoring ParametersCBC with differential (MDS: weekly for first 8 weeks; MM: every 2 weeks for the first 3 months), then monthly thereafter; serum creatinine, liver function tests, thyroid function tests; ECG when clinically indicated; monitor for signs and symptoms of thromboembolism

Women of childbearing potential: Pregnancy test 10-14 days **and** 24 hours prior to initiating therapy, then every 2-4 weeks through 4 weeks after therapy discontinued

Nursing: Physical Assessment/MonitoringVerify that patient is not pregnant prior to initiating therapy. Instruct patient on the need to use two reliable forms of contraception beginning 4 weeks prior to, during, and for 4 weeks after therapy and during therapy interruptions. Monitor for signs of thromboembolism (shortness of breath, chest pain, or arm or leg swelling), infection, or bleeding. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Monitoring: Lab TestsCBC with differential (MDS: weekly for first 8 weeks; MM: every 2 weeks for the first 3 months), then monthly thereafter; serum creatinine, liver function tests, thyroid function tests. Women of childbearing potential: Pregnancy test 10-14 days **and** 24 hours prior to initiating therapy, then every 2-4 weeks through 4 weeks after therapy discontinued

Patient EducationDo not take any new medication during therapy without consulting prescriber. You will need frequent blood tests while taking this medication. Maintain adequate hydration (2-3 L/day) unless instructed to restrict intake by prescriber. If you have diabetes, monitor blood glucose closely. Can cause hyperglycemia. You may be susceptible to infections. Avoid crowds and exposure to infections. Avoid vaccinations unless approved by prescriber. You may experience headache, fever, fatigue, dizziness (use caution when driving or engaging in activities requiring alertness until response to drug is known), swelling of extremities, rash, itching, nausea, diarrhea (buttermilk, boiled milk, or yogurt may help), constipation (increasing exercise, fluids, fruit/fiber may help), abdominal pain, upper respiratory infections, or sore throat. Report shortness of breath; chest pain; arm or leg swelling; extreme weakness or fatigue; muscle cramping; unusual bleeding or bruising; or nosebleeds. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. May cause fetal harm. Two forms of contraception are required beginning 4 weeks prior to, during, and for 4 weeks after therapy and during therapy interruptions. Male patients must use a latex condom even if he has undergone a successful vasectomy when having sexual contact with females of childbearing age. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Revlimid®: 5 mg, 10 mg, 15 mg, 25 mg

Generic AvailableNo

ManufacturerCelgene Corp

Mechanism of ActionImmunomodulatory, antiangiogenic, and antineoplastic characteristics via multiple mechanisms. Selectively inhibits secretion of proinflammatory cytokines (potent inhibitor of tumor necrosis factor-alpha secretion); enhances cell-mediated immunity by stimulating proliferation of anti-CD3 stimulated T cells (resulting in increased IL-2 and interferon gamma secretion); inhibits trophic signals to angiogenic factors in cells. Inhibits the growth of myeloma cells by inducing cell cycle arrest and cell death.

Pharmacodynamics/Kinetics

Absorption: Rapid

Protein binding: ~30%

Half-life elimination: ~3 hours

Time, to peak, plasma: Healthy volunteers: 0.6-1.5 hours; Myeloma patients: 0.5-4 hours

Excretion: Urine (~67% as unchanged drug)

Pharmacotherapy PearlsPregnancy tests are required prior to beginning therapy, throughout treatment and during therapy interruptions for all women of childbearing age. The pregnancy test must be verified by the prescriber and the pharmacist prior to dispensing. Effective contraception with at least two reliable forms of contraception (IUD, hormonal contraception, tubal ligation or partner's vasectomy plus latex condom, diaphragm, or cervical cap) should be used for 4 weeks prior to beginning therapy, during therapy, and for 4 weeks following discontinuance of therapy. Women who have undergone a hysterectomy or have been postmenopausal for at least 24 consecutive months are the only exception. Do not prescribe, administer, or dispense to women of childbearing age or males who may have intercourse with women of childbearing age unless both female and male are capable of complying with contraceptive measures. Even males who have undergone vasectomy must acknowledge these risks in writing, and must use a latex condom during any sexual contact with women of childbearing age. Oral and written warnings concerning contraception and the hazards of thalidomide must be conveyed to females and males and they must acknowledge their understanding in writing. Parents or guardians must consent and sign acknowledgment for patients 12-18 years of age following therapy. A maximum 28-day supply should be dispensed.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and fatigue are common; may cause insomnia or depression (check thyroid function tests)

Mental Health: Effects on Psychiatric TreatmentHematologic side effects are common; concomitant use with clozapine and carbamazepine are best avoided. GI side effects are common; concomitant use with SSRIs, lithium, valproic acid, and carbamazepine may produce additive effects. May cause hypothyroidism; concomitant use with lithium may produce additive effects.

Index Terms CC-5013; IMid-3; NSC-703813

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International Brand Names Revlimid (BE, CH, CZ, DE, DK, EE, GB, IE, NO, SE)

Lepirudin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(leh puh ROO din)
U.S. Brand NamesRefludan®
Canadian Brand NamesRefludan®
Pharmacologic CategoryAnticoagulant, Thrombin Inhibitor
Use: Labeled IndicationsIndicated for anticoagulation in patients with heparin-induced thrombocytopenia (HIT) and associated thromboembolic disease in order to prevent further thromboembolic complications
Use: Unlabeled/InvestigationalInvestigational: Prevention or reduction of ischemic complications associated with unstable angina
Dosing: Adults**Note:** Maximum infusion dose: Do not exceed 0.21 mg/kg/hour unless an evaluation of coagulation abnormalities limiting response has been completed.

Heparin-induced thrombocytopenia: Bolus dose: 0.4 mg/kg IVP (over 15-20 seconds), followed by continuous infusion at 0.15 mg/kg/hour (maximum initial bolus dose: 44 mg; maximum initial infusion dose: 16.5 mg/hour); bolus and infusion must be reduced in renal insufficiency

or

Alternate dosing regimen (unlabeled dose; Selleng, 2007; Warkentin, 2008): Bolus dose: 0.2 mg/kg (use only if life- or limb-threatening thrombosis present) followed by continuous infusion of 0.05-0.1 mg/kg/hour. Further dosage reduction may be required in patients with renal dysfunction. This alternate dosing regimen has been recommended due to higher rates of bleeding associated with the FDA-approved dosing regimen.

Concomitant use with thrombolytic therapy: I.V.: Bolus dose: 0.2 mg/kg IVP (over 15-20 seconds), followed by continuous infusion at 0.1 mg/kg/hour

Dosing adjustments during infusions: Monitor first aPTT 4 hours after the start of the infusion. Subsequent determinations of aPTT should be obtained at least once daily during treatment. More frequent monitoring is recommended in renally- or hepatically-impaired patients. Any aPTT ratio measurement out of range (1.5-2.5) should be confirmed prior to adjusting dose, unless a clinical need for immediate reaction exists. If the aPTT is below target range, increase infusion by 20%. If the aPTT is in excess of the target range, stop infusion for 2 hours and when restarted the infusion rate should be decreased by 50%. A repeat aPTT should be obtained 4 hours after any dosing change.

Transition to oral anticoagulants: Once platelets normalize, reduce lepirudin dose gradually to reach aPTT ratio just above 1.5 before starting warfarin therapy. Monitor PT/INR closely until results stabilize in therapeutic range. When lepirudin is discontinued, there may be a small reduction in INR.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentAll patients with a creatinine clearance of <60 mL/minute or a serum creatinine of >1.5 mg/dL require dosage reduction; there is only limited information on the therapeutic use of lepirudin in patients with HIT and significant renal impairment; the following dosage recommendations are mainly based on single-dose studies in a small number of patients with renal impairment. An alternate dosing regimen has also been recommended for patients with serum creatinine >1 mg/dL (Warkentin, 2008).

Initial: Bolus dose: 0.2 mg/kg IVP (over 15-20 seconds), followed by adjusted infusion based on renal function; refer to the following infusion rate adjustments based on creatinine clearance (mL/minute) and serum creatinine (mg/dL):

Note: Acute renal failure or hemodialysis: Infusion is to be avoided or stopped. Following the bolus dose, additional bolus doses of 0.1 mg/kg may be administered every other day only if aPTT falls below lower therapeutic limit (1.5-times patient baseline [or mean laboratory] aPTT).

Lepirudin infusion rates in patients with renal impairment: See tables.

Lepirudin Infusion Rates in Patients With Renal Impairment

Creatinine Clearance (mL/min)	Serum Creatinine (mg/dL)	Adjusted Infusion Rate	
		% of Standard Initial Infusion Rate	mg/kg/h
45-60	1.6-2.0	50%	0.075

30-44	2.1-3.0	30%	0.045
15-29	3.1-6.0	15%	0.0225
<15	>6.0	***Avoid or STOP infusion***	

Alternate Dosing Regimen for Renal Impairment (based on *Chest* 2008 guidelines[1])

Serum Creatinine (mg/dL)	**Adjusted Infusion Rate**	
	% of Standard Initial Infusion Rate[2]	**mg/kg/h**
1.0-1.6	50%	0.05
1.7-4.5	10%	0.01
>4.5-6.0	5%	0.005
>6.0	***Avoid or STOP infusion[3]***	
[1] Recommendation based on low or very low-quality evidence.		
[2] Recommended standard initial infusion rate: 0.1 mg/kg/hour		
[3] Recommendation based on manufacturer's labeling.		
Note: The initial bolus should either be omitted, or in the case of perceived life- or limb-threatening thrombosis, be given at a reduced dose of 0.2 mg/kg.		

Calculations

- Creatinine Clearance: Adults

Administration: I.V.I.V. bolus: Inject slowly for continuous infusion; solutions with 0.2 or 0.4 mg/mL may be used.

Administration: OralAdminister **only** intravenously

Storage

Intact vials should be stored at 2°C to 25°C (36°F to 77°F). Manufacturer recommends using reconstituted solution immediately after preparation. Reconstituted solutions of lepirudin are stable for 24 hours at room temperature.

Reconstitution

Intravenous bolus: Use a solution with a concentration of 5 mg/mL: Reconstitute one vial (50 mg) of lepirudin with 1 mL of sterile water for injection or 0.9% sodium chloride injection. The final concentration of 5 mg/mL is obtained by transferring the contents of the vial into a sterile, single-use syringe (of at least 10 mL capacity) and diluting the solution to a total volume of 10 mL using sterile water for injection, 0.9% sodium chloride, or 5% dextrose in water.

Intravenous infusion: For continuous intravenous infusion, solutions with concentrations of 0.2 or 0.4 mg/mL may be used. Reconstitute 2 vials (50 mg each) of lepirudin with 1 mL each using either sterile water for injection or 0.9% sodium chloride injection. The final concentration of 0.2 mg/mL or 0.4 mg/mL is obtained by transferring the contents of both vials into an infusion bag containing 500 mL or 250 mL of 0.9% sodium chloride injection or 5% dextrose injection.

CompatibilityStable in D_5W, NS.

Y-site administration: Visually compatible (Chalmers, 2001): Amiodarone.

ContraindicationsHypersensitivity to hirudins or any component of the formulation

Allergy Considerations

- Hirudin Derivatives Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Allergic and hypersensitivity reactions, including anaphylaxis have been reported. Be cautious in re-exposing patients (anaphylaxis has been reported).

- Bleeding: The most common complication is bleeding. Certain patients are at increased risk of bleeding; risk factors include bacterial endocarditis; congenital or acquired bleeding disorders; recent puncture of large vessels or organ biopsy; recent CVA, stroke, intracerebral surgery, or other neuraxial procedure; severe uncontrolled hypertension; renal impairment; recent major surgery; recent major bleeding (intracranial, GI, intraocular, or pulmonary). Monitor for signs and symptoms of bleeding.

Disease-related concerns:

- Cirrhosis: Use with caution in patients with cirrhosis.

- Renal impairment: Use with caution in patients with renal impairment, relative overdose might occur even with standard dosage regimen. The bolus dose and rate of infusion must be reduced in patients with known or suspected renal insufficiency.

- Thrombolytic episode: Cautiously administer after a thrombolytic episode; risk of intracranial bleeding.

Concurrent drug therapy issues:

- Streptokinase: Allergic reactions may occur frequently in patients treated concomitantly with streptokinase.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Monitoring: Strict monitoring of aPTT is required; formation of antihirudin antibodies can increase the anticoagulant effect of lepirudin.

Pregnancy Risk FactorB

Pregnancy ConsiderationsLepirudin crosses the placenta in pregnant rats; however, it is not known if lepirudin crosses the placenta in humans.

LactationEnters breast milk/consult prescriber

Adverse ReactionsAs with all anticoagulants, bleeding is the most common adverse event associated with lepirudin. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables.

HIT patients:

>10%: Hematologic: Anemia (12%), bleeding from puncture sites (11%), hematoma (11%)

1% to 10%:

Cardiovascular: Heart failure (3%), pericardial effusion (1%), ventricular fibrillation (1%)

Central nervous system: Fever (7%)

Dermatologic: Maculopapular rash (4%), eczema (3%)

Gastrointestinal: GI bleeding/rectal bleeding (5%)

Genitourinary: Vaginal bleeding (2%)

Hepatic: Transaminases increased (6%)

Renal: Hematuria (4%)

Respiratory: Epistaxis (4%)

<1% (Limited to important or life-threatening): Allergic reactions, anaphylaxis, hemoperitoneum, hemoptysis, intracranial bleeding, liver bleeding, pulmonary bleeding, retroperitoneal bleeding, mouth bleeding, pruritus, urticaria, injection site reactions, thrombocytopenia

Non-HIT populations (including those receiving thrombolytics and/or contrast media):

1% to 10%: Respiratory: Bronchospasm/stridor/dyspnea/cough

<1% (Limited to important or life-threatening): Angioedema, laryngeal edema, tongue edema, intracranial bleeding (0.6%), allergic reactions (unspecified), anaphylactoid reactions, anaphylaxis, thrombocytopenia

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid cat's claw, dong quai, evening primrose, feverfew, garlic, ginger, ginkgo, red clover, horse chestnut, green tea, ginseng (all have additional antiplatelet activity)

Test InteractionsPT/INR levels may become elevated in the absence of warfarin. If warfarin is initiated, initial PT/INR goals while on lepirudin may require modification.

Monitoring ParametersMonitor aPTT levels; obtain baseline aPTT, then monitor first aPTT 4 hours after the start of the infusion and every 4 hours until steady state is reached (2 consecutive aPTTs in the same range) (Warkentin, 2008). Subsequent determinations of aPTT should be obtained at least once daily during treatment. More frequent monitoring is recommended in renally- or hepatically-impaired patients. Any aPTT ratio measurement out of range (1.5-2.5) should be confirmed prior to adjusting dose, unless a clinical need for immediate reaction exists

Reference RangeaPTT 1.5 to 2.5 times the control value

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (especially anything that will affect coagulation or platelet function). Note Administration for infusion specifics. Bleeding precautions should be observed. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, hypersensitivity reaction, bleeding, chest pain, rash) regularly during therapy. Teach possible side effects/appropriate interventions (eg, bleeding precautions) and adverse symptoms to report.

Monitoring: Lab TestsMonitor aPTT levels; obtain baseline aPTT, then monitor first aPTT 4 hours after the start of the infusion and every 4 hours until steady state is reached (2 consecutive aPTTs in the same range) (Warkentin, 2008). Subsequent determinations of aPTT should be obtained at least once daily during treatment. More frequent monitoring is recommended in renally- or hepatically-impaired patients. Any aPTT ratio measurement out of range (1.5-2.5) should be confirmed prior to adjusting dose, unless a clinical need for immediate reaction exists

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug can only be administered by infusion. Report immediately any pain, swelling, burning, or bleeding at infusion site. You may have a tendency to bleed easily while taking this drug (brush teeth with soft brush, floss with waxed floss, use electric razor, avoid scissors or sharp knives, and avoid potentially harmful activities). Report unusual bleeding or bruising (bleeding gums, nosebleed, blood in urine, dark stool); pain in joints or back; CNS changes (fever, confusion); unusual fever; persistent nausea or GI upset; or swelling or pain at injection site. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 50 mg

Generic AvailableNo

Mechanism of ActionLepirudin is a highly specific direct inhibitor of thrombin; lepirudin is a recombinant hirudin derived from yeast cells

Pharmacodynamics/Kinetics

Distribution: Two-compartment model; confined to extracellular fluids.

Metabolism: Via release of amino acids via catabolic hydrolysis of parent drug

Half-life elimination: Initial: ~10 minutes: Terminal: Healthy volunteers: 1.3 hours; Marked renal impairment (Cl_{cr} <15 mL/minute and on hemodialysis): ≤2 days

Excretion: Urine (~48%, 35% as unchanged drug and unchanged drug fragments of parent drug); systemic clearance is proportional to glomerular filtration rate or creatinine clearance

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentContraindicated in patients with a recent stroke

Cardiovascular Considerations

Heparin-Induced Thrombocytopenia (HIT): In a case series of 9 patients with HIT, the combination of intravenous lepirudin and a GPIIb/IIIa inhibitor was safe and effective during PCI (Pinto DS, 2003). Another case report describes use in patients with HIT during cardiopulmonary bypass (Liu H, 2002). During prolonged treatment (>5 days) in HIT patients, anticoagulant activity should be monitored daily (Eichler P, 2000). Antihirudin antibodies develop frequently and may enhance lepirudin's activity. In this trial, about half of the patients who developed antihirudin antibodies required a 45% (range: 17% to 90%) decrease in dose.

Subcutaneous Administration of Lepirudin: Initial data for the subcutaneous administration of lepirudin shows promise. A multicenter, prospective, dose-ranging trial of lepirudin for the treatment of deep venous thrombosis demonstrated that a dose of lepirudin 1.25 mg/kg every 12 hours was safe and effective at reducing the incidence of subsequent thromboembolic events when compared to heparin; however, this trial was small with only 155 patients enrolled (Schiele F, 1997). Another small trial of 19 patients with either heparin-induced thrombocytopenia (HIT) and thromboembolism, isolated HIT, or history of HIT and needing interruption of oral anticoagulation, evaluated the subcutaneous administration of lepirudin at a dose of 25 mg twice daily (Hule G, 2000). Patients with HIT and thromboembolic complications were administered continuous intravenous lepirudin to maintain a therapeutic aPTT for the first 10 days of therapy then switch to subcutaneous lepirudin. The authors found that administration of subcutaneous lepirudin was safe and effective. One important observation was 63% of patients developed antibodies to lepirudin prolonging the peak and trough aPTTs when compared to the group without antibodies to lepirudin. The duration of administration ranged from 20-26 days. Based on these trials, there is emerging evidence that subcutaneous administration of lepirudin may be safe and effective; however, large trials are needed to fully describe how to utilize this therapy.

Anaphylaxis: Fatal anaphylactic reactions have been reported in patients re-exposed to lepirudin in a second or subsequent treatment course. Consider alternative treatment options. Since these reactions are immune-mediated, patient with recent exposure to hirudins may be at increased risk.

Anesthesia and Critical Care Concerns/Other Considerations

Evidence-Based Information:

Heparin-Induced Thrombocytopenia (HIT): In a case series of 9 patients with HIT, the combination of lepirudin and a GP IIb/IIIa inhibitor was safe and effective during PCI (Pinto, 2003). Another case report describes use in patients with HIT during cardiopulmonary bypass (Liu, 2002). During prolonged treatment (>5 days) in HIT patients, anticoagulant activity should be monitored daily (Eichler, 2000). Antihirudin antibodies develop frequently and may enhance lepirudin's activity. In this trial, about half of the patients who developed antihirudin antibodies required a 45% (range: 17% to 90%) decrease in dose.

The American College of Chest Physicians Evidence Based Clinical Practice Guidelines (8th Edition, 2008) recommend reducing the initial lepirudin dose based on serum creatinine concentrations (Cr) for the treatment of heparin-induced thrombocytopenia (see Dosing: Renal Impairment).

Index TermsLepirudin (rDNA); Recombinant Hirudin

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International Brand NamesRefludan (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, HU, IE, IT, NL, NO, PL, PT, RU, SE, TR)

Letrozole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Femara® may be confused with Famvir®, femhrt®, Provera®

Letrozole may be confused with anastrozole

Pronunciation(LET roe zole)
U.S. Brand NamesFemara®
Canadian Brand NamesFemara®
Pharmacologic CategoryAntineoplastic Agent, Aromatase Inhibitor
Use: Labeled IndicationsFor use in postmenopausal women in the adjuvant treatment of hormone receptor positive early breast cancer, extended adjuvant treatment of early breast cancer after 5 years of tamoxifen, advanced breast cancer with disease progression following antiestrogen therapy, hormone receptor positive or hormone receptor unknown, locally-advanced, or metastatic breast cancer
Use: Unlabeled/InvestigationalTreatment of ovarian (epithelial) cancer, endometrial cancer
Dosing: Adults

Breast cancer: Females: Oral: 2.5 mg once daily

Ovarian (epithelial) cancer (unlabeled use): Oral: 2.5 mg once daily (Ramirez, 2008)

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo dosage adjustment is required in patients with renal impairment if Cl_{cr} is ≥10 mL/minute.
Dosing: Hepatic Impairment

Mild-to-moderate impairment (Child-Pugh class A and B): No adjustment recommended

Severe impairment (Child-Pugh class C): 2.5 mg every other day

Administration: OralAdminister with or without food.
Dietary ConsiderationsMay be taken without regard to meals. Calcium and vitamin D supplementation are recommended.
StorageStore at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to letrozole or any component of the formulation; women of premenopausal endocrine status
Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- CNS depression: May cause dizziness, fatigue, and somnolence; patients should be cautioned before performing tasks which require mental alertness (eg, operating machinery or driving).

- Decreased bone mineral density: May cause decreases in bone mineral density.

- Increased cholesterol: May increase total serum cholesterol.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dose adjustment may be required. Increases in transaminases ≥5 times the upper limit of normal and in bilirubin ≥1.5 times the upper limit of normal were most often, but not always, associated with metastatic liver disease.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo dosage adjustment recommended.
Pregnancy Risk FactorD
Pregnancy ConsiderationsLetrozole may cause fetal harm when administered to pregnant women. Animal studies have demonstrated embryotoxicity and fetotoxicity. There are no adequate and well-controlled studies in pregnant women. If used in pregnancy, or if patient becomes pregnant during treatment, the patient should be apprised of potential hazard to the fetus. Letrozole is FDA indicated for postmenopausal women only. Women who are perimenopausal or recently postmenopausal should use adequate contraception until postmenopausal status is fully established.
LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Cardiovascular: Edema (7% to 18%)

Central nervous system: Headache (4% to 20%), dizziness (2% to 14%), fatigue (6% to 13%)

Endocrine & metabolic: Hot flashes (5% to 50%), hypercholesterolemia (3% to 16%)

Gastrointestinal: Nausea (9% to 17%), constipation (2% to 11%), weight gain (2% to 11%)

Neuromuscular & skeletal: Weakness (4% to 34%), bone pain (22%), arthralgia (8% to 22%), arthritis (7% to 21%), back pain (5% to 18%)

Respiratory: Dyspnea (6% to 18%), cough (5% to 13%)

Miscellaneous: Diaphoresis (≤24%), night sweats (14%)

2% to 10%:

Cardiovascular: Chest pain (3% to 8%), hypertension (5% to 8%), peripheral edema (5%)

Central nervous system: Insomnia (6% to 7%), pain (5%), somnolence (2% to 3%), depression (<5%), anxiety (<5%), vertigo (<5%)

Dermatologic: Rash (4% to 5%), alopecia (<5%), pruritus (1% to 2%)

Endocrine & metabolic: Breast pain (7%), hypercalcemia (<5%)

Gastrointestinal: Diarrhea (5% to 8%), vomiting (3% to 7%), weight loss (7%), abdominal pain (5% to 6%), anorexia (3% to 5%), dyspepsia (3% to 4%)

Genitourinary: Urinary tract infection (6%), vaginal bleeding (5%), vaginal dryness (5%), vaginal hemorrhage (5%), vaginal irritation (4%)

Hepatic: Transaminases increased (≤3%)

Neuromuscular & skeletal: Limb pain (10%), myalgia (6% to 7%), bone fractures (≤6%), bone mineral density decreased/osteoporosis (2% to 7%)

Renal: Renal disorder (5%)

Respiratory: Pleural effusion (<5%)

Miscellaneous: Infection (7%), flu (6%), viral infection (5% to 6%)

<2%, postmarketing, and/or case reports: Anaphylactic reaction, angina, angioedema, appetite increase, arterial thrombosis, bilirubin increased, blurred vision, cardiac ischemia, cardiac failure, cataract, coronary artery disease, dry skin, dysesthesia, endometrial cancer, endometrial proliferation disorder, eye irritation, fever, hemiparesis, hemorrhagic stroke, hypoesthesia, irritability, leukopenia, lymphopenia, MI, memory impairment, nervousness, palpitations, paresthesia, portal vein thrombosis, pulmonary embolism, secondary malignancy, stomatitis, tachycardia, taste disturbance, thirst, thrombocytopenia, thrombophlebitis, thromboembolic event, thrombotic stroke, transient ischemic attack, urinary frequency increased, urticaria, vaginal discharge, venous thrombosis, xerostomia

Oncology: Emetic PotentialLow (10% to 30%)

Metabolism/Transport Effects**Substrate** (minor) of CYP2A6, 3A4; **Inhibits** CYP2A6 (strong), 2C19 (weak)

Drug Interactions

CYP2A6 Substrates: CYP2A6 Inhibitors (Strong) may decrease the metabolism of CYP2A6 Substrates. *Risk D: Consider therapy modification*

Tamoxifen: May decrease the serum concentration of Letrozole. *Risk C: Monitor therapy*

Monitoring ParametersMonitor periodically during therapy: Complete blood counts, thyroid function tests; serum electrolytes, cholesterol, transaminases, and creatinine; blood pressure; bone density

Nursing: Physical Assessment/MonitoringFor use in postmenopausal women only. Assess potential for interactions or toxicity with other pharmacological agents or herbal products patient may be taking. Evaluate results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, hypertension, pain, gastrointestinal upset, hot flashes) on a regular basis throughout therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC, cholesterol, thyroid function tests, serum electrolytes, serum transaminases, serum creatinine

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take exactly as directed. You may experience nausea, vomiting, hot flashes, or loss of appetite (frequent mouth care, small, frequent meals, chewing gum, or sucking lozenges may help); musculoskeletal pain or headache (consult prescriber for analgesics relief); sleepiness, fatigue, or dizziness (use caution when driving, climbing stairs, or engaging in tasks that require alertness until response to drug is known); constipation (increased exercise or dietary fruit or fluids may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or loss of hair (will grow back). Report chest pain, pressure, palpitations, or swollen extremities; weakness, severe headache, numbness, or loss of strength in any part of the body; difficulty speaking; vaginal bleeding; unusual signs of bleeding or bruising; respiratory difficulty; severe nausea; or muscle pain; or skin rash.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Femara®: 2.5 mg

Generic AvailableNo

ManufacturerNovartis Pharmaceuticals Corp
Pricing: U.S. (www.drugstore.com)

Tablets (Femara)

2.5 mg (10): $126.93

Mechanism of ActionNonsteroidal competitive inhibitor of the aromatase enzyme system which binds to the heme group of aromatase, a cytochrome P450 enzyme which catalyzes conversion of androgens to estrogens (specifically, androstenedione to estrone and testosterone to estradiol). This leads to inhibition of the enzyme and a significant reduction in plasma estrogen (estrone, estradiol and estrone sulfate) levels. Does not affect synthesis of adrenal or thyroid hormones, aldosterone, or androgens.
Pharmacodynamics/Kinetics

Absorption: Rapid and well absorbed; not affected by food

Distribution: V_d: ~1.9 L/kg

Protein binding, plasma: Weak

Metabolism: Hepatic via CYP3A4 and 2A6 to an inactive carbinol metabolite

Half-life elimination: Terminal: ~2 days

Time to steady state, plasma: 2-6 weeks

Excretion: Urine (90%; 6% as unchanged drug, 75% as glucuronide carbinol metabolite, 9% as unidentified metabolites)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsCGS-20267; NSC-719345
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International Brand NamesFemar (NO); Femara (AE, AR, AT, AU, BD, BE, BG, BH, BO, BR, CH, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EE, EG, ES, FI, FR, GB, GT, HK, HN, HU, ID, IE, IL, IN, IQ, IR, IT, JO, JP, KP, KW, LB, LY, MX, MY, NI, NL, OM, PA, PE, PH, PK, PL, PR, PT, PY, QA, SA, SE, SG, SV, SY, TH, TW, UY, VE, YE); Trozet (IN)

Leucovorin Calcium

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Leucovorin may be confused with Leukeran®, Leukine®, LEVOleucovorin

Folinic acid may be confused with folic acid

Folinic acid is an error prone synonym and should not be used

Pronunciation(loo koe VOR in KAL see um)

Pharmacologic CategoryAntidote; Chemotherapy Modulating Agent; Rescue Agent (Chemotherapy); Vitamin, Water Soluble

Use: Labeled IndicationsAntidote for folic acid antagonists (methotrexate, trimethoprim, pyrimethamine) and rescue therapy following high-dose methotrexate; in combination with fluorouracil in the treatment of colon cancer; treatment of megaloblastic anemias when folate is deficient as in infancy, sprue, pregnancy, and nutritional deficiency when oral folate therapy is not possible

Use: Unlabeled/InvestigationalI.T. administration following I.T. methotrexate overdose; adjunctive cofactor therapy in methanol toxicity

Dosing: Adults

Treatment of folic acid antagonist overdosage: Oral: 5-15 mg/day

Folate-deficient megaloblastic anemia: I.M.: ≤1 mg/day

High-dose methotrexate-rescue dose: Initial: Oral, I.M., I.V.: 15 mg (~10 mg/m^2); start 24 hours after beginning methotrexate infusion; continue every 6 hours for 10 doses, until methotrexate level is <0.05 micromole/L. Adjust dose as follows:

Normal methotrexate elimination: Oral, I.M., I.V.: 15 mg every 6 hours

Delayed early methotrexate elimination: I.V.: 150 mg every 3 hours until methotrexate level is <1 micromole/L, then 15 mg every 3 hours until methotrexate level is <0.05 micromole/L

Colorectal cancer (also refer to Combination Regimens):

I.V.: 200 mg/m^2 over at least 3 minutes (used in combination with fluorouracil 370 mg/m^2)

or

I.V.: 20 mg/m^2 (used in combination with fluorouracil 425 mg/m^2)

Pemetrexed toxicity (unlabeled dose): I.V.: 100 mg/m^2 once, followed by 50 mg/m^2 every 6 hours for 8 days was used in clinical trial for CTC grade 4 leukopenia ≥3 days; CTC grade 4 neutropenia ≥3 days; immediately for CTC grade 4 thrombocytopenia, bleeding associated with grade 3 thrombocytopenia, or grade 3 or 4 mucositis

Cofactor therapy in methanol toxicity (unlabeled use): I.V.: 50 mg every 4-6 hours. Therapy should continue until methanol and formic acid have been completely eliminated.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Treatment of folic acid antagonist overdosage: Refer to adult dosing.

Folate-deficient megaloblastic anemia: Refer to adult dosing.

High-dose methotrexate-rescue dose: Refer to adult dosing.

Dosing: Combination Regimens

Bladder cancer: MVAC (Bladder Cancer)

Breast cancer:

MF

MVAC (Breast Cancer)

NFL

Colorectal cancer:

- Bevacizumab-Fluorouracil-Leucovorin
- Bevacizumab-Irinotecan-Fluorouracil-Leucovorin
- Bevacizumab-Oxaliplatin-Fluorouracil-Leucovorin
- Cetuximab-FOLFOX4
- FLOX (Nordic FLOX)
- Fluorouracil-Leucovorin
- Fluorouracil-Leucovorin-Irinotecan (Saltz Regimen)
- FOIL
- FOLFOX 2
- FOLFOX 3
- FOLFOX 4
- FOLFOX 7
- FU-LV-CPT-11
- PFL (Colorectal Cancer)

Gastric cancer:

- ELF
- FAMTX

Gestational trophoblastic tumor:

- CHAMOCA (Modified Bagshawe Regimen)
- CHAMOMA (Bagshawe Regimen)
- EMA/CO
- EP/EMA

Head and neck cancer:

- PFL (Head and Neck Cancer)
- PFL + IFN

Leukemia, acute lymphocytic:

- Hyper-CVAD + Imatinib
- Hyper-CVAD (Leukemia, Acute Lymphocytic)
- Linker Protocol
- PVA (POG 8602)

Lymphoma, non-Hodgkin's:

- CODOX-M/IVAC
- COMLA
- Hyper-CVAD (Lymphoma, non-Hodgkin's)
- MACOP-B
- m-BACOD
- Pro-MACE-CytaBOM

Lymphoma, non-Hodgkin's (Burkitt's): CODOX-M/IVAC

Lymphoma, non-Hodgkin's: (Mantle cell): Hyper-CVAD + Rituximab

Osteosarcoma:

- HDMTX
- MTX-CDDPAdr
- POG-8651

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Due to calcium content, do not administer I.V. solutions at a rate >160 mg/ minute.

Refer to individual protocols. Should be administered I.M., I.V. push, or I.V. infusion (15 minutes to 2 hours). Leucovorin should not be administered concurrently with methotrexate. It is commonly initiated 24 hours after the start of methotrexate. Toxicity to normal tissues may be irreversible if leucovorin is not initiated by ~40 hours after the start of methotrexate.

As a rescue after folate antagonists: Administer by I.V. bolus, I.M., or orally.

In combination with fluorouracil: Fluorouracil activity, the fluorouracil is usually given after, or at the midpoint, of the leucovorin infusion. Leucovorin is usually administered by I.V. bolus injection or short (10-120 minutes) I.V. infusion. Other administration schedules have been used; refer to individual protocols.

Administration: I.V. DetailpH: 8.1 (vials)

Administration: OralDo not administer orally in the presence of nausea or vomiting. Doses >25 mg should be administered parenterally.

Dietary ConsiderationsSolutions for injection contain calcium 0.004 mEq per leucovorin 1 mg

Storage

Powder for injection: Store at room temperature of 25°C (77°F). Protect from light. Solutions reconstituted with bacteriostatic water for injection U.S.P., must be used within 7 days. Solutions reconstituted with SWFI must be used immediately. Parenteral admixture is stable for 24 hours stored at room temperature (25°C) and for 4 days when stored under refrigeration (4°C).

Solution for injection: Prior to dilution, store vials under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light.

Tablet: Store at room temperature of 15°C to 30°C (59°F to 86°F).

ReconstitutionPowder for injection: Reconstitute with SWFI or BWFI; dilute in 100-1000 mL NS, D_5W for infusion. When doses >10 mg/m^2 are required, reconstitute using sterile water for injection, not a solution containing benzyl alcohol.

CompatibilityStable in D_{10}NS, D_5W, D_{10}W, LR, sterile water for injection, bacteriostatic water, bacteriostatic NS; **variable stability (consult detailed reference)** in NS.

Y-site administration: Compatible: Amifostine, aztreonam, bleomycin, cefepime, cisplatin, cladribine, cyclophosphamide, docetaxel, doxorubicin, doxorubicin liposome, etoposide phosphate, filgrastim, fluconazole, fluorouracil, furosemide, gatifloxacin, gemcitabine, granisetron, heparin, irinotecan, linezolid, methotrexate, metoclopramide, mitomycin, piperacillin/tazobactam, tacrolimus, teniposide, thiotepa, vinblastine, vincristine. **Incompatible:** Amphotericin B cholesteryl sulfate complex, droperidol, foscarnet, sodium bicarbonate.

Compatibility in syringe: Compatible: Bleomycin, cisplatin, cyclophosphamide, doxorubicin, fluorouracil, furosemide, heparin, methotrexate, metoclopramide, mitomycin, vinblastine, vincristine. **Incompatible:** Droperidol.

Compatibility when admixed: Compatible: Cisplatin, cisplatin with floxuridine, floxuridine. **Incompatible:** Concentrations >2 mg/mL of leucovorin and >25 mg/mL of fluorouracil.

ContraindicationsPernicious anemia or vitamin B_{12}-deficient megaloblastic anemias

Warnings/Precautions

Concurrent drug therapy issues:

- Fluorouracil: Leucovorin may increase the toxicity of 5-fluorouracil; dose of 5-fluorouracil may need decreased.
- Sulfamethoxazole-trimethoprim: Combination of leucovorin and sulfamethoxazole-trimethoprim for the acute treatment of PCP in patients with HIV infection has been reported to cause increased rates of treatment failure.

Dosage form specific issues:

- Powder for injection: When doses >10 mg/m^2 are required, reconstitute using sterile water for injection, not a solution containing benzyl alcohol.
- Injection: Due to calcium content, do not administer I.V. solutions at a rate >160 mg/minute. Not intended for intrathecal use.

Other warnings and precautions:

- Folic acid antagonist overdose: When used for the treatment of accidental folic acid antagonist overdose, administer as soon as possible.
- Methotrexate rescue therapy: Methotrexate serum concentrations should be monitored to determine dose and duration of leucovorin therapy. Dose may need increased or administration prolonged in situations where methotrexate excretion may be delayed (eg, ascites, pleural effusion, renal insufficiency, inadequate hydration)

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Leucovorin is a biologically active form of folic acid. Adequate amounts of folic acid are recommended during pregnancy. Refer to Folic Acid monograph.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsLeucovorin is a biologically active form of folic acid. Adequate amounts of folic acid are recommended in breast-feeding women. Refer to Folic Acid monograph.

Adverse ReactionsFrequency not defined. Toxicities (especially gastrointestinal toxicity) of fluorouracil is higher when used in combination with leucovorin.

Dermatologic: Rash, pruritus, erythema, urticaria

Hematologic: Thrombocytosis

Respiratory: Wheezing

Miscellaneous: Allergic reactions, anaphylactoid reactions

Oncology: VesicantNo
Oncology: Emetic PotentialLow
Drug Interactions

Capecitabine: Leucovorin-Levoleucovorin may enhance the adverse/toxic effect of Capecitabine. *Risk C: Monitor therapy*

Fluorouracil: Leucovorin-Levoleucovorin may enhance the adverse/toxic effect of Fluorouracil. This effect is associated with the ability of leucovorin or levoleucovorin to enhance the anticancer effects of fluorouracil. *Risk C: Monitor therapy*

PHENobarbital: Leucovorin-Levoleucovorin may decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Phenytoin: Leucovorin-Levoleucovorin may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Primidone: Leucovorin-Levoleucovorin may decrease the serum concentration of Primidone. Additionally, leucovorin/levoleucovorin may decrease concentrations of active metabolites of primidone (e.g., phenobarbital). *Risk C: Monitor therapy*

Raltitrexed: Leucovorin-Levoleucovorin may diminish the therapeutic effect of Raltitrexed. *Risk X: Avoid combination*

Trimethoprim: Leucovorin-Levoleucovorin may diminish the therapeutic effect of Trimethoprim. *Risk D: Consider therapy modification*

Monitoring Parameters

High-dose methotrexate therapy: Plasma methotrexate concentration; leucovorin is continued until the plasma methotrexate level <0.05 micromole/L. With 4- to 6-hour high-dose methotrexate infusions, plasma drug values in excess of 50 and 1 micromole/L at 24 and 48 hours after starting the infusion, respectively, are often predictive of delayed methotrexate clearance.

Fluorouracil therapy: CBC with differential and platelets, liver function tests, electrolytes

Nursing: Physical Assessment/MonitoringAssess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report. Monitor laboratory tests, adverse reactions, and therapeutic response.
Monitoring: Lab Tests

High-dose methotrexate therapy: Plasma methotrexate concentration; leucovorin is continued until the plasma methotrexate level <0.05 micromole/L. With 4- to 6-hour high-dose methotrexate infusions, plasma drug values in excess of 50 and 1 micromole/L at 24 and 48 hours after starting the infusion, respectively, are often predictive of delayed methotrexate clearance.

Fluorouracil therapy: CBC with differential and platelets, liver function tests, electrolytes

Patient EducationTake as directed, at evenly spaced intervals around-the-clock. Maintain hydration (2-3 L of water/day while taking for rescue therapy). For folic acid deficiency, eat foods high in folic acid (eg, meat proteins, bran, dried beans, asparagus, green leafy vegetables). Report respiratory difficulty, lethargy, or rash or itching. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. **Note:** Strength expressed as base

Injection, powder for reconstitution: 50 mg, 100 mg, 200 mg, 350 mg

Injection, solution [preservative free]: 10 mg/mL (50 mL)

Tablet: 5 mg, 10 mg, 15 mg, 25 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Leucovorin Calcium)

10 mg (24): $152.99

Mechanism of ActionA reduced form of folic acid, leucovorin supplies the necessary cofactor blocked by methotrexate, enters the cells via the same active transport system as methotrexate. Stabilizes the binding of 5-dUMP and thymidylate synthetase, enhancing the activity of fluorouracil.

Methanol toxicity treatment: Formic acid (methanol’s toxic metabolite) is normally metabolized to carbon dioxide and water by 10-formyltetrahydrofolate dehydrogenase after being bound to tetrahydrofolate. Administering a source of tetrahydrofolate may aid the body in eliminating formic acid.

Pharmacodynamics/Kinetics

Absorption: Oral, I.M.: Well absorbed

Metabolism: Intestinal mucosa and hepatically to 5-methyl-tetrahydrofolate (5MTHF; active)

Bioavailability: Saturable at oral doses >25 mg; 25 mg (97%), 50 mg (75%), 100 mg (37%)

Half-life elimination: ~4-8 hours

Time to peak: Oral: ~2 hours; I.V.: Total folates: 10 minutes; 5MTHF: ~1 hour

Excretion: Urine (primarily); feces

Related Information

- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index Terms5-Formyl Tetrahydrofolate; Calcium Leucovorin; Citrovorum Factor; Folinic Acid (error prone synonym)
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International Brand NamesAcido Folinico/Leucovorina (CN); Antrex (FI, PL); Asovorin (AR); Calciumfolinat Faulding (SE); Calciumfolinat Pharmalink (SE); Calciumfolinat ”Faulding” (DK); Calciumfolinat-Ebewe (PL, TW); Calfonat (DK); Dalisol (MX); Estroquin (PE); Folina 15 (TH, TW); Folinato de Calcio Dakota Farma (PT); Kalcij-folinat (HR); Lederfolin (ES, IE, IT); Lederfoline (FR, PT); Ledervorin Calcium (BE, LU, NL); Leucocalcin (PY); Leuconolver (VE); Leucovorin (AT, BG, CH, DE, GR, IE, IL, NZ, PL, TH, UY); Leucovorin Ca (PL); Leucovorin Calcium (AU, CZ, HK, HN, ID, IN, MY, TH); Leucovorine Abic (NL); Lovorin (PH); Medifolin (PT); Medsavorina (MX); Nyrin (KP, MY); Refolinon (GB, LU); Rescufolin (NO); Rescuvolin (BE, CH, DK, GR, ID, LU, PH, SE, TH); Robin (KP); Rontafur (AR); Tecnovorin (BR, EC)

Leuprolide

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Lupron® may be confused with Nuprin®

Lupron Depot®-3 Month may be confused with Lupron Depot-Ped®

Pronunciation(loo PROE lide)

U.S. Brand NamesEligard®; Lupron Depot-Ped®; Lupron Depot®; Lupron®; Viadur® [DSC]

Canadian Brand NamesEligard®; Lupron®; Lupron® Depot®; Viadur®

Pharmacologic CategoryAntineoplastic Agent, Gonadotropin-Releasing Hormone Agonist; Gonadotropin Releasing Hormone Agonist

Use: Labeled IndicationsPalliative treatment of advanced prostate cancer; management of endometriosis; treatment of anemia caused by uterine leiomyomata (fibroids); central precocious puberty

Use: Unlabeled/InvestigationalTreatment of breast, ovarian, and endometrial cancer; infertility; prostatic hyperplasia

Dosing: Adults

Advanced prostate cancer:

SubQ:

Eligard®: 7.5 mg monthly **or** 22.5 mg every 3 months **or** 30 mg every 4 months **or** 45 mg every 6 months

Lupron®: 1 mg/day

Viadur®: 65 mg implanted subcutaneously every 12 months

I.M.:

Lupron Depot®: 7.5 mg/dose given monthly (every 28-33 days) **or**

Lupron Depot®-3: 22.5 mg every 3 months **or**

Lupron Depot®-4: 30 mg every 4 months

Breast cancer, premenopausal ovarian ablation (unlabeled use): I.M.:

Lupron Depot®: 3.75 mg every 28 days **or**

Lupron Depot®-3: 11.25 mg every 3 months

Endometriosis: I.M.: Initial therapy may be with leuprolide alone or in combination with norethindrone; if retreatment for an additional 6 months is necessary, norethindrone should be used. Retreatment is not recommended for longer than one additional 6-month course.

Lupron Depot®: 3.75 mg/month for up to 6 months **or**

Lupron Depot®-3: 11.25 mg every 3 months for up to 2 doses (6 months total duration of treatment)

Uterine leiomyomata (fibroids): I.M. (in combination with iron):

Lupron Depot®: 3.75 mg/month for up to 3 months **or**

Lupron Depot®-3: 11.25 mg as a single injection

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Precocious puberty (consider discontinuing by age 11 for females and by age 12 for males):

SubQ (Lupron®): Initial: 50 mcg/kg/day (per manufacturer, doses of 20-45 mcg/kg/day have also been reported); titrate dose upward by 10 mcg/kg/day if down-regulation is not achieved

I.M. (Lupron Depot-Ped®): 0.3 mg/kg/dose given every 28 days (minimum dose: 7.5 mg)

≤25 kg: 7.5 mg

>25-37.5 kg: 11.25 mg

>37.5 kg: 15 mg

Titrate dose upward in increments of 3.75 mg every 4 weeks if down-regulation is not achieved.

Dosing: Combination Regimens

Prostate cancer:

Bicalutamide + LHRH-A

FL

Administration: I.M.Lupron Depot®: Vary injection site periodically

Administration: Other

SubQ:

Eligard®: Vary injection site; choose site with adequate subcutaneous tissue (eg, abdomen, upper buttocks)

Lupron®: Vary injection site; if an alternate syringe from the syringe provided is required, insulin syringes should be used

Implant (Viadur®): Requires surgical implantation (subcutaneous) and removal at 12-month intervals

Storage

Lupron®: Store unopened vials of injection in refrigerator, vial in use can be kept at room temperature of ≤30°C (86°F) for several months with minimal loss of potency. Protect from light and store vial in carton until use. Do not freeze.

Eligard®: Store at 2°C to 8°C (36°F to 46°C). Allow to reach room temperature prior to using; once mixed, must be administered within 30 minutes.

Lupron Depot® may be stored at room temperature of 15°C to 30°C (59°F to 86°F). Upon reconstitution, the suspension does not contain a preservative and should be used immediately.

Viadur® may be stored at room temperature of 15°C to 30°C (59°F and 86°F).

Reconstitution

Eligard®: Packaged in two syringes; one contains the Atrigel® polymer system and the second contains leuprolide acetate powder; follow package instructions for mixing

Lupron Depot®: Reconstitute only with diluent provided

ContraindicationsHypersensitivity to leuprolide, GnRH, GnRH-agonist analogs, or any component of the formulation; undiagnosed abnormal vaginal bleeding; pregnancy; breast-feeding

Lupron Depot®-4 month (30 mg) is not indicated for use in women

Eligard® and Viadur® are contraindicated in women and children

Allergy Considerations

- GnRH Agonist Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Abnormal menses: Females treated for precocious puberty may experience menses or spotting during the first 2 months of treatment; notify healthcare provider if bleeding continues after the second month.
- Decreased bone density: Has been reported when used for ≥6 months.
- Endometriosis: Exacerbation of endometriosis or uterine leiomyomata may occur initially.
- Pituitary apoplexy: Rare cases of pituitary apoplexy (frequently secondary to pituitary adenoma) have been observed with leuprolide administration (onset from 1 hour to usually <2 weeks); may present as sudden headache, vomiting, visual or mental status changes, and infrequently cardiovascular collapse; immediate medical attention required.
- Spinal cord compression: Has been reported when used for prostate cancer; closely observe patients for weakness and paresthesias in first few weeks of therapy. Observe patients with metastatic vertebral lesions closely.
- Tumor flare: Transient increases in testosterone can lead to tumor flare, bone pain, hematuria, bladder outlet obstruction and neuropathy in prostate cancer patients during the first few weeks of therapy.
- Urinary tract obstruction: Has been reported when used for prostate cancer; closely observe patients for urinary tract obstruction and hematuria in first few weeks of therapy. Observe patients with urinary obstruction closely.

Disease-related concerns:

- Psychiatric illness: Use with caution in patients with a history of psychiatric illness; alteration in mood, memory impairment, and depression have been associated with use.

Dosage form specific issues:

- Vehicle used in injectable (polylactide-co-glycolide microspheres): Has rarely been associated with retinal artery occlusion in patients with abnormal arteriovenous anastomosis (eg, patent foramen ovale).

Geriatric ConsiderationsLeuprolide has the advantage of not increasing risk of atherosclerotic vascular disease, causing swelling of breasts, fluid retention, and thromboembolism as compared to estrogen therapy.

Pregnancy Risk FactorX

Pregnancy ConsiderationsPregnancy must be excluded prior to the start of treatment. Although leuprolide usually inhibits ovulation and stops menstruation, contraception is not ensured and a nonhormonal contraceptive should be used. Fetal abnormalities and increased fetal mortality have been noted in animal studies.

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions

Children:

2% to 10%:

Central nervous system: Pain (2%)

Dermatologic: Acne (2%), rash (2% including erythema multiforme), seborrhea (2%)

Genitourinary: Vaginitis (2%), vaginal bleeding (2%), vaginal discharge (2%)

Local: Injection site reaction (5%)

<2%: Alopecia, body odor, cervix disorder, dysphagia, emotional lability, epistaxis, fever, gingivitis, gynecomastia, headache, nausea, nervousness, peripheral edema, personality disorder, sexual maturity accelerated, skin striae, somnolence, syncope, urinary incontinence, vasodilation, vomiting, weight gain

Adults: Note: For prostate cancer treatment, an initial rise in serum testosterone concentrations may cause “tumor flare” or worsening of symptoms, including bone pain, neuropathy, hematuria, or ureteral or bladder outlet obstruction during the first 2 weeks. Similarly, an initial increase in estradiol levels, with a temporary worsening of symptoms, may occur in women treated with leuprolide.

Delayed release formulations:

10%:

Cardiovascular: Edema (≤14%)

Central nervous system: Headache (≤65%), pain (<2% to 33%), depression (≤31%), insomnia (≤31%), fatigue (≤17%), dizziness/vertigo (≤16%)

Dermatologic: Skin reaction (≤12%)

Endocrine & metabolic: Hot flashes (25% to 98%), testicular atrophy (≤20%), hyperlipidemia (≤12%), libido decreased (≤11%)

Gastrointestinal: Nausea/vomiting (≤25%), weight gain/loss (≤13%)

Genitourinary: Vaginitis (11% to 28%), urinary disorder (13% to 15%)

Local: Implant site bruising (35%), injection site burning/stinging (transient: ≤35%)

Neuromuscular & skeletal: Joint disorder (≤12%), weakness (≤12%)

Miscellaneous: Flu-like syndrome (≤12%)

1% to 10% (limited to important or life-threatening):

Cardiovascular: Angina (<5%), arrhythmia (<5%), atrial fibrillation (<5%), bradycardia (<5%), CHF (<5%), deep thrombophlebitis (<5%), hyper-/hypotension (<5%), palpitation (<5%), syncope (<5%), tachycardia (<5%)

Central nervous system: Nervousness (≤8%), anxiety (≤6%), confusion (<5%), delusions (<5%), dementia (<5%), fever (<5%), seizure (<5%)

Dermatologic: Acne (≤10%), alopecia (≤5%), bruising (≤5%), cellulitis (<5%), pruritus (≤3%), hirsutism (<2%), rash (<2%)

Endocrine & metabolic: Dehydration (≤8%), gynecomastia (≤7%), breast tenderness/pain (≤6%), bicarbonate decreased (≥5%), hyper-/hypocholesterolemia (≥5%), hyperglycemia (≥5%), hyperphosphatemia (≥5%), hyperuricemia (≥5%), hypoalbuminemia (≥5%), hypoproteinemia (≥5%), lactation (<5%), testicular pain (≤4%), menstrual disorder (≤2%)

Gastrointestinal: Dysphagia (<5%), gastrointestinal hemorrhage (<5%), intestinal obstruction (<5%), ulcer (<5%), gastroenteritis/colitis (≤3%), diarrhea (≤2%), constipation (≤2%)

Genitourinary: Prostatic acid phosphatase increased/decreased (≥5%), urine specific gravity increased/decreased (≥5%), impotence (≤5%), balanitis (<5%), incontinence (<5%), penile/testis disorder (<5%), urinary tract infection (<5%), nocturia (≤4%), polyuria (2% to 4%), bladder spasm (<2%), dysuria (<2%), erectile dysfunction (<2%), hematuria (<2%), urinary retention (<2%), urinary urgency (<2%)

Hematologic: Eosinophilia (≥5%), leukopenia (≥5%), platelets increased (≥5%), anemia

Hepatic: Liver function tests abnormal (≥5%), partial thromboplastin time increased (≥5%), prothrombin time increased (≥5%), hepatomegaly (<5%)

Local: Implant site reaction (persistent or delayed: 9% to 10%), implant site burning (6%), injection site pain (2% to 5%), injection site erythema (1% to 3%)

Neuromuscular & skeletal: Myalgia (≤8%), paresthesia (≤8%), neuropathy (<5%), paralysis (<5%), pathologic fracture (<5%), bone pain (<2%)

Renal: BUN increased (≥5%), creatinine increased (≥5%)

Respiratory: Emphysema (<5%), epistaxis (<5%), hemoptysis (<5%), pleural effusion (<5%), pulmonary edema (<5%), dyspnea (≤2%)

Miscellaneous: Diaphoresis (≤5%), allergic reaction (<5%), infection (5%), lymphadenopathy (<5%)

Immediate release formulation:

>10%:

Cardiovascular: ECG changes/ischemia (19%), peripheral edema (12%)

Central nervous system: Pain (13%)

Endocrine & metabolic: Hot flashes (55%)

1% to 10% (limited to important or life-threatening):

Cardiovascular: Hypertension (8%), murmur (3%), thrombosis/phlebitis (2%), CHF (1%), angina, arrhythmia, MI, syncope

Central nervous system: Headache (7%), insomnia (7%), dizziness/lightheadedness (5%), anxiety, depression, fatigue, fever, nervousness

Dermatologic: Dermatitis (5%), alopecia, bruising, itching, lesions, pigmentation

Endocrine & metabolic: Gynecomastia/breast tenderness/pain (7%), testicular size decreased (7%), diabetes, hypercalcemia, hypoglycemia, libido decreased, thyroid enlarged

Gastrointestinal: Constipation (7%), anorexia (6%), nausea/vomiting (5%), diarrhea, dysphagia, gastrointestinal bleeding, peptic ulcer, rectal polyps

Genitourinary: Urinary frequency/urgency (6%), impotence (4%), urinary tract infection (3%), bladder spasm, dysuria, incontinence, testicular pain, urinary obstruction

Hematologic: Anemia (5%)

Local: Injection site reaction

Neuromuscular & skeletal: Weakness (10%), bone pain (5%), peripheral neuropathy

Ocular: Blurred vision

Renal: Hematuria (6%), BUN increased, creatinine increased

Respiratory: Dyspnea (2%), cough, pneumonia, pulmonary embolus, pulmonary fibrosis

Miscellaneous: Infection, inflammation

Children and Adults:*Any formulations:* Postmarketing and/or case reports (limited to important or life-threatening): Anaphylactic/anaphylactoid reactions, asthmatic reactions, bone density decreased; fibromyalgia-like symptoms (arthralgia/myalgia, headaches, GI distress); hemoptysis, hepatic dysfunction, hypokalemia, hypoproteinemia, implant extrusion, implant migration, injection site induration/abscess, MI, pelvic fibrosis, penile swelling, photosensitivity; pituitary apoplexy (cardiovascular collapse, mental status altered, ophthalmoplegia, sudden headache, visual changes, vomiting); prostate pain, pulmonary embolism, pulmonary infiltrate, spinal fracture/paralysis, stroke, tenosynovitis-like symptoms, thrombocytopenia, transient ischemia attack, uric acid increased, urticaria, WBC increased

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

Antidiabetic Agents: Luteinizing Hormone-Releasing Hormone Analogs may diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Test InteractionsInterferes with pituitary gonadotropic and gonadal function tests during and up to 3 months after monthly administration of leuprolide therapy. Viadur®: Efficacy and stability of product not affected by MRI or radiographic exposure, although device will be visualized during these diagnostic procedures.
Monitoring ParametersBone mineral density

Precocious puberty: GnRH testing (blood LH and FSH levels), measurement of bone age every 6-12 months, testosterone in males and estradiol in females; Tanner staging

Prostatic cancer: LH and FSH levels, serum testosterone (2-4 weeks after initiation of therapy), PSA; weakness, paresthesias, and urinary tract obstruction in first few weeks of therapy

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, weakness, paresthesias, and urinary tract obstruction in first few weeks of therapy) on a regular basis throughout therapy. Teach patient (or caregiver) proper use (eg, storage, injection technique, syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment and do not give to females of childbearing age unless capable of complying with contraceptive measures 1 month prior to therapy, during therapy, and 1 month following therapy. Instruct patient in appropriate contraceptive measures.

Monitoring: Lab TestsPrecocious puberty: GnRH testing (blood LH and FSH levels), testosterone in males and estradiol in females

Patient EducationUse as directed. Do not discontinue without consulting prescriber. You may experience disease flare (increased bone pain) and urinary retention during early treatment (usually resolves); dizziness, headache, lethargy, or faintness (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea or vomiting (small frequent meals or analgesics may help); hot flashes, flushing, or redness (cold cloth and cool environment may help); breast swelling or tenderness; or decreased libido. Report irregular or rapid heartbeat, palpitations, chest pain; shortness or breath; swelling of extremities; unexplained weight gain of 3-5 pounds/week; inability to void or changes in urinary pattern; unresolved nausea or vomiting; numbness of extremities; breast swelling or pain, respiratory difficulty, or redness, swelling or pain at injection sites. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant. Consult prescriber for appropriate contraceptive use during and for a time following therapy. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Implant, subcutaneous:

- Viadur®: 65 mg [released over 12 months; packaged with administration kit] [DSC]

Injection, solution, as acetate: 5 mg/mL (2.8 mL)

- Lupron®: 5 mg/mL (2.8 mL) [contains benzyl alcohol; packaged with syringes and alcohol swabs]

Injection, powder for reconstitution, as acetate [depot formulation]:

- Eligard®:
  - 7.5 mg [released over 1 month; contains polylactide-co-glycolide]
  - 22.5 mg [released over 3 months; contains polylactide-co-glycolide]
  - 30 mg [released over 4 months; contains polylactide-co-glycolide]
  - 45 mg [released over 6 months; contains polylactide-co-glycolide]
- Lupron Depot®: 3.75 mg, 7.5 mg [released over 1 month; contains polysorbate 80, polylactide-co-glycolide]
- Lupron Depot®-3 Month: 11.25 mg, 22.5 mg [released over 3 months; contains polysorbate 80, polylactide-co-glycolide]
- Lupron Depot®-4 Month: 30 mg [released over 4 months; contains polysorbate 80, polylactide-co-glycolide]
- Lupron Depot-Ped®: 7.5 mg, 11.25 mg, 15 mg [released over 1 month; contains polysorbate 80, polylactide-co-glycolide]

Generic AvailableYes: Injection (solution)

Pricing: U.S. (www.drugstore.com)

Kit (Leuprolide Acetate)

- 1 mg/0.2 mL (1): $335.97

Kit (Lupron)

- 5 mg/mL (1): $522.25

Kit (Lupron Depot)

- 3.75 mg (1): $619.31
- 7.5 mg (1): $723.67
- 11.25 mg (1): $1820.12
- 22.5 mg (1): $2172.25
- 30 mg (1): $2879.59

Kit (Lupron Depot-Ped)

- 7.5 mg (1): $730.55
- 11.25 mg (1): $1405.08

Mechanism of ActionLeuprolide, is an agonist of luteinizing hormone-releasing hormone (LHRH). Acting as a potent inhibitor of gonadotropin secretion; continuous administration results in suppression of ovarian and testicular steroidogenesis due to decreased levels of LH and FSH with subsequent decrease in testosterone (male) and estrogen (female) levels. In males, testosterone levels are reduced to below castrate levels. Leuprolide may also have a direct inhibitory effect on the testes, and act by a different mechanism not directly related to reduction in serum testosterone.

Pharmacodynamics/Kinetics

Onset of action: Following transient increase, testosterone suppression occurs in ~2-4 weeks of continued therapy

Distribution: Males: V_d: 27 L

Protein binding: 43% to 49%

Metabolism: Major metabolite, pentapeptide (M-1)

Bioavailability: Oral: None; SubQ: 94%

Excretion: Urine (<5% as parent and major metabolite)

Related Information

- Management of Nausea and Vomiting
- Safe Handling of Hazardous Drugs

Pharmacotherapy Pearls

Eligard® Atrigel®: A nongelatin-based, biodegradable, polymer matrix

Viadur®: Leuprolide acetate implant containing 72 mg of leuprolide acetate, equivalent to 65 mg leuprolide free base. One Viadur® implant delivers 120 mcg of leuprolide/day over 12 months.

Oncology Comment: Guidelines from the American Society of Clinical Oncology (ASCO) for hormonal management of advanced prostate cancer which is androgen-sensitive (Loblaw, 2007) recommend either orchiectomy or luteinizing hormone-releasing hormone (LHRH) agonists as initial treatment for androgen deprivation.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Gum hemorrhage, gingivitis, dry mucous membranes, and dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDepression is common; may cause drowsiness, dizziness, or insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other Considerations

Eligard® is a nongelatin-based, biodegradable, polymer matrix.

Viadur® is a leuprolide acetate implant containing 72 mg of leuprolide acetate, equivalent to 65 mg leuprolide free base. One Viadur® implant delivers 120 mcg of leuprolide/day over 12 months.

Index TermsAbbott-43818; Leuprolide Acetate; Leuprorelin Acetate; TAP-144

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International Brand Names Eligard (AU, BG, DE, EE, FR); Enanton Depot (DK, FI, NO, SE); Enantone (AT, DE, FR); Enantone Depot (IT); Enantone LP (TH); Enantone SR (HK); Endrolin (ID); Lectrum (ID); Leuplin (KP); Leuplin Depot (TW); Lorelin (MX, PK); Lorelin Depot (HK, KP); Lucrin (AU, KP, MY, SG); Lucrin Depot (BE, CH, CZ, HN, IL, KP, MX, NL, SG, TR); Lucrin Depot Inj (AU); Lupride (IN); Lupride Depot (IN); Luprolex (PH); Luprolex Depot (PH); Lupron (AR, BR, CN, CO, EC, PY, UY, VE); Lupron Depot (AR, BR, CN, CO, EC, PE, PY, UY, VE); Prelar Depot (MX); Procren Depot (DK, FI, NO, SE); Procrin (ES); Prostap (GB, IE); Tapros (ID)

Levalbuterol

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English

English

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Special Alerts

FDA Advisory: Transition to HFA-Propelled Albuterol Inhalers - June 2008

The Food and Drug Administration (FDA) has issued a Public Health Advisory to announce a phase out of albuterol chlorofluorocarbon (CFC) propelled inhalers to hydrofluoralkane (HFA) propelled albuterol inhalers. The CFC propelled albuterol inhalers will not be available in the U.S. after December 31, 2008, and patients should be transitioned to a hydrofluoralkane (HFA) propelled albuterol inhaler now. To date, the three HFA-propelled albuterol inhalation aerosol inhalers on the market include ProAir™ HFA, Proventil® HFA, and Ventolin® HFA. In addition, levalbuterol, the (R) enantiomer of racemic albuterol, is also available as Xoponex HFA™ inhalation aerosol.

This national transition from CFC-propelled inhalers to HFA-propelled inhalers is ongoing and other medications using CFC-propelled inhalers will be phased out over the next several years.

Additional information may be found at http://www.fda.gov/cder/drug/advisory/albuterol_cfc.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Xopenex® may be confused with Xanax®

Pronunciation(leve al BYOO ter ole)

U.S. Brand NamesXopenex HFA™; Xopenex®

Canadian Brand NamesXopenex®

Pharmacologic CategoryBeta$_2$ Agonist

Use: Labeled IndicationsTreatment or prevention of bronchospasm in children and adults with reversible obstructive airway disease

Dosing: Adults

Bronchospasm:

Metered-dose inhaler: 2 puffs every 4-6 hours

Solution for nebulization: 0.63 mg 3 times/day at intervals of 6-8 hours; dosage may be increased to 1.25 mg 3 times/day with close monitoring for adverse effects

Exacerbation of asthma (acute, severe)*(NIH Guidelines, 2007):*

Metered-dose inhaler: 4-8 puffs every 20 minutes for up to 4 hours, then every 1-4 hours as needed

Solution for nebulization: 1.25-2.5 mg every 20 minutes for 3 doses, then 1.25-5 mg every 1-4 hours as needed

Dosing: ElderlyOnly a small number of patients have been studied. Although greater sensitivity of some elderly patients cannot be ruled out, no overall differences in safety or effectiveness were observed. An initial dose of 0.63 mg should be used in all patients >65 years of age.

Dosing: Pediatric

Bronchospasm:

Metered-dose inhaler: Children ≥4 years: 2 puffs every 4-6 hours as needed

Solution for nebulization:

Children ≤4 years (NIH Guidelines, 2007): 0.31-1.25 mg every 4-6 hours as needed

Children 5-11 years (NIH Guidelines, 2007): 0.31-0.63 mg 3 times/day as needed

Children ≥12 years: 0.63-1.25 mg every 8 hours as needed

Exacerbation of asthma (acute, severe)*(NIH Guidelines, 2007):*

Metered-dose inhaler: Children ≥4 years: 4-8 puffs every 20 minutes for 3 doses, then every 1-4 hours as needed

Solution for nebulization:

Children <12 years: 0.075 mg/kg (minimum: 1.25 mg) every 20 minutes for 3 doses, then 0.075-0.15 mg/kg (maximum: 5 mg) every 1-4 hours as needed

Children ≥12 years: 1.25-2.5 mg every 20 minutes for 3 doses, then 1.25-5 mg every 1-4 hours as needed

Administration: Inhalation

Metered-dose inhaler: Shake well before use; prime with 4 test sprays prior to first use or if inhaler has not been use of more than 3 days. Clean actuator (mouthpiece) weekly. A spacer device or valved holding chamber is recommended when using a metered-dose inhaler.

Solution for nebulization: Safety and efficacy were established when administered with the following nebulizers: PARI LC Jet™, PARI LC Plus™, as well as the following compressors: PARI Master®, Dura-Neb® 2000, and Dura-Neb® 3000. Concentrated solution should be diluted prior to use. Blow-by administration is not recommended, use a mask device if patient unable to hold mouthpiece in mouth for administration.

Storage

Aerosol: Store at room temperature of 20°C to 25°C (68°F to 77°F); protect from freezing and direct sunlight. Store with mouthpiece down. Discard after 200 actuations.

Solution for nebulization: Store in protective foil pouch at room temperature of 20°C to 25°C (68°F to 77°F). Protect from light and excessive heat. Vials should be used within 2 weeks after opening protective pouch. Use within 1 week and protect from light if removed from pouch. Vials of concentrated solution should be used immediately after removing from protective pouch.

ReconstitutionConcentrated solution should be diluted with 2.5 mL NS prior to use.

CompatibilitySolution for nebulization:**Compatible** with budesonide suspension

ContraindicationsHypersensitivity to levalbuterol, albuterol, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.
- Hypersensitivity reactions: Immediate hypersensitivity reactions (urticaria, angioedema, rash, bronchospasm) have been reported.

Disease-related concerns:

- Asthma: Appropriate use: Optimize anti-inflammatory treatment before initiating maintenance treatment with levalbuterol. Do not use as a component of chronic therapy without an anti-inflammatory agent. Only the mildest form of asthma (Step 1 and/or exercise-induced) would not require concurrent use based upon asthma guidelines.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (arrhythmia or hypertension or HF); beta-agonists may cause elevation in blood pressure, heart rate and result in CNS stimulation/excitation. Beta$_2$-agonists may also increase risk of arrhythmias.
- Diabetes: Use with caution in patients with diabetes mellitus; beta$_2$-agonists may increase serum glucose.
- Glaucoma: Use with caution in patients with glaucoma; may elevate intraocular pressure.
- Hyperthyroidism: Use with caution in hyperthyroidism; may stimulate thyroid activity.
- Hypokalemia: Use with caution in patients with hypokalemia; beta$_2$-agonists may decrease serum potassium.
- Seizures: Use with caution in patients with seizure disorders; beta-agonists may result in CNS stimulation/excitation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <4 years of age.

Other warnings/precautions:

- Appropriate use: Do not exceed recommended dose; serious adverse events, including fatalities, have been associated with excessive use of inhaled sympathomimetics.
- Patient information: Patients must be instructed to seek medical attention in cases where acute symptoms are not relieved or a previous level of response is diminished. The need to increase frequency of use may indicate deterioration of asthma, and treatment must not be delayed. A spacer device or valved holding chamber is recommended when using a metered-dose inhaler.

Geriatric ConsiderationsFor aerosol formulation, start with low end of dosage range. Refer to dosing information for nebulization dosing specifics.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; however, racemic albuterol was teratogenic in some species. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if benefit exceeds risk. Use caution if needed for bronchospasm during labor and delivery; has potential to interfere with uterine contractions.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known whether levalbuterol is excreted in human milk. Plasma levels following oral inhalation are low. Racemic albuterol was shown to be tumorigenic in animal studies.

Adverse Reactions

>10%:

Endocrine & metabolic: Serum glucose increased, serum potassium decreased

Neuromuscular & skeletal: Tremor (≤7%)

Respiratory: Rhinitis (3% to 11%)

Miscellaneous: Viral infection (7% to 12%)

>2% to 10%:

Central nervous system: Headache (8% to 12%), nervousness (3% to 10%), dizziness (1% to 3%), anxiety (≤3%), migraine (≤3%), weakness (3%)

Cardiovascular: Tachycardia (~3%)

Dermatologic: Rash (≤8%)

Gastrointestinal: Diarrhea (2% to 6%), dyspepsia (1% to 3%)

Neuromuscular & skeletal: Leg cramps (≤3%)

Respiratory: Asthma (9%), pharyngitis (3% to 10%), cough (1% to 4%), sinusitis (1% to 4%), nasal edema (1% to 3%)

Miscellaneous: Flu-like syndrome (1% to 4%), accidental injury (≤3%)

<2%: Abnormal ECG, acne, anaphylaxis, angina, angioedema, arrhythmia, atrial fibrillation, chest pain, chills, constipation, conjunctivitis, cough, diaphoresis, dysmenorrhea, dyspnea, epistaxis, extrasystole, gastroenteritis, hematuria, hyper-/hypotension, hypoesthesia (hand), hypokalemia, insomnia, itching eyes, lymphadenopathy, myalgia, nausea, oropharyngeal dryness, paresthesia, supraventricular arrhythmia, syncope, vaginal moniliasis, vertigo, vomiting, wheezing, xerostomia

Note: Immediate hypersensitivity reactions have occurred (including angioedema, oropharyngeal edema, urticaria, and anaphylaxis).

Drug Interactions

Alpha-/Beta-Blockers: May diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Atomoxetine: May enhance the tachycardic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Betahistine: May diminish the therapeutic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Monitoring ParametersAsthma symptoms; FEV_1, peak flow, and/or other pulmonary function tests; heart rate, blood pressure, CNS stimulation; arterial blood gases (if condition warrants); serum potassium, serum glucose (in selected patients)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness (patient response and laboratory values), adverse reactions (eg, anaphylaxis or hypertension, first dose administered under supervision), or overdose. Patients with diabetes should monitor serum glucose on a regular basis (possibility of hyperglycemia). Assess knowledge/teach patient appropriate use (safe use of nebulizer), interventions to reduce side effects, and adverse reactions to report.

Monitoring: Lab TestsFEV_1 and/or peak expiratory flow rate, arterial blood gases (if condition warrants); serum potassium, serum glucose (in selected patients)

Patient EducationUse only when necessary or as prescribed; tolerance may develop with overuse. Do not administer more frequently than prescribed. First dose should not be used when you are alone. Avoid OTC medications without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Stress or excessive exercising may exacerbate wheezing or bronchospasm (controlled breathing or relaxation techniques may help). If you have diabetes, you will need to monitor serum glucose levels closely until response is known; notify diabetic advisor if hyperglycemia occurs. You may experience tremor, anxiety, or dizziness (use caution when driving or engaging in hazardous activities until response to drug is known); headache; or temporarily upset stomach, nausea, or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help). Paradoxical bronchospasm can occur. Stop drug immediately and notify prescriber if any of the following occur: chest pain, tightness, palpitations; severe headache; respiratory difficulty; increased nervousness, restlessness, or trembling; muscle cramps or weakness; or seizures. Report unusual signs of flu or infection, leg or muscle cramps, unusual cough, persistent GI problems, vision changes, or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: Strength expressed as base.

Aerosol, for oral inhalation, as tartrate:

Xopenex HFA™: 45 mcg/actuation (15 g) [200 actuations; chlorofluorocarbon free]

Solution for nebulization, as hydrochloride [preservative free]:

Xopenex®: 0.31 mg/3 mL (24s); 0.63 mg/3 mL (24s); 1.25 mg/3 mL (24s)

Solution for nebulization, as hydrochloride [concentrate; preservative free]:

Xopenex®: 1.25 mg/0.5 mL (30s)

Generic AvailableNo

ManufacturerSepracor, Inc

Pricing: U.S. (www.drugstore.com)

Aerosol (Xopenex HFA)

45 mcg/ACT (15): $53.84

Nebulization (Xopenex)

0.31 mg/3 mL (72): $100.11

0.63 mg/3 mL (72): $102.78

1.25 mg/3 mL (72): $101.59

Mechanism of ActionRelaxes bronchial smooth muscle by action on beta$_2$-receptors with little effect on heart rate

Pharmacodynamics/Kinetics

Onset of action (as measured by a 15% increase in FEV$_1$):

Aerosol: 5.5-10.2 minutes

Peak effect: ~77 minutes

Nebulization: 10-17 minutes

Peak effect: 1.5 hours

Duration (as measured by a 15% increase in FEV$_1$):

Aerosol: 3-4 hours (up to 6 hours in some patients)

Nebulization: 5-6 hours (up to 8 hours in some patients)

Absorption: A portion of inhaled dose is absorbed to systemic circulation

Half-life elimination: 3.3-4 hours

Time to peak, serum:

Aerosol: Children: 0.8 hours, Adults: 0.5 hours

Nebulization: Children: 0.3-0.6 hours, Adults: 0.2 hours

Related Information

- Asthma
- Inhalant Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness, anxiety, and dizziness; may rarely cause insomnia

Mental Health: Effects on Psychiatric TreatmentEffects of anxiolytics may be ameliorated; cardiac effects may be potentiated with MAO inhibitors and TCAs

Index TermsLevalbuterol Hydrochloride; Levalbuterol Tartrate; R-albuterol

References

Expert Panel Report 3, “Guidelines for the Diagnosis and Management of Asthma,” *Clinical Practice Guidelines*, National Institutes of Health, National Heart, Lung, and Blood Institute, NIH Publication No. 08-4051, prepublication 2007. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

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Levetiracetam

Lexi-Drugs Online

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Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

Keppra® may be confused with Keppra XR™

Levetiracetam may be confused with levofloxacin

Potential for dispensing errors between Keppra® and Kaletra® (lopinavir/ritonavir)

Pronunciation(lee va tye RA se tam)

U.S. Brand NamesKeppra XR™; Keppra®

Canadian Brand NamesApo-Levetiracetam; CO Levetiracetam; DOM-Levetiracetam; Keppra®; PHL-Levetiracetam; PMS-Levetiracetam

Pharmacologic CategoryAnticonvulsant, Miscellaneous

Use: Labeled IndicationsAdjunctive therapy in the treatment of partial onset, myoclonic, and/or primary generalized tonic-clonic seizures

Use: Unlabeled/InvestigationalBipolar disorder

Dosing: Adults

Myoclonic seizures: Oral: Immediate release: Initial: 500 mg twice daily; may increase every 2 weeks by 500 mg/dose to the recommended dose of 1500 mg twice daily. Efficacy of doses >3000 mg/day has not been established.

Partial onset seizures:

Oral:

Immediate release: Initial: 500 mg twice daily; may increase every 2 weeks by 500 mg/dose to a maximum of 1500 mg twice daily. Doses >3000 mg/day have been used in trials; however, there is no evidence of increased benefit.

Extended release: Initial: 1000 mg once daily; may increase every 2 weeks by 1000 mg/day to a maximum of 3000 mg once daily.

I.V.: Initial: 500 mg twice daily; may increase every 2 weeks by 500 mg/dose to a maximum of 1500 mg twice daily. Doses >3000 mg/day have been used in trials; however, there is no evidence of increased benefit.

Note: When switching from oral to I.V. formulations, the total daily dose should be the same.

Tonic-clonic seizures: Oral: Immediate release: Initial: 500 mg twice daily; may increase every 2 weeks by 500 mg/dose to the recommended dose of 1500 mg twice daily. Efficacy of doses >3000 mg/day has not been established.

Bipolar disorder (unlabeled use): Oral: Immediate release: Initial: 500 mg twice daily; if tolerated, increase by 500 mg twice daily; dose may be increased every 3 days until target dose of 3000 mg/day is reached; maximum: 4000 mg/day

Loading dose (unlabeled): Immediate release: Initial doses of 1500-2000 mg have been well-tolerated (Koubeissi, 2008; Betts, 2000), although the necessity of a loading dose has not been established

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Myoclonic seizures: Oral: Children ≥12 years: Immediate release: Initial: 500 mg twice daily; may increase every 2 weeks by 500 mg/dose to the recommended dose of 1500 mg twice daily. Efficacy of doses >3000 mg/day has not been established.

Partial onset seizures: Oral:

Children 4-15 years: Partial onset seizures: Immediate release: 10 mg/kg/dose given twice daily; may increase every 2 weeks by 10 mg/kg/dose to a maximum of 30 mg/kg/dose twice daily

Children ≥16 years: Refer to adult dosing.

Tonic-clonic seizures: Oral:

Children 6-15 years: Immediate release: Initial: 10 mg/kg dose given twice daily; may increase every 2 weeks by 10 mg/kg/dose to the recommended dose of 30 mg/kg twice daily. Efficacy of doses >60 mg/kg/day has not been established.

Children ≥16 years: Refer to adult dosing.

Bipolar disorder (unlabeled use): Oral: Children ≥16 years: Refer to adult dosing.

Dosing: Renal ImpairmentAdults:

Immediate release and I.V. formulations:

Cl_{cr} >80 mL/minute: 500-1500 mg every 12 hours

Cl_{cr} 50-80 mL/minute: 500-1000 mg every 12 hours

Cl_{cr} 30-50 mL/minute: 250-750 mg every 12 hours

Cl_{cr} <30 mL/minute: 250-500 mg every 12 hours

End-stage renal disease patients using dialysis: 500-1000 mg every 24 hours; a supplemental dose of 250-500 mg following dialysis is recommended

Extended release tablets:

Cl_{cr} >80 mL/minute: 1000-3000 mg every 24 hours

Cl_{cr} 50-80 mL/minute: 1000-2000 mg every 24 hours

Cl_{cr} 30-50 mL/minute: 500-1500 mg every 24 hours

Cl_{cr} <30 mL/minute: 500-1000 mg every 24 hours

Dosing: Hepatic ImpairmentNo adjustment required

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Infuse over 15 minutes

Administration: I.V. DetailpH: 5.5

Administration: Oral

May be taken with or without food.

Oral solution: Should be administered with a calibrated measuring device (not a household teaspoon or tablespoon)

Tablet (immediate release and extended release): Only administer as whole tablet; do not crush, break or chew.

Dietary ConsiderationsMay be taken with or without food.

Storage

Oral solution, tablets: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Injection solution: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Admixed solution is stable for 24 hours in PVC bags kept at room temperature.

Reconstitution

Injection solution: Must dilute dose in 100 mL of NS, LR, or D_5W.

Compatibility

Stable in NS, LR, D_5W

Compatibility when admixed: Compatible: Diazepam, lorazepam, valproic acid

ContraindicationsHypersensitivity to levetiracetam or any component of the formulation

Allergy Considerations

- Levetiracetam Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Weakness, dizziness, and somnolence occur mostly during the first month of therapy.

- Hematologic effects: Although rare, decreases in red blood cell counts, hemoglobin, hematocrit, white blood cell counts and neutrophils have been observed.

- Psychotic symptoms: Psychosis, hallucinations and behavioral symptoms (including aggression, anger, anxiety, depersonalization, depression, personality disorder) may occur; dose reduction may be required.

Disease-related concerns:

- Renal impairment: Use caution with renal impairment; dosage adjustment may be necessary.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <4 years of age (oral formulation) or <16 years (I.V. formulation and extended release tablets). Children may have increased incidence of psychotic symptoms; dose reduction may be required.

Other warnings/precautions:

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsIn a study of 16 older adults (61-88 years of age) receiving levetiracetam daily and with creatinine clearances ranging from 30-74 mL/minute, a decrease in creatinine clearance (38%) and a 2.5 hour longer half-life were recorded in the elderly compared to younger adults. The authors concluded that the difference was due to renal function. Other studies show no overall difference in safety and efficacy, although larger numbers in studies are needed to verify efficacy. Levetiracetam has demonstrated a low incidence of cognitive effects. When using the drug in elderly, it is essential to base the dose on estimated creatinine clearance and adjust appropriately.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDevelopmental toxicities were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Two registries are available for women exposed to levetiracetam during pregnancy:

Antiepileptic Drug Pregnancy Registry (888-233-2334 or http://www.mgh.harvard.edu/aed/)

Keppra® pregnancy registry (888-537-7734 or http://www.keppra.com)

LactationEnters breast milk/not recommended

Adverse Reactions

>10%:

Central nervous system: Behavioral symptoms (agitation, aggression, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesias, irritability, nervousness, neurosis and personality disorder: adults 5% to 13%; children 5% to 38%), somnolence (8% to 23%), headache (14%), hostility (2% to 12%)

Gastrointestinal: Vomiting (15%), anorexia (3% to 13%)

Neuromuscular & skeletal: Weakness (9% to 15%)

Respiratory: Pharyngitis (6% to 14%), rhinitis (4% to 13%), cough (2% to 11%)

Miscellaneous: Accidental injury (17%), infection (2% to 13%)

1% to 10%:

Cardiovascular: Facial edema (2%)

Central nervous system: Fatigue (10%), nervousness (4% to 10%), dizziness (5% to 9%), personality disorder (8%), pain (6% to 7%), agitation (6%), irritability (6% to 7%), emotional lability (2% to 6%), mood swings (5%), depression (3% to 5%), vertigo (3% to 5%), ataxia (3%), amnesia (2%), anxiety (2%), confusion (2%)

Dermatologic: Bruising (4%), pruritus (2%), rash (2%), skin discoloration (2%)

Endocrine & metabolic: Dehydration (2%)

Gastrointestinal: Diarrhea (8%), nausea (5%), gastroenteritis (4%), constipation (3%)

Genitourinary: Urine abnormality (2%)

Hematologic: Leukocytes decreased (2% to 3%)

Neuromuscular & skeletal: Neck pain (2% to 8%), paresthesia (2%), reflexes increased (2%)

Ocular: Conjunctivitis (3%), diplopia (2%), amblyopia (2%)

Otic: Ear pain (2%)

Renal: Albuminuria (4%)

Respiratory: Influenza (5%), asthma (2%), sinusitis (2%)

Miscellaneous: Flu-like syndrome (3% to 8%), viral infection (2%)

<1%, postmarketing and/or case reports: Alopecia, anemia, catatonia, hematocrit decreased, hemoglobin decreased, hepatic failure, hepatitis, leukopenia, LFTs abnormal, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression), psychotic symptoms, red blood cells decreased, suicide attempt, suicide behavior, suicide ideation, thrombocytopenia, weight loss

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Food may delay, but does not affect the extent of absorption.

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness, laboratory values, and adverse reactions at beginning of therapy and periodically with long-term use. Monitor for CNS depression (somnolence and fatigue), behavioral abnormalities (psychosis, hallucinations, psychotic depression), and other behavioral symptoms (agitation, anger, aggression, irritability, hostility, anxiety, apathy, emotional lability, depersonalization, and depression). Taper dosage slowly when discontinuing. Observe and teach seizure/safety precautions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea, vomiting, loss of appetite, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Wear identification of epileptic status and medications. Report CNS changes, mentation changes, suicidal ideation, depression, or changes in cognition; muscle cramping, weakness, tremors, changes in gait; persistent GI symptoms (cramping, constipation, vomiting, anorexia); rash or skin irritations; unusual bruising or bleeding (mouth, urine, stool); or worsening of seizure activity or loss of seizure control. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Keppra®: 100 mg/mL (5 mL)

Solution, oral:

Keppra®: 100 mg/mL (480 mL) [dye free; grape flavor]

Tablet: 250 mg, 500 mg, 750 mg

Keppra®: 250 mg, 500 mg, 750 mg, 1000 mg

Tablet, extended release:

Keppra XR™: 500 mg

Generic AvailableYes: Tablet

ManufacturerUCB Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Solution (Keppra)

100 mg/mL (473): $326.04

Tablets (Keppra)

250 mg (10): $37.99

500 mg (30): $111.03

750 mg (30): $150.00

1000 mg (60): $450.32

Tablets (Levetiracetam)

250 mg (120): $245.98

500 mg (30): $85.99

750 mg (120): $399.97

Mechanism of Action The precise mechanism by which levetiracetam exerts its antiepileptic effect is unknown. However, several studies have suggested the mechanism may involve one or more of the following central pharmacologic effects: inhibition of voltage-dependent N-type calcium channels; facilitation of GABA-ergic inhibitory transmission through displacement of negative modulators; reduction of delayed rectifier potassium current; and/or binding to synaptic proteins which modulate neurotransmitter release.

Pharmacodynamics/Kinetics

Absorption: Oral: Rapid and almost complete

Distribution: V_d: Similar to total body water

Protein binding: <10%

Metabolism: Not extensive; primarily by enzymatic hydrolysis; forms metabolites (inactive)

Bioavailability: 100%

Half-life elimination: ~6-8 hours; extended release tablet: ~7 hours; half-life increased in renal dysfunction

Time to peak, plasma: Oral: Immediate release: ~1 hour; Extended release: ~4 hours

Excretion: Urine (66% as unchanged drug)

Related Information

- Anticonvulsants by Seizure Type

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Associated with somnolence and fatigue, psychosis, hallucinations, psychotic depression, and other behavioral symptoms (agitation, anger, aggression, irritability, hostility, anxiety, apathy, emotional lability, depersonalization, and depression)

Mental Health: Effects on Psychiatric Treatment May cause leukopenia, neutropenia, pancytopenia, and thrombocytopenia; use caution with clozapine, carbamazepine, and valproic acid

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International Brand Names Ceumid (UY); Keppra (AR, AT, AU, BE, BG, CH, CL, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IT, KP, MX, MY, NL, NO, PE, PH, PL, PT, RU, SE, SG, TH, TR, TW); Kopodex (CN, PY)

Levobunolol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Levobunolol may be confused with levocabastine

Betagan® may be confused with Betadine®, Betoptic® S

International issues:

Betagan® may be confused with Betagon® which is a brand name for mepindolol in Italy

Pronunciation(lee voe BYOO noe lole)

U.S. Brand Names Betagan®

Canadian Brand Names Apo-Levobunolol®; Betagan®; Novo-Levobunolol; Optho-Bunolol®; PMS-Levobunolol; Sandoz-Levobunolol

Pharmacologic Category Beta Blocker, Nonselective; Ophthalmic Agent, Antiglaucoma

Use: Labeled Indications To lower intraocular pressure in chronic open-angle glaucoma or ocular hypertension

Dosing: Adults Glaucoma: Ophthalmic: Instill 1 drop in the affected eye(s) 1-2 times/day

Dosing: Elderly Refer to adult dosing.

ContraindicationsHypersensitivity to levobunolol or any component of the formulation; bronchial asthma, severe COPD, sinus bradycardia, second- or third-degree AV block, cardiac failure, cardiogenic shock

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Concerns related to adverse events:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.
- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.
- Heart failure (HF): Use with caution in patients with compensated heart failure and monitor for a worsening of the condition.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; may worsen disease.
- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).
- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

Special populations:

- Contact lens wearers: Some products contain benzalkonium chloride which may be absorbed by soft contact lenses; remove lens prior to administration and wait 15 minutes before reinserting.
- Elderly: Use with caution in the elderly with other disease states or syndromes that may be affected by a beta-blocker (CHF, COPD, etc); systemic absorption does occur with ophthalmic administration; monitor closely.
- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Metabisulfite: Ophthalmic solutions contain metabisulfite.

Other warnings/precautions:

- Absorption: Systemic absorption and adverse effects may occur with ophthalmic use, including bradycardia and/or hypotension.

Geriatric ConsiderationsBecause systemic absorption does occur with ophthalmic administration, the elderly with other disease states or syndromes that may be affected by a beta-blocker (CHF, COPD, etc) should be monitored closely

Pregnancy Risk FactorC

Adverse Reactions

>10%: Ocular: Stinging/burning eyes

1% to 10%:

Cardiovascular: Bradycardia, arrhythmia, hypotension

Central nervous system: Dizziness, headache

Dermatologic: Alopecia, erythema

Local: Stinging, burning

Ocular: Blepharoconjunctivitis, conjunctivitis

Respiratory: Bronchospasm

<1%: Rash, itching, visual disturbances, keratitis, decreased visual acuity

Drug Interactions

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring ParametersIntraocular pressure, heart rate, funduscopic exam, visual field testing

Patient EducationMay sting on instillation; do not touch dropper to eye. Visual acuity may be decreased after administration. Night vision may be decreased. Distance vision may be altered. Apply finger pressure between the bridge of the nose and corner of the eye to decrease systemic absorption. Assess patient's or caregiver's ability to administer.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic, as hydrochloride: 0.25% (5 mL, 10 mL); 0.5% (5 mL, 10 mL, 15 mL) [contains benzalkonium chloride and sodium metabisulfite]

Betagan®: 0.25% (5 mL, 10 mL); 0.5% (2 mL, 5 mL, 10 mL, 15 mL) [contains benzalkonium chloride and sodium metabisulfite]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Betagan)

0.5% (10): $58.99

0.5% (15): $83.99

Solution (Levobunolol HCl)

0.25% (5): $14.99

Mechanism of ActionA nonselective beta-adrenergic blocking agent that lowers intraocular pressure by reducing aqueous humor production and possibly increases the outflow of aqueous humor

Pharmacodynamics/Kinetics

Onset of action: ~1 hour

Peak effect: 2-6 hours

Duration: 1-7 days

Excretion: Not well defined

Related Information

- Glaucoma Drug Therapy

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Levobunolol is a nonselective beta-blocker and may enhance the pressor response to epinephrine, resulting in hypertension and bradycardia. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay increase the effects of oral beta-blockers

Cardiovascular ConsiderationsIt is important to recognize that levobunolol eye drops may have systemic effects, particularly when patients are also on oral beta-blocker therapy or therapy with other negative chronotropic agents.

Index Terms*l*-Bunolol Hydrochloride; Levobunolol Hydrochloride

References

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International Brand NamesBetagan (AE, AR, AU, BE, BH, BR, CN, CY, DK, EG, ES, FR, GB, HK, IE, IL, IN, IQ, IR, JO, KP, KW, LB, LU, LY, MX, NL, OM, PT, QA, SA, SY, TH, UY, YE, ZA); Bunolgan (TW); Levosan (PK); Vistagan (AT, CH, CO, CZ, DE, GR, HN, HR, HU, IT, PE, PL, RU, VE)

Levobupivacaine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (epidural administration) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(LEE voe byoo PIV a kane)

U.S. Brand NamesChirocaine® [DSC]

Canadian Brand NamesChirocaine®

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsProduction of local or regional anesthesia for surgery and obstetrics, and for postoperative pain management

Dosing: Adults**Note:** Rapid injection of a large volume of local anesthetic solution should be avoided. Fractional (incremental) doses are recommended.

Guidelines (individual response varies): See table.

	Concentration	**Volume**	**Dose**	**Motor Block**
Surgical Anesthesia				
Epidural for surgery	0.5%-0.75%	10-20 mL	50-150 mg	Moderate to complete
Epidural for C-section	0.5%	20-30 mL	100-150 mg	Moderate to complete
Peripheral nerve	0.25%-0.5%	0.4 mL/kg (30 mL)	1-2 mg/kg (75-150 mg)	Moderate to complete
Ophthalmic	0.75%	5-15 mL	37.5-112.5 mg	Moderate to complete
Local infiltration	0.25%	60 mL	150 mg	Not applicable
Pain Management				
Levobupivacaine can be used epidurally with fentanyl or clonidine; dilutions for epidural administration should be made with preservative free 0.9% saline according to standard hospital procedures for sterility				
Labor analgesia (epidural bolus)	0.25%	10-20 mL	25-50 mg	Minimal to moderate
Postoperative pain (epidural infusion)	0.125%[1]-0.25%	4-10 mL/h	5-25 mg/h	Minimal to moderate
[1] 0.125%: Adjunct therapy with fentanyl or clonidine.				

Maximum dosage: Epidural doses up to 375 mg have been administered incrementally to patients during a surgical procedure.

Intraoperative block and postoperative pain: 695 mg in 24 hours

Postoperative epidural infusion over 24 hours: 570 mg

Single-fractionated injection for brachial plexus block: 300 mg

Dosing: ElderlyRefer to adult dosing.

Administration: OtherIsopropyl or ethyl alcohol are recommended to disinfect the surface of the vial. Disinfectants containing heavy metals should not be used for mucous membrane disinfection since they have been related to incidents of swelling and edema. Prior to administration, it is essential that aspiration for blood or cerebrospinal fluid (where applicable) be performed prior to injecting any local anesthetic, both before the original dosage and at all subsequent doses (to avoid intravascular or intrathecal injection). A negative aspiration does not ensure against intrathecal or intravascular injection. Rapid injection of a large volume of local anesthetic solution should be avoided. Fractional (incremental) doses are recommended. Monitor patient during and after injection for symptoms of CNS or cardiac toxicity.

StorageStore at room temperature (20°C to 25°C/68°F to 77°F). Disinfectants containing heavy metals should not be used for mucous membrane disinfection since they have been related to incidents of swelling and edema. Isopropyl or ethyl alcohol is recommended. Stability of solution in vial has been demonstrated following an autoclave cycle at 121°C for 15 minutes.

CompatibilityStable in 0.9% sodium chloride injection USP, and with saline solutions containing morphine, fentanyl, and clonidine. Stable for 24 hours in PVC bags at room temperature when diluted to 0.625-2.5 mg levobupivacaine per mL; **incompatible** with alkaline pH solutions (pH >8.5).

ContraindicationsHypersensitivity to levobupivacaine, any component of the formulation, bupivacaine, or any local anesthetic of the amide type

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS toxicity: Careful and constant monitoring of the patient's state of consciousness should be done following each local anesthetic injection; at such times, restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of CNS toxicity. Treatment is primarily symptomatic and supportive.
- Respiratory arrest: Local anesthetics have been associated with rare occurrences of sudden respiratory arrest, especially when administered near the head or neck.
- Seizures: Convulsions due to systemic toxicity leading to cardiac arrest have also been reported, presumably following unintentional intravascular injection or administration near the head or neck.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with hypotension, hypovolemia, heart block, or cardiac impairment.
- Hepatic impairment: Use with caution in patients with hepatic impairment.

Concurrent drug therapy issues:

- Other local anesthetics: Use with caution in patients receiving other local anesthetics or structurally related agents.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- High concentration formulations: Use with caution when the higher concentration formulations are used; more likely to produce cardiac toxicity.
- Obstetrical anesthesia: The 0.75% is not recommended for obstetrical anesthesia.

Other warnings/precautions:

- Administration: Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided. Not for use in intravenous regional anesthesia (Bier block) or to produce obstetrical paracervical block anesthesia.
- Trained personnel: Clinicians using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorB

Pregnancy ConsiderationsLocal anesthetics rapidly cross the placenta and may cause varying degrees of maternal, fetal, and neonatal toxicity. Close maternal and fetal monitoring (heart rate and electronic fetal monitoring advised) are required during obstetrical use.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Cardiovascular: Hypotension (20% to 31%)

Central nervous system: Pain (postoperative) (7% to 18%), fever (7% to 17%)

Gastrointestinal: Nausea (12% to 21%), vomiting (8% to 14%)

Hematologic: Anemia (10% to 12%)

1% to 10%:

Cardiovascular: Abnormal ECG (3%), bradycardia (2%), tachycardia (2%), hypertension (1%)

Central nervous system: Pain (4% to 8%), headache (5% to 7%), dizziness (5% to 6%), hypoesthesia (3%), somnolence (1%), anxiety (1%), hypothermia (2%)

Dermatologic: Pruritus (4% to 9%), purpura (1%)

Endocrine & metabolic: Breast pain - female (1%)

Gastrointestinal: Constipation (3% to 7%), enlarged abdomen (3%), flatulence (2%), abdominal pain (2%), dyspepsia (2%), diarrhea (1%)

Genitourinary: Urinary incontinence (1%), urine flow decreased (1%), urinary tract infection (1%)

Hematologic: Leukocytosis (1%)

Local: Anesthesia (1%)

Neuromuscular & skeletal: Back pain (6%), rigors (3%), paresthesia (2%)

Ocular: Diplopia (3%)

Renal: Albuminuria (3%), hematuria (2%)

Respiratory: Cough (1%)

Miscellaneous: Fetal distress (5% to 10%), delayed delivery (6%), hemorrhage in pregnancy (2%), uterine abnormality (2%), increased wound drainage (1%)

<1%: Asthenia, edema, postural hypotension, hypokinesia, involuntary muscle contraction, generalized spasm, tremor, syncope, arrhythmia, extrasystoles, atrial fibrillation, cardiac arrest, ileus, elevated bilirubin, confusion, apnea, bronchospasm, dyspnea, pulmonary edema, respiratory insufficiency, diaphoresis increased, skin discoloration

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 3A4

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease levobupivacaine levels.

Monitoring ParametersMonitor the patient during and after injection for symptoms of CNS or cardiac toxicity

Nursing: Physical Assessment/MonitoringMonitor for effectiveness of anesthesia according to purpose for use. Monitor closely during and after injection for symptoms of CNS, cardiac toxicity, or hypotension. Monitor for return of sensation. Use appropriate patient safety measures until full return of sensation. Teach patient adverse symptoms to report.

Patient EducationThis medication is given to reduce sensation and pain. You will experience decreased sensation to pain, heat, or cold in the area and/or decreased muscle strength (depending on area of application). Until sensation returns, use caution to prevent injury (eg, avoid extremes of heat or cold to area, do not use sharp objects, avoid driving, climbing stairs, or sudden moves if muscle strength is affected). Immediately report chest pain or palpitations; increased restlessness, anxiety, dizziness or lightheadedness; sensation of sudden muscle weakness; swelling or tingling of mouth or lips; metallic taste; vision changes or hearing. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution [preservative free]: 2.5 mg/mL (10 mL, 30 mL); 5 mg/mL (10 mL, 30 mL); 7.5 mg/mL (10 mL, 30 mL) [DSC]

Generic AvailableNo

Mechanism of ActionLevobupivacaine is the S-enantiomer of bupivacaine. It blocks both the initiation and transmission of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction. Local anesthetics reversibly prevent generation and conduction of electrical impulses in neurons by decreasing the transient increase in permeability to sodium. The differential sensitivity generally depends on the size of the fiber; small fibers are more sensitive than larger fibers and require a longer period for recovery. Sensory pain fibers are usually blocked first, followed by fibers that transmit sensations of temperature, touch, and deep pressure. High concentrations block sympathetic somatic sensory and somatic motor fibers. The spread of anesthesia depends upon the distribution of the solution. This is primarily dependent on the site of administration and volume of drug injected.

Pharmacodynamics/Kinetics

Onset of action: Epidural: 10-14 minutes

Duration (dose dependent): 1-8 hours

Absorption: Dependent on route of administration and dose

Distribution: 67 L

Protein binding, plasma: >97%

Metabolism: Extensively hepatic via CYP3A4 and CYP1A2

Half-life elimination: 1.3 hours

Time to peak: Epidural: 30 minutes

Excretion: Urine (71%) and feces (24%) as metabolites

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, dizziness or somnolence; may rarely cause confusion

Mental Health: Effects on Psychiatric TreatmentFluvoxamine and nefazodone may increase the levels of levobupivacaine; carbamazepine and barbiturates may lower levels

Anesthesia and Critical Care Concerns/Other Considerations

Local anesthetic toxicity: Cardiac arrest: Lipid infusion has been used in animal studies and several human cases (Bupivacaine: Rosenblatt, 2006; Levobupivacaine: Foxall, 2007; Ropivacaine: Litz, 2006) where cardiovascular toxicity, unresponsive to conventional resuscitation, resulted. Additional information is available at http://www.lipidrescue.org. The protocol from the website is: **20% Fat Emulsion:** 1.5 mL/kg administered over 1 minute, followed immediately by an infusion of 0.25 mL/kg/minute. Continue chest compressions (lipid must circulate). Repeat bolus every 3-5 minutes up to 3 mL/kg total dose until circulation restored. Continue infusion until hemodynamic stability is restored. Increase the infusion rate to 0.5 mL/kg/minute if BP declines. A maximum total dose of 8 mL/kg is recommended.

References

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Foxall G, McCahon R, Lamb J, et al, "Levobupivacaine-Induced Seizures and Cardiovascular Collapse Treated With Intralipid," *Anaesthesia*, 2007, 62(5):516-8.[PubMed 17448066]

Litz RJ, Popp M, Stehr SN, et al, "Successful Resuscitation of a Patient With Ropivacaine-Induced Asystole After Axillary Plexus Block Using Lipid Infusion," *Anaesthesia*, 2006, 61(8):800-1.[PubMed 16867094]

Rosenblatt MA, Abel M, Fischer GW, et al, "Successful Use of a 20% Lipid Emulsion to Resuscitate a Patient After a Presumed Bupivacaine-Related Cardiac Arrest," *Anesthesiology*, 2006, 105(1):217-8.[PubMed 16810015]

International Brand NamesBupinest (CO); Chirocaina (CN); Chirocaine (AR, AU, BE, BR, CH, CZ, FI, FR, GB, HK, HN, IE, IT, JP, NL, NO, PE, PL, SE, SG); Quirocaine (MX); SensiBloq (PH)

Levocabastine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Levocabastine may be confused with levobunolol, levocarnitine

Livostin® may be confused with lovastatin

International issues:

Livostin® may be confused with Limoxin® which is a brand name for amoxicillin in Mexico

Livostin® may be confused with Lovastin® which is a brand name for lovastatin in Malaysia and Poland

Pronunciation(LEE voe kab as teen)
U.S. Brand NamesLivostin® [DSC]
Canadian Brand NamesLivostin®
Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation
Use: Labeled IndicationsTreatment of allergic conjunctivitis
Dosing: AdultsAllergic conjunctivitis: Ophthalmic: Instill 1 drop in affected eye(s) 4 times/day for up to 2 weeks
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren ≥12 years: Refer to adult dosing.
ContraindicationsHypersensitivity to levocabastine any component of product; use while soft contact lenses are being worn
Warnings/Precautions

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.
- Soft contact lens wearers: Do not use while wearing soft contact lenses.

Other warnings/precautions:

- Appropriate use: For topical ophthalmic use only; avoid touching the dropper tip to surfaces to avoid contamination.

Pregnancy Risk FactorC
Adverse Reactions

>10%: Local: Transient burning, stinging, discomfort

1% to 10%:

Central nervous system: Headache, somnolence, fatigue

Dermatologic: Rash

Gastrointestinal: Xerostomia

Ocular: Blurred vision, eye pain, somnolence, red eyes, eyelid edema

Respiratory: Dyspnea

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic response and adverse effects. Teach patient proper use, side effects/appropriate interventions, and symptoms to report.

Patient EducationFor use in eyes only. Shake well before using. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Do not wear contact lenses during treatment. This medication may cause drowsiness in some patients. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Suspension, ophthalmic: 0.05% (5 mL, 10 mL) [contains benzalkonium chloride] [DSC]

Generic AvailableNo

Mechanism of ActionPotent, selective histamine H_1-receptor antagonist for topical ophthalmic use

Pharmacodynamics/KineticsAbsorption: Topical: Systemic

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsLevocabastine Hydrochloride

International Brand NamesBilina (ES); Histimet (AR, PL); Levophta (DE, FR); Livocab (ES, NL); Livostin (AE, AT, AU, BE, BG, BH, BR, CH, CL, CN, CO, CY, CZ, DK, EE, EG, FI, GB, GR, HN, HR, HU, IL, IQ, IR, IT, JO, KP, KW, LB, LU, LY, MX, NO, OM, PY, QA, SA, SE, SY, UY, VE, YE); Livostin ED (ZA)

Levocarnitine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Levocarnitine may be confused with levocabastine

Pronunciation(lee voe KAR ni teen)

U.S. Brand Names Carnitor®; Carnitor® SF

Canadian Brand Names Carnitor®

Pharmacologic Category Dietary Supplement

Use: Labeled Indications

Oral: Primary systemic carnitine deficiency; acute and chronic treatment of patients with an inborn error of metabolism which results in secondary carnitine deficiency

I.V.: Acute and chronic treatment of patients with an inborn error of metabolism which results in secondary carnitine deficiency; prevention and treatment of carnitine deficiency in patients with end-stage renal disease (ESRD) who are undergoing hemodialysis.

Dosing: Adults

Carnitine deficiency:

Oral: 990 mg (tablet) 2-3 times/day or 1-3 g/day (solution)

I.V.: 50 mg/kg/day in divided doses; titrate based on patient response. Maximum reported dose: 300 mg/kg. An equivalent loading dose may be used in patients in severe metabolic crisis.

ESRD patients on hemodialysis: I.V.: 20 mg/kg dry body weight as a slow 2- to 3-minute bolus after each dialysis session

Note: Safety and efficacy of oral carnitine have not been established in ESRD. Chronic administration of high **oral** doses to patients with severely compromised renal function or ESRD patients on dialysis may result in accumulation of **potentially toxic** metabolites.

Dosing: Elderly Refer to adult dosing.

Dosing: Pediatric

Carnitine deficiency:

Oral: Infants and Children: Initial: 50 mg/kg/day; titrate to 50-100 mg/kg/day in divided doses with a maximum dose of 3 g/day

I.V.: Refer to adult dosing.

Administration: I.V.

Hemodialysis patients: Injection should be given over 2-3 minutes into the venous return line after each dialysis session.

Carnitine deficiency: Administer as a bolus dose over 2-3 minutes or by infusion. Doses should be administered every 3-6 hours.

Administration: Oral Solution may be dissolved in either drink or liquid food. The oral solution should be consumed slowly and spaced evenly throughout the day to improve tolerance. Doses should be spaced every 3-4 hours throughout the day, preferably during or following meals.

StorageIntravenous solution: Store at 25°C (77°F). Compatible at concentrations between 0.5-8 mg/mL in 0.9% sodium chloride or lactated Ringer's solution. Stable in PVC bags for 24 hours.

Warnings/Precautions

Disease-related concerns:

- Renal impairment: Safety and efficacy of oral carnitine have not been established in ESRD. Chronic administration of high oral doses to patients with severely compromised renal function or ESRD patients on dialysis may result in accumulation of potentially toxic metabolites.
- Seizure disorder: Use with caution in patients with seizure disorders or in those at risk of seizures (CNS mass or medications which may lower seizure threshold; both new-onset seizure activity as well as an increased frequency of seizures has been observed.

Pregnancy Risk FactorB

Pregnancy Considerations Teratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. However, carnitine is a naturally occurring substance in mammalian metabolism.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIn breast-feeding women, use must be weighed against the potential exposure of the infant to increased carnitine intake.

Adverse ReactionsFrequencies noted with I.V. therapy (hemodialysis patients).

>10%:

- Cardiovascular: Hypertension (18% to 21%), chest pain (6% to 15%)
- Central nervous system: Headache (3% to 37%), dizziness (10% to 18%), fever (5% to 12%)
- Endocrine & metabolic: Hypercalcemia (6% to 15%)
- Gastrointestinal: Diarrhea (9% to 35%), vomiting (9% to 21%), abdominal pain (5% to 21%), nausea (9% to 12%)
- Hematologic: Anemia (3% to 12%)
- Neuromuscular & skeletal: Weakness (8% to 12%), paresthesia (3% to 12%)
- Respiratory: Cough (10% to 18%), rhinitis (6% to 11%)
- Miscellaneous: Infection (10% to 24%)

1% to 10%:

- Cardiovascular: Tachycardia (5% to 9%), hemorrhage (2% to 9%), palpitation (3% to 8%), peripheral edema (3% to 6%), atrial fibrillation (2% to 6%), ECG abnormality (2% to 6%), vascular disorder (2% to 6%)
- Central nervous system: Depression (5% to 6%), vertigo (2% to 6%)
- Dermatologic: Rash (3% to 5%)
- Endocrine & metabolic: Parathyroid disorder (2% to 6%)
- Gastrointestinal: Taste perversion (2% to 9%), weight loss (3% to 8%), anorexia (3% to 6%), gastrointestinal disorder (2% to 6%), melena (2% to 6%), weight gain (2% to 6%)
- Ocular: Amblyopia (3% to 6%), eye disorder (3% to 6%)
- Respiratory: Bronchitis (3% to 5%)
- Miscellaneous: Allergic reaction (2% to 6%)

Frequency not defined: Body odor, gastritis, seizure

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersPlasma concentrations should be obtained prior to beginning parenteral therapy, and should be monitored weekly to monthly. In metabolic disorders: monitor blood chemistry, vital signs, and plasma carnitine levels (maintain between 35-60 µmol/L). In ESRD patients on dialysis: National Kidney Foundation guidelines recommend basing treatment on clinical signs and symptoms; evaluate response at 3-month intervals and discontinue if no clinical improvement noted within 9-12 months. Reimbursement may require documentation of a plasma free carnitine level <40 µmol/L.

Reference RangeNormal carnitine levels are 40-50 µmol/L; levels should be maintained on therapy between 35-60 µmol/L

Nursing: Physical Assessment/MonitoringMonitor therapeutic effectiveness (according to rationale for therapy) and adverse reactions (eg, CNS, hypertension). **Oral:** Monitor therapeutic effectiveness and assess severity. Assess knowledge and teach patient appropriate use, interventions to reduce side effects, and adverse reactions to report.

Monitoring: Lab TestsPlasma concentrations should be obtained prior to beginning parenteral therapy, and should be monitored weekly to monthly. In metabolic disorders: monitor blood chemistry and plasma carnitine levels (maintain between 35-60 µmol/L). In ESRD patients on dialysis: National Kidney Foundation guidelines recommend basing treatment on clinical signs and symptoms; evaluate response at 3-month intervals and discontinue if no clinical improvement noted within 9-12 months. Reimbursement may require documentation of a plasma free carnitine level <40 µmol/L.

Patient EducationI.V.: Report immediately any dizziness, loss of feeling, acute headache, tremors, or nausea.

Oral: Take exactly as directed; do not alter dose or frequency except as directed by prescriber. Dissolve solution in any liquid and drink with or following meals. The oral solution should be consumed slowly and spaced evenly throughout the day to improve tolerance. You may experience abdominal pain, nausea, or vomiting (small frequent meals, chewing gum, or sucking hard candy); diarrhea (yogurt, boiled milk, or buttermilk may help); or dizziness (use caution driving or engaging in hazardous activities until response to drug is known). Report acute headache, chest pain, tremors, or visual changes; muscle or skeletal weakness; skin rash; swelling of extremities; or other adverse effects. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 250 mg

Injection, solution: 200 mg/mL (5 mL, 12.5 mL)

- Carnitor®: 200 mg/mL (5 mL)

Solution, oral: 100 mg/mL (118 mL)

- Carnitor®: 100 mg/mL (118 mL) [cherry flavor]

Carnitor® SF: 100 mg/mL (118 mL) [sugar free; cherry flavor]

Tablet: 330 mg, 500 mg

Carnitor®: 330 mg

Generic AvailableYes

ManufacturerSigma-Tau Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Solution (Carnitor)

1 g/10 mL (118): $39.99

Solution (Levocarnitine)

1 g/10 mL (118): $29.98

Tablets (Carnitor)

330 mg (90): $84.99

Tablets (Levocarnitine)

330 mg (90): $69.99

Mechanism of ActionCarnitine is a naturally occurring metabolic compound which functions as a carrier molecule for long-chain fatty acids within the mitochondria, facilitating energy production. Carnitine deficiency is associated with accumulation of excess acyl CoA esters and disruption of intermediary metabolism. Carnitine supplementation increases carnitine plasma concentrations. The effects on specific metabolic alterations have not been evaluated. ESRD patients on maintenance HD may have low plasma carnitine levels because of reduced intake of meat and dairy products, reduced renal synthesis, and dialytic losses. Certain clinical conditions (malaise, muscle weakness, cardiomyopathy and arrhythmias) in HD patients may be related to carnitine deficiency.

Pharmacodynamics/Kinetics

Metabolism: Hepatic (limited with moderate renal impairment), to trimethylamine (TMA) and trimethylamine N-oxide (TMAO)

Bioavailability: Oral: ~10% to 20%

Half-life elimination: 17.4 hours

Time to peak: Oral: 3.3 hours

Excretion: Urine (76%, 4% to 9% as unchanged drug); feces (<1%)

Pharmacotherapy PearlsAlthough supplemental carnitine has been shown to increase carnitine concentrations, effects on the signs and symptoms of carnitine deficiency have not been determined.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsL-Carnitine

References

Eknoyan G, Latos DL, and Lindberg J, “Practice Recommendations for the Use of L-Carnitine in Dialysis-Related Carnitine Disorder. National Kidney Foundation Carnitine Consensus Conference,” *Am J Kidney Dis*, 2003, 41(4):868-76[PubMed 12666074]

Schreiber B, “Levocarnitine and Dialysis: A Review,” *Nutr Clin Pract*, 2005, 20(2):218-43.[PubMed 16207659]

International Brand NamesAbedine (JP); Albicar (AR); Bio-Carnitine (BE); Biocarn (CH, DE); Branigen (IT); Cardispan (CR, DO, GT, HN, MX, NI, PA); Carnicor (ES, PH); Carnil (GR); Carnin (KP); Carnitene (CH, HK, NL); Carnitina (AR, ES); Carnitor (GB, HK); Carnivit (PL); Carry FA (KP); Chudex (PL); Disocor (PT); Elcarnitol (CH); Entomin (JP); Fitmax L-Karnityna (PL); Hardbody L-Karnityna (PL); L-Cadul (KP); L-Carnitin (AT, CZ, PL); L-Karnityna (PL); Levocarnil (FR); Monocamin (JP); Nefrocarnit (EE); Neurex (AR); Neuroactil (AR); Secabiol (ES)

Levocetirizine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Levocetirizine may be confused with cetirizine

Pronunciation(LEE vo se TI ra zeen)

U.S. Brand NamesXyzal®

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation

Use: Labeled IndicationsRelief of symptoms of perennial and seasonal allergic rhinitis; treatment of skin manifestations (uncomplicated) of chronic idiopathic urticaria

Dosing: AdultsAllergic rhinitis, chronic urticaria: Oral: 5 mg once daily (in the evening); some patients may experience relief of symptoms with 2.5 mg once daily

Dosing: ElderlyRefer to adult dosing; dosing should begin at the lower end of the dosing range.

Dosing: PediatricAllergic rhinitis, chronic urticaria: Children: Oral:

6-11 years: 2.5 mg once daily (in the evening); maximum: 2.5 mg/day

≥12 years: Refer to adult dosing.

Dosing: Renal Impairment

Children 6-11 years with renal impairment: Contraindicated

Children ≥12 and Adults:

Cl_{cr} 50-80 mL/minute: 2.5 mg once daily

Cl_{cr} 30-50 mL/minute: 2.5 mg once every other day

Cl_{cr} 10-30 mL/minute: 2.5 mg twice weekly (every 3 or 4 days)

Cl_{cr} <10 mL/minute, hemodialysis patients: Contraindicated

Dosing: Hepatic ImpairmentNo adjustment required.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister in the evening. May be administered with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at room temperature of 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to levocetirizine, cetirizine, or any component of the formulation; end-stage renal disease; hemodialysis; children 6-11 years of age with renal impairment

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Renal impairment: Levocetirizine is excreted primarily by the kidneys; use with caution in adults with mild-to-moderate renal impairment; dosage adjustments may be needed. Use is contraindicated in end-stage renal disease (Cl_{cr} <10 mL/minute), patients undergoing hemodialysis, and in children 6-11 years of age with renal impairment.

Special populations:

- Elderly: Use with caution in the elderly.
- Pediatrics: Not FDA approved for use in children <6 years of age.

Geriatric ConsiderationsSee Dosage - Renal Impairment.

Pregnancy Risk FactorB

Pregnancy ConsiderationsLevocetirizine was not shown to be teratogenic in animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsCetirizine is excreted in breast milk; therefore, levocetirizine would be expected to enter breast milk. Use is not recommended while breast-feeding.

Adverse Reactions

1% to 10%:

Central nervous system: Somnolence (3% to 6%), fever (children 4%), fatigue (1% to 4%)

Gastrointestinal: Xerostomia (2% to 3%)

Neuromuscular & skeletal: Weakness (2%)

Respiratory: Nasopharyngitis (4% to 6%), cough (children 3%), epistaxis (children 2%), pharyngitis (1% to 2%)

<1%, postmarketing, and/or case reports: Aggression, agitation, anaphylaxis, angioneurotic edema, bilirubin increased, dyspnea, fixed-drug eruption, hepatitis, hypersensitivity, myalgia, nausea, palpitation, pruritus, rash, seizure, syncope, transaminases increased, urticaria, visual disturbances, weight gain

The following potentially-severe adverse reactions have been reported with cetirizine and, therefore, may also occur with levocetirizine: Cholestasis, glomuleronephritis, hallucination, hypotension (severe), orofacial dyskinesia, suicidal ideation

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersCreatinine clearance (prior to treatment for dosing adjustment)

Nursing: Physical Assessment/MonitoringMonitor therapeutic response and adverse reactions at the beginning and periodically throughout therapy. Assess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Monitoring: Lab TestsCreatinine clearance (prior to treatment for dosing adjustment)

Patient EducationYou may experience drowsiness (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Avoid alcohol or use of other central nervous system depressants; may increase drowsiness. Maintain adequate hydration (2-3 L/day) unless instructed to restrict intake by prescriber. Report excessive sedation. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral, as dihydrochloride:

Xyzal®: 0.5 mg/mL (150 mL)

Tablet, as dihydrochloride [scored]:

Xyzal®: 5 mg

Generic AvailableNo

ManufacturerUCB, Inc and Sanofi-Aventis

Pricing: U.S. (www.drugstore.com)

Solution (Xyzal)

2.5 mg/5 mL (148): $89.23

Tablets (Xyzal)

5 mg (90): $261.41

Mechanism of ActionLevocetirizine is an antihistamine which selectively competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract. Levocetirizine, the active enantiomer of cetirizine, has twice the binding affinity at the H1-receptor compared to cetirizine.

Pharmacodynamics/Kinetics

Onset of action: 1 hour

Duration: 24 hours

Absorption: Rapid and extensive

Distribution: 0.4 L/kg

Protein binding: 91% to 92%

Metabolism: Minimal (<14%); via aromatic oxidation, N and O-dealkylation (via CYPA4), and taurine conjugation

Half-life elimination: Children: ~6 hours; Adults: ~8-9 hours; Renal impairment: 11-34 hours; End-stage renal disease: 46 hours

Time to peak, plasma: Children: 1.2 hours; Adults: Oral solution: 0.5 hours, Tablet: 0.9 hours

Excretion: Urine (85%); feces (13%)

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause CNS depression; use with caution. Rare reports of aggression and agitation.

Mental Health: Effects on Psychiatric Treatment Acetylcholinesterase inhibitors may diminish the therapeutic effect of levocetirizine. Conversely, levocetirizine may diminish the therapeutic effect of centrally-acting acetylcholinesterase inhibitors. May cause anticholinergic and sedative adverse effects; concomitant use with psychotropics with anticholinergic or sedative activity may produce additive effects. Antihistamines may enhance the arrhythmogenic effect of phenothiazine antipsychotic agents.

Index Terms Levocetirizine Dihydrochloride

References

Nettis E, Colanardi MC, Barra L, et al, “Levocetirizine in the Treatment of Chronic Idiopathic Urticaria: A Randomized, Double-Blind, Placebo-Controlled Study,” *Br J Dermatol*, 2006, 154(3):533-8.[PubMed 16445787]

Simons FE and Simons KJ, “Levocetirizine: Pharmacokinetics and Pharmacodynamics in Children Age 6 to 11 Years,” *J Allergy Clin Immunol*, 2005, 116(2):355-61.[PubMed 16083790]

International Brand Names Alergocit (PK); Alermax (PY); Cetriler (PE); Degraler (CN, PE); Histaplen (UY); Levaler (DO, GT, PA, SV); Levocet (IN); Levomine (AR); Xazal (ES); Xusal (DE, MX); Xuzal (EC); Xyzal (BG, CH, CL, CZ, DE, DK, EE, FI, FR, GB, HK, ID, IE, KP, MY, NO, PH, PT, SE, SG, TH, TW); Xyzall (BE); Zyxem (BR, CO, MX)

Levodopa, Carbidopa, and Entacapone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(lee voe DOE pa, kar bi DOE pa, & en TA ka pone)
U.S. Brand NamesStalevo®
Canadian Brand NamesStalevo®
Pharmacologic CategoryAnti-Parkinson's Agent, COMT Inhibitor; Anti-Parkinson's Agent, Dopamine Agonist
Use: Labeled IndicationsTreatment of idiopathic Parkinson's disease
Dosing: Adults

Note: All strengths of Stalevo® contain a carbidopa/levodopa ratio of 1:4 plus entacapone 200 mg.

Parkinson's disease: Oral: Dose should be individualized based on therapeutic response; doses may be adjusted by changing strength or adjusting interval. Fractionated doses are not recommended and only 1 tablet should be given at each dosing interval; maximum daily dose: 8 tablets of Stalevo® 50, 75, 100, 125, or 150, **or** 6 tablets of Stalevo® 200.

Patients previously treated with carbidopa/levodopa immediate release tablets (ratio of 1:4):

With current entacapone therapy: May switch directly to corresponding strength of combination tablet. No data available on transferring patients from controlled release preparations or products with a 1:10 ratio of carbidopa/levodopa.

Without entacapone therapy:

If current levodopa dose is >600 mg/day: Levodopa dose reduction may be required when adding entacapone to therapy; therefore, titrate dose using individual products first (carbidopa/levodopa immediate release with a ratio of 1:4 plus entacapone 200 mg); then transfer to combination product once stabilized.

If current levodopa dose is <600 mg without dyskinesias: May transfer to corresponding dose of combination product; monitor, dose reduction of levodopa may be required.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentUse caution with severe renal impairment; specific dosing recommendations not available.
Dosing: Hepatic ImpairmentUse with caution; specific dosing recommendations not available.
Administration: OralSwallow tablet whole; do not crush, break, or chew. Only 1 tablet should be administered at each dosing interval.
Dietary ConsiderationsMay take with or without food. Distribute protein intake throughout the day to avoid fluctuations in levodopa absorption. Separate dosing of iron supplements and multivitamins with minerals.
StorageStore at controlled room temperature of 25°C (77°F).
ContraindicationsHypersensitivity to levodopa, carbidopa, entacapone, or any component of the formulation; use of nonselective MAO inhibitor therapy with or within prior 14 days; narrow-angle glaucoma; undiagnosed skin lesions or history of melanoma
Allergy Considerations

- COMT Inhibitor Allergy
- Levodopa Allergy

Warnings/Precautions

Concerns related to adverse effects:

• Dyskinesias: May cause or exacerbate dyskinesias; may require dose adjustment.

• Hallucinations: May cause hallucinations.

• Impulsive control disorders: Dopamine agonists used for Parkinson’s disease or restless legs syndrome have been associated with compulsive behaviors and/or loss of impulse control, which has manifested as pathological gambling, libido increases (hypersexuality), and/or binge eating. Causality has not been established, and controversy exists as to whether this phenomenon is related to the underlying disease, prior behaviors/addictions and/or drug therapy. Dose reduction or discontinuation of therapy has been reported to reverse these behaviors in some, but not all cases.

• Pleural/retroperitoneal fibrosis: Ergot-derived dopamine agonists have also been associated with fibrotic complications (eg, retroperitoneal fibrosis, pleural effusions, pleural thickening, and pulmonary infiltrates); monitor closely for signs and symptoms of fibrosis.

• Rhabdomyolysis: Severe cases have been reported; may be related to severe, prolonged motor activity/dyskinesia.

• Syncope: May cause syncope; incidence may be increased in patients with documented hypotension.

Disease-related concerns:

• Cardiovascular disease: Use with caution in patients with cardiovascular disease, including a history of myocardial infarction and arrhythmias.

- Endocrine disease: Use with caution when interpreting plasma/urine catecholamine levels; falsely diagnosed pheochromocytoma has been rarely reported.

- Glaucoma: Use with caution in patients with wide-angle glaucoma; monitor IOP carefully; contraindicated in patients with narrow-angle glaucoma.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including biliary obstruction.

- Peptic ulcer disease: Use with caution in patients with a history of peptic ulcer disease; risk of gastrointestinal hemorrhage may be increased.

- Psychotic disorders: Use with extreme caution in patients with psychotic disorders; observe patients closely for development of depression with concomitant suicidal tendencies.

- Renal impairment: Use with caution in patients with severe renal impairment.

Concurrent drug therapy concerns:

- Catecholamines: Use caution with agents metabolized by COMT (eg, epinephrine, dopamine, methyldopa) regardless of route of administration; effects may be enhanced when used with entacapone.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Discontinuation of therapy: Dopaminergic agents have been associated with a syndrome resembling neuroleptic malignant syndrome on abrupt withdrawal or significant dosage reduction after long-term use.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were observed with levodopa, carbidopa, and entacapone in animal studies. There are case reports of levodopa crossing the placenta in humans. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if potential benefit exceeds risks.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsSee individual agents.

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antipsychotics (Atypical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Antipsychotics (Typical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

COMT Substrates: COMT Inhibitors may decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Levodopa. Only applies to oral iron preparations. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

MAO Inhibitors: Levodopa may enhance the adverse/toxic effect of MAO Inhibitors. Of particular concern is the development of hypertensive reactions when levodopa is used with nonselective MAOI. *Risk D: Consider therapy modification*

MAO Inhibitors: COMT Inhibitors may enhance the adverse/toxic effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Methionine: May diminish the therapeutic effect of Levodopa. Probably only with large doses of methionine. Data was generated using 4.5gm daily. *Risk D: Consider therapy modification*

Metoclopramide: May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk C: Monitor therapy*

Phenytoin: May diminish the therapeutic effect of Levodopa. *Risk C: Monitor therapy*

Pyridoxine: May diminish the therapeutic effect of Levodopa. *Risk D: Consider therapy modification*

Sapropterin: May enhance the adverse/toxic effect of Levodopa. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: High-protein diets and increased stomach acid may delay absorption of levodopa. Iron may decrease bioavailability of levodopa. Entacapone has been reported to chelate iron and decreasing serum iron levels were noted in clinical trials; however, clinically significant anemia has not been observed.

Test InteractionsFalse-negative reaction using glucose-oxidase tests for glucosuria; false-positive urine ketones; false diagnosis for pheochromocytoma (rare) based on plasma and urine levels of catecholamines

Monitoring ParametersSigns and symptoms of Parkinson's disease; liver function tests, renal function; blood pressure, mental status; signs and symptoms of neuroleptic malignant syndrome if abrupt discontinuation required (as with surgery); serum iron (if signs of anemia); IOP (in patients with wide-angle glaucoma)

Nursing: Physical Assessment/MonitoringSee individual agents (Carbidopa and Levodopa; Entacapone).

Monitoring: Lab TestsLiver function tests, serum iron (if signs of anemia)

Patient EducationSee individual agents (Carbidopa and Levodopa; Entacapone). Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant or intend to become pregnant or are breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Stalevo® 50: Levodopa 50 mg, carbidopa 12.5 mg, and entacapone 200 mg

Stalevo® 75: Levodopa 75 mg, carbidopa 18.75 mg, and entacapone 200 mg

Stalevo® 100: Levodopa 100 mg, carbidopa 25 mg, and entacapone 200 mg

Stelevo® 125: Levodopa 125 mg, carbidopa 31.25 mg, and entacapone 200 mg

Stalevo® 150: Levodopa 150 mg, carbidopa 37.5 mg, and entacapone 200 mg

Stalevo® 200: Levodopa 200 mg, carbidopa 50 mg, and entacapone 200 mg

Generic AvailableNo
ManufacturerNovartis Pharm Corp
Pricing: U.S. (www.drugstore.com)

Tablets (Stalevo 100)

25-100-200 mg (90): $259.33

Tablets (Stalevo 150)

37.5-150-200 mg (30): $93.62

Tablets (Stalevo 200)

50-200-200 mg (100): $298.18

Tablets (Stalevo 50)

12.5-50-200 mg (30): $90.31

Mechanism of Action

Levodopa: The metabolic precursor of dopamine, a chemical depleted in Parkinson's disease. Levodopa is able to circulate in the plasma and cross the blood-brain-barrier (BBB), where it is converted by striatal enzymes to dopamine.

Carbidopa: Inhibits the peripheral plasma breakdown of levodopa by inhibiting its decarboxylation; increases available levodopa at the BBB

Entacapone: A reversible and selective inhibitor of catechol-O-methyltransferase (COMT). Alters the pharmacokinetics of levodopa, resulting in more sustained levodopa serum levels and increased concentrations available for absorption across the BBB.

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Antiparkinsonian Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Index TermsCarbidopa, Levodopa, and Entacapone; Entacapone, Carbidopa, and Levodopa
References

Factor SA, “Current Status of Symptomatic Medical Therapy in Parkinson’s Disease,” *Neurotherapeutics*, 2008, 5(2):164-80. [PubMed 18394561]

Molina JA, Sàinz-Artiga MJ, Fraile A, et al, “Pathologic Gambling in Parkinson's Disease: A Behavioral Manifestation of Pharmacologic Treatment,” *Mov Disord*, 2000, 15(5):869-72.[PubMed 11009192]

Weintraub D, Siderowf AD, Potenza MN, et al, “Association of Dopamine Agonist Use With Impulse Control Disorders in Parkinson Disease,” *Arch Neurol*, 2006, 63(7):969-73.[PubMed 16831966]

International Brand NamesStalev (PH); Stalevo (AR, AT, AU, BE, BG, BR, CH, CN, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IT, KP, MY, NL, NO, PE, PT, RU, SE, SG, TH, TR, TW, VE)

Levofloxacin

Lexi-Drugs Online

English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Levaquin® may be confused with Levoxyl®, Levsin/SL®, Lovenox®

Levofloxacin may be confused with levetiracetam, levodopa, levothyroxine

Pronunciation(lee voe FLOKS a sin)

U.S. Brand NamesIquix®; Levaquin®; Quixin®

Canadian Brand NamesLevaquin®; Novo-Levofloxacin

Pharmacologic CategoryAntibiotic, Quinolone; Respiratory Fluoroquinolone

Use: Labeled Indications

Systemic: Treatment of community-acquired pneumonia, including multidrug resistant strains of *S. pneumoniae* (MDRSP); nosocomial pneumonia; chronic bronchitis (acute bacterial exacerbation); acute bacterial sinusitis; prostatitis, urinary tract infection (uncomplicated or complicated); acute pyelonephritis; skin or skin structure infections (uncomplicated or complicated); reduce incidence or disease progression of inhalational anthrax (postexposure)

Ophthalmic: Treatment of bacterial conjunctivitis caused by susceptible organisms (Quixin™ 0.5% ophthalmic solution); treatment of corneal ulcer caused by susceptible organisms (Iquix® 1.5% ophthalmic solution)

Use: Unlabeled/InvestigationalDiverticulitis, enterocolitis (*Shigella* spp.), epididymitis (nongonococcal), gonococcal infections, Legionnaires' disease, peritonitis, PID

Note: As of April 2007, the CDC no longer recommends the use of fluoroquinolones for the treatment of gonococcal disease.

Dosing: Adults**Note:** Sequential therapy (intravenous to oral) may be instituted based on prescriber's discretion.

Anthrax (inhalational): 500 mg every 24 hours for 60 days, beginning as soon as possible after exposure

Chronic bronchitis (acute bacterial exacerbation): Oral, I.V.: 500 mg every 24 hours for at least 7 days

Conjunctivitis (0.5% ophthalmic solution): Ophthalmic:

Treatment day 1 and day 2: Instill 1-2 drops into affected eye(s) every 2 hours while awake, up to 8 times/day

Treatment day 3 through day 7: Instill 1-2 drops into affected eye(s) every 4 hours while awake, up to 4 times/day

Corneal ulceration (1.5% ophthalmic solution): Ophthalmic:

Treatment day 1 through day 3: Instill 1-2 drops into affected eye(s) every 30 minutes to 2 hours while awake and 4-6 hours after retiring.

Treatment day 4 through completion: Instill 1-2 drops into affected eye(s) every 1 to 4 hours while awake.

Diverticulitis, peritonitis (unlabeled use): Oral, I.V.: 750 mg every 24 hours for 7-10 days; use adjunctive metronidazole therapy

Dysenteric enterocolitis,*Shigella spp.*(unlabeled use): Oral, I.V.: 500 mg every 24 hours for 3-5 days

Epididymitis, nongonococcal (unlabeled use): 500 mg once daily for 10 days

Gonococcal infection (unlabeled use): Oral, I.V.:

Cervicitis, urethritis: 250 mg for one dose with azithromycin or doxycycline; **Note:** As of April 2007, the CDC no longer recommends the use of fluoroquinolones for the treatment of uncomplicated gonococcal disease.

Disseminated infection: 250 mg I.V. once daily; 24 hours after symptoms improve may change to 500 mg orally every 24 hours to complete total therapy of 7 days; **Note:** As of April 2007, the CDC no longer recommends the use of fluoroquinolones for the treatment of more serious gonococcal disease, unless no other options exist and susceptibility can be confirmed via culture.

Pelvic inflammatory disease (unlabeled use): 500 mg once daily for 14 days with or without adjunctive metronidazole; **Note:** The CDC recommends use only if standard cephalosporin therapy is not feasible and community prevalence of quinolone-resistant gonococcal organisms is low. Culture sensitivity must be confirmed.

Pneumonia: Oral, I.V.:

Community-acquired: 500 mg every 24 hours for 7-14 days or 750 mg every 24 hours for 5 days (efficacy of 5-day regimen for MDRSP not established)

Nosocomial: 750 mg every 24 hours for 7-14 days

Prostatitis (chronic bacterial): Oral, I.V.: 500 mg every 24 hours for 28 days

Sinusitis (acute bacterial): Oral, I.V.: 500 mg every 24 hours for 10-14 days or 750 mg every 24 hours for 5 days

Skin and skin structure infections: Oral, I.V.:

Uncomplicated: 500 mg every 24 hours for 7-10 days

Complicated: 750 mg every 24 hours for 7-14 days

Traveler's diarrhea (unlabeled use): Oral, I.V.: 500 mg for one dose

Urinary tract infections: Oral, I.V.:

Uncomplicated: 250 mg once daily for 3 days

Complicated, including acute pyelonephritis: 250 mg once daily for 10 days **or** 750 mg once daily for 5 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Anthrax (inhalational, postexposure): : Oral, I.V.

Children ≥6 months and ≤50 kg: 8 mg/kg every 12 hours for 60 days (do not exceed 250 mg/dose), beginning as soon as possible after exposure

>50 kg : 500 mg every 24 hours for 60 days, beginning as soon as possible after exposure

Conjunctivitis (bacterial): Ophthalmic: Children ≥1 year: Refer to adult dosing.

Corneal ulceration: Ophthalmic: Children ≥6 years: Refer to adult dosing.

Dosing: Renal Impairment

Normal renal function dosing of 750 mg/day:

Cl_{cr} 20-49 mL/minute: Administer 750 mg every 48 hours

Cl_{cr} 10-19 mL/minute: Administer 750 mg initial dose, followed by 500 mg every 48 hours

Hemodialysis/CAPD: Administer 750 mg initial dose, followed by 500 mg every 48 hours

Normal renal function dosing of 500 mg/day:

Cl_{cr} 20-49 mL/minute: Administer 500 mg initial dose, followed by 250 mg every 24 hours

Cl_{cr} 10-19 mL/minute: Administer 500 mg initial dose, followed by 250 mg every 48 hours

Hemodialysis/CAPD: Administer 500 mg initial dose, followed by 250 mg every 48 hours

Normal renal function dosing of 250 mg/day:

Cl_{cr} 20-49 mL/minute: No dosage adjustment required

Cl_{cr} 10-19 mL/minute: Administer 250 mg every 48 hours (except in uncomplicated UTI, where no dosage adjustment is required)

Hemodialysis/CAPD: No information available

CRRT: **Note:** Clearance dependent on filter type, flow rates, and other variables.

CVVH/CVVHD/CVVHDF: Alternative recommendations exist:

500 mg every 48 hours **or**

250 mg every 24 hours (**Note:** This regimen has been shown to be equivalent to 500 mg/day in normal renal function. Appropriateness of this regimen for target dosing equal to 750 mg/day is not known.)

Calculations

- Creatinine Clearance: Adults

Administration: I.V.Infuse 250-500 mg I.V. solution over 60 minutes; infuse 750 mg I.V. solution over 90 minutes. Too rapid of infusion can lead to hypotension. Avoid administration through an intravenous line with a solution containing multivalent cations (eg, magnesium, calcium). Maintain adequate hydration of patient to prevent crystalluria.

Administration: I.V. DetailpH: 3.8-5.8

Administration: OralTablets may be administered without regard to meals. Oral solution should be administered 1 hour before or 2 hours after meals. Maintain adequate hydration of patient to prevent crystalluria.

Dietary ConsiderationsTablets may be taken without regard to meals. Oral solution should be administered on an empty stomach (1 hour before or 2 hours after a meal). Take 2 hours before or 2 hours after multiple vitamins, antacids, or other products containing magnesium, aluminum, iron, or zinc.

Storage

Solution for injection:

Vial: Store at room temperature. Protect from light. Diluted solution is stable for 72 hours when stored at room temperature; stable for 14 days when stored under refrigeration. When frozen, stable for 6 months; do not refreeze. Do not thaw in microwave or by bath immersion.

Premixed: Store at ≤25°C (77°F); do not freeze. Brief exposure to 40°C (104°F) does not affect product. Protect from light.

Tablet, oral solution: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Ophthalmic solution: Store at 15°C to 25°C (59°F to 77°F).

ReconstitutionSolution for injection: Single-use vials must be further diluted in compatible solution to a final concentration of 5 mg/mL prior to infusion.

CompatibilityStable in D_5LR, D_5NS, $D_5{}^1/_2$NS with 0.15% KCl, D_5W, NS, Plasma-Lyte® 56/5% dextrose, sodium lactate (M/6); **incompatible** with mannitol 20%, sodium bicarbonate 5%.

Y-site administration: Compatible: Amikacin, aminophylline, ampicillin, bivalirudin, caffeine citrate, cefotaxime, cimetidine, clindamycin, daptomycin, dexamethasone sodium phosphate, dobutamine, dopamine, epinephrine, fenoldopam, fentanyl, gentamicin, isoproterenol, lidocaine, linezolid, lorazepam, metoclopramide, morphine, oxacillin, pancuronium, penicillin G sodium, phenobarbital, phenylephrine, sodium bicarbonate, vancomycin. **Incompatible:** Acyclovir, alprostadil, azithromycin, drotrecogin alfa, furosemide, heparin, indomethacin, lansoprazole, nitroglycerin, propofol, sodium nitroprusside. **Variable (consult detailed reference):** Insulin (regular).

RestrictionsAn FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to levofloxacin, any component of the formulation, or other quinolones

Allergy Considerations

- Fluoroquinolone Allergy

Warnings/Precautions

Boxed Warnings:

- Tendon inflammation/rupture: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Altered cardiac conduction: Fluoroquinolones may prolong QT_c interval; avoid use in patients with a history of QT_c prolongation, uncorrected hypokalemia, hypomagnesemia, or concurrent administration of other medications known to prolong the QT interval (including Class Ia and Class III antiarrhythmics, cisapride, erythromycin, antipsychotics, and tricyclic antidepressants).

- CNS stimulation: Tremor, restlessness, confusion, and very rarely hallucinations or seizures may occur; use with caution in patients with known or suspected CNS disorder. Discontinue in patients who experience significant CNS adverse effects (eg, dizziness, hallucinations, suicidal ideations or actions).

- Glucose regulation: Fluoroquinolones have been associated with the development of serious, and sometimes fatal, hypoglycemia. These events have occurred most often in elderly patients with diabetes, but have also been reported in patients without a prior history of diabetes. Prompt identification and treatment of hypoglycemia is essential. Individual quinolones may differ in their potential to cause this effect. It was most evident with gatifloxacin (no longer marketed as systemic formulation). Hyperglycemia has also been associated with the use of fluoroquinolones. Patients should be monitored closely for signs/symptoms of disordered glucose regulation.

- Hepatotoxicity: Unrelated to hypersensitivity, severe hepatotoxicity (including acute hepatitis and fatalities) has been reported. Elderly patients may be at greater risk. Discontinue therapy immediately if signs and symptoms of hepatitis occur.

- Hypersensitivity reactions: Severe hypersensitivity reactions, including anaphylaxis, have occurred with quinolone therapy. The spectrum of these reactions can vary widely; reactions may present as typical allergic symptoms (eg, itching, urticaria, rash, edema) after a single dose, or may manifest as severe idiosyncratic dermatologic (eg, Stevens-Johnson, toxic epidermal necrolysis), vascular (eg, vasculitis), pulmonary (eg, pneumonitis), renal (eg, nephritis), hepatic (eg, hepatic failure or necrosis), and/or hematologic (eg, anemia, cytopenias) events, usually after multiple doses. Prompt discontinuation of drug should occur if skin rash or other symptoms arise.

- Peripheral neuropathy: The use of quinolones has been linked to peripheral neuropathy (rare); discontinue if symptoms of sensory or sensorimotor neuropathy occur.

- Phototoxicity: Avoid excessive sunlight and take precautions to limit exposure (eg, loose fitting clothing, sunscreen); may cause moderate-to-severe phototoxicity reactions. Discontinue use if photosensitivity occurs.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

- Tendon inflammation/rupture: **[U.S. Boxed Warning]: There have been reports of tendon inflammation and/or rupture with quinolone antibiotics; risk may be increased with concurrent corticosteroids, organ transplant recipients, and in patients >60 years of age.** Rupture of the Achilles tendon sometimes requiring surgical repair has been reported most frequently; but other tendon sites (eg, rotator cuff, biceps) have also been reported. Strenuous physical activity may be an independent risk factor for tendonitis. Discontinue at first sign of tendon inflammation or pain. May occur even after discontinuation of therapy.

Disease-related concerns:

- Myasthenia gravis: Some quinolones may exacerbate myasthenia gravis, use with caution (rare, potentially life-threatening weakness of respiratory muscles may occur).

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required. May increase risk of tendon rupture.

- Rheumatoid arthritis: Use with caution in patients with rheumatoid arthritis; may increase risk of tendon rupture.

- Seizures: Use with caution in individuals at risk of seizures (CNS disorders or concurrent therapy with medications which may lower seizure threshold). Potential for seizures, although very rare, may be increased with concomitant NSAID therapy.

Special populations:

- Elderly: Adverse effects (eg, hepatotoxicity, tendon rupture, QT changes) may be increased in the elderly.

- G6PD deficiency: Hemolytic reactions may (rarely) occur with quinolone use in patients with latent or actual G6PD deficiency.

- Pediatrics: Safety and efficacy have not been established in children <1 year of age for Quixin™ and in children <6 years of age for Iquix®. Systemic use is only recommended in children <18 years of age for the prevention of inhalational anthrax (postexposure); increased incidence of musculoskeletal disorders (eg, arthralgia, tendon rupture) has been observed in children.

Dosage form specific issues:

- Ophthalmic solution: For topical use only. Do not inject subconjunctivally or introduce into anterior chamber of the eye. Contact lenses should not be worn during treatment for bacterial conjunctivitis. Indications for ophthalmic solutions are product concentration-specific and should not be used interchangeably.

Geriatric ConsiderationsThe risk of torsade de pointes and tendon inflammation and/or rupture associated with the concomitant use of corticosteroids and quinolones is increased in the elderly population. See Warnings/Precautions regarding tendon rupture in patients >60 years of age. Adjust dose for renal function.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in some animal studies; therefore, the manufacturer classifies levofloxacin as pregnancy category C. Levofloxacin crosses the placenta. Quinolone exposure during human pregnancy has been reported with other agents (see Ciprofloxacin, Ofloxacin, and Norfloxacin monographs). To date, no specific teratogenic effect or increased pregnancy risk has been identified; however, because of concerns of cartilage damage in immature animals exposed to quinolones and the limited levofloxacin specific data, levofloxacin should only be used during pregnancy if a safer option is not available.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsBased on data from a case report, small amounts of levofloxacin are excreted in breast milk. Breast-feeding is not recommended by the manufacturer. Levofloxacin is the L-isomer of ofloxacin. Ofloxacin has also been shown to have minimal concentrations in human milk and is considered “usually compatible with breastfeeding” by the AAP. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Levofloxacin in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Cardiovascular: Chest pain (1%), edema (1%)

Central nervous system: Headache (6%), insomnia (4%), dizziness (3%), fatigue (1%), pain (1%)

Dermatologic: Rash (2%), pruritus (1%)

Gastrointestinal: Taste disturbance (8% to 10% [ophthalmic]), nausea (7%), diarrhea (5%), constipation (3%), abdominal pain (2%), dyspepsia (2%), vomiting (2%)

Genitourinary: Vaginitis (1%)

Local: Injection site reaction (1%)

Ocular (with ophthalmic solution use): Decreased vision (transient), foreign body sensation, transient ocular burning, ocular pain or discomfort, photophobia

Respiratory: Pharyngitis (4%), dyspnea (1%)

Miscellaneous: Moniliasis (1%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening):

Systemic: Acute renal failure, agitation, agranulocytosis; allergic reaction (including anaphylaxis, angioedema, pneumonitis rash, pneumonitis, and serum sickness); anaphylactoid reaction, arrhythmia (including atrial/ventricular tachycardia/fibrillation and torsade de pointes), aplastic anemia, arthralgia, ascites, bradycardia, bronchospasm, carcinoma, cardiac failure, cholecystitis, cholelithiasis, confusion, depression, EEG abnormalities, encephalopathy, eosinophilia, erythema multiforme, GI hemorrhage, granulocytopenia, hallucination, heart block, hemolytic anemia, hemoptysis, hepatic failure (some fatal), hepatitis, hyper-/hypoglycemia, hyperkalemia, hyperkinesias, hyper-/hypotension, infection, INR increased, intestinal obstruction, intracranial hypertension, involuntary muscle contractions, jaundice, leukocytosis, leukopenia, leukorrhea, lymphadenopathy, MI, migraine, multiple organ failure, myalgia, nephritis (interstitial), palpitation, pancreatitis, pancytopenia, paralysis, paresthesia, peripheral neuropathy, photosensitivity (<0.1%), pleural effusion, pneumonitis, postural hypotension, prothrombin time increased/decreased, pseudomembraneous colitis, psychosis, pulmonary edema, pulmonary embolism, purpura, QT_c prolongation, respiratory depression, rhabdomyolysis, seizure, skin disorder, somnolence, speech disorder, Stevens-Johnson syndrome, stupor, suicide attempt/ideation, syncope, tendonitis, tendon rupture, tongue edema, toxic epidermal necrolysis, transaminases increased, thrombocythemia, thrombocytopenia, tremor, urticaria, WBC abnormality

Ophthalmic solution: Allergic reaction, lid edema, ocular dryness, ocular itching

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. **Exceptions:** Sodium Bicarbonate. *Risk D: Consider therapy modification*

Calcium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Calcium Chloride. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Quinolone Antibiotics may enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Didanosine: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents (excludes enteric coated formulation of didanosine). *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Insulin: May enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Mycophenolate: Quinolone Antibiotics may decrease the serum concentration of Mycophenolate. Specifically, quinolones may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nonsteroidal Anti-Inflammatory Agents: May enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Probenecid: May increase the serum concentration of Quinolone Antibiotics. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Quinapril: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sevelamer: May decrease the absorption of Quinolone Antibiotics. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sulfonylureas: Quinolone Antibiotics may enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Quinolone Antibiotics may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zinc Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Test InteractionsSome quinolones may produce a false-positive urine screening result for opiates using commercially-available immunoassay kits. This has been demonstrated most consistently for levofloxacin and ofloxacin, but other quinolones have shown cross-reactivity in certain assay kits. Confirmation of positive opiate screens by more specific methods should be considered.

Monitoring ParametersEvaluation of organ system functions (renal, hepatic, ophthalmologic, and hematopoietic) is recommended periodically during therapy; the possibility of crystalluria should be assessed; WBC and signs of infection

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests prior to beginning therapy. Use caution in patients with known or suspected CNS disorder, current or potential for QT prolongation, renal or hepatic impairment, or diabetes. Assess other pharmacological or herbal products patient may be taking for potential interactions. See Administration for infusion specifics. Patient should be monitored closely; if an allergic reaction occurs (itching, urticaria, dyspnea or facial edema, loss of consciousness, tingling, cardiovascular collapse), drug should be discontinued immediately and prescriber notified. Evaluate results of laboratory tests, therapeutic effectiveness (resolution of infection), and adverse reactions (eg, hypersensitivity reactions [severe reactions, including anaphylaxis, have occurred with quinolone therapy], opportunistic infection, tendon rupture, persistent diarrhea [*C. difficile*-associated colitis can occur up to 2 months post treatment]) regularly during prolonged therapy. Teach patient proper use (according to formulation), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy. Monitor CBC periodically during therapy. Monitor renal or hepatic function if therapy is prolonged.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. If administered by infusion, report immediately any chest or back pain; tightness in chest; difficulty swallowing; swelling of face or mouth; or redness, swelling, or pain at infusion site.

Oral: Take exactly as directed (timing with meals, dairy products, antacids, or products containing calcium, iron, or zinc differs with each formulation). Take entire prescription, even if feeling better. If you have diabetes, monitor glucose levels closely; may cause hypoglycemia. May cause dizziness, lightheadedness, or confusion (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid exposure to direct sunlight or tanning situations). Report chest pain or palpitations; persistent diarrhea, abdominal pain, or constipation; signs of infection (unusual fever or chills, vaginal itching, or foul-smelling vaginal discharge); unusual bruising or bleeding; or other persistent adverse effects. If tendon inflammation or pain occurs or you experience signs of an allergic reaction (eg, itching, skin rash, respiratory difficulty, facial edema, difficulty swallowing, chest pain, palpitations) discontinue use and contact prescriber immediately. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Ophthalmic: Wash hands before instilling solution. Sit or lie down to instill. Open eye, look at ceiling, and instill prescribed amount of solution. Close eye, roll eye in all directions, and apply gentle pressure to inner corner of eye. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Temporary stinging or blurred vision may occur. Report persistent pain, burning, vision changes, swelling, itching, or worsening of condition. Discontinue medication and contact prescriber immediately if you develop a rash or allergic reaction. Do not wear contact lenses.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion, premixed in D_5W [preservative free]:

Levaquin®: 250 mg (50 mL); 500 mg (100 mL); 750 mg (150 mL)

Injection, solution [preservative free]

Levaquin®: 25 mg/mL (20 mL, 30 mL)

Solution, ophthalmic [drops]:

Iquix®: 1.5% (5 mL)

Quixin®: 0.5% (5 mL) [contains benzalkonium chloride]

Solution, oral:

Levaquin®: 25 mg/mL (480 mL) [contains benzyl alcohol, propylene glycol]

Tablet, oral:

Levaquin®: 250 mg, 500 mg, 750 mg

Levaquin® Leva-Pak: 750 mg (5s)

Generic AvailableNo

ManufacturerOrtho-McNeil Pharmaceutical, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Levaquin)

250 mg (10): $119.91

500 mg (10): $139.09

750 mg (30): $773.29

Tablets (Levaquin LEVA-pak)

750 mg (5): $130.69

Mechanism of ActionAs the S (-) enantiomer of the fluoroquinolone, ofloxacin, levofloxacin, inhibits DNA-gyrase in susceptible organisms thereby inhibits relaxation of supercoiled DNA and promotes breakage of DNA strands. DNA gyrase (topoisomerase II), is an essential bacterial enzyme that maintains the superhelical structure of DNA and is required for DNA replication and transcription, DNA repair, recombination, and transposition.

Pharmacodynamics/Kinetics

Absorption: Rapid and complete

Distribution: V_d: 74-112 L; CSF concentrations ~15% of serum levels; high concentrations are achieved in prostate, lung, and gynecological tissues, sinus, saliva

Protein binding: ~24% to 38%; primarily to albumin

Metabolism: Minimally hepatic

Bioavailability: ~99%

Half-life elimination: ~6-8 hours

Time to peak, serum: Oral: 1-2 hours

Excretion: Urine (~87% as unchanged drug, <5% as metabolites); feces (<4%)

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Tuberculosis

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsLevofloxacin is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay cause agitation, anxiety, confusion, depression, dizziness, hallucinations, insomnia, nervousness, paranoia, and sedation

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; inhibits CYP1A2 isoenzyme; caution with clozapine and other psychotropics; monitor for adverse effects

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International Brand Names Adlox (IN); Cina (MX); Cravit (CL, ID, JP, MY, PK, SG, TH, TW); Cravit Ophthalmic (HK, ID); Cravox (ID); Elequine (BB, BM, BS, BZ, GY, JM, MX, NL, SR, TT); Faxlev (ID); Flevox (MX); Floxel (PH); Glevo (MY); Lavor (IN); Leflodal (TW); Lefloxin (TH); Lefos-500 (ID); Leroxacin (KP); Levaquin (AR, BR, CO, PE); Levo (IL); Levobact (PH); Levocin (ID, PH, TH); Levokacin (KP); Levomicin (KP); Levoquin (PH); Levores (ID); Levotamin (KP); Levovid (ID); Levox (PH); Levoxacin (IT, KP); Lexa (ID); Lovequin (ID); Loxof (MY); Mosardal (ID); Nislev (ID); Nofaxin (KP); Nufalev (ID); Oftaquix (BG, CZ, DE, DK, EE, FI, GB, IE, PH, SE); Ovelquin (MX); Ran-Levo (MX); Reskuin (ID); Rinvox (ID); Rozoxin (TW); Tavanic (AR, AT, BB, BE, BG, BM, BS, BZ, CH, CN, CR, CZ, DE, DO, EC, EE, ES, FI, FR, GB, GT, GY, HN, IE, IL, JM, MX, NI, NL, PA, PE, PL, PT, PY, SE, SR, SV, TT, UY, VE); Voflaxin (MX); Volequin (ID); Wilovex (PH)

LEVOleucovorin

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English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

LEVOleucovorin may be confused with leucovorin calcium, Leukeran®, Leukine®

Pronunciation

(lee voe loo koe VOR in)

U.S. Brand NamesFusilev™

Pharmacologic CategoryAntidote; Rescue Agent (Chemotherapy)

Use: Labeled IndicationsRescue agent after high-dose methotrexate therapy in osteosarcoma; antidote for impaired methotrexate elimination and for inadvertent overdosage of folic acid antagonists

Use: Unlabeled/InvestigationalTreatment of colorectal cancer (in combination with fluorouracil)

Dosing: Adults**Note:** Levoleucovorin is dosed at **one-half** the usual dose of the racemic form (leucovorin calcium):

High-dose methotrexate rescue: I.V.: Usual dose: 7.5 mg (~5 mg/m^2) every 6 hours for 10 doses, beginning 24 hours after the start of the methotrexate infusion (based on a methotrexate dose of 12 g/m^2 I.V. over 4 hours). Levoleucovorin (and hydration and urinary alkalinization) should be continued and/or adjusted until the methotrexate level is <0.05 micromolar (5 x 10^{-8} M) as follows:

Normal methotrexate elimination (serum methotrexate levels ~10 micromolar at 24 hours post administration, 1 micromolar at 48 hours and <0.2 micromolar at 72 hours post infusion): 7.5 mg I.V. every 6 hours for 10 doses

Delayed late methotrexate elimination (serum methotrexate levels >0.2 micromolar at 72 hours and >0.05 micromolar at 96 hours post methotrexate infusion): Continue 7.5 mg I.V. every 6 hours until methotrexate level is <0.05 micromolar

Delayed early methotrexate elimination and/or evidence of acute renal injury (serum methotrexate level ≥50 micromolar at 24 hours, ≥5 micromolar at 48 hours or a doubling or more of the serum creatinine level at 24 hours post methotrexate infusion): 75 mg I.V. every 3 hours until methotrexate level is <1 micromolar, followed by 7.5 mg I.V. every 3 hours until methotrexate level is <0.05 micromolar

Significant clinical toxicity in the presence of less severe abnormalities in methotrexate elimination or renal function (as described above): Extend levoleucovorin treatment for an additional 24 hours (total of 14 doses) in subsequent treatment cycles.

Delayed methotrexate elimination due to third space fluid accumulation, renal insufficiency, or inadequate hydration: May require higher levoleucovorin doses or prolonged administration.

Methotrexate overdose (inadvertent): I.V.: 7.5 mg (~5 mg/m^2) every 6 hours; continue until the methotrexate level is <0.01 micromolar (10^{-8} M). Initiate treatment as soon as possible after methotrexate overdose. Increase the levoleucovorin dose to 50 mg/m^2 I.V. every 3 hours if the 24-hour serum creatinine has increased 50% over baseline, or if the 24 hour methotrexate level is >5 micromolar (5 x 10^{-6} M), or if the 48-hour methotrexate level is >0.9 micromolar (9 x 10^{-7} M); continue levoleucovorin until the methotrexate level is <0.01 micromolar (10^{-8} M). Hydration (3 L/day) and urinary alkalinization (with sodium bicarbonate) should also be maintained.

Treatment of colorectal cancer (in combination with fluorouracil; unlabeled use): I.V.: Levoleucovorin is dosed at **one-half** the usual dose of the racemic form (leucovorin)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Levoleucovorin is dosed at **one-half** the usual dose of the racemic form (leucovorin calcium):

High-dose methotrexate rescue: Refer to adult dosing.

Methotrexate overdose (inadvertent): Refer to adult dosing.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.For I.V. administration only; do not administer intrathecally. Due to calcium content, do not administer I.V. solutions at a rate >160 mg/minute.

For colorectal cancer (unlabeled use): Levoleucovorin has been administered as I.V. push and as I.V. infusion over 2 hours in clinical trials.

Administration: OtherDo not administer intrathecally.

StoragePrior to reconstitution, store intact vials at 25°C (77°F); excursions permitted up to 15°C to 30°C (59°F to 86°F). Protect from light.

Reconstituted solutions in the vial and further diluted for infusion in NS are stable for 12 hours at room temperature. Solutions further diluted for infusion in D_5W are stable for 4 hours at room temperature.

ReconstitutionReconstitute the 50 mg vial with 5.3 mL NS (preservative free) to a concentration of 10 mg/mL. Do not use if solution appears cloudy or contains a precipitate. May further dilute for infusion in NS or D_5W to a final concentration of 0.5-5 mg/mL.

CompatibilityStable in NS, D_5W

ContraindicationsHistory of prior allergic reaction to folic acid or leucovorin (folinic acid)

Warnings/Precautions

Concurrent drug therapy issues:

- Fluorouracil: The toxicity of fluorouracil is enhanced by leucovorin and levoleucovorin. Deaths due to severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin in combination with fluorouracil.
- Sulfamethoxazole-trimethoprim: Concomitant use of leucovorin and sulfamethoxazole-trimethoprim for the acute treatment of PCP in patients with HIV infection has been associated with increased rates of treatment failure and morbidity; may also occur with levoleucovorin.

Other warnings/precautions:

- Administration: For I.V. administration only; do not administer intrathecally. Due to calcium content, do not administer I.V. solutions at a rate >160 mg levoleucovorin/minute.
- Appropriate use: Levoleucovorin is not approved for and should not be used to treat pernicious anemia or megaloblastic anemias secondary to vitamin B_{12} deficiency; improper use may induce hematologic remission with progressive neurologic manifestations.
- Folic acid antagonist overdose: When used for the treatment of accidental folic acid antagonist overdose, administer as soon as possible.
- Methotrexate rescue therapy: Methotrexate serum concentrations should be monitored to determine dose and duration of levoleucovorin therapy. Dose may need to be increased or administration prolonged in situations where methotrexate excretion may be delayed (eg, ascites, pleural effusion, renal insufficiency, inadequate hydration).

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Levoleucovorin is the levo isomeric form of racemic leucovorin, a biologically active form of folic acid. Adequate amounts of folic acid are recommended during pregnancy. Refer to Folic Acid monograph.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsLevoleucovorin is the levo isomeric form of racemic leucovorin, a biologically active form of folic acid. Adequate amounts of folic acid are recommended in breast-feeding women. Refer to Folic Acid monograph.

Adverse Reactions**Note:** Adverse reactions reported with levoleucovorin following high-dose methotrexate treatment.

>10%: Gastrointestinal: Stomatitis (38%), vomiting (38%), nausea (19%)

1% to 10%:

Central nervous system: Confusion (6%)

Dermatologic: Dermatitis (6%)

Gastrointestinal: Diarrhea (6%), dyspepsia (6%), taste perversion (6%), typhlitis (6%)

Neuromuscular & skeletal: Neuropathy (6%)

Renal: Renal function abnormal (6%)

Respiratory: Dyspnea (6%)

<1%, postmarketing, and/or case reports: Pruritus, rash, rigors, temperature changes

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

Capecitabine: Leucovorin-Levoleucovorin may enhance the adverse/toxic effect of Capecitabine. *Risk C: Monitor therapy*

Fluorouracil: Leucovorin-Levoleucovorin may enhance the adverse/toxic effect of Fluorouracil. This effect is associated with the ability of leucovorin or levoleucovorin to enhance the anticancer effects of fluorouracil. *Risk C: Monitor therapy*

PHENobarbital: Leucovorin-Levoleucovorin may decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Phenytoin: Leucovorin-Levoleucovorin may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Primidone: Leucovorin-Levoleucovorin may decrease the serum concentration of Primidone. Additionally, leucovorin/levoleucovorin may decrease concentrations of active metabolites of primidone (e.g., phenobarbital). *Risk C: Monitor therapy*

Raltitrexed: Leucovorin-Levoleucovorin may diminish the therapeutic effect of Raltitrexed. *Risk X: Avoid combination*

Trimethoprim: Leucovorin-Levoleucovorin may diminish the therapeutic effect of Trimethoprim. *Risk D: Consider therapy modification*

Monitoring ParametersHigh-dose methotrexate therapy: Serum methotrexate and creatinine levels at least once daily. Monitor fluid and electrolyte status in patients with delayed methotrexate elimination (likely to experience renal toxicity).

Nursing: Physical Assessment/MonitoringTeach patient side effects and symptoms to report. Monitor laboratory tests, adverse reactions, and therapeutic response.

Monitoring: Lab TestsHigh-dose methotrexate therapy: Serum methotrexate and creatinine levels at least once daily. Monitor fluid and electrolyte status in patients with delayed methotrexate elimination (likely to experience renal toxicity).

Patient EducationYou may experience nausea and vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help), diarrhea (buttermilk, boiled milk, or yogurt may help), heartburn, change in taste, sores in mouth or on skin. Report respiratory difficulty, confusion, decreased urine output, swelling of extremities and unusual weight gain, or lethargy. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: Strength expressed as base.

Injection, powder for reconstitution:

Fusilev™: 50 mg

Generic AvailableNo

ManufacturerSpectrum Pharmaceuticals, Inc

Mechanism of ActionLevoleucovorin counteracts the toxic (and therapeutic) effects of folic acid antagonists (eg, methotrexate) which act by inhibiting dihydrofolate reductase. Levoleucovorin is the levo isomeric and pharmacologic active form of leucovorin (levoleucovorin does not require reduction by dihydrofolate reductase). A reduced derivative of folic acid, leucovorin supplies the necessary cofactor blocked by methotrexate, enters the cells via the same active transport system as methotrexate.

Leucovorin enhances the activity (and toxicity) of fluorouracil by stabilizing the binding of 5-dUMP and thymidylate synthetase.

Pharmacodynamics/Kinetics

Metabolism: Converted to the active reduced form of folate, 5-methyl-tetrahydrofolate (5-methyl-THF; active)

Half-life elimination: 15 mg: 5-7 hours; 300 mg: elimination half life: 16-30 hours

Time to peak, serum: I.V.: 0.9 hours

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause confusion

Mental Health: Effects on Psychiatric TreatmentLevoleucovorin may decrease the serum concentration of primidone, phenytoin, and phenobarbital

Index Terms6S-leucovorin; Calcium Levoleucovorin; L-leucovorin; Levo-folinic Acid; Levo-leucovorin; Levoleucovorin Calcium Pentahydrate; S-leucovorin

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International Brand NamesElvorine (BE); Isovorin (DK, FI, GB, SE)

Levonorgestrel

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(LEE voe nor jes trel)
U.S. Brand NamesMirena®; Plan B® [RX/OTC]
Canadian Brand NamesMirena®; Norplant® Implant; Plan B™
Pharmacologic CategoryContraceptive; Progestin
Use: Labeled Indications

Intrauterine device (IUD): Prevention of pregnancy

Oral: Emergency contraception following unprotected intercourse or possible contraceptive failure

Use: Unlabeled/InvestigationalIUD: Idiopathic menorrhagia; protection against endometrial hyperplasia in menopausal women using estrogen
Dosing: AdultsFemales:

Long-term prevention of pregnancy: Intrauterine device (Mirena®): To be inserted into uterine cavity; should be inserted within 7 days of onset of menstruation or immediately after 1st trimester abortion. Releases 20 mcg levonorgestrel/day over 5 years. May be removed and replaced with a new unit at anytime during menstrual cycle. Do not leave any one system in place for >5 years.

Emergency contraception: Oral tablet (Plan B™): One 0.75 mg tablet as soon as possible within 72 hours of unprotected sexual intercourse. A second 0.75 mg tablet should be taken 12 hours after the first dose; may be used at any time during menstrual cycle.

Unlabeled dosing for emergency contraception: Two 0.75 mg tablets as a single dose **or** one 0.75 mg tablet followed by a second 0.75 mg tablet within 12-24 hours. Either regimen should be taken as soon as possible, but within 120 hours, following unprotected sexual intercourse.

Dosing: ElderlyNot indicated for use in postmenopausal women.
Dosing: Renal ImpairmentSafety and efficacy have not been established.
Dosing: Hepatic ImpairmentSafety and efficacy have not been established; use of the intrauterine device is contraindicated with active hepatic disease or hepatic tumor.
Administration: OtherIntrauterine device: Inserted in the uterine cavity, to a depth of 6-9 cm, with the provided insertion device; should not be forced into the uterus
StorageStore at room temperature of 25°C (77°F).
RestrictionsPlan B® is approved for OTC use by women ≥18 years of age and available by prescription only for women ≤17 years of age. Sales of Plan B® will be limited to pharmacies or healthcare clinics with a valid license to distribute prescription products. Because there will be one package for both OTC and prescription use, pharmacies are required to keep the product behind the counter.
ContraindicationsHypersensitivity to levonorgestrel or any component of the formulation; pregnancy
Additional product-specific contraindications:

Intrauterine device: Congenital or acquired uterine anomaly, acute pelvic inflammatory disease, history of pelvic inflammatory disease (unless there has been a subsequent intrauterine pregnancy), postpartum endometritis or infected abortion within past 3 months, known or suspected uterine or cervical neoplasia, unresolved/abnormal Pap smear, untreated acute cervicitis or vaginitis, conditions which increase susceptibility to pelvic infections, unremoved IUD, undiagnosed abnormal uterine bleeding, active hepatic disease or hepatic tumors, known or suspected carcinoma of the breast

Oral: It is not known if the same contraindications associated with long term progestin only contraceptives apply to the use of levonorgestrel and the emergency 2-dose regimen. A history of ectopic pregnancy is not a contraindication to use in emergency contraception.

Warnings/Precautions

Concerns related to adverse effects:

- Abdominal pain: Patients taking progestin-only contraceptives and presenting with lower abdominal pain should be evaluated for follicular atresia and ectopic pregnancy.

- Bleeding irregularities: Menstrual bleeding patterns may be altered with use of the intrauterine device; the possibility of pregnancy should be considered if menstruation does not occur within 6 weeks of the previous menstrual period. If bleeding irregularities continue with prolonged use, appropriate diagnostic measures should be taken to rule out endometrial pathology. An increase in menstrual bleeding may indicate a partial or complete expulsion of the IUD. If expulsion occurs, device may be replaced within 7 days once pregnancy is ruled out. When using the oral tablet, the possibility of pregnancy should be considered if menstruation is delayed for >7 days of the expected menstrual period.

- Bradycardia/syncope: Bradycardia or syncope may occur during insertion or removal of the intrauterine device.

- Breast cancer: The use of combination hormonal contraceptives has been associated with a slight increase in the frequency of breast cancer, however, studies are not consistent. Data is insufficient to determine if progestin only contraceptives also increase this risk.

- Carbohydrate intolerance: May have adverse effects on glucose tolerance; use caution in women with diabetes.

- Ectopic pregnancy: Use caution in patients with previous ectopic pregnancy. Women with history of ectopic pregnancy were excluded from clinical trials; women with previous ectopic pregnancy, tubal surgery or pelvic infection may be at increased risk ectopic pregnancy. The possibility of ectopic pregnancy should be considered in patients with abdominal pain or vaginal bleeding in women with prior amenorrhea.

Disease-related concerns:

- Renal impairment: Safety and efficacy have not been established for use in renal impairment.

Concurrent drug therapy issues:

- Hepatic enzyme-inducing medications: Patients receiving hepatic enzyme-inducing medications should be evaluated for an alternative method of contraception.

Special populations:

- Pediatrics: Not for use prior to menarche.

- Postmenopausal women: Not indicated for use in postmenopausal women.

- Smokers: The risk of cardiovascular side effects increases in women using estrogen containing combined hormonal contraceptives and who smoke cigarettes, especially those who are >35 years of age. This risk relative to progestin-only contraceptives has not been established. Women who take contraceptives should be advised not to smoke.

Dosage form specific issues:

- Intrauterine device: Increased incidence of group A streptococcal sepsis and pelvic inflammatory disease (may be asymptomatic). May perforate uterus or cervix; risk of perforation is increased in lactating women. Pregnancy may result if perforation occurs; delayed detection of perforation may result in migration of IUD outside of uterine cavity. Partial penetration or embedment in the myometrium may decrease effectiveness and lead to difficult removal. Use caution in patients with coagulopathy or receiving anticoagulants. Use caution in patients with congenital heart disease or other heart conditions which may increase the risk of infective endocarditis during insertion of the device (prophylactic antibiotics may be required at time of insertion).

- Oral tablet: Not intended to be used for routine contraception and will not terminate an existing pregnancy.

Other warnings/precautions:

- Appropriate use: Intrauterine device: Insertion should be done by a trained health care provider. The device should be removed for the following reasons: Bleeding which causes anemia; if the patient or her partner become HIV positive or acquire a sexually-transmitted disease; pelvic infection, endometritis, symptomatic genital actinomycosis; intractable pelvic pain, pain during intercourse; endometrial or cervical cancer; uterine or cervical perforation; pregnancy. Embedded devices should also be removed. Use with caution or consider removal of the intrauterine device if any of the following conditions occur for the first time during therapy: Migraine, severe headache, jaundice, marked increase in blood pressure, severe arterial disease (eg, stroke, MI). Use is contraindicated in patients with vaginitis or cervicitis. Postpone insertion until after treatment for infection is complete and cause of the cervicitis is proven not to be due to gonorrhea or chlamydia.

- HIV infection protection: Hormonal contraceptives do not protect against HIV infection or other sexually-transmitted diseases.

Pregnancy Risk FactorX
Pregnancy ConsiderationsEpidemiologic studies have not shown an increased risk of birth defects when used prior to pregnancy or inadvertently during early pregnancy, although rare reports of congenital anomalies have been reported. In doses larger than those used for oral contraception, progestins have been reported to increase the risk of masculinization of female genitalia.

Intrauterine device: Pregnancy should be ruled out prior to insertion. Women who become pregnant with an IUD in place risk septic abortion (septic shock and death may occur). Removal of the device is recommended, however, removal or manipulation of IUD may result in pregnancy loss. In addition, miscarriage, premature labor, and premature delivery may occur if pregnancy is continued with IUD in place. Following pregnancy, insertion of the device should not take place until 6 weeks postpartum or until involution of the uterus is complete. Consider waiting until 12 weeks postpartum if involution is substantially delayed. The device may be inserted immediately following a first trimester abortion. Following removal of the device, ~80% of women who wished to conceive became pregnant within 12 months.

LactationEnters breast milk/use caution (AAP rates “compatible”)
Breast-Feeding ConsiderationsLevonorgestrel is found in breast milk. Following long-term use of oral levonorgestrel, infant serum levels range from 1% to 6% of the maternal level; detectable levels may be found in nursing infants. Isolated cases of decreased milk production have been reported. Risk of perforation with IUD is increased in lactating women. Following pregnancy, insertion of the device should not take place until 6 weeks postpartum or until involution of the uterus is complete. Consider waiting until 12 weeks postpartum if involution is substantially delayed.
Adverse Reactions
Intrauterine device:

>5%:

Cardiovascular: Hypertension

Central nervous system: Headache, depression, nervousness

Dermatologic: Acne

Endocrine & metabolic: Breast pain, dysmenorrhea, libido decreased, amenorrhea (20% at 1 year), enlarged follicles (12%), ovarian cysts

Gastrointestinal: Abdominal pain, nausea, weight gain

Genitourinary: Cervicitis, leukorrhea, pelvic pain, uterine/vaginal bleeding, vaginitis

Neuromuscular & skeletal: Back pain

<5%, postmarketing and/or case reports: Abdominal distension, alopecia, anemia, angioedema, device breakage, dyspareunia, eczema, edema, failed insertion, hirsutism, migraine, mood changes, pruritus, rash,sepsis, urticaria, vomiting

Oral tablets:

>10%:

Central nervous system: Fatigue (17%), headache (17%), dizziness (11%)

Endocrine & metabolic: Heavier menstrual bleeding (14%), lighter menstrual bleeding (12%), breast tenderness (11%)

Gastrointestinal: Nausea (23%), abdominal pain (18%)

1% to 10%: Gastrointestinal: Vomiting (6%), diarrhea (5%)

Metabolism/Transport Effects **Substrate** of CYP3A4 (major)
Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions Herb/Nutraceutical: St John's wort (an enzyme inducer) may decrease serum levels of levonorgestrel.
Test Interactions Decreased concentrations of sex hormone-binding globulin; decreased thyroxine concentrations (slight); increased triiodothyronine uptake

Monitoring ParametersIUD: Re-examine 4-12 weeks following insertion and then yearly. Threads should be visible; if length of thread has changed device may have become displaced, broken, perforated the uterus, or expelled. Transvaginal ultrasound may be used to check placement. Monitor for prolonged menstrual bleeding, amenorrhea, irregularity of menses, Pap smear, blood pressure, serum glucose in patients with diabetes, LDL levels in patients with hyperlipidemias; re-examine following first menses post-insertion of IUD. Patients presenting with lower abdominal pain should be evaluated for follicular atresia and ectopic pregnancy. Signs of infection following IUD insertion, especially in patients at increased risk (eg, patients on chronic corticosteroids, patients with type 1 diabetes mellitus).

Reference RangeIntrauterine device: Plasma levels range from 150-200 pg/mL which are lower than those observed with other dosage forms of levonorgestrel

Nursing: Physical Assessment/MonitoringPregnancy should be ruled out prior to insertion of IUD. Monitor for prolonged menstrual bleeding, amenorrhea, irregularity of menses, and other adverse effects. Caution patient about need for annual medical exams. **Pregnancy risk factor X.**

Monitoring: Lab TestsIUD: Monitor serum glucose in patients with diabetes, LDL levels in patients with hyperlipidemias

Patient EducationThis drug does not protect against HIV infection or other sexually-transmitted diseases. Cigarette smoking is not recommended. You may experience cramping, headache, abdominal discomfort, hair loss, weight changes, or unusual menses (breakthrough bleeding, irregularity, excessive bleeding). Report sudden acute headache or visual disturbance, unusual nausea or vomiting, any loss of feeling in arms or legs, or lower abdominal pain. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding

Intrauterine device: This method provides up to 5 years of birth control from a T-shaped device inserted into the uterus. It will be inserted and removed by your prescriber. Notify your prescriber if the system comes out by itself, if you have long-lasting or heavy bleeding, unusual vaginal discharge, low abdominal pain, painful sexual intercourse, chills or fever. There is an increased risk of ectopic pregnancy with this product. Thread placement should be checked following each menstrual cycle; do not pull thread.

Tablet: This method provides emergency contraception. It is used after your normal form of birth control has failed, or following unprotected sexual intercourse. It should be used within 72 hours. Contact prescriber if you vomit within 1 hour of taking either dose.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Intrauterine device:

Mirena®: 52 mg/unit [releases levonorgestrel 20 mcg/day]

Tablet:

Plan B®: 0.75 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Plan B)

0.75 mg (2): $47.38

Mechanism of ActionPregnancy may be prevented through several mechanisms: Thickening of cervical mucus, which inhibits sperm passage through the uterus and sperm survival; inhibition of ovulation, from a negative feedback mechanism on the hypothalamus, leading to reduced secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH); and inhibition of implantation. Levonorgestrel is not effective once the implantation process has begun.

Pharmacodynamics/Kinetics

Duration: Intrauterine device: Up to 5 years

Absorption: Oral: Rapid and complete

Protein binding: Highly bound to albumin (~50%) and sex hormone-binding globulin (~47%)

Metabolism: To inactive metabolites

Half-life elimination: Oral: ~24 hours

Excretion: Primarily urine

Pharmacotherapy PearlsIntrauterine device: The cumulative 5-year pregnancy rate is ~0.7 pregnancies/100 users. Over 70% of women in the trials had previously used IUDs. The reported pregnancy rate after 12 months was ≤0.2 pregnancies/100 users. Approximately 80% of women who wish to conceive have become pregnant within 12 months of device removal. The recommended patient profile for this product: A woman who has at least one child, is in a stable and mutually-monogamous relationship, no history of pelvic inflammatory disease, and no history of ectopic pregnancy or predisposition to ectopic pregnancy. Keep a copy of the consent form and record lot number of device.

Oral tablet: When used as directed for emergency contraception, the expected pregnancy rate is decreased from 8% to 1%. Approximately 87% of women have their next menstrual period at approximately the expected time. A rapid return to fertility following use is expected.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness or dizziness

Mental Health: Effects on Psychiatric TreatmentCarbamazepine may decrease the effects of levonorgestrel

Index TermsLNg 20

References

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International Brand Names Ange 28 (JP); duofem (DE); ECEEZ (IN); Follistrel (NO); Glanique (EC); Imediat N (UY); Jadelle (NZ, TH); Levonelle (GB, IE, NZ); Levonelle-2 (AU); Levonova (NO, SE); Madonna (MY); Microlut (CO, LU); Microluton (NO); Microval (LU); Mirena (AR, AT, AU, BB, BE, BG, BM, BS, BZ, CH, CO, CZ, DE, ES, GB, GY, HK, HU, ID, IE, IL, IT, JM, KP, LU, MY, NL, PH, SR, TT, UY, ZA); Norlevo (AU, DK, ES, FR, IN, KP, SE, ZA); Norplant (CL, LU, PH, TH, TW); Plan B (DO, HN, NI); Postinor (BE, CH, CL, EE, FI, HU, PL, SE); Postinor-2 (AU, BR, CN, HK, ID, MX, PE, SG, TW, VE); Pronta (PY); Rigesoft (HU); Vikela (AT)

Levorphanol

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English

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(lee VOR fa nole)

U.S. Brand NamesLevo-Dromoran®

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled IndicationsRelief of moderate to severe pain; also used parenterally for preoperative sedation and an adjunct to nitrous oxide/oxygen anesthesia

Dosing: Adults**Note:** These are guidelines and do not represent the maximum doses that may be required in all patients. Doses should be titrated to pain relief/prevention.

Acute pain (moderate to severe):

Oral: Initial: Opiate-naive: 2 mg every 6-8 hours as needed; patients with prior opiate exposure may require higher initial doses; usual dosage range: 2-4 mg every 6-8 hours as needed

I.M., SubQ: Initial: Opiate-naive: 1 mg every 6-8 hours as needed; patients with prior opiate exposure may require higher initial doses; usual dosage range: 1-2 mg every 6-8 hours as needed

I.V. (slow): Initial: Opiate-naive: Up to 1 mg/dose every 3-6 hours as needed; patients with prior opiate exposure may require higher initial doses

Chronic pain: Patients taking opioids chronically may become tolerant and require doses higher than the usual dosage range to maintain the desired effect. Tolerance can be managed by appropriate dose titration. **There is no optimal or maximal dose for levorphanol in chronic pain. The appropriate dose is one that relieves pain throughout its dosing interval without causing unmanageable side effects.**

Premedication: I.M., SubQ: 1-2 mg/dose 60-90 minutes prior to surgery; older or debilitated patients usually require less drug

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic ImpairmentReduce dose in patients with liver disease.

Calculations

- Opioid Agonist Conversion

Administration: I.V.Inject 3 mg over 4-5 minutes

Administration: I.V. DetailpH: 4.3 (adjusted)

Administration: OralFor lactating women, administer 4-6 hours prior to breast-feeding.

StorageStore at room temperature; do not freeze.

Compatibility

Y-site administration: Compatible: Propofol.

Compatibility in syringe: Compatible: Glycopyrrolate.

Compatibility when admixed: Incompatible: Aminophylline, ammonium chloride, amobarbital, chlorothiazide, heparin, pentobarbital, phenobarbital, phenytoin, sodium bicarbonate, thiopental.

RestrictionsC-II

ContraindicationsHypersensitivity to levorphanol or any component of the formulation; pregnancy (prolonged use or high doses at term)

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with severe liver dysfunction.
- Obesity: Use with caution in patients who are morbidly obese.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Renal impairment: Use with caution in patients with severe renal insufficiency.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.
- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Sulfites: Some preparations contain sulfites which may cause allergic reactions.

Other warnings/precautions:

- Optimal regimen: An opioid-containing analgesic regimen should be tailored to each patient's needs and based upon the type of pain being treated (acute versus chronic), the route of administration, degree of tolerance for opioids (naive versus chronic user), age, weight, and medical condition. The optimal analgesic dose varies widely among patients; doses should be titrated to pain relief/prevention.
- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsThe elderly may be particularly susceptible to the CNS depressant and constipating effects of narcotics.
Pregnancy Risk FactorB/D (prolonged use or high doses at term)
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation, hypotension, bradycardia, peripheral vasodilation, cardiac arrest, shock, tachycardia

Central nervous system: CNS depression, fatigue, drowsiness, dizziness, nervousness, headache, restlessness, anorexia, malaise, confusion, coma, convulsion, insomnia, amnesia, mental depression, hallucinations, paradoxical CNS stimulation, intracranial pressure increased

Dermatologic: Pruritus, urticaria, rash

Endocrine & metabolic: Antidiuretic hormone release

Gastrointestinal: Nausea, vomiting, dyspepsia, stomach cramps, xerostomia, constipation, abdominal pain, dry mouth, biliary tract spasm, paralytic ileus

Genitourinary: Decreased urination, urinary tract spasm, urinary retention

Local: Pain at injection site

Neuromuscular & skeletal: Weakness

Ocular: Miosis, diplopia

Respiratory: Respiratory depression, apnea, hypoventilation, cyanosis

Miscellaneous: Histamine release, physical and psychological dependence

Oncology: VesicantNo

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol (may increase CNS depression). Watch for sedation.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersPain relief, respiratory and mental status, blood pressure

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for additive or adverse interactions. Monitor therapeutic effectiveness, adverse reactions, and signs of overdose. Monitor vital signs, CNS and respiratory status, at beginning of therapy and at regular intervals with long-term use. May cause physical and/or psychological dependence. Safety measures required for inpatients. Assess knowledge/teach patient appropriate use (if self-administered). Teach patient to monitor for adverse reactions, adverse reactions to report, and appropriate interventions to reduce side effects. Discontinue slowly after prolonged use.

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause hypotension, dizziness, drowsiness, impaired coordination, or blurred vision (use caution when driving, climbing stairs, or changing position - rising from sitting or lying to standing, or when engaging in tasks requiring alertness until response to drug is known); loss of appetite, nausea, or vomiting (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help; if unresolved, consult prescriber about use of stool softeners). Report chest pain, slow or rapid heartbeat, acute dizziness, or persistent headache; swelling of extremities or unusual weight gain; changes in urinary elimination; acute headache; back or flank pain or spasms; blurred vision; skin rash; or shortness of breath. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as tartrate: 2 mg/mL (1 mL, 10 mL)

Tablet, as tartrate: 2 mg

Generic AvailableYes: Tablet

Mechanism of ActionLevorphanol tartrate is a synthetic opioid agonist that is classified as a morphinan derivative. Opioids interact with stereospecific opioid receptors in various parts of the central nervous system and other tissues. Analgesic potency parallels the affinity for these binding sites. These drugs do not alter the threshold or responsiveness to pain, but the perception of pain.

Pharmacodynamics/Kinetics

Onset of action: Oral: 10-60 minutes

Duration: 4-8 hours

Metabolism: Hepatic

Half-life elimination: 11-16 hours

Excretion: Urine (as inactive metabolite)

Related Information

- Narcotic / Opioid Analgesics

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and dizziness are common; may cause nervousness, restlessness, or confusion; may rarely cause depression, hallucinations, or paradoxical CNS stimulation

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation

Index TermsLevorphan Tartrate; Levorphanol Tartrate

References

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Levothyroxine

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English

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Levothyroxine may be confused with levofloxacin, liothyronine

Levoxyl® may be confused with Lanoxin®, Levaquin®, Luvox®

Synthroid® may be confused with Symmetrel®

To avoid errors due to misinterpretation of a decimal point, always express dosage in mcg (**not** mg).

Significant differences exist between oral and I.V. dosing. Use caution when converting from one route of administration to another.

Pronunciation(lee voe thye ROKS een)

U.S. Brand NamesLevothroid®; Levoxyl®; Synthroid®; Unithroid®

Canadian Brand NamesEltroxin®; Euthyrox; Levothyroxine Sodium; Synthroid®

Pharmacologic CategoryThyroid Product

Use: Labeled IndicationsReplacement or supplemental therapy in hypothyroidism; pituitary TSH suppression

Dosing: AdultsDoses should be adjusted based on clinical response and laboratory parameters.

Hypothyroidism:

Oral: 1.7 mcg/kg/day in otherwise healthy adults <50 years old, children in whom growth and puberty are complete, and older adults who have been recently treated for hyperthyroidism or who have been hypothyroid for only a few months. Titrate dose every 6 weeks. Average full replacement dose is 100-125 mcg/day for a 70 kg adult; usual doses are ≤200 mcg/day; doses ≥300 mcg/day are rare (consider poor compliance, malabsorption, and/or drug interactions). **Note:** For patients >50 years or patients with cardiac disease, refer to elderly dosing.

I.M., I.V.: 50% of the oral dose

Severe hypothyroidism: Oral: Initial: 12.5-25 mcg/day; adjust dose by 25 mcg/day every 2-4 weeks as appropriate

Subclinical hypothyroidism (if treated): Oral: 1 mcg/kg/day

TSH suppression: Oral:

Well-differentiated thyroid cancer: Highly individualized; Doses >2 mcg/kg/day may be needed to suppress TSH to <0.1 mU/L. High-risk tumors may need a target level of <0.01 mU/L for TSH suppression.

Benign nodules and nontoxic multinodular goiter: Goal TSH suppression: 0.1-0.5 mU/L (benign nodules) and 0.5-1 mU/L (multinodular goiter)

Myxedema coma or stupor: I.V.: 200-500 mcg, then 100-300 mcg the next day if necessary; smaller doses should be considered in patients with cardiovascular disease

Dosing: ElderlyDoses should be adjusted based on clinical response and laboratory parameters.

Hypothyroidism:

Oral:

>50 years without cardiac disease **or** <50 years with cardiac disease: Initial: 25-50 mcg/day; adjust dose at 6- to 8-week intervals as needed

>50 years with cardiac disease: Initial: 12.5-25 mcg/day; adjust dose by 12.5-25 mcg increments at 4- to 6-week intervals. (**Note:** Many clinicians prefer to adjust at 6- to 8-week intervals.)

Note: Elderly patients may require <1 mcg/kg/day

I.M., I.V.: 50% of the oral dose

Myxedema coma: I.V.: Refer to adult dosing; lower doses may be needed

Dosing: PediatricDoses should be adjusted based on clinical response and laboratory parameters.

Hypothyroidism:

Oral:

Newborns: Initial: 10-15 mcg/kg/day. Lower doses of 25 mcg/day should be considered in newborns at risk for cardiac failure. Newborns with T_4 levels <5 mcg/dL should be started at 50 mcg/day. Adjust dose at 4- to 6-week intervals.

Infants and Children: Dose based on body weight and age as listed below. Children with severe or chronic hypothyroidism should be started at 25 mcg/day; adjust dose by 25 mcg every 2-4 weeks. In older children, hyperactivity may be decreased by starting with $^{1}/_{4}$ of the recommended dose and increasing by $^{1}/_{4}$ dose each week until the full replacement dose is reached. Refer to adult dosing once growth and puberty are complete.

0-3 months: 10-15 mcg/kg/day

3-6 months: 8-10 mcg/kg/day

6-12 months: 6-8 mcg/kg/day

1-5 years: 5-6 mcg/kg/day

6-12 years: 4-5 mcg/kg/day

>12 years: 2-3 mcg/kg/day

I.M., I.V.: 50% of the oral dose

Administration: I.V.Dilute vial with 5 mL normal saline; use immediately after reconstitution; do not mix with other IV fluids

Administration: I.V. DetailDilute vial with 5 mL normal saline. Use immediately after reconstitution. I.V. form must be prepared immediately prior to administration. Should not be admixed with other solutions.

Administration: OralAdminister in the morning on an empty stomach, at least 30 minutes before food. Tablets may be crushed and suspended in 1-2 teaspoonfuls of water; suspension should be used immediately. Levoxyl® should be administered with a full glass of water to prevent gagging (due to tablet swelling).

Dietary ConsiderationsShould be taken on an empty stomach, at least 30 minutes before food.

StorageStore tablets and injection at room temperature of 15°C to 30°C (59°F to 86°F). Protect tablets from light and moisture.

ReconstitutionDilute vial for injection with 5 mL normal saline. Reconstituted concentrations for the 200 mcg and 500 mcg vials are 40 mcg/mL and 100 mcg/mL, respectively. Shake well and use immediately after reconstitution; discard any unused portions.

CompatibilityDo not mix I.V. solution with other I.V. infusion solutions.

ContraindicationsHypersensitivity to levothyroxine sodium or any component of the formulation; recent MI or thyrotoxicosis; uncorrected adrenal insufficiency

Allergy Considerations

- Levothyroxine Allergy

Warnings/Precautions

Boxed warnings:

- Weight reduction: See "Other warnings/precautions" below.

Disease-related concerns:

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency; symptoms may be exaggerated or aggravated.
- Cardiovascular disease: Use with caution and reduce dosage in patients with angina pectoris or other cardiovascular disease; chronic hypothyroidism predisposes patients to coronary artery disease.
- Diabetes: Use with caution in patients with diabetes mellitus and insipidus; symptoms may be exaggerated or aggravated.
- Myxedema: Use with caution in patients with myxedema; symptoms may be exaggerated or aggravated.
- Osteoporosis: Long-term therapy can decrease bone mineral density. Postmenopausal women and women using suppressive doses should receive the lowest dose necessary for clinical response.

Special populations:

- Elderly: Use with caution; may be more likely to have compromised cardiovascular function; decrease initial dose.

Dosage form specific issues:

- Levoxyl®: Product may rapidly swell and disintegrate causing choking or gagging (should be administered with a full glass of water); use caution in patients with dysphagia or other swallowing disorders.

Other warnings/precautions:

- Weight reduction: **[U.S. Boxed Warning]: Thyroid supplements are ineffective and potentially toxic for weight reduction. High doses may produce serious or even life-threatening toxic effects particularly when used with some anorectic drugs.**

Geriatric ConsiderationsElderly do not have a change in serum thyroxine associated with aging; however, plasma T_3 concentrations are decreased 25% to 40% in the elderly. There is not a compensatory rise in thyrotropin suggesting that lower T_3 is not reacted upon as a deficiency by the pituitary. This indicates a slightly lower than normal dosage of thyroid hormone replacement is usually sufficient in elderly patients than in younger adult patients. TSH must be monitored since insufficient thyroid replacement (elevated TSH) is a risk for coronary artery disease and excessive replacement (low TSH) may cause signs of hyperthyroidism and excessive bone loss. Some clinicians suggest levothyroxine is the drug of choice for replacement therapy.

Pregnancy Risk FactorA

Pregnancy ConsiderationsUntreated maternal hypothyroidism may have adverse effects on fetal growth and development and is associated with higher rate of complications (spontaneous abortion, pre-eclampsia, stillbirth, premature delivery). Treatment should not be discontinued during pregnancy. TSH levels should be monitored during each trimester and 6-8 weeks postpartum. Increased doses may be needed during pregnancy.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsMinimally excreted in human milk; adequate levels are needed to maintain normal lactation

Adverse ReactionsFrequency not defined.

Cardiovascular: Angina, arrhythmia, blood pressure increased, cardiac arrest, flushing, heart failure, MI, palpitation, pulse increased, tachycardia

Central nervous system: Anxiety, emotional lability, fatigue, fever, headache, hyperactivity, insomnia, irritability, nervousness, pseudotumor cerebri (children), seizure (rare)

Dermatologic: Alopecia

Endocrine & metabolic: Fertility impaired, menstrual irregularities

Gastrointestinal: Abdominal cramps, appetite increased, diarrhea, vomiting, weight loss

Hepatic: Liver function tests increased

Neuromuscular & skeletal: Bone mineral density decreased, muscle weakness, tremor, slipped capital femoral epiphysis (children)

Respiratory: Dyspnea

Miscellaneous: Diaphoresis, heat intolerance, hypersensitivity (to inactive ingredients, symptoms include urticaria, pruritus, rash, flushing, angioedema, GI symptoms, fever, arthralgia, serum sickness, wheezing)

Levoxyl®: Choking, dysphagia, gagging

Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Thyroid Products. *Risk C: Monitor therapy*

CarBAMazepine: May decrease the serum concentration of Thyroid Products. *Risk C: Monitor therapy*

Estrogen Derivatives: May diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Ferrous Sulfate: May decrease the serum concentration of Levothyroxine. *Risk D: Consider therapy modification*

Orlistat: May decrease the serum concentration of Levothyroxine. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Thyroid Products. Phenytoin may also displace thyroid hormones from protein binding sites. *Risk C: Monitor therapy*

Raloxifene: May decrease the absorption of Levothyroxine. *Risk D: Consider therapy modification*

Rifampin: May decrease the serum concentration of Thyroid Products. *Risk C: Monitor therapy*

Sodium Iodide I131: Thyroid Products may diminish the therapeutic effect of Sodium Iodide I131. *Risk X: Avoid combination*

Sucralfate: May decrease the serum concentration of Levothyroxine. *Risk C: Monitor therapy*

Theophylline Derivatives: Thyroid Products may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Thyroid Products may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Taking levothyroxine with enteral nutrition may cause reduced bioavailability and may lower serum thyroxine levels leading to signs or symptoms of hypothyroidism. Soybean flour (infant formula), cottonseed meal, walnuts, and dietary fiber may decrease absorption of levothyroxine from the GI tract.

Test InteractionsMany drugs may have effects on thyroid function tests (see Additional Information or Pharmacotherapy Pearls). Pregnancy, infectious hepatitis, and acute intermittent porphyria may increase TBG concentrations; nephrosis, severe hypoproteinemia, severe liver disease, and acromegaly may decrease TBG concentrations.

Monitoring ParametersThyroid function test (serum thyroxine, thyrotropin concentrations), resin triiodothyronine uptake (rT_3U), free thyroxine index (FTI), T_4, TSH, heart rate, blood pressure, clinical signs of hypo- and hyperthyroidism; TSH is the most reliable guide for evaluating adequacy of thyroid replacement dosage. TSH may be elevated during the first few months of thyroid replacement despite patients being clinically euthyroid. In cases where T_4 remains low and TSH is within normal limits, an evaluation of "free" (unbound) T_4 is needed to evaluate further increase in dosage

Infants: Monitor closely for cardiac overload, arrhythmias, and aspiration from avid suckling

Infants/children: Monitor closely for under/overtreatment. Undertreatment may decrease intellectual development and linear growth, and lead to poor school performance due to impaired concentration and slowed mentation. Overtreatment may adversely affect brain maturation, accelerate bone age (leading to premature closure of the epiphyses and reduced adult height); craniosynostosis has been reported in infants. Treated children may experience a period of catch-up growth. Monitor TSH and total or free T_4 at 2 and 4 weeks after starting treatment; every 1-2 months for first year of life; every 2-3 months during years 1-3; every 3-12 months until growth completed.

Adults: Monitor TSH every 6-8 weeks until normalized; 8-12 weeks after dosage changes; every 6-12 months throughout therapy

Reference RangePediatrics: Cord T_4 and values in the first few weeks are much higher, falling over the first months and years. ≥10 years: ~5.8-11 mcg/dL (SI: 75-142 nmol/L). Borderline low: ≤4.5-5.7 mcg/dL (SI: 58-73 nmol/L); low: ≤4.4 mcg/dL (SI: 57 nmol/L); results <2.5 mcg/dL (SI: <32 nmol/L) are strong evidence for hypothyroidism.

Approximate adult normal range: 4-12 mcg/dL (SI: 51-154 nmol/L). Borderline high: 11.1-13 mcg/dL (SI: 143-167 nmol/L); high: ≥13.1 mcg/dL (SI: 169 nmol/L). Normal range is increased in women on birth control pills (5.5-12 mcg/dL); normal range in pregnancy: ~5.5-16 mcg/dL (SI: ~71-206 nmol/L). TSH: 0.4-10 (for those ≥80 years) mIU/L; T_4: 4-12 mcg/dL (SI: 51-154 nmol/L); T_3 (RIA) (total T_3): 80-230 ng/dL (SI: 1.2-3.5 nmol/L); T_4 free (free T_4): 0.7-1.8 ng/dL (SI: 9-23 pmol/L).

Nursing: Physical Assessment/MonitoringUse with caution in presence of cardiovascular disease, adrenal insufficiency, diabetes mellitus. Assess potential for interactions with other pharmacological agents patient may be taking (eg, toxic effects with some anorectic drugs, decreased effect of oral hypoglycemics, decreased or increased effect of levothyroxine). Assess results of laboratory tests, therapeutic benefits, and adverse effects on a regular basis during therapy (eg, hypo-/hyperthyroidism). **Important:** Many drugs may have effects on thyroid function tests and results of laboratory tests. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsThyroid function (serum thyroxine, thyrotropin concentrations), resin triiodothyronine uptake (rT_3U), free thyroxine index (FTI), T_4, TSH, TSH may be elevated during the first few months of thyroid replacement despite patients being clinically euthyroid. In cases where T_4 remains low and TSH is within normal limits, an evaluation of "free" (unbound) T_4 is needed to evaluate further increase in dosage.

Patient EducationConsult prescriber before taking new medication or herbal products during therapy; some other medications or herbals may cause adverse effects with levothyroxine. Thyroid replacement therapy is generally for life. Take as directed, in the morning 30 minutes before breakfast. Do not take antacids or iron preparations within 8 hours of thyroid medication. Do not change brands and do not discontinue without consulting prescriber. Report chest pain, rapid heart rate, palpitations, heat intolerance, excessive sweating, increased nervousness, agitation, or lethargy.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as sodium: 0.2 mg, 0.5 mg

Tablet, as sodium: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg

Levothroid®: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg

Levoxyl®: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg

Synthroid®: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg

Unithroid®: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Levothroid)

25 mcg (30): $14.99

50 mcg (30): $13.99

75 mcg (30): $14.99

88 mcg (30): $14.99

112 mcg (30): $14.99

125 mcg (30): $15.99

137 mcg (30): $14.99

150 mcg (30): $15.99

175 mcg (30): $15.99

200 mcg (30): $16.99

300 mcg (30): $20.78

Tablets (Levothyroxine Sodium)

25 mcg (30): $12.99

50 mcg (30): $8.99

75 mcg (30): $12.99

88 mcg (30): $14.99

100 mcg (30): $14.99

112 mcg (30): $12.44

125 mcg (30): $10.99

137 mcg (30): $12.99

150 mcg (30): $10.99

175 mcg (30): $14.99

200 mcg (30): $16.99

300 mcg (30): $18.99

Tablets (Levoxyl)

25 mcg (30): $16.99

50 mcg (30): $17.99

75 mcg (30): $18.99

88 mcg (30): $19.99

100 mcg (30): $17.99

112 mcg (30): $19.99

125 mcg (30): $19.99

137 mcg (30): $19.99

150 mcg (30): $19.99

175 mcg (30): $20.99

200 mcg (30): $21.99

Tablets (Synthroid)

25 mcg (30): $19.99

50 mcg (30): $20.99

75 mcg (30): $23.99

88 mcg (30): $22.99

100 mcg (30): $23.99

112 mcg (30): $25.99

125 mcg (30): $26.99

137 mcg (30): $27.99

150 mcg (30): $25.99

175 mcg (30): $37.99

200 mcg (30): $30.99

300 mcg (30): $38.99

Tablets (Unithroid)

25 mcg (30): $16.99

50 mcg (30): $16.99

75 mcg (30): $17.99

100 mcg (30): $17.99

112 mcg (30): $19.99

125 mcg (30): $19.99

150 mcg (30): $20.99

175 mcg (30): $21.99

200 mcg (30): $21.99

Mechanism of ActionExact mechanism of action is unknown; however, it is believed the thyroid hormone exerts its many metabolic effects through control of DNA transcription and protein synthesis; involved in normal metabolism, growth, and development; promotes gluconeogenesis, increases utilization and mobilization of glycogen stores, and stimulates protein synthesis, increases basal metabolic rate

Pharmacodynamics/Kinetics

Onset of action: Therapeutic: Oral: 3-5 days; I.V. 6-8 hours

Peak effect: I.V.: 24 hours

Absorption: Oral: Erratic (40% to 80%); may be decreased by age and specific foods and drugs

Protein binding: >99%

Metabolism: Hepatic to triiodothyronine (active)

Time to peak, serum: 2-4 hours

Half-life elimination: Euthyroid: 6-7 days; Hypothyroid: 9-10 days; Hyperthyroid: 3-4 days

Excretion: Urine and feces; decreases with age

Pharmacotherapy PearlsEquivalent doses: The following statement on relative potency of thyroid products is included in a joint statement by American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE) and The Endocrine Society (TES): For purposes of conversion, levothyroxine sodium (T_4) 100 mcg is usually considered equivalent to desiccated thyroid 60 mg, thyroglobulin 60 mg, or liothyronine sodium (T_3) 25 mcg. However, these are rough guidelines only and do not obviate the careful re-evaluation of a patient when switching thyroid hormone preparations, including a change from one brand of levothyroxine to another. Joint position statement is available at http://www.thyroid.org/professionals/advocacy/04_12_08_thyroxine.html.

Note: Several medications have effects on thyroid production or conversion. The impact in thyroid replacement has not been specifically evaluated, but patient response should be monitored:

Methimazole: Decreases thyroid hormone secretion, while propylthiouracil decrease thyroid hormone secretion and decreases conversion of T_4 to T_3.

Beta-adrenergic antagonists: Decrease conversion of T_4 to T_3 (dose related, propranolol ≥160 mg/day); patients may be clinically euthyroid.

Iodide, iodine-containing radiographic contrast agents may decrease thyroid hormone secretion; may also increase thyroid hormone secretion, especially in patients with Graves' disease.

Other agents reported to impact on thyroid production/conversion include aminoglutethimide, amiodarone, chloral hydrate, diazepam, ethionamide, interferon-alpha, interleukin-2, lithium, lovastatin (case report), glucocorticoids (dose-related), mercaptopurine, sulfonamides, thiazide diuretics, and tolbutamide.

In addition, a number of medications have been noted to cause transient depression in TSH secretion, which may complicate interpretation of monitoring tests for levothyroxine, including corticosteroids, octreotide, and dopamine. Metoclopramide may increase TSH secretion

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo precautions with vasoconstrictor are necessary if patient is well controlled with levothyroxine

Mental Health: Effects on Mental StatusMay rarely cause nervousness or insomnia

Mental Health: Effects on Psychiatric TreatmentUsed to augment antidepressants; TCAs may increase toxic potential of both drugs

Cardiovascular ConsiderationsThe treatment of patients with combined hypothyroidism and ischemic heart disease needs to be approached very carefully, preferably under the guidance of an endocrinologist and cardiologist. This is because administration of substantial doses of thyroid hormone may precipitate acute cardiac ischemia in patients who have been chronically hypothyroid. Therefore, recognizing that dosing regimens may vary, the general approach is to start at very low doses of thyroid supplementation with very gradual increases in dosage every 3-6 weeks. It is important that patients be monitored very carefully for development of cardiac ischemia during thyroid hormone supplementation. Similarly, patients with heart failure and hypothyroidism should be closely followed.

The possibility of underlying hypothyroidism (and also hyperthyroidism) should be considered in patients with atrial fibrillation. Correction of the underlying thyroid disorder may help in restoration of normal sinus rhythm. Hypothyroidism may also constitute an underlying etiology for obstructive sleep apnea.

Anesthesia and Critical Care Concerns/Other ConsiderationsEquivalent doses: The following statement on relative potency of thyroid products is included in a joint statement by American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE), and The Endocrine Society (TES): For purposes of conversion, levothyroxine sodium (T_4) 100 mcg is usually considered equivalent to desiccated thyroid 60 mg, thyroglobulin 60 mg, or liothyronine sodium (T_3) 25 mcg. However, these are rough guidelines only and do not obviate the careful re-evaluation of a patient when switching thyroid hormone preparations, including a change from one brand of levothyroxine to another. Joint position statement is available at http://www.thyroid.org/professionals/advocacy/04_12_08_thyroxine.html.

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In addition, a number of medications have been noted to cause transient depression in TSH secretion, which may complicate interpretation of monitoring tests for levothyroxine, including corticosteroids, octreotide, and dopamine. Metoclopramide may increase TSH secretion

Soy protein may interfere with absorption of levothyroxine sodium. An enteral formula without soy protein should be selected and thyroid function monitored during tube feeding.

Index Terms *L*-Thyroxine Sodium; Levothyroxine Sodium; T_4

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International Brand Names Elthyrone (BE); Berlthyrox (DE); Cynocuatro (MX); Droxine (AU); Eferox (DE, PL); Elthyro (TH); Eltroxin (AE, BB, BD, BF, BH, BJ, BM, BS, BZ, CH, CI, CL, CO, CY, CZ, DK, EG, ET, GB, GH, GM, GN, GY, HK, HN, ID, IL, IN, IQ, IR, JM, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NZ, OM, PH, PK, PL, QA, SA, SC, SD, SG, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Euthyrox (AR, AT, BE, BG, BR, CH, CL, CZ, DE, EE, HN, ID, MY, NL, PH, PL, SE, SG, TH, VE); Eutirox (CN, CR, DO, ES, GT, HN, IT, MX, NI, PA, PE, SV); Eutroxsig (AU); L-Thyroxine (FR); Letrox (PL); Levaxin (SE); Levhexal (MX); Levoroxin (PL); Levothyrox (FR); Levotirox (IT); Narval (UY); Oroxine (AU, MY); Pondtroxin (TH); Synox (IN); Synthroid (BR, KP, PH); T4 (PY); T4KP (TH); Thevier (DE); Thyradin S (JP); Thyrax (BE, CZ, ID, NL, PH, PL, PT); Thyrax Duotab (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Thyrex (AT); Thyro-4 (BG, GR); Thyrosit (TH); Thyroxin (FI); Thyroxin-Natrium (NO); Tiroidine (MX); Tiroxin (CO); Vobenol (PL)

Lidocaine and Bupivacaine

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Pronunciation(LYE doe kane & byoo PIV a kane)

U.S. Brand NamesDuocaine™

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsLocal or regional anesthesia in ophthalmologic surgery by peripheral nerve block techniques such as peribulbar, retrobulbar, and facial blocks; may be used with or without epinephrine

Dosing: Adults**Note:** Use lowest effective dose to limit toxic effects. Dosing based on lidocaine 1% and bupivacaine 0.375%

Retrobulbar injection: 2-5 mL; a portion of dose is injected retrobulbarly and remainder may be used to block the facial nerve

Peribulbar block: 6-12 mL

Maximum dose: 0.18 mL/kg or 12 mL; if used with epinephrine, the dose should not exceed 0.28 mL/kg or 20 mL

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Use lowest effective dose to limit toxic effects. Dosing based on lidocaine 1% and bupivacaine 0.375%

Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentLidocaine: Accumulation of metabolites may increase with renal impairment

Dosing: Hepatic Impairment

Lidocaine: Half-life of lidocaine is increased twofold with hepatic impairment

Bupivacaine: Toxicities may be increased with hepatic impairment

StorageStore at 15°C to 25°C (59°F to 77°F).

ContraindicationsHypersensitivity to lidocaine, bupivacaine, amide-type local anesthetics (etidocaine, mepivacaine, prilocaine, ropivacaine) or any component of the formulation; Stokes-Adams syndrome; Wolff-Parkinson-White syndrome; severe degrees of sinoatrial, atrioventricular, or intraventricular block without artificial pacemaker

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS toxicity: Careful and constant monitoring of the patient's state of consciousness should be done following each local anesthetic injection; at such times, restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of CNS toxicity. Treatment is primarily symptomatic and supportive.
- Respiratory arrest: Local anesthetics have been associated with rare occurrences of sudden respiratory arrest, especially when administered near the head or neck.
- Seizures: Convulsions due to systemic toxicity leading to cardiac arrest have also been reported, presumably following unintentional intravascular injection or administration near the head or neck.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with shock, heart block without functional pacemakers, or cardiac dysfunction.
- Hepatic impairment: Use with caution in patients with hepatic impairment.

Special populations:

- Acutely ill patients: Use with caution in acutely ill patients.
- Debilitated patients: Use with caution in debilitated patients.
- Elderly: Use with caution in the elderly.
- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Administration: Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

- Repeated doses: May lead to significant increases in blood levels due to accumulation of drug and metabolites.
- Spinal anesthesia: Use not intended for spinal anesthesia.
- Trained personnel: Clinicians using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies with lidocaine have not shown teratogenic effects. Lidocaine and bupivacaine cross the placenta; effects to the fetus may depend on procedure performed. Use during pregnancy only if the potential benefit to the mother outweighs any potential risk to the fetus.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsBupivacaine and lidocaine are both excreted in human milk. The American Academy of Pediatrics considers lidocaine to be “compatible” with breast-feeding.

Adverse ReactionsFrequency not defined; reactions may be dose related or due to unintentional intravascular injection.

Cardiovascular: Bradycardia, cardiac arrest, cardiac output decreased, heart block, hypotension, myocardium depression, ventricular arrhythmia

Central nervous system: Anxiety, chills, convulsions, depression, dizziness, drowsiness, excitation, restlessness

Gastrointestinal: Nausea, vomiting

Neuromuscular & skeletal: Tremors

Ocular: Blurred vision, pupil constriction, permanent injury to extraocular muscle

Otic: Tinnitus

Respiratory: Respiratory arrest

Miscellaneous: Allergic reaction

Following unintentional subarachnoid injection: Backache, cranial nerve palsies, headache, incontinence (fecal or urinary), meningismus, paralysis, paresthesia, perineal sensation loss, persistent anesthesia, septic meningitis, sexual function loss, spinal block, urinary retention, weakness

Metabolism/Transport EffectsLidocaine: **Substrate** of CYP1A2 (minor), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2D6 (major), 3A4 (major); **Inhibits** CYP1A2 (strong), 2D6 (moderate), 3A4 (moderate)

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: Lidocaine hydrochloride 1% and bupivacaine hydrochloride 0.375% (10 mL)

Generic AvailableNo

ManufacturerAmphastar Pharmaceuticals, Inc

Mechanism of ActionBlocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction.

Pharmacodynamics/KineticsAlso see individual agents.

Protein binding: Lidocaine: Fraction bound decreases with increased concentration; also dependent upon plasma concentration of alpha$_1$-acid glycoprotein

Metabolism: Lidocaine: Hepatic, forms metabolites; Bupivacaine: hepatic, forms metabolites

Half-life elimination: Lidocaine: I.V.: 1.5-2 hours; Bupivacaine: I.V.: 2.7 hours

Time to peak, plasma: Following peribulbar block: Lidocaine: 20 minutes; Bupivacaine: 21 minutes

Excretion: Urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, depression, dizziness, drowsiness, excitation, or restlessness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBupivacaine and Lidocaine; Lidocaine Hydrochloride and Bupivacaine Hydrochloride

References

“American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk,” *Pediatrics*, 2001, 108(3):776-89.[PubMed 11533352]

Lidocaine and Epinephrine

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Medication Safety Issues

Transdermal patch may contain conducting metal (eg, aluminum); remove patch prior to MRI.

Pronunciation(LYE doe kane & ep i NEF rin)

U.S. Brand NamesLidoSite™; Lignospan® Forte; Lignospan® Standard; Xylocaine® MPF With Epinephrine; Xylocaine® With Epinephrine

Canadian Brand NamesXylocaine® With Epinephrine

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsLocal infiltration anesthesia; AVS for nerve block; topical local analgesia for superficial dermatologic procedures

Use: DentalAmide-type anesthetic used for local infiltration anesthesia injection near nerve trunks to produce nerve block

Dosing: AdultsDosage varies with the anesthetic procedure, degree of anesthesia needed, vascularity of tissue, duration of anesthesia required, and physical condition of patient.

Dental anesthesia, infiltration, or conduction block:

Children <10 years: 20-30 mg (1-1.5 mL) of lidocaine hydrochloride as a 2% solution with epinephrine 1:100,000; maximum: 4-5 mg of lidocaine hydrochloride/kg of body weight or 100-150 mg as a single dose

Children >10 years and Adults: Do not exceed 6.6 mg/kg body weight or 300 mg of lidocaine hydrochloride and 3 mcg (0.003 mg) of epinephrine/kg of body weight or 0.2 mg epinephrine per dental appointment. The effective anesthetic dose varies with procedure, intensity of anesthesia needed, duration of anesthesia required, and physical condition of the patient. Always use the lowest effective dose along with careful aspiration.

For most routine dental procedures, lidocaine hydrochloride 2% with epinephrine 1:100,000 is preferred. When a more pronounced hemostasis is required, a 1:50,000 epinephrine concentration should be used.

Dermatologic procedure: Topical: Place 1 transdermal patch over area requiring analgesia; attach patch to iontophoretic controller and leave on for 10 minutes. Remove patch and perform procedure within 10-20 minutes of patch removal. Do not use another patch for 30 minutes.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricLocal anesthetic:

Infiltration: Use lidocaine concentrations of 0.5% to 1% (or even more diluted) to decrease possibility of toxicity. Lidocaine dose should not exceed 7 mg/kg/dose; do not repeat within 2 hours.

Dermatologic procedure: Topical: Children ≥5 years: Refer to adult dosing.

Administration: Other

Injection solution for infiltration: Before injecting, withdraw syringe plunger to ensure injection is not into vein or artery. Aspirate the syringe after tissue penetration and before injection to minimize chance of direct vascular injection.

Transdermal system: Use on normal intact skin. Avoid use on hair-covered skin: adherence may not be adequate. Do not use disinfecting agents containing heavy metal ions (eg, mercury, zinc, copper); they are associated with increased swelling and edema. Before application, wipe area with alcohol. After skin is dry, position circular reservoir on the area to be treated. Apply light pressure from the center of the circular reservoir outward to the edges. Repeat for the oblong reservoir. Connect the controller and turn on for 10 minutes. Consult controller instructions for further details. If controller flashes yellow light (4 times/sec) medication may not have been delivered to application site; may be caused by higher than normal skin resistance, and not a malfunction of patch or controller. A tactile check of the application site may determine subjectively the level of anesthetic effect. Restrict motion of application site. A second application using a new patch may be applied after 30 minutes to a different skin site. Do not reapply to same skin site.

StorageSolutions with epinephrine should be protected from light. Transdermal system (LidoSite™) should be stored at 20°C to 25°C (68°F to 77°F); do not freeze.

ContraindicationsHypersensitivity to lidocaine, epinephrine, or any component of the formulation; hypersensitivity to other local anesthetics of the amide type; myasthenia gravis; shock; cardiac conduction disease; angle-closure glaucoma

LidoSite™: Hypersensitivity to lidocaine, epinephrine, other local anesthetics of the amide type, or any component of the formulation; patients with electrically-sensitive devices (eg, pacemakers, implantable defibrillators)

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS toxicity: Careful and constant monitoring of the patient's state of consciousness should be done following each local anesthetic injection; at such times, restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of CNS toxicity. Treatment is primarily symptomatic and supportive.

- Respiratory arrest: Local anesthetics have been associated with rare occurrences of sudden respiratory arrest.

- Seizures: Convulsions due to systemic toxicity leading to cardiac arrest have also been reported, presumably following unintentional intravascular injection.

Disease-related concerns:

- Cardiovascular disease: Use minimal amounts in patients with significant cardiovascular problems (because of epinephrine component).

- Endocrine disease: Use with caution in patients with endocrine disease.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Thyroid disease: Use with caution in patients with thyroid disease; avoid in patients with uncontrolled hyperthyroidism.

Concurrent drug therapy issues:

- Flammable anesthetics: Avoid use in presence of flammable anesthetics.

Special populations:

- Acutely ill patients: Use with caution in acutely ill; reduce dose consistent with age and physical status.

- Debilitated patients: Use with caution in debilitated patients; reduce dose consistent with age and physical status.

- Elderly: Use with caution in the elderly; reduce dose consistent with age and physical status.

- Pediatrics: Use with caution in children; reduce dose consistent with age and physical status.

Dosage form specific issues:

- Injection: Aspirate the syringe (injection solution for infiltration formulation) after tissue penetration and before injection to minimize chance of direct vascular injection.

- LidoSite™: Do not use near flammable anesthetics. Use with caution in patients with peripheral vascular disease; may have exaggerated vasoconstriction. Use with caution in patients with severe coronary artery disease, hypertension, cardiac dysrhythmias, or patients taking MAO inhibitors or tricyclic antidepressants. Use caution in patients with skin susceptible to injury.

- Sodium metabisulfite: May contain sodium metabisulfite; use caution in patients with a sulfite allergy.

- Topical formulation: Avoid application of topical formulation to distal portions of body (eg, digits, nose, ears, penis).

- Transdermal patch: May contain conducting metal (eg, aluminum); remove patch prior to MRI.

Other warnings/precautions:

- Administration: Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

- Trained personnel: Dental practitioners and/or clinicians using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorB
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/compatible
Breast-Feeding ConsiderationsUsual infiltration doses of lidocaine with epinephrine given to nursing mothers has not been shown to affect the health of the nursing infant.
Adverse ReactionsDegree of adverse effects in the central nervous system and cardiovascular system are directly related to the blood levels of lidocaine. The effects below are more likely to occur after systemic administration rather than infiltration.

Cardiovascular: Myocardial effects include a decrease in contraction force as well as a decrease in electrical excitability and myocardial conduction rate resulting in bradycardia and reduction in cardiac output.

Central nervous system: High blood levels result in anxiety, restlessness, disorientation, confusion, dizziness, tremor, and seizure. This is followed by depression of CNS resulting in somnolence, unconsciousness and possible respiratory arrest. In some cases, symptoms of CNS stimulation may be absent and the primary CNS effects are somnolence and unconsciousness.

Gastrointestinal: Nausea and vomiting may occur

Hypersensitivity reactions: Extremely rare, but may be manifest as dermatologic reactions and edema at injection site. Asthmatic syndromes have occurred. Patients may exhibit hypersensitivity to bisulfites contained in local anesthetic solution to prevent oxidation of epinephrine. In general, patients reacting to bisulfites have a history of asthma and their airways are hyper-reactive to asthmatic syndrome.

Psychogenic reactions: It is common to misinterpret psychogenic responses to local anesthetic injection as an allergic reaction. Intraoral injections are perceived by many patients as a stressful procedure in dentistry. Common symptoms to this stress are diaphoresis, palpitation, hyperventilation, generalized pallor and a fainting feeling

Topical formulation:

>10%: Dermatologic: Papules (up to 12%)

1% to 10%: Dermatologic: Burns (up to 8%), rash (5%), skin irritation, burning sensation, blanching

<1%: Erythema, hematoma, urticaria

Metabolism/Transport EffectsLidocaine: **Substrate** of CYP1A2 (minor), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2D6 (major), 3A4 (major); **Inhibits** CYP1A2 (strong), 2D6 (strong), 3A4 (moderate)

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Beta-Blockers: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. *Risk D: Consider therapy modification*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

COMT Inhibitors: May decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

Inhalational Anesthetics: May enhance the arrhythmogenic effect of EPINEPHrine. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

0.5% / 1:200,000: Lidocaine hydrochloride 0.5% and epinephrine 1:200,000 (50 mL)

1% / 1:100,000: Lidocaine hydrochloride 1% and epinephrine 1:100,000 (20 mL, 30 mL, 50 mL)

1% / 1:200,000: Lidocaine hydrochloride 1% and epinephrine 1:200,000 (30 mL)

1.5% / 1:200,000: Lidocaine hydrochloride 1.5% and epinephrine 1:200,000 (30 mL)

2% / 1:50,000: Lidocaine hydrochloride 2% and epinephrine 1:50,000 (1.8 mL)

2% / 1:100,000: Lidocaine hydrochloride 2% and epinephrine 1:100,000 (1.8 mL, 30 mL, 50 mL)

2% / 1:200,000: Lidocaine hydrochloride 2% and epinephrine 1:200,000 (20 mL)

Lignospan® Forte: 2% / 1:50,000: Lidocaine hydrochloride 2% and epinephrine 1:50,000 (1.7 mL) [contains edetate disodium, potassium metabisulfite]

Lignospan® Standard: 2% / 1:100,000: Lidocaine hydrochloride 2% and epinephrine 1:100,000 (1.7 mL) [contains edetate disodium, potassium metabisulfite]

Xylocaine® with Epinephrine:

0.5% / 1:200,000: Lidocaine hydrochloride 0.5% and epinephrine 1:200,000 (50 mL) [contains methylparaben]

1% / 1:100,000: Lidocaine hydrochloride 1% and epinephrine 1:100,000 (10 mL, 20 mL, 50 mL) [contains methylparaben]

2% / 1:50,000: Lidocaine hydrochloride 2% and epinephrine 1:50,000 (1.8 mL) [contains sodium metabisulfite]

2% / 1:100,000: Lidocaine hydrochloride 2% and epinephrine 1:100,000 (1.8 mL) [contains sodium metabisulfite]; (10 mL, 20 mL, 50 mL)

[contains methylparaben]

Xylocaine®-MPF with Epinephrine:

1% / 1:200,000: Lidocaine hydrochloride 1% and epinephrine 1:200,000 (5 mL, 10 mL, 30 mL) [contains sodium metabisulfite]

1.5% / 1:200,000: Lidocaine hydrochloride 1.5% and epinephrine 1:200,000 (5 mL, 10 mL, 30 mL) [contains sodium metabisulfite]

2% / 1:200,000: Lidocaine hydrochloride 2% and epinephrine 1:200,000 (5 mL, 10 mL, 20 mL) [contains sodium metabisulfite]

Transdermal system (LidoSite™): Lidocaine hydrochloride 10% and epinephrine 0.1% (25s) [contains sodium metabisulfite; for use only with LidoSite™ controller]

Generic AvailableYes: Excludes transdermal system

Mechanism of ActionLidocaine blocks both the initiation and conduction of nerve impulses via decreased permeability of sodium ions; epinephrine increases the duration of action of lidocaine by causing vasoconstriction (via alpha effects) which slows the vascular absorption of lidocaine

Pharmacodynamics/Kinetics

Onset of action: Peak effect: ~5 minutes

Duration: ~2 hours; dose and anesthetic procedure dependent

Absorption: Topical: Lidocaine: Minimal; Epinephrine: Minimal

See individual agents.

Related Information

- EPINEPHrine
- Lidocaine

Dental Health: Effects on Dental TreatmentIt is common to misinterpret psychogenic responses to local anesthetic injection as an allergic reaction. Intraoral injections are perceived by many patients as a stressful procedure in dentistry. Common symptoms to this stress are diaphoresis, palpitations, hyperventilation. Patients may exhibit hypersensitivity to bisulfites contained in local anesthetic solution to prevent oxidation of epinephrine. In general, patients reacting to bisulfites have a history of asthma and their airways are hyper-reactive to asthmatic syndrome.

Degree of adverse effects in the CNS and cardiovascular system is directly related to the blood levels of lidocaine: Bradycardia, hypersensitivity reactions (rare; may be manifest as dermatologic reactions and edema at injection site), asthmatic syndromes

High blood levels: Anxiety, restlessness, disorientation, confusion, dizziness, tremors, seizures, CNS depression (resulting in somnolence, unconsciousness and possible respiratory arrest), nausea, and vomiting.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusHigh blood levels may cause anxiety, confusion, dizziness, disorientation, restlessness, and somnolence.

Mental Health: Effects on Psychiatric TreatmentConcomitant use with propranolol and TCAs may result in an increase in blood pressure.

Cardiovascular ConsiderationsSympathomimetic or sympathomimetic-containing combination products may increase blood pressure. These preparations are relatively contraindicated in patients with significant hypertension, particularly in poorly controlled hypertension. In young, healthy patients presenting with new onset blood pressure elevations, it is important to exclude the recent use of sympathomimetics as a cause for the blood pressure elevation.

Index TermsEpinephrine and Lidocaine

References

Jastak JT and Yagiela JA, “Vasoconstrictors and Local Anesthesia: A Review and Rationale for Use,” *J Am Dent Assoc*, 1983, 107(4):623-30. [PubMed 6355236]

MacKenzie TA and Young ER, “Local Anesthetic Update,” *Anesth Prog*, 1993, 40(2):29-34. [PubMed 8185087]

Wynn RL, “Epinephrine Interactions With Beta-Blockers,” *Gen Dent*, 1994, 42(1):16, 18. [PubMed 7911769]

Wynn RL, “Recent Research on Mechanisms of Local Anesthetics,” *Gen Dent*, 1995, 43(4):316-8. [PubMed 8940589]

Yagiela JA, “Local Anesthetics,” *Anesth Prog*, 1991, 38(4-5):128-41.[PubMed 1819966]

Lidocaine and Hydrocortisone

Lexi-Drugs Online

English

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Pronunciation(LYE doe kane & hye droe KOR ti sone)

U.S. Brand NamesAnaMantle HC® Forte; AnaMantle® HC; Lida-Mantle® HC; Peranex™ HC; Peranex™ HC Medi-Pad; Rectacreme HC; RectaGel™ HC; Senatec HC [DSC]; Xyralid™; Xyralid™ LP; Xyralid™ RC

Pharmacologic CategoryAnesthetic/Corticosteroid

Use: Labeled IndicationsTopical anti-inflammatory and anesthetic for skin disorders; rectal for the treatment of hemorrhoids, anal fissures, pruritus ani, or similar conditions

Dosing: AdultsAnti-inflammatory/anesthetic:

Topical: Apply 2-3 times/day

Rectal: One applicatorful twice daily

Dosing: ElderlyRefer to adult dosing.

Administration: TopicalTopical: Apply thin film to affected area; avoid use of occlusive dressings

Administration: OtherRectal: Applicator tip should be gently inserted into the anal area; apply to areas of discomfort and anal opening. Do not completely insert applicator and tube; do not insert deep in the anus or rectum.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F); do not freeze.

ContraindicationsHypersensitivity to lidocaine, hydrocortisone, local anesthetics of the amide type, corticosteroids, or any component of the formulation; topical tuberculous, viral or fungal infections

Allergy Considerations

- Corticosteroid Allergy
- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.
- Infection: Discontinue if infection occurs.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

Concurrent drug therapy issues:

- Class I antiarrhythmics: Use with caution in patients taking class I antiarrhythmics.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Application site: For external use only; avoid contact with eyes, nose, or ears.

Pregnancy Risk FactorB

Pregnancy ConsiderationsSee individual agents.

LactationSee individual agents.

Metabolism/Transport Effects

Lidocaine: **Substrate** of CYP1A2 (minor), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2D6 (major), 3A4 (major); **Inhibits** CYP1A2 (strong), 2D6 (strong), 3A4 (moderate)

Hydrocortisone: **Substrate** of CYP3A4 (minor); **Induces** CYP3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, rectal:

AnaMantle HC® Forte: Lidocaine hydrochloride 3% and hydrocortisone acetate 1% (7 g) [kit contains 20 tubes (7 g each), 20 single-use applicators, and 20 single-use wipes]

AnaMantle® HC: Lidocaine hydrochloride 3% and hydrocortisone acetate 0.5% (7 g) [kit contains 14 single-use tubes (7 g each) and 14 applicators]

Peranex™ HC: Lidocaine hydrochloride 2% and hydrocortisone acetate 2% (7 g) [kit contains 24 single-use tubes with built-in applicators (7 g each) and 24 cleansing wipes]

Rectacreme HC: Lidocaine hydrochloride 3% and hydrocortisone acetate 0.5% (7 g) [kit contains 20 single-use tubes with applicators (7 g each) and cleansing towlette]

Xyralid™ RC: Lidocaine hydrochloride 3% and hydrocortisone acetate 1% (7 g) [packaged with 7 Konsyl® psyllium packets]

Cream, topical: Lidocaine hydrochloride 3% and hydrocortisone acetate 0.5% (30 g)

Lida-Mantle® HC: Lidocaine hydrochloride 3% and hydrocortisone acetate 0.5% (30 g, 85 g)

Xyralid™: Lidocaine hydrochloride 3% and hydrocortisone acetate 1% (85 g)

Gel, rectal:

AnaMantle HC®: Lidocaine hydrochloride 3% and hydrocortisone acetate 2.5% (7 g) [kit contains 20 single-use tubes with applicators (7 g each) and 20 cleansing wipes]

RectaGel™ HC: Lidocaine hydrochloride 2.8% and hydrocortisone acetate 0.55% (20 g) [kit contains 5 tubes (20 g each) and 15 single-use applicators]

Lotion, topical: Lidocaine hydrochloride 3% and hydrocortisone acetate 0.5% (177 mL)

Lida-Mantle® HC, Senatec HC [DSC], Xyralid™ LP: Lidocaine hydrochloride 3% and hydrocortisone acetate 0.5% (177 mL)

Pad, topical:

Peranex™ HC Medi-Pad: Lidocaine hydrochloride 3% and hydrocortisone acetate 1% (60s) [6 mL solution/pad]

Generic AvailableYes: Excludes gel
Pricing: U.S. (www.drugstore.com)

Cream (AnaMantle HC)

3-0.5% (98): $199.95

Cream (LidaMantle HC)

3-0.5% (85): $160.26

Gel (RectaGel HC)

2.8-0.55% (100): $115.49

Kit (AnaMantle HC)

3-2.5% (20): $265.97

Kit (Peranex HC)

2-2% (1): $269.99

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Hydrocortisone
- Lidocaine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsHydrocortisone and Lidocaine

References

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Lidocaine and Prilocaine

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English English

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Special Alerts

Topical Anesthetic Use for Cosmetic or Medical Procedures: Public Health Advisory - January 2009

The Food and Drug Administration (FDA) is issuing a Public Health Advisory to remind consumers, caregivers, and healthcare professionals of potential life-threatening side effects associated with the use of topical anesthetics available as prescription and over-the-counter (OTC) products for a variety of uses, including numbing skin prior to cosmetic or medical procedures (topical lidocaine has been recently evaluated to relieve mammography discomfort). Topical application can result in high systemic levels and lead to toxic effects (eg, irregular heart beats, seizures, coma, respiratory depression, death). At risk are consumers, particularly without the supervision of trained professionals, who apply large amounts of anesthetics (or cover large areas of the skin), leave these products on for long periods of time, or use materials, wraps, or dressings to cover the skin after anesthetic application. The FDA is working with healthcare professional organizations and other media to spread the message about the potential hazards and safe use of topical anesthetics. The FDA is recommending that if topical anesthetics are needed prior to procedures, consumers ask their healthcare provider for instructions on safe use of these products, use only FDA-approved products, and use products with the lowest amount of anesthetic while applying the least amount possible to relieve pain. If a high degree of pain is expected that is not controlled by appropriate amounts of topical anesthetics, consumers should ask their physician for alternatives techniques for pain control.

Additional information can be found at http://www.fda.gov/medwatch/safety/2009/safety09.htm#Anesthetics

Pronunciation(LYE doe kane & PRIL oh kane)

U.S. Brand NamesEMLA®; Oraquix®

Canadian Brand NamesEMLA®

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsTopical anesthetic for use on normal intact skin to provide local analgesia for minor procedures such as I.V. cannulation or venipuncture; has also been used for painful procedures such as lumbar puncture and skin graft harvesting; for superficial minor surgery of genital mucous membranes and as an adjunct for local infiltration anesthesia in genital mucous membranes.

Use: Dental

Periodontal gel (Oraqix®): Use in adults who require localized anesthesia in periodontal pockets during scaling and/or root planning.

Topical: Amide-type topical anesthetic for use on normal intact skin to provide local analgesia for minor procedures such as I.V. cannulation or venipuncture

Dosing: Adults

Anesthetic: Topical:

EMLA® cream and EMLA® anesthetic disc: A thick layer of EMLA® cream is applied to intact skin and covered with an occlusive dressing, or alternatively, an EMLA® anesthetic disc is applied to intact skin

Note: Dermal analgesia can be expected to increase for up to 3 hours under occlusive dressing and persist for 1-2 hours after removal of the cream

Minor dermal procedures (eg, I.V. cannulation or venipuncture): Topical: Apply 2.5 g of cream (1/2 of the 5 g tube) over 20-25 cm of skin surface area, or 1 anesthetic disc (1 g over 10 cm^2) for at least 1 hour. **Note:** In clinical trials, 2 sites were usually prepared in case there was a technical problem with cannulation or venipuncture at the first site.

Major dermal procedures (eg, more painful dermatological procedures involving a larger skin area such as split thickness skin graft harvesting): Topical: Apply 2 g of cream per 10 cm^2 of skin and allow to remain in contact with the skin for at least 2 hours.

Adult male genital skin (eg, pretreatment prior to local anesthetic infiltration): Apply a thick layer of cream (1 g/10 cm^2) to the skin surface for 15 minutes. Local anesthetic infiltration should be performed immediately after removal of EMLA® cream.

Adult female genital mucous membranes: Minor procedures (eg, removal of condylomata acuminata, pretreatment for local anesthetic infiltration): Apply 5-10 g (thick layer) of cream for 5-10 minutes

Periodontal gel (Oraqix®): Apply on gingival margin around selected teeth using the blunt-tipped applicator included in package. Wait 30 seconds, then fill the periodontal pockets using the blunt-tipped applicator until gel becomes visible at the gingival margin. Wait another 30 seconds before starting treatment. Maximum recommended dose: One treatment session: 5 cartridges (8.5 g)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** EMLA® should **not** be used in neonates with a gestational age <37 weeks nor in infants <12 months of age who are receiving treatment with methemoglobin-inducing agents

Local anesthetic (procedures): Topical: Children (intact skin):

Note: Dosing is based on child's age and weight: Although the incidence of systemic adverse effects with EMLA® is very low, caution should be exercised, particularly when applying over large areas and leaving on for >2 hours

Age 0-3 months or <5 kg: Apply a maximum of 1 g over no more than 10 cm^2 of skin; leave on for no longer than 1 hour.

Age 3 months to 12 months and >5 kg: Apply no more than a maximum 2 g total over no more than 20 cm^2 of skin; leave on for no longer than 4 hours.

Age 1-6 years and >10 kg: Apply no more than a maximum of 10 g total over no more than 100 cm^2 of skin; leave on for no longer than 4 hours.

Age 7-12 years and >20 kg: Apply no more than a maximum 20 g total over no more than 200 cm^2 of skin; leave on for no longer than 4 hours.

Note: If a patient greater than 3 months old does not meet the minimum weight requirement, the maximum total dose should be restricted to the corresponding maximum based on patient weight.

Dosing: Renal ImpairmentSmaller areas of treatment are recommended for patients with renal dysfunction.
Dosing: Hepatic ImpairmentSmaller areas of treatment are recommended for patients with hepatic dysfunction.
Administration: TopicalFor external use only. Avoid application to open wounds or near the eyes. In small infants and children, observe patient to prevent accidental ingestion of cream, disc, or dressing. Choose two application sites available for intravenous access. Apply a thick layer (2.5 g/site ~$^{1}/_{2}$ of a 5 g tube) of cream to each designated site of intact skin. Cover each site with the occlusive dressing (Tegaderm®). Mark the time on the dressing. **Allow at least 1 hour for optimum therapeutic effect.** Remove the dressing and wipe off excess EMLA® cream (gloves should be worn). **Smaller areas of treatment are recommended for debilitated patients.**
StorageStore at room temperature.
ContraindicationsHypersensitivity to amide-type anesthetic agents (eg, lidocaine, prilocaine, dibucaine, mepivacaine, bupivacaine, etidocaine); hypersensitivity to any component of the formulation selected; application on mucous membranes or broken or inflamed skin; infants <1 month of age if gestational age is <37 weeks; infants <12 months of age receiving therapy with methemoglobin-inducing agents; children with congenital or idiopathic methemoglobinemia, or in children who are receiving medications associated with drug-induced methemoglobinemia (eg, acetaminophen [overdosage], benzocaine, chloroquine, dapsone, nitrofurantoin, nitroglycerin, nitroprusside, phenazopyridine, phenelzine, phenobarbital, phenytoin, quinine, sulfonamides)
Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

Concurrent drug therapy issues:

- Class I and III antiarrhythmics: Use with caution in patients receiving class I and III antiarrhythmic drugs, since systemic absorption occurs and synergistic toxicity is possible.

Special populations:

- Acutely ill patients: Use with caution in acutely ill; reduce dose consistent with age and physical status.

- Debilitated patients: Use with caution in debilitated patients; reduce dose consistent with age and physical status.

- Elderly: Use with caution in the elderly; reduce dose consistent with age and physical status.

Other warnings/precautions:

- Appropriate use: Although the incidence of systemic adverse reactions with EMLA® is very low, caution should be exercised, particularly when applying over large areas and leaving on for longer than 2 hours. Avoid use on open wounds or near the eyes.

Pregnancy Risk FactorB
Pregnancy ConsiderationsRefer to Lidocaine monograph.
LactationEnters breast milk/compatible
Breast-Feeding ConsiderationsUsual infiltration doses of lidocaine and prilocaine given to nursing mothers has not been shown to affect the health of the nursing infant.
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension, angioedema

Central nervous system: Shock

Dermatologic: Hyperpigmentation, erythema, itching, rash, burning, urticaria

Genitourinary: Blistering of foreskin (rare)

Local: Burning, stinging, edema

Respiratory: Bronchospasm

Miscellaneous: Alteration in temperature sensation, hypersensitivity reactions

Oncology: Emetic PotentialVery low (<10%)

Metabolism/Transport EffectsLidocaine: **Substrate** of CYP1A2 (minor), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2D6 (major), 3A4 (major); **Inhibits** CYP1A2 (strong), 2D6 (strong), 3A4 (moderate)

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringUse on intact skin only. Monitor for effectiveness of anesthesia and adverse reactions. Monitor for return of sensation.

Patient EducationThis drug will block sensation to the applied area. Report irritation, pain, burning at application site.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical: Lidocaine 2.5% and prilocaine 2.5% (5 g, 30 g)

EMLA®: Lidocaine 2.5% and prilocaine 2.5% (5 g, 30 g) [each packaged with Tegaderm® dressings]

Disc, topical: Lidocaine 2.5% and prilocaine 2.5% per disc (2s, 10s) [each 1 g disc is 10 cm^2]

Gel, periodontal: Lidocaine 2.5% and prilocaine 2.5% (1.7 g) [cartridge]

Generic AvailableYes: Cream

Pricing: U.S. (www.drugstore.com)

Cream (Lidocaine-Prilocaine)

2.5-2.5% (30): $41.99

Mechanism of ActionLocal anesthetic action occurs by stabilization of neuronal membranes and inhibiting the ionic fluxes required for the initiation and conduction of impulses

Pharmacodynamics/Kinetics

EMLA®:

Onset of action: 1 hour

Peak effect: 2-3 hours

Duration: 1-2 hours after removal

Absorption: Related to duration of application and area where applied

3-hour application: 3.6% lidocaine and 6.1% prilocaine

24-hour application: 16.2% lidocaine and 33.5% prilocaine

See individual agents.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Application site reactions in the oral cavity in 52/391 patients (13%) included pain, soreness, irritation, numbness, ulcerations, vesicles, edema, abscess and/or redness in the treated area. The 13% represented adverse effects occurring in more than one patient. Each patient was counted only once per adverse event. Taste perversion also reported (2%) including complaints of bad or bitter taste for up to 4 hours after administration.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentContraindicated with phenytoin, phenobarbital, and phenelzine

Index TermsPrilocaine and Lidocaine

References

Broadman LM, Soliman IE, Hannallah RS, et al, “Analgesic Efficacy of Eutectic Mixture of Local Anesthetics (EMLA®) vs Intradermal Infiltration Prior to Venous Cannulation in Children,” *Am J Anaesthesiol*, 1987, 34:S56.

Halperin DL, Koren G, Attias D, et al, “Topical Skin Anesthesia for Venous Subcutaneous Drug Reservoir and Lumbar Puncture in Children,” *Pediatrics*, 1989, 84(2):281-4. [PubMed 2748256]

Robieux I, Kumar R, Radhakrishnan S, et al, “Assessing Pain and Analgesia With a Lidocaine-Prilocaine Emulsion in Infants and Toddlers During Venipuncture,” *J Pediatr*, 1991, 118(6):971-3. [PubMed 2040936]

Taddio A, Shennan AT, Stevens B, et al, “Safety of Lidocaine-Prilocaine Cream in the Treatment of Preterm Neonates,” *J Pediatr*, 1995, 127(6):1002-5. [PubMed 8523173]

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International Brand NamesAnestecin crema (CO); Ansederm (FR); Duo-Caine (IL); Emla (AE, AR, AT, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CY, CZ, DE, DK, EG, ET, FR, GB, GH, GM, GN, GR, GY, HK, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PH, PY, QA, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Emla Cream (NZ); Emla Patch (NZ); Lipril Cream (KP); Oraqix (SE)

Lidocaine and Tetracaine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Topical Anesthetic Use for Cosmetic or Medical Procedures: Public Health Advisory - January 2009

The Food and Drug Administration (FDA) is issuing a Public Health Advisory to remind consumers, caregivers, and healthcare professionals of potential life-threatening side effects associated with the use of topical anesthetics available as prescription and over-the-counter (OTC) products for a variety of uses, including numbing skin prior to cosmetic or medical procedures (topical lidocaine has been recently evaluated to relieve mammography discomfort). Topical application can result in high systemic levels and lead to toxic effects (eg, irregular heart beats, seizures, coma, respiratory depression, death). At risk are consumers, particularly without the supervision of trained professionals, who apply large amounts of anesthetics (or cover large areas of the skin), leave these products on for long periods of time, or use materials, wraps, or dressings to cover the skin after anesthetic application. The FDA is working with healthcare professional organizations and other media to spread the message about the potential hazards and safe use of topical anesthetics. The FDA is recommending that if topical anesthetics are needed prior to procedures, consumers ask their healthcare provider for instructions on safe use of these products, use only FDA-approved products, and use products with the lowest amount of anesthetic while applying the least amount possible to relieve pain. If a high degree of pain is expected that is not controlled by appropriate amounts of topical anesthetics, consumers should ask their physician for alternatives techniques for pain control.

Additional information can be found at http://www.fda.gov/medwatch/safety/2009/safety09.htm#Anesthetics

Pronunciation(LYE doe kane & TET ra kane)

U.S. Brand NamesPliaglis™; Synera™

Pharmacologic CategoryAnalgesic, Topical; Local Anesthetic

Use: Labeled IndicationsTopical anesthetic for use on normal intact skin for minor procedures (eg, I.V. cannulation or venipuncture) and superficial dermatologic procedures

Dosing: Adults

Superficial dermatological procedures (eg, dermal filler injection, facial laser ablation): Topical cream (Pliaglis™): Apply 20-30 minutes prior to procedure

Laser-assisted tattoo removal: Topical cream (Pliaglis™): Apply 60 minutes prior to procedure

Note: The amount of Pliaglis™ required is determined by the size of the treatment area. Use the ruler on the carton and in the packaging to measure out the proper amount (cm length of cream). Apply evenly and thinly (~1 mm or the thickness of a dime) over the area using a flat tool (eg, spatula, tongue depressor).

If surface area of treatment site:

10 cm^2: Apply 3 cm Pliaglis™

20 cm^2: Apply 6 cm Pliaglis™

40 cm^2: Apply 12 cm Pliaglis™

80 cm^2: Apply 24 cm Pliaglis™

100 cm^2: Apply 30 cm Pliaglis™

150 cm^2: Apply 46 cm Pliaglis™

200 cm^2: Apply 61 cm Pliaglis™

250 cm^2: Apply 76 cm Pliaglis™

300 cm^2: Apply 91 cm Pliaglis™

350 cm^2: Apply 106 cm Pliaglis™

400 cm^2: Apply 121 cm Pliaglis™

After waiting the required application time, remove the Pliaglis™ by grasping a free edge and pulling it away from the skin.

Venipuncture or intravenous cannulation: Transdermal patch: Prior to procedure, apply to intact skin for 20-30 minutes; **Note:** Adults can use another patch at a new location to facilitate venous access after a failed attempt; remove previous patch.

Superficial dermatological procedures: Transdermal patch: Prior to procedure, apply to intact skin for 30 minutes

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Venipuncture or intravenous cannulation: Children ≥3 years: Transdermal patch: Refer to adult dosing.

Superficial dermatological procedures: Children ≥3 years: Transdermal patch: Refer to adult dosing.

Dosing: Hepatic Impairment

Use caution in patients with severe hepatic dysfunction.

Administration: Topical

Cream: Pliaglis™: Apply to intact, healthy skin. Remove if irritation or burning occur. After proper application time, remove from skin and dispose of carefully. Wash hands after applying.

Transdermal patch: Synera™: Apply to intact, healthy skin. Use immediately after opening pouch. Patch begins to heat once removed from pouch. May increase skin temperature by 5°C, will not exceed 40°C. If irritation or burning occurs during application, remove patch. Wash hands after applying. Do not cut the patch or remove the top cover. Do not cover the holes on the top side of the patch. Carefully dispose of used patches as they contain large amounts of lidocaine and tetracaine. Fold adhesive together.

Storage

Pliaglis™: Store at 2°C to 8°C (36°F to 46°F). Do not freeze.

Synera™: Store at 23°C to 27°C (73°F to 81°F).

ContraindicationsHypersensitivity to lidocaine, tetracaine, amide or ester-type anesthetic agents, para-aminobenzoid acid (PABA), or any other component of the formulation
Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity/anaphylactic reactions: May occur.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

Concurrent drug therapy issues:

- Class I antiarrhythmics: Use with caution in patients receiving class I antiarrhythmic drugs, since systemic absorption occurs and synergistic toxicity is possible.

- Methemoglobinemia: Has been reported with local anesthetics including tetracaine. Use caution in patients with lung diseases (asthma, bronchitis, emphysema, in smokers), inflamed/damaged mucosa, heart disease, children <12 months of age, concurrent use with methemoglobin-inducing medications, and hemoglobin or enzyme abnormalities (glucose-6-phosphodiesterase deficiency, hemoglobin-M disease, NADH-methemoglobin reductase deficiency, pyruvate-kinase deficiency).

- Other local anesthetics: If being used with other products containing local anesthetic, consider potential for additive effects.

Special populations:

- Acutely-ill patients: Use with caution in acutely ill patients.

- Debilitated patients: Use with caution in debilitated patients.

- Elderly: Use with caution in the elderly.

- Pediatrics: Synera™ transdermal patch: Efficacy has not been established in patients <3 years of age (safety has been documented in limited trials). Pliaglis™ topical cream: Safety and efficacy in children have not been established.

- Pseudocholinesterase deficiency: Use with caution in patients with pseudocholinesterase deficiency; greater risk of lidocaine/tetracaine toxicity.

Other warnings/precautions:

- Appropriate use: Avoid contact with eye; loss of protective reflexes may predispose to corneal irritation and/or abrasion. Application to broken or inflamed skin or mucous membranes may lead to increased systemic absorption. Not for use at home.

- MRI: Synera™: Remove patch prior to MRI.

- Multiple patch application: Synera™: Although the incidence of systemic adverse reactions is very low, caution should be exercised when applying simultaneous or sequential application of multiple patches to adults; this practice is not recommended with children.

Geriatric ConsiderationsThe manufacturer reports that in clinical studies there were no significant differences in safety between geriatric adjustments and younger subjects.

Pregnancy Risk FactorB

Pregnancy ConsiderationsSee individual agents.

LactationEnters breast milk (lidocaine in small amounts)/compatible

Adverse Reactions

>10%: Dermatologic: Erythema (47% to 71%), skin discoloration (<4% to 16%), edema (12% to 14%), blanching (12%)

1% to 10%: Dermatologic: Application site reactions (contact dermatitis, rash)

<1%: Acne, allergic reaction, anaphylactoid reaction, angioedema, blister, bronchospasm, bruising, confusion, dehydration, diaphoresis, dizziness, fever, headache, hyperventilation, hypotension, infection, nausea, nervousness, pain, pallor, paresthesia, petechiae, pharyngitis, pruritus, somnolence, stupor, syncope, urticaria, vesiculobullous rash, vomiting

Metabolism/Transport EffectsLidocaine: **Substrate** of CYP1A2 (minor), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2D6 (major), 3A4 (major); **Inhibits** CYP1A2 (strong), 2D6 (strong), 3A4 (moderate)

Drug InteractionsThere are no known significant interactions.

Monitoring Parameters

Effectiveness of anesthesia

Nursing: Physical Assessment/MonitoringAssess for history of allergies. Explain change in sensation patient will experience. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Patient EducationSynera™: The patch is used short-term for the purpose of local anesthetic prior to a procedure such as venipuncture. Wash hands after handling the patch. Avoid contact to eye, mucous membranes, or on broken or inflamed skin. Dispose of patch carefully. Used patches will still have residual medication which could harm a small child or animal if chewed or ingested. Remove from body prior to magnetic resonance imaging.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical:

Pliaglis™: Lidocaine 7% and tetracaine 7% (30 g)

Transdermal system:

Synera™: Lidocaine 70 mg and tetracaine 70 mg (10s) [contains heating component; each patch is ~50 cm^2]

Generic AvailableNo

Mechanism of Action Local anesthetic action occurs by stabilization of neuronal membranes and inhibiting the sodium ion fluxes required for the initiation and conduction of impulses.

Synera™: A heating mechanism within the patch enhances drug delivery.

Pharmacodynamics/KineticsAlso see individual agents.

Duration: Cream: ~11 hours

Absorption: Related to duration of application and area where applied.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsTetracaine and Lidocaine

International Brand NamesRapydan (SE)

Lidocaine Transoral

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(LYE doe kane trans OR al)
U.S. Brand NamesDentiPatch®
Pharmacologic CategoryLocal Anesthetic, Transoral
Use: Labeled IndicationsLocal anesthesia of the oral mucosa prior to oral injections and soft-tissue dental procedures
Use: Dental

Local anesthesia of the oral mucosa prior to oral injections and soft-tissue dental procedures

Dosing: AdultsLocal anesthesia of the oral mucosa (prior to oral injections): Topical: One patch on selected area of oral mucosa
Dosing: ElderlyRefer to adult dosing.
Dietary ConsiderationsOral patch with lidocaine 46.1 mg/2 cm^2 contains phenylalanine 0.62 mg.
ContraindicationsHypersensitivity to lidocaine or any of component of the formulation
Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Adverse ReactionsNo data reported
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Patch, oral: 46.1 mg/2 cm^2 (50s, 100s) [contains phenylalanine 0.62 mg/patch; spearmint flavor]

Generic AvailableNo
Mechanism of ActionBlocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction
Pharmacodynamics/Kinetics

Onset of action: 2 minutes

Duration: Anesthesia: 40 minutes after 15-minute wear period

Dental Health Professional ConsiderationsPeak plasma levels were 10% of those seen following local infiltration anesthesia with 1.8 mL lidocaine and 1:100,000 epinephrine.

The manufacturer claims DentiPatch® is safe, with “negligible systemic absorption” of lidocaine. The agent is “clinically proven to prevent injection pain from 25-gauge needles that are inserted to the level of the bone.” Data from controlled studies (235 patients) have shown no serious adverse effects with the application of lidocaine patch to the oral mucosa for 15 minutes.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
References

Hersh EV, Houpt MI, Cooper SA, et al, “Analgesic Efficacy and Safety of an Intraoral Lidocaine Patch,” *J Am Dent Assoc*, 1996, 127(11):1626-34. [PubMed 8952239]

Houpt MI, Heins P, Lamster I, et al, “An Evaluation of Intraoral Lidocaine Patches in Reducing Needle-Insertion Pain,” *Compendium*, 1997, 4:309-16.

“The Lidocaine Patch: A New Delivery System,” *Biological Therapies in Dentistry*, Sept 1997, vol 13.

Lidocaine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Topical Anesthetic Use for Cosmetic or Medical Procedures: Public Health Advisory - January 2009

The Food and Drug Administration (FDA) is issuing a Public Health Advisory to remind consumers, caregivers, and healthcare professionals of potential life-threatening side effects associated with the use of topical anesthetics available as prescription and over-the-counter (OTC) products for a variety of uses, including numbing skin prior to cosmetic or medical procedures (topical lidocaine has been recently evaluated to relieve mammography discomfort). Topical application can result in high systemic levels and lead to toxic effects (eg, irregular heart beats, seizures, coma, respiratory depression, death). At risk are consumers, particularly without the supervision of trained professionals, who apply large amounts of anesthetics (or cover large areas of the skin), leave these products on for long periods of time, or use materials, wraps, or dressings to cover the skin after anesthetic application. The FDA is working with healthcare professional organizations and other media to spread the message about the potential hazards and safe use of topical anesthetics. The FDA is recommending that if topical anesthetics are needed prior to procedures, consumers ask their healthcare provider for instructions on safe use of these products, use only FDA-approved products, and use products with the lowest amount of anesthetic while applying the least amount possible to relieve pain. If a high degree of pain is expected that is not controlled by appropriate amounts of topical anesthetics, consumers should ask their physician for alternatives techniques for pain control.

Additional information can be found at http://www.fda.gov/medwatch/safety/2009/safety09.htm#Anesthetics

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (epidural administration; I.V. formulation) among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Transdermal patch may contain conducting metal (eg, aluminum); remove patch prior to MRI.

International issues:

Lidpen® may be confused with Linoten® which is a brand name for pamidronate in Spain

Pronunciation(LYE doe kane)

U.S. Brand NamesAkten™; Anestacon®; Anestafoam™ [OTC]; Band-Aid® Hurt-Free™ Antiseptic Wash [OTC]; Burn Jel® [OTC]; Burn-O-Jel [OTC]; Burnamycin [OTC]; L-M-X™ 4 [OTC]; L-M-X™ 5 [OTC]; LidaMantle®; Lidoderm®; LTA® 360; Premjact® [OTC]; Solarcaine® Aloe Extra Burn Relief [OTC]; Topicaine® [OTC]; Unburn®; Xylocaine®; Xylocaine® MPF; Xylocaine® Viscous; Zilactin-L® [OTC]; Zingo™

Canadian Brand NamesBetacaine®; Lidodan™; Lidoderm®; Xylocaine®; Xylocard®; Zilactin®

Pharmacologic CategoryAnalgesic, Topical; Antiarrhythmic Agent, Class Ib; Local Anesthetic; Local Anesthetic, Ophthalmic

Use: Labeled IndicationsLocal anesthetic and acute treatment of ventricular arrhythmias (such as from myocardial infarction or cardiac manipulation)

Intradermal: To provide local anesthesia prior to venipuncture or peripheral I.V. cannulation

Ophthalmic: To provide local anesthesia to ocular surface during ophthalmologic procedures

Rectal: Temporary relief of pain and itching due to anorectal disorders

Topical: Local anesthetic for use in laser, cosmetic, and outpatient surgeries; minor burns, cuts, and abrasions of the skin

Lidoderm® Patch: Relief of allodynia (painful hypersensitivity) and chronic pain in postherpetic neuralgia

Use: Unlabeled/InvestigationalACLS guidelines (not considered drug of choice): Stable monomorphic VT (preserved ventricular function), polymorphic VT (preserved ventricular function), drug-induced monomorphic VT

Use: DentalAmide-type injectable local anesthetic and topical local anesthetic; Patch: Production of mild topical anesthesia of accessible mucous membranes of the mouth prior to superficial dental procedures

Dosing: Adults

Antiarrhythmic:

I.V.: 1-1.5 mg/kg bolus over 2-3 minutes; may repeat doses of 0.5-0.75 mg/kg in 5-10 minutes up to a total of 3 mg/kg; continuous infusion: 1-4 mg/minute

Ventricular fibrillation or pulseless ventricular tachycardia (after defibrillation, CPR, and vasopressor administration): I.V.: Initial: 1-1.5 mg/kg. Refractory ventricular tachycardia or ventricular fibrillation, a repeat 0.5-0.75 mg/kg bolus may be given every 5-10 minutes after initial dose for a maximum of 3 doses. Total dose should not exceed 3 mg/kg. Follow with continuous infusion (1-4 mg/minute) after return of perfusion. Reappearance of arrhythmia during constant infusion: 0.5 mg/kg bolus and reassessment of infusion.

E.T. (loading dose only): 2-2.5 times the I.V. dose

Note: Decrease dose in patients with CHF, shock, or hepatic disease.

Anesthesia, local injectable: Varies with procedure, degree of anesthesia needed, vascularity of tissue, duration of anesthesia required, and physical condition of patient; maximum: 4.5 mg/kg/dose; do not repeat within 2 hours.

Anesthesia, ocular: Apply 2 drops to ocular surface in area where procedure will occur; may reapply to maintain effect

Anesthetic, topical:

Cream:

LidaMantle®: Skin irritation: Apply to affected area 2-3 times/day as needed

L-M-X™ 4: Apply $^{1}/_{4}$ inch thick layer to intact skin. Leave on until adequate anesthetic effect is obtained. Remove cream and cleanse area before beginning procedure.

L-M-X™ 5: Relief of anorectal pain and itching: Rectal: Apply topically to clean, dry area **or** using applicator, insert rectally, up to 6 times/day

Gel, ointment, solution: Apply to affected area ≤3 times/day as needed (maximum dose: 4.5 mg/kg, not to exceed 300 mg)

Jelly: Maximum dose: 30 mL (600 mg) in any 12-hour period:

Anesthesia of male urethra: 5-30 mL (100-600 mg)

Anesthesia of female urethra: 3-5 mL (60-100 mg)

Lubrication of endotracheal tube: Apply a moderate amount to external surface only

Liquid: Cold sores and fever blisters: Apply to affected area every 6 hours as needed

Patch: Postherpetic neuralgia: Apply patch to most painful area. Up to 3 patches may be applied in a single application. Patch may remain in place for up to 12 hours in any 24-hour period.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Antiarrhythmic:

I.V., I.O.: **Note:** For use in pulseless VT or VF, give after defibrillation, CPR, and epinephrine:

Loading dose: 1 mg/kg (maximum 100 mg); follow with continuous infusion; may administer second bolus of 0.5-1 mg/kg if delay between bolus and start of infusion is >15 minutes

Continuous infusion: 20-50 mcg/kg/minute. Use 20 mcg/kg/minute in patients with shock, hepatic disease, cardiac arrest, mild CHF; moderate-to-severe CHF may require $^{1}/_{2}$ loading dose and lower infusion rates to avoid toxicity.

E.T.: 2-3 mg/kg; flush with 5 mL of NS and follow with 5 assisted manual ventilations

Anesthetic, ocular: Refer to adult dosing

Anesthetic, topical:

Cream:

LidaMantle®: Skin irritation: Refer to adult dosing.

L-M-X™ 4: Children ≥2 years: Refer to adult dosing.

L-M-X™ 5: Relief of anorectal pain and itching: Rectal: Children ≥12 years: Refer to adult dosing.

Jelly: Children ≥10 years: Dose varies with age and weight (maximum dose: 4.5 mg/kg)

Liquid: Cold sores and fever blisters: Children ≥5 years: Refer to adult dosing.

Injectable local anesthetic: Refer to adult dosing.

Anesthesia, intradermal: Children 3-18 years: Zingo™: 0.5 mg to site of venipuncture or peripheral I.V. cannulation, 1-3 minutes prior to procedure. Procedure should be started within 10 minutes of application.

Dosing: Renal ImpairmentNot dialyzable (0% to 5%) by hemo- or peritoneal dialysis; supplemental dose is not necessary.

Dosing: Hepatic ImpairmentReduce dose in acute hepatitis and decompensated cirrhosis by 50%.

Calculations

- Lidocaine

Administration: I.V.Use microdrip (60 drops/mL) or infusion pump to administer an accurate dose.

Infusion rates: 2 g/250 mL D_5W (infusion pump should be used):

1 mg/minute: 7.5 mL/hour

2 mg/minute: 15 mL/hour

3 mg/minute: 22.5 mL/hour

4 mg/minute: 30 mL/hour

Buffered lidocaine for injectable local anesthetic: Add 2 mL of sodium bicarbonate 8.4% to 18 mL of lidocaine 1%

Administration: I.V. DetailLocal thrombophlebitis may occur in patients receiving prolonged I.V. infusions.

pH: 5-7 (injection); 3.5-6.0 (premixed infusion solution in D_5W)

Administration: Topical

Gel (Topicaine®): Avoid mucous membranes; remove prior to laser treatment.

Transdermal: Apply to painful area of skin immediately after removal from protective envelope. May be cut to appropriate size. After removal from skin, fold used transdermal systems so the adhesive side sticks to itself. Remove immediately if burning sensation occurs. Wash hands after application.

Intradermal (Zingo™): Apply to intact skin do not use on mucous membranes. When placing intradermal injection system on skin, hold device perpendicular to skin and seal to avoid gaps between system and skin which would impair drug delivery. A "popping" sound will indicate dose has been discharged. If needed, may apply at a new location following failed attempt at venous access; do not apply multiple times at the same site.

Administration: OtherEndotracheal: Dilute in NS or distilled water. Absorption is greater with distilled water, but causes more adverse effects on PaO_2. Pass catheter beyond tip of tracheal tube, stop compressions, spray drug quickly down tube. Follow immediately with several quick insufflations and continue chest compressions.

Dietary ConsiderationsPremixed injection may contain corn-derived dextrose and its use is contraindicated in patients with allergy to corn-related products.

Storage

Injection: Stable at room temperature. Stability of parenteral admixture at room temperature (25°C) is the expiration date on premixed bag; out of overwrap stability is 30 days.

Ophthalmic: Store at 15°C to 25°C (59°F to 77°F). Protect from light. Discard after use.

ReconstitutionStandard diluent: 2 g/250 mL D_5W.

CompatibilityStable in D_5LR, $D_5{}^1/_2NS$, D_5NS, D_5W, LR, ${}^1/_4NS$, NS.

Y-site administration: Compatible: Alteplase, amiodarone, cefazolin, ciprofloxacin, cisatracurium, clarithromycin, diltiazem, dobutamine, dobutamine with dopamine, dobutamine with nitroglycerin, dobutamine with sodium nitroprusside, dopamine, dopamine with nitroglycerin, dopamine with sodium nitroprusside, enalaprilat, etomidate, famotidine, gatifloxacin, haloperidol, heparin, heparin with hydrocortisone sodium succinate, inamrinone, labetalol, levofloxacin, linezolid, meperidine, morphine, nitroglycerin, nitroglycerin with sodium nitroprusside, potassium chloride, propofol, remifentanil, sodium nitroprusside, streptokinase, theophylline, tirofiban, vitamin B complex with C, warfarin. **Incompatible:** Amphotericin B cholesteryl sulfate complex, thiopental.

Compatibility in syringe: Compatible: Clonidine with fentanyl, glycopyrrolate, heparin, hydroxyzine, ketamine with morphine, metoclopramide, milrinone, moxalactam, nalbuphine. **Incompatible:** Cefazolin. **Variable (consult detailed reference):** Ampicillin, ceftriaxone, sodium bicarbonate.

Compatibility when admixed: Compatible: Alteplase, aminophylline, amiodarone, atracurium, bretylium, bupivacaine, calcium chloride, calcium gluconate, chloramphenicol, chlorothiazide, cimetidine, clonidine, dexamethasone sodium phosphate, digoxin, diphenhydramine, dobutamine, dopamine, ephedrine, erythromycin lactobionate, fentanyl, floxacillin, flumazenil, furosemide, heparin, hydrocortisone sodium succinate, hydroxyzine, insulin (regular), ketamine, mephentermine, metaraminol, morphine, nafcillin, nitroglycerin, penicillin G potassium, pentobarbital, phenylephrine, potassium chloride, procainamide, prochlorperazine edisylate, promazine, propafenone, ranitidine, sodium bicarbonate, sodium lactate, tetracaine, theophylline, verapamil, vitamin B complex with C. **Incompatible:** Amphotericin B, dacarbazine, methohexital, phenytoin. **Variable (consult detailed reference):** Epinephrine, isoproterenol, norepinephrine.

ContraindicationsHypersensitivity to lidocaine or any component of the formulation; hypersensitivity to another local anesthetic of the amide type; Adam-Stokes syndrome; severe degrees of SA, AV, or intraventricular heart block (except in patients with a functioning artificial pacemaker); premixed injection may contain corn-derived dextrose and its use is contraindicated in patients with allergy to corn-related products

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Disease-related concerns:

- Hepatic dysfunction: Use extreme caution in patients with severe hepatic dysfunction; may have increased risk of lidocaine toxicity.

- Pseudocholinesterase deficiency: Use caution in patients with pseudocholinesterase deficiency; may have increased risk of lidocaine toxicity

Dosage form specific issues:

- Injectable anesthetic: Follow appropriate administration techniques so as not to administer any intravascularly. Solutions containing antimicrobial preservatives should not be used for epidural or spinal anesthesia. Some solutions contain a bisulfite; avoid in patients who are allergic to bisulfite. Resuscitative equipment, medicine and oxygen should be available in case of emergency. Use products containing epinephrine cautiously in patients with significant vascular disease, compromised blood flow, or during or following general anesthesia (increased risk of arrhythmias). Adjust the dose for the elderly, pediatric, acutely ill, and debilitated patients.

- Intradermal: For use on intact skin where adequate seal can be maintained. Do not apply to body orifices or mucous membranes. Use caution in patients with bleeding tendencies or platelet disorders; may have increased risk of superficial dermal bleeding. Safety and efficacy have not been established in children <3 years of age or adults.

- Intravenous: Constant ECG monitoring is necessary during I.V. administration. Use cautiously in hepatic impairment, any degree of heart block, Wolff-Parkinson-White syndrome, HF, marked hypoxia, severe respiratory depression, hypovolemia, history of malignant hyperthermia, or shock. Increased ventricular rate may be seen when administered to a patient with atrial fibrillation. Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy. Correct any underlying causes of ventricular arrhythmias. Monitor closely for signs and symptoms of CNS toxicity. The elderly may be prone to increased CNS and cardiovascular side effects. Reduce dose in hepatic dysfunction and CHF.

- Ophthalmic: For ophthalmic use only; not for injection. Prolonged use may cause permanent corneal ulceration and/or opacification with loss of vision.

- Topical: Do not leave on large body areas for >2 hours. Potentially life threatening side effects (eg, irregular heart beat, seizures, coma, respiratory depression, death) have occurred when used prior to cosmetic procedures. Observe young children closely to prevent accidental ingestion. Not for ophthalmic use. Some products are not recommended for use on mucous membranes; consult specific product labeling.

- Transdermal patch: Safety and efficacy have not been established in children.

Other warnings/precautions:

- CAST trial: In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, non-life-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide. An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. Antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Geriatric ConsiderationsDue to decreases in Phase I metabolism and possibly decrease in splanchnic perfusion with age, there may be a decreased clearance or increased half-life in the elderly and increased risk for CNS side effects and cardiac effects.
Pregnancy Risk FactorB
Pregnancy ConsiderationsAnimal studies with lidocaine have not shown teratogenic effects. Use is not contraindicated during labor and delivery. Systemic exposure following use of the intradermal system is below the limit of detection.
LactationEnters breast milk (small amounts)/use caution (AAP rates “compatible”)
Adverse ReactionsEffects vary with route of administration. Many effects are dose related.

Frequency not defined.

Cardiovascular: Arrhythmia, bradycardia, arterial spasms, cardiovascular collapse, defibrillator threshold increased, edema, flushing, heart block, hypotension, sinus node supression, vascular insufficiency (periarticular injections)

Central nervous system: Agitation, anxiety, apprehension, coma, confusion, disorientation, dizziness, drowsiness, euphoria, hallucinations, headache, hyperesthesia, hypoesthesia, lethargy, lightheadedness, nervousness, psychosis, seizure, slurred speech, somnolence, unconsciousness

Dermatologic: Angioedema, bruising (transdermal system), contact dermatitis, depigmentation (transdermal system), edema of the skin, itching, petechia (transdermal system), pruritus, rash, urticaria

Gastrointestinal: Metallic taste, nausea, vomiting

Local: Burning (ophthalmic), irritation (transdermal system), thrombophlebitis

Neuromuscular & skeletal: Pain exacerbation (transdermal system), paresthesia, transient radicular pain (subarachnoid administration; up to 1.9%), tremor, twitching, weakness

Ocular: Conjunctival hyperemia (ophthalmic), corneal epithelial changes (ophthalmic), diplopia, visual changes

Otic: Tinnitus

Respiratory: Bronchospasm, dyspnea, respiratory depression or arrest

Miscellaneous: Allergic reactions, anaphylactoid reaction, sensitivity to temperature extremes

Intradermal system: Application site reactions: Erythema (53%), petechiae (44%), edema (8%), bruising/burning/contusion/hemorrhage/pain (4%), pruritus (1%; equal to placebo)

Following spinal anesthesia: Positional headache (3%), shivering (2%) nausea, peripheral nerve symptoms, respiratory inadequacy and double vision (<1%), hypotension, cauda equina syndrome

Postmarketing and/or case reports: ARDS (inhalation), asystole, disorientation, methemoglobinemia, skin reaction

Metabolism/Transport Effects **Substrate** of CYP1A2 (minor), 2A6 (minor), 2B6 (minor), 2C9 (minor), 2D6 (major), 3A4 (major); **Inhibits** CYP1A2 (strong), 2D6 (moderate), 3A4 (moderate)

Drug Interactions

Amiodarone: May decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. *Risk C: Monitor therapy*

Beta-Blockers: May decrease the metabolism of Lidocaine. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Strong) may decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of Lidocaine. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disopyramide: May enhance the arrhythmogenic effect of Lidocaine. Disopyramide may increase the serum concentration of Lidocaine. Specifically, the unbound/free fraction of lidocaine. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions Herb/Nutraceutical: St John's wort may decrease lidocaine levels; avoid concurrent use.

Reference Range

Therapeutic: 1.5-5.0 mcg/mL (SI: 6-21 µmol/L)

Potentially toxic: >6 mcg/mL (SI: >26 µmol/L)

Toxic: >9 mcg/mL (SI: >38 µmol/L)

Nursing: Physical Assessment/Monitoring Assess other medications patient may be taking for adverse interactions. **Local anesthetic:** Monitor for effectiveness of anesthesia and adverse reactions. **Dental/local anesthetic:** Use caution to prevent gagging or choking. Avoid food or drink for 1 hour. Teach patient adverse reactions to report; use and teach appropriate interventions to promote safety. **Antiarrhythmic: I.V.:** ECG and vital signs must be closely and continually monitored. Keep patient supine to reduce hypotensive effects. Assess frequently for adverse reactions or signs of CNS toxicity. Teach patient adverse reactions to report and appropriate interventions to promote safety.

Monitoring: Lab TestsI.V.: Serum lidocaine levels. Therapeutic levels range from 1.5-5 mcg/mL; >6 mcg/mL is associated with toxicity.

Patient EducationI.V.: You will be monitored during infusion. Do not get up without assistance. Report dizziness, numbness, double vision, nausea, pain or burning at infusion site, nightmares, hearing strange noises, seeing unusual visions, or respiratory difficulty.

Dermatologic: You will experience decreased sensation to pain, heat, or cold in the area and/or decreased muscle strength (depending on area of application) until effects wear off; use necessary caution to reduce incidence of possible injury until full sensation returns. Report irritation, pain, persistent numbness, tingling, swelling; restlessness, dizziness, acute weakness; blurred vision; ringing in ears; or respiratory difficulty.

Dental/local anesthetic: Lidocaine can cause numbness of tongue, cheeks, and throat. Do not eat or drink for 1 hour after use. Take small sips of water at first to ensure that you can swallow without difficulty. Your tongue and mouth may be numb; use caution avoid biting yourself. Immediately report swelling of face, lips, or tongue

Transdermal patch: Patch may be cut to appropriate size. Apply patch to most painful area. Up to 3 patches may be applied in a single application. Patch may remain in place for up to 12 hours in any 24-hour period. Remove immediately if burning sensation occurs. Wash hands after application.

Ophthalmic: May cause burning when applied.

Pregnancy precaution: Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol, topical [foam]:

Anestafoam™: 4% (30 g) [contains benzalkonium chloride and benzyl alcohol]

Cream, rectal (L-M-X™ 5): 5% (15 g) [contains benzyl alcohol; packaged with applicator]; (30 g) [contains benzyl alcohol]

Cream, topical (L-M-X™ 4): 4% (5 g) [contains benzyl alcohol; packaged with Tegaderm™ dressing]; (15 g, 30 g) [contains benzyl alcohol]

Cream, topical, as hydrochloride: 3% (30 g)

LidaMantle®: 3% (30 g, 85 g)

Gel, ophthalmic:

Akten™: 3.5% (5 mL) [preservative free]

Gel, topical:

Burn-O-Jel: 0.5% (90 g)

Topicaine®: 4% (10 g, 30 g, 113 g) [contains alcohol 35%, benzyl alcohol, aloe vera, and jojoba]

Gel, topical, as hydrochloride:

Burn Jel®: 2% (3.5 g, 120 g)

Solarcaine® Aloe Extra Burn Relief: 0.5% (113 g, 226 g) [contains aloe vera gel and tartrazine]

Unburn®: 2.5% (3.5 g, 59 mL, 118 mL) [contains vitamin E]

Infusion, as hydrochloride [premixed in D_5W]: 0.4% [4 mg/mL] (250 mL, 500 mL); 0.8% [8 mg/mL] (250 mL, 500 mL)

Injection, solution, as hydrochloride: 0.5% [5 mg/mL] (50 mL); 1% [10 mg/mL] (2 mL, 10 mL, 20 mL, 30 mL, 50 mL); 2% [20 mg/mL] (2 mL, 5 mL, 20 mL, 50 mL)

Xylocaine®: 0.5% [5 mg/mL] (50 mL); 1% [10 mg/mL] (10 mL, 20 mL, 50 mL); 2% [20 mg/mL] (1.8 mL, 10 mL, 20 mL, 50 mL)

Injection, solution, as hydrochloride [preservative free]: 0.5% [5 mg/mL] (50 mL); 1% [10 mg/mL] (2 mL, 5 mL, 30 mL); 1.5% [15 mg/mL] (20 mL); 2% [20 mg/mL] (2 mL, 5 mL, 10 mL); 4% [40 mg/mL] (5 mL)

Xylocaine®: 10% [100 mg/mL] (5 mL) [for ventricular arrhythmias]

Xylocaine® MPF: 0.5% [5 mg/mL] (50 mL); 1% [10 mg/mL] (2 mL, 5 mL, 10 mL, 30 mL); 1.5% [15 mg/mL] (10 mL, 20 mL); 2% [20 mg/mL] (2 mL, 5 mL, 10 mL); 4% [40 mg/mL] (5 mL)

Injection, solution, as hydrochloride [premixed in $D_{7.5}W$, preservative free]: 5% (2 mL)

Xylocaine® MPF: 1.5% (2 mL) [DSC]

Jelly, topical, as hydrochloride: 2% (5 mL, 30 mL)

Anestacon®: 2% (15 mL) [contains benzalkonium chloride]

Xylocaine®: 2% (5 mL, 30 mL)

Liquid, topical (Zilactin®-L): 2.5% (7.5 mL)

Lotion, topical, as hydrochloride (LidaMantle®): 3% (177 mL)

Ointment, topical: 5% (37 g, 50 g)

Powder, intradermal, as hydrochloride:

Zingo™: 0.5 mg

Solution, topical, as hydrochloride: 4% [40 mg/mL] (50 mL)

Band-Aid® Hurt-Free™ Antiseptic Wash: 2% (180 mL)

LTA® 360: 4% [40 mg/mL] (4 mL) [packaged with cannula for laryngotracheal administration]

Xylocaine®: 4% [40 mg/mL] (50 mL)

Solution, viscous, as hydrochloride: 2% [20 mg/mL] (20 mL, 100 mL)

Xylocaine® Viscous: 2% [20 mg/mL] (100 mL, 450 mL)

Spray, topical:

Burnamycin: 0.5% (60 mL) [contains aloe vera gel and menthol]

Premjact®: 9.6% (13 mL)

Solarcaine® Aloe Extra Burn Relief: 0.5% (127 g) [contains aloe vera]

Transdermal system, topical (Lidoderm®): 5% (30s)

Generic AvailableYes: Cream, infusion, injection, jelly, lotion, ointment, solution

Pricing: U.S. (www.drugstore.com)

Cream (LidaMantle)

3% (85): $139.15

Cream (LMX 5)

5% (30): $59.99

Gel (Lidocaine HCl)

2% (10): $10.99

Kit (LMX 4 Plus)

4% (1): $47.59

Lotion (LidaMantle)

3% (177): $195.39

Ointment (Lidocaine)

5% (35.44): $15.99

Patch (Lidoderm)

5% (30): $206.47

Solution (Lidocaine HCl)

4% (50): $16.99

4% (100): $235.41

Solution (Lidocaine Viscous)

2% (100): $13.99

Solution (Xylocaine)

2% (50): $16.99

Mechanism of ActionClass Ib antiarrhythmic; suppresses automaticity of conduction tissue, by increasing electrical stimulation threshold of ventricle, His-Purkinje system, and spontaneous depolarization of the ventricles during diastole by a direct action on the tissues; blocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction

Pharmacodynamics/Kinetics

Onset of action: Single bolus dose: 45-90 seconds; Intradermal: 1-3 minutes; Ophthalmic: 20 seconds to 5 minutes (median: 40 seconds)

Duration: 10-20 minutes; Intradermal: Decreases after 10 minutes; Ophthalmic: 5-30 minutes (median: 15 minutes)

Absorption: Intradermal: Below limit of detection (<5 ng/mL)

Distribution: V_d: 1.1-2.1 L/kg; alterable by many patient factors; decreased in CHF and liver disease; crosses blood-brain barrier

Protein binding: 60% to 80% to alpha_1 acid glycoprotein

Metabolism: 90% hepatic; active metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX) can accumulate and may cause CNS toxicity

Half-life elimination: Biphasic: Prolonged with congestive heart failure, liver disease, shock, severe renal disease; Initial: 7-30 minutes; Terminal: Infants, premature: 3.2 hours, Adults: 1.5-2 hours

Excretion: Urine (<10% as unchanged drug, ~90% as metabolites)

Related Information

- Antiarrhythmic Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Metallic taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause agitation, anxiety, euphoria, or hallucinations

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsThe prophylactic use of lidocaine in patients after myocardial infarction confers no benefit and in fact may be harmful. Great care is needed in administration of lidocaine in the elderly and in patients with heart failure, shock, or hepatic disease, as toxic effects of lidocaine may become evident earlier in these patients. This is especially problematic since lidocaine-induced seizures may induce extension of underlying myocardial infarction. It is important to recognize that lidocaine has a narrow therapeutic index. Severe toxicity may occur at levels slightly above the therapeutic range, particularly when lidocaine is administered together with other antiarrhythmic drugs. While lidocaine toxicity may elicit seizures, lidocaine may also cause respiratory arrest and cardiac toxicity (AV block, asystole, and hypotension).

Anesthesia and Critical Care Concerns/Other Considerations

Cardiac Arrest: Amiodarone was recently compared to lidocaine (ALIVE trial) in out-of-hospital cardiac arrest victims whose ventricular fibrillation was resistant to 3 defibrillation attempts in addition to epinephrine and a fourth defibrillation attempt (Dorian, 2002). Other inclusion criteria included ventricular fibrillation unrelated to trauma (or with other arrhythmias that converted to ventricular fibrillation) and recurrent ventricular fibrillation after successful initial defibrillation. This was a randomized, double-blind comparison. The primary endpoint was the number of patients who were admitted to the hospital intensive care unit alive. Three hundred and forty-seven patients were enrolled. The initial amiodarone dose was 5 mg/kg and the lidocaine dose was 1.5 mg/kg. If ventricular fibrillation persisted after another shock, then the study drug could be administered again (amiodarone 2.5 mg/kg, lidocaine 1.5 mg/kg). Significantly more amiodarone patients (~23%) were admitted to the hospital alive than lidocaine patients (12%). The majority (>90%) of patients in the ALIVE trial had ventricular fibrillation as the initial arrhythmia. The authors concluded that intravenous amiodarone is superior to lidocaine in the treatment of shock-resistant, out-of-hospital ventricular fibrillation. Lidocaine is not as effective as amiodarone for improving intermediate outcomes, but neither has improved survival until hospital discharge among patients with VF cardiac arrest.

Monitoring: Great care is needed in administration of lidocaine in the elderly and in patients with heart failure, shock, or hepatic disease, as toxic effects of lidocaine may become evident earlier in these patients. The half-life of lidocaine increases after 24-48 hours as the drug inhibits its own hepatic metabolism. The dose should be reduced after 24 hours or blood levels should be monitored. While lidocaine toxicity may elicit seizures, lidocaine may also cause respiratory arrest and cardiac toxicity (eg, sinus arrest, AV block, asystole, and hypotension).

Local anesthetic toxicity: Cardiac arrest: Lipid infusion has been used in animal studies and several human cases (Bupivacaine: Rosenblatt, 2006; Levobupivacaine: Foxall, 2007; Ropivacaine: Litz, 2006) where cardiovascular toxicity, unresponsive to conventional resuscitation, resulted. Additional information is available at http://www.lipidrescue.org. The protocol from the website is: **20% Fat Emulsion:** 1.5 mL/kg administered over 1 minute, followed immediately by an infusion of 0.25 mL/kg/minute. Continue chest compressions (lipid must circulate). Repeat bolus every 3-5 minutes up to 3 mL/kg total dose until circulation restored. Continue infusion until hemodynamic stability is restored. Increase the infusion rate to 0.5 mL/kg/minute if BP declines. A maximum total dose of 8 mL/kg is recommended.

Index TermsLidocaine Hydrochloride; Lignocaine Hydrochloride

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International Brand Names Aeroderm (ES); Anelok (HR); Anestecidan (ES); Betacaine (IL, MX); Cidancaina (ES); Cuivasil Spray (IL); Curadent (ES); Dentinox (LU); Dimecaina (CN); Dube Spray (SG); Dynexan (FR); Esracain Jelly (IL); Farmacaina (CO); Gesicain Jelly (IN); Gesicain Ointment (IN); Gesicain Viscous (IN); Hipoden (MX); Lecasin (KP); Leostesin Jelly (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Leostesin Ointment (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Lidocain (HU, PL); Lidocain Braun (LU); Lidocain Gel (BG, DE, FI, HN); Lidocain Ointment (BG); Lidocain Spray (BG, HN); Lidocaina IV Braun (ES); Lidocainhydrochlorid-Braun (LU); Lidogel (PL); Lidokain (HR); Lidokaina (EE); Lidokain[inj.] (HR); Lidonest (ID); Lignocain (PL); Lignocaine Gel (AU); Lignocainum (PL); Lignocainum Hydrochloricum (PL); Lignox (PL); Ora (TW); Otoralgyl (LU); Penles (JP); Peterkaien (ZA); Plidocain (PL); Roxicaina (CO); Sedodent (HR); Sensipharma (MX); Solarcaine (HK); Sunicaine (MX); Uvega (MX); Versatis Plaster (GB, IE); Xilina (PL); Xilocaina Viscosa (PT); Xilonest Pomada (PE); Xilotane Gel (PT); Xilotane Oral (PT); Xylocain (CZ); Xylocain Aerosol (DK, SE); Xylocain Creme (DK, NO); Xylocain Gargle (FI, SE); Xylocain Gel (AT, CH, DE, DK, FI, NO, SE); Xylocain Liniment (DK); Xylocain Ointment (AT, CH, DE, FI, SE); Xylocain Salve (DK); Xylocain Spray (AT, CH, DE, NO); Xylocain Viscous (AT, CH); Xylocain Viskos (DE, SE); Xylocain Visks (FI); Xylocaina (MX); Xylocaina Ointment (IT); Xylocaina Pomada (AR, BR); Xylocaina Spray (IT); Xylocaine (LU, PL); Xylocaine Aerosol (AU, FR, HK, NL); Xylocaine Gel (AE, BE, BH, CY, EG, FR, GB, GR, IE, IL, IQ, IR, JO, KW, LB, LY, OM, PK, QA, SA, SY, YE); Xylocaine Heavy (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Xylocaine Jalea (UY); Xylocaine Jelly (BF, BJ, CI, ET, GH, GM, GN, HK, ID, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, NZ, PH, SC, SD, SL, SN, TN, TW, TZ, UG, ZA, ZM, ZW); Xylocaine Ointment (AE, AU, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, GR, IL, IN, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PH, QA, SA, SC, SD, SL, SN, SY, TH, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Xylocaine Pomada (VE); Xylocaine Solution (FR); Xylocaine Spray (BE, BF, BJ, CI, ET, FR, GH, GM, GN, GR, HK, ID, IL, KE, KP, LR, MA, ML, MR, MU, MW, MY, NE, NG, NL, PH, SC, SD, SL, SN, TH, TN, TW, TZ, UG, ZA, ZM, ZW); Xylocaine Topical Solution (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Xylocaine Viscosa (PY, VE); Xylocaine Viscous (GB, IE, IN, MY, TH, TW); Xylocaine Viscous Topical Solution (AU, GB); Xylocaine Viscus (GR); Xylocaine Viskeus Topical Solution (NL); Xylocaine Visquese (FR); Xylocaine Visqueuse (BE); Xylocaine-Astra (LU); Xylocard (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LU, LY, OM, QA, SA, SY, YE); Xyloctin (DE); Xylonibsa (ES); Xylonor (ES)

Lincomycin

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Lincocin® may be confused with Cleocin®, Indocin®, Minocin®

International issues:

Lincocin® may be confused with Lidosen® which is a brand name for lidocaine in Italy

Lincocin® may be confused with Limoxin® which is a brand name for amoxicillin in Mexico

Pronunciation(lin koe MYE sin)

U.S. Brand NamesLincocin®

Canadian Brand NamesLincocin®

Pharmacologic CategoryAntibiotic, Lincosamide

Use: Labeled IndicationsTreatment of serious susceptible bacterial infections, mainly those caused by streptococci, pneumococci, and staphylococci resistant to other agents

Dosing: Adults **Note:** Frequency may be increased if needed due to severity of infection

Susceptible infections:

I.M.: 600 mg every 12-24 hours

I.V.: 600 mg to 1 g every 8-12 hours; maximum dose: 8 g/day

Subconjunctival injection: 75 mg (ocular fluid levels with sufficient MICs last for at least 5 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Frequency may be increased if needed due to severity of infection

Susceptible infections in Children >1 month:

I.M.: 10 mg/kg every 12-24 hours

I.V.: 10-20 mg/kg/day in divided doses every 8-12 hours

Dosing: Renal ImpairmentSevere impairment: Decrease dose by 70% to 75%; not removed by peritoneal or hemodialysis.

Dosing: Hepatic ImpairmentUse caution in hepatic impairment. No specific guidelines available; consider dosage adjustment and/or monitor levels closely.

Administration: I.V.Administer over at least 1 hour per 100 mL; cardiopulmonary arrest and hypotension have been reported following too rapid I.V. infusion.

StoragePrior to dilution, store vials at controlled room temperature of 20°C to 25°C (68°F to 77°F). Once diluted, may store for 24 hours at room temperature.

ReconstitutionEach gram of lincomycin for I.V. administration should be diluted with at least 100 mL of solution. Dilute 600 mg in 100 mL of solution.

CompatibilityStable in dextran 6% in NS, D_5NS, $D_{10}NS$, D_5W, $D_{10}W$, NS.

Compatibility in syringe: Compatible: Cloxacillin, doxapram, heparin, penicillin G sodium. **Incompatible:** Ampicillin.

Compatibility when admixed: Compatible: Amikacin, ampicillin, chloramphenicol, cimetidine, cytarabine, heparin, polymyxin B sulfate, ranitidine, vitamin B complex, vitamin B complex with C. **Incompatible:** Kanamycin, phenytoin. **Variable (consult detailed reference):** Colistimethate, penicillin G potassium, penicillin G sodium.

ContraindicationsHypersensitivity to lincomycin, clindamycin, or any component of the formulation

Allergy Considerations

- Lincosamide Allergy

Warnings/Precautions

Boxed warnings:

• Colitis: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Colitis: **[U.S. Boxed Warning]: Can cause mild-to-severe (and possibly fatal) colitis.** Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment. Discontinue drug if significant diarrhea, abdominal cramps, or passage of blood and mucus occurs.

- Hypersensitivity reactions: Hypersensitivity reactions including anaphylaxis and rarely, erythema multiforme (resembling Stevens-Johnson syndrome) have been reported.

Disease-related concerns:

- Allergies: Use with caution in patients with significant allergies.

- Asthma: Use with caution in patients with asthma.

- Gastrointestinal disease: Use with caution in patients with a history of gastrointestinal disease (particularly colitis); discontinue if significant diarrhea occurs.

- Hepatic impairment: Use with caution in patients with hepatic impairment; half-life may be prolonged twofold.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment may be necessary with severe impairment.

Special populations:

- Elderly: Use with caution in the elderly; monitor closely for bowel changes.

Dosage form specific issues:

- Benzyl alcohol: Solution for injection contains benzyl alcohol which has been associated with "gasping syndrome" in neonates.

Other warnings/precautions:

- Appropriate use: Generally reserved for use when treatment with other antibiotics is inappropriate. Not appropriate for use in the treatment of meningitis due to inadequate penetration into the CSF.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
LactationEnters breast milk/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiopulmonary arrest and hypotension (related to rapid I.V. infusion; rare)

Central nervous system: Vertigo

Dermatologic: Dermatitis (includes exfoliative and vesiculobullous; rare), erythema multiforme (rare; some resembling SJS), rash, urticaria

Gastrointestinal: Colitis, diarrhea, glossitis, nausea, pruritus ani, stomatitis, vomiting

Genitourinary: Vaginitis

Hematologic: Agranulocytosis, aplastic anemia (rare), leukopenia, neutropenia, pancytopenia (rare), thrombocytopenic purpura

Hepatic: Jaundice, liver function test abnormal

Otic: Tinnitus

Renal: Azotemia (rare), proteinuria (rare), oliguria (rare)

Miscellaneous: Hypersensitivity reactions (anaphylaxis, angioneurotic edema, serum sickness)

Drug Interactions

Erythromycin: Lincosamide Antibiotics may diminish the therapeutic effect of Erythromycin. *Risk X: Avoid combination*

Kaolin: May decrease the absorption of Lincosamide Antibiotics. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Lincosamide Antibiotics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Monitoring ParametersChange in bowel frequency; periodic liver and kidney function tests and complete blood counts during prolonged therapy
Monitoring: Lab TestsPeriodic liver and kidney function tests and complete blood counts during prolonged therapy
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride: 300 mg/mL (2 mL, 10 mL) [contains benzyl alcohol]

Generic AvailableNo
Mechanism of ActionLincosamide antibiotic which was isolated from a strain of *Streptomyces lincolnensis*; lincomycin, like clindamycin, inhibits bacterial protein synthesis by specifically binding on the 50S subunit and affecting the process of peptide chain initiation. Other

macrolide antibiotics (erythromycin) also bind to the 50S subunit. Since only one molecule of antibiotic can bind to a single ribosome, the concomitant use of erythromycin and lincomycin is not recommended.

Pharmacodynamics/Kinetics

Metabolism: Hepatic

Half-life elimination, serum: ~5 hours; prolonged with renal or hepatic impairment

Time to peak, serum: I.M.: 1 hour

Excretion: Urine (2% to 30%); bile

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Glossitis and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause granulocytopenia; use caution with clozapine and carbamazepine

Index TermsLincomycin Hydrochloride

International Brand NamesAlbiotic (DE); Biolincom (ID); Cillimicina (IT); Cillimycin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE); Clordelin (EC); Frademicina (AR, BR); Libiocid (MX); Licoxin (TW); Linco ANB (TH); Lincocin (AE, AU, BE, BF, BG, BH, BJ, CH, CI, CN, CO, CR, CY, CZ, EC, EG, ES, ET, GH, GM, GN, GT, HK, HN, HR, ID, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NI, NL, OM, PA, PE, PH, PK, PL, QA, SA, SC, SD, SL, SN, SV, SY, TH, TN, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Lincocina (PT); Lincocine (FR); Lincomed (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Lincomycin (PL); Lincono (TH); Lincophar (ID); Lincoplus (PE); Lincosa (MY); Lincosan (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Linkam (IN); Linmycin (TH); Lintropsin (ID); Medoglycin (HK); Neloren (HR, PL); Nichomycin (ID); Nolipo (ID); Princol (MX); Pritaline (ID); Tamcocin (ID); Zumalin (ID)

Lindane

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(LIN dane)

Canadian Brand NamesHexit™; PMS-Lindane

Pharmacologic CategoryAntiparasitic Agent, Topical; Pediculocide; Scabicidal Agent

Use: Labeled IndicationsTreatment of *Sarcoptes scabiei* (scabies), *Pediculus capitis* (head lice), and *Phthirus pubis* (crab lice); FDA recommends reserving lindane as a second-line agent or with inadequate response to other therapies

Dosing: Adults

Scabies: Topical: Apply a thin layer of lotion and massage it on skin from the neck to the toes; after 8-12 hours, bathe and remove the drug

Head lice, crab lice: Topical: Apply shampoo to dry hair and massage into hair for 4 minutes; add small quantities of water to hair until lather forms, then rinse hair thoroughly and comb with a fine tooth comb to remove nits. Amount of shampoo needed is based on length and density of hair; most patients will require 30 mL (maximum: 60 mL).

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: OralNever administer orally.

Administration: TopicalFor topical use only. Caregivers should apply with gloves (avoid natural latex, may be permeable to lindane). Rinse off with warm (not hot) water.

Lotion: Apply to dry, cool skin; do not apply to face or eyes. Wait at least 1 hour after bathing or showering (wet or warm skin increases absorption). Skin should be clean and free of any other lotions, creams, or oil prior to lindane application.

Shampoo: Apply to clean, dry hair. Wait at least 1 hour after washing hair before applying lindane shampoo. Hair should be washed with a shampoo not containing a conditioner; hair and skin of head and neck should be free of any lotions, oils, or creams prior to lindane application.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to lindane or any component of the formulation; uncontrolled seizure disorders; crusted (Norwegian) scabies, acutely-inflamed skin or raw, weeping surfaces or other skin conditions which may increase systemic absorption

Allergy Considerations

- Lindane Allergy

Warnings/Precautions

Boxed warnings:

- Appropriate use: See “Other warnings/precautions” below.
- Medication guide: See “Other warnings/precautions” below.
- Neurologic toxicities: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Neurologic toxicities: **[U.S. Boxed Warning]: May be associated with severe neurologic toxicities (contraindicated in premature infants and uncontrolled seizure disorders).** Seizures and death have been reported with use; use with caution in infants, small children, patients <50 kg, or patients with a history of seizures; use caution with conditions which may increase risk of seizures or medications which decrease seizure threshold.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

Other warnings/precautions:

- Appropriate use: **[U.S. Boxed Warning]: Not considered a drug of first choice; use only in patients who have failed first-line treatments, or in patients who cannot tolerate these agents.** Because of the potential for systemic absorption and CNS side effects, lindane should be used with caution; consider permethrin or crotamiton agent first. Oil-based hair dressing may increase toxic potential. For external use only; avoid contact with face, eyes, mucous membranes, and urethral meatus.
- Medication guide: **[U.S. Boxed Warning]: A lindane medication use guide must be given to all patients along with instructions for proper use.** Patients should be informed that itching may occur following successful killing of lice and re-treatment may not be indicated. Should

be used as a part of an overall lice management program.

Geriatric ConsiderationsBecause of the potential for systemic absorption and CNS side effects, lindane should be used with caution. Not considered a drug of first choice; consider permethrin or crotamiton agent first.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no well-controlled studies in pregnant women.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsNursing mothers should interrupt breast-feeding, express and discard milk for at least 24 hours following use.

Adverse ReactionsFrequency not defined (includes postmarketing and/or case reports).

Cardiovascular: Cardiac arrhythmia

Central nervous system: Ataxia, dizziness, headache, restlessness, seizure, pain

Dermatologic: Alopecia, contact dermatitis, skin and adipose tissue may act as repositories, eczematous eruptions, pruritus, urticaria

Gastrointestinal: Nausea, vomiting

Hematologic: Aplastic anemia

Hepatic: Hepatitis

Local: Burning and stinging

Neuromuscular & skeletal: Paresthesia

Renal: Hematuria

Respiratory: Pulmonary edema

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringAssess head, hair, and skin surfaces for presence of lice and nits. Assess knowledge/teach patient appropriate application, use, and adverse symptoms to report.

Patient EducationFor external use only. Do not apply to face and avoid getting in eyes. Do not apply immediately after hot, soapy bath. For scabies, Apply from neck to toes. Bathe to remove drug after 8-12 hours. For head lice or crab lice, massage into dry hair for 4 minutes; add water to hair to form lather, then rinse thoroughly. Clothing and bedding must be washed in hot water or dry cleaned to kill nits. Wash combs and brushes with lindane shampoo and thoroughly rinse. May need to treat all members of household and all sexual contacts concurrently. Report if condition persists or infection occurs. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Lotion, topical: 1% (60 mL)

Shampoo, topical: 1% (60 mL) [contains alcohol 0.5%]

Generic AvailableYes

Mechanism of ActionDirectly absorbed by parasites and ova through the exoskeleton; stimulates the nervous system resulting in seizures and death of parasitic arthropods

Pharmacodynamics/Kinetics

Absorption: ≤13% systemically

Distribution: Stored in body fat; accumulates in brain; skin and adipose tissue may act as repositories

Metabolism: Hepatic

Half-life elimination: Children: 17-22 hours

Time to peak, serum: Children: 6 hours

Excretion: Urine and feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or restlessness

Mental Health: Effects on Psychiatric TreatmentMay cause aplastic anemia; use caution with clozapine and carbamazepine

Index TermsBenzene Hexachloride; Gamma Benzene Hexachloride; Hexachlorocyclohexane

References

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Solomon BA, Haut SR, Carr EM, et al, “Neurotoxic Reaction to Lindane in an HIV-Sero Positive Patient, An Old Medication's New Problem,” *J Fam Pract*, 1995, 40(3):291-5-6.[PubMed 7533205]

International Brand NamesAgalin (PL); Aphtiria (FR); Aprurol (UY); Bicide (IL); Davesol (EC); Delice (TW); Delitex (DE); Demar (VE); Desintan (FI, GB); Elentol (FR); Gama Acaderm (CN); Gamaderm (IN); Gambex (ZA); Gatox (HR); Herklin (MX); Hexa-Defital (AR); Jacutin (CH, CZ, DE, HN, LU, PL); Kwellada (GR); Lencid (BE, LU); Lendianon (BR); Lindano (AR); Lindano-GBHG (PY); Linden Lotion (KP); Milinor (HR); Nedax (BR); Paracid (BE); Pruritrat (BR); Quellada (BE, IE, LU); Quellada Cream (AU); Quellada Creme Rinse (AU); Quellada Head Lice Treatment (AU); Quellada Lotion (AU, NZ); Sarcoderma (PT); Scabecid (FR); Scabene (PK); Scabi (TW); Scabix (BR); Skabicid (CZ); Texa (BE)

Linezolid

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Medication Safety Issues

Sound-alike/look-alike issues:

Zyvox® may be confused with Ziox™, Zosyn®, Zovirax®

Pronunciation(li NE zoh lid)
U.S. Brand NamesZyvox®
Canadian Brand NamesZyvoxam®
Pharmacologic CategoryAntibiotic, Oxazolidinone
Use: Labeled IndicationsTreatment of vancomycin-resistant *Enterococcus faecium* (VRE) infections, nosocomial pneumonia caused by *Staphylococcus aureus* including MRSA or *Streptococcus pneumoniae* (including multidrug-resistant strains [MDRSP]), complicated and uncomplicated skin and skin structure infections (including diabetic foot infections without concomitant osteomyelitis), and community-acquired pneumonia caused by susceptible gram-positive organisms
Dosing: Adults

VRE infections including concurrent bacteremia: Oral, I.V.: 600 mg every 12 hours for 14-28 days

MRSA: Oral, I.V: 600 mg every 12 hours

Nosocomial pneumonia, complicated skin and skin structure infections, community-acquired pneumonia including concurrent bacteremia: Oral, I.V.: 600 mg every 12 hours for 10-14 days

Uncomplicated skin and skin structure infections: Oral: 400 mg every 12 hours for 10-14 days

Note: 400 mg dose is recommended in the product labeling; however, 600 mg dose is commonly employed clinically

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

VRE infections including concurrent bacteremia: Oral, I.V.:

Preterm neonates (<34 weeks gestational age): 10 mg/kg every 12 hours; neonates with a suboptimal clinical response can be advanced to 10 mg/kg every 8 hours. By day 7 of life, all neonates should receive 10 mg/kg every 8 hours.

Infants (excluding preterm neonates <1 week) and Children ≤11 years: 10 mg/kg every 8 hours for 14-28 days

Children ≥12 years: Refer to adult dosing.

Nosocomial pneumonia, complicated skin and skin structure infections, community acquired pneumonia including concurrent bacteremia: Oral, I.V.:

Preterm neonates (<34 weeks gestational age): 10 mg/kg every 12 hours; neonates with a suboptimal clinical response can be advanced to 10 mg/kg every 8 hours. By day 7 of life, all neonates should receive 10 mg/kg every 8 hours.

Infants (excluding preterm neonates <1 week) and Children ≤11 years: 10 mg/kg every 8 hours for 10-14 days

Children ≥12 years: Refer to adult dosing.

Uncomplicated skin and skin structure infections: Oral:

Preterm neonates (<34 weeks gestational age): 10 mg/kg every 12 hours; neonates with a suboptimal clinical response can be advanced to 10 mg/kg every 8 hours. By day 7 of life, all neonates should receive 10 mg/kg every 8 hours.

Infants (excluding preterm neonates <1 week) and Children <5 years: 10 mg/kg every 8 hours for 10-14 days

Children 5-11 years: 10 mg/kg every 12 hours for 10-14 days

Children ≥12-18 years: 600 mg every 12 hours for 10-14 days

Dosing: Renal ImpairmentNo adjustment is recommended. The two primary metabolites may accumulate in patients with renal impairment but the clinical significance is unknown. Weigh the risk of accumulation of metabolites versus the benefit of therapy. Monitor for hematopoietic (eg, anemia, leukopenia, thrombocytopenia) and neuropathic (eg, peripheral neuropathy) adverse events when administering for extended periods. Both linezolid and the two metabolites are eliminated by dialysis. Linezolid should be given after hemodialysis.

Continuous renal replacement therapy (CRRT): No adjustment needed.

Dosing: Hepatic ImpairmentNo dosage adjustment required for mild to moderate hepatic insufficiency (Child-Pugh class A or B). Use in severe hepatic insufficiency has not been adequately evaluated.

Administration: I.V.Administer intravenous infusion over 30-120 minutes. Do not mix or infuse with other medications. When the same intravenous line is used for sequential infusion of other medications, flush line with D_5W, NS, or LR before and after infusing linezolid. The yellow color of the injection may intensify over time without affecting potency.

Administration: OralOral suspension: Invert gently to mix prior to administration, do not shake

Dietary ConsiderationsTake with or without food. Avoid consuming large amounts of tyramine-containing foods/beverages. Some examples include aged or matured cheese, air-dried or cured meats (including sausages and salamis), fava or broad bean pods, tap/draft beers, Marmite concentrate, sauerkraut, soy sauce and other soybean condiments.

Suspension contains 20 mg phenylalanine per teaspoonful. Sodium content: 0.1 mEq/tablet; 0.4 mEq/5 mL; 1.7 mEq/100 mL infusion; 3.3 mEq/200 mL infusion; 5 mEq/300 mL infusion

Storage

Infusion: Store at 25°C (77°F). Protect from light. Keep infusion bags in overwrap until ready for use. Protect infusion bags from freezing.

Oral suspension: Following reconstitution, store at 25°C (77°F). Use reconstituted suspension within 21 days. Protect from light.

Tablet: Store at 25°C (77°F). Protect from light; protect from moisture.

ReconstitutionOral suspension: Reconstitute with 123 mL of distilled water (in 2 portions); shake vigorously. Concentration is 100 mg/5 mL. Prior to administration mix gently by inverting bottle; do not shake.

CompatibilityStable in D_5W, LR, NS

Y-site administration: Compatible: Acyclovir, alfentanil, amikacin, aminophylline, ampicillin, ampicillin sulbactam, aztreonam, bretylium, buprenorphine, butorphanol, calcium gluconate, carboplatin, cefazolin, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cimetidine, ciprofloxacin, cisatracurium, cisplatin, clindamycin, cyclophosphamide, cyclosporine, cytarabine, dexamethasone, dexmedetomidine, D51/2 NS, D5NS, digoxin, diphenhydramine, dobutamine, dopamine, doxorubicin, doxycycline, droperidol, enalaprilat, Esmolol, etoposide phosphate, famotidine, fenoldopam, fentanyl, fluconazole, fluorouracil, furosemide, ganciclovir, gemcitabine, gentamicin, granisetron, haloperidol, heparin, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, ifosfamide, imipenem, labetalol, leucovorin, levofloxacin, lidocaine, lorazepam, magnesium sulfate, mannitol, ,meperidine, meropenem, mesna, methotrexate, methylprednisolone sodium succinate, metoclopramide, metronidazole, midazolam, mitoxantrone, morphine, nalbuphine, naloxone, nicardipine, nitroglycerin, ofloxacin, ondansetron, paclitaxel, pentobarbital, phenobarbital, piperacillin (tazobactam), potassium chloride, prochlorperazine, promethazine, propranolol, ranitidine remifentanil, sodium bicarbonate, sufentanil, theophylline, tobramycin, vancomycin, vecuronium, verapamil, vincristine, zidovudine. **Incompatible:** Amphotericin B, chlorpromazine, diazepam, erythromycin, pentamidine, phenytoin, sulfamethoxazole/trimethoprim.

Compatibility when admixed: Compatible: Aztreonam, cefazolin, ceftazidime, ciprofloxacin, gentamicin, levofloxacin, ofloxacin, tobramycin. **Incompatible:** Ceftriaxone, erythromycin, sulfamethoxazole/trimethoprim.

ContraindicationsHypersensitivity to linezolid or any other component of the formulation; concurrent use or within 2 weeks of MAO inhibitors; patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis, and/or taking sympathomimetics (eg, pseudoephedrine), vasopressive agents (eg, epinephrine, norepinephrine), or dopaminergic agents (eg, dopamine, dobutamine) unless closely monitored for increased blood pressure; patients with carcinoid syndrome and/or taking SSRIs, tricyclic antidepressants, serotonin 5-$HT_{1B,1D}$ receptor agonists, meperidine, or buspirone unless closely monitored for sign/symptoms of serotonin syndrome

Allergy Considerations

- Linezolid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Lactic acidosis: Has been reported with use. Patients who develop recurrent nausea and vomiting, unexplained acidosis, or low bicarbonate levels need immediate evaluation.
- Myelosuppression: Has been reported and may be dependent on duration of therapy (generally >2 weeks of treatment); use with caution in patients with pre-existing myelosuppression, in patients receiving other drugs which may cause bone marrow suppression, or in chronic infection (previous or concurrent antibiotic therapy). Weekly CBC monitoring is recommended; discontinue therapy in patients developing myelosuppression (or in whom myelosuppression worsens during treatment).
- Peripheral and optic neuropathy (with vision loss): Has been reported and may occur primarily with extended courses of therapy >28 days; any symptoms of visual change or impairment warrant immediate ophthalmic evaluation and possible discontinuation of therapy.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Carcinoid syndrome: Use with caution and closely monitor for serotonin syndrome in patients with carcinoid syndrome; linezolid has not been studied in patients with this condition. Use is contraindicated in the absence of close monitoring.
- Hypertension: Use with caution and closely monitor blood pressure in patients with uncontrolled hypertension; linezolid has not been studied in patients with this condition. Use is contraindicated in the absence of close monitoring.
- Hyperthyroidism: Use with caution and closely monitor blood pressure in patients with untreated hyperthyroidism; linezolid has not been studied in patients with this condition. Use is contraindicated in the absence of close monitoring.
- Pheochromocytoma: Use with caution and closely monitor blood pressure in patients with pheochromocytoma; linezolid has not been

studied in patients with this condition. Use is contraindicated in the absence of close monitoring.

- Seizure disorder: Seizures have been reported; use with caution in patients with a history of seizures.

Concurrent drug therapy issues:

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (eg, SSRIs/SNRIs or triptans) or agents which reduce linezolid's metabolism; concurrent use with these medications is contraindicated unless patient is closely monitored for signs/symptoms of serotonin syndrome.

Special populations:

- Pediatrics: The manufacturer states that empiric use in pediatric patients with CNS infections is not recommended due to inconsistent concentrations in the CSF; however, there are multiple case reports describing successful treatment of documented VRE and *Staphylococcus aureus* CNS and shunt infections in the literature.

Dosage form specific issues:

- Phenylalanine: Oral suspension contains phenylalanine.

Other warnings/precautions:

- Appropriate use: Unnecessary use may lead to the development of resistance to linezolid; consider alternatives before initiating outpatient treatment.

- MAO inhibitor properties: Exhibits mild MAO inhibitor properties and has the potential to have the same interactions as other MAO inhibitors.

Geriatric ConsiderationsAccording to the manufacturer the pharmacokinetics of linezolid are not significantly altered in persons ≥65 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsBecause adverse effects were observed in some animal studies, linezolid is classified pregnancy category C. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if linezolid is excreted in human milk. Linezolid has low protein binding and is 100% bioavailable orally which may increase the exposure to a nursing infant. The manufacturer advises caution if administering linezolid to a breast-feeding woman. Linezolid is used therapeutically in infants. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Linezolid in Pregnancy & Lactation

Adverse ReactionsPercentages as reported in adults; frequency similar in pediatric patients

>10%:

Central nervous system: Headache (<1% to 11%)

Gastrointestinal: Diarrhea (3% to 11%)

1% to 10%:

Central nervous system: Insomnia (3%), dizziness (≤2%), fever (2%)

Dermatologic: Rash (2%)

Gastrointestinal: Nausea (3% to 10%), vomiting (1% to 4%), pancreatic enzymes increased (≤4%), constipation (2%), taste alteration (1% to 2%), tongue discoloration (≤1%), oral moniliasis (≤1%), pancreatitis

Genitourinary: Vaginal moniliasis (1% to 2%)

Hematologic: Hemoglobin decreased (1% to 7%), thrombocytopenia (≤3%), anemia, leukopenia, neutropenia; **Note:** Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia; may be more common in patients receiving linezolid for >2 weeks)

Hepatic: Abnormal LFTs (≤10%), bilirubin increased (≤1%)

Renal: BUN increased (≤2%)

Miscellaneous: Fungal infection (0.1% to 2%), lactate dehydrogenase increased (<1% to 2%)

<1% or frequency not defined: Blurred vision, *C. difficile*-related complications, creatinine increased, dyspepsia, hypertension, localized abdominal pain, pruritus

Postmarketing and/or case reports: Anaphylaxis, angioedema, bullous skin disorders, lactic acidosis, peripheral neuropathy, optic neuropathy, seizures, serotonin syndrome (with concurrent use of other serotonergic agents), Stevens-Johnson syndrome, vision loss

Drug Interactions

Alpha-/Beta-Agonists (Direct-Acting): MAO Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists (Indirect-Acting): MAO Inhibitors may enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X:*

Avoid combination

Alpha1-Agonists: MAO Inhibitors may enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Alpha2-Agonists (Ophthalmic): MAO Inhibitors may enhance the hypertensive effect of Alpha2-Agonists (Ophthalmic). *Risk X: Avoid combination*

Altretamine: May enhance the orthostatic effect of MAO Inhibitors. *Risk C: Monitor therapy*

Amphetamines: MAO Inhibitors may enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Anilidopiperidine Opioids: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. *Risk D: Consider therapy modification*

Atomoxetine: MAO Inhibitors may enhance the neurotoxic (central) effect of Atomoxetine. *Risk X: Avoid combination*

Beta2-Agonists: MAO Inhibitors may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: MAO Inhibitors may enhance the neurotoxic (central) effect of BuPROPion. *Risk X: Avoid combination*

BusPIRone: May enhance the adverse/toxic effect of MAO Inhibitors. Elevated blood pressure has been reported. *Risk X: Avoid combination*

COMT Inhibitors: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Cyclobenzaprine: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

Dexmethylphenidate: MAO Inhibitors may enhance the hypertensive effect of Dexmethylphenidate. *Risk X: Avoid combination*

Dextromethorphan: MAO Inhibitors may enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

Levodopa: May enhance the adverse/toxic effect of MAO Inhibitors. Of particular concern is the development of hypertensive reactions when levodopa is used with nonselective MAOI. *Risk D: Consider therapy modification*

Lithium: MAO Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the adverse/toxic effect of Linezolid. *Risk X: Avoid combination*

Maprotiline: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

Meperidine: MAO Inhibitors may enhance the serotonergic effect of Meperidine. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methyldopa: MAO Inhibitors may enhance the adverse/toxic effect of Methyldopa. *Risk X: Avoid combination*

Methylphenidate: MAO Inhibitors may enhance the hypertensive effect of Methylphenidate. *Risk X: Avoid combination*

Mirtazapine: MAO Inhibitors may enhance the neurotoxic (central) effect of Mirtazapine. *Risk X: Avoid combination*

Propoxyphene: May enhance the adverse/toxic effect of MAO Inhibitors. Specifically, the risk of serotonin syndrome or other serotonergic adverse events may be increased. *Risk X: Avoid combination*

Rauwolfia Alkaloids: MAO Inhibitors may enhance the adverse/toxic effect of Rauwolfia Alkaloids. Existing MAOI therapy can result in paradoxical effects of added rauwolfia alkaloids (eg, excitation, hypertension). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: MAO Inhibitors may decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. **Exceptions:** Eletriptan; Frovatriptan; Naratriptan. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tetrabenazine: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

TraMADol: May enhance the neuroexcitatory and/or seizure-potentiating effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: MAO Inhibitors may enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (based on CNS depressant effects and potential tyramine content)

Food: Concurrent ingestion of foods rich in tyramine may cause sudden and severe high blood pressure (hypertensive crisis). Avoid tyramine-containing foods with MAO-Is. Food's freshness is also an important concern; improperly stored or spoiled food can create an environment where tyramine concentrations may increase.

Herb/Nutraceutical: Avoid supplements containing caffeine, tyrosine, tryptophan or phenylalanine. Ingestion of large quantities may increase the risk of severe side effects (eg, hypertensive reactions, serotonin syndrome).

Monitoring ParametersWeekly CBC and platelet counts, particularly in patients at increased risk of bleeding, with pre-existing myelosuppression, on concomitant medications that cause bone marrow suppression, in those who require >2 weeks of therapy, or in those with chronic infection who have received previous or concomitant antibiotic therapy; visual function with extended therapy (≥3 months) or in patients with new onset visual symptoms, regardless of therapy length

Nursing: Physical Assessment/MonitoringAssess for previous drug allergies before administering first dose. Assess other pharmacological agents patient may be taking for effectiveness and interactions (eg, serotonergic agents may increase resistance to linezolid and increase risk of serotonin syndrome, hypertension with adrenergic agents, or myelosuppression with other drugs that may cause bone marrow suppression). Assess results of laboratory tests (weekly CBC and platelet count), therapeutic effectiveness (resolution of infection), and adverse reactions (eg, myelosuppression [anemia, leukopenia, pancytopenia, and thrombocytopenia; may be more common in patients receiving linezolid for >2 weeks], lactic acidosis; peripheral or optic neuropathy) on a regular basis. Teach patient proper use (oral), possible side effects/appropriate interventions (eg, tyramine-free diet; see Tyramine Contents of Foods list), and adverse symptoms to report.

Monitoring: Lab TestsWeekly CBC and platelet counts, particularly in patients at increased risk of bleeding, with pre-existing myelosuppression, on concomitant medications that cause bone marrow suppression, in those who require >2 weeks of therapy, or in those with chronic infection who have received previous or concomitant antibiotic therapy.

Patient EducationOral: Take exactly as directed. Suspension; store at room temperature and use within 21 days. Do not alter dosage without consulting prescriber. Complete full course of therapy even if condition appears controlled. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid alcohol. Avoid tyramine-containing foods (eg, pickles, aged cheese, wine).

Oral/I.V.: You may experience mild headache (analgesic may help); GI discomfort, nausea, vomiting, taste alteration (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or constipation (increase exercise, fluids, fruit, or fiber may help). Report immediately unresolved, white plaques in mouth; skin rash or irritation; acute headache, dizziness, blurred vision, or changes in visual acuity; tingling or numbness in extremities; persistent diarrhea; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed]:

Zyvox®: 200 mg (100 mL) [contains sodium 1.7 mEq]; 600 mg (300 mL) [contains sodium 5 mEq]

Powder for oral suspension:

Zyvox®: 20 mg/mL (150 mL) [contains phenylalanine 20 mg/5 mL, sodium benzoate, and sodium 0.4 mEq/5 mL; orange flavor]

Tablet:

Zyvox®: 600 mg [contains sodium 0.1 mEq/tablet]

Generic AvailableNo

ManufacturerPharmacia

Pricing: U.S. (www.drugstore.com)

Tablets (Zyvox)

600 mg (20): $1642.39

Mechanism of ActionInhibits bacterial protein synthesis by binding to bacterial 23S ribosomal RNA of the 50S subunit. This prevents the formation of a functional 70S initiation complex that is essential for the bacterial translation process. Linezolid is bacteriostatic against enterococci and staphylococci and bactericidal against most strains of streptococci.

Pharmacodynamics/Kinetics

Absorption: Rapid and extensive

Distribution: V_{dss}: Adults: 40-50 L

Protein binding: Adults: 31%

Metabolism: Hepatic via oxidation of the morpholine ring, resulting in two inactive metabolites (aminoethoxyacetic acid, hydroxyethyl glycine); does not involve CYP

Bioavailability: Oral: ~100%

Half-life elimination: Children ≥1 week (full-term) to 11 years: 1.5-3 hours; Adults: 4-5 hours

Time to peak: Adults: Oral: 1-2 hours

Excretion: Urine (30% as parent drug, 50% as metabolites); feces (9% as metabolites)

Nonrenal clearance: ~65%; increased in children ≥1 week to 11 years

Related Information

- Tyramine Content of Foods

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral moniliasis, taste alteration, and tongue discoloration.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsLinezolid has mild monoamine oxidase inhibitor properties. The clinician is reminded that vasoconstrictors have the potential to interact with MAO-Is to result in elevation of blood pressure. Caution is suggested.

Mental Health: Effects on Mental StatusMay cause insomnia and dizziness

Mental Health: Effects on Psychiatric TreatmentHas mild MAO inhibitor properties and has the potential to have the same interactions as other MAO inhibitors; thrombocytopenia has been reported and may be dependent on duration of therapy (generally >2 weeks of treatment), caution with valproic acid; avoid use with serotonergic agents such as TCAs, venlafaxine, trazodone, sibutramine, meperidine, dextromethorphan, and SSRIs; may cause leukopenia, use caution with clozapine and carbamazepine

Cardiovascular ConsiderationsLinezolid has mild MAO inhibitor properties and should be used with caution in patients with cardiovascular disease, particularly those with hypertension. Avoid use with sympathomimetic and dopaminergic agents. Linezolid can cause thrombocytopenia. Use cautiously in patients with thrombocytopenia, or in patients being started on medications that can cause thrombocytopenia (eg, heparin).

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Linezolid has mild MAO inhibitor properties and should be used with caution in patients with cardiovascular disease, particularly those with hypertension. Avoid use with sympathomimetic and dopaminergic agents (serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT_1 receptor agonists, meperidine, or buspirone).

Linezolid has time-dependent kill characteristics; time for which the serum concentration remains above the MIC for a dosing period is the best predictor of efficacy. With prolonged exposure (>2 weeks), monitor closely for anemia, leukopenia, and thrombocytopenia.

Evidence-Based Information:

Trial Showing Increased Rate of Death in Catheter-Related Bloodstream Infections - March, 2007: The U.S. Food and Drug Administration (FDA) has issued an alert to healthcare professionals regarding an increased rate of death among patients treated with linezolid (Zyvox®) for catheter-related bacteremia and catheter-site infections. Healthcare professionals are reminded that linezolid is not approved for the treatment of catheter-related bloodstream, catheter-site, or gram-negative infections. Additional information is available at http://www.fda.gov/medwatch/safety/2007/safety07.htm#zyvox

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International Brand NamesLinox (IN); Zyvox (AE, AR, AU, BH, BR, CL, CN, CR, CY, EC, EG, GB, GT, HK, ID, IE, IL, IQ, IR, JO, KP, KW, LB, LY, MY, NI, OM, PA, PE, PH, QA, SA, SG, SV, SY, TH, UY, VE, YE); Zyvoxam (MX); Zyvoxid (BE, CH, CO, CZ, DE, DK, EE, FI, FR, HN, IL, IT, NL, NO, PL, SE, ZA)

Linker Protocol

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Leukemia, Acute Lymphocytic]

Regimen UseLeukemia, acute lymphocytic

Regimen

Remission induction:

Daunorubicin: I.V.: 50 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 150 mg/m^2]

Vincristine: I.V.: 2 mg/day days 1, 8, 15, and 22

[total dose/cycle = 8 mg]

Prednisone: Oral: 60 mg/m^2/day days 1 to 28

[total dose/cycle = 1680 mg/m^2]

Asparaginase: I.M.: 6000 units/m^2/day days 17 to 28

[total dose/cycle = 72,000 units/m^2]

If residual leukemia in bone marrow on day 14:

Daunorubicin: I.V.: 50 mg/m^2 day 15

[total dose/cycle = 50 mg/m^2]

If residual leukemia in bone marrow on day 28:

Daunorubicin: I.V.: 50 mg/m^2/day days 29 and 30

[total dose/cycle = 100 mg/m^2]

Vincristine: I.V.: 2 mg/day days 29 and 36

[total dose/cycle = 4 mg]

Prednisone: Oral: 60 mg/m^2/day days 29 to 42

[total dose/cycle = 840 mg/m^2]

Asparaginase: I.M.: 6000 units/m^2/day days 29 to 35

[total dose/cycle = 42,000 units/m^2]

Consolidation therapy:

Treatment A (cycles 1, 3, 5, and 7)

Daunorubicin: I.V.: 50 mg/m^2/day days 1 and 2

[total dose/cycle = 100 mg/m^2]

Vincristine: I.V.: 2 mg/day days 1 and 8

[total dose/cycle = 4 mg]

Prednisone: Oral: 60 mg/m^2/day days 1 to 14

[total dose/cycle = 840 mg/m^2]

Asparaginase: I.M.: 12,000 units/m^2/day days 2, 4, 7, 9, 11, and 14

[total dose/cycle = 72,000 units/m^2]

Treatment B (cycles 2, 4, 6, and 8)

Teniposide: I.V.: 165 mg/m^2/day days 1, 4, 8, and 11

[total dose/cycle = 660 mg/m^2]

Cytarabine: I.V.: 300 mg/m^2/day days 1, 4, 8, and 11

[total dose/cycle = 1200 mg/m^2]

Treatment C (cycle 9)

Methotrexate: I.V.: 690 mg/m^2 continuous infusion day 1 (over 42 hours)

[total dose/cycle = 690 mg/m^2]

Leucovorin: I.V.: 15 mg/m^2 every 6 hours for 12 doses (start at end of methotrexate infusion)

[total dose/cycle = 180 mg/m^2]

Administer remission induction regimen for one cycle only. Repeat consolidation cycle every 28 days.

References

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Liothyronine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Liothyronine may be confused with levothyroxine

T3 is an error-prone abbreviation (mistaken as acetaminophen and codeine [ie, Tylenol® #3])

Pronunciation(lye oh THYE roe neen)

U.S. Brand NamesCytomel®; Triostat®

Canadian Brand NamesCytomel®

Pharmacologic CategoryThyroid Product

Use: Labeled Indications

Oral: Replacement or supplemental therapy in hypothyroidism; management of nontoxic goiter; a diagnostic aid

I.V.: Treatment of myxedema coma/precoma

Dosing: Adults

Hypothyroidism: Oral: 25 mcg/day increase by 12.5-25 mcg/day every 1-2 weeks to a maximum of 100 mcg/day; usual maintenance dose: 25-75 mcg/day

Patients with cardiovascular disease: Refer to elderly dosing.

Suppression test: (T_3): Oral: 75-100 mcg/day for 7 days; use lowest dose for elderly

Myxedema: Oral: Initial: 5 mcg/day; increase in increments of 5-10 mcg/day every 1-2 weeks. When 25 mcg/day is reached, dosage may be increased at intervals of 5-25 mcg/day every 1-2 weeks. Usual maintenance dose: 50-100 mcg/day.

Myxedema coma: I.V.: 25-50 mcg

Patients with known or suspected cardiovascular disease: 10-20 mcg

Note: Normally, at least 4 hours should be allowed between doses to adequately assess therapeutic response and no more than 12 hours should elapse between doses to avoid fluctuations in hormone levels. Oral therapy should be resumed as soon as the clinical situation has been stabilized and the patient is able to take oral medication. If levothyroxine rather than liothyronine sodium is used in initiating oral therapy, the prescriber should bear in mind that there is a delay of several days in the onset of levothyroxine activity and that I.V. therapy should be discontinued gradually.

Simple (nontoxic) goiter: Oral: Initial: 5 mcg/day; increase by 5-10 mcg every 1-2 weeks; after 25 mcg/day is reached, may increase dose by 12.5-25 mcg. Usual maintenance dose: 75 mcg/day.

Dosing: ElderlyOral: 5 mcg/day; increase by 5 mcg/day every 2 weeks

Dosing: PediatricCongenital hypothyroidism: Oral: 5 mcg/day increase by 5 mcg every 3-4 days until the desired response is achieved. Usual maintenance dose: 20 mcg/day for infants, 50 mcg/day for children 1-3 years of age, and adult dose for children >3 years.

Administration: I.V.For I.V. use only; **do not administer I.M. or SubQ.** Administer doses at least 4 hours, and no more than 12 hours, apart. Resume oral therapy as soon as the clinical situation has been stabilized and the patient is able to take oral medication. If **levothyroxine** is used for oral therapy, there is a delay of several days in the onset of activity; therefore, discontinue I.V. therapy gradually.

Administration: OralWhen switching to tablets, discontinue the injectable, initiate oral therapy at a low dosage, and increase gradually according to response.

StorageVials must be stored under refrigeration at 2°C to 8°C (36°F to 46°F). Store tablets at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to liothyronine sodium or any component of the formulation; undocumented or uncorrected adrenal insufficiency; recent myocardial infarction or thyrotoxicosis; artificial rewarming (injection)

Warnings/Precautions

Boxed warnings:

- Weight reduction: See “Other warnings/precautions” below.

Disease-related concerns:

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency; symptoms may be exaggerated or aggravated.

- Cardiovascular disease: Use with caution and reduce dosage in patients with angina pectoris or other cardiovascular disease; chronic hypothyroidism predisposes patients to coronary artery disease.

- Diabetes: Use with caution in patients with diabetes mellitus and insipidus; symptoms may be exaggerated or aggravated.

- Myxedema: Use with caution in patients with myxedema; symptoms may be exaggerated or aggravated.

Special populations:

- Elderly: Use with caution in elderly patients; they may be more likely to have compromised cardiovascular function.

Other warnings/precautions:

- Monitoring: Thyroid replacement requires periodic assessment of thyroid status.

- Weight reduction: **[U.S. Boxed Warning]: Thyroid supplements are ineffective and potentially toxic for weight reduction. High doses may produce serious or even life-threatening toxic effects particularly when used with some anorectic drugs.**

Geriatric ConsiderationsElderly do not have a change in serum thyroxine associated with aging; however, plasma T_3 concentrations are decreased 25% to 40% in the elderly. There is not a compensatory rise in thyrotropin suggesting that lower T_3 is not reacted upon as a deficiency by the pituitary. This indicates a slightly lower than normal dosage of thyroid hormone replacement is usually sufficient in elderly patients than in younger adult patients. TSH must be monitored since insufficient thyroid replacement (elevated TSH) is a risk for coronary artery disease and excessive replacement (low TSH) may cause signs of hyperthyroidism and excessive bone loss.

Pregnancy Risk FactorA

Pregnancy ConsiderationsUntreated hypothyroidism may have adverse effects on fetal growth and development, and is associated with higher rate of complications; treatment should not be discontinued during pregnancy.

LactationEnters breast milk (small amounts)/compatible

Adverse Reactions

1% to 10%: Cardiovascular: Arrhythmia (6%), tachycardia (3%), cardiopulmonary arrest (2%), hypotension (2%), MI (2%)

<1%: Allergic skin reactions, angina, CHF, fever, hypertension, phlebitis, twitching

Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Thyroid Products. *Risk C: Monitor therapy*

CarBAMazepine: May decrease the serum concentration of Thyroid Products. *Risk C: Monitor therapy*

Estrogen Derivatives: May diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Thyroid Products. Phenytoin may also displace thyroid hormones from protein binding sites. *Risk C: Monitor therapy*

Rifampin: May decrease the serum concentration of Thyroid Products. *Risk C: Monitor therapy*

Sodium Iodide I131: Thyroid Products may diminish the therapeutic effect of Sodium Iodide I131. *Risk X: Avoid combination*

Theophylline Derivatives: Thyroid Products may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Thyroid Products may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Monitoring ParametersT_3, TSH, heart rate, blood pressure, renal function, clinical signs of hypo- and hyperthyroidism; TSH is the most reliable guide for evaluating adequacy of thyroid replacement dosage. TSH may be elevated during the first few months of thyroid replacement despite patients being clinically euthyroid. In cases where T_4 remains low and TSH is within normal limits, an evaluation of "free" (unbound) T_4 is needed to evaluate further increase in dosage.

Reference RangeFree T_3, serum: 250-390 pg/dL; TSH: 0.4 and up to 10 (≥80 years) mIU/L; remains normal in pregnancy

Nursing: Physical Assessment/MonitoringSee Contraindications, Warnings/Precautions, and Dosing for use cautions. Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (see extensive list of Drug Interactions). See I.V. Administration. Assess results of laboratory tests (see above), therapeutic effectiveness, and adverse effects (eg, hypo-/hyperthyroidism - see Adverse Reactions and Overdose/Toxicology) regularly during therapy. **Important:** See Effects on Lab Values above when considering results of thyroid function tests. Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report (see Patient Education).

Monitoring: Lab TestsT_3, T_4, TSH. TSH may be elevated during the first few months of thyroid replacement despite patients being clinically euthyroid. In cases where T_4 remains low and TSH is within normal limits, an evaluation of "free" (unbound) T_4 is needed to evaluate further increase in dosage.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. Thyroid replacement therapy is generally for life. Take as directed, in the morning before breakfast. Do not take antacids or iron preparations within 8 hours of thyroid medication. Do not discontinue without consulting prescriber. Report chest pain, rapid heart rate, palpitations, excessive sweating or heat intolerance, excessive sweating, increased nervousness, agitation, or lethargy.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 10 mcg/mL (1 mL)

Triostat®: 10 mcg/mL (1 mL) [contains ethanol 6.8%]

Tablet, oral:

Cytomel®: 5 mcg, 25 mcg, 50 mcg

Generic AvailableYes: Injection
ManufacturerMonarch Pharmaceuticals (distributor)
Pricing: U.S. (www.drugstore.com)

Tablets (Cytomel)

5 mcg (100): $78.95

25 mcg (100): $101.66

50 mcg (100): $152.49

Mechanism of ActionExact mechanism of action is unknown; however, it is believed the thyroid hormone exerts its many metabolic effects through control of DNA transcription and protein synthesis; involved in normal metabolism, growth, and development; promotes gluconeogenesis, increases utilization and mobilization of glycogen stores, and stimulates protein synthesis, increases basal metabolic rate
Pharmacodynamics/Kinetics

Onset of action: 2-4 hours

Peak response: 2-3 days

Absorption: Oral: Well absorbed (95% in 4 hours)

Half-life elimination: 2.5 days

Excretion: Urine

Pharmacotherapy PearlsEquivalent doses: The following statement on relative potency of thyroid products is included in a joint statement by American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE) and The Endocrine Society (TES): For purposes of conversion, levothyroxine sodium (T_4) 100 mcg is usually considered equivalent to desiccated thyroid 60 mg, thyroglobulin 60 mg, or liothyronine sodium (T_3) 25 mcg. However, these are rough guidelines only and do not obviate the careful re-evaluation of a patient when switching thyroid hormone preparations, including a change from one brand of levothyroxine to another. Joint position statement is available at http://www.thyroid.org/professionals/advocacy/04_12_08_thyroxine.html.

A synthetic form of *L*-Triiodothyronine (T_3) can be used in patients allergic to products derived from pork or beef.

Note: Several medications have effects on thyroid production or conversion. The impact in thyroid replacement has not been specifically evaluated, but patient response should be monitored:

Methimazole: Decreases thyroid hormone secretion, while propylthiouracil decrease thyroid hormone secretion and decreases conversion of T_4 to T_3.

Beta-adrenergic antagonists: Decrease conversion of T_4 to T_3 (dose related, propranolol ≥160 mg/day); patients may be clinically euthyroid.

Iodide, iodine-containing radiographic contrast agents may decrease thyroid hormone secretion; may also increase thyroid hormone secretion, especially in patients with Graves' disease.

Other agents reported to impact on thyroid production/conversion include aminoglutethimide, amiodarone, chloral hydrate, diazepam, ethionamide, interferon-alpha, interleukin-2, lithium, lovastatin (case report), glucocorticoids (dose-related), mercaptopurine, sulfonamides, thiazide diuretics, and tolbutamide.

In addition, a number of medications have been noted to cause transient depression in TSH secretion, which may complicate interpretation of monitoring tests for thyroid hormones, including corticosteroids, octreotide, and dopamine. Metoclopramide may increase TSH secretion.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo precautions with vasoconstrictor are necessary if patient is well controlled with liothyronine
Mental Health: Effects on Mental StatusMay cause nervousness or insomnia
Mental Health: Effects on Psychiatric TreatmentUsed to augment antidepressants
Anesthesia and Critical Care Concerns/Other ConsiderationsEquivalent doses: The following statement on relative potency of thyroid products is included in a joint statement by American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE) and The Endocrine Society (TES): For purposes of conversion, levothyroxine sodium (T_4) 100 mcg is usually considered equivalent to desiccated thyroid 60 mg, thyroglobulin 60 mg, or liothyronine sodium (T_3) 25 mcg. However, these are rough guidelines only and do not obviate the careful re-evaluation of a patient when switching thyroid hormone preparations, including a change from one brand of levothyroxine to another. Joint position statement is available at http://www.thyroid.org/professionals/advocacy/04_12_08_thyroxine.html.
Index TermsLiothyronine Sodium; Sodium *L*-Triiodothyronine; T_3 Sodium (error-prone abbreviation)
References

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Watts NB, "Use of a Sensitive Thyrotropin Assay for Monitoring Treatment With Levothyroxine," *Arch Intern Med*, 1989, 149(2):309-12.[PubMed 2644903]

International Brand NamesCynomel (BF, BJ, CI, ET, FR, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MX, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Cytomel (BE, LU, NL); Cytomel 25 (IL); Dispon (IT); Halotri (ES); Iobolin (BR); Liothyronin (NO, PL, SE); Neo-Tiroimade (PT); T3 (GR); Tertroxin (AU, CZ, GB); Thybon Henning (DE); Thyronine (JP); Thyrotardin inject. (DE); Ti-Tre (IT); Tri-Iodo-Tironina (AR); Trijodthyronin (AT, PL); Trijodthyronin BC (DE); Triyodotironina (ES); Triyotex (CR, DO, GT, HN, MX, PA, SV)

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Liotrix may be confused with Klotrix®

Thyrolar® may be confused with Thyrogen®, Thytropar®

Pronunciation(LYE oh triks)

U.S. Brand NamesThyrolar®

Canadian Brand NamesThyrolar®

Pharmacologic CategoryThyroid Product

Use: Labeled IndicationsReplacement or supplemental therapy in hypothyroidism (uniform mixture of T_4:T_3 in 4:1 ratio by weight); little advantage to this product exists and cost is not justified

Dosing: AdultsHypothyroidism (dose of thyroid equivalent): Oral: 30 mg/day (15 mg/day if cardiovascular impairment), increasing by increments of 15 mg/day at 2- to 3-week intervals to a maximum of 180 mg/day (usual maintenance dose: 60-120 mg/day)

Dosing: ElderlyInitial: 15 mg, adjust dose at 2- to 4-week intervals by increments of 15 mg

Dosing: PediatricCongenital hypothyroidism: Oral:

Children (dose of T_4 or levothyroxine/day):

0-6 months: 8-10 mcg/kg or 25-50 mcg/day

6-12 months: 6-8 mcg/kg or 50-75 mcg/day

1-5 years: 5-6 mcg/kg or 75-100 mcg/day

6-12 years: 4-5 mcg/kg or 100-150 mcg/day

>12 years: 2-3 mcg/kg or >150 mcg/day

StorageStore at 2°C to 8°C (36°F to 46°F). Protect from light.

ContraindicationsHypersensitivity to liotrix or any component of the formulation; recent myocardial infarction or thyrotoxicosis, uncomplicated by hypothyroidism; uncorrected adrenal insufficiency, hypersensitivity to active or extraneous constituents

Warnings/Precautions

Boxed warnings:

- Weight reduction: See “Other warnings/precautions” below.

Disease-related concerns:

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency; symptoms may be exaggerated or aggravated.
- Cardiovascular disease: Use with caution and reduce dosage in patients with angina pectoris or other cardiovascular disease; chronic hypothyroidism predisposes patients to coronary artery disease.
- Diabetes: Use with caution in patients with diabetes mellitus and insipidus; symptoms may be exaggerated or aggravated.
- Myxedema: Use with caution in patients with myxedema; symptoms may be exaggerated or aggravated.

Special populations:

- Elderly: Use with caution in the elderly; since they may be more likely to have compromised cardiovascular function.

Other warnings/precautions:

- Weight reduction: **[U.S. Boxed Warning]: Thyroid supplements are ineffective and potentially toxic for weight reduction. High doses may produce serious or even life-threatening toxic effects particularly when used with some anorectic drugs.**

Geriatric ConsiderationsElderly do not have a change in serum thyroxine associated with aging; however, plasma T_3 concentrations are decreased 25% to 40% in older adults. There is not a compensatory rise in thyrotropin suggesting that lower T_3 is not reacted upon as a deficiency by the pituitary. This indicates a slightly lower than normal dosage of thyroid hormone replacement is usually sufficient in older patients than in younger adult patients. TSH must be monitored since insufficient thyroid replacement (elevated TSH) is a risk for coronary artery disease and excessive replacement (low TSH) may cause signs of hyperthyroidism and excessive bone loss.

Pregnancy Risk FactorA

Pregnancy ConsiderationsUntreated hypothyroidism may have adverse effects on fetal growth and development, and is associated with higher rate of complications; treatment should not be discontinued during pregnancy.

Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiac arrhythmia, chest pain, palpitation, tachycardia

Central nervous system: Ataxia, fever, headache, insomnia, nervousness

Dermatologic: Alopecia

Endocrine & metabolic: Changes in menstrual cycle, increased appetite, weight loss

Gastrointestinal: Abdominal cramps, constipation, diarrhea, vomiting

Neuromuscular & skeletal: Hand tremor, myalgia, tremor

Respiratory: Dyspnea

Miscellaneous: Allergic skin reactions (rare), diaphoresis

Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Thyroid Products. *Risk C: Monitor therapy*

CarBAMazepine: May decrease the serum concentration of Thyroid Products. *Risk C: Monitor therapy*

Estrogen Derivatives: May diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Thyroid Products. Phenytoin may also displace thyroid hormones from protein binding sites. *Risk C: Monitor therapy*

Rifampin: May decrease the serum concentration of Thyroid Products. *Risk C: Monitor therapy*

Sodium Iodide I131: Thyroid Products may diminish the therapeutic effect of Sodium Iodide I131. *Risk X: Avoid combination*

Theophylline Derivatives: Thyroid Products may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Thyroid Products may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Test InteractionsMany drugs may have effects on thyroid function tests; para-aminosalicylic acid, aminoglutethimide, amiodarone, barbiturates, carbamazepine, chloral hydrate, clofibrate, colestipol, corticosteroids, danazol, diazepam, estrogens, ethionamide, fluorouracil, I.V. heparin, insulin, lithium, methadone, methimazole, mitotane, nitroprusside, oxyphenbutazone, phenylbutazone, PTU, perphenazine, phenytoin, propranolol, salicylates, sulfonylureas, and thiazides

Monitoring ParametersT_4, TSH, heart rate, blood pressure, clinical signs of hypo- and hyperthyroidism; TSH is the most reliable guide for evaluating adequacy of thyroid replacement dosage. TSH may be elevated during the first few months of thyroid replacement despite patients being clinically euthyroid. In cases where T_4 remains low and TSH is within normal limits, an evaluation of “free” (unbound) T_4 is needed to evaluate further increase in dosage.

Reference Range

TSH: 0.4-10 (for those ≥80 years) mIU/L

T_4: 4-12 mcg/dL (SI: 51-154 nmol/L)

T_3 (RIA) (total T_3): 80-230 ng/dL (SI: 1.2-3.5 nmol/L)

T_4 free (Free T_4): 0.7-1.8 ng/dL (SI: 9-23 pmol/L)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

$^1/_4$ [levothyroxine sodium 12.5 mcg and liothyronine sodium 3.1 mcg]

$^1/_2$ [levothyroxine sodium 25 mcg and liothyronine sodium 6.25 mcg]

1 [levothyroxine sodium 50 mcg and liothyronine sodium 12.5 mcg]

2 [levothyroxine sodium 100 mcg and liothyronine sodium 25 mcg]

3 [levothyroxine sodium 150 mcg and liothyronine sodium 37.5 mcg]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Thyrolar-1)

60 (12.5-50) mg (mcg) (30): $29.99

Tablets (Thyrolar-1/2)

30 (6.25-25) mg (mcg) (30): $26.99

Tablets (Thyrolar-1/4)

15 (3.1-12.5) mg (mcg) (30): $23.99

Tablets (Thyrolar-2)

120 (25-100) mg (mcg) (30): $32.99

Tablets (Thyrolar-3)

180 (73.5-150) mg (mcg) (30): $39.99

Mechanism of ActionThe primary active compound is T_3 (triiodothyronine), which may be converted from T_4 (thyroxine) and then circulates throughout the body to influence growth and maturation of various tissues. Liotrix is uniform mixture of synthetic T_4 and T_3 in 4:1 ratio; exact mechanism of action is unknown; however, it is believed the thyroid hormone exerts its many metabolic effects through control of DNA transcription and protein synthesis; involved in normal metabolism, growth, and development; promotes gluconeogenesis, increases utilization and mobilization of glycogen stores and stimulates protein synthesis, increases basal metabolic rate

Pharmacodynamics/Kinetics

Absorption: 50% to 95%

Metabolism: Partially hepatic, renal, and in intestines

Half-life elimination: 6-7 days

Time to peak, serum: 12-48 hours

Excretion: Partially feces (as conjugated metabolites)

Pharmacotherapy PearlsEquivalent doses: The following statement on relative potency of thyroid products is included in a joint statement by American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE) and The Endocrine Society (TES): For purposes of conversion, levothyroxine sodium (T_4) 100 mcg is usually considered equivalent to desiccated thyroid 60 mg, thyroglobulin 60 mg, or liothyronine sodium (T_3) 25 mcg. However, these are rough guidelines only and do not obviate the careful re-evaluation of a patient when switching thyroid hormone preparations, including a change from one brand of levothyroxine to another. Joint position statement is available at http://www.thyroid.org/professionals/advocacy/04_12_08_thyroxine.html.

Since T_3 is produced by monodeiodination of T_4 in peripheral tissues (80%) and since elderly have decreased T_3 (25% to 40%), little advantage to this product exists and cost is not justified; no advantage over synthetic levothyroxine sodium.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo precautions with vasoconstrictor are necessary if patient is well controlled with liotrix

Mental Health: Effects on Mental StatusMay cause nervousness or insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other ConsiderationsSince T_3 is produced by monodeiodination of T_4 in peripheral tissues (80%) and since elderly have decreased T_3 (25% to 40%), little advantage to this product exists and cost is not justified. Its use has no advantage over synthetic levothyroxine sodium.

Equivalent doses: The following statement on relative potency of thyroid products is included in a joint statement by American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE) and The Endocrine Society (TES): For purposes of conversion, levothyroxine sodium (T_4) 100 mcg is usually considered equivalent to desiccated thyroid 60 mg, thyroglobulin 60 mg, or liothyronine sodium (T_3) 25 mcg. However, these are rough guidelines only and do not obviate the careful re-evaluation of a patient when switching thyroid hormone preparations, including a change from one brand of levothyroxine to another. Joint position statement is available at http://www.thyroid.org/professionals/advocacy/04_12_08_thyroxine.html.

Index TermsT_3/T_4 Liotrix

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Binimelis J, Bassas L, Marruecos L, et al, “Massive Thyroxine Intoxication: Evaluation of Plasma Extraction,” *Intensive Care Med*, 1987, 13(1):33-8. [PubMed 3558934]

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Mandel SH, Magnusson AR, Burton BT, et al, “Massive Levothyroxine Ingestion: Conservative Management,” *Clin Pediatr (Phila)*, 1989, 28(8):374-6.

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Watts NB, “Use of a Sensitive Thyrotropin Assay for Monitoring Treatment With Levothyroxine,” *Arch Intern Med*, 1989, 149(2):309-12.[PubMed 2644903]

International Brand Names Thyreotom (CY, EG, IQ, JO, LY, SY); Thyreotom Forte (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE)

Lisdexamfetamine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death, especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) has issued a statement in April 2008 recommending that all children diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the recommendations due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: Methylphenidate, amphetamine, dextroamphetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children's Healthcare Quality.

For more information, refer to:

- http://americanheart.mediaroom.com/index.php?s=43&item=422
- http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1
- http://americanheart.mediaroom.com/index.php?s=43&item=398
- http://www.fda.gov/medwatch/safety/2007/safety07.htm
- http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html

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"Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder," *J Am Acad*

Child Adolesc Psychiatry, 2007, 46(7):894-921.

Vetter VL, Elia J, Erickson CH, et al, “Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing,” *Circulation*, 2008, 117:2407-23.

Wilens TE, Prince JB, Spencer TJ, et al, “Stimulants and Sudden Death: What is a Physician to do?” *Pediatrics*, 2006, 118(3):1215-19.

Medication Safety Issues

Sound-alike/look-alike issues:

Vyvanse™ may be confused with Vytorin®, Glucovance®, Vivactil®

Pronunciation(lis dex am FET a meen)
U.S. Brand NamesVyvanse™
Pharmacologic CategoryStimulant
Use: Labeled IndicationsTreatment of attention-deficit/hyperactivity disorder (ADHD)
Dosing: AdultsADHD: Oral: Initial: 30 mg once daily in the morning; may increase in increments of 10 mg or 20 mg/day at weekly intervals until optimal response is obtained; maximum: 70 mg/day

Note: Individualize dosage based on patient need and response to therapy. Administer at the lowest effective dose.

Dosing: PediatricADHD: Oral: Children: 6-12 years: Initial: 30 mg once daily in the morning; may increase in increments of 10 mg or 20 mg/day at weekly intervals until optimal response is obtained; maximum: 70 mg/day

Note: Individualize dosage based on patient need and response to therapy. Administer at the lowest effective dose.

Administration: OralAdminister in the morning with or without food; swallow capsule whole, do not chew; capsule may be opened and the contents dissolved in glass of water; consume the resulting solution immediately; do not store solution.
Dietary ConsiderationsMay be taken with or without food.
StorageStore at controlled room temperature of 25°C (77°F) excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.
RestrictionsC-II

An FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsKnown hypersensitivity or idiosyncratic reaction sympathomimetic amines; advanced arteriosclerosis, symptomatic cardiovascular disease, moderate-to-severe hypertension; hyperthyroidism; glaucoma; agitated states; history of drug abuse; concurrent use or within 2 weeks of use of MAO inhibitors
Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Drug abuse: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Cardiovascular events: **[U.S. Boxed Warning]: Use of CNS stimulants has been associated with serious cardiovascular events, including sudden death in patients with pre-existing structural cardiac abnormalities or other serious heart problems (sudden death in children and adolescents; sudden death, stroke and MI in adults).** These products should be avoided in the patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease (adults), or other serious cardiac problems that could increase the risk of sudden death that these conditions alone carry. Patients should be carefully evaluated for these cardiac disorders prior to initiation of therapy.
- CNS effects: Amphetamines may impair the ability to engage in potentially hazardous activities.
- Visual disturbance: Difficulty in accommodation and blurred vision has been reported with the use of stimulants.

Disease-related concerns:

- ADHD treatment: Appropriate use: Recommended to be used as part of a comprehensive treatment program for attention deficit disorders.
- Drug abuse: **[U.S. Boxed Warning]: Potential for drug dependency exists; prolonged use may lead to drug dependency.** Use is contraindicated in patients with history of ethanol or drug abuse. Prescriptions should be written for the smallest quantity consistent with good patient care to minimize possibility of overdose.
- Hypertension: Use with caution in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases in blood pressure or heart rate. Use is contraindicated in patients with moderate-to-severe hypertension, arteriosclerosis, hyperthyroidism, or symptomatic CVD.
- Psychiatric disorders: Use with caution in patients with pre-existing psychosis, bipolar disorder (may induce mixed/manic episode), aggressive behavior, or hostility. May exacerbate symptoms of behavior and thought disorder in psychotic patients; new onset psychosis or mania may occur with stimulant use; observe for symptoms of aggression and/or hostility.

- Seizure disorder: Use with caution in patients with a history of seizure disorder; may lower seizure threshold leading to new onset or breakthrough seizure activity.

- Tourette's syndrome/tics: Use with caution in patients with Tourette's syndrome; stimulants may exacerbate tics (motor and phonic) and Tourette’s syndrome. Evaluate for tics and Tourette’s syndrome prior to therapy initiation.

Special populations:

- Pediatrics: Safety and efficacy in children <6 years of age or children >12 years of age have not been established. Amphetamines are not recommended in children <3 years of age. Appetite suppression may occur; monitor weight during therapy, particularly in children. Use of stimulants has been associated with slowing of growth rate; monitor growth rate during treatment. Treatment interruption may be necessary in patients who are not growing or gaining weight as expected.

Other warnings/precautions:

- Discontinuation of therapy: Abrupt discontinuation following high doses or for prolonged periods may result in symptoms for withdrawal.

- Long-term use: Safety and efficacy of long-term use have not yet been established.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have shown that amphetamines may cause embryotoxic and teratogenic effects and that pre- or early postnatal exposure to amphetamines may lead to lasting changes in behavior, including impaired learning, memory, and motor skills, as well as changes to libido. There are no adequate and well-controlled studies in pregnant women. No reproductive studies have been performed with lisdexamfetamine. Infants born to mothers dependent on amphetamines are more likely to arrive prematurely with low birth weight and may experience withdrawal symptoms including irritation, restlessness, anxiousness, weakness, listlessness, or lethargy.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsManufacturer advises nursing mothers taking amphetamines to refrain from breast-feeding.

Adverse Reactions

>10%:

Central nervous system: Headache (children 12%), insomnia (19% to 27%; 4% [initially])

Gastrointestinal: Appetite decreased (27% to 39%), xerostomia (children 5%; adults 26%), abdominal pain (children 12%)

1% to 10%:

Cardiovascular: Blood pressure increased (adults 3%), heart rate increased (adults 2%)

Central nervous system: Irritability (children 10%), anxiety (adults 6%), dizziness (children 5%), jitteriness (adults 4%), affect lability (children 3%), agitation (adults 3%), restlessness (adults 3%), fever (children 2%), somnolence (children 2%), tic (children 2%)

Dermatologic: Hyperhidrosis (adults 3%), rash (children 3%)

Gastrointestinal: Vomiting (children 9%), weight loss (children 9%), diarrhea (adults 7%), nausea (6% to 7%), anorexia (adult: 5%)

Neuromuscular & skeletal: Tremor (adults 2%)

Respiratory: Dyspnea (adults 2%)

Additional adverse reaction associated with amphetamines; frequency not defined.

Cardiovascular: Cardiomyopathy, hypertension, MI, palpitation, sudden death, tachycardia

Central nervous system: Depression, dyskinesia, dysphoria, euphoria, exacerbation of motor and phonic tics, Tourette's syndrome, overstimulation, psychotic episodes, seizure, stroke

Dermatologic: Angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Endocrine & metabolic: Libido changes

Gastrointestinal: Abnormal taste, constipation

Genitourinary: Impotence

Miscellaneous: Anaphylaxis

Drug Interactions

Alkalinizing Agents: May decrease the excretion of Amphetamines. *Risk D: Consider therapy modification*

Ammonium Chloride: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

Analgesics (Opioid): Amphetamines may enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Antihistamines: Amphetamines may diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antipsychotics: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Amphetamines. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Ethosuximide: Amphetamines may diminish the therapeutic effect of Ethosuximide. Amphetamines may decrease the serum concentration of Ethosuximide. *Risk C: Monitor therapy*

Gastrointestinal Acidifying Agents: May decrease the serum concentration of Amphetamines. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Methenamine: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

PHENobarbital: Amphetamines may decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Phenytoin: Amphetamines may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: High-fat meal prolongs T_{max} by ~1 hour.

Test InteractionsAmphetamines may interfere with urinary steroid determinations.

Monitoring ParametersCardiac evaluation should be completed on any patient who develops chest pain, unexplained syncope, and any symptom of cardiac disease during treatment with stimulants; growth and CNS activity in all patients

When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure, and consider obtaining ECG prior to initiation (Vetter, 2008).

Nursing: Physical Assessment/MonitoringMonitor therapeutic response and adverse reactions at the beginning and periodically throughout therapy. Assess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Perform careful cardiovascular assessment prior to initiating therapy. Monitor weight and blood pressure at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed. Drug may cause physical and/or psychological dependence. Do not take any new medications without consulting prescriber. Avoid alcohol use. Use caution when driving or engaging in tasks requiring alertness until response to drug is known. May cause problems with sleeping, headache, irritability, dizziness, nausea, vomiting (small, frequent meals, frequent oral care, sucking lozenges, or chewing gum may help), abdominal pain, and decreased appetite. Report chest pain, shortness of breath, fainting, abnormal thinking or behavior, increased aggression, hallucinations, seizures, change in vision, or persistent abdominal pain.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage Forms

Capsule, as dimesylate:

Vyvanse™: 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg

Generic AvailableNo

ManufacturerShire

Pricing: U.S. (www.drugstore.com)

Capsules (Vyvanse)

20 mg (20): $102.71

30 mg (20): $103.02

50 mg (20): $95.01

70 mg (30): $137.38

Mechanism of ActionLisdexamfetamine dimesylate is a prodrug that is converted to the active component dextroamphetamine (a noncatecholamine, sympathomimetic amine); CNS stimulant effects are thought to result from the interference of norepinephrine and dopamine reuptake into presynaptic neurons as well as increasing their release from nerve terminals; inhibits the actions of monoamine oxidase; peripheral actions include increase in systolic and diastolic blood pressure as well as weak bronchodilator and respiratory stimulant action.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: Dextroamphetamine: V_d: Adults: 3.5-4.6 L/kg; distributes into CNS; mean CSF concentrations are 80% of plasma; enters breast milk

Metabolism: Non-CYP-mediated hepatic or intestinal metabolism to dextroamphetamine and l-lysine

Half-life elimination: Lisdexamfetamine: <1 hour; Dextroamphetamine: 10-13 hours

Time to peak, serum: T_{max}: Lisdexamfetamine: ~1 hour; Dextroamphetamine: ~3.5 hours

Excretion: Urine (96%, 42% as amphetamine-related compounds, 2% as lisdexamfetamine, 25% hippuric acid); feces (minimal)

Related Information

- Stimulant Agents Used for ADHD

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Lisdexamfetamine is a prodrug that is converted to the active component dextroamphetamine (a noncatecholamine, sympathomimetic amine); dextroamphetamine is known to increase blood pressure. Monitor blood pressure prior to using local anesthetic with vasoconstrictors.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse vasoconstrictor with caution in patients taking lisdexamfetamine. Amphetamines enhance the sympathomimetic response of epinephrine or mepivacaine and levonordefrin (Carbocaine® 2% with Neo-Cobefrin®) leading to potential hypertension and cardiotoxicity.

Index TermsLisdexamfetamine Dimesylate; Lisdexamphetamine; NRP104

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Lisinopril and Hydrochlorothiazide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(lyse IN oh pril & hye droe klor oh THYE a zide)

U.S. Brand NamesPrinzide®; Zestoretic®

Canadian Brand NamesApo-Lisinopril/Hctz; Gen-Lisinopril/Hctz; Novo-Lisinopril/Hctz; Prinzide®; Sandoz Lisinopril/Hctz; Zestoretic®

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension

Dosing: AdultsHypertension: Oral: Initial: Lisinopril 10 mg/hydrochlorothiazide 12.5 mg or lisinopril 20 mg/hydrochlorothiazide 12.5 mg with further increases of either or both components could depend on clinical response. Doses >80 mg/day lisinopril or >50 mg/day hydrochlorothiazide are not recommended.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentDosage adjustments should be made with caution. Usual regimens of therapy need not be adjusted as long as patient's Cl_{cr} >30 mL/minute. In patients with more severe renal impairment, loop diuretics are preferred.

ContraindicationsHypersensitivity to lisinopril, any other ACE inhibitor, hydrochlorothiazide, sulfonamide-derived drugs, or any component of the formulation; angioedema related to previous treatment with an ACE inhibitor; patients with idiopathic or hereditary angioedema; anuria

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose), angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with idiopathic or hereditary angioedema or previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Electrolyte disturbances: Hyperkalemia may occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE Inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use lisinopril with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity. Hydrochlorothiazide can cause systemic lupus erythematosus (SLE) exacerbation or activation.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use fosinopril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use lisinopril with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment. Avoid hydrochlorothiazide in severe renal disease (ineffective). Contraindicated in anuric patients.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Pregnancy Risk FactorC/D (2nd and 3rd trimesters)
Pregnancy Considerations**[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.** See individual agents.
Lactation

Hydrochlorothiazide: Compatible

Lisinopril: Excretion in breast milk unknown

Breast-Feeding ConsiderationsSee individual monographs.
Adverse ReactionsSee individual agents.
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can

not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure; BUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsBUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: 10/12.5: Lisinopril 10 mg and hydrochlorothiazide 12.5 mg; 20/12.5: Lisinopril 20 mg and hydrochlorothiazide 12.5 mg; 20/25: Lisinopril 20 mg and hydrochlorothiazide 25 mg

Prinizide®:

- 10/12.5: Lisinopril 10 mg and hydrochlorothiazide 12.5 mg
- 20/12.5: Lisinopril 20 mg and hydrochlorothiazide 12.5 mg [DSC]
- 20/25: Lisinopril 20 mg and hydrochlorothiazide 25 mg

Zestoretic®:

- 10/12.5: Lisinopril 10 mg and hydrochlorothiazide 12.5 mg
- 20/12.5: Lisinopril 20 mg and hydrochlorothiazide 12.5 mg
- 20/25: Lisinopril 20 mg and hydrochlorothiazide 25 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Lisinopril-Hydrochlorothiazide)

10-12.5 mg (30): $23.99

20-12.5 mg (30): $21.99

20-25 mg (30): $21.99

Tablets (Prinzide)

10-12.5 mg (30): $40.99

20-12.5 mg (30): $45.99

Tablets (Zestoretic)

10-12.5 mg (30): $56.78

20-12.5 mg (30): $60.05

20-25 mg (30): $60.18

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Hydrochlorothiazide
- Lisinopril

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or fatigue; may rarely cause sedation, insomnia, or depression

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for lisinopril and hydrochlorothiazide combination therapy may include improved compliance and synergistic reductions in blood pressure with an accompanied reduction in side effects. ACE inhibitors and thiazides are also standard therapy for left ventricular systolic dysfunction. See Cardiovascular Considerations for individual agents.

Index TermsHydrochlorothiazide and Lisinopril

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9824192]

International Brand NamesAcercomp (DE); Acerdil D (CN, PY); Carace Plus (GB, IE); Cipril - H (IN); Coric Plus (DE); Lisiletic (VE); Novazyd (NL); Prinzide (AT, BG, BR, CH, FR, GR, IT, MX, NZ); Tensolisin D (DO, HN); Zestoretic (AE, AR, BB, BE, BF, BH, BJ, BM, BR, BS, BZ, CH, CI, CY, DK, EG, ES, ET, GB, GH, GM, GN, GR, GY, HK, ID, IE, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, OM, PE, PH, PK, PT, QA, SA, SC, SD, SE, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW)

Lisinopril

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Lisinopril may be confused with fosinopril, Lioresal®, Risperdal®

Prinivil® may be confused with Plendil®, Pravachol®, Prevacid®, Prilosec®, Proventil®

Zestril® may be confused with Desyrel®, Restoril®, Vistaril®, Zetia®, Zostrix®

International issues:

Acepril® [Denmark] may be confused with Accupril® which is a brand name for quinapril in the U.S.

Acepril®: Brand name for enalapril in Hungary and Switzerland; brand name for captopril in Great Britain

Carace® [Ireland; Great Britain] may be confused with Carac™ which is a brand name for fluorouracil in the U.S.

Zestril® may be confused with Nostril® which is a brand name for chlorhexidine/cetrimonium in France

Pronunciation(lyse IN oh pril)

U.S. Brand NamesPrinivil®; Zestril®

Canadian Brand NamesApo-Lisinopril®; CO Lisinopril; Gen-Lisinopril; Novo-Lisinopril; PMS-Lisinopril; Prinivil®; Pro-Lisinopril; Ran-Lisinopril; ratio-Lisinopril; Riva-Lisinopril; Zestril®

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor

Use: Labeled IndicationsTreatment of hypertension, either alone or in combination with other antihypertensive agents; adjunctive therapy in treatment of heart failure (HF); treatment of acute myocardial infarction (MI) within 24 hours in hemodynamically-stable patients to improve survival

Dosing: Adults

Hypertension: Oral: Usual dosage range (JNC 7): 10-40 mg/day

Not maintained on diuretic: Initial: 10 mg/day

Maintained on diuretic: Initial: 5 mg/day

Note: Antihypertensive effect may diminish toward the end of the dosing interval especially with doses of 10 mg/day. An increased dose may aid in extending the duration of antihypertensive effect. Doses up to 80 mg/day have been used, but do not appear to give greater effect.

Patients taking diuretics should have them discontinued 2-3 days prior to initiating lisinopril if possible. Restart diuretic after blood pressure is stable if needed. If diuretic cannot be discontinued prior to therapy, begin with 5 mg with close supervision until stable blood pressure. In patients with hyponatremia (<130 mEq/L), start dose at 2.5 mg/day.

Heart failure: Oral: Initial: 2.5-5 mg once daily; then increase by no more than 10 mg increments at intervals no less than 2 weeks to a maximum daily dose of 40 mg. Usual maintenance: 5-40 mg/day as a single dose. Target dose: 20-40 mg once daily (ACC/AHA 2005 Heart Failure Guidelines)

Note: If patient has hyponatremia (serum sodium <130 meq/L) or renal impairment (Cl_{cr} <30 mL/minute or creatinine >3 mg/dL), then initial dose should be 2.5 mg/day

Acute myocardial infarction (within 24 hours in hemodynamically stable patients): Oral: 5 mg immediately, then 5 mg at 24 hours, 10 mg at 48 hours, and 10 mg every day thereafter for 6 weeks. Patients should continue to receive standard treatments such as thrombolytics, aspirin, and beta-blockers.

Dosing: ElderlyOral:

Initial: 2.5-5 mg/day; increase doses 2.5-5 mg/day at 1- to 2-week intervals; maximum daily dose: 40 mg

Patients taking diuretics should have them discontinued 2-3 days prior to initiating lisinopril if possible. Restart diuretic after blood pressure is stable if needed. In patients with hyponatremia (<130 mEq/L), start dose at 2.5 mg/day (see Renal Impairment).

Dosing: Pediatric

Hypertension: Children ≥6 years: Oral: Initial: 0.07 mg/kg once daily (up to 5 mg); increase dose at 1- to 2-week intervals; doses >0.61 mg/kg or

>40 mg have not been evaluated.

Dosing: Renal Impairment

Hypertension:

Adults: Initial doses should be modified and upward titration should be cautious, based on response (maximum: 40 mg/day)

Cl_{cr} >30 mL/minute: Initial: 10 mg/day

Cl_{cr} 10-30 mL/minute: Initial: 5 mg/day

Hemodialysis: Initial: 2.5 mg/day; dialyzable (50%)

Children: Use in not recommended in pediatric patients with GFR <30 mL/minute/1.73 m^2

Heart failure: Adults: Cl_{cr} <30 mL/minute or creatinine >3 mg/dL): Initial: 2.5 mg/day

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralWatch for hypotensive effects within 1-3 hours of first dose or new higher dose.

Dietary ConsiderationsUse potassium-containing salt substitutes cautiously in patients with diabetes, patients with renal dysfunction, or those maintained on potassium supplements or potassium-sparing diuretics.

Extemporaneously Prepared**Preparation of oral suspension (1 mg/mL): Note:** Mix in a polyethylene terephthalate bottle. Add 10 mL of purified water (USP) to a bottle containing ten lisinopril 20 mg tablets (total 200 mg). Shake for at least 1 minute; then add 30 mL Bicitra® and 160 mL Ora-Sweet SF™ and shake gently to suspend contents. Store at 25°C (77°F); stable for up to 4 weeks.

ContraindicationsHypersensitivity to lisinopril or any component of the formulation; angioedema related to previous treatment with an ACE inhibitor; patients with idiopathic or hereditary angioedema

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose), angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with idiopathic or hereditary angioedema or previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE Inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 years of age or with a Cl_{cr} ≤30 mL/minute.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric Considerations Due to frequent decreases in glomerular filtration (also creatinine clearance) with aging, elderly patients may have exaggerated responses to ACE inhibitors. Differences in clinical response due to hepatic changes are not observed. ACE inhibitors may be preferred agents in elderly patients with congestive heart failure and diabetes mellitus. Diabetic proteinuria is reduced and insulin sensitivity is enhanced. In general, the side effect profile is favorable in the elderly and causes little or no CNS confusion. Use lowest dose recommendations initially. Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.

Pregnancy Risk Factor C (1st trimester); D (2nd and 3rd trimesters)

Pregnancy Considerations Due to adverse events observed in some animal studies, lisinopril is considered pregnancy category C during the first trimester. Based on human data, lisinopril is considered pregnancy category D if used during the second and third trimesters (per the manufacturer; however, one study suggests that fetal injury may occur at anytime during pregnancy). Lisinopril crosses the placenta. First trimester exposure to ACE inhibitors may cause major congenital malformations. An increased risk of cardiovascular and/or central nervous system malformations was observed in one study; however, an increased risk of teratogenic events was not observed in other studies. Second and third trimester use of an ACE inhibitor is associated with oligohydramnios. Oligohydramnios due to decreased fetal renal function may lead to fetal limb contractures, craniofacial deformation, and hypoplastic lung development. The use of ACE inhibitors during the second and third trimesters is also associated with anuria, hypotension, renal failure (reversible or irreversible), skull hypoplasia, and death in the fetus/neonate. Chronic maternal hypertension itself is also associated with adverse events in the fetus/infant. ACE inhibitors are not recommended during pregnancy to treat maternal hypertension or heart failure. Those who are planning a pregnancy should be considered for other medication options if an ACE inhibitor is currently prescribed or the ACE inhibitor should be discontinued as soon as possible once pregnancy is detected. The exposed fetus should be monitored for fetal growth, amniotic fluid volume, and organ formation. Infants exposed to an ACE inhibitor *in utero*, especially during the second and third trimester, should be monitored for hyperkalemia, hypotension, and oliguria.

[U.S. Boxed Warning]: Based on human data, ACE inhibitors can cause injury and death to the developing fetus when used in the second and third trimesters. ACE inhibitors should be discontinued as soon as possible once pregnancy is detected.

Lactation Excretion in breast milk unknown/not recommended

Breast-Feeding Considerations It is not known if lisinopril is excreted in breast milk. Breast-feeding is not recommended by the manufacturer.

Pregnancy & Lactation, In-Depth

- Lisinopril in Pregnancy & Lactation

Adverse Reactions **Note:** Frequency ranges include data from hypertension and heart failure trials. Higher rates of adverse reactions have generally been noted in patients with CHF. However, the frequency of adverse effects associated with placebo is also increased in this population.

1% to 10%:

Cardiovascular: Orthostatic effects (1%), hypotension (1% to 4%)

Central nervous system: Headache (4% to 6%), dizziness (5% to 12%), fatigue (3%)

Dermatologic: Rash (1% to 2%)

Endocrine & metabolic: Hyperkalemia (2% to 5%)

Gastrointestinal: Diarrhea (3% to 4%), nausea (2%), vomiting (1%), abdominal pain (2%)

Genitourinary: Impotence (1%)

Hematologic: Decreased hemoglobin (small)

Neuromuscular & skeletal: Chest pain (3%), weakness (1%)

Renal: BUN increased (2%); deterioration in renal function (in patients with bilateral renal artery stenosis or hypovolemia); serum creatinine increased (often transient)

Respiratory: Cough (4% to 9%), upper respiratory infection (1% to 2%)

<1%: Acute renal failure, alopecia, anaphylactoid reactions, angioedema, anuria, arrhythmia, arthralgia, arthritis, asthma, ataxia, azotemia, bilirubin increased, bone marrow suppression, bronchospasm, cardiac arrest, cutaneous pseudolymphoma, decreased libido, gout, hemolytic anemia, hepatic necrosis, hepatitis, hyponatremia, leukopenia, jaundice (cholestatic), MI, neutropenia, oliguria, orthostatic hypotension, pancreatitis, paresthesia, pemphigus, peripheral neuropathy, photosensitivity, pleural effusion, pulmonary embolism, pulmonary infiltrates, SIADH, Stevens-Johnson syndrome, stroke, syncope, systemic lupus erythematosus, thrombocytopenia, TIA, toxic epidermal necrolysis, transaminases increased, tremor, urticaria, vasculitis, vertigo, vision loss, volume overload, vomiting, weight gain/loss, wheezing, xerostomia

In addition, a syndrome which may include fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash, eosinophilia, positive ANA, and elevated ESR has been reported with ACE inhibitors.

Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Potassium-containing salt substitutes may increase risk of hyperkalemia.

Herb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Test InteractionsMay cause false-positive results in urine acetone determinations using sodium nitroprusside reagent

Monitoring ParametersBUN, serum creatinine, renal function, WBC, and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringAssess patient carefully for use cautions prior to beginning therapy. Assess potential for interactions with other pharmacological agents or herbal products patient is taking that may impact fluid balance or cardiac status. Patient should be monitored for adverse reactions following first dose, following any increase in dose and regularly during therapy (eg, angioedema that may potentially affect airway or intestine, hypovolemia, postural hypotension, or anaphylactic reaction). Evaluate results of laboratory tests and therapeutic effectiveness on a (normotensive) regular basis. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsBUN, serum creatinine, renal function, WBC, and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed; do not discontinue without consulting prescriber. Take first dose at bedtime. Take all doses on an empty stomach, 1 hour before or 2 hours after meals. Do not use potassium supplement or salt substitutes without consulting prescriber. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); or nausea, vomiting, abdominal pain, dry mouth, or transient loss of appetite (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help), report if these persist. Report chest pain or palpitations; mouth sores; fever or chills; swelling of extremities, face, mouth, or tongue; skin rash; numbness, tingling, or pain in muscles; respiratory difficulty or unusual cough; other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg

Prinivil®: 5 mg, 10 mg, 20 mg

Zestril®: 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Lisinopril)

2.5 mg (30): $12.99

5 mg (30): $14.89

10 mg (30): $12.99

20 mg (30): $13.99

30 mg (30): $20.99

40 mg (30): $17.99

Tablets (Prinivil)

2.5 mg (60): $42.99

5 mg (60): $65.99

20 mg (90): $104.51

Tablets (Zestril)

2.5 mg (30): $38.58

5 mg (30): $50.70

10 mg (30): $55.11

20 mg (30): $59.35

30 mg (30): $72.74

40 mg (30): $77.15

Mechanism of ActionCompetitive inhibitor of angiotensin-converting enzyme (ACE); prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor; results in lower levels of angiotensin II which causes an increase in plasma renin activity and a reduction in aldosterone secretion; a CNS mechanism may also be involved in hypotensive effect as angiotensin II increases adrenergic outflow from CNS; vasoactive kallikreins may be decreased in conversion to active hormones by ACE inhibitors, thus reducing blood pressure

Pharmacodynamics/Kinetics

Onset of action: 1 hour

Peak effect: Hypotensive: Oral: ~6 hours

Duration: 24 hours

Absorption: Well absorbed; unaffected by food

Protein binding: 25%

Metabolism: Not metabolized

Bioavailability: Decreased with NYHA Class II-IV heart failure

Half-life elimination: 11-12 hours

Time to peak: ~7 hours

Excretion: Primarily urine (as unchanged drug)

Related Information

- Angiotensin Agents
- Heart Failure (Systolic)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic effects.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or fatigue; may rarely cause sedation, insomnia, or depression

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Congestive Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines recommend that ACE inhibitors be used in patients with a reduced EF (with or without heart failure symptoms) unless contraindicated. ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. In this situation, they decrease hospitalizations for, and retard progression to, congestive heart failure. When used in patients with heart failure, the target dose should be achieved, if possible. Lower daily doses of ACE inhibitors have demonstrated the same mortality effects as high doses, but have not decreased hospitalizations to the extent that high-dose ACE inhibitors have, as demonstrated in the ATLAS study (Packer M, 1999).

Hypertension: The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) can be beneficial in patients with hypertension and LVH without symptoms of heart failure. JNC 7 suggests that patients can benefit from treatment with an ACE inhibitor if they have hypertension **and** heart failure, acute myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, or history of stroke.

Vascular Disease: The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors can be useful in preventing heart failure in patients who have a history of atherosclerotic vascular disease, diabetes, or hypertension with associated cardiovascular risk factors. The HOPE trial (Heart Outcomes Prevention Evaluation Study Investigators, 2000) investigated the value of an ACE inhibitor (ramipril 5-10 mg daily) versus placebo in patients who had evidence of vascular disease or diabetes (one other cardiovascular risk factor) and were at least 55 years of age. Patients were excluded if they had a low ejection fraction, heart failure, or were on an ACE inhibitor. The primary outcome was a composite of death from cardiovascular cause, myocardial infarction, or stroke; 9297 patients were enrolled and randomized. Ramipril significantly reduced the risk of death from CV causes, MI, or stroke over placebo. New cases of diabetes were also reduced in the ramipril group. In the EUROPA trial, patients with stable coronary artery disease (at low risk for cardiovascular events) received perindopril or placebo and were evaluated for incidence of cardiovascular events after four years of treatment. In this randomized, placebo-controlled, prospective study, 12,218 patients received either perindopril (8 mg/day, n=6110) or placebo (n=6108) and were assessed for the primary endpoint of a cardiovascular event, defined as cardiovascular death, myocardial infarction, or cardiac arrest. The study population was well balanced with respect to baseline demographics and concomitant medication use (including beta-blockers, platelet inhibitors, antihyperlipidemics, calcium channel blockers, nitrates, and diuretics). Intent-to-treat analysis revealed that 603 (10%) of placebo patients experienced the primary endpoint of a cardiovascular event compared to 488 (8%) of perindopril-receiving patients, for a 20% relative risk reduction (p=0.0003). This result was not influenced by presence of other comorbidities (eg, diabetes, hypertension) or concomitant beta-blocker, calcium channel blocker, or lipid-lowering therapies. Withdrawal from the study (postrandomization) due to adverse reactions was similar between treatment groups. Number needed to treat analysis suggests that treatment of 50 patients over a 4-year period will prevent one major cardiovascular event.

Acute Coronary Syndromes: In the treatment of unstable angina/non-ST-segment elevation MI, ACE inhibitors are recommended when hypertension persists despite treatment with nitroglycerin and a beta-blocker in patients with LV systolic dysfunction or CHF and in ischemic patients with diabetes (Class I). ACE inhibitors are also recommended for all post-ACS individuals (Class IIa). According to 2004 ACC/AHA STEMI guidelines, an ACE inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF <0.4, in the absence of hypotension or known contraindications to this class of medicines. In the emergency management of complicated STEMI, a short-acting ACEI (eg, captopril 1-6.25 mg) may be added once the patient's systolic blood pressure is >100 mm Hg and not <30 mm Hg below baseline. The VALIANT trial evaluated the effects of valsartan (target dose: 160 mg twice daily), captopril (target dose: 50 mg twice daily), and the combination (target doses: valsartan 80 mg twice daily and captopril 150 mg once daily) in a randomized, double-blind trial of patients with acute MI (0.5-10 days post-MI) complicated by left ventricular systolic dysfunction, heart failure, or both. Enrollment in the study numbered 14,703 patients and followed for a median of 24.7 months. There was no difference in the primary endpoint (all cause mortality) among the 3 groups. There was no difference in incidence of CV death, recurrent MI, or hospitalization for heart failure either. Hypotension and renal dysfunction occurred significantly more often in the valsartan group than captopril alone. Cough, rash, and taste disturbances occurred more often in the captopril group. The authors (Pfeffer MA, 2003) concluded that valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after MI. Combining valsartan with captopril increased the rate of adverse events without improving survival.

Potential Adverse Events: ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. In those patients experiencing cough on an ACE inhibitor, the ACE inhibitor may be discontinued and, if necessary, ARB therapy instituted. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Drug Interactions: Concomitant indomethacin therapy may blunt the reduction in sitting and 24-hour ambulatory diastolic blood pressure. Use of NSAIDs should be avoided or limited, with monitoring of blood pressure control in this setting. In patients with heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

Anesthesia and Critical Care Concerns/Other ConsiderationsDue to decreases in glomerular filtration (also creatinine clearance) with aging, severe congestive heart failure and renal failure, these patients may experience renal dysfunction with ACE inhibitor administration.

ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. Concomitant NSAID therapy may attenuate blood pressure control. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

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International Brand NamesAcemin (AT); Acepril (MY); Acerbon (DE); Acerdil (CN); Aklis (UY); Alapril (IT); Alfaken (MX); Carace (GB, IE); Cipril (HK, IN); Coric (DE); Dapril (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SG, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Diroton (EE, PL); Dosteril (MX); Doxapril (AR); ES (IN); Eucor (EC); Fersivag (MX); Fibsol (AU); Genopril (TW); Inopril (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Irumed (HR); Linopril (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Linoxal (ID); Linvas (IN); Liprace (AU); Lipril (IN); Lisdene (SG); Lisibeta (DE); Lisigamma (DE); Lisihexal (DE, PL); Lisinobell (AU); Lisinoratio (PL); Lisipril (CO, DO); Lisiprol (PL); Lisir (TH); Lisodur (AU); Lisopress (BB, BM, BS, BZ, GY, HU, JM, SR, TT); Lisoril (IN, SG); Lispril (TH); Listril (IN); Longes (JP); Nafordyl (SG); Noperten (ID); Novatec (BE, LU, NL); Odace (ID); Pesatril (MX); Presiten (DO); Prinil (CH); Prinivil (AT, AU, BB, BG, BM, BR, BS, BZ, CZ, FR, GR, GY, HK, HU, IT, JM, MX, PL, RU, SR, TT, VE); Ranopril (MY); Rowenopril (CR, EC, GT, HN, NI, PA, SV); Safepril (TW); Sinopren (ZA); Sinopril (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Tensiphar (ID); Tensopril (AR, IL); Tensyn (CO); Vivatec (DK, FI, NO); Zestril (AE, AU, BB, BE, BF, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CY, DK, EG, ES, ET, FR, GB, GH, GM, GN, GR, GY, HK, ID, IE, IL, IQ, IR, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, OM, PE, PH, PK, PT, PY, QA, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Zinopril (AU)

Lithium

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Eskalith® may be confused with Estratest®

Lithobid® may be confused with Levbid®, Lithostat®

Do not confuse **mEq** (milliequivalent) with **mg** (milligram). **Note:** 8 mEq lithium carbonate equals 300 mg lithium carbonate. Dosage should be written in **mg** (milligrams) to avoid confusion. Check prescriptions for unusually high volumes of the syrup for dosing errors.

Pronunciation(LITH ee um)

U.S. Brand NamesEskalith CR® [DSC]; Eskalith® [DSC]; Lithobid®

Canadian Brand NamesApo-Lithium® Carbonate; Apo-Lithium® Carbonate SR; Carbolith™; Duralith®; Euro-Lithium; Lithane™; PMS-Lithium Carbonate; PMS-Lithium Citrate

Pharmacologic CategoryAntimanic Agent

Use: Labeled IndicationsManagement of bipolar disorders; treatment of mania in individuals with bipolar disorder (maintenance treatment prevents or diminishes intensity of subsequent episodes)

Use: Unlabeled/InvestigationalPotential augmenting agent for antidepressants; aggression, post-traumatic stress disorder, conduct disorder in children

Dosing: Adults

Bipolar disorders: Oral: 900-2400 mg/day in 3-4 divided doses or 900-1800 mg/day in two divided doses of sustained release

Note: Monitor serum concentrations and clinical response (efficacy and toxicity) to determine proper dose

Dosing: ElderlyBipolar disorders: Oral: Initial: 300 mg twice daily; increase weekly in increments of 300 mg/day, monitoring levels; rarely need to go >900-1200 mg/day.

Dosing: Pediatric

Bipolar disorders (unlabeled use): Oral: Children 6-12 years: 15-60 mg/kg/day in 3-4 divided doses; dose not to exceed usual adult dosage. **Note:** Monitor serum concentrations and clinical response (efficacy and toxicity) to determine proper dose.

Conduct disorder (unlabeled use): Oral: Children 6-12 years: 15-30 mg/kg/day in 3-4 divided doses; dose not to exceed usual adult dosage

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer 50% to 75% of normal dose.

Cl_{cr} <10 mL/minute: Administer 25% to 50% of normal dose.

Dialyzable (50% to 100%); 4-7 times more efficient than peritoneal dialysis

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister with meals to decrease GI upset. Slow release tablets must be swallowed whole; do not crush or chew.

Dietary ConsiderationsMay be taken with meals to avoid GI upset; have patient drink 2-3 L of water daily.

ContraindicationsHypersensitivity to lithium or any component of the formulation; avoid use in patients with severe cardiovascular or renal disease, or with severe debilitation, dehydration, or sodium depletion; pregnancy

Allergy Considerations

- Lithium Allergy

Warnings/Precautions

Boxed warnings:

- Monitoring: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Renal effects: Chronic therapy results in diminished renal concentrating ability (nephrogenic DI); this is usually reversible when lithium is discontinued. Changes in renal function should be monitored, and re-evaluation of treatment may be necessary. Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported in patients on chronic lithium therapy; morphologic changes have also been reported in manic-depressive patients never exposed to lithium. The relationship between morphologic changes and renal function, and the association with lithium therapy, have not been established.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with mild-moderate cardiovascular disease.

- Dehydration: Use with caution in patients with significant fluid loss (protracted sweating, diarrhea, or prolonged fever); temporary reduction or cessation of therapy may be warranted.

- Depression/suicidal ideation: Use with caution in patients at risk of suicide (suicidal thoughts or behavior).

- Renal impairment: Use with caution in patients with mild-moderate renal impairment.

- Thyroid disease: Use with caution in patients with thyroid disease.

Concurrent drug therapy issues:

- Medications altering sodium excretion: Use caution in patients receiving medications which alter sodium excretion (eg, diuretics, ACE inhibitors, NSAIDs).

- Neuroleptic medications: Use with caution in patients receiving neuroleptic medications - a syndrome resembling NMS has been associated with concurrent therapy.

- Neuromuscular-blocking agents: Administered neuromuscular-blocking agents with caution; the response may be prolonged.

Special populations:

- Elderly: Use with caution in the elderly; may be extremely sensitive to the effects of lithium, see Dosage and Reference Range.

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Acute manic phase: Higher serum concentrations may be required and tolerated during an acute manic phase; however, the tolerance decreases when symptoms subside.

- Monitoring: **[U.S. Boxed Warning]: Lithium toxicity is closely related to serum concentrations and can occur at therapeutic doses; serum lithium determinations are required to monitor therapy.** Normal fluid and salt intake must be maintained during therapy.

Geriatric ConsiderationsSome elderly patients may be extremely sensitive to the effects of lithium. Initial doses need to be adjusted for renal function in the elderly; thereafter, adjust doses based upon serum concentrations and response.

Pregnancy Risk FactorD

Pregnancy ConsiderationsCardiac malformations in the infant, including Ebstein's anomaly, are associated with use of lithium during the first trimester of pregnancy. Nontoxic effects to the newborn include shallow respiration, hypotonia, lethargy, cyanosis, diabetes insipidus, thyroid depression, and nontoxic goiter when lithium is used near term. Efforts should be made to avoid lithium use during the first trimester; if an alternative therapy is not appropriate, the lowest possible dose of lithium should be used throughout the pregnancy. Fetal echocardiography and ultrasound to screen for anomalies should be conducted between 16-20 weeks of gestation. Lithium levels should be monitored in the mother and may need to be adjusted following delivery.

LactationEnters breast milk/contraindicated

Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiac arrhythmia, hypotension, sinus node dysfunction, flattened or inverted T waves (reversible), edema, bradycardia, syncope

Central nervous system: Dizziness, vertigo, slurred speech, blackout spells, seizure, sedation, restlessness, confusion, psychomotor retardation, stupor, coma, dystonia, fatigue, lethargy, headache, pseudotumor cerebri, slowed intellectual functioning, tics

Dermatologic: Dry or thinning of hair, folliculitis, alopecia, exacerbation of psoriasis, rash

Endocrine & metabolic: Euthyroid goiter and/or hypothyroidism, hyperthyroidism, hyperglycemia, diabetes insipidus

Gastrointestinal: Polydipsia, anorexia, nausea, vomiting, diarrhea, xerostomia, metallic taste, weight gain, salivary gland swelling, excessive salivation

Genitourinary: Incontinence, polyuria, glycosuria, oliguria, albuminuria

Hematologic: Leukocytosis

Neuromuscular & skeletal: Tremor, muscle hyperirritability, ataxia, choreoathetoid movements, hyperactive deep tendon reflexes, myasthenia gravis (rare)

Ocular: Nystagmus, blurred vision, transient scotoma

Miscellaneous: Coldness and painful discoloration of fingers and toes

Drug Interactions

ACE Inhibitors: May increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Amphetamines: Lithium may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: May increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Antipsychotics: Lithium formulations may enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the neurotoxic effect of Lithium. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Lithium. Decreased or unaltered lithium concentrations have also been reported with this combination. *Risk C: Monitor therapy*

CarBAMazepine: May enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Desmopressin: Lithium may diminish the therapeutic effect of Desmopressin. Desmopressin may increase the serum concentration of Lithium. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the adverse/toxic effect of Lithium. **Exceptions:** Moclobemide. *Risk C: Monitor therapy*

Methyldopa: May enhance the adverse/toxic effect of Lithium. This may occur without notable changes in serum lithium concentrations. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Lithium may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May increase the serum concentration of Lithium. **Exceptions:** Sulindac. *Risk D: Consider therapy modification*

Phenytoin: May enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Potassium Iodide: May enhance the adverse/toxic effect of Lithium. Specifically the hypothyroid/goiter-potentiating effects. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sodium Bicarbonate: May increase the excretion of Lithium. *Risk C: Monitor therapy*

Sodium Chloride: May increase the excretion of Lithium. *Risk C: Monitor therapy*

Theophylline Derivatives: May increase the excretion of Lithium. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Thiazide Diuretics: May decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Lithium may enhance the neurotoxic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Lithium serum concentrations may be increased if taken with food. Limit caffeine.

Monitoring ParametersSerum lithium every 4-5 days during initial therapy; draw lithium serum concentrations 8-12 hours postdose; renal, thyroid, and cardiovascular function; fluid status; serum electrolytes; CBC with differential, urinalysis; monitor for signs of toxicity; beta-hCG pregnancy test for all females not known to be sterile

Reference RangeLevels should be obtained twice weekly until both patient's clinical status and levels are stable then levels may be obtained every 1-3 months

Timing of serum samples: Draw trough just before next dose (8-12 hours after previous dose)

Therapeutic levels:

Acute mania: 0.6-1.2 mEq/L (SI: 0.6-1.2 mmol/L)

Protection against future episodes in most patients with bipolar disorder: 0.8-1 mEq/L (SI: 0.8-1.0 mmol/L); a higher rate of relapse is described in subjects who are maintained at <0.4 mEq/L (SI: 0.4 mmol/L)

Elderly patients can usually be maintained at lower end of therapeutic range (0.6-0.8 mEq/L)

Toxic concentration: >1.5 mEq/L (SI: >2 mmol/L)

Adverse effect levels:

GI complaints/tremor: 1.5-2 mEq/L

Confusion/somnolence: 2-2.5 mEq/L

Seizures/death: >2.5 mEq/L

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor cardiovascular status; assess for fluid retention. Monitor laboratory results at beginning of therapy, when adjusting dose, and periodically thereafter. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. **Note:** Lithium has a very small window of safety (TI). Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and importance of reporting adverse symptoms promptly.

Monitoring: Lab TestsSerum lithium every 4-5 days during initial therapy. Monitor renal and thyroid; serum electrolytes; CBC with differential, urinalysis.

Levels should be obtained twice weekly until both patient's clinical status and levels are stable then levels may be obtained every 1-3 months.

Timing of serum samples: Draw trough just before next dose (8-12 hours after previous dose).

Therapeutic levels:

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Elderly patients can usually be maintained at lower end of therapeutic range (0.6-0.8 mEq/L).

Toxic concentration: >1.5 mEq/L (SI: >2 mmol/L)

Adverse effect levels:

GI complaints/tremor: 1.5-2 mEq/L

Confusion/somnolence: 2-2.5 mEq/L

Seizures/death: >2.5 mEq/L

Patient EducationTake exactly as directed; do not change dosage without consulting prescriber. Do not crush or chew extended or slow release tablets or capsules. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake (especially in summer). Avoid changes in sodium content (eg, low sodium diets); reduction of sodium can increase lithium toxicity. Limit caffeine intake (diuresis can increase lithium toxicity). Frequent blood test and monitoring will be necessary. You may experience decreased appetite or altered taste sensation (small frequent meals may help maintain nutrition); or drowsiness or dizziness, especially during early therapy (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Immediately report unresolved diarrhea, abrupt changes in weight, muscular tremors or lack of coordination, fever, or changes in urinary volume. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, as carbonate: 150 mg, 300 mg, 600 mg

Eskalith®: 300 mg [contains benzyl alcohol] [DSC]

Solution, as citrate: 300 mg/5 mL (5 mL, 500 mL) [equivalent to amount of lithium in lithium carbonate]

Syrup, as citrate: 300 mg/5 mL (480 mL) [equivalent to amount of lithium in lithium carbonate]

Tablet, as carbonate: 300 mg

Tablet, controlled release, as carbonate: 450 mg

Eskalith CR®: 450 mg [DSC]

Tablet, slow release, as carbonate: 300 mg

Lithobid®: 300 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Lithium Carbonate)

150 mg (90): $18.99

300 mg (90): $17.99

600 mg (90): $39.99

Syrup (Lithium Citrate)

8 mEq/5 mL (500): $60.00

Tablet, controlled release (Lithium Carbonate)

300 mg (30): $14.99

450 mg (60): $28.99

Tablet, controlled release (Lithobid)

300 mg (90): $180.05

Tablets (Lithium Carbonate)

300 mg (90): $24.99

Mechanism of ActionAlters cation transport across cell membrane in nerve and muscle cells and influences reuptake of serotonin and/or norepinephrine; second messenger systems involving the phosphatidylinositol cycle are inhibited; postsynaptic D2 receptor supersensitivity is inhibited

Pharmacodynamics/Kinetics

Absorption: Rapid and complete

Distribution: V_d: Initial: 0.3-0.4 L/kg; V_{dss}: 0.7-1 L/kg; crosses placenta; enters breast milk at 35% to 50% the concentrations in serum; distribution is complete in 6-10 hours

CSF, liver concentrations: $^1/_3$ to $^1/_2$ of serum concentration

Erythrocyte concentration: ~$^1/_2$ of serum concentration

Heart, lung, kidney, muscle concentrations: Equivalent to serum concentration

Saliva concentration: 2-3 times serum concentration

Thyroid, bone, brain tissue concentrations: Increase 50% over serum concentrations

Protein binding: Not protein bound

Metabolism: Not metabolized

Bioavailability: Not affected by food; Capsule, immediate release tablet: 95% to 100%; Extended release tablet: 60% to 90%; Syrup: 100%

Half-life elimination: 18-24 hours; can increase to more than 36 hours in elderly or with renal impairment

Time to peak, serum: Nonsustained release: ~0.5-2 hours; slow release: 4-12 hours; syrup: 15-60 minutes

Excretion: Urine (90% to 98% as unchanged drug); sweat (4% to 5%); feces (1%)

Clearance: 80% of filtered lithium is reabsorbed in the proximal convoluted tubules; therefore, clearance approximates 20% of GFR or 20-40 mL/minute

Related Information

- Adverse Effects of Approved Mood Stabilizers / Anticonvulsants
- Agents Approved for Bipolar Disorder
- Antacid Drug Interactions
- Liquid Compatibility
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), salivary gland swelling, and metallic taste. Avoid NSAIDs if analgesics are required since lithium toxicity has been reported with concomitant administration; acetaminophen products (ie, singly or with narcotics) are recommended.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Child/Adolescent ConsiderationsInformation regarding the safety and effectiveness of lithium carbonate in children <12 years of age is not available; its use in this population group is not recommended.

Mental Health CommentLithium remains the gold standard for bipolar disorder. It is most useful for the management of euphoric mania and least effective for the mixed and rapid-cycling types of bipolar disorder. Among patients treated for bipolar disorder, risk of suicide attempt and suicide death is lower during treatment with lithium than during treatment with divalproex (Goodwin, 2003). Fine hand tremor associated with lithium therapy may be treated with propranolol. Incidence of hypothyroidism secondary to lithium therapy is 7% to 8% with a 9:1 female to male ratio. Diabetes insipidus may be treated with a thiazide diuretic (hydrochlorothiazide 25-50 mg/day) or amiloride (5-10 mg twice daily). The thiazide diuretics are thought to work by decreasing intracellular volume via sodium depletion, thereby enhancing reabsorption of sodium and water proximally leading to a decrease in fluid volume to the distal convoluted tubule and collecting duct which increases sodium reabsorption and decreases water excretion. Leukocytosis (without a left shift) begins in the first week of lithium therapy, peaks at 2 weeks.

Goodwin GM and Young AH, “The British Association for Psychopharmacology Guidelines for Treatment of Bipolar Disorder: A Summary,” *J Psychopharmacol*, 2003, 17(4 Suppl):3-6.

Index TermsLithium Carbonate; Lithium Citrate

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International Brand NamesCalith (TW); Camcolit (AE, BE, BH, CY, EG, HK, IE, IL, IQ, IR, JO, KW, LB, LU, LY, OM, QA, SA, SG, SY, TW, YE); Carbolim (BR); Carbolit (CN, CO, MX); Carbolithium (IT); Carlit (PY); Ceglution (AR); Ceglution 300 (EC); Contemnol (CZ); Eskalith (BB, BM, BS, BZ, GY, JM, SR, TT); Frimania (ID); Hynorex Retard (DE); Karlit (AR); Licab (IN); Licarb (TH); Licarbium (IL); Limas (JP); Liskonum (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Litarex (DK, NO); Litheum 300 (MX); Lithicarb (AU, MY); Lithionate (TW); Lithionit (NO, SE); Lithium Carbonicum (PL); Lithiumkarbonat ”Oba” (DK); Lithocap (IN); Liticarb (HU); Litij-karbonat (HR); Litil (DO); Litium-Karbonat (HN); Litiumkarbonat ”Dak” (DK); Lito (FI); Litocarb (PE); Maniprex (BE, LU); Neurolepsin (AT); Phanate (TH); Plenur (ES); Priadel (BE, GB, LU, NL, NO, NZ, PT); Priadel Retard (CH, GR); Quilonium-R (PH); Quilonorm (AT); Quilonorm Retardtabletten (CH); Quilonum Retard (DE); Quilonum retard (LU); Quilonum SR (AU); Sicolitio (UY); Teralithe (FR); Theralite (CO)

Lodoxamide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

International issues:

Thilomide® [Turkey] may be confused with Thalomid® which is a brand name for thalidomide in the U.S.

Pronunciation(loe DOKS a mide)
U.S. Brand NamesAlomide®
Canadian Brand NamesAlomide®
Pharmacologic CategoryMast Cell Stabilizer
Use: Labeled IndicationsTreatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis
Dosing: AdultsVernal conjunctivitis, keratitis: Ophthalmic: Children ≥2 years and Adults: Instill 1-2 drops in eye(s) 4 times/day for up to 3 months
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren ≥2 years: Refer to adult dosing.
ContraindicationsHypersensitivity to lodoxamide tromethamine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Irritation: May cause transient burning or stinging.

Special populations:

- Contact lens wearers: Contains benzalkonium chloride which may be adsorbed by contact lenses; remove contacts prior to administration and wait 15 minutes before reinserting.

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Other warnings/precautions:

- Appropriate use: For ophthalmic use only; not for injection.

Geriatric ConsiderationsAssure the patient or caregiver can adequately administer ophthalmic medication.
Pregnancy Risk FactorB
Adverse Reactions

>10%: Local: Transient burning, stinging, discomfort

1% to 10%:

Central nervous system: Headache

Ocular: Blurred vision, corneal erosion/ulcer, eye pain, corneal abrasion, blepharitis

<1%: Dizziness, somnolence, rash, nausea, stomach discomfort, sneezing, dry nose

Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess patient response. Teach patient proper use, side effects/appropriate interventions, and symptoms to report.
Patient EducationFor use in eyes only. Avoid wearing soft contact lenses while using this medication. Wash hands before using. Lie down or tilt your head back and look upward. Hold dropper tip as near as possible to your eyelid without touching it. Pull the lower lid of eye down to form a pocket. Drop the prescribed number of drops into the pocket made by the lower lid and the eye. (Placing drops on the surface of the eyeball can cause stinging.) Do not blink or rub eye. Close your eye and press lightly against the inside corner of your eye for about 1 minute. Repeat in other eye if directed by prescriber. Replace and tighten cap right away, do not allow tip of dropper to become contaminated. Wipe off any excess liquid from cheek. Wash your hands again. Do not use any other eye medication without consulting prescriber. Do not share mediation with anyone else. You may experience temporary stinging or burning in the eyes, headache, increased eye tearing or dry eye, sneezing, or blurred vision. Inform prescriber if you experience eye pain, disturbance of vision; skin rash; swelling in or around the eyes; any other adverse response; or if condition worsens or fails to improve. Store medication at room temperature, away from excess heat and moisture. Do not use if solution has changed color, is cloudy, or contains particles.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic: 0.1% (10 mL) [contains benzalkonium chloride]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Solution (Alomide)

0.1% (10): $97.78

Mechanism of ActionMast cell stabilizer that inhibits the *in vivo* type I immediate hypersensitivity reaction to increase cutaneous vascular permeability associated with IgE and antigen-mediated reactions

Pharmacodynamics/KineticsAbsorption: Topical: Negligible

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsLodoxamide Tromethamine

International Brand NamesAlconmide (PH); Almide (FR); Alomide (AR, AT, BE, BF, BG, BJ, BR, CH, CI, CL, CN, CO, CZ, DE, DK, ES, ET, FI, GB, GH, GM, GN, GR, HK, HN, HU, ID, IE, IL, IT, KE, LR, LU, MA, ML, MR, MU, MW, MX, MY, NE, NG, NO, PE, PK, PL, PT, PY, SC, SD, SG, SL, SN, TH, TN, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Lomide (AU)

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Lomustine may be confused with carmustine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Lomustine should only be administered as a single dose once every 6 weeks; serious errors have occurred when lomustine was inadvertently administered daily.

Pronunciation(loe MUS teen)

U.S. Brand NamesCeeNU®

Canadian Brand NamesCeeNU®

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent

Use: Labeled IndicationsTreatment of brain tumors and Hodgkin's disease

Use: Unlabeled/InvestigationalNon-Hodgkin's lymphoma, melanoma, renal carcinoma, lung cancer, colon cancer

Dosing: AdultsRefer to individual protocols.

Chemotherapy: Oral: 100-130 mg/m^2 as a single dose once every 6 weeks; readjust after initial treatment according to platelet and leukocyte counts

With compromised marrow function: Initial dose: 100 mg/m^2 as a single dose once every 6 weeks

Note: Repeat courses should only be administered after adequate recovery: Leukocytes >4000/mm^3 and platelet counts >100,000/mm^3

Subsequent dosing adjustment based on nadir:

Leukocytes 2000-2999/mm^3, platelets 25,000-74,999/mm^3: Administer 70% of prior dose

Leukocytes <2000/mm^3, platelets <25,000/mm^3: Administer 50% of prior dose

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChemotherapy: Oral (refer to individual protocols): Children: 75-150 mg/m^2 as a single dose once every 6 weeks; subsequent doses are readjusted after initial treatment according to platelet and leukocyte counts.

Dosing: Renal Impairment

The FDA-approved labeling does not contain renal dosing adjustment guidelines. The following guidelines have been used by some clinicians:

Aronoff, 2007: Adults:

Cl_{cr} 10-50 mL/minute: Administer 75% of dose

Cl_{cr} <10 mL/minute: Administer 25% to 50% of dose

Hemodialysis: Supplemental dose is not necessary

Continuous ambulatory peritoneal dialysis (CAPD): Administer 25% to 50% of dose

Kintzel, 1995:

Cl_{cr} 46-60 mL/minute: Administer 75% of normal dose

Cl_{cr} 31-45 mL/minute: Administer 70% of normal dose

Cl_{cr} ≤30 mL/minute: Avoid use

Dosing: Hepatic ImpairmentThe FDA-approved labeling does not contain hepatic adjustment guidelines; lomustine is hepatically metabolized and caution should be used in patients with hepatic dysfunction.

Dosing: Combination Regimens

Brain tumors:

8 in 1 (Brain Tumors)

PCV

POC

Gastric cancer: FAMe

Lymphoma, Hodgkin's disease: CAD/MOPP/ABV

Melanoma:

BOLD

BOLD + Interferon

BOLD (Melanoma)

Retinoblastoma: 8 in 1 (Retinoblastoma)

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralTake with fluids on an empty stomach; no food or drink for 2 hours after administration.

Dietary ConsiderationsShould be taken with fluids on an empty stomach; no food or drink for 2 hours after administration to decrease nausea.

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to lomustine, any component of the formulation, or other nitrosoureas; pregnancy

Allergy Considerations

- Nitrosourea Allergy

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warnings]: Bone marrow suppression, notably thrombocytopenia and leukopenia, may lead to bleeding and overwhelming infections in an already compromised patient;** will last for at least 6 weeks after a dose. Do not administer courses more frequently than every 6 weeks because the toxicity is delayed. Use with caution in patients with depressed platelet, leukocyte or erythrocyte counts. Bone marrow toxicity is cumulative; dose adjustments should be based on nadir counts from prior dose.
- Pulmonary toxicity: May cause delayed pulmonary toxicity (infiltrates and/or fibrosis); usually related to cumulative doses >1100 mg/m^2.
- Secondary malignancies: Long-term use may be associated with the development of secondary malignancies.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment; may require dosage adjustment.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenic effects and embryotoxicity have been observed in animal studies. There are no adequate and well-controlled studies in pregnant women. May cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid pregnancy and should be advised of the potential harm to the fetus.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is contraindicated

Adverse Reactions

>10%:

Gastrointestinal: Nausea and vomiting, usually within 3-6 hours after oral administration. Administration of the dose at bedtime, with an antiemetic, significantly reduces both the incidence and severity of nausea.

Hematologic: Myelosuppression, common, dose-limiting, may be cumulative and irreversible; leukopenia (65%; nadir: 5-6 weeks; recovery 6-8 weeks); thrombocytopenia (nadir: 4 weeks; recovery 5-6 weeks)

Frequency not defined: Acute leukemia, alkaline phosphatase increased, alopecia, anemia, ataxia, azotemia (progressive), bilirubin increased, blindness, bone marrow dysplasia, disorientation, dysarthria, kidney size decreased, lethargy, optic atrophy, pulmonary fibrosis, pulmonary infiltrates, renal failure, stomatitis, transaminases increased, visual disturbances

Oncology: Emetic PotentialHigh (60% to 90%)
Metabolism/Transport Effects**Substrate** of CYP2D6 (major); **Inhibits** CYP2D6 (weak), 3A4 (weak)
Drug Interactions

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to GI irritation).
Test InteractionsLiver function tests
Monitoring ParametersCBC with differential and platelet count (for at least 6 weeks after dose), hepatic and renal function tests (periodic), pulmonary function tests (baseline and periodic)
Nursing: Physical Assessment/MonitoringAssess patient's hematology and liver stature prior to beginning therapy; bone marrow depression may lead to bleeding and overwhelming infections in an already compromised patient. Assess potential for interactions with other pharmacological agents patient may be taking (eg, decreased levels/effects of lomustine, increased toxicity). Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions prior to each treatment and on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.
Monitoring: Lab TestsCBC with differential and platelet count (for at least 6 weeks after dose), hepatic and renal function tests (periodic), pulmonary function tests (baseline and periodic)
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take with fluids on an empty stomach; do not eat or drink for 2 hours prior to or following administration to reduce nausea and vomiting. Your prescriber may recommend that you take your medication at bedtime with a prescribed antiemetic to reduce the severity of nausea. During therapy, do not use excessive alcohol. It is important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition (small, frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). You may experience hair loss (reversible); nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help or consult prescriber for approved antiemetic); mouth sores (frequent mouth care and use of a soft toothbrush or cotton swabs may help); or diarrhea (buttermilk, boiled milk, or yogurt may help reduce diarrhea - consult prescriber for approved medication). Report persistent nausea, vomiting, or diarrhea; bleeding or bruising; fever, chills, sore throat; vaginal discharge; rash; blood in urine, stool, or vomitus; delayed healing of any wounds; yellowing of skin or eyes; or changes in color of urine of stool.
Pregnancy/breast-feeding precautions: Do not get pregnant while taking this medication and for 1 month following therapy. Consult prescriber for appropriate contraceptives measures. This drug may cause severe fetal birth defects. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

CeeNU®: 10 mg, 40 mg, 100 mg

Capsule [dose pack]:

CeeNU®: 10 mg (2s); 40 mg (2s); 100 mg (2s) [DSC]

Generic AvailableNo
ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)
Pricing: U.S. (www.drugstore.com)

Capsules (CeeNU)

10 mg (30): $328.46

300 mg (1): $25.99

Mechanism of ActionInhibits DNA and RNA synthesis via carbamylation of DNA polymerase, alkylation of DNA, and alteration of RNA, proteins, and enzymes
Pharmacodynamics/Kinetics

Duration: Marrow recovery: ~5-8 weeks

Absorption: Complete

Distribution: Crosses blood-brain barrier to a greater degree than BCNU; CNS concentrations are ≥50% of plasma concentrations

Metabolism: Rapidly hepatic via hydroxylation producing at least two active metabolites; enterohepatically recycled

Half-life elimination: Parent drug: 16-72 hours; Active metabolite: 16-48 hours

Time to peak, serum: Active metabolite: ~3 hours

Excretion: Urine (~50%); feces (<5%); expired air (<10%)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause sedation or disorientation

Mental Health: Effects on Psychiatric TreatmentMyelosuppression is common; avoid usage with clozapine and carbamazepine; concurrent use with phenobarbital may result in diminished efficacy of both drugs

Index TermsCCNU; NSC-79037

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Wasserman TH, Slavik M, and Carter SK, “Clinical Comparison of the Nitrosoureas,” *Cancer*, 1975, 36(4);1258-68.

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International Brand NamesBelustine (ES, HN, IT, RU, TR); C.C.N.U. (ES); CCNU (AE, BH, CY, EG, GB, IL, IQ, IR, JO, KW, LB, LY, OM, PK, QA, SA, SY, TR, YE); Cecenu (BE, CZ, DE, GR, NL, PL); CEENU (AR, CN, MX, UY); CeeNU (AU, BF, BJ, CI, CL, ET, GH, GM, GN, HK, KE, LR, MA, ML, MR, MU, MW, NE, NG, PH, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Citostal (BR); Lomustine (IN, SE); Lomustine ”Medac” (DK); Lomustinum (PL); Lucostin (AT); Lucostine (FI); Prava (CH)

Loperamide and Simethicone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(loe PER a mide & sye METH i kone)

U.S. Brand NamesImodium® Advanced

Pharmacologic CategoryAntidiarrheal; Antiflatulent

Use: Labeled IndicationsControl of symptoms of diarrhea and gas (bloating, pressure, and cramps)

Dosing: Adults**Acute diarrhea:** Oral: 1 caplet or tablet after first loose stool, followed by 1 caplet or tablet with each subsequent loose stool (maximum: 4 caplets or tablets/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Acute diarrhea** (weight-based dosing is preferred):

Children 6-8 years (48-59 lbs): 1 caplet or tablet after first loose stool, followed by $^1/_2$ caplet/tablet with each subsequent loose stool (maximum: 2 caplets or tablets/24 hours)

Children 9-11 years (60-95 lbs): 1 caplet or tablet after first loose stool, followed by $^1/_2$ caplet or tablet with each subsequent loose stool (maximum: 3 caplets or tablets/24 hours)

Children >12 years: Refer to adult dosing.

Administration: OralAdminister each dose with 4–8 ounces of water.

StorageStore between 20°C and 25°C (68°F and 77°F). Protect from light.

ContraindicationsHypersensitivity to loperamide, simethicone, or any component of the formulation; bloody or black stool

Warnings/Precautions

Other warnings/precautions:

- OTC labeling: Consult healthcare provider prior to using, if taking antibiotics, if pregnant, or in the presence of fever, mucus in stool, or a history of liver disease. Do not take if diarrhea is bloody or black. Use should be stopped and healthcare provider consulted if symptoms get worse, diarrhea persists for >2 days, or abdominal swelling or bulging occurs. Tiredness, drowsiness, or dizziness may occur; use caution if performing tasks which require mental alertness (eg, operating machinery or driving).

Geriatric Considerations

Elderly are particularly sensitive to fluid and electrolyte loss. This generally results in lethargy, weakness, and confusion. Repletion and maintenance of electrolytes and water are essential in the treatment of diarrhea. Drug therapy must be limited in order to avoid toxicity with this agent. Before treating excess gas or pain due to gas accumulation, a thorough evaluation must be made to determine cause since many bowel diseases may present with flatulence and bloating.

Pregnancy ConsiderationsSee individual agents.

Breast-Feeding ConsiderationsSee individual agents.

Adverse ReactionsSee individual agents.

Drug Interactions

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringAttempt to identify for cause of diarrhea before administering. Use caution in presence of fever, mucus in stool, or history of liver disease; avoid use if stool is bloody or black. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis medication is for relief of symptoms of diarrhea and relief from bloating, pressure, and cramps. Do not use if you have bloody or black stool. Consult health care professional before taking this medication if you have fever, mucus in stool, a history of liver disease, taking antibiotics, or are pregnant. Use exactly as directed; do not take more than recommended. Maintain adequate fluid intake to prevent dehydration caused by diarrhea. You may experience unusual tiredness, drowsiness, or dizziness (use caution when driving or engaging is potentially hazardous tasks until response to medication is known). Stop taking and consult healthcare professional if symptoms get worse, diarrhea persists for > 2 days, or abdominal pain occurs.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet: Loperamide hydrochloride 2 mg and simethicone 125 mg

Tablet, chewable: Loperamide hydrochloride 2 mg and simethicone 125 mg [mint flavor]

Generic AvailableNo

Manufacturer

McNeil Consumer

Mechanism of Action

Loperamide acts by slowing intestinal motility and by affecting water and electrolyte movement through the bowel.

Simethicone acts in the stomach and intestines by altering the surface tension of gas bubbles enabling them to coalesce thereby freeing and eliminating the gas more easily by belching or passing flatus.

Pharmacodynamics/KineticsSee individual agents.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness
Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation and dry mouth
Index TermsSimethicone and Loperamide Hydrochloride

Loperamide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Imodium® A-D may be confused with Indocin®, Ionamin®

Pronunciation(loe PER a mide)

U.S. Brand NamesDiamode [OTC]; Imodium® A-D [OTC]; K-Pek II [OTC]; Kao-Paverin® [OTC]

Canadian Brand NamesApo-Loperamide®; Diarr-Eze; Dom-Loperamide; Imodium®; Loperacap; Novo-Loperamide; PMS-Loperamine; Rhoxal-Loperamide; Rho®-Loperamine; Riva-Loperamide; Sandoz-Loperamide

Pharmacologic CategoryAntidiarrheal

Use: Labeled IndicationsTreatment of chronic diarrhea associated with inflammatory bowel disease; acute nonspecific diarrhea; increased volume of ileostomy discharge

OTC labeling: Control of symptoms of diarrhea, including Traveler’s diarrhea

Use: Unlabeled/InvestigationalCancer treatment-induced diarrhea (eg, irinotecan induced); chronic diarrhea caused by bowel resection

Dosing: Adults

Acute diarrhea: Oral: Initial: 4 mg, followed by 2 mg after each loose stool, up to 16 mg/day

Chronic diarrhea: Oral: Initial: Follow acute diarrhea; maintenance dose should be slowly titrated downward to minimum required to control symptoms (typically, 4-8 mg/day in divided doses)

Traveler's diarrhea: Oral: Initial: 4 mg after first loose stool, followed by 2 mg after each subsequent stool (maximum dose: 8 mg/day)

Irinotecan-induced diarrhea (unlabeled use): Oral: 4 mg after first loose or frequent bowel movement, then 2 mg every 2 hours until 12 hours have passed without a bowel movement. If diarrhea recurs, then repeat administration

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Acute diarrhea: Initial doses (in first 24 hours):

2-5 years (13-20 kg): 1 mg 3 times/day

6-8 years (20-30 kg): 2 mg twice daily

8-12 years (>30 kg): 2 mg 3 times/day

Maintenance: After initial dosing, 0.1 mg/kg doses after each loose stool, but not exceeding initial dosage

Traveler's diarrhea:

6-8 years: 2 mg after first loose stool, followed by 1 mg after each subsequent stool (maximum dose: 4 mg/day)

9-11 years: 2 mg after first loose stool, followed by 1 mg after each subsequent stool (maximum dose: 6 mg/day)

≥12 years: Refer to adult dosing.

Dosing: Hepatic ImpairmentNo specific guidelines available.

Dietary Considerations

Imodium® A-D [new formulation] contains sodium 10 mg/30 mL.

StorageStore at 15°C to 25°C (59°F to 77°F).

ContraindicationsHypersensitivity to loperamide or any component of the formulation; abdominal pain without diarrhea; children <2 years

Avoid use as primary therapy in acute dysentery, acute ulcerative colitis, bacterial enterocolitis, pseudomembranous colitis

Warnings/Precautions

Concerns related to adverse effects:

- Allergic reactions: Rare cases of anaphylaxis and anaphylactic shock have been reported.
- GI effects: Discontinue if constipation, abdominal pain, or ileus develop.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment because of reduced first-pass metabolism; monitor for signs of CNS toxicity.

Special populations:

- AIDS patients: Use with caution in treatment of AIDS patients; stop therapy at the sign of abdominal distention. Cases of toxic megacolon have occurred in AIDS patients with infectious colitis.

- Pediatrics: Use with caution in young children as response may be variable because of dehydration.

Other warnings/precautions:

- Appropriate use: Loperamide is a symptom-directed treatment; if an underlying diagnosis is made, other disease-specific treatment may be indicated. Should not be used if diarrhea is accompanied by high fever or blood in stool. Should not be used when inhibition of peristalsis is undesirable or dangerous. Concurrent fluid and electrolyte replacement is often necessary in all age groups depending upon severity of diarrhea.

- OTC labeling: If diarrhea lasts longer than 2 days, patient should stop taking loperamide and consult healthcare provider.

Geriatric ConsiderationsElderly are particularly sensitive to fluid and electrolyte loss. This generally results in lethargy, weakness, and confusion. Repletion and maintenance of electrolytes and water are essential in the treatment of diarrhea. Drug therapy must be limited in order to avoid toxicity with this agent.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies.

LactationEnters breast milk/not recommended.

Adverse Reactions1% to 10%:

Central nervous system: Dizziness (1%)

Gastrointestinal: Constipation (2% to 5%), abdominal cramping (<1% to 3%), nausea (<1% to 3%)

Postmarketing and/or case reports: Abdominal distention, abdominal pain, allergic reactions, anaphylactic shock, anaphylactoid reactions, angioedema, bullous eruption (rare), drowsiness, dry mouth, dyspepsia, erythema multiforme (rare), fatigue, flatulence, paralytic ileus, megacolon, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, toxic megacolon, urinary retention, urticaria, vomiting

Metabolism/Transport Effects**Substrate** (minor) of CYP2B6

Drug Interactions

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringAssess for cause of diarrhea before administering first dose. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationAdults should not take more than 8 capsules or 80 mL in 24 hours. May cause drowsiness; use caution. Increased exercise, identifying and avoiding foods that cause diarrhea, safe food preparation and storage, use of buttermilk, yogurt, or boiled milk may help reduce diarrhea. If acute diarrhea lasts longer than 48 hours, consult prescriber. Do not take if diarrhea is bloody. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to be pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet, as hydrochloride: 2 mg

Diamode, Imodium® A-D, Kao-Paverin®: 2 mg

Capsule, as hydrochloride: 2 mg

Liquid, oral, as hydrochloride: 1 mg/5 mL (5 mL, 10 mL, 120 mL)

Imodium® A-D: 1 mg/5 mL (60 mL, 120 mL) [contains alcohol, sodium benzoate, benzoic acid; cherry mint flavor]

Imodium® A-D [new formulation]: 1 mg/7.5 mL (60 mL, 120 mL, 360 mL) [contains sodium 10 mg/30 mL, sodium benzoate; creamy mint flavor]

Tablet, as hydrochloride: 2 mg

K-Pek II: 2 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Loperamide HCl)

2 mg (30): $11.99

Mechanism of ActionActs directly on circular and longitudinal intestinal muscles, through the opioid receptor, to inhibit peristalsis and prolong transit time; reduces fecal volume, increases viscosity, and diminishes fluid and electrolyte loss; demonstrates antisecretory activity.

Loperamide increases tone on the anal sphincter

Pharmacodynamics/Kinetics

Absorption: Poor

Distribution: Poor penetration into brain; low amounts enter breast milk

Metabolism: Hepatic via oxidative N-demethylation

Half-life elimination: 7-14 hours

Time to peak, plasma: Liquid: 2.5 hours; Capsule: 5 hours

Excretion: Urine and feces (1% as metabolites, 30% to 40% as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation and dry mouth

Index TermsLoperamide Hydrochloride

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International Brand NamesAlphamid (ID); Amerol (ID); Antidia (ID); Arestal (KP); Betaperamide (ZA); Binaldan (CH); Colidium (ID); Colifilm (AR); Coliper (CN); D-Stop-ratiopharm (LU); Diacure (NL); Diadium (ID); Diamide (PH); Diaperol (MX); Diarlop (IN); Diarodil (TH); Diatabs (PH); Dicap (NZ); Dissenten (IT, PL); Distrol (MY); Donafan (PE); Dyspagon (LU); Elcoman (AR); Fortasec (ES); Gastro-Stop (AU); Gastron (ZA); Harmonise (AU); Hexal Lopedium (AU); Imodium (AE, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CL, CO, CY, CZ, DE, DK, EC, EE, EG, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PH, PK, PL, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Imodonil (HK); Imosec (BR); Imosen (TW); Imossel (FR); Imossellingual (FR); Lenide-T (ZA); Licodium (ID); Lomotil (MX); Lopamide (IN); Lopedin (TW); Lopedium (HU, LU); Lopemid (IT); Loper (HK); Loperamid (PL); Loperamid-ratiopharm (LU); Loperamide-Eurogenerics (LU); Loperamide-Generics (LU); Loperamil (HK, SG); Loperhoe (DE); Loperium (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Lopermide (HK); Loperyl (IT); Lopicare (IL); Motilex (ID); Negastro (AU); Oramide (ID); Pangetan NF (CO); Perasian (TH); Regulane (AR); Rexamide (IL); Safe (TW); Salvacolina (DO, ES, GT, HN, PA, SV); Sanpo (TW); Seldiar (HR); Shilshul X2 (IL); Stoperan (PL); Stopit (IL); Suprasec (AR); Tanitril (ID); Tebloc (IT); Toban (PE); Tymedon (PH); Undiarrhea (TW); Vacontil (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Vancotil (SG); Velaral (EC)

Lopinavir and Ritonavir

Lexi-Drugs Online

English

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Potential for dispensing errors between Kaletra™ and Keppra® (levetiracetam)

Administration issues:

Children's doses are based on weight and calculated by milligrams of lopinavir. Care should be taken to accurately calculate the dose. The oral solution contains lopinavir 80 mg and ritonavir 20 mg per one mL. Children <12 years of age (and ≤40 kg) who are not taking certain concomitant antiretroviral medications will receive <5 mL of solution per dose.

Pronunciation(loe PIN a veer & rit ON uh veer)

U.S. Brand NamesKaletra®

Canadian Brand NamesKaletra®

Pharmacologic CategoryAntiretroviral Agent, Protease Inhibitor

Use: Labeled IndicationsTreatment of HIV infection in combination with other antiretroviral agents

Dosing: Adults

HIV infection (as a component of combination therapy): Oral:

Therapy-naive: Lopinavir 800 mg/ritonavir 200 mg once daily **or** lopinavir 400 mg/ritonavir 100 mg twice daily. **Note:** Once-daily dosing regimen should not be used with concurrent indinavir, maraviroc, saquinavir, phenytoin, carbamazepine, or phenobarbital therapy.

Therapy-experienced: Lopinavir 400 mg/ritonavir 100 mg twice daily. **Note:** For therapy-experienced patients receiving efavirenz or nevirapine, clinicians may use lopinavir 600 mg/ritonavir 150 mg twice daily **or** lopinavir 533 mg/ritonavir 133 mg solution twice daily (AIDS info guidelines)

Dosage adjustment for combination therapy: Oral:

*When taken with amprenavir, efavirenz, fosamprenavir, nelfinavir, or nevirapine:***Note:** Once-daily dosing regimen should not be used.

Therapy-naive and therapy-experienced patients:

Solution: Lopinavir 533 mg/ritonavir 133 mg (6.5 mL) twice daily

Tablet: Lopinavir 500 mg/ritonavir 125 mg twice daily

When taken with maraviroc (Selzentry™): Lopinavir 400 mg/ritonavir 100 mg twice daily

When taken with saquinavir (Invirase®): Lopinavir 400 mg/ritonavir 100 mg twice daily

Dosing: ElderlyInitial studies did not include enough elderly patients to determine effects based on age. Use with caution due to possible decreased hepatic, renal, and cardiac function.

Dosing: Pediatric

HIV infection (component of combination therapy): Oral: Dosage based on weight or body surface area (BSA), **presented based on lopinavir component** (maximum dose: Lopinavir 400 mg/ritonavir 100 mg).

14 days to 6 months: 16 mg/kg or 300 mg/m^2 twice daily

6 months to 18 years: **Note:** FDA-approved dose is approximately equivalent to lopinavir 230 mg/m^2 per dose.

<15 kg: 12 mg/kg twice daily

15-40 kg: 10 mg/kg twice daily

>40 kg: Lopinavir 400 mg/ritonavir 100 mg twice daily

Note: For therapy-experienced patients with suspected reduced susceptibility to lopinavir, refer to adult dosing.

Children >12 years: Therapy-naive: Lopinavir 400 mg/ritonavir 100 mg twice daily. (AIDS Info guidelines). **Note:** For therapy-experienced patients with suspected reduced susceptibility to lopinavir, refer to adult dosing.

Dosage adjustment for combination therapy: Oral:

When taken with amprenavir, efavirenz, fosamprenavir, nelfinavir, or nevirapine: **Note:** Once-daily dosing regimen should not be used.

Children 14 days to 6 months: Combination therapy with these agents is not recommended due to lack of data.

Children 6 months to 18 years: Solution or tablet (**based on mg of lopinavir component**): FDA-approved dose is approximately equivalent to lopinavir 300 mg/m^2 per dose:

<15 kg: 13 mg/kg twice daily (**Note:** Tablets are not recommended)

15-45 kg: 11 mg/kg twice daily

>45 kg: Refer to adult dosing.

When taken with maraviroc (Selzentry™): Lopinavir 400 mg/ritonavir 100 mg twice daily

When taken with saquinavir (Invirase®): Lopinavir 400 mg/ritonavir 100 mg twice daily

Dosing: Renal Impairment Has not been studied in patients with renal impairment; however, a decrease in clearance is not expected.

Dosing: Hepatic Impairment Lopinavir AUC may be increased ~30% in patients with mild-to-moderate hepatic impairment. No data available in patients with severe impairment.

Administration: Oral Once-daily dosing is not recommended in therapy-experienced patients, those receiving efavirenz, nevirapine, nelfinavir, amprenavir, or fosamprenavir, or in children <18 years of age.

Solution: Administer with food; if using didanosine, take didanosine 1 hour before or 2 hours after lopinavir/ritonavir. Administer using calibrated dosing syringe.

Tablet: May be taken with or without food. Swallow whole, do not break, crush, or chew. May be taken with didanosine when taken without food. Tablets are not recommended in patients <15 kg.

Dietary Considerations Solution should be taken with food. Tablet may be taken with or without food

Storage

Oral solution: Store at 2°C to 8°C (36°F to 46°F). Avoid exposure to excessive heat. If stored at room temperature (25°C or 77°F), use within 2 months.

Tablet: Store at USP controlled room temperature of 20°C to 25°C (68°F to 77°F). Exposure to high humidity outside of the original container for >2 weeks is not recommended.

Contraindications Hypersensitivity (eg, Stevens-Johnson syndrome, erythema multiforme) to lopinavir, ritonavir, or any component of the formulation; coadministration with medications highly dependent upon CYP3A4 for clearance for which increased levels are associated with serious and/or life-threatening events; coadministration with strong CYP3A4 inducers, including cisapride, ergot alkaloids (eg, dihydroergotamine, ergonovine, ergotamine, methylergonovine), lovastatin, midazolam (oral), pimozide, rifampin, simvastatin, St John's wort, triazolam

Allergy Considerations

- Ritonavir Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Increased cholesterol: Increases in total cholesterol and triglycerides have been reported; screening should be done prior to therapy and periodically throughout treatment.

Disease-related concerns:

- Diabetes: Changes in glucose tolerance, hyperglycemia, exacerbation of diabetes, DKA, and new-onset diabetes mellitus have been reported in patients receiving protease inhibitors.
- Hemophilia A or B: Use with caution in patients with hemophilia A or B; increased bleeding during protease inhibitor therapy has been reported.
- Hepatic impairment: May cause hepatitis and/or exacerbate pre-existing hepatic dysfunction; use with caution in patients with underlying hepatic disease, such as hepatitis B or C, cirrhosis, or unspecified hepatic impairment.
- Pancreatitis: Use with caution in patients with increased triglycerides; pancreatitis has been observed. Patients with history of pancreatitis may be at increased risk. Monitor serum lipase and amylase.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); contraindicated with certain CYP3A4 substrates and inducers (see Contraindications); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

Special populations:

- Pediatrics: Safety and efficacy have not been established for children <14 days of age.

Dosage form specific issues:

- Oral solution: The oral solution is highly concentrated and contains large amounts of alcohol. Healthcare providers should pay special attention to accurate calculation, measurement, and administration of dose. Overdose in a child may lead to lethal alcohol toxicity.

Other warnings/precautions:

- Appropriate use: Once-daily dosing is not recommended in therapy-experienced patients, those receiving efavirenz, nevirapine, nelfinavir, amprenavir, or fosamprenavir, or in children <18 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events were not seen in animal studies, except at doses which were also maternally toxic. Safety and pharmacokinetic studies of the tablet in pregnant women are not completed. Preliminary information suggests increased dosage may be needed during pregnancy, although specific recommendations with the tablet formulation are not yet available. Once-daily dosing is not recommended during pregnancy. Lopinavir/ritonavir crosses the placenta, however, teratogenic effects have not been observed in humans. The Perinatal HIV Guidelines Working Group considers this a recommended combination for use during pregnancy. Pregnancy and protease inhibitors are both associated with an increased risk of hyperglycemia. Glucose levels should be closely monitored. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse ReactionsData presented for short- and long-term combination antiretroviral therapy in both protease inhibitor experienced and naïve patients.

>10%:

Dermatologic: Rash (children 12%; adults up to 5%)

Endocrine & metabolic: Hypercholesterolemia (3% to 39%), triglycerides increased (4% to 36%)

Gastrointestinal: Diarrhea (5% to 28%), abnormal taste/taste perversion (children 22%; adults <2%), vomiting (children 21%; adults 2% to 6%), nausea (5% to 16%), abdominal pain (2% to 11%)

Hepatic: GGT increased (10% to 29%), ALT increased (grade 3/4: 3% to 11%)

2% to 10%:

Cardiovascular: Hypertension (up to 2%), vein distension (up to 3%)

Central nervous system: Headache (2% to 6%), insomnia (up to 3%), chills (up to 2%), depression (up to 2%), fever (2%)

Endocrine & metabolic: Amenorrhea (up to 5%), hyperglycemia (1% to 5%), hyperuricemia (up to 5%), sodium decreased or increased (3% children), hypogonadism (males: up to 2%), inorganic phosphorus decreased (1% to 2%), libido decreased (up to 2%)

Gastrointestinal: Amylase increased (3% to 8%), dyspepsia (up to 6%), flatulence (1% to 4%), weight loss (up to 3%), dysphagia (up to 2%), anorexia (up to 2%)

Hematologic: Platelets decreased (grade 3/4: 4% children), neutropenia (grade 3/4: 1% to 5%)

Hepatic: AST increased (grade 3/4: 2% to 10%), bilirubin increased (1%, children 3%)

Neuromuscular & skeletal: Weakness (up to 9%), myalgia (up to 2%), paresthesia (up to 2%)

Respiratory: Bronchitis (up to 2%)

<2%:

Cardiovascular: Atrial fibrillation, cerebral infarction, chest pain, deep vein thrombosis, edema, facial edema, MI, palpitation, peripheral edema, postural hypotension, vasculitis

Central nervous system: Abnormal dreams, abnormal thinking, agitation, amnesia, anxiety, apathy, ataxia, confusion, dizziness, emotional lability, encephalopathy, extrapyramidal symptoms, facial paralysis, malaise, migraine, nervousness, neuropathy, peripheral neuritis, seizure, somnolence, vertigo

Dermatologic: Acne, alopecia, benign neoplasm, dry skin, eczema, exfoliative dermatitis, furunculosis, maculopapular rash, nail disorder, pruritus, seborrhea, skin discoloration, skin ulcer, striae

Endocrine & metabolic: Breast enlargement, Cushing's syndrome, diabetes mellitus, glucose intolerance, gynecomastia, hypothyroidism, lactic acidosis

Gastrointestinal: Appetite increased, constipation, dehydration, enteritis, enterocolitis, eructation, esophagitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, hemorrhagic colitis, mouth ulceration, pancreatitis, periodontitis, sialadenitis, stomatitis, ulcerative stomatitis, weight gain, xerostomia

Genitourinary: Abnormal ejaculation, impotence

Hematologic: Anemia, leukopenia, lymphadenopathy

Hepatic: Cholangitis, cholecystitis, fatty deposits, hepatic dysfunction, hepatitis, hepatomegaly, jaundice, liver tenderness

Local: Thrombophlebitis

Neuromuscular & skeletal: Arthralgia, arthrosis, back pain, dyskinesia, hypertonia, joint disorder, myasthenia, paresthesia, tremor

Ocular: Abnormal vision, eye disorder

Otic: Otitis media, tinnitus

Renal: Kidney calculus, nephritis, urine abnormality

Respiratory: Asthma, cough, dyspnea, lung edema, pharyngitis, rhinitis, sinusitis

Miscellaneous: Allergic reaction, avitaminosis, bacterial infection, bone necrosis, cyst, diaphoresis, flu-like syndrome, hypertrophy, obesity, viral infection

Postmarketing and/or case reports: Body fat redistribution, bradyarrhythmia, erythema multiforme, immune reconstitution syndrome, neoplasm, Stevens-Johnson syndrome

Metabolism/Transport Effects

Lopinavir: **Substrate** of CYP3A4 (major); **Inhibits** P-glycoprotein

Ritonavir: **Substrate** of CYP1A2 (minor), 2B6 (minor), 2D6 (major), 3A4 (major); **Inhibits** CYP2C8 (strong), 2C9 (weak), 2C19 (weak), 2D6 (strong), 2E1 (weak), 3A4 (strong); **Induces** CYP1A2 (weak), 2C8 (weak), 2C9 (weak), 3A4 (weak)

Drug Interactions

Abacavir: Protease Inhibitors may decrease the serum concentration of Abacavir. *Risk C: Monitor therapy*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amiodarone: Protease Inhibitors may decrease the metabolism of Amiodarone. *Risk X: Avoid combination*

Antacids: May decrease the absorption of Protease Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Atovaquone: Ritonavir may decrease the serum concentration of Atovaquone. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Protease Inhibitors may decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

BuPROPion: Ritonavir may decrease the serum concentration of BuPROPion. *Risk C: Monitor therapy*

BuPROPion: Lopinavir may decrease the serum concentration of BuPROPion. Concentrations of the active metabolite, hydroxybupropion, may also be decreased. *Risk C: Monitor therapy*

Calcium Channel Blockers (Dihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Protease Inhibitors. Protease Inhibitors may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cisapride: Protease Inhibitors may decrease the metabolism of Cisapride. The resultant increase in serum cisapride concentrations may result in QTc prolongation and malignant cardiac arrhythmias. *Risk X: Avoid combination*

Clarithromycin: Protease Inhibitors may diminish the therapeutic effect of Clarithromycin. Specifically, certain protease inhibitors may decrease formation of the active 14-hydroxy-clarithromycin metabolite, which may negatively impact clarithromycin effectiveness vs. H. influenzae and other non-MAC infections. Protease Inhibitors may increase the serum concentration of Clarithromycin. Clarithromycin dose adjustment in renally impaired patients may be needed. Clarithromycin may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Codeine: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): Protease Inhibitors may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk D: Consider therapy modification*

CycloSPORINE: Protease Inhibitors may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

CYP2C19 Substrates: CYP2C19 Inducers (Strong) may increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Strong) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Strong) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Darunavir: Lopinavir may decrease the serum concentration of Darunavir. Darunavir may increase the serum concentration of lopinavir *Risk X: Avoid combination*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Delavirdine: Protease Inhibitors may decrease the serum concentration of Delavirdine. Delavirdine may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Didanosine: Lopinavir may decrease the serum concentration of Didanosine. This interaction refers only to lopinavir/ritonavir oral solution, which must be taken with food, and is principally the result of a food-didanosine interaction. Management: Didanosine should be administered 1 hour prior to or 2 hours after administration of lopinavir/ritonavir oral solution (which must be taken with food). Didanosine and lopinavir/ritonavir tablets can be administered together. *Risk D: Consider therapy modification*

Digoxin: Protease Inhibitors may increase the serum concentration of Digoxin. Increased serum concentrations of digoxin may increase risk of AV nodal blockade. *Risk C: Monitor therapy*

Disulfiram: May enhance the adverse/toxic effect of Ritonavir. This is specific for the lopinavir/ritonavir (Kaletra) oral solution due to its alcohol content (42%). Management: Concomitant use of Kaletra (lopinavir/ritonavir) oral solution and disulfiram should be avoided. Kaletra contains 42% alcohol. *Risk X: Avoid combination*

Dronabinol: Ritonavir may increase the serum concentration of Dronabinol. *Risk C: Monitor therapy*

Efavirenz: May decrease the serum concentration of Lopinavir. Management: An increased dose of lopinavir/ritonavir to 500mg/125mg (for tablets) or 533mg/133mg (for oral solution) twice daily is recommended when used concurrently with efavirenz. Avoid once daily use of lopinavir/ritonavir when used with efavirenz. *Risk D: Consider therapy modification*

Enfuvirtide: Protease Inhibitors may increase the serum concentration of Enfuvirtide. Enfuvirtide may increase the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

Eplerenone: Protease Inhibitors may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Protease Inhibitors may decrease the metabolism of Ergot Derivatives. **Exceptions:** Cabergoline. *Risk X: Avoid combination*

Etravirine: Ritonavir may decrease the serum concentration of Etravirine. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

FentaNYL: Protease Inhibitors may decrease the metabolism of FentaNYL. *Risk C: Monitor therapy*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Flecainide: Ritonavir may decrease the metabolism of Flecainide. *Risk X: Avoid combination*

Fusidic Acid: Protease Inhibitors may decrease the metabolism of Fusidic Acid. Fusidic Acid may decrease the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Garlic: May decrease the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Protease Inhibitors may increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. **Exceptions:** Fluvastatin. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

LamoTRIgine: Ritonavir may decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Maraviroc: Lopinavir may increase the serum concentration of Maraviroc. Management: Reduce maraviroc dose to 150mg twice daily when maraviroc is used concurrently with lopinavir/ritonavir. *Risk D: Consider therapy modification*

Meperidine: Protease Inhibitors may enhance the adverse/toxic effect of Meperidine. Protease Inhibitors may decrease the serum concentration of Meperidine. Concentrations of the toxic Normeperidine metabolite may be increased. *Risk D: Consider therapy modification*

Methadone: Protease Inhibitors may decrease the metabolism of Methadone. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nefazodone: Protease Inhibitors may decrease the metabolism of Nefazodone. *Risk C: Monitor therapy*

Nevirapine: May increase the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): May diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May decrease the serum concentration of Lopinavir. Lopinavir may decrease the serum concentration of Phenytoin. Management: The manufacturer of lopinavir/ritonavir recommends avoiding once-daily administration if used together with phenytoin. *Risk D: Consider therapy modification*

Phenytoin: May decrease the serum concentration of Ritonavir. Ritonavir may decrease the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Phosphodiesterase 5 Inhibitors: Protease Inhibitors may decrease the metabolism of Phosphodiesterase 5 Inhibitors. Management: Dose restrictions for tadalafil, and/or sildenafil and vardenafil are recommended in combination with ritonavir, atazanavir, indinavir, darunavir and saquinavir. Consult specific prescribing information for detailed recommendations. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Protease Inhibitors may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Propafenone: Ritonavir may decrease the metabolism of Propafenone. *Risk X: Avoid combination*

Protease Inhibitors: May increase the serum concentration of other Protease Inhibitors. Management: Atazanavir--indinavir combination contraindicated. Amprenavir oral solution not recommended with ritonavir oral solution; tipranavir/ritonavir or atazanavir/ritonavir not recommended with other protease inhibitors. Other combos may require dose changes. *Risk D: Consider therapy modification*

QuiNIDine: Protease Inhibitors may decrease the metabolism of QuiNIDine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: Protease Inhibitors may decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Protease Inhibitors may increase the serum concentration of Sirolimus. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Protease Inhibitors. *Risk X: Avoid combination*

Tacrolimus: Protease Inhibitors may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Strong) may decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

Temsirolimus: Protease Inhibitors may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tenofovir: Lopinavir may enhance the nephrotoxic effect of Tenofovir. Lopinavir may increase the serum concentration of Tenofovir. *Risk C: Monitor therapy*

Tetrabenazine: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Tetrabenazine. Specifically, concentrations of the active alpha- and beta-dihydrotetrabenazine metabolites may be increased. Management: Tetrabenazine dose should be reduced by 50% when starting a strong CYP2D6 inhibitor. Maximum tetrabenazine dose is 50mg/day when used with a strong CYP2D6 inhibitor. *Risk D: Consider therapy modification*

Theophylline Derivatives: Protease Inhibitors may decrease the serum concentration of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

TraZODone: Protease Inhibitors may increase the serum concentration of TraZODone. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Protease Inhibitors may increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Valproic Acid: Protease Inhibitors may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

VinBLAStine: Lopinavir may increase the serum concentration of VinBLAStine. Management: Monitor closely for signs and symptoms of vinblastine toxicity; consider temporary interruption of lopinavir/ritonavir antiviral therapy if patients develop significant toxicity with concurrent use. *Risk D: Consider therapy modification*

VinCRIStine: Lopinavir may increase the serum concentration of VinCRIStine. Management: Monitor closely for signs and symptoms of vincristine toxicity; consider temporary interruption of lopinavir/ritonavir antiviral therapy if patients develop significant toxicity with concurrent use. *Risk D: Consider therapy modification*

Voriconazole: Ritonavir may increase the metabolism of Voriconazole. High-dose ritonavir (400 mg every 12 hours) is contraindicated. Use caution with lower doses. *Risk X: Avoid combination*

Voriconazole: Lopinavir may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Warfarin: Lopinavir may decrease the serum concentration of Warfarin. *Risk C: Monitor therapy*

Warfarin: Ritonavir may decrease the serum concentration of Warfarin. *Risk C: Monitor therapy*

Zidovudine: Protease Inhibitors may decrease the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Moderate- to high-fat meals increase the C_{max} and AUC of lopinavir/ritonavir oral solution; no significant changes observed with oral tablets.

Herb/Nutraceutical: St John's wort may decrease levels of protease inhibitors and lead to possible resistance; concurrent use is contraindicated.

Monitoring ParametersTriglycerides, cholesterol, LFTs, electrolytes, basic HIV monitoring, viral load and CD4 count, glucose
Nursing: Physical Assessment/MonitoringSee individual agent for Ritonavir.
Patient EducationSee individual agent for Ritonavir.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral:

Kaletra®: Lopinavir 80 mg and ritonavir 20 mg per mL (160 mL) [contains alcohol 42.4%]

Tablet:

Kaletra®:

Lopinavir 100 mg and ritonavir 25 mg

Lopinavir 200 mg and ritonavir 50 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Solution (Kaletra)

400-100 mg/5 mL (160): $419.98

Tablets (Kaletra)

100-25 mg (30): $99.99

200-50 mg (30): $198.99

Mechanism of ActionA coformulation of lopinavir and ritonavir. The lopinavir component is the active inhibitor of HIV protease. Lopinavir inhibits HIV protease and renders the enzyme incapable of processing polyprotein precursor which leads to production of noninfectious immature HIV particles. The ritonavir component inhibits the CYP3A metabolism of lopinavir, allowing increased plasma levels of lopinavir.
Pharmacodynamics/Kinetics

Ritonavir: See Ritonavir monograph.

Lopinavir:

Protein binding: 98% to 99%; decreased with mild-to-moderate hepatic dysfunction

Metabolism: Hepatic via CYP3A4; 13 metabolites identified

Half-life elimination: 5-6 hours

Time to peak, plasma: ~4 hours

Excretion: Feces (83%, 20% as unchanged drug); urine (10%; <3% as unchanged drug)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV
- Perinatal HIV Guidelines

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause abnormal dreams, agitation, amnesia, anxiety, ataxia, confusion, dizziness, emotional lability, insomnia, nervousness, somnolence, and abnormal thinking

Mental Health: Effects on Psychiatric TreatmentContraindicated with ergot derivatives, midazolam, pimozide, and triazolam. Avoid concurrent use with St John's wort; may lead to loss of virologic response and/or resistance. Dyslipidemia is common; use caution with clozapine, olanzapine, and quetiapine. Diarrhea is common; use caution with lithium, valproic acid, and SSRIs. Increased LFTs is common; use caution with olanzapine and valproic acid. May cause hyperglycemia; use caution with clozapine and olanzapine. May cause thrombocytopenia; use caution with valproic acid. Carbamazepine, phenytoin, and phenobarbital may decrease levels of lopinavir. Ritonavir may increase levels of zolpidem. The solution contains ethanol; use caution with disulfiram.

Index TermsRitonavir and Lopinavir

References

"Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection," November 3, 2008. Available at http://www.aidsinfo.nih.gov

"Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States," July 8, 2008. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection," July 29, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesKaletra (AE, AR, AT, AU, BB, BE, BG, BH, BM, BO, BR, BS, BZ, CH, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, FI, FR, GB, GR, GT, GY, HK, HN, IE, IL, IQ, IR, IT, JM, JO, KP, KW, LB, LY, MX, MY, NI, NL, NO, NZ, OM, PA, PE, PR, PT, PY, QA, RU, SA, SE, SG, SR, SV, SY, TH, TR, TT, TW, UY, VE, YE)

LOPP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Lymphoma, Hodgkin's Disease]

Regimen UseLymphoma, Hodgkin's disease

Regimen

Chlorambucil: Oral: 10 mg/day days 1 to 10

[total dose/cycle = 100 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day (maximum 2 mg) days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Procarbazine: Oral: 100 mg/m^2/day days 1 to 10

[total dose/cycle = 1000 mg/m^2]

Prednisone: Oral: 25 mg/m^2/day (maximum 60 mg) days 1 to 14

[total dose/cycle = 350 mg/m^2]

or

Prednisolone: Oral: 25 mg/m^2/day (maximum 60 mg) days 1 to 14

[total dose/cycle = 350 mg/m^2]

Repeat cycle every 28 days

References

Hancock BW, âRandomised Study of MOPP (Mustine, Oncovin, Procarbazine, Prednisone) Against LOPP (Leukeran Substituted for Mustine) in Advanced Hodgkin's Disease. British National Lymphoma Investigation,â *Radiother Oncol*, 1986, 7(3):215-21.[PubMed 3544084]

Loratadine and Pseudoephedrine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(lor AT a deen & soo doe e FED rin)
U.S. Brand NamesAlavert™ Allergy and Sinus [OTC]; Claritin-D® 12 Hour Allergy & Congestion [OTC]; Claritin-D® 24 Hour Allergy & Congestion [OTC]
Canadian Brand NamesChlor-Tripolon ND®; Claritin® Extra; Claritin® Liberator
Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation
Use: Labeled IndicationsTemporary relief of symptoms of seasonal allergic rhinitis, other upper respiratory allergies, or the common cold
Dosing: AdultsSeasonal allergic rhinitis/nasal congestion:

Oral: 1 tablet every 12 hours

Extended release: 1 tablet daily

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricSeasonal allergic rhinitis/nasal congestion: Children ≥12 years: Refer to adult dosing.
Dosing: Renal ImpairmentCl_{cr} <30 mL/minute:

Claritin-D® 12-Hour: 1 tablet daily

Claritin-D® 24-Hour: 1 tablet every other day

Dosing: Hepatic ImpairmentShould be avoided.
Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

ContraindicationsHypersensitivity to loratadine, pseudoephedrine, or any component of the formulation; use with or within 14 days of MAO inhibitors
Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Diabetes: Use with caution in patients with diabetes mellitus.
- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment recommended.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Dosage form specific issues:

- Claritin-D® 24-Hour: Patients with swallowing difficulties (eg, upper GI narrowing or abnormal esophageal peristalsis) should not use Claritin-D® 24-Hour.

Other warnings/precautions:

- Self-medication (OTC use): When used for self medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever. Discontinue and contact healthcare provider if nervousness, dizziness or sleeplessness occur.

Pregnancy Risk FactorB
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/not recommended
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsLoratadine: **Substrate** (minor) of CYP2D6, 3A4; **Inhibits** CYP2C8 (weak), 2C19 (moderate), 2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, extended release: Loratadine 10 mg and pseudoephedrine sulfate 240 mg

Alavert™ Allergy and Sinus: Loratadine 5 mg and pseudoephedrine sulfate 120 mg

Claritin-D® 12 Hour Allergy & Congestion: Loratadine 5 mg and pseudoephedrine sulfate 120 mg [contains calcium 30 mg/tablet]

Claritin-D® 24 Hour Allergy & Congestion: Loratadine 10 mg and pseudoephedrine sulfate 240 mg [contains calcium 25 mg/tablet]

Generic AvailableYes

ManufacturerSchering-Plough Corp

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Loratadine
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDizziness, drowsiness, nervousness, and insomnia are common; may cause anxiety or depression; may rarely cause hallucinations

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors

Index TermsPseudoephedrine and Loratadine

International Brand NamesAiret (CO); Aldisa-SR (ID); Alergicol LP (PE); Allerpid (MY); Bonalerg - D (GT); Carinox (MY); Clariflu (MX); Clarifriol (MX); Clarinase (AE, BH, CY, EG, HK, ID, IL, IQ, IR, JO, KP, KW, LB, LY, MY, OM, PH, QA, SA, SY, TH, TW, VE, YE); Clarinase 24 Hour Extended Release (MY, SG); Clarinase 24 Hour Relief (AU); Clarinase Repetabs (CL, TH); Clarityne (MX); Clarityne D Repetabs (CO, EC, PE); Clarityne-D (CR, DO, GR, GT, HN, NI, PA, PY, SV, UY); Dimegan D (MX); Gralddep (MX); Lertamine D (MX); Loracert P (CO); Lorfast-D (IN); Lorimox (MX); Rhilor D (PK); Rhinase (PH); Rhinos SR (ID, PH); Sensibit (MX); Talorat D (CR, DO, GT, HN, NI, PA, SV); Theraflu (MX)

Loratadine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Claritin® may be confused with clarithromycin

Pronunciation(lor AT a deen)
U.S. Brand NamesAlavert™ Allergy Relief 24-Hour [OTC]; Alavert™ [OTC]; Allergy Relief [OTC]; Claritin® 24 Hour Allergy [OTC]; Claritin® Children's Allergy [OTC]; Claritin® Children's [OTC]; Claritin® Hives Relief [OTC]; Dimetapp® ND Children's [OTC]; Loradamed [OTC]; Tavist® ND ALLERGY [OTC]
Canadian Brand NamesApo-Loratadine®; Claritin®; Claritin® Kids
Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation
Use: Labeled IndicationsRelief of nasal and non-nasal symptoms of seasonal allergic rhinitis; treatment of chronic idiopathic urticaria
Dosing: AdultsSeasonal allergic rhinitis, chronic idiopathic urticaria: Oral: 10 mg/day
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Children 2-5 years: Seasonal allergic rhinitis, chronic idiopathic urticaria: Oral: 5 mg once daily

Children ≥6 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} ≤30 mL/minute:

Children 2-5 years: 5 mg every other day

Children ≥6 years and Adults: 10 mg every other day

Dosing: Hepatic Impairment

Elimination half-life increases with severity of disease.

Children 2-5 years: 5 mg every other day

Children ≥6 years and Adults: 10 mg every other day

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralTake on an empty stomach.
Dietary ConsiderationsTake on an empty stomach. Alavert® and Dimetapp® Children's ND contain phenylalanine 8.4 mg per 10 mg tablet. Claritin® Children's Allergy 5 mg contains phenylalanine 1.4 mg per tablet.
StorageStore at 2°C to 25°C (36°F to 77°F).

Rapidly-disintegrating tablets: Use within 6 months of opening foil pouch, and immediately after opening individual tablet blister. Store in a dry place.

ContraindicationsHypersensitivity to loratadine or any component of the formulation
Warnings/Precautions

Disease-related concerns:

• Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment recommended.

• Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Special populations:

• Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Dosage form specific issues:

• Phenylalanine: Some products may contain phenylalanine.

Geriatric ConsiderationsLoratadine is a nonsedating antihistamines; because of its low incidence of side effects, it seems to be a good choice in the elderly. However, there is a wide variation in loratadine half-life reported in the elderly and this should be kept in mind when initiating dosing. Because of its new OTC status, patients should be advised of appropriate use.

Pregnancy Risk FactorB

Pregnancy ConsiderationsLoratadine was not found to be teratogenic in animal studies. There are no adequate and well-controlled studies in pregnant woman; use during pregnancy only if clearly needed.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Adverse Reactions

Adults:

Central nervous system: Headache (12%), somnolence (8%), fatigue (4%)

Gastrointestinal: Xerostomia (3%)

Children:

Central nervous system: Nervousness (4% ages 6-12 years), fatigue (3% ages 6-12 years, 2% to 3% ages 2-5 years), malaise (2% ages 6-12 years)

Dermatologic: Rash (2% to 3% ages 2-5 years)

Gastrointestinal: Abdominal pain (2% ages 6-12 years), stomatitis (2% to 3% ages 2-5 years)

Neuromuscular & skeletal: Hyperkinesia (3% ages 6-12 years)

Ocular: Conjunctivitis (2% ages 6-12 years)

Respiratory: Wheezing (4% ages 6-12 years), dysphonia (2% ages 6-12 years), upper respiratory infection (2% ages 6-12 years), epistaxis (2% to 3% ages 2-5 years), pharyngitis (2% to 3% ages 2-5 years)

Miscellaneous: Flu-like syndrome (2% to 3% ages 2-5 years), viral infection (2% to 3% ages 2-5 years)

Adults and Children: <2%: Agitation, altered lacrimation, altered micturition, altered salivation, altered taste, amnesia, angioneurotic edema, anorexia, anxiety, appetite increased, arthralgia, back pain, blepharospasm, blurred vision, breast pain, bronchitis, bronchospasm, chest pain, confusion, constipation, cough, depression, dermatitis, diaphoresis increased, diarrhea, dizziness, dry hair, dry skin, dysmenorrhea, dyspepsia, dysphonia, dyspnea, earache, eye pain, flatulence, flushing, gastritis, hemoptysis, hiccup, hypertension, hypertonia, hypoesthesia, hypotension, impaired concentration, impotence, insomnia, irritability, laryngitis, leg cramps, libido decreased, loose stools, malaise, menorrhagia, migraine, myalgia, nasal dryness, nausea, palpitation, paresthesia, paroniria, photosensitivity, pruritus, purpura, rigors, sinusitis, sneezing, supraventricular tachyarrhythmia, syncope, tachycardia, thirst, tinnitus, tremor, urinary discoloration, urinary incontinence, urinary retention, urticaria, vaginitis, vertigo, vomiting, weakness, weight gain

Postmarketing and/or case reports: Abnormal hepatic function, alopecia, anaphylaxis, breast enlargement, erythema multiforme, hepatitis, hepatic necrosis, jaundice, peripheral edema, seizure, thrombocytopenia

Metabolism/Transport Effects**Substrate** (minor) of CYP2D6, 3A4; **Inhibits** CYP2C8 (weak), 2C19 (moderate), 2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (although sedation is limited with loratadine, may increase risk of CNS depression).

Food: Increases bioavailability and delays peak.

Herb/Nutraceutical: St John's wort may decrease loratadine levels.

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake as directed; do not exceed recommended dose. Avoid use of other depressants, alcohol, or sleep-inducing medications unless approved by prescriber. You may experience drowsiness or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or dry mouth or nausea (small frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help). Report persistent dizziness, sedation, or seizures; chest pain, rapid heartbeat, or palpitations; swelling of face, mouth, lips, or tongue; respiratory difficulty; changes in urinary pattern; yellowing of skin or eyes; dark urine or pale stool; or lack of improvement or worsening or condition. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Rapidly-disintegrating tablets: Place tablet on tongue; it dissolves rapidly. May be used with or without water. Use within 6 months of opening foil pouch, and immediately after opening individual tablet blister.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral: 5 mg/5 mL (120 mL)

Syrup, oral: 1 mg/mL (120 mL)

Allergy Relief: 1 mg/mL (120 mL)

Claritin® Children's: 5 mg/5 mL (60 mL, 120 mL) [alcohol free, dye free, sugar free; contains propylene glycol, sodium benzoate, and sodium 6 mg/5 mL; grape flavor]

Claritin® Children's Allergy: 1 mg/mL (120 mL) [alcohol free, dye free; contains propylene glycol and sodium benzoate; fruit flavor]

Tablet, oral: 10 mg

Alavert™: 10 mg

Claritin® 24 Hour Allergy: 10 mg

Claritin® Hives Relief: 10 mg

Loradamed: 10 mg

Tavist® ND ALLERGY: 10 mg

Tablet, chewable, oral:

Claritin® Children's Allergy: 5 mg [contains phenylalanine 1.4 mg/tablet; grape flavor]

Tablet, orally disintegrating, oral:

Alavert™ Allergy Relief 24-Hour: 10 mg [contains phenylalanine 8.4 mg/tablet]

Dimetapp® ND Children's: 10 mg [contains phenylalanine 8.4 mg/tablet]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, orally-disintegrating (Claritin Reditabs)

10 mg (10): $10.19

Tablets (Claritin)

10 mg (30): $29.99

Tablets (Loratadine)

10 mg (30): $21.99

Mechanism of ActionLong-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonistic properties

Pharmacodynamics/Kinetics

Onset of action: 1-3 hours

Peak effect: 8-12 hours

Duration: >24 hours

Absorption: Rapid

Distribution: Significant amounts enter breast milk

Metabolism: Extensively hepatic via CYP2D6 and 3A4 to active metabolite

Half-life elimination: 12-15 hours

Excretion: Urine (40%) and feces (40%) as metabolites

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and stomatitis in children (2-5 years).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause anxiety or depression

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsAt recommended doses, loratadine has not been associated with clinically relevant QT prolongation or ventricular arrhythmias (eg, torsade de pointes). Loratadine has been associated with supraventricular tachyarrhythmia.

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International Brand NamesAerotina (AR); Albatrina (MX); Alegra (PL); Alerfan (PL); Alerfast (PE); Aleric (PL); Alernitis (ID); Alledine (AU); Allereze (AU); Allergyx (IL); Allerta (PH); Allertyn (HK, SG); Allohex (ID); Ambrace (HK); Anlos (ID); Ardin (SG); Bonalerg (GT); Caradine (TH); Carin (MY); Civeran (ES); Clalodine (TH); Claratyne (AU); Clarid (TH); Clarihist (PH); Clarin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Clarinese (ZA); Claritin (BR, ID, PH); Claritine (AE, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CY, CZ, EE, EG, ET, GH, GM, GN, GY, HN, HR, HU, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PK, PL, PT, QA, RU, SA, SC, SD, SL, SN, SR, SY, TN, TR, TT, TZ, UG, YE, ZA, ZM, ZW); Clarityn (AT, DK, FI, GB, IE, IT, NO, SE); Clarityne (AR, CL, CN, CO, CR, DO, EC, ES, FR, GR, GT, HK, HN, KP, MX, MY, PA, PE, PY, SV, TH, TW, UY, VE); CPLoradine (HK); Cronitin (ID); Curyken (MX); Dimegan (MX); Dymaten (MX); Efectine (MX); Erolin (BB, BM, BS, BZ, GY, JM, SR, TT); Ezede (SG); Finska (TW); Flonidan (PL); Frenaler (CN); Fristamin (IT); Genadine (TW); Halodin (TH); Hislorex (ID); Histalor (SG); Inigrin (MX); J-Tadine (KP); Klarihist (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Laredine (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Laritol (MX); Laura (ZA); Lertamine (MX); Lindine (TH); Lisino (DE); Lobeta (DE); Lodain (KP); Lora (TW); Lora-Lich (DE); Lora-Tabs (NZ); Lorabasics (DE); Loracert (CO); Loraclar (DE); Loraclear Hayfever Relief (NZ); Loraderm (DE); Loradex (PH); Loradin (HK); Loradine (PH); Lorahexal (PL); Lorahist (PH); Loralerg (DE); Loram (PL); Lorano (DE, PH, ZA); Loranox (TH); Lorapozzan (PL); Lorastine (IL); Lorastyne (AU); Loratadura (DE); Loratadyna (PL); Loratan (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE); Loratine (PL); Loratio (PL); Loraton (HK); Loratrim (IL); Loratyne (PH); Lordam (PH); Loremix (BR); Lorfast (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Loridin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SG, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Lorihis (ID); Lorimox (MX); Lorin (IN); Lorita (TH); Loropoz (PL); Lotadine (HK); Lotan (MX); Lotarin (TW); Mosedin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Nalergine (PL); Neoalexil (MX); Noratin (KP); Nufalora (ID); Onemin (PH); Optimin (ES); Restamine (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ridamin (SG, TH); Rihest (ID); Rinityn (PH, SG); Rityne (TH); Roletra (SG); Rotadin (PL); Rotifar (HK); Sanelor (LU); Sensibit (MX); Sohotin (ID); Talorat (CR, DO, GT, HN, NI, PA, SV); Tidilor (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Toradine (TH); Velodan (ES); Vincidal (MX); Zeos (ID)

LORazepam

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

LORazepam may be confused with ALPRAZolam, clonazePAM, diazepam, temazepam

Ativan® may be confused with Atarax®, Atgam®, Avitene®

Injection dosage form contains propylene glycol. Monitor for toxicity when administering continuous lorazepam infusions.

Pronunciation(lor A ze pam)
U.S. Brand NamesAtivan®; Lorazepam Intensol®
Canadian Brand NamesApo-Lorazepam®; Ativan®; Lorazepam Injection, USP; Novo-Lorazepam; Nu-Loraz; PHL-Lorazepam; PMS-Lorazepam; Riva-Lorazepam
Pharmacologic CategoryBenzodiazepine
Use: Labeled Indications

Oral: Management of anxiety disorders or short-term (≤4 months) relief of the symptoms of anxiety or anxiety associated with depressive symptoms

I.V.: Status epilepticus, preanesthesia for desired amnesia

Use: Unlabeled/InvestigationalEthanol detoxification; insomnia; psychogenic catatonia; partial complex seizures; agitation (I.V.); antiemetic adjunct
Use: DentalShort-term relief of anxiety prior to dental appointment
Dosing: Adults

Antiemetic: Oral, I.V. (**Note:** May be administered sublingually; not a labeled route): 0.5-2 mg every 4-6 hours as needed

Anxiety and sedation: Oral: 1-10 mg/day in 2-3 divided doses; usual dose: 2-6 mg/day in divided doses; initial dose should not exceed 2 mg in debilitated patients

Insomnia: Oral: 2-4 mg at bedtime

Preoperative:

I.M.: 0.05 mg/kg administered 2 hours before surgery; maximum: 4 mg/dose

I.V.: 0.044 mg/kg 15-20 minutes before surgery; usual maximum: 2 mg/dose

Operative amnesia: I.V.: Up to 0.05 mg/kg; maximum: 4 mg/dose

Status epilepticus: I.V.: 4 mg/dose given slowly over 2-5 minutes; may repeat in 5-10 minutes; usual maximum dose: 8 mg

Rapid tranquilization of agitated patient (administer every 30-60 minutes):

Oral: 1-2 mg

I.M.: 0.5-1 mg

Average total dose for tranquilization: 4-8 mg

Agitation in the ICU patient (unlabeled):

I.V.: 0.02-0.06 mg/kg every 2-6 hours

I.V. infusion: 0.01-0.1 mg/kg/hour

Concurrent use of probenecid or valproic acid: Reduce lorazepam dose by 50%

Dosing: ElderlyAnxiety and sedation: Oral, I.V.: 0.5-4 mg/day; refer to adult dosing for other indications. Dose selection should generally be on the low end of the dosage range (ie, initial dose not to exceed 2 mg)
Dosing: Pediatric

Antiemetic: Children 2-15 years (unlabeled): I.V.: 0.05 mg/kg (up to 2 mg/dose) prior to chemotherapy

Anxiety and sedation: Infants and Children (unlabeled except for oral use in children >12 years): Oral, I.V.: Usual: 0.05 mg/kg/dose (range: 0.02-0.09 mg/kg) every 4-8 hours

Sedation (preprocedure): Infants and Children (unlabeled):

Oral, I.M., I.V.: Usual: 0.05 mg/kg; range: 0.02-0.09 mg/kg

I.V.: May use smaller doses (eg, 0.01-0.03 mg/kg) and repeat every 20 minutes, as needed to titrate to effect

Status epilepticus: I.V.:

Infants and Children (unlabeled): 0.05-0.1 mg/kg slow I.V. over 2-5 minutes, do not exceed 4 mg/single dose; may repeat second dose of 0.05 mg/kg slow I.V. in 5-10 minutes if needed

Adolescents: 0.07 mg/kg slow I.V. over 2-5 minutes; maximum: 4 mg/dose; may repeat in 5-10 minutes

Dosing: Renal ImpairmentI.V.: Risk of propylene glycol toxicity. Monitor closely if using for prolonged periods or at high doses.

Dosing: Hepatic ImpairmentUse cautiously.

Administration: I.M.Should be administered deep into the muscle mass.

Administration: I.V.Continuous infusion solutions should have an in-line filter and the solution should be checked frequently for possible precipitation. Avoid intra-arterial administration. Monitor I.V. site for extravasation.

Administration: I.V. Detail

Dilute I.V. dose with equal volume of compatible diluent (D_5W, NS, SWI).

Storage

I.V.: Intact vials should be refrigerated. Protect from light. Do not use discolored or precipitate-containing solutions. May be stored at room temperature for up to 60 days. Parenteral admixture is stable at room temperature (25°C) for 24 hours.

Tablet: Store at room temperature.

Reconstitution

Injection: Dilute with equal volume of compatible diluent (D_5W, NS, SWI).

Infusion: Use 2 mg/mL injectable vial to prepare; there may be deceased stability when using 4 mg/mL vial. Dilute ≤1 mg/mL and mix in glass bottle. Precipitation may develop. Can also be administered undiluted via infusion.

Compatibility**Variable stability (consult detailed reference)** in D_5W, LR, NS.

Y-site administration: Compatible: Acyclovir, alatrofloxacin, albumin, allopurinol, amifostine, amikacin, amphotericin B cholesteryl sulfate complex, amsacrine, atracurium, bumetanide, cefepime, cefotaxime, ciprofloxacin, cisatracurium, cisplatin, cladribine, clonidine, co-trimoxazole, cyclophosphamide, cytarabine, dexamethasone sodium phosphate, diltiazem, dobutamine, docetaxel, dopamine, doxorubicin, doxorubicin liposome, epinephrine, erythromycin lactobionate, etomidate, etoposide phosphate, famotidine, fentanyl, filgrastim, fluconazole, fludarabine, fosphenytoin, furosemide, gatifloxacin, gemcitabine, gentamicin, granisetron, haloperidol, heparin, hydrocortisone sodium succinate, hydromorphone, ketanserin, labetalol, levofloxacin, linezolid, melphalan, methotrexate, metronidazole, midazolam, milrinone, morphine, nicardipine, nitroglycerin, norepinephrine, paclitaxel, pancuronium, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, tacrolimus, teniposide, thiotepa, vancomycin, vecuronium, vinorelbine, zidovudine. **Incompatible:** Aldesleukin, aztreonam, floxacillin, idarubicin, imipenem/cilastatin, omeprazole, ondansetron, sargramostim, sufentanil. **Variable (consult detailed reference):** Foscarnet, thiopental, TPN.

Compatibility in syringe: Compatible: Cimetidine, hydromorphone. **Incompatible:** Sufentanil. **Variable (consult detailed reference):** Ranitidine.

Compatibility when admixed: Incompatible: Buprenorphine, dexamethasone sodium phosphate with diphenhydramine and metoclopramide.

RestrictionsC-IV

ContraindicationsHypersensitivity to lorazepam or any component of the formulation (cross-sensitivity with other benzodiazepines may exist); acute narrow-angle glaucoma; sleep apnea (parenteral); intra-arterial injection of parenteral formulation; severe respiratory insufficiency (except during mechanical ventilation)

Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.

Disease-related concerns:

- Drug abuse: Use with caution in patients with a history of drug abuse, alcoholism, or significant personality disorders; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use. Risk of dependence increases with higher dosage and longer duration of therapy.
- Hepatic impairment: Use with caution in patients with hepatic impairment. Dose adjustment may be needed. May worsen hepatic encephalopathy.

- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.

- Psychiatric disorders: Use caution in patients with depression, particularly if suicidal risk may be present. Pre-existing depression may emerge or worsen during therapy. Not recommended for use in primary depressive or psychotic disorders.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with respiratory disease, including COPD or sleep apnea. Benzodiazepines may cause significant respiratory depression.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; initial doses should be at the lower end of dosing range.

- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury. Initial doses should at the lower end of dosing range.

- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Dosage form specific issues:

- Benzyl alcohol: Some products may contain benzyl alcohol which has been associated with "gasping syndrome" in neonates.

- Polyethylene glycol: Parenteral formulation contains polyethylene glycol. May be associated with toxicity in high dose and/or longer term therapy.

- Propylene glycol: Parenteral formulation contains propylene glycol. May be associated with toxicity in high dose and/or longer term therapy.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.

- Hypnotic: Appropriate use: As a hypnotic, should be used only after evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric or medical illness. A worsening of insomnia or the emergence of new abnormalities of thought or behavior may represent unrecognized psychiatric or medical illness and requires immediate and careful evaluation.

- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause acute withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsBecause lorazepam is relatively short-acting with an inactive metabolite, it is a preferred agent to use in elderly patients when a benzodiazepine is indicated.

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenic effects have been observed in some animal studies. Lorazepam crosses the human placenta. Respiratory depression, withdrawal symptoms, or hypotonia may occur if administered late in pregnancy or near the time of delivery.

LactationEnters breast milk/not recommended (AAP rates “of concern”)

Breast-Feeding ConsiderationsSedation and impaired nursing may occur in infants exposed to lorazepam from breast milk.

Adverse Reactions

>10%:

Central nervous system: Sedation

Respiratory: Respiratory depression

1% to 10%:

Cardiovascular: Hypotension

Central nervous system: Akathisia, amnesia, ataxia, confusion, depression, disorientation, dizziness, headache

Dermatologic: Dermatitis, rash

Gastrointestinal: Changes in appetite, nausea, weight gain/loss

Neuromuscular & skeletal: Weakness

Ocular: Visual disturbances

Respiratory: Apnea, hyperventilation, nasal congestion

<1% or frequency not defined: Asthenia, blood dyscrasias, disinhibition, euphoria, fatigue, increased salivation, menstrual irregularities,

physical and psychological dependence (with prolonged use), reflex slowing, polyethylene glycol or propylene glycol poisoning (prolonged I.V. infusion), suicidal ideation, seizure, vertigo

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Loxapine: May enhance the adverse/toxic effect of LORazepam. Specifically, prolonged stupor, respiratory depression, and/or hypotension. *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Probenecid: May decrease the metabolism of LORazepam. *Risk D: Consider therapy modification*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of LORazepam. *Risk D: Consider therapy modification*

Yohimbine: May diminish the therapeutic effect of Antianxiety Agents. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersRespiratory and cardiovascular status, blood pressure, heart rate, symptoms of anxiety
Reference RangeTherapeutic: 50-240 ng/mL (SI: 156-746 nmol/L)
Nursing: Physical Assessment/MonitoringAssess other medications the patient may be taking for effectiveness and interactions. **Oral:** Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance; periodically evaluate need for continued use. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. **I.V./I.M.:** Monitor vital signs and CNS status (possible retrograde amnesia with I.V.), and ability to void. Maintain bedrest for 2-3 hours, and observe when up.
Patient Education**Oral:** Take exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. Do not use alcohol or other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); altered sexual drive or ability (reversible); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report persistent CNS effects (eg, confusion, depression, increased sedation, excitation, headache, agitation, insomnia or nightmares, dizziness, fatigue, impaired coordination, changes in personality, or changes in cognition); changes in urinary pattern; chest pain, palpitations, or rapid heartbeat; muscle cramping, weakness, tremors, or rigidity; ringing in ears or visual disturbances; excessive perspiration; excessive GI symptoms (cramping, constipation, vomiting, anorexia); or worsening of condition. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 2 mg/mL (1 mL, 10 mL); 4 mg/mL (1 mL, 10 mL)

Ativan®: 2 mg/mL (1 mL, 10 mL); 4 mg/mL (1 mL, 10 mL) [contains benzyl alcohol, polyethylene glycol, and propylene glycol]

Solution, oral concentrate:

Lorazepam Intensol®: 2 mg/mL (30 mL) [alcohol free, dye free]

Tablet: 0.5 mg, 1 mg, 2 mg

Ativan®: 0.5 mg, 1 mg, 2 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Concentrate (Lorazepam Intensol)

2 mg/mL (30): $43.25

Tablets (Ativan)

0.5 mg (30): $74.36

1 mg (30): $86.62

2 mg (30): $133.97

Tablets (Lorazepam)

1 mg (30): $14.99

2 mg (30): $21.99

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Onset of action:

Hypnosis: I.M.: 20-30 minutes

Sedation: I.V.: 5-20 minutes

Anticonvulsant: I.V.: 5 minutes, oral: 30-60 minutes

Duration: 6-8 hours

Absorption: Oral, I.M.: Prompt

Distribution:

V_d: Neonates: 0.76 L/kg, Adults: 1.3 L/kg; crosses placenta; enters breast milk

Protein binding: 85%; free fraction may be significantly higher in elderly

Metabolism: Hepatic to inactive compounds

Bioavailability: Oral: 90%

Half-life elimination: Neonates: 40.2 hours; Older children: 10.5 hours; Adults: 12.9 hours; Elderly: 15.9 hours; End-stage renal disease: 32-70 hours

Time to peak: Oral: 2 hours

Excretion: Urine; feces (minimal)

Related Information

- Antacid Drug Interactions
- Benzodiazepines
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Status Epilepticus
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsOral doses >0.09 mg/kg produced increased ataxia without increased sedative benefit vs lower doses; preferred anxiolytic when I.M. route needed. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Lorazepam is a short half-life benzodiazepine. Duration of action after a single dose is determined by redistribution rather than metabolism. Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include personal or family history of substance abuse and personality disorder.

Lorazepam is rapidly and completely absorbed after I.M. injection; undergoes phase II metabolism and, therefore, is less likely to be affected in patients with hepatic dysfunction.

Cardiovascular ConsiderationsHypotension may result in orthostatic lightheadedness or syncope. Benzodiazepines, as a class, may depress respiration. These medications may often be prescribed for difficulty in sleeping but may exacerbate sleep-disordered breathing.

Anesthesia and Critical Care Concerns/Other ConsiderationsLorazepam 2 mg/mL and 4 mg/mL each contains propylene glycol 830 mg/mL (80% v/v).

Agitation in the ICU Patient: Lorazepam has a slower onset of action than midazolam or diazepam, making it less useful for treatment of acute agitation. The polyethylene glycol and propylene glycol solvents in lorazepam injection can accumulate and lead to reversible acute tubular necrosis, lactic acidosis and hyperosmolar states with prolonged, high-dose infusions. Yaucher (2003) and colleagues recently performed a retrospective review of patients who received lorazepam infusions and developed increases in serum creatinine. Eight patients from the medical-surgical intensive care unit or burn unit were evaluated. Lorazepam infusions ranged from 2-28 mg/hour. The mean cumulative dose of lorazepam was 4305 mg and the mean propylene glycol level determined at the time of peak serum creatinine concentration was 1103 mcg/mL. The duration of lorazepam infusion and magnitude of serum creatinine concentration rise correlated (r: 0.60). Propylene glycol levels strongly correlated with both serum osmolality and osmol gap. These authors suggest that serum osmolality and osmol gap may be useful markers of propylene glycol toxicity. A recent case report described a critically-ill man who developed acute tubular necrosis while receiving a lorazepam infusion and sulfamethoxazole-trimethoprim (Hayman, 2003). The addition of sulfamethoxazole-trimethoprim contributed to the development of propylene glycol toxicity.

More recently, a prospective, observational study was performed in a medical intensive care unit evaluating patients receiving high-dose lorazepam (≥10 mg/hour) infusions (Arroliga, 2004). The primary objective was to evaluate the relationship between high-dose lorazepam and serum propylene glycol concentrations. Nine patients met the criteria for entry. Baseline creatinine clearances were 50-100 mL/minute. Propylene glycol accumulation was observed in these patients receiving high-dose lorazepam infusions for ≥48 hours. A significant correlation between high-dose lorazepam infusion rate and serum propylene glycol concentrations was observed. However, osmol gap was the strongest predictor ($R^2 = 0.80$) of serum propylene glycol concentrations. Study findings suggest that in critically ill adults with normal renal function, serum propylene glycol concentrations may be predicted by the osmol gap. Based on these findings, propylene glycol accumulation may occur as early as 48 hours when using high-dose lorazepam infusions.

To calculate osmolarity: [2 x sodium (mEq/L)] + [glucose (mg/dL)/18] + [BUN (mg/dL)/2.8]

To calculate osmol gap (normal range: 0-5): (measured osmolality minus calculated osmolarity)

Lorazepam is recommended for the sedation of most patients. Use a defined endpoint in titration of the dose. Use a system to minimize prolonged sedative effects. If patient has received high-dose or >7 days of continuous therapy, consider tapering infusion to prevent withdrawal symptoms.

Status Epilepticus: A randomized, double-blind trial (Treiman, 1998) evaluated the efficacy of four treatments in overt status epilepticus. Treatment arms were designed based upon accepted practices of North American neurologists. The treatments were: 1) lorazepam 0.1 mg/kg, 2) diazepam 0.15 mg/kg followed by phenytoin 18 mg/kg, 3) phenytoin 18 mg/kg alone, and 4) phenobarbital 15 mg/kg. Treatment was considered successful if the seizures were terminated (clinically and by EEG) within 20 minutes of start of therapy without seizure recurrence within 60 minutes from the start of therapy. Patients who failed the first treatment received a second and a third, if necessary. Patients did not receive randomized treatments after the first one, but the treating physician remained blinded. Treatment success: Lorazepam 64.9%, phenobarbital 58.2%, diazepam/phenytoin 55.8%, and phenytoin alone 43.6%. Using an "intention-to-treat" analysis, there was no statistical difference between the groups. Results of subsequent treatments in patients who failed the first therapy indicated that response rate significantly dropped regardless of treatment. Aggregate response rate to the second treatment was 7.0% and third treatment 2.3%.

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International Brand Names Abinol (CN); Ansilor (PT); Anxira (TH); Anzepam (TW); Aplacasse (AR); Aripax (GR); Ativan (AU, BF, BJ, CI, CO, CR, DO, ET, GB, GH, GM, GN, GT, HN, ID, IE, IN, KE, KP, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, PA, PE, PH, PK, SC, SD, SL, SN, SV, TN, TR, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Bonatranquan (DE); Control (IT); Emoten (AU); Emotival (AR); Larpose (IN); Laubeel (DE); Lauracalm (LU); Lonza (TH); Lopam (TW); Lora (CL); Lorabenz (DK); Lorafen (PL); Loram (HR); Lorans (AE, BH, CY, EG, HK, IL, IQ, IR, IT, JO, KW, LB, LY, MY, OM, QA, SA, SY, YE); Lorapam (TH); Lorax (BR); Lorazene (TH); Lorazep (TH); Lorazepam-Efeka (LU); Lorazepam-Eurogenerics (LU); Lorazin (TW); Lorazon (TW); Lorenin (PT); Loridem (BE, LU); Lorivan (IL); Lorsilan (HR); Lorzem (NZ); Merlit (AT, RU); Merlopam (ID); Nervistop L (AR); Neuropam (TW); Novhepar (GR); Orfidal (ES); Psicopax (PY); Renaquil (ID); Sedatival (AR); Sidenar (AR); Silence (HK, TW); Stapam (TW); Tavor (BG, CZ, DE, GR, IT); Temesta (AT, BE, CH, DK, FI, FR, LU, NL, SE); Titus (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, GR, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Tranqipam (ZA); Trapax (AR); Trapex (IN); Vigiten (LU); Zora (TH)

Losartan and Hydrochlorothiazide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Hyzaar® may be confused with Cozaar®

Pronunciation(loe SAR tan & hye droe klor oh THYE a zide)

U.S. Brand NamesHyzaar®

Canadian Brand NamesHyzaar®; Hyzaar® DS

Pharmacologic CategoryAngiotensin II Receptor Blocker; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension; stroke risk reduction in patients with HTN and left ventricular hypertrophy (LVH)

Dosing: Adults**Note:** Dose is individualized (combination substituted for individual components); dose may be titrated after 2-4 weeks of therapy**Hypertension/stroke reduction in hypertension (with LVH):** Usual recommended starting dose of losartan: 50 mg once daily when used as monotherapy in patients who are not volume depleted

Dosing: ElderlyRefer to dosing in individual monographs.

Dosing: Renal Impairment Cl_{cr} ≤30 mL/minute: Use of combination formulation is not recommended.

Dosing: Hepatic ImpairmentUse is not recommended.

Calculations

- Creatinine Clearance: Adults

ContraindicationsHypersensitivity to losartan, hydrochlorothiazide, or any component of the formulation; sulfonamide-derived drugs; anuria

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Electrolyte disturbances: Hyperkalemia may occur with angiotensin II receptor antagonists; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.

- Renal artery stenosis: Use losartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use losartan with caution with pre-existing renal insufficiency and severe renal impairment. Avoid hydrochlorothiazide in severe renal disease (ineffective); may precipitate azotemia; discontinue or consider withholding if renal impairment occurs.

- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Special populations:

- African-American patients: When used to reduce the risk of stroke in patients with HTN and LVH, may not be effective in the African-American population.

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Pregnancy Risk FactorC/D (2nd and 3rd trimesters)
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/contraindicated
Adverse ReactionsBased on clinical trials of the combination product in patients with essential hypertension. Also see individual agents.

1% to 10%:

Cardiovascular: Edema (1%), palpitation (1%)

Central nervous system: Dizziness (6%)

Dermatologic: Skin rash (1%)

Gastrointestinal: Abdominal pain (1%)

Neuromuscular & skeletal: Back pain (2%)

Respiratory: Upper respiratory infection (6%), cough (3%), sinusitis (1%)

<1%, postmarketing, case reports, or frequency not defined (some reactions attributed to single component): Bilirubin increased (serum), BUN increased, hematocrit decreased, hemoglobin decreased, hyper-/hypotension, hyponatremia, liver enzymes increased, rhabdomyolysis, serum creatinine increased, thrombocytopenia

Metabolism/Transport EffectsLosartan: **Substrate** (major) of CYP2C9, 3A4; **Inhibits** CYP1A2 (weak), 2C8 (moderate), 2C9 (moderate), 2C19 (weak), 3A4 (weak)
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Losartan. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Losartan. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Hyzaar® 50-12.5: Losartan potassium 50 mg and hydrochlorothiazide 12.5 mg

Hyzaar® 100-12.5: Losartan potassium 100 mg and hydrochlorothiazide 12.5 mg

Hyzaar® 100-25: Losartan potassium 100 mg and hydrochlorothiazide 25 mg

Generic AvailableNo
ManufacturerMerck & Co
Pricing: U.S. (www.drugstore.com)

Tablets (Hyzaar)

50-12.5 mg (30): $80.32

100-12.5 mg (30): $104.42

100-25 mg (30): $105.56

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Hydrochlorothiazide

- Losartan

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness or insomnia; may rarely cause anxiety, confusion, depression, and sleep disorders
Mental Health: Effects on Psychiatric TreatmentBarbiturates may decrease the effects of losartan; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels
Cardiovascular Considerations

Congestive Heart Failure: Currently, the use of angiotensin II receptor blockers (ARBs) should not supersede angiotensin converting enzyme inhibitors (ACEIs) in the treatment of congestive heart failure. One may be considered, however, when an ACEI cannot be tolerated. Because they are angiotensin II blockers rather than inhibitors of ACE, ARBs do not cause increases in bradykinin levels. *ELITE II* (Pitt, 2000) compared losartan (50 mg/day) with captopril (150 mg/day) in a heart failure population (mean EF 31%). There were 280 deaths in the losartan group and 250 in the captopril group. Mortality was insignificantly higher for losartan (17.7% vs 16% for captopril). The secondary endpoint (sudden cardiac death or resuscitated cardiac arrest) favored captopril, but the improvement did not achieve statistical significance. The discontinuation rate for adverse events was significantly lower for losartan. In the doses used, losartan appears to be less effective or as effective as captopril.

CHARM-Alternative is a prospective, randomized trial (Granger, 2003) in ACE inhibitor-intolerant patients with CHF. Patients were randomized to candesartan (target dose: 32 mg/day; mean dose at 6 months: 23 mg/day) or placebo. Baseline characteristics included NYHA Class II or III (97% of patients), and mean LVEF 30%. Therapy included beta-blocker (55%), diuretic (86%), spironolactone (24%), and digitalis (46%). During a 33-month follow up, the combined primary endpoint (CV death or heart failure hospitalizations) was significantly reduced in the candesartan group mainly because of reduced hospitalization. Death due to cardiovascular disease was not significantly different. There were significantly more MIs (75) in the candesartan group than in the placebo group (48). Candesartan was discontinued because of hypotension, renal dysfunction, and hyperkalemia.

Congestive Heart Failure: Concomitant ACE-I Therapy: The *Val-HeFT study* (Cohn, 2001) randomized CHF patients maintained on standard therapy to valsartan (320 mg/day; mean dose 254 mg/day) or placebo. The primary outcome was mortality and a combined endpoint of morbidity and mortality (cardiac arrest, hospitalization for CHF, need for intravenous inotrope or vasodilator). Patients (5010 in number) with predominately NYHA class II or III heart failure (85% on diuretic; 67% on digoxin; 35% on beta-blocker; ~93% on ACEI; 5% on spironolactone) were randomized to valsartan or placebo. The mean duration of follow-up was 23 months. Overall mortality was similar in both groups. The incidence of combined endpoints was lower with valsartan than placebo (p=.009) primarily because of decreased heart failure hospitalizations in the valsartan group. In a post hoc analysis of the endpoints in subgroups defined by baseline treatments (ACEI or beta-blockers), valsartan had a positive effect on patients receiving neither or one of these drugs. A higher incidence of mortality was seen in patients receiving valsartan in combination with an ACEI and a beta-blocker.

CHARM-Added trial is a prospective, randomized trial (McMurray, 2003) evaluating the addition of candesartan therapy (target dose: 32 mg/day; mean dose at 6 months: 24 mg/day) to CHF patients maintained on an ACEI. Baseline characteristics: NYHA class II (24%), class III (73%), and mean LVEF 28%. Baseline therapy was similar to CHARM-Alternative except all patients were maintained on an ACEI and ~55% were on a beta-blocker. The median duration of follow-up was 41 months. The combined primary endpoint (CV death or heart failure hospitalizations) was significantly reduced in the candesartan group.

Hypertension: According to the 2003 JNC 7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Myocardial Infarction: The 2004 ACC/AHA STEMI guidelines suggest an angiotensin receptor blocker should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF <0.4. The *OPTIMAAL trial* evaluated whether losartan (50 mg/day) would be superior or noninferior to captopril (150 mg/day) in post-MI patients. They were randomized to one of two treatments and followed up for 2.7 years. There was no difference between the two treatment groups (499 deaths in losartan group; 447 deaths in the captopril-treated group). The VALIANT trial compared the effects of valsartan, captopril, and the combination in patients who had suffered a recent MI (0.5 to 10 days prior) complicated by left ventricular systolic dysfunction (Pfeffer, 2003). The primary endpoint was mortality from any cause. Mortality in the valsartan group and the valsartan-captopril group was similar to the captopril group alone. Valsartan was found to be noninferior to captopril in this patient population. Combining valsartan with captopril increased the rate of adverse events without improving survival. Hypotension and renal dysfunction were more common in the valsartan group. Cough, rash, and taste disturbances were more common in the captopril group.

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Index Terms Hydrochlorothiazide and Losartan

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International Brand Names Combizar (PH); Convertal D (UY); Corodin-D (CN, PY); Corus-H (BR); Cosaar Plus (CH); Cozaar Plus (DK, ES, KP, PT); Cozaar-Comp (GB, IE, NO); Cozaarex D (AR); Fortzaar (FR, MY, PT, SE, TH); Hipress (BR); Hyzaar (BB, BM, BS, BZ, CL, CN, CO, CR, EC, FR, GT, GY, HK, HN, JM, MX, MY, NI, NL, NZ, PA, PE, PH, PK, SG, SR, SV, TH, TT, VE); Hyzaar DS (PH); Hyzaar forte (HK, SG); Hyzaar Plus (HK); Lorzaar Plus (DE); Losacor D (AR); Lotan Plus (IL); Lozap H (BG, EE); Nefrotal H (EC); Nefrotal Plus (CR, DO, GT, NI, PA, SV); Ocsaar Plus (IL); Satoren H (CO); Tensarten-HCT (CO); Zaart-H (IN)

Losartan

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Cozaar® may be confused with Colace®, Coreg®, Hyzaar®, Zocor®

Losartan may be confused with valsartan

Pronunciation(loe SAR tan)

U.S. Brand NamesCozaar®

Canadian Brand NamesCozaar®

Pharmacologic CategoryAngiotensin II Receptor Blocker

Use: Labeled IndicationsTreatment of hypertension (HTN); treatment of diabetic nephropathy in patients with type 2 diabetes mellitus (noninsulin dependent, NIDDM) and a history of hypertension; stroke risk reduction in patients with HTN and left ventricular hypertrophy (LVH)

Use: Unlabeled/InvestigationalTo slow the rate of progression of aortic-root dilation in pediatric patients with Marfan’s syndrome

Dosing: Adults

Hypertension: Oral: Usual starting dose: 50 mg once daily; can be administered once or twice daily with total daily doses ranging from 25-100 mg

Usual initial doses in patients receiving diuretics or those with intravascular volume depletion: 25 mg once daily

Nephropathy in patients with type 2 diabetes and hypertension: Oral: Initial: 50 mg once daily; can be increased to 100 mg once daily based on blood pressure response

Stroke reduction (HTN with LVH): Oral: 50 mg once daily (maximum daily dose: 100 mg); may be used in combination with a thiazide diuretic

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Hypertension:** Oral: Children 6-16 years:

U.S. labeling: 0.7 mg/kg once daily (maximum: 50 mg/day); doses >1.4 mg/kg (maximum: 100 mg) have not been studied

Canadian labeling:

≥20 kg to <50 kg: 25 mg once daily (maximum: 50 mg once daily)

≥50 kg: 50 mg once daily (maximum: 100 mg once daily)

Aortic-root dilation with Marfan’s syndrome (unlabeled use): Children 14 months to 16 years: Initial: 0.6 mg/kg/day; can be increased to a maximum of 1.4 mg/kg/day (not to exceed adult maximum of 100 mg/day)

Dosing: Renal Impairment

Children: Use is not recommended if GFR <30 mL/minute/1.73m^2

Adults: No adjustment necessary.

Dosing: Hepatic Impairment

Children 6-16 years:

U.S. labeling: No specific dosing recommendations are provided in the approved labeling, however it may be advisable to initiate therapy at a reduced dosage.

Canadian labeling: Use is not recommended.

Adults: Reduce the initial dose to 25 mg/day

Calculations

- Creatinine Clearance: Pediatrics

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light.

Extemporaneously PreparedTo prepare losartan suspension, combine 10 mL of purified water and ten (10) losartan 50 mg tablets in an 8 ounce bottle. Shake well for ≥2 minutes. Allow concentrate to stand for 1 hour then shake for 1 minute. Separately, prepare 190 mL of a 50/50 mixture of Ora-Plus™ and Ora-Sweet SF™. Add to tablet and water mixture; shake for 1 minute. Resulting 200 mL suspension will contain losartan 2.5 mg/mL. Store under refrigeration for up to 4 weeks; shake well before use.

Product information, October, 2004; Merck & Company, Inc

ContraindicationsHypersensitivity to losartan or any component of the formulation

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See "Special populations" below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose), angioedema may occur rarely. It may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). Patients with idiopathic or hereditary angioedema or previous angioedema associated with ACE-inhibitor therapy may be at an increased risk. Prolonged frequent monitoring may be required, especially if tongue, glottis, or larynx are involved, as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early management is critical. Intramuscular (I.M.) administration of epinephrine may be necessary.

- Hyperkalemia: May occur; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.

- Hepatic impairment: Use with caution in patients with hepatic impairment; dose adjustment may be needed.

- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.

- Renal artery stenosis: Use with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution with pre-existing renal insufficiency and severe renal impairment.

Special populations:

- African-American patients: When used to reduce the risk of stroke in patients with HTN and LVH, may not be effective in the African-American population.

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Geriatric ConsiderationsSerum concentrations of losartan and its metabolites are not significantly different and no initial dose adjustment is necessary even in low creatinine clearance states (<30 mL/minute). Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.

Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)

Pregnancy ConsiderationsMedications which act on the renin-angiotensin system are reported to have the following fetal/neonatal effects: Hypotension, neonatal skull hypoplasia, anuria, renal failure, and death; oligohydramnios is also reported. These effects are reported to occur with exposure during the second and third trimesters. There are no adequate and well-controlled studies in pregnant women. **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if losartan is found in breast milk; the manufacturer recommends discontinuing the drug or discontinuing nursing based on the importance of the drug to the mother.

Adverse Reactions

Note: The incidence of some adverse reactions varied based on the underlying disease state. Notations are made, where applicable, for data derived from trials conducted in diabetic nephropathy and hypertensive patients, respectively.

>10%:

Cardiovascular: Chest pain (12% diabetic nephropathy)

Central nervous system: Fatigue (14% diabetic nephropathy)

Endocrine: Hypoglycemia (14% diabetic nephropathy)

Gastrointestinal: Diarrhea (2% hypertension to 15% diabetic nephropathy)

Genitourinary: Urinary tract infection (13% diabetic nephropathy)

Hematologic: Anemia (14% diabetic nephropathy)

Neuromuscular & skeletal: Weakness (14% diabetic nephropathy), back pain (2% hypertension to 12% diabetic nephropathy)

Respiratory: Cough (≤3% to 11%; similar to placebo; incidence higher in patients with previous cough related to ACE inhibitor therapy)

1% to 10%:

Cardiovascular: Hypotension (7% diabetic nephropathy), orthostatic hypotension (4% hypertension to 4% diabetic nephropathy), first-dose hypotension (dose related: <1% with 50 mg, 2% with 100 mg)

Central nervous system: Dizziness (4%), hypoesthesia (5% diabetic nephropathy), fever (4% diabetic nephropathy), insomnia (1%)

Dermatology: Cellulitis (7% diabetic nephropathy)

Endocrine: Hyperkalemia (<1% hypertension to 7% diabetic nephropathy)

Gastrointestinal: Gastritis (5% diabetic nephropathy), weight gain (4% diabetic nephropathy), dyspepsia (1% to 4%), abdominal pain (2%), nausea (2%)

Neuromuscular & skeletal: Muscular weakness (7% diabetic nephropathy), knee pain (5% diabetic nephropathy), leg pain (1% to 5%), muscle cramps (1%), myalgia (1%)

Respiratory: Bronchitis (10% diabetic nephropathy), upper respiratory infection (8%), nasal congestion (2%), sinusitis (1% hypertension to 6% diabetic nephropathy)

Miscellaneous: Infection (5% diabetic nephropathy), flu-like syndrome (10% diabetic nephropathy)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Acute psychosis with paranoid delusions, ageusia, allergic reaction, alopecia, anaphylactic reactions, anemia, angina, angioedema, anorexia, anxiety, arrhythmia, arthralgia, arthritis, ataxia, AV block (second degree), bilirubin increased, blurred vision, bradycardia, bronchitis, BUN increased, confusion, conjunctivitis, constipation, CVA, depression, dermatitis, dysgeusia, dyspnea, ecchymosis, epistaxis, erythroderma, erythema, facial edema, fever, flatulence, flushing, gastritis, gout, hematocrit decreased, hemoglobin decreased, Henoch-Schönlein purpura, hepatitis, hyperkalemia, hyponatremia, hypotension, impotence, joint swelling, maculopapular rash, myositis, memory impairment, MI, migraine, muscle weakness, nervousness, orthostatic effects, pancreatitis, paresthesia, peripheral neuropathy, pharyngitis, photosensitivity, pruritus, rash, rhabdomyolysis, rhinitis, serum creatinine increased, sleep disorder, somnolence, syncope, tachycardia, taste perversion, thrombocytopenia, tinnitus, transaminases increased, tremor, urinary frequency, urticaria, vasculitis, ventricular arrhythmia, vertigo, visual acuity decreased, vomiting, xerostomia

Metabolism/Transport Effects **Substrate** (major) of CYP2C9, 3A4; **Inhibits** CYP1A2 (weak), 2C8 (moderate), 2C9 (moderate), 2C19 (weak), 3A4 (weak)

Drug Interactions

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Losartan. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Losartan. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease levels of losartan. Avoid bayberry, blue cohosh, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh; california poppy; coleus; golden seal; hawthorn; mistletoe; periwinkle; quinine; shepherd's purse (may increase risk for hypotension). Hypoglycemic effects of losartan may be enhanced by alfalfa; aloe; bilberry; bitter melon; burdock; celery; damiana; fenugreek; garcinia; garlic; ginger; ginseng (American); gymnema; marshmallow; stinging nettle.

Monitoring ParametersSupine blood pressure, electrolytes, serum creatinine, BUN, urinalysis, symptomatic hypotension and tachycardia, CBC

Nursing: Physical Assessment/MonitoringUse caution in presence of impaired renal function, significant aortic/mitral stenosis, or history of angioedema or airway surgery. Assess potential for interactions with other pharmacological or herbal products patient may be taking (eg, decreased or increased levels/effects of losartan, risk of toxicities). Assess results of laboratory tests, therapeutic effectiveness (normotensive), and adverse response (eg, hypotension) on a regular basis during therapy. Caution patients with diabetes to monitor glucose levels closely; may alter glucose control. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsElectrolytes, serum creatinine, BUN, urinalysis, CBC

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take exactly as directed and do not discontinue without consulting prescriber. Preferable to take at same time each day without regard to meals. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. Do not use potassium supplement or salt substitutes without consulting prescriber. If you have diabetes, you may be cautioned to monitor glucose levels closely; may alter glucose control. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); diarrhea (boiled milk, buttermilk, or yogurt may help). Report immediately swelling of face, lips, or mouth; difficulty swallowing; chest pain or palpitations; unrelenting headache; CNS changes (delusions or depression); or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, oral, as potassium:

Cozaar®: 25 mg [contains potassium 2.12 mg (0.054 mEq)]

Cozaar®: 50 mg [contains potassium 4.24 mg (0.108 mEq)]

Cozaar®: 100 mg [contains potassium 8.48 mg (0.216 mEq)]

Generic AvailableNo

ManufacturerMerck & Co

Pricing: U.S. (www.drugstore.com)

Tablets (Cozaar)

25 mg (30): $58.99

50 mg (30): $71.47

100 mg (30): $92.22

Mechanism of ActionAs a selective and competitive, nonpeptide angiotensin II receptor antagonist, losartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II; losartan interacts reversibly at the AT1 and AT2 receptors of many tissues and has slow dissociation kinetics; its affinity for the AT1 receptor is 1000 times greater than the AT2 receptor. Angiotensin II receptor antagonists may induce a more complete inhibition of the renin-angiotensin system than ACE inhibitors, they do not affect the response to bradykinin, and are less likely to be associated with nonrenin-angiotensin effects (eg, cough and angioedema). Losartan increases urinary flow rate and in addition to being natriuretic and kaliuretic, increases excretion of chloride, magnesium, uric acid, calcium, and phosphate.

Pharmacodynamics/Kinetics

Onset of action: 6 hours

Distribution: V_d: Losartan: 34 L; E-3174: 12 L; does not cross blood brain barrier

Protein binding, plasma: High

Metabolism: Hepatic (14%) via CYP2C9 and 3A4 to active metabolite, E-3174 (40 times more potent than losartan); extensive first-pass effect

Bioavailability: 25% to 33%; AUC of E-3174 is four times greater than that of losartan

Half-life elimination: Losartan: 1.5-2 hours; E-3174: 6-9 hours

Time to peak, serum: Losartan: 1 hour; E-3174: 3-4 hours

Excretion: Urine (4% as unchanged drug, 6% as active metabolite)

Clearance: Plasma: Losartan: 600 mL/minute; Active metabolite: 50 mL/minute

Related Information

- Angiotensin Agents
- Heart Failure (Systolic)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness or insomnia; may rarely cause anxiety, confusion, depression, and sleep disorders
Mental Health: Effects on Psychiatric TreatmentBarbiturates may decrease the effects of losartan
Cardiovascular Considerations

Congestive Heart Failure: Currently, the use of angiotensin II receptor blockers (ARBs) should not supersede angiotensin converting enzyme inhibitors (ACEIs) in the treatment of congestive heart failure. One may be considered, however, when an ACEI cannot be tolerated. Because they are angiotensin II blockers rather than inhibitors of ACE, ARBs do not cause increases in bradykinin levels. *ELITE II* (Pitt, 2000) compared losartan (50 mg/day) with captopril (150 mg/day) in a heart failure population (mean EF 31%). There were 280 deaths in the losartan group and 250 in the captopril group. Mortality was insignificantly higher for losartan (17.7% vs 16% for captopril). The secondary endpoint (sudden cardiac death or resuscitated cardiac arrest) favored captopril, but the improvement did not achieve statistical significance. The discontinuation rate for adverse events was significantly lower for losartan. In the doses used, losartan appears to be less effective or as effective as captopril.

CHARM-Alternative is a prospective, randomized trial (Granger, 2003) in ACE inhibitor-intolerant patients with CHF. Patients were randomized to candesartan (target dose: 32 mg/day; mean dose at 6 months: 23 mg/day) or placebo. Baseline characteristics included NYHA Class II or III (97% of patients), and mean LVEF 30%. Therapy included beta-blocker (55%), diuretic (86%), spironolactone (24%), and digitalis (46%). During a 33-month follow up, the combined primary endpoint (CV death or heart failure hospitalizations) was significantly reduced in the candesartan group mainly because of reduced hospitalization. Death due to cardiovascular disease was not significantly different. There were significantly more MIs (75) in the candesartan group than in the placebo group (48). Candesartan was discontinued because of hypotension, renal dysfunction, and hyperkalemia.

Congestive Heart Failure: Concomitant ACE-I Therapy: The *Val-HeFT study* (Cohn, 2001) randomized CHF patients maintained on standard therapy to valsartan (320 mg/day; mean dose 254 mg/day) or placebo. The primary outcome was mortality and a combined endpoint of morbidity and mortality (cardiac arrest, hospitalization for CHF, need for intravenous inotrope or vasodilator). Patients (5010 in number) with predominately NYHA class II or III heart failure (85% on diuretic; 67% on digoxin; 35% on beta-blocker; ~93% on ACEI; 5% on spironolactone) were randomized to valsartan or placebo. The mean duration of follow-up was 23 months. Overall mortality was similar in both groups. The incidence of combined endpoints was lower with valsartan than placebo (p=.009) primarily because of decreased heart failure hospitalizations in the valsartan group. In a post hoc analysis of the endpoints in subgroups defined by baseline treatments (ACEI or beta-blockers), valsartan had a positive effect on patients receiving neither or one of these drugs. A higher incidence of mortality was seen in patients receiving valsartan in combination with an ACEI and a beta-blocker.

CHARM-Added trial is a prospective, randomized trial (McMurray, 2003) evaluating the addition of candesartan therapy (target dose: 32 mg/day; mean dose at 6 months: 24 mg/day) to CHF patients maintained on an ACEI. Baseline characteristics: NYHA class II (24%), class III (73%), and mean LVEF 28%. Baseline therapy was similar to CHARM-Alternative except all patients were maintained on an ACEI and ~55% were on a beta-blocker. The median duration of follow-up was 41 months. The combined primary endpoint (CV death or heart failure hospitalizations) was significantly reduced in the candesartan group.

Hypertension: According to the 2003 JNC 7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Marfan's Syndrome: Marfan's syndrome is a genetic disorder due to a mutation in the gene encoding for fibrillin-1 (FBN-1) and is associated with progressive aortic root dilation and may subsequently result in aortic dissection. The deficiency of FBN-1 leads to an increase in the activity of transforming growth factor β (TGF-β) which is thought to contribute to aortic root dilation and other Marfan's syndrome characteristics. Angiotensin II receptor blockers have been shown to inhibit TGF-β signaling.

Recently, a retrospective study evaluated the use of angiotensin II receptor blockers specifically losartan (1 patient received irbesartan) in a cohort of 18 pediatric patients (age range 14 months to 16 years) with Marfan's syndrome. All patients had evidence of severe aortic root enlargement. Patients who received losartan were initiated with 0.6 mg/kg/day and increased to a maximum dose of 1.4 mg/kg/day. The patient who received irbesartan was initiated with 1.4 mg/kg/day and increased to a maximum dose of 2 mg/kg/day. Patients were followed for a median of 26 months. The mean rate of change in aortic-root diameter prior to initiation of ARB therapy was 3.54 ± 2.87 mm per year. After initiation of ARB therapy, the rate of change decreased to 0.46 ± 0.62 mm per year ($p<0.001$). A similar decline in rate of change was seen in the patient treated with irbesartan. This small cohort study demonstrates that ARB therapy in patients with aortic-root dilation due to Marfan's syndrome may be of benefit. Future randomized controlled clinical trials will be needed to confirm these findings (Brooke, 2008).

Myocardial Infarction: The 2004 ACC/AHA STEMI guidelines suggest an angiotensin receptor blocker should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF <0.4. The *OPTIMAAL trial* evaluated whether losartan (50 mg/day) would be superior or noninferior to captopril (150 mg/day) in post-MI patients. They were randomized to one of two treatments and followed up for 2.7 years. There was no difference between the two treatment groups (499 deaths in losartan group; 447 deaths in the captopril-treated group). The VALIANT trial compared the effects of valsartan, captopril, and the combination in patients who had suffered a recent MI (0.5 to 10 days prior) complicated by left ventricular systolic dysfunction (Pfeffer, 2003). The primary endpoint was mortality from any cause. Mortality in the valsartan group and the valsartan-captopril group was similar to the captopril group alone. Valsartan was found to be noninferior to captopril in this patient population. Combining valsartan with captopril increased the rate of adverse events without improving survival. Hypotension and renal dysfunction were more common in the valsartan group. Cough, rash, and taste disturbances were more common in the captopril group.

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Anesthesia and Critical Care Concerns/Other Considerations The angiotensin II receptor antagonists appear to have similar indications as the ACE inhibitors. In heart failure, the angiotensin II antagonists are especially useful in providing an alternative therapy in those patients who have intractable cough in response to ACE inhibitor therapy. Candesartan has been studied as an alternative therapy in chronic heart failure patients who cannot tolerate an ACE-I (CHARM-Alternative) and as an added therapy in heart failure patients who are maintained on an ACE-I (CHARM-Added). In both studies, the combined endpoint of cardiovascular death or heart failure hospitalizations was significantly improved over the placebo-treated group. Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

Index Terms DuP 753; Losartan Potassium; MK594

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International Brand NamesAcetensa (ID); Angioten (ID); Angizaar (PH); Bepsar (PH); Convertal (PY, UY); Cosaar (CH); Cozaar (AT, AU, BB, BE, BG, BM, BR, BS, BZ, CH, CL, CN, CO, CZ, DE, DK, EC, ES, FI, FR, GB, GR, GY, HK, HN, HR, HU, ID, IE, IT, JM, KP, LU, MX, MY, NL, NO, PE, PH, PK, PL, PT, RU, SE, SG, SR, TH, TR, TT, TW, VE); Cozaarex (AR); Ecozar (PH); Insaar (ID); Lasa (TW); Lifezar (PH); Loranta (TH); Lorista (PL); Lortaan (IT); Lorzaar (DE); Losacar (IN); Losacor (AR, PE); Lotim (HR); Lozaris (TH); Nefrotal (CR, DO, GT, HN, NI, PA, SV); Normoten (PH); Ocsaar (IL); Sartaxal (ID); Satoren (CO); Sluxdin (TW); Tanzaril (TH); Tensaar (ID); Tozaar (IN); Xartan (PL)

Loteprednol and Tobramycin

English

Jump To Field (Select Field Name)

Pronunciation(loe te PRED nol & toe bra MYE sin)

U.S. Brand NamesZylet™

Pharmacologic CategoryAntibiotic/Corticosteroid, Ophthalmic

Use: Labeled IndicationsTreatment of steroid-responsive ocular inflammatory conditions where either a superficial bacterial ocular infection or the risk of a superficial bacterial ocular infection exists

Dosing: AdultsOphthalmic: Instill 1-2 drops into the affected eye(s) every 4-6 hours; may increase frequency during the first 24-48 hours to every 1-2 hours. Interval should increase as signs and symptoms improve. Further evaluation should occur for use of greater than 20 mL.

Dosing: ElderlyRefer to adult dosing.

Administration: OtherContact lenses should not be worn during therapy. Shake suspension vigorously before using; instill into conjunctival sac.

StorageStore upright between 15°C to 25°C (59°F to 77°F); do not freeze.

ContraindicationsHypersensitivity to tobramycin, loteprednol, other corticosteroids, or any component of the formulation; viral, fungal, or tuberculosis diseases of the eye

Warnings/Precautions

Concerns related to adverse effects:

- Infection: Steroids may mask infection or enhance existing ocular infection; prolonged use may result in secondary infections due to immunosuppression.
- Ocular effects: Prolonged use of corticosteroids may result in glaucoma. Damage to the optic nerve, defects in visual acuity and fields of vision, and formation of posterior subcapsular cataract may occur.
- Sensitivity reactions: Sensitivity to tobramycin may develop; discontinue if sensitivity reaction occurs. Cross-sensitivity to other aminoglycoside antibiotics may occur.

Special populations:

- Cataract surgery patients: Use following cataract surgery may delay healing or increase the incidence of bleb formation.
- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Benzalkonium chloride: Suspension contains benzalkonium chloride which may be adsorbed by contact lenses; contact lenses should not be worn during treatment of ophthalmic infections.

Other warnings/precautions:

- Appropriate use: For ophthalmic use only. A maximum of 20 mL of suspension should be prescribed initially; patients should be evaluated prior to additional refills. Prescriptions extending beyond 14 days should include exams using magnification.

Geriatric ConsiderationsAssess patient's ability to correctly self-administer eye drops.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate or well-controlled studies in pregnant women. Use only if the potential benefit to the mother justifies the potential risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsAlso see individual agents.

>10%:

Central nervous system: Headache (14%)

Ocular: Superficial punctate keratitis (15%)

4% to 10%:

Local: Burning & stinging (9%)

Ocular: Intraocular pressure increased (10%)

<4%:

Local: Discharge, itching

Ocular: Corneal deposits, eye disorders unspecified, eyelid disorder, lacrimation disorder, ocular discomfort, photophobia

Drug Interactions

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Monitoring ParametersRe-evaluate if signs and symptoms persist beyond 2 days; measure intraocular pressure if used for >10 days; culture for fungus with long-term use. Re-examine with use of >20 mL; exams for use >14 days should include magnification and (when appropriate) fluorescein staining

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, ophthalmic: Loteprednol 0.5% and tobramycin 0.3% (2.5 mL, 5 mL, 10 mL) [contains benzalkonium chloride]

Generic AvailableNo

ManufacturerBausch & Lomb, Inc

Pricing: U.S. (www.drugstore.com)

Suspension (Zylet)

0.5-0.3% (5): $94.94

0.5-0.3% (10): $167.99

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsLoteprednol Etabonate and Tobramycin; Tobramycin and Loteprednol Etabonate

English

Jump To Field (Select Field Name)

Medication Safety Issues

International issues:

Lotemax® may be confused with Lotanax® which is a brand name for terfenadine in the Czech Republic

Pronunciation(loe te PRED nol)

U.S. Brand NamesAlrex®; Lotemax®

Canadian Brand NamesAlrex®; Lotemax®

Pharmacologic CategoryCorticosteroid, Ophthalmic

Use: Labeled Indications

Suspension, 0.2% (Alrex®): Temporary relief of signs and symptoms of seasonal allergic conjunctivitis

Suspension, 0.5% (Lotemax®): Inflammatory conditions (treatment of steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitis, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation) and treatment of postoperative inflammation following ocular surgery

Dosing: Adults

Seasonal allergic conjunctivitis: Ophthalmic: 0.2% suspension (Alrex®): Instill 1 drop into affected eye(s) 4 times/day.

Inflammatory conditions: Ophthalmic: 0.5% suspension (Lotemax®): Apply 1-2 drops into the conjunctival sac of the affected eye(s) 4 times/day. During the initial treatment within the first week, the dosing may be increased up to 1 drop every hour. Advise patients not to discontinue therapy prematurely. If signs and symptoms fail to improve after 2 days, re-evaluate the patient.

Postoperative inflammation: Ophthalmic: 0.5% suspension (Lotemax®): Apply 1-2 drops into the conjunctival sac of the operated eye(s) 4 times/day beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to loteprednol, other corticosteroids, and any component of the formulation; viral diseases of the cornea and conjunctiva; mycobacterial infection of the eye; fungal diseases of ocular structures

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Infection: Steroids may mask infection or enhance existing ocular infection; prolonged use may result in secondary infections due to immunosuppression.
- Ocular effects: Prolonged use may result in glaucoma and injury to the optic nerve. Visual defects in acuity and field of vision may occur. Posterior subcapsular cataracts may form after long-term use. Use with caution in presence of glaucoma (steroids increase intraocular pressure). Perforation may occur with topical steroids in diseases which thin the cornea or sclera. Steroid use may delay healing after cataract surgery. Intraocular pressure should be monitored if this product is used >10 days.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: For ophthalmic use only; patients should be re-evaluated if symptoms fail to improve after 2 days.

Geriatric ConsiderationsAssess patient's ability to administer eye drops.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Headache

Respiratory: Rhinitis, pharyngitis

1% to 10%: Ocular: Abnormal vision/blurring, burning on instillation, chemosis, dry eyes, itching, injection, conjunctivitis/irritation, corneal abnormalities, eyelid erythema, papillae uveitis

<1%: Cataract formation, changes in visual acuity and/or field defects, global perforation in disease which thins cornea or sclera, increased intraocular pressure, secondary ocular infection

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Monitoring ParametersIntraocular pressure (if >10 days)

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic response and adverse effects. Teach patient proper use, side effects/appropriate interventions, and symptoms to report.

Patient EducationFor use in eyes only. Store in a cool place. Shake well before using. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Tilt head back, place medication in conjunctival sac, and close eyes. Apply finger pressure at corner of eye for 1 minute following application. May cause temporary sensitivity to bright light, blurring or stinging, changes in visual acuity, headache, runny nose, or sore throat. Do not discontinue therapy prematurely. If improvement is not noted within 2 days, notify prescriber. Report persistent vision changes, signs of increased infection, swollen eyelids, extreme itching, or if inflammation does not improve. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, ophthalmic, as etabonate:

Alrex®: 0.2% (5 mL, 10 mL) [contains benzalkonium chloride]

Lotemax®: 0.5% (2.5 mL, 5 mL, 10 mL, 15 mL) [contains benzalkonium chloride]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Suspension (Alrex)

0.2% (5): $66.13

0.2% (10): $134.27

Suspension (Lotemax)

0.5% (5): $57.32

0.5% (10): $105.32

0.5% (15): $135.41

Mechanism of ActionCorticosteroids inhibit the inflammatory response including edema, capillary dilation, leukocyte migration, and scar formation. Loteprednol is highly lipid soluble and penetrates cells readily to induce the production of lipocortins. These proteins modulate the activity of prostaglandins and leukotrienes.

Pharmacodynamics/KineticsAbsorption: None

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsLoteprednol Etabonate

International Brand NamesAlrex (BR, HK); Lotemax (AR, GB, HK, IE, SG, UY); Lotepred (IN); Loterex (MX); Lotesoft (PY, VE); Oftol (CN)

Lovastatin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

HMG-CoA Reductase Inhibitors: Evidence Does Not Suggest Increased Incidence of Amyotrophic Lateral Sclerosis (ALS) - Results of FDA Analysis - September 30, 2008

The U.S. Food and Drug Administration's (FDA) review of 41 long-term controlled clinical trials of HMG-CoA reductase inhibitors finds no evidence of an increased incidence of ALS (also known as Lou Gehrig's disease) related to these medications. This analysis occurred after the FDA had received notice of numerous adverse events of which 109 of these reports mentioned ALS, Lou Gehrig's disease, or motor neurone disease. The clinical trials included in the analysis had a median duration of treatment of 3.3 years (range of duration: 6 months to 5 years) and involved 120,964 patients. The analysis identified a total of 19 cases of ALS – 9 cases per 64,602 patients (0.014%) with statin therapy and 10 cases per 56,362 patients (0.017%) with placebo. The incidence rates, based on approximately 400,000 person-years, were 4.2 per 100,000 person-years in the statin-treated group and 5 per 100,000 person-years in the placebo-treated group.

The FDA recommends that health care providers continue to prescribe, and patients continue to use these products as described within their labeling.

For more information, healthcare professionals may refer to the following:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Statin

Colman E, Szarfman A, Wyeth J, et al, "An Evaluation of a Data Mining Signal for Amyotrophic Lateral Sclerosis and Statins Detected in FDA's Spontaneous Adverse Event Reporting System," *Pharmacoepidemiol Drug Saf*, 2008 (epub ahead of print)

Medication Safety Issues

Sound-alike/look-alike issues:

Lovastatin may be confused with Leustatin®, Livostin®, Lotensin®

Mevacor® may be confused with Mivacron®

International issues:

Lovacol® [Chile and Finland] may be confused with Levatol® which is a brand name for penbutolol in the U.S.

Lovastin® [Poland] may be confused with Livostin® which is a brand name for levocabastine in the U.S.

Pronunciation(LOE va sta tin)

U.S. Brand NamesAltoprev®; Mevacor®

Canadian Brand NamesApo-Lovastatin®; CO Lovastatin; DOM-Lovastatin; Gen-Lovastatin; Mevacor®; Novo-Lovastatin; Nu-Lovastatin; PHL-Lovastatin; PMS-Lovastatin; PRO-Lovastatin; RAN™-Lovastatin; ratio-Lovastatin; Riva-Lovastatin; Sandoz-Lovastatin

Pharmacologic CategoryAntilipemic Agent, HMG-CoA Reductase Inhibitor

Use: Labeled Indications

Adjunct to dietary therapy to decrease elevated serum total and LDL-cholesterol concentrations in primary hypercholesterolemia

Primary prevention of coronary artery disease (patients without symptomatic disease with average to moderately elevated total and LDL-cholesterol and below average HDL-cholesterol); slow progression of coronary atherosclerosis in patients with coronary heart disease

Adjunct to dietary therapy in adolescent patients (10-17 years of age, females >1 year postmenarche) with heterozygous familial hypercholesterolemia having LDL >189 mg/dL, **or** LDL >160 mg/dL with positive family history of premature cardiovascular disease (CVD), **or** LDL >160 mg/dL with the presence of at least two other CVD risk factors

Dosing: Adults

Dyslipidemia and primary prevention of CAD: Oral: Initial: 20 mg with evening meal, then adjust at 4-week intervals; maximum: 80 mg/day immediate release tablet **or** 60 mg/day extended release tablet.

Dosage modification/limits based on concurrent therapy:

Cyclosporine and other immunosuppressant drugs: Initial dose: 10 mg/day with a maximum recommended dose of 20 mg/day

Concurrent therapy with fibrates, danazol, and/or lipid-lowering doses of niacin (>1 g/day): Maximum recommended dose: 20 mg/day. Concurrent use with fibrates should be avoided unless risk to benefit favors use.

Concurrent therapy with amiodarone or verapamil: Maximum recommended dose: 40 mg/day of regular release or 20 mg/day with extended release.

Dosage adjustment in renal impairment: Cl_{cr} <30 mL/minute: Use doses >20 mg/day with caution.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Heterozygous familial hypercholesterolemia: Oral (immediate release tablet): Adolescents 10-17 years:

LDL reduction <20%: Initial: 10 mg/day with evening meal

LDL reduction ≥20%: Initial: 20 mg/day with evening meal

Usual range: 10-40 mg with evening meal, then adjust dose at 4-week intervals

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute: Use with caution and carefully consider doses >20 mg/day.
Administration: OralAdminister immediate release tablet with meals. Administer extended release tablet at bedtime; do not crush or chew.
Dietary ConsiderationsBefore initiation of therapy, patients should be placed on a standard cholesterol-lowering diet for 6 weeks and the diet should be continued during drug therapy. Avoid intake of large quantities of grapefruit juice (≥1 quart/day); may increase toxicity. Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.
Storage

Tablet, immediate release: Store between 5°C to 30°C (41°F to 86°F). Protect from light.

Tablet, extended release: Store between 20°C to 25°C (68°F to 77°F). Avoid excessive heat and humidity.

ContraindicationsHypersensitivity to lovastatin or any component of the formulation; active liver disease; unexplained persistent elevations of serum transaminases; pregnancy; breast-feeding
Warnings/Precautions

Concerns related to adverse effects:

- Myopathy/rhabdomyolysis: Patients receiving HMG-CoA reductase inhibitors have developed rhabdomyolysis with acute renal failure and/or myopathy; patients should be monitored closely. This risk is dose-related and is increased with concurrent use of other lipid lowering medications. Temporarily discontinue for elective major surgery, acute medical or surgical conditions, or in any patient experiencing an acute or serious condition predisposing to renal failure (eg, sepsis, hypotension, trauma, uncontrolled seizures). Based upon current evidence, HMG-CoA reductase inhibitor therapy should be continued in the perioperative period unless risk outweighs cardioprotective benefit. Use caution in patients with renal impairment, inadequately treated hypothyroidism, and those taking other drugs associated with myopathy (eg, colchicine); these patients are predisposed to myopathy. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine.

Disease-related concerns:

- Hepatic impairment and/or ethanol use: Use with caution in patients who consume large amounts of ethanol or have a history of liver disease.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors (see drug interactions); consider alternative agents that avoid or lessen potential for CYP-mediated interactions.

Special populations:

- Elderly: Use with caution in patients with advanced age, these patients are predisposed to myopathy.

- Pediatrics: Safety and efficacy of the immediate release tablet has not been evaluated in prepubertal patients, patients <10 years of age, or doses >40 mg/day; extended release tablets have not been studied in patients <20 years of age.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

- Liver function tests: Must be monitored by periodic laboratory assessment.

Geriatric ConsiderationsThe definition of and, therefore, when to treat hyperlipidemia in the elderly is a controversial issue. The National Cholesterol Education Program recommends that all adults maintain a plasma cholesterol <160 mg/dL. Elderly with one additional risk factor, goal LDL would be <130 mg/dL. It is the authors' belief that pharmacologic treatment be reserved for those who are unable to obtain a desirable plasma cholesterol concentration by diet alone and for whom the benefits of treatment are believed to outweigh the potential adverse effects, drug interactions, and cost of treatment.
Pregnancy Risk FactorX
Pregnancy ConsiderationsCholesterol biosynthesis may be important in fetal development. Contraindicated in pregnancy. Administer to women of childbearing potential only when conception is highly unlikely and patients have been informed of potential hazards.
LactationExcretion unknown/contraindicated
Adverse ReactionsPercentages as reported with immediate release tablets; similar adverse reactions seen with extended release tablets.

>10%: Neuromuscular & skeletal: CPK increased (>2x normal) (11%)

1% to 10%:

Central nervous system: Headache (2% to 3%), dizziness (0.5% to 1%)

Dermatologic: Rash (0.8% to 1%)

Gastrointestinal: Abdominal pain (2% to 3%), constipation (2% to 4%), diarrhea (2% to 3%), dyspepsia (1% to 2%), flatulence (4% to 5%), nausea (2% to 3%)

Neuromuscular & skeletal: Myalgia (2% to 3%), weakness (1% to 2%), muscle cramps (0.6% to 1%)

Ocular: Blurred vision (0.8% to 1%)

<1% (Limited to important or life-threatening): Acid regurgitation, alopecia, arthralgia, chest pain, dermatomyositis, eye irritation, insomnia, leg pain, paresthesia, pruritus, vomiting, xerostomia

Additional class-related events or case reports (not necessarily reported with lovastatin therapy): Alkaline phosphatase increased, alopecia, alteration in taste, anaphylaxis, angioedema, anorexia, anxiety, arthritis, cataracts, chills, cholestatic jaundice, cirrhosis, CPK increased (>10x normal), depression, dryness of skin/mucous membranes, dyspnea, eosinophilia, erectile dysfunction, erythema multiforme, ESR increased, facial paresis, fatty liver, fever, flushing, fulminant hepatic necrosis, GGT increased, gynecomastia, hemolytic anemia, hepatitis, hepatoma, hyperbilirubinemia, hypersensitivity reaction, impaired extraocular muscle movement, impotence, leukopenia, libido decreased, malaise, memory loss, myopathy, nail changes, nodules, ophthalmoplegia, pancreatitis, paresthesia, peripheral nerve palsy, peripheral neuropathy, photosensitivity, polymyalgia rheumatica, positive ANA, pruritus, psychic disturbance, purpura, rash, renal failure (secondary to rhabdomyolysis), rhabdomyolysis, skin discoloration, Stevens-Johnson syndrome, systemic lupus erythematosus-like syndrome, thrombocytopenia, thyroid dysfunction, toxic epidermal necrolysis, transaminases increased, tremor, urticaria, vasculitis, vertigo, vomiting

Metabolism/Transport Effects **Substrate** of CYP3A4 (major); **Inhibits** CYP2C9 (weak), 2D6 (weak), 3A4 (weak)

Drug Interactions

Amiodarone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. Management: Dose of HMG-CoA reductase inhibitor may need to be reduced (e.g., simvastatin prescribing information recommends not exceeding 20 mg/day during concurrent therapy). *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Bosentan: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Colchicine: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CycloSPORINE: May increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Danazol: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

DAPTOmycin: HMG-CoA Reductase Inhibitors may enhance the adverse/toxic effect of DAPTOmycin. Specifically, the risk of skeletal muscle toxicity may be increased. Management: Consider temporarily stopping HMG-CoA reductase inhibitor therapy prior to daptomycin. If used together, regular (i.e., at least weekly) monitoring of CPK concentrations is recommended. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Etravirine: May decrease the serum concentration of HMG-CoA Reductase Inhibitors. This applies to atorvastatin, lovastatin and simvastatin. Conversely, levels of fluvastatin may be increased. Management: Dose adjustment of the HMG-CoA reductase inhibitor may be warranted. No interaction is expected with rosuvastatin or pravastatin. *Risk C: Monitor therapy*

Fenofibrate: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fenofibric Acid: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Gemfibrozil: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Gemfibrozil may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Grapefruit Juice: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Macrolide Antibiotics: May decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Niacin: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Niacinamide: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Protease Inhibitors: May increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Sildenafil: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

St Johns Wort: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): HMG-CoA Reductase Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid excessive ethanol consumption (due to potential hepatic effects).

Food: Food **decreases** the bioavailability of lovastatin extended release tablets and **increases** the bioavailability of lovastatin immediate release tablets. Lovastatin serum concentrations may be increased if taken with grapefruit juice; avoid concurrent intake of large quantities (>1 quart/day). Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.

Herb/Nutraceutical: St John's wort may decrease lovastatin levels.

Test InteractionsAltered thyroid function tests

Monitoring ParametersObtain baseline LFTs and total cholesterol profile. LFTs should also be assessed prior to upwards dosage adjustment to ≥40 mg daily or when otherwise indicated clinically. Enzyme levels should be followed periodically thereafter as clinically warranted.

Reference RangeNCEP classification of pediatric patients with familial history of hypercholesterolemia or premature CVD: Acceptable total cholesterol: <170 mg/dL, LDL: <110 mg/dL

Nursing: Physical Assessment/MonitoringUse caution with history of hepatic disease. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, other lipid-lowering agents may increase risk of myopathy or rhabdomyolysis). Evaluate results of laboratory tests (LFTs and lipid profile) at baseline and periodically. Assess patient response on a regular basis throughout therapy (eg, rash, myalgia, gastrointestinal effects). Teach patient proper use (as adjunct to diet and exercise program), possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to women of childbearing age unless they are capable of complying with effective contraceptive use. Instruct patient in appropriate contraceptive measures.

Monitoring: Lab TestsObtain baseline LFTs and total cholesterol profile. LFTs should be performed before initiation of therapy, at 6 and 12 weeks after initiation or first dose, and periodically thereafter.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take as directed with food at evening meal. Follow diet and exercise regimen as prescribed. You will have periodic blood tests to assess effectiveness. You may experience mild nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea (buttermilk, boiled milk, or yogurt may help); constipation (increased exercise, fruit, fluids, or fiber may help); or headache, dizziness, or insomnia (use caution when driving or engaged in potentially hazardous tasks until response to drug in known). Contact prescriber immediately with persistent muscle pain or cramping, skeletal or joint pain, or numbness. Report other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber for appropriate barrier contraceptive measures to use during and for 1 month following therapy. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 10 mg, 20 mg, 40 mg

Mevacor®: 20 mg, 40 mg

Tablet, extended release:

Altoprev®: 20 mg, 40 mg, 60 mg

Generic AvailableYes: Immediate release tablet

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Altoprev)

10 mg (30): $77.98

20 mg (30): $153.72

60 mg (30): $173.83

Tablets (Lovastatin)

10 mg (45): $47.99

20 mg (30): $22.99

40 mg (30): $35.99

Tables (Mevacor)

10 mg (30): $45.99

20 mg (30): $74.99

40 mg (30): $125.99

Mechanism of ActionLovastatin acts by competitively inhibiting 3-hydroxyl-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis

Pharmacodynamics/Kinetics

Onset of action: LDL-cholesterol reductions: 3 days

Absorption: 30%; increased with extended release tablets when taken in the fasting state

Protein binding: 95%

Metabolism: Hepatic; extensive first-pass effect; hydrolyzed to B-hydroxy acid (active)

Bioavailability: Increased with extended release tablets

Half-life elimination: 1.1-1.7 hours

Time to peak, serum: 2-4 hours

Excretion: Feces (~80% to 85%); urine (10%)

Related Information

- Hyperlipidemia Management
- Lipid-Lowering Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular Considerations

Primary Prevention: HMG-CoA reductase inhibitors are effective in primary and secondary prevention of cardiovascular events in patients with hyperlipidemia. For primary prevention, a patient's major risk factors (cigarette smoking, hypertension or currently taking antihypertensives, low HDL-C, family history, age, gender) should be evaluated. Patients with multiple risk factors (≥2) require more intensive therapy guided by the calculation of a 10-year absolute CHD risk (eg, the percent probability of having a CHD event in next 10 years). An individual's 10-year absolute CHD risk can be calculated at www.med-decisions.com/cvtool/phys/phys.html. LDL cholesterol goals, therapeutic lifestyle changes, and drug therapy are determined based upon a patient's risk factor profile.

Primary prevention trials show that cholesterol-lowering drugs reduce the risk of major coronary events, coronary death, and cerebrovascular events even in the first 6-12 months of use. The WOSCOP trial suggested a trend towards enhanced survival using pravastatin in their patients (mean LDL-cholesterol of 192 mg/dL and no history of MI). In a recent trial (Sever, 2003), patients with HTN and at least three other risk factors were randomized to 10 mg daily of atorvastatin or placebo. These patients had a total nonfasting cholesterol <250 mg/dL before treatment. LDL-C levels were 132 mg/dL before treatment and fell to an average of 90 mg/dL in the atorvastatin-treated group. There was a significant reduction in stroke, cardiovascular events, and coronary events in the atorvastatin-treated group as compared to the placebo group. There was no difference in mortality between the groups.

HMG-CoA reductase inhibitors decrease C-reactive protein (CRP), an inflammatory marker and an acute phase reactant. Elevated levels of high sensitive CRP (hsCRP), which detects CRP levels as low as 0.175 mg/L, have been shown to be associated with an increased risk of cardiovascular events. Recently, the JUPITER trial demonstrated that the use of rosuvastatin in healthy patients (men ≥50 years and women ≥60 years) without a history of cardiovascular disease with LDL <130 mg/dL and a hsCRP level ≥2 mg/L reduced the risk of major cardiovascular events (eg, nonfatal MI, stroke, death from cardiovascular causes), The number needed to treat over 5 years to prevent 1 cardiovascular event is 25. Current guidelines do not recommend drug treatment for patients with an LDL <130 mg/dL. However, identification of the patient at higher risk of cardiovascular events within this subgroup using hsCRP is now important given that statins may prevent the occurrence of these serious cardiovascular events (Ridker, 2008).

Secondary Prevention: Secondary prevention trials indicate that “statin” therapy reduces mortality, major coronary events, coronary artery procedures, and stroke. The Heart Protection Study proved that lowering serum cholesterol levels reduces the rate of major vascular events among high-risk individuals with documented vascular disease (CHD, cerebrovascular, peripheral vascular) or diabetes regardless of initial cholesterol concentrations. PROVE IT is a randomized, double-blind trial evaluating hospitalized patients with acute coronary syndrome to determine the effects of intense LDL-C lowering therapy. Four thousand patients with an LDL-C levels of 106 mg/dL were randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily. After 2 years, the combined cardiovascular endpoint (death, MI, unstable angina requiring hospitalization, revascularization and stroke) was ~26% in the pravastatin patients (median LDL-C 95 mg/dL) and ~22% in the atorvastatin treated patients (median LDL-C 62 mg/dL).

LaRosa and colleagues assessed the efficacy and safety of lowering LDL cholesterol <100 mg/dL in patients with stable coronary heart disease (LaRosa, 2005). Ten thousand and one patients with baseline LDL levels <130 mg/dL were randomized to atorvastatin 10 mg or 80 mg daily and followed for a median of 4.9 years. The primary endpoint was the occurrence of the first major cardiovascular event (death from CVD, MI, resuscitation after cardiac arrest, or stroke). A primary event occurred in 434 patients (8.7%) receiving 80 mg daily (mean LDL 77 mg/dL) and 548 patients (10.9%) receiving 10 mg dose (mean LDL 101 mg/dL) (95% CI, 0.69-0.89; p <0.001). There was no mortality difference between the two treatment groups.

In addition to the ability of HMG-CoA reductase inhibitors to decrease levels of high-sensitivity C-reactive protein (hs-CRP), they also possess pleiotropic properties including improved endothelial function, reduced inflammation at the site of the coronary plaque, inhibition of platelet aggregation, and anticoagulant effects. These nonlipid effects may be beneficial when HMG-CoA reductase inhibitors are introduced early in the management of acute coronary syndromes (de Denus, 2002).

Myopathy: Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years of age), women more frequently than men, small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, drug interactions (use with caution or avoid). The combination of a HMG-CoA reductase inhibitor plus nicotinic acid seems to carry a lower risk of myopathy than does a HMG-CoA reductase inhibitor plus a fibrate. Other medications, when used concurrently, may enhance the risk of myopathy associated with statins; these include drugs that inhibit CYP3A4 isoenzymes (lovastatin, simvastatin, atorvastatin) or CYP2C9 isoenzymes (fluvastatin). HMG-CoA reductase inhibitors may exacerbate exercise-induced skeletal muscle injury. Many experts favor getting a baseline creatine kinase (CK) measurement before initiating therapy (asymptomatic CK elevations are common). Obtain a CK measurement if patient complains of muscle soreness, tenderness, or pain.

Anesthesia and Critical Care Concerns/Other Considerations

Myopathy: Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years), gender (occurs in women more frequently than men), small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, and drug interactions (use with caution or avoid).

Based on current research, HMG-CoA reductase inhibitors should be continued in the perioperative period. Postoperative discontinuation of statin therapy is associated with an increased risk of cardiac morbidity and mortality.

Index Terms Mevinolin; Monacolin K

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International Brand NamesAnlostin (PL); Apo-Lova (PL); Asacor (TW); Basterol (KP); Cholvastin (ID); Colevastina (PE); Deolip (CL); Dilucid (MX); Ellanco (HK); Elstatin (SG); Favolip (IN); Hipovastin (AR); Holetar (EE); Justin (ID); Lestric (MY); Liperol (MX); Lipovas (ID); Liprox (PL); Lostatin (SG); Lovac (PL); Lovacel (KP); Lovachol (ZA); Lovalord (KP); Lovastatinum (PL); Lovasterol (CO, PL); Lovastin (KP, PL, SG); Lovatadin (KP); Medisorbin (GT, HN, NI, SV); Medostatin (AE, BG, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, MY, OM, QA, SA, SG, SY, YE); Mevacor (AT, BB, BM, BR, BS, BZ, CN, CZ, DK, FI, GY, HK, HN, JM, MX, NL, PE, PK, PL, SR, TT); Meverstin (KP); Mevinacor (DE); Ovasta (KP); Rovacor (IN, SG); Sancos (TW); Sidevar (MX)

Loxapine

Lexi-Drugs Online

English

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Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

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Medication Safety Issues

Sound-alike/look-alike issues:

Loxitane® may be confused with Lexapro®, Soriatane®

International issues:

Loxitane® may be confused with Lexotan® which is a brand name for bromazepam in multiple international markets

Pronunciation(LOKS a peen)

U.S. Brand Names Loxitane®

Canadian Brand Names Apo-Loxapine®; Loxapac® IM; Nu-Loxapine; PMS-Loxapine

Pharmacologic Category Antipsychotic Agent, Typical

Use: Labeled Indications Management of psychotic disorders

Use: Unlabeled/Investigational Psychosis/agitation related to Alzheimer's dementia

Dosing: Adults

Psychosis: Oral: 10 mg twice daily, increase dose until psychotic symptoms are controlled; usual dose range: 20-100 mg/day in divided doses 2-4 times/day; dosages >250 mg/day are not recommended.

Dosing: ElderlyOral: 20-60 mg/day

StorageProtect from light. Dispense in amber or opaque vials.

ContraindicationsHypersensitivity to loxapine or any component of the formulation; severe CNS depression; coma

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics. Avoid use in patients with underlying QT prolongation, in those taking medicines that prolong the QT interval, or cause polymorphic ventricular tachycardia; monitor ECG closely for dose-related QT effects.

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to other antipsychotics, loxapine has a low potency of cholinergic blockade.

- Blood dyscrasias: Myelosuppression (eg, leukopenia, agranulocytosis) has been observed with antipsychotic use; check blood counts periodically and discontinue at first signs of blood dyscrasias.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is moderate-high relative to other neuroleptics). Risk of dystonia (and possibly other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Pigmentary retinopathy: May be associated with pigmentary retinopathy.

- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Dementia: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo. An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Loxapine is not approved for this indication.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsMany elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior. Before initiating antipsychotic medication, the clinician should investigate any possible reversible cause; any stress or stress from any disease can cause acute “confusion” or worsening of baseline nonpsychotic behavior. Most commonly acute changes in behavior are due to increases in drug dose or addition of new drug to regimen; fluid electrolyte loss; infections; and changes in environment.

Any changes in disease status in any organ system can result in behavior changes.

In the treatment of agitated, demented, elderly patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Abnormal T waves with prolonged ventricular repolarization, arrhythmia, hyper-/hypotension, orthostatic hypotension, tachycardia, syncope

Central nervous system: Agitation, altered central temperature regulation, ataxia, confusion, dizziness, drowsiness, extrapyramidal reactions (akathisia, akinesia, dystonia, pseudoparkinsonism, tardive dyskinesia), faintness, headache, insomnia, lightheadedness, neuroleptic malignant syndrome (NMS), seizure, slurred speech, tension

Dermatologic: Alopecia, dermatitis, photosensitivity, pruritus, rash, seborrhea

Endocrine & metabolic: Amenorrhea, enlargement of breasts, galactorrhea, gynecomastia, menstrual irregularity

Gastrointestinal: Adynamic ileus, constipation, nausea, polydipsia, vomiting, weight gain/loss, xerostomia

Genitourinary: Sexual dysfunction, urinary retention

Hematologic: Agranulocytosis, leukopenia, thrombocytopenia

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision

Respiratory: Nasal congestion

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

LORazepam: Loxapine may enhance the adverse/toxic effect of LORazepam. Specifically, prolonged stupor, respiratory depression, and/or hypotension. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Test InteractionsFalse-positives for phenylketonuria, amylase, uroporphyrins, urobilinogen

Monitoring ParametersVital signs, orthostatic blood pressures 3-5 days after initiation of therapy or a dose increase; lipid profile, fasting blood glucose/Hgb A_{1c}; BMI; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms (EPS)

Nursing: Physical Assessment/MonitoringAssess other medications patient is taking for effectiveness and interactions. Review ophthalmic screening laboratory results, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. Initiate at lower doses and taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsLiver and kidney function, CBC prior to and at regular intervals, lipid profile, fasting blood glucose/Hgb A_{1c}; BMI; ophthalmic screening

Patient EducationUse exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results; do not discontinue without consulting prescriber. Do not take within 2 hours of any antacid. Avoid alcohol or caffeine and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience excess drowsiness, restlessness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); nausea, vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); urinary retention (void before taking medication); or decreased perspiration (avoid strenuous exercise in hot environments). Report persistent CNS effects (eg, trembling fingers, altered gait or balance, excessive sedation, seizures, unusual movements, anxiety, abnormal thoughts, confusion, personality changes); chest pain, palpitations, rapid heartbeat, severe dizziness; unresolved urinary retention or changes in urinary pattern; vision changes; skin rash or yellowing of skin; respiratory difficulty; or worsening of condition.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as succinate: 5 mg, 10 mg, 25 mg, 50 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Loxitane)

5 mg (60): $91.99

10 mg (60): $118.90

25 mg (60): $164.51

Mechanism of ActionLoxapine is a dibenzoxazepine antipsychotic which blocks postsynaptic mesolimbic D_1 and D_2 receptors in the brain, and also possesses serotonin 5-HT_2 blocking activity

Pharmacodynamics/Kinetics

Onset of action: Neuroleptic: Oral: 20-30 minutes

Peak effect: 1.5-3 hours

Duration: ~12 hours

Metabolism: Hepatic to glucuronide conjugates

Half-life elimination: Biphasic: Initial: 5 hours; Terminal: 12-19 hours

Excretion: Urine; feces (small amounts)

Related Information

- Antipsychotic Agents
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Liquid Compatibility
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Significant hypotension may occur, especially when the drug is administered parenterally; orthostatic hypotension is due to alpha-receptor blockade, the elderly are at greater risk for orthostatic hypotension.

Tardive dyskinesia: Prevalence rate may be 40% in elderly; development of the syndrome and the irreversible nature are proportional to duration and total cumulative dose over time. Extrapyramidal reactions are more common in elderly with up to 50% developing these reactions after 60 years of age. Drug-induced Parkinson's syndrome occurs often; akathisia is the most common extrapyramidal reaction in elderly.

Increased confusion, memory loss, psychotic behavior, and agitation frequently occur as a consequence of anticholinergic effects. Antipsychotic associated sedation in nonpsychotic patients is extremely unpleasant due to feelings of depersonalization, derealization, and dysphoria.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsMost pharmacology textbooks state that in presence of phenothiazines, systemic doses of epinephrine paradoxically decrease the blood pressure. This is the so called “epinephrine reversal” phenomenon. This has never been observed when epinephrine is given by infiltration as part of the anesthesia procedure. Loxapine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health CommentLoxapine is not commonly used. Older antipsychotic medications (chlorpromazine, haloperidol), which do not meet specific criteria for “atypical” antipsychotics, are often referred to as typical antipsychotics. They are associated with the troubling side effect, EPS. However, it is commonly believed that in order for a drug to treat psychosis, it must block dopamine is some manner.

Common side effects include sedation and neuroleptic effect (reduced initiative, interest in the environment, and display of emotion or affect). All **typical** antipsychotics are considered to be equally effective if given in equipotent doses. An inverse relationship exists between intrinsic antimuscarinic activity and propensity to cause extrapyramidal side effects. If dystonia or pseudoparkinsonism occurs, antiparkinsonian agents should be considered. If akathisia occurs, beta-blockers (eg, propranolol), benzodiazepines, or antiparkinsonian agents should be considered. Tardive dyskinesia (TD) secondary to typical antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. After this time period, the incidence is estimated to be 2% to 3% per year. Prevalence rates are ~15% to 20%. Female gender and age constitute risk factors for TD. Indeed, prevalence rates have been reported to be as high as 70% in elderly females. No specific treatment exists for TD, however, patients are often initiated on/switched to an atypical antipsychotic because of their lower incidence to cause TD and hopes of suppression.

Typical antipsychotics are usually only indicated for schizophrenia, but are generally effective for mania and psychosis and/or behavioral syndromes secondary to other mental conditions. Nonpsychiatric uses include Tourette's syndrome, Huntington's disease, and occasionally, intractable hiccups, pruritus, nausea, and vomiting.

These drugs are thought to exert their antipsychotic activity by blocking dopamine D_2 receptors in the mesolimbic dopaminergic pathway. Side effects are often related to their ability to antagonize dopamine receptors in the nigrostriatal and tuberoinfundibular pathways.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Index TermsLoxapine Succinate; Oxilapine Succinate

References

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International Brand NamesDesconex (ES); Desconex[gtt./inj.] (ES); Lopac (TW); Loxapac (BE, DK, ES, FR, GB, IE, IN, LU, NL); Rosup (TW)

Lubiprostone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(loo bi PROS tone)
U.S. Brand NamesAmitiza®
Pharmacologic CategoryChloride Channel Activator; Gastrointestinal Agent, Miscellaneous
Use: Labeled IndicationsTreatment of chronic idiopathic constipation; treatment of irritable bowel syndrome with constipation in adult women
Dosing: Adults

Chronic idiopathic constipation: Adults: 24 mcg twice daily

Irritable bowel syndrome with constipation: Females ≥18 years: 8 mcg twice daily

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentHas not been studied.
Dosing: Hepatic ImpairmentHas not been studied.
Dosing: Adjustment for Toxicity

Chronic idiopathic constipation: May decrease dose to 24 mcg once daily in case of severe nausea

Administration: OralAdminister with food and water. Swallow whole; do not break or chew.
Dietary ConsiderationsMay take with food to decrease nausea.
StorageStore at controlled room temperature of 25°C (77°F).
ContraindicationsKnown or suspected mechanical bowel obstruction
Warnings/Precautions

Concerns related to adverse effects:

- Dyspnea: Often described as chest tightness, dyspnea has been observed with use, including postmarketing reports; generally occurs following the first dose with an acute onset (within 30-60 minutes following the first dose) and resolves within a few hours; however, has been frequently reported with subsequent dosing.
- Nausea: Nausea may occur; administer with food to reduce symptoms. In long-term clinical studies for chronic idiopathic constipation, patients were allowed to reduce the dose to 24 mcg once daily if nausea was severe.

Disease-related concerns:

- Diarrhea: Avoid use in patients with severe diarrhea.
- Gastrointestinal obstruction: Symptoms of mechanical gastrointestinal obstruction should be evaluated before prescribing this medicine; use is contraindicated in patients with bowel obstruction.
- Hepatic impairment: Use with caution in patients with hepatic impairment; has not been studied in hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment; has not been .studied in renal impairment.

Special populations:

- Males: Not approved for use in males with irritable bowel syndrome with constipation.
- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo studies have been done in elderly populations to date. Data in subpopulation analysis demonstrate lubiprostone is safe and well tolerated in all sexes, races, and age groups.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies suggest that lubiprostone may cause fetal loss, teratogenic effects were not observed. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should have a negative pregnancy test prior to starting therapy and should be capable of complying with effective contraception.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%:

Central nervous system: Headache (11%)

Gastrointestinal: Nausea (8% to 29%; severe: 4%; dose related), diarrhea (7% to 12%; severe 2%)

1% to 10%:

Cardiovascular: Edema (3%), chest discomfort/pain (2%), hypertension (1%)

Central nervous system: Dizziness (3%), fatigue (2%), fever (1%), insomnia (1%)

Gastrointestinal: Abdominal pain (5% to 8%), abdominal distention (3% to 6%), flatulence (6%), vomiting (3%), loose stools (3%), dyspepsia (2%), stomach/abdominal discomfort (1% to 2%), xerostomia (1%), weight gain (1%)

Neuromuscular & skeletal: Arthralgia (3%), back pain (2%)

Renal: Urinary tract infection (4%)

Respiratory: Sinusitis (5%), upper respiratory tract infection (4%), nasopharyngitis (3%), bronchitis (2%), dyspnea (2%)

<1%, postmarketing, and/or case reports: Abnormal taste, allergic reactions, anorexia, anxiety, appetite decreased, asthma, cold sweat, constipation, cough, defecation urgency, eructation, erythema, fecal incontinence, flushing, frequent bowel movements, gastritis, heart rate increased, hyperhidrosis, hypoesthesia, influenza, joint swelling, lethargy, liver enzymes increased, malaise, muscle cramp, muscle spasm, myalgia, nervousness, pain, palpitation, paresthesia, pharyngolaryngeal pain, pollakiuria, rash, rectal hemorrhage, retching, rigors, syncope, tremor, urinary tract infection, urticaria, vertigo, viral infection, watery stools, weakness

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, softgel:

Amitiza®: 8 mcg, 24 mcg

Generic AvailableNo
ManufacturerSucampo Pharmaceuticals, Inc
Pricing: U.S. (www.drugstore.com)

Capsules (Amitiza)

8 mcg (60): $219.98

24 mcg (30): $114.28

Mechanism of ActionBicyclic fatty acid that acts locally at the apical portion of the intestine as a chloride channel activator, increasing intestinal fluid secretion and intestinal motility. Does not alter serum sodium or potassium concentrations.
Pharmacodynamics/Kinetics

Absorption: Systemic: Parent drug: Poor (below levels of detection); Active metabolite (M3): Low

Distribution: Gastrointestinal tissue; minimal beyond gastrointestinal tissue

Metabolism: Rapid and extensive within stomach and jejunum by carbonyl reductase to M3 (active metabolite) and others

Bioavailability: Minimal

Half-life elimination: M3: 0.9-1.4 hours

Excretion: Parent drug and M3: Feces (trace amounts)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause insomnia, dizziness, depression, or anxiety
Mental Health: Effects on Psychiatric TreatmentNausea and diarrhea are common; concomitant use with SSRIs, lithium, valproic acid, and carbamazepine may produce additive effects
Index TermsRU 0211; SPI 0211
References

Johanson JF and Ueno R, "Lubiprostone, a Locally Acting Chloride Channel Activator, In Adult Patients With Chronic Constipation: A Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate Efficacy and Safety," *Aliment Pharmacol Ther*, 2007, 25(11):1351-61.[PubMed 17509103]

Lutropin Alfa

Lexi-Drugs Online

English

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Pronunciation(LOO troe pin AL fa)
U.S. Brand NamesLuveris®
Pharmacologic CategoryGonadotropin; Ovulation Stimulator
Use: Labeled IndicationsStimulation of follicular development in infertile hypogonadotropic hypogonadal (HH) women with profound luteinizing hormone (LH) deficiency; to be used in combination with follitropin alfa
Dosing: Adults**Infertility:** Females: SubQ: 75 int. units daily until adequate follicular development is noted; maximum duration of treatment: 14 days; to be used concomitantly with follitropin alfa
Administration: OtherSubQ: Administer on the stomach, a few inches above or below the navel.
StorageStore under refrigeration or at room temperature of 2°C to 25°C (36°F to 77°F). Protect from light. Use immediately after reconstitution.
ReconstitutionReconstitute with SWFI. Mix gently, do not shake.
ContraindicationsHypersensitivity to lutropin alfa or any component of the formulation; primary ovarian failure; uncontrolled thyroid or adrenal dysfunction; uncontrolled organic intracranial lesion; abnormal uterine bleeding of undetermined origin; ovarian cyst or enlargement of undetermined origin; sex hormone-dependent tumors of the reproductive tract and accessory organs; pregnancy
Warnings/Precautions

Concerns related to adverse effects:

- Ovarian enlargement: May be accompanied by abdominal distention or abdominal pain and generally regresses without treatment within 2-3 weeks. If ovaries are abnormally enlarged on the last day of treatment, withhold hCG to reduce the risk of ovarian hyperstimulation syndrome (OHSS).

- Ovarian hyperstimulation syndrome (OHSS): OHSS is characterized by severe ovarian enlargement, abdominal pain/distention, nausea, vomiting, diarrhea, dyspnea, and oliguria, and may be accompanied by ascites, pleural effusion, hypovolemia, electrolyte imbalance, hemoperitoneum, and thromboembolic events. If severe hyperstimulation occurs, stop treatment and hospitalize patient. This syndrome develops rapidly with 24 hours to several days and generally occurs during the 7-10 days immediately following treatment.

- Thromboembolism: In association with and separate from ovarian hyperstimulation syndrome (OHSS), thromboembolic events have been reported.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; safety and efficacy have not been established.

- Renal impairment: Use with caution in patients with renal impairment; safety and efficacy have not been established.

Special populations:

- Elderly: Safety and efficacy have not been established in the elderly.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: To minimize risks, use only at the lowest effective dose. Monitor ovarian response with serum estradiol and vaginal ultrasound on a regular basis.

- Experienced physician: These medications should only be used by physicians who are thoroughly familiar with infertility problems and their management.

- Multiple births: May result from the use of these medications; advise patients of the potential risk of multiple births before starting the treatment.

Pregnancy Risk FactorX
Pregnancy ConsiderationsAn increase in pre- and postimplantation loss was observed in animal studies. Lutropin alfa is contraindicated for use during pregnancy.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

1% to 10%:

Central nervous system: Headache (10%), fatigue (2% to 3%)

Endocrine & metabolic: Ovarian hyperstimulation (6%)

Gastrointestinal: Nausea (7%), constipation (2% to 3%), diarrhea (2% to 3%)

Adverse events reported with gonadotropin or menotropin therapy: Adnexal torsion, arterial thromboembolism, congenital abnormalities, ectopic pregnancy, hemoperitoneum, ovarian enlargement (mild-to-moderate), ovarian neoplasms (infrequent), postpartum fever, premature labor, pulmonary complications, spontaneous abortion, vascular complications

Drug InteractionsThere are no known significant interactions.

Monitoring Parameters

Prior to therapy: Baseline LH <1.2 int. units/L, FSH <5 int. units/L, negative progestin challenge test

During therapy: Signs and symptoms of OHSS, ovarian enlargement; follicular maturation (vaginal ultrasound, serum estradiol levels); ovulation (basal body temperature, serum progesterone, menstruation)

Nursing: Physical Assessment/MonitoringThis medication should only be prescribed by a fertility specialist. For subcutaneous use only. Administer around navel area. Instruct patient in appropriate administration technique and disposal of used needles and syringes. **Pregnancy risk factor X:** Pregnancy must be excluded before starting medication. Consult prescriber if breast-feeding.

Patient EducationFor subcutaneous injection only. Follow administration schedule as directed by prescriber. Do not alter dosage or miss a dose. If a dose is missed, notify prescriber. You may experience headache, nausea (small frequent meals, frequent oral care, sucking lozenges, or chewing gum may help), fatigue, constipation, or diarrhea. Report immediately abdominal pain/distension, persistent nausea. **Pregnancy/breast-feeding precautions:** Pregnancy must be excluded before starting medication. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Luveris®: 75 int. units [contains sucrose; packaged with SWFI]

Generic AvailableNo

ManufacturerSerono, Inc

Mechanism of ActionLutropin alfa is a recombinant luteinizing hormone prepared using Chinese hamster cell ovaries. Administration leads to increased follicular estradiol secretion needed for follicle stimulating hormone induced follicular development.

Pharmacodynamics/Kinetics

Distribution: V_d: 10

Bioavailability: 56% ± 23%

Half-life elimination: Terminal: ~18 hours

Time to peak, serum: 4-16 hours

Excretion: Urine (<5% unchanged)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue

Mental Health: Effects on Psychiatric TreatmentMay cause GI side effects; concurrent use with SSRIs, lithium, or valproic acid may produce additive GI effects

Index Termsr-hLH; Recombinant Human Luteinizing Hormone

International Brand NamesLuver-I.S. (MX); Luveris (AR, AU, BE, BR, CH, CZ, DE, DK, EE, ES, FI, GB, HK, ID, IE, IL, IT, KP, NL, NO, PH, PL, PT, SE, SG, TW, UY, VE)

M-2

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Pharmacologic CategoryChemotherapy Regimen, Multiple Myeloma

Regimen UseMultiple myeloma

Regimen

Vincristine: I.V.: 0.03 mg/kg (maximum 2 mg) day 1

[total dose/cycle = 0.03 mg/kg]

Carmustine: I.V.: 0.5-1 mg/kg day 1

[total dose/cycle = 0.5-1 mg/kg]

Cyclophosphamide: I.V.: 10 mg/kg day 1

[total dose/cycle = 10 mg/kg]

Melphalan: Oral: 0.25 mg/kg/day days 1 to 4

[total dose/cycle = 1 mg/kg]

or 0.1 mg/kg/day days 1 to 7 or 1 to 10

[total dose/cycle = 0.7 or 1 mg/kg]

Prednisone: Oral: 1 mg/kg/day days 1 to 7

[total dose/cycle = 7 mg/kg]

Repeat cycle every 35-42 days

References

Case DC Jr, Lee DJ 3rd, and Clarkson BD, âImproved Survival Times in Multiple Myeloma Treated With Melphalan, Prednisone, Cyclophosphamide, Vincristine, and BCNU: M-2 Protocol,â *Am J Med*, 1977, 63(6):897-903.[PubMed 605911]

Pharmacologic Category Chemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen Use Lymphoma, non-Hodgkin's

Regimen

Methotrexate: I.V.: 200 mg/m^2/day days 8 and 15

[total dose/cycle = 400 mg/m^2]

Leucovorin calcium: Oral: 10 mg/m^2 every 6 hours for 8 doses (beginning 24 hours after each methotrexate dose) days 9 and 16

[total dose/cycle = 160 mg/m^2]

Bleomycin: I.V.: 4 units/m^2 day 1

[total dose/cycle = 4 units/m^2]

Doxorubicin: I.V.: 45 mg/m^2 day 1

[total dose/cycle = 45 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Vincristine: I.V.: 1 mg/m^2 day 1

[total dose/cycle = 1 mg/m^2]

Dexamethasone: Oral: 6 mg/m^2/day days 1 to 5

[total dose/cycle = 30 mg/m^2]

Repeat cycle every 21 days

References

Salles G, Shipp MA, and Coiffier B, “Chemotherapy of Non-Hodgkin's Aggressive Lymphomas,” *Semin Hematol*, 1994, 31(1):46-69. [PubMed 8122135]

Urba WJ, Duffey PL, and Longo DL, “Treatment of Patients With Aggressive Lymphomas: An Overview,” *J Natl Cancer Inst Monogr*, 1990, (10):29-37.[PubMed 2189474]

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m-Cresyl Acetate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(em-KREE sil AS e tate)
U.S. Brand NamesCresylate速
Pharmacologic CategoryOtic Agent, Anti-infective
Use: Labeled IndicationsProvides an acid medium; for external otitis infections caused by susceptible bacteria or fungus
Dosing: AdultsOtitis externa: Otic: Instill 2-4 drops as required
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, otic: 25% (15 mL) [with isopropanol 25%, chlorobutanol 1%, benzyl alcohol 1%, and castor oil 5% in propylene glycol]

Generic AvailableNo
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported

M-VAC (Bladder Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Bladder Cancer
Regimen UseBladder cancer
RegimenNOTE: Multiple variations are listed below.

Variation 1:

Methotrexate: I.V.: 30 mg/m^2/day days 1, 15, and 22

[total dose/cycle = 90 mg/m^2]

Vinblastine: I.V.: 3 mg/m^2/day days 2, 15, and 22

[total dose/cycle = 9 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 2

[total dose/cycle = 30 mg/m^2]

Cisplatin: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Repeat cycle every 4 weeks

Variation 2:

Methotrexate: I.V.: 40 or 50 mg/m^2/day days 1, 15, and 22

[total dose/cycle = 120 or 150 mg/m^2]

Vinblastine: I.V.: 4 or 5 mg/m^2/day days 2, 15, and 22

[total dose/cycle = 12 or 15 mg/m^2]

Doxorubicin: I.V.: 40 or 50 mg/m^2 day 2

[total dose/cycle = 40 or 50 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 2

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 4 weeks

Variation 3:

Methotrexate: I.V.: 30 mg/m^2/day days 1, 15, and 22

[total dose/cycle = 90 mg/m^2]

Vinblastine: I.V.: 3 mg/m^2 day 2

[total dose/cycle = 3 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 2

[total dose/cycle = 30 mg/m^2]

Cisplatin: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Repeat cycle every 4 weeks

Variation 4:

Methotrexate: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

followed by I.V.: 30 mg/m^2 day 16

[total dose/cycle = 30 mg/m^2]

Vinblastine: I.V.: 4 mg/m^2/day days 2 and 16

[total dose/cycle = 8 mg/m^2]

Doxorubicin: I.V.: 60 mg/m^2 day 2

[total dose/cycle = 60 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 2

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 23 days

Variation 5:

Methotrexate: I.V.: 30 mg/m^2/day days 1, 16, and 23

[total dose/cycle = 90 mg/m^2]

Vinblastine: I.V.: 4 mg/m^2/day days 1, 16, and 23

[total dose/cycle = 12 mg/m^2]

Doxorubicin: I.V.: 60 mg/m^2 day 2

[total dose/cycle = 60 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 2

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 23 days

Variation 6:

Methotrexate: I.V.: 30 or 35 mg/m^2 day 1

[total dose/cycle = 30 or 35 mg/m^2]

Vinblastine: I.V.: 3 or 3.5 mg/m^2 day 2

[total dose/cycle = 3 or 3.5 mg/m^2]

Doxorubicin: I.V.: 30 or 35 mg/m^2 day 2

[total dose/cycle = 30 or 35 mg/m^2]

Cisplatin: I.V.: 70 or 80 mg/m^2 day 2

[total dose/cycle = 70 or 80 mg/m^2]

Repeat cycle every 2 weeks

Variation 7:

Methotrexate: I.V.: 30 mg/m^2 day 1

[total dose/cycle = 30 mg/m^2]

Vinblastine: I.V.: 3 mg/m^2 day 2

[total dose/cycle = 3 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 2

[total dose/cycle = 30 mg/m^2]

Cisplatin: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Repeat cycle every 14 days

Variation 8:

Methotrexate: I.V.: 30 mg/m^2/day days 1, 15, and 22

[total dose/cycle = 90 mg/m^2]

Vinblastine: I.V.: 3 mg/m^2/day days 1, 15, and 22

[total dose/cycle = 9 mg/m^2]

Doxorubicin: I.V.: 45 mg/m^2 day 2

[total dose/cycle = 45 mg/m^2]

Cisplatin: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Repeat cycle every 4 weeks

Variation 9:

Methotrexate: I.V.: 40 mg/m^2/day days 1 and 15

[total dose/cycle = 80 mg/m^2]

Vinblastine: I.V.: 4 mg/m^2/day days 1, 16, and 23

[total dose/cycle = 12 mg/m^2]

Doxorubicin: I.V.: 60 mg/m^2 day 2

[total dose/cycle = 60 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 2

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 23 days

Variation 10:

Methotrexate: I.V.: 30 mg/m^2/day days 1, 15, and 22

[total dose/cycle = 90 mg/m^2]

Vinblastine: I.V.: 3 mg/m^2/day days 1, 16, and 22

[total dose/cycle = 9 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 1

[total dose/cycle = 30 mg/m^2]

Cisplatin: I.V.: 70 mg/m^2 day 1

[total dose/cycle = 70 mg/m^2]

Repeat cycle every 4 weeks

Variation 11:

Methotrexate: I.V.: 30 mg/m^2/day days 1, 15, and 22

[total dose/cycle = 90 mg/m^2]

Vinblastine: I.V.: 3 mg/m^2/day days 2, 15, and 22

[total dose/cycle = 9 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 2

[total dose/cycle = 30 mg/m^2]

Cisplatin: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Leucovorin: Oral: 15 mg every 6 hours for 4 doses, days 2, 16, and 23

[total dose/cycle = 180 mg]

Repeat cycle every 4 weeks

Variation 12:

Methotrexate: I.V.: 30 mg/m^2/day days 1 and 15

[total dose/cycle = 60 mg/m^2]

Vinblastine: I.V.: 3 mg/m^2/day days 2 and 15

[total dose/cycle = 6 mg/m^2]

Doxorubicin: I.V.: 30 or 40 mg/m^2 day 3

[total dose/cycle = 30 or 40 mg/m^2]

Cisplatin: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Repeat cycle every 4 weeks

Variation 13:

Methotrexate: I.V.: 30 mg/m^2/day days 1 and 15

[total dose/cycle = 60 mg/m^2]

Vinblastine: I.V.: 3 mg/m^2/day days 2 and 15

[total dose/cycle = 6 mg/m^2]

Doxorubicin: I.V.: 30 or 40 mg/m^2 day 2

[total dose/cycle = 30 or 40 mg/m^2]

Cisplatin: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Repeat cycle every 4 weeks

References

Variation 1:

Sternberg CN, de Mulder PH, Schornagel JH, et al, “Randomized Phase III Trial of High-Dose-Intensity Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (MVAC) Chemotherapy and Recombinant Human Granulocyte Colony-Stimulating Factor Versus Classic MVAC in Advanced Urothelial Tract Tumors: European Organization for Research and Treatment of Cancer Protocol No. 30924,” *J Clin Oncol*, 2001, 19(10):2638-46.[PubMed 11352955]

Sternberg CN, Yagoda A, Scher HI, et al, “Preliminary Results of M-VAC (Methotrexate, Vinblastine, Doxorubicin, and Cisplatin) for Transitional Cell Carcinoma of the Urothelium,” *J Urol*, 1985, 133(3):403-7. [PubMed 4038749]

Variation 2:

Loehrer PJ Sr, Elson P, Dreicer R, et al, “Escalated Dosages of Methotrexate, Vinblastine, Doxorubicin, and Cisplatin Plus Recombinant Human Granulocyte Colony-Stimulating Factor in Advanced Urothelial Carcinoma: An Eastern Cooperative Oncology Group Trial,” *J Clin Oncol*, 1994, 12(3):483-8. [PubMed 7509853]

Variation 3:

Loehrer PJ Sr, Einhorn LH, Elson PJ, et al, “A Randomized Comparison of Cisplatin Alone or in Combination With Methotrexate, Vinblastine, and Doxorubicin in Patients With Metastatic Urothelial Carcinoma: A Cooperative Group Study,” *J Clin Oncol*, 1992, 10(7):1066-73. [PubMed 1607913]

Variation 4:

Logothetis CJ, Finn LD, Smith T, et al, “Escalated MVAC With or Without Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor for the Initial Treatment of Advanced Malignant Urothelial Tumors: Results of a Randomized Trial,” *J Clin Oncol*, 1995, 13(9):2272-7. [PubMed 7666085]

Variation 5:

Logothetis CJ, Dexeus FH, Sella A, et al, “Escalated Therapy for Refractory Urothelial Tumors: Methotrexate-Vinblastine-Doxorubicin-Cisplatin

Plus Unglycosylated Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor,” *J Natl Cancer Inst*, 1990, 82(8):667-72. [PubMed 2181151]

Variation 6:

Sternberg CN, de Mulder PH, van Oosterom AT, et al, “Escalated M-VAC Chemotherapy and Recombinant Human Granulocyte-Macrophage Colony Stimulating Factor (rhGM-CSF) in Patients With Advanced Urothelial Tract Tumors,” *Ann Oncol*, 1993, 4(5):403-7. [PubMed 8353075]

Variation 7:

Sternberg CN, de Mulder PH, Schornagel JH, et al, “Randomized Phase III Trial of High-Dose-Intensity Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (M-VAC) Chemotherapy and Recombinant Human Granulocyte Colony-Stimulating Factor Versus Classic M-VAC in Advanced Urothelial Tract Tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924,” *J Clin Oncol*, 2001, 19(10):2638-46. [PubMed 11352955]

Variation 8 and 9:

Seidman AD, Scher HI, Gabrilove JL, et al, “Dose-Intensification of MVAC With Recombinant Granulocyte Colony-Stimulating Factor as Initial Therapy in Advanced Urothelial Cancer,” *J Clin Oncol*, 1993, 11(3):408-14. [PubMed 7680373]

Variation 10:

Bamias A, Aravantinos G, Deliveliotis C, et al, “Docetaxel and Cisplatin With Granulocyte Colony-Stimulating Factor (G-CSF) Versus M-VAC With G-CSF in Advanced Urothelial Carcinoma: A Multicenter, Randomized, Phase III Study From the Hellenic Cooperative Oncology Group,” *J Clin Oncol*, 2004, 22(2):220-8. [PubMed 14665607]

Variation 11:

Simon SD and Srougi M, “Neoadjuvant M-VAC Chemotherapy and Partial Cystectomy for Treatment of Locally Invasive Transitional Cell Carcinoma of the Bladder,” *Prog Clin Biol Res*, 1990, 353:169-74. [PubMed 2217415]

Variation 12:

Farah R, Chodak GW, Vogelzang NJ, et al, “Curative Radiotherapy Following Chemotherapy for Invasive Bladder Carcinoma (A Preliminary Report),” *Int J Radiat Oncol Biol Phys*, 1991, 20(3):413-7. [PubMed 1995525]

Variation 13:

Vogelzang NJ, Moormeier JA, Awan AM, et al, “Methotrexate, Vinblastine, Doxorubicin, and Cisplatin Followed by Radiotherapy or Surgery for Muscle Invasive Bladder Cancer: The University of Chicago Experience,” *J Urol*, 1993, 149(4):753-7.[PubMed 8455237]

M-VAC (Breast Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Breast Cancer]

Regimen UseBreast cancer

Regimen

Methotrexate: I.V.: 30 mg/m^2/day days 1, 15, and 22

[total dose/cycle = 90 mg/m^2]

Vinblastine: I.V.: 3 mg/m^2/day days 2, 15, and 22

[total dose/cycle = 9 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 2

[total dose/cycle = 30 mg/m^2]

Cisplatin: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Leucovorin: Oral: 10 mg every 6 hours for 6 doses days 2, 16, and 23

[total dose/cycle = 180 mg]

Repeat cycle every 4 weeks

References

Morrell LE, Lee YJ, Hurley J, et al, âA Phase II Trial of Neoadjuvant Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in the Treatment of Patients With Locally Advanced Breast Carcinoma,â *Cancer*, 1998, 82(3):503-11.[PubMed 9452268]

M-VAC (Cervical Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Cervical Cancer
Regimen UseCervical cancer
Regimen

Methotrexate: I.V.: 30 mg/m^2/day days 1, 15, and 22

[total dose/cycle = 90 mg/m^2]

Vinblastine: I.V.: 3 mg/m^2/day days 2, 15, and 22

[total dose/cycle = 9 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 2

[total dose/cycle = 30 mg/m^2]

Cisplatin: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Repeat cycle every 4 weeks

References

Wilson TO, âNeoadjuvant MVAC (Methotrexate, Vinblastine, Doxorubicin, Cisplatin) Chemotherapy for Locally Advanced or Metastatic Cervical and Vaginal Cancer,â *Adjuvant Therapy of Cancer VII*, Salmon SE, ed, Philadelphia, PA: J B Lipincott Co, 1997, 366-71.

M-VAC (Endometrial Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Endometrial Cancer]

Regimen UseEndometrial cancer

Regimen

Methotrexate: I.V.: 30 mg/m^2/day days 1, 15, and 22

[total dose/cycle = 90 mg/m^2]

Vinblastine: I.V.: 3 mg/m^2/day days 2, 15, and 22

[total dose/cycle = 9 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2/day day 2

[total dose/cycle = 30 mg/m^2]

Cisplatin: I.V.: 70 mg/m^2/day day 2

[total dose/cycle = 70 mg/m^2]

Repeat cycle every 4 weeks

References

Long HJ 3rd, Langdon RM Jr, Cha SS, et al, âPhase II Trial of Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in Advanced/Recurrent Endometrial Carcinoma,â *Gynecol Oncol*, 1995, 58(2):240-3.[PubMed 7622111]

M-VAC (Head and Neck Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Head and Neck Cancer]()
Regimen UseHead and neck cancer
Regimen

Methotrexate: I.V.: 30 mg/m^2/day days 1, 15, and 22

[total dose/cycle = 90 mg/m^2]

Vinblastine: I.V.: 3 mg/m^2/day days 2, 15, and 22

[total dose/cycle = 9 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 2

[total dose/cycle = 30 mg/m^2]

Cisplatin: I.V.: 70 mg/m^2 day 2

[total dose/cycle = 70 mg/m^2]

Repeat cycle every 4 weeks

References

Okuno SH, Mailliard JA, Suman VJ, et al, âPhase II Study of Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in Patients With Squamous Cell Carcinoma of the Upper Respiratory or Alimentary Passages of the Head and Neck,â *Cancer*, 2002, 94(8):2224-31.[PubMed 12001121]()

MACOP-B

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's

Regimen

Methotrexate: I.V. bolus: 100 mg/m^2 weeks 2, 6, 10

followed by I.V.: 300 mg/m^2 over 4 hours weeks 2, 6, and 10

[total dose/cycle = 1200 mg/m^2]

Doxorubicin: I.V.: 50 mg/m^2 weeks 1, 3, 5, 7, 9, and 11

[total dose/cycle = 300 mg/m^2]

Cyclophosphamide: I.V.: 350 mg/m^2 weeks 1, 3, 5, 7, 9, and 11

[total dose/cycle = 2100 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 (maximum 2 mg) weeks 2, 4, 6, 8, 10, and 12

[total dose/cycle = 8.4 mg/m^2; maximum 12 mg]

Bleomycin: I.V.: 10 units/m^2 weeks 4, 8, and 12

[total dose/cycle = 30 units/m^2]

Prednisone: Oral: 75 mg/day for 12 weeks, then taper over 2 weeks

Leucovorin calcium: Oral: 15 mg/m^2 every 6 hours, for 6 doses (beginning 24 hours after methotrexate) weeks 2, 6, and 10

[total dose/cycle = 270 mg/m^2]

Administer one cycle

References

Klimo P and Conors JM, âMACOP-B Chemotherapy for the Treatment of Diffuse Large-Cell Lymphoma,â *Ann Intern Med*, 1985, 102(5):596-602.[PubMed 2580468]

Mafenide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(MA fe nide)
U.S. Brand NamesSulfamylon®
Pharmacologic CategoryAntibiotic, Topical
Use: Labeled Indications

Cream: Adjunctive antibacterial agent in the treatment of second- and third-degree burns

Solution: Adjunctive antibacterial agent for use under moist dressings over meshed autografts on excised burn wounds

Dosing: AdultsBurns: Topical:

Cream: Apply once or twice daily with a sterile-gloved hand; apply to a thickness of approximately $^{1}/_{16}$ inch; the burned area should be covered with cream at all times

Solution: Cover graft area with 1 layer of fine mesh gauze. Wet an 8-ply burn dressing with mafenide solution and cover graft area. Keep dressing wet using syringe or irrigation tubing every 4 hours (or as necessary), or by moistening dressing every 6-8 hours (or as necessary). Irrigation dressing should be secured with bolster dressing and wrapped as appropriate. May leave dressings in place for up to 5 days.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Dosing: Adjustment for Toxicity

Acidosis: Discontinuing treatment for 24-48 hours may aid in restoring acid-base balance

Administration: TopicalCream: Keep burn area covered with cream at all times; use thinner layer if dressings are used. Apply to clean debrided area with a sterile gloved hand
Storage

Cream: Avoid exposure to excessive heat, >40°C (>104°F).

Powder: Prior to reconstitution, store powder at room temperature of 15°C to 30°C (59°F to 86°F). Store prepared solution at 20°C to 25°C (68°F to 77°F); may store at room temperature for limited periods. Solution may be stored in unopened containers for up to 28 days; once container is open, discard unused portion within 48 hours.

Reconstitution Powder: To prepare a 5% topical solution, add mafenide 50 g to 1000 mL of NS for irrigation or sterile water for irrigation. Mix until dissolved.
ContraindicationsHypersensitivity to mafenide or any component of the formulation
Allergy Considerations

- Sulfonamide Antibiotic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- G6PD deficiency: Use caution in patients with G6PD deficiency; may increase risk of DIC or hemolytic anemia

- Renal impairment: Use with caution in patients with renal impairment; accumulation of parent drug and metabolite may enhance carbonic anhydrase inhibition and increase risk of metabolic acidosis.

Dosage forms specific issues:

- Sulfites: Some dosage forms contain sulfites which may cause allergic reactions in certain individuals.

Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies using an oral preparation. Safety and efficacy have not been established in pregnant women. The manufacturer does not recommended use in women of childbearing potential unless the burn area

covers >20% of the total body surface or when benefits of treatment outweigh possible risks to the fetus.
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Edema, facial edema

Dermatologic: Erythema, maceration, pruritus, rash, urticaria

Endocrine & metabolic: Hyperchloremia, metabolic acidosis

Gastrointestinal: Diarrhea (following accidental ingestion)

Hematologic: Bleeding, bone marrow suppression, DIC, eosinophilia, hemolytic anemia, porphyria

Local: Blisters, burning sensation, excoriation, pain

Respiratory: Dyspnea, hyperventilation, pCO_2 decreased, tachypnea

Miscellaneous: Hypersensitivity

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersAcid base balance; signs of infection; signs of healing
Nursing: Physical Assessment/MonitoringSee Warnings/Precautions and Contraindications for use cautions. Assess for effectiveness of therapy and symptoms of infection. Assess knowledge/teach patient appropriate application and use and adverse symptoms (see Adverse Reactions) to report. **Pregnancy risk factor C.** Note breast-feeding caution.
Monitoring: Lab TestsAcid-base balance
Patient EducationFor external use only. Apply exactly as directed with sterile-gloved hand so that burned areas are covered with cream at all times. Avoid getting in eyes. Report facial swelling, skin rash, unusual bleeding, respiratory difficulty, persistent diarrhea, or signs of infections. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical:

Sulfamylon®: 85 mg/g (60 g, 120 g, 454 g) [contains sodium metabisulfite]

Powder, for topical solution, as acetate:

Sulfamylon®: 50 g/packet (5s)

Generic AvailableNo
Mechanism of ActionAs a sulfonamide, mafenide interferes with bacterial folic acid synthesis through competitive inhibition of para-aminobenzoic acid. Spectrum of activity encompasses both gram positive and negative organisms, including *Pseudomonas* and some anaerobes.
Pharmacodynamics/Kinetics

Absorption: Diffuses through devascularized areas and is rapidly absorbed from burned surface

Metabolism: To para-carboxybenzene sulfonamide; mafenide and metabolite are carbonic anhydrase inhibitors

Time to peak, serum: Cream 11%: 2-4 hours

Burn tissue: Cream 11%: 2 hours, Solution 5%: 4 hours

Excretion: Urine (as metabolites)

Related Information

- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsMafenide Acetate
International Brand NamesHomonal (JP); Mafatate (JP); Sulfomyl (GB)

Magaldrate and Simethicone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Riopan Plus® may be confused with Repan®

Pronunciation(MAG al drate & sye METH i kone)
U.S. Brand NamesRiopan Plus® Double Strength [OTC] [DSC]; Riopan Plus® [OTC] [DSC]
Pharmacologic CategoryAntacid; Antiflatulent
Use: Labeled IndicationsRelief of hyperacidity associated with peptic ulcer, gastritis, peptic esophagitis, and hiatal hernia which are accompanied by symptoms of gas
Dosing: Adults**Hyperacidity/gas:** Oral: 5-10 mL (540-1080 mg magaldrate) between meals and at bedtime
Dosing: ElderlyRefer to adult dosing.
Dietary ConsiderationsShould be taken on empty stomach.
Contraindications

Based on **magaldrate** component: Hypersensitivity to magaldrate or any component of the formulation; patients with colostomy or an ileostomy; appendicitis; ulcerative colitis; diverticulitis

Based on **simethicone** component: Hypersensitivity to simethicone or any component of the formulation

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/compatible
Adverse ReactionsFrequency not defined.

Based on **magaldrate** component:

Central nervous system: Encephalopathy

Gastrointestinal: Constipation, chalky taste, stomach cramps, fecal impaction, diarrhea, nausea, vomiting, discoloration of feces (white speckles), rebound hyperacidity

Endocrine & metabolic: Hypophosphatemia, hypermagnesemia, milk-alkali syndrome

Neuromuscular & metabolic: Osteomalacia

Miscellaneous: Aluminum intoxication

Based on **simethicone** component: No data reported

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C:*

Monitor therapy

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Mesalamine: Antacids may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids. *Risk X: Avoid combination*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Patient EducationSee individual agent for Simethicone.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Suspension, oral: Magaldrate 540 mg and simethicone 20 mg per 5 mL (360 mL)

Riopan Plus®: Magaldrate 540 mg and simethicone 20 mg per 5 mL (360 mL) [DSC]

Riopan Plus® Double Strength: Magaldrate 1080 mg and simethicone 40 mg per 5 mL (360 mL) [DSC]

Generic AvailableYes

Related Information

- Simethicone

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Chalky taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentConstipation is common; concurrent use with psychotropics may produce additive effects

Index TermsSimethicone and Magaldrate

Magnesium Chloride

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(mag NEE zhum KLOR ide)
U.S. Brand NamesChloromag®; Mag 64™ [OTC]; Mag Delay® [OTC]; Slow-Mag® [OTC]
Pharmacologic CategoryElectrolyte Supplement, Oral; Electrolyte Supplement, Parenteral; Magnesium Salt
Use: Labeled IndicationsCorrection or prevention of hypomagnesemia; dietary supplement
Dosing: Adults**Note:** Serum magnesium is poor reflection of repletional status as the majority of magnesium is intracellular; serum levels may be transiently normal for a few hours after a dose is given, therefore, aim for consistently high normal serum levels in patients with normal renal function for most efficient repletion.

Dietary supplement: Oral (Mag 64™, Mag Delay®, Slow-Mag®): 2 tablets once daily

Parenteral nutrition supplementation: I.V. (elemental magnesium): 8-24 mEq/day

RDA (elemental magnesium):

19-30 years:

Female: 310 mg/day

Pregnant female: 350 mg/day

Male: 400 mg/day

≥31 years:

Female: 320 mg/day

Pregnant female: 360 mg/day

Male: 420 mg/day

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Note:** Serum magnesium is poor reflection of repletional status as the majority of magnesium is intracellular; serum levels may be transiently normal for a few hours after a dose is given, therefore, aim for consistently high normal serum levels in patients with normal renal function for most efficient repletion.

Parenteral nutrition supplementation: I.V. (elemental magnesium):

<50 kg: 0.3-0.5 mEq/kg/day

>50 kg: 10-30 mEq/day

RDA (elemental magnesium):

1-3 years: 80 mg/day

4-8 years: 130 mg/day

9-13 years: 240 mg/day

14-18 years:

Female: 360 mg/day

Pregnant female: 400 mg/day

Male: 410 mg/day

Dosing: Renal Impairment Cl_{cr} <30 mL/minute: Use with caution; monitor for hypermagnesemia
Dietary ConsiderationsWhole grains, legumes, and dark-green leafy vegetables are dietary sources of magnesium.
StorageInjection: Prior to reconstitution, store at controlled room temperature of 15°C to 30°C (59°F to 86°F).
ReconstitutionDilute magnesium chloride 4 g in 250 mL D_5W.
ContraindicationsHypersensitivity to any component of the formulation; renal impairment; myocardial disease; coma
Warnings/Precautions

Disease-related concerns:

- Neuromuscular disease: Use with extreme caution in patients with myasthenia gravis or other neuromuscular disease.
- Renal impairment: Use with caution in patients with renal impairment; accumulation of magnesium may lead to magnesium intoxication.

Special populations:

- Obstetrics: Vigilant monitoring and safe administration techniques (ISMP Medication Safety Alert, 2005) recommended to avoid potential for errors resulting in toxicity. Monitor patient and fetal status, and serum magnesium levels closely.

Dosage form specific issues:

- Aluminum: Solutions may contain aluminum; toxic levels may occur following prolonged administration in premature neonates or patients with renal impairment.

Other warnings/precautions:

- Electrolyte abnormalities: Concurrent hypokalemia or hypocalcemia can accompany a magnesium deficit. Hypomagnesemia is associated with hypokalemia and requires correction in order to normalize potassium.
- Parenteral administration: Monitor serum magnesium level, respiratory rate, blood pressure, deep tendon reflex, and renal function when administered parenterally, particularly with repeated dosing; magnesium toxicity can lead to fatal cardiovascular arrest and/or respiratory paralysis.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. Magnesium crosses the placenta; serum levels in the fetus correlate with those in the mother.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsMagnesium is found in breast milk. The amount is not influenced by dietary intake under normal conditions.

Adverse ReactionsFrequency not defined: Gastrointestinal: Diarrhea (excessive oral doses)

Drug Interactions

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Eltrombopag: Magnesium Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., magnesium-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Monitoring Parameters

I.V.: Rapid administration: ECG monitoring, vital signs, deep tendon reflexes; magnesium, calcium, and potassium levels; renal function during administration

Oral: Renal function; magnesium levels; bowel movements

Reference RangeSerum magnesium: 1.5-2.5 mg/dL; slightly different ranges are reported by different laboratories

Monitoring: Lab Tests

Magnesium, calcium, potassium, and renal function

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 200 mg/mL [1.97 mEq/mL] (50 mL)

Chloromag®: 200 mg/mL [1.97 mEq/mL] (50 mL)

Tablet [enteric coated]:

Slow-Mag®: Elemental magnesium 64 mg [contains elemental calcium 106 mg]

Tablet, delayed release:

Mag 64™, Mag Delay®: Magnesium chloride hexahydrate 535 mg [equivalent to elemental magnesium 64 mg; contains elemental calcium 110 mg]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, controlled release (Slow-Mag)

64 mg (60): $18.99

Mechanism of ActionMagnesium is important as a cofactor in many enzymatic reactions in the body involving protein synthesis and carbohydrate metabolism (at least 300 enzymatic reactions require magnesium). Actions on lipoprotein lipase have been found to be important in reducing serum cholesterol and on sodium/potassium ATPase in promoting polarization (eg, neuromuscular functioning).

Pharmacodynamics/Kinetics

Absorption: Oral: Inversely proportional to amount ingested; 40% to 60% under controlled dietary conditions; 15% to 36% at higher doses

Distribution: Bone (50% to 60%); extracellular fluid (1% to 2%)

Protein binding: 30%, to albumin

Excretion: Urine (as magnesium)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Magnesium products may prevent GI absorption of tetracyclines by forming a large ionized chelated molecule with the tetracyclines in the stomach. Tetracyclines should be given at least 1 hour before magnesium.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause somnolence

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation

References

Bashuk RG and Krendel DA, “Myasthenia Gravis Presenting as Weakness After Magnesium Administration,” *Muscle Nerve*, 1990, 13(8):708-12.[PubMed 2385256]

Chernow B, Smith J, Rainey TG, et al, “Hypomagnesemia: Implications for the Critical Care Specialist,” *Crit Care Med*, 1982, 10(3):193-6. [PubMed 7037303]

“Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine,” National Academy of Sciences, Washington, DC: National Academy Press, 1997. Available at: http://www.nap.edu.

Dube L and Granry JC, “The Therapeutic Use Of Magnesium In Anesthesiology, Intensive Care And Emergency Medicine: A Review,” *Can J Anaesth*, 2003, 50(7):732-46.[PubMed 12944451]

Gams JG, “Clinical Significance of Magnesium: A Review,” *Drug Intell Clin Pharm*, 1987, 21(3):240-6. [PubMed 3552543]

Mirtallo J, Canada T, Johnson D, et al, “Safe Practices for Parenteral Nutrition,” *JPEN J Parenter Enteral Nutr*, 2004, 28(6):39-70.

International Brand NamesSlow-Mag (PL); Solural (MX)

Magnesium Citrate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(mag NEE zhum SIT rate)

U.S. Brand NamesCitroma® [OTC]

Canadian Brand NamesCitro-Mag®

Pharmacologic CategoryLaxative, Saline; Magnesium Salt

Use: Labeled IndicationsEvacuation of bowel prior to certain surgical and diagnostic procedures or overdose situations

Dosing: AdultsCathartic: Oral: Adults: $^1/_2$ to 1 full bottle (120-300 mL)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricCathartic: Oral: Children:

<6 years: 0.5 mL/kg up to a maximum of 200 mL repeated every 4-6 hours until stools are clear

6-12 years: 100-150 mL

≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentPatients in severe renal failure should not receive magnesium due to toxicity from accumulation. Patients with a Cl_{cr} <25 mL/minute should be monitored by serum magnesium levels.

Administration: OralTo increase palatability, chill the solution prior to administration.

Dietary ConsiderationsCitroma® 290 mg/5 mL (300 mL) cherry and lemon flavors contains magnesium 48 mg and potassium 13 mg per 5 mL; Citroma® grape and lemony flavors contains magnesium 48 mg and sodium 7.5 mg per 5 mL

ContraindicationsRenal failure, appendicitis, abdominal pain, intestinal impaction, obstruction or perforation, diabetes mellitus, complications in gastrointestinal tract, patients with colostomy or ileostomy, ulcerative colitis or diverticulitis

Warnings/Precautions

Disease-related concerns:

- Constipation (self-medication, OTC use): Appropriate use: For occasional use only; serious side effects may occur with prolonged use. For use only under the supervision of a healthcare provider in patients with kidney dysfunction, or with a sudden change in bowel habits which persist for >2 weeks. Do not use if abdominal pain, nausea, or vomiting are present.
- Neuromuscular disease: Use with extreme caution in patients with myasthenia gravis or other neuromuscular disease.
- Renal impairment: Use with caution in patients with renal impairment; accumulation of magnesium may lead to magnesium intoxication.

Geriatric ConsiderationsElderly, due to disease or drug therapy, may be predisposed to diarrhea. Diarrhea may result in electrolyte imbalance. Decreased renal function (Cl_{cr} <30 mL/minute) may result in toxicity; monitor for toxicity and Cl_{cr} <30 mL/minute.

Pregnancy Risk FactorB

Adverse Reactions1% to 10%:

Cardiovascular: Hypotension

Endocrine & metabolic: Hypermagnesemia

Gastrointestinal: Abdominal cramps, diarrhea, gas formation

Respiratory: Respiratory depression

Drug Interactions

Aluminum Hydroxide: Citric Acid Derivatives may increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Eltrombopag: Magnesium Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., magnesium-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Test InteractionsIncreased magnesium; decreased protein, decreased calcium (S), decreased potassium (S)

Reference RangeSerum magnesium: 1.5-2.5 mg/dL; slightly different ranges are reported by different laboratories

Nursing: Physical Assessment/MonitoringAssess therapeutic response and adverse effects.

Patient EducationTake with a glass of water, fruit juice, or citrus-flavored carbonated beverage to improve taste. Chill before using. Report severe abdominal pain to prescriber.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral: 290 mg/5 mL (300 mL) [cherry and lemon flavors]

Citroma®: 290 mg/5 mL (300 mL) [contains magnesium 48 mg and potassium 13 mg per 5 mL; cherry and lemon flavors]; (300 mL) [contains magnesium 48 mg and sodium 7.5 mg per 5 mL; grape and lemony flavors]

Tablet: 100 mg [as elemental magnesium]

Generic AvailableYes

Mechanism of ActionPromotes bowel evacuation by causing osmotic retention of fluid which distends the colon with increased peristaltic activity

Pharmacodynamics/Kinetics

Absorption: Oral: 15% to 30%

Excretion: Urine

Related Information

- Laxatives, Classification and Properties

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Magnesium products may prevent GI absorption of tetracyclines by forming a large ionized chelated molecule with the tetracyclines in the stomach. Tetracyclines should be given at least 1 hour before magnesium.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCitrate of Magnesia

References

Chernow B, Smith J, Rainey TG, et al, “Hypomagnesemia: Implications for the Critical Care Specialist,” *Crit Care Med*, 1982, 10(3):193-6. [PubMed 7037303]

Gams JG, “Clinical Significance of Magnesium: A Review,” *Drug Intell Clin Pharm*, 1987, 21(3):240-6. [PubMed 3552543]

Vuignier BI, Oderda GM, Gorman RL, et al, “Effects of Magnesium Citrate and Clidinium Bromide on the Excretion of Activated Charcoal in Normal Subjects,” *DICP*, 1989, 23(1):26-9.[PubMed 2718479]

International Brand NamesArgocytromag (PL); Citramag (GB); Magnesol (PL); Usanimals (MX)

Magnesium Glucoheptonate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(mag NEE zhum gloo koh HEP toh nate)

Canadian Brand NamesMagnelium®; Magnolex®; Magnorol® Sirop; ratio-Magnesium

Pharmacologic CategoryMagnesium Salt

Use: Labeled IndicationsTreatment and prevention of hypomagnesemia

Dosing: AdultsThe recommended dietary allowance (RDA) of magnesium is 4.5 mg/kg which is a total daily allowance of 350-400 mg for adult men and 280-300 mg for adult women. During pregnancy the RDA is 300 mg and during lactation the RDA is 355 mg. Average daily intakes of dietary magnesium have declined in recent years due to processing of food.

Note: Serum magnesium is poor reflection of repletional status as the majority of magnesium is intracellular; serum levels may be transiently normal for a few hours after a dose is given, therefore, aim for consistently high normal serum levels in patients with normal renal function for most efficient repletion

Hypomagnesemia: Oral: 100-600 mg (5-30 mg elemental magnesium) 1-2 times/day with food.

Maintenance electrolyte requirements:

Daily requirements: 0.2-0.5 mEq/kg/24 hours or 3-10 mEq/1000 kcal/24 hours

Maximum: 8-16 mEq/24 hours

Dosing adjustment/comments in renal impairment: Cl_{cr} <25 mL/minute: Do not administer or monitor serum magnesium levels carefully.

Dosing: ElderlyRefer to adult dosing.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsMagnesium glucoheptonate oral solution: Mix with water and administer on an empty stomach. 100 mg magnesium glucoheptonate = 0.42 mEq magnesium = 5 mg elemental magnesium

RestrictionsNot available in U.S.

ContraindicationsHeart block, serious renal impairment, myocardial damage, hepatitis, Addison's disease

Warnings/Precautions

Disease-related concerns:

- Constipation (self-medication, OTC use): Appropriate use: For occasional use only; serious side effects may occur with prolonged use. For use only under the supervision of a healthcare provider in patients with kidney dysfunction, or with a sudden change in bowel habits which persist for >2 weeks. Do not use if abdominal pain, nausea, or vomiting are present.
- Neuromuscular disease: Use with extreme caution in patients with myasthenia gravis or other neuromuscular disease.
- Renal impairment: Use with caution in patients with renal impairment; accumulation of magnesium may lead to magnesium intoxication.

Geriatric Considerations

Elderly, due to disease or drug therapy, may be predisposed to diarrhea. Diarrhea may result in electrolyte imbalance. Decreased renal function (Cl_{cr} <30 mL/minute) may result in toxicity; monitor for toxicity and Cl_{cr} <30 mL/minute.

Adverse ReactionsAdverse effects on neuromuscular function may occur at lower levels in patients with neuromuscular disease (eg, myasthenia gravis).

Serum magnesium levels >3 mg/dL:

Central nervous system: Depressed CNS

Gastrointestinal: Diarrhea

Neuromuscular & skeletal: Blocked peripheral neuromuscular transmission leading to anticonvulsant effects

Serum magnesium levels >5 mg/dL:

Cardiovascular: Flushing

Central nervous system: Somnolence

Serum magnesium levels >12.5 mg/dL:

Cardiovascular: Complete heart block, cardiac conduction affected

Respiratory: Respiratory paralysis

Drug Interactions

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Eltrombopag: Magnesium Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., magnesium-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Test InteractionsIncreased magnesium; decreased protein, calcium (S), decreased potassium (S)

Monitoring ParametersSerum magnesium levels should be monitored to avoid overdose; monitor for diarrhea

Reference RangeSerum magnesium: 1.5-2.5 mg/dL; slightly different ranges are reported by different laboratories

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Magnelium®, Magnorol®: 20 mg [contains 20 mg elemental magnesium]

Magnolex®: 300 mg [contains 15 mg elemental magnesium]

Solution, oral (ratio-Magnesium): 100 mg/mL (500 mL, 2000 mL) [contains 5 mg/mL elemental magnesium]

Syrup (Magnorol® Sirop): 90 mg/mL (400 mL) [contains 4.5 mg/mL elemental magnesium]

Generic AvailableYes

Mechanism of ActionWhen taken orally, magnesium promotes bowel evacuation by causing osmotic retention of fluid which distends the colon with increased peristaltic activity; parenterally, magnesium decreases acetylcholine in motor nerve terminals and acts on myocardium by slowing rate of S-A node impulse formation and prolonging conduction time.

Pharmacodynamics/KineticsExcretion: Urine (as magnesium)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Magnesium products may prevent GI absorption of tetracyclines by forming a large ionized chelated molecule with the tetracyclines in the stomach. Tetracyclines should be given at least 1 hour before magnesium.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation or CNS depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive CNS depression

Anesthesia and Critical Care Concerns/Other ConsiderationsHypomagnesemia can hinder the replenishment of intracellular potassium and should be corrected in order to correct hypokalemia.

Index TermsMagnesium Gluceptate

References

Bashuk RG and Krendel DA, “Myasthenia Gravis Presenting as Weakness After Magnesium Administration,” *Muscle Nerve*, 1990, 13(8):708-12.

Bohman VR and Cotton DB, “Supralethal Magnesemia With Patient Survival,” *Obstet Gynecol*, 1990, 76(5 Pt 2):984-6.

Engel J, “Normal Laboratory Values,” *Pocket Guide to Pediatric Assessment*, St Louis, MO: CV Mosby, 1989, 259.

Gams JG, “Clinical Significance of Magnesium: A Review,” *Drug Intell Clin Pharm*, 1987, 21(3):240-6.

Kaeser HE, “Drug-Induced Myasthenia Gravis,” *Acta Neurol Scand Suppl*, 1984, 100:39-47.

Nichols B, “Minerals,” *Pediatrics*, Norwalk, CT: Appleton & Lange, 1987, 176-7.

International Brand NamesMagnelium (CA); Magnolex (CA); Magnorol Sirop (CA); ratio-Magnesium (CA)

Magnesium Gluconate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(mag NEE zhum GLOO koe nate)

U.S. Brand NamesAlmora® [OTC]; Mag G® [OTC]; Magonate® [OTC]; Magtrate® [OTC]

Pharmacologic CategoryElectrolyte Supplement, Oral; Magnesium Salt

Use: Labeled IndicationsDietary supplement

Dosing: Adults**RDA (elemental magnesium):** Oral:

19-30 years:

- Female: 310 mg/day
- Pregnant female: 350 mg/day
- Male: 400 mg/day

≥31 years:

- Female: 320 mg/day
- Pregnant female: 360 mg/day
- Male: 420 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**RDA (elemental magnesium):** Oral:

1-3 years: 80 mg/day

4-8 years: 130 mg/day

9-13 years: 240 mg/day

14-18 years:

- Female: 360 mg/day
- Pregnant female: 400 mg/day
- Male: 410 mg/day

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute: Use with caution; monitor for hypermagnesemia

Administration: OralAdminister on an empty stomach

Dietary ConsiderationsWhole grains, legumes, and dark-green leafy vegetables are dietary sources of magnesium.

ContraindicationsHypersensitivity to any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Constipation (self-medication, OTC use): Appropriate use: For occasional use only; serious side effects may occur with prolonged use. For use only under the supervision of a healthcare provider in patients with kidney dysfunction, or with a sudden change in bowel habits which persist for >2 weeks. Do not use if abdominal pain, nausea, or vomiting are present.
- Neuromuscular disease: Use with extreme caution in patients with myasthenia gravis or other neuromuscular disease.
- Renal impairment: Use with caution in patients with renal impairment; accumulation of magnesium may lead to magnesium intoxication.

Pregnancy ConsiderationsMagnesium crosses the placenta; serum levels in the fetus correlate with those in the mother.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsMagnesium is found in breast milk. The amount is not influenced by dietary intake under normal conditions.

Adverse ReactionsFrequency not defined: Gastrointestinal: Diarrhea (excessive oral doses)

Drug Interactions

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of

Calcium Channel Blockers. *Risk C: Monitor therapy*

Eltrombopag: Magnesium Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., magnesium-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Reference RangeSerum magnesium: 1.5-2.5 mg/dL; slightly different ranges are reported by different laboratories

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution:

Magonate®: 1000 mg/5 mL (355 mL) [magnesium 4.8 mEq/5 mL; equivalent to elemental magnesium 54 mg/5 mL; contains sodium benzoate]

Tablet: 500 mg [magnesium 2.4 mEq; equivalent to elemental magnesium 27 mg]

Almora®, Mag G®, Magonate®, Magtrate®): 500 mg [magnesium 2.4 mEq; equivalent to elemental magnesium 27 mg]

Generic AvailableYes: Tablet

Mechanism of ActionMagnesium is important as a cofactor in many enzymatic reactions in the body involving protein synthesis and carbohydrate metabolism (at least 300 enzymatic reactions require magnesium). Actions on lipoprotein lipase have been found to be important in reducing serum cholesterol and on sodium/potassium ATPase in promoting polarization (eg, neuromuscular functioning).

Pharmacodynamics/Kinetics

Absorption: Oral: Inversely proportional to amount ingested; 40% to 60% under controlled dietary conditions; 15% to 36% at higher doses

Distribution: Bone (50% to 60%); extracellular fluid (1% to 2%)

Protein binding: 30%, to albumin

Excretion: Urine (as magnesium)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Magnesium products may prevent GI absorption of tetracyclines by forming a large ionized chelated molecule with the tetracyclines in the stomach. Tetracyclines should be given at least 1 hour before magnesium.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Bashuk RG and Krendel DA, “Myasthenia Gravis Presenting as Weakness After Magnesium Administration,” *Muscle Nerve*, 1990, 13(8):708-12.[PubMed 2385256]

“Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine,” National Academy of Sciences, Washington, DC: National Academy Press, 1997. Available at: http://www.nap.edu.

Gams JG, “Clinical Significance of Magnesium: A Review,” *Drug Intell Clin Pharm*, 1987, 21(3):240-6. [PubMed 3552543]

International Brand NamesBiogam Mg (BE, CH); Gammadyn Mg (BE); Magnerot[inj.] (DE); Magnesio (AR); Magnesium Gluconicum (AT); Magnesium Oligosol (FR); Mikroplex Magnesium (DE); Oligogranul Magnesium (FR); Oligosol Mg (BE, CH, FR); Oligostim Magnesium (FR); Oligostim Mg (BE); Provitina Magnesium (PL); Ultra Mg (LU); Ultra-Mag (AT); Ultra-Mg (BE)

Magnesium Hydroxide and Mineral Oil

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(mag NEE zhum hye DROKS ide & MIN er al oyl)

U.S. Brand NamesPhillips'® M-O [OTC]

Pharmacologic CategoryLaxative

Use: Labeled IndicationsShort-term treatment of occasional constipation

Dosing: AdultsLaxative: OTC labeling: Oral: 45-60 mL at bedtime

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricLaxative: OTC labeling: Oral:

Children <6 years: Use not recommended

Children 6-11 years: 20-30 mL at bedtime

Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentPatients in severe renal failure should not receive magnesium due to toxicity from accumulation. Patients with a Cl_{cr} <30 mL/minute should be monitored by serum magnesium levels.

Administration: OralShake well before using. Do not take with meals. Dose should be followed by 8 oz of liquid.

Dietary ConsiderationsPhillips'® M-O contains magnesium 125 mg and sodium 1.5 mg per 5 mL

ContraindicationsHypersensitivity magnesium hydroxide, mineral oil, or any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Renal impairment: Use magnesium with caution in patients with severe renal impairment (especially when doses are >50 mEq magnesium/day); hypermagnesemia and toxicity may occur due to decreased renal clearance of absorbed magnesium. Decreased renal function (Cl_{cr} <30 mL/minute) may result in toxicity; monitor for toxicity.

Other warnings/precautions:

- Self-medication (OTC use): Patients should notify healthcare provider of any sudden change in bowel habits which last >14 days, stomach pain, nausea, vomiting, or if use is needed for >1 week. Not for OTC use in children <6 years of age, in pregnant or bedridden patients, or patients with dysphagia. Avoid concomitant use with stool softener laxatives.

Geriatric ConsiderationsThe use of mineral oil products may be hazardous in the elderly with conditions predisposing them to aspiration. Elderly, due to disease or drug therapy, may be predisposed to diarrhea. Diarrhea may result in electrolyte imbalance. Decreased renal function (Cl_{cr} <30 mL/minute) may result in toxicity from magnesium absorption; monitor for toxicity.

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Antacids may decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of

Calcium Channel Blockers. *Risk C: Monitor therapy*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

Eltrombopag: Magnesium Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., magnesium-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Fexofenadine: Antacids may decrease the serum concentration of Fexofenadine. Management: No specific recommendations concerning the time required between their administration are provided. Separate administration of each agent by as much time as possible to decrease the risk of an interaction. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Mesalamine: Antacids may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids. *Risk X: Avoid combination*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, oral:

Phillips'® M-O: Magnesium hydroxide 300 mg and mineral oil 1.25 mL per 5 mL (360 mL, 780 mL) [contains magnesium 125 mg and sodium 1.5 mg per 5 mL mint flavors]

Generic AvailableNo
Pharmacodynamics/Kinetics

Onset of action: Laxative: 30 minutes to 6 hours hours

Excretion: Magnesium: Urine (up to 30% as absorbed magnesium ions); feces (as unabsorbed drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Magnesium products may prevent GI absorption of tetracyclines by forming a large ionized chelated molecule with the tetracyclines in the stomach. Tetracyclines should be given at least 1 hour before magnesium.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsHaley's M-O; MOM/Mineral Oil Emulsion

Magnesium Hydroxide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(mag NEE zhum hye DROKS ide)

U.S. Brand NamesPhillips'® Chews [OTC]; Phillips'® Milk of Magnesia [OTC]

Pharmacologic CategoryAntacid; Laxative; Magnesium Salt

Use: Labeled IndicationsShort-term treatment of occasional constipation and symptoms of hyperacidity, laxative; dietary supplement

Dosing: Adults

Antacid: OTC labeling: Oral:

Liquid: Magnesium hydroxide 400 mg/5 mL: 5-15 mL as needed up to 4 times/day

Tablet: Magnesium hydroxide 311 mg/tablet: 2-4 tablets every 4 hours up to 4 times/day

Dietary supplement: OTC labeling (Phillips'® Chews): Oral: Magnesium 500 mg: 2-4 tablets/day once daily at bedtime or in divided doses

Laxative: OTC labeling: Oral:

Liquid:

Magnesium hydroxide 400 mg/5 mL: 30-60 mL/day once daily at bedtime or in divided doses

Magnesium hydroxide 800 mg/5 mL: 15-30 mL/day once daily at bedtime or in divided doses

Tablet: Magnesium hydroxide 311 mg/tablet: 8 tablets/day once daily at bedtime or in divided doses

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Antacid: OTC labeling: Oral:

Liquid: Children ≥12 years: Refer to adult dosing.

Tablet:

Children <12 years: Use not recommended.

Children ≥12 years: Refer to adult dosing.

Dietary supplement: OTC labeling (Phillips'® Chews): Oral:

Children <12 years: Use not recommended.

Children ≥12 years: Refer to adult dosing.

Laxative: Oral:

Liquid: Magnesium hydroxide 400 mg/5 mL: 1-3 mL/kg/day; adjust dose to induce daily bowel movement

OTC labeling:

Children <2 years: Use not recommended.

Children 2-5 years: Magnesium hydroxide 400 mg/5 mL: 5-15 mL/day once daily at bedtime or in divided doses

Children 6-11 years:

Magnesium hydroxide 400 mg/5 mL: 15-30 mL/day once daily at bedtime or in divided doses

Magnesium hydroxide 800 mg/5 mL: 7.5-15 mL/day once daily at bedtime or in divided doses

Children ≥12 years: Refer to adult dosing.

Tablet: OTC labeling:

Children <3 years: Use not recommended.

Children 3-5 years: Magnesium hydroxide 311 mg/tablet: 2 tablets/day once daily at bedtime or in divided doses

Children 6-11 years: Magnesium hydroxide 311 mg/tablet: 4 tablets/day once daily at bedtime or in divided doses

Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentPatients in severe renal failure should not receive magnesium due to toxicity from accumulation. Patients with a Cl_{cr} <30 mL/minute should be monitored by serum magnesium levels.

Administration: OralLiquid doses may be diluted with a small amount of water prior to administration. All doses should be followed by 8 ounces of water.

Dietary Considerations

Liquid (400 mg/5 mL) contains magnesium 167 mg/5 mL.

Phillips'® Chews contain magnesium 500 mg/tablet, sodium 10 mg/tablet, coconut oil and soybean oil

Phillips'® Milk of Magnesia cherry flavor liquid contains sodium 2 mg/5 mL

Phillips'® Milk of Magnesia chewable tablets contain magnesium 130 mg/tablet

ContraindicationsHypersensitivity to magnesium hydroxide or any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Neuromuscular disease: Use with extreme caution in patients with myasthenia gravis or other neuromuscular disease.
- Renal impairment: Use with caution in patients with renal impairment; accumulation of magnesium may lead to magnesium intoxication.

Other warnings/precautions:

- OTC use: For occasional use only; serious side effects may occur with prolonged use. For use only under the supervision of a healthcare provider in patients with kidney dysfunction, or with a sudden change in bowel habits which persist for >2 weeks. Do not use if abdominal pain, nausea, or vomiting are present. Patients should notify healthcare provider of any sudden change in bowel habits which last >14 days, stomach pain, nausea, or vomiting or if use is needed for >1 week. Not for OTC use in children <2 years of age.

Geriatric ConsiderationsElderly, due to disease or drug therapy, may be predisposed to diarrhea. Diarrhea may result in electrolyte imbalance. Decreased renal function (Cl_{cr} <30 mL/minute) may result in toxicity; monitor for toxicity.

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Antacids may decrease the absorption of Allopurinol. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Antacids may decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

Eltrombopag: Magnesium Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., magnesium-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Fexofenadine: Antacids may decrease the serum concentration of Fexofenadine. Management: No specific recommendations concerning the time required between their administration are provided. Separate administration of each agent by as much time as possible to decrease the risk of an interaction. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Mesalamine: Antacids may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids. *Risk X: Avoid combination*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Mycophenolate: Antacids may decrease the absorption of Mycophenolate. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Quinolone Antibiotics: Antacids may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Sodium Polystyrene Sulfonate: May enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Test InteractionsIncreased magnesium; decreased protein, calcium (S), decreased potassium (S)
Reference RangeSerum magnesium: 1.5-2.5 mg/dL; slightly different ranges are reported by different laboratories
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, oral: 400 mg/5 mL (360 mL, 480 mL, 960 mL, 3780 mL)

Phillips'® Milk of Magnesia: 400 mg/5 mL (120 mL, 360 mL, 780 mL) [contains magnesium 167 mg/5 mL, cherry flavor also contains sodium 2 mg/5 mL; original, cherry, and mint flavors]

Liquid, oral concentrate: 800 mg/5 mL (100 mL, 400 mL)

Phillips'® Milk of Magnesia [concentrate]: 800 mg/5 mL (240 mL) [strawberry flavor]

Tablet, chewable:

Phillips'® Chews: Magnesium 500 mg [contains sodium 10 mg/tablet, coconut oil and soybean oil; chocolate flavor]

Phillips'® Milk of Magnesia: 311 mg [contains magnesium 130 mg/tablet; mint flavor]

Generic AvailableYes: Liquid
Pricing: U.S. (www.drugstore.com)

Suspension (Milk of Magnesia)

400 mg/5 mL (480): $12.00

Mechanism of ActionPromotes bowel evacuation by causing osmotic retention of fluid which distends the colon with increased peristaltic activity; reacts with hydrochloric acid in stomach to form magnesium chloride

Pharmacodynamics/Kinetics

Onset of action: Laxative: 30 minutes to 6 hours

Excretion: Urine (up to 30% as absorbed magnesium ions); feces (as unabsorbed drug)

Related Information

- Laxatives, Classification and Properties

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Magnesium products may prevent GI absorption of tetracyclines by forming a large ionized chelated molecule with the tetracyclines in the stomach. Tetracyclines should be given at least 1 hour before magnesium.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMagnesia Magma; Milk of Magnesia; MOM

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Constipation Guideline Committee, “Clinical Practice Guideline. Evaluation and Treatment of Constipation of Infants and Children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition,” *J Pediatr Gastroenterol Nutr*, 2006, 43(3):e1-13.[PubMed 16954945]

Gams JG, “Clinical Significance of Magnesium: A Review,” *Drug Intell Clin Pharm*, 1987, 21(3):240-6.[PubMed 3552543]

International Brand NamesMilk of Magnesia (PL); Milmag (PL)

Magnesium L-aspartate Hydrochloride

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(mag NEE zhum el as PAR tate hye droe KLOR ide)

U.S. Brand NamesMaginex™ DS [OTC]; Maginex™ [OTC]

Pharmacologic CategoryElectrolyte Supplement, Oral; Magnesium Salt

Use: Labeled IndicationsDietary supplement

Dosing: Adults

RDA (elemental magnesium):

- 19-30 years:
    - Female: 310 mg/day
    - Pregnant female: 350 mg/day
    - Male: 400 mg/day
- ≥31 years:
    - Female: 320 mg/day
    - Pregnant female: 360 mg/day
    - Male: 420 mg/day

Dietary supplement: Oral: Magnesium-L-aspartate 1230 mg (magnesium 122 mg) up to 3 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

RDA (elemental magnesium):

- 1-3 years: 80 mg/day
- 4-8 years: 130 mg/day
- 9-13 years: 240 mg/day
- 14-18 years:
    - Female: 360 mg/day
    - Pregnant female: 400 mg/day
    - Male: 410 mg/day

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute: Use with caution; monitor for hypermagnesemia

Administration: Oral

Granules: Mix each packet in 4 ounces of water or juice prior to administration

Tablet, enteric coated: Do not crush or chew

Dietary ConsiderationsTake with food. Whole grains, legumes, and dark-green leafy vegetables are dietary sources of magnesium.

ContraindicationsHypersensitivity to any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Constipation (self-medication, OTC use): Appropriate use: For occasional use only; serious side effects may occur with prolonged use. For use only under the supervision of a healthcare provider in patients with kidney dysfunction, or with a sudden change in bowel habits which persist for >2 weeks. Do not use if abdominal pain, nausea, or vomiting are present.
- Neuromuscular disease: Use with extreme caution in patients with myasthenia gravis or other neuromuscular disease.
- Renal impairment: Use with caution in patients with renal impairment; accumulation of magnesium may lead to magnesium intoxication.

Geriatric ConsiderationsElderly, due to disease or drug therapy, may be predisposed to diarrhea. Diarrhea may result in electrolyte imbalance. Decreased renal function (Cl_{cr} <30 mL/minute) may result in toxicity; monitor for toxicity. Monitor for signs of confusion or worsening signs of dementia.

Pregnancy ConsiderationsMagnesium crosses the placenta; serum levels in the fetus correlate with those in the mother.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsMagnesium is found in breast milk. The amount is not influenced by dietary intake under normal conditions.

Adverse ReactionsFrequency not defined: Gastrointestinal: Diarrhea (excessive oral doses)

Drug Interactions

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Eltrombopag: Magnesium Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., magnesium-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Reference RangeSerum magnesium: 1.5-2.5 mg/dL; slightly different ranges are reported by different laboratories

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Granules:

Maginex™ DS: 1230 mg/packet (30s) [magnesium 10 mEq; equivalent to magnesium 122 mg; lemon flavor]

Tablet [enteric coated]:

Maginex™: 615 mg [magnesium 5 mEq; equivalent to magnesium 61 mg]

Generic AvailableNo

ManufacturerGeist Pharmaceuticals, LLC

Pricing: U.S. (www.drugstore.com)

Tablet, EC (Maginex)

615 mg (30): $17.99

Mechanism of ActionMagnesium is important as a cofactor in many enzymatic reactions in the body involving protein synthesis and carbohydrate metabolism (at least 300 enzymatic reactions require magnesium). Actions on lipoprotein lipase have been found to be important in reducing serum cholesterol and on sodium/potassium ATPase in promoting polarization (eg, neuromuscular functioning).

Pharmacodynamics/Kinetics

Absorption: Oral: Inversely proportional to amount ingested; 40% to 60% under controlled dietary conditions; 15% to 36% at higher doses. Absorption of the Maginex™ formulation may be increased compared to other magnesium salts.

Distribution: Bone (50% to 60%); extracellular fluid (1% to 2%)

Protein binding: 30%, to albumin

Excretion: Urine (as magnesium)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Magnesium ions prevent GI absorption of tetracycline by forming a large, ionized, chelated molecule with the magnesium ion and tetracyclines in the stomach. Magnesium supplement should not be taken within 2-4 hours of oral tetracycline or other members of the tetracycline family.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause diarrhea; concomitant use with lithium, valproic acid, and SSRIs may produce additive effects. Diarrhea may lead to dehydration and alteration of serum lithium levels; monitor.

Index TermsMAH

References

Bashuk RG and Krendel DA, “Myasthenia Gravis Presenting as Weakness After Magnesium Administration,” *Muscle Nerve*, 1990, 13(8):708-12.[PubMed 2385256]

“Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine,” National Academy of Sciences, Washington, DC: National Academy Press, 1997. Available at: http://www.nap.edu.

Gams JG, “Clinical Significance of Magnesium: A Review,” *Drug Intell Clin Pharm*, 1987, 21(3):240-6. [PubMed 3552543]

English

Jump To Field (Select Field Name)

Pronunciation(mag NEE zhum el LAK tate)
U.S. Brand NamesMag-Tab® SR
Pharmacologic CategoryElectrolyte Supplement; Magnesium Salt
Use: Labeled IndicationsDietary supplement
Dosing: Adults

Dietary supplement: Oral:1-2 caplets every 12 hours

RDA (elemental magnesium):

- 19-30 years:
    - Female: 310 mg/day
    - Pregnant female: 350 mg/day
    - Male: 400 mg/day
- ≥31 years:
    - Female: 320 mg/day
    - Pregnant female: 360 mg/day
    - Male: 420 mg/day

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**RDA (elemental magnesium):**

Children:

- 1-3 years: 80 mg/day
- 4-8 years: 130 mg/day
- 9-13 years: 240 mg/day
- 14-18 years:
    - Female: 360 mg/day
    - Pregnant female: 400 mg/day
    - Male: 410 mg/day

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute: Use with caution; monitor for hypermagnesemia
Administration: OralShould be administered with food.
Dietary ConsiderationsShould be taken with food. Whole grains, legumes, and dark-green leafy vegetables are dietary sources of magnesium.
ContraindicationsHypersensitivity to any component of the formulation
Warnings/Precautions

Disease-related concerns:

- Constipation (self-medication, OTC use): Appropriate use: For occasional use only; serious side effects may occur with prolonged use. For use only under the supervision of a healthcare provider in patients with kidney dysfunction, or with a sudden change in bowel habits which persist for >2 weeks. Do not use if abdominal pain, nausea, or vomiting are present.
- Neuromuscular disease: Use with extreme caution in patients with myasthenia gravis or other neuromuscular disease.
- Renal impairment: Use with caution in patients with renal impairment; accumulation of magnesium may lead to magnesium intoxication.

Geriatric ConsiderationsElderly, due to disease or drug therapy, may be predisposed to diarrhea. Diarrhea may result in electrolyte imbalance. Decreased renal function (Cl_{cr} <30 mL/minute) may result in toxicity; monitor for toxicity and Cl_{cr} <30 mL/minute.
Pregnancy ConsiderationsMagnesium crosses the placenta; serum levels in the fetus correlate with those in the mother.
LactationEnters breast milk/compatible
Breast-Feeding ConsiderationsMagnesium is found in breast milk. The amount is not influenced by dietary intake under normal conditions.

Adverse ReactionsFrequency not defined: Gastrointestinal: Diarrhea

Drug Interactions

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Eltrombopag: Magnesium Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., magnesium-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Reference RangeSerum magnesium: 1.5-2.5 mg/dL; slightly different ranges are reported by different laboratories

Patient EducationTake with food. Report severe, persistent diarrhea.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet, sustained-release:

Mag-Tab® SR: Elemental magnesium 84 mg (7 mEq)

Generic AvailableNo

ManufacturerNiche

Pricing: U.S. (www.drugstore.com)

Tablet, controlled release (Mag-Tab SR)

84 MG (7MEQ) (30): $15.99

Mechanism of ActionMagnesium is important as a cofactor in many enzymatic reactions in the body involving protein synthesis and carbohydrate metabolism (at least 300 enzymatic reactions require magnesium). Actions on lipoprotein lipase have been found to be important in reducing serum cholesterol and on sodium/potassium ATPase in promoting polarization (eg, neuromuscular functioning).

Pharmacodynamics/Kinetics

Absorption: Oral: Inversely proportional to amount ingested; 40% to 60% under controlled dietary conditions; 15% to 36% at higher doses; majority occurs in jejunum and ileum.

Distribution: Bone (50% to 60%); extracellular fluid (1% to 2%)

Protein binding: 30%, to albumin

Bioavailability: 41%

Excretion: Urine (as magnesium)

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMagnesium L-lactate Dihydrate

References

Bashuk RG and Krendel DA, “Myasthenia Gravis Presenting as Weakness After Magnesium Administration,” *Muscle Nerve*, 1990, 13(8):708-12.[PubMed 2385256]

“Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine,” National Academy of Sciences, Washington, DC: National Academy Press, 1997. Available at: http://www.nap.edu.

Gams JG, “Clinical Significance of Magnesium: A Review,” *Drug Intell Clin Pharm*, 1987, 21(3):240-6. [PubMed 3552543]

Magnesium Oxide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(mag NEE zhum OKS ide)

U.S. Brand NamesMag-Caps [OTC]; Mag-Ox® 400 [OTC]; MagGel™ [OTC]; Uro-Mag® [OTC]

Pharmacologic CategoryElectrolyte Supplement, Oral; Magnesium Salt

Use: Labeled IndicationsElectrolyte replacement

Dosing: Adults

RDA (elemental magnesium): Oral:

19-30 years:

Female: 310 mg/day

Pregnant female: 350 mg/day

Male: 400 mg/day

≥31 years:

Female: 320 mg/day

Pregnant female: 360 mg/day

Male: 420 mg/day

Dietary supplement: Oral:

Mag-Ox 400®: 2 tablets daily with food

Mag-Caps, Uro-Mag®: 4-5 capsules daily with food

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**RDA (elemental magnesium):** Oral:

1-3 years: 80 mg/day

4-8 years: 130 mg/day

9-13 years: 240 mg/day

14-18 years:

Female: 360 mg/day

Pregnant female: 400 mg/day

Male: 410 mg/day

Dosing: Renal Impairment Cl_{cr} <30 mL/minute: Use with caution; monitor for hypermagnesemia

Dietary ConsiderationsShould be taken with food. Whole grains, legumes, and dark-green leafy vegetables are dietary sources of magnesium.

ContraindicationsHypersensitivity to any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Constipation (self-medication, OTC use): Appropriate use: For occasional use only; serious side effects may occur with prolonged use. For use only under the supervision of a healthcare provider in patients with kidney dysfunction, or with a sudden change in bowel habits which persist for >2 weeks. Do not use if abdominal pain, nausea, or vomiting are present.
- Neuromuscular disease: Use with extreme caution in patients with myasthenia gravis or other neuromuscular disease.
- Renal impairment: Use with caution in patients with renal impairment; accumulation of magnesium may lead to magnesium intoxication.

Geriatric ConsiderationsElderly, due to disease or drug therapy, may be predisposed to diarrhea. Diarrhea may result in electrolyte imbalance. Decreased renal function (Cl_{cr} <30 mL/minute) may result in toxicity; monitor for toxicity.

Pregnancy ConsiderationsMagnesium crosses the placenta; serum levels in the fetus correlate with those in the mother.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsMagnesium is found in breast milk. The amount is not influenced by dietary intake under normal conditions.

Adverse ReactionsFrequency not defined: Gastrointestinal: Diarrhea (excessive oral doses)

Drug Interactions

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Eltrombopag: Magnesium Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., magnesium-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Reference RangeSerum magnesium: 1.5-2.5 mg/dL; slightly different ranges are reported by different laboratories

Nursing: Physical Assessment/MonitoringAssess therapeutic response and adverse effects.

Patient EducationMay cause diarrhea (buttermilk, boiled milk, or yogurt may help).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet: 250 mg

Capsule:

Mag-Caps: Elemental magnesium 85 mg

Uro-Mag®: 140 mg [magnesium 7 mEq; equivalent to elemental magnesium 84.5 mg]

Capsule, softgel:

MagGel™: 600 mg [magnesium 28.64 mEq; equivalent to elemental magnesium 348 mg]

Tablet: 400 mg [magnesium 20 mEq; equivalent to elemental magnesium 242 mg], 500 mg

Mag-Ox® 400: 400 mg [magnesium 20 mEq; equivalent to elemental magnesium 242 mg]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Mag-Ox 400)

400 mg (120): $22.00

Tablets (Mag-Oxide)

400 mg (30): $11.99

Mechanism of ActionMagnesium is important as a cofactor in many enzymatic reactions in the body involving protein synthesis and carbohydrate metabolism (at least 300 enzymatic reactions require magnesium). Actions on lipoprotein lipase have been found to be important in reducing serum cholesterol and on sodium/potassium ATPase in promoting polarization (eg, neuromuscular functioning).

Pharmacodynamics/Kinetics

Absorption: Oral: Inversely proportional to amount ingested; 40% to 60% under controlled dietary conditions; 15% to 36% at higher doses

Distribution: Bone (50% to 60%); extracellular fluid (1% to 2%)

Protein binding: 30%, to albumin

Excretion: Urine (as magnesium)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Magnesium products may prevent GI absorption of tetracyclines by forming a large ionized chelated molecule with the tetracyclines in the stomach. Tetracyclines should be given at least 1 hour before magnesium.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May rarely cause depression

Mental Health: Effects on Psychiatric Treatment None reported

References

Bashuk RG and Krendel DA, “Myasthenia Gravis Presenting as Weakness After Magnesium Administration,” *Muscle Nerve*, 1990, 13(8):708-12.[PubMed 2385256]

Chernow B, Smith J, Rainey TG, et al, “Hypomagnesemia: Implications for the Critical Care Specialist,” *Crit Care Med*, 1982, 10(3):193-6. [PubMed 7037303]

“Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine,” National Academy of Sciences, Washington, DC: National Academy Press, 1997. Available at: http://www.nap.edu.

Gams JG, “Clinical Significance of Magnesium: A Review,” *Drug Intell Clin Pharm*, 1987, 21(3):240-6. [PubMed 3552543]

International Brand Names Magnez (PL); Oximag (PL); Plusssz Magnez (PL)

Magnesium Salicylate

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(mag NEE zhum sa LIS i late)

U.S. Brand NamesDoan's® Extra Strength [OTC]; Keygesic [OTC]; Momentum® [OTC]; Novasal™

Pharmacologic CategorySalicylate

Use: Labeled IndicationsMild-to-moderate pain, fever, various inflammatory conditions; relief of pain and inflammation of rheumatoid arthritis and osteoarthritis

Dosing: Adults

Relief of mild-to-moderate pain:

Doan's® Extra Strength, Momentum®: Two caplets every 6 hours as needed (maximum: 8 caplets/24 hours)

Keygesic: One tablet every 4 hours as needed (maximum 4 tablets/24 hours)

Treatment of arthritis (Novasal™): Initial: 1 tablet 3-4 times/day. Maximum: 8 tablets/day

Dosing: ElderlyTreatment of arthritis (Novasal™): Refer to adult dosing. Reduce adult dose to lowest effective dose; monitor for signs of toxicity.

Dosing: Pediatric**Relief of mild-to-moderate pain:** Children ≥12 years: Refer to adult dosing.

Administration: OralAdminister with a full glass of water.

ContraindicationsHypersensitivity to magnesium salicylate, salicylates, other NSAIDs, or any component of the formulation; advanced chronic renal dysfunction; concomitant use with uricosuric agents

In patients ≥65 years of age: Also contraindicated with a history of chronic salicylate use, carditis, chronic liver dysfunction

Allergy Considerations

- Salicylate Allergy/Sensitivity

Warnings/Precautions

Boxed warnings:

- Hepatic impairment: See “Disease-related concerns” below.
- Hypoprothrombinemia/vitamin K deficiency: See “Disease-related concerns” below.
- Surgical patients: See “Special populations” below.

Concerns related to adverse effects:

- Salicylate sensitivity: Patients with sensitivity to tartrazine dyes, nasal polyps, and asthma may have an increased risk of salicylate sensitivity.
- Tinnitus: Discontinue use if tinnitus or impaired hearing occurs.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with bleeding disorders.
- Dehydration: Use with caution in patients with dehydration.
- Ethanol use: Heavy ethanol use (>3 drinks/day) can increase bleeding risks.
- Gastrointestinal disease: Use with caution in patients with erosive gastritis or peptic ulcer.
- Hepatic impairment: **[U.S. Boxed Warning]: Use with caution in patients with hepatic impairment;** avoid in severe impairment.
- Hypoprothrombinemia/vitamin K deficiency: **[U.S. Boxed Warning]: Use high doses with caution in patients with hypoprothrombinemia and/or vitamin K deficiency.**
- Renal impairment: Use with caution in patients with renal impairment; avoid use in severe impairment.

Special populations:

- Elderly: The lowest effective dose should be used in patients ≥65 years of age.

- Pediatrics: Children and teenagers who have or are recovering from chickenpox or flu-like symptoms should not use this product. Changes in behavior (along with nausea and vomiting) may be an early sign of Reye's syndrome; patients should be instructed to contact their healthcare provider if these occur. Safety and efficacy have not been established in children <12 years of age.

- Surgical patients: **[U.S. Boxed Warning]: Use with caution prior to surgery;** surgical patients should avoid salicylates if possible, for 1-2 weeks prior to surgery, to reduce the risk of excessive bleeding.

Pregnancy Risk FactorC

Pregnancy ConsiderationsSpecific reproduction studies have not been conducted with this agent. Refer to Aspirin monograph for additional information.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsSalicylates are excreted into human milk. Breast-feeding is not recommended by the manufacturer. Refer to Aspirin monograph for additional information.

Adverse ReactionsRefer to Aspirin monograph.

Drug Interactions

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Eltrombopag: Magnesium Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., magnesium-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsRefer to Aspirin monograph.

Reference RangeTherapeutic range of salicylate for arthritis treatment: 20-30 mg/dL

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet, as anhydrous: 467 mg

Doan's® Extra Strength: 467 mg

Momentum®: 467 mg

Tablet, chelated:

Keygesic: 650 mg

Tablet, as tetrahydrate [scored]:

Novasal™: 600 mg

Generic AvailableYes

Pharmacodynamics/Kinetics

Absorption: Rapid from stomach and upper intestine

Distribution: Readily into most body fluids and tissues; crosses the placenta, enters breast milk

Protein binding: 50% to 90%; primarily albumin

Metabolism: Released into the plasma as salicylic acid which is enzymatically converted to salicyluric acid and salicylphenolic glucuronide

Half-life elimination: 2 hours; increased with repeated dosing

Time to peak: 1.5 hours

Excretion: Urine

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Department of Health and Human Services, Food and Drug Administration, “Labeling for Oral and Rectal Over-the-Counter Drug Products Containing Aspirin and Nonaspirin Salicylates; Reye's Syndrome Warning; Final Rule (29 CFR Part 201),” *Fed Regist*, April 17, 2003, 18861-9.[PubMed 10177739]

International Brand NamesBexidermil (ES); Dencorub (AU); Geniol Flex (AR); Metsal AR (AU); Salimag (PL); Topicrem (ES)

Magnesium Sulfate

Lexi-Drugs Online

English

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Magnesium sulfate may be confused with manganese sulfate, morphine sulfate

$MgSO_4$ is an error-prone abbreviation (mistaken as morphine sulfate)

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V. formulation) among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(mag NEE zhum SUL fate)

Pharmacologic Category[Anticonvulsant, Miscellaneous](); [Electrolyte Supplement, Parenteral](); [Magnesium Salt]()

Use: Labeled IndicationsTreatment and prevention of hypomagnesemia; prevention and treatment of seizures in severe pre-eclampsia or eclampsia, pediatric acute nephritis; torsade de pointes; treatment of cardiac arrhythmias (VT/VF) caused by hypomagnesemia; soaking aid

Use: Unlabeled/Investigational

Asthma exacerbation (life-threatening)

Dosing: AdultsDose represented as magnesium sulfate unless stated otherwise. **Note:** Serum magnesium is poor reflection of repletional status as the majority of magnesium is intracellular; serum levels may be transiently normal for a few hours after a dose is given, therefore, aim for consistently high normal serum levels in patients with normal renal function for most efficient repletion.

Note: 1 g of magnesium sulfate = 98.6 mg elemental magnesium = 8.12 mEq elemental magnesium

Hypomagnesemia:Note: Treatment depends on severity and clinical status:

Mild deficiency: I.M.: 1 g every 6 hours for 4 doses, or as indicated by serum magnesium levels

Severe deficiency:

I.M.: Up to 250 mg/kg within a 4-hour period

I.V.: Severe, non-life-threatening: 1-2 g/hour for 3-6 hours then 0.5-1 g/hour as needed to correct deficiency

Symptomatic deficiency: I.V.: 1-2 g over 5-60 minutes; maintenance infusion may be required to correct deficiency (0.5-1 g/hour).

Arrhythmia (ACLS guidelines, 2005), hypomagnesemia-induced (life-threatening): 1-2 g over 5-20 minutes (torsades with cardiac arrest) or over 5-60 minutes (symptomatic arrhythmias without cardiac arrest)

Seizures, hypomagnesemia-induced: I.V.: 2 g over 10 minutes; calcium administration may also be appropriate as many patients are also hypocalcemic.

Asthma (life-threatening or severe exacerbation after 1 hour of intensive conventional therapy; unlabeled use): I.V.: 2 g

Eclampsia:

I.V.: 4-5 g infusion; followed by a 1-2 g/hour continous infusion; or may follow with I.M. doses of 4-5 g in each buttock every 4 hours. **Note:** Initial infusion may be given over 3-4 minutes if eclampsia is severe; maximum: 40 g/24 hours

ACOG Practice Bulletin 2002: 4-6 g over 15-20 minutes followed by 2 g/hour continuous infusion

Pre-eclampsia (severe): I.V. 4-5 g infusion; followed by a 1-2 g/hour continous infusion; or may follow with I.M. doses of 4-5 g in each buttock every 4 hours; maximum: 40 g/24 hour

Torsade de pointes: I.V.:

Pulseless: 1-2 g over 5-20 minutes

With pulse: 1-2 g over 5-60 minutes. **Note:** Slower administration preferable for stable patients.

Parenteral nutrition supplementation: I.V.: 8-24 mEq elemental magnesium/day

Soaking aid: Topical: Dissolve 2 cupfuls of powder per gallon of warm water

RDA:

19-30 years:

Female: 310 mg elemental magnesium/day

Pregnant female: 350 mg elemental magnesium/day

Male: 400 mg elemental magnesium/day

≥31 years:

Female: 320 mg elemental magnesium/day

Pregnant female: 360 mg elemental magnesium/day

Male: 420 mg elemental magnesium/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDose represented as magnesium sulfate unless stated otherwise. **Note:** Serum magnesium is poor reflection of repletional status as the majority of magnesium is intracellular; serum levels may be transiently normal for a few hours after a dose is given, therefore, aim for consistently high normal serum levels in patients with normal renal function for most efficient repletion.

Note: 1 g of magnesium sulfate = 98.6 mg elemental magnesium = 8.12 mEq elemental magnesium

Hypomagnesemia:Note: Treatment depends on severity and clinical status: I.V., I.O.: 25-50 mg/kg/dose over 10-20 minutes (faster in cardiac arrest); maximum single dose: 2000 mg

Asthma (life-threatening or severe exacerbation after 1 hour of intensive conventional therapy; unlabeled use): I.V.: 25-75 mg/kg (maximum: 2 g)

Parenteral nutrition supplementation: I.V.:

<50 kg: 0.3-0.5 mEq elemental magnesium/kg/day

>50 kg: 10-30 mEq elemental magnesium/day

RDA: Children:

1-3 years: 80 mg elemental magnesium/day

4-8 years: 130 mg elemental magnesium/day

9-13 years: 240 mg elemental magnesium/day

14-18 years:

Female: 360 mg elemental magnesium/day

Pregnant female: 400 mg elemental magnesium/day

Male: 410 mg elemental magnesium/day

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute: Use with caution; monitor for hypermagnesemia; do not exceed 20 g/48 hours as per manufacturer. Close monitoring is required.

Calculations

- Magnesium Sulfate

Administration: I.M.A 25% or 50% concentration may be used for adults and dilution to a ≤20% solution is recommended for children

Administration: I.V.Magnesium should be diluted to a ≤20% solution for I.V. infusion and may be administered IVP, IVPB or I.V.; when giving I.V. push, must dilute first and should not be given any faster than 150 mg/minute. Hypotension and asystole may occur with rapid administration.

Maximal rate of infusion: 2 g/hour to avoid hypotension; doses of 4 g/hour have been given in emergencies (eclampsia, seizures); optimally, should add magnesium to I.V. fluids, but bolus doses are also effective

Administration: Topical

Dissolve 2 cups of powder per gallon of warm water to use as a soaking aid. To make a compress, dissolve 2 cups of powder per 2 cups of hot water and use a towel to apply as a wet dressing.

Dietary ConsiderationsWhole grains, legumes and dark-green leafy vegetables are dietary sources of magnesium.

10% elemental magnesium; 8.1 mEq magnesium/g; 4 mmol magnesium/g

500 mg magnesium sulfate = 4.06 mEq magnesium = 49.3 mg elemental magnesium

StoragePrior to use, store at room temperature of 20°C to 25°C (68°F to 77°F). Refrigeration of solution may result in precipitation or crystallization.

CompatibilityStable in D_5W, LR, NS; **incompatible** with fat emulsion 10%

Y-site administration: Compatible: Acyclovir, aldesleukin, amifostine, amikacin, ampicillin, aztreonam, cefamandole, cefazolin, cefoperazone, cefotaxime, cefoxitin, chloramphenicol, cisatracurium, clindamycin, dobutamine, docetaxel, doxorubicin liposome, doxycycline, enalaprilat, erythromycin lactobionate, esmolol, etoposide, famotidine, fludarabine, gatifloxacin, gentamicin, granisetron, heparin, hydrocortisone sodium succinate, hydromorphone, idarubicin, insulin (regular), kanamycin, labetalol, linezolid, meperidine, metronidazole, milrinone, minocycline, morphine, nafcillin, ondansetron, oxacillin, paclitaxel, penicillin G potassium, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, remifentanil, sargramostim, thiotepa, ticarcillin, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, vitamin B complex with C. **Incompatible:** Alatrofloxacin, amphotericin B cholesteryl sulfate complex, cefepime. **Variable (consult detailed reference):** Ciprofloxacin.

Compatibility in syringe: Compatible: Metoclopramide. **Incompatible:** Hydrocortisone sodium succinate.

Compatibility when admixed: Compatible: Calcium gluconate, chloramphenicol, cisplatin, heparin, hydrocortisone sodium succinate, isoproterenol, meropenem, methyldopate, norepinephrine, penicillin G potassium, potassium phosphates, verapamil. **Incompatible:** Amphotericin B, clindamycin, cyclosporine, dobutamine, polymyxin B sulfate, procaine, sodium bicarbonate.

ContraindicationsHypersensitivity to any component of the formulation; heart block; myocardial damage

Warnings/Precautions

Disease-related concerns:

- Neuromuscular disease: Use with extreme caution in patients with myasthenia gravis or other neuromuscular disease.
- Renal impairment: Use with caution in patients with renal impairment; accumulation of magnesium may lead to magnesium intoxication.

Special populations:

- Obstetrics: Vigilant monitoring and safe administration techniques (ISMP Medication Safety Alert, 2005) recommended to avoid potential for errors resulting in toxicity. Monitor patient and fetal status, and serum magnesium levels closely.

Dosage form specific issues:

- Aluminum: Solutions may contain aluminum; toxic levels may occur following prolonged administration in premature neonates or patients with renal impairment.

Other warnings/precautions:

- Electrolyte abnormalities: Concurrent hypokalemia or hypocalcemia can accompany a magnesium deficit. Hypomagnesemia is frequently associated with hypokalemia and requires correction in order to normalize potassium.
- Parenteral administration: Monitor serum magnesium level, respiratory rate, blood pressure, deep tendon reflex, and renal function when administered parenterally, particularly with repeated dosing; magnesium toxicity can lead to fatal cardiovascular arrest and/or respiratory paralysis.

Pregnancy Risk FactorA/C (manufacturer dependent)

Pregnancy ConsiderationsMagnesium crosses the placenta; serum levels in the fetus correlate with those in the mother. Magnesium sulfate is used during pregnancy for the treatment of eclampsia and severe pre-eclampsia.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsMagnesium is found in breast milk. The amount is not influenced by dietary intake under normal conditions. In women receiving parenteral magnesium sulfate for the treatment of eclampsia, magnesium levels in breast milk returned to normal 24 hours following discontinuation of treatment.

Adverse ReactionsAdverse effects on neuromuscular function may occur at lower levels in patients with neuromuscular disease (eg, myasthenia gravis).

Frequency not defined:

Cardiovascular: Flushing (I.V.; dose related), hypotension (I.V.; rate related), vasodilation (I.V.; rate related)

Gastrointestinal: Diarrhea

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Magnesium Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcitriol: May increase the serum concentration of Magnesium Salts. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Eltrombopag: Magnesium Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., magnesium-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Mycophenolate: Magnesium Salts may decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Magnesium Salts may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Phosphate Supplements: Magnesium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Magnesium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Magnesium Salts may decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Magnesium may enhance the CNS depressant effect of alcohol (ethyl).

Monitoring Parameters

I.V.: Rapid administration: ECG monitoring, vital signs, deep tendon reflexes; magnesium, calcium, and potassium levels; renal function during administration

Obstetrics: Patient status including vital signs, oxygen saturation, deep tendon reflexes, level of consciousness, fetal heart rate, maternal uterine activity.

Reference RangeSerum magnesium: 1.5-2.5 mg/dL; slightly different ranges are reported by different laboratories

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effect, and adverse/toxic effects. Assess knowledge/teach patient proper use, appropriate interventions to reduce side effects, and adverse symptoms to report.

When administered parenterally, monitor serum magnesium level, respiratory rate, deep tendon reflex, and renal function.

Monitoring: Lab TestsI.V.: Rapid administration: ECG monitoring, vital signs, deep tendon reflexes; magnesium, calcium, and potassium levels; renal function during administration

Patient EducationTake in divided doses. Report diarrhea (>5 stools/day) or changes in mental function to prescriber.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed in D_5W]: 10 mg/mL (100 mL); 20 mg/mL (500 mL)

Infusion [premixed in water for injection]: 40 mg/mL (100 mL, 500 mL, 1000 mL); 80 mg/mL (50 mL)

Injection, solution: 500 mg/mL (2 mL, 10 mL, 20 mL, 50 mL)

Powder, oral/topical: Magnesium sulfate USP (227 g, 454 g, 480 g, 1810 g, 1920 g, 2720 g)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Magnesium Sulfate)

50% (50): $22.99

Mechanism of ActionWhen taken orally, magnesium promotes bowel evacuation by causing osmotic retention of fluid which distends the colon with increased peristaltic activity; parenterally, magnesium decreases acetylcholine in motor nerve terminals and acts on myocardium by slowing rate of S-A node impulse formation and prolonging conduction time. Magnesium is necessary for the movement of calcium, sodium, and potassium in and out of cells, as well as stabilizing excitable membranes.

Pharmacodynamics/Kinetics

Onset of action: Anticonvulsant: I.M.: 1 hour; I.V.: Immediate

Duration of anticonvulsant activity: I.M.: 3-4 hours; I.V.: 30 minutes

Distribution: Bone (50% to 60%); extracellular fluid (1% to 2%)

Protein binding: 30%, to albumin

Excretion: Urine (as magnesium)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Magnesium products may prevent GI absorption of tetracyclines by forming a large ionized chelated molecule with the tetracyclines in the stomach. Tetracyclines should be given at least 1 hour before magnesium.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation or CNS depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive CNS depression

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Hypomagnesemia can hinder the replenishment of intracellular potassium and should be corrected in order to correct hypokalemia.

Index Terms Epsom Salts; $MgSO_4$ (error-prone abbreviation)

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International Brand Names Cholal modificado (MX); Inj. Magnesii Sulfurici (PL); Kiddi Pharmaton (MX); Magnesii Sulfas (PL); Magnesii Sulfas Siccatus (PL); Magnesium Sulfuricum (PL); Vivioptal Junior (MX)

MAID

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Soft Tissue Sarcoma]

Regimen UseSoft tissue sarcoma

Regimen

Mesna: I.V.: 2500 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 10,000 mg/m^2]

Doxorubicin: I.V.: 20 mg/m^2/day continuous infusion days 1 to 3

[total dose/cycle = 60 mg/m^2]

Ifosfamide: I.V.: 2500 mg/m^2/day continuous infusion days 1 to 3

[total dose/cycle = 7500 mg/m^2]

Dacarbazine: I.V.: 300 mg/m^2/day continuous infusion days 1 to 3

[total dose/cycle = 900 mg/m^2]

Repeat cycle every 21-28 days

References

Elias A, Ryan L, Sulkes A, et al, âResponse to Mesna, Doxorubicin, Ifosfamide, and Dacarbazine in 108 Patients With Metastatic or Unresectable Sarcoma and No Prior Chemotherapy,â *J Clin Oncol*, 1989, 7(9):1208-16.[PubMed 2504890]

Malathion

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(mal a THYE on)
U.S. Brand NamesOvide®
Pharmacologic Category[Antiparasitic Agent, Topical]; [Pediculocide]; [Scabicidal Agent]
Use: Labeled IndicationsTreatment of head lice and their ova
Dosing: AdultsHead lice: Topical: Sprinkle Ovide® lotion on dry hair and rub gently until the scalp is thoroughly moistened; pay special attention to the back of the head and neck. Allow to dry naturally - use no heat and leave uncovered. After 8-12 hours, the hair should be washed with a nonmedicated shampoo; rinse and use a fine-toothed comb to remove dead lice and eggs. If required, repeat with second application in 7-9 days. Further treatment is generally not necessary. Other family members should be evaluated to determine if infested and if so, receive treatment.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing. Use is contraindicated in neonates and infants.
Administration: TopicalRefer to Dosing.
ContraindicationsHypersensitivity to malathion or any component of the formulation; use in neonates and/or infants
Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue use temporarily if skin irritation occurs.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Other warnings/precautions:

- Appropriate use: For topical use only; avoid contact with eyes.
- Flammable: Lotion is flammable; do not expose to open flames; patients should avoid electric heat sources (eg, hair dryers, curling irons).

Pregnancy Risk FactorB
Pregnancy ConsiderationsNo evidence of teratogenicity in animal models. There are no adequate and well-controlled studies in pregnant women. Use (or handle) during pregnancy only if clearly needed.
Adverse ReactionsFrequency not defined.

Dermatologic: Skin/scalp irritation

Ocular: Conjunctivitis (following contact with eyes)

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Lotion: 0.5% (59 mL) [contains isopropyl alcohol 78%]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Lotion (Ovide)

0.5% (59): $118.11

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
References

"Drugs for Parasitic Infections," *Med Lett Drugs Ther*, 1993, 35(911):111-22.[PubMed 8246830]

International Brand NamesA-Lices 1% (MY); Derbac-M (IE); Lice Care (SG); Lice Rid (AU); Lusap (CH); Malation (EE, NO); Malthionex (LU); Olicide (PT); Organoderm (DE); Prioderm (AE, BE, BF, BH, BJ, CH, CI, CY, DK, EG, ET, FR, GB, GH, GM, GN, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SE, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Quellada-M (GB); Radikal (BE, LU); Sinpar (UY)

Jump To Field (Select Field Name)

Pronunciation(mal toe DEK strin)
U.S. Brand NamesMultidex® [OTC]; OraRinse™ [OTC]
Pharmacologic CategoryAnti-inflammatory, Locally Applied
Use: Labeled IndicationsTopical: Treatment of infected or noninfected wounds
Use: DentalOral: Management and relief of pain due to oral lesions (including mucositis/stomatitis), oral ulcers, or irritation; treatment of aphthous ulcers
Dosing: Adults

Management of pain due to oral lesions: Oral: OraRinse™: 1 tablespoonful, swish or gargle for ~1 minute, 4 times/day or more if needed

Wound dressing: Topical: Multidex®: After debridement and irrigation of wound, apply and cover with a nonadherent, nonocclusive dressing. May be applied to moist or dry, infected or noninfected wounds.

Dosing: ElderlyRefer to adult dosing.
ReconstitutionOraRinse™: Fill bottle with water to first arrow; shake vigorously until suspended; continue to fill to second arrow; shake well
ContraindicationsHypersensitivity to maltodextrin or any component of the formulation
Warnings/Precautions

Dosage form specific issues:

- Oral: Avoid eating or drinking for 1 hour; products are not harmful if accidentally swallowed; notify healthcare provider if improvement is not seen within 7 days

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel, topical dressing:

Multidex®: (4 mL, 7 mL, 14 mL, 85 mL)

Powder, for oral suspension:

OraRinse™: (19 g) [contains phenylalanine; also contains aloe vera, fructose, and sodium benzoate; vanilla flavor]

Powder, topical dressing:

Multidex®: (6 g, 12 g, 25 g, 45 g)

Generic AvailableNo
Mechanism of ActionForms a protective barrier over wound providing an environment which promotes tissue growth.
Dental Health Professional ConsiderationsOraRinse™: Fill bottle with water to first arrow; shake vigorously until suspended; continue to fill to second arrow; shake well
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported

Manganese

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Manganese sulfate may be confused with magnesium sulfate

Pronunciation(MAN ga nees)
U.S. Brand NamesMangimin [OTC]
Pharmacologic Category[Trace Element, Parenteral]
Use: Labeled IndicationsTrace element added to total parenteral nutrition (TPN) solution to prevent manganese deficiency; orally as a dietary supplement
Dosing: Adults

Adequate intake: Oral:

Male: 1.9-2.3 mg/day

Female: 1.6-1.8 mg/day

Pregnancy: 2 mg/day

Lactation: 2.6 mg/day

Deficiency prevention: I.V.: 150-800 mcg/day usually administered in TPN solutions

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Adequate intake: Oral:

0-6 months: 0.003 mg/day

7-12 months: 0.6 mg/day

1-3 years: 1.2 mg/day

4-8 years: 1.5 mg/day

≥9 years: Refer to adult dosing.

Deficiency prevention: I.V.: Children: 2-10 mcg/kg/day usually administered in TPN solutions

Note: Use caution in premature neonates; manganese chloride solution for injection contains aluminum.

Dosing: Renal ImpairmentUse caution; manganese chloride solution for injection contains aluminum.
Dosing: Hepatic ImpairmentUse caution; dose may need to be decreased or withheld.
Administration: I.V.Solution for injection: Do not administer I.M. or by direct I.V. injection; acidic pH of the solution may cause tissue irritations and it is hypotonic
StorageSolution for injection: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F). Compatible with electrolytes usually present in amino acid/dextrose solution used for TPN solutions.
ContraindicationsHigh manganese levels; severe liver dysfunction or cholestasis (conjugated bilirubin >2 mg/dL) due to reduced biliary excretion
Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

Dosage form specific issues:

- Aluminum: Manganese chloride solution for injection contains aluminum; use caution with impaired renal function and in premature infants.

Pregnancy Risk FactorC
LactationEnters breast milk/compatible
Breast-Feeding ConsiderationsNormal concentrations of manganese found in human milk are generally lower than cow's milk or those found in food sources.

Drug Interactions There are no known significant interactions.

Monitoring Parameters Periodic manganese plasma level

Reference Range Plasma: 0.6-2 ng/mL

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as chloride [preservative free]: 0.1 mg/mL (10 mL) [contains aluminum ≤100 mcg/mL]

Injection, solution, as sulfate: 0.1 mg/mL (10 mL)

Tablet, as aspartate: 93 mg [equivalent to elemental manganese 25 mg]

Tablet, as gluconate: 5.7 mg [as elemental manganese]; 550 mg [equivalent to elemental manganese 30 mg]; 600 mg [equivalent to elemental manganese 50 mg]

Tablet, chelated: 50 mg [as elemental manganese]

Mangimin: 10 mg [as elemental manganese]

Generic Available Yes

Mechanism of Action Cofactor in many enzyme systems, stimulates synthesis of cholesterol and fatty acids in liver, and influences mucopolysaccharide synthesis

Pharmacodynamics/Kinetics

Absorption: Oral: Poor (3% to 4%)

Distribution: Concentrated in mitochondria of pituitary gland, pancreas, liver, kidney, and bone

Excretion: Bile (primarily); urine (negligible)

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment Chronic poisoning may present with extrapyramidal symptoms

Index Terms Manganese Chloride; Manganese Sulfate

Mannitol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Osmitrol® may be confused with esmolol

Pronunciation(MAN i tole)
U.S. Brand NamesOsmitrol®; Resectisol®
Canadian Brand NamesOsmitrol®
Pharmacologic CategoryDiuretic, Osmotic; Genitourinary Irrigant
Use: Labeled IndicationsReduction of increased intracranial pressure associated with cerebral edema; promotion of diuresis in the prevention and/or treatment of oliguria or anuria due to acute renal failure; reduction of increased intraocular pressure; promoting urinary excretion of toxic substances; genitourinary irrigant in transurethral prostatic resection or other transurethral surgical procedures
Dosing: Adults

Test dose (to assess adequate renal function): I.V.: 12.5 g (200 mg/kg) over 3-5 minutes to produce a urine flow of at least 30-50 mL of urine per hour. If urine flow does not increase, a second test dose may be given. If test dose does not produce an acceptable urine output, then need to reassess management.

Edema (osmotic diuretic): Initial: 0.5-1 g/kg; Maintenance: 0.25-0.5 g/kg every 4-6 hours; usual daily dose: 20-200 g/24 hours

Intracranial pressure/Cerebral edema: I.V.: 0.25-1.5 g/kg/dose I.V. as a 15% to 20% solution over ≥30 minutes; maintain serum osmolality 310 to <320 mOsm/kg.

Prevention of acute renal failure (oliguria): 50-100 g dose

Reduction of intraocular pressure: 1.5-2 g/kg as a 15% to 20% solution; administer over 30 minutes

Treatment of oliguria: 100 g dose

Preoperative for neurosurgery: I.V.: 1.5-2 g/kg administered 1-1.5 hours prior to surgery.

Transurethral: Irrigation: Use urogenital solution as required for irrigation.

Dosing: ElderlyRefer to adult dosing. Consider initiation at lower end of dosing range.
Dosing: Pediatric

Test dose (to assess adequate renal function): I.V.: Children: 200 mg/kg over 3-5 minutes to produce a urine flow of at least 1 mL/kg for 1-3 hours

Edema (osmotic diuretic): I.V.: Children: Initial: 0.25-1 g/kg; Maintenance: 0.25-0.5 g/kg given every 4-6 hours

Dosing: Renal Impairment

Contraindicated in severe renal impairment. If test dose does not produce adequate urine output reassess options. Use caution in patients with underlying renal disease.

Dosing: Hepatic Impairment

No adjustment required.

Administration: I.V.Vesicant. Do not administer with blood. Crenation and agglutination of red blood cells may occur if administered with whole blood. Inspect for crystals prior to administration. If crystals present redissolve by warming solution. Use filter-type administration set.
Administration: I.V. DetailAvoid extravasation.

pH: 4.5-7

StorageShould be stored at room temperature (15°C to 30°C); do not freeze. Crystallization may occur at low temperatures; do not use solutions that contain crystals. Heating in a hot water bath and vigorous shaking may be utilized for resolubilization. Cool solutions to body temperature before using.
Compatibility

Y-site administration: Compatible: Allopurinol, amifostine, amphotericin B cholesteryl sulfate complex, aztreonam, cisatracurium, cladribine, docetaxel, etoposide, fludarabine, fluorouracil, gatifloxacin, gemcitabine, idarubicin, linezolid, melphalan, ondansetron, paclitaxel, piperacillin/tazobactam, propofol, remifentanil, sargramostim, teniposide, thiotepa, vinorelbine. **Incompatible:** Cefepime, doxorubicin liposome, filgrastim.

Compatibility when admixed: Compatible: Amikacin, bretylium, cefamandole, cefoxitin, cimetidine, cisplatin, dopamine, fosphenytoin, furosemide, gentamicin, metoclopramide, nizatidine, ofloxacin, ondansetron, sodium bicarbonate, tobramycin, verapamil. **Incompatible:** Imipenem/cilastatin, meropenem. **Variable (consult detailed reference):** Etoposide with cisplatin and potassium chloride, potassium chloride.

Contraindications

Hypersensitivity to mannitol or any component or the formulation; severe renal disease (anuria); severe dehydration; active intracranial bleeding except during craniotomy; progressive heart failure, pulmonary congestion, or renal dysfunction after mannitol administration; severe pulmonary edema or congestion

Allergy Considerations

- Mannitol Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Fluid/electrolyte loss: Excess amounts can lead to profound diuresis with fluid and electrolyte loss; close medical supervision and dose evaluation are required. Watch for and correct electrolyte disturbances; adjust dose to avoid dehydration.

- Nephrotoxicity: May cause renal dysfunction especially with high doses; use caution in patients taking other nephrotoxic agents, with sepsis or pre-existing renal disease. To minimize adverse renal effects, adjust to keep serum osmolality less than 320 mOsm/L. Discontinue if evidence of acute tubular necrosis.

Disease-related concerns:

- Cerebral edema: In patients being treated for cerebral edema, mannitol may accumulate in the brain (causing rebound increases in intracranial pressure) if circulating for long periods of time as with continuous infusion; intermittent boluses preferred. Cardiovascular status should also be evaluated; do not administer electrolyte-free mannitol solutions with blood. If hypotension occurs monitor cerebral perfusion pressure to insure adequate.

Other warnings/precautions:

- Adequate renal function: Should not be administered until adequacy of renal function and urine flow is established; use 1-2 test doses to assess renal response.

Pregnancy Risk Factor

C

Pregnancy Considerations

Reproduction studies have not been conducted.

Lactation

Excretion in breast milk unknown/use caution

Adverse Reactions

Frequency not defined.

Cardiovascular: Chest pain, CHF, circulatory overload, hyper-/hypotension, tachycardia

Central nervous system: Chills, convulsions, dizziness, headache

Dermatologic: Rash, urticaria

Endocrine & metabolic: Fluid and electrolyte imbalance, dehydration and hypovolemia secondary to rapid diuresis, hyperglycemia, hypernatremia, hyponatremia (dilutional), hyperosmolality-induced hyperkalemia, metabolic acidosis (dilutional), osmolar gap increased, water intoxication

Gastrointestinal: Nausea, vomiting, xerostomia

Genitourinary: Dysuria, polyuria

Local: Pain, thrombophlebitis, tissue necrosis

Ocular: Blurred vision

Renal: Acute renal failure, acute tubular necrosis (>200 g/day; serum osmolality >320 mOsm/L)

Respiratory: Pulmonary edema, rhinitis

Miscellaneous: Allergic reactions

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring ParametersRenal function, daily fluid I & O, serum electrolytes, serum and urine osmolality; for treatment of elevated intracranial pressure, maintain serum osmolality 310 to <320 mOsm/kg.

Nursing: Physical Assessment/MonitoringAssess for adequate renal function and urine flow prior to administration. Lithium toxicity is increased with concurrent use, and concurrent use of other nephrotic agents may increase potential for renal dysfunction. Infusion site must be closely monitored for extravasation; this is a vesicant. Renal and cardiovascular status should be monitored during infusion. Assess results of laboratory tests, therapeutic effectiveness (according to purpose for use), and adverse response (eg, circulatory overload, CHF, rash, water intoxication). Patient teaching should be appropriate to patient condition.

Monitoring: Lab TestsRenal function, serum electrolytes, serum and urine osmolality. For treatment of elevated intracranial pressure, maintain serum osmolality 310-320 mOsm/kg.

Patient EducationReport immediately any muscle weakness, numbness, tingling, acute headache, nausea, dizziness, blurred vision, eye pain, respiratory difficulty, chest pain, or pain at infusion site. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 5% [50 mg/mL] (1000 mL); 10% [100 mg/mL] (500 mL, 1000 mL); 15% [150 mg/mL] (500 mL); 20% [200 mg/mL] (150 mL, 250 mL, 500 mL); 25% [250 mg/mL] (50 mL)

Osmitrol®: 5% [50 mg/mL] (1000 mL); 10% [100 mg/mL] (500 mL, 1000 mL); 15% [150 mg/mL] (500 mL); 20% [200 mg/mL] (250 mL, 500 mL)

Solution, urogenital (Resectisol®): 5% [50 mg/mL] (2000 mL, 4000 mL)

Generic AvailableYes

Mechanism of ActionIncreases the osmotic pressure of glomerular filtrate, which inhibits tubular reabsorption of water and electrolytes and increases urinary output

Pharmacodynamics/Kinetics

Onset of action: Diuresis: Injection: 1-3 hours; Reduction in intracranial pressure: ~15-30 minutes

Duration: Reduction in intracranial pressure: 1.5-6 hours

Distribution: Remains confined to extracellular space (except in extreme concentrations); does not penetrate the blood-brain barrier (generally, penetration is low)

Metabolism: Minimally hepatic to glycogen

Half-life elimination: 1.1-1.6 hours

Excretion: Primarily urine (as unchanged drug)

Related Information

- Management of Drug Extravasations

Pharmacotherapy PearlsMay autoclave or heat to redissolve crystals; mannitol 20% has an approximate osmolarity of 1100 mOsm/L and mannitol 25% has an approximate osmolarity of 1375 mOsm/L

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentHas been used to treat lithium toxicity/overdose but its overall effect in lowering serum lithium level is minimum; if toxicity is severe, hemodialysis is the treatment of choice

Anesthesia and Critical Care Concerns/Other Considerations

Management of Intracerebral Hemorrhage (ICH): Rapid identification of patients experiencing ICH is essential and should be considered a medical emergency due to the progressive deterioration, severe clinical deficits, and high mortality and morbidity. Treatment for ICH has evolved rapidly in recent years. According to the 2007 ACC/AHA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults, patients with ICH should be treated in a balanced and graded approach with therapies that reduce intracranial pressure (ICP) (eg, mannitol, hypertonic saline solutions, barbiturate coma, head of bed elevation) (Class IIa recommendation). Direct monitoring of ICP and central perfusion pressure (CPP) may be necessary if patient is treated more aggressively. Treatment of ICH with recombinant factor VIIa (rFVIIa) within the first 3-4 hours after onset to slow progression of bleeding has shown promise; however, at this time it cannot be routinely recommended in all patients experiencing ICH (Class IIb recommendation).

Blood pressure (BP) management in patients who are hypertensive is also of paramount importance in treating ICH. The primary rationale for lowering BP is to prevent further progression of the bleed. This can be accomplished using a number of different pharmacologic treatments (eg, nicardipine, labetalol, nitroprusside). Nitroprusside may increase ICP due to the pronounced vasodilatory actions and as a result may be less preferable. Specific BP targets are not supported by available evidence. The 2007 ACC/AHA Guidelines recommend initiating antihypertensive therapy if the SBP >180 mm Hg or if MAP is > 130 mm Hg.

Other information:

May autoclave or heat mannitol solution to redissolve crystals.

Mannitol 20% has an approximate osmolarity of 1100 mOsm/L.

Mannitol 25% has an approximate osmolarity of 1375 mOsm/L.

Index Terms*D*-Mannitol

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International Brand NamesAnol (TW); Ardeaosmosol MA (CZ); D-Mannitol (KP); Diurecide (PE); Isotol (IT); Manitol (ID); Mannisol A (HN); Mannisol B (HN, PL); Mannit (AT); Mannit-Losung (DE); Mannitol (KP, PL); Mannits (EE); Osmitrol (AU); Osmofusin-M (BG); Photoderm Max Bio (MX); Sunnytol (TW)

Maprotiline

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Ludiomil may be confused with Lamictal®, lamotrigine, Lomotil®

Pronunciation(ma PROE ti leen)

Canadian Brand NamesNovo-Maprotiline

Pharmacologic CategoryAntidepressant, Tetracyclic

Use: Labeled IndicationsTreatment of depression and anxiety associated with depression

Use: Unlabeled/InvestigationalBulimia; duodenal ulcers; enuresis; urinary symptoms of multiple sclerosis; pain; panic attacks; tension headache; cocaine withdrawal

Dosing: AdultsDepression/anxiety: Oral: 75 mg/day to start, increase by 25 mg every 2 weeks up to 150-225 mg/day; given in 3 divided doses or in a single daily dose

Dosing: ElderlyInitial: 25 mg at bedtime, increase by 25 mg every 3 days for inpatients and weekly for outpatients if tolerated. Usual maintenance dose: 50-75 mg/day, higher doses may be necessary in nonresponders.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to maprotiline or any component of the formulation; use of MAO inhibitors within 14 days; use in a patient during the acute recovery phase of MI

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Maprotiline is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Maprotiline is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. The degree of anticholinergic blockade produced by this agent is moderate relative to other antidepressants.

- Orthostatic hypotension: May cause orthostatic hypotension (risk is moderate relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is high relative to other antidepressants.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk conduction abnormalities with this agent is moderate relative to other antidepressants.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

- Thyroid dysfunction: Use with caution in patients with hyperthyroidism or those receiving thyroid supplementation.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Discontinuation of therapy: Therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

Geriatric ConsiderationsUse with caution due to sedation and anticholinergic effects (eg, confusion, constipation, difficulty urinating, dry mouth).
Pregnancy Risk FactorB
Adverse Reactions

>10%:

Central nervous system: Drowsiness

Gastrointestinal: Xerostomia

1% to 10%:

Central nervous system: Anxiety, agitation, dizziness, fatigue, headache, insomnia, nervousness

Gastrointestinal: Constipation, nausea

Neuromuscular & skeletal: Tremor, weakness

Ocular: Blurred vision

<1%: Abdominal cramps, accommodation disturbances, akathisia, arrhythmia, ataxia, bitter taste, breast enlargement, confusion, decreased libido, delusions, diaphoresis (excessive), diarrhea, disorientation, dysarthria, dysphagia, edema of testicles, epigastric distress, EPS, exacerbation of psychosis, hallucinations, heart block, hyperglycemia, hyper-/hypotension, hypomania, impotence, mania, motor hyperactivity, mydriasis, nightmares, numbness, palpitation, petechiae, photosensitivity, rash, restlessness, seizure, syncope, tachycardia, tingling, tinnitus, urinary retention, vomiting, weight gain/loss

Metabolism/Transport Effects**Substrate** of CYP2D6 (major)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

MAO Inhibitors: Maprotiline may enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sulfonylureas: Cyclic Antidepressants may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersMonitor blood pressure and pulse rate prior to and during initial therapy; evaluate mood and somatic complaints, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased); monitor appetite and weight; ECG in older adults

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 25 mg, 50 mg, 75 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Maprotiline HCl)

25 mg (60): $33.99

50 mg (60): $39.99

75 mg (60): $55.99

Mechanism of ActionTraditionally believed to increase the synaptic concentration of norepinephrine in the central nervous system by inhibition of their reuptake by the presynaptic neuronal membrane. However, additional receptor effects have been found including desensitization of adenyl cyclase, down regulation of beta-adrenergic receptors, and down regulation of serotonin receptors.

Pharmacodynamics/Kinetics

Absorption: Slow

Protein binding: 88%

Metabolism: Hepatic to active and inactive compounds

Half-life elimination, serum: 27-58 hours (mean: 43 hours)

Time to peak, serum: Within 12 hours

Excretion: Urine (70%); feces (30%)

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile

Pharmacotherapy PearlsOdorless, bitter tasting; seizures are rarely seen 5-30 hours postdrug ingestion.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAlthough maprotiline is not a tricyclic antidepressant, it does block norepinephrine reuptake within CNS synapses as part of its mechanisms. It has been suggested that vasoconstrictor be administered with caution and to monitor vital signs in dental patients taking antidepressants that affect norepinephrine in this way, including maprotiline. Epinephrine and levonordefrin have been shown to have an increased pressor response in combination with TCAs. Maprotiline is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Index TermsLudiomil; Maprotiline Hydrochloride

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Wyss PA, Serena S, and Meier PJ, “Dose-Dependency of Seizures in Maprotiline (Ludiomil®) Intoxications,” *Vet Hum Toxicol*, 1993, 35:341.

International Brand NamesKeproline (TW); Ladiomil (HR); Ludiomil (AE, AR, AT, BB, BD, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, NZ, OM, PE, PH, PK, PL, PT, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Ludiomil[inj.] (HU, LU); Ludios (ID); Maprolu (HU, LU); Matilina (PY); Melodil (IL); Mirpan (DE); Psymion (DE); Retinyl (GR); Sandepril (ID); Tilsan (ID)

Maraviroc

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(mah RAV er rock)

U.S. Brand NamesSelzentry™

Canadian Brand NamesCelsentri™

Pharmacologic CategoryAntiretroviral Agent, CCR5 Antagonist

Use: Labeled IndicationsTreatment of CCR5-tropic HIV-1 infection, in combination with other antiretroviral agents in treatment-experienced patients with evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral therapy

Dosing: AdultsHIV treatment: Oral: 300 mg twice daily

Dosage adjustment for concomitant CYP3A inhibitors/inducers:

CYP3A inhibitors (with or without a CYP3A inducer): 150 mg twice daily; dose recommended when maraviroc administered concomitantly with strong CYP3A inhibitors including (but not limited to) protease inhibitors (excluding tipranavir/ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, nefazodone, and telithromycin.

CYP3A inducers (without a strong CYP3A inhibitor): 600 mg twice daily; dose recommended when maraviroc administered concomitantly with CYP3A inducers including (but not limited to) efavirenz, rifampin, carbamazepine, phenobarbital, and phenytoin

Dosing: PediatricHIV treatment: Oral: Adolescents ≥16 years: Refer to adult dosing.

Dosing: Renal ImpairmentNot studied in renal dysfunction; maraviroc levels may be increased.

Cl_{cr} <50 mL/minute (with concomitant CYP3A inhibitor): Not recommended; if no appropriate alternative exists, monitor for increased maraviroc adverse effects

Dosing: Hepatic ImpairmentUse caution; not adequately studied in hepatic dysfunction.

Administration: OralAdminister without regards to meals.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

RestrictionsAn FDA-approved medication guide is available at http://www.selzentry.com/content/SELZENTRY_MedicationGuide.pdf; distribute to each patient to whom this medication is dispensed.

ContraindicationsThere are no contraindications listed within the manufacturer’s labeling.

Warnings/Precautions

Boxed warnings:

- Hepatotoxicity: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Hepatotoxicity: **[U.S. Boxed Warning]: Possible drug-induced hepatotoxicity with allergic type features has been reported;** hepatotoxicity may be preceded by allergic type reactions (eg, pruritic rash, eosinophilia or increased IgE) and/or hepatic adverse events (transaminase increases or signs/symptoms of hepatitis). Consider discontinuation in any patient with possible hepatitis or with elevated transaminases combined with systemic allergic events.

- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.

- Infections: Monitor closely for signs/symptoms of developing infections; associated with a small increase of certain upper respiratory tract infections and herpes virus infections during clinical trials.

- Postural hypotension: Symptomatic postural hypotension has occurred; use caution in patients at risk for postural hypotension due to concomitant medication or history of condition.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease or cardiac risk factors. During trials, a small increase in cardiovascular events (myocardial ischemia and/or infarction) occurred in treated patients compared to placebo, although a contributory relationship relative to therapy is unknown. Of note, patients experiencing events generally had cardiac disease/risk factors prior to therapy.

- Hepatic impairment: Safety and efficacy has not been adequately studied in patients with hepatic impairment; use caution in patients with hepatic dysfunction or concomitant viral hepatitis B or C.

- Renal impairment: Safety and efficacy not adequately studied in renal impairment; renal impairment may increase maraviroc concentrations. Concomitant therapy with CYP3A inhibitors in presence of renal impairment is expected to further increase levels and may lead to increased adverse events; therefore, avoid maraviroc in patients on concomitant CYP3A inhibitors with Cl_{cr} <50 mL/minute unless potential benefits outweighs potential risk.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4/P-glycoprotein inhibitors and moderate or strong CYP3A4/P-glycoprotein inducers (see Drug Interactions); may require dosage adjustments.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <16 years of age.

Other warnings/precautions:

- Appropriate use: Prior to therapy, tropism testing should be performed for presence of CCR5-tropic HIV-1 infection. Therapy not recommended for use in patients with CXCR4- or dual/mixed tropic HIV-1 infection; efficacy not demonstrated in this population. Safety and efficacy not established in treatment naive patients.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse fetal effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women and available data is insufficient to recommend use in pregnancy. An antiretroviral registry has been established to monitor maternal and fetal outcomes in women receiving antiretroviral drugs. Physicians are encouraged to register patients at 1-800-258-4263 or www.APRegistry.com.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse Reactions

>10%:

Central nervous system: Fever (13%)

Respiratory: Upper respiratory tract infection (23%), cough (14%)

2% to 10%:

Cardiovascular: Vascular hypertensive disorder (3%)

Central nervous system: Dizziness (9%), insomnia (8%), anxiety (4%), consciousness disturbances (4%), depression (4%), pain (4%)

Dermatologic: Rash (11%), pruritus (4%), folliculitis (3%), skin neoplasms (benign; 3%), erythema (2%)

Endocrine & metabolic: Lipodystrophy (3%)

Gastrointestinal: Appetite disorders (8%), constipation (6%)

Genitourinary: Urinary tract/bladder symptoms (3% to 5%), genital warts (2%)

Hematologic: Neutropenia (grades 3/4: 4%)

Hepatic: Transaminases increased (grades 3/4: 2% to 5%), bilirubin increased (grades 3/4: 6%)

Neuromuscular & skeletal: Joint disorders (7%), paresthesia (5%), peripheral neuropathy (4%), sensory abnormality (4%), muscle pain (3%)

Ocular: Conjunctivitis (2%), infection/inflammation (2%)

Otic: Otitis media (2%)

Respiratory: Bronchitis (7%), sinusitis (7%), respiratory tract/sinus disorder (3% to 6%), breathing abnormality (4%)

Miscellaneous: Herpes infection (8%), sweat gland disturbances (5%), influenza (2%)

<2%, postmarketing, and/or case reports: Acute cardiac failure, anal cancer, angina, basal cell carcinoma, bile duct neoplasm, bone marrow depression, cerebrovascular accident, cholestatic jaundice, coronary artery disease, coronary artery occlusion, creatine kinase increased, endocarditis, endocrine neoplasm, esophageal carcinoma, hepatic cirrhosis, hepatic failure, hepatotoxicity, hypoplastic anemia, liver metastases, lymphoma, MI, myocardial ischemia, myositis, osteonecrosis, pneumonia, portal vein thrombosis, rhabdomyolysis, seizure, septic shock, squamous cell carcinoma, syncope, T-cell lymphoma, tongue neoplasm, tremor, viral meningitis

Metabolism/Transport Effects**Substrate** of CYP3A4 (major), P-glycoprotein

Drug Interactions

CYP3A4 Inducers: May decrease the serum concentration of Maraviroc. **Exceptions:** Ritonavir. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors: May increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Lopinavir: May increase the serum concentration of Maraviroc. Management: Reduce maraviroc dose to 150mg twice daily when maraviroc is used concurrently with lopinavir/ritonavir. *Risk D: Consider therapy modification*

St Johns Wort: May decrease the serum concentration of Maraviroc. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St. John’s wort may decrease maraviroc concentrations leading to loss of therapeutic efficacy and potentially increased risk of resistance; concomitant use not recommended.

Monitoring ParametersViral load, CD4 count, transaminases; signs/symptoms of infection, hepatitis and/or allergic reaction; postural hypotension; tropism testing (prior to initiation)

Nursing: Physical Assessment/MonitoringUse caution in presence of hepatic impairment, cardiovascular disease, or cardiac risk factors. Assess all other pharmacological or herbal products patient may be taking for potential interactions or toxicity; dosing adjustments may be necessary. An FDA-approved medication guide is available with prescription and patients should be cautioned to read this information. Evaluate results of laboratory tests and effectiveness of therapy (viral load, CD4 count, transaminase levels) and adverse reactions (hepatotoxicity, upper respiratory infections, hyper- or hypotension, CNS changes, gastrointestinal upset) periodically during therapy. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions, and adverse symptoms to report (eg, rash, gastrointestinal upset).

Monitoring: Lab TestsViral load, CD4 count, transaminases; tropism testing (prior to initiation)

Patient EducationYou will be provided with a medication guide with each prescription that includes a list of specific medications that should not be used during therapy; do not take any new prescription or OTC medications or herbal products during therapy (even if they are not on the list) without consulting prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. This drug is prescribed as one part of a multidrug combination; take exactly as directed for full course of therapy. May be taken with or without food; do not break or chew tablets; swallow whole. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. You may be susceptible to infection (avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber). Frequent blood tests may be required with prolonged therapy. May cause nausea, vomiting, or stomach pain (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); dizziness, insomnia, or consciousness disturbances (use caution when driving or engaging in hazardous tasks until response to drug is known); constipation (increased fluids and exercise may help); postural hypotension (use caution when changing position from lying or sitting to standing or when climbing stairs); or muscle or joint pain (consult prescriber for analgesic). Report skin rash or irritation; persistent muscle pain, headache, fatigue, or gastrointestinal upset; unusual cough, fever, or cold symptoms; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Selzentry™: 150 mg, 300 mg

Generic AvailableNo

ManufacturerPfizer, Inc

Mechanism of ActionMaraviroc, a CCR5 antagonist, selectively and reversibly binds to the chemokine (C-C motif receptor 5 [CCR5]) coreceptors located on human CD4 cells. CCR5 antagonism prevents interaction between the human CCR5 coreceptor and the gp120 subunit of the viral envelope glycoprotein, thereby inhibiting gp120 conformational change required for CCR5-tropic HIV-1 fusion with the CD4 cell and subsequent cell entry.

Pharmacodynamics/Kinetics

Distribution: V_d: ~194 L

Protein binding: ~76%

Metabolism: Hepatic, via CYP3A to inactive metabolites

Bioavailability: 23% to 33%

Half-life elimination: 14-18 hours

Time to peak, plasma: 0.5-4 hours

Excretion: Urine (~20%, 8% as unchanged drug); feces (76%, 25% as unchanged drug)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Perinatal HIV Guidelines

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis has been observed.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, insomnia, or depression

Mental Health: Effects on Psychiatric TreatmentMay produce postural hypotension; concomitant use with psychotropic agents may produce additive effects. May cause neutropenia; use caution with clozapine and carbamazepine. High potential for drug-drug interactions. Carbamazepine, phenobarbital, and phenytoin may decrease the levels/effects of maraviroc; dosage adjustment of maraviroc may be recommended. Nefazodone may increase the levels/effects of maraviroc; dosage adjustment of maraviroc may be recommended. St John's wort may decrease levels of maraviroc and lead to possible resistance; concurrent use is not recommended.

Index TermsUK-427,857

References

Dorr P, Westby M, Dobbs S, et al, "Maraviroc (UK-427,857), a Potent, Orally Bioavailable, and Selective Small-Molecule Inhibitor of Chemokine Receptor CCR5 with Broad-Spectrum Anti-Human Immunodeficiency Virus Type 1 Activity," *Antimicrob Agents Chemother*, 2005, 49(11):4721-32.[PubMed 16251317]

"Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States," July 8, 2008. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection," July 29, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand Names Celsentri (CH, CZ, DE, DK, GB, IE, NO, SE)

Measles Virus Vaccine (Live)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Attenuvax® may be confused with Meruvax®

Pronunciation(MEE zels VYE rus vak SEEN, live)

U.S. Brand NamesAttenuvax®

Pharmacologic CategoryVaccine, Live (Viral)

Use: Labeled IndicationsActive immunization against measles (rubeola)

Note: Trivalent measles - mumps - rubella (MMR) is the vaccine of choice if recipients are likely to be susceptible to rubella and/or mumps as well as to measles.

Dosing: AdultsImmunization: SubQ: 0.5 mL in outer aspect of the upper arm. **Note:** Trivalent measles - mumps - rubella (MMR) vaccine should be used unless contraindicated in adults and children ≥12 months of age.

Adults born in or after 1957 without documentation of live vaccine on or after first birthday, without physician-diagnosed measles, or without laboratory evidence of immunity should be vaccinated, ideally with 2 doses of vaccine separated by no less than 1 month. For those previously vaccinated with 1 dose of measles vaccine, revaccination is recommended for students entering colleges and other institutions of higher education, for healthcare workers at the time of employment, and for international travelers who visit endemic areas. Persons vaccinated between 1963 and 1967 with a killed measles vaccine, followed by live vaccine within 3 months, or with a vaccine of unknown type should be revaccinated with live measles virus vaccine.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricImmunization: SubQ: Children ≥6 months: 0.5 mL in outer aspect of the upper arm. **Note:** Trivalent measles - mumps - rubella (MMR) vaccine should be used unless contraindicated in adults and children ≥12 months of age.

Primary vaccination recommended at 12-15 months of age and repeated at 4-6 years of age. Children requiring vaccination with measles virus vaccine prior to 12 months of age (eg, during local outbreak, international travel to endemic area) should receive another dose between 12-15 months and again prior to elementary school.

Administration: OtherVaccine should not be administered I.V.; SubQ injection preferred with a 25-gauge $^5/_8$" needle

StorageDuring shipment, store at ≤10°C (50°F). Prior to and following reconstitution, refrigerate at 2°C to 8°C (36°F to 46°F). Protect from light at all times. Following reconstitution, use within 8 hours.

ContraindicationsHypersensitivity to measles vaccine or any component of the formulation; current febrile illness; patients receiving immunosuppressive therapy (not including steroid replacement); primary and acquired immunodeficiency states; blood dyscrasias, cancers affecting the bone marrow or lymphatic systems; pregnancy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use. Use extreme caution in patients with immediate-type hypersensitivity reactions to eggs.
- Neomycin sensitivity: Contact dermatitis to neomycin is not a contraindication to the vaccine.

Disease-related concerns:

- Acute illness: The manufacturer contraindicates use with febrile infections; however, the ACIP notes that patients with minor illnesses with or without fever (diarrhea, mild upper respiratory tract infection, otitis media) may receive vaccines.
- CNS disorders: Use with caution in patients with history of cerebral injury, seizures, or other conditions where stress due to fever should be avoided.
- Measles exposure: Exposure to measles is not a contraindication to vaccine; use within 72 hours of exposure may provide some protection.
- Thrombocytopenia: Use with caution in patients with thrombocytopenia and those who develop thrombocytopenia after first dose; thrombocytopenia may worsen.
- Tuberculosis: Therapy to treat tuberculosis should be started prior to administering vaccine to patients with untreated, active tuberculosis.

Concurrent drug therapy issues:

- Immune globulins: Recent administration of immune globulins may interfere with immune response.

Special populations:

- Altered immunocompetence: Use is contraindicated in severely immunocompromised patients (eg, patients receiving chemo-/radiation therapy or other immunosuppressive therapy (including high-dose corticosteroids)); may have a reduced response to vaccination. Patients with HIV infection, who are asymptomatic and not severely immunosuppressed may be vaccinated. Patients with leukemia who are in remission and who have not received chemotherapy for at least 3 months may be vaccinated.

- Healthcare workers: Acceptable evidence of immunity is recommended healthcare workers at time of employment.

- Pediatrics: Safety and efficacy have not been established in children <6 months of age.

- Students: Acceptable evidence of immunity is recommended for students entering institutions of higher learning.

- Travelers to endemic areas: Acceptable evidence of immunity is recommended for travelers to endemic areas.

Dosage form specific issues:

- Albumin: Products may contain albumin.

- Gelatin: Products may contain gelatin.

- Neomycin: Products may contain neomycin.

Other warnings/precautions:

- Blood products: Recent administration of blood or blood products may interfere with immune response.

Geriatric ConsiderationsGenerally not recommended for adults since most have become immune; if from an isolated community where measles is not endemic, may require vaccination; no dose reduction is necessary

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. Vaccine should not be administered to pregnant women and the ACIP recommends that pregnancy be avoided for 28 days following vaccination. Infection with natural measles during pregnancy may increase the risk of spontaneous abortion, stillbirth, congenital defects and prematurity.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsBreast-feeding is not a contraindication to vaccination.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Frequency not defined.

Cardiovascular: Peripheral edema, syncope, vasculitis

Central nervous system: Ataxia, dizziness, encephalitis, encephalopathy, febrile seizure, fever, Guillain-Barré syndrome, headache, irritability, malaise, seizure

Dermatologic: Angioneurotic edema, erythema multiforme, panniculitis, purpura, rash, Stevens-Johnson syndrome, urticaria

Gastrointestinal: Diarrhea, nausea, vomiting

Hematologic: Leukocytosis, thrombocytopenia

Local: Injection site reactions: Burning, redness, stinging, swelling, vesiculation, wheal and flare

Neuromuscular & skeletal: Arthralgia, myalgia

Ocular: Conjunctivitis, ocular palsies, optic neuritis, papillitis, retinitis, retrobulbar neuritis

Otic: Nerve deafness, otitis media

Respiratory: Bronchial spasm, cough, pneumonitis, rhinitis

Miscellaneous: Anaphylaxis/anaphylactoid reactions, atypical measles, facial edema, lymphadenopathy, measles inclusion body encephalitis, subacute sclerosing pancephalitis

Drug Interactions

Immune Globulins: May diminish the therapeutic effect of Vaccines (Live). *Risk D: Consider therapy modification*

Immunosuppressants: May enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Tuberculin Tests: Vaccines (Live) may diminish the diagnostic effect of Tuberculin Tests. *Risk D: Consider therapy modification*

Test InteractionsMay temporarily depress tuberculin skin test sensitivity; tuberculin test may be given simultaneously on the same day as vaccine or ≥4 weeks later.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Attenuvax®: ≥1000 TCID_{50} [contains albumin (human), bovine serum, chicken egg protein, gelatin, neomycin, sorbitol, and sucrose (1.9 mg/vial)]

Generic AvailableNo

Mechanism of ActionPromotes active immunity to measles virus by inducing specific measles IgG and IgM antibodies. Measles antibodies develop in ~95% of children vaccinated at 12 months of age and in 98% of children vaccinated at 15 months of age. Life-long immunity is induced in most persons completing vaccination schedule.

Related Information

- Immunization Recommendations
- Prophylaxis for Patients Exposed to Common Communicable Diseases

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Acceptable presumptive evidence of immunity includes one of the following:

1. Documentation of adequate vaccination. Adequate vaccination is defined as 1 dose of a live mumps virus vaccine for preschool children and adults not at high risk; 2 doses of a live mumps virus vaccine for school-aged children and high-risk adults. Healthcare workers, international travelers, and students in institutions of higher learning are considered high-risk adults.

2. Laboratory evidence of immunity

3. Birth prior to 1957

4. Documentation of physician-diagnosed disease

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMore Attenuated Enders Strain; Rubeola Vaccine

References

Centers for Disease Control and Prevention, “Measles, Mumps, and Rubella – Vaccine Use and Strategies for Elimination of Measles, Rubella, and Congenital Rubella Syndrome and Control of Mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP),” *MMWR Recomm Rep*, 1998, 47(RR-8):1-57.[PubMed 9639369]

Centers for Disease Control and Prevention, “Notice to Readers: Revised ACIP Recommendation for Avoiding Pregnancy After Receiving a Rubella-Containing Vaccine,” *MMWR Morb Mortal Wkly Rep*, 2001, 50(49):1117.[PubMed 11794623]

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.[PubMed 17136024]

Gardner P and Schaffner W, “Immunization of Adults,” *N Engl J Med*, 1993, 328(17):1252-8.[PubMed 8464436]

International Brand NamesAttenuvax (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE); Cam-Kovac (KP); Diplovax (ZA); Ervevax (AU, MY); Lirugen Measles (PH); M-VAC (IN); Meruvax II (AU); Morbilvax (TH, TW); Rimevax (AE, AT, AU, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, MY, OM, PH, QA, SA, SY, TH, TW, YE, ZA); Rouvax (BF, BJ, CI, ET, GH, GM, GN, HK, IL, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TH, TN, TW, TZ, UG, ZA, ZM, ZW)

Measles, Mumps, and Rubella Virus Vaccine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

MMR (measles, mumps and rubella virus vaccine) may be confused with MMRV (measles, mumps, rubella, and varicella) vaccine

Pronunciation(MEE zels, mumpz & roo BEL a VYE rus vak SEEN)

U.S. Brand NamesM-M-R® II

Canadian Brand NamesM-M-R® II; Priorix™

Pharmacologic CategoryVaccine, Live (Viral)

Use: Labeled IndicationsMeasles, mumps, and rubella prophylaxis

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for the following:

- All children (first dose given at 12-15 months of age)
- Adults born 1957 or later (without evidence of immunity or documentation of vaccination).
- Adults at higher risk for exposure to and transmission of measles mumps and rubella should receive special consideration for vaccination. This includes international travelers, persons attending colleges and other post-high school education, persons working in healthcare facilities.

Dosing: Adults**Immunization:***Born ≥1957 without evidence of immunity* (also see Additional Information or Pharmacotherapy Pearls): SubQ: 1 or 2 doses (0.5 mL/dose); minimum interval between doses is 28 days

Mumps outbreak:

Healthcare workers born <1957 without other evidence of immunity: Consider 2 doses of a live mumps virus vaccine; minimum interval between doses is 28 days

Low-risk adults: A second dose of a live mumps virus vaccine should be considered in adults who previously received 1 dose; minimum interval between doses is 28 days

Measles outbreak:

Students and personnel in affected schools and healthcare workers born <1957 without evidence of measles immunity: One dose of MMR vaccine

Students and personnel in affected schools and healthcare workers born ≥1957 without adequate documentation of 2 previous doses of a measles-containing vaccine after their first birthday or evidence of measles immunity: Two doses of MMR vaccine; minimum interval between doses is 28 days

Dosing: Pediatric

Immunization: SubQ: *Children ≥12 months:*

Primary immunization: 12-15 months of age: 0.5 mL

Revaccination: 4-6 years of age: 0.5 mL; revaccination is recommended prior to elementary school. If the second dose was not received, the schedule should be completed by the 11- to 12-year old visit.

Measles outbreak: SubQ:

Infants 6-11 months: If there is risk of exposure to measles, single-antigen measles vaccine should be administered. If single-antigen vaccine is not readily available, MMR is an acceptable alternative. Children should be revaccinated at ≥12 months with standard 2-dose series.

Children ≥12 months: Revaccination with MMR is recommended for attendees and siblings of daycare facilities or schools if they cannot provide adequate documentation of 2 previous doses of a measles-containing vaccine after their first birthday or evidence of measles immunity.

Mumps outbreak: SubQ: *Children ≥12 months:* During a mumps outbreak, children ages 1-4 years should consider a second dose of a live mumps virus vaccine; minimum interval between doses is 28 days

Administration: I.V.Not for I.V. administration.

Administration: OtherAdminister SubQ in outer aspect of the upper arm in patients ≥12 months

Administration with other vaccines:

MMR with inactivated vaccines: May be given simultaneously or at any interval between doses

MMR with other live vaccines:

Intranasal or injectable: If not given simultaneously, wait at least 4 weeks between administration

Oral: May be given simultaneously or at any interval between doses of live or inactivated injectable vaccines

Vaccine administration with antibody-containing products*: Do not give MMR simultaneously.

Measles-containing vaccines should be given:

≥3 months following hepatitis A immune globulin, hepatitis B immune globulin, tetanus immune globulin or red blood cells (adenine-saline added)

≥4 months after rabies immune globulin

≥5 months after measles immune globulin prophylaxis in a nonimmunocompromised contact

≥6 months after measles immune globulin in an immunocompromised contact, packed red blood cells (hematocrit 65%), whole blood (hematocrit 35% to 50%), or cytomegalovirus I.V. immune globulin

≥8 months after IVIG replacement therapy for immune deficiencies (excluding children with asymptomatic or mildly symptomatic HIV infection), immune thrombocytopenic purpura (lower dose), or postexposure varicella prophylaxis (see CDC reference for details)

≥10 months after IVIG for the treatment of immune thrombocytopenic purpura (higher dose)

≥11 months after IVIG for the treatment of Kawasaki disease

*Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products

StorageDuring shipment, store at ≤10°C (≤50°F). Prior to reconstitution, store the powder at 2°C to 8°C (36°F to 46°F) or colder (freezing does not affect potency). Protect from light. Diluent may be stored in refrigerator or at room temperature. Do not freeze diluent.

ReconstitutionUse entire contents of the provided diluent to reconstitute vaccine. Gently agitate to mix thoroughly. Discard if powder does not dissolve. Use as soon as possible following reconstitution (may be stored at 2°C to 8°C/36°F to 46°F; protect from light); discard if not used within 8 hours.

ContraindicationsHypersensitivity to measles, mumps, and rubella vaccine or any component of the formulation; current febrile respiratory illness or other febrile infection; patients receiving immunosuppressive therapy; primary and acquired immunodeficiency states; blood dyscrasias, cancers affecting the bone marrow or lymphatic systems; pregnancy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever). Per the ACIP, may administer to patients with mild acute illness (with or without fever).

- CNS disorders: Use with caution in patients with history of cerebral injury, seizures, or other conditions where stress due to fever should be avoided.

- Measles exposure: Exposure to measles is not a contraindication to vaccine; use within 72 hours of exposure may provide some protection.

- Thrombocytopenia: Use with caution in patients with thrombocytopenia and those who develop thrombocytopenia after first dose; thrombocytopenia may worsen.

- Tuberculosis: Therapy to treat tuberculosis should be started prior to administering vaccine to patients with active tuberculosis. Patients with untreated, active tuberculosis should not receive vaccine.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Altered immunocompetence: Use is contraindicated in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy [including high-dose corticosteroids]); may have a reduced response to vaccination. Patients with HIV infection, who are asymptomatic and not severely immunosuppressed may be vaccinated. Patients with leukemia who are in remission and who have not received chemotherapy for at least 3 months may be vaccinated.

- Pediatrics: Safety and efficacy of measles vaccine has not been established in children <6 months of age and safety and efficacy of mumps and rubella vaccines have not been established in <12 months of age. Local health departments may recommend vaccine to children 6-12 months of age in outbreak situations, but this would not count towards their immunization series.

Dosage form specific issues:

- Eggs allergy: Vaccine contains trace amounts of chick embryo antigen. Use caution in patients with history of immediate hypersensitivity/anaphylactic reactions following egg ingestion.

- Gelatin: Contains gelatin; do not use in patients with a history of anaphylactic/anaphylactoid reaction to gelatin.

- Neomycin sensitivity: Manufactured with neomycin. Patients with history of anaphylaxis should not receive vaccine; contact dermatitis to neomycin is not a contraindication to the vaccine.

Geriatric ConsiderationsMost adults and elderly are immune to measles (rubeola) and it is not necessary to vaccinate. If no history of measles exposure or patient is from an isolated community where measles is not endemic, vaccination may be required. Testing may be indicated; may need to test for rubella. Vaccinate those traveling into endemic areas with no evidence of immunity. No dose restriction necessary.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. It is not known whether the drug can cause fetal harm or affect reproduction capacity (contracting natural measles during pregnancy can increase fetal risk). Do not administer to pregnant females. The Advisory Committee on Immunization Practices (ACIP) recommends that pregnancy should be avoided for 28 days following vaccination.

Lactation

Measles/mumps: Excretion in breast milk unknown/use caution

Rubella: Enters breast milk/use caution

Breast-Feeding ConsiderationsEvidence of rubella infection has occurred in breast-fed infants following maternal immunization, most without severe disease.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Frequency not defined:

Cardiovascular: Syncope, vasculitis

Central nervous system: Ataxia, dizziness, febrile seizure, fever, encephalitis, encephalopathy, Guillain-Barré syndrome, headache, irritability, malaise, measles inclusion body encephalitis, polyneuritis, polyneuropathy, seizure, subacute sclerosing panencephalitis

Dermatologic: Angioneurotic edema, erythema multiforme, measles-like rash, pruritus, purpura, rash, Stevens-Johnson syndrome, urticaria

Endocrine & metabolic: Diabetes mellitus, parotitis

Gastrointestinal: Diarrhea, nausea, pancreatitis, sore throat, vomiting

Genitourinary: Epididymitis, orchitis

Hematologic: Leukocytosis, thrombocytopenia

Local: Injection site reactions which include burning, induration, redness, stinging, swelling, tenderness, wheal and flare, vesiculation

Neuromuscular & skeletal: Arthralgia/arthritis (variable; highest rates in women, 12% to 26% versus children, up to 3%), myalgia, paresthesia

Ocular: Conjunctivitis, ocular palsies, optic neuritis, papillitis, retinitis, retrobulbar neuritis

Otic: Nerve deafness, otitis media

Respiratory: Bronchospasm, cough, pneumonia, pneumonitis, rhinitis

Miscellaneous: Anaphylactoid reactions, anaphylaxis, atypical measles, panniculitis, regional lymphadenopathy

Postmarketing and/or case reports: Aseptic meningitis (associated with Urabe strain of mumps vaccine)

Drug Interactions

Immune Globulins: May diminish the therapeutic effect of Vaccines (Live). *Risk D: Consider therapy modification*

Immunosuppressants: May enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Tuberculin Tests: Vaccines (Live) may diminish the diagnostic effect of Tuberculin Tests. *Risk D: Consider therapy modification*

Test InteractionsTemporary suppression of TB skin test reactivity with onset approximately 3 days after administration

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

M-M-R® II: Measles virus ≥1000 TCID$_{50}$, mumps virus ≥20,000 TCID$_{50}$, and , rubella virus ≥1000 TCID$_{50}$ [contains albumin (human), bovine serum, chicken egg protein, gelatin, neomycin, sorbitol, and sucrose 1.9 mg/vial]

Generic AvailableNo

ManufacturerMerck & Co

Pricing: U.S. (www.drugstore.com)

Injection (M-M-R II)

(1): $57.62

Mechanism of ActionAs a live, attenuated vaccine, MMR vaccine offers active immunity to disease caused by the measles, mumps, and rubella viruses.

Related Information

- Immunization Recommendations

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Acceptable presumptive evidence of immunity includes one of the following:

1. Documentation of adequate vaccination (for measles, mumps, and rubella). Adequate vaccination for mumps is defined as 1 dose of a live mumps virus vaccine for preschool children and adults not at high risk; 2 doses of a live mumps virus vaccine for school-aged children and high-risk adults. Healthcare workers, international travelers, and students in institutions of higher learning are considered high-risk adults.
2. Laboratory evidence of immunity (for measles, mumps, and rubella)
3. Birth prior to 1957 (measles and mumps); for women of childbearing potential, birth prior to 1957 is not acceptable evidence of immunity to rubella
4. Documentation of physician-diagnosed disease (for measles, mumps, and rubella)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental Status

May cause dizziness, encephalopathy, irritability, and malaise

Mental Health: Effects on Psychiatric Treatment

None reported

Index TermsMMR; Mumps, Measles and Rubella Vaccines, Combined; Rubella, Measles and Mumps Vaccines, Combined

References

Centers for Disease Control and Prevention (CDC), “Notice to Readers: Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP) for the Control and Elimination of Mumps,” *MMWR Recomm Rep*, 2006, 55(early release):1-2. Available at http://www.cdc.gov/mmwr/pdf/wk/mm55e601.pdf

Centers for Disease Control and Prevention (CDC), “Revised ACIP Recommendation for Avoiding Pregnancy After Receiving a Rubella-Containing Vaccine,” *MMWR Morb Mortal Wkly Rep*, 2001, 50(49):1117.[PubMed 11794623]

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.[PubMed 17136024]

Centers for Disease Control, “Simultaneous Administration of Varicella Vaccine and Other Recommended Childhood Vaccine,” *MMWR*, 2001, 50(47):1058-61. [PubMed 11808928]

Plichta AM, “Immunization: Protecting Older Patients From Infectious Disease,” *Geriatrics*, 1996, 51(9):47-52.

Watson JC, Hadler SC, Dykewicz CA, et al, “Measles, Mumps, and Rubella – Vaccine Use and Strategies for Elimination of Measles, Rubella, and Congenital Rubella Syndrome and Control of Mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP),” *MMWR Recomm Rep*, 1998, 47(RR-8):1-57.

International Brand NamesM-M-R II (CZ, ID, MY, NZ, TH); M-M-R Vax (AT, DE); M.M.R. Vaccine (KP); MMR II (AR, CH, CL, GB, HK, NO, PH, SE, TW); Morupar (MX, PH); Mumeru Vax (PH); Pluserix (BB, BF, BJ, BM, BS, BZ, CI, ET, GH, GM, GN, GY, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, SC, SD, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Priorix (AU, BB, BM, BS, BZ, GB, GY, IE, IL, JM, KP, NL, NO, PH, SE, SR, TT, TW); R.O.R. Vax (FR); Trimovax (BG, HK, IT, PK, TH, TW); Triviraten Berna (HK, MY, NZ, PH, TH)

Measles, Mumps, Rubella, and Varicella Virus Vaccine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Measles, Mumps, Rubella, and Varicella (MMRV) Virus Vaccine: ACIP Recommendations Updated - April 2008

Due to reports of an increased risk of febrile seizures associated with the combination MMRV vaccine (ProQuad®), the Advisory Committee on Immunization Practices (ACIP) has altered their opinion on using MMRV combination vaccine preferentially over administration of MMR and varicella as 2 separate vaccines. The new language states “Combination MMRV vaccine is approved for use among healthy children ages 12 months to 12 years. MMRV is indicated for simultaneous vaccination against measles, mumps, rubella, and varicella. ACIP does not express a preference for use of MMRV vaccine over separate injections of equivalent component vaccines (ie, MMR vaccine and varicella vaccine).” Preliminary data from a CDC-sponsored postmarketing study and interim results from a postlicensure study done by Merck have found an increased rate of febrile seizures occurring within 7-10 days after vaccination with MMRV in children 12-23 months of age compared to vaccination with MMR and varicella as separate vaccines. While MMR is also associated with an increased risk of febrile seizures, results suggest that use of the combination product results in 2 times more risk of febrile seizures. A working group will be established to further investigate these findings and will communicate updates as necessary. Merck updated their package insert to include the postmarketing adverse events in February of 2008. MMRV is currently on shortage in the U.S. due to manufacturing issues, the shortage is not expected to resolve before 2009. All clinically significant adverse events following vaccine should be reported to the Vaccine Adverse Event Reporting System (VAERS) (1-800-822-7967).

For additional information:

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5710a3.htm?s_cid=mm5710a3_e

http://www.fda.gov/cber/label/proquadlbinfo.htm

http://www.cdc.gov/vaccinesafety/vsd/mmrv.htm

VAERS website: http://www.fda.gov/cber/vaers/vaers.htm

Pronunciation(MEE zels, mumpz, roo BEL a, & var i SEL a VYE rus vak SEEN)
U.S. Brand NamesProQuad®
Pharmacologic CategoryVaccine, Live (Viral)
Use: Labeled IndicationsTo provide simultaneous active immunization against measles, mumps, rubella, and varicella
Dosing: PediatricImmunization: Children 12 months to 12 years: SubQ: One dose (0.5 mL)

Administer on or after the first birthday, as soon as child becomes eligible for vaccination. It may be used whenever all components of the vaccine are needed in children within this age group. (Refer to current CDC Recommended Immunization Schedule)

Allow at least 1 month between administering a dose of a measles containing vaccine (eg, M-M-R® II) and ProQuad®.

Allow at least 3 months between administering a varicella containing vaccine (eg, Varivax®) and ProQuad®.

Administration: OtherFor SubQ injection only; inject in the outer aspect of the deltoid region of the upper arm or in the higher anterolateral area of the thigh. Administer immediately following reconstitution.
Storage

Vaccine: During shipment, powder should be stored at or below -15˚C (5°F). Prior to reconstitution, may be stored in a freezer for up to 18 months at temperatures at or below -15˚C (5°F). May store under refrigeration at 2°C to 8˚C (36°F to 46˚F) for up to 72 hours prior to reconstitution. Protect from light at all times. Following reconstitution, use within 30 minutes.

Diluent: Store under refrigeration at 2°C to 8˚C (36°F to 46˚F) or at room temperature of 20°C to 25˚C (68°F to 77˚F).

ReconstitutionUse only diluent provided. Gently agitate to dissolve powder. Use only sterile syringes that are free of preservatives, antiseptics, detergents, or other antiviral substances.
ContraindicationsHypersensitivity to measles, mumps, rubella, and/or varicella vaccines, or any component of the formulation; anaphylactic reaction to neomycin; individuals with blood dyscrasias, leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic systems; those receiving immunosuppressive therapy (including high-dose systemic corticosteroids); primary and acquired immunodeficiency states; family history of congenital or hereditary immunodeficiency; active untreated tuberculosis; current febrile illness with fever >38.5°C (>101.3°F); pregnancy
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

- Febrile seizures: Children 12-23 months of age have been reported to have a higher risk of developing febrile seizures with the use of the combination product (MMRV) compared to administration of MMR and varicella separately.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).

- CNS disorders: Use with caution in patients with history of cerebral injury, seizures, or other conditions where stress due to fever should be avoided.

- HIV: Safety and efficacy have not been established in patients with HIV infection.

- Thrombocytopenia: Use with caution in patients with thrombocytopenia and those who develop thrombocytopenia after first dose; thrombocytopenia may worsen.

Concurrent drug therapy issues:

- Salicylates: Avoid use of salicylates for 6 weeks following vaccination; varicella may increase the risk of Reye's syndrome.

Special populations:

- Pediatrics: This combination vaccine is for use in primary immunization of children 12 months to 12 years of age; may also be used if a second dose of measles, mumps, and rubella vaccine is to be administered.

Dosage form specific issues:

- Albumin: Products may contain albumin.

- Egg allergy: Vaccine contains trace amounts of chick embryo antigen. Use caution in patients with history of immediate hypersensitivity/anaphylactic reactions following egg ingestion

- Gelatin: Products may contain gelatin.

- Neomycin sensitivity: Manufactured with neomycin. Patients with history of anaphylaxis should not receive vaccine; contact dermatitis to neomycin is not a contraindication to the vaccine.

Other warnings/precautions:

- Blood products: Recent administration of blood or blood products may interfere with immune response.

- Transmission of virus: Vaccinated individuals should not have close association with susceptible high-risk individuals (newborns of women without positive history of varicella, pregnant women without positive history of varicella, immunocompromised persons) for 6 weeks following vaccination; transmission of varicella virus may occur.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. It is not known whether the vaccine can cause fetal harm or affect reproduction capacity (contracting natural measles during pregnancy can increase fetal risk). Rates of spontaneous abortion may be increased if mumps infection occurs during the first trimester. Although mumps vaccine virus can infect the placenta and fetus, there is not good evidence that it causes congenital malformations. Do not administer to pregnant females and pregnancy should be avoided for 3 months following vaccination. A pregnancy registry has been established for pregnant women exposed to varicella virus vaccine (800-986-8999).

Lactation

Measles, mumps, varicella: Excretion in breast milk unknown/use caution

Rubella: Enters breast milk/use caution

Breast-Feeding Considerations

Following vaccination of the mother, rubella virus may be transmitted to the nursing infant via breast milk.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Also refer to Measles, Mumps, and Rubella Vaccines (Combined) (M-M-R® II) and Varicella Virus Vaccine (Varivax®) monographs for additional adverse reactions reported with those agents.

>10%:

Central nervous system: Fever ≥38.9˚C (≥102˚F) (22%)

Local: Injection site reaction including pain, tenderness, soreness (22%); erythema (14%)

1% to 10%:

Central nervous system: Irritability (7%)

Dermatologic: Measles-like rash (3%), varicella-like rash (2%), rash (2%), viral exanthema (1%)

Gastrointestinal: Diarrhea (1%)

Local: Injection site reaction: Swelling (8%), bruising (2%)

Respiratory: Upper respiratory tract infection (1%)

<1%: Anorexia, cough, crying, dermatitis, injection site hemorrhage, injection site rash, insomnia, malaise, miliaria ruba, nasal congestion, otitis, otitis media, pharyngitis, respiratory congestion, rhinorrhea, rubella-like rash, sleep disorder, somnolence, viral infection, vomiting

Postmarketing and/or case reports: Anaphylactic reaction, convulsion, encephalitis, febrile seizure (usually occurring 5-12 days after vaccination; highest risk in 12-23 months of age), herpes zoster, pruritus

Drug Interactions

5-ASA Derivatives: May enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. The primary concern is the potential development of Reye's Syndrome, a condition that has been associated with the use of salicylates in children with varicella infections. *Risk D: Consider therapy modification*

Immune Globulins: May diminish the therapeutic effect of Vaccines (Live). *Risk D: Consider therapy modification*

Immunosuppressants: May enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Salicylates: May enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Tuberculin Tests: Vaccines (Live) may diminish the diagnostic effect of Tuberculin Tests. *Risk D: Consider therapy modification*

Test InteractionsMay interfere with sensitivity to tuberculin skin test; administer before, simultaneously with, or at least 4-6 weeks after vaccine.

Monitoring ParametersRash, fever

Nursing: Physical Assessment/MonitoringFor use in children 12 months to 12 years. Assess hypersensitivity history and health status (eg, contraindicated conditions) prior to administration. Epinephrine injection and other appropriate agents and equipment must be immediately available in event of anaphylactic or serious allergic reactions. **Note:** All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS). Record date of administration, name of manufacturer, lot number, and administering person’s name, title and address into patient’s permanent medical record. Teach patient/caregiver possible side effects, appropriate interventions (eg, avoid use of salicylates for 6 weeks following vaccination), and adverse symptoms to report.

Patient EducationChildren who are moderately to severely ill (with or without fever) should not get this vaccination until they have recovered. Inform prescriber of all previous allergic reactions, any health conditions, and any other medications being used. Do not use aspirin or aspirin-containing products for 6 weeks following vaccination. You may experience fever (consult prescriber for antipyretic), mild pain, redness, swelling at injection site, headache, mild gastrointestinal upset, irritability, mild rash, or upper respiratory tract infection. Report immediately any severe reaction at injection site; any chills or fever; persistent diarrhea; severe rash or other adverse reactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

ProQuad®: Measles virus ≥3.00 log$_{10}$ TCID$_{50}$, mumps virus ≥4.3 log$_{10}$ TCID$_{50}$, rubella virus ≥3.00 log$_{10}$ TCID$_{50}$, and varicella virus ≥3.99 log$_{10}$ PFU [contains albumin (human), bovine serum, chicken egg protein, gelatin, neomycin, sorbitol, and sucrose (≤21 mg/vial)]

Generic AvailableNo

ManufacturerMerck and Co, Inc

Mechanism of ActionA live, attenuated virus; offers active immunity to disease caused by the measles, mumps, rubella, and varicella-zoster virus.

Related Information

- Immunization Recommendations

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause irritability; may rarely cause insomnia or malaise

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMMR-V; MMRV; Mumps, Rubella, Varicella, and Measles Vaccine; Rubella, Varicella, Measles, and Mumps Vaccine; Varicella, Measles, Mumps, and Rubella Vaccine

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Mebendazole

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(me BEN da zole)
U.S. Brand NamesVermox® [DSC]
Canadian Brand NamesVermox®
Pharmacologic Category[Anthelmintic]
Use: Labeled IndicationsTreatment of pinworms (*Enterobius vermicularis*), whipworms (*Trichuris trichiura*), roundworms (*Ascaris lumbricoides*), and hookworms (*Ancylostoma duodenale*)
Dosing: Adults

Pinworms: Oral: 100 mg as a single dose; may need to repeat after 2 weeks; treatment should include family members in close contact with patient.

Whipworms, roundworms, hookworms: Oral: 1 tablet twice daily, morning and evening on 3 consecutive days; if patient is not cured within 3-4 weeks, a second course of treatment may be administered.

Capillariasis: Oral: 200 mg twice daily for 20 days

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren ≥2 years: Refer to adult dosing.
Dosing: Renal ImpairmentNot dialyzable (0% to 5%)
Dosing: Hepatic ImpairmentDosage reduction may be necessary in patients with liver dysfunction.
Administration: OralTablets may be chewed, swallowed whole, or crushed and mixed with food.
Dietary ConsiderationsTablet can be crushed and mixed with food, swallowed whole, or chewed.
ContraindicationsHypersensitivity to mebendazole or any component of the formulation
Allergy Considerations

- Benzimidazole Anthelmintics Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bone marrow suppression: Neutropenia and agranulocytosis have been reported with high doses and prolonged use.

Disease-related concerns:

- Hydatid disease: Not effective for hydatid disease.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsSince only 2% to 10% of mebendazole is absorbed, it is unlikely that it is excreted in breast milk in significant quantities.
Adverse ReactionsFrequency not defined.

Cardiovascular: Angioedema

Central nervous system: Fever, dizziness, headache, seizure

Dermatologic: Rash, itching, alopecia (with high doses)

Gastrointestinal: Abdominal pain, diarrhea, nausea, vomiting

Hematologic: Neutropenia (sore throat, unusual fatigue)

Neuromuscular & skeletal: Unusual weakness

Drug Interactions

Aminoquinolines (Antimalarial): May decrease the serum concentration of Anthelmintics. *Risk C: Monitor therapy*

CarBAMazepine: May decrease the serum concentration of Mebendazole. *Risk D: Consider therapy modification*

MetroNIDAZOLE: Mebendazole may enhance the adverse/toxic effect of MetroNIDAZOLE. Particularly the risk for Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis may be increased. *Risk D: Consider therapy modification*

Phenytoin: May decrease the serum concentration of Mebendazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Mebendazole serum levels may be increased if taken with food.
Monitoring ParametersCheck for helminth ova in feces within 3-4 weeks following the initial therapy
Nursing: Physical Assessment/MonitoringSince worm infestations are easily transmitted, all persons sharing same household should be treated. Teach proper use, transmission prevention, side effects/appropriate interventions, and adverse reactions to report.
Monitoring: Lab TestsCheck for helminth ova in feces within 3-4 weeks following the initial therapy. Periodically assess hematologic and hepatic function.
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed for full course of medication. Tablets may be chewed, swallowed whole, or crushed and mixed with food. Increase dietary intake of fruit juices. All family members and close friends should also be treated. To reduce possibility of reinfection, wash hands and scrub nails carefully with soap and hot water before handling food, before eating, and before and after toileting. Keep hands out of mouth. Disinfect toilet daily and launder bed linens, undergarments, and nightclothes daily with hot water and soap. Do not go barefoot and do not sit directly on grass or ground. May cause abdominal pain, nausea, or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or hair loss (reversible). Report skin rash or itching, unusual fatigue or sore throat, unresolved diarrhea or vomiting, or CNS changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, chewable: 100 mg

Generic AvailableYes
ManufacturerMcNeil Consumer Products Co
Pricing: U.S. (www.drugstore.com)

Chewable (Mebendazole)

100 mg (1): $13.99

Mechanism of ActionSelectively and irreversibly blocks glucose uptake and other nutrients in susceptible adult intestine-dwelling helminths
Pharmacodynamics/Kinetics

Absorption: 2% to 10%

Distribution: To serum, cyst fluid, liver, omental fat, and pelvic, pulmonary, and hepatic cysts; highest concentrations found in liver; relatively high concentrations found in muscle-encysted *Trichinella spiralis* larvae; crosses placenta

Protein binding: 95%

Metabolism: Extensively hepatic

Half-life elimination: 1-11.5 hours

Time to peak, serum: 2-4 hours

Excretion: Primarily feces; urine (5% to 10%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness
Mental Health: Effects on Psychiatric TreatmentCarbamazepine may decrease the effects of mebendazole; may rarely cause neutropenia; use caution with clozapine and carbamazepine
References

de Silva N, Guyatt H, and Bundy D, "Anthelmintics. A Comparative Review of Their Clinical Pharmacology," *Drugs*, 1997, 53(5):769-88. [PubMed 9129865]

"Drugs for Parasitic Infections," *Med Lett Drugs Ther*, 1998, 40(1017):1-12. [PubMed 9442765]

Hotez PJ, "Hookworm Disease in Children," *Pediatr Infect Dis J*, 1989, 8(8):516-20.[PubMed 2671907]

International Brand NamesAdec (TW); Anelmin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Antiox (PH); Bendrax (BR); Big-Ben (TH); Combantrin-1 with mebendazole (AU); Conquer (TW); D-Worm (ZA); Diacor (CN); Helmacon (PH); Hitolin (TW); L-Ombrix (MX); Lomper (ES); Mebedal (MX); Mebendazol (MX); Mebensole (MX); Mebex (IN); Mebezol (TW); Nemasole (AR); Pantelmin (AT, CO, PT, PY, UY, VE); Parasitex (PE); Penalcol (PE); Pharaxis M (CO); Quemox (MY); Revapol (MX); Ridworm (AU); Sqworm (AU); Surfont (DE); Thelmox (MY, PR); Toloxim (PT); Vermin-Dazol (MX); Vermox (AE, AU, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CL, CY, CZ, DE, DK, EE, EG, ET, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PK, PL, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Vertizole (MX); Wormex (PH); Wormgo (ZA); Wormin (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IN, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Zadomen (MY)

Mecamylamine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Mecamylamine may be confused with mesalamine

Pronunciation(mek a MIL a meen)
U.S. Brand NamesInversine®
Canadian Brand NamesInversine®
Pharmacologic CategoryGanglionic Blocking Agent
Use: Labeled IndicationsTreatment of moderately severe to severe hypertension and in uncomplicated malignant hypertension
Use: Unlabeled/InvestigationalTourette's syndrome
Dosing: AdultsHypertension: Oral: 2.5 mg twice daily after meals for 2 days; increased by increments of 2.5 mg at intervals ≥2 days until desired blood pressure response is achieved; average daily dose: 25 mg (usually in 3 divided doses)

Note: Reduce dosage of other antihypertensives when combined with mecamylamine with exception of thiazide diuretics which may be maintained at usual dose while decreasing mecamylamine by 50%

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentUse with caution, if at all, although no specific guidelines are available.
Dietary ConsiderationsShould be taken after meals.
ContraindicationsCoronary insufficiency, pyloric stenosis, glaucoma, uremia, recent myocardial infarction, unreliable, uncooperative patients
Warnings/Precautions

Disease-related concerns:

- CNS abnormalities: Use with caution in patients with previous CNS abnormalities.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia, bladder obstruction, or urethral stricture; may cause urinary retention.
- Renal impairment: Use with caution in patients with renal impairment.

Other warnings/precautions:

- Abrupt discontinuation: Do not abruptly discontinue.

Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined.

Cardiovascular: Postural hypotension

Central nervous system: Drowsiness, convulsions, confusion, mental depression

Endocrine & metabolic: Sexual ability decreased

Gastrointestinal: Xerostomia, loss of appetite, nausea, vomiting, bloating; frequent stools followed by severe constipation

Genitourinary: Dysuria

Neuromuscular & skeletal: Uncontrolled movements of hands, arms, legs, or face; trembling

Ocular: Blurred vision; enlarged pupils

Respiratory: Dyspnea

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersMonitor for orthostatic hypotension; aid with ambulation
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 2.5 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Inversine)

2.5 mg (30): $152.72

Mechanism of ActionMecamylamine is a ganglionic blocker. This agent inhibits acetylcholine at the autonomic ganglia, causing a decrease in blood pressure. Mecamylamine also blocks central nicotinic cholinergic receptors, which inhibits the effects of nicotine and may suppress the desire to smoke.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, confusion, or depression

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMecamylamine Hydrochloride

References

Harington M and Kincaid-Smith P, “Psychosis and Tremor Due to Mecamylamine,” *Lancet*, 1958, 1(7019):499-501.

Rokseth R and Storstein O, “Pulmonary Complications During Mecamylamine Therapy,” *Acta Med Scand*, 1960, 167(1):23-7. [PubMed 14438495]

Sanberg PR, Shytle RD, and Silver AA, “Treatment of Tourette's Syndrome With Mecamylamine,” *Lancet*, 1998, 352(9129):705-6.

International Brand NamesInversine (CA)

Mecasermin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(mek a SER min)

U.S. Brand NamesIncrelex™; Iplex™ [DSC]

Pharmacologic CategoryGrowth Hormone

Use: Labeled IndicationsTreatment of growth failure in children with severe primary insulin-like growth factor-1 deficiency (IGF-1 deficiency; primary IGFD), or with growth hormone (GH) gene deletions who have developed neutralizing antibodies to GH

Dosing: Pediatric

Primary IGFD: SubQ:

Increlex™: Children ≥2 years: Initial: 0.04-0.08 mg/kg twice daily; if tolerated for 7 days, may increase by 0.04 mg/kg/dose (maximum dose: 0.12 mg/kg given twice daily). Must be administered within 20 minutes of a meal or snack; omit dose if patient is unable to eat. Reduce dose if hypoglycemia occurs despite adequate food intake.

Iplex™: Children ≥3 years: Initial: 0.5 mg/kg once daily; dose may be increased to 1-2 mg/kg/day, given once daily. Withhold dose if hypoglycemia is present.

Administration: I.V.Do not administer I.V.

Administration: OtherFor SubQ injection only. Omit dose and do not make up for omitted dose if patient is unable to eat. Rotate injection site.

Increlex™: Must be administered within 20 minutes of a meal or snack. May cause hypoglycemic effects; patients should avoid high-risk activities within 2-3 hours of dosing until a tolerated dose is established.

Iplex™: Prior to administration, gently swirl vial; do not shake. Do not use if solution is cloudy (may indicate thawing during storage); do not use if stored at room temperature >2 hours. Dose should be administered once daily, at the same time each day. May cause hypoglycemic effects; patients should avoid high risk activities for 3-5 days until a tolerated dose is established. Withhold dose if hypoglycemia is present.

Dietary ConsiderationsIncrelex™ must be administered within 20 minutes of a meal or snack. Patients using Iplex™ should avoid missing meals and maintain a balanced diet.

Storage

Increlex™: Store under refrigeration at 2°C to 8°C (35°F to 46°F); do not freeze. Protect from direct light. After initial entry into vial, use within 30 days.

Iplex™: Must be kept frozen. Store at -70°C (-94°F) during distribution and at -20°C (-4°F) once in the patients home freezer. Transport to home freezer on dry ice. Do not use if product thaws during transportation or storage. If solution is cloudy, it may indicate that it has thawed during storage and should not bet used. May be stored up to 2 months at -20˚C (-4˚F). Prior to use, remove from freezer and allow to thaw at room temperature of 20˚C to 25˚C (68˚ to 77˚F) for ~45 minutes. Use within 1 hour of reaching room temperature. Do not use if vial was kept at room temperature for >2 hours.

ContraindicationsHypersensitivity to mecasermin or any component of the formulation; patients with closed epiphyses; active or suspected neoplasia

Warnings/Precautions

Concerns related to adverse effects:

- Hypoglycemia: May cause hypoglycemic effects; patients should avoid high risk activities until a tolerated dose is established. Do not administer on days a patient cannot or will not eat. Increlex™ should be administered with a meal or a snack; patients using Iplex™ should avoid missing meals and maintain a balanced diet.

- Intracranial hypertension (IH): With headache, nausea, papilledema, visual changes, and/or vomiting has been reported with growth hormone product, funduscopic examinations are recommended.

- Lymphoid hypertrophy: Has been reported and may lead to complications such as snoring, sleep apnea, and chronic middle-ear effusions.

- Progression of scoliosis: May occur in children experiencing rapid growth.

- Slipped capital epiphyses: Patients with growth hormone deficiency may develop slipped capital epiphyses more frequently, evaluate any child with new onset of a limp or with complaints of hip or knee pain.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes or with risk factors for glucose intolerance; may decrease insulin sensitivity.

Special populations:

- Adults: Safety and efficacy have not been established in adults.
- Pediatrics: Safety and efficacy have not been established in children <2 years of age (Increlex™) or <3 years of age (Iplex™).

Dosage form specific issues:

- Benzyl alcohol: Products may contain benzyl alcohol which may cause "gasping" syndrome in neonates.

Other warnings/precautions:

- Appropriate use: Correct thyroid or nutritional deficiencies prior to therapy. Not intended for use in patients with secondary forms of IGF-1 deficiency (GH deficiency, malnutrition, hypothyroidism, chronic anti-inflammatory steroid therapy).

Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies
LactationExcretion in breast milk unknown/ use caution
Adverse Reactions

≥5%:

Cardiovascular: Cardiac murmur

Central nervous system: Convulsion, dizziness, headache (Iplex™: 22%)

Endocrine & metabolic: Hyper-/hypoglycemia (Increlex™: 42%; Iplex™ 31%), iron-deficiency anemia, ovarian cysts, thymus hypertrophy, thyromegaly

Gastrointestinal: Vomiting

Hepatic: Liver enzymes increased

Local: Injection site reactions: Erythema, bruising, hair growth, lipohypertrophy

Neuromuscular & skeletal: Arthralgia, bone pain, extremity pain, muscular atrophy

Ocular: Papilledema

Otic: Ear pain, hypoacusis, middle ear fluid, otitis media, serous otitis media, tympanometry abnormal

Renal: Hematuria

Respiratory: Snoring, tonsillar hypertrophy (Increlex™: 15%; Iplex™ 19%)

Miscellanous: Lymphadenopathy

<5% or frequency not defined: Hypoglycemic seizure, intracranial hypertension, loss of consciousness secondary to hypoglycemia, thickening of soft facial tissue

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersPreprandial glucose during treatment initiation and dose adjustment; facial features; lymphoid tissue; fundoscopic examination; growth; new onset of a limp or complaints of hip or knee pain. Monitor small children closely due to potentially erratic food intake.

Iplex™: Adjust dose based on IGF-1 level obtained 8-18 hours after previous dose.

Target treatment IGF-1 level: 0 to +2 SD score for age

Decrease dose for adverse events and/or IGF-1 levels ≥3 SD above normal

Reference RangeSevere primary IGFD is defined as follows:

Height standard deviation score ≤ -3.0 **and**

Basal IGF-1 standard deviation score ≤ -3.0 **and**

Growth hormone: Normal or elevated

Nursing: Physical Assessment/MonitoringMeasure height at the beginning of therapy and periodically during treatment. Teach signs of hypoglycemia and corrective actions if it should occur. Instruct parents in proper subcutaneous administration techniques and appropriate disposal of needles. Monitor injection sites and teach parents to rotate injection sites. Assess for signs of enlarged tonsils. Monitor therapeutic response and adverse reactions at the beginning and periodically throughout therapy.
Monitoring: Lab TestsPreprandial glucose during treatment initiation and dose adjustment; fundoscopic examination; growth

Iplex™: Adjust dose based on IGF-1 level obtained 8-18 hours after previous dose.

Target treatment IGF-1 level: 0 to +2 SD score for age

Decrease dose for adverse events and/or IGF-1 levels ≥3 SD above normal

Patient EducationFor subcutaneous injection only. You will be instructed on the proper injection technique and disposal of needles. Must be administered shortly before or after a meal or snack. May cause hypoglycemia. Rotate injection sites. Administer per the directions of the prescriber. Do not alter dosage unless instructed to do so. Do not make up a missed dose by giving two doses. Do not administer if unable to eat. May cause enlarged tonsils. Report increased snoring, difficulty breathing or swallowing, sleep apnea, severe headaches, vomiting, hip or knee pain, or walking with a limp.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Increlex™: 10 mg/mL (4 mL) [contains benzyl alcohol]

Injection, solution, as rinfabate [preservative free]:

Iplex™: 36 mg/0.6 mL (0.6 mL) [DSC]

Generic AvailableNo

Mechanism of ActionMecasermin is an insulin-like growth factor (IGF-1) produced using recombinant DNA technology to replace endogenous IGF-1. Endogenous IGF-1 circulates predominately bound to insulin-like growth factor-binding protein-3 (IGFBP-3) and a growth hormone-dependent acid-labile subunit (ALS). Acting at receptors in the liver and other tissues, endogenous growth hormone (GH) stimulates the synthesis and secretion of IGF-1. In patients with primary severe IGF-1 deficiency, growth hormone receptors in the liver are unresponsive to GH, leading to reduced endogenous IGF-I concentrations and decreased growth (skeletal, cell, and organ). Endogenous IGF-1 also suppresses liver glucose production, stimulates peripheral glucose utilization and has an inhibitory effect on insulin secretion.

Mecasermin rinfabate is a complex of IGF-1 and IGFBP-3, both produced by recombinant DNA technology.

Pharmacodynamics/Kinetics

Distribution: V_d: Severe primary IGFD: 0.184-0.33 L/kg

Protein binding: >80% bound to IGFBP-3 and an acid-labile subunit (IGFBP-3 reduced with severe primary IGFD)

Metabolism: Hepatic and renal

Half-life elimination: Severe primary IGFD: Mecasermin: 5.8 hours; Mecasermin rinfabate: >12 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMecasermin (rDNA Origin) ; Mecasermin Rinfabate; Recombinant Human Insulin-Like Growth Factor-1; rhIGF-1; rhIGF-1/rhIGFBP-3

References

Backeljauw PF, Underwood LE, and GHIS Collaborative Group, "Therapy for 6.5-7.5 Years With Recombinant Insulin-Like Growth Factor I in Children With Growth Hormone Insensitivity Syndrome: A Clinical Research Center Study Syndrome," *J Clin Endocrinol Metab*, 2001, 86(4):1504-10.[PubMed 11297575]

Mechlorethamine

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English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(me klor ETH a meen)

U.S. Brand NamesMustargen®

Canadian Brand NamesMustargen®

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent (Nitrogen Mustard)

Use: Labeled IndicationsHodgkin's disease; non-Hodgkin's lymphoma; intracavitary injection for treatment of metastatic tumors; pleural and other malignant effusions; topical treatment of mycosis fungoides

Dosing: AdultsRefer to individual protocols. Dosage should be based on ideal dry weight. The presence of edema or ascites must be considered so that dosage will be based on actual weight unaugmented by these conditions.

MOPP: I.V.: 6 mg/m^2 on days 1 and 8 of a 28-day cycle

Typical dose: I.V.: 0.4 mg/kg **or** 12-16 mg/m^2 for one dose **or** divided into 0.1 mg/kg/day for 4 days, repeated at 4- to 6-week intervals

Intracavitary: 10-20 mg diluted in 10 mL of SWI or 0.9% sodium chloride

Intrapericardially: 0.2-0.4 mg/kg diluted in up to 100 mL of 0.9% sodium chloride

Mycosis fungoides: Topical mechlorethamine has been used in the treatment of cutaneous lesions of mycosis fungoides. A skin test should be performed prior to treatment with the topical preparation to detect sensitivity and possible irritation (use fresh mechlorethamine 0.1 mg/mL and apply over a 3 x 5 cm area of normal skin).

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols. Dosage should be based on ideal dry weight; the presence of edema or ascites must be considered so that dosage will be based on actual weight unaugmented by these conditions.

MOPP: Children: I.V.: 6 mg/m^2 on days 1 and 8 of a 28-day cycle

Dosing: Renal Impairment

Hemodialysis: Not removed; supplemental dosing is not necessary.

Peritoneal dialysis: Not removed; supplemental dosing is not necessary.

Dosing: Combination Regimens

Brain tumors:

MOP

MOPP (Medulloblastoma)

Lymphoma, Hodgkin's:

CAD/MOPP/ABV

MOPP (Lymphoma, Hodgkin's Disease)

MOPP/ABV Hybrid

MOPP/ABVD

MVPP

Stanford V Regimen

Oncology: Bone Marrow - High DoseI.V.: 0.3-2 mg/kg

Calculations

- Body Surface Area: Adults

- Body Surface Area: Pediatrics

Administration: I.V.Vesicant. Margin of error is very slight. Check dosage carefully before administration. Administer with caution. Administer I.V. push through a free-flowing I.V. over 1-3 minutes at a concentration not to exceed 1 mg/mL.
Administration: I.V. DetailMechlorethamine may cause extravasation. Use within 1 hour of preparation. Avoid extravasation since mechlorethamine is a potent vesicant.

pH: 3-5

StorageStore intact vials at room temperature. Solution is stable for only 15-60 minutes after dilution
ReconstitutionMust be prepared immediately before use. Dilute powder with 10 mL SWI to a final concentration of 1 mg/mL. May be diluted in up to 100 mL NS for intracavitary or topical administration.
CompatibilityStable in sterile water for injection; **incompatible** with D_5W; **variable stability (consult detailed reference)** in NS.

Y-site administration: Compatible: Amifostine, aztreonam, filgrastim, fludarabine, granisetron, melphalan, ondansetron, sargramostim, teniposide, vinorelbine. **Incompatible:** Allopurinol, cefepime.

Compatibility when admixed: Incompatible: Methohexital.

ContraindicationsHypersensitivity to mechlorethamine or any component of the formulation; pre-existing profound myelosuppression or infection
Allergy Considerations

- Nitrogen Mustard Allergy

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.
- Extravasation: See “Other warnings/precautions” below.
- Hazardous agent: See “Special handling” below.
- Pregnancy: See “Special populations” below.

Special handling:

- Hazardous agent: **[U.S. Boxed Warning]: Use appropriate precautions for handling and disposal.** Avoid contact with skin or eyes.

Concerns related to adverse effects:

- Bone marrow suppression: May cause lymphopenia, granulocytopenia, thrombocytopenia and anemia.
- Hyperuricemia: May occur, especially with lymphomas; ensure adequate hydration.

Special populations:

- Pregnancy: **[U.S. Boxed Warning]: Avoid exposure during pregnancy.**

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**
- Extravasation: **[U.S. Boxed Warning]: Mechlorethamine is a potent vesicant; if extravasation occurs, severe tissue damage (leading to ulceration and necrosis) and pain may occur.** Sodium thiosulfate should be available for treatment of extravasation.

Pregnancy Risk FactorD
Pregnancy ConsiderationsAnimal studies have demonstrated teratogenic effects. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential are advised not to become pregnant. Use only when potential benefit justifies potential risk to the fetus. **[U.S. Boxed Warning]: Avoid exposure during pregnancy.**
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsIt is not known if mechlorethamine is excreted in human breast milk. Due to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.
Adverse Reactions

>10%:

Dermatologic: Alopecia; hyperpigmentation of veins; contact and allergic dermatitis (50% with topical use)

Endocrine & metabolic: Chromosomal abnormalities, delayed menses, oligomenorrhea, amenorrhea, impaired spermatogenesis

Gastrointestinal: Nausea and vomiting (almost 100%), onset may be within minutes of drug administration

Genitourinary: Azoospermia

Hematologic: Myelosuppression, leukopenia, and thrombocytopenia

Onset: 4-7 days

Nadir: 14 days

Recovery: 21 days

1% to 10%:

Central nervous system: Fever

Gastrointestinal: Diarrhea, anorexia, metallic taste

Otic: Tinnitus

<1%: Vertigo, rash, hemolytic anemia, hepatotoxicity, weakness, peripheral neuropathy

Oncology: VesicantYes; see Management of Drug Extravasations.
Oncology: Emetic PotentialVery high (>90%)
Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to GI irritation).
Monitoring ParametersCBC with differential, hemoglobin, and platelet count
Nursing: Physical Assessment/MonitoringThis is a powerful vesicant; see Administration for infusion specifics. Premedication with antiemetic recommended (highly emetogenic; emesis may begin within minutes of starting infusion). Infusion site must be closely monitored; extravasation can cause severe sloughing or tissue necrosis. Assess results of laboratory tests prior to each treatment and on a regular basis throughout therapy. Patient must be monitored closely during infusion and between treatments (eg, adverse reactions can be severe and involve several systems). Teach patient possible side effects/appropriate interventions (eg, importance of adequate hydration) and adverse symptoms to report.
Monitoring: Lab TestsCBC with differential and platelet count
Patient EducationThis medication can only be given by infusion. Report immediately any swelling, redness, pain, or burning at infusion site. Do not use alcohol during treatment; may increase gastric irritation. Maintain adequate fluid balance (2-3 L/day) unless instructed to restrict fluid intake, and adequate nutrition (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may reduce anorexia and nausea). May cause discoloration (brown color) of veins used for infusion; hair loss (reversible); easy bleeding or bruising (use soft toothbrush or cotton swabs and frequent mouth care, use electric razor, avoid sharp knives or scissors); or increased susceptibility to infection (avoid crowds and exposure to infection and do not have any vaccinations unless approved by prescriber). This drug may cause menstrual irregularities, permanent sterility, and birth defects. Report changes in auditory or visual acuity; unusual bleeding or bruising or persistent fever or sore throat; blood in urine, stool, or vomitus; delayed healing of any wounds; skin rash; yellowing of skin or eyes; changes in color of urine of stool; acute or unresolved nausea or vomiting; diarrhea; or loss of appetite. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Do not get pregnant while taking this medication and for 1 month following therapy; consult prescriber for appropriate barrier contraceptives if necessary or if you suspect you might be pregnant. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as hydrochloride: 10 mg

Generic AvailableNo
Mechanism of ActionBifunctional alkylating agent that inhibits DNA and RNA synthesis via formation of carbonium ions; cross-links strands of DNA, causing miscoding, breakage, and failure of replication; produces interstrand and intrastrand cross-links in DNA resulting in miscoding, breakage, and failure of replication. Although not cell phase-specific *per se,* mechlorethamine effect is most pronounced in the S phase, and cell proliferation is arrested in the G_2 phase.
Pharmacodynamics/Kinetics

Duration: Unchanged drug is undetectable in blood within a few minutes

Absorption: Intracavitary administration: Incomplete secondary to rapid deactivation by body fluids

Metabolism: Rapid hydrolysis and demethylation, possibly in plasma

Half-life elimination: <1 minute

Excretion: Urine (50% as metabolites, <0.01% as unchanged drug)

Related Information

- Management of Drug Extravasations

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness
Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; avoid use with clozapine and carbamazepine

Index Terms Chlorethazine; Chlorethazine Mustard; HN_2; Mechlorethamine Hydrochloride; Mustine; Nitrogen Mustard; NSC-762

References

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DeVita VT, Serpick A, and Carbone PP, “Combination Chemotherapy in the Treatment of Advanced Hodgkin's Disease,” *Ann Intern Med*, 1970, 73:881-95. [PubMed 5525541]

Dorr RT, Soble M, and Alberts DS, “Efficacy of Sodium Thiosulfate as a Local Antidote to Mechlorethamine Skin Toxicity in the Mouse,” *Cancer Chemother Pharmacol*, 1988, 22(4):299-302. [PubMed 3168143]

Loutsidis A, Bellenis I, Argiriou M, et al, “Tetracycline Compared With Mechlorethamine in the Treatment of Malignant Pleural Effusions. A Randomized Trial,” *Respir Med*, 1994, 88(7):523-6. [PubMed 7972977]

Price NM, Hoppe RT, and Deneau DG, “Ointment Based Mechlorethamine Treatment for Mycosis Fungoides,” *Cancer*, 1983, 52:2214-9. [PubMed 6640491]

Taylor JR, Halprin KM, Levine V, et al, “Mechlorethamine Hydrochloride Solutions and Ointments,” *Arch Dermatol*, 1980, 116:783-5. [PubMed 7396542]

Vonderheid EC, “Topical Mechlorethamine Chemotherapy: Considerations on its Use in Mycosis Fungoides,” *Int J Dermatol*, 1984, 23(3):180-6.[PubMed 6373639]

International Brand Names Caryolysine (FR); Mustargen (IL, MX); Mustine Hydrochloride Boots (MY); Nitromin (JP)

Meclizine

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English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Antivert® may be confused with Axert™

Pronunciation(MEK li zeen)

U.S. Brand NamesAntivert®; Bonine® [OTC]; Dramamine® Less Drowsy Formula [OTC]; Medi-Meclizine [OTC]

Canadian Brand NamesBonamine™; Bonine®

Pharmacologic CategoryAntiemetic; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsPrevention and treatment of symptoms of motion sickness; management of vertigo with diseases affecting the vestibular system

Dosing: Adults

Motion sickness: Oral: 12.5-25 mg 1 hour before travel, repeat dose every 12-24 hours if needed; doses up to 50 mg may be needed

Vertigo: Oral: 25-100 mg/day in divided doses

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren >12 years: Refer to adult dosing.

ContraindicationsHypersensitivity to meclizine or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Asthma: Use with caution in patients with asthma.
- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Pyloric/duodenal obstruction: Use with caution in patients with pyloric or duodenal obstruction.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Other warnings/precautions:

- Lack of response: If vertigo does not respond in 1-2 weeks, it is advised to discontinue use.

Geriatric ConsiderationsDue to anticholinergic action, use lowest dose in divided doses to avoid side effects and their inconvenience. Limit use if possible. May cause confusion or aggravate symptoms of confusion in those with dementia. If vertigo does not respond in 1-2 weeks, discontinue use.

Pregnancy Risk FactorB

Pregnancy ConsiderationsNo data available on crossing the placenta. Probably no effect on the fetus (insufficient data). Available evidence suggests safe use during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Central nervous system: Slight to moderate drowsiness

Respiratory: Thickening of bronchial secretions

1% to 10%:

Central nervous system: Headache, fatigue, nervousness, dizziness

Gastrointestinal: Appetite increase, weight gain, nausea, diarrhea, abdominal pain, xerostomia

Respiratory: Pharyngitis

<1%: Palpitation, hypotension, depression, sedation, photosensitivity, rash, angioedema, urinary retention, hepatitis, myalgia, tremor, paresthesia, blurred vision, bronchospasm, epistaxis

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Nursing: Physical Assessment/MonitoringDetermine cause of vomiting before beginning therapy. Assess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy and adverse response. Assess knowledge/teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Patient EducationTake exactly as prescribed; do not increase dose. Avoid alcohol, other CNS depressants, sleeping aids without consulting prescriber. You may experience dizziness, drowsiness, or blurred vision (use caution when driving or engaging in tasks that require alertness until response to drug is known); dry mouth (frequent mouth care, sucking lozenges, or chewing gum may help); constipation (increased exercise, fluids, fruit, or may help); or heat intolerance (avoid excessive exercise, hot environments, maintain adequate hydration). Report CNS change (hallucination, confusion, nervousness); sudden or unusual weight gain; unresolved nausea or diarrhea; chest pain or palpitations; muscle pain; or changes in urinary pattern. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 12.5 mg, 25 mg

Antivert®: 12.5 mg, 25 mg, 50 mg

Dramamine® Less Drowsy Formula: 25 mg

Medi-Meclizine: 25 mg

Tablet, chewable, as hydrochloride (Bonine®): 25 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Antivert)

12.5 mg (30): $27.29

25 mg (30): $36.74

50 mg (30): $59.52

Tablets (Meclizine HCl)

12.5 mg (30): $12.99

25 mg (30): $19.99

25 mg (100): $79.99

Mechanism of ActionHas central anticholinergic action by blocking chemoreceptor trigger zone; decreases excitability of the middle ear labyrinth and blocks conduction in the middle ear vestibular-cerebellar pathways

Pharmacodynamics/Kinetics

Onset of action: ~1 hour

Duration: 8-24 hours

Metabolism: Hepatic

Half-life elimination: 6 hours

Excretion: Urine (as metabolites); feces (as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Slight to moderate drowsiness, thickening of bronchial secretions, significant xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause dizziness or nervousness; may rarely cause sedation or depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropic may produce additive sedation and dry mouth

Index TermsMeclizine Hydrochloride; Meclozine Hydrochloride

References

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International Brand NamesAgyrax (BE, FR); Bonadoxina (CR, GT, HN, MX, NI, PA, SV); Bonamina (CN); Bonamine (PH); Clizine (TW); Navicalm (PT); Postadoxine (PH); Postafen (DK, FI, NO, SE); Postafene (BE); Suprimal (NL); Vertigol (PY); Vomiseda (TW)

Meclofenamate

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English

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Pronunciation(me kloe fen AM ate)

Canadian Brand NamesMeclomen®

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsTreatment of inflammatory disorders, arthritis, mild to moderate pain, dysmenorrhea

Dosing: Adults

Mild to moderate pain: Oral: 50 mg every 4-6 hours; increases to 100 mg may be required; maximum dose: 400 mg

Rheumatoid arthritis/osteoarthritis: Oral: 50 mg every 4-6 hours; increase, over weeks, to 200-400 mg/day in 3-4 divided doses; do not exceed 400 mg/day; maximal benefit for any dose may not be seen for 2-3 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren >14 years: Refer to adult dosing

Dietary ConsiderationsMay be taken with food, milk, or antacids.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to meclofenamate, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.
- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.
- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.
- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT.

Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Safety and efficacy have not been established in children <14 years of age.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (3rd trimester)

Pregnancy ConsiderationsMay cause premature closure of the ductus arteriosus in the 3rd trimester of pregnancy.

Lactation

Enters breast milk/not recommended

Adverse Reactions

>10%:

Central nervous system: Dizziness

Dermatologic: Rash

Gastrointestinal: Abdominal cramps, heartburn, indigestion, nausea

1% to 10%:

Central nervous system: Headache, nervousness

Dermatologic: Itching

Endocrine & metabolic: Fluid retention

Gastrointestinal: Vomiting

Otic: Tinnitus

<1%: CHF, hypertension, arrhythmia, tachycardia, confusion, hallucinations, aseptic meningitis, mental depression, drowsiness, insomnia, urticaria, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, polydipsia, hot flashes, gastritis, GI ulceration, cystitis, polyuria, agranulocytosis, anemia, hemolytic anemia, bone marrow suppression, leukopenia, thrombocytopenia, hepatitis, peripheral neuropathy, toxic amblyopia, blurred vision, conjunctivitis, dry eyes, decreased hearing, acute renal failure, allergic rhinitis, dyspnea, epistaxis

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol;

Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Test InteractionsIncreased chloride (S), increased sodium (S)
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as sodium: 50 mg, 100 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsules (Meclofenamate Sodium)

50 mg (30): $24.99

100 mg (30): $34.64

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Duration: 2-4 hours

Distribution: Crosses placenta

Protein binding: 99%

Half-life elimination: 2-3.3 hours

Time to peak, serum: 0.5-1.5 hours

Excretion: Primarily urine and feces (as metabolites)

Related Information

- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®). Recovery of platelet function usually occurs 1-2 days after discontinuation of NSAIDs.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause drowsiness, confusion, hallucinations, or depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine or carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A meta-analysis (Pope, 1993) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 Heart Failure Guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin’s inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

Index TermsMeclofenamate Sodium

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International Brand NamesEthos (TW); Eucome (TW); Meclomen (AT, CN, HK, MY, PK, TH); Medomen (SG); Melvon (KP)

Medium Chain Triglycerides

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(mee DEE um chane trye GLIS er ides)

U.S. Brand NamesMCT Oil® [OTC]

Canadian Brand NamesMCT Oil®

Pharmacologic Category[Nutritional Supplement]

Use: Labeled IndicationsDietary supplement for those who cannot digest long chain fats; malabsorption associated with disorders such as pancreatic insufficiency, bile salt deficiency, short bowel syndrome, and bacterial overgrowth of the small bowel; induce ketosis as a prevention for seizures

Dosing: Adults

Cystic fibrosis: 3 tablespoons/day in divided doses

Malabsorption syndromes: Oral: 15 mL 3-4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Nutritional supplement:

Infants: Oral: Initial: 0.5 mL every other feeding, then advance to every feeding, then increase in increments of 0.25-0.5 mL/feeding at intervals of 2-3 days as tolerated

Seizures: Oral: About 40 mL with each meal or 50% to 70% (800-1120 kcal) of total calories (1600 kcal) as the oil will induce ketosis necessary for seizure control

Cystic fibrosis: Oral: 3 tablespoons/day in divided doses

Administration: OralDilute with at least an equal volume of water or mix with some other vehicle such as fruit juice (flavoring may be added); mixture should be sipped slowly; administer no more than 15-20 mL at any one time (up to 100 mL may be administered in divided doses in a 24-hour period); formulas should not be cold. May also be used on salads or vegetables; may incorporate into sauces or used in cooking or baking.

Possible gastrointestinal side effects from medication can be prevented if therapy is initiated with small supplements at meals and gradually increased according to patient's tolerance

Dietary ConsiderationsMay be taken with meals (115 calories/15 mL); derived from coconut oil

StorageAfter opening, keep tightly closed and use within 3 months.

Adverse ReactionsFrequency not defined.

Endocrine & metabolic: HDL serum levels decreased and triglycerides serum levels increased (>6 months daily use)

Gastrointestinal: Abdominal pain, bloating, cramping, diarrhea, nausea

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Oil: 14 g/15 mL (960 mL) [115 calories/15 mL; derived from coconut oil]

Generic AvailableNo

Mechanism of ActionMCTs are saturated fatty acids in chains of 6-12 carbon atoms. They are water soluble and can pass directly through intestinal cell membranes and blood stream. Once taken up by the liver, they are used for metabolic energy before being stored.

Pharmacotherapy PearlsMay damage plastic containers and utensils. In patients with steatorrhea, MCT increases usable caloric intake; weight gain is increased; diarrhea and steatorrhea are decreased; calcium and magnesium absorption are increased.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay produce coma in cirrhotic patients

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMCT; Triglycerides, Medium Chain

References

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MedroxyPROGESTERone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

MedroxyPROGESTERone may be confused with hydroxyprogesterone, methylPREDNISolone, methylTESTOSTERone

Provera® may be confused with Covera®, Femara®, Parlodel®, Premarin®

The injection dosage form is available in different formulations. Carefully review prescriptions to assure the correct formulation and route of administration.

Pronunciation(me DROKS ee proe JES te rone)

U.S. Brand NamesDepo-Provera®; Depo-Provera® Contraceptive; depo-subQ provera 104™; Provera®

Canadian Brand NamesAlti-MPA; Apo-Medroxy®; Depo-Prevera®; Depo-Provera®; Gen-Medroxy; Novo-Medrone; Provera-Pak; Provera®

Pharmacologic CategoryContraceptive; Progestin

Use: Labeled IndicationsEndometrial carcinoma or renal carcinoma; secondary amenorrhea or abnormal uterine bleeding due to hormonal imbalance; reduction of endometrial hyperplasia in nonhysterectomized postmenopausal women receiving conjugated estrogens; prevention of pregnancy; management of endometriosis-associated pain

Dosing: Adults

Amenorrhea: Oral: 5-10 mg/day for 5-10 days

Abnormal uterine bleeding: Oral: 5-10 mg for 5-10 days starting on day 16 or 21 of cycle

Contraception:

Depo-Provera® Contraceptive: I.M.: 150 mg every 3 months

depo-subQ provera 104™: SubQ: 104 mg every 3 months (every 12-14 weeks)

Endometriosis: depo-subQ provera 104™: SubQ: 104 mg every 3 months (every 12-14 weeks)

Endometrial or renal carcinoma (Depo-Provera®): I.M.: 400-1000 mg/week

Accompanying cyclic estrogen therapy, postmenopausal: Oral: 5-10 mg for 12-14 consecutive days each month, starting on day 1 or day 16 of the cycle; lower doses may be used if given with estrogen continuously throughout the cycle

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAdolescents:

Amenorrhea: Refer to adult dosing.

Abnormal uterine bleeding: Refer to adult dosing.

Contraception: Refer to adult dosing.

Endometriosis: Refer to adult dosing.

Dosing: Hepatic ImpairmentUse is contraindicated with severe impairment. Consider lower dose or less frequent administration with mild-to-moderate impairment. Use of the contraceptive injection has not been studied in patients with hepatic impairment; consideration should be given to not readminister if jaundice develops

Administration: I.M.Depo-Provera® Contraceptive: Administer first dose during the first 5 days of menstrual period, or within the first 5 days postpartum if not breast-feeding, or at the sixth week postpartum if breast feeding exclusively. Shake vigorously prior to administration. Administer by deep I.M. injection in the gluteal or deltoid muscle.

Administration: OtherSubQ: depo-subQ provera 104™: Administer first dose during the first 5 days of menstrual period, or at the sixth week postpartum if breast-feeding. Shake vigorously prior to administration. Administer by SubQ injection in the upper thigh or abdomen; avoid boney areas and the umbilicus. Administer over 5-7 seconds. Do not rub the injection area. When switching from combined hormonal contraceptives (estrogen plus progestin), the first injection should be within 7 days after the last active pill, or removal of patch or ring. If switching from the I.M. to SubQ formulation, the next dose should be given within the prescribed dosing period for the I.M. injection.

Dietary ConsiderationsEnsure adequate calcium and vitamin D intake when used for the prevention of pregnancy

StorageStore at controlled room temperature.

ContraindicationsHypersensitivity to medroxyprogesterone or any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); cerebral vascular disease; severe hepatic dysfunction or disease; carcinoma of the breast or genital organs, undiagnosed vaginal bleeding; missed abortion, diagnostic test for pregnancy, pregnancy

Warnings/Precautions

Boxed warnings:

- Bone mineral density loss: See “Concerns related to adverse effects” below.
- Long-term use: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Bone mineral density loss: **[U.S. Boxed Warning]: Prolonged use of medroxyprogesterone contraceptive injection may result in a loss of bone mineral density (BMD).** Loss is related to the duration of use, and may not be completely reversible on discontinuation of the drug. The impact on peak bone mass in adolescents should be considered in treatment decisions.
- Breast cancer: An increased risk of invasive breast cancer was observed in postmenopausal women using medroxyprogesterone acetate (MPA) in combination with conjugated equine estrogens (CEE). An increase in abnormal mammograms has also been reported with estrogen and progestin therapy.
- Dementia: The risk of dementia may be increased in postmenopausal women; increased incidence was observed in women ≥65 years of age taking MPA in combination with CEE.
- Retinal vascular thrombosis: Discontinue pending examination in cases of sudden partial or complete vision loss, sudden onset of proptosis, diplopia, or migraine; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease or dysfunction. MPA used in combination with estrogen may increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using CEE in combination with MPA. MPA in combination with estrogens should not be used to prevent coronary heart disease.
- Depression: Use with caution in patients with a history of depression.
- Diabetes: Use with caution in patients with diabetes mellitus; may cause glucose intolerance.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes, or renal dysfunction.
- Osteoporosis: Consider other methods of birth control in women with (or at risk for) osteoporosis.

Special populations:

- Pediatrics: Not for use prior to menarche.
- Surgical patients: Whenever possible, progestins in combination with estrogens should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- Long-term use: **[U.S. Boxed Warning]: Long-term use (ie, >2 years) should be limited to situations where other birth control methods are inadequate.**
- Risks vs. benefits: Before prescribing progestin therapy in combination with estrogen to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of estrogen when added to progestin therapy. Progestins with or without estrogen should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.

Pregnancy Risk FactorX

Pregnancy ConsiderationsThere is an increased risk of minor birth defects in children whose mothers take progesterones during the first 4 months of pregnancy. Hypospadias has been reported in male and mild masculinization of the external genitalia has been reported in female babies exposed during the first trimester. High doses are used to impair fertility. Low birth weight has been reported in neonates from unexpected pregnancies which occurred 1-2 months following injection of medroxyprogesterone (MPA) contraceptive. Ectopic pregnancies have been reported with use of the MPA contraceptive injection. When therapy is discontinued, fertility returns sooner in women of lower body weight. Median time to conception/return to ovulation following discontinuation of MPA contraceptive injection is 10 months following the last injection.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsComposition, quality and quantity of breast milk are not affected; adverse developmental and behavioral effects have not been noted following exposure of infant to MPA while breast-feeding.

Adverse ReactionsAdverse effects as reported with any dosage form; percent ranges presented are noted with the MPA contraceptive injection:

>5%:

Central nervous system: Dizziness, headache, nervousness

Endocrine & metabolic: Libido decreased, menstrual irregularities (includes bleeding, amenorrhea, or both)

Gastrointestinal: Abdominal pain/discomfort, weight changes (average 3-5 pounds after 1 year, 8 pounds after 2 years)

Neuromuscular & skeletal: Weakness

1% to 5%:

Cardiovascular: Edema

Central nervous system: Depression, fatigue, insomnia, irritability, pain

Dermatologic: Acne, alopecia, rash

Endocrine & metabolic: Anorgasmia, breast pain, hot flashes

Gastrointestinal: Bloating, nausea

Genitourinary: Cervical smear abnormal, leukorrhea, menometrorrhagia, menorrhagia, pelvic pain, urinary tract infection, vaginitis, vaginal infection, vaginal hemorrhage

Local: Injection site atrophy, injection site reaction, injection site pain

Neuromuscular & skeletal: Arthralgia, backache, leg cramp

Respiratory: Respiratory tract infections

<1%: Allergic reaction, anemia, angioedema, appetite changes, asthma, axillary swelling, blood dyscrasia, body odor, breast cancer, breast changes, cervical cancer, chest pain, chills, chloasma, convulsions, deep vein thrombosis, diaphoresis, drowsiness, dry skin, dysmenorrhea, dyspareunia, dyspnea, facial palsy, fever, galactorrhea, genitourinary infections, glucose tolerance decreased, hirsutism, hoarseness, jaundice, lack of return to fertility, lactation decreased, libido increased, melasma, nipple bleeding, osteoporosis, paralysis, paresthesia, pruritus, pulmonary embolus, rectal bleeding, scleroderma, sensation of pregnancy, somnolence, syncope, tachycardia, thirst, thrombophlebitis, uterine hyperplasia, vaginal cysts, varicose veins; residual lump, sterile abscess, or skin discoloration at the injection site

Postmarketing and/or case reports: Anaphylaxis, anaphylactoid reactions, bone mineral density decreased, osteoporotic fractures

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Induces** CYP3A4 (weak)
Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase risk of osteoporosis).

Food: Bioavailability of the oral tablet is increased when taken with food; half-life is unchanged.

Herb/Nutraceutical: St John's wort may diminish the therapeutic effect of progestin contraceptives (contraceptive failure is possible).

Test Interactions

The following tests may be decreased: Steroid levels (plasma and urinary), gonadotropin levels, SHBG concentration, T_3 uptake

The following tests may be increased: Protein-bound iodine, butanol extractable protein-bound iodine, Factors II, VII, VIII, IX, X

Pathologist should be advised of estrogen/progesterone therapy when specimens are submitted.

Monitoring ParametersBefore starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate prior to administration of MPA contraceptive injection; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision; sudden onset of proptosis, diplopia, or migraine; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glucose in patients with diabetes; or blood pressure.

Nursing: Physical Assessment/MonitoringMonitor for effectiveness of therapy and adverse effects. Instruct patient on appropriate dose scheduling (according to purpose of therapy), possible side effects, and symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to sexually-active female patients unless capable of complying with contraceptive use.

Monitoring: Lab Tests**Must have pregnancy test prior to beginning therapy.**

Patient EducationFollow dosage schedule and do not take more than prescribed. You may experience sensitivity to sunlight (use sunblock, wear protective clothing and eyewear, and avoid extensive exposure to direct sunlight); dizziness, anxiety, depression (use caution when driving or engaging in tasks that require alertness until response to drug is known); changes in appetite; maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake and diet; decreased libido or increased body hair (reversible when drug is discontinued); hot flashes (cool clothes and environment may help). May cause discoloration of stool (green). Report swelling of face, lips, or mouth; absence or altered menses; abdominal pain; vaginal itching, irritation, or discharge; heat, warmth, redness, or swelling of extremities; or sudden onset change in vision. **Pregnancy precaution:** Inform prescriber if you are pregnant. Consult prescriber for instruction on appropriate contraceptive measures.

Injection for contraception: This product does not protect against HIV or other sexually-transmitted diseases.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension, as acetate: 150 mg/mL (1 mL)

Depo-Provera®: 400 mg/mL (2.5 mL)

Depo-Provera® Contraceptive: 150 mg/mL (1 mL) [prefilled syringe or vial]

depo-subQ provera 104™: 104 mg/0.65 mL (0.65 mL) [prefilled syringe]

Tablet, as acetate: 2.5 mg, 5 mg, 10 mg

Provera®: 2.5 mg, 5 mg, 10 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Suspension (Depo-Provera)

150 mg/mL (1): $87.99

400 mg/mL (2.5): $178.24

Suspension (Depo-SubQ Provera 104)

104 mg/0.65 mL (0.65): $104.81

Suspension (MedroxyPROGESTERone Acetate)

150 mg/mL (1): $49.99

150 mg/mL (1): $52.99

Tablets (MedroxyPROGESTERone Acetate)

2.5 mg (30): $12.99

5 mg (90): $19.00

10 mg (30): $12.99

Tablets (Provera)

2.5 mg (30): $37.79

5 mg (30): $47.24

10 mg (30): $57.32

Mechanism of ActionInhibits secretion of pituitary gonadotropins, which prevents follicular maturation and ovulation; causes endometrial thinning

Pharmacodynamics/Kinetics

Absorption: Oral: Well absorbed; I.M.: Slow

Protein binding: 86% to 90% primarily to albumin; does not bind to sex hormone-binding globulin

Metabolism: Extensively hepatic via hydroxylation and conjugation; forms metabolites

Time to peak: Oral: 2-4 hours

Half-life elimination: Oral: 12-17 hours; I.M. (Depo-Provera® Contraceptive): 50 days; SubQ: ~40 days

Excretion: Urine

Dental Health: Effects on Dental TreatmentProgestins may predispose the patient to gingival bleeding.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, headache, depression, insomnia, nervousness, irritability, and mood disturbances

Mental Health: Effects on Psychiatric TreatmentThe Women's Health Initiative (WHI) Memory Study reported an increased risk of developing dementia in postmenopausal women ≥65 years of age during 4 years of treatment with oral conjugated equine estrogens and medroxyprogesterone acetate relative to placebo (1.8% vs 0.9%). Relative risk was 2.05 (95% CI 1.21-3.48). Therefore, estrogens and progestins should not be used for the prevention of dementia. The WHI also reported an increased risk of stroke (29 vs 21 per 10,000 women-years) compared to women receiving placebo. The increase in risk was observed after the first year and persisted. May cause hypertriglyceridemia; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.

Index TermsAcetoxymethylprogesterone; Medroxyprogesterone Acetate; Methylacetoxyprogesterone; MPA

International Brand NamesApo-Medroxy (HK); Climanor (GB, IE); Clinofem (DE); Condep (MY); Cycrin (AR, BR); Depo-M (TH); Depo-Prodasone (FR); Depo-Provera (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE); Deporeva (PH); Depotrust (PH); Enaf-150 (TH); Farlutal (AE, BE, BH, BR, CY, EG, FR, IL, IQ, IR, IT, JO, KW, LB, LY, NL, OM, PL, QA, SA, SY, YE); GestaPolar (DE); Gestapuran (FI, SE); Gestomikron (PL); Lyndavel (PH); Manodepa (TH); Medrone (TW); Medroxine (PY, UY); Medroxyhexal (AU); Megestron (MX); Meprate (IN); MPA Gyn 5 (DE); Perlutex (BB, BM, BS, BZ, DK, GY, JM, NO, SR, TT); Perlutex Leo (CR, DO, GT, HN, NI, PA, SV); Planibu (ID); Prodafem (AT, CH); Progevera (ES); Provera (AE, AU, BE, BF, BG, BH, BJ, CI, CL, CN, CO, CY, CZ, DK, EC, EE, EG, ET, FI, GB, GH, GM, GN, GR, HK, HN, ID, IE, IL, IN, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, OM, PE, PH, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SY, TH, TN, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Provera LD (MY); Ralovera (AU); Triclofem (ID); Veraplex (ID, TH)

Medrysone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(ME dri sone)

U.S. Brand NamesHMS Liquifilm® [DSC]

Pharmacologic CategoryCorticosteroid, Ophthalmic

Use: Labeled IndicationsTreatment of allergic conjunctivitis, vernal conjunctivitis, episcleritis, ophthalmic epinephrine sensitivity reaction

Dosing: AdultsConjunctivitis: Ophthalmic: Instill 1 drop in conjunctival sac 2-4 times/day up to every 4 hours; may use every 1-2 hours during first 1-2 days.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥3 years: Refer to adult dosing.

Administration: OtherOphthalmic: Shake well before using. Do not touch dropper to the eye.

StorageStore at room temperature of 25°C (77°F); do not freeze.

ContraindicationsHypersensitivity to medrysone or any component of the formulation; fungal, viral, or untreated pus-forming bacterial ocular infections; not for use in iritis and uveitis

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Infection: Steroids may mask infection or enhance existing ocular infection; prolonged use may result in secondary infections due to immunosuppression.
- Ocular effects: Prolonged use may result in glaucoma and injury to the optic nerve. Visual defects in acuity and field of vision may occur. Posterior subcapsular cataracts may form after long-term use. Use with caution in presence of glaucoma (steroids increase intraocular pressure). Perforation may occur with topical steroids in diseases which thin the cornea or sclera. Steroid use may delay healing after cataract surgery. Intraocular pressure should be monitored if this product is used >10 days.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <3 years of age.

Other warnings/precautions:

- Duration of therapy: 3-4 days to several weeks dependent on type and severity of disease; taper dose to avoid disease exacerbation.
- Lack of improvement: If no improvement after several days of treatment, discontinue medrysone and institute other therapy.
- Synthetic corticosteroid: Medrysone is a synthetic corticosteroid; structurally related to progesterone.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined: Ocular: Acute anterior uveitis, allergic reactions, blurred vision (mild, temporary), burning, cataracts, conjunctivitis, corneal thinning, corneal ulcers, delayed wound healing, foreign body sensation, glaucoma, IOP increased, keratitis, mydriasis, optic nerve damage, ptosis, secondary ocular infection stinging, visual activity defects

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Monitoring ParametersIntraocular pressure (if duration of therapy is >10 days); periodic examination of lens (with prolonged use)

Nursing: Physical Assessment/MonitoringAssess knowledge/teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis medication is only for use in your eyes. Use exactly as directed. Wash hands thoroughly before using. Shake well before using. Do not allow applicator tip to touch eye. Gently pull down lower lid and put drop(s) into inner corner of eye. Close eye and roll eyeball in all directions. Do not blink for 30 seconds. Apply gentle pressure to inner corner of eye for 30 seconds. Gently wipe away any excess from skin around eye. Do not use any other eye medication for 10-15 minutes. May cause sensitivity to light (dark glasses may help); or temporary stinging, burning, or blurred vision. Report pain, swelling, scratchiness, itching, watering, or dryness of eye; drainage, redness, or sign of eye infection; change in vision (eg, double vision, reduced visual field, halo around lights); or worsening of condition or lack of improvement in 3-4 days. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, ophthalmic: 1% (5 mL, 10 mL) [contains benzalkonium chloride] [DSC]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Suspension (HMS Liquifilm)

1% (5): $23.99

1% (10): $33.99

Mechanism of ActionDecreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability

Pharmacodynamics/Kinetics

Absorption: Through aqueous humor

Metabolism: Hepatic if absorbed

Excretion: Urine and feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other ConsiderationsMedrysone is a synthetic corticosteroid structurally related to progesterone. If no improvement after several days of treatment, discontinue medrysone and institute other therapy. Duration of therapy is 3-4 days to several weeks, dependent on type and severity of disease.

International Brand NamesHMS (AU, CH); HMS Liquifilm (NL); Liquipom (ES); Medrixon (MX); Medrysone Faure (FR); Ophtocortin (DE); Spectramedryn (DE)

Mefenamic Acid

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Ponstel® may be confused with Pronestyl®

Pronunciation(me fe NAM ik AS id)

U.S. Brand NamesPonstel®

Canadian Brand NamesApo-Mefenamic®; Dom-Mefenamic Acid; Mefenamic-250; Nu-Mefenamic; PMS-Mefenamic Acid; Ponstan®

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsShort-term relief of mild to moderate pain including primary dysmenorrhea

Dosing: AdultsMild-moderate pain: Oral: Initial: 500 mg; then 250 mg every 4 hours as needed; maximum therapy: 1 week

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren >14 years: Refer to adult dosing.

Dosing: Renal ImpairmentNot recommended for use

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to mefenamic acid, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery; active ulceration or chronic inflammation of the GI tract; renal disease

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.
- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Safety and efficacy have not been established in children <14 years of age.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers, omeprazole, and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high-dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (3rd trimester)

LactationEnters breast milk (trace amounts)/not recommended (AAP rates “compatible”)

Adverse Reactions

1% to 10%:

Central nervous system: Headache, nervousness, dizziness (3% to 9%)

Dermatologic: Itching, rash

Endocrine & metabolic: Fluid retention

Gastrointestinal: Abdominal cramps, heartburn, indigestion, nausea (1% to 10%), vomiting (1% to 10%), diarrhea (1% to 10%), constipation (1% to 10%), abdominal distress/cramping/pain (1% to 10%), dyspepsia (1% to 10%), flatulence (1% to 10%), gastric or duodenal ulcer with bleeding or perforation (1% to 10%), gastritis (1% to 10%)

Hematologic: Bleeding (1% to 10%)

Hepatic: Elevated LFTs (1% to 10%)

Otic: Tinnitus (1% to 10%)

<1%: CHF, hypertension, arrhythmia, tachycardia, confusion, hallucinations, aseptic meningitis, mental depression, drowsiness, insomnia, urticaria, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, polydipsia, hot flashes, gastritis, GI ulceration, cystitis, polyuria, agranulocytosis, anemia, hemolytic anemia, bone marrow suppression, leukopenia, thrombocytopenia, hepatitis, peripheral neuropathy, toxic amblyopia, blurred vision, conjunctivitis, dry eyes, decreased hearing, acute renal failure, dyspnea, allergic rhinitis, epistaxis, stomatitis

Metabolism/Transport Effects**Substrate** of CYP2C9 (minor); **Inhibits** CYP2C9 (strong)

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Test InteractionsIncreased chloride (S), increased sodium (S), positive Coombs' [direct], false-positive urinary bilirubin
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 250 mg

Ponstel®: 250 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsules (Mefenamic Acid)

250 mg (100): $609.99

Capsules (Ponstel)

250 mg (100): $746.35

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: Peak effect: 2-4 hours

Duration: ≤6 hours

Protein binding: High

Metabolism: Conjugated hepatically

Half-life elimination: 3.5 hours

Excretion: Urine (50%) and feces as unchanged drug and metabolites

Related Information

- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®). Recovery of platelet function usually occurs 1-2 days after discontinuation of NSAIDs.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness, may rarely cause confusion, hallucination, or depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine or carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A meta-analysis (Pope, 1993) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 Heart Failure Guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin’s inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

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International Brand NamesAlgastel (PH); Algifort (PH); Antalv (PL); Apo-Mefen (PL); Aprostal (PH); Atmose (PH); Beafemic (MY); Dolfenal (TH); Dyspen (MY); Ecopan (CH); Eurostan (PH); Femen (TH); Fenamic (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Fenamin (ZA); Fenamol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Fengic (PH); Fensik (ID); Gardan (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Hispen (PH); Hostan (HK); Inflasic (PH); Johnstal (TW); Lysalgo (IT); Manic (TH); Manomic (TH); Masafen (TH); Mecid A (PH); Mefacit (PL); Mefast (ID); Mefen (MY); Mefic (AU, NZ); Namic (MY); Napan (HK); Nichostan (ID); Painstop (TW); Parkemed (AT); Passton (TW); Poncofen (ID); Pondex (ID); Pondnadysmen (TH); Pongesic (HK); Ponser (PH); Ponstan (500 mg) (CO); Ponstan (AE, AU, BD, BH, CH, CL, CY, EC, EG, FI, GB, GH, GR, HK, ID, IL, IN, IQ, IR, JO, JP, KE, KP, KW, LB, LY, MU, MY, OM, PH, PK, PT, QA, SA, SG, SY, TH, TR, TW, TZ, UG, VE, YE, ZA, ZW); Ponstan Forte (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE, ZA); Ponstan-500 (MX); Ponstil (UY); Ponstyl (FR, MU); Pontal (KP); Pontalon (SG); Potarlon (TW); Pynamic (TH); Ralgec (PH); Sefmic (HK); Selmac (PH); Sicadol (CN, PY); Tropistan (ID); Vandifen (PH)

Mefloquine

Lexi-Drugs Online

English

English

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Pronunciation(ME floe kwin)
U.S. Brand NamesLariam® [DSC]
Canadian Brand NamesApo-Mefloquine®; Lariam®
Pharmacologic CategoryAntimalarial Agent
Use: Labeled IndicationsTreatment of acute malarial infections and prevention of malaria
Dosing: AdultsDose expressed as mg of mefloquine hydrochloride:

Malaria treatment (mild to moderate infection): Oral: 5 tablets (1250 mg) as a single dose. If clinical improvement is not seen within 48-72 hours, an alternative therapy should be used for retreatment.

Malaria prophylaxis: Oral: 1 tablet (250 mg) weekly starting 1 week before arrival in endemic area, continuing weekly during travel and for 4 weeks after leaving endemic area

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricDose expressed as mg of mefloquine hydrochloride: Children ≥6 months and >5 kg:

Malaria treatment: Oral: 20-25 mg/kg in 2 divided doses, taken 6-8 hours apart (maximum: 1250 mg). If clinical improvement is not seen within 48-72 hours, an alternative therapy should be used for retreatment.

Malaria prophylaxis: Oral: 5 mg/kg/once weekly (maximum dose: 250 mg) starting 1 week before arrival in endemic area, continuing weekly during travel and for 4 weeks after leaving endemic area

Dosing: Renal ImpairmentNo dosage adjustment needed in patients with renal impairment or on dialysis.
Dosing: Hepatic ImpairmentHalf-life may be prolonged and plasma levels may be higher. Specific dosing adjustments are not available.
Administration: OralAdminister with food and with at least 8 oz of water. When used for malaria prophylaxis, dose should be taken once weekly on the same day each week. If vomiting occurs within 30 minutes after the dose , an additional full dose should be given; if it occurs within 30-60 minutes after dose, an additional half-dose should be given. Tablets may be crushed and suspended in a small amount of water, milk, or another beverage for persons unable to swallow tablets.
Dietary ConsiderationsTake with food and with at least 8 oz of water.
StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
RestrictionsAn FDA-approved medication guide and wallet card must be distributed when dispensing an outpatient prescription (new or refill) to prevent malaria where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.
ContraindicationsHypersensitivity to mefloquine, related compounds (eg, quinine and quinidine), or any component of the formulation; prophylactic use in patients with a history of seizures or severe psychiatric disorder (including active or recent history of depression, generalized anxiety disorder, psychosis, or schizophrenia)
Allergy Considerations

- QuiNIDine/QuiNINE Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Dizziness, loss of balance, and other CNS disorders (eg, seizures) have been reported; due to long half-life, effects may persist after mefloquine is discontinued. Use caution in activities requiring alertness and fine motor coordination (eg, driving, piloting planes, operating machinery).

- Psychiatric effects: May cause a range of psychiatric symptoms (anxiety, paranoia, depression, hallucinations and psychosis). Occasionally, symptoms have been reported to persist long after mefloquine has been discontinued. Suicidal ideation and suicide have been reported rarely (no causal relationship established). The appearance of psychiatric symptoms such as acute anxiety, depression, restlessness or confusion may be considered a prodrome to more serious events. Discontinue if unexplained neuropsychiatric disturbances occur. Use with caution in patients with a previous history of depression; prophylactic use is contraindicated in patients with active or recent history of psychiatric disorders.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with significant cardiac disease; ECG changes have been reported.

- Hepatic impairment: Use with caution in patients with hepatic impairment; elimination may be prolonged.

- *Plasmodium falciparum* infections: Appropriate use: In cases of life-threatening, serious, or overwhelming malaria infections due to *Plasmodium falciparum*, patients should be treated with intravenous antimalarial drug. Mefloquine may be given orally to complete the course.

- Seizure disorder: When using for treatment, use with caution in patients with a history of seizures; increase risk of seizures. Prophylactic use is conctraindicated in patients with seizure disorder.

Concurrent drug therapy issues:

- Chloroquine: Concurrent use with chloroquine may increase risk of seizures.
- Quinine derivatives: Concurrent use with quinidine and quinine may increase risk of ECG abnormalities and seizures.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 months of age. Early vomiting leading to treatment failure in children has been reported in some studies; consider alternate therapy if a second dose is not tolerated.

Other warnings/precautions:

- Prolonged use: If mefloquine is to be used for a prolonged period, liver function tests and ophthalmic examinations should be performed periodically. (Retinal abnormalities have not been observed with mefloquine in humans; however, it has with long-term administration to rats.)

Pregnancy Risk FactorC

Pregnancy ConsiderationsMefloquine crosses the placenta and is teratogenic in animals. There are no adequate and well-controlled studies in pregnant women, however, clinical experience has not shown teratogenic or embryotoxic effects; use with caution during pregnancy if travel to endemic areas cannot be postponed. Nonpregnant women of childbearing potential are advised to use contraception and avoid pregnancy during malaria prophylaxis and for 3 months thereafter. In case of an unplanned pregnancy, treatment with mefloquine is not considered a reason for pregnancy termination.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsExcreted in small quantities; effect to nursing infant is unknown. Breast-feeding is not recommended during therapy and the long half-life of mefloquine should also be considered once therapy is complete.

Adverse Reactions

1% to 10%:

Central nervous system: Chills, dizziness, fatigue, fever, headache

Dermatologic: Rash

Gastrointestinal: Vomiting (3%), abdominal pain, appetite decreased, diarrhea, nausea

Neuromuscular & skeletal: Myalgia

Otic: Tinnitus

<1%: Alopecia, bradycardia, emotional lability, extrasystoles, pruritus, seizure, syncope, weakness

Postmarketing and/or case reports: Abnormal dreams, ataxia, aggressive behavior, agitation, anxiety, arthralgia, AV block, bradycardia, cardiac arrest (with concomitant use of propranolol), chest pain, conduction abnormalities (transient), confusion, depression, diaphoresis increased, dyspepsia, dyspnea, edema, encephalopathy, erythema, erythema multiforme, exanthema, flushing, forgetfulness, hallucinations, hearing impairment, hematocrit decreased, hyper-/hypotension, insomnia, irregular pulse, leukocytosis, liver function tests increased, loss of balance, malaise, mood changes, muscle cramps/weakness, palpitation, panic attacks, paranoia, paresthesia, pneumonitis (allergic etiology), psychosis, restlessness, somnolence, Stevens-Johnson syndrome, suicidal ideation and behavior (causal relationship not established), tachycardia, thrombocytopenia, tremor, urticaria, vertigo, visual disturbances

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP2D6 (weak), 3A4 (weak)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Aminoquinolines (Antimalarial): May enhance the adverse/toxic effect of Mefloquine. Specifically, the risk for QTc-prolongation and the risk for convulsions may be increased. Mefloquine may increase the serum concentration of Aminoquinolines (Antimalarial). Management: Avoid concurrent use, and delay administration of mefloquine until at least 12 hours after the last dose of an aminoquinoline antimalarial when possible. *Risk X: Avoid combination*

Anticonvulsants: Mefloquine may diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antimalarial Agents may increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Halofantrine: Mefloquine may enhance the QTc-prolonging effect of Halofantrine. *Risk X: Avoid combination*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: May enhance the adverse/toxic effect of Mefloquine. Specifically, the risk for QTc-prolongation and the risk for convulsions may be increased. Management: Avoid concurrent use, and delay administration of mefloquine until at least 12 hours after the last dose of quinidine when possible. *Risk X: Avoid combination*

QuiNINE: May enhance the adverse/toxic effect of Mefloquine. Specifically, the risk for QTc-prolongation and the risk for convulsions may be increased. Mefloquine may increase the serum concentration of QuiNINE. Management: Avoid concurrent use, and delay administration of mefloquine until at least 12 hours after the last dose of quinine when possible. *Risk X: Avoid combination*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Typhoid Vaccine: Mefloquine may enhance the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Food increases bioavailability by ~40%.

Herb/Nutraceutical: Mefloquine serum concentration may be decreased by St John's wort; avoid concurrent use.

Monitoring ParametersWhen use is prolonged, periodic liver function tests and ocular examinations

Nursing: Physical Assessment/MonitoringPrior to beginning therapy, assess potential for interactions with pharmacological or herbal products patient may be taking. Assess therapeutic effects and adverse reactions (eg, hypertension, cardiomyopathy, hyperglycemia, hepatotoxicity) on a regular basis throughout therapy. Monitor patient closely for any development of psychiatric symptoms (anxiety, paranoia, depression, hallucinations, and psychosis); may persist long after mefloquine has been discontinued. Advise patient about the importance of carrying medication guide and wallet provided when mefloquine is dispensed for malaria. Teach patient proper use, possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report..

Monitoring: Lab TestsWhen use is prolonged, periodically monitor liver function tests.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Follow exact dosage schedule and do not take more than prescribed. Take with food and at least 8 oz of water. Maintain adequate nutrition and maintain adequate hydration (2-3 L/day of fluids unless instructed to restrict fluid intake). Carry drug information card in wallet for as long as you are taking this drug. May cause dizziness, anxiety, loss of balance (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea, vomiting, or decreased appetite (small, frequent meals, frequent mouth care, or chewing gum may help). Report immediately any anxiety, confusion, agitation, restlessness, paranoia, depression, hallucinations, suicidal ideation. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to be pregnant or breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, as hydrochloride: 250 mg [equivalent to 228 mg base]

Lariam®: 250 mg [equivalent to 228 mg base] [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Lariam)

250 mg (25): $309.97

Mechanism of ActionMefloquine is a quinoline-methanol compound structurally similar to quinine; mefloquine's effectiveness in the treatment and prophylaxis of malaria is due to the destruction of the asexual blood forms of the malarial pathogens that affect humans, *Plasmodium falciparum*, *P. vivax*, *P. malariae*, *P. ovale*

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: V_d: ~20 L/kg; blood, urine, CSF, tissues; enters breast milk

Protein binding: 98%

Metabolism: Extensively hepatic to 2,8-bis-trifluoromethyl-4-quinoline carboxylic acid (inactive) and other metabolites

Bioavailability: Increased by food

Half-life elimination: ~3 weeks (range: 2-4 weeks)

Time to peak, plasma: 6-24 hours (median: ~17 hours)

Excretion: Primarily bile and feces; urine (9% as unchanged drug, 4% as primary metabolite)

Related Information

- Immunization Recommendations
- Malaria Treatment

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, agitation, confusion, paranoia, depression, hallucinations, and psychotic behavior. Case reports of suicide and suicidal ideation have been reported.

Mental Health: Effects on Psychiatric TreatmentContraindicated with ziprasidone. Concurrent use with valproic acid may alter valproate blood levels; monitor levels. Contraindicated in patients with active depression, recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, or with a history of convulsions. In patients taking anticonvulsants (valproic acid, carbamazepine) the concomitant use of mefloquine may reduce seizure control by lowering plasma concentrations.

Index TermsMefloquine Hydrochloride

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International Brand NamesLariam (AE, AT, AU, BE, BF, BG, BH, BJ, CH, CI, CN, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, HU, IE, IL, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, NO, OM, PE, PH, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SY, TN, TR, TZ, UG, UY, YE, ZA, ZM, ZW); Laricam (JP); Larimef (IN); Mefliam (ZA); Mephaquin (BB, BM, BR, BS, BZ, CH, CR, EC, GT, GY, HK, HN, IL, JM, NI, PE, PT, SG, SR, SV, TT); Mequin (TH); Suton (TW); Tropicur (AR)

Megestrol

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Megace® may be confused with Reglan®

Pronunciation(me JES trole)

U.S. Brand NamesMegace®; Megace® ES

Canadian Brand NamesApo-Megestrol®; Megace®; Megace® OS; Nu-Megestrol

Pharmacologic CategoryAntineoplastic Agent, Hormone; Appetite Stimulant; Progestin

Use: Labeled IndicationsPalliative treatment of breast and endometrial carcinoma; treatment of anorexia, cachexia, or unexplained significant weight loss in patients with AIDS

Dosing: Adults**Note:** Megace® ES suspension is not equivalent to other formulations on a mg-per-mg basis.

Breast carcinoma (females): Refer to individual protocols: Oral: Tablet: 40 mg 4 times/day

Endometrial carcinoma: Refer to individual protocols: Oral: Tablet: 40-320 mg/day in divided doses; use for 2 months to determine efficacy; maximum doses used have been up to 800 mg/day.

HIV-related cachexia (males/females): Oral: Suspension:

Megace®: Initial dose: 800 mg/day; daily doses of 400 and 800 mg/day were found to be clinically effective

Megace® ES: 625 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo data available; however, the urinary excretion of megestrol acetate administered in doses of 4-90 mg ranged from 57% to 78% within 10 days.

Administration: OralMegestrol acetate (Megace®) oral suspension is compatible with water, orange juice, apple juice, or Sustacal H.C. for immediate consumption. Shake suspension well before use.

Storage

Suspension: Store at 15°C to 25°C (59°F to 77°F); protect from heat.

Tablet: Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F); protect from heat (temperatures >40°C [>104°F])

ContraindicationsHypersensitivity to megestrol or any component of the formulation; pregnancy (suspension)

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Adrenal suppression: May suppress hypothalamic-pituitary-adrenal (HPA) axis during chronic administration; consider the possibility of adrenal suppression in any patient receiving or being withdrawn from chronic therapy when signs/symptoms suggestive of hypoadrenalism are noted (during stress or in unstressed state). Laboratory evaluation and replacement/stress doses of rapid-acting glucocorticoid should be considered.

Disease-related concerns:

- Diabetes: New-onset diabetes mellitus and exacerbation of pre-existing diabetes have been reported with long-term use.

- Thromboembolism: Use with caution in patients with a history of thromboembolic disease.

Special populations:

- Females: Vaginal bleeding or discharge may occur.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Concentrated suspension: Megace® ES suspension in not equivalent to other formulations on a mg-per-mg basis; Megace® ES suspension 625 mg/5 mL is equivalent to megestrol acetate suspension 800 mg/20 mL.

Geriatric ConsiderationsElderly females may have vaginal bleeding or discharge and need to be forewarned of this side effect and inconvenience. No specific changes in dose are required for the elderly. Megestrol has been used in the treatment of the failure to thrive syndrome in cachectic elderly in addition to proper nutrition. Data does not support the use of megestrol for weight gain. The increase in weight tends to be mostly fat instead of lean body mass. Also, this agent is associated with DVTs.

Pregnancy Risk FactorD (tablet) / X (suspension)

Pregnancy ConsiderationsAdverse effects were demonstrated in animal studies. Use during pregnancy is contraindicated (suspension).

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsDue to the potential for adverse reaction in the newborn, the manufacturer recommends discontinuing breast feeding while receiving megestrol. In addition, HIV-infected mothers are discouraged from breast-feeding to decrease the potential transmission of HIV.

Adverse Reactions

Frequency not always defined.

Cardiovascular: Hypertension (≤8%), cardiomyopathy (1% to 3%), chest pain (1% to 3%), edema (1% to 3%), palpitation (1% to 3%), peripheral edema (1% to 3%), heart failure

Central nervous system: Headache (≤10%), insomnia (≤6%), fever (1% to 6%), pain (≤6%, similar to placebo), abnormal thinking (1% to 3%), confusion (1% to 3%), depression (1% to 3%), hypoesthesia (1% to 3%), seizure (1% to 3%), mood changes, malaise, lethargy

Dermatologic: Rash (2% to 12%), alopecia (1% to 3%), pruritus (1% to 3%), vesiculobullous rash (1% to 3%)

Endocrine & metabolic: Hyperglycemia (≤6%), gynecomastia (1% to 3%), adrenal insufficiency, amenorrhea, breakthrough bleeding, cervical erosion and secretions (changes), breast tenderness increased, Cushing's syndrome, diabetes, glucose intolerance, HPA axis suppression, hot flashes, hypercalcemia, menstrual flow changes, spotting, vaginal bleeding pattern changes

Gastrointestinal: Diarrhea (6% to 15%, similar to placebo), flatulence (≤10%), vomiting (≤6%), nausea (≤5%), dyspepsia (≤4%), abdominal pain (1% to 3%), constipation (1% to 3%), salivation increased (1% to 3%), xerostomia (1% to 3%), weight gain (not attributed to edema or fluid retention)

Genitourinary: Impotence (4% to 14%), decreased libido (≤5%), urinary incontinence (1% to 3%), urinary tract infection (1% to 3%), urinary frequency (≤2%)

Hematologic: Anemia (≤5%), leukopenia (1% to 3%)

Hepatic: Hepatomegaly (1% to 3%), LDH increased (1% to 3%), cholestatic jaundice, hepatotoxicity

Neuromuscular & skeletal: Weakness (2% to 6%), neuropathy (1% to 3%), paresthesia (1% to 3%), carpal tunnel syndrome

Ocular: Amblyopia (1% to 3%)

Renal: Albuminuria (1% to 3%)

Respiratory: Dyspnea (1% to 3%), cough (1% to 3%), pharyngitis (1% to 3%), pneumonia (≤2%), hyperpnea

Miscellaneous: Diaphoresis (1% to 3%), herpes infection (1% to 3%), infection (1% to 3%), moniliasis (1% to 3%), tumor flare

Postmarketing and/or case reports: Thromboembolic phenomena (including deep vein thrombosis, pulmonary embolism, thrombophlebitis)

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid herbs with progestogenic properties (eg, bloodroot, chasteberry, damiana, oregano, and yucca); may enhance the adverse/toxic effect of megestrol.

Test InteractionsAltered thyroid and liver function tests

Monitoring ParametersObserve for signs of thromboembolic phenomena; blood pressure, weight; serum glucose

Nursing: Physical Assessment/MonitoringPrior to beginning therapy, assess potential for interactions with herbal products patient may be taking. Assess therapeutic effects (according to purpose for use) and adverse reactions (eg, hypertension, CNS changes [confusion, convulsions, insomnia], rash, changes in menses, gastrointestinal upset, jaundice, thrombophlebitis) regularly during therapy. Teach patient proper use, possible side effects/appropriate interventions (eg, importance of adequate hydration, importance of avoiding pregnancy), and adverse symptoms to report.

Monitoring: Lab TestsSerum glucose

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Follow dosage schedule and do not take more than prescribed. May cause sensitivity to sunlight (use sunblock, wear protective clothing, and avoid extended exposure to direct sunlight); dizziness, anxiety, depression (use caution when driving or engaging in tasks that require alertness until response to drug is known); change in appetite (maintain adequate hydration [2-3 L/day of fluids, unless instructed to restrict fluid intake] and diet); decreased libido or increased body hair (reversible when drug is discontinued); or hot flashes (cool clothes and environment may help). Report swelling of face, lips, or mouth; absent or altered menses; abdominal pain; vaginal itching, irritation, or discharge; heat, warmth, redness, or swelling of extremities; or sudden onset change in vision. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication and for 1 month following therapy; consult prescriber for appropriate contraceptives. This drug may cause fetal defects. Do not donate blood during or for 1 month following therapy. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, oral, as acetate: 40 mg/mL (10 mL, 20 mL, 240 mL, 480 mL)

Megace®: 40 mg/mL (240 mL) [contains ethanol 0.06% and sodium benzoate; lemon-lime flavor]

Megace® ES: 125 mg/mL (150 mL) [contains ethanol 0.06% and sodium benzoate; lemon-lime flavor]

Tablet, as acetate: 20 mg, 40 mg

Generic AvailableYes: Excludes Megace® ES

Pricing: U.S. (www.drugstore.com)

Suspension (Megace ES)

625 mg/5 mL (150): $590.12

Suspension (Megace Oral)

40 mg/mL (240): $167.52

Suspension (Megestrol Acetate)

40 mg/mL (240): $131.33

Tablets (Megestrol Acetate)

20 mg (100): $37.99

40 mg (100): $52.99

Mechanism of ActionA synthetic progestin with antiestrogenic properties which disrupt the estrogen receptor cycle. Megestrol interferes with the normal estrogen cycle and results in a lower LH titer. May also have a direct effect on the endometrium. Megestrol is an antineoplastic progestin thought to act through an antileutenizing effect mediated via the pituitary. May stimulate appetite by antagonizing the metabolic effects of catabolic cytokines.

Pharmacodynamics/Kinetics

Absorption: Well absorbed orally

Metabolism: Hepatic (to free steroids and glucuronide conjugates)

Half-life elimination: 13-105 hours

Time to peak, serum: 1-3 hours

Excretion: Urine (57% to 78%; 5% to 8% as metabolites); feces (8% to 30%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia or depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause myelosuppression; use caution with clozapine and carbamazepine

Index Terms5071-1DL(6); Megestrol Acetate; NSC-71423

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International Brand NamesApetrol (KP); Endace (IN); Gestar (PL); Maygace (ES); Megace (AR, AT, AU, BD, BG, CL, CN, CO, CZ, EE, GB, GR, HK, HN, ID, IE, IN, JP, KP, MY, NL, NO, PE, PH, PK, PL, PT, RU, SG, TH, TW, UY); Megaplex (ID, TH); Megase (VE); Megastrol (PY); Megejohn (TW); Megesin (PL); Megestat (BR, DE); Megetrol (KP); Megostat (AU); Mestrel (MX, TH); Neoxia (KP); Taromeg (PL)

Meloxicam

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(mel OKS i kam)

U.S. Brand NamesMobic®

Canadian Brand NamesApo-Meloxicam®; CO Meloxicam; Gen-Meloxicam; Mobicox®; Mobic®; Novo-Meloxicam; PMS-Meloxicam

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsRelief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis (JRA)

Dosing: AdultsOsteoarthritis, rheumatoid arthritis: Oral: Initial: 7.5 mg once daily; some patients may receive additional benefit from increasing dose to 15 mg once daily; maximum dose: 15 mg/day.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricJRA: Oral: Children ≥2 years: 0.125 mg/kg/day; maximum dose: 7.5 mg/day

Dosing: Renal Impairment

Mild to moderate impairment: No specific dosage recommendations

Significant impairment (Cl_{cr} ≤15 mL/minute): Patients with severe renal impairment have not been adequately studied; use not recommended.

Hemodialysis: Supplemental dose after dialysis not necessary.

Dosing: Hepatic Impairment

Mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic dysfunction: No dosage adjustment is necessary

Severe hepatic impairment: Patients with severe hepatic impairment have not been adequately studied

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Dietary ConsiderationsShould be taken with food or milk to minimize gastrointestinal irritation.

StorageStore at 25°C (77°F). Protect tablets from moisture.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity (eg, asthma, urticaria, allergic-type reactions) to meloxicam, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.

- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsMen ≥65 years of age exhibited steady-state plasma concentrations and pharmacokinetics similar to younger men. Elderly women (≥65 years of age) had nearly a 50% greater AUC and 32% higher C_{max} compared to younger women.

Pregnancy Risk FactorC/D (3rd trimester)

Pregnancy ConsiderationsMay cause premature closure of the ductus arteriosus in the 3rd trimester of pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known whether meloxicam is excreted in human milk. Due to a potential for serious adverse reactions, the manufacturer recommends that a decision be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Adverse ReactionsPercentages reported in adult patients; abdominal pain, diarrhea, fever, headache, pyrexia, and vomiting were reported more commonly in pediatric patients

2% to 10%:

Cardiovascular: Edema (≤5%)

Central nervous system: Headache (2% to 8%), pain (1% to 5%), dizziness (≤4%), insomnia (≤4%)

Dermatologic: Pruritus (≤2%), rash (≤3%)

Gastrointestinal: Dyspepsia (4% to 10%), diarrhea (2% to 8%), nausea (2% to 7%), abdominal pain (2% to 5%), constipation (≤3%), flatulence (≤3%), vomiting (≤3%)

Genitourinary: Urinary tract infection (≤7%), micturition (≤2%)

Hematologic: Anemia (≤4%)

Neuromuscular & skeletal: Arthralgia (≤5%), back pain (≤3%)

Respiratory: Upper respiratory infection (≤8%), cough (≤2%), pharyngitis (≤3%)

Miscellaneous: Flu-like syndrome (2% to 6%), falls (≤3%)

<2%: Abnormal dreams, abnormal vision, albuminuria, allergic reaction, alopecia, angina, angioedema, anxiety, appetite increased, arrhythmia, asthma, bilirubinemia, bronchospasm, bullous eruption, BUN increased, cardiac failure, colitis, confusion, conjunctivitis, creatinine increased, dehydration, depression, diaphoresis, duodenal perforation, duodenal ulcer, dyspnea, edema (facial), eructation, esophagitis, fatigue, fever, gastric perforation, gastric ulcer, gastritis, gastroesophageal reflux, gastrointestinal hemorrhage, GGT increased, hematemesis, hematuria, hepatitis, hot flushes, hyper-/hypotension, intestinal perforation, leukopenia, malaise, melena, MI, nervousness, palpitation, pancreatitis, paresthesia, photosensitivity reaction, pruritus, purpura, renal failure, seizure, somnolence, syncope, tachycardia, taste perversion, thrombocytopenia, tinnitus, transaminases increased, tremor, ulcerative stomatitis, urticaria, vasculitis, vertigo, xerostomia, weight gain/loss

Postmarketing and/or case reports: Agranulocytosis, anaphylactoid reactions, erythema multiforme, exfoliative dermatitis, hepatic failure, interstitial nephritis, jaundice, mood alterations, shock, Stevens-Johnson syndrome, toxic epidermal necrolysis, urinary retention (acute)

Metabolism/Transport Effects **Substrate** (minor) of CYP2C9, 3A4; **Inhibits** CYP2C9 (weak)

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Monitoring ParametersPeriodic CBC, serum chemistries, liver function, renal function (serum BUN, and creatinine) with long-term use; signs and symptoms of bleeding

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess effectiveness and interactions of other medications patient may be taking. Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically throughout therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsPeriodic CBC, serum chemistries, liver function, renal function (serum BUN, and creatinine) with long-term use

Patient EducationTake this medication exactly as directed; do not increase dose without consulting prescriber. Take with food or milk to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid alcohol, excessive vitamin C intake, or salicylate-containing foods (eg, curry powder, prunes, raisins, tea, or licorice). Do not use aspirin or aspirin-containing medication, or any other anti-inflammatory medications without consulting prescriber. You may experience anorexia, nausea, vomiting, or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); drowsiness, dizziness, nervousness, or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or fluid retention (weigh yourself weekly and report unusual [3-5 lb/week] weight gain). GI bleeding, ulceration, or perforation can occur with or without pain; discontinue medication and contact prescriber if persistent abdominal pain or cramping, or blood in stool occurs. Report breathlessness, respiratory difficulty, or unusual cough; chest pain, rapid heartbeat, palpitations; slurring of speech; unusual bruising/bleeding; blood in urine, stool, mouth, or vomitus; swollen extremities; skin blisters, rash, or itching; acute fatigue, jaundice, flu-like symptoms, hearing changes (ringing in ears); or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension: 7.5 mg/5 mL (100 mL)

Mobic®: 7.5 mg/5 mL (100 mL) [contains sodium benzoate; raspberry flavor]

Tablet: 7.5 mg, 15 mg

Mobic®: 7.5 mg, 15 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Suspension (Meloxicam)

7.5 mg/5 mL (100): $82.39

Tablets (Meloxicam)

7.5 mg (30): $16.36

Tablets (Mobic)

7.5 mg (30): $123.40

15 mg (30): $183.89

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Distribution: 10 L

Protein binding: ~99%, primarily to albumin

Metabolism: Hepatic via CYP2C9 and CYP3A4 (minor); forms 4 metabolites (inactive)

Bioavailability: 89%

Half-life elimination: Adults: 15-20 hours

Time to peak: Initial: 4-5 hours; Secondary: 12-14 hours

Excretion: Urine and feces (as inactive metabolites)

Related Information

- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste perversion, ulcerative stomatitis, and xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness; may rarely cause abnormal dreams, anxiety, confusion, depression, nervousness, and somnolence

Mental Health: Effects on Psychiatric TreatmentRare reports of agranulocytosis, use caution with clozapine and carbamazepine; lithium levels can be increased; avoid concurrent use if possible or monitor lithium levels and adjust dose. When NSAID is stopped, lithium will need adjustment again.

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A meta-analysis (Pope, 1993) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 Heart Failure Guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin’s inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other Considerations

The 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

References

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Pope JE, Anderson JJ, and Felson DT, “A Meta-analysis of the Effects of Nonsteroidal Anti-inflammatory Drugs on Blood Pressure,” *Arch Intern Med*, 1993, 153(4):477-84. [PubMed 8435027]

International Brand Names

Aflamid (MX); Afloxx (PE); Arrox (HK); Artrilox (ID); Aspicam (PL); Bexxam (PH); Caxlem (PH); Coxicam (EC); Dormelox (BR); Ecax (CN); Exel (MX); Flamoxi (ID); Loxibest (MX); Loxil (ID); Lutrol (PL); Mecaron (KP); Mecon (TW); Mecox (ID); Mel-OD (IN, MY); Melcam (HK, TH); Melcox (KP); Melflam (HK); Melicam (TW); Melocam (AE, BH, CO, CY, EG, IL, IQ, IR, JO, KP, KW, LB, LY, MY, OM, QA, SA, SY, YE); Melocox (KP); Meloflam (PH); Meloksam (PL); Melosteral (MX); Melox (AE, BH, CY, EG, HK, IL, IQ, IR, JO, KP, KW, LB, LY, MY, OM, QA, SA, SG, SY, TH, TW, YE); Meloxin (ID); Merapiran (AR); Mevamox (BR); Mexpharm (ID); Miloxam (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Miovalis (AU); Mobec (DE); Mobic (AE, AR, AT, AU, BB, BE, BF, BH, BJ, BM, BS, BZ, CI, CL, CO, CY, DK, EG, ET, FI, FR, GB, GH, GM, GN, GY, HK, IE, IL, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NO, OM, PE, PH, PY, QA, SA, SC, SD, SE, SG, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Mobicox (CH, CR, DO, GT, HN, MX, NI, PA, SV); Mobiflex (ID); Mobix (PK); Movalis (BG, CZ, EE, ES, HN, PL, PT); Movi-Cox (ID); Movicox (NL); Moxic (ID); Muvera (IN); Newsicam (KP); Ostelox (ID); Rafree (MY, PH); Rumonal (CO)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Multiple Myeloma

Regimen UseMultiple myeloma

Regimen

Melphalan: Oral: 4 mg/m^2/day days 1 to 7

[total dose/cycle = 28 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 7

[total dose/cycle = 280 mg/m^2]

Thalidomide: Oral: 100 mg/day days 1 to 28

[total dose/cycle = 2800 mg]

Repeat cycle every 28 days for 6 cycles

followed by

Thalidomide: Oral: 100 mg daily (as maintenance)

References

Palumbo A, Bertola A, Musto P, et al, “Oral Melphalan, Prednisone, and Thalidomide for Newly Diagnosed Patients With Myeloma,” *Cancer* , 2005, 104(7):1428-33.[PubMed 16116606]

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Melphalan

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Melphalan may be confused with Mephyton®, Myleran®

Alkeran® may be confused with Alferon®, Leukeran®, Myleran®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(MEL fa lan)

U.S. Brand NamesAlkeran®

Canadian Brand NamesAlkeran®

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent

Use: Labeled IndicationsPalliative treatment of multiple myeloma and nonresectable epithelial ovarian carcinoma

Use: Unlabeled/InvestigationalTreatment of neuroblastoma, rhabdomyosarcoma, breast cancer; part of an induction regimen for marrow and stem cell transplantation

Dosing: AdultsRefer to individual protocols; oral dose should always be adjusted to patient response and weekly blood counts.

Multiple myeloma:

Oral: Multiple regimens have been employed: **Note:** Response is gradual; may require repeated courses to realize benefit:

6 mg daily for 2-3 weeks initially, followed by up to 4 weeks rest, then a maintenance dose of 2 mg daily as hematologic recovery begins **or**

10 mg daily for 7-10 days; institute 2 mg daily maintenance dose after WBC >4000 cells/mm^3 and platelets >100,000 cells/mm^3 (~4-8 weeks); titrate maintenance dose to hematologic response **or**

0.15 mg/kg/day for 7 days, with a 2-6 week rest, followed by a maintenance dose of ≤0.05 mg/kg/day as hematologic recovery begins **or**

0.25 mg/kg/day for 4 days (or 0.2 mg/kg/day for 5 days); repeat at 4- to 6-week intervals as ANC and platelet counts return to normal

I.V.: 16 mg/m^2 administered at 2-week intervals for 4 doses, then administer at 4-week intervals after adequate hematologic recovery.

Ovarian carcinoma: Oral: 0.2 mg/kg/day for 5 days, repeat every 4-5 weeks

High dose BMT: I.V.: 140-240 mg/m^2 as a single dose or divided into 2-5 daily doses. Infuse over 20-60 minutes.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols; oral dose should always be adjusted to patient response and weekly blood counts.

Various protocols (unlabeled use): Oral: 4-20 mg/m^2/day for 1-21 days

Pediatric rhabdomyosarcoma (unlabeled use): I.V.: 10-35 mg/m^2/dose every 21-28 days

High-dose melphalan with bone marrow transplantation for neuroblastoma (unlabeled use): I.V.: 70-100 mg/m^2/day on day 7 and 6 before BMT **or**

140-220 mg/m^2 single dose before BMT **or**

50 mg/m^2/day for 4 days **or**

70 mg/m^2/day for 3 days

Dosing: Renal Impairment

The FDA-approved labeling contains the following adjustment recommendations based on route of administration:

Oral: Moderate-to-severe renal impairment: Consider a reduced dose initially

I.V.: BUN >30 mg/dL: Reduce dose by up to 50%

The following guidelines have been used by some clinicians:

Aronoff, 2007 (route of administration not specified): Adults:

  - Cl_{cr} 10-50 mL/minute: Administer 75% of dose
  - Cl_{cr} <10 mL/minute: Administer 50% of dose
  - Hemodialysis: Administer dose after hemodialysis
  - Continuous ambulatory peritoneal dialysis (CAPD): Administer 50% of dose
  - Continuous renal replacement therapy (CRRT): Administer 75% of dose

Kintzel, 1995:

  - Oral: Adjust dose in the presence of hematologic toxicity
  - I.V.:
    - Cl_{cr} 46-60 mL/minute: Administer 85% of normal dose
    - Cl_{cr} 31-45 mL/minute: Administer 75% of normal dose
    - Cl_{cr} <30 mL/minute: Administer 70% of normal dose

Dosing: Hepatic Impairment   Melphalan is hepatically metabolized; however, dosage adjustment does not appear to be necessary (King, 2001).

Dosing: Combination Regimens

Gestational trophoblastic tumor:

  - CHAMOCA (Modified Bagshawe Regimen)
  - CHAMOMA (Bagshawe Regimen)

Lymphoma, Hodgkin's disease:

  - CAD/MOPP/ABV
  - mini-BEAM

Multiple myeloma:

  - Bortezomib-Melphalan-Prednisone
  - Bortezomib-Melphalan-Prednisone-Thalidomide
  - M-2
  - Melphalan-Prednisone-Thalidomide
  - MP (Multiple Myeloma)
  - VBMCP

Oncology: Bone Marrow - High DoseI.V.: 100-240 mg/m^2 administered as a single dose or divided into 2-4 daily doses. Maximum dose as a single agent: 200-400 mg/m^2. Maximum dose with total body irradiation (TBI): 110-140 mg/m^2; other high-dose chemotherapeutic drugs: 100-180 mg/m^2. Generally infused over 20-60 minutes.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Due to limited stability, complete administration of I.V. dose should occur within 60 minutes of reconstitution

  - I.V. infusion: Infuse over 15-20 minutes
  - I.V. bolus:
    - Central line: I.V. bolus doses of 17-200 mg/m^2 (reconstituted and not diluted) have been infused over 2-20 minutes
    - Peripheral line: I.V. bolus doses of 2-23 mg/m^2 (reconstituted and not diluted) have been infused over 1-4 minutes

Administration: I.V. DetailAvoid skin contact with I.V. formulation.

BMT only: Saline-based hydration (100-125 mg/m^2/hour) preceding (2-4 hours), during, and following (6-12 hours) administration reduces risk of drug precipitation in renal tubules. Hydrolysis causes loss of 1% melphalan injection per 10 minutes. Infusion of admixture must be completed within 100 minutes of preparation to deliver ordered dose. Reconstitute dose to 5 mg/mL in diluent provided by manufacturer. Dose may be infused via central or peripheral venous access without further dilution to minimize volume of infusion.

pH: 6.5-7.0

Administration: OralAdminister on an empty stomach.

Dietary ConsiderationsShould be taken on an empty stomach (1 hour prior to or 2 hours after meals).

Storage

Tablet: Store in refrigerator at 2°C to 8°C (36°F to 46°F). Protect from light.

Injection: Store at room temperature (15°C to 30°C). Protect from light. Reconstituted solution is chemically and physically stable for at least 90 minutes when stored at 25°C (77°F). Diluted solution is physically and chemically stable for at least 60 minutes at 25°C (77°F).

ReconstitutionInjection must be prepared fresh. **The time between reconstitution/dilution and administration of parenteral melphalan must be kept to a minimum (manufacturer recommends <60 minutes) because reconstituted and diluted solutions are unstable.** Dissolve powder initially with 10 mL of diluent to a concentration of 5 mg/mL. Shake vigorously to dissolve. **Immediately** dilute dose in 250-500 mL NS to a concentration of 0.1-0.45 mg/mL.

Compatibility**Incompatible** with D_5W, LR; **variable stability (consult detailed reference)** in NS.

Y-site administration: Compatible: Acyclovir, amikacin, aminophylline, ampicillin, aztreonam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, carmustine, cefazolin, cefepime, cefoperazone, cefotaxime, cefotetan, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cimetidine, cisplatin, clindamycin, co-trimoxazole, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, dexamethasone sodium phosphate, diphenhydramine, doxorubicin, doxycycline, droperidol, enalaprilat, etoposide, famotidine, floxuridine, fluconazole, fludarabine, fluorouracil, furosemide, ganciclovir, gentamicin, granisetron, haloperidol, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, idarubicin, ifosfamide, imipenem/cilastatin, lorazepam, mannitol, mechlorethamine, meperidine, mesna, methotrexate, methylprednisolone sodium succinate, metoclopramide, metronidazole, minocycline, mitomycin, mitoxantrone, morphine, nalbuphine, netilmicin, ondansetron, pentostatin, piperacillin, plicamycin, potassium chloride, prochlorperazine edisylate, promethazine, ranitidine, sodium bicarbonate, streptozocin, teniposide, thiotepa, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, vinblastine, vincristine, vinorelbine, zidovudine. **Incompatible:** Amphotericin B, chlorpromazine.

ContraindicationsHypersensitivity to melphalan or any component of the formulation; severe bone marrow suppression; patients whose disease was resistant to prior melphalan therapy; pregnancy

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.
- Hypersensitivity reactions: See “Concerns related to adverse effects” below.
- Secondary malignancies: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: Bone marrow suppression is common;** use with caution in patients with prior bone marrow suppression, impaired renal function (consider dose reduction), or who have received prior chemotherapy or irradiation.
- Fertility effects: Suppresses ovarian function and produces amenorrhea; may also cause testicular suppression.
- Hypersensitivity reactions: **[U.S. Boxed Warning]: Hypersensitivity has been reported with I.V. administration** and oral melphalan; may occur after multiple treatment cycles.
- Secondary malignancies: **[U.S. Boxed Warning]: Is potentially mutagenic, leukemogenic, and carcinogenic.**

Disease-related concerns:

- Infection: Signs of infection, such as fever and WBC rise, may not occur; lethargy and confusion may be more prominent signs of infection.

Special populations:

- Elderly: Toxicity to immunosuppressives is increased in elderly; start with lowest recommended adult doses.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Geriatric ConsiderationsToxicity to immunosuppressives is increased in the elderly. Start with lowest recommended adult doses. Signs of infection, such as fever and WBC rise, may not occur. Lethargy and confusion may be more prominent signs of infection.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated embryotoxicity and teratogenicity. Therapy may suppress ovarian function leading to amenorrhea. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid pregnancy while on melphalan therapy.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Gastrointestinal: Vomiting (oral low-dose: <10%; I.V.: 30% to 90%)

Hematologic: Myelosuppression, leukopenia (onset 7 days; nadir 14-35 days; recovery 28-56 days), thrombocytopenia (onset 7 days; nadir 14-35 days; recovery 28-56 days)

Miscellaneous: Secondary malignancy (<2% to 20%; cumulative dose and duration dependent)

1% to 10%: Miscellaneous: Hypersensitivity (I.V.: 2%)

Infrequent, frequency undefined, postmarketing, and/or case reports: Agranulocytosis, allergic reactions, alopecia, amenorrhea, anaphylaxis, anemia, bladder irritation, bone marrow failure (irreversible), diarrhea, hemolytic anemia, hemorrhagic cystitis, hemorrhagic necrotic enterocolitis, hepatic veno-occlusive disease (I.V. melphalan), hepatitis, interstitial pneumonitis, jaundice, nausea, ovarian suppression, pruritus, pulmonary fibrosis, radiation myelopathy, rash, secondary carcinoma, secondary leukemia, secondary myeloproliferative syndrome, SIADH, skin hypersensitivity, skin necrosis, skin ulceration (injection site), skin vesiculation, sterility, stomatitis, testicular suppression, transaminases increased, vasculitis

Oncology: VesicantNo

Oncology: Emetic Potential

Oral: Very low (<10%)

I.V. (>50 mg/m^2): High (60% to 90%)

Oncology: Bone Marrow - Unique Toxicity

Cardiovascular: Atrial fibrillation, left ventricular heart failure

Dermatologic: Alopecia

Gastrointestinal: Mucositis (severity increases with Cl_{cr} ≤40 mL/minute; pretreatment with amifostine or glutamine may decrease mucositis), nausea and vomiting (moderate), diarrhea

Hematologic: Myelosuppression, secondary leukemia

Renal: Increased serum creatinine and azotemia possible without adequate hydration

Rare side effects: Abnormal LFTs, atrial fibrillation, interstitial pneumonitis, secondary leukemia, SIADH, vasculitis

Drug Interactions

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

CycloSPORINE: Melphalan may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Nalidixic Acid: May enhance the adverse/toxic effect of Melphalan. Necrotic enterocolitis has been reported in pediatric patients. *Risk X: Avoid combination*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (due to GI irritation).

Food: Food interferes with oral absorption.

Test InteractionsFalse-positive Coombs' test [direct]

Monitoring ParametersCBC with differential and platelet count, serum electrolytes, serum uric acid

Nursing: Physical Assessment/MonitoringEvaluate patient for use cautions prior to beginning treatment. Assess potential for interactions with other pharmacological agents patient may be taking. For intravenous infusion, see Administration and Reconstitution specifics. Assess results of laboratory tests (especially hematologic parameters), patient response, and adverse reactions (eg, gastrointestinal upset, myelosuppression [leukopenia], diarrhea, hypersensitivity reaction) regularly during therapy. Teach patient proper use (oral), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, platelet count, serum electrolytes, serum uric acid

Patient Education**I.V.:** Report immediately any burning, swelling, pain, or redness at infusion or injection site. **Oral:** Preferable to take oral doses on an empty stomach, 1 hour before or 2 hours after meals. Avoid excessive alcohol (may increase gastric irritation). Maintain adequate nutrition (small, frequent meals may help) and adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations unless approved by prescriber). May cause nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); hair loss (reversible); easy bleeding or bruising (use soft toothbrush or cotton swabs and frequent mouth care, use electric razor, avoid sharp knives or scissors). Report persistent or severe nausea or vomiting; diarrhea or abdominal pain; chest pain or palpitations; difficulty or pain on urination; unusual bruising/bleeding; respiratory difficulty; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 50 mg [diluent contains ethanol and propylene glycol]

Tablet: 2 mg

Generic AvailableNo

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Tablets (Alkeran)

2 mg (50): $239.99

Mechanism of ActionAlkylating agent which is a derivative of mechlorethamine that inhibits DNA and RNA synthesis via formation of carbonium ions; cross-links strands of DNA; acts on both resting and rapidly dividing tumor cells.

Pharmacodynamics/Kinetics

Absorption: Oral: Variable and incomplete

Distribution: V_d: 0.5-0.6 L/kg throughout total body water

Protein binding: 60% to 90%; primarily to albumin, 20% to α_1-acid glycoprotein

Metabolism: Hepatic; chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan

Bioavailability: Unpredictable; 61% ± 26%, decreasing with repeated doses

Half-life elimination: Terminal: I.V.: 1.5 hours; oral: 1-1.25 hours

Time to peak, serum: ~1-2 hours

Excretion: Oral: Feces (20% to 50%); urine (10% to 30% as unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMyelosuppression is common; avoid concurrent use with clozapine and carbamazepine

Oncology: Bone Marrow CommentsSaline-based hydration (100-125 mg/m^2/hour) preceding (2-4 hours), during, and following (6-12 hours) administration reduces risk of drug precipitation in renal tubules. Hydrolysis causes loss of 1% melphalan injection per 10 minutes. Infusion of admixture must be completed within 100 minutes of preparation to deliver ordered dose. Reconstitute dose to 5 mg/mL in diluent provided by manufacturer. Dose may be infused via central or peripheral venous access without further dilution to minimize volume of infusion.

Index TermsL-PAM; L-Sarcolysin; NSC-8806; Phenylalanine Mustard

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International Brand NamesAlkeran (AT, AU, BE, BR, CH, CZ, DE, DK, FI, GB, HR, HU, IN, IT, LU, MX, NL, NO, PL, PT); Alkerana (AR, FR); Alkeran[inj.] (GB, IT, SE); Melfalan (ES)

Memantine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(me MAN teen)

U.S. Brand NamesNamenda™

Canadian Brand NamesEbixa®

Pharmacologic CategoryN-Methyl-D-Aspartate Receptor Antagonist

Use: Labeled IndicationsTreatment of moderate-to-severe dementia of the Alzheimer's type

Use: Unlabeled/InvestigationalTreatment of mild-to-moderate vascular dementia; mild cognitive impairment

Dosing: Adults

Alzheimer's disease: Oral: Initial: 5 mg/day; increase dose by 5 mg/day to a target dose of 20 mg/day; wait at least 1 week between dosage changes. Doses >5 mg/day should be given in 2 divided doses.

Suggested titration: 5 mg/day for ≥1 week; 5 mg twice daily for ≥1 week; 15 mg/day given in 5 mg and 10 mg separated doses for ≥1 week; then 10 mg twice daily.

Mild-to-moderate vascular dementia (unlabeled use): Oral: 10 mg twice daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Mild-to-moderate impairment: No adjustment required.

Severe impairment: Cl_{cr} 5-29 mL/minute): 5 mg twice daily

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsMay be taken with or without food.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to memantine or any component of the formulation

Allergy Considerations

- Adamantane Derivative Allergy

Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Renal impairment: Use with caution in patients with severe renal impairment; dose adjustment recommended.
- Seizure disorder: Use with caution in patients with a history of seizure disorder; may increase risk of seizures.

Other warnings/precautions:

- Urine pH: Clearance is significantly reduced by alkaline urine; use caution with medications, dietary changes, or patient conditions which may alter urine pH.

Geriatric ConsiderationsIn clinical trials, patients on memantine had less of a decline in cognitive function and activities of daily living (ADL) as compared to placebo. This was true for monotherapy with memantine, as well as combination therapy with donepezil, an acetylcholinesterase inhibitor.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Cardiovascular: Hypertension (4%), cardiac failure, syncope, cerebrovascular accident, transient ischemic attack

Central nervous system: Dizziness (7%), confusion (6%), headache (6%), hallucinations (3%), pain (3%), somnolence (3%), fatigue (2%), aggressive reaction, ataxia, vertigo

Dermatologic: Rash

Gastrointestinal: Constipation (5%), vomiting (3%), weight loss

Genitourinary: Micturition

Hematologic: Anemia

Hepatic: Alkaline phosphatase increased

Neuromuscular & skeletal: Back pain (3%), hypokinesia

Ocular: Cataract, conjunctivitis

Respiratory: Cough (4%), dyspnea (2%), pneumonia

<1%: Allergic reaction, alopecia, amnesia, angina, apathy, aphasia, apnea, appetite increased, asthma, atrial fibrillation, blepharitis, blurred vision, bradycardia, cardiac arrest, cellulitis, cerebral hemorrhage, conjunctival hemorrhage, convulsions, coordination abnormal, corneal opacity, crying abnormal, dehydration, delirium, delusion, depersonalization, dermatitis, diabetes mellitus aggravated, diplopia, diverticulitis, dysuria, eczema, emotional lability, erythematous rash, esophageal ulceration, extrapyramidal disorder, eye pain, gastroenteritis, gastrointestinal hemorrhage, glaucoma, hearing decreased, hematuria, hemiplegia, hemoptysis, hyperkinesias, hypertonia, hypoesthesia, hyponatremia, hypotension, hypothermia, involuntary muscle contractions, lacrimation abnormal, leukopenia, libido increased, macula lutea degeneration, melena, MI, myopia, nervousness, neuralgia, neuropathy, neurosis, paranoid reaction, paresthesia, paroniria, personality disorder, postural hypotension, pruritus, psychosis, ptosis, pulmonary edema, pulmonary embolism, retinal detachment, retinal hemorrhage, skin ulceration, sleep disorder, stupor, suicide attempt, thinking abnormal, thrombophlebitis, tinnitus, tremor, urinary retention, urticaria, visual acuity decreased, xerophthalmia

Postmarketing and/or case reports (limited to important or life-threatening): AV block, cerebral infarction, dyskinesia, dysphagia, hepatic failure, hyperlipidemia, hypoglycemia, ileus, NMS, pancreatitis, renal failure, QT prolongation, seizure, Stevens-Johnson syndrome, sudden death, tardive dyskinesia, thrombocytopenia

Drug Interactions

Carbonic Anhydrase Inhibitors: May decrease the excretion of Memantine. *Risk C: Monitor therapy*

Sodium Bicarbonate: May decrease the excretion of Memantine. *Risk C: Monitor therapy*

Trimethoprim: May enhance the adverse/toxic effect of Memantine. Specifically, the risk of myoclonus and/or delerium may be increased. Trimethoprim may increase the serum concentration of Memantine. Memantine may increase the serum concentration of Trimethoprim. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringAssess therapeutic effectiveness and adverse reactions on a regular basis throughout therapy (eg, hypertension, CNS changes, rash, constipation). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Patient EducationTake as directed with or without food. May cause hypertension (monitor if recommended); headache (consult prescriber for analgesic). Report increase or changes in CNS symptoms (confusion, hallucinations, fatigue, aggressive reaction); chest pain or palpitations, dizziness or fainting; difficulty breathing of tightness in chest; rash; alteration in elimination patterns, or other persistent adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral: 2 mg/mL (360 mL) [alcohol free, dye free, sugar free; peppermint flavor]

Tablet, as hydrochloride: 5 mg, 10 mg

Combination package [titration pack contains two separate tablet formulations]: Memantine hydrochloride 5 mg (28s) and memantine hydrochloride 10 mg (21s)

Generic AvailableNo

ManufacturerForest Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Namenda)

5 mg (60): $171.18

10 mg (60): $169.98

Tablets (Namenda Titration Pak)

(49): $140.22

Mechanism of ActionGlutamate, the primary excitatory amino acid in the CNS, may contribute to the pathogenesis of Alzheimer's disease (AD) by overstimulating various glutamate receptors leading to excitotoxicity and neuronal cell death. Memantine is an uncompetitive antagonist of the N-methyl-D-aspartate (NMDA) type of glutamate receptors, located ubiquitously throughout the brain. Under normal physiologic conditions, the (unstimulated) NMDA receptor ion channel is blocked by magnesium ions, which are displaced after agonist-induced depolarization. Pathologic or excessive receptor activation, as postulated to occur during AD, prevents magnesium from reentering and blocking the channel pore resulting in a chronically open state and excessive calcium influx. Memantine binds to the intra-pore magnesium site, but with longer dwell time, and thus functions as an effective receptor blocker only under conditions of excessive stimulation; memantine does not affect normal neurotransmission.

Pharmacodynamics/Kinetics

Distribution: 9-11 L/kg

Protein binding: 45%

Metabolism: Forms 3 metabolites (minimal activity)

Half-life elimination: Terminal: 60-80 hours; severe renal impairment (Cl_{cr} 5-29 mL/minute): 117-156 hours

Time to peak, serum: 3-7 hours

Excretion: Urine (57% to 82% unchanged); excretion reduced by alkaline urine pH

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Index TermsMemantine Hydrochloride
References

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International Brand NamesAbixa (PH); Admed (KP); Admenta (IN); Akatinol (CO, DO, GT, HN, PA, PY, SV, UY); Albix (KP); Axura (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PL, PT, RU, SE, TR); Ebix (BR); Ebixa (AR, AT, AU, BE, BG, CH, CL, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, MX, MY, NL, NO, PK, PL, PT, RU, SE, SG, TH, TR, TW); Eutebrol (EC, PE); Limember (PE); Manotin (TW); Memanto (KP); Memox (IL); Witgen (TW)

Meningococcal Group C-CRM197 Conjugate Vaccine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(me NIN joe kok al groop see see ahr em wuhn nahyn tee sev uhn KON joo gate vak SEEN)

Canadian Brand NamesMenjugate®

Pharmacologic CategoryVaccine

Use: Labeled IndicationsTo provide active immunization against invasive meningococcal disease caused by *N. meningitidis* serogroup C, in children ≥2 months and adults

The National Advisory Committee on Immunization (NACI) recommendations for persons considered at an increased risk for meningococcal disease:

Chemoprophylaxis and immunoprophylaxis: Selection of meningococcal vaccination to be based upon serogroup(s):

Individuals living in the same household or with close contact (eg, kissing, shared cigarettes, shared eating or drinking utensils) of infected patient

Employees and children of nursery schools or day care

Immunoprophylaxis: Selection of meningococcal vaccination to be based upon serogroup(s):

Adolescents and young adults

Laboratory workers routinely exposed to isolates of *N. meningitidis*

Military recruits

Persons traveling to or who reside in countries where *N. meningitidis* is hyperendemic or epidemic, particularly if contact with local population will be prolonged

Persons with terminal complement component deficiencies

Persons with anatomic or functional asplenia

Note: Use is also recommended during meningococcal outbreaks caused by serogroup C.

Chemoprophylaxis:

Healthcare workers with intensive unprotected contact with infected patients

Airline passengers sitting directly next to an infected patient for duration of at least 8 hours

See NACI guidelines for specific drug treatment at http://www.phac-aspc.gc.ca/naci-ccni

Dosing: AdultsImmunization: I.M.: 0.5 mL as a single dose

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricImmunization: I.M.:

Infants:

≥2-12 months: 0.5 mL as a single dose for a total of 3 doses administered at least 4 weeks apart

≥4-11 months without prior vaccination: 0.5 mL as a single dose for a total of 2 doses administered at least 4 weeks apart

Note: The NACI recommends at least 1 of the 3 sequential doses for infants ≥2-12 months be administered beyond 5 months of age.

Children ≥1 year: Refer to adult dosing.

Administration: I.M.Administer by deep intramuscular injection only into the anterolateral thigh in infants and the deltoid area in older children, adolescents, and adults. Use separate injection sites if administering multiple vaccinations on the same day.

Administration: I.V.

Do not administer via I.V., SubQ, or I.D. routes.

StorageStore at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Upon reconstitution, use immediately.

Alternative storage: Prior to reconstitution; store up to 25°C (77°F); do not freeze. Protect from light. Use or discard within 6 months of date removed from refrigerator or upon reaching expiration date on outside packaging (whichever comes first).

Reconstitution

Menjugate® vial: Gently agitate diluent vial, then withdraw 0.6 mL of diluent and inject into Menjugate® vial. Gently shake vial until content dissolves.

Menjugate® syringe: Gently agitate diluent syringe, then inject entire content of syringe into Menjugate® vial. Gently shake vial until contents dissolves and then withdraw contents of vial back into syringe. Change needle prior to administration.

CompatibilityDo not mix with other vaccines in the same syringe.
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to meningococcal group C-CRM197 conjugate vaccine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness without fever.
- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.
- Diphtheria infection: Vaccine is not intended for immunization against diphtheria. Vaccinations with diphtheria toxoid should still be administered as regularly scheduled.
- Meningococcal infections: Not to be used to treat meningococcal infections or to provide immunity against *N. meningitidis* serogroups A, B, 29-E, H, I, K, L, W-135, X, Y, or Z. Vaccination against other serogroups if needed should be administered at least 2 weeks after the administration of Menjugate®.

Special populations:

Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, HIV, patients receiving chemo/radiation therapy or other immunosuppressive therapy); safety and efficacy have not been established.

Pregnancy ConsiderationsAnimal studies have not demonstrated risks to the fetus. Reproductive studies in humans have not been conducted.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%:

Central nervous system: Temperature <38°C (5% to 47%), headache (34%), irritability (10% to 30%), malaise (25% adults), sleepiness (9% to 19% children), chills (13%)

Gastrointestinal: Diarrhea (8% to 18%), appetite changes (6% to 16%), nausea (16%)

Local: Injection site: Pain (22% to 81%; severe ≤2%), erythema (16% to 28%), induration (7% to 24%)

Neuromuscular & skeletal: Myalgia (29%), arthralgia (16%)

1% to 10%:

Central nervous system: Fever ≥38°C (2% to 9%), crying (unusual/persistent; up to 4%)

Dermatologic: Rash (4% to 9%)

Gastrointestinal: Vomiting (5% to 9%)

<1%, postmarketing, and/or case reports: Agitation, anaphylaxis, angioedema, bronchospasm, dizziness, facial edema, hypersensitivity reactions, hypoesthesia, hypotonia, lymphadenopathy, maculopapular rash, paresthesia, pruritus, seizure, syncope, urticaria

Drug Interactions

Immunosuppressants: Safety and immunogenicity have not been established. Reduced responses to vaccine may occur.

Vaccines: Using separate sites and syringes, may be administered concomitantly with diphtheria tetanus (DT); diphtheria tetanus and pertussis (DTaP); *Haemophilus* influenza type B (Hib); mumps, measles, and rubella (MMR); and polio virus vaccine (IPV or OPV).

Nursing: Physical Assessment/MonitoringUse caution in immunocompromised patients, patients with bleeding disorders, or those taking anticoagulants. Anaphylactoid and/or hypersensitivity reactions may occur; treatment should be available for immediate use. Note specific administration directions. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.
Patient EducationYou may experience mild headache, fever or chills, nausea or vomiting, or unusual sleepiness. Report persistent pain, redness, or swelling at injection site or other acute or persistent adverse reactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN = Canadian brand name]

Injection, powder for reconstitution:

Menjugate® [CAN]: 10 mcg of oligosaccharide antigen group [conjugated to diphtheria toxin protein carrier CRM 197; packaged with of diluent containing aluminum hydroxide; not available in U.S.]

Generic AvailableNo

ManufacturerNovartis Vaccines and Diagnostics S.R.L.

Mechanism of ActionInduces immunity against meningococcal disease via the formation of bactericidal antibodies directed toward the polysaccharide capsular components of *Neisseria meningitidis* serogroup C.

Index TermsMenC-CRM197; MenCC

References

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Trotter CL, Andrews NJ, Kaczmarski EB, et al, “Effectiveness of Meningococcal Serogroup C Conjugate Vaccine 4 Years After Introduction,” *Lancet*, 2004, 364(9431):365-7.[PubMed 5276396]

International Brand NamesMenjugate (AR, AU, BE, CH, CZ, DE, FI, GB, IE)

Meningococcal Polysaccharide (Groups A / C / Y and W-135) Diphtheria Toxoid Conjugate Vaccine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Administration issue:

Menactra® (MCV) should be administered by intramuscular (I.M.) injection only. Inadvertent subcutaneous (SubQ) administration has been reported; possibly due to confusion of this product with Menomume® (MPSV), also a meningococcal polysaccharide vaccine, which is administered by the SubQ route.

Pronunciation(me NIN joe kok al pol i SAK a ride groops aye, see, why & dubl yoo won thur tee fyve dif THEER ee a TOKS oyds KON joo gate vak SEEN)

U.S. Brand NamesMenactra®

Pharmacologic CategoryVaccine, Inactivated (Bacterial)

Use: Labeled IndicationsProvide active immunization of children and adults (2-55 years of age) against invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, Y, and W-135

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of all persons 11-18 years of age at the earliest opportunity. Adolescents should be vaccinated at the 11-12 year visit. For adolescents not previously vaccinated, vaccine should be administered prior to high school entry (~15 years of age).

The ACIP also recommends vaccination for persons at increased risk for meningococcal disease. (Meningococcal conjugate vaccine [MCV] is preferred for persons aged 2-55 years; meningococcal polysaccharide vaccine [MPSV] may be used if MCV is not available). Persons at increased risk include:

College freshmen living in dormitories

Microbiologists routinely exposed to isolates of *N. meningitides*

Military recruits

Persons traveling to or who reside in countries where *N. meningitides* is hyperendemic or epidemic, particularly if contact with local population will be prolonged

Persons with terminal complement component deficiencies

Persons with anatomic or functional asplenia

Use is also recommended during meningococcal outbreaks caused by vaccine preventable serogroups.

Dosing: Adults**Immunization:** I.M.: Adults ≤55 years: 0.5 mL

Note: Revaccination: May be indicated in patients previously vaccinated with MPSV who remain at increased risk for infection. The ACIP recommends the use of MCV for revaccination, however, use of MPSV is also acceptable. The need for revaccination in patients previously vaccinated with MCV is currently under study. Adults who received MPSV ≥5 years previously, and who are still at increased risk for meningococcal disease should be revaccinated with MCV.

Dosing: ElderlySafety and efficacy not established in patients >55 years.

Dosing: Pediatric**Immunization:** I.M.: Children ≥2 years: 0.5 mL

Note: Revaccination: May be indicated in patients previously vaccinated with MPSV who remain at increased risk for infection. The ACIP recommends the use of MCV for revaccination; however, use of MPSV is also acceptable. The need for revaccination in patients previously vaccinated with MCV is currently under study. Children 2-10 years who received MPSV ≥3 years previously, or older children and adults who received MPSV ≥5 years previously, and who are still at increased risk for meningococcal disease should be revaccinated with MCV.

Administration: I.M.Administer by the intramuscular route, preferably into the upper deltoid region. For patients at risk of hemorrhage, the ACIP recommends “it should be administered intramuscularly if, in the opinion of a physician familiar with the patient's bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (≤23 gauge) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient or family should be instructed concerning the risk of hematoma from the injection.”

Administration with other vaccines:

MCV with other inactivated vaccines: May be given simultaneously or at any interval between doses. A one month interval between tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis vaccine and MCV is suggested if they are not administered simultaneously

MCV with live vaccines: May be given simultaneously or at any interval between doses

Vaccine administration with antibody-containing products: MCV may be given simultaneously at different sites or at any interval between doses with antibody-containing products. Examples of antibody containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

Administration: I.V.Do not administer via I.V., SubQ or I.D. route.

Administration: OtherFor I.M. administration only. Based on limited data, inadvertent SubQ administration provides a lower serologic response, however the response is still considered to be protective. If inadvertently administered by the SubQ route, revaccination is not necessary.

StorageStore between 2°C to 8°C (35°F to 46°F); do not freeze. Discard product exposed to freezing. Do not mix with other vaccines in the same syringe.

ContraindicationsHypersensitivity to any component of the formulation, including diphtheria toxoid; latex hypersensitivity; history of Guillain-Barré syndrome

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.
- Guillain-Barré syndrome: Risk of developing Guillain-Barré syndrome may be increased following vaccination with MCV. Persons previously diagnosed with Guillain-Barré syndrome should not be vaccinated with MCV.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).
- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.
- Meningococcal infections: Not to be used to treat meningococcal infections or to provide immunity against *N. meningitidis* serogroup B or diphtheria.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Adults: Safety and efficacy have not been established adults >55 years.
- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy [including high dose corticosteroids); may have a reduced response to vaccination.
- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Dosage form specific issues:

- Latex: Packaging may contain natural latex rubber.

Geriatric ConsiderationsMay be used though safety and efficacy have not been established in patients >55 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. An isolated teratogenic effect was observed in an animal developmental toxicity study; not necessarily vaccine related. Carcinogenic or mutagenic studies have not been performed. There are no adequate and well-controlled studies in pregnant women. Patients should contact the Sanofi Pasteur Inc vaccine registry at 1-800-822-2463 if they are pregnant or become aware they were pregnant at the time of Menactra® vaccination.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967 or www.vaers.org.**

>10%:

Central nervous system: Pain (45% to 59%), headache (36% to 41%), fatigue (30% to 35%), malaise (22% to 24%), irritability (12%), drowsiness (11%)

Gastrointestinal: Diarrhea (11% to 16%), anorexia (8% to 12%)

Local: Redness (11% to 22%), swelling (11% to 17%), induration (16% to 19%)

Neuromuscular & skeletal: Arthralgia (7% to 20%)

1% to 10%:

Central nervous system: Chills (7% to 10%), fever (2% to 5%)

Gastrointestinal: Vomiting (2% to 3%)

Local: Rash (1% to 3%)

Postmarketing and/or case reports: Acute disseminated encephalomyelitis, anaphylactic/anaphylactoid reactions, breathing difficulties, erythema, facial palsy, Guillain-Barré syndrome, hypotension, myalgia, pruritus, transverse myelitis, upper airway swelling, urticaria, vasovagal syncope, wheezing

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Monitoring Parameters Monitor for syncope for ≥15 minutes following vaccination

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [MCV; preservative free]:

Menactra®: 4 mcg each of polysaccharide antigen groups A, C, Y, and W-135 [bound to diphtheria toxoid 48 mcg] per 0.5 mL [contains natural rubber/natural latex in packaging of vials]

Generic Available No

Manufacturer Sanofi Pasteur Inc

Pricing: U.S. (www.drugstore.com)

Injection (Menactra)

(0.5): $110.20

Mechanism of Action Induces immunity against meningococcal disease via the formation of bactericidal antibodies directed toward the polysaccharide capsular components of *Neisseria meningitidis* serogroups A, C, Y and W-135.

Pharmacotherapy Pearls Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title and address be entered into the patient's permanent medical record.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Malaise and fatigue are common

Mental Health: Effects on Psychiatric Treatment Diarrhea is common; concomitant use with SSRIs may produce additive effects

Index Terms MCV; Meningococcal Conjugate Vaccine

References

Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC), “Report from the Advisory Committee on Immunization Practices (ACIP): Decision Not to Recommend Routine Vaccination of All Children Aged 2-10 Years With Quadrivalent Meningococcal Conjugate Vaccine (MCV4),” *MMWR Morb Mortal Wkly Rep*, 2008, 57(17):462-5.[PubMed 18451758]

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Meningococcal Polysaccharide Vaccine (Groups A / C / Y and W-135)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Administration issue:

Menomume® (MPSV) should be administered by subcutaneous (SubQ) injection. Menactra® (MCV), also a meningococcal polysaccharide vaccine, is to be administered by intramuscular (I.M.) injection only.

Pronunciation(me NIN joe kok al pol i SAK a ride vak SEEN groops aye, see, why & dubl yoo won thur tee fyve)
U.S. Brand NamesMenomune®-A/C/Y/W-135
Pharmacologic CategoryVaccine, Inactivated (Bacterial)
Use: Labeled IndicationsProvide active immunity to meningococcal serogroups contained in the vaccine
The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for persons at increased risk for meningococcal disease. (Meningococcal conjugate vaccine [MCV] is preferred for persons aged 2-55 years; meningococcal polysaccharide vaccine [MPSV] may be used if MCV is not available.) Persons at increased risk include:

College freshmen living in dormitories

Microbiologists routinely exposed to isolates of *N. meningitides*

Military recruits

Persons traveling to or who reside in countries where *N. meningitides* is hyperendemic or epidemic, particularly if contact with local population will be prolonged

Persons with terminal complement component deficiencies

Persons with anatomic or functional asplenia

Use is also recommended during meningococcal outbreaks caused by vaccine preventable serogroups.

Dosing: Adults**Immunization:** SubQ: 0.5 mL

Note: Revaccination: May be indicated in patients previously vaccinated with MPSV who remain at increased risk for infection. The ACIP recommends the use of MCV for revaccination; however, use of MPSV is also acceptable. Adults who received MPSV ≥5 years previously and who are still at increased risk for meningococcal disease should be revaccinated with MCV.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric
Immunization: SubQ:

Children <2 years: Not usually recommended. Two doses (0.5 mL/dose), 3 months apart, may be considered in children 3-18 months to elicit short-term protection against serogroup A disease. A single dose may be considered in children 19-23 months. (ACIP recommendations)

Children ≥2 years: Refer to adult dosing.

Revaccination: Children 2-10 years who received MPSV ≥3 years previously, or older children who received MPSV ≥5 years previously, and who are still at increased risk for meningococcal disease should be revaccinated with MCV.

Administration: OtherAdminister by SubQ injection; do not administer intradermally, I.M., or I.V.

Administration with other vaccines:

MPSV with other inactivated vaccines: May be given simultaneously or at any interval between doses.

MPSV with live vaccines: May be given simultaneously or at any interval between doses.

Vaccine administration with antibody-containing products: MPSV may be given simultaneously at different sites or at any interval between doses with antibody-containing products. Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StoragePrior to and following reconstitution, store at 2°C to 8°C (35°F to 46°F).
ReconstitutionReconstitute using provided diluent; shake well. Use single-dose vial within 30 minutes of reconstitution. Use multidose vial within 35 days of reconstitution.
ContraindicationsHypersensitivity to any component of the formulation; defer immunization during acute illness
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Meningococcal infections: Not to be used to treat meningococcal infections or to provide immunity against *N. meningitidis* serogroup B.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination.

- Pediatrics: Use in pediatric patients <2 years of age is usually not recommended.

Dosage form specific issues:

- Latex: Packaging may contain natural latex rubber.

- Thimerosal: Some dosage forms contain thimerosal.

Geriatric ConsiderationsNo specific data; only recommended when traveling to highly endemic areas.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies have not been conducted. Based on limited data, teratogenic effects have not been reported when used during pregnancy. Pregnancy should not preclude vaccination with MPSV if indicated. Patients may contact the Sanofi Pasteur Inc vaccine registry at 1-800-822-2463 if they are pregnant or become aware they were pregnant at the time of vaccination.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.** Percentages reported in adults; incidence of erythema, swelling, or tenderness may be higher in children

>10%: Local: Tenderness (9% to 36%)

1% to 10%:

Central nervous system: Headache (2% to 5%), malaise (2%), fever (100°F to 106°F: 3%), chills (2%)

Local: Pain at injection site (2% to 3%), erythema (1% to 4%), induration (1% to 4%)

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Monitoring ParametersMonitor for syncope for ≥15 minutes following vaccination.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [MPSV]:

Menomune®-A/C/Y/W-135: 50 mcg each of polysaccharide antigen groups A, C, Y, and W-135 per 0.5 mL dose [contains lactose 2.5-5 mg/0.5 mL, natural rubber/natural latex in packaging, thimerosal in diluent for multidose vial]

Generic AvailableNo
ManufacturerSanofi Pasteur Inc
Pricing: U.S. (www.drugstore.com)

Injection (Menactra)

(1): $199.97

Mechanism of ActionInduces the formation of bactericidal antibodies to meningococcal antigens; the presence of these antibodies is strongly correlated with immunity to meningococcal disease caused by *Neisseria meningitidis* groups A, C, Y and W-135.
Pharmacodynamics/Kinetics

Onset of action: Antibody levels: 7-10 days

Duration: Antibodies against group A and C polysaccharides decline markedly (to prevaccination levels) over the first 3 years following a single dose of vaccine, especially in children <4 years of age

Related Information

- Immunization Recommendations

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title and address be entered into the patient's permanent medical record.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsMeningococcal Polysaccharide Vaccine; MPSV
References

Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC), "Report From the Advisory Committee on Immunization Practices (ACIP): Decision Not to Recommend Routine Vaccination of All Children Aged 2-10 Years With Quadrivalent Meningococcal Conjugate Vaccine (MCV4)," *MMWR Morb Mortal Wkly Rep*, 2008, 57(17):462-5.[PubMed 18451758]

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Menotropins

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Repronex® may be confused with Regranex®

Pronunciation(men oh TROE pins)

U.S. Brand NamesMenopur®; Repronex®

Canadian Brand NamesMenopur®; Repronex®

Pharmacologic CategoryGonadotropin; Ovulation Stimulator

Use: Labeled IndicationsFemale:

In conjunction with hCG to induce ovulation and pregnancy in infertile females experiencing oligoanovulation or anovulation when the cause of anovulation is functional and not caused by primary ovarian failure (Repronex®)

Stimulation of multiple follicle development in ovulatory patients as part of an assisted reproductive technology (ART) (Menopur®, Repronex®)

Use: Unlabeled/InvestigationalMale: Stimulation of spermatogenesis in primary or secondary hypogonadotropic hypogonadism

Dosing: Adults

Repronex®: I.M., SubQ:

Induction of ovulation in patients with oligoanovulation (Female): Initial: 150 int. units daily for the first 5 days of treatment. Adjustments should not be made more frequently than once every 2 days and should not exceed 75-150 int. units per adjustment. Maximum daily dose should not exceed 450 int. units and dosing beyond 12 days is not recommended. If patient's response is appropriate, hCG 5000-10,000 units should be given one day following the last dose of Repronex®. Hold dose if serum estradiol is >2000 pg/mL, if the ovaries are abnormally enlarged, or if abdominal pain occurs; the patient should also be advised to refrain from intercourse. May repeat process if follicular development is inadequate or if pregnancy does not occur.

Assisted reproductive technologies (Female): Initial (in patients who have received GnRH agonist or antagonist pituitary suppression): 225 int. units; adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75-150 int. units per adjustment. The maximum daily doses of Repronex® given should not exceed 450 int. units and dosing beyond 12 days is not recommended. Once adequate follicular development is evident, hCG (5000-10,000 units) should be administered to induce final follicular maturation in preparation for oocyte retrieval. Withhold treatment when ovaries are abnormally enlarged on last day of therapy (to reduce chance of developing OHSS).

Menopur®: SubQ: *Assisted reproductive technologies (ART):* Initial (in patients who have received GnRH agonist for pituitary suppression): 225 int. units; adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 150 int. units per adjustment. The maximum daily dose given should not exceed 450 int. units and dosing beyond 20 days is not recommended. Once adequate follicular development is evident, hCG should be administered to induce final follicular maturation in preparation for oocyte retrieval. Withhold treatment when ovaries are abnormally enlarged on last day of therapy (to reduce chance of developing OHSS).

Spermatogenesis (Male) (unlabeled use): I.M.: Following pretreatment with hCG: 75 int. units 3 times/week and hCG 2000 units twice weekly until sperm is detected in the ejaculate (4-6 months); may then be increased to menotropins 150 int. units 3 times/week

Administration: I.M.Repronex®: Administer deep in a large muscle.

Administration: OtherSubQ:

Menopur®: Administer to alternating sites of the abdomen. When administration to the lower abdomen is not possible, the injection may be given into the thigh.

Repronex®: Administer to alternating sites of the lower abdomen.

StorageLyophilized powder may be refrigerated or stored at room temperature. Protect from light.

ReconstitutionAfter reconstitution inject immediately; discard any unused portion.

ContraindicationsHypersensitivity to menotropins or any component of the formulation; primary ovarian failure as indicated by a high follicle-stimulating hormone (FSH) level; uncontrolled thyroid and adrenal dysfunction; abnormal bleeding of undetermined origin; intracranial lesion (ie, pituitary tumor); ovarian cyst or enlargement not due to polycystic ovary syndrome; infertility due to any cause other than anovulation (except candidates for *in vitro* fertilization); sex hormone-dependent tumors of the reproductive tract and accessory organs; pregnancy

Warnings/Precautions

Concerns related to adverse effects:

- Ovarian enlargement: May be accompanied by abdominal distention or abdominal pain and generally regresses without treatment within 2-3 weeks. If ovaries are abnormally enlarged on the last day of treatment, withhold hCG to reduce the risk of ovarian hyperstimulation syndrome (OHSS).

- Ovarian hyperstimulation syndrome (OHSS): OHSS is characterized by severe ovarian enlargement, abdominal pain/distention, nausea, vomiting, diarrhea, dyspnea, and oliguria, and may be accompanied by ascites, pleural effusion, hypovolemia, electrolyte imbalance, hemoperitoneum, and thromboembolic events. If severe hyperstimulation occurs, stop treatment and hospitalize patient. This syndrome develops rapidly with 24 hours to several days and generally occurs during the 7-10 days immediately following treatment.

- Pulmonary effects: Serious pulmonary conditions (atelectasis, acute respiratory distress syndrome, and exacerbation of asthma) have been reported.

- Thromboembolism: In association with and separate from ovarian hyperstimulation syndrome (OHSS), thromboembolic events have been reported.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; safety and efficacy have not been established.

- Renal impairment: Use with caution in patients with renal impairment; safety and efficacy have not been established.

Special populations:

- Elderly: Safety and efficacy have not been established in the elderly.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Lactose: Products may contain lactose.

Other warnings/precautions:

- Experienced physician: These medications should only be used by physicians who are thoroughly familiar with infertility problems and their management.

- Multiple births: May result from the use of these medications; advise patients of the potential risk of multiple births before starting the treatment.

Pregnancy Risk FactorX
Pregnancy ConsiderationsEctopic pregnancy and congenital abnormalities have been reported. The incidence of congenital abnormality is similar during natural conception.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsAdverse effects may vary according to specific product, route, and/or dosage.

>10%:

Central nervous system: Headache (up to 34%)

Gastrointestinal: Abdominal pain (up to 18%), nausea (up to 12%)

Genitourinary: OHSS (up to 13%, dose related)

Local: Injection site reaction (4% to 12%)

1% to 10%:

Cardiovascular: Flushing

Central nervous system: Dizziness, malaise, migraine

Endocrine & metabolic: Breast tenderness, hot flashes, menstrual irregularities

Gastrointestinal: Abdominal cramping, abdominal fullness, constipation, diarrhea, enlarged abdomen, vomiting

Genitourinary: Ectopic pregnancy, ovarian disease, vaginal hemorrhage

Local: Injection site edema/pain

Neuromuscular & skeletal: Back pain

Respiratory: Cough increased, respiratory disorder

Miscellaneous: Infection, flu-like syndrome

Frequency not defined:

Cardiovascular: Stroke, tachycardia, thrombosis (venous or arterial)

Dermatologic: Angioedema, rash, urticaria

Genitourinary: Adnexal torsion, hemoperitoneum, ovarian enlargement

Neuromuscular & skeletal: Limb necrosis

Respiratory: Acute respiratory distress syndrome, atelectasis, dyspnea, embolism, laryngeal edema pulmonary infarction tachypnea

Miscellaneous: Allergic reaction, anaphylaxis

Drug InteractionsThere are no known significant interactions.

Monitoring ParametershCG levels, serum estradiol; vaginal ultrasound; in cases of suspected OHSS, monitor fluid intake and output, weight, hematocrit, serum and urinary electrolytes, urine specific gravity, BUN and creatinine, and abdominal girth

Nursing: Physical Assessment/MonitoringFemale: Assess knowledge/teach appropriate method for measuring basal body temperature to indicate ovulation. Stress importance of following prescriber's instructions for timing intercourse. If self-administered, assess/teach appropriate injection technique and needle disposal. **Pregnancy risk factor X:** Determine pregnancy status prior to beginning therapy.

Patient EducationSelf injection: Follow prescriber's recommended schedule for injections. Multiple ovulations resulting in multiple pregnancies have been reported. Male infertility and/or breast enlargement may occur. You may experience headache, nausea, abdominal pain, flushing, dizziness, or menstrual irregularities. Report pain at injection site; enlarged breasts (male); respiratory difficulty; nosebleeds; acute abdominal discomfort; abdominal distention; fever; or warmth, swelling, weight gain, pain, or redness in calves.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Menopur®: Follicle stimulating hormone activity 75 int. units and luteinizing hormone activity 75 int. units [packaged with diluent; contains lactose]

Repronex®: Follicle stimulating hormone activity 75 int. units and luteinizing hormone activity 75 int. units [packaged with diluent; contains lactose]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Menopur)

75 unit (1): $73.23

Solution (reconstituted) (Repronex)

75 unit (5): $363.34

Mechanism of ActionActions occur as a result of both follicle stimulating hormone (FSH) effects and luteinizing hormone (LH) effects; menotropins stimulate the development and maturation of the ovarian follicle (FSH), cause ovulation (LH), and stimulate the development of the corpus luteum (LH); in males it stimulates spermatogenesis (LH)

Pharmacodynamics/KineticsExcretion: Urine (~10% as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermshMG; Human Menopausal Gonadotropin

International Brand NamesH.M.G. Organon (ES); HMG (KP); HMG Lepori (ES); HMG Massone[inj.] (AR); Humegon (AR, AT, AU, BF, BJ, CI, DE, ET, GH, GM, GN, GR, HN, IT, KE, KP, LR, LU, MA, ML, MR, MU, MW, NE, NG, PL, RU, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Menogon (FR, HK, KP, PK, PL, SG, TH); Menogon 75 (AE, BH, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Menopur (AE, BH, CH, CY, DK, EG, FI, GB, HK, IE, IL, IQ, IR, JO, KW, LB, LY, NO, OM, PL, PT, QA, SA, SE, SY, TH, TW, YE); Merional (GB); Pergonal (AR, CZ, DE, ES, GR, HN, HR, HU, NL, PL, RU, UY); Pergonal 500 (AE, BE, BG, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Pergonal 75 75 (AT); Preg Norm (IN); Progonadyl (AR)

Mepenzolate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cantil® may be confused with Bentyl®

Pronunciation(me PEN zoe late)

U.S. Brand NamesCantil® [DSC]

Canadian Brand NamesCantil®

Pharmacologic CategoryAnticholinergic Agent; Antispasmodic Agent, Gastrointestinal

Use: Labeled IndicationsAdjunctive treatment of peptic ulcer disease

Dosing: Adults**Peptic ulcer disease:** Oral: 25-50 mg 4 times/day with meals and at bedtime

Dosing: ElderlyRefer to adult dosing.

Administration: OralMay be administered with meals.

Dietary ConsiderationsMay be taken with meals.

ContraindicationsHypersensitivity to mepenzolate or any component of the formulation; angle-closure glaucoma; obstructive uropathy (ie, bladder neck obstruction due to prostatic hyperplasia); obstructive gastrointestinal disease (ie, pyloroduodenal stenosis, achalasia); paralytic ileus; intestinal atony of the debilitated or elderly patient; unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis or toxic megacolon complicating ulcerative colitis; myasthenia gravis; allergic or idiosyncratic reactions of related compounds

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause drowsiness and/or blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Diarrhea: May be a sign of incomplete intestinal obstruction, treatment should be discontinued if this occurs.
- Heat prostration: May occur in the presence of increased environmental temperature; use caution in hot weather and/or exercise.
- Psychosis: Has been reported in patients with an extreme sensitivity to anticholinergic effects or at excessive dosages.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease, tachyarrhythmias, heart failure, or hypertension; evaluate tachycardia prior to administration.
- Gastric ulcer treatment: Use of anticholinergics in gastric ulcer treatment may cause a delay in gastric emptying due to antral statis.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hiatal hernia: Use with caution in patients with hiatal hernia with reflux esophagitis.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Neuropathy: Use with caution in patients with autonomic neuropathy.
- Prostatic hyperplasia: Use with caution in patients with prostatic hyperplasia.
- Renal impairment: Use with caution in patients with renal impairment.
- Ulcerative colitis: Use with caution in patients with ulcerative colitis; may precipitate/aggravate toxic megacolon.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for anticholinergic effects, confusion, and hallucinations.
- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Tartrazine: Tablets contain tartrazine, which may cause allergic reactions in certain individuals.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsMepenzolate may suppress lactation.

Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation, tachycardia

Central nervous system: Headache, nervousness, drowsiness, dizziness, CNS stimulation may be produced with large doses, confusion, insomnia

Dermatologic: Dry skin, urticaria

Gastrointestinal: Constipation, xerostomia, dysphagia, nausea, vomiting, delayed gastric emptying, loss of taste

Genitourinary: Impotence, urinary hesitation, urinary retention

Neuromuscular & skeletal: Weakness

Ophthalmic: Cycloplegia, blurred vision, ocular tension increased, pupil dilation

Miscellaneous: Diaphoresis decreased, hypersensitivity reactions, anaphylaxis, lactation suppressed

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, as bromide: 25 mg [contains tartrazine] [DSC]

Generic AvailableNo

Mechanism of ActionMepenzolate is a postganglionic parasympathetic inhibitor. It decreases gastric acid and pepsin secretion and suppresses spontaneous contractions of the colon.

Pharmacodynamics/Kinetics

Absorption: Oral: Low

Excretion: Urine (3% to 33%); feces

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), dry throat, dysphagia, and loss of taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause confusion, amnesia, drowsiness, nervousness, or insomnia

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive drowsiness or anticholinergic side effects (dry mouth)

Index TermsMepenzolate Bromide

International Brand NamesCantil (GB, SE); Colibantil (IT); Eftoron (JP); Tralanta (JP); Trancolon P (JP)

Meperidine and Promethazine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Mepergan may be confused with meprobamate

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(me PER i deen & proe METH a zeen)

Pharmacologic CategoryAnalgesic Combination (Opioid)

Use: Labeled IndicationsManagement of moderate pain

Dosing: AdultsAnalgesic: Oral: One capsule every 4-6 hours as needed

Dosing: ElderlyRefer to dosing in individual monographs.

Dosing: Renal Impairment**Note:** Repeated use in renal impairment **should be avoided** due to potential accumulation of neuroexcitatory meperidine metabolite.

Dosing: Hepatic ImpairmentIncreased narcotic effect in cirrhosis

RestrictionsC-II

ContraindicationsHypersensitivity to meperidine, promethazine, or any component of the formulation (cross-reactivity between phenothiazines may occur); use with or within 14 days of MAO inhibitors; pregnancy (prolonged use or high doses near term)

Allergy Considerations

- Phenothiazine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines).
- Anticholinergic effects: Phenothiazines may cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); therefore, they should be used with caution in patients with decreased gastrointestinal motility, urinary retention, BPH, xerostomia, or visual problems.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- CNS events: Normeperidine (an active metabolite and CNS stimulant) may accumulate and precipitate anxiety, tremors, or seizures; risk increases with renal dysfunction and cumulative dose.
- Extrapyramidal symptoms: Promethazine may cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia.
- Neuroleptic malignant syndrome (NMS): Promethazine use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity and/or autonomic instability.
- Orthostatic hypotension: Promethazine may cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).
- Temperature regulation: Promethazine may impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- Bone marrow suppression: Use promethazine with caution in patients with bone marrow suppression; leukopenia and agranulocytosis have been reported.
- Cardiovascular disease: Use promethazine with caution in patients with severe cardiovascular disease.
- Drug abuse: Use meperidine with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency

exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Glaucoma: Use promethazine with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.
- Head trauma: Use meperidine with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic disorders.
- Myasthenia gravis: Use promethazine with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.
- Parkinson's disease: Use promethazine with caution in patients with parkinson's disease; may have increased risk of tardive dyskinesia.
- Prolactin-dependent tumors: Use promethazine with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Psychoses: Use with caution in patients with toxic psychoses.
- Renal impairment: Avoid repeated administration of meperidine in patients with renal impairment.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.
- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: Promethazine may mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.
- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Meperidine is not recommended as a drug of first choice for the treatment of chronic pain in the elderly due to the accumulation of normeperidine; for acute pain, its use should be limited to 1-2 doses.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Pregnancy ConsiderationsSee individual agents.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsMeperidine enters breast milk; refer to Meperidine monograph for additional information. Excretion of promethazine is unknown.

Adverse ReactionsSee individual agents.

Metabolism/Transport EffectsPromethazine: **Substrate** (major) of CYP2B6, 2D6; **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Barbiturates: May enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2B6 Inducers (Strong): May increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Strong): May decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Meperidine. This may cause serotonin syndrome. *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Meperidine. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Protease Inhibitors: May enhance the adverse/toxic effect of Meperidine. Protease Inhibitors may decrease the serum concentration of Meperidine. Concentrations of the toxic Normeperidine metabolite may be increased. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: Meperidine hydrochloride 50 mg and promethazine hydrochloride 25 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsules (Meprozine)

50-25 mg (20): $15.55

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Meperidine
- Promethazine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusSedation is common; may cause nervousness or confusion; may rarely produce depression, hallucinations, or paradoxical CNS stimulation
Mental Health: Effects on Psychiatric TreatmentCYP2D6 enzyme substrate; may aggravate the adverse effects of MAO inhibitors, fluoxetine, and other serotonin uptake inhibitors. CNS depressants, tricyclic antidepressants, and phenothiazines may potentiate the effects of meperidine. Phenothiazines inhibit the ability of bromocriptine to lower serum prolactin concentrations; benztropine (and other anticholinergics) may inhibit the therapeutic response to promethazine and excess anticholinergic effects may occur.
Index TermsMepergan; Promethazine and Meperidine

References

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand NamesPamergan P100 (GB)

Meperidine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Avoid the use of meperidine for pain control, especially in elderly and renally-compromised patients (Institute for Safe Medication Practices [ISMP], 2007)

Sound-alike/look-alike issues:

Meperidine may be confused with meprobamate

Demerol® may be confused with Demulen®, Desyrel®, dicumarol, Dilaudid®, Dymelor®, Pamelor®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(me PER i deen)

U.S. Brand NamesDemerol®

Canadian Brand NamesDemerol®

Pharmacologic Category[Analgesic, Opioid]

Use: Labeled IndicationsManagement of moderate-to-severe pain; adjunct to anesthesia and preoperative sedation

Use: Unlabeled/Investigational

Reduce postoperative shivering; reduce rigors from amphotericin

Use: DentalAdjunct in preoperative intravenous conscious sedation in patients undergoing dental surgery; alternate oral narcotic in patients allergic to codeine to treat moderate to moderate-severe pain

Dosing: Adults**Note:** The American Pain Society (2003) and ISMP (2007) do not recommend meperidine’s use as an analgesic. If use in acute pain (in patients without renal or CNS disease) cannot be avoided, treatment should be limited to ≤48 hours and doses should not exceed 600 mg/24 hours.

Pain (analgesic):

Oral: Initial: Opiate-naive: 50 mg every 3-4 hours as needed; usual dosage range: 50-150 mg every 2-4 hours as needed (manufacturers recommendation; oral route is not recommended for acute pain)

I.M., SubQ: Initial: Opiate-naive: 50-75 mg every 3-4 hours as needed; patients with prior opiate exposure may require higher initial doses.

Preoperatively: 50-100 mg given 30-90 minutes before the beginning of anesthesia

Slow I.V.: Initial: 5-10 mg every 5 minutes as needed

Dosing: Elderly**Note:** The American Pain Society (2003) and ISMP (2007) do not recommend meperidine’s use as an analgesic.

Oral: 50 mg every 4 hours

I.M.: 25 mg every 4 hours

Dosing: Pediatric**Note:** The American Pain Society (2003) and ISMP (2007) do not recommend meperidine’s use as an analgesic.

Pain (analgesic): Oral, I.M., I.V., SubQ: Children: 1-1.5 mg/kg/dose every 3-4 hours as needed; 1-2 mg/kg as a single dose preoperative medication may be used; maximum 100 mg/dose. (Oral route is not recommended for acute pain.)

Dosing: Renal Impairment

Avoid use in renal impairment.

Dosing: Hepatic ImpairmentIncreased narcotic effect in cirrhosis; reduction in dose is more important for oral than I.V. route.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Fentanyl Transdermal Conversion
- Opioid Agonist Conversion

Administration: I.V.Meperidine may be administered I.M., SubQ, or I.V. IVP should be given slowly, use of a 10 mg/mL concentration has been recommended. For continuous I.V. infusions, a more dilute solution (eg, 1 mg/mL) should be used.

Administration: I.V. DetailpH: 3.5-6.0 (adjusted)

Administration: OralAdminister syrup diluted in $^1/_2$ glass of water; undiluted syrup may exert topical anesthetic effect on mucous membranes

StorageMeperidine injection should be stored at room temperature; do not freeze. Protect from light. Protect oral dosage forms from light.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, $^1/_2NS$, NS.

Y-site administration: Compatible: Amifostine, amikacin, ampicillin, ampicillin/sulbactam, atenolol, aztreonam, bumetanide, cefamandole, cefazolin, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, chloramphenicol, cisatracurium, cladribine, clindamycin, co-trimoxazole, dexamethasone sodium phosphate, diltiazem, diphenhydramine, dobutamine, docetaxel, dopamine, doxycycline, droperidol, erythromycin lactobionate, etoposide phosphate, famotidine, filgrastim, fluconazole, fludarabine, gatifloxacin, gemcitabine, gentamicin, granisetron, heparin, hydrocortisone sodium succinate, insulin (regular), kanamycin, labetalol, lidocaine, linezolid, magnesium sulfate, melphalan, methyldopate, methylprednisolone sodium succinate, metoclopramide, metoprolol, metronidazole, ondansetron, oxacillin, oxytocin, paclitaxel, penicillin G potassium, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, propranolol, ranitidine, remifentanil, sargramostim, teniposide, thiotepa, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, verapamil, vinorelbine. **Incompatible:** Allopurinol, amphotericin B cholesteryl sulfate complex, cefepime, cefoperazone, doxorubicin liposome, idarubicin, imipenem/cilastatin, minocycline. **Variable (consult detailed reference):** Acyclovir, furosemide, nafcillin.

Compatibility in syringe: Compatible: Atropine, atropine with hydroxyzine, atropine with promethazine, butorphanol, chlorpromazine, cimetidine, dimenhydrinate, diphenhydramine, droperidol, fentanyl, glycopyrrolate, hydroxyzine, ketamine, metoclopramide, midazolam, ondansetron, pentazocine, pentazocine with perphenazine, perphenazine, prochlorperazine edisylate, promazine, promethazine, ranitidine, scopolamine. **Incompatible:** Heparin, morphine, pentobarbital.

Compatibility when admixed: Compatible: Cefazolin, dobutamine, metoclopramide, ondansetron, scopolamine, succinylcholine, triflupromazine, verapamil. **Incompatible:** Aminophylline, amobarbital, floxacillin, furosemide, heparin, morphine, phenobarbital, phenytoin, thiopental. **Variable (consult detailed reference):** Sodium bicarbonate.

RestrictionsC-II

ContraindicationsHypersensitivity to meperidine or any component of the formulation; use with or within 14 days of MAO inhibitors; pregnancy (prolonged use or high doses near term)

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- CNS events: Normeperidine (an active metabolite and CNS stimulant) may accumulate and precipitate anxiety, tremors, or seizures; risk increases with renal dysfunction and cumulative dose.
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic disorders.
- Obesity: Use with caution in patients who are morbidly obese.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Psychoses: Use with caution in patients with toxic psychoses.
- Renal impairment: Avoid use in patients with renal impairment.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.
- Sickle-cell disease: Use is not recommended; increased risk of normeperidine-induced seizures.
- Tachycardias: Use with caution in patients with supraventricular tachycardias.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Avoid use in the elderly.

Dosage form specific issues:

- Sulfites: Some preparations contain sulfites which may cause allergic reaction.

Other warnings/precautions:

- Abuse/misuse/diversion: Healthcare provider should be alert to problems of abuse, misuse, and diversion.

- Acute pain management: Meperidine offers no advantage over other opioids as an analgesic and has unique neurotoxicity. The use of meperidine in this setting should be avoided (American Pain Society [APS], 2003; ISMP, 2007).

- Chronic pain management: Use is not recommended for the management of chronic pain.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsMeperidine is not recommended as a drug of first choice for the treatment of chronic pain in the elderly due to the accumulation of its metabolite, normeperidine, which leads to serious CNS side effects (eg, tremor, seizures). If used for acute pain, its use should be limited to 1-2 doses.
Pregnancy Risk FactorC/D (prolonged use or high doses at term)
Pregnancy ConsiderationsMeperidine is known to cross the placenta, which may result in respiratory or CNS depression in the newborn.
LactationEnters breast milk/contraindicated (AAP rates “compatible”)
Breast-Feeding ConsiderationsMeperidine is excreted in breast milk and may cause CNS and/or respiratory depression in the nursing infant.
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension

Central nervous system: Fatigue, drowsiness, dizziness, nervousness, headache, restlessness, malaise, confusion, mental depression, hallucinations, paradoxical CNS stimulation, increased intracranial pressure, seizure (associated with metabolite accumulation), serotonin syndrome

Dermatologic: Rash, urticaria

Gastrointestinal: Nausea, vomiting, constipation, anorexia, stomach cramps, xerostomia, biliary spasm, paralytic ileus, sphincter of Oddi spasm

Genitourinary: Ureteral spasms, decreased urination

Local: Pain at injection site

Neuromuscular & skeletal: Weakness

Respiratory: Dyspnea

Miscellaneous: Histamine release, physical and psychological dependence

Oncology: VesicantNo
Metabolism/Transport Effects**Substrate** (minor) of CYP2B6, 2C19, 3A4
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Barbiturates: May enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Meperidine. This may cause serotonin syndrome. *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Meperidine. *Risk C: Monitor therapy*

Protease Inhibitors: May enhance the adverse/toxic effect of Meperidine. Protease Inhibitors may decrease the serum concentration of Meperidine. Concentrations of the toxic Normeperidine metabolite may be increased. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol (may increase CNS depression). Watch for sedation.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsIncreased amylase (S), increased BSP retention, increased CPK (I.M. injections)

Monitoring ParametersPain relief, respiratory and mental status, blood pressure; observe patient for excessive sedation, CNS depression, seizures, respiratory depression

Reference RangeTherapeutic: 70-500 ng/mL (SI: 283-2020 nmol/L); Toxic: >1000 ng/mL (SI: >4043 nmol/L)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for additive or adverse interactions. Monitor therapeutic effectiveness and adverse reactions or overdose at beginning of therapy and at regular intervals with long-term use. Monitor frequently for need, may cause physical and/or psychological dependence. For inpatients, implement safety measures. Assess knowledge/teach patient appropriate use (if self-administered), adverse reactions to report, and appropriate interventions to reduce side effects. Discontinue slowly after prolonged use.

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause hypotension, dizziness, drowsiness, impaired coordination, or blurred vision (use caution when driving, climbing stairs, or changing position - rising from sitting or lying to standing, or when engaging in tasks requiring alertness until response to drug is known); loss of appetite, nausea, or vomiting (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help; if unresolved, consult prescriber about use of stool softeners). Report chest pain, slow or rapid heartbeat, acute dizziness or persistent headache; changes in mental status; seizures; swelling of extremities or unusual weight gain; changes in urinary elimination; acute headache; back or flank pain or muscle spasms; blurred vision; skin rash; or shortness of breath. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution, as hydrochloride [ampul]: 25 mg/0.5 mL (0.5 mL); 25 mg/mL (1 mL); 50 mg/mL (1 mL, 1.5 mL, 2 mL); 75 mg/mL (1 mL); 100 mg/mL (1 mL)

Injection, solution, as hydrochloride [prefilled syringe]: 25 mg/mL (1 mL); 50 mg/mL (1 mL); 75 mg/mL (1 mL); 100 mg/mL (1 mL)

Injection, solution, as hydrochloride [for PCA pump]: 10 mg/mL (30 mL, 50 mL [DSC], 60 mL)

Injection, solution, as hydrochloride [vial]: 25 mg/mL (1 mL); 50 mg/mL (1 mL, 30 mL); 75 mg/mL (1 mL); 100 mg/mL (1 mL, 20 mL) [may contain sodium metabisulfite]

Solution, oral, as hydrochloride: 50 mg/5 mL (500 mL)

Syrup, as hydrochloride:

Demerol®: 50 mg/5 mL (480 mL) [contains benzoic acid; banana flavor] [DSC]

Tablet, as hydrochloride: 50 mg, 100 mg

Demerol®: 50 mg, 100 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Meperidine HCl)

50 mg/5 mL (30): $8.99

100 mg/mL (1): $33.99

Tablets (Demerol)

50 mg (30): $45.56

100 mg (20): $54.97

Tablets (Meperidine HCl)

50 mg (20): $18.66

100 mg (20): $26.66

Mechanism of ActionBinds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression

Pharmacodynamics/Kinetics

Onset of action: Analgesic: Oral, SubQ: 10-15 minutes; I.V.: ~5 minutes

Peak effect: SubQ.: ~1 hour; Oral: 2 hours

Duration: Oral, SubQ.: 2-4 hours

Absorption: I.M.: Erratic and highly variable

Distribution: Crosses placenta; enters breast milk

Protein binding: 65% to 75%

Metabolism: Hepatic; hydrolyzed to meperidinic acid (inactive) or undergoes N-demethylation to normeperidine (active; has $^{1}/_{2}$ the analgesic effect and 2-3 times the CNS effects of meperidine)

Bioavailability: ~50% to 60%; increased with liver disease

Half-life elimination:

Parent drug: Terminal phase: Adults: 2.5-4 hours, Liver disease: 7-11 hours

Normeperidine (active metabolite): 15-30 hours; can accumulate with high doses (>600 mg/day) or with decreased renal function

Excretion: Urine (as metabolites)

Related Information

- Narcotic / Opioid Analgesics

Dental Health Professional ConsiderationsMeperidine is not to be used as the narcotic drug of first choice. It is recommended only to be used in codeine-allergic patients when a narcotic analgesic is indicated. Meperidine is not an anti-inflammatory agent. Meperidine, as with other narcotic analgesics, is recommended only for limited acute dosing (ie, 3 days or less); common adverse effects in the dental patient are nausea, sedation, and constipation. Meperidine has a significant addiction liability, especially when given long-term.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause nervousness or confusion; may rarely produce depression, hallucinations, or paradoxical CNS stimulation

Mental Health: Effects on Psychiatric TreatmentSedation is common; may cause nervousness or confusion; may rarely produce depression, hallucinations, or paradoxical CNS stimulation

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) recommend against using meperidine repetitively. The guidelines recommend fentanyl in patients who need immediate pain relief because of its rapid onset of action; fentanyl or hydromorphone is preferred in patients who are hypotensive or have renal dysfunction. Morphine or hydromorphone is recommended for intermittent, scheduled therapy. Both have a longer duration of action requiring less frequent administration.

Index TermsIsonipecaine Hydrochloride; Meperidine Hydrochloride; Pethidine Hydrochloride

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International Brand NamesAlodan "Gerot" (AT); Cluyer (AR); Demero (UY, VE); Demerol HCl (CN, MX, PH); Dolantin (DE); Dolantine (BE); Dolargan (HN); Dolestine (IL); Dolosal (BR); Dolsin (CZ); Lydol (BG); Meperdol (PY); Pethidin (CH); Pethidine (GB, IN, KP, PK); Pethidine Injection (AU); Pethidine Roche (ZA); Pethidine Tablet (NZ); Petidin (DK, NO, SE)

Mephobarbital

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Mephobarbital may be confused with methocarbamol

Mebaral® may be confused with Medrol®, Mellaril®, Tegretol®

Pronunciation(me foe BAR bi tal)

U.S. Brand NamesMebaral®

Canadian Brand NamesMebaral®

Pharmacologic CategoryBarbiturate

Use: Labeled IndicationsSedative; treatment of grand mal and petit mal epilepsy

Dosing: Adults

Epilepsy: Oral: 200-600 mg/day in 2-4 divided doses

Sedation: Oral: 32-100 mg 3-4 times/day

Dosing: ElderlyRefer to adult dosing. Start at lowest recommended doses.

Dosing: Pediatric

Epilepsy: Oral:

Children: 6-12 mg/kg/day in 2-4 divided doses

Sedation: Oral:

Children:

<5 years: 16-32 mg 3-4 times/day

>5 years: 32-64 mg 3-4 times/day

Dosing: Renal ImpairmentUse with caution and reduce dose.

Dietary ConsiderationsHigh doses of pyridoxine may decrease drug effect; barbiturates may increase the metabolism of vitamin D & K; dietary requirements of vitamin D, K, C, B_{12}, folate and calcium may be increased with long-term use.

RestrictionsC-IV

ContraindicationsHypersensitivity to mephobarbital, other barbiturates, or any component of the formulation; pre-existing CNS depression; respiratory depression; severe uncontrolled pain; history of porphyria; pregnancy

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity

Geriatric ConsiderationsUsing barbiturates in the elderly may induce paradoxical stimulation, cause or aggravate depression and confusion. Due to mephobarbital's long half-life and risk of dependence, it is not a drug of choice in the elderly as a sedative/hypnotic. Interpretive guidelines from Centers for Medicare and Medicaid Services (CMS) OBRA regulations discourage the use of barbiturates as sedative/hypnotics in nursing home patients.

Pregnancy Risk FactorD

Adverse Reactions

>10%: Central nervous system: Dizziness, lightheadedness, drowsiness, “hangover” effect

1% to 10%:

Central nervous system: Confusion, mental depression, unusual excitement, nervousness, faint feeling, headache, insomnia, nightmares

Gastrointestinal: Constipation, nausea, vomiting

Metabolism/Transport Effects**Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (major); **Inhibits** CYP2C19 (weak); **Induces** CYP2A6 (weak)

Drug Interactions

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

Griseofulvin: Barbiturates may decrease the absorption of Griseofulvin. *Risk D: Consider therapy modification*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Voriconazole: Barbiturates may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 32 mg, 50 mg, 100 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Mebaral)

32 mg (100): $96.13

50 mg (100): $134.08

100 mg (100): $175.94

Mechanism of ActionIncreases seizure threshold in the motor cortex; depresses monosynaptic and polysynaptic transmission in the CNS

Pharmacodynamics/Kinetics

Onset of action: 20-60 minutes

Duration: 6-8 hours

Absorption: ~50%

Half-life elimination, serum: 34 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and drowsiness are common; may cause confusion, nervousness, depression, nightmares, or insomnia; may rarely cause hallucinations

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may induce hepatic enzymes resulting in an increase or decrease effect of concurrent psychotropic; monitor to altered response

Index TermsMethylphenobarbital

References

Pond SM, Olson KR, Osterloh JD, et al, “Randomized Study of the Treatment of Phenobarbital Overdose With Repeated Doses of Activated Charcoal,” *JAMA*, 1984, 251(23):3104-8. [PubMed 6726981]

Zawada ET, Nappi J, Done G, et al, “Advances in the Hemodialysis Management of Phenobarbital Overdose,” *South Med J*, 1983, 76(1):6-8.[PubMed 6823579]

International Brand NamesMephytaletten (DE); Phemiton (HR); Prominal (AU, ES)

Mepivacaine (Dental)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Mepivacaine may be confused with bupivacaine

Pronunciation(me PIV a kane, DEN tl)

U.S. Brand NamesCarbocaine®; Polocaine®

Canadian Brand NamesPolocaine®

Pharmacologic CategoryLocal Anesthetic

Use: DentalAmide-type anesthetic used for local infiltration anesthesia; injection near nerve trunks to produce nerve block

Dosing: Adults

Dental anesthesia, single site in upper or lower jaw: Infiltration: 54 mg (1.8 mL) as a 3% solution

Infiltration and nerve block of entire oral cavity: 270 mg (9 mL) as a 3% solution; up to a maximum of 6.6 mg/kg of body weight but not to exceed 300 mg per appointment. Manufacturer's maximum recommended dose is not more than 400 mg to normal healthy adults. The effective anesthetic dose varies with procedure, intensity of anesthesia needed, duration of anesthesia required, and physical condition of the patient. Always use the lowest effective dose along with careful aspiration.

Note: Adult and children doses of mepivacaine dental anesthetic cited from USP Dispensing Information (USP DI), 17th ed, The United States Pharmacopeial Convention, Inc, Rockville, MD, 1997, 138-9.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Dental anesthetic: Infiltration and nerve block: Children <10 years: Up to 5-6 mg/kg of body weight; maximum pediatric dosage must be carefully calculated on the basis of patient's weight but must not exceed 270 mg (9 mL) of the 3% solution

Children >10 years; Refer to adult dosing.

Note: Adult and children doses of mepivacaine dental anesthetic cited from USP Dispensing Information (USP DI), 17th ed, The United States Pharmacopeial Convention, Inc, Rockville, MD, 1997, 138-9.

ContraindicationsHypersensitivity to local anesthetics of the amide type or any component of the formulation

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Other warnings/precautions:

• Administration: Aspirate the syringe after tissue penetration and before injection to minimize chance of direct vascular injection.

Pregnancy Risk FactorC

Breast-Feeding ConsiderationsUsual infiltration doses of mepivacaine dental anesthetic given to nursing mothers has not been shown to affect the health of the nursing infant.

Adverse ReactionsDegree of adverse effects in the CNS and cardiovascular system is directly related to the blood levels of local anesthetic.

Cardiovascular: Myocardial effects include a decrease in contraction force as well as a decrease in electrical excitability and myocardial conduction rate resulting in bradycardia and reduction in cardiac output

Central nervous system: High blood levels result in anxiety, restlessness, disorientation, confusion, dizziness, and seizure. This is followed by depression of CNS resulting in somnolence, unconsciousness and possible respiratory arrest. In some cases, symptoms of CNS stimulation may be absent and the primary CNS effects are somnolence and unconsciousness.

Gastrointestinal: Nausea and vomiting may occur

Hypersensitivity reactions: May manifest as dermatologic reactions and edema at injection site. Asthmatic syndromes have occurred.

Neuromuscular & skeletal: Tremors

Psychogenic reactions: It is common to misinterpret psychogenic responses to local anesthetic injection as an allergic reaction. Intraoral injection is perceived by many patients as a stressful procedure in dentistry. Common symptoms to this stress are diaphoresis, palpitation, hyperventilation, generalized pallor and a fainting feeling.

Drug InteractionsNo data reported

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride: 3% (1.8 mL) [dental cartridges]

Generic AvailableNo

Mechanism of ActionLocal anesthetics bind selectively to the intracellular surface of sodium channels to block influx of sodium into the axon. As a result, depolarization necessary for action potential propagation and subsequent nerve function is prevented. The block at the sodium channel is reversible. When drug diffuses away from the axon, sodium channel function is restored and nerve propagation returns.

Pharmacodynamics/Kinetics

Onset of action: Upper jaw: 30-120 seconds; Lower jaw: 1-4 minutes

Duration: Upper jaw: 20 minutes; Lower jaw: 40 minutes

Half-life elimination, serum: 1.9 hours

Dental Health: Effects on Dental TreatmentIt is common to misinterpret psychogenic responses to local anesthetic injection as an allergic reaction. Intraoral injections are perceived by many patients as a stressful procedure in dentistry. Common symptoms to this stress are diaphoresis, palpitations, hyperventilation, generalized pallor, and a fainting feeling.

Degree of adverse effects in the CNS and cardiovascular system is directly related to the blood levels of mepivacaine.

Frequency not defined: Bradycardia and reduction in cardiac output, nausea, vomiting, tremors, asthmatic syndromes, hypersensitivity reactions (may manifest as dermatologic reactions and edema at injection site)

High blood levels: Anxiety, restlessness, disorientation, confusion, dizziness, tremors and seizures, followed by CNS depression resulting in somnolence, unconsciousness and possible respiratory arrest. In some cases, symptoms of CNS stimulation may be absent and the primary CNS effects are somnolence and unconsciousness.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusHigh blood levels may result in anxiety, confusion, disorientation, restlessness, or somnolence

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Ayoub ST and Coleman AE, “A Review of Local Anesthetics,” *Gen Dent*, 1992, 40(4):285-7, 289-90. [PubMed 1397990]

Wynn RL, “Recent Research on Mechanisms of Local Anesthetics,” *Gen Dent*, 1995, 43(4):316-8.[PubMed 8940589]

International Brand NamesPolocaine (CA)

Mepivacaine and Levonordefrin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(me PIV a kane & lee voe nor DEF rin)
U.S. Brand NamesCarbocaine® 2% with Neo-Cobefrin®; Polocaine® Dental with Levonordefrin; Scandonest® 2% L
Canadian Brand NamesPolocaine® 2% and Levonordefrin 1:20,000
Pharmacologic Category[Local Anesthetic]
Use: DentalAmide-type anesthetic used for local infiltration anesthesia; injection near nerve trunks to produce nerve block
Dosing: Adults

Dental (local) anesthetic:

Dental infiltration and nerve block, single site: 36 mg (1.8 mL) of mepivacaine hydrochloride as a 2% solution with levonordefrin 1:20,000

Entire oral cavity: 180 mg (9 mL) of mepivacaine hydrochloride as a 2% solution with levonordefrin 1:20,000; up to a maximum of 6.6 mg/kg of body weight but not to exceed 400 mg of mepivacaine hydrochloride per appointment. The effective anesthetic dose varies with procedure, intensity of anesthesia needed, duration of anesthesia required, and physical condition of the patient. Always use the lowest effective dose along with careful aspiration.

Note: Adult and children doses of mepivacaine hydrochloride with levonordefrin cited from USP Dispensing Information (USP DI), 17th ed, The United States Pharmacopeial Convention, Inc, Rockville, MD, 1997, 139.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Dental (local) anesthetic: Infiltration and nerve block:

Children <10 years: Maximum pediatric dosage must be carefully calculated on the basis of patient's weight but should not exceed 6.6 mg/kg of body weight or 180 mg of mepivacaine hydrochloride as a 2% solution with levonordefrin 1:20,000

Children >10 years: Refer to adult dosing.

Note: Adult and children doses of mepivacaine hydrochloride with levonordefrin cited from USP Dispensing Information (USP DI), 17th ed, The United States Pharmacopeial Convention, Inc, Rockville, MD, 1997, 139.

ContraindicationsHypersensitivity to local anesthetics of the amide-type or any component of the formulation
Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Should be used in minimal amounts in patients with significant cardiovascular problems (because of levonordefrin component).
- Hyperthyroidism: Should be avoided in patients with uncontrolled hyperthyroidism.

Special populations:

- Acutely ill patients: Use with caution in acutely ill; reduce dose consistent with age and physical status.
- Debilitated patients: Use with caution in debilitated patients; reduce dose consistent with age and physical status.
- Elderly: Use with caution in the elderly; reduce dose consistent with age and physical status.
- Pediatrics: Use with caution in children; reduce dose consistent with age and physical status.

Dosage form specific issues:

- Sodium bisulfite: Contains sodium bisulfite which may cause allergic reactions in some individuals.

Other warnings/precautions:

- Administration: Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided.
- Trained personnel: Dental practitioners using local anesthetic agents should be well trained in diagnosis and management of

emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorC

Breast-Feeding ConsiderationsUsual infiltration doses of mepivacaine with levonordefrin given to nursing mothers has not been shown to affect the health of the nursing infant.

Adverse ReactionsDegree of adverse effects in the CNS and cardiovascular system is directly related to the blood levels of mepivacaine. The effects below are more likely to occur after systemic administration rather than infiltration.

Cardiovascular: Myocardial effects include a decrease in contraction force as well as a decrease in electrical excitability and myocardial conduction rate resulting in bradycardia and reduction in cardiac output.

Central nervous system: High blood levels result in anxiety, restlessness, disorientation, confusion, dizziness, and seizure. This is followed by depression of CNS resulting in somnolence, unconsciousness and possible respiratory arrest. In some cases, symptoms of CNS stimulation may be absent and the primary CNS effects are somnolence and unconsciousness.

Gastrointestinal: Nausea and vomiting may occur

Hypersensitivity reactions: Extremely rare, but may be manifest as dermatologic reactions and edema at injection site. Asthmatic syndromes have occurred. Patients may exhibit hypersensitivity to bisulfites contained in local anesthetic solution to prevent oxidation of levonordefrin. In general, patients reacting to bisulfites have a history of asthma and their airways are hyper-reactive to asthmatic syndrome.

Neuromuscular & skeletal: Tremors

Psychogenic reactions: It is common to misinterpret psychogenic responses to local anesthetic injection as an allergic reaction. Intraoral injections are perceived by many patients as a stressful procedure in dentistry. Common symptoms to this stress are diaphoresis, palpitation, hyperventilation, generalized pallor and a fainting feeling.

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Beta-Blockers: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. *Risk D: Consider therapy modification*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Carbocaine® 2% with Neo-Cobefrin®: Mepivacaine hydrochloride 2% and levonordefrin 1:20,000 (1.8 mL) [dental cartridges; contains sodium bisulfite]

Polocaine® Dental with Levonordefrin: Mepivacaine hydrochloride 2% and levonordefrin 1:20,000 (1.8 mL) [dental cartridges; contains sodium metabisulfite]

Scandonest® 2% L: Mepivacaine hydrochloride 2% and levonordefrin 1:20,000 (1.7 mL) [dental cartridges; contains sodium metabisulfite]

Generic AvailableNo

Mechanism of ActionLocal anesthetics bind selectively to the intracellular surface of sodium channels to block influx of sodium into the axon. As a result, depolarization necessary for action potential propagation and subsequent nerve function is prevented. The block at the sodium channel is reversible. When drug diffuses away from the axon, sodium channel function is restored and nerve propagation returns.

Levonordefrin prolongs the duration of the anesthetic actions of mepivacaine by causing vasoconstriction (alpha-adrenergic receptor agonist) of the vasculature surrounding the nerve axons. This prevents the diffusion of mepivacaine away from the nerves resulting in a longer retention in the axon.

Pharmacodynamics/Kinetics

Duration: Upper jaw: 1-2.5 hours; Lower jaw: 2.5-5.5 hours

Infiltration: 50 minutes

Inferior alveolar block: 60-75 minutes

Dental Health: Effects on Dental Treatment It is common to misinterpret psychogenic responses to local anesthetic injection as an allergic reaction. Intraoral injections are perceived by many patients as a stressful procedure in dentistry. Common symptoms to this stress are diaphoresis, palpitations, hyperventilation, generalized pallor and a fainting feeling. Patients may exhibit hypersensitivity to bisulfites contained in local anesthetic solution to prevent oxidation of levonordefrin. In general, patients reacting to bisulfites have a history of asthma and their airways are hyper-reactive to asthmatic syndrome.

Degree of adverse effects in the CNS and cardiovascular system is directly related to the blood levels of mepivacaine (frequency not defined; more likely to occur after systemic administration rather than infiltration): Bradycardia and reduction in cardiac output, nausea, vomiting, tremors, hypersensitivity reactions (extremely rare; may be manifest as dermatologic reactions and edema at injection site), asthmatic syndromes

High blood levels: Anxiety, restlessness, disorientation, confusion, dizziness, and seizures, followed by CNS depression resulting in somnolence, unconsciousness and possible respiratory arrest.

In some cases, symptoms of CNS stimulation may be absent and the primary CNS effects are somnolence and unconsciousness.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status High blood levels may result in anxiety, confusion, disorientation, restlessness, or somnolence

Mental Health: Effects on Psychiatric Treatment Use with tricyclic antidepressants or MAO inhibitors could result in increased pressor response secondary to the levonordefrin component. Use with propranolol could result in serious hypertension and reflex bradycardia.

Index Terms Levonordefrin and Mepivacaine Hydrochloride

References

Ayoub ST and Coleman AE, “A Review of Local Anesthetics,” *Gen Dent*, 1992, 40(4):285-7, 289-90. [PubMed 1397990]

Jastak JT and Yagiela JA, “Vasoconstrictors and Local Anesthesia: A Review and Rationale for Use,” *J Am Dent Assoc*, 1983, 107(4):623-30. [PubMed 6355236]

MacKenzie TA and Young ER, “Local Anesthetic Update,” *Anesth Prog*, 1993, 40(2):29-34. [PubMed 8185087]

Wynn RL, “Epinephrine Interactions With Beta-Blockers,” *Gen Dent*, 1994, 42(1):16, 18. [PubMed 7911769]

Wynn RL, “Recent Research on Mechanisms of Local Anesthetics,” *Gen Dent*, 1995, 43(4):316-8. [PubMed 8940589]

Yagiela JA, “Local Anesthetics,” *Anesth Prog*, 1991, 38(4-5):128-41.[PubMed 1819966]

International Brand Names Polocaine 2% and Levonordefrin 1:20,000 (CA)

Mepivacaine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Mepivacaine may be confused with bupivacaine

Polocaine® may be confused with prilocaine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (epidural administration) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(me PIV a kane)

U.S. Brand NamesCarbocaine®; Polocaine®; Polocaine® Dental; Polocaine® MPF; Scandonest® 3% Plain

Canadian Brand NamesCarbocaine®; Polocaine®

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsLocal or regional analgesia; anesthesia by local infiltration, peripheral and central neural techniques including epidural and caudal blocks; **not** for use in spinal anesthesia

Use: DentalLocal anesthesia by nerve block, infiltration in dental procedures

Dosing: Adults

Injectable local anesthetic: Dose varies with procedure, degree of anesthesia needed, vascularity of tissue, duration of anesthesia required, and physical condition of patient. The smallest dose and concentration required to produce the desired effect should be used.

Maximum dose: 400 mg; do not exceed 1000 mg/24 hours

Cervical, brachial, intercostal, pudenal nerve block: 5-40 mL of a 1% solution (maximum: 400 mg) **or** 5-20 mL of a 2% solution (maximum: 400 mg). For pudenal block, inject $^1/_2$ the total dose each side.

Transvaginal block (paracervical plus pudenal): Up to 30 mL (both sides) of a 1% solution (maximum: 300 mg). Inject $^1/_2$ the total dose each side.

Paracervical block: Up to 20 mL (both sides) of a 1% solution (maximum: 200 mg). Inject $^1/_2$ the total dose to each side. This is the maximum recommended dose per 90-minute procedure; inject slowly with 5 minutes between sides.

Caudal and epidural block (preservative free solutions only): 15-30 mL of a 1% solution (maximum: 300 mg) **or** 10-25 mL of a 1.5% solution (maximum: 375 mg) **or** 10-20 mL of a 2% solution (maximum: 400 mg)

Infiltration: Up to 40 mL of a 1% solution (maximum: 400 mg)

Therapeutic block (pain management): 1-5 mL of a 1% solution (maximum: 50 mg) **or** 1-5 mL of a 2% solution (maximum: 100 mg)

Dental anesthesia:

Single site in upper or lower jaw: 54 mg (1.8 mL) as a 3% solution

Infiltration and nerve block of entire oral cavity: 270 mg (9 mL) as a 3% solution. Manufacturer's maximum recommended dose is not more than 400 mg to normal healthy adults.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Injectable local anesthetic:** Dose varies with procedure, degree of anesthesia needed, vascularity of tissue, duration of anesthesia required, and physical condition of patient. The smallest dose and concentration required to produce the desired effect should be used.

Maximum dose: 5-6 mg/kg; only concentrations <2% should be used in children <3 years or <14 kg (30 lbs)

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Brief exposure up to 40°C (104°F) does not adversely affect the product. Solutions may be sterilized. Dental solutions should be protected from light.

ContraindicationsHypersensitivity to mepivacaine, other amide-type local anesthetics, or any component of the formulation

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS toxicity: Careful and constant monitoring of the patient's state of consciousness should be done following each local anesthetic injection; at such times, restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of CNS toxicity. Treatment is primarily symptomatic and supportive.
- Respiratory arrest: Local anesthetics have been associated with rare occurrences of sudden respiratory arrest.
- Seizures: Convulsions due to systemic toxicity leading to cardiac arrest have also been reported, presumably following unintentional intravascular injection.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Acutely ill patients: Use with caution in acutely ill patients; dose reduction may be required.
- Debilitated patients: Use with caution in debilitated patients; dose reduction may be required.
- Elderly: Use with caution in the elderly; dose reduction may be required.

Dosage form specific issues:

- Preservative-containing solutions: Do not use solutions containing preservatives for caudal or epidural block.

Other warnings/precautions:

- Administration: Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided.
- Test dose: A test dose is recommended prior to epidural administration and all reinforcing doses with continuous catheter technique.
- Trained personnel: Dental practitioners and/or clinicians using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Mepivacaine has been used in obstetrical analgesia.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsDegree of adverse effects in the CNS and cardiovascular system is directly related to the blood levels of mepivacaine, route of administration, and physical status of the patient. The effects below are more likely to occur after systemic administration rather than infiltration.

Cardiovascular: Bradycardia, cardiac arrest, cardiac output decreased, heart block, hyper-/hypotension, myocardial depression, syncope, tachycardia, ventricular arrhythmias

Central nervous system: Anxiety, chills, convulsions, depression, dizziness, excitation, restlessness, tremors

Dermatologic: Angioneurotic edema, diaphoresis, erythema, pruritus, urticaria

Gastrointestinal: Fecal incontinence, nausea, vomiting

Genitourinary: Incontinence, urinary retention

Neuromuscular & skeletal: Paralysis

Ocular: Blurred vision, pupil constriction

Otic: Tinnitus

Respiratory: Apnea, hypoventilation, sneezing

Miscellaneous: Allergic reaction, anaphylactoid reaction

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersVital signs, state of consciousness; signs of CNS toxicity
Nursing: Physical Assessment/MonitoringMonitor for effectiveness of anesthesia and adverse reactions. Monitor for return of sensation. **Oral:** Use caution to prevent gagging or choking and avoid food or drink for 1 hour. Teach patient adverse reactions to report; use and teach appropriate interventions to promote safety.
Patient EducationYou will experience decreased sensation to pain, heat, or cold in the area and/or decreased muscle strength (depending on area of application) until effects wear off; use necessary caution to reduce incidence of possible injury until full sensation returns. Report irritation, pain, burning at injection site; chest pain or palpitations; or respiratory difficulty.

Oral injection: This will cause numbness of your mouth. Do not eat or drink for 1 hour after use. Take small sips of water at first to ensure that you can swallow without difficulty. Your tongue and/or mouth may be numb, use caution to avoid biting yourself. Report irritation, pain, burning at injection site; chest pain or palpitations; or respiratory difficulty.

Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride [contains methylparabens]:

Carbocaine®: 1% (50 mL); 2% (50 mL)

Polocaine®: 1% (50 mL); 2% (50 mL)

Scandonest® 3% Plain: 3% (1.7 mL) [dental cartridge]

Injection, solution, as hydrochloride [preservative free]:

Carbocaine®: 1% (30 mL); 1.5% (30 mL); 2% (20 mL); 3% (1.8 mL) [dental cartridge]

Polocaine® Dental: 3% (1.8 mL) [dental cartridge]

Polocaine® MPF: 1% (30 mL); 1.5% (30 mL); 2% (20 mL)

Generic AvailableNo

Mechanism of ActionMepivacaine is an amide local anesthetic similar to lidocaine; like all local anesthetics, mepivacaine acts by preventing the generation and conduction of nerve impulses

Pharmacodynamics/Kinetics

Onset of action (route and dose dependent): Range: 3-20 minutes

Duration (route and dose dependent): 2-2.5 hours

Protein binding: ~75%

Metabolism: Primarily hepatic via N-demethylation, hydroxylation, and glucuronidation

Half-life elimination: Neonates: 8.7-9 hours; Adults: 1.9-3 hours

Excretion: Urine (95% as metabolites)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Degree of adverse effects in the CNS and cardiovascular system is directly related to blood levels of mepivacaine (frequency not defined; more likely to occur after systemic administration rather than infiltration): Bradycardia, cardiovascular collapse, hypotension, myocardial depression, ventricular arrhythmias, nausea, vomiting, respiratory arrest, anaphylactoid reactions, blurred vision, heart block, transient stinging or burning at injection site

High blood levels: Anxiety, restlessness, disorientation, confusion, dizziness, and seizures, followed by CNS depression resulting in somnolence, unconsciousness, and possible respiratory arrest.

In some cases, symptoms of CNS stimulation may be absent and the primary CNS effects are somnolence and unconsciousness.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause anxiety, restlessness, confusion, drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other Considerations

Local anesthetic toxicity: Cardiac arrest: Lipid infusion has been used in animal studies and several human cases (Bupivacaine: Rosenblatt, 2006; Levobupivacaine: Foxall, 2007; Ropivacaine: Litz, 2006) where cardiovascular toxicity, unresponsive to conventional resuscitation, resulted. Additional information is available at http://www.lipidrescue.org. The protocol from the website is: **20% Fat Emulsion:** 1.5 mL/kg administered over 1 minute, followed immediately by an infusion of 0.25 mL/kg/minute. Continue chest compressions (lipid must circulate). Repeat bolus every 3-5 minutes up to 3 mL/kg total dose until circulation restored. Continue infusion until hemodynamic stability is restored. Increase the infusion rate to 0.5 mL/kg/minute if BP declines. A maximum total dose of 8 mL/kg is recommended.

Index TermsMepivacaine Hydrochloride

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Litz RJ, Popp M, Stehr SN, et al, "Successful Resuscitation of a Patient With Ropivacaine-Induced Asystole After Axillary Plexus Block Using Lipid Infusion," *Anaesthesia*, 2006, 61(8):800-1.[PubMed 16867094]

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International Brand NamesCarbocain (DK, FI, SE); Carbocain Dental (NO); Carbocaina (IT); Carbocaine Dental (PL, ZA); Carbocaine HCl (FR); Isocaine 3% (IL); Lentocaine (MX); Meaverin (DE); Mepicaton 3% (TH); Mepidont (PL); Mepigobbi (AR); Mepivastesin (CZ, HK, IL, PL); Scandicain (AT, CH); Scandicaine (BE, LU, NL); Scandinibsa (ES, PT); Scandonest (AU, BG, EE); Scandonest Sans Vasoconstricteur (PL)

Meprobamate and Aspirin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(me proe BA mate & AS pir in)

U.S. Brand NamesEquagesic®

Canadian Brand Names292 MEP®

Pharmacologic CategoryAntianxiety Agent, Miscellaneous; Salicylate

Use: Labeled IndicationsAdjunct to the short-term treatment of pain in patients with skeletal-muscular disease exhibiting tension and/or anxiety

Dosing: Adults**Pain with muscular disorders/anxiety (adjunct):** Oral: 1-2 tablet 3-4 times/day for up to 10 days

Dosing: ElderlyRefer to adult dosing and dosing in individual agents; use with caution.

Dosing: Pediatric

Pain with muscular disorders/anxiety (adjunct): Oral: Children ≥12 years: Refer to adult dosing.

Dietary ConsiderationsMay be taken with food to minimize GI upset.

RestrictionsC-IV

ContraindicationsHypersensitivity to aspirin, meprobamate, carisoprodol, NSAIDs, other related compounds, or any component of the formulation; acute intermittent porphyria; asthma; rhinitis; nasal polyps; children or teenagers for viral infections (chickenpox or flu symptoms), with or without fever, due to a potential association with Reye's syndrome; pregnancy, breast-feeding

Allergy Considerations

- Salicylate Allergy/Sensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Allergic reactions: May occur in patients with history of dermatological condition (usually by fourth dose).
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Salicylate sensitivity: Patients with sensitivity to tartrazine dyes, nasal polyps, and asthma may have an increased risk of salicylate sensitivity.
- Tinnitus: Discontinue use if tinnitus or impaired hearing occurs.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Bleeding disorders: Use with caution in patients with platelet and bleeding disorders.
- Depression: Use with caution in patients with depression or suicidal tendencies.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Ethanol use: Heavy ethanol use (>3 drinks/day) can increase bleeding risks.
- Gastrointestinal disease: Use with caution in patients with erosive gastritis or peptic ulcer disease.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Renal impairment: Use with caution in patients with renal impairment.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly.
- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Abrupt discontinuation: May precipitate withdrawal.

Also refer to individual agents.

Pregnancy Risk FactorX
Pregnancy ConsiderationsSee indiivudal agents.
LactationEnters breast milk/contraindicated
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsAspirin: **Substrate** of CYP2C9 (minor)
Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Yohimbine: May diminish the therapeutic effect of Antianxiety Agents. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Equagesic®: Meprobamate 200 mg and aspirin 325 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Equagesic)

200-325 mg (30): $62.70

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Aspirin
- Meprobamate

Dental Health Professional ConsiderationsThere is no scientific evidence to warrant discontinuance of aspirin prior to dental surgery. Patients taking one aspirin tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with the physician before removal of the aspirin relative to prevention of postoperative bleeding.

The Food and Drug Administration (FDA), has issued a letter updating information and considerations regarding the use of ibuprofen (400 mg doses) in patients who are taking low dose aspirin (81 mg, immediate release; not enteric coated) for cardioprotection and stroke prevention. Ibuprofen, at these doses, may interfere with aspirin's antiplatelet effect depending upon when it is administered. Patients initiated on aspirin first (for ~1 week) then ibuprofen (400 mg 3 times/day for 10 days) seem to maintain aspirin's platelet effect (Cryer B, 2005). Ibuprofen has the greatest impact on aspirin if administered less than 8 hours before aspirin (Catella-Lawson F, 2001).

Patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. With occasional use of ibuprofen, a clinically-significant interaction with aspirin in unlikely. To avoid interference during chronic dosing, a single dose of ibuprofen should be taken 30-120 minutes after aspirin ingestion or at least 8 hours should elapse after ibuprofen dosing before giving aspirin (FDA, 2006; Catella-Lawson F, 2001).

The clinical implications of the interaction are unclear. There have not been any clinical endpoint studies conducted at this time. Avoidance of this interaction is potentially important because aspirin's vascular protection could be decreased or negated.

Other nonselective NSAIDs may have potential for a similar interaction with aspirin. Such has been described with naproxen (Capone ML, 2005). Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin. Other clinical scenarios (use of smaller ibuprofen doses, other aspirin products, other doses of aspirin) have not been evaluated.

Additional information is available at: http://www.fda.gov/cder/drug/infopage/aspirin/default.htm

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Aspirin: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity (see Dental Comment).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusSedation is common
Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; may displace valproic acid from binding sites resulting in an increase of unbound drug; monitor for toxicity; meprobamate is a CNS depressant; monitor for

additive effects with concurrent psychotropic use

Index Terms Aspirin and Meprobamate

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Forbes JA, Butterworth GA, Burchfield WH, et al, “Evaluation of Ketorolac, Aspirin, and an Acetaminophen-Codeine Combination in Postoperative Oral Surgery Pain,” *Pharmacotherapy*, 1990, 10(6 Pt 2):77S-93S. [PubMed 2082317]

Forbes JA, Keller CK, Smith JW, et al, “Analgesic Effect of Naproxen Sodium, Codeine, a Naproxen-Codeine Combination and Aspirin on the Postoperative Pain of Oral Surgery,” *Pharmacotherapy*, 1986, 6(5):211-8.[PubMed 3540871]

International Brand Names 292 MEP (CA)

Meprobamate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Meprobamate may be confused with Mepergan, meperidine

Equanil may be confused with Elavil®

Pronunciation(me proe BA mate)
U.S. Brand NamesMiltown® [DSC]
Canadian Brand NamesNovo-Mepro
Pharmacologic CategoryAntianxiety Agent, Miscellaneous
Use: Labeled IndicationsManagement of anxiety disorders
Use: Unlabeled/InvestigationalDemonstrated value for muscle contraction, headache, premenstrual tension, external sphincter spasticity, muscle rigidity, opisthotonos-associated with tetanus
Use: DentalTreatment of muscle spasm associated with acute temporomandibular joint (TMJ) pain; management of dental anxiety disorders
Dosing: Adults**Anxiety:** Oral: 400 mg 3-4 times/day, up to 2400 mg/day
Dosing: ElderlyOral (use lowest effective dose): Initial: 200 mg 2-3 times/day
Dosing: Pediatric**Anxiety:** Oral: 6-12 years: 100-200 mg 2-3 times/day
Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer every 9-12 hours.

Cl_{cr} <10 mL/minute: Administer every 12-18 hours.

Moderately dialyzable (20% to 50%)

Dosing: Hepatic ImpairmentProbably necessary in patients with liver disease; no specific recommendations.
Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

RestrictionsC-IV
ContraindicationsHypersensitivity to meprobamate, related compounds (including carisoprodol), or any component of the formulation; acute intermittent porphyria; pre-existing CNS depression; narrow-angle glaucoma; severe uncontrolled pain; pregnancy
Warnings/Precautions

Concerns related to adverse effects:

- Allergic reactions: May occur in patients with history of dermatological condition (usually by fourth dose).
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Depression: Use with caution in patients with depression or suicidal tendencies.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may cause confusion, cognitive impairment, or excessive sedation.

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Other warnings/precautions:

- Abrupt discontinuation: May precipitate withdrawal.

Geriatric ConsiderationsMeprobamate is not considered a drug of choice in the elderly because of its potential to cause physical and psychological dependence. Interpretive guidelines from the Centers for Medicare and Medicaid Services (CMS) strongly discourage the use of meprobamate in residents of long-term care facilities.
Pregnancy Risk FactorD
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsBreast milk concentrations are higher than plasma; effects are unknown.
Adverse ReactionsFrequency not defined.

Cardiovascular: Syncope, peripheral edema, palpitation, tachycardia, arrhythmia

Central nervous system: Drowsiness, ataxia, dizziness, paradoxical excitement, confusion, slurred speech, headache, euphoria, chills, vertigo, paresthesia, overstimulation

Dermatologic: Rashes, purpura, dermatitis, Stevens-Johnson syndrome, petechiae, ecchymosis

Gastrointestinal: Diarrhea, vomiting, nausea

Hematologic: Leukopenia, eosinophilia, agranulocytosis, aplastic anemia

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision, impairment of accommodation

Renal: Renal failure

Respiratory: Wheezing, dyspnea, bronchospasm, angioneurotic edema

Drug Interactions

Yohimbine: May diminish the therapeutic effect of Antianxiety Agents. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersMental status
Reference RangeTherapeutic: 6-12 mcg/mL (SI: 28-55 µmol/L); Toxic: >60 mcg/mL (SI: >275 µmol/L)
Nursing: Physical Assessment/MonitoringAssess other medications the patient may be taking for effectiveness and interactions. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance; periodically evaluate need for continued use. Monitor therapeutic effectiveness and adverse reactions or overdose at beginning of therapy and periodically with long-term use. Monitor for CNS depression. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Patient EducationTake exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. Do not use alcohol or other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea (boiled milk, yogurt, or buttermilk may help). Report persistent CNS effects, skin rash or irritation, changes in urinary pattern, wheezing or respiratory difficulty, or worsening of condition. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: 200 mg, 400 mg [DSC]

Miltown®: 200 mg, 400 mg [DSC]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Miltown)

200 mg (30): $69.83

Mechanism of ActionAffects the thalamus and limbic system; also appears to inhibit multineuronal spinal reflexes
Pharmacodynamics/Kinetics

Onset of action: Sedation: ~1 hour

Distribution: Crosses placenta; enters breast milk

Metabolism: Hepatic

Half-life elimination: 10 hours

Excretion: Urine (8% to 20% as unchanged drug); feces (10% as metabolites)

Pharmacotherapy PearlsWithdrawal should be gradual over 1-2 weeks. Benzodiazepine and buspirone are better choices for treatment of anxiety disorders.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Anesthesia and Critical Care Concerns/Other ConsiderationsWithdrawal should be gradual over 1-2 weeks. Benzodiazepines and buspirone are better choices for treatment of anxiety disorders.

Index TermsEquanil

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International Brand NamesAndaxin (HN, HU); Ansiowas (ES); Centryl (TW); Dapaz (ES); Ecuanil (UY); Epikur (AT); Equanil (AU, FR, GB, IE, ZA); Koligin (TW); Meprate (GB); Mepro (BE, IL); Meprobamat (DE, GB, HR); Meprobamate Richard (FR); Meprodil (CH); Meprospan (ES); Miltaun (AT); Miltown (ES); Oasil (ES, LU); Oasil Simes (ES); Pertranquil (AT, BE, LU); Praol (GR); Probamato (PT); Probamyl (BE); Procalmadiol (BE, LU); Quaname (BE, LU); Quanil (IT); Reposo-Mono (BE); Restenil (DK, NO); Sanobamat (BE); Sedans Tranquilizante (ES); Tranquilin (LU); Visano (DE)

Mequinol and Tretinoin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(ME kwi nole & TRET i noyn)

U.S. Brand NamesSolagé®

Canadian Brand NamesSolagé®

Pharmacologic CategoryRetinoic Acid Derivative; Vitamin A Derivative; Vitamin, Topical

Use: Labeled IndicationsTreatment of solar lentigines; the efficacy of using Solagé® daily for >24 weeks has not been established

Dosing: Adults**Solar lentigines:** Topical: Apply twice daily to solar lentigines using the applicator tip while avoiding application to the surrounding skin. Separate application by at least 8 hours or as directed by physician.

Dosing: ElderlyRefer to adult dosing.

Administration: TopicalUse applicator tip. Avoid application to surrounding skin, eyes, mouth, paranasal creases, or mucous membranes.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from light; store in original carton. Flammable, keep away from heat and open flame.

ContraindicationsHypersensitivity to mequinol, tretinoin, or any component of the formulation; pregnancy, women of childbearing potential

Allergy Considerations

- Retinoid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity: Discontinue if hypersensitivity is noted.
- Photosensitivity: Avoid sun (including sun lamps) or use protective clothing. Do not use in sunburned patients until they have fully recovered. Use extreme caution in patients who have significant exposure to the sun through their occupation. Not to be taken with photosensitizing drugs (eg, thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides).
- Skin irritation: May cause irritation, erythema, burning, stinging, tingling, peeling and/or pruritus; may cause severe irritation of eczematous skin.

Disease-related concerns:

- Eczema: Use extreme caution in eczematous skin conditions.
- Moderately/heavily pigmented skin: Safety and efficacy have not been established in moderately or heavily pigmented skin.
- Vitiligo: Use with caution in patients with history or family history of vitiligo.

Special populations:

- Pediatrics: Do not use in children.

Other warnings/precautions:

- Appropriate use: For external use only; no bathing or showering for at least 6 hours after application. Avoid application to the eyes, mouth, paranasal creases, and mucous membranes.
- Chronic use: Effects of chronic use (>52 weeks) are unknown.
- Weather extremes: Wind and cold may be irritating.

Pregnancy Risk FactorX

Pregnancy ConsiderationsMay cause fetal harm when administered to a pregnant woman.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Dermatologic: Erythema (41%), burning, stinging or tingling (18%), desquamation (12%), pruritus (10%)

1% to 10%: Dermatologic: Skin irritation (6%), halo hypopigmentation (6%), hypopigmentation (4%), skin discomfort (4%), dry skin (3%), crusting (2%), dermatitis (2%), rash (2%), vesicular bullae rash (1%), contact allergic reaction (1%), irritant dermatitis (1%)

Metabolism/Transport EffectsTretinoin: **Substrate** (minor) of CYP2A6, 2B6, 2C8/9; **Inhibits** CYP2C8/9 (weak); **Induces** CYP2E1 (weak)

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersIf patient experiences significant local irritation (redness, burning, stinging, peeling, or itching) then direct patient to use less medication, decrease frequency of use, discontinue temporarily, or discontinue altogether.

Nursing: Physical Assessment/Monitoring

See individual agent for Tretinoin (Topical).

Patient Education

See individual agent for Tretinoin (Topical).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, topical:

Solagé®: Mequinol 2% and tretinoin 0.01% (30 mL) [contains alcohol 78%; dispensed in applicator bottle]

Generic AvailableNo
ManufacturerContract Pharmaceutical Laboratories
Pricing: U.S. (www.drugstore.com)

Solution (Solage)

2-0.01% (30): $168.67

Mechanism of ActionSolar lentigines are localized, pigmented, macular lesions of the skin on areas of the body chronically exposed to the sun. Mequinol is a substrate for the enzyme tyrosinase and acts as a competitive inhibitor of the formation of melanin precursors. The mechanisms of depigmentation for both drugs is unknown.
Pharmacodynamics/Kinetics

Absorption: Percutaneous absorption was 4.4% of tretinoin when applied as 0.8 mL of Solagé® to a 400 cm^2 area of the back

Time to peak: Mequinol: 2 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentPhotosensitizing drugs such as psychotropics can further increase sun sensitivity; avoid concurrent use
Index TermsSolage; Tretinoin and Mequinol
International Brand NamesSolagé® (CA)

Mercaptopurine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Purinethol® may be confused with propylthiouracil

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

To avoid potentially serious dosage errors, the terms “6-mercaptopurine” or “6-MP” should be avoided; use of these terms has been associated with sixfold overdosages.

Azathioprine is metabolized to mercaptopurine; concurrent use of these commercially-available products has resulted in profound myelosuppression.

Pronunciation(mer kap toe PYOOR een)

U.S. Brand NamesPurinethol®

Canadian Brand NamesPurinethol®

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite; Immunosuppressant Agent

Use: Labeled IndicationsTreatment (maintenance and induction) of acute lymphoblastic leukemia (ALL)

Use: Unlabeled/InvestigationalSteroid-sparing agent for corticosteroid-dependent Crohn’s disease (CD) and ulcerative colitis (UC); maintenance of remission in CD; fistulizing Crohn’s disease

Dosing: Adults Refer to individual protocols.

ALL:

Induction: Oral: 2.5-5 mg/kg/day (100-200 mg)

Maintenance: Oral: 1.5-2.5 mg/kg/day **or** 80-100 mg/m^2/day given once daily

Note: In ALL, administration in the evening (vs morning administration) may lower the risk of relapse.

Reduction of steroid use in CD or UC, maintenance of remission in CD or fistulizing disease (unlabeled uses): Oral: Initial: 50 mg daily; may increase by 25 mg/day every 1-2 weeks as tolerated to target dose of 1-1.5 mg/kg/day

Dosage adjustment with concurrent allopurinol: Reduce mercaptopurine dosage to $^1/_4$ to $^1/_3$ the usual dose.

Dosage adjustment in TPMT-deficiency: Not established; substantial reductions are generally required only in homozygous deficiency.

Dosing: ElderlyDue to renal decline with age, start with lower recommended doses for adults.

Dosing: Pediatric**ALL:** Refer to individual protocols: Oral:

Induction: 2.5-5 mg/kg/day **or** 70-100 mg/m^2/day given once daily

Maintenance: 1.5-2.5 mg/kg/day **or** 50-75 mg/m^2/day given once daily

Note: In ALL, administration in the evening (vs morning administration) may lower the risk of relapse.

Dosing: Renal ImpairmentThe FDA-approved labeling recommends starting with reduced doses in patients with renal impairment to avoid accumulation; however, specific guidelines are not available. The following guidelines have been used by some clinicians (Aronoff, 2007): Children:

Cl_{cr} <50 mL/minute: Administer every 48 hours

Hemodialysis: Administer every 48 hours

Continuous ambulatory peritoneal dialysis (CAPD): Administer every 48 hours

Continuous renal replacement therapy (CRRT): Administer every 48 hours

Dosing: Hepatic ImpairmentThe FDA-approved labeling recommends considering a reduced dose in patients with hepatic impairment; however, specific guidelines are not available.

Dosing: Combination Regimens

Leukemia, acute lymphocytic:

Hyper-CVAD (Leukemia, Acute Lymphocytic)

MTX/6-MP/VP (Maintenance)

POMP

PVA (POG 8602)

Leukemia, acute promyelocytic: Tretinoin-Idarubicin

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: OralPreferably on an empty stomach (1 hour before or 2 hours after meals)
Dietary ConsiderationsShould not be administered with meals.
StorageStore at room temperature of 15°C to 25°C (59°F to 77°F). Protect from moisture.
Extemporaneously PreparedA 50 mg/mL oral suspension can be prepared by crushing thirty 50 mg tablets in a mortar, and then mixing in a small amount of vehicle (a 1:1 combination of methylcellulose 1% and syrup) to create a uniform paste. Add a sufficient quantity of vehicle to make 30 mL of suspension. Label “shake well.” Room temperature stability is 14 days.

Dressman JB and Poust RI, “Stability of Allopurinol and of Five Antineoplastics in Suspension,” *Am J Hosp Pharm*, 1983, 40:616-8.

Nahata MC, Morosco RS, and Hipple TF, 4th ed, *Pediatric Drug Formulations*, Cincinnati, OH: Harvey Whitney Books Co, 2000.

ContraindicationsHypersensitivity to mercaptopurine or any component of the formulation; patients whose disease showed prior resistance to mercaptopurine or thioguanine; severe liver disease, severe bone marrow suppression; pregnancy
Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Hepatotoxicity: May occur; use with caution with other hepatotoxic drugs or in dosages >2.5 mg/kg/day.
- Infection: Common signs of infection, such as fever and leukocytosis may not occur; lethargy and confusion may be more prominent signs of infection.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with prior bone marrow suppression.
- Thiopurine methyltransferase deficiency: Patients with genetic deficiency of thiopurine methyltransferase (TPMT) may be sensitive to myelosuppressive effects.

Concurrent drug therapy issues:

- Azathioprine: Because azathioprine is metabolized to mercaptopurine, concomitant use with azathioprine may result in profound myelosuppression and should be avoided.
- TPMT or xanthine oxidase inhibitors: Patients on concurrent therapy with drugs which may inhibit TPMT (eg, olsalazine) or xanthine oxidase (eg, allopurinol) may be sensitive to myelosuppressive effects.

Other warnings/precautions:

- Error-prone terms: To avoid potentially serious dosage errors, the terms “6-mercaptopurine” or “6-MP” should be avoided; use of these terms has been associated with sixfold overdosages.
- Vaccines: Immune response to vaccines may be diminished.

Geriatric ConsiderationsToxicity to immunosuppressives is increased in the elderly. Start with lowest recommended adult doses. Signs of infection, such as fever and WBC rise, may not occur. Lethargy and confusion may be more prominent signs of infection.
Pregnancy Risk FactorD
LactationEnters breast milk/contraindicated
Adverse Reactions

>10%:

Hematologic: Myelosuppression; leukopenia, thrombocytopenia, anemia

Onset: 7-10 days

Nadir: 14-16 days

Recovery: 21-28 days

Hepatic: Intrahepatic cholestasis and focal centralobular necrosis (40%), characterized by hyperbilirubinemia, increased alkaline phosphatase and AST, jaundice, ascites, encephalopathy; more common at doses >2.5 mg/kg/day. Usually occurs within 2 months of therapy but may occur within 1 week, or be delayed up to 8 years.

1% to 10%:

Central nervous system: Drug fever

Dermatologic: Hyperpigmentation, rash

Endocrine & metabolic: Hyperuricemia

Gastrointestinal: Nausea, vomiting, diarrhea, stomatitis, anorexia, stomach pain, mucositis

Renal: Renal toxicity

<1%: Alopecia, dry and scaling rash, glossitis, oligospermia, tarry stools, eosinophilia

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

5-ASA Derivatives: May decrease the metabolism of Thiopurine Analogs. *Risk C: Monitor therapy*

Allopurinol: May decrease the metabolism of Mercaptopurine. *Risk D: Consider therapy modification*

AzaTHIOprine: May enhance the myelosuppressive effect of Mercaptopurine. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Mercaptopurine may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Monitoring ParametersCBC with differential and platelet count, liver function tests, uric acid, urinalysis; TPMT genotyping may identify individuals at risk for toxicity

For use as immunomodulatory therapy in CD or UC, monitor CBC with differential weekly for 1 month, then biweekly for 1 month, followed by monitoring every 1-2 months throughout the course of therapy. LFTs should be assessed every 3 months.

Nursing: Physical Assessment/MonitoringDo not use the terms "6-mercaptopurine" or "6-MP" when writing prescriptions; use of these terms has been associated with sixfold overdosage. Assess potential for interactions with other pharmacological agents patient may be taking (increased potential for liver toxicity or mercaptopurine toxicity). Assess results of laboratory tests, therapeutic response, and adverse reactions (eg, hepatic function, jaundice, ascites, encephalopathy can occur some time following therapy; nutritional status, dehydration; myelosuppression, anemia, leukopenia; and renal status) on a regular basis throughout therapy. Teach patient proper use, possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report.
Monitoring: Lab TestsCBC with differential, platelet count, liver function, uric acid, renal function

For use as immunomodulatory therapy in CD or UC, monitor CBC with differential weekly for 1 month, then biweekly for 1 month, followed by monitoring every 1-2 months throughout the course of therapy. LFTs should be assessed every 3 months.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take daily dose at the same time each day. Preferable to take an on empty stomach, 1 hour before or 2 hours after meals. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea and vomiting, diarrhea, or loss of appetite (small, frequent meals may help/request medication); weakness or lethargy (use caution when driving or engaging in tasks that require alertness until response to drug is known); mouth sores; or headache (consult prescriber for approved medications). Report signs of persistent fever; opportunistic infection (eg, fever, chills, sore throat, burning urination, fatigue); bleeding (eg, tarry stools, easy bruising); unresolved mouth sores; nausea or vomiting; swelling of extremities; respiratory difficulty; unusual weight gain; or changes in urinary pattern. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet [scored]: 50 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Mercaptopurine)

50 mg (30): $92.99

Tablets (Purinethol)

50 mg (30): $150.13

Mechanism of ActionPurine antagonist which inhibits DNA and RNA synthesis; acts as false metabolite and is incorporated into DNA and RNA, eventually inhibiting their synthesis; specific for the S phase of the cell cycle

Pharmacodynamics/Kinetics

Absorption: Variable and incomplete (16% to 50%)

Distribution: V_d = total body water; CNS penetration is poor

Protein binding: 19%

Metabolism: Hepatic and in GI mucosa; hepatically via xanthine oxidase and methylation via TPMT to sulfate conjugates, 6-thiouric acid, and other inactive compounds; first-pass effect

Half-life elimination (age dependent): Children: 21 minutes; Adults: 47 minutes

Time to peak, serum: ~2 hours

Excretion: Urine (46% as mercaptopurine and metabolites)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis and mucositis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine or carbamazepine

Index Terms6-Mercaptopurine (error-prone abbreviation); 6-MP (error-prone abbreviation); NSC-755

References

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Lennard L, “The Clinical Pharmacology of 6-Mercaptopurine,” *Eur J Clin Pharmacol*, 1992, 43(4):329-39. [PubMed 1451710]

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Mosesso P and Palitti F, "The Genetic Toxicology of 6-Mercaptopurine," *Mutat Res*, 1993, 296(3):279-94.[PubMed 7680107]

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Sandborn WJ, “A Review of Immune Modifier Therapy for Inflammatory Bowel Disease: Azathioprine, 6-mercaptopurine, Cyclosporine, and Methotrexate,” *Am J Gastroenterol*, 1996, 91(3):423-33.[PubMed 8633486]

Van Scoik KG, Johnson CA, and Porter WR, “The Pharmacology and Metabolism of the Thiopurine Drugs 6-Mercaptopurine and Azathioprine,” *Drug Metab Rev*, 1985, 16(1-2):157-74. [PubMed 3905317]

Zimm S, Ettinger LJ, Holcenberg JS, et al, “Phase I and Clinical Pharmacological Study of Mercaptopurine Administered as a Prolonged Intravenous Infusion,” *Cancer Res*, 1988, 45(4):1869-73.[PubMed 4038917]

International Brand NamesEmpurine (PH, TH); Mercaptopurina Wellcome (ES); Mercaptopurinum (PL); Merkaptopurin (TW); Merpurine (TW); Puri-Nethol (AE, AT, BE, BF, BG, BH, BJ, BR, CH, CI, CY, CZ, DE, EE, EG, ET, FI, GB, GH, GM, GN, HK, HR, ID, IE, IL, IN, IQ, IR, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NO, NZ, OM, PY, QA, SA, SC, SD, SE, SL, SN, SY, TH, TN, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Purinethol (AR, AU, CN, FR, GR, IT, MX, NL, PH, PL, RU); Purinetone (PK); Varimer (PE)

Meropenem

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Meropenem may be confused with ertapenem, imipenem, metronidazole.

Pronunciation(mer oh PEN em)
U.S. Brand NamesMerrem® I.V.
Canadian Brand NamesMerrem®
Pharmacologic CategoryAntibiotic, Carbapenem
Use: Labeled IndicationsTreatment of intra-abdominal infections (complicated appendicitis and peritonitis); treatment of bacterial meningitis in pediatric patients ≥3 months of age caused by *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*; treatment of complicated skin and skin structure infections caused by susceptible organisms
Use: Unlabeled/Investigational*Burkholderia pseudomallei* (melioidosis), febrile neutropenia, liver abscess, meningitis (adults), otitis externa, pneumonia, urinary tract infections
Dosing: Adults

Burkholderia pseudomallei*(melioidosis) (unlabeled use),*Pseudomonas: 1 g every 8 hours

Cholangitis, intra-abdominal infections: 1 g every 8 hours

Febrile neutropenia, otitis externa, pneumonia (unlabeled uses): 1 g every 8 hours

Liver abscess (unlabeled use): I.V.: 1 g every 8 hours for 2-3 weeks, then oral therapy for duration of 4-6 weeks

Meningitis (unlabeled use): 2 g every 8 hours

Mild-to-moderate infection, other severe infections (unlabeled use): 1.5-3 g/day divided every 8 hours

Skin and skin structure infections (complicated): I.V.: 500 mg every 8 hours; diabetic foot: 1 g every 8 hours

Urinary tract infections, complicated (unlabeled use): I.V.: 500 mg to 1 g every 8 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Febrile neutropenia (unlabeled use): I.V.:

Children ≥3 months (<50 kg): 20 mg/kg every 8 hours (maximum dose: 1 g every 8 hours)

Children >50 kg: Refer to adult dosing.

Intra-abdominal infections: I.V.:

Children ≥3 months (<50 kg): 20 mg/kg every 8 hours (maximum dose: 1 g every 8 hours)

Children >50 kg: 1 g every 8 hours

Meningitis: I.V.: Children ≥3 months (<50 kg): 40 mg/kg every 8 hours (maximum dose: 2 g every 8 hours)

Skin and skin structure infections (complicated): I.V.:

Children ≥3 months (<50 kg): 10 mg/kg every 8 hours (maximum dose: 500 mg every 8 hours)

Children >50 kg: Refer to adult dosing.

Dosing: Renal Impairment
Cl_{cr} 26-50 mL/minute: Administer recommended dose based on indication every 12 hours

Cl_{cr} 10-25 mL/minute: Administer one-half recommended dose based on indication every 12 hours

Cl_{cr} <10 mL/minute: Administer one-half recommended dose based on indication every 24 hours

Dialysis: Meropenem and its metabolites are readily dialyzable; administer dose after dialysis

Continuous renal replacement therapy (CRRT): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH or CVVHD/CVVHDF: 1 g every 12 hours to achieve target trough of ~ 4 mg/L; 500 mg every 12 hours may be considered for highly sensitive organisms. **Note:** Substantial variability exists in various published recommendations, ranging from 1-3 g/day given in 2-3 divided doses.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Administer I.V. infusion over 15-30 minutes; I.V. bolus injection over 3-5 minutes.
Administration: I.V. DetailpH: 7.3-8.3
Dietary Considerations1 g of meropenem contains 90.2 mg of sodium as sodium carbonate (3.92 mEq)
Storage Dry powder should be stored at controlled room temperature 20°C to 25°C (68°F to 77°F).
Injection reconstitution: Stability in vial when constituted (up to 50 mg/mL) with:

SWFI: Stable for up to 2 hours at controlled room temperature of 15°C to 25°C (59°F to 77°F) or for up to 12 hours under refrigeration.

Sodium chloride: Stable for up to 2 hours at controlled room temperature of 15°C to 25°C (59°F to 77°F) or for up to 18 hours under refrigeration.

Dextrose 5% injection: Stable for 1 hour at controlled room temperature of 15°C to 25°C (59°F to 77°F) or for 8 hours under refrigeration.

Infusion admixture (1-20 mg/mL): Solution stability when diluted in NS is 4 hours at controlled room temperature of 15°C to 25°C (59°F to 77°F) or 24 hours under refrigeration. Stability in D_5W is 1 hour at controlled room temperature of 15°C to 25°C (59°F to 77°F) or for 4 hours under refrigeration.

ReconstitutionMeropenem infusion vials may be reconstituted with SWFI or a compatible diluent (eg, NS). The 500 mg vials should be reconstituted with 10 mL, and 1 g vials with 20 mL. May be further diluted with compatible solutions for infusion. Consult detailed reference/product labeling for compatibility.
Compatibility**Compatible** in NS for 4 hours at controlled room temperature and up to 24 hours refrigerated. **Variable stability (consult detailed reference)** in D_5LR, $D_5{}^1/_4NS$, D_5NS, D_5W, $D_{10}W$, LR, $^1/_2NS$, mannitol 2.5%, mannitol 10%, sodium bicarbonate 5%.

Y-site administration: Compatible: Aminophylline, atenolol, atropine, cimetidine, dexamethasone sodium phosphate, digoxin, diphenhydramine, docetaxel, enalaprilat, fluconazole, furosemide, gentamicin, heparin, insulin (regular), linezolid, metoclopramide, milrinone, morphine, norepinephrine, phenobarbital, potassium chloride, vancomycin. **Incompatible:** Amphotericin B, diazepam, metronidazole. **Variable (consult detailed reference):** Acyclovir, calcium gluconate, doxycycline, ondansetron, zidovudine.

Compatibility in syringe: Incompatible with pantoprazole.

Compatibility when admixed: Compatible: Aminophylline, atropine, cimetidine, dexamethasone sodium phosphate, dobutamine, dopamine, enalaprilat, fluconazole, furosemide, gentamicin, heparin, insulin (regular), magnesium sulfate, metoclopramide, morphine, norepinephrine, phenobarbital, ranitidine, vancomycin. **Incompatible:** Amphotericin B, metronidazole, multivitamins. **Variable (consult detailed reference):** Acyclovir, doxycycline, ondansetron, zidovudine.

ContraindicationsHypersensitivity to meropenem, any component of the formulation, or other carbapenems (eg, imipenem); patients who have experienced anaphylactic reactions to other beta-lactams
Allergy Considerations

- Carbapenem Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Serious hypersensitivity reactions, including anaphylaxis, have been reported (some without a history of previous allergic reactions to beta-lactams).

- CNS effects: Has been associated with CNS adverse effects, including confusional states and seizures; use caution with CNS disorders (eg, brain lesions, history of seizures, or renal impairment).

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required in patients with moderate-to-severe renal dysfunction. Increased seizure risk and thrombocytopenia have been reported in patients with renal dysfunction.

Special populations:

- Elderly: Lower doses (based upon renal function) are often required in the elderly.

Geriatric ConsiderationsAdjust dose based on renal function.
Pregnancy Risk FactorB
Pregnancy ConsiderationsMeropenem is classified as pregnancy category B because no evidence of impaired fertility or fetal harm has been found in animals. Adequate and well-controlled studies have not been conducted in pregnant women and it is not known whether meropenem can cause fetal harm.
LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if meropenem is excreted in breast milk. The manufacturer recommends that caution be exercised when administering meropenem to breast-feeding women. Most penicillins and carbapenems are safe for use in breast-feeding. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Meropenem in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Cardiovascular: Peripheral vascular disorder

Central nervous system: Headache (2% to 8%), pain (≤5%)

Dermatologic: Rash (2% to 3%, includes diaper-area moniliasis in pediatrics), pruritus (1%)

Endocrine & metabolic: Hypoglycemia

Gastrointestinal: Diarrhea (4% to 7%), nausea/vomiting (1% to 8%), constipation (1% to 7%), oral moniliasis (up to 2% in pediatric patients), glossitis (1%)

Hematologic: Anemia (≤6%)

Local: Inflammation at the injection site (2%), phlebitis/thrombophlebitis (1%), injection site reaction (1%)

Respiratory: Apnea (1%), pharyngitis, pneumonia

Miscellaneous: Sepsis (2%), shock (1%)

<1%: Abdominal enlargement, abdominal pain, agitation/delirium, alkaline phosphatase increased, ALT increased, AST increased, anemia (hypochromic), anorexia, anxiety, asthma, back pain, bilirubin increased, bradycardia, BUN increased, chest pain, chills, cholestatic jaundice/jaundice, confusion, cough, creatinine increased, depression, diaphoresis, dizziness, dyspepsia, dyspnea, dysuria, eosinophilia, epistaxis (0.2%), fever, flatulence, gastrointestinal hemorrhage (0.5%), hallucinations, heart failure, hemoglobin/hematocrit decreased, hemoperitoneum (0.2%), hepatic failure, hyper-/hypotension, hypervolemia, hypokalemia, hypoxia, ileus, insomnia, intestinal obstruction, LDH increased, leukocytosis, melena (0.3%), MI, nervousness, paresthesia, pelvic pain, peripheral edema, platelets decreased/increased, pleural effusion, prothrombin time decreased, pulmonary edema, pulmonary embolism, renal failure, respiratory disorder, seizure, skin ulcer, somnolence, syncope, tachycardia, urinary incontinence, urticaria, vaginal moniliasis, weakness, WBC decreased, whole body pain

Postmarketing and/or case reports: Agranulocytosis, angioedema, erythema multiforme, hemolytic anemia, leukopenia, neutropenia, positive Coombs test, Stevens-Johnson syndrome, toxic epidermal necrolysis

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Carbapenems. Management: Avoid concomitant use of doripenem and probenecid. *Risk C: Monitor therapy*

Valproic Acid: Carbapenems may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Monitoring ParametersPerform culture and sensitivity testing prior to initiating therapy. Monitor for signs of anaphylaxis during first dose. During prolonged therapy, monitor renal function, liver function, CBC.

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's allergy history prior to beginning treatment. Use caution in presence of renal impairment or neurologic disorder. Infusion site should be monitored closely for phlebitis/thrombophlebitis. Assess renal and hepatic function and CBC, therapeutic effectiveness (resolution of infection), and adverse reactions. Teach patient proper use (according to formulation), possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity testing prior to initiating therapy. During prolonged therapy, monitor renal function, liver function, CBC.

Patient EducationThis medication can only be given by infusion. Report immediately any burning, pain, swelling, or redness at infusion site. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea (boiled milk, buttermilk, or yogurt may help); or headache. Report persistent GI distress, persistent diarrhea, mouth sores, respiratory difficulty, headache, or CNS changes (agitation, delirium). **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Merrem® I.V: 500 mg [contains sodium 45.1 mg as sodium carbonate (1.96 mEq)]; 1 g [contains sodium 90.2 mg as sodium carbonate (3.92 mEq)]

Generic AvailableNo

ManufacturerAstraZeneca Pharmaceuticals LP

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Merrem)

500 mg (1): $47.37

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to several of the penicillin-binding proteins, which in turn inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis; bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested

Pharmacodynamics/Kinetics

Distribution: V_d: Adults: ~0.3 L/kg, Children: 0.4-0.5 L/kg; penetrates well into most body fluids and tissues; CSF concentrations approximate those of the plasma

Protein binding: ~2%

Metabolism: Hepatic; metabolized to open beta-lactam form (inactive)

Half-life elimination:

Normal renal function: 1-1.5 hours

Cl_{cr} 30-80 mL/minute: 1.9-3.3 hours

Cl_{cr} 2-30 mL/minute: 3.82-5.7 hours

Time to peak, tissue: 1 hour following infusion

Excretion: Urine (~25% as inactive metabolites)

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Neutropenic Fever Guidelines

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral moniliasis (pediatric patients) and glossitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause agitation, confusion, insomnia, hallucinations, or depression

Mental Health: Effects on Psychiatric TreatmentNone reported

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Wiseman LR, Wagstaff AJ, Brogden RN, et al, “Meropenem. A Review of its Antibacterial Activity, Pharmacokinetic Properties and Clinical Efficacy,” *Drugs*, 1995, 50(1):73-101.[PubMed 7588092]

International Brand NamesEnem (TH); Lanmer (ID); Mapenem (TH); Mepem (CL, TW); Merofen (ID); Meronem (BB, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CN, CO, CR, CZ, DE, DK, DO, EC, EE, ES, ET, FI, GB, GH, GM, GN, GR, GT, GY, HK, HN, HU, ID, IE, IL, IN, JM, KE, LR, LU, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, NO, PA, PE, PH, PK, PL, PT, RU, SC, SD, SE, SG, SL, SN, SR, SV, TH, TN, TT, TZ, UG, UY, VE, ZA, ZM, ZW); Meropen (JP, KP); Merosan (ID); Merozen (PY); Merrem (AU, IT, MX); Monem (TH); Myron (TW); Optinem (AT); Ronem (ID); Tripenem (ID); Zeropenem (AR)

Mesalamine

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Mesalamine may be confused with mecamylamine, methenamine

Apriso™ may be confused with Apri®

Asacol® may be confused with Ansaid®, Os-Cal®

Lialda™ may be confused with Aldara®

Pronunciation(me SAL a meen)

U.S. Brand NamesApriso™; Asacol®; Canasa®; Lialda™; Pentasa®; Rowasa®

Canadian Brand NamesAsacol®; Asacol® 800; Mesasal®; Mezavant®; Novo-5 ASA; Pendo-5 ASA; Pentasa®; Quintasa®; Rowasa®; Salofalk®

Pharmacologic Category5-Aminosalicylic Acid Derivative

Use: Labeled Indications

Oral: Treatment and maintenance of remission of mildly- to moderately-active ulcerative colitis

Rectal: Treatment of active mild-to-moderate distal ulcerative colitis, proctosigmoiditis, or proctitis

Dosing: Adults

Treatment of ulcerative colitis: Oral: Usual course of therapy is 3-8 weeks:

Capsule: 1 g 4 times/day

Tablet: Initial:

Asacol®: 800 mg 3 times/day for 6 weeks

Lialda™, Mezavant®: 2.4-4.8 g once daily for up to 8 weeks

Maintenance of remission of ulcerative colitis: Oral:

Capsule:

Apriso™: 1.5 g once daily in the morning

Pentasa®: 1 g 4 times/day

Tablet (Asacol®): 1.6 g/day in divided doses; **Note:** Lialda™ and Mezavant® tablets are approved for treatment only.

Distal ulcerative colitis, proctosigmoiditis, or proctitis: Rectal: Retention enema: 60 mL (4 g) at bedtime, retained overnight, approximately 8 hours

Active ulcerative proctitis: Rectal: Rectal suppository (Canasa®): Insert one 1000 mg suppository in rectum daily at bedtime

Note: Suppositories should be retained for at least 1-3 hours to achieve maximum benefit.

Note: Some patients may require rectal and oral therapy concurrently.

Dosing: ElderlyRefer to adult dosing.

Administration: OralSwallow capsules or tablets whole, do not chew or crush.

Apriso™: Administer with or without food; do not administer with antacids

Asacol®: Do not break outer coating.

Lialda™: Do not break outer coating; should be administered once daily with a meal

Mezavant®: Do not break outer coating; should be administered once daily with a meal

Administration: Other

Rectal enema: Shake bottle well. Retain enemas for 8 hours or as long as practical.

Suppository: Remove foil wrapper; avoid excessive handling. Should be retained for at least 1-3 hours to achieve maximum benefit.

Dietary Considerations

Apriso™: Take with or without food; do not administer with antacids. Contains 0.56 mg phenylalanine per capsule.

Canasa® rectal suppository contains saturated vegetable fatty acid esters.

Storage

Capsule:

Apriso™: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F)

Pentasa®: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

Enema: Store at controlled room temperature. Use promptly once foil wrap is removed. Contents may darken with time (do not use if dark brown).

Suppository: Store below 25°C (below 77°F). May store under refrigeration; do not freeze. Protect from direct heat, light, and humidity.

Tablet: Store at controlled room temperature:

Asacol®: 20°C to 25°C (68°F to 77°F)

Lialda™: 15°C to 30°C (59°F to 86°F)

Mezavant®: 15°C to 25°C (59°F to 77°F)

Contraindications

Hypersensitivity to mesalamine, aminosalicylates, salicylates, or any component of the formulation

Allergy Considerations

- 5-Aminosalicylic Acid Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Abdominal discomfort: Pancreatitis should be considered in patients with new abdominal discomfort.
- Cardiac effects: Pericarditis or myocarditis have been reported with use and should be considered in patients with chest pain. Use with caution in patients predisposed to these conditions.
- Colitis: Symptomatic worsening of colitis/IBD may occur following initiation of therapy.
- Intolerance syndrome: May cause an acute intolerance syndrome (cramping, acute abdominal pain, bloody diarrhea; sometimes fever, headache, rash); discontinue if this occurs.
- Oligospermia: In males, oligospermia (rare, reversible) has been reported.
- Sulfasalazine hypersensitivity: Patients with hypersensitivity to sulfasalazine may react to mesalamine; although usually well-tolerated in this population, use with caution.

Disease-related concerns:

- Hepatic impairment: Use caution in patients with hepatic dysfunction; hepatic failure has been reported.
- Peptic ulcer: Use with caution in patients with active peptic ulcers.
- Pyloric stenosis: Patients with pyloric stenosis may have prolonged gastric retention of tablets, delaying the release of mesalamine in the colon.
- Renal impairment: Use with caution in patients with renal impairment or a history of renal disease. Renal disease (including minimal change nephropathy, acute/chronic interstitial nephritis, nephrotic syndrome, and renal failure) has been reported; use caution with other medications converted to mesalamine. An evaluation of renal function is recommended prior to initiation of mesalamine products and periodically during treatment.

Special populations:

- Elderly: Use with caution in the elderly; postmarketing reports suggest an increased incidence of blood dyscrasias in patients >65 years of age. In addition, elderly may have difficulty administering and retaining rectal suppositories or may have decreased renal function.
- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Apriso™: Contains phenylalanine.
- Canasa® suppositories: Contain saturated vegetable fatty acid esters (contraindicated in patients with allergy to these components).
- Rowasa® enema: Contains potassium metabisulfite; may cause severe hypersensitivity reactions (ie, anaphylaxis) in patients with sulfite allergies.

Geriatric Considerations

Use with caution. Elderly may have difficulty administering and retaining rectal suppositories. Given renal function decline with aging, monitor serum creatinine often during therapy.

Pregnancy Risk Factor

B

Pregnancy ConsiderationsAnimal studies have not demonstrated teratogenicity or fertility impairment. There are no adequate and well-controlled studies in pregnant women. Mesalamine is known to cross the placenta.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsAdverse effects (diarrhea) in a nursing infant have been reported while the mother received rectal administration of mesalamine within 12 hours after the first dose. The AAP recommends to monitor the infant stool for consistency and to use with caution. Low concentrations of the parent drug and higher concentrations of the N-acetyl metabolite of the parent drug have been detected in human breast milk.

Adverse ReactionsAdverse effects vary depending upon dosage form. Incidence usually on lower end with enema and suppository dosage forms.

>10%:

Central nervous system: Headache (2% to 35%), pain (≤14%)

Gastrointestinal: Abdominal pain (1% to 18%), eructation (16%), nausea (3% to 13%)

Respiratory: Pharyngitis (11%)

1% to 10%:

Cardiovascular: Chest pain (3%), peripheral edema (3%)

Central nervous system: Dizziness (2% to 8%), fever (1% to 6%), chills (3%), malaise (2% to 3%), fatigue (<3%), vertigo (<3%), insomnia (2%)

Dermatologic: Rash (1% to 6%), pruritus (1% to 3%), alopecia (<3%), acne (1% to 2%)

Endocrine & metabolic: Triglyceride increased (<3%)

Gastrointestinal: Diarrhea (8%), dyspepsia (6%), flatulence (2% to 6%), constipation (5%), vomiting (1% to 5%), colitis exacerbation (1% to 3%), rectal bleeding (<3%), rectal pain (1% to 2%), hemorrhoids (1%)

Hematologic: Hematocrit/hemoglobin decreased (<3%)

Hepatic: Cholestatic hepatitis (<3%), transaminases increased (<3%), ALT increased (1%)

Local: Pain on insertion of enema tip (1%)

Neuromuscular & skeletal: Back pain (1% to 7%), arthralgia (≤5%), hypertonia (5%), myalgia (3%), arthritis (2%), leg/joint pain (2%)

Ocular: Conjunctivitis (2%)

Otic: Tinnitus (<3%)

Renal: Creatinine clearance decreased (<3%), hematuria (<3%)

Respiratory: Nasopharyngitis (4%), dyspnea (<3%), cough (2%)

Miscellaneous: Flu-like syndrome (3% to 5%), diaphoresis (3%), intolerance syndrome (3%)

Postmarketing and/or case reports: Abdominal distention, agranulocytosis, albuminuria, alkaline phosphatase increased, amenorrhea, anxiety, anemia, angioedema, anorexia, aplastic anemia, asthma exacerbation, bilirubin increased, bloody diarrhea, bronchitis, BUN increased, cholestatic jaundice, cholecystitis, cramping, depression, disorientation, drug fever, dysphagia, dysuria, ear pain, edema, emotional lability, eosinophilia, eosinophilic pneumonia, epididymitis, erythema nodosum, eye pain, facial edema, fecal incontinence, fibrosing alveolitis, gastritis, gastroenteritis, gastrointestinal bleeding, GGT increased, gout, granulocytopenia, Guillain-Barré syndrome, hepatic failure, hepatic necrosis, hepatitis, hepatocellular damage, hepatotoxicity, hyperesthesia, hypersensitivity pneumonitis, hyper-/hypotension, indigestion, infertility, interstitial nephritis, interstitial pneumonia, jaundice, Kawasaki-like syndrome, LDH increased, leukopenia, libido decreased, lichen planus, lupus-like syndrome, lymphadenopathy, menorrhagia, metrorrhagia, migraine, minimal change nephrotic syndrome, myocarditis, neck pain, nephropathy, nephrotoxicity, neutropenia, oligospermia, oral moniliases, oral ulcers, palpitation, pancreatitis, pancytopenia, paresthesia, perforated peptic ulcer, pericardial effusion, pericarditis, peripheral neuropathy, pharyngolaryngeal pain, photosensitivity, pleuritis, pneumonitis, prurigo, psoriasis, pyoderma gangrenosum, rectal polyp, renal failure, rheumatoid arthritis, rhinitis, serum creatinine increased, somnolence, stomatitis, stool abnormalities, systemic lupus erythematosus, tachycardia, taste perversion, tenesmus, thrombocythemia, thrombocytopenia, transverse myelitis, tremor, T-wave abnormalities, urinary frequency, urinary urgency, urticaria, vasodilation, vision abnormalities, weakness, xerostomia

Drug Interactions

Antacids: May diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids. *Risk X: Avoid combination*

Cardiac Glycosides: 5-ASA Derivatives may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

H2-Antagonists: May diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids; H2-antagonists would be expected to interact in a similar manner. *Risk X: Avoid combination*

Proton Pump Inhibitors: May diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids; proton pump inhibitors would be expected to interact in a similar manner. *Risk X: Avoid combination*

Thiopurine Analogs: 5-ASA Derivatives may decrease the metabolism of Thiopurine Analogs. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: 5-ASA Derivatives may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. The primary concern is the potential development of Reye's Syndrome, a condition that has been associated with the use of salicylates in children with varicella infections. *Risk D: Consider therapy modification*

Monitoring ParametersCBC and renal function, particularly in elderly patients

Nursing: Physical Assessment/MonitoringAssess history of allergy to salicylates prior to beginning treatment. Use caution in presence of impaired hepatic or renal function and in predisposition to pericarditis or myocarditis. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (chest pain, CNS effects, gastrointestinal upset, exacerbation of colitis) on a regular basis throughout therapy. Teach patient proper use (according to formulation), possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report.

Monitoring: Lab TestsCBC and renal function, particularly in elderly patients

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed. You may experience headache; gastrointestinal upset; back, joint, or muscle pain; flu-like syndrome; or cough. Report severe abdominal pain, unresolved diarrhea, jaundice, severe headache, any unusual pain (back, joint, muscle, swelling of extremities, or chest pain), other persistent adverse effects, or lack of improvement.

Oral: Do not chew or break tablets or capsules. Notify prescriber if whole or partial tablets are repeatedly found in stool; should be taken with a meal.

Enema: Shake well before using; retain for 8 hours or as long as possible. May cause staining of clothing and undergarments. Do not use if solution is dark brown.

Suppository: Store below 25° C (77° F). May store in refrigerator; do not freeze. After removing foil wrapper, insert high in rectum without excessive handling (warmth will melt suppository). Lubricating gel may be used if needed to assist insertion. Retain suppositories for at least 1-3 hours to achieve maximum benefit. May cause staining of clothing and undergarments.

Breast-feeding precaution: Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Capsule, controlled release:

Pentasa®: 250 mg, 500 mg

Capsule, extended release:

Apriso™: 0.375 g [contains phenylalanine 0.56 mg/capsule]

Suppository, rectal:

Canasa®: 1000 mg [contains saturated vegetable fatty acid esters]

Suspension, rectal: 4 g/60 mL (7s, 28s) [contains potassium metabisulfite and sodium benzoate]

Rowasa®: 4 g/60 mL (7s, 28s) [contains potassium metabisulfite and sodium benzoate]

Tablet, delayed release [enteric coated]:

Asacol®: 400 mg

Lialda™: 1.2 g

Tablet, delayed and extended release:

Mezavant® [CAN]: 1.2 g [not available in U.S.]

Generic AvailableYes: Rectal suspension

Pricing: U.S. (www.drugstore.com)

Capsule, controlled release (Pentasa)

250 mg (240): $246.62

500 mg (30): $60.99

Enema (Mesalamine)

4 g (420): $90.01

Enema (Rowasa)

4 g (420): $180.01

Suppository (Canasa)

1000 mg (30): $446.36

Tablet, EC (Asacol)

400 mg (30): $53.49

Tablet, EC (Lialda)

1.2 g (120): $607.39

Mechanism of ActionMesalamine (5-aminosalicylic acid) is the active component of sulfasalazine; the specific mechanism of action of mesalamine is unknown; however, it is thought that it modulates local chemical mediators of the inflammatory response, especially leukotrienes, and is also postulated to be a free radical scavenger or an inhibitor of tumor necrosis factor (TNF); action appears topical rather than systemic

Pharmacodynamics/Kinetics

Absorption: Rectal: Variable and dependent upon retention time, underlying GI disease, and colonic pH; Oral: Tablet: ~21% to 28%, Capsule: ~20% to 40%

Distribution: ~18 L

Protein binding: 43%

Metabolism: Hepatic and via GI tract to N-acetyl-5-aminosalicylic acid

Half-life elimination: 5-ASA: 0.5-10 hours; N-acetyl-5-ASA: 2-15 hours

Time to peak, serum:

Capsule: Apriso™: ~4 hours; Pentasa®: 3 hours

Rectal: 4-7 hours

Tablet: Asacol®: 4-12 hours; Lialda™: 9-12 hours; Mezavant®: 8 hours

Excretion: Urine (primarily as metabolites, <8% as unchanged drug); feces (<2%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pharyngitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMalaise is common

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms5-Aminosalicylic Acid; 5-ASA; Fisalamine; Mesalazine

References

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International Brand Names5-ASA 400 (AR, PY); Asacol (BE, CH, DK, FI, GB, GR, IL, IT, LU, MX, NL, NO, NZ, PK, PT, SE, SG, TW); Asacol DR (KP); Asacol Enema (KP); Asacolon (IE); Asalit (BR); Claversal (AT, BE, DE, ES, IT, LU, PT); Colitan (PL); Colitofalk (BE, LU); Huma-Col-Asa (HU); Jucolon (PL); Mesacol (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Mesalazyna (PL); Mesalin (KP); Mesasal (AU, DK, NO, ZA); Mesren MR (GB); Pentasa (AE, AU, BE, BH, CH, CL, CY, DK, EG, FR, GB, HK, HU, IL, IQ, IR, JO, KW, LB, LU, LY, MY, NL, NO, OM, PH, PL, QA, SA, SE, SY, TH, TW, YE); Pentasa Enema (NZ); Pentasa SR (AE, BH, CY, EG, IL, IQ, IR, JO, KP, KW, LB, LY, OM, QA, SA, SY, YE); Pentasa Tab (NZ); Rafassal (IL); Salofalk (AT, AU, BG, CH, CN, CO, CZ, DE, EC, EE, GB, HK, HN, HR, HU, ID, IE, IT, KP, MY, NL, PE, PH, PL, TH, UY); Salofalk Foam Enema (AU); Salozinal (PL)

Mesna

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(MES na)

U.S. Brand NamesMesnex®

Canadian Brand NamesMesnex®; Uromitexan

Pharmacologic CategoryAntidote; Uroprotectant

Use: Labeled IndicationsPreventative agent to reduce the incidence of ifosfamide-induced hemorrhagic cystitis

Use: Unlabeled/InvestigationalPreventative agent to reduce the incidence of cyclophosphamide-induced hemorrhagic cystitis with high-dose cyclophosphamide

Dosing: Adults **Note:** Details concerning dosing in combination regimens should also be consulted. Mesna dosing schedule should be repeated each day ifosfamide is received. If ifosfamide dose is adjusted, the mesna dose should also be modified to maintain the mesna-to-ifosfamide ratio.

Prevention of ifosfamide-induced hemorrhagic cystitis:

- I.V.:
    - Short infusion standard-dose ifosfamide (<2.5 g/m^2/day): Mesna dose is equal to 60% of the ifosfamide dose given in 3 divided doses (0, 4, and 8 hours after the start of ifosfamide)
    - Continuous infusion standard-dose ifosfamide (<2.5 g/m^2/day): ASCO guidelines: Mesna dose (as an I.V. bolus) is equal to 20% of the ifosfamide dose, followed by a continuous infusion of mesna at 40% of the ifosfamide dose, continue mesna infusion for 12-24 hours after completion of ifosfamide infusion (Hensley, 2008)
    - High-dose ifosfamide (>2.5 g/m^2/day): ASCO guidelines: Evidence for use is inadequate; more frequent and prolonged mesna administration regimens may be required.
- I.V. followed by oral (for ifosfamide doses ≤2 g/m^2/day): Mesna dose is equal to 100% of the ifosfamide dose, given as 20% of the ifosfamide dose I.V. at hour 0, followed by 40% of the ifosfamide dose given orally 2- and 6 hours after start of ifosfamide

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Dosing: Combination Regimens

Breast cancer: ICE-T

Cervical cancer: BIP

Esophageal cancer: TIP

Head and neck cancer: TIP

Leukemia, acute lymphocytic:

- Hyper-CVAD + Imatinib
- Hyper-CVAD (Leukemia, Acute Lymphocytic)

Lung cancer (small cell): VIP (Small Cell Lung Cancer)

Lymphoma, non-Hodgkin's:

- ICE (Lymphoma, non-Hodgkin's)
- IMVP-16
- MINE
- MINE-ESHAP
- RICE

Lymphoma, non-Hodgkin's (Burkitt's): CODOX-M/IVAC

Lymphoma, non-Hodgkin's (Mantle cell): Hyper-CVAD + Rituximab

Multiple myeloma: Hyper-CVAD (Multiple Myeloma)

Neuroblastoma:

CI (Neuroblastoma)

HIPE-IVAD

Sarcoma, soft tissue:

AI

ICE-T

IE

MAID

Testicular cancer:

Paclitaxel-Ifosfamide-Cisplatin

VIP (Etoposide) (Testicular Cancer)

Administration: I.V.Administer by short (15-30 minutes) infusion or continuous infusion (maintain continuous infusion for 12-24 after completion of ifosfamide infusion) (Hensley, 2008)

Administration: I.V. DetailpH: 6.5-8.5

Administration: OralAdminister orally in tablet formulation or parenteral solution diluted in water, milk, juice, or carbonated beverages; patients who vomit within 2 hours after taking oral mesna should repeat the dose or receive I.V. mesna

StorageStore intact vials and tablets at room temperature of 20°C to 25°C (68°F to 77°F). Opened multidose vials may be stored and used for use to 8 days after opening. Solutions diluted for infusion are stable for at least 24 hours at room temperature. Solutions in plastic syringes are stable for 9 days under refrigeration, or at room or body temperature. Solutions of mesna and ifosfamide in lactated Ringer's are stable for 7 days in a PVC ambulatory infusion pump reservoir. Solutions of mesna (0.5-3.2 mg/mL) and cyclophosphamide (1.8-10.8 mg/mL) in D_5W are stable for 48 hours refrigerated or 6 hours at room temperature (Menard, 2003). Mesna injection is stable for at least 7 days when diluted 1:2 or 1:5 with grape- and orange-flavored syrups or 11:1 to 1:100 in carbonated beverages for oral administration.

ReconstitutionDilute in 50-1000 mL D_5W, NS, $D_5{}^1/_4NS$, $D_5{}^1/_3NS$, $D_5{}^1/_2NS$, or lactated Ringer's (the manufacturer recommends a final concentration of 20 mg/mL).

CompatibilityStable in $D_5{}^1/_4NS$, $D_5{}^1/_3NS$, $D_5{}^1/_2NS$, D_5W, LR, NS.

Y-site administration: Compatible: Allopurinol, amifostine, aztreonam, cefepime, cladribine, docetaxel, doxorubicin liposome, etoposide phosphate, filgrastim, fludarabine, gallium nitrate, gemcitabine, granisetron, linezolid, melphalan, methotrexate, micafungin, ondansetron, oxaliplatin, paclitaxel, pemetrexed, piperacillin/tazobactam, sargramostim, sodium bicarbonate, teniposide, thiotepa, vinorelbine. **Incompatible:** Amphotericin B cholesteryl sulfate complex.

Compatibility in syringe: Compatible: Ifosfamide. **Incompatible:** Ifosfamide with epirubicin.

Compatibility when admixed: Compatible: Hydroxyzine HCl, ifosfamide. **Incompatible:** Carboplatin, cisplatin, ifosfamide with epirubicin. **Variable (consult detailed reference):** Cyclophosphamide.

ContraindicationsHypersensitivity to mesna or other thiol compounds, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Allergic reactions have been reported; symptoms ranged from mild hypersensitivity to systemic anaphylactic reactions. Patients with autoimmune disorders receiving cyclophosphamide and mesna may be at increased risk.

- Hematuria: Examine morning urine specimen for hematuria prior to ifosfamide or cyclophosphamide treatment; if hematuria (>50 RBC/HPF) develops, reduce the ifosfamide/cyclophosphamide dose or discontinue the drug; will not prevent hemorrhagic cystitis in all patients.

- Ifosfamide/cyclophosphamide toxicities: Will not prevent or alleviate toxicities associated with ifosfamide or cyclophosphamide, other than hemorrhagic cystitis.

Disease related concerns:

- Thrombocytopenia: Mesna will not reduce the risk of thrombocytopenia-related hematuria.

Dosage form specific issues:

- Benzyl alcohol: I.V. formulation contains benzyl alcohol which has been associated with "gasping syndrome" in neonates.

Other warnings/precautions:

- Hydration: Patients should receive adequate hydration during treatment.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding Considerations

Due to the potential for adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

Mesna alone (frequency not defined):

Cardiovascular: Flushing

Central nervous system: Dizziness, fever, headache, hyperesthesia, somnolence

Dermatologic: Rash

Gastrointestinal: Anorexia, constipation, diarrhea, flatulence, nausea, taste alteration/bad taste (with oral administration), vomiting

Local: Injection site reactions

Neuromuscular: Arthralgia, back pain, rigors

Ocular: Conjunctivitis

Respiratory: Cough, pharyngitis, rhinitis

Miscellaneous: Flu-like syndrome

Mesna alone or in combination: Postmarketing and/or case reports: Allergic reaction, anaphylactic reaction, hypersensitivity, hyper-/hypotension, injection site erythema, injection site pain, limb pain, malaise, myalgia, platelets decreased, ST-segment increased, tachycardia, tachypnea, transaminases increased

Oncology: VesicantNo

Oncology: Emetic PotentialWhen administered orally, the unpleasant taste may result in vomiting.

Drug InteractionsThere are no known significant interactions.

Test InteractionsFalse-positive urinary ketones with Multistix® or Labstix®

Monitoring ParametersUrinalysis

Nursing: Physical Assessment/MonitoringMonitor laboratory results and assess frequently for hematuria/bladder hemorrhage.

Monitoring: Lab TestsUrinalysis

Patient EducationThis drug is given to help prevent side effects of other chemotherapeutic agents you are taking. Report blood in urine. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 100 mg/mL (10 mL) [contains benzyl alcohol]

Mesnex®: 100 mg/mL (10 mL) [contains benzyl alcohol]

Tablet:

Mesnex®: 400 mg

Generic AvailableYes: Solution for injection

Mechanism of ActionIn blood, mesna is oxidized to dimesna which in turn is reduced in the kidney back to mesna, supplying a free thiol group which binds to and inactivates acrolein, the urotoxic metabolite of ifosfamide and cyclophosphamide

Pharmacodynamics/Kinetics

Distribution: No tissue penetration

Protein binding: 69% to 75%

Metabolism: Rapidly oxidized intravascularly to mesna disulfide (dimesna); dimesna is reduced in renal tubules back to mesna following glomerular filtration

Bioavailability: Oral: 45% to 79%

Half-life elimination:

I.V.: Mesna: ~22 minutes; Dimesna: ~70 minutes

I.V. followed by oral: 1-8 hours

Time to peak, plasma: 2-3 hours

Excretion: Urine (18% to 32% as mesna; 33% as dimesna)

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy Pearls**Oncology Comment:** Guidelines from the American Society of Clinical Oncology (ASCO) for the use of chemotherapy and radiotherapy protectants (Schuchter, 2002; Hensley, 2008 [update]) recommend mesna to decrease the incidence of ifosfamide-induced urotoxicity associated with short infusion and continuous infusion standard-dose ifosfamide (<2.5 g/m^2/day). Although evidence is inadequate regarding mesna's uroprotective effects in high-dose ifosfamide (>2.5 g/m^2/day), the guidelines suggest more frequent and prolonged mesna administration times may be required. For prevention high-dose cyclophosphamide-induced urotoxicity (associated with stem cell transplantation), the guidelines recommend mesna in conjunction with saline diuresis (or forced saline diuresis alone).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause malaise

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMercaptoethane Sulfonate; Sodium 2-Mercaptoethane Sulfonate

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Siu LL and Moore MJ, “Use of Mesna to Prevent Ifosfamide-Induced Urotoxicity,” *Support Care Cancer*, 1998, 6(2):144-54.[PubMed 9540174]

International Brand NamesAnti-Uron (PL); Delinar (AR); Mescryo (MX); Mesnil (MX, PE, PY); Mesodal (MX); Mistabron (KP, LU, PH, PL); Mitexan (BR); Mucofluid (ES, PL); Uromitexan (AT, AU, BE, BG, CH, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, HR, HU, ID, IE, IN, IT, LU, NL, NO, PK, PL, PT, RU, SE, SG, TH, TR, TW, UY); Uroprot (MX, TH)

Metaproterenol

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Metaproterenol may be confused with metipranolol, metoprolol

Alupent® may be confused with Atrovent®

Pronunciation(met a proe TER e nol)

U.S. Brand NamesAlupent® [DSC]

Canadian Brand NamesApo-Orciprenaline®; ratio-Orciprenaline®; Tanta-Orciprenaline®

Pharmacologic CategoryBeta$_2$ Agonist

Use: Labeled IndicationsBronchodilator in reversible airway obstruction due to asthma or COPD; because of its delayed onset of action (1 hour) and prolonged effect (4 or more hours), this may not be the drug of choice for assessing response to a bronchodilator

Dosing: Adults

Bronchoconstriction (Asthma, COPD):

Oral: 20 mg 3-4 times/day

Inhalation: 2-3 inhalations every 3-4 hours, up to 12 inhalations in 24 hours

Nebulizer: 5-20 breaths of full strength 5% metaproterenol **or** 0.2 to 0.3 mL 5% metaproterenol in 2.5-3 mL normal saline until nebulized every 4-6 hours (can be given more frequently according to need)

Dosing: ElderlyOral: Initial: 10 mg 3-4 times/day; increase as necessary up to 20 mg 3-4 times/day.

Dosing: Pediatric

Bronchoconstriction (asthma):

Oral:

<2 years: 0.4 mg/kg/dose given 3-4 times/day; in infants, the dose can be given every 8-12 hours

2-6 years: 1-2.6 mg/kg/day divided every 6 hours

6-9 years: 10 mg/dose 3-4 times/day

>9 years: 20 mg 3-4 times/day

Inhalation: >12 years: Refer to adult dosing.

Nebulizer:

Infants and Children: 0.01-0.02 mL/kg of 5% solution; minimum dose: 0.1 mL; maximum dose: 0.3 mL diluted in 2-3 mL normal saline every 4-6 hours (may be given more frequently according to need)

Adolescents: Refer to adult dosing.

Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels.

Administration: InhalationDo not use solutions for nebulization if they are brown or contain a precipitate. Shake inhaler well before using.

StorageStore in a tight, light-resistant container. Do not use if brown solution or contains a precipitate.

ContraindicationsHypersensitivity to metaproterenol or any component of the formulation; pre-existing cardiac arrhythmias associated with tachycardia

Warnings/Precautions

Concerns related to adverse effects:

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.
- Hypersensitivity reactions: Immediate hypersensitivity reactions (urticaria, angioedema, rash, bronchospasm) have been reported.
- Serious effects/fatalities: Do not exceed recommended dose; serious adverse events, including fatalities, have been associated with excessive use of inhaled sympathomimetics.

Disease-related concerns:

- Asthma: Appropriate use: Optimize anti-inflammatory treatment before initiating maintenance treatment with metaproterenol. Do not use as a component of chronic therapy without an anti-inflammatory agent. Only the mildest form of asthma (Step 1 and/or exercise-induced) would not require concurrent use based upon asthma guidelines.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (arrhythmia or hypertension or HF); beta-agonists may cause elevation in blood pressure, heart rate and result in CNS stimulation/excitation. Beta$_2$-agonists may also increase risk of arrhythmias.

- Diabetes: Use with caution in patients with diabetes mellitus; beta$_2$-agonists may increase serum glucose.

- Glaucoma: Use with caution in patients with glaucoma; may elevate intraocular pressure.

- Hyperthyroidism: Use with caution in hyperthyroidism; may stimulate thyroid activity.

- Hypokalemia: Use with caution in patients with hypokalemia; beta$_2$-agonists may decrease serum potassium.

- Seizures: Use with caution in patients with seizure disorders; beta-agonists may result in CNS stimulation/excitation.

Special populations:

- Pediatrics: Face masks should be used in children <4 years of age.

Dosage form specific issues:

- Syrup/tablets: Oral use should be avoided due to the increased incidence of adverse effects.

Other warnings/precautions:

- Beta activity: Metaproterenol has more beta$_1$ activity than beta$_2$-selective agents such as albuterol and, therefore, may no longer be the beta-agonist of first choice.

- Patient information: Patients must be instructed to seek medical attention in cases where acute symptoms are not relieved or a previous level of response is diminished. The need to increase frequency of use may indicate deterioration of asthma, and treatment must not be delayed. All patients should utilize a spacer device when using a metered-dose inhaler.

Geriatric ConsiderationsElderly may find it useful to utilize a spacer device when using a metered dose inhaler. Oral use should be avoided due to the increased incidence of adverse effects.

Pregnancy Risk FactorC

Pregnancy ConsiderationsNo data on crossing the placenta. Reported association with polydactyly in 1 study; may be secondary to severe maternal disease or chance.

LactationExcretion in breast milk unknown

Breast-Feeding ConsiderationsNo data on crossing into breast milk or clinical effects on the infant.

Adverse Reactions

>10%:

Cardiovascular: Tachycardia (<17%)

Central nervous system: Nervousness (3% to 14%)

Endocrine & metabolic: Serum glucose increased, serum potassium decreased

Neuromuscular & skeletal: Tremor (1% to 33%)

1% to 10%:

Cardiovascular: Palpitation (<4%)

Central nervous system: Headache (<4%), dizziness (1% to 4%), insomnia (2%)

Gastrointestinal: Nausea, vomiting, bad taste, heartburn (≥4%), xerostomia

Neuromuscular & skeletal: Trembling, muscle cramps, weakness (1%)

Respiratory: Coughing, pharyngitis (≤4%)

Miscellaneous: Diaphoresis increased (≤4%)

<1%: Paradoxical bronchospasm, hypertension, hypokalemia, chest pain, angina, drowsiness, diarrhea, taste change

Drug Interactions

Alpha-/Beta-Blockers: May diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Atomoxetine: May enhance the tachycardic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Betahistine: May diminish the therapeutic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Test InteractionsIncreased potassium (S)

Monitoring ParametersAssess lung sounds, heart rate, and blood pressure before administration and during peak of medication; observe patient for wheezing after administration, if this occurs, call physician; monitor respiratory rate, arterial or capillary blood gases if applicable; FEV$_1$, peak flow, and/or other pulmonary function tests; CNS stimulation; serum glucose, serum potassium

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy (relief of airway obstruction) and adverse reactions at beginning of therapy and periodically with long-term use. For inpatient care, vital signs and lung sounds should be monitored prior to and periodically during therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsFEV$_1$, peak flow, and/or other pulmonary function tests; serum potassium, serum glucose (in selected patients)

Patient EducationUse exactly as directed (see following administration information). Do not use more often than recommended. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience nervousness, dizziness, or fatigue (use caution when driving or engaging in tasks requiring alertness until response to drug is known); dry mouth, unpleasant aftertaste, stomach upset (small frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help); or increased perspiration. If you have diabetes, check blood sugar; blood glucose level may be increased. Report unresolved GI upset; dizziness or fatigue; vision changes; chest pain, rapid heartbeat, or palpitations; nervousness or insomnia; muscle cramping or tremor; or unusual cough. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Self-administered inhalation: Store canister upside down; do not freeze. Shake canister before using. Sit when using medication. Close eyes when administering metaproterenol to avoid spray getting into eyes. Exhale slowly and completely through nose; inhale deeply through mouth while administering aerosol. Hold breath for 5-10 seconds after inhalation. Wait at least 1 full minute between inhalations. Wash mouthpiece between use. If more than one inhalation medication is used, use bronchodilator first and wait 5 minutes between medications.

Self-administered nebulizer: Wash hands before and after treatment. Wash and dry nebulizer after each treatment. Twist open the top of one unit dose vial and squeeze contents into nebulizer reservoir. Connect nebulizer reservoir to the mouthpiece or face mask. Connect nebulizer to compressor. Sit in comfortable, upright position. Place mouthpiece in your mouth or put on face mask and turn on compressor. If face mask is used, avoid leakage around the mask to avoid mist getting into eyes which may cause vision problems. Breathe calmly and deeply until no more mist is formed in nebulizer (about 5 minutes). At this point treatment is finished.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol for oral inhalation, as sulfate:

Alupent®: 0.65 mg/inhalation (14 g) [contains chlorofluorocarbon; 200 doses] [DSC]

Solution for nebulization, as sulfate [preservative free]: 0.4% [4 mg/mL] (2.5 mL); 0.6% [6 mg/mL] (2.5 mL)

Syrup, as sulfate: 10 mg/5 mL (480 mL)

Tablet, as sulfate: 10 mg, 20 mg

Generic AvailableYes: Excludes inhaler

Pricing: U.S. (www.drugstore.com)

Aerosol powder (Alupent)

0.65 mg/ACT (14): $49.99

Mechanism of ActionRelaxes bronchial smooth muscle by action on beta$_2$-receptors with very little effect on heart rate

Pharmacodynamics/Kinetics

Onset of action: Bronchodilation: Oral: ~15 minutes; Inhalation: ~60 seconds

Peak effect: Oral: ~1 hour

Duration: ~1-5 hours

Related Information

- Bronchodilators
- Inhalant Agents

Pharmacotherapy PearlsUse with caution perioperatively due to beta$_1$ effect of agent. Hypertension and tachycardia are increased with exogenous sympathomimetics. During endotracheal intubation, beta$_2$-specific agent is more appropriate for perioperative use.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Bad taste and xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNervousness is common; may cause dizziness, restlessness, or insomnia

Mental Health: Effects on Psychiatric TreatmentConcurrent use with TCAs and MAO inhibitors may result in additive toxicity

Anesthesia and Critical Care Concerns/Other ConsiderationsHypertension and tachycardia are increased with exogenous sympathomimetics. Beta$_2$-specific agent is more appropriate for use.

Index TermsMetaproterenol Sulfate; Orciprenaline Sulfate

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Gilman MJ, Meyer L, Carter J, et al, “Comparison of Aerosolized Glycopyrrolate and Metaproterenol in Acute Asthma,” *Chest*, 1990, 98(5):1095-8. [PubMed 2225951]

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International Brand NamesAlupent (AE, AT, BH, CY, EG, GB, GR, ID, IE, IL, IN, IQ, IR, IT, JO, KW, LB, LY, NL, OM, PE, QA, RU, SA, SY, YE); Nonasma (TW)

Metaxalone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Metaxalone may be confused with metolazone

Pronunciation(me TAKS a lone)
U.S. Brand NamesSkelaxin®
Canadian Brand NamesSkelaxin®
Pharmacologic CategorySkeletal Muscle Relaxant
Use: Labeled IndicationsRelief of discomfort associated with acute, painful musculoskeletal conditions
Dosing: Adults**Muscle discomfort:** Oral: 800 mg 3-4 times/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren >12 years: Refer to adult dosing.
Administration: OralMay be administered with or without food. However, serum concentrations may be increased when administered with food; clinical significance has not been established. Patients should be monitored.
Dietary ConsiderationsAdministration with food may increase serum concentrations.
StorageStore at room temperature at 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to metaxalone or any component of the formulation; impaired hepatic or renal function, history of drug-induced hemolytic anemias or other anemias
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; routine monitoring of transaminases is recommended.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to CNS effects.
- Females: An increase in bioavailability and half-life have been observed in female patients.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Central nervous system: Dizziness, drowsiness, headache, irritability, paradoxical stimulation

Dermatologic: Rash (with or without pruritus)

Gastrointestinal: Gastrointestinal upset, nausea, vomiting

Hematologic: Hemolytic anemia, leukopenia

Hepatic: Jaundice

Miscellaneous: Hypersensitivity (including anaphylactoid reactions)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Bioavailability may be increased (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John’s wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsFalse-positive Benedict's test

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: 400 mg [DSC], 800 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Skelaxin)

800 mg (30): $110.27

Mechanism of ActionPrecise mechanism has not been established; however, efficacy appears to result from disruption of the spasm-pain-spasm cycle, probably by a general CNS depressant effect. Does not have a direct effect on skeletal muscle.

Pharmacodynamics/Kinetics

Onset of action: ~1 hour

Duration: ~4-6 hours

Metabolism: Hepatic

Bioavailability: Not established; food may increase

Half-life elimination: 9 hours

Time to peak: T_{max}: 3 hours

Excretion: Urine (as metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and dizziness are common; may cause paradoxical stimulation

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation

References

Toth PP and Urtis J, “Commonly Used Muscle Relaxant Therapies for Acute Low Back Pain: A Review of Carisoprodol, Cyclobenzaprine Hydrochloride, and Metaxalone,” *Clin Ther*, 2004, 26(9):1355-67.[PubMed 15530999]

International Brand NamesSkelaxin (CA)

MetFORMIN

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

MetFORMIN may be confused with metroNIDAZOLE

Glucophage® may be confused with Glucotrol®, Glutofac®

Pronunciation(met FOR min)

U.S. Brand NamesFortamet®; Glucophage®; Glucophage® XR; Glumetza™; Riomet®

Canadian Brand NamesApo-Metformin®; CO-Metformin; DOM-Metformin; Gen-Metformin; Glucophage®; Glumetza™; Glycon; MED-Metformin; Novo-Metformin; Nu-Metformin; PHL-Metformin; PMS-Metformin; RAN™-Metformin; RATIO-Metformin; RHOXAL-Metformin; RIVA-Metformin; Sandoz-Metformin FC

Pharmacologic CategoryAntidiabetic Agent, Biguanide

Use: Labeled IndicationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as monotherapy when hyperglycemia cannot be managed with diet and exercise alone. In adults, may be used concomitantly with a sulfonylurea or insulin to improve glycemic control.

Use: Unlabeled/InvestigationalGestational diabetes mellitus (GDM); polycystic ovary syndrome (PCOS)

Dosing: Adults**Management of type 2 diabetes mellitus:** Oral: **Note:** Allow 1-2 weeks between dose titrations: Generally, clinically significant responses are not seen at doses <1500 mg daily; however, a lower recommended starting dose and gradual increased dosage is recommended to minimize gastrointestinal symptoms.

Immediate release tablet or solution: Adults ≥17 years: Initial: 500 mg twice daily **or** 850 mg once daily; increase dosage incrementally.

Incremental dosing recommendations based on dosage form:

500 mg tablet: One tablet/day at weekly intervals

850 mg tablet: One tablet/day every other week

Oral solution: 500 mg twice daily every other week

Doses of up to 2000 mg/day may be given twice daily. If a dose >2000 mg/day is required, it may be better tolerated in three divided doses. Maximum recommended dose 2550 mg/day.

*Extended release tablet:***Note:** If glycemic control is not achieved at maximum dose, may divide dose and administer twice daily.

Fortamet®: Initial: 1000 mg once daily; dosage may be increased by 500 mg weekly; maximum dose: 2500 mg once daily

Glucophage® XR: Initial: 500 mg once daily; dosage may be increased by 500 mg weekly; maximum dose: 2000 mg once daily

Glumetza™: Initial: 1000 mg once daily; dosage may be increased by 500 mg weekly; maximum dose: 2000 mg once daily

Transfer from other antidiabetic agents: No transition period is generally necessary except when transferring from chlorpropamide. When transferring from chlorpropamide, care should be exercised during the first 2 weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

Concomitant metformin and oral sulfonylurea therapy: If patients have not responded to 4 weeks of the maximum dose of metformin monotherapy, consider a gradual addition of an oral sulfonylurea, even if prior primary or secondary failure to a sulfonylurea has occurred. Continue metformin at the maximum dose. If adequate response has not occurred following 3 months of metformin and sulfonylurea combination therapy, consider switching to insulin with or without metformin.

Failed sulfonylurea therapy: Patients with prior failure on glyburide may be treated by gradual addition of metformin. Initiate with glyburide 20 mg and metformin 500 mg daily. Metformin dosage may be increased by 500 mg/day at weekly intervals, up to a maximum metformin dose (dosage of glyburide maintained at 20 mg/day).

Concomitant metformin and insulin therapy: Initial: 500 mg metformin once daily, continue current insulin dose; increase by 500 mg metformin weekly until adequate glycemic control is achieved

Maximum daily dose: Immediate release and solution: 2550 mg metformin; Extended release: 2000-2500 mg (varies by product)

Decrease insulin dose 10% to 25% when FPG <120 mg/dL; monitor and make further adjustments as needed

Dosing: ElderlyThe initial and maintenance dosing should be conservative, due to the potential for decreased renal function. Generally, elderly patients should **not** be titrated to the maximum dose of metformin. Do not use in patients ≥80 years of age unless normal renal function has been established. See Geriatric Considerations.

Dosing: Pediatric **Management of type 2 diabetes mellitus:** Oral: **Note:** Allow 1-2 weeks between dose titrations: Generally, clinically significant responses are not seen at doses <1500 mg daily; however, a lower recommended starting dose and gradual increased dosage is recommended to minimize gastrointestinal symptoms.

Immediate release tablet or solution:

Children 10-16 years: Initial: 500 mg twice daily; increases in daily dosage should be made in increments of 500 mg at weekly intervals, given in divided doses, up to a maximum of 2000 mg/day

Children ≥17 years: Refer to adult dosing.

Extended release tablet: Children ≥17 years: **Note:** If glycemic control is not achieved at maximum dose, may divide dose and administer twice daily.

Fortamet®: Initial: 1000 mg once daily; dosage may be increased by 500mg weekly; maximum dose: 2500 mg once daily

Glucophage® XR: Initial: 500 mg once daily; dosage may be increased by 500 mg weekly; maximum dose: 2000 mg once daily

Dosing: Renal Impairment The plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance. Per the manufacturer, metformin is contraindicated in the presence of renal dysfunction defined as a serum creatinine >1.5 mg/dL in males, or >1.4 mg/dL in females and in patients with abnormal clearance. Clinically, it has been recommended that metformin be avoided in patients with Cl_{cr} <60-70 mL/minute (DeFronzo, 1999).

Dosing: Hepatic Impairment Avoid metformin; liver disease is a risk factor for the development of lactic acidosis during metformin therapy.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: Oral Extended release dosage form should be swallowed whole; do not crush, break, or chew; administer with food (to decrease GI upset). Administer Fortamet® with a glass of water.

Dietary Considerations Drug may cause GI upset; take with food (to decrease GI upset). Take at the same time each day. Dietary modification based on ADA recommendations is a part of therapy. Monitor for signs and symptoms of vitamin B_{12} and/or folic acid deficiency; supplementation may be required.

Storage

Oral solution: Store at 15°C to 30°C (59°F to 86°F).

Tablets: Store at 20°C to 25°C (68°F to 77°F); excursion permitted to 15°C to 30°C (59°F to 86°F). Protect from light and moisture.

Contraindications Hypersensitivity to metformin or any component of the formulation; renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females) or abnormal creatinine clearance from any cause, including shock, acute myocardial infarction, or septicemia; acute or chronic metabolic acidosis with or without coma (including diabetic ketoacidosis)

Note: Temporarily discontinue in patients undergoing radiologic studies in which intravascular iodinated contrast media are utilized.

Allergy Considerations

- Biguanide Allergy

Warnings/Precautions

Boxed warnings:

- Lactic acidosis: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Cardiovascular mortality: Administration of oral antidiabetic drugs has been reported to be associated with increased cardiovascular mortality; metformin does not appear to share this risk.
- Lactic acidosis: **[U.S. Boxed Warning]: Lactic acidosis is a rare, but potentially severe consequence of therapy with metformin.** Lactic acidosis should be suspected in any patient with diabetes receiving metformin with evidence of acidosis but without evidence of ketoacidosis. Discontinue metformin in clinical situations predisposing to hypoxemia, including conditions such as cardiovascular collapse, respiratory failure, acute myocardial infarction, acute congestive heart failure, and septicemia. The risk of accumulation and lactic acidosis increases with the degree of impairment of renal function.

Disease-related concerns:

- Heart failure: Use caution in patients with congestive heart failure requiring pharmacologic management, particularly in patients with unstable or acute heart failure; risk of lactic acidosis may be increased secondary to hypoperfusion.
- Hepatic impairment: Avoid use in patients with impaired liver function due to potential for lactic acidosis.
- Renal impairment: Metformin is substantially excreted by the kidney; patients with renal function below the limit of normal for their age should not receive therapy. Use of concomitant medications that may affect renal function (ie, affect tubular secretion) may also affect metformin disposition. Metformin should be withheld in patients with dehydration and/or prerenal azotemia.
- Stress-related states: It may be necessary to discontinue metformin and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Special populations:

- Elderly: Metformin should not be initiated in patients ≥80 years of age unless normal renal function is confirmed.
- Pediatrics: Safety and efficacy have not been established in children <10 years of age. In addition, safety and efficacy for the extended release preparation have not been established in children <17 years of age.

Dosage form specific issues:

- Extended release tablet: Insoluble tablet shell (Glumetza™ 1000 mg tablet) may remain intact and be visible in the stool. Other extended released tablets (Fortamet®, Glucophage® XR, Glumetza™ 500 mg) may appear in the stool as a soft mass resembling the tablet.

Other warnings/precautions:

- Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism.
- Iodinated contrast: Therapy should be temporarily discontinued prior to or at the time of intravascular administration of iodinated contrast media (potential for acute alteration in renal function). Metformin should be withheld for 48 hours after the radiologic study and restarted only after renal function has been confirmed as normal.
- Surgical procedures: Therapy should be suspended for any surgical procedures (resume only after normal intake resumed and normal renal function is verified).

Geriatric ConsiderationsLimited data suggest that metformin's total body clearance may be decreased and AUC and half-life increased in elderly patients; presumably due to decreased renal clearance. Metformin has been well tolerated by the elderly but lower doses and frequent monitoring are recommended. In one study of elderly subjects, its effects could not be distinguished from tolbutamide, except for weight loss. The initial and maintenance dosing should be conservative, due to the potential for decreased renal function. Generally, elderly patients should not be titrated to the maximum dose of metformin. Do not use in patients ≥80 years of age unless normal renal function has been established. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, metformin is classified as pregnancy category B. Metformin has been found to cross the placenta in levels which may be comparable to those found in the maternal plasma. Pharmacokinetic studies suggest that clearance of metformin may be increased during pregnancy and dosing may need adjusted in some women when used during the third trimester.

Fetal, neonatal, and maternal outcomes have been evaluated following maternal use of metformin for the treatment of GDM and type 2 diabetes. Available information suggests that metformin use during pregnancy may be safe as long as good glycemic control is maintained; however, many studies used metformin during the second or third trimester only. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

Metformin has also been evaluated for the treatment of PCOS, a syndrome which may exhibit oligomenorrhea and in some women, hyperinsulinemia. When used to treat infertility related to PCOS, current guidelines restrict the use of metformin to women with glucose intolerance.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsLow amounts of metformin (generally ≤1% of the weight-adjusted maternal dose) are excreted into breast milk. Breast-feeding is not recommended by the manufacturer. Because breast milk levels of metformin stay relatively constant, avoiding nursing around peak plasma concentrations in the mother would not be helpful in reducing metformin exposure to the infant. Growth and development were not found to be affected in infants born to mothers with PCOS and who took metformin while breast-feeding.

Pregnancy & Lactation, In-Depth

- MetFORMIN in Pregnancy & Lactation

Adverse Reactions

>10%:

Gastrointestinal: Diarrhea (10% to 53%), nausea/vomiting (7% to 26%), flatulence (12%)

Neuromuscular & skeletal: Weakness (9%)

1% to 10%:

Cardiovascular: Chest discomfort, flushing, palpitation

Central nervous system: Headache (6%), chills, dizziness, lightheadedness

Dermatologic: Rash

Endocrine & metabolic: Hypoglycemia

Gastrointestinal: Indigestion (7%), abdominal discomfort (6%), abdominal distention, abnormal stools, constipation, dyspepsia/heartburn, taste disorder

Neuromuscular & skeletal: Myalgia

Respiratory: Dyspnea, upper respiratory tract infection

Miscellaneous: Diaphoresis increased, vitamin B_{12} levels decreased (7%), flu-like syndrome, nail disorder

<1%: Megaloblastic anemia

Postmarketing and/or case reports: Lactic acidosis, leukocytoclastic vasculitis, pneumonitis

Drug Interactions

Cephalexin: May increase the serum concentration of MetFORMIN. *Risk C: Monitor therapy*

Cimetidine: May decrease the excretion of MetFORMIN. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Iodinated Contrast Agents: May enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol (incidence of lactic acidosis may be increased; may cause hypoglycemia).

Food: Food decreases the extent and slightly delays the absorption. May decrease absorption of vitamin B_{12} and/or folic acid.

Herb/Nutraceutical: Caution with chromium, garlic, gymnema (may cause hypoglycemia).

Monitoring Parameters

Urine for glucose and ketones, fasting blood glucose, and hemoglobin A_{1c}. Initial and periodic monitoring of hematologic parameters (eg, hemoglobin/hematocrit and red blood cell indices) and renal function should be performed, at least annually. Check vitamin B_{12} and folate if anemia is present.

Reference Range

Recommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/Monitoring

Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, anything that may effect glucose levels). Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, assess for signs and symptoms of vitamin B_{12} and/or folic acid deficiency; supplementation may be required) during therapy. Teach patient (or refer patient to diabetic educator for instruction) in appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab Tests

Urine for glucose and ketones, fasting blood glucose, hemoglobin A_{1c}, and fructosamine. Initial and periodic monitoring of hematologic parameters (eg, hemoglobin/hematocrit and red blood cell indices) and renal function should be performed, at least annually. While megaloblastic anemia has been rarely seen with metformin, if suspected, vitamin B_{12} deficiency should be excluded.

Patient Education

Do not take any new medication during therapy unless approved by prescriber. Take as directed (may take with food to decrease GI upset). Do not chew or crush tablets. Parts of extended-release tablets may be excreted in the stool (normal). Do not change dosage or discontinue without consulting prescriber. Avoid overuse of alcohol (could cause severe reaction). It is important to follow dietary and lifestyle recommendations of prescriber. You will be instructed in signs of hypo- or hyperglycemia by prescriber or diabetic educator. May cause drowsiness or dizziness (use caution driving or engaging in potentially hazardous tasks until response to drug is known); nausea or vomiting (taking with meals, eating small frequent meals, frequent mouth care, or sucking lozenges may help); or abdominal distention, flatulence, diarrhea, constipation, or heartburn (if these persist consult prescriber for approved medication). Report immediately unusual weakness or fatigue; unusual muscle pain; persistent GI discomfort; dizziness or lightheadedness; unusual somnolence; sudden respiratory difficulty, chest discomfort, slow or irregular heartbeat; or other adverse reactions. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral, as hydrochloride:

Riomet®: 100 mg/mL (118 mL, 473 mL) [contains saccharin; cherry flavor]

Tablet, as hydrochloride: 500 mg, 850 mg, 1000 mg

Glucophage®: 500 mg, 850 mg, 1000 mg

Tablet, extended release, as hydrochloride: 500 mg, 750 mg

Fortamet®: 500 mg, 1000 mg

Glucophage® XR: 500 mg

Glumetza™: 500 mg, 1000 mg

Generic AvailableYes: Excludes solution
ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)
Pricing: U.S. (www.drugstore.com)

Solution (Riomet)

500 mg/5 mL (473): $87.98

Tablet, 24-hour (Fortamet)

500 mg (60): $118.22

1000 mg (60): $262.79

Tablet, 24-hour (Glucophage XR)

500 mg (60): $69.99

750 mg (30): $53.99

Tablet, 24-hour (Glumetza)

500 mg (100): $153.71

Tablet, 24-hour (Metformin HCl)

500 mg (90): $18.99

Tablets (Glucophage)

500 mg (60): $69.99

850 mg (60): $113.29

1000 mg (60): $141.08

Mechanism of ActionDecreases hepatic glucose production, decreasing intestinal absorption of glucose and improves insulin sensitivity (increases peripheral glucose uptake and utilization)
Pharmacodynamics/Kinetics

Onset of action: Within days; maximum effects up to 2 weeks

Distribution: V_d: 654 ± 358 L; partitions into erythrocytes

Protein binding: Negligible

Metabolism: Not metabolized by the liver

Bioavailability: Absolute: Fasting: 50% to 60%

Half-life elimination: Plasma: 4-9 hours

Time to peak, serum: Immediate release: 2-3 hours; Extended release: 7 hours (range: 4-8 hours)

Excretion: Urine (90% as unchanged drug; active secretion)

Related Information

- Diabetes Mellitus Management, Adults

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste disorder.

Metformin-dependent patients with diabetes (noninsulin dependent, Type 2) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation

Cardiovascular ConsiderationsMetformin, alone or in combination with other agents (sulfonylurea), is effective in the management of diabetes. Lactic acidosis is an uncommon side effect in patients without renal or respiratory insufficiency, hepatic failure, or conditions that predispose to hypoxemia. As heart failure may affect renal and pulmonary function, metformin should be avoided or used with caution in patients with diabetes and heart failure.

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: While megaloblastic anemia has been rarely seen with metformin, if suspected, vitamin B_{12} deficiency should be excluded. Metformin has a large volume of distribution in liver, kidney, and GI tract where concentration is much larger than in the plasma.

Lactic acidosis is an uncommon side effect in patients without renal or respiratory insufficiency, hepatic failure, or conditions that predispose to hypoxemia.

Index TermsMetformin Hydrochloride

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International Brand NamesBiguax (CO); Dabex (MX); Deson (TH); Diabetase (DE); Diabetmin (HK, MY); Diabetmin Retard (HK); Diabetol (PY); Diabex (AU, ID); Diabex XR (AU); Diafat (PH); Diaformin (AU, HK); Diaformina (UY); Diaformina LP (UY); Diamelton (PH); Dianben (ES); Diformin (FI); Diformin Retard (FI); Dimefor (BR, CO, MX, PE); Dybis (KP); Eraphage (ID); Euform Retard (PH); Formet (AU); Formin (IN); Fornidd (PH); Glafornil (CN); Glibudon (TW); Gliformin (ID); Glucobeta (AU); Glucofage (EC, VE); Glucofor (ID); Glucoform (PH); Glucoformin (BR); Glucohexal (AU); Glucoless (TH); Glucomet (AU, HK); Glucomin (IL); Glucomine (TW); Glucophage (MX); Glucophage (AE, AR, AT, AU, BB, BE, BF, BH, BJ, BM, BS, BZ, CH, CI, CL, CY, CZ, DK, EE, EG, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HR, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NO, OM, PE, PH, PK, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TN, TR, TT, TZ, UG, YE, ZA, ZM, ZW); Glucophage Forte (CZ, NL, PH); Glucophage Retard (IL); Glucophage SR (GB, IE); Glucophage XR (HK, MY); Glucophage-Mite (DE); Glucotika (ID); Gludepatic (ID); Gludin (PH); Glufor (ID, IL); Gluformin (PL, TH); Glumet (MY, PH); Glumin (ID); Glumin XR (ID); Glupa (KP); Glustress (TH); Glyciphage (IN); Glycomet (SG); Glycomin (KP); Glyformin (TW); Glymet (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Guamet (HK); I-Max (PH); Islotin (AR); Maformin (TH); Marphage (PH); Medformin (AU); Meglucon (DE); Melbin (JP); Merckformin (HU); Mescorit (DE); Metfogamma (DE); Metforal (CR, DO, GT, HN, IT, NI, PA, SG, SV); Metforatio (PL); Metformax (PL); Metformin (PL); Metformina Anpharm (PL); Metifor (PL); Metomin (NZ); Miformin (TH); Neoform (PH); Orabet (AT, DK, GB, IE); Reglus-500 (ID); Riomet (MY); Riomet OD (MY); Siamformet (TH); Siofor (BG, DE, HN, PL); Sucranorm (PH); Thiabet (DE); Walaphage (IN); Xmet (MY)

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(meth a KOLE leen)

U.S. Brand NamesProvocholine®

Canadian Brand NamesMethacholine Omega; Provocholine®

Pharmacologic CategoryDiagnostic Agent

Use: Labeled IndicationsDiagnosis of bronchial airway hyperactivity

Dosing: Adults**Note:** For inhalation only.

Challenge test: Before inhalation challenge, perform baseline pulmonary function tests; the patient must have an FEV_1 of at least 70% of the predicted value. The following is a suggested schedule for administration of methacholine challenge. Calculate cumulative units by multiplying number of breaths by concentration given. Total cumulative units is the sum of cumulative units for each concentration given. See following breakdown:

Methacholine

Vial	Serial Concentration (mg/mL)	No. of Breaths	Cumulative Units per Concentration	Total Cumulative Units
E	0.025	5	0.125	0.125
D	0.25	5	1.25	1.375
C	2.5	5	12.5	13.88
B	10	5	50	63.88
A	25	5	125	188.88

Determine FEV_1 within 5 minutes of challenge, a positive challenge is a 20% reduction in FEV_1

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Children ≥5 years: Refer to adult dosing.

Administration: InhalationAdminister by inhalation only; oral and injection administration has been associated with nausea, vomiting, substernal pain/pressure, hypotension, fainting, transient complete heartblock, and cardiac arrest.

StorageStore unreconstituted powder at 15°C to 30°C (59°F to 86°F). Store dilutions (A-D, serial concentrations 0.25-25 mg/mL) in refrigerator 2°C to 8°C (36°F to 46°F) for up to 2 weeks. Dilution E (serial concentration 0.025 mg/mL) must be prepared day of test.

ReconstitutionAll dilutions should be made with 0.9% sodium chloride or 0.9% sodium chloride containing 0.4% phenol. Use same diluent to prepare all concentrations. After dilution, shake well until solution is clear.

ContraindicationsHypersensitivity to methacholine, other parasympathomimetic agents, or any component of the formulation; concomitant use of beta-blockers; repeat administration (other than day of challenge test with increasing doses)

Warnings/Precautions

Boxed warnings:

- Appropriate use: See “Other warnings/precautions” below.
- Bronchoconstriction: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Bronchoconstriction: **[U.S. Boxed Warning]: Administer only by inhalation; severe bronchoconstriction and reduction in respiratory function can result.** Patients with severe hyper-reactivity of the airways can experience bronchoconstriction at a dosage as low as 0.025 mg/mL (0.125 cumulative units). If severe bronchoconstriction occurs, reverse immediately by administration of a rapid-acting inhaled bronchodilator (eg, albuterol).

Disease-related concerns:

- Risk to benefit: Use only in patients with cardiovascular disease, peptic ulcer disease, seizures, thyroid disease, urinary tract obstruction, and vagotonia if benefit outweighs risk.

Special populations:

- Females of childbearing potential: Administration should be within 10 days of the onset of menses or within 2 weeks of a negative pregnancy test.

- Pediatrics: Safety and efficacy have not been established in children <5 years of age.

Other warnings/precautions:

- Appropriate use: **[U.S. Boxed Warning]: Methacholine is a bronchoconstrictor for diagnostic purposes only.** Perform inhalation challenge under the supervision of a physician trained in and thoroughly familiar with all aspects of the technique, all contraindications, warnings, and precautions of methacholine challenge and the management of respiratory distress. Have emergency equipment and medication immediately available to treat acute respiratory distress. Product should not be handled by persons with asthma or hay fever.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. There are no adequate and well-controlled studies in pregnant women. Avoid use in pregnant women unless the potential benefit justifies the potential risk to the fetus. Administration should be within 10 days of the onset of menses or within 2 weeks of a negative pregnancy test.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Central nervous system: Headache, lightheadedness

Dermatologic: Itching

Gastrointestinal: Throat irritation

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Beta-Blockers: May enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for reconstitution, for oral inhalation, as chloride:

Provocholine®: 100 mg

Generic AvailableNo

Manufacturer

Methapharm Inc

Mechanism of ActionMethacholine chloride is a cholinergic (parasympathomimetic) synthetic analogue of acetylcholine. The drug stimulates muscarinic, postganglionic parasympathetic receptors, which results in smooth muscle contraction of the airways and increased tracheobronchial secretions.

Pharmacodynamics/Kinetics

Onset of action: Rapid

Peak effect: 1-4 minutes

Duration: 15-75 minutes or 5 minutes if methacholine challenge is followed with a beta-agonist agent

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause lightheadedness

Mental Health: Effects on Psychiatric TreatmentContraindicated with beta-blockers

Index TermsMethacholine Chloride

International Brand NamesProvocholine (IL); Provokit (DE)

Methadone

Lexi-Drugs Online

English

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Methadone: Recommendations for QT_c Interval Screening Before and During Methadone Treatment - Updated: January 2009

The Center for Substance Abuse and Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration has developed a consensus guideline statement outlining recommendations regarding ECG monitoring in patients being considered for and being treated with methadone regardless of indication. Of note, these recommendations should not supersede clinical judgment or patient preferences and may not apply to patients with terminal, intractable cancer pain.

Five recommendations have been developed:

Recommendation 1 [Disclosure]: Clinicians should inform patients of arrhythmia risk when methadone is prescribed.

Recommendation 2 [Clinical History]: Clinicians should inquire about any history of structural heart disease, arrhythmia, and syncope.

Recommendation 3 [Screening]: Clinicians should obtain pretreatment ECG for all patients to measure QTc interval, follow up ECG within 30 days, then annually (monitor more frequently if patient receiving >100 mg/day or if unexplained syncope or seizure occurs while on methadone).

Recommendation 4 [Risk Stratification]: If before or at anytime during therapy:

QT_c >450-499 msecs: Discuss potential risks and benefits; monitor QT_c more frequently

QT_c ≥500 msecs: Consider discontinuation or reducing methadone dose or eliminate factors promoting QT_c prolongation (eg, potassium-wasting drugs) or use alternative therapy (eg, buprenorphine)

Recommendation 5 [Drug Interactions]: Clinicians should be aware of interactions between methadone and other drugs that either prolong the QT interval or reduce methadone elimination.

The panel also concluded that the arrhythmia risk is directly associated with methadone's ability to block the delayed rectifier potassium channel (Ikr) and prolong repolarization. The guideline further states that the use of the Bazett formula is adequate even though it is likely to overcorrect with high heart rates. The patient should remain supine for at least 5 minutes prior to obtaining ECG. In addition, screening for QT_c prolongation using automated readings does not require a specialist (eg, cardiologist) and may be performed in a primary care setting. However, in cases when uncertainty exists about whether or not clinically significant QT_c prolongation is present, the ECG should be repeated or interpreted by a cardiologist.

For more information, refer to: Krantz MJ, Martin J, Stimmel B, et al, “QT_c Interval Screening in Methadone Treatment,” *Ann Int Med*, 2009, 150(1):1-10 (epub ahead of print).

Medication Safety Issues

Sound-alike/look-alike issues:

Methadone may be confused with dexmethylphenidate, Mephyton®, methylphenidate, Metadate® CD, and Metadate® ER

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(METH a done)

U.S. Brand NamesDolophine®; Methadone Diskets®; Methadone Intensol™; Methadose®

Canadian Brand NamesMetadol™

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled IndicationsManagement of moderate-to-severe pain; detoxification and maintenance treatment of opioid addiction (if used for detoxification and maintenance treatment of narcotic addiction, it must be part of an FDA-approved program)

Dosing: AdultsRegulations regarding methadone use may vary by state and/or country. Obtain advice from appropriate regulatory agencies and/or consult with pain management/palliative care specialists. **Note:** These are guidelines and do not represent the maximum doses that may be required in all patients. Methadone accumulates with repeated doses and dosage may need reduction after 3-5 days to prevent CNS depressant effects. Some patients may benefit from every 8-12 hour dosing interval for chronic pain management. Doses should be titrated to appropriate effects.

Acute pain (moderate-to-severe):

Opioid-naive: *Oral:* Initial: 2.5-10 mg every 8-12 hours; more frequent administration may be required during initiation to maintain adequate analgesia. Dosage interval may range from 4-12 hours, since duration of analgesia is relatively short during the first days of therapy, but increases substantially with continued administration.

Chronic pain (opioid-tolerant): Conversion from oral morphine to oral methadone:

Daily oral morphine dose <100 mg: Estimated daily oral methadone dose: 20% to 30% of total daily morphine dose

Daily oral morphine dose 100-300 mg: Estimated daily oral methadone dose: 10% to 20% of total daily morphine dose

Daily oral morphine dose 300-600 mg: Estimated daily oral methadone dose: 8% to 12% of total daily morphine dose

Daily oral morphine dose 600-1000 mg: Estimated daily oral methadone dose: 5% to 10% of total daily morphine dose.

Daily oral morphine dose >1000 mg: Estimated daily oral methadone dose: <5% of total daily morphine dose.

Note: The total daily methadone dose should then be divided to reflect the intended dosing schedule.

I.V.: Manufacturers labeling: Initial: 2.5-10 mg every 8-12 hours in opioid-naive patients; titrate slowly to effect; may also be administered by SubQ or I.M. injection

Conversion from oral to parenteral dose: Initial dose: Parenteral:Oral ratio: 1:2 (eg, 5 mg parenteral methadone equals 10 mg oral methadone)

Detoxification:*Oral:*

Initial: A single dose of 20-30 mg is usually sufficient to suppress symptoms. Should not exceed 30 mg; lower doses should be considered in patients with low tolerance at initiation (eg, absence of opioids ≥5 days); an additional 5-10 mg of methadone may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear after 2-4 hours; total daily dose on the first day should not exceed 40 mg, unless the program physician documents in the patient's record that 40 mg did not control opiate abstinence symptoms.

Maintenance: Titrate to a dosage which prevents craving, attenuates euphoric effect of self-administered opiates, and tolerance to sedative effects of methadone. Usual range: 80-120 mg/day (titration should occur cautiously)

Withdrawal: Dose reductions should be <10% of the maintenance dose, every 10-14 days

Detoxification (short-term):*Oral:*

Initial: Titrate to ~40 mg/day in divided doses to achieve stabilization. May continue 40 mg dose for 2-3 days

Maintenance: Titrate to a dosage which prevents/attenuates euphoric effects of self-administered opioids, reduces drug craving, and withdrawal symptoms are prevented for 24 hours.

Withdrawal: Requires individualization. Decrease daily or every other day, keeping withdrawal symptoms tolerable; hospitalized patients may tolerate a 20% reduction/day; ambulatory patients may require a slower reduction

Dosage adjustment during pregnancy: Methadone dose may need to be increased, or the dosing interval decreased; see Pregnancy Implications - use should be reserved for cases where the benefits clearly outweigh the risks

Dosing: ElderlyOral, I.M.: 2.5 mg every 8-12 hours; refer to adult dosing.

Dosing: PediatricRegulations regarding methadone use may vary by state and/or country. Obtain advice from appropriate regulatory agencies and/or consult with pain management/palliative care specialists. **Note:** These are guidelines and do not represent the maximum doses that may be required in all patients. Methadone accumulates with repeated doses and dosage may need reduction after 3-5 days to prevent CNS depressant effects. Some patients may benefit from every 8-12 hour dosing interval for chronic pain management. Doses should be titrated to appropriate effects.

Pain (analgesia) (unlabeled use):

Oral: Initial: 0.1-0.2 mg/kg 4-8 hours initially for 2-3 doses, then every 6-12 hours as needed. Dosing interval may range from 4-12 hours during initial therapy; decrease in dose or frequency may be required (~ days 2-5) due to accumulation with repeated doses (maximum dose: 5-10 mg)

I.V. (unlabeled use): 0.1 mg/kg every 4-8 hours initially for 2-3 doses, then every 6-12 hours as needed. Dosing interval may range from 4-12 hours during initial therapy; decrease in dose or frequency may be required (~ days 2-5) due to accumulation with repeated doses (maximum dose: 5-8 mg)

Iatrogenic narcotic dependency (unlabeled use): Oral: General guidelines: Initial: 0.05-0.1 mg/kg/dose every 6 hours; increase by 0.05 mg/kg/dose until withdrawal symptoms are controlled; after 24-48 hours, the dosing interval can be lengthened to every 12-24 hours; to taper dose, wean by 0.05 mg/kg/day; if withdrawal symptoms recur, taper at a slower rate

Dosing: Renal ImpairmentCl_{cr} <10 mL/minute: Administer 50% to 75% of normal dose.

Dosing: Hepatic ImpairmentAvoid in severe liver disease.

Dosing: Adjustment for Toxicity

QT_c >450-499 msecs: Monitor QT_c more frequently

QT_c ≥500 msecs: Consider discontinuation or reducing methadone dose

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Fentanyl Transdermal Conversion
- Opioid Agonist Conversion

Administration: I.V. DetailpH: 4.5-6.5

Administration: OralOral dose for detoxification and maintenance may be administered in fruit juice or water. Dispersible tablet should not be chewed or swallowed; add to liquid and allow to dissolve before administering. May rinse if residual remains.

Storage

Injection: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

Oral concentrate, oral solution, tablet: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F).

CompatibilityStable in NS.

RestrictionsC-II

When used for treatment of opioid addiction: May only be dispensed in accordance to guidelines established by the Substance Abuse and Mental Health Services Administration’s (SAMHSA) Center for Substance Abuse Treatment (CSAT). Regulations regarding methadone use may vary by state and/or country. Obtain advice from appropriate regulatory agencies and/or consult with pain management/palliative care specialists.

Note: Regulatory Exceptions to the General Requirement to Provide Opioid Agonist Treatment (per manufacturer's labeling):

1. During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction, to facilitate the treatment of the primary admitting diagnosis.

2. During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility.

ContraindicationsHypersensitivity to methadone or any component of the formulation; respiratory depression (in the absence of resuscitative equipment or in an unmonitored setting); acute bronchial asthma or hypercarbia; paralytic ileus; concurrent use of selegiline

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Opioid addiction use: See “Other warnings/precautions” below.

- QT prolongation: See “Concerns related to adverse effects” below.

- Respiratory depression: See “Concerns related to adverse effects” below.

- Tablets: See “Dosage form specific issues” below.

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

- QT_c prolongation: **[U.S. Boxed Warning]: May prolong the QT_c interval and increase risk for torsade de pointes.** Patients should be informed of the potential arrhythmia risk, evaluated for any history of structural heart disease, arrhythmia, syncope, and for existence of potential drug interactions including drugs that possess QT_c interval-prolonging properties, promote hypokalemia, hypomagnesemia, or hypocalcemia, or reduce elimination of methadone (eg, CYP3A4 inhibitors). Obtain baseline ECG for all patients and risk stratify according to QT_c interval (see Monitoring Parameters). Use with caution in patients at risk for QT_c prolongation, with medications known to prolong the QT_c interval, promote electrolyte depletion, or inhibit CYP3A4, or history of conduction abnormalities. QT_c interval prolongation and torsade de pointes may be associated with doses >100 mg/day, but have also been observed with lower doses.

- Respiratory depression: **[U.S. Boxed Warning]: Severe respiratory depression has occurred with administration.** Use extreme caution during treatment initiation, dose titration and conversion from other opioid agonists to methadone. Peak respiratory depressant effects occur later and persist longer than peak analgesic effects possibly contributing to cases of iatrogenic overdose.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.

- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.

- CNS depression/coma: Use with caution in patients with CNS depression or coma.

- Depression: Use with caution in patients with depression or suicidal tendencies.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Hepatic impairment: Use with caution in patients with severe hepatic failure.

- Obesity: Use with caution in patients who are morbidly obese.

- Prostatic hyperplasia/urethral stricture: Use with caution in patients with prostatic hyperplasia and/or urethral stricture.

- Renal impairment: Use with caution in patients with severe renal failure.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages. Because the respiratory effects last longer than the analgesic effects, slow titration is required.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients receiving concurrent use of medications known to inhibit CYP3A4, prolong the QT_c interval, or promote hypokalemia, hypomagnesemia, or hypocalcemia; may require dosage adjustments or use of alternative therapy.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Tablets: **[U.S. Boxed Warning]: For oral administration only;** excipients to deter use by injection are contained in tablets.

Other warnings/precautions:

- Acute pain management: Patients maintained on stable doses may need higher and/or more frequent doses in case of acute pain (eg, postoperative pain, physical trauma).

- Anxiety use: Methadone is ineffective for the relief of anxiety.

- Incomplete cross tolerance: Use caution in converting patients from other opioids to methadone. Follow appropriate conversion schedules. Patients tolerant to other mu opioid agonists may not be tolerant to methadone and at risk for severe respiratory depression when converted to methadone.

- Narcotic addiction use: **[U.S. Boxed Warning]: When used for treatment of narcotic addiction:May only be dispensed by opioid treatment programs when used for treatment of narcotic addiction:** These programs must be certified by the designated state authority; exceptions include inpatient treatment of other conditions and emergency period (not >3 days) while definitive substance abuse treatment is being sought.

- Optimal regimen: An opioid-containing analgesic regimen should be tailored to each patient's needs and based upon the type of pain being treated (acute versus chronic), the route of administration, degree of tolerance for opioids (naive versus chronic user), age, weight, and medical condition. The optimal analgesic dose varies widely among patients; doses should be titrated to pain relief/prevention.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsBecause of it's long half-life and risk of accumulation, methadone is difficult to titrate and is not considered a drug of first choice. It should be prescribed only by physicians who are experienced in using it. Elderly may be particularly susceptible to the CNS depressant and constipating effects of narcotics.

Pregnancy Risk FactorC/D (prolonged use or high doses at term)

Pregnancy ConsiderationsTeratogenic effects have been observed in some, but not all, animal studies. Data collected by the Teratogen Information System are complicated by maternal use of illicit drugs, nutrition, infection, and psychosocial circumstances. However, pregnant women in methadone treatment programs are reported to have improved fetal outcomes compared to pregnant women using illicit drugs. Methadone can be detected in the amniotic fluid, cord plasma, and newborn urine. Fetal growth, birth weight, length, and/or head circumference may be decreased in infants born to narcotic-addicted mothers treated with methadone during pregnancy. Growth deficits do not appear to persist; however, decreased performance on psychometric and behavioral tests has been found to continue into childhood. Abnormal fetal nonstress tests have also been reported. Withdrawal symptoms in the neonate may be observed up to 2-4 weeks after delivery. The manufacturer states that methadone should be used during pregnancy only if clearly needed. Because methadone clearance in pregnant women is increased and half-life is decreased during the 2nd and 3rd trimesters of pregnancy, withdrawal symptoms may be observed in the mother; dosage of methadone may need increased or dosing interval decreased during pregnancy.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsPeak methadone levels appear in breast milk 4-5 hours after an oral dose. Methadone has been detected in the plasma of some breast-fed infants whose mothers are taking methadone. Use during breast-feeding is not recommended, and the manufacturer recommends that women on high dose methadone maintenance who already are breast-feeding be instructed to wean breast-feeding gradually to avoid neonatal abstinence syndrome. Sedation and respiratory depression have been reported in nursing infants. Unless otherwise contraindicated (concurrent medical conditions, other medications of abuse), the AAP rates methadone “compatible” with breast-feeding.

Adverse ReactionsFrequency not defined. During prolonged administration, adverse effects may decrease over several weeks; however, constipation and sweating may persist.

Cardiovascular: Arrhythmia, bigeminal rhythms, bradycardia, cardiac arrest, cardiomyopathy, ECG changes, edema, extrasystoles, faintness, flushing, heart failure, hypotension, palpitation, peripheral vasodilation, phlebitis, orthostatic hypotension, QT interval prolonged, shock, syncope, tachycardia, torsade de pointes, T-wave inversion, ventricular fibrillation, ventricular tachycardia,

Central nervous system: Agitation, confusion, disorientation, dizziness, drowsiness, dysphoria, euphoria, hallucination, headache, insomnia, lightheadedness, sedation, seizure

Dermatologic: Hemorrhagic urticaria, pruritus, rash, urticaria

Endocrine & metabolic: Antidiuretic effect, amenorrhea, hypokalemia, hypomagnesemia, libido decreased

Gastrointestinal: Abdominal pain, anorexia, biliary tract spasm, constipation, glossitis, nausea, stomach cramps, vomiting, weight gain, xerostomia

Genitourinary: Impotence, urinary retention or hesitancy

Hematologic: Thrombocytopenia (reversible, reported in patients with chronic hepatitis)

Neuromuscular & skeletal: Weakness

Local: I.M./SubQ injection: Erythema, pain, swelling; I.V. injection: Hemorrhagic urticaria (rare), pruritus, urticaria, rash

Ocular: Miosis, visual disturbances

Respiratory: Pulmonary edema, respiratory depression, respiratory arrest

Miscellaneous: Death, diaphoresis, physical and psychological dependence

Oncology: VesicantNo

Metabolism/Transport Effects**Substrate** of CYP2C9 (minor), 2C19 (minor), 2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (moderate), 3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Methadone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Methadone. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Didanosine: Methadone may decrease the serum concentration of Didanosine. *Risk C: Monitor therapy*

Etravirine: May decrease the serum concentration of Methadone. *Risk C: Monitor therapy*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Methadone. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Methadone. **Exceptions:** Atazanavir; Indinavir. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Reverse Transcriptase Inhibitors (Non-Nucleoside): May increase the metabolism of Methadone. **Exceptions:** Delavirdine; Etravirine. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Methadone. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Methadone. Fluvoxamine appears to be the only interacting SSRI. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Zidovudine: Methadone may increase the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS effects). Watch for sedation.

Herb/Nutraceutical: Avoid St John's wort (may decrease methadone levels; may increase CNS depression). Avoid valerian, kava kava, gotu kola (may increase CNS depression). Methadone is metabolized by CYP3A4 in the intestines; avoid concurrent use of grapefruit juice.

Test InteractionsSome quinolones may produce a false-positive urine screening result for opiates using commercially-available immunoassay kits. This has been demonstrated most consistently for levofloxacin and ofloxacin, but other quinolones have shown cross-reactivity in certain assay kits. Confirmation of positive opiate screens by more specific methods should be considered.

Monitoring ParametersObtain baseline ECG (evaluate QT_c interval), within 30 days of initiation, and then annually for all patients receiving methadone. Increase ECG monitoring if patient receiving >100 mg/day or if unexplained syncope or seizure occurs while on methadone (Krantz, 2008).

If before or at anytime during therapy:

QT_c >450-499 msecs: Discuss potential risks and benefits; monitor QT_c more frequently

QT_c ≥500 msecs: Consider discontinuation or reducing methadone dose **or** eliminate factors promoting QT_c prolongation (eg, potassium-wasting drugs) **or** use alternative therapy (eg, buprenorphine)

Pain relief, respiratory and mental status, blood pressure

Reference RangePrevention of opiate withdrawal: Therapeutic: 100-400 ng/mL (SI: 0.32-1.29 µmol/L); Toxic: >2 mcg/mL (SI: >6.46 µmol/L)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for additive or adverse interactions. Monitor therapeutic effectiveness and adverse reactions of overdose at beginning of therapy and at regular intervals with long-term use. May cause physical and/or psychological dependence. Monitor blood pressure, respiratory and CNS status (degree of sedation). For inpatients, implement safety measures. Assess knowledge/teach patient appropriate use (if self-administered) adverse reactions to report, and appropriate interventions to reduce side effects. Discontinue slowly after prolonged use.

Patient Education If self-administered, use exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause hypotension, dizziness, drowsiness, impaired coordination, or blurred vision (use caution when driving, climbing stairs, or changing position - rising from sitting or lying to standing, or when engaging in tasks requiring alertness until response to drug is known); loss of appetite, nausea, or vomiting (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help; if unresolved, consult prescriber about use of stool softeners). Report chest pain, slow or rapid heartbeat, acute dizziness or persistent headache; changes in mental status; swelling of extremities or unusual weight gain; changes in urinary elimination; acute headache; back or flank pain or muscle spasms; blurred vision; skin rash; or shortness of breath. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. If you are breast-feeding, consult prescriber.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride: 10 mg/mL (20 mL)

Solution, oral, as hydrochloride: 5 mg/5 mL (500 mL); 10 mg/5 mL (500 mL) [contains alcohol 8%; citrus flavor]

Solution, oral, as hydrochloride [concentrate]: 10 mg/mL (946 mL)

- Methadone Intensol™: 10 mg/mL (30 mL)
- Methadose®: 10 mg/mL (1000 mL) [cherry flavor]
- Methadose®: 10 mg/mL (1000 mL) [dye free, sugar free, unflavored]

Tablet, as hydrochloride: 5 mg, 10 mg

- Dolophine®: 5 mg, 10 mg
- Methadose®: 5 mg, 10 mg [DSC]

Tablet, dispersible, as hydrochloride: 40 mg

- Methadose®: 40 mg
- Methadone Diskets®: 40 mg [orange-pineapple flavor]

Generic Available Yes

Pricing: U.S. (www.drugstore.com)

Tablet,Dispersible (Methadone HCl Diskets)

- 40 mg (20): $16.66

Tablets (Methadone HCl)

- 5 mg (20): $11.99
- 10 mg (20): $11.33

Tablets (Methadose)

- 5 mg (20): $11.33
- 10 mg (20): $11.99

Mechanism of Action Binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression

Pharmacodynamics/Kinetics

Onset of action: Oral: Analgesic: 0.5-1 hour; Parenteral: 10-20 minutes

- Peak effect: Parenteral: 1-2 hours; Oral: continuous dosing: 3-5 days

Duration of analgesia: Oral: 4-8 hours, increases to 22-48 hours with repeated doses

Distribution: V_{dss}: 1-8 L/kg

Protein binding: 85% to 90%

Metabolism: Hepatic; N-demethylation primarily via CYP3A4, CYP2B6, and CYP2C19 to inactive metabolites

Bioavailability: Oral: 36% to 100%

Half-life elimination: 8-59 hours; may be prolonged with alkaline pH, decreased during pregnancy

Time to peak, plasma: 1-7.5 hours

Excretion: Urine (<10% as unchanged drug); increased with urine pH <6

Related Information

- Addiction Treatments

- Narcotic / Opioid Analgesics

Dental Health Professional ConsiderationsThis drug is known to prolong the QT interval. The QT interval is measured as the time and distance between the Q point of the QRS complex and the end of the T wave in the ECG tracing. After adjustment for heart rate, the QT interval is defined as prolonged if it is more than 450 msec in men and 460 msec in women. A long QT syndrome was first described in the 1950s and 60s as a congenital syndrome involving QT interval prolongation and syncope and sudden death. Some of the congenital long QT syndromes were characterized by a peculiar electrocardiographic appearance of the QRS complex involving a premature atria beat followed by a pause, then a subsequent sinus beat showing marked QT prolongation and deformity. This type of cardiac arrhythmia was originally termed “torsade de pointes” (translated from the French as “twisting of the points”).

Prolongation of the QT interval is thought to result from delayed ventricular repolarization. The repolarization process within the myocardial cell is due to the efflux of intracellular potassium. The channels associated with this current can be blocked by many drugs and predispose the electrical propagation cycle to torsade de pointes.

Methadone is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation) and glossitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index TermsMethadone Hydrochloride

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International Brand NamesAdolan (IL); Amidona (CN); Aseptone (MY); Biodone (NZ); Biodone Extra Forte (NZ); Biodone Forte (AU); Depridol (HN, HU); Dolmed (FI); Eptadone (IT); Gobbidona (AR); Heptadon (AT); Heptanon (HR); Ketalgin (CH); Mephenon (BE, LU); Metadol (PE); Metadon (BR, DK, SE, UY); Metadone Cloridrato (IT); Metasedin (ES); Methaddict (DE); Methadon FNA (NL); Methadone chlorhydrate (FR); Methadone Hydrochloride (PL); Methadose (CO); Pallidone (NZ); Phymet DTF (IE); Physeptone (AU, GB); Rubidexol (MX); Symoron (NL)

Methamphetamine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.
Special Alerts

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) has issued a statement in April 2008 recommending that all children diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the recommendations due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: Methylphenidate, amphetamine, dextroamphetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children's Healthcare Quality.

For more information, refer to:

http://americanheart.mediaroom.com/index.php?s=43&item=422

http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1

http://americanheart.mediaroom.com/index.php?s=43&item=398

http://www.fda.gov/medwatch/safety/2007/safety07.htm

http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html

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Medication Safety Issues

Sound-alike/look-alike issues:

Desoxyn® may be confused with digoxin

Pronunciation(meth am FET a meen)
U.S. Brand NamesDesoxyn®
Canadian Brand NamesDesoxyn®
Pharmacologic CategoryAnorexiant; Stimulant; Sympathomimetic
Use: Labeled IndicationsTreatment of attention-deficit/hyperactivity disorder (ADHD); exogenous obesity (short-term adjunct)
Use: Unlabeled/InvestigationalNarcolepsy
Dosing: Adults

ADHD: Oral: 5 mg 1-2 times/day, may increase by 5 mg increments weekly until optimum response is achieved, usually 20-25 mg/day

Exogenous obesity: Oral: 5 mg, 30 minutes before each meal; treatment duration should not exceed a few weeks

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

ADHD: Oral: Children ≥6 years: Refer to adult dosing.

Exogenous obesity: Oral: Children ≥12 years: Refer to adult dosing.

Calculations

- Body Mass Index

Dietary ConsiderationsMost effective when combined with a low calorie diet and behavior modification counseling.
StorageStore below 30°C (86°F). Protect from light.
RestrictionsC-II

An FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/drug/infopage/ADHD/default.htm.

Pharmacotherapy for weight loss is recommended only for obese patients with a body mass index ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of other risk factors such as hypertension, diabetes, and/or dyslipidemia or a high waist circumference; therapy should be used in conjunction with a comprehensive weight management program. Rule out organic causes of obesity (eg, untreated hypothyroidism) prior to use.

Note: Methamphetamine is not approved for long-term use. The limited usefulness of medications in this class should be weighed against possible risks associated with their use. Consult weight loss guidelines for current pharmacotherapy recommendations.

ContraindicationsHypersensitivity to methamphetamine, any component of the formulation, or idiosyncrasy to amphetamines or other sympathomimetic amines; patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate-to-severe hypertension, hyperthyroidism, glaucoma, agitated states; patients with a history of drug abuse; use during or within 14 days following MAO inhibitor therapy; stimulant medications are contraindicated for use in children with attention-deficit/hyperactivity disorders and concomitant Tourette's syndrome or tics
Allergy Considerations

- Amphetamine Allergy

Warnings/Precautions

Boxed warnings:

- Drug abuse: See “Disease-related concerns” below.
- Weight reduction: Appropriate use: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Cardiovascular events: Use has been associated with serious cardiovascular events including sudden death in patients with pre-existing structural cardiac abnormalities or other serious heart problems (sudden death in children and adolescents; sudden death, stroke and MI in adults). These products should be avoided in the patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that could increase the risk of sudden death that these conditions alone carry. Patients should be carefully evaluated for cardiac disease prior to initiation of therapy.

- CNS effects: Amphetamines may impair the ability to engage in potentially hazardous activities.

- Visual disturbance: Difficulty in accommodation and blurred vision has been reported with the use of stimulants.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; antidiabetic agent requirements may be altered with anorexigens and concomitant dietary restrictions.

- Drug abuse: **[U.S. Boxed Warning]: Potential for drug dependency exists; prolonged use may lead to drug dependency.** Use is contraindicated in patients with history of ethanol or drug abuse. Prescriptions should be written for the smallest quantity consistent with good patient care to minimize possibility of overdose.

- Hypertension: Use with caution in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases in blood pressure or heart rate. Use is contraindicated in patients with moderate to severe hypertension.

- Psychiatric disorders: Use with caution in patients with pre-existing psychosis or bipolar disorder (may induce mixed/manic episode). May exacerbate symptoms of behavior and thought disorder in psychotic patients; new onset psychosis or mania may occur with stimulant use; observe for symptoms of aggression and/or hostility.

- Seizure disorder: Use with caution in patients with a history of seizure disorder; may lower seizure threshold leading to new onset or breakthrough seizure activity.

- Tourette's syndrome: Use with caution in patients with Tourette's syndrome; stimulants may unmask tics.

- Weight reduction: Appropriate use: **[U.S. Boxed Warning]: Use in weight reduction programs only when alternative therapy has been ineffective.**

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age for obesity. Use of stimulants has been associated with suppression of growth; monitor growth rate during treatment.

Other warnings/precautions:

- Discontinuation of therapy: Abrupt discontinuation following high doses or for prolonged periods may result in symptoms for withdrawal. Discontinue if satisfactory weight loss has not occurred within the first 4 weeks of treatment, or if tolerance develops.

Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic and embryocidal effects have been observed in animal studies. Infants may deliver prematurely and suffer withdrawal symptoms. There are no adequate and well-controlled studies in pregnant women.
LactationEnters breast milk/contraindicated
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypertension, tachycardia, palpitation

Central nervous system: Restlessness, headache, exacerbation of motor and phonic tics and Tourette's syndrome, dizziness, psychosis, dysphoria, overstimulation, euphoria, insomnia

Dermatologic: Rash, urticaria

Endocrine & metabolic: Change in libido

Gastrointestinal: Diarrhea, nausea, vomiting, stomach cramps, constipation, anorexia, weight loss, xerostomia, unpleasant taste

Genitourinary: Impotence

Neuromuscular & skeletal: Tremor

Miscellaneous: Suppression of growth in children, tolerance and withdrawal with prolonged use

Metabolism/Transport Effects**Substrate** of CYP2D6 (major)
Drug Interactions

Alkalinizing Agents: May decrease the excretion of Amphetamines. *Risk D: Consider therapy modification*

Ammonium Chloride: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

Analgesics (Opioid): Amphetamines may enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Antihistamines: Amphetamines may diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antipsychotics: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Amphetamines. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Ethosuximide: Amphetamines may diminish the therapeutic effect of Ethosuximide. Amphetamines may decrease the serum concentration of Ethosuximide. *Risk C: Monitor therapy*

Gastrointestinal Acidifying Agents: May decrease the serum concentration of Amphetamines. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Methenamine: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

PHENobarbital: Amphetamines may decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Phenytoin: Amphetamines may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause CNS depression).

Food: Amphetamine serum levels may be altered if taken with acidic food, juices, or vitamin C. Avoid caffeine.

Herb/Nutraceutical: Avoid ephedra (may cause hypertension or arrhythmias).

Monitoring ParametersHeart rate, respiratory rate, blood pressure, CNS activity, body weight (BMI); growth rate in children

When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure, and consider obtaining ECG prior to initiation (Vetter, 2008).

Reference Range

Adult classification of weight by BMI (kg/m^2):

Underweight: <18.5

Normal: 18.5-24.9

Overweight: 25-29.9

Obese, class I: 30-34.9

Obese, class II: 35-39.9

Extreme obesity (class III): ≥40

Waist circumference: In adults with a BMI of 25-34.9 kg/m^2, high-risk waist circumference is defined as:

Men >102 cm (>40 in)

Women >88 cm (>35 in)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 5 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Desoxyn)

5 mg (90): $366.81

Mechanism of ActionA sympathomimetic amine related to ephedrine and amphetamine with CNS stimulant activity; peripheral actions include elevation of systolic and diastolic blood pressure and weak bronchodilator and respiratory stimulant action

Pharmacodynamics/Kinetics

Absorption: Rapid from GI tract

Metabolism: Hepatic; forms metabolite

Half-life elimination: 4-5 hours

Excretion: Urine primarily (dependent on urine pH)

Related Information

- Obesity Treatment Guidelines for Adults
- Stimulant Agents Used for ADHD

Pharmacotherapy PearlsIllicit methamphetamine may contain lead; alkalinizing urine can result in longer methamphetamine half-life and elevated blood level; ephedrine is a precursor in the illicit manufacture of methamphetamine; ephedrine is extracted by dissolving ephedrine tablets in water or alcohol (50,000 tablets can result in 1 kg of ephedrine); conversion to methamphetamine occurs at a rate of 50% to 70% of the weight of ephedrine. 3,4-methylene dioxymethamphetamine (slang: XTC, Ecstasy, Adam) affects the serotonergic, dopaminergic, and noradrenergic pathways. As such, it can cause the serotonin syndrome associated with malignant hyperthermia and rhabdomyolysis.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and unpleasant taste. Up to 10% of patients taking methamphetamine may present with hypertension. Monitor blood pressure prior to using local anesthetic with vasoconstrictors.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse vasoconstrictor with caution in patients taking methamphetamine. Amphetamines enhance the sympathomimetic response of epinephrine and norepinephrine leading to potential hypertension and cardiotoxicity.

Cardiovascular ConsiderationsAmphetamines should be avoided in patients with known or suspected cardiovascular disease. They may precipitate marked increases in blood pressure, tachycardia, and tachyarrhythmias. These drugs are often used recreationally and inappropriately, particularly for appetite suppressant effects. Recreational use of amphetamines should be considered in otherwise healthy patients with new onset hypertension, tachycardia, or tachyarrhythmias.

Index TermsDesoxyephedrine Hydrochloride; Methamphetamine Hydrochloride

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International Brand NamesCidrin (CL); Desoxyn (CA)

Methazolamide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Methazolamide may be confused with methenamine, metolazone

Neptazane® may be confused with Nesacaine®

Pronunciation(meth a ZOE la mide)

Canadian Brand NamesApo-Methazolamide®

Pharmacologic CategoryCarbonic Anhydrase Inhibitor; Diuretic, Carbonic Anhydrase Inhibitor; Ophthalmic Agent, Antiglaucoma

Use: Labeled IndicationsAdjunctive treatment of open-angle or secondary glaucoma; short-term therapy of narrow-angle glaucoma when delay of surgery is desired

Dosing: Adults**Glaucoma:** Oral: 50-100 mg 2-3 times/day

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to methazolamide or any component of the formulation; marked kidney or liver dysfunction; severe pulmonary obstruction

Allergy Considerations

- Carbonic Anhydrase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May impair mental alertness and/or physical coordination.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonylurea allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Diabetes: Use with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Respiratory acidosis: Use with caution in patients with respiratory acidosis.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to side effects.

Geriatric ConsiderationsMalaise and complaints of tiredness and myalgia are signs of excessive dosing and acidosis in the elderly.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined.

Central nervous system: Malaise, fever, mental depression, drowsiness, dizziness, nervousness, headache, confusion, seizure, fatigue, trembling, unsteadiness

Dermatologic: Urticaria, pruritus, photosensitivity, rash, Stevens-Johnson syndrome

Endocrine & metabolic: Hyperchloremic metabolic acidosis, hypokalemia, hyperglycemia

Gastrointestinal: Metallic taste, anorexia, nausea, vomiting, diarrhea, constipation, weight loss, GI irritation, xerostomia, black tarry stools

Genitourinary: Polyuria, crystalluria, hematuria, renal calculi, impotence

Hematologic: Bone marrow depression, thrombocytopenia, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia, agranulocytosis

Hepatic: Hepatic insufficiency

Neuromuscular & skeletal: Weakness, ataxia, paresthesia

Miscellaneous: Hypersensitivity

Drug Interactions

Alpha-/Beta-Agonists: Carbonic Anhydrase Inhibitors may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amphetamines: Carbonic Anhydrase Inhibitors may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Barbiturate): Carbonic Anhydrase Inhibitors may enhance the adverse/toxic effect of Anticonvulsants (Barbiturate). Specifically, osteomalacia and rickets. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Carbonic Anhydrase Inhibitors may enhance the adverse/toxic effect of Anticonvulsants (Hydantoin). Specifically, osteomalacia and rickets. *Risk C: Monitor therapy*

CarBAMazepine: Carbonic Anhydrase Inhibitors may increase the serum concentration of CarBAMazepine. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Flecainide: Carbonic Anhydrase Inhibitors may decrease the excretion of Flecainide. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Memantine: Carbonic Anhydrase Inhibitors may decrease the excretion of Memantine. *Risk C: Monitor therapy*

Methenamine: Carbonic Anhydrase Inhibitors may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Primidone: Carbonic Anhydrase Inhibitors may enhance the adverse/toxic effect of Primidone. Specifically, osteomalacia and rickets. Carbonic Anhydrase Inhibitors may decrease the serum concentration of Primidone. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: Carbonic Anhydrase Inhibitors may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Trientine: Carbonic Anhydrase Inhibitor Diuretics may decrease the serum concentration of Trientine. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringAssess allergy history. Monitor blood pressure prior to beginning therapy and after first few doses, especially patients on another concomitant diuretic therapy. If you have diabetes, blood glucose levels may be elevated. Monitor blood sugars closely. Monitor for and/or teach patient to monitor and report adverse reactions. Use and teach patient postural hypotension precautions.

Patient EducationTake with food; swallow whole, do not chew or crush. You may experience GI upset and loss of appetite; small frequent meals are advised to reduce these effects and the metallic taste that sometimes occurs with this medication. You may experience lightheadedness, depression, dizziness, or weakness for a few days; use caution when driving or engaging in tasks that require alertness until response to drug is known. Report excessive tiredness; loss of appetite; cramping, pain, or weakness in muscles; acute GI symptoms; CNS changes (depression, drowsiness); difficulty or pain on urination; visual changes; or skin rash. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 25 mg, 50 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Methazolamide)

25 mg (60): $22.99

50 mg (60): $20.99

Mechanism of ActionNoncompetitive inhibition of the enzyme carbonic anhydrase; thought that carbonic anhydrase is located at the luminal border of cells of the proximal tubule. When the enzyme is inhibited, there is an increase in urine volume and a change to an alkaline pH with a subsequent decrease in the excretion of titratable acid and ammonia.

Pharmacodynamics/Kinetics

Onset of action: Slow in comparison with acetazolamide (2-4 hours)

Peak effect: 6-8 hours

Duration: 10-18 hours

Absorption: Slow

Distribution: Well into tissue

Protein binding: ~55%

Metabolism: Slowly from GI tract

Half-life elimination: ~14 hours

Excretion: Urine (~25% as unchanged drug)

Related Information

- Glaucoma Drug Therapy
- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and metallic taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause dizziness or depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause bone marrow suppression; use caution with clozapine and carbamazepine; may increase lithium excretion but overall effect is minimal; if lithium toxicity is severe, hemodialysis is the treatment of choice

International Brand NamesGlaumetax (AR); Neptazane (FR)

Methenamine and Sodium Acid Phosphate

Lexi-Drugs Online

English

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Pronunciation(meth EN a meen & SOW dee um AS id FOS fate)

U.S. Brand NamesUroqid-Acid® No. 2

Pharmacologic CategoryAntibiotic, Miscellaneous

Use: Labeled IndicationsProphylaxis or suppression of bacteriuria associated with recurrent urinary tract infections

Dosing: AdultsProphylaxis or suppression of bacteriuria: Oral: Initial: 2 tablets 4 times daily; maintenance: 2-4 tablets daily in divided doses

Dosing: ElderlyRefer to adult dosing.

Administration: OralAdminister each dose with a full glass of water.

Dietary ConsiderationsLarge amounts of citrus fruit, vegetables, milk or dairy products should not be consumed until the effects on urine pH are known. Each tablet contains 83 mg of sodium

StorageStore at 20°C to 25°C (68°F to 77°F). Protect from light.

ContraindicationsHypersensitivity to methenamine or any component of the formulation; patients with renal insufficiency, severe hepatic disease, severe dehydration, or hyperphosphatemia

Warnings/Precautions

Concerns related to adverse effects:

- Increased serum phosphate: May cause increased serum phosphate levels and subsequent peripheral calcification deposits.
- Metabolic acidosis: Possible risk of metabolic acidosis.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease, edema, and/or hypertension.
- Hypoparathyroidism: Use with caution in patients with hypoparathyroidism.
- Pancreatitis: Use with caution in patients with acute pancreatitis.
- Parenchymal infection: Appropriate use: Should not be used as monotherapy in patients with parenchymal infection associated with fever/chills.

Concurrent drug therapy issues:

- Drugs known to alkalinize urine: Avoid drugs (eg, antacids) which are known to alkalinize the urine (bactericidal activity is lost at urinary pH >6).

Special populations:

- Pregnancy: Use with caution in patients with toxemia of pregnancy.
- Sodium-restricted diet: Use with caution in patients on a sodium-restricted diet.

Other warnings/precautions:

- Appropriate use: Avoid drugs foods (eg, fruits, milk or dairy products) which are known to alkalinize the urine (bactericidal activity is lost at urinary pH >6). Conduct frequent urine pH tests; do not use if acidification of the urine is not achievable. Proteus vulgaris and urea-splitting strains of *Pseudomonas* and *Aerobacter* may be particularly difficult to treat at higher pH. Doses of 8 g/day of methenamine for 3-4 weeks may cause bladder irritation.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Methenamine does cross the placental barrier. Use only if benefit outweighs risk.

LactationEnters breast milk/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Edema, irregular heartbeat, tachycardia

Central nervous system: Asthenia, dizziness, headaches, mental confusion, numbness, pain, seizure, tingling

Dermatologic: Skin rash

Endocrine & metabolic: Metabolic acidosis, thirst

Gastrointestinal: Diarrhea, nausea, vomiting, stomach pain, weight gain

Genitourinary: Bladder irritation, dysuria, painful urination

Neuromuscular & skeletal: Bone/joint pain, muscle cramps

Renal: Albuminuria, hematuria, oliguria

Respiratory: Dyspnea

Drug Interactions

Amphetamines: Methenamine may decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

Antacids: May diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Carbonic Anhydrase Inhibitors: May diminish the therapeutic effect of Methenamine. **Exceptions:** Brinzolamide; Dorzolamide. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Citrus fruit, vegetables, and certain milk and dairy products may decrease efficacy of methenamine by raising urinary pH.

Test InteractionsPresence of urinary formaldehyde may lead to falsely-elevated levels of of urinary catecholamines and vanillylmandelic acid (fluorometric detection); falsely-elevated urinary estriol (acid hydrolysis technique) and 17-hydroxycorticosteroid (Porter-Silber method) and decreased 5-hydroxyindolacetate (nitrosonaphthol method).

Monitoring ParametersUrine pH, renal function, serum sodium and phosphate levels

Monitoring: Lab TestsUrine pH, renal function, serum sodium and phosphate levels

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Methenamine mandelate 500 mg and sodium acid phosphate 500 mg [contains 83 mg sodium]

Manufacturer

Beach Products Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Uroqid #2)

500-500 mg (30): $21.99

Mechanism of ActionMethenamine is hydrolyzed in acidic urine (pH <5.5) to produce formaldehyde, which exerts local nonspecific bactericidal activity. Mandelic acid aids in the acidification of the urine and also exhibits some additional bactericidal activity.

Mental Health: Effects on Mental StatusMay cause confusion or dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMethenamine Mandelate and Sodium Acid Phosphate; Sodium Acid Phosphate and Methenamine

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Methenamine, Phenyl Salicylate, Methylene Blue, Benzoic Acid, and Hyoscyamine

Lexi-Drugs Online

English

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Pronunciation(meth EN a meen, fen nil sa LIS i late, METH i leen bloo, ben ZOE ik AS id & hye oh SYE a meen)
U.S. Brand NamesProsed®/DS
Pharmacologic CategoryAntibiotic, Miscellaneous
Use: Labeled IndicationsUrinary tract discomfort secondary to hypermotility resulting from infection or diagnostic procedures
Dosing: Adults**Urinary tract symptoms:** Oral: One tablet 4 times daily
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Urinary tract symptoms:** Children >12 years: Oral: Dosage must be individualized
Administration: OralAdministration should be followed by liberal fluid intake.
Dietary ConsiderationsFoods/diets which alkalinize urine pH >5.5 decrease activity of methenamine; cranberry juice can be used to acidify urine and increase activity of methenamine.
StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to methenamine, hyoscyamine, methylene blue, phenyl salicylate, benzoic acid, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Belladonna alkaloid allergy: Use with caution in patients with a history of intolerance to belladonna alkaloids.
- Blurred vision: Discontinue use immediately if blurred vision occurs.
- Dizziness: Discontinue use immediately if dizziness occurs.
- Salicylate allergy: Use with caution in patients with a history of intolerance to salicylates.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.
- Tachycardia: Discontinue use immediately if tachycardia occurs.

Disease-related concerns:

- Gastrointestinal disease: Use with caution in patients with pyloric or duodenal obstruction, or gastric ulcers.
- Glaucoma: Use with caution in patients with glaucoma.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis.
- Obstructive uropathy: Use with caution in patients with obstructive uropathy (bladder neck obstruction or prostatic hyperplasia).

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to anticholinergic effects of hyoscyamine.
- Pediatrics: This combination is not recommended for use in children ≤12 years of age.

Other warnings/precautions:

- Urine/stool discoloration: May cause urinary and/or stool discoloration (blue).

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination.
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsMethenamine and hyoscyamine are excreted in breast milk. Refer to individual monographs.
Adverse ReactionsFrequency not defined.

Cardiovascular: Flushing, tachycardia

Central nervous system: Dizziness

Gastrointestinal: Discoloration of stool (blue), nausea, vomiting, xerostomia

Genitourinary: Discoloration of urine (blue), micturition difficulty, urinary retention (acute)

Ocular: Blurred vision

Respiratory: Dyspnea

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Amphetamines: Methenamine may decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

Antacids: May diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May diminish the therapeutic effect of Methenamine. **Exceptions:** Brinzolamide; Dorzolamide. *Risk D: Consider therapy modification*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, oral:

Prosed®/DS: Methenamine 81.6 mg, phenyl salicylate 36.2 mg, methylene blue 10.8 mg, benzoic acid 9 mg, hyoscyamine sulfate 0.12 mg

Generic AvailableNo

ManufacturerFerring Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Prosed/DS)

81.6 mg (100): $169.57

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause anticholinergic side effects; concomitant use with psychotropic agents may produce additive effects

Index TermsBenzoic Acid, Methenamine, Methylene Blue, Phenyl Salicylate, and Hyoscyamine; Hyoscyamine, Methenamine, Benzoic Acid, Phenyl Salicylate, and Methylene Blue; Methylene Blue, Methenamine, Benzoic Acid, Phenyl Salicylate, and Hyoscyamine; Phenyl Salicylate, Methenamine, Methylene Blue, Benzoic Acid, and Hyoscyamine

Methenamine, Sodium Biphosphate, Phenyl Salicylate, Methylene Blue, and Hyoscyamine

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English

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Pronunciation(meth EN a meen, SOW dee um bye FOS fate, fen nil sa LIS i late, METH i leen bloo, & hye oh SYE a meen)

U.S. Brand NamesUrelle®; Urimar-T; Uta®; Utira™-C

Pharmacologic CategoryAntibiotic, Miscellaneous

Use: Labeled IndicationsTreatment of symptoms of irritative voiding; relief of local symptoms associated with urinary tract infections; relief of urinary tract symptoms caused by diagnostic procedures

Dosing: Adults**Urinary tract symptoms:** Oral: One tablet 4 times daily (follow by liberal fluid intake)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Urinary tract symptoms:** Children >6 years: Oral: Dosage must be individualized

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to methenamine, hyoscyamine, methylene blue, or any component of the formulation

Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Belladonna alkaloid allergy: Use with caution in patients with a history of intolerance to belladonna alkaloids.
- Blurred vision: Discontinue use immediately if blurred vision occurs.
- Dizziness: Discontinue use immediately if dizziness occurs.
- Salicylate allergy: Use with caution in patients with a history of intolerance to salicylates.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea and pseudomembranous colitis.
- Tachycardia: Discontinue use immediately if tachycardia occurs.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (cardiac arrhythmias, HF, coronary heart disease, mitral stenosis).
- Gastrointestinal tract obstruction: Use with caution in patients with gastrointestinal tract obstruction.
- Glaucoma: Use with caution in patients with glaucoma.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis.
- Obstructive uropathy: Use with caution in patients with obstructive uropathy (bladder neck obstruction or prostatic hyperplasia).

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to anticholinergic effects of hyoscyamine.
- Pediatrics: Safety and efficacy have not been established in children ≤6 years of age.

Other warnings/precautions:

- Urine discoloration: May cause urinary discoloration (blue).

Pregnancy Risk FactorC

LactationEnters breast milk/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Tachycardia, flushing

Central nervous system: Dizziness

Gastrointestinal: Xerostomia, nausea, vomiting

Genitourinary: Urinary retention (acute), micturition difficulty, discoloration of urine (blue)

Ocular: Blurred vision

Respiratory: Dyspnea

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Amphetamines: Methenamine may decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

Antacids: May diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May diminish the therapeutic effect of Methenamine. **Exceptions:** Brinzolamide; Dorzolamide. *Risk D: Consider therapy modification*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, oral:

Uta®: Methenamine 120 mg, sodium biphosphate 40.8 mg, phenyl salicylate 36 mg, methylene blue 10 mg, hyoscyamine sulfate 0.12 mg

Tablet, oral:

Urelle®: Methenamine 81 mg, sodium biphosphate 40.8 mg, phenyl salicylate 32.4 mg, methylene blue 10.8 mg, hyoscyamine sulfate 0.12 mg

Urimar-T: Methenamine 81.6 mg, sodium biphosphate 40.8 mg, phenyl salicylate 36.2 mg, methylene blue 10.8 mg, hyoscyamine sulfate 0.12 mg

Utira™-C: Methenamine 81.6 mg, sodium biphosphate 40.8 mg, phenyl salicylate 36.2 mg, methylene blue 10.8 mg, hyoscyamine sulfate 0.12 mg

Generic AvailableNo

ManufacturerIntegrity Pharmaceutical Corp

Pricing: U.S. (www.drugstore.com)

Capsules (UTA)

120 mg (30): $35.79

Tablets (Urelle)

81 mg (30): $55.66

Tablets (Urimar T)

81.6 mg (120): $82.99

Tablets (Utira-C)

81.6 mg (100): $119.99

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause anticholinergic side effects which may be additive with psychotropics

Index TermsHyoscyamine, Methenamine, Sodium Biphosphate, Phenyl Salicylate, and Methylene Blue; Methylene Blue, Methenamine, Sodium Biphosphate, Phenyl Salicylate, and Hyoscyamine; Phenyl Salicylate, Methenamine, Methylene Blue, Sodium Biphosphate, and Hyoscyamine; Sodium Biphosphate, Methenamine, Methylene Blue, Phenyl Salicylate, and Hyoscyamine

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Methenamine

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English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Methenamine may be confused with mesalamine, methazolamide, methionine

Urex® may be confused with Eurax®, Serax®

International issues:

Urex®: Brand name for furosemide in Australia

Pronunciation(meth EN a meen)

U.S. Brand NamesHiprex®; Mandelamine® [DSC]; Urex™

Canadian Brand NamesDehydral®; Hiprex®; Mandelamine®; Urasal®; Urex™

Pharmacologic CategoryAntibiotic, Miscellaneous

Use: Labeled IndicationsProphylaxis or suppression of recurrent urinary tract infections; urinary tract discomfort secondary to hypermotility

Dosing: Adults**Urinary tract infection:** Oral:

Hippurate: 1 g twice daily

Mandelate: 1 g 4 times/day after meals and at bedtime

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Urinary tract infection:** Oral:

>2-6 years: *Mandelate:* 50-75 mg/kg/day in 3-4 doses or 0.25 g/30 lb 4 times/day

6-12 years:

Hippurate: 0.5-1 g twice daily

Mandelate: 50-75 mg/kg/day in 3-4 doses or 0.5 g 4 times/day

>12 years: Refer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <50 mL/minute: Avoid use.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister around-the-clock to promote less variation in effect. Foods/diets which alkalinize urine pH >5.5 decrease activity of methenamine.

Dietary ConsiderationsFoods/diets which alkalinize urine pH >5.5 decrease activity of methenamine; cranberry juice can be used to acidify urine and increase activity of methenamine. Hiprex® contains tartrazine dye.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

ContraindicationsHypersensitivity to methenamine or any component of the formulation; severe dehydration, renal insufficiency, severe hepatic insufficiency; concurrent treatment with sulfonamides

Warnings/Precautions

Concerns related to adverse effects:

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Gout: Use with caution in patients with gout.

- Hepatic impairment: Use with caution in patients with hepatic impairment; reversible increases in LFTs have occurred during therapy especially in patients with hepatic dysfunction. Contraindicated in patients with severe impairment.

Special populations:

- Elderly: Use with caution in the elderly.

Dosage form specific issues:

- Tartrazine: Hiprex® contains tartrazine dye, which may cause allergic reactions in certain individuals.

Other warnings/precautions:

- Appropriate use: Should not be used to treat infections outside of the lower urinary tract; doses of 8 g/day for 3-4 weeks may cause bladder irritation. Use care to maintain an acid pH of the urine, especially when treating infections due to urea splitting organisms (eg, *Proteus* and strains of *Pseudomonas*)

Geriatric ConsiderationsMethenamine has little, if any, role in the treatment or prevention of infections in patients with indwelling urinary (Foley) catheters. Furthermore, in noncatheterized patients, more effective antibiotics are available for the prevention or treatment of urinary tract infections. The influence of decreased renal function on the pharmacologic effects of methenamine results are unknown.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAdverse events were observed in some animal studies. Following a single 1 g dose of methenamine hippurate given prior to delivery, methenamine was found to slowly pass through the placental barrier. There were no signs of accumulation in the fetal circulation. Actual concentrations in the amniotic fluid varied. Methenamine has been considered to be "probably safe" for use during pregnancy. Methenamine has been shown to interfere with urine oestriol concentrations during pregnancy; serum levels are not affected.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsThe concentration of methenamine hippurate in breast milk is approximately the same as that in the maternal plasma. The amount ingested by a breast-feeding infant is considered to be below a therapeutic dose.
Adverse Reactions<4%:

Dermatologic: Pruritus, rash

Gastrointestinal: Dyspepsia, nausea, vomiting

Hepatic: ALT increased (reversible; rare), AST increased (reversible; rare)

Note: Large doses (higher than recommended) have resulted in bladder irritation, frequent/painful micturition, albuminuria, and hematuria.

Drug Interactions

Amphetamines: Methenamine may decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

Antacids: May diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Carbonic Anhydrase Inhibitors: May diminish the therapeutic effect of Methenamine. **Exceptions:** Brinzolamide; Dorzolamide. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Foods/diets which alkalinize urine pH >5.5 decrease therapeutic effect of methenamine.
Test InteractionsIncreased urinary catecholamines, 17-hydroxycorticosteroid and vanillylmandelic acid (VMA) levels; decreased urinary 5-hydroxyindoleacetic acid (5HIAA) and estriol levels
Monitoring ParametersUrinalysis, periodic liver function tests
Nursing: Physical Assessment/MonitoringMethenamine should not be used to treat infections outside of the lower urinary tract. Assess potential for interactions with other pharmacological agents patient may be taking (eg, anything that alkalizes urine or sulfonamides). Assess therapeutic effectiveness (urinalysis, indicates resolution of infection) and adverse response. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsUrinalysis, periodic liver function
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take per recommended schedule, at regular intervals around-the-clock. Complete full course of therapy; do not skip doses. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid excessive citrus fruits, milk, or alkalizing medications. May cause nausea or vomiting or GI upset (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report pain on urination or blood in urine, skin rash, other persistent adverse effects, or if condition does not improve. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, as hippurate: 1 g

Hiprex®, Urex™: 1 g [Hiprex® contains tartrazine dye]

Tablet, as mandelate: 500 mg [DSC], 1 g [DSC]

Mandelamine®: 500 mg [DSC], 1 g [DSC]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Hiprex)

1 g (20): $49.90

Tablets (Mandelamine)

0.5 g (120): $76.00

Tablets (Methenamine Hippurate)

1 g (100): $99.99

Tablets (Urex)

1 g (30): $45.99

Mechanism of ActionMethenamine is hydrolyzed to formaldehyde and ammonia in acidic urine; formaldehyde has nonspecific bactericidal action. Other components, hippuric acid or mandelic acid, aid in maintaining urine acidity and may aid in suppressing bacteria.

Pharmacodynamics/Kinetics

Absorption: Readily

Metabolism: Gastric juices: Hydrolyze 10% to 30% unless protected via enteric coating; Hepatic: ~10% to 25%

Half-life elimination: 3-6 hours

Excretion: Urine (90% as unchanged drug) within 24 hours

Pharmacotherapy PearlsShould not be used to treat infections outside of the lower urinary tract. Methenamine has little, if any, role in the treatment or prevention of infections in patients with indwelling urinary (Foley) catheters. Furthermore, in noncatheterized patients, more effective antibiotics are available for the prevention or treatment of urinary tract infections. The influence of decreased renal function on the pharmacologic effects of methenamine results are unknown.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsHexamethylenetetramine; Methenamine Hippurate; Methenamine Mandelate

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International Brand NamesAntihydral (CH, LU); Haiprex (DK); Hexamandin (PL); Hipeksal (FI); Hiprex (AE, AT, BB, BF, BJ, BM, BS, BZ, CI, CR, DO, ET, FI, GB, GH, GM, GN, GT, GY, HN, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, NO, OM, PA, PH, SC, SD, SE, SL, SN, SR, SV, TN, TT, TZ, UG, ZA, ZM, ZW); Mandehexan (PL); Mandelamine (PL); Mandepiril-S (MX); Pedipur (PL); Stoppot (PL); Urotractan (DE)

Methimazole

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Methimazole may be confused with metolazone

Pronunciation(meth IM a zole)

U.S. Brand NamesNorthyx™; Tapazole®

Canadian Brand NamesDom-Methimazole; PHL-Methimazole; Tapazole®

Pharmacologic Category[Antithyroid Agent](); [Thioamide]()

Use: Labeled IndicationsPalliative treatment of hyperthyroidism, return the hyperthyroid patient to a normal metabolic state prior to thyroidectomy, and to control thyrotoxic crisis that may accompany thyroidectomy

Dosing: Adults

Hyperthyroidism: Oral:

Initial: 15 mg/day in 3 divided doses (approximately every 8 hours) for mild hyperthyroidism; 30-40 mg/day in moderately severe hyperthyroidism; 60 mg/day in severe hyperthyroidism; maintenance: 5-15 mg/day (may be given as a single daily dose in many patients)

Adjustment: Adjust dosage as required to achieve and maintain serum T_3, T_4, and TSH levels in the normal range. An elevated T_3 may be the sole indicator of inadequate treatment. An elevated TSH indicates excessive antithyroid treatment.

Thyrotoxic crisis: Recommendations vary widely and have not been evaluated in comparative trials: Dosages of 20-30 mg every 6-12 hours have been recommended for short-term initial therapy, followed by gradual reduction to a maintenance dosage (5-15 mg/day). Rectal administration has been described (Nabil, 1982).

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Administer in 3 equally divided doses at approcximately 8-hour intervals.

Hyperthyroidism: Oral:

Initial: 0.4 mg/kg/day in 3 divided doses; maintenance: 0.2 mg/kg/day in 3 divided doses up to 30 mg/24 hours maximum

Alternatively: Initial: 0.5-0.7 mg/kg/day **or** 15-20 mg/m^2/day in 3 divided doses

Maintenance:$^1/_3$ to $^2/_3$ of the initial dose beginning when the patient is euthyroid

Maximum: 30 mg/24 hours

Calculations

- [Body Surface Area: Pediatrics]()

Administration: OtherIn thyroid storm, rectal administration has been attempted (Nabil, 1982).

Dietary ConsiderationsShould be taken consistently in relation to meals every day.

StorageProtect from light.

ContraindicationsHypersensitivity to methimazole or any component of the formulation; breast-feeding (per manufacturer; however, expert analysis and the AAP state this drug may be used in nursing mothers)

Allergy Considerations

- [Thioureylene Allergy]()

Warnings/Precautions

Concerns related to adverse effects:

- Acneiform eruptions: May cause acneiform eruptions.
- Bleeding: May cause hypoprothrombinemia and bleeding; use with particular caution in patients >40 years of age.
- Bone marrow suppression: May cause significant bone marrow depression; the most severe manifestation is agranulocytosis. Aplastic anemia, thrombocytopenia, and leukopenia may also occur. Use with caution in patients receiving other drugs known to cause myelosuppression particularly agranulocytosis, in patients >40 years of age, and avoid doses >40 mg/day. Discontinue if significant bone marrow suppression occurs, particularly agranulocytosis or aplastic anemia.
- Dermatitis: Antithyroid agents have been associated with rare but severe dermatologic reactions. Rash and urticaria are more common

dermatologic reactions which may not require discontinuation in all cases; discontinue in the presence of exfoliative dermatitis.

- Fever: Discontinue in the presence of unexplained fever.
- Hepatic reactions: Rare, severe hepatic reactions (hepatic necrosis, hepatitis) may occur. Symptoms suggestive of hepatic dysfunction should prompt evaluation. Discontinue in the presence of hepatitis (transaminase >3 times upper limit of normal).
- Lupus-like syndrome: Antithyroid agents have been associated with a variety of autoimmune reactions, including a lupus-like syndrome. Discontinuation may be warranted.
- Vasculitis: Antithyroid agents have been associated (rarely) with the development of ANCA-positive vasculitis or leukocytoclastic vasculitis; prompt discontinuation is warranted in patients who develop vasculitis during therapy.

Geriatric ConsiderationsThe use of antithyroid thioamides is as effective in the elderly as they are in younger adults.
Pregnancy Risk FactorD
Pregnancy ConsiderationsMethimazole crosses the placenta and because adverse events may occur in the fetus following maternal use, it is classified as pregnancy category D. Rare cases of aplasia cutis congenital have been reported in the neonate, as well as a syndrome which includes choanal atresia, facial abnormalities, growth restriction and developmental abnormalities. Additional data is needed to determine any association of these adverse events with maternal methimazole use. Fetal thyroid function may also be transiently suppressed. Untreated hyperthyroidism may also cause adverse events in the mother (eg, heart failure, miscarriage, preeclampsia, thyroid storm); fetus (eg, goiter, growth restriction, hypo/hyperthyroidism, still birth); and neonate (eg, hyper-/hypothyroidism, neuropsychologic damage). The thioamides are treatment of choice for hyperthyroidism during pregnancy. In order to prevent adverse events to the fetus, the lowest effective dose should be used in order to achieve maternal levels of T_4 in the high euthyroid or low hyperthyroid range. Thyroid function should be monitored closely.
LactationEnters breast milk/contraindicated (per manufacturer) (AAP rates “compatible”)
Breast-Feeding ConsiderationsMethimazole is found in breast milk at levels ~0.14% of the weight adjusted maternal dose. Although breast-feeding is contraindicated by the manufacturer, the AAP and other expert analysis have concluded that breast-feeding is generally considered safe. Reviews of thionamide use in breast-feeding have not shown that thyroid function of the breast-fed infant is significantly affected.
Adverse ReactionsFrequency not defined.

Cardiovascular: ANCA-positive vasculitis, edema, leukocytoclastic vasculitis, periarteritis

Central nervous system: CNS stimulation, depression, drowsiness, fever, headache, vertigo

Dermatologic: Alopecia, erythema nodosum, exfoliative dermatitis, pruritus, skin pigmentation, skin rash, urticaria

Endocrine & metabolic: Goiter

Gastrointestinal: Nausea, vomiting, stomach pain, abnormal taste, constipation, weight gain, salivary gland swelling

Hematologic: Agranulocytosis, aplastic anemia, granulocytopenia, hypoprothrombinemia, leukopenia, thrombocytopenia

Hepatic: Cholestatic jaundice, hepatitis, jaundice

Neuromuscular & skeletal: Arthralgia, paresthesia

Renal: Nephritis, nephrotic syndrome

Miscellaneous: SLE-like syndrome

Metabolism/Transport Effects**Inhibits** CYP1A2 (weak), 2A6 (weak), 2B6 (weak), 2C9 (weak), 2C19 (weak), 2D6 (moderate), 2E1 (weak), 3A4 (weak)
Drug Interactions

Sodium Iodide I131: Antithyroid Agents may diminish the therapeutic effect of Sodium Iodide I131. Management: Discontinue antithyroid therapy 3-4 days prior to sodium iodide I-131 administration. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antithyroid Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Monitoring ParametersMonitor for signs of hypothyroidism, hyperthyroidism, T_4, T_3; CBC with differential, liver function (baseline and as needed), serum thyroxine, free thyroxine index
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological or herbal agents patient may be taking (eg, extreme caution with anything that may cause myelosuppression, may increase or decrease levels/effects of other agents). Assess results of laboratory tests at baseline and periodically. Evaluate therapeutic effectiveness (clinical and laboratory indicators) and adverse reactions during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsT_4, T_3, CBC with differential, liver function (baseline and as needed), serum thyroxine, free thyroxine index
Patient EducationDo not take any new prescription, OTC medications, or herbal products during therapy unless approved by prescriber. Take as directed, at the same time each day, around-the-clock (eg, every 8 hours). Do not miss doses or make up missed doses. This drug will need to be taken for an extended period of time to achieve appropriate results. May cause nausea, vomiting, abdominal pain, or abnormal taste (small, frequent meals may help); dizziness or drowsiness; or unusual CNS stimulation (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report rash, fever, unusual bleeding or bruising, unresolved headache, yellowing of eyes or skin, changes in color of urine or feces, or unresolved malaise. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant and do not get pregnant while taking this medicine. Consult prescriber for appropriate contraceptive measures. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 5 mg, 10 mg, 20 mg

Northyx™: 5 mg, 10 mg, 15 mg, 20 mg

Tapazole®: 5 mg, 10 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Methimazole)

5 mg (90): $31.00

10 mg (100): $63.99

Tablets (Tapazole)

5 mg (100): $81.73

10 mg (100): $134.71

Mechanism of ActionInhibits the synthesis of thyroid hormones by blocking the oxidation of iodine in the thyroid gland, blocking iodine's ability to combine with tyrosine to form thyroxine and triiodothyronine (T_3), does not inactivate circulating T_4 and T_3
Pharmacodynamics/Kinetics

Onset of action: Antithyroid: Oral: 12-18 hours

Duration: 36-72 hours

Distribution: Concentrated in thyroid gland; crosses placenta; enters breast milk (1:1)

Protein binding, plasma: None

Metabolism: Hepatic

Bioavailability: 80% to 95%

Half-life elimination: 4-13 hours

Excretion: Urine (80%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Abnormal taste and salivary gland swelling.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness
Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; use caution with clozapine and carbamazepine; concurrent use with lithium may increase the effects on the thyroid
Anesthesia and Critical Care Concerns/Other ConsiderationsHypothyroidism and congenital defects (rare) may occur. Agranulocytosis, when it occurs, is usually seen during the first several months of therapy and with maintenance doses >40 mg/day.
Index TermsThiamazole
References

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Nabil N, Miner DJ, and Amatruda JM, “Methimazole: An Alternative Route of Administration,” *J Clin Endocrinol Metab*, 1982, 54(1):180-1.[PubMed 7054215]

Nayak B and Burman K, “Thyrotoxicosis and Thyroid Storm,” *Endocrinol Metab Clin North Am*, 2006, 35(4):663-86.[PubMed 17127140]

Ozaki N, Miura Y, Sakakibara A, et al, “A Case of Hypersensitivity Syndrome induced by Methimazole for Graves' Disease,” *Thyroid*, 2005, 15(12):1333-6.[PubMed 16405404]

Raby C, Lagorce JF, Jambut-Absil AC, et al, “The Mechanism of Action of Synthetic Antithyroid Drugs: Iodine Complexation During Oxidation of Iodide,” *Endocrinology*, 1990, 126(3):1683-91.[PubMed 1689656]

International Brand Names Athyrazol (HR); Based (TW); Danantizol (AR, PY); Favistan (AT, CZ, DE, HR, HU); Methimazol (PL); Methizol (DE); Metibasol (PT); Metizol (PL); Metothyrin (HU); Strumazol (BE, LU, NL); Tapazol (BR, CO, PE, VE); Tapazole (CH, IT, PH, TH); Tapdin (PH); Thacapzol (SE); Thiamazol Henning (AT, DE); Thycaprol (DK); Thyrazol (PH); Thyrozol (CN, DE, LU, PL); Timazol (TH); Tirodril (ES)

Methocarbamol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Methocarbamol may be confused with mephobarbital

Robaxin® may be confused with ribavirin, Rubex®

Pronunciation(meth oh KAR ba mole)

U.S. Brand NamesRobaxin®

Canadian Brand NamesRobaxin®

Pharmacologic CategorySkeletal Muscle Relaxant

Use: Labeled IndicationsTreatment of muscle spasm associated with acute painful musculoskeletal conditions; supportive therapy in tetanus

Use: DentalTreatment of muscle spasm associated with acute temporomandibular joint pain (TMJ)

Dosing: Adults

Muscle spasm:

Oral: 1.5 g 4 times/day for 2-3 days (up to 8 g/day may be given in severe conditions), then decrease to 4-4.5 g/day in 3-6 divided doses

I.M., I.V.: 1 g every 8 hours if oral not possible; injection should not be used for more than 3 consecutive days. If condition persists, may repeat course of therapy after a drug-free interval of 48 hours.

Tetanus: I.V.: Initial dose: 1-3 g; may repeat dose every 6 hours until oral dosing is possible; injection should not be used for more than 3 consecutive days

Dosing: ElderlyMuscle spasm: Oral: Initial: 500 mg 4 times/day; titrate to response

Dosing: Pediatric

Tetanus (recommended **only** for use in tetanus): I.V.: 15 mg/kg/dose or 500 mg/m^2/dose, may repeat every 6 hours if needed; maximum dose: 1.8 g/m^2/day for 3 days only

Muscle spasm: Children ≥16 years: Refer to adult dosing.

Dosing: Renal ImpairmentDo not administer parenteral formulation to patients with renal dysfunction.

Dosing: Hepatic ImpairmentSpecific dosing guidelines are not available. Plasma protein binding and clearance are decreased; half-life is increased.

Calculations

- Body Surface Area: Pediatrics

Administration: I.M.A maximum of 5 mL can be administered into each gluteal region.

Administration: I.V.Maximum rate: 3 mL/minute; injection should not be used for more than 3 consecutive days; may be administered undiluted

Administration: I.V. DetailMonitor closely for extravasation. Administer I.V. while in recumbent position. Maintain position 15-30 minutes following infusion.

Administration: OralTablets may be crushed and mixed with food or liquid if needed. Avoid alcohol.

Storage

Injection: Prior to dilution, store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Injection when diluted to 4 mg/mL in sterile water, 5% dextrose, or 0.9% saline is stable for 6 days at room temperature. Do **not** refrigerate after dilution.

Tablet: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to methocarbamol or any component of the formulation; renal impairment (injection formulation)

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use oral with caution in patients with renal impairment.
- Seizure disorder: Use injection with caution in patients with a history of seizure disorder.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Pediatrics: Oral formulation: Safety and efficacy have not been established in children <16 years of age.

Dosage form specific issues:

- Injection: Rate of injection should not exceed 3 mL/minute; solution is hypertonic; avoid extravasation. Vial stopper contains latex.

Geriatric ConsiderationsThere is no specific information on the use of skeletal muscle relaxants in the elderly. Methocarbamol has a short half-life, so it may be considered one of the safer agents in this class.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. The manufacturer notes that fetal and congenital abnormalities have been rarely reported following *in utero* exposure. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Flushing of face, bradycardia, hypotension, syncope

Central nervous system: Drowsiness, dizziness, lightheadedness, convulsion, vertigo, headache, fever, amnesia, confusion, insomnia, sedation, coordination impaired (mild)

Dermatologic: Allergic dermatitis, urticaria, pruritus, rash, angioneurotic edema

Gastrointestinal: Nausea, vomiting, metallic taste, dyspepsia

Hematologic: Leukopenia

Hepatic: Jaundice

Local: Pain at injection site, thrombophlebitis

Ocular: Nystagmus, blurred vision, diplopia, conjunctivitis

Renal: Renal impairment

Respiratory: Nasal congestion

Miscellaneous: Allergic manifestations, anaphylactic reaction

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pyridostigmine: Methocarbamol may diminish the therapeutic effect of Pyridostigmine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsMay cause color interference in certain screening tests for 5-HIAA using nitrosonaphthol reagent and in screening tests for urinary VMA using the Gitlow method.

Nursing: Physical Assessment/MonitoringAssess other medications for excess CNS depression. Monitor effectiveness of therapy (according to rationale for therapy) and adverse reactions at beginning and periodically during therapy. Monitor I.V. site closely to prevent extravasation. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed. Do not increase dose or discontinue without consulting prescriber. Do not use alcohol, prescriptive or OTC antidepressants, sedatives, or pain medications without consulting prescriber. You may experience drowsiness, dizziness, lightheadedness (avoid driving or engaging in tasks requiring alertness until response to drug is known); or nausea or vomiting (small frequent meals, frequent mouth care, or sucking hard candy may help). Report excessive drowsiness or mental agitation, chest pain, skin rash, swelling of mouth/face, difficulty speaking, or vision changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 100 mg/mL (10 mL) [in polyethylene glycol; vial stopper contains latex]

Tablet: 500 mg, 750 mg

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Tablets (Methocarbamol)

500 mg (60): $14.97

Tablets (Robaxin)

500 mg (30): $39.55

Tablets (Robaxin-750)

750 mg (30): $50.54

Mechanism of ActionCauses skeletal muscle relaxation by general CNS depression

Pharmacodynamics/Kinetics

Onset of action: Muscle relaxation: Oral: ~30 minutes

Protein binding: 46% to 50%

Metabolism: Hepatic via dealkylation and hydroxylation

Half-life elimination: 1-2 hours

Time to peak, serum: ~2 hours

Excretion: Urine (as metabolites)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Metallic taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and dizziness are common

Mental Health: Effects on Psychiatric TreatmentMay rarely cause leukopenia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation

References

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Preston KL, Guarino JJ, Kirk WT, et al, “Evaluation of the Abuse Potential of Methocarbamol,” *J Pharmacol Exp Ther*, 1989, 248(3):1146-57.[PubMed 2703967]

International Brand NamesBolaxin (TW); Carbaflex (HN, NI, SV); Carbamol (KP); Lumirelax (FR); Manobaxine (TH); Methocarbamol (PL); Miowas (ES, IT); Myolax (TW); New-Rexan (KP); Ortoton (DE); Rebamol (TW); Rexivin (MX); Robaxin (AE, BB, BH, BM, BS, BZ, CH, CO, CY, EG, ES, FI, GY, HK, IL, IQ, IR, JM, JO, KP, KW, LB, LY, NL, OM, QA, SA, SR, SY, TT, YE, ZA); Robaxin-750 (GB); Robinax (IN); Sinaxar (CO)

Methohexital

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Brevital® may be confused with Brevibloc®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(meth oh HEKS i tal)

U.S. Brand NamesBrevital® Sodium

Canadian Brand NamesBrevital®

Pharmacologic CategoryBarbiturate; General Anesthetic

Use: Labeled IndicationsFor induction of anesthesia prior to the use of other general anesthetic agents; as an adjunct to subpotent inhalational anesthetic agents for short surgical procedures; for short surgical, diagnostic, or therapeutic procedures associated with minimal painful stimuli

Additional indications for adults: For use with other parenteral agents, usually narcotic analgesics, to supplement subpotent inhalational anesthetic agents for longer surgical procedures; as an agent to induce a hypnotic state

Use: Unlabeled/InvestigationalWada test

Use: DentalInduction and maintenance of general anesthesia for short procedures

Dosing: Adults

Anesthesia (doses must be titrated to effect): I.V.: Induction: 1-1.5 mg/kg; maintenance: 50-120 mcg/kg/minute (or 20-40 mg every 4-7 minutes)

Wada test (unlabeled): I.V.: 2-4 mg

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Anesthesia: Doses must be titrated to effect

Infants <1 month: Safety and efficacy not established

Infants ≥1 month and Children: Induction:

I.M.: 6.6-10 mg/kg of a 5% solution

Rectal: Usual: 25 mg/kg of a 1% solution

I.V. (unlabeled dose): 1-2 mg/kg/dose of a 1% solution

Procedural sedation (unlabeled dose): Infants ≥1 month and Children:

I.V.: Initial: 0.5 mg/kg given immediately prior to procedure; if sedation not adequate, repeat 0.5 mg/kg to a maximum total dose of 2 mg/kg

Rectal: 25 mg/kg of a 10% (100 mg/mL) solution given 5-15 minutes prior to procedure; maximum dose 500 mg

Dosing: Hepatic ImpairmentLower dosage and monitor closely.

Administration: I.M.I.M. administration: Use 5% (50 mg/mL) solution

Administration: I.V.

I.V.: Dilute to a maximum concentration of 1% for I.V. use

Induction and maintenance of anesthesia: 1% (10 mg/mL) solution is administered I.V. at a rate of ~1 mL/5 seconds or ~2 mg/second

Wada testing: Dilution of 0.1% (1 mg/mL) has been used; administer I.V. at a rate of 1 mg/second

Continuous I.V. infusion: Use 0.2% (2 mg/mL) solution

Administration: OtherRectal administration: Use 1% (10 mg/mL) solution; 10% (100 mg/mL) solution has also been used (Pomeranz, 2000)

StorageStore at 20°C to 25°C (68°F to 77°F). Reconstituted solutions are chemically stable at room temperature for 24 hours; 0.2% (2 mg/mL) solutions in D_5W or NS are stable at room temperature for 24 hours.

ReconstitutionDo not dilute with solutions containing bacteriostatic agents. Solutions should be freshly prepared and used promptly.

For a 1% (10 mg/mL) solution:

500 mg vial: Dilute with 50 mL with SWFI (preferred), D_5W, or NS

2.5 g vial: Dilute with 15 mL of SWFI (preferred), D_5W, or NS, then add to 235 mL for a total volume of 250 mL

For a 5% (50 mg/mL) solution:

500 mg vial: Dilute with 10 mL of SWFI (preferred), D_5W, or NS

2.5 g vial: Dilute with 50 mL of SWFI (preferred), D_5W, or NS

For a 10% (100 mg/mL) solution:

500 mg vial: Dilute with 5 mL of SWFI (Pomeranz, 2000)

2.5 g vial: Dilute with 25 mL of SWFI (Pomeranz, 2000)

For continuous I.V. anesthesia: Prepare a 0.2% (2 mg/mL) solution by adding 500 mg to 250 mL of D_5W or NS. Do not dilute with SWFI (use of SWFI to make the 0.2% solution will result in extreme hypotonicity).

CompatibilityStable in D_5NS, D_5W, NS.

Note: Solutions are alkaline (pH 9.5-11) and **incompatible** with acids (eg, atropine sulfate, succinylcholine, silicone); also **incompatible** with phenol-containing solutions and silicone.

Y-site administration: Incompatible: Fenoldopam

Compatibility in syringe: Incompatible: Atropine, glycopyrrolate. **Variable (consult detailed reference):** Pancuronium.

Compatibility when admixed: Incompatible: Atracurium, atropine, chlorpromazine, cimetidine, clindamycin, droperidol, fentanyl, hydralazine, kanamycin, lidocaine, mechlorethamine, metaraminol, methyldopate, metocurine, pancuronium, penicillin G, pentazocine, prochlorperazine mesylate, promazine, promethazine, propiomazine, scopolamine, streptomycin, succinylcholine, thiamine, tubocurarine. **Variable (consult detailed reference):** Isoproterenol, norepinephrine.

RestrictionsC-IV

ContraindicationsHypersensitivity to barbiturates, methohexital, or any component of the formulation; porphyria (latent or manifest); patients in whom general anesthesia is contraindicated

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Administration: See "Other warnings/precautions" below.

Concerns related to adverse effects:

- Hypersensitivity reactions: Postmarketing studies have indicated that the use of hypnotic/sedative agents for sleep has been associated with hypersensitivity reactions including anaphylaxis as well as angioedema.

- Hypotension: May cause hypotension; use with caution in hemodynamically unstable patients (hypotension or shock) or severe hypertension.

Disease-related concerns:

- Anemia: Use with caution in patients with severe anemia; respiratory depression may occur leading to further inadequate tissue oxygenation.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease including heart failure; consider monitoring cardiac function.

- Hepatic impairment: Use with caution in patients with hepatic impairment; may prolong or potentiate hypnotic effect.

- Obesity: Use with caution in patients with extreme obesity.

- Pulmonary disease: May cause respiratory depression; use with caution in patients with pulmonary disease. Use with caution in patients with asthma and chronic obstructive pulmonary disease. Use with extreme caution in patients with ongoing status asthmaticus; hiccups, coughing, laryngospasm, and muscle twitching have occurred impairing ventilation.

- Renal impairment: Use with caution in patients with renal impairment; may prolong or potentiate hypnotic effect.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Elderly: Use with caution in the elderly; closely monitor elderly or debilitated patients for impaired cognitive or motor performance.
- Pediatrics: Use with caution in children.

Other warnings/precautions:

- Administration: **[U.S. Boxed Warning]: Should only be administered in hospitals or ambulatory care settings with continuous monitoring of respiratory function; resuscitative drugs, age- and size-appropriate intubation equipment and trained personnel experienced in handling their use should be readily available. For deeply sedated patients, a healthcare provider other than the individual performing the procedure should be present to continuously monitor the patient.**
- Cumulative effect: Repeated dosing or continuous infusions may cause cumulative effects.
- Intravenous (I.V.) administration: Prior to I.V. administration, ensure patient has adequate I.V. access; extravasation or intra-arterial injection causes necrosis.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAnimal studies have not shown fetal or maternal harm. There are no adequate and well-controlled studies in pregnant women. Methohexital crosses the placenta. Use only if potential benefit outweighs risk to fetus.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsMethohexital is minimally excreted in breast milk and levels decline rapidly after administration. Interruption of breast-feeding is unnecessary.

Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiorespiratory arrest, circulatory depression, hypotension, peripheral vascular collapse, tachycardia

Central nervous system: Anxiety, emergence delirium, headache, restlessness, seizure

Dermatologic: Erythema, pruritus, urticaria

Gastrointestinal: Abdominal pain, nausea, salivation, vomiting

Hepatic: Transaminases increased

Local: Injection site pain, nerve injury adjacent to injection site, thrombophlebitis

Neuromuscular & skeletal: Involuntary muscle movement, radial nerve palsy, rigidity, tremor, twitching

Respiratory: Apnea, bronchospasm, cough, dyspnea, hiccups, laryngospasm, respiratory depression, rhinitis

Miscellaneous: Anaphylaxis (rare)

Drug Interactions

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Monitoring ParametersRespiratory status (for conscious sedation, includes pulse oximetry), cardiovascular status, CNS status (when used for procedures monitor sedation score); cardiac monitor and blood pressure monitor required

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance. Periodically evaluate the need for continued use. I.V.: Keep patient under observation. Monitor cardio/respiratory status and institute patient safety precautions. Monitor effectiveness of therapy and adverse reactions. Monitor respiratory status (for conscious sedation, includes pulse oximetry), cardiovascular status, CNS status (when used for procedures monitor sedation score); cardiac monitor and blood pressure monitor required.

Patient EducationMay cause drowsiness

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as sodium:

Brevital® Sodium: 500 mg, 2.5 g

Generic AvailableNo

Mechanism of ActionUltra short-acting I.V. barbiturate anesthetic

Pharmacodynamics/Kinetics

Onset of action: I.V.: Immediate; I.M. (pediatrics): 2-10 minutes; Rectal (pediatrics): 5-15 minutes

Duration: Single dose: I.V.: 10-20 minutes; Rectal: 45 minutes

Metabolism: Hepatic via demethylation and oxidation

Excretion: Urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common

Mental Health: Effects on Psychiatric TreatmentUsed as induction anesthesia for electroconvulsive therapy (ECT); concurrent use with psychotropics may produce additive CNS depression

Anesthesia and Critical Care Concerns/Other ConsiderationsMethohexital does not possess analgesic properties.

Index TermsMethohexital Sodium

References

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Sedik H, “Use of Intravenous Methohexital as a Sedative in Pediatric Emergency Departments,” *Arch Pediatr Adolesc Med*, 2001, 155(6):665-8.[PubMed 11386953]

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Wells D, Davies G, and Wagner D, “Accidental Injection of Epidural Methohexital,” *Anesthesiology*, 1987, 67(5):846-8.[PubMed 3674498]

International Brand NamesBrevimytal Natrium (DE); Brevital (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Brietal (AT, DK, FI, GB, HN, HU, NL, NO, PL, RU, SE, TW); Brietal sodique (FR, LU); Brietal Sodium (BF, BJ, CH, CI, ET, GB, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Brietal-Sodium (AU, CZ, HU)

Methotrexate-Vinblastine (Desmoid Tumor)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category: Chemotherapy Regimen, Soft Tissue Sarcoma

Regimen Use: Soft tissue sarcoma (Desmoid tumor)

Index Terms: Vinblastine-Methotrexate (Desmoid Tumor)

Regimen

Methotrexate: I.V.: 30 mg/m^2 every 7-10 days

[total dose/treatment = 30 mg/m^2]

Vinblastine: I.V.: 6 mg/m^2 every 7-10 days

[total dose/treatment = 6 mg/m^2]

Continue treatment for 1 year (52 treatments)

References

Azzarelli A, Gronchi A, Bertulli R, et al, "Low-Dose Chemotherapy With Methotrexate and Vinblastine for Patients With Advanced Aggressive Fibromatosis," *Cancer*, 2001, 92(5):1259-64.[PubMed 11571741]

Methotrexate

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Methotrexate may be confused with metolazone, mitoxantrone

MTX is an error-prone abbreviation (mistaken as mitoxantrone)

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Errors have occurred (resulting in death) when methotrexate was administered as “daily” dose instead of the recommended “weekly” dose.

International issues:

Trexall™ may be confused with Truxal® which is a brand name for chlorprothixene in Belgium

Trexall™ may be confused with Trexol® which is a brand name for tramadol in Mexico

Pronunciation(meth oh TREKS ate)

U.S. Brand NamesRheumatrex® Dose Pack®; Trexall™

Canadian Brand NamesApo-Methotrexate®; ratio-Methotrexate

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite (Antifolate); Antirheumatic, Disease Modifying

Use: Labeled IndicationsTreatment of trophoblastic neoplasms; leukemias; psoriasis; rheumatoid arthritis (RA), including polyarticular-course juvenile rheumatoid arthritis (JRA); breast, head and neck, and lung carcinomas; osteosarcoma; soft-tissue sarcomas; carcinoma of gastrointestinal tract, esophagus, testes; lymphomas

Use: Unlabeled/InvestigationalTreatment and maintenance of remission in Crohn’s disease; ectopic pregnancy

Dosing: AdultsRefer to individual protocols.

Note: Doses between 100-500 mg/m^2 **may require** leucovorin rescue. Doses >500 mg/m^2 **require** leucovorin rescue: I.V., I.M., Oral: Leucovorin 10-15 mg/m^2 every 6 hours for 8 or 10 doses, starting 24 hours after the start of methotrexate infusion. Continue until the methotrexate level is ≤0.1 micromolar (10^{-7} M). Some clinicians continue leucovorin until the methotrexate level is <0.05 micromolar (5×10^{-8} M) or 0.01 micromolar (10^{-8} M).

If the 48-hour methotrexate level is >1 micromolar (10^{-6} M) or the 72-hour methotrexate level is >0.2 micromolar (2×10^{-7} M): I.V., I.M, Oral: Leucovorin 100 mg/m^2 every 6 hours until the methotrexate level is ≤0.1 micromolar (10^{-7} M). Some clinicians continue leucovorin until the methotrexate level is <0.05 micromolar (5×10^{-8} M) or 0.01 micromolar (10^{-8} M).

Antineoplastic dosage range: I.V.: Range is wide from 30-40 mg/m^2/week to 100-12,000 mg/m^2 with leucovorin rescue

Trophoblastic neoplasms:

Oral, I.M.: 15-30 mg/day for 5 days; repeat in 7 days for 3-5 courses

I.V.: 11 mg/m^2 days 1 through 5 every 3 weeks

Head and neck cancer: Oral, I.M., I.V.: 25-50 mg/m^2 once weekly

Mycosis fungoides (cutaneous T-cell lymphoma): Oral, I.M.: Initial (early stages):

5-50 mg once weekly **or**

15-37.5 mg twice weekly

Bladder cancer: I.V.:

30 mg/m^2 day 1 and 8 every 3 weeks **or**

30 mg/m^2 day 1, 15, and 22 every 4 weeks

Breast cancer: I.V.: 30-60 mg/m^2 Day 1 and 8 every 3-4 weeks

Gastric cancer: I.V.: 1500 mg/m^2 every 4 weeks

Lymphoma, non-Hodgkin's: I.V.:

30 mg/m^2 days 3 and 10 every 3 weeks **or**

120 mg/m^2 day 8 and 15 every 3-4 weeks **or**

200 mg/m^2 day 8 and 15 every 3 weeks **or**

400 mg/m^2 every 4 weeks for 3 cycles **or**

1 g/m^2 every 3 weeks **or**

1.5 g/m^2 every 4 weeks

Sarcoma: I.V.: 8-12 g/m^2 weekly for 2-4 weeks

Rheumatoid arthritis: Oral: 7.5 mg once weekly **or** 2.5 mg every 12 hours for 3 doses/week, not to exceed 20 mg/week

Psoriasis: Oral: 2.5-5 mg/dose every 12 hours for 3 doses given weekly **or** Oral, I.M.: 10-25 mg/dose given once weekly

Ectopic pregnancy (unlabeled use): I.M.: 50 mg/m^2 single-dose

Active Crohn's disease (unlabeled use): Induction of remission: I.M., SubQ: 15-25 mg once weekly; remission maintenance: 15 mg once weekly

Note: Oral dosing has been reported as effective but oral absorption is highly variable. If patient relapses after a switch to oral, may consider returning to injectable.

Dosing: ElderlyRefer to individual protocols; adjust for renal impairment.

Rheumatoid arthritis/psoriasis: Oral: Initial: 5-7.5 mg/week, not to exceed 20 mg/week

Dosing: PediatricRefer to individual protocols.

Note: Doses between 100-500 mg/m^2**may require** leucovorin rescue. Doses >500 mg/m^2**require** leucovorin rescue: I.V., I.M., Oral: Leucovorin 10-15 mg/m^2 every 6 hours for 8 or 10 doses, starting 24 hours after the start of methotrexate infusion. Continue until the methotrexate level is ≤0.1 micromolar (10^{-7} M). Some clinicians continue leucovorin until the methotrexate level is <0.05 micromolar (5 x 10^{-8} M) or 0.01 micromolar (10^{-8} M).

If the 48-hour methotrexate level is >1 micromolar (10^{-6} M) or the 72-hour methotrexate level is >0.2 micromolar (2 x 10^{-7} M): I.V., I.M, Oral: Leucovorin 100 mg/m^2 every 6 hours until the methotrexate level is ≤0.1 micromolar (10^{-7} M). Some clinicians continue leucovorin until the methotrexate level is <0.05 micromolar (5 x 10^{-8} M) or 0.01 micromolar (10^{-8} M).

Dermatomyositis: Oral: 15-20 mg/m^2/week as a single dose once weekly **or** 0.3-1 mg/kg/dose once weekly

Juvenile rheumatoid arthritis: Oral, I.M.:10 mg/m^2 once weekly, then 5-15 mg/m^2/week as a single dose **or** as 3 divided doses given 12 hours apart

Antineoplastic dosage range:

Oral, I.M.: 7.5-30 mg/m^2/week **or** every 2 weeks

I.V.: 10-18,000 mg/m^2 bolus dosing **or** continuous infusion over 6-42 hours

Pediatric solid tumors (high-dose): I.V.:

<12 years: 12-25 g/m^2

≥12 years: 8 g/m^2

Acute lymphocytic leukemia (intermediate-dose): I.V.: Loading: 100 mg/m^2 bolus dose, followed by 900 mg/m^2/day infusion over 23-41 hours.

Meningeal leukemia: I.T.: 10-15 mg/m^2 (maximum dose: 15 mg) **or** an age-based dosing regimen; one possible system is:

≤3 months: 3 mg/dose

4-11 months: 6 mg/dose

1 year: 8 mg/dose

2 years: 10 mg/dose

≥3 years: 12 mg/dose

Dosing: Renal ImpairmentThe FDA-approved labeling does not contain dosage adjustment guidelines.

The following guidelines have been used by some clinicians:

- Cl_{cr} 61-80 mL/minute: Administer 75% of dose
- Cl_{cr} 51-60 mL/minute: Administer 70% of dose
- Cl_{cr} 10-50 mL/minute: Administer 30% to 50% of dose
- Cl_{cr} <10 mL/minute: Avoid use
- Hemodialysis: Not dialyzable (0% to 5%); supplemental dose is not necessary
- Peritoneal dialysis effects: Supplemental dose is not necessary
- CAVH effects: Unknown

Aronoff, 2007:

- Children:
  - Cl_{cr} 10-50 mL/minute: Administer 50% of dose
  - Cl_{cr} <10 mL/minute: Administer 30% of dose
  - Hemodialysis: Administer 30% of dose
  - Continuous ambulatory peritoneal dialysis (CAPD): Administer 30% of dose
  - Continuous renal replacement therapy (CRRT): Administer 50% of dose
- Adults:
  - Cl_{cr} 10-50 mL/minute: Administer 50% of dose
  - Cl_{cr} <10 mL/minute: Avoid use
  - Hemodialysis: Administer 50% of dose
  - Continuous renal replacement therapy (CRRT): Administer 50% of dose

Kintzel, 1995:

- Cl_{cr} 46-60 mL/minute: Administer 65% of normal dose
- Cl_{cr} 31-45 mL/minute: Administer 50% of normal dose
- Cl_{cr} <30 mL/minute: Avoid use

Dosing: Hepatic ImpairmentThe FDA-approved labeling does not contain dosage adjustment guidelines. The following guidelines have been used by some clinicians (Floyd, 2006):

Bilirubin 3.1-5 mg/dL **or** transaminases >3 times ULN: Administer 75% of dose

Bilirubin >5 mg/dL: Avoid use

Dosing: Combination Regimens

Bladder cancer:

- CMV
- M-VAC (Bladder Cancer)

Breast cancer:

- CMF
- CMF-IV
- CMFP
- CMFVP (Cooper Regimen, VPCMF)
- Dox-CMF (Sequential)
- MF
- M-VAC (Breast Cancer)

Cervical cancer: M-VAC (Cervical Cancer)

Endometrial cancer: MVAC (Endometrial Cancer)

Gastric cancer: FAMTX

Gestational trophoblastic tumor:

CHAMOCA (Modified Bagshawe Regimen)

CHAMOMA (Bagshawe Regimen)

EMA/CO

EP/EMA

Head and neck cancer:

CABO

MVAC (Head and Neck)

Leukemia, acute lymphocytic:

Hyper-CVAD + Imatinib

Hyper-CVAD (Leukemia, Acute Lymphocytic)

Linker Protocol

MTX/6-MP/VP (Maintenance)

POMP

PVA (POG 8602)

Leukemia, acute promyelocytic:Tretinoin-Idarubicin

Lymphoma, Hodgkin's disease: COMP

Lymphoma, non-Hodgkin's:

COMLA

Hyper-CVAD (Lymphoma, non-Hodgkin's)

IMVP-16

MACOP-B

m-BACOD

Pro-MACE-CytaBOM

Lymphoma, non-Hodgkin's (Burkitt's): CODOX-M/IVAC

Lymphoma, non-Hodgkin's: (Mantle Cell): Hyper-CVAD + Rituximab

Osteosarcoma:

HDMTX

MTX-CDDPAdr

POG-8651

Soft tissue sarcoma: Methotrexate-Vinblastine (Desmoid Tumor)

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.May be administered I.M.

Administration: I.V.May be administered I.V.; I.V. administration may be as slow push, short bolus infusion, or 24- to 42-hour continuous infusion

Specific dosing schemes vary, but high dose should be followed by leucovorin calcium to prevent toxicity; refer to Leucovorin monograph

Administration: OtherMay be administered I.T or SubQ.

Dietary Considerations

Sodium content of 100 mg injection: 20 mg (0.86 mEq)

Sodium content of 100 mg (low sodium) injection: 15 mg (0.65 mEq)

StorageStore tablets and intact vials at room temperature (15°C to 25°C). Protect from light. Solution diluted in D_5W or NS is stable for 24 hours at room temperature (21°C to 25°C). Reconstituted solutions with a preservative may be stored under refrigeration for up to 3 months, and up to 4 weeks at room temperature. Intrathecal dilutions are stable at room temperature for 7 days, but it is generally recommended that they be used within 4-8 hours.

ReconstitutionDilute powder with D_5W or NS to a concentration ≤25 mg/mL (20 mg and 50 mg vials) and 50 mg/mL (1 g vial). Intrathecal solutions may be reconstituted to 2.5-5 mg/mL with NS, D_5W, lactated Ringer's, or Elliott's B solution. **Use preservative free preparations for intrathecal or high-dose administration.**

CompatibilityStable in D_5NS, D_5W, NS.

Y-site administration: Compatible: Allopurinol, amifostine, amphotericin B cholesteryl sulfate complex, asparaginase, aztreonam, bleomycin, cefepime, ceftriaxone, cimetidine, cisplatin, cyclophosphamide, cytarabine, daunorubicin, dexchlorpheniramine, diphenhydramine, doxorubicin, doxorubicin liposome, etoposide, etoposide phosphate, famotidine, filgrastim, fludarabine, fluorouracil, furosemide, ganciclovir, gatifloxacin, granisetron, heparin, hydromorphone, imipenem/cilastatin, leucovorin, linezolid, lorazepam, melphalan, mesna, methylprednisolone sodium succinate, metoclopramide, mitomycin, morphine, ondansetron, oxacillin, paclitaxel, piperacillin/tazobactam, prochlorperazine edisylate, ranitidine, sargramostim, teniposide, thiotepa, vinblastine, vincristine, vindesine, vinorelbine. **Incompatible:** Chlorpromazine, gemcitabine, idarubicin, ifosfamide, midazolam, nalbuphine, promethazine, propofol. **Variable (consult detailed reference):** Dexamethasone sodium phosphate, droperidol, vancomycin.

Compatibility in syringe: Compatible: Bleomycin, cisplatin, cyclophosphamide, doxapram, doxorubicin, fluorouracil, furosemide, heparin, leucovorin, mitomycin, vinblastine, vincristine. **Incompatible:** Droperidol. **Variable (consult detailed reference):** Metoclopramide.

Compatibility when admixed: Compatible: Cyclophosphamide, cyclophosphamide with fluorouracil, cytarabine, dacarbazine, fluorouracil, hydrocortisone, hydroxyzine, mercaptopurine, ondansetron, sodium bicarbonate, vincristine. **Incompatible:** Bleomycin.

ContraindicationsHypersensitivity to methotrexate or any component of the formulation; severe renal or hepatic impairment; pre-existing profound bone marrow suppression in patients with psoriasis or rheumatoid arthritis, alcoholic liver disease, AIDS, pre-existing blood dyscrasias; pregnancy (in patients with psoriasis or rheumatoid arthritis); breast-feeding

Allergy Considerations

- Methotrexate/Trimetrexate Allergy

Warnings/Precautions

Boxed Warnings:

- Acute renal failure: See “Concerns related to adverse effects” below.
- Ascites/pleural effusion: See “Disease-related concerns” below.
- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Dermatologic reactions: See “Concerns related to adverse effects” below.
- Diarrhea/stomatitis: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.
- Hepatotoxicity: See “Concerns related to adverse effects” below.
- Lymphomas: See “Concerns related to adverse effects” below.
- NSAID's: See “Concurrent drug therapy issues” below.
- Opportunistic infections: See “Concerns related to adverse effects” below.
- Pneumonitis: See “Concerns related to adverse effects” below.
- Pregnancy: See “Special populations” below.
- Preservative containing formulations/diluents: See “Dosage form specific issues” below.
- Radiotherapy recipients: See “Special populations” below..
- Renal impairment: See “Disease-related concerns” below.
- Tumor lysis syndrome: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Acute renal failure: **[U.S. Boxed Warning]: May cause renal damage leading to acute renal failure, especially with high-dose methotrexate;** monitor renal function and methotrexate levels closely, maintain adequate hydration and urinary alkalinization. Use caution in osteosarcoma patients treated with high-dose methotrexate in combination with nephrotoxic chemotherapy (eg, cisplatin).
- Bone marrow suppression: **[U.S. Boxed Warning]: Bone marrow suppression may occur,** resulting in anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia. Use caution in patients with pre-existing bone marrow suppression. Discontinue therapy in RA or psoriasis if a significant decrease in hematologic components is noted.

- Dermatologic reactions: **[U.S. Boxed Warning]: Any dose level or route of administration may cause severe and potentially fatal dermatologic reactions,** including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme. Radiation dermatitis and sunburn may be precipitated by methotrexate administration. Psoriatic lesions may be worsened by concomitant exposure to ultraviolet radiation.

- Diarrhea/stomatitis: **[U.S. Boxed Warning]: Diarrhea and ulcerative stomatitis may require interruption of therapy;** death from hemorrhagic enteritis or intestinal perforation has been reported. Use with caution in patients with peptic ulcer disease, ulcerative colitis.

- Fertility: May cause impairment of fertility, oligospermia, and menstrual dysfunction.

- Hepatotoxicity: **[U.S. Boxed Warning]: Methotrexate has been associated with acute (elevated transaminases) and potentially fatal chronic (fibrosis, cirrhosis) hepatotoxicity.** Risk is related to cumulative dose and prolonged exposure. Monitor closely (with liver function tests, including serum albumin) for liver toxicities. Liver enzyme elevations may be noted, but may not be predictive of hepatic disease in long term treatment for psoriasis (but generally is predictive in rheumatoid arthritis [RA] treatment). With long-term use, liver biopsy may show histologic changes, fibrosis or cirrhosis; periodic liver biopsy is recommended with long-term use for psoriasis and for persistent abnormal liver function tests with RA; discontinue methotrexate with moderate-to-severe change in liver biopsy. Ethanol abuse, obesity, advanced age, and diabetes may increase the risk of hepatotoxic reactions. Use caution with preexisting liver impairment; may require dosage reduction. Use caution when used with other hepatotoxic agents (azathioprine, retinoids, sulfasalazine).

- Lymphomas: **[U.S. Boxed Warning]: Use of low dose methotrexate has been associated with the development of malignant lymphomas;** may regress upon discontinuation of therapy; treat lymphoma appropriately if regression is not induced by cessation of methotrexate.

- Neurotoxicity: May cause neurotoxicity including seizures (usually in pediatric ALL patients), leukoencephalopathy (usually with concurrent cranial irradiation) and stroke-like encephalopathy (usually with high-dose regimens). Chemical arachnoiditis (headache, back pain, nuchal rigidity, fever), myelopathy and chronic leukoencephalopathy may result from intrathecal administration.

- Opportunistic infections: **[U.S. Boxed Warning]: Immune suppression may lead to potentially fatal opportunistic infections.**

- Pneumonitis: **[U.S. Boxed Warning]: May cause potentially life-threatening pneumonitis** (may occur at any time during therapy and at any dosage); monitor closely for pulmonary symptoms, particularly dry, nonproductive cough. Other potential symptoms include fever, dyspnea, hypoxemia, or pulmonary infiltrate.

- Tumor lysis syndrome: **[U.S. Boxed Warning]: Tumor lysis syndrome may occur in patients with high tumor burden;** use appropriate prevention and treatment.

Disease-related concerns:

- Ascites/pleural effusions: **[U.S. Boxed Warning]: Elimination is reduced in patients with ascites and/or pleural fluid;** may require dose reduction or discontinuation. Monitor closely for toxicity.

- Hepatic impairment: Use with caution in patients with pre-existing liver impairment.

- Peptic ulcer disease: Use with caution in patients with peptic ulcer disease; diarrhea and stomatitis may occur.

- Renal impairment: **[U.S. Boxed Warning]: Methotrexate elimination is reduced in patients with renal impairment;** may require dose reduction or discontinuation; monitor closely for toxicity.

- Ulcerative colitis: Use with caution in patients with ulcerative colitis; diarrhea and stomatitis may occur.

Concurrent drug therapy issues:

- Hepatotoxic agents: Use caution when used with other hepatotoxic agents (azathioprine, retinoids, sulfasalazine).

- Nephrotoxic chemotherapy: Use caution in osteosarcoma patients treated with high-dose methotrexate in combination with nephrotoxic chemotherapy (eg, cisplatin).

- NSAID's: **[U.S. Boxed Warning]: Concurrent administration with NSAIDs may cause severe bone marrow suppression, aplastic anemia, and GI toxicity.** Do not administer NSAIDs prior to or during high dose methotrexate therapy; may increase and prolong serum methotrexate levels. Doses used for psoriasis may still lead to unexpected toxicities; use caution when administering NSAIDs or salicylates with lower doses of methotrexate for RA. Methotrexate may increase the levels and effects of mercaptopurine; may require dosage adjustments. Vitamins containing folate may decrease response to systemic methotrexate; folate deficiency may increase methotrexate toxicity.

Special populations:

- Elderly: Use caution in the elderly; increased risk of toxicity.

- Pregnancy: **[U.S. Boxed Warning]: May cause fetal death or congenital abnormalities; do not use for psoriasis or RA treatment in pregnant women.**

- Radiotherapy recipients: **[U.S. Boxed Warning]: Concomitant methotrexate administration with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.**

Dosage form specific issues:

- Benzyl alcohol: Injection may contain benzyl alcohol which has been associated with "gasping syndrome" in neonates.

- Preservative containing formulations/diluents: **[U.S. Boxed Warnings]: Methotrexate formulations and/or diluents containing preservatives should not be used for intrathecal or high-dose therapy.**

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warnings]: Should be administered under the supervision of a physician experienced in the use of antimetabolite therapy;** serious and fatal toxicities have occurred at all dose levels. For rheumatoid arthritis and psoriasis, immunosuppressive therapy should only be used when disease is active and less toxic, traditional therapy is ineffective.

Geriatric ConsiderationsToxicity to methotrexate or any immunosuppressive is increased in the elderly. Must monitor carefully. For rheumatoid arthritis and psoriasis, immunosuppressive therapy should only be used when disease is active and less toxic, traditional therapy is ineffective. Recommended doses should be reduced when initiating therapy in the elderly due to possible decreased metabolism, reduced renal function, and presence of interacting diseases and drugs. Adjust dose as needed for renal function (Cl_{cr}).

Pregnancy Risk FactorX (psoriasis, rheumatoid arthritis)

Pregnancy Considerations**[U.S. Boxed Warning]: May cause fetal death or congenital abnormalities; do not use for psoriasis or RA treatment in pregnant women.** Use for the treatment of neoplastic diseases only when the potential benefit to the mother outweighs the possible risk to the fetus. Pregnancy should be excluded prior to therapy in women of childbearing potential. Pregnancy should be avoided for ≥3 months following treatment in male patients and ≥1 ovulatory cycle in female patients.

LactationEnters breast milk/contraindicated

Adverse Reactions**Note:** Adverse reactions vary by route and dosage. Hematologic and/or gastrointestinal toxicities may be common at dosages used in chemotherapy; these reactions are much less frequent when used at typical dosages for rheumatic diseases.

>10%:

- Central nervous system (with I.T. administration or very high-dose therapy):
  - Arachnoiditis: Acute reaction manifested as severe headache, nuchal rigidity, vomiting, and fever; may be alleviated by reducing the dose
  - Subacute toxicity: 10% of patients treated with 12-15 mg/m^2 of I.T. methotrexate may develop this in the second or third week of therapy; consists of motor paralysis of extremities, cranial nerve palsy, seizure, or coma. This has also been seen in pediatric cases receiving very high-dose I.V. methotrexate.
  - Demyelinating encephalopathy: Seen months or years after receiving methotrexate; usually in association with cranial irradiation or other systemic chemotherapy
- Dermatologic: Reddening of skin
- Endocrine & metabolic: Hyperuricemia, defective oogenesis or spermatogenesis
- Gastrointestinal: Ulcerative stomatitis, glossitis, gingivitis, nausea, vomiting, diarrhea, anorexia, intestinal perforation, mucositis (dose dependent; appears in 3-7 days after therapy, resolving within 2 weeks)
- Hematologic: Leukopenia, thrombocytopenia
- Renal: Renal failure, azotemia, nephropathy
- Respiratory: Pharyngitis

1% to 10%:

- Cardiovascular: Vasculitis
- Central nervous system: Dizziness, malaise, encephalopathy, seizure, fever, chills
- Dermatologic: Alopecia, rash, photosensitivity, depigmentation or hyperpigmentation of skin
- Endocrine & metabolic: Diabetes
- Genitourinary: Cystitis
- Hematologic: Hemorrhage
- Myelosuppressive: This is the primary dose-limiting factor (along with mucositis) of methotrexate; occurs about 5-7 days after methotrexate therapy, and should resolve within 2 weeks
  - WBC: Mild
  - Platelets: Moderate
  - Onset: 7 days
  - Nadir: 10 days
  - Recovery: 21 days
- Hepatic: Cirrhosis and portal fibrosis have been associated with chronic methotrexate therapy; acute elevation of liver enzymes are common after high-dose methotrexate, and usually resolve within 10 days.
- Neuromuscular & skeletal: Arthralgia
- Ocular: Blurred vision
- Renal: Renal dysfunction: Manifested by an abrupt rise in serum creatinine and BUN and a fall in urine output; more common with high-dose methotrexate, and may be due to precipitation of the drug.
- Respiratory: Pneumonitis: Associated with fever, cough, and interstitial pulmonary infiltrates; treatment is to withhold methotrexate during the acute reaction; interstitial pneumonitis has been reported to occur with an incidence of 1% in patients with RA (dose 7.5-15 mg/week)

<1% (Limited to important or life-threatening): Acute neurologic syndrome (at high dosages - symptoms include confusion, hemiparesis, transient blindness, and coma); anaphylaxis, alveolitis, cognitive dysfunction (has been reported at low dosage), decreased resistance to infection, erythema multiforme, hepatic failure, leukoencephalopathy (especially following craniospinal irradiation or repeated high-dose therapy), lymphoproliferative disorders, osteonecrosis and soft tissue necrosis (with radiotherapy), pericarditis, plaque erosions (psoriasis), seizure (more frequent in pediatric patients with ALL), Stevens-Johnson syndrome, thromboembolism

Oncology: VesicantNo

Oncology: Emetic Potential

Low (10% to 30%): <250 mg/m^2

Moderate (30% to 90%): ≥250 mg/m^2

Methotrexate (oral): Very low (<10%)

Drug Interactions

Acitretin: May enhance the hepatotoxic effect of Methotrexate. *Risk X: Avoid combination*

Bile Acid Sequestrants: May decrease the absorption of Methotrexate. *Risk C: Monitor therapy*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Ciprofloxacin: May increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

CycloSPORINE: Methotrexate may increase the serum concentration of CycloSPORINE. This may result in nephrotoxicity. CycloSPORINE may increase the serum concentration of Methotrexate. This may result in nausea, vomiting, oral ulcers, hepatotoxicity and/or nephrotoxicity. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Leflunomide: Methotrexate may enhance the myelosuppressive effect of Leflunomide. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nonsteroidal Anti-Inflammatory Agents: May decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Penicillins: May decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Proton Pump Inhibitors: May decrease the excretion of Methotrexate. Antirheumatic doses of methotrexate probably hold minimal risk. *Risk C: Monitor therapy*

Salicylates: May increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Sapropterin: Methotrexate may decrease the serum concentration of Sapropterin. Specifically, methotrexate may decrease tissue concentrations of tetrahydrobiopterin. *Risk C: Monitor therapy*

Sulfonamide Derivatives: May enhance the adverse/toxic effect of Methotrexate. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Trimethoprim: May enhance the adverse/toxic effect of Methotrexate. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may be associated with increased liver injury).

Food: Methotrexate peak serum levels may be decreased if taken with food. Milk-rich foods may decrease methotrexate absorption. Folate may decrease drug response.

Herb/Nutraceutical: Avoid echinacea (has immunostimulant properties).

Monitoring ParametersFor prolonged use (especially rheumatoid arthritis, psoriasis) a baseline liver biopsy, repeated at each 1-1.5 g cumulative dose interval, should be performed; WBC and platelet counts every 4 weeks; CBC and creatinine, LFTs every 3-4 months; chest x-ray

Reference RangeTherapeutic levels: Variable; Toxic concentration: Variable; therapeutic range is dependent upon therapeutic approach.

High-dose regimens produce drug levels that are between 0.1-1 micromole/L 24-72 hours after drug infusion

Toxic: Low-dose therapy: >0.2 micromole/L; high-dose therapy: >1 micromole/L

Nursing: Physical Assessment/MonitoringMonitor closely if used in presence of preexisting conditions that increase potential for toxicity (eg, renal impairment, peptic ulcer disease, ulcerative colitis, hepatic impairment, bone marrow suppression). Assess potential for interactions with other pharmacological agents and herbal products patient may be using (eg, NSAIDs and salicylates or other hepatotoxic agents, or drugs that may effect the levels/effects of methotrexate). Evaluate results of laboratory tests prior to therapy and at frequent intervals during therapy. Patient should be monitored closely for adverse reactions (eg, hyper- or hypothyroidism, pneumonitis [dry, nonproductive cough], gastrointestinal disturbance [ulcerative stomatitis, pain, intestinal perforation], renal failure [decreased urine output]). Assess effectiveness at regular intervals (according to purpose for use). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Instruct patient of childbearing age (or males who may have intercourse with women of childbearing age) in appropriate use of contraceptive measures during therapy and for 3 months following treatment of males or 1 ovulatory cycle in females.

Monitoring: Lab TestsFor prolonged use (especially rheumatoid arthritis, psoriasis) a baseline liver biopsy, repeated at each 1-1.5 g cumulative dose interval, should be performed; WBC and platelet counts every 4 weeks; CBC and creatinine, LFTs every 3-4 months; chest x-ray

Patient EducationDo not take any new medication during therapy unless approved by prescriber. **Infusion/injection:** Report immediately any redness, swelling, pain, or burning at infusion/injection site. It is very important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake and nutrition (small frequent meals may help). Avoid alcohol to prevent serious side effects. You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause sensitivity to sunlight (use sunscreen, wear protective clothing, and eyewear); nausea or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help; if unresolved, contact prescriber); drowsiness, dizziness, numbness, or blurred vision (use caution when driving or engaging in tasks that require alertness until response to drug is known); loss of hair (may be reversible); color change of skin; permanent sterility; or mouth sores (frequent mouth care with soft toothbrush or cotton swabs and frequent rinses may help). Report immediately any rash, excessive or unusual fatigue, or respiratory difficulty. Report rapid heartbeat or palpitations, black or tarry stools, fever, chills, unusual bleeding or bruising, shortness of breath, persistent GI disturbances, diarrhea, constipation, pain on urination or change in urinary patterns, or any other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. This drug may cause birth defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]: 20 mg, 1 g

Injection, solution: 25 mg/mL (2 mL, 10 mL) [contains benzyl alcohol]

Injection, solution [preservative free]: 25 mg/mL (2 mL, 4 mL, 8 mL, 10 mL, 40 mL)

Tablet: 2.5 mg

Trexall™: 5 mg, 7.5 mg, 10 mg, 15 mg

Tablet, as sodium [dose pack] (Rheumatrex® Dose Pack): 2.5 mg (4 cards with 2, 3, 4, 5, or 6 tablets each)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Methotrexate Sodium)

25 mg/mL (2): $8.99

25 mg/mL (2): $14.99

25 mg/mL (10): $24.99

25 mg/mL (40): $58.99

Solution (Methotrexate Sodium LPF)

25 mg/mL (2): $7.99

Tablets (Rheumatrex)

2.5 mg (8): $49.99

Tablets (Trexall)

10 mg (30): $426.29

Mechanism of ActionMethotrexate is a folate antimetabolite that inhibits DNA synthesis. Methotrexate irreversibly binds to dihydrofolate reductase, inhibiting the formation of reduced folates, and thymidylate synthetase, resulting in inhibition of purine and thymidylic acid synthesis. Methotrexate is cell cycle specific for the S phase of the cycle.

The MOA in the treatment of rheumatoid arthritis is unknown, but may affect immune function. In psoriasis, methotrexate is thought to target rapidly proliferating epithelial cells in the skin.

In Crohn's disease, it may have immune modulator and anti-inflammatory activity.

Pharmacodynamics/Kinetics

Onset of action: Antirheumatic: 3-6 weeks; additional improvement may continue longer than 12 weeks

Absorption: Oral: Rapid; well absorbed at low doses (<30 mg/m^2), incomplete after large doses; I.M.: Complete

Distribution: Penetrates slowly into 3rd space fluids (eg, pleural effusions, ascites), exits slowly from these compartments (slower than from plasma); crosses placenta; small amounts enter breast milk; sustained concentrations retained in kidney and liver

Protein binding: 50%

Metabolism: <10%; degraded by intestinal flora to DAMPA by carboxypeptidase; hepatic aldehyde oxidase converts methotrexate to 7-OH methotrexate; polyglutamates are produced intracellularly and are just as potent as methotrexate; their production is dose- and duration-dependent and they are slowly eliminated by the cell once formed

Half-life elimination: Low dose: 3-10 hours; High dose: 8-12 hours

Time to peak, serum: Oral: 1-2 hours; I.M.: 30-60 minutes

Excretion: Urine (44% to 100%); feces (small amounts)

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy Pearls**Latex-free products:** 50 mg/2 mL, 100 mg/4 mL, and 250 mg/10 mL vials with and without preservatives by Immunex

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Ulcerative stomatitis, gingivitis, glossitis, and mucositis (dose dependent; appears 3-7 days post-therapy and resolves within 2 weeks). Dental professionals should note before prescribing NSAIDS that concurrent administration with methotrexate may cause severe bone marrow suppression, aplastic anemia, and GI toxicity (see Warnings). Although the risk is lower at the methotrexate dosages used for rheumatoid conditions/psoriasis, the addition of an NSAID or salicylate may still lead to unexpected toxicities; caution is warranted.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness

Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; avoid clozapine and carbamazepine

Index TermsAmethopterin; Methotrexate Sodium; MTX (error-prone abbreviation) ; NSC-740

References

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International Brand NamesAbitrexate (AT, IL, TH, TW); Artrait (UY); Atrexel (MX); Biotrexate (IN); Brimexate (IT); Canceren (KP); Emthexat (SE); Emthexate (BE, DK, GR, KP, MY, NL, NO, NZ, PH, PK, PT, TH, TR, TW); Lantarel (DE); Ledertrexate (BE, FR, LU, MX, NL, NZ, PT); Maxtrex (GB, PH); Medsatrexate (MX); Methoblastin (AU); Methotrexat (HR, PL); Methotrexat Bigmar (CH); Methotrexat Ebewe (CH, PL); Methotrexat Farmos (CH); Methotrexat Lachema (HU); Methotrexat Lederle (CH); Methotrexat Teva (CH); Methotrexat-Ebewe (HU); Methotrexat-Teva (HU); Methotrexate (AU, HK, ID, IL, MY, PH, PL, TH, TW); Methotrexate Faulding (SE); Methotrexate Pharmacia (SE); Methotrexate Wyeth Lederle (SE); Methotrexate "Lederle" (HU); Methotrexate[inj.] (HR, IT); Methotrexato (AR); Meticil (PE); Metoject (ES, FR); Metotreksat (HR); Metotreksat-Knoll (PL); Metotressato Teva (IT); Metotrexato (CN, EC); Metotrexato DBL (IT); Metotrexin (BR); Metrex (PY); MTX (KP); MTX Hexal (LU); Neotrexate (IN); Novatrex (FR); Otaxem (MX); P&U Methotrexate (ZA); Pterin (PH); Reumatrex (PE); Texate (MX); Trexan (EE, FI, HN, HU, PL, RU, TR, TW); Trixilem (BG, MX, TH); Zexate (PH, VE)

Methotrimeprazine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(meth oh trye MEP ra zeen)

Canadian Brand NamesApo-Methoprazine®; Novo-Meprazine; Nozinan®; PMS-Methotrimeprazine

Pharmacologic CategoryAnalgesic, Nonopioid

Use: Labeled IndicationsTreatment of schizophrenia or psychosis; management of pain, including pain caused by neuralgia or cancer; adjunct to general anesthesia; management of nausea and vomiting; sedation

Use: Unlabeled/InvestigationalBipolar disorder, agitation

Dosing: Adults

Anxiety, mild-moderate pain: Oral: 6-25 mg/day in 3 divided doses

Psychoses, severe pain: Oral: 50-75 mg/day in 2-3 divided doses; titrate to effect (doses up to 1000 mg/day or greater have been used in treatment of some patients with psychoses). If higher dosages are used to initiate therapy (100-200 mg/day), patients should be restricted to bed for the first few days of therapy.

Sedative: Oral: 10-25 mg at bedtime

Psychoses, severe pain: I.M.: 75-100 mg (administered in 3-4 deep I.M. injections)

Analgesia (postoperative): I.M.: 10-25 mg every 8 hours (2.5-7.5 mg every 4-6 hours is suggested postoperatively if residual effects of anesthetic may be present)

Premedication: I.M.: 10-25 mg every 8 hours (final preoperative dose may be 25-50 mg administered ~1 hour prior to surgery)

During surgical procedures/labor: I.V.: 20-50 mcg/minute (some patients may require up to 100 mcg/minute)

Palliative care: SubQ (continuous infusion): 25-200 mg/day (via syringe driver)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Treatment of psychosis: Children >2 years:

Oral: 0.25 mg/kg/day in 2-3 divided doses; may increase gradually based on response.

Maximum dose: 40 mg/day in children <12 years

I.M.: 0.06-0.125 mg/kg/day in 1-3 divided doses

Dosing: Renal ImpairmentAdminister cautiously although no specific guidelines are available.

Dosing: Hepatic ImpairmentAdminister cautiously although no specific guidelines are available

StorageInjection: Protect from light.

Compatibility**Compatible:** Stable in NS; **incompatible** with alkaline solutions.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to methotrimeprazine, phenothiazines, or any component of the formulation; severe cardiac or hepatic disease; hematologic disorders (blood dyscrasia); history of convulsive disorders; severe CNS depression or coma; concurrent use of MAO inhibitors

Allergy Considerations

- Phenothiazine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction; life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines.

- Anticholinergic effects: Phenothiazines may cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); therefore, they should be used with caution in patients with decreased gastrointestinal motility, urinary retention, BPH, xerostomia, or visual problems. Conditions which also may be exacerbated by cholinergic blockade include narrow-angle glaucoma (screening is recommended) and myasthenia gravis.

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Extrapyramidal symptoms: May cause extrapyramidal symptoms and/or tardive dyskinesia.

- Neuroleptic malignant syndrome (NMS): May be associated with NMS.
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of hypotension or where transient hypotensive episodes would be poorly tolerated (cardiovascular disease or cerebrovascular disease). Hypotension may occur following administration, particularly when parenteral form is used or in high dosages.
- Temperature regulation: May alter temperature regulation.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with bone marrow suppression.
- Cardiac disease: Use with caution in patients with severe cardiac disease.
- Hemodynamic instability: Use with caution in patients who are hemodynamically unstable.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Parkinson's disease: Use with caution in patients with Parkinson's disease.
- Prolactin-dependent tumors: Use with caution in breast cancer or other prolactin-dependent tumors (may elevate prolactin levels).
- Renal impairment: Use with caution in patients with severe renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.
- Seizure disorder: Use with caution in patients with a predisposition to seizures.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Other warnings/precautions:

- Antiemetic effects: May mask toxicity of other drugs due to antiemetic effects.

Pregnancy Risk FactorC
Adverse Reactions**Note:** Frequencies not defined; some reactions listed are based on reports for other agents in this same pharmacologic class, and may not be specifically reported for methotrimeprazine.

Cardiovascular: Hypotension, orthostatic hypotension, tachycardia, QT_c prolongation (rare)

Central nervous system: Extrapyramidal symptoms (pseudoparkinsonism, akathisia, dystonias, tardive dyskinesia), dizziness, seizure, headache, drowsiness, neuroleptic malignant syndrome (NMS), impairment of temperature regulation

Dermatologic: Photosensitivity (rare), rash

Endocrine & metabolic: Gynecomastia, weight gain, menstrual irregularity, libido (changes in)

Gastrointestinal: Constipation, vomiting, nausea, xerostomia, ileus

Genitourinary: Difficulty in urination, ejaculatory disturbances, incontinence, polyuria, ejaculating dysfunction, priapism

Hematologic: Agranulocytosis (rare), leukopenia, eosinophilia, hemolytic anemia, thrombocytopenic purpura, pancytopenia

Hepatic: Cholestatic jaundice, hepatotoxicity

Miscellaneous: Diaphoresis

Metabolism/Transport Effects**Inhibits** CYP2D6
Drug Interactions**Inhibits** CYP2D6 (moderate)

Acetylcholinesterase inhibitors (central): May increase the risk of antipsychotic-related extrapyramidal symptoms; monitor.

Aluminum salts: May decrease the absorption of phenothiazines; monitor.

Amphetamines: Efficacy may be diminished by antipsychotics; in addition, amphetamines may increase psychotic symptoms; avoid concurrent use.

Anticholinergics: May inhibit the therapeutic response to phenothiazines and excess anticholinergic effects may occur; includes benztropine, trihexyphenidyl, biperiden, and drugs with significant anticholinergic activity (TCAs, antihistamines, disopyramide).

Antihypertensives: Concurrent use of phenothiazines with an antihypertensive may produce additive hypotensive effects (particularly orthostasis).

Bromocriptine: Phenothiazines inhibit the ability of bromocriptine to lower serum prolactin concentrations.

CNS depressants: Sedative effects may be additive with phenothiazines. If a patient is receiving methotrimeprazine, the dose of a barbiturate or narcotic should be reduced by 50%. Monitor for increased effects of benzodiazepines, ethanol and other sedative agents.

CYP2D6 substrates: Methotrimeprazine may increase the levels/effects of CYP2D6 substrates. Example substrates include amphetamines, selected beta-blockers, dextromethorphan, fluoxetine, lidocaine, mirtazapine, nefazodone, paroxetine, risperidone, ritonavir, thioridazine, tricyclic antidepressants, and venlafaxine.

CYP2D6 prodrug substrates: Methotrimeprazine may decrease the levels/effects of CYP2D6 prodrug substrates. Example prodrug substrates include codeine, hydrocodone, oxycodone, and tramadol.

Epinephrine: Low potency antipsychotics may diminish the pressor effects of epinephrine.

Guanethidine and guanadrel: Antihypertensive effects may be inhibited by phenothiazines.

Levodopa: Phenothiazines may inhibit the antiparkinsonian effect of levodopa; avoid this combination.

Lithium: Phenothiazines may produce neurotoxicity with lithium; this is a rare effect.

MAO inhibitors: Concurrent use of MAO inhibitors may result in toxicity; these combinations are best avoided.

Metoclopramide: May increase extrapyramidal symptoms (EPS) or risk.

Phenytoin: May reduce serum levels of phenothiazines; phenothiazines may increase phenytoin serum levels.

Polypeptide antibiotics: Rare cases of respiratory paralysis have been reported with concurrent use of phenothiazines.

Propranolol: Serum concentrations of phenothiazines may be increased; propranolol also increases phenothiazine concentrations.

Sulfadoxine-pyrimethamine: May increase phenothiazine concentrations.

Trazodone: Phenothiazines and trazodone may produce additive hypotensive effects.

Tricyclic antidepressants: Concurrent use may produce increased toxicity or altered therapeutic response.

Valproic acid: Serum levels may be increased by phenothiazines.

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Limit caffeine.

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization). Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Monitoring ParametersLiver function should be obtained at baseline and every 2-3 months during therapy.
Monitoring: Lab TestsLiver function should be obtained at baseline and every 2-3 months during therapy.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride: 25 mg/mL (1 mL)

Solution, oral: 5 mg/mL (500 mL) [contains ethanol 2%]

Solution, oral drops: 40 mg/mL (100 mL) [contains ethanol 16.5%]

Tablet, as maleate: 2 mg, 5 mg, 25 mg, 50 mg

Generic AvailableNo
Mechanism of ActionDopamine antagonist; also binds alpha-1, alpha-2, and serotonin receptors
Pharmacodynamics/Kinetics

Onset of action: Injection: 1 hour

Duration: 2-4 hours

Bioavailability: 50%

Time to peak, serum: I.M.: 0.5-1.5 hours; Oral: 1-3 hours

Half-life elimination: 30 hours

Pharmacotherapy PearlsNot available in U.S.
Dental Health Professional ConsiderationsThis drug is known to prolong the QT interval. The QT interval is measured as the time and distance between the Q point of the QRS complex and the end of the T wave in the ECG tracing. After adjustment for heart rate, the QT interval is defined as prolonged if it is more than 450 msec in men and 460 msec in women. A long QT syndrome was first described in the 1950s and 60s as a congenital syndrome involving QT interval prolongation and syncope and sudden death. Some of the congenital long QT syndromes were characterized by a peculiar electrocardiographic appearance of the QRS complex involving a premature atria beat followed by a pause, then a subsequent sinus beat showing marked QT prolongation and deformity. This type of cardiac arrhythmia was originally termed “torsade de pointes” (translated from the French as “twisting of the points”).

Prolongation of the QT interval is thought to result from delayed ventricular repolarization. The repolarization process within the myocardial cell is due to the efflux of intracellular potassium. The channels associated with this current can be blocked by many drugs and predispose the electrical propagation cycle to torsade de pointes.

Methotrimeprazine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged

QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Anticholinergic side effects can cause a reduction of saliva production or secretion, contributing to discomfort and dental disease (ie, caries, oral candidiasis, and periodontal disease). Phenothiazines can cause extrapyramidal reactions which may appear as muscle twitching or increased motor activity of the face, neck, or head.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions (see Dental Comment)

Mental Health: Effects on Mental StatusIs a phenothiazine; dizziness and extrapyramidal symptoms are common; may rarely cause neuroleptic malignant syndrome

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors and patient with hypersensitivity to phenothiazines; may rarely cause agranulocytosis; use caution with clozapine and carbamazepine

Index TermsLevomepromazine; Methotrimeprazine Hydrochloride

References

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand NamesHirnamin (TW); Levium (DE); Levomepromazina (AR); Levozin (FI); Methozane (IL); Neozine (BR); Neurocil (DE); Nozinan (AR, AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, HR, ID, IE, IT, LU, NL, NO, NZ, PH, PT, PY, RU, SE, TR, UY); Ronexine (IL); Sinogan (CO, MX, PE, VE); Tiscerin (KP); Tisercin (HU, PL); Tisercin [compr.] (PL); Togrel (AR)

Methoxsalen

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Methoxsalen soft gelatin capsules (Oxsoralen-Ultra®) may be confused with methoxsalen hard gelatin capsules (8-MOP®, Oxsoralen®); bioavailability and photosensitization onset differ between the two products.

Pronunciation(meth OKS a len)

U.S. Brand Names8-MOP®; Oxsoralen-Ultra®; Oxsoralen®; Uvadex®

Canadian Brand NamesOxsoralen-Ultra®; Oxsoralen®; Ultramop™; Uvadex®

Pharmacologic CategoryPsoralen

Use: Labeled Indications

Oral: Symptomatic control of severe, recalcitrant disabling psoriasis; repigmentation of idiopathic vitiligo; palliative treatment of skin manifestations of cutaneous T-cell lymphoma (CTCL)

Topical: Repigmentation of idiopathic vitiligo

Extracorporeal: Palliative treatment of skin manifestations of CTCL

Dosing: Adults**Note:** Refer to treatment protocols for UVA exposure guidelines.

Psoriasis: Oral:

Initial: 10-70 mg 1.5-2 hours (Oxsoralen-Ultra®) or 2 hours (8-MOP®) before exposure to UVA light; dose may be repeated 2-3 times per week, based on UVA exposure; doses must be given at least 48 hours apart; dosage is based upon patient's body weight and skin type:

<30 kg: 10 mg

30-50 kg: 20 mg

51-65 kg: 30 mg

66-80 kg: 40 mg

81-90 kg: 50 mg

91-115 kg: 60 mg

>115 kg: 70 mg

Note: Dosage may be increased (one time) by 10 mg after 15th treatment if minimal or no response.

Maintenance: When 95% psoriasis clearing achieved, may begin 1 treatment every week for at least 2 treatments; followed by 1 treatment every 2 weeks for at least 2 treatments; then every 3 weeks for at least 2 treatments then as needed to maintain response while minimizing UVA exposure.

Vitiligo:

Oral (8-MOP®): 20 mg 2-4 hours before exposure to UVA light; dose may be repeated based on erythema and tenderness of skin; do not give on 2 consecutive days

Topical (Oxsoralen®): Lotion is applied prior to UVA light exposure, usually no more than once weekly

CTCL: Extracorporeal (Uvadex®): 200 mcg injected into the photoactivation bag during the collection cycle using the UVAR® photopheresis system (consult user's guide). Treatment schedule: Two consecutive days every 4 weeks for a minimum of 7 treatment cycles, may accelerate to two consecutive days every 2 weeks if skin score worsens (eg, increases from baseline) after assessment during the fourth treatment cycle. If skin score improves by 25% after 4 consecutive weeks of accelerated therapy, may resume regular treatment schedule. Maximum: 20 accelerated therapy cycles.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricVitiligo: Topical: Children >12 years: Refer to adult dosing.

Administration: TopicalHands and fingers of person applying the lotion should be protected to prevent possible photosensitization and/or burns.

Dietary ConsiderationsTo reduce nausea, oral drug can be administered with food or milk or in 2 divided doses 30 minutes apart.

ContraindicationsHypersensitivity to methoxsalen (psoralens) or any component of the formulation; diseases associated with photosensitivity (eg, albinism, lupus erythematosus, porphyria [cutanea tarda, erythropoietic and variegate], xeroderma pigmentosum); invasive squamous cell cancer; aphakia; melanoma or history of melanoma; children <12 years of age (Oxsoralen® lotion)

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.
- Product interchange: See “Dosage form specific issues” below.

Concerns related to adverse effects:

- Burns: Serious burns may occur from ultraviolet radiation or sunlight (even if exposed through glass) if recommended dose and/or exposure schedule is not maintained.
- Cataracts: Methoxsalen concentrates in the lens; eyes should be shielded from direct and indirect sunlight for 24 hours to prevent possible formation of cataracts.
- Photosensitivity: Avoid sun (including sun lamp) exposure for 8 hours after methoxsalen ingestion. Protective clothing, eyewear, and sunscreen (do not apply sunscreen to psoriatic areas) should be used for 24 hours after combined methoxsalen/UVA therapy. Do not use in sunburned patients until they have fully recovered; pre-existing sunburn may obscure evaluation of response; advise patients to avoid sunbathing for 24 hours prior to treatment and for 48 hours after treatment. Use extreme caution in patients who have significant exposure to the sun through their occupation.
- Skin cancer: Therapy may lead to increased risk of skin cancer (basal cell, melanoma and squamous cell); this risk may be increased with fair skin or prior exposure to prolonged tar and UVB treatment, ionizing radiation, or arsenic.

Disease-related concerns:

- Basal cell carcinoma: Use with caution in patients with multiple basal cell carcinomas or a history of basal cell carcinoma; observe closely.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (may not be able to tolerate the heat stress or prolonged standing related to UVA treatment conditions).
- CTCL: Appropriate use: For use only if inadequate response to other forms of therapy. Used in conjunction with long wave radiation of white blood cells using the UVAR® photopheresis system.
- Hepatic impairment: Methoxsalen undergoes hepatic metabolism; use with caution in patients with hepatic impairment.
- Psoriasis: Appropriate use: For use only if inadequate response to other therapies when the diagnosis is biopsy proven. Administer only in conjunction with scheduled controlled doses of long wave ultraviolet (UVA) radiation (combination referred to as PUVA).
- Vitiligo: Appropriate use: Used in conjunction with controlled doses of long wave ultraviolet radiation or sunlight. Lotion should only be applied under direct supervision of prescriber and should not be dispensed to the patient.

Concurrent drug therapy issues:

- Photosensitizing agents: Use caution with other (systemic or topical) photosensitizing drugs (eg, thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides, anthralin, coal tar preparations).

Special populations:

- Elderly: Use with caution in the elderly.
- Pediatrics: Safety and efficacy have not been established in children for CTCL or psoriasis and <12 years of age for vitiligo. The long-term effects of treatment (including potential cataract formation, skin cancer development, and premature skin aging) are unknown in children.

Dosage form specific issues:

- Product interchange: **[U.S. Boxed Warning]: Soft-gelatin capsule (Oxsoralen-Ultra®) and hard-gelatin capsule (8-MOP®, Oxsoralen®) are not interchangeable; retitration is required if the formulation is changed.** Oxsoralen-Ultra® has a greater bioavailability and shorter onset of photosensitization.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced physician with special competence in the diagnosis and treatment of dermatologic diseases.**

Pregnancy Risk FactorC/D (Uvadex®)

Pregnancy ConsiderationsFetal toxicity has been observed in animal studies, however, there are no adequate and well-controlled studies in pregnant women. Use during pregnancy is not recommended. Women of childbearing potential should be advised to avoid pregnancy.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not always defined.

Cardiovascular: Edema, hypotension

Central nervous system: Depression, dizziness, headache, insomnia, malaise, nervousness, vertigo

Dermatologic: Pruritus (10%), blistering (painful), bullae formation, burning, erythema, folliculitis, freckling, hypopigmentation, miliaria, peeling of skin, premature aging, rash, skin cancer, tenderness (cutaneous), urticaria, vesiculation

Gastrointestinal: Nausea (10%), gastrointestinal disturbance

Neuromuscular & skeletal: Loss of muscle coordination, leg cramps

Ocular: Cataract

Miscellaneous: Herpes simplex, infection

Metabolism/Transport Effects**Substrate** of CYP2A6 (minor); **Inhibits** CYP1A2 (strong), 2A6 (strong), 2C9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak), 3A4 (weak)

Drug Interactions

Bendamustine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Strong) may decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2A6 Substrates: CYP2A6 Inhibitors (Strong) may decrease the metabolism of CYP2A6 Substrates. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Methoxsalen serum concentrations may be increased if taken with food. Avoid furocoumarin-containing foods (limes, figs, parsley, celery, cloves, lemon, mustard, carrots).

Monitoring ParametersCBC with differential (baseline and every 6-12 months), liver and renal function tests (baseline and every 6-12 months), antinuclear antibodies (baseline and every 6-12 months); ophthalmic exam (pretreatment and yearly)

Nursing: Physical Assessment/Monitoring**Note:** This drug is administered in conjunction with ultraviolet light or ultraviolet radiation therapy. Teach patient proper use, side effects/appropriate interventions (eg, sunlight precautions), and adverse reactions to report.

Monitoring: Lab TestsCBC with differential (baseline and every 6-12 months), liver and renal function tests (baseline and every 6-12 months), antinuclear antibodies (baseline and every 6-12 months)

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is used in conjunction with specific ultraviolet treatment. Take as directed, with food or milk to reduce nausea. Consult prescriber for specific dietary instructions. Avoid use of any other skin treatments unless approved by prescriber. Control exposure to direct sunlight as per prescriber's instructions. If sunlight cannot be avoided, use sunblock (consult prescriber for specific SPF level); wear protective clothing and wraparound protective eyewear. Consult prescriber immediately if burning, blistering, or skin irritation occur. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

8-MOP®: 10 mg [hard-gelatin capsule]

Oxsoralen-Ultra®: 10 mg [soft-gelatin capsule]

Lotion (Oxsoralen®): 1% (30 mL) [contains alcohol 71%]

Solution, for extracorporeal administration (Uvadex®): 20 mcg/mL (10 mL) **[not for injection]**

Generic AvailableNo

ManufacturerICN Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Capsules (8-Mop)

10 mg (50): $1145.73

Capsules (Oxsoralen Ultra)

10 mg (30): $680.36

Mechanism of ActionBonds covalently to pyrimidine bases in DNA, inhibits the synthesis of DNA, and suppresses cell division. The augmented sunburn reaction involves excitation of the methoxsalen molecule by radiation in the long-wave ultraviolet light (UVA), resulting in transference of energy to the methoxsalen molecule producing an excited state (“triplet electronic state”). The molecule, in this “triplet state”, then reacts with cutaneous DNA.

Pharmacodynamics/Kinetics

Protein binding: Reversibly bound to albumin

Metabolism: Hepatic; forms metabolites

Bioavailability: Bioavailability increased with soft-gelatin capsules (Oxsoralen-Ultra®) compared to hard-gelatin capsules (8-MOP®, Oxsoralen®); exposure using Uvadex® with the UVAR® photopheresis system is ~200 times less than with oral methoxsalen administration

Time to peak, serum:

Hard-gelatin capsules (8-MOP®, Oxsoralen®): 1.5-6 hours (peak photosensitivity: ~4 hours)

Soft-gelatin capsules (Oxsoralen-Ultra®): 0.5-4 hours (peak photosensitivity: 1.5-2 hours)

Half-life elimination: ~2 hours

Excretion: Urine (~95% as metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness, dizziness, or depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive photosensitivity

Index Terms8-Methoxypsoralen; 8-MOP; Methoxypsoralen

References

Stern RS, “Psoralen and Ultraviolet a Light Therapy for Psoriasis,” *N Engl J Med*, 2007, 357(7):682-90.[PubMed 17699818]

Stern RS, Nichols KT and Vateva LH, “Malignant Melanoma in Patients Treated for Psoriasis With Methoxsalen (Psoralen) and Ultraviolet A Radiation (PUVA). The PUVA Follow-Up Study,” *N Engl J Med*, 1997, 336(15):1041-5.[PubMed 9091799]

International Brand Names8-MOP Ultra (AR); Delsoralen (ID); Deltasoralen (IE); Geralen (PL); Geroxalen (DK, HN, HU, NL, NO); Meladinina (CR, DO, GT, MX, NI, PA, PY, SV); Meladinine (CH, DE, FR, NO, PL); Melanocyl (IN); Melaoline (GR); Metoxaleno Fides (UY); Mopsalem (CO); Mopsoralen (BE); Oxsoralen (AE, AT, AU, BH, BR, CH, CY, CZ, EG, HK, IL, IQ, IR, IT, JO, JP, KW, LB, LY, NL, OM, PH, PK, PL, QA, SA, SY, YE); Oxsoralen Ultra (MY, TW); Oxsoralen-Ultra (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Oxsoralon (ES); Puvalen (FI, PL); Sorialen (TW)

Methscopolamine

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English

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Medication Safety Issues

International issues:

> Pamine® may be confused with Pemine® which is a brand name for penicillamine in Italy

Pronunciation(meth skoe POL a meen)
U.S. Brand NamesPamine®; Pamine® Forte
Canadian Brand NamesPamine®
Pharmacologic CategoryAnticholinergic Agent
Use: Labeled IndicationsAdjunctive therapy in the treatment of peptic ulcer
Dosing: Adults**Peptic ulcer (adjunctive):** Oral: 2.5 mg 30 minutes before meals or food and 2.5-5 mg at bedtime; may increase dose to 5 mg twice daily
Dosing: ElderlyRefer to adult dosing.
Administration: OralAdminister 30 minutes before meals or food.
Dietary ConsiderationsShould be taken 30 minutes before meals or food.
ContraindicationsHypersensitivity to methscopolamine, any component of the formulation, or related drugs; reflux esophagitis; glaucoma; obstructed uropathy; obstructed disease of the GI tract (pyloroduodenal stenosis); paralytic ileus; intestinal atony of elderly or debilitated individuals; unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon; complicated ulcerative colitis; myasthenia gravis
Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause drowsiness and/or blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Diarrhea: May be a sign of incomplete intestinal obstruction, treatment should be discontinued if this occurs.
- Heat prostration: May occur in the presence of increased environmental temperature; use caution in hot weather and/or exercise.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease, tachyarrhythmias, heart failure, or hypertension; evaluate tachycardia prior to administration.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Neuropathy: Use with caution in patients with autonomic neuropathy.
- Prostatic hyperplasia: Use with caution in patients with prostatic hyperplasia.
- Renal impairment: Use with caution in patients with renal impairment.
- Ulcerative colitis: Use with caution in patients with ulcerative colitis; may precipitate/aggravate toxic megacolon.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for anticholinergic effects, confusion, and hallucinations.
- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Methscopolamine is a derivative of scopolamine. Scopolamine is reported to cross the placenta; fetal toxicity noted in case reports.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsAnticholinergics may suppress lactation. The AAP considers atropine and scopolamine to be “compatible” with breast-feeding.
Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation, tachycardia

Central nervous system: Headache, insomnia, flushing, nervousness, drowsiness, dizziness, confusion, fever, CNS stimulation may be produced with large doses

Dermatologic: Dry skin, urticaria

Endocrine & metabolic: Lactation suppressed

Gastrointestinal: Constipation, xerostomia, dry throat, dysphagia, nausea, vomiting, loss of taste

Genitourinary: Impotence, urinary hesitancy, urinary retention

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision, cycloplegia, ocular tension increased, pupil dilation

Respiratory: Dry nose

Miscellaneous: Allergic reaction, diaphoresis decreased, hypersensitivity reactions, anaphylaxis

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as bromide: 2.5 mg, 5 mg

Pamine®: 2.5 mg [lactose free]

Pamine® Forte: 5 mg [lactose free; dosepak]

Generic Available

Yes

Pricing: U.S. (www.drugstore.com)

Tablets (Methscopolamine Bromide)

2.5 mg (100): $149.98

5 mg (60): $117.99

Tablets (Pamine)

2.5 mg (120): $237.59

Tablets (Pamine Forte)

5 mg (60): $189.64

Mechanism of Action

Methscopolamine is a peripheral anticholinergic agent with limited ability to cross the blood-brain barrier and provides a peripheral blockade of muscarinic receptors. This agent reduces the volume and the total acid content of gastric secretions, inhibits salivation, and reduces gastrointestinal motility.

Pharmacodynamics/Kinetics

Onset of action: 1 hour

Duration: 4-6 hours

Excretion: Bile, urine

Dental Health: Effects on Dental Treatment

Key adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), and dry throat and nose. Anticholinergic side effects can cause a reduction of saliva production or secretion, contributing to discomfort and dental disease (ie, caries, oral candidiasis and periodontal disease).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions

No information available to require special precautions

Mental Health: Effects on Mental Status

May rarely cause drowsiness, confusion, amnesia, or nervousness

Mental Health: Effects on Psychiatric Treatment

Concurrent use with psychotropics may produce additive sedation and dry mouth

Index Terms

Methscopolamine Bromide

References

"American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk," *Pediatrics*, 2001, 108(3):776-

89.[PubMed 11533352]

International Brand NamesPamine (CA)

Methsuximide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

Methsuximide may be confused with ethosuximide

Pronunciation(meth SUKS i mide)

U.S. Brand NamesCelontin®

Canadian Brand NamesCelontin®

Pharmacologic CategoryAnticonvulsant, Succinimide

Use: Labeled IndicationsControl of absence (petit mal) seizures that are refractory to other drugs

Use: Unlabeled/InvestigationalPartial complex (psychomotor) seizures

Dosing: Adults**Anticonvulsant:** Oral: 300 mg/day for the first week; may increase by 300 mg/day at weekly intervals up to 1.2 g/day in 2-4 divided doses/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Anticonvulsant:** Oral: Children: Initial: 10-15 mg/kg/day in 3-4 divided doses; increase weekly up to maximum of 30 mg/kg/day

StorageProtect from high temperature.

ContraindicationsHypersensitivity to succinimides or any component of the formulation

Allergy Considerations

- Succinimide Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Blood dyscrasias: Succinimides have been associated with severe blood dyscrasias.
- SLE: Succinimides have been associated with cases of systemic lupus erythematosus (SLE).

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Infection: Consider evaluation of blood counts in patients with signs/symptoms of infection.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Other warnings/precautions:

- Appropriate use: Must be used in combination with other anticonvulsants in patients with both absence and tonic-clonic seizures. May increase tonic-clonic seizures in patients with mixed seizure disorders.
- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsNo specific data available for the elderly. This drug is rarely used in the elderly, however, if it is used for partial complex seizure control, monitor closely.
Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined.

Cardiovascular: Hyperemia

Central nervous system: Ataxia, dizziness, drowsiness, headache, aggressiveness, mental depression, irritability, nervousness, insomnia, confusion, psychosis, suicidal behavior, auditory hallucinations

Dermatologic: Stevens-Johnson syndrome, rash, urticaria, pruritus

Gastrointestinal: Anorexia, nausea, vomiting, weight loss, diarrhea, epigastric and abdominal pain, constipation

Genitourinary: Proteinuria, hematuria (microscopic); cases of blood dyscrasias have been reported with succinimides

Hematologic: Leukopenia, pancytopenia, eosinophilia, monocytosis

Neuromuscular & skeletal: Cases of systemic lupus erythematosus have been reported

Ocular: Blurred vision, photophobia, peripheral edema

Metabolism/Transport Effects**Substrate** of CYP2C19 (major); **Inhibits** CYP2C19 (weak)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Monitoring ParametersCBC, hepatic function tests, urinalysis
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 150 mg, 300 mg

Generic AvailableNo
ManufacturerPfizer Inc
Pricing: U.S. (www.drugstore.com)

Capsules (Celontin)

300 mg (30): $46.37

Mechanism of ActionIncreases the seizure threshold and suppresses paroxysmal spike-and-wave pattern in absence seizures; depresses nerve transmission in the motor cortex
Pharmacodynamics/Kinetics

Metabolism: Hepatic; rapidly demethylated to N-desmethylmethsuximide (active metabolite)

Half-life elimination: 2-4 hours

Time to peak, serum: Within 1-3 hours

Excretion: Urine (<1% as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
References

Baehler RW, Work J, Smith W, et al, “Charcoal Hemoperfusion in the Therapy for Methsuximide and Phenytoin Overdose,” *Arch Intern Med*, 1980, 140(11):1466-8. [PubMed 6893655]

Karch SB, “Methsuximide Overdose: Delayed Onset of Profound Coma,” *JAMA*, 1973, 223(13):1463-5. [PubMed 4740029]

Miles MV, Tennison MB, and Greenwood RS, “Pharmacokinetics of N-desmethylmethsuximide in Pediatric Patients,” *J Pediatr*, 1989, 114(4 Pt 1):647-50. [PubMed 2926578]

Tennison MB, Greenwood RS, Miles MV, “Methsuximide for Intractable Childhood Seizures,” *Pediatrics*, 1991, 87(2):186-9.[PubMed 1987529]

Methyclothiazide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Enduron® may be confused with Empirin®, Imuran®, Inderal®

Pronunciation(meth i kloe THYE a zide)

U.S. Brand NamesEnduron® [DSC]

Canadian Brand NamesAquatensen®; Enduron®

Pharmacologic CategoryDiuretic, Thiazide

Use: Labeled IndicationsManagement of mild to moderate hypertension; treatment of edema in congestive heart failure and nephrotic syndrome

Dosing: Adults

Edema: Oral: 2.5-10 mg/day

Hypertension: Oral: 2.5-5 mg/day; may add another antihypertensive if 5 mg is not adequate after a trial of 8-12 weeks of therapy

Dosing: ElderlyRefer to adult dosing.

Administration: OralMay be taken with food or milk. Take early in day to avoid nocturia. Take the last dose of multiple doses no later than 6 PM unless instructed otherwise.

ContraindicationsHypersensitivity to methyclothiazide or any component, thiazides, or sulfonamide-derived drugs; anuria; renal decompensation

Allergy Considerations

- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, and hyponatremia can occur.
- Photosensitivity: Photosensitization may occur.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with thiazide or sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Diabetes: Use with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated.
- Hepatic impairment: Use with caution in patients with severe hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations.
- Hypokalemia: Use with caution in patients with hypokalemia; correct before initiating therapy.
- Renal impairment: Avoid in severe renal disease (ineffective).
- Systemic lupus erythematosus (SLE): Can cause SLE exacerbation or activation.

Pregnancy Risk FactorB

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Cardiovascular: Orthostatic hypotension

Dermatologic: Photosensitivity

Endocrine & metabolic: Hypokalemia

Gastrointestinal: Anorexia, epigastric distress

<1% (Limited to important or life-threatening): Agranulocytosis, aplastic anemia, cutaneous vasculitis, erythema multiforme, hemolytic anemia, hepatic function impairment, hypercalcemia, leukopenia, necrotizing angiitis, pancreatitis, respiratory distress, Stevens-Johnson syndrome, thrombocytopenia, vasculitis

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid dong quai, St John's wort (may also cause photosensitization). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure, fluids, weight loss, serum potassium

Nursing: Physical Assessment/MonitoringMonitor positional blood pressure and fluid balance on a regular basis. Monitor for signs of hypokalemia. If used to treat CHF, monitor for signs of effectiveness. Monitor and teach patient to monitor for effectiveness of therapy, possible side effects, precautions, and symptoms to report (see Patient Education). Note breast-feeding caution.

Monitoring: Lab TestsSerum potassium, renal function

Patient EducationTake exactly as directed - with meals. May take early in day to avoid nocturia. Include bananas or orange juice in daily diet but do not take dietary supplements without advice or consultation of prescriber. Do not use OTC medication without consulting prescriber. Weigh weekly at the same time, in the same clothes. Report weight gain >5 lb/week. May cause dizziness or weakness; change position slowly when rising from sitting or lying position and avoid driving or tasks requiring alertness until response to drug is known. You may experience nausea or loss of appetite (small, frequent meals may help); impotence (reversible); constipation (increased exercise, fluids, fruit, or fiber may help); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). This medication does not replace other antihypertensive interventions; follow instructions for diet and lifestyle changes. Report flu-like symptoms, headache, joint soreness or weakness, respiratory difficulty, skin rash, or excessive fatigue, swelling of extremities, or respiratory difficulty. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 5 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Methyclothiazide)

5 mg (30): $24.40

Mechanism of ActionInhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water, as well as, potassium and hydrogen ions

Pharmacodynamics/Kinetics

Onset of action: Diuresis: 2 hours

Peak effect: 6 hours

Duration: ~1 day

Distribution: Crosses placenta; enters breast milk

Excretion: Urine (as unchanged drug)

Related Information

- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may cause photosensitivity; use psychotropics with caution; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular ConsiderationsThiazide diuretics are effective first-line therapeutic agents in the management of hypertension and have proven to be of benefit in terms of cardiovascular outcome. They may act synergistically to lower blood pressure when combined with an ACE inhibitor or beta-blocker. The initial concern about thiazide diuretic-induced hypokalemia, glucose intolerance, and lipid profiles does not appear to be of substantial clinical consequence in the treatment of hypertension. The benefits of this class of agents in the treatment of hypertension is established and compares well with other first-line therapeutic agents.

Diuretics are standard therapy for the management of edema in patients with heart failure.

References

Chobanian AV, Bakris GL, Black HR, et al, “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report,” *JAMA*, 2003, 289(19):2560-71.[PubMed 12748199]

International Brand NamesEnduron (AU, GB); Urimor (AU)

Methylcellulose

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Citrucel® may be confused with Citracal®

Pronunciation(meth il SEL yoo lose)

U.S. Brand NamesCitrucel® Fiber Shake [OTC]; Citrucel® Fiber Smoothie [OTC]; Citrucel® [OTC]

Pharmacologic CategoryLaxative

Use: Labeled IndicationsAdjunct in treatment of constipation

Dosing: Adults**Constipation:** Oral:

Citrucel® caplet: 2-4 caplets 1-3 times/day; follow each dose with 8 oz of water

Citrucel® powder: 1 heaping tablespoon (19 g) in 8 oz of cold water, 1-3 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Constipation:** Oral:

Children 6-12 years:

Citrucel® caplet: 1 caplet up to 6 times/day; follow each dose with 8 oz of water

Citrucel® powder: Half the adult dose in 4 oz of cold water, 1-3 times/day

Children ≥12 years: Refer to adult dosing.

Dietary ConsiderationsCitrucel® sugar free formulation: 2 g/level scoop contains phenylalanine 52 mg/level scoop; 2 g/packet contains phenylalanine 52 mg/packet

Warnings/Precautions

Other warnings/precautions:

- OTC labeling: Should not be used for longer than 1 week unless directed by healthcare provider. Healthcare provider should be notified if abdominal pain, nausea, or vomiting are present or in case of a sudden change in bowel habits. All doses must be taken with 8 ounces of water.

Pregnancy Risk FactorC

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/Monitoring**Pregnancy risk factor C** - benefits of use should outweigh possible risks.

Patient EducationTake with a full glass of water. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet:

Citrucel®: 500 mg

Powder: 2 g/level scoop (454 g)

Citrucel® Fiber Smoothie: 2 g/level scoop (275 g, 539 g) [contains sodium 3 mg/level scoop; lemon lime flavor]

Citrucel®:

2 g/level scoop (448 g, 840 g, 1418g, 1843 g) [contains sodium 3 mg and potassium 105 mg per scoop]

2 g/packet (20s) [orange flavor] [DSC]

Citrucel® [sugar free formulation]:

2 g/level scoop (473 g, 907g, 1190 g) [contains phenylalanine 52 mg/level scoop; orange flavor]

2 g/packet (20s) [contains phenylalanine 52 mg/packet; orange flavor] [DSC]

Citrucel® Fiber Shake: 2 g/level scoop (204 g, 413 g) [sugar free; contains sodium 20 mg/level scoop, phenylalanine 49 mg/level scoop and soy lecithin; chocolate flavor]

Generic AvailableYes: Powder

Pricing: U.S. (www.drugstore.com)

Powder (Citrucel)

1% (507): $13.03

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesBulk (AT); Celevac (GB, IE); Cellulone (AU); Citrucel (BE, LU); Cologel (GB); Dacryolarmes (FR); Davilose (PT); Lacril (BR, DK); Lacrisyn (CZ); Methylcellulose-Bournonville (LU); Muciplasma (ES); Oftan MC (FI); Tear cell (IN)

Methyldopa and Hydrochlorothiazide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Aldoril® may be confused with Aldoclor®, Aldomet®, Elavil®

Pronunciation(meth il DOE pa & hye droe klor oh THYE a zide)

U.S. Brand NamesAldoril®

Canadian Brand NamesApo-Methazide®

Pharmacologic CategoryAlpha$_2$-Adrenergic Agonist; Diuretic, Thiazide

Use: Labeled IndicationsManagement of moderate-to-severe hypertension

Dosing: Adults**Hypertension:** Oral: Dosage titrated on individual components, then switch to combination product; no more than methyldopa 3 g/day and/or hydrochlorothiazide 50 mg/day; maintain initial dose for first 48 hours, then decrease or increase at intervals of not less than 2 days until an adequate response is achieved

Methyldopa 250 mg and hydrochlorothiazide 15 mg: 2-3 times/day

Methyldopa 250 mg and hydrochlorothiazide 25 mg: Twice daily

Dosing: ElderlyRefer to dosing in individual monographs.

Dosing: Renal ImpairmentCl$_{cr}$ 30 mL/minute: Thiazides are recommended; loop diuretics are preferred.

Contraindications

Based on **methyldopa** component: Hypersensitivity to methyldopa or any component of the formulation; active hepatic disease; liver disorders previously associated with use of methyldopa; on MAO inhibitors

Based on **hydrochlorothiazide** component: Hypersensitivity to hydrochlorothiazide or any component of the formulation, thiazides, or sulfonamide-derived drugs; anuria; renal decompensation; pregnancy

Allergy Considerations

- Methyldopa Allergy
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Appropriate use: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, and hyponatremia can occur with hydrochlorothiazide.

- Hemolytic anemia: Methyldopa may rarely produce hemolytic anemia; positive Coombs' test occurs in 10% to 20% of patients (perform periodic CBCs).

- Hepatic effects: Methyldopa may rarely produce liver disorders; use with caution in patients with previous liver disease or dysfunction.

- Photosensitivity: Photosensitization may occur with hydrochlorothiazide.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use hydrochlorothiazide with caution in patients with severe hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use hydrochlorothiazide with caution in patients with moderate or high cholesterol concentrations.
- Hypokalemia: Use hydrochlorothiazide with caution in patients with hypokalemia; correct before initiating therapy.
- Renal impairment: Avoid hydrochlorothiazide in severe renal disease (ineffective). The active metabolites of methyldopa accumulate in uremia.
- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Other warnings/precautions:

- Appropriate use: **[U.S. Boxed Warning]: Fixed-dose therapy is not indicated as the initial treatment for hypertension.**

Pregnancy Risk FactorC
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/compatible
Adverse ReactionsSee individual agents.
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

COMT Inhibitors: May decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Iobenguane I 123: Methyldopa may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Iron Salts: May decrease the absorption of Methyldopa. Only oral iron salts are of concern. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: Methyldopa may enhance the adverse/toxic effect of Lithium. This may occur without notable changes in serum lithium concentrations. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the adverse/toxic effect of Methyldopa. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Methyldopa 250 mg and hydrochlorothiazide 15 mg

Methyldopa 250 mg and hydrochlorothiazide 25 mg

Aldoril® 25: Methyldopa 250 mg and hydrochlorothiazide 25 mg

Generic Available Yes

Pricing: U.S. (www.drugstore.com)

Tablets (Methyldopa-Hydrochlorothiazide)

250-25 mg (60): $22.99

Pharmacodynamics/Kinetics See individual agents.

Related Information

- Hydrochlorothiazide
- Methyldopa

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Anticholinergic side effects can cause a reduction of saliva production or secretion, contributing to discomfort and dental disease (ie, caries, oral candidiasis, and periodontal disease).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause drowsiness, dizziness, anxiety, nightmares, or depression

Mental Health: Effects on Psychiatric Treatment Contraindicated with MAO inhibitors; may rarely cause leukopenia; use caution with clozapine and carbamazepine; associated with lithium toxicity; use alternative antihypertensive agent; methyldopa may interact with psychotropics; monitor blood pressure and clinical status; thiazides may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations Combination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for methyldopa and hydrochlorothiazide combination therapy may include improved compliance and synergistic reductions in blood pressure with an accompanied reduction in side effects. Thiazide therapy improves cardiovascular outcomes in patients with hypertension. Methyldopa is infrequently used alone for the treatment of essential hypertension. See Cardiovascular Considerations for individual agents.

Index Terms Hydrochlorothiazide and Methyldopa

References

Chobanian AV, Bakris GL, Black HR, et al, "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report," *JAMA*, 2003, 289(19):2560-71. [PubMed 12748199]

Kaplan NM and Sever PS, "Combination Therapy: A Key to Comprehensive Patient Care," *Am J Hypertens*, 1997, 10(7 Pt 2):127S. [PubMed 9231887]

Moser M and Black HR, "The Role of Combination Therapy in the Treatment of Hypertension," *Am J Hypertens*, 1998, 11(6 Pt 2):73S-8S, 95S-100S.[PubMed 9655566]

International Brand Names Dopatens-H (GR); Hydromet (BR, JP, NL); Tensifort (ID)

Methyldopa

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Methyldopa may be confused with L-dopa, levodopa

Pronunciation(meth il DOE pa)

Canadian Brand NamesApo-Methyldopa®; Nu-Medopa

Pharmacologic CategoryAlpha$_2$-Adrenergic Agonist

Use: Labeled IndicationsManagement of moderate to severe hypertension

Dosing: Adults**Hypertension:**

Oral: Initial: 250 mg 2-3 times/day; increase every 2 days as needed (maximum dose: 3 g/day); usual dose range (JNC 7): 250-1000 mg/day in 2 divided doses

I.V.: 250-1000 mg every 6-8 hours; maximum: 1 g every 6 hours

Dosing: ElderlyOral: Initial: 125 mg 1-2 times/day; increase by 125 mg every 2-3 days as needed. Adjust for renal impairment. See Geriatric Considerations.

Dosing: Pediatric**Hypertension:**

Oral: Initial: 10 mg/kg/day in 2-4 divided doses; increase every 2 days as needed to maximum dose of 65 mg/kg/day. Do not exceed 3 g/day.

I.V.: 5-10 mg/kg/dose every 6-8 hours up to a total dose of 65 mg/kg/24 hours or 3 g/24 hours

Dosing: Renal Impairment

Cl$_{cr}$ >50 mL/minute: Administer every 8 hours.

Cl$_{cr}$ 10-50 mL/minute: Administer every 8-12 hours.

Cl$_{cr}$ <10 mL/minute: Administer every 12-24 hours.

Slightly dialyzable (5% to 20%)

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Infuse over 30 minutes.

Dietary ConsiderationsDietary requirements for vitamin B$_{12}$ and folate may be increased with high doses of methyldopa.

StorageInjectable dosage form is most stable at acid to neutral pH. Stability of parenteral admixture at room temperature (25°C) is 24 hours. Stability of parenteral admixture at refrigeration temperature (4°C) is 4 days.

Reconstitution

Standard diluent: 250-500 mg/100 mL D$_5$W

CompatibilityStable in dextran 6% in NS, D$_5$NS, D$_5$W, sodium bicarbonate 5%, NS.

Y-site administration: Compatible: Esmolol, heparin, meperidine, morphine, theophylline. **Variable (consult detailed reference):** TPN.

Compatibility when admixed: Compatible: Aminophylline, ascorbic acid injection, chloramphenicol, diphenhydramine, heparin, magnesium sulfate, multivitamins, potassium chloride, promazine, sodium bicarbonate, succinylcholine, verapamil, vitamin B complex with C. **Incompatible:** Amphotericin B, methohexital.

ContraindicationsHypersensitivity to methyldopa or any component of the formulation; active hepatic disease; liver disorders previously associated with use of methyldopa; on MAO inhibitors; bisulfite allergy if using oral suspension or injectable

Allergy Considerations

- Methyldopa Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hemolytic anemia: May rarely produce hemolytic anemia; positive Coombs' test occurs in 10% to 20% of patients (perform periodic CBCs).

- Hepatic effects: May rarely produce liver disorders; use with caution in patients with previous liver disease or dysfunction.

- Sedation: Usually transient, sedation may occur during initial therapy or whenever the dose is increased.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; may respond to smaller doses. The active metabolites of methyldopa accumulate in uremia.

Special populations:

- Elderly: Use with caution in the elderly; may experience syncope (avoid by giving smaller doses). Not considered a drug of choice.

- Pregnancy: Often considered the drug of choice for treatment of hypertension in pregnancy.

Dosage form specific issues:

- Injection: Do not use injectable if bisulfite allergy.

Other warnings/precautions:

- Tolerance: May occur usually between the second and third month of therapy; adding a diuretic or increasing the dosage of methyldopa frequently restores blood pressure control.

Geriatric ConsiderationsBecause of its CNS effects, methyldopa is not considered a drug of first choice in the elderly. Adjust dose for renal function.

Pregnancy Risk FactorB

Pregnancy ConsiderationsCrosses the placenta. Hypotension reported. A large amount of clinical experience with the use of these drugs for the management of hypertension during pregnancy is available. Available evidence suggests safe use during pregnancy.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsCrosses into breast milk at extremely low levels. AAP considers **compatible** with breast-feeding.

Adverse Reactions

>10%: Cardiovascular: Peripheral edema

1% to 10%:

Central nervous system: Drug fever, mental depression, anxiety, nightmares, drowsiness, headache

Gastrointestinal: Dry mouth

<1% (Limited to important or life-threatening): Orthostatic hypotension, bradycardia (sinus), sodium retention, sexual dysfunction, gynecomastia, hyperprolactinemia, thrombocytopenia, hemolytic anemia, positive Coombs' test, leukopenia, transient leukopenia or granulocytopenia, cholestasis or hepatitis and heptocellular injury, increased liver enzymes, jaundice, cirrhosis, dyspnea, SLE-like syndrome

Drug Interactions

COMT Inhibitors: May decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Methyldopa may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Iron Salts: May decrease the absorption of Methyldopa. Only oral iron salts are of concern. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Lithium: Methyldopa may enhance the adverse/toxic effect of Lithium. This may occur without notable changes in serum lithium concentrations. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the adverse/toxic effect of Methyldopa. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression). Avoid natural licorice (causes sodium and water retention and increases potassium loss). Avoid garlic (may have increased antihypertensive effect).

Test InteractionsMethyldopa interferes with the following laboratory tests: urinary uric acid, serum creatinine (alkaline picrate method), AST (colorimetric method), and urinary catecholamines (falsely high levels)

Monitoring ParametersBlood pressure, standing and sitting/lying down, CBC, liver enzymes, Coombs' test (direct); blood pressure monitor required during I.V. administration

Nursing: Physical Assessment/MonitoringEvaluate hepatic and renal status prior to beginning therapy. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, anything that affects blood pressure). See Administration for infusion specifics (eg, do not use injectable in presence of bisulfite allergy). Assess results of laboratory tests at baseline and regularly during therapy. Monitor therapeutic effectiveness (normotensive) and adverse reactions (eg, hypotension, bradycardia, CNS changes) on a regular basis. Teach patient use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC, liver enzymes, Coombs' test (direct)

Patient EducationDo not take any new medication during therapy unless approved by prescriber (especially any cough or cold remedies, diet pills, stay-awake medications). **Oral:** Take as directed. Do not skip dose or discontinue without consulting prescriber. Follow recommended diet and exercise program. Periodic laboratory tests may be required. This medication may cause altered color of urine (normal); drowsiness, dizziness, or impaired judgment (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from sitting or lying position or when climbing stairs); or dry mouth or nausea (frequent mouth care or sucking lozenges may help). Report altered CNS status (eg, nightmares, depression, anxiety, increased nervousness); sudden weight gain (weigh yourself in the same clothes at the same time of day once a week); unusual or persistent swelling of ankles, feet, or extremities; palpitations or rapid heartbeat; persistent weakness, fatigue, or unusual bleeding; or other persistent side effects.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as methyldopate hydrochloride: 50 mg/mL (5 mL) [contains sodium bisulfite]

Tablet: 250 mg, 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Methyldopa)

250 mg (120): $25.98

500 mg (60): $25.99

Mechanism of ActionStimulation of central alpha-adrenergic receptors by a false transmitter that results in a decreased sympathetic outflow to the heart, kidneys, and peripheral vasculature

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Hypotensive: Oral/parenteral: 3-6 hours

Duration: 12-24 hours

Distribution: Crosses placenta; enters breast milk

Protein binding: <15%

Metabolism: Intestinal and hepatic

Half-life elimination: 75-80 minutes; End-stage renal disease: 6-16 hours

Excretion: Urine (85% as metabolites) within 24 hours

Related Information

- Depression
- Hypertension

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Anticholinergic side effects can cause a reduction of saliva production or secretion, contributing to discomfort and dental disease (ie, caries, oral candidiasis, and periodontal disease).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, anxiety, nightmares, or depression

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors; may rarely cause leukopenia; use caution with clozapine and carbamazepine; associated with lithium toxicity; use alternative antihypertensive agent; methyldopa may interact with psychotropics; monitor blood pressure and clinical status

Cardiovascular ConsiderationsMethyldopa is not routinely used for the treatment of essential hypertension. However, it is still used in the management of pregnancy-associated hypertension. Although the drug crosses the placenta and may cause hypotension, there is a large body of experience using this drug in the treatment of pregnancy-associated hypertension. Overall, the medication appears to be safe during pregnancy and lactation. Important side effects to note are hemolytic anemia, drowsiness, and depression.

Anesthesia and Critical Care Concerns/Other ConsiderationsMost effective if used with diuretic. Titrate dose to optimal blood pressure control with minimal side effects. Patients on methyldopa may need less anesthetic agents. Hypotension readily responds to vasopressors because the adrenergic receptors remain sensitive.

It is used in the management of pregnancy-associated hypertension. Although the drug crosses the placenta and may cause hypotension, there is a large body of experience using this drug in the treatment of pregnancy-associated hypertension. Overall, the medication appears to be safe during pregnancy and lactation.

Index TermsAldomet; Methyldopate Hydrochloride

References

Chobanian AV, Bakris GL, Black HR, et al, "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report," *JAMA*, 2003, 289(19):2560-71.[PubMed 12748199]

International Brand NamesAdopal (FI); Aldin (TW); Aldomet (AE, AR, AU, BE, BF, BH, BJ, BR, CH, CI, CY, DK, EG, ES, ET, FR, GB, GH, GM, GN, GR, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, OM, PE, PH, PK, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SY, TH, TN, TR, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Aldomet M (MY); Aldomet-Forte (HK); Aldometil (AT); Alphadopa (IN); Bekanta (JP); Domecin (JP); Dopagyt (IN); Dopamet (ID, MY, NO, PH); Dopanol (PL); Dopasian (TH); Dopegyt (AE, BB, BG, BH, BM, BS, BZ, CY, CZ, EG, GY, HK, HN, HU, IL, IQ, IR, JM, JO, KW, LB, LY, MY, OM, PL, PR, QA, SA, SR, SY, TH, TT, YE); Emdopa (IN); Hy-po-tone (ZA); Hydopa (AU); Hypolag (BB, BF, BJ, BM, BS, BZ, CI, ET, GH, GM, GN, GY, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, PR, SC, SD, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Medopa (JP, TH); Medopren (IT); Methoplain (JP); Methyldopa (PL); Metildopa (HR); Metpata (TH); Normopress (ZA); Nudopa (AU); Pharmet (ZA); Presinol (AT, DE); Presinol 500 (DE); Prodopa (NZ); Rivapress (TW); Sembrina (BF, BJ, CI, ET, FI, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Siamdopa (TH)

Methylene Blue

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English English

Jump To Field (Select Field Name)

Medication Safety IssuesDue to potential toxicity (hemolytic anemia), do not use methylene blue to color enteral feedings to detect aspiration.

Pronunciation(METH i leen bloo)

U.S. Brand NamesUrolene Blue® [DSC]

Pharmacologic CategoryAntidote

Use: Labeled IndicationsAntidote for cyanide poisoning and drug-induced methemoglobinemia, indicator dye

Use: Unlabeled/InvestigationalTreatment/prevention of ifosfamide-induced encephalopathy; topically, in conjunction with polychromatic light to photoinactivate viruses such as herpes simplex; alone or in combination with vitamin C for the management of chronic urolithiasis

Dosing: Adults

Methemoglobinemia: I.V.: 1-2 mg/kg or 25-50 mg/m^2 over several minutes; may be repeated in 1 hour if necessary

Genitourinary antiseptic: Oral: 65-130 mg 3 times/day with a full glass of water (maximum: 390 mg/day)

Ifosfamide-induced encephalopathy (unlabeled use): Oral, I.V.:

Prevention: 50 mg every 6-8 hours

Treatment: 50 mg as a single dose or every 4-8 hours until symptoms resolve

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

NADPH-methemoglobin reductase deficiency: Oral: 1-1.5 mg/kg/day (maximum: 300 mg/day) given with 5-8 mg/kg/day of ascorbic acid

Methemoglobinemia: Children: Refer to adult dosing.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Administer undiluted by direct I.V. injection over several minutes. For the treatment of ifosfamide-induced encephalopathy, methylene blue may be administered either undiluted as a slow I.V. push over at least 5 minutes or diluted in 50 mL NS or D_5W and infused over at least 5 minutes. Consider concomitant dextrose administration, especially in patients who are hypoglycemic, to ensure efficacy of methylene blue.

Administration: OralAdminister after meals with a full glass of water. When given for the treatment of ifosfamide-induced encephalopathy, may be mixed with fruit juice to mask unpleasant taste.

ContraindicationsHypersensitivity to methylene blue or any component of the formulation; intraspinal injection; renal insufficiency

Warnings/Precautions

Concerns related to adverse effects:

- Anemia: Continued use can cause profound anemia.
- Methemoglobinemia: At high doses or in patients with G6PD-deficiency and infants, methylene blue may catalyze the oxidation of ferrous iron in hemoglobin to ferric iron causing paradoxical methemoglobinemia. Monitor methemoglobin concentrations regularly during administration.

Special populations:

- G6PD deficiency: Use with caution in patients with G6PD deficiency.
- Young patients: Use with caution in young patients.

Other warnings/precautions:

- Administration: Do not inject SubQ or intrathecally.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypertension, precordial pain

Central nervous system: Dizziness, mental confusion, headache, fever

Dermatologic: Staining of skin

Gastrointestinal: Fecal discoloration (blue-green), nausea, vomiting, abdominal pain

Genitourinary: Discoloration of urine (blue-green), bladder irritation

Hematologic: Anemia

Miscellaneous: Diaphoresis

Drug Interactions There are no known significant interactions.

Monitoring Parameters Arterial blood gases; cardiac monitoring (patients with pre-existing pulmonary and/or cardiac disease); CBC; methemoglobin levels (co-oximetry yields a direct and accurate measure of methemoglobin levels); pulse oximeter (will not provide accurate measurement of oxygenation when methemoglobin levels are >35%); renal function; signs and symptoms of methemoglobinemia such as pallor, cyanosis, nausea, muscle weakness, dizziness, confusion, agitation, dyspnea and tachycardia; transcutaneous O_2 saturation

Reference Range Methemoglobin levels: **Note:** The level of methemoglobin is expressed as a percent of total hemoglobin affected.

10% to 25%: Cyanosis

35% to 40%: Fatigue, dizziness, dyspnea, headache, tachycardia

60%: Lethargy, stupor

>70%: Death (adults)

Monitoring: Lab Tests Arterial blood gases; CBC; methemoglobin levels (co-oximetry yields a direct and accurate measure of methemoglobin levels); pulse oximeter (will not provide accurate measurement of oxygenation when methemoglobin levels are >35%); renal function; transcutaneous O_2 saturation

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 10 mg/mL (1 mL, 10 mL)

Tablet:

  Urolene Blue®: 65 mg [DSC]

Generic Available Yes: Injection

Pricing: U.S. (www.drugstore.com)

Tablets (Urolene Blue)

  65 mg (30): $19.99

Mechanism of Action Weak germicide in low concentrations, hastens the conversion of methemoglobin to hemoglobin; has opposite effect at high concentrations by converting ferrous ion of reduced hemoglobin to ferric ion to form methemoglobin; in cyanide toxicity, it combines with cyanide to form cyanmethemoglobin preventing the interference of cyanide with the cytochrome system

Pharmacodynamics/Kinetics

Onset of action: Reduction of methemoglobin: I.V.: 30-60 minutes

Absorption: Oral: 53% to 97%

Excretion: Urine and feces

Pharmacotherapy Pearls Skin stains may be removed using a hypochlorite solution.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause confusion or dizziness

Mental Health: Effects on Psychiatric Treatment None reported

References

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Patel PN, “Methylene Blue for Management of Ifosfamide-Induced Encephalopathy,” *Ann Pharmacother*, 2006, 40(2):299-303.[PubMed 16391008]

Pelgrims J, DeVos F, Van den Brande J, et al, “Methylene Blue in the Treatment and Prevention of Ifosfamide-Induced Encephalopathy: Report of 12 Cases and a Review of the Literature,” *Br J Cancer*, 2000, 82(2) 291-4.[PubMed 10646879]

Preiser JC, Lejeune P, Roman A, et al, “Methylene Blue Administration in Septic Shock: A Clinical Trial,” *Crit Care Med*, 1995, 23(2):259-64. [PubMed 7532559]

Turner AR, Duong CD, and Good DJ, “Methylene Blue for the Treatment and Prophylaxis of Ifosfamide-Induced Encephalopathy,” *Clin Oncol (R Coll Radiol)*, 2003, 15(7):435-9.[PubMed 14570094]

Wright RO, Lewander WJ, and Woolf AD, “Methemoglobinemia: Etiology, Pharmacology, and Clinical Management,” *Ann Emerg Med*, 1999, 34(5):646-56. [PubMed 10533013]

Zulian GB, Tullen E, and Maton B, “Methylene Blue for Ifosfamide-Associated Encephalopathy,” *N Engl J Med*, 1995, 332(18):1239-40.[PubMed 7700329]

Methylergonovine

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Medication Safety Issues

Sound-alike/look-alike issues:

> Methylergonovine and terbutaline parenteral dosage forms look similar. Due to their contrasting indications, use care when administering these agents.

Pronunciation(meth il er goe NOE veen)

U.S. Brand NamesMethergine®

Canadian Brand NamesMethergine®

Pharmacologic CategoryErgot Derivative

Use: Labeled IndicationsPrevention and treatment of postpartum and postabortion hemorrhage caused by uterine atony or subinvolution

Dosing: Adults**Prevention of hemorrhage:**

Oral: 0.2 mg 3-4 times/day in the puerperium for 2-7 days

I.M., I.V.: 0.2 mg after delivery of anterior shoulder, after delivery of placenta, or during puerperium; may be repeated as required at intervals of 2-4 hours

Dosing: ElderlyRefer to adult dosing.

Administration: I.V.Administer over ≥60 seconds. Should not be routinely administered I.V. because of possibility of inducing sudden hypertension and cerebrovascular accident.

Administration: I.V. DetailpH: 2.7-3.5

Storage

Ampul: Store under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light.

Tablet: Store below 25°C (77°F).

CompatibilityStable in NS.

Y-site administration: Compatible: Heparin, hydrocortisone sodium succinate, potassium chloride, vitamin B complex with C.

ContraindicationsHypersensitivity to methylergonovine or any component of the formulation; ergot alkaloids are contraindicated with potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics); hypertension; toxemia; pregnancy

Allergy Considerations

- Ergot Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac valvular fibrosis: Ergot alkaloids have been associated with fibrotic valve thickening (eg, aortic, mitral, tricuspid); usually associated with long-term, chronic use.
- Ergotism: Ergot alkaloid use may result in ergotism (intense vasoconstriction) resulting in peripheral vascular ischemia and possible gangrene. Ergotism is usually associated with overdosage or prolonged chronic use; do not exceed dosing guidelines and avoid prolonged administration.
- Pleural/retroperitoneal fibrosis: Rare cases of pleural and/or retroperitoneal fibrosis have been reported with prolonged daily use of other ergot alkaloids.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Labor: Use with caution in the second stage of labor.
- Renal impairment: Use with caution in patients with renal impairment.
- Sepsis: Use with caution in patients with sepsis.
- Vascular disease: Use with caution in patients with obliterative vascular disease.

Concurrent drug therapy issues:

- CYP3A4 inhibitors: Concomitant use with potent inhibitors of CYP3A4 (includes protease inhibitors, azole antifungals, and some macrolide antibiotics) and ergot alkaloids has been associated with acute ergot toxicity (ergotism); concurrent use of certain ergot alkaloids (eg, ergotamine and dihydroergotamine) are not recommended by the manufacturer.

Special populations:

- Elderly: Use with extreme caution or avoid use in the elderly; due to vasoconstrictive properties and cardiovascular adverse effects associated with ergot alkaloids.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- I.V. administration: Use with extreme caution when administering intravenously; risk of inducing sudden hypertensive and cerebrovascular accidents.

Pregnancy Risk FactorC

Pregnancy ConsiderationsProlonged constriction of the uterine vessels and/or increased myometrial tone may lead to reduced placental blood flow. This has contributed to fetal growth retardation in animals. Methylergonovine is intended for use after delivery of the infant.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsAt normal doses used to control postpartum uterine bleeding, small amounts are excreted in breast milk.

Adverse ReactionsFrequency not defined.

Cardiovascular: Acute MI, arterial spasm, bradycardia, hyper-/hypotension, palpitation, tachycardia, temporary chest pain

Central nervous system: Dizziness, hallucinations, headache, seizure

Dermatologic: Rash

Endocrine & metabolic: Water intoxication

Gastrointestinal: Diarrhea, foul taste, nausea, vomiting

Local: Thrombophlebitis

Neuromuscular & skeletal: Leg cramps

Otic: Tinnitus

Renal: Hematuria

Respiratory: Dyspnea, nasal congestion

Miscellaneous: Anaphylaxis, diaphoresis

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)

Drug Interactions

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Efavirenz: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically, the risk for peripheral vasospasm and ischemia may be increased. *Risk X: Avoid combination*

Macrolide Antibiotics: May enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Posaconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Protease Inhibitors: May decrease the metabolism of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: Ergot Derivatives may enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Ergot Derivatives. This may cause serotonin syndrome. *Risk X: Avoid combination*

Voriconazole: May increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Nursing: Physical Assessment/MonitoringBlood pressure, CNS status, and vaginal bleeding should be monitored on a regular basis - especially with infusion or injection. Assess therapeutic effectiveness and adverse response (eg, ergotamine toxicity [headache, ringing in ears, nausea and vomiting, diarrhea, numbness or coldness of extremities, confusion, hallucinations, dyspnea, chest pain, convulsions]). Teach patient proper use (when self-administered), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis drug will generally not be needed for more than a week. May cause nausea and vomiting (small, frequent meals may help), dizziness, headache, or ringing in the ears (will reverse when drug is discontinued). Report immediately any chest pain or tightness, jaw, shoulder or midback pain; difficulty breathing; acute headache; numb, cold, or cramping extremities; or severe abdominal cramping. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as maleate: 0.2 mg/mL (1 mL)

Methergine®: 0.2 mg/mL (1 mL)

Tablet, as maleate:

Methergine®: 0.2 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Methergine)

0.2 mg (30): $43.47

Mechanism of ActionSimilar smooth muscle actions as seen with ergotamine; however, it affects primarily uterine smooth muscles producing sustained contractions and thereby shortens the third stage of labor and reduces blood loss.

Pharmacodynamics/Kinetics

Onset of action: Oxytocic: Oral: 5-10 minutes; I.M.: 2-5 minutes; I.V.: Immediately

Duration: Oral: ~3 hours; I.M.: ~3 hours; I.V.: 45 minutes

Absorption: Rapid

Distribution: V_d: 39-73 L

Rapid; primarily to plasma and extracellular fluid following I.V. administration; tissues

Metabolism: Hepatic

Bioavailability: Oral: 60%; I.M.: 78%

Half-life elimination: Biphasic: Initial: 1-5 minutes; Terminal: 0.5-2 hours

Time to peak, serum: Oral: 0.3-2 hours; I.M.: 0.2-0.6 hours

Excretion: Urine and feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause dizziness or hallucinations

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsThis drug should be used extremely carefully because of its potent vasoconstrictor action. Administration may elicit marked increases in blood pressure and intracranial hemorrhage. Use should be avoided in patients with cardiovascular disease, including hypertension, coronary artery disease and peripheral vascular disease.

Anesthesia and Critical Care Concerns/Other ConsiderationsThis drug should be used extremely carefully because of it's potent vasoconstrictor action. I.V. use may induce sudden hypertension and cerebrovascular accidents. As a last resort, give I.V. slowly over several minutes and monitor blood pressure closely.

Index TermsMethylergometrine Maleate; Methylergonovine Maleate

References

de Groot AN, van Dongen PW, Vree TB, et al, “Ergot Alkaloids. Current Status and Review of Clinical Pharmacology and Therapeutic Use Compared With Other Oxytocics in Obstetrics and Gynaecology,” *Drugs*, 1998, 56(4):523-35.[PubMed 9806101]

International Brand NamesBasofortina (AR, PY); Bledstop (ID); Comthergin (PH); Demergin (GR); Expogin (TH); Ingagen-M (IN); Medisyl (PH); Mergot (PH); Mergotrex (PH); Methergin (AT, BD, BE, BF, BG, BJ, BR, CH, CI, CL, CO, CZ, DE, DK, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, ID, IE, IL, IN, IT, JP, KE, KP, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, PE, PH, PK, PT, RU, SC, SD, SE, SG, SL, SN, TH, TN, TR, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Metiagin (ID); Metrine (TH); Metvell (ID); Mitrotan (BG, GR); Myotonic (ID); Obtrin (PH); Pospargin (ID); Usamema (PH)

Methylfolate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(meth il FO late)

U.S. Brand NamesDeplin™

Pharmacologic CategoryDietary Supplement

Use: Labeled IndicationsMedicinal food for management of patients with low plasma and/or low red blood cell folate

Dosing: Adults**Medicinal food:** Oral: One tablet (7.5 mg) daily

Dosing: ElderlyRefer to adult dosing.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from light and moisture.

ContraindicationsHypersensitivity to any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Anemia: Monotherapy: Not appropriate for monotherapy with pernicious or other megaloblastic anemias when anemia is present with vitamin B_{12} deficiency.

- Pernicious anemia: Doses >0.1 mg/day may obscure pernicious anemia with continuing irreversible nerve damage progression.

Other warnings/precautions:

- Medicinal food: Product is a medicinal food for use only under the supervision of a healthcare provider.

Geriatric ConsiderationsNo special recommendations. Elderly frequently have combined nutritional deficiencies. Must rule out vitamin B_{12} deficiency before initiating folate therapy. Elderly, due to decreased nutrient intake, may benefit from daily intake of a multiple vitamin with minerals.

Drug Interactions

CarBAMazepine: Methylfolate may decrease the serum concentration of CarBAMazepine. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the serum concentration of Methylfolate. *Risk C: Monitor therapy*

Colestipol: May decrease the serum concentration of Methylfolate. *Risk C: Monitor therapy*

PHENobarbital: Methylfolate may decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Phenytoin: Methylfolate may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Primidone: Methylfolate may decrease the serum concentration of Primidone. *Risk C: Monitor therapy*

Pyrimethamine: Methylfolate may diminish the therapeutic effect of Pyrimethamine. *Risk C: Monitor therapy*

Raltitrexed: Methylfolate may diminish the therapeutic effect of Raltitrexed. *Risk X: Avoid combination*

Sulfasalazine: May decrease the serum concentration of Methylfolate. *Risk C: Monitor therapy*

Valproic Acid: Methylfolate may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Deplin™: L-methylfolate 7.5 mg [gluten free, lactose free, sugar free, yeast free]

Generic AvailableNo

ManufacturerPamLab

Pricing: U.S. (www.drugstore.com)

Tablets (Deplin)

7.5 mg (30): $49.99

Mechanism of ActionMethylfolate, or L-methylfolate, is the active form of folate in the body, which can be transported into peripheral tissues and across the blood brain barrier. Folate is necessary for formation of numerous coenzymes in many metabolic systems, particularly for purine, pyrimidine, and nucleoprotein synthesis, and maintenance in erythropoiesis; stimulates WBC and platelet production in folate deficiency anemia.

Pharmacotherapy PearlsInformation in this monograph is currently limited to the fields presented. Consult product labeling for additional details.

The manufacturer of Deplin™ indicates a use of methylfolate in individuals who have a major depressive disorder that has not fully responded or may not fully respond to antidepressant therapy. Limited data exists of the investigational use of folate supplementation as an adjunct to the treatment of major depressive disorder. Adjunctive use in major depressive disorders requires further studies, but some studies (using various forms of folic acid) suggest a possible benefit of supplementation by augmentation of response to antidepressants, particularly in patients with low serum folate levels prior to supplementation.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health Comment Pilot studies have explored the potential to improve response to antidepressant treatment with the addition of folate, a water-soluble B vitamin. Alpert et al, evaluated the efficacy of methylfolate as an adjunctive treatment in 22 adults with major depression who had an inadequate response to SSRI therapy in an 8 week prospective trial. Leucovorin (folinic acid), which is metabolized to methylfolate, was added to SSRI therapy at 15-30 mg/day. Hamilton Depression Rating Scale scores decrease significantly ($p < 0.01$) in the 16 completers. Thirty-one percent of the completers and 27% of the intent-to-treat sample achieved response and 19% of the completers and 18% of the intent-to-treat sample achieved remission.

In support of the finding by Alpert et al, assessed the relationship between serum folate, vitamin B_{12}, homocysteine levels, and clinical response in patients with major depression who had previously failed to respond to open treatment with fluoxetine 20 mg/day. Low serum folate levels but not elevated homocysteine or low vitamin B_{12} levels were associated with poorer response to treatment. The response rate for patients with and without low folate levels was 7.1% and 44.7% respectively.

In part two of the above study, Papakostas et al, evaluated the relationship between serum folate, vitamin B_{12}, and homocysteine levels on the rate of relapse in outpatients with remitted major depression during a 28-week continuation phase of treatment with fluoxetine. Low serum folate levels but not elevated homocysteine or low vitamin B_{12} levels were associated with relapse during continuation treatment with fluoxetine. The relapse rate for patients with and without low folate levels was 42.9% and 3.2% respectively.

Further study is necessary to determine to role of methylfolate in the management of major depressive disorder.

Alpert JE, Mischoulon D, Rubenstein GE, et al, "Folinic Acid (Leucovorin) as an Adjunctive Treatment for SSRI-Refractory Depression," *Ann Clin Psychiatry*, 2002, 14(1):33-8.

Papakostas GI, Petersen T, Mischoulon D, et al, "Serum Folate, Vitamin B_{12}, and Homocysteine in Major Depressive Disorder, Part 2: Predictors of Relapse During the Continuation Phase of Pharmacotherapy," *J Clin Psychiatry*, 2004, 65(8):1096-8.

Index Terms6(S)-5-methyltetrahydrofolate; 6(S)-5-MTHF; L-methylfolate

References

Alpert JE, Mischoulon D, Rubenstein GE, et al, "Folinic Acid (Leucovorin) as an Adjunctive Treatment for SSRI-Refractory Depression," *Ann Clin Psychiatry*, 2002, 14(1):33-8.[PubMed 12046638]

Coppen A and Bailey J, "Enhancement of the Antidepressant Action of Fluoxetine by Folic Acid: A Randomised, Placebo Controlled Trial," *J Affect Disord*, 2000, 60(2):121-30.[PubMed 10967371]

Papakostas GI, Petersen T, Mischoulon D, et al, "Serum Folate, Vitamin B_{12}, and Homocysteine in Major Depressive Disorder, Part 1: Predictors of Clinical Response in Fluoxetine-Resistant Depression," *J Clin Psychiatry*, 2004, 65(8):1090-5.[PubMed 15323594]

Papakostas GI, Petersen T, Mischoulon D, et al, "Serum Folate, Vitamin B_{12}, and Homocysteine in Major Depressive Disorder, Part 2: Predictors of Relapse During the Continuation Phase of Pharmacotherapy," *J Clin Psychiatry*, 2004, 65(8):1096-8.[PubMed 15323595]

Methylnaltrexone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Methylnaltrexone may be confused with naltrexone

Pronunciation(meth il nal TREKS one)
U.S. Brand NamesRelistor™
Canadian Brand NamesRelistor™
Pharmacologic CategoryGastrointestinal Agent, Miscellaneous; Opioid Antagonist, Peripherally-Acting
Use: Labeled IndicationsTreatment of opioid-induced constipation in patients with advanced illness receiving palliative care with inadequate response to conventional laxative regimens
Dosing: Adults**Opioid-induced constipation:** SubQ: Dosing is according to body weight: Administer 1 dose every other day as needed; maximum: 1 dose/24 hours

<38 kg: 0.15 mg/kg (round dose up to nearest 0.1 mL of volume)

38 to <62 kg: 8 mg

62-114 kg: 12 mg

>114 kg: 0.15 mg/kg (round dose up to nearest 0.1 mL of volume)

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal Impairment
Mild-to-moderate renal impairment: No adjustment required.

Severe renal impairment (Cl_{cr} <30 mL/minute): Administer 50% of normal dose.

End-stage renal impairment (dialysis-dependent): Has not been studied.

Dosing: Hepatic Impairment

Mild-to-moderate hepatic impairment (Child-Pugh class A and B): No adjustment required.

Severe hepatic impairment: Has not been studied.

Calculations

- Creatinine Clearance: Adults

Administration: OtherSubQ: Administer subcutaneously into upper arm, abdomen, or thigh. Rotate injection site. Do not use tender, bruised, red, or hard areas.
StorageStore intact vials at room temperature of 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Do not freeze, protect from light. Solution for injection is stable in a syringe for 24 hours at room temperature (protection from light during this 24 hours is not necessary).
ContraindicationsKnown or suspected mechanical bowel obstruction
Warnings/Precautions

Concerns related to adverse effects:

- Diarrhea: Discontinue treatment for severe or persistent diarrhea.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended for severe renal impairment (Cl_{cr} <30 mL/minute). Has not been studied in patients with end-stage renal impairment requiring dialysis.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Peritoneal catheters: Use has not been studied in patients with peritoneal catheters.

Other warnings/precautions:

- Appropriate use: Use beyond 4 months has not been studied. Discontinue methylnaltrexone if opioids are discontinued.

Geriatric ConsiderationsIn small studies (Phase 2 and 3), no differences in safety and efficacy were noted between elderly and young adults. No dose adjustment is required in elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Gastrointestinal: Abdominal pain (29%), flatulence (13%), nausea (12%)

1% to 10%:

Central nervous system: Dizziness (7%)

Gastrointestinal: Diarrhea (6%)

<1%, postmarketing, and/or case reports: Abdominal cramps, body temperature increased, muscle spasm, syncope

Metabolism/Transport Effects**Inhibits** CYP2D6 (weak)

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringUse caution in presence of renal impairment (dosage adjustment may be necessary). Evaluate effectiveness and adverse response on a regular basis (discontinue for severe or persistent diarrhea). Must be discontinued if opioids are discontinued. Teach patient or caregiver proper use if self-administered (appropriate injection technique and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new prescription or over-the-counter medications, or herbal products during therapy without consulting prescriber. This medication can only be administered via injection. If self-administered, follow instructions for injection and syringe/needle disposal. May cause dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report immediately any severe or persistent diarrhea or gastrointestinal upset (pain, nausea, vomiting). **Breast-feeding precautions:** Inform prescriber if you are or intend to breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Relistor™: 12 mg/0.6 mL (0.6 mL) [contains edetate calcium disodium]

Generic AvailableNo

ManufacturerWyeth Pharmaceuticals, Inc

Mechanism of ActionAn opioid receptor antagonist which blocks opioid binding at the mu receptor, methylnaltrexone is a quaternary derivative of naltrexone with ability to cross the blood-brain barrier restricted. It therefore functions as a peripheral acting opioid antagonist, including actions on the gastrointestinal tract to inhibit opioid-induced decreased gastrointestinal motility and delay in gastrointestinal transit time, decreasing opioid-induced constipation. Does not affect opioid analgesic effects or induce opioid withdrawal symptoms.

Pharmacodynamics/Kinetics

Onset of action: Usually within 30-60 minutes (in responding patients)

Absorption: SubQ: Rapid

Distribution: V_{ss}: 1.1 L/kg

Protein binding: 11% to 15%

Metabolism: Metabolized to methyl-6-naltrexol isomers, methylnaltrexone sulfate. and other minor metabolites

Half-life elimination: Terminal: ~8 hours

Time to peak, plasma: SubQ: 30 minutes

Excretion: Urine (~50%, primarily as unchanged drug); feces (<50%, primarily as unchanged drug)

Pharmacotherapy PearlsIn some clinical trials, patients who received methylnaltrexone were on a palliative opioid therapy equivalent to a mean daily oral morphine dose of 172 mg, at a stable dose for ≥3 days. Constipation was defined as <3 bowel movements/week or no bowel movement for >2 days. Patients maintained their regular laxative regimen for at least 3 days prior to treatment and throughout the study.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with SSRIs, lithium, carbamazepine, or valproic acid may produce additive effects.

Index TermsMethylnaltrexone Bromide; N-methylnaltrexone Bromide

References

Portenoy RK, Thomas J, Moehl Boatwright ML, et al, “Subcutaneous Methylnaltrexone for the Treatment of Opioid-Induced Constipation in Patients With Advanced Illness: A Double-Blind Randomized, Parallel Group, Dose-Ranging Study,” *J Pain Symptom Manage*, 2008, 35(5):458-68.[PubMed 18440447]

Thomas J, “Opioid-Induced Bowel Dysfunction,” *J Pain Symptom Manage*, 2008, 35(1):103-13.[PubMed 17981003]

Thomas J, Karver S, Cooney GA, et al, “Methylnaltrexone for Opioid-Induced Constipation in Advanced Illness,” *N Engl J Med*, 2008, 358(22):2332-43. [PubMed 18509120]

Yuan CS, “Methylnaltrexone Mechanisms of Action and Effects on Opioid Bowel Dysfunction and Other Opioid Adverse Effects,” *Ann Pharmacother*, 2007, 41(6):984-93.[PubMed 17504835]

International Brand NamesRelistor (DK)

Methylphenidate

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) has issued a statement in April 2008 recommending that all children diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the recommendations due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: Methylphenidate, amphetamine, dextroamphetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children’s Healthcare Quality.

For more information, refer to:

- http://americanheart.mediaroom.com/index.php?s=43&item=422
- http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1
- http://americanheart.mediaroom.com/index.php?s=43&item=398
- http://www.fda.gov/medwatch/safety/2007/safety07.htm
- http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html

Nissen SE, “ADHD Drugs and Cardiovascular Risk,” *N Engl J Med*, 2006, 354(14):1445-48.

“Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder,” *J Am Acad*

Child Adolesc Psychiatry, 2007, 46(7):894-921.

Vetter VL, Elia J, Erickson CH, et al, "Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing," *Circulation*, 2008, 117:2407-23.

Wilens TE, Prince JB, Spencer TJ, et al, "Stimulants and Sudden Death: What is a Physician to do?" *Pediatrics*, 2006, 118(3):1215-19.

Medication Safety Issues

Sound-alike/look-alike issues:

Metadate® CD may be confused with Metadate® ER

Metadate® ER may be confused with Metadate® CD, methadone

Methylphenidate may be confused with methadone

Ritalin® may be confused with Ismelin®, Rifadin®, ritodrine

Pronunciation(meth il FEN i date)

U.S. Brand NamesConcerta®; Daytrana™; Metadate® CD; Metadate® ER; Methylin®; Methylin® ER; Ritalin-SR®; Ritalin®; Ritalin® LA

Canadian Brand NamesApo-Methylphenidate®; Apo-Methylphenidate® SR; Biphentin®; Concerta®; PHL-Methylphenidate; PMS-Methylphenidate; RATIO-Methylphenidate; Riphenidate; Ritalin®; Ritalin® SR

Pharmacologic CategoryCentral Nervous System Stimulant

Use: Labeled IndicationsTreatment of attention-deficit/hyperactivity disorder (ADHD); symptomatic management of narcolepsy

Use: Unlabeled/InvestigationalDepression (especially elderly or medically ill)

Dosing: Adults

ADHD: Oral:

Patients not currently taking methylphenidate: Initial dose: 18-36 mg once daily in the morning

Patients currently taking methylphenidate: **Note:** Initial dose: Dosing based on current regimen and clinical judgment; suggested dosing listed below:

- Patients taking methylphenidate 5 mg 2-3 times/day: 18 mg once every morning
- Patients taking methylphenidate 10 mg 2-3 times/day: 36 mg once every morning
- Patients taking methylphenidate 15 mg 2-3 times/day: 54 mg once every morning
- Patients taking methylphenidate 20 mg 2-3 times/day: 72 mg once every morning

Narcolepsy: Oral: 10 mg 2-3 times/day, up to 60 mg/day

Depression (unlabeled use): Oral: Initial: 2.5 mg every morning before 9 AM; dosage may be increased by 2.5-5 mg every 2-3 days as tolerated to a maximum of 20 mg/day; may be divided (ie, 7 AM and 12 noon), but should not be given after noon; do not use sustained release product

Note: Discontinue periodically to re-evaluate or if no improvement occurs within 1 month.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**ADHD:**

Immediate release products Oral: Children ≥6 years: Initial: 5 mg/dose (~0.3 mg/kg/dose) given twice daily before breakfast and lunch; increase by 5-10 mg/day (0.2 mg/kg/day) at weekly intervals; maximum dose: 60 mg/day (2 mg/kg/day). **Note:** Discontinue periodically to re-evaluate or if no improvement occurs within 1 month.

Extended release products: Oral:

Children ≥6 years:

Metadate® ER, Methylin® ER, Ritalin® SR: May be given in place of immediate release products, once the daily dose is titrated and the titrated 8-hour dosage corresponds to sustained or extended release tablet size; maximum: 60 mg/day

Metadate® CD, Ritalin® LA: Initial: 20 mg once daily; may be adjusted in 10-20 mg increments at weekly intervals; maximum: 60 mg/day

Children 6-12 years and Adolescents 13-17 years: *Concerta®:*

Patients not currently taking methylphenidate: Initial dose: 18 mg once daily in the morning

Patients currently taking methylphenidate: **Note:** Initial dose: Dosing based on current regimen and clinical judgment; suggested dosing listed below:

- Patients taking methylphenidate 5 mg 2-3 times/day **or** 20 mg/day sustained release formulation: 18 mg once every morning
- Patients taking methylphenidate 10 mg 2-3 times/day **or** 40 mg/day sustained release formulation: 36 mg once every morning
- Patients taking methylphenidate 15 mg 2-3 times/day **or** 60 mg/day sustained release formulation: 54 mg once every morning

Dose adjustment: May increase dose in increments of 18 mg; dose may be adjusted at weekly intervals. A dosage strength of 27 mg is available for situations in which a dosage between 18-36 mg is desired. Maximum dose should not exceed 2 mg/kg/day **or** 54 mg/day in children 6-12 years or 72 mg/day in children 13-17 years.

Transdermal (Daytrana™): Children ≥6 years: Initial: 10 mg patch once daily; remove up to 9 hours after application. Titrate based on response and tolerability; may increase to next transdermal dose no more frequently than every week. **Note:** Application should occur 2 hours prior to desired effect. Drug absorption may continue for a period of time after patch removal; patients converting from another formulation of methylphenidate should be initiated at 10 mg regardless of their previous dose and titrated as needed due to the differences in bioavailability of the transdermal formulation.

Administration: OralDo not crush or allow patient to chew sustained or extended release dosage form. To effectively avoid insomnia, dosing should be completed by noon.

Concerta®: Administer dose once daily in the morning. May be taken with or without food, but must be taken with water, milk, or juice.

Metadate® CD, Ritalin® LA: Capsules may be opened and the contents sprinkled onto a small amount (equal to 1 tablespoon) of applesauce. Swallow applesauce without chewing. Do not crush or chew capsule contents.

Methylin® chewable tablet: Administer with at least 8 ounces of water or other fluid.

Administration: TopicalTransdermal (Daytrana™): Apply to clean, dry, non-oily, intact skin to the hip area, avoiding the waistline. Apply at the same time each day to alternating hips. Press firmly for 30 seconds to ensure proper adherence. Avoid exposure of application site to external heat source, which may increase the amount of drug absorbed. Do not use a patch that has been damaged or torn; do not cut patch. If patch should dislodge, may replace with new patch (to different site) but total wear time should not exceed 9 hours; do not reapply with dressings, tape, or common adhesives. Patch may be removed early if a shorter duration of effect is desired or if late day side effects occur. Wash hands with soap and water after handling. Avoid touching the sticky side of the patch. If patch removal is difficult, an oil-based product (eg, petroleum jelly, olive oil) may be applied to the patch edges to aid removal; never apply acetone-based products (eg, nail polish remover) to patch. Dispose of used patch by folding adhesive side onto itself, and discard in toilet or appropriate lidded container.

Dietary ConsiderationsShould be taken 30-45 minutes before meals. Concerta® is not affected by food and should be taken with water, milk, or juice. Metadate® CD should be taken before breakfast. Metadate® ER should be taken before breakfast and lunch. Methylin® chewable tablets contain phenylalanine 0.42 mg/methylphenidate 2.5 mg.

Storage

Capsule,*extended release:* Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light.

Solution: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F).

Tablet:

Chewable: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light and moisture.

Extended and sustained release: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light and moisture.

Immediate release: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light and moisture.

Osmotic controlled release (Concerta®): Store at controlled room temperature of 25°C; excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from humidity.

Transdermal system: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Keep patches stored in protective pouch. Once tray is opened, use patches within 2 months. Do not refrigerate or freeze.

RestrictionsC-II

An FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to methylphenidate, any component of the formulation, or idiosyncratic reactions to sympathomimetic amines; marked anxiety, tension, and agitation; glaucoma; use during or within 14 days following MAO inhibitor therapy; family history or diagnosis of Tourette's syndrome or tics

Metadate® CD and Metadate® ER: Additional contraindications: Severe hypertension, heart failure, arrhythmia, hyperthyroidism, recent MI or angina; concomitant use of halogenated anesthetics

Allergy Considerations

- Amphetamine Allergy

Warnings/Precautions

Boxed warnings:

- Drug abuse: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Cardiovascular events: CNS stimulant use has been associated with serious cardiovascular events including sudden death in patients with pre-existing structural cardiac abnormalities or other serious heart problems (sudden death in children and adolescents; sudden death, stroke, and MI in adults). These products should be avoided in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that could further increase their risk of sudden death. Patients should be carefully evaluated for cardiac disease prior to initiation of therapy. Some products are contraindicated in patients with heart failure, arrhythmias or recent MI.

- Visual disturbance: Difficulty in accommodation and blurred vision has been reported with the use of stimulants.

Disease-related concerns:

- Drug abuse: **[U.S. Boxed Warning]: Potential for drug dependency exists; avoid abrupt discontinuation in patients who have received for prolonged periods.** Use caution in patients with history of ethanol or drug abuse.

- Hypertension: Use with caution in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases in blood pressure or heart rate. Some products are contraindicated in patients with severe hypertension, hyperthyroidism or angina.

- Psychiatric disorders: Use with caution in patients with pre-existing psychosis or bipolar disorder (may induce mixed/manic episode). May exacerbate symptoms of behavior and thought disorder in psychotic patients; new onset psychosis or mania may occur with stimulant use; observe for symptoms of aggression and/or hostility.

- Seizure disorder: Use with caution in patients with a history of seizure disorder; may lower seizure threshold leading to new onset or breakthrough seizure activity.

Special populations:

- Pediatrics: Not labeled for use in children <6 years of age. Use of stimulants has been associated with suppression of growth in children; monitor growth rate during treatment.

Dosage form specific issues:

- Concerta®: Should not be used with pre-existing severe gastrointestinal narrowing conditions, such as esophageal motility disorders, small bowel disease, “short” gut syndrome, cystic fibrosis, history of peritonitis, chronic intestinal pseudo-obstruction, or Meckel’s diverticulum.

- Daytrana™: Transdermal system may cause allergic contact sensitization, characterized by intense local reactions (eg, edema, papules); sensitization may subsequently manifest systemically with other routes of methylphenidate administration; monitor closely. Avoid exposure of application site to any direct external heat sources (eg, hair dryers, heating pads, electric blankets); may increase risk of overdose. Efficacy of therapy for >7 weeks has not been established.

- Metadate® CD: Contains sucrose; avoid administration in hereditary galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption. Concomitant use with halogenated anesthetics is contraindicated; may cause sudden elevations in blood pressure; if surgery is planned, do not administer Metadate® CD on the day of surgery.

- Metadate® ER: Contains lactose; avoid administration in hereditary galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption. Concomitant use with halogenated anesthetics is contraindicated; may cause sudden elevations in blood pressure; if surgery is planned, do not administer Metadate® ER on the day of surgery.

Other warnings/precautions:

- ADHD treatment: Appropriate use: Recommended to be used as part of a comprehensive treatment program for attention deficit disorders.

- Long-term use: Safety and efficacy of long-term use of methylphenidate have not yet been established.

Geriatric ConsiderationsMethylphenidate is often useful in treating elderly patients who are discouraged, withdrawn, apathetic, or disinterested in their activities. In particular, it is useful in patients who are starting a rehabilitation program but have resigned themselves to fail; these patients may not have a major depressive disorder; will not improve memory or cognitive function; use with caution in patients with dementia who may have increased agitation and confusion.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have shown teratogenic effects to the fetus. There are no adequate and well-controlled studies in pregnant women. Do not use in women of childbearing age unless the potential benefit outweighs the possible risk.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsMethylphenidate excretion into breast milk has been noted in case reports. In both cases, the authors calculated the relative infant dose to be ≤0.2% of the weight adjusted maternal dose. Adverse events were not noted in either infant, however, both were older (6 months of age and 11 months of age) and exposure was limited.

Adverse Reactions

Transdermal system: Frequency of adverse events as reported in trials of 7-week duration. Incidence of some events higher with extended use.

>10%:

Central nervous system: Headache (long-term use in children: 28%), insomnia (13%; long-term use in children: 30%)

Gastrointestinal: Appetite decreased (26%), nausea (12%)

Miscellaneous: Viral infection (long-term use in children: 28%)

1% to 10%:

Central nervous system: Tic (7%), emotional instability (6%)

Gastrointestinal: Vomiting (10%), weight loss (9%), anorexia (5%; long-term use in children: 46%)

Local: Application site reaction

Respiratory: Nasal congestion (6%) nasopharyngitis (5%)

Postmarketing and/or case reports (limited to important or life-threatening): Allergic contact sensitization, anaphylaxis, angioedema, hallucinations, seizures

All dosage forms: Frequency not defined:

Cardiovascular: Angina, cardiac arrhythmia, cerebral arteritis, cerebral occlusion, hyper-/hypotension, MI, murmur, palpitation, pulse increased/decreased, Raynaud's phenomenon, tachycardia

Central nervous system: Aggression, agitation, anger, anxiety, confusional state, depression, dizziness, drowsiness, fatigue, fever, headache, hypervigilance, insomnia, irritability, lethargy, mood alterations, nervousness, neuroleptic malignant syndrome (NMS) (rare), restlessness, stroke, tension, Tourette's syndrome (rare), toxic psychosis, tremor, vertigo

Dermatologic: Alopecia, erythema multiforme, exfoliative dermatitis, hyperhidrosis, rash, urticaria

Endocrine & metabolic: Dysmenorrhea, growth retardation, libido decreased

Gastrointestinal: Abdominal pain, anorexia, appetite decreased, bruxism, constipation, diarrhea, dyspepsia, nausea, vomiting, weight loss, xerostomia

Genitourinary: Erectile dysfunction

Hematologic: Anemia, leukopenia, pancytopenia, thrombocytopenic purpura, thrombocytopenia

Hepatic: Bilirubin increased, liver function tests abnormal, hepatic coma, transaminases increased

Neuromuscular & skeletal: Arthralgia, dyskinesia, muscle tightness, paresthesia

Ocular: Blurred vision, dry eyes, mydriasis, visual accommodation disturbance

Renal: Necrotizing vasculitis

Respiratory: Cough increased, dyspnea, pharyngitis, pharyngolaryngeal pain, rhinitis, sinusitis, upper respiratory tract infection

Miscellaneous: Accidental injury, hypersensitivity reactions

Postmarketing and/or case reports: Alkaline phosphatase increased, angina pectoris, bradycardia, chest pain, diplopia, disorientation, extrasystole, mydriasis; hypersensitivity reactions (eg, angioedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticaria, pruritus, rash, eruptions, exanthemas); muscle twitching, hallucinations, mania, erythema, seizure, supraventricular tachycardia, ventricular extrasystole

Metabolism/Transport Effects **Inhibits** CYP2D6 (weak)

Drug Interactions

Antihypertensives: Methylphenidate may diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CloNIDine: Methylphenidate may enhance the adverse/toxic effect of CloNIDine. *Risk C: Monitor therapy*

Inhalational Anesthetics: Methylphenidate may enhance the hypertensive effect of Inhalational Anesthetics. *Risk X: Avoid combination*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Methylphenidate. *Risk X: Avoid combination*

Phenytoin: Methylphenidate may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Methylphenidate may decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause CNS depression).

Food: Food may increase oral absorption; Concerta® formulation is not affected. Food delays early peak and high-fat meals increase C_{max} and AUC of Metadate® CD formulation.

Herb/Nutraceutical: Avoid ephedra (may cause hypertension or arrhythmias) and yohimbe (also has CNS stimulatory activity).

Monitoring Parameters Blood pressure, heart rate, signs and symptoms of depression, aggression, or hostility; CBC, differential and platelet counts, liver function tests; growth rate in children, signs of central nervous system stimulation

Transdermal: Signs of worsening erythema, blistering or edema which does not improve within 24 hours of patch removal, or spreads beyond patch site.

When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure, and consider obtaining ECG prior to initiation (Vetter, 2008).

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance. Evaluate periodically for need for continued use. After long-term use, taper dosage slowly when discontinuing. In children, monitor growth pattern. If growth/weight gain is not as expected, may need to discontinue medication. Perform careful cardiovascular assessment prior to initiating therapy. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. Monitor blood pressure and pulse periodically. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and importance of reporting adverse symptoms promptly.

Monitoring: Lab TestsPeriodic CBC, differential, and platelet counts with prolonged use; liver function tests

Patient EducationTake exactly as directed. Do not change dosage or discontinue without consulting prescriber. Response may take some time. Do not crush or chew sustained release dosage forms. Tablets and sustained release tablets should be taken 30-45 minutes before meals. Concerta® may be taken with or without food, but must be taken with water, milk, or juice. Metadate® CD and Ritalin® LA capsules may be opened and the contents sprinkled onto a small amount (equal to 1 tablespoon) of applesauce; swallow applesauce without chewing. **Transdermal:** Apply to clean, dry skin, immediately after removing from package. Firmly press in place and hold for 30 seconds. Avoid exposing application site to external heat sources (eg, heating pad, electric blanket, hot tub, heat lamp). Total wear time should not exceed 9 hours. Avoid alcohol, caffeine, or other stimulants. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience decreased appetite or weight loss (small frequent meals may help maintain adequate nutrition); restlessness, impaired judgment, or dizziness, especially during early therapy (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Report unresolved rapid heartbeat; excessive agitation, nervousness, worsening of mental symptoms; insomnia, tremors, or dizziness; change in vision; blackened stool; skin rash or irritation; or altered gait or movement. Concerta® tablet shell may appear intact in stool; this is normal. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, extended release, oral, as hydrochloride [bi-modal release]:

Metadate CD®: 10 mg [contains sucrose; 3 mg immediate release, 7 mg extended release]

Metadate CD®: 20 mg [contains sucrose; 6 mg immediate release, 14 mg extended release]

Metadate CD®: 30 mg [contains sucrose; 9 mg immediate release, 21 mg extended release]

Metadate CD®: 40 mg [contains sucrose; 12 mg immediate release, 28 mg extended release]

Metadate CD®: 50 mg [contains sucrose; 15 mg immediate release, 35 mg extended release]

Metadate CD®: 60 mg [contains sucrose; 18 mg immediate release, 42 mg extended release]

Ritalin LA®: 10 mg [5 mg immediate release, 5 mg extended release]

Ritalin LA®: 20 mg [10 mg immediate release, 10 mg extended release]

Ritalin LA®: 30 mg [15 mg immediate release, 15 mg extended release]

Ritalin LA®: 40 mg [20 mg immediate release, 20 mg extended release]

Solution, oral, as hydrochloride:

Methylin®: 5 mg/5 mL (500 mL) [grape flavor]; 10 mg/5 mL (500 mL) [grape flavor]

Tablet, as hydrochloride: 5 mg, 10 mg, 20 mg

Methylin®, Ritalin®: 5 mg, 10 mg, 20 mg

Tablet, chewable, as hydrochloride:

Methylin®: 2.5 mg [contains phenylalanine 0.42 mg; grape flavor]; 5 mg [contains phenylalanine 0.84 mg; grape flavor]; 10 mg [contains phenylalanine 1.68 mg; grape flavor]

Tablet, extended release, as hydrochloride: 20 mg

Metadate® ER: 10 mg [contains lactose]; 20 mg [contains lactose]

Methylin® ER: 10 mg, 20 mg

Tablet, extended release, as hydrochloride [bi-modal release]:

Concerta®: 18 mg [4 mg immediate release, 14 mg extended release]

Concerta®: 27 mg [6 mg immediate release, 21 mg extended release]

Concerta®: 36 mg [8 mg immediate release, 28 mg extended release]

Concerta®: 54 mg [12 mg immediate release, 42 mg extended release]

Tablet, sustained release, as hydrochloride: 20 mg

Ritalin-SR®: 20 mg [dye free]

Transdermal system [once-daily patch]:

Daytrana™: 10 mg/9 hours (10s [DSC], 30s) [12.5 cm^2, total methylphenidate 27.5 mg]

Daytrana™: 15 mg/9 hours (10s [DSC], 30s) [18.75 cm^2, total methylphenidate 41.3 mg]

Daytrana™: 20 mg/9 hours (10s [DSC], 30s) [25 cm^2, total methylphenidate 55 mg]

Daytrana™: 30 mg/9 hours (10s [DSC], 30s) [37.5 cm^2, total methylphenidate 82.5 mg]

Generic AvailableYes: Immediate release tablet, extended release tablet, sustained release tablet
Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Ritalin LA)

10 mg (20): $80.51

20 mg (20): $80.51

30 mg (20): $80.51

40 mg (20): $80.51

Capsule, controlled release (Metadate CD)

10 mg (20): $78.57

20 mg (20): $76.64

30 mg (20): $78.57

Patch (Daytrana)

10 mg/9 hrs (10): $53.73

15 mg/9 hrs (30): $162.63

20 mg/9 hrs (20): $104.14

30 mg/9 hrs (30): $161.79

Tablet, controlled release (Concerta)

18 mg (20): $88.02

27 mg (20): $88.03

54 mg (20): $99.03

Tablet, controlled release (Metadate ER)

20 mg (20): $27.84

Tablet, controlled release (Methylin ER)

20 mg (20): $25.99

Tablet, controlled release (Methylphenidate HCl CR)

20 mg (20): $23.99

Tablet, controlled release (Ritalin SR)

20 mg (20): $38.66

Tablets (Methylin)

20 mg (20): $13.99

Tablets (Methylphenidate HCl)

5 mg (20): $14.99

10 mg (20): $15.99

10 mg (20): $17.99

20 mg (20): $20.99

Tablets (Ritalin)

5 mg (20): $41.20

10 mg (20): $27.99

20 mg (20): $42.39

Mechanism of ActionMild CNS stimulant; blocks the reuptake of norepinephrine and dopamine into presynaptic neurons; appears to stimulate the cerebral cortex and subcortical structures similar to amphetamines

Pharmacodynamics/Kinetics

Onset of action: Peak effect:

Immediate release tablet: Cerebral stimulation: ~2 hours

Extended release capsule (Metadate® CD): Biphasic; initial peak similar to immediate release product, followed by second rising portion (corresponding to extended release portion)

Sustained release tablet: 4-7 hours

Osmotic release tablet (Concerta®): Initial: 1-2 hours

Transdermal: ~2 hours; may be expedited by the application of external heat

Duration: Immediate release tablet: 3-6 hours; Sustained release tablet: 8 hours; Extended release tablet: Methylin® ER, Metadate® ER: 8 hours, Concerta®: 12 hours

Absorption:

Oral: Readily absorbed

Transdermal: Absorption increased when applied to inflamed skin or exposed to heat. Absorption is continuous for 9 hours after application.

Metabolism: Hepatic via de-esterification to minimally active metabolite

Half-life elimination: *d*-methylphenidate: 3-4 hours; *l*-methylphenidate: 1-3 hours

Time to peak: Concerta®: C_{max}: 6-8 hours; Daytrana™: 7.5-10.5 hours

Excretion: Urine (90% as metabolites and unchanged drug)

Related Information

- Stimulant Agents Used for ADHD

Pharmacotherapy PearlsTreatment with methylphenidate may include "drug holidays" or periodic discontinuation in order to assess the patient's requirements and to decrease tolerance and limit suppression of linear growth and weight. Specific patients may require 3 doses/day for treatment of ADHD (ie, additional dose at 4 PM).

Concerta® is an osmotic controlled release formulation (OROS®) of methylphenidate. The tablet has an immediate-release overcoat that provides an initial dose of methylphenidate within 1 hour. The overcoat covers a trilayer core. The trilayer core is composed of two layers containing the drug and excipients, and one layer of osmotic components. As water from the gastrointestinal tract enters the core, the osmotic components expand and methylphenidate is released.

Metadate® CD capsules contain a mixture of immediate release and extended release beads, designed to release 30% of the dose immediately and 70% over an extended period.

Ritalin® LA uses a combination of immediate release and enteric coated, delayed release beads.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Up to 10% of patients taking amphetamine-like drugs may present with hypertension. Monitor blood pressure prior to using local anesthetic with vasoconstrictors.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Cardiovascular ConsiderationsAmphetamines should be avoided in patients with known or suspected cardiovascular disease. They may precipitate marked increases in blood pressure, tachycardia, and tachyarrhythmias. These drugs are often used recreationally and inappropriately, particularly for appetite suppressant effects. Recreational use of amphetamines should be considered in otherwise healthy patients with new onset hypertension, tachycardia, or tachyarrhythmias.

There have been cases of sudden death, heart-related death, and stroke in children and adults taking regular recommended doses of Adderall® and Adderall XR®. In Canada, sales of Adderall XR® were suspended for about six months, but have now resumed. Education and additional surveillance will be done of all stimulants used to treat attention deficit hyperactivity disorder. According to the FDA, five of the 12 reported cases of sudden death in pediatric patients occurred in children with cardiac risk factors, including undiagnosed cardiac abnormalities. The other seven cases were complicated by other illness, rigorous exercise, or family history of ventricular arrhythmia. In addition, unexplained or unusual drug accumulation (resulting in toxic levels despite usual dosing) has been noted in several cases. The drug should not be used in patients with structural heart disease. Further information is available at the following websites:

http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005_01.html

http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#Adderall

http://www.fda.gov/bbs/topics/news/2005/NEW01156.html

Index TermsMethylphenidate Hydrochloride

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International Brand NamesAdaphen (ZA); Adaphen XL (ZA); Aradix (CN); Attenta (AU); Concerta (AU, BB, BE, BG, BM, BS, BZ, CH, CL, CO, CR, DO, EC, ES, FI, GT, GY, HK, HN, IL, JM, MX, MY, NI, NL, PA, PH, SE, SR, SV, TH, TT, TW); Concerta LP (FR); Concerta Oros (KP); Concerta XL (GB); Equasym XL (GB, IE); Lorentin (AU); Metadate CD SR (KP); Penid (KP); Prohiper (ID); Rilatine (LU); Ritalin (AE, AT, AU, BF, BH, BJ, CH, CI, CY, CZ, DE, DK, EG, ET, GB, GH, GM, GN, HK, HN, ID, IE, IL, IQ, IR, JO, JP, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PK, QA, SA, SC, SD, SE, SG, SL, SN, SY, TN, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Ritalin LA (AU, HK, ID, IL, MY, PE); Ritalin-SR (CH, HK, ID, MY, NZ, SG); Ritalina (AR, BR, PY, UY); Ritaline (BE, FR); Ritaline LP (FR); Rubifen (CN, ES, MY, NZ, SG); Tradea (MX)

MethylPREDNISolone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

MethylPREDNISolone may be confused with medroxyPROGESTERone, predniSONE

Depo-Medrol® may be confused with Solu-Medrol®

Medrol® may be confused with Mebaral®

Solu-Medrol® may be confused with Depo-Medrol®, salmeterol, Solu-Cortef®

International issues:

Medor® may be confused with Medral® which is a brand name for omeprazole in Mexico

Pronunciation(meth il pred NIS oh lone)

U.S. Brand NamesDepo-Medrol®; Medrol®; Solu-Medrol®

Canadian Brand NamesDepo-Medrol®; Medrol®; Methylprednisolone Acetate; Solu-Medrol®

Pharmacologic CategoryCorticosteroid, Systemic

Use: Labeled IndicationsPrimarily as an anti-inflammatory or immunosuppressant agent in the treatment of a variety of diseases including those of hematologic, allergic, inflammatory, neoplastic, and autoimmune origin. Prevention and treatment of graft-versus-host disease following allogeneic bone marrow transplantation.

Use: DentalTreatment of a variety of oral diseases of allergic, inflammatory, or autoimmune origin

Dosing: Adults**Only sodium succinate may be given I.V.;** methylprednisolone sodium succinate is highly soluble and has a rapid effect by I.M. and I.V. routes. Methylprednisolone acetate has a low solubility and has a sustained I.M. effect.

Anti-inflammatory or immunosuppressive:

Oral: 2-60 mg/day in 1-4 divided doses to start, followed by gradual reduction in dosage to the lowest possible level consistent with maintaining an adequate clinical response.

I.M. (sodium succinate): 10-80 mg/day once daily

I.M. (acetate): 10-80 mg every 1-2 weeks

I.V. (sodium succinate): 10-40 mg over a period of several minutes and repeated I.V. or I.M. at intervals depending on clinical response; when high dosages are needed, give 30 mg/kg over a period ≥30 minutes and may be repeated every 4-6 hours for 48 hours.

Allergic conditions: Oral: Tapered-dosage schedule:

Day 1: 24 mg on day 1 administered as 8 mg before breakfast, 4 mg after lunch, 4 mg after supper, and 8 mg at bedtime **OR** 24 mg as a single dose or divided into 2 or 3 doses upon initiation (regardless of time of day)

Day 2: 20 mg on day 2 administered as 4 mg before breakfast, 4 mg after lunch, 4 mg after supper, and 8 mg at bedtime

Day 3: 16 mg on day 3 administered as 4 mg before breakfast, 4 mg after lunch, 4 mg after supper, and 4 mg at bedtime

Day 4: 12 mg on day 4 administered as 4 mg before breakfast, 4 mg after lunch, and 4 mg at bedtime

Day 5: 8 mg on day 5 administered as 4 mg before breakfast and 4 mg at bedtime

Day 6: 4 mg on day 6 administered as 4 mg before breakfast

Status asthmaticus: I.V. (sodium succinate): Loading dose: 2 mg/kg/dose, then 0.5-1 mg/kg/dose every 6 hours for up to 5 days

Acute spinal cord injury: I.V. (sodium succinate): 30 mg/kg over 15 minutes, followed in 45 minutes by a continuous infusion of 5.4 mg/kg/hour for 23 hours

Lupus nephritis: High-dose “pulse” therapy: I.V. (sodium succinate): 1 g/day for 3 days

Aplastic anemia: I.V. (sodium succinate): 1 mg/kg/day or 40 mg/day (whichever dose is higher), for 4 days. After 4 days, change to oral and continue until day 10 or until symptoms of serum sickness resolve, then rapidly reduce over approximately 2 weeks.

Pneumonia in AIDS patients due to*Pneumocystis:* I.V.: 30 mg twice daily for 5 days, then 30 mg once daily for 5 days, then 15 mg once daily for 11 days

Arthritis: Intra-articular (acetate): Administer every 1-5 weeks.

Large joints: 20-80 mg

Small joints: 4-10 mg

Intralesional (acetate): 20-60 mg every 1-5 weeks

Dosing: ElderlyOnly sodium succinate salt may be given I.V. Use the lowest effective adult dose.
Dosing: PediatricDosing should be based on the lesser of ideal body weight or actual body weight. **Only sodium succinate may be given I.V.;** methylprednisolone sodium succinate is highly soluble and has a rapid effect by I.M. and I.V. routes. Methylprednisolone acetate has a low solubility and has a sustained I.M. effect.

Acute spinal cord injury: I.V. (sodium succinate): 30 mg/kg over 15 minutes, followed in 45 minutes by a continuous infusion of 5.4 mg/kg/hour for 23 hours

Anti-inflammatory or immunosuppressive: Oral, I.M., I.V. (sodium succinate): 0.5-1.7 mg/kg/day **or** 5-25 mg/m^2/day in divided doses every 6-12 hours; "Pulse" therapy: 15-30 mg/kg/dose over ≥30 minutes given once daily for 3 days

Asthma exacerbations, including status asthmaticus (emergency medical care or hospital doses) (NIH Asthma Guidelines, NAEPP, 2007): Children <12 years: Oral, I.V.: 1-2 mg/kg/day in 2 divided doses (maximum: 60 mg/day) until peak expiratory flow is 70% of predicted or personal best

Lupus nephritis: I.V. (sodium succinate): 30 mg/kg over ≥30 minutes every other day for 6 doses

Status asthmaticus: I.V. (sodium succinate): Previous NAEPP guidelines still encountered in clinical practice: Loading dose: 2 mg/kg/dose, then 0.5-1 mg/kg/dose every 6 hours for up to 5 days; **Note:** See new dosing guidelines for asthma exacerbations above.

Dosing: Renal Impairment

Hemodialysis effects: Slightly dialyzable (5% to 20%)

Administer dose posthemodialysis.

Dosing: Combination Regimens

Brain tumors: 8 in 1 (Brain Tumors)

Leukemia, acute lymphocytic: Hyper-CVAD (Leukemia, Acute Lymphocytic)

Lymphoma, non-Hodgkin's: ESHAP

Retinoblastoma: 8 in 1 (Retinoblastoma)

Calculations

- Body Surface Area: Pediatrics
- Corticosteroid Conversion

Administration: I.V.Only sodium succinate formulation may be given I.V. Acetate salt should not be given I.V.
Parenteral: Methylprednisolone sodium succinate may be administered I.M. or I.V.; I.V. administration may be IVP over one to several minutes or IVPB or continuous I.V. infusion.

I.V.: Succinate:

Low dose: ≤1.8 mg/kg or ≤125 mg/dose: I.V. push over 3-15 minutes

Moderate dose: ≥2 mg/kg or 250 mg/dose: I.V. over 15-30 minutes

High dose: 15 mg/kg or ≥500 mg/dose: I.V. over ≥30 minutes

Doses >15 mg/kg or ≥1 g: Administer over 1 hour

Do **not** administer high-dose I.V. push; hypotension, cardiac arrhythmia, and sudden death have been reported in patients given high-dose methylprednisolone I.V. push (>0.5 g over <10 minutes). Intermittent infusion over 15-60 minutes; maximum concentration: I.V. push 125 mg/mL.

Administration: I.V. DetailpH: 7-8 (adjusted with sodium hydroxide)
Administration: OralGive oral formulation with meals to decrease GI upset. Give daily dose in the morning to mimic normal peak blood levels.
Administration: TopicalFor external use only. Apply sparingly.
Dietary ConsiderationsShould be taken after meals or with food or milk; need diet rich in pyridoxine, vitamin C, vitamin D, folate, calcium, phosphorus, and protein.

Sodium content of 1 g sodium succinate injection: 2.01 mEq; 53 mg of sodium succinate salt is equivalent to 40 mg of methylprednisolone base

Methylprednisolone acetate: Depo-Medrol®

Methylprednisolone sodium succinate: Solu-Medrol®

StorageIntact vials of methylprednisolone sodium succinate should be stored at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light. Reconstituted solutions of methylprednisolone sodium succinate should be stored at room temperature of 20°C to 25°C (68°F to 77°F) and used within 48 hours. Stability of parenteral admixture at room temperature (25°C) and at refrigeration temperature (4°C) is 48 hours.

Reconstitution

Standard diluent (Solu-Medrol®): 40 mg/50 mL D_5W; 125 mg/50 mL D_5W.

Minimum volume (Solu-Medrol®): 50 mL D_5W.

Compatibility**Incompatible** with $D_5{}^1/_2NS$; **variable stability (consult detailed reference)** in D_5NS, D_5W, LR, NS.

Y-site administration: Compatible: Acyclovir, amifostine, amiodarone, amphotericin B cholesteryl sulfate complex, aztreonam, cefepime, cisplatin, cladribine, cyclophosphamide, cytarabine, dopamine, doxorubicin, doxorubicin liposome, enalaprilat, famotidine, fludarabine, gatifloxacin, granisetron, heparin, inamrinone, linezolid, melphalan, meperidine, methotrexate, metronidazole, midazolam, morphine, piperacillin/tazobactam, remifentanil, sodium bicarbonate, tacrolimus, teniposide, theophylline, thiotepa, topotecan. **Incompatible:** Allopurinol, amsacrine, ciprofloxacin, docetaxel, etoposide phosphate, filgrastim, gemcitabine, ondansetron, paclitaxel, propofol, sargramostim, vinorelbine. **Variable (consult detailed reference):** Cisatracurium, diltiazem, heparin with hydrocortisone sodium succinate, potassium chloride, vitamin B complex with C.

Compatibility in syringe: Compatible: Diatrizoate meglumine 52% and diatrizoate sodium 8%, diatrizoate sodium 60%, granisetron, iohexol, iopamidol, iothalamate meglumine 60%, ioxaglate meglumine 39.3% and ioxaglate sodium 19.6%, metoclopramide. **Incompatible:** Doxapram.

Compatibility when admixed: Compatible: Chloramphenicol, cimetidine, clindamycin, dopamine, granisetron, heparin, norepinephrine, penicillin G potassium, ranitidine, theophylline, verapamil. **Incompatible:** Calcium gluconate, glycopyrrolate, insulin (regular), metaraminol, nafcillin, penicillin G sodium. **Variable (consult detailed reference):** Aminophylline, amphotericin B, cytarabine.

ContraindicationsHypersensitivity to methylprednisolone or any component of the formulation; viral, fungal, or tubercular skin lesions; administration of live virus vaccines; serious infections, except septic shock or tuberculous meningitis. Methylprednisolone formulations containing benzyl alcohol preservative are contraindicated in infants. I.M. administration contraindicated in idiopathic thrombocytopenia purpura.

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox should be avoided; corticosteroids should not be used to treat ocular herpes simplex. Corticosteroids should not be used for cerebral malaria or viral hepatitis. Close observation is required in patients with latent tuberculosis and/or TB reactivity; restrict use in active TB (only in conjunction with antituberculosis treatment).

- Myopathy: Acute myopathy has been reported with high dose corticosteroids, usually in patients with neuromuscular transmission disorders; may involve ocular and/or respiratory muscles; monitor creatine kinase; recovery may be delayed.

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with HF; long-term use has been associated with fluid retention and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.

- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.

- Head injury: Increased mortality was observed in patients receiving high-dose I.V. methylprednisolone; high-dose corticosteroids should not be used for the management of head injury.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids.

- Myocardial infarct (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Consider routine eye exams in chronic users.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Elderly: Because of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly in the smallest possible effective dose for the shortest duration.

- Pediatrics: May affect growth velocity; growth should be routinely monitored in pediatric patients.

Other warnings/precautions:

- Discontinuation of therapy: Withdraw therapy with gradual tapering of dose.

Geriatric ConsiderationsBecause of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly, in the smallest possible dose, and for the shortest possible time.

Pregnancy ConsiderationsAdverse events have been observed with corticosteroids in animal reproduction studies. Methylprednisolone crosses the placenta. Some studies have shown an association between first trimester systemic corticosteroid use and oral clefts; adverse events in the fetus/neonate have been noted in case reports following large doses of systemic corticosteroids during pregnancy. Pregnant women exposed to methylprednisolone for antirejection therapy following a transplant may contact the National Transplantation Pregnancy Registry (NTPR) at 215-955-4820. Women exposed to methylprednisolone during pregnancy for the treatment of an autoimmune disease may contact the OTIS Autoimmune Diseases Study at 877-311-8972.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsLow levels of methylprednisolone are excreted in breast milk

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, edema, hypertension

Central nervous system: Delirium, euphoria, hallucinations, headache, insomnia, mood swings, nervousness, pseudotumor cerebri, psychosis, seizure, vertigo

Dermatologic: Acne, bruising, hirsutism, hyperpigmentation, skin atrophy

Endocrine & metabolic: Adrenal suppression, alkalosis, amenorrhea, Cushing's syndrome, diabetes mellitus, glucose intolerance, hyperglycemia, hyperlipidemia, hypokalemia, growth suppression, pituitary-adrenal axis suppression, sodium and water retention

Gastrointestinal: Abdominal distention, appetite Increased, indigestion, nausea, pancreatitis, peptic ulcer, ulcerative esophagitis, vomiting

Hematologic: Leukocytosis (transient)

Neuromuscular & skeletal: Arthralgia, fractures, muscle weakness, osteoporosis

Ocular: Cataracts, glaucoma

Miscellaneous: Avascular necrosis, hypersensitivity reactions, infection, intractable hiccups, secondary malignancy

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP2C8 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase gastric mucosal irritation).

Food: Methylprednisolone interferes with calcium absorption. Limit caffeine.

Herb/Nutraceutical: St John's wort may decrease methylprednisolone levels. Avoid cat's claw, echinacea (have immunostimulant properties).

Test InteractionsInterferes with skin tests

Monitoring ParametersBlood pressure, blood glucose, electrolytes

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor for effectiveness of therapy and adverse reactions according to dose, route, and length of therapy (especially with systemic administration). Assess knowledge/teach patient appropriate use, possible side effects/interventions, and adverse symptoms to report (ie, opportunistic infection, adrenal suppression). Instruct patients with diabetes to monitor serum glucose levels closely; corticosteroids can alter glycemic response. Dose may need to be increased if patient is experiencing higher than normal levels of stress. When discontinuing, taper dose and frequency slowly.

Monitoring: Lab TestsBlood glucose, electrolytes

Patient EducationMaintain adequate nutritional intake; consult prescriber for possibility of special dietary instructions. If you have diabetes, monitor serum glucose closely and notify prescriber of any changes; this medication can alter glycemic response. Avoid alcohol. Inform prescriber if you are experiencing unusual stress; dosage may need to be adjusted. You will be susceptible to infection (avoid crowds and and exposure to infection). You may experience insomnia or nervousness; use caution when driving or engaging in tasks requiring alertness until response to drug is known. Report increased pain, swelling, or redness in area being treated; excessive or sudden weight gain; swelling of extremities; respiratory difficulty; muscle pain or weakness; change in menstrual pattern; vision changes; signs of hyperglycemia; signs of infection (eg, fever, chills, mouth sores, perianal itching, vaginal discharge); blackened stool; other persistent side effects; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Oral: Take as directed, with food or milk. Take once-a-day dose in the morning. Do not take more than prescribed or discontinue without consulting prescriber.

Intra-articular: Refrain from excessive use of joint following therapy, even if pain is gone.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as sodium succinate: 40 mg, 125 mg, 500 mg, 1 g [strength expressed as base]

Solu-Medrol®: 40 mg, 125 mg, 500 mg, 1 g, 2 g [contains benzyl alcohol (in diluent); strength expressed as base]

Solu-Medrol®: 500 mg, 1 g

Injection, suspension, as acetate: 40 mg/mL (5 mL, 10 mL); 80 mg/mL (5 mL)

Depo-Medrol®: 20 mg/mL (5 mL); 40 mg/mL (5 mL); 80 mg/mL (5 mL) [contains benzyl alcohol; strength expressed as base]

Depo-Medrol®: 40 mg/mL (1 mL); 80 mg/mL (1 mL)

Tablet: 4 mg

Medrol®: 2 mg, 4 mg, 8 mg, 16 mg, 32 mg

Tablet, dose-pack: 4 mg (21s)

Medrol® Dosepak™: 4 mg (21s)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Suspension (Depo-Medrol)

20 mg/mL (5): $28.65

Tablets (Medrol)

4 mg (25): $42.98

8 mg (30): $68.24

16 mg (30): $102.52

32 mg (25): $123.45

Tablets (Medrol (Pak))

4 mg (21): $37.79

Tablets (MethylPREDNISolone)

4 mg (30): $17.99

8 mg (25): $45.99

Mechanism of ActionIn a tissue-specific manner, corticosteroids regulate gene expression subsequent to binding specific intracellular receptors and translocation into the nucleus. Corticosteroids exert a wide array of physiologic effects including modulation of carbohydrate, protein, and lipid metabolism and maintenance of fluid and electrolyte homeostasis. Moreover cardiovascular, immunologic, musculoskeletal, endocrine, and neurologic physiology are influenced by corticosteroids. Decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability.

Pharmacodynamics/Kinetics

Onset of action: Peak effect (route dependent): Oral: 1-2 hours; I.M.: 4-8 days; Intra-articular: 1 week; methylprednisolone sodium succinate is highly soluble and has a rapid effect by I.M. and I.V. routes

Duration (route dependent): Oral: 30-36 hours; I.M.: 1-4 weeks; Intra-articular: 1-5 weeks; methylprednisolone acetate has a low solubility and has a sustained I.M. effect

Distribution: V_d: 0.7-1.5 L/kg

Half-life elimination: 3-3.5 hours; reduced in obese

Excretion: Clearance: Reduced in obese

Related Information

- Contrast Media Reactions, Premedication for Prophylaxis
- Corticosteroids

Pharmacotherapy PearlsSodium content of 1 g sodium succinate injection: 2.01 mEq; 53 mg of sodium succinate salt is equivalent to 40 mg of methylprednisolone base

Methylprednisolone acetate: Depo-Medrol®

Methylprednisolone sodium succinate: Solu-Medrol®

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Ulcerative esophagitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNervousness and insomnia are common; may rarely cause delirium, mood swings, euphoria, or hallucinations

Mental Health: Effects on Psychiatric TreatmentBarbiturates may increase the clearance of methylprednisolone

Cardiovascular ConsiderationsLong-term steroid therapy is associated with fluid retention and hypertension. Glucocorticoid agents have some mineralocorticoid activity with consequent hemodynamic effects. Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. In discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that the steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia.

Oral and intravenous steroid therapy in patients with heart failure should be administered cautiously with special attention given to signs and symptoms of fluid retention.

Although glucocorticoids can provide relief from pericarditis postmyocardial infarctions, these drugs may cause thinning of the developing scar and myocardial rupture.

Anesthesia and Critical Care Concerns/Other Considerations

Evidence-Based Information:

Neuromuscular Effects: ICU-acquired paresis was recently studied in five ICUs (three medical and two surgical ICUs) at four French hospitals. All ICU patients without pre-existing neuromuscular disease admitted from March 1999 through June 2000 were evaluated (de Jonghe, 2002). Each patient had to be mechanically-ventilated for ≥7 days and was screened daily for awakening. The first day the patient was considered awake was Study Day 1. Patients with severe muscle weakness on Study Day 7 were considered to have ICU-acquired paresis. Among the 95 patients who were evaluated, about 25% developed ICU-acquired paresis. Independent predictors included female gender, the number of days with ≥2 organ dysfunction, and administration of corticosteroids. Further studies may be required to verify and characterize the association between the development of ICU-acquired paresis and use of corticosteroids. Concurrent use of a corticosteroid and muscle relaxant appears to increase the risk of certain ICU myopathies; avoid or administer the corticosteroid at the lowest dose possible.

Adrenal Insufficiency: Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. When discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that the steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia. Patients on long-term steroid supplementation will require higher corticosteroid doses when subject to stress (eg, trauma, surgery, severe infection). Guidelines for glucocorticoid replacement during various surgical procedures have been published (Coursin, 2002; Salem, 1994).

Septic Shock: Annane, et al (2002) randomized 300 septic shock patients to either hydrocortisone (50 mg I.V. push every 6 hours) and fludrocortisone (50 mcg tablet daily via nasogastric tube) or matching placebos for 7 days. The mean Simplified Acute Physiology Score II (SAPS II) was 57 ± 19 in the placebo group and 60 ± 19 in the active treatment group. The Logistic Organ Dysfunction score was 9 ± 3 in the placebo group and 9 ± 3 in the active treatment group. In patients who did not appropriately respond to corticotropin (nonresponders), there were significantly fewer deaths in the active treatment group. Vasopressor therapy was withdrawn more frequently in this subset of the active treatment group. Adverse events were similar in both groups.

In the CORTICUS trial (Sprung, 2008), 484 septic shock patients were randomized within 72 hours of onset to receive either hydrocortisone (50 mg I.V. push every 6 hours) or placebo for 5 days followed by a 6-day taper. The primary endpoint was 28 day mortality in patients who did not respond to corticotropin. The SAPS II score in the treatment group was 49.5 ± 17.8 and 48.6 ± 16.7 in the placebo group. The Sequential Organ Failure Assessment scores were 10.6 ± 3.4 in the treatment group and 10.6 ± 3.2 in the placebo group. Different than the Annane study, in the patients who did not respond to corticotropin, there was no mortality difference at 28 days; 39.2% (95% CI: 30.5-47.9) mortality in the hydrocortisone group and 36.1% (95% CI: 26.9-45.3, P=0.69) mortality in the placebo group. A trend towards increased incidence of superinfection was noted in hydrocortisone patients. New septic shock episodes, hyperglycemia, and hypernatremia were more frequent in the hydrocortisone group. Hydrocortisone did not improve survival in this population of septic shock patients regardless of corticotropin response.

The 2008 Surviving Sepsis Campaign Guidelines suggest the following: Intravenous hydrocortisone be given only to adult septic shock patients after blood pressure is identified to be poorly responsive to fluid resuscitation and vasopressor therapy (Grade 2C); ACTH stimulation test not be used to identify the subset of adults with septic shock who should receive hydrocortisone (Grade 2B); patients with septic shock should not receive dexamethasone if hydrocortisone is available (Grade 2B); the addition of fludrocortisone if hydrocortisone is not available and the steroid that is substituted does not have significant mineralocorticoid activity (Grade 2C); doses of corticosteroids comparable to >300 mg hydrocortisone daily **not** be used in severe sepsis or septic shock for the purpose of treating septic shock (Grade 1A). They also recommend corticosteroids **not** be administered for the treatment of sepsis in the absence of shock. There is, however, no contraindication to continuing maintenance steroid therapy or to using stress dose steroids if the patient's endocrine or corticosteroid administration history warrants (Grade 1D).

The 2008 Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients recommend a diagnosis of critical illness related corticosteroid insufficiency can be made by a delta cortisol level (after 250 mcg cosyntropin) of <9 mcg/dL or a random cortisol <10 mcg/dL (Grade 2B). However, they recommend **against** the use of ACTH stimulation test to determine if septic shock or ARDS patients should receive steroid therapy (Grade 2B). They recommend to consider using hydrocortisone in septic shock patients who have responded poorly to resuscitation and vasopressors (Grade 2B) and glucocorticoid treatment should be tapered slowly and not stopped abruptly (Grade 2B). Dexamethasone is **not** recommended for the treatment of septic shock or ARDS (Grade 1B). Fludrocortisone therapy is considered optional (Grade 2B).

Index Terms 6-α-Methylprednisolone; A-Methapred; Methylprednisolone Acetate; Methylprednisolone Sodium Succinate

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International Brand Names Adrena (PH); Advantan (MX); Belon (TW); Cipridanol (PY); Cryosolona (MX); Depo-Medrol (LU, MX); Esametone (IT); Firmacort (IT); Medrol (BB, BM, BS, BZ, CO, CR, ES, GR, GT, GY, HR, IT, JM, LU, NI, NZ, PA, PL, PT, RU, SR, SV, TR, TT); Methylprednisolon Kristallsuspension (PL); Methylprednisolone David Bull (LU); Methysol (KP); Metypred (PL); Predlitem (MX); Solomet (FI); Solu Medrol (BF, BJ, CI, EC, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Solu-Medrol (AE, AR, AT, AU, BE, BG, BH, CH, CL, CN, CY, CZ, DK, EE, EG, FI, FR, HK, HN, ID, IL, IN, IQ, IR, JO, KW, LB, LY, MX, MY, NL, NO, OM, PE, PH, PK, QA, SA, SE, SY, TH, UY, VE, YE); Solu-Medrone (GB, IE); Solu-Ped (PH); Solucin (PH); Unimedrol (BR); Urbason (ES, HR); Urbason Retard (IT); Urbason Solubile (AT, CZ, DE, DK)

MethylTESTOSTERone

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Medication Safety Issues

Sound-alike/look-alike issues:

MethylTESTOSTERone may be confused with medroxyPROGESTERone

Virilon® may be confused with Verelan®

Pronunciation(meth il tes TOS te rone)
U.S. Brand NamesAndroid®; Methitest™; Testred®; Virilon®
Pharmacologic CategoryAndrogen
Use: Labeled Indications

Male: Hypogonadism; delayed puberty; impotence and climacteric symptoms

Female: Palliative treatment of metastatic breast cancer

Dosing: Adults **Note:** Buccal absorption produces twice the androgenic activity of oral tablets.

Hypogonadism; delayed puberty; impotence and climacteric symptoms (Male): Oral: 10-40 mg/day

Androgen deficiency (Male):

Oral: 10-50 mg/day

Buccal: 5-25 mg/day

Postpubertal cryptorchidism (Male): Oral: 30 mg/day

Breast pain/engorgement (Female):

Oral: 80 mg/day for 3-5 days

Buccal: 40 mg/day for 3-5 days

Breast cancer (Female):

Oral: 50-200 mg/day

Buccal: 25-100 mg/day

Dosing: ElderlyRefer to adult dosing.
RestrictionsC-III
ContraindicationsHypersensitivity to methyltestosterone or any component of the formulation; in males, known or suspected carcinoma of the breast or the prostate; pregnancy
Allergy Considerations

- Androgen Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hepatic effects: Prolonged use and/or high doses may cause peliosis hepatis or liver cell tumors which may not be apparent until liver failure or intra-abdominal hemorrhage develops. Discontinue in case of cholestatic hepatitis with jaundice or abnormal liver function tests.

Disease-related concerns:

- Breast cancer: Use with caution in patients with breast cancer; may cause hypercalcemia by stimulating osteolysis.

- Diabetes: Use with caution in patients with diabetes mellitus; monitor carefully.

- Edematous conditions: Use with caution in patients with conditions influenced by edema (eg, cardiovascular disease, migraine, seizure disorder, renal impairment); may cause fluid retention.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

Special populations:

- Elderly: Use with caution in elderly patients, they may be at greater risk for prostatic hyperplasia, fluid retention, and transaminase elevations.
- Pediatrics: May accelerate bone maturation without producing compensatory gain in linear growth in children; in prepubertal children perform radiographic examination of the hand and wrist every 6 months to determine the rate of bone maturation and to assess the effect of treatment on the epiphyseal centers.
- Women: Discontinue with evidence of mild virilization in women.

Geriatric ConsiderationsSince elderly males have prostate changes with age, it would be best to obtain a PSA initially and periodically. Retention of sodium and water could be a problem in patients with CHF and hypertension.
Pregnancy Risk FactorX
LactationExcretion in breast milk unknown/contraindicated
Adverse ReactionsFrequency not defined.

Male: Virilism, priapism, prostatic hyperplasia, prostatic carcinoma, impotence, testicular atrophy, gynecomastia

Female: Virilism, menstrual problems (amenorrhea), breast soreness, hirsutism (increase in pubic hair growth), atrophy

Cardiovascular: Edema

Central nervous system: Headache, anxiety, depression

Dermatologic: Acne, “male pattern” baldness, seborrhea

Endocrine & metabolic: Hypercalcemia, hypercholesterolemia

Gastrointestinal: GI irritation, nausea, vomiting

Hematologic: Leukopenia, polycythemia

Hepatic: Hepatic dysfunction, hepatic necrosis, cholestatic hepatitis

Miscellaneous: Hypersensitivity reactions

Drug Interactions

CycloSPORINE: Androgens may enhance the hepatotoxic effect of CycloSPORINE. Androgens may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Androgens may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Monitoring ParametersIn prepubertal children, perform radiographic examination of the hand and wrist every 6 months to determine the rate of bone maturation and to assess the effect of treatment on the epiphyseal centers.
Nursing: Physical Assessment/MonitoringUse extreme caution in presence of hepatic, renal, or cardiovascular disease. Assess potential for interactions with other pharmacological agents patient may be taking (eg, effects of hypoglycemic agents may be increased). Assess therapeutic effects (according to purpose for use) and adverse response (eg, virilism [male and female], edema, CNS changes [anxiety, depression], acne, baldness, GI irritation, leukopenia, hepatic dysfunction) frequently during therapy. Caution patients with diabetes; effects of hypoglycemic agents may be increased. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Instruct patients of childbearing age or males who may have intercourse with women of childbearing age on appropriate contraceptive measures. Breast-feeding is contraindicated.
Patient EducationTake as directed; do not discontinue without consulting prescriber. If you have diabetes, monitor serum glucose closely and notify prescriber of changes; this medication can alter hypoglycemic requirements. May cause acne, growth of body hair, loss of libido, impotence, or menstrual irregularity (usually reversible); or nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report changes in menstrual pattern; deepening of voice or unusual growth of body hair; gynecomastia or breast soreness; priapism; fluid retention (swelling of ankles, feet, or hands, respiratory difficulty, or sudden weight gain); change in color of urine or stool; yellowing of eyes or skin; unusual bruising or bleeding; unusual fatigue or weakness; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant or cause a pregnancy (males) during or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule (Android®, Testred®, Virilon®): 10 mg

Tablet (Methitest™): 10 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Capsules (Android)

10 mg (60): $405.98

Capsules (Testred)

10 mg (60): $405.98

Mechanism of ActionStimulates receptors in organs and tissues to promote growth and development of male sex organs and maintains secondary sex characteristics in androgen-deficient males

Pharmacodynamics/Kinetics

Metabolism: Hepatic

Excretion: Urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine

International Brand NamesBuild (TW); Gynosterone (IL); Mesteron (PL); Testormon (PT); Testotonic B (IL); Testovis (IT)

Metipranolol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Metipranolol may be confused with metaproterenol

International issues:

Betanol® [Monaco] may be confused with Beta-Val® which is a brand name for betamethasone in the U.S.

Betanol® [Monaco] may be confused with Patanol® which is a brand name for olopatadine in the U.S.

Betanol® [Monaco] may be confused with Betimol® which is a brand name for timolol in the U.S.

Pronunciation(met i PRAN oh lol)

U.S. Brand NamesOptiPranolol®

Canadian Brand NamesOptiPranolol®

Pharmacologic CategoryBeta Blocker, Nonselective; Ophthalmic Agent, Antiglaucoma

Use: Labeled IndicationsAgent for lowering intraocular pressure in patients with chronic open-angle glaucoma

Dosing: AdultsGlaucoma: Ophthalmic: Instill 1 drop in the affected eye(s) twice daily

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to metipranolol or any component of the formulation; bronchial asthma, sinus bradycardia, second- and third-degree AV block, cardiac failure, cardiogenic shock

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Concerns related to adverse events:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.
- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.
- Heart failure (HF): Use with caution in patients with compensated heart failure and monitor for a worsening of the condition.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis.
- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).
- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

Special populations:

- Contact lens wearers: Some products may contain benzalkonium chloride which may be absorbed by soft contact lenses; remove lens prior to administration and wait 15 minutes before reinserting.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.
- Absorption: Systemic absorption and adverse effects may occur with ophthalmic use, including bradycardia and/or hypotension.

Geriatric ConsiderationsBecause systemic absorption occurs with ophthalmic administration, elderly patients with other disease states or syndromes that may be affected by a beta-blocker (ie, CHF, COPD, etc) should be closely monitored.

Pregnancy Risk FactorC

Adverse Reactions

>10%: Ocular: Mild ocular stinging and discomfort, eye irritation

1% to 10%: Ocular: Blurred vision, browache

<1%: Bradycardia, AV block, CHF, erythema, weakness, conjunctivitis, blepharitis, tearing, itching eyes, keratitis, photophobia, decreased corneal sensitivity, bronchospasm

Drug Interactions

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Patient EducationIntended for twice-daily dosing. Keep eye open and do not blink for 30 seconds after instillation. Wear sunglasses to avoid photophobic discomfort.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic: 0.3% (5 mL, 10 mL) [contains benzalkonium chloride]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Optipranolol)

0.3% (5): $25.99

0.3% (10): $42.99

Mechanism of ActionBeta-adrenoceptor-blocking agent; lacks intrinsic sympathomimetic activity and membrane-stabilizing effects and possesses only slight local anesthetic activity; mechanism of action of metipranolol in reducing intraocular pressure appears to be via reduced production of aqueous humor. This effect may be related to a reduction in blood flow to the iris root-ciliary body. It remains unclear if the reduction in intraocular pressure observed with beta-blockers is actually secondary to beta-adrenoceptor blockade.

Pharmacodynamics/Kinetics

Onset of action: ≤30 minutes

Peak effect: Maximum: ~2 hours

Duration: Intraocular pressure reduction: Up to 24 hours

Metabolism: Rapid and complete to deacetyl metipranolol, an active metabolite

Half-life elimination: ~3 hours

Related Information

- Glaucoma Drug Therapy

Dental Health: Effects on Dental TreatmentMetipranolol is a nonselective beta-blocker and may enhance the pressor response to epinephrine, resulting in hypertension and bradycardia. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay produce CNS depression; concurrent use with psychotropic agents may produce additive effects

Cardiovascular ConsiderationsIt is important to recognize that metipranolol eye drops may have systemic effects, particularly when patients are also on oral beta-blocker therapy or therapy with other negative chronotropic agents.

Index TermsMetipranolol Hydrochloride

References

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International Brand NamesBeta Ophtiole (AT, BE, NL, PH, PT, TW); Betamann (LU, PL); Betanol (FR); Glauline (GB); Minims Metipranolol (GB); Normoglaucon (DE); Trimepranol (CZ); Turoptin (CH, IT)

Metoclopramide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Metoclopramide may be confused with metolazone

Reglan® may be confused with Megace®, Regonol®, Renagel®

Pronunciation(met oh KLOE pra mide)

U.S. Brand NamesReglan®

Canadian Brand NamesApo-Metoclop®; Metoclopramide Hydrochloride Injection; Nu-Metoclopramide

Pharmacologic CategoryAntiemetic; Gastrointestinal Agent, Prokinetic

Use: Labeled Indications

Oral: Symptomatic treatment of diabetic gastric stasis; gastroesophageal reflux

I.V., I.M.: Symptomatic treatment of diabetic gastric stasis; postpyloric placement of enteral feeding tubes; prevention and/or treatment of nausea and vomiting associated with chemotherapy, or postsurgery; to stimulate gastric emptying and intestinal transit of barium during radiological examination

Dosing: Adults

Gastroesophageal reflux: Oral: 10-15 mg/dose up to 4 times/day 30 minutes before meals or food and at bedtime; single doses of 20 mg are occasionally needed for provoking situations. Treatment >12 weeks has not been evaluated.

Diabetic gastric stasis:

Oral: 10 mg 30 minutes before each meal and at bedtime

I.M., I.V. (for severe symptoms): 10 mg over 1-2 minutes; 10 days of I.V. therapy may be necessary for best response

Chemotherapy-induced emesis:

I.V.: 1-2 mg/kg 30 minutes before chemotherapy and repeated every 2 hours for 2 doses, then every 3 hours for 3 doses (manufacturer labeling)

Alternate dosing (with or without diphenhydramine):

Moderate emetic risk chemotherapy: 0.5 mg/kg every 6 hours on days 2-4

Low and minimal risk chemotherapy: 1-2 mg/kg every 3-4 hours

Breakthrough treatment: 1-2 mg/kg every 3-4 hours

Oral (unlabeled use; with or without diphenhydramine):

Moderate emetic risk chemotherapy: 0.5 mg/kg every 6 hours or 20 mg 4 times/day on days 2-4

Low and minimal risk chemotherapy: 20-40 mg every 4-6 hours

Breakthrough treatment: 20-40 mg every 4-6 hours

Postoperative nausea and vomiting: I.M., I.V.: 10-20 mg near end of surgery

Postpyloric feeding tube placement, radiological exam: I.V.: 10 mg

Dosing: Elderly

Gastroesophageal reflux: Oral: 5 mg 4 times/day (30 minutes before meals or food and at bedtime); increase dose to 10 mg 4 times/day if no response at lower dose

Gastrointestinal hypomotility:

Oral: Initial: 5 mg 30 minutes before meals and at bedtime; increase if necessary to 10 mg doses

I.V.: Initiate at 5 mg over 1-2 minutes; increase to 10 mg if necessary

Postoperative nausea and vomiting: I.M., I.V.: 5 mg near end of surgery; may repeat dose if necessary

Dosing: Pediatric

Gastroesophageal reflux (unlabeled use): Oral: 0.1-0.2 mg/kg/dose 4 times/day

Chemotherapy-induced emesis (unlabeled use): I.V.: 1-2 mg/kg 30 minutes before chemotherapy and every 2-4 hours

Postpyloric feeding tube placement: I.V.:

<6 years: 0.1 mg/kg

6-14 years: 2.5-5 mg

>14 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} <40 mL/minute: Administer 50% of normal dose.

Not dialyzable (0% to 5%); supplemental dose is not necessary.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.May be administered I.M.

Administration: I.V.Injection solution may be given I.M., direct I.V. push, short infusion (15-30 minutes), or continuous infusion; lower doses (≤10 mg) of metoclopramide can be given I.V. push undiluted over 1-2 minutes; higher doses to be given IVPB over at least 15 minutes; continuous SubQ infusion and rectal administration have been reported. **Note:** Rapid I.V. administration may be associated with a transient (but intense) feeling of anxiety and restlessness, followed by drowsiness.

Administration: I.V. DetailpH: 3.0-6.5

Administration: OtherContinuous SubQ infusion and rectal administration have been reported

Storage

Injection: Store intact vial at controlled room temperature; injection is photosensitive and should be protected from light during storage; parenteral admixtures in D_5W or NS are stable for at least 24 hours and do not require light protection if used within 24 hours.

Tablet: Store at controlled room temperature.

CompatibilityStable in $D_5{}^1/_2NS$, D_5W, mannitol 20%, LR, NS; **variable stability (consult detailed reference)** in TPN.

Y-site administration: Compatible: Acyclovir, aldesleukin, amifostine, aztreonam, bleomycin, ciprofloxacin, cisatracurium, cisplatin, cladribine, clarithromycin, cyclophosphamide, cytarabine, diltiazem, docetaxel, doxorubicin, droperidol, etoposide phosphate, famotidine, filgrastim, fluconazole, fludarabine, fluorouracil, foscarnet, gatifloxacin, gemcitabine, granisetron, heparin, idarubicin, leucovorin, levofloxacin, linezolid, melphalan, meperidine, meropenem, methotrexate, mitomycin, morphine, ondansetron, paclitaxel, piperacillin/tazobactam, remifentanil, sargramostim, sufentanil, tacrolimus, teniposide, thiotepa, topotecan, vinblastine, vincristine, vinorelbine, zidovudine. **Incompatible:** Allopurinol, amphotericin B cholesteryl sulfate complex, amsacrine, cefepime, doxorubicin liposome, furosemide, propofol. **Variable (consult detailed reference):** TPN.

Compatibility in syringe: Compatible: Aminophylline, ascorbic acid injection, atropine, benztropine, bleomycin, butorphanol, chlorpromazine, cisplatin, cyclophosphamide, cytarabine, dexamethasone sodium phosphate, diamorphine, dimenhydrinate, diphenhydramine, doxorubicin, droperidol, fentanyl, fluorouracil, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydroxyzine, insulin (regular), leucovorin, lidocaine, magnesium sulfate, meperidine, methotrimeprazine, methylprednisolone sodium succinate, midazolam, mitomycin, morphine, ondansetron, pentazocine, perphenazine, prochlorperazine edisylate, promazine, promethazine, ranitidine, scopolamine, sufentanil, vinblastine, vincristine, vitamin B complex with C. **Incompatible:** Ampicillin, calcium gluconate, chloramphenicol, furosemide, penicillin G potassium, sodium bicarbonate. **Variable (consult detailed reference):** Methotrexate.

Compatibility when admixed: Compatible: Cimetidine, clindamycin, diamorphine, meperidine, meropenem, morphine, multivitamins, potassium acetate, potassium chloride, potassium phosphate, verapamil. **Incompatible:** Dexamethasone sodium phosphate with lorazepam and diphenhydramine, erythromycin lactobionate, floxacillin, fluorouracil, furosemide.

ContraindicationsHypersensitivity to metoclopramide or any component of the formulation; GI obstruction, perforation or hemorrhage; pheochromocytoma; history of seizures

Warnings/Precautions

Concerns related to adverse effects:

- Depression: Mental depression has occurred, symptoms range from mild to severe (suicidal ideation and suicide); use with caution in patients with a history of mental illness.

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is higher in pediatric patients and adults <30 years of age). Typically occurs within the initial 24-48 hours of treatment; risk is increased at higher dosages. Use caution with concurrent use of other drugs associated with EPS.

- Neuroleptic malignant syndrome (NMS): Use may be associated (rarely) with neuroleptic malignant syndrome (NMS); monitor for mental status changes, fever, muscle rigidity and/or autonomic instability.

Disease-related concerns:

- Edematous conditions: Use with caution in patients who are at risk of fluid overload (HF, cirrhosis). May cause transient increase in serum aldosterone; use lowest recommended doses initially.

- Hypertension: Use with caution in patients with hypertension.
- NADH-cytochrome b5 reductase deficiency: Patients with NADH-cytochrome b5 reductase deficiency are at increased risk of methemoglobinemia and/or sulfhemoglobinemia.
- Parkinson's disease: Use with caution in patients with parkinson's disease; may have increased risk of tardive dyskinesia.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment may be needed.
- Surgical anastomosis/closure: Use with caution following surgical anastomosis/closure; promotility agents may theoretically increase pressure in suture lines.

Special populations:

- Elderly: Use with caution in the elderly; may have increased risk of tardive dyskinesia.

Other warnings/precautions:

- Discontinuation of therapy: Abrupt discontinuation may (rarely) result in withdrawal symptoms (dizziness, headache, nervousness).

Geriatric ConsiderationsElderly are more likely to develop tardive dyskinesia syndrome (especially elderly females) reactions than younger adults. Use lowest recommended doses initially. Must consider renal function (estimate creatinine clearance). It is recommended to do involuntary movement assessments on elderly using this medication at high doses and for long-term therapy.

Pregnancy Risk FactorB

Pregnancy ConsiderationsCrosses the placenta; available evidence suggests safe use during pregnancy.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsEnters breast milk; may increase milk production

Adverse ReactionsFrequency not always defined.

Cardiovascular: AV block, bradycardia, CHF, fluid retention, flushing (following high I.V. doses), hyper-/hypotension, supraventricular tachycardia

Central nervous system: Drowsiness (~10% to 70%; dose related), acute dystonic reactions (<1% to 25%; dose and age related), fatigue (~10%), restlessness (~10%), akathisia, confusion, depression, dizziness, hallucinations (rare), headache, insomnia, neuroleptic malignant syndrome (rare), Parkinsonian-like symptoms, suicidal ideation, seizure, tardive dyskinesia

Dermatologic: Angioneurotic edema (rare), rash, urticaria

Endocrine & metabolic: Amenorrhea, galactorrhea, gynecomastia, impotence

Gastrointestinal: Diarrhea, nausea

Genitourinary: Incontinence, urinary frequency

Hematologic: Agranulocytosis, leukopenia, neutropenia, porphyria

Hepatic: Hepatotoxicity (rare)

Ocular: Visual disturbance

Respiratory: Bronchospasm, laryngeal edema (rare)

Miscellaneous: Allergic reactions, methemoglobinemia, sulfhemoglobinemia

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 2D6; **Inhibits** CYP2D6 (weak)

Drug Interactions

Anti-Parkinson's Agents (Dopamine Agonist): Metoclopramide may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk C: Monitor therapy*

CycloSPORINE: Metoclopramide may increase the absorption of CycloSPORINE. *Risk C: Monitor therapy*

Sertraline: Metoclopramide may enhance the adverse/toxic effect of Sertraline. Specifically, the risk of serotonin syndrome may be increased. *Risk C: Monitor therapy*

Venlafaxine: Metoclopramide may enhance the adverse/toxic effect of Venlafaxine. Specifically, the risk of serotonin syndrome may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Test InteractionsIncreased aminotransferase [ALT/AST] (S), increased amylase (S)

Monitoring ParametersDystonic reactions; signs of hypoglycemia in patients using insulin and those being treated for gastroparesis; agitation, and onfusion

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking (eg, any antipsychotic agents, opioids, anticholinergics). Vital signs should be monitored during intravenous administration. Inpatients should use safety measures (eg, side rails up, call light within reach) and caution patient to call for assistance with ambulation. Assess results of laboratory tests (periodic renal function tests), therapeutic effectiveness (relief of symptoms), and adverse reactions (eg, extrapyramidal effects, parkinsonian-like reactions, seizures, fluid retention, adverse CNS changes). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, CNS restlessness, drowsiness, depression, rash).

Monitoring: Lab TestsPeriodic renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Oral: Take this drug as prescribed, 30 minutes prior to eating. Do not increase dosage. Avoid alcohol; may increase adverse effects. May cause dizziness, drowsiness, or blurred vision (use caution when driving or engaging in tasks that require alertness until response to drug is known); cause restlessness, anxiety, depression, or insomnia (will reverse when medication is discontinued). Report any CNS changes, spasticity or involuntary movements, unresolved diarrhea, fluid retention (swelling of extremities, weight gain); visual disturbances; palpitations or rapid heart beat; or any other persistent adverse effects. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 5 mg/mL (2 mL)

Reglan®: 5 mg/mL (2 mL, 10 mL, 30 mL)

Solution, oral: 5 mg/5 mL (10 mL, 480 mL)

Tablet: 5 mg, 10 mg

Reglan®: 5 mg, 10 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Metoclopramide HCl)

5 mg/5 mL (240): $15.99

Tablets (Metoclopramide HCl)

5 mg (30): $12.99

10 mg (90): $15.99

Tablets (Reglan)

5 mg (30): $32.99

10 mg (30): $54.99

Mechanism of ActionBlocks dopamine receptors and (when given in higher doses) also blocks serotonin receptors in chemoreceptor trigger zone of the CNS; enhances the response to acetylcholine of tissue in upper GI tract causing enhanced motility and accelerated gastric emptying without stimulating gastric, biliary, or pancreatic secretions; increases lower esophageal sphincter tone

Pharmacodynamics/Kinetics

Onset of action: Oral: 0.5-1 hour; I.V.: 1-3 minutes; I.M.: 10-15 minutes

Duration: Therapeutic: 1-2 hours, regardless of route

Distribution: V_d: 2-4 L/kg

Protein binding: 30%

Bioavailability: Oral: 65% to 95%

Half-life elimination: Normal renal function: 4-6 hours (may be dose dependent)

Time to peak, serum: Oral: 1-2 hours

Excretion: Urine (~85%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and restlessness are common; may cause insomnia or depression. Depression has occurred in patients with and without a prior history of depression. Symptoms have ranged from mild to severe, and have included suicidal ideation and suicide. Metoclopramide is a D_2 blocker; may cause extrapyramidal symptoms especially when used in high dosages (dystonia) or in the elderly (tardive dyskinesia). Dystonic reactions occur in approximately 1 in 500 patients with the usual adult dosage of 30-40 mg/day. These reactions are usually seen during the first 1-2 days of therapy with metoclopramide, occurring more frequently in pediatric patients and adults <30 years of age, and are more frequent when higher doses are used in prophylaxis of vomiting due to cancer chemotherapy. NMS has rarely been reported.

Mental Health: Effects on Psychiatric TreatmentAnticholinergics may antagonize metoclopramide's effects; concurrent use with psychotropic may produce additive sedation

Cardiovascular ConsiderationsMetoclopramide dose not cause QT prolongation.

Anesthesia and Critical Care Concerns/Other Considerations

Evidence-Based Information: The consensus guidelines for postoperative nausea and vomiting (Gan, 2003) does not recommend the use of metoclopramide.

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International Brand NamesAfipran (NO); Ametic (ZA); Biclomet (PH); Bondigest (CO); Carnotprim (MX); Cerucal (DE, EE, HU, PL); Clomitene (PH); Clopamon (ZA); Clopan (IT); Clopram (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Dart (BR); Dibertil (BE, LU, RU); Dirpasid (MX); Emetal (TH); Emetic (BR); Emperal (BG, DK); Enzimar (CO); Gastro-Timelets (LU); Gastrobi (KP); Gastronerton (DE, LU); Gastrosil (CH, DE, LU, PL, RU); Gavistal (ID); Gensil (TH); Hemesys (PE); Imperan (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Itan (CN); Legir (UY); Macperan (KP); Manosil (TH); Maril (HK, TH); Martomide (HK); Maxeron (IN); Maxolon (AE, AU, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GB, GH, GM, GN, GY, IE, IL, IQ, IR, JM, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); MCP-Beta Tropfen (DE); MCP-ratiopharm (LU); Meclomid (MX); Metamide (NZ); Metlazel (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Metoclamid (LU); Metoclopramid (PL); Metoclopramide-Eurogenerics (LU); Metoclopramidum (PL); Metoclor (TH); Metocobil (IT); Metocyl (MY); Metolon (MY); Metopram (FI); Movistal (LU); Nausil (TH); Nilatika (ID); Norvom (ID); Paspertin (HU); Perinorm (IN, ZA); Perone (TW); Pharmyork (GR); Plasil (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, ID, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, OM, PH, PY, QA, SA, SC, SD, SL, SN, SY, TH, TN, TZ, UG, YE, ZA, ZM, ZW); Polcotec (MX); Pramidin (PL); Pramin (AU, IL); Primperan (AT, BE, BF, BG, BJ, CH, CI, CR, CZ, DE, DK, DO, EC, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, HK, HN, IE, IT, JP, KE, LR, LU, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, NO, PA, PE, PT, RU, SC, SD, SE, SL, SN, SV, TN, TR, TW, TZ, UG, VE, ZA, ZM, ZW); Primperil (AR); Prinparl (JP); Prokinyl (LU); Prowel (TW); Pulin (MY, SG); Regelan (PK); Reglan (HR, IN); Reglomar (PH); Reliveran (AR); Setin (ZA); Sotatic-10 (ID); Vertivom (ID)

Metolazone

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Medication Safety Issues

Sound-alike/look-alike issues:

Metolazone may be confused with metaxalone, methazolamide, methimazole, methotrexate, metoclopramide, metoprolol, minoxidil

Zaroxolyn® may be confused with Zarontin®

Pronunciation(me TOLE a zone)

U.S. Brand NamesZaroxolyn®

Canadian Brand NamesZaroxolyn®

Pharmacologic CategoryDiuretic, Thiazide-Related

Use: Labeled IndicationsManagement of mild to moderate hypertension; treatment of edema in congestive heart failure and nephrotic syndrome, impaired renal function

Dosing: Adults

Edema: Oral: 2.5-20 mg/dose every 24 hours (ACC/AHA 2005 Heart Failure Guidelines)

Hypertension: Oral: 2.5-5 mg/dose every 24 hours

Dosing: ElderlyOral: Initial: 2.5 mg/day or every other day

Dosing: Renal ImpairmentNot dialyzable (0% to 5%) via hemo- or peritoneal dialysis; supplemental dose is not necessary

Administration: OralMay be taken with food or milk. Take early in day to avoid nocturia. Take the last dose of multiple doses no later than 6 PM unless instructed otherwise.

Dietary ConsiderationsShould be taken after breakfast; may require potassium supplementation

Extemporaneously Prepared

A 1 mg/mL suspension may be made by crushing twelve 10 mg Zaroxolyn® tablets; add Ora-Sweet®, Ora-Sweet® SF, Ora-Plus®, or cherry syrup diluted 1:4 with simple syrup to total volume of 120 mL. Label “shake well”; stable 60 days refrigerated.

A 0.25 mg/mL suspension may be made by crushing one 2.5 mg tablet; add 1:1 mixture 1% methylcellulose:simple syrup mixture to a total volume of 10 mL; label "shake well"; refrigerate; stable 91 days refrigerated; 28 days at room temperature in plastic and 14 days at room temperature in glass.

Nahata, MC, Pai VB, and Hipple TF, *Pediatric Drug Formulations*, 5th ed, Cincinnati, OH: Harvey Whitney Books Co, 2004.

ContraindicationsHypersensitivity to metolazone, any component of the formulation, other thiazides, and sulfonamide derivatives; anuria; hepatic coma; pregnancy (expert analysis)

Allergy Considerations

- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, and hyponatremia can occur.
- Photosensitivity: Photosensitization may occur.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with thiazide or sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Diabetes: Use with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated.
- Hepatic impairment: Use with caution in patients with severe hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations.
- Hypokalemia: Use with caution in patients with hypokalemia; correct before initiating therapy.

- Renal impairment: Avoid in severe renal disease (ineffective).

- Systemic lupus erythematosus (SLE): Can cause SLE exacerbation or activation.

Concurrent drug therapy issues:

- Furosemide: Large or prolonged fluid and electrolyte losses may occur with concomitant furosemide administration.

Geriatric ConsiderationsWhen metolazone is used in combination with other diuretics, there is an increased risk of azotemia and electrolyte depletion, particularly in the elderly, monitor closely. May be effective in patients with glomerular filtration rate <20 mL/minute. Metolazone is often used in combination with a loop diuretic in patients who are unresponsive to the loop diuretic alone.

Pregnancy Risk FactorB (manufacturer); D (expert analysis)

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Metolazone crosses the placenta and appears in cord blood. Hypoglycemia, hypokalemia, hyponatremia, jaundice, and thrombocytopenia are reported as complications to the fetus or newborn following maternal use of thiazide diuretics.

LactationEnters breast milk/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Chest pain/discomfort, necrotizing angiitis, orthostatic hypotension, palpitation, syncope, venous thrombosis, vertigo, volume depletion

Central nervous system: chills, depression, dizziness, drowsiness, fatigue, headache, lightheadedness, restlessness

Dermatologic: Petechiae, photosensitivity, pruritus, purpura, rash, skin necrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Endocrine & metabolic: Gout attacks, hypercalcemia, hyperglycemia, hyperuricemia, hypochloremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia

Gastrointestinal: Abdominal bloating, abdominal pain, anorexia, constipation, diarrhea, epigastric distress, nausea, pancreatitis, vomiting, xerostomia

Genitourinary: Impotence

Hematologic: Agranulocytosis, aplastic/hypoplastic anemia, hemoconcentration, leukopenia, thrombocytopenia

Hepatic: Cholestatic jaundice, hepatitis

Neuromuscular & skeletal: Joint pain, muscle cramps/spasm, neuropathy, paresthesia, weakness

Ocular: Blurred vision (transient)

Renal: BUN increased, glucosuria

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: May potentiate hypotensive effect of metazolone.

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid dong quai, St John's wort (may also cause photosensitization). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid natural licorice. Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersSerum electrolytes (potassium, sodium, chloride, bicarbonate), renal function, blood pressure (standing, sitting/supine)

Nursing: Physical Assessment/MonitoringEvaluate patient's renal status and allergy history (thiazides and sulfonamide derivatives) prior to beginning therapy. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, especially anything that will affect blood pressure). Assess electrolytes and renal function, therapeutic effectiveness, and adverse reactions (eg, hypersensitivity reactions, electrolyte imbalance, hypotension) on a regular basis during therapy. Caution patients with diabetes (may see a change in glucose control). Teach patient proper use, possible side effects/appropriate interventions (eg, orthostatic hypotension precautions), and adverse symptoms to report.

Monitoring: Lab TestsSerum electrolytes (potassium, sodium, chloride, bicarbonate), renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed, after breakfast. Include bananas or orange juice in daily diet but do not take potassium supplements without advice of prescriber. This medication does not replace other antihypertensive interventions; follow prescriber's instructions for diet and lifestyle changes. Weigh yourself weekly at the same time, in the same clothes. Report weight gain >5 lb/week. May cause dizziness or weakness (change position slowly when rising from sitting or lying, avoid driving or tasks requiring alertness until response to drug is known); nausea or loss of appetite (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); impotence (reversible); constipation (increased exercise, fluids, fruit, or fiber may help); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report chest pain, palpitations; acute dizziness; flu-like symptoms; headache; joint soreness, pain, or weakness; respiratory difficulty; skin rash; excessive fatigue; swelling of extremities; unresolved gastrointestinal upset (pain, constipation, diarrhea, nausea, vomiting, change in appetite); or other persistent adverse reactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 2.5 mg, 5 mg, 10 mg

Zaroxolyn®: 2.5 mg, 5 mg, 10 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Metolazone)

2.5 mg (30): $42.99

5 mg (30): $37.37

Tablets (Zaroxolyn)

2.5 mg (30): $64.84

5 mg (30): $69.47

10 mg (30): $63.47

Mechanism of ActionInhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water, as well as, potassium and hydrogen ions

Pharmacodynamics/Kinetics

Onset of action: Diuresis: ~60 minutes

Duration: ≥24 hours

Absorption: Incomplete

Distribution: Crosses placenta; enters breast milk

Protein binding: 95%

Half-life elimination: 20 hours

Excretion: Urine (80%); bile (10%)

Related Information

- Heart Failure (Systolic)
- Sulfonamide Derivatives

Pharmacotherapy PearlsMetolazone 5 mg is approximately equivalent to hydrochlorothiazide 50 mg.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes

upon discontinuation) and orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause drowsiness

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular ConsiderationsMetolazone is a potent diuretic and is often used in patients refractory to thiazide or loop diuretics. It is important that the patient be closely monitored to avoid profound volume depletion. Also watch for hypomagnesemia.

Anesthesia and Critical Care Concerns/Other ConsiderationsMetolazone 5 mg is approximately equivalent to hydrochlorothiazide 50 mg. When taken the day of surgery, it may cause hypovolemia and the hypertensive patient undergoing general anesthesia to have labile blood pressure; use with caution prior to surgery or perioperatively

Metolazone is a potent diuretic and is often used in patients refractory to thiazide or loop diuretics. It is important that the patient be closely monitored to avoid profound volume depletion. Also watch for hypomagnesemia.

References

Arnold WC, “Efficacy of Metolazone and Furosemide in Children With Furosemide-Resistant Edema,” *Pediatrics*, 1984, 74(5):872-5. [PubMed 6493882]

Channer KS, McLean KA, Lawson-Matthew P, et al, “Combination Diuretic Treatment in Severe Heart Failure: A Randomised Controlled Trial,” *Br Heart J*, 1994, 71(2):146-50. [PubMed 8130022]

Hunt SA, Abraham WT, Chin MH , et al, "ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure)," available at http://www.acc.org/qualityandscience/clinical/guidelines/failure/update/index.pdf.

Wells TG, “The Pharmacology and Therapeutics of Diuretics in the Pediatric Patient,” *Pediatr Clin North Am*, 1990, 37(2):463-504.[PubMed 2184406]

International Brand NamesBarolyn (FI); Birobin (AT); Diondel (ES); Diulo (AU, HK, PT); Metenix 5 (GB, IE); Metolaz (IN); Metos (KP); Mykrox (TW); Oldren (AR); Pavedal (CN); Urazone (KP); Zaroxolyn (CH, DE, HK, IL, IT, KP)

Metoprolol and Hydrochlorothiazide

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(me toe PROE lole & hye droe klor oh THYE a zide)

U.S. Brand NamesLopressor HCT®

Pharmacologic CategoryBeta Blocker, Beta$_1$ Selective; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension (not recommended for initial treatment)

Dosing: AdultsHypertension: Oral: Dosage should be determined by titration of the individual agents and the combination product substituted based upon the daily requirements.

Usual dose: Metoprolol 50-100 mg and hydrochlorothiazide 25-50 mg administered daily as single or divided doses (twice daily)

> **Note:** Hydrochlorothiazide >50 mg/day is not recommended.

Concomitant therapy: It is recommended that if an additional antihypertensive agent is required, gradual titration should occur using $^1/_2$ the usual starting dose of the other agent to avoid hypotension.

Dosing: ElderlyRefer to adult dosing.

Administration: OralAdminister with or immediately following meals (or as directed). To avoid nocturia, doses should be taken early in the day and last dose of multiple doses should be taken no later than 6 pm.

StorageStore at controlled room temperature of 25°C (77°F). Protect from moisture.

ContraindicationsHypersensitivity to metoprolol, hydrochlorothiazide, sulfonamide-derived drugs or any component of the formulation; sick sinus syndrome, sinus bradycardia, heart block (greater than first degree), cardiogenic shock, overt cardiac failure; severe peripheral arterial disease; pheochromocytoma (without alpha blockade); anuria

Allergy Considerations

- Beta-Blocker Allergy
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Abrupt withdrawal: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.
- Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, and hyponatremia can occur with hydrochlorothiazide.
- Photosensitivity: Photosensitization may occur.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; however, metoprolol, with B$_1$ selectivity, has been used cautiously with close monitoring.
- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating metoprolol.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.
- Heart failure: Use metoprolol with caution in patients with compensated heart failure and monitor for a worsening of the condition (only the extended release product is indicated for heart failure).
- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Myasthenia gravis: Use metoprolol with caution in patients with myasthenia gravis.

- Peripheral vascular disease (PVD): Use metoprolol with caution in patients with PVD (including Raynaud's).

- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.

- Psychiatric disease: Use metoprolol with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

- Renal impairment: Avoid hydrochlorothiazide in severe renal disease (ineffective).

- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

- Thyrotoxicosis: Beta-blockade may mask signs of hyperthyroidism (eg, tachycardia). Abrupt discontinuation of beta-blockade may exacerbate symptoms of hyperthyroidism and may also induce thyroid storm.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents (eg, ether, cyclopropane and trichloroethylene) which decrease myocardial function.

- Calcium channel blockers (nondihydropyridines): Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: **[U.S. Boxed Warning]: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered over 1-2 weeks to avoid acute tachycardia, hypertension, and/or ischemia.**

- Appropriate use: Used as a replacement for separate dosing of components or combination when response to single agent is suboptimal; the fixed combination is not indicated for initial treatment of hypertension.

Geriatric ConsiderationsSee individual agents.
Pregnancy Risk FactorC/D (expert analysis)
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsReactions noted here have been reported with the combination product; see individual drug monographs for additional adverse reactions that may be expected from each agent.

1% to 10%:

Cardiovascular: Bradycardia (6%), edema (1%)

Central nervous system: Fatigue (10%), dizziness (10%), drowsiness (10%), headache (10%), vertigo (10%), abnormal dreams (1%)

Dermatologic: Purpura (1%)

Endocrine & metabolic: Hypokalemia (<10%), gout (1%)

Gastrointestinal: Anorexia (1%), constipation (1%), diarrhea (1%), nausea (1%), vomiting (1%), xerostomia (1%)

Genitourinary: Impotence (1%)

Neuromuscular & skeletal: Myalgia (1%)

Ocular: Blurred vision (1%)

Otic: Earache (1%), tinnitus (1%)

Respiratory: Dyspnea (1%)

Miscellaneous: Flu-like syndrome (10%), diaphoresis (1%), exercise tolerance decreased (1%)

Metabolism/Transport EffectsMetoprolol: **Substrate** of CYP2C19 (minor), 2D6 (major); Inhibits CYP2D6 (weak)
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor*

therapy

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsSee individual agents.
Test InteractionsSee individual agents.
Monitoring ParametersWeight, I & O; blood pressure, heart rate; serum electrolytes, BUN, creatinine
Monitoring: Lab TestsSerum electrolytes, BUN, creatinine
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

50/25: Metoprolol tartrate 50 mg and hydrochlorothiazide 25 mg

100/25: Metoprolol tartrate 100 mg and hydrochlorothiazide 25 mg

100/50: Metoprolol tartrate 100 mg and hydrochlorothiazide 50 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Lopressor HCT)

50-25 mg (60): $109.88

100-25 mg (30): $57.56

100-50 mg (30): $81.99

Mechanism of ActionSee individual agents.
Pharmacodynamics/KineticsSee individual agents.
Pharmacotherapy PearlsA loss of B_1 selectivity is associated with increased doses of metoprolol.
Dental Health: Effects on Dental Treatment

Metoprolol: Metoprolol is a cardioselective beta-blocker. Local anesthetic with vasoconstrictor can be safely used in patients medicated with metoprolol. Nonselective beta-blockers (ie, propranolol, nadolol) enhance the pressor response to epinephrine, resulting in hypertension and bradycardia; this has not been reported for metoprolol. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Hydrochlorothiazide: Key adverse event(s) related to dental treatment: Orthostatic hypotension and hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, or abnormal dreams
Mental Health: Effects on Psychiatric TreatmentHydrochlorothiazide decreases lithium clearance resulting in an increase in serum lithium levels and potential for lithium toxicity; monitor lithium levels. Beta-blockers may increase the effects of psychotropics; monitor clinical status for potential changes.
Index TermsHydrochlorothiazide and Metoprolol; Hydrochlorothiazide and Metoprolol Tartrate; Metoprolol Tartrate and Hydrochlorothiazide
International Brand NamesBeloc Comp (AT); Beloc-Zok Comp (DE); Seloken Retard Comp. (AT); Selokomb 200 (NL); Selokomb Zoc 100 (NL); Selopres Zok (MX); Selozide (BE)

Metoprolol

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Lopressor® may be confused with Lyrica®

Metoprolol may be confused with metaproterenol, metolazone, misoprostol

Toprol-XL® may be confused with Tegretol®, Tegretol®-XR, Topamax®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Significant differences exist between oral and I.V. dosing. Use caution when converting from one route of administration to another.

Pronunciation(me toe PROE lole)

U.S. Brand NamesLopressor®; Toprol-XL®

Canadian Brand NamesApo-Metoprolol®; Betaloc®; Betaloc® Durules®; Dom-Metoprolol; Gen-Metoprolol; Lopressor®; Metoprolol Tartrate Injection, USP; Metoprolol-25; Novo-Metoprolol; Nu-Metop; PHL-Metoprolol; PMS-Metoprolol; RIVA-Metoprolol ; Sandoz-Metoprolol; Toprol-XL®

Pharmacologic CategoryBeta Blocker, Beta$_1$ Selective

Use: Labeled IndicationsTreatment of angina pectoris, hypertension, or hemodynamically-stable acute myocardial infarction

Extended release: Treatment of angina pectoris or hypertension; to reduce mortality/hospitalization in patients with heart failure (stable NYHA Class II or III) already receiving ACE inhibitors, diuretics, and/or digoxin

Use: Unlabeled/InvestigationalTreatment of ventricular arrhythmias, atrial ectopy; migraine prophylaxis, essential tremor, aggressive behavior (not recommended for dementia-associated aggression); prevention of myocardial infarction, atrial fibrillation, and atrial flutter; symptomatic treatment of hypertrophic obstructive cardiomyopathy

Dosing: Adults

Hypertension: Oral: 100-450 mg/day in 2-3 divided doses, begin with 50 mg twice daily and increase doses at weekly intervals to desired effect; usual dosage range (JNC 7): 50-100 mg/day

Extended release: Initial: 25-100 mg/day (maximum: 400 mg/day)

Angina, SVT, MI prophylaxis: Oral: 100-450 mg/day in 2-3 divided doses, begin with 50 mg twice daily and increase doses at weekly intervals to desired effect

Extended release: Initial: 100 mg/day (maximum: 400 mg/day)

Hypertension/ventricular rate control: I.V. (in patients having nonfunctioning GI tract): Initial: 1.25-5 mg every 6-12 hours; titrate initial dose to response. Initially, low doses may be appropriate to establish response; however, up to 15 mg every 3-6 hours has been employed.

Congestive heart failure: Oral (extended release): Initial: 25 mg once daily (reduce to 12.5 mg once daily in NYHA class higher than class II); may double dosage every 2 weeks as tolerated (maximum: 200 mg/day)

Myocardial infarction (acute): I.V.: 5 mg every 2 minutes for 3 doses in early treatment of myocardial infarction; thereafter give 50 mg orally every 6 hours 15 minutes after last I.V. dose and continue for 48 hours; then administer a maintenance dose of 100 mg twice daily.

Note: Switching dosage forms:

When switching from immediate release metoprolol to extended release, the same total daily dose of metoprolol should be used.

When switching between oral and intravenous dosage forms, equivalent beta-blocking effect is achieved when doses in a 2.5:1 (Oral:I.V.) ratio is used.

Dosing: ElderlyRefer to adult dosing. Select dose cautiously, starting at the lower end of the dosing range.

Dosing: Pediatric

Hypertension: Oral:

Immediate release tablet: Children: 1-17 years (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004): Initial: 1-2 mg/kg/day; maximum 6 mg/kg/day (≤200 mg/day); administer in 2 divided doses

Extended release tablet: Children ≥6 years: Initial: 1 mg/kg once daily (maximum initial dose: 50 mg/day). Adjust dose based on patient response (maximum: 2 mg/kg/day or 200 mg/day)

Dosing: Renal ImpairmentNo adjustment required.

Dosing: Hepatic ImpairmentReduced dose may be necessary.

Administration: I.V.When administered acutely for cardiac treatment, monitor ECG and blood pressure. May administer by rapid infusion (I.V. push) over 1 minute or by slow infusion (ie, 5-10 mg of metoprolol in 50 mL of fluid) over ~30 minutes. Necessary monitoring for surgical patients who are unable to take oral beta-blockers (prolonged ileus) has not been defined. Some institutions require monitoring of baseline and postinfusion heart rate and blood pressure when a patient's response to beta-blockade has not been characterized (ie, the patient's initial dose or following a change in dose). Consult individual institutional policies and procedures.

Administration: I.V. DetailpH: 7.5

Administration: OralExtended release tablets may be divided in half; do not crush or chew.

Dietary ConsiderationsRegular tablets should be taken with food. Extended release tablets may be taken without regard to meals.

Storage

Injection: Store at controlled room temperature of 25°C (77°F). Protect from light.

Tablet: Store at controlled room temperature of 25°C (77°F). Protect from moisture.

CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Alteplase, meperidine, morphine. **Incompatible:** Amphotericin B cholesteryl sulfate complex.

Extemporaneously PreparedTo prepare a metoprolol 10 mg/mL liquid, crush 12 metoprolol tartrate 100 mg tablets into a fine powder. Add ~20 mL of either Ora-Sweet® and Ora-Plus® (1:1 preparation), or Ora-Sweet® SF and Ora-Plus® (1:1 preparation), or cherry syrup. Mix to a uniform paste. Continue to add the vehicle to bring the final volume to 120 mL. The preparation is stable for 60 days; shake well before using and protect from light.

> Allen LV and Erickson III MA, "Stability of Labetalol Hydrochloride, Metoprolol Tartrate, Verapamil Hydrochloride, and Spironolactone With Hydrochlorothiazide in Extemporaneously Compounded Oral Liquids," *Am J Health Syst Pharm*, 1996, 53:2304-9.

Contraindications**Note:** Contraindications are indication-specific.

Hypersensitivity to metoprolol, any component of the formulation, or other beta-blockers; additionally:

> **Hypertension and angina:** Sick sinus syndrome (except in patients with a functioning artificial pacemaker); severe peripheral arterial disease; pheochromocytoma (without alpha blockade)
>
> **Myocardial infarction:** Severe sinus bradycardia (heart rate <45 beats/minute); significant first-degree heart block (P-R interval ≥0.24 seconds); second- and third-degree heart block; systolic blood pressure <100 mm Hg; moderate-to-severe cardiac failure; cardiogenic shock

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Boxed warnings:

- Abrupt withdrawal: See "Other warnings/precautions" below.

Concerns related to adverse events:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated allergen challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

- Atrioventricular (AV) block: Metoprolol commonly produces mild first-degree heart block (P-R interval >0.2-0.24 sec). Metoprolol may also produce severe first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Patients with acute myocardial infarction (especially right ventricular myocardial infarction) have a high risk of developing heart block of varying degrees. If severe heart block occurs, metoprolol should be discontinued and measures to increase heart rate should be employed.

- Hypotension: Symptomatic hypotension may occur with use.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; however, metoprolol, with B_1 selectivity, has been used cautiously with close monitoring.

- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.

- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.

- Heart failure: Use with caution in patients with compensated heart failure; monitor for a worsening of heart failure (only the extended release product is indicated for use in heart failure).

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis.

- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).

- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.

- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

- Thyrotoxicosis: Beta-blockade may mask signs of hyperthyroidism (eg, tachycardia). Abrupt discontinuation of beta-blockade may exacerbate symptoms of hyperthyroidism and may also induce thyroid storm.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving inhalation anesthetic agents which may decrease myocardial function.

- Calcium channel blockers (nondihydropyridines): Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur. Avoid concurrent I.V. use of both agents.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <1 year of age.

Dosage form specific issues:

- Extended release: Use care in compensated heart failure and monitor closely for a worsening of the condition. May need to increase diuretics and wait until clinically stable to advance dose to target.

Other warnings/precautions:

- Abrupt withdrawal: **[U.S. Boxed Warning]: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered over 1-2 weeks to avoid acute tachycardia, hypertension, and/or ischemia.**

Geriatric Considerations Due to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (ie, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20% to 50% in the elderly populations. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults.

Pregnancy Risk Factor C (manufacturer); D (2nd and 3rd trimesters - expert analysis)

Pregnancy Considerations Teratogenic effects were not observed in animal studies. Metoprolol crosses the placenta. Maternal use of beta-blockers has been associated with fetal bradycardia, hypotension, and IUGR; IUGR is probably related to maternal hypertension. Available evidence suggests beta-blockers are generally safe during pregnancy (JNC 7). Cases of neonatal hypoglycemia have been reported following maternal use of beta-blockers at parturition. Information specific to metoprolol is limited.

Lactation Enters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding Considerations Metoprolol is considered compatible by the AAP. However, monitor the infant for signs of beta-blockade (hypotension, bradycardia, etc) with long-term use.

Adverse Reactions Frequency may not be defined.

Cardiovascular: Hypotension (1% to 27%), bradycardia (2% to 16%), first-degree heart block (P-R interval ≥0.26 sec; 5%), arterial insufficiency (usually Raynaud type; 1%), chest pain (1%), CHF (1%), edema (peripheral; 1%), palpitation (1%), syncope (1%)

Central nervous system: Dizziness (2% to 10%), fatigue (1% to 10%), depression (5%), confusion, hallucinations, headache, insomnia, memory loss (short-term), nightmares, sleep disturbances, somnolence, vertigo

Dermatology: Pruritus (5%), rash (5%), photosensitivity, psoriasis exacerbated

Endocrine & metabolic: Libido decreased, Peyronie’s disease (<1%), diabetes exacerbated

Gastrointestinal: Diarrhea (5%), constipation (1%), flatulence (1%), gastrointestinal pain (1%), heartburn (1%), nausea (1%), xerostomia (1%), vomiting

Hematologic: Claudication

Neuromuscular & skeletal: Musculoskeletal pain

Ocular: Blurred vision, visual disturbances

Otic: Tinnitus

Respiratory: Dyspnea (1% to 3%), bronchospasm (1%), wheezing (1%), rhinitis

Miscellaneous: Cold extremities (1%)

Postmarketing and/or case reports: Agranulocytosis, alkaline phosphatase increased, alopecia (reversible), arthralgia, arthritis, anxiety, cardiogenic shock, diaphoresis increased, dry eyes, gangrene, hepatitis, HDL decreased, impotence, jaundice, lactate dehydrogenase increased, nervousness, paresthesia, retroperitoneal fibrosis, second-degree heart block, taste disturbance, third-degree heart block, thrombocytopenia, transaminases increased, triglycerides increased, urticaria, vomiting, weight gain

Other events reported with beta-blockers: Catatonia, emotional lability, fever, hypersensitivity reactions, laryngospasm, nonthrombocytopenic purpura, respiratory distress, thrombocytopenic purpura

Metabolism/Transport Effects **Substrate** of CYP2C19 (minor), 2D6 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Food increases absorption. Metoprolol serum levels may be increased if taken with food.

Herb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), gotu kola, licorice, (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Monitoring ParametersAcute cardiac treatment: Monitor ECG and blood pressure with I.V. administration; heart rate and blood pressure with oral administration

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. **I.V.:** See Administration specifics and monitor blood pressure and cardiac status. Assess therapeutic effectiveness and adverse reactions (eg, fluid balance, CHF, postural hypotension). Caution patients with diabetes to monitor serum glucose closely; may decrease the effect of sulfonylureas and can mask prominent hypoglycemic symptoms. Teach patient proper use (oral), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationI.V. use in emergency situations: Patient information is appropriate to patient condition.

Oral: Do not take any new medication during therapy unless approved by prescriber. Take exactly as directed. Do not change dosage or discontinue without consulting prescriber. Take pulse daily, prior to medication and follow prescriber's instruction about holding medication. Do not take with antacids. If you have diabetes, monitor blood glucose closely (drug may alter glucose tolerance or mask signs of hypoglycemia). May cause fatigue, dizziness, or postural hypotension (use caution when changing position from lying or sitting to standing, when driving, or when climbing stairs until response to medication is known); or alteration in sexual performance (reversible). Report unresolved swelling of extremities, respiratory difficulty or new cough, unresolved fatigue, unusual weight gain, unresolved constipation, or unusual muscle weakness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as tartrate: 1 mg/mL (5 mL)

Lopressor®: 1 mg/mL (5 mL)

Tablet, as tartrate: 25 mg, 50 mg, 100 mg

Lopressor®: 50 mg, 100 mg

Tablet, extended release, as succinate: 25 mg, 50 mg, 100 mg, 200 mg [expressed as mg equivalent to tartrate]

Toprol-XL®: 25 mg, 50 mg, 100 mg, 200 mg [expressed as mg equivalent to tartrate]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Metoprolol Succinate)

25 mg (30): $29.99

50 mg (30): $33.88

200 mg (90): $204.58

Tablet, 24-hour (Toprol XL)

25 mg (30): $39.99

50 mg (30): $39.99

100 mg (30): $52.99

200 mg (90): $231.48

Tablets (Lopressor)

50 mg (60): $100.00

100 mg (60): $136.20

Tablets (Metoprolol Tartrate)

25 mg (30): $12.99

100 mg (60): $15.99

Mechanism of ActionSelective inhibitor of beta$_1$-adrenergic receptors; competitively blocks beta$_1$-receptors, with little or no effect on beta$_2$-receptors at doses <100 mg; does not exhibit any membrane stabilizing or intrinsic sympathomimetic activity

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Oral: 1.5-4 hours; I.V.: 20 minutes (when infused over 10 minutes)

Duration: Oral: Immediate release: 10-20 hours, Extended release: ~24 hours; I.V.: 5-8 hours

Absorption: 95%, rapid and complete

Protein binding: 12% to albumin

Metabolism: Extensively hepatic via CYP2D6; significant first-pass effect (~50%)

Bioavailability: Oral: ~50%

Half-life elimination: 3-8 hours (dependent on rate of CYP2D6 metabolism)

Excretion: Urine (<5% to 10% as unchanged drug)

Related Information

- Antiarrhythmic Drugs
- Beta-Blockers

Dental Health: Effects on Dental TreatmentMetoprolol is a cardioselective beta-blocker. Local anesthetic with vasoconstrictor can be safely used in patients medicated with metoprolol. Nonselective beta-blockers (ie, propranolol, nadolol) enhance the pressor response to epinephrine, resulting in hypertension and bradycardia; this has not been reported for metoprolol. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation and dizziness are common; may cause depression; may rarely cause insomnia, confusion, amnesia, or nightmares

Mental Health: Effects on Psychiatric TreatmentBarbiturates may decrease the effects of metoprolol; beta-blockers may increase the effects of psychotropics; monitor clinical status for potential changes

Cardiovascular Considerations

Atrial Fibrillation: Beta-blocker therapy provides effective rate control in patients with atrial fibrillation.

Chronic Stable Angina: Beta-blockers are effective in the treatment of angina as monotherapy or when combined with nitrates and/or calcium channel blockers. In patients with severe intractable angina requiring negative cardiac chronotropic medications, pacemaker placement has been carried out to maintain heart rate in the setting of large doses of beta-blockers and/or calcium channel blockers. Beta-blockers are ineffective in the treatment of pure vasospastic (Prinzmetal) angina.

Heart Failure: Strong evidence supports that beta-blocker therapy, without intrinsic sympathomimetic activity (ISA), should be initiated in select patients with **stable** congestive heart failure (NYHA Class II-III). To date, carvedilol, sustained release metoprolol, and bisoprolol have demonstrated a beneficial effect on morbidity and mortality. It is important that beta-blocker therapy be instituted initially at very low doses with gradual and very careful titration.

Hypertension: Beta-blocker therapy in the treatment of hypertension has been associated with improved cardiovascular outcomes. According to the 2003 JNC-VII guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists that requires the use of other drugs, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Beta-blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for a beta-blocker include patients with heart failure, postmyocardial infarction, high coronary disease risk, or diabetes. In type 2 diabetic patients, a UK Prospective Diabetes Study Group (UKPDS) trial showed that beta-blocker therapy (atenolol) was as effective as an ACE inhibitor in reducing cardiovascular events and that the benefits of therapy were related more to the degree of antihypertensive efficacy rather than the class of drug used.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Neurocardiogenic Syncope: Metoprolol has also been used in the treatment of neurocardiogenic (vasovagal) syncope.

ST-Segment Elevation Myocardial Infarction (STEMI): Beta-blockers, without intrinsic sympathomimetic activity (ISA), have been shown to decrease morbidity and mortality when initiated in the acute treatment of STEMI and continued long-term. Oral beta-blockade should be initiated promptly in patients without contraindications (eg, signs of heart failure, evidence of a low output state, risk of cardiogenic shock, or other beta-blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade may be considered and given promptly if the patient is experiencing concomitant hypertension unless any of the aforementioned contraindications exist (Class IIa recommendation). Patients at risk of cardiogenic shock include patients with age >70 years, systolic blood pressure <120 mm Hg, heart rate >110 bpm or <60 bpm, or late presentation.

Unstable Angina/Non-ST-Segment Elevation MI (UA/NSTEMI): In the treatment of UA/NSTEMI, oral beta-blockade should be initiated within the first 24 hours in patients without contraindications (eg, signs of heart failure, evidence of a low output state, risk of cardiogenic shock, or other beta-blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade should only be considered if the patient is experiencing concomitant hypertension upon presentation (Class IIa recommendation).

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia and hypertension.

Anesthesia and Critical Care Concerns/Other Considerations

Surgery: Based on available evidence, beta-blockers should be started days to weeks before elective surgery in selected patients when possible and titrated to a heart rate <65 beats per minute. Additional data suggest that long acting beta-blockers may be superior to short acting ones (Redelmeier, 2005). The ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery recommend beta-blockers be continued in patients undergoing surgery who are receiving beta-blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA Class I guideline indications (Class I recommendation). The guidelines also recommend that beta-blockers be given to patients undergoing vascular surgery who have myocardial ischemia demonstrated during preoperative testing (Class I recommendation).

The guidelines also state that beta-blockers are probably recommended in patients undergoing intermediate risk (eg, carotid endarterectomy, prostate surgery) or vascular surgery in whom preoperative assessment identifies coronary heart disease or high cardiac risk (Class IIa recommendation). High cardiac risk is defined as having >1 of the following clinical risk factors: History of ischemic heart disease, compensated or prior heart failure, cerebrovascular disease, diabetes mellitus, or renal insufficiency. The use of beta-blockers is uncertain in patients undergoing intermediate risk or vascular surgery with ≤1 clinical risk factor (Class IIb recommendation).

The majority of published trials suggest a benefit of perioperative beta-blocker use during noncardiac surgery; however, more recent clinical trials have not shown a benefit to perioperative beta-blockade for noncardiac surgery (Juul, 2006; POISE Study Group, 2008; Yang, 2006). One such clinical trial randomized 8351 patients with, or at risk of, atherosclerotic disease who underwent noncardiac surgery to either extended release metoprolol succinate or placebo. To receive study drug, first dose (metoprolol extended release 100 mg or matching placebo) administered 2-4 hours prior to surgery, patients were to have a heart rate ≥50 bpm or systolic blood pressure (SBP) ≥100 mm Hg. If during the first 6 hours after surgery heart rate was ≥80 bpm and SBP ≥100 mm Hg, the first postoperative dose (metoprolol extended release 100 mg or matching placebo) was administered. If not given during the first 6 hours, metoprolol extended release 100 mg (or matching placebo) was administered at 6 hours after surgery. Twelve hours after administration of the first postoperative dose, metoprolol extended release 200 mg (or matching placebo) was administered once daily for 30 days. Therefore, patients may have received up to 400 mg during the first 24 hours; an initial dose not recommended for any indication. Study drug was withheld when heart rate was consistently <45 bpm or systolic blood pressure was <100 mm Hg. The primary outcome of the trial was a composite of cardiovascular death, nonfatal MI, and nonfatal cardiac arrest at 30 days after randomization. Compared to those who received placebo, fewer patients receiving metoprolol experienced the primary outcome (244 [5.8%] vs 290 [6.9%], p=0.0399) or developed MI (176 [4.2%] vs 239 [5.7%], p=0.0017). However, more deaths occurred in the metoprolol group compared to placebo (129 [3.1%] vs 97 [2.3%], p=0.0317). In addition, more strokes occurred in the metoprolol group compared to placebo (41 [1%] vs 19 [0.5%], p=0.0053). Death was associated with a number of risk factors (eg, clinically significant hypotension, MI, significant bleeding). Stroke was associated with history of stroke or TIA, postoperative hypotension, new-onset atrial fibrillation, and significant bleeding (POISE Study Group, 2008). The negative results of this trial are thought to be due to the aggressive administration of metoprolol leading to an excessive amount of clinically significant hypotension which then contributed to the incidence of stroke and mortality. Therefore, when administering beta-blockers to eligible patients undergoing elective surgery, patients should be titrated days to weeks in advance when possible and careful monitoring of heart rate (goal <65 bpm) and blood pressure is necessary.

Extemporaneously Prepared: To prepare a metoprolol 10 mg/mL liquid, crush 12 metoprolol tartrate 100 mg tablets into a fine powder. Add ~20 mL of either Ora-Sweet® and Ora-Plus® (1:1 preparation), or Ora-Sweet® SF and Ora-Plus® (1:1 preparation), or cherry syrup. Mix to a uniform paste. Continue to add the vehicle to bring the final volume to 120 mL. The preparation is stable for 60 days; shake well before using and protect from light.

Index Terms

Metoprolol Succinate; Metoprolol Tartrate

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International Brand NamesBeatrolol (MY); Beloc (AR, AT, CO, DE); Beloc Duriles (AT); Beloc Zok (CH); Beloken (IE); Betaloc (AU, CL, GB, HK, HN, HU, IN, MY, PH, PL, RU, TH); Betaloc Zoc (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Betaloc Zok (CL, CO, EC, EE, HK, HU, PK, PL, SG, TW); Betazok (PH); Betrol (PH); Bloxan (HR); Cardeloc (TH); Cardiosel (ID, PH); Cardiostat (PH); Cardiotab (PH); Denex (MY, SG); Egilok (PL); Gerbloc (PH); Huma-Metoprol (HU); Jutabloc (DE); Lofarbil (GR); Lopresor (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CI, CN, CO, CY, CZ, EG, ES, ET, GB, GH, GM, GN, GR, GY, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, OM, PT, PY, QA, RU, SA, SC, SD, SL, SN, SR, SY, TN, TR, TT, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Lopresor Divitab (IL); Lopresor OROS (LU); Lopresor Retard (AT, BG, CH, GR, IT, PT); Lopresor SR (GB); Lopressor (BR, FR); Loprolol (ID); Meto-Hennig (DE); Metobeta (AU); Metocard (PL); Metocare (PH); Metohexal (AU, HU, LU, PL); Metolol (TH); Metop (IE); Metoprim (PH); Metoprogamma (DE); Metoprolol (PL); Metoprolol Stada (HU); Metoprolol-B (HU); Metoprolol-rpm (LU); Metostad (PH); Mezelol (MX); Minax (AU, HK, TW); Montebloc (PH); Nipresol (MX); Prolol SR (KP); Promiced (MX); Ritmetol (HU); Sefloc (TH); Selo-zok (DK, NO); Selokeen (NL); Seloken (BE, DK, FI, FR, ID, IT, JP, NO, SE); Seloken Retard (AT, IT); Seloken Zoc (FI, SE); Seloken-Zok (MX); Selopral (FI); Selozok (BE, DK, LU); Selozok LP (FR); Slow-Lopresor (LU, NZ); Toprol XL (AU)

Metronidazole and Nystatin

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English

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Pronunciation(met roe NYE da zole & nye STAT in)

Canadian Brand NamesFlagystatin®

Pharmacologic CategoryAntifungal Agent, Vaginal; Antiprotozoal, Nitroimidazole

Use: Labeled IndicationsTreatment of mixed vaginal infection due to *T. vaginalis* and *C. albicans*

Dosing: Adults**Mixed vaginal infection:** Intravaginal:

Vaginal tablet (ovule): Insert 1 tablet/day at bedtime for 10 consecutive days. May repeat for an additional 10 days if cure is not achieved.

Vaginal cream: Insert 1 applicatorful daily at bedtime for 10 consecutive days. May repeat for an additional 10 days if cure is not achieved.

Note: If *Trichomonas vaginalis* is not completely eliminated, oral (systemic) metronidazole (250 mg twice daily for 10 days) should be administered.

Dosing: ElderlyRefer to adult dosing.

StorageVaginal insert: Store in refrigerator. Protect from temperature extremes, moisture, and light.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to metronidazole, nystatin, or any component of the formulation. Combined treatment with oral metronidazole should be avoided in active neurological disorders or in patients with a history of blood dyscrasia, hypothyroidism, or hypoadrenalism (unless the benefits outweigh the possible risk to the patient).

Also refer to Metronidazole monograph.

Warnings/Precautions

Concerns related to adverse effects:

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.
- Systemic effects: Systemic absorption of metronidazole from vaginal administration may occur. Adverse effects normally associated with systemic administration of metronidazole may occur following the vaginal administration.

Concurrent drug therapy issues:

- Oral metronidazole: Consult additional warnings in Metronidazole monograph when used concurrently with systemic metronidazole (patients should be warned against consuming alcohol due to possible disulfiram-like reaction). No disulfiram-like reactions have been reported after **topical/vaginal** application of metronidazole alone, although metronidazole can be detected in the blood. Oral treatment should be discontinued if ataxia or any other symptom of CNS involvement occurs.

Special populations:

- Sexual partners: Sexual partners should receive concurrent treatment (oral metronidazole) when there is evidence of trichomonal infestation.

Other warnings/precautions:

- Appropriate use: May not be effective in bacterial vaginal infections and should not be prescribed unless there is direct evidence of trichomonal infestation. Nystatin possesses little or no antibacterial activity while metronidazole is selective against certain anaerobic bacteria.

Pregnancy ConsiderationsMetronidazole crosses the placenta. Although it has been given to pregnant women without apparent complication, oral/systemic use should be avoided in pregnant patients and the drug be withheld during the first trimester of pregnancy. Vaginal metronidazole is absorbed systemically in small amounts.

Lactation

Metronidazole: Enters breast milk/not recommended (AAP rates “of concern”)

Nystatin: Does not enter breast milk/compatible

Adverse Reactions**Note:** Adverse effects are infrequent and generally minor.

Central nervous system: Headache

Dermatologic: Pruritus, spots on skin (around knees), welts on body

Gastrointestinal: Coated tongue, nausea, taste disturbance (bitter), vomiting

Genitourinary: Vaginal: Burning, granular sensation

Neuromuscular & skeletal: Fatigue, swelling/aching or wrists

Drug Interactions

Alcohol (Ethyl): MetroNIDAZOLE may enhance the adverse/toxic effect of Alcohol (Ethyl). A disulfiram-like reaction may occur. *Risk C: Monitor therapy*

Amprenavir: MetroNIDAZOLE may enhance the adverse/toxic effect of Amprenavir. This is specifically related to the propylene glycol contained in amprenavir oral solution, not capsules. *Risk X: Avoid combination*

Busulfan: MetroNIDAZOLE may increase the serum concentration of Busulfan. *Risk D: Consider therapy modification*

Calcineurin Inhibitors: MetroNIDAZOLE may decrease the metabolism of Calcineurin Inhibitors. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May enhance the adverse/toxic effect of MetroNIDAZOLE. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mebendazole: May enhance the adverse/toxic effect of MetroNIDAZOLE. Particularly the risk for Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis may be increased. *Risk D: Consider therapy modification*

Mycophenolate: MetroNIDAZOLE may decrease the serum concentration of Mycophenolate. Specifically, metronidazole may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Tipranavir: MetroNIDAZOLE may enhance the adverse/toxic effect of Tipranavir. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): MetroNIDAZOLE may decrease the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Cream, vaginal (Flagystatin®) [CAN]: Metronidazole 500 mg and nystatin 100,000 units per applicatorful (55 g) [packaged with applicator]

Tablet, vaginal (Flagystatin® Ovule) [CAN]: Metronidazole 500 mg and nystatin 100,000 units (10s) [packaged with applicator]

Mechanism of ActionSee individual agents.

Related Information

- MetroNIDAZOLE
- Nystatin

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste disturbances (bitter) and coated tongue.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesEtron nistatina (EC); Flagyl Nistatina (BR, CO); Flagystatin (AR, PH, PY, SG, UY); Flagystatin V (CR, DO, GT, HN, MX, NI, PA, SV); Flagystatine (PE); Nistatina Metronidazol L.CH. (CN); Vagistin (ID)

MetroNIDAZOLE

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English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

MetroNIDAZOLE may be confused with meropenem, metFORMIN

Pronunciation(met roe NYE da zole)

U.S. Brand NamesFlagyl ER®; Flagyl®; MetroCream®; MetroGel-Vaginal®; MetroGel®; MetroLotion®; Noritate®; Vandazole™

Canadian Brand NamesApo-Metronidazole®; Flagyl®; Florazole® ER; MetroCream®; Metrogel®; Nidagel™; Noritate®; Trikacide

Pharmacologic CategoryAmebicide; Antibiotic, Miscellaneous; Antibiotic, Topical; Antiprotozoal, Nitroimidazole

Use: Labeled IndicationsTreatment of susceptible anaerobic bacterial and protozoal infections in the following conditions: Amebiasis, symptomatic and asymptomatic trichomoniasis; skin and skin structure infections; CNS infections; intra-abdominal infections (as part of combination regimen); systemic anaerobic infections; treatment of antibiotic-associated pseudomembranous colitis (AAPC), bacterial vaginosis; as part of a multidrug regimen for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence

Topical: Treatment of inflammatory lesions and erythema of rosacea

Use: Unlabeled/InvestigationalCrohn's disease

Use: DentalTreatment of oral soft tissue infections due to anaerobic bacteria including all anaerobic cocci, anaerobic gram-negative bacilli (*Bacteroides*), and gram-positive spore-forming bacilli (*Clostridium*). Useful as single agent or in combination with amoxicillin, Augmentin®, or ciprofloxacin in the treatment of periodontitis associated with the presence of *Actinobacillus actinomycetemcomitans* (AA).

Dosing: Adults

Anaerobic infections (diverticulitis, intra-abdominal, peritonitis, cholangitis, or abscess): Oral, I.V.: 500 mg every 6-8 hours, not to exceed 4 g/day

Acne rosacea: Topical:

0.75%: Apply and rub a thin film twice daily, morning and evening, to entire affected areas after washing. Significant therapeutic results should be noticed within 3 weeks. Clinical studies have demonstrated continuing improvement through 9 weeks of therapy.

1%: Apply thin film to affected area once daily

Amebiasis: Oral: 500-750 mg every 8 hours for 5-10 days

Antibiotic-associated pseudomembranous colitis: Oral: 250-500 mg 3-4 times/day for 10-14 days; **Note:** Due to the emergence of a new strain of C. difficile, some clinicians recommend converting to oral vancomycin therapy if the patient does not show a clear clinical response after 2 days of metronidazole therapy.

Giardiasis: 500 mg twice daily for 5-7 days

Peptic ulcer disease:*Helicobacter pylori*eradication: Oral: 250-500 mg with meals and at bedtime for 14 days; requires combination therapy with at least one other antibiotic and an acid-suppressing agent (proton pump inhibitor or H_2 blocker)

Bacterial vaginosis or vaginitis due to *Gardnerella,Mobiluncus*:

Oral: 500 mg twice daily (regular release) or 750 mg once daily (extended release tablet) for 7 days

Vaginal: 1 applicatorful (~37.5 mg metronidazole) intravaginally once or twice daily for 5 days; apply once in morning and evening if using twice daily, if daily, use at bedtime

Trichomoniasis: Oral: 250 mg every 8 hours for 7 days **or** 375 mg twice daily for 7 days **or** 2 g as a single dose

Dosing: ElderlyUse the lower end of the dosing recommendations for adults; do not administer as single dose as efficacy has not been established.

Dosing: Pediatric

Anaerobic infections:

Infants and Children:

Oral: 15-35 mg/kg/day in divided doses every 8 hours

I.V.: 30 mg/kg/day in divided doses every 6 hours

Colitis due to*Clostridium difficile*: Oral: 20 mg/kg/day divided every 6 hours. Maximum dose: 2 g/day

Amebiasis: Infants and Children: Oral: 35-50 mg/kg/day in divided doses every 8 hours for 10 days

Trichomoniasis: Infants and Children: Oral: 15-30 mg/kg/day in divided doses every 8 hours for 7 days

Dosing: Renal Impairment

Cl_{cr} <10 mL/minute, but not on dialysis: Recommendations vary: To reduce possible accumulation in patients receiving multiple doses, consider reduction to 50% of dose or every 12 hours; **Note:** Dosage reduction is unnecessary in short courses of therapy. Clinical recommendations and practice vary. Some references do not recommend reduction at any level of renal impairment (Lamp, 1999).

Hemodialysis effects: Extensively removed by hemodialysis and peritoneal dialysis (50% to 100%); dosage reduction not recommended; administer full dose posthemodialysis. During peritoneal dialysis, dose as for Cl_{cr} <10 mL/minute.

Continuous arteriovenous or venovenous hemofiltration: Dose as for normal renal function

Dosing: Hepatic ImpairmentUnchanged in mild liver disease; reduce dosage in severe liver disease.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V. DetailpH: 5-7 (ready to use); 0.5-2.0 (reconstituted); 6-7 (further dilution)

Administration: OralMay be taken with food to minimize stomach upset. Extended release tablets should be taken on an empty stomach (1 hour before or 2 hours after meals).

Administration: TopicalNo disulfiram-like reactions have been reported after **topical** application, although metronidazole can be detected in the blood. Apply to clean, dry skin. Cosmetics may be used after application (wait at least 5 minutes after using lotion).

Dietary ConsiderationsTake on an empty stomach. Drug may cause GI upset; if GI upset occurs, take with food. Extended release tablets should be taken on an empty stomach (1 hour before or 2 hours after meals). Sodium content of 500 mg (I.V.): 322 mg (14 mEq). The manufacturer recommends that ethanol be avoided during treatment and for 3 days after therapy is complete.

StorageMetronidazole injection should be stored at 15°C to 30°C and protected from light. Product may be refrigerated but crystals may form. Crystals redissolve on warming to room temperature. Prolonged exposure to light will cause a darkening of the product. However, short-term exposure to normal room light does not adversely affect metronidazole stability. Direct sunlight should be avoided. Stability of parenteral admixture at room temperature (25°C): Out of overwrap stability: 30 days.

ReconstitutionStandard diluent: 500 mg/100 mL NS.

CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Acyclovir, allopurinol, amiodarone, amifostine, cefepime, cisatracurium, clarithromycin, cyclophosphamide, diltiazem, docetaxel, dopamine, doxorubicin liposome, enalaprilat, esmolol, etoposide phosphate, fluconazole, foscarnet, gatifloxacin, gemcitabine, granisetron, heparin, hydromorphone, labetalol, linezolid, lorazepam, magnesium sulfate, melphalan, meperidine, methylprednisolone sodium succinate, midazolam, morphine, perphenazine, piperacillin/tazobactam, remifentanil, sargramostim, tacrolimus, teniposide, theophylline, thiotepa, vinorelbine. **Incompatible:** Amphotericin B cholesteryl sulfate complex, aztreonam, filgrastim, meropenem, warfarin.

Compatibility when admixed: Compatible: Amikacin, aminophylline, ampicillin, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, chloramphenicol, ciprofloxacin, clindamycin, disopyramide, floxacillin, fluconazole, gentamicin, heparin, hydrocortisone sodium succinate, multivitamins, netilmicin, penicillin G potassium, tobramycin. **Incompatible:** Aztreonam, dopamine, meropenem. **Variable (consult detailed reference):** Cefamandole, cefepime.

Extemporaneously PreparedA 20 mg/mL oral suspension can be prepared by crushing ten 250 mg tablets in a mortar, and then adding 10 mL purified water USP to create a uniform paste. Add a small quantity of syrup, then transfer to a graduate and add a sufficient quantity of syrup to make 125 mL. Label “shake well” and “refrigerate.” Refrigerated stability is 10 days.

Irwin DB, Dupuis LL, Prober CG, et al, “The Acceptability, Stability, and Relative Bioavailability of an Extemporaneous Metronidazole Suspension,” *Can J Hosp Pharm*, 1987, 40:42-6.

Nahata MC, Morosco RS, and Hipple TF, 4th ed, *Pediatric Drug Formulations*, Cincinnati, OH: Harvey Whitney Books Co, 2000.

ContraindicationsHypersensitivity to metronidazole, nitroimidazole derivatives, or any component of the formulation; pregnancy (1st trimester - found to be carcinogenic in rats)

Allergy Considerations

- Nitroimidazole Allergy

Warnings/Precautions

Boxed warnings:

- Carcinogenic: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Carcinogenic: **[U.S. Boxed Warning]: Possibly carcinogenic based on animal data.**

- CNS effects: Seizures and neuropathies have been reported especially with increased doses and chronic treatment; if this occurs, discontinue therapy. Use with caution in patients with a history of seizure disorder; reduce doses with patients with CNS disease.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Blood dyscrasias: Use with caution in patients with blood dyscrasias.
- Heart failure: Use with caution in patients with heart failure or other sodium retaining states.
- Hepatic impairment: Use with caution in patients with liver impairment due to potential accumulation; reduce dosage in patients with severe impairment.
- *H. pylori* infection: If *H. pylori* is not eradicated in patients being treated with metronidazole in a regimen, it should be assumed that metronidazole-resistance has occurred and it should not again be used.
- Renal impairment: Consider dosage reduction in longer-term therapy with severe renal failure (Cl_{cr} <10 mL/minute).

Geriatric ConsiderationsAdjust dose based on renal function.

Pregnancy Risk FactorB (may be contraindicated in 1st trimester)

Pregnancy ConsiderationsCrosses the placenta (carcinogenic in rats); contraindicated for the treatment of trichomoniasis during the first trimester of pregnancy, unless alternative treatment is inadequate. Until safety and efficacy for other indications have been established, use only during pregnancy when the benefit to the mother outweighs the potential risk to the fetus.

LactationEnters breast milk/not recommended (AAP rates “of concern”)

Breast-Feeding ConsiderationsIt is suggested to stop breast-feeding for 12-24 hours following single dose therapy to allow excretion of dose.

Adverse Reactions

Systemic: Frequency not defined:

Cardiovascular: Flattening of the T-wave, flushing

Central nervous system: Ataxia, confusion, coordination impaired, dizziness, fever, headache, insomnia, irritability, seizure, vertigo

Dermatologic: Erythematous rash, urticaria

Endocrine & metabolic: Disulfiram-like reaction, dysmenorrhea, libido decreased

Gastrointestinal: Nausea (~12%), anorexia, abdominal cramping, constipation, diarrhea, furry tongue, glossitis, proctitis, stomatitis, unusual/metallic taste, vomiting, xerostomia

Genitourinary: Cystitis, darkened urine (rare), dysuria, incontinence, polyuria, vaginitis

Hematologic: Neutropenia (reversible), thrombocytopenia (reversible, rare)

Neuromuscular & skeletal: Peripheral neuropathy, weakness

Respiratory: Nasal congestion, rhinitis, sinusitis, pharyngitis

Miscellaneous: Flu-like syndrome, moniliasis

Topical: Frequency not defined:

Central nervous system: Headache

Dermatologic: Burning, contact dermatitis, dryness, erythema, irritation, pruritus, rash

Gastrointestinal: Unusual/metallic taste, nausea, constipation

Local: Local allergic reaction

Neuromuscular & skeletal: Tingling/numbness of extremities

Ocular: Eye irritation

Vaginal:

>10%: Genitourinary: Vaginal discharge (12%)

1% to 10%:

Central nervous system: Headache (5%), dizziness (2%)

Gastrointestinal: Gastrointestinal discomfort (7%), nausea and/or vomiting (4%), unusual/metallic taste (2%), diarrhea (1%)

Genitourinary: Vaginitis (10%), vulva/vaginal irritation (9%), pelvic discomfort (3%)

Hematologic: WBC increased (2%)

<1%: Abdominal bloating, abdominal gas, darkened urine, depression, fatigue, itching, rash, thirst, xerostomia

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)

Metabolism/Transport Effects**Inhibits** CYP2C9 (weak), 3A4 (moderate)

Drug Interactions

Alcohol (Ethyl): MetroNIDAZOLE may enhance the adverse/toxic effect of Alcohol (Ethyl). A disulfiram-like reaction may occur. *Risk C: Monitor therapy*

Amprenavir: MetroNIDAZOLE may enhance the adverse/toxic effect of Amprenavir. This is specifically related to the propylene glycol contained in amprenavir oral solution, not capsules. *Risk X: Avoid combination*

Busulfan: MetroNIDAZOLE may increase the serum concentration of Busulfan. *Risk D: Consider therapy modification*

Calcineurin Inhibitors: MetroNIDAZOLE may decrease the metabolism of Calcineurin Inhibitors. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May enhance the adverse/toxic effect of MetroNIDAZOLE. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mebendazole: May enhance the adverse/toxic effect of MetroNIDAZOLE. Particularly the risk for Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis may be increased. *Risk D: Consider therapy modification*

Mycophenolate: MetroNIDAZOLE may decrease the serum concentration of Mycophenolate. Specifically, metronidazole may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Tipranavir: MetroNIDAZOLE may enhance the adverse/toxic effect of Tipranavir. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): MetroNIDAZOLE may decrease the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: The manufacturer recommends to avoid all ethanol or any ethanol-containing drugs (may cause disulfiram-like reaction characterized by flushing, headache, nausea, vomiting, sweating, or tachycardia).

Food: Peak antibiotic serum concentration lowered and delayed, but total drug absorbed not affected.

Test InteractionsMay interfere with AST, ALT, triglycerides, glucose, and LDH testing

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions according to dose, route of administration, and purpose of therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed. May take with or without food. Take with food if medication causes upset stomach. Extended release tablets should be taken on an empty stomach. Avoid alcohol during and for 72 hours after last dose. With alcohol you may experience severe flushing, headache, nausea, vomiting, or chest and abdominal pain. May discolor urine (brown/black/dark) (normal). You may experience "metallic" taste disturbance or nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Refrain from intercourse or use a contraceptive if being treated for trichomoniasis. Report unresolved or severe fatigue; weakness; fever or chills; mouth or vaginal sores; numbness, tingling, or swelling of extremities; respiratory difficulty; or lack of improvement or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended.

Topical: Wash hands and area before applying. Apply medication thinly. Wash hands after applying. Avoid contact with eyes. Do not cover with occlusive dressing. Report severe skin irritation or if condition does not improve.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 375 mg

Flagyl®: 375 mg

Cream, topical: 0.75% (45 g)

MetroCream®: 0.75% (45 g) [contains benzyl alcohol]

Noritate®: 1% (60 g)

Gel, topical: 0.75% (45 g)

MetroGel®: 1% (46 g, 60 g) [60 g tube also packaged in a kit with Cetaphil® skin cleanser]

Gel, vaginal: 0.75% (70 g)

MetroGel-Vaginal®, Vandazole™: 0.75% (70 g)

Infusion [premixed iso-osmotic sodium chloride solution]: 500 mg (100 mL)

Lotion, topical: 0.75% (60 mL)

MetroLotion®: 0.75% (60 mL) [contains benzyl alcohol]

Tablet: 250 mg, 500 mg

Flagyl®: 250 mg, 500 mg

Tablet, extended release:

Flagyl® ER: 750 mg

⇧ Generic AvailableYes: Capsule, cream, gel, infusion, lotion, tablet
⇧ Pricing: U.S. (www.drugstore.com)

Capsules (Flagyl)

375 mg (30): $130.08

Cream (MetroCream)

0.75% (45): $214.17

Cream (Metronidazole)

0.75% (45): $59.99

Cream (Noritate)

1% (60): $136.62

Emulsion (Rozex)

0.75% (60): $85.00

Gel (Metrogel)

1% (60): $159.15

Gel (Metronidazole)

0.75% (70): $59.99

Gel (Vandazole)

0.75% (70): $46.99

Kit (Metrogel)

1% (1): $155.75

Lotion (MetroLotion)

0.75% (59): $202.38

Lotion (Metronidazole)

0.75% (59): $79.99

Tablet, 24-hour (Flagyl ER)

750 mg (30): $328.51

Tablet, 24-hour (Metronidazole)

750 mg (30): $201.98

Tablets (Flagyl)

250 mg (30): $94.49

500 mg (30): $160.64

Tablets (Metronidazole)

500 mg (30): $12.99

⇧ Mechanism of ActionAfter diffusing into the organism, interacts with DNA to cause a loss of helical DNA structure and strand breakage resulting in inhibition of protein synthesis and cell death in susceptible organisms

Pharmacodynamics/Kinetics

Absorption: Oral: Well absorbed; Topical: Concentrations achieved systemically after application of 1 g topically are 10 times less than those obtained after a 250 mg oral dose

Distribution: To saliva, bile, seminal fluid, breast milk, bone, liver, and liver abscesses, lung and vaginal secretions; crosses placenta and blood-brain barrier

CSF:blood level ratio: Normal meninges: 16% to 43%; Inflamed meninges: 100%

Protein binding: <20%

Metabolism: Hepatic (30% to 60%)

Half-life elimination: Neonates: 25-75 hours; Others: 6-8 hours, prolonged with hepatic impairment; End-stage renal disease: 21 hours

Time to peak, serum: Oral: Immediate release: 1-2 hours

Excretion: Urine (20% to 40% as unchanged drug); feces (6% to 15%)

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Unusual/metallic taste, glossitis, stomatitis, xerostomia (normal salivary flow resumes upon discontinuation), and furry tongue.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; case reports of depression, insomnia, confusion, panic, delusions, hallucinations, exacerbation of schizophrenia

Mental Health: Effects on Psychiatric TreatmentMay rarely cause leukopenia; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular ConsiderationsMetronidazole may have effects similar to that of disulfiram (Antabuse®). If ethanol is taken during and within 24 hours of the last dose of metronidazole, patients may have severe flushing, headache, nausea, vomiting, or chest and abdominal pain.

Index TermsMetronidazole Hydrochloride

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“Treatment of *Clostridium difficile* Diarrhea,” *Med Lett Drugs Ther*, 1989, 31(803):94-5.[PubMed 2796843]

International Brand NamesAcea Gel (GB, IE); Amebidal (MX); Amevan (EC); Anaerobex (AT); Anaeromet (LU); Anerobizol (PH); Arcazol (TW); Arilin (CH, DE); Ariline (AT); Asiazole (TH); Biatron (ID); Camezol (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Clont (DE); Deflamon (CZ, IT); Dumozol (ID, PT); Efloran (CZ, HR, PL); Elyzol (CH, DK, FI, NO); Elyzol-S (MX); Endazole (PH); Entizol (CZ); Epaq (MX); Farizol (ID); Fladex (ID, SG); Flagenase (MX); Flagesol (PY, UY); Flagizole (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Flagyl (AR, AU, BE, BG, CH, CN, CR, CZ, DO, EC, ES, FR, GB, GR, GT, HN, HR, ID, IE, IL, IN, LU, MX, NI, NL, PA, PE, PH, PK, PL, PT, RU, SV, TW, VE); Flasinyl (KP); Flazol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Frotin (MY, TW); Grinazole (PL); Gynoplix (HK); Helminzol (BR); Klion (CZ, HN, HU); Marphazole (HK); Medazol (HR); Meronidal (JP); MetroCream (MX); Metroderme (PT); MetroGel (MX, TW); Metrogyl (AU, BR, GR); Metrolag (AE, BB, BF, BH, BJ, BM, BS, BZ, CH, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PR, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Metrolex (TH); Metronidazol (HR, PL); Metronidazol Genericon (HR); Metronidazole Braun (LU); Metronidazole IV (AU); Metronidazole-Fandre (LU); Metronide (AU); Metrosept (PL); Metrozin (CO); Metrozole Gel (KP); Molazol (ID); Nalox (AR); Noritate (IL); Novazole (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Otrozol (MX); Patryl (PH); Pharmaflex (LU); Protozol (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Qualigyl (HK); Robaz (PH, TH); Rodazid (PH); Rosaced Gel (FR); Rozacreme (FR); Rozagel (FR); Rozamet (HR); Rozex (AT, AU, BE, CH, EE, ES, FR, GB, HK, IE, IT, LU, MY, NO, PL, SE, ZA); Rozex Gel (IL, NL, PE, PY, UY, VE); Sawagyl (JP); Sharizole (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Supplin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Trichex (AT); Trichocide (JP); Trichozole (NZ); Triconex (PH); Trikacide (ID); Trogiar (ID); Unigo (HK, TH); Vertisal (MX); Zidoval Gel (IL); Zol (PH)

Metyrapone

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Metyrapone may be confused with metyrosine

Pronunciation(me TEER a pone)
U.S. Brand NamesMetopirone®
Pharmacologic CategoryDiagnostic Agent
Use: Labeled IndicationsDiagnostic test for hypothalamic-pituitary ACTH function
Dosing: Adults**Diagnostic test:** Oral: 750 mg every 4 hours for 6 doses
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Diagnostic test:** Oral: Children: 15 mg/kg every 4 hours for 6 doses; minimum dose: 250 mg
StorageDo not store above 30°C (86°F). Protect from moisture.
ContraindicationsHypersensitivity to metyrapone or any component of the formulation; patient with adrenal cortical insufficiency
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Reduced adrenal secretory capacity: Acute adrenal insufficiency may be induced in patients with reduced adrenal secretory capacity.

- Thyroid disease: Response to test may be subnormal in patients with hypo- or hyperthyroidism.

Pregnancy Risk FactorC
Pregnancy ConsiderationsUse during pregnancy only if clearly needed. Subnormal response may occur in pregnant women and the fetal pituitary may be affected.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Central nervous system: Headache, dizziness, sedation

Dermatologic: Allergic rash

Gastrointestinal: Nausea, vomiting, abdominal discomfort or pain

Hematologic: Rarely, decreased white blood cell count or bone marrow suppression

Metabolism/Transport Effects**Inhibits** CYP2A6 (weak); **Induces** CYP3A4 (weak)
Drug Interactions

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Phenytoin: May increase the metabolism of Metyrapone. The oral metyrapone test would thus be unreliable unless the metapyrone dosage was substantially increased (eg, 750 mg every 2 hours). *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 250 mg

Generic AvailableNo
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness or sedation
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesMetopiron (CH, NL, NO, SE); Metopirone (AU, CZ, FR, GB, IE)

Metyrosine

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Metyrosine may be confused with metyrapone

Pronunciation(me TYE roe seen)
U.S. Brand NamesDemser®
Canadian Brand NamesDemser®
Pharmacologic CategoryTyrosine Hydroxylase Inhibitor
Use: Labeled IndicationsShort-term management of pheochromocytoma before surgery, long-term management when surgery is contraindicated or when chronic malignant pheochromocytoma exists
Dosing: Adults**Pheochromocytoma (preoperative):** Oral: Initial: 250 mg 4 times/day, increased by 250-500 mg/day up to 4 g/day; maintenance: 2-3 g/day in 4 divided doses; for preoperative preparation, administer optimum effective dosage for 5-7 days
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren >12 years: Refer to adult dosing.
Dosing: Renal ImpairmentAdjustment should be considered.
ContraindicationsHypersensitivity to metyrosine or any component of the formulation; hypertension of unknown etiology
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Appropriate use: Maintain fluid volume during and after surgery.

Pregnancy Risk FactorC
Adverse Reactions

>10%:

Central nervous system: Drowsiness, extrapyramidal symptoms

Gastrointestinal: Diarrhea

1% to 10%:

Endocrine & metabolic: Galactorrhea, edema of the breasts

Gastrointestinal: Nausea, vomiting, xerostomia

Genitourinary: Impotence

Respiratory: Nasal congestion

<1%: Lower extremity edema, depression, hallucinations, disorientation, parkinsonism, urticaria, urinary problems, anemia, eosinophilia, hematuria, hyperstimulation after withdrawal

Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 250 mg

Generic AvailableNo

Mechanism of ActionBlocks the rate-limiting step in the biosynthetic pathway of catecholamines. It is a tyrosine hydroxylase inhibitor, blocking the conversion of tyrosine to dihydroxyphenylalanine. This inhibition results in decreased levels of endogenous catecholamines. Catecholamine biosynthesis is reduced by 35% to 80% in patients treated with metyrosine 1-4 g/day.

Pharmacodynamics/Kinetics

Half-life elimination: 7.2 hours

Excretion: Primarily urine (as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and extrapyramidal symptoms are common; may cause depression, hallucinations, or confusion

Mental Health: Effects on Psychiatric TreatmentConcurrent use with antipsychotics may increase the risk of extrapyramidal symptoms

Index TermsAMPT; OGMT

International Brand NamesDemser (CA)

Mexiletine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(meks IL e teen)

U.S. Brand NamesMexitil® [DSC]

Canadian Brand NamesNovo-Mexiletine

Pharmacologic CategoryAntiarrhythmic Agent, Class Ib

Use: Labeled IndicationsManagement of serious ventricular arrhythmias; suppression of PVCs

Use: Unlabeled/InvestigationalDiabetic neuropathy

Dosing: Adults**Arrhythmias:** Oral: Initial: 200 mg every 8 hours (may load with 400 mg if necessary); adjust dose every 2-3 days; usual dose: 200-300 mg every 8 hours; maximum: 1.2 g/day (some patients respond to every 12-hour dosing). When switching from another antiarrhythmic, initiate a 200 mg dose 6-12 hours after stopping former agents, 3-6 hours after stopping procainamide.

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic ImpairmentPatients with hepatic impairment or CHF may require dose reduction; reduce dose to 25% to 30% of usual dose

Administration: I.V. DetailpH: 3-4 (adjusted with hydrochloric acid)

Administration: OralAdminister with food. Administer around-the-clock to promote less variation in peak and trough serum levels.

ContraindicationsHypersensitivity to mexiletine or any component of the formulation; cardiogenic shock; second- or third-degree AV block (except in patients with a functioning artificial pacemaker)

Warnings/Precautions

Boxed warnings:

- CAST trial: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Hepatotoxicity: Rare hepatic toxicity may occur; may cause acute hepatic injury.
- Proarrhythmic effects: Watch for proarrhythmic effects; monitor and adjust dose to prevent QT_c prolongation.

Disease-related concerns:

- Conduction disturbances: Use with caution in patients with intraventricular conduction delays, first-degree heart block and/or pre-existing sinus node dysfunction.
- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.
- Heart failure (HF): Use with caution in patients with severe HF; may precipitate or exacerbate condition.
- Hepatic impairment: Use with caution in patients with significant hepatic impairment.
- Hypotension: Use with caution in patients with hypotension.

Other warnings/precautions:

- CAST trial: **[U.S. Boxed Warning]: In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, non-life-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide.** An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. Antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.
- Urinary pH: Alterations in urinary pH may change urinary excretion.

Geriatric ConsiderationsNo specific changes in dose are necessary.

Pregnancy Risk FactorC

LactationEnters breast milk/compatible

Adverse Reactions

>10%:

Central nervous system: Lightheadedness (11% to 25%), dizziness (20% to 25%), nervousness (5% to 10%), incoordination (10%)

Gastrointestinal: GI distress (41%), nausea/vomiting (40%)

Neuromuscular & skeletal: Trembling, unsteady gait, tremor (13%), ataxia (10% to 20%)

1% to 10%:

Cardiovascular: Chest pain (3% to 8%), premature ventricular contractions (1% to 2%), palpitation (4% to 8%), angina (2%), proarrhythmia (10% to 15% in patients with malignant arrhythmia)

Central nervous system: Confusion, headache, insomnia (5% to 7%), depression (2%)

Dermatologic: Rash (4%)

Gastrointestinal: Constipation or diarrhea (4% to 5%), xerostomia (3%), abdominal pain (1%)

Neuromuscular & skeletal: Weakness (5%), numbness of fingers or toes (2% to 4%), paresthesia (2%), arthralgia (1%)

Ocular: Blurred vision (5% to 7%), nystagmus (6%)

Otic: Tinnitus (2% to 3%)

Respiratory: Dyspnea (3%)

<1% (Limited to important or life-threatening): Agranulocytosis, alopecia, AV block, cardiogenic shock, CHF (patients with pre-existing ventricular dysfunction), conduction disturbances, diaphoresis, diplopia, drug-induced lupus-like syndrome, dysphagia, edema, esophageal ulceration, exfoliative dermatitis, hallucinations, hepatic necrosis, hepatitis, hot flashes, hyper-/hypotension, impotence, leukopenia, LFTs increased, libido decreased, malaise, myelofibrosis (patients with pre-existing myeloid abnormalities), pancreatitis (rare), peptic ulcer, pharyngitis, positive antinuclear antibody, psychological changes, psychosis, salivary changes, seizure, short-term memory loss, sinus arrest, SLE syndrome, Stevens-Johnson syndrome, syncope, thrombocytopenia, torsade de pointes, transaminases increased, upper GI bleeding, urinary hesitancy, urinary retention

Postmarketing and/or case reports: Pulmonary fibrosis, urticaria

Metabolism/Transport Effects**Substrate** (major) of CYP1A2, 2D6; **Inhibits** CYP1A2 (strong)

Drug Interactions

Bendamustine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inhibitors (Strong) may decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Mexiletine. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Mexiletine. **Exceptions:** Sertraline. *Risk D: Consider therapy modification*

Theophylline Derivatives: Mexiletine may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Food may decrease the rate, but not the extent of oral absorption; diets which affect urine pH can increase or decrease excretion of mexiletine. Avoid dietary changes that alter urine pH.

Test InteractionsAbnormal liver function test, positive ANA, thrombocytopenia

Reference RangeTherapeutic range: 0.5-2 mcg/mL; potentially toxic: >2 mcg/mL

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor cardiac status. Assess for CNS changes. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy, when titrating dosage, and on a regular basis with long-term therapy. **Note:** Mexiletine has a low toxic:therapeutic ratio and overdose may easily produce severe and life-threatening reactions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsRegular serum levels

Patient EducationTake exactly as directed with food or antacids, around-the-clock. Do not take additional doses or discontinue without consulting prescriber. Do not change diet without consulting prescriber. You will need regular cardiac checkups and blood tests while taking this medication. You may experience drowsiness or dizziness, numbness, or visual changes (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or heartburn (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or headaches or sleep disturbances (usually temporary, if persistent consult prescriber). Report chest pain, palpitation, or erratic heartbeat; increased weight or swelling of hands or feet; chills, fever, or persistent sore throat; numbness, weakness, trembling, or unsteady gait; blurred vision or ringing in ears; or respiratory difficulty. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, as hydrochloride: 150 mg, 200 mg, 250 mg

Mexitil®: 150 mg, 200 mg, 250 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Mexiletine HCl)

150 mg (90): $34.98

200 mg (90): $48.20

250 mg (90): $55.99

Mechanism of ActionClass IB antiarrhythmic, structurally related to lidocaine, which inhibits inward sodium current, decreases rate of rise of phase 0, increases effective refractory period/action potential duration ratio

Pharmacodynamics/Kinetics

Absorption: Elderly have a slightly slower rate, but extent of absorption is the same as young adults

Distribution: V_d: 5-7 L/kg

Protein binding: 50% to 70%

Metabolism: Hepatic; low first-pass effect

Half-life elimination: Adults: 10-14 hours (average: elderly: 14.4 hours, younger adults: 12 hours); prolonged with hepatic impairment or heart failure

Time to peak: 2-3 hours

Excretion: Urine (10% to 15% as unchanged drug); urinary acidification increases excretion, alkalinization decreases excretion

Related Information

- Antiarrhythmic Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and nervousness are common; may cause confusion and insomnia

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; barbiturates may decrease the effects of mexiletine; monitor

Cardiovascular ConsiderationsMexiletine has a very narrow therapeutic index and significant toxicity may occur slightly above the therapeutic range. This is particularly problematic when other antiarrhythmic drugs are also being administered. Symptoms of mexiletine excess include sedation, confusion, seizures, respiratory arrest, and cardiac toxicity (sinus arrest, AV block, asystole, hypotension). Note that the QRS and QT intervals are usually normal, although they may be prolonged after massive overdose. As with other antiarrhythmic agents, mexiletine is also proarrhythmic, particularly in patients with underlying cardiovascular disease and electrolyte abnormalities.

Anesthesia and Critical Care Concerns/Other ConsiderationsAs with other antiarrhythmic agents, mexiletine is also proarrhythmic, particularly in patients with underlying cardiovascular disease and electrolyte abnormalities.

References

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Flaker GC, Blackshear JL, McBride R, et al, “Antiarrhythmic Drug Therapy and Cardiac Mortality in Atrial Fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators,” *J Am Coll Cardiol*, 1992, 20:527-32.[PubMed 1512329]

International Brand NamesKaten (PL); Mexicord (PL); Mexitec (ID); Mexitil (AE, AT, AU, BB, BE, BG, BH, BM, BR, BS, BZ, CH, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, GY, HN, HR, HU, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KW, LB, LU, LY, MY, NL, NO, OM, PL, PT, QA, RU, SA, SE, SR, SY, TR, TT, TW, YE); Mexitil Depot (PL); Mexitilen (AR); Mugadine (TW); Ritalmex (HU); Tumetil (VE)

MF

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Pharmacologic Category[Chemotherapy Regimen, Breast Cancer]
Regimen UseBreast cancer
Regimen

Methotrexate: I.V. 100 mg/m^2/day days 1 and 8

[total dose/cycle = 200 mg/m^2]

Fluorouracil: I.V.: 600 mg/m^2/day (start 1 hour after methotrexate) days 1 and 8

[total dose/cycle = 1200 mg/m^2]

Leucovorin: Oral, I.V.: 10 mg/m^2 every 6 hours for 6 doses (start 24 hours after methotrexate)

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 28 days for 12 cycles

References

Fisher B, Dignam J, Mamounas EP, et al, âSequential Methotrexate and Fluorouracil for the Treatment of Node-Negative Breast Cancer Patients With Estrogen Receptor-Negative Tumors: Eight-Year Results from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-13 and First Report of Findings from NSABP B-19 Comparing Methotrexate and Fluorouracil With Conventional Cyclophosphamide, Methotrexate, and Fluorouracil,â *J Clin Oncol*, 1996, 14(7):1982-92.[PubMed 8683228]

Micafungin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(mi ka FUN gin)

U.S. Brand NamesMycamine®

Canadian Brand NamesMycamine®

Pharmacologic CategoryAntifungal Agent, Parenteral; Echinocandin

Use: Labeled IndicationsTreatment of esophageal candidiasis; *Candida* prophylaxis in patients undergoing hematopoietic stem cell transplant (HSCT); treatment of candidemia, acute disseminated candidiasis, and other *Candida* infections (peritonitis and abscesses)

Use: Unlabeled/InvestigationalTreatment of infections due to *Aspergillus* spp; prophylaxis of HIV-related esophageal candidiasis

Dosing: Adults

Candidemia, acute disseminated candidiasis, and*Candida*peritonitis and abscesses: I.V.: 100 mg daily; mean duration of therapy (from clinical trials) was 15 days (range: 10-47 days)

Esophageal candidiasis: I.V.: 150 mg daily; mean duration of therapy (from clinical trials) was 15 days (range: 10-30 days)

Prophylaxis of*Candida*infection in hematopoietic stem cell transplantation: 50 mg daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment required.

Dosing: Hepatic ImpairmentNo dosage adjustment required for moderate hepatic impairment (Child-Pugh score 7-9). Patients with severe hepatic dysfunction have not been studied.

Administration: I.V.For intravenous use only; infuse over 1 hour

Administration: I.V. DetailFlush line with NS prior to administration.

pH: 5-7

StorageStore at controlled room temperature of 25°C (77°F). Reconstituted and diluted solutions are stable for 24 hours at room temperature. Protect from light.

ReconstitutionAseptically add 5 mL of NS (preservative-free) to each 50 or 100 mg vial. Swirl to dissolve; do not shake. Further dilute 50-150 mg in 100 mL NS. Protect from light. Alternatively, D_5W may be used for reconstitution and dilution.

CompatibilityDo not mix or coinfuse with other intravenous solutions.

ContraindicationsHypersensitivity to micafungin, other echinocandins, or any component of the formulation

Allergy Considerations

- Echinocandin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactic reactions: Anaphylactic reactions, including shock, have been reported.
- Hemolytic anemia/hemoglobinuria: Hemolytic anemia and hemoglobinuria have been reported.
- Hepatic failure: New onset or worsening hepatic failure has been reported; use caution in pre-existing mild-moderate hepatic impairment; safety in severe liver failure has not been evaluated.
- Renal impairment: Increased BUN, serum creatinine, renal dysfunction, and/or acute renal failure has been reported; use with caution in patients with pre-existing renal impairment and monitor closely.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsVisceral teratogenic and abortifacient effects were noted in animal studies. There are no adequate and well-controlled studies in pregnant women. Use only if benefit outweighs risk.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsPercentages reflect incidence across all approved indications (prophylaxis and treatment); however, in general, a higher frequency of adverse reactions was observed in studies with HSCT patients.

>10%:

Central nervous system: Fever (20%), headache (16%)

Endocrine & metabolic: Hypokalemia (18%), hypomagnesemia (13%)

Gastrointestinal: Diarrhea (23%), nausea (22%), vomiting (22%), mucosal inflammation (14%), constipation (11%)

Hematologic: Thrombocytopenia (15%), neutropenia (14%)

1% to 10%:

Cardiovascular: Hypotension (9%), tachycardia (8%), hypertension (7%), peripheral edema (7%), phlebitis (6%), edema (5%)

Central nervous system: Insomnia (10%), anxiety (6%), fatigue (6%)

Dermatologic: Rash (9%), pruritus (6%)

Endocrine & metabolic: Hypocalcemia (7%), hyperglycemia (6%)

Gastrointestinal: Abdominal pain (10%), anorexia (6%), dyspepsia (6%)

Hematologic: Anemia (10%), febrile neutropenia (6%)

Hepatic: AST increased (6%), ALT increased (5%), serum alkaline phosphatase increased (5%)

Neuromuscular & skeletal: Rigors (9%), back pain (5%)

Respiratory: Cough (8%), dyspnea (6%), epistaxis (6%)

Miscellaneous: Bacteremia (6%), sepsis (5%)

<1%, postmarketing and/or case reports, or frequency not defined: Acidosis, acute renal failure, anuria, apnea, arrhythmia, arthralgia, atrial fibrillation, BUN increased, cardiac arrest, coagulopathy, creatinine increased, cyanosis, deep vein thrombosis, delirium, hypoxia, encephalopathy, erythema multiforme, facial edema, hemoglobinuria, hemolysis, hemolytic anemia, hepatic dysfunction, hepatic failure, hepatocellular damage, hepatomegaly, hiccups, hyperbilirubinemia, hyponatremia, hypoxia, infection, injection site necrosis, injection site thrombosis, intracranial hemorrhage, jaundice, MI, mucosal inflammation, oliguria, pancytopenia, pneumonia, pulmonary embolism, renal impairment, renal tubular necrosis, seizure, shock, skin necrosis, thrombotic thrombocytopenia purpura, thrombophlebitis, urticaria, vasodilatation, WBC decreased

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor); **Inhibits** CYP3A4 (weak)

Drug Interactions

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Monitoring ParametersLiver function tests

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as sodium [preservative-free]:

Mycamine®: 50 mg, 100 mg [contains lactose]

Generic AvailableNo

Mechanism of ActionConcentration-dependent inhibition of 1,3-beta-D-glucan synthase resulting in reduced formation of 1,3-beta-D-glucan, an essential polysaccharide comprising 30% to 60% of *Candida* cell walls (absent in mammalian cells); decreased glucan content leads to osmotic instability and cellular lysis

Pharmacodynamics/Kinetics

Distribution: 0.28-0.5 L/kg

Protein binding: >99%; primarily to albumin

Metabolism: Hepatic; forms M-1 (catechol) and M-2 (methoxy) metabolites (activity unknown)

Half-life elimination: 11-21 hours

Excretion: Primarily feces (71%); urine (<15%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause delirium, dizziness, or sedation

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMicafungin Sodium

References

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Kohno S, Masaoka T, Yamaguchi H, et al, "A Multicenter, Open-Label Clinical Study of Micafungin (FK463) in the Treatment of Deep-Seated Mycosis in Japan," *Scand J Infect Dis*, 36(5):372-9.

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Pettengell K, Mynhardt J, Kluyts T, et al, "Successful Treatment of Oesophageal Candidiasis by Micafungin: A Novel Systemic Antifungal Agent," *Aliment Pharmacol Ther*, 2004, 20(4):475-81. [PubMed 15298643]

Yokote T, Akioka T, Oka S, et al, “Successful Treatment With Micafungin of Invasive Pulmonary Aspergillosis in Acute Myeloid Leukemia, With Renal Failure Due to Amphotericin B Therapy,” *Ann Hematol*, 2004, 83(1):64-6.[PubMed 14661114]

International Brand NamesMycamine (CL, CZ, GB, HK, IE, KP, TW)

Miconazole and Zinc Oxide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(mi KON a zole & zink OKS ide)

U.S. Brand NamesVusion®

Pharmacologic CategoryAntifungal Agent, Topical

Use: Labeled IndicationsAdjunctive treatment of diaper dermatitis complicated by *Candida albicans* infection

Dosing: Adults**Diaper dermatitis:** Topical: Refer to pediatric dosing.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Diaper dermatitis:** Topical: Children ≥4 weeks: Apply to affected area with each diaper change for 7 days. Treatment should continue for 7 days, even with initial improvement. Do not use for >7 days.

Administration: TopicalApply thin film to clean, dry skin. Do not rub into skin. Avoid use of scented soaps, shampoos, or lotions in the diaper area. Frequent diaper changes are recommended.

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to miconazole, zinc oxide, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue if sensitivity or irritation occurs, or if condition worsens.

Special populations:

- Immunocompromised patients: Has not been studied in immunocompromised patients.
- Incontinent adults: Safety and efficacy have not been established in incontinent adults.
- Pediatrics: Safety and efficacy have not been established in children <4 weeks of age or very low-birth-weight infants.

Other warnings/precautions:

- Appropriate use: For topical use only; avoid contact with eyes or vagina. For use with a candidal infection documented by microscopic evaluation; not for prophylactic use.
- Duration of therapy: Safety and efficacy have not been established for use >7 days.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. See individual agents.

LactationExcretion in breast milk unknown/use caution

Drug Interactions

Alfentanil: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amphotericin B: Antifungal Agents (Azole Derivatives, Systemic) may diminish the therapeutic effect of Amphotericin B. *Risk C: Monitor therapy*

Aprepitant: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Aprepitant. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Quazepam. *Risk D: Consider therapy modification*

Bosentan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Bosentan. *Risk C: Monitor therapy*

BusPIRone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Busulfan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Busulfan. *Risk C: Monitor therapy*

Calcium Channel Blockers: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CarBAMazepine. *Risk C: Monitor therapy*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cilostazol: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Cinacalcet: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Cinacalcet. *Risk C: Monitor therapy*

Cisapride: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Cisapride. *Risk X: Avoid combination*

Codeine: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Conivaptan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Conivaptan. *Risk X: Avoid combination*

Corticosteroids (Orally Inhaled): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2A6 Substrates: CYP2A6 Inhibitors (Strong) may decrease the metabolism of CYP2A6 Substrates. *Risk D: Consider therapy modification*

CYP2B6 Substrates: CYP2B6 Inhibitors (Strong) may decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Strong) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk D: Consider therapy modification*

CYP2E1 Substrates: CYP2E1 Inhibitors (Moderate) may decrease the metabolism of CYP2E1 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Docetaxel: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Docetaxel. *Risk D: Consider therapy modification*

Dofetilide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Dofetilide. *Risk X: Avoid combination*

Eletriptan: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Eletriptan. *Risk D: Consider therapy modification*

Eplerenone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eplerenone. *Risk D: Consider therapy modification*

Erlotinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Erlotinib. *Risk C: Monitor therapy*

Eszopiclone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eszopiclone. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Fosaprepitant: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Fosaprepitant. Specifically, concentrations of aprepitant are likely to be increased. *Risk C: Monitor therapy*

Gefitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Gefitinib. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Imatinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Imatinib. *Risk C: Monitor therapy*

Irinotecan: Antifungal Agents (Azole Derivatives, Systemic) may enhance the adverse/toxic effect of Irinotecan. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Losartan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Losartan. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Antifungal Agents (Azole Derivatives, Systemic). Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Macrolide Antibiotics. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Methadone. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Phosphodiesterase 5 Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

QuiNIDine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of QuiNIDine. Management: Itraconazole, voriconazole, and posaconazole are specifically contraindicated with quinidine. Use of quinidine with any azole antifungal may require quinidine dose adjustment and should be done with caution and close monitoring. *Risk X: Avoid combination*

Ramelteon: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ranolazine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Repaglinide. Management: Concurrent use of an azole antifungal with both repaglinide and gemfibrozil should be avoided. *Risk C: Monitor therapy*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Sirolimus. Management: Sirolimus dose reductions of up to 50-90% may be necessary when starting an azole antifungal. Use of sirolimus with the azole antifungals voriconazole and posaconazole is contraindicated. *Risk D: Consider therapy modification*

Solifenacin: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Solifenacin. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Sunitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Strong) may decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

Temsirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Temsirolimus. Concentrations of the active metabolite, sirolimus, are likely to be increased more substantially than those of the parent temsirolimus. *Risk D: Consider therapy modification*

Tetrabenazine: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Tetrabenazine. Specifically, concentrations of the active alpha- and beta-dihydrotetrabenazine metabolites may be increased. Management: Tetrabenazine dose should be reduced by 50% when starting a strong CYP2D6 inhibitor. Maximum tetrabenazine dose is 50mg/day when used with a strong CYP2D6 inhibitor. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Tolterodine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Tolterodine. This is likely only of concern in CYP2D6-deficient patients (ie, "poor metabolizers") *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

VinCRIStine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of VinCRIStine. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Miconazole may increase the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ziprasidone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ziprasidone. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringFor topical use only when diaper dermatitis is complicated by documented candidiasis (microscopic evaluation). Teach caregiver proper application and adverse symptoms to report (see Patient Education).
Patient EducationVusion® is for topical use only. This ointment should not be used as a substitute for frequent diaper changes or to prevent diaper rash; nor should it be used on anyone for whom it is not prescribed. Use exactly as directed; complete full course of treatment, do not use longer than prescribed.

Application: Cleanse diaper area gently with lukewarm water or a very mild soap and pat dry with soft towel before applying Vusion®. Gently apply ointment to the diaper area with the fingertips after each diaper change. Do not rub ointment into the skin (may cause additional irritation). Wash hands after applying ointment. Use for full 7 days (or as directed), even if there is improvement. If symptoms have not improved after 7 days, notify prescriber. If skin condition in diaper area worsens, contact prescriber.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Ointment, topical:

Vusion®: Miconazole nitrate 0.25% and zinc oxide 15% (30 g [DSC]; 60 g)

Generic AvailableNo
ManufacturerBarrier Therapeutics, Inc
Pricing: U.S. (www.drugstore.com)

Ointment (Vusion)

0.25-15-81.35% (50): $251.16

0.25-15-81.35% (90): $267.11

Mechanism of Action

Miconazole inhibits the biosynthesis of ergosterol, damaging the fungal cell wall membrane.

Zinc oxide is a mild astringent with weak antiseptic properties.

Pharmacodynamics/KineticsAbsorption: Topical: Miconazole: Undetectable to 3.8 ng/mL in infants with dermatitis
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsZinc Oxide and Miconazole Nitrate
International Brand NamesBebektin (MX)

Miconazole

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Miconazole may be confused with Micronase®, Micronor®

Lotrimin® may be confused with Lotrisone®, Otrivin®

Micatin® may be confused with Miacalcin®

Pronunciation(mi KON a zole)

U.S. Brand NamesAloe Vesta® 2-n-1 Antifungal [OTC]; Baza® Antifungal [OTC]; Carrington Antifungal [OTC]; Critic-Aid® Clear AF [OTC]; DermaFungal [OTC]; Dermagran® AF [OTC]; DiabetAid™ Antifungal Foot Bath [OTC]; Fungoid® Tincture [OTC]; Lotrimin® AF Jock Itch Powder Spray [OTC]; Lotrimin® AF Powder/Spray [OTC]; Micaderm® [OTC]; Micatin® Athlete's Foot [OTC]; Micatin® Jock Itch [OTC]; Micro-Guard® [OTC]; Mitrazol™ [OTC]; Monistat-Derm® [DSC]; Monistat® 1 Combination Pack [OTC]; Monistat® 3 Combination Pack [OTC]; Monistat® 3 [OTC]; Monistat® 7 [OTC]; Neosporin® AF [OTC]; Podactin Cream [OTC]; Secura® Antifungal [OTC]; Zeasorb®-AF [OTC]

Canadian Brand NamesDermazole; Micatin®; Micozole; Monistat®; Monistat® 3

Pharmacologic CategoryAntifungal Agent, Topical; Antifungal Agent, Vaginal

Use: Labeled IndicationsTreatment of vulvovaginal candidiasis and a variety of skin and mucous membrane fungal infections

Dosing: Adults

Tinea corporis: Topical: Apply twice daily for 4 weeks

Tinea pedis: Topical: Apply twice daily for 4 weeks

Effervescent tablet: Dissolve 1 tablet in ~1 gallon of water; soak feet for 15-30 minutes; pat dry

Tinea cruris: Topical: Apply twice daily for 2 weeks

Vulvovaginal candidiasis: Vaginal:

Cream, 2%: Insert 1 applicatorful at bedtime for 7 days

Cream, 4%: Insert 1 applicatorful at bedtime for 3 days

Suppository, 100 mg: Insert 1 suppository at bedtime for 7 days

Suppository, 200 mg: Insert 1 suppository at bedtime for 3 days

Suppository, 1200 mg: Insert 1 suppository (a one-time dose); may be used at bedtime or during the day

Note: Many products are available as a combination pack, with a suppository for vaginal instillation and cream to relieve external symptoms. External cream may be used twice daily, as needed, for up to 7 days.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Tinea corporis, tinea pedis, tinea cruris: Topical: **Note:** Not for OTC use in children <2 years: Refer to adult dosing.

Vulvovaginal candidiasis: Vaginal: Children ≥12 years: Refer to adult dosing.

ContraindicationsHypersensitivity to miconazole or any component of the formulation

Allergy Considerations

- Azole Antifungal Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue if sensitivity or irritation occurs.

Special populations:

- Pediatrics: Topical products are not for self-medication (OTC use) in children <2 years of age; vaginal products are not for OTC use in children <12 years of age.

Dosage form specific issues:

- Fungoid® tincture: Patients with diabetes, circulatory problems, renal or hepatic dysfunction should contact healthcare provider prior to self-medication (OTC use).

- Petrolatum-based: Vaginal products are petrolatum-based and may damage rubber or latex condoms or diaphragms; separate use by 3 days.

- Vaginal products: Consult with healthcare provider prior to self-medication (OTC use) if experiencing vaginal itching/discomfort, lower abdominal pain, back or shoulder pain, chills, nausea, vomiting, foul-smelling discharge, if this is the first vaginal yeast infection, or if exposed to HIV. Contact healthcare provider if symptoms do not begin to improve after 3 days or last longer than 7 days. May damage condoms or diaphragms.

Other warnings/precautions:

- Appropriate use: For topical use only; avoid contact with eyes.

Geriatric ConsiderationsNo specific data for the elderly; use does not require alteration in dose or dose intervals. Assess patient's ability to self administer, may be difficult in patients with arthritis or limited range of motion.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Topical: Allergic contact dermatitis, burning, maceration

Vaginal: Abdominal cramps, burning, irritation, itching

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (moderate), 2A6 (strong), 2B6 (weak), 2C9 (strong), 2C19 (strong), 2D6 (strong), 2E1 (moderate), 3A4 (strong)
Drug Interactions

Alfentanil: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amphotericin B: Antifungal Agents (Azole Derivatives, Systemic) may diminish the therapeutic effect of Amphotericin B. *Risk C: Monitor therapy*

Aprepitant: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Aprepitant. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Quazepam. *Risk D: Consider therapy modification*

Bosentan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Bosentan. *Risk C: Monitor therapy*

BusPIRone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Busulfan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Busulfan. *Risk C: Monitor therapy*

Calcium Channel Blockers: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CarBAMazepine. *Risk C: Monitor therapy*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cilostazol: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Cinacalcet: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Cinacalcet. *Risk C: Monitor therapy*

Cisapride: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Cisapride. *Risk X: Avoid combination*

Codeine: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Conivaptan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Conivaptan. *Risk X: Avoid combination*

Corticosteroids (Orally Inhaled): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2A6 Substrates: CYP2A6 Inhibitors (Strong) may decrease the metabolism of CYP2A6 Substrates. *Risk D: Consider therapy modification*

CYP2B6 Substrates: CYP2B6 Inhibitors (Strong) may decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Strong) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk D: Consider therapy modification*

CYP2E1 Substrates: CYP2E1 Inhibitors (Moderate) may decrease the metabolism of CYP2E1 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Docetaxel: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Docetaxel. *Risk D: Consider therapy modification*

Dofetilide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Dofetilide. *Risk X: Avoid combination*

Eletriptan: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Eletriptan. *Risk D: Consider therapy modification*

Eplerenone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eplerenone. *Risk D: Consider therapy modification*

Erlotinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Erlotinib. *Risk C: Monitor therapy*

Eszopiclone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eszopiclone. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Fosaprepitant: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Fosaprepitant. Specifically, concentrations of aprepitant are likely to be increased. *Risk C: Monitor therapy*

Gefitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Gefitinib. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Imatinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Imatinib. *Risk C: Monitor therapy*

Irinotecan: Antifungal Agents (Azole Derivatives, Systemic) may enhance the adverse/toxic effect of Irinotecan. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Losartan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Losartan. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Antifungal Agents (Azole Derivatives, Systemic). Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Macrolide Antibiotics. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Methadone. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Phosphodiesterase 5 Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

QuiNIDine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of QuiNIDine. Management: Itraconazole, voriconazole, and posaconazole are specifically contraindicated with quinidine. Use of quinidine with any azole antifungal may require quinidine dose adjustment and should be done with caution and close monitoring. *Risk X: Avoid combination*

Ramelteon: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ranolazine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Repaglinide. Management: Concurrent use of an azole antifungal with both repaglinide and gemfibrozil should be avoided. *Risk C: Monitor therapy*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Sirolimus. Management: Sirolimus dose reductions of up to 50-90% may be necessary when starting an azole antifungal. Use of sirolimus with the azole antifungals voriconazole and posaconazole is contraindicated. *Risk D: Consider therapy modification*

Solifenacin: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Solifenacin. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Sunitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Strong) may decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

Temsirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Temsirolimus. Concentrations of the active metabolite, sirolimus, are likely to be increased more substantially than those of the parent temsirolimus. *Risk D: Consider therapy modification*

Tetrabenazine: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Tetrabenazine. Specifically, concentrations of the active alpha- and beta-dihydrotetrabenazine metabolites may be increased. Management: Tetrabenazine dose should be reduced by 50% when starting a strong CYP2D6 inhibitor. Maximum tetrabenazine dose is 50mg/day when used with a strong CYP2D6 inhibitor. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Tolterodine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Tolterodine. This is likely only of concern in CYP2D6-deficient patients (ie, "poor metabolizers") *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

VinCRIStine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of VinCRIStine. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Miconazole may increase the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ziprasidone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ziprasidone. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease miconazole levels.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Caution patients with diabetes to test serum glucose regularly; may inhibit the metabolism of oral sulfonylureas. Teach patient proper use, possible side effects/appropriate interventions (eg, bleeding precautions), and adverse symptoms to report.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy. Use full course of therapy as directed; do not discontinue without consulting prescriber. Some infections may require long periods of therapy. Practice good hygiene measures to prevent reinfection. If you have diabetes, you should test serum glucose regularly - this medication may inhibit the metabolism of oral sulfonylureas. Report persistent burning, itching, or irritation to healthcare provider. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Topical: Wash and dry area before applying medication; apply thinly. Do not get in or near eyes. Not for OTC use in children <2 years of age.

Vaginal: Consult with healthcare provider if using for a vaginal yeast infection for the first time. Insert high in vagina. Refrain from intercourse during treatment. Condoms and diaphragms may not be effective during therapy. Do not use tampons, douches, spermicides, or other vaginal products during treatment. Deodorant-free pads or panty shields may be used to protect clothing during use.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Combination products: Miconazole nitrate vaginal suppository 200 mg (3s) and miconazole nitrate external cream 2%

Monistat® 1 Combination Pack: Miconazole nitrate vaginal insert 1200 mg (1) and miconazole nitrate external cream 2% (5 g) [Note: Do not confuse with 1-Day™ (formerly Monistat® 1) which contains tioconazole]

Monistat® 3 Combination Pack:

Miconazole nitrate vaginal insert 200 mg (3s) and miconazole nitrate external cream 2%

Miconazole nitrate vaginal cream 4% and miconazole nitrate external cream 2%

Monistat® 7 Combination Pack:

Miconazole nitrate vaginal suppository 100 mg (7s) and miconazole nitrate external cream 2%

Miconazole nitrate vaginal cream 2% (7 prefilled applicators) and miconazole nitrate external cream 2%

Cream, topical, as nitrate: 2% (15 g, 30 g, 45 g)

Baza® Antifungal: 2% (4 g, 57 g, 142 g) [zinc oxide based formula]

Carrington Antifungal: 2% (150 g)

Micaderm®, Neosporin® AF, Podactin: 2% (30 g)

Micatin® Athlete's Foot, Micatin® Jock Itch: 2% (15 g)

Micro-Guard®, Mitrazol™: 2% (60 g)

Monistat-Derm®: 2% (15 g, 30 g, 85 g) [DSC]

Secura® Antifungal: 2% (60 g, 98 g)

Cream, vaginal, as nitrate [prefilled or refillable applicator]: 2% (45 g)

Monistat® 3: 4% (15 g, 25 g)

Monistat® 7: 2% (45 g)

Gel, topical, as nitrate:

Zeasorb®-AF: 2% (24 g)

Liquid, spray, topical, as nitrate:

Micatin® Athlete's Foot: 2% (90 mL) [contains alcohol]

Neosporin AF®: 2% (105 mL)

Lotion, powder, as nitrate:

Zeasorb®-AF: 2% (56 g) [contains alcohol 36%] [DSC]

Ointment, topical, as nitrate:

Aloe Vesta® 2-n-1 Antifungal: 2% (60 g, 150 g)

Critic-Aid® Clear AF: 2% (4 g, 57 g, 142 g)

DermaFungal: 2% (113 g)

Dermagran® AF: (113 g) [contains vitamin A and zinc]

Powder, topical, as nitrate:

Lotrimin® AF: 2% (160 g)

Micro-Guard®: 2% (90 g)

Mitrazol™: 2% (30 g)

Zeasorb®-AF: 2% (70 g)

Powder spray, topical, as nitrate:

Lotrimin® AF, Lotrimin® AF Jock Itch: 2% (140 g)

Micatin® Athlete’s Foot, Micatin® Jock Itch: 2% (90 g) [contains alcohol]

Neosporin® AF: 2% (85 g)

Suppository, vaginal, as nitrate: 100 mg (7s); 200 mg (3s)

Monistat® 3: 200 mg (3s)

Monistat® 7: 100 mg (7s)

Tablet, for solution, topical, as nitrate [effervescent]:

DiabetAid™ Antifungal Foot Bath: 2% (10s)

Tincture, topical, as nitrate (Fungoid®): 2% (30 mL, 473 mL) [contains isopropyl alcohol 30%]; 30 mL size also available in a treatment kit which contains nail scrub and nail brush]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Cream (Miconazole Nitrate)

2% (28): $12.99

Cream (Monistat-Derm)

2% (15): $24.99

2% (28.35): $41.99

Powder (Zeasorb-AF)

2% (70): $14.99

Solution (Fungoid Tincture)

2% (29.57): $29.99

Suppository (Miconazole 3)

200 mg (3): $34.99

Suppository (Monistat 3)

200 mg (3): $52.99

Mechanism of ActionInhibits biosynthesis of ergosterol, damaging the fungal cell wall membrane, which increases permeability causing leaking of nutrients

Pharmacodynamics/Kinetics

Absorption: Topical: Negligible

Distribution: Widely to body tissues; penetrates well into inflamed joints, vitreous humor of eye, and peritoneal cavity, but poorly into saliva and sputum; crosses blood-brain barrier but only to a small extent

Protein binding: 91% to 93%

Metabolism: Hepatic

Half-life elimination: Multiphasic: Initial: 40 minutes; Secondary: 126 minutes; Terminal: 24 hours

Excretion: Feces (~50%); urine (<1% as unchanged drug)

Related Information

- Antifungal Agents
- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMiconazole Nitrate

References

Coulthard K, Martin J, and Matthews N, “Convulsions After Miconazole Overdose,” *Med J Aust*, 1987, 146(1):57-8. [PubMed 3796399]

Fainstein V and Bodey GP, “Cardiorespiratory Toxicity Due to Miconazole,” *Ann Intern Med*, 1980, 93:432-3. [PubMed 7436161]

Kanarek KS and Williams PR, “Toxicity of Intravenous Miconazole Overdosage in a Preterm Infant,” *Pediatr Infect Dis*, 1986, 5(4):486-8.[PubMed 3725663]

International Brand NamesAlbistat (LU); Aloid (MX); Andergin (IT); Antifungal (TW); Becarin (MY); Brentan (DK); Candiplas (TW); Candizol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Candizol oral (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Dacta Oral Gel (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Dacta Topical Gel (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Daktar (DE, LU, NO, SE); Daktarin (AR, AT, AU, BB, BD, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CZ, EC, EE, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HR, ID, IE, IL, IN, IT, JM, JP, KE, KP, LR, LU, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, PE, PH, PK, PL, PT, PY, RU, SC, SD, SG, SL, SN, SR, TH, TN, TT, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Daktazol (ID); De-Ol (PH); Decozol (SG); Deralbine (AR); Derma-Mycotral (DE); Dermon (TH); Dermonistat (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Diamifan (CN); Escortin (ID); Fungares (ID); Fungi-M (TH); Fungo Powder (AU); Fungos (CN); Fungtopic (PH); Gyno-Daktar (DE); Gyno-Daktarin (AE, AT, BD, BE, BG, BH, BR, CL, CO, CY, CZ, EE, EG, FI, FR, GB, HK, HR, ID, IE, IL, IN, IQ, IR, JO, JP, KP, KW, LB, LU, LY, MX, MY, OM, PH, PK, PL, PT, QA, RU, SA, SG, SY, TH, TW, YE, ZA); Gyno-Femidazol (PL); Gynospor (ZA); Hipo Femme (MX); Huma-Miconazole (HN); Loramyc (FR, GB); Lotrimin AF (MX); Medacter (GR); Micatin (EC); Miconal (IT, PL); Miconazol (MX); Micotef (IT); Micreme (NZ); Mikonazol (PL); Mikozal (EC); Minaza (TH); Minazol (SG); Miracol (CO); Moladerm (ID); Monistat-7 (AU); Mycoban (SG); Mycoheal Cream (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Mycoheal Oral Gel (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Mycorine (ID); Mysocort (TH); Nacomic (MX); Neomicol (CR, DO, GT, HN, MX, NI, PA, SV); Nilozanoc (ID); Noxraxin (TH); Pitrion (IL); Podakrin (TW); Ranozol (TH); Resolve (SG); Resolve Thrush (AU, MY, SG); Resolve Tinea (MY, SG); Rojazol (HR); Skindure (TH); Tara (TH); Tinazol (MY); Zolagel (ID); Zole (IN)

Midazolam

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Versed may be confused with VePesid®, Vistaril®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(MID aye zoe lam)

Canadian Brand NamesApo-Midazolam®; Midazolam Injection

Pharmacologic CategoryBenzodiazepine

Use: Labeled IndicationsPreoperative sedation and provides conscious sedation prior to diagnostic or radiographic procedures; ICU sedation (continuous infusion); intravenous anesthesia (induction); intravenous anesthesia (maintenance)

Use: Unlabeled/InvestigationalAnxiety, status epilepticus

Use: DentalSedation component in I.V. conscious sedation in oral surgery patients; syrup formulation is used for children to help alleviate anxiety before a dental procedure

Dosing: Adults

Note: The dose of midazolam needs to be individualized based on the patient's age, underlying diseases, and concurrent medications. Decrease dose (by ~30%) if narcotics or other CNS depressants are administered concomitantly. **Personnel and equipment needed for standard respiratory resuscitation should be immediately available during midazolam administration.**

Preoperative sedation:

I.M.: 0.07-0.08 mg/kg 30-60 minutes prior to surgery/procedure; usual dose: 5 mg; **Note:** Reduce dose in patients with COPD, high-risk patients, patients ≥60 years of age, and patients receiving other narcotics or CNS depressants

I.V.: 0.02-0.04 mg/kg; repeat every 5 minutes as needed to desired effect or up to 0.1-0.2 mg/kg

Intranasal (not an approved route): 0.2 mg/kg (up to 0.4 mg/kg in some studies); administer 30-45 minutes prior to surgery/procedure

Conscious sedation: I.V.: Initial: 0.5-2 mg slow I.V. over at least 2 minutes; slowly titrate to effect by repeating doses every 2-3 minutes if needed; usual total dose: 2.5-5 mg; use decreased doses in elderly.

Healthy Adults <60 years:

Initial: Some patients respond to doses as low as 1 mg; no more than 2.5 mg should be administered over a period of 2 minutes. Additional doses of midazolam may be administered after a 2-minute waiting period and evaluation of sedation after each dose increment. A total dose >5 mg is generally not needed. If narcotics or other CNS depressants are administered concomitantly, the midazolam dose should be reduced by 30%. *Refer to elderly dosing for patients ≥60 years, debilitated, or chronically ill.*

Maintenance: 25% of dose used to reach sedative effect

Anesthesia: I.V.:

Induction:

Unpremedicated patients: 0.3-0.35 mg/kg (up to 0.6 mg/kg in resistant cases)

Premedicated patients: 0.15-0.35 mg/kg

Maintenance: 0.05-0.3 mg/kg as needed, or continuous infusion 0.25-1.5 mcg/kg/minute

Sedation in mechanically-ventilated patients: I.V. continuous infusion: 100 mg in 250 mL D_5W or NS (if patient is fluid-restricted, may concentrate up to a maximum of 0.5 mg/mL); initial dose: 0.02-0.08 mg/kg (~1 mg to 5 mg in 70 kg adult) initially and either repeated at 5-15 minute intervals until adequate sedation is achieved or continuous infusion rates of 0.04-0.2 mg/kg/hour and titrate to reach desired level of sedation

Refractory status epilepticus (unlabeled use): I.V.: Initial: 0.2 mg/kg bolus, then 0.05-0.6 mg/kg/hour

Dosing: ElderlyThe dose of midazolam needs to be individualized based on the patient's age, underlying diseases, and concurrent medications. Decrease dose (by ~30%) if narcotics or other CNS depressants are administered concomitantly. **Personnel and equipment needed for standard respiratory resuscitation should be immediately available during midazolam administration.**

I.V.: Conscious sedation: Initial: 0.5 mg slow I.V.; give no more than 1.5 mg in a 2-minute period. If additional titration is needed, give no more than 1 mg over 2 minutes, waiting another 2 or more minutes to evaluate sedative effect. A total dose >3.5 mg is rarely necessary.

Dosing: Pediatric

Notes: The dose of midazolam needs to be individualized based on the patient's age, underlying diseases, and concurrent medications. Decrease dose (by ~30%) if narcotics or other CNS depressants are administered concomitantly. **Personnel and equipment needed for standard respiratory resuscitation should be immediately available during midazolam administration.** Children <6 years may require higher doses and closer monitoring than older children; calculate dose on ideal body weight

Conscious sedation for procedures or preoperative sedation:

Oral: 0.25-0.5 mg/kg as a single dose preprocedure, up to a maximum of 20 mg; administer 30-40 minutes prior to procedure. Children <6 years, or less cooperative patients may require as much as 1 mg/kg as a single dose; 0.25 mg/kg may suffice for children 6-16 years of age.

Intranasal (not an approved route): 0.2 mg/kg (up to 0.4 mg/kg in some studies), administered 30-45 minutes prior to procedure

I.M.: 0.1-0.15 mg/kg 30-60 minutes before surgery or procedure; range 0.05-0.15 mg/kg; doses up to 0.5 mg/kg have been used in more anxious patients; maximum total dose: 10 mg

I.V.:

Infants <6 months: Limited information is available in nonintubated infants; dosing recommendations not clear; infants <6 months are at higher risk for airway obstruction and hypoventilation; titrate dose in small increments to desired effect; monitor carefully

Infants 6 months to Children 5 years: Initial: 0.05-0.1 mg/kg; titrate dose carefully; total dose of 0.6 mg/kg may be required; usual maximum total dose: 6 mg

Children 6-12 years: Initial: 0.025-0.05 mg/kg; titrate dose carefully; total doses of 0.4 mg/kg may be required; usual maximum total dose: 10 mg

Children 12-16 years: Dose as adults; usual maximum total dose: 10 mg

Conscious sedation during mechanical ventilation: I.V.: Children: Loading dose: 0.05-0.2 mg/kg, followed by initial continuous infusion: 1-2 mcg/kg/minute; titrate to the desired effect; usual range: 0.4-6 mcg/kg/minute

Status epilepticus refractory to standard therapy (unlabeled use): I.V.: Infants >2 months and Children: Loading dose: 0.15 mg/kg followed by a continuous infusion of 0.06 mg/kg/hour; titrate dose upward every 5 minutes until clinical seizure activity is controlled; mean infusion rate required in 24 children was 0.14 mg/kg/hour (2.3 mcg/kg/minute) with a range of 0.06-1.1 mg/kg/hour

Dosing: Renal Impairment

Hemodialysis: Supplemental dose is not necessary.

Peritoneal dialysis: Significant drug removal is unlikely based on physiochemical characteristics.

Administration: I.M.Give deep I.M. into large muscle.

Administration: I.V.Administer by slow I.V. injection over at least 2-5 minutes at a concentration of 1-5 mg/mL or by I.V. infusion. Continuous infusions should be administered via an infusion pump.

Administration: I.V. DetailpH: 3 (adjusted)

Administration: OralDo not mix with any liquid (such as grapefruit juice) prior to administration.

Administration: OtherIntranasal: Administer using a 1 mL needleless syringe into the nares over 15 seconds; use the 5 mg/mL injection; $^1/_2$ of the dose may be administered to each nare

Dietary ConsiderationsInjection: Sodium content of 1 mL: 0.14 mEq

StorageThe manufacturer states that midazolam, at a final concentration of 0.5 mg/mL, is stable for up to 24 hours when diluted with D_5W or NS. A final concentration of 1 mg/mL in NS has been documented to be stable for up to 10 days (McMullen, 1995). Admixtures do not require protection from light for short-term storage.

CompatibilityStable in D_5NS, D_5W, NS; **incompatible** with LR.

Y-site administration: Compatible: Alatrofloxacin, amikacin, amiodarone, atracurium, calcium gluconate, cefazolin, cefotaxime, cimetidine, ciprofloxacin, cisatracurium, clindamycin, digoxin, diltiazem, dopamine, epinephrine, erythromycin lactobionate, esmolol, etomidate, famotidine, fentanyl, fluconazole, gatifloxacin, gentamicin, haloperidol, heparin, hydromorphone, insulin (regular), ketanserin, labetalol, linezolid, lorazepam, methylprednisolone sodium succinate, metronidazole, milrinone, morphine, nicardipine, nitroglycerin, norepinephrine, pancuronium, piperacillin, potassium chloride, ranitidine, remifentanil, sodium nitroprusside, sufentanil, theophylline, tobramycin, vancomycin, vecuronium. **Incompatible:** Albumin, amphotericin B cholesteryl sulfate complex, ampicillin, bumetanide, butorphanol, ceftazidime, cefuroxime, clonidine, dexamethasone sodium succinate, floxacillin, foscarnet, fosphenytoin, furosemide, hydrocortisone sodium succinate, imipenem/cilastatin, methotrexate, nafcillin, omeprazole, sodium bicarbonate, thiopental, trimethoprim/sulfamethoxazole. **Variable (consult detailed reference):** Dobutamine, propofol.

Compatibility in syringe: Compatible: Alfentanil, atracurium, atropine, buprenorphine, butorphanol, chlorpromazine, cimetidine, diamorphine, diphenhydramine, droperidol, fentanyl, glycopyrrolate, hydromorphone, hydroxyzine, meperidine, metoclopramide, morphine, nalbuphine, ondansetron, promazine, promethazine, scopolamine, sufentanil, thiethylperazine, trimethobenzamide. **Incompatible:** Dimenhydrinate, pentobarbital, perphenazine, prochlorperazine edisylate, ranitidine.

Compatibility when admixed: Compatible: Hydromorphone.

RestrictionsC-IV

ContraindicationsHypersensitivity to midazolam or any component of the formulation, including benzyl alcohol (cross-sensitivity with other benzodiazepines may exist); parenteral form is not for intrathecal or epidural injection; narrow-angle glaucoma; concurrent use of potent inhibitors of CYP3A4 (amprenavir, atazanavir, or ritonavir); pregnancy

Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Boxed warnings:

- Benzyl alcohol: See “Dosage form specific issues” below.
- Debilitated patients: See “Special populations” below.
- Elderly: See “Special populations” below.
- Respiratory depression: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). A minimum of 1 day should elapse after midazolam administration before attempting these tasks.
- Hypotension: May cause hypotension; hemodynamic events are more common in pediatric patients or patients with hemodynamic instability. Hypotension may occur more frequently in patients who have received opioid analgesics.
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.
- Respiratory depression: **[U.S. Boxed Warning]: May cause severe respiratory depression, respiratory arrest, or apnea. Use with extreme caution, particularly in noncritical care settings.** Appropriate resuscitative equipment and qualified personnel must be available for administration and monitoring. Initial dosing must be cautiously titrated and individualized, particularly in elderly or debilitated patients, patients with hepatic impairment (including alcoholics), or in renal impairment, particularly if other CNS depressants (including opiates) are used concurrently.

Disease-related concerns:

- Heart failure (HF): Use with caution in patients with HF.
- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: **[U.S. Boxed Warning]: Initial doses in debilitated patients should be conservative; start at the lower end of dosing range.**
- Elderly: **[U.S. Boxed Warning]: Initial doses in elderly should be conservative; start at the lower end of dosing range.**
- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.
- Obese patients: Use with caution in obese patients; may have prolonged action when discontinued.

Dosage form specific issues:

- Benzyl alcohol: **[U.S. Boxed Warning]: Parenteral form contains benzyl alcohol; avoid rapid injection in neonates or prolonged infusions.**

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties. Does not protect against increases in heart rate or blood pressure during intubation. Should not be used in shock, coma, or acute alcohol intoxication. Avoid intra-arterial administration or extravasation of parenteral formulation. Use during upper airway procedures may increase risk of hypoventilation. Prolonged responses have been noted following extended administration by continuous infusion (possibly due to metabolite accumulation) or in the presence of drugs which inhibit midazolam metabolism.
- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsIn the elderly if concomitant CNS depressant medications are used, the midazolam dose will be at least 50% less than doses used in healthy, young, unpremedicated patients.

Pregnancy Risk FactorD

Pregnancy Considerations Midazolam has been found to cross the placenta; not recommended for use during pregnancy.
Lactation Enters breast milk/not recommended (AAP rates "of concern")
Adverse Reactions As reported in adults unless otherwise noted:

>10%: Respiratory: Decreased tidal volume and/or respiratory rate decrease, apnea (3% children)

1% to 10%:

Cardiovascular: Hypotension (3% children)

Central nervous system: Drowsiness (1%), oversedation, headache (1%), seizure-like activity (1% children)

Gastrointestinal: Nausea (3%), vomiting (3%)

Local: Pain and local reactions at injection site (4% I.M., 5% I.V.; severity less than diazepam)

Ocular: Nystagmus (1% children)

Respiratory: Cough (1%)

Miscellaneous: Physical and psychological dependence with prolonged use, hiccups (4%, 1% children), paradoxical reaction (2% children)

<1%: Acid taste, agitation, amnesia, bigeminy, bradycardia, bronchospasm, confusion, dyspnea, emergence delirium, euphoria, excessive salivation, hallucinations, hyperventilation, laryngospasm, PVC, rash, tachycardia, wheezing

Metabolism/Transport Effects **Substrate** of CYP2B6 (minor), 3A4 (major); **Inhibits** CYP2C8 (weak), 2C9 (weak), 3A4 (weak)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Atorvastatin: May increase the serum concentration of Midazolam. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Efavirenz: May increase the serum concentration of Midazolam. *Risk X: Avoid combination*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Yohimbine: May diminish the therapeutic effect of Antianxiety Agents. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Grapefruit juice may increase serum concentrations of midazolam; avoid concurrent use with oral form.

Herb/Nutraceutical: Avoid concurrent use with St John's wort (may decrease midazolam levels, may increase CNS depression). Avoid concurrent use with valerian, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersRespiratory and cardiovascular status, blood pressure, blood pressure monitor required during I.V. administration

Nursing: Physical Assessment/MonitoringAssess other medications the patient may be taking for effectiveness and interactions. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. **I.V.:** Monitor cardiac and respiratory status continuously. Monitor I.V. infusion site carefully for extravasation. **I.V./I.M.:** Monitor closely following administration. Bedrest and assistance with ambulation necessary for several hours. **Note:** Full recovery usually occurs within 2-3 hours, but may take 6 hours.

Patient EducationAvoid use of alcohol, prescription or OTC sedatives, or hypnotics for a minimum of 24 hours after administration. Avoid driving or engaging in any tasks that require alertness for 24 hours following administration. You may experience some loss of memory following administration. **Pregnancy/breast-feeding precautions:** Advise prescriber if you are pregnant; this medication is contraindicated for pregnant women. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 1 mg/mL (2 mL, 5 mL, 10 mL); 5 mg/mL (1 mL, 2 mL, 5 mL, 10 mL) [contains benzyl alcohol 1%]

Injection, solution [preservative free]: 1 mg/mL (2 mL, 5 mL); 5 mg/mL (1 mL, 2 mL)

Syrup: 2 mg/mL (118 mL) [contains sodium benzoate; cherry flavor]

Generic AvailableYes

ManufacturerRoche Laboratories Inc

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Onset of action: I.M.: Sedation: ~15 minutes; I.V.: 1-5 minutes

Peak effect: I.M.: 0.5-1 hour

Duration: I.M.: Up to 6 hours; Mean: 2 hours

Absorption: Oral: Rapid

Distribution: V_d: 0.8-2.5 L/kg; increased with congestive heart failure (CHF) and chronic renal failure

Protein binding: 95%

Metabolism: Extensively hepatic via CYP3A4

Bioavailability: Mean: 45%

Half-life elimination: 1-4 hours; prolonged with cirrhosis, congestive heart failure, obesity, and elderly

Excretion: Urine (as glucuronide conjugated metabolites); feces (~2% to 10%)

Related Information

- Benzodiazepines
- Discontinuation of Psychotropic Drugs
- Status Epilepticus
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsAbrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms. For neonates, since both concentrations of the injection contain 1% benzyl alcohol, use the 5 mg/mL injection and dilute to 0.5 mg/mL with SWI without preservatives to decrease the amount of benzyl alcohol delivered to the neonate; with continuous infusion, midazolam may accumulate in peripheral tissues; use lowest effective infusion rate to reduce accumulation effects; midazolam is 3-4 times as potent as diazepam; paradoxical reactions associated with midazolam use in children (eg, agitation, restlessness, combativeness) have been successfully treated with flumazenil (Massanari, 1997).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Midazolam is a short half-life benzodiazepine and may be of benefit in patients where a rapidly and short-acting agent is desired (acute agitation). Duration of action after a single dose is determined by redistribution rather than metabolism. Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include personal or family history of substance abuse and personality disorder.

Midazolam is rapidly and completely absorbed after I.M. injection.

Cardiovascular ConsiderationsHypotension may result in orthostatic lightheadedness or syncope. Benzodiazepines, as a class, may depress respiration. These medications may often be prescribed for difficulty in sleeping but may exacerbate sleep-disordered breathing.

Anesthesia and Critical Care Concerns/Other Considerations

Agitation in the ICU Patient: Diazepam or midazolam is recommended for rapid sedation of the acutely-agitated patient. Midazolam may accumulate in obesity, in patients with hypoalbuminemia, or renal failure. Concurrent use of CYP3A4 inhibitors may inhibit midazolam's metabolism and prolong its sedative effects. The ACCM/SCCM task force does not recommend midazolam use for ongoing sedation in the practice guidelines for sustained use of sedatives and analgesics in the critically-ill adult. Midazolam is 3-4 times as potent as diazepam. Paradoxical reactions associated with midazolam use in children (eg, agitation, restlessness, combativeness) have been successfully treated with flumazenil.

Index TermsMidazolam Hydrochloride; Versed

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International Brand NamesDalam (AR); Doricum (VE); Dormicum (AE, AR, AT, BB, BD, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CL, CO, CY, CZ, DE, DK, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PH, PK, PL, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Dormicum[inj.] (HR); Dormonid (BR, CN, PE); Fortanest (ID); Fulsed (CL, IN, MY, PL); Hypnovel (AU, BE, CO, CR, DO, FR, GB, GT, HN, IE, NI, PA, SV); Ipnovel (IT); Midacum (ZA); Midanium (PL); Midazo (TW); Midazol (IL); Midazolam Torrex (PL); Midolam (IL); Midozor (MX); Miloz (ID); Mizolam (MY); Relacum (MX); Sedacum (ID); Sopodorm (PL); Uzolam (TW); Versed (FR)

Midodrine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

ProAmatine® may be confused with protamine

Pronunciation(MI doe dreen)

U.S. Brand NamesProAmatine®

Canadian Brand NamesAmatine®; Apo-Midodrine®

Pharmacologic CategoryAlpha$_1$ Agonist

Use: Labeled Indications**Orphan drug:** Treatment of symptomatic orthostatic hypotension

Use: Unlabeled/InvestigationalInvestigational: Management of urinary incontinence

Dosing: Adults**Orthostatic hypotension:** Oral: 10 mg 3 times/day during daytime hours (every 3-4 hours) when patient is upright (maximum: 40 mg/day)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment2.5 mg 3 times/day; gradually increase as tolerated.

Hemodialysis: Dialyzable

Administration: OralDoses may be given in approximately 3- to 4-hour intervals (eg, shortly before or upon rising in the morning, at midday, in the late afternoon not later than 6 PM). Avoid dosing after the evening meal or within 4 hours of bedtime. Continue therapy only in patients who appear to attain symptomatic improvement during initial treatment. Standing systolic blood pressure may be elevated 15-30 mm Hg at 1 hour after a 10 mg dose. Some effect may persist for 2-3 hours.

ContraindicationsHypersensitivity to midodrine or any component of the formulation; severe organic heart disease; urinary retention; pheochromocytoma; thyrotoxicosis; persistent and significant supine hypertension

Warnings/Precautions

Boxed warnings:

- Appropriate use: See "Other warnings/precautions" below.

Concerns related to adverse effects:

- Hypertension: May cause hypertension.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Urinary retention: Use with caution in patients with urinary retention; reduce initial dose.

- Visual problems: Use with caution in patients with visual problems, especially if receiving fludrocortisone.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: **[U.S. Boxed Warning]: Indicated for patients for whom orthostatic hypotension significantly impairs their daily life despite standard clinical care.** Use is not recommended with supine hypertension.

- Monitoring: Monitor renal and hepatic function prior to and periodically during therapy.

Geriatric ConsiderationsAdjust dosage for renal impairment.

Pregnancy Risk FactorC

Pregnancy ConsiderationsIncreased rate of embryo resorption and decreased fetal weight were observed in animal studies. Use during pregnancy should be avoided unless the potential benefit outweighs the risk to the fetus.

LactationExcretion in breast milk is unknown/use caution

Adverse Reactions

>10%:

Cardiovascular: Supine hypertension (7% to 13%)

Dermatologic: Piloerection (13%), pruritus (12%)

Genitourinary: Urinary urgency, retention, or polyuria, dysuria (up to 13%)

Neuromuscular & skeletal: Paresthesia (18%)

1% to 10%:

Central nervous system: Chills (5%), pain (5%)

Dermatologic: Rash (2%)

Gastrointestinal: Abdominal pain

<1%: Anxiety, canker sore, confusion, dizziness, dry skin, erythema multiforme, facial flushing, flatulence, flushing, headache, hyperesthesia, insomnia, ICP increased, leg cramps, nausea, somnolence, visual changes, weakness, xerostomia

Drug Interactions

Beta-Blockers: May enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Cardiac Glycosides: May enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Monitoring ParametersBlood pressure, renal and hepatic parameters

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, risk for increased bradycardia with cardiac glycosides, psychotherapeutics, beta-blockers). Assess therapeutic effectiveness (reduction of hypotension) and adverse reactions (eg, supine hypertension, urinary urgency/retention, rash) at beginning of therapy and periodically thereafter. **Note:** Standing blood pressure may be elevated 1 hour after administration and remain slightly elevated 3-4 hours. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsKidney and liver function tests

Patient EducationDo not take any new medication during therapy unless approved by prescriber (especially anything that may affect blood pressure; cough or cold medications, diet, weight reduction, stay-awake products). Take exactly as directed; take when sitting upright. Do not take within 4 hours of bedtime or when lying down for any length of time. Follow instructions for checking blood pressure and pulse routinely (same time of day; for 1 week at least). May cause urinary urgency or retention (void before taking or consult prescriber if difficulty persists); or dizziness, drowsiness, or headache (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report skin rash, severe gastric upset or pain, muscle weakness or pain, or other persistent side effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 2.5 mg, 5 mg, 10 mg

ProAmatine®: 2.5 mg, 5 mg, 10 mg [scored]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Midodrine HCl)

2.5 mg (30): $34.99

5 mg (100): $200.00

10 mg (100): $290.16

Tablets (ProAmatine)

2.5 mg (100): $139.99

5 mg (100): $255.98

Mechanism of ActionMidodrine forms an active metabolite, desglymidodrine, that is an alpha$_1$-agonist. This agent increases arteriolar and venous tone resulting in a rise in standing, sitting, and supine systolic and diastolic blood pressure in patients with orthostatic hypotension. See table.

Causes of Orthostatic Hypotension

Primary Autonomic Causes

Pure autonomic failure (Bradbury-Eggleston syndrome, idiopathic orthostatic hypotension)
Autonomic failure with multiple system atrophy (Shy-Drager syndrome)
Familial dysautonomia (Riley-Day syndrome)
Dopamine beta-hydroxylase deficiency
Secondary Autonomic Causes
Chronic alcoholism
Parkinson's disease
Diabetes mellitus
Porphyria
Amyloidosis
Various carcinomas
Vitamin B_1 or B_{12} deficiency
Nonautonomic Causes
Hypovolemia (such as associated with hemorrhage, burns, or hemodialysis) and dehydration
Diminished homeostatic regulation (such as associated with aging, pregnancy, fever, or prolonged bedrest)
Medications (eg, antihypertensives, insulin, tricyclic antidepressants)

Pharmacodynamics/Kinetics

Onset of action: ~1 hour

Duration: 2-3 hours

Absorption: Rapid

Distribution: V_d (desglymidodrine): <1.6 L/kg; poorly across membrane (eg, blood brain barrier)

Protein binding: Minimal

Metabolism: Hepatic; midodrine is a prodrug which undergoes rapid deglycination to desglymidodrine (active metabolite); metabolism occurs in many tissues and plasma

Bioavailability: Desglymidodrine: 93%

Half-life elimination: Desglymidodrine: ~3-4 hours; Midodrine: 25 minutes

Time to peak, serum: Desglymidodrine: 1-2 hours; Midodrine: 30 minutes

Excretion: Urine (2% to 4%)

Clearance: Desglymidodrine: 385 mL/minute (predominantly by renal secretion)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, dizziness, confusion, or insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsMidodrine may increase blood pressure and should be carefully monitored in patients with underlying coronary artery disease. Midodrine should not be administered after 6 PM or within 4 hours of bedtime since the key therapeutic aim is to attenuate orthostatic hypotension. Midodrine may also worsen supine hypertension, a problem seen frequently in patients with diabetic autonomic neuropathy.

Index TermsMidodrine Hydrochloride

International Brand NamesGutron (AT, BG, CH, CL, CN, CZ, DE, FR, HK, HN, HU, IL, IT, NL, NZ, PL, PT, RU, SG, UY); Metligine (JP); Midon (IE); Midorine (TW); Midron (KP)

Mifepristone

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Mifeprex® may be confused with Mirapex®

Mifepristone may be confused with misoprostol

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(mi FE pris tone)

U.S. Brand NamesMifeprex®

Pharmacologic CategoryAbortifacient; Antineoplastic Agent, Hormone Antagonist; Antiprogestin

Use: Labeled IndicationsMedical termination of intrauterine pregnancy, through day 49 of pregnancy. Patients may need treatment with misoprostol and possibly surgery to complete therapy

Use: Unlabeled/InvestigationalTreatment of unresectable meningioma; has been studied in the treatment of breast cancer, ovarian cancer, and adrenal cortical carcinoma

Dosing: Adults

Termination of pregnancy: Oral: Treatment consists of three office visits by the patient; the patient must read medication guide and sign patient agreement prior to treatment:

Day 1: 600 mg (three 200 mg tablets) taken as a single dose under physician supervision

Day 3: Patient must return to the healthcare provider 2 days following administration of mifepristone; unless abortion has occurred (confirmed using ultrasound or clinical examination): 400 mcg (two 200 mcg tablets) of misoprostol; patient may need treatment for cramps or gastrointestinal symptoms at this time

Day 14: Patient must return to the healthcare provider ~14 days after administration of mifepristone; confirm complete termination of pregnancy by ultrasound or clinical exam. Surgical termination is recommended to manage treatment failures.

Dosing for unlabeled uses: Refer to individual protocols. The dose used in meningioma is usually 200 mg/day, continued based on toxicity and response.

Dosing: ElderlySafety and efficacy have not been established.

Dosing: Renal ImpairmentSafety and efficacy have not been established.

Dosing: Hepatic ImpairmentSafety and efficacy have not been established; use with caution due to CYP3A4 metabolism.

StorageStore at room temperature of 25°C (77°F).

RestrictionsInvestigators wishing to obtain the agent for use in oncology patients must apply for a patient-specific IND from the FDA. Mifepristone will be supplied only to licensed physicians who sign and return a “Prescriber's Agreement.” Distribution of mifepristone will be subject to specific requirements imposed by the distributor. Mifepristone will **not** be available to the public through licensed pharmacies. An FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

Not available in Canada

ContraindicationsHypersensitivity to mifepristone, misoprostol, other prostaglandins, or any component of the formulation; chronic adrenal failure; porphyrias; hemorrhagic disorder or concurrent anticoagulant therapy; pregnancy termination >49 days; intrauterine device (IUD) in place; ectopic pregnancy or undiagnosed adnexal mass; concurrent long-term corticosteroid therapy; inadequate or lack of access to emergency medical services; inability to understand effects and/or comply with treatment

Warnings/Precautions

Boxed warnings:

- Bacterial infections: See “Concerns related to adverse effects” below.
- Bleeding: See “Concerns related to adverse effects” below.
- Medication guide: See “Other warnings/precautions” below.

- Patient instruction: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Bacterial infections: **[U.S. Boxed Warning]: Bacterial infections have been reported following use of this product.** In rare cases, these infections may be serious and/or fatal, with septic shock as a potential complication. A causal relationship has not been established. Sustained fever, abdominal pain, or pelvic tenderness should prompt evaluation; however, healthcare professionals are warned that atypical presentations of serious infection without these symptoms have also been noted. Patients presenting with nausea, vomiting, diarrhea, or weakness, with or without abdominal pain or fever, should be evaluated for serious bacterial infection when symptoms occur >24 hours after taking misoprostol. Treatment with antibiotics, including coverage for anaerobic bacteria (eg, *Clostridium sordellii*) should be initiated.

- Bleeding: **[U.S. Boxed Warning]: Patients should be counseled to seek medical attention in cases of excessive bleeding.** Bleeding occurs and should be expected (average 9-16 days, may be ≥30 days). In some cases, bleeding may be prolonged and heavy, potentially leading to hypovolemic shock; the manufacturer cites soaking through two thick sanitary pads per hour for two consecutive hours as an example of excessive bleeding. Bleeding may require blood transfusion (rare), curettage, saline infusions, and/or vasoconstrictors.

Disease-related concerns:

- Anemia: Safety and efficacy have not been established for use in women with severe anemia.

- Cardiovascular disease: Safety and efficacy have not been established for use in women with chronic cardiovascular disease as well as hypertension.

- Diabetes: Safety and efficacy have not been established for use in women with insulin-dependent diabetes mellitus.

- Hepatic impairment: Safety and efficacy have not been established for use in women with hepatic impairment.

- Renal impairment: Safety and efficacy have not been established for use in women with renal impairment.

- Respiratory disease: Safety and efficacy have not been established for use in women with respiratory disease.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Smokers: Use with caution in patients who are heavy smoker (>10 cigarettes/day); these patients were excluded from clinical trials.

- Women >35 years: Use with caution in women >35 years; these patients were excluded from clinical trials.

Other warnings/precautions:

- Confirmation of terminated pregnancy: 14 days following treatment confirmation of pregnancy termination by clinical exam or ultrasound must be made. Manufacturer recommends surgical termination of pregnancy when medical termination fails or is not complete. Prescriber should determine in advance whether they will provide such care themselves or through other providers. Preventative measures to prevent rhesus immunization must be taken prior to surgical abortion.

- Ectopic pregnancy: Ultrasound should be used if an ectopic pregnancy is suspected or if duration of pregnancy is uncertain. Ultrasonography may not identify all ectopic pregnancies, and healthcare providers should be alert for signs and symptoms which may be related to undiagnosed ectopic pregnancy in any patient who receives mifepristone.

- Experienced physician: To be administered only by physicians who can date pregnancy, diagnose ectopic pregnancies, provide access to surgical abortion (if needed), and can provide access to emergency care. Medication will be distributed directly to these physicians following signed agreement with the distributor. Must be administered under supervision by the qualified physician.

- Medication guide: **[U.S. Boxed Warning]: Patients undergoing treatment with mifepristone should be instructed to bring their Medication Guide with them when an obtaining treatment from an emergency room or healthcare provider that did not prescribe the medication initially in order to identify that they are undergoing a medical abortion.**

- Patient instruction: **[U.S. Boxed Warning]: Patient must be instructed of the treatment procedure and expected effects.** A signed agreement form must be kept in the patient's file. Physicians may obtain patient agreement forms, physician enrollment forms, and medical consultation directly from Danco Laboratories at 1-877-432-7596. Prescriber should also give the patient clear instructions on whom to call and what to do in the event of an emergency following administration of therapy.

- Pregnancy dating: Pregnancy is dated from day 1 of last menstrual period (presuming a 28-day cycle, ovulation occurring midcycle). Pregnancy duration can be determined using menstrual history and clinical examination. Ultrasound should be used if duration of pregnancy is uncertain.

- Reporting of adverse effects: Adverse effects (including blood transfusions, hospitalization, ongoing pregnancy, and other major complications) must be reported in writing to the medication distributor.

Pregnancy Risk FactorX

Pregnancy ConsiderationsThis medication is used to terminate pregnancy; there are no approved treatment indications for its use during pregnancy. Prostaglandins (including mifepristone and misoprostol) may have teratogenic effects when used during pregnancy. If treatment fails, there is a risk of fetal malformation. In sexually active women, pregnancy can occur prior to the first menstrual period following treatment. Appropriate contraception can be started as soon as termination of pregnancy is confirmed or before sexual intercourse is resumed.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsBreast milk should be discarded for a few days following use of this medication.

Adverse ReactionsVaginal bleeding and uterine cramping are expected to occur when this medication is used to terminate a pregnancy; 90% of women using this medication for this purpose also report adverse reactions. Bleeding or spotting occurs in most women for a period of 9-16 days. Up to 8% of women will experience some degree of bleeding or spotting for 30 days or more. In some cases, bleeding may be prolonged and heavy, potentially leading to hypovolemic shock.

>10%:

Central nervous system: Headache (2% to 31%), dizziness (1% to 12%)

Gastrointestinal: Abdominal pain (cramping) (96%), nausea (43% to 61%), vomiting (18% to 26%), diarrhea (12% to 20%)

Genitourinary: Uterine cramping (83%)

1% to 10%:

Cardiovascular: Syncope (1%)

Central nervous system: Fatigue (10%), fever (4%), insomnia (3%), anxiety (2%), fainting (2%)

Gastrointestinal: Dyspepsia (3%)

Genitourinary: Uterine hemorrhage (5%), vaginitis (3%), pelvic pain (2%), endometriosis/salpingitis/pelvic inflammatory disease (1%)

Hematologic: Decreased hemoglobin >2 g/dL (6%), anemia (2%), leukorrhea (2%)

Neuromuscular & skeletal: Back pain (9%), rigors (3%), leg pain (2%), weakness (2%)

Respiratory: Sinusitis (2%)

Miscellaneous: Viral infection (4%)

<1%: Significant ALT/AST, alkaline phosphatase, and GT changes have been reported rarely

Postmarketing and/or case reports: Adult respiratory distress syndrome (ADRS), allergic reaction including urticaria and hives, bacterial infection (including an ectopic bacteria such as *Clostridium sordellii*), Crohn's disease (exacerbation), disseminated intravascular coagulopathy (DIC), dyspnea, hypotension, lightheadedness, loss of consciousness, MI, pancreatitis (acute), postabortal infection, QT prolongation, ruptured ectopic pregnancy, sepsis, septic shock, sickle cell crisis (exacerbation), tachycardia, toxic shock syndrome

In trials for unresectable meningioma, the most common adverse effects included fatigue, hot flashes, gynecomastia or breast tenderness, hair thinning, and rash. In premenopausal women, vaginal bleeding may be seen shortly after beginning therapy and cessation of menses is common. Thyroiditis and effects related to antiglucocorticoid activity have also been noted.

Oncology: VesicantNo
Oncology: Emetic PotentialMild
Metabolism/Transport Effects**Substrate** of CYP3A4 (minor); **Inhibits** CYP2D6 (weak), 3A4 (weak)
Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb Interactions

Food: Do not take with grapefruit juice; grapefruit juice may inhibit mifepristone metabolism leading to increased levels.

Herb/Nutraceutical: Avoid St John's wort (may induce mifepristone metabolism, leading to decreased levels).

Test InteractionshCG levels will not be useful to confirm pregnancy termination until at least 10 days following mifepristone treatment
Monitoring ParametersClinical exam and/or ultrasound to confirm complete termination of pregnancy; hemoglobin, hematocrit, and red blood cell count in cases of heavy bleeding. Consider CBC in any patient who reports nausea, vomiting, or diarrhea and weakness with or without abdominal pain, and without fever or other signs of infection more than 24 hours after administration of misoprostol.
Nursing: Physical Assessment/MonitoringMay only be administered under supervision of a qualified physician. Patient must be instructed in procedure and sign patient agreement forms. Assess results of laboratory tests and adverse reactions. Monitor for excessive bleeding. Monitor vital signs. Assess knowledge/teach patient interventions to reduce side effects, and adverse reactions to report. **Pregnancy risk factor X:** This medication is used to terminate pregnancy.
Monitoring: Lab TestsConsider CBC in any patient who reports nausea, vomiting, or diarrhea and weakness with or without abdominal pain, and without fever or other signs of infection more than 24 hours after administration of misoprostol.
Patient EducationThis medication is used to terminate pregnancy under 7 weeks. It must be administered under direction of a qualified physician. You will need follow-up visits as directed by your prescriber (approximately 3 days and 14 days after treatment). Surgical termination of pregnancy may be required if medication fails; there is a risk of fetal malformation if treatment fails. You may experience vaginal bleeding and cramping that is heavier than a normal menstrual period; report immediately if severe or persistent. You may experience nausea, vomiting, and diarrhea. It is possible to get pregnant before your next period. Once the pregnancy has proved to be ended, contraception should be started before having sexual intercourse. Read carefully all information about this medication provided by your prescriber. **Pregnancy/breast-feeding precautions:** Your physician will give you a phone number to call for problems, questions, or emergencies; you should not use this medication if you do not have access to emergency care. You will be given a medication guide to help you understand this medication and its effects. It is important to review this carefully. Ask any questions you may have. You will also be required to sign a form saying that you understand the effects of this treatment and are able to return to the physician for follow-up appointments. Do not breast-feed. Discard breast milk for a few days following use of this medication.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 200 mg

Generic AvailableNo
ManufacturerDanco Laboratories
Mechanism of ActionMifepristone, a synthetic steroid, competitively binds to the intracellular progesterone receptor, blocking the effects of

progesterone. When used for the termination of pregnancy, this leads to contraction-inducing activity in the myometrium. In the absence of progesterone, mifepristone acts as a partial progesterone agonist. Mifepristone also has weak antiglucocorticoid and antiandrogenic properties; it blocks the feedback effect of cortisol on corticotropin secretion.

Pharmacodynamics/Kinetics

Absorption: Oral: rapid

Protein binding: 98% to albumin and α_1-acid glycoprotein

Metabolism: Hepatic via CYP3A4 to three metabolites (may possess some antiprogestin and antiglucocorticoid activity)

Bioavailability: Oral: 69%

Half-life elimination: Terminal: 18 hours following a slower phase where 50% eliminated between 12-72 hours

Time to peak: Oral: 90 minutes

Excretion: Feces (83%); urine (9%)

Pharmacotherapy PearlsMedication will be distributed directly to qualified physicians following signed agreement with the distributor, Danco Laboratories. It will not be available through pharmacies. Major adverse reactions (hospitalization, blood transfusion, ongoing pregnancy, etc) should be reported to Danco Laboratories.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, fatigue, insomnia, or anxiety

Mental Health: Effects on Psychiatric TreatmentGastrointestinal side effects are common; use caution with lithium, valproic acid, and SSRIs. Fluoxetine, fluvoxamine, and nefazodone may increase mifepristone serum levels and/or toxicity; monitor. Carbamazepine, phenobarbital, and St John's wort may increase the metabolism of mifepristone, resulting in decreased mifepristone levels and/or effect; monitor.

Index TermsRU-38486; RU-486

References

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Spitz IM and Bardin CW, “Mifepristone (RU486) - A Modulator of Progestin and Glucocorticoid Action,” *N Engl J Med*, 1993, 329(6):404-12.[PubMed 8326975]

International Brand NamesMifegyne (BE, CH, DE, DK, EE, FI, FR, GB, IL, NL, NO, NZ, SE); Mifonewle (CL); Unwanted (IN)

Miglitol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(MIG li tol)

U.S. Brand NamesGlyset®

Canadian Brand NamesGlyset®

Pharmacologic CategoryAntidiabetic Agent, Alpha-Glucosidase Inhibitor

Use: Labeled IndicationsType 2 diabetes mellitus (noninsulin-dependent, NIDDM):

Monotherapy adjunct to diet to improve glycemic control in patients with type 2 diabetes mellitus (noninsulin-dependent, NIDDM) whose hyperglycemia cannot be managed with diet alone

Combination therapy with a sulfonylurea when diet plus either miglitol or a sulfonylurea alone do not result in adequate glycemic control. The effect of miglitol to enhance glycemic control is additive to that of sulfonylureas when used in combination.

Dosing: Adults**Type 2 diabetes (noninsulin dependent, NIDDM):** Oral: 25 mg 3 times/day with the first bite of food at each meal; the dose may be increased to 50 mg 3 times/day after 4-8 weeks; maximum recommended dose: 100 mg 3 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentMiglitol is primarily excreted by the kidneys; there is little information of miglitol in patients with a Cl_{cr} <25 mL/minute.

Dosing: Hepatic ImpairmentNo adjustment necessary.

Administration: OralShould be taken orally at the start (with the first bite) of each main meal.

ContraindicationsHypersensitivity to miglitol or any of component of the formulation; diabetic ketoacidosis; inflammatory bowel disease; colonic ulceration; partial intestinal obstruction or predisposition to intestinal obstruction; chronic intestinal diseases associated with marked disorders of digestion or absorption or with conditions that may deteriorate as a result of increased gas formation in the intestine

Warnings/Precautions

Concerns related to adverse effects:

- GI symptoms: Most common reactions are gastrointestinal related; incidence of abdominal pain and diarrhea tend to diminish considerably with continued treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment (serum creatinine >2 mg/dL); studies in this population have not been conducted and treatment is not recommended.

- Stress-related states: It may be necessary to discontinue miglitol and administer insulin if the patient is exposed to stress (ie, fever, trauma, infection, surgery).

Concurrent drug therapy issues:

- Sulfonylureas: In combination with a sulfonylurea will cause a further lowering of blood glucose and may increase the hypoglycemic potential of the sulfonylurea.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsIn a double-blind randomized, placebo-controlled trial, glyburide caused significantly greater reductions in hemoglobin A_{1c} compared to miglitol 25 mg or 50 mg three times per day, but was associated with more weight gain. Diarrhea, soft stools, and flatulence were more common with miglitol. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been reported in animal reproduction studies; therefore, miglitol is classified as pregnancy category B. Information specific to the use of miglitol during pregnancy has not been located. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

LactationEnters breast milk (small amounts)/not recommended

Breast-Feeding ConsiderationsMiglitol is found in breast milk. The exposure to a nursing infant is ~0.4% of a 100 mg maternal dose. Breast-feeding is not recommended by the manufacturer.

Pregnancy & Lactation, In-Depth

- Miglitol in Pregnancy & Lactation

Adverse Reactions

>10%: Gastrointestinal: Flatulence (42%), diarrhea (29%), abdominal pain (12%)

1% to 10%: Dermatologic: Rash

Drug Interactions

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Monitoring ParametersMonitor therapeutic response by periodic blood glucose tests; measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests, therapeutic effectiveness, and adverse response on a regular basis throughout therapy. Teach patient proper use (or refer patient to diabetic educator), possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report.

Monitoring: Lab TestsBlood glucose tests; measurement of glycosylated hemoglobin is recommended for the monitoring of long-term glycemic control.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. Take exactly as directed, with the first bite of each main meal. Do not change dosage or discontinue without first consulting prescriber. Avoid alcohol. It is important to follow dietary and lifestyle recommendations of prescriber. You will be instructed in signs of hypo- or hyperglycemia by prescriber or diabetic educator. If combining this medication with other diabetic medication (eg, sulfonylureas, insulin), keep source of glucose in the form of dextrose (NOT table sugar, candy, or cookies) on hand in case hypoglycemia occurs. May cause mild side effects during first weeks of therapy (eg, bloating, flatulence, diarrhea, abdominal discomfort); these should diminish over time. Report severe or persistent side effects, fever, extended vomiting or flu, or change in color of urine or stool. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 25 mg, 50 mg, 100 mg

Generic AvailableNo

ManufacturerPharmacia & Upjohn

Pricing: U.S. (www.drugstore.com)

Tablets (Glyset)

25 mg (90): $87.99

50 mg (90): $96.80

100 mg (90): $109.99

Mechanism of ActionIn contrast to sulfonylureas, miglitol does not enhance insulin secretion; the antihyperglycemic action of miglitol results from a reversible inhibition of membrane-bound intestinal alpha-glucosidases which hydrolyze oligosaccharides and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. In patients with diabetes, this enzyme inhibition results in delayed glucose absorption and lowering of postprandial hyperglycemia.

Pharmacodynamics/Kinetics

Absorption: Saturable at high doses: 25 mg dose: Completely absorbed; 100 mg dose: 50% to 70% absorbed

Distribution: V_d: 0.18 L/kg

Protein binding: <4%

Metabolism: None

Half-life elimination: ~2 hours

Time to peak: 2-3 hours

Excretion: Urine (as unchanged drug)

Related Information

- Diabetes Mellitus Management, Adults

Dental Health: Effects on Dental TreatmentAlthough miglitol does not cause hypoglycemia, it is frequently used in combination and may complicate the management of hypoglecemic episodes caused by other medications. As part of its therapeutic effect, miglitol slows the absorption of complex sugars or disaccharides such as sucrose. This would delay effective treatment of hypoglycemia. Simple sugars, including glucose (dextrose), are not affected. If a patient experiences hypoglycemia, use of food items such as table sugar, candy, or cookies will NOT effectively increase blood glucose. Administration of oral glucose is required in mild-moderate hypoglycemia, and parenteral glucose is required for severe hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with SSRIs, carbamazepine, valproic acid, and lithium may produce additive effects

References

American Diabetes Association, “Standards of Medical Care in Diabetes Mellitus -- 2009,” *Diabetes Care*, 2009, 32(Suppl 1):13-61.[PubMed 19118286]

International Brand NamesDiamig (IT); Diastabol (AT, CH, CZ, DE, FI, FR, HN, MX, NL, PL, SE); Plumarol (ES)

Miglustat

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(MIG loo stat)
U.S. Brand NamesZavesca®
Canadian Brand NamesZavesca®
Pharmacologic CategoryEnzyme Inhibitor
Use: Labeled IndicationsTreatment of mild-to-moderate type 1 Gaucher disease when enzyme replacement therapy is not a therapeutic option
Dosing: Adults**Type 1 Gaucher disease:** Oral: 100 mg 3 times/day; dose may be reduced to 100 mg 1-2 times/day in patients with adverse effects (ie, tremor, GI distress)
Dosing: ElderlyRefer to adult dosing.
Dosing: Renal Impairment

Cl_{cr} 50-75 mL/minute: 100 mg twice daily

Cl_{cr} 30-50 mL/minute: 100 mg once daily

Cl_{cr} <30 mL/minute: Not recommended

Calculations

- Creatinine Clearance: Adults

Administration: OralCapsules should be swallowed whole and taken at the same time each day. May be taken with or without food.
Dietary ConsiderationsMay be taken with or without food. Patients with diarrhea should avoid foods with high carbohydrate content.
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).
ContraindicationsHypersensitivity to miglustat or any component of the formulation; pregnancy
Warnings/Precautions

Concerns related to adverse effects:

- Diarrhea: Observed in the majority of patients, many also reported weight loss. Incidence decreases over time; foods with high carbohydrate content should be avoided. If symptoms persist, patients should be evaluated for underlying GI disease.

- Peripheral neuropathy: Has been reported; neurologic monitoring is required. Weigh risk versus benefit of therapy if patient develops numbness and tingling.

- Tremor: Exacerbations of existing tremor or tremor may occur; may resolve over time or respond to dosage reduction.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustments recommended. Not recommended in patients with severe impairment.

- Severe type 1 Gaucher disease: Safety and efficacy have not been established in severe type 1 Gaucher disease.

Concurrent drug therapy issues:

- Imiglucerase: Miglustat increases the clearance of imiglucerase; combination therapy is not indicated.

Pregnancy Risk FactorX
Pregnancy ConsiderationsDecreased fetus weight, fetal loss, and difficult or delayed births were observed in animal studies. Women with reproduction potential should use effective contraception during therapy. In addition, adverse effects on spermatogenesis and reduced fertility were observed in male animal studies. The manufacturer recommends that male patients use reliable contraception during therapy and for 3 months following treatment.
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsPercentages reported from open-label, uncontrolled monotherapy trials.

>10%:

Central nervous system: Headache (21% to 22%), dizziness (up to 11%)

Gastrointestinal: Diarrhea (89% to 100%), weight loss (39% to 67%), abdominal pain (18% to 67%), flatulence (29% to 50%), nausea (8% to 22%), vomiting (4% to 11%)

Neuromuscular & skeletal: Tremor (11% to 30%), weakness (17%), leg cramps (4% to 11%)

Ocular: Visual disturbances (up to 17%)

1% to 10%:

Central nervous system: Memory impairment (8%), migraine (up to 6%)

Endocrine & metabolic: Menstrual disorder (up to 6%)

Gastrointestinal: Constipation (8%), xerostomia (8%), bloating (up to 8%), anorexia (up to 7%), dyspepsia (up to 7%), epigastric pain (up to 6%)

Hematologic: Thrombocytopenia (6% to 7%)

Neuromuscular & skeletal: Paresthesia (up to 7%)

Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb Interactions

Food: Food decreases the rate, but not the extent, of absorption.

Monitoring ParametersNeurologic evaluations baseline and repeated every 6 months; adverse effects; weight
Nursing: Physical Assessment/MonitoringUse caution with renal impairment. Not to be used in combination with imiglucerase. Assess results of neurological evaluations at beginning of therapy and every 6 months during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (tremor, peripheral neuropathy). **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Do not give to women of childbearing age or males who may have intercourse with childbearing age females unless they are capable of complying with effective contraceptive measures during therapy. Men should continue contraceptive measures for 3 months following treatment.
Patient EducationCapsules should be swallowed whole and taken at the same time each day, with or without food. May cause headache and dizziness (use caution when driving or engaging in hazardous tasks until response to drug is known); nausea, vomiting, or loss of appetite (small, frequent meals and good mouth care may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Notify prescriber at once of persistent diarrhea, numbness or tingling in extremities, change in vision, or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug can cause fetal abnormalities. Both females and males should use (consult prescriber) appropriate contraception during therapy. Males should continue contraceptive use for 3 months following therapy. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Zavesca®: 100 mg

Generic AvailableNo
ManufacturerAlmac Pharma Services; marketed by Actelion Pharmaceuticals
Mechanism of ActionMiglustat competitively and reversibly inhibits the enzyme needed to produce glycosphingolipids and decreases the rate of glycosphingolipid glucosylceramide formation. Glucosylceramide accumulates in type 1 Gaucher disease, causing complications specific to this disease.
Pharmacodynamics/Kinetics

Distribution: V_d: 83-105 L

Protein binding: No binding to plasma proteins

Metabolism: No evidence of metabolism in humans

Bioavailability: 97%

Half-life elimination: 6-7 hours

Time to peak, plasma: 2-2.5 hours

Excretion: Urine (as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDizziness is common
Mental Health: Effects on Psychiatric TreatmentGI side effects are common; use caution with SSRIs
Index TermsOGT-918
International Brand NamesZavesca (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IL, IT, NL, NO, PT, RU, SE, TR, TW)

Milnacipran

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Savella™ may be confused with cevimeline, sevelamer

Pronunciation(mil NAY ci pran)

U.S. Brand NamesSavella™

Pharmacologic CategoryAntidepressant, Serotonin/Norepinephrine Reuptake Inhibitor

Use: Labeled IndicationsManagement of fibromyalgia

Dosing: Adults**Fibromyalgia:** Oral: 50 mg twice daily (maximum dose: 200 mg/day). **Note:** Recommended titration schedule: 12.5 mg once on day one, then 12.5 mg twice daily on days 2-3, 25 mg twice daily on days 4-7, then 50 mg twice daily thereafter.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Mild renal impairment: No dose adjustment is recommended.

Moderate renal impairment: Use with caution.

Severe renal impairment (Cl_{cr} ≤29 mL/minute): Reduce maintenance dose to 25 mg twice daily; dose may be increased to 50 mg twice daily, based on individual tolerance.

End-stage renal disease (ESRD): Use not recommended.

Dosing: Hepatic Impairment

Mild-to-moderate hepatic impairment: No dose adjustment is recommended.

Severe hepatic impairment: Use with caution.

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered with or without food; food may improve tolerability.

Dietary ConsiderationsMay be taken with or without food; food may improve tolerability.

StorageStore at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

RestrictionsAn FDA-approved medication guide is available. Distribute to each patient to whom this medication is dispensed.

ContraindicationsConcomitant use or within 2 weeks of MAO inhibitors; uncontrolled narrow-angle glaucoma

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See "Major psychiatric warnings" below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor for clinical worsening, suicidality, or unusual changes in behavior; the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants in children and teenagers should be dispensed with each prescription. **Milnacipran is not FDA approved for the treatment of major depressive disorder or for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Milnacipran is not FDA approved for the treatment of bipolar disorder.**

Concerns related to adverse effects:

- Bleeding risk: May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin or NSAIDs due to ulcerogenic potential. Data are inconclusive regarding extent of bleeding risk of SNRIs in combination with warfarin or other anticoagulants. Bleeding related to SNRI use has been reported to range from relatively minor bruising and epistaxis to life-threatening hemorrhage.

- Cardiovascular effects: May increase blood pressure and heart rate; blood pressure and heart rate should be evaluated prior to initiating therapy and periodically thereafter; consider dose reduction or gradual discontinuation of therapy in individuals with sustained hypertension or tachycardia during therapy; use with caution in patients with pre-existing hypertension, tachyarrhythmias (eg, atrial fibrillation), or other cardiovascular disease.

- Hepatotoxicity: Avoid use in patients with substantial ethanol intake, evidence of chronic liver disease or hepatic impairment. Cases of increased liver enzymes and severe liver injury (including fulminant hepatitis) have been reported. Discontinue therapy with the presentation of jaundice or other signs of hepatic dysfunction and do not reinitiate therapy unless another source or cause is identified.

- SIADH and hyponatremia: SSRIs and SNRIs have been associated with the development of SIADH; hyponatremia has been reported rarely (including severe cases with serum sodium <110 mmol/L), predominately in the elderly. Volume depletion and/or concurrent use of diuretics likely increases risk.

- Urinary hesitancy: May cause increased urinary resistance; advise patient to report symptoms of urinary hesitation/difficulty.

Disease-related concerns:

- Narrow-angle glaucoma: Associated with an increased risk of mydriasis in patients with controlled narrow-angle glaucoma.

- Seizure disorders: Use caution with a previous seizure disorder or condition predisposing to seizures such as brain damage or alcoholism.

Concurrent drug therapy issues:

- MAO inhibitors: Potential for severe reaction when used with MAO inhibitors; autonomic instability, coma, death, delirium, diaphoresis, hyperthermia, mental status changes/agitation, muscular rigidity, myoclonus, neuroleptic malignant syndrome features, and seizures may occur. Do not use milnacipran in combination with an MAO inhibitor or within 14 days of discontinuing an MAO inhibitor; do not start an MAO inhibitor until ≥5 days after discontinuing milnacipran.

- Serotonin modulators: Serotonin syndrome with symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, nausea/vomiting, diarrhea, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce milnacipran's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

Special populations:

- Elderly: Use caution in elderly patients; risk of hyponatremia may be increased.

- Pediatrics: Safety and efficacy have not been established in children <17 years of age.

Dosage form specific issues:

- Tartrazine: Contains tartrazine (FD&C Yellow No. 5); may cause allergic reactions (eg, bronchial asthma) in susceptible individuals.

Other warnings/precautions:

- Withdrawal syndrome: May cause dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. To discontinue therapy with milnacipran, gradually taper dose. If intolerable symptoms occur following a decrease in dosage or upon discontinuation of therapy, then resuming the previous dose with a more gradual taper should be considered.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefits justify the risks.

Nonteratogenic effects in the newborn following SSRI/SNRI exposure late in the third trimester include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hyper- or hypotonia, hyper-reflexia, jitteriness, irritability, constant crying, and tremor. The long-term effects on neurobehavior have not been studied.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is unknown if milnacipran is excreted in human milk; there are no adequate and well-controlled studies in nursing mothers. Animal studies have shown milnacipran or its metabolites excreted in breast milk. Use during lactation only if the potential benefits to the mother outweigh the potential risks to the infant.

Adverse Reactions

>10%:

Central nervous system: Headache (18%), insomnia (12%)

Endocrine & metabolic: Hot flashes (12%)

Gastrointestinal: Nausea (37%), constipation (16%)

1% to 10%:

Cardiovascular: Palpitation (7%), heart rate increased (6%), hypertension (5%), flushing (3%), blood pressure increased (3%), tachycardia (2%), peripheral edema (≥1%)

Central nervous system: Dizziness (10%), migraine (5%), chills (2%), tremor (2%), depression (≥1%), fatigue (≥1%), fever (≥1%), irritability (≥1%), somnolence (≥1%)

Dermatologic: Hyperhidrosis (9%), rash (3%)

Endocrine & metabolic: Hypercholesterolemia (≥1%)

Gastrointestinal: Vomiting (7%), xerostomia (5%), abdominal pain (3%), appetite decreased (2%), abdominal distension (≥1%), abnormal taste (≥1%), diarrhea (≥1%), dyspepsia (≥1%), flatulence (≥1%), gastroesophageal reflux disease (≥1%)

Genitourinary: Dysuria (≥2%), ejaculation disorder/failure (≥2%), erectile dysfunction (≥2%), libido decreased (≥2%), prostatitis (≥2%), scrotal pain (≥2%), testicular pain (≥2%), testicular swelling (≥2%), urethral pain (≥2%), urinary hesitation (≥2%), urinary retention (≥2%), urine flow decreased (≥2%), cystitis (≥1%), urinary tract infection (≥1%)

Neuromuscular & skeletal: Falling (≥1%)

Ocular: Blurred vision (2%)

Respiratory: Dyspnea (2%)

Miscellaneous: Night sweats (≥1%)

<1%, postmarketing, and/or case reports: Accommodation disorder, acute renal failure, anorexia, delirium, erythema multiforme, galactorrhea, hallucination, hepatitis, hyperprolactinemia, hypertensive crisis, hyponatremia, leukopenia, loss of consciousness, neuroleptic malignant syndrome, neutropenia, parkinsonism, rhabdomyolysis, seizures, serotonin syndrome, Stevens-Johnson syndrome, supraventricular tachycardia, thrombocytopenia

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha-/Beta-Agonists: Serotonin/Norepinephrine Reuptake Inhibitors may enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Alpha2-Agonists: Serotonin/Norepinephrine Reuptake Inhibitors may diminish the antihypertensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk C: Monitor therapy*

Aspirin: Serotonin/Norepinephrine Reuptake Inhibitors may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

ClomiPRAMINE: May enhance the adverse/toxic effect of Milnacipran. Specifically, the incidence of euphoria and postural hypotension were higher in patients changing from clomipramine to milnacipran. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Digoxin: Milnacipran may enhance the adverse/toxic effect of Digoxin. The risk of postural hypotension and tachycardia may be increased, particularly with IV digoxin. Management: Avoid concurrent use of intravenous (IV) digoxin in patients receiving milnacipran. Use caution when using oral digoxin and milnacipran together, monitoring closely for possible postural hypotension and tachycardia. *Risk D: Consider therapy modification*

Iobenguane I 123: Serotonin/Norepinephrine Reuptake Inhibitors may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

NSAID (Nonselective): Serotonin/Norepinephrine Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol use.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava, tryptophan (may increase risk of serotonin syndrome and/or excessive sedation).

Monitoring ParametersBlood pressure and heart rate should be regularly monitored; renal function should be monitored for dosing purposes; mental status for suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased); intraocular pressure should be monitored in those with baseline elevations or a history of glaucoma

Monitoring: Lab TestsRenal function should be monitored for dosing purposes

Product AvailabilitySavella™: FDA approved January 2009; availability anticipated in March 2009

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Savella™: 12.5 mg, 25 mg, 50 mg, 100 mg

Generic AvailableNo

ManufacturerForest Laboratories, Inc

Mechanism of ActionPotent inhibitor of norepinephrine and serotonin reuptake (3:1). Milnacipran has no significant activity for serotonergic, alpha- and beta-adrenergic, muscarinic, histaminergic, dopaminergic, opiate, benzodiazepine, and GABA receptors. It does not possess MAO-inhibitory activity.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: I.V: V_d: ~400 L

Protein binding: 13%

Metabolism: Hepatic to inactive metabolites

Bioavailability: 85% to 90%

Half-life elimination: 6-8 hours

Time to peak, plasma: Oral: 2-4 hours

Excretion: Urine (55% as unchanged drug)

References

Gendreau RM, Thorn MD, Gendreau JF, et al, “Efficacy of Milnacipran in Patients With Fibromyalgia,” *J Rheumatol*, 2005, 32(10):1975-85.[PubMed 16206355]

Vitton O, Gendreau M, Gendreau J, et al, “A Double-Blind Placebo-Controlled Trial of Milnacipran in the Treatment of Fibromyalgia,” *Hum Psychopharmacol*, 2004, 19(Suppl 1):27-35.[PubMed 15378666]

Milrinone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Primacor® may be confused with Primaxin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(MIL ri none)

U.S. Brand NamesPrimacor®

Canadian Brand NamesMilrinone Lactate Injection; Primacor®

Pharmacologic Category[Phosphodiesterase Enzyme Inhibitor]()

Use: Labeled IndicationsShort-term I.V. therapy of acutely-decompensated heart failure

Use: Unlabeled/InvestigationalInotropic therapy for patients unresponsive to other acute heart failure therapies (eg, dobutamine); outpatient inotropic therapy for heart transplant candidates; palliation of symptoms in end-stage heart failure patients who cannot otherwise be discharged from the hospital and are not transplant candidates

Dosing: Adults**CHF/Hemodynamic support:** I.V.: Loading dose (optional): 50 mcg/kg administered over 10 minutes followed by a maintenance dose titrated according to the hemodynamic and clinical response; Maintenance dose: I.V. infusion: 0.375-0.75 mcg/kg/minute.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 50 mL/minute: Administer 0.43 mcg/kg/minute.

Cl_{cr} 40 mL/minute: Administer 0.38 mcg/kg/minute.

Cl_{cr} 30 mL/minute: Administer 0.33 mcg/kg/minute.

Cl_{cr} 20 mL/minute: Administer 0.28 mcg/kg/minute.

Cl_{cr} 10 mL/minute: Administer 0.23 mcg/kg/minute.

Cl_{cr} 5 mL/minute: Administer 0.2 mcg/kg/minute.

Calculations

- [Creatinine Clearance: Adults]()
- [Milrinone]()

Administration: I.V.Infuse via infusion pump.

Administration: I.V. DetailInjectable solution and premixed solution: pH: 3.2-4.0

StorageStore at 15°C to 30°C (59°F to 86°F). Avoid freezing. Stable at 0.2 mg/mL in $^1/_2$NS, NS, or D_5W for 72 hours at room temperature in normal light.

ReconstitutionStandard dilution: For a final concentration of 0.2 mg/mL: Dilute Primacor® 1 mg/mL (20 mL) with 80 mL diluent (final volume: 100 mL) of ½ NS, NS or D_5W. May also dilute 1 mg/mL (10 mL) with 40 mL diluent (final volume: 50 mL).

CompatibilityStable in D_5W, LR, $^1/_2$NS, NS.

Y-site administration: Compatible: Atracurium, bumetanide, calcium gluconate, cimetidine, digoxin, diltiazem, dobutamine, dopamine, epinephrine, fentanyl, heparin, hydromorphone, insulin (regular), isoproterenol, labetalol, lorazepam, magnesium sulfate, midazolam, morphine, nicardipine, nitroglycerin, norepinephrine, pancuronium, potassium chloride, propofol, propranolol, quinidine gluconate, ranitidine, rocuronium, sodium bicarbonate, sodium nitroprusside, theophylline, thiopental, torsemide, vecuronium. **Incompatible:** Furosemide, imipenem-cilastin, procainamide.

Compatibility in syringe: Compatible: Atropine, calcium chloride, digoxin, epinephrine, lidocaine, morphine, propranolol, sodium bicarbonate, verapamil. **Incompatible:** Furosemide.

Compatibility when admixed: Compatible: Quinidine gluconate. **Incompatible:** Bumetanide, furosemide, procainamide.

ContraindicationsHypersensitivity to milrinone, inamrinone, or any component of the formulation; concurrent use of inamrinone

Warnings/Precautions

Concerns related to adverse effects:

- Arrhythmias: Observe for arrhythmias in this very high-risk patient population. Ventricular or atrial arrhythmias may persist even after discontinuation of inamrinone especially in patients with renal dysfunction. Ensure that ventricular rate is controlled in atrial fibrillation/flutter before initiating; may increase ventricular response rate. In heart transplant candidates, institute appropriate measures to protect patient against risks of sudden cardiac death.

- Hepatic effects: Discontinue therapy if dose-related elevations in LFTs and clinical symptoms of hepatotoxicity occur; monitor liver function.

- Hypotension: Monitor blood pressure/ heart rate closely. Mean arterial pressure decreases by ~5% at doses between 0.375-5 mcg/kg/minute and by 17% at 0.75 mcg/kg/minute (includes loading doses ranging between 37.5-75 mcg/kg). Infusion may require reduction in dose or temporary discontinuation if hypotension occurs. Hypotension may be prolonged especially in patients with renal dysfunction. Vigorous diuresis may contribute to hypotension; cautious administration of fluids may be required to prevent hypotension.

Disease-related concerns:

- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.

- Myocardial infarction (MI): Not recommended in acute MI treatment.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended. Hypotension may be prolonged in patients with renal dysfunction.

Other warnings/precautions:

- Long-term therapy: According to the ACC/AHA chronic heart failure 2005 guidelines, long-term, regularly-scheduled intermittent infusions are strongly discouraged.

- Monitoring: Monitor fluid status closely; patients may require adjustment of diuretic and electrolyte replacement therapy.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%: Cardiovascular: Ventricular arrhythmia (ectopy 9%, NSVT 3%, sustained ventricular tachycardia 1%, ventricular fibrillation <1%)

1% to 10%:

Cardiovascular: Supraventricular arrhythmia (4%), hypotension (3%), angina/chest pain (1%)

Central nervous system: Headache (3%)

<1% (Limited to important or life-threatening): Atrial fibrillation, hypokalemia, MI, thrombocytopenia, tremor, ventricular fibrillation

Postmarketing and/or case reports: Anaphylaxis, bronchospasm, injection site reaction, liver function abnormalities, rash, torsade de pointes

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersPlatelet count, CBC, electrolytes (especially potassium and magnesium), liver function and renal function tests; ECG, CVP, SBP, DBP, heart rate; infusion site

If pulmonary artery catheter is in place, monitor cardiac index, stroke volume, systemic vascular resistance, pulmonary capillary wedge pressure and pulmonary vascular resistance.

Nursing: Physical Assessment/MonitoringUse infusion pump. Monitor cardiac/hemodynamic status continuously during therapy and serum potassium at regular intervals. Monitor for fluid retention.
Monitoring: Lab TestsPlatelet count, CBC, electrolytes (especially potassium and magnesium), liver function and renal function tests
Patient EducationThis drug can only be given intravenously. If you experience increased urination, call for assistance. Weigh daily; report weight gain of 3-5 pounds/week. Report pain at infusion site; numbness, tingling, or swelling of extremities; or respiratory difficulty.
Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Infusion [premixed in D_5W]: 200 mcg/mL (100 mL, 200 mL)

Primacor®: 200 mcg/mL (200 mL)

Injection, solution: 1 mg/mL (10 mL, 20 mL, 50 mL)

Generic AvailableYes
ManufacturerSanofi Winthrop Pharmaceuticals
Mechanism of ActionA selective phosphodiesterase inhibitor in cardiac and vascular tissue, resulting in vasodilation and inotropic effects with little chronotropic activity.
Pharmacodynamics/Kinetics

Onset of action: I.V.: 5-15 minutes

Distribution: V_{dss}: 0.32-0.45 L/kg

Protein binding, plasma: ~70%

Metabolism: Hepatic (12%)

Half-life elimination: ~2.5 hours

Excretion: Urine (85% as unchanged drug) within 24 hours; active tubular secretion is a major elimination pathway for milrinone

Related Information

- Hemodynamic Support, Intravenous

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentMay cause hypotension; concurrent use with a psychotropic may further this risk; monitor. May rarely cause thrombocytopenia; use caution with valproic acid; monitor.
Cardiovascular ConsiderationsMilrinone may be useful for severe CHF patients on a beta-blocker and require an I.V. inotrope. Long-term use of phosphodiesterase enzyme inhibitor therapy in heart failure provides some symptomatic relief but is associated with clear cut increases in mortality. Milrinone has been used for short-term improvement in hemodynamics. Chronic administration of milrinone does not confer beneficial effects on cardiovascular morbidity and mortality.
Anesthesia and Critical Care Concerns/Other ConsiderationsIf hypotension is a problem, loading doses may be omitted and maintenance infusions initiated. There is some delay in hemodynamic effects, but it is minimal (1-3 hours). Lower initial maintenance infusions have also been used (0.18-0.25 mcg/kg/minute).
Index TermsMilrinone Lactate
References

Adams KF, Lindenfeld J, Arnold JMO, et al, “HFSA 2006 Comprehensive Heart Failure Practice Guideline,” *J Card Fail*, 2006, 12(1):e1–122. Available at http://www.heartfailureguideline.org[PubMed 16500560]

Aronoff GR, Bennett WM, Berns JS, et al, *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*, 5th ed. Philadelphia, PA: American College of Physicians; 2007, p 45, 145.

Baruch L, Patacsil P, Hameed A, et al, “Pharmacodynamic Effects of Milrinone With and Without a Bolus Loading Infusion,” *Am Heart J*, 2001, 141(2):266-73. [PubMed 11174341]

Cuffe MS, Califf RM, Adams KF Jr, et al, “Short-Term Intravenous Milrinone for Acute Exacerbation of Chronic Heart Failure: A Randomized Controlled Trial,” *JAMA*, 2002, 287(12):1541-7.[PubMed 11911756]

Cusick DA, Pfeifer PB, and Quigg RJ, “Effects of Intravenous Milrinone Followed by Titration of High-Dose Vasodilator Therapy on Clinical Outcome and Rehospitalization Rates in Patients With Severe Heart Failure,” *Am J Cardiol*, 1998, 82(9):1060-5. [PubMed 9817482]

Felker GM, Benza RL, Chandler AB, et al, “Heart Failure Etiology and Response to Milrinone in Decompensated Heart Failure: Results From the OPTIME-CHF Study,” *J Am Coll Cardiol*, 2003, 41(6):997-1003. [PubMed 12651048]

Hatzizacharias A, Makris T, Krespi P, et al, “Intermittent Milrinone Effect on Long-Term Hemodynamic Profile in Patients With Severe Congestive Heart Failure,” *Am Heart J*, 1999, 138(2 Pt 1):241-6. [PubMed 10426834]

Hunt SA, Abraham WT, Chin MH , et al, “ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure).” Available at http://www.acc.org/qualityandscience/clinical/guidelines/failure/index.pdf.[PubMed 16160202]

Pamboukian SV, Carere RG, Webb JG, et al, “The Use of Milrinone in Pretransplant Assessment of Patients With Congestive Heart Failure and Pulmonary Hypertension,” *J Heart Lung Transplant*, 1999, 18(4):367-71. [PubMed 10226902]

Stevenson LW, “Inotropic Therapy for Heart Failure,” *N Engl J Med*, 1998, 339(25):1848-50.[PubMed 9854124]

International Brand NamesCoritrope (ID); Corotrop (AT, CH, CZ, ES, SE); Corotrope (AR, BE, CN, CO, ES, FR, GR, HN, LU, NL, PE, PL, UY, VE); Milicor (IN); Primacor (AU, BR, GB, HK, IL, IN, KP, MX, MY, PH, TH, TW)

MINE-ESHAP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's

Regimen

Mesna: I.V.: 1.33 g/m^2 concurrent with ifosfamide dose, then 500 mg orally (4 hours after ifosfamide) days 1, 2, and 3

[total dose/cycle = 4 g/m^2/1500 mg]

Ifosfamide: I.V.: 1.33 g/m^2/day days 1, 2, and 3

[total dose/cycle = 4 g/m^2]

Mitoxantrone: I.V.: 8 mg/m^2 day 1

[total dose/cycle = 8 mg/m^2]

Etoposide: I.V.: 65 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 195 mg/m^2]

Repeat cycle every 21 days for 6 cycles, followed by 3-6 cycles of ESHAP

References

Rodriguez MA, Cabanillas FC, Velasquez W, et al, âResults of a Salvage Treatment Program for Relapsing Lymphoma: MINE Consolidated With ESHAP,â *J Clin Oncol*, 1995, 13(7):1734-41.[PubMed 7602363]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's

Regimen

Mesna: I.V.: 1.33 g/m^2/day concurrent with ifosfamide dose, then 500 mg orally (4 hours after each ifosfamide infusion) days 1, 2, and 3

[total dose/cycle = 3.99 g/m^2/1500 mg]

Ifosfamide: I.V.: 1.33 g/m^2/day days 1, 2, and 3

[total dose/cycle = 3.99 g/m^2]

Mitoxantrone: I.V.: 8 mg/m^2 day 1

[total dose/cycle = 8 mg/m^2]

Etoposide: I.V.: 65 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 195 mg/m^2]

Repeat cycle every 28 days

References

Rodriguez-Monge EJ and Cabanillas F, âLong-Term Follow-up of Platinum-Based Lymphoma Salvage Regimens. The M.D. Anderson Cancer Center Experience,â *Hematol Oncol Clin North Am*, 1997, 11(5):937-47.[PubMed 9336723]

Mineral Oil

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(MIN er al oyl)

U.S. Brand NamesFleet® Mineral Oil Enema [OTC]; Kondremul® [OTC]; Liqui-Doss® [OTC] [DSC]

Pharmacologic CategoryLaxative, Lubricant

Use: Labeled IndicationsTemporary relief of occasional constipation, relief of fecal impaction; removal of barium sulfate residues following barium administration

Dosing: Adults

Constipation:

Oral: 15-45 mL/day

Kondremul®: 30-75 mL/day

Liqui-Doss®: 15-45 mL at bedtime

Rectal (Fleet® Mineral Oil): 118 mL as a single dose

Fecal impaction or following barium studies: Rectal (Fleet® Mineral Oil): 118 mL as a single dose

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Constipation:

Oral:

Children ≥1 year (practice guidelines):

Disimpaction: 15-30 mL per year of age; maximum 240 mL/day

Maintenance: 1-3 mL/kg/day; adjust to induce daily bowel movement for 1-2 months

Children 6-11 years:

Kondremul®: 10-25 mL/day

Liqui-Doss®: 5-15 mL at bedtime

Children ≥12 years: Refer to adult dosing.

Rectal (Fleet® Mineral Oil):

Children 2-12 years: 59 mL as a single dose

Children ≥12 years: Refer to adult dosing.

Fecal impaction or following barium studies: Rectal (Fleet® Mineral Oil):

Children 2-12 years: 59 mL as a single dose

Children ≥12 years: Refer to adult dosing.

Administration: Oral Oral: Mineral oil may be more palatable if refrigerated. Administer on an empty stomach in an upright position.

Kondremul®: Shake well before use.

Liqui-Doss®: Shake well before use. Prior to use, mix with 120 mL of any beverage; administer only at bedtime.

Administration: OtherRectal (Fleet® Mineral Oil): Gently insert enema rectally with patient lying on left side and left knee slightly bent, right knee drawn to chest.

Dietary ConsiderationsDo not administer with food or meals because of the risk of aspiration; prolonged administration of mineral oil may decrease absorption of lipid-soluble vitamins A, D, E, and K. Light sterile mineral oils are not for injection.

ContraindicationsPatients with colostomy or an ileostomy, appendicitis, ulcerative colitis, diverticulitis

Warnings/Precautions

Concerns related to adverse effects:

- Aspiration: Lipid pneumonitis results from aspiration of mineral oil; risk is increased in patients in prolonged supine position or conditions which interfere with swallowing or epiglottal function (eg, stroke, Parkinson's disease, Alzheimer's disease, esophageal dysmotility).

Other warnings/precautions:

- OTC labeling: Healthcare provider should be contacted in case of sudden changes in bowel habits which last over 2 weeks or if abdominal pain, nausea, vomiting, or rectal bleeding occur following use; do not use for >1 week, unless otherwise directed by healthcare provider. Do not use orally in children <6 years of age or rectally in children <2 years of age.

Geriatric Considerations Other therapies should be attempted before using mineral oil to relieve constipation to avoid complications with mineral oil; doses, if used, should begin low and should be used as infrequently as possible.

Adverse Reactions Frequency not defined.

Gastrointestinal: Abdominal cramps, diarrhea, nausea, vomiting

Respiratory: Lipid pneumonitis with aspiration

Miscellaneous: Large doses may cause anal leakage causing anal itching, irritation, hemorrhoids, perianal discomfort, soiling of clothes

Drug Interactions There are no known significant interactions.

Monitoring Parameters Monitor for response (stool frequency, consistency). Avoid use in patients who may aspirate.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, oral:

Liqui-Doss®: 13.5 mL/15 mL (480 mL) [self-emulsifying oily liquid; alcohol free, sugar free] [DSC]

Microemulsion, oral:

Kondremul®: 2.5 mL/5 mL (480 mL) [sugar free; mint flavor]

Oil, rectal [enema]:

Fleet® Mineral Oil: 100% (118 mL)

Oil, oral: 100% (30 mL, 480 mL, 3840 mL)

Oil, topical: 100% (480 mL) [light]

Generic Available Yes: Oral oil

Mechanism of Action Eases passage of stool by decreasing water absorption and lubricating the intestine; retards colonic absorption of water

Pharmacodynamics/Kinetics

Onset of action: Oral: 6-8 hours; Rectal: 2-15 minutes

Distribution: Site of action is the colon

Excretion: Feces

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment Patients with Parkinson's and Alzheimer's disease who have difficulty swallowing and are at an increased risk for aspiration may develop lipid pneumonitis.

Index Terms Heavy Mineral Oil; Liquid Paraffin; White Mineral Oil

References

Baker SS, Liptak GS, Colletti RB, et al, “Constipation in Infants and Children: Evaluation and Treatment. A Medical Position Statement of the North American Society for Pediatric Gastroenterology and Nutrition,” *J Pediatr Gastroenterol Nutr*, 1999, 29(5):612-26.[PubMed 10554136]

Constipation Guideline Committee, “Clinical Practice Guideline. Evaluation and Treatment of Constipation of Infants and Children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition,” *J Pediatr Gastroenterol Nutr*, 2006, 43(3):e1-13.[PubMed 16954945]

International Brand Names Fleet enema para Adulto (MX)

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Lymphoma, Hodgkin's Disease]

Regimen UseLymphoma, Hodgkin's disease

Regimen

Carmustine: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Etoposide: I.V.: 75 mg/m^2/day days 2 to 5

[total dose/cycle = 300 mg/m^2]

Cytarabine: I.V.: 100 mg/m^2 every 12 hours days 2 to 5 (8 doses)

[total dose/cycle = 800 mg/m^2]

Melphalan: I.V.: 30 mg/m^2 day 6

[total dose/cycle = 30 mg/m^2]

Repeat cycle every 4-6 weeks

References

Colwill R, Crump M, Couture F, et al, âMini-BEAM as Salvage Therapy for Relapsed or Refractory Hodgkin's Disease Before Intensive Therapy and Autologous Bone Marrow Transplantation,â *J Clin Oncol*, 1995, 13(2):396-402.[PubMed 7844600]

Minocycline Hydrochloride Periodontal Microspheres

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation

(mi noe SYE kleen hye droe KLOR ide pair ee oh DON tol MI kro SFEERS)

U.S. Brand NamesArestin®
Pharmacologic CategoryAntibiotic, Tetracycline Derivative
Use: DentalAdjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis. May be used as part of a periodontal maintenance program which includes good oral hygiene, scaling, and root planing.
Dosing: AdultsVariable-dose product; dependent upon the size, shape, and number of pockets being treated
Dosing: ElderlyRefer to adult dosing.
Administration: OralAdministration of Arestin® does not require local anesthesia. Professional subgingival administration is accomplished by inserting the unit-dose cartridge to the base of the periodontal pocket and then pressing the thumb ring in the handle mechanism to expel the powder while gradually withdrawing the tip from the base of the pocket. The handle mechanism should be sterilized between patients. Arestin® does not have to be removed (it is bioresorbable) nor is an adhesive dressing required.
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Avoid excessive heat.
ContraindicationsKnown hypersensitivity to minocycline, tetracyclines, or any component of the formulation
Allergy Considerations

- Tetracycline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Autoimmune syndromes: Lupus-like, hepatitis, and vasculitis autoimmune syndromes have been reported with oral minocycline use; no further treatment should be given if symptoms occur.
- Hypersensitivity reactions: Anaphylaxis, angioneurotic edema, urticaria, rash, swelling of the face, and pruritus have been reported.
- Photosensitivity: May cause photosensitivity; discontinue if skin erythema occurs. Use skin protection and avoid prolonged exposure to sunlight; do not use tanning equipment.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Special populations:

- Pediatrics: May cause tissue hyperpigmentation, enamel hypoplasia, or permanent tooth discoloration; use of tetracyclines should be avoided during tooth development (children ≤8 years of age) unless other drugs are not likely to be effective or are contraindicated.
- Pregnancy: Do not use during pregnancy. In addition to affecting tooth development, tetracycline use has been associated with retardation of skeletal development and reduced bone growth.

Other warnings/precautions:

- Appropriate use: Use in an acutely abscessed periodontal pocket has not been studied and is not recommended. The effects of treatment for >6 months have not been studied. Should be used with caution in patients having a history of predisposition to oral candidiasis. Safety and effectiveness have not been established for the treatment of periodontitis in patients with coexistent oral candidiasis. Not clinically tested in immunocompromised patients (such as those immunocompromised by diabetes, chemotherapy, radiation therapy, or infection with HIV). Not clinically tested for use in the regeneration of alveolar bone, either in preparation for or in conjunction with the placement of endosseous (dental) implants or in the treatment of failing implants.

Pregnancy Risk FactorD
Pregnancy ConsiderationsRefer to Warnings/Precautions.
LactationEnters breast milk/not recommended
Adverse Reactions

>10%: Gastrointestinal: Tooth disorder (12%)

1% to 10%:

Central nervous system: Headache (9%), pain (4%)

Gastrointestinal: Dental caries (10%), dental pain (10%), gingivitis (9%), mouth ulceration (5%), dyspepsia (4%), mucous membrane disorder (3%)

Respiratory: Pharyngitis (4%)

Miscellaneous: Infection (8%), flu-like syndrome (5%)

Postmarketing and/or case reports: Anaphylaxis, angioneurotic edema, erythema multiforme (oral minocycline), pruritus, rash, Stevens-Johnson syndrome (oral minocylcine), swelling of face, urticaria

Patient Education

Report persistent diarrhea.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder, sustained release [microspheres for subgingival application]:

Arestin®: 1 mg (12s) [each unit-dose cartridge delivers minocycline hydrochloride equivalent to minocycline free base 1 mg]

Generic AvailableNo

Mechanism of ActionMinocycline, a member of the tetracycline class of antibiotics, has a broad spectrum of activity. It is bacteriostatic and exerts its antimicrobial activity by inhibiting protein synthesis.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Patients should avoid the following postadministration: Eating hard, crunchy, or sticky foods for 1 week; brushing for a 12-hour period; touching treated areas; use of interproximal cleaning devices for 10 days.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Minocycline

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Dynacin® may be confused with Dyazide®, Dynabac®, DynaCirc®, Dynapen®

Minocin® may be confused with Indocin®, Lincocin®, Minizide®, Mithracin®, niacin

Pronunciation(mi noe SYE kleen)
U.S. Brand NamesDynacin®; Minocin® PAC; myrac™; Solodyn™
Canadian Brand NamesAlti-Minocycline; Apo-Minocycline®; Gen-Minocycline; Minocin®; Novo-Minocycline; PMS-Minocycline; Rhoxal-minocycline; Sandoz-Minocycline
Pharmacologic CategoryAntibiotic, Tetracycline Derivative
Use: Labeled IndicationsTreatment of susceptible bacterial infections of both gram-negative and gram-positive organisms; treatment of anthrax (inhalational, cutaneous, and gastrointestinal); moderate-to-severe acne; meningococcal (asymptomatic) carrier state; Rickettsial diseases (including Rocky Mountain spotted fever, Q fever); nongonococcal urethritis, gonorrhea; acute intestinal amebiasis

Extended release (Solodyn™): Only indicated for treatment of inflammatory lesions of non-nodular moderate-to-severe acne

Use: Unlabeled/InvestigationalRheumatoid arthritis (patients with low disease activity of short duration)
Dosing: Adults

Usual dosage range: Oral: Initial: 200 mg, followed by 100 mg every 12 hours; more frequent dosing intervals may be used (100-200 mg initially, followed by 50 mg 4 times daily)

Acne: Oral: Capsule or immediate-release tablet: 50-100 mg twice daily

Inflammatory, non-nodular, moderate-to-severe acne (Solodyn™):

45-59 kg: 45 mg once daily

60-90 kg: 90 mg once daily

91-136 kg: 135 mg once daily

Note: Therapy should be continued for 12 weeks. Higher doses do not confer greater efficacy, and safety of use beyond 12 weeks has not been established.

Chlamydial or*Ureaplasma urealyticum*infection, uncomplicated: Urethral, endocervical, or rectal: Oral: 100 mg every 12 hours for at least 7 days

Gonococcal infection, uncomplicated (males): Oral:

Without urethritis or anorectal infection: Initial: 200 mg, followed by 100 mg every 12 hours for at least 4 days (cultures 2-3 days post-therapy)

Urethritis: 100 mg every 12 hours for 5 days

Meningococcal carrier state: Oral: 100 mg every 12 hours for 5 days

Mycobacterium marinum: Oral: 100 mg every 12 hours for 6-8 weeks

Nocardiosis, cutaneous (non-CNS): Oral: 100 mg every 12 hours

Rheumatoid arthritis (unlabeled use): 100 mg twice daily (O'Dell, 2001)

Syphilis: Oral: Initial: 200 mg, followed by 100 mg every 12 hours for 10-15 days

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Usual dosage range: Children >8 years: Oral: Initial: 4 mg/kg followed by 2 mg/kg/dose every 12 hours

Inflammatory, non-nodular, moderate-to-severe acne (Solodyn™): Children ≥12 years: Oral: Refer to adult dosing.

Dosing: Renal ImpairmentUse with caution; monitor BUN and creatinine clearance. Consider decreasing dose or increasing dosing interval (extended release).
Administration: OralMay be taken with or without food. Administer with adequate fluid to decrease the risk of esophageal irritation and ulceration. Swallow pellet-filled capsule and extended release tablet whole; do not chew, crush, or split.
Dietary ConsiderationsMay be taken with or without food.

Storage

Capsule (including pellet-filled), tablet: Store at 20°C to 25°C (68°F to 77°F); protect from heat. Protect from light and moisture.

Extended release tablet: Store at 15°C to 30°C (59°F to 86°F); protect from heat. Protect from light and moisture.

ContraindicationsHypersensitivity to minocycline, other tetracyclines, or any component of the formulation

Allergy Considerations

- Tetracycline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Autoimmune syndromes: Lupus-like, hepatitis, and vasculitis autoimmune syndromes have been reported; discontinue if symptoms.
- CNS effects: Lightheadedness and vertigo may occur; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Increased BUN: May be associated with increases in BUN secondary to antianabolic effects; use caution in patients with renal impairment.
- Photosensitivity: May cause photosensitivity; discontinue if skin erythema occurs. Use skin protection and avoid prolonged exposure to sunlight; do not use tanning equipment.
- Pseudotumor cerebri: Has been (rarely) reported with tetracycline use; usually resolves with discontinuation.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hepatic impairment: Hepatotoxicity has been reported; use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment (Cl_{cr} <80 mL/minute).

Special populations:

- Pediatrics: May cause tissue hyperpigmentation, enamel hypoplasia, or permanent tooth discoloration; use of tetracyclines should be avoided during tooth development (children ≤8 years of age) unless other drugs are not likely to be effective or are contraindicated. However, recommended in treatment of anthrax exposure.
- Pregnancy: Do not use during pregnancy. In addition to affecting tooth development, tetracycline use has been associated with retardation of skeletal development and reduced bone growth.
- Rheumatoid arthritis (unlabeled/investigational): Contraindicated in pregnancy and breast-feeding; Child-Pugh Class C and acute hepatitis B and C. (Saag KG, 2008)

Geriatric ConsiderationsMinocycline has not been studied in the elderly but its CNS effects may limit its use. Dose reduction for renal function not necessary.

Pregnancy Risk FactorD

Pregnancy ConsiderationsTetracyclines, including minocycline, cross the placenta, enter fetal circulation, and may cause permanent discoloration of teeth if used during the second or third trimester. Congenital anomalies after minocycline use have been reported postmarketing. Because use during pregnancy may cause fetal harm, minocycline is classified as pregnancy category D.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsSmall amounts of minocycline are excreted in breast milk and therefore, breast-feeding is not recommended by the manufacturer. Minocycline absorption is not affected by dairy products. This may lead to increased absorption from maternal milk when compared to other tetracyclines which are bound by the calcium in the maternal milk. Nondose-related effects could include modification of bowel flora. There have been case reports of black discoloration of breast milk in women taking minocycline.

Pregnancy & Lactation, In-Depth

- Minocycline in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Cardiovascular: Myocarditis, pericarditis, vasculitis

Central nervous system: Bulging fontanels, dizziness, fatigue, fever, headache, hypoesthesia, malaise, mood changes, paresthesia, pseudotumor cerebri, sedation, seizure, somnolence, vertigo

Dermatologic: Alopecia, angioedema, erythema multiforme, erythema nodosum, erythematous rash, exfoliative dermatitis, hyperpigmentation of nails, maculopapular rash, photosensitivity, pigmentation of the skin and mucous membranes, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Endocrine & metabolic: Thyroid discoloration, thyroid dysfunction

Gastrointestinal: Anorexia, diarrhea, dyspepsia, dysphagia, enamel hypoplasia, enterocolitis, esophageal ulcerations, esophagitis, glossitis, inflammatory lesions (oral/anogenital), moniliasis, nausea, oral cavity discoloration, pancreatitis, pseudomembranous colitis, stomatitis, tooth discoloration, vomiting, xerostomia

Genitourinary: Balanitis, vulvovaginitis

Hematologic: Agranulocytosis, eosinophilia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia

Hepatic: Hepatic cholestasis, hepatic failure, hepatitis, hyperbilirubinemia, jaundice, liver enzyme increases

Neuromuscular & skeletal: Arthralgia, arthritis, bone discoloration, joint stiffness, joint swelling, myalgia

Otic: Hearing loss, tinnitus

Renal: Acute renal failure, BUN increased, interstitial nephritis

Respiratory: Asthma, bronchospasm, cough, dyspnea, pneumonitis, pulmonary infiltrate (with eosinophilia)

Miscellaneous: Anaphylaxis, hypersensitivity, lupus erythematosus, lupus-like syndrome, serum sickness

Drug Interactions

Antacids: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Bismuth: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Bismuth Subsalicylate: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Tetracycline Derivatives. Only a concern with orally administered products. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Tetracycline Derivatives may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Penicillins: Tetracycline Derivatives may diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Quinapril: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: Tetracycline Derivatives may enhance the adverse/toxic effect of Retinoic Acid Derivatives. The development of pseudotumor cerebri is of particular concern. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Tetracycline Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zinc Salts: May decrease the absorption of Tetracycline Derivatives. Only a concern when both products are administered orally. **Exceptions:** Zinc Chloride. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Minocycline serum concentrations are not significantly altered if taken with food or dairy products.

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization).

Test InteractionsMay cause interference with fluorescence test for urinary catecholamines (false elevations)

Monitoring ParametersCulture and sensitivity testing prior to initiating therapy; LFTs, BUN, renal function with long-term treatment; if symptomatic for autoimmune disorder, include ANA, CBC

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and allergy history before beginning therapy. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, warfarin, antacids, hydantoins, carbamazepine). Assess therapeutic effectiveness (resolution of infection) and adverse reactions on a regular basis during therapy. Teach patient proper use, possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity testing prior to initiating therapy; LFTs, BUN, renal function with long-term treatment; if symptomatic for autoimmune disorder, include ANA, CBC monitoring.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed; may be taken with or without food. Do not chew, break, or dissolve extended release tablet. Complete full course of therapy; do not discontinue even if condition is resolved. May cause photosensitivity reaction (avoid sun, use sunscreen, or wear protective clothing); nausea (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea (boiled milk, buttermilk, or yogurt may help). Report rash or itching, unresolved or persistent nausea or diarrhea, change in urinary output (excess); or opportunistic infection (eg, fever, chills, sore throat, burning urination, fatigue). **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule: 50 mg, 75 mg, 100 mg

Dynacin®: 75 mg [DSC], 100 mg [DSC]

Capsule, pellet filled: 50 mg, 100 mg

Minocin® PAC: 50 mg, 100 mg [packaged with wipes, serum, and masque]

Tablet: 50 mg, 75 mg, 100 mg

Dynacin®, myrac™: 50 mg, 75 mg, 100 mg

Tablet, extended release:

Solodyn™: 45 mg, 90 mg, 135 mg

Generic AvailableYes: Excludes extended release tablet

Pricing: U.S. (www.drugstore.com)

Capsules (Dynacin)

50 mg (30): $97.30

75 mg (30): $195.99

Capsules (Minocin)

50 mg (30): $136.03

Capsules (Minocycline HCl)

50 mg (30): $15.99

75 mg (30): $48.99

100 mg (30): $23.00

Tablet, 24-hour (Solodyn)

90 mg (100): $1901.74

Tablets (Dynacin)

75 mg (30): $300.74

100 mg (30): $364.53

Tablets (Minocycline HCl)

75 mg (30): $143.99

100 mg (50): $189.99

Tablets (Myrac)

100 mg (50): $222.00

Mechanism of ActionInhibits bacterial protein synthesis by binding with the 30S and possibly the 50S ribosomal subunit(s) of susceptible bacteria; cell wall synthesis is not affected

Rheumatoid arthritis: The mechanism of action of minocycline in rheumatoid arthritis is not completely understood. It is thought to have antimicrobial, antiinflammatory, immunomodulatory, and chondroprotective effects. More specifically, it is thought to be a potent inhibitor of metalloproteinases, which are active in rheumatoid arthritis joint destruction.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Protein binding: 70% to 75%

Metabolism: Hepatic to inactive metabolites

Half-life elimination: 16 hours (range: 11-22 hours)

Time to peak: Capsule, pellet filled: 1-4 hours; Extended release tablet: 3.5-4 hours

Excretion: Urine, feces

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Discoloration of teeth (children). Opportunistic “superinfection” with *Candida albicans*; tetracyclines are not recommended for use during pregnancy or in children ≤8 years of age since they have been reported to cause enamel hypoplasia and permanent teeth discoloration. The use of tetracycline's should only be used in these patients if other agents are contraindicated or alternative antimicrobials will not eradicate the organism. Long-term use associated with oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Psychiatric Treatment Barbiturates and carbamazepine may decrease the effects of tetracyclines; tetracyclines may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels. No data documenting these effects with minocycline; use caution.

Index Terms Minocycline Hydrochloride

References

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O’Dell JR, Blakely KW, Mallek JA, et al, “Treatment of Early Seropositive Rheumatoid Arthritis: A Two-Year, Double-Blind Comparison of Minocycline and Hydroxychloroquine,” *Arthritis Rheum*, 2001, 44(10):2235-41.[PubMed 11665963]

Saag, KG, Teng GG, Patkar NM, et al, “American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis,” *Arthritis Rheum*, 2008, 59(6):762-84.[PubMed 18512708]

Smilack JD, Wilson WR, and Cockerill FR 3d, “Tetracyclines, Chloramphenicol, Erythromycin, Clindamycin, and Metronidazole,” *Mayo Clin Proc*, 1991, 66(12):1270-80.[PubMed 1749296]

International Brand Names Akamin (AU); Bagomicina (EC); Borymycin (MY, SG); Cyclimycin (ZA); Cynomycin (IN); Klinomycin (LU); Lederderm (DE); Melicid (TW); Mestacine (FR); Micromycin (MX); Mino-50 (LU); Minocin (AR, AT, BE, BO, BR, CH, CL, CN, CO, CR, DO, EC, ES, GB, GR, GT, HK, HN, ID, IT, KP, LU, MX, MY, NI, NL, PA, PE, PH, PK, PR, PT, PY, SV, UY, VE); Minocin G (TW); Minocin SA (IE); Minoclin (IL); Minocyclin (CZ); Minocyclin 50 Stada (DE); Minoline (TW); Minomax (BR); Minomycin (AU); Minot (PE); Minotab (LU); Minotab 50 (BE, NZ, ZA); Mirosin (TW); Mynocine (FR); Parocline (FR); Periocline (JP)

Minoxidil

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Minoxidil may be confused with metolazone, midodrine, Minipress®, Minocin®, Monopril®, Noxafil®

International issues:

Noxidil® [Thailand] may be confused with Noxafil® which is a brand name for posaconazole in the U.S.

Pronunciation(mi NOKS i dil)

U.S. Brand NamesRogaine® Extra Strength for Men [OTC]; Rogaine® for Men [OTC]; Rogaine® for Women [OTC]

Canadian Brand NamesApo-Gain®; Loniten®; Minox; Rogaine®

Pharmacologic CategoryTopical Skin Product; Vasodilator, Direct-Acting

Use: Labeled IndicationsManagement of severe hypertension (usually in combination with a diuretic and beta-blocker); treatment (topical formulation) of alopecia androgenetica in males and females

Dosing: Adults

Hypertension: Oral: Initial: 5 mg once daily, increase gradually every 3 days (maximum: 100 mg/day); usual dosage range (JNC 7): 2.5-80 mg/day in 1-2 divided doses

Note: Dosage adjustment is needed when added to concomitant therapy.

Alopecia: Topical: Apply twice daily; 4 months of therapy may be necessary for hair growth.

Dosing: ElderlyHypertension: Initial: 2.5 mg once daily; increase gradually.

Dosing: Pediatric

Hypertension: Oral:

Children <12 years: Initial: 0.1-0.2 mg/kg once daily; maximum: 5 mg/day; increase gradually every 3 days; usual dosage range: 0.25-1 mg/kg/day in 1-2 divided doses; maximum: 50 mg/day

Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentPatient with renal failure and/or receiving dialysis may require dosage reduction.

Supplemental dose is not necessary via hemo- or peritoneal dialysis.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to minoxidil or any component of the formulation; pheochromocytoma

Warnings/Precautions

Boxed warnings:

- Appropriate use: See "Other warnings/precautions" below.
- Pericardial effusion/tamponade: See "Concerns related to adverse effects" below.
- Sinus tachycardia: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Fluid retention: May cause salt and water retention; administer with a diuretic, preferably a loop diuretic (eg, furosemide) to prevent fluid retention and subsequent local and generalized edema. Use with extreme caution in patients with heart failure.
- Hypertrichosis: Inform patients of excessive hair growth patterns before initiating therapy; may take 1-6 months for hypertrichosis to reverse itself after discontinuation of the drug.
- Pericardial effusion/tamponade: **[U.S. Boxed Warning]: May cause pericarditis and pericardial effusion that may progress to tamponade;** patients with renal impairment not on dialysis may be at higher risk. Use with caution in patients with heart failure. Observe patients closely.
- Rapid blood pressure control: Rapid control of blood pressure in patients with severe hypertension can lead to syncope, CVA, MI, and/or ischemia of other special sense organs (eg, vision).

- Sinus tachycardia: **[U.S. Boxed Warning]: May increase oxygen demand and exacerbate angina pectoris;** concomitant use with a beta-blocker (if no contraindication exists) may help reduce the effect. Use with caution in patients with ischemic heart disease.

Disease-related concerns:

- Acute myocardial infarct (MI): Avoid use for a month after acute MI. Use with extreme caution; ensure patient is receiving a beta blocker prior to initiation.
- Heart failure: Compared to placebo minoxidil increased the frequency of clinical events, including increased need for diuretics, angina, ventricular arrhythmias, worsening heart failure and death (Franciosa, 1984).
- Renal impairment: Use with caution in patients with significant renal impairment; renal failure and dialysis patients may require a smaller dose.

Special populations:

- Elderly: Use with caution in the elderly; initiate at the low end of the dosage range and monitor closely.

Other warnings/precautions:

- Appropriate use: **[U.S. Boxed Warning]: Maximum therapeutic doses of a diuretic and two antihypertensives should be used before this drug is ever added. Should be given with a diuretic to minimize fluid gain and a beta-blocker (if no contraindications) to prevent tachycardia. Anyone with malignant hypertension should be hospitalized with close medical supervision to ensure blood pressure is reducing and to prevent too rapid of a reduction in blood pressure.**

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events were observed in some animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsExcretion in breast milk has been reported in one case report of a woman receiving 10 mg/day orally.

Adverse Reactions

Oral: Incidence of reactions not always reported.

Cardiovascular: ECG changes (T-wave changes 60%), peripheral edema (7%), pericardial effusion with tamponade (3%), pericardial effusion without tamponade (3%), angina pectoris, heart failure, pericarditis, rebound hypertension (in children after a gradual withdrawal), sodium and water retention, tachycardia

Dermatologic: Hypertrichosis (common; 80%), bullous eruption (rare), rash, Stevens-Johnson syndrome (rare)

Endocrine & metabolic: Breast tenderness (rare; <1%)

Gastrointestinal: Nausea, vomiting, weight gain

Hematologic: Leukopenia (rare), thrombocytopenia (rare), transient decreased erythrocyte count (hemodilution), transient decreased hematocrit/hemoglobin (hemodilution)

Hepatic: Alkaline phosphatase increased

Renal: Serum BUN/creatinine increased (transient)

Respiratory: Pulmonary edema

Topical: Incidence of adverse events is not always reported.

Cardiovascular: Blood pressure increased/decreased, cardiac output increased, chest pain (transient), edema, left ventricular mass increased, left ventricular end-diastolic volume increased, palpitation, tachycardia

Central nervous system: Anxiety (rare), dizziness, faintness, headache, mental depression (rare), taste alterations

Dermatologic: Allergic contact dermatitis (7.4%), alopecia, dryness, eczema, exacerbation of hair loss, flushing, folliculitis; hair growth increased outside the area of application (face, beard, eyebrows, ear, arm); hypertrichosis, local erythema, papular rash, pruritus, scaling/flaking, seborrhea

Endocrine & metabolic: Menstrual changes

Gastrointestinal: Diarrhea, nausea

Genitourinary: Epididymitis (rare), impotence (rare), prostatitis (rare), renal calculi (rare), urethritis (rare), urinary tract infection (rare)

Hematologic: Lymphadenopathy, thrombocytopenia

Neuromuscular & skeletal: Back pain, fractures, retrosternal chest pain of muscular origin, tendonitis (2.6%), weakness

Ocular: Conjunctivitis, visual acuity decreased, visual disturbances

Respiratory: Bronchitis, upper respiratory infection

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can

not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

CycloSPORINE: May enhance the adverse/toxic effect of Minoxidil. Severe hypertrichosis has been reported. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice may diminish the antihypertensive effects of minoxidil. Black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse may enhance the hypotensive effects of minoxidil.

Monitoring ParametersBlood pressure, standing and sitting/supine; fluid and electrolyte balance and body weight should be monitored. Any tests that are abnormal at the time of initiation (including, renal function tests, ECG, echocardiogram, chest x-ray) should be repeated initially every 1-3 months then every 6-12 months once stable.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol, topical [foam]:

Rogaine for Men®: 5% (60 g)

Solution, topical: 2% (60 mL); 5% (60 mL)

Rogaine® for Men: (60 mL) [DSC] [supplied with dropper applicator]

Rogaine® for Women: 2% (60 mL) [supplied with dropper applicator]

Rogaine® Extra Strength for Men: 5% (60 mL) [supplied with dropper applicator]

Tablet: 2.5 mg, 10 mg

Generic AvailableYes: Excludes aerosol, topical solution

Pricing: U.S. (www.drugstore.com)

Solution (Rogaine)

2% (60): $22.44

2% (180): $45.77

Solution (Rogaine Extra Strength for Men)

5% (60): $29.71

Tablets (Minoxidil)

2.5 mg (60): $19.99

10 mg (90): $53.99

Mechanism of ActionProduces vasodilation by directly relaxing arteriolar smooth muscle, with little effect on veins; effects may be mediated by cyclic AMP; stimulation of hair growth is secondary to vasodilation, increased cutaneous blood flow and stimulation of resting hair follicles

Pharmacodynamics/Kinetics

Onset of action: Hypotensive: Oral: ~30 minutes

Peak effect: 2-8 hours

Duration: 2-5 days

Protein binding: None

Metabolism: 88%, primarily via glucuronidation

Bioavailability: Oral: 90%

Half-life elimination: Adults: 3.5-4.2 hours

Excretion: Urine (12% as unchanged drug)

Related Information

- Hypertension

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay rarely cause leukopenia; use caution with clozapine and carbamazepine

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International Brand NamesAlopexy (ES, IL, LU); Alopexyl (FR); Alostil (FR); Aloxid (ID); Apo-Gain (MY); Depressan (HU); Growell (SG); Hair Max (PK); Hair Retreva (AU); Hair-Treat (IL); Hair-Treat Forte (IL); Hairex (IN); Hairgrow (HK); Headway (NZ); Hexal Reztore Extra Strength (AU); Kenacin (PY); Lacovin (ES); Locemix (AR); Loniten (AT, AU, BR, CH, CZ, GB, GR, HN, HR, HU, IE, IT, MY, PL, PT, RU, TH, TW, ZA); Lonnoten (BE, FI, LU, NL); Lonolox (DE); Lonoten (FR); Loxon (PL); Manoxidil (TH); Minodil (TH); Minona (FI); Minoxidil Isac (PH); Minoxidil MK (CO); Minoximen (IT); Minoxiten (DO); Minoxitrim (SG); Minoxyl (KP); Moxidil (KP); Neocapil (CH); Neoxidil (LU); Nuhair (TH); Pilfud (HR); Piloxidil (PL); Recrea (SE); Regaine (AE, AT, AU, BE, BG, BH, BR, CH, CN, CY, CZ, DK, EE, EG, FI, FR, GR, HK, HN, HR, HU, IL, IQ, IR, IT, JO, KW, LB, LU, LY, MX, MY, NL, OM, PE, PL, PT, QA, RU, SA, SY, TH, TW, VE, YE); Regalok (PL); Regroe (PH); Regrou (ID); Regrowth (TH); Remox (UY); Replete Extra Strength (AU); Replete Regular Strength (AU); Revital (PH); Rogaine (NO, NZ, SE); Topgain (IN); Ylox (AR)

Mirtazapine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Remeron® may be confused with Premarin®, ramelteon, Rozerem®, Zemuron®

International issues:

Avanza® [Australia] may be confused with Albenza® which is a brand name for albendazole in the U.S.

Avanza® [Australia] may be confused with Avandia® which is a brand name for rosiglitazone in the U.S.

Remeron® my be confused with Reneuron® which is a brand name for fluoxetine in Spain

Pronunciation(mir TAZ a peen)

U.S. Brand NamesRemeron SolTab®; Remeron®

Canadian Brand NamesApo-Mirtazapine; CO Mirtazapine; DOM-Mirtazapine; Gen-Mirtazapine; Novo-Mirtazapine; PHL-Mirtazapine; PMS-Mirtazapine; PRO-Mirtazapine; ratio-Mirtazapine; Remeron®; Remeron® RD; Riva-Mirtazapine; Sandoz-Mirtazapine; Sandoz-Mirtazapine FC

Pharmacologic CategoryAntidepressant, Alpha-2 Antagonist

Use: Labeled IndicationsTreatment of depression

Dosing: AdultsDepression: Oral: Initial: 15 mg nightly, titrate up to 15-45 mg/day with dose increases made no more frequently than every 1-2 weeks. There is an inverse relationship between dose and sedation.

Dosing: ElderlyInitial: 7.5 mg/day as a single bedtime dose; increase by 7.5-15 mg/day every 1-2 weeks; usual dose: 15-30 mg/day; maximum dose: 45 mg/day

Alzheimer's dementia-related depression: Initial: 7.5 mg at bedtime; may increase at 7.5-15 mg increments to 45-60 mg/day

Dosing: Renal Impairment

Cl_{cr} 11-39 mL/minute: 30% decreased clearance

Cl_{cr} <10 mL/minute: 50% decreased clearance

Dosing: Hepatic ImpairmentClearance is decreased by 30%.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsRemeron SolTab® contains phenylalanine: 2.6 mg per 15 mg tablet; 5.2 mg per 30 mg tablet; 7.8 mg per 45 mg tablet

StorageStore at controlled room temperature.

SolTab®: Protect from light and moisture. Use immediately upon opening tablet blister.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to mirtazapine or any component of the formulation; use of MAO inhibitors within 14 days

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See "Major psychiatric warnings" below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Mirtazapine is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Mirtazapine is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. The degree of anticholinergic blockade produced by this agent is low relative to other antidepressants.

- Blood dyscrasias: Discontinue immediately if signs and symptoms of neutropenia/agranulocytosis occur.

- Hyperlipidemia: May increase serum cholesterol and triglyceride levels.

- Orthostatic hypotension: May cause orthostatic hypotension (risk is low relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is moderate to high relative to other antidepressants.

- Sexual dysfunction: The incidence of sexual dysfunction with mirtazapine is generally lower than with SSRIs.

- Weight gain: May increase appetite and stimulate weight gain. Weight gain of >7% of body weight reported in 7.5% of patients treated with mirtazapine compared to 0% for placebo; 8% of patients receiving mirtazapine discontinued treatment due to the weight gain. In an 8-week pediatric clinical trial, 49% of mirtazapine-treated patients had a weight gain of at least 7% (mean increase 4 kg) as compared to 5.7% of placebo-treated patients (mean increase 1 kg).

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- MAO inhibitors: Potential for severe reaction when used with MAO inhibitors; autonomic instability, coma, death, delirium, diaphoresis, hyperthermia, mental status changes/agitation, muscular rigidity, myoclonus, neuroleptic malignant syndrome features, and seizures may occur.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly.

Dosage form specific issues:

- Phenylalanine: SolTab® formulation contains phenylalanine.

Geriatric ConsiderationsLimited published data specifically in the elderly or addressing *in vivo* drug interactions.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events were observed in some animal studies; therefore, the manufacturer classifies mirtazapine as pregnancy category C. A significant increase in major teratogenic effects has not been observed in humans following exposure to mirtazapine during pregnancy; however, some nonteratogenic adverse events (similar to those observed with SSRI agents) have been reported. Mirtazapine was found to cross the placenta following a maternal overdose. Pregnancy itself does not provide “protection” against depression. Women treated for major depression and who are euthymic prior to pregnancy are more likely to experience a relapse when medication is discontinued as compared to pregnant women who continue taking antidepressant medications. The ACOG recommends that therapy with antidepressants during pregnancy be individualized. According to their recommendations, treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary care provider, and pediatrician. If treatment during pregnancy is required, consider tapering therapy during the third trimester in order to prevent withdrawal symptoms in the infant. If this is done, and the woman is considered to be at risk of relapse from her major depressive disorder, the medication can be restarted following delivery, although the dose should be readjusted to that required before pregnancy.

LactationExcreted in breast milk/use caution

Breast-Feeding ConsiderationsMirtazapine and its active metabolite are found in breast milk, with higher levels in the hindmilk than foremilk. Adverse events have not been observed in nursing infants. The manufacturer recommends that caution be used if administered to a breast-feeding woman.

Pregnancy & Lactation, In-Depth

- Mirtazapine in Pregnancy & Lactation

Adverse Reactions

>10%:

Central nervous system: Somnolence (54%)

Endocrine & metabolic: Cholesterol increased

Gastrointestinal: Xerostomia (25%), appetite increased (17%), constipation (13%), weight gain (12%; weight gain of >7% reported in 8% of adults, ≤49% of pediatric patients)

1% to 10%:

Cardiovascular: Peripheral edema (2%), edema (1%), hypertension, vasodilatation

Central nervous system: Dizziness (7%), abnormal dreams (4%), abnormal thoughts (3%), confusion (2%), malaise

Endocrine & metabolic: Triglycerides increased

Gastrointestinal: Abdominal pain, anorexia, vomiting

Genitourinary: Urinary frequency (2%)

Neuromuscular & skeletal: Weakness (8%), back pain (2%), myalgia (2%), tremor (2%), arthralgia

Respiratory: Dyspnea (1%)

Miscellaneous: Flu-like syndrome (5%), thirst

<1%: Abdomen enlarged, abnormal ejaculation, accommodation abnormality, acne, agitation, agranulocytosis, akathisia, alopecia, amenorrhea, amnesia, anemia, angina pectoris, anxiety, apathy, aphasia, aphthous stomatitis, arthrosis, arthritis, asphyxia, asthma, ataxia, atrial arrhythmia, bigeminy, blepharitis, bone pain, bradycardia, breast engorgement, breast enlargement, breast pain, bronchitis, bursitis, cardiomegaly, cellulitis, cerebral ischemia, chest pain, chills, cholecystitis, cirrhosis, colitis, conjunctivitis, coordination abnormal, cough, cystitis, deafness, dehydration, delirium, delusions, dementia, depersonalization, depression, diabetes mellitus, diplopia, drug dependence, dry skin, dysarthria, dyskinesia, dysmenorrhea, dystonia, dysuria, ear pain, emotional lability, epistaxis, eructation, euphoria, exfoliative dermatitis, extrapyramidal syndrome, eye pain, facial edema, fever, fracture, gastritis, gastroenteritis, glaucoma, glossitis, goiter, gout, grand mal seizure, gum hemorrhage, hallucinations, hematuria, herpes simplex, herpes zoster, hiccup, hostility, hypokinesia, hyperacusis, hyperkinesias, hypoesthesia, hypotension, hypothyroidism, hypotonia, impotence, increased salivation, intestinal obstruction, keratoconjunctivitis, kidney calculus, lacrimation disorder, laryngitis, left heart failure, leukopenia, leukorrhea, libido increased, liver function tests abnormal, lymphadenopathy, lymphocytosis, manic reaction, menorrhagia, metrorrhagia, migraine, MI, myoclonus, myositis, nausea, neck pain, neck rigidity, neurosis, nystagmus, oral moniliasis, osteoporosis, otitis media, pancreatitis, pancytopenia, paralysis, paranoid reaction, paresthesia, parosmia, petechia, phlebitis, photosensitivity reaction, pneumonia, pneumothorax, polyuria, pruritus, psychotic depression, pulmonary embolus, rash, reflexes increased, salivary gland enlargement, seborrhea, sinusitis, skin hypertrophy, skin ulcer, stomatitis, stupor, syncope, taste loss, tendon rupture, tenosynovitis, thrombocytopenia, tongue discoloration, tongue edema, twitching, ulcer, ulcerative stomatitis, urethritis, urinary incontinence, urinary retention, urinary tract infection, urinary urgency, urticaria, vaginitis, vascular headache, ventricular extrasystoles, vertigo, weight loss, withdrawal syndrome

Postmarketing and/or case reports: Torsade de pointes (1 case reported)

Metabolism/Transport Effects

Substrate of CYP1A2 (major), 2C9 (minor), 2D6 (major), 3A4 (major); **Inhibits** CYP1A2 (weak), 3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha2-Agonists: Antidepressants (Alpha2-Antagonist) may diminish the hypotensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the neurotoxic (central) effect of Mirtazapine. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid St John's wort (may decrease mirtazapine levels). Avoid valerian, St John's wort, SAMe, kava kava (may increase CNS depression).

Monitoring ParametersPatients should be monitored for signs of agranulocytosis or severe neutropenia such as sore throat, stomatitis or other signs of infection or a low WBC; mental status for depression, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased), anxiety, social functioning, mania, panic attacks; lipid profile

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Has potential for psychological or physiological dependence, abuse, or tolerance. Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Monitor for CNS depression/sedation. Monitor for clinical worsening and suicidal ideation. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC

Patient EducationTake exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results. Take once-a-day dose at bedtime. Avoid alcohol, caffeine, and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or lightheadedness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, anorexia, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or orthostatic hypotension (use caution when climbing stairs or changing position from lying or sitting to standing). Report persistent insomnia, agitation, or confusion; suicidal ideation; muscle cramping, tremors, weakness, or change in gait; breathlessness or respiratory difficulty; chest pain, palpitations, or rapid heartbeat; change in urinary pattern; vision changes or eye pain; yellowing of eyes or skin; pale stools/dark urine; or worsening of condition.

SolTab®: Open blister pack and place tablet on the tongue. Do not split tablet. Tablet is formulated to dissolve on the tongue without water.

Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 7.5 mg, 15 mg, 30 mg, 45 mg

Remeron®: 15 mg, 30 mg, 45 mg

Tablet, orally disintegrating: 15 mg, 30 mg

Remeron SolTab®:

15 mg [contains phenylalanine 2.6 mg/tablet; orange flavor]

30 mg [contains phenylalanine 5.2 mg/tablet; orange flavor]

45 mg [contains phenylalanine 7.8 mg/tablet; orange flavor]

Generic AvailableYes

ManufacturerOrganon Inc

Pricing: U.S. (www.drugstore.com)

Tablet, orally-disintegrating (Mirtazapine)

15 mg (30): $70.38

45 mg (30): $71.49

Tablet, orally-disintegrating (Remeron SolTab)

15 mg (30): $97.24

30 mg (30): $101.30

45 mg (30): $108.04

Tablets (Mirtazapine)

15 mg (30): $50.00

30 mg (30): $45.99

45 mg (30): $45.99

Tablets (Remeron)

15 mg (30): $116.32

30 mg (30): $109.99

45 mg (30): $133.63

Mechanism of Action Mirtazapine is a tetracyclic antidepressant that works by its central presynaptic alpha$_2$-adrenergic antagonist effects, which results in increased release of norepinephrine and serotonin. It is also a potent antagonist of 5-HT$_2$ and 5-HT$_3$ serotonin receptors and H1 histamine receptors and a moderate peripheral alpha$_1$-adrenergic and muscarinic antagonist; it does not inhibit the reuptake of norepinephrine or serotonin.

Pharmacodynamics/Kinetics

Absorption: Rapid and complete

Distribution: 4.5 L/kg

Protein binding: 85%

Metabolism: Extensively hepatic via CYP1A2, 2C9, 2D6, 3A4 and via demethylation (forms demethylmirtazapine, an active metabolite) and hydroxylation (forms inactive metabolites)

Bioavailability: 50%

Half-life elimination: 20-40 hours; hampered with renal or hepatic impairment

Time to peak, serum: 2 hours

Excretion: Urine (75%) and feces (15%) as metabolites

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile

Pharmacotherapy Pearls **Note:** At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of therapy with mirtazapine; at least 14 days should be allowed after discontinuing mirtazapine before starting an MAO inhibitor.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Although mirtazapine is not a tricyclic antidepressant, it does block norepinephrine reuptake within CNS synapses as part of its mechanisms. It has been suggested that vasoconstrictor be administered with caution and to monitor vital signs in dental patients taking antidepressants that affect norepinephrine in this way, including mirtazapine.

References

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“Mirtazapine - A New Antidepressant,” *Med Lett Drugs Ther*, 1996, 38(990):113-4. [PubMed 8988154]

Pass SE and Simpson RW, “Discontinuation and Reinstitution of Medications During the Perioperative Period,” *Am J Health Syst Pharm*, 2004, 61(9):899-912. [PubMed 15156966]

Rabins PV, Blacker D, Rovner BW, et al, “Practice Guidelines for the Treatment of Patients With Alzheimer’s Disease and Other Dementias,” October, 2007. Available at http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm.

Stimmel GL, Dopheide JA, and Stahl SM, “Mirtazapine: An Antidepressant With Noradrenergic and Specific Serotonergic Effects,” *Pharmacotherapy*, 1997, 17(1):10-21.[PubMed 9017762]

International Brand Names Afloyan (ES); Avanza (AU); Avanza Soltab (AU); Axit (AU); Ciblex (CN); Mirazep (IN, PH); Mirtapax (CO, EC); Mirtazon (AU); Norset (FR); Remergil (DE); Remergon (BE); Remeron (AE, AR, AT, AU, BH, BR, CH, CL, CR, CY, CZ, DK, DO, EE, EG, FI, GT, HN, ID, IL, IQ, IR, IT, JO, KW, LB, LY, MX, MY, NI, NL, NO, OM, PA, PE, PK, PL, PT, QA, SA, SE, SG, SV, SY, TW, UY, VE, YE, ZA); Remeron SolTab (AU, HK, PH); Vastat Flas (ES); Zispin (GB, IE)

Misoprostol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Cytotec® may be confused with Cytoxan®, Sytobex®

Misoprostol may be confused with metoprolol, mifepristone

Pronunciation(mye soe PROST ole)

U.S. Brand NamesCytotec®

Canadian Brand NamesApo-Misoprostol®; Novo-Misoprostol

Pharmacologic CategoryProstaglandin

Use: Labeled IndicationsPrevention of NSAID-induced gastric ulcers; medical termination of pregnancy of ≤49 days (in conjunction with mifepristone)

Use: Unlabeled/InvestigationalCervical ripening and labor induction; NSAID-induced nephropathy; fat malabsorption in cystic fibrosis

Dosing: Adults

Prevention of NSAID-induced ulcers: Oral: 200 mcg 4 times/day with food; if not tolerated, may decrease dose to 100 mcg 4 times/day with food or 200 mcg twice daily with food. Last dose of the day should be taken at bedtime.

Labor induction or cervical ripening (unlabeled uses): Intravaginal: 25 mcg ($^1/_4$ of 100 mcg tablet); may repeat at intervals no more frequent than every 3-6 hours. Do not use in patients with previous cesarean delivery or prior major uterine surgery.

Medical termination of pregnancy: Oral: Refer to Mifepristone monograph.

Dosing: ElderlyOral: 100-200 mcg 4 times/day with food; if 200 mcg 4 times/day not tolerated, reduce to 100 mcg 4 times/day or 200 mcg twice daily with food. **Note:** To avoid the diarrhea potential, doses can be initiated at 100 mcg/day and increased 100 mcg/day at 3-day intervals until desired dose is achieved; also, recommend administering with food to decrease diarrhea incidence.

Dosing: Pediatric**Fat absorption in cystic fibrosis (unlabeled use):** Oral: Children 8-16 years: 100 mcg 4 times/day

Administration: OralIncidence of diarrhea may be lessened by having patient take dose right after meals. Therapy is usually begun on the second or third day of the next normal menstrual period.

Dietary ConsiderationsShould be taken with food; incidence of diarrhea may be lessened by having patient take dose right after meals.

StorageStore at or below 25°C (77°F).

ContraindicationsHypersensitivity to misoprostol, prostaglandins, or any component of the formulation; pregnancy (when used to reduce NSAID-induced ulcers)

Warnings/Precautions

Boxed warnings:

- Women of childbearing potential: See "Special populations" below.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Elderly: Use with caution in the elderly.
- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: Uterine perforation and/or rupture have been reported in association with intravaginal use to induce labor or with combined oral/intravaginal use to induce abortion. The manufacturer states that Cytotec® should not be used as a cervical-ripening agent for induction of labor. However, The American College of Obstetricians and Gynecologists (ACOG) continues to support this off-label use.
- Women of childbearing potential: **[U.S. Boxed Warning]: Not to be used in women of childbearing potential unless woman is capable of complying with effective contraceptive measures;** therapy is normally begun on the second or third day of next normal menstrual period.

Geriatric ConsiderationsElderly, due to extensive use of NSAIDs and the high percentage of asymptomatic hemorrhage and perforation from NSAIDs, are at risk for NSAID-induced ulcers and may be candidates for misoprostol use. However, routine use for prophylaxis is not justified. Patients must be selected upon demonstration that they are at risk for NSAID-induced lesions. Misoprostol should not be used as a first-line therapy for gastric or duodenal ulcers.

Pregnancy Risk FactorX

Pregnancy Considerations**[U.S. Boxed Warning]: Not to be used in women of childbearing potential unless woman is capable of complying with effective contraceptive measures; therapy is normally begun on the second or third day of next normal menstrual period.** Misoprostol is an abortifacient. During pregnancy, use to prevent NSAID-induced ulcers is contraindicated. Reports of fetal death, congenital anomalies, uterine perforation, and abortion have been received after the use of misoprostol in pregnancy.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsIt is not known if misoprostol is excreted in human milk, however, because significant diarrhea may occur in a nursing infant, breast-feeding is contraindicated

Adverse Reactions

>10%: Gastrointestinal: Diarrhea, abdominal pain

1% to 10%:

Central nervous system: Headache

Gastrointestinal: Constipation, flatulence, nausea, dyspepsia, vomiting

<1%: Cramps, uterine stimulation, vaginal bleeding

Postmarketing and/or case reports: Abnormal taste, abnormal vision, alkaline phosphatase increased, alopecia, anaphylaxis, anemia, amylase increase, anxiety, appetite changes, arrhythmia, arterial thrombosis, arthralgia, back pain, breast pain, bronchospasm, cardiac enzymes increased, chest pain, confusion, deafness, depression, dermatitis, diaphoresis, drowsiness, dysphagia, dyspnea, earache, edema, epistaxis, ESR increased, fetal or infant death (when used during pregnancy), fever, GI bleeding, GI inflammation, gingivitis, glycosuria, gout, hyper-/hypotension, impotence, loss of libido, MI, muscle cramps, myalgia, neuropathy, neurosis, nitrogen increased, pallor, phlebitis, pulmonary embolism, purpura, rash, reflux, rigors, stiffness, syncope, thirst, thrombocytopenia, tinnitus, uterine rupture, weakness, weight changes

Drug Interactions

Oxytocin: Misoprostol may enhance the therapeutic effect of Oxytocin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Misoprostol peak serum concentrations may be decreased if taken with food (not clinically significant).

Nursing: Physical Assessment/MonitoringAssess knowledge/teach appropriate antiulcer diet and lifestyle. Monitor renal function and fluid balance. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment and do not give to women of childbearing age or to males who may have intercourse with women of childbearing age unless both male and female are capable of complying with contraceptive measures during therapy and for 1 month following therapy.

Patient EducationTake as directed; continue taking your NSAIDs while taking this medication. Take with meals or after meals to prevent nausea, diarrhea, and flatulence. Avoid using antacids. You may experience increased menstrual pain, or cramping; request analgesics. Report abnormal menstrual periods, spotting (may occur even in postmenstrual women), or severe menstrual bleeding. **Pregnancy/breast-feeding precautions:** When used to prevent NSAID-induced ulcers: Inform prescriber if you are pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Do not get pregnant during or for 1 month following therapy. Male: Do not cause a female to become pregnant. Male/female: Consult prescriber for instruction on appropriate contraceptive measures if necessary or if you suspect you might be pregnant. This drug may cause severe fetal defects, miscarriage, or abortion; do not share medication with others. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 100 mcg, 200 mcg

Generic AvailableYes

ManufacturerSearle

Pricing: U.S. (www.drugstore.com)

Tablets (Cytotec)

100 mcg (60): $72.76

200 mcg (60): $104.99

Tablets (Misoprostol)

100 mcg (60): $39.99

200 mcg (60): $56.99

Mechanism of ActionMisoprostol is a synthetic prostaglandin E_1 analog that replaces the protective prostaglandins consumed with prostaglandin-inhibiting therapies (eg, NSAIDs); has been shown to induce uterine contractions

Pharmacodynamics/Kinetics

Absorption: Rapid

Metabolism: Hepatic; rapidly de-esterified to misoprostol acid (active)

Half-life elimination: Metabolite: 20-40 minutes

Time to peak, serum: Active metabolite: Fasting: 15-30 minutes

Excretion: Urine (64% to 73%) and feces (15%) within 24 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
References

"Induction of Labor," American College of Obstetricians and Gynecologists, ACOG Practice Guidelines Bulletin 10, Washington, DC; ACOG, 1999.

"Induction of Labor With Misoprostol," American College of Obstetricians and Gynecologists, ACOG Committee Opinion 228, Washington, DC; ACOG, 1999.

Cleghorn GJ, Shepherd RW, and Holt TL, "The Use of a Synthetic Prostaglandin E1 Analogue (Misoprostol) as an Adjunct to Pancreatic Enzyme Replacement in Cystic Fibrosis," *Scand J Gastroenterol Suppl*, 1988, 143:142-7. [PubMed 3133753]

Robinson PJ, Smith AL, and Sly PD, "Duodenal pH in Cystic Fibrosis and Its Relationship to Fat Malabsorption," *Dig Dis Sci*, 1990, 35(10):1299-304. [PubMed 2120019]

Walt RP, "Misoprostol for the Treatment of Peptic Ulcer and Anti-inflammatory Drug-Induced Gastroduodenal Ulceration," *N Engl J Med*, 1992, 327(22):1575-80. [PubMed 1435885]

Wing, DA, "Labor Induction With Misoprostol," *Am J Obstet Gynecol*, 1999, 181(2):339-45.[PubMed 10454679]

International Brand NamesAlsoben (KP); Cityl (CO); Cyprostol (AT); Cytolog (IN); Cytotec (AE, AR, AT, AU, BE, BF, BG, BH, BJ, BR, CH, CI, CR, CY, CZ, DE, DK, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, HU, ID, IE, IL, IQ, IR, IT, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PL, PT, QA, RU, SA, SC, SD, SE, SG, SL, SN, SV, SY, TH, TN, TR, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Gastotec (KP); Gastrul (ID); Gymiso (FR); Misel (KP); Misotrol (CN); Noprostol (ID)

Mitomycin-Vinblastine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Breast Cancer]

Regimen UseBreast cancer

Index TermsMV

Regimen

Mitomycin: I.V.: 20 mg/m^2 day 1

[total dose/cycle = 20 mg/m^2]

Vinblastine: I.V.: 0.15 mg/kg/day days 1 and 21

[total dose/cycle = 0.3 mg/kg]

Repeat cycle every 6-8 weeks

References

Konits PH, Aisner J, van Echo DA, et al, âMitomycin C and Vinblastine Chemotherapy for Advanced Breast Cancer,â *Cancer*, 1981, 48(6):1295-8.[PubMed 6791808]

Mitomycin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

> Mitomycin may be confused with mithramycin, mitotane, mitoxantrone

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(mye toe MYE sin)

Canadian Brand NamesMutamycin®

Pharmacologic CategoryAntineoplastic Agent, Antibiotic

Use: Labeled IndicationsTreatment of adenocarcinoma of stomach or pancreas, bladder cancer, breast cancer, or colorectal cancer

Use: Unlabeled/InvestigationalPrevention of excess scarring in glaucoma filtration procedures in patients at high risk of bleb failure

Dosing: AdultsRefer to individual protocols:

Single-agent therapy: I.V.: 20 mg/m^2 every 6-8 weeks

Combination therapy: I.V.: 10 mg/m^2 every 6-8 weeks

Bladder carcinoma: Intravesicular instillations (unapproved route): 20-40 mg instilled into the bladder and retained for 3 hours up to 3 times/week for up to 20 procedures per course.

Glaucoma surgery (unlabeled use): 0.2-0.5 mg (0.2-0.5 mg/mL solution)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricUnlabeled use. Refer to adult dosing.

Dosing: Renal ImpairmentThe FDA-approved labeling states to avoid use in patients with serum creatine >1.7 mg/dL, but offers no other dosage adjustment guidelines. The following guidelines have been used by some clinicians (Aronoff, 2007): Adults:

Cl_{cr} <10 mL/minute: Administer 75% of dose

Continuous ambulatory peritoneal dialysis (CAPD): Administer 75% of dose

Dosing: Hepatic ImpairmentAlthough some mitomycin may be excreted in the bile, no specific guidelines regarding dosage adjustment in hepatic impairment are available.

Dosing: Combination Regimens

Breast cancer: VM

Gastric cancer: FAM

Pancreatic cancer: FAM

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Vesicant. Administer slow I.V. push or by slow (15-30 minute) infusion via a freely-running dextrose or saline infusion. Consider using a central venous catheter.

Administration: I.V. DetailpH: 6-8

Administration: Other

Intravesicular (unlabeled route): Instill into bladder for up to 3 hours (rotate patient every 15-30 minutes)

Glaucoma surgery (unlabeled route): Apply to pledget and place in contact with surgical wound for 2-5 minutes (doses and techniques may vary)

StorageStore intact vials at controlled room temperature. Mitomycin solution is stable for 7 days at room temperature and 14 days when refrigerated if protected from light. Solution of 0.5 mg/mL in a syringe is stable for 7 days at room temperature and 14 days when refrigerated and protected from light.

Further dilution to 20-40 mcg/mL:

In normal saline: Stable for 12 hours at room temperature.

In sodium lactate: Stable for 24 hours at room temperature.

ReconstitutionDilute powder with SWFI or 0.9% sodium chloride to a concentration of 0.5-1 mg/mL.
CompatibilityStable in LR; **variable stability (consult detailed reference)** in D_5W, NS.

Y-site administration: Compatible: Amifostine, bleomycin, cisplatin, cyclophosphamide, doxorubicin, droperidol, fluorouracil, furosemide, granisetron, heparin, leucovorin, melphalan, methotrexate, metoclopramide, ondansetron, teniposide, thiotepa, vinblastine, vincristine. **Incompatible:** Aztreonam, cefepime, etoposide phosphate, filgrastim, gemcitabine, piperacillin/tazobactam, sargramostim, topotecan, vinorelbine.

Compatibility in syringe: Compatible: Bleomycin, cisplatin, cyclophosphamide, doxorubicin, droperidol, fluorouracil, furosemide, heparin, leucovorin, methotrexate, metoclopramide, vinblastine, vincristine.

Compatibility when admixed: Compatible: Dexamethasone sodium phosphate, hydrocortisone sodium succinate. **Incompatible:** Bleomycin. **Variable (consult detailed reference):** Heparin.

ContraindicationsHypersensitivity to mitomycin or any component of the formulation; thrombocytopenia; coagulation disorders, increased bleeding tendency; pregnancy
Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.
- Hemolytic-uremic syndrome: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bladder fibrosis/contraction: With intravesical administration, bladder fibrosis/contraction has been reported.
- Bone marrow suppression: **[U.S. Boxed Warning]: May cause bone marrow suppression (thrombocytopenia and leukopenia);** monitor for infections.
- Hemolytic-uremic syndrome: **[U.S. Boxed Warning]: Hemolytic-uremic syndrome, potentially fatal, has been reported;** is correlated with total dose (single doses ≥60 mg or cumulative doses ≥50 mg/m^2) and total duration of therapy (>5-11 months).
- Potent vesicant: **Mitomycin is a potent vesicant, may cause ulceration, necrosis, cellulitis, and tissue sloughing if infiltrated.**

Disease-related concerns:

- Renal impairment: Do not administer if serum creatinine is >1.7 mg/dL; monitor for renal toxicity.

Concurrent drug therapy issues:

- Vinca alkaloids: Shortness of breath and bronchospasm have been reported in patients receiving vinca alkaloids in combination with or after mitomycin; may be managed with bronchodilators, steroids and/or oxygen.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Radiation therapy recipients: Use with caution in patients who have received radiation therapy or in the presence of hepatobiliary dysfunction; reduce dosage in patients who are receiving radiation therapy simultaneously.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD
Pregnancy ConsiderationsMitomycin can cause fetal harm in humans. Animal studies show delayed fetal development, fetal external anomalies, and neonatal anomalies.
LactationEnters breast milk/contraindicated
Adverse Reactions

>10%:

Cardiovascular: CHF (3% to 15%) (doses >30 mg/m^2)

Central nervous system: Fever (14%)

Dermatologic: Alopecia, nail banding/discoloration

Gastrointestinal: Nausea, vomiting and anorexia (14%)

Hematologic: Anemia (19% to 24%); myelosuppression, common, dose limiting, delayed

Onset: 3 weeks

Nadir: 4-6 weeks

Recovery: 6-8 weeks

1% to 10%:

Dermatologic: Rash

Gastrointestinal: Stomatitis

Neuromuscular: Paresthesia

Renal: Creatinine increased (2%)

Respiratory: Interstitial pneumonitis, infiltrates, dyspnea, cough (7%)

<1%: Malaise, pruritus, extravasation reactions, hemolytic uremic syndrome, renal failure, bladder fibrosis/contraction (intravesical administration)

Oncology: VesicantYes; see Management of Drug Extravasations.

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

Antineoplastic Agents (Vinca Alkaloids): May enhance the adverse/toxic effect of Mitomycin. Specifically, the risk of pulmonary toxicity may be increased. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid black cohosh, dong quai in estrogen-dependent tumors.

Monitoring ParametersPlatelet count, CBC with differential, hemoglobin, prothrombin time, renal and pulmonary function tests

Nursing: Physical Assessment/MonitoringUse with caution in presence of hepatobiliary dysfunction or radiation therapy (past or present). Assess potential for interactions with other pharmacological and herbal products patient may be taking. See Administration for infusion specifics; infusion site must be closely monitored to prevent extravasation. Mitomycin is a potent vesicant; may cause ulceration, necrosis, cellulitis, and tissue sloughing if infiltrated. Evaluate results of laboratory tests, therapeutic response, and adverse reactions (eg, signs of CHF, hydration and nutritional status, and opportunistic infection) on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsPlatelet count, CBC with differential, prothrombin time, renal and pulmonary function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug is administered intravenously; report immediately any redness, swelling, burning, or pain at infusion site. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition. You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations unless approved by prescriber). May cause nausea, vomiting, or anorexia (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); mouth sores (use soft toothbrush, waxed dental floss, and frequent mouth rinses); or loss of hair or discoloration of nails (may be reversible when therapy is discontinued). Report rash or itching, unresolved nausea or diarrhea; respiratory difficulty, swelling of extremities, sudden weight gain, or unusual cough; any numbness, tingling, or loss of sensation; or opportunistic infection (fever, chills, sore throat, burning urination, fatigue). **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 5 mg, 20 mg, 40 mg

Generic AvailableYes

Mechanism of ActionActs like an alkylating agent and produces DNA cross-linking (primarily with guanine and cytosine pairs); cell-cycle nonspecific; inhibits DNA and RNA synthesis; degrades preformed DNA, causes nuclear lysis and formation of giant cells. While not phase-specific *per se*, mitomycin has its maximum effect against cells in late G and early S phases.

Pharmacodynamics/Kinetics

Distribution: V_d: 22 L/m^2; high drug concentrations found in kidney, tongue, muscle, heart, and lung tissue; probably not distributed into the CNS

Metabolism: Hepatic

Half-life elimination: 23-78 minutes; Terminal: 50 minutes

Excretion: Urine (<10% as unchanged drug), with elevated serum concentrations

Related Information

- Management of Drug Extravasations
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Stomatitis.
Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions
Mental Health: Effects on Mental Status May cause drowsiness
Mental Health: Effects on Psychiatric Treatment Myelosuppression is common; avoid with clozapine and carbamazepine
Index Terms Mitomycin-C; Mitomycin-X; MTC; NSC-26980

References

Aronoff GR, Bennett WM, Berns JS, et al, *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*, 5th ed. Philadelphia, PA: American College of Physicians; 2007, p 101.

Bradner WT, "Mitomycin C: A Clinical Update," *Cancer Treat Rev*, 2001, 27(1):35-50.[PubMed 11237776]

den Hartigh J, Verweij J, and Pinedo HM, "Mitomycin C," *Cancer Chemother Biol Response Modif*, 1987, 9:56-62. [PubMed 3152789]

Doll DC, Weiss RB and Issell BF, "Mitomycin: Ten Years After Approval for Marketing," *J Clin Oncol*, 1985, 3(2):276-86. [PubMed 3881563]

Gandolfi SA, Vecchi M and Braccio L, "Decrease of Intraocular Pressure After Subconjunctival Injection of Mitomycin in Human Glaucoma," *Arch Ophthalmol*, 1995, 113(5):582-5. [PubMed 7748127]

Gibson NW, Phillips RM, and Ross D, "Mitomycin C," *Cancer Chemother Biol Response Modif*, 1994, 15:51-7.[PubMed 7779596]

Hortobagyi GN, "Mitomycin: Its Evolving Role in the Treatment of Breast Cancer," *Oncology*, 1993, 50(Suppl 1):1-8.

Rodriguez JA, Ferrari C, and Hernandez GA, "Intraoperative Application of Topical Mitomycin C 0.05% for Pterygium Surgery," *Bol Asoc Med P R*, 2004, 96(2):100-2.[PubMed 15580913]

Verweij J, "Mitomycins," *Cancer Chemother Biol Response Modif*, 1996, 16:48-56.[PubMed 8639396]

Verweij J and Pinedo HM, "Mitomycin C: Mechanism of Action, Usefulness and Limitations," *Anticancer Drugs*, 1990, 1(1):5-13.[PubMed 2131038]

Wilkins M, Indar A, and Wormald R, "Intra-Operative Mitomycin C for Glaucoma Surgery," *Cochrane Database Syst Rev*, 2001, (1):CD002897.

International Brand Names Ametycine (FR); Baxmicin (BR); Datisan (AR); Metomit (CN); Mitocyna (PY); Mitomicina-C (PT); Mitomycin (DE, DK, MY, SE); Mitomycin C (ES, HK, IL, IN, PL); Mitomycin-C (AT, BG, CH, GR, HN, ID, IT, NL, PH, RU, TH, TR, TW); Mitomycin-C Kyowa (AU, CZ, GB, HU, LU); Mitomycine (BE); Mitostat (FI); Mitotie (EC, MX); Mutamycin (DK, EE, FI, HR, NO, PT, UY); Mytomycin C (JP); Mytoxid (PH); Riptam (PE); Vetio (AR)

Mitotane

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Mitotane may be confused with mitomycin

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(MYE toe tane)

U.S. Brand NamesLysodren®

Canadian Brand NamesLysodren®

Pharmacologic CategoryAntineoplastic Agent, Miscellaneous

Use: Labeled IndicationsTreatment of adrenocortical carcinoma

Use: Unlabeled/InvestigationalTreatment of Cushing's syndrome

Dosing: Adults**Adrenocortical carcinoma:** Oral: Start at 2-6 g/day in 3-4 divided doses, then increase incrementally to 9-10 g/day in 3-4 divided doses (maximum daily dose: 18 g)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Adrenocortical carcinoma (unlabeled use):** Oral: 1-2 g/day in divided doses, increasing gradually to a maximum of 5-7 g/day

Dosing: Hepatic ImpairmentDose may need to be decreased in patients with liver disease.

StorageStore at room temperature.

ContraindicationsHypersensitivity to mitotane or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Adrenal insufficiency: See "Concerns related to adverse effects" below.
- Experienced physician: See "Other warnings/precautions" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Adrenal insufficiency: **[U.S. Boxed Warning]: Acute adrenal insufficiency may occur in the face of shock, trauma, or infection.** Mitotane should be discontinued temporarily in this setting and appropriate steroid coverage should be administered.
- Neurotoxicity: Observe patients for neurotoxicity with long-term (>2 years) use.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; metabolism may be decreased.
- Metastatic masses: Surgically remove tumor tissues from metastatic masses prior to initiation of treatment; rapid cytotoxic effect may cause tumor hemorrhage.

Concurrent drug therapy issues:

- Corticosteroid replacement therapy: Steroid replacement with glucocorticoid, and sometimes mineralocorticoid, is necessary. It has been recommended that replacement therapy be initiated at the start of therapy, rather than waiting for evidence of adrenal insufficiency. Because mitotane can increase the metabolism of hydrocortisone, higher than usual replacement doses of the latter may be required.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning] Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have not been conducted. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

>10%:

Central nervous system: CNS depression (32%), somnolence (25%), dizziness/vertigo (15%)

Dermatologic: Skin rash (15%)

Gastrointestinal: Anorexia (24%), nausea (39%), vomiting (37%), diarrhea (13%)

Neuromuscular & skeletal: Weakness (12%)

1% to 10%:

Central nervous system: Headache (5%), confusion (3%)

Neuromuscular & skeletal: Muscle tremor (3%)

<1% and/or frequency not defined: Albuminuria, blurred vision, diplopia, flushing, hematuria, hemorrhagic cystitis, hypertension, hyperpyrexia, lens opacity, myalgia, orthostatic hypotension, protein bound iodine decreased, toxic retinopathy

Oncology: Emetic PotentialModerate (30% to 60%)

Drug Interactions

Potassium-Sparing Diuretics: May diminish the therapeutic effect of Mitotane. High dose diuretics (eg, Cushings syndrome) may present significantly higher risk than low doses (eg, CHF). *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersAdrenal function; neurologic assessments with chronic (>2 years) use

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological and herbal products patient may be taking. Evaluate therapeutic response and adverse reactions on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Patient EducationTake as directed; do not alter dose or discontinue without consulting prescriber. Desired effects of this drug may not be seen for 2-3 months. Wear identification that alerts medical personnel that you are taking this drug in event of shock or trauma. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition. Avoid alcohol. May cause dizziness, headache, confusion (avoid driving or performing tasks requiring alertness until response to drug is known); nausea, vomiting, or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report severe vomiting or diarrhea; rash; or muscular twitching, tremor, numbness, or weakness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet [scored]:

Lysodren®: 500 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Lysodren)

500 mg (30): $154.06

Mechanism of ActionCauses adrenal cortical atrophy; drug affects mitochondria in adrenal cortical cells and decreases production of cortisol; also alters the peripheral metabolism of steroids

Pharmacodynamics/Kinetics

Absorption: Oral: ~35% to 40%

Distribution: Stored mainly in fat tissue but is found in all body tissues

Metabolism: Hepatic and other tissues

Half-life elimination: 18-159 days

Time to peak, serum: 3-5 hours

Excretion: Urine (10% as metabolites) and feces (1% to 17% as metabolites)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and depression are common; may cause sedation, irritability, or confusion

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation

Index TermsNSC-38721; o,p′-DDD

References

Boscaro M, Barzon L, Fallo F, et al, "Cushing's Syndrome," *Lancet*, 2001, 357(9258):783-91.[PubMed 11253984]

De Leon DD, Lange BJ, Walterhouse D, et al, "Long-Term (15 years) Outcome in an Infant with Metastatic Adrenocortical Carcinoma," *J Clin Endocrinol Metab*, 2002, 87(10):4452-6.[PubMed 12364417]

Kasperlik-Zaluska AA, "Clinical Results of the Use of Mitotane for Adrenocortical Carcinoma," *Braz J Med Biol Res*, 2000, 33(10):1191-6.[PubMed 11004719]

Newell-Price J, Bertagna X, Grossman AB, et al, "Cushing's Syndrome," *Lancet*, 2006, 367(9522):1605-17.[PubMed 16698415]

Rodriguez-Galindo C, Figueiredo BC, Zambetti GP, et al, "Biology, Clinical Characteristics, and Management of Adrenocortical Tumors in Children," *Pediatr Blood Cancer*, 2005, 45(3):265-73.[PubMed 15747338]

International Brand NamesLisodren (BR); Lysodren (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, KP, NL, NO, PT, RU, SE, TR, TW); Opeprim (JP)

Mitoxantrone + Hydrocortisone

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer

Regimen UseProstate cancer

Regimen

Mitoxantrone: I.V.: 14 mg/m^2 day 1

[total dose/cycle = 14 mg/m^2]

Hydrocortisone: Oral: 40 mg daily

[total dose/cycle = 840 mg]

Repeat cycle every 3 weeks

References

Kantoff PW, Halabi S, Conaway M, et al, âHydrocortisone With or Without Mitoxantrone in Men With Hormone-Refractory Prostate Cancer: Results of the Cancer and Leukemia Group B 9182 Study,â *J Clin Oncol*, 1999, 17(8):2506-13.[PubMed 10561316]

Mitoxantrone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Mitoxantrone Cardiac Monitoring Recommendations - July 30, 2008

The U.S. Food and Drug Administration (FDA) issued an alert re-enforcing the need for left ventricular ejection fraction (LVEF) evaluation with mitoxantrone (Novantrone®) use. In 2005, the product labeling was updated, recommending LVEF evaluation before treatment initiation and prior to each dose in patients with multiple sclerosis (MS). This was in response to postmarketing reports of decreases in LVEF and heart failure in patients who had received cumulative doses of <100 mg/m^2. The FDA has received further information from a postmarketing safety study demonstrating a lack of adherence to these recommendations. In addition to reminding healthcare providers to follow cardiac monitoring recommendations, the FDA is now advising that all MS patients who have completed treatment with mitoxantrone should receive an annual LVEF evaluation to monitor for delayed cardiotoxicity.

Additional information can be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Mitoxantrone

Medication Safety Issues

Sound-alike/look-alike issues:

Mitoxantrone may be confused with methotrexate, mitomycin, Mutamycin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(mye toe ZAN trone)

U.S. Brand NamesNovantrone®

Canadian Brand NamesMitoxantrone Injection®; Novantrone®

Pharmacologic CategoryAntineoplastic Agent, Anthracenedione

Use: Labeled IndicationsTreatment of acute nonlymphocytic leukemias, prostate cancer, lymphoma, secondary progressive or relapsing-remitting multiple sclerosis (MS)

Use: Unlabeled/InvestigationalTreatment of pediatric acute leukemias, pediatric sarcoma

Dosing: AdultsDetails concerning dosing in combination regimens should also be consulted. I.V. (may dilute in D_5W or NS):

Acute leukemias: I.V.:

Induction: 12 mg/m^2 once daily for 3 days; for incomplete response, may repeat at 12 mg/m^2 once daily for 2 days

Consolidation: 12 mg/m^2 once daily for 2 days, repeat in 4 weeks

Solid tumors: I.V.: 12-14 mg/m^2 every 3-4 weeks **or** 2-4 mg/m^2/day for 5 days

Hormone-refractory prostate cancer: I.V.: 12-14 mg/m^2 every 3 weeks

Multiple sclerosis: I.V.: 12 mg/m^2 every 3 months (maximum lifetime cumulative dose: 140 mg/m^2; discontinue use with LVEF <50% or clinically significant reduction in LVEF)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDetails concerning dosing in combination regimens should also be consulted.

Acute leukemias (unlabeled use): I.V. (may dilute in D_5W or NS):

Children ≤2 years: 0.4 mg/kg/day once daily for 3-5 days

Children >2 years: Refer to adult dosing.

Solid tumors (unlabeled use): I.V.: Children: 18-20 mg/m^2 every 3-4 weeks **or** 5-8 mg/m^2 every week

Dosing: Renal ImpairmentSafety and efficacy have not been established.

Hemodialysis: Supplemental dose is not necessary

Peritoneal dialysis: Supplemental dose is not necessary

Elderly: Clearance is decreased in elderly patients; use with caution

Dosing: Hepatic ImpairmentOfficial dosage adjustment recommendations have not been established. Clearance is reduced in hepatic dysfunction; patients with severe hepatic dysfunction (bilirubin >3.4 mg/dL) have an AUC of 3 times greater than patients with normal hepatic function. Consider dose adjustments. **Note:** MS patients with hepatic impairment should not receive mitoxantrone.

Dosing: Combination Regimens

Breast cancer:

CNF

NFL

Leukemia, acute lymphocytic: FIS-HAM

Leukemia, acute myeloid:

7 + 3 (Mitoxantrone)

EMA 86

FIS-HAM

MV

Leukemia, acute promyelocytic: Tretinoin-Idarubicin

Lymphoma, non-Hodgkin's:

CNOP

Fludarabine-Cyclophosphamide-Mitoxantrone-Rituximab

Fludarabine-Mitoxantrone

Fludarabine-Mitoxantrone-Dexamethasone (NHL)

Fludarabine-Mitoxantrone-Dexamethasone-Rituximab

Fludarabine-Mitoxantrone-Rituximab

MINE

MINE-ESHAP

Prostate cancer:

Mitoxantrone + Hydrocortisone

MP (Prostate Cancer)

Oncology: Bone Marrow - High DoseI.V.: 24-48 mg/m^2 as a single dose; duration of infusion is 1-4 hours; total doses of 75-90 mg/m^2 have been used. Generally combined with other high-dose chemotherapeutic drugs.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Irritant. Administered as a short (5-30 minutes) I.V. infusion; continuous 24-hour infusions are occasionally used. Although not generally recommended, mitoxantrone has been given as a rapid bolus over 1-3 minutes. High doses for bone marrow transplant are usually given as 1- to 4-hour infusions.

Administration: I.V. DetailAvoid extravasation - although has not generally been proven to be a vesicant.

StorageStore intact vials at 15°C to 25°C (59°F to 77°F); do not freeze. Opened vials may be stored at room temperature for 7 days or under refrigeration for up to 14 days. Solutions diluted for administration are stable for 7 days at room temperature or under refrigeration.

ReconstitutionDilute in at least 50 mL of NS or D$_5$W.

CompatibilityStable in D$_5$NS, D$_5$W, NS.

Y-site administration: Compatible: Allopurinol, amifostine, cladribine, etoposide phosphate, filgrastim, fludarabine, gatifloxacin, gemcitabine, granisetron, linezolid, melphalan, ondansetron, sargramostim, teniposide, thiotepa, vinorelbine. **Incompatible:** Amphotericin B cholesteryl sulfate complex, aztreonam, cefepime, doxorubicin liposome, paclitaxel, piperacillin/tazobactam, propofol.

Compatibility when admixed: Compatible: Cyclophosphamide, cytarabine, fluorouracil, hydrocortisone sodium succinate, potassium chloride. **Incompatible:** Heparin. **Variable (consult detailed reference):** Hydrocortisone sodium phosphate.

ContraindicationsHypersensitivity to mitoxantrone or any component of the formulation; multiple sclerosis with left ventricular ejection fraction (LVEF) <50% or clinically significant decrease in LVEF

Warnings/Precautions

Boxed warnings:

- Appropriate administration: See “Other warnings/precautions” below.

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.
- Myocardial toxicity: See “Concerns related to adverse effects” below.
- Secondary malignancy: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Treatment may lead to severe myelosuppression; use with caution in patients with pre-existing myelosuppression. **[U.S. Boxed Warning]: Do not use if baseline neutrophil count <1500 cells/mm^3 (except for in the treatment of ANLL).**
- Myocardial toxicity: **[U.S. Boxed Warning]: May cause myocardial toxicity and potentially-fatal heart failure; risk increases with cumulative dosing.** Effects may be delayed. Predisposing factors for mitoxantrone-induced cardiotoxicity include prior anthracycline therapy, prior cardiovascular disease, concomitant use of cardiotoxic drugs, and mediastinal/pericardial irradiation. Not recommended for use when left ventricular ejection fraction (LVEF) <50%, or baseline LVEF below the lower limit of normal (LLN) for MS patients. Use in MS should be limited to a cumulative dose of ≤140 mg/m^2, and discontinued if LVEF falls below LLN or a significant decrease in LVEF is observed; decreases in LVEF and heart failure have been observed in patients with MS who have received cumulative doses <100 mg/m^2. Patients with MS should undergo annual LVEF evaluation following discontinuation of therapy to monitor for delayed cardiotoxicity.
- Secondary malignancy: **[U.S. Boxed Warning]: Has been associated with the development of secondary acute myelogenous leukemia and myelodysplasia;** risk is increased in patients who are heavily pretreated, with higher doses, and with combination chemotherapy.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment recommended. Not for treatment of multiple sclerosis in patients with concurrent hepatic impairment.
- Multiple sclerosis: Not for treatment of primary progressive multiple sclerosis.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate administration: **[U.S. Boxed Warning]: For I.V. administration only; may cause severe local tissue damage if extravasation occurs. Do not administer intrathecally; may cause serious and permanent neurologic damage.**
- Blue-green coloration: May cause urine, saliva, tears, and sweat to turn blue-green for 24 hours postinfusion; whites of eyes may have blue-green tinge.
- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsAdverse effects were noted in animal studies. May cause fetal harm if administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. Pregnancy should be avoided while on treatment. Women with multiple sclerosis and who are biologically capable of becoming pregnant should have a pregnancy test prior to each dose.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsMitoxantrone is excreted in human milk and significant concentrations (180 mg/mL) have been reported for 28 days after the last administration. Because of the potential for serious adverse reactions in infants from mitoxantrone, breast-feeding should be discontinued before starting treatment.

Adverse ReactionsIncludes events reported with any indication; incidence varies based on treatment/dose

>10%:

Cardiovascular: Arrhythmia (3% to 18%), edema (10% to 31%), ECG changes (11%)

Central nervous system: Pain (8% to 41%), fatigue (up to 39%), fever (6% to 78%), headache (6% to 13%)

Dermatologic: Alopecia (20% to 61%), nail bed changes (11%)

Endocrine & metabolic: Amenorrhea (28% to 53%), menstrual disorder (26% to 61%), hyperglycemia (10% to 31%)

Gastrointestinal: Abdominal pain (9% to 15%), anorexia (22% to 25%), nausea (26% to 76%), constipation (10% to 16%), diarrhea (14% to 47%), GI bleeding (2% to 16%), mucositis (10% to 29%), stomatitis (8% to 29%), dyspepsia (5% to 14%), vomiting (6% to 11%), weight gain/loss (13% to 17%)

Genitourinary: Abnormal urine (6% to 11%), urinary tract infection (7% to 32%)

Hematologic: Neutropenia (79% to 100%), leukopenia (9% to 100%), lymphopenia (72% to 95%), anemia (5% to 75%), hemoglobin decreased (43%), thrombocytopenia (33% to 39%), petechiae/bruising (6% to 11%); myelosuppression (WBC: mild; platelets: mild; onset: 7-10 days; nadir: 14 days; recovery: 21 days)

Hepatic: Alkaline phosphatase increased (37%), transaminases increased (5% to 20%), GGT increased (3% to 15%)

Neuromuscular & skeletal: Weakness (24%)

Renal: BUN increased (22%), creatinine increased (13%), hematuria (11%)

Respiratory: Cough (5% to 13%), dyspnea (6% to 18%), upper respiratory tract infection (7% to 53%)

Miscellaneous: Fungal infection (9% to 15%), infection (4% to 18%), sepsis (ANLL 31% to 34%)

1% to 10%:

Cardiovascular: Ischemia (5%), LVEF decreased (≤5%), hypertension (4%), CHF (2% to 5%)

Central nervous system: Chills (5%), anxiety (5%), depression (5%), seizure (2% to 4%)

Dermatologic: Skin infection

Endocrine & metabolic: Hypocalcemia (10%), hypokalemia (7% to 10%), hyponatremia (9%), menorrhagia (7%)

Gastrointestinal: Aphthosis (10%)

Genitourinary: Impotence (7%), sterility (5%)

Hematologic: Granulocytopenia (6%), hemorrhage (6%)

Hepatic: Jaundice (3% to 7%)

Neuromuscular & skeletal: Back pain (8%), myalgia (5%), arthralgia (5%)

Ocular: Conjunctivitis (5%), blurred vision (3%)

Renal: Renal failure (8%), proteinuria (6%)

Respiratory: Rhinitis (10%), pneumonia (9%), sinusitis (6%)

Miscellaneous: Systemic infection, diaphoresis (9%), development of secondary leukemia (~1% to 2%)

<1% or frequency not defined: Acute leukemia, allergic reaction, anaphylactoid reactions, anaphylaxis, chest pain, extravasation and phlebitis at the infusion site, interstitial pneumonitis (has occurred during combination chemotherapy), irritant chemotherapy with blue skin discoloration, rash, tachycardia

Oncology: VesicantNo; may be an irritant
Oncology: Emetic PotentialLow (10% to 30%)
Oncology: Bone Marrow - Unique Toxicity

Cardiovascular: Bradycardia (infusion-related), heart failure

Dermatologic: Alopecia

Gastrointestinal: Severe mucositis, skin discoloration

Metabolism/Transport Effects**Inhibits** CYP3A4 (weak)
Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid echinacea (may diminish the immunosuppressant effect).
Monitoring ParametersCBC, serum uric acid (for treatment of leukemia), liver function tests; signs and symptoms of cardiac disease; evaluate ECG and LVEF prior to start of therapy and regularly during treatment, especially with the development of signs and symptoms of heart failure. In addition, for the treatment of multiple sclerosis, obtain pregnancy test and monitor LVEF prior to each dose and annually after completion of therapy (to monitor for delayed cardiotoxicity).
Nursing: Physical Assessment/MonitoringShould only be administered under the supervision of an experienced cancer chemotherapy physician. Assess patient carefully for cautious use indications and contraindications. Note Administration for infusion specifics. Infusion site must be monitored closely to prevent extravasation. Evaluate results of laboratory tests prior to start of therapy and regularly during treatment. Evaluate evidence of therapeutic effectiveness and adverse response (eg, arrhythmia, hypersensitivity reactions, myelosuppression [anemia], gastrointestinal upset [nutritional and hydration status], opportunistic infection, gout, CHF [rales, dyspnea, edema]) with each dose and throughout therapy. Teach patient possible side effects/appropriate interventions (eg, avoid crowds, maintain hydrations) and adverse symptoms to report (eg, symptoms of cardiotoxicity).
Monitoring: Lab TestsCBC, serum uric acid, liver function, echocardiogram; LVEF prior to start of therapy and regularly during treatment, especially with the development of signs and symptoms of heart failure. In addition, in the treatment of multiple sclerosis, obtain pregnancy test prior to all doses and LVEF prior to each dose and annually after completion of therapy (to monitor for delayed cardiotoxicity)
Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. This drug is only administered by infusion; report immediately any redness, swelling, burning, or pain at infusion site. Maintain

adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition (small, frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause urine, saliva, tears, sweat, and whites of eyes to turn blue-green for 24 hours postinfusion (this is normal); nausea, vomiting, or GI upset (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); mouth sores (use soft toothbrush or cotton swabs, waxed dental floss, and frequent mouth rinses); headache, dizziness, or blurred vision (use caution when driving or engaging in tasks that are potentially hazardous until response to drug is known); or loss of hair (may be reversible). Report chest pain or palpitations; rapid or erratic heartbeat; difficulty breathing or constant cough; swelling of extremities or sudden weight gain; persistent fever or chills; or opportunistic infection (eg, fever, chills, sore throat, burning urination, fatigue); changed or decreased urine output. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution [concentrate; preservative free]: 2 mg/mL (10 mL, 12.5 mL, 15 mL, 20 mL)

Novantrone®: 2 mg/mL (10 mL, 15 mL [DSC])

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Concentrate (Novantrone)

2 mg/mL (10): $1340.73

Mechanism of ActionAnalogue of the anthracyclines, mitoxantrone intercalates DNA; binds to nucleic acids and inhibits DNA and RNA synthesis by template disordering and steric obstruction; replication is decreased by binding to DNA topoisomerase II and seems to inhibit the incorporation of uridine into RNA and thymidine into DNA; active throughout entire cell cycle

Pharmacodynamics/Kinetics

Absorption: Oral: Poor

Distribution: V_d: 14 L/kg; distributes into pleural fluid, kidney, thyroid, liver, heart, and red blood cells

Protein binding: >95%, 76% to albumin

Metabolism: Hepatic; pathway not determined

Half-life elimination: Terminal: 23-215 hours; may be prolonged with hepatic impairment

Excretion: Urine (6% to 11%; 65% as unchanged drug); feces (25%; 65% as unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine

Oncology: Bone Marrow CommentsExtensive pretreatment with anthracyclines increases risk of cardiac toxicity.

Index TermsCL-232315; DHAD; DHAQ; Dihydroxyanthracenedione Dihydrochloride; Mitoxantrone Hydrochloride; Mitozantrone; NSC-301739

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International Brand NamesBluxantron (EC); Domitrone (PH); Elsep (FR); Misostol (PY, VE); Mitoxantrone (PL); Mitoxgen (AR, MX); Mitroxone

(MX); Mittrone (KP); Neotalem (CN, TH); Novantron (AT, CH, DE); Novantrone (AU, BE, BG, BR, CZ, DK, ES, FI, FR, GB, HN, HR, HU, IL, IT, JP, LU, NL, NO, PK, PT, RU, SE, TR, TW); Oncotron (IN); Onkotrone (AU, EE, HU); Pralifan (ES)

Moclobemide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(moe KLOE be mide)

Canadian Brand NamesApo-Moclobemide®; Dom-Moclobemide; Manerix®; Novo-Moclobemide; Nu-Moclobemide; PMS-Moclobemide

Pharmacologic Category[Antidepressant, Monoamine Oxidase Inhibitor, Reversible]

Use: Labeled IndicationsSymptomatic relief of depressive illness

Dosing: Adults**Depressive illness:** Oral: Initial: 300 mg/day in 2 divided doses; increase gradually to maximum of 600 mg/day. **Note:** Individual patient response may allow a reduction in daily dose in long-term therapy.

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic ImpairmentDecrease daily dose by $^{1}/_{3}$ to $^{1}/_{2}$

Administration: OralAdminister immediately after meals.

Dietary ConsiderationsShould be taken immediately after meals. Manufacturer states no special dietary restrictions are required; may be taken with tyramine-containing foods. However, patients should be instructed to recognize occipital headache, palpitations, neck stiffness, or other signs of a severe reaction.

StorageStore at 15°C to 30°C (59°F to 86°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to moclobemide or any component of the formulation; uncontrolled hypertension; hepatic disease; confusional states; concurrent use of sympathomimetics (and related compounds), MAO inhibitors, meperidine, tricyclic antidepressants, serotonergic drugs (including SSRIs) - do not use within 5 weeks of fluoxetine discontinuation or 2 weeks of other antidepressant discontinuation; general anesthesia, local vasoconstrictors; spinal anesthesia (hypotension may be exaggerated). Not approved for use in patients <18 years of age.

Warnings/Precautions

Concerns related to adverse effects:

- Suicidal thinking/behavior: The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Use caution in high-risk patients during initiation of therapy. Prescriptions should be written for the smallest quantity consistent with good patient care.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dose adjustment required.
- Pheochromocytoma: Use with caution in patients with pheochromocytoma.
- Renal impairment: Use with caution in patients with renal impairment.
- Thyroid dysfunction: Use with caution in patients with thyrotoxicosis.

Concurrent drug therapy issues:

- Anesthesia: Discontinue 2 days prior to local or general anesthesia.
- Buspirone: Use with caution in patients receiving concurrent buspirone.
- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.
- Serotonergic agents: Severe reactions may occur if MAO inhibitors and serotonergic agents, including SSRIs are used concurrently.

Other warnings/precautions:

- Tyramine restriction: Dietary restriction of tyramine does not appear to be necessary for patients receiving moclobemide (patients must be informed of signs/symptoms of reaction).

Pregnancy Risk FactorNot available

Pregnancy ConsiderationsSafety has not been established, use only if benefits outweigh the risks.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsLess than 1% of maternal dose is excreted in breast milk; benefits should outweigh risks.

Adverse Reactions

1% to 10%:

Cardiovascular: Tachycardia (4%), hypotension (3%)

Central nervous system: Headache (8%), dizziness (7%), sleep disturbance (7%), agitation (5%), nervousness (5%), sedation (4%), somnolence (4%), anxiety (3%)

Endocrine & metabolic: Appetite increased (1%)

Gastrointestinal: Xerostomia (9%), nausea (5%), constipation (4%), abdominal pain (2%), diarrhea (2%), vomiting (2%)

Neuromuscular & skeletal: Weakness (1%)

Ocular: Blurred vision (2%)

Miscellaneous: Diaphoresis increased (2%)

<1%: Aggression, allergic reaction, angina, apathy, bradycardia, confusion, conjunctivitis, delusions, disorientation, dysarthria, dyspnea, dysuria, extrapyramidal effects, flushing, gastritis, gingivitis, hallucinations, hypertension, insomnia, irritability, mania, metrorrhagia, migraine, muscular pain, nightmares, paresthesia, photopsia, polyuria, prolonged menstruation, pruritus, rash, skeletal pain, stomatitis, taste alteration, tenesmus, tinnitus, transaminases increased, urticaria, visual disturbances

Metabolism/Transport Effects **Substrate** (major) of CYP2C19, 2D6; **Inhibits** CYP1A2 (weak), 2C19 (weak), 2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): MAO Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists (Indirect-Acting): MAO Inhibitors may enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Alpha1-Agonists: MAO Inhibitors may enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Alpha2-Agonists (Ophthalmic): MAO Inhibitors may enhance the hypertensive effect of Alpha2-Agonists (Ophthalmic). *Risk X: Avoid combination*

Altretamine: May enhance the orthostatic effect of MAO Inhibitors. *Risk C: Monitor therapy*

Amphetamines: MAO Inhibitors may enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Anilidopiperidine Opioids: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. *Risk D: Consider therapy modification*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Atomoxetine: MAO Inhibitors may enhance the neurotoxic (central) effect of Atomoxetine. *Risk X: Avoid combination*

Beta2-Agonists: MAO Inhibitors may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: MAO Inhibitors may enhance the neurotoxic (central) effect of BuPROPion. *Risk X: Avoid combination*

BusPIRone: May enhance the adverse/toxic effect of MAO Inhibitors. Elevated blood pressure has been reported. *Risk X: Avoid combination*

Cimetidine: May decrease the metabolism of Moclobemide. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

COMT Inhibitors: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Cyclobenzaprine: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dexmethylphenidate: MAO Inhibitors may enhance the hypertensive effect of Dexmethylphenidate. *Risk X: Avoid combination*

Dextromethorphan: MAO Inhibitors may enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

Levodopa: May enhance the adverse/toxic effect of MAO Inhibitors. Of particular concern is the development of hypertensive reactions when levodopa is used with nonselective MAOI. *Risk D: Consider therapy modification*

Linezolid: MAO Inhibitors may enhance the adverse/toxic effect of Linezolid. *Risk X: Avoid combination*

Maprotiline: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

Meperidine: MAO Inhibitors may enhance the serotonergic effect of Meperidine. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methyldopa: MAO Inhibitors may enhance the adverse/toxic effect of Methyldopa. *Risk X: Avoid combination*

Methylphenidate: MAO Inhibitors may enhance the hypertensive effect of Methylphenidate. *Risk X: Avoid combination*

Mirtazapine: MAO Inhibitors may enhance the neurotoxic (central) effect of Mirtazapine. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the adverse/toxic effect of MAO Inhibitors. Specifically, the risk of serotonin syndrome or other serotonergic adverse events may be increased. *Risk X: Avoid combination*

Rauwolfia Alkaloids: MAO Inhibitors may enhance the adverse/toxic effect of Rauwolfia Alkaloids. Existing MAOI therapy can result in paradoxical effects of added rauwolfia alkaloids (eg, excitation, hypertension). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: MAO Inhibitors may decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. **Exceptions:** Eletriptan; Frovatriptan; Naratriptan. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tetrabenazine: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

TraMADol: May enhance the neuroexcitatory and/or seizure-potentiating effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: MAO Inhibitors may enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Dietary restriction of tyramine does not appear to be necessary.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, ginseng. Avoid ginkgo (may lead to MAO inhibitor toxicity). Avoid ephedra, yohimbe (can cause hypertension). Avoid kava (may increase CNS depression).

Monitoring ParametersBlood pressure, warning signs of suicide

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet: 150 mg, 300 mg

Alti-Moclobemide [CAN], Apo-Moclobemide® [CAN], Dom-Moclobemide® [CAN], Manerix®e [CAN], Novo-Moclobemidee [CAN], Nu-Moclobemidee [CAN], PMS-Moclobemide [CAN]: 150 mg, 300 mg [not available in the U.S.]

Generic AvailableYes

ManufacturerHoffman-La Roche Ltd (Canada)

Mechanism of ActionMoclobemide is a benzamide derivative which acts as a short-acting reversible inhibitor of monoamine oxidase (MAO), which inhibits the metabolism (deamination) of serotonin, norepinephrine, and dopamine. It has a relative specificity for the A subtype of monoamine oxidase (MAO type A). Its action leads to increased concentrations of these neurotransmitters, which may account for the antidepressant activity of moclobemide.

Pharmacodynamics/Kinetics

Absorption: 98% from GI tract

Distribution: 1.2 L/kg

Protein binding: ~50% to albumin

Metabolism: Oxidative reactions

Half-life elimination: Terminal: 1-2 hours

Excretion: Urine (95%, as metabolites)

Pharmacotherapy PearlsNot available in U.S.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

References

Manerix® prescribing information, Hoffman-La Roche Ltd, Ontario, February 1998.

International Brand NamesAkenex (AR); Amira (AU); Animex (UY); Arima (AU); Aurorex (EC, MX, PE); Aurorix (AR, AT, AU, BE, BG, BR, CH, CN, CZ, DK, EE, FI, GR, HK, HN, HR, HU, ID, IT, KP, LU, NL, NO, PH, PK, PL, PT, SE, TH, TR, UY); Biorix (TW); Clorix (ZA); Feraken (MX); Inpront (CN); Manerix (ES, GB, IE); Maosig (AU); Mobemid (PL); Mobemide (IL, SG); Moclamine (FR); Moclod (TW); Moclodura (DE); Mocloxil (PL); Moklar (PL); Morex (IN); Rimarex (IN)

Modafinil

Lexi-Drugs Online

English

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Special Alerts

Medications for ADHD: AHA Clarification of Cardiovascular Screening Recommendation - May 2008

In an effort to reduce the rate of sudden cardiac death especially in pediatric patients receiving stimulant medications for the treatment of attention-deficit/hyperactivity disorder (ADHD), the American Heart Association (AHA) has issued a statement in April 2008 recommending that all children diagnosed with ADHD who may be candidates for stimulant medications have a thorough cardiovascular assessment prior to initiation of drug therapy. The AHA scientific statement was issued by the Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. On May 16, 2008, the AHA issued a clarification of the recommendations due to the language regarding ECG recommendations and subsequent interpretations.

These recommendations are based on the Food and Drug Administration (FDA) reports of serious cardiovascular adverse events (including sudden death) in patients (both children and adults) taking usual doses of stimulant medications. Most of these patients were found to have underlying structural heart disease (eg, hypertrophic obstructive cardiomyopathy). In 2006, these reports prompted the FDA to recommend labeling changes of these medications to include warnings about cardiovascular events and to develop patient medication guides to be distributed with each prescription.

Stimulant medications theoretically increase cardiovascular risk due to potential effects on blood pressure elevation and increased heart rate. These effects have generally been considered clinically insignificant in most children, however, may be detrimental in certain patients with underlying cardiovascular disease. None of the medications have been shown to cause heart conditions or proven to have caused sudden cardiac death.

The committee suggests that patients needing the following ADHD medications receive a thorough cardiovascular assessment: Methylphenidate, amphetamine, dextroamphetamine, atomoxetine, clonidine, guanfacine, desipramine, imipramine, bupropion, and modafinil.

According to the clarified AHA recommendations, this assessment should include a combination of thorough medical history, family history, and physical examination with the intent to identify risk factors for sudden death. Although not mandatory, physicians should consider obtaining an ECG.

Patients already maintained on ADHD medications should not stop taking their medication. Instead, patients or their caregivers should contact their healthcare provider. It is reasonable that these patients undergo a similar cardiovascular assessment without interruption of therapy.

Press releases and clarified recommendations from the AHA note that the intent of this statement is not to reduce appropriate use of these medications, but to provide physicians with useful tools to identify heart conditions in children with ADHD in order to make more informed prescribing decisions. ECG testing is recommended as one option to be used as part of a combination screening process. They do suggest that a lack of ECG testing should not necessarily mean that treatment not be initiated.

The clarified statement has been endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, and the National Initiative for Children’s Healthcare Quality.

For more information, refer to:

- http://americanheart.mediaroom.com/index.php?s=43&item=422
- http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.189473/DC1
- http://americanheart.mediaroom.com/index.php?s=43&item=398
- http://www.fda.gov/medwatch/safety/2007/safety07.htm
- http://www.fda.gov/bbs/topics/NEWS/2007/NEW01568.html

Nissen SE, “ADHD Drugs and Cardiovascular Risk,” *N Engl J Med*, 2006, 354(14):1445-48.

“Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder,” *J Am Acad Child Adolesc Psychiatry*, 2007, 46(7):894-921.

Vetter VL, Elia J, Erickson CH, et al, “Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing,” *Circulation*, 2008, 117:2407-23.

Wilens TE, Prince JB, Spencer TJ, et al, “Stimulants and Sudden Death: What is a Physician to do?” *Pediatrics*, 2006, 118(3):1215-19.

Pronunciation(moe DAF i nil)
U.S. Brand NamesProvigil®
Canadian Brand NamesAlertec®; APO-Modafinil
Pharmacologic CategoryStimulant
Use: Labeled IndicationsImprove wakefulness in patients with excessive daytime sleepiness associated with narcolepsy and shift work sleep disorder (SWSD); adjunctive therapy for obstructive sleep apnea/hypopnea syndrome (OSAHS)
Use: Unlabeled/InvestigationalAttention-deficit/hyperactivity disorder (ADHD); treatment of fatigue in MS and other disorders
Dosing: Adults

ADHD (unlabeled use): Oral: 100-300 mg once daily

Narcolepsy, obstructive sleep apnea/hypopnea syndrome (OSAHS): Oral: Initial: 200 mg as a single daily dose in the morning.

Shift work sleep disorder (SWSD): Oral: Initial: 200 mg as a single dose taken ~1 hour prior to start of work shift.

Note: Doses of 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit.

Dosing: ElderlyElimination of modafinil and its metabolites may be reduced as a consequence of aging and as a result, consider initiating dose at 100 mg once daily.
Dosing: Pediatric

ADHD (unlabeled use): Oral: 50-100 mg once daily

Dosing: Renal ImpairmentSafety and efficacy have not been established in severe renal impairment.
Dosing: Hepatic ImpairmentDose should be reduced to one-half of that recommended for patients with normal liver function.
RestrictionsC-IV
ContraindicationsHypersensitivity to modafinil, armodafinil, or any component of the formulation
Allergy Considerations

- Modafinil Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May impair the ability to engage in potentially hazardous activities. The degree of sleepiness should be reassessed frequently; some patients may not return to a normal level of wakefulness.

- Dermatologic effects (severe): Serious and life-threatening rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported with modafinil. Although initially reported in children during clinical trials, postmarketing cases have occurred in both children and adults. Most cases have occurred within the first 5 weeks of therapy; however, rare cases have occurred after long-term use. No risk factors have been identified to predict occurrence or severity. Patients should be advised to discontinue at first sign of rash.

- Hypersensitivity reactions: Rare cases of multiorgan hypersensitivity reactions in association with modafinil use and lone cases of angioedema and anaphylactoid reactions with armodafinil have been reported. Signs and symptoms are diverse, reflecting the involvement of specific organs. Patients typically present with fever and rash associated with organ-system dysfunction. Patients should be advised to report any signs and symptoms related to these effects; discontinuation of therapy is recommended.

Disease-related concerns:

- Cardiovascular disease: Use is not recommended in patients with a history of angina, cardiac ischemia, recent history of myocardial infarction, left ventricular hypertrophy, or patients with mitral valve prolapse who have developed mitral valve prolapse syndrome with previous CNS stimulant use. Increase monitoring in patients with hypertension; additional therapy may be necessary.

- Hepatic impairment: Use with caution in patients with hepatic impairment. Dosage reduction is recommended.

- Psychiatric disorders: Use with caution in patients with pre-existing psychosis or bipolar disorder (may induce mixed/manic episode). May exacerbate symptoms of behavior and thought disorder in psychotic patients; new onset psychosis or mania may occur with stimulant use; observe for symptoms of aggression, hostility, or suicidal ideation.

- Renal impairment: Use with caution in patients with renal impairment.

- Sleep disorders: Appropriate use: For use following complete evaluation of sleepiness and in conjunction with other standard treatments (eg, CPAP). The degree of sleepiness should be reassessed frequently; some patients may not return to a normal level of wakefulness.

- Tourette's syndrome: Use with caution in patients with Tourette's syndrome; stimulants may unmask tics.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <16 years of age (U.S. labeling) or <18 years of age (Canadian labeling).

Geriatric ConsiderationsClearance of modafinil may be reduced in the elderly. Safety and effectiveness in persons >65 years of age have not been established. In the limited number of elderly patients studied, the incidence of adverse events was similar to younger patients.

Pregnancy Risk FactorC

Pregnancy ConsiderationsEmbryotoxic effects have been observed in some, but not all animal studies. There are no adequate and well-controlled studies in pregnant women; use only when the potential risk of drug therapy is outweighed by the drug's benefits. Efficacy of steroidal contraceptives may be decreased; alternate means of contraception should be considered during therapy and for 1 month after modafinil is discontinued.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Headache (34%, dose related)

Gastrointestinal: Nausea (11%)

1% to 10%:

Cardiovascular: Chest pain (3%), hypertension (3%), palpitation (2%), tachycardia (2%), vasodilation (2%), edema (1%)

Central nervous system: Nervousness (7%), dizziness (5%), depression (2%), anxiety (5%; dose related), insomnia (5%), somnolence (2%), chills (1%), agitation (1%), confusion (1%), emotional lability (1%), vertigo (1%)

Dermatologic: Rash (1%; includes some severe cases requiring hospitalization)

Gastrointestinal: Diarrhea (6%), dyspepsia (5%), xerostomia (4%), anorexia (4%), constipation (2%), flatulence (1%), mouth ulceration (1%), taste perversion (1%)

Genitourinary: Abnormal urine (1%), hematuria (1%), pyuria (1%)

Hematologic: Eosinophilia (1%)

Hepatic: LFTs abnormal (2%)

Neuromuscular & skeletal: Back pain (6%), paresthesia (2%), dyskinesia (1%), hyperkinesia (1%), hypertonia (1%), neck rigidity (1%), tremor (1%)

Ocular: Amblyopia (1%), eye pain (1%), vision abnormal (1%)

Respiratory: Pharyngitis (4%), rhinitis (7%), lung disorder (2%), asthma (1%), epistaxis (1%)

Miscellaneous: Diaphoresis

Postmarketing and/or case reports: Agranulocytosis, anaphylactic reaction, angioedema, DRESS syndrome, erythema multiforme, hypersensitivity syndrome (multiorgan), mania, psychosis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (weak), 2A6 (weak), 2C9 (weak), 2C19 (strong), 2E1 (weak), 3A4 (weak); **Induces** CYP1A2 (weak), 2B6 (weak), 3A4 (weak)

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Modafinil may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol.

Food: Delays absorption, but does not affect bioavailability.

Monitoring Parameters Levels of sleepiness; blood pressure in patients with hypertension

When used for the treatment of ADHD, thoroughly evaluate for cardiovascular risk. Monitor heart rate, blood pressure, and consider obtaining ECG prior to initiation (Vetter, 2008).

Nursing: Physical Assessment/Monitoring Assess effectiveness and interactions of other medications, especially those that are metabolized by P450 enzymes. Note that modafinil has potential for abuse; caution patient about inappropriate or overuse. Perform careful cardiovascular assessment prior to initiating therapy. Assess knowledge/teach patient appropriate use, adverse symptoms to report. and interventions to reduce side effects.

Patient Education Take exactly as prescribed; do not exceed recommended dosage without consulting prescriber. Avoid drinking alcohol. Do not share medication with anyone else. Void before taking medication. You may experience headache, nervousness, confusion, or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); diarrhea (yogurt or buttermilk may help); or dry mouth or sore mouth, loss of appetite, or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). If you have diabetes, monitor glucose levels closely. Report chest pain or palpitations; respiratory difficulty; excessive insomnia, CNS agitation, depression, or memory disturbances; rash; vision changes; changes in urinary pattern or ejaculation disturbances; or persistent joint pain or stiffness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Provigil®: 100 mg, 200 mg

Generic Available No

Pricing: U.S. (www.drugstore.com)

Tablets (Provigil)

100 mg (30): $248.91

200 mg (30): $348.63

Mechanism of Action The exact mechanism of action is unclear, it does not appear to alter the release of dopamine or norepinephrine, it may exert its stimulant effects by decreasing GABA-mediated neurotransmission, although this theory has not yet been fully evaluated; several studies also suggest that an intact central alpha-adrenergic system is required for modafinil's activity; the drug increases high-frequency alpha waves while decreasing both delta and theta wave activity, and these effects are consistent with generalized increases in mental alertness

Pharmacodynamics/Kinetics Modafinil is a racemic compound (10% *d*-isomer and 90% *l*-isomer at steady state) whose enantiomers have different pharmacokinetics

Distribution: V_d: 0.9 L/kg

Protein binding: 60%, primarily to albumin

Metabolism: Hepatic; multiple pathways including CYP3A4

Half-life elimination: Effective half-life: 15 hours; Steady-state: 2-4 days

Time to peak, serum: 2-4 hours

Excretion: Urine (as metabolites, <10% as unchanged drug)

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), oral ulceration, gingivitis, and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Use vasoconstrictor with caution. Patients may experience heart palpitations and increased heart rate when taking modafinil.

Mental Health: Child/Adolescent Considerations Across three large randomized, double-blind, placebo-controlled trials, a total of 638 children and adolescents (range: 6-17 years of age) with ADHD were treated with modafanil (170-425 mg once daily) or placebo for 7-9 weeks (Biederman, 2005; Greenhill, 2006; Swanson, 2006). Modafanil treatment was associated with significant decreases in the ADHD-RS-IV scores compared relative to baseline and significantly compared to placebo ($p<0.0001$) for all three studies. Despite the demonstrated efficacy, these studies revealed a high rate of serious dermatological reactions (including Stevens-Johnson syndrome) in these patients.

Biederman J, Swanson JM, Wigal SB, et al, “Efficacy and Safety of Modafinil Film-Coated Tablets in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Results of a Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose Study,” *Pediatrics*, 2005, 116(6):e777-84.

Greenhill LL, Biederman J, Boellner SW, et al, “A Randomized, Double-Blind, Placebo-Controlled Study of Modafinil Film-Coated Tablets in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder,” *J Am Acad Child Adolesc Psychiatry*, 2006, 45(5):503-11.

Swanson JM, Greenhill LL, Lopez FA, et al, “Modafinil Film-Coated Tablets in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Results of a Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose Study Followed by Abrupt Discontinuation,” *J Clin Psychiatry,* 2006, 67(1):137-47.

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Broughton, RJ, “Randomized, Double-Blind, Placebo-Controlled Crossover Trial of Modafinil in the Treatment of Excessive Daytime Sleepiness in Narcolepsy,” *Neurology*, 1997, 49(2):444-451. [PubMed 9270575]

Grozinger M, “Interaction of Modafinil and Clomipramine as Comedication in a Narcoleptic Patient,” *Clin Neuropharmacol*, 1998, 21(2):127-129. [PubMed 9579300]

Rugino TA and Copley TC, “Effects of Modafinil in Children With Attention-Deficit/Hyperactivity Disorder: An Open-Label Study,” *J Am Acad Child Adolesc Psychiatry*, 2001, 40(2):230-5. [PubMed 11211372]

Taylor FB and Russo J, “Efficacy of Modafinil Compared to Dextroamphetamine for the Treatment of Attention Deficit Hyperactivity Disorder in Adults,” *J Child Adolesc Psychopharmacol*, 2000, 10(4):311-20. [PubMed 11191692]

U.S. Modafinil in Narcolepsy Multicenter Study Group, “Randomized Trial of Modafinil for the Treatment of Pathological Somnolence in Narcolepsy,” *Ann Neurol*, 1998, 43(1):88-97. [PubMed 9450772]

Vetter VL, Elia J, Erickson CH, et al, “Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs. A Scientific Statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing,” *Circulation*, 2008, 117:2407-23.[PubMed 18427125]

Wong, YN, “Single-Dose Pharmacokinetics of Modafinil and Methylphenidate Given Alone or in Combination in Healthy Male Volunteers,” *J Clin Pharmacol*, 1998, 38(3):276-282.[PubMed 9549666]

International Brand Names Activigil (UY); Alertex (CN); Modasomil (AT, CH); Modavigil (AU); Modiodal (DK, ES, FR, MX, NL, NO, PT, SE); Provigil (BE, GB, IE, IL, IT, KP, PY, TW); Vigia (CO); Vigicer (AR); Vigil (DE, PL)

Moexipril and Hydrochlorothiazide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(mo EKS i pril & hye droe klor oh THYE a zide)

U.S. Brand NamesUniretic®

Canadian Brand NamesUniretic®

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension; not indicated for initial treatment of hypertension

Dosing: Adults**Hypertension:** Oral: 7.5-30 mg of moexipril, taken either in a single or divided dose one hour before meals; hydrochlorothiazide dose should be ≤50 mg/day

Dosing: ElderlyOverall safety and efficacy are not different in elderly patients, although a higher moexipril AUC was observed in elderly patients. Greater sensitivity to effects may be observed in some older individuals. Refer to adult dosing.

ContraindicationsHypersensitivity to moexipril, hydrochlorothiazide, sulfonamide-derived drugs, or any component of the formulation; angioedema related to previous treatment with an ACE inhibitor; anuria

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See "Special populations" below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose), angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Electrolyte disturbances: Hyperkalemia may occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use ACE inhibitors with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity. Hydrochlorothiazide can cause systemic lupus erythematosus (SLE) exacerbation or activation.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use moexipril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use ACE inhibitors with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment. Avoid hydrochlorothiazide in severe renal disease (ineffective). Contraindicated in anuric patients.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Pregnancy Risk FactorC/D (2nd and 3rd trimesters)
Pregnancy Considerations

[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected. See individual agents.

LactationEnters breast milk/use caution
Adverse ReactionsSee individual agents.
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure, BUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential
Nursing: Physical Assessment/MonitoringSee individual agents.
Monitoring: Lab TestsBUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet [scored]:

7.5/12.5: Moexipril hydrochloride 7.5 mg and hydrochlorothiazide 12.5 mg

15/12.5: Moexipril hydrochloride 15 mg and hydrochlorothiazide 12.5 mg

15/25: Moexipril hydrochloride 15 mg and hydrochlorothiazide 25 mg

Uniretic®:

7.5/12.5: Moexipril hydrochloride 7.5 mg and hydrochlorothiazide 12.5 mg

15/12.5: Moexipril hydrochloride 15 mg and hydrochlorothiazide 12.5 mg

15/25: Moexipril hydrochloride 15 mg and hydrochlorothiazide 25 mg

Generic AvailableYes

ManufacturerSchwarz Pharma

Pricing: U.S. (www.drugstore.com)

Tablets (Moexipril-Hydrochlorothiazide)

7.5-12.5 mg (30): $37.99

15-12.5 mg (100): $109.98

15-25 mg (30): $36.99

Tablets (Uniretic)

7.5-12.5 mg (30): $50.54

15-12.5 mg (30): $49.99

15-25 mg (30): $52.07

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Hydrochlorothiazide
- Moexipril

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness; may rarely cause anxiety or mood changes

Mental Health: Effects on Psychiatric TreatmentThiazides and ACE inhibitors may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels; may cause neutropenia; use caution with clozapine and carbamazepine

Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for moexipril and hydrochlorothiazide combination therapy may include improved compliance and synergistic reductions in blood pressure with an accompanied reduction in side effects. ACE inhibitors and thiazides are also standard therapy for left ventricular systolic dysfunction. See Cardiovascular Considerations for individual agents.

Index TermsHydrochlorothiazide and Moexipril

References

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International Brand NamesFempress Plus (DE); Moex Plus (BG); Uniretic (PH)

Moexipril

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Moexipril may be confused with Monopril®

Pronunciation(mo EKS i pril)

U.S. Brand NamesUnivasc®

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor

Use: Labeled IndicationsTreatment of hypertension, alone or in combination with thiazide diuretics

Dosing: Adults**Hypertension, LV dysfunction (post MI):** Oral: Initial: 7.5 mg once daily (in patients **not** receiving diuretics), 1 hour prior to a meal **or** 3.75 mg once daily (when combined with thiazide diuretics); maintenance dose: 7.5-30 mg/day in 1 or 2 divided doses 1 hour before meals

Dosing: ElderlyDose the same as adults; adjust for renal impairment. Tablet may be cut in half (3.75 mg) for starting therapy (see Renal Impairment).

Dosing: Renal ImpairmentCl_{cr} ≤40 mL/minute: Patients may be cautiously placed on 3.75 mg once daily, then upwardly titrated to a maximum of 15 mg/day.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsAdminister on an empty stomach.

ContraindicationsHypersensitivity to moexipril or any component of the formulation; angioedema related to previous treatment with an ACE inhibitor

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose), angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss, or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsDue to frequent decreases in glomerular filtration (also creatinine clearance) with aging, elderly patients may have exaggerated responses to ACE inhibitors; differences in clinical response due to hepatic changes are not observed. ACE inhibitors may be preferred agents in elderly patients with congestive heart failure and diabetes mellitus. Diabetic proteinuria is reduced and insulin sensitivity is enhanced. In general, the side effect profile is favorable in the elderly and causes little or no CNS confusion; use lowest dose recommendations initially; adjust dose for renal function in the elderly. Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.

Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)

Pregnancy ConsiderationsDue to adverse events observed in some animal studies, moexipril is considered pregnancy category C during the first trimester. Based on human data, moexipril is considered pregnancy category D if used during the second and third trimesters (per the manufacturer; however, one study suggests that fetal injury may occur at anytime during pregnancy). First trimester exposure to ACE inhibitors may cause major congenital malformations. An increased risk of cardiovascular and/or central nervous system malformations was observed in one study; however, an increased risk of teratogenic events was not observed in other studies. Second and third trimester use of an ACE inhibitor is associated with oligohydramnios. Oligohydramnios due to decreased fetal renal function may lead to fetal limb contractures, craniofacial deformation, and hypoplastic lung development. The use of ACE inhibitors during the second and third trimesters is also associated with anuria, hypotension, renal failure (reversible or irreversible), skull hypoplasia, and death in the fetus/neonate. Chronic maternal hypertension itself is also associated with adverse events in the fetus/infant. ACE inhibitors are not recommended during pregnancy to treat maternal hypertension or heart failure. Those who are planning a pregnancy should be considered for other medication options if an ACE inhibitor is currently prescribed or the ACE inhibitor should be discontinued as soon as possible once pregnancy is detected. The exposed fetus should be monitored for fetal growth, amniotic fluid volume, and organ formation. Infants exposed to an ACE inhibitor *in utero*, especially during the second and third trimester, should be monitored for hyperkalemia, hypotension, and oliguria

[U.S. Boxed Warning]: Based on human data, ACE inhibitors can cause injury and death to the developing fetus when used in the second and third trimesters. ACE inhibitors should be discontinued as soon as possible once pregnancy is detected.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if moexipril is excreted into breast milk. The manufacturer recommends that caution be exercised when administering moexipril to nursing women.

Pregnancy & Lactation, In-Depth

- Moexipril in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Cardiovascular: Hypotension, peripheral edema

Central nervous system: Dizziness, fatigue, headache

Dermatologic: Alopecia, flushing, rash

Endocrine & metabolic: Hyperkalemia, hyponatremia

Gastrointestinal: Diarrhea, heartburn, nausea

Genitourinary: Polyuria

Neuromuscular & skeletal: Myalgia

Renal: Reversible increases in creatinine or BUN

Respiratory: Cough, pharyngitis, sinusitis, upper respiratory infection

<1% (Limited to important or life-threatening): Alopecia, anemia, angioedema, arrhythmia, bronchospasm, cerebrovascular accident, chest pain, dyspnea, eosinophilic pneumonitis, hepatitis, hypercholesterolemia, LFTs increased, MI, oliguria, orthostatic hypotension, palpitation, proteinuria, syncope

Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Food may delay and reduce peak serum levels.

Herb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Test InteractionsIncreases BUN, creatinine, potassium, positive Coombs' [direct]; decreases cholesterol (S); may cause false-positive results in urine acetone determinations using sodium nitroprusside reagent

Monitoring ParametersBlood pressure; serum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (especially anything that may impact fluid balance or cardiac status). Evaluate results of laboratory tests on a regular basis during therapy. Patient should be monitored closely for anaphylactic reaction or angioedema which can occur at any time during treatment and may involve head and neck. Evaluate therapeutic effectiveness (blood pressure) and adverse responses (eg, hypotension, rash, diarrhea, myalgia, electrolyte imbalance) regularly during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Do not use potassium supplements or salt substitutes without consulting prescriber. Take exactly as directed; do not discontinue without consulting prescriber. Take first dose at bedtime. Take all doses on an empty stomach, 1 hour before or 2 hours after meals. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); nausea, vomiting, abdominal pain, dry mouth, or transient loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report immediately unusual swelling of mouth, tongue, face, throat. Report respiratory difficulty or unusual cough, rash, excessive urination, chest pain or palpitations, mouth sores, fever or chills, numbness, tingling or pain in muscles, or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride [scored]: 7.5 mg, 15 mg

Univasc®: 7.5 mg, 15 mg

Generic AvailableYes

ManufacturerSchwarz Pharma

Pricing: U.S. (www.drugstore.com)

Tablets (Moexipril HCl)

7.5 mg (30): $36.99

15 mg (30): $34.99

Tablets (Univasc)

7.5 mg (30): $51.99

15 mg (30): $53.84

Mechanism of ActionCompetitive inhibitor of angiotensin-converting enzyme (ACE); prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor; results in lower levels of angiotensin II which causes an increase in plasma renin activity and a reduction in aldosterone secretion

Pharmacodynamics/Kinetics

Absorption: Incomplete

Onset of action: Peak effect: 1-2 hours

Duration: >24 hours

Distribution: V_d (moexiprilat): 180 L

Protein binding, plasma: Moexipril: 90%; Moexiprilat: 50% to 70%

Metabolism: Parent drug: Hepatic and via GI tract to moexiprilat, 1000 times more potent than parent

Bioavailability: Moexiprilat: 13%; reduced with food (AUC decreased by ~40%)

Half-life elimination: Moexipril: 1 hour; Moexiprilat: 2-9 hours

Time to peak: 1.5 hours

Excretion: Feces (50%)

Related Information

- Angiotensin Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness; may rarely cause anxiety or mood changes

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Congestive Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines recommend that ACE inhibitors be used in patients with a reduced EF (with or without heart failure symptoms) unless contraindicated. ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. In this situation, they decrease hospitalizations for, and retard progression to, congestive heart failure. When used in patients with heart failure, the target dose should be achieved, if possible. Lower daily doses of ACE inhibitors have demonstrated the same mortality effects as high doses, but have not decreased hospitalizations to the extent that high-dose ACE inhibitors have, as demonstrated in the ATLAS study (Packer M, 1999).

Hypertension: The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) can be beneficial in patients with hypertension and LVH without symptoms of heart failure. JNC 7 suggests that patients can benefit from treatment with an ACE inhibitor if they have hypertension **and** heart failure, acute myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, or history of stroke.

Vascular Disease: The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors can be useful in preventing heart failure in patients who have a history of atherosclerotic vascular disease, diabetes, or hypertension with associated cardiovascular risk factors. The HOPE trial (Heart Outcomes Prevention Evaluation Study Investigators, 2000) investigated the value of an ACE inhibitor (ramipril 5-10 mg daily) versus placebo in patients who had evidence of vascular disease or diabetes (one other cardiovascular risk factor) and were at least 55 years of age. Patients were excluded if they had a low ejection fraction, heart failure, or were on an ACE inhibitor. The primary outcome was a composite of death from cardiovascular cause, myocardial infarction, or stroke; 9297 patients were enrolled and randomized. Ramipril significantly reduced the risk of death from CV causes, MI, or stroke over placebo. New cases of diabetes were also reduced in the ramipril group. In the EUROPA trial, patients with stable coronary artery disease (at low risk for cardiovascular events) received perindopril or placebo and were evaluated for incidence of cardiovascular events after four years of treatment. In this randomized, placebo-controlled, prospective study, 12,218 patients received either perindopril (8 mg/day, n = 6110) or placebo (n = 6108) and were assessed for the primary endpoint of a cardiovascular event, defined as cardiovascular death, myocardial infarction, or cardiac arrest. The study population was well balanced with respect to baseline demographics and concomitant medication use (including beta-blockers, platelet inhibitors, antihyperlipidemics, calcium channel blockers, nitrates, and diuretics). Intent-to-treat analysis revealed that 603 (10%) of placebo patients experienced the primary endpoint of a cardiovascular event compared to 488 (8%) of perindopril-receiving patients, for a 20% relative risk reduction (p = 0.0003). This result was not influenced by presence of other comorbidities (eg, diabetes, hypertension) or concomitant beta-blocker, calcium channel blocker, or lipid-lowering therapies. Withdrawal from the study (postrandomization) due to adverse reactions was similar between treatment groups. Number needed to treat analysis suggests that treatment of 50 patients over a 4-year period will prevent one major cardiovascular event.

Acute Coronary Syndromes: In the treatment of unstable angina/non-ST-segment elevation MI, ACE inhibitors are recommended when hypertension persists despite treatment with nitroglycerin and a beta-blocker in patients with LV systolic dysfunction or CHF and in ischemic patients with diabetes (Class I). ACE inhibitors are also recommended for all post-ACS individuals (Class IIa). According to 2004 ACC/AHA STEMI guidelines, an ACE inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF <0.4, in the absence of hypotension or known contraindications to this class of medicines. In the emergency management of complicated STEMI, a short-acting ACEI (eg, captopril 1-6.25 mg) may be added once the patient's systolic blood pressure is >100 mm Hg and not <30 mm Hg below baseline. The VALIANT trial evaluated the effects of valsartan (target dose: 160 mg twice daily), captopril (target dose: 50 mg twice daily), and the combination (target doses: valsartan 80 mg twice daily and captopril 150 mg once daily) in a randomized, double-blind trial of patients with acute MI (0.5-10 days post-MI) complicated by left ventricular systolic dysfunction, heart failure, or both. Enrollment in the study numbered 14,703 patients and followed for a median of 24.7 months. There was no difference in the primary endpoint (all cause mortality) among the 3 groups. There was no difference in incidence of CV death, recurrent MI, or hospitalization for heart failure either. Hypotension and renal dysfunction occurred significantly more often in the valsartan group than captopril alone. Cough, rash, and taste disturbances occurred more often in the captopril group. The authors (Pfeffer MA, 2003) concluded that valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after MI. Combining valsartan with captopril increased the rate of adverse events without improving survival.

Potential Adverse Events: ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. In those patients experiencing cough on an ACE inhibitor, the ACE inhibitor may be discontinued and, if necessary, ARB therapy instituted. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Drug Interactions: Concomitant indomethacin therapy may blunt the reduction in sitting and 24-hour ambulatory diastolic blood pressure. Use of NSAIDs should be avoided or limited, with monitoring of blood pressure control in this setting. In patients with heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

Index TermsMoexipril Hydrochloride

References

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, "Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)," *JAMA*, 2002, 288(23):2981-97.[PubMed 12479763]

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International Brand NamesCardiotensin (PL); Femipres (IT); Fempress (AT, BG, CH, DE); Moex (CZ, DK, FR, HK); Perdix (GB, IL); Univasc (KP, PH)

Molindone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

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Medication Safety Issues

Sound-alike/look-alike issues:

Molindone may be confused with Mobidin®

Moban® may be confused with Mobidin®, Modane®

Pronunciation(moe LIN done)

U.S. Brand NamesMoban®

Canadian Brand NamesMoban®

Pharmacologic CategoryAntipsychotic Agent, Typical

Use: Labeled IndicationsManagement of schizophrenia

Use: Unlabeled/InvestigationalManagement of psychotic disorders; behavioral symptoms associated with dementia (elderly); psychosis/agitation related to Alzheimer's dementia

Dosing: Adults**Schizophrenia/psychoses:** Oral:

Initial: 50-75 mg/day, may increase to 100 mg/day in 3-4 days; may further increase dose gradually to maximum of 225 mg/day

Maintenance: 5-15 mg (mild symptoms) or 10-25 mg (moderate symptoms) 3-4 times/day (up to 225 mg/day may be required in severe cases)

Dosing: ElderlyBehavioral symptoms associated with dementia in the elderly (unlabeled use): Oral: Initial: 5-10 mg 1-2 times/day; increase at 4- to 7-day intervals by 5-10 mg/day; increase dosing intervals (eg, twice daily, 3 times/day) as necessary to control response or side effects. Maximum dose: 112 mg/day. Gradual increases (titration) may prevent some side effects or decrease their severity.

Dosing: Pediatric**Schizophrenia/psychosis (unlabeled use):** Oral: Children:

3-5 years: 1-2.5 mg/day divided into 4 doses

5-12 years: 0.5-1 mg/kg/day in 4 divided doses

StorageStore at controlled room temperature of 25°C (77°F). Protect from light.

ContraindicationsHypersensitivity to molindone or any component of the formulation (cross-reactivity between phenothiazines may occur); severe CNS depression; coma

Allergy Considerations

- Molindone Allergy

Warnings/Precautions

Boxed warnings:

- Dementia: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics. Avoid use in patients with underlying QT prolongation, in those taking medicines that prolong the QT interval, or cause polymorphic ventricular tachycardia; monitor ECG closely for dose-related QT effects.

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to other neuroleptics, molindone has a low potency of cholinergic blockade.

- Blood dyscrasias: Myelosuppression (eg, leukopenia, agranulocytosis) has been observed with antipsychotic use; check blood counts periodically and discontinue at first signs of blood dyscrasias.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is moderate-high relative to other neuroleptics). Risk of dystonia (and possibly other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: May rarely cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Pigmentary retinopathy: May be associated with pigmentary retinopathy.

- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Dementia: **[U.S. Boxed Warning]: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo.** An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Molindone is not approved for this indication.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

- Phenytoin/tetracyclines: Due to calcium sulfate content in the tablet, concomitant use may decrease the absorption of phenytoin and tetracyclines.

Special populations:

- Debilitated/elderly patients: Initiate therapy at a reduced dose; may be more susceptible to adverse effects.

Geriatric Considerations Any changes in disease status in any organ system can result in behavior changes.

Many elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior. Before initiating antipsychotic medication, the clinician should investigate any possible reversible cause; any stress or stress from any disease can cause acute “confusion” or worsening of baseline nonpsychotic behavior. Most commonly acute changes in behavior are due to increases in drug dose or addition of new drug to regimen, fluid electrolyte loss, infections, and changes in environment.

In the treatment of agitated, demented, elderly patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control.

Pregnancy Risk Factor C

Lactation Excretion in breast milk unknown

Adverse Reactions Frequency not defined.

Cardiovascular: Arrhythmia, orthostatic hypotension, tachycardia, T wave changes (transient; rare)

Central nervous system: Central temperature regulation altered, drowsiness, euphoria, extrapyramidal reactions (akathisia, pseudoparkinsonism, dystonia, tardive dyskinesia), hyperactivity, mental depression, neuroleptic malignant syndrome (NMS), restlessness, sedation, seizure

Dermatologic: Rash

Endocrine & metabolic: Amenorrhea, change in menstrual periods, galactorrhea, gynecomastia, libido increased

Gastrointestinal: Constipation, nausea, salivation, weight gain (minimal compared to other antipsychotics), weight loss, xerostomia

Genitourinary: Priapism, urinary retention

Hematologic: Leukopenia (rare), leukocytosis (rare)

Hepatic: Liver function tests altered (rare)

Ocular: Blurred vision, lens opacities, retinal pigmentation

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Monitoring Parameters Vital signs; lipid profile, fasting blood glucose/Hgb A_{1c}; BMI; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms (EPS)

Nursing: Physical Assessment/Monitoring Assess other medications patient is taking for effectiveness and interactions. Review ophthalmic screening and monitor laboratory results, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. Initiate at lower doses and taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsLipid profile, fasting blood glucose/Hgb A_{1c}, baseline liver and kidney function, CBC prior to and periodically during therapy; BMI

Patient EducationUse exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results; do not discontinue without consulting prescriber. Avoid alcohol or caffeine and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience excess drowsiness, restlessness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); constipation (increased exercise, fluids, fruit, or fiber may help); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); or decreased perspiration (avoid strenuous exercise in hot environments). Report persistent CNS effects (eg, trembling fingers, altered gait or balance, excessive sedation, seizures, unusual movements, anxiety, abnormal thoughts, confusion, personality changes); chest pain, palpitations, rapid heartbeat, severe dizziness; unresolved urinary retention or changes in urinary pattern; changes in menstrual pattern or breast tenderness; vision changes; skin rash or yellowing of skin; respiratory difficulty; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 5 mg, 10 mg, 25 mg, 50 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Moban)

5 mg (90): $119.99

10 mg (90): $166.99

25 mg (90): $246.97

50 mg (90): $323.24

Mechanism of ActionMolindone is a dihydroindoline antipsychotic whose mechanism of action mimics that of chlorpromazine; however, it produces more extrapyramidal symptoms and less sedation than chlorpromazine

Pharmacodynamics/Kinetics

Metabolism: Hepatic

Half-life elimination: 1.5 hours

Time to peak, serum: ~1.5 hours

Excretion: Urine and feces (90%) within 24 hours

Related Information

- Antipsychotic Agents
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation) and orthostatic hypotension. Anticholinergic side effects can cause a reduction of saliva production or secretion, contributing to discomfort and dental disease (ie, caries, oral candidiasis, and periodontal disease). Molindone can cause extrapyramidal reactions which may appear as muscle twitching or increased motor activity of the face, neck, or head.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentMolindone is not commonly used, and is an intermediate-potency antipsychotic. Older antipsychotic medications (chlorpromazine, haloperidol), which do not meet specific criteria for “atypical” antipsychotics, are often referred to as typical antipsychotics. They are associated with the troubling side effect, EPS. However, it is commonly believed that in order for a drug to treat psychosis, it must block dopamine is some manner.

Common side effects include sedation and neuroleptic effect (reduced initiative, interest in the environment, and display of emotion or affect). All **typical** antipsychotics are considered to be equally effective if given in equipotent doses. An inverse relationship exists between intrinsic antimuscarinic activity and propensity to cause extrapyramidal side effects. If dystonia or pseudoparkinsonism occurs, antiparkinsonian agents should be considered. If akathisia occurs, beta-blockers (eg, propranolol), benzodiazepines, or antiparkinsonian agents should be considered. Tardive dyskinesia (TD) secondary to typical antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. After this time period, the incidence is estimated to be 2% to 3% per year. Prevalence rates are ~15% to 20%. Female gender and age constitute risk factors for TD. Indeed, prevalence rates have been reported to be as high as 70% in elderly females. No specific treatment exists for TD, however, patients are often initiated on/switched to an atypical antipsychotic because of their lower incidence to cause TD and hopes of suppression.

Typical antipsychotics are usually only indicated for schizophrenia, but are generally effective for mania and psychosis and/or behavioral syndromes secondary to other mental conditions. Nonpsychiatric uses include Tourette's syndrome, Huntington's disease, and occasionally, intractable hiccups, pruritus, nausea, and vomiting.

These drugs are thought to exert their antipsychotic activity by blocking dopamine D_2 receptors in the mesolimbic dopaminergic pathway. Side effects are often related to their ability to antagonize dopamine receptors in the nigrostriatal and tuberoinfundibular pathways.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Index Terms Molindone Hydrochloride

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International Brand Names Moban (FI)

Mometasone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Elocon® lotion may be confused with ophthalmic solutions. Manufacturer's labeling emphasizes the product is **NOT** for use in the eyes.

Pronunciation(moe MET a sone)

U.S. Brand NamesAsmanex® Twisthaler®; Elocon®; Nasonex®

Canadian Brand NamesElocom®; Nasonex®; PMS-Mometasone; ratio-Mometasone; Taro-Mometasone

Pharmacologic CategoryCorticosteroid, Inhalant (Oral); Corticosteroid, Nasal; Corticosteroid, Topical

Use: Labeled IndicationsRelief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (medium potency topical corticosteroid); treatment of nasal symptoms of seasonal and perennial allergic rhinitis; prevention of nasal symptoms associated with seasonal allergic rhinitis; treatment of nasal polyps in adults; maintenance treatment of asthma as prophylactic therapy or as a supplement in asthma patients requiring oral corticosteroids for the purpose of decreasing or eliminating the oral corticosteroid requirement

Dosing: Adults

Treatment of seasonal and perennial allergic rhinitis: Nasal spray: 2 sprays (100 mcg) in each nostril daily

Prevention of seasonal and perennial allergic rhinitis: Nasal spray: 2 sprays (100 mcg) in each nostril daily beginning 2-4 weeks prior to pollen season

Treatment of corticosteroid-responsive dermatoses: Topical: Apply sparingly, do not use occlusive dressings. Therapy should be discontinued when control is achieved; if no improvement is seen in 2 weeks, reassessment of diagnosis may be necessary.

Cream, ointment: Apply a thin film to affected area once daily

Lotion: Apply a few drops to affected area once daily

Treatment of nasal polyps: Nasal spray: 2 sprays (100 mcg) in each nostril twice daily; 2 sprays (100 mcg) once daily may be effective in some patients

Asthma: Oral inhalation:

Bronchodilators or inhaled corticosteroids: Initial: 1 inhalation (220 mcg) daily (maximum 2 inhalations or 440 mcg/day); may be given in the evening or in divided doses twice daily

Oral corticosteroids: Initial: 440 mcg twice daily (maximum 880 mcg/day); prednisone should be reduced no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of mometasone furoate use

NIH Asthma Guidelines (NIH, 2007):

"Low" dose: 220 mcg/day

"Medium" dose: 440 mcg/day

"High" dose: >440 mcg/day

Note: Maximum effects may not be evident for 1-2 weeks or longer; dose should be titrated to effect, using the lowest possible dose

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Treatment of seasonal and perennial allergic rhinitis treatment:

Nasal spray:

Children 2-11 years: 1 spray (50 mcg) in each nostril daily

Children ≥12 years: Refer to adult dosing.

Treatment of corticosteroid-responsive dermatoses: Topical:

Cream, ointment: Children ≥2 years: Refer to adult dosing. Do not use in pediatric patients for longer than 3 weeks.

Lotion: Children ≥12 years: Refer to adult dosing.

Asthma: Oral inhalation:

Children 4-11 years: 110 mcg once daily in the evening (maximum 110 mcg/day)

Children ≥12 years: Refer to adult dosing.

Administration: Inhalation

Nasal spray: Prior to first use, prime pump by actuating 10 times or until fine spray appears; may store for a maximum of 1 week without repriming. Spray should be administered once or twice daily, at a regular interval. Shake well prior to use.

Oral inhalation: Exhale fully prior to bringing the Twisthaler® up to the mouth. Place between lips and inhale quickly and deeply. Do not breathe out through the inhaler. Remove inhaler and hold breath for 10 seconds if possible.

Administration: Topical

Apply sparingly; avoid eyes, face, underarms, and groin. Do not wrap or bandage affected area.

Dietary Considerations

Asmanex® Twisthaler® contains lactose.

Storage

Cream: Store between 2°C to 25°C (36°F to 77°F).

Lotion: Store between 2°C to 30°C (36°F to 86°F).

Nasal spray: Store at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

Ointment: Store at room temperature of 15°C to 30°C (59°F to 86°F).

Oral Inhaler: Store at room temperature of 25°C (77°F). Discard when oral dose counter reads "00" (or 45 days after opening the foil pouch).

Contraindications

Hypersensitivity to mometasone or any component of the formulation; treatment of acute bronchospasm (oral inhaler)

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections.

- Bronchospasm: May occur with wheezing after inhalation; if this occurs stop steroid and treat with a fast-acting bronchodilator.

- Delayed wound healing: Avoid nasal corticosteroid use in patients with recent nasal septal ulcers, nasal surgery or nasal trauma until healing has occurred.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox should be avoided. Corticosteroids should not be used to treat ocular herpes simplex, cerebral malaria, or viral hepatitis. Close observation is required in patients with latent tuberculosis and/or TB reactivity; restrict use in active TB (only in conjunction with antituberculosis treatment).

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

Disease-related concerns:

- Asthma: Supplemental steroids (oral or parenteral) may be needed during stress or severe asthma attacks. Not to be used in status asthmaticus or for the relief of acute bronchospasm.

- Cardiovascular disease: Use with caution in patients with HF; long-term use has been associated with fluid retention and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.

- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids.

- Myocardial infarct (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Consider routine eye exams in chronic users.

- Osteoporosis: Use with caution in patients with or who are at risk for osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Pediatrics: Orally-inhaled and intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients (~1 centimeter per year [range: 0.3-1.8 cm per year] and related to dose and duration of exposure). To minimize the systemic effects of orally-inhaled and intranasal corticosteroids, each patient should be titrated to the lowest effective dose. Growth should be routinely monitored in pediatric patients.

Other warnings/precautions:

- Appropriate use: Prior to use, the dose and duration of treatment should be based on the risk versus benefit for each individual patient. In general, use the smallest effective dose for the shortest duration of time to minimize adverse events. A gradual tapering of dose may be required prior to discontinuing therapy. There have been reports of systemic corticosteroid withdrawal symptoms (eg, joint/muscle pain, lassitude, depression) when withdrawing inhalation therapy.

- Transfer to oral inhaler: When transferring to oral inhaler, previously-suppressed allergic conditions (rhinitis, conjunctivitis, eczema) may be unmasked.

Geriatric ConsiderationsDue to age-related changes in skin, limit use of topical glucocorticosteroids.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies using topical or inhaled mometasone during pregnancy. However, teratogenicity and intrauterine growth retardation has been reported in animal studies with some topical steroids. Avoid use of large amounts for long periods of time during pregnancy. Hypoadrenalism may occur in infants born to women receiving corticosteroids during pregnancy. Monitor these infants closely after birth. Following oral inhalation, <1% of a single 400 mcg dose is available systemically in the mother; inhaled corticosteroids are considered first-line agents for the treatment of persistent of asthma during pregnancy.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsSystemic corticosteroids are excreted in human milk. The extent of topical absorption is variable; do not apply topical products to nipples. Following oral inhalation, <1% of a single 400 mcg dose is available systemically which would limit the amount available in breast milk.

Adverse Reactions

Nasal/oral inhalation:

>10%:

Central nervous system: Headache (17% to 26%), fatigue (oral inhalation 1% to 13%), depression (oral inhalation 11%)

Neuromuscular & skeletal: Musculoskeletal pain (1% to 22%), arthralgia (oral inhalation 13%)

Respiratory: Rhinitis (2% to 20%), upper respiratory infection (5% to 15%), pharyngitis (8% to 13%), cough (nasal inhalation 7% to 13%), epistaxis (1% to 11%)

Miscellaneous: Viral infection (nasal inhalation 8% to 14%), oral candidiasis (oral inhalation 4% to 22%)

1% to 10%:

Cardiovascular: Chest pain

Central nervous system: Pain

Gastrointestinal: Abdominal pain, anorexia, dry throat (oral inhalation), diarrhea, dyspepsia, flatulence, gastroenteritis, nausea, vomiting

Genitourinary: Dysmenorrhea

Neuromuscular & skeletal: Back pain, myalgia

Ocular: Conjunctivitis

Otic: Earache, otitis media

Respiratory: Asthma, bronchitis, dysphonia, nasal irritation, sinusitis, wheezing

Miscellaneous: Accidental injury, flu-like syndrome

<1%: Nasal candidiasis, nasal ulcers, oral candidiasis (nasal inhalation)

Postmarketing and/or case reports: Anaphylaxis, angioedema, growth suppression, nasal burning and irritation, nasal septal perforation, smell disturbance (rare), taste disturbance (rare)

Topical:

1% to 10%: Dermatologic: Bacterial skin infection, burning, furunculosis, pruritus, skin atrophy, tingling/stinging

<1%: Folliculitis, glucocorticoid levels decreased (pediatric patients), moniliasis, paresthesia, skin depigmentation, skin atrophy

Postmarketing and/or case reports: Rosacea

Cataract formation, reduction in growth velocity, and HPA axis suppression have been reported with other corticosteroids

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)
Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Monitoring ParametersHPA axis suppression

Asthma: FEV_1, peak flow, and/or other pulmonary function tests

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess patient response. Teach patient proper use (according to formulation), side effects/appropriate interventions, and symptoms to report. Long-term use: Assess for glaucoma and cataracts periodically. Monitor growth with long-term use in pediatric patients.
Patient EducationDo not take anything new during treatment without consulting prescriber. Use exactly as directed and for no longer than the period prescribed. Not a bronchodilator and not indicated for relief of bronchospasm or acute episodes of asthma. May take 1-2 weeks before effects of medication are seen. Avoid exposure to chickenpox or measles. Consult prescriber immediately if exposure does occur. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Nasal: Read complete instructions in package. Prime the pump as directed. Gently blow your nose to clear nostrils. Close one nostril. Tilt your head forward slightly and, keeping the bottle upright, carefully insert the nasal applicator into the other nostril. After the spray, breath gently inward through the nostril, then breath out through the mouth. Repeat in other nostril. You may experience headache, cough, or nosebleed. Report unusual chest pain, gastrointestinal upset, muscle pain, flu-like symptoms, other persistent adverse reactions, worsening of condition or failure to improve. Store at room temperature, away from light.

Topical: Do not use for eyes, mucous membranes, or open wounds. Use exactly as directed and for no longer than the period prescribed. Before using, wash and dry area gently. Apply in a thin layer (cream, ointment) or a few drops (lotion) and rub in lightly. Apply light dressing (if necessary) to area being treated. Do not use occlusive dressing unless so advised by prescriber. Avoid prolonged or excessive use around sensitive tissues, underarms, genital, or rectal areas. Avoid exposing treated area to direct sunlight (severe sunburn may occur). Inform prescriber if condition worsens (redness, swelling, irritation, signs of infection, or open sores) or fails to improve.

Oral inhalation: Discard inhaler 45 days after opening foil pouch or when dose counter reads "00." Rinse mouth after using. Keep the inhaler clean and dry.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical, as furoate: 0.1% (15 g, 45 g)

Elocon®: 0.1% (15 g, 45 g)

Lotion, topical, as furoate: 0.1% (30 mL, 60 mL)

Elocon®: 0.1% (30 mL, 60 mL) [contains isopropyl alcohol 40%]

Ointment, topical, as furoate: 0.1% (15 g, 45 g)

Elocon®: 0.1% (15 g, 45 g)

Powder for oral inhalation, as furoate:

Asmanex® Twisthaler®: 110 mcg (30 units) [contains lactose; delivers 100 mcg/actuation]; 220 mcg (14 units, 30 units, 60 units, 120 units) [contains lactose; delivers 200 mcg/actuation]

Suspension, intranasal, as furoate [spray]:

Nasonex®: 50 mcg/spray (17 g) [delivers 120 sprays; contains benzalkonium chloride]

Generic AvailableYes: Cream, lotion, ointment
Pricing: U.S. (www.drugstore.com)

Aerosol powder (Asmanex 120 Metered Doses)

220 mcg/INH (0.24): $186.43

Aerosol powder (Asmanex 30 Metered Doses)

110 mcg/INH (0.135): $105.99

220 mcg/INH (0.24): $130.06

Aerosol powder (Asmanex 60 Metered Doses)

220 mcg/INH (0.24): $140.91

Cream (Elocon)

0.1% (15): $47.68

0.1% (45): $79.12

Cream (Mometasone Furoate)

0.1% (15): $26.61

0.1% (45): $39.99

Lotion (Elocon)

0.1% (30): $49.85

0.1% (60): $86.71

Ointment (Elocon)

0.1% (15): $49.85

0.1% (45): $76.44

Ointment (Mometasone Furoate)

0.1% (15): $19.19

0.1% (45): $35.99

Solution (Mometasone Furoate)

0.1% (30): $29.99

0.1% (60): $56.99

Suspension (Nasonex)

50 mcg/ACT (17): $100.81

Mechanism of ActionMay depress the formation, release, and activity of endogenous chemical mediators of inflammation (kinins, histamine, liposomal enzymes, prostaglandins). Leukocytes and macrophages may have to be present for the initiation of responses mediated by the above substances. Inhibits the margination and subsequent cell migration to the area of injury, and also reverses the dilatation and increased vessel permeability in the area resulting in decreased access of cells to the sites of injury.

Pharmacodynamics/Kinetics

Absorption:

Nasal inhalation: Mometasone furoate monohydrate: Undetectable in plasma

Ointment: 0.7%; increased by occlusive dressings

Oral inhalation: Systemic absorption <1%

Protein binding: Mometasone furoate: 98% to 99%

Metabolism: Mometasone furoate: Hepatic via CYP3A4; forms metabolite

Half-life elimination: Oral inhalation: 5 hours

Excretion: Feces, bile, urine

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression, dizziness, euphoria, fatigue, insomnia, mood swings, and personality changes; may cause exacerbation of pre-existing psychiatric conditions

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other Considerations

Surgery: For patients who have received oral systemic corticosteroids during the past 6 months and for selected patients on long-term, high-dose, inhaled corticosteroid (ICS), give stress doses of hydrocortisone intravenously during the surgical period and reduce the dose rapidly within 24 hours after surgery (Expert Panel Report 3, 2007). Clinically important adrenal suppression has been reported in patients receiving high doses of an ICS, particularly children.

Index TermsMometasone Furoate

References

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Todd GR, Acerini CL, Ross-Russell R, et al, "Survey of Adrenal Crisis Associated With Inhaled Corticosteroids in the United Kingdom," *Arch Dis Child*, 2002, 87(6):457-61.[PubMed 12456538]

International Brand NamesAsmanex Twisthaler (CH, CR, DO, GB, GT, HN, IE, NI, NZ, PA, SE, SV); Dermovel (ID); Ecural (DE); Elica (MX, PH); Elocom (AE, BE, BF, BG, BH, BJ, BR, CH, CI, CN, CO, CR, CY, CZ, DO, EG, ES, ET, GH, GM, GN, GT, HN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NI, OM, PA, PE, PK, QA, RU, SA, SC, SD, SL, SN, SV, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Elocon (AR, AT, BB, BM, BS, BZ, DK, EE, FI, GB, GR, GY, ID, IE, IN, IT, JM, NL, NO, PH, PY, SE, SR, TR, TT, UY, VE); Elocon Cream (AU); Elocon Ointment (AU); Elomet (EC, HK, MX, MY, TH, TW); Eloskin (ID); Eloson (CL); Elovent Twisthaler (MX); Elox (ID); Inpura (KP); Intercon (ID); Mefurosan (ID); Mesone (ID); Metaspray (IN); Mofulex (ID); Momate (PH); Momet (ID); Monovel (AE, BH, CO, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Nasonex (AR, AU, BR, CH, CN, CO, CR, DO, EC, GB, GT, HN, IL, NI, PA, PE, SE, SV, TW); Nasonex Nasal Spray (AU, DE, EE, GB, HK, ID, IE, KP, MY, PH, SG); Novasone Cream (AU); Novasone Lotion (AU); Novasone Ointment (AU); Rinelon (MX); Rivelon (PH); Topcort (HK); Uniclar (CO, MX)

English

Jump To Field (Select Field Name)

Pronunciation(mon oh BEN zone)
U.S. Brand NamesBenoquin®
Pharmacologic CategoryTopical Skin Product
Use: Labeled IndicationsFinal depigmentation in extensive vitiligo
Dosing: Adults**Vitiligo:** Topical: Apply 2-3 times daily; once desired degree of pigmentation is obtained, may apply as needed (usually 2 times/week)
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Vitiligo:** Topical: Children ≥12 years: Refer to adult dosing.
Administration: TopicalApply thin layer to affected area.
StorageStore at 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to monobenzone or any component of the formulation; use as cosmetic skin bleach; use as hydroquinone substitute
Warnings/Precautions

Concerns related to adverse effects:

- Photosensitivity: Skin will be sensitive to the sun following application and for the rest of the patient's life; sunscreen must be used.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Appropriate use: For external use only. For use only as a final depigmentation in extensive vitiligo; not recommended for use in freckling, hyperpigmentation caused by photosensitization, melasma, hyperpigmentation resulting from skin inflammation, cafe-au-lait spots, pigmented nevi, or malignant melanoma.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Local: Burning sensation, depigmentation of skin distant to application site, dermatitis, irritation

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical: 20% (35 g)

Generic AvailableNo
ManufacturerICN Pharmaceuticals
Pricing: U.S. (www.drugstore.com)

Cream (Benoquin)

20% (35.4): $54.99

Mechanism of ActionIncreases excretion of melanin from melanocytes; causes melanocyte destruction and permanent depigmentation
Pharmacodynamics/KineticsOnset of action: 1-4 months
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesBenoquin (IN); Monobenzone (PL)

Montelukast

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Montelukast (Singulair®) and the Possible Association With Behavior/Mood Changes and Suicide - March 2008

The Food and Drug Administration (FDA) is informing healthcare professionals of the possible association between montelukast (Singulair®) use and suicidality (suicidal thinking and behavior), suicide, and behavior or mood changes. This review is ongoing and the FDA will continue to work with Merck & Co, Inc. to further evaluate this possible association of suicidality with montelukast use. The analysis is expected to take up to 9 months before completion. After the completed evaluation, the FDA will communicate any final conclusions to the public. The FDA is also reviewing postmarketing reports of behavior/mood changes, suicidality, and suicide received with other leukotriene-modifying medications, including zafirlukast (Accolate®) and zileuton (Zyflo®, Zyflo CR™), to determine if further evaluation of these agents is necessary. Patients should not discontinue Singulair® therapy and should discuss any concerns with their healthcare provider. Healthcare professionals and caregivers should monitor for any changes in behavior or mood in patients receiving montelukast.

Additional information can be found at

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Singulair

Medication Safety Issues

Sound-alike/look-alike issues:

Singulair® may be confused with Sinequan®

Pronunciation(mon te LOO kast)

U.S. Brand NamesSingulair®

Canadian Brand NamesSingulair®

Pharmacologic CategoryLeukotriene Receptor Antagonist

Use: Labeled IndicationsProphylaxis and chronic treatment of asthma; relief of symptoms of seasonal allergic rhinitis and perennial allergic rhinitis; prevention of exercise-induced bronchospasm

Use: Unlabeled/InvestigationalAcute asthma

Dosing: Adults

Asthma, allergic seasonal or perennial rhinitis: Oral: One 10 mg tablet daily in the evening

Asthma, acute (unlabeled use): 10 mg as a single dose administered with first-line therapy

Bronchoconstriction, exercise-induced (prevention): 10 mg at least 2 hours prior to exercise; additional doses should not be administered within 24 hours. Daily administration to prevent exercise-induced bronchoconstriction has not been evaluated.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Asthma: Oral:

6-11 months (unlabeled use): 4 mg (oral granules) once daily, taken in the evening

12-23 months: 4 mg (oral granules) once daily, taken in the evening

Seasonal or perennial allergic rhinitis: Oral: *6-23 months:* 4 mg (oral granules) once daily

Asthma, seasonal or perennial allergic rhinitis: Oral:

2-5 years: 4 mg (chewable tablet or oral granules) once daily, taken in the evening

6-14 years: 5 mg (chewable tablet) once daily, taken in the evening

≥15 years: Refer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentNo adjustment necessary in mild-to-moderate hepatic disease. Patients with severe hepatic disease were **not** studied.

Administration: OralWhen treating asthma, administer dose in the evening. Patients with allergic rhinitis may individualize administration time. Granules may be administered directly in the mouth or mixed with applesauce, carrots, rice, ice cream, baby formula, or breast milk; do not add to any other liquids. Administer within 15 minutes of opening packet.

Dietary ConsiderationsTablet, chewable: 4 mg strength contains phenylalanine 0.674 mg; 5 mg strength contains phenylalanine 0.842 mg

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from moisture and light.

Granules: Use within 15 minutes of opening packet.

ContraindicationsHypersensitivity to montelukast or any component of the formulation

Allergy Considerations

- Leukotriene Antagonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Eosinophilia and vasculitis: In rare cases, patients may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. Healthcare providers should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between montelukast and these underlying conditions has not been established.

Concurrent drug therapy issues:

- Corticosteroids: Appropriate clinical monitoring and caution are recommended when systemic corticosteroid reduction is considered in patients receiving montelukast.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 months of age.

Dosage form specific issues:

- Chewable tablet: Contains phenylalanine.

Other warnings/precautions:

- Aspirin-sensitive asthmatics: Montelukast will not interrupt bronchoconstrictor response to aspirin or other NSAIDs. Patients with known aspirin sensitivity should continue to avoid these agents.

- Reversal of bronchospasm: Not FDA approved for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. Some clinicians, however, support its use (Cylly, 2003; Camargo, 2003; Ferreira, 2001). Appropriate rescue medication should be available.

Geriatric ConsiderationsThe pharmacokinetic profile in the elderly is similar to younger adults except the half-life is slightly longer in the elderly. Despite this difference, no adjustment in dose is necessary in the elderly. Elimination is mostly fecal and bile with insignificant amounts from renal elimination, which is an advantage for the elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsMontelukast was not teratogenic in animal studies, however, there are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed. Based on limited data, structural defects have been reported in neonates exposed to montelukast *in utero*, however, a specific pattern and relationship to montelukast has not been established. Healthcare providers should report any prenatal exposures to the montelukast pregnancy registry at (800) 986-8999.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsZafirlukast, another leukotriene receptor antagonist, is excreted in breast milk and use while breast-feeding is not recommended.

Adverse Reactions(As reported in adults)

1% to 10%:

Central nervous system: Dizziness (2%), fatigue (2%), fever (2%)

Dermatologic: Rash (2%)

Gastrointestinal: Abdominal pain (3%), dyspepsia (2%), dental pain (2%), gastroenteritis (2%)

Hepatic: AST increased (2%)

Neuromuscular & skeletal: Weakness (2%)

Respiratory: Cough (3%), nasal congestion (2%)

Postmarketing and/or case reports: Aggression, agitation, anaphylaxis, angioedema, arthralgia, behavior/mood changes, bleeding tendency, bruising, cholestasis (rare), Churg-Strauss syndrome (rare), depression, diarrhea, dream abnormalities, drowsiness, dyspepsia, edema, eosinophilia (systemic; rare), erythema nodosum, hallucinations, hepatic eosinophilic infiltration (rare); hepatitis (mixed pattern, hepatocellular, and cholestatic); hypersensitivity, hypoesthesia, insomnia, irritability, muscle cramps, myalgia, nausea, palpitation, pancreatitis (rare), paresthesia, pruritus, psychomotor hyperactivity, restlessness, seizure (rare), suicidal thinking/behavior (suicidality), suicide, tremor, urticaria, vasculitis (rare), vomiting

Metabolism/Transport Effects**Substrate** (major) of CYP2C9, 3A4; **Inhibits** CYP2C8 (weak), 2C9 (weak)

Drug Interactions

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease montelukast levels.

Monitoring ParametersMood or behavior changes, including suicidal thinking/behavior

Nursing: Physical Assessment/MonitoringNot for use in acute asthma attacks, including status asthmaticus. Assess effectiveness and interactions of other medications patient may be taking. Monitor mental and mood status. Be alert to thoughts of suicide. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationDo not stop other asthma medication unless advised by prescriber. Chewable tablet contains phenylalanine. Take every evening on a continuous basis; do not discontinue even if feeling better (this medication may help reduce incidence of acute attacks). Granules may be administered directly in the mouth or mixed with applesauce, carrots, rice, ice cream, baby formula, or breast milk (do not add to any other liquids); administer within 15 minutes of opening packet. You may experience mild headache (mild analgesic may help); or fatigue or dizziness (use caution when driving). Report skin rash or itching, abdominal pain or persistent GI upset, unusual cough or congestion, behavior and mood changes including suicide thoughts, feeling of numbness in arms or legs, flu-like illness, or worsening of asthmatic condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Granules:

Singulair®: 4 mg/packet (30s)

Tablet:

Singulair®: 10 mg

Tablet, chewable:

Singulair®: 4 mg [contains phenylalanine 0.674 mg; cherry flavor]; 5 mg [contains phenylalanine 0.842 mg; cherry flavor]

Generic AvailableNo

ManufacturerMerck & Co

Pricing: U.S. (www.drugstore.com)

Chewable (Singulair)

4 mg (30): $114.39

5 mg (30): $116.46

Pack (Singulair)

4 mg (30): $121.14

Tablets (Singulair)

10 mg (30): $116.73

Mechanism of ActionSelective leukotriene receptor antagonist that inhibits the cysteinyl leukotriene receptor. Cysteinyl leukotrienes and leukotriene receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process, which contribute to the signs and symptoms of asthma. Cysteinyl leukotrienes are also released from the nasal mucosa following allergen exposure leading to symptoms associated with allergic rhinitis.

Pharmacodynamics/Kinetics

Duration: >24 hours

Absorption: Rapid

Distribution: V_d: 8-11 L

Protein binding, plasma: >99%

Metabolism: Extensively hepatic via CYP3A4 and 2C9

Bioavailability: Tablet: 10 mg: Mean: 64%; 5 mg: 63% to 73%

Half-life elimination, plasma: Mean: 2.7-5.5 hours

Time to peak, serum: Tablet: 10 mg: 3-4 hours; 5 mg: 2-2.5 hours; 4 mg: 2 hours

Excretion: Feces (86%); urine (<0.2%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dental pain.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness or drowsiness

Mental Health: Effects on Psychiatric Treatment Barbiturates may decrease the effects of montelukast; CYP3A4 substrate; nefazodone may increase effects

Index Terms Montelukast Sodium

References

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Cylly A, Kara A, Ozdemir T, et al, “Effects of Oral Montelukast on Airway Function in Acute Asthma,” *Respir Med*, 2003, 97(5):533-6. [PubMed 12735671]

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Sarkar M and Koren G, “Pregnancy Outcome Following Gestational Exposure to Montelukast: A Prospective Controlled Study,” *Clin Pharmacol Ther*, 2005, 77(2):30. From “Abstracts of the American Society for Clinical Pharmacology and Therapeutics Annual Meeting,” *Clin Pharmacol Ther*, 2005, 77(2):1-146.[PubMed 15712411]

International Brand Names Anxokast (TW); Immunobron (PY); Kastair (PH); Kastair EZ (PH); Kipres (JP); Montair (IN, PH); Monteka (TW); Montemax (PH); Montiget (PH); Singulair (AR, AT, AU, BB, BE, BG, BM, BO, BR, BS, BZ, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, EE, ES, FI, FR, GB, GT, GY, HK, HN, HU, IE, IL, IT, JM, KP, MX, MY, NI, NL, NO, PA, PE, PH, PK, PL, PR, PY, SE, SG, SR, SV, TH, TT, TW, UY, VE); Singulair Chew (KP)

MOP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Brain Tumors

Regimen UseBrain tumors

Regimen

Mechlorethamine: I.V.: 6 mg/m^2/day days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2/day (maximum 2 mg) days 1 and 8

[total dose/cycle = 3 mg/m^2]

Procarbazine: Oral: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Repeat cycle every 28 days

References

Kretschmar CS, Tarbell NJ, Kupsky W, et al, âPreirradiation Chemotherapy for Infants and Children With Medulloblastoma: A Preliminary Report,â *J Neurosurg*, 1989, 71(6):820-5.[PubMed 2585072]

MOPP (Lymphoma, Hodgkin's Disease)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, Hodgkin's Disease
Regimen UseLymphoma, Hodgkin's disease
RegimenNOTE: Multiple variations are listed below.

Variation 1:

Mechlorethamine: I.V.: 6 mg/m^2/day days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Procarbazine: Oral: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14 (cycles 1 and 4)

[total dose/cycle = 560 mg/m^2]

Repeat cycle every 28 days for 6-8 cycles

Variation 2:

Mechlorethamine: I.V.: 6 mg/m^2/day (maximum 15 mg) days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day (maximum 2 mg) days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Procarbazine: Oral: 100 mg/m^2/day days 1 to 10

[total dose/cycle = 1000 mg/m^2]

Prednisone: Oral: 25 mg/m^2/day (maximum 60 mg) days 1 to 14

[total dose/cycle = 350 mg/m^2]

or

Prednisolone: Oral: 25 mg/m^2/day (maximum 60 mg) days 1 to 14

[total dose/cycle = 350 mg/m^2]

Repeat cycle every 28 days

Variation 3:

Mechlorethamine: I.V.: 6 mg/m^2/day days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Procarbazine: Oral: 50 mg day 1, 100 mg day 2, 100 mg/m^2/day days 3 to 14

[total dose/cycle = 150 mg / 1200 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14

[total dose/cycle = 560 mg/m^2]

Repeat cycle every 28 days

Variation 4:

Mechlorethamine: I.V.: 6 mg/m^2/day days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Procarbazine: Oral: 50 mg day 1, 100 mg day 2, 100 mg/m^2/day days 3 to 10

[total dose/cycle = 150 mg / 800 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14

[total dose/cycle = 560 mg/m^2]

Repeat cycle every 28 days

Variation 5:

Mechlorethamine: I.V.: 6 mg/m^2/day days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Procarbazine: Oral: 50 mg/m^2 day 1, then 100 mg/m^2/day days 2 to 14

[total dose/cycle = 1350 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14

[total dose/cycle = 560 mg/m^2]

Repeat cycle every 28 days

References

Variation 1:

Devita VT Jr, Serpick AA, and Carbone PP, “Combination Chemotherapy in the Treatment of Advanced Hodgkin's Disease,” *Ann Intern Med*, 1970, 73(6):881-95. [PubMed 5525541]

Variation 2:

Hancock BW, “Randomised Study Of MOPP (Mustine, Oncovin, Procarbazine, Prednisone) Against LOPP (Leukeran Substituted for Mustine) in Advanced Hodgkin's Disease. British National Lymphoma Investigation,” *Radiother Oncol*, 1986, 7(3):215-21. [PubMed 3544084]

Variation 3:

Nissen NI, Pajak TF, Glidewell O, et al, “A Comparative Study of a BCNU Containing 4-Drug Program Versus MOPP Versus 3-Drug Combinations in Advanced Hodgkin's Disease: A Cooperative Study by the Cancer and Leukemia Group B,” *Cancer*, 1979, 43(1):31-40. [PubMed 367570]

Variation 4:

Huguley CM Jr, Durant JR, Moores RR, et al, “A Comparison of Nitrogen Mustard, Vincristine, Procarbazine, and Prednisone (MOPP) vs Nitrogen Mustard In Advanced Hodgkin's Disease,” *Cancer*, 1975, 36(4):1227-40. [PubMed 1175125]

Variation 5:

Bakemeier RF, Anderson JR, Costello W, et al, “BCVPP Chemotherapy for Advanced Hodgkin's Disease: Evidence for Greater Duration of Complete Remission, Greater Survival, and Less Toxicity Than With a MOPP Regimen. Results of the Eastern Cooperative Oncology Group Study,” *Ann Intern Med*, 1984, 101(4):447-56.[PubMed 6089632]

MOPP (Medulloblastoma)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Brain Tumors]
Regimen UseBrain tumors
Regimen

Mechlorethamine: I.V.: 3 mg/m^2/day days 1 and 8

[total dose/cycle = 6 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day (maximum 2 mg) days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 10

[total dose/cycle = 400 mg/m^2]

Procarbazine: Oral: 50 mg day 1

[total dose/cycle = 50 mg]

followed by Oral: 100 mg day 2

[total dose/cycle = 100 mg]

followed by Oral: 100 mg/m^2/day days 3 to 10

[total dose/cycle = 800 mg/m^2]

Repeat cycle every 28 days

References

Krischer JP, Ragab AH, Kun L, et al, âNitrogen Mustard, Vincristine, Procarbazine, and Prednisone as Adjuvant Chemotherapy in the Treatment of Medulloblastoma. A Pediatric Oncology Group Study,â *J Neurosurg*, 1991, 74(6):905-9.[PubMed 2033450]

MOPP/ABV Hybrid

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, Hodgkin's Disease

Regimen UseLymphoma, Hodgkin's disease

Regimen

Mechlorethamine: I.V.: 6 mg/m^2 day 1

[total dose/cycle = 6 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 (maximum 2 mg) day 1

[total dose/cycle = 1.4 mg/m^2]

Procarbazine: Oral: 100 mg/m^2/day days 1 to 7

[total dose/cycle = 700 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14

[total dose/cycle = 560 mg/m^2]

Doxorubicin: I.V.: 35 mg/m^2 day 8

[total dose/cycle = 35 mg/m^2]

Bleomycin: I.V.: 10 units/m^2 day 8

[total dose/cycle = 10 units/m^2]

Vinblastine: I.V.: 6 mg/m^2 day 8

[total dose/cycle = 6 mg/m^2]

Repeat cycle every 28 days

References

Klimo P and Connors JM, âMOPP/ABV Hybrid Program: Combination Chemotherapy Based on Early Introduction of Seven Effective Drugs for Advanced Hodgkin's Disease,â *J Clin Oncol*, 1985, 3(9):1174-82.[PubMed 2411881]

MOPP/ABVD

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, Hodgkin's Disease

Regimen UseLymphoma, Hodgkin's disease

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Mechlorethamine: I.V.: 6 mg/m^2/day days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day (maximum 2 mg) days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Procarbazine: I.V.: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14 (during cycles 1, 4, 7, and 10 only)

[total dose/cycle = 560 mg/m^2]

Doxorubicin: I.V.: 25 mg/m^2/day days 29 and 43

[total dose/cycle = 50 mg/m^2]

Bleomycin: I.V.: 10 units/m^2/day days 29 and 43

[total dose/cycle = 20 units/m^2]

Vinblastine: I.V.: 6 mg/m^2/day days 29 and 43

[total dose/cycle = 12 mg/m^2]

Dacarbazine: I.V.: 375 mg/m^2/day days 29 and 43

[total dose/cycle = 750 mg/m^2]

Repeat cycle every 56 days

Variation 2:

Mechlorethamine: I.V.: 6 mg/m^2/day days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day (maximum 2 mg) days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Procarbazine: I.V.: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14 (during cycles 1 and 7 only)

[total dose/cycle = 560 mg/m^2]

Doxorubicin: I.V.: 25 mg/m^2/day days 29 and 43

[total dose/cycle = 50 mg/m^2]

Bleomycin: I.V.: 10 units/m^2/day days 29 and 43

[total dose/cycle = 20 units/m^2]

Vinblastine: I.V.: 6 mg/m^2/day days 29 and 43

[total dose/cycle = 12 mg/m^2]

Dacarbazine: I.V.: 375 mg/m^2/day days 29 and 43

[total dose/cycle = 750 mg/m^2]

Repeat cycle every 56 days

Variation 3:

Mechlorethamine: I.V.: 6 mg/m^2/day days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day (maximum 2 mg) days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Procarbazine: I.V.: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14 (every cycle)

[total dose/cycle = 560 mg/m^2]

Doxorubicin: I.V.: 25 mg/m^2/day days 29 and 43

[total dose/cycle = 50 mg/m^2]

Bleomycin: I.V.: 10 units/m^2/day days 29 and 43

[total dose/cycle = 20 units/m^2]

Vinblastine: I.V.: 6 mg/m^2/day days 29 and 43

[total dose/cycle = 12 mg/m^2]

Dacarbazine: I.V.: 375 mg/m^2/day days 29 and 43

[total dose/cycle = 750 mg/m^2]

Repeat cycle every 56 days

Variation 4:

MOPP Regimen:

Mechlorethamine: I.V.: 6 mg/m^2/day days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day (maximum 2 mg) days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Procarbazine: I.V.: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Prednisone: Oral: 25 mg/m^2/day days 1 to 14

[total dose/cycle = 350 mg/m^2]

ABVD Regimen:

Doxorubicin: I.V.: 25 mg/m^2/day days 1 and 15

[total dose/cycle = 50 mg/m^2]

Bleomycin: I.V.: 6 units/m^2/day days 1 and 15

[total dose/cycle = 12 units/m^2]

Vinblastine: I.V.: 6 mg/m^2/day days 1 and 15

[total dose/cycle = 12 mg/m^2]

Dacarbazine: I.V.: 250 mg/m^2/day days 1 and 15

[total dose/cycle = 500 mg/m^2]

Each regimen cycle is 28 days. Administer regimens in alternating fashion as follows: 2 cycles of MOPP alternating with 2 cycles of ABVD for a total of 8 cycles

Variation 5 (pediatrics):

Mechlorethamine: I.V.: 6 mg/m^2/day days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Procarbazine: Oral: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14

[total dose/cycle = 560 mg/m^2]

Doxorubicin: I.V.: 25 mg/m^2/day days 29 and 42

[total dose/cycle = 50 mg/m^2]

Bleomycin: I.V.: 10 units/m^2/day days 29 and 42

[total dose/cycle = 20 units/m^2]

Vinblastine: I.V.: 6 mg/m^2/day days 29 and 42

[total dose/cycle = 12 mg/m^2]

Dacarbazine: I.V.: 150 mg/m^2/day days 29 to 33

[total dose/cycle = 750 mg/m^2]

Repeat cycle every 56 days for 4 cycles

Variation 6 (pediatrics):

Mechlorethamine: I.V.: 6 mg/m^2/day days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day days 1 and 8

[total dose/cycle = 2.8 mg/m^2]

Procarbazine: Oral: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14

[total dose/cycle = 560 mg/m^2]

Doxorubicin: I.V.: 25 mg/m^2/day days 29 and 42

[total dose/cycle = 50 mg/m^2]

Bleomycin: I.V.: 10 units/m^2/day days 29 and 42

[total dose/cycle = 20 units/m^2]

Vinblastine: I.V.: 6 mg/m^2/day days 29 and 42

[total dose/cycle = 12 mg/m^2]

Dacarbazine: I.V.: 375 mg/m^2/day days 29 and 43

[total dose/cycle = 750 mg/m^2]

Repeat cycle every 56 days for 4 cycles

References

Variation 1:

Bonadonna G, Valagussa P, and Santoro A, “Alternating Noncross-Resistant Combination Chemotherapy or MOPP in State IV Hodgkin's Disease. A Report of 8-Year Results,” *Ann Int Med*, 1986, 104(6):739-46. [PubMed 2422994]

Variation 2:

Canellos, GP, Anderson JR, Propert KJ, et al, “Chemotherapy of Advanced Hodgkin's Disease With MOPP, ABVD, or MOPP Alternating With ABVD,” *N Engl J Med*, 1992, 327(21):1478-84. [PubMed 1383821]

Variation 3:

Glick JH, Young ML, Harrington D, et al, “MOPP/ABV Hybrid Chemotherapy for Advanced Hodgkin's Disease Significantly Improves Failure-Free and Overall Survival. The 8-Year Results of the Intergroup Trial,” *J Clin Oncol* 1998, 16(1):19-26. [PubMed 9440718]

Variation 4:

Somers R, Carde P, Henry-Amar M, et al, “A Randomized Study in State IIIB and IV Hodgkin's Disease Comparing Eight Courses of MOPP Versus an Alternation of MOPP With ABVD. A European Organization for Research and Treatment of Cancer Lymphoma Cooperative Group and Groupe Pierre-et-Marie-Curie Controlled Clinical Trial,” *J Clin Oncol*, 1994, 12(2):279-87. [PubMed 7509381]

Variation 5 (pediatrics):

Weiner MA, Leventhal BG, Marcus R, et al, “Intensive Chemotherapy and Low-Dose Radiotherapy for the Treatment of Advanced-Stage Hodgkin's Disease in Pediatric Patients. A Pediatric Oncology Group Study,” *J Clin Oncol*, 1991, 9(9):1591-8. [PubMed 1714950]

Variation 6 (pediatrics):

Weiner MA, Leventhal B, Brecher ML, et al, “Randomized Study of Intensive MOPP-ABVD With or Without Low-Dose Total-Nodal Radiation Therapy in the Treatment of Stages IIB, IIIA2, IIIB, and IV Hodgkin's Disease in Pediatric Patients. A Pediatric Oncology Group Study,” *J Clin Oncol*, 1997, 15(8):2769-79.[PubMed 9256118]

Moricizine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Ethmozine® may be confused with Erythrocin®, erythromycin

Pronunciation(mor I siz een)

U.S. Brand NamesEthmozine® [DSC]

Canadian Brand NamesEthmozine®

Pharmacologic CategoryAntiarrhythmic Agent, Class I

Use: Labeled IndicationsTreatment of ventricular tachycardia and life-threatening ventricular arrhythmias

Use: Unlabeled/InvestigationalPVCs, complete and nonsustained ventricular tachycardia, atrial arrhythmias

Dosing: Adults**Ventricular arrhythmias:** Oral: 200-300 mg every 8 hours, adjust dosage at 150 mg/day at 3-day intervals. See table for dosage recommendations of transferring from other antiarrhythmic agents to Ethmozine®. Hospitalization required to start therapy.

Moricizine

Transferred From	**Start Ethmozine®**
Encainide, propafenone, tocainide, or mexiletine	8-12 hours after last dose
Flecainide	12-24 hours after last dose
Procainamide	3-6 hours after last dose
Quinidine, disopyramide	6-12 hours after last dose

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentStart at 600 mg/day or less.

Dosing: Hepatic ImpairmentStart at 600 mg/day or less.

Dietary ConsiderationsBest if taken on an empty stomach.

ContraindicationsHypersensitivity to moricizine or any component of the formulation; pre-existing second- or third-degree AV block (except in patients with a functioning artificial pacemaker); right bundle branch block when associated with left hemiblock or bifascicular block (unless functional pacemaker in place); cardiogenic shock

Warnings/Precautions

Boxed warnings:

- CAST II Trial: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Conduction disturbances: Dose-related increases in PR and QRS intervals occur.

Disease-related concerns:

- Cardiovascular disease: Avoid use in patients with CAD, previous history of MI, HF, pre-existing conduction abnormalities, and cardiomegaly.

- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.

- Hepatic impairment: Use with caution in patients with significant hepatic impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- CAST II Trial: **[U.S. Boxed Warning]: The CAST II trial demonstrated a decreased trend in survival for patients receiving moricizine.**

Geriatric ConsiderationsDue to moricizine binding to plasma albumin and alpha-glycoprotein, other highly bound drugs may displace moricizine. Since elderly may require multiple drugs, caution with highly bound drugs is necessary. Consider changes in renal and hepatic function with age and monitor closely since half-life may be prolonged.

Pregnancy Risk FactorB

LactationEnters breast milk/not recommended

Adverse Reactions

>10%: Central nervous system: Dizziness

1% to 10%:

- Cardiovascular: Proarrhythmia, palpitation, cardiac death, ECG abnormalities, CHF
- Central nervous system: Headache, fatigue, insomnia
- Endocrine & metabolic: Decreased libido
- Gastrointestinal: Nausea, diarrhea, ileus
- Ocular: Blurred vision, periorbital edema
- Respiratory: Dyspnea

<1% (Limited to important or life-threatening): Ventricular tachycardia, cardiac chest pain, hyper-/hypotension, syncope, supraventricular arrhythmia, MI, apnea

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Induces** CYP1A2 (weak), 3A4 (weak)

Drug Interactions

Cimetidine: May decrease the metabolism of Moricizine. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Theophylline Derivatives: Moricizine may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Moricizine peak serum concentrations may be decreased if taken with food.

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor cardiac status. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy, when titrating dosage, and on a regular basis with long-term therapy. **Note:** Moricizine has a low toxic:therapeutic ratio and overdose may easily produce severe and life-threatening reactions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsElectrolytes (correct any imbalance) prior to beginning therapy

Patient EducationTake exactly as directed; do not take additional doses or discontinue without consulting prescriber. You will need regular cardiac checkups and blood tests while taking this medication. You may experience dizziness or visual changes (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or headaches, sleep disturbances, or decreased libido (usually temporary, if persistent consult prescriber). Report chest pain, palpitation, or erratic heartbeat; increased weight or swelling of hands or feet; blurred vision or facial swelling; acute diarrhea; changes in bowel or bladder patterns; or respiratory difficulty. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, as hydrochloride:

- Ethmozine®: 200 mg, 250 mg, 300 mg [DSC]

Generic AvailableNo

ManufacturerRoberts Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Ethmozine)

- 200 mg (100): $123.66
- 250 mg (100): $147.94
- 300 mg (100): $167.83

Mechanism of ActionClass I antiarrhythmic agent; reduces the fast inward current carried by sodium ions, shortens Phase I and Phase II repolarization, resulting in decreased action potential duration and effective refractory period

Pharmacodynamics/Kinetics

Protein binding, plasma: 95%

Metabolism: Significant first-pass effect; some enterohepatic recycling

Bioavailability: 38%

Half-life elimination: Healthy volunteers: 3-4 hours; Cardiac disease: 6-13 hours

Excretion: Feces (56%); urine (39%)

Related Information

- Antiarrhythmic Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause sedation or insomnia; may rarely cause anxiety, confusion, amnesia

Mental Health: Effects on Psychiatric TreatmentUse caution with TCAs may produce QT prolongation

Cardiovascular ConsiderationsThis class Ic antiarrhythmic agent was associated with a trend toward increased mortality in the CAST trial and therefore should not be used in patients with cardiovascular disease. Although moricizine was effective in suppressing asymptomatic ventricular arrhythmias in patients after myocardial infarction, it was accompanied by increased mortality. Cardiotoxic arrhythmic effects of moricizine and other class Ic drugs should not be treated using Class Ia antiarrhythmics.

Anesthesia and Critical Care Concerns/Other ConsiderationsThis class Ic antiarrhythmic agent was associated with a trend toward increased mortality in the CAST trial and therefore should not be used in patients with cardiovascular disease. Cardiotoxic arrhythmic effects of moricizine and other Class Ic drugs should not be treated using class Ia antiarrhythmics.

Index TermsMoricizine Hydrochloride

References

Buxton AE, Lee KL, Fisher JD, et al, “A Randomized Study of the Prevention of Sudden Death in Patients With Coronary Artery Disease. Multicenter Unsustained Tachycardia Trial Investigators,” *N Engl J Med*, 1999, 341:1882-90. [PubMed 10601507]

Echt DS, Liebson PR, Mitchell LB, et al, “Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo. The Cardiac Arrhythmia Suppression Trial,” *N Engl J Med*, 1991, 324(12):781-8. [PubMed 1900101]

“Effect of the Antiarrhythmic Agent Moricizine on Survival After Myocardial Infarction. The Cardiac Arrhythmia Suppression Trial II Investigators,” *N Engl J Med*, 1992, 327(4):227-33. [PubMed 1377359]

Flaker GC, Blackshear JL, McBride R, et al, “Antiarrhythmic Drug Therapy and Cardiac Mortality in Atrial Fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators,” *J Am Coll Cardiol*, 1992, 20:527-32.[PubMed 1512329]

International Brand NamesEthmozine (CA)

Morphine Sulfate

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Morphine Tablets: Recall Due to Potential for Oversized Tablets - November 2008

Certain lots of generic morphine tablets have been recalled due to possibility of oversized tablets. Oversized tablets may contain up to twice the amount of the active ingredient which may result in serious or life-threatening effects.

For more information, including lots involved, please refer to the FDA MedWatch alert: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Ethex

Medication Safety Issues

Sound-alike/look-alike issues:

Morphine may be confused with HYDROmorphone

Morphine sulfate may be confused with magnesium sulfate

MS Contin® may be confused with Oxycontin®

MSO_4 and MS are error-prone abbreviations (mistaken as magnesium sulfate)

Avinza® may be confused with Evista®, Invanz®

Roxanol™ may be confused with OxyFast®, Roxicet™, Roxicodone®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V. formulation) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Use care when prescribing and/or administering morphine solutions. These products are available in different concentrations. Always prescribe dosage in mg; **not** by volume (mL).

Use caution when selecting a morphine formulation for use in neurologic infusion pumps (eg, Medtronic delivery systems). The product should be appropriately labeled as "preservative-free" and suitable for intraspinal use via continuous infusion. In addition, the product should be formulated in a pH range that is compatible with the device operation specifications.

Significant differences exist between oral and I.V. dosing. Use caution when converting from one route of administration to another.

Pronunciation(MOR feen SUL fate)

U.S. Brand NamesAstramorph/PF™; Avinza®; DepoDur®; Duramorph®; Infumorph®; Kadian®; MS Contin®; Oramorph SR®; Roxanol™

Canadian Brand NamesDoloral; Kadian®; M-Eslon®; M.O.S.-SR®; M.O.S.-Sulfate®; M.O.S.® 10; M.O.S.® 20; M.O.S.® 30; Morphine HP®; Morphine LP® Epidural; MS Contin®; MS-IR®; Novo-Morphine SR; PMS-Morphine Sulfate SR; Ratio-Morphine; Ratio-Morphine SR; Statex®; Zomorph®

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled IndicationsRelief of moderate to severe acute and chronic pain; relief of pain of myocardial infarction; relief of dyspnea of acute left ventricular failure and pulmonary edema; preanesthetic medication

DepoDur®: Epidural (lumbar) single-dose management of surgical pain

Infumorph®: Used in continuous microinfusion devices for intrathecal or epidural administration in treatment of intractable chronic pain

Controlled, extended, or sustained release products: Only intended/indicated for use when repeated doses for an extended period of time are required. The 100 mg and 200 mg tablets or capsules of Kadian®, MS Contin®, and morphine sulfate controlled-release tablets and the 60 mg, 90 mg, and 120 mg capsules of Avinza® should only be used in opioid-tolerant patients.

Dosing: Adults**Note:** These are guidelines and do not represent the doses that may be required in all patients. Doses and dosage intervals should be titrated to pain relief/prevention.

Acute pain (moderate-to-severe):

Oral (immediate release formulations: Opiate-naive: Initial: 10 mg every 4 hours as needed; patients with prior opiate exposure may require higher initial doses: usual dosage range: 10-30 mg every 4 hours as needed

I.M., SubQ: **Note:** Repeated SubQ administration causes local tissue irritation, pain, and induration.

Initial: Opiate-naive: 5-10 mg every 4 hours as needed; patients with prior opiate exposure may require higher initial doses; usual dosage range: 5-20 mg every 4 hours as needed

Rectal: 10-20 mg every 3-4 hours

I.V.: Initial: Opiate-naive: 2.5-5 mg every 3-4 hours; patients with prior opiate exposure may require higher initial doses. **Note:** Repeated doses (up to every 5 minutes if needed) in small increments (eg, 1-4 mg) may be preferred to larger and less frequent doses.

Acute myocardial infarction, analgesia (ACC/AHA 2004 Guidelines): Initial management: 2-4 mg, give 2-8 mg every 5-15 minutes as needed

Critically-ill patients (unlabeled dose): 0.7-10 mg (based on 70 kg patient) **or** 0.01-0.15 mg/kg every 1-2 hours as needed. **Note:** More frequent dosing may be needed (eg, mechanically-ventilated patients).

I.V., SubQ continuous infusion: 0.8-10 mg/hour; usual range: Up to 80 mg/hour

Continuous infusion: Usual dosage range: 5-35 mg/hour (based on 70 kg patient) **or** 0.07-0.5 mg/kg/hour

Patient-controlled analgesia (PCA): (Opiate-naive: Consider lower end of dosing range):

Usual concentration: 1 mg/mL

Demand dose: Usual: 1 mg; range: 0.5-2.5 mg

Lockout interval: 5-10 minutes

*Intrathecal (I.T.):***Note:** Administer with extreme caution and in reduced dosage to geriatric or debilitated patients. I.T. dose is usually $^1/_{10}$ that of epidural dosage.

Opioid-naive: 0.2-1 mg/dose (may provide adequate relief for 24 hours); repeat doses are **not** recommended

Continuous microinfusion (Infumorph®): Initial: 0.2-1 mg/day

Opioid-tolerant: 1-10 mg/day

Continuous microinfusion (Infumorph®): Initial: 1-10 mg/day, titrate to effect; usual maximum is ~20 mg/day

Epidural: Pain management: **Note:** Administer with extreme caution and in reduced dosage to geriatric or debilitated patients. Vigilant monitoring is particularly important in these patients.

Single-dose (Astromorph/PF™, Duramorph®): Initial: 5 mg, if pain relief not achieved in 1 hour, careful administration of 1-2 mg at intervals sufficient to assess effectiveness may be given; maximum: 10 mg/24 hours

Infusion: Bolus dose: 1-6 mg; infusion rate: 0.1-0.2 mg/hour; maximum dose: 10 mg/24 hours

Continuous microinfusion (Infumorph®):

Opioid-naive: Initial: 0.2-1 mg/day

Opioid-tolerant: Initial: 1-10 mg/day, titrate to effect; usual maximum is ~20 mg/day

Surgical anesthesia: Epidural: Single-dose (extended release, DepoDur®): Lumbar epidural only; not recommended in patients <18 years of age:

Cesarean section: 10 mg (after clamping umbilical cord)

Lower abdominal/pelvic surgery: 10-15 mg

Major orthopedic surgery of lower extremity: 15 mg

For DepoDur®: To minimize the pharmacokinetic interaction resulting in higher peak serum concentrations of morphine, administer the test dose of the local anesthetic at least 15 minutes prior to DepoDur® administration. Use of DepoDur® with epidural local anesthetics has not been studied. Other medications should not be administered into the epidural space for at least 48 hours after administration of DepoDur®.

Note: Some patients may benefit from a 20 mg dose, however, the incidence of adverse effects may be increased.

Chronic pain: Note: Patients taking opioids chronically may become tolerant and require doses higher than the usual dosage range to maintain the desired effect. Tolerance can be managed by appropriate dose titration. There is no optimal or maximal dose for morphine in chronic pain. The appropriate dose is one that relieves pain throughout its dosing interval without causing unmanageable side effects.

Oral: Controlled-, extended-, or sustained-release formulations: A patient's morphine requirement should be established using prompt-release formulations. Conversion to long-acting products may be considered when chronic, continuous treatment is required. Higher dosages should be reserved for use only in opioid-tolerant patients.

Capsules, extended release (Avinza®): Daily dose administered once daily (for best results, administer at same time each day)

Capsules, sustained release (Kadian®): Daily dose administered once daily or in 2 divided doses daily (every 12 hours)

Tablets, controlled release (MS Contin®), sustained release (Oramorph SR®), or extended release: Daily dose divided and administered every 8 or every 12 hours

Dosing: ElderlyRefer to adult dosing. Use with caution; may require reduced dosage in the elderly and debilitated patients.
Dosing: Pediatric**Note:** These are guidelines and do not represent the doses that may be required in all patients. Doses and dosage intervals should be titrated to pain relief/prevention.

Acute pain (moderate-to-severe): Children >6 months and <50 kg:

Oral (prompt release): 0.15-0.2 mg/kg every 3-4 hours as needed

I.M., I.V.: 0.1-0.2 mg/kg every 3-4 hours as needed

I.V. infusion: Range: 10-60 mcg/kg/hour

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Children and Adults: Administer at 75% of normal dose

Cl_{cr} <10 mL/minute: Children and Adults: Administer at 50% of normal dose

Intermittent HD:

Children: Administer 50% of normal dose

Adults: No dosage adjustment necessary

Peritoneal dialysis: Children: Administer 50% of normal dose

CRRT: Children and Adults: Administer 75% of normal dose, titrate

Dosing: Hepatic ImpairmentUnchanged in mild liver disease; substantial extrahepatic metabolism may occur. Excessive sedation may occur in cirrhosis.
Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Fentanyl Transdermal Conversion
- Opioid Agonist Conversion

Administration: I.V.When giving morphine I.V. push, it is best to first dilute in 4-5 mL of sterile water, and then to administer slowly (eg, 15 mg over 3-5 minutes).
Administration: I.V. DetailpH: 2.5-6.0
Administration: OralDo not crush controlled release drug product, swallow whole. Kadian® and Avinza® can be opened and sprinkled on applesauce; do not crush or chew the beads. Contents of Kadian® capsules may be opened and sprinkled over 10 mL water and flushed through prewetted 16F gastrostomy tube; do not administer Kadian® through nasogastric tube.
Administration: OtherUse preservative-free solutions for intrathecal or epidural use.

Epidural, extended release liposomal suspension (DepoDur®): Intended for lumbar administration only. Thoracic administration has not been studied. May be administered undiluted or diluted up to 5 mL total volume in preservative-free NS. Do not use an in-line filter during administration. Not for I.V., I.M., or intrathecal administration.

Resedation may occur following epidural administration; this may be delayed ≥48 hours in patients receiving extended-release (DepoDur®) injections.

Administration of an epidural test dose (lidocaine 1.5% and epinephrine 1:200,000) may affect the release of morphine from the liposomal preparation. Delaying the dose for an interval of at least 15 minutes following the test dose minimizes this pharmacokinetic interaction. Except for a test dose, other epidural local anesthetics or medications should not be administered epidurally before or after this product for a minimum of 48 hours.

Dietary ConsiderationsMorphine may cause GI upset; take with food if GI upset occurs. Be consistent when taking morphine with or without meals.
Storage

Capsule, sustained release (Avinza®, Kadian®): Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light and moisture.

Injection: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F); do not freeze. Protect from light. Degradation depends on pH and presence of oxygen; relatively stable in pH ≤4; darkening of solutions indicate degradation.

DepoDur®: Store under refrigeration at 2°C to 8°C (36°F to 46°F); keep vials in carton during refrigeration; do not freeze. Check freeze indicator before administration; do not administer if bulb is pink or purple. May store at room temperature for up to 30 days in sealed, unopened vials. Gently invert to suspend particles prior to removal from vial. Once vial is opened, use within 4 hours.

Oral solution: Store at controlled room temperature of 25°C (68°F to 77°F). Do not freeze.

Suppositories: Store at controlled room temperature 25°C (77°F). Protect from light.

Tablet, extended release: Store at controlled room temperature of 25°C (77°F).

Tablet, immediate release: Store at controlled room temperature of 25°C (77°F). Protect from moisture.

Reconstitution Usual concentration for continuous I.V. infusion: 0.1-1 mg/mL in D_5W. DepoDur® may be diluted in preservative-free NS to a volume of 5 mL.

Compatibility Stable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, ${}^1/_2NS$, NS; **variable stability (consult detailed reference)** in TPN.

Y-site administration: Compatible: Allopurinol, amifostine, amikacin, aminophylline, amiodarone, ampicillin, ampicillin/sulbactam, amsacrine, atenolol, atracurium, aztreonam, bumetanide, calcium chloride, cefamandole, cefazolin, cefoperazone, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, chloramphenicol, cisatracurium, cisplatin, cladribine, clindamycin, co-trimoxazole, cyclophosphamide, cytarabine, dexamethasone sodium phosphate, digoxin, diltiazem, dobutamine, docetaxel, dopamine, doxorubicin, doxycycline, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, etomidate, etoposide phosphate, famotidine, fentanyl, filgrastim, fluconazole, fludarabine, foscarnet, gatifloxacin, gemcitabine, gentamicin, granisetron, heparin, hydrocortisone sodium succinate, hydromorphone, IL-2, insulin (regular), kanamycin, labetalol, levofloxacin, lidocaine, linezolid, lorazepam, magnesium sulfate, melphalan, meropenem, methotrexate, methyldopate, methylprednisolone sodium succinate, metoclopramide, metoprolol, metronidazole, midazolam, milrinone, nafcillin, nicardipine, nitroglycerin, norepinephrine, ondansetron, oxacillin, oxytocin, paclitaxel, pancuronium, penicillin G potassium, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, propranolol, ranitidine, remifentanil, sodium bicarbonate, sodium nitroprusside, tacrolimus, teniposide, thiotepa, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, vecuronium, vinorelbine, vitamin B complex with C, warfarin, zidovudine. **Incompatible:** Alatrofloxacin, amphotericin B cholesteryl sulfate complex, cefepime, doxorubicin liposome, minocycline, sargramostim. **Variable (consult detailed reference):** Acyclovir, furosemide, thiopental, TPN.

Compatibility in syringe: Compatible: Atropine, bupivacaine, bupivacaine with clonidine, butorphanol, cimetidine, dimenhydrinate, diphenhydramine, droperidol, fentanyl, glycopyrrolate, hydroxyzine, hyoscine, ketamine, ketamine with lidocaine, metoclopramide, midazolam, milrinone, ondansetron, pentazocine, perphenazine, promazine, ranitidine, scopolamine. **Incompatible:** Meperidine, thiopental. **Variable (consult detailed reference):** Chlorpromazine, haloperidol, heparin, pentobarbital, prochlorperazine edisylate, promethazine.

Compatibility when admixed: Compatible: Alteplase, atracurium, baclofen, bupivacaine, dobutamine, fluconazole, furosemide, ketamine, meropenem, metoclopramide, ondansetron, succinylcholine, verapamil. **Incompatible:** Aminophylline, amobarbital, chlorothiazide, fluorouracil, heparin, meperidine, phenobarbital, phenytoin, sodium bicarbonate, thiopental.

DepoDur®: Do not mix with other medications.

Restrictions C-II

Contraindications **Note:** Some contraindications are product specific. For details, please see detailed product prescribing information.

Hypersensitivity to morphine sulfate or any component of the formulation; severe respiratory depression (without resuscitative equipment); acute or severe asthma; known or suspected paralytic ileus; sustained release products are not recommended with gastrointestinal obstruction or in acute/postoperative pain; pregnancy (prolonged use or high doses at term). Oral solutions contraindicated in patients with heart failure due to chronic lung disease, cardiac arrhythmias, head injuries, brain tumors, acute alcoholism, deliriums tremens, seizure disorders, Injectable solution contraindicated during labor when a premature birth is anticipated. Some products contraindicated in patients with head injuries or increased intracranial pressure. DepoDur® contraindicated in circulatory shock and upper airway obstruction. MS Contin® and Kadian® contraindicated in patients with hypercarbia. Some immediate release formulations (tablets and solution) contraindicated in post biliary tract surgery, suspected surgical abdomen, surgical anastomosis, MAO inhibitor use (concurrent or within 14 days), general CNS depression.

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Abuse/misuse/diversion: See “Other warnings/precautions” below.
- Avinza®: See “Dosage form specific issues” below.
- Duramorph®: See “Dosage form specific issues” below.
- Extended/sustained release products: See “Dosage form specific issues” below.
- Intrathecal: See “Other warnings/precautions” below.
- Highly concentrated oral solutions: See “Dosage form specific issues” below.

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), circulatory shock, or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics). May cause orthostatic hypotension and syncope in ambulatory patients.
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).
- Respiratory depression: May cause respiratory depression. Risk increased in elderly patients, debilitated patients, and patients with conditions associated with hypoxia or hypercapnia.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions. May worsen gastrointestinal ileus due to the effects on GI motility. Some dosage forms are contraindicated in patients with a paralytic ileus.

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.

- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction and acute pancreatitis. Use may cause constriction of sphincter of Oddi diminishing biliary and pancreatic secretions. Some dosage forms are contraindicated in post biliary tract surgery.

- CNS depression/coma: Use with caution in patients with CNS depression or coma.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure (ICP); exaggerated elevation of ICP may occur. Some dosage forms are contraindicated with increased ICP or head trauma.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Obesity: Use with caution in patients who are morbidly obese.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages. Some dosage forms may be contraindicated in patients with severe respiratory disorders.

- Seizure disorders: Use with caution in patients with seizure disorders, may cause seizures if high doses used.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs, CNS depressants, antihistamines, psychotropic drugs, or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Infants <3 months of age are more susceptible to respiratory depression; use with caution and generally in reduced doses in this age group.

Dosage form specific issues:

- Avinza®: **[U.S. Boxed Warning]: Do not administer with alcoholic beverages or ethanol-containing products, which may disrupt extended-release characteristic of product.**

- DepoDur®: **For lumbar administration only.** Intrathecal administration has resulted in prolonged respiratory depression. Freezing may adversely affect modified-release mechanism of drug; check freeze indicator within carton prior to administration.

- Duramorph®: **[U.S. Boxed Warning]: Due to the risk of severe and/or sustained cardiopulmonary depressant effects of Duramorph® it must be administered in a fully equipped and staffed environment.** Naloxone injection should be immediately available. Patient should remain in this environment for at least 24 hours following the initial dose.

- Extended/sustained release products: **[U.S. Boxed Warning]: Extended or sustained release dosage forms should not be crushed or chewed.** Controlled-, extended-, or sustained-release products are not intended for “as needed (PRN)” use. **MS Contin® 100 mg or 200 mg tablets and Kadian® 100 mg or 200 mg capsules are for use only in opioid-tolerant patients.** Avinza®, Kadian®, MS Contin®: **[U.S. Boxed Warning]: Indicated for the management of moderate-to-severe pain when around the clock pain control is needed for an extended time period.**

- Infumorph® solutions: **For use in microinfusion devices only**; not for I.V., I.M., or SubQ administration or for single-dose administration. Monitor closely, especially in the first 24 hours.

- Injections: Products are designed for administration by specific routes (I.V., intrathecal, epidural). Use caution when prescribing, dispensing, or administering to use formulations only by intended route(s).

- Sulfites: Some intravenous preparations contain sulfites which may cause allergic reactions in sulfite sensitive patients.

Other warnings/precautions:

- Abuse/misuse/diversion: Kadian®, MS Contin®: **[U.S. Boxed Warning]: Healthcare provider should be alert to problems of abuse, misuse, and diversion.**

- Epidural use: When used as an epidural injection, monitor for delayed sedation. Physician should evaluate patient for contraindications for epidural injection (eg, anticoagulant therapy, bleeding, diathesis, etc).

- Intrathecal: **[U.S. Boxed Warning]: Intrathecal dosage is usually $^{1}/_{10}$ that of epidural dosage.**

- Optimal regimen: An opioid-containing analgesic regimen should be tailored to each patient's needs and based upon the type of pain being treated (acute versus chronic), the route of administration, degree of tolerance for opioids (naive versus chronic user), age, weight, and medical condition. The optimal analgesic dose varies widely among patients; doses should be titrated to pain relief/prevention.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsThe elderly may be particularly susceptible to the CNS depressant and constipating effects of narcotics. For chronic administration of narcotic analgesics, morphine is preferable in the elderly due to its pharmacokinetics and side effect profile as compared to meperidine and methadone.

Pregnancy Risk FactorC/D (prolonged use or high doses at term)

Pregnancy ConsiderationsMorphine crosses the placenta. The frequency of congenital malformations has not been reported to be greater than expected in children from mothers treated with morphine during pregnancy. Reduced growth and behavioral abnormalities in offspring have been observed in animal studies. Neonates born to mothers receiving chronic opioids during pregnancy should be monitored for neonatal withdrawal syndrome.

DepoDur® may be used in women undergoing cesarean section following clamping of the umbilical cord; not for use in vaginal labor and delivery.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsMorphine concentrates in breast milk, with a milk to plasma ratio of 2.5:1. Detectable serum levels of morphine can be found in infants following morphine administration to nursing mothers. Treatment of the mother with single doses of morphine is not expected to cause detrimental effects in nursing infants. Breast-feeding following chronic use or in neonates with hepatic or renal dysfunction may lead to higher levels of morphine in the infant and a risk of adverse effects. Some clinicians recommend administering morphine immediately after breast-feeding or 3-4 hours prior to the next feeding. Breast-feeding should be delayed for 48 hours after DepoDur® administration.

Adverse Reactions**Note:** Individual patient differences are unpredictable, and percentage may differ in acute pain (surgical) treatment. Reactions may be dose, formulation, and/or route dependent.

Frequency not defined:

Cardiovascular: Circulatory depression, flushing, shock

Central nervous system: Physical and psychological dependence, sedation

Endocrine & metabolic: Antidiuretic hormone release

>10%:

Cardiovascular: Bradycardia, hypotension

Central nervous system: Drowsiness (9% to 48%; tolerance usually develops to drowsiness with regular dosing for 1-2 weeks), dizziness (6% to 20%), fever (<3% to >10%), confusion, headache (following epidural or intrathecal use)

Dermatologic: Pruritus (may be dose related)

Gastrointestinal: Xerostomia (78%), constipation (9% to 40%; tolerance develops very slowly if at all), nausea (7% to 28%; tolerance usually develops to nausea and vomiting with chronic use), vomiting

Genitourinary: Urinary retention (16%; may be prolonged, up to 20 hours, following epidural or intrathecal use)

Hematologic: Anemia (following intrathecal use)

Local: Pain at injection site

Neuromuscular & skeletal: Weakness

Respiratory: Oxygen saturation decreased

Miscellaneous: Histamine release

1% to 10%:

Cardiovascular: Atrial fibrillation (<3%), chest pain (<3%), edema, hypertension, palpitation, peripheral edema, syncope, tachycardia, vasodilation

Central nervous system: Amnesia, agitation, anxiety, apathy, ataxia, chills, coma, delirium, depression, dream abnormalities, euphoria, false sense of well being, hallucination, hypoesthesia, insomnia, lethargy, malaise, nervousness, restlessness, seizure, slurred speech, somnolence, vertigo

Dermatologic: Dry skin, rash, urticaria

Endocrine & metabolic: Gynecomastia (<3%), hypokalemia, hyponatremia, libido decreased

Gastrointestinal: Abdominal distension, abdominal pain, anorexia, biliary colic, diarrhea, dyspepsia, dysphagia, flatulence, gastroenteritis, GERD, GI irritation, paralytic ileus, rectal disorder, taste perversion, weight loss

Genitourinary: Bladder spasm, dysuria, ejaculation abnormal, impotence, urination decreased

Hematologic: Leukopenia (<3%), thrombocytopenia (<3%), hematocrit decreased

Hepatic: Liver function tests increased

Neuromuscular & skeletal: Arthralgia, back pain, bone pain, foot drop, gait abnormalities, paresthesia, rigors, skeletal muscle rigidity, tremor

Ocular: Amblyopia, conjunctivitis, eye pain, vision problems/disturbance

Renal: Oliguria

Respiratory: Asthma, atelectasis, dyspnea, hiccups, hypercapnia, hypoxia, pulmonary edema (noncardiogenic), respiratory depression, rhinitis

Miscellaneous: Diaphoresis, flu-like syndrome, infection, thirst, voice alteration, withdrawal syndrome

<1%, postmarketing, and/or case reports: Amenorrhea, anaphylaxis, apnea, biliary tract spasm, blurred vision, bronchospasm, cardiac arrest, cough reflex decreased, dehydration, diplopia, disorientation, hemorrhagic urticaria, intestinal obstruction, intracranial pressure increased, laryngospasm, menstrual irregularities, miosis, myoclonus, nystagmus, paradoxical CNS stimulation, respiratory arrest, sepsis, urinary tract spasm, thermal dysregulation, toxic psychoses

Oncology: VesicantNo

Oncology: Emetic PotentialHigh (60% to 90%)

Metabolism/Transport Effects**Substrate** of CYP2D6 (minor)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Morphine Sulfate. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Trovafloxacin: Morphine Sulfate may decrease the serum concentration of Trovafloxacin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol, including alcoholic beverages or ethanol-containing products (may increase CNS depression).

Avinza®: Alcoholic beverages or ethanol-containing products may disrupt extended-release formulation resulting in rapid release of entire morphine dose.

Food: Administration of oral morphine solution with food may increase bioavailability (ie, a report of 34% increase in morphine AUC when morphine oral solution followed a high-fat meal). The bioavailability of Avinza®, Oramorph SR®, or Kadian® does not appear to be affected by food.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsSome quinolones may produce a false-positive urine screening result for opiates using commercially-available immunoassay kits. This has been demonstrated most consistently for levofloxacin and ofloxacin, but other quinolones have shown cross-reactivity in certain assay kits. Confirmation of positive opiate screens by more specific methods should be considered.

Monitoring ParametersPain relief, respiratory and mental status, blood pressure

Astromorph/PF™, Duramorph®, Infumorph®: Patients should be observed in a fully-equipped and staffed environment for at least 24 hours following initiation, and as appropriate for the first several days after catheter implantation.

DepoDur®: Patient should be monitored for at least 48 hours following administration.

Reference RangeTherapeutic: Surgical anesthesia: 65-80 ng/mL (SI: 227-280 nmol/L); Toxic: 200-5000 ng/mL (SI: 700-17,500 nmol/L)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for additive or adverse interactions. Monitor vital signs, respiratory and CNS status, therapeutic effectiveness, and adverse reactions or overdose at regular intervals with long-term use. May cause physical and/or psychological dependence. For inpatients, implement safety measures. Assess knowledge/teach patient appropriate use (if self-administered), adverse reactions to report, and appropriate interventions to reduce side effects. Discontinue slowly after prolonged use.

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Do not crush or chew controlled release tablet or capsule. May cause physical and/or psychological dependence. While using this medication, do not use alcohol (especially if using Avinza®) and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause itching, hypotension, dizziness, drowsiness, impaired coordination, or blurred vision (use caution when driving, climbing stairs, or changing position - rising from sitting or lying to standing, or when engaging in tasks requiring alertness until response to drug is known); loss of appetite, dry mouth, nausea, or vomiting (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help; if unresolved, consult prescriber about use of stool softeners and/or laxatives). Report chest pain, slow or rapid heartbeat, acute dizziness, or persistent headache; changes in mental status; swelling of extremities or unusual weight gain; changes in urinary elimination or pain on urination; acute headache; back or flank pain; muscle spasms; blurred vision; skin rash; or shortness of breath. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. If you are breast-feeding, consult prescriber.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product; [CAN] Canadian brand name

Capsule, extended release:

Avinza®: 30 mg, 60 mg, 90 mg, 120 mg

Kadian®: 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, 200 mg

Infusion [premixed in D_5W]: 1 mg/mL (100 mL, 250 mL)

Injection, extended release liposomal suspension [lumbar epidural injection, preservative free]:

DepoDur®: 10 mg/mL (1 mL, 1.5 mL, 2 mL)

Injection, solution: 2 mg/mL (1 mL); 4 mg/mL (1 mL); 5 mg/mL (1 mL); 8 mg/mL (1 mL); 10 mg/0.7 mL (0.7 mL); 10 mg/mL (1 mL, 10 mL); 15 mg/mL (1 mL, 20 mL); 25 mg/mL (4 mL, 10 mL, 20 mL, 40 mL, 50 mL, 100 mL, 250 mL); 50 mg/mL (20 mL, 40 mL) [some preparations contain sodium metabisulfite]

Injection, solution [epidural, intrathecal, or I.V. infusion; preservative free]:

Astramorph/PF™: 0.5 mg/mL (2 mL, 10 mL); 1 mg/mL (2 mL, 10 mL)

Duramorph®: 0.5 mg/mL (10 mL); 1 mg/mL (10 mL)

Injection, solution [epidural or intrathecal infusion via microinfusion device; preservative free]:

Infumorph®: 10 mg/mL (20 mL); 25 mg/mL (20 mL)

Injection, solution [I.V. infusion via PCA pump]: 0.5 mg/mL (30 mL); 1 mg/mL (30 mL, 50 mL); 2 mg/mL (30 mL); 5 mg/mL (30 mL, 50 mL)

Injection, solution [preservative free]: 0.5 mg/mL (10 mL); 1 mg/mL (10 mL); 25 mg/mL (4 mL, 10 mL, 20 mL)

Solution, oral: 10 mg/5 mL (5 mL, 100 mL, 500 mL); 20 mg/5 mL (100 mL, 500 mL); 20 mg/mL (30 mL, 120 mL, 240 mL)

Doloral [CAN]: 1 mg/mL (10 mL, 250 mL, 500 mL); 5 mg/mL (10 mL, 250 mL, 500 mL) [not available in U.S.]

Solution, oral [concentrate]: 5 mg/0.25 mL (0.25 mL) [DSC]; 10 mg/0.5 mL (0.5 mL) [DSC]; 20 mg/mL (1 mL [DSC], 15 ml, 30 mL, 120 mL, 240 mL)

Roxanol™: 20 mg/mL (30 mL, 120 mL); 100 mg/5 mL (240 mL)

Suppository, rectal: 5 mg (12s), 10 mg (12s), 20 mg (12s), 30 mg (12s)

Tablet: 10 mg [DSC], 15 mg, 30 mg

Tablet, controlled release:

MS Contin®: 15 mg, 30 mg, 60 mg, 100 mg, 200 mg

Tablet, extended release: 15 mg, 30 mg, 60 mg, 100 mg, 200 mg

Tablet, sustained release:

Oramorph SR®: 15 mg, 30 mg, 60 mg, 100 mg

Generic AvailableYes: Excludes capsule, controlled release tablet, sustained release tablet, extended release liposomal suspension for injection

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (AVINza)

30 mg (20): $70.32

60 mg (20): $140.66

90 mg (20): $224.35

120 mg (20): $226.66

Capsule, 24-hour (Kadian)

10 mg (20): $69.99

20 mg (20): $80.11

30 mg (20): $80.87

50 mg (20): $129.71

60 mg (20): $152.59

100 mg (20): $235.98

Solution (Morphine Sulfate)

10 mg/5 mL (100): $21.99

20 mg/5 mL (100): $21.99

Solution (Roxanol)

20 mg/mL (20): $29.79

20 mg/mL (30): $17.99

20 mg/mL (30): $22.99

Suppository (RMS)

5 mg (12): $18.99

10 mg (12): $21.99

20 mg (12): $25.99

30 mg (12): $33.99

Tablet, 12-hour (Morphine Sulfate CR)

15 mg (30): $27.99

30 mg (30): $48.99

60 mg (20): $59.99

100 mg (20): $86.66

200 mg (100): $896.53

Tablet, 12-hour (MS Contin)

15 mg (20): $37.22

30 mg (20): $57.02

60 mg (20): $99.79

100 mg (20): $155.23

200 mg (20): $285.11

Tablet, 12-hour (Oramorph SR)

15 mg (30): $24.99

Tablets (Morphine Sulfate)

15 mg (20): $12.99

30 mg (20): $12.99

Mechanism of ActionBinds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression

Pharmacodynamics/Kinetics

Onset of action (patient dependent; dosing must be individualized): Oral (immediate release): ~30 minutes; I.V.: 5-10 minutes

Duration (patient dependent; dosing must be individualized): Pain relief:

Immediate release formulations: 4 hours

Extended release capsule and tablet: 8-24 hours (formulation dependent)

Extended release epidural injection (DepoDur®): >48 hours

Absorption: Variable

Distribution: V_d: 3-4 L/kg; binds to opioid receptors in the CNS and periphery (eg, GI tract)

Protein binding: 30% to 35%

Metabolism: Hepatic via conjugation with glucuronic acid primarily to morphine-6-glucoronide (active analgesic) morphine-3-glucuronide (inactive as analgesic); minor metabolites include morphine-3-6-diglucuronide; other minor metabolites include normorphine (active) and morphine 3-ethereal sulfate

Bioavailability: Oral: 17% to 33% (first-pass effect limits oral bioavailability; oral:parenteral effectiveness reportedly varies from 1:6 in opioid naive patients to 1:3 with chronic use)

Half-life elimination: Adults: 2-4 hours (immediate release forms)

Time to peak, plasma: Avinza®: 30 minutes (maintained for 24 hours); Kadian®: ~10 hours; Oramorph® SR: ~4 hours

Excretion: Urine (primarily as morphine-3-glucuronide, ~2% to 12% excreted unchanged); feces (~7% to 10%). It has been suggested that accumulation of morphine-6-glucuronide might cause toxicity with renal insufficiency. All of the metabolites (ie, morphine-3-glucuronide, morphine-6-glucuronide, and normorphine) have been suggested as possible causes of neurotoxicity (eg, myoclonus).

Related Information

- Narcotic / Opioid Analgesics

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and dysphagia. Anticholinergic side effects can cause a reduction of saliva production or secretion, contributing to discomfort and dental disease (ie, caries, oral candidiasis, and periodontal disease).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause dysphoric reactions, toxic psychosis, dizziness, euphoria, anxiety, restlessness, confusion, and depression; may rarely cause insomnia

Mental Health: Effects on Psychiatric TreatmentMay cause severe hypotension in patients receiving phenothiazines; monitor blood pressure. The depressant effects of morphine are potentiated by alcohol and psychotropic medications. Use of typical antipsychotics with neuraxial morphine may increase the risk of respiratory depression.

Cardiovascular ConsiderationsMorphine may be used for pain relief after myocardial infarction. It is important that the risk for respiratory depressant effects of morphine be considered. Morphine may cause constipation which may be problematic in patients with unstable angina, and patients after myocardial infarction. The hemodynamic responses to valsalva-like maneuvers due to straining may have adverse cardiovascular consequences in patients with critical coronary artery disease.

In the treatment of unstable angina/non-ST-segment elevation MI, morphine sulfate is recommended when symptoms are not relieved with nitroglycerin or when acute pulmonary edema and/or agitation are present, in the absence of contraindications. It should not be assumed that reperfusion has occurred if patient experiences resolution of chest discomfort after administration of any analgesic, including morphine.

Of concern are the results from the recent CRUSADE Quality Improvement Initiative (Meine TJ, 2005). In a nonrandomized, retrospective, observational registry that enrolls patients with non-ST segment elevation acute coronary syndrome (NSTE ACS) across the U.S., intravenous morphine was reviewed versus not and between patients treated with morphine versus intravenous nitroglycerin. A total of over 17,000 patients received morphine within 24 hours of presentation. Patients treated with morphine had a higher adjusted risk of death (CI 1.33-1.64) than patients not treated with morphine. Relative to those receiving nitroglycerin, patients treated with morphine also had a higher adjusted likelihood of death. This analysis raises questions about the safety of morphine administration in this group of patients. A well designed trial may be required to further evaluate this finding.

Anesthesia and Critical Care Concerns/Other ConsiderationsWhen developing a therapeutic plan for pain control, scheduled, intermittent opioid dosing or continuous infusion is preferred over the “as needed” regimen. The 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) recommend fentanyl in patients who need immediate pain relief because of its rapid onset of action; fentanyl or hydromorphone is preferred in patients who are hypotensive or have renal dysfunction. Morphine or hydromorphone is recommended for intermittent, scheduled therapy. Both have a longer duration of action requiring less frequent administration. If the patient has required high-dose analgesia or has used for a prolonged period (~7 days), taper dose to prevent withdrawal; monitor for signs and symptoms of withdrawal. Use only preservative-free injections for epidural or intrathecal administration; less adverse effects are associated with epidural compared to intrathecal route of administration.

Index TermsMS (error-prone abbreviation and should not be used) ; MSO_4 (error-prone abbreviation and should not be used)

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International Brand NamesAlgedol (UY); Anafil (MX); Anamorph (AU); Contalgin (DK); Continue DR (KP); Dimorf SP (PY); Dolcontin (FI, SE); Dolcontin Depottab (NO); Doltard (PL); Graten (MX); Kapanol (AU, PL); Kapanol LP (FR); La Morph (NZ); Longphine SR (KP); M-Eslon (CN, EC, PE, PL); M-Long (DE); M.Elson (HK); M.I.R. (IL); Meslon (CO); Morcontin Continus (IN); Morficontin (GR); Morin (PH); Morphanton (DE); Morphgesic SR (GB); Morphine Mixtures (AU); Morphini sulfas (PL); Moscontin (FR); MS Contin (AU, BE, CL, IT, VE); MS Mono (AU); MS-Contin (KP); MSI (DE); MSP (IL); MST 10 Mundipharma (DE); MST 100 Mundipharma (DE); MST 200 Mundipharma (DE); MST 30 Mundipharma (DE); MST 60 Mundipharma (DE); MST

Continus (AE, AR, BB, BF, BG, BH, BJ, BM, BR, BS, BZ, CI, CY, CZ, EE, EG, ET, GB, GH, GM, GN, GY, HN, ID, IE, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PH, PK, PL, PR, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); MST Continus Retard (CH); Mundidol Retard (AT); Oramorph (ES, FR, GB, IE, SE); RA-Morph (NZ); Relimal (PH); S-Morphine (KP); Sevredol (AU, CH, PL); Skenan (PL); Slovalgin (PL); Statex (SG); Vendal (UY); Vendal retard (PL)

Morrhuate Sodium

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(MOR yoo ate SOW dee um)
U.S. Brand NamesScleromate®
Pharmacologic CategorySclerosing Agent
Use: Labeled IndicationsTreatment of small, uncomplicated varicose veins of the lower extremities
Dosing: Adults**Varicose veins:** I.V.: 50-250 mg, repeated at 5- to 7-day intervals (50-100 mg for small veins, 150-250 mg for large veins)
Dosing: ElderlyRefer to adult dosing.
Administration: I.V.Avoid extravasation. Use only clear solutions, solution should become clear when warmed.
StorageRefrigerate
ContraindicationsHypersensitivity to morrhuate sodium or any component of the formulation; arterial disease, thrombophlebitis
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis: Anaphylactoid and allergic reactions have occurred.
- Extravasation: Sloughing and necrosis of tissue may occur following extravasation.

Other warnings/precautions:

- Experienced physician: This drug should only be administered by a physician familiar with proper injection techniques.
- Test dose: A test dose of 0.25-5 mL of a 5% injection should be given 24 hours before full-dose treatment.

Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined.

Cardiovascular: Thrombosis, valvular incompetency, vascular collapse

Central nervous system: Dizziness, drowsiness, headache

Dermatologic: Urticaria

Gastrointestinal: Nausea, vomiting

Local: Burning at the site of injection, severe extravasation effects

Neuromuscular & skeletal: Weakness

Respiratory: Asthma

Miscellaneous: Anaphylaxis, hypersensitivity reactions

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 50 mg/mL (30 mL)

Generic AvailableYes
Mechanism of ActionBoth varicose veins and esophageal varices are treated by the thrombotic action of morrhuate sodium. By causing inflammation of the vein's intima, a thrombus is formed. Occlusion secondary to the fibrous tissue and the thrombus results in the obliteration of the vein.
Pharmacodynamics/Kinetics

Onset of action: ~5 minutes

Absorption: Most stays at site of injection

Distribution: Esophageal varices treatment: ~20% of dose to lungs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness
Mental Health: Effects on Psychiatric TreatmentNone reported

Mouthwash

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(MOUTH wosh)
Pharmacologic CategoryAntimicrobial Mouth Rinse; Antiplaque Agent; Mouthwash
Use: DentalAid in prevention and reduction of plaque and gingivitis; halitosis
Dosing: Adults **Plaque/gingivitis prevention:** Oral: Rinse full strength for 30 seconds with 20 mL ($^2/_3$ fluid ounce or 4 teaspoonfuls) morning and night
Dosing: ElderlyRefer to adult dosing.
ContraindicationsHypersensitivity to any component of the formulation
Adverse ReactionsNo data reported
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Rinse: 250 mL, 500 mL, 1000 mL

Dental Health Professional ConsiderationsActive ingredients:

Listerine® Antiseptic: Thymol 0.064%, eucalyptus 0.092%, methyl salicylate 0.060%, menthol 0.042%, alcohol 26.9%, water, benzoic acid, poloxamer 407, sodium benzoate, caramel

Fresh Burst Listerine® Antiseptic: Thymol 0.064%, eucalyptus 0.092%, methyl salicylate 0.060%, menthol 0.042%, alcohol 26.9%, water, benzoic acid, poloxamer 407, sodium benzoate, flavoring, sodium, saccharin, sodium citrate, citric acid, D&C yellow #10, FD&C green #3

Cool Mint Listerine® Antiseptic: Thymol 0.064%, eucalyptus 0.092%, methyl salicylate 0.060%, menthol 0.042%, alcohol 26.9%, water, benzoic acid, poloxamer 407, sodium benzoate, flavoring, sodium, saccharin, sodium citrate, citric acid, FD&C green #3

The following information is endorsed on the label of the Listerine® products by the Council on Scientific Affairs, American Dental Association: "Listerine® Antiseptic has been shown to help prevent and reduce supragingival plaque accumulation and gingivitis when used in a conscientiously applied program of oral hygiene and regular professional care. Its effect on periodontitis has not been determined."

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsAntiseptic Mouthwash
International Brand NamesCorsodyl Mouthwash (PL)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

> Avelox® may be confused with Avonex®

International issues:

> Vigamox™ may be confused with Fisamox® which is a brand name for amoxicillin in Australia

Pronunciation(moxs i FLOKS a sin)

U.S. Brand NamesAvelox®; Avelox® I.V.; Vigamox™

Canadian Brand NamesAvelox®; Avelox® I.V.; Vigamox™

Pharmacologic CategoryAntibiotic, Ophthalmic; Antibiotic, Quinolone; Respiratory Fluoroquinolone

Use: Labeled IndicationsTreatment of mild-to-moderate community-acquired pneumonia, including multidrug-resistant *Streptococcus pneumoniae* (MDRSP); acute bacterial exacerbation of chronic bronchitis; acute bacterial sinusitis; complicated and uncomplicated skin and skin structure infections; complicated intra-abdominal infections; bacterial conjunctivitis (ophthalmic formulation)

Use: Unlabeled/Investigational*Legionella*

Dosing: Adults

Acute bacterial sinusitis: Oral, I.V.: 400 mg every 24 hours for 10 days

Bacterial conjunctivitis: Ophthalmic: Instill 1 drop into affected eye(s) 3 times/day for 7 days

Chronic bronchitis, acute bacterial exacerbation: Oral, I.V.: 400 mg every 24 hours for 5 days

Intra-abdominal infections, complicated: Oral, I.V.: 400 mg every 24 hours for 5-14 days (initiate with I.V.)

Pneumonia, community-acquired (including MDRSP): Oral, I.V.: 400 mg every 24 hours for 7-14 days

Skin and skin structure infections: Oral, I.V.:

> *Complicated:* 400 mg every 24 hours for 7-21 days
>
> *Uncomplicated:* 400 mg every 24 hours for 7 days

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricBacterial conjunctivitis: Ophthalmic: Children ≥1 year: Refer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is necessary, including patients on hemodialysis, CRRT, or CAPD.

Dosing: Hepatic ImpairmentNo dosage adjustment is required in mild, moderate, or severe hepatic insufficiency (Child-Pugh class A, B, or C); however, use with caution in this patient population secondary to the risk of QT prolongation.

Administration: I.V.Infuse over 60 minutes; do not infuse by rapid or bolus intravenous infusion

Dietary ConsiderationsMay be taken with or without food. Take 4 hours before or 8 hours after multiple vitamins, antacids, or other products containing magnesium, aluminum, iron, or zinc.

Avelox® I.V. infusion (premixed in sodium chloride 0.8%) contains sodium 34.2 mEq (~787mg)/250 mL.

StorageStore at controlled room temperature of 25°C (77°F). Do not refrigerate infusion solution.

CompatibilityStable in NS, D$_5$W, D$_{10}$W, SWFI, LR; do not add other medications to intravenous solution.

RestrictionsAn FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to moxifloxacin, other quinolone antibiotics, or any component of the formulation

Allergy Considerations

- Fluoroquinolone Allergy

Warnings/Precautions

Boxed Warnings:

> • Tendon inflammation/rupture: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Altered cardiac conduction: Fluoroquinolones may prolong QT_c interval; avoid use in patients with a history of QT_c prolongation, uncorrected hypokalemia, hypomagnesemia, or concurrent administration of other medications known to prolong the QT interval (including Class Ia and Class III antiarrhythmics, cisapride, erythromycin, antipsychotics, and tricyclic antidepressants).

- CNS stimulation: Tremor, restlessness, confusion, and very rarely hallucinations or seizures may occur; use with caution in patients with known or suspected CNS disorder. Discontinue in patients who experience significant CNS adverse effects (eg, dizziness, hallucinations, suicidal ideations or actions).

- Glucose regulation: Fluoroquinolones have been associated with the development of serious, and sometimes fatal, hypoglycemia. These events have occurred most often in elderly patients with diabetes, but have also been reported in patients without a prior history of diabetes. Prompt identification and treatment of hypoglycemia is essential. Individual quinolones may differ in their potential to cause this effect. It was most evident with gatifloxacin (no longer marketed as s systemic formulation). Hyperglycemia has also been associated with the use of fluoroquinolones. Patients should be monitored closely for signs/symptoms of disordered glucose regulation.

- Hypersensitivity reactions: Severe hypersensitivity reactions, including anaphylaxis, have occurred with quinolone therapy. The spectrum of these reactions can vary widely; reactions may present as typical allergic symptoms (eg, itching, urticaria, rash, edema) after a single dose, or may manifest as severe idiosyncratic dermatologic (eg, Stevens-Johnson, toxic epidermal necrolysis), vascular (eg, vasculitis), pulmonary (eg, pneumonitis), renal (eg, nephritis), hepatic (eg, hepatic failure or necrosis), and/or hematologic (eg, anemia, cytopenias) events, usually after multiple doses. Prompt discontinuation of drug should occur if skin rash or other symptoms arise.

- Peripheral neuropathy: The use of quinolones has been linked to peripheral neuropathy (rare); discontinue if symptoms of sensory or sensorimotor neuropathy occur.

- Photosensitivity: Avoid excessive sunlight and take precautions to limit exposure (eg, loose fitting clothing, sunscreen); may rarely cause moderate-to-severe phototoxicity reactions. Discontinue use if phototoxicity occurs.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

- Tendon inflammation/rupture: **[U.S. Boxed Warning]: There have been reports of tendon inflammation and/or rupture with quinolone antibiotics; risk may be increased with concurrent corticosteroids, organ transplant recipients, and in patients >60 years of age.** Rupture of the Achilles tendon sometimes requiring surgical repair has been reported most frequently; but other tendon sites (eg, rotator cuff, biceps) have also been reported. Strenuous physical activity may be an independent risk factor for tendonitis. Discontinue at first sign of tendon inflammation or pain. Tendon rupture may occur even after discontinuation of therapy.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with significant bradycardia or acute myocardial ischemia.

- Diabetes: Use with caution in patients with diabetes mellitus; glucose regulation may be altered.

- Hepatic impairment: Use with caution in patients with mild, moderate, or severe hepatic impairment or liver cirrhosis; may increase the risk of QT prolongation.

- Myasthenia gravis: Some quinolones may exacerbate myasthenia gravis, use with caution (rare, potentially life-threatening weakness of respiratory muscles may occur).

- Renal impairment: Use with caution in patients with renal failure; may increase risk of tendon rupture.

- Rheumatoid arthritis: Use with caution in patients with rheumatoid arthritis; may increase risk of tendon rupture.

- Seizures: Use with caution in individuals at risk of seizures (CNS disorders or concurrent therapy with medications which may lower seizure threshold). Potential for seizures, although very rare, may be increased with concomitant NSAID therapy.

Special populations:

- Elderly: Adverse effects (eg, tendon rupture, QT changes) may be increased in the elderly.

- G6PD deficiency: Hemolytic reactions may (rarely) occur with quinolone use in patients with latent or actual G6PD deficiency.

- Pediatrics: Safety and efficacy of systemically-administered moxifloxacin (oral, intravenous) have not been established in children.

Dosage form specific issues:

- Ophthalmic solution: Eye drops should not be injected subconjunctivally or introduced directly into the anterior chamber of the eye. Contact lenses should not be worn during therapy.

Geriatric ConsiderationsSee Warnings/Precautions regarding tendon rupture in patients >60 years of age. No dosage adjustments are required based on age. Assess patient's ability to self-administer eye drops.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in some animal studies; therefore, the manufacturer classifies moxifloxacin as pregnancy category C. Quinolone exposure during human pregnancy has been reported with other agents (see Ciprofloxacin, Ofloxacin, and Norfloxacin monographs). To date, no specific teratogenic effect or increased pregnancy risk has been identified; however, because of concerns of cartilage damage in immature animals exposed to quinolones and the limited moxifloxacin specific data, moxifloxacin should only be used during pregnancy if a safer option is not available.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if moxifloxacin is excreted into breast milk. Breast-feeding is not recommended by the manufacturer. Although there is no information on the use of moxifloxacin during breast-feeding, other quinolones are considered compatible. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Moxifloxacin in Pregnancy & Lactation

Adverse Reactions

Systemic:

2% to 10%:

Central nervous system: Dizziness (2%)

Endocrine & metabolic: Serum chloride increased (≥2%), serum ionized calcium increased (≥2%), serum glucose decreased (≥2%)

Gastrointestinal: Nausea (6%), diarrhea (5%), amylase decreased (≥2%)

Hematologic: Decreased serum levels of the following (≥2%): Basophils, eosinophils, hemoglobin, RBC, neutrophils; increased serum levels of the following (≥2%): MCH, neutrophils, WBC

Hepatic: Bilirubin decreased/increased (≥2%)

Renal: Serum albumin increased (≥2%)

Respiratory: PO_2 decreased (≥2%)

0.1% to <2%:

Cardiovascular: Cardiac arrhythmias, palpitation, QT_c prolongation, tachycardia, vasodilation

Central nervous system: Anxiety, headache, insomnia, malaise, nervousness, pain, somnolence, vertigo

Dermatologic: Pruritus, rash (maculopapular, purpuric, pustular), urticaria

Gastrointestinal: Abdominal pain, amylase increased, anorexia, constipation, dyspepsia, flatulence, glossitis, lactic dehydrogenase increased, stomatitis, taste perversion, vomiting, xerostomia

Genitourinary: Vaginal moniliasis, vaginitis

Hematologic: Eosinophilia, leukopenia, prothrombin time prolonged, increased INR, thrombocythemia

Hepatic: GGTP increased, liver function test abnormal

Local: Injection site reaction

Neuromuscular & skeletal: Arthralgia, myalgia, tremor, weakness

Respiratory: Pharyngitis, pneumonia, rhinitis, sinusitis

Miscellaneous: Allergic reaction, infection, diaphoresis, oral moniliasis

<0.1%, postmarketing, and/or case reports: Abnormal dreams, abnormal gait, agitation, amblyopia, amnesia, anaphylactic reaction, anaphylactic shock, anemia, angioedema, aphasia, arthritis, asthma, atrial fibrillation, back pain, *C. difficile*-positive diarrhea, chest pain, cholestasis, confusion, depersonalization, depression, dysphagia, dyspnea, ECG abnormalities, emotional lability, face edema, gastritis, hallucinations, hepatic failure, hepatitis, hyperglycemia, hyperlipidemia, hyper-/hypotension, hypertonia, hyperuricemia, hypoesthesia, incoordination, INR decreased, jaundice (cholestatic), laryngeal edema, leg pain, nightmares, paresthesia, parosmia, pelvic pain, peripheral edema, peripheral neuropathy, photosensitivity/toxicity, prothrombin time decreased, pseudomembranous colitis, psychotic reaction, renal dysfunction, renal failure, seizure, sleep disorder, speech disorder, Stevens-Johnson syndrome, supraventricular tachycardia, syncope, taste loss, tendonitis, tendon rupture, thinking abnormal, thrombocytopenia, thromboplastin decreased, tinnitus, tongue discoloration, toxic epidermal necrolysis, ventricular tachyarrhythmias (including torsade de pointes and cardiac arrest [usually in patients with concurrent, severe proarrhythmic conditions]), vision abnormalities

Additional reactions with **ophthalmic** preparation: 1% to 6%: Conjunctivitis, dry eye, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, subconjunctival hemorrhage, tearing, visual acuity decreased

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. **Exceptions:** Sodium Bicarbonate. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Quinolone Antibiotics may enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Didanosine: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents (excludes enteric coated formulation of didanosine). *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Insulin: May enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics.

Risk C: Monitor therapy

Iron Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Mycophenolate: Quinolone Antibiotics may decrease the serum concentration of Mycophenolate. Specifically, quinolones may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nonsteroidal Anti-Inflammatory Agents: May enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Probenecid: May increase the serum concentration of Quinolone Antibiotics. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Quinapril: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sevelamer: May decrease the absorption of Quinolone Antibiotics. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sulfonylureas: Quinolone Antibiotics may enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Quinolone Antibiotics may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zinc Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: Absorption is not affected by administration with a high-fat meal or yogurt.

Test InteractionsSome quinolones may produce a false-positive urine screening result for opiates using commercially-available immunoassay kits. This has been demonstrated most consistently for levofloxacin and ofloxacin, but other quinolones have shown cross-reactivity in certain assay kits. Confirmation of positive opiate screens by more specific methods should be considered.

Monitoring ParametersWBC, signs of infection

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient’s allergy history before initiating therapy. Use caution with known or suspected CNS disorders; myasthenia gravis; current or potential for QT prolongation; renal impairment; or diabetes. Assess potential for interactions with other pharmacological or herbal agents patient may be taking. See Administration for infusion specifics. Patient should be monitored closely; if an allergic reaction occurs (itching, urticaria, dyspnea or facial edema, loss of consciousness, tingling, cardiovascular collapse), drug should be discontinued immediately and prescriber notified. Evaluate results of laboratory tests, therapeutic effectiveness (resolution of infection), and adverse reactions (eg, hypersensitivity reactions [severe reactions, including anaphylaxis, have occurred with quinolone therapy], opportunistic infection, tendon rupture, persistent diarrhea [*C. difficile*-associated colitis can occur up to 2 months post treatment]) regularly during prolonged therapy. Teach patient proper use (according to formulation), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsWBC

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. If administered by infusion: Report immediately any redness, swelling, or pain at infusion site; any swelling of mouth, lips, tongue, or throat; chest pain or tightness; respiratory difficulty; back pain; itching; skin rash; tingling; tendon pain; dizziness; abnormal thinking; or anxiety. May cause dizziness, lightheadedness, or confusion (use caution to avoid falls or injury); nausea or vomiting (request antiemetic from prescriber). Report any tendon pain, chest pain, palpitations, or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Oral: Take exactly as directed with or without food. Do not take antacids 4 hours before or 8 hours after taking this medication. Do not miss a dose (take a missed dose as soon as possible, unless it is almost time for your next dose). Take entire prescription even if feeling better. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Consult prescriber before having any vaccinations. May cause nausea, vomiting, or taste perversion (small, frequent meals, good mouth care, chewing gum, or sucking hard candy may help); headache; dizziness; insomnia; or anxiety (use caution when driving or engaging in tasks requiring alertness until response to drug is known). If inflammation or tendon pain occurs or you experience signs of an allergic reaction (eg, itching, urticaria, respiratory difficulty, facial edema or difficulty swallowing, loss of consciousness, tingling, chest pain, palpitations), discontinue use and contact prescriber immediately. Report persistent GI disturbances; CNS changes (eg, excessive sleepiness, agitation, tremors); skin rash; vision changes; respiratory difficulty; signs of opportunistic infection (eg, sore throat, chills, fever, burning, itching on urination, vaginal discharge, white plaques in mouth); persistent diarrhea (especially if it lasts after completing prescription); or worsening of condition.

Ophthalmic: Wash hands before instilling solution. Sit or lie down to instill. Open eye, look at ceiling, and instill prescribed amount of solution as directed. Do not touch tip of applicator or let tip of applicator touch eye. Do not wear contact lenses during therapy. Temporary stinging, blurred vision, or dry eyes may occur. Report persistent pain, burning, excessive tearing, decreased visual acuity, swelling, itching, or worsening of condition.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed in sodium chloride 0.8%]:

Avelox® I.V.: 400 mg (250 mL) [contains sodium ~787mg (34.2 mEq)/250 mL]

Solution, ophthalmic:

Vigamox™: 0.5% (3 mL)

Tablet:

Avelox®: 400 mg

Avelox® ABC Pack [unit-dose pack]: 400 mg (5s)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Vigamox)

0.5% (3): $78.53

Tablets (Avelox)

400 mg (30): $372.14

Mechanism of ActionMoxifloxacin is a DNA gyrase inhibitor, and also inhibits topoisomerase IV. DNA gyrase (topoisomerase II) is an essential bacterial enzyme that maintains the superhelical structure of DNA. DNA gyrase is required for DNA replication and transcription, DNA repair, recombination, and transposition; inhibition is bactericidal.

Pharmacodynamics/Kinetics

Absorption: Well absorbed; not affected by high-fat meal or yogurt

Distribution: V_d: 1.7 to 2.7 L/kg; tissue concentrations often exceed plasma concentrations in respiratory tissues, alveolar macrophages, abdominal tissues/fluids, and sinus tissues

Protein binding: ~30% to 50%

Metabolism: Hepatic (~52% of dose) via glucuronide (~14%) and sulfate (~38%) conjugation

Bioavailability: ~90%

Half-life elimination: Single dose: Oral: 12-16 hours; I.V.: 8-15 hours

Excretion: Urine (as unchanged drug [20%] and glucuronide conjugates); feces (as unchanged drug [25%] and sulfate conjugates)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dry mouth, glossitis, stomatitis, and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsMoxifloxacin is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay cause dizziness, insomnia; may rarely produce abnormal thinking, agitation, anorexia, anxiety, asthenia, ataxia, confusion, depersonalization, depression, euphoria, hallucination, hostility, nervousness, panic attacks, paranoia, psychosis, sedation, somnolence, or stress

Mental Health: Effects on Psychiatric TreatmentContraindicated with ziprasidone; may have potential to prolong QT interval; should avoid in patients with uncorrected hypokalemia, or concurrent administration of other medications known to prolong the QT interval (antipsychotics and tricyclic antidepressants)

Cardiovascular ConsiderationsMoxifloxacin causes a dose-dependent QT prolongation. Coadministration of moxifloxacin with other drugs that also prolong the QT interval or induce bradycardia (eg, beta-blockers, amiodarone) should be avoided. Careful consideration should be given in the use of moxifloxacin in patients with cardiovascular disease, particularly in those with conduction abnormalities.

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Moxifloxacin causes a dose-dependent QT prolongation. Coadministration of moxifloxacin with other drugs that also prolong the QT interval or induce bradycardia (eg, beta-blockers, amiodarone) should be avoided. Careful consideration should be given in the use of moxifloxacin in patients with cardiovascular disease, in those with conduction abnormalities.

Index TermsMoxifloxacin Hydrochloride

References

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Frothingham R, “Glucose Homeostasis Abnormalities Associated With Use of Gatifloxacin,” *Clin Infect Dis*, 2005, 41(9):1269-76.[PubMed 16206101]

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Trotman RL, Williamson JC, Shoemaker DM, et al, “Antibiotic Dosing in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy,” *Clin Infect Dis*, 2005, 41(8):1159-66.[PubMed 16163635]

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Zacher JL and Givone DM, “False-Positive Urine Opiate Screening Associated with Fluoroquinolone Use,” *Ann Pharmacother*, 2004, 38:1525-28.[PubMed 15252190]

International Brand NamesAvalox (AE, BH, BR, CH, CY, DE, EG, IL, IQ, IR, IT, JO, KW, LB, LY, OM, QA, SA, SY, YE); Avelon (ZA); Avelox (AR, AU, BB, BE, BF, BG, BJ, BM, BS, BZ, CI, CL, CN, CO, CZ, DK, DO, EC, EE, ET, FI, GB, GH, GM, GN, GY, HK, HN, ID, IE, JM, KE, KP, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, PE, PH, PK, PL, PY, SC, SD, SE, SG, SL, SN, SR, TH, TN, TT, TZ, UG, UY, VE, ZA, ZM, ZW); Bacterol (CO); Izilox (FR); Megaxin (IL); Moxif (IN); Proflox (ES, PT); Vigamox (AR, CH, CL, CR, GT, HK, HN, IL, KP, MY, NI, PA, PE, PH, SG, SV, TH, TW, UY); Vigamoxi (MX)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Multiple Myeloma

Regimen UseMultiple myeloma

Regimen

Melphalan: Oral: 8-10 mg/m^2/day days 1 to 4

[total dose/cycle = 32-40 mg/m^2]

Prednisone: Oral: 40-60 mg/m^2/day days 1 to 4

[total dose/cycle = 160-240 mg/m^2]

Repeat cycle every 28-42 days

References

Belch A, Shelley W, Bergsagel D, et al, âA Randomized Trial of Maintenance Versus No Maintenance Melphalan and Prednisone in Responding Multiple Myeloma Patients,â *Br J Cancer*, 1988, 57(1):94-9.[PubMed 3279997]

MP (Prostate Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer

Regimen UseProstate cancer

Index TermsMitoxantrone + Prednisone

Regimen

Mitoxantrone: I.V.: 12 mg/m^2 day 1

[total dose/cycle = 12 mg/m^2]

Prednisone: Oral: 5 mg twice daily

[total dose/cycle = 210 mg]

Repeat cycle every 21 days

References

Moore MJ, Osoba D, Murphy K, et al, âUse of Palliative Endpoints to Evaluate the Effects of Mitoxantrone and Low-Dose Prednisone in Patients With Hormonally Resistant Prostate Cancer,â *J Clin Oncol*, 1994, 12(4):689-94.[PubMed 7512127]

MTX/6-MP/VP (Maintenance)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Leukemia, Acute Lymphocytic]

Regimen UseLeukemia, acute lymphocytic

Regimen

Methotrexate: Oral: 20 mg/m^2 weekly

[total dose/cycle = 80 mg/m^2]

Mercaptopurine: Oral: 75 mg/m^2/day

[total dose/cycle = 2250 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2 day 1

[total dose/cycle = 1.5 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 5

[total dose/cycle = 200 mg/m^2]

Repeat monthly for 2-3 years

References

Bleyer WA, Sather HN, Nickerson HJ, et al, âMonthly Pulses of Vincristine and Prednisone Prevent Bone Marrow and Testicular Relapse in Low-Risk Childhood Acute Lymphoblastic Leukemia: A Report of the CCG-161 Study by the Childrens Cancer Study Group,â *J Clin Oncol*, 1991, 9(6):1012-21.[PubMed 2033414]

MTX-CDDPAdr

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Osteosarcoma]

Regimen UseOsteosarcoma

Regimen

Cisplatin: I.V.: 75 mg/m^2 day 1 of cycles 1-7, then 120 mg/m^2 for cycles 8, 9, and 10

Doxorubicin: I.V.: 25 mg/m^2/day days 1, 2, and 3 of cycles 1 to 7

Methotrexate: I.V.: 12 g/m^2/day days 21 and 28

Leucovorin calcium rescue: I.V.: 20 mg/m^2 every 3 hours (beginning 16 hours after completion of methotrexate) for 8 doses, then orally every 6 hours for 8 doses

References

Meyers PA, Heller G, Healey J, et al, âChemotherapy for Nonmetastatic Osteogenic Sarcoma: The Memorial Sloan-Kettering Experience,â *J Clin Oncol*, 1992, 10(1):5-15.[PubMed 1370176]

Mumps Virus Vaccine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(mumpz VYE rus vak SEEN)
U.S. Brand NamesMumpsvax®
Pharmacologic CategoryVaccine
Use: Labeled IndicationsMumps prophylaxis by promoting active immunity

Note: Trivalent measles-mumps-rubella (MMR) vaccine is the preferred agent for most children and many adults; persons born prior to 1957 are generally considered immune and need not be vaccinated

Dosing: Adults**Immunization:** SubQ: 0.5 mL as a single dose
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren ≥12-15 months: Refer to adult dosing.
Administration: OtherFor SubQ administration in outer aspect of the upper arm using a 25G 5/8" needle.
StorageProduct is shipped at ≤10˚C (50˚F). Prior to reconstitution, vaccine must be stored at ≤2°C to 8˚C (36°F to 46˚F). Following reconstitution, use as soon as possible, but may be stored at 2°C to 8˚C (36°F to 46˚F) for up to 8 hours. Protect from light prior to and after reconstitution.
ReconstitutionReconstitute using entire contents of one vial of provided preservative free diluent.
Contraindications

Hypersensitivity to mumps vaccine or any component of the formulation, including gelatin; febrile respiratory illness or active febrile infection; immunosuppressant therapy; primary or acquired immunodeficiency states; blood dyscrasias, leukemia, lymphoma or other malignant neoplasm affecting bone marrow or lymphatic systems; untreated tuberculosis; pregnancy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use. Use with caution in patients with hypersensitivity to eggs or neomycin; patients with history of anaphylactic reaction may be at increased risk of immediate-type hypersensitivity reaction.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).

- Thrombocytopenia: Use with caution in patients with thrombocytopenia and those who develop thrombocytopenia after first dose; thrombocytopenia may worsen.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination. May be used in asymptomatic children with HIV. Patients with a history of congenital or hereditary immunodeficiency should not receive immunization until immune competence is demonstrated. Patients with leukemia who are in remission and who have not received chemotherapy for at least 3 months may be vaccinated.

- Pediatrics: Safety and efficacy have not been established in children <12 months of age.

Geriatric ConsiderationsMost adults are immune to mumps and vaccination is not necessary for those born prior to 1957; elderly who have lived in isolated communities may have no immunity; for those who fail to demonstrate immunity by testing, vaccination would be desired if exposure is likely (travel to endemic area, etc); the trivalent MMR is preferred, however
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted. Rates of spontaneous abortion may be increased if mumps infection occurs during the first trimester. Although mumps vaccine virus can infect the placenta and fetus, there is not good evidence that it causes congenital malformations. Pregnancy should be avoided for 3 months following vaccination.
Lactation

Excretion in breast milk unknown/use caution

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Frequency not defined.

Cardiovascular: Syncope, vasculitis

Central nervous system: Encephalitis, febrile seizure, fever, Guillain-Barré syndrome, irritability

Dermatologic: Angioneurotic edema, erythema multiforme, purpura, Stevens-Johnson syndrome, urticaria

Endocrine & metabolic: Diabetes mellitus, parotitis

Gastrointestinal: Diarrhea, pancreatitis

Genitourinary: Orchitis

Hematologic: Leukocytosis, thrombocytopenia

Local: Burning/stinging at injection site, wheal and flare at injection site

Ocular: Conjunctivitis, ocular palsies, optic neuritis, papillitis, retrobulbar neuritis

Otic: Nerve deafness, otitis media

Respiratory: Bronchial spasm, cough, rhinitis

Miscellaneous: Anaphylaxis, anaphylactoid reactions, lymphadenopathy

Drug Interactions

Immune Globulins: May diminish the therapeutic effect of Vaccines (Live). *Risk D: Consider therapy modification*

Immunosuppressants: May enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Tuberculin Tests: Vaccines (Live) may diminish the diagnostic effect of Tuberculin Tests. *Risk D: Consider therapy modification*

Test Interactions Temporary suppression of tuberculosis skin test

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Mumpsvax®: ≥20,000 TCID_{50} [contains albumin (human), bovine serum, chicken egg protein, gelatin, sorbitol, and sucrose (1.9 mg/vial)]

Generic Available No

Mechanism of Action Promotes active immunity to mumps virus by inducing specific antibodies.

Related Information

- Immunization Recommendations
- Skin Tests

Pharmacotherapy Pearls Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Acceptable presumptive evidence of immunity includes one of the following:

1. Documentation of adequate vaccination. Adequate vaccination for mumps is defined as 1 dose of a live mumps virus vaccine for preschool children and adults not at high risk; 2 doses of a live mumps virus vaccine for school-aged children and high-risk adults. Healthcare workers, international travelers, and students in institutions of higher learning are considered high-risk adults.

2. Laboratory evidence of immunity to mumps

3. Birth prior to 1957

4. Documentation of physician-diagnosed mumps

During a mumps outbreak, additional doses of a mumps virus vaccine may need to be considered. MMR vaccine is recommended; refer to Measles Mumps Rubella Vaccine (Combined) monograph. Minimum interval between doses is 28 days.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May rarely cause confusion

Mental Health: Effects on Psychiatric Treatment None reported

References

Centers for Disease Control and Prevention (CDC), “Notice to Readers: Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP) for the Control and Elimination of Mumps,” *MMWR Recomm Rep*, 2006, 55(early release):1-2. Available at http://www.cdc.gov/mmwr/pdf/wk/mm55e601.pdf

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 1994, 43(RR-1):23.

Watson JC, Hadler SC, Dykewicz CA, et al, “Measles, Mumps, and Rubella − Vaccine Use and Strategies for Elimination of Measles, Rubella, and Congenital Rubella Syndrome and Control of Mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP),” *MMWR Recomm Rep*, 1998, 47(RR-8):1-57.

Mupirocin

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Bactroban® may be confused with bacitracin, baclofen, Bactrim™

Pronunciation(myoo PEER oh sin)

U.S. Brand NamesBactroban®; Bactroban® Nasal; Centany™ [DSC]

Canadian Brand NamesBactroban®

Pharmacologic CategoryAntibiotic, Topical

Use: Labeled Indications

Intranasal: Eradication of nasal colonization with MRSA in adult patients and healthcare workers

Topical: Treatment of impetigo or secondary infected traumatic skin lesions due to *S. aureus* and *S. pyogenes*

Use: Unlabeled/InvestigationalIntranasal: Surgical prophylaxis to prevent wound infections

Dosing: Adults

Impetigo: Topical: Ointment: Apply to affected area 3 times/day; re-evaluate after 3-5 days if no clinical response

Secondary skin infections: Topical: Cream: Apply to affected area 3 times/day for 10 days; re-evaluate after 3-5 days if no clinical response

Elimination of MRSA colonization: Intranasal: Approximately one-half of the ointment from the single-use tube should be applied into one nostril and the other half into the other nostril twice daily for 5 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Eradication of nasal MRSA: Intranasal: Children ≥12 years: Refer to adult dosing.

Impetigo: Topical: Ointment: Children ≥2 months: Refer to adult dosing.

Secondary skin infections: Topical: Cream: Children ≥3 months: Refer to adult dosing.

Administration: Topical

Intranasal ointment: After application into nostrils, press sides of nose together and gently massage to spread ointment throughout the insides of the nostrils; discard tube after use

Topical cream, ointment: For external use only; area may be covered with gauze if desired

ContraindicationsHypersensitivity to mupirocin or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: If skin irritation occurs, discontinue use.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Pediatrics: Safety and efficacy of the nasal product have not been established in children <12 years of age.

Dosage form specific issues:

- Polyethylene glycol: Potentially toxic amounts of polyethylene glycol contained in some topical products may be absorbed percutaneously in patients with extensive burns or open wounds.

Other warnings/precautions:

- Appropriate use: For external use only; avoid contact with eyes. Not for treatment of pressure sores.

Geriatric ConsiderationsNot for treatment of pressure sores.
Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women; use during pregnancy only if clearly needed.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Central nervous system: Dizziness, headache

Dermatologic: Cellulitis, dermatitis, dry skin, erythema, hives, pruritus, rash

Gastrointestinal: Abdominal pain, diarrhea, nausea, taste perversion, ulcerative stomatitis, xerostomia

Local: Burning, edema, pain, stinging, tenderness

Ocular: Blepharitis

Otic: Ear pain

Respiratory: Cough, pharyngitis, rhinitis, upper respiratory tract congestion

Miscellaneous: Secondary wound infection

Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringAssess for effectiveness of therapy and symptoms of infection. Assess knowledge/teach patient appropriate application and use and adverse symptoms to report.
Patient EducationFor external use only. Wash hands before and after application. Apply thin film over affected areas exactly as directed. Avoid getting in eyes. Report rash, persistent burning, stinging, swelling, itching, or pain. Contact prescriber if no improvement is seen in 3-5 days. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Note: Strength expressed as base

Cream, topical, as calcium:

Bactroban®: 2% (15 g, 30 g) [contains benzyl alcohol]

Ointment, intranasal, as calcium:

Bactroban® Nasal: 2% (1 g) [single-use tube]

Ointment, topical: 2% (0.9 g, 22 g)

Bactroban®: 2% (22 g) [contains polyethylene glycol]

Centany™: 2% (15 g) [DSC]

Generic AvailableYes: Topical ointment
Pricing: U.S. (www.drugstore.com)

Cream (Bactroban)

2% (15): $56.37

2% (30): $83.64

Ointment (Bactroban)

2% (22): $69.99

Ointment (Mupirocin)

2% (22): $34.99

Mechanism of ActionBinds to bacterial isoleucyl transfer-RNA synthetase resulting in the inhibition of protein synthesis
Pharmacodynamics/Kinetics

Absorption: Topical: Penetrates outer layers of skin; systemic absorption minimal through intact skin

Metabolism: Skin: 3% to monic acid (inactive)

Excretion: Urine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and taste perversion.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Mupirocin Calcium; Pseudomonic Acid A

References

Blumer JL, Lemon E, O'Horo J, et al, “Changing Therapy for Skin and Soft Tissue Infections in Children: Have We Come Full Circle?” *Pediatr Infect Dis J*, 1987, 6(1):117-22. [PubMed 3547287]

Britton JW, Fajardo JE, and Krafte-Jacobs B, “Comparison of Mupirocin and Erythromycin in the Treatment of Impetigo,” *J Pediatr*, 1990, 117(5):827-9. [PubMed 2121951]

Goldfarb J, Crenshaw D, O'Horo J, et al, “Randomized Clinical Trial of Topical Mupirocin Versus Oral Erythromycin for Impetigo,” *Antimicrob Agents Chemother*, 1988, 32(12):1780-3. [PubMed 3149884]

Perl TM, Cullen JJ, Wenzel RP, et al, “Intranasal Mupirocin to Prevent Postoperative *Staphylococcus aureus* Infections,” *N Engl J Med*, 2002, 346(24):1871-7.[PubMed 12063371]

International Brand Names Bacidal (TH); Bactifree (PH); Bactocin (PH); Bactoderm (ID); Bactoxil (TH); Bactroban (AE, AR, AT, AU, BB, BD, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CY, CZ, DK, DO, EG, ES, ET, FI, FR, GB, GH, GM, GN, GT, GY, HK, HN, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, OM, PA, PH, PK, PL, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SV, SY, TH, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Bagobiotic (EC); Betrion (HR); Dermasafe (TW); Foskina (PH); Mupiderm (FR); Mupiroban (KP); Mupirox (PE, PL); Muporin (TH); Muprin (MY); Pibaksin (ID); Sinpebac (MX); Spectroderm (PE); Supirocin (SG); Turixin (DE)

Muromonab-CD3

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(myoo roe MOE nab see dee three)

U.S. Brand NamesOrthoclone OKT® 3

Canadian Brand NamesOrthoclone OKT® 3

Pharmacologic CategoryImmunosuppressant Agent

Use: Labeled IndicationsTreatment of acute allograft rejection in renal transplant patients; treatment of acute hepatic, and kidney rejection episodes resistant to conventional treatment

Use: Unlabeled/InvestigationalTreatment of acute pancreas rejection episodes resistant to conventional treatment

Dosing: Adults**Treatment of acute allograft rejection or acute graft-versus-host disease:** I.V. (refer to individual protocols): 5 mg/day once daily for 10-14 days

Note: Suggested prevention/treatment of muromonab-CD3 first-dose effects (grouped by adverse reaction):

Severe pulmonary edema:

- Effective prevention or palliation: Clear chest x-ray within 24 hours preinjection; weight restriction to ≤3% gain over 7days preinjection
- Supportive treatment: Prompt intubation and oxygenation; 24 hours close observation

Fever, chills:

- Effective prevention or palliation: 15 mg/kg methylprednisolone sodium succinate 1 hour preinjection; fever reduction to <37.8°C (100°F) 1 hour preinjection; acetaminophen (1 g orally) and diphenhydramine(50 mg orally) 1 hour preinjection
- Supportive treatment: Cooling blanket; acetaminophen as needed

Respiratory effects:

- Effective prevention or palliation: 100 mg hydrocortisone sodium succinate 30 minutes postinjection
- Supportive treatment: Additional 100 mg hydrocortisone sodium succinate as needed for wheezing; if respiratory distress, give epinephrine 1:1000 (0.3 mL SubQ)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols.

Treatment of acute allograft rejection or acute graft-versus-host disease: I.V.

Children <30 kg: 2.5 mg/day once daily for 7-14 days

Children >30 kg: 5 mg/day once daily for 7-14 days

or

Children <12 years: 0.1 mg/kg/day once daily for 10-14 days

Children ≥12 years: Refer to adult dosing.

Note: Suggested prevention/treatment of muromonab-CD3 first-dose effects (grouped by adverse reaction): Refer to adult dosing.

Dosing: Renal ImpairmentRemoval by dialysis: Molecular size of OKT3 is 150,000 daltons. Not dialyzed by most standard dialyzers; however, may be dialyzed by high flux dialysis. OKT3 will be removed by plasmapheresis. Administer following dialysis treatments.

Administration: I.V.**Not for I.M. administration.** Give I.V. push over <1 minute at a final concentration of 1 mg/mL. Methylprednisolone sodium succinate 1 mg/kg I.V. given prior to first muromonab-CD3 administration, and I.V. hydrocortisone sodium succinate 50-100 mg, given 30 minutes after administration are strongly recommended to decrease the incidence of reactions to the first dose.

Administration: I.V. DetailFilter each dose through a low protein-binding 0.22 micron filter (Millex GV) before administration. Patient temperature should not exceed 37.8°C (100°F) at time of administration.

Dietary ConsiderationsInjection solution contains sodium 43 mg/5 mL.

StorageRefrigerate; do not freeze. Do not shake. Stable in Becton Dickinson syringe for 16 hours at room temperature or refrigeration.

ContraindicationsHypersensitivity to OKT3 or any murine product; patients with uncompensated heart failure or uncontrolled hypertension, in fluid overload or those with >3% weight gain within 1 week prior to start of OKT3; mouse antibody titers >1:1000; history of seizures; known or suspected pregnancy; breast-feeding

Warnings/Precautions

Boxed warnings:

- Anaphylactic/anaphylactoid reactions: See "Concerns related to adverse effects" below.

- Experienced physician: See "Other warnings/precautions" below.

Concerns related to adverse effects:

- Anaphylactic/anaphylactoid reactions: **[U.S. Boxed Warning]: Anaphylactic and anaphylactoid reactions may occur after administration of any dose of muromonab-CD3;** acute hypersensitivity reactions may be characterized by cardiovascular collapse, cardiorespiratory arrest, loss of consciousness, shock, tachycardia, tingling, angioedema, airway obstruction, bronchospasm, dyspnea, urticaria, and pruritus. These reactions may be difficult to differentiate from the cytokine release syndrome associated with use; however, hypersensitivity reactions are more likely to occur within the first 10 minutes after administration.

- Central nervous system events: Seizures, encephalopathy, cerebral edema, aseptic meningitis, and headache have been reported following muromonab-CD3. Contraindicated for use in patients with a history of seizures or those who are predisposed to seizures.

- Cytokine release syndrome (CRS): May occur in a significant proportion of patients following the first couple of doses of muromonab-CD3; symptoms usually begin 30-60 minutes after administration of dose and may persist for several hours; symptoms range from a mild, self-limiting "flu-like reaction" to severe, life-threatening shock-like reaction. Signs and symptoms of CRS are characterized by pyrexia, chills, dyspnea, nausea, vomiting, chest pain, diarrhea, tremor, wheezing, headache, tachycardia, rigor, hypertension, pulmonary edema, and/or other cardiorespiratory manifestations. Patients at higher risk for serious complications include those with unstable angina, recent MI or ischemic heart disease, heart failure, pulmonary edema, COPD, intravascular volume overload or depletion, cerebrovascular disease, patients with advanced symptomatic vascular disease or neuropathy, history of seizures, and septic shock. Pretreatment with corticosteroids may decrease serum levels of cytokines and manifestations of the syndrome, but it is not known if this decreases organ damage and sequelae associated with it. Frequency and severity of this syndrome usually decreases with subsequent doses.

- Immunosuppression: May result in an increased susceptibility to infection.

- Lymphoproliferative disorders: Risk of development of lymphoproliferative disorders (particularly of the skin) is increased. Patients should be monitored appropriately, instructed to limit exposure to sunlight/UV light, and given supportive treatment should these conditions occur.

- Pulmonary edema: Severe pulmonary edema has occurred in patients with fluid overload.

- Thrombosis: Arterial, venous, and capillary thrombosis of allografts and other vascular beds have been reported with use; use with caution in patients with history of thrombosis or underlying vascular disease.

Disease-related concerns:

- Fever: If the patient's temperature is >37.8°C, reduce before administering OKT3.

Concurrent drug therapy issues:

- Other immunosuppressants: May result in an increased susceptibility to infection; dosage of concomitant immunosuppressants should be reduced during OKT3 therapy; cyclosporine should be decreased to 50% usual maintenance dose and maintenance therapy resumed about 4 days before stopping OKT3.

Others warnings/precautions:

- Appropriate use: It is imperative, especially prior to the first few doses, that there be no clinical evidence of volume overload, uncontrolled hypertension, or uncompensated heart failure, including a clear chest x-ray and weight restriction of ≤3% above the patient's minimum weight during the week prior to injection.

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of a physician experienced in immunosuppressive therapy in a facility appropriate for monitoring and resuscitation.** Cardiopulmonary resuscitation may be needed.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions**Note:** Signs and symptoms of cytokine release syndrome (characterized by pyrexia, chills, dyspnea, nausea, vomiting, chest pain, diarrhea, tremor, wheezing, headache, tachycardia, rigor, hypertension, pulmonary edema and/or other cardiorespiratory manifestations) occurs in a significant proportion of patients following the first couple of doses of muromonab-CD3. See Warnings/Precautions. Additionally, some patients have experienced immediate hypersensitivity reactions to muromonab-CD3 (characterized by cardiovascular collapse, cardiorespiratory arrest, loss of consciousness, hypotension/shock, tachycardia, tingling, angioedema (including laryngeal, pharyngeal, or facial edema), airway obstruction, bronchospasm, dyspnea, urticaria, and/or pruritus) upon initial exposure and re-exposure.

>10%:

Cardiovascular: Tachycardia (26%), hypotension (25%), hypertension (19%), edema (12%)

Central nervous system: Pyrexia (77%), chills (43%), headache (28%)

Dermatologic: Rash (14%; erythematous 2%)

Gastrointestinal: Diarrhea (37%), nausea (32%), vomiting (25%)

Respiratory: Dyspnea (16%)

1% to 10%:

Cardiovascular: Chest pain (9%), vasodilation (7%), arrhythmia (4%), bradycardia (4%), vascular occlusion (2%)

Central nervous system: Fatigue (9%), confusion (6%), dizziness (6%), lethargy (6%), pain trunk (6%), malaise (5%), nervousness (5%), depression (3%), somnolence (2%), meningitis (1%), seizure (1%)

Dermatologic: Pruritus (7%)

Gastrointestinal: Gastrointestinal pain (7%), abdominal pain (6%), anorexia (4%)

Hematologic: Leukopenia (7%), anemia (2%), thrombocytopenia (2%), leukocytosis (1%)

Neuromuscular & skeletal: Weakness (10%), arthralgia (7%), myalgia (1%), tremor (14%)

Ocular: Photophobia (1%)

Otic: Tinnitus (1%)

Renal: Renal dysfunction (3%)

Respiratory: Abnormal chest sound (10%), hyperventilation (7%), wheezing (6%), respiratory congestion (4%), pulmonary edema (2%), hypoxia (1%), pneumonia (1%)

Miscellaneous: Diaphoresis (7%), infections (various)

<1%: ALT increased, AST increased, angina, anuria, apnea, cardiac arrest, coagulation disorder, coma, conjunctivitis, encephalopathy, epilepsy, GI hemorrhage, hallucinations, hearing decreased, heart failure, hepatitis, hypotonia, lymphadenopathy, lymphopenia, MI, mood changes, neoplasms (various), oliguria, paranoia, pneumonitis, psychosis, shock, thrombosis

Oncology: VesicantNo
Oncology: Emetic PotentialModerate (30% to 60%)
Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersChest x-ray, weight gain, CBC with differential, temperature, vital signs (blood pressure, temperature, pulse, respiration); immunologic monitoring of T cells, serum levels of OKT3
Reference Range

OKT3serum concentrations:

Serum level monitoring should be performed in conjunction with lymphocyte subset determinations; Trough concentration sampling best correlates with clinical outcome. Serial monitoring may provide a better early indicator of inadequate dosing during induction or rejection.

Mean serum trough levels rise during the first 3 days, then average 0.9 mcg/mL on days 3-14

Circulating levels ≥0.8 mcg/mL block the function of cytotoxic T cells *in vitro* and *in vivo*

Several recent analysis have suggested appropriate dosage adjustments of OKT3 induction course are better determined with OKT3 serum levels versus lymphocyte subset determination; however, no prospective controlled trials have been performed to validate the equivalency of these tests in predicting clinical outcome.

Lymphocyte subset monitoring: CD3+ cells: Trough sample measurement is preferable and reagent utilized defines reference range.

OKT3-FITC: <10-50 cells/mm^3 or <3% to 5%

CD3(IgG1)-FITC: similar to OKT3-FITC

Leu-4a: Higher number of CD3+ cells appears acceptable

Dosage adjustments should be made in conjunction with clinical response and based upon trends over several consecutive days

Nursing: Physical Assessment/MonitoringMonitor pretreatment laboratory results prior to beginning therapy. Monitor closely for acute adverse pulmonary and cardiac effects, and anaphylactic-type effects during and for 24 hours following first infusion. Monitor vital signs, cardiac status, respiratory status, and adverse reactions on a regular basis. Assess knowledge/instruct patient about adverse reactions to report (eg, opportunistic infection) and appropriate interventions to reduce side effects.
Monitoring: Lab TestsChest x-ray, CBC with differential, immunologic monitoring of T cells, serum levels of OKT3
Patient EducationThere may be a severe reaction to the first infusion of this medication. You may experience high fever, chills, respiratory difficulty, or congestion. You will be closely monitored and comfort measures provided. Effects are substantially reduced with subsequent infusions. During the period of therapy and for some time after the regimen of infusions you will be susceptible to infection. People may wear masks and gloves while caring for you to protect you as much as possible from infection (avoid crowds and exposure to infection). You may

experience dizziness, faintness, or trembling (use caution until response to medication is known); nausea or vomiting (small frequent meals, frequent mouth care); or sensitivity to direct sunlight (wear dark glasses, and protective clothing, use sunscreen, or avoid exposure to direct sunlight); headache, fever, chills, rash, and diarrhea. Report chest pain or tightness; symptoms of respiratory infection, wheezing, or respiratory difficulty; vision change; swelling of the extremities; sudden weight gain (>3-5 lbs/week); or muscular trembling. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 1 mg/mL (5 mL) [contains sodium 43 mg/5 mL]

Generic AvailableNo

ManufacturerOrtho Biotech, Inc

Mechanism of ActionReverses graft rejection by binding to T cells and interfering with their function by binding T-cell receptor-associated CD3 glycoprotein

Pharmacodynamics/Kinetics

Duration: 7 days after discontinuation

Time to peak: Steady-state: Trough: 3-14 days

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may rarely cause sedation, confusion, or hallucinations

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMonoclonal Antibody; OKT3

References

Ettenger RB, Marik JL, Rosenthal JT, et al, "OKT3 for Rejection Reversal in Pediatric Renal Transplantation," *Clin Transpl*, 1988, 2:180-4.

Hooks MA, Wade CS, and Millikan WJ Jr, "Muromonab CD-3: A Review of Its Pharmacology, Pharmacokinetics, and Clinical Use in Transplantation," *Pharmacotherapy*, 1991, 11(1):26-37.

Niaudet P, Murcia I, Jean G, et al, "A Comparative Trial of OKT3 and Antilymphocyte Serum in the Preventive Treatment of Rejection After Kidney Transplantation in Children," *Ann Pediatr (Paris)*, 1990, 37(2):83-5.

Ross SJ, "Immunologic Monitoring of OKT3 Therapy," *Transplantation Pharm Newslet*, 1995:2-5.

Todd PA and Brogden RN, "Muromonab CD3 A Review of Its Pharmacology and Therapeutic Potential," *Drugs*, 1989, 37(6):871-99.[PubMed 2503348]

International Brand NamesIOR t3 (AR); OKT 3 (KP); Orthoclone (PL, ZA); Orthoclone OKT3 (AR, AT, AU, BE, BG, BR, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, JP, KP, LU, MX, MY, NL, NO, PL, PT, RU, SE, TR)

MV

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Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid

Regimen UseLeukemia, acute myeloid

RegimenInduction:

Mitoxantrone: I.V.: 10 mg/m^2/day days 1 to 5

[total dose/cycle = 50 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Second cycle may be given based on individual response; time between cycles not specified

References

Ho AD, Lipp T, Ehninger G, et al, âCombination of Mitoxantrone and Etoposide in Refractory Acute Myelogenous Leukemia an Active and Well-Tolerated Regimen,â *J Clin Oncol*, 1988, 6(2):213-17.[PubMed 3422260]

MVPP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Lymphoma, Hodgkin's Disease]

Regimen UseLymphoma, Hodgkin's disease

Regimen

Mechlorethamine: I.V.: 6 mg/m^2/day days 1 and 8

[total dose/cycle = 12 mg/m^2]

Vinblastine: I.V.: 4 mg/m^2/day days 1 and 8

[total dose/cycle = 8 mg/m^2]

Procarbazine: Oral: 100 mg/m^2/day days 1 to 14

[total dose/cycle = 1400 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 14

[total dose/cycle = 560 mg/m^2]

Repeat cycle every 4-6 weeks

References

Cooper MR, Pajak TF, Nissen NI, et al, âA New Effective Four-Drug Combination of CCNU (1-[2-Chloroethyl]-3-Cyclohexyl-1-Nitrosourea) (NSC-79038), Vinblastine, Prednisone, and Procarbazine for the Treatment of Advanced Hodgkin's Disease,â *Cancer*, 1980, 46(4):654-62.[PubMed 7397630]

Mycophenolate

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Mycophenolate Mofetil (CellCept®) and Mycophenolic Acid (Myfortic®): Association with Progressive Multifocal Leukoencephalopathy (PML) - June 2008

These product labeling changes have been incorporated into the mycophenolate Lexi-Comp monograph.

The FDA MedWatch alert can be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#mycophenolate

Mycophenolate Mofetil (CellCept®) and Mycophenolic Acid (Myfortic®): Healthcare Professional Information Sheet Issued Regarding Fetal Risk Associated With Use - May 2008

The U.S. Food and Drug Administration (FDA) is reminding healthcare professionals of reports of spontaneous abortions and structural abnormalities (including microtia) occurring following exposure to mycophenolate during pregnancy. Product labeling for both mycophenolate mofetil (CellCept®) and mycophenolic acid (Myfortic®) was updated in November 2007 to reflect these fetal risks and include a change from pregnancy category C to category D.

The FDA has issued a Healthcare Professional Information Sheet with recommendations for clinicians prescribing mycophenolate mofetil (MMF) or mycophenolic acid (MPA) to women of childbearing potential. Clinicians should provide information to women concerning the fetal risks prior to patients receiving therapy and counsel women on the proper use of contraceptives. Clinicians should confirm that women are not pregnant by verifying a negative blood or urine pregnancy test (sensitivity at least 25 mIU/mL) within one week prior to beginning therapy. Woman of childbearing potential must use two reliable forms of effective contraception initiated 4 weeks prior to beginning treatment and continue for 6 weeks after the last dose of MMF or MPA. Women may also choose abstinence as their only form of birth control. Women who choose oral contraceptives as one of their methods should be made aware that MMF and MPA may decrease the serum level of the hormones and reduce their efficacy.

Additional information, including a copy of the Information for Healthcare Professionals, is available at http://www.fda.gov/medwatch/safety/2008/safety08.htm#MMF

Pronunciation(mye koe FEN oh late)

U.S. Brand NamesCellCept®; Myfortic®

Canadian Brand NamesCellCept®; Myfortic®

Pharmacologic CategoryImmunosuppressant Agent

Use: Labeled IndicationsProphylaxis of organ rejection concomitantly with cyclosporine and corticosteroids in patients receiving allogeneic renal (CellCept®, Myfortic®), cardiac (CellCept®), or hepatic (CellCept®) transplants

Use: Unlabeled/InvestigationalTreatment of rejection in liver transplant patients unable to tolerate tacrolimus or cyclosporine due to neurotoxicity; mild rejection in heart transplant patients; treatment of moderate-severe psoriasis; treatment of proliferative lupus nephritis; treatment of myasthenia gravis; prevention and treatment of graft-versus-host disease (GVHD)

Dosing: Adults**Note:** May be used I.V. for up to 14 days; transition to oral therapy as soon as tolerated.

Renal transplant:

CellCept®:

Oral: 1 g twice daily. Doses >2 g/day are not recommended.

I.V.: 1 g twice daily

Myfortic®: Oral: 720 mg twice daily (1440 mg/day)

Cardiac transplantation:

Oral (CellCept®): 1.5 g twice daily

I.V. (CellCept®): 1.5 g twice daily

Hepatic transplantation:

Oral (CellCept®): 1.5 g twice daily

I.V. (CellCept®): 1 g twice daily

Myasthenia gravis (unlabeled use): Oral (CellCept®): 1 g twice daily (range 1-3 g/day)

Dosing: ElderlyDosage is the same as younger patients, however, dosing should be cautious due to possibility of increased hepatic, renal, or cardiac dysfunction. Elderly patients may be at an increased risk of certain infections, gastrointestinal hemorrhage, and pulmonary edema, as compared to younger patients.

Dosing: Pediatric

Renal transplant: Oral:

CellCept® suspension: 600 mg/m^2/dose twice daily; maximum dose: 1 g twice daily

Alternatively, may use solid dosage forms according to BSA as follows:

BSA 1.25-1.5 m^2: 750 mg capsule twice daily

BSA >1.5 m^2: 1 g capsule or tablet twice daily

Myfortic®: 400 mg/m^2/dose twice daily; maximum dose: 720 mg twice daily

BSA <1.19 m^2: Use of this formulation is not recommended

BSA 1.19-1.58 m^2: 540 mg twice daily (maximum: 1080 mg/day)

BSA >1.58 m^2: 720 mg twice daily (maximum: 1440 mg/day)

Dosing: Renal Impairment

Renal transplant: GFR <25 mL/minute in patients outside the immediate post-transplant period:

CellCept®: Doses of >1 g administered twice daily should be avoided; patients should also be carefully observed; no dose adjustments are needed in renal transplant patients experiencing delayed graft function postoperatively

Myfortic®: Cl_{cr} <25 mL/minute: Monitor carefully

Cardiac or liver transplant: No data available; mycophenolate may be used in cardiac or hepatic transplant patients with severe chronic renal impairment if the potential benefit outweighs the potential risk.

Hemodialysis: Not removed; supplemental dose is not necessary.

Peritoneal dialysis: Supplemental dose is not necessary.

Dosing: Hepatic ImpairmentNo dosage adjustment is recommended for renal patients with severe hepatic parenchymal disease; however, it is not currently known whether dosage adjustments are necessary for hepatic disease with other etiologies.

Dosing: Adjustment for ToxicityANC <1.3 x 10^3/µL: Dosing should be interrupted or the dose reduced, appropriate diagnostic tests performed and patients managed appropriately

Calculations

- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Intravenous solutions should be given over at least 2 hours. Do not administer intravenous solution by rapid or bolus injection.

Administration: I.V. Detail

Reconstituted solution: pH 2.4-4.1

Administration: OralOral dosage formulations (tablet, capsule, suspension) should be administered on an empty stomach to avoid variability in MPA absorption. The oral solution may be administered via a nasogastric tube (minimum 8 French, 1.7 mm interior diameter); oral suspension should not be mixed with other medications. Delayed release tablets should not be crushed, cut, or chewed.

Dietary ConsiderationsOral dosage formulations should be taken on an empty stomach to avoid variability in MPA absorption. However, in stable renal transplant patients, may be administered with food if necessary. Oral suspension contains 0.56 mg phenylalanine/mL; use caution if administered to patients with phenylketonuria.

Storage

Capsules: Store at room temperature of 15°C to 39°C (59°F to 86°F).

Tablets: Store at room temperature of 15°C to 39°C (59°F to 86°F). Protect from light.

Oral suspension: Store powder for oral suspension at room temperature of 15°C to 39°C (59°F to 86°F). Once reconstituted, the oral solution may be stored at room temperature or under refrigeration. Do not freeze. The mixed suspension is stable for 60 days.

Injection: Store intact vials at room temperature 15°C to 30°C (59°F to 86°F). Store solutions at 15°C to 30°C (59°F to 86°F). Begin infusion within 4 hours of reconstitution.

Reconstitution

Oral suspension: Should be constituted prior to dispensing to the patient and **not** mixed with any other medication. Add 47 mL of water to the bottle and shake well for ~1 minute. Add another 47 mL of water to the bottle and shake well for an additional minute. Final concentration is 200 mg/mL of mycophenolate mofetil.

I.V.: Reconstitute the contents of each vial with 14 mL of 5% dextrose injection; dilute the contents of a vial with 5% dextrose in water to a final concentration of 6 mg mycophenolate mofetil per mL. **Note:** Vial is vacuum-sealed; if a lack of vacuum is noted during preparation, the vial should not be used.

CompatibilityStable in D_5W.

ContraindicationsHypersensitivity to mycophenolate mofetil, mycophenolic acid, mycophenolate sodium, or any component of the formulation; intravenous formulation is contraindicated in patients who are allergic to polysorbate 80

Warnings/Precautions

Boxed warnings:

- Experienced physician: See "Other warnings/precautions" below.
- Infection: See "Concerns related to adverse effects" below.
- Lymphoproliferative disorders: See "Concerns related to adverse effects" below.
- Pregnancy: See "Special populations" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal. Because mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits, tablets should not be crushed, and capsules should not be opened or crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in the capsules and the powder for oral suspension. Caution should be exercised in the handling and preparation of solutions of intravenous mycophenolate. Avoid skin contact with the intravenous solution and reconstituted suspension. If such contact occurs, wash thoroughly with soap and water, rinse eyes with plain water.

Concerns related to adverse effects:

- Infection: **[U.S. Boxed Warning]: Risk for infection is increased.**
- Lymphoproliferative disorders: **[U.S. Boxed Warning]: Risk of development of lymphoma and skin malignancy is increased.** Patients should be monitored appropriately, instructed to limit exposure to sunlight/UV light, and given supportive treatment should these conditions occur.
- Neutropenia: Severe neutropenia may occur, requiring interruption of treatment (risk greater from day 31-180 post-transplant).
- Progressive multifocal leukoencephalopathy (PML): PML, a rare and potentially fatal condition affecting the CNS as a result of activation of the John Cunningham virus (JCV), has been reported. Symptoms of PML include apathy, ataxia, cognitive deficiencies, confusion, and hemiparesis. Risk factors for the development of PML include immunosuppression and treatment with immunosuppressant therapy. The onset of PML may warrant a reduction in immunosuppressive therapy; however, in transplant recipients, the risk of reduced immunosuppression and graft rejection should be considered.

Disease-related concerns:

- Hypoxanthine-guanine phosphoribosyltransferase deficiency: Theoretically, use should be avoided in patients with the rare hereditary deficiency of hypoxanthine-guanine phosphoribosyltransferase (such as Lesch-Nyhan or Kelley-Seegmiller syndrome).
- Peptic ulcer disease: Use with caution in patients with active peptic ulcer disease; may be associated with GI bleeding and/or perforation.
- Renal impairment: Use with caution in patients with renal impairment as toxicity may be increased; may require dosage adjustment in severe impairment.

Dosage form specific issues:

- Non-interchangeability of forms: **Note: CellCept® and Myfortic® dosage forms should not be used interchangeably due to differences in absorption.**
- Phenylalanine: Some dosage forms may contain phenylalanine.

Special populations:

- Pregnancy: **[U.S. Boxed Warning]: Mycophenolate is associated with an increased risk of congenital malformations and spontaneous abortions when used during pregnancy.** Females of childbearing potential should have a negative pregnancy test within 1 week prior to beginning therapy. Two reliable forms of contraception should be used beginning 4 weeks prior to, during, and for 6 weeks after therapy.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of a physician experienced in immunosuppressive therapy.**
- I.V. administration: Intravenous solutions should be given over at least 2 hours; **never** administer intravenous solution by rapid or bolus injection.

Pregnancy Risk FactorD

Pregnancy Considerations**[U.S. Boxed Warning]: Mycophenolate is associated with an increased risk of congenital malformations and spontaneous abortions when used during pregnancy.** Adverse events have been reported in animal studies at doses less than the equivalent recommended human dose. Data from the National Transplantation Pregnancy Registry (NTPR) have observed an increase in structural malformations (including ear malformations) in infants born to mothers taking mycophenolate during pregnancy. Spontaneous abortions have also been noted. Females of childbearing potential should have a negative pregnancy test within 1 week prior to beginning therapy. Two reliable forms of contraception should be used beginning 4 weeks prior to, during, and for 6 weeks after therapy. The effectiveness of hormonal contraceptive agents may be affected by mycophenolate.

The National Transplantation Pregnancy Registry (NTPR, Temple University) is a registry for pregnant women taking immunosuppressants following any solid organ transplant. The NTPR encourages reporting of all immunosuppressant exposures during pregnancy in transplant recipients at 877-955-6877.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is unknown if mycophenolate is excreted in human milk. Due to potentially serious adverse reactions, the decision to discontinue the drug or discontinue breast-feeding should be considered. Breast-feeding is not recommended during therapy or for 6 weeks after treatment is complete.

Adverse ReactionsAs reported in adults following oral dosing of CellCept® alone in renal, cardiac, and hepatic allograft rejection studies. In general, lower doses used in renal rejection patients had less adverse effects than higher doses. Rates of adverse effects were similar for each indication, except for those unique to the specific organ involved. The type of adverse effects observed in pediatric patients was similar to those seen in adults; abdominal pain, anemia, diarrhea, fever, hypertension, infection, pharyngitis, respiratory tract infection, sepsis, and vomiting were seen in higher proportion; lymphoproliferative disorder was the only type of malignancy observed. Percentages of adverse reactions were similar in studies comparing CellCept® to Myfortic® in patients following renal transplant.

>20%:

Cardiovascular: Hypertension (28% to 77%), hypotension (up to 33%), peripheral edema (27% to 64%), edema (27% to 28%), tachycardia (20% to 22%)

Central nervous system: Pain (31% to 76%), headache (16% to 54%), insomnia (41% to 52%), fever (21% to 52%), dizziness (up to 29%), anxiety (28%)

Dermatologic: Rash (up to 22%)

Endocrine & metabolic: Hyperglycemia (44% to 47%), hypercholesterolemia (41%), hypomagnesemia (up to 39%), hypokalemia (32% to 37%), hypocalcemia (up to 30%), hyperkalemia (up to 22%)

Gastrointestinal: Abdominal pain (25% to 62%), nausea (20% to 54%), diarrhea (31% to 52%), constipation (18% to 41%), vomiting (33% to 34%), anorexia (up to 25%), dyspepsia (22%)

Genitourinary: Urinary tract infection (37%)

Hematologic: Leukopenia (23% to 46%), hypochromic anemia (26% to 43%), leukocytosis (22% to 40%), thrombocytopenia (24% to 36%)

Hepatic: Liver function tests abnormal (up to 25%), ascites (24%)

Neuromuscular & skeletal: Back pain (35% to 47%), weakness (35% to 43%), tremor (24% to 34%), paresthesia (21%)

Renal: Creatinine increased (up to 39%), BUN increased (up to 35%)

Respiratory: Dyspnea (31% to 37%), respiratory tract infection (22% to 37%), cough (31%), lung disorder (22% to 30%)

Miscellaneous: Infection (18% to 27%), *Candida* (11% to 22%), herpes simplex (10% to 21%)

3% to <20%:

Cardiovascular: Angina, arrhythmia, arterial thrombosis, atrial fibrillation, atrial flutter, bradycardia, cardiac arrest, cardiac failure, CHF, extrasystole, facial edema, hypervolemia, pallor, palpitation, pericardial effusion, peripheral vascular disorder, postural hypotension, supraventricular extrasystoles, supraventricular tachycardia, syncope, thrombosis, vasodilation, vasospasm, venous pressure increased, ventricular extrasystole, ventricular tachycardia

Central nervous system: Agitation, chills with fever, confusion, convulsion, delirium, depression, emotional lability, hallucinations, hypoesthesia, malaise, nervousness, psychosis, somnolence, thinking abnormal, vertigo

Dermatologic: Acne, alopecia, bruising, cellulitis, hirsutism, petechia, pruritus, skin carcinoma, skin hypertrophy, skin ulcer, vesiculobullous rash

Endocrine & metabolic: Acidosis, Cushing's syndrome, dehydration, diabetes mellitus, gout, hypercalcemia, hyperlipemia, hyperphosphatemia, hyperuricemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, hypothyroidism, parathyroid disorder, weight gain/loss

Gastrointestinal: Abdomen enlarged, dry mouth, dysphagia, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, gum hyperplasia, ileus, melena, mouth ulceration, oral moniliasis, stomach disorder, stomatitis

Genitourinary: Impotence, nocturia, pelvic pain, prostatic disorder, scrotal edema, urinary frequency, urinary incontinence, urinary retention, urinary tract disorder

Hematologic: Coagulation disorder, hemorrhage, neutropenia, pancytopenia, polycythemia, prothrombin time increased, thromboplastin increased

Hepatic: Alkaline phosphatase increased, alkalosis, bilirubinemia, cholangitis, cholestatic jaundice, GGT increased, hepatitis, jaundice, liver damage, transaminases increased

Local: Abscess

Neuromuscular & skeletal: Arthralgia, hypertonia, joint disorder, leg cramps, myalgia, myasthenia, neck pain, neuropathy, osteoporosis

Ocular: Amblyopia, cataract, conjunctivitis, eye hemorrhage, lacrimation disorder, vision abnormal

Otic: Deafness, ear disorder, ear pain, tinnitus

Renal: Albuminuria, creatinine increased, dysuria, hematuria, hydronephrosis, kidney failure, kidney tubular necrosis, oliguria

Respiratory: Apnea, asthma, atelectasis, bronchitis, epistaxis, hemoptysis, hiccup, hyperventilation, hypoxia, respiratory acidosis, lung edema, pharyngitis, pleural effusion, pneumonia, pneumothorax, pulmonary hypertension, respiratory moniliasis, rhinitis, sinusitis, sputum increased, voice alteration

Miscellaneous: *Candida* (mucocutaneous 15% to 18%), CMV viremia/syndrome (12% to 14%), CMV tissue invasive disease (6% to 11%), herpes zoster cutaneous disease (4% to 10%), cyst, diaphoresis, flu-like syndrome, fungal dermatitis, healing abnormal, hernia, ileus infection, lactic dehydrogenase increased, peritonitis, pyelonephritis, thirst

Postmarketing and/or case reports: Atypical mycobacterial infection, colitis, gastrointestinal perforation, gastrointestinal ulcers, infectious endocarditis, interstitial lung disorder, intestinal villous atrophy, meningitis, pancreatitis, progressive multifocal leukoencephalopathy, pulmonary fibrosis (fatal), tuberculosis

Drug Interactions

Acyclovir-Valacyclovir: May increase the serum concentration of Mycophenolate. Mycophenolate may increase the serum concentration of Acyclovir-Valacyclovir. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Mycophenolate. **Exceptions:** Sodium Bicarbonate. *Risk D: Consider therapy modification*

Cholestyramine Resin: May decrease the serum concentration of Mycophenolate. *Risk X: Avoid combination*

CycloSPORINE: May decrease the serum concentration of Mycophenolate. Specifically, cyclosporine may decrease concentrations of the active metabolite mycophenolic acid. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Ganciclovir-Valganciclovir: Mycophenolate may increase the serum concentration of Ganciclovir-Valganciclovir. Ganciclovir-Valganciclovir may increase the serum concentration of Mycophenolate. *Risk C: Monitor therapy*

Magnesium Salts: May decrease the absorption of Mycophenolate. This only applies to oral magnesium salts. *Risk D: Consider therapy modification*

MetroNIDAZOLE: May decrease the serum concentration of Mycophenolate. Specifically, metronidazole may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Mycophenolate may decrease the serum concentration of Oral Contraceptive (Estrogens). Average AUC values were unchanged, but there was evidence of substantial patient-to-patient variability in response to this combination. *Risk D: Consider therapy modification*

Oral Contraceptive (Progestins): Mycophenolate may decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Mycophenolate. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May decrease the serum concentration of Mycophenolate. Specifically, concentrations of the active mycophenolic acid may be reduced. *Risk C: Monitor therapy*

Quinolone Antibiotics: May decrease the serum concentration of Mycophenolate. Specifically, quinolones may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Mycophenolate. Specifically, rifamycin derivatives may decrease the concentration of the active metabolite mycophenolic acid. *Risk X: Avoid combination*

Sevelamer: May decrease the serum concentration of Mycophenolate. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Decreases C_{max} of MPA by 40% following CellCept® administration and 33% following Myfortic® use; the extent of absorption is not changed

Herb/Nutraceutical: Avoid cat's claw, echinacea (have immunostimulant properties)

Monitoring ParametersComplete blood count; signs and symptoms of infection; pregnancy test (prior to initiation in females of childbearing potential)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions. Patient is at risk for lymphoproliferative disease and certain other malignancies, monitor closely. Monitor blood pressure periodically while receiving this medication. Assess for peripheral edema and other signs of fluid retention periodically. Patients with diabetes should monitor glucose levels closely (this medication may alter glucose levels). Monitor/instruct patient on appropriate interventions to reduce side effects, to monitor for signs of opportunistic infection, and adverse reactions to report.

Monitoring: Lab TestsRenal and liver function, CBC; pregnancy test (prior to initiation in females of childbearing potential)

Patient EducationTake oral formulations as directed, preferably 1 hour before or 2 hours after meals. Do not cut, chew, or crush delayed-release tablets. Do not take within 1 hour before or 2 hours after antacids or cholestyramine medications. Do not alter dose and do not discontinue without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) during entire course of therapy unless instructed to restrict fluid intake. You will be susceptible to infection (avoid crowds and exposure to infection). You may be at increased risk for skin cancer, wear protective clothing and use sunscreen with high protective factor to help limit exposure to sunlight and UV light. If you have diabetes, monitor glucose levels closely (drug may alter glucose levels). You may experience dizziness or trembling (use caution until response to medication is known); trouble sleeping; nausea or vomiting (small frequent meals, frequent mouth care may help); diarrhea (boiled milk, yogurt, or buttermilk may help); sores or white plaques in mouth (frequent rinsing of mouth and frequent mouth care may help); or muscle or back pain (mild analgesics may be recommended). Report chest pain; irregular heartbeat; acute headache or dizziness; swelling of extremities; unusual weight gain; symptoms of respiratory infection, cough, or respiratory difficulty; unresolved GI effects; fatigue, chills, fever unhealed sores, white plaques in mouth; irritation in genital area or unusual discharge; change in mental status, memory loss, loss of coordination or clumsiness, weakness in legs, difficulty speaking or understanding what others say; unusual bruising or bleeding; or other unusual effects related to this medication. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Two reliable forms of contraception should be used prior to, during, and for 6 weeks after therapy. The effectiveness of hormonal contraceptive agents may be reduced by mycophenolate. Consult prescriber if you suspect you might be pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as mofetil:

CellCept®: 250 mg

Injection, powder for reconstitution, as mofetil hydrochloride:

CellCept®: 500 mg [contains polysorbate 80]

Powder for oral suspension, as mofetil:

CellCept®: 200 mg/mL (225 mL) [provides 175 mL suspension following reconstitution; contains phenylalanine 0.56 mg/mL; mixed fruit flavor]

Tablet, as mofetil:

CellCept®: 500 mg [may contain ethyl alcohol]

Tablet, delayed release, as mycophenolic acid:

Myfortic®: 180 mg, 360 mg [formulated as a sodium salt]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (CellCept)

250 mg (30): $129.47

Suspension (reconstituted) (CellCept)

200 mg/mL (175): $676.94

Tablet, EC (Myfortic)

360 mg (120): $801.37

Tablets (CellCept)

500 mg (100): $787.64

Mechanism of ActionMPA exhibits a cytostatic effect on T and B lymphocytes. It is an inhibitor of inosine monophosphate dehydrogenase (IMPDH) which inhibits *de novo* guanosine nucleotide synthesis. T and B lymphocytes are dependent on this pathway for proliferation.

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Correlation of toxicity or efficacy is still being developed, however, one study indicated that 12-hour AUCs >40 mcg/mL/hour were correlated with efficacy and decreased episodes of rejection

T_{max}: Oral: MPA:

CellCept®: 1-1.5 hours

Myfortic®: 1.5-2.5 hours

Absorption: AUC values for MPA are lower in the early post-transplant period versus later (>3 months) post-transplant period. The extent of absorption in pediatrics is similar to that seen in adults, although there was wide variability reported.

Oral: Myfortic®: 93%

Distribution:

CellCept®: MPA: Oral: 4 L/kg; I.V.: 3.6 L/kg

Myfortic®: MPA: Oral: 54 L (at steady state); 112 L (elimination phase)

Protein binding: MPA: 97%, MPAG 82%

Metabolism: Hepatic and via GI tract; CellCept® is completely hydrolyzed in the liver to mycophenolic acid (MPA; active metabolite); enterohepatic recirculation of MPA may occur; MPA is glucuronidated to MPAG (inactive metabolite)

Bioavailability: Oral: CellCept®: 94%; Myfortic®: 72%

Half-life elimination:

CellCept®: MPA: Oral: 18 hours; I.V.: 17 hours

Myfortic®: MPA: Oral: 8-16 hours; MPAG: 13-17 hours

Excretion:

CellCept®: MPA: Urine (<1%), feces (6%); MPAG: Urine (87%)

Myfortic®: MPA: Urine (3%), feces; MPAG: Urine (>60%)

Related Information

- Antacid Drug Interactions
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mouth ulceration, gum hyperplasia, gingivitis, dry mouth, dysphagia, oral moniliasis, and stomatitis.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDizziness and insomnia are common
Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; avoid clozapine and carbamazepine
Cardiovascular ConsiderationsHypertension may accompany the use of mycophenolate in patients post-transplantation. Furthermore, this drug may also induce increases in cholesterol, increases in serum phosphate, hyperkalemia, and hyperglycemia.
Anesthesia and Critical Care Concerns/Other ConsiderationsAvoid inhalation or direct contact with skin or mucous membranes of the powder in CellCept® capsules. If such contact occurs, wash with soap and water; rinse eyes with plain water. Capsules should not be opened or crushed.

Hypertension may accompany the use of mycophenolate in patients post-transplantation. Furthermore, this drug may also induce increases in cholesterol and potassium, and impair glucose tolerance and phosphate and potassium depletion.

Index TermsMMF; MPA; Mycophenolate Mofetil; Mycophenolate Sodium; Mycophenolic Acid
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International Brand NamesCellCept (AT, BB, BF, BJ, BM, BS, BZ, CI, CL, CO, ET, GH, GM, GN, GR, GY, HK, IT, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, PT, PY, RU, SC, SD, SG, SL, SN, SR, TN, TR, TT, TZ, UG, ZA, ZM, ZW); Cellcept (PL); Cellmune (IN); Myfortic (AR, AU, BE, BG, BR, CH, CN, CZ, DE, DK, EC, EE, ES, FI, FR, GB, HN, ID, IE, IL, KP, MX, MY, NL, NO, PE, PH, PK, SE, TH, TW, UY, VE)

N4SE Protocol

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Neuroblastoma]

Regimen UseNeuroblastoma

Regimen

Vincristine: I.V.: 0.05 mg/kg/day days 1 and 2

[total dose/cycle = 0.1 mg/kg]

Doxorubicin: I.V.: 15 mg/m^2/day days 1 and 2

[total dose/cycle = 30 mg/m^2]

Cyclophosphamide: I.V.: 30 mg/kg/day days 1 and 2

[total dose/cycle = 60 mg/kg]

Fluorouracil: I.V.: 1 mg/kg/day days 3, 8, and 9

[total dose/cycle = 3 mg/kg]

Cytarabine: I.V.: 3 mg/kg/day days 3, 8, and 9

[total dose/cycle = 9 mg/kg]

Hydroxyurea: Oral: 40 mg/kg/day days 3, 8, and 9

[total dose/cycle = 120 mg/kg]

Repeat cycle every 21-28 days

References

Kushner BH and Helson L, âCoordinated Use of Sequentially Escalated Cyclophosphamide and Cell-Cycle-Specific Chemotherapy (N4SE Protocol) for Advanced Neuroblastoma: Experience With 100 Patients,â *J Clin Oncol*, 1987, 5(11):1746-51.[PubMed 3316512]

N6 Protocol

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Neuroblastoma]

Regimen UseNeuroblastoma

Regimen

Course 1, 2, 4, and 6:

Cyclophosphamide: I.V.: 70 mg/kg/day days 1 and 2

[total dose/cycle = 140 mg/kg]

Doxorubicin: I.V.: 25 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 75 mg/m^2]

Vincristine: I.V.: 0.033 mg/kg/day continuous infusion days 1, 2, and 3

[total dose/cycle = 0.099 mg/kg]

Vincristine: I.V.: 1.5 mg/m^2 day 9

[total dose/cycle = 1.5 mg/m^2]

Course 3, 5, and 7:

Etoposide: I.V.: 200 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 600 mg/m^2]

Cisplatin: I.V.: 50 mg/m^2/day days 1 to 4

[total dose/cycle = 200 mg/m^2]

References

Kushner BH, LaQuaglia MP, Bonilla MA, et al, âHighly Effective Induction Therapy for Stage 4 Neuroblastoma in Children Over 1 Year of Age,â *J Clin Oncol*, 1994, 12(12):2607-13.[PubMed 7527454]

Nabilone

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English English

Jump To Field (Select Field Name)

Pronunciation(NA bi lone)
U.S. Brand NamesCesamet™
Canadian Brand NamesCesamet™
Pharmacologic CategoryAntiemetic
Use: Labeled IndicationsTreatment of refractory nausea and vomiting associated with cancer chemotherapy
Dosing: AdultsRefer to individual protocols.

Nausea and vomiting associated with cancer chemotherapy: Oral: 1-2 mg twice daily (maximum: 6 mg divided in 3 doses daily)

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to individual protocols.

Nausea and vomiting associated with cancer chemotherapy (unlabeled use): Oral: Children >4 years:

<18 kg: 0.5 mg twice daily

18-30 kg: 1 mg twice daily

>30 kg: 1 mg 3 times/day

Dosing: Renal ImpairmentNo adjustment required.
Administration: OralInitial dose should be given 1-3 hours before chemotherapy; may be given 2-3 times a day during the entire chemotherapy course and for up to 48 hours after the last dose of chemotherapy; a dose of 1-2 mg the night before chemotherapy may be useful.
StorageStore at room temperature between 15°C and 30°C (59°F and 86°F).
RestrictionsC-II
ContraindicationsHypersensitivity to nabilone, cannabinoids, tetrahydrocannabinol, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Cardiovascular effects: May cause tachycardia and/or orthostatic hypotension; use with caution in patients with cardiovascular disease.
- CNS depression: May impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists (drug is psychoactive substance in marijuana). Tolerance, psychological and physical dependence may occur with prolonged use.
- Psychiatric disorders: Use with caution in patients with mania, depression, or schizophrenia; cannabinoid use may reveal symptoms of psychiatric disorders. Careful psychiatric monitoring is recommended; psychiatric adverse reactions may persist for up to 3 days after discontinuing treatment.

Concurrent drug therapy issues:

- CNS depressants: Effects may be potentiated when used with other psychoactive drugs, sedatives and/or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may cause postural hypotension.
- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies did not demonstrate teratogenic effects; however, dose-related decreased fetal weights and increased fetal resorptions were observed. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsBecause some cannabinoids are excreted in breast milk, use in breast-feeding is not recommended.
Adverse Reactions

>10%:

Central nervous system: Dizziness (59%), drowsiness (52% to 66%), vertigo (52% to 59%), euphoria (11% to 38%), ataxia (13% to 14%), depression (14%), concentration decreased (12%), sleep disturbance (11%)

Gastrointestinal: Xerostomia (22% to 36%)

Ocular: Visual disturbance (13%)

1% to 10%:

Cardiovascular: Hypotension (8%)

Central nervous system: Dysphoria (9%), headache (6% to 7%), sedation (3%), depersonalization (2%), disorientation (2%)

Gastrointestinal: Anorexia (8%), nausea (4%), appetite increased (2%)

Neuromuscular & skeletal: Weakness (8%)

<1%, postmarketing, or frequency not reported: Abdominal pain, abnormal dreams, akathisia, allergic reaction, amblyopia, anemia, anhydrosis, anxiety, apathy, aphthous ulcer, arrhythmia, back pain, cerebral vascular accident, chest pain, chills, constipation, cough, diaphoresis, diarrhea, dyspepsia, dyspnea, dystonia, emotional disorder, emotional lability, epistaxis, equilibrium dysfunction, eye irritation, fatigue, fever, flushing, gastritis, hallucinations, hot flashes, hyperactivity, hypertension, infection, insomnia, irritation, joint pain, leukopenia, lightheadedness, malaise, memory disturbance, mood swings, mouth irritation, muscle pain, nasal congestion, neck pain, nervousness, neurosis (phobic), numbness, orthostatic hypotension, pain, palpitation, panic disorder, paranoia, paresthesia, perception disturbance, pharyngitis, photophobia, photosensitivity, polyuria, pruritus, psychosis (toxic), pupil dilation, rash, seizure, sinus headache, speech disorder, stupor, syncope, tachycardia, taste perversion, thirst, thought disorder, tinnitus, tremor, urination decreased, urinary retention, vomiting, wheezing, withdrawal, xerophthalmia

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Anticholinergic Agents: May enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Cocaine: May enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Sympathomimetics: Cannabinoids may enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersBlood pressure, heart rate; signs and symptoms of excessive use, abuse, or misuse

Nursing: Physical Assessment/MonitoringFor use when other antiemetic agents have proved ineffective. Use caution with history of substance abuse or mental illness. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking that may cause additive CNS effects (eg, sedatives, hypnotics, psychoactive agents). Assess effectiveness of therapy and monitor closely for adverse psychotic reactions which may persist for up to 3 days following discontinuation; this drug has the psychoactive properties of marijuana and has the potential for abuse or dependence. Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber (especially sedatives or hypnotics). Take exactly as directed; do not increase dose or take more often than prescribed. Avoid alcohol. May cause psychotic reaction, impaired coordination or judgment, faintness, dizziness, drowsiness, unsteadiness, sleep disturbance or visual disturbances (do not drive or engage in activities that require alertness and coordination until response to drug is known); orthostatic hypotension (change position slowly and use caution when climbing stairs); dry mouth or decreased appetite (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report excessive or persistent CNS changes (euphoria, anxiety, depression, memory lapse, bizarre thought patterns, excitability, inability to control thoughts or behavior, fainting); respiratory difficulties; rapid heartbeat; or other adverse reactions.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Cesamet™: 1 mg

Generic AvailableNo

ManufacturerValeant Pharmaceuticals International

Mechanism of ActionNot fully characterized; antiemetic activity may be due to effect on cannabinoid receptors (CB1) within the central nervous system.

Pharmacodynamics/Kinetics

Absorption: Rapid and complete

Distribution: ~12.5 L/kg

Metabolism: To several active metabolites by oxidation and stereospecific enzyme reduction; CYP450 enzymes may also be involved

Half-life elimination: Parent compound: 2 hours; Metabolites: 35 hours

Time to peak, serum: Within 2 hours

Excretion: Feces (~60%); renal (~24%)

Mental Health: Effects on Mental StatusDizziness, drowsiness, and euphoria are common; may cause depression. May rarely cause confusion or hallucinations.

Mental Health: Effects on Psychiatric TreatmentConcomitant use with psychotropic agents may produce additive CNS depression

References

Dupuis LL and Nathan PC, “Options for the Prevention and Management of Acute Chemotherapy-Induced Nausea and Vomiting in Children,” *Pediatr Drug*, 2003, 5(9):597-613.

Tramer MR, Carroll D, Campbell FA, et al, ”Cannabinoids for Control of Chemotherapy Induced Nausea and Vomiting: Quantitative Systematic Review,” *BMJ*, 2001, 323(7303):16-21.[PubMed 11440936]

Ward A and Holmes B, “Nabilone: A Preliminary Review of Its Pharmacological Properties and Therapeutic Use,” *Drugs*, 1985, 30(2):127-44.[PubMed 2863127]

Nabumetone

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(na BYOO me tone)

Canadian Brand NamesApo-Nabumetone®; Gen-Nabumetone; Novo-Nabumetone; Relafen®; Rhoxal-nabumetone; Sandoz-Nabumetone

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsManagement of osteoarthritis and rheumatoid arthritis

Use: Unlabeled/InvestigationalModerate pain

Dosing: Adults**Osteoarthritis, rheumatoid arthritis:** Oral: 1000 mg/day; an additional 500-1000 mg may be needed in some patients to obtain more symptomatic relief; may be administered once or twice daily; maximum dose: 2000 mg/day

Note: Patients <50 kg are less likely to require doses >1000 mg/day.

Dosing: ElderlyRefer to adult dosing; do not exceed 2000 mg/day.

Dosing: Renal Impairment In general, NSAIDs are not recommended for use in patients with advanced renal disease, but the manufacturer of nabumetone does provide some guidelines for adjustment in renal dysfunction:

Moderate impairment (Cl_{cr} 30-49 mL/minute): Initial dose: 750 mg/day; maximum dose: 1500 mg/day

Severe impairment (Cl_{cr} <30 mL/minute): Initial dose: 500 mg/day; maximum dose: 1000 mg/day

Calculations

- Creatinine Clearance: Adults

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to nabumetone, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.
- Photosensitivity reactions: May cause photosensitivity reactions.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsIn trials with nabumetone, no significant differences were noted between young and the elderly in regards to efficacy and safety. However, the elderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but the elderly may demonstrate these adverse effects at lower doses than younger adults.
Pregnancy Risk FactorC/D (3rd trimester)
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%: Gastrointestinal: Abdominal pain (12%), diarrhea (14%), dyspepsia (13%)

1% to 10%:

Cardiovascular: Edema (3% to 9%)

Central nervous system: Dizziness (3% to 9%), headache (3% to 9%), fatigue (1% to 3%), insomnia (1% to 3%), nervousness (1% to 3%), somnolence (1% to 3%)

Dermatologic: Pruritus (3% to 9%), rash (3% to 9%)

Gastrointestinal: Constipation (3% to 9%), flatulence (3% to 9%), guaiac positive (3% to 9%), nausea (3% to 9%), gastritis (1% to 3%), stomatitis (1% to 3%), vomiting (1% to 3%), xerostomia (1% to 3%)

Otic: Tinnitus

Miscellaneous: Diaphoresis (1% to 3%)

<1%: Abnormal vision, acne, agitation, albuminuria, alopecia, anemia, angina, angioneurotic edema, anorexia, anxiety, arrhythmia, asthma, azotemia, bilirubinemia duodenitis, bullous eruptions, chills, confusion, cough, depression, duodenal ulcer, dysphagia, dyspnea, dysuria, eructation, fever, gallstones, gastric ulcer, gastroenteritis, gingivitis, GI bleeding, glossitis, granulocytopenia, hematuria, hyperglycemia, hypertension, hypokalemia, impotence, jaundice, leukopenia, liver function abnormalities, malaise, melena, MI, nightmares, palpitation, pancreatitis, paresthesia, photosensitivity, pseudoporphyria cutanea tarda, rectal bleeding, renal stones, syncope, taste disorder, thrombophlebitis, tremor, urticaria, vasculitis, vertigo, weakness, weight gain/loss

Postmarketing and/or case reports: Anaphylactoid reaction, anaphylaxis, CHF, eosinophilic pneumonia, erythema multiforme, hepatic failure, hypersensitivity pneumonitis, hyperuricemia, interstitial nephritis, interstitial pneumonitis, nephrotic syndrome, renal failure, Stevens-Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Nabumetone peak serum concentrations may be increased if taken with food or dairy products.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Monitoring ParametersPatients with renal insufficiency: Baseline renal function followed by repeat test within weeks (to determine if renal function has deteriorated)

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess effectiveness and interactions of other medications patient may be taking. Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, GI effects, hepatotoxicity, or ototoxicity) at beginning of therapy and periodically throughout therapy. Schedule ophthalmic evaluations for patients who develop eye complaints during long-term NSAID therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsPatients with renal insufficiency: Baseline renal function followed by repeat test within weeks (to determine if renal function has deteriorated)

Patient EducationTake this medication exactly as directed; do not increase dose without consulting prescriber. Do not crush tablets. Take with food or milk to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol, aspirin or aspirin-containing medication, or any other anti-inflammatory medications without consulting healthcare prescriber. You may experience drowsiness, dizziness, nervousness, or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); anorexia, nausea, vomiting, or heartburn (small frequent meals, frequent oral care, sucking lozenges, or chewing gum may help); fluid retention (weigh yourself weekly and report unusual [3-5 lb/week] weight gain). GI bleeding, ulceration, or perforation can occur with or without pain; discontinue medication and contact prescriber if persistent abdominal pain or cramping, or blood in stool occurs. Report breathlessness, respiratory difficulty, or unusual cough; chest pain, rapid heartbeat, palpitations; unusual bruising/bleeding; blood in urine, stool, mouth, or vomitus; swollen extremities; skin rash or itching; acute fatigue; or hearing changes (ringing in ears).
Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: 500 mg, 750 mg

Relafen®: 500 mg, 750 mg [DSC]

Generic AvailableYes

ManufacturerSmithKline Beecham Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Nabumetone)

500 mg (60): $39.99

750 mg (60): $39.98

Tablets (Relafen)

750 mg (60): $137.70

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: Several days

Distribution: Diffusion occurs readily into synovial fluid

V_d: 6MNA: 29-82 L

Protein binding: 6MNA: >99%

Metabolism: Prodrug, rapidly metabolized in the liver to an active metabolite [6-methoxy-2-naphthylacetic acid (6MNA)] and inactive metabolites; extensive first-pass effect

Half-life elimination: 6MNA: ~24 hours

Time to peak, serum: 6MNA: Oral: 2.5-4 hours; Synovial fluid: 4-12 hours

Excretion: 6MNA: Urine (80%) and feces (9%)

Related Information

- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and stomatitis. NSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness; may rarely cause insomnia, confusion, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A meta-analysis (Pope, 1993) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 Heart Failure Guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin’s inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

Index TermsRelafen

References

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International Brand NamesAflex (TH); Balmox (PT); Bumetone (KP, TH); Coxalgan (PL); Coxeton (PL); Ensaid (TH); Goflex (AE, BH, CY, EG, ID, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Labuton (TW); Lavex (KP); Mebutan (NL); Nabentac (KP); Nabone (TH); Nabuco (IL); Nabuflam (IN); Naburen (CO, DO, GT, HN, PA, SV); Nabuser (IT); Nabuton (PL); Naflex (TH); Namerin (KP); Nametone (TH); Noac (UY); Recox (PL); Relafen (CL, KP); Relifen (JP, ZA); Relifex (AE, BB, BF, BG, BH, BJ, BM, BR, BS, BZ, CI, CY, CZ, DE, DK, EE, EG, ET, FI, GB, GH, GM, GN, GR, GY, HN, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NO, OM, PH, PK, PL, QA, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Relisan (ZA); Relitone (ZA); Rodanol S (PL); Unimetone (KP)

Nadolol and Bendroflumethiazide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(NAY doe lol & ben droe floo meth EYE a zide)

U.S. Brand NamesCorzide®

Pharmacologic CategoryBeta Blocker, Nonselective; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension; combination product should not be used for initial therapy

Dosing: Adults**Treatment of hypertension:** Oral: Initial: Nadolol 40 mg and bendroflumethiazide 5 mg once daily. May increase dose to nadolol 80 mg and bendroflumethiazide 5 mg once daily if needed.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} >50 mL/minute/1.73 m^2: Administer dose every 24 hours

Cl_{cr} 31-50 mL/minute/1.73 m^2: Administer dose every 24-36 hours

Cl_{cr} 10-30 mL/minute/1.73 m^2: Administer dose every 24-48 hours

Cl_{cr} <10 mL/minute/1.73 m^2: Administer dose every 40-60 hours

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered with or without meals.

StorageStore at room temperature; avoid excessive heat.

ContraindicationsHypersensitivity to bendroflumethiazide, sulfonamide-derived drugs, or any component of the formulation; bronchial asthma; sinus bradycardia; heart block greater than first degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; uncompensated cardiac failure; anuria

Allergy Considerations

- Beta-Blocker Allergy
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Abrupt withdrawal: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

- Electrolyte disturbances: Hypokalemia, hypochloremic alkalosis, and hyponatremia can occur with bendroflumethiazide.

- Photosensitivity: Photosensitization may occur.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.

- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating nadolol.

- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms (eg, diaphoresis, tachycardia). May also reduce insulin secretion in response to hyperglycemia; adjustment of antidiabetic drugs may be necessary.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by bendroflumethiazide.

- Heart failure (HF): Use nadolol with caution in patients with compensated heart failure and monitor for a worsening of the condition. Cardiac failure has occurred in patients without prior history; monitor.

- Hepatic impairment: Use bendroflumethiazide with caution in patients with severe hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypokalemia: Use bendroflumethiazide with caution in patients with hypokalemia; correct before initiating.

- Myasthenia gravis: Use nadolol with caution in patients with myasthenia gravis.

- Peripheral vascular disease (PVD): May precipitate or aggravate symptoms of arterial insufficiency in patients with PVD and Raynaud’s disease; use with caution and monitor for progression of arterial obstruction.

- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.

- Psychiatric disease: Use nadolol with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustments are required. May precipitate azotemia; discontinue or consider withholding if renal impairment occurs.

- Systemic lupus erythematosus (SLE): Bendroflumethiazide can cause SLE exacerbation or activation.

- Thyroid disease: May mask signs of hyperthyroidism (eg, tachycardia). If thyrotoxicosis is suspected, carefully manage and monitor; abrupt withdrawal may exacerbate symptoms of hyperthyroidism or precipitate thyroid storm.

Concurrent drug therapy issues:

- Anesthetic agents: Use nadolol with caution in patients receiving anesthetic agents which decrease myocardial function.

- Calcium channel blockers: Use nadolol with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: **[U.S. Boxed Warning]: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.**

- Appropriate use: Used as a replacement for separate dosing of components or combination when response to single agent is suboptimal; the fixed combination is not indicated for initial treatment of hypertension.

Pregnancy Risk FactorC
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsSee individual agents.
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsSee individual agents.

Test InteractionsBendroflumethiazide may produce false negative results with phentolamine and tyramine; may interfere with phenolsulfonphthalein test; may cause diagnostic interference with electrolyte levels (serum), glucose (serum, urine), and decreased PBI (serum) levels without signs of thyroid disturbance.

Monitoring ParametersAssess weight, fluid status; blood pressure, heart rate; serum electrolytes, BUN, creatinine

Monitoring: Lab TestsSerum electrolytes, BUN, creatinine

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Nadolol 40 mg and bendroflumethiazide 5 mg; nadolol 80 mg and bendroflumethiazide 5 mg

Corzide® 40/5: Nadolol 40 mg and bendroflumethiazide 5 mg [scored]

Corzide® 80/5: Nadolol 80 mg and bendroflumethiazide 5 mg [scored]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Corzide)

40-5 mg (30): $96.99

80-5 mg (30): $82.99

Tablets (Nadolol-Bendroflumethiazide)

40-5 mg (100): $219.99

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsAlso see individual agents.

Bioavailability: Bendroflumethiazide: When used in this combination, bioavailability is increased 30% compared to single agent administration.

Dental Health: Effects on Dental TreatmentNadolol is a nonselective beta-blocker and may enhance the pressor response to epinephrine, resulting in hypertension and bradycardia. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution; epinephrine has interacted with nonselective beta-blockers to result in initial hypertensive episode followed by bradycardia

Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, depression, insomnia, or confusion

Mental Health: Effects on Psychiatric TreatmentBarbiturates may decrease the effects of beta-blockers. Nadolol has been used to treat akathisia; propranolol preferred. Concurrent use with antipsychotics may potentiate antihypertensive effect or antipsychotic blood levels. Use with MAO inhibitors may cause bradycardia. Effects of benzodiazepines may be increased by beta-blockers; monitor for clinical changes. There are rare reports of agranulocytosis with bendroflumethiazide; use caution with clozapine, carbamazepine, and mirtazapine. May decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor.

Index TermsBendroflumethiazide and Nadolol

International Brand NamesCorgaretic (AE, JO, QA, SA); Corgaretic-40 (ZA); Corgaretic-80 (ZA)

Nadolol

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Nadolol may be confused with Mandol®

Corgard® may be confused with Cognex®, Coreg®

Pronunciation(NAY doe lol)

U.S. Brand NamesCorgard®

Canadian Brand NamesAlti-Nadolol; Apo-Nadol®; Corgard®; Novo-Nadolol

Pharmacologic CategoryBeta Blocker, Nonselective

Use: Labeled IndicationsTreatment of hypertension and angina pectoris; prophylaxis of migraine headaches

Use: Unlabeled/InvestigationalPrimary and secondary prophylaxis of variceal hemorrhage

Dosing: Adults

Hypertension, angina: Oral: Initial: 40-80 mg/day, increase dosage gradually by 40-80 mg increments at 3- to 7-day intervals until optimum clinical response is obtained with profound slowing of heart rate. Doses up to 160-240 mg/day in angina and 240-320 mg/day in hypertension may be necessary. Doses as high as 640 mg/day have been used.

Usual dosage range (JNC 7): 40-120 mg once daily

Variceal hemorrhage prophylaxis (unlabeled use) (Garcia-Tsao, 2007): Oral:

Primary prophylaxis: Initial: 40 mg once daily; adjust to maximal tolerated dose. **Note:** Risk factors for hemorrhage include Child-Pugh class B/C or variceal red wale markings on endoscopy.

Secondary prophylaxis: Initial: 40 mg once daily; adjust to maximal tolerated dose

Dosing: ElderlyOral: Initial: 20 mg/day; increase doses by 20 mg increments at 3- to 7-day intervals; usual dosage range: 20-240 mg/day. Adjust for renal impairment.

Dosing: Renal Impairment

Cl_{cr} 31-40 mL/minute: Administer every 24-36 hours or administer 50% of normal dose.

Cl_{cr} 10-30 mL/minute: Administer every 24-48 hours or administer 50% of normal dose.

Cl_{cr} <10 mL/minute: Administer every 40-60 hours or administer 25% of normal dose.

Hemodialysis effects: Moderately dialyzable (20% to 50%) via hemodialysis. Administer dose postdialysis or administer 40 mg supplemental dose. Supplemental dose is not necessary following peritoneal dialysis.

Dosing: Hepatic ImpairmentReduced dose is probably necessary.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsMay be taken without regard to meals.

ContraindicationsHypersensitivity to nadolol or any component of the formulation; bronchial asthma; sinus bradycardia; sinus node dysfunction; heart block greater than first degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; uncompensated cardiac failure

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Boxed warnings:

- Abrupt withdrawal: See “Other warnings/precautions” below.

Concerns related to adverse events:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.

- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.

- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.

- Heart failure (HF): Use with caution in patients with compensated heart failure and monitor for a worsening of the condition (efficacy of nadolol in HF has not been demonstrated).

- Myasthenia gravis: Use with caution in patients with myasthenia gravis.

- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).

- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.

- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustments are required.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents which decrease myocardial function.

- Calcium channel blockers: Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: **[U.S. Boxed Warning]: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.**

Geriatric Considerations Due to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (ie, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20% to 50% in elderly populations. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults. Must adjust dose for renal function.

Pregnancy Risk Factor C

Pregnancy Considerations No data available on crossing the placenta. Beta-blockers have been associated with bradycardia, hypotension, and IUGR; IUGR is probably related to maternal hypertension. Alternative beta-blockers are preferred for use during pregnancy due to limited data and prolonged half-life. Cases of neonatal hypoglycemia have been reported following maternal use of beta-blockers at parturition or during breast-feeding. Monitor breast-fed infant for symptoms of beta-blockade.

Lactation Enters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding Considerations Considered compatible by the AAP. However, monitor the infant for signs of beta-blockade (hypotension, bradycardia, etc) with long-term use.

Adverse Reactions

>10%:

Central nervous system: Drowsiness, insomnia

Endocrine & metabolic: Decreased sexual ability

1% to 10%:

Cardiovascular: Bradycardia, palpitation, edema, CHF, reduced peripheral circulation

Central nervous system: Mental depression

Gastrointestinal: Diarrhea or constipation, nausea, vomiting, stomach discomfort

Respiratory: Bronchospasm

Miscellaneous: Cold extremities

<1% (Limited to important or life-threatening): Arrhythmias, chest pain, confusion (especially in the elderly), depression, dyspnea, hallucinations, headache, leukopenia, nervousness, orthostatic hypotension, thrombocytopenia

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, garlic, yohimbe, ginseng (may worsen hypertension). Avoid natural licorice (causes sodium and water retention and increases potassium loss).

Nursing: Physical Assessment/MonitoringAssess other medications the patient may be taking for effectiveness and interactions. Assess blood pressure and heart rate prior to and following first dose, any change in dosage, and periodically thereafter. Monitor or advise patient to monitor weight and fluid balance, assess for signs of CHF, and assess therapeutic effectiveness. Monitor serum glucose levels of patients with diabetes since beta-blockers may alter glucose tolerance. Use/teach postural hypotension precautions.

Patient EducationCheck pulse daily prior to taking medication. If pulse is <50, hold medication and consult prescriber. Take exactly as directed; do not adjust dosage or discontinue without consulting prescriber. May cause dizziness, fatigue, blurred vision; change position slowly (lying/sitting to standing) and use caution when driving or engaging in tasks that require alertness until response to drug is known. Exercise and increasing bulk or fiber in diet may help resolve constipation. If you have diabetes, monitor serum glucose closely (the drug may mask symptoms of hypoglycemia). Report swelling in feet or legs, respiratory difficulty or persistent cough, unresolved fatigue, unusual weight gain >5 lb/week, or unresolved constipation. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: 20 mg, 40 mg, 80 mg

Corgard®: 20 mg, 40 mg, 80 mg, 120 mg [DSC], 160 mg [DSC]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Corgard)

20 mg (30): $87.19

40 mg (30): $97.12

80 mg (30): $103.90

120 mg (30): $99.99

160 mg (30): $113.99

Tablets (Nadolol)

20 mg (30): $11.99

40 mg (30): $15.99

80 mg (30): $19.99

160 mg (30): $33.59

Mechanism of ActionCompetitively blocks response to beta$_1$- and beta$_2$-adrenergic stimulation; does not exhibit any membrane stabilizing or intrinsic sympathomimetic activity. Nonselective beta-adrenergic blockers (propranolol, nadolol) reduce portal pressure by producing splanchnic vasoconstriction (beta$_2$ effect) thereby reducing portal blood flow.
Pharmacodynamics/Kinetics

Duration: 17-24 hours

Absorption: 30% to 40%

Distribution: Concentration in human breast milk is 4.6 times higher than serum

Protein binding: 28%

Half-life elimination: Adults: 10-24 hours; prolonged with renal impairment; End-stage renal disease: 45 hours

Time to peak, serum: 2-4 hours

Excretion: Urine (as unchanged drug)

Related Information

- Beta-Blockers

Dental Health: Effects on Dental TreatmentNadolol is a nonselective beta-blocker and may enhance the pressor response to epinephrine, resulting in hypertension and bradycardia. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution; epinephrine has interacted with nonselective beta-blockers to result in initial hypertensive episode followed by bradycardia
Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, depression, insomnia, or confusion
Mental Health: Effects on Psychiatric TreatmentBarbiturates may decrease the effects of beta-blockers; has been used to treat akathisia; propranolol preferred; concurrent use with antipsychotics may potentiate antihypertensive effect or antipsychotic blood levels; use with MAO inhibitors may cause bradycardia; effects of benzodiazepines may be increased by beta-blockers; monitor for clinical changes
Cardiovascular ConsiderationsNadolol is a nonspecific beta$_1$- and beta$_2$-blocker.

Atrial Fibrillation: Beta-blocker therapy provides effective rate control in patients with atrial fibrillation.

Chronic Stable Angina: Beta-blockers are effective in the treatment of chronic stable angina as monotherapy or when combined with nitrates and/or calcium channel blockers. In patients with severe intractable angina requiring negative cardiac chronotropic medications, pacemaker placement has been carried out to maintain heart rate in the setting of large doses of beta-blockers and/or calcium channel blockers. Beta-blockers are ineffective in the treatment of pure vasospastic (Prinzmetal) angina.

Hypertension: Beta-blocker therapy in the treatment of hypertension has been associated with improved cardiovascular outcomes. According to the 2003 JNC-VII guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists that requires the use of other drugs, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Beta-blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for a beta-blocker include patients with heart failure, postmyocardial infarction, high coronary disease risk, or diabetes. In type 2 diabetic patients, a UK Prospective Diabetes Study Group (UKPDS) trial showed that beta-blocker therapy (atenolol) was as effective as an ACE inhibitor in reducing cardiovascular events and that the benefits of therapy were related more to the degree of antihypertensive efficacy rather than the class of drug used.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

ST-Segment Elevation Myocardial Infarction (STEMI): Beta-blockers, without intrinsic sympathomimetic activity (ISA), have been shown to decrease morbidity and mortality when initiated in the acute treatment of STEMI and continued long-term. Oral beta-blockade should be initiated promptly in patients without contraindications (eg, signs of heart failure, evidence of a low output state, risk of cardiogenic shock, or other beta-blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade may be considered and given promptly if the patient is experiencing concomitant hypertension or a tachyarrhythmia (Class IIa recommendation).

Unstable Angina/Non-ST-Segment Elevation MI (UA/NSTEMI): In the treatment of UA/NSTEMI, oral beta-blockade should be initiated within the first 24 hours in patients without contraindications (eg, signs of heart failure, evidence of a low output state, risk of cardiogenic shock, or other beta-blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade should only be considered if the patient is experiencing concomitant hypertension upon presentation (Class IIa recommendation).

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia and hypertension.

Anesthesia and Critical Care Concerns/Other Considerations**Surgery:** Based on available evidence, beta-blockers should be started days to weeks before elective surgery in selected patients when possible and titrated to a heart rate <65 beats per minute. Additional data suggest that long acting beta-blockers may be superior to short acting ones (Redelmeier, 2005). The ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery recommend beta-blockers be continued in patients undergoing surgery who are receiving beta-blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA Class I guideline indications (Class I recommendation). The guidelines also recommend that beta-blockers be given to patients undergoing vascular surgery who have myocardial ischemia demonstrated during preoperative testing (Class I recommendation).

The guidelines also state that beta-blockers are probably recommended in patients undergoing intermediate risk (eg, carotid endarterectomy, prostate surgery) or vascular surgery in whom preoperative assessment identifies coronary heart disease or high cardiac risk (Class IIa recommendation). High cardiac risk is defined as having >1 of the following clinical risk factors: History of ischemic heart disease, compensated or prior heart failure, cerebrovascular disease, diabetes mellitus, or renal insufficiency. The use of beta-blockers is uncertain in patients undergoing intermediate risk or vascular surgery with ≤1 clinical risk factor (Class IIb recommendation).

The majority of published trials suggest a benefit of perioperative beta-blocker use during noncardiac surgery especially in high-risk patients; however, more recent clinical trials have not shown a benefit to perioperative beta-blockade for noncardiac surgery (Jul, 2006; Yang, 2006).

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International Brand NamesAnabet (PT); Apo-Nadol (PL); Apo-Nadolol (NZ); Corgard (AR, BB, BE, BM, BR, BS, BZ, CH, CL, CN, CO, CZ, ES, FR, GB, GY, IE, IT, JM, KE, LU, MX, MY, NG, NL, NZ, PE, PH, PK, RU, SR, TR, TT, TW, TZ, UG, UY, VE, ZA, ZM); Farmagard (ID); Solgol (AT, DE, ES)

Nadroparin

Lexi-Drugs Online

English

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(nad roe PA rin)
Canadian Brand NamesFraxiparine™; Fraxiparine™ Forte
Pharmacologic CategoryLow Molecular Weight Heparin
Use: Labeled IndicationsProphylaxis of thromboembolic disorders (particularly deep venous thrombosis and pulmonary embolism) in general and orthopedic surgery; treatment of deep venous thrombosis; prevention of clotting during hemodialysis
Dosing: Adults

Prophylaxis of thromboembolic disorders:

General surgery: SubQ: 2850 anti-Xa int. units; begin 2-4 hours before surgery and continue for 7 days

Hip replacement surgery: SubQ: 38 anti-Xa int. units/kg 12 hours before and 12 hours after surgery, **followed by** 38 anti-Xa int. units/kg/day up to and including day 3, **then** 57 anti-Xa int. units/kg/day for up to 10 days total therapy

Treatment of thromboembolic disorders: SubQ: 171 anti-Xa int. units/kg/day to a maximum of 17,100 int. units; plasma anti-Xa levels should be 1.2-1.8 anti-Xa int. units/mL 3-4 hours postinjection

Patients at increased risk of bleeding: 86 anti-Xa int. units/kg twice daily; plasma anti-Xa levels should be 0.5-1.1 anti-Xa int. units/mL 3-4 hours postinjection

Prevention of clotting during hemodialysis: SubQ: Single dose of 65 anti-Xa int. units/kg into arterial line at start of each dialysis session; may give additional dose if session lasts longer than 4 hours

Patients at risk of hemorrhage: Administer 50% of dose

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentReduced dosage is recommended.
Administration: I.M.Do not administer I.M.
Administration: OtherSubQ injection into anterolateral abdominal wall with subsequent doses to be administered alternately on right and left side of abdominal wall. The thigh may also be used.
StorageStore between 15°C to 30°C (59°F to 86°F); do not freeze or refrigerate.
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to nadroparin or any component of the formulation; acute infective endocarditis; hemorrhage or increased risk of hemorrhage (hemostasis disorder), except for disseminated intravascular coagulation (DIC) not induced by heparin; history of thrombocytopenia with nadroparin; organic lesions likely to bleed (active peptic ulceration); hemorrhagic cerebrovascular event; severe uncontrolled hypertension; diabetic or hemorrhagic retinopathy; injuries to or operations on the CNS, eyes, or ears. Not for I.M. administration.
Allergy Considerations

- Low Molecular Weight Heparin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: Monitor patient closely for signs or symptoms of bleeding. Certain patients are at increased risk of bleeding. Risk factors include bacterial endocarditis; congenital or acquired bleeding disorders; active ulcerative or angiodysplastic GI diseases; severe uncontrolled hypertension; hemorrhagic stroke; or use shortly after brain, spinal, or ophthalmology surgery; in patient treated concomitantly with platelet inhibitors; recent GI bleeding; thrombocytopenia or platelet defects; severe liver disease; hypertensive or diabetic retinopathy; or in patients undergoing invasive procedures. Discontinue if bleeding occurs.

- Hyperkalemia: Monitor for hyperkalemia. Heparin can cause hyperkalemia by affecting aldosterone; similar reactions could occur with LMWHs.

- Thrombocytopenia: Rare cases of thrombocytopenia have occurred. Use with caution in patients with history of heparin-induced thrombocytopenia; monitor platelet count closely. Consider discontinuation of therapy in any patient developing significant thrombocytopenia. Rare cases of thrombocytopenia with thrombosis have occurred. Use caution in patients with congenital or drug-induced thrombocytopenia or platelet defects.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with severe hepatic disease.

- Renal impairment: Use with caution in patients with severe renal disease.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: Do not use when abortion is imminent or threatened.

Other warnings/precautions:

- Conversion to other products: Not to be used interchangeably (unit for unit) with heparin or any other low molecular weight heparins.
- Neuraxial anesthesia: Patients with recent or anticipated neuraxial anesthesia (epidural or spinal anesthesia) are at risk of spinal or epidural hematoma and subsequent paralysis. Consider risk versus benefit prior to neuraxial anesthesia; risk is increased by concomitant agents which may alter hemostasis, as well as traumatic or repeated epidural or spinal puncture. Patient should be observed closely for bleeding and signs and symptoms of neurological impairment if therapy is administered during or immediately following diagnostic lumbar puncture, epidural anesthesia, or spinal anesthesia.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAnimal and human reports have not shown any teratogenic of fetotoxic effects. Data concerning transplacental passage is limited, but has not been detected.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Dermatologic: Rash

Endocrine & metabolic: Hypoaldosteronism (causing hyperkalemia and/or hyponatremia)

Hematological: Bleeding, thrombocytopenia

Hepatic: ALT increased, AST increased

Local: Injection site hematoma, pain at injection site

Neuromuscular & skeletal: Osteopenic effects

Miscellaneous: Allergic reactions

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Drotrecogin Alfa: Heparin (Low Molecular Weight) may enhance the adverse/toxic effect of Drotrecogin Alfa. This is of most concern with therapeutic doses of LMW heparin. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid cat's claw, dong quai, evening primrose, garlic, ginseng (all have anticoagulant or antiplatelet activity).

Monitoring ParametersBleeding complications including stool occult blood tests, hemoglobin, antifactor Xa determinations, platelet counts

Monitoring: Lab TestsBleeding complications including stool occult blood tests, hemoglobin, antifactor Xa determinations, platelet counts

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, solution, as calcium:

Fraxiparine™ [CAN]:

9500 anti-Xa int. units/mL (0.2 mL, 0.3 mL, 0.4 mL) [ungraduated prefilled syringe]

9500 anti-Xa int. units/mL (0.6 mL, 0.8 mL, 1 mL) [graduated prefilled syringe]

Fraxiparine™ Forte [CAN]: 19,000 anti-Xa int. units/mL (0.6 mL, 0.8 mL, 1 mL) [graduated prefilled syringe]

Generic AvailableNo
ManufacturerAventis Pharma (Canada)
Mechanism of ActionNadroparin has high anti-Xa activity, but low anti-IIa activity. The greater ratio of anti-Xa activity has the potential to provide equivalent antithrombic efficacy with reduced hemorrhagic complications.
Pharmacodynamics/Kinetics

Duration: 18 hours

Absorption: SubQ: ≥89%

Time to peak, serum: 3-5 hours

Half-life elimination: 3.5 hours; Renal impairment: 6 hours

Excretion: Urine

Pharmacotherapy PearlsNot available in U.S.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentMay cause thrombocytopenia; concomitant use with valproic acid may increase the risk; monitor
Cardiovascular ConsiderationsLow molecular weight heparins (LMWHs) compare favorably to unfractionated heparin (UFH) in the prevention and treatment of venous thromboembolism. LMWHs are associated with less thrombocytopenia, compared to heparin, and do not require routine therapeutic monitoring. The role of nadroparin in the treatment of acute coronary syndromes is not established.

Obesity/Renal Dysfunction: There is no consensus for adjusting/correcting the weight-based dosage of LMWH for patients who are morbidly obese. Monitoring of antifactor Xa concentration 4 hours after injection may be warranted. Patients who have a reduction in calculated creatinine clearance are at risk of accumulated anticoagulant effect when they are treated with certain LMWHs. All LMWHs may not behave the same in patients with renal dysfunction. Some clinicians monitor anti-Xa levels for patients with Cl_{cr} <30 mL/minute.

Index TermsNadroparin Calcium
References

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International Brand NamesFraxiparin (AT, DE, DO, GT, HN, NI, PA, SV); Fraxiparina (BR, ES, IT, PT, VE); Fraxiparine (AR, AU, BE, BG, CH, CL, CN, CZ, EC, EE, FI, FR, GR, HK, HN, HR, HU, ID, IL, IN, KP, LU, MX, MY, NL, NO, NZ, PH, PK, PL, PY, SE, SG, TH, TW, UY); Fraxiparine Forte (PH, TH); Fraxiparine TX (CO, CR, MX, PE, UY); Fraxodi (BE, GR, PL); Seleparina (IT)

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Nafarelin may be confused with Anafranil®, enalapril

Pronunciation(naf a REL in)

U.S. Brand NamesSynarel®

Canadian Brand NamesSynarel®

Pharmacologic CategoryGonadotropin Releasing Hormone Agonist

Use: Labeled IndicationsTreatment of endometriosis, including pain and reduction of lesions; treatment of central precocious puberty (CPP; gonadotropin-dependent precocious puberty) in children of both sexes

Dosing: Adults**Endometriosis:** Intranasal: Female: 1 spray (200 mcg) in 1 nostril each morning and the other nostril each evening starting on days 2-4 of menstrual cycle (total: 2 sprays/day). Dose may be increased to 2 sprays (400 mcg; 1 spray in each nostril) in the morning and evening if amenorrhea is not achieved (total: 8 sprays [1600 mcg]/day). Total duration of therapy should not exceed 6 months due to decreases in bone mineral density; retreatment is not recommended by the manufacturer.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Central precocious puberty:** Intranasal: Male/Female: 2 sprays (400 mcg) into each nostril in the morning and 2 sprays (400 mcg) into each nostril in the evening (total: 8 sprays [1600 mcg]/day). If inadequate suppression, may increase dose to 3 sprays (600 mcg) into alternating nostrils 3 times/day (total: 9 sprays [1800 mcg]/day).

Administration: InhalationNasal spray: Do not use topical nasal decongestant for at least 2 hours after nafarelin use. Allow ~30 seconds to elapse between sprays. Sneezing during or immediately after dosing should be avoided (may decrease drug absorption).

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

ContraindicationsHypersensitivity to gonadotropin-releasing hormone (GnRH), GnRH-agonist analogs, or any component of the formulation; undiagnosed abnormal vaginal bleeding; pregnancy; breast-feeding

Allergy Considerations

- GnRH Agonist Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Ovarian cysts: May occur within the first 2 months of therapy and may occur more commonly in women with polycystic ovarian disease.

Disease-related concerns:

- CPP use: When used for the treatment of CPP, some signs of puberty (eg vaginal bleeding, breast enlargement) may occur but should resolve within the first 2 months of therapy.

- Decreased bone mineral density: Use with caution in patients with risk factors for decreased bone mineral density; may pose an additional risk.

Pregnancy Risk FactorX

Pregnancy ConsiderationsMajor fetal abnormalities have been reported in some animal studies; a dose-related increase in fetal mortality and decrease in fetal weight was also observed. Ovulation is inhibited and menstruation is stopped when used appropriately for the treatment of endometriosis, however contraception is not assured. Nonhormonal contraception is recommended. Pregnancy should be excluded prior to initiating treatment. There is no evidence that pregnancy rates are enhanced or adversely affected by use.

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions**Note:** Adverse events may be more frequent in the first 6 weeks of treatment due to stimulation of the pituitary-gonadal axis. Sensitivity reactions included chest pain, pruritus, shortness of breath, rash.

CPP: 1% to 10%:

Central nervous system: Emotional lability (6%)

Dermatologic: Acne (10%), seborrhea (3%)

Endocrine & metabolic: Breast enlargement (8%; transient), vaginal bleeding (8%), hot flashes (3%; transient), vaginal discharge (3%)

Respiratory: Rhinitis (5%)

Miscellaneous: Pubic hair increased (5%; transient), body odor (4%), sensitivity reactions (3%)

Endometriosis:

- >10%:
  - Central nervous system: Headache, emotional lability
  - Dermatologic: Acne
  - Endocrine & metabolic: Hot flashes (90%), hyperphosphatemia, hypertriglyceridemia, hypocalcemia, libido decreased
  - Genitourinary: Vaginal dryness
  - Hematologic: Leukopenia
- 1% to 10%:
  - Cardiovascular: Edema
  - Central nervous system: Depression, insomnia
  - Dermatologic: Hirsutism, seborrhea
  - Endocrine & metabolic: Breast size reduced, cholesterol increased, hyperlipidemia, libido increased
  - Gastrointestinal: Weight gain/loss
  - Neuromuscular & skeletal: Bone mineral density decreased, myalgia
  - Respiratory: Nasal irritation

<1%: Arthralgia, breast engorgement, chloasma, eye pain, lactation, maculopapular rash, palpitation, paresthesia, sensitivity reactions, weakness

Postmarketing and/or case reports (any indication): ALT increased, AST increased, pituitary apoplexy, pituitary gland changes

Drug Interactions

Antidiabetic Agents: Luteinizing Hormone-Releasing Hormone Analogs may diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Test InteractionsDiagnostic tests of pituitary gonadotropic and gonadal functions during and up to 4-8 weeks after discontinuing treatment may be misleading.

Monitoring Parameters

CPP: Bone mineral density, GnRH testing (blood LH and FSH levels), measurement of bone age, Tanner staging

Endometriosis: Menstruation, vaginal bleeding or spotting which persists after 2 months of treatment

Nursing: Physical Assessment/MonitoringFor treatment of precocious puberty, consult appropriate pediatric reference. Assess therapeutic effectiveness and adverse response. Teach patient (caregiver) proper use (correct timing and administration of nasal spray), possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that female patient is not pregnant before beginning therapy. Do not give to childbearing age female unless capable of complying with contraceptive use.

Monitoring: Lab TestsCPP: GnRH testing (blood LH and FSH levels)

Patient EducationEndometriosis: You will begin this treatment between days 2-4 of your regular menstrual cycle. Use as directed, daily at the same time (arising and bedtime), and rotate nostrils. Maintain regular follow-up schedule. May cause hot flashes, flushing, or redness (cold cloth and cool environment may help); decreased or increased libido; emotional lability; weight gain; decreased breast size; or hirsutism. Report any breakthrough bleeding or continuing menstruation or musculoskeletal pain. Do not use a nasal decongestant within 2 hours after nafarelin. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for instruction on appropriate contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, intranasal [spray]:

- Synarel®: 2 mg/mL (8 mL) [200 mcg/spray: 60 metered sprays; contains benzalkonium chloride]

Generic AvailableNo

ManufacturerSearle

Pricing: U.S. (www.drugstore.com)

Solution (Synarel)

- 2 mg/mL (8): $948.26

Mechanism of ActionPotent synthetic decapeptide analogue of gonadotropin-releasing hormone (GnRH; LHRH) which is approximately 200 times more potent than GnRH in terms of pituitary release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Effects on the pituitary gland and sex hormones are dependent upon its length of administration. After acute administration, an initial stimulation of the release of LH and FSH from the pituitary is observed; an increase in androgens and estrogens subsequently follows. Continued administration of nafarelin, however, suppresses gonadotrope responsiveness to endogenous GnRH resulting in reduced secretion of LH and FSH and, secondarily, decreased ovarian and testicular steroid production.

Pharmacodynamics/Kinetics

Protein binding, plasma: 80%

Metabolism: Degraded by peptidase; forms metabolites

Bioavailability: ~1% to 6%

Half-life elimination: ~3 hours; Metabolites: ~86 hours

Time to peak, serum: 10-45 minutes

Excretion: Urine (44% to 55%, ~3% as unchanged drug); feces (19% to 44%)

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Emotional lability is common; may cause insomnia

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Nafarelin Acetate

References

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Tahara M, Matsuoka T, Yokoi T, et al, "Treatment of Endometriosis With a Decreasing Dosage of a Gonadotropin-Releasing Hormone Agonist (Nafarelin): A Pilot Study With Low-Dose Agonist Therapy ("Draw-Back" Therapy)," *Fertil Steril*, 2000, 73(4):799-804.[PubMed 10731543]

International Brand Names Nasanyl (JP); Nasarel (IN); Synarel (AU, BE, BF, BG, BJ, BR, CI, CZ, DE, ES, ET, FR, GB, GH, GM, GN, GR, HN, HU, IE, KE, LR, LU, MA, ML, MR, MU, MW, MX, NE, NG, NL, PL, PT, RU, SC, SD, SL, SN, TN, TW, TZ, UG, ZA, ZM, ZW); Synarela (DK, FI, NO, SE); Synrelin (AR); Synrelina (CH)

Nafcillin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(naf SIL in)

Canadian Brand NamesNallpen®; Unipen®

Pharmacologic CategoryAntibiotic, Penicillin

Use: Labeled IndicationsTreatment of infections such as osteomyelitis, septicemia, endocarditis, and CNS infections caused by susceptible strains of staphylococci species

Dosing: Adults

Susceptible infections:

I.M.: 500 mg every 4-6 hours

I.V.: 500-2000 mg every 4-6 hours

Endocarditis: MSSA:

Native valve: I.V.: 12 g/24 hours in 4-6 divided doses for 6 weeks

Prosthetic valve: I.V.: 12 g/24 hours in 6 divided doses for ≥6 weeks (use with rifampin and gentamicin)

Joint:

Bursitis, septic: I.V.: 2 g every 4 hours

Prosthetic: I.V.: 2 g every 4-6 hours with rifampin for 6 weeks

***Staphylococcus aureus,*methicillin-susceptible infections, including brain abscess, empyema, erysipelas, mastitis, myositis, orbital cellulitis, osteomyelitis, pneumonia, splenic abscess, toxic shock, urinary tract (perinephric abscess):** I.V.: 2 g every 4 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Neonates:

Usual dosage range: I.M., I.V.:

1200-2000 g, <7 days: 50 mg/kg/day divided every 12 hours

>2000 g, <7 days: 75 mg/kg/day divided every 8 hours

1200-2000 g, ≥7 days: 75 mg/kg/day divided every 8 hours

>2000 g, ≥7 days: 100-140 mg/kg/day divided every 6 hours

Children:

I.M.: 25 mg/kg twice daily

I.V.:

Mild-to-moderate infections: 50-100 mg/kg/day in divided doses every 6 hours

Severe infections: 100-200 mg/kg/day in divided doses every 4-6 hours (maximum: 12 g/day)

Staphylococcal endocarditis:

Native valve: 200 mg/kg/day in divided doses every 4-6 hours for 6 weeks

Prosthetic valve: 200 mg/kg/day in divided doses every 4-6 hours for ≥6 weeks (use with rifampin and gentamicin)

Dosing: Renal ImpairmentNot necessary unless renal impairment is in the setting of concomitant hepatic impairment.

Hemodialysis effects: Not dialyzable (0% to 5%) via hemodialysis. Supplemental dose is not necessary with hemo- or peritoneal dialysis or continuous arteriovenous or venovenous hemofiltration.

Dosing: Hepatic ImpairmentIn patients with both hepatic and renal impairment, modification of dosage may be necessary; no data available.

Administration: I.M.Rotate injection sites.

Administration: I.V.Vesicant. Administer around-the-clock to promote less variation in peak and trough serum levels. Infuse over 30-60 minutes.

Administration: I.V. Detail**Extravasation management:** Use cold packs.

Hyaluronidase: Add 1 mL NS to 150 unit vial to make 150 units/mL of concentration; mix 0.1 mL of above with 0.9 mL NS in 1 mL syringe to make final concentration = 15 units/mL.

pH: 6.0-8.5

Dietary ConsiderationsPremixed injection may contain corn-derived dextrose and its use is contraindicated in patients with allergy to corn-related products. Sodium content of 1 g: 76.6 mg (3.33 mEq).

Storage

Premixed infusions: Store in a freezer at -20°C (4°F). Thaw at room temperature or under refrigeration only. Thawed bags are stable for 21 days under refrigeration or 72 hours at room temperature. Do not refreeze.

Vials: Reconstituted parenteral solution is stable for 3 days at room temperature and 7 days when refrigerated or 12 weeks when frozen. For I.V. infusion in NS or D_5W, solution is stable for 24 hours at room temperature and 96 hours when refrigerated.

CompatibilityStable in dextran 40 10% in dextrose, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}NS$, $D_{10}W$, LR, NS; **variable stability (consult detailed reference)** in peritoneal dialysis solution, TPN.

Y-site administration: Compatible: Acyclovir, atropine, cyclophosphamide, diazepam, enalaprilat, esmolol, famotidine, fentanyl, fluconazole, foscarnet, heparin, hydromorphone, magnesium sulfate, morphine, nicardipine, perphenazine, propofol, theophylline, zidovudine. **Incompatible:** Droperidol, fentanyl and droperidol, insulin (regular), labetalol, midazolam, nalbuphine, pentazocine, verapamil. **Variable (consult detailed reference):** Diltiazem, meperidine, TPN, vancomycin.

Compatibility in syringe: Compatible: Cimetidine, heparin.

Compatibility when admixed: Compatible: Chloramphenicol, chlorothiazide, dexamethasone sodium phosphate, diphenhydramine, ephedrine, heparin, hydroxyzine, lidocaine, potassium chloride, prochlorperazine edisylate, sodium bicarbonate, sodium lactate. **Incompatible:** Ascorbic acid injection, aztreonam, bleomycin, cytarabine, gentamicin, hydrocortisone sodium succinate, methylprednisolone sodium succinate, promazine. **Variable (consult detailed reference):** Aminophylline, verapamil, vitamin B complex with C.

ContraindicationsHypersensitivity to nafcillin, or any component of the formulation, or penicillins; premixed injection may contain corn-derived dextrose and its use is contraindicated in patients with allergy to corn-related products

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hepatic/renal impairment: Use with caution in patients with concomitant hepatic and renal impairment; dosage adjustment recommended.

Special populations:

- Neonates: Use with caution in neonates; elimination of drug is slow.

Other warnings/precautions:

- Extravasation: Avoid extravasation of I.V. infusions.

Geriatric ConsiderationsNafcillin has not been studied exclusively in the elderly, however, given its route of elimination, dosage adjustments based upon age and renal function is not necessary

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, nafcillin is classified as pregnancy category B. There is no available data on the placental transfer of nafcillin. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsIt is not known if nafcillin crosses into human milk. The manufacturer recommends that caution be exercised when administering nafcillin to nursing women. Other penicillins distribute into human milk and are considered safe for use during breast-feeding. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Nafcillin in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Neurotoxicity (high doses)

Gastrointestinal: Pseudomembranous colitis

Hematologic: Agranulocytosis, bone marrow depression, neutropenia

Local: Inflammation, pain, phlebitis, skin sloughing, swelling, and thrombophlebitis at the injection site; oxacillin (less likely to cause phlebitis) is often preferred in pediatric patients; tissue necrosis with sloughing (SubQ extravasation)

Renal: Interstitial nephritis (rare), renal tubular damage (rare)

Miscellaneous: Anaphylaxis, hypersensitivity reactions (immediate and delayed; general incidence of 1% to 10% for penicillins), serum sickness

Oncology: VesicantYes; see Management of Drug Extravasations.
Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Induces** CYP3A4 (strong)
Drug Interactions

Calcium Channel Blockers: Nafcillin may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CycloSPORINE: Nafcillin may increase the metabolism of CycloSPORINE. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Nafcillin may increase the metabolism of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Nafcillin may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Test InteractionsPositive Coombs' test (direct), false-positive urinary and serum proteins; may inactivate aminoglycosides *in vitro*
Monitoring ParametersBaseline and periodic CBC with differential; periodic urinalysis, BUN, serum creatinine, AST and ALT; observe for signs and symptoms of anaphylaxis during first dose
Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and allergy history prior to starting therapy. Assess potential for interactions with other pharmacological agents patient may be taking (eg, increased [toxic] or decreased [subtherapeutic] levels/effects. Infusion/Injection site must be monitored closely to prevent extravasation (use ice packs). Assess for therapeutic effect (resolution of infection) and adverse reactions (eg, hypersensitivity, opportunistic infection [eg, fever, chills, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge, fatigue)]. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.
Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating drug therapy. Monitor renal, hepatic, CBC with prolonged therapy.
Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by infusion or injection. Report immediately any redness, swelling, burning, or pain at injection/infusion site; respiratory difficulty or swallowing; chest pain; persistent diarrhea; or rash. May cause nausea (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or opportunistic infection (eg, fever, chills, sore throat, burning urination, fatigue). Report persistent side effects or if condition does not respond to treatment. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed iso-osmotic dextrose solution]: 1 g (50 mL); 2 g (100 mL)

Injection, powder for reconstitution, as sodium: 1 g, 2 g, 10 g

Generic AvailableYes
Mechanism of ActionInterferes with bacterial cell wall synthesis during active multiplication, causing cell wall death and resultant bactericidal activity against susceptible bacteria
Pharmacodynamics/Kinetics

Distribution: Widely distributed; CSF penetration is poor but enhanced by meningeal inflammation

Protein binding: ~90%; primarily to albumin

Metabolism: Primarily hepatic; undergoes enterohepatic recirculation

Half-life elimination:

Neonates: <3 weeks: 2.2-5.5 hours; 4-9 weeks: 1.2-2.3 hours

Children 3 months to 14 years: 0.75-1.9 hours

Adults: Normal renal/hepatic function: 30-60 minutes

Time to peak, serum: I.M.: 30-60 minutes

Excretion: Primarily feces; urine (10% to 30% as unchanged drug)

Related Information

- Antibiotic Treatment of Adults With Infective Endocarditis
- Community-Acquired Pneumonia in Adults
- Skin Tests

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Prolonged use of penicillins may lead to the development of oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusPenicillins reported to cause apprehension, illusions, hallucinations, depersonalization, agitation, insomnia, and encephalopathy

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine

Index TermsEthoxynaphthamido Penicillin Sodium; Nafcillin Sodium; Nallpen; Sodium Nafcillin

References

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Naftifine

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English

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Pronunciation(NAF ti feen)

U.S. Brand NamesNaftin®

Pharmacologic CategoryAntifungal Agent, Topical

Use: Labeled IndicationsTopical treatment of tinea cruris (jock itch), tinea corporis (ringworm), and tinea pedis (athlete's foot)

Dosing: Adults**Tinea infection:** Topical: Apply cream once daily and gel twice daily (morning and evening) for up to 4 weeks

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to naftifine or any component of the formulation

Allergy Considerations

- Allylamine Antifungal Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue if sensitivity or irritation occurs

Special population:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: For topical use only; avoid contact with eyes, nose, mouth, or mucous membranes.

Geriatric ConsiderationsNo specific recommendations for use in the elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic events were not observed in animal studies.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Dermatologic: Burning/stinging (5% to 6%), erythema (≤2%), pruritus (1% to 2%)

Local: Dryness (3%), irritation (2%)

<1%: Rash, skin tenderness

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, as hydrochloride:

Naftin®: 1% (15 g, 30 g, 60 g, 90 g) [contains benzyl alcohol]

Gel, as hydrochloride:

Naftin®: 1% (20 g, 40 g, 60 g, 90 g) [contains alcohol 52%]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Cream (Naftin)

1% (30): $79.08

1% (60): $129.25

Gel (Naftin)

1% (20): $68.90

1% (40): $118.78

1% (60): $154.44

Mechanism of ActionSynthetic, broad-spectrum antifungal agent in the allylamine class; appears to have both fungistatic and fungicidal activity. Exhibits antifungal activity by selectively inhibiting the enzyme squalene epoxidase in a dose-dependent manner which results in a reduced synthesis of ergosterol, the primary sterol within the fungal membrane.

Pharmacodynamics/Kinetics

Absorption: Systemic: Cream: 6%; Gel: ≤4%

Half-life elimination: 2-3 days

Excretion: Urine and feces (as unchanged drug and/or metabolites)

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Naftifine Hydrochloride

International Brand Names Exoderil (AE, AT, BG, BH, CY, CZ, DE, EE, EG, GR, HK, HN, ID, IL, IQ, IR, JO, KP, KW, LB, LY, MY, OM, PK, PL, QA, RU, SA, SY, TR, TW, YE); Fetimin (HR); Jia Mei (TW); Micosona (ES); Suadian (IT)

Nalbuphine

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English

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Nubain® may be confused with Navane®, Nebcin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(NAL byoo feen)

U.S. Brand NamesNubain®

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled IndicationsRelief of moderate to severe pain; preoperative analgesia, postoperative and surgical anesthesia, and obstetrical analgesia during labor and delivery

Use: Unlabeled/InvestigationalOpioid-induced pruritus

Dosing: Adults

Pain management: I.M., I.V., SubQ: 10 mg/70 kg every 3-6 hours; maximum single dose in nonopioid-tolerant patients: 20 mg; maximum daily dose: 160 mg

Surgical anesthesia supplement: I.V.: Induction: 0.3-3 mg/kg over 10-15 minutes; maintenance doses of 0.25-0.5 mg/kg may be given as required

Opioid-induced pruritus (unlabeled use): I.V. 2.5-5 mg; may repeat dose

Dosing: ElderlyRefer to adult dosing; use with caution.

Dosing: Pediatric**Pain management (unlabeled use):** Children ≥1 year: I.M., I.V., SubQ: 0.1-0.2 mg/kg every 3-4 hours as needed; maximum: 20 mg/dose and/or 160 mg/day

Dosing: Renal ImpairmentUse with caution and reduce dose. Monitor.

Dosing: Hepatic ImpairmentUse with caution and reduce dose.

Calculations

- Opioid Agonist Conversion

Administration: I.V. DetailpH: 3.5-3.7 (adjusted)

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

CompatibilityStable in D_5NS, $D_{10}W$, LR, NS.

Y-site administration: Compatible: Amifostine, aztreonam, cisatracurium, cladribine, etoposide, filgrastim, fludarabine, gatifloxacin, gemcitabine, granisetron, linezolid, melphalan, paclitaxel, propofol, remifentanil, teniposide, thiotepa, vinorelbine. **Incompatible:** Allopurinol, amphotericin B cholesteryl sulfate complex, cefepime, docetaxel, ketorolac, methotrexate, nafcillin, piperacillin/tazobactam, sargramostim, sodium bicarbonate.

Compatibility in syringe: Compatible: Atropine, cimetidine, diphenhydramine, droperidol, glycopyrrolate, hydroxyzine, lidocaine, midazolam, prochlorperazine edisylate, ranitidine, scopolamine, trimethobenzamide. **Incompatible:** Diazepam, ketorolac, pentobarbital. **Variable (consult detailed reference):** Promethazine, thiethylperazine.

Compatibility when admixed: Variable (consult detailed reference): Promethazine.

ContraindicationsHypersensitivity to nalbuphine or any component of the formulation

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.

- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.

- CNS depression/coma: Use with caution in patients with CNS depression or coma.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Hepatic impairment: Use with caution in patients with decreased hepatic function.

- Obesity: Use with caution in patients who are morbidly obese.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Renal impairment: Use with caution in patients with decreased renal function.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: Use with caution in pregnancy; close neonatal monitoring required when used in labor and delivery.

Other warnings/precautions:

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsThe elderly may be particularly susceptible to CNS effects; monitor closely.
Pregnancy Risk FactorB/D (prolonged use or high doses at term)
Pregnancy ConsiderationsSevere fetal bradycardia has been reported following use in labor/delivery. Fetal bradycardia may occur when administered earlier in pregnancy (not documented). Use only if clearly needed, with monitoring to detect and manage possible adverse fetal effects. Naloxone has been reported to reverse bradycardia. Newborn should be monitored for respiratory depression or bradycardia following nalbuphine use in labor.
LactationEnters breast milk/use caution
Adverse Reactions

>10%: Central nervous system: Sedation (36%)

1% to 10%:

Central nervous system: Dizziness (5%), headache (3%)

Gastrointestinal: Nausea/vomiting (6%), xerostomia (4%)

Miscellaneous: Clamminess (9%)

<1%: Anaphylaxis, anaphylactoid reaction, asthma, bitter taste, blurred vision, bradycardia, cardiac arrest, confusion, crying, delusion, depersonalization, depression, diaphoresis, dreams (abnormal), dyspepsia, dysphoria, dyspnea, euphoria, faintness, floating sensation, flushing, gastrointestinal cramps, hallucinations, hostility, hypertension, hypotension, laryngeal edema, nervousness, numbness, pruritus, rash, respiratory depression, respiratory distress, restlessness, sensation of warmth/burning, speech disorder, stridor, tachycardia, tingling, tremor, unreality, urinary urgency, urticaria

Postmarketing and/or case reports: Abdominal pain, agitation, allergic reaction, anxiety, fever ; injection site reactions (pain, swelling, redness, burning); loss of consciousness, pulmonary edema, seizure, somnolence

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic

doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersRelief of pain, respiratory and mental status, blood pressure

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness (eg, pain relief) and adverse reactions at beginning of therapy and periodically throughout therapy. Monitor blood pressure, CNS and respiratory status, and degree of sedation at beginning of therapy and at regular intervals during use. For inpatients, implement safety measures. Generally used in conjunction with surgical anesthesia or during labor and delivery; however, if self-administered for relief of pain, assess knowledge/teach patient appropriate use, adverse reactions to report, and appropriate interventions to reduce side effects.

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause hypotension, dizziness, drowsiness, impaired coordination, or blurred vision (use caution when driving, climbing stairs, or changing position - rising from sitting or lying to standing, or when engaging in tasks requiring alertness until response to drug is known); loss of appetite, nausea, or vomiting (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help; if unresolved, consult prescriber about use of stool softeners). Report chest pain, slow or rapid heartbeat, acute dizziness or persistent headache; changes in mental status; swelling of extremities or unusual weight gain; changes in urinary elimination or pain on urination; acute headache; back or flank pain or muscle spasms; blurred vision; skin rash; or shortness of breath. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. If you are breast-feeding, take medication immediately after breast-feeding or 3-4 hours prior to next feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution, as hydrochloride: 10 mg/mL (10 mL); 20 mg/mL (10 mL)

Nubain®: 10 mg/mL (10 mL) [DSC]; 20 mg/mL (10 mL)

Injection, solution, as hydrochloride [preservative free]: 10 mg/mL (1 mL); 20 mg/mL (1 mL)

Nubain®: 10 mg/mL (1 mL); 20 mg/mL (1 mL)

Generic AvailableYes

Mechanism of ActionAgonist of kappa opiate receptors and partial antagonist of mu opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression

Pharmacodynamics/Kinetics

Onset of action: Peak effect: SubQ, I.M.: <15 minutes; I.V.: 2-3 minutes

Metabolism: Hepatic

Half-life elimination: 5 hours

Excretion: Feces; urine (~7% as metabolites)

Related Information

- Narcotic / Opioid Analgesics

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation). Anticholinergic side effects can cause a reduction of saliva production or secretion, contributing to discomfort and dental disease (ie, caries, oral candidiasis, and periodontal disease).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause dizziness; may rarely cause restlessness, nervousness, confusion, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropic may produce additive sedation

Anesthesia and Critical Care Concerns/Other ConsiderationsAbrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

Mixed agonist-antagonist: Incidence of psychomimetic effect is lower than with pentazocine; may precipitate withdrawal in narcotic-dependent patients.

Index Terms Nalbuphine Hydrochloride

References

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Errick JK and Heel RC, “Nalbuphine: A Preliminary Review of Its Pharmacological Properties and Therapeutic Efficacy,” *Drugs*, 1983, 26(3):191-211. [PubMed 6137354]

Jaillon P, Gardin ME, Lecocq B, et al, “Pharmacokinetics of Nalbuphine in Infants, Young Healthy Volunteers, and Elderly Patients,” *Clin Pharmacol Ther*, 1989, 46(2):226-33. [PubMed 2758732]

Leikin JB, Ehrenpreis ED, Barkin RL, et al, “Nalbuphine vs Meperidine in Sickle Cell Anemia,” *DICP*, 1990, 24(7-8):781-2. [PubMed 2375146]

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

Yoo YC, Chung HS, Kim IS, et al, “Determination of Nalbuphine in Drug Abusers' Urine,” *J Anal Toxicol*, 1995, 19(2):120-3.[PubMed 7769781]

International Brand Names Azerty (FR); Bain (TW); Bufigen (MX); Nalbufina (UY); Nalbuphin OrPha (CH); Nalcryn SP (MX); Nubain (AE, AT, BF, BH, BJ, BR, CI, CY, CZ, DE, EE, EG, ET, GB, GH, GM, GN, GR, HN, HU, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PH, PK, PL, QA, SA, SC, SD, SL, SN, SY, TN, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Nubaina (AR); Nukaine (PH); Onfor (AR, PY)

Nalmefene

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Revex® may be confused with Nimbex®, ReVia®, Rubex®

Color-coded ampuls denote indication-specific concentrations:

Blue-labeled ampul (for postoperative use) contains 1 mL (100 mcg/mL)

Green-labeled ampul (for overdose management) contains 2 mL (1 mg/mL)

International issues:

Revex® may be confused with Brivex® which is a brand name for brivudine in Switzerland

Revex® may be confused with Rubex® which is a brand name for ascorbic acid in Ireland

Pronunciation(NAL me feen)

U.S. Brand NamesRevex® [DSC]

Pharmacologic CategoryAntidote; Opioid Antagonist

Use: Labeled IndicationsComplete or partial reversal of opioid drug effects, including respiratory depression induced by natural or synthetic opioids; reversal of postoperative opioid depression; management of known or suspected opioid overdose

Dosing: Adults

Reversal of postoperative opioid depression: I.V.: Blue-labeled product (100 mcg/mL): Titrate to reverse the undesired effects of opioids; initial dose for nonopioid dependent patient: 0.25 mcg/kg followed by 0.25 mcg/kg incremental doses at 2- to 5-minute intervals. After a total dose >1 mcg/kg, further therapeutic response is unlikely.

Note: In patients with increased cardiovascular risks, dilute 1:1 in NS or SWFI, and initiate/titrate with 0.1 mcg/kg doses.

Management of known/suspected opioid overdose: I.V. (preferred route): Green-labeled product (1 mg/mL):

Nonopioid-dependent patients: 0.5 mg/70 kg; may repeat with 1 mg/70 kg in 2-5 minutes; further increase beyond a total dose of 1.5 mg/70 kg will not likely result in improved response and may result in cardiovascular stress and precipitated withdrawal syndrome

Opioid-dependent patients: Administer a challenge dose of 0.1 mg/70 kg; if no withdrawal symptoms are observed in 2 minutes, give 0.5 mg/70 kg; may repeat with 1 mg/70 kg in 2-5 minutes; further increase beyond a total dose of 1.5 mg/70 kg will not likely result in improved response and may result in cardiovascular stress and precipitated withdrawal syndrome

Recurrence of respiratory depression: If noted, dose may again be titrated to clinical effect using incremental doses.

Loss of I.V. access: If I.V. access is lost or not readily obtainable, a single SubQ or I.M. dose of 1 mg may be effective in 5-15 minutes.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot necessary with single use, however, slow administration (over 60 seconds) of incremental doses is recommended to minimize hypertension and dizziness.

Dosing: Hepatic ImpairmentNo adjustment necessary with single use.

Administration: I.M.If I.V. access is lost or not readily obtainable, a single SubQ or I.M. dose of 1 mg may be effective in 5-15 minutes.

Administration: I.V.Slow administration (over 60 seconds) of incremental doses is recommended to minimize hypertension and dizziness in renal patients.

Administration: I.V. DetailCheck dosage strength carefully before use to avoid error. Dilute drug (1:1) with diluent and use smaller doses in patients known to be at increased cardiovascular risk. May be administered via I.M. or SubQ routes if I.V. access is not feasible.

pH: 3.9 (adjusted)

StorageStore at controlled room temperature.

CompatibilityStable in D_5LR, $D_5{}^1/_2NS$, D_5W, LR, sodium bicarbonate 5%, $^1/_2NS$, NS.

ContraindicationsHypersensitivity to nalmefene or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Acute opioid withdrawal: May precipitate symptoms of acute withdrawal in opioid-dependent patients, including pain, hypertension, sweating, agitation, and irritability.

- Buprenorphine-induced respiratory depression: Animal studies indicate nalmefene may not completely reverse buprenorphine-induced respiratory depression.

- Hypersensitivity: Nalmefene is structurally similar to both naltrexone and naloxone; patients with hypersensitivity to these agents may also react to nalmefene.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease or in patients receiving medications with potential adverse cardiovascular effects (eg, hypotension, pulmonary edema or arrhythmias); pulmonary edema and cardiovascular instability, including ventricular fibrillation, have been reported in association with abrupt reversal when using narcotic antagonists.

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Flumazenil: Concurrent use of flumazenil and nalmefene may increase the risk of seizures.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Concentrated product: Two products are available at different concentrations. A blue-labeled ampul contains a 100 mcg/mL solution of nalmefene and is intended for postoperative use. A green-labeled ampul contains a 1 mg/mL (**10** times as concentrated; **20** times as much drug) and is intended to be used for the management of an overdose.

Other warnings/precautions:

- Opioid dependence: Discharged patients who are opioid-dependent may attempt to override the narcotic-blocking effect of nalmefene. Patients are at a greater risk of overdose when nalmefene wears off if megadosing of opiates has occurred. Adequate duration of monitoring should be provided.

- Opioid overdose: Recurrence of respiratory depression is possible if the opioid involved is long-acting; observe patients until there is no reasonable risk of recurrent respiratory depression.

- Postoperative reversal: Appropriate use: Excessive dosages should be avoided after use of opiates in surgery. Abrupt postoperative reversal may result in nausea, vomiting, sweating, tachycardia, hypertension, seizures, and other cardiovascular events (including pulmonary edema and arrhythmias).

Pregnancy Risk FactorB
Pregnancy ConsiderationsAnimal studies have not demonstrated fetal harm or fertility impairment. There are no adequate and well-controlled studies in pregnant women. Use only if clearly needed.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsLimited information available; do not use in lactating women if possible.
Adverse Reactions

>10%: Gastrointestinal: Nausea (18%)

1% to 10%:

Cardiovascular: Tachycardia (5%), hypertension (5%), hypotension (1%), vasodilation (1%)

Central nervous system: Fever (3%), dizziness (3%), headache (1%), chills (1%)

Gastrointestinal: Vomiting (9%)

Miscellaneous: Postoperative pain (4%)

<1%: Agitation, arrhythmia, AST increased, bradycardia, confusion, depression, diarrhea, myoclonus, nervousness, pharyngitis, pruritus, somnolence, tremor, urinary retention, withdrawal syndrome, xerostomia

Postmarketing and/or case reports: Pulmonary edema

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersSymptoms of withdrawal; neurological status, oxygenation, pain, vital signs
Nursing: Physical Assessment/MonitoringAssess patient for opioid dependency. Monitor vital signs, respiratory, and cardiac status carefully during infusion and for some time thereafter (effects may continue for several days, use nonopioid analgesics for pain).
Patient EducationThis drug can only be administered I.V. You may experience drowsiness, dizziness, or blurred vision for several days; use caution when driving or engaging in tasks requiring alertness until response to drug is known. Small frequent meals and good mouth care may reduce any nausea or vomiting. Report yellowing of eyes or skin, unusual bleeding, dark or tarry stools, acute headache, respiratory difficulty, or palpitations. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Revex®: 100 mcg/mL (1 mL) [blue label]; 1 mg/mL (2 mL) [green label] [DSC]

Generic AvailableNo
ManufacturerBaxter Pharmaceuticals Products, Inc

Mechanism of Action As a 6-methylene analog of naltrexone, nalmefene acts as a competitive antagonist at opioid receptor sites, preventing or reversing the respiratory depression, sedation, and hypotension induced by opiates; no pharmacologic activity of its own (eg, opioid agonist activity) has been demonstrated

Pharmacodynamics/Kinetics

Onset of action: I.M., SubQ: 5-15 minutes

Distribution: V_d: 8.6 L/kg; rapid

Protein binding: 45%

Metabolism: Hepatic via glucuronide conjugation to metabolites with little or no activity

Bioavailability: I.M., SubQ: 100%

Half-life elimination: 10.8 hours

Time to peak, serum: Serum: I.M.: 2.3 hours; I.V.: <2 minutes; SubQ: 1.5 hours

Excretion: Feces (17%); urine (<5% as unchanged drug)

Clearance: 0.8 L/hour/kg

Pharmacotherapy Pearls Proper steps should be used to prevent use of the incorrect dosage strength. The goal of treatment in the postoperative setting is to achieve reversal of excessive opioid effects without inducing a complete reversal and acute pain.

If opioid dependence is suspected, nalmefene should only be used in opioid overdose if the likelihood of overdose is high based on history or the clinical presentation of respiratory depression with concurrent pupillary constriction is present.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness; may rarely cause agitation, confusion, depression, nervousness, and sedation

Mental Health: Effects on Psychiatric Treatment May precipitate opioid withdrawal in dependent patients

Anesthesia and Critical Care Concerns/Other Considerations Proper steps should be used to prevent use of the incorrect dosage strength. The goal of treatment in the postoperative setting is to achieve reversal of excessive opioid effects without inducing a complete reversal and acute pain. If opioid dependence is suspected, nalmefene should only be used in opioid overdose if the likelihood of overdose is high, based on history or the clinical presentation of respiratory depression with concurrent pupillary constriction present.

Index Terms Nalmefene Hydrochloride

References

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

Naloxone

Lexi-Drugs Online

English

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Naloxone may be confused with naltrexone

Narcan® may be confused with Marcaine®, Norcuron®

International issues:

Narcan® may be confused with Marcen® which is a brand name for ketazolam in Spain

Pronunciation(nal OKS one)

Canadian Brand NamesNaloxone Hydrochloride Injection®

Pharmacologic CategoryAntidote; Opioid Antagonist

Use: Labeled Indications

Complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including heroin, morphine, propoxyphene, methadone, and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, and butorphanol

Diagnosis of suspected opioid dependence or acute opioid overdose

Adjunctive agent to increase blood pressure in the management of septic shock

Use: Unlabeled/InvestigationalOpioid-induced pruritus

Use: DentalReverse overdose effects of the two narcotic agents, fentanyl and meperidine, used in the technique of I.V. conscious sedation

Dosing: Adults**Note:** I.M., I.V. (preferred), and SubQ routes are available. Endotracheal administration is the least desirable and is supported by only anecdotal evidence (case report) (ACLS guidelines, 2005):

Opioid intoxication: Respiratory depression: I.V.: 0.4-2 mg; may need to repeat doses every 2-3 minutes; after reversal, may need to readminister dose(s) at a later interval (ie, 20-60 minutes) depending on type/duration of opioid. If no response is observed after 10 mg, consider other causes of respiratory depression. **Note:** Opioid-dependent patients may require lower doses (0.1 mg) titrated incrementally to avoid precipitating acute withdrawal.

Continuous infusion: I.V.: Calculate dosage/hour based on effective intermittent dose used and duration of adequate response seen **or** use $^{2}/_{3}$ of the initial effective naloxone bolus on an hourly basis (typically 0.25-6.25 mg/hour); $^{1}/_{2}$ of the initial bolus dose should be readministered 15 minutes after initiation of the continuous infusion to prevent a drop in naloxone levels; adjust infusion rate as needed to assure adequate ventilation and prevent withdrawal symptoms

Opioid-dependent patients being treated for cancer pain (unlabeled; NCCN guidelines, 2008): I.V.: 0.04-0.08 mg (40-80 mcg) slow I.V. push; administer every 30-60 seconds until improvement in symptoms, if no response is observed after total naloxone dose 1 mg, consider other causes of respiratory depression. **Note:** May dilute 0.4 mg/mL (1 mL) ampule into 9 mL of normal saline for a total volume of 10 mL to achieve a 0.04 mg/mL (40 mcg/mL) concentration.

Postoperative reversal: I.V.: 0.1-0.2 mg every 2-3 minutes until desired response (adequate ventilation and alertness without significant pain). **Note:** Repeat doses may be needed within 1-2 hour intervals depending on type, dose, and timing of the last dose of opioid administered.

Opioid-induced pruritus (unlabeled use): I.V. infusion: 0.25 mcg/kg/hour; **Note:** Monitor pain control; verify that the naloxone is not reversing analgesia.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** I.M., I.V. (preferred), and SubQ routes are available. Endotracheal administration is the least desirable and is supported by only anecdotal evidence (case report) (ACLS guidelines, 2005):

Opiate intoxication: Respiratory depression: I.V.:

Birth (including premature infants) to 5 years or <20 kg: Initial: 0.1 mg/kg (maximum dose: 2 mg) (*Drugs for Pediatric Emergencies*, 1998)

>5 years or ≥20 kg: 2 mg/dose; if no response, repeat every 2-3 minutes (*Drugs for Pediatric Emergencies*, 1998)

Continuous infusion: I.V.: If continuous infusion is required, calculate dosage/hour based on effective intermittent dose used and duration of adequate response seen **or** use $^{2}/_{3}$ of the initial effective naloxone bolus on an hourly basis; titrate dose (typically 0.04-0.16 mg/kg/hour for 2-5 days in children); $^{1}/_{2}$ of the initial bolus dose should be readministered 15 minutes after initiation of the continuous infusion to prevent a drop in naloxone levels; increase infusion rate as needed to assure adequate ventilation and prevent withdrawal symptoms

Postoperative reversal: Infants and Children: I.V.: 0.01 mg/kg; may repeat every 2-3 minutes as needed based on response (adequate ventilation without significant pain)

Administration: I.V.

I.V. push: Administer over 30 seconds as undiluted preparation **or** (unlabeled) administer as diluted preparation slow I.V. push by diluting 0.4 mg (1 mL) ampul with 9 mL of normal saline for a total volume of 10 mL to achieve a concentration of 0.04 mg/mL

I.V. continuous infusion: Dilute to 4 mcg/mL in D_5W or normal saline

Administration: Other

Endotracheal: There is only anecdotal support for this route of administration. May require a slightly higher dose than used in other routes. Dilute to 1-2 mL with normal saline; flush with 5 cc of saline and then administer 5 ventilations

Intratracheal: Dilute to 1-2 mL with normal saline

StorageStore at 25°C (77°F). Protect from light.
ReconstitutionStable in 0.9% sodium chloride and D_5W at 4 mcg/mL for 24 hours.
CompatibilityStable in D_5W, NS; do not mix with alkaline solutions.

Y-site administration: Compatible: Gatifloxacin, linezolid, propofol. **Incompatible:** Amphotericin B cholesteryl sulfate complex.

Compatibility in syringe: Compatible: Heparin, ondansetron.

Compatibility when admixed: Compatible: Verapamil.

ContraindicationsHypersensitivity to naloxone or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Acute opioid withdrawal: May precipitate symptoms of acute withdrawal in opioid-dependent patients, including pain, hypertension, sweating, agitation, irritability; in neonates: shrill cry, failure to feed. Carefully titrate dose to reverse hypoventilation; do not fully awaken patient or reverse analgesic effect (postoperative patient).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease or in patients receiving medications with potential adverse cardiovascular effects (eg, hypotension, pulmonary edema or arrhythmias); pulmonary edema and cardiovascular instability, including ventricular fibrillation, have been reported in association with abrupt reversal when using narcotic antagonists. Administration of naloxone causes the release of catecholamines; may precipitate acute withdrawal or unmask pain in those who regularly take opioids.

- Seizures: Use caution in patients with history of seizures; avoid use in treatment of meperidine-induced seizures.

Other warnings/precautions:

- Opioid overdose: Recurrence of respiratory depression is possible if the opioid involved is long-acting; observe patients until there is no reasonable risk of recurrent respiratory depression.

- Postoperative reversal: Appropriate use: Excessive dosages should be avoided after use of opiates in surgery. Abrupt postoperative reversal may result in nausea, vomiting, sweating, tachycardia, hypertension, seizures, and other cardiovascular events (including pulmonary edema and arrhythmias).

Geriatric ConsiderationsIn small trials, naloxone has shown temporary improvement in Alzheimer's disease; however, is not recommended for treatment.
Pregnancy Risk FactorC
Pregnancy ConsiderationsConsider benefit to the mother and the risk to the fetus before administering to a pregnant woman who is known or suspected to be opioid dependent. May precipitate withdrawal in both the mother and fetus.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsNo data reported. Since naloxone is used for opiate reversal the concern should be on opiate drug levels in a breast-feeding mother and transfer to the infant rather than naloxone exposure. The safest approach would be **not** to breast-feed.
Adverse ReactionsAdverse reactions are related to reversing dependency and precipitating withdrawal. Withdrawal symptoms are the result of sympathetic excess. Adverse events occur secondarily to reversal (withdrawal) of narcotic analgesia and sedation.

Central nervous system: Narcotic withdrawal

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersRespiratory rate, heart rate, blood pressure, temperature, level of consciousness, ABGs or pulse oximetry
Nursing: Physical Assessment/MonitoringAssess patient for opioid dependency. Monitor vital signs and cardiorespiratory status continuously during infusion, maintain patent airway.
Patient EducationIf patient is responsive, instructions are individualized. Report respiratory difficulty, palpitations, or tremors. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride: 0.4 mg/mL (1 mL, 10 mL)

Injection, solution, as hydrochloride [preservative free]: 0.4 mg/mL (1 mL); 1 mg/mL (2 mL)

Generic AvailableYes

Mechanism of ActionPure opioid antagonist that competes and displaces narcotics at opioid receptor sites

Pharmacodynamics/Kinetics

Onset of action: Endotracheal, I.M., SubQ: 2-5 minutes; I.V.: ~2 minutes

Duration: ~30-120 minutes depending on route of administration; I.V. has a shorter duration of action than I.M. administration; since naloxone's action is shorter than that of most opioids, repeated doses are usually needed

Distribution: Crosses placenta

Metabolism: Primarily hepatic via glucuronidation

Half-life elimination: Neonates: 3-4 hours; Adults: 0.5-1.5 hours

Excretion: Urine (as metabolites)

Pharmacotherapy PearlsMay contain methyl and propylparabens

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Cardiovascular ConsiderationsBecause of the very short duration of action of naloxone (20-60 minutes) the reversal of opiate-induced respiratory depression by naloxone may cease while the opiate action persists. Therefore, respiratory depression may recur and patients should continue to be very closely observed. Also note that naloxone reverses the effects of narcotics. Excessive doses of naloxone in the perioperative period may cause an increase in blood pressure and reversal of anesthesia. Furthermore, naloxone may precipitate symptoms of opioid withdrawal (eg, pain, hypertension, irritability) in patients addicted to opioids.

Anesthesia and Critical Care Concerns/Other ConsiderationsNaloxone may contain methyl and propylparabens. Proper steps should be used to prevent use of the incorrect dosage strength. The goal of treatment in the postoperative setting is to achieve reversal of excessive opioid effects without inducing a complete reversal and acute pain.

Index Terms*N*-allylnoroxymorphine Hydrochloride; Naloxone Hydrochloride; Narcan

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International Brand NamesAntioplaz (AR); Jin Er Lun (CL); Mapin (HK, MY); Min-I-Jet Naloxone (GB); Naloxon (BG, CH, DE); Naloxone Abello (ES); Naloxone Hydrochlorid (GB); Naloxonum Hydrochloricum (PL); Naloxonum Prolongatum (PL); Narcan (AE, AU, BE, BF, BH, BJ, BR, CI, CY, EG, ET, FR, GB, GH, GM, GN, GR, IE, IL, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, NZ, OM, PK, PL, QA, SA, SC, SD, SL, SN, SY, TN, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Narcanti (AR, AT, CZ, DK, FI, HN, HU, MX, NO, PL, SE, UY); Narcotan (IN); Narlox (PH); Naxan (PT); Naxone (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Zynox (ZA)

Naltrexone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Naltrexone (Vivitrol™): Injection Site Reactions – August 2008

The U.S. Food and Drug Administration (FDA) is notifying healthcare professionals of reports of serious injection site reactions associated with naltrexone injectable suspension (Vivitrol™). The FDA has received 196 reports of reactions (including cellulitis, induration, hematoma, abscess, and necrosis) following administration. Surgical intervention was required for management of some of the reactions. Instruct patients to report injection site pain, swelling, bruising, pruritus, or redness at the injection site that does not improve (or worsens) within 2 weeks; consider surgical consult for worsening reactions. Naltrexone injectable suspension is for I.M. gluteal administration only, using the provided 1.5 inch 20-gauge administration needle. Alternate treatment should be considered in patients not able to receive an I.M. gluteal injection with the provided needle. Do not administer I.V., SubQ, or into fatty tissue (the risk of serious injection site reaction is increased if given SubQ or into fatty tissue). Patients with higher gluteal fat thickness may be at increased risk for injection site reactions.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#naltrexone

Medication Safety Issues

Sound-alike/look-alike issues:

Naltrexone may be confused with methylnaltrexone, naloxone

ReVia® may be confused with Revatio®, Revex®

Administration issues: Vivitrol™: For intramuscular (I.M.) gluteal injection only

Pronunciation(nal TREKS one)

U.S. Brand NamesDepade®; ReVia®; Vivitrol™

Canadian Brand NamesReVia®

Pharmacologic CategoryAntidote; Opioid Antagonist

Use: Labeled IndicationsTreatment of ethanol dependence; blockade of the effects of exogenously administered opioids

Dosing: Adults

Alcohol dependence (do not give until patient is opioid-free for 7-10 days as required by urinalysis):

Oral: 25 mg; if no withdrawal signs within 1 hour give another 25 mg; maintenance regimen is flexible, variable and individualized (50 mg/day to 100-150 mg 3 times/week for 12 weeks); up to 800 mg/day has been tolerated in a small number of healthy adults without an adverse effect.

I.M.: 380 mg once every 4 weeks

Opioid antidote (do not give until patient is opioid-free for 7-10 days as required by urinalysis): Oral: 25 mg; if no withdrawal signs within 1 hour give another 25 mg; maintenance regimen is flexible, variable and individualized (50 mg/day to 100-150 mg 3 times/week for 12 weeks); up to 800 mg/day has been tolerated in a small number of healthy adults without an adverse effect.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentUse caution. No adjustment needed in mild impairment. Not adequately studied in moderate-to-severe renal impairment.

Dosing: Hepatic ImpairmentUse caution. An increase in naltrexone AUC of approximately five- and 10-fold in patients with compensated or decompensated liver cirrhosis respectively, compared with normal liver function has been reported No adjustment required with mild-to-moderate hepatic impairment. Not adequately studied in severe hepatic impairment.

Administration: I.M.Vivitrol™ should be administered I.M. into the upper outer quadrant of the gluteal area; use provided 1.5 inch 20-gauge needle for administration. Avoid inadvertent injection into a blood vessel; do not administer I.V., SubQ, or into fatty tissue (the risk of serious injection site reaction is increased if given SubQ or into fatty tissue. Injection should alternate between the two buttocks. Do not substitute any components of the dose-pack.

Administration: OralTo minimize adverse gastrointestinal effects, administer with food or antacids or after meals; advise patient not to self-administer opiates while receiving naltrexone therapy.

Storage

Injection: Store unopened kit at 2°C to 8°C (36°F to 46°F). Kit may be kept at room temperature of ≤25°C (77°F) for ≤7 days prior to use; do not freeze.

Tablet: Store at 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to naltrexone or any component of the formulation; narcotic dependence or current use of opioid analgesics; acute opioid withdrawal; failure to pass Narcan® challenge or positive urine screen for opioids; acute hepatitis; liver failure

Warnings/Precautions

Boxed warnings:

- Hepatocellular injury: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Accidental overdose: Patients who had been treated with naltrexone may respond to lower opioid doses than previously used. This could result in potentially life-threatening opioid intoxication. Patients should be aware that they may be more sensitive to lower doses of opioids after naltrexone treatment is discontinued. Warn patients that attempts to overcome opioid blockade could lead to fatal overdose.

- Acute opioid withdrawal: May precipitate symptoms of acute withdrawal in opioid-dependent patients, including pain, hypertension, sweating, agitation, and irritability; in neonates: shrill cry, failure to feed.

- Eosinophilic pneumonia: Cases of eosinophilic pneumonia have been reported; monitor for hypoxia and dyspnea.

- Hepatocellular injury: **[U.S. Boxed Warning]: Dose-related hepatocellular injury is possible; the margin of separation between the apparent safe and hepatotoxic doses appears to be ≤ fivefold.**

- Injection site reactions: Serious injection site reactions (eg, cellulitis, induration, hematoma, abscess, necrosis) have been reported with use. Patients should report injection site pain, swelling, bruising, pruritus, or redness that does not improve (or worsens) within 2 weeks; consider surgical consult for worsening reactions. For I.M. use only, do not administer I.V., SubQ, or into fatty tissue; may increase the risk of injection site reactions.

- Suicidal thoughts/depression: Suicidal thoughts and depression have been reported; monitor closely.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.

- Hepatic impairment: Use with caution in patients with hepatic impairment; not studied in severe impairment.

- Renal impairment: Use with caution in patients with renal impairment; not studied in moderate-to-severe impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Vehicle used in injectable (polylactide-co-glycolide microspheres): Has rarely been associated with retinal artery occlusion in patients with abnormal arteriovenous anastomosis (eg, patent foramen ovale).

Other warnings/precautions:

- Detoxified opioid addiction: Patients should be opioid-free for a minimum of 7-10 days; use naloxone challenge test to confirm. Use of naltrexone does not eliminate or diminish withdrawal symptoms.

Pregnancy Risk FactorC

Pregnancy ConsiderationsEvidence of early fetal loss has been observed in animal studies with oral naltrexone. There are no adequate and well-controlled studies in pregnant women.

LactationEnters breast milk/not recommended

Adverse ReactionsCombined reporting of adverse events from oral and injectable formulations:

>10%:

Cardiovascular: Syncope (13%)

Central nervous system: Headache (25%), insomnia (14%), dizziness (13%), anxiety (12%), somnolence (4%), nervousness, fatigue

Gastrointestinal: Nausea (33%), vomiting (14%), appetite decreased (14%), diarrhea (13%), abdominal pain (11%), abdominal cramping

Local: Injection site reaction (69%; includes bruising, induration, nodules, pain, pruritus, swelling, tenderness)

Neuromuscular & skeletal: Arthralgia (12%), CPK increased (11%)

Respiratory: Upper respiratory tract infection (13%), pharyngitis (11%)

1% to 10%:

Central nervous system: Depression (8%), suicidal thoughts (1%), energy increased, feeling down

Dermatologic: Rash (6%)

Endocrine & metabolic: Polydipsia

Gastrointestinal: Dry mouth (5%)

Genitourinary: Delayed ejaculation, impotency

Hepatic: AST increased (2%)

Neuromuscular & skeletal: Muscle cramps (8%), back pain (6%)

<1% (Limited to important or life-threatening): ALT increased, angina, atrial fibrillation, blood pressure increased, cerebral aneurysm, chest pain, chest tightness, CHF, cholecystitis, cholelithiasis, colitis, COPD, dehydration, delirium, disorientation, DVT, dyspnea, eosinophilic pneumonia, euphoria, GI hemorrhage, hallucinations, hypercholesterolemia, hypersensitivity reaction (includes angioedema and urticaria), hypertension, influenza, ischemic stroke, leukocytosis, lymphadenopathy, MI, narcotic withdrawal, palpitation, paralytic ileus, paranoia, PE, perirectal abscess, pneumonia, pyrexia, rigors, seizure, suicide attempts, tachycardia, thrombocytopenia, tooth abscess, UTI

Drug InteractionsThere are no known significant interactions.

Test InteractionsMay cause cross-reactivity with some opioid immunoassay methods.

Monitoring ParametersFor narcotic withdrawal; liver function tests; injection site reactions

Nursing: Physical Assessment/MonitoringDo not use until patient has been opioid-free for 7-10 days. Assess carefully for several days following start of therapy for narcotic withdrawal symptoms or severe adverse reactions. Monitor injection site for reaction. Use non-narcotic analgesics for pain. Monitor for suicide ideation. Assess results of laboratory tests. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsPeriodic LFTs

Patient EducationThis medication will help you achieve abstinence from opiates if taken as directed. Do not increase or change dose. Do not use opiates or any medications not approved by your prescriber during naltrexone therapy. Carry documentation to alert medical personnel you are taking medication in the event of an emergency. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); trouble sleeping; decreased appetite; abdominal cramping, nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); low energy; or decreased sexual function (reversible when drug is discontinued). Report yellowing of skin or eyes, change in color of stool or urine, thoughts of suicide, increased perspiration or chills, acute headache, palpitations, unusual joint pain, signs and symptoms of pneumonia (trouble breathing, coughing, or wheezing), or injection site pain, swelling, or unresolved redness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, microspheres for suspension, extended release:

Vivitrol™: 380 mg [contains polylactide-co-glycolide; packaged with diluent, syringe, needles, and safety device]

Tablet, as hydrochloride: 50 mg

Depade®: 25 mg, 50 mg, 100 mg

ReVia®: 50 mg

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Tablets (Naltrexone HCl)

50 mg (30): $103.99

Tablets (ReVia)

50 mg (30): $248.19

Mechanism of ActionNaltrexone (a pure opioid antagonist) is a cyclopropyl derivative of oxymorphone similar in structure to naloxone and nalorphine (a morphine derivative); it acts as a competitive antagonist at opioid receptor sites, showing the highest affinity for mu receptors.

Pharmacodynamics/Kinetics

Duration: Oral: 50 mg: 24 hours; 100 mg: 48 hours; 150 mg: 72 hours; I.M.: 4 weeks

Absorption: Oral: Almost complete

Distribution: V_d: 19 L/kg; widely throughout the body but considerable interindividual variation exists

Protein binding: 21%

Metabolism: Noncytochrome-mediated dehydrogenase conversion to 6-beta-naltrexol and related minor metabolites; Oral: Extensive first-pass effect

Half-life elimination: Oral: 4 hours; 6-beta-naltrexol: 13 hours; I.M.: naltrexone and 6-beta-naltrexol: 5-10 days

Time to peak, serum: Oral: ~60 minutes; I.M.: Biphasic: 2 hours (first peak), 2-3 days (second peak)

Excretion: Primarily urine (as metabolites and unchanged drug)

Related Information

- Addiction Treatments

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dry mouth.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Anesthesia and Critical Care Concerns/Other Considerations May also be used in detoxification with special guidelines

Index Terms Naltrexone Hydrochloride

References

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O'Connor PG and Kosten TR, “Rapid and Ultrarapid Opioid Detoxification Techniques,” *JAMA*, 1998, 279(3):229-34.[PubMed 9438745]

Tang J, and Weiter JJ, “Branch Retinal Artery Occlusion After Injection of a Long-Acting Risperidone Preparation,” *Annals Intern Med*, 2007, 147(4): 283-3.[PubMed 17709768]

International Brand Names Antaxone (ES, IT); Celupan (ES); Nalerona (CN, PE, PY); Nalorex (BE, FR, GB, IE, NL, PT); Naltrexin (KP); Nemexin (AT, CH, DE, PL); Nodict (IN); Nutrexon (ID); Opizone (GB); Re-Via (MX); Regental (UY); Revez (AR); Revia (AU, BG, BR, CZ, DK, EE, FI, FR, HK, HN, HU, KP, NO, SE, TW); Traxone (KP); Trexan (PK)

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(NAN droe lone)

Canadian Brand NamesDeca-Durabolin®; Durabolin®

Pharmacologic CategoryAndrogen

Use: Labeled IndicationsControl of metastatic breast cancer; management of anemia of renal insufficiency

Dosing: Adults

Breast cancer, male/female (phenpropionate): I.M.: 50-100 mg/week

Anemia of renal insufficiency (decanoate): I.M.:

Male: 100-200 mg/week

Female: 50-100 mg/week

Note: Deep I.M. (into gluteal muscle)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDeep I.M. (into gluteal muscle): Children 2-13 years (decanoate): 25-50 mg every 3-4 weeks

Administration: I.M.Inject deeply I.M., preferably into the gluteal muscle.

RestrictionsC-III

ContraindicationsHypersensitivity to nandrolone or any component of the formulation; carcinoma of breast or prostate; nephrosis; pregnancy; not for use in infants

Allergy Considerations

- Androgen Allergy

Warnings/Precautions

Boxed warnings:

- Blood lipid changes: See “Concerns related to adverse effects” below.
- Hepatic effects: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Blood lipid changes: **[U.S. Boxed Warning]: Anabolic steroids may cause blood lipid changes with increased risk of arteriosclerosis.**
- Hepatic effects: **[U.S. Boxed Warning]: Anabolic steroids may cause peliosis hepatis or liver cell tumors which may not be apparent until liver failure or intra-abdominal hemorrhage develops.**

Disease-related concerns:

- Breast cancer: Use with caution in patients with breast cancer; may cause hypercalcemia by stimulating osteolysis.
- Diabetes: Use with caution in patients with diabetes mellitus; monitor carefully.
- Edematous conditions: Use with caution in patients with conditions influenced by edema (eg, cardiovascular disease, migraine, seizure disorder, renal impairment); may cause fluid retention.
- Hepatic impairment: Use with caution in patients with hepatic impairment.

Special populations:

- Elderly: Use with caution in elderly patients, they may be at greater risk for prostatic hyperplasia, fluid retention, and transaminase elevations.
- Pediatrics: May accelerate bone maturation without producing compensatory gain in linear growth in children; in prepubertal children perform radiographic examination of the hand and wrist every 6 months to determine the rate of bone maturation and to assess the effect of treatment on the epiphyseal centers.
- Women: Discontinue with evidence of mild virilization in women.

Pregnancy Risk FactorX

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions

Male:

Postpubertal:

>10%:

Dermatologic: Acne

Endocrine & metabolic: Gynecomastia

Genitourinary: Bladder irritability, priapism

1% to 10%:

Central nervous system: Insomnia, chills

Endocrine & metabolic: Decreased libido, hepatic dysfunction

Gastrointestinal: Nausea, diarrhea

Genitourinary: Prostatic hyperplasia (elderly)

Hematologic: Iron-deficiency anemia, suppression of clotting factors

<1%: Hepatic necrosis, hepatocellular carcinoma

Prepubertal:

>10%:

Dermatologic: Acne

Endocrine & metabolic: Virilism

1% to 10%:

Central nervous system: Chills, insomnia

Dermatologic: Hyperpigmentation

Gastrointestinal: Diarrhea, nausea

Hematologic: Iron deficiency anemia, suppression of clotting

<1%: Hepatocellular carcinoma, necrosis

Female:

>10%: Endocrine & metabolic: Virilism

1% to 10%:

Central nervous system: Chills, insomnia

Endocrine & metabolic: Hypercalcemia

Gastrointestinal: Nausea, diarrhea

Hematologic: Iron deficiency anemia, suppression of clotting factors

Hepatic: Hepatic dysfunction

<1%: Hepatic necrosis, hepatocellular carcinoma

Drug Interactions

CycloSPORINE: Androgens may enhance the hepatotoxic effect of CycloSPORINE. Androgens may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Androgens may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Test InteractionsAltered glucose tolerance tests

Nursing: Physical Assessment/MonitoringUse caution is presence of cardiac, renal, or hepatic disease or epilepsy. Assess potential for interactions with other pharmacological agents. Assess results of LFTs, therapeutic effectiveness (according to purpose of use), and adverse response on a regular basis (adverse reactions may differ according to gender and age). Caution patients with diabetes to monitor serum glucose closely (may increase the effect of hypoglycemic agents). Teach patient possible side effects/appropriate interventions and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to females of childbearing age unless patient is capable of complying with barrier contraceptive use.

Monitoring: Lab TestsLFTs on a regular basis

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug can only be given injection. Report immediately any redness, swelling, burning, or pain at injection site. If you have diabetes, monitor serum glucose closely and notify prescriber of significant changes (nandrolone may increase the effect of insulin and oral hypoglycemic agents). May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, yogurt may help). **Male:** Acne, swelling of breasts, loss of libido, impotence. **Female:** Virilism, menstrual irregularity (usually reversible). Report changes in menstrual pattern; enlarged or painful breasts; deepening of voice or unusual growth of body hair; fluid retention (eg, swelling of ankles, feet, or hands, respiratory difficulty, or sudden weight gain); bladder irritability; unresolved CNS changes (eg, nervousness, chills, insomnia); change in color of urine or stool; yellowing of eyes or skin; unusual bruising or bleeding; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as decanoate [in sesame oil]: 100 mg/mL (2 mL); 200 mg/mL (1 mL) [contains benzyl alcohol] [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Oil (Nandrolone Decanoate)

200 mg/mL (25): $416.50

Mechanism of ActionPromotes tissue-building processes, increases production of erythropoietin, causes protein anabolism; increases hemoglobin and red blood cell volume

Pharmacodynamics/Kinetics

Onset of action: 3-6 months

Duration: Up to 30 days

Absorption: I.M.: 77%

Metabolism: Hepatic

Excretion: Urine

Pharmacotherapy PearlsBoth phenpropionate and decanoate are injections in oil.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsNandrolone Decanoate; Nandrolone Phenpropionate

International Brand NamesActivin (ES); Anabolicus (ES); Anador (FR); Anadur (AT, LU, NL); Colirio Ocul Nandrol (ES); Deca-Durabol (SE); Deca-Durabolin (AR, AU, BE, BF, BJ, BO, BR, CH, CI, CN, CO, CR, CZ, DE, DO, EC, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, HK, HN, ID, IE, IT, KE, LR, LU, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NO, PA, PE, PL, PR, PT, PY, SC, SD, SL, SN, SV, TH, TN, TZ, UG, UY, VE, ZA, ZM, ZW); Durabolin (FR, PK); Fherbolico (ES); Keratyl (FR); Metabol (IN); Nandrol (ES); Nerobolil (HU); Neurabol (IN); Protosin (TW); Retabolic (HN); Retabolil (BG, HU); Rubolin (TW); Superanabolon (CZ); Vinone (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE)

Naphazoline and Pheniramine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Visine® may be confused with Visken®

Pronunciation(naf AZ oh leen & fen NIR a meen)

U.S. Brand NamesNaphcon-A® [OTC]; Opcon-A® [OTC]; Visine-A® [OTC]

Canadian Brand NamesNaphcon-A®; Visine® Advanced Allergy

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation; Ophthalmic Agent, Vasoconstrictor

Use: Labeled IndicationsTreatment of ocular congestion, irritation, and itching

Dosing: AdultsOphthalmic: 1-2 drops up to 4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricOphthalmic: Children ≥6 years: Refer to adult dosing.

ContraindicationsHypersensitivity to naphazoline, pheniramine, or any component of the formulation

Warnings/Precautions

Other warnings/precautions:

- OTC labeling: Not for use >72 hours. Notify healthcare provider of eye pain or vision changes. Not recommended for use in patients with cardiovascular disease, hypertension, narrow-angle glaucoma, or children <6 years of age. Not for use with contact lenses.

Geriatric ConsiderationsEvaluate patient's ability to self-administer; use cautiously in patients with cardiovascular disease.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Ocular: Pupillary dilation, increase in intraocular pressure

Systemic effects due to absorption:

Cardiovascular: Hypertension, cardiac irregularities

Endocrine & metabolic: Hyperglycemia

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic:

Naphcon-A®: Naphazoline hydrochloride 0.025% and pheniramine maleate 0.3% (5 mL) [contains benzalkonium chloride; 2 bottles/box], (15 mL) [contains benzalkonium chloride]

Opcon-A®: Naphazoline hydrochloride 0.027% and pheniramine maleate 0.3% (15 mL) [contains benzalkonium chloride]

Visine-A®: Naphazoline hydrochloride 0.025% and pheniramine maleate 0.3% (15 mL) [contains benzalkonium chloride]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Naphcon-A)

0.025-0.3% (15): $12.36

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness or dizziness

Mental Health: Effects on Psychiatric TreatmentTCAs and MAO inhibitors may potentiate the pressor response of decongestants; monitor for changes in response

Index TermsPheniramine and Naphazoline

International Brand NamesFlamergi (ID); Isotic Azora (ID); Konjunktiva (HK); Naphcon-A (AU, BE, CL, CN, EC, HK, MY, PE, PH, PK, SG, TH); Oqifresh (CO); Vistallerg (PH)

Naphazoline

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(naf AZ oh leen)

U.S. Brand NamesAK-Con™; Albalon® [DSC]; Clear eyes® for Dry Eyes and ACR Relief [OTC]; Clear eyes® for Dry Eyes and Redness Relief [OTC]; Clear eyes® Redness Relief [OTC]; Clear eyes® Seasonal Relief [OTC]; Naphcon® [OTC]; Privine® [OTC]

Canadian Brand NamesNaphcon Forte®; Vasocon®

Pharmacologic CategoryAlpha$_1$ Agonist; Imidazoline Derivative; Ophthalmic Agent, Vasoconstrictor

Use: Labeled IndicationsTopical ocular vasoconstrictor; temporary relief of nasal congestion associated with the common cold, upper respiratory allergies or sinusitis; relief of redness of the eye due to minor irritation

Dosing: Adults

Nasal congestion (decongestant): Nasal: 0.05%, instill 1-2 drops or sprays every 6 hours if needed; therapy should not exceed 3 days

Decrease in eye redness (vasoconstrictor): Ophthalmic:

> 0.1% (prescription): 1-2 drops into conjuctival sac every 3-4 hours as needed
>
> 0.012% or 0.025% (OTC): 1-2 drops into affected eye(s) up to 4 times a day; therapy should not exceed 3 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Nasal congestion (decongestant):** Intranasal: Children >12 years: Refer to adult dosing.

Administration: OtherOphthalmic: Contact lenses should be removed prior to administering products containing benzalkonium chloride.

StorageStore at controlled room temperature.

ContraindicationsHypersensitivity to naphazoline or any component of the formulation; narrow-angle glaucoma

Warnings/Precautions

Concerns related to adverse effects:

- Rebound nasal congestion: May occur with extended use.

Disease-related concerns:

- Asthma: Use with caution in patients with chronic asthma.
- Cardiovascular disease: Use with caution in patients with hypertension, heart failure, or coronary artery disease.
- Cerebral arteriosclerosis: Use with caution in patients with cerebral arteriosclerosis.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Infection/injury: Use with caution in patients with local infection or injury.
- Prostatic hyperplasia: Use with caution in patients with benign prostatic hyperplasia.

Concurrent drug therapy issues:

- MAO inhibitors: Avoid concurrent use with MAO inhibitors; may cause hypertensive crisis.

Special populations:

- Pediatrics: Not recommended for use in children <6 years of age; may cause CNS depression, coma and marked reduction in body temperature, especially in infants.

Dosage form specific issues:

- Benzalkonium chloride: Ophthalmic products may contain benzalkonium chloride which may be absorbed by soft contact lenses.

Other warnings/precautions:

- OTC labeling: Patients should notify healthcare provider if symptoms last >72 hours or if condition worsens. In addition with ophthalmic products, contact prescriber in case of eye pain or if changes in vision occur.

Geriatric ConsiderationsEvaluate patient's ability to self-administer; use cautiously in patients with cardiovascular disease.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiac irregularities, hypertension

Central nervous system: Body temperature decreased, dizziness, drowsiness, headache, nervousness

Endocrine & metabolic: Hyperglycemia

Gastrointestinal: Nausea

Local: Transient stinging, nasal mucosa irritation, dryness, rebound congestion

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision, discomfort, intraocular pressure increased, irritation, lacrimation, mydriasis, punctuate keratitis, redness

Respiratory: Sneezing

Miscellaneous: Diaphoresis

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, intranasal, as hydrochloride [drops]:

Privine®: 0.05% (25 mL)

Solution, intranasal, as hydrochloride [spray]:

Privine®: 0.05% (20 mL)

Solution, ophthalmic, as hydrochloride:

AK-Con™, Albalon® [DSC]: 0.1% (15 mL) [contains benzalkonium chloride]

Clear eyes® for Dry Eyes and ACR Relief: 0.025% (15 mL) [contains hypromellose, and zinc sulfate]

Clear eyes® for Dry Eyes and Redness Relief: 0.012% (15 mL) [contains hypromellose, glycerin and benzalkonium chloride]

Clear eyes® Redness Relief: 0.012% (6 mL, 15 mL, 30 mL) [contains glycerin and benzalkonium chloride]

Clear eyes® Seasonal Relief: 0.012% (15 mL, 30 mL) [contains glycerin, zinc sulfate and benzalkonium chloride]

Naphcon®: 0.012% (15 mL) [contains benzalkonium chloride]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Albalon)

0.1% (15): $29.99

Mechanism of ActionStimulates alpha-adrenergic receptors in the arterioles of the conjunctiva and the nasal mucosa to produce vasoconstriction

Pharmacodynamics/Kinetics

Onset of action: Decongestant: Topical: ~10 minutes

Duration: 2-6 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness or dizziness

Mental Health: Effects on Psychiatric TreatmentTCAs and MAO inhibitors may potentiate the pressor response of decongestants; monitor for changes in response

Index TermsNaphazoline Hydrochloride

References

Higgins GL, Campbell B, Wallace K, et al, “Pediatric Poisoning From Over-the-Counter Imidazoline-Containing Products,” *Ann Emerg Med*, 1991, 20(6):655-8.[PubMed 2039105]

International Brand NamesAfazol Grin (MX); Albalon (AE, BH, CH, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LU, LY, NL, OM, QA, SA, SY, YE); Albalon Liquifilm (AU, PH); Albasol (CN, CO, CR, GT, PA, PE, SV); Alfa (ES); All Clear (HK); Alphadinal (MX); Benil (HR); Celunaf (MX); Clear Eyes (AU); Colirio

Alfa (ES); Dazolin (AR); Gotinal (MX); Imizol (IT); Miraclar (ES); Mirafrin (CO); Murine Clear Eyes (AU); Nafazolin (HR); Naftazolina (IT); Naphazolin (DE); Naphcon (AE, BE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, GR, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, VE, YE, ZA, ZM, ZW); Naphcon Forte (AE, AU, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TH, TN, TZ, UG, YE, ZA, ZM, ZW); Naphcon forte (LU); Naphtears (PY, UY); Nasal Yer (ES); Piniol (DE); Privin (AT); Privina (BR); Proculin (DE); Rhinaf (EC); Rhinazin (PL); Rhinex (DE); Rimidol (SE); Rinal (PT); Rintal (PE); Sanorin (CZ, EE); Tele-Stulln (DE); Vasocedine (LU); Vasoclear-V (PH); Vasoconstrictor (ES); VasoNit (DE); Vistalbalon (DE); Zolin (PE)

Naproxen and Pseudoephedrine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(na PROKS en & soo doe e FED rin)

U.S. Brand NamesAleve® Cold & Sinus [OTC] [DSC]; Aleve® Sinus & Headache [OTC] [DSC]; Aleve®-D Sinus & Cold [OTC]; Aleve®-D Sinus & Headache [OTC]

Pharmacologic CategoryDecongestant/Analgesic

Use: Labeled IndicationsTemporary relief of cold, sinus, and flu symptoms (including nasal congestion, sinus congestion/pressure, headache, minor body aches and pains, and fever)

Dosing: Adults**Cold, sinus, and flu symptoms (Aleve®-D Cold & Sinus, Aleve®-D Sinus & Headache):** Oral: One caplet every 12 hours (maximum dose: 2 caplets/24 hours); treatment for >10 days is not recommended unless directed by healthcare provider.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Cold, sinus, and flu symptoms:** Children ≥12 years: Refer to adult dosing.

Administration: OralDo not crush or chew; swallow whole. Drink a full glass of water with each dose. May administer with food or milk if upset stomach occurs.

Dietary ConsiderationsDrink a full glass of water with each dose. May take with food or milk if upset stomach occurs.

StorageStore at 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to pseudoephedrine, naproxen, aspirin, other NSAIDs, or any component of the formulation; during or within 14 days of MAO inhibitor therapy; immediately prior to or after coronary artery bypass graft (CABG) surgery

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.

- Aseptic meningitis: May increase the risk of aseptic meningitis, especially in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders.

- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.

- Cardiovascular events: NSAIDs are associated with an increased risk of adverse cardiovascular events, including MI, stroke, and new onset or worsening of pre-existing hypertension. Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin's cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.

- Gastrointestinal events: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation. These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: Use is contraindicated immediately prior to or after coronary artery bypass graft (CABG) surgery. Risk of MI and stroke may be increased with use following CABG surgery.

- Diabetes: Use with caution in patients with diabetes mellitus.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or angle-closure glaucoma.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or urinary obstruction.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

- Thyroid disease: Use with caution in patients with thyroid disease.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.
- Pediatrics: Safety and efficacy of this combination product have not been established in children <12 years of age.

Other warnings/precautions:

- Self-medication (OTC use): Prior to self-medication, patients should contact healthcare provider if they have had recurring heartburn, stomach pain or upset, ulcers, bleeding problems, high blood pressure, heart or kidney disease, thyroid disease, diabetes, glaucoma, enlarged prostate, other serious medical problems, are currently taking a diuretic, aspirin, anticoagulant, or are ≥60 years of age. Recommended dosages should not be exceeded, due to an increased risk of GI bleeding. Stop use and consult a healthcare provider if symptoms get worse, newly appear, or continue; if an allergic reaction occurs; if nervousness, dizziness, or sleeplessness occurs; if having difficulty swallowing, or if fever lasts for >3 days, congestion lasts for >7 days, or pain >10 days. Consuming ≥3 alcoholic beverages/day or taking longer than recommended may increase the risk of GI bleeding.

Pregnancy ConsiderationsSee individual agents.
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsNaproxen: **Substrate** (minor) of CYP1A2, 2C9
Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Naproxen absorption rate/levels may be decreased if taken with food. Onset of effect may be delayed if pseudoephedrine is taken with food.

Herb/Nutraceutical: *Naproxen:* Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity). *Pseudoephedrine:* Avoid ephedra, yohimbe (may cause hypertension).

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet, extended release:

Aleve® Cold & Sinus [DSC], Aleve® Sinus & Headache [DSC], Aleve®-D Sinus & Cold, Aleve®-D Sinus & Headache: Naproxen sodium 220 mg [equivalent to naproxen 200 mg and sodium 20 mg] and pseudoephedrine hydrochloride 120 mg

Generic AvailableNo

ManufacturerBayer HealthCare

Mechanism of Action

Naproxen: Reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pseudoephedrine: Directly stimulates alpha-adrenergic receptors of respiratory mucosa causing vasoconstriction; directly stimulates beta-adrenergic receptors causing bronchial relaxation

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Naproxen
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

NSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response.

Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, confusion, insomnia, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 2 weeks of discontinuing an MAO inhibitor. May decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels.

Index TermsNaproxen Sodium and Pseudoephedrine; Pseudoephedrine and Naproxen

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Naproxen

Lexi-Drugs Online

English

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Naproxen may be confused with Natacyn®, Nebcin®

Aleve® may be confused with Alesse®

Anaprox® may be confused with Anaspaz®, Avapro®

Naprelan® may be confused with Naprosyn®

Naprosyn® may be confused with Naprelan®, Natacyn®, Nebcin®

International issues:

Flogen® [Mexico] may be confused with Flovent® which is a brand name for fluticasone in the U.S.

Flogen® [Mexico] may be confused with Floxin® which is a brand name for ofloxacin in the U.S.

Pronunciation(na PROKS en)

U.S. Brand NamesAleve® [OTC]; Anaprox®; Anaprox® DS; EC-Naprosyn®; Mediproxen [OTC]; Midol® Extended Relief; Naprelan®; Naprosyn®; Pamprin® Maximum Strength All Day Relief [OTC]

Canadian Brand NamesAnaprox®; Anaprox® DS; Apo-Napro-Na DS®; Apo-Napro-Na®; Apo-Naproxen EC®; Apo-Naproxen SR®; Apo-Naproxen®; Gen-Naproxen EC; Naprosyn®; Naxen®; Naxen® EC; Novo-Naproc EC; Novo-Naprox; Novo-Naprox Sodium; Novo-Naprox Sodium DS; Novo-Naprox SR; Nu-Naprox; PMS-Naproxen EC; Pro-Naproxen EC; Riva-Naproxen; Sab-Naproxen

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsManagement of ankylosing spondylitis, osteoarthritis, and rheumatoid disorders (including juvenile rheumatoid arthritis); acute gout; mild-to-moderate pain; tendonitis, bursitis; dysmenorrhea; fever

Use: DentalManagement of pain and swelling

Dosing: Adults**Note:** Dosage expressed as naproxen base; 200 mg naproxen base is equivalent to 220 mg naproxen sodium.

Gout, acute: Oral: Initial: 750 mg, followed by 250 mg every 8 hours until attack subsides. **Note:** EC-Naprosyn® is not recommended.

Migraine, acute (unlabeled use): Initial: 500-750 mg; an additional 250-500 mg may be given if needed (maximum: 1250 mg in 24 hours). **Note:** EC-Naprosyn® is not recommended.

Pain (mild-to-moderate), dysmenorrhea, acute tendonitis, bursitis: Oral: Initial: 500 mg, then 250 mg every 6-8 hours; maximum: 1250 mg/day naproxen base

Rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis: 500-1000 mg/day in 2 divided doses; may increase to 1.5 g/day of naproxen base for limited time period

OTC labeling: Pain/fever:

Adults ≤65 years: 200 mg naproxen base every 8-12 hours; if needed, may take 400 mg naproxen base for the initial dose; maximum: 600 mg naproxen base/24 hours

Adults >65 years: Refer to elderly dosing.

Dosing: ElderlyRefer to adult dosing and Geriatric Considerations.

OTC labeling: Pain/fever: Adults >65 years: 200 mg naproxen base every 12 hours

Dosing: Pediatric**Note:** Dosage expressed as naproxen base; 200 mg naproxen base is equivalent to 220 mg naproxen sodium.

Juvenile arthritis: Oral: Children >2 years: 10 mg/kg/day in 2 divided doses

OTC labeling: Pain/fever: Oral: Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute: use is not recommended.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister with food, milk, or antacids to decrease GI adverse effects

Suspension: Shake suspension well before administration.

Tablet, extended release: Swallow tablet whole; do not break, crush, or chew.

Dietary ConsiderationsDrug may cause GI upset, bleeding, ulceration, perforation; take with food or milk to minimize GI upset.

StorageStore oral suspension and tablet at 15°C to 30°C (59°F to 86°F).

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to naproxen, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Aseptic meningitis: May increase the risk of aseptic meningitis, especially in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.
- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.
- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.
- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.
- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.
- Pediatrics: Safety and efficacy have not been established in children <2 years of age. Not for self-medication (OTC use) in children <12 years of age.

Other warnings/precautions:

- Self-medication (OTC use): Prior to self-medication, patients should contact healthcare provider if they have had recurring stomach pain or upset, ulcers, bleeding problems, high blood pressure, heart or kidney disease, other serious medical problems, are currently taking a diuretic, or are ≥60 years of age. Recommended dosages should not be exceeded, due to an increased risk of GI bleeding. Consuming ≥3 alcoholic beverages/day or taking longer than recommended may increase the risk of GI bleeding.

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of the elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high-dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (3rd trimester)

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Adverse Reactions

1% to 10%:

Cardiovascular: Edema (3% to 9%), palpitation (<3%)

Central nervous system: Dizziness (3% to 9%), drowsiness (3% to 9%), headache (3% to 9%), lightheadedness (<3%), vertigo (<3%)

Dermatologic: Pruritus (3% to 9%), skin eruption (3% to 9%), ecchymosis (3% to 9%), purpura (<3%), rash

Endocrine & metabolic: Fluid retention (3% to 9%)

Gastrointestinal: Abdominal pain (3% to 9%), constipation (3% to 9%), nausea (3% to 9%), heartburn (3% to 9%), diarrhea (<3%), dyspepsia (<3%), stomatitis (<3%), flatulence, gross bleeding/perforation, indigestion, ulcers, vomiting

Genitourinary: Abnormal renal function

Hematologic: Hemolysis (3% to 9%), ecchymosis (3% to 9%), anemia, bleeding time increased

Hepatic: LFTs increased

Ocular: Visual disturbances (<3%)

Otic: Tinnitus (3% to 9%), hearing disturbances (<3%)

Respiratory: Dyspnea (3% to 9%)

Miscellaneous: Diaphoresis (<3%), thirst (<3%)

<1%: Agranulocytosis, alopecia, anaphylactic/anaphylactoid reaction, angioneurotic edema, arrhythmia, aseptic meningitis, asthma, blurred vision, cognitive dysfunction, colitis, coma, confusion, CHF, conjunctivitis, cystitis, depression, dream abnormalities, dysuria, eosinophilia, eosinophilic pneumonitis, erythema multiforme, exfoliative dermatitis, glossitis, granulocytopenia, hallucinations, hematemesis, hepatitis, hyper-/hypoglycemia, hyper-/hypotension, infection, interstitial nephritis, melena, jaundice, leukopenia, liver failure, lymphadenopathy, menstrual disorders, malaise, MI, muscle weakness, myalgia, oliguria, pancreatitis, pancytopenia, paresthesia, photosensitivity, pneumonia, polyuria, proteinuria, pyrexia, rectal bleeding, renal failure, renal papillary necrosis, respiratory depression, sepsis, Stevens-Johnson syndrome, tachycardia, seizure, syncope, thrombocytopenia, toxic epidermal necrolysis ulcerative stomatitis, vasculitis

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 2C9

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Naproxen absorption rate/levels may be decreased if taken with food.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Test InteractionsNaproxen may interfere with 5-HIAA urinary assays; due to an interaction with m-dinitrobenzene, naproxen should be discontinued 72 hours before adrenal function testing if the Porter-Silber test is used.

Monitoring ParametersOccult blood loss, periodic liver function test, CBC, BUN, serum creatinine; urine output

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess effectiveness and interactions of other medications patient may be taking. Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, GI effects, hepatotoxicity, or ototoxicity) at beginning of therapy and periodically throughout therapy. Schedule ophthalmic evaluations for patients who develop eye complaints during long-term NSAID therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsPeriodic liver function, CBC, BUN, serum creatinine

Patient EducationTake this medication exactly as directed; do not increase dose without consulting prescriber. Do not crush tablets. Take with food or milk to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol, aspirin or aspirin-containing medication, or any other anti-inflammatory medications without consulting prescriber. You may experience drowsiness, dizziness, lightheadedness, or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); anorexia, nausea, vomiting, or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or fluid retention (weigh yourself weekly and report unusual [3-5 lb/week] weight gain), GI bleeding, ulceration, or perforation can occur with or without pain; or discontinue medication and contact prescriber if persistent abdominal pain or cramping, or blood in stool occurs. Report breathlessness, respiratory difficulty, or unusual cough; chest pain, rapid heartbeat, palpitations; unusual bruising/bleeding; blood in urine, stool, mouth, or vomitus; swollen extremities; skin rash or itching; acute fatigue; or changes in eyesight (double vision, color changes, blurred vision), hearing, or ringing in ears. **Pregnancy/breast-feeding precautions:** Notify prescriber if you are or intend to become pregnant. Do not take this drug during last trimester of pregnancy. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet, as sodium: 220 mg [equivalent to naproxen 200 mg and sodium 20 mg]

Aleve®, Midol® Extended Relief, Pamprin® Maximum Strength All Day Relief: 220 mg [equivalent to naproxen 200 mg and sodium 20 mg]

Capsule, liquid gel, as sodium:

Aleve®: 220 mg [equivalent to naproxen 200 mg and sodium 20 mg]

Gelcap, as sodium:

Aleve®: 220 mg [equivalent to naproxen 200 mg and sodium 20 mg]

Suspension, oral: 125 mg/5 mL (500 mL)

Naprosyn®: 125 mg/5 mL (480 mL) [contains sodium 39 mg (1.5 mEq/5 mL); orange-pineapple flavor]

Tablet: 250 mg, 375 mg, 500 mg

Naprosyn®: 250 mg, 375 mg, 500 mg

Tablet, as sodium: 220 mg [equivalent to naproxen 200 mg and sodium 20 mg]; 275 mg [equivalent to naproxen 250 mg and sodium 25 mg]; 550 mg [equivalent to naproxen 500 mg and sodium 50 mg]

Aleve®: 220 mg [equivalent to naproxen 200 mg and sodium 20 mg]

Anaprox®: 275 mg [equivalent to naproxen 250 mg and sodium 25 mg]

Anaprox® DS: 550 mg [equivalent to naproxen 500 mg and sodium 50 mg]

Mediproxen: 220 mg [equivalent to naproxen 200 mg and sodium 20 mg]

Tablet, controlled release, as sodium: 550 mg [equivalent to naproxen 500 mg and sodium 50 mg]

Naprelan®: 412.5 mg [equivalent to naproxen 375 mg and sodium 37.5 mg]; 550 mg [equivalent to naproxen 500 mg and sodium 50 mg]

Tablet, delayed release, enteric coated: 375 mg, 500 mg

EC-Naprosyn®: 375 mg, 500 mg

Tablet, extended release, as sodium: 550 mg [equivalent to naproxen 500 mg and sodium 50 mg]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Suspension (Naprosyn)

125 mg/5 mL (300): $47.25

Suspension (Naproxen)

125 mg/5 mL (500): $51.50

Tablet, 24-hour (Naprelan)

375 mg (30): $106.17

500 mg (30): $108.80

Tablet, EC (EC-Naprosyn)

375 mg (30): $54.94

500 mg (30): $60.44

Tablet, EC (Naproxen DR)

375 mg (60): $35.99

500 mg (60): $64.99

Tablets (Anaprox)

275 mg (30): $70.76

Tablets (Anaprox DS)

550 mg (30): $96.04

Tablets (Naprosyn)

375 mg (100): $157.14

500 mg (30): $65.93

Tablets (Naproxen)

250 mg (90): $16.00

375 mg (90): $17.00

500 mg (60): $17.99

Tablets (Naproxen Sodium)

275 mg (60): $15.99

550 mg (30): $14.99

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: Analgesic: 1 hour; Anti-inflammatory:~2 weeks

Peak effect: Anti-inflammatory: 2-4 weeks

Duration: Analgesic: ≤7 hours; Anti-inflammatory: ≤12 hours

Absorption: Almost 100%

Protein binding: >99%; increased free fraction in elderly

Half-life elimination: Normal renal function: 12-17 hours; End-stage renal disease: No change

Time to peak, serum: 1-4 hours

Excretion: Urine (95%)

Related Information

- Antacid Drug Interactions
- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Naproxen and naproxen sodium have the potential to interfere with the antiplatelet effect of low-dose aspirin. One study of naproxen and low-dose aspirin has suggested that naproxen may interfere with aspirin's antiplatelet activity when they are coadministered (Steinhubl, 2005). However, naproxen 500 mg administered 2 hours before or after aspirin 100 mg did not interfere with aspirin's antiplatelet effect. The FDA stated that there is no data looking at doses of naproxen <500 mg. Naproxen over-the-counter strength is 220 mg tablets.

The FDA has warned that ibuprofen can interfere with the antiplatelet effect of low-dose aspirin (81 mg/day), potentially rendering aspirin less effective when used for cardioprotection and stroke protection. In situations where these drugs could be used concomitantly, the FDA has proved the following information: Patients who use immediate release aspirin (not enteric-coated aspirin) and take single doses of ibuprofen 400 mg, should dose the ibuprofen at least 30 minutes or longer after aspirin ingestion or more than 8 hours before aspirin ingestion to avoid attenuation of aspirin's effect. Similar recommendations may hold for concomitant may hold for concomitant naproxen and aspirin use.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness; may rarely cause drowsiness, confusion, insomnia, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A meta-analysis (Pope, 1993) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 Heart Failure Guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin's inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other Considerations The 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients. Should not be used to treat perioperative pain after coronary bypass surgery (CABG).

Index Terms Naproxen Sodium

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International Brand NamesAcusprain (ZA); Aflamax (PE); Aleve (AU, EE, PL, PY, SG, UY); Alpron (PH); Anapran (PL); Anexopen (GR); Antalgin (ES); Apo-Naproxen (PL); Apranax (BG, CR, DO, FR, GT, HN, NI, PA, PL, RU, SV, VE); Artagen (IN); Artroxen (IT); Boloxen (PL); Bonyl (DK); Complement (PE); Crysanal (AU); Daprox (DK); Dysmenalgit (DE); Emochol (PL); Femex (NL); Femme Free (AU); Flanax (BR); Floginax (IT); Gibixen (IT); Hexal Naproleve (AU); Inza (AU, HK); Iraxen (PE); Laser (IT); Leniartil (IT); Licorax (KP); Nafasol (ZA); Nalgesin (PL); Nalgesin Forte (PL); Naposin (TW); Naprex (PK); Naprium (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Naprius (IT); Naprodil (MX); Naproflex (TH); Naprontag (AR); Naprorex (AE, BH, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Naprosyn (AE, AU, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, CZ, DK, EC, EG, ES, ET, FI, GB, GH, GM, GN, GR, GY, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NO, OM, PE, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Naprosyn LE (TH); Naprosyn LLE (PH); Naprosyn LLE Forte (PH); Naprosyne (BE, FR, NL); Naproxen (PL); Naproxi 250 (IL); Naproxi 500 (IL); Naprux (AR); Napsen (TH); Naxen (MX, NZ); Naxen F (KP); Naxen-F CR (KP); Naxopren (FI); Naxyn 250 (IL); Naxyn 500 (IL); Norswel (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Novaxen (MX); Nycopren (AT, DK, FI); Prexan (IT); Priaxen (BB, BF, BJ, BM, BS, BZ, CI, ET, GH, GM, GN, GY, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Primeral (IT); Prodexin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Pronaxen (MY, SE); Proxen (AE, AT, BH, CH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, TW, YE); Sanaprox (PL); Seladin (MY, SG); Sutolin (TW); Synflex (GB, IE); Tarproxen (PL); Veradol (AR); Vero (PL); Xenar (IT); Xenifar (ID)

Naratriptan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Amerge® may be confused with Altace®, Amaryl®

Pronunciation(NAR a trip tan)

U.S. Brand NamesAmerge®

Canadian Brand NamesAmerge®

Pharmacologic CategoryAntimigraine Agent; Serotonin $5\text{-HT}_{1B, 1D}$ Receptor Agonist

Use: Labeled IndicationsTreatment of acute migraine headache with or without aura

Dosing: Adults**Migraine:** Oral: 1 mg to 2.5 mg at the onset of headache. It is recommended to use the lowest possible dose to minimize adverse effects. If headache returns or dose not fully resolve, the dose may be repeated after 4 hours. Do not exceed 5 mg in 24 hours.

Dosing: ElderlyNot recommended for use in the elderly.

Dosing: Renal Impairment

Cl_{cr} 18-39 mL/minute: Initial: 1 mg; do not exceed 2.5 mg in 24 hours.

Cl_{cr} <15 mL/minute: Do not use.

Dosing: Hepatic ImpairmentContraindicated in patients with severe liver failure. The maximum dose is 2.5 mg in 24 hours for patients with mild or moderate liver failure. The recommended starting dose is 1 mg.

Calculations

- Creatinine Clearance: Adults

Administration: OralDo **not** crush or chew tablet; swallow whole with water.

ContraindicationsHypersensitivity to naratriptan or any component of the formulation; cerebrovascular, peripheral vascular disease (ischemic bowel disease), ischemic heart disease (angina pectoris, history of myocardial infarction, or proven silent ischemia); or in patients with symptoms consistent with ischemic heart disease, coronary artery vasospasm, or Prinzmetal's angina; uncontrolled hypertension or patients who have received within 24 hours another 5-HT agonist (sumatriptan, zolmitriptan) or ergotamine-containing product; patients with known risk factors associated with coronary artery disease; patients with severe hepatic or renal disease (Cl_{cr} <15 mL/minute); do not administer naratriptan to patients with hemiplegic or basilar migraine

Allergy Considerations

- Serotonin $5\text{-HT}_{1B,1D}$ Receptor Agonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac events: Coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia/fibrillation, cardiac arrest, and death have been reported with 5-HT_1 agonist administration. Patients who experience sensations of chest pain/pressure/tightness or symptoms suggestive of angina following dosing should be evaluated for coronary artery disease or Prinzmetal's angina before receiving additional doses.

- Cerebrovascular events: Cerebral/subarachnoid hemorrhage and stroke have been reported with 5-HT_1 agonist administration.

- Elevated blood pressure: Significant elevation in blood pressure, including hypertensive crisis, has also been reported on rare occasions in patients with and without a history of hypertension.

- Vasospasm-related events: Peripheral vascular ischemia and colonic ischemia have been reported with 5-HT_1 agonist.

Disease-related concerns:

- Coronary artery disease: Should not be given to patients who have risk factors for CAD (eg, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, menopause, male >40 years of age) without adequate cardiac evaluation. Patients with suspected CAD should have cardiovascular evaluation to rule out CAD before considering use; if cardiovascular evaluation “is satisfactory”, first dose should be given in the healthcare provider's office. Periodic evaluation of cardiovascular status should be done in all patients.

Concurrent drug therapy issues:

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce naratriptan's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

Other warnings/precautions:

- Appropriate use: Only indicated for treatment of acute migraine; if a patient does not respond to the first dose, the diagnosis of migraine should be reconsidered.

Geriatric ConsiderationsNaratriptan was not studied in patients >65 years of age. Use in elderly patients is not recommended because of the presence of risk factors associated with adverse effects. These include the presence of coronary artery disease, decreased liver or renal function, and the risk of pronounced blood pressure increases.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies using naratriptan in pregnant women. Use only if potential benefit to the mother outweighs the potential risk to the fetus. A pregnancy registry has been established to monitor outcomes of women exposed to naratriptan during pregnancy (800-336-2176). In animal studies, administration was associated with embryolethality, fetal abnormalities, and pup mortality and growth retardation. Tremors were observed in the offspring of female rats when exposed to naratriptan late in gestation.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Central nervous system: Dizziness, drowsiness, malaise/fatigue

Gastrointestinal: Nausea, vomiting

Neuromuscular & skeletal: Paresthesia

Miscellaneous: Pain or pressure in throat or neck

<1% (Limited to important or life-threatening): Coronary artery vasospasm, transient myocardial ischemia, MI, ventricular tachycardia, ventricular fibrillation, palpitation, hypertension, ECG changes (PR prolongation, QT_c prolongation, premature ventricular contractions, atrial flutter, or atrial fibrillation) hypotension, heart murmurs, bradycardia, hyperlipidemia, hypercholesterolemia, hypothyroidism, hyperglycemia, glycosuria, ketonuria, eye hemorrhage, abnormal liver function tests, abnormal bilirubin tests, convulsions, allergic reaction, panic, hallucinations

Drug Interactions

Ergot Derivatives: May enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Nursing: Physical Assessment/MonitoringAssess for clear diagnosis of migraine and risk factors for CAD prior to beginning therapy. Assess potential for interactions with other pharmacological agents patient may be taking (eg, ergot-containing drugs, SSRIs). Monitor closely, especially after the first dose. Evaluate therapeutic effectiveness and adverse response (eg, drowsiness, nausea/vomiting, paresthesias, hypertension). If no response to first dose, diagnosis of migraine should be re-evaluated. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Do not crush or chew tablet; swallow whole with water. This drug is to be used to reduce your migraine, not to prevent or reduce the number of attacks. If headache returns or is not fully resolved, the dose may be repeated after 4 hours. If you have no relief with first dose, do not take a second dose without consulting prescriber. **Do not exceed 5 mg in 24 hours. Do not take within 24 hours of any other migraine medication without first consulting prescriber.** May cause dizziness, fatigue, or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known); or nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report immediately any chest pain, palpitations, or rapid heartbeat; tightness in throat or neck; or rash, itching, or hives. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 1 mg, 2.5 mg

Generic AvailableNo

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Tablets (Amerge)

1 mg (9): $250.04

2.5 mg (9): $251.69

Mechanism of ActionThe therapeutic effect for migraine is due to serotonin agonist activity

Pharmacodynamics/Kinetics

Onset of action: 30 minutes

Absorption: Well absorbed

Protein binding, plasma: 28% to 31%

Metabolism: Hepatic via CYP

Bioavailability: 70%

Time to peak: 2-3 hours

Excretion: Urine

Related Information

- Antimigraine Drugs: 5-HT1 Receptor Agonists

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, or fatigue; may rarely cause panic reactions or hallucinations

Mental Health: Effects on Psychiatric TreatmentSSRIs may cause hyper-reflexia, weakness, or lack of coordination when used with naratriptan; these combinations should be avoided

Cardiovascular ConsiderationsCoronary vasospasm has been associated with 5-HT$_{1B/1D}$ agonists. These agents are contraindicated in patients with documented ischemic of vasospastic coronary artery disease. Patients with risk factors for CAD may receive these agents, provided a cardiovascular evaluation yields satisfactory evidence that the patient is free of cardiovascular disease. In patients with risk factors for CAD, administration of the initial dose in a medically staffed/equipped facility (ie, physician's office) is recommended. In addition, ECG monitoring after the initial dose should be considered. Patients who acquire risk factors for CAD, or long-term users of agents from this class of medications, should undergo periodic cardiovascular evaluation.

Anesthesia and Critical Care Concerns/Other ConsiderationsNaratriptan should not be used in patients with a history of vasospastic disease, Prinzmetal's angina, or any critical vascular disease.

Index TermsNaratriptan Hydrochloride

References

Boyer EW and Shannon M, “The Serotonin Syndrome,” *N Engl J Med*, 2005, 352:1112-20.[PubMed 15784664]

International Brand NamesAntimigrin (AT); Naragran (DK); Naramig (AE, AR, AU, BE, BG, BH, BR, CH, CN, CO, CY, CZ, DE, EE, EG, FI, FR, GB, HU, IL, IQ, IR, JO, KP, KW, LB, LY, MX, NL, NO, OM, PE, PT, QA, SA, SE, SG, SY, TH, UY, YE)

Natalizumab

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Natalizumab: Additional Reports of Progressive Multifocal Leukoencephalopathy - August 2008

Two new cases of progressive multifocal leukoencephalopathy (PML) have been reported to the Food and Drug Administration (FDA) by Biogen Idec and Elan, the manufacturer and distributor of natalizumab (Tysabri®). Both cases were noted in European patients and are the first cases reported since the reintroduction of natalizumab since June 2006. PML has been previously reported following the use of natalizumab and its use is contraindicated in patients with a history of PML. As opposed to the previous cases of PML which were associated with natalizumab in conjunction with a beta-interferon, the two new cases were reported in patients on monotherapy for multiple sclerosis. One patient, however, had a history of beta-interferon use.

In the United States, all patients must be enrolled in the Tysabri® Outreach Unified Commitment to Health (TOUCH™) Prescribing Program in order to receive natalizumab. As part of the TOUCH program, patients are monitored closely for the development of opportunistic infections, including PML. Based on the available data, the FDA still believes that the risk of PML is lower with natalizumab monotherapy. Natalizumab should be discontinued in patients where PML is suspected.

Refer to the following FDA website for additional information:http://www.fda.gov/medwatch/safety/2008/safety08.htm#Tysabri2

Natalizumab: Postmarketing Reports of Hepatotoxicity - February 2008; Updated - Hypersensitivity Reactions/Serious Herpes Infections - June 2008

Biogen Idec and Elan and Biogen Idec Canada Inc, in conjunction with the U.S. Food and Drug Administration (FDA) and Health Canada, have issued respective "Dear Healthcare Professional" letters regarding updates to the warnings and precautions section in the labeling of natalizumab (Tysabri®). Labeling updates were prompted by reports of clinically significant liver injury that have occurred in the postmarketing setting. In addition, Health Canada is warning their healthcare professionals of postmarketing reports of hypersensitivity reactions, as well as rare cases of serious herpes infections.

Hepatotoxicity has been reported as early as 6 days after the first dose of Tysabri® and may include transaminase and bilirubin elevation. Some patients have experienced a recurrence of hepatotoxicity with treatment rechallenge. In addition, an analysis of patients exposed to a brief initial course of natalizumab therapy (≤3 treatments) followed by an interruption of therapy (≥3 months), suggests an increased risk for hypersensitivity reactions in association with the reinitiation of therapy. Healthcare professionals should also be aware of rare postmarketing case reports of serious herpes infections associated with the use of natalizumab.

The manufacturer recommends that Tysabri® be discontinued in patients who develop jaundice, other signs of hepatotoxicity, or hypersensitivity reactions. Antibody testing is now recommended in the Canadian labeling for patients who have received brief initial courses of natalizumab therapy followed by an extended interruption in therapy. Patients who develop serious herpes infections should discontinue therapy until successful resolution of the infection.

Additional information may be found at

U.S.: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Tysabri

Canada: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/tysabri_hpc-cps-eng.php

Pronunciation(na ta LIZ u mab)

U.S. Brand NamesTysabri®

Canadian Brand NamesTysabri®

Pharmacologic CategoryGastrointestinal Agent, Miscellaneous; Monoclonal Antibody, Selective Adhesion-Molecule Inhibitor

Use: Labeled Indications

U.S. labeling: Monotherapy for the treatment of relapsing forms of multiple sclerosis; treatment of moderately- to severely-active Crohn's disease

Canada labeling: Treatment of relapsing forms of multiple sclerosis

Dosing: Adults

Multiple sclerosis: I.V.: 300 mg infused over 1 hour every 4 weeks

Crohn's disease: I.V.: 300 mg infused over 1 hour every 4 weeks; discontinue if therapeutic benefit is not observed within initial 12 weeks of therapy

Concomitant use with corticosteroids: For patients who begin treatment while on chronic oral corticosteroids, begin tapering oral steroids when the onset of natalizumab therapeutic benefit is observed; discontinue use if patient cannot be tapered off of oral corticosteroids within 6 months of therapy initiation. If additional concomitant corticosteroids are required and exceed 3 months/year (in addition to initial corticosteroid taper), consider discontinuing therapy.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot studied.

Dosing: Hepatic ImpairmentNot studied. Discontinue use with jaundice or signs/symptoms of hepatic injury.

Administration: I.V.Solution may be warmed to room temperature prior to administration. Diluted solution should be infused over 1 hour; do not administer by I.V. bolus or push. Patients should be closely monitored for signs and symptoms of hypersensitivity during the infusion and for at least 1 hour after the infusion is complete. The infusion should be discontinued if a reaction occurs, and treatment of the reaction should be instituted. Following infusion, flush line with NS.

Administration: I.V. DetailpH: 6.1

StorageStore concentrated solution under refrigeration between 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Do not shake. Following dilution, may store refrigerated for use within up to 8 hours.

ReconstitutionDilute natalizumab 300 mg in NS 100 mL to a final concentration of 2.6 mg/mL. Gently invert to mix; do not shake.

RestrictionsPatients must be enrolled in the Tysabri® Outreach Unified Commitment to Health (TOUCH™) Prescribing Program (800-456-2255) to receive natalizumab (MS-TOUCH™ for multiple sclerosis or CD-TOUCH™ for Crohn’s disease). Healthcare providers must also register with the program in order to prescribe, dispense or administer natalizumab. Treatment must be reauthorized every 6 months. Natalizumab is available only through infusion centers registered with the TOUCH™ program; infusion center information is available at 1-800-456-2255.

Medication guides are available at http://www.fda.gov/cder/Offices/ODS/MG/natalizumabMG.pdf and should be provided to every patient prior to initiation of therapy.

ContraindicationsHypersensitivity to natalizumab, murine proteins, or any component of the formulation; current or history of progressive multifocal leukoencephalopathy (PML)

Canada labeling: Additional contraindications (not in U.S. labeling): Immunocompromised patients as a result of immunosuppressant or antineoplastic therapy, or immunodeficiencies (eg, HIV, leukemia, lymphoma)

Warnings/Precautions

Boxed warnings:

- Progressive multifocal leukoencephalopathy (PML): See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Hepatotoxicity: Hepatotoxicity, including transaminase and bilirubin elevation, has been reported with use; may occur as early as 6 days after the first dose; may recur with treatment rechallenge; discontinue use with jaundice or signs/symptoms of hepatic injury.

- Hypersensitivity/infusion-related reactions: During clinical studies, up to 24% of patients experienced an infusion-related reaction; serious systemic hypersensitivity reactions occurred in ≤1% of patients. Severe reactions, including anaphylaxis, may occur rarely. Patients treated with brief initial courses of therapy (≤3 infusions) followed by an extended interruption in therapy (≥3 months) may be at an increased risk for hypersensitivity reactions following reinitiation of therapy. Retreatment is not recommended in patients developing hypersensitivity reactions. Infusion-related reactions may occur more frequently in patients with antibody to natalizumab. Antibody formation (which occurs in about 10% of patients) is associated with a decrease in natalizumab levels and a decrease in the efficacy of natalizumab. The Canadian labeling recommends antibody testing in patients who have received brief initial courses of natalizumab therapy followed by an extended interruption in therapy.

- Infections: Use may be associated with an increased risk of infections, including opportunistic infections and serious herpes infections (rare, postmarketing reports; concurrent use of antineoplastic, immunosuppressant [including short-course corticosteroids], or immunomodulating agents may increase this risk). In the presence of a serious herpes infection, discontinue therapy until successful resolution of the infection.

- Progressive multifocal leukoencephalopathy (PML): **[U.S. Boxed Warning]: Increased risk of developing fatal or disabling PML (an opportunistic infection caused by the JC virus); patients must be routinely monitored for signs of PML with baseline and periodic MRI evaluations; access to and provision of therapy requires registration of patients and healthcare providers with the TOUCH™ prescribing program;** concurrent immunomodulator therapy or immunosuppression may be risk factors for the development of PML, however, PML has also been reported with natalizumab monotherapy. A brain MRI scan (baseline) should be obtained prior to initiating therapy in MS patients and should be considered in Crohn’s patients.

Disease-related concerns:

- Crohn’s disease: Natalizumab should not be used in combination with immunosuppressants or tumor necrosis factor (TNF) inhibitors in patients with Crohn’s disease; aminosalicylates may be used concurrently with natalizumab. For patients who begin treatment while on chronic oral corticosteroids, begin tapering oral steroids when the onset of natalizumab therapeutic benefit is observed; discontinue use if patient cannot be tapered off of oral corticosteroids within 6 months of therapy initiation. If additional concomitant corticosteroids are required and exceed 3 months/year (in addition to initial corticosteroid taper), consider discontinuing therapy.

- Depression: Use with caution in patients with a history of depression; closely monitor.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Use should be restricted to patients with inadequate response to or intolerant of other therapies for Crohn's disease or multiple sclerosis.

- Long-term therapy: Safety and efficacy have not been established for therapy >2 years or in chronic progressive multiple sclerosis.

Pregnancy Risk FactorC

Pregnancy Considerations Adverse events have been observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use only if clearly needed. Pregnant women exposed to natalizumab should be enrolled in the Tysabri® Pregnancy Exposure Registry (800-456-2255).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding Considerations It is not known whether natalizumab is excreted in human milk. Because many immunoglobulins are secreted in milk and the potential for serious adverse reactions exists, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Adverse Reactions

>10%:

Central nervous system: Headache (32% to 38%), fatigue (10% to 27%), depression (≤19%)

Dermatologic: Rash (6% to 12%)

Gastrointestinal: Nausea (≤17%), gastroenteritis (≤11%), abdominal discomfort (≤11%)

Genitourinary: Urinary tract infection (3% to 21%)

Neuromuscular & skeletal: Arthralgia (8% to 19%), extremity pain (16%), back pain (≤12%)

Respiratory: Upper respiratory infection (≤22%), lower respiratory infection (≤17%)

Miscellaneous: Infusion-related reaction (11% to 24%), influenza (≤12%), flu-like syndrome (≤11%)

1% to 10%:

Cardiovascular: Peripheral edema (5% to 6%), chest discomfort (≤5%)

Central nervous system: Vertigo (≤6%), dysesthesia (3%), syncope (≤2%), somnolence (≤2%)

Dermatologic: Dermatitis (≤7%), pruritus (≤4%), urticaria (≤2%), dry skin (≤1%)

Endocrine & metabolic: Menstrual irregularities (≤5%), dysmenorrhea (2% to 6%), amenorrhea (≤2%), ovarian cyst (≤2%)

Gastrointestinal: Diarrhea (10%), dyspepsia (≤5%), abdominal pain (≤4%), constipation (≤4%), flatulence (≤3%), aphthous stomatitis (≤2%), weight changes (≤2%), cholelithiasis (≤1%), gingival infection (1%)

Genitourinary: Vaginitis/vaginal infections (4% to 10%), urinary frequency (≤9%), urinary incontinence (≤4%)

Hematologic: Hematoma (1%)

Hepatic: Transaminase increased (≤5%)

Local: Bleeding at injection site (≤3%)

Neuromuscular & skeletal: Muscle cramp (≤5%), tremor (1% to 3%), rigors (≤3%), joint swelling (≤2%)

Respiratory: Sinusitis (≤8%), cough (≤7%), tonsillitis (≤7%), pharyngolaryngeal pain (≤6%), epistaxis (2%)

Miscellaneous: Antibody formation (9% to 10%), tooth infection (≤9%), herpes infection (≤8%), viral infection (≤7%), hypersensitivity reactions (acute: 2% to 4%; serious acute: ≤1%; delayed: ≤5%), toothache (≤4%), serious infection (2% to 3%), night sweats (≤1%)

<1%, postmarketing, and/or case reports: Acne, agitation, anaphylaxis/anaphylactoid reactions, anemia, angina, appendicitis, bilirubin increased, bronchopulmonary aspergillosis, *Burkholderia cepacia*, Crohn's disease exacerbation, cryptosporidial gastroenteritis, cytomegalovirus hepatitis, dizziness, dyspnea, erythema. fever, flushing, hemoglobin decreased (mild, transient), hepatotoxicity, herpes encephalitis, herpes meningitis, hypotension, joint stiffness, lethargy, leukocytosis, nasopharyngitis, opportunistic infections (including progressive multifocal leukoencephalopathy [PML], meningitis, and bronchopulmonary infections), muscle spasms, muscle weakness, onychorrhexis, paresis, petechiae, pharyngitis, *Pneumocystis jiroveci* pneumonia, pneumonia, psychomotor hyperactivity, pulmonary *Mycobacterium avium intracellulare*, suicidal ideation, tachycardia, thrombocytopenia, thrombophlebitis, varicella pneumonia, vasodilatation

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Immunosuppressants: May enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersMonitor for hypersensitivity reactions during, and for 1 hour after, infusion; signs and symptoms of hepatotoxicity (eg, serum transaminases, bilirubin)

Baseline brain MRI scan; if PML is suspected, obtain gadolinium-enhanced brain MRI scan and CSF analysis for JC viral DNA. Evaluate for signs or symptoms of progressive multifocal leukoencephalopathy (focal neurologic deficits, which may present as hemiparesis, visual field deficits, cognitive impairment, aphasia, ataxia, and/or cranial nerve deficits) at 3 and 6 months after first infusion; every 6 months thereafter. **Note:** Transient and reversible leukocytosis (excluding neutrophils) and mildly reduced hemoglobin may occur with treatment and may require ~4 months for return to baseline values after the last dose.

Canadian labeling recommends antibody testing in patients who have received brief initial courses of natalizumab therapy followed by an extended interruption in therapy.

Nursing: Physical Assessment/MonitoringPatient and prescriber must be registered with the Tysabri Outreach Unified Commitment to Health Prescribing Program (TOUCH™). Patient should be monitored closely for infusion-related reactions during and for 1 hour following infusion. If hypersensitivity reaction occurs, infusion should be promptly discontinued; retreatment is not recommended. See Administration and Dosing specifics. Evaluate laboratory tests, effectiveness of treatment (according to indications for use), and adverse effects (hepatotoxicity [jaundice], opportunistic infection [including herpes], excessive fatigue, depression). Provide patient/caregiver with medication guide and teach patient/caregiver possible side effects, appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSigns and symptoms of hepatotoxicity (eg, serum transaminases, bilirubin). Canadian labeling recommends antibody testing in patients who have received brief initial courses of natalizumab therapy followed by an extended interruption in therapy.

Patient EducationThis drug can only be administered by intravenous infusion. You will be monitored closely during and following infusion. Report immediately any skin rash; dizziness; nausea; flushing; difficulty breathing; chest pain; or tightness, redness, swelling, or pain at infusion site. Following infusion, you may experience headache or joint pain (consult prescriber for appropriate analgesic) or unusual fatigue (adequate and frequent rest periods may help). Report immediately any signs of urinary tract infection (itching, pain, discharge); dark urine or altered frequency of urination; lower respiratory infection (cough, difficulty breathing, chest tightness); unusual sores or unhealed sores; chest discomfort or pain; back pain; unusual depression; worsening of symptoms; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or are breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Tysabri®: 300 mg/15 mL (15 mL) [contains polysorbate-80]

Generic AvailableNo

ManufacturerBiogen Idec Inc

Mechanism of ActionNatalizumab is a monoclonal antibody against the alpha-4 subunit of integrin molecules. These molecules are important to adhesion and migration of cells from the vasculature into inflamed tissue. Natalizumab blocks integrin association with vascular receptors, limiting adhesion and transmigration of leukocytes. Efficacy in specific disorders may be related to reduction in specific inflammatory cell populations in target tissues. In multiple sclerosis, efficacy may be related to blockade of T-lymphocyte migration into the central nervous system; treatment results in a decreased frequency of relapse. In Crohn's disease, natalizumab decreases inflammation by binding to alpha-4 integrin, blocking adhesion and migration of leukocytes in the gut.

Pharmacodynamics/Kinetics

Distribution: Crohn's disease: 2.4-8 L; Multiple sclerosis: 3.8-7.6 L

Half-life elimination: Crohn's disease: 3-17 days; Multiple sclerosis: 7-15 days

Pharmacotherapy Pearls

U.S. patients and healthcare providers (eg, pharmacies, physicians) must register with the TOUCH Program (800-456-2255) to ensure the safe and appropriate use of natalizumab. Enrollment in the program insures that participants acknowledge and adhere to the following requirements:

Healthcare providers/prescribers: Ability to diagnose, including management or referral of potential PML complications; educate patients on program enrollment procedures, including risk/benefit of treatment; file appropriate program paperwork with manufacturer; report serious infections to manufacturer and FDA; evaluate patient response to therapy and assess appropriateness of continued treatment.

Patients: Understand medication guide; promptly report worsening symptoms (including hypersensitivity); inform other healthcare providers of their therapy with natalizumab.

Canadian patients are encouraged to enroll in the Canadian Tysabri® Care Program™ (888)-827-2827, a patient registry for those prescribed natalizumab.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause depression, suicidal ideation has been reported; use caution in patients with a history of depression; monitor for depressive symptoms

Mental Health: Effects on Psychiatric TreatmentConcomitant use with psychotropic agents may produce additive effects; monitor

Index TermsAN100226; Anti-4 Alpha Integrin; IgG4-Kappa Monoclonal Antibody

References

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Rudick RA, Stuart WH, Calabresi PA et al, "Natalizumab Plus Interferon Beta-1a for Relapsing Multiple Sclerosis," *N Engl J Med*, 2006, 354:911-23.[PubMed 16510745]

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Van Assche G, Van Ranst M, Sciot R, et al, "Progressive Multifocal Leukoencephalopathy After Natalizumab Therapy for Crohn's Disease," *N Engl J Med*, 2005, 353(4):362-8.[PubMed 15947080]

Yousry TA, Major EO, Ryschkewitsch C et al, "Evaluation of Patients Treated With Natalizumab for Progressive Multifocal Leukoencephalopathy," *N Engl J Med* 2006, 354:924-33.

International Brand Names Tysabri (AT, AU, BE, BG, CH, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HN, IE, IL, IT, NL, NO, PT, RU, SE, TR)

Natamycin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Natacyn® may be confused with Naprosyn®

Pronunciation(na ta MYE sin)
U.S. Brand NamesNatacyn®
Canadian Brand NamesNatacyn®
Pharmacologic CategoryAntifungal Agent, Ophthalmic
Use: Labeled IndicationsTreatment of blepharitis, conjunctivitis, and keratitis caused by susceptible fungi (*Aspergillus*, *Candida*, *Cephalosporium*, *Fusarium*, and *Penicillium*)
Dosing: Adults

Fungal keratitis: Ophthalmic: Instill 1 drop in conjunctival sac every 1-2 hours, after 3-4 days reduce to one drop 6-8 times/day; usual course of therapy is 2-3 weeks or until resolution of active fungal keratitis (may be useful to gradually reduce dosage at 4-7 day intervals to assure elimination of organism)

Fungal blepharitis or conjunctivitis: Ophthalmic: Instill 1 drop in conjunctival sac every 4-6 hours

Dosing: ElderlyRefer to adult dosing.
Administration: TopicalOphthalmic: Shake well before using, do not touch dropper to eye.
StorageStore at 2°C to 24°C (36°F to 75°F); do not freeze. Protect from excessive heat and light.
ContraindicationsHypersensitivity to natamycin or any component of the formulation
Warnings/Precautions

Disease-related concerns:

- Epithelial ulceration: Suspension may adhere to epithelial ulcers; retention of the suspension in the fornices occurs regularly.

Special populations:

- Contact lens wearers: Contact lens should not be worn if signs/symptoms of fungal blepharitis, conjunctivitis, and/or keratitis are present. Contains benzalkonium chloride which may be absorbed by contact lenses; remove contact lens prior to administration and wait 15 minutes before reinserting.

Other warnings/precautions:

- Appropriate use: For topical eye use only. Failure to improve (keratitis) after 7-10 days of administration suggests infection caused by a microorganism not susceptible to natamycin; efficacy as a single agent in fungal endophthalmitis has not been established.

Geriatric ConsiderationsAssess patient's ability to self-administer ophthalmic drops.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsPostmarketing and/or case reports: Allergic reaction, chest pain, corneal opacity, dyspnea, eye discomfort, edema, hyperemia, irritation and/or pain, foreign body sensation, parasthesia, tearing, vision changes
Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringMonitor effectiveness of therapy. Teach patient appropriate administration, possible side effects/interventions, and adverse symptoms to report.
Patient EducationThis medication is for ophthalmic use only. Administer exactly as directed for as long as directed. Do not discontinue early without contacting prescriber. Store at room temperature. Shake before using. Wash hands before instilling solution. Sit or lie down to instill. Open eye, gently pull down lower lid, and put drop(s) in inner corner of eye. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Close eye and roll eye in all directions; apply gentle pressure to inner corner of eye. Do not blink for $^{1}/_{2}$ minute. Wipe away excess from skin around eye. May cause sensitivity to bright light (dark glasses may help). Temporary stinging or blurred vision may occur. Report persistent pain, burning, vision changes, swelling, itching, worsening of condition, or lack of improvement in 2-3 weeks. Discontinue medication and contact prescriber immediately if you develop a rash or allergic reaction.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, ophthalmic:

Natacyn®: 5% (15 mL) [contains benzalkonium chloride]

Generic AvailableNo

Mechanism of ActionIncreases cell membrane permeability in susceptible fungi
Pharmacodynamics/Kinetics

Absorption: Ophthalmic: Systemic, <2%; Gastrointestinal: Poor

Distribution: Adheres to cornea, retained in conjunctival fornices; does not produce effective intraocular fluid concentrations

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsPimaricin
International Brand NamesDeronga (DE); Fukricin (ID); Miconacina (MX); Natacyn (AR, MY, PL, SG, TH, TW); Natadrops (IN); Natafucin (GB, IT); Natamycyna (PL); Ophth-natamycin (PK); Pima-Biciron (DE); Pimafucin (BE, CZ, DE, FI, HU, LU, PL, PT)

Nateglinide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(na te GLYE nide)
U.S. Brand NamesStarlix®
Canadian Brand NamesStarlix®
Pharmacologic CategoryAntidiabetic Agent, Meglitinide Derivative
Use: Labeled IndicationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as monotherapy when hyperglycemia cannot be managed by diet and exercise alone; in combination with metformin or a thiazolidinedione to lower blood glucose in patients whose hyperglycemia cannot be controlled by exercise, diet, or a single agent alone
Dosing: Adults**Management of type 2 diabetes mellitus:** Oral: Initial and maintenance dose: 120 mg 3 times/day, 1-30 minutes before meals; may be given alone or in combination with metformin or a thiazolidinedione; patients close to Hb A_{1c} goal may be started at 60 mg 3 times/day
Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo specific dosage adjustment is recommended for patients with mild-to-severe renal disease. Patients on dialysis showed reduced medication exposure and plasma protein binding. Patients with severe renal dysfunction are more susceptible to glucose-lowering effect; use with caution.
Dosing: Hepatic ImpairmentIncreased serum levels are seen with mild hepatic insufficiency; no dosage adjustment is needed. Has not been studied in patients with moderate to severe liver disease; use with caution.
Dietary ConsiderationsNateglinide should be taken 1-30 minutes prior to meals. Scheduled dose should not be taken if meal is missed. Dietary modification based on ADA recommendations is a part of therapy. Decreases blood glucose concentration. Hypoglycemia may occur. Must be able to recognize symptoms of hypoglycemia (palpitations, sweaty palms, lightheadedness).
StorageStore at 25°C (77°F).
ContraindicationsHypersensitivity to nateglinide or any component of the formulation; diabetic ketoacidosis, with or without coma (treat with insulin); type 1 diabetes mellitus (insulin dependent, IDDM)
Warnings/Precautions

Concerns related to adverse effects:

- Hypoglycemia: May cause hypoglycemia; appropriate patient selection, dosage, and patient education are important to avoid hypoglycemic episodes.

Disease-related concerns:

- Adrenal/pituitary impairment: Use with caution in patients with adrenal and/or pituitary impairment; may be more susceptible to glucose-lowering effects.
- Hepatic impairment: Use with caution in patients with moderate-to-severe hepatic impairment.
- Renal impairment: Use with caution in patients with severe renal impairment; may be more susceptible to glucose-lowering effects.
- Stress-related states: It may be necessary to discontinue nateglinide and administer insulin if the patient is exposed to stress (ie, fever, trauma, infection, surgery).

Concurrent drug therapy issues:

- Agents stimulating insulin release: Patients not adequately controlled on oral agents which stimulate insulin release (eg, glyburide) should not be switched to nateglinide or have nateglinide added to therapy.
- Metformin: Indicated for adjunctive therapy with metformin; not to be used as a substitute for metformin monotherapy.
- Sulfonylureas: Combination treatment with sulfonylureas is not recommended (no additional benefit).

Special populations:

- Elderly: Use with caution in the elderly; may be more susceptible to glucose-lowering effects.
- Malnourished patients: Use with caution in malnourished patients; may be more susceptible to glucose-lowering effects.
- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo changes in safety and efficacy were seen in patients ≥65 years; however, some older adults may show increased sensitivity to dosing. How “tightly” a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar of <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well they recognize hypoglycemic or hyperglycemic symptoms, and how to respond to them and their other disease states. Intensive glucose control (Hb

A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in animal reproduction studies; therefore, nateglinide is classified as pregnancy category C. Information describing the effects of nateglinide on pregnancy outcomes is limited. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if nateglinide is excreted in breast milk. Breast -feeding is not recommended by the manufacturer.

Pregnancy & Lactation, In-Depth

- Nateglinide in Pregnancy & Lactation

Adverse ReactionsAs reported with nateglinide monotherapy:

1% to 10%:

Central nervous system: Dizziness (4%)

Endocrine & metabolic: Hypoglycemia (2%), increased uric acid

Gastrointestinal: Weight gain

Neuromuscular & skeletal: Arthropathy (3%)

Respiratory: Upper respiratory infection (10%)

Miscellaneous: Flu-like syndrome (4%)

Postmarketing and/or case reports: Cholestatic hepatitis, jaundice, liver enzymes increased, rash, pruritus, urticaria

Metabolism/Transport Effects**Substrate** (major) of CYP2C9, 3A4; **Inhibits** CYP2C9 (weak)

Drug Interactions

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (increased risk of hypoglycemia).

Food: Rate of absorption is decreased and time to T_{max} is delayed when taken with food. Food does not affect AUC. Multiple peak plasma concentrations may be observed if fasting. Not affected by composition of meal.

Herb/Nutraceutical: Avoid alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, and stinging nettle (may enhance the hypoglycemic effects of antidiabetic agents). St. John's wort may decrease the levels/effect of nateglinide.

Monitoring ParametersGlucose and Hb A_{1c} levels, weight, lipid profile

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response on a regular basis throughout therapy. Teach patient proper use (or refer patient to diabetic educator), possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report

Monitoring: Lab TestsGlucose and Hb A_{1c} levels, lipid profile

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take this medication exactly as directed, 1-30 minutes before a meal. If you skip a meal (or add an extra meal), skip (or add) a dose for that meal. Do not change dosage or discontinue without first consulting prescriber. Follow dietary and lifestyle recommendations of provider. You will be instructed in signs of hypo- or hyperglycemia by prescriber or diabetic educator; be alert for adverse hypoglycemia (tachycardia, profuse perspiration, tingling of lips and tongue, seizures, or change in sensorium) and follow prescriber's instructions for intervention. Note that unusual strenuous exercise, excessive alcohol intake, or acute reduction in caloric intake may increase risk of hypoglycemia. Persistent nausea or vomiting, or severely decreased dietary intake may increase risk of hyperglycemia. May cause mild side effects during first weeks of therapy (dizziness, weight gain, mild muscle aches or pain, or flu-like symptoms); if these do not diminish, notify prescriber. Report signs of respiratory infection or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Starlix®: 60 mg, 120 mg

Generic AvailableNo

ManufacturerNovartis Pharmaceuticals Corp

Pricing: U.S. (www.drugstore.com)

Tablets (Starlix)

60 mg (30): $56.45

120 mg (30): $60.40

Mechanism of ActionA phenylalanine derivative, nonsulfonylurea hypoglycemic agent used in the management of type 2 diabetes mellitus (noninsulin dependent, NIDDM); stimulates insulin release from the pancreatic beta cells to reduce postprandial hyperglycemia; amount of insulin release is dependent upon existing glucose levels

Pharmacodynamics/Kinetics

Onset of action: Insulin secretion: ~20 minutes

Peak effect: 1 hour

Duration: 4 hours

Absorption: Rapid

Distribution: 10 L

Protein binding: 98%, primarily to albumin

Metabolism: Hepatic via hydroxylation followed by glucuronide conjugation via CYP2C9 (70%) and CYP3A4 (30%) to metabolites

Bioavailability: 73%

Half-life elimination: 1.5 hours

Time to peak: ≤1 hour

Excretion: Urine (83%, 16% as unchanged drug); feces (10%)

Related Information

- Diabetes Mellitus Management, Adults

Pharmacotherapy PearlsAn increase in weight was seen in nateglinide monotherapy, which was not seen when used in combination with metformin.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause weight gain; psychotropics may produce additive effects. Beta-blockers and MAO inhibitors may potentiate the hypoglycemic effects of nateglinide. May cause flu-like symptoms; take this into consideration if also concerned about SSRI discontinuation syndrome.

References

American Diabetes Association, “Standards of Medical Care in Diabetes Mellitus -- 2009,” *Diabetes Care*, 2009, 32(Suppl 1):13-61.[PubMed 19118286]

International Brand NamesFastic (JP, KP); Glinate (IN); Glunat (TW); Starlix (AR, AT, BE, BG, BR, CH, CL, CN, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HN, ID, IE, IT, MX, MY, NL, NO, PE, PH, PL, PT, RU, SE, SG, TR, TW, UY, VE); Starsis (JP); Trazec (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Nebivolol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(ne BIV oh lole)

U.S. Brand NamesBystolic™

Pharmacologic CategoryBeta Blocker, Beta$_1$ Selective

Use: Labeled IndicationsTreatment of hypertension, alone or in combination with other agents

Use: Unlabeled/InvestigationalHeart failure

Dosing: Adults

Hypertension: Oral: Initial: 5 mg once daily; if initial response is inadequate, may be increased at 2-week intervals to a maximum dose of 40 mg once daily

Heart failure (unlabeled use): Adults ≥70 years: Oral: Initial: 1.25 mg once daily; if tolerated, may increase by 2.5 mg at 1- to 2-week intervals to a maximum dose of 10 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentSevere impairment (Cl_{cr} <30 mL/minute): Initial: 2.5 mg/day; increase cautiously.

Dosing: Hepatic ImpairmentModerate impairment (Child-Pugh class B): Initial: 2.5 mg/day; increase cautiously.

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken without regard to meals.

StorageStore at 20°C to 25°C (68°F to 77°F). Protect from light.

ContraindicationsHypersensitivity to nebivolol or any component of the formulation; severe bradycardia; heart block greater than first-degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; decompensated cardiac failure; sick sinus syndrome (unless a permanent pacemaker is in place); severe hepatic impairment (Child-Pugh class C)

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to a variety of allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; for patients with bronchospastic disease who do not respond to or cannot tolerate other therapies, initial low doses of beta$_1$-selective nebivolol may be employed and used cautiously with close monitoring. Ensure patient has an inhaled beta$_2$-agonist immediately available.

- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.

- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.

- Heart failure (HF): Use with caution in patients with compensated heart failure and monitor for a worsening of the condition. If condition worsens, consider temporary discontinuation or dosage reduction of nebivolol. Patients should be stabilized on heart failure regimen prior to initiation of beta-blocker. Beta-blocker therapy should be initiated at very low doses with gradual and very careful titration. Adjustment of other medications (ACE inhibitors and/or diuretics) may be required.

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment required with moderate impairment (Child-Pugh class B). Use is contraindicated in patients with Child-Pugh class C hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis.

- Peripheral vascular disease (PVD): Can precipitate or aggravate symptoms of arterial insufficiency in patients with PVD and Raynaud’s disease; use with caution and monitor for progression of arterial obstruction.

- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.

- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required with severe renal impairment (Cl_{cr}

<30 mL/minute). Nebivolol has not been evaluated in dialysis-dependent patients.

- Thyrotoxicosis: Beta-blockade may mask signs of hyperthyroidism (eg, tachycardia). Abrupt discontinuation may exacerbate symptoms of hyperthyroidism and may also induce thyroid storm.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents which decrease myocardial function (eg, ether, cyclopropane and trichloroethylene).

- Calcium channel blockers: Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block may occur.

- CYP2D6 Inhibitors: Use with caution in patients receiving CYP2D6 inhibitors (eg, chlorpromazine, fluoxetine, propafenone, propoxyphene, quinidine, ritonavir) (see Drug Interactions).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with coronary artery disease), but gradually tapered over 1-2 weeks to avoid acute tachycardia, hypertension, and/or ischemia.

Geriatric Considerations Due to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (eg, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20% to 50% in elderly populations. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults.

Pregnancy Risk Factor C (manufacturer); D (2nd and 3rd trimesters - expert analysis)

Pregnancy Considerations Adverse events were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Beta-blockers have been associated with persistent bradycardia, hypotension, and IUGR; IUGR is probably related to maternal hypertension. Available evidence suggests beta-blockers are generally safe during pregnancy (JNC 7).

Lactation Excretion in breast milk unknown/not recommended

Breast-Feeding Considerations Cases of neonatal hypoglycemia have been reported following maternal use of beta-blockers at parturition or during breast-feeding. Due to the potential for serious adverse effects (eg, bradycardia, hypotension) in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

1% to 10%:

Cardiovascular: Peripheral edema (1%), bradycardia (≤1%), chest pain (≤1%)

Central nervous system: Headache (6% to 9%), fatigue (dose related; 2% to 5%), dizziness (2% to 4%), insomnia (1%)

Dermatologic: Rash (≤1%)

Endocrine & metabolic: Hypercholesterolemia (≥1%), HDL levels decreased (≥1%), hyperuricemia (≥1%), triglyceride levels increased (≥1%), uric acid levels increased (≥1%)

Gastrointestinal: Diarrhea (dose related; 2% to 3%), nausea (1% to 3%), abdominal pain (≥1%)

Hematologic: Thrombocytopenia (≥1%)

Neuromuscular & skeletal: Paresthesia (≥1%), weakness (≥1%)

Renal: BUN increased (≥1%)

Respiratory: Dyspnea (≤1%)

<1%, postmarketing, and/or case reports: Acute pulmonary edema, acute renal failure, allergic vasculitis, angioedema, AST increased, ALT increased, AV block (second and third degree), bilirubin increased, bronchospasm, claudication, erectile dysfunction, hepatic function abnormal, hypersensitivity reaction, MI, peripheral ischemia, pruritus, psoriasis, Raynaud's phenomenon, skin disorder, somnolence, syncope, urticaria, vertigo, vomiting

Metabolism/Transport Effects **Substrate** of CYP2D6 (major)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Beta1 Selective) may diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may increase antihypertensive effect).

Monitoring ParametersBlood pressure, ECG; neurologic status; serum glucose (in diabetic patients)

Nursing: Physical Assessment/MonitoringMonitor therapeutic response (especially pulse rate and blood pressure) and adverse reactions at the beginning and periodically throughout therapy. Assess other prescription, herbal, and OTC medications the patient may be taking to avoid duplications and interactions. Taper dosage slowly when discontinuing; do not discontinue abruptly. If you have diabetes, this medication may mask the symptoms of hypoglycemia; monitor glucose levels closely. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Monitoring: Lab TestsSerum glucose (regularly in patients with diabetes)

Patient EducationInform prescriber of all prescription or OTC medications or herbal products you are taking. Do not take any new medications or stop taking this medication without consulting prescriber. If you have diabetes, monitor blood glucose levels closely; may mask the signs of hypoglycemia. May cause postural hypotension. Use caution when climbing stairs or changing position. Report signs of fluid retention (unusual weight gain of >3-5 lb/week, swelling of the extremities); shortness of breath; or chest pain. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Bystolic™: 2.5 mg, 5 mg, 10 mg

Generic AvailableNo

ManufacturerForest Pharmaceuticals Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Bystolic)

2.5 mg (30): $57.99

5 mg (30): $57.99

10 mg (30): $59.99

Mechanism of ActionHighly-selective inhibitor of beta$_1$-adrenergic receptors; at doses ≤10 mg nebivolol preferentially blocks beta$_1$-receptors. Nebivolol, unlike other beta-blockers, also produces an endothelium-derived nitric oxide-dependent vasodilation resulting in a reduction of systemic vascular resistance.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: V$_d$: 8-12 L/kg

Protein binding: ~98%

Metabolism: Hepatic; via glucuronidation and CYP2D6; extensive first-pass metabolism to multiple active metabolites with variable activity

Bioavailability: ~12% (extensive metabolizers); 96% (poor metabolizers)

Half-life elimination: Terminal: 10-12 hours (extensive metabolizers); 19-32 hours in poor metabolizers

Time to peak, plasma: 0.5-4 hours

Excretion: Urine (38%; 67% in poor metabolizers; <0.5% of unchanged drug); feces (44%; 13% in poor metabolizers; <0.5% of unchanged drug)

Dental Health: Effects on Dental TreatmentNebivolol is a cardioselective beta-blocker. Local anesthetic with vasoconstrictor can be safely used in patients medicated with nebivolol. Nonselective beta-blockers (ie, propranolol, nadolol) enhance the pressor response to epinephrine, resulting in hypertension and bradycardia; this has not been reported for nebivolol. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause CNS depression, fatigue, dizziness, or insomnia

Mental Health: Effects on Psychiatric TreatmentAcetylcholinesterase inhibitors and SSRIs may enhance the bradycardic effect of beta-blockers; monitor. Amphetamines may diminish the antihypertensive effect of beta-blockers. Chlorpromazine, fluoxetine, paroxetine, pergolide, and ropinirole may increase the levels/effects of nebivolol.

Cardiovascular Considerations

Heart Failure: Strong evidence supports that beta-blocker therapy, without intrinsic sympathomimetic activity (ISA), should be initiated in select patients with **stable** heart failure (NYHA Class II-III). To date, carvedilol, sustained release metoprolol, and bisoprolol have demonstrated a beneficial effect on morbidity and mortality. It is important that beta-blocker therapy be instituted initially at very low doses with gradual and very careful titration.

The SENIORS trial evaluated the use of nebivolol versus placebo in 2128 elderly patients (≥70 years) with chronic heart failure. The initial dose of nebivolol was 1.25 mg once daily. If tolerated, nebivolol was increased by 2.5 mg every 1-2 weeks to a maximum dose of 10 mg (reached by 68% of patients). Mean dose achieved during the study was 7.7 mg. Mean duration of follow-up was 21 months. Nebivolol reduced the composite endpoint of all cause mortality or cardiovascular hospital admission (31.1% vs 35.3%, p=0.039) compared to placebo. Nebivolol's effects on all-cause mortality alone, a secondary endpoint, did not reach statistical significance. The authors concluded that nebivolol is an effective and well-tolerated beta-blocker in the treatment of heart failure in the elderly. Future clinical trials should be conducted to determine applicability to other populations with chronic heart failure. Furthermore, comparisons to proven beta-blockers for chronic heart failure are needed.

Hypertension: Beta-blocker therapy in the treatment of hypertension has been associated with improved cardiovascular outcomes. According to the 2003 JNC-VII guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Beta-blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for a beta-blocker include patients with heart failure, post myocardial infarction, high coronary disease risk, or diabetes. In type-2 diabetic patients, a UK Prospective Diabetes Study Group (UKPDS) trial showed that beta-blocker therapy (atenolol) was as effective as an ACE inhibitor in reducing cardiovascular events and that the benefits of therapy were related more to the degree of antihypertensive efficacy rather than the class of drug used.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia and hypertension.

Anesthesia and Critical Care Concerns/Other Considerations

Surgery: Based on available evidence, beta-blockers should be started days to weeks before elective surgery in selected patients when possible and titrated to a heart rate <65 beats per minute. Additional data suggest that long acting beta-blockers may be superior to short acting ones (Redelmeier, 2005). The ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery recommend beta-blockers be continued in patients undergoing surgery who are receiving beta-blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA Class I guideline indications (Class I recommendation). The guidelines also recommend that beta-blockers be given to patients undergoing vascular surgery who have myocardial ischemia demonstrated during preoperative testing (Class I recommendation).

The guidelines also state that beta-blockers are probably recommended in patients undergoing intermediate risk (eg, carotid endarterectomy, prostate surgery) or vascular surgery in whom preoperative assessment identifies coronary heart disease or high cardiac risk (Class IIa recommendation). High cardiac risk is defined as having >1 of the following clinical risk factors: History of ischemic heart disease, compensated or prior heart failure, cerebrovascular disease, diabetes mellitus, or renal insufficiency. The use of beta-blockers is uncertain in patients undergoing intermediate risk or vascular surgery with ≤1 clinical risk factor (Class IIb recommendation).

The majority of published trials suggest a benefit of perioperative beta-blocker use during noncardiac surgery especially in high-risk patients; however, more recent clinical trials have not shown a benefit to perioperative beta-blockade for noncardiac surgery (Juul. 2006; Yang, 2006).

Index Terms

Nebivolol Hydrochloride

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Nedocromil

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English English

Jump To Field (Select Field Name)

Pronunciation(ne doe KROE mil)

U.S. Brand NamesAlocril®; Tilade® [DSC]

Canadian Brand NamesAlocril®; Tilade®

Pharmacologic CategoryMast Cell Stabilizer

Use: Labeled Indications

Aerosol: Maintenance therapy in patients with mild to moderate bronchial asthma

Ophthalmic: Treatment of itching associated with allergic conjunctivitis

Dosing: Adults

Asthma: Inhalation: 2 inhalations 4 times/day; may reduce dosage to 2-3 times/day once desired clinical response to initial dose is observed. Drug has no known therapeutic systemic activity when delivered by inhalation.

Allergic conjunctivitis: Ophthalmic: 1-2 drops in each eye twice daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Asthma: Inhalation: Children ≥6 years: Refer to adult dosing.

Allergic conjunctivitis: Ophthalmic: Children ≥3 years: Refer to adult dosing.

Administration: OtherOphthalmic: Do not allow tip of container to touch eye, surrounding structures, fingers, or other surfaces to avoid bacterial contamination.

Storage

Alocril®: Store at 2°C to 25°C (36°F to 77°F).

Tilade®: Store at 2°C to 30°C (36°F to 86°F); do not freeze.

ContraindicationsHypersensitivity to nedocromil or any component of the formulation

Warnings/Precautions

Dosage form specific issues:

- Aerosol: Safety and efficacy have not been established in children <6 years of age; if systemic or inhaled steroid therapy is at all reduced, monitor patients carefully; nedocromil is **not** a bronchodilator and, therefore, should not be used for reversal of acute bronchospasm

- Ophthalmic solution: Contains benzalkonium chloride, which may be absorbed by contact lenses; users of contact lenses should not wear them during periods of symptomatic allergic conjunctivitis; safety and efficacy have not been established in children <3 years of age.

Geriatric ConsiderationsElderly may have difficulty using inhaler delivery system, especially if they have physical or medical impairment (eg, Parkinson's disease, stroke). If this prophylactic modality is desired but patient cannot tolerate nedocromil inhalations, consider cromolyn sodium solution for nebulizer use.

Pregnancy Risk FactorB

Pregnancy ConsiderationsThere are no well-controlled studies in pregnant women. Animal studies show no evidence of teratogenicity or harm to fetus. Additionally, nedocromil has minimal systemic absorption.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

Inhalation aerosol:

>10%: Gastrointestinal: Unpleasant taste (12%)

1% to 10%:

Central nervous system: Headache (8%), fatigue (1 %)

Gastrointestinal: Nausea (4%), vomiting (3%), dyspepsia (2%), diarrhea (1%), abdominal pain (2%)

Ocular: Conjunctivitis (1%)

Respiratory: Cough (9%), pharyngitis (8%), rhinitis (7%), upper respiratory infection

Ophthalmic solution:

>10%:

Central nervous system: Headache (40%)

Gastrointestinal: Unpleasant taste

Ocular: Burning, irritation, stinging

Respiratory: Nasal congestion

1% to 10%:

Ocular: Conjunctivitis, eye redness, photophobia

Respiratory: Asthma, rhinitis

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringNot for use during acute bronchospasm. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationAerosol: Do not use during acute bronchospasm. Use exactly as directed; do not use more often than instructed or discontinue without consulting prescriber. You may experience drowsiness, dizziness, fatigue, especially during early therapy (use caution when driving or engaging in tasks requiring alertness until response to drug is known); dry mouth, nausea, or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report persistent runny nose, cough, cold symptoms; unresolved GI effects; skin rash; joint pain or tremor; or if breathing difficulty persists or worsens. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Inhaler: Review use with prescriber or follow package insert for directions. Prime with 3 activations prior to first use or if unused more than 7 days. Keep inhaler clean and unobstructed. Always rinse mouth and throat after use of inhaler to prevent advantageous infection. If you are also using a steroid bronchodilator, wait 10 minutes before using this aerosol.

Ophthalmic: Do not wear contact lenses with allergic conjunctivitis. For the eye only. Open eyes, look up, and pull lower lid down. Squeeze medicine into lower eyelid and close eye. Do not touch bottle tip to eye, eyelid, or other skin.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol for oral inhalation, as sodium:

Tilade®: 1.75 mg/activation (16.2 g; at least 104 inhalations) [DSC]

Solution, ophthalmic, as sodium:

Alocril®: 2% (5 mL) [contains benzalkonium chloride]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Alocril)

2% (5): $85.99

Mechanism of ActionInhibits the activation of and mediator release from a variety of inflammatory cell types associated with asthma including eosinophils, neutrophils, macrophages, mast cells, monocytes, and platelets; it inhibits the release of histamine, leukotrienes, and slow-reacting substance of anaphylaxis; it inhibits the development of early and late bronchoconstriction responses to inhaled antigen

Pharmacodynamics/Kinetics

Onset of action: Inhalation: Full therapeutic effect may not occur until ≥1 week of therapy

Duration: Therapeutic effect: Inhalation: 2 hours

Absorption: Inhalation: Low; Ophthalmic: Low

Protein binding, plasma: 89%

Bioavailability: Inhalation: 2% to 17%; Ophthalmic: <4%

Half-life elimination: 1.5-3.3 hours

Excretion: Urine 70% (as unchanged drug); feces 30% (as unchanged drug)

Related Information

- Asthma
- Inhalant Agents

Pharmacotherapy PearlsNedocromil has no known therapeutic systemic activity when delivered by inhalation.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Unpleasant taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness or drowsiness

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Nedocromil Sodium

International Brand Names Brionil (ES); Cetimil (ES); Halamid (DE); Ildor (ES); Irtan (DE, MX); Kovilen (IT); Kovinal (IT); Nedocromil-Natrium ”Schoeller Pharma” (AT); Telavist (FR); Tilad (ES); Tilade (AR, AT, BR, CZ, DE, DK, ES, FI, GB, GR, HU, ID, IE, IT, LU, NL, PL); Tilade CFC Free (AU); Tilade Mint (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Tilarin (AT, FI, IT, PL); Tilavist (AT, CH, DK, ES, IL, IT, NL, NO, PL, PT, SE)

Nefazodone

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Serzone® may be confused with selegiline, Serentil®, Seroquel®, sertraline

Pronunciation(nef AY zoe done)

Pharmacologic CategoryAntidepressant, Serotonin Reuptake Inhibitor/Antagonist

Use: Labeled IndicationsTreatment of depression

Use: Unlabeled/InvestigationalPost-traumatic stress disorder

Dosing: Adults**Depression:** Oral: 200 mg/day, administered in two divided doses initially, with a range of 300-600 mg/day in two divided doses thereafter.

Dosing: ElderlyOral: Initial: 50 mg twice daily; increase dose to 100 mg twice daily in 2 weeks; usual maintenance dose: 200-400 mg/day

Dosing: Pediatric**Depression (unlabeled use):** Oral: Children and Adolescents: Target dose: 300-400 mg/day (mean: 3.4 mg/kg)

Administration: OralDosing after meals may decrease lightheadedness and postural hypotension, but may also decrease absorption and therefore effectiveness.

StorageStore at room temperature, below 40°C (104°F) in a tight container.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to nefazodone, related compounds (phenylpiperazines), or any component of the formulation; liver injury due to previous nefazodone treatment, active liver disease, or elevated serum transaminases; concurrent use or use of MAO inhibitors within previous 14 days; use in a patient during the acute recovery phase of MI; concurrent use with carbamazepine, cisapride, or pimozide; concurrent therapy with triazolam or alprazolam is generally contraindicated (dosage must be reduced by 75% for triazolam and 50% for alprazolam; such reductions may not be possible with available dosage forms).

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Nefazodone is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Nefazodone is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. The degree of anticholinergic blockade produced by this agent is very low relative to other antidepressants.

- Hepatic failure: Cases of life-threatening hepatic failure have been reported (risk should be considered when choosing an agent for the treatment of depression); discontinue if clinical signs or symptoms suggest liver failure.

- Orthostatic hypotension: May cause orthostatic hypotension (risk is low relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is low relative to other antidepressants.

- Sexual dysfunction: Rare reports of priapism have occurred. The incidence of sexual dysfunction with nefazodone is generally lower than with SSRIs.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk conduction abnormalities with this agent is very low relative to other antidepressants.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs; does not potentiate ethanol but use is not advised.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Discontinuation of therapy: Therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

Geriatric ConsiderationsData on nefazodone in the elderly are limited, specifically regarding efficacy; clinical trials in adult patients have found it superior to placebo and similar to imipramine; nefazodone's C_{max} and AUC have been reported to be increased twofold in the elderly and women after a single dose compared to younger patients, however, these differences were markedly reduced with multiple dosing with women having AUC values of nefazodone and its hydroxy metabolite remaining approximately 50% higher

Pregnancy Risk FactorC

Pregnancy ConsiderationsNefazodone is classified as pregnancy category C due to adverse effects observed in animal studies. When nefazodone is taken during pregnancy, an increased risk of major malformations has not been observed in the small number of pregnancies studied. The long-term effects on neurobehavior have not been evaluated.

Women treated for major depression and who are euthymic prior to pregnancy are more likely to experience a relapse when medication is discontinued as compared to pregnant women who continue taking antidepressant medications. Therapy during pregnancy should be individualized; treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary healthcare provider, and pediatrician. If treatment during pregnancy is required, consider tapering therapy during the third trimester to prevent potential withdrawal symptoms in the infant. If this is done and the woman is considered to be at risk of relapse from her major depressive disorder, the medication can be restarted following delivery.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsNefazodone and its metabolites are excreted in breast milk. Drowsiness, lethargy, poor feeding, and failure to maintain body temperature have been reported in a premature nursing infant. Adverse events were not observed in two case reports of older infants. The long-term effects on neurobehavior have not been studied. The manufacturer recommends that caution be exercised when administering nefazodone to nursing women.

Pregnancy & Lactation, In-Depth

- Nefazodone in Pregnancy & Lactation

Adverse Reactions

>10%:

Central nervous system: Headache, drowsiness, insomnia, agitation, dizziness

Gastrointestinal: Xerostomia, nausea, constipation

Neuromuscular & skeletal: Weakness

1% to 10%:

Cardiovascular: Bradycardia, hypotension, peripheral edema, postural hypotension, vasodilation

Central nervous system: Chills, fever, incoordination, lightheadedness, confusion, memory impairment, abnormal dreams, decreased concentration, ataxia, psychomotor retardation, tremor

Dermatologic: Pruritus, rash

Endocrine & metabolic: Breast pain, impotence, libido decreased

Gastrointestinal: Gastroenteritis, vomiting, dyspepsia, diarrhea, increased appetite, thirst, taste perversion

Genitourinary: Urinary frequency, urinary retention

Hematologic: Hematocrit decreased

Neuromuscular & skeletal: Arthralgia, hypertonia, paresthesia, neck rigidity, tremor

Ocular: Blurred vision (9%), abnormal vision (7%), eye pain, visual field defect

Otic: Tinnitus

Respiratory: Bronchitis, cough, dyspnea, pharyngitis

Miscellaneous: Flu syndrome, infection

<1%: Abdomen enlarged, abnormal gait, accommodation abnormality, acne, allergic reaction, alopecia, ALT increased, amenorrhea, anemia, angina pectoris, anorgasmia, apathy, arthritis, AST increased, asthma, attention decreased, AV block, breast enlargement, bruising, bursitis, cellulitis, cerebrovascular accident, colitis, CHF, conjunctivitis, cystitis, deafness, depersonalization, derealization, diplopia, dry eyes, dry skin, dehydration, dysarthria, ear pain, eczema, ejaculation abnormal, epistaxis, eructation, esophagitis, euphoria, face edema, gastritis, gingivitis, glaucoma, gout, halitosis, hallucinations, hangover effect, hematuria, hemorrhage, hernia, hiccup, hostility, hyperacusis, hypercholesteremia, hyperesthesia, hyperkinesia, hypertension, hyperventilation, hypoglycemia, hypotonia, keratoconjunctivitis, kidney calculus, lactic dehydrogenase increased, laryngitis, leukopenia, libido increased, liver function tests abnormal, lymphadenopathy, maculopapular rash, malaise, menorrhagia, metrorrhagia, mouth ulceration, muscle stiffness, myoclonus, mydriasis, neuralgia, neuroleptic malignant syndrome, night blindness, nocturia, oliguria, oral moniliasis, pallor, paranoid reaction, pelvic pain, periodontal abscess, peptic ulcer, photophobia, photosensitivity, pneumonia, polyuria, ptosis, rectal hemorrhage, salivation increased, stomatitis, suicide attempt, suicidal thoughts, suicide, syncope, tachycardia, taste loss, tendonitis, contracture, tenosynovitis, thinking abnormal, twitching, ulcerative colitis, urticaria, uterine fibroids enlarged, uterine hemorrhage, urinary incontinence, urinary urgency, ventricular extrasystoles, vaginal hemorrhage, varicose vein, vertigo, vesiculobullous rash, voice alteration, weight loss, yawn

Postmarketing and/or case reports: Angioedema, convulsions, galactorrhea, grand mal seizure, gynecomastia, hepatic failure, hepatic necrosis, hepatitis, hyponatremia, priapism, prolactin increased, rhabdomyolysis (with lovastatin/simvastatin), serotonin syndrome, Stevens-Johnson syndrome, thrombocytopenia

⇧ Metabolism/Transport Effects**Substrate** (major) of CYP2D6, 3A4; **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C8 (weak), 2D6 (weak), 3A4 (strong)
⇧ Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Nefazodone may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

BusPIRone: May enhance the serotonergic effect of Antidepressants (Serotonin Reuptake Inhibitor/Antagonist). This may cause serotonin syndrome. *Risk C: Monitor therapy*

Cardiac Glycosides: Nefazodone may increase the serum concentration of Cardiac Glycosides. *Risk C: Monitor therapy*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cisapride: Nefazodone may decrease the metabolism of Cisapride. *Risk X: Avoid combination*

Clozapine: Nefazodone may decrease the metabolism of Clozapine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Nefazodone may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Pravastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Nefazodone may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Protease Inhibitors: May decrease the metabolism of Nefazodone. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Selective Serotonin Reuptake Inhibitors: May enhance the serotonergic effect of Antidepressants (Serotonin Reuptake Inhibitor/Antagonist). This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Tacrolimus: Antidepressants (Serotonin Reuptake Inhibitor/Antagonist) may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Nefazodone absorption may be delayed and bioavailability may be decreased if taken with food.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava (may increase risk of serotonin syndrome and/or excessive sedation).

Monitoring ParametersIf AST/ALT increase >3 times ULN, the drug should be discontinued and not reintroduced; mental status for depression, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased), anxiety, social functioning, mania, panic attacks

Reference RangeTherapeutic plasma levels have not yet been defined

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Monitor for clinical worsening and suicidal ideation. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsIf AST/ALT increase >3 times ULN, the drug should be discontinued and not reintroduced.

Patient EducationTake exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results. Avoid alcohol, caffeine, and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or lightheadedness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or orthostatic hypotension (use caution when climbing stairs or changing position from lying or sitting to standing). Report persistent insomnia or excessive daytime sedation; suicidal ideation; muscle cramping, tremors, weakness, tiredness, or change in gait; chest pain, palpitations, or rapid heartbeat; vision changes or eye pain; respiratory difficulty or breathlessness; malaise, loss of appetite, GI complaints, abdominal pain, or blood in stool; yellowing of skin or eyes (jaundice); or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 50 mg, 100 mg, 150 mg, 200 mg, 250 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Nefazodone HCl)

50 mg (60): $34.00

100 mg (60): $43.00

150 mg (30): $22.99

200 mg (60): $45.99

250 mg (60): $44.99

Mechanism of Action Inhibits neuronal reuptake of serotonin and norepinephrine; also blocks 5-HT$_2$ and alpha$_1$ receptors; has no significant affinity for alpha$_2$, beta-adrenergic, 5-HT$_{1A}$, cholinergic, dopaminergic, or benzodiazepine receptors

Pharmacodynamics/Kinetics

Onset of action: Therapeutic: Up to 6 weeks

Distribution: V$_d$: 0.22-0.87 L/kg

Protein binding: >99%

Metabolism: Hepatic to three active metabolites: Triazoledione, hydroxynefazodone, and m-chlorophenylpiperazine (mCPP)

Bioavailability: 20% (variable)

Half-life elimination: Parent drug: 2-4 hours; active metabolites persist longer

Time to peak, serum: 1 hour, prolonged in presence of food

Excretion: Primarily urine (as metabolites); feces

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile

Pharmacotherapy Pearls May cause less sexual dysfunction than other antidepressants. Women and elderly receiving single doses attain significant higher peak concentrations than male volunteers.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation) and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Nefazodone inhibits reuptake of both serotonin and norepinephrine and also blocks some serotonin receptors. No precautions with vasoconstrictors appear to be necessary.

Mental Health: Child/Adolescent Considerations Seven treatment-refractory and very comorbid children and adolescents (mean age: 12.4 years) with a juvenile mood disorder were treated with a mean daily dose of 357 mg (3.4 mg/kg) for 13 weeks (Wilens, 1997).

Wilens TE, Spencer TJ, Biederman J, et al, “Case Study: Nefazodone for Juvenile Mood Disorders,” *J Am Acad Child Adolesc Psychiatry*, 1997, 36(4):481-5.

Mental Health Comment Due to its 5-HT$_2$ antagonistic activity, nefazodone is associated with a low incidence of sexual dysfunction. Nefazodone may be useful for individuals with post-traumatic stress disorder. Nefazodone has a lower incidence of sedation and orthostasis than trazodone, primarily related to its noradrenergic activity.

Index Terms Nefazodone Hydrochloride; Serzone

References

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Wilens TE, Spencer TJ, Biederman J, et al, “Case Study: Nefazodone for Juvenile Mood Disorders,” *J Am Acad Child Adolesc Psychiatry*, 1997, 36(4):481-5.[PubMed 9100422]

International Brand Names Deprefax (AR); Dutonin (AT, ES, GB, IE); Menfazona (ES); Nefadar (CH, DE, DK, NO, SE); Nefaril (UY); Nefazodone ”BMS” (AT); Reseril (IT); Rulivan (ES); Serzone (AU, BB, BM, BR, BS, BZ, GY, JM, NL, NZ, PL, SR, TT, ZA)

Nelarabine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(nel AY re been)

U.S. Brand NamesArranon®

Canadian Brand NamesAtriance™

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite

Use: Labeled IndicationsTreatment of relapsed or refractory T-cell acute lymphoblastic leukemia (ALL) and T-cell lymphoblastic lymphoma

Use: Unlabeled/InvestigationalCML (Philadelphia chromosome positive) T-Cell blast phase

Dosing: Adults**T-cell ALL, T-cell lymphoblastic lymphoma:** I.V.: 1500 mg/m^2/day on days 1, 3, and 5; repeat every 21 days.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**T-cell ALL, T-cell lymphoblastic lymphoma:** I.V.: 650 mg/m^2/day on days 1 through 5; repeat every 21 days.

Dosing: Renal Impairment

Cl_{cr} ≥50 mL/minute: No adjustment recommended.

Cl_{cr} <50 mL/minute: Safety has not been established.

Cl_{cr} <30 mL/minute: Closely monitor.

Dosing: Hepatic ImpairmentSafety has not been established; closely monitor with severe impairment (bilirubin >3 mg/dL).

Dosing: Adjustment for Toxicity

Neurologic toxicity ≥ grade 2: Discontinue treatment.

Hematologic or other (non-neurologic) toxicity: Consider treatment delay.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Adequate I.V. hydration recommended to prevent tumor lysis syndrome; allopurinol may be used if hyperuricemia is anticipated.

Children: Infuse over 1 hour daily for 5 consecutive days

Adults: Infuse over 2 hours on days 1, 3, and 5

Administration: I.V. DetailpH: 5-7

StorageStore unopened vials at 15°C to 30°C (59°F to 86°F). Stable in plastic or glass containers for up to 8 hours at room temperature.

ReconstitutionReconstitution is not required; the appropriate dose should be added to empty plastic bag or glass container.

CompatibilityStable in sodium chloride 0.45%.

ContraindicationsHypersensitivity to nelarabine or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.
- Neurotoxicity: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Leukopenia, thrombocytopenia, anemia, and neutropenia commonly occur.

- Neurotoxicity: **[U.S. Boxed Warning]: Neurotoxicity is the dose-limiting toxicity;** observe closely for signs and symptoms of neurotoxicity (somnolence, confusion, convulsions, ataxia, paresthesia, hypoesthesia, coma, status epilepticus, craniospinal demyelination, or ascending neuropathy). Risk of neurotoxicity may increase in patients with concurrent or previous intrathecal chemotherapy or history of craniospinal irradiation.

- Tumor lysis syndrome: Appropriate measures must be taken to prevent hyperuricemia and tumor lysis syndrome; use extreme caution in patients with increased uric acid, gout, and history of uric acid stones; monitor, consider allopurinol and hydrate accordingly.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; monitor closely. Risk of adverse reactions may be higher with hepatic dysfunction.

- Renal impairment: Use with caution in patients with renal impairment; monitor closely. Ara-G clearance may be reduced with renal dysfunction

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

- Vaccines: Avoid administration of live vaccines.

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenic effects were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant during therapy.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions**Note:** Pediatric adverse reactions fell within a range similar to adults except where noted.

>10%:

Cardiovascular: Peripheral edema (15%), edema (11%)

Central nervous system: Fatigue (50%), fever (23%), somnolence (7% to 23%; grades 2-4: 1% to 6%), dizziness (21%; grade 2: 8% adults), headache (15% to 17%; grades 2-4: 4% to 8%), hypoesthesia (6% to 17%; grades 2-4: children 5%, adults 12%), pain (11%)

Dermatologic: Petechiae (12%)

Endocrine & metabolic: Hypokalemia (11%)

Gastrointestinal: Nausea (41%), diarrhea (22%), vomiting (10% to 22%), constipation (21%)

Hematologic: Anemia (95% to 99%; grade 4: 10% to 14%), neutropenia (81% to 94%; grade 4: children 62%, adults 49%), thrombocytopenia (86% to 88%; grade 4: 22% to 32%), leukopenia (38%; grade 4: 7%), febrile neutropenia (12%; grade 4: 1%)

Hepatic: Transaminases increased (12%)

Neuromuscular & skeletal: Peripheral neuropathy (12% to 21%; grades 2-4: 11% to 14%), weakness (6% to 17%; grade 4: 1%), paresthesia (4% to 15%; grades 2-4: 3% to 4%), myalgia (13%)

Respiratory: Cough (25%), dyspnea (7% to 20%)

1% to 10%:

Cardiovascular: Hypotension (8%), tachycardia (8%), chest pain (5%)

Central nervous system: Ataxia (2% to 9%; grades 2-4: children 1%, adults 8%), confusion (8%), insomnia (7%), depressed level of consciousness (6%; grades 2-4: 2%), depression (6%), seizure (grade 3: 1% adults; grade 4: 6% children), motor dysfunction (4%; grades 2-4: 2%), amnesia (3%; grades 2-4: 1%), balance disorder (2%; grades 2-4: 1%), nerve paralysis (2%), sensory loss (1% to 2%), aphasia (1%), cerebral hemorrhage (1%), coma (1%), encephalopathy (1%), hemiparesis (1%), hydrocephalus (1%), lethargy (1%), leukoencephalopathy (1%), loss of consciousness (1%), mental impairment (1%), neuropathic pain (1%), nerve palsy (1%), nystagmus (1%), paralysis (1%), sciatica (1%), sensory disturbance (1%), speech disorder (1%), demyelination, ascending peripheral neuropathy

Endocrine & Metabolic: Hypocalcemia (8%), dehydration (7%), hyper-/hypoglycemia (6%), hypomagnesemia (6%)

Gastrointestinal: Abdominal pain (9%), anorexia (9%), stomatitis (8%), abdominal distension (6%), taste perversion (3%)

Hepatic: Albumin decreased (10%), bilirubin increased (10%), AST increased (6%)

Neuromuscular & skeletal: Arthralgia (9%), back pain (8%), muscle weakness (8%), rigors (8%), limb pain (7%), abnormal gait (6%), noncardiac chest pain (5%), tremor (4% to 5%; grades 2-4: 2% to 3%), dysarthria (1%), hyporeflexia (1%), hypertonia (1%), incoordination (1%)

Ocular: Blurred vision (4%)

Renal: Creatinine increased (6%)

Respiratory: Pleural effusion (10%), epistaxis (8%), pneumonia (8%), sinusitis (7%), wheezing (5%), sinus headache (1%)

Miscellaneous: Infection (5% to 9%)

Postmarketing and/or case reports: Tumor lysis syndrome

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersClosely monitor for neurologic toxicity (severe somnolence, seizure, peripheral neuropathy, confusion, ataxia, paresthesia, hypoesthesia, coma, or craniospinal demyelination); signs and symptoms of tumor lysis syndrome; hydration status; CBC with platelet counts, liver and kidney function

Nursing: Physical Assessment/MonitoringShould be administered only under the supervision of a physician experienced in the use of antineoplastic therapy. Assess results of laboratory tests (eg, CBC, renal and hepatic function), therapeutic response, and adverse reactions (eg, neurotoxicity [somnolence, confusion, convulsions, hypoesthesia, paresthesia, peripheral neuropathy], gastrointestinal [diarrhea, nausea, vomiting, pain, dehydration], hematologic [anemia, neutropenia, thrombocytopenia], cardiovascular [edema]), at beginning and regularly throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with platelet counts, liver and kidney function

Patient EducationThis medication can only be administered via intravenous infusion. You will be monitored closely during treatment. Report any burning, pain, redness, or swelling at infusion site. You may experience dizziness or sleepiness (use caution when driving, climbing stairs, making sudden movements, or engaging in hazardous tasks). Report immediately any sign of nervous system reactions (eg, excessive sleepiness, seizures, numbness or tingling in hands, fingers, feet, or toes; problems with fine motor skills [eg, buttoning clothes]; unsteadiness, tripping while walking, increased weakness when getting out of a chair, bed, or walking up stairs); unresponsiveness or coma; persistent vomiting or diarrhea; blurred vision; difficulty breathing; or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, solution:

Arranon®: 5 mg/mL (50 mL)

Atriance™ [CAN]: 5 mg/ml (50 mL)

Generic AvailableNo

ManufacturerGlaxoSmithKline

Mechanism of ActionNelarabine, a prodrug of ara-G, is demethylated by adenosine deaminase to ara-G and then converted to ara-GTP. Ara-GTP is incorporated into the DNA of the leukemic blasts, leading to inhibition of DNA synthesis and inducing apoptosis. Ara-GTP appears to accumulate at higher levels in T-cells, which correlates to clinical response.

Pharmacodynamics/Kinetics

Distribution: V_{ss}:

Nelarabine: Children: ~213 L/m^2; Adults: ~197 L/m^2

Ara-G: Children: ~50 L/m^2; Adults: ~33 L/m^2

Protein binding: Nelarabine and ara-G: <25%

Metabolism: Hepatic; demethylated by adenosine deaminase to form ara-G (active); also hydrolyzed to form methylguanine. Both ara-G and methylguanine metabolized to guanine. Guanine is deaminated into xanthine, which is further oxidized to form uric acid, which is then oxidized to form allantoin.

Half-life elimination: Nelarabine: 30 minutes; ara-G: 3 hours

Time to peak: Ara-G: 3-25 hours

Excretion: Urine (nelarabine 7%, ara-G 27%) within 24 hours of infusion on day 1

Related Information

- Common Toxicity Criteria
- Management of Nausea and Vomiting
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste perversion and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause amnesia, confusion, depression, dizziness, fatigue, insomnia, somnolence, and coma

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with SSRIs, lithium, valproic acid, and carbamazepine may produce additive effects. Hematologic side effects are common; use caution with clozapine.

Index Terms2-Amino-6-Methoxypurine Arabinoside; 506U78; GW506U78

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International Brand NamesAtriance (CH, CZ, DK, EE, FR, GB, IE, IL, NO, SE)

Nelfinavir

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Nelfinavir: Health Canada Issues Update on Impurity Warning - August 2008

Health Canada has notified Canadian healthcare professionals that they have reached agreement with Pfizer Canada, on acceptable limits of the impurity, ethyl methanesulfonate (EMS), created during the manufacturing process of nelfinavir (Viracept®). A similar agreement previously was reached between Pfizer and the U.S. Food and Drug Administration (FDA). Health Canada is reassuring Canadians that the nelfinavir product presently on the Canadian market contains acceptable levels of EMS and that warnings against its use in **HIV-infected nonpregnant adults and children** no longer apply. In contrast to the U.S. FDA recommendations, Health Canada **does not recommend** the use of nelfinavir during pregnancy due to concerns related to EMS exposure.

Further information may be obtained at:

http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_144-eng.php

Medication Safety Issues

Sound-alike/look-alike issues:

Nelfinavir may be confused with nevirapine

Viracept® may be confused with Viramune®

Pronunciation(nel FIN a veer)

U.S. Brand NamesViracept®

Canadian Brand NamesViracept®

Pharmacologic CategoryAntiretroviral Agent, Protease Inhibitor

Use: Labeled IndicationsIn combination with other antiretroviral therapy in the treatment of HIV infection

Dosing: Adults**HIV infection:** Oral: 750 mg 3 times/day or 1250 mg twice daily with meals in combination with other antiretroviral therapies

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**HIV infection:** Oral: Children 2-13 years: 45-55 mg/kg twice daily **or** 25-35 mg/kg 3 times/day (maximum: 2500 mg/day). If tablets are unable to be taken, use oral powder in small amount of water, milk, formula, or dietary supplements; do not use acidic food/juice or store for >6 hours.

Dosing: Renal ImpairmentNo pharmacokinetic data in patients with renal impairment. However, <2% of dose excreted in urine; no dose adjustment is needed.

Dosing: Hepatic ImpairmentNo dose adjustment necessary in mild impairment (Child-Pugh class A); not recommended in patients with moderate-to-severe impairment (Child-Pugh class B or C)

Administration: Oral

Oral powder: Administer with a meal. Mix powder in a small amount of water, milk, formula, soy milk, soy formula, pudding, ice cream, or dietary supplement. Do not reconstitute the oral powder in its original container. Be sure entire contents is consumed to receive full dose. Do not use acidic food/juice to dilute due to bitter taste. Once mixed, solution should be used immediately, but may be stored for up to 6 hours if refrigerated.

Tablets: Administer with a meal. If unable to swallow tablets, may dissolve tablets in a small amount of water; mix cloudy liquid well and consume immediately. Rinse glass with water to ensure receiving full dose. Tablets may also be crushed and mixed with pudding.

Dietary ConsiderationsShould be taken as scheduled with a meal. Oral powder contains phenylalanine 11.2 mg/g.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Oral powder (or dissolved tablets) diluted in nonacidic liquid is stable for 6 hours under refrigeration.

ContraindicationsHypersensitivity to nelfinavir or any component of the formulation; concurrent therapy with amiodarone, ergot derivatives, midazolam, pimozide, quinidine, triazolam

Allergy Considerations

- Nelfinavir Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory

response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.

Disease-related concerns:

- Diabetes: Changes in glucose tolerance, hyperglycemia, exacerbation of diabetes, DKA, and new-onset diabetes mellitus have been reported in patients receiving protease inhibitors.

- Hemophilia A or B: Use with caution in patients with hemophilia A or B; increased bleeding during protease inhibitor therapy has been reported.

- Hepatic impairment: May cause hepatitis and/or exacerbate pre-existing hepatic dysfunction; use with caution in patients with underlying hepatic disease, such as hepatitis B or C or cirrhosis; use not recommended with moderate-to-severe impairment.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

- Not recommended for use with rifampin, St John’s wort, lovastatin, simvastatin, phosphodiesterase-5 (PDE-5) inhibitors, or proton pump inhibitors (based on omeprazole data)

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Dosage form specific issues:

- Oral powder: Formulation contains phenylalanine.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events were not observed in animal studies and no increased risk of overall birth defects has been observed following 1st trimester exposure in humans according to data collected by the antiretroviral pregnancy registry. Nelfinavir crosses the placenta. The Perinatal HIV Guidelines Working Group recommends nelfinavir as an alternative PI in combination regimens during pregnancy with HAART for perinatal prophylaxis. A dose of 1250 mg twice daily has been shown to provide adequate plasma concentrations although lower and variable levels may occur late in pregnancy. Pregnancy and protease inhibitors are both associated with an increased risk of hyperglycemia. Glucose levels should be closely monitored. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsNelfinavir is minimally excreted in breast milk. HIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse ReactionsData presented on experience in adults, unless otherwise noted.

>10%: Gastrointestinal: Diarrhea (14% to 20%; children: 39% to 47%)

2% to 10%:

Dermatologic: Rash (1% to 3%)

Gastrointestinal: Nausea (3% to 7%), flatulence (1% to 5%)

Hematologic: Lymphocytes decreased (1% to 6%), neutrophils decreased (1% to 5%)

<2% (Limited to important or life-threatening): Abdominal pain, acute iritis, alkaline phosphatase increased, allergic reaction, amylase increased, anemia, anorexia, anxiety, arthralgia, arthritis, back pain, body fat redistribution/accumulation, cramps, creatinine phosphokinase increased, dehydration, depression, dermatitis, diaphoresis, dizziness, dyspepsia, dyspnea, emotional lability, epigastric pain, eye disorder, fever, folliculitis, fungal dermatitis, gastrointestinal bleeding, GGTP increased, headache, hepatitis, hyperkinesia, hyper-/hypoglycemia, hyperlipemia, hyperuricemia, insomnia, kidney calculus, lactic dehydrogenase increased, leukopenia, lipoatrophy, lipodystrophy, liver function tests abnormal, maculopapular rash, malaise, migraine, mouth ulceration, myalgia, myasthenia, myopathy, pain, pancreatitis, paresthesia, pharyngitis, pruritus, rhinitis, seizure, sexual dysfunction, sinusitis, sleep disorder, somnolence, suicidal ideation, transaminases increased, thrombocytopenia, urine abnormality, urticaria, vomiting, weakness

Postmarketing and/or case reports: Bilirubinemia; hypersensitivity reaction (bronchospasm, rash, edema); immune reconstitution syndrome, jaundice, metabolic acidosis, QT_c prolongation, torsade de pointes

Metabolism/Transport Effects**Substrate** of CYP2C9 (minor), 2C19 (major), 2D6 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 3A4 (strong)

Drug Interactions

Abacavir: Protease Inhibitors may decrease the serum concentration of Abacavir. *Risk C: Monitor therapy*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amiodarone: Protease Inhibitors may decrease the metabolism of Amiodarone. *Risk X: Avoid combination*

Antacids: May decrease the absorption of Protease Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Azithromycin: Nelfinavir may decrease the excretion of Azithromycin. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Protease Inhibitors may decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Dihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Protease Inhibitors. Protease Inhibitors may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cisapride: Protease Inhibitors may decrease the metabolism of Cisapride. The resultant increase in serum cisapride concentrations may result in QTc prolongation and malignant cardiac arrhythmias. *Risk X: Avoid combination*

Clarithromycin: Protease Inhibitors may diminish the therapeutic effect of Clarithromycin. Specifically, certain protease inhibitors may decrease formation of the active 14-hydroxy-clarithromycin metabolite, which may negatively impact clarithromycin effectiveness vs. H. influenzae and other non-MAC infections. Protease Inhibitors may increase the serum concentration of Clarithromycin. Clarithromycin dose adjustment in renally impaired patients may be needed. Clarithromycin may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): Protease Inhibitors may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk D: Consider therapy modification*

CycloSPORINE: Protease Inhibitors may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Delavirdine: Protease Inhibitors may decrease the serum concentration of Delavirdine. Delavirdine may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Digoxin: Protease Inhibitors may increase the serum concentration of Digoxin. Increased serum concentrations of digoxin may increase risk of AV nodal blockade. *Risk C: Monitor therapy*

Efavirenz: May increase the metabolism of Protease Inhibitors. This specifically includes amprenavir, indinavir, and saquinavir. Efavirenz may increase the serum concentration of Protease Inhibitors. This specifically includes nelfinavir and ritonavir. *Risk D: Consider therapy modification*

Enfuvirtide: Protease Inhibitors may increase the serum concentration of Enfuvirtide. Enfuvirtide may increase the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

Eplerenone: Protease Inhibitors may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Protease Inhibitors may decrease the metabolism of Ergot Derivatives. **Exceptions:** Cabergoline. *Risk X: Avoid combination*

Etravirine: Protease Inhibitors may decrease the serum concentration of Etravirine. This effect is anticipated with darunavir & saquinavir (with low-dose ritonavir). Etravirine may increase the serum concentration of Protease Inhibitors. This effect is anticipated with nelfinavir. Protease Inhibitors may increase the serum concentration of Etravirine. This is expected with lopinavir/ritonavir. Management: Low-dose ritonavir boosting MUST be used when these protease inhibitors are used with etravirine. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

FentaNYL: Protease Inhibitors may decrease the metabolism of FentaNYL. *Risk C: Monitor therapy*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fusidic Acid: Protease Inhibitors may decrease the metabolism of Fusidic Acid. Fusidic Acid may decrease the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Garlic: May decrease the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

H2-Antagonists: May decrease the serum concentration of Nelfinavir. Concentrations of the active M8 metabolite may also be reduced. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Protease Inhibitors may increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. **Exceptions:** Fluvastatin. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Meperidine: Protease Inhibitors may enhance the adverse/toxic effect of Meperidine. Protease Inhibitors may decrease the serum concentration of Meperidine. Concentrations of the toxic Normeperidine metabolite may be increased. *Risk D: Consider therapy modification*

Methadone: Protease Inhibitors may decrease the metabolism of Methadone. *Risk C: Monitor therapy*

Nefazodone: Protease Inhibitors may decrease the metabolism of Nefazodone. *Risk C: Monitor therapy*

Nevirapine: May increase the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): May diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: Protease Inhibitors may decrease the metabolism of Phosphodiesterase 5 Inhibitors. Management: Dose restrictions for tadalafil, and/or sildenafil and vardenafil are recommended in combination with ritonavir, atazanavir, indinavir, darunavir and saquinavir. Consult specific prescribing information for detailed recommendations. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Protease Inhibitors may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Protease Inhibitors: May increase the serum concentration of other Protease Inhibitors. Management: Atazanavir--indinavir combination contraindicated. Amprenavir oral solution not recommended with ritonavir oral solution; tipranavir/ritonavir or atazanavir/ritonavir not recommended with other protease inhibitors. Other combos may require dose changes. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May decrease serum concentrations of the active metabolite(s) of Nelfinavir. Proton Pump Inhibitors may decrease the serum concentration of Nelfinavir. *Risk X: Avoid combination*

QuiNIDine: Protease Inhibitors may decrease the metabolism of QuiNIDine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: Protease Inhibitors may decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Protease Inhibitors may increase the serum concentration of Sirolimus. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Protease Inhibitors. *Risk X: Avoid combination*

Tacrolimus: Protease Inhibitors may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Temsirolimus: Protease Inhibitors may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tenofovir: May decrease the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Tenofovir. *Risk C: Monitor therapy*

Theophylline Derivatives: Protease Inhibitors may decrease the serum concentration of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

TraZODone: Protease Inhibitors may increase the serum concentration of TraZODone. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Protease Inhibitors may increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Valproic Acid: Protease Inhibitors may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Zidovudine: Protease Inhibitors may decrease the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Nelfinavir taken with food increases plasma concentration time curve (AUC) by two- to threefold. Do not administer with acidic food or juice (orange juice, apple juice, or applesauce) since the combination may have a bitter taste.

Herb/Nutraceutical: St John's wort may decrease the levels/effects of protease inhibitors; concurrent use should probably be avoided.

Monitoring ParametersLiver function tests, viral load, CD4 count, triglycerides, cholesterol, blood glucose, CBC with differential

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions or toxicity (multiple liver enzyme interactions may increase or decrease levels/effects of drugs and increase potential for severe toxicity or loss of effectiveness); dosing adjustments may be necessary. A list of medications that should not be used concurrently is available in each bottle and patients should be provided with this information. Assess therapeutic response (CD4 count, hepatic function, CBC, serum glucose) and adverse reactions at regular intervals during therapy. Caution patients to monitor glucose levels closely; may cause hyperglycemia or new-onset diabetes. Teach patient proper use (eg, timing of multiple medications), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsLiver function tests, blood glucose levels, CBC with differential, CD4 cell count, plasma levels of HIV RNA

Patient EducationYou will be provided with a list of specific medications that should not be used during therapy; do not take any new prescription or OTC medications or herbal products during therapy - even if they are not on the list - without consulting prescriber. This is not a cure for HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other people. Take as directed with food. Mix powder with nonacid, noncitric water or dairy products - milk, pudding, or ice cream. If unable to swallow tablets whole, the tablet may be dissolved in a small amount of water and consumed immediately; rinse glass with water to ensure receiving full dose. Maintain adequate hydration (2-3 L/day of fluids unless instructed to restrict fluid intake). You may be susceptible to infection (avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber). This medication will be prescribed with a combination of other medications; time these medications as directed by prescriber. You may be advised to check your glucose levels; this drug can cause hyperglycemia. Frequent blood tests may be required with prolonged therapy. May cause body changes due to redistribution of body fat, facial atrophy, or breast enlargement (normal effects of drug); diarrhea (buttermilk, boiled milk, or yogurt may help - if persistent, contact prescriber for appropriate antidiarrheal); or nausea (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Inform prescriber if you experience unusual or persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder, oral:

Viracept®: 50 mg/g (144 g) [contains phenylalanine 11.2 mg/g]

Tablet:

Viracept®: 250 mg, 625 mg

Generic AvailableNo

ManufacturerAgouron Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Powder (Viracept)

50 mg/g (144): $63.62

Tablets (Viracept)

250 mg (300): $670.98

Mechanism of ActionInhibits the HIV-1 protease; inhibition of the viral protease prevents cleavage of the gag-pol polyprotein resulting in the production of immature, noninfectious virus

Pharmacodynamics/Kinetics

Absorption: Food increases AUC of nelfinavir by two- to fivefold

Distribution: V_d: 2-7 L/kg

Protein binding: >98%

Metabolism: Hepatic via CYP2C19 and 3A4; major metabolite has activity comparable to parent drug

Half-life elimination: 3.5-5 hours

Time to peak, serum: 2-4 hours

Excretion: Feces (98% to 99%, 78% as metabolites, 22% as unchanged drug); urine (1% to 2%)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV
- Perinatal HIV Guidelines

Pharmacotherapy PearlsA patient package insert (PPI), including a list of medications that should not be taken with nelfinavir, is available and should be dispensed with medication.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mouth ulcers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, anxiety, insomnia, difficulty concentrating, depression, and suicidal ideation

Mental Health: Effects on Psychiatric TreatmentMay rarely cause leukopenia; use caution with clozapine and carbamazepine; concurrent use with midazolam and triazolam may produce oversedation; barbiturates and carbamazepine may decrease the effectiveness of nelfinavir. Concomitant use of nelfinavir and St John's wort is not recommended. Coadministration of protease inhibitors (nelfinavir) with St John's wort is expected to substantially decrease protease inhibitor serum concentrations leading to a loss of virologic response and possible resistance to nelfinavir or to the class of protease inhibitors. Concomitant use with trazodone may increase plasma levels of trazodone; monitor for nausea, dizziness, hypotension, and syncope; consider using a lower dose of trazodone.

Index TermsNFV

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International Brand NamesElfivir (PE); Nelvir (IN); Viracept (AR, AT, AU, BB, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CN, CO, CZ, DE, DK, EC, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, IE, IL, IT, JM, JP, KE, KP, LR, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, PH, PL, PT, PY, RU, SC, SD, SE, SL, SN, SR, TH, TN, TR, TT, TZ, UG, UY, VE, ZA, ZM, ZW)

Neomycin and Polymyxin B

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English English

Jump To Field (Select Field Name)

Pronunciation(nee oh MYE sin & pol i MIKS in bee)

U.S. Brand NamesNeosporin速 G.U. Irrigant

Canadian Brand NamesNeosporin速 Irrigating Solution

Pharmacologic CategoryAntibiotic, Topical; Genitourinary Irrigant

Use: Labeled IndicationsShort-term as a continuous irrigant or rinse in the urinary bladder to prevent bacteriuria and gram-negative rod septicemia associated with the use of indwelling catheters; to help prevent infection in minor cuts, scrapes, and burns

Dosing: AdultsBladder irrigation: **Not for I.V. injection**; add 1 mL irrigant to 1 L isotonic saline solution and connect container to the inflow of lumen of 3-way catheter. Continuous irrigant or rinse in the urinary bladder for up to a maximum of 10 days with administration rate adjusted to patient's urine output; usually no more than 1 L of irrigant is used per day.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: OtherBladder irrigant: Do not inject irrigant solution; concentrated irrigant solution must be diluted in 1 L normal saline before administration; connect irrigation container to the inflow lumen of a 3-way catheter to permit continuous irrigation of the urinary bladder

StorageStore irrigation solution in refrigerator. Aseptic prepared dilutions (1 mL/1 L) should be stored in the refrigerator and discarded after 48 hours.

ContraindicationsHypersensitivity to neomycin, polymyxin B, or any component of the formulation; pregnancy (GU irrigant)

Pregnancy Risk FactorC/D (for G.U. irrigant)

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined.

Dermatologic: Contact dermatitis, erythema, rash, urticaria

Genitourinary: Bladder irritation

Local: Burning

Neuromuscular & skeletal: Neuromuscular blockade

Otic: Ototoxicity

Renal: Nephrotoxicity

Drug Interactions

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Polymyxin B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

Cardiac Glycosides: Aminoglycosides may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

Colistimethate: Polymyxin B may enhance the neuromuscular-blocking effect of Colistimethate. *Risk C: Monitor therapy*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Polymyxin B may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, irrigation: Neomycin 40 mg and polymyxin B 200,000 units per mL (1 mL, 20 mL)

Neosporin速 G.U. Irrigant: Neomycin 40 mg and polymyxin B 200,000 units per mL (1 mL, 20 mL)

Generic AvailableYes
Mechanism of ActionSee individual agents.
Pharmacodynamics/Kinetics

Absorption: Topical: Not absorbed following application to intact skin; absorbed through denuded or abraded skin, peritoneum, wounds, or ulcers

See individual agents.

Related Information

- Neomycin
- Polymyxin B

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsPolymyxin B and Neomycin
International Brand NamesAlosol (MX); Maxitrol (MX); Statrol (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW)

Neomycin, Colistin, Hydrocortisone, and Thonzonium

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(nee oh MYE sin, koe LIS tin, hye droe KOR ti sone, & thon ZOE nee um)

U.S. Brand NamesColy-Mycin® S; Cortisporin®-TC

Pharmacologic CategoryAntibiotic/Corticosteroid, Otic

Use: Labeled IndicationsTreatment of superficial and susceptible bacterial infections of the external auditory canal; for treatment of susceptible bacterial infections of mastoidectomy and fenestration cavities

Dosing: Adults**Ear inflammation/infection:** Otic:

Calibrated dropper: 5 drops in affected ear 3-4 times/day

Dropper bottle: 4 drops in affected ear 3-4 times/day

Note: Alternatively, a cotton wick may be inserted in the ear canal and saturated with suspension every 4 hours; wick should be replaced at least every 24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Ear inflammation/infection:** Otic:

Calibrated dropper: 4 drops in affected ear 3-4 times/day

Dropper bottle: 3 drops in affected ear 3-4 times/day

Note: Alternatively, a cotton wick may be inserted in the ear canal and saturated with suspension every 4 hours; wick should be replaced at least every 24 hours

ContraindicationsHypersensitivity to any component of the formulation and/or aminoglycosides; herpes simplex, vaccinia, varicella

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue if irritation occurs.

- Neomycin sensitization: May cause cutaneous sensitization, including itching, reddening, edema, and failure to heal. Neomycin may also cause sensorineural hearing loss (due to cochlear damage); risk is greater with prolonged use.

- Ototoxicity: Risk of ototoxicity is increased in patients with longstanding otitis media or tympanic perforation; use with caution.

Other warnings/precautions:

- Appropriate use: For otic use only; avoid contact with eyes. Avoid contaminating dropper.

- Duration of therapy: Do not use for longer than 10 days; prolonged treatment may result in overgrowth of nonsusceptible organisms.

Geriatric ConsiderationsMany elderly will overuse eye drops or use for nonindicated reasons; limit use.

Adverse ReactionsFrequency not defined.

Dermatologic: Hypersensitivity reaction, irritation

Otic: Ototoxicity (rare)

Metabolism/Transport EffectsHydrocortisone: **Substrate** of CYP3A4 (minor); **Induces** CYP3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

Cardiac Glycosides: Aminoglycosides may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents for Neomycin and Hydrocortisone.
Patient EducationSee individual agents for Neomycin and Hydrocortisone.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, otic [drops]:

Coly-Mycin® S: Neomycin 0.33%, colistin 0.3%, hydrocortisone acetate 1%, and thonzonium bromide 0.05% (5 mL) [contains thimerosal; packaged with dropper]

Cortisporin®-TC: Neomycin 0.33%, colistin 0.3%, hydrocortisone acetate 1%, and thonzonium bromide 0.05% (10 mL) [contains thimerosal; packaged with dropper]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Suspension (Coly-Mycin S)

3.3-3-10 mg/mL (5): $44.73

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsColistin, Neomycin, Hydrocortisone, and Thonzonium; Hydrocortisone, Neomycin, Colistin, and Thonzonium; Thonzonium, Neomycin, Colistin, and Hydrocortisone

Neomycin, Polymyxin B, and Dexamethasone

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

AK-Trol® may be confused with AKTob®

Pronunciation(nee oh MYE sin, pol i MIKS in bee, & deks a METH a sone)
U.S. Brand NamesAK-Trol® [DSC]; Maxitrol®; Poly-Dex™
Canadian Brand NamesDioptrol®; Maxitrol®
Pharmacologic CategoryAntibiotic/Corticosteroid, Ophthalmic
Use: Labeled IndicationsSteroid-responsive inflammatory ocular conditions in which a corticosteroid is indicated and where bacterial infection or a risk of bacterial infection exists
Dosing: Adults **Ocular inflammation/infection:** Ophthalmic:

Ointment: Place a small amount (~$^{1}/_{2}$”) in the affected eye 3-4 times/day or apply at bedtime as an adjunct with drops

Suspension: Instill 1-2 drops into affected eye(s) every 3-4 hours; in severe disease, drops may be used hourly and tapered to discontinuation

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Administration: OtherContact lenses should not be worn during therapy.

Ointment: Do not touch tip of tube to eye. Instill ointment into pocket between eyeball and lower lid; patient should look downward before closing eye.

Suspension: Shake suspension before use. Tilt head back, instill suspension in conjunctival sac and close eye(s). Do not touch dropper to eye. Apply light finger pressure on lacrimal sac for 1 minute following instillation.

ContraindicationsHypersensitivity to neomycin, polymyxin B, dexamethasone, or any component of the formulation; viral, fungal, or tuberculosis diseases of the eye
Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Infection: Steroids may mask infection or enhance existing ocular infection; prolonged use may result in secondary infections due to immunosuppression.
- Ocular effects: Prolonged use of corticosteroids may result in glaucoma; damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation may occur.
- Sensitivity reactions: Sensitivity to neomycin may develop; discontinue if sensitivity reaction occurs.

Special populations:

- Cataract surgery patients: Use following cataract surgery may delay healing or increase the incidence of bleb formation.

Dosage form specific issues:

- Benzalkonium chloride: Suspension contains benzalkonium chloride which may be adsorbed by contact lenses; contact lenses should not be worn during treatment of ophthalmic infections.

Other warnings/precautions:

- Appropriate use: For ophthalmic use only. A maximum of 8 g of ointment or 20 mL of suspension should be prescribed initially; patients should be evaluated prior to additional refills.

Geriatric ConsiderationsAssess patients ability to self-administer.
Pregnancy Risk FactorC
Pregnancy ConsiderationsSee individual agents.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsIt is unknown if topical use results in sufficient absorption to produce detectable quantities in breast milk.
Adverse ReactionsFrequency not defined: Ocular: Allergic sensitivity, cutaneous sensitization, eye pain, development of glaucoma, cataract, increased intraocular pressure, optic nerve damage, wound healing delayed

Metabolism/Transport EffectsDexamethasone: **Substrate** of CYP3A4 (minor); **Induces** CYP2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Polymyxin B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

Cardiac Glycosides: Aminoglycosides may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

Caspofungin: Inducers of Drug Clearance may decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) when coadministered with known inducers of drug clearance. *Risk D: Consider therapy modification*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

Colistimethate: Polymyxin B may enhance the neuromuscular-blocking effect of Colistimethate. *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Lenalidomide: Dexamethasone may enhance the thrombogenic effect of Lenalidomide. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents: Polymyxin B may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nisoldipine. *Risk X: Avoid combination*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Thalidomide: Dexamethasone may enhance the dermatologic adverse effect of Thalidomide. Dexamethasone may enhance the thrombogenic effect of Thalidomide. *Risk D: Consider therapy modification*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Monitoring ParametersMonitor intraocular pressure with use longer than 10 days

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Ointment, ophthalmic (Maxitrol®, Poly-Dex™): Neomycin 3.5 mg, polymyxin B sulfate 10,000 units, and dexamethasone 0.1% per g (3.5 g)

Suspension, ophthalmic (AK-Trol® [DSC], Maxitrol®, Poly-Dex™): Neomycin 3.5 mg, polymyxin B sulfate 10,000 units, and dexamethasone 0.1% per mL (5 mL) [contains benzalkonium chloride]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Ointment (Maxitrol)

0.1-5-10000 (3.5): $79.70

Ointment (Neomycin-Polymyxin-Dexameth)

5-10000-0.1 (3.5): $11.99

Suspension (Maxitrol)

5-10000-0.1 (5): $69.47

Suspension (Neomycin-Polymyxin-Dexameth)

5-10000-0.1 (5): $11.99

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDexamethasone, Neomycin, and Polymyxin B; Polymyxin B, Neomycin, and Dexamethasone

International Brand NamesBiodexan Ofteno (MX); Dexaron Plus (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Dexosyn Plus (IN); Dexsul (MX); Inmatrol (ID); Isopto Maxitrol (GR); Isore (PH); Maxitrol (BB, BE, BF, BG, BJ, BM, BS, BZ, CH, CI, CN, CO, CZ, EE, ET, FI, GB, GH, GM, GN, GY, HK, IE, IL, JM, KE, KP, LR, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, NZ, PE, PH, PK, SC, SD, SL, SN, SR, TH, TN, TT, TW, TZ, UG, VE, ZA, ZM, ZW); Miratrol (CO); Neobacigrin (MX); Neodex-V (PH); Oregan (ID); Osatrol (ID); Soldrin Oftálmico (MX); Ximex Optixitrol (ID)

Neomycin, Polymyxin B, and Gramicidin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(nee oh MYE sin, pol i MIKS in bee, & gram i SYE din)
U.S. Brand NamesNeosporin® Ophthalmic Solution
Canadian Brand NamesNeosporin®; Optimyxin Plus®
Pharmacologic CategoryAntibiotic, Ophthalmic
Use: Labeled IndicationsTreatment of superficial ocular infection
Dosing: AdultsOphthalmic: Instill 1-2 drops 4-6 times/day or more frequently as required for severe infections
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
ContraindicationsHypersensitivity to neomycin, polymyxin B, gramicidin or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Neomycin sensitization: Symptoms of neomycin sensitization include itching, reddening, edema, and failure to heal.
- Ocular effects (prolonged use): Glaucoma, defects in visual acuity, posterior subcapsular cataract formation, and secondary ocular infections may result from prolonged use.

Geriatric ConsiderationsAssess patient's ability to self-administer ophthalmic drops.
Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined: Ocular: Transient irritation, burning, stinging, itching, inflammation, angioneurotic edema, urticaria, vesicular and maculopapular dermatitis
Drug Interactions

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Polymyxin B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

Cardiac Glycosides: Aminoglycosides may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

Colistimethate: Polymyxin B may enhance the neuromuscular-blocking effect of Colistimethate. *Risk C: Monitor therapy*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Polymyxin B may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic: Neomycin 1.75 mg, polymyxin B 10,000 units, and gramicidin 0.025 mg per 1 mL (10 mL)

Neosporin® Ophthalmic Solution: Neomycin 1.75 mg, polymyxin B 10,000 units, and gramicidin 0.025 mg per 1 mL (10 mL)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Neomycin-Polymyxin-Gramicidin)

2.5-10000-0.025 (10): $26.00

Solution (Neosporin)

0.025-2.5-10000 (10): $55.07

Mechanism of ActionInterferes with bacterial protein synthesis by binding to 30S ribosomal subunits; binds to phospholipids, alters permeability, and damages the bacterial cytoplasmic membrane permitting leakage of intracellular constituents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsGramicidin, Neomycin, and Polymyxin B; Polymyxin B, Neomycin, and Gramicidin

References

Abramowicz M, “Antimicrobial Prophylaxis in Surgery,” *Medical Letter on Drugs and Therapeutics, Handbook of Antimicrobial Therapy*, 16th ed, New York, NY: Medical Letter, 2002.

International Brand NamesNeosporin (CA); Optimyxin Plus (CA)

Neomycin, Polymyxin B, and Hydrocortisone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(nee oh MYE sin, pol i MIKS in bee, & hye droe KOR ti sone)
U.S. Brand NamesCortisporin® Cream; Cortisporin® Ophthalmic [DSC]; Cortisporin® Otic; PediOtic®
Canadian Brand NamesCortimyxin®; Cortisporin® Otic
Pharmacologic CategoryAntibiotic, Ophthalmic; Antibiotic, Otic; Antibiotic, Topical; Corticosteroid, Ophthalmic; Corticosteroid, Otic; Corticosteroid, Topical
Use: Labeled IndicationsSteroid-responsive inflammatory condition for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial infection exists
Dosing: Adults

Note: Duration of use of ophthalmic and otic preparations should be limited to 10 days unless otherwise directed by the healthcare provider.

Auditory canal inflammation/infection: Otic: Instill 4 drops 3-4 times/day; otic suspension is the preferred otic preparation. **Note:** Otic solution is used **only** for bacterial infections of external auditory canal (eg, swimmer's ear).

Ocular inflammation/infection: Ophthalmic: Instill 1-2 drops 2-4 times/day, or more frequently as required for severe infections

Dermatologic inflammation/infection: Topical: Apply a thin layer 1-4 times/day. Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Note: Duration of use of ophthalmic and otic preparations should be limited to 10 days unless otherwise directed by the healthcare provider.

Auditory canal inflammation/infection: Otic:

Children 6 months to 2 years (unlabeled use): Instill 3 drops into affected ear 3-4 times/day

Children ≥2 years: Instill 3 drops into affected ear 3-4 times/day

Note: Otic solution is used **only** for bacterial infections of external auditory canal (eg, swimmer's ear).

Ocular inflammation/infection: Ophthalmic: Children (unlabeled use): Instill 1-2 drops 2-4 times/day, or more frequently as required for severe infections

Dermatologic inflammation/infection: Topical: Children (unlabeled use): Apply a thin layer 1-4 times/day. Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.

Administration: OtherShake otic suspension well before using. Otic preparations should not be used when the integrity of the tympanic membrane is in question.
ContraindicationsHypersensitivity to neomycin, polymyxin B, hydrocortisone, or any component of the formulation; not for use in viral infections, fungal diseases, mycobacterial infections
Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines.

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Neomycin sensitization: Symptoms of neomycin sensitization include itching, reddening, edema, and failure to heal.

- Ototoxicity (otic preparations): Risk of ototoxicity is increased in patients with extended use or tympanic perforation; avoid use with tympanic perforation, limit therapy to 10 days.

- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, and fluid and electrolyte changes.

Dosage form specific issues:

- Sulfites: Some formulations may contain sulfites, which may cause allergic-type reactions in susceptible individuals.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined. For additional information, see individual agents.

Ophthalmic ointment:

Dermatologic: Delayed wound healing, rash

Ocular: Cataracts, corneal thinning, glaucoma, irritation, keratitis (bacterial), intraocular pressure increase, optic nerve damage, scleral thinning

Miscellaneous: Hypersensitivity (including anaphylaxis), secondary infection, sensitization to kanamycin, paromomycin, streptomycin, and gentamicin

Otic solution and suspension:

Dermatologic: Acneiform eruptions, allergic contact dermatitis, burning skin, dryness, folliculitis, hypertrichosis, hypopigmentation, irritation, maceration of skin, miliaria, ocular hypertension, perioral dermatitis, pruritus, skin atrophy, striae

Otic: Burning, ototoxicity, stinging

Renal: Nephrotoxicity

Miscellaneous: Hypersensitivity (including anaphylaxis), secondary infection, sensitization to karamycin, paromycin, streptomycin, and gentamicin

Metabolism/Transport EffectsHydrocortisone: **Substrate** of CYP3A4 (minor); **Induces** CYP3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Polymyxin B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

Cardiac Glycosides: Aminoglycosides may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

Colistimethate: Polymyxin B may enhance the neuromuscular-blocking effect of Colistimethate. *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents: Polymyxin B may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical (Cortisporin®): Neomycin 3.5 mg, polymyxin B 10,000 units, and hydrocortisone acetate 5 mg per g (7.5 g)

Solution, otic (Cortisporin®): Neomycin 3.5 mg, polymyxin B 10,000 units, and hydrocortisone 10 mg per mL (10 mL) [contains potassium metabisulfite]

Suspension, ophthalmic (Cortisporin® [DSC]): Neomycin 3.5 mg, polymyxin B 10,000 units, and hydrocortisone 10 mg per mL (7.5 mL) [contains thimerosal]

Suspension, otic: Neomycin 3.5 mg, polymyxin B 10,000 units, and hydrocortisone 10 mg per mL (10 mL)

Cortisporin®: Neomycin 3.5 mg, polymyxin B 10,000 units, and hydrocortisone 10 mg per mL (10 mL) [contains thimerosal]

PediOtic®: Neomycin 3.5 mg, polymyxin B 10,000 units, and hydrocortisone 10 mg per mL (7.5 mL) [contains thimerosal]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Cream (Cortisporin)

0.5-0.5-10000 (7.5): $48.61

Solution (Cortisporin)

3.5-10000-1 (10): $79.55

Solution (Neomycin-Polymyxin-HC)

3.5-10000-1 (10): $21.99

Suspension (Cortisporin)

3.5-10000-1 (10): $79.55

Suspension (Cortomycin)

3.5-10000-1 (10): $30.49

Suspension (Neomycin-Polymyxin-HC)

3.5-10000-1 (7.5): $66.47

3.5-10000-1 (10): $21.99

Suspension (Pediotic)

3.5-10000-1 (7.5): $57.33

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Hydrocortisone
- Neomycin
- Polymyxin B

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsHydrocortisone, Neomycin, and Polymyxin B; Polymyxin B, Neomycin, and Hydrocortisone

International Brand NamesCortisporin Cream (BB, BM, BS, BZ, GY, JM, NL, PK, SR, TT); Cortisporin Ear (BB, BM, BS, BZ, GY, JM, NL, PH, SR, TT); Cortisporin Ophthalmic Suspension (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Ircos (PH); Isonep H (PH)

Neomycin, Polymyxin B, and Prednisolone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(nee oh MYE sin, pol i MIKS in bee, & pred NIS oh lone)

U.S. Brand NamesPoly-Pred速

Pharmacologic CategoryAntibiotic/Corticosteroid, Ophthalmic

Use: Labeled IndicationsSteroid-responsive inflammatory ocular condition in which bacterial infection or a risk of bacterial ocular infection exists

Dosing: Adults**Ocular inflammation/infection:** Ophthalmic: Instill 1-2 drops every 3-4 hours; acute infections may require every 30-minute instillation initially with frequency of administration reduced as the infection is brought under control. To treat the lids: Instill 1-2 drops every 3-4 hours, close the eye and rub the excess on the lids and lid margins.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

ContraindicationsHypersensitivity to neomycin, polymyxin B, prednisolone, or any component of the formulation

Allergy Considerations

- Corticosteroid Allergy

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Dermatologic: Cutaneous sensitization, skin rash, delayed wound healing

Ocular: Increased intraocular pressure, glaucoma, optic nerve damage, cataracts, conjunctival sensitization, transient irritation, burning, stinging, itching, inflammation, angioneurotic edema, urticaria, vesicular and maculopapular dermatitis

Metabolism/Transport EffectsPrednisolone: **Substrate** of CYP3A4 (minor); **Inhibits** CYP3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Polymyxin B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

Cardiac Glycosides: Aminoglycosides may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

Colistimethate: Polymyxin B may enhance the neuromuscular-blocking effect of Colistimethate. *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents: Polymyxin B may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, ophthalmic: Neomycin 0.35%, polymyxin B 10,000 units per mL, and prednisolone acetate 0.5% (5 mL; 10 mL [DSC]) [contains thimerosal]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Suspension (Poly-Pred)

0.5% (5): $30.99

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPolymyxin B, Neomycin, and Prednisolone; Prednisolone, Neomycin, and Polymyxin B

Neomycin

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(nee oh MYE sin)

U.S. Brand NamesNeo-Fradin™; Neo-Rx

Pharmacologic CategoryAmmonium Detoxicant; Antibiotic, Aminoglycoside; Antibiotic, Topical

Use: Labeled IndicationsOrally to prepare GI tract for surgery; topically to treat minor skin infections; treatment of diarrhea caused by *E. coli*; adjunct in the treatment of hepatic encephalopathy; bladder irrigation; ocular infections

Dosing: Adults

Dermatologic infections: Topical: Topical solutions containing 0.1% to 1% neomycin have been used for irrigation

Preoperative intestinal antisepsis: Oral: 1 g each hour for 4 doses then 1 g every 4 hours for 5 doses; or 1 g at 1 PM, 2 PM, and 11 PM on day preceding surgery as an adjunct to mechanical cleansing of the bowel and oral erythromycin; or 6 g/day divided every 4 hours for 2-3 days

Hepatic encephalopathy: Oral: 500-2000 mg every 6-8 hours or 4-12 g/day divided every 4-6 hours for 5-6 days

Chronic hepatic insufficiency: Oral: 4 g/day for an indefinite period

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Preoperative intestinal antisepsis: Oral: Children: 90 mg/kg/day divided every 4 hours for 2 days; or 25 mg/kg at 1 PM, 2 PM, and 11 PM on the day preceding surgery as an adjunct to mechanical cleansing of the intestine and in combination with erythromycin base

Hepatic encephalopathy: Oral: Children: 50-100 mg/kg/day in divided doses every 6-8 hours or 2.5-7 g/m^2/day divided every 4-6 hours for 5-6 days not to exceed 12 g/day

Dermatologic infections: Topical: Children: Refer to adult dosing.

ContraindicationsHypersensitivity to neomycin or any component of the formulation, or other aminoglycosides; intestinal obstruction

Warnings/Precautions

Boxed warnings:

- Nephrotoxicity: See “Concerns related to adverse effects” below.
- Neuromuscular blockade and respiratory paralysis: See “Concerns related to adverse effects” below.
- Neurotoxicity: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Nephrotoxicity: **[U.S. Boxed Warning]: May cause nephrotoxicity;** usual risk factors include pre-existing renal impairment, concomitant nephrotoxic medications, advanced age and dehydration. Discontinue treatment if signs of nephrotoxicity occur; renal damage is usually reversible.
- Neuromuscular blockade and respiratory paralysis: **[U.S. Boxed Warning]: May cause neuromuscular blockade and respiratory paralysis;** especially when given soon after anesthesia or muscle relaxants.
- Neurotoxicity: **[U.S. Boxed Warning]: May cause neurotoxicity;** usual risk factors include pre-existing renal impairment, concomitant neuro-/nephrotoxic medications, advanced age and dehydration. Ototoxicity is proportional to the amount of drug given and the duration of treatment. Tinnitus or vertigo may be indications of vestibular injury and impending bilateral irreversible damage. Discontinue treatment if signs of ototoxicity occur.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hearing impairment: Use with caution in patients with pre-existing vertigo, tinnitus, or hearing loss.
- Neuromuscular disorders: Use with caution in patients with neuromuscular disorders, including myasthenia gravis.
- Renal impairment: Use with caution in patients with pre-existing renal insufficiency; dosage modification required.

Dosage form specific issues:

- Topical: It is a contact sensitizer with sensitivity occurring in 5% to 15% of patients treated with the drug; symptoms include itching, reddening, edema, and failure to heal when used topically.

Other warnings/precautions:

- Parenteral administration: More toxic than other aminoglycosides when given parenterally; **do not administer parenterally.**

- Peritoneal lavage: **Do not use as peritoneal lavage** due to significant systemic adsorption of the drug.

Pregnancy Risk FactorD

Pregnancy ConsiderationsNeomycin crosses the placenta. Because neomycin has limited maternal absorption, the portion of an orally administered maternal dose available to cross the placenta is very low. Because of several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy, the manufacturer classifies neomycin as pregnancy risk factor D. There have been no reports of fetal toxicity in humans from neomycin. No adequate and well-controlled studies have been conducted in pregnant women and it is not known whether neomycin can cause fetal harm. Although the manufacturer considers neomycin pregnancy risk factor D, neomycin-specific clinical data would suggest a pregnancy risk factor C.

LactationExcretion in breast milk unknown

Breast-Feeding ConsiderationsIt is not known if neomycin is excreted into breast milk; however, limited oral absorption by both the mother and infant would minimize exposure to the nursing infant. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Neomycin in Pregnancy & Lactation

Adverse Reactions

Oral:

>10%: Gastrointestinal: Nausea, diarrhea, vomiting, irritation or soreness of the mouth or rectal area

<1% (Limited to important or life-threatening): Dyspnea, eosinophilia, nephrotoxicity, neurotoxicity, ototoxicity (auditory), ototoxicity (vestibular)

Topical: >10%: Dermatologic: Contact dermatitis

Drug Interactions

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

Cardiac Glycosides: Aminoglycosides may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Monitoring ParametersRenal function tests, audiometry in symptomatic patients

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, ototoxicity, nephrotoxicity, neurotoxicity). Assess knowledge/teach patient appropriate use (application of cream/ointment), possible side effects/interventions, and adverse symptoms to report. Minimal absorption across GI mucosa or skin surfaces; however with ulceration, open or burned surfaces (especially large surfaces), absorption is possible.

Monitoring: Lab TestsRenal function; perform culture and sensitivity prior to initiating therapy.

Patient EducationOral: Take as directed. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience nausea or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); constipation (increased exercise, fluids, fruit, or fiber may help, or consult prescriber); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report immediately any change in hearing; ringing or sense of fullness in ears; persistent diarrhea; changes in voiding patterns; or numbness, tingling, or pain in any extremity. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder, micronized, as sulfate [for prescription compounding] (Neo-Rx): (10 g, 100 g)

Solution, oral, as sulfate (Neo-Fradin™): 125 mg/5 mL (60 mL, 480 mL) [contains benzoic acid; cherry flavor]

Tablet, as sulfate: 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Neomycin Sulfate)

500 mg (30): $37.99

Mechanism of ActionInterferes with bacterial protein synthesis by binding to 30S ribosomal subunits

Pharmacodynamics/Kinetics

Absorption: Oral, percutaneous: Poor (3%)

Distribution: 97% of an orally administered dose remains in the GI tract. Absorbed neomycin distributes to tissues and concentrates in the renal cortex. With repeated doses, accumulation also occurs in the inner ear.

V_d: 0.36 L/kg

Protein binding: 0% to 30%

Metabolism: Slightly hepatic

Half-life elimination (age and renal function dependent): 3 hours

Time to peak, serum: Oral: 1-4 hours

Excretion: Feces (97% of oral dose as unchanged drug); urine (30% to 50% of absorbed drug as unchanged drug)

Related Information

- Prevention of Wound Infection and Sepsis in Surgical Patients

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsNeomycin Sulfate

References

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Edson RS and Terrell CL, “The Aminoglycosides,” *Mayo Clin Proc*, 1991, 66(11):1158-64. [PubMed 1943249]

Feigin RD and Cherry JD, *Textbook of Pediatric Infectious Diseases*, 4th ed, Philadelphia, PA: WB Saunders Co, 1997.

International Brand NamesApokalin (NO); Biofradin (ES); Burn-Gel (ES); Bykomycin (AT, CZ, DE); Coliriocilina Neomicina (ES); Concatag (AR); Cysto-Myacyne N (DE); Endomixin (IT); Enteromicina (PT); Fradyl (BE, LU); Glubacida (MX); Minims Neomycin (BE, NL); Myacyne (DE); Mycifradin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Nebacetin N Spruhverband (DE); Nebapol B (AR); Neo-Mix (AT); Neobiotic (ID); Neointestin (ES); Neomas (AR); Neomicina Estersa (ES); Neomicina Roger (ES); Neomicina Salvat (ES); Neomycin (IL); Neomycin Drossapharm (CH); Neomycine (BE); Neomycine Diamant (BE, FR, LU); Neomycine Minims (NL); Neomycinsulfat Chevita (AT); Neomycinum (PL); Neosulf (AU); Nivemycin (GB, IE); Ofodex (MX); Rovicine (CH); Sulfate de Neomycine-Chauvin (LU); Trioftín (MX); Unguentum Neomycini (PL); Uro-Beniktol N (CH); Uro-Nebacetin N (DE); Vagicillin (DE); Vinacil (MX); Vitacilina (MX); Xyloderm (MX)

Neostigmine

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English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Prostigmin® may be confused with physostigmine

Pronunciation(nee oh STIG meen)

U.S. Brand NamesProstigmin®

Canadian Brand NamesProstigmin®

Pharmacologic CategoryAcetylcholinesterase Inhibitor

Use: Labeled IndicationsDiagnosis and treatment of myasthenia gravis; prevention and treatment of postoperative bladder distention and urinary retention; reversal of the effects of nondepolarizing neuromuscular-blocking agents after surgery

Dosing: Adults

Myasthenia gravis, diagnosis: I.M.: 0.02 mg/kg as a single dose

Myasthenia gravis, treatment:

Oral: 15 mg/dose every 3-4 hours up to 375 mg/day maximum; interval between doses must be individualized to maximal response

I.M., I.V., SubQ: 0.5-2.5 mg every 1-3 hours up to 10 mg/24 hours maximum

Reversal of nondepolarizing neuromuscular blockade after surgery in conjunction with atropine: I.V.: 0.5-2.5 mg; total dose not to exceed 5 mg; must administer atropine several minutes prior to neostigmine

Bladder atony: I.M., SubQ:

Prevention: 0.25 mg every 4-6 hours for 2-3 days

Treatment: 0.5-1 mg every 3 hours for 5 doses after bladder has emptied

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Myasthenia gravis, diagnosis: I.M.: Children: 0.04 mg/kg as a single dose

Myasthenia gravis, treatment: Children:

Oral: 2 mg/kg/day divided every 3-4 hours

I.M., I.V., SubQ: 0.01-0.04 mg/kg every 2-4 hours

Reversal of nondepolarizing neuromuscular blockade after surgery in conjunction with atropine (must administer atropine several minutes prior to neostigmine): I.V.:

Infants: 0.025-0.1 mg/kg/dose

Children: 0.025-0.08 mg/kg/dose

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer 50% of normal dose.

Cl_{cr} <10 mL/minute: Administer 25% of normal dose.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.In the diagnosis of myasthenia gravis, all anticholinesterase medications should be discontinued for at least 8 hours before administering neostigmine.

Administration: I.V. DetailpH: 5.9 (adjusted)

CompatibilityStable in NS.

Y-site administration: Compatible: Heparin, hydrocortisone sodium succinate, potassium chloride, vitamin B complex with C.

Compatibility in syringe: Compatible: Glycopyrrolate, heparin, ondansetron, pentobarbital, thiopental.

ContraindicationsHypersensitivity to neostigmine, bromides, or any component of the formulation; GI or GU obstruction

Allergy Considerations

- Cholinesterase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anticholinesterase insensitivity: For brief or prolonged periods, anticholinesterase insensitivity can develop.
- Cholinergic effects: Discontinue if symptoms of excess cholinergic activity (eg, salivation, sweating, urinary incontinence); overdosage may result in cholinergic crisis, which must be distinguished from myasthenic crisis.
- Hypersensitivity reactions: Have atropine and epinephrine ready to treat hypersensitivity reactions.

Disease-related concerns:

- Asthma: Use with caution in patients with asthma.
- Cardiovascular disease: Use with caution in patients with bradycardia and cardiac arrhythmias.
- GI disease: Use with caution in patients with GI disease, including peptic ulcer disease.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Myasthenia gravis: Adequate facilities should be available for cardiopulmonary resuscitation when testing and adjusting dose for myasthenia gravis.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.
- Vagotonia: Not generally recommended for use in patients with vagotonia.

Concurrent drug therapy issues:

- Muscle relaxants: Does **not** antagonize and may prolong the Phase I block of depolarizing muscle relaxants (eg, succinylcholine).

Geriatric ConsiderationsMany elderly will have diseases which may influence the use of neostigmine. Also, many elderly will need doses reduced 50% due to creatinine clearances in the 10-50 mL/minute range (common in the aged). Side effects or concomitant disease may warrant use of pyridostigmine.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias (especially bradycardia), hypotension, tachycardia, AV block, nodal rhythm, nonspecific ECG changes, cardiac arrest, syncope, flushing

Central nervous system: Convulsions, dysarthria, dysphonia, dizziness, loss of consciousness, drowsiness, headache

Dermatologic: Skin rash, thrombophlebitis (I.V.), urticaria

Gastrointestinal: Hyperperistalsis, nausea, vomiting, salivation, diarrhea, stomach cramps, dysphagia, flatulence

Genitourinary: Urinary urgency

Neuromuscular & skeletal: Weakness, fasciculations, muscle cramps, spasms, arthralgia

Ocular: Small pupils, lacrimation

Respiratory: Increased bronchial secretions, laryngospasm, bronchiolar constriction, respiratory muscle paralysis, dyspnea, respiratory depression, respiratory arrest, bronchospasm

Miscellaneous: Diaphoresis increased, anaphylaxis, allergic reactions

Drug Interactions

Beta-Blockers: Acetylcholinesterase Inhibitors may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Cholinergic Agonists: Acetylcholinesterase Inhibitors may enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Ginkgo Biloba: May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): Acetylcholinesterase Inhibitors may diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Succinylcholine: Acetylcholinesterase Inhibitors may enhance the neuromuscular-blocking effect of Succinylcholine. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringUsed for MG diagnosis by prescribers. For bladder atony, assess bladder adequacy prior to administering medication. Monitor therapeutic effectiveness and adverse effects (including cholinergic crisis). Teach patient symptoms to report.

Patient EducationTake this drug exactly as prescribed. You may experience visual difficulty (eg, blurring and dark adaptation, use caution at night) or urinary frequency. Promptly report any muscle weakness, respiratory difficulty, severe or unresolved diarrhea, persistent abdominal cramping or vomiting, sweating, or tearing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as methylsulfate: 0.5 mg/mL (1 mL, 10 mL); 1 mg/mL (10 mL)

Tablet, as bromide: 15 mg

Generic AvailableYes: Injection

Mechanism of ActionInhibits destruction of acetylcholine by acetylcholinesterase which facilitates transmission of impulses across myoneural junction

Pharmacodynamics/Kinetics

Onset of action: I.M.: 20-30 minutes; I.V.: 1-20 minutes

Duration: I.M.: 2.5-4 hours; I.V.: 1-2 hours

Absorption: Oral: Poor, <2%

Metabolism: Hepatic

Half-life elimination: Normal renal function: 0.5-2.1 hours; End-stage renal disease: Prolonged

Excretion: Urine (50% as unchanged drug)

Pharmacotherapy PearlsIn the diagnosis of myasthenia gravis, all anticholinesterase medications should be discontinued for at least 8 hours before administering neostigmine.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause drowsiness, restlessness, or agitation

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other ConsiderationsNeostigmine has occasionally been used to improve gastrointestinal motility. Researchers from Amsterdam evaluated a neostigmine infusion (0.4-0.8 mg/hour over 24 hours) in patients with critical illness-related colonic ileus in a randomized, placebo-controlled, double-blind manner (van der Spoel, 2001). Twenty four ICU patients were evaluated and 13 patients initially received neostigmine. Eleven of the patients in the active treatment group passed stools whereas none of the placebo group did. The median time to defecation was 6 hours. None of the patients had the infusion stopped or reduced because of adverse events. Three patients had an increase in saliva and sputum production. No cardiac complications were observed. Three patients developed ischemic colon 7-10 days after treatment. No difference was found in APACHE scores between patients with colonic ischemia and those without, but the median dopamine dose was significantly higher (16 mcg/kg/minute) in patients with ischemia than those without (8 mcg/kg/minute).

Ponec and his associates (1999) studied the use of a single intravenous dose of neostigmine (2 mg over 3-5 minutes) in 21 surgical or medical patients with acute colonic pseudo-obstruction (cecal diameter >10 cm). Patients were randomized to receive neostigmine or placebo and a blinded physician evaluated their responses. Patients received continuous ECG monitoring and atropine was immediately available for treatment of bradycardia. Ten of the 11 patients receiving neostigmine had prompt colonic decompression with a median time to response of 4 minutes. Two that had an initial response to neostigmine required colonic decompression for recurrence of distention. Adverse events included abdominal pain, excessive salivation, and vomiting. In addition, 2 patients had symptomatic bradycardia requiring atropine.

Index TermsNeostigmine Bromide; Neostigmine Methylsulfate

References

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International Brand NamesFadastigmina (AR); Intrastigmina (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PT, QA, SA, SY, YE); Metastigmin[inj.] (FI); Neostigmin (HR, SE); Neostigmina Braun (ES); Normastigmin (AT); Polstigminum (PL); Prostig (PH); Prostigmin (AE, AT, BB, BF, BH, BJ, BM, BS, BZ, CH, CI, CY, CZ, DE, EC, EG, ET, GH, GM, GN, GY, ID, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PK, PR, PY, QA, SA, SC, SD, SL, SN, SR, SY, TH, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Prostigmin INJ (AU); Prostigmina (IT); Prostigmine (BE, BR, CN, CO, ES, FR, LU, MX, PE, PT, UY); Prostigmin[inj.] (GB, HR, IE); Stigmin (KP); Stigmosan (HU); Tilstigmin (IN); Vagostin (TW)

Nepafenac

Lexi-Drugs Online

English

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Pronunciation(ne pa FEN ak)
U.S. Brand NamesNevanac™
Canadian Brand NamesNevanac™
Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Ophthalmic
Use: Labeled IndicationsTreatment of pain and inflammation associated with cataract surgery
Dosing: Adults**Pain, inflammation associated with cataract surgery:** Ophthalmic: Instill 1 drop into affected eye(s) 3 times/day, beginning 1 day prior to surgery, the day of surgery, and through the first 2 weeks of the postoperative period
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Pain, inflammation associated with cataract surgery:** Ophthalmic: Children ≥10 years: Refer to adult dosing.
Administration: Other

Ophthalmic: Shake well prior to use.

StorageStore at 2°C to 25˚C (36°F to 77˚F).
ContraindicationsHypersensitivity to nepafenac, other NSAIDs, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Aspirin/NSAID sensitivity: Use with caution in patients with previous sensitivity to acetylsalicylic acid and phenylacetic acid derivatives, including patients who experience bronchospasm, asthma, rhinitis, or urticaria following NSAID or aspirin.
- Keratitis: May cause keratitis; continued use in a patient with keratitis may cause severe corneal adverse reactions, potentially resulting in loss of vision. Immediately discontinue use in patients with evidence of corneal epithelial damage.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with a predisposition to bleeding (bleeding tendencies or medications which interfere with coagulation).
- Diabetes: Use with caution in patients with diabetes mellitus; may be at risk of corneal adverse events, potentially resulting in loss of vision.
- Ocular disease: Use with caution in patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, ocular surface disease, or repeat ocular surgeries (within a short timeframe); may be at risk of corneal adverse events, potentially resulting in loss of vision.
- Rheumatoid arthritis: Use with caution in patients with rheumatoid arthritis; may be at risk of corneal adverse events, potentially resulting in loss of vision.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <10 years of age.
- Surgery patients: May slow/delay healing or prolong bleeding time following surgery.

Other warnings/precautions:

- Duration of therapy: Use for more than 1 day prior to surgery or for 14 days beyond surgery may increase risk and severity of corneal adverse events.
- Soft contact lenses: Patients using ophthalmic drops should not wear soft contact lenses.

Geriatric ConsiderationsNo differences in safety and efficacy noted between elderly and younger adults. No dosage adjustment necessary. Elderly may be taking other medications that will increase bleeding.
Pregnancy Risk FactorC/D (3rd trimester)
Pregnancy ConsiderationsTeratogenic events were not observed in animal studies. Safety and efficacy in pregnant women have not been established. Exposure to nonsteroidal anti-inflammatory drugs late in pregnancy may lead to premature closure of the ductus arteriosus.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions1% to 10%:

Cardiovascular: Hypertension (1% to 4%)

Central nervous system: Headache (1% to 4%)

Gastrointestinal: Nausea (1% to 4%), vomiting (1% to 4%)

Ocular: Capsular opacity (5% to 10%), foreign body sensation (5% to 10%), intraocular pressure increased (5% to 10%), sticky sensation (5% to 10%), visual acuity decreased (5% to 10%), conjunctival edema (1% to 5%), corneal edema (1% to 5%), dry eye (1% to 5%), lid margin crusting (1% to 5%), ocular discomfort (1% to 5%), ocular hyperemia (1% to 5%), ocular pain (1% to 5%), ocular pruritus (1% to 5%), photophobia (1% to 5%), tearing (1% to 5%), vitreous detachment (1% to 5%)

Respiratory: Sinusitis (1% to 4%)

Drug Interactions

Latanoprost: NSAID (Ophthalmic) may diminish the therapeutic effect of Latanoprost. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringAssess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Patient EducationOphthalmic: Instill drops as often as recommended. Wash hands before instilling. Sit or lie down to instill. Open eye, look at the ceiling, and instill prescribed amount. Close eye and roll eye in all directions. Apply gentle pressure to inner corner of eye for 1-2 minutes after instillation. Do not wear soft contract lenses while using this medication. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, ophthalmic: 0.1% (3 mL) [contains benzalkonium chloride]

Generic AvailableNo

ManufacturerAlcon Laboratories

Pricing: U.S. (www.drugstore.com)

Suspension (Nevanac)

0.1% (3): $92.14

Mechanism of ActionNepafenac is a prodrug which once converted to amfenac inhibits prostaglandin synthesis by decreasing the activity of the enzyme, cyclooxygenase, which results in decreased formation of prostaglandin precursors.

Pharmacodynamics/Kinetics

Absorption: Low levels (0.2-0.5 ng/mL) of nepafenac and amfenac are detected in the plasma following ophthalmic administration

Metabolism: Hydrolyzed in ocular tissue to amfenac (active)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesNevanac (AR, CN, CR, CZ, GT, HN, NI, PA, PH, SE, SV, TH)

Nesiritide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

International issues:

Natrecor® may be confused with Nitrocor® which is a brand name for nitroglycerin in Chile and Italy

Pronunciation(ni SIR i tide)
U.S. Brand NamesNatrecor®
Canadian Brand NamesNatrecor®
Pharmacologic CategoryNatriuretic Peptide, B-type, Human
Use: Labeled IndicationsTreatment of acutely decompensated congestive heart failure (CHF) in patients with dyspnea at rest or with minimal activity
Dosing: Adults

Acute decompensated heart failure: I.V.: Initial: 2 mcg/kg (bolus); followed by continuous infusion at 0.01 mcg/kg/minute. **Note:** Should not be initiated at a dosage higher than initial recommended dose. There is limited experience with increasing the dose >0.01 mcg/kg/minute; in one trial, a limited number of patients received higher doses that were increased no faster than every 3 hours by 0.005 mcg/kg/minute (preceded by a bolus of 1 mcg/kg), up to a maximum of 0.03 mcg/kg/minute. Increases beyond the initial infusion rate should be limited to selected patients and accompanied by close hemodynamic and renal function monitoring.

Patients experiencing hypotension during the infusion: Infusion dose should be reduced or discontinued. Other measures to support blood pressure should be initiated (eg, I.V. fluids, Trendelenburg position). May attempt to restart at a lower dose (reduce previous infusion dose by 30% and omit bolus).

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo adjustment required but use cautiously in patients with renal impairment or those patients who rely on the renin-angiotensin-aldosterone system for renal perfusion. Monitor renal function closely.
Dosing: Hepatic Impairment

No dosage adjustment recommended.

Calculations

- Nesiritide

Administration: I.V.Do not administer through a heparin-coated catheter (concurrent administration of heparin via a separate catheter is acceptable, per manufacturer).
Administration: I.V. DetailPrime I.V. tubing with 5 mL of infusion prior to connection with vascular access port and prior to administering bolus or starting the infusion. Withdraw bolus from the prepared infusion bag and administer over 60 seconds. Begin infusion immediately following administration of the bolus.
StorageVials may be stored below 25°C (77°F); do not freeze. Protect from light. Following reconstitution, vials are stable at 2°C to 25°C (36°F to 77°F) for up to 24 hours. Use reconstituted solution within 24 hours.
ReconstitutionReconstitute 1.5 mg vial with 5 mL of diluent removed from a preprefilled 250 mL plastic I.V. bag (compatible with D_5W, $D_5{}^1/_2NS$, $D_5{}^1/_4NS$, NS). Do not shake vial to dissolve (roll gently). Withdraw entire contents of vial and add to 250 mL I.V. bag. Invert several times to mix. Resultant concentration of solution is ~6 mcg/mL.
CompatibilityStable in D_5W, $D_5{}^1/_2NS$, $D_5{}^1/_4NS$, NS.

Physically **incompatible** with heparin, insulin, ethacrynate sodium, bumetanide, enalaprilat, hydralazine, and furosemide. Do not administer through the same catheter. Do not administer with any solution containing sodium metabisulfite. Catheter must be flushed between administration of nesiritide and physically incompatible drugs.

ContraindicationsHypersensitivity to natriuretic peptide or any component of the formulation; cardiogenic shock (when used as primary therapy); hypotension (systolic blood pressure <90 mm Hg)
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactic/hypersensitivity reactions: Prepared through recombinant technology using *E. coli*; monitor for allergic or anaphylactic reactions.
- Hypotension: May cause hypotension; administer in clinical situations when blood pressure may be closely monitored. Use caution in patients with systolic blood pressure <100 mm Hg (contraindicated if <90 mm Hg); more likely to experience hypotension. Effects may

be additive with other agents capable of causing hypotension. Hypotensive effects may last for several hours.

- Renal effects: May be associated with development of azotemia; use caution in patients with renal impairment or in patients where renal perfusion is dependent on renin-angiotensin-aldosterone system (eg, severe heart failure); avoid initiation at doses higher than recommended; increases in serum creatinine may occur at an elevated rate.

Disease-related concerns:

- Cardiovascular disease: Should not be used in patients with low cardiac filling pressures, or in patients with conditions which depend on venous return including significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, and pericardial tamponade.

- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Prolonged infusions: Use caution with prolonged infusions; limited experience for infusions >48 hours.

Geriatric ConsiderationsNo specific data to date; elderly are liable to have hypotension, see Warnings/Precautions for blood pressure criteria. Elderly with reduced renal function should be monitored closely.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse Reactions**Note:** Frequencies cited below were recorded in VMAC trial at dosages similar to approved labeling. Higher frequencies have been observed in trials using higher dosages of nesiritide. The percentages marked with an asterisk (*) indicate frequency less than or equal to placebo or other standard therapy.

>10%:

Cardiovascular: Hypotension (total: 11%; symptomatic: 4% at recommended dose, up to 17% at higher doses)

Renal: Increased serum creatinine (28% with >0.5 mg/dL increase over baseline)

1% to 10%:

Cardiovascular: Ventricular tachycardia (3%)*, ventricular extrasystoles (3%)*, angina (2%)*, bradycardia (1%), tachycardia, atrial fibrillation, AV node conduction abnormalities

Central nervous system: Headache (8%)*, dizziness (3%)*, insomnia (2%)*, anxiety (3%), fever, confusion, paresthesia, somnolence, tremor

Dermatologic: Pruritus, rash

Gastrointestinal: Nausea (4%)*, abdominal pain (1%)*, vomiting (1%)*

Hematologic: Anemia

Local: Injection site reaction

Neuromuscular & skeletal: Back pain (4%), leg cramps

Ocular: Amblyopia

Respiratory: Cough increased, hemoptysis, apnea

Miscellaneous: Diaphoresis increased

Postmarketing and/or case reports: Hypersensitivity reactions (rare)

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, and licorice (may increase blood pressure). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, and shepherd's purse (may enhance decreased blood pressure).

Monitoring ParametersBlood pressure, hemodynamic responses (PCWP, RAP, CI), BUN, creatinine; urine output

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, other hypotensive agents or diuretics). Blood pressure and cardiac function should be monitored before and at frequent intervals during and for 24 hours following infusion (hemodynamic monitoring with larger doses). Assess results of laboratory tests, renal function, and patient response on a regular basis throughout therapy (eg, hypersensitivity, hypotension). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Patient EducationThis medication can only be administered by infusion; you will be monitored closely during and following infusion. Report immediately any pain, burning, swelling at infusion site, or any signs of allergic reaction (eg, respiratory or swallowing difficulty, back pain, chest tightness, rash, hives, swelling of lips or mouth). Remain in bed until advised otherwise; call for assistance with turning or changing position. Report any chest pain, respiratory difficulty, confusion, nausea, leg cramps, swelling of extremities, sudden or excessive weight gain, or any other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Natrecor®: 1.5 mg

Generic AvailableNo

ManufacturerScios

Mechanism of ActionBinds to guanylate cyclase receptor on vascular smooth muscle and endothelial cells, increasing intracellular cyclic GMP, resulting in smooth muscle cell relaxation. Has been shown to produce dose-dependent reductions in pulmonary capillary wedge pressure (PCWP) and systemic arterial pressure.

Pharmacodynamics/Kinetics

Onset of action: 15 minutes (60% of 3-hour effect achieved)

Duration: >60 minutes (up to several hours) for systolic blood pressure; hemodynamic effects persist longer than serum half-life would predict

Distribution: V_{ss}: 0.19 L/kg

Metabolism: Proteolytic cleavage by vascular endopeptidases and proteolysis following receptor binding and cellular internalization

Half-life elimination: Initial (distribution) 2 minutes; Terminal: 18 minutes

Time to peak: 1 hour

Excretion: Urine

Pharmacotherapy PearlsThe duration of symptomatic improvement with nesiritide following discontinuation of the infusion has been limited (generally lasting several days). Atrial natriuretic peptide, which is related to nesiritide, has been associated with increased vascular permeability. This has not been observed in clinical trials with nesiritide, but patients should be monitored for this effect.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation, insomnia, anxiety, or confusion

Mental Health: Effects on Psychiatric TreatmentMay cause hypotension; use caution with antipsychotics and TCAs. May cause cardiac conduction abnormalities; use caution with TCAs and ziprasidone.

Cardiovascular ConsiderationsA retrospective review evaluated the renal effects of nesiritide in acutely decompensated heart failure (ADHF) (Sackner-Bernstein, 2005). It included randomized clinical trials comparing nesiritide with placebo (or an active control). Worsening renal function was defined as an increase in serum creatinine >0.5 mg/dL. Five randomized studies (1269 patients) were reviewed. Use of nesiritide in the doses outlined by the FDA significantly increased the risk of worsening renal function compared with noninotrope based controls.

These investigators performed a meta-analysis of randomized clinical trials comparing the safety of nesiritide to noninotrope based controls in ADHF (Sackner-Bernstein, 2005). There were 3 trials (485 patients) which met the criteria. Death within 30 days tended to occur more often among patient randomized to nesiritide therapy. The authors concluded that the possibility of increased risk of death with nesiritide should be investigated in a large-scale trial.

Scios released a “Dear Healthcare Provider” letter on July 18, 2005, to provide information regarding an expert panel’s review of nesiritide. Here are their final recommendations: The use of nesiritide should be strictly limited to patients presenting to the hospital with acutely decompensated heart failure who have dyspnea at rest. Nesiritide should not be used to replace diuretics, to enhance diuresis, to improve renal function, for intermittent outpatient infusion, or for scheduled repetitive use.

Additional information is available at http://www.fda.gov/medwatch/safety/2005/safety05.htm#Natrecor2, last accessed July 19, 2005.

Index TermsB-type Natriuretic Peptide (Human); hBNP; Natriuretic Peptide

References

Colucci WS, Elkayam U, Horton DP, et al, “Intravenous Nesiritide, A Natriuretic Peptide, in the Treatment of Decompensated Congestive Heart Failure. Nesiritide Study Group,” *N Engl J Med*, 2000, 343(4):246-53.[PubMed 10911006]

Sackner-Bernstein JD, Kowalski M, Fox M, et al, "Short-Term Risk of Death After Treatment With Nesiritide for Decompensated Heart Failure: A Pooled Analysis of Randomized Controlled Trials," *JAMA*, 2005, 293(15):1900-5.[PubMed 15840865]

Sackner-Bernstein JD, Skopicki HA, and Aaronson KD, "Risk of Worsening Renal Function With Nesiritide in Patients With Acutely

Decompensated Heart Failure," *Circulation*, 2005, 111(12):1487-9.[PubMed 15781736]

International Brand NamesNatrecor (AR, BB, BM, BS, BZ, CO, GY, ID, JM, NL, SR, TT, VE); Noratak (CH, IL)

Nevirapine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Nevirapine may be confused with nelfinavir

Viramune® may be confused with Viracept®

Pronunciation(ne VYE ra peen)

U.S. Brand NamesViramune®

Canadian Brand NamesViramune®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Non-nucleoside)

Use: Labeled IndicationsIn combination therapy with other antiretroviral agents for the treatment of HIV-1

Dosing: Adults

HIV infection: Oral: Initial: 200 mg once daily for 14 days; maintenance: 200 mg twice daily (in combination with an additional antiretroviral agents).

Note: If patient experiences a rash during the 14-day lead-in period, dose should not be increased until the rash has resolved. Lead-in period should not exceed 28 days; alternative treatment should be considered at that point. Discontinue if severe rash, rash with constitutional symptoms, or rash with elevated hepatic transaminases is noted. Use of prednisone to prevent nevirapine-associated rash is not recommended. Permanently discontinue if symptomatic hepatic events occur. If therapy is interrupted for >7 days, restart with initial dose for 14 days.

Prevention of maternal-fetal HIV transmission (AIDSinfo guidelines): Note: Nevirapine is used in combination with zidovudine (and possibly lamivudine) in select situations (eg, infants born to mothers with suboptimal viral suppression at delivery, infants born to mothers with only intrapartum therapy or no therapy, or infants born to mothers with known antiretroviral drug-resistant virus)

Mother: 200 mg as a single dose at onset of labor

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

HIV infection: Oral:

Infants ≥15 days and Children <13 years: 150 mg/m^2 once daily for first 14 days (maximum dose: 200 mg/day); increase dose to 150 mg/m^2 twice daily if no rash or untoward effects (maximum dose: ≤400 mg/day). Children ≤8 years of age: May require 200 mg/m^2 twice daily.

Adolescents: Refer to adult dosing.

Note: If patient experiences a rash during the 14-day lead-in period, dose should not be increased until the rash has resolved. Lead-in period should not exceed 28 days; alternative treatment should be considered at that point. Discontinue if severe rash, rash with constitutional symptoms, or rash with elevated hepatic transaminases is noted. Use of prednisone to prevent nevirapine-associated rash is not recommended. Permanently discontinue if symptomatic hepatic events occur. If therapy is interrupted for >7 days, restart with initial dose for 14 days.

Prevention of maternal-fetal HIV transmission (AIDSinfo guidelines): Note: Nevirapine is used in combination with zidovudine (and possibly lamivudine) in select situations (eg, infants born to mothers with suboptimal viral suppression at delivery, infants born to mothers with only intrapartum therapy or no therapy, or infants born to mothers with known antiretroviral drug-resistant virus)

Neonate: 2 mg/kg as a single dose between birth and 72 hours if mother received intrapartum dose of nevirapine. If maternal dose was given ≤2 hours prior to delivery, administer infant dose as soon as possible following birth.

Dosing: Renal Impairment

Cl_{cr} ≥20 mL/minute: No adjustment required

Hemodialysis: An additional 200 mg dose is recommended following dialysis.

Dosing: Hepatic ImpairmentUse is contraindicated with moderate-to-severe hepatic impairment. Permanently discontinue if symptomatic hepatic events.

Administration: OralMay be administered with or without food. May be administered with an antacid or didanosine. Shake suspension gently prior to administration.

StorageStore at 25°C (77°F); excursion permitted to 15°C to 30˚C (59°F to 86°F).

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to nevirapine or any component of the formulation; moderate-to-severe hepatic impairment (Child-Pugh class B or C)

Allergy Considerations

- Nevirapine Allergy

Warnings/Precautions

Boxed warnings:

- Hepatotoxicity: See “Concerns related to adverse effects” below.
- Skin reactions: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Hepatotoxicity: **[U.S. Boxed Warning]: Severe hepatotoxic reactions may occur (fulminant and cholestatic hepatitis, hepatic necrosis) and, in some cases, have resulted in hepatic failure and death.** The greatest risk of these reactions is within the initial 6 weeks of treatment; **intensive monitoring is required during the initial 18 weeks of therapy to detect potentially life-threatening hepatic reactions.** Patients with a history of chronic hepatitis (B or C) or increased baseline transaminase levels may be at increased risk of hepatotoxic reactions. Female gender and patients with increased CD4$^+$-cell counts may be at substantially greater risk of hepatic events (often associated with rash). Therapy should not be started with elevated CD4$^+$-cell counts unless the benefit of therapy outweighs the risk of serious hepatotoxicity (females: CD4$^+$-cell counts >250 cells/mm^3; males: CD4$^+$-cell counts >400 cells/mm^3). If signs and symptoms of hepatitis occur, nevirapine should be permanently discontinued with immediate evaluation of liver function.
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Rhabdomyolysis: Has been observed in conjunction with skin and/or hepatic adverse events during postmarketing surveillance. Termination of therapy is warranted with evidence of severe skin or liver toxicity.
- Skin reactions: **[U.S. Boxed Warning]: Severe life-threatening skin reactions (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity reactions with rash and organ dysfunction) have occurred;intensive monitoring is required during the initial 18 weeks of therapy to detect potentially life-threatening dermatologic and hypersensitivity reactions.** If a severe dermatologic or hypersensitivity reaction occurs, nevirapine should be permanently discontinued; these events may include a severe rash, or a rash associated with fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, transaminase increases, general malaise, hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction. Use of the 14-day lead-in dosing period is necessary to decrease the incidence of rash events. If nonsevere rash (in absence of transaminase elevations) occurs, do not increase dose until resolution of rash.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

Other warnings/precautions:

- Appropriate use: A 14-day lead-in dose should be used to decrease risk of skin reactions. An alternative regimen should be used if the lead-in dose exceeds 28 days.

Pregnancy Risk FactorB

Pregnancy ConsiderationsNevirapine crosses the placenta. No increased risk of overall birth defects has been observed following 1st trimester exposure according to data collected by the antiretroviral pregnancy registry. Pharmacokinetics are not altered during pregnancy and dose adjustment is not needed. The Perinatal HIV Guidelines Working Group recommends nevirapine as the NNRTI for use during pregnancy. When used to prevent perinatal transmission in women who do not need therapy for their own health, use is not recommended if CD4$^+$ lymphocyte counts >250/mm^3 (monitor for liver toxicity during first 18 weeks of therapy). It may also be used in combination with zidovudine in HIV-infected women who are in labor, but have had no prior antiretroviral therapy, in order to reduce the maternal-fetal transmission of HIV; consider adding intrapartum and postpartum zidovudine and lamivudine to reduce nevirapine resistance. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse Reactions**Note:** Potentially life-threatening nevirapine-associated adverse effects may present with the following symptoms: Abrupt onset of flu-like symptoms, abdominal pain, jaundice, or fever with or without rash; may progress to hepatic failure with encephalopathy. Skin rash is present in ~50% of cases.

Percentages of adverse effects vary by clinical trial:

>10%:

Dermatologic: Rash (grade 1/2: 13%; grade 3/4: 1.5%) is the most common toxicity; occurs most frequently within the first 6 weeks of therapy; women may be at higher risk than men

Hepatic: ALT >250 units/L (5% to 14%); symptomatic hepatic events (4%, range: up to 11%) are more common in women, women with CD4$^+$ cell counts >250 cells/mm^3, and men with CD4$^+$ cell counts >400 cells/mm^3

1% to 10%:

Central nervous system: Headache (1% to 4%), fatigue (up to 5%)

Gastrointestinal: Nausea (<1% to 9%), abdominal pain (<1% to 2%), diarrhea (up to 2%)

Hepatic: AST >250 units/L (4% to 8%); coinfection with hepatitis B or C and/or increased liver function tests at the beginning of therapy are associated with a greater risk of asymptomatic transaminase elevations (ALT or AST >5 times ULN: 6%, range: up to 9%) or symptomatic events occurring ≥6 weeks after beginning treatment

Postmarketing and/or case reports: Allergic reactions, anaphylaxis, anemia, angioedema, arthralgia, blisters, bullous eruptions, conjunctivitis, eosinophilia, facial edema, fever, fulminant and cholestatic hepatitis, granulocytopenia, hepatic failure, hepatic necrosis, hypersensitivity syndrome, jaundice, lymphadenopathy, malaise, neutropenia, oral lesions, paresthesia, redistribution/accumulation of body fat, renal dysfunction, rhabdomyolysis, Stevens-Johnson syndrome, somnolence, toxic epidermal necrolysis, ulcerative stomatitis, urticaria, vomiting

Metabolism/Transport Effects **Substrate** of CYP2B6 (minor), 2D6 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2D6 (weak), 3A4 (weak); **Induces** CYP2B6 (strong), 3A4 (strong)

Drug Interactions

Caspofungin: Inducers of Drug Clearance may decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) when coadministered with known inducers of drug clearance. *Risk D: Consider therapy modification*

CYP2B6 Substrates: CYP2B6 Inducers (Strong) may increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Etravirine: Reverse Transcriptase Inhibitors (Non-Nucleoside) may decrease the serum concentration of Etravirine. This has been observed with the NNRTIs efavirenz and nevirapine. Reverse Transcriptase Inhibitors (Non-Nucleoside) may increase the serum concentration of Etravirine. This has been observed with delavirdine. *Risk X: Avoid combination*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Reverse Transcriptase Inhibitors (Non-Nucleoside) may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Protease Inhibitors: Nevirapine may increase the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifabutin: May decrease the serum concentration of Nevirapine. Nevirapine may decrease the serum concentration of Rifabutin. Nevirapine may increase the serum concentration of Rifabutin. *Risk C: Monitor therapy*

Rifampin: May decrease the serum concentration of Nevirapine. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Voriconazole: Reverse Transcriptase Inhibitors (Non-Nucleoside) may decrease the serum concentration of Voriconazole. Voriconazole may increase the serum concentration of Reverse Transcriptase Inhibitors (Non-Nucleoside). Management: Efavirenz and voriconazole should not be coadministered at standard doses. Concurrent therapy is acceptable if voriconazole is dosed at 400 mg every 12 hours and efavirenz is dosed at 300 mg daily throughout the course of therapy. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions Herb/Nutraceutical: Nevirapine serum concentration may be decreased by St John's wort; avoid concurrent use.

Monitoring Parameters Monitor CBC and viral load. Baseline liver function tests should be obtained prior to nevirapine's initiation. AIDS guidelines recommend serum transaminase monitoring every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, followed by every 3-4 months. Assess/evaluate AST/ALT immediately in any patients with a rash. Permanently discontinue if patient experiences severe rash, constitutional symptoms associated with rash, rash with elevated AST/ALT, or clinical hepatitis, Mild-to-moderate rash without AST/ALT elevation may continue treatment per discretion of prescriber. If mild-to-moderate urticarial rash, do not restart if treatment is interrupted.

Nursing: Physical Assessment/Monitoring Use caution in presence of or history of hepatic disease. Assess other pharmacological or herbal products patient may be taking for potential interactions or toxicity; dosing adjustments may be necessary. Patient response should be followed closely during 14-day lead-in dosing period to assess for hypersensitivity prior to increasing daily dose. Assess results of laboratory tests (especially LFTs at baseline and frequently during therapy). Assess patient regularly and frequently during initial 18 weeks of therapy to identify any symptoms of hypersensitivity (hepatic and or dermatologic reactions which may include severe rash, rash with fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, jaundice, hepatitis, or renal dysfunction). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsMonitor CBC and viral load. Baseline liver function tests should be obtained prior to nevirapine's initiation. AIDS guidelines recommend serum transaminase monitoring every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, followed by every 3-4 months. Assess/evaluate AST/ALT immediately in any patients with a rash. Permanently discontinue if patient experiences severe rash, constitutional symptoms associated with rash, rash with elevated AST/ALT, or clinical hepatitis, Mild-to-moderate rash without AST/ALT elevation may continue treatment per discretion of prescriber. If mild-to-moderate urticarial rash, do not restart if treatment is interrupted.

Patient EducationYou will be provided with an FDA-approved medication guide with your prescription: Read this guide carefully. Do not take any new prescription, over-the-counter medications, or herbal products during therapy (without consulting prescriber). This is not a cure for HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. Take as directed, with food. Shake suspension gently prior to use. When using dosing cups, rinse cup with water and drink. If you miss a dose, take as soon as possible and return to regular schedule (never take a double dose). Frequent blood tests may be required with prolonged therapy. If rash, blisters, or facial edema develops, stop medicine and contact prescriber immediately. Report any change in urinary pattern, dark urine or light stool, easy bleeding, unusual fatigue, flu-like symptoms, abdominal pain, or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Effectiveness of oral contraceptives may be decreased; consult prescriber for appropriate contraceptives. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, oral:

Viramune®: 50 mg/5 mL (240 mL)

Tablet:

Viramune®: 200 mg

Generic AvailableNo

ManufacturerBoehringer Ingelheim Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Viramune)

200 mg (60): $472.75

Mechanism of ActionAs a non-nucleoside reverse transcriptase inhibitor, nevirapine has activity against HIV-1 by binding to reverse transcriptase. It consequently blocks the RNA-dependent and DNA-dependent DNA polymerase activities including HIV-1 replication. It does not require intracellular phosphorylation for antiviral activity.

Pharmacodynamics/Kinetics

Absorption: >90%

Distribution: Widely; V_d: 1.2-1.4 L/kg; CSF penetration approximates 40% to 50% of plasma

Protein binding, plasma: 60%

Metabolism: Extensively hepatic via CYP3A4 (hydroxylation to inactive compounds); may undergo enterohepatic recycling

Half-life elimination: Decreases over 2- to 4-week time with chronic dosing due to autoinduction (ie, half-life = 45 hours initially and decreases to 25-30 hours)

Time to peak, serum: 2-4 hours

Excretion: Urine (~81%, primarily as metabolites, <3% as unchanged drug); feces (~10%)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV
- Perinatal HIV Guidelines

Pharmacotherapy PearlsPotential compliance problems, frequency of administration, and adverse effects should be discussed with patients before initiating therapy to help prevent the emergence of resistance. Early virologic failure was observed with tenofovir and didanosine delayed release capsules, plus either efavirenz or nevirapine; use caution in treatment-naive patients with high baseline viral loads.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Ulcerative stomatitis and oral lesions.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNeutropenia is common; avoid clozapine and carbamazepine

Index TermsNVP

References

D'Aquila RT, Hughes MD, Johnson VA, et al, "Nevirapine, Zidovudine, and Didanosine Compared With Zidovudine and Didanosine in Patients With HIV-1 Infection. A Randomized, Double-Blind, Placebo-Controlled Trial. National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group Protocol 241 Investigators," *Ann Intern Med*, 1996, 124(12):1019-30. [PubMed 8633815]

"Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Developed by the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children," July 29, 2008. Available at http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf

"Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection," January 29, 2008. Available at http://www.aidsinfo.nih.gov

Hammer SM, Kessler HA, and Saag MS, “Issues in Combination Antiretroviral Therapy: A Review,” *J Acquir Immune Defic Syndr*, 1994, 7(Suppl 2):24-35. [PubMed 8263750]

Havlir DV and Lange JM, “New Antiretrovirals and New Combinations,” *AIDS*, 1998, 12(Suppl A):165-74.

Hilts AE and Fish DN, “Dosage Adjustment of Antiretroviral Agents in Patients With Organ Dysfunction,” *Am J Health Syst Pharm*, 1998, 55:2528-33. [PubMed 9853641]

Mueller BU, Sei S, Anderson B, et al, “Comparison of Virus Burden in Blood and Sequential Lymph Node Biopsy Specimens From Children Infected With Human Immunodeficiency Virus,” *J Pediatr*, 1996, 129(3):410-8. [PubMed 8804331]

“Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,” July 8, 2008. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

Weverling GJ, Lange JM, Jurriaans S, et al, “Alternative Multidrug Regimen Provides Improved Suppression of HIV-1 Replication Over Triple Therapy,” *AIDS*, 1998, 12(11):F117-22. [PubMed 9708401]

International Brand NamesNevimune (IN); Nevipan (MY); Viramune (AE, AR, AT, AU, BE, BF, BG, BH, BJ, BR, CH, CI, CL, CN, CO, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, HU, ID, IE, IL, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PL, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SY, TH, TN, TR, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Mitoxantrone: I.V.: 12 mg/m^2 day 1

[total dose/cycle = 12 mg/m^2]

Fluorouracil: I.V.: 350 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 1050 mg/m^2]

Leucovorin: I.V.: 300 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 900 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Mitoxantrone: I.V.: 10 mg/m^2 day 1

[total dose/cycle = 10 mg/m^2]

Fluorouracil: I.V.: 1000 mg/m^2/day continuous infusion days 1, 2, and 3

[total dose/cycle = 3000 mg/m^2]

Leucovorin: I.V.: 100 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 300 mg/m^2]

Repeat cycle every 21 days

References

Variation 1:

Hainsworth JD, Andrews MB, Johnson DH, et al, “Mitoxantrone, Fluorouracil, and High-Dose Leucovorin: An Effective, Well-Tolerated Regimen for Metastatic Breast Cancer,” *J Clin Oncol*, 1991, 9(10):1731-5. [PubMed 1919624]

Variation 2:

Jones SE, Mennel RG, Brooks B, et al, “Phase II Study of Mitoxantrone, Leucovorin, and Infusional Fluorouracil for Treatment of Metastatic Breast Cancer,” *J Clin Oncol*, 1991, 9(10):1736-9.[PubMed 1919625]

Niacin and Lovastatin

Special Alerts

HMG-CoA Reductase Inhibitors: Evidence Does Not Suggest Increased Incidence of Amyotrophic Lateral Sclerosis (ALS) - Results of FDA Analysis - September 30, 2008

The U.S. Food and Drug Administration's (FDA) review of 41 long-term controlled clinical trials of HMG-CoA reductase inhibitors finds no evidence of an increased incidence of ALS (also known as Lou Gehrig's disease) related to these medications. This analysis occurred after the FDA had received notice of numerous adverse events of which 109 of these reports mentioned ALS, Lou Gehrig's disease, or motor neurone disease. The clinical trials included in the analysis had a median duration of treatment of 3.3 years (range of duration: 6 months to 5 years) and involved 120,964 patients. The analysis identified a total of 19 cases of ALS – 9 cases per 64,602 patients (0.014%) with statin therapy and 10 cases per 56,362 patients (0.017%) with placebo. The incidence rates, based on approximately 400,000 person-years, were 4.2 per 100,000 person-years in the statin-treated group and 5 per 100,000 person-years in the placebo-treated group.

The FDA recommends that health care providers continue to prescribe, and patients continue to use these products as described within their labeling.

For more information, healthcare professionals may refer to the following:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Statin

Colman E, Szarfman A, Wyeth J, et al, "An Evaluation of a Data Mining Signal for Amyotrophic Lateral Sclerosis and Statins Detected in FDA's Spontaneous Adverse Event Reporting System," *Pharmacoepidemiol Drug Saf*, 2008 (epub ahead of print)

Medication Safety Issues

Sound-alike/look-alike issues:

Advicor® may be confused with Advair, Altocor™

Pronunciation(NYE a sin & LOE va sta tin)

U.S. Brand NamesAdvicor®

Canadian Brand NamesAdvicor®

Pharmacologic CategoryAntilipemic Agent, HMG-CoA Reductase Inhibitor; Antilipemic Agent, Miscellaneous

Use: Labeled IndicationsFor use when treatment with both extended-release niacin and lovastatin is appropriate in combination with a standard cholesterol-lowering diet:

Extended-release niacin: Adjunctive treatment of dyslipidemias (types IIa and IIb or primary hypercholesterolemia) to lower the risk of recurrent MI and/or slow progression of coronary artery disease, including combination therapy with other antidyslipidemic agents when additional triglyceride-lowering or HDL-increasing effects are desired; treatment of hypertriglyceridemia in patients at risk of pancreatitis

Lovastatin: Treatment of primary hypercholesterolemia (Frederickson types IIa and IIb); primary and secondary prevention of cardiovascular disease

Dosing: AdultsDosage forms are a fixed combination of niacin and lovastatin.

Dyslipidemia: Oral: Lowest dose: Niacin 500 mg/lovastatin 20 mg; may increase by not more than 500 mg (niacin) at 4-week intervals (maximum dose: niacin 2000 mg/lovastatin 40 mg daily); should be taken at bedtime with a low-fat snack. **Note:** If therapy is interrupted for >7 days, reinstitution of therapy should begin with the lowest dose followed by retitration as needed.

Not for use as initial therapy of dyslipidemias. May be substituted for equivalent dose of Niaspan®, however, manufacturer does not recommend direct substitution with other niacin products.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Mild-to-moderate impairment: No dosage adjustment required

Cl_{cr} <30 mL/minute: Use doses of lovastatin >20 mg/day with caution

Dosing: Hepatic ImpairmentDo not use in active liver disease or unexplained persistent elevations of serum transaminases.

Administration: OralTablet must be swallowed whole; do not crush or chew. Should be taken with a low-fat snack at bedtime.

Dietary ConsiderationsContinue standard cholesterol-lowering diet during therapy. Should be taken with a low-fat snack.

StorageStore at 20°C to 25°C (68°F to 77°F).

Contraindications Hypersensitivity to lovastatin, niacin, or any component of the formulation; active liver disease; unexplained persistent elevations of serum transaminases; active peptic ulcer disease; arterial bleeding; pregnancy; breast-feeding

Allergy Considerations

- HMG-CoA Reductase Inhibitor Allergy
- Niacin and Derivatives Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Flushing: A common adverse effect of niacin and can be attenuated with a gradual increase in dose, and/or by taking aspirin or another NSAID (eg, ibuprofen) 30-60 minutes before dosing; avoid concurrent ingestion of ethanol or hot liquids to minimize flushing.

- Myopathy/rhabdomyolysis: Patients receiving HMG-CoA reductase inhibitors have developed rhabdomyolysis with acute renal failure and/or myopathy; patients should be monitored closely. This risk is dose-related and is increased with concurrent use of other lipid-lowering medications, including niacin at doses ≥1 g/day. Temporarily discontinue for elective major surgery, acute medical or surgical conditions, or in any patient experiencing an acute or serious condition predisposing to renal failure (eg, sepsis, hypotension, trauma, uncontrolled seizures). Based upon current evidence, HMG-CoA reductase inhibitor therapy should be continued in the perioperative period unless risk outweighs cardioprotective benefit. Use caution in patients with renal impairment, inadequately treated hypothyroidism, concurrent use of potent CYP3A4 inhibitors (eg, cyclosporine, azole antifungals, macrolide antibiotics, telithromycin, protease inhibitors, and nefazodone), and those taking other drugs associated with myopathy (eg, colchicine); these patients are predisposed to myopathy. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine.

Disease-related concerns:

- Cardiovascular disease: Use niacin with caution in patients with unstable angina or MI; risk of arrhythmias at high doses.

- Diabetes: Use niacin with caution in patients with diabetes mellitus; interferes with glucose control. Monitor glucose closely.

- Gallbladder disease: Use niacin with caution in patients with active gallbladder disease; can exacerbate.

- Gout: Use niacin with caution in patients with gout.

- Hepatic impairment and/or ethanol use: Use with caution in patients who consume large amounts of ethanol or have a history of liver disease; use is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases. Obtain baseline transaminase levels prior to initiation of therapy; repeat in 6-12 weeks and again with any subsequent increase in dosage, then periodically once a stable dose has been reached.

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- High potential for interactions: Use lovastatin with caution in patients taking strong CYP3A4 inhibitors (see drug interactions); consider alternative agents that avoid or lessen potential for CYP-mediated interactions.

Special populations:

- Elderly: Use with caution in patients with advanced age, these patients are predisposed to myopathy.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

Advicor®: Formulations of niacin (regular release versus extended release) are not interchangeable; cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted niacin products at equivalent doses

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

Geriatric Considerations The definition of and, therefore, when to treat hyperlipidemia in the elderly is a controversial issue. The National Cholesterol Education Program recommends that all adults maintain a plasma cholesterol <160 mg/dL. Elderly with one additional risk factor, goal LDL would be <130 mg/dL. It is the authors' belief that pharmacologic treatment be reserved for those who are unable to obtain a desirable plasma cholesterol concentration by diet alone and for whom the benefits of treatment are believed to outweigh the potential adverse effects, drug interactions, and cost of treatment.

Pregnancy Risk Factor X

Pregnancy Considerations See individual agents.

Lactation Enters breast milk/contraindicated

Breast-Feeding Considerations Niacin is excreted in breast milk. The excretion of lovastatin is unknown, although similar agents are known to be excreted in breast milk. Use during breast-feeding is contraindicated.

Adverse Reactions

>10%: Cardiovascular: Flushing (71%)

1% to 10%:

Central nervous system: Headache (9%), pain (8%)

Dermatologic: Pruritus (7%), rash (5%)

Endocrine & metabolic: Hyperglycemia (4%)

Gastrointestinal: Nausea (7%), diarrhea (6%), abdominal pain (4%), dyspepsia (3%), vomiting (3%)

Neuromuscular & skeletal: Back pain (5%), weakness (5%), myalgia (3%)

Miscellaneous: Flu-like syndrome (6%)

Other uncommon adverse reactions reported with niacin and/or lovastatin include: Alkaline phosphatase increased, alopecia, anaphylaxis, angioedema, anemia, anorexia, anxiety, arthritis, atrial fibrillation, cataracts, chest pain, chills, cholestatic jaundice, cirrhosis, CPK increased (>10x normal), depression, dryness of skin/mucous membranes, dyspnea, edema, eosinophilia, erectile dysfunction, erythema multiforme, ESR increased, facial paresis, fatty liver, fever, GGT increased, gout, gynecomastia, hemolytic anemia, hepatitis, hepatic necrosis (fulminant), hepatoma, hyperbilirubinemia, hypersensitivity reaction, hyperuricemia, hypophosphatemia, hypotension, impotence, impaired extraocular muscle movement, leukopenia, libido decreased, memory loss, malaise, myopathy, nail changes, nodules, ophthalmoplegia, palpitation, pancreatitis, paresthesia, peptic ulcer, peripheral nerve palsy, peripheral neuropathy, photosensitivity, polymyalgia rheumatica, psychic disturbance, positive ANA, purpura, rhabdomyolysis, rash, renal failure, skin discoloration, Stevens-Johnson syndrome, syncope, systemic lupus erythematosus-like syndrome, tachycardia, taste alteration, thrombocytopenia, thyroid dysfunction, toxic epidermal necrolysis, transaminases increased, tremor, urticaria, vasculitis, vertigo

Metabolism/Transport EffectsLovastatin: **Substrate** of CYP3A4 (major); **Inhibits** CYP2C9 (weak), 2D6 (weak), 3A4 (weak)

Drug Interactions

Amiodarone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. Management: Dose of HMG-CoA reductase inhibitor may need to be reduced (e.g., simvastatin prescribing information recommends not exceeding 20 mg/day during concurrent therapy). *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Niacin. *Risk D: Consider therapy modification*

Bosentan: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Colchicine: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CycloSPORINE: May increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Danazol: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

DAPTOmycin: HMG-CoA Reductase Inhibitors may enhance the adverse/toxic effect of DAPTOmycin. Specifically, the risk of skeletal muscle toxicity may be increased. Management: Consider temporarily stopping HMG-CoA reductase inhibitor therapy prior to daptomycin. If used together, regular (i.e., at least weekly) monitoring of CPK concentrations is recommended. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Etravirine: May decrease the serum concentration of HMG-CoA Reductase Inhibitors. This applies to atorvastatin, lovastatin and simvastatin. Conversely, levels of fluvastatin may be increased. Management: Dose adjustment of the HMG-CoA reductase inhibitor may be warranted. No interaction is expected with rosuvastatin or pravastatin. *Risk C: Monitor therapy*

Fenofibrate: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fenofibric Acid: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Gemfibrozil: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Gemfibrozil may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Grapefruit Juice: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: Niacin may enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Niacin: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Niacinamide: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Protease Inhibitors: May increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Sildenafil: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

St Johns Wort: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): HMG-CoA Reductase Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Consumption of large amounts of ethanol may increase the risk of liver damage with HMG-CoA reductase inhibitors. Concurrent ingestion of ethanol may increase the risk of flushing associated with niacin.

Food: Lovastatin absorption may be decreased with food, however, the combination product is recommended to be taken with a low-fat snack at bedtime. Lovastatin serum concentrations may be increased if taken with grapefruit juice; avoid concurrent use. Concurrent ingestion of hot liquids may increase the risk of flushing associated with niacin.

Herb/Nutraceutical: St John's wort may decrease lovastatin levels. Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.

Test InteractionsNiacin: False elevations in some fluorometric determinations of urinary catecholamines; false-positive urine glucose (Benedict's reagent)

Monitoring ParametersBlood glucose, CBC, LFTs, prothrombin time (surgical patients), and serum phosphorus. Baseline CK levels, hepatic transaminase levels, and total cholesterol profile should be obtained prior to initiation of therapy. Repeat CK level with onset of unexplained muscle symptoms. Obtain repeat hepatic transaminase levels in 6-12 weeks and with any subsequent increase in dosage, then annually or more frequently if indicated once a stable dose has been reached.

Monitoring: Lab TestsBlood glucose, CBC, LFTs, prothrombin time (surgical patients), and serum phosphorus. Baseline CK levels, hepatic transaminase levels, and total cholesterol profile should be obtained prior to initiation of therapy. Repeat CK level with onset of unexplained muscle symptoms. Obtain repeat hepatic transaminase levels in 6-12 weeks and with any subsequent increase in dosage, then annually or more frequently if indicated once a stable dose has been reached.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, variable release (Advicor®):

500/20: Niacin 500 mg [extended release] and lovastatin 20 mg [immediate release] [contains polysorbate 80]

750/20: Niacin 750 mg [extended release] and lovastatin 20 mg [immediate release] [contains polysorbate 80]

1000/20: Niacin 1000 mg [extended release] and lovastatin 20 mg [immediate release] [contains polysorbate 80]

1000/40: Niacin 1000 mg [extended release] and lovastatin 40 mg [immediate release] [contains polysorbate 80]

Generic AvailableNo

ManufacturerKos

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Advicor)

500-20 mg (60): $206.70

Mechanism of ActionLovastatin acts by competitively inhibiting 3-hydroxyl-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis. Niacin is a component of two coenzymes which is necessary for tissue respiration, lipid metabolism, and glycogenolysis; inhibits the synthesis of very low density lipoproteins.

Pharmacodynamics/KineticsSee individual agents.

Bioavailability: Tablet strengths (eg, two tablets of 500 mg/20 mg and one tablet of 1000 mg/40 mg) are not interchangeable; bioavailability varies.

Related Information

- Hyperlipidemia Management
- Lipid-Lowering Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness; may rarely cause anxiety and depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with fluvoxamine or nefazodone may increase the risk of myopathy and/or rhabdomyolysis. May rarely cause leukopenia and thrombocytopenia; use caution with clozapine, carbamazepine, and valproic acid.

Cardiovascular ConsiderationsNiacin lowers LDL-cholesterol (LDL-C) and triglycerides (TGs) and increases HDL-cholesterol (HDL-C). It causes a shift from small, dense to large, buoyant LDL particles that are less atherogenic. Niacin also significantly lowers lipoprotein A levels.

Primary Prevention: HMG-CoA reductase inhibitors are effective in primary and secondary prevention of cardiovascular events in patients with hyperlipidemia. For primary prevention, a patient's major risk factors (cigarette smoking, hypertension or currently taking antihypertensives, low HDL-C, family history, age, gender) should be evaluated. Patients with multiple risk factors (≥2) require more intensive therapy guided by the calculation of a 10-year absolute CHD risk (eg, the percent probability of having a CHD event in next 10 years). An individual's 10-year absolute CHD risk can be calculated at www.med-decisions.com/cvtool/phys/phys.html. LDL cholesterol goals, therapeutic lifestyle changes, and drug therapy are determined based upon a patient's risk factor profile.

Primary prevention trials show that cholesterol-lowering drugs reduce the risk of major coronary events, coronary death, and cerebrovascular events even in the first 6-12 months of use. The WOSCOP trial suggested a trend towards enhanced survival using pravastatin in their patients (mean LDL-cholesterol of 192 mg/dL and no history of MI). In a recent trial (Sever, 2003), patients with HTN and at least three other risk factors were randomized to 10 mg daily of atorvastatin or placebo. These patients had a total nonfasting cholesterol <250 mg/dL before treatment. LDL-C levels were 132 mg/dL before treatment and fell to an average of 90 mg/dL in the atorvastatin-treated group. There was a significant reduction in stroke, cardiovascular events, and coronary events in the atorvastatin-treated group as compared to the placebo group. There was no difference in mortality between the groups.

HMG-CoA reductase inhibitors decrease C-reactive protein (CRP), an inflammatory marker and an acute phase reactant. Elevated levels of high sensitive CRP (hsCRP), which detects CRP levels as low as 0.175 mg/L, have been shown to be associated with an increased risk of cardiovascular events. Recently, the JUPITER trial demonstrated that the use of rosuvastatin in healthy patients (men ≥50 years and women ≥60 years) without a history of cardiovascular disease with LDL <130 mg/dL and a hsCRP level ≥2 mg/L reduced the risk of major cardiovascular events (eg, nonfatal MI, stroke, death from cardiovascular causes), The number needed to treat over 5 years to prevent 1 cardiovascular event is 25. Current guidelines do not recommend drug treatment for patients with an LDL <130 mg/dL. However, identification of the patient at higher risk of cardiovascular events within this subgroup using hsCRP is now important given that statins may prevent the occurrence of these serious cardiovascular events (Ridker, 2008).

Secondary Prevention: Secondary prevention trials indicate that “statin” therapy reduces mortality, major coronary events, coronary artery procedures, and stroke. The Heart Protection Study proved that lowering serum cholesterol levels reduces the rate of major vascular events among high-risk individuals with documented vascular disease (CHD, cerebrovascular, peripheral vascular) or diabetes regardless of initial cholesterol concentrations. PROVE IT is a randomized, double-blind trial evaluating hospitalized patients with acute coronary syndrome to determine the effects of intense LDL-C lowering therapy. Four thousand patients with an LDL-C levels of 106 mg/dL were randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily. After 2 years, the combined cardiovascular endpoint (death, MI, unstable angina requiring hospitalization, revascularization and stroke) was ~26% in the pravastatin patients (median LDL-C 95 mg/dL) and ~22% in the atorvastatin treated patients (median LDL-C 62 mg/dL).

LaRosa and colleagues assessed the efficacy and safety of lowering LDL cholesterol <100 mg/dL in patients with stable coronary heart disease (LaRosa, 2005). Ten thousand and one patients with baseline LDL levels <130 mg/dL were randomized to atorvastatin 10 mg or 80 mg daily and followed for a median of 4.9 years. The primary endpoint was the occurrence of the first major cardiovascular event (death from CVD, MI, resuscitation after cardiac arrest, or stroke). A primary event occurred in 434 patients (8.7%) receiving 80 mg daily (mean LDL 77 mg/dL) and 548 patients (10.9%) receiving 10 mg dose (mean LDL 101 mg/dL) (95% CI, 0.69-0.89; p <0.001). There was no mortality difference between the two treatment groups.

In addition to the ability of HMG-CoA reductase inhibitors to decrease levels of high-sensitivity C-reactive protein (hs-CRP), they also possess pleiotropic properties including improved endothelial function, reduced inflammation at the site of the coronary plaque, inhibition of platelet aggregation, and anticoagulant effects. These nonlipid effects may be beneficial when HMG-CoA reductase inhibitors are introduced early in the management of acute coronary syndromes (de Denus, 2002).

Myopathy: Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years of age), women more frequently than men, small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, drug interactions (use with caution or avoid). The combination of a HMG-CoA reductase inhibitor plus nicotinic acid seems to carry a lower risk of myopathy than does a HMG-CoA reductase inhibitor plus a fibrate. Other medications, when used concurrently, may enhance the risk of myopathy associated with statins; these include drugs that inhibit CYP3A4 isoenzymes (lovastatin, simvastatin, atorvastatin) or CYP2C9 isoenzymes (fluvastatin). HMG-CoA reductase inhibitors may exacerbate exercise-induced skeletal muscle injury. Many experts favor getting a baseline creatine kinase (CK) measurement before initiating therapy (asymptomatic CK elevations are common). Obtain a CK measurement if patient complains of muscle soreness, tenderness, or pain.

Anesthesia and Critical Care Concerns/Other Considerations**Myopathy:** Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years), gender (occurs in women more frequently than men), small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, and drug interactions (use with caution or avoid).

Based on current research, HMG-CoA reductase inhibitors should be continued in the perioperative period. Postoperative discontinuation of statin therapy is associated with an increased risk of cardiac morbidity and mortality.

Index TermsLovastatin and Niacin

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International Brand Names Advicor (CA)

Niacin and Simvastatin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

HMG-CoA Reductase Inhibitors: Evidence Does Not Suggest Increased Incidence of Amyotrophic Lateral Sclerosis (ALS) - Results of FDA Analysis - September 30, 2008

The U.S. Food and Drug Administration's (FDA) review of 41 long-term controlled clinical trials of HMG-CoA reductase inhibitors finds no evidence of an increased incidence of ALS (also known as Lou Gehrig's disease) related to these medications. This analysis occurred after the FDA had received notice of numerous adverse events of which 109 of these reports mentioned ALS, Lou Gehrig's disease, or motor neurone disease. The clinical trials included in the analysis had a median duration of treatment of 3.3 years (range of duration: 6 months to 5 years) and involved 120,964 patients. The analysis identified a total of 19 cases of ALS – 9 cases per 64,602 patients (0.014%) with statin therapy and 10 cases per 56,362 patients (0.017%) with placebo. The incidence rates, based on approximately 400,000 person-years, were 4.2 per 100,000 person-years in the statin-treated group and 5 per 100,000 person-years in the placebo-treated group.

The FDA recommends that health care providers continue to prescribe, and patients continue to use these products as described within their labeling.

For more information, healthcare professionals may refer to the following:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Statin

Colman E, Szarfman A, Wyeth J, et al, "An Evaluation of a Data Mining Signal for Amyotrophic Lateral Sclerosis and Statins Detected in FDA's Spontaneous Adverse Event Reporting System," *Pharmacoepidemiol Drug Saf*, 2008 (epub ahead of print)

Ezetimibe (Zetia®), Simvastatin (Zocor®), and Ezetimibe/Simvastatin (Vytorin®): Preliminary Results From the SEAS Trial - Updated September 2008

The U.S. Food and Drug Administration (FDA) has communicated important information regarding an ongoing safety review of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial. The SEAS trial (Rossebo, 2008), recently available online, evaluated the effects of the combination ezetimibe/simvastatin (Vytorin®) on clinical outcomes in patients with mild-to-moderate asymptomatic aortic stenosis. The 5-year trial demonstrated that ezetimibe/simvastatin was no better than placebo in reducing the primary composite outcomes – major cardiovascular events (eg, death from cardiovascular causes, aortic-valve replacement, heart failure) or the composite outcome of aortic-valve-related clinical events and ischemia. Additionally, a higher incidence of newly diagnosed cancer of any type (105 patients taking ezetimibe/simvastatin vs 70 patients taking placebo, p=0.01) and cancer-related death (39 patients taking ezetimibe/simvastatin vs 23 patients taking placebo, p=0.05) was observed in the patients receiving ezetimibe/simvastatin compared to those receiving placebo. Of note, 8 patients diagnosed with cancer prior to randomization experienced recurrence (3 in the ezetimibe/simvastatin group vs 5 in the placebo group).

Subsequently, an interim analysis of the ongoing Study of Heart and Renal Protection (SHARP) trial and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) with a total of 20,617 randomized patients demonstrated no overall excess of cancer (313 active-treatment vs 326 control, p=0.61) (Peto, 2008). The SHARP trial randomized patients with chronic kidney disease to either ezetimibe/simvastatin or placebo. The IMPROVE-IT trial randomized patients with acute coronary syndrome to either ezetimibe/simvastatin or simvastatin alone. When the SEAS trial data is included in this analysis, there still is no significant excess of cancer (414 active-treatment vs 391 control, p=0.46). However, cancer-associated deaths were significantly higher when compared to controls (134 vs 92, respectively; p=0.007). Previous trials and meta-analyses involving the use of ezetimibe, simvastatin, or ezetimibe/simvastatin also have not shown an increased risk of cancer.

The FDA estimates that it will take approximately 6 months to fully evaluate the clinical trial data after receipt of the final SEAS trial report. At this time, the FDA recommends that patients continue taking their cholesterol-lowering medications.

For more information, U.S. healthcare professionals may refer to the following:

FDA: http://www.fda.gov/medwatch/safety/2008/safety08.htm#ezetimibe2

Peto R, Emberson J, Landray M, et al, "Analysis of Cancer Data From Three Ezetimibe Trials," *N Engl J Med*, 2008, http://content.nejm.org/cgi/content/full/NEJMsa0806603

Rossebo AB, Pederson TR, Boman K, et al, "Intensive Lipid Lowering With Simvastatin and Ezetimibe in Aortic Stenosis," *N Engl J Med*, 2008, http://content.nejm.org/cgi/content/full/NEJMoa0804602

Simvastatin and Amiodarone Concurrent Therapy: Dose-Related Increased Risk of Rhabdomyolysis - August 2008

The U.S. Food and Drug Administration (FDA) has issued an alert to remind practitioners of a dose-related increased risk of rhabdomyolysis when amiodarone is used concurrently with simvastatin at doses >20 mg. If patients require simvastatin >20 mg, an alternative HMG-CoA reductase inhibitor (statin) should be used. This information has previously been incorporated into the Lexi-Comp monograph.

Additional information may be found at http://www.fda.gov/cder/drug/InfoSheets/HCP/simvastatin_amiodaroneHCP.htm

Medication Safety Issues
International issue:

Simcor® is also a brand name for simvastatin in Indonesia.

Pronunciation(NYE a sin & sim va STAT in)

U.S. Brand NamesSimcor®

Pharmacologic Category[Antilipemic Agent, HMG-CoA Reductase Inhibitor](); [Antilipemic Agent, Miscellaneous]()

Use: Labeled IndicationsTreatment of primary hypercholesterolemia, mixed dyslipidemia (types IIa and IIb), or hypertriglyceridemia (type IV hyperlipidemia) in combination with standard cholesterol-lowering diet when simvastatin or niacin monotherapy is inadequate

Dosing: AdultsDosage forms are a fixed combination of niacin extended-release and simvastatin.

Dyslipidemia: Oral:

Lowest dose (initiate in patients naïve to niacin therapy or those currently receiving niacin immediate-release): Niacin 500 mg/simvastatin 20 mg once daily at bedtime with a low-fat snack; may increase by not more than 500 mg (niacin) at 4-week intervals

Maintenance dose: Niacin 1000 mg/simvastatin 20 mg to niacin 2000 mg/simvastatin 40 mg once daily (maximum: Niacin 2000 mg/simvastatin 40 mg once daily)

Note: If therapy is interrupted for >7 days, reinstitution of therapy should begin with the lowest dose followed by retitration as tolerated. Not for use as initial therapy of dyslipidemias. May be substituted for equivalent dose of niacin extended-release, however, manufacturer does not recommend direct substitution with immediate-release preparations.

Dosing: Renal Impairment

Mild-to-moderate impairment: No dosage adjustment required; use caution.

Severe renal impairment: Use with extreme caution or avoid unless patient already tolerating simvastatin doses ≥10 mg.

Dosing: Hepatic ImpairmentContraindicated in active liver disease or unexplained persistent elevations of serum transaminases.

Dosing: Adjustment for ToxicityDiscontinue therapy if transaminases >3 times ULN persist or are accompanied by symptoms (nausea, fever, malaise).

Administration: OralTablets must be swallowed whole; do not crush or chew. Should be taken with a low-fat snack at bedtime.

Dietary ConsiderationsContinue standard cholesterol-lowering diet during therapy. Should be taken with a low-fat snack.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to niacin, simvastatin, or any component of the formulation; active liver disease; unexplained persistent elevations of transaminases; active peptic ulcer disease; arterial bleeding; pregnancy; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

- Flushing: A common adverse effect of niacin and can be attenuated with a gradual increase in dose, and/or by taking aspirin or another NSAID (eg, ibuprofen) 30-60 minutes before dosing. Avoid concurrent ingestion of ethanol, hot liquids, or spicy foods to minimize flushing.

- Hepatotoxicity: Cases of severe hepatotoxicity have occurred when immediate release (crystalline) niacin products have been substituted with sustained-release (modified release, timed-release) niacin products at equivalent doses. Initiate niacin at lower doses and titrate to achieve desired response.

- Myopathy/rhabdomyolysis: Patients receiving HMG-CoA reductase inhibitors have developed rhabdomyolysis with acute renal failure and/or myopathy; patients should be monitored closely. This risk is dose-related and is increased with concurrent use of other lipid lowering medications. Temporarily discontinue for elective major surgery, acute medical or surgical conditions, or in any patient experiencing an acute or serious condition predisposing to renal failure (eg, sepsis, hypotension, trauma, uncontrolled seizures). Based upon current evidence, HMG-CoA reductase inhibitor therapy should be continued in the perioperative period unless risk outweighs cardioprotective benefit. Use caution in patients with renal impairment, inadequately treated hypothyroidism, and those taking other drugs associated with myopathy (eg, colchicine); these patients are predisposed to myopathy. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine. Discontinue treatment if CK levels rise to >10 times ULN with concomitant muscle symptoms.

Disease-related concerns:

- Cardiovascular disease: Use niacin with caution in patients with unstable angina or MI; risk of arrhythmias at high doses.

- Diabetes: Use niacin with caution in patients with diabetes mellitus; niacin may increase fasting blood glucose, although clinical data suggest increases are generally modest (<5%). Monitor glucose; adjustment of hypoglycemic therapy may be necessary.

- Gallbladder disease: Use niacin with caution in patients with active gallbladder disease; use can exacerbate.

- Gout: Use niacin with caution in patients with gout; may increase uric acid levels.

- Hepatic impairment and/or ethanol use: Use with caution in patients who consume large amounts of ethanol or have a history of liver disease; use is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases. Transaminases should be monitored during therapy; if levels elevated, repeat test (confirmatory) and monitor frequently until transaminases return to normal; therapy should be discontinued if transaminase levels >3 times ULN persist or are accompanied by symptoms (nausea, fever, malaise).

- Renal impairment: Use with caution in renal impairment; use with extreme caution or avoid in severe impairment unless patient already tolerating simvastatin doses ≥10 mg.

Concurrent drug therapy issues:

- High potential for interactions: Use simvastatin with caution in patients taking strong CYP3A4 inhibitors (see Drug Interactions); consider alternative agents that avoid or lessen potential for CYP-mediated interactions.

Special populations:

- Elderly: Use with caution in elderly patients; these patients are predisposed to myopathy.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Product interchangeability: Bioavailability of niacin formulations vary (regular release versus extended release) and are not interchangeable; cases of severe hepatic toxicity, including fulminant hepatic necrosis, have occurred in patients who have substituted niacin products at equivalent doses. In addition, bioequivalence between different Simcor® dosage strengths has not been evaluated and strengths should not be considered exchangeable.

Other warnings/precautions:

- Appropriate use: Prior to initiation, secondary causes for hypercholesterolemia (eg, poorly controlled diabetes mellitus, hypothyroidism) should be excluded.

Pregnancy Risk FactorX
Pregnancy ConsiderationsSee individual agents.
LactationExcretion in breast milk unknown/contraindicated
Breast-Feeding ConsiderationsNiacin is excreted in breast milk. The excretion of simvastatin is unknown, although similar agents are known to be excreted in breast milk. Use during breast-feeding is contraindicated.
Adverse ReactionsReactions/percentages reported with combination product; also refer to individual agents.

>10%: Cardiovascular: Flushing (up to 59%)

1% to 10%:

Central nervous system: Headache (5%)

Dermatologic: Pruritus (3%)

Gastrointestinal: Diarrhea (3%), nausea (3%)

Neuromuscular & skeletal: Back pain (3%)

Frequency not defined: Alkaline phosphatase increased, amylase increased, bilirubin increased, creatinine kinase increased, fasting blood glucose increased, GGT increased, LDH increased, phosphorus decreased, platelets decreased, prothrombin time increased, thyroid function test abnormalities, transaminases increased, uric acid increased

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP2C8 (weak), 2C9 (weak), 2D6 (weak)
Drug Interactions

Amiodarone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. Management: Dose of HMG-CoA reductase inhibitor may need to be reduced (e.g., simvastatin prescribing information recommends not exceeding 20 mg/day during concurrent therapy). *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Niacin. *Risk D: Consider therapy modification*

Bosentan: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Colchicine: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CycloSPORINE: May increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Danazol: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

DAPTOmycin: HMG-CoA Reductase Inhibitors may enhance the adverse/toxic effect of DAPTOmycin. Specifically, the risk of skeletal muscle toxicity may be increased. Management: Consider temporarily stopping HMG-CoA reductase inhibitor therapy prior to daptomycin. If used together, regular (i.e., at least weekly) monitoring of CPK concentrations is recommended. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Etravirine: May decrease the serum concentration of HMG-CoA Reductase Inhibitors. This applies to atorvastatin, lovastatin and simvastatin. Conversely, levels of fluvastatin may be increased. Management: Dose adjustment of the HMG-CoA reductase inhibitor may be warranted. No interaction is expected with rosuvastatin or pravastatin. *Risk C: Monitor therapy*

Fenofibrate: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fenofibric Acid: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Gemfibrozil: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Gemfibrozil may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Grapefruit Juice: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: Niacin may enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Imatinib: May decrease the metabolism of Simvastatin. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Niacin: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Niacinamide: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Protease Inhibitors: May increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. *Risk D: Consider therapy modification*

Ranolazine: May increase the serum concentration of Simvastatin. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Sildenafil: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

St Johns Wort: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): HMG-CoA Reductase Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Consumption of large amounts of ethanol may increase the risk of liver damage with HMG-CoA reductase inhibitors. Concurrent ingestion of ethanol may increase the risk of flushing associated with niacin.

Food: Simvastatin serum concentrations may be increased when taken with grapefruit juice; avoid concurrent intake of large quantities (>1 quart/day). Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice. Concurrent ingestion of hot liquids or spicy foods may increase the risk of niacin associated flushing.

Herb/Nutraceutical: St John's wort may decrease simvastatin levels.

Test InteractionsFalse elevations in some fluorometric determinations of urinary catecholamines; false-positive urine glucose (Benedict's reagent)

Monitoring ParametersBlood glucose, CBC, LFTs, prothrombin time (surgical patients), and serum phosphorus. Baseline CK levels, hepatic transaminase levels, and total cholesterol profile should be obtained prior to initiation of therapy. Repeat CK level with onset of unexplained muscle symptoms. Repeat hepatic transaminase levels every 12 weeks for first 6 months and periodically thereafter (approximately every 6 months).

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsBlood glucose, CBC, LFTs, prothrombin time (surgical patients), and serum phosphorus. Baseline CK levels, hepatic transaminase levels, and total cholesterol profile should be obtained prior to initiation of therapy. Repeat CK level with onset of unexplained muscle symptoms. Repeat hepatic transaminase levels every 12 weeks for first 6 months and periodically thereafter (approximately every 6 months).

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, variable release:

Simcor®:

500/20: Niacin 500 mg [extended release] and simvastatin 20 mg [immediate release]

750/20: Niacin 750 mg [extended release] and simvastatin 20 mg [immediate release]

1000/20: Niacin 1000 mg [extended release] and simvastatin 20 mg [immediate release]

Generic AvailableNo

ManufacturerAbbott Laboratories

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Simcor)

500-20 mg (90): $199.29

Mechanism of Action

Niacin is a component of two coenzymes which is necessary for tissue respiration, lipid metabolism, and glycogenolysis; inhibits the synthesis of very low density lipoproteins.

Simvastatin is a derivative of lovastatin that acts by competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Hyperlipidemia Management
- Lipid-Lowering Agents
- Niacin
- Simvastatin

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression, dizziness, nervousness, or insomnia

Mental Health: Effects on Psychiatric TreatmentModerate-to-strong inhibitors of CYP3A4 (eg, nefazodone, caffeine, desipramine, haloperidol, sertraline, and verapamil) may elevate simvastatin levels and the risk of myopathy and renal failure. St John's wort may decrease simvastatin levels; monitor.

Cardiovascular ConsiderationsNiacin lowers LDL-cholesterol (LDL-C) and triglycerides (TGs) and increases HDL-cholesterol (HDL-C). It causes a shift from small, dense to large, buoyant LDL particles that are less atherogenic. Niacin also significantly lowers lipoprotein A levels.

Primary Prevention: HMG-CoA reductase inhibitors are effective in primary and secondary prevention of cardiovascular events in patients with hyperlipidemia. For primary prevention, a patient's major risk factors (cigarette smoking, hypertension or currently taking antihypertensives, low HDL-C, family history, age, gender) should be evaluated. Patients with multiple risk factors (≥2) require more intensive therapy guided by the calculation of a 10-year absolute CHD risk (eg, the percent probability of having a CHD event in next 10 years). An individual's 10-year absolute CHD risk can be calculated at www.med-decisions.com/cvtool/phys/phys.html. LDL cholesterol goals, therapeutic lifestyle changes, and drug therapy are determined based upon a patient's risk factor profile.

Primary prevention trials show that cholesterol-lowering drugs reduce the risk of major coronary events, coronary death, and cerebrovascular events even in the first 6-12 months of use. The WOSCOP trial suggested a trend towards enhanced survival using pravastatin in their patients (mean LDL-cholesterol of 192 mg/dL and no history of MI). In a recent trial (Sever, 2003), patients with HTN and at least three other risk factors were randomized to 10 mg daily of atorvastatin or placebo. These patients had a total nonfasting cholesterol <250 mg/dL before treatment. LDL-C levels were 132 mg/dL before treatment and fell to an average of 90 mg/dL in the atorvastatin-treated group. There was a significant reduction in stroke, cardiovascular events, and coronary events in the atorvastatin-treated group as compared to the placebo group. There was no difference in mortality between the groups.

HMG-CoA reductase inhibitors decrease C-reactive protein (CRP), an inflammatory marker and an acute phase reactant. Elevated levels of high sensitive CRP (hsCRP), which detects CRP levels as low as 0.175 mg/L, have been shown to be associated with an increased risk of cardiovascular events. Recently, the JUPITER trial demonstrated that the use of rosuvastatin in healthy patients (men ≥50 years and women ≥60 years) without a history of cardiovascular disease with LDL <130 mg/dL and a hsCRP level ≥2 mg/L reduced the risk of major cardiovascular events (eg, nonfatal MI, stroke, death from cardiovascular causes), The number needed to treat over 5 years to prevent 1 cardiovascular event is 25. Current guidelines do not recommend drug treatment for patients with an LDL <130 mg/dL. However, identification of the patient at higher risk of cardiovascular events within this subgroup using hsCRP is now important given that statins may prevent the occurrence of these serious cardiovascular events (Ridker, 2008).

Secondary prevention: Secondary prevention trials indicate that “statin” therapy reduces mortality, major coronary events, coronary artery procedures, and stroke. The Heart Protection Study proved that lowering serum cholesterol levels reduces the rate of major vascular events among high-risk individuals with documented vascular disease (CHD, cerebrovascular, peripheral vascular) or diabetes regardless of initial cholesterol concentrations. PROVE IT is a randomized, double-blind trial evaluating hospitalized patients with acute coronary syndrome to determine the effects of intense LDL-C lowering therapy. Four thousand patients with an LDL-C levels of 106 mg/dL were randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily. After 2 years, the combined cardiovascular endpoint (death, MI, unstable angina requiring hospitalization, revascularization and stroke) was ~26% in the pravastatin patients (median LDL-C 95 mg/dL) and ~22% in the atorvastatin treated patients (median LDL-C 62 mg/dL).

LaRosa and colleagues assessed the efficacy and safety of lowering LDL cholesterol <100 mg/dL in patients with stable coronary heart disease (LaRosa, 2005). Ten thousand and one patients with baseline LDL levels <130 mg/dL were randomized to atorvastatin 10 mg or 80 mg daily and followed for a median of 4.9 years. The primary endpoint was the occurrence of the first major cardiovascular event (death from CVD, MI, resuscitation after cardiac arrest, or stroke). A primary event occurred in 434 patients (8.7%) receiving 80 mg daily (mean LDL 77 mg/dL) and 548 patients (10.9%) receiving 10 mg dose (mean LDL 101 mg/dL) (95% CI, 0.69-0.89; $p < 0.001$). There was no mortality difference between the two treatment groups.

In addition to the ability of HMG-CoA reductase inhibitors to decrease levels of high-sensitivity C-reactive protein (hs-CRP), they also possess pleiotropic properties including improved endothelial function, reduced inflammation at the site of the coronary plaque, inhibition of platelet aggregation, and anticoagulant effects. These nonlipid effects may be beneficial when HMG-CoA reductase inhibitors are introduced early in the management of acute coronary syndromes (de Denus, 2002).

Myopathy: Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years of age), women more frequently than men, small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, drug interactions (use with caution or avoid). The combination of a HMG-CoA reductase inhibitor plus nicotinic acid seems to carry a lower risk of myopathy than does a HMG-CoA reductase inhibitor plus a fibrate. Other medications, when used concurrently, may enhance the risk of myopathy associated with statins; these include drugs that inhibit CYP3A4 isoenzymes (lovastatin, simvastatin, atorvastatin) or CYP2C9 isoenzymes (fluvastatin). HMG-CoA reductase inhibitors may exacerbate exercise-induced skeletal muscle injury. Many experts favor getting a baseline creatine kinase (CK) measurement before initiating therapy (asymptomatic CK elevations are common). Obtain a CK measurement if patient complains of muscle soreness, tenderness, or pain.

Index TermsSimvastatin and Niacin

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Niacin

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English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Niacin may be confused with Minocin®, Niaspan®, Nispan®

Niaspan® may be confused with niacin

Nicobid® may be confused with Nitro-Bid®

International issues:

Niacor® may be confused with Nacor® which is a brand name for enalapril in Spain

Pronunciation(NYE a sin)

U.S. Brand NamesNiacin-Time®; Niacor®; Niaspan®; Slo-Niacin® [OTC]

Canadian Brand NamesNiaspan®

Pharmacologic CategoryAntilipemic Agent, Miscellaneous; Vitamin, Water Soluble

Use: Labeled IndicationsAdjunctive treatment of dyslipidemias (types IIa and IIb or primary hypercholesterolemia) to lower the risk of recurrent MI and/or slow progression of coronary artery disease, including combination therapy with other antidyslipidemic agents when additional triglyceride-lowering or HDL-increasing effects are desired; treatment of hypertriglyceridemia in patients at risk of pancreatitis; treatment of peripheral vascular disease and circulatory disorders; treatment of pellagra; dietary supplement

Dosing: Adults**Note:** Formulations of niacin (regular release versus extended release) are not interchangeable.

Recommended daily allowances:

Male: 25-50 years: 19 mg/day; >51 years: 15 mg/day

Female: 25-50 years: 15 mg/day; >51 years: 13 mg/day

Hyperlipidemia: Oral: Usual target dose: Regular release: 1.5-6 g/day in 3 divided doses with or after meals using a dosage titration schedule; extended release: 500 mg to 2 g once daily at bedtime

Regular release formulation (Niacor®): Initial: 250 mg once daily (with evening meal); increase frequency and/or dose every 4-7 days to desired response or first-level therapeutic dose (1.5-2 g/day in 2-3 divided doses); after 2 months, may increase at 2- to 4-week intervals to 3 g/day in 3 divided doses (maximum dose: 6 g/day in 3 divided doses)

Extended release formulation (Niaspan®): Initial: 500 mg at bedtime for 4 weeks, then 1 g at bedtime for 4 weeks; adjust dose to response and tolerance; can increase to a maximum of 2 g/day, but only at 500 mg/day at 4-week intervals

With lovastatin: Recommended initial dose: 20 mg/day; Maximum lovastatin dose: 40 mg/day

Pellagra: Oral: 50-100 mg 3-4 times/day, maximum: 500 mg/day

Niacin deficiency: Oral: 10-20 mg/day, maximum: 100 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Formulations of niacin (regular release versus extended release) are not interchangeable.

Pellagra: Oral: Children: 50-100 mg/dose 3 times/day

Recommended daily allowances:

0-0.5 years: 5 mg/day

0.5-1 year: 6 mg/day

1-3 years: 9 mg/day

4-6 years: 12 mg/day

7-10 years: 13 mg/day

RDA: Children and Adolescents:

Male:

11-14 years: 17 mg/day

    15-18 years: 20 mg/day

    19-24 years: 19 mg/day

  Female: 11-24 years: 15 mg/day

Dosing: Renal ImpairmentUse with caution.
Dosing: Hepatic ImpairmentContraindicated in patients with significant or unexplained hepatic dysfunction, active liver disease or unexplained transaminase elevations.
Dosing: Adjustment for ToxicityHepatic toxicity: Transaminases rise ≥3 times ULN, either persistent or if symptoms of nausea, fever, and/or malaise occur: Discontinue therapy.
Administration: OralAdminister with food. Administer Niaspan® at bedtime. Niaspan® tablet strengths are not interchangeable. When switching from immediate release tablet, initiate Niaspan® at lower dose and titrate. Long-acting forms should not be crushed, broken, or chewed. Do not substitute long-acting forms for immediate release ones.
Dietary ConsiderationsShould be taken with meal; low-fat meal if treating hyperlipidemia. Avoid hot drinks around the time of niacin dose.
Storage

Niaspan®: Store at room temperature of 20°C to 25°C (68°F to 77°F).

Niacor®: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to niacin, niacinamide, or any component of the formulation; active hepatic disease or significant or unexplained hepatic dysfunction; active peptic ulcer; arterial hemorrhage
Allergy Considerations

- Niacin and Derivatives Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Flushing: Common and can be attenuated with a gradual increase in dose, and/or by taking aspirin or an NSAID 30-60 minutes before dosing. Compliance is enhanced with twice daily dosing.

- Hepatotoxicity: Cases of severe hepatotoxicity, including fulminant hepatic necrosis, have occurred when immediate release (crystalline) niacin products have been substituted with sustained-release (modified release, timed-release) niacin products at equivalent doses. Patients should be initiated with low doses (eg, 500 mg at bedtime) with titration to achieve desired response. Liver function tests should be monitored in all patients receiving lipid-lowering doses of niacin.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with unstable angina or MI.

- Diabetes: Use niacin with caution in patients with diabetes mellitus; niacin may increase fasting blood glucose, although clinical data suggest increases are generally modest (<5%). Monitor glucose; adjustment of hypoglycemic therapy may be necessary.

- Gallbladder disease: Use with caution in patients with active gallbladder disease; can exacerbate.

- Gout: Use may be associated with hyperuricemia. Use with caution in patients with gout.

- Hepatic impairment: Use with caution in patients with a past history of hepatic impairment; monitor liver function tests. Contraindicated with active liver disease or unexplained transaminase elevation.

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Anticoagulants: Use with caution in patients taking anticoagulants; may slightly increase prothrombin time.

- HMG-CoA reductase inhibitors: Rare cases of rhabdomyolysis have occurred during concomitant use with HMG-CoA reductase inhibitors; with concurrent use or if symptoms suggestive of myopathy occur, monitor creatinine phosphokinase (CPK) and potassium.

Special populations:

- Heavy ethanol users: Use with caution in heavy ethanol users.

Dosage form specific issues:

- Product interchangeability: **Note:** Formulations of niacin (regular release versus extended release) are not interchangeable; the bioavailability varies.

Other warnings/precautions:

- Appropriate use: Prior to initiation, secondary causes for hypercholesterolemia (eg, poorly controlled diabetes mellitus, hypothyroidism) should be excluded; management with diet and other nonpharmacologic measures (eg, exercise or weight reduction) should be attempted prior to initiation.

Geriatric ConsiderationsThe definition of and, therefore, when to treat hyperlipidemia in the elderly is a controversial issue. The National Cholesterol Education Program recommends that all adults maintain a plasma cholesterol <160 mg/dL. Elderly with one additional risk factor, goal LDL would be <130 mg/dL. It is the authors' belief that pharmacologic treatment be reserved for those who are unable to obtain a desirable plasma cholesterol concentration by diet alone and for whom the benefits of treatment are believed to outweigh the potential adverse effects, drug interactions, and cost of treatment.

Pregnancy Risk FactorA/C (dose exceeding RDA recommendation)

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. It is unknown whether or not niacin at lipid-lowering doses is harmful to the developing fetus. If a woman becomes pregnant while receiving niacin for primary hypercholesterolemia, niacin should be discontinued. If a woman becomes pregnant while receiving niacin for hypertriglyceridemia, the benefits and risks of continuing niacin should be assessed on an individual basis.

LactationEnters breast milk/consult prescriber

Breast-Feeding ConsiderationsNiacin is excreted in human breast milk. Because lipid-lowering doses of niacin may cause serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, atrial fibrillation, edema, flushing, hypotension, orthostasis, palpitation, syncope (rare), tachycardia

Central nervous system: Chills, dizziness, headache, insomnia, migraine, nervousness, pain

Dermatologic: Acanthosis nigricans, dry skin, hyperpigmentation, maculopapular rash, pruritus, rash, urticaria

Endocrine & metabolic: Glucose tolerance decreased, gout, phosphorous levels decreased, hyperuricemia

Gastrointestinal: Abdominal pain, diarrhea, dyspepsia, eructation, flatulence, nausea, peptic ulcers, vomiting

Hematologic: Platelet counts decreased

Hepatic: Hepatic necrosis (rare), jaundice, transaminases increased (dose-related), prothrombin time increased

Neuromuscular & skeletal: Leg cramps, myalgia, myasthenia, myopathy (with concurrent HMG-CoA reductase inhibitor), paresthesia, rhabdomyolysis (with concurrent HMG-CoA reductase inhibitor; rare), weakness

Ocular: Cystoid macular edema, toxic amblyopia

Respiratory: Dyspnea

Miscellaneous: Diaphoresis, hypersensitivity reactions (rare)

Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Niacin. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: Niacin may enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid heavy use; avoid use around niacin dose.

Test InteractionsFalse elevations in some fluorometric determinations of plasma or urinary catecholamines; false-positive urine glucose (Benedict's reagent)

Monitoring ParametersBlood glucose (in diabetic patients); CPK and serum potassium (if on concurrent HMG-CoA reductase inhibitor); liver function tests pretreatment, every 6-12 weeks for first year, then periodically (approximately every 6 months), monitor liver function more frequently if history of transaminase elevation with prior use; lipid profile; platelets; PT (if on anticoagulants); uric acid (if predisposed to gout); phosphorus (if predisposed to hypophosphatemia)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for increased risk of drug/drug interactions. Teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsBlood glucose (in diabetic patients); CPK and serum potassium (if on concurrent HMG-CoA reductase inhibitor); liver function tests pretreatment, every 6-12 weeks for first year, then periodically (approximately every 6 months), monitor liver function more frequently if history of transaminase elevation with prior use; lipid profile; platelets; PT (if on anticoagulants); uric acid (if predisposed to gout); phosphorus (if predisposed to hypophosphatemia)

Patient EducationTake exactly as directed; do not exceed recommended dosage. Take with food to reduce incidence of GI upset. Do not crush sustained release capsules. You may experience flushing, sensation of heat, or headache; these reactions may be decreased by increasing dose slowly or by taking aspirin (consult prescriber) 30-60 minutes prior to taking niacin. Avoid alcohol or hot drinks around time of taking medication to minimize flushing. Taking at bedtime, after a low-fat snack, is also recommended. You may experience dizziness, lightheadedness (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Report persistent GI disturbance or changes in color of urine or stool. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release: 125 mg, 250 mg, 400 mg, 500 mg

Capsule, timed release: 250 mg, 500 mg

Tablet: 50 mg, 100 mg, 250 mg, 500 mg

Niacor®: 500 mg

Tablet, controlled release (Slo-Niacin®): 250 mg, 500 mg, 750 mg

Tablet, extended release (Niaspan®): 500 mg, 750 mg, 1000 mg

Tablet, timed release: 250 mg, 500 mg, 750 mg, 1000 mg

Niacin-Time®: 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, controlled release (Niaspan)

500 mg (30): $72.38

750 mg (30): $101.35

1000 mg (30): $126.91

Tablet, controlled release (Slo-Niacin)

500 mg (100): $25.30

Tablets (Niacin)

500 mg (100): $11.99

Mechanism of ActionComponent of two coenzymes which is necessary for tissue respiration, lipid metabolism, and glycogenolysis; inhibits the synthesis of very low density lipoproteins (VLDL) and low density lipoproteins (LDL); may also increase the rate of chylomicron triglyceride removal from plasma.

Pharmacodynamics/Kinetics

Absorption: Rapid and extensive (60% to 76%)

Distribution: Mainly to hepatic, renal, and adipose tissue

Metabolism: Extensive first-pass effects; converted to nicotinamide adenine dinucleotide, nicotinuric acid, and other metabolites

Half-life elimination: 20-45 minutes

Time to peak, serum: Immediate release formulation: 30-60 minutes; extended release formulation: 4-5 hours

Excretion: Urine 60% to 88% (unchanged drug and metabolites)

Related Information

- Hyperlipidemia Management
- Lipid-Lowering Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, insomnia, or nervousness

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsNiacin lowers LDL-cholesterol (LDL-C) and triglycerides (TGs) and increases HDL-cholesterol (HDL-C). It causes a shift from small, dense to large, buoyant LDL particles that are less atherogenic. Niacin also significantly lowers lipoprotein A levels. Immediate-release niacin may cause itching, flushing, headache and requires frequent daily dosing. Adverse effects may be attenuated by increasing the dose slowly and/or by taking aspirin 30-60 minutes before dosing. Compliance is enhanced with twice daily dosing. Extended release niacin may offer lipoprotein benefits similar to immediate-release dosage forms with less flushing and once daily dosing. Sustained release products may be less efficacious and cause an increased incidence of hepatotoxicity.

Index TermsNicotinic Acid; Vitamin B_3

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International Brand Names Acido Nicotinico (CO); Acidum nicotinicum (HU); Apo-Nicotinic Acid (NZ); Natinate (TH); Niacyn (PL); Niaspan (CH, CL, GB, HK, IE, TH); Niaspanor (KP); Nicangin (NO, SE); Nicobid (HK); Nicotabs (TH); Nicotinic Acid (AU); Nyclin (TW); Pepevit (MX)

Niacinamide

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English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Niacinamide may be confused with niCARdipine

Pronunciation(nye a SIN a mide)
U.S. Brand NamesNicomide-T™
Pharmacologic CategoryVitamin, Water Soluble
Use: Labeled Indications

Oral: Prophylaxis and treatment of pellagra

Topical: Improve the appearance of acne and decrease visible inflammation and irritation caused by acne medications

Dosing: Adults

Pellagra: Oral: 300-500 mg/day

Acne: Topical: Apply to affected area on face twice daily

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Pellagra: Oral: Children: 100-300 mg/day in divided doses

Administration: TopicalPrior to using cream or gel, wash face with mild cleanser. Apply thin layer to affected area. May apply under make-up or other acne medications. Re-evaluate after 8-12 weeks.
ContraindicationsHypersensitivity to niacin, niacinamide, or any component of the formulation; liver disease; active peptic ulcer
Allergy Considerations

- Niacin and Derivatives Allergy

Warnings/Precautions

Disease-related concerns:

- Allergies: Use with caution in patients with allergies.
- Cardiovascular disease: Use with caution in patients with unstable angina or CAD; risk of arrhythmias at high doses.
- Diabetes: Use with caution in patients with diabetes mellitus; interferes with glucose control.
- Gallbladder disease: Use with caution in patients with active gallbladder disease; can exacerbate.
- Gout: Use with caution in patients predisposed to gout.
- Hepatic impairment: Avoid large pharmacological amounts in patients with a history of liver disease; monitor liver function tests with high doses.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Heavy ethanol users: Use with caution in heavy ethanol users.

Geriatric ConsiderationsShould not be confused with niacin.
Pregnancy Risk FactorA/C (dose exceeding RDA recommendation)
Adverse ReactionsFrequency not defined.

Cardiovascular: Tachycardia

Dermatologic: Increased sebaceous gland activity, rash

Endocrine & metabolic: Hyperglycemia, hyperuricemia

Gastrointestinal: Bloating, flatulence, nausea

Neuromuscular & skeletal: Paresthesia in extremities

Ocular: Blurred vision

Respiratory: Wheezing

Drug Interactions

HMG-CoA Reductase Inhibitors: Niacinamide may enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Test InteractionsFalse elevations of urinary catecholamines in some fluorometric determinations
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream (Nicomide-T™): 4% (30 g) [contains benzyl alcohol]

Gel (Nicomide-T™): 4% (30 g) [contains alcohol]

Tablet: 100 mg, 250 mg, 500 mg

Generic AvailableYes: Tablet
Pricing: U.S. (www.drugstore.com)

Cream (Nicomide-T)

4% (30): $42.99

Gel (Nicomide-T)

4% (30): $45.99

Mechanism of ActionUsed by the body as a source of niacin; is a component of two coenzymes which is necessary for tissue respiration, lipid metabolism, and glycogenolysis; does not have hypolipidemia or vasodilating effects. Niacinamide has anti-inflammatory properties which are believed to help decrease inflammatory acne lesions.
Pharmacodynamics/Kinetics

Absorption: Oral: Rapid; Topical: Absorbed systemically

Metabolism: Hepatic

Half-life elimination: 45 minutes

Time to peak, serum: 20-70 minutes

Excretion: Urine (as metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsNicotinamide; Nicotinic Acid Amide; Vitamin B_3
References

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International Brand NamesBepella (CZ); Farmobion Pp (IT); Micril PP (PT); Nicobion (CH, DE, FR); Nicotinamide (IT); Nicotinsaureamid Jenapharm (DE); Nicovitol (AT); Papulex (GB); Ucemine PP (BE, LU); Vitamin B3 (AU); Vitamina PP Angelini (IT); Vitaminum PP (PL)

NiCARdipine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

NiCARdipine may be confused with niacinamide, NIFEdipine, niMODipine

Cardene® may be confused with Cardizem®, Cardura®, codeine

International issues:

Cardene® may be confused with Cardem® which is a brand name for celiprolol in Spain

Cardene® may be confused with Cardin® which is a brand name for methyldopa in Brazil and a brand name for simvastatin in Poland

Significant differences exist between oral and I.V. dosing. Use caution when converting from one route of administration to another.

Pronunciation(nye KAR de peen)

U.S. Brand NamesCardene®; Cardene® I.V.; Cardene® SR

Pharmacologic CategoryCalcium Channel Blocker

Use: Labeled IndicationsChronic stable angina (immediate-release product only); management of hypertension (immediate and sustained release); parenteral only for short-term use when oral treatment is not feasible

Use: Unlabeled/InvestigationalCongestive heart failure, control of blood pressure in acute ischemic stroke and spontaneous intracranial hemorrhage, postoperative hypertension associated with carotid endarterectomy, perioperative hypertension, prevention of migraine headaches, subarachnoid hemorrhage associated cerebral vasospasm

Dosing: Adults

Angina: Immediate release: Oral: 20 mg 3 times/day; usual range: 60-120 mg/day; increase dose at 3-day intervals

Hypertension: Oral:

Immediate release: Initial: 20 mg 3 times/day; usual: 20-40 mg 3 times/day (allow 3 days between dose increases)

Sustained release: Initial: 30 mg twice daily, titrate up to 60 mg twice daily

Note: The total daily dose of immediate-release product may not automatically be equivalent to the daily sustained-release dose; use caution in converting.

Acute hypertension: I.V.: Initial: 5 mg/hour increased by 2.5 mg/hour every 15 minutes to a maximum of 15 mg/hour; consider reduction to 3 mg/hour after response is achieved. Monitor and titrate to lowest dose necessary to maintain stable blood pressure.

Substitution for oral therapy (approximate equivalents):

20 mg every 8 hours oral, equivalent to 0.5 mg/hour I.V. infusion

30 mg every 8 hours oral, equivalent to 1.2 mg/hour I.V. infusion

40 mg every 8 hours oral, equivalent to 2.2 mg/hour I.V. infusion

Dosing: ElderlyInitiate at the low end of the dosage range. Specific guidelines for adjustment of nicardipine are not available, but careful monitoring is warranted and adjustment may be necessary.

Dosing: Renal ImpairmentTitrate dose beginning with 20 mg 3 times/day (immediate release) or 30 mg twice daily (sustained release capsule). Specific guidelines for adjustment of nicardipine are not available, but careful monitoring is warranted and adjustment may be necessary.

Dosing: Hepatic ImpairmentStarting dose: 20 mg twice daily (immediate release) with titration. Refer to "Note" in adult dosing. Specific guidelines for adjustment of nicardipine are not available, but careful monitoring is warranted and adjustment may be necessary.

Administration: I.V.

Ampuls must be diluted before use. Administer as a slow continuous infusion.

Premixed bags: No further dilution needed. For single use only, discard any unused portion. Use only if solution is clear; the manufacturer recommends not to admix or run in the same line as other medications.

Administration: I.V. DetailAvoid extravasation.

pH: 3.5 (buffered)

Administration: OralDo not chew or crush the sustained release formulation, swallow whole. Do not open or cut capsules.

Storage

I.V.:

Premixed bags: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F) . Protect from light and excessive heat. Do not freeze.

Vials: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Diluted solutions are stable for 24 hours at room temperature. Protect from light.

Oral (Cardene®, Cardene SR®): Store at 15°C to 30°C (59°F to 86°F). Protect from light. Freezing does not affect stability.

ReconstitutionI.V.: Vial: Dilute 25 mg ampul with 240 mL of compatible solution to provide a 250 mL total volume solution and a final concentration of 0.1 mg/mL.

CompatibilityStable in D$_5$W with KCl 40 mEq, D$_5{}^1/_2$NS, D$_5$NS, D$_5$W, $^1/_2$NS, NS; **incompatible** with sodium bicarbonate 5%, LR.

Y-site administration: Compatible: Amikacin, aminophylline, aztreonam, butorphanol, calcium gluconate, cefazolin, ceftizoxime, chloramphenicol, cimetidine, clindamycin, diltiazem, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin, esmolol, famotidine, fenoldopam, fentanyl, gatifloxacin, gentamicin, hydrocortisone sodium succinate, hydromorphone, labetalol, lidocaine, linezolid, lorazepam, magnesium, methylprednisolone sodium succinate, metronidazole, midazolam, milrinone, morphine, nafcillin, nitroglycerin, nitroprusside, norepinephrine, penicillin G potassium, potassium chloride, potassium phosphate, ranitidine, sodium acetate, sulfamethoxazole and trimethoprim, tobramycin, vancomycin, vecuronium. **Incompatible:** Ampicillin, ampicillin/sulbactam, cefepime, furosemide, lansoprazole, thiopental. **Variable (consult detailed reference):** Ceftazidime, heparin.

Compatibility when admixed: Compatible: Potassium chloride.

ContraindicationsHypersensitivity to nicardipine or any component of the formulation; advanced aortic stenosis

Allergy Considerations

- Calcium Channel Blocker, Dihydropyridine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Angina/MI: Increased angina and/or MI has occurred with initiation or dosage titration of dihydropyridine calcium channel blockers; reflex tachycardia may occur resulting in angina and/or MI in patients with obstructive coronary disease especially in the absence of concurrent beta blockade.
- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition.
- Peripheral edema: A common side effect is peripheral edema (dose-dependent); occurs within 2-3 weeks of starting therapy.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.
- Heart failure (HF): Use with caution in patients with HF. Use in patients with severe left ventricular dysfunction, particularly with concomitant beta-blockade, may experience worsened symptoms of HF due to mild negative inotropic effects of nicardipine.
- Hepatic impairment: Use with caution in patients with hepatic impairment; may require lower starting dose.
- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.
- Portal hypertension: Use with caution in patients with portal hypertension, can cause increase in hepatic pressure gradient.
- Renal impairment: Increase dose cautiously in patients with renal impairment since clearance of nicardipine is diminished in this population.

Concurrent drug therapy issues:

- Fentanyl anesthesia: Concurrent fentanyl anesthesia and I.V. nicardipine (with a beta-blocker) may result in hypotension. Careful volume resuscitation may be required to overcome hypotensive effects.

Special populations:

- Elderly: Nicardipine should be initiated at the low end of the dosage range in the elderly.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Infusion sites: Peripheral infusion sites (for I.V. therapy) should be changed every 12 hours.
- Withdrawal: Abrupt withdrawal may cause rebound angina in patients with CAD.

Geriatric ConsiderationsElderly may experience a greater hypotensive response. Constipation may be more of a problem in the elderly. Calcium channel blockers are no more effective in the elderly than other therapies; however, they do not cause significant CNS effects which is an advantage over some antihypertensive agents.

Pregnancy Risk FactorC

Pregnancy ConsiderationsCrosses the placenta; may exhibit tocolytic effect

LactationEnters breast milk/not recommended

Adverse Reactions

1% to 10%:

Cardiovascular: Cardiovascular: Flushing (6% to 10%), peripheral edema (dose related; 6% to 8%), hypotension (I.V. 6%), increased angina (dose related; 6%), palpitation (3% to 4%), tachycardia (1% to 4%), vasodilation (1% to 5%), chest pain (I.V. 1%), ECG abnormal (I.V. 1%), extrasystoles (I.V. 1%), hemopericardium (I.V. 1%), hypertension (I.V. 1%), orthostasis (1%), supraventricular tachycardia (I.V. 1%), syncope (1%), ventricular extrasystoles (I.V. 1%), ventricular tachycardia (I.V. 1%)

Central nervous system: Headache (6% to 15%), dizziness (1% to 7%), hypoesthesia (1%), intracranial hemorrhage (1%) pain (1%), somnolence (1%)

Dermatologic: Rash (1%)

Endocrine & metabolic: Hypokalemia (I.V. 1%)

Gastrointestinal: Nausea (2% to 5%), vomiting (I.V. 5%), dyspepsia (oral 2%), abdominal pain (I.V. 1%), dry mouth (1%)

Genitourinary: Polyuria (1%)

Local: Injection site pain (I.V. 1%), injection site reaction (I.V. 1%)

Neuromuscular & skeletal: Weakness (1% to 6%), myalgia (1%), paresthesia (1%)

Renal: Hematuria (1%)

Respiratory: Dyspnea (1%)

Miscellaneous: Diaphoresis (1%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Allergic reaction, confusion, constipation, deep vein thrombophlebitis; ECG effects (AV block, inverted T wave, ST segment depression); gingival hyperplasia, hypertonia, hypophosphatemia, insomnia, malaise, nervousness, nocturia, parotitis, thrombocytopenia, tinnitus, tremor

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2C9 (minor), 2D6 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP2C9 (strong), 2C19 (moderate), 2D6 (moderate), 3A4 (strong)

Drug Interactions

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CycloSPORINE: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk D: Consider therapy modification*

QuiNIDine: Calcium Channel Blockers (Dihydropyridine) may decrease the serum concentration of QuiNIDine. *Risk C: Monitor therapy*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Nicardipine average peak concentrations may be decreased if taken with food. Serum concentrations/toxicity of nicardipine may be increased by grapefruit juice; avoid concurrent use.

Herb/Nutraceutical: St John's wort may decrease levels. Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, increased risk for toxicity). See Administration for infusion specifics; infusion site must be monitored closely to prevent extravasation; peripheral infusion sites should be changed ever 12 hours. Evaluate therapeutic effectiveness (cardiac status and blood pressure) and adverse reactions (eg, rash, hypotension, bradycardia, confusion, nausea) when starting, adjusting dose, or discontinuing. Teach patient proper use, possible side effects/appropriate interventions (eg, orthostatic precautions), and adverse symptoms to report.

Patient EducationThis medication may be administered by intravenous infusion; report immediately and swelling, redness, burning, or pain at infusion site. **Oral:** Take as directed; do not alter dose or decrease without consulting prescriber. Do not crush or chew sustained release forms; swallow whole. Take with nonfatty food. Avoid caffeine and alcohol. Consult prescriber before increasing exercise routine (decreased angina does not mean it is safe to increase exercise). May cause orthostatic hypotension (change position slowly from sitting or lying to standing, or when climbing stairs); sore mouth (inspect gums for swelling or redness, use soft toothbrush, waxed dental floss, and frequent mouth rinses); dizziness or fatigue (use caution when driving or engaging in tasks that require alertness until response to drug is known); or nausea and dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report chest pain, palpitations, rapid heartbeat; swelling of extremities; muscle weakness or pain; respiratory difficulty; or nervousness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, oral, as hydrochloride: 20 mg, 30 mg

Cardene®: 20 mg, 30 mg

Capsule, sustained release, oral, as hydrochloride:

Cardene® SR: 30 mg, 45 mg, 60 mg

Infusion, premixed in iso-osmotic dextrose, as hydrochloride:

Cardene® IV: 20 mg (200 mL); 40 mg (200 mL)

Infusion, premixed in iso-osmotic sodium chloride, as hydrochloride:

Cardene® IV: 20 mg (200 mL); 40 mg (200 mL)

Injection, solution, as hydrochloride: 2.5 mg/mL (10 mL)

Cardene® IV: 2.5 mg/mL (10 mL)

Generic AvailableYes: Capsule, injection

Pricing: U.S. (www.drugstore.com)

Capsule, 12-hour (Cardene SR)

45 mg (60): $160.99

60 mg (60): $125.99

Capsules (Cardene)

20 mg (90): $69.12

30 mg (90): $99.52

Capsules (NiCARdipine HCl)

20 mg (90): $23.00

30 mg (90): $28.99

Mechanism of ActionInhibits calcium ion from entering the “slow channels” or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary vascular smooth muscle and coronary vasodilation; increases myocardial oxygen delivery in patients with vasospastic angina

Pharmacodynamics/Kinetics

Onset of action: Oral: 0.5-2 hours; I.V.: 10 minutes; Hypotension: ~20 minutes

Duration:

I.V.: ≤8 hours

Oral: Immediate release capsules: ≤8 hours; Sustained release capsules: 8-12 hours

Absorption: Oral: ~100%

Protein binding: >95%

Metabolism: Hepatic; CYP3A4 substrate (major); extensive first-pass effect (saturable)

Bioavailability: 35%

Half-life elimination: 2-4 hours

Time to peak, serum: Oral: Immediate release: 30-120 minutes; Sustained release: 60-240 minutes

Excretion: Urine (49% to 60% as metabolites); feces (43% as metabolites)

Related Information

- Calcium Channel Blockers
- Hypertension

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Other drugs of this class can cause gingival hyperplasia (ie, nifedipine). The first case of nicardipine-induced gingival hyperplasia has been reported in a child taking 40-50 mg daily for 20 months.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and dizziness are common; may rarely cause insomnia

Mental Health: Effects on Psychiatric TreatmentConcurrent use with propranolol may increase AV nodal effects

Cardiovascular ConsiderationsNicardipine alone or in combination with other agents is effective in the management of hypertension and angina. Nicardipine should be used with caution in patients with heart failure.

Patients in whom beta-blockade is contraindicated who experience continuing or frequent ischemic pain should be given a nondihydropyridine calcium channel blocker (eg, diltiazem or verapamil) (Class I). Dihydropyridine calcium channel blockers exhibiting a longer duration of action (eg, nicardipine SR or amlodipine) may be considered in addition to adequate beta-blockade or nitrates if patients experience ongoing ischemic chest pain or hypertension. Immediate release dihydropyridine calcium channel blockers should not be administered to patients experiencing continuing or frequent ischemic chest pain in the absence of adequate beta-blockade.

Intravenous nicardipine is an effective agent for the treatment of hypertensive emergencies. In contrast to other shorter-acting agents (eg, nitroprusside), nicardipine exhibits a longer duration of action. Therefore, if hypotension occurs, the duration of hypotension may be prolonged.

Anesthesia and Critical Care Concerns/Other Considerations

Management of Intracerebral Hemorrhage (ICH): Rapid identification of patients experiencing ICH is essential and should be considered a medical emergency due to the progressive deterioration, severe clinical deficits, and high mortality and morbidity. Treatment for ICH has evolved rapidly in recent years. According to the 2007 ACC/AHA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults, patients with ICH should be treated in a balanced and graded approach with therapies that reduce intracranial pressure (ICP) (eg, mannitol, hypertonic saline solutions, barbiturate coma, head of bed elevation) (Class IIa recommendation). Direct monitoring of ICP and central perfusion pressure (CPP) may be necessary if patient is treated more aggressively. Treatment of ICH with recombinant factor VIIa (rFVIIa) within the first 3-4 hours after onset to slow progression of bleeding has shown promise; however, at this time it cannot be routinely recommended in all patients experiencing ICH (Class IIb recommendation).

Blood pressure (BP) management in patients who are hypertensive is also of paramount importance in treating ICH. The primary rationale for lowering BP is to prevent further progression of the bleed. This can be accomplished using a number of different pharmacologic treatments (eg, nicardipine, labetalol, nitroprusside). Nitroprusside may increase ICP due to the pronounced vasodilatory actions and as a result may be less preferable. Specific BP targets are not supported by available evidence. The 2007 ACC/AHA Guidelines recommend initiating antihypertensive therapy if the SBP >180 mm Hg or if MAP >130 mm Hg.

Index TermsNicardipine Hydrochloride

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International Brand NamesAntagonil (DE); Barizin (HR); Cardene (IE, NL); Cardene SR (GB, NL); Cardepine (MY, PH); Cardepine SR (MY); Cardibloc (SG); Cardipene (TH); Convertal (PE); Dacarel (PY, UY); Dafil (AR); Karden (AT); Lincil (HN); Loxen (FR, ID); Nerdipina (ES, PT); Nicardal (IT); Nimicor (IT); Perdipina (IT); Perdipine (CL, ID, JP, KP, PH, TW); Perdipine LA (JP); Ridene (MX); Rydene (BE, LU); Saf Card (ID); Vasodin (TH); Vasonase (ES)

Nicotine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

NicoDerm® may be confused with Nitroderm

Nicorette® may be confused with Nordette®

Transdermal patch may contain conducting metal (eg, aluminum); remove patch prior to MRI.

Pronunciation(nik oh TEEN)

U.S. Brand NamesCommit® [OTC]; NicoDerm® CQ® [OTC]; Nicorette® [OTC]; Nicotrol® Inhaler; Nicotrol® NS; Thrive™ [OTC]

Canadian Brand NamesHabitrol®; Nicoderm®; Nicorette®; Nicorette® Plus; Nicotrol®

Pharmacologic CategorySmoking Cessation Aid

Use: Labeled IndicationsTreatment to aid smoking cessation for the relief of nicotine withdrawal symptoms (including nicotine craving)

Use: Unlabeled/InvestigationalManagement of ulcerative colitis (transdermal)

Use: DentalTreatment to aid smoking cessation for the relief of nicotine withdrawal symptoms (including nicotine craving)

Dosing: Adults

Tobacco cessation (patients should be advised to completely stop smoking upon initiation of therapy):

Gum: Chew 1 piece of gum when urge to smoke, up to 24 pieces/day. Patients who smoke <25 cigarettes/day should start with 2-mg strength; patients smoking ≥25 cigarettes/day should start with the 4-mg strength. Use according to the following 12-week dosing schedule:

Weeks 1-6: Chew 1 piece of gum every 1-2 hours; to increase chances of quitting, chew at least 9 pieces/day during the first 6 weeks

Weeks 7-9: Chew 1 piece of gum every 2-4 hours

Weeks 10-12: Chew 1 piece of gum every 4-8 hours

Inhaler: Oral: Usually 6-16 cartridges per day; best effect was achieved by frequent continuous puffing (20 minutes); recommended duration of treatment is 3 months, after which patients may be weaned from the inhaler by gradual reduction of the daily dose over 6-12 weeks

Lozenge: Oral: Patients who smoke their first cigarette within 30 minutes of waking should use the 4-mg strength; otherwise the 2-mg strength is recommended. Use according to the following 12-week dosing schedule:

Weeks 1-6: One lozenge every 1-2 hours

Weeks 7-9: One lozenge every 2-4 hours

Weeks 10-12: One lozenge every 4-8 hours

Note: Use at least 9 lozenges/day during first 6 weeks to improve chances of quitting; do not use more than one lozenge at a time (maximum: 5 lozenges every 6 hours, 20 lozenges/day)

Spray: Nasal: 1-2 sprays/hour; do not exceed more than 5 doses (10 sprays) per hour [maximum: 40 doses/day (80 sprays); each dose (2 sprays) contains 1 mg of nicotine]

Transdermal patch: Topical: Apply new patch every 24 hours to nonhairy, clean, dry skin on the upper body or upper outer arm; each patch should be applied to a different site. **Note:** Adjustment may be required during initial treatment (move to higher dose if experiencing withdrawal symptoms; lower dose if side effects are experienced).

NicoDerm CQ®:

Patients smoking ≥10 cigarettes/day: Begin with step 1 (21 mg/day) for 6 weeks, **followed by** step 2 (14 mg/day) for 2 weeks; **finish with** step 3 (7 mg/day) for 2 weeks

Patients smoking <10 cigarettes/day: Begin with step 2 (14 mg/day) for 6 weeks, **followed by** step 3 (7 mg/day) for 2 weeks

Note: Patients who are receiving >600 mg/day of cimetidine: Decrease to the next lower patch size

Benefits of use of nicotine transdermal patches beyond 3 months have not been demonstrated

Ulcerative colitis (unlabeled use): Topical: Transdermal: Titrated to 22-25 mg/day

Dosing: ElderlyRefer to adult dosing.

Administration: Oral

Gum: Should be chewed slowly to avoid jaw ache and to maximize benefit. Chew slowly until it tingles, then park gum between cheek and gum until tingle is gone; repeat process until most of tingle is gone (~30 minutes).

Lozenge: Should not be chewed or swallowed; allow to dissolve slowly (~20-30 minutes)

Administration: TopicalDo not cut patch; causes rapid evaporation, rendering the patch useless. Use of an aerosol corticosteroid may diminish local irritation under patches.

Dietary Considerations

Commit®: Each lozenge contains phenylalanine 3.4 mg and sodium 18 mg.

Nicorette®: Fresh mint and fruit chill flavors: The 2-mg strength contains calcium 94 mg/gum and sodium 11 mg/gum. The 4-mg strength contains calcium 94 mg/gum and sodium 13 mg/gum.

StorageNicotrol®: Store inhaler cartridge at room temperature not to exceed 30°C (86°F). Protect cartridges from light.

ContraindicationsHypersensitivity to nicotine or any component of the formulation; patients who are smoking during the postmyocardial infarction period; patients with life-threatening arrhythmias, or severe or worsening angina pectoris; active temporomandibular joint disease (gum); pregnancy; not for use in nonsmokers

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: The risk versus the benefits should be weighed in patients with CAD, serious cardiac arrhythmias, or vasospastic disease; use caution in patients with angina or hypertension.
- Diabetes: Use with caution in patients with insulin-dependent diabetes.
- Gastrointestinal disease: Use with caution in patients with oropharyngeal inflammation, history of esophagitis, or peptic ulcer disease; healing may be delayed.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment; effects on metabolism unknown.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Pheochromocytoma: Use with caution in patients with pheochromocytoma.
- Renal impairment: Use with caution in patients with severe renal impairment; effects on elimination unknown.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Chewing gum: Dental problems may be worsened by chewing gum.
- Inhaler: Use with caution in patients with bronchospastic disease due to potential airway irritation (other forms of nicotine replacement may be preferred).
- Nasal products: Use of nasal product is not recommended with chronic nasal disorders (eg, allergy, rhinitis, nasal polyps, and sinusitis).
- Topical products: Cautious use of topical nicotine in patients with certain skin diseases. Hypersensitivity to the topical products can occur.
- Transdermal patch: May contain conducting metal (eg, aluminum); remove patch prior to MRI.

Other warnings/precautions:

- Appropriate use: Urge patients to stop smoking completely when initiating therapy.

Geriatric ConsiderationsMust evaluate benefit in the elderly who may have chronic diseases mentioned in Warning and Contraindications. The transdermal systems are as effective in the elderly as they are in younger adults; however, complaints of body aches, dizziness, and asthenia were reported more often in the elderly.

Pregnancy Risk FactorD (nasal)

Pregnancy ConsiderationsNicotine is teratogenic in animal studies. Nicotine exposure via cigarette smoke may cause increased ectopic pregnancy, low birth weight, increased risk of spontaneous abortion, increased perinatal mortality; increased aortic blood flow, increased heart rate, decreased uterine blood flow, and decreased breathing have been reported in the fetus. Smoking during pregnancy is associated with sudden infant death syndrome (SIDS), an increased risk of asthma, infantile colic, and childhood obesity. Women who are pregnant should be encouraged not to smoke. The use of nicotine replacement products to aid in smoking cessation has not been adequately studied in pregnant women (amount of nicotine exposure is varied). Nonpharmacologic treatments are recommended. If the benefits of nicotine replacement therapy outweigh the unknown risks, products with intermittent dosing are suggested to be tried first. If a patch is used, it is suggested to remove it overnight while sleeping to decrease fetal exposure.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsNicotine from cigarette smoke is found in breast milk at 1.5-3 times the maternal plasma concentrations. The amount from nicotine replacement products is not known. Women who are breastfeeding are encouraged not to smoke.

Adverse Reactions

Nasal spray/inhaler:

>10%:

Central nervous system: Headache (18% to 26%)

Gastrointestinal: Inhaler: Mouth/throat irritation (66%), dyspepsia (18%)

Respiratory: Inhaler: Cough (32%), rhinitis (23%)

1% to 10%:

Dermatologic: Acne (3%)

Endocrine & metabolic: Dysmenorrhea (3%)

Gastrointestinal: Flatulence (4%), gum problems (4%), diarrhea, hiccup, nausea, taste disturbance, tooth disorder

Neuromuscular & skeletal: Back pain (6%), arthralgia (5%), jaw/neck pain

Respiratory: Sinusitis

Miscellaneous: Withdrawal symptoms

<1%: Allergy, amnesia, aphasia, bronchitis, bronchospasm, edema, migraine, numbness, pain, purpura, rash, sputum increased, vision abnormalities, xerostomia

Adverse events previously reported in prescription labeling for chewing gum, lozenge and/or transdermal systems. Frequency not defined; may be product or dose specific:

Central nervous system: Concentration impaired, depression, dizziness, headache, insomnia, nervousness, pain

Gastrointestinal: Aphthous stomatitis, constipation, cough, diarrhea, dyspepsia, flatulence, gingival bleeding, glossitis, hiccups, jaw pain, nausea, salivation increased, stomatitis, taste perversion, tooth disorder, ulcerative stomatitis, xerostomia

Dermatologic: Rash

Local: Application site reaction, local edema, local erythema

Neuromuscular & skeletal: Arthralgia, myalgia, paresthesia

Respiratory: Cough, sinusitis

Miscellaneous: Allergic reaction, diaphoresis

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4; **Inhibits** CYP2A6 (weak), 2E1 (weak)

Drug Interactions

Adenosine: Nicotine may enhance the AV-blocking effect of Adenosine. Nicotine may enhance the tachycardic effect of Adenosine. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Nicotine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Lozenge: Acidic foods/beverages decrease absorption of nicotine.

Monitoring ParametersHeart rate and blood pressure periodically during therapy; discontinue therapy if signs of nicotine toxicity occur (eg, severe headache, dizziness, mental confusion, disturbed hearing and vision, abdominal pain; rapid, weak and irregular pulse; salivation, nausea, vomiting, diarrhea, cold sweat, weakness); therapy should be discontinued if rash develops; discontinuation may be considered if other adverse effects of patch occur such as myalgia, arthralgia, abnormal dreams, insomnia, nervousness, dry mouth, sweating

Nursing: Physical Assessment/MonitoringMonitor cardiac status and vital signs prior to, when beginning, and periodically during therapy. Monitor effectiveness of therapy (according to rationale for therapy), and adverse reactions at beginning and periodically during therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report for prescribed form of drug.

Patient EducationUse exactly as directed; do not use more often than prescribed. Stop smoking completely during therapy. Do not smoke, chew tobacco, use snuff, nicotine gum, or any other form of nicotine. Nicotine overdose could occur.

Gum: Chew slowly for 30 minutes. Discard chewed gum away from access by children.

Lozenge: Allow to dissolve slowly in the mouth. Do not chew or swallow lozenge whole. Avoid food or drink 15 minutes prior to, during, or after lozenge.

Transdermal patch: Follow directions in package for dosing schedule and use. Do not cut patches or wear more than one patch at a time. Remove backing from patch and press immediately on skin. Hold for 10 seconds. Apply to clean, dry skin in different site each day. Do not touch eyes; wash hands after application. You may experience vivid dreams and sleep disturbances, dizziness or lightheadedness (use caution driving or when engaging in tasks requiring alertness until response to drug is known). For nausea, vomiting or GI upset, small frequent meals, chewing gum, and frequent oral care may help. Report persistent vomiting, diarrhea, chills, sweating, chest pain or palpitations, or burning or redness at application site.

Spray: Follow directions in package. Blow nose gently before use. Use 1-2 sprays/hour; do not exceed 5 doses (10 sprays) per hour. Excessive use can result in severe (even life-threatening) reactions. You may experience temporary stinging or burning after spray.

Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Consult prescriber for instruction on appropriate contraceptive measures.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gum, chewing, as polacrilex: 2 mg (20s, 50s, 110s); 4 mg (20s, 50s, 110s)

- Nicorette®:
    - 2 mg (48s, 50s, 108s, 110s, 168s, 170s, 192s, 200s, 216s) [original and mint flavors]; (48s, 108s, 110s) [orange flavor]; (40s, 100s) [contains calcium 94 mg/gum and sodium 11 mg/gum; fresh mint and fruit chill flavors]
    - 4 mg (48s, 50s, 108s, 110s, 168s, 170s, 192s, 200s, 216s) [original and mint flavors]; (48s, 108s, 110s) [orange flavor]; (40s, 100s) [contains calcium 94 mg/gum and sodium 13 mg/gum; fresh mint and fruit chill flavors]
- Thrive™:
    - 2 mg (40s) [gluten free, sucrose free; mint flavor]
    - 4 mg (40s) [gluten free, sucrose free; mint flavor]

Lozenge, as polacrilex:

- Commit®:
    - 2 mg (48s, 72s, 84s, 168s) [contains phenylalanine 3.4 mg/lozenge, sodium 18 mg/lozenge; mint flavor]; (108s) [contains phenylalanine 3.4 mg/lozenge, sodium 18 mg/lozenge; original flavor]
    - 4 mg (48s, 72s, 84s, 168s, 192s) [contains phenylalanine 3.4 mg/lozenge, sodium 18 mg/lozenge; mint flavor]; (108s) [contains phenylalanine 3.4 mg/lozenge, sodium 18 mg/lozenge; original flavor]

Oral inhalation system:

- Nicotrol® Inhaler: 10 mg cartridge (168s) [cartridge delivers nicotine 4 mg; each unit consists of 5 mouthpieces, 28 storage trays each containing 6 cartridges, and 1 storage case]

Solution, intranasal [spray]:

- Nicotrol® NS: 10 mg/mL (10 mL) [delivers 0.5 mg/spray; 200 sprays]

Transdermal system, topical: 7 mg/24 (30s); 14 mg/24 hours (30s); 21 mg/24 hours (30s)

- NicoDerm® CQ®: 7 mg/24 hours (14s) [step 3; available in tan or clear patch]; 14 mg/24 hours (14s) [step 2; available in tan or clear patch]; 21 mg/24 hours (7s, 14s) [step 1; available in tan or clear patch]

Generic AvailableYes: Transdermal patch and gum

Pricing: U.S. (www.drugstore.com)

Gum (Nicorette Starter Kit)

- 4 mg (110): $52.76

Patch, 24-hour (Nicotine)

- 14 mg/24 hrs (30): $179.98
- 21 mg/24 hrs (30): $168.99

Mechanism of ActionNicotine is one of two naturally-occurring alkaloids which exhibit their primary effects via autonomic ganglia stimulation. The other alkaloid is lobeline which has many actions similar to those of nicotine but is less potent. Nicotine is a potent ganglionic and central nervous system stimulant, the actions of which are mediated via nicotine-specific receptors. Biphasic actions are observed depending upon the dose administered. The main effect of nicotine in small doses is stimulation of all autonomic ganglia; with larger doses, initial stimulation is followed by blockade of transmission. Biphasic effects are also evident in the adrenal medulla; discharge of catecholamines occurs with small doses, whereas prevention of catecholamines release is seen with higher doses as a response to splanchnic nerve stimulation. Stimulation of the central nervous system (CNS) is characterized by tremors and respiratory excitation. However, convulsions may occur with higher doses, along with respiratory failure secondary to both central paralysis and peripheral blockade to respiratory muscles.

Pharmacodynamics/Kinetics

Onset of action: Intranasal: More closely approximate the time course of plasma nicotine levels observed after cigarette smoking than other dosage forms

Duration: Transdermal: 24 hours

Absorption: Transdermal: Slow

Metabolism: Hepatic, primarily to cotinine ($^1/_5$ as active)

Half-life elimination: 4 hours

Time to peak, serum: Transdermal: 8-9 hours

Excretion: Urine

Clearance: Renal: pH dependent

Related Information

- Addiction Treatments
- Nicotine Products

Pharmacotherapy PearlsA cigarette has 10-25 mg nicotine.
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Chewing gum: Excessive salivation, mouth/throat soreness, jaw muscle ache, hiccups, tachycardia, headache (mild), vomiting, belching, nausea, xerostomia (normal salivary flow resumes upon discontinuation), dizziness, nervousness, GI distress, hoarseness, and muscle pain.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Index TermsHabitrol
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International Brand NamesHabitrol Gum (NZ); Nicabate (AU); Nicabate CQ Clear (AU); Nicabate CQ Lozenges (AU); Nicomild (TH); Nicopass sans sucre menthe fraicheur (FR); Nicopass sans sucre reghsse menthe (FR); Nicopatch (FR); Nicorest (FR); Nicorette (AE, AT, AU, BE, BF, BG, BH, BJ, BR, CH, CI, CN, CO, CR, CY, CZ, DE, DK, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, HK, HN, HU, IE, IL, IQ, IR, IT, JO, JP, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, NO, OM, PA, PH, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SV, SY, TH, TN, TR, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Nicorette Fruit (FR); Nicorette Inhaler (AU); Nicorette Menthe (AE, BH, CY, EG, FR, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Nicorette Menthe Fraiche (FR); Nicorette Microtab (PL); Nicorette Orange (FR); Nicorette Orange sans sucre (FR); Nicostop (PT); Nicotab (SE); Nicotinell (AT, BE, BG, CH, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PL, PT, SE); Nicotinell Chewing Gum (HK, SG); Nicotinell Fruit sans sucre (FR); Nicotinell Menthe sans sucre (FR); Nicotinell Mint Lozenge (KP, SG); Nicotinell TTS (AE, AR, BB, BF, BH, BJ, BM, BS, BZ, CI, CN, CY, EE, EG, ET, FR, GH, GM, GN, GY, HK, HR, HU, IL, IQ, IR, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NZ, OM, PL, PR, PY, QA, SA, SC, SD, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Nicotrans (IT); Nicotrol Gum (NZ); Nikofrenon (DE); Niquitin (BR, MX, PL); Niquitin CQ (IL); Niquitin CQ Clear (IL); Niquitin sans sucre (FR)

NIFEdipine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

NIFEdipine may be confused with niCARdipine, niMODipine, nisoldipine

Procardia XL® may be confused with Cartia® XT

International issues:

Nipin® [Italy and Singapore] may be confused with Nipent® which is a brand name for pentostatin in the U.S.

Pronunciation(nye FED i peen)

U.S. Brand NamesAdalat® CC; Afeditab™ CR; Nifediac™ CC; Nifedical™ XL; Procardia XL®; Procardia®

Canadian Brand NamesAdalat® XL®; Apo-Nifed PA®; Apo-Nifed®; GEN-Nifedipine XL; Nifedipine PA; Novo-Nifedin; Nu-Nifed; Nu-Nifedipine-PA; PMS-Nifedipine; Procardia®

Pharmacologic CategoryCalcium Channel Blocker

Use: Labeled IndicationsAngina and hypertension (sustained release only), pulmonary hypertension

Dosing: Adults**Hypertension:** Oral: Initial: 10 mg 3 times/day as capsules or 30 mg once daily as sustained release

Usual dose: 10-30 mg 3 times/day as capsules or 30-60 mg once daily as sustained release

Maximum: 120-180 mg/day

Note: Adjustment of sustained release formulations should be made at 7- to 14-day intervals; **Note:** When switching from immediate release to sustained release formulations, total daily dose will start the same.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Hypertrophic cardiomyopathy (unlabeled use): Oral: Children: 0.6-0.9 mg/kg/24 hours in 3-4 divided doses

Hypertension: Oral: Children 1-17 years: Extended release tablet: Initial: 0.25-0.5 mg/kg/day once daily or in 2 divided doses; maximum: 3 mg/kg/day up to 120 mg/day

Dosing: Hepatic ImpairmentReduce oral dose by 50% to 60% in patients with cirrhosis.

Administration: Oral

Immediate release: In general, may be administered with or without food.

Extended release: Tablets should be swallowed whole; do not crush or chew.

Adalat®CC, Afeditab™ CR, Nifediac™ CC: Administer on an empty stomach (per manufacturer). Other extended release products may not have this recommendation; consult product labeling.

Dietary ConsiderationsAvoid grapefruit juice with all products.

Immediate release: Capsule is rapidly absorbed orally if it is administered without food, but may result in vasodilator side effects; if flushing is problematic, administration with low-fat meals may decrease. In general, can take with or without food.

Extended release: Adalat®CC, Afeditab™ CR, Nifediac™ CC: Take on an empty stomach (manufacturer recommendation). Other extended release products may not have this recommendation; consult product labeling.

ContraindicationsHypersensitivity to nifedipine or any component of the formulation; immediate release preparation for treatment of urgent or emergent hypertension; acute MI

Allergy Considerations

- Calcium Channel Blocker, Dihydropyridine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Angina/MI: Increased angina and/or MI has occurred with initiation or dosage titration of calcium channel blockers.
- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. **The use of sublingual short-acting nifedipine in hypertensive emergencies and urgencies is**

neither safe nor effective and SHOULD BE ABANDONED! Serious adverse events (eg, cerebrovascular ischemia, syncope, stroke, acute myocardial infarction, and fetal distress) have been reported in relation to such use.

- Peripheral edema: The most common side effect is peripheral edema; occurs within 2-3 weeks of starting therapy.
- Reflex tachycardia: May occur with use.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis.
- Heart failure (HF): Use with caution in patients with HF; may cause worsening of symptoms.
- Hepatic impairment: Use with caution in patients with hepatic impairment; may require lower starting dose.
- Idiopathic hypertrophic subaortic stenosis (IHSS): Use with caution in patients with IHSS.

Concurrent drug therapy issues:

- Beta-blockers and fentanyl: Severe hypotension may occur in patients taking immediate release nifedipine concurrently with beta-blockers when undergoing CABG with high dose fentanyl anesthesia. When considering surgery with high dose fentanyl, may consider withdrawing nifedipine (>36 hours) before surgery if possible.

Special populations:

- Elderly: The elderly may be more susceptible to adverse effects.

Dosage form specific issues:

- Extended release formulation: Consists of drug within a nondeformable matrix; following drug release/absorption, the matrix/shell is expelled in the stool. The use of nondeformable products in patients with known stricture/narrowing of the GI tract has been associated with symptoms of obstruction.

Other warnings/precautions:

- Withdrawal: Abrupt withdrawal may cause rebound angina in patients with CAD.

Geriatric ConsiderationsElderly may experience a greater hypotensive response. Theoretically, constipation may be more of a problem in elderly patients. The half-life of nifedipine is extended in elderly patients (6.7 hours) as compared to younger subjects (3.8 hours).

Pregnancy Risk FactorC

Pregnancy ConsiderationsUse in pregnancy only when clearly needed and when the benefits outweigh the potential hazard to the fetus. No data on crossing the placenta. Hypotension, IUGR reported. IUGR probably related to maternal hypertension. May exhibit tocolytic effects. Available evidence suggests safe use during pregnancy.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsCrosses into breast milk. Available evidence suggests safe use during breast-feeding. AAP considers **compatible** with breast-feeding.

Adverse Reactions

>10%:

Cardiovascular: Flushing (10% to 25%), peripheral edema (dose related 7% to 10%; up to 50%)

Central nervous system: Dizziness/lightheadedness/giddiness (10% to 27%), headache (10% to 23%)

Gastrointestinal: Nausea/heartburn (10% to 11%)

Neuromuscular & skeletal: Weakness (10% to 12%)

≥1% to 10%:

Cardiovascular: Palpitation (≤2% to 7%), transient hypotension (dose related 5%), CHF (2%)

Central nervous system: Nervousness/mood changes (≤2% to 7%), shakiness (≤2%), jitteriness (≤2%), sleep disturbances (≤2%), difficulties in balance (≤2%), fever (≤2%), chills (≤2%)

Dermatologic: Dermatitis (≤2%), pruritus (≤2%), urticaria (≤2%)

Endocrine & metabolic: Sexual difficulties (≤2%)

Gastrointestinal: Diarrhea (≤2%), constipation (≤2%), cramps (≤2%), flatulence (≤2%), gingival hyperplasia (≤10%)

Neuromuscular & skeletal: Muscle cramps/tremor (≤2% to 8%), inflammation (≤2%), joint stiffness (≤2%)

Ocular: Blurred vision (≤2%)

Respiratory: Cough/wheezing (6%), nasal congestion/sore throat (≤2% to 6%), chest congestion (≤2%), dyspnea (≤2%)

Miscellaneous: Diaphoresis (≤2%)

<1% (Limited to important or life-threatening): Syncope, erythromelalgia, thrombocytopenia, anemia, leukopenia, purpura, allergic hepatitis, angioedema, gingival hyperplasia, depression, paranoid syndrome, transient blindness, tinnitus, nocturia, photosensitivity, polyuria, arthritis with positive ANA, exfoliative dermatitis, gynecomastia, myalgia, memory dysfunction, fever, bezoars (sustained-release preparations), reflux, myoclonus, angina, ischemia, myoclonus

Postmarketing and/or case reports: EPS, aplastic anemia, agranulocytosis, purpura, Stevens-Johnson syndrome, cerebral ischemia, parotitis, dysgeusia, dysosmia, nocturnal enuresis, erythema multiforme

Reported with use of sublingual short-acting nifedipine: Cerebrovascular ischemia, syncope, heart block, stroke, sinus arrest, severe hypotension, acute MI, ECG changes, and fetal distress

Metabolism/Transport Effects **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP1A2 (moderate), 2C9 (weak), 2D6 (weak), 3A4 (weak)

Drug Interactions

Alcohol (Ethyl): May increase the serum concentration of NIFEdipine. *Risk C: Monitor therapy*

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Cisapride: May increase the serum concentration of NIFEdipine. Reported with sustained release nifedipine product. *Risk C: Monitor therapy*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

CycloSPORINE: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk D: Consider therapy modification*

QuiNIDine: Calcium Channel Blockers (Dihydropyridine) may decrease the serum concentration of QuiNIDine. *Risk C: Monitor therapy*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

VinCRIStine: NIFEdipine may decrease the excretion of VinCRIStine. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression and may increase the effects of nifedipine). Monitor.

Food: Nifedipine serum levels may be decreased if taken with food. Food may decrease the rate but not the extent of absorption of Procardia XL®. Increased therapeutic and vasodilator side effects, including severe hypotension and myocardial ischemia, may occur if nifedipine is taken by patients ingesting grapefruit.

Herb/Nutraceutical: St John's wort may decrease nifedipine levels. Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersHeart rate, blood pressure, signs and symptoms of CHF, peripheral edema

Nursing: Physical Assessment/MonitoringUse caution in severe aortic stenosis or severe hepatic impairment. Assess potential for interactions with other pharmacological agents or herbal products patient is taking that may increase risk of hypotension and toxicity. Assess therapeutic effectiveness (blood pressure and cardiac status) and adverse reactions (eg, hypotension, peripheral edema, gastrointestinal upset, CNS changes) when starting, adjusting dose, or discontinuing. Teach patient proper use, possible side effects/appropriate interventions (eg, orthostatic precautions), and adverse symptoms to report.

Patient EducationDo not take any new medication or over-the-counter medications, or herbal products during therapy unless approved by prescriber (especially anything that may act as a stimulant or depressant). Take exactly as directed; do not alter dose or decrease without consulting prescriber. Do not crush or chew sustained release forms, swallow whole. Avoid grapefruit juice and excess alcohol or caffeine. Consult prescriber before increasing exercise routine (decreased angina does not mean it is safe to increase exercise). May cause orthostatic hypotension (change position slowly from sitting or lying to standing, or when climbing stairs); sore mouth (inspect gums for swelling or redness, use soft toothbrush, waxed dental floss, and frequent mouth rinses); dizziness, difficulties in balance, or fatigue (use caution when driving or engaging in tasks that require alertness until response to drug is known); or nausea or heartburn (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report chest pain, palpitations, rapid heartbeat; swelling of extremities; muscle weakness or pain; respiratory difficulty; nervousness or mood change, rash; or vision changes. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, softgel: 10 mg, 20 mg

Procardia®: 10 mg

Tablet, extended release: 30 mg, 60 mg, 90 mg

Adalat® CC, Procardia XL®: 30 mg, 60 mg, 90 mg

Afeditab™ CR, Nifedical™ XL: 30 mg, 60 mg

Nifediac™ CC: 30 mg, 60 mg, 90 mg [90 mg tablet contains tartrazine]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (NIFEdipine)

10 mg (90): $65.99

20 mg (90): $109.99

Capsules (Procardia)

10 mg (90): $97.35

Tablet, 24-hour (Adalat CC)

30 mg (30): $54.19

90 mg (30): $98.63

Tablet, 24-hour (Afeditab CR)

30 mg (30): $39.99

60 mg (30): $57.92

Tablet, 24-hour (Nifediac CC)

30 mg (100): $108.99

60 mg (30): $49.99

90 mg (30): $60.99

Tablet, 24-hour (Nifedical XL)

30 mg (30): $32.99

60 mg (30): $55.99

Tablet, 24-hour (NIFEdipine CR Osmotic)

30 mg (30): $33.99

60 mg (30): $59.99

90 mg (30): $67.99

Tablet, 24-hour (Procardia XL)

30 mg (30): $68.24

60 mg (30): $110.24

90 mg (30): $121.26

Mechanism of ActionInhibits calcium ion from entering the “slow channels” or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary vascular smooth muscle and coronary vasodilation; increases myocardial oxygen delivery in patients with vasospastic angina

Pharmacodynamics/Kinetics

Onset of action: Immediate release: ~20 minutes

Protein binding (concentration dependent): 92% to 98%

Metabolism: Hepatic to inactive metabolites

Bioavailability: Capsule: 40% to 77%; Sustained release: 65% to 89% relative to immediate release capsules

Half-life elimination: Adults: Healthy: 2-5 hours, Cirrhosis: 7 hours; Elderly: 6.7 hours

Excretion: Urine (as metabolites)

Related Information

- Calcium Channel Blockers

Pharmacotherapy PearlsWhen measuring smaller doses from the liquid-filled capsules, consider the following concentrations (for Procardia®) 10 mg capsule = 10 mg/0.34 mL; 20 mg capsule = 20 mg/0.45 mL; may be used preoperative to treat hypertensive urgency.

Considerable attention has been directed to potential increases in mortality and morbidity when short-acting nifedipine is used in treating hypertension. The rapid reduction in blood pressure may precipitate adverse cardiovascular events. At this time, there is no indication for the use of short-acting calcium channel blocker therapy. Nifedipine also has potent negative inotropic effects and can worsen heart failure.

Dental Health: Effects on Dental TreatmentNifedipine has been reported to cause 10% incidence of gingival hyperplasia; effects from 30-100 mg/day have appeared after 1-9 months. Discontinuance results in complete disappearance or marked regression of symptoms; symptoms will reappear upon remedication. Marked regression occurs after 1 week and complete disappearance of symptoms has occurred within 15 days. If a gingivectomy is performed and use of the drug is continued or resumed, hyperplasia usually will recur. The success of the gingivectomy usually requires that the medication be discontinued or that a switch to a noncalcium channel blocker be made. If for some reason nifedipine cannot be discontinued, hyperplasia has not recurred after gingivectomy when extensive plaque control was performed. If nifedipine is changed to another class of cardiovascular agent, the gingival hyperplasia will probably regress and resolve. Switching to another calcium channel blocker may result in continued hyperplasia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness, sedation, or mood changes

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; concurrent use with propranolol may increase AV nodal effects; barbiturates may decrease effects of nifedipine

Cardiovascular ConsiderationsConsiderable attention has been directed to potential increases in mortality and morbidity when short-acting nifedipine is used in treating hypertension. The rapid reduction in blood pressure may precipitate adverse cardiovascular events. At this time, there is no indication for the use of short-acting calcium channel blocker therapy for angina and hypertension. Nifedipine also has potent negative inotropic effects and can worsen heart failure.

In the treatment of unstable angina/non-ST-segment elevation MI, a nondihydropyridine calcium antagonist (diltiazem or verapamil) may be considered in patients with continuing or frequently recurring ischemia when beta-blockers are contraindicated (Class I). Oral long-acting calcium antagonists may also be considered in addition to beta-blockers and nitrates (Class IIa).

Anesthesia and Critical Care Concerns/Other ConsiderationsConsiderable attention has been directed to potential increases in mortality and morbidity when short-acting nifedipine is used in treating hypertension. The rapid reduction in blood pressure may precipitate adverse cardiovascular events. At this time, there is no indication for the use of short-acting calcium channel blocker therapy for angina and hypertension. Nifedipine also has potent negative inotropic effects and can worsen heart failure.

References

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International Brand Names

Adalat (AR, AT, BE, BF, BG, BJ, BR, CH, CI, CN, CZ, DE, DK, EE, ES, ET, FI, GB, GH, GM, GN, GR, HK, HN, HR, HU, ID, IE, IT, JP, KE, KP, LR, LU, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, PE, PH, PK, PL, PT, SC, SD, SE, SL, SN, TH, TN, TZ, UG, UY, VE, ZA, ZM, ZW); Adalat 10 (AU); Adalat 20 (AU); Adalat 5 (AU); Adalat CC (PL); Adalat CR (BG, CH, GR, JP, TH); Adalat Crono (IT); Adalat GITS (CL, HK); Adalat GITS 30 (PH); Adalat L (JP); Adalat LA (GB, MY); Adalat LP (FR); Adalat Oros (AU, BB, BM, BR, BS, BZ, CN, CO, CR, DK, DO, EC, EE, ES, FI, GT, GY, ID, JM, KP, NI, NL, NO, PA, PE, PY, SE, SR, SV, TT, TW, UY, VE); Adalat pro Infusione (PL); Adalat Retard (AE, AT, BF, BH, BJ, BR, CI, CN, CY, CZ, DE, EG, ES, ET, GB, GH, GM, GN, GR, HK, ID, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NZ, OM, PE, PH, PY, QA, SA, SC, SD, SL, SN, SY, TH, TN, TZ, UG, YE, ZA, ZM, ZW); Adalat SL (PL); Adalate (FR); Addos XR (AU); Adefin XL (AU); Adipine XL (GB); Alpha-Nifedipine Retard (NZ); Apo-Nifed (PL); Aprical (DE, LU); Atanaal Softcap (TW); Calcheck (PH); Calcibloc (PH); Calcibloc OD (PH); Calcigard (IN, SG, TH); Cardifen (ZA); Cardionorm (PH); Chronadalate LP (FR); Citilat (IT); Coracten (AE, BH, CY, DE, EG, GB, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Coral (IT); Cordafen (PL); Cordaflex (HU); Cordalat (ID); Cordilat (MX); Cordipen (SG); Cordipen Retard (SG); Cordipin (HK, HR, PL); Cordipin Retard (PL); Corinfar (HU, PL); Corinfar Retard (PL); Coronpin (ID); Corotrend (DE); Depin (IN); Depin-E Retard (TH); Dignokonstant (DE); Dipinkor (ID); Duranifin (DE); Ecodipin (CH); Fedcor (PH); Fedipin (ID); Fedipine 24 CR (KP); Fenamon (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, QA, SA, SC, SD, SG, SL, SN, SY, TH, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Fenamon SR (TH); Ficor (ID); Glopir (GR); Hartigard SR (PH); Hexadilat (DK); Huma-Nifedin (HU); Jutadilat (DE); Myogard (AE, BH, CY, EG, IL, IN, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Nedipin (TW); Nelapine (PH); Nicardia CD (TH); Nidipin (HU); Nifadil (HR); Nifangin (FI); Nifar (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Nifar-GB (MX); Nifdemin (FI); Nifebene (AT); Nifecard (AT, HR, PL); Nifecor (DE); Nifedepat (DE); Nifedicor (IT, PL); Nifedigel (MX); NIfedilat (ZA); Nifedin (IT); Nifedine (IN); Nifedipin (HR); Nifedipin AL (HU); Nifedipin Pharmavit (HU); Nifedipin Stada (LU); Nifedipin-ratiopharm (LU); Nifedipine (PL); Nifegis (PL); Nifehexal (AU, LU, PL); Nifelat (AR, HK, TH); Nifelat-Q (TH); Nifensar (PE); Nifensar Retard (PE); Niferon CR (KP); Nifeslow (LU); Nifestad (PH); Nifezzard (MX); Nificard (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, TH, YE); Nifipen (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Niften (IE); Nipin (SG); Normadil (PH); Noviken LP (MX); Nyefax (AU); Nyefax Retard (NZ); Odipin (PH); Orix (GR); Osmo-Adalat (IL); Pidilat (DE); Pressolat (IL); Sepamit (JP); Slow-Nifine (LU); Stada Uno (SG); Unidipin (HU, LU); Vasdalat (ID); Vasdalat Retard (ID); Zenusin (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PL, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW)

Nilotinib

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Nilotinib may be confused with nilutamide

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(nye LOE ti nib)

U.S. Brand NamesTasigna®

Canadian Brand NamesTasigna®

Pharmacologic CategoryAntineoplastic Agent, Tyrosine Kinase Inhibitor

Use: Labeled IndicationsTreatment of Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) in chronic and accelerated phase (refractory or intolerant to prior therapy, including imatinib)

Use: Unlabeled/InvestigationalTreatment of Ph+ acute lymphoblastic leukemia (ALL), systemic mastocytosis (with c-kit activation), hypereosinophilic syndrome

Dosing: Adults**Ph+ CML:** Oral: 400 mg twice daily (continue treatment until disease progression or unacceptable toxicity)

Dosage adjustment for concomitant CYP3A4 inhibitors/inducers:

CYP3A4 inhibitors: The concomitant use of a strong CYP3A4 inhibitor with nilotinib is not recommended. If a strong CYP3A4 inhibitor is required, interruption of nilotinib treatment is recommended; if therapy cannot be interrupted and concurrent use can not be avoided, consider reducing the nilotinib dose by 50%, to 400 mg once daily, with careful monitoring, especially of the QT interval. When a strong CYP3A4 inhibitor is discontinued, allow a washout period prior to adjusting nilotinib dose upward.

CYP3A4 inducers: The concomitant use of a strong CYP3A4 inducer with nilotinib is not recommended. If a strong CYP3A4 inducer is required, the nilotinib dose may need to be increased, with careful monitoring. When the strong CYP3A4 inducer is discontinued, reduce nilotinib to the indicated dose.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot studied in patients with serum creatinine >1.5 times ULN, however, nilotinib and its metabolites have minimal renal excretion; dosage adjustments for renal dysfunction may not be needed.

Dosing: Hepatic ImpairmentNot studied in patients with hepatic impairment; nilotinib metabolism is primarily hepatic, use caution.

For hepatotoxicity during treatment:

If bilirubin >3 times ULN (≥ grade 3): Withhold treatment, monitor bilirubin, resume treatment at 400 mg once daily when bilirubin returns to ≤1.5 times ULN (≤ grade 1)

If ALT or AST >5 times ULN (≥ grade 3): Withhold treatment, monitor transaminases, resume treatment at 400 mg once daily when ALT or AST returns to ≤2.5 times ULN (≤ grade 1)

Dosing: Adjustment for Toxicity

Dosage adjustment for hematologic toxicity:

ANC <1000/mm^3 and/or platelets <50,000/mm^3: Withhold treatment, monitor blood counts

If ANC >1000/mm^3 and platelets >50,000/mm^3 within 2 weeks: Continue at 400 mg twice daily

If ANC <1000/mm^3 and/or platelets <50,000/mm^3 for >2 weeks: Reduce dose to 400 mg once daily

Dosage adjustment for nonhematologic toxicity:

Amylase or lipase ≥2 times ULN (≥ grade 3): Withhold treatment, monitor serum amylase or lipase, resume treatment at 400 mg once daily when lipase or amylase returns to ≤1.5 times ULN (≤ grade 1)

Clinically-significant moderate or severe nonhematologic toxicity: Withhold treatment, upon resolution of toxicity, resume at 400 mg once daily; may escalate back to 400 mg twice daily if clinically appropriate.

Dosage adjustment for QT prolongation:

QT$_c$ >480 msec: Withhold treatment, monitor and correct potassium and magnesium levels.

If within 2 weeks:

QT_cF returns to <450 msec and to within 20 msec of baseline within 2 weeks: Continue at 400 mg twice daily

QT_cF returns to 450-480 msec: Reduce dose to 400 mg once daily

If QT_cF >480 msec after dosage reduction to 400 mg once daily, discontinue therapy.

Calculations

- ANC: Absolute Neutrophil Count

Administration: OralAdminister twice daily, ~12 hours apart. Swallow capsules whole with water. Administer on an empty stomach, at least 1 hour before or 2 hours after food.

Dietary ConsiderationsThe bioavailability of nilotinib is increased with food. Take on an empty stomach, at least 1 hour before or 2 hours after food. Avoid grapefruit juice.

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsUse in patients with hypokalemia, hypomagnesemia, or long QT syndrome

Warnings/Precautions

Boxed warnings:

- Administration: See “Other warnings/precautions” below.
- Hepatic impairment: See “Disease-related concerns” below.
- QT prolongation/sudden death: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Reversible myelosuppression, including grades 3 and 4 thrombocytopenia, neutropenia and anemia may occur; may require dose reductions and/or treatment delay.
- Electrolyte imbalance: Electrolyte abnormalities may occur during treatment, including hypophosphatemia, hyper-/hypokalemia, hypocalcemia and hyponatremia. Correct electrolyte abnormalities prior to treatment initiation.
- Hepatotoxicity: May cause hepatotoxicity, including dose-limiting elevations in bilirubin, transaminases, and alkaline phosphatase; monitor liver function.
- QT prolongation/sudden death: **[U.S. Boxed Warning]: May prolong the QT interval; sudden deaths have been reported.** The sudden deaths reported appear to be related to dose-dependent ventricular repolarization abnormalities. Prolonged QT interval may result in torsade de pointes, which may cause syncope, seizure, and/or death. Use in patients with hypokalemia, hypomagnesemia, or long QT syndrome is contraindicated. Correct electrolyte imbalance prior to initiating therapy; monitor ECG. Avoid the use of QT-prolonging agents and strong CYP3A4 inhibitors. Patients with uncontrolled or significant cardiovascular disease were excluded from studies.

Disease-related concerns:

- Hepatic impairment: **[U.S. Boxed Warning]: Use with caution in patients with hepatic impairment;** nilotinib metabolism is primarily hepatic; carefully monitor for QT prolongation. Nilotinib use in patients with ALT and/or AST >2.5 times ULN (>5 times ULN if disease-related) and/or bilirubin >1.5 times ULN has not been studied.
- Pancreatitis: Use with caution in patients with a history of pancreatitis, may cause dose-limiting elevations of serum lipase and amylase; monitor.

Concurrent drug therapy issues:

- CYP3A4 inhibitors/inducers: Concurrent use with CYP3A4 inhibitors/inducers is not recommended; dosage adjustments are recommended if concurrent use cannot be avoided.
- QT-prolonging agents: Concurrent use with other drugs which may prolong QT interval may increase the risk of potentially-fatal arrhythmias.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Lactose: Capsules contain lactose; do not use with galactose intolerance, severe lactase deficiency, or glucose-galactose malabsorption syndromes.

Other warnings/precautions:

- Administration: **[U.S. Boxed Warning]: Administer on an empty stomach, at least 1 hour before and 2 hours after food.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated embryo-fetal toxicity and maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to use effective contraception during treatment.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse effects in the nursing infant, breast-feeding is not recommended.

Adverse ReactionsFrequency not always defined.

10%:

Cardiovascular: Peripheral edema (11%)

Central nervous system: Headache (21% to 31%), fatigue (16% to 28%), fever (14% to 24%)

Dermatologic: Rash (28% to 33%), pruritus (20% to 29%)

Endocrine & metabolic: Hyperglycemia (grades 3/4: 4% to 11%)

Gastrointestinal: Nausea (18% to 31%), diarrhea (19% to 22%), constipation (18% to 21%), vomiting (10% to 21%), lipase increased (grades 3/4: 15% to 17%), abdominal pain (11% to 13%)

Hematologic: Neutropenia (grades 3/4: 28% to 37%; median duration: 15 days), thrombocytopenia (grade 3: 7% to 11%; grade 4: 17% to 30%; median duration: 22 days), anemia (grades 3/4: 8% to 23%)

Neuromuscular & skeletal: Arthralgia (16% to 18%), limb pain (13% to 16%), myalgia (14%), weakness (12% to 14%), muscle spasm (11% to 14%), bone pain (11% to 13%), back pain (10% to 12%)

Respiratory: Cough (13% to 17%), nasopharyngitis (11% to 16%), dyspnea (8% to 11%)

1% to 10%:

Cardiovascular: Flushing, hypertension, palpitation, QT interval prolonged

Central nervous system: Dizziness, dysphonia, insomnia, vertigo

Dermatologic: Alopecia, dry skin, eczema, erythema, hyperhidrosis, urticaria

Endocrine & metabolic: Hypophosphatemia (grades 3/4: 10%), hypokalemia (grades 3/4: 1% to 5%), hyperkalemia (grades 3/4: 3% to 4%), hypocalcemia (grades 3/4: 1% to 4%), hyponatremia (grades 3/4: 3%), albumin decreased (grades 3/4: 1%), hypomagnesemia

Gastrointestinal: Abdominal discomfort, amylase increased, anorexia, dyspepsia, flatulence, pancreatitis (≤1%)

Hematologic: Neutropenic fever, pancytopenia

Hepatic: Hyperbilirubinemia (grades 3/4: 9% to 10%), ALT increased (grades 3/4: 2% to 4%), alkaline phosphatase increased (grades 3/4: 1% to 3%), AST increased (grades 3/4: 1%), GGT increased

Neuromuscular & skeletal: Musculoskeletal pain, paresthesia

Respiratory: Dyspnea (exertional), pleural effusion (≤1%)

Miscellaneous: Night sweats

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Angina, atrial fibrillation, blurred vision, bradycardia, brain edema, bruising, BUN increased, candidiasis, cardiac failure, cardiac flutter, cardiac murmur, cardiomegaly, chest pain, confusion, coronary artery disease, creatinine elevated, depression, diabetes mellitus, diplopia, dysuria, epistaxis, erectile dysfunction, erythema nodosum, exfoliative rash, extrasystoles, eye hemorrhage, facial edema, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal ulcer perforation, gynecomastia, hematemesis, hematoma, hematuria, hemorrhagic shock, hepatitis, hepatomegaly, hepatotoxicity, herpes simplex, hypercalcemia, hyper-/hypothyroidism, hyperphosphatemia, hypertensive crisis, hypoglycemia, hypotension, influenza-like illness, interstitial lung disease, intracranial hemorrhage, jaundice, joint swelling, lactic dehydrogenase increased, leukocytosis, loss of consciousness, melena, MI, migraine, mouth ulceration, optic neuritis, papilledema, pericardial effusion, pericarditis, periorbital edema, peripheral neuropathy, petechiae, pneumonia, pulmonary edema, pulmonary hypertension, renal failure, retroperitoneal hemorrhage, sepsis, stomatitis, subileus, thrombocytosis, thrombosis, thyroiditis, troponin increased, ulcerative esophagitis, urinary tract infection, ventricular dysfunction, visual acuity decreased

Oncology: Emetic PotentialLow (10% to 30%)

Metabolism/Transport Effects**Substrate** of CYP3A4 (major), P-glycoprotein (P-gp, ABCB1); **Inhibits** CYP3A4, 2C8, 2C9, 2D6, UGT1A1, P-glycoprotein (P-gp, ABCB1); **Induces** CYP2B6, 2C8, 2C9

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

QTc-Prolonging Agents: Nilotinib may enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid St John's wort (may decrease nilotinib levels).

Monitoring ParametersCBC with differential (every 2 weeks for first 2 months, then monthly); electrolytes (including potassium and magnesium; baseline and periodic); hepatic function (ALT/AST, bilirubin, alkaline phosphatase; baseline and periodic); serum lipase (baseline and periodic); bone marrow assessments; ECG (baseline, 7 days after treatment initiation or dosage adjustments, and periodically thereafter)

Nursing: Physical Assessment/MonitoringUse caution in presence of hepatic or left ventricular dysfunction. Assess all other pharmacological or herbal products patient may be taking for potential adverse interactions (eg, anything that may prolong QT interval or strong CYP3A4 inducers or inhibitors); dose adjustment may be necessary. Evaluate results of laboratory tests at baseline and on a regular basis (eg, CBC, electrolytes, LFTs, serum lipase). Assess therapeutic effectiveness and adverse reactions periodically during therapy (eg, cardiac changes, gastrointestinal disturbance, hyperglycemia, pulmonary status). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential (every 2 weeks for first 2 months, then monthly); electrolytes (including potassium and magnesium; baseline and periodic); hepatic function (ALT/AST, bilirubin, alkaline phosphatase; baseline and periodic); serum lipase (baseline and periodic);

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take as directed on an empty stomach, 1 hour before or 2 hours after a meal. Avoid grapefruit or grapefruit juice while taking this medication. Maintain adequate hydration (2-3 L/day unless instructed to restrict fluid intake). You may be required to have regularly scheduled laboratory tests while on this medication. You will be more susceptible to infection (avoid crowds and exposure to infection and do not receive any vaccination unless approved by prescriber). You may experience diarrhea (buttermilk, boiled milk, or yogurt may help); constipation (increased exercise, dietary fluid, or fiber may help); insomnia or fatigue (use caution when driving or engaging in hazardous tasks until response to drug is known); nausea, vomiting, stomach pain, or dyspepsia (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or unusual pain or weakness in joints, muscles, or bone (contact prescriber for appropriate analgesia). Report chest pain, rapid heart beat, or palpitations; swelling or unusual weight gain; unusual cough, respiratory difficulty, or wheezing; easy bruising or unusual bleeding; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant. Consult prescriber for appropriate contraception while using this medication. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Tasigna®: 200 mg

Generic AvailableNo

Manufacturer

Novartis Pharmaceuticals Corp

Mechanism of ActionSelective tyrosine kinase inhibitor that targets BCR-ABL kinase, c-KIT and platelet derived growth factor receptor (PDGFR); does not have activity against the SRC family. Inhibits BCR-ABL mediated proliferation of leukemic cell lines by binding to the ATP-binding site of BCR-ABL and inhibiting tyrosine kinase activity. Nilotinib has activity in imatinib-resistant BCR-ABL kinase mutations.

Pharmacodynamics/Kinetics

Protein binding: ~98%

Metabolism: Hepatic; oxidation and hydroxylation, via CYP3A4 to primarily inactive metabolites

Bioavailability: Increased 82% when administered 30 minutes after a high-fat meal

Half-life elimination: ~15-17 hours

Time to peak: 3 hours

Excretion: Feces (93%; 69% as parent drug)

Related Information

- Common Toxicity Criteria
- Management of Nausea and Vomiting
- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsIf clinically indicated, may be administered in combination with hematopoietic growth factors (eg, erythropoietin, filgrastim) and with hydroxyurea or anagrelide.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mouth ulcerations, stomatitis

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNilotinib is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusFatigue is common; may cause dizziness and insomnia

Mental Health: Effects on Psychiatric TreatmentNilotinib may decrease the levels/effects of CYP2B6 substrates (eg, bupropion, promethazine, selegiline, and sertraline). Nilotinib may alter (increase or decrease) the levels/effects of CYP2C9 substrates (eg, fluoxetine, phenytoin). May decrease the levels/effects of active metabolites generated by CYP2D6 (eg, codeine and tramadol). May increase the levels/effects of CYP2D6 substrates (eg, amphetamines, select beta-blockers, dextromethorphan, fluoxetine, mirtazapine, nefazodone, paroxetine, risperidone, thioridazine, tricyclic antidepressants, and venlafaxine). Carbamazepine, phenobarbital, and phenytoin may decrease the levels/effects of nilotinib; avoid concurrent use. Avoid concurrent use with nefazodone. Nilotinib may increase the levels/effects of CYP3A4 substrates (eg, benzodiazepines, mirtazapine, nefazodone, and venlafaxine). Avoid concurrent use of nilotinib with other drugs which may prolong QT interval (includes thioridazine and ziprasidone); may increase the risk of potentially-fatal arrhythmias. GI side effects are common; use caution with SSRIs, lithium, and carbamazepine. Hematologic side effects are common; use caution with clozapine, carbamazepine, and valproic acid.

Index TermsAMN107; Nilotinib Hydrochloride Monohydrate

References

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Verstovsek S, Giles FJ, Quintas-Cardama A, et al, “Activity of AMN107, a Novel Aminopyrimidine Tyrosine Kinase Inhibitor, Against Human FIP1L1-PDGFR-Alpha-Expressing Cells, *Leuk Res*, 2006, 30(12):1499-505.[PubMed 16682077]

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Proliferation of Philadelphia-Positive Acute Lymphoblastic Leukemia Cells," *Cancer*, 2005, 104(6):1230-6.[PubMed 16078266]

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International Brand NamesTasigna (CH, CZ, DK, EE, GB, IE, IL, NO, NZ, PH, SE)

Nilutamide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Nilutamide may be confused with nilotinib

Pronunciation(ni LOO ta mide)

U.S. Brand NamesNilandron®

Canadian Brand NamesAnandron®

Pharmacologic CategoryAntiandrogen; Antineoplastic Agent, Antiandrogen

Use: Labeled IndicationsTreatment of metastatic prostate cancer

Dosing: AdultsRefer to individual protocols. **Prostate cancer:** Oral: 300 mg daily for 30 days starting the same day or day after surgical castration, then 150 mg/day

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsMay be taken without regard to food.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

ContraindicationsHypersensitivity to nilutamide or any component of the formulation; severe hepatic impairment; severe respiratory insufficiency

Allergy Considerations

- Nilutamide Allergy

Warnings/Precautions

Boxed warnings:

- Interstitial pneumonitis: See "Concerns related to adverse effects" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Hepatic effects: Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in 1% of nilutamide patients. Rare cases of elevated hepatic enzymes followed by death have been reported.

- Interstitial pneumonitis: **[U.S. Boxed Warning]: Interstitial pneumonitis has been reported in 2% of patients exposed to nilutamide.** Patients typically experienced progressive exertional dyspnea, and possibly cough, chest pain and fever. X-rays showed interstitial or alveolo-interstitial changes. The suggestive signs of pneumonitis most often occurred within the first 3 months of nilutamide treatment.

- Vision effects: 13% to 57% of patients receiving nilutamide reported a delay in adaptation to the dark, ranging from seconds to a few minutes. This effect sometimes does not abate as drug treatment is continued. Caution patients who experience this effect about driving at night or through tunnels. This effect can be alleviated by wearing tinted glasses.

Geriatric ConsiderationsYour eyes may be slow to adapt to darkness; be careful when driving at night; tinted glasses may help.

Pregnancy Risk FactorC

Pregnancy ConsiderationsNot indicated for use in women

LactationNot indicated for use in women

Adverse Reactions

>10%:

Central nervous system: Headache, insomnia

Endocrine & metabolic: Hot flashes (30% to 67%), gynecomastia (10%)

Gastrointestinal: Nausea (mild - 10% to 32%), abdominal pain (10%), constipation, anorexia

Genitourinary: Testicular atrophy (16%), libido decreased

Hepatic: Transaminases increased (8% to 13%; transient)

Ocular: Impaired dark adaptation (13% to 57%), usually reversible with dose reduction, may require discontinuation of the drug in 1% to 2% of patients

Respiratory: Dyspnea (11%)

1% to 10%:

Cardiovascular: Chest pain, edema, heart failure, hypertension, syncope

Central nervous system: Dizziness, drowsiness, malaise, hypoesthesia, depression

Dermatologic: Pruritus, alopecia, dry skin, rash

Endocrine & metabolic: Disulfiram-like reaction (hot flashes, rash) (5%); Flu-like syndrome, fever

Gastrointestinal: Vomiting, diarrhea, dyspepsia, GI hemorrhage, melena, weight loss, xerostomia

Genitourinary: Hematuria, nocturia

Hematologic: Anemia

Hepatic: Hepatitis (1%)

Neuromuscular & skeletal: Arthritis, paresthesia

Ocular: Chromatopsia (9%), abnormal vision (6% to 7%), cataracts, photophobia

Respiratory: Interstitial pneumonitis (2% - typically exertional dyspnea, cough, chest pain, and fever; most often occurring within the first 3 months of treatment); rhinitis

Miscellaneous: Diaphoresis

<1%, postmarketing, and/or case reports: Aplastic anemia

Oncology: Emetic PotentialLow (10% to 30)

Metabolism/Transport Effects**Substrate** of CYP2C19 (major); **Inhibits** CYP2C19 (weak)

Drug Interactions

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol. Up to 5% of patients may experience a systemic reaction (flushing, hypotension, malaise) when combined with nilutamide.

Herb/Nutraceutical: St John's wort may decrease nilutamide levels.

Monitoring ParametersObtain a chest x-ray if a patient reports dyspnea; if there are findings suggestive of interstitial pneumonitis, discontinue treatment with nilutamide. Measure serum hepatic enzyme levels at baseline and at regular intervals (3 months); if transaminases increase over 2-3 times the upper limit of normal, discontinue treatment. Perform appropriate laboratory testing at the first symptom/sign of liver injury (eg, jaundice, dark urine, fatigue, abdominal pain or unexplained GI symptoms).

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, agents that may increase or decrease levels/effects of nilutamide). Evaluate results of chest x-rays and laboratory tests at baseline and at regular 3-month intervals. Assess effectiveness and adverse response (eg, signs of interstitial pneumonitis [dyspnea, chest pain, cough, fever], hepatitis, visual changes [impaired dark adaptation]). Teach patient proper use, possible side effects/appropriate interventions (eg, orthostatic precautions), and adverse symptoms to report.

Monitoring: Lab TestsChest x-rays prior to and regularly during treatment. Measure serum hepatic enzyme levels at baseline and at regular intervals (3 months). If transaminases increase over 2-3 times the upper limit of normal, discontinue treatment. Perform appropriate laboratory testing at the first symptom/sign of liver injury (eg, jaundice, dark urine, fatigue, abdominal pain, or unexplained GI symptoms).

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as prescribed; do not change dosing schedule or stop taking without consulting prescriber. Avoid alcohol while taking this medication; may cause severe adverse reaction. Periodic laboratory tests are necessary while taking this medication. May cause loss of light accommodation (avoid night driving and use caution in poorly lighted or changing light situations such as tunnels); dizziness, confusion, or blurred vision (avoid driving or engaging in tasks that are potentially hazardous until response to drug is known); nausea or anorexia (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or hot flashes, gynecomastia, decreased libido, impotence or sexual dysfunction (consult prescriber). Report any decreased respiratory function (eg, dyspnea, increased cough); unexplained fever; difficulty or painful voiding or blood in urine; or other persistent adverse effects.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 150 mg

Generic AvailableNo

ManufacturerAventis Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Nilandron)

150 mg (30): $402.53

Mechanism of ActionNonsteroidal antiandrogen that inhibits androgen uptake or inhibits binding of androgen in target tissues. It specifically blocks the action of androgens by interacting with cytosolic androgen receptor F sites in target tissue

Pharmacodynamics/Kinetics

Absorption: Rapid and complete

Protein binding: 72% to 85%

Metabolism: Hepatic, forms active metabolites

Half-life elimination: Terminal: 23-87 hours; Metabolites: 35-137 hours

Excretion: Urine (up to 78% at 120 hours; <1% as unchanged drug); feces (1% to 7%)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia is common; may cause dizziness or depression

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsNSC-684588; RU-23908

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International Brand NamesAnandron (AR, AU, BR, CH, CZ, FI, FR, GR, HN, HR, HU, MX, NL, NO, PL, PT, SE)

NiMODipine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

NiMODipine may be confused with niCARdipine, NIFEdipine, nisoldipine

Administration issues: **For oral administration only.** For patients unable to swallow a capsule, the drug should be dispensed in an oral syringe labeled **"for oral use only."** Nimodipine has inadvertently been administered I.V. when withdrawn from capsules into a syringe for subsequent nasogastric administration. Severe cardiovascular adverse events, including fatalities, have resulted. Employ precautions against such an event.

Pronunciation(nye MOE di peen)

U.S. Brand NamesNimotop® [DSC]

Canadian Brand NamesNimotop®

Pharmacologic CategoryCalcium Channel Blocker

Use: Labeled IndicationsSpasm following subarachnoid hemorrhage from ruptured intracranial aneurysms regardless of the patients neurological condition postictus (Hunt and Hess grades I-V)

Dosing: Adults**Note:** Capsules and contents are for oral administration **ONLY.**

Subarachnoid hemorrhage: Oral: 60 mg every 4 hours for 21 days, start therapy within 96 hours after subarachnoid hemorrhage.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot removed by hemo- or peritoneal dialysis; supplemental dose is not necessary.

Dosing: Hepatic ImpairmentReduce dosage to 30 mg every 4 hours in patients with liver failure.

Administration: OralFor oral administration **ONLY.** If the capsules cannot be swallowed, the liquid may be removed by making a hole in each end of the capsule with an 18-gauge needle and extracting the contents into a syringe. If given via NG tube, follow with a flush of 30 mL NS.

ContraindicationsHypersensitivity to nimodipine or any component of the formulation

Allergy Considerations

- Calcium Channel Blocker, Dihydropyridine Allergy

Warnings/Precautions

Boxed warnings:

- Inadvertent I.V. administration: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Angina/MI: Increased angina and/or MI has occurred with initiation or dosage titration of calcium channel blockers.
- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition.
- Ileus/ pseudo-obstruction: Intestinal pseudo-obstruction and ileus have been reported during therapy; use caution in patients with decreased GI motility of a history of bowel obstruction.
- Peripheral edema: The most common side effect is peripheral edema; occurs within 2-3 weeks of starting therapy.
- Reflex tachycardia: May occur with use.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; may require lower starting dose.
- Idiopathic hypertrophic subaortic stenosis (IHSS): Use with caution in patients with IHSS.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Inadvertent I.V. administration: **[U.S. Boxed Warning]: Nimodipine has inadvertently been administered I.V. when withdrawn from capsules into a**

syringe for subsequent nasogastric administration. Severe cardiovascular adverse events, including fatalities, have resulted; precautions should be employed against such an event.

Geriatric ConsiderationsElderly may experience a greater hypotensive response. Constipation may be more of a problem in the elderly. Studies in the treatment of Alzheimer's disease have not demonstrated clear clinical effect.

Pregnancy Risk FactorC

Pregnancy ConsiderationsUse in pregnancy only when clearly needed and when the benefits outweigh the potential hazard to the fetus. Teratogenic and embryotoxic effects have been demonstrated in small animals. No well-controlled studies have been conducted in pregnant women.

LactationEnters breast milk/not recommended

Adverse Reactions

1% to 10%:

Cardiovascular: Reductions in systemic blood pressure (1% to 8%)

Central nervous system: Headache (1% to 4%)

Dermatologic: Rash (1% to 2%)

Gastrointestinal: Diarrhea (2% to 4%), abdominal discomfort (2%)

<1% (Limited to important or life-threatening): Edema (≤1%), ECG abnormalities (≤1%), tachycardia (0% to 1%), bradycardia (≤1%), depression (≤1%), acne (≤1%), nausea (≤1%), hemorrhage, hepatitis, muscle cramps/pain (≤1%), dyspnea (≤1%). itching, GI hemorrhage, thrombocytopenia, anemia, palpitation, vomiting, flushing, diaphoresis, wheezing, lightheadedness, dizziness, rebound vasospasm, jaundice, hypertension, hematoma, neurological deterioration, CHF, hyponatremia, disseminated intravascular coagulation, deep vein thrombosis

Case report: Disseminated intravascular coagulation (DIC)

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)

Drug Interactions

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

CycloSPORINE: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk D: Consider therapy modification*

QuiNIDine: Calcium Channel Blockers (Dihydropyridine) may decrease the serum concentration of QuiNIDine. *Risk C: Monitor therapy*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Nimodipine has shown a 1.5-fold increase in bioavailability when taken with grapefruit juice; avoid concurrent use.

Herb/Nutraceutical: St John's wort may decrease levels. Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, increased risk of hypotension with other antihypertensives). Assess therapeutic effectiveness (blood pressure and cardiac status) and adverse response (eg, rash, hypotension, diarrhea, confusion) when starting or adjusting dose and periodically during long-term therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed; do not alter dose or decrease without consulting prescriber. Avoid grapefruit juice while taking this medication. May cause orthostatic hypotension (change position slowly from sitting or lying to standing, or when climbing stairs); headache (consult prescriber for approved analgesic); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report chest pain, palpitations, slow heartbeat, respiratory difficulty, or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, liquid filled: 30 mg

Nimotop®: 30 mg [DSC]

Generic AvailableYes

ManufacturerBayer Corp (Biological and Pharmaceutical Division)

Pricing: U.S. (www.drugstore.com)

Capsules (Nimodipine)

30 mg (100): $599.99

Mechanism of ActionNimodipine shares the pharmacology of other calcium channel blockers; animal studies indicate that nimodipine has a greater effect on cerebral arterials than other arterials; this increased specificity may be due to the drug's increased lipophilicity and cerebral distribution as compared to nifedipine; inhibits calcium ion from entering the “slow channels” or select voltage sensitive areas of vascular smooth muscle and myocardium during depolarization

Pharmacodynamics/Kinetics

Protein binding: >95%

Metabolism: Extensively hepatic

Bioavailability: 13%

Half-life elimination: 1-2 hours; prolonged with renal impairment

Time to peak, serum: ~1 hour

Excretion: Urine (50%) and feces (32%) within 4 days

Related Information

- Calcium Channel Blockers

Dental Health: Effects on Dental TreatmentOther drugs of this class can cause gingival hyperplasia (ie, nifedipine) but there have been no reports for nimodipine.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness; may rarely cause depression

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsNimodipine is primarily used in the treatment of subarachnoid hemorrhage and is not used in the management of essential hypertension or angina.

Anesthesia and Critical Care Concerns/Other ConsiderationsAnimal studies suggest nimodipine may have a greater effect on cerebral arterioles, possibly due to its lipophilicity which increases cerebral distribution.

References

Ramoska EA, Spiller HA, and Myers A, “Calcium Channel Blocker Toxicity,” *Ann Emerg Med*, 1990, 19(6):649-53. [PubMed 2344082]

Steele RM, Schuna AA, and Schreiber RT, “Calcium Antagonist-Induced Gingival Hyperplasia,” *Ann Intern Med*, 1994, 120(8):663-4.[PubMed 8135450]

International Brand NamesAdmon (ES); Amocure (TW); Brainal (ES); Calnit (ES); Eugerial (AR, BR, CO, PE); Grifonimod (PE); Irrigor (PE); Kenesil (ES); Kenzolol (MX); Modip (CR, DO, GT, NI, PA, SV); Modus (ES); Nidip (CO); Nimodilat (AR); Nimodipino Bayvit (ES); Nimotop (AT, AU, BB, BE, BG, BM, BR, BS, BZ, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, EE, ES, FI, FR, GB, GR, GT, GY, HK, HN, HR, HU, ID, IE, IL, IT, JM, KP, LU, MX, MY, NI, NL, NO, PA, PE, PH, PK, PL, PT, PY, SE, SR, SV, TH, TT, TW, UY, VE, ZA); Nimotop S (PL); Nisom (CO); Periplum (IT); Remontal (ES); Tropocer (CO, VE); Vasoflex (CN); Vasotop (IN)

Nisoldipine

Lexi-Drugs Online

English

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Special Alerts

Nisoldipine (Sular®): New Formulation and Dosing - May 2008

Sular® (nisoldipine) has been reformulated (March 2008). Sular® is now available in 8.5 mg, 17 mg, 25.5 mg, and 34 mg extended release tablets.

Sular® Dosing Changes

Old Dose	New Dose
10 mg	8.5 mg
20 mg	17 mg
30 mg	25.5 mg
40 mg	34 mg

Medication Safety Issues

Sound-alike/look-alike issues:

Nisoldipine may be confused with NIFEdipine, niMODipine

Pronunciation(nye SOL di peen)
U.S. Brand NamesSular®
Pharmacologic CategoryCalcium Channel Blocker
Use: Labeled IndicationsManagement of hypertension, alone or in combination with other antihypertensive agents
Dosing: Adults

Hypertension: Oral: Initial: 17 mg once daily, then increase by 8.5 mg/week (or longer intervals) to attain adequate control of blood pressure

Usual dose range:

17-34 mg once daily; doses >34 mg once daily are not recommended.

Dosing: ElderlyInitial dose: 8.5 mg/day, increase by 8.5 mg/week (or longer intervals) to attain adequate blood pressure control.
Dosing: Hepatic ImpairmentA starting dose not exceeding 8.5 mg/day is recommended for patients with hepatic impairment.
Administration: OralAdminister at the same time each day to ensure minimal fluctuation of serum levels. Avoid high-fat diet. Administer on an empty stomach (1 hour before or 2 hours after a meal). Swallow whole; do not crush, break, split, or chew.
Dietary ConsiderationsTake on an empty stomach (1 hour before or 2 hours after a meal).
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light; protect from moisture.
ContraindicationsHypersensitivity to nisoldipine, any component of the formulation, or other dihydropyridine calcium channel blockers
Allergy Considerations

- Calcium Channel Blocker, Dihydropyridine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Angina/MI: With initiation or dosage titration of dihydropyridine calcium channel blockers, reflex tachycardia may occur resulting in angina and/or MI in patients with obstructive coronary disease especially in the absence of concurrent beta-blockade.
- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Monitor closely during initial dosing and with dosage adjustment.
- Peripheral edema: The most common side effect is peripheral edema; occurs within 2-3 weeks of starting therapy.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis.

- Heart failure (HF): Use with caution in patients with HF; safety and efficacy has not been established.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment; lower starting dose required.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

Dosage form specific issues:

- Tartrazine: Contains tartrazine, which may cause allergic reactions in certain individuals (eg, aspirin hypersensitivity).

Special populations:

- Elderly: Use with caution in patients >65 years of age; lower starting dose recommended.

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsElderly have been found to have two- to threefold greater serum concentrations than younger adults. Therefore, begin therapy at lowest recommended doses. Elderly may experience a greater hypotensive response. Constipation may be more of a problem in the elderly. Calcium channel blockers are no more effective in the elderly than other therapies; however, they do not cause significant CNS effects which is an advantage over some antihypertensive agents.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have demonstrated fetotoxic but not teratogenic effects. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if potential benefit to the mother outweighs potential risk to the fetus.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Cardiovascular: Peripheral edema (dose related; 7% to 27%)

Central nervous system: Headache (22%)

1% to 10%:

Cardiovascular: Vasodilation (4%), palpitation (3%), angina exacerbation (2%), chest pain (2%)

Central nervous system: Dizziness (3% to 7%)

Dermatologic: Rash (2%)

Gastrointestinal: Nausea (2%)

Respiratory: Pharyngitis (5%), sinusitis (3%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Alopecia, amblyopia, amnesia, anemia, angina, anxiety, arthralgia, arthritis, asthma, ataxia, atrial fibrillation, blepharitis, BUN increased, bruising, cellulitis, cerebral ischemia, chills, colitis, confusion, conjunctivitis, cough, creatinine increased, creatine kinase increased, CVA, depression, diabetes mellitus, diaphoresis, diarrhea, dyspepsia, dysphagia, dyspnea, dysuria, end inspiratory wheeze, epistaxis, exfoliative dermatitis, facial edema, fever, first-degree AV block, flu-like syndrome, fungal dermatitis, gastritis, gastrointestinal hemorrhage, gingival hyperplasia, glaucoma, glossitis, gout, gynecomastia, heart failure, hematuria, hepatomegaly, herpes simplex, herpes zoster; hypersensitivity reaction (eg, angioedema, shortness of breath, tachycardia, chest tightness, hypotension, and rash); hyper-/hypotension, hypertonia, hypoesthesia, hypokalemia, jugular venous distention, keratoconjunctivitis, laryngitis, leg cramps, leukopenia, libido decreased, liver function tests abnormal, maculopapular rash, malaise, melena, migraine, mouth ulceration, myalgia, myasthenia, MI, myositis, nervousness, nocturia, nonprotein nitrogen increased, otitis media, paresthesia, petechiae, photosensitivity, pleural effusion, postural hypotension, pruritus, pustular rash, rales, retinal detachment, skin discoloration, skin ulcer, somnolence, supraventricular tachycardia, syncope, systolic ejection murmur, temporary unilateral loss of vision, tenosynovitis, thyroiditis, tinnitus, tremor; T-wave abnormalities on ECG (flattening, inversion, nonspecific changes); urinary frequency, urticaria, vaginal hemorrhage, vaginitis, venous insufficiency, ventricular extrasystoles, vertigo, vision abnormal, vitreous floater, weight gain/loss, xerostomia

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (weak), 3A4 (weak)

Drug Interactions

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

CycloSPORINE: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Nisoldipine. *Risk X: Avoid combination*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk D: Consider therapy modification*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Nisoldipine bioavailability may be increased if taken with high-lipid foods or with grapefruit juice. Avoid grapefruit products before and after dosing.

Herb/Nutraceutical: Avoid St John's wort (may decrease nisoldipine levels). Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure, heart rate

Nursing: Physical Assessment/MonitoringUse caution in presence of severe aortic stenosis, HF, hypertrophic cardiomyopathy with outflow tract obstruction or hepatic impairment. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, increased potential for hypotension with other antihypertensives). Assess therapeutic effectiveness (cardiac status and blood pressure) and adverse response (eg, chest pain, dyspnea, cough, edema, rash, nausea, confusion) when starting or adjusting dose and periodically during long-term therapy. When discontinuing, taper dose gradually (over 2 weeks). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new prescription or over-the-counter medications, or herbal products during therapy without consulting prescriber. Take exactly as directed; do not alter dose or decrease without consulting prescriber. Do not crush or chew tablets; swallow whole. Take on an empty stomach (1 hour before or 2 hours after a meal). This drug does not replace diet and other exercise recommendations of prescriber. May cause orthostatic hypotension (change position slowly when rising from sitting or lying, or when climbing stairs); headache (consult prescriber for approved analgesic); dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known); or nausea (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report weight gain or swelling of extremities; chest pain, palpitations, irregular heartbeat; persistent dizziness; respiratory difficulty; unusual cough; rash; vision changes; anxiety, confusion, depression, or other CNS changes; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, extended release [original formulation]: 20 mg, 30 mg, 40 mg

Sular®: 10 mg, 20 mg, 30 mg 40 mg [DSC]

Tablet, extended release [Geomatrix® delivery system]:

Sular®: 8.5 mg; 17 mg [contains tartrazine]; 25.5 mg, 34 mg

Generic AvailableYes: Extended release tablet

ManufacturerSciele Pharma, Inc

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Sular)

8.5 mg (100): $228.10

10 mg (30): $65.99

17 mg (100): $280.58

25.5 mg (100): $307.93

30 mg (30): $86.99

34 mg (100): $307.93

40 mg (30): $85.99

Mechanism of ActionAs a dihydropyridine calcium channel blocker, structurally similar to nifedipine, nisoldipine impedes the movement of calcium ions into vascular smooth muscle and cardiac muscle. Dihydropyridines are potent vasodilators and are not as likely to suppress cardiac contractility and slow cardiac conduction as other calcium antagonists such as verapamil and diltiazem; nisoldipine is 5-10 times as potent a vasodilator as nifedipine.

Pharmacodynamics/Kinetics

Duration: >24 hours

Absorption: Well absorbed

Protein binding: >99%

Metabolism: Extensively hepatic; 1 active metabolite (10% of parent); first-pass effect

Bioavailability: ~5%

Half-life elimination: 9-18 hours

Time to peak: 4-14 hours

Excretion: Urine (as metabolites)

Related Information

- Calcium Channel Blockers

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Unlike other calcium channel blockers, information is sparse as to whether nisoldipine causes gingival hyperplasia. Consultation with physician is suggested if hyperplasia is observed in patients taking nisoldipine.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsNisoldipine alone or in combination with other agents is effective in the management of hypertension and angina. Nisoldipine should be avoided in patients with left ventricular systolic dysfunction because of negative inotropic effects.

In the treatment of unstable angina/non-ST-segment elevation MI, a nondihydropyridine calcium antagonist (diltiazem or verapamil) may be considered in patients with continuing or frequently recurring ischemia when beta-blockers are contraindicated (Class I). Oral long-acting calcium antagonists may also be considered in addition to beta-blockers and nitrates (Class IIa).

References

Braunwald E, Antman EM, Beasley JW, et al, “ACC/AHA Guidelines for the Management of Patients With Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina),” *J Am Coll Cardiol*, 2000, 36(3):970-1062. [PubMed 10987629]

Chobanian AV, Bakris GL, Black HR, et al, “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report,” *JAMA*, 2003, 289(19):2560-71. [PubMed 12748199]

Estacio RO, Jeffers BW, Hiatt WR, et al, “The Effect of Nisoldipine as Compared With Enalapril on Cardiovascular Outcomes in Patients With Noninsulin-Dependent Diabetes and Hypertension,” *N Engl J Med*, 1998, 338(10):645-52.[PubMed 9486993]

International Brand NamesAngiolat (UY); Baymycard (BG, DE, HN, HU, JP); Corasol (CN); Nisodipen (AR); Nisoldin (KP); Syscor (AT, BE, CH, ES, FI, GR, IT, LU, NL, NZ, PL, TW); Syscor AP (BR); Syscor CC (BB, BM, BS, BZ, GY, JM, NL, NZ, SR, TT); Syscor ER (KP); Syscor MR (GB)

Nitazoxanide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(nye ta ZOX a nide)
U.S. Brand NamesAlinia®
Pharmacologic CategoryAntiprotozoal
Use: Labeled IndicationsTreatment of diarrhea caused by *Cryptosporidium parvum* or *Giardia lamblia*
Dosing: Adults**Diarrhea caused by *Cryptosporidium parvum* or *Giardia lamblia*:** Oral: 500 mg every 12 hours for 3 days
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Diarrhea caused by *Cryptosporidium parvum* or *Giardia lamblia*:** Oral:
Children 1-3 years: 100 mg every 12 hours for 3 days

Children 4-11 years: 200 mg every 12 hours for 3 days

Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentSpecific recommendations are not available; use with caution.
Dosing: Hepatic ImpairmentSpecific recommendations are not available; use with caution.
Administration: OralAdminister with food. Shake suspension well prior to administration.
Dietary ConsiderationsShould be taken with food. Suspension contains sucrose 1.48 g/5 mL.
Storage

Suspension: Prior to and following reconstitution, store at room temperature of 15°C to 30°C (59°F to 86°F). Following reconstitution, discard unused portion of suspension after 7 days.

Tablet: Store at room temperature.

ReconstitutionFor preparation at time of dispensing, add 48 mL incrementally to 60 mL bottle; shake vigorously. Resulting suspension is 20 mg/mL (100 mg per 5 mL).
ContraindicationsHypersensitivity to nitazoxanide or any component of the formulation
Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- HIV: Safety and efficacy have not been established in patients with HIV infection.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Immunocompromised patients: Safety and efficacy have not been established in patients with immunodeficiency.
- Pediatrics:

  Oral suspension: Safety and efficacy have not been established in children <1 year of age.

  Tablet: Safety and efficacy have not been established in children <12 years of age.

Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsRates of adverse effects were similar to those reported with placebo.

1% to 10%:

Central nervous system: Headache (1% to 3%)

Gastrointestinal: Abdominal pain (7% to 8%), diarrhea (2% to 4%), nausea (3%), vomiting (1%)

<1% (Limited to important or life-threatening): Allergic reaction, ALT increased, anemia, anorexia, appetite increased, creatinine increased, diaphoresis, dizziness, eye discoloration (pale yellow), fever, flatulence, hypertension, infection, malaise, nausea, pruritus, rhinitis, salivary glands enlarged, tachycardia, urine discoloration

Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb InteractionsFood: Food increases AUC.
Patient EducationAdminister exactly as directed. Do not alter dose; administer with food. Shake suspension well before using. Store at

room temperature and discard any unused portion of suspension after 7 days. May cause headache, abdominal pain, diarrhea, or vomiting. If severe or persistent, contact prescriber. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for suspension, oral: 100 mg/5 mL (60 mL) [contains sucrose 1.48 g/5 mL, sodium benzoate; strawberry flavor]

Tablet: 500 mg

Alinia® 3-Day Therapy Packs™ [unit-dose pack]: 500 mg (6s)

Generic AvailableNo
ManufacturerRomark Laboratories
Pricing: U.S. (www.drugstore.com)

Tablets (Alinia)

500 mg (60): $1233.31

Mechanism of ActionNitazoxanide is rapidly metabolized to the active metabolite tizoxanide *in vivo*. Activity may be due to interference with the pyruvate:ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction which is essential to anaerobic metabolism. *In vitro*, nitazoxanide and tizoxanide inhibit the growth of sporozoites and oocysts of *Cryptosporidium parvum* and trophozoites of *Giardia lamblia*.

Pharmacodynamics/Kinetics

Protein binding: Tizoxanide: >99%

Bioavailability: Relative bioavailability of suspension compared to tablet: 70%

Metabolism: Hepatic, to an active metabolite, tizoxanide. Tizoxanide undergoes conjugation to form tizoxanide glucuronide. Nitazoxanide is not detectable in the serum following oral administration.

Time to peak, plasma: Tizoxanide and tizoxanide glucuronide: 1-4 hours

Excretion: Tizoxanide: Urine, bile, and feces; Tizoxanide glucuronide: Urine and bile

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay rarely cause dizziness
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsNTZ
International Brand NamesAnelmin (PY); Annita (BR); Celectan (CO, EC, VE); Colufase (PE); Daxon (MX); Dexidex (MX); Heliton (AR); Kidonax (MX); Nodik (GT); Pacovanton (MX); Paramix (MX); Repinox (CR, DO, GT, HN, NI, PA, SV)

Nitisinone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(ni TIS i known)

U.S. Brand NamesOrfadin®

Pharmacologic Category4-Hydroxyphenylpyruvate Dioxygenase Inhibitor

Use: Labeled IndicationsTreatment of hereditary tyrosinemia type 1 (HT-1); to be used with dietary restriction of tyrosine and phenylalanine

Dosing: Adults**Note:** Must be used in conjunction with a low protein diet restricted in tyrosine and phenylalanine.

HT-1: Oral: Initial: 1 mg/kg/day in divided doses, given in the morning and evening, 1 hour before meals; doses do not need to be divided evenly

Dose adjustment: If biochemical parameters (see Monitoring Laboratory Tests) are not normalized within in 1-month period, dose may be increased to 1.5 mg/kg/day (maximum dose: 2 mg/kg/day).

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Must be used in conjunction with a low protein diet restricted in tyrosine and phenylalanine.

HT-1: Oral: Infants and Children: Refer to adult dosing. Infants may require maximal dose once liver function has improved.

Administration: OralAdminister 1 hour prior to a meal. Capsules may be opened and contents suspended in a small quantity of water, formula, or apple sauce; use immediately.

Dietary ConsiderationsBecause the effect of food is unknown, nitisinone should be taken 1 hour prior to a meal. Dietary restriction of tyrosine and phenylalanine is required.

StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F).

RestrictionsDistributed by Rare Disease Therapeutics, Inc (contact 615-399-0700)

ContraindicationsThere are no contraindications listed within the manufacturer's labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Hematologic effects: Transient leukopenia and/or thrombocytopenia may occur.

Other warnings/precautions:

- Dietary restrictions: Must be used with dietary restriction of tyrosine and phenylalanine; inadequate restriction can result in toxic effects to the eyes, skin, and nervous system (nutritional consultation required).

- Experienced physician: For use by physicians experienced in treating HT-1.

- Eye examination: Patients should have slit-lamp examination of the eyes prior to beginning treatment.

- Monitoring: Careful monitoring of liver, platelet and white blood cell counts, plasma tyrosine levels and other recommended laboratory parameters are required.

Pregnancy Risk FactorC

Pregnancy ConsiderationsSafety and efficacy have not been established for pregnant women; use only if potential benefit to the mother outweighs possible risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Dermatologic: Alopecia (1%), dry skin (1%), exfoliative dermatitis (1%), maculopapular rash (1%), pruritus (1%)

Hematologic: Thrombocytopenia (3%), leukopenia (3%), porphyria (1%), epistaxis (1%)

Hepatic: Hepatic neoplasm (8%), hepatic failure (7%)

Ocular: Conjunctivitis (2%), corneal opacity (2%), keratitis (2%), photophobia (2%), cataracts (1%), blepharitis (1%), eye pain (1%)

<1%: Abdominal pain, amenorrhea, brain tumor, bronchitis, cyanosis, dehydration, diarrhea, enanthema, encephalopathy, gastritis, gastroenteritis, gastrointestinal hemorrhage, headache, hepatic dysfunction, hepatomegaly, hyperkinesias, infection, liver enzymes increased, melena, nervousness, otitis, pathologic fracture, respiratory insufficiency, seizure, septicemia, somnolence, thirst, tooth discoloration

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsFood: Effect of taking with food is unknown. Tyrosine toxicity can occur without proper dietary restriction of tyrosine and phenylalanine.

Monitoring Parameters

Dietary tyrosine and phenylalanine

Liver: Ultrasound, computerized tomography, magnetic resonance imaging

Ophthalmic exam: Slit-lamp examination prior to treatment; repeat during therapy in patients with photophobia, eye pain, redness, swelling, or burning of the eyes.

Plasma tyrosine: Levels should be kept <500 µmol/L to avoid toxicity.

Plasma succinylacetone: May take up to 3 months to normalize after start of therapy

Platelets, white blood cell counts

Serum alpha-fetoprotein: To monitor effectiveness of treatment and potential liver neoplasia.

Serum phosphate in patients with renal dysfunction

Urine succinylacetone: Should not be detectable during treatment; dose should be increased if detectable after the first month of treatment.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 2 mg, 5 mg, 10 mg

Generic AvailableNo

ManufacturerSwedish Orphan International AB

Mechanism of ActionIn patients with HT-1, tyrosine metabolism is interrupted due to a lack of the enzyme (fumarylacetoacetate hydrolase) needed in the last step of tyrosine degradation. Toxic metabolites of tyrosine accumulate and cause liver and kidney toxicity. Nitisinone competitively inhibits 4-hydroxyphenyl-pyruvate dioxygenase, an enzyme needed earlier in the tyrosine degradation pathway, and therefore prevents the build-up of the damaging metabolites.

Pharmacodynamics/KineticsLimited pharmacokinetic studies in children or HT-1 patients.

Bioavailability: Animal studies: >90%

Half-life elimination: Terminal: Male: Healthy: 54 hours

Time to peak: 3 hours

Excretion (animal studies): Urine

Pharmacotherapy PearlsUse has been associated with increased 2- to 4-year survival probabilities of HT-1 and lower risk of early onset hepatic failure.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause nervousness

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia and thrombocytopenia; use caution with clozapine, carbamazepine, and valproic acid

International Brand NamesOrfadin (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR, TW)

Nitrazepam

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(nye TRA ze pam)

Canadian Brand NamesApo-Nitrazepam®; Mogadon; Nitrazadon; Nitrazepam (Pro-Doc); Sandoz-Nitrazepam

Pharmacologic CategoryBenzodiazepine

Use: Labeled IndicationsShort-term management of insomnia; treatment of myoclonic seizures

Dosing: Adults**Insomnia:** Oral: 5-10 mg at bedtime; treatment should not exceed 7-10 consecutive days; use for more than 2-3 consecutive weeks requires complete re-evaluation of patient

Dosing: ElderlyInsomnia: Elderly or debilitated patients: Oral: 2.5-5 mg at bedtime

Dosing: Pediatric**Myoclonic seizures:** Children ≤30 kg: Oral: 0.3-1 mg/kg/day in 3 divided doses

Administration: OralAdminister at bedtime; tablets may be swallowed whole, crushed, or dissolved in liquid

StorageStore at room temperature. Protect from light and moisture.

RestrictionsCDSA IV; Not available in U.S.

ContraindicationsHypersensitivity to nitrazepam or any component of the formulation (cross sensitivity with other benzodiazepines may exist); myasthenia gravis; narrow-angle glaucoma; severe respiratory insufficiency; sleep apnea syndrome; severe hepatic insufficiency

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Nitrazepam may induce anterograde amnesia; caution patients to ensure they have uninterrupted sleep of 7-8 hours after ingestion of dose.
- Aspiration pneumonia: Bronchial hypersecretion and excessive salivation/drooling leading to aspiration pneumonia in young and elderly patients may occur rarely.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in debilitated patients
- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury.
- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.
- Pediatrics: Associated with sudden death in children <5 years of age being treated for seizure disorders. Use should be restricted to children unresponsive to other antiepileptic agents. Safety and efficacy for use as a hypnotic not established in children <18 years of age.
- Pregnancy: Safety and efficacy in pregnancy and lactation have not been established.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.
- Hypnotic: Appropriate use: Should be used only after evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric or medical illness. A worsening of insomnia or the emergence of new

abnormalities of thought or behavior may represent unrecognized psychiatric or medical illness and requires immediate and careful evaluation.

- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsSince this medication has a moderately-long half-life, it is not a drug of choice for use in the elderly.

Pregnancy ConsiderationsNot recommended; crosses placenta: Benzodiazepine use during pregnancy is associated with increased risks of congenital malformations. Hypotonia, lethargy, feeding problems, and withdrawal symptoms have been reported with benzodiazepine use near time of delivery.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsClinical effects on the infant include sedation. With respect to other benzodiazepines, AAP reports that USE MAY BE OF CONCERN.

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension, palpitation

Central nervous system: Agitation, aggressiveness, amnesia, ataxia, confusion, delusions, disorientation, dizziness, fatigue, hallucination, hangover, headache, irritability, nightmares, psychoses, rage, restlessness, sedation

Dermatologic: Rash

Endocrine & metabolic: Changes in libido

Gastrointestinal: Constipation, diarrhea, excessive salivation, heartburn, nausea, vomiting

Hematologic: Granulocytopenia, leukopenia

Neuromuscular & skeletal: Falling, muscle weakness

Ocular: Blurred vision, double vision

Otic: Tinnitus (associated with withdrawal)

Respiratory: Aspiration, bronchial hypersecretion, dyspnea

Drug Interactions

CNS depressants: Sedative effects and/or respiratory depression may be additive with CNS depressants; includes ethanol, barbiturates, opioid analgesics, and other sedative agents; monitor for increased effect.

Theophylline (and related compounds): May partially antagonize some of the effects of benzodiazepines; monitor for decreased response; may require higher doses for sedation.

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, kava kava, St John’s wort, gotu kola (may increase CNS depression).

Test InteractionsNitrazepam can cause a false elevation (about 15%) of clozapine serum levels

Monitoring ParametersRespiratory and cardiovascular status

Reference RangeSteady state levels after 4 days: 40 ng/mL

Nursing: Physical Assessment/MonitoringMonitor therapeutic response and adverse reactions at the beginning and periodically throughout therapy. May cause hypotension. Monitor blood pressure periodically. Assess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Patient EducationInform prescriber of all prescription medications, OTC medications, or herbal products you are taking. Take as directed; this drug can be habit-forming. If taken for an extended period of time, do not stop taking medications abruptly. Consult your prescriber. Sedative effects may be additive when taken with other CNS depressants such as pain medications, antihistamines, sedatives, or hypnotics. Avoid alcohol use. Do not take any new medications without consulting prescriber. Only take this medication when you can plan to have 7-8 hours of uninterrupted sleep. May cause sedation, excitation, headache, nightmares, dizziness, fatigue, muscle weakness (use caution when driving or engaging in activities requiring alertness until response to drug is known), or changes in libido. Report continued insomnia; rapid heart beat; CNS effects such as hallucinations, psychoses, confusion, impaired coordination, or changes in personality; changes in your vision, hearing, or speech; or difficulty breathing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet:

Apo-Nitrazepam® [CAN], Mogadon [CAN], Nitrazadon [CAN], Nitrazepam [CAN], Sandoz-Nitrazepam [CAN]: 5 mg, 10 mg [not available in the U.S.]

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the CNS, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Onset of action: 20-50 minutes

Absorption: Rapid

Distribution: V_d: 2.4 L/kg, Elderly: 4.8 L/kg; also distributes into CSF, saliva, placenta

Protein binding: 87%

Metabolism: Hepatic: Nitroreduction, acetylation; no active metabolites

Bioavailability: ~80%

Half-life elimination: 30 hours, Elderly/ill patients: 40 hours

Time to peak, plasma: 2-3 hours

Excretion: Urine (65% to 70%, ~1% as unchanged drug); feces (14% to 20%)

Pharmacotherapy PearlsAbrupt discontinuation after sustained use may cause withdrawal symptoms.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Excessive salivation has been reported. The mechanism of this effect is unknown, since many benzodiazepines cause xerostomia rather than salivation excess.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions.

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Nitrazepam is a long half-life benzodiazepine. Duration of action after a single dose is determined by redistribution rather than metabolism. Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle-relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include alcohol abuse, personality disorders in the patient or the patient's parent(s).

Nitrazepam is contraindicated in patients with sleep apnea and myasthenia gravis and should not be used alone to treat psychosis or depression. Concomitant use with psychotropics may produce additive sedative effects. Benzodiazepines have been associated with anterograde and retrograde amnesia.

Index TermsNitrozepamum

International Brand NamesAlodorm (AU); Alozepam (AU); Apodorm (NO, SE); Arem (ZA); Berlidorm (BG); Dormalon (DE); Dumolid (ID); Eunoctin (HN); Hipnax (PT); Hypnotex (IN); Imeson (DE); Insoma (NZ); Insomin (FI); Mogadon (AT, AU, BE, CH, DK, FR, HK, IT, MY, NL, NO, PK, SE, SG, TW); Nitavan (IN); Nitrados (NZ, PH); Nitrapan (BR); Nitravet (IN); Nitrazepam (PL); Nitrazepol (BR); Novanox (DE); Numbon (IL); Onirema (VE); Ormodon (ZA); Paxadorm (ZA); Radedorm (EE); Rohypnol (PL)

Nitric Oxide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(NYE trik OKS ide)
U.S. Brand NamesINOmax®
Canadian Brand NamesINOmax®
Pharmacologic CategoryVasodilator, Pulmonary
Use: Labeled IndicationsTreatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with pulmonary hypertension; used concurrently with ventilatory support and other agents
Use: Unlabeled/InvestigationalTreatment of adult respiratory distress syndrome (ARDS)
Dosing: PediatricNeonates (up to 14 days old): Inhalation: 20 ppm. Treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from therapy. In the CINRGI trial, patients whose oxygenation improved had their dose reduced to 5 ppm at the end of 4 hours of treatment. Doses above 20 ppm should not be used because of the risk of methemoglobinemia and elevated NO_2.
Administration: InhalationIn the ventilated neonate, precise monitoring of inspired nitric oxide and NO_2 should be instituted using a calibrated analysis device with alarms. Sample gas for analysis should be drawn before the Y-piece, proximal to the patient. In addition, oxygen levels should be measured. A backup delivery system should be available in the event of power failure. Do not discontinue abruptly.
StorageStore at 25°C (77°C).
ContraindicationsHypersensitivity to nitric oxide or any component of the formulation; neonates dependent on right-to-left shunting of blood
Warnings/Precautions

Other warnings/precautions:

- Abrupt discontinuation: May lead to worsening hypotension, oxygenation, and increasing pulmonary artery pressure (PAP).
- Appropriate use: Doses above 20 ppm should not be used because of the increased risk of methemoglobinemia and elevated nitrogen dioxide (NO_2) levels. Methemoglobin levels and NO_2 should be monitored.
- Lack of response: Worsening oxygenation and increasing PAP may occur in patients who do not respond.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
LactationExcretion in breast milk unknown
Breast-Feeding ConsiderationsNitric oxide is not indicated for use in adults.
Adverse Reactions

>10%:

Cardiovascular: Hypotension (13%)

Miscellaneous: Withdrawal syndrome (12%)

1% to 10%:

Dermatologic: Cellulitis (5%)

Endocrine & metabolic: Hyperglycemia (8%)

Genitourinary: Hematuria (8%)

Respiratory: Atelectasis (9% - same as placebo), stridor (5%)

Miscellaneous: Sepsis (7%), infection (6%)

Postmarketing and/or case reports: Headache (environmental exposure, eg, hospital staff); hypoxemia; pulmonary edema (in CREST syndrome patients)

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersRespiratory status including arterial blood gases with close attention to PaO_2, methemoglobin, NO_2 , vital signs, blood sugar, signs and symptoms of infection.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gas, for inhalation:

100 ppm [nitric oxide 0.01% and nitrogen 99.99%] (353 L) [delivers 344 L], (1963 L) [delivers 1918 L]

800 ppm [nitric oxide 0.08% and nitrogen 99.92%] (353 L) [delivers 344 L], (1963 L) [delivers 1918 L]

Generic AvailableNo

ManufacturerINO Therapeutics

Mechanism of ActionIn neonates with persistent pulmonary hypertension, nitric oxide improves oxygenation. Nitric oxide relaxes vascular smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3',5'-monophosphate, which leads to vasodilation. When inhaled, pulmonary vasodilation occurs and an increase in the partial pressure of arterial oxygen results. Dilation of pulmonary vessels in well ventilated lung areas redistributes blood flow away from lung areas where ventilation/perfusion ratios are poor.

Pharmacodynamics/Kinetics

Absorption: Systemic after inhalation

Metabolism: Nitric oxide combines with hemoglobin that is 60% to 100% oxygenated. Nitric oxide combines with oxyhemoglobin to produce methemoglobin and nitrate. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite respectively, which interact with oxyhemoglobin to then produce methemoglobin and nitrate. At 80 ppm the methemoglobin percent is ~5% after 8 hours of administration. Methemoglobin levels >7% were attained only in patients receiving 80 ppm.

Excretion: Urine (as nitrate)

Clearance: Nitrate: At a rate approaching the glomerular filtration rate

Pharmacotherapy PearlsElevations in methemoglobin and nitrogen dioxide may be signs of overdose. Elevated nitrogen dioxide may cause acute lung injury and elevations of methemoglobin reduce the oxygen delivery capacity of the circulation. NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of or discontinuing INOmax®. Methemoglobinemia that does not resolve with dosage reduction or discontinuation of therapy may require intravenous vitamin C, intravenous methylene blue, or blood transfusion, depending on the clinical situation.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

American Academy of Pediatrics, Committee on Fetus and Newborn, “Use of Inhaled Nitric Oxide,” *Pediatrics*, 2000, 106(2 Pt 1):344-5. [PubMed 10920164]

Davidson D, Barefield ES, Kattwinkel J, et al, “Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the Term Newborn: A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study: I-NO/PPHN Study Group.” *Pediatrics*, 1998, 101(3 Pt 1):325-34. [PubMed 9480993]

“Inhaled Nitric Oxide in Full-Term and Nearly Full-term Infants With Hypoxic Respiratory Failure.” The Neonatal Inhaled Nitric Oxide Study Group, *N Engl J Med*, 1997, 336(9):597-604.

International Brand NamesINOmax (CH, CZ, DK, EE, ES, FR, NO, SE)

Nitrofurantoin

Lexi-Drugs Online

English English

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Medication Safety Issues

International issues:

Macrobid® may be confused with Mikrozid® which is a brand name for ethanol/propanol combination in Great Britain

Pronunciation(nye troe fyoor AN toyn)
U.S. Brand NamesFuradantin®; Macrobid®; Macrodantin®
Canadian Brand NamesApo-Nitrofurantoin®; Macrobid®; Macrodantin®; Novo-Furantoin
Pharmacologic CategoryAntibiotic, Miscellaneous
Use: Labeled IndicationsPrevention and treatment of urinary tract infections caused by susceptible strains of *E. coli*, *S. aureus, Enterococcus, Klebsiella,* and *Enterobacter*
Dosing: Adults

UTI treatment:

Furadantin®, Macrodantin®: Oral: 50-100 mg/dose every 6 hours; administer for 7 days or at least 3 days after obtaining sterile urine

Macrobid®: Oral: 100 mg twice daily for 7 days

UTI prophylaxis (Furadantin®, Macrodantin®): Oral: 50-100 mg/dose at bedtime

Dosing: ElderlyRefer to adult dosing (see Geriatric Considerations).
Dosing: Pediatric

UTI treatment:

Children >1 month (Furadantin®, Macrodantin®): Oral: 5-7 mg/kg/day in divided doses every 6 hours (maximum: 400 mg/day). Administer for 7 days or at least 3 days after obtaining sterile urine.

Children >12 years (Macrobid®): Oral: Refer to adult dosing.

UTI prophylaxis: Children >1 month (Furadantin®, Macrodantin®): Oral: 1-2 mg/kg/day in divided doses every 12-24 hours (maximum: 100 mg/day)

Dosing: Renal Impairment

Cl_{cr} <60 mL/minute: Contraindicated

Contraindicated in hemo- and peritoneal dialysis and continuous arteriovenous or venovenous hemofiltration.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister with meals to improve absorption and decrease adverse effects; suspension may be mixed with water, milk, fruit juice, or infant formula. Shake suspension well before use.
StorageStore at room temperature 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to nitrofurantoin or any component of the formulation; renal impairment (anuria, oliguria, significantly elevated serum creatinine, or Cl_{cr}< 60 mL/minute); infants <1 month (due to the possibility of hemolytic anemia); pregnancy at term (38-42 weeks gestation), during labor and delivery, or when the onset of labor is imminent
Allergy Considerations

- Furantoin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hepatic reactions: Rare, but severe hepatic reactions have been associated with use (onset may be insidious); discontinue immediately if hepatitis occurs.

- Peripheral neuropathy: Has been associated with peripheral neuropathy (rare); risk may be increased by renal impairment, diabetes, vitamin B deficiency, or electrolyte imbalance; use caution.

- Pulmonary toxicity: Acute, subacute, or chronic (usually after 6 months of therapy) pulmonary reactions have been observed; if these occur, discontinue therapy immediately. Monitor closely for malaise, dyspnea, cough, fever, radiologic evidence of diffuse interstitial pneumonitis or fibrosis.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Anemia: Use with caution in patients with anemia.

- Renal impairment: Therapeutic concentrations are not attained in urine of patients with Cl_{cr}<60 mL/minute.

Special populations:

- G6PD deficiency: Use with caution in patients with G6PD deficiency .

- Pediatrics: Safety and efficacy have not been established in children <1 month of age.

Geriatric ConsiderationsBecause of nitrofurantoin's decreased efficacy in patients with a Cl_{cr} <60 mL/minute and its side effect profile, it is not an antibiotic of choice for acute or prophylactic treatment of urinary tract infections in the elderly. An increased rate of severe hepatic toxicity has been suggested by postmarketing reports.

Pregnancy Risk FactorB (contraindicated at term)

Pregnancy ConsiderationsTeratogenic effects have not been observed in animal studies, however, may cause hemolytic anemia in infants. Use of nitrofurantoin is contraindicated at term (38-42 weeks gestation), during labor and delivery, or when the onset of labor is imminent.

LactationEnters breast milk/not recommended (infants <1 month); AAP rates “compatible”

Breast-Feeding ConsiderationsExcreted in trace amounts in breast milk; may cause hyperbilirubinemia or hemolytic anemia in infants (<1 month of age). AAP rates “compatible.” Use caution in G6PD deficiency.

Adverse ReactionsFrequency not defined.

Cardiovascular: Chest pain, cyanosis, ECG changes

Central nervous system: Bulging fontanels (infants), chills, confusion, depression, dizziness, drowsiness, fever, headache, malaise, pseudotumor cerebri, psychotic reaction, vertigo

Dermatologic: Alopecia, angioedema, erythema multiforme, exfoliative dermatitis, pruritus, rash (eczematous, erythematous, maculopapular), Stevens-Johnson syndrome, urticaria

Gastrointestinal: Abdominal pain, *C. difficile* colitis, constipation, diarrhea, dyspepsia, flatulence, nausea, pancreatitis, sialadenitis, vomiting

Hematologic: Agranulocytosis, eosinophilia, granulocytopenia, hemolytic anemia, leukopenia, megaloblastic anemia, thrombocytopenia

Hepatic: Cholestasis, hepatitis, hepatic necrosis, transaminases increased, jaundice (cholestatic)

Neuromuscular & skeletal: Arthralgia, myalgia, numbness, paresthesia, peripheral neuropathy, weakness

Ocular: Amblyopia, nystagmus, optic neuritis

Respiratory: Cough, dyspnea, pneumonitis, pulmonary fibrosis (with long-term use), pulmonary infiltration

Miscellaneous: Anaphylaxis, hypersensitivity (including acute pulmonary hypersensitivity), lupus-like syndrome

Drug Interactions

Norfloxacin: Nitrofurantoin may diminish the therapeutic effect of Norfloxacin. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Nitrofurantoin serum concentrations may be increased if taken with food.

Test InteractionsFalse-positive urine glucose (Benedict's and Fehling's methods); no false positives with enzymatic tests

Monitoring ParametersSigns of pulmonary reaction, signs of numbness or tingling of the extremities, periodic liver function tests

Nursing: Physical Assessment/MonitoringAssess allergy history and renal status prior to beginning therapy. Assess results of laboratory tests, therapeutic effectiveness, and adverse response. Advise patients with diabetes about use of Clinitest® (may cause false-positive urine glucose). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC, periodic liver function. Perform culture and sensitivity prior to initiating therapy.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take entire prescription, even if you are feeling better. Take with food. Suspension may be mixed with water, milk, fruit juice, or infant formula. Shake suspension well before use. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, drug may cause false test results with Clinitest® urine glucose monitoring; use of another type of glucose monitoring is preferable. May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report immediately and rash; swelling of face, tongue, mouth, or throat; or chest tightness. Report if condition being treated worsens or does not improve by the time prescription is completed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule [macrocrystal]: 50 mg, 100 mg

Macrodantin®: 25 mg, 50 mg, 100 mg

Capsule [macrocrystal/monohydrate]: 100 mg [nitrofurantoin macrocrystal 25% and nitrofurantoin monohydrate 75%]

Macrobid®: 100 mg [nitrofurantoin macrocrystal 25% and nitrofurantoin monohydrate 75%]

Suspension, oral:

Furadantin®: 25 mg/5 mL (470 mL)

Generic AvailableYes: Excludes suspension

Pricing: U.S. (www.drugstore.com)

Capsules (Macrobid)

100 mg (20): $49.99

Capsules (Macrodantin)

25 mg (30): $36.99

50 mg (30): $45.99

100 mg (30): $68.99

Capsules (Nitrofurantoin Macrocrystal)

50 mg (30): $27.99

100 mg (30): $56.27

Capsules (Nitrofurantoin Monohyd Macro)

100 mg (20): $26.99

Suspension (Furadantin)

25 mg/5 mL (60): $77.04

Mechanism of ActionInhibits several bacterial enzyme systems including acetyl coenzyme A interfering with metabolism and possibly cell wall synthesis

Pharmacodynamics/Kinetics

Absorption: Well absorbed; macrocrystalline form absorbed more slowly due to slower dissolution (causes less GI distress)

Distribution: V_d: 0.8 L/kg; crosses placenta; enters breast milk

Protein binding: 60% to 90%

Metabolism: Body tissues (except plasma) metabolize 60% of drug to inactive metabolites

Bioavailability: Increased with food

Half-life elimination: 20-60 minutes; prolonged with renal impairment

Excretion:

Suspension: Urine (40%) and feces (small amounts) as metabolites and unchanged drug

Macrocrystals: Urine (20% to 25% as unchanged drug)

Related Information

- Antacid Drug Interactions
- Antimicrobial Drugs of Choice

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with anticholinergic/antiparkinsonian medications may increase the absorption of nitrofurantoin

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“Practice Parameter: The Diagnosis, Treatment, and Evaluation of the Initial Urinary Tract Infection in Febrile Infants and Young Children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection,” *Pediatrics*, 1999, 103(4 Pt 1):843-52.[PubMed 10103321]

International Brand NamesChemiofurin (ES); Furadantin (AT, CH, GB, IE, IN, IT, NO, SE, ZA); Furadantina (AR, CN, MX, PT); Furadantine (LU, NL); Furadantine MC (BE); Furadin (PK); Furadina (VE); Furadoine (FR); Furanpur (UY); Furantoina (DO, ES); Furobactina (ES); Infurin (PE); Macrodantin (AU, IL, PH); Macrodantina (BR, CO, MX); Macrodin (CY); Macrofuran (ID); Micturol Simple (ES); Nifuran (NZ); Nifurantin (CZ); Nifuratio (PL); Nifuratio Retard (PL); Nifuryl (EC); Nitrofurantoin ”Dak” (DK); Nitrofurantoin-ratiopharm (LU); Orafuran (BG); Piyeloseptyl (PL); Siraliden (PL); Tanding (CL); Uro-tablinen (DE); Urofuran (FI); Urotoina (PY); Uvamin (IL); Uvamin 1 (GT, HN, NI, PA, SV); Uvamin Retard (CR, TT)

Nitroglycerin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Nitroglycerin may be confused with nitroprusside

Nitro-Bid® may be confused with Nicobid®

Nitroderm may be confused with NicoDerm®

Nitrol® may be confused with Nizoral®

Nitrostat® may be confused with Nilstat®, nystatin

Nitroglycerin transdermal patches should be removed prior to defibrillation or MRI study.

International issues:

Nitrocor® [Chile and Italy] may be confused with Natrecor® which is a brand name for nesiritide in the U.S.

Nitrocor® [Chile and Italy] may be confused with Nutracort® which is a brand name for hydrocortisone in the U.S.

Nitro-Dur® may be confused with Nitrocor® [Chile and Italy]

Pronunciation(nye troe GLI ser in)

U.S. Brand NamesMinitran™; Nitrek® [DSC]; Nitro-Bid®; Nitro-Dur®; Nitrolingual®; NitroQuick®; Nitrostat®; NitroTime®

Canadian Brand NamesGen-Nitro; Minitran™; Nitro-Dur®; Nitroglycerin Injection, USP; Nitrol®; Nitrostat™; Rho®-Nitro; Transderm-Nitro®; Trinipatch® 0.2; Trinipatch® 0.4; Trinipatch® 0.6

Pharmacologic CategoryVasodilator

Use: Labeled IndicationsTreatment of angina pectoris; I.V. for congestive heart failure (especially when associated with acute myocardial infarction); pulmonary hypertension; hypertensive emergencies occurring perioperatively (especially during cardiovascular surgery)

Use: Unlabeled/InvestigationalEsophageal spastic disorders (sublingual)

Dosing: Adults**Note:** Hemodynamic and antianginal tolerance often develop within 24-48 hours of continuous nitrate administration. Nitrate-free interval (10-12 hours/day) is recommended to avoid tolerance development; gradually decrease dose in patients receiving NTG for prolonged period to avoid withdrawal reaction.

Angina/coronary artery disease:

Oral: 2.5-9 mg 2-4 times/day (up to 26 mg 4 times/day)

I.V.: 5 mcg/minute, increase by 5 mcg/minute every 3-5 minutes to 20 mcg/minute. If no response at 20 mcg/minute increase by 10 mcg/minute every 3-5 minutes, up to 200 mcg/minute.

Topical ointment: Include a nitrate free interval, ~10 to 12 hours; Apply 0.5" to 2" every 6 hours with a nitrate free interval.

Topical patch, transdermal: 0.2-0.4 mg/hour initially and titrate to doses of 0.4-0.8 mg/hour. Tolerance is minimized by using a patch-on period of 12-14 hours and patch-off period of 10-12 hours.

Sublingual: 0.2-0.6 mg every 5 minutes for maximum of 3 doses in 15 minutes; may also use prophylactically 5-10 minutes prior to activities which may provoke an attack.

Esophageal spastic disorders (unlabeled use): 0.3-0.4 mg 5 minutes before meals

Translingual: 1-2 sprays into mouth under tongue every 3-5 minutes for maximum of 3 doses in 15 minutes, may also be used 5-10 minutes prior to activities which may provoke an attack prophylactically.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Pulmonary hypertension: I.V. Continuous infusion: Children: Start 0.25-0.5 mcg/kg/minute and titrate by 1 mcg/kg/minute at 20- to 60-minute intervals to desired effect; usual dose: 1-3 mcg/kg/minute; maximum: 5 mcg/kg/minute

Note: Hemodynamic and antianginal tolerance often develop within 24-48 hours of continuous nitrate administration.

Calculations

- Nitroglycerin
- Nitroglycerin: Pediatrics

Administration: I.V.I.V. must be prepared in glass bottles and use special sets intended for nitroglycerin. Glass I.V. bottles and administration sets provided by manufacturer.

Administration: I.V. DetailNitroglycerin can be absorbed by plastic (polyvinyl chloride) tubing or containers. Infusion pump may not infuse accurately with different tubing. Be alert to potential for unregulated flow.

pH: 3.0-6.5

Administration: Oral

Sublingual: Do not crush sublingual product (tablet). Place under tongue and allow to dissolve.

Translingual spray: Do not shake container. Release spray onto or under tongue. Do not rinse the mouth for at least 5-10 minutes. Priming sprays should be directed away from patient and others. The end of the pump should be covered by the fluid in the bottle.

Nitrolingual®: Prime prior to first use (5 sprays into the air). If unused for 6 weeks, a single priming spray should be completed.

StorageDoses should be made in glass bottles, Excel® or PAB® containers. Adsorption occurs to soft plastic (eg, PVC). Nitroglycerin diluted in D_5W or NS in glass containers is physically and chemically stable for 48 hours at room temperature and 7 days under refrigeration. In D_5W or NS in Excel®/PAB® containers it is physically and chemically stable for 24 hours at room temperature and 14 days under refrigeration. Premixed bottles are stable according to the manufacturer's expiration dating. Store sublingual tablets and ointment in tightly closed containers at 15°C to 30°C. Store spray and transdermal patch at 25°C; excursions permitted to 15°C to 30°C (59°F to 86°F).

Reconstitution

Standard diluent: 50 mg/250 mL D_5W; 50 mg/500 mL D_5W.

Minimum volume: 100 mg/250 mL D_5W; concentration should not exceed 400 mcg/mL.

CompatibilityStable in D_5LR, $D_5{}^1/_2NS$, D_5NS, LR, ${}^1/_2NS$; **variable stability (consult detailed reference)** in D_5W, NS.

Y-site administration: Compatible: Alatrofloxacin, amiodarone, amphotericin B cholesteryl sulfate complex, atracurium, cisatracurium, diltiazem, dobutamine, dobutamine with dopamine, dobutamine with lidocaine, dobutamine with sodium nitroprusside, dopamine, dopamine with lidocaine, dopamine with sodium nitroprusside, epinephrine, esmolol, famotidine, fentanyl, fluconazole, furosemide, gatifloxacin, haloperidol, heparin, hydromorphone, inamrinone, insulin (regular), labetalol, lidocaine, lidocaine with sodium nitroprusside, linezolid, lorazepam, midazolam, milrinone, morphine, nicardipine, norepinephrine, pancuronium, propofol, ranitidine, remifentanil, sodium nitroprusside, streptokinase, tacrolimus, theophylline, thiopental, vecuronium, warfarin. **Incompatible:** Alteplase, levofloxacin. **Variable (consult detailed reference):** Hydralazine.

Compatibility in syringe: Compatible: Heparin.

Compatibility when admixed: Dose is variable and may require titration, therefore, it is not advisable to mix with other agents. **Compatible:** Alteplase, aminophylline, dobutamine, dopamine, enalaprilat, furosemide, lidocaine, verapamil. **Incompatible:** Hydralazine, phenytoin. **Variable (consult detailed reference):** Bretylium, dobutamine with sodium nitroprusside.

ContraindicationsHypersensitivity to organic nitrates; hypersensitivity to isosorbide, nitroglycerin, or any component of the formulation; concurrent use with phosphodiesterase-5 (PDE-5) inhibitors (sildenafil, tadalafil, or vardenafil); angle-closure glaucoma (intraocular pressure may be increased); head trauma or cerebral hemorrhage (increase intracranial pressure); severe anemia; allergy to adhesive (transdermal product)

Additional contraindications for I.V. product: Hypotension; uncorrected hypovolemia; inadequate cerebral circulation; constrictive pericarditis; pericardial tamponade

Allergy Considerations

- Nitrate Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypotension/bradycardia: Severe hypotension can occur; paradoxical bradycardia and increased angina pectoris can accompany hypotension. Orthostatic hypotension can also occur; ethanol can accentuate this. Use with caution in volume depletion, hypotension, and right ventricular infarctions.

Disease-related concerns:

- Hypertrophic cardiomyopathy: Use with caution in patients with hypertrophic cardiomyopathy; nitrates may reduce preload, exacerbating obstruction and cause hypotension and/or worsening of heart failure.

Concurrent drug therapy issues:

- PDE-5 inhibitors: Avoid concurrent use with PDE-5 inhibitors (eg, sildenafil, tadalafil, vardenafil).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Long-acting agents: Avoid use of long-acting agents in acute MI or HF; cannot easily reverse if adverse events develop.
- Transdermal patches: Patches should be removed prior to defibrillation or MRI study.

Other warnings/precautions:

- Tolerance: Appropriate dosing is needed to minimize tolerance development.

Geriatric ConsiderationsCaution should be used when using nitrate therapy in the elderly due to hypotension. Hypotension is enhanced in the elderly due to decreased baroreceptor response, decreased venous tone, and often hypovolemia (dehydration) or other hypotensive drugs.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

Frequency not always defined:

Cardiovascular: Hypotension (4%), postural hypotension, crescendo angina (2%), tachycardia, flushing, peripheral edema

Central nervous system: Headache (most common; 50% to 63%), lightheadedness (6%), syncope (4%), dizziness

Gastrointestinal: Nausea, vomiting, bowel incontinence, xerostomia

Genitourinary: Urinary incontinence

Ocular: Blurred vision

Miscellaneous: Diaphoresis

<1% (Limited to important or life-threatening): Allergic reactions, application site irritation (patch), cardiovascular collapse, exfoliative dermatitis, methemoglobinemia (rare; overdose), pallor, palpitation, rash, rebound hypertension, restlessness, shock, vertigo, weakness

Drug Interactions

Alteplase: Nitroglycerin may decrease the serum concentration of Alteplase. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Heparin: Nitroglycerin may diminish the anticoagulant effect of Heparin. Nitroglycerin may decrease the serum concentration of Heparin. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: May enhance the vasodilatory effect of Vasodilators (Organic Nitrates). *Risk X: Avoid combination*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rosiglitazone: Vasodilators (Organic Nitrates) may enhance the adverse/toxic effect of Rosiglitazone. Specifically, a greater risk of myocardial ischemia was reported for users of this combination in a meta-analysis. Management: Consider alternatives to this combination when possible. Rosiglitazone prescribing information states that the combination of rosiglitazone and a nitrate is not recommended. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase the hypotensive effects of nitroglycerin). Monitor.

Herb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (american), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may cause hypotension).

Monitoring ParametersBlood pressure, heart rate

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking (eg, heparin, ergot alkaloids, sildenafil, tadalafil, or vardenafil). See Administration specifics for different formulations. Evaluate therapeutic effectiveness (cardiac status) and adverse response (eg, hypotension, arrhythmias, CNS changes, GI disturbances). Dose should be reduced gradually when discontinuing after long-term therapy. Teach patient proper use (according to purpose and formulation), possible side effects/appropriate interventions (eg, drug-free intervals; removes transdermal patches for specific period of time), and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as per directions (see below). Do not change brands without consulting prescriber. Do not discontinue abruptly. Keep medication in original container, tightly closed. If anginal chest pain is unresolved in 15 minutes, seek emergency medical help at once. Daily use may cause dizziness or lightheadedness (use caution when driving or engaging in hazardous activities until response to drug is known); headache (consult prescriber for approved analgesic);

hypotension (use care when changing position from sitting or lying to standing, when climbing stairs or when engaging in tasks that are potentially hazardous until response to drug is known); GI disturbances (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report acute headache, rapid heartbeat, unusual restlessness or dizziness, muscular weakness, or blurred vision or seeing abnormal colors. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Oral: Take as directed. Do not chew or swallow sublingual tablets; allow to dissolve under tongue. Sit down before using sublingual or buccal tablet or spray form. Do not chew or crush extended release capsules; swallow with 8 oz of water.

Spray: Follow exact instructions in product insert. Spray directly on mucous membranes; do not inhale.

Topical: Spread prescribed amount thinly on applicator; rotate application sites.

Transdermal: Use as directed; place on hair-free area of skin, rotate sites (usually, patches will be removed for a period each day)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release: 2.5 mg, 6.5 mg, 9 mg

Nitro-Time®: 2.5 mg, 6.5 mg, 9 mg

Infusion [premixed in D_5W]: 25 mg (250 mL) [0.1 mg/mL]; 50 mg (250 mL) [0.2 mg/mL]; 50 mg (500 mL) [0.1 mg/mL]; 100 mg (250 mL) [0.4 mg/mL]; 200 mg (500 mL) [0.4 mg/mL]

Injection, solution: 5 mg/mL (5 mL, 10 mL) [contains ethanol and propylene glycol]

Ointment, topical:

Nitro-Bid®: 2% [20 mg/g] (1 g, 30 g, 60 g)

Solution, translingual [spray]:

Nitrolingual®: 0.4 mg/metered spray (4.9 g) [contains ethanol 20%; 60 metered sprays]; (12 g) [contains ethanol 20%; 200 metered sprays]; (16.9 g) [contains ethanol 20%; 260 metered sprays]

Tablet, sublingual: 0.3 mg, 0.4 mg, 0.6 mg

NitroQuick®, Nitrostat®: 0.3 mg, 0.4 mg, 0.6 mg

Transdermal system [once-daily patch]: 0.1 mg/hour (30s); 0.2 mg/hour (30s); 0.4 mg/hour (30s); 0.6 mg/hour (30s)

Minitran™: 0.1 mg/hour (30s); 0.2 mg/hour (30s); 0.4 mg/hour (30s); 0.6 mg/hour (30s)

Nitrek®: 0.2 mg/hour (30s); 0.4 mg/hour (30s); 0.6 mg/hour (30s) [DSC]

Nitro-Dur®: 0.1 mg/hour (30s); 0.2 mg/hour (30s); 0.3 mg/hour (30s); 0.4 mg/hour (30s); 0.6 mg/hour (30s); 0.8 mg/hour (30s)

Generic AvailableYes: Capsule, injection, patch, tablet

Pricing: U.S. (www.drugstore.com)

Capsule, controlled release (Nitroglycerin CR)

2.5 mg (30): $13.99

6.5 mg (30): $13.38

9 mg (30): $14.99

Ointment (Nitro-Bid)

2% (60): $19.99

2% (60): $27.95

Patch, 24-hour (Minitran)

0.1 mg/hour (30): $78.98

0.2 mg/hour (30): $79.09

0.4 mg/hour (30): $87.72

0.6 mg/hour (30): $94.88

Patch, 24-hour (Nitro-Dur)

0.1 mg/hour (30): $88.28

0.2 mg/hour (30): $99.72

0.3 mg/hour (30): $98.77

0.4 mg/hour (30): $110.57

0.6 mg/hour (30): $109.47

0.8 mg/hour (30): $110.56

Patch, 24-hour (Nitroglycerin)

0.1 mg/hour (30): $25.99

0.2 mg/hour (30): $28.99

0.4 mg/hour (30): $36.99

0.6 mg/hour (30): $39.99

Solution (Nitrolingual)

0.4 mg/spray (4.9): $113.87

0.4 mg/spray (12): $184.92

Sublingual (Nitroglycerin)

0.3 mg (100): $13.99

0.4 mg (100): $14.99

Sublingual (NitroQuick)

0.3 mg (100): $9.99

0.4 mg (25): $7.99

0.6 mg (100): $8.99

Sublingual (Nitrostat)

0.3 mg (100): $27.76

0.4 mg (25): $19.31

0.4 mg (100): $29.89

Sublingual (NitroTab)

0.4 mg (25): $8.99

Mechanism of ActionWorks by relaxation of smooth muscle, producing a vasodilator effect on the peripheral veins and arteries with more prominent effects on the veins. Primarily reduces cardiac oxygen demand by decreasing preload (left ventricular end-diastolic pressure); may modestly reduce afterload; dilates coronary arteries and improves collateral flow to ischemic regions

Pharmacodynamics/Kinetics

Onset of action: Sublingual tablet: 1-3 minutes; Translingual spray: 2 minutes; Sustained release: 20-45 minutes; Topical: 15-60 minutes; Transdermal: 40-60 minutes; I.V. drip: Immediate

Peak effect: Sublingual tablet: 4-8 minutes; Translingual spray: 4-10 minutes; Sustained release: 45-120 minutes; Topical: 30-120 minutes; Transdermal: 60-180 minutes; I.V. drip: Immediate

Duration: Sublingual tablet: 30-60 minutes; Translingual spray: 30-60 minutes; Sustained release: 4-8 hours; Topical: 2-12 hours; Transdermal: 18-24 hours; I.V. drip: 3-5 minutes

Protein binding: 60%

Metabolism: Extensive first-pass effect

Half-life elimination: 1-4 minutes

Excretion: Urine (as inactive metabolites)

Related Information

- Hemodynamic Support, Intravenous
- Hypertension
- Nitrates

Pharmacotherapy PearlsI.V. preparations contain alcohol and/or propylene glycol; may need to use nitrate-free interval (10-12 hours/day) to avoid tolerance development. Tolerance may possibly be reversed with acetylcysteine; gradually decrease dose in patients receiving NTG for prolonged period to avoid withdrawal reaction.

Concomitant use of sildenafil (Viagra®) or other phosphodiesterase-5 enzyme inhibitors (PDE-5) may precipitate acute hypotension, myocardial infarction, or death. Nitrates used in right ventricular infarction may induce acute hypotension. Nitrate use in severe pericardial effusion may reduce cardiac filling pressure and precipitate cardiac tamponade. In the management of heart failure, the combination of isosorbide dinitrate and hydralazine confers beneficial effects on disease progression and cardiac outcomes.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness

Mental Health: Effects on Psychiatric Treatment None reported, but monitor for hypotension if receiving a psychotropic

Cardiovascular Considerations Nitrates improve the balance between myocardial oxygen supply and demand, primarily by decreasing oxygen demand. Nitrates decreases myocardial oxygen demand by reducing preload via dilation of peripheral veins. Nitrates improve myocardial oxygen supply by dilating epicardial coronary arteries and collateral vessels, leaving resistance vessels alone. Nitrates are unlikely to induce a coronary steal syndrome. Nitrates improve exercise tolerance in stable angina patients. An adequate nitroglycerin-free period must be provided with all nitrate products to prevent nitrate tolerance from developing. In the treatment of unstable angina/non-ST-segment elevation MI, I.V. NTG is indicated for immediate relief of ischemia when sublingual nitroglycerin (tablet or spray) and intravenous beta-blocker have failed. I.V. NTG may also be of benefit in nonhypotensive high-risk patients. Caution should be observed if administering nitrates to individuals who are volume-depleted or are experiencing a right ventricular infarction. Additionally, nitrates should not be given to an individual who has received a phosphodiesterase-5 enzyme inhibitor within the past 24 hours. In a stabilized patient, intravenous nitroglycerin should be converted within 24 hours to a nonparenteral alternative in a regimen that is designed to prevent tolerance.

The 2004 STEMI guidelines suggest that healthcare providers should instruct patients, with sublingual nitroglycerin on hand, to take one dose sublingually in response to chest discomfort/pain. If chest pain is unimproved or worsening 5 minutes after the dose has been taken, the patient or family should call an ambulance. Use I.V. nitroglycerin for relief of ongoing ischemic discomfort (if S.L. nitroglycerin has been ineffective), control of hypertension, or management of pulmonary congestion. Nitrates should not be used if hypotension limits the addition of a beta-blocker.

Anesthesia and Critical Care Concerns/Other Considerations Nitroglycerin 5 mg/mL contains propylene glycol 518 mg/mL (30% v/v).

In the treatment of unstable angina/non-ST-segment elevation MI, nitroglycerin (sublingual tablet or spray), followed by intravenous administration, is recommended for immediate relief of ischemia and associated symptoms. Note that nitrate use may result in significant hypotension in individuals who are volume depleted.

Nitrate use in right ventricular infarction may induce acute hypotension. Nitrate use in severe pericardial effusion may reduce cardiac filling pressure and precipitate cardiac tamponade.

Index Terms Glyceryl Trinitrate; Nitroglycerol; NTG

References

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International Brand Names Anginine (AU); Angised (HR, SG); Deponit (CL, DE, HU, LU, MY, PE, PH); Deponit NT (HK); Deponit TTS 10 (IL); Deponit TTS 5 (IL); Diafusor (LU); Epinitril (FR); Glytrin Spray (NZ); Herzer (JP); Lenitral (HK); Lycinate (AU); Millisrol (JP); Minitran (AR, AU, CR, DO, GR, GT, HN, LU, PA, PH, PY, SV, UY, VE); Myovin (IN); Natispray (LU); Nit-Ret (CZ); Nitracor (PL); Nitradisc (BR, HK, LU, MX, PE, PT); Nitradisc TTS (GR); Nitriderm TTS (FR); Nitro (FI, HU); Nitro Dur TTS (CH); Nitro Mack (LU); Nitro Mack Retard (AE, AT, BH, CH, CY, CZ, EG, GR, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Nitro Pohl (HU); Nitro-Bid (AU, MY); Nitro-Dur (ES, HU, IT, NO, PL, PT); Nitro-Dur 10 (IL); Nitro-M-Bid (BE); Nitro-Mack (PL); Nitro-Pflaster (DE); Nitro-Pflaster-ratiopharm (LU); Nitrobaat (BE, NL); Nitrocard (PL); Nitrocerin (GR); Nitrocine (TW); Nitrocine 5 (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Nitrocontin (BF, BJ, CI, ET, GH, GM, GN, IE, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Nitrocontin Continus (AE, BH, CY, EG, IL, IN, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Nitrocor (IT, PT); Nitroderm TTS (AE, AR, AT, BB, BE, BF, BH, BJ, BM, BR, BS, BZ, CH, CI, CY, DE, EC, EG, ES, ET, GH, GM, GN, GY, HR, HU, IL, IN, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NZ, OM, PK, PL, PT, QA, SA, SC, SD, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Nitroderm TTS Ext (CZ); Nitroderm TTS-5 (CR, DO, GT, HN, NI, PA, SV); Nitrodisc (BB, BM, BS, BZ, GY, JM, MY, SR, TT); Nitrodor (CN); Nitrodyl (GR, LU); Nitrodyl TTS (GR); Nitroglycerinum (PL); Nitroglycerinum prolongatum (PL); Nitrokaf Forte (ID); Nitrokaf Retard (ID); Nitrol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PH, QA, SA, SY, YE); Nitrolingual (AT, BE, CH, DE, DK, GB, GR, HK, HN, HU, IE, LU, NL, PH, PT, SE); Nitrolingual Spray (KP, NZ, PH); Nitromack Retard (PY); Nitromex (DK, FI, NO, SE); Nitromint (HN, HU, PL, TH); Nitromint Aerosol (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Nitromint Retard (AE, BB, BH, BM, BS, BZ, CY, EG, GY, IL, IQ, IR, JM, JO, KW, LB, LY, OM, QA, SA, SR, SY, TT, YE); Nitronal (FR, IE); Nitronal Aqueous (PH); Nitronal Spray (FR); Nitrong (BE, FI, HN, LU); Nitrong Retard (AT, GR); Nitroplast (ES); Nitropront (FI); Nitrostat (HK, PH, TW); Nitrozell Retard (AT, NL); Nysconitrine (BE, LU); Percutol Oint. (GB, IE); Perlinganit (HU, KP, LU, PL); Ratiopharm (DE); Rectogesic (AU, FR); Suscard (GB, IE); Sustac (AE, BB, BH, BM, BS, BZ, CY, EG, GY, HR, HU, IL, IQ, IR, JM, JO, KW, LB, LY, OM, QA, SA, SR, SY, TT, YE); Sustonit (PL); Transiderm Nitro (AU, FI, HN, IE, NL, NO, SE); Trimonit (PL); Trinipatch (LU); Trinter (GB, IE); Venitrin (IT); Willlong (LU)

Nitroprusside

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Nitroprusside may be confused with nitroglycerin

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(nye troe PRUS ide)

U.S. Brand NamesNitropress®

Pharmacologic CategoryVasodilator

Use: Labeled IndicationsManagement of hypertensive crises; congestive heart failure; used for controlled hypotension to reduce bleeding during surgery

Dosing: Adults

Acute hypertension: I.V.: Initial: 0.3-0.5 mcg/kg/minute; increase in increments of 0.5 mcg/kg/minute, titrating to the desired hemodynamic effect or the appearance of headache or nausea; usual dose: 3 mcg/kg/minute; rarely need >4 mcg/kg/minute; maximum: 10 mcg/kg/minute. When >500 mcg/kg is administered by prolonged infusion of faster than 2 mcg/kg/minute, cyanide is generated faster than an unaided patient can handle.

Note: Administration requires the use of an infusion pump. Average dose: 5 mcg/kg/minute.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Pulmonary hypertension: I.V.: Children: Initial: 1 mcg/kg/minute by continuous I.V. infusion; increase in increments of 1 mcg/kg/minute at intervals of 20-60 minutes; titrating to the desired response; usual dose: 3 mcg/kg/minute, rarely need >4 mcg/kg/minute; maximum: 5 mcg/kg/minute.

Note: Administration requires the use of an infusion pump. Average dose: 5 mcg/kg/minute.

Dosing: Renal ImpairmentLimit use; accumulation of thiocyanate may occur.

Dosing: Hepatic ImpairmentLimit use; risk of cyanide toxicity.

Calculations

- Nitroprusside

Administration: I.V.I.V. infusion only, use only as an infusion with 5% dextrose in water. Infusion pump required. Not for direct injection.

Administration: I.V. DetailContinuously monitor patient's blood pressure.

pH: 3.5-6.0

Storage

Use only clear solutions; solutions of nitroprusside exhibit a color described as brownish, brown, brownish-pink, light orange, and straw. Solutions are highly sensitive to light. Exposure to light causes decomposition, resulting in a highly colored solution of orange, dark brown or blue. **A blue color indicates almost complete degradation and breakdown to cyanide.**

Solutions should be wrapped with aluminum foil or other opaque material to protect from light (do as soon as possible).

Stability of parenteral admixture at room temperature (25°C) and at refrigeration temperature (4°C) is 24 hours.

ReconstitutionBrownish solution is usable, discard if bluish in color. Nitroprusside sodium should be reconstituted freshly by diluting 50 mg in 250-1000 mL of D_5W.

CompatibilityStable in LR; **variable stability (consult detailed reference)** in D_5W, NS.

Y-site administration: Compatible: Atracurium, diltiazem, dobutamine, dobutamine with dopamine, dobutamine with lidocaine, dobutamine with nitroglycerin, dopamine, dopamine with lidocaine, dopamine with nitroglycerin, enalaprilat, esmolol, famotidine, heparin, inamrinone, indomethacin, insulin (regular), labetalol, lidocaine, lidocaine with nitroglycerin, midazolam, milrinone, morphine, nitroglycerin, pancuronium, propofol, tacrolimus, theophylline, vecuronium. **Incompatible:** Levofloxacin. **Variable (consult detailed reference):** Cisatracurium, haloperidol, TPN.

Compatibility in syringe: Compatible: Heparin.

Compatibility when admixed: Compatible: Cimetidine, enalaprilat, ranitidine, verapamil. **Incompatible:** Atracurium. **Variable (consult detailed reference):** Dobutamine with nitroglycerin.

ContraindicationsHypersensitivity to nitroprusside or any component of the formulation; treatment of compensatory hypertension (aortic coarctation, arteriovenous shunting); high output failure; congenital optic atrophy or tobacco amblyopia

Warnings/Precautions

Boxed warnings:

- Administration: See "Other warnings/precautions" below.
- Continuous monitoring: See "Other warnings/precautions" below.
- Cyanide toxicity: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Cyanide toxicity: **[U.S. Boxed Warning]: Except when used briefly or at low (<2 mcg/kg/minute) infusion rates, nitroprusside gives rise to large cyanide quantities. Do not use the maximum dose for more than 10 minutes; if blood pressure is not controlled then discontinue infusion. Monitor for cyanide toxicity via acid-base balance and venous oxygen concentration.**
- Thiocyanate toxicity: Can occur in patients with renal impairment or those on prolonged infusions.

Disease-related concerns:

- Increased intracranial pressure: Use with extreme caution in patients with elevated intracranial pressure.
- Hepatic impairment: Use with extreme caution in patients with hepatic impairment.
- Renal impairment: Use with extreme caution in patients with renal impairment; use the lowest end of the dosage range.

Other warnings/precautions:

- Administration: **[U.S. Boxed Warning]: Should not be administered by direct injection; must be further diluted with 5% dextrose in water.**
- Continuous monitoring: **[U.S. Boxed Warning]: Continuous blood pressure monitoring is needed.**

Geriatric ConsiderationsElderly patients may have an increased sensitivity to nitroprusside possibly due to a decreased baroreceptor reflex, altered sensitivity to vasodilating effects or a resistance of cardiac adrenergic receptors to stimulation by catecholamines.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown

Adverse Reactions1% to 10%:

Cardiovascular: Excessive hypotensive response, palpitation, substernal distress

Central nervous system: Disorientation, psychosis, headache, restlessness

Endocrine & metabolic: Thyroid suppression

Gastrointestinal: Nausea, vomiting

Neuromuscular & skeletal: Weakness, muscle spasm

Otic: Tinnitus

Respiratory: Hypoxia

Miscellaneous: Diaphoresis, thiocyanate toxicity

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Calcium Channel Blockers: May enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure, heart rate; monitor for cyanide and thiocyanate toxicity; monitor acid-base status as acidosis can be the earliest sign of cyanide toxicity; monitor thiocyanate levels if requiring prolonged infusion (>3 days) or dose ≥4 mcg/kg/minute or patient has renal dysfunction; monitor cyanide blood levels in patients with decreased hepatic function; cardiac monitor and blood pressure monitor required

Reference RangeMonitor thiocyanate levels if requiring prolonged infusion (>4 days) or ≥4 mcg/kg/minute; not to exceed 100 mcg/mL (or 10 mg/dL) plasma thiocyanate

Thiocyanate:

Therapeutic: 6-29 mcg/mL

Toxic: 35-100 mcg/mL

Fatal: >200 mcg/mL

Cyanide: Normal <0.2 mcg/mL; normal (smoker): <0.4 mcg/mL

Toxic: >2 mcg/mL

Potentially lethal: >3 mcg/mL

Nursing: Physical Assessment/MonitoringSee Administration and Reconstitution for infusion specifics and warnings. Infusion site must be monitored closely to prevent extravasation. Continuous patient monitoring (including blood pressure) is needed. Evaluate patient response and assess adverse reactions (eg, acid/base balance [metabolic acidosis is early sign of cyanide toxicity], disorientation, hypoxia, muscular twitching). Provide patient teaching according to patient condition.

Patient EducationPatient condition should indicate extent of education and instruction needed. This drug can only be given I.V. You will be monitored at all times during infusion. Promptly report any chest pain or pain/burning at site of infusion. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sodium: 25 mg/mL (2 mL)

Generic AvailableYes

Mechanism of ActionCauses peripheral vasodilation by direct action on venous and arteriolar smooth muscle, thus reducing peripheral resistance; will increase cardiac output by decreasing afterload; reduces aortal and left ventricular impedance

Pharmacodynamics/Kinetics

Onset of action: BP reduction <2 minutes

Duration: 1-10 minutes

Metabolism: Nitroprusside is converted to cyanide ions in the bloodstream; decomposes to prussic acid which in the presence of sulfur donor is converted to thiocyanate (hepatic and renal rhodanase systems)

Half-life elimination: Parent drug: <10 minutes; Thiocyanate: 2.7-7 days

Excretion: Urine (as thiocyanate)

Related Information

- Hemodynamic Support, Intravenous
- Hypertension

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause restlessness, disorientation, or psychosis

Mental Health: Effects on Psychiatric TreatmentNone reported, but monitor for hypotension if receiving a psychotropic

Cardiovascular ConsiderationsThiocyanate levels should be monitored if high doses are used for more than 24 hours, particularly in patients with renal dysfunction and hepatic dysfunction. Nitroprusside is a very effective agent for controlled blood pressure lowering because of the very short half-life. Reasonably accurate titrations, based on target blood pressure, can be achieved. Because of restricted cardiac output conditions, nitroprusside should be avoided in patients with aortic stenosis or coarctation. Nitroprusside should also be used cautiously in patients with acute myocardial infarction because of hemodynamic effects and possible coronary steal.

Acute Decompensated Heart Failure: Nitroprusside may also be useful for short-term afterload reduction in patients with acute decompensated heart failure. Patients with refractory end-stage heart failure, once stabilized, should be switched to an oral regimen that can maintain symptomatic improvement and reduce the risk of subsequent deterioration if possible.

Anesthesia and Critical Care Concerns/Other ConsiderationsElderly patients may have an increased sensitivity to nitroprusside possibly due to a decreased baroreceptor reflex, altered sensitivity to vasodilating effects or a resistance of cardiac adrenergic receptors to stimulation by catecholamines.

Thiocyanate levels should be monitored if high doses are used for more than 24 hours. Nitroprusside may also be useful for afterload reduction in patients with severe heart failure. Nitroprusside should be avoided in patients with aortic stenosis or coarctation. Nitroprusside should also be used cautiously in patients with acute myocardial infarction, because of hemodynamic effects and possible coronary steal.

Management of Intracerebral Hemorrhage (ICH): Rapid identification of patients experiencing ICH is essential and should be considered a medical emergency due to the progressive deterioration, severe clinical deficits, and high mortality and morbidity. Treatment for ICH has evolved rapidly in recent years. According to the 2007 ACC/AHA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults, patients with ICH should be treated in a balanced and graded approach with therapies that reduce intracranial pressure (ICP) (eg, mannitol, hypertonic saline solutions, barbiturate coma, head of bed elevation) (Class IIa recommendation). Direct monitoring of ICP and central perfusion pressure (CPP) may be necessary if patient is treated more aggressively. Treatment of ICH with recombinant factor VIIa (rFVIIa) within the first 3-4 hours after onset to slow progression of bleeding has shown promise; however, at this time it cannot be routinely recommended in all patients experiencing ICH (Class IIb recommendation).

Blood pressure (BP) management in patients who are hypertensive is also of paramount importance in treating ICH. The primary rationale for lowering BP is to prevent further progression of the bleed. This can be accomplished using a number of different pharmacologic treatments (eg, nicardipine, labetalol, nitroprusside). Nitroprusside may increase ICP due to the pronounced vasodilatory actions and as a result may be less preferable. Specific BP targets are not supported by available evidence. The 2007 ACC/AHA Guidelines recommend initiating antihypertensive therapy if the SBP >180 mm Hg or if MAP >130 mm Hg.

Index TermsNitroprusside Sodium; Sodium Nitroferricyanide; Sodium Nitroprusside

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International Brand NamesDoketrol (AR); Ketostix (AU); Naniprus (PL); Nipride (BE, CH, FR, GB, IE, LU, NL); Niprusodio (UY); Nipruss (DE, LU); Nitan (MX); Nitriate (FR); Nitropresabbott (BR); Nitroprusiato de sodio (PE, PY, VE); Nitroprusiato de sodio-ecar (CO); Nitroprussiat Fides (ES); Sodio Nitroprussiato (IT); Sodium Nitroprusside (GB); Sodium Nitroprusside BP (AU); Sonide (IN)

Nitrous Oxide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(NYE trus OKS ide)

Pharmacologic CategoryDental Gases; General Anesthetic

Use: Labeled IndicationsProduces sedation and analgesia; principal adjunct to inhalation and intravenous general anesthesia

Use: DentalInduction of sedation and analgesia in anxious dental patients

Dosing: Adults

Surgical sedation and analgesia: Concentrations of 25% to 50% nitrous oxide with oxygen. For general anesthesia, concentrations of 40% to 70% via mask or endotracheal tube. Minimal alveolar concentration (MAC), which can be considered the ED_{50} of inhalational anesthetics, is 105%; therefore delivery in a hyperbaric chamber is necessary to use as a complete anesthetic. When administered at 70%, reduces the MAC of other anesthetics by half.

Dental: Sedation and analgesia: Concentrations of 25% to 50% nitrous oxide with oxygen

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

ContraindicationsHypersensitivity to nitrous oxide or any component of the formulation; nitrous oxide should not be administered without oxygen; should not be given to patients after a full meal

Warnings/Precautions

Concerns related to adverse effects:

- Addictive: May be associated with abuse and/or addiction.
- Bone marrow suppression: Prolonged use may produce bone marrow suppression; patients with vitamin B_{12} deficiency (pernicious anemia) and those with other nutritional deficiencies (alcoholics) are at increased risk.
- Nausea/vomiting: Occurs postoperatively in ~15% of patients.
- Neurologic effects: Prolonged use may produce neurologic dysfunction; patients with vitamin B_{12} deficiency (pernicious anemia) and those with other nutritional deficiencies (alcoholics) are at increased risk.

Other warnings/precautions:

- Oxygen use: Oxygen should be briefly administered during emergence from prolonged anesthesia with nitrous oxide to prevent diffusion hypoxia.

Pregnancy Risk FactorNo data reported

Adverse ReactionsAn increased risk of renal and hepatic diseases and peripheral neuropathy similar to that of vitamin B_{12} deficiency have been reported in dental personnel who work in areas where nitrous oxide is frequently used without an enclosed gas scavenging system

Methionine synthase, a vitamin B_{12} dependent enzyme, is inactivated following prolonged administration of nitrous oxide, and the subsequent interference with DNA synthesis prevents production of both leukocytes and red blood cells by bone marrow. These effects do not occur within the time frame of clinical use.

Female dental personnel who were exposed to unscavenged nitrous oxide for more than 5 hours/week were significantly less fertile than women who were not exposed, or who were exposed to lower levels of scavenged or unscavenged nitrous oxide. Fertility was measured by the number of menstrual cycles, without use of contraception, required to become pregnant. Women who were exposed to nitrous oxide for more than 5 hours/week were only 41% as likely as unexposed women to conceive during each monthly cycle.

Frequency not defined:

Cardiovascular: Hypotension

Central nervous system: Headache, dizziness, confusion, CNS excitation

Gastrointestinal: Possibly nausea and vomiting

Respiratory: Apnea

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Supplied in blue cylinders

Generic AvailableYes
Mechanism of ActionGeneral CNS depressant action; may act similarly as inhalant general anesthetics by stabilizing axonal membranes to partially inhibit action potentials leading to sedation; may partially act on opiate receptor systems to cause mild analgesia; central sympathetic stimulating action supports blood pressure, systemic vascular resistance, and cardiac output; it does not depress carbon dioxide drive to breath. Nitrous oxide increases cerebral blood flow and intracranial pressure while decreasing hepatic and renal blood flow; has analgesic action similar to morphine.
Pharmacodynamics/Kinetics

Onset of action: Inhalation: 2-5 minutes

Absorption: Rapid via lungs; blood/gas partition coefficient is 0.47

Metabolism: Body: <0.004%

Excretion: Primarily exhaled gases; skin (minimal amounts)

Pharmacotherapy PearlsNitrous oxide's central sympathetic stimulating action supports blood pressure, systemic vascular resistance, and cardiac output. It does not depress carbon dioxide drive to breath. It increases cerebral blood flow and intracranial pressure while decreasing hepatic and renal blood flow; has analgesic action similar to morphine.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause confusion, dizziness, or excitation
Mental Health: Effects on Psychiatric TreatmentNone reported
Anesthesia and Critical Care Concerns/Other ConsiderationsNitrous oxide's central sympathetic stimulating action supports blood pressure, systemic vascular resistance, and cardiac output. It does not depress carbon dioxide drive to breathe. It increases cerebral blood flow and intracranial pressure while decreasing hepatic and renal blood flow. Nitrous oxide has analgesic action similar to morphine.
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International Brand NamesMaxicool (IL)

Nizatidine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Axid® may be confused with Ansaid®

International issues:

Tazac® [Australia] may be confused with Tiazac® which is a brand name for diltiazem in the U.S.

Pronunciation(ni ZA ti deen)
U.S. Brand NamesAxid®; Axid® AR [OTC]
Canadian Brand NamesApo-Nizatidine®; Axid®; Gen-Nizatidine; Novo-Nizatidine; Nu-Nizatidine; PMS-Nizatidine
Pharmacologic CategoryHistamine H_2 Antagonist
Use: Labeled IndicationsTreatment and maintenance of duodenal ulcer; treatment of benign gastric ulcer; treatment of gastroesophageal reflux disease (GERD); OTC tablet used for the prevention of meal-induced heartburn, acid indigestion, and sour stomach
Use: Unlabeled/InvestigationalPart of a multidrug regimen for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence
Dosing: Adults

Duodenal ulcer: Oral:

Treatment of active ulcer: 300 mg at bedtime or 150 mg twice daily

Maintenance of healed ulcer: 150 mg/day at bedtime

Gastric ulcer: Oral: 150 mg twice daily or 300 mg at bedtime

GERD: Oral: 150 mg twice daily

Meal-induced heartburn, acid indigestion, and sour stomach (OTC labeling): Oral: 75 mg tablet [OTC] twice daily, 30-60 minutes prior to consuming food or beverages

Eradication of*Helicobacter pylori*(unlabeled use): Oral: 150 mg twice daily; requires combination therapy

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

GERD (unlabeled use): Oral:

Children <12 years: 10 mg/kg/day in divided doses given twice daily; may not be as effective in children <12 years

Children ≥12 years: Refer to adult dosing.

Meal-induced heartburn, acid indigestion and sour stomach: Oral: Children ≥12 years: Refer to adult dosing.

Dosing: Renal Impairment

Active treatment:

Cl_{cr} 20-50 mL/minute: 150 mg/day

Cl_{cr} <20 mL/minute: 150 mg every other day

Maintenance treatment:

Cl_{cr} 20-50 mL/minute: 150 mg every other day

Cl_{cr} <20 mL/minute: 150 mg every 3 days

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

ContraindicationsHypersensitivity to nizatidine or any component of the formulation; hypersensitivity to other H_2 antagonists (cross-sensitivity has been observed)
Allergy Considerations

- Histamine H_2 Antagonist Allergy

Warnings/Precautions

Disease-related concerns:

- Gastric malignancy: Relief of symptoms does not preclude the presence of a gastric malignancy.
- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment recommended.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Special populations:

- Pediatrics: Use with caution in children <12 years of age.

Geriatric Considerations H_2 blockers are the preferred drugs for treating peptic ulcer disorder (PUD) in the elderly due to cost and ease of administration. These agents are no less or more effective than any other therapy. The preferred agents (due to side effects and drug interaction profile and pharmacokinetics) are ranitidine, famotidine, and nizatidine. Treatment for PUD in the elderly is recommended for 12 weeks since their lesions are larger, and therefore, take longer to heal. Always adjust dose based upon creatinine clearance.

Pregnancy Risk Factor B

Pregnancy Considerations Teratogenic effects were not observed in animal studies.

Lactation Enters breast milk/may be compatible

Breast-Feeding Considerations The amount of nizatidine excreted in breast milk is 0.1%.

Adverse Reactions

>10%: Central nervous system: Headache (16%)

1% to 10%:

Central nervous system: Anxiety, dizziness, fever (reported in children), insomnia, irritability (reported in children), somnolence, nervousness

Dermatologic: Pruritus, rash

Gastrointestinal: Abdominal pain, anorexia, constipation, diarrhea, dry mouth, flatulence, heartburn, nausea, vomiting

Respiratory: Reported in children: Cough, nasal congestion, nasopharyngitis

<1% (Limited to important or life-threatening): Alkaline phosphatase increased, ALT increased, anaphylaxis, anemia, AST increased, bronchospasm, confusion, eosinophilia, exfoliative dermatitis, gynecomastia, hepatitis, jaundice, laryngeal edema, serum-sickness like reactions, thrombocytopenia, thrombocytopenic purpura, vasculitis, ventricular tachycardia

Metabolism/Transport Effects **Inhibits** 3A4 (weak)

Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): H2-Antagonists may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole; Voriconazole. *Risk D: Consider therapy modification*

Atazanavir: H2-Antagonists may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Cefpodoxime: H2-Antagonists may decrease the absorption of Cefpodoxime. Separate oral doses by at least 2 hours. *Risk C: Monitor therapy*

Cefuroxime: H2-Antagonists may decrease the absorption of Cefuroxime. Separate oral doses by at least 2 hours. *Risk C: Monitor therapy*

Dasatinib: H2-Antagonists may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Erlotinib: H2-Antagonists may decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Fosamprenavir: H2-Antagonists may decrease the serum concentration of Fosamprenavir. Cimetidine may also inhibit the metabolism of the active metabolite amprenavir, making its effects on fosamprenavir/amprenavir concentrations difficult to predict. *Risk C: Monitor therapy*

Indinavir: H2-Antagonists may decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Iron Salts: H2-Antagonists may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk C: Monitor therapy*

Mesalamine: H2-Antagonists may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids; H2-antagonists would be expected to interact in a similar manner. *Risk X: Avoid combination*

Nelfinavir: H2-Antagonists may decrease the serum concentration of Nelfinavir. Concentrations of the active M8 metabolite may also be reduced. *Risk C: Monitor therapy*

Saquinavir: H2-Antagonists may increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause gastric mucosal irritation).

Food: Administration with apple juice may decrease absorption.

Test InteractionsFalse-positive urine protein using Multistix®, gastric acid secretion test, skin tests allergen extracts, serum creatinine and serum transaminase concentrations, urine protein test

Nursing: Physical Assessment/MonitoringAssess therapeutic effectiveness and adverse response. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed; do not change dose or discontinue without consulting prescriber. Do not take within 1 hour of any antacids. Follow diet instructions of prescriber. May cause drowsiness; use caution when driving or engaging in tasks that require alertness until response to drug is known. Report fever, sore throat, tarry stools, CNS changes, or muscle or joint pain. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Axid®: 150 mg, 300 mg [DSC]

Solution, oral:

Axid®: 15 mg/mL (120 mL, 480 mL) [bubble gum flavor]

Tablet:

Axid® AR: 75 mg

Generic AvailableYes: Capsule

ManufacturerEli Lilly and Co

Pricing: U.S. (www.drugstore.com)

Capsules (Axid)

150 mg (60): $172.97

Capsules (Nizatidine)

150 mg (60): $51.98

300 mg (30): $53.99

Solution (Axid)

15 mg/mL (480): $326.98

Tablets (Axid AR)

75 mg (30): $9.99

75 mg (50): $13.50

Mechanism of ActionCompetitive inhibition of histamine at H$_2$-receptors of the gastric parietal cells resulting in reduced gastric acid secretion, gastric volume and hydrogen ion concentration reduced. In healthy volunteers, nizatidine suppresses gastric acid secretion induced by pentagastrin infusion or food.

Pharmacodynamics/Kinetics

Distribution: V$_d$: 0.8-1.5 L/kg

Protein binding: 35% to α_1-acid glycoprotein

Metabolism: Partially hepatic; forms metabolites

Bioavailability: >70%

Half-life elimination: 1-2 hours; prolonged with renal impairment

Time to peak, plasma: 0.5-3.0 hours

Excretion: Urine (90%; ~60% as unchanged drug); feces (<6%)

Pharmacotherapy PearlsGiving dose at 6 PM (rather than 10 PM) may better suppress nocturnal acid secretion

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness; may rarely cause insomnia

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine

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Sullivan TJ, Reese JH, Buchmann KA, et al, "Bioavailability Study of Nizatidine When Administered in Food," *Am J Ther*, 1995, 2:275-8. [PubMed 11850662]

Vargas R, Ryan J, McMahon G, et al, "Pharmacokinetics and Pharmacodynamics of Oral Nizatidine," *J Clin Pharmacol*, 1988, 28(1):71-5.[PubMed 2895125]

International Brand Names Acinon (JP); Axadine (KP); Axatidin (KP); Axid (CZ, HR, HU, MX, PL); Axid Pulvules (BF, BG, BJ, BR, CI, CL, ET, GB, GH, GM, GN, GR, HN, ID, IE, KE, KP, LR, MA, ML, MR, MU, MW, MY, NE, NG, PH, PK, SC, SD, SE, SG, SL, SN, TN, TZ, UG, VE, ZA, ZM, ZW); Calmaxid (CH); Cronizat (IT); Distaxid (ES); Gastrax (DE); Jadin (KP); Nacid (KP); Naxidin (HU); Naxidine (NL); Nijatan (KP); Nizac (AU); Nizaction (AU); Nizadin (TW); Nizaractine (KP); Nizax (DE, DK, FI, IT, NO); Nizaxid (CN, FR, KP, LU, PT); Panaxid (BE, LU); Tazac (AU, TW); Ulcosal (ES); Ulxit (AT); Zanizal (IT)

Nonoxynol 9

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Delfen® may be confused with Delsym®

Pronunciation(non OKS i nole nine)

U.S. Brand NamesAdvantage-S® [OTC]; Conceptrol® [OTC]; Delfen® [OTC]; Encare® [OTC]; Gynol II® Extra Strength [OTC] ; Gynol II® [OTC]; Today® [OTC]; VCF™ [OTC]

Pharmacologic CategoryContraceptive; Spermicide

Use: Labeled IndicationsPrevention of pregnancy

Dosing: Adults**Note:** Prior to use, refer to specific product labeling for complete instructions.

Prevention of pregnancy: Vaginal:

Advantage-S®, Conceptrol®: Insert 1 applicatorful vaginally up to 1 hour prior to intercourse

Encare®: Unwrap and insert 1 suppository vaginally at least 10 minutes prior to intercourse; effective for 1 hour

Today® Sponge: Insert 1 sponge vaginally prior to intercourse; allow to remain in place for 6 hours after intercourse before removing; effective for use up to 24 continuous hours. Do not leave in place for >30 hours.

VCF®:

Film: Insert 1 film vaginally at least 15 minutes, but no more than 3 hours, prior to intercourse. Insert new film for each act of intercourse or if more than 3 hours have elapsed.

Foam: Insert 1 applicatorful at least 15 minutes prior to intercourse; effective for up to 1 hour

Dosing: ElderlyRefer to adult dosing.

Administration: Other

Today® Sponge: Prior to use, wet sponge with clean water and squeeze gently until sudsy in order to activate spermicide. Fold sponge in half with dimple side inside and string loop on bottom end, then insert into vagina. May be inserted up to 24 hours prior to intercourse. Sponge should not be reinserted if it accidentally falls out (insert new sponge).

VCF®:

Film: Remove film from pouch and fold in half; insert vaginally using finger.

Foam: Shake well prior to use.

ContraindicationsHypersensitivity to nonoxynol 9 or any component of the formulation

Today® Sponge: Hypersensitivity to sulfites; use within 6 weeks after giving birth; history of toxic shock syndrome; use during menstrual period

Warnings/Precautions

Concerns related to adverse effects:

- Toxic shock syndrome: Has been reported with barrier contraceptive use.
- Vaginal irritation: May cause vaginal irritation (eg, burning, itching or rash); irritation may also be present without symptoms. Irritation may be associated with an increased risk of getting HIV from an infected partner.

Dosage form specific issues:

- Today® Sponge: Prior to use, patients should consult healthcare provider following recent miscarriage or abortion, or with vaginal or uterine conditions which may make the product ineffective (eg, vaginal septum, uterine prolapse).

Other warnings/precautions:

- Appropriate use: Patients should consult with healthcare provider concerning the best form of birth control. For use in persons with only one partner and when neither partner is infected with HIV or has HIV risk factors; may be used with or without a diaphragm or condom.
- HIV infection protection: Nonoxynol 9 does not protect against HIV infection or other sexually-transmitted diseases and use may increase the risk of getting HIV from an infected partner. Not for use in persons with HIV or those who have a sexual partner with HIV; another form of birth control should be used. Proper use of a latex condom will help reduce the risk of infection from HIV.
- Rectal use: Not for use as a microbicide or lubricant during anal intercourse. Rectal use may cause irritation, which may increase the risk

of getting HIV from an infected partner.

Adverse Reactions Frequency not defined: Genitourinary: Irritation, burning, or itching of mucous membranes (including vaginal/urethral)

Drug Interactions There are no known significant interactions.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol, vaginal [foam]:

Delfen®: 12.5% (18 g) [contains benzoic acid]

VCF™: 12.5% (40 g)

Film, vaginal:

VCF™: 28% (3s, 6s,12s)

Gel, vaginal:

Advantage-S®: 3.5% (1.5 g) [packaged in 3s or with 6 prefilled applicators]; (30g) [packaged with reusable applicator]

Conceptrol®: 4% (2.7 g) [packaged in 6s and 10s with disposable applicators]

Gynol II®: 2% (85 g, 114 g)

Gynol II® Extra Strength: 3% (85.5 g)

Sponge, vaginal:

Today®: 1 g (3s, 6s, 12s) [contains benzoic acid, sodium metabisulfite]

Suppository, vaginal:

Encare®: 100 mg (12s, 18s)

Generic Available No

Mechanism of Action

Nonoxynol 9 is a surfactant which prevents pregnancy by damaging the cell membrane of sperm; some product formulations may also provide a physical barrier

Pharmacotherapy Pearls

The CDC does not recommend the use of condoms lubricated with spermicides due to increased cost, shorter shelf-life, and association with urinary tract infections in young women.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms N-9

References

Centers for Disease Control and Prevention, "Sexually Transmitted Diseases Treatment Guidelines 2006," *MMWR Recomm Rep*, 2006, 55(RR-11):1-8.[PubMed 16888612]

International Brand Names Delfen (IL, IN, PT); Delfen II (ZA); Gynol-Plus (SE); Ortho-Creme (AU)

Norepinephrine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(nor ep i NEF rin)

U.S. Brand NamesLevophed®

Canadian Brand NamesLevophed®

Pharmacologic CategoryAlpha/Beta Agonist

Use: Labeled IndicationsTreatment of shock which persists after adequate fluid volume replacement

Dosing: Adults**Note:** Norepinephrine dosage is stated in terms of norepinephrine base and intravenous formulation is norepinephrine bitartrate.

Norepinephrine bitartrate 2 mg = norepinephrine base 1 mg

Hypotension/shock: Continuous I.V. infusion:

Adults: Initial: 0.5-1 mcg/minute and titrate to desired response; 8-30 mcg/minute is usual range; range used in clinical trials: 0.01-3 mcg/kg/minute;

ACLS dosing range: 0.5-30 mcg/minute

Rate of infusion: 4 mg in 500 mL D_5W

2 mcg/minute = 15 mL/hour

4 mcg/minute = 30 mL/hour

6 mcg/minute = 45 mL/hour

8 mcg/minute = 60 mL/hour

10 mcg/minute = 75 mL/hour

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Administration requires the use of an infusion pump**

Note: Norepinephrine dosage is stated in terms of norepinephrine base and intravenous formulation is norepinephrine bitartrate.

Norepinephrine bitartrate 2 mg = Norepinephrine base 1 mg

Hypotension/shock: Continuous I.V. infusion: Children: Initial: 0.05-0.1 mcg/kg/minute; titrate to desired effect; maximum dose: 1-2 mcg/kg/minute

Calculations

- Norepinephrine
- Norepinephrine, Weight-Based

Administration: I.V.Administer into large vein to avoid the potential for extravasation; potent drug, must be diluted prior to use; do not administer $NaHCO_3$ through an I.V. line containing norepinephrine. Central line administration is required. Do not administer $NaHCO_3$ through an I.V. line containing norepinephrine.

Administration: I.V. DetailAdminister into large vein to avoid the potential for extravasation. Potent drug, must be diluted prior to use.

Extravasation management: Use phentolamine as antidote. Mix 5 mg with 9 mL of NS. Inject a small amount of this dilution into extravasated area. Blanching should reverse immediately. Monitor site; if blanching should recur, additional injections of phentolamine may be needed.

pH: 3.0-4.5

StorageReadily oxidized. Protect from light. Do not use if brown coloration. Stability of parenteral admixture at room temperature (25°C) is 24 hours.

ReconstitutionDilute with D_5W or D_5NS, but not recommended to dilute in normal saline.

CompatibilityStable in D_5NS, D_5W, LR; **incompatible** with normal saline, alkaline solutions.

Y-site administration: Compatible: Amiodarone, cisatracurium, diltiazem, dobutamine, dopamine, epinephrine, esmolol, famotidine, fentanyl, furosemide, haloperidol, heparin, hydrocortisone sodium succinate, hydromorphone, inamrinone, labetalol, lorazepam, meropenem, midazolam, milrinone, morphine, nicardipine, nitroglycerin, potassium chloride, propofol, ranitidine, remifentanil, vecuronium, vitamin B complex with C. **Incompatible:** Insulin (regular), thiopental.

Compatibility in syringe: Compatible: Heparin.

Compatibility when admixed: Compatible: Amikacin, calcium chloride, calcium gluconate, cimetidine, corticotropin, dimenhydrinate, dobutamine, heparin, hydrocortisone sodium succinate, magnesium sulfate, meropenem, methylprednisolone sodium succinate, multivitamins, potassium chloride, succinylcholine, verapamil, vitamin B complex with C. **Incompatible:** Aminophylline, amobarbital, chlorothiazide, chlorpheniramine, pentobarbital, phenobarbital, phenytoin, sodium bicarbonate, streptomycin, thiopental. **Variable (consult detailed reference):** Nafcillin, ranitidine.

ContraindicationsHypersensitivity to norepinephrine, bisulfites (contains metabisulfite), or any component of the formulation; hypotension from hypovolemia except as an emergency measure to maintain coronary and cerebral perfusion until volume could be replaced; mesenteric or peripheral vascular thrombosis unless it is a lifesaving procedure; during anesthesia with cyclopropane or halothane anesthesia (risk of ventricular arrhythmias)

Warnings/Precautions

Boxed warnings:

- Extravasation: See “Other warnings/precautions” below.

Concurrent drug therapy issues:

- Monoamine oxidase inhibitors (MAO-I): Use with extreme caution in patients taking MAO-Inhibitors; prolong hypertension may result from concurrent use.

Dosage form specific issues:

- Sodium metasulfite: Product may contain sodium metasulfite.

Other warnings/precautions:

- Appropriate use: Assure adequate circulatory volume to minimize need for vasoconstrictors. Avoid hypertension; monitor blood pressure closely and adjust infusion rate.
- Extravasation: Avoid extravasation; infuse into a large vein if possible. Avoid infusion into leg veins. Watch I.V. site closely. **[U.S. Boxed Warning]: If extravasation occurs, infiltrate the area with diluted phentolamine (5-10 mg in 10-15 mL of saline) with a fine hypodermic needle. Phentolamine should be administered as soon as possible after extravasation is noted.**

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, arrhythmia, peripheral (digital) ischemia

Central nervous system: Headache (transient), anxiety

Local: Skin necrosis (with extravasation)

Respiratory: Dyspnea, respiratory difficulty

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Beta-Blockers: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. *Risk D: Consider therapy modification*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

COMT Inhibitors: May decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking. Monitor blood pressure and cardiac status, CNS status, skin temperature and color during and following infusion. Monitor fluid status. Assess infusion site frequently for extravasation. Blanching along vein pathway is a preliminary sign of extravasation.

Patient EducationThis drug is used in emergency situations. Patient information is based on patient condition.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as bitartrate: 1 mg/mL (4 mL) [contains sodium metabisulfite]

Generic AvailableYes

Mechanism of ActionStimulates beta$_1$-adrenergic receptors and alpha-adrenergic receptors causing increased contractility and heart rate as well as vasoconstriction, thereby increasing systemic blood pressure and coronary blood flow; clinically alpha effects (vasoconstriction) are greater than beta effects (inotropic and chronotropic effects)

Pharmacodynamics/Kinetics

Onset of action: I.V.: Very rapid-acting

Duration: vasopressor: 1-2 minutes

Metabolism: Via catechol-o-methyltransferase (COMT) and monoamine oxidase (MAO)

Excretion: Urine (84% to 96% as inactive metabolites)

Related Information

- Hemodynamic Support, Intravenous

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, dizziness, or insomnia

Mental Health: Effects on Psychiatric TreatmentMonitor for increased pressor effect when used with TCAs, MAO inhibitors, and antihistamines

Anesthesia and Critical Care Concerns/Other ConsiderationsNorepinephrine is effective at increasing arterial blood pressure through vasoconstriction with little change in heart rate or cardiac output. Adequate fluid resuscitation is essential to the success of norepinephrine in raising blood pressure; may successfully increase blood pressure without causing a deterioration in cardiac index or organ function in patients with septic shock. It should be used early and not withheld as a last resort. The 2008 Surviving Sepsis Campaign guidelines recommend that either norepinephrine or dopamine is the first-choice vasopressor agent in adult patients (Grade 1C). Norephinephrine is more potent than dopamine and may be more effective at reversing hypotension in septic shock.

Index TermsLevarterenol Bitartrate; Noradrenaline; Noradrenaline Acid Tartrate; Norepinephrine Bitartrate

References

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International Brand NamesAdine (CN); Adrenor (ES, IN); Arterenol (DE); Fioritina (AR); Levofin (PH); Levonor (PL, PY, UY); Levophed (GB, IE, LU); Levophed Bitartrate (AE, AU, BE, BH, BR, CY, EG, IL, IQ, IR, JO, KP, KW, LB, LY, MY, OM, QA, SA, SY, YE); N-Epi (ID); Noradrenalin Jenapharm (DE); Noradrenalina Tartrato (IT); Noradrenaline (GB); Noradrenaline Aguettant (FR); Norpin (KP); Rhinopront (LU); Vascon (ID); Xylonor [+ Lidocaine hydrochloride] (PL)

Norethindrone and Mestranol

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Norinyl® may be confused with Nardil®

Pronunciation(nor eth IN drone & MES tra nole)

U.S. Brand NamesNecon® 1/50; Norinyl® 1+50; Ortho-Novum® 1/50 [DSC]

Canadian Brand NamesOrtho-Novum® 1/50

Pharmacologic CategoryContraceptive; Estrogen and Progestin Combination

Use: Labeled IndicationsPrevention of pregnancy

Use: Unlabeled/InvestigationalTreatment of hypermenorrhea (menorrhagia); pain associated with endometriosis; dysmenorrhea; dysfunctional uterine bleeding

Dosing: AdultsFemale: Contraception: Oral:

Schedule 1 (Sunday starter): Dose begins on first Sunday after onset of menstruation; if the menstrual period starts on Sunday, take first tablet that very same day. **With a Sunday start, an additional method of contraception should be used until after the first 7 days of consecutive administration.**

For 21-tablet package: Dosage is 1 tablet daily for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken.

For 28-tablet package: Dosage is 1 tablet daily without interruption.

Schedule 2 (Day 1 starter): Dose starts on first day of menstrual cycle taking 1 tablet daily.

For 21-tablet package: Dosage is 1 tablet daily for 21 consecutive days, followed by 7 days off of the medication; a new course begins on the 8th day after the last tablet is taken.

For 28-tablet package: Dosage is 1 tablet daily without interruption.

Note: If all doses have been taken on schedule and one menstrual period is missed, continue dosing cycle. If two consecutive menstrual periods are missed, pregnancy test is required before new dosing cycle is started.

Missed doses: Monophasic formulations (refer to package insert for complete information):

One dose missed: Take as soon as remembered or take 2 tablets next day

Two consecutive doses missed in the first 2 weeks: Take 2 tablets as soon as remembered or 2 tablets next 2 days. **An additional method of contraception should be used for 7 days after missed dose.**

*Two consecutive doses missed in week 3 or three consecutive doses missed at any time:***An additional method of contraception must be used for 7 days after a missed dose:**

Schedule 1 (Sunday starter): Continue dose of 1 tablet daily until Sunday, then discard the rest of the pack, and a new pack should be started that same day.

Schedule 2 (Day 1 starter): Current pack should be discarded, and a new pack should be started that same day.

Dosing: PediatricFemale: Contraception: Oral: See adult dosing; not to be used prior to menarche.

Dosing: Renal ImpairmentSpecific guidelines not available; use with caution and monitor blood pressure closely. Consider other forms of contraception.

Dosing: Hepatic ImpairmentContraindicated in patients with hepatic impairment.

Administration: OralAdminister at the same time each day. Administer at bedtime to minimize occurrence of adverse effects.

Dietary ConsiderationsShould be taken at same time each day.

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to mestranol, norethindrone, or any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); cerebral vascular disease, coronary artery disease, valvular heart disease with complications, severe hypertension; diabetes mellitus with vascular involvement; severe headache with focal neurological symptoms; known or suspected breast carcinoma, endometrial cancer, estrogen-dependent neoplasms, undiagnosed abnormal genital bleeding; hepatic dysfunction or tumor, cholestatic jaundice of pregnancy, jaundice with prior combination hormonal contraceptive use; major surgery with prolonged immobilization; heavy smoking (≥15 cigarettes/day) in patients >35 years of age; pregnancy

Allergy Considerations

- Estrogen Allergy

Warnings/Precautions

Boxed warnings:

- Smokers: See “Special populations” below.

Concerns related to adverse effects:

- Breast cancer: The use of combination hormonal contraceptives has been associated with a slight increase in frequency of breast cancer, however, studies are not consistent.

- Glucose intolerance: Combination hormonal contraceptives may cause glucose intolerance.

- Lipid effects: Combination hormonal contraceptives may effect serum triglyceride and lipoprotein levels. Estrogen compounds are generally associated with lipid effects such as increased HDL-cholesterol and decreased LDL-cholesterol. Triglycerides may also be increased; use with caution in patients with familial defects of lipoprotein metabolism.

- Retinal vascular thrombosis: Estrogens may cause retinal vascular thrombosis (has been reported rarely with combination hormonal contraceptives); discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

- Thromboembolism: May increase the risk of thromboembolism.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with risk factors for coronary artery disease; may lead to increased risk of myocardial infarction. May have a dose-related risk of vascular disease and hypertension; women with hypertension should be encouraged to use a nonhormonal form of contraception.

- Depression: Use with caution in patients with depression.

- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes or renal dysfunction.

- Gallbladder disease: May have a dose-related risk of gallbladder disease.

- Migraine: Use with caution in patients with a history of migraine.

- Renal impairment: Women with renal disease should be encouraged to use a nonhormonal form of contraception.

Special populations:

- Pediatrics: Not for use prior to menarche.

- Smokers: **[U.S. Boxed Warning]: The risk of cardiovascular side effects increases in women who smoke cigarettes, especially those who are >35 years of age; women who use combination hormonal contraceptives should be strongly advised not to smoke.**

- Surgical patients: Whenever possible, should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Other warnings/precautions:

- HIV infection protection: Combination hormonal contraceptives do not protect against HIV infection or other sexually-transmitted diseases.

- Minimum effective dosage: The minimum dosage combination of estrogen/progestin that will effectively treat the individual patient should be used. New patients should be started on products containing ≤0.035 mg of estrogen per tablet.

Pregnancy Risk FactorX

Pregnancy ConsiderationsPregnancy should be ruled out prior to treatment and discontinued if pregnancy occurs. In general, the use of combination hormonal contraceptives when inadvertently taken early in pregnancy have not been associated with teratogenic effects. Due to increased risk of thromboembolism postpartum, combination hormonal contraceptives should not be started earlier than 4-6 weeks following delivery. Hormonal contraceptives may be less effective in obese patients. An increase in oral contraceptive failure was noted in women with a BMI >27.3. Similar findings were noted in patients weighing ≥90 kg (198 lb) using the contraceptive patch.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsJaundice and breast enlargement in the nursing infant have been reported following the use of combination hormonal contraceptives. May decrease the quality and quantity of breast milk; a nonhormonal form of contraception is recommended.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, edema, hypertension, mesenteric thrombosis, MI

Central nervous system: Depression, dizziness, headache, migraine, nervousness, premenstrual syndrome, stroke

Dermatologic: Acne, erythema multiforme, erythema nodosum, hirsutism, loss of scalp hair, melasma (may persist), rash (allergic)

Endocrine & metabolic: Amenorrhea, breakthrough bleeding, breast enlargement, breast secretion, breast tenderness, carbohydrate intolerance, lactation decreased (postpartum), glucose tolerance decreased, libido changes, menstrual flow changes, sex hormone-binding globulins (SHBG) increased, spotting, temporary infertility (following discontinuation), thyroid-binding globulin increased, triglycerides increased

Gastrointestinal: Abdominal cramps, appetite changes, bloating, cholestasis, colitis, gallbladder disease, jaundice, nausea, vomiting, weight gain/loss

Genitourinary: Cervical erosion changes, cervical secretion changes, cystitis-like syndrome, vaginal candidiasis, vaginitis

Hematologic: Antithrombin III decreased, folate levels decreased, hemolytic uremic syndrome, norepinephrine induced platelet aggregability increased, porphyria, prothrombin increased; factors VII, VIII, IX, and X increased

Hepatic: Benign liver tumors, Budd-Chiari syndrome, cholestatic jaundice, hepatic adenomas

Local: Thrombophlebitis

Ocular: Cataracts, change in corneal curvature (steepening), contact lens intolerance, optic neuritis, retinal thrombosis

Renal: Impaired renal function

Respiratory: Pulmonary thromboembolism

Miscellaneous: Hemorrhagic eruption

Metabolism/Transport Effects

Mestranol: **Substrate** of CYP2C9 (major); Based on active metabolite ethinyl estradiol: **Substrate** of CYP3A4 (major), 3A5-7 (minor); **Inhibits** CYP1A2 (weak), 2B6 (weak), 2C19 (weak), 3A4 (weak)

Norethindrone: **Substrate** of CYP3A4 (major); **Induces** CYP2C19 (weak)

Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Armodafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Estrogens) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Colesevelam: May decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Estrogen Derivatives may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Darunavir: May decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Oral Contraceptive (Estrogens). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Griseofulvin: May increase the metabolism of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Herbs (Estrogenic Properties): May enhance the adverse/toxic effect of Estrogen Derivatives. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

LamoTRIgine: Oral Contraceptive (Estrogens) may decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Modafinil: May decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Average AUC values were unchanged, but there was evidence of substantial patient-to-patient variability in response to this combination. *Risk D: Consider therapy modification*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

Nafcillin: May increase the metabolism of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Protease Inhibitors: Oral Contraceptive (Estrogens) may diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Ropinirole: Estrogen Derivatives may increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Rufinamide: May decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Estrogens) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Thyroid Products: Estrogen Derivatives may diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Tipranavir: Estrogen Derivatives may enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

TiZANidine: Oral Contraceptive (Estrogens) may increase the serum concentration of TiZANidine. *Risk C: Monitor therapy*

Topiramate: May decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Oral Contraceptive (Estrogens) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Estrogens). Oral Contraceptive (Estrogens) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: CNS effects of caffeine may be enhanced if oral contraceptives are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations and would be expected to increase progesterone serum levels as well; clinical implications are unclear.

Herb/Nutraceutical: St John's wort may decrease the effectiveness of combination hormonal contraceptives by inducing hepatic enzymes. Avoid dong quai and black cohosh (have estrogen activity). Avoid saw palmetto, red clover, ginseng.

Monitoring ParametersBefore starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision; sudden onset of proptosis, diplopia, or migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in patients with diabetes; or lipid profiles in patients being treated for hyperlipidemias. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Nursing: Physical Assessment/MonitoringSee individual agent for Norethindrone.

Patient EducationSee individual agent for Norethindrone.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, monophasic formulations:

Necon® 1/50: Norethindrone 1 mg and mestranol 0.05 mg [21 light blue tablets and 7 white inactive tablets] (28s)

Norinyl® 1+50: Norethindrone 1 mg and mestranol 0.05 mg [21 white tablets and 7 orange inactive tablets] (28s)

Ortho-Novum® 1/50: Norethindrone 1 mg and mestranol 0.05 mg [21 yellow tablets and 7 green inactive tablets] (28s) [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Necon 1/50 (28))

1-50 mg-mcg (84): $75.00

Mechanism of ActionCombination oral contraceptives inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of gonadotropin secretion of a follicle-stimulating hormone (FSH) and luteinizing hormone by the anterior pituitary. The follicular phase FSH and midcycle surge of gonadotropins are inhibited. In addition, combination hormonal contraceptives produce alterations in the genital tract, including changes in the cervical mucus, rendering it unfavorable for sperm penetration even if ovulation occurs. Changes in the endometrium may also occur, producing an unfavorable environment for nidation. Combination hormonal contraceptive drugs may alter the tubal transport of the ova through the fallopian tubes. Progestational agents may also alter sperm fertility.

Pharmacodynamics/Kinetics

Mestranol: Metabolism: Hepatic via demethylation to ethinyl estradiol

Norethindrone: See Norethindrone monograph for additional information.

Pharmacotherapy PearlsThe World Health Organization (WHO) has issued revised management recommendations for missed combined oral contraceptive pills. Refer to the following reference for a complete presentation and discussion of the guidelines:

Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit, "Faculty Statement from the CEU on a New Publication: WHO Selected Practice Recommendations for Contraceptive Use Update. Missed Pills: New Recommendations," *J Fam Plann Reprod Health Care*, 2005, 31(2):153-5.

Dental Health: Effects on Dental TreatmentWhen prescribing antibiotics, patient must be advised to use additional methods of birth control if on hormonal contraceptives.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety or depression

Mental Health: Effects on Psychiatric TreatmentHepatic metabolism of TCAs, benzodiazepines (oxidatively metabolized) and beta-blockers may be decreased by oral contraceptives; monitor increased/toxic effects; may increase the clearance of benzodiazepines (glucuronidation); barbiturates may increase the metabolism of oral contraceptives resulting in decreased effectiveness

Cardiovascular ConsiderationsIt is important to recognize that oral contraceptives may induce or worsen hypertension. These problems are less severe with low-dose oral contraceptives. Furthermore, oral contraceptives may precipitate thromboembolic events, particularly in women who smoke. It is important that patients on long-term oral contraceptives undergo monitoring of blood pressure and avoid cigarette use.

Index TermsMestranol and Norethindrone; Ortho Novum 1/50

References

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Burkman R, Schlesselman JJ, and Zieman M, “Safety Concerns and Health Benefits Associated With Oral Contraception,” *Am J Obstet Gynecol*, 2004, 190(4 Suppl):5-22.

“Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection,” August 13, 2001. Available at: http://www.aidsinfo.nih.gov. Accessed September 5, 2001.

Holt VL, Scholes D, Wicklund KG, et al, “Body Mass Index, Weight, and Oral Contraceptive Failure Risk,” *Obstet Gynecol*, 2005, 105(1):46-52. [PubMed 15625141]

Orme ML, Back DJ, and Breckenridge AM, “Clinical Pharmacokinetics of Oral Contraceptive Steroids,” *Clin Pharmacokinet*, 1983, 8(2):95-136. [PubMed 6342899]

Shenfield GM and Griffin JM, “Clinical Pharmacokinetics of Contraceptive Steroids. An Update,” *Clin Pharmacokinet*, 1991, 20(1):15-37.[PubMed 2029800]

International Brand Names Combiginor (UY); Norace (MX); Norinyl-1 (AU, BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Norinyl-1 28 (AU, ZA); Ortho-Novin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ortho-Novum 1 50 (AE, AT, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE)

Norethindrone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Micronor® may be confused with miconazole, Micronase®

Pronunciation(nor ETH in drone)

U.S. Brand NamesAygestin®; Camila™; Errin™; Jolivette™; Nor-QD®; Nora-BE™; Ortho Micronor®

Canadian Brand NamesMicronor®; Norlutate®

Pharmacologic CategoryContraceptive; Progestin

Use: Labeled IndicationsTreatment of amenorrhea; abnormal uterine bleeding; endometriosis; prevention of pregnancy

Dosing: Adults

Contraception (females): Oral: Progesterone only: Norethindrone 0.35 mg every day (no missed days)

Initial dose: Start on first day of menstrual period or the day after a miscarriage or abortion. If switching from a combined oral contraceptive, begin the day after finishing the last active combined tablet.

Missed dose: Take as soon as remembered. A back up method of contraception should be used for 48 hours if dose is taken ≥3 hours late.

Amenorrhea and abnormal uterine bleeding: Oral: Norethindrone acetate: 2.5-10 mg/day for 5-10 days during the second half of the menstrual cycle

Endometriosis: Oral: Norethindrone acetate: 5 mg/day for 14 days; increase at increments of 2.5 mg/day every 2 weeks to reach 15 mg/day; continue for 6-9 months or until breakthrough bleeding demands temporary termination

Dosing: PediatricAdolescents: Refer to adult dosing

Administration: Oral

Administer at the same time each day. When used for the prevention of pregnancy, a back up method of contraception should be used for 48 hours if dose is missed or taken ≥3 hours late.

Dietary ConsiderationsShould be taken at same time each day.

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to norethindrone or any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); hepatic dysfunction or tumor; known or suspected breast carcinoma; undiagnosed vaginal bleeding; pregnancy; missed abortion or as a diagnostic test for pregnancy

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: Irregular menstrual bleeding patterns are common with progestin only contraceptives; nonpharmacologic causes of abnormal bleeding should be ruled out.
- Breast cancer: The use of combination hormonal contraceptives has been associated with a slight increase in the frequency of breast cancer, however studies are not consistent. Data is insufficient to determine if progestin only contraceptives also increase this risk.
- Carbohydrate intolerance: May have adverse effects on glucose tolerance; use caution in women with diabetes.
- Lipid effects: May have adverse effects on lipid metabolism; use caution in women with hyperlipidemias.
- Retinal vascular lesions: Progestin use has been associated with retinal vascular lesions; discontinue pending examination in case of sudden vision loss, complete loss of vision, sudden onset of proptosis, diplopia, or migraine.
- Thromboembolism: Use caution in patients at increased risk of thromboembolism; includes elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Disease-related concerns:

- Depression: Use with caution in patients with depression.
- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, cardiac or renal dysfunction.
- Hepatic adenomas: Extremely rare hepatic adenomas and focal nodular hyperplasia resulting in fatal intra-abdominal hemorrhage have been reported in association with long-term combination oral contraceptive use. Data is insufficient to determine if progestin-only contraceptives also increase this risk.
- Migraine: Use with caution in patients with a history of migraine.

Special populations:

- Pediatrics: Not for use prior to menarche.
- Smokers: The risk of cardiovascular side effects increases in women using estrogen containing combined hormonal contraceptives and who smoke cigarettes, especially those who are >35 years of age. This risk relative to progestin-only contraceptives has not been established.

Other warnings/precautions:

- HIV infection protection: Progestin-only contraceptives do not protect against HIV infection or other sexually-transmitted diseases.

Pregnancy Risk FactorX
Pregnancy ConsiderationsFirst trimester exposure may cause genital abnormalities including hypospadias in male infants and mild virilization of external female genitalia. Significant adverse events related to growth and development have not been observed (limited studies). Use is contraindicated during pregnancy. May be started immediately postpartum if not breast-feeding.
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsSmall amounts of progestins are found in breast milk (1% to 6% of maternal serum concentration). Norethindrone can cause changes in milk production in the mother. When used for contraception, may start 3 weeks after delivery in women who are partially breast-feeding, or 6 weeks after delivery in women who are fully breast-feeding.
Adverse ReactionsFrequency not defined.

Cardiovascular: Cerebral embolism, cerebral thrombosis, DVT, edema

Central nervous system: Depression, dizziness, headache, insomnia, migraine, mood swings

Dermatologic: Acne, chloasma, hirsutism, melasma, pruritus, rash, urticaria

Endocrine & metabolic: Amenorrhea, breakthrough bleeding, breast enlargement/tenderness, menstrual flow changes, spotting

Gastrointestinal: Nausea, weight gain/loss

Genitourinary: Cervical erosion changes, cervical secretion changes

Hepatic: Cholestatic jaundice, liver function test abnormalities

Ocular: Optic neuritis (with or without vision loss), retinal vascular thrombosis

Respiratory: Pulmonary embolism

Miscellaneous: Anaphylactic/anaphylactoid reactions

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Induces** CYP2C19 (weak)
Drug Interactions

Acitretin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Contraceptive (Progestins). *Risk D: Consider therapy modification*

Barbiturates: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Oral Contraceptive (Progestins) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

CarBAMazepine: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Colesevelam: May decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Darunavir: May decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Contraceptive (Progestins). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Griseofulvin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk X: Avoid combination*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

Mycophenolate: May decrease the serum concentration of Oral Contraceptive (Progestins). *Risk D: Consider therapy modification*

OXcarbazepine: May decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: May diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Rufinamide: May decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

Selegiline: Oral Contraceptive (Progestins) may increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

St Johns Wort: May diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Contraceptive (Progestins) may diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Voriconazole: May decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid bloodroot, chasteberry, damiana, oregano, and yucca; may enhance the adverse/toxic effect of progestins. Avoid St John's wort; may diminish the therapeutic effect of progestin contraceptives; contraceptive failure is possible.

Test InteractionsMay increase prothrombin, factors VII, VIII, IX and X, PBI, and BEI. May decrease T_3 uptake; may decrease sex hormone-binding globulin (SHBG); may have a reduced response to metyrapone test.

Monitoring ParametersContraception: Before starting therapy, a physical exam with reference to the breasts and pelvis are recommended, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision, sudden onset of proptosis, diplopia, migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in patients with diabetes; lipid profiles in patients being treated for hyperlipidemias. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding.

Nursing: Physical Assessment/MonitoringAssess patient knowledge/teach appropriate administration schedule and adverse signs to report. Physical exam with reference to the breasts and pelvis, including a Papanicolaou smear. Exam may be deferred if appropriate; pregnancy should be ruled out prior to use. Monitor patient closely for loss of vision, sudden onset of proptosis, diplopia, migraine; blood pressure; signs and symptoms of thromboembolic disorders; signs or symptoms of depression; glycemic control in diabetics; lipid profiles in patients being treated for hyperlipidemias. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Teach appropriate breast self-exam and the need for regular breast self-exam and necessity of annual physical check-up with long-term use. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment.

Patient EducationTake according to prescribed schedule. Follow instructions for regular self-breast exam. You may experience dizziness or lightheadedness; use caution when driving or engaging in tasks that require alertness until response to drug is known. Limit intake of caffeine. Avoid high-dose vitamin C. If you have diabetes, monitor blood glucose closely. You may experience photosensitivity; use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight. You may experience loss of hair (reversible), swelling of hands or feet, weight gain or loss. Report sudden severe headache or vomiting, disturbances of vision or speech, sudden blindness, numbness of weakness in an extremity, chest pain, calf pain, respiratory difficulty, weight gain >5 lb/week, depression or acute fatigue, unusual bleeding, spotting, or changes in menstrual flow. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Camila™, Errin™, Jolivette™, Ortho Micronor®, Nora-BE™, Nor-QD®: 0.35 mg

Tablet, as acetate:

Aygestin®: 5 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Aygestin)

5 mg (30): $85.31

Tablets (Camila)

0.35 mg (28): $34.99

Tablets (Errin)

0.35 mg (28): $30.99

Tablets (Jolivette)

0.35 mg (28): $33.99

Tablets (Nor-QD)

0.35 mg (28): $65.87

Tablets (Nora-BE)

0.35 mg (28): $33.99

Tablets (Norethindrone Acetate)

5 mg (30): $56.99

Tablets (Ortho Micronor)

0.35 mg (28): $48.36

Mechanism of ActionInhibits secretion of pituitary gonadotropin (LH) which prevents follicular maturation and ovulation

Pharmacodynamics/Kinetics

Absorption: Oral: Rapidly absorbed

Distribution: V_d: 4 L/kg

Protein binding: 61% to albumin; 36% to sex hormone-binding globulin (SHBG); SHBG capacity affected by plasma ethinyl estradiol levels

Metabolism: Oral: Hepatic via reduction and conjugation; first-pass effect

Bioavailability: 64%

Half-life elimination: ~8 hours

Time to peak: 1-2 hours

Excretion: Urine (>50% as metabolites); feces (20% to 40% as metabolites)

Dental Health: Effects on Dental TreatmentUntil we know more about the mechanism of interaction, caution is required in prescribing antibiotics to female dental patients taking progestin-only hormonal contraceptives.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia or depression

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsNorethindrone Acetate; Norethisterone

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International Brand NamesAminor (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Micro-Novom (ZA); Micronor (AE, AU, BF, BH, BJ, BR, CI, CY, EG, ET, GB, GH, GM, GN, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Micronovum (AT, CH, DE, ZA); Mini-PE (DK); Norcolut (BB, BM, BS, BZ, EE, GY, HK, HU, JM, MY, PR, SR, TT); Norestin (BR); Noriday (AU, BF, BJ, CI, ET, GB, GH, GM, GN, IE, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, NZ, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Norluten (FR); Oretes (PH); Ortho-Novum (MX); Primolut (PK); Primolut N (AE, BB, BD, BF, BH, BJ, BM, BS, BZ, CH, CI, CL, CY, DE, EG, ET, FI, GB, GH, GM, GN, GY, HK, ID, IE, IL, IN, IQ, IR, JM, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PH, PK, PR, QA, SA, SC, SD, SG, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Primolut Nor (AR, BE, BG, CZ, IT, PT, PY, SE, UY); Primolut-N (KP); Primolutin (DE); Regamen (ID); Shiton (TW); Steron (TH); Styptin 5 (IN); Sunolut (MY); Utovlan (GB)

Norfloxacin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Norfloxacin may be confused with Norflex™, Noroxin®

Noroxin® may be confused with Neurontin®, Norflex™, norfloxacin

Pronunciation(nor FLOKS a sin)

U.S. Brand NamesNoroxin®

Canadian Brand NamesApo-Norflox®; CO Norfloxacin; Norfloxacine®; Noroxin® ; Novo-Norfloxacin; PMS-Norfloxacin; Riva-Norfloxacin

Pharmacologic Category[Antibiotic, Quinolone]()

Use: Labeled IndicationsUncomplicated and complicated urinary tract infections caused by susceptible gram-negative and gram-positive bacteria; sexually-transmitted disease (eg, uncomplicated urethral and cervical gonorrhea) caused by *N. gonorrhoeae*; prostatitis due to *E. coli*

Note: As of April 2007, the CDC no longer recommends the use of fluoroquinolones for the treatment of gonococcal disease.

Dosing: Adults

Dysenteric enterocolitis(*Shigella*unlabeled use): Oral: 400 mg twice daily for 5 days

Prostatitis: Oral: 400 mg every 12 hours for 4-6 weeks

Traveler's diarrhea (unlabeled use): Oral: 400 mg twice daily for 3 days, single dose may also be effective

Uncomplicated gonorrhea: Oral: 800 mg as a single dose. **Note:** As of April 2007, the CDC no longer recommends the use of fluoroquinolones for the treatment of uncomplicated gonococcal disease.

Urinary tract infections: Oral:

Uncomplicated due to *E. coli, K. pneumoniae, P. mirabilis*: 400 mg twice daily for 3 days

Uncomplicated due to other organisms: 400 mg twice daily for 7-10 days

Complicated: 400 mg twice daily for 10-21 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment Cl_{cr} ≤30 mL/minute/1.73 m^2: Administer 400 mg every 24 hours

Calculations

- [Creatinine Clearance: Adults]()

Administration: OralHold antacids, sucralfate, or multivitamins/supplements containing iron, zinc, magnesium, or aluminum for 2 hours after giving norfloxacin; do not administer together. Best taken on an empty stomach with water (1 hour before or 2 hours after meals, milk, or other dairy products).

Dietary ConsiderationsOral formulations should be administered on an empty stomach with water (1 hour before or 2 hours after meals, milk, or other dairy products). Maintain fluid intake to ensure adequate hydration and urinary output.

StorageStore at 25°C (77°F). Keep container tightly closed.

RestrictionsAn FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to norfloxacin, quinolones, or any component of the formulation; history of tendonitis or tendon rupture associated with quinolone use

Allergy Considerations

- [Fluoroquinolone Allergy]()

Warnings/Precautions

Boxed Warnings:

- Tendon inflammation/rupture: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Altered cardiac conduction: Fluoroquinolones may prolong QT_c interval; avoid use in patients with a history of QT_c prolongation, uncorrected hypokalemia, hypomagnesemia, or concurrent administration of other medications known to prolong the QT interval (including Class Ia and Class III antiarrhythmics, cisapride, erythromycin, antipsychotics, and tricyclic antidepressants).

- CNS stimulation: Tremor, restlessness, confusion, and very rarely hallucinations or seizures may occur; use with caution in patients with known or suspected CNS disorder. Discontinue in patients who experience significant CNS adverse effects (eg, dizziness, hallucinations, suicidal ideations or actions).

- Glucose regulation: Fluoroquinolones have been associated with the development of serious, and sometimes fatal, hypoglycemia. These events have occurred most often in elderly patients with diabetes, but have also been reported in patients without a prior history of diabetes. Prompt identification and treatment of hypoglycemia is essential. Individual quinolones may differ in their potential to cause this effect. It was most evident with gatifloxacin (no longer marketed as s systemic formulation). Hyperglycemia has also been associated with the use of fluoroquinolones. Patients should be monitored closely for signs/symptoms of disordered glucose regulation.

- Hypersensitivity reactions: Severe hypersensitivity reactions, including anaphylaxis, have occurred with quinolone therapy. The spectrum of these reactions can vary widely; reactions may present as typical allergic symptoms (eg, itching, urticaria, rash, edema) after a single dose, or may manifest as severe idiosyncratic dermatologic (eg, Stevens-Johnson, toxic epidermal necrolysis), vascular (eg, vasculitis), pulmonary (eg, pneumonitis), renal (eg, nephritis), hepatic (eg, hepatic failure or necrosis), and/or hematologic (eg, anemia, cytopenias) events, usually after multiple doses. Prompt discontinuation of drug should occur if skin rash or other symptoms arise.

- Peripheral neuropathy: The use of quinolones has been linked to peripheral neuropathy (rare); discontinue if symptoms of sensory or sensorimotor neuropathy occur.

- Phototoxicity: Avoid excessive sunlight and take precautions to limit exposure (eg, loose fitting clothing, sunscreen); may cause moderate-to-severe phototoxicity reactions. Discontinue use if photosensitivity occurs.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

- Tendon inflammation/rupture: **[U.S. Boxed Warning]: There have been reports of tendon inflammation and/or rupture with quinolone antibiotics; risk may be increased with concurrent corticosteroids, organ transplant recipients, and in patients >60 years of age.** Rupture of the Achilles tendon sometimes requiring surgical repair has been reported most frequently; but other tendon sites (eg, rotator cuff, biceps) have also been reported. Strenuous physical activity may be an independent risk factor for tendonitis. Discontinue at first sign of tendon inflammation or pain. May occur even after discontinuation of therapy.

Disease-related concerns:

- Myasthenia gravis: Some quinolones may exacerbate myasthenia gravis, use with caution (rare, potentially life-threatening weakness of respiratory muscles may occur).

- Renal impairment: Use caution with renal impairment; dose adjustment required. May increase risk of tendon rupture.

- Rheumatoid arthritis: Use with caution in patients with rheumatoid arthritis; may increase risk of tendon rupture.

- Seizures: Use with caution in individuals at risk of seizures (CNS disorders or concurrent therapy with medications which may lower seizure threshold). Potential for seizures, although very rare, may be increased with concomitant NSAID therapy.

- Syphilis: Since norfloxacin is ineffective in the treatment of syphilis and may mask symptoms, all patients should be tested for syphilis at the time of gonorrheal diagnosis and 3 months later.

Special populations:

- Elderly: Adverse effects (eg, tendon rupture, QT changes) may be increased in the elderly.

- G6PD deficiency: Hemolytic reactions may (rarely) occur with quinolone use in patients with latent or actual G6PD deficiency.

- Pediatrics: Safety and efficacy have not been established in children; other quinolones have caused transient arthropathy in children.

Geriatric ConsiderationsSee Warnings/Precautions regarding tendon rupture in patients >60 years of age. Adjust dose for renal function.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in some animal studies; therefore, the manufacturer classifies norfloxacin as pregnancy category C. Norfloxacin crosses the placenta, distributing to cord blood and amniotic fluid. An increased risk of teratogenic effects has not been observed in animals or humans following norfloxacin use during pregnancy; however, because of concerns of cartilage damage in immature animals, norfloxacin should only be used during pregnancy if a safer option is not available.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsNorfloxacin was not detected in the milk of nursing mothers administered an oral 200 mg dose. It is not known if concentrations would be detectable after a higher dose or multiple doses. Breast-feeding is not recommended by the manufacturer.

Pregnancy & Lactation, In-Depth

- Norfloxacin in Pregnancy & Lactation

Adverse Reactions

>1% to 10%:

Central nervous system: Headache (2% to 3%), dizziness (2% to 3%)

Gastrointestinal: Nausea (3%to 4%), abdominal cramping (2%)

Hematologic: Eosinophilia (1% to 2%)

Hepatic: Liver enzymes increased (1% to 2%)

≥0.3% to 1%:

Central nervous system: Fever, somnolence

Dermatologic: Hyperhidrosis, pruritus, rash

Gastrointestinal: Abdominal pain, anorectal pain, anorexia, constipation, diarrhea, dyspepsia, flatulence, loose stools, vomiting, xerostomia

Hematologic: Hematocrit/hemoglobin decreased (1%), leukopenia (1%), thrombocytopenia (1%)

Neuromuscular & skeletal: Back pain, paresthesia, weakness

Renal: Proteinuria (1%)

<0.3%, postmarketing, and/or case reports: Abdominal swelling, acute renal failure, agranulocytosis, albuminuria, alkaline phosphatase increased, allergy, anaphylactoid reactions, anaphylaxis, angioedema, anxiety, arthralgia, arthritis, ataxia, bitter taste, blurred vision, bursitis, candiduria, chest pain, chills, cholestatic jaundice, cholesterol increased, confusion, CPK increased, crystalluria, cylinduria, depression, diplopia, dysgeusia, dysmenorrhea, dyspnea, edema, erythema, erythema multiforme, exacerbation of myasthenia gravis, exfoliative dermatitis, GI bleeding, glycosuria, Guillain-Barré syndrome, hearing loss, heartburn, hematuria, hemolytic anemia (sometimes associated with G6PD deficiency), hepatic failure, hepatic necrosis, hepatitis, hyper-/hypoglycemia, hyperkalemia, hypersensitivity, hypoesthesia, insomnia, interstitial nephritis, jaundice, LDH increased, MI, mouth ulcer, myalgia, myoclonus, neutropenia, nystagmus, palpitation, pancreatitis (rare), peripheral edema, peripheral neuropathy, photosensitivity/toxicity, postural hypotension, prothrombin time increased, pruritus ani, pseudomembraneous colitis, psychotic reactions, QT_c prolongation, renal colic, seizure, serum creatinine/BUN increased, Stevens-Johnson syndrome, stomatitis, tendon rupture, tendonitis, tingling of fingers, tinnitus, torsade de pointes, toxic epidermal necrolysis, tremor, triglyceridemia, urticaria, vaginal candidiasis , vasculitis, ventricular arrhythmia

Metabolism/Transport Effects **Inhibits** CYP1A2 (strong), 3A4 (moderate)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. **Exceptions:** Sodium Bicarbonate. *Risk D: Consider therapy modification*

Bendamustine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. *Risk C: Monitor therapy*

Caffeine: Quinolone Antibiotics may decrease the metabolism of Caffeine. *Risk C: Monitor therapy*

Calcium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Calcium Chloride. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Quinolone Antibiotics may enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

CycloSPORINE: Norfloxacin may decrease the metabolism of CycloSPORINE. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Strong) may decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Didanosine: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents (excludes enteric coated formulation of didanosine). *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Insulin: May enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mycophenolate: Quinolone Antibiotics may decrease the serum concentration of Mycophenolate. Specifically, quinolones may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nitrofurantoin: May diminish the therapeutic effect of Norfloxacin. *Risk X: Avoid combination*

Nonsteroidal Anti-Inflammatory Agents: May enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Probenecid: May increase the serum concentration of Quinolone Antibiotics. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Quinapril: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Sevelamer: May decrease the absorption of Quinolone Antibiotics. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sulfonylureas: Quinolone Antibiotics may enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Theophylline Derivatives: Quinolone Antibiotics may decrease the metabolism of Theophylline Derivatives. Ciprofloxacin and enoxacin are of greatest concern. Theophylline/quinolone therapy might augment the seizure-producing potential of each of the individual agents. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Quinolone Antibiotics may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zinc Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Norfloxacin average peak serum concentrations may be decreased if taken with dairy products. Use caution with caffeine-containing beverages/foods; quinolones may increase blood levels of caffeine.

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization); avoid administration within 2 hours of multivitamins or other supplements containing iron, zinc, magnesium, or aluminum.

Nursing: Physical Assessment/MonitoringAssess allergy history before initiating therapy. See Contraindications and Warnings/Precautions for use cautions. Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (see extensive list of Drug Interactions). Assess results of laboratory tests (see Monitoring Laboratory Tests), therapeutic effectiveness, and adverse effects (see Adverse Reactions and Overdose/Toxicology). Teach patient appropriate use (according to formulation), possible side effects/appropriate interventions, and adverse symptoms to report (see Patient Education). **Pregnancy risk factor C** - benefits of use should outweigh possible risks. Breast-feeding is contraindicated.

Monitoring: Lab TestsPerform culture and sensitivity prior to beginning therapy. Monitor CBC, renal and hepatic function periodically if therapy is prolonged.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. Take as directed for as long as directed, preferably on an empty stomach, 1 hour before or 2 hours after meals. Do not alter dose or discontinue without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience dizziness, lightheadedness, or headache (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea, vomiting, anorexia, or dry mouth (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). If inflammation or tendon pain occurs discontinue use immediately and report to prescriber. If allergic reaction occurs (itching urticaria, respiratory difficulty, facial edema, difficulty swallowing, loss of consciousness, tingling, chest pain, palpitations), discontinue use immediately and report to prescriber. Contact prescriber if you experience pain in your extremities, burning, tingling, numbness, and/or weakness. Report palpitations or chest pain; persistent diarrhea or constipation; signs of infection (unusual fever or chills; vaginal itching or foul-smelling vaginal discharge; easy bruising or bleeding); excessive sleepiness; or agitation. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Noroxin®: 400 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Noroxin)

400 mg (20): $79.99

400 mg (30): $117.98

Mechanism of ActionNorfloxacin is a DNA gyrase inhibitor. DNA gyrase is an essential bacterial enzyme that maintains the superhelical structure of DNA. DNA gyrase is required for DNA replication and transcription, DNA repair, recombination, and transposition; bactericidal

Pharmacodynamics/Kinetics

Absorption: Oral: Rapid, up to 40%

Protein binding: 10% to 15%

Metabolism: Hepatic

Half-life elimination: 3-4 hours; Renal impairment (Cl_{cr} ≤30 mL/minute): 6.5 hours; Elderly: 4 hours

Time to peak, serum: 1-2 hours

Excretion: Urine (26% to 32% as unchanged drug; 5% to 8% as metabolites); feces (39%)

Related Information

- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNorfloxacin is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, or insomnia; quinolones reported to cause restlessness, hallucinations, euphoria, depression, panic, and paranoia

Mental Health: Effects on Psychiatric TreatmentInhibits CYP1A2 isoenzyme; use caution with clozapine and other psychotropics; monitor for adverse effects

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International Brand NamesAmbigram (CO); Amicrobin (ES); Ampliron (PE); Anquin (IL); Baccidal (JP, TW); Biofloxin (IN); Chibroxin (AE, BH, BR, CN, CY, EG, ES, HR, IL, IQ, IR, JO, KW, LB, LY, OM, PE, PL, QA, SA, SY, VE, YE); Chibroxine (FR, UY); Chibroxol (LU, NL); Euroflox (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PH, QA, SA, SY, YE); Floxacin (MX); Fluseminal (GR); Foxgoria (SG); Foxinon (TH); Fulgram (IT); Gonorcin (TH); Grenis (PE); Gyrablock (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SG, SY, YE); Heiwin (PH); Janacin (HK, MY, TH); Lexinor (BD, CL, FI, HK, ID, IN, JP, KP, MY, PH, PK, SE, SG, TH, TW); Loxone (TH); M-Flox (TH); Manoflox (TH); Mitatonin (HK); Myfloxin (TH); Negaflox (BG); Nolicin (CZ, EE, HN, HR, HU, PL); Noracin (BR); Norbactin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, PL, SC, SD, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Norbactin Eye Drops (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Norex (PH); Norflohexal (DE); Norflosal (CR, DO, GT, HN, NI, PA, SV); Norflox (IN); Norflox Eye (IN); Norflox-AZU (DE); Norfloxbeta (DE); Normax Eye Ear Drops (IN); Norocin (GR); Noroxin (AU, BB, BF, BJ, BM, BS, BZ, CH, CI, CN, ET, FI, GB, GH, GM, GN, GY, IT, JM, KE, LR, MA, ML, MR, MU, MW, MX, NE, NG, NL, PE, PK, PT, SC, SD, SL, SN, SR, TN, TT, TZ, UG, VE, ZA, ZM, ZW); Noroxin Oftalmico (MX); Noroxine (FR); Norsol (AR); Noxoratio (PL); Nufloxib (AU); Oranor (MX); Orsanic (PY); Proxinor (TH); Pyrflox (ID); Respexil (BR); Roxin (AU); Sefnor (TH); Senro (ES); Septinor (PH); Sofasin (GR); Surflox (HK); Tenusin (PH); Trizolin (MY); Urekacin (KP); Urinex (MY); Urisold (GR); Uritracin (TH); Urobacid (MY); Uroctal (AE, BH, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Uroflox (IN); Uronor (UY); Uroseptal (EC); Uroxacin (AR); UT-in (ZA); Utiflox (SG); Utinor (GB, PH); Winaflox (PH); Xacin (TH); Yeloz (CO); Zoroxin (AT, BE, DK, LU)

Nortriptyline

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Aventyl® HCl may be confused with Bentyl®

Nortriptyline may be confused with amitriptyline, desipramine, Norpramin®

Pamelor® may be confused with Demerol®, Dymelor®, Panlor® DC

Pronunciation(nor TRIP ti leen)

U.S. Brand NamesPamelor®

Canadian Brand NamesAlti-Nortriptyline; Apo-Nortriptyline®; Aventyl®; Gen-Nortriptyline; Norventyl; Novo-Nortriptyline; Nu-Nortriptyline; PMS-Nortriptyline

Pharmacologic CategoryAntidepressant, Tricyclic (Secondary Amine)

Use: Labeled IndicationsTreatment of symptoms of depression

Use: Unlabeled/InvestigationalChronic pain, anxiety disorders, enuresis, attention-deficit/hyperactivity disorder (ADHD); adjunctive therapy for smoking cessation

Use: DentalTreatment of myofascial pain, neuralgia, burning mouth syndrome

Dosing: Adults

Depression: Oral: 25 mg 3-4 times/day up to 150 mg/day; doses may be given once daily.

Chronic urticaria, angioedema, nocturnal pruritus (unlabeled use): Oral: 75 mg/day

Myofascial pain, neuralgia, burning mouth syndrome (dental use): Initial: 10-25 mg at bedtime; dosage may be increased by 25 mg/day weekly, if tolerated; usual maintenance dose: 75 mg as a single bedtime dose or 2 divided doses

Smoking cessation (unlabeled use): Oral: 25-75 mg/day beginning 10-14 days before "quit" day; continue therapy for ≥12 weeks after "quit" day

Dosing: ElderlyInitial: 30-50 mg/day, given as a single daily dose or in divided doses. **Note:** Nortriptyline is one of the best tolerated TCAs in the elderly)

Dosing: Pediatric

Nocturnal enuresis (unlabeled use): Oral: 10-20 mg/day; titrate to a maximum of 40 mg/day

Depression (unlabeled use): Oral: 1-3 mg/kg/day

Dosing: Hepatic ImpairmentLower doses and slower titration are recommended dependent on individualization of dosage.

StorageStore at 20°C to 25°C (68°F to 77°F). Protect from light.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to nortriptyline and similar chemical class, or any component of the formulation; use of MAO inhibitors within 14 days; use in a patient during the acute recovery phase of MI

Allergy Considerations

- Tricyclic Antidepressant and Related Compounds Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See "Major psychiatric warnings" below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Nortriptyline is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Nortriptyline is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. The degree of anticholinergic blockade produced by this agent is moderate relative to other antidepressants.

- Hematologic effects: TCAs may rarely cause bone marrow suppression; monitor for any signs of infection and obtain CBC if symptoms (eg, fever, sore throat) evident.

- Orthostatic hypotension: May cause orthostatic hypotension (risk is low relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is low-moderate relative to other antidepressants.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk of conduction abnormalities with this agent is moderate relative to other antidepressants.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose regulation.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

- Thyroid dysfunction: Use with caution in patients with hyperthyroidism or those receiving thyroid supplementation due to concerns of pro-arrhythmogenesis.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Discontinuation of therapy: Recommended to discontinue prior to elective surgery requiring general anesthesia. Therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

Geriatric ConsiderationsSince nortriptyline is the least likely of the tricyclic antidepressants (TCAs) to cause orthostatic hypotension and one of the least anticholinergic and sedating TCAs, it is a preferred agent when a TCA is indicated. Data from a clinical trial comparing fluoxetine to tricyclics suggests that fluoxetine is significantly less effective than nortriptyline in hospitalized elderly patients with unipolar affective disorder, especially those with melancholia and concurrent cardiovascular disease. Paroxetine has been shown to be an equally effective antidepressant compared to nortriptyline in patients with ischemic heart disease. However, nortriptyline was associated a significantly higher rate of adverse cardiac events (sustained increase in heart rate, sinus tachycardia, and asymptomatic increase in ventricular ectopy) compared to placebo.

LactationEnters breast milk/contraindicated (AAP rates “of concern”)

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, flushing, heart block, hypertension, MI, palpitation, postural hypotension, tachycardia

Central nervous system: Agitation, anxiety, ataxia, confusion, delirium, delusions, disorientation, dizziness, drowsiness, EEG changes, exacerbation of psychosis, extrapyramidal symptoms, fatigue, hallucinations, headache, hypomania, incoordination, insomnia, nightmares, panic, restlessness, seizure

Dermatologic: Alopecia, itching, petechiae, photosensitivity, rash, urticaria

Endocrine & metabolic: Blood sugar increases/decreases, breast enlargement, galactorrhea, gynecomastia, increase or decrease in libido, sexual dysfunction, SIADH

Gastrointestinal: Abdominal cramps, anorexia, black tongue, constipation, diarrhea, epigastric distress, nausea, paralytic ileus, stomatitis, taste disturbance, vomiting, weight gain/loss, xerostomia

Genitourinary: Delayed micturition, impotence, nocturia, polyuria, testicular edema, urinary retention

Hematologic: Agranulocytosis (rare), eosinophilia, purpura, thrombocytopenia

Hepatic: Cholestatic jaundice, transaminases increased

Neuromuscular & skeletal: Numbness, paresthesia, peripheral neuropathy, tingling, tremor, weakness

Ocular: Blurred vision, disturbances in accommodation, eye pain, mydriasis

Otic: Tinnitus

Miscellaneous: Allergic reactions (eg, general edema or of the face/tongue), diaphoresis (excessive), withdrawal symptoms

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2C19 (minor), 2D6 (major), 3A4 (minor); **Inhibits** CYP2D6 (weak), 2E1 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Tricyclic Antidepressants may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Agonists: Tricyclic Antidepressants may enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Alpha2-Agonists: Tricyclic Antidepressants may diminish the antihypertensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Altretamine: May enhance the orthostatic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Amphetamines: Tricyclic Antidepressants may enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Beta2-Agonists: Tricyclic Antidepressants may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cinacalcet: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Desmopressin: Tricyclic Antidepressants may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dexmethylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

DULoxetine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Iobenguane I 123: Tricyclic Antidepressants may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May enhance the neurotoxic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Tricyclic Antidepressants may enhance the QTc-prolonging effect of QuiNIDine. QuiNIDine may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

St Johns Wort: May increase the metabolism of Tricyclic Antidepressants. The risk of serotonin syndrome may theoretically be increased. *Risk D: Consider therapy modification*

Sulfonylureas: Cyclic Antidepressants may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Terbinafine: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

TraMADol: Tricyclic Antidepressants may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. *Risk C: Monitor therapy*

Valproic Acid: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Tricyclic Antidepressants may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Yohimbine: Tricyclic Antidepressants may increase the serum concentration of Yohimbine. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava (may increase risk of serotonin syndrome and/or excessive sedation).

Monitoring ParametersBlood pressure and pulse rate (ECG, cardiac monitoring) prior to and during initial therapy in older adults; weight; blood levels are useful for therapeutic monitoring; suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased)

Reference Range

Plasma levels do not always correlate with clinical effectiveness

Therapeutic: 50-150 ng/mL (SI: 190-570 nmol/L)

Toxic: >500 ng/mL (SI: >1900 nmol/L)

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess for suicidal tendencies before beginning therapy. May cause physiological or psychological dependence, tolerance, or abuse; periodically evaluate need for continued use. Assess therapeutic effectiveness (mental status, mood, affect) and adverse reactions (eg, suicidal ideation) at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing (allow 3-4 weeks between discontinuing this medication and starting another antidepressant). Caution patients with diabetes to monitor glucose levels closely; may increase or decrease serum glucose levels. Teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed; take once-a-day dose at bedtime. Do not increase dose or frequency; may take 2-3 weeks to achieve desired results. This drug may cause physical and/or psychological dependence. Avoid alcohol and grapefruit juice. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, loss of appetite, or disturbed taste (small frequent meals, good mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); urinary retention (void before taking medication); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); altered sexual drive or ability (reversible); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report chest pain, palpitations, or rapid heartbeat; persistent adverse CNS effects (eg, suicidal ideation, nervousness, restlessness, insomnia, anxiety, excitation, headache, agitation, impaired coordination, changes in cognition); muscle cramping, weakness, tremors, or rigidity; blurred vision or eye pain; breast enlargement or swelling; yellowing of skin or eyes; or worsening of condition.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 10 mg, 25 mg, 50 mg, 75 mg

Pamelor®: 10 mg, 25 mg, 50 mg, 75 mg [may contain benzyl alcohol; 50 mg may also contain sodium bisulfite]

Solution:

Pamelor®: 10 mg/5 mL (473 mL) [contains ethanol 4% and benzoic acid]

Generic AvailableYes: Excludes solution

Pricing: U.S. (www.drugstore.com)

Capsules (Nortriptyline HCl)

25 mg (30): $12.99

50 mg (30): $12.99

75 mg (30): $12.99

Capsules (Pamelor)

10 mg (30): $627.85

25 mg (30): $627.85

50 mg (30): $616.34

75 mg (30): $540.38

Solution (Nortriptyline HCl)

10 mg/5 mL (473): $52.98

Mechanism of ActionTraditionally believed to increase the synaptic concentration of serotonin and/or norepinephrine in the central nervous system by inhibition of their reuptake by the presynaptic neuronal membrane. However, additional receptor effects have been found including desensitization of adenyl cyclase, down regulation of beta-adrenergic receptors, and down regulation of serotonin receptors.

Pharmacodynamics/Kinetics

Onset of action: Therapeutic: 1-3 weeks

Distribution: V_d: 21 L/kg

Protein binding: 93% to 95%

Metabolism: Primarily hepatic; extensive first-pass effect

Half-life elimination: 28-31 hours

Time to peak, serum: 7-8.5 hours

Excretion: Urine (as metabolites and small amounts of unchanged drug); feces (small amounts)

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Dental Health Professional ConsiderationsNortriptyline is known to prolong the QT interval. The QT interval is measured as the time and distance between the Q point of the QRS complex and the end of the T wave in the ECG tracing. After adjustment for heart rate, the QT interval is defined as prolonged if it is more than 450 msec in men and 460 msec in women. A long QT syndrome was first described in the 1950s and 60s as a congenital syndrome involving QT interval prolongation and syncope and sudden death. Some of the congenital long QT syndromes were characterized by a peculiar electrocardiographic appearance of the QRS complex involving a premature atria beat followed by a pause, then a subsequent sinus beat showing marked QT prolongation and deformity. This type of cardiac arrhythmia was originally termed “torsade de pointes” (translated from the French as “twisting of the points”).

Prolongation of the QT interval is thought to result from delayed ventricular repolarization. The repolarization process within the myocardial cell is due to the efflux of intracellular potassium. The channels associated with this current can be blocked by many drugs and predispose the electrical propagation cycle to torsade de pointes.

Nortriptyline is considered as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. It is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), black tongue, and unpleasant taste. Long-term treatment with TCAs, such as nortriptyline, increases the risk of caries by reducing salivation and salivary buffer capacity.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Nortriptyline is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution. See Dental Comment.

Mental Health Comment Tricyclic antidepressants may be classified as tertiary (amitriptyline, doxepin, clomipramine, imipramine, trimipramine) or secondary amines (nortriptyline, desipramine, protriptyline). The tertiary amines are not recommended to treat depression in the elderly. If a TCA is used in the elderly, it should be a secondary amine. The tertiary amines are commonly used in low dosages for various conditions associated with pain. Toxicity is generally dose dependent. Relatively small overdoses (1-week supply) can be potentially fatal.

Plasma concentrations correlate with clinical response. A curvilinear relationship exists.

Anesthesia and Critical Care Concerns/Other Considerations Its maximum antidepressant effect may not be seen for ≥2 weeks after initiation of therapy.

Index Terms Nortriptyline Hydrochloride

References

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International Brand NamesAllegron (AU, GB, IE); Altilev (UY); Ateben (AR); Aventyl (MY); Martimil (ES); Noritren (DK, EE, FI, IT, NO); Norline (TH); Norpress (NZ); Norterol (PT); Nortrilen (AE, AT, BE, BF, BH, BJ, CH, CI, CY, CZ, DE, EG, ET, GH, GM, GN, GR, HK, ID, IL, IQ, IR, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Nortylin (IL); Nortyline (TH); Ortrip (TH); Pamelor (BR); Paxtibi (ES); Sensaval (SE); Sensival (IN); Vividyl (IT)

Nylidrin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(NYE li drin)

Canadian Brand NamesArlidin®

Pharmacologic CategoryVasodilator, Peripheral

Use: Labeled IndicationsConsidered “possibly effective” for increasing blood supply to treat peripheral disease (arteriosclerosis obliterans, diabetic vascular disease, nocturnal leg cramps, Raynaud's disease, frost bite, ischemic ulcer, thrombophlebitis) and circulatory disturbances of the inner ear (cochlear ischemia, macular or ampullar ischemia, etc)

Dosing: Adults**Circulatory insufficiency:** Oral: 3-12 mg 3-4 times/day

Dosing: ElderlyRefer to adult dosing.

Pregnancy Risk FactorC

Adverse Reactions

1% to 10%:

Central nervous system: Nervousness

Neuromuscular & skeletal: Trembling

<1%: Dizziness, nausea, palpitation, postural hypotension, vomiting, weakness

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Mechanism of ActionNylidrin is a peripheral vasodilator; this results from direct relaxation of vascular smooth muscle and beta-agonist action. Nylidrin does not appear to affect cutaneous blood flow; it reportedly increases heart rate and cardiac output; cutaneous blood flow is not enhanced to any appreciable extent.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness or dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesArlidin (IN)

Nystatin and Triamcinolone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Mycolog®-II may be confused with Halog®

Pronunciation(nye STAT in & trye am SIN oh lone)

U.S. Brand NamesMycolog®-II [DSC]

Pharmacologic CategoryAntifungal Agent, Topical; Corticosteroid, Topical

Use: Labeled IndicationsTreatment of cutaneous candidiasis

Use: DentalTreatment of angular cheilitis and cutaneous candidiasis

Dosing: Adults**Cutaneous *Candida*:** Topical: Apply sparingly 2-4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: TopicalExternal use only; do not use on open wounds. Apply sparingly to occlusive dressings; should not be used in the presence of open or weeping lesions.

ContraindicationsHypersensitivity to nystatin, triamcinolone, or any component of the formulation

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Special populations:

- Pediatrics: Chronic use of corticosteroids in children may interfere with growth and development.

Geriatric ConsiderationsNo specific dose adjustment or use consideration necessary in the elderly; for oral infections, patients who wear dentures must have them removed and cleaned in order to eliminate source of reinfection.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown

Breast-Feeding Considerations

Nystatin: Compatible

Triamcinolone: No data reported

Adverse Reactions1% to 10%:

Dermatologic: Dryness, folliculitis, hypertrichosis, acne, hypopigmentation, allergic dermatitis, maceration of the skin, skin atrophy

Local: Burning, itching, irritation

Miscellaneous: Increased incidence of secondary infection

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antidiabetic Agents: Corticosteroids (Orally Inhaled) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] =

Discontinued product

Cream (Mycolog®-II [DSC]): Nystatin 100,000 units and triamcinolone acetonide 0.1% (15 g, 30 g, 60 g)

Ointment: Nystatin 100,000 units and triamcinolone acetonide 0.1% (15 g, 30 g, 60 g)

Mycolog®-II: Nystatin 100,000 units and triamcinolone acetonide 0.1% (15 g, 30 g, 60 g) [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Cream (Nystatin-Triamcinolone)

100000-0.1 units/g-% (15): $11.99

100000-0.1 units/g-% (30): $12.99

100000-0.1 units/g-% (60): $12.99

Ointment (Nystatin-Triamcinolone)

100000-0.1 units/g-% (15): $11.99

Mechanism of ActionNystatin is an antifungal agent that binds to sterols in fungal cell membrane, changing the cell wall permeability allowing for leakage of cellular contents. Triamcinolone is a synthetic corticosteroid; it decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability. It suppresses the immune system reducing activity and volume of the lymphatic system. It suppresses adrenal function at high doses.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Nystatin
- Triamcinolone

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsTriamcinolone and Nystatin

References

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International Brand NamesFungiderma (TW)

Nystatin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Nystatin may be confused with Nilstat®, Nitrostat®

Nilstat may be confused with Nitrostat®, nystatin

Pronunciation(nye STAT in)
U.S. Brand NamesBio-Statin®; Mycostatin®; Nyamyc™; Nystat-Rx®; Nystop®; Paddock Nystatin™; Pedi-Dri®
Canadian Brand NamesCandistatin®; Nilstat; Nyaderm; PMS-Nystatin
Pharmacologic CategoryAntifungal Agent, Oral Nonabsorbed; Antifungal Agent, Topical; Antifungal Agent, Vaginal
Use: Labeled IndicationsTreatment of susceptible cutaneous, mucocutaneous, and oral cavity fungal infections normally caused by the *Candida* species
Use: DentalTreatment of susceptible cutaneous, mucocutaneous, and oral cavity fungal infections normally caused by the *Candida* species
Dosing: Adults

Oral candidiasis: Suspension (swish and swallow orally): 400,000-600,000 units 4 times/day

Mucocutaneous infections: Topical: Apply 2-3 times/day to affected areas; very moist topical lesions are treated best with powder.

Intestinal infections: Oral tablets: 500,000-1,000,000 units every 8 hours

Vaginal infections: Vaginal tablets: Insert 1 tablet/day at bedtime for 2 weeks. (May also be given orally.)

Note: Powder for compounding: $^{1}/_{8}$ teaspoon (500,000 units) to equal approximately $^{1}/_{2}$ cup of water; give 4 times/day

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Oral candidiasis:

Suspension (swish and swallow orally):

Premature infants: 100,000 units 4 times/day

Infants: 200,000 units 4 times/day or 100,000 units to each side of mouth 4 times/day

Children: 400,000-600,000 units 4 times/day

Powder for compounding: Children: Refer to adult dosing.

Mucocutaneous infections: Children: Refer to adult dosing.

Administration: OralSuspension: Shake well before using. Should be swished about the mouth and retained in the mouth for as long as possible (several minutes) before swallowing.
Storage

Vaginal insert: Store in refrigerator. Protect from temperature extremes, moisture, and light.

Oral tablet, ointment, topical powder, and oral suspension: Store at controlled room temperature 15°C to 25°C (59°F to 77°F).

ContraindicationsHypersensitivity to nystatin or any component of the formulation
Geriatric ConsiderationsFor oral infections, patients who wear dentures must have them removed and cleaned in order to eliminate source of reinfection.
Pregnancy Risk FactorB/C (oral)
LactationDoes not enter breast milk/compatible (not absorbed orally)
Adverse Reactions

Frequency not defined: Dermatologic: Contact dermatitis, Stevens-Johnson syndrome

1% to 10%: Gastrointestinal: Nausea, vomiting, diarrhea, stomach pain

<1%: Hypersensitivity reactions

Oncology: Emetic PotentialLow (10% to 30%)
Drug Interactions

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringDetermine that cause of infection is fungal. Avoid skin contact when applying. Monitor therapeutic effectiveness, adverse reactions at beginning of therapy and periodically throughout therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake as directed. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not allow medication to come in contact with eyes. Report persistent nausea, vomiting, or diarrhea; or if condition being treated worsens or does not improve. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Oral tablet: Swallow whole; do not crush or chew.

Oral suspension: Shake well before using. Remove dentures, clean mouth (do not replace dentures until after using medications). Swish suspension in mouth for several minutes before swallowing

Oral troche: Remove dentures, clean mouth (do not replace dentures until after using medication). Allow troche to dissolve in mouth; do not chew or swallow whole.

Topical: Wash and dry area before applying (do not reuse towels without washing, apply clean clothing after use). Report unresolved burning, redness, or swelling in treated areas.

Vaginal tablet: Wash hands before using. Lie down to insert high into vagina at bedtime.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

Bio-Statin®: 500,000 units, 1 million units

Cream: 100,000 units/g (15 g, 30 g)

Mycostatin®: 100,000 units/g (30 g)

Ointment, topical: 100,000 units/g (15 g, 30 g)

Powder, for prescription compounding: 50 million units (10 g); 150 million units (30 g); 500 million units (100 g); 2 billion units (400 g)

Nystat-Rx®: 50 million units (10 g); 150 million units (30 g); 500 million units (100 g); 1 billion units (190 g); 2 billion units (350 g)

Powder, for prescription compounding: 1 billion units (190 g); 150 million units (30 g); 2 billion units (350 g); 50 million units (10 g); 500 million units (100 g)

Bio-Statin®: 2 billion units (30 g)

Powder for suspension, oral [preservative free]:

Paddock Nystatin™: 150 million units (30 g); 2 billion units (400 g); 50 million units (10 g); 500 million units (100 g) [sugar free]

Powder, topical:

Mycostatin®: 100,000 units/g (15 g) [contains talc] [DSC]

Nyamyc™: 100,000 units/g (15 g, 30 g) [contains talc]

Nystop®: 100,000 units/g (15 g, 30 g, 60 g) [contains talc]

Pedi-Dri®: 100,000 units/g (56.7 g) [contains talc]

Suspension, oral: 100,000 units/mL (5 mL, 60 mL, 480 mL)

Tablet: 500,000 units

Tablet, vaginal: 100,000 units (15s) [packaged with applicator]

Generic AvailableYes: Cream, ointment, powder, suspension, tablet

Pricing: U.S. (www.drugstore.com)

Cream (Nystatin)

100000 units/g (30): $12.99

Ointment (Nystatin)

100000 units/g (15): $12.99

Powder (Mycostatin)

100000 units/g (15): $36.99

Powder (Nystatin)

(1): $39.99

(30): $2835.02

Powder (Pedi-Dri)

100000 units/g (56.7): $93.80

Suspension (Nystatin)

100000 units/mL (180): $42.98

Tablets (Nystatin)

100000 unit (15): $72.27

500000 unit (60): $36.99

Mechanism of ActionBinds to sterols in fungal cell membrane, changing the cell wall permeability allowing for leakage of cellular contents
Pharmacodynamics/Kinetics

Onset of action: Symptomatic relief from candidiasis: 24-72 hours

Absorption: Topical: None through mucous membranes or intact skin; Oral: Poorly absorbed

Excretion: Feces (as unchanged drug)

Related Information

- Antifungal Agents
- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
References

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International Brand NamesAfunginal (PH); Biofanal (DE); Biofanal Mundgel (DE); Candio-Hermal (AT, DE, LU); Candistin (ID); Enystin (ID); Fungatin (ID); Fungicidin (CZ); Fungostatin (BG); Gynostatin (PE); Kandistatin (ID); Lystin (HK, MY); Mibesan-S (MX); Micad (PY); Micostatin (AR, BR, CN, CO, PE, UY, VE); Mikostat (MY); Moronal (DE); Mycastatin (JP); Mycocide (TW); Mycostatin (AT, BF, BJ, CH, CI, DK, ES, ET, FI, GH, GM, GN, GR, HK, ID, IE, IN, IT, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, NO, NZ, PH, PT, SC, SD, SE, SL, SN, TH, TN, TW, TZ, UG, ZA, ZM, ZW); Mycostatin EVT (CL); Mycostatine (FR, KP); Mykoderm (DE); N-Statin (AU); Nadostine (TW); Nilstat (AE, AR, BE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LU, LY, OM, PK, QA, SA, SY, TW, YE); Nistaquim (MX); Nistatin (HR); Nizin-V (MX); Nymiko (HK, IN); Nystacid (FI); Nystan (GB); Nystatin (IL, PL); Nystatine (BE, LU); Nystatyna (PL)

Octreotide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Sandostatin® may be confused with Sandimmune®, Sandostatin LAR®, sargramostim, simvastatin

Pronunciation(ok TREE oh tide)

U.S. Brand NamesSandostatin LAR®; Sandostatin®

Canadian Brand NamesOctreotide Acetate Injection; Octreotide Acetate Omega; Sandostatin LAR®; Sandostatin®

Pharmacologic CategoryAntidiarrheal; Antidote; Somatostatin Analog

Use: Labeled IndicationsControl of symptoms in patients with metastatic carcinoid and vasoactive intestinal peptide-secreting tumors (VIPomas); treatment of acromegaly

Use: Unlabeled/InvestigationalAIDS-associated secretory diarrhea (including *Cryptosporidiosis*); control of bleeding of esophageal varices; second-line treatment for thymic malignancies; Cushing's syndrome (ectopic); insulinomas; glucagonoma; small bowel fistulas; pancreatic tumors; gastrinoma; postgastrectomy dumping syndrome; chemotherapy-induced diarrhea; graft-versus-host disease (GVHD) induced diarrhea; Zollinger-Ellison syndrome; congenital hyperinsulinism; hypothalamic obesity; treatment of hypoglycemia secondary to sulfonylurea poisoning (as an adjunct to dextrose)

Dosing: Adults

Acromegaly:

SubQ, I.V.: Initial: 50 mcg 3 times/day; titrate to achieve growth hormone levels <5 ng/mL or IGF-I (somatomedin C) levels <1.9 units/mL in males and <2.2 units/mL in females. Usual effective dose 100-200 mcg 3 times/day; range 300-1500 mcg/day. **Note:** Should be withdrawn yearly for a 4-week interval (8 weeks for depot injection) in patients who have received irradiation. Resume if levels increase and signs/symptoms recur.

I.M. depot injection: Patients must be stabilized on subcutaneous octreotide for at least 2 weeks before switching to the long-acting depot. Upon switch: 20 mg I.M. intragluteally every 4 weeks for 3 months, then the dose may be modified based upon response.

Dosage adjustment for acromegaly: After 3 months of depot injections, the dosage may be continued or modified as follows:

GH ≤1 ng/mL, IGF-1 normal, and symptoms controlled: Reduce octreotide LAR® to 10 mg I.M. every 4 weeks

GH ≤2.5 ng/mL, IGF-1 normal, and symptoms controlled: Maintain octreotide LAR® at 20 mg I.M. every 4 weeks

GH >2.5 ng/mL, IGF-1 elevated, and/or symptoms uncontrolled: Increase octreotide LAR® to 30 mg I.M. every 4 weeks

Note: Patients not adequately controlled at a dose of 30 mg may increase dose to 40 mg every 4 weeks. Dosages >40 mg are not recommended.

Carcinoid tumors:

SubQ, I.V.: Initial 2 weeks: 100-600 mcg/day in 2-4 divided doses; usual range 50-750 mcg/day (some patients may require up to 1500 mcg/day)

I.M. depot injection: Patients must be stabilized on subcutaneous octreotide for at least 2 weeks before switching to the long-acting depot. Upon switch: 20 mg I.M. intragluteally every 4 weeks for 2 months, then the dose may be modified based upon response.

Note: Patients should continue to receive their SubQ injections for the first 2 weeks at the same dose in order to maintain therapeutic levels (some patients may require 3-4 weeks of continued SubQ injections). Patients who experience periodic exacerbations of symptoms may require temporary SubQ injections in addition to depot injections (at their previous SubQ dosing regimen) until symptoms have resolved.

Dosage adjustment: See dosing adjustment for VIPomas.

VIPomas:

SubQ, I.V.: Initial 2 weeks: 200-300 mcg/day in 2-4 divided doses; titrate dose based on response/tolerance. Range: 150-750 mcg/day (doses >450 mcg/day are rarely required)

I.M. depot injection: Patients must be stabilized on subcutaneous octreotide for at least 2 weeks before switching to the long-acting depot. Upon switch: 20 mg I.M. intragluteally every 4 weeks for 2 months, then the dose may be modified based upon response.

Note: Patients receiving depot injection should continue to receive their SubQ injections for the first 2 weeks at the same dose in order to maintain therapeutic levels (some patients may require 3-4 weeks of continued SubQ injections). Patients who experience periodic exacerbations of symptoms may require temporary SubQ injections in addition to depot injections (at their previous SubQ dosing regimen) until symptoms have resolved.

Dosage adjustment for carcinoid tumors and VIPomas: After 2 months of depot injections, the dosage may be continued or modified as follows:

Increase to 30 mg I.M. every 4 weeks if symptoms are inadequately controlled

Decrease to 10 mg I.M. every 4 weeks, for a trial period, if initially responsive to 20 mg dose

Dosage >30 mg is not recommended

Diarrhea (unlabeled use): I.V.: Initial: 50-100 mcg every 8 hours; increase by 100 mcg/dose at 48-hour intervals; maximum dose: 500 mcg every 8 hours

Esophageal varices bleeding (unlabeled use): I.V. bolus: 25-50 mcg followed by continuous I.V. infusion of 25-50 mcg/hour

Hypoglycemia in sulfonylurea poisoning (unlabeled use): SubQ is the preferred route of administration; repeat dosing or initiation of a continuous infusion may be required in patients who experience recurrent hypoglycemia. Duration of treatment may exceed 24 hours. Optimal care decisions should be made based upon patient-specific details:

SubQ (preferred route of administration): 50-100 mcg; repeat in 6-12 hours as needed based upon blood glucose concentrations

I.V.: Doses up to 100-125 mcg/hour have been used successfully

Dosing: ElderlyRefer to adult dosing. Elimination half-life is increased by 46% and clearance is decreased by 26%; dose adjustment may be required. Dosing should generally begin at the lower end of dosing range.

Dosing: PediatricInfants and Children:

Secretory diarrhea (unlabeled use): I.V., SubQ: Doses of 1-10 mcg/kg every 12 hours have been used in children beginning at the low end of the range and increasing by 0.3 mcg/kg/dose at 3-day intervals. Suppression of growth hormone (animal data) is of concern when used as long-term therapy.

Congenital hyperinsulinism (unlabeled use): SubQ: Doses of 3-40 mcg/kg/day have been used.

Hypoglycemia in sulfonylurea poisoning (unlabeled use): SubQ is the preferred route of administration; repeat dosing or initiation of a continuous infusion may be required in patients who experience recurrent hypoglycemia. Duration of treatment may exceed 24 hours. Optimal care decisions should be made based upon patient-specific details: SubQ: 1-1.5 mcg/kg (maximum dose: 50 mcg); repeat in 6-12 hours as needed based upon blood glucose concentrations

Dosing: Renal Impairment
Nondialysis-dependent renal impairment: No dosage adjustment required

Dialysis-dependent renal impairment: Depot injection: Initial dose: 10 mg I.M. every 4 weeks; titrate based upon response (clearance is reduced by ~50%)

Dosing: Hepatic ImpairmentPatients with established cirrhosis of the liver: Depot injection: Initial dose: 10 mg I.M. every 4 weeks; titrate based upon response.

Administration: I.M.Depot formulation: Administer I.M. intragluteal (avoid deltoid administration); alternate gluteal injection sites to avoid irritation. Do not administer Sandostatin LAR® intravenously or subcutaneously; must be administered immediately after mixing.

Administration: I.V.Regular injection only (not suspension): IVP should be administered undiluted over 3 minutes. IVPB should be administered over 15-30 minutes. Continuous I.V. infusion rates have ranged from 25-50 mcg/hour for the treatment of esophageal variceal bleeding (unlabeled route/use); continuous I.V. infusion rates of 100-125 mcg/hour have been used for the treatment of sulfonylurea-induced hypoglycemia (unlabeled use).

Administration: I.V. DetailDo not use if solution contains particles or is discolored. I.V. administration may be IVP, IVPB, or continuous I.V. infusion (unlabeled route).

pH: 4.0-4.6

Administration: OtherSubQ: Regular injection formulation (not depot) can be administered SubQ. Use the concentration with smallest volume to deliver dose to reduce injection site pain. Rotate injection site; may bring to room temperature prior to injection.

Dietary ConsiderationsSchedule injections between meals to decrease GI effects. May alter absorption of dietary fats.

Storage

Solution: Octreotide is a clear solution and should be stored at refrigerated temperatures between 2°C and 8°C (36°F and 46°F). Protect from light. May be stored at room temperature of 20°C to 30°C (70°F and 86°F) for up to 14 days when protected from light. Stability of parenteral admixture is stable in NS for 96 hours at room temperature (25°C) and in D_5W for 24 hours. Discard multidose vials within 14 days after initial entry.

Suspension: Prior to dilution, store at refrigerated temperatures between 2°C and 8°C (36°F and 46°F) and protect from light. Depot drug product kit may be at room temperature for 30-60 minutes prior to use. Use suspension immediately after preparation.

CompatibilitySolution: Stable in D_5W, NS; **incompatible** with fat emulsion 10%; **variable stability** in TPN (The manufacturer states that octreotide solution is not compatible in TPN solutions due to the formation of a glycosyl octreotide conjugate which may have decreased activity; other sources give it limited compatibility.)

Y-site administration:Incompatible: Micafungin. **Variable (consult detailed reference):** Pantoprazole, TPN.

Compatibility when admixed: Compatible: Heparin. **Incompatible:** Pantoprazole.

ContraindicationsHypersensitivity to octreotide or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Abnormal Schillings test: Chronic treatment has been associated with abnormal Schillings test; monitor vitamin B_{12} levels.

- Cholelithiasis: May impair gallbladder function (inhibits gallbladder contractility and decreases bile secretion); monitor patients for cholelithiasis.

- Hypothyroidism: Suppresses secretion of TSH; monitor for hypothyroidism.

- Pancreatitis: May alter absorption of dietary fats; monitor for pancreatitis.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with heart failure or concomitant medications that alter heart rate or rhythm; bradycardia, conduction abnormalities, and arrhythmia have been observed in acromegalic and carcinoid syndrome patients. Cardiovascular medication requirements may change.

- Diabetes: Somatostatin analogs may affect glucose regulation. In type I diabetes, severe hypoglycemia may occur; in type II diabetes or patients without diabetes, hyperglycemia may occur. Insulin and other hypoglycemic medication requirements may change.

- Excessive fluid loss: May reduce excessive fluid loss in patients with conditions that cause such a loss; periodic monitoring for elevations in zinc levels is recommended in such patients that are maintained on total parenteral nutrition (TPN).

- Hepatic impairment: Use caution in patients with hepatic impairment; dosage adjustment required in patients with established cirrhosis

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required in patients receiving dialysis.

Concurrent drug therapy issues:

- QT_c-prolonging agents: Octreotide may enhance the adverse/toxic effects of other QT_c-prolonging agents.

Dosage form specific issues:

- Depot formulation: Do not use depot formulation for the treatment of sulfonylurea-induced hypoglycemia.

- Vehicle used in depot injection (polylactide-co-glycolide microspheres): Has rarely been associated with retinal artery occlusion in patients with abnormal arteriovenous anastomosis (eg, patent foramen ovale).

Special populations:

- Elderly: Dosage adjustment may be necessary; significant increases in elimination half-life have been observed in older adults.

- Females: Therapy may restore fertility; females of childbearing potential should use adequate contraception.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Octreotide crosses the human placenta; data concerning use in pregnancy is limited. Women of childbearing potential should use adequate contraception during treatment with octreotide; normalization of IGF-1 and GH may restore fertility in women with acromegaly. In case reports of acromegalic women who received normal doses of octreotide during pregnancy, no congenital malformations were reported.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsAdverse reactions vary by route of administration and dosage form. Frequency of cardiac, endocrine, and gastrointestinal adverse reactions was generally higher in acromegalics.

>16%:

Cardiovascular: Sinus bradycardia (19% to 25%), chest pain (≤20%; non-depot formulations)

Central nervous system: Fatigue (1% to 32%), headache (6% to 30%), malaise (16% to 20%), fever (16% to 20%), dizziness (5% to 20%)

Dermatologic: Pruritus (≤18%)

Endocrine & metabolic: Hyperglycemia (2% to 27%)

Gastrointestinal: Abdominal pain (5% to 61%), loose stools (5% to 61%), nausea (5% to 61%), diarrhea (34% to 58%), flatulence (≤38%), cholelithiasis (13% to 38%; length of therapy dependent), biliary sludge (24%; length of therapy dependent), constipation (9% to 21%), vomiting (4% to 21%), biliary duct dilatation (12%)

Local: Injection site pain (2% to 50%; dose and formulation related)

Neuromuscular & skeletal: Back pain (1% to 27%), arthropathy (8% to 19%), myalgia (≤18%)

Respiratory: Upper respiratory infection (10% to 23%), dyspnea (≤20%; non-depot formulations)

Miscellaneous: Antibodies to octreotide (up to 25%; no efficacy change), flu symptoms (1% to 20%)

5% to 15%:

Cardiovascular: Hypertension (≤13%), conduction abnormalities (9% to 10%), arrhythmia (3% to 9%), palpitation, peripheral edema

Central nervous system: Pain (4% to 15%), anxiety, confusion, hypoesthesia, insomnia

Dermatologic: Rash (15%; depot formulation), alopecia (≤13%)

Endocrine & metabolic: Hypothyroidism (≤12%; non-depot formulations), goiter (≤8%; non-depot formulations)

Gastrointestinal: Anorexia, cramping, tenesmus (4% to 6%), dyspepsia (4% to 6%), steatorrhea (4% to 6%), feces discoloration (4% to 6%)

Hematologic: Anemia (≤15%; non-depot formulations: <1%)

Neuromuscular & skeletal: Arthralgia, myalgia, paresthesia, rigors, weakness

Otic: Earache

Renal: Renal calculus

Respiratory: Cough, pharyngitis, sinusitis, rhinitis

Miscellaneous: Allergy, diaphoresis

1% to 4%:

Cardiovascular: Angina, cardiac failure, edema, flushing, hematoma, phlebitis

Central nervous system: Abnormal gait, amnesia, depression, dysphonia, hallucinations, nervousness, neuralgia, somnolence, vertigo

Dermatologic: Acne, bruising, cellulitis

Endocrine & metabolic: Hypoglycemia (2% to 4%), hypokalemia, hypoproteinemia, gout, cachexia, breast pain, impotence

Gastrointestinal: Colitis, diverticulitis, dysphagia, fat malabsorption, gastritis, gastroenteritis, gingivitis, glossitis, melena, stomatitis, taste perversion, xerostomia

Genitourinary: Incontinence, pollakuria (non-depot formulations), urinary tract infection

Local: Injection site hematoma

Neuromuscular & skeletal: Hyperkinesia, hypertonia, joint pain, neuropathy, tremor

Ocular: Blurred vision, visual disturbance

Otic: Tinnitus

Renal: Albuminuria, renal abscess

Respiratory: Bronchitis, epistaxis

Miscellaneous: Bacterial infection, cold symptoms, moniliasis

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Anaphylactic shock, anaphylactoid reaction, aneurysm, aphasia, appendicitis, arthritis, ascending cholangitis, ascites, atrial fibrillation, basal cell carcinoma, Bell's palsy, biliary obstruction, breast carcinoma, cardiac arrest, cerebral vascular disorder, CHF, cholestatic hepatitis, CK increased, creatinine increased, deafness, diabetes insipidus, diabetes mellitus, facial edema, fatty liver, galactorrhea, gallbladder polyp, GI bleeding, GI hemorrhage, GI ulcer, glaucoma, gynecomastia, hearing loss, hematuria, hemiparesis, hemorrhoids, hepatitis, hyperesthesia, hypertensive reaction, hypoadrenalism, intestinal obstruction, intracranial hemorrhage, intraocular pressure increased, ischemia, jaundice, joint effusion, lactation, LFTs increased, libido decreased, malignant hyperpyrexia, menstrual irregularities, MI, migraine, nephrolithiasis, neuritis, orthostatic hypotension, pancreatitis, pancytopenia, paresis, petechiae, pituitary apoplexy, pleural effusion, pneumonia, pneumothorax, pulmonary embolism, pulmonary hypertension, pulmonary nodule, Raynaud’s syndrome, rectal bleeding, renal failure, renal insufficiency, retinal vein thrombosis, scotoma, seizure, status asthmaticus, suicide attempt, syncope, tachycardia, thrombocytopenia, thrombophlebitis, thrombosis, urticaria, visual field defect, weight loss, wheal/erythema

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Codeine: Somatostatin Analogs may decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

CycloSPORINE: Somatostatin Analogs may decrease the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pegvisomant: Somatostatin Analogs may enhance the adverse/toxic effect of Pegvisomant. Specifically, this combination may increase the risk for significant elevations of liver enzymes. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Herb/Nutraceutical: Avoid hypoglycemic herbs, including alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, and stinging nettle (may enhance the hypoglycemic effect of octreotide).

Monitoring Parameters

Acromegaly: Growth hormone, somatomedin C (IGF-1)

Carcinoid: 5-HIAA, plasma serotonin and plasma substance P

VIPomas: Vasoactive intestinal peptide

Chronic therapy: Thyroid function (baseline and periodic), vitamin B_{12} level, blood glucose, cardiac function (heart rate, EKG), zinc level (patients with excessive fluid loss maintained on TPN)

Reference RangeVasoactive intestinal peptide: <75 ng/L; levels vary considerably between laboratories

Nursing: Physical Assessment/MonitoringUse caution in presence of renal and/or hepatic impairment (dosage adjustment may be necessary). Assess all other pharmacological or herbal products patient may be taking for potential interactions or toxicity (eg, may effect response to insulin or sulfonylureas and/or response to cardiovascular medications). See Administration for I.V., I.M., and SubQ specifics. Follow specific dosing directions when switching from SubQ to long-acting depot formulation. Assess results of laboratory tests on a regular basis with chronic therapy. Evaluate therapeutic effectiveness according to purpose for use and adverse effects (eg, hypo-/hyperglycemia, hypothyroidism, cardiovascular changes, GI disturbances, CNS changes, dyspnea). Caution patients with diabetes to monitor serum glucose closely; may affect response to insulin or sulfonylureas. Teach patient proper use if self-administered (appropriate injection technique and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab Tests

Acromegaly: Growth hormone, somatomedin C (IGF-1)

Carcinoid: 5-HIAA, plasma serotonin and plasma substance P

VIPomas: Vasoactive intestinal peptide

Chronic therapy: Thyroid function (baseline and periodic), vitamin B_{12} level, blood glucose, zinc level (patients with excessive fluid loss maintained on TPN)

Patient EducationDo not take any new prescription or over-the-counter medications, or herbal products during therapy without consulting prescriber (especially any other antidiarrheals or “stomach” medications). If self-administered, follow instructions for injection and syringe/needle disposal. Schedule injections between meals to decrease GI effects. Consult prescriber about appropriate diet. If you have diabetes, monitor serum glucose closely and notify prescriber of significant changes (this drug may alter the effects of insulin or sulfonylureas). May cause skin flushing; nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); dizziness, fatigue, or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known); joint or muscle pain (consult prescriber for appropriate analgesia). Report unusual weight gain, swelling of extremities, or respiratory difficulty; acute or persistent GI distress (eg, diarrhea, vomiting, constipation, abdominal pain); muscle weakness or tremors or loss of motor function; chest pain or palpitations; blurred vision; depression; or redness, swelling, burning, or pain at injection site; or any other persistent adverse effect. **Breast-feeding precaution:** Inform prescriber if you are breast feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, microspheres for suspension, as acetate [depot formulation]:

Sandostatin LAR®: 10 mg, 20 mg, 30 mg [contains polylactide-co-glycolide; packaged with diluent and syringe]

Injection, solution, as acetate: 0.2 mg/mL (5 mL); 1 mg/mL (5 mL)

Sandostatin®: 0.2 mg/mL (5 mL); 1 mg/mL (5 mL)

Injection, solution, as acetate [preservative free]: 0.05 mg/mL (1 mL); 0.1 mg/mL (1 mL); 0.5 mg/mL (1 mL)

Sandostatin®: 0.05 mg/mL (1 mL); 0.1 mg/mL (1 mL); 0.5 mg/mL (1 mL)

Generic AvailableYes: Injection solution (excludes depot formulation)

Pricing: U.S. (www.drugstore.com)

Kit (Sandostatin LAR Depot)

20 mg (1): $2311.99

Solution (Sandostatin)

50 mcg/mL (1): $19.99

1000 mcg/mL (5): $1052.89

Mechanism of ActionMimics natural somatostatin by inhibiting serotonin release, and the secretion of gastrin, VIP, insulin, glucagon, secretin, motilin, and pancreatic polypeptide. Decreases growth hormone and IGF-1 in acromegaly. Octreotide provides more potent inhibition of growth hormone, glucagon, and insulin as compared to endogenous somatostatin. Also suppresses LH response to GnRH, secretion of thyroid-stimulating hormone and decreases splanchnic blood flow.

Pharmacodynamics/Kinetics

Duration: SubQ: 6-12 hours

Absorption: SubQ: Rapid and complete; I.M. (depot formulation): Released slowly (via microsphere degradation in the muscle)

Distribution: V_d: 14 L (13-30 L in acromegaly)

Protein binding: 65%, mainly to lipoprotein (41% in acromegaly)

Metabolism: Extensively hepatic

Bioavailability: SubQ: 100%; I.M: 60% to 63% of SubQ dose

Half-life elimination: 1.7-1.9 hours; Increased in elderly patients; Cirrhosis: Up to 3.7 hours; Fatty liver disease: Up to 3.4 hours; Renal impairment: Up to 3.1 hours

Time to peak, plasma: SubQ: 0.4 hours (0.7 hours acromegaly); I.M.: 1 hour

Excretion: Urine (32% as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), gingivitis, glossitis, stomatitis, taste perversion, and dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsOctreotide is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, or depression; may rarely cause anxiety

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsNSC-671663; Octreotide Acetate

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International Brand NamesCryostatin (MX); Nomactril (MX); Octride (CO, TH); Proclose (MX); Sandostatin (AE, AR, AT, AU, BD, BE, BG, BH, BR, CH, CL, CN, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IN, IQ, IR, IT, JO, JP, KP, KW, LB, LY, MY, NL, NO, OM, PE, PH, PK, PL, PT, PY, QA, RU, SA, SE, SG, SY, TH, TR, TW, UY, VE, YE); Sandostatin LAR (AR, AU, BR, CH, CN, EC, EE, ID, IL, KP, MY, NO, PE, PH, PL, SE, SG, TH, TW, UY); Sandostatina (IT, MX, PT); Sandostatine (BE, FR, NL)

Ofloxacin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Floxin® may be confused with Flexeril®

Ocuflox® may be confused with Occlusal®-HP, Ocufen®

International issues:

Floxin® may be confused with Flogen® which is a brand name for naproxen in Mexico

Floxin® may be confused with Fluoxin® which is a brand name for fluoxetine in the Czech Republic and Romania

Floxin® may be confused with Flexin® which is a brand name for orphenadrine in Israel and indomethacin in Great Britain

Pronunciation(oh FLOKS a sin)

U.S. Brand NamesFloxin®; Ocuflox®

Canadian Brand NamesApo-Ofloxacin® ; Apo-Oflox®; Floxin®; Novo-Ofloxacin; Ocuflox®; PMS-Ofloxacin

Pharmacologic CategoryAntibiotic, Quinolone

Use: Labeled Indications Quinolone antibiotic for the treatment of acute exacerbations of chronic bronchitis, community-acquired pneumonia, skin and skin structure infections (uncomplicated), urethral and cervical gonorrhea (acute, uncomplicated), urethritis and cervicitis (nongonococcal), mixed infections of the urethra and cervix, pelvic inflammatory disease (acute), cystitis (uncomplicated), urinary tract infections (complicated), prostatitis

Note: As of April 2007, the CDC no longer recommends the use of fluoroquinolones for the treatment of gonococcal disease.

Ophthalmic: Treatment of superficial ocular infections involving the conjunctiva or cornea due to strains of susceptible organisms

Otic: Otitis externa, chronic suppurative otitis media, acute otitis media

Use: Unlabeled/InvestigationalEpididymitis (nongonococcal), leprosy, Traveler's diarrhea

Dosing: Adults

Cervicitis/urethritis (nongonococcal):

Nongonococcal: 300 mg every 12 hours for 7 days

Gonococcal (acute, uncomplicated): 400 mg as a single dose; **Note:** As of April 2007, the CDC no longer recommends the use of fluoroquinolones for the treatment of uncomplicated gonococcal disease.

Chronic bronchitis (acute exacerbation), community-acquired pneumonia, skin and skin structure infections (uncomplicated): 400 mg every 12 hours for 10 days

Conjunctivitis: Ophthalmic: Instill 1-2 drops in affected eye(s) every 2-4 hours for the first 2 days, then use 4 times/day for an additional 5 days.

Corneal ulcer: Ophthalmic: Instill 1-2 drops every 30 minutes while awake and every 4-6 hours after retiring for the first 2 days; beginning on day 3, instill 1-2 drops every hour while awake for 4-6 additional days; thereafter, 1-2 drops 4 times/day until clinical cure.

Epididymitis, nongonococcal (unlabeled use): 300 mg twice daily for 10 days

Leprosy (unlabeled use): 400 mg once daily

Otitis media, chronic suppurative with perforated tympanic membranes: Otic: Instill 10 drops (or the contents of 2 single-dose containers) into affected ear twice daily for 14 days

Otitis externa: Otic: Instill 10 drops (or the contents of 2 single-dose containers) into affected ear(s) once daily for 7 days

Pelvic inflammatory disease (acute): 400 mg every 12 hours for 10-14 days; **Note:** The CDC recommends use only if standard cephalosporin therapy is not feasible and community prevalence of quinolone-resistant gonococcal organisms is low. Culture sensitivity must be confirmed.

Prostatitis:

Acute: 400 mg for 1 dose, then 300 mg twice daily for 10 days

Chronic: 200 mg every 12 hours for 6 weeks

Traveler's diarrhea (unlabeled use): 300 mg twice daily for 3 days

UTI:

Uncomplicated: 200 mg every 12 hours for 3-7 days

Complicated: 200 mg every 12 hours for 10 days

Dosing: ElderlyOral: 200-400 mg every 12-24 hours (based on estimated renal function) for 7 days to 6 weeks depending on indication.
Dosing: PediatricNot for systemic use

Acute otitis media with tympanotomy tubes: Otic: Children 1-12 years: Instill 5 drops (or the contents of 1 single-dose container) into affected ear twice daily for 10 days.

Conjunctivitis: Ophthalmic: Children ≥1 year: Refer to adult dosing.

Corneal ulcer: Ophthalmic: Children ≥1 year: Refer to adult dosing.

Otitis externa: Otic:

Children 6 months to 13 years: Instill 5 drops (or the contents of 1 single-dose container) into affected ear(s) once daily for 7 days

Children ≥13 years: Refer to adult dosing.

Otitis media, chronic suppurative with perforated tympanic membranes: Otic: Children >12 years: Refer to adult dosing.

Dosing: Renal ImpairmentAdults: Oral: After a normal initial dose, adjust as follows:

Cl_{cr} 20-50 mL/minute: Administer usual dose every 24 hours

Cl_{cr} <20 mL/minute: Administer half the usual dose every 24 hours

Continuous arteriovenous or venovenous hemodiafiltration effects: Administer 300 mg every 24 hours

Dosing: Hepatic ImpairmentSevere impairment: Maximum dose: 400 mg/day
Calculations

- Creatinine Clearance: Adults

Administration: OralDo not take within 2 hours of food or any antacids which contain zinc, magnesium, or aluminum.
Administration: Other

Ophthalmic: For ophthalmic use only; avoid touching tip of applicator to eye or other surfaces.

Otic: Prior to use, warm solution by holding container in hands for 1-2 minutes. Patient should lie down with affected ear upward and medication instilled. Pump tragus 4 times to ensure penetration of medication. Patient should remain in this position for 5 minutes.

Storage

Ophthalmic and otic solution: Store between 15°C to 25°C (59°F to 77°F).

Otic Singles™: Store between 15°C to 30°C (59°F to 86°F). Store in pouch to protect from light.

Tablet: Store below 30°C (86°F).

RestrictionsAn FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.
ContraindicationsHypersensitivity to ofloxacin or other members of the quinolone group, such as nalidixic acid, oxolinic acid, cinoxacin, norfloxacin, and ciprofloxacin; hypersensitivity to any component of the formulation
Warnings/Precautions

Boxed Warnings:

- Tendon inflammation/rupture: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Altered cardiac conduction: Fluoroquinolones may prolong QT_c interval; avoid use in patients with a history of QT_c prolongation, uncorrected hypokalemia, hypomagnesemia, or concurrent administration of other medications known to prolong the QT interval (including Class Ia and Class III antiarrhythmics, cisapride, erythromycin, antipsychotics, and tricyclic antidepressants).

- CNS stimulation: Tremor, restlessness, confusion, and very rarely hallucinations or seizures may occur; use with caution in patients with known or suspected CNS disorder. Discontinue in patients who experience significant CNS adverse effects (eg, dizziness, hallucinations, suicidal ideations or actions).

- Glucose regulation: Fluoroquinolones have been associated with the development of serious, and sometimes fatal, hypoglycemia. These events have occurred most often in elderly patients with diabetes, but have also been reported in patients without a prior history of diabetes. Prompt identification and treatment of hypoglycemia is essential. Individual quinolones may differ in their potential to cause this effect. It was most evident with gatifloxacin (no longer marketed as s systemic formulation). Hyperglycemia has also been associated with the use of fluoroquinolones. Patients should be monitored closely for signs/symptoms of disordered glucose regulation.

- Hypersensitivity reactions: Severe hypersensitivity reactions, including anaphylaxis, have occurred with quinolone therapy. The spectrum of these reactions can vary widely; reactions may present as typical allergic symptoms (eg, itching, urticaria, rash, edema) after a single dose, or may manifest as severe idiosyncratic dermatologic (eg, Stevens-Johnson, toxic epidermal necrolysis), vascular (eg, vasculitis), pulmonary (eg, pneumonitis), renal (eg, nephritis), hepatic (eg, hepatic failure or necrosis), and/or hematologic (eg, anemia, cytopenias) events, usually after multiple doses. Prompt discontinuation of drug should occur if skin rash or other symptoms arise.

- Peripheral neuropathy: The use of quinolones has been linked to peripheral neuropathy (rare); discontinue if symptoms of sensory or sensorimotor neuropathy occur.

- Phototoxicity: Avoid excessive sunlight and take precautions to limit exposure (eg, loose fitting clothing, sunscreen); may cause moderate-to-severe phototoxicity reactions. Discontinue use if photosensitivity occurs.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

- Tendon inflammation/rupture: **[U.S. Boxed Warning]: There have been reports of tendon inflammation and/or rupture with quinolone antibiotics; risk may be increased with concurrent corticosteroids, organ transplant recipients, and in patients >60 years of age.** Rupture of the Achilles tendon sometimes requiring surgical repair has been reported most frequently; but other tendon sites (eg, rotator cuff, biceps) have also been reported. Strenuous physical activity may be an independent risk factor for tendonitis. Discontinue at first sign of tendon inflammation or pain. May occur even after discontinuation of therapy.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Myasthenia gravis: Some quinolones may exacerbate myasthenia gravis; use with caution (rare, potentially life-threatening weakness of respiratory muscles may occur).

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required. May increase risk of tendon rupture.

- Rheumatoid arthritis: Use with caution in patients with rheumatoid arthritis; may increase risk of tendon rupture.

- Seizures: Use with caution in individuals at risk of seizures (CNS disorders or concurrent therapy with medications which may lower seizure threshold). Potential for seizures, although very rare, may be increased with concomitant NSAID therapy.

- Syphilis: Since ofloxacin is ineffective in the treatment of syphilis and may mask symptoms, all patients should be tested for syphilis at the time of gonorrheal diagnosis and 3 months later.

Special populations:

- Elderly: Adverse effects (eg, tendon rupture, QT changes) may be increased in the elderly.

- G6PD deficiency: Hemolytic reactions may (rarely) occur with quinolone use in patients with latent or actual G6PD deficiency.

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsDosage must be carefully adjusted to renal function. The half-life of ofloxacin may be prolonged and serum concentrations are elevated in elderly patients even in the absence of overt renal impairment. The risk of torsade de pointes and tendon inflammation and/or rupture associated with the concomitant use of corticosteroids and quinolones is increased in the elderly population. See Warnings/Precautions regarding tendon rupture in patients >60 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in some animal studies; therefore, the manufacturer classifies ofloxacin as pregnancy category C. Ofloxacin crosses the placenta and produces measurable concentrations in the amniotic fluid. An increased risk of teratogenic effects has not been observed in animals or humans following ofloxacin use during pregnancy; however, because of concerns of cartilage damage in immature animals, ofloxacin should only be used during pregnancy if a safer option is not available. Serum concentrations of ofloxacin may be lower during pregnancy than in nonpregnant patients.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsOfloxacin is excreted in breast milk. Breast-feeding is not recommended by the manufacturer. The AAP considers ofloxacin to be “usually compatible with breast-feeding.” Due to the low concentrations in human milk, minimal toxicity would be expected in the nursing infant. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Ofloxacin in Pregnancy & Lactation

Adverse Reactions

Systemic:

1% to 10%:

Cardiovascular: Chest pain (1% to 3%)

Central nervous system: Headache (1% to 9%), insomnia (3% to 7%), dizziness (1% to 5%), fatigue (1% to 3%), somnolence (1% to 3%), sleep disorders (1% to 3%), nervousness (1% to 3%), pyrexia (1% to 3%)

Dermatologic: Rash/pruritus (1% to 3%)

Gastrointestinal: Diarrhea (1% to 4%), vomiting (1% to 4%), GI distress (1% to 3%), abdominal cramps (1% to 3%), flatulence (1% to 3%), abnormal taste (1% to 3%), xerostomia (1% to 3%), appetite decreased (1% to 3%), nausea (3% to 10%), constipation (1% to 3%)

Genitourinary: Vaginitis (1% to 5%), external genital pruritus in women (1% to 3%)

Ocular: Visual disturbances (1% to 3%)

Respiratory: Pharyngitis (1% to 3%)

Miscellaneous: Trunk pain

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Anaphylaxis reactions, anxiety, blurred vision, chills, cognitive change, cough, depression, dream abnormality, ecchymosis, edema, erythema nodosum, euphoria, extremity pain, hallucinations, hearing acuity decreased, hepatic dysfunction, hepatic failure (some fatal), hepatitis, hyper-/hypoglycemia, hypertension, interstitial nephritis, lightheadedness, malaise, myasthenia gravis exacerbation, palpitation, paresthesia, peripheral neuropathy, photophobia, photosensitivity, pneumonitis, psychotic reactions, rhabdomyolysis, seizure, Stevens-Johnson syndrome, syncope, tendonitis and tendon rupture, thirst, tinnitus, torsade de pointes, Tourette's syndrome, toxic epidermal necrolysis, vasculitis, vasodilation, vertigo, weakness, weight loss

Ophthalmic: Frequency not defined:

Central nervous system: Dizziness

Gastrointestinal: Nausea

Ocular: Blurred vision, burning, chemical conjunctivitis/keratitis, discomfort, dryness, edema, eye pain, foreign body sensation, itching, photophobia, redness, stinging, tearing

Otic:

>10%: Local: Application site reaction (<1% to 17%)

1% to 10%:

Central nervous system: Dizziness (≤1%), vertigo (≤1%)

Dermatologic: Pruritus (1% to 4%), rash (1%)

Gastrointestinal: Taste perversion (7%)

Neuromuscular & skeletal: Paresthesia (1%)

<1% (Limited to important or life-threatening): Diarrhea, fever, headache, hearing loss (transient), hypertension, nausea, otorrhagia, tinnitus, tremor, vomiting, xerostomia

Postmarketing and/case reports: Transient neuropsychiatric disturbances

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Metabolism/Transport Effects**Inhibits** CYP1A2 (strong)

Drug Interactions

Antacids: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. **Exceptions:** Sodium Bicarbonate. *Risk D: Consider therapy modification*

Bendamustine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. *Risk C: Monitor therapy*

Calcium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Calcium Chloride. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Quinolone Antibiotics may enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Strong) may decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Didanosine: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents (excludes enteric coated formulation of didanosine). *Risk D: Consider therapy modification*

Insulin: May enhance the hyperglycemic effect of Quinolone Antibiotics. Insulin may enhance the hypoglycemic effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Mycophenolate: Quinolone Antibiotics may decrease the serum concentration of Mycophenolate. Specifically, quinolones may decrease concentrations of the active metabolite of mycophenolate. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Probenecid: May increase the serum concentration of Quinolone Antibiotics. *Risk C: Monitor therapy*

Quinapril: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sevelamer: May decrease the absorption of Quinolone Antibiotics. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Sulfonylureas: Quinolone Antibiotics may enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Theophylline Derivatives: Quinolone Antibiotics may decrease the metabolism of Theophylline Derivatives. Ciprofloxacin and enoxacin are of greatest concern. Theophylline/quinolone therapy might augment the seizure-producing potential of each of the individual agents. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Quinolone Antibiotics may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zinc Salts: May decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Ofloxacin average peak serum concentrations may be decreased by 20% if taken with food.

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization).

Test InteractionsSome quinolones may produce a false-positive urine screening result for opiates using commercially-available immunoassay kits. This has been demonstrated most consistently for levofloxacin and ofloxacin, but other quinolones have shown cross-reactivity in certain assay kits. Confirmation of positive opiate screens by more specific methods should be considered.

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's allergy history before initiating therapy. Use caution with known or suspected CNS disorders; current or potential for QT prolongation; renal impairment; or diabetes. Assess potential for interactions with other pharmacological or herbal agents patient may be taking. See administration specifics for different formulations (otic, ophthalmic, oral). Patient should be monitored closely; if an allergic reaction occurs (itching, urticaria, dyspnea or facial edema, loss of consciousness, tingling, cardiovascular collapse), drug should be discontinued immediately and prescriber notified. Evaluate results of laboratory tests, therapeutic effectiveness (resolution of infection), and adverse reactions (eg, hypersensitivity reactions [severe reactions, including anaphylaxis, have occurred with quinolone therapy], opportunistic infection, tendon rupture, persistent diarrhea [*C. difficile*-associated colitis can occur up to 2 months post treatment]) regularly during prolonged therapy. Teach patient proper use (according to formulation), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity studies before initiating therapy. Monitor CBC, renal and hepatic function periodically if therapy is prolonged.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take oral tablets as directed on an empty stomach (2 hours before or 2 hours after meals, dairy products, antacids, or other medication). Complete full course of therapy, even if symptoms resolve. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Consult prescriber before having any vaccination. May cause dizziness, lightheadedness, or headache (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea, vomiting, or taste perversion (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). If inflammation or tendon pain occurs or you experience signs of an allergic reaction (eg, itching, urticaria, respiratory difficulty, facial edema or difficulty swallowing, loss of consciousness, tingling, chest pain, palpitations), discontinue use and contact prescriber immediately. Report GI disturbances; CNS changes (eg, excessive sleepiness, agitation, tremors); skin rash; vision changes; respiratory difficulty; signs of opportunistic infection (eg, sore throat, chills, fever, burning, itching on urination, vaginal discharge, white plaques in mouth); persistent diarrhea (especially if it lasts after completing prescription); or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Ophthalmic: Wash hands before instilling solution. Sit or lie down to instill. Open eye, look at ceiling, and instill prescribed amount of solution as directed. Close eye, roll eye in all directions, and apply gentle pressure to inner corner of eye. Do not touch tip of applicator or let tip of applicator touch eye (may cause eye infection, eye damage, or vision loss). Do not wear contact lenses during therapy. Temporary stinging, blurred vision, dry eyes, or a bad taste in your mouth may occur after installation. Report persistent pain, burning, excessive tearing, decreased visual acuity, swelling, itching, or worsening of condition.

Otic: Wash hands before and after applying drops. Warm solution by holding container in hands for a few minutes. Lie with affected ear up and instill prescribed number of drops into ear. Remain on side with ear up for 5 minutes.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic [drops]: 0.3% (5 mL, 10 mL)

Ocuflox®: 0.3% (5 mL) [contains benzalkonium chloride]

Solution, otic [drops]: 0.3% (5 mL, 10 mL)

Floxin®: 0.3% (5 mL, 10 mL) [contains benzalkonium chloride]

Floxin® Otic Singles™: 0.3% (0.25 mL) [contains benzalkonium chloride; packaged as 2 single-dose containers per pouch, 10 pouches per carton, total net volume 5 mL]

Tablet: 200 mg, 300 mg, 400 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Floxin Otic)

0.3% (5): $75.99

0.3% (10): $136.04

Solution (Ocuflox)

0.3% (5): $52.99

0.3% (10): $91.61

Solution (Ofloxacin)

0.3% (5): $17.99

0.3% (5): $59.99

0.3% (10): $40.00

0.3% (10): $92.99

Tablets (Ofloxacin)

200 mg (14): $53.99

300 mg (14): $65.99

400 mg (30): $125.00

Mechanism of ActionOfloxacin is a DNA gyrase inhibitor. DNA gyrase is an essential bacterial enzyme that maintains the superhelical structure of DNA. DNA gyrase is required for DNA replication and transcription, DNA repair, recombination, and transposition; bactericidal

Pharmacodynamics/Kinetics

Absorption: Well absorbed; food causes only minor alterations

Distribution: V_d: 2.4-3.5 L/kg

Protein binding: 32%

Bioavailability: Oral: 98%

Half-life elimination: Biphasic: 4-5 hours and 20-25 hours (accounts for <5%); prolonged with renal impairment

Excretion: Primarily urine (as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and abnormal taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, nervousness, or insomnia; quinolones reported to cause restlessness, hallucinations, euphoria, depression, panic, and paranoia

Mental Health: Effects on Psychiatric TreatmentInhibits CYP1A2 isoenzyme; use caution with clozapine and other psychotropics; monitor for adverse effects

Index TermsFloxin Otic Singles

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International Brand NamesBactocin (MX); Boravid (IE); Danoflox (ID); Dizoflox (PH); Earflo Otic (TW); Exen (KP); Exocin (IE); Exocine (FR); Flobacin (IT); Flotavid (ID); Flovid (HK, PH); Floxal (CH, DE, PL); Floxil (AR, MX); Floxstat (BB, BM, BS, BZ, CO, EC, GY, JM, MX, NL, SR, TT, VE); Floxy (TH); Fluraxid (PH); Hyflox (TH); Inoflox (MY, PH); Iquinol (PH); Kinoxacin (KP); Loxinter (ID); Marfloxacin (HK); Medofloxine (MY); Mergexin (PH); Novecin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Nufafloqo (ID); Occidal (TH); Ocuflox (AU, KP, MX); Ofcin (MY, TH); Oflin (IN); Oflo (CR, DO, GT, HN, NI, PA, SV); Oflocee (TH); Oflocet (FR, NZ); Oflocin (IT); Oflodex (IL); Oflodinex (PL); Oflodura (DE); Oflox (AE, AR, BH, BR, CN, CO, CY, EC, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PE, QA, SA, SY, UY, VE, YE); Ofloxin (PL, TH); Ofus (HK, KP); Oltrex (GT); Onexacin (PH); Orivid (TH); Orocin (KP); Otonil (PY); Oxacin (TW); Pharflox (ID); Qinolon (PH); Qipro (ID); Quinolon (TH); Quotavil (HK); Tabrin (GR); Tafloc (ZA); Taravid (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Tariflox (ID); Tarivid (AT, BE, BF, BG, BJ, CH, CI, CL, CZ, DE, DK, ES, ET, FI, FR, GB, GH, GM, GN, GR, HN, ID, IE, IL, IN, IT, JP, KE, KP, LR, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, PK, PT, RU, SC, SD, SE, SG, SL, SN, TH, TN, TR, TW, TZ, UG, ZA, ZM, ZW); Tarivid Eye Ear (HK); Tarivid Otic (MY, SG); Tarivid [inj.] (PL); Tructum (PE); Uro Tarivid (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Vioflox (KP); Vioson (PH); Viotisone (TH); Zanocin (IN, PL, ZA)

Olanzapine and Fluoxetine

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

Gill SS, Bronskill SE, Normand SL, et al, “Antipsychotic Drug Use and Mortality in Older Adults With Dementia,” *Ann Intern Med*, 2007, 146(11):775-86.[PubMed 17548409]

Schneeweiss S, Setoguchi S, Brookhart A, et al, “Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients,” *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Pronunciation(oh LAN za peen & floo OKS e teen)

U.S. Brand NamesSymbyax®

Pharmacologic CategoryAntidepressant, Selective Serotonin Reuptake Inhibitor; Antipsychotic Agent, Atypical

Use: Labeled IndicationsTreatment of depressive episodes associated with bipolar disorder

Dosing: Adults**Depression associated with bipolar disorder:** Oral: Initial: Olanzapine 3-6 mg/fluoxetine 25 mg once daily in the evening. Dosing range: Olanzapine 6-12 mg/fluoxetine 25-50 mg. Lower doses (olanzapine 3 mg/fluoxetine 25 mg) should be used in patients predisposed to hypotension, in hepatic impairment, with combined factors for reduced metabolism (females, the elderly, nonsmokers), or enhanced sensitivity to olanzapine; use caution in dose adjustments in these patients. Safety of daily doses of olanzapine >18 mg/fluoxetine >75 mg have not been evaluated.

Dosing: ElderlyOral: Initial: Olanzapine 3-6 mg/fluoxetine 25 mg once daily in the evening; use caution adjusting dose (metabolism may be decreased). Safety and efficacy have not been established in patients >65 years of age.

Dosing: Hepatic ImpairmentInitial: Olanzapine 6 mg/fluoxetine 25 mg once daily in the evening; use caution adjusting dose (metabolism may be decreased).

Administration: OralCapsules should be taken once daily in the evening. May be taken with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from moisture.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to olanzapine, fluoxetine, or any component of the formulation; patients currently receiving MAO inhibitors, thioridazine, pimozide, or mesoridazine; treatment within 14 days of MAO therapy

Allergy Considerations

- OLANZapine Allergy
- Selective Serotonin Reuptake Inhibitor (SSRI) Allergy

Warnings/Precautions

Boxed warnings:

- Dementia: See “Disease-related concerns” below.

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **This combination is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **This combination is FDA approved for the treatment of depressive episodes associated with bipolar disorder.**

Concerns related to adverse effects:

- Allergic events and rash: Fluoxetine use has been associated with occurrences of significant rash and allergic events, including vasculitis, lupus-like syndrome, laryngospasm, anaphylactoid reactions, and pulmonary inflammatory disease.

- Altered cardiac conduction: May alter cardiac conduction; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics.

- Anticholinergic effects: Olanzapine may cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, urinary retention, BPH, xerostomia, or visual problems. Relative to other neuroleptics, olanzapine has a moderate potency of cholinergic blockade.

- Bleeding risk: May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin, NSAIDs, warfarin or other anticoagulants. Bleeding related to SSRI use has been reported to range from relatively minor bruising and epistaxis to life-threatening hemorrhage.

- Esophageal dysmotility/Aspiration: Has been associated with antipsychotic use; use with caution in patients at risk of pneumonia (eg, Alzheimer’s disease).

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is generally much lower relative to typical/conventional antipsychotics). Risk of dystonia (and probably other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Hyperglycemia: Atypical antipsychotics have been associated with development of hyperglycemia; in some cases, may be extreme and associated with ketoacidosis, hyperosmolar coma, or death. Olanzapine may have a greater association with hyperglycemia than other atypical antipsychotics. Use with caution in patients with diabetes or other disorders of glucose regulation; monitor for worsening of glucose control. Patients with risk factors for diabetes (eg, obesity or family history) should have a baseline fasting blood sugar (FBS) and periodic assessment of glucose regulation.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: Moderate to highly sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Sexual dysfunction: May cause or exacerbate sexual dysfunction.

- SIADH and hyponatremia: SSRIs and SNRIs have been associated with the development of SIADH; hyponatremia has been reported rarely (including severe cases with serum sodium <110 mmol/L), predominately in the elderly. Volume depletion and/or concurrent use of diuretics likely increases risk.

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

- Weight gain: Significant weight gain (>7% of baseline weight) has been observed with antipsychotic therapy; incidence varies with product. Monitor waist circumference and BMI.

Disease-related concerns:

- Dementia: **[U.S. Boxed Warning]: Elderly patients with dementia-related behavioral disorders treated with atypical antipsychotics are at an increased risk of death compared to placebo.** An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Olanzapine is not approved for this indication.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended. Relative to other neuroleptics, olanzapine has a moderate potency of cholinergic blockade.

- Hepatic impairment: Use with caution in patients with hepatic disease or impairment; lowest starting dose recommended.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade. Relative to other neuroleptics, olanzapine has a moderate potency of cholinergic blockade.

- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Prolactin-dependent tumors: Use with caution in breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Renal impairment: Use with caution in patients with renal disease; a lower dosage may be needed.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold. Elderly patients may be at increased risk of seizures due to an increased prevalence of predisposing factors.

Concurrent drug therapy issues:

- Anticoagulants/Antiplatelets: Use caution with concomitant use of NSAIDs, ASA, or other drugs that affect coagulation; the risk of bleeding may be potentiated.

- MAO inhibitors: Potential for severe reaction when used with MAO inhibitors; autonomic instability, coma, death, delirium, diaphoresis, hyperthermia, mental status changes/agitation, muscular rigidity, myoclonus, neuroleptic malignant syndrome features, and seizures may occur. MAO inhibitor therapy must be stopped for 14 days before olanzapine/fluoxetine is initiated. Treatment with MAO inhibitors, thioridazine, or mesoridazine should not be initiated until 5 weeks after the discontinuation of olanzapine/fluoxetine.

- Pimozide and thioridazine: Fluoxetine may elevate plasma levels of these agents; increasing risk of QTc interval prolongation; this may lead to serious ventricular arrhythmias such as torsade de pointes-type arrhythmias and sudden death. **Use is contraindicated.**

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce fluoxetine's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

Special populations:

- Elderly: Use caution in elderly patients; risk of hyponatremia and other adverse events may be increased. Safety and efficacy have not been established in patients >65 years of age.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Duration of therapy: Antidepressant efficacy with treatment >8 weeks duration has not been established.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

- Long half-life: Due to the long half-life of fluoxetine and its metabolites, the effects and interactions noted may persist for prolonged periods following discontinuation.

- Withdrawal syndrome: May cause dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Upon discontinuation of therapy, gradually taper dose. If intolerable symptoms occur following a decrease in dosage or upon discontinuation of therapy, then resuming the previous dose with a more gradual taper should be considered.

Pregnancy Risk FactorC
Pregnancy ConsiderationsA decrease in fetal weight, testicular degeneration and atrophy, depletion of epididymal sperm, and infertility in males was reported in some animal reproduction studies using this combination. Use during pregnancy is not recommended. Refer to individual agents for additional information.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsFluoxetine enters breast milk. AAP rates use during breast-feeding as “of concern.”
Adverse ReactionsAs reported with combination product (also see individual agents):

>10%:

Central nervous system: Somnolence (21% to 22%)

Gastrointestinal: Weight gain (17% to 21%), diarrhea (8% to 19%), appetite increased (13% to 16%), xerostomia (11% to 16%)

Neuromuscular & skeletal: Weakness (13% to 15%)

1% to 10%:

Cardiovascular: Peripheral edema (4% to 8%), edema (up to 5%), hypertension (2%), tachycardia (2%), vasodilation

Central nervous system: Thinking abnormal (6%), fever (3% to 4%), amnesia (1% to 3%), personality disorder (1% to 2%), sleep disorder (1% to 2%), speech disorder (up to 2%), chills, migraine

Dermatologic: Photosensitivity

Endocrine & metabolic: Ejaculation abnormal (2% to 7%), impotence (2% to 4%), libido decreased (2% to 4%), anorgasmia (1% to 3%), breast pain, menorrhagia

Gastrointestinal: Tooth disorder (1% to 2%), salivation increased, taste perversion, thirst, weight loss

Genitourinary: Urinary frequency, urinary incontinence, urinary tract infection

Neuromuscular & skeletal: Tremor (8% to 9%), twitching (2% to 6%), arthralgia (3% to 5%), hyperkinesias (1% to 2%), joint disorder (1% to 2%), bruising, neck pain/rigidity

Ocular: Amblyopia (4% to 5%), vision abnormal

Otic: Ear pain (1% to 2%), otitis media (up to 2%), tinnitus

Respiratory: Pharyngitis (4% to 6%), dyspnea (1% to 2%), bronchitis, lung disorder

Frequency not defined: Alkaline phosphate increased, cholesterol increased, GGT increased, hemoglobin decreased, prolactin increased, uric acid increased

Postmarketing (limited to significant or life-threatening): Acidosis, acute brain syndrome, anemia, angina pectoris, apnea, arrhythmia (various), asthma, ataxia, behavioral/personality changes (eg, hostility, emotional lability), bilirubinemia, bradycardia, breast carcinoma, bundle branch block, cellulitis, cerebral ischemia, cholelithiasis, coagulation disorder, colitis, coma, confusion, congestive heart failure, conjunctivitis, creatinine increased, deafness, dehydration, dystonia, emphysema, exfoliative dermatitis, extrapyramidal syndrome, eye hemorrhage, fatty liver, gastrointestinal hemorrhage, hematuria, hemoptysis, hepatomegaly, hyperkalemia, hyperlipemia, hyperprolactinemia, hyperventilation, hypoesthesia, hypoglycemia, hypokalemia, hyponatremia, hypokinesia, hypotension, hypothyroidism, incontinence, intestinal obstruction, jaundice, kidney calculus, leukocytosis, leukopenia, liver damage (cholestatic or mixed), lymphadenopathy, maculopapular rash, menopause, menstrual disorders, myasthenia, myocardial infarct, myoclonus, myopathy, neoplasm, neuralgia, osteoporosis, ovarian disorder, pancreatitis, pelvic pain, peptic ulcer, periodontal abscess, peripheral vascular disorder, pneumonia, purpura, QT interval increased, rheumatoid arthritis, seizure, subarachnoid hemorrhage, suicide attempt, tendinous contracture, tenosynovitis, thrombocythemia, transaminases increased, T-wave inverted, urination impaired, uterine fibroids enlarged, vesiculobullous rash, withdrawal syndrome

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alpha-/Beta-Blockers: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Alpha-/Beta-Blockers. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Analgesics (Opioid): May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin Reuptake Inhibitor/Antagonist): Selective Serotonin Reuptake Inhibitors may enhance the serotonergic effect of Antidepressants (Serotonin Reuptake Inhibitor/Antagonist). This may cause serotonin syndrome. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Atypical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Aspirin: Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Beta-Blockers: Selective Serotonin Reuptake Inhibitors may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Acebutolol; Atenolol;

Carteolol; Esmolol; Levobunolol; Metipranolol; Nadolol; Penbutolol. *Risk C: Monitor therapy*

BusPIRone: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. Selective Serotonin Reuptake Inhibitors may decrease the metabolism of BusPIRone. *Risk C: Monitor therapy*

CarBAMazepine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of CarBAMazepine. Specifically those SSRIs that inhibit CYP3A4 isoenzymes. CarBAMazepine may increase the metabolism of Selective Serotonin Reuptake Inhibitors. Specifically those agents metabolized via CYP1A2, 2C, and/or 3A4 isoenzymes. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Selective Serotonin Reuptake Inhibitors. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Clozapine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Strong) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk D: Consider therapy modification*

Cyproheptadine: May diminish the therapeutic effect of Selective Serotonin Reuptake Inhibitors. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Desmopressin: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dextromethorphan: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Dextromethorphan. *Risk D: Consider therapy modification*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Fluvoxamine: May decrease the metabolism of OLANZapine. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Galantamine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Galantamine. *Risk C: Monitor therapy*

Haloperidol: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Haloperidol. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Iobenguane I 123: Selective Serotonin Reuptake Inhibitors may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

LamoTRIgine: May enhance the sedative effect of OLANZapine. *Risk C: Monitor therapy*

Lithium: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Selective Serotonin Reuptake Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methadone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Methadone. Fluvoxamine appears to be the only interacting SSRI. *Risk D: Consider therapy modification*

Mexiletine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Mexiletine. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

NSAID (COX-2 Inhibitor): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk D: Consider therapy modification*

NSAID (Nonselective): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Phenytoin: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Pimozide: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Pimozide. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propafenone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Propafenone. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of QuiNIDine. Fluvoxamine appears to be the only SSRI of concern. *Risk D: Consider therapy modification*

Risperidone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Risperidone. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tamoxifen: CYP2D6 Inhibitors (Strong) may decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

TraMADol: Selective Serotonin Reuptake Inhibitors may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. TraMADol may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tryptophan: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Selective Serotonin Reuptake Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsSee individual agents.

Monitoring ParametersVital signs; lipid profile, fasting blood glucose/Hgb A_{1c}; BMI; mental status; abnormal involuntary movement scale (AIMS), extrapyramidal symptoms (EPS); signs and symptoms of depression, anxiety, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased), sleep; liver function tests in patients with hepatic disease

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsLipid profile, fasting blood glucose/Hgb A_{1c}; BMI

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

- Symbyax® 3/25: Olanzapine 3 mg and fluoxetine 25 mg
- Symbyax® 6/25: Olanzapine 6 mg and fluoxetine 25 mg
- Symbyax® 6/50: Olanzapine 6 mg and fluoxetine 50 mg
- Symbyax® 12/25: Olanzapine 12 mg and fluoxetine 25 mg
- Symbyax® 12/50: Olanzapine 12 mg and fluoxetine 50 mg

Generic AvailableNo

ManufacturerEli Lilly and Company

Pricing: U.S. (www.drugstore.com)

Capsules (Symbyax)

- 6-25 mg (30): $310.34
- 6-50 mg (30): $389.68
- 12-25 mg (30): $496.76
- 12-50 mg (30): $470.72

Mechanism of ActionOlanzapine is a second generation thienobenzodiazepine antipsychotic which displays potent antagonism of serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$, dopamine D$_{1-4}$, histamine H$_1$ and alpha$_1$-adrenergic receptors. Olanzapine shows moderate antagonism of 5-HT$_3$ and muscarinic M$_{1-5}$ receptors, and weak binding to GABA-A, BZD, and beta-adrenergic receptors. Fluoxetine inhibits CNS neuron serotonin reuptake; minimal or no effect on reuptake of norepinephrine or dopamine; does not significantly bind to alpha-adrenergic, histamine, or cholinergic receptors. The enhanced antidepressant effect of the combination may be due to synergistic increases in serotonin, norepinephrine, and dopamine.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Agents Approved for Bipolar Disorder
- FLUoxetine
- OLANZapine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia or salivation increased (normal salivary flow resumes upon discontinuation), tooth disorder, and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentA small trial has demonstrated the olanzapine and fluoxetine combination formulation to be efficacious for the treatment of bipolar depression. However, in the clinical setting, this fixed-drug combination is uncommonly used due to inability to titrate individual components.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Index TermsFluoxetine and Olanzapine; Olanzapine and Fluoxetine Hydrochloride

References

Boyer EW and Shannon M, “The Serotonin Syndrome,” *N Engl J Med*, 2005, 352:1112-20.[PubMed 15784664]

Pass SE and Simpson RW, “Discontinuation and Reinstitution of Medications During the Perioperative Period,” *Am J Health Syst Pharm*, 2004, 61(9):899-912.[PubMed 15156966]

OLANZapine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

Gill SS, Bronskill SE, Normand SL, et al, "Antipsychotic Drug Use and Mortality in Older Adults With Dementia," *Ann Intern Med*, 2007, 146(11):775-86.[PubMed 17548409]

Schneeweiss S, Setoguchi S, Brookhart A, et al, "Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients," *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Medication Safety Issues

Sound-alike/look-alike issues:

OLANZapine may be confused with olsalazine, QUEtiapine

Zyprexa® may be confused with Celexa™, Zyrtec®

Pronunciation(oh LAN za peen)

U.S. Brand NamesZyprexa®; Zyprexa® Zydis®

Canadian Brand NamesNovo-Olanzapine; Zyprexa®; Zyprexa® Zydis®

Pharmacologic CategoryAntimanic Agent; Antipsychotic Agent, Atypical

Use: Labeled IndicationsTreatment of the manifestations of schizophrenia; treatment of acute or mixed mania episodes associated with Bipolar I Disorder (as monotherapy or in combination with lithium or valproate); maintenance treatment of bipolar disorder; acute agitation (patients with schizophrenia or bipolar mania)

Use: Unlabeled/InvestigationalTreatment of psychosis/schizophrenia in children or adolescents; chronic pain; prevention of chemotherapy-associated delayed nausea or vomiting; psychosis/agitation related to Alzheimer's dementia

Dosing: Adults

Schizophrenia: Initial: 5-10 mg once daily (increase to 10 mg once daily within 5-7 days); thereafter, adjust by 5 mg/day at 1-week intervals, up to a recommended maximum of 20 mg/day. Maintenance: 10-20 mg once daily. **Note:** Doses of 30-50 mg/day have been used; however, doses >10 mg/day have not demonstrated better efficacy, and safety and efficacy of doses >20 mg/day have not been evaluated.

Acute mania associated with bipolar disorder: Oral:

Monotherapy: Initial: 10-15 mg once daily; increase by 5 mg/day at intervals of not less than 24 hours. Maintenance: 5-20 mg/day; recommended maximum dose: 20 mg/day.

Combination therapy (with lithium or valproate): Initial: 10 mg once daily; dosing range: 5-20 mg/day

Agitation (acute, associated with bipolar disorder or schizophrenia): I.M.: Initial dose: 5-10 mg (a lower dose of 2.5 mg may be considered when clinical factors warrant); additional doses (2.5-10 mg) may be considered; however, 2-4 hours should be allowed between doses to evaluate response (maximum total daily dose: 30 mg, per manufacturer's recommendation)

Prevention of chemotherapy-associated delayed nausea or vomiting (unlabeled use; in combination with a corticosteroid and serotonin [$5HT_3$] antagonist): Oral: 10 mg once daily for 3-5 days, beginning on day 1 of chemotherapy **or** 5 mg once daily for 2 days before chemotherapy, followed by 10 mg once daily (beginning on the day of chemotherapy) for 3-8 days

Dosing: ElderlyRefer to adult dosing. Consider lower starting dose of 2.5-5 mg/day for elderly or debilitated patients; may increase as clinically indicated and tolerated with close monitoring of orthostatic blood pressure.

Psychosis/agitation related to Alzheimer's dementia (unlabeled use): Initial: 1.25-5 mg/day; if necessary, gradually increase as tolerated not to exceed 10 mg/day

Dosing: Pediatric**Schizophrenia/bipolar disorder (unlabeled use):** Oral: Initial: 2.5 mg/day; titrate as necessary to 20 mg/day (0.12-0.29 mg/kg/day)

Dosing: Renal ImpairmentNo dosage adjustment required. Not removed by dialysis.

Dosing: Hepatic ImpairmentDosage adjustment may be necessary, however, there are no specific recommendations. Monitor closely.

Administration: I.M.Injection: For I.M. administration only; inject slowly, deep into muscle. If dizziness and/or drowsiness are noted, patient should remain recumbent until examination indicates postural hypotension and/or bradycardia are not a problem. Concurrent use of I.M./I.V. benzodiazepines is not recommended (fatalities have been reported, though causality not determined).

Administration: I.V.Do not administer injection intravenously.

Administration: Oral

Tablet: May be administered with or without food.

Orally-disintegrating tablet: Remove from foil blister by peeling back (do not push tablet through the foil). Place tablet in mouth immediately upon removal. Tablet dissolves rapidly in saliva and may be swallowed with or without liquid. May be administered with or without food/meals.

Dietary ConsiderationsTablets may be taken with or without food. Zyprexa® Zydis®: 5 mg tablet contains phenylalanine 0.34 mg; 10 mg tablet contains phenylalanine 0.45 mg; 15 mg tablet contains phenylalanine 0.67 mg; 20 mg tablet contains phenylalanine 0.9 mg.

Storage

Injection, powder for reconstitution: Store at room temperature 15°C to 30°C (59°F to 86°F); do not freeze. Protect from light.

Tablet and orally-disintegrating tablet: Store at room temperature of 15°C to 30°C (59°F to 86°F). Protect from light and moisture.

ReconstitutionInjection, powder for reconstitution: Reconstitute 10 mg vial with 2.1 mL SWFI. Resulting solution is ~5 mg/mL. Use immediately (within 1 hour) following reconstitution. Discard any unused portion.

ContraindicationsHypersensitivity to olanzapine or any component of the formulation

Allergy Considerations

- OLANZapine Allergy

Warnings/Precautions

Boxed warnings:

- Dementia: See "Disease-related concerns" below.

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics.

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to other neuroleptics, olanzapine has a moderate potency of cholinergic blockade.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is generally much lower relative to typical/conventional antipsychotics). Risk of dystonia (and probably other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Hyperglycemia: Atypical antipsychotics have been associated with development of hyperglycemia; in some cases, may be extreme and associated with ketoacidosis, hyperosmolar coma, or death. Olanzapine may have a greater association with hyperglycemia than other atypical antipsychotics. Use with caution in patients with diabetes or other disorders of glucose regulation; monitor for worsening of glucose control. Patients with risk factors for diabetes (eg, obesity or family history) should have a baseline fasting blood sugar (FBS) and periodic assessment of glucose regulation.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).
- Sedation: May be moderate to highly sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Suicidal ideation: The possibility of a suicide attempt is inherent in psychotic illness or bipolar disorder; use with caution in high-risk patients during initiation of therapy. Prescriptions should be written for the smallest quantity consistent with good patient care.
- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.
- Weight gain: Significant weight gain (>7% of baseline weight) has been observed with antipsychotic therapy; incidence varies with product. Monitor waist circumference and BMI.

Disease-related concerns:

- Dementia: **[U.S. Boxed Warning]: Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo.** An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Olanzapine is not approved for this indication.
- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.
- Hepatic impairment: Use with caution in patients with hepatic disease or impairment.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.
- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.
- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.
- Renal impairment: Use with caution in patients with renal disease.
- Seizures: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold. Elderly patients may be at increased risk of seizures due to an increased prevalence of predisposing factors.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Smokers: Olanzapine levels may be lower in patients who smoke, requiring dosage adjustment.

Dosage form-specific concerns:

- Intramuscular administration: Patients should remain recumbent if drowsy/dizzy until hypotension, bradycardia, and/or hypoventilation has been ruled out. Concurrent use of I.M./I.V. benzodiazepines is not recommended (fatalities have been reported, though causality not determined).

Geriatric ConsiderationsElderly patients have an increased risk of adverse response to side effects or adverse reactions to antipsychotics. A higher incidence of falls has been reported in elderly patients, particularly in debilitated patients. Olanzapine half-life that was 1.5 times that of younger (<65 years of age) adults; therefore, lower initial doses are recommended. Olanzapine is not indicated in dementia-related psychosis.

Studies with patients ≥65 years of age with schizophrenia showed no difference in tolerability compared to younger adults. Studies in the elderly with dementia-related psychosis suggested a different tolerability compared to younger patients with schizophrenia. In light of significant risks and adverse effects in the elderly population (compared with limited data demonstrating efficacy in the treatment of dementia-related psychosis, aggression, and agitation), an extensive risk:benefit analysis should be performed prior to use. Therefore, use with caution and at lower recommended doses.

Pregnancy Risk FactorC

Pregnancy ConsiderationsNo evidence of teratogenicity reported in animal studies. However, fetal toxicity and prolonged gestation have been observed. There are no adequate and well-controlled studies in pregnant women. Healthcare providers are encouraged to enroll women 18-45 years of age exposed to olanzapine during pregnancy in the Atypical Antipsychotics Pregnancy Registry (1-866-961-2388).

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsAt steady-state concentrations, it is estimated that a breast-fed infant may be exposed to ~2% of the maternal dose.

Adverse Reactions

>10%:

Central nervous system: Somnolence (6% to 39% dose dependent), extrapyramidal symptoms (15% to 32% dose dependent), insomnia (up to 12%), dizziness (4% to 18%)

Gastrointestinal: Dyspepsia (7% to 11%), constipation (9% to 11%), weight gain (5% to 6%, has been reported as high as 40%), xerostomia (9% to 22% dose dependent)

Neuromuscular & skeletal: Weakness (2% to 20% dose dependent)

Miscellaneous: Accidental injury (12%)

1% to 10%:

Cardiovascular: Postural hypotension (1% to 5%), tachycardia (up to 3%), peripheral edema (up to 3%), chest pain (up to 3%), hyper-/hypotension (up to 2%)

Central nervous system: Personality changes (8%), speech disorder (7%), fever (up to 6%), abnormal dreams, euphoria, amnesia, delusions, emotional lability, mania, schizophrenia

Dermatologic: Bruising (up to 5%)

Endocrine & metabolic: Cholesterol increased (4%), prolactin increased

Gastrointestinal: Nausea (up to 9% dose dependent), appetite increased (3% to 6%), vomiting (up to 4%), flatulence, salivation increased, thirst

Genitourinary: Incontinence (up to 2%), UTI (up to 2%), vaginitis

Hepatic: ALT increased (2%)

Local: Injection site pain (I.M. administration)

Neuromuscular & skeletal: Tremor (1% to 7% dose dependent), abnormal gait (6%), back pain (up to 5%), joint/extremity pain (up to 5%), akathisia (3% to 5% dose dependent), hypertonia (up to 3%), articulation impairment (up to 2%), falling (particularly in older patients), joint stiffness, paresthesia, twitching

Ocular: Amblyopia (up to 3%), conjunctivitis

Respiratory: Rhinitis (up to 7%), cough (up to 6%), pharyngitis (up to 4%), dyspnea

Miscellaneous: Dental pain, diaphoresis, flu-like syndrome

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Acidosis, akinesia, albuminuria, anaphylactoid reaction, anemia, angioedema, apnea, arteritis, asthma, ataxia, atelectasis, atrial fibrillation, AV block, cerebrovascular accident, coma, confusion, congestive heart failure, deafness, diabetes mellitus, diabetic acidosis, diabetic coma, dyskinesia, dysphagia, dystonia, dysuria, encephalopathy, facial paralysis, glaucoma, gynecomastia, heart arrest, heart block, heart failure, hematuria, hemoptysis, hemorrhage (eye, rectal, subarachnoid, vaginal), hepatitis, hyper-/hypoglycemia, hyper-/hypokalemia, hyperlipemia, hyper-/hyponatremia, hyperuricemia, hyper-/hypoventilation, hypoesthesia, hypokinesia, hypoproteinemia, hypoxia, jaundice, ileus, ketosis, leukocytosis (eosinophilia), leukopenia, liver damage (cholestatic or mixed), liver fatty deposit, lung edema, lymphadenopathy, menstrual irregularities, migraine, myasthenia, myopathy, neuralgia, neuroleptic malignant syndrome, neuropathy, neutropenia, osteoporosis, pancreatitis, paralysis, priapism, pulmonary embolus, rhabdomyolysis, seizure, stridor, sudden death, suicide attempt, syncope, tardive dyskinesia, thrombocythemia, thrombocytopenia, tongue edema, venous thrombotic events, vomiting, withdrawal syndrome

Metabolism/Transport Effects **Substrate** of CYP1A2 (major), 2D6 (minor); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Atypical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Fluvoxamine: May decrease the metabolism of OLANZapine. *Risk D: Consider therapy modification*

LamoTRIgine: May enhance the sedative effect of OLANZapine. *Risk C: Monitor therapy*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization). Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Monitoring ParametersVital signs; fasting lipid profile and fasting blood glucose/Hgb A_{1c} (prior to treatment, at 3 months, then annually); periodic assessment of hepatic transaminases (in patients with hepatic disease); BMI, personal/family history of obesity, waist circumference; orthostatic blood pressure; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms (EPS). Weight should be assessed prior to treatment, at 4 weeks, 8 weeks, 12 weeks, and then at quarterly intervals. Consider titrating to a different antipsychotic agent for a weight gain ≥5% of the initial weight.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Initiate at lower doses. Taper dosage slowly when discontinuing. Instruct patients with diabetes to monitor blood glucose levels closely (may cause hyperglycemia). Monitor therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. Monitor weight prior to initiating therapy and at least monthly. Consider titrating to a different antipsychotic agent for a weight gain ≥ 5% of initial weight. Teach patient appropriate administration, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsFasting lipid profile and fasting blood glucose/Hgb A_{1c} (prior to treatment, at 3 months, then annually); periodic assessment of hepatic transaminases (in patients with hepatic disease)

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Use exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results; do not discontinue without consulting prescriber. Avoid alcohol or caffeine and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, you may experience increased blood sugars. Monitor blood sugars closely. If you have glaucoma, periodic ophthalmic exams are recommended. You may experience excess drowsiness, restlessness, weakness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); constipation (increased exercise, fluids, fruit, or fiber may help); heartburn; dry mouth; or weight gain. Report persistent CNS effects (eg, trembling fingers, altered gait or balance, excessive sedation, seizures, unusual movements, anxiety, abnormal thoughts, confusion, personality changes); suicidal ideation; unresolved constipation or GI effects; vision changes; respiratory difficulty; unusual cough or flu-like symptoms; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Orally-disintegrating tablet: Remove from foil blister by peeling back (do not push tablet through the foil). Place tablet in mouth immediately upon removal. Tablet dissolves rapidly in saliva and may be swallowed with or without liquid.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution (Zyprexa® IntraMuscular): 10 mg [contains lactose 50 mg]

Tablet (Zyprexa®): 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg

Tablet, orally disintegrating (Zyprexa® Zydis®): 5 mg [contains phenylalanine 0.34 mg/tablet], 10 mg [contains phenylalanine 0.45 mg/tablet], 15 mg [contains phenylalanine 0.67 mg/tablet], 20 mg [contains phenylalanine 0.9 mg/tablet]

Generic AvailableNo

ManufacturerEli Lilly and Co

Pricing: U.S. (www.drugstore.com)

Tablet, orally-disintegrating (Zyprexa Zydis)

5 mg (30): $303.76

Tablets (Zyprexa)

2.5 mg (30): $215.63

5 mg (30): $264.34

7.5 mg (30): $320.20

10 mg (30): $392.96

15 mg (30): $587.16

20 mg (30): $725.93

Mechanism of ActionOlanzapine is a second generation thienobenzodiazepine antipsychotic which displays potent antagonism of serotonin 5-HT_{2A} and 5-HT_{2C}, dopamine D_{1-4}, histamine H_1 and alpha$_1$-adrenergic receptors. Olanzapine shows moderate antagonism of 5-HT_3 and muscarinic M_{1-5} receptors, and weak binding to GABA-A, BZD, and beta-adrenergic receptors. Although the precise mechanism of action in schizophrenia and bipolar disorder is not known, the efficacy of olanzapine is thought to be mediated through combined antagonism of dopamine and serotonin type 2 receptor sites.

Pharmacodynamics/Kinetics

Absorption:

I.M.: Rapidly absorbed

Oral: Well absorbed; not affected by food; tablets and orally-disintegrating tablets are bioequivalent

Distribution: V_d: Extensive, 1000 L

Protein binding, plasma: 93% bound to albumin and alpha$_1$-glycoprotein

Metabolism: Highly metabolized via direct glucuronidation and cytochrome P450 mediated oxidation (CYP1A2, CYP2D6); 40% removed via first pass metabolism

Bioavailability: >57%

Half-life elimination: 21-54 hours; ~1.5 times greater in elderly

Time to peak, plasma: Maximum plasma concentrations after I.M. administration are 5 times higher than maximum plasma concentrations produced by an oral dose.

I.M.: 15-45 minutes

Oral: ~6 hours

Excretion: Urine (57%, 7% as unchanged drug); feces (30%)

Clearance: 40% increase in olanzapine clearance in smokers; 30% decrease in females

Related Information

- Agents Approved for Bipolar Disorder
- Antipsychotic Agents
- Antipsychotic Receptor Profile
- Atypical Antipsychotics
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Child/Adolescent ConsiderationsFive hospitalized children 6-11 years of age with varying diagnoses were treated with a mean daily dose of 7.5 mg/day (2.5-10 mg/day) or 0.22 mg/kg/day (0.12-0.29 mg/kg/day) for a mean of 32 days (Krishnamoorthy, 1998). Seven adolescents 12-17 years of age with DSM-IV bipolar disorder, manic episode were treated with a mean dose of 11 mg/day or 0.146 ± 0.086 mg/kg/day (Soutullo, 1999).

Krishnamoorthy J and King BH, "Open-Label Olanzapine Treatment in Five Preadolescent Children," *J Child Adolesc Psychopharmacol*, 1998, 8(2):107-13.

Soutullo CA, Sorter MT, Foster KD, et al, "Olanzapine in the Treatment of Adolescent Acute Mania: A Report of Seven Cases," *J Affect Disord*, 1999, 53(3):279-83.

Schizophrenia: Olanzapine has shown modest efficacy in pediatric schizophrenia, although treatment effects appear inferior to clozapine. However, the more favorable safety profile (compared to clozapine) may justify its continued use in this patient population.

In an open-label, single-arm pilot study, 8 children/adolescents (mean age: 15.3 years) diagnosed with childhood-onset schizophrenia (DSM-III-R) that was refractory to two prior typical neuroleptic regimens were evaluated for efficacy on olanzapine therapy for 8 weeks (Kumra, 1998). Rating instruments included the CGI, SANS, SAPS, and BPRS scales. In a separate study, a cohort of 15 children who received clozapine for 6 weeks was used as a comparative control group. Overall, olanzapine was well tolerated and did not cause any hematologic, EEG, or epileptogenic adverse effects, whereas 4 patients on clozapine required prophylactic anticonvulsant treatment. Body weight increases did not differ significantly between groups. Olanzapine dosing was initiated at 2.5 mg every other day (<40 kg) or every day (>40 kg), and titrated every 5-9 days by 2.5-5 mg up to a maximum of 20 mg/day. By the 6th week of treatment, the mean daily olanzapine dose was 17.5 mg (range: 12.5-20 mg) or 0.27 mg/kg. After 8 weeks of treatment, improvements relative to baseline were noted in each of the rating scales, ranging from 6% to 33%. However, the magnitude of response as measured by these scales was approximately threefold lower than the improvements seen with clozapine (using the same instruments) at the 6-week mark. Further, none of the olanzapine treated patients were rated as responders (based on standard criteria) at 6 weeks of therapy, and only 3 (38%) were responsive or partially responsive at 8 weeks. In comparison, 8 (53%) of clozapine-receiving patients were considered responders at the 6-week time point.

A double-blind, randomized, 8 week trial of olanzapine compared to clozapine was conducted in children/adolescents aged 7-16 years who met DSM-IV criteria for treatment-refractory schizophrenia (Shaw, 2006). The primary outcome measures were the CGI-S and SANS/SAPS scales. Patients randomized to olanzapine (n=13) were 12.8 years of age on average and received an average daily dose of 18.1 mg (20 mg/day maximum). Clozapine patients (n=12) were 11.7 years of age and received a mean daily dose of 387 mg (900 mg/day maximum). Side effects were reported more frequently in the clozapine arm (55 events) compared to the olanzapine arm (28 events, $p<0.001$), including significantly more cardiovascular events noted. Body weight increases and incidence of neutropenia did not differ significantly between groups. Relative to baseline antipsychotic-free scores, patients receiving clozapine showed improvements in the assessment scales of 23% to 48%, compared to 15% to 29% for olanzapine treated patients. Based on differential treatment effects, this equated to a 2.5-fold greater treatment effect in the clozapine arm.

Kumra S, Jacobsen LK, Lenane M, et al, "Childhood-Onset Schizophrenia: An Open-Label Study of Olanzapine in Adolescents," *J Am Acad Child Adolesc Psychiatry*, 1998, 37(4):377-85.

Shaw P, Sporn A, Gogtay N, et al, “Childhood-Onset Schizophrenia: A Double-Blind, Randomized Clozapine-Olanzapine Comparison,” *Arch Gen Psychiatry*, 2006, 63(7):721-30.

Mental Health Comment Olanzapine is an antipsychotic agent of a class often referred to as atypical. It should be noted that the definition of the term “atypical” is not universally agreed upon. Some prefer to describe antipsychotics based on their pharmacological properties. A common feature of all definitions used to describe “atypical” antipsychotics is the lack of significant acute or subacute EPS, at dosages generally associated with antipsychotic actions. Other experts have included definitions of atypicality that include a) failure to increase serum prolactin levels; b) superior efficacy for positive, negative, and cognitive symptoms; and c) lack of evidence of tardive dyskinesia or dystonia following chronic administration. Olanzapine meets most of these criteria, but is associated with dose-dependent EPS. Fortunately, if doses are kept within the approved dosage range (5-20 mg/day), EPS is low.

Tardive dyskinesia (TD) secondary to **typical** antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. The incidence of TD associated with the atypical antipsychotics is estimated to be 0.5% to 1%. It is not clear if this estimate represents a risk associated with mental illness or to what extent drug therapy can be implicated. Atypical antipsychotics appear less likely to cause tardive dyskinesia than typical antipsychotics (fluphenazine, haloperidol).

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Index TermsLY170053; Zyprexa Zydis

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International Brand Names Midax (PY); Olan (PH); Oleanz (IN); Placet (PY, UY); Zelta (CO); Zolafren (PL); Zyprexa (AR, AT, AU, BE, BF, BG, BJ, BR, CH, CI, CL, CN, CR, CZ, DE, DK, DO, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, HK, HN, ID, IE, IL, IT, KE, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, PA, PE, PH, PK, PL, PT, RU, SC, SD, SE, SG, SL, SN, SV, TH, TN, TR, TZ, UG, VE, ZA, ZM, ZW); Zyprexa Velotab (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Zyprexa Zydis (AR, HK, MY, NZ, SG, TW)

Olmesartan and Hydrochlorothiazide

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English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ole me SAR tan & hye droe klor oh THYE a zide)

U.S. Brand NamesBenicar HCT®

Canadian Brand NamesOlmetec Plus®

Pharmacologic CategoryAngiotensin II Receptor Blocker; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension (not recommended for initial treatment)

Dosing: Adults

Hypertension: Oral: Dosage must be individualized; may be titrated at 2- to 4-week intervals.

Replacement therapy: May be substituted for titrated components.

Patients not controlled with single-agent therapy: Initiate by adding the lowest available dose of the alternative component (hydrochlorothiazide 12.5 mg or olmesartan 20 mg). Titrate to effect (maximum hydrochlorothiazide dose: 25 mg, maximum olmesartan dose: 40 mg).

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot recommended in patients with Cl_{cr} <30 mL/minute.

Calculations

- Creatinine Clearance: Adults

StorageStore at 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to olmesartan, hydrochlorothiazide, or any component of the formulation; sulfonamide-derived drugs; anuria

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Electrolyte disturbances: Hyperkalemia may occur with angiotensin II receptor antagonists; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.

- Renal artery stenosis: Use olmesartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use olmesartan with caution with pre-existing renal insufficiency and severe renal impairment. Avoid hydrochlorothiazide in severe renal disease (ineffective); may precipitate azotemia; discontinue or consider withholding if renal impairment occurs.

- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Pregnancy Risk FactorC/D (2nd and 3rd trimesters)

Pregnancy ConsiderationsThe drug should be discontinued as soon as possible when pregnancy is detected. Drugs which act directly on renin-angiotensin can cause fetal and neonatal morbidity and death.

LactationExcretion in breast milk unknown/contraindicated

Adverse ReactionsFrequencies reported with combination product. See individual monographs for additional adverse effects reported with each agent.

Cardiovascular: Chest pain, peripheral edema

Central nervous system: Dizziness (9%), vertigo

Dermatologic: Rash

Endocrine & metabolic: Hyperuricemia (4%), hyperglycemia

Gastrointestinal: Nausea (3%), abdominal pain, dyspepsia, gastroenteritis, diarrhea

Genitourinary: Hematuria

Hepatic: Transaminases increased

Neuromuscular & skeletal: Back pain, arthritis, arthralgia, myalgia

Respiratory: Upper respiratory infection (7%), cough

Miscellaneous: CPK increased

Angioedema and rhabdomyolysis have been reported with angiotensin-receptor blockers. Severe dermatologic reactions, hypokalemia, and pancreatitis have been reported with hydrochlorothiazide.

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure; serum potassium
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

20/12.5: Olmesartan medoxomil 20 mg and hydrochlorothiazide 12.5 mg

40/12.5: Olmesartan medoxomil 40 mg and hydrochlorothiazide 12.5 mg

40/25: Olmesartan medoxomil 40 mg and hydrochlorothiazide 25 mg

Generic AvailableNo
ManufacturerSankyo
Pricing: U.S. (www.drugstore.com)

Tablets (Benicar HCT)

20-12.5 mg (30): $78.51

40-12.5 mg (30): $86.71

40-25 mg (30): $96.34

Mechanism of ActionOlmesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II. Hydrochlorothiazide inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions.
Pharmacodynamics/KineticsSee individual agents.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness
Mental Health: Effects on Psychiatric TreatmentMay cause hyperglycemia and hypertriglyceridemia; combined use with psychotropics (atypical antipsychotics and mirtazapine) may produce additive effects. May cause diarrhea, these effects may be additive with concurrent use of SSRIs, lithium, or valproate. May cause flu-like symptoms, take this into consideration if also concerned about SSRI discontinuation syndrome. Combined use with lithium may produce lithium toxicity; monitor lithium levels.
Cardiovascular Considerations

Hypertension: According to the 2003 JNC 7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Index TermsHydrochlorothiazide and Olmesartan Medoxomil; Olmesartan Medoxomil and Hydrochlorothiazide

References

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International Brand NamesAlteisduo (FR); CoOLMETEC (FR); Olmetec Comp (NO); Olmetec D (AR); Olmetec HCT (BR, EC); Olmetec Plus (BE, DE, DK, DO, EE, FI, GB, GT, HK, HN, KP, MY, NI, PH, SG, SV, TW); Olmetec Plus H (CZ); Omesar Plus (IE)

Olmesartan

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ole me SAR tan)

U.S. Brand NamesBenicar®

Canadian Brand NamesOlmetec®

Pharmacologic CategoryAngiotensin II Receptor Blocker

Use: Labeled IndicationsTreatment of hypertension with or without concurrent use of other antihypertensive agents

Dosing: Adults**Antihypertensive:** Oral: Initial: Usual starting dose is 20 mg once daily; if initial response is inadequate, may be increased to 40 mg once daily after 2 weeks. May administer with other antihypertensive agents if blood pressure inadequately controlled with olmesartan. Consider lower starting dose in patients with possible depletion of intravascular volume (eg, patients receiving diuretics).

Dosing: ElderlyInitial: May start at 5-10 mg/day (due to concomitant disease or age changes).

Dosing: Renal ImpairmentNo specific guidelines for dosage adjustment; patients undergoing hemodialysis have not been studied.

Dosing: Hepatic ImpairmentNo adjustment necessary.

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to olmesartan or any component of the formulation

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Hyperkalemia: May occur; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic/mitral stenosis: Use caution in patients with significant aortic/mitral stenosis.

- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.

- Renal artery stenosis: Use olmesartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution with pre-existing renal insufficiency and severe renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Geriatric ConsiderationsNo dosage adjustment is necessary when initiating angiotensin II receptor antagonists in the elderly. In clinical studies, no differences between younger adults and the elderly were demonstrated.

For age alone, consider hydration status to avoid hypotension; many elderly are volume depleted due to age-related blunting of the thirst reflex and diuretic use. May consider starting this medication at 5-10 mg once daily.

Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)

Pregnancy ConsiderationsMedications which act on the renin-angiotensin system are reported to have the following fetal/neonatal effects:

Hypotension, neonatal skull hypoplasia, anuria, renal failure, and death; oligohydramnios is also reported. These effects are reported to occur with exposure during the second and third trimesters. There are no adequate and well-controlled studies in pregnant women. **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions

1% to 10%:

Central nervous system: Dizziness (3%), headache

Endocrine & metabolic: Hyperglycemia, hypertriglyceridemia

Gastrointestinal: Diarrhea

Neuromuscular & skeletal: Back pain, CPK increased

Renal: Hematuria

Respiratory: Bronchitis, pharyngitis, rhinitis, sinusitis

Miscellaneous: Flu-like syndrome

<1%: Abdominal pain, arthralgia, arthritis, bilirubin increased, chest pain, dyspepsia, facial edema, fatigue, gastroenteritis, hypercholesterolemia, hyperlipidemia, hyperuricemia, insomnia, liver enzymes increased, myalgia, nausea, pain, peripheral edema, rash, skeletal pain, tachycardia, urinary tract infection, vertigo

Postmarketing and/or case reports: Acute renal failure, alopecia, angioedema, hyperkalemia, pruritus, rhabdomyolysis, serum creatinine increased, urticaria, vomiting, weakness

Drug Interactions

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Does not affect olmesartan bioavailability.

Herb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure, serum potassium

Nursing: Physical Assessment/MonitoringUse caution in presence of volume depletion, renal insufficiency, aortic/mitral stenosis. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking. Evaluate therapeutic effectiveness (blood pressure) and adverse response (eg, tachycardia, hypotension, diarrhea, bronchitis) on a regular basis throughout therapy. Instruct patients with diabetes to monitor glucose levels closely (may cause hyperglycemia). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum potassium

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Do not use potassium supplement or salt substitutes without consulting prescriber. Take exactly as directed. Do not alter dose or discontinue without consulting prescriber. May be taken with or without food. This drug does not eliminate the need for diet or exercise regimen as recommended by prescriber. If you have diabetes, check glucose levels closely (drug may alter glucose levels). May cause headache or dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known); diarrhea (boiled milk, buttermilk, or yogurt may help); or back or joint pain (consult prescriber for approved analgesic). Report chest pain or palpitations; unrelieved headache; flu-like symptoms or upper respiratory infection; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as medoxomil:

Benicar®: 5 mg, 20 mg, 40 mg

Generic AvailableNo

ManufacturerSankyo Pharma Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Benicar)

5 mg (30): $61.64

20 mg (30): $67.06

40 mg (30): $75.34

Mechanism of ActionAs a selective and competitive, nonpeptide angiotensin II receptor antagonist, olmesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II; olmesartan interacts reversibly at the AT1 and AT2 receptors of many tissues and has slow dissociation kinetics; its affinity for the AT1 receptor is 12,500 times greater than the AT2 receptor. Angiotensin II receptor antagonists may induce a more complete inhibition of the renin-angiotensin system than ACE inhibitors, they do not affect the response to bradykinin, and are less likely to be associated with nonrenin-angiotensin effects (eg, cough and angioedema). Olmesartan increases urinary flow rate and, in addition to being natriuretic and kaliuretic, increases excretion of chloride, magnesium, uric acid, calcium, and phosphate.

Pharmacodynamics/Kinetics

Distribution: 17 L; does not cross the blood-brain barrier (animal studies)

Protein binding: 99%

Metabolism: Olmesartan medoxomil is hydrolyzed in the GI tract to active olmesartan. No further metabolism occurs.

Bioavailability: 26%

Half-life elimination: Terminal: 13 hours

Time to peak: 1-2 hours

Excretion: All as unchanged drug: Feces (50% to 65%); urine (35% to 50%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause hyperglycemia and hypertriglyceridemia; combined use with psychotropics (atypical antipsychotics and mirtazapine) may produce additive effects; may cause diarrhea, these effects may be additive with concurrent use of SSRIs, lithium, or valproate. May cause flu-like symptoms, take this into consideration if also concerned about SSRI discontinuation syndrome. Combined use with lithium may produce lithium toxicity; monitor lithium levels.

Cardiovascular Considerations

Hypertension: According to the 2003 JNC 7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Anesthesia and Critical Care Concerns/Other Considerations The angiotensin II receptor antagonists appear to have similar indications as the ACE inhibitors. In heart failure, the angiotensin II antagonists are especially useful in providing an alternative therapy in those patients who have intractable cough in response to ACE inhibitor therapy. Candesartan has been studied as an alternative therapy in chronic heart failure patients who cannot tolerate an ACE-I (CHARM-Alternative) and as an added therapy in heart failure patients who are maintained on an ACE-I (CHARM-Added). In both studies, the combined endpoint of cardiovascular death or heart failure hospitalizations was significantly improved over the placebo-treated group. Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

Index Terms Olmesartan Medoxomil

References

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International Brand Names Almetec (MX); Alteis (FR); Benetor (IE); Benicar (BR); Olmec (AR); Olmetec (BE, CH, CL, CO, CZ, DE, DK, DO, EC, EE, ES, FI, FR, GB, GT, HK, HN, ID, IL, IT, KP, MY, NI, NL, NO, PH, PT, SG, SV, TH, TW, VE); Olmezar (PH); Omesar (IE); Tensar (BG); Votum (CH, DE)

Olopatadine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Patanol® may be confused with Platinol®

International issues:

Patanol® may be confused with Betanol® which is a brand name for metipranolol in Monaco and a brand name for atenolol in Bangladesh

Pronunciation(oh la PAT a deen)
U.S. Brand NamesPataday™; Patanase®; Patanol®
Canadian Brand NamesPatanol®
Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, Second Generation
Use: Labeled Indications

Nasal spray: Treatment of the symptoms of seasonal allergic rhinitis

Ophthalmic: Treatment of the signs and symptoms of allergic conjunctivitis

Dosing: Adults**Allergic conjunctivitis:** Ophthalmic:

Patanol®: Instill 1drop into affected eye(s) twice daily (allowing 6-8 hours between doses); results from an environmental study demonstrated that olopatadine was effective when dosed twice daily for up to 6 weeks

Pataday™: Instill 1 drop into affected eye(s) once daily

Seasonal allergic rhinitis: Intranasal (Patanase®): 2 sprays into each nostril twice daily

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Allergic conjunctivitis: Ophthalmic: Children ≥3 years: Refer to adult dosing.

Seasonal allergic rhinitis: Intranasal: Children ≥12 years: Refer to adult dosing.

Administration: InhalationInhalation (Patanase®): For intranasal use only. Before initial use of the nasal spray, the delivery system should be primed with 5 sprays or until a fine mist appears. If 7 or more days have elapsed since last use, the delivery system should be reprimed with 2 sprays or until a fine mist appears. Blow nose to clear nostrils. Keep head tilted downward when spraying. Insert applicator into nostril, keeping bottle upright, and close off the other nostril. Breathe in through nose. While inhaling, press pump to release spray. Alternate sprays between nostrils. After each use, wipe the spray tip with a clean tissue or cloth.
Administration: OtherOphthalmic (Patanol®, Pataday™): For topical ophthalmic use only. After instilling drops, wait at least 10 minutes before inserting contact lenses. Do not insert contacts if eyes are red.
Storage

Nasal spray: Store at 4°C to 25°C (39°F to 77°F).

Ophthalmic solution: Store at 2°C to 25°C (36°F to 77°F).

ContraindicationsHypersensitivity to olopatadine hydrochloride or any component of the formulation
Warnings/Precautions

Dosage form specific issues:

- Nasal spray: May cause drowsiness in some patients; instruct patient to use caution when driving or operating machinery. Effects may be additive with CNS depressants and/or ethanol. Periodically examine nasal mucosa for ulceration and consider discontinuing if ulceration occurs. Safety and efficacy have not been established in children <12 years of age.

- Ophthalmic: Not for use to treat contact lens-related irritation. Solution contains benzalkonium chloride; remove lens prior to administration and wait at least 10 minutes before reinserting. Do not use contact lenses if eyes are red. Safety and efficacy have not been established in children <3 years of age.

Geriatric ConsiderationsNo specific information in the elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; however, a decrease in fetal weight and a decrease in

live births were observed. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

Nasal spray:

>10%: Gastrointestinal: Bitter taste (13%)

1% to 10%:

Central nervous system: Somnolence (1%)

Gastrointestinal: Xerostomia (1%)

Genitourinary: Urinary tract infection (1%)

Neuromuscular & skeletal: CPK increased (1%)

Respiratory: Nasal ulceration (9%), epistaxis (3%), pharyngolaryngeal pain (2%), postnasal drip (2%), cough (1%), throat irritation (1%)

Miscellaneous: Influenza (1%)

<1%: Weight gain

Ophthalmic:

>5%:

Central nervous system: Cold syndrome (up to 10%), headache (up to 7%)

Respiratory: Pharyngitis (up to 10%)

≤5%:

Gastrointestinal: Nausea, taste perversion

Neuromuscular & skeletal: Back pain, weakness

Ocular: Blurred vision, burning, conjunctivitis, dry eyes, eye pain, eyelid edema, foreign body sensation, hyperemia, itching, keratitis, ocular pruritus, stinging

Respiratory: Cough, rhinitis, sinusitis

Miscellaneous: Flu-like syndrome, hypersensitivity, infection

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may cause increased somnolence or fatigue).

Monitoring ParametersObserve patients periodically for adverse nasal effects (eg, ulceration, perforation)

Nursing: Physical Assessment/MonitoringAssess therapeutic response and adverse effects. Assess nasal mucosa periodically for ulceration. Teach patient proper use, side effects/appropriate interventions, and symptoms to report.

Patient Education**Pregnancy precaution:** Inform prescriber if you are pregnant.

Ophthalmic: For use in eyes only. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Do not wear contact lenses if eyes are red. Can cause cold-like symptoms and headache.

Inhalation: May cause drowsiness. Do not operate machinery or participate in activities requiring alertness until response to medication is known. May cause bitter taste. Avoid alcohol use. Report ulcers or discomfort in nose.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, intranasal [spray]:

Patanase®: 0.6% (30.5 g) [contains benzalkonium chloride; equivalent to olopatadine hydrochloride 665 mcg/100 microliters; 240 metered sprays]

Solution, ophthalmic:

Patanol®: 0.1% (5 mL) [contains benzalkonium chloride]

Pataday™: 0.2% (2.5 mL) [contains benzalkonium chloride]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Pataday)

0.2% (2.5): $90.49

Solution (Patanase)

0.6% (30.5): $89.99

Solution (Patanol)

0.1% (5): $89.99

Mechanism of Action

Selective histamine H_1-antagonist; inhibits release of histamine from mast cells. Inhibits histamine induced effects on conjunctival epithelial cells and the respiratory tract. Has no effect on alpha-adrenergic, dopaminergic, and muscarinic type 1 and 2 receptors.

Pharmacodynamics/Kinetics

Onset of action: Intranasal: 30 minutes in seasonal allergy patients

Absorption: Ophthalmic: Low systemic absorption

Protein binding: ~55% (primarily albumin)

Metabolism: Not extensively metabolized

Bioavailability: Intranasal: 57%

Half-life elimination: Ophthalmic: ~3 hours ; Intranasal: 8-12 hours

Time to peak, serum: Intranasal: 15 minutes to 2 hours

Excretion: Urine (60% to 70%, mostly as unchanged drug); feces (17%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsOlopatadine Hydrochloride

International Brand NamesAllelock (KP); Opatanol (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PL, PT, RU, SE, TR); Patanol (AR, AU, BO, BR, CL, CN, CO, CR, DO, EC, GT, HK, HN, ID, IL, MX, MY, NI, PA, PE, PH, PR, PY, SG, SV, TH, TW, UY, VE, ZA)

Olsalazine

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Medication Safety Issues

Sound-alike/look-alike issues:

Olsalazine may be confused with OLANZapine

Dipentum® may be confused with Dilantin®

Pronunciation(ole SAL a zeen)
U.S. Brand NamesDipentum®
Canadian Brand NamesDipentum®
Pharmacologic Category5-Aminosalicylic Acid Derivative
Use: Labeled IndicationsMaintenance of remission of ulcerative colitis in patients intolerant to sulfasalazine
Dosing: Adults**Ulcerative colitis:** Oral: 1 g/day in 2 divided doses
Dosing: ElderlyRefer to adult dosing.
Administration: OralAdminister with food in evenly divided doses.
Dietary ConsiderationsTake with food, increases residence of drug in body.
ContraindicationsHypersensitivity to olsalazine, salicylates, or any component of the formulation
Allergy Considerations

- 5-Aminosalicylic Acid Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

• Colitis: May exacerbate symptoms of colitis.

• Diarrhea: A common adverse effect is diarrhea.

Disease-related concerns:

• Asthma: Use with caution in patients with severe allergies or asthma.

• Hepatic impairment: Use with caution in patients with hepatic impairment.

• Renal impairment: Use with caution in patients with renal impairment.

Special populations:

• Elderly: Use with caution.

• Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo specific data is available on elderly to suggest the drug needs alterations in dose. Since so little is absorbed, dosing should not be changed for reasons of age. Diarrhea may pose a serious problem for elderly in that it may cause dehydration, electrolyte imbalance, hypotension, and confusion.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies have demonstrated fetal developmental toxicities. There are no well-controlled studies in pregnant women. Use during pregnancy only if clearly necessary.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsThe active metabolite, 5-aminosalicylic acid may pass into breast milk. Diarrhea has been reported in breast-fed infants whose mothers took olsalazine.
Adverse Reactions

>10%: Gastrointestinal: Diarrhea (11% to 17%; dose related)

1% to 10%:

Central nervous system: Headache (5%), depression (2%). fatigue (2%), vertigo (1%)

Dermatologic: Rash (2%), pruritus (1%)

Gastrointestinal: Abdominal pain/cramps (10%), heartburn (2%), nausea (5%), stomatitis (1%), vomiting (1%)

Neuromuscular & skeletal: Arthralgia (4%)

Respiratory: Upper respiratory infection (2%)

Postmarketing and/or case reports: Alopecia, angioedema, anorexia, aplastic anemia, bilirubin increase, blood dyscrasias, blood in stool, blurred vision, bronchospasm, cholestatic jaundice, chills, cirrhosis, dehydration, dry eyes, dyspnea, dysuria, eosinophilia, erythema, erythema nodosum, fever, flare of symptoms, flatulence, heart block (second degree), hematuria, hemolytic anemia, hepatitis, hepatic failure, hepatic necrosis, hot flashes, hypertension, impotence, insomnia, interstitial nephritis, interstitial pneumonia, irritability, jaundice, Kawasaki-like syndrome, leukopenia, lymphopenia, menorrhagia, muscle cramps, myalgia, myocarditis, nephritic syndrome, neutropenia, orthostatic hypotension, palpitation, pancreatitis, pancytopenia, paresthesia, pericarditis, peripheral edema, photosensitivity, proteinuria, rectal bleeding, rectal discomfort, rigors, tachycardia, thrombocytopenia, tinnitus, transaminase increase, tremor, urinary frequency, watery eyes, xerostomia

Drug Interactions

Cardiac Glycosides: 5-ASA Derivatives may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

Thiopurine Analogs: 5-ASA Derivatives may decrease the metabolism of Thiopurine Analogs. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: 5-ASA Derivatives may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. The primary concern is the potential development of Reye's Syndrome, a condition that has been associated with the use of salicylates in children with varicella infections. *Risk D: Consider therapy modification*

Test InteractionsIncreased ALT, AST (S), GGT, LDH, alkaline phosphatase, bilirubin

Monitoring ParametersCBC, hepatic function, renal function; stool frequency

Nursing: Physical Assessment/MonitoringAssess allergy history before initiating therapy (salicylates, sulfasalazine, or mesalamine). Assess effectiveness (reduction of clinical signs of ulcerative colitis) and adverse effects (eg, diarrhea). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report

Monitoring: Lab TestsCBC, hepatic function, renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, with meals, in evenly divided doses. May cause flu-like symptoms or muscle pain (consult prescriber for approved analgesic); diarrhea (buttermilk, boiled milk, or yogurt may help); or nausea or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report persistent diarrhea or abdominal cramping, skin rash or itching, or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as sodium: 250 mg

Generic AvailableNo

ManufacturerUCB, Inc

Pricing: U.S. (www.drugstore.com)

Capsules (Dipentum)

250 mg (100): $179.99

Mechanism of ActionMesalamine (5-aminosalicylic acid) is the active component of olsalazine; the specific mechanism of action of mesalamine is unknown; however, it is thought that it modulates local chemical mediators of the inflammatory response, especially leukotrienes, and is also postulated to be a free radical scavenger or an inhibitor of tumor necrosis factor (TNF); action appears topical rather than systemic.

Pharmacodynamics/Kinetics

Absorption: <3%; very little intact olsalazine is systemically absorbed

Protein binding, plasma: >99%

Metabolism: Primarily via colonic bacteria to active drug, 5-aminosalicylic acid

Half-life elimination: 56 minutes

Time to peak: ~1 hour

Excretion: Primarily feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or depression

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsOlsalazine Sodium

International Brand NamesDipentum (AE, AR, AT, AU, BH, CH, CY, DE, DK, EG, FI, FR, GB, GR, HN, HU, IE, IL, IQ, IR, IT, JO, KW, LB, LY, NL, NO, OM, QA, SA, SE, SY, YE, ZA); Rasal (ES)

Omalizumab

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(oh mah lye ZOO mab)

U.S. Brand NamesXolair®

Canadian Brand NamesXolair®

Pharmacologic CategoryMonoclonal Antibody, Anti-Asthmatic

Use: Labeled IndicationsTreatment of moderate-to-severe, persistent allergic asthma not adequately controlled with inhaled corticosteroids

Dosing: Adults**Asthma:** SubQ: Dose is based on pretreatment IgE serum levels and body weight. Dosing should not be adjusted based on IgE levels taken during treatment or <1 year following discontinuation of therapy; doses should be adjusted during treatment for significant changes in body weight.

IgE ≥30-100 int. units/mL:

  30-90 kg: 150 mg every 4 weeks

  >90-150 kg: 300 mg every 4 weeks

IgE >100-200 int. units/mL:

  30-90 kg: 300 mg every 4 weeks

  >90-150 kg: 225 mg every 2 weeks

IgE >200-300 int. units/mL:

  30-60 kg: 300 mg every 4 weeks

  >60-90 kg: 225 mg every 2 weeks

  >90-150 kg: 300 mg every 2 weeks

IgE >300-400 int. units/mL:

  30-70 kg: 225 mg every 2 weeks

  >70-90 kg: 300 mg every 2 weeks

  >90 kg: Do not administer dose

IgE >400-500 int. units/mL:

  30-70 kg: 300 mg every 2 weeks

  >70-90 kg: 375 mg every 2 weeks

  >90 kg: Do not administer dose

IgE >500-600 int. units/mL:

  30-60 kg: 300 mg every 2 weeks

  >60-70 kg: 375 mg every 2 weeks

  >70 kg: Do not administer dose

IgE >600-700 int. units/mL:

  30-60 kg: 375 mg every 2 weeks

  >60 kg: Do not administer dose

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Asthma:** Children ≥12 years: SubQ: Refer to adult dosing.

Administration: OtherFor SubQ injection only; doses >150 mg should divided over more than one site. Injections may take 5-10 seconds to administer. Administer only under direct medical supervision and observe patient for a minimum of 2 hours following administration of any dose given.

StoragePrior to reconstitution, store under refrigeration at 2°C to 8°C (36°F to 46°F); product may be shipped at room temperature. Following reconstitution, protect from direct sunlight. May be stored for up to 8 hours if refrigerated or 4 hours if stored at room temperature.

ReconstitutionPrepare using SWFI, USP only; add SWFI 1.4 mL to upright vial and swirl gently for 5-10 seconds every 5 minutes until dissolved; may take >20 minutes to dissolve completely. Resulting solution is 150 mg/1.2 mL. Do not use if powder takes >40 minutes to dissolve.

RestrictionsAn FDA-approved medication guide is available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm; distribute to each patient to whom this medication is dispensed.

ContraindicationsHypersensitivity to omalizumab or any component of the formulation; acute bronchospasm, status asthmaticus

Warnings/Precautions

Boxed warnings:

- Anaphylaxis: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: **[U.S. Boxed Warning]: Anaphylaxis, including delayed-onset anaphylaxis, has been reported following administration; reactions usually occur within 2 hours of administration, but may occur up to 24 hours and in some cases >1 year after initiation of regular treatment.** Patients should receive treatment only under direct medical supervision and be observed for a minimum of 2 hours following administration; appropriate medications for the treatment of anaphylactic reactions should be available. Hypersensitivity reactions may occur following any dose, even during chronic therapy; discontinue therapy following any severe reaction.

- Malignant neoplasms: Have been reported with use in short-term studies; impact of long-term use is not known.

Disease-related concerns:

- Patients at risk for parasitic infections: Use with caution and monitor patients at risk for parasitic (helminth) infections; risk of infection may be increased.

Concurrent drug therapy issues:

- Corticosteroid therapy: Gradually taper corticosteroid therapy, do not discontinue abruptly.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Appropriate use: For use in patients with a documented reactivity to a perennial aeroallergen and with symptoms uncontrolled using inhaled corticosteroids; not used to control acute asthma symptoms.

- Dosing/IgE levels: Dosing is based on pretreatment IgE serum levels and body weight. IgE levels remain elevated up to 1 year following treatment, therefore, levels taken during treatment cannot be used as a dosage guide.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. IgG molecules are known to cross the placenta; use during pregnancy only if clearly needed. A registry has been established to monitor outcomes of women exposed to omalizumab during pregnancy or within 8 weeks prior to pregnancy (866-496-5247).

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIgG is excreted in human milk and excretion of omalizumab is expected. Effects to nursing infant are not known; use with caution.

Adverse Reactions

>10%:

Central nervous system: Headache (15%)

Local: Injection site reaction (45%; placebo 43%; severe 12%). Most reactions occurred within 1 hour, lasted <8 days, and decreased in frequency with additional dosing.

Respiratory: Upper respiratory tract infection (20%), sinusitis (16%), pharyngitis (11%)

Miscellaneous: Viral infection (23%)

1% to 10%:

Central nervous system: Pain (7%), fatigue (3%), dizziness (3%)

Dermatologic: Dermatitis (2%), pruritus (2%)

Neuromuscular & skeletal: Arthralgia (8%), leg pain (4%), arm pain (2%), fracture (2%)

Otic: Earache (2%)

<1%, postmarketing, and/or case reports: Alopecia; anaphylaxis (angioedema of the throat or tongue, bronchospasm, chest tightness, cough, cutaneous angioedema, dyspnea, hypotension, generalized pruritus, syncope, and urticaria); antibody formation to omalizumab, hot flushes, malignancy (0.5%; placebo 0.2%), throat edema, thrombocytopenia, tongue edema, urticaria, wheezing

Drug InteractionsThere are no known significant interactions.

Test InteractionsTotal IgE levels are elevated for up to 1 year following treatment. Total serum IgE may be retested after interruption of therapy for 1 year or more.

Monitoring ParametersAnaphylactic/hypersensitivity reactions, baseline IgE; FEV_1, peak flow, and/or other pulmonary function tests;

monitor for signs of infection

Nursing: Physical Assessment/MonitoringFor SubQ use only. Evaluate results of laboratory tests and pulmonary function tests at baseline and as necessary with treatment. Anaphylactic reactions have been reported within 2 -24 hours (or longer) of initial dose; patient should be monitored for a minimum of 2 hours following injection and appropriate medications for the treatment of hypersensitivity reactions should be available. Evaluate patient response (relief of asthmatic symptoms) and adverse reactions (eg, hypersensitivity reaction, upper respiratory tract infection, viral infection, dermatitis, arthralgia) at beginning and periodically during therapy. Caution patient to read the FDA-approved medication guide distributed when medication is dispensed. Teach patient possible side effects/interventions and adverse symptoms to report (eg, signs of hypersensitivity reaction).

Monitoring: Lab TestsAnaphylactic/hypersensitivity reactions, baseline IgE; FEV$_1$, peak flow, and/or other pulmonary function tests

Patient EducationThis medication is administered by injection and you will be closely monitored for some time following injection. Report immediately any sign of allergic response (redness, swelling, pain or itching at injection site; chest pain or tightness; difficulty breathing or swallowing; swelling of mouth or tongue; skin rash). If allergic response occurs after you leave, follow prescriber's directions for contacting emergency treatment immediately. May cause headache or dizziness (use caution when driving or engaging in hazardous tasks until response to drug is known); joint, bone, or ear pain (consult prescriber for analgesic). Report unusual or increased respiratory difficulty, signs of infection, skin rash, or other persistent reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if you are breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Xolair®: 150 mg [contains sucrose 145.5 g]

Generic AvailableNo

ManufacturerGenentech, Inc

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Xolair)

150 mg (1): $671.91

Mechanism of ActionOmalizumab is an IgG monoclonal antibody (recombinant DNA derived) which inhibits IgE binding to the high-affinity IgE receptor on mast cells and basophils. By decreasing bound IgE, the activation and release of mediators in the allergic response (early and late phase) is limited. Serum-free IgE levels and the number of high-affinity IgE receptors are decreased. Long-term treatment in patients with allergic asthma showed a decrease in asthma exacerbations and corticosteroid usage.

Pharmacodynamics/Kinetics

Absorption: Slow following SubQ injection

Distribution: V$_d$: 78 ± 32 mL/kg

Metabolism: Hepatic; IgG degradation by reticuloendothelial system and endothelial cells

Bioavailability: 62%

Half-life elimination: 26 days

Time to peak: 7-8 days

Excretion: Primarily via hepatic degradation; intact IgG may be secreted in bile

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness and fatigue

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsrhuMAb-E25

References

Casale TB, Condemi J, LaForce C, et al, “Effect of Omalizumab on Symptoms of Seasonal Allergic Rhinitis: A Randomized Controlled Trial,” *JAMA*, 2001, 286(23):2956-67. [PubMed 11743836]

Marcus P, “Incorporating Anti-IgE (Omalizumab) Therapy Into Pulmonary Medicine Practice,” *Chest*, 2006, 129(2):466-74.[PubMed 16478867]

Milgrom H, Berger W, Nayak A, et al, “Treatment of Childhood Asthma With Anti-immunoglobulin E Antibody (Omalizumab),” *Pediatrics*, 2001, 108(2):E36. [PubMed 11483846]

Milgrom H, Fick RB Jr, Su JQ, et al, “Treatment of Allergic Asthma With Monoclonal Anti-IgE Antibody. rhuMAb-E25 Study Group,” *N Engl J Med*, 1999, 341(26):1966-73.[PubMed 10607813]

International Brand NamesXolair (AR, AT, AU, BE, BG, BR, CH, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, MY, NL, NO, PH, PT, RU, SE, SG, TH, TR, TW, VE)

Omega-3-Acid Ethyl Esters

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Omacor® may be confused with Amicar®

Pronunciation(oh MEG a three AS id ETH il ES ters)

U.S. Brand NamesLovaza®; Omacor® [DSC]

Pharmacologic CategoryAntilipemic Agent, Miscellaneous

Use: Labeled IndicationsLovaza®: Adjunct to diet therapy in the treatment of hypertriglyceridemia (≥500 mg/dL)

Note: A number of OTC formulations containing omega-3 fatty acids are marketed as nutritional supplements; these do not have FDA-approved indications and may not contain the same amounts of the active ingredient.

Use: Unlabeled/InvestigationalLovaza®: Treatment of IgA nephropathy

Dosing: Adults

Hypertriglyceridemia: Oral: 4 g/day as a single daily dose or in 2 divided doses.

Treatment of IgA nephropathy (unlabeled use): Oral: 4 g/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment required.

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken with or without food. Dietary modification is important in the control of severe hypertriglyceridemia. Maintain standard cholesterol-lowering diet during therapy..

StorageStore at controlled room temperature of 25°C (77°F); do not freeze.

ContraindicationsHypersensitivity to omega-3-acid ethyl esters or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Fish allergy: Use with caution in patients with known allergy or sensitivity to fish.
- Hepatic effects: ALT may increase without concurrent AST increase; periodically monitor hepatic transaminases.
- Lipid effects: May increase LDL levels; periodically monitor LDL levels.
- Prolongation of bleeding time: Prolongation of bleeding time has been observed in some clinical studies; use with caution in patients with coagulopathy or in those receiving therapeutic anticoagulation. Monitor for changes in INR following initiation and dosage changes of omega-2-acid ethyl esters in patients receiving warfarin.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Should be used as an adjunct to diet therapy and exercise and only in those with very high triglyceride levels (≥500 mg/dL). Secondary causes of hyperlipidemia should be ruled out prior to therapy.
- Inadequate response: If triglyceride levels do not adequately respond after 2 months of treatment with omega-3-acid ethyl esters, discontinue treatment.

Geriatric ConsiderationsSpecific information about the safety and efficacy of omega-3-acid ethyl esters is limited. The manufacturer states there were no apparent differences between persons <60 and >60 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsIn some animal studies, embryocidal and maternal effects have been observed at high doses. There are no adequate or well-controlled studies in pregnant women. Use during pregnancy only if potential benefit outweighs possible risk.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

Cardiovascular: Angina (1%)

Central nervous system: Pain (2%)

Dermatologic: Rash (2%)

Gastrointestinal: Eructation (5%), dyspepsia (3%), taste perversion (3%)

Neuromuscular & skeletal: Back pain (2%)

Miscellaneous: Flu-like syndrome (4%), infection (4%)

<1%, postmarketing, and/or case reports: Abdominal distention, alopecia, anorexia, appetite increased, arrhythmia, arthralgia, arthritis, asthma, body odor, bronchitis, cardiac arrest, cataract, chest pain, chills, colitis, constipation, cough, depression, diaphoresis, dizziness, dysphagia, dyspnea, eczema, edema, emotional lability, epididymitis, epistaxis, facial paralysis, fecal incontinence, fever, fracture, fungal infection, gastritis, gastroenteritis, GI disorder, hyperglycemia, hyperlipemia, hypertension, impotence, insomnia, intestinal obstruction, laryngitis, LDL increased, liver transaminases increased, lymphadenopathy, malaise, melena, MI, migraine, myalgia, myocardial ischemia, neck pain, neoplasm, pancreatitis, peripheral vascular disorder, pharyngitis, pneumonia, pruritus, rheumatoid arthritis, rhinitis, sinusitis, sudden death, suicide, syncope, tachycardia, tendon disorder, tenesmus, vasodilatation, vertigo, viral infection, vomiting, weakness, xerostomia

Drug Interactions

Antiplatelet Agents: Omega-3-Acid Ethyl Esters may enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Warfarin: Omega-3-Acid Ethyl Esters may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Monitor ethanol use (alcohol use may increase triglycerides).

Monitoring ParametersTriglycerides and other lipids (LDL-C) should be monitored at baseline and periodically. Hepatic transaminase levels, particularly ALT, should be monitored periodically.

Nursing: Physical Assessment/MonitoringDo not use if allergic to fish. Encourage diet and exercise along with use of this medication.

Monitoring: Lab TestsTriglycerides and other lipids (LDL-C) should be monitored at baseline and periodically. Hepatic transaminase levels, particularly ALT, should be monitored periodically.

Patient EducationDo not use if allergic to fish. This medication should be used in addition to diet and exercise. Avoid alcohol use. You may experience flu-like syndrome, fever, burping, or an "upset stomach." Report any significant or continued problems to prescriber. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber before breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

Lovaza®, Omacor® [DSC]: 1 g [contains EPA ~465 mg and DHA ~375 mg]

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Capsules (Lovaza)

1 g (120): $162.36

Mechanism of ActionMechanism has not been completely defined. Possible mechanisms include inhibition of acyl CoA:1,2 diacylglycerol acyltransferase, increased hepatic beta-oxidation, a reduction in the hepatic synthesis of triglycerides, or an increase in plasma lipoprotein lipase activity.

Pharmacotherapy Pearls

Due to reports of prescribing errors associated with the similarity between Omacor® and Amicar,® (aminocaproic acid) the name Omacor® has been changed to Lovaza®. The size, strength, ingredients, and dose all remain the same

Mental Health: Effects on Mental StatusMay cause flu-like syndrome; rule out antidepressant withdrawal syndrome

Mental Health: Effects on Psychiatric TreatmentMay prolong bleeding time; concomitant use with SSRIs may produce additive effects; monitor. Beta-blockers may decrease the effects of omega-3-acid ethyl esters; monitor.

Index TermsEthyl Esters of Omega-3 Fatty Acids; Fish Oil

References

Donadio JV and Grande JP, “The Role of Fish Oil/Omega-3 Fatty Acids in the Treatment of IgA Nephropathy,” *Semin Nephrol*, 2004, 24(3):225-43. [PubMed 15156528]

Donadio JV Jr, Larson TS, Bergstralh EJ, et al, “A Randomized Trial of High-Dose Compared With Low-Dose Omega-3 Fatty Acids in Severe IgA Nephropathy,” *J Am Soc Nephrol*, 2001, 12(4):791-9. [PubMed 11274240]

Durrington PN, Bhatnagar D, Mackness MI, et al, “An Omega-3 Polyunsaturated Fatty Acid Concentrate Administered for One Year Decreased Triglycerides in Simvastatin Treated Patients With Coronary Heart Disease and Persisting Hypertriglyceridaemia,” *Heart*, 2001, 85(5):544-8. [PubMed 11303007]

Harris WS, Ginsberg HN, Arunakul N, et al, “Safety and Efficacy of Omacor in Severe Hypertriglyceridemia,” *J Cardiovasc Risk*, 1997, 4(5-6):385-91. [PubMed 9865671]

Stalenhoef AF, de Graaf J, Wittekoek ME, et al, “The Effect of Concentrated n-3 Fatty Acids Versus Gemfibrozil on Plasma Lipoproteins, Low Density Lipoprotein Heterogeneity and Oxidizability in Patients With Hypertriglyceridemia,” *Atherosclerosis*, 2000, 153(1):129-38.[PubMed 11058707]

International Brand NamesAgemo (PK); Omacor (AT, BE, BG, CZ, DE, EE, FI, FR, GB, HN, IE, IL, KP, NL, NO, PT); Triomar (IL); Ysomega (FR)

Omeprazole and Sodium Bicarbonate

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Special Alerts

Clopidogrel (Plavix®) and Proton Pump Inhibitors (PPIs): Ongoing Safety Review - January 2009

The U.S. Food and Drug Administration (FDA) is communicating important information regarding an ongoing safety review of clopidogrel and its effectiveness when used with proton pump inhibitors (PPIs).

Clopidogrel is a prodrug requiring hepatic conversion via CYP3A4 and/or CYP2C19 to its active metabolite. Impaired clopidogrel conversion to its active metabolite may be due to either CYP450 polymorphisms or drug-drug interactions resulting in suboptimal antiplatelet activity.

A PPI is often prescribed with the combination of aspirin and clopidogrel to prevent gastrointestinal bleeding. A number of PPIs are available and include esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. Several studies have reported greater clinical event rates (eg, myocardial infarction, death) or greater platelet reactivity associated with concurrent use of clopidogrel and a PPI (Ho, 2008; Pezella, 2008; Gilard, 2006). Similarly, a prospective, randomized, double-blind trial demonstrated a reduction in antiplatelet activity when omeprazole and clopidogrel are used concurrently (Gilard, 2008). Another controlled trial with the PPI lansoprazole also found evidence of a possible interaction resulting in less antiplatelet activity (Small, 2008). This interaction is thought to result from competitive inhibition of the CYP2C19-mediated activation of clopidogrel by omeprazole and other PPIs, which are all metabolized to at least some degree by CYP2C19. In contrast, one study with esomeprazole and pantoprazole did not find evidence of reduced antiplatelet activity when administered with clopidogrel (Siller-Matula, 2009), highlighting the need for additional studies to determine the degree to which individual PPIs may differ in their potential for interacting with clopidogrel.

The manufacturer of Plavix® has agreed to conduct further studies to better understand the effect of other drugs (including PPIs) and genetic factors on the effectiveness of clopidogrel. The FDA is recommending that healthcare providers continue to prescribe clopidogrel while reevaluating the need for prescription or over-the-counter (OTC) PPIs in patients taking clopidogrel. Patients should continue taking clopidogrel as directed. If taking a PPI with clopidogrel, patients should consult with their healthcare provider.

For more information, healthcare professionals may refer to the following FDA website:
http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm

References:

Ho PM, Maddox TM, Wang L, et al, “Proton Pump Inhibitors May Attenuate the Benefits of Clopidogrel Among ACS Patients: Using Registry Data to Address Medication Effectiveness,” United States Department of Veterans Affairs, 2008 QUERI National Meeting Abstract. Available at http://www.hsrd.research.va.gov/meetings/QUERI08/display_abstract.cfm?RecordID=118; accessed October 30, 2008).

Pezalla E, Day D, and Pulliadath I, “Initial Assessment of Clinical Impact of a Drug Interaction Between Clopidogrel and Proton Pump Inhibitors,” *J Am Coll Cardiol*, 2008, 52(12): 1038-9.

Gilard M, Arnaud B, Le Gal G, et al, “Influence of Omeprazol on the Antiplatelet Action of Clopidogrel Associated to Aspirin,” *J Thromb Haemost*, 2006, 4(11):2508-9.

Gilard M, Arnaud B, Cornily JC, et al, “Influence of Omeprazole on the Antiplatelet Action of Clopidogrel Associated With Aspirin: The Randomized, Double-Blind Ocla (Omeprazole Clopidogrel Aspirin) Study,” *J Am Coll Cardiol*, 2008, 51(3):256-60.

Siller-Matula JM, Spiel AO, Lang IM, et al, “Effects of Pantoprazole and Esomeprazole on Platelet Inhibition by Clopidogrel,” *Am Heart J*, 2009, 157(1): 148.e1-5.

Small DS, Farid NA, Payne CD, et al, “Effects of the Proton Pump Inhibitor Lansoprazole on the Pharmacokinetics and Pharmacodynamics of Prasugrel and Clopidogrel,” *J Clin Pharmacol*, 2008, 48(4):475-84.

Pronunciation(oh MEP ra zole & SOW dee um bye KAR bun ate)

U.S. Brand NamesZegerid®

Pharmacologic CategoryProton Pump Inhibitor; Substituted Benzimidazole

Use: Labeled IndicationsShort-term (4-8 weeks) treatment of active duodenal ulcer disease or active benign gastric ulcer; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); short-term (4-8 weeks) treatment of endoscopically-diagnosed erosive esophagitis; maintenance healing of erosive esophagitis; reduction of risk of upper gastrointestinal bleeding in critically-ill patients

Dosing: Adults

Active duodenal ulcer: Oral: 20 mg/day for 4-8 weeks

Gastric ulcers: Oral: 40 mg/day for 4-8 weeks

Symptomatic GERD: Oral: 20 mg/day for up to 4 weeks

Erosive esophagitis: Oral: 20 mg/day for 4-8 weeks; maintenance of healing: 20 mg/day for up to 12 months total therapy (including treatment period of 4-8 weeks)

Risk reduction of upper GI bleeding in critically-ill patients (Zegerid® powder for oral suspension): Oral:

Loading dose: Day 1: 40 mg every 6-8 hours for two doses

Maintenance dose: 40 mg/day for up to 14 days; therapy >14 days has not been evaluated

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo adjustment is necessary.
Dosing: Hepatic ImpairmentSpecific guidelines are not available; bioavailability is increased with chronic liver disease.
Administration: Oral

Capsule: Should be swallowed whole; do not chew or crush. Capsules should **not** be opened, sprinkled on food, or administered via NG. Best if taken before breakfast.

Powder for oral suspension: Administer 1 hour before a meal. Mix with 2 tablespoons of water; stir well and drink immediately. Rinse cup with water and drink.

Administration: OtherNasogastric/orogastric tube: Powder for oral suspension: Mix well with 20 mL of water and administer immediately; flush tube with an additional 20 mL of water. Suspend enteral feeding for 3 hours before and 1 hour after administering.
Dietary ConsiderationsTake 1 hour before a meal. Each 20 mg or 40 mg packet contains sodium bicarbonate 1680 mg (20 mEq), equivalent to sodium 460 mg (20 mEq) per dose; each 20 mg or 40 mg capsule contains sodium bicarbonate 1100 mg equivalent to sodium 300 mg (13 mEq) per dose.
StorageStore at 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to omeprazole, substituted benzimidazoles (eg, esomeprazole, lansoprazole, pantoprazole, rabeprazole), or any component of the formulation
Allergy Considerations

- Proton Pump Inhibitor, Benzimidazole Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Atrophic gastritis: Long-term omeprazole therapy has caused atrophic gastritis (by biopsy).
- Carcinoma: In long-term (2-year) studies in rats, omeprazole produced a dose-related increase in gastric carcinoid tumors. While available endoscopic evaluations and histologic examinations of biopsy specimens from human stomachs have not detected a risk from short-term exposure to omeprazole, further human data on the effect of sustained hypochlorhydria and hypergastrinemia are needed to rule out the possibility of an increased risk for the development of tumors in humans receiving long-term therapy.

Disease-related concerns:

- Bartter’s syndrome: Use with caution in patients with Bartter’s syndrome; contains sodium bicarbonate.
- Gastric malignancy: Relief of symptoms does not preclude the presence of a gastric malignancy.
- Gastrointestinal infection (eg, *Salmonella, Campylobacter*): Use of proton pump inhibitors may increase risk of these infections.
- Hepatic impairment: Bioavailability may be increased in patients with hepatic dysfunction.
- Hypocalcemia: Use with caution in patients with hypocalcemia; contains sodium bicarbonate.
- Hypokalemia: Use with caution in patients with hypokalemia; contains sodium bicarbonate.
- Respiratory alkalosis: Use with caution in patients with respiratory alkalosis; contains sodium bicarbonate.

Special populations:

- Asian ethnicity: Bioavailability may be increased in patients of Asian descent.
- Elderly: Bioavailability may be increased in the elderly.
- Pediatrics: Safety and efficacy have not been established in children.
- Sodium-restricted diets: Use with caution in patients on sodium-restricted diets; contains sodium bicarbonate.

Geriatric ConsiderationsThe incidence of side effects in the elderly is no different than that of younger adults (≤65 years of age) despite slight decrease in elimination and increase in bioavailability. Dosage adjustments are not necessary. Use cautiously in patients requiring sodium restriction, hypertension, or congestive heart failure.
Pregnancy Risk FactorC
Pregnancy ConsiderationsCrosses the placenta; congenital abnormalities have been reported sporadically following omeprazole use during pregnancy. Based on data collected by the Teratogen Information System (TERIS), it was concluded that therapeutic doses used during pregnancy would be unlikely to pose a substantial teratogenic risk (quantity/quality of data: fair). Because the possibility of harm still exists, the manufacturer recommends use during pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus. Chronic use of sodium bicarbonate-containing products may lead to systemic alkalosis, edema, and weight gain; metabolic alkalosis and fluid overload may occur in mother and fetus.

Lactation Enters breast milk/not recommended

Adverse Reactions

Frequency of adverse events reported for 40 mg dose of oral powder for suspension. **Note:** Asterisked (*) percentages indicate frequency reported from a controlled clinical trial of 359 critically-ill patients.

>10%:

Central nervous system: Pyrexia (20%*)

Endocrine & metabolic: Hypokalemia (12%*), hyperglycemia (11%*)

Respiratory: Nosocomial pneumonia (11%*)

1% to 10%:

Cardiovascular: Hypotension (10%*), hypertension (8%*), atrial fibrillation (6%*), ventricular tachycardia (5%*), bradycardia (4%*), tachycardia (3%*), supraventricular tachycardia (3%*), edema (3%*)

Central nervous system: Hyperpyrexia (5%), agitation (3%), headache (2%)

Dermatological: Rash (6%*), decubitus ulcer (3%)

Endocrine & metabolic: Hypomagnesemia (10%*), hypocalcemia (6%*), hypophosphatemia (6%*), fluid overload (5%*), hypoglycemia (3%*), hyponatremia (4%*), hypernatremia (2%*), hyperkalemia (2%*)

Gastrointestinal: Constipation (5%*), diarrhea (4%*), hypomotility (2%*)

Genitourinary: Urinary tract infection (2%*)

Hematological: Thrombocytopenia (10%*), anemia (8%*), anemia increased (2%*)

Hepatic: LFTs increased (2%*)

Respiratory: ARDS (3%*), respiratory failure (2%*), URI (2%), cough (1%)

Miscellaneous: Sepsis (5%*), oral candidiasis (4%*), candidal infection (2%)

<1% (adverse event occurrence may vary based on formulation): Abdominal swelling, abnormal dreams, aggression, agranulocytosis, alkaline phosphatase increased, allergic reactions, alopecia, anaphylaxis, anemia, angina, angioedema, anorexia, anxiety, apathy, atrophic gastritis, benign gastric polyps, blurred vision, confusion, creatinine increased, depression, diaphoresis, double vision, dry mouth, dry skin, epistaxis, erythema multiforme, esophageal candidiasis, fatigue, fecal discoloration, flatulence, glycosuria, gynecomastia, hallucinations, hematuria, hemifacial dysesthesia, hemolytic anemia, hepatic encephalopathy, hepatic failure, hepatic necrosis, hyperhidrosis, hypertension, hypoglycemia, hyponatremia, insomnia, interstitial nephritis, irritable colon, jaundice, joint pain, leg pain, leukocytosis, leukopenia, liver disease (hepatocellular, cholestatic, mixed), malaise, microscopic pyuria, mucosal atrophy (tongue), muscle cramps, muscle weakness, myalgia, nausea, nervousness, neutropenia, ocular irritation, optic neuropathy, pain, palpitation, pancreatitis, pancytopenia, paresthesia, peripheral edema, petechiae, pharyngeal pain, photosensitivity, pneumothorax, proteinuria, pruritus, psychic disturbance, purpura, rash, skin inflammation, somnolence, Stevens-Johnson syndrome, stomatitis, tachycardia, taste perversion, testicular pain, thrombocytopenia, tinnitus, toxic epidermal necrolysis, tremor, urinary frequency, urinary tract infection, urticaria, vertigo, weight gain

Metabolism/Transport Effects **Substrate** of CYP2A6 (minor), 2C9 (minor), 2C19 (major), 2D6 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2C9 (moderate), 2C19 (strong), 2D6 (weak), 3A4 (weak); **Induces** CYP1A2 (weak)

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Alkalinizing Agents may decrease the excretion of Amphetamines. *Risk D: Consider therapy modification*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Atazanavir: Proton Pump Inhibitors may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Proton Pump Inhibitors may increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Cilostazol: Omeprazole may enhance the adverse/toxic effect of Cilostazol. *Risk D: Consider therapy modification*

Clopidogrel: Proton Pump Inhibitors may diminish the therapeutic effect of Clopidogrel. This appears to be due to reduced formation of the active clopidogrel metabolite. *Risk C: Monitor therapy*

Clozapine: Omeprazole may decrease the serum concentration of Clozapine. Omeprazole may increase the serum concentration of Clozapine. *Risk C: Monitor therapy*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dabigatran Etexilate: Proton Pump Inhibitors may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Dasatinib: Proton Pump Inhibitors may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

Erlotinib: Proton Pump Inhibitors may decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Fluconazole: May increase the serum concentration of Proton Pump Inhibitors. *Risk C: Monitor therapy*

Indinavir: Proton Pump Inhibitors may decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Iron Salts: Proton Pump Inhibitors may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk C: Monitor therapy*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Itraconazole: Proton Pump Inhibitors may decrease the serum concentration of Itraconazole. *Risk D: Consider therapy modification*

Ketoconazole: Proton Pump Inhibitors may decrease the serum concentration of Ketoconazole. Ketoconazole may increase the serum concentration of Proton Pump Inhibitors. *Risk D: Consider therapy modification*

Lithium: Sodium Bicarbonate may increase the excretion of Lithium. *Risk C: Monitor therapy*

Memantine: Sodium Bicarbonate may decrease the excretion of Memantine. *Risk C: Monitor therapy*

Mesalamine: Antacids may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids. *Risk X: Avoid combination*

Mesalamine: Proton Pump Inhibitors may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids; proton pump inhibitors would be expected to interact in a similar manner. *Risk X: Avoid combination*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Methotrexate: Proton Pump Inhibitors may decrease the excretion of Methotrexate. Antirheumatic doses of methotrexate probably hold minimal risk. *Risk C: Monitor therapy*

Mycophenolate: Proton Pump Inhibitors may decrease the serum concentration of Mycophenolate. Specifically, concentrations of the active mycophenolic acid may be reduced. *Risk C: Monitor therapy*

Nelfinavir: Proton Pump Inhibitors may decrease serum concentrations of the active metabolite(s) of Nelfinavir. Proton Pump Inhibitors may decrease the serum concentration of Nelfinavir. *Risk X: Avoid combination*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phenytoin: Proton Pump Inhibitors may increase the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Saquinavir: Proton Pump Inhibitors may increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tipranavir: May decrease the serum concentration of Proton Pump Inhibitors. These data are derived from studies with Ritonavir-boosted Tipranavir. *Risk C: Monitor therapy*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Voriconazole: Proton Pump Inhibitors may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Warfarin: Proton Pump Inhibitors may increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause gastric mucosal irritation).

Food: Food delays absorption. When given 1 hour after a meal, absorption is reduced.

Herb/Nutraceutical: St John's wort may decrease omeprazole levels.

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, immediate release:

Zegerid®: 20 mg, 40 mg [both strengths contain sodium bicarbonate 1100 mg, equivalent to sodium 300 mg (13 mEq) per capsule]

Powder for oral suspension:

Zegerid®: 20 mg/packet (30s), 40 mg/packet (30s) [both strengths contain sodium bicarbonate 1680 mg, equivalent to sodium 460 mg per packet]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Zegerid)

40-1100 mg (30): $150.84

Pack (Zegerid)

20-1680 mg (30): $157.43

40-1680 mg (30): $166.97

Mechanism of ActionSuppresses gastric basal and stimulated acid secretion by inhibiting the parietal cell H+/K+ ATP pump

Pharmacodynamics/Kinetics

Onset of action: Antisecretory: ~1 hour

Peak effect: 2 hours

Duration: 72 hours

Protein binding: 95%

Metabolism: Extensively hepatic to inactive metabolites

Bioavailability: Oral: 30% to 40%; increased in Asian patients and patients with hepatic dysfunction

Half-life elimination: 0.4-3.2 hours

Excretion: Urine (77% as metabolites, very small amount as unchanged drug); feces

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, agitation, aggression, depression, confusion, insomnia, nervousness, anxiety, or hallucinations; may rarely cause sedation

Mental Health: Effects on Psychiatric TreatmentMay inhibit the metabolism of diazepam; monitor for increased sedation

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Omeprazole

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Special Alerts

Clopidogrel (Plavix®) and Proton Pump Inhibitors (PPIs): Ongoing Safety Review - January 2009

The U.S. Food and Drug Administration (FDA) is communicating important information regarding an ongoing safety review of clopidogrel and its effectiveness when used with proton pump inhibitors (PPIs).

Clopidogrel is a prodrug requiring hepatic conversion via CYP3A4 and/or CYP2C19 to its active metabolite. Impaired clopidogrel conversion to its active metabolite may be due to either CYP450 polymorphisms or drug-drug interactions resulting in suboptimal antiplatelet activity.

A PPI is often prescribed with the combination of aspirin and clopidogrel to prevent gastrointestinal bleeding. A number of PPIs are available and include esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. Several studies have reported greater clinical event rates (eg, myocardial infarction, death) or greater platelet reactivity associated with concurrent use of clopidogrel and a PPI (Ho, 2008; Pezella, 2008; Gilard, 2006). Similarly, a prospective, randomized, double-blind trial demonstrated a reduction in antiplatelet activity when omeprazole and clopidogrel are used concurrently (Gilard, 2008). Another controlled trial with the PPI lansoprazole also found evidence of a possible interaction resulting in less antiplatelet activity (Small, 2008). This interaction is thought to result from competitive inhibition of the CYP2C19-mediated activation of clopidogrel by omeprazole and other PPIs, which are all metabolized to at least some degree by CYP2C19. In contrast, one study with esomeprazole and pantoprazole did not find evidence of reduced antiplatelet activity when administered with clopidogrel (Siller-Matula, 2009), highlighting the need for additional studies to determine the degree to which individual PPIs may differ in their potential for interacting with clopidogrel.

The manufacturer of Plavix® has agreed to conduct further studies to better understand the effect of other drugs (including PPIs) and genetic factors on the effectiveness of clopidogrel. The FDA is recommending that healthcare providers continue to prescribe clopidogrel while reevaluating the need for prescription or over-the-counter (OTC) PPIs in patients taking clopidogrel. Patients should continue taking clopidogrel as directed. If taking a PPI with clopidogrel, patients should consult with their healthcare provider.

For more information, healthcare professionals may refer to the following FDA website:
http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm

References:

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Medication Safety Issues

Sound-alike/look-alike issues:

Prilosec® may be confused with Plendil®, Prevacid®, predniSONE, prilocaine, Prinivil®, Proventil®, Prozac®

International issues:

Norpramin®: Brand name for desipramine in the U.S.

Pronunciation(oh MEP ra zole)

U.S. Brand NamesPrilosec OTC™ [OTC]; Prilosec®

Canadian Brand NamesApo-Omeprazole®; Losec MUPS®; Losec®; PMS-Omeprazole DR; ratio-Omeprazole; Sandoz Omeprazole

Pharmacologic CategoryProton Pump Inhibitor; Substituted Benzimidazole

Use: Labeled IndicationsShort-term (4-8 weeks) treatment of active duodenal ulcer disease or active benign gastric ulcer; treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD); short-term (4-8 weeks) treatment of endoscopically-diagnosed erosive esophagitis; maintenance healing of erosive esophagitis; long-term treatment of pathological hypersecretory conditions; as part of a multidrug regimen for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence

OTC labeling: Short-term treatment of frequent, uncomplicated heartburn occurring ≥2 days/week

Use: Unlabeled/InvestigationalHealing NSAID-induced ulcers; prevention of NSAID-induced ulcer; stress-ulcer prophylaxis in the critically-ill

Dosing: Adults

Active duodenal ulcer: Oral: 20 mg/day for 4-8 weeks

Gastric ulcers: Oral: 40 mg/day for 4-8 weeks

Symptomatic GERD (without esophageal lesions): Oral: 20 mg/day for up to 4 weeks

Erosive esophagitis: Oral: 20 mg/day for 4-8 weeks; maintenance of healing: 20 mg/day for up to 12 months total therapy (including treatment period of 4-8 weeks)

Peptic ulcer disease:*Helicobacter pylori* eradication: Oral: Dose varies with regimen: 40 mg/day as single dose or in 2 divided doses; requires combination therapy with antibiotics for 10-14 days; may require an additional 14-18 days of Prilosec® 20 mg/day (monotherapy) after combination treatment complete if ulcer is present

Pathological hypersecretory conditions: Oral: Initial: 60 mg once daily; doses up to 120 mg 3 times/day have been administered; administer daily doses >80 mg in divided doses

Stress-ulcer prophylaxis (ICU patients; unlabeled use): Oral: 40 mg once daily; periodically evaluate patient for continued need.

Frequent heartburn (OTC labeling): Oral: 20 mg/day for 14 days; treatment may be repeated after 4 months if needed

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

GERD or other acid-related disorders: Oral: Children 1-16 years:

5 kg to <10 kg: 5 mg once daily

10 kg to <20 kg: 10 mg once daily

≥20 kg: 20 mg once daily

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentBioavailability is increased with chronic liver disease. Consider dosage adjustment for maintenance of erosive esophagitis ulcer healing. Specific guidelines are not available.

Administration: OralBest if taken before breakfast.

Capsule: Should be swallowed whole; do not chew or crush. Delayed release capsule may be opened and contents added to 1 tablespoon of applesauce (use immediately after adding to applesauce). Administration via NG tube should be in an acidic juice.

Tablet: Should be swallowed whole; do not crush or chew.

Dietary ConsiderationsShould be taken on an empty stomach; best if taken before breakfast.

StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light and moisture.

Extemporaneously PreparedA 2 mg/mL oral omeprazole solution (Simplified Omeprazole Solution) can be prepared with five omeprazole 20 mg delayed release capsules and 50 mL 8.4% sodium bicarbonate. Empty capsules into beaker. Add sodium bicarbonate solution. Gently stir (about 15 minutes) until a white suspension is formed. Transfer to amber-colored syringe or bottle. Stable for 14 days at room temperature or for 30 days under refrigeration.

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Sharma V, “Comparison of 24-hour Intragastric pH Using Four Liquid Formulations of Lansoprazole and Omeprazole,” *Am J Health Syst Pharm*, 1999, 56(Suppl 4):S18-21.

Extemporaneous preparation for NG administration (Prilosec®): The manufacturer recommends the use of an acidic juice for preparation to administer via nasogastric (NG) tube. Alternative methods have been described as follows. NG tube administration for the prevention of stress-related mucosal damage in ventilated, critically-ill patients. The manufacturer makes no judgment regarding the safety or efficacy of these practices.

The contents of one or two 20 mg omeprazole delayed release capsules were poured into a syringe; 10-20 mL of an 8.4% sodium bicarbonate solution was withdrawn in the syringe; 30 minutes were allowed for the enteric-coated omeprazole granules to break down. The resulting milky substance was shaken prior to administration. The NG tube was then flushed with 5-10 mL of water and then clamped for at least 1 hour. Patients received omeprazole 40 mg once, then 40 mg 6-8 hours later, then 20 mg once daily using this technique.

Another study used a different technique. The omeprazole delayed release capsule (20 mg or 40 mg) was opened; then the intact granules were poured into a container holding 30 mL of water. With the plunger removed, $^1/_3$ to $^1/_2$ of the granules were then poured into a 30 mL syringe which was attached to a nasogastric tube (NG). The plunger was replaced with 1 cm of air between the granules and the plunger top while the plunger was depressed. This process was repeated until all the granules were flushed, then a final 15 mL of water was flushed through the tube. Patients who received omeprazole 40 mg in this manner had a more predictable increase in intragastric pH than patients who received omeprazole 20 mg.

ContraindicationsHypersensitivity to omeprazole, substituted benzimidazoles (ie, esomeprazole, lansoprazole, pantoprazole, rabeprazole), or any component of the formulation

Allergy Considerations

- Proton Pump Inhibitor, Benzimidazole Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Atrophic gastritis: Long-term omeprazole therapy has caused atrophic gastritis (by biopsy).
- Carcinoma: In long-term (2-year) studies in rats, omeprazole produced a dose-related increase in gastric carcinoid tumors. While available endoscopic evaluations and histologic examinations of biopsy specimens from human stomachs have not detected a risk from short-term exposure to omeprazole, further human data on the effect of sustained hypochlorhydria and hypergastrinemia are needed to rule out the possibility of an increased risk for the development of tumors in humans receiving long-term therapy.

Disease-related concerns:

- Gastric malignancy: Relief of symptoms does not preclude the presence of a gastric malignancy.
- Gastrointestinal infection (eg, *Salmonella, Campylobacter*): Use of proton pump inhibitors may increase risk of these infections.
- Hepatic impairment: Bioavailability may be increased in patients with hepatic dysfunction; consider dosage reductions.

Special populations:

- Asian ethnicity: Bioavailability may be increased in patients of Asian descent; consider dosage reductions.
- Elderly: Bioavailability may be increased in the elderly.
- Pediatrics: Safety and efficacy have not been established in children <1 year of age. OTC use is not approved for children <18 years of age.

Other warnings/precautions:

- Self-medication (OTC use): When used for self-medication (OTC), do not use for >14 days; treatment should not be repeated more often than every 4 months.

Geriatric ConsiderationsIn clinical trials, the incidence of side effects in the elderly is no different than that of younger adults (≤65 years) despite slight decrease in elimination and increase in bioavailability. Bioavailability may be increased in the elderly (≥65 years of age), however, dosage adjustments are not necessary.

Pregnancy Risk FactorC

Pregnancy ConsiderationsCrosses the placenta; congenital abnormalities have been reported sporadically following omeprazole use during pregnancy. Based on data collected by the Teratogen Information System (TERIS), it was concluded that therapeutic doses used during pregnancy would be unlikely to pose a substantial teratogenic risk (quantity/quality of data: fair). Because the possibility of harm still exists, the manufacturer recommends use during pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus.

LactationEnters breast milk/not recommended

Adverse Reactions

1% to 10%:

Central nervous system: Headache (3% to 7%), dizziness (2%)

Dermatologic: Rash (2%)

Gastrointestinal: Diarrhea (3% to 4%), abdominal pain (2% to 5%), nausea (2% to 4%), vomiting (2% to 3%), flatulence (≤3%), acid regurgitation (2%), constipation (1% to 2%), taste perversion

Neuromuscular & skeletal: Back pain (1%), weakness (1%)

Respiratory: Upper respiratory infection (2%), cough (1%)

1%, postmarketing, and/or case reports (adverse event occurrence may vary based on formulation): Abdominal swelling, abnormal dreams, aggression, agitation, agranulocytosis, alkaline phosphatase increased, allergic reactions, alopecia, ALT increased, AST increased, anaphylaxis, anemia, angina, angioedema, anorexia, anxiety, apathy, atrophic gastritis, benign gastric polyps, bilirubin increased, blurred vision, bradycardia, bronchospasm, chest pain, cholestatic hepatitis, confusion, creatinine increased, depression, diaphoresis, double vision, dry skin, epistaxis, erythema multiforme, esophageal candidiasis, fatigue, fecal discoloration, fever, gastroduodenal carcinoids, GGT increased, glycosuria, gynecomastia, hallucinations, hematuria, hemifacial dysesthesia, hemolytic anemia, hepatic encephalopathy, hepatic failure, hepatic necrosis, hepatitis, hepatocellular hepatitis, hyperhidrosis, hypersensitivity, hypertension, hypoglycemia, hyponatremia, insomnia, interstitial nephritis, irritable colon, jaundice, joint pain, leg pain, leukocytosis, leukopenia, liver disease (hepatocellular, cholestatic, mixed), malaise, microscopic pyuria, mucosal atrophy (tongue), muscle cramps, muscle weakness, myalgia, nervousness, neutropenia, ocular irritation, optic atrophy, optic neuritis, optic neuropathy (anterior ischemic), pain, palpitation, pancreatitis, pancytopenia, paresthesia, peripheral edema, petechiae, pharyngeal pain, photosensitivity, pneumothorax, proteinuria, pruritus, psychic disturbance, purpura, skin inflammation, sleep disturbance, somnolence, Stevens-Johnson syndrome, stomatitis, tachycardia, testicular pain, thrombocytopenia, tinnitus, toxic epidermal necrolysis, tremor, urinary frequency, urinary tract infection, urticaria, vertigo, weight gain, xerophthalmia, xerostomia

Metabolism/Transport Effects **Substrate** of CYP2A6 (minor), 2C9 (minor), 2C19 (major), 2D6 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2C9 (moderate), 2C19 (strong), 2D6 (weak), 3A4 (weak); **Induces** CYP1A2 (weak)

Drug Interactions

Atazanavir: Proton Pump Inhibitors may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Proton Pump Inhibitors may increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cilostazol: Omeprazole may enhance the adverse/toxic effect of Cilostazol. *Risk D: Consider therapy modification*

Clopidogrel: Proton Pump Inhibitors may diminish the therapeutic effect of Clopidogrel. This appears to be due to reduced formation of the active clopidogrel metabolite. *Risk C: Monitor therapy*

Clozapine: Omeprazole may decrease the serum concentration of Clozapine. Omeprazole may increase the serum concentration of Clozapine. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

Dabigatran Etexilate: Proton Pump Inhibitors may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Proton Pump Inhibitors may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Erlotinib: Proton Pump Inhibitors may decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Fluconazole: May increase the serum concentration of Proton Pump Inhibitors. *Risk C: Monitor therapy*

Indinavir: Proton Pump Inhibitors may decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Iron Salts: Proton Pump Inhibitors may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk C: Monitor therapy*

Itraconazole: Proton Pump Inhibitors may decrease the serum concentration of Itraconazole. *Risk D: Consider therapy modification*

Ketoconazole: Proton Pump Inhibitors may decrease the serum concentration of Ketoconazole. Ketoconazole may increase the serum concentration of Proton Pump Inhibitors. *Risk D: Consider therapy modification*

Mesalamine: Proton Pump Inhibitors may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids; proton pump inhibitors would be expected to interact in a similar manner. *Risk X: Avoid combination*

Methotrexate: Proton Pump Inhibitors may decrease the excretion of Methotrexate. Antirheumatic doses of methotrexate probably hold minimal risk. *Risk C: Monitor therapy*

Mycophenolate: Proton Pump Inhibitors may decrease the serum concentration of Mycophenolate. Specifically, concentrations of the active mycophenolic acid may be reduced. *Risk C: Monitor therapy*

Nelfinavir: Proton Pump Inhibitors may decrease serum concentrations of the active metabolite(s) of Nelfinavir. Proton Pump Inhibitors may decrease the serum concentration of Nelfinavir. *Risk X: Avoid combination*

Phenytoin: Proton Pump Inhibitors may increase the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Saquinavir: Proton Pump Inhibitors may increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

Tipranavir: May decrease the serum concentration of Proton Pump Inhibitors. These data are derived from studies with Ritonavir-boosted Tipranavir. *Risk C: Monitor therapy*

Voriconazole: Proton Pump Inhibitors may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Warfarin: Proton Pump Inhibitors may increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause gastric mucosal irritation).

Food: Food delays absorption.

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions (especially those dependent on cytochrome P450 metabolism or those dependent on a acid environment for absorption). Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically throughout therapy. Assess knowledge/teach appropriate use of this medication, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake as directed, before eating. Do not crush or chew capsules. Delayed release capsule may be opened and contents added to applesauce. Avoid alcohol. You may experience anorexia; small frequent meals may help to maintain adequate nutrition. Report severe headache or unresolved severe diarrhea. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, delayed release: 10 mg, 20 mg, 40 mg

Prilosec®: 10 mg, 20 mg, 40 mg

Tablet, delayed release: 20 mg

Prilosec OTC™: 20 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsule, delayed release (Omeprazole)

10 mg (30): $32.99

20 mg (90): $63.97

40 mg (30): $169.99

Capsule, delayed release (Prilosec)

20 mg (30): $148.70

40 mg (30): $224.95

Tablet, EC (Prilosec OTC)

20 mg (14): $19.99

Mechanism of ActionProton pump inhibitor; suppresses gastric basal and stimulated acid secretion by inhibiting the parietal cell H+/K+ ATP pump

Pharmacodynamics/Kinetics

Onset of action: Antisecretory: ~1 hour

Peak effect: Within 2 hours

Duration: Up to 72 hours; 50% of maximum effect at 24 hours

Absorption: Rapid

Protein binding: ~95%

Metabolism: Extensively hepatic by cytochrome P450 system to inactive metabolites

Bioavailability: Oral: ~30% to 40%; increased in Asian patients and patients with hepatic dysfunction

Half-life elimination: Delayed release capsule: 0.5-1 hour; hepatic impairment: ~3 hours

Time to peak, plasma: 0.5-3.5 hours

Excretion: Urine (77% as metabolites, very small amount as unchanged drug); feces

Related Information

- ***Helicobacter pylori*** Treatment

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste perversion, dry mouth, esophageal candidiasis, and mucosal atrophy (tongue).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, agitation, aggression, depression, confusion, insomnia, nervousness, anxiety, or hallucinations; may rarely cause sedation

Mental Health: Effects on Psychiatric TreatmentMay inhibit the metabolism of diazepam; monitor for increased sedation

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: A 2 mg/mL oral omeprazole solution (Simplified Omeprazole Solution) can be prepared with five omeprazole 20 mg delayed release capsules and 50 mL 8.4% sodium bicarbonate. Empty capsules into beaker. Add sodium bicarbonate solution. Gently stir (about 15 minutes) until a white suspension is formed. Transfer to amber-colored syringe or bottle. Stable for 14 days at room temperature or for 30 days under refrigeration.

DiGiancinto JL, Olsen KM, Bergman KL, et al, “Stability of Suspension Formulations of Lansoprazole and Omeprazole Stored in Amber-Colored Plastic Oral Syringes,” *Ann Pharmacother*, 2000, 34:600-5.

Quercia R, Fan C, Liu X, et al, “Stability of Omeprazole in an Extemporaneously Prepared Oral Liquid,” *Am J Health Syst Pharm*, 1997, 54:1833-6.

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Evidence-Based Information: The 2008 Surviving Sepsis Campaign guidelines recommend that stress ulcer prophylaxis using an H_2 blocker (Grade 1A) or proton pump inhibitor (Grade 1B) be given to patients with severe sepsis to prevent upper GI bleed. Benefit of prevention of upper GI bleed must be weighed against potential effect of increased stomach pH on development of ventilator-associated pneumonia.

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Andersson T, Hasan-Alin M, Hasselgren G, et al, "Drug Interactions Studies With Esomeprazole, the (S)-Isomer of Omeprazole," *Clin Pharmacokinet*, 2001, 40(7):523-37.[PubMed 11510629]

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International Brand NamesAleprozil (MX); Antra (IT); Azoran (MX); Baromezole (KP); Bioprazol (PL); Crismel (HU); Desec (TH); Domer (MX); Dudencer (ID); Duogas (TH); Epirazole (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Exter (PL); Gasec (BB, BM, BS, BZ, GY, JM, MY, SR, TT); Gasec Gastrocaps (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, PL, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Gastec (AR); Gastop (PE); Gastracid (DE); Groprazol (PL); Helicid (PL); Hovizol (PH); Hyposec (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Inhibitron (MX); Inhipump (ID); Lensor (LU); Logastric (BE); Lomac (IN); Losec (AE, AR, AT, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CI, CL, CN, CY, CZ, DK, EE, EG, ES, ET, FI, GB, GH, GM, GN, GR, GY, HK, HN, HU, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, NZ, OM, PH, PK, PL, PT, PY, QA, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Losec MUPS (CO, PH); Losec Mups (PL); Madiprazole (TH); Medoprazole (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Meiceral (TH); Mepha Gasec (CR, GT, HN, NI, PA, SV); Mepracid (PH); Meprazol (AU); Mepzol (KP); Miracid (TH); Mopral (FR, MX); Nocid (TH); Notis (PL); Ocid (IN, SG); Ogal (CO); Olexin (MX); Olit (SG); Omar (PL); Omed (BF, BJ, CH, CI, ET, GH, GM, GN, IN, KE, KP, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Omedar (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Omelon (MY); Omenole (PH); OMEP (DE); Omep (PL); Omepra (IL); Omepradex (IL); Omepradex-Z (IL); Omepral (AU, JP); Omeprazol (PL); Omeprazol-Egis (PL); Omeprazon (JP); Omepril (EC); Omeq (KP); Omesec (MY, SG); Omez (TH); Omezol (AE, BH, CY, EG, IL, IN, IQ, IR, JO, KW, LB, LY, NZ, OM, QA, SA, SY, YE); Omezole (SG, TW); Omezzol (EC); Omisec (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Omizac (IN); OMP (KP); Omprazole (KP); OMZ (ID); Onic (ID); Opal (PE);

Oprax (PE); Ortanol (HR, PL); Parizac (ES); Penrazole (SG); Peptizole (TH); Polprazol (PL); Prazidec (MX); Prazol (PL); Probitor (AU, PL); Proceptin (SG); Prohibit (ID); Pumpitor (ID); Ramezol (KP); Result (KP); Risek (PH); Severon (TH); Siozole (IN); Stomacer (ID); Stomec (TH); Suifac (MX); Ulcozol (BR, PE); Ulcuprazol (CR, DO, GT, HN, NI, PA, SV); Ulnor (DE); Ulsek (PH); Ulsen (MX); Ultop (HR); Ulzec (ZA); Ulzol (ID, PL); Vulcasid (MX); Wonmp (KP); Xoprin (PE); Zatrol (CN); Zefxon (TH); Zenpro (SG); Zimor (MY, SG)

Ondansetron

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Medication Safety Issues

Sound-alike/look-alike issues:

Ondansetron may be confused with dolasetron, granisetron, palonosetron

Zofran® may be confused with Zantac®, Zosyn®

Pronunciation(on DAN se tron)

U.S. Brand NamesZofran®; Zofran® ODT

Canadian Brand NamesApo-Ondansetron®; DOM-Ondansetron; Gen-Ondansetron; JAMP-Ondansetron; MINT-Ondansetron; Novo-Ondansetron; Ondansetron Injection; Ondansetron-Omega; PHL-Ondansetron; PMS-Ondansetron; RAN-Ondansetron; RATIO-Ondansetron; Sandoz-Ondansetron; Zofran®; Zofran® ODT

Pharmacologic CategoryAntiemetic; Selective 5-HT$_3$ Receptor Antagonist

Use: Labeled IndicationsPrevention of nausea and vomiting associated with moderately- to highly-emetogenic cancer chemotherapy; radiotherapy in patients receiving total body irradiation or fractions to the abdomen; prevention of postoperative nausea and vomiting (PONV); treatment of PONV if no prophylactic dose received

Use: Unlabeled/InvestigationalTreatment of early-onset alcoholism; hyperemesis gravidarum

Dosing: Adults **Note:** Studies in adults have shown a single daily dose of 8-12 mg I.V. or 8-24 mg orally to be as effective as mg/kg dosing, and should be considered for **all** patients whose mg/kg dose exceeds 8-12 mg I.V.; oral solution and ODT formulations are bioequivalent to corresponding doses of tablet formulation.

Prevention of chemotherapy-induced emesis:

I.V.:

0.15 mg/kg 3 times/day beginning 30 minutes prior to chemotherapy **or**

0.45 mg/kg once daily **or**

8-10 mg 1-2 times/day **or**

24 mg or 32 mg once daily

Highly-emetogenic agents/single-day therapy: Oral: 24 mg given 30 minutes prior to the start of therapy

Moderately-emetogenic agents: Oral: 8 mg every 12 hours beginning 30 minutes before chemotherapy, continuously for 1-2 days after chemotherapy completed

Total body irradiation: Oral: 8 mg 1-2 hours before each daily fraction of radiotherapy

Single high-dose fraction radiotherapy to abdomen: Oral: 8 mg 1-2 hours before irradiation, then 8 mg every 8 hours after first dose for 1-2 days after completion of radiotherapy

Daily fractionated radiotherapy to abdomen: 8 mg 1-2 hours before irradiation, then 8 mg 8 hours after first dose for each day of radiotherapy

Postoperative nausea and vomiting (PONV):

Oral: 16 mg given one hour prior to induction of anesthesia

I.M., I.V.: 4 mg as a single dose immediately before induction of anesthesia, or shortly following procedure if vomiting occurs

Note: Repeat doses given in response to inadequate control of nausea/vomiting from preoperative doses are generally ineffective.

Treatment of hyperemesis gravidum (unlabeled use):

Oral: 8 mg every 12 hours

I.V.: 8 mg administered over 15 minutes every 12 hours or 1 mg/hour infused continuously for up to 24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric **Note:** Studies in adults have shown a single daily dose of 8-12 mg I.V. or 8-24 mg orally to be as effective as mg/kg dosing, and should be considered for **all** patients whose mg/kg dose exceeds 8-12 mg I.V.; oral solution and ODT formulations are bioequivalent to corresponding doses of tablet formulation.

Prevention of chemotherapy-induced emesis:

I.V.: Children 6 months to 18 years: 0.15 mg/kg/dose administered 30 minutes prior to chemotherapy, 4 and 8 hours after the first dose **or** 0.45 mg/kg/day as a single dose

Oral:

4-11 years: 4 mg 30 minutes before chemotherapy; repeat 4 and 8 hours after initial dose, then 4 mg every 8 hours for 1-2 days after chemotherapy completed

≥12 years: Refer to adult dosing.

Prevention of postoperative nausea and vomiting (PONV): I.V.: Children 1 month to 12 years:

≤40 kg: 0.1 mg/kg as a single dose

>40 kg: 4 mg as a single dose

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentSevere liver disease (Child-Pugh C): Maximum daily dose: 8 mg

Administration: I.M.Should be given undiluted.

Administration: I.V.

IVPB: Dilute in 50 mL D_5W or NS. Infuse over 15-30 minutes; 24-hour continuous infusions have been reported, but are rarely used.

Chemotherapy-induced nausea and vomiting: Give first dose 30 minutes prior to beginning chemotherapy.

I.V. push: Prevention of postoperative nausea and vomiting: Single doses may be administered I.V. injection over 2-5 minutes as undiluted solution.

Administration: I.V. DetailpH: 3-4

Administration: OralOral dosage forms should be given 30 minutes prior to chemotherapy; 1-2 hours before radiotherapy; 1 hour prior to the induction of anesthesia.

Orally-disintegrating tablets: Do not remove from blister until needed. Peel backing off the blister, do not push tablet through. Using dry hands, place tablet on tongue and allow to dissolve. Swallow with saliva.

The I.V. preparation has been successful when administered orally.

Dietary ConsiderationsTake without regard to meals.

Orally-disintegrating tablet contains <0.03 mg phenylalanine

Storage

Oral solution: Store between 15°C and 30°C (59°F and 86°F). Protect from light.

Premixed bag: Store between 2°C and 30°C (36°F and 86°F). Protect from light.

Tablet: Store between 2°C and 30°C (36°F and 86°F).

Vial: Store between 2°C and 30°C (36°F and 86°F). Protect from light. Stable when mixed in D_5W or NS for 48 hours at room temperature.

ReconstitutionPrior to I.V. infusion, dilute in 50 mL D_5W or NS.

CompatibilityStable in $D_5{}^1/_2$NS, D_5NS, D_5W, mannitol 10%, LR, NS, sodium chloride 3%; do not mix injection with alkaline solutions.

Y-site administration: Compatible: Alatrofloxacin, aldesleukin, amifostine, amikacin, aztreonam, bleomycin, carboplatin, carmustine, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftizoxime, cefuroxime, chlorpromazine, cimetidine, cisatracurium, cisplatin, cladribine, clindamycin, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, dexamethasone sodium phosphate, diphenhydramine, docetaxel, dopamine, doxorubicin, doxorubicin liposome, doxycycline, droperidol, etoposide, etoposide phosphate, famotidine, filgrastim, floxuridine, fluconazole, fludarabine, gatifloxacin, gemcitabine, gentamicin, haloperidol, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, ifosfamide, imipenem/cilastatin, linezolid, magnesium sulfate, mannitol, mechlorethamine, melphalan, meperidine, mesna, methotrexate, metoclopramide, mitomycin, mitoxantrone, morphine, paclitaxel, paclitaxel with ranitidine, pentostatin, piperacillin/tazobactam, potassium chloride, prochlorperazine edisylate, promethazine, ranitidine, remifentanil, sodium acetate, streptozocin, teniposide, thiotepa, ticarcillin, ticarcillin/clavulanate, topotecan, vancomycin, vinblastine, vincristine, vinorelbine, zidovudine. **Incompatible:** Acyclovir, allopurinol, aminophylline, amphotericin B, amphotericin B cholesteryl sulfate complex, ampicillin, ampicillin/sulbactam, amsacrine, cefepime, cefoperazone, furosemide, ganciclovir, lorazepam, methylprednisolone sodium succinate, piperacillin, sargramostim, sodium bicarbonate. **Variable (consult detailed reference):** Fluorouracil, meropenem.

Extemporaneously PreparedA 0.8 mg/mL syrup may be made by crushing ten 8 mg tablets; flaking of the tablet coating occurs. Mix thoroughly with 50 mL of the suspending vehicle, Ora-Plus® (Paddock), in 5 mL increments. Add sufficient volume of any of the following syrups: Cherry syrup USP, Syrpalta® (Humco), Ora-Sweet® (Paddock), or Ora-Sweet® Sugar-Free (Paddock) to make a final volume of 100 mL. Stability is 42 days refrigerated.

Trissel LA, “Trissel's Stability of Compounded Formulations,” American Pharmaceutical Association, 1996.

Rectal suppositories: Calibrate a suppository mold for the base being used. Determine the displacement factor (DF) for ondansetron for the base being used (Fattibase® = 1.1; Polybase® = 0.6). Weigh the ondansetron tablet. Divide the tablet weight by the DF. Subtract the weight of base displaced from the calculated weight of base required for each suppository. Grind the ondansetron tablets to a fine powder in a mortar. Weigh out the appropriate weight of suppository base. Melt the base over a water bath (<55°C). Add the ondansetron powder to the suppository base and mix well. Pour the mixture into the suppository mold and cool. Stable for at least 30 days under refrigeration.

Allen LV, “Ondansetron Suppositories,” *US Pharm*, 20(7):84-6.

ContraindicationsHypersensitivity to ondansetron, other selective 5-HT$_3$ antagonists, or any component of the formulation

Allergy Considerations

- Serotonin 5-HT$_3$ Antagonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Allergic reactions: Use with caution in patients allergic to other 5-HT$_3$ receptor antagonists; cross-reactivity has been reported.
- ECG effects: Selective 5-HT$_3$ antagonists, including ondansetron, have been associated with a number of dose-dependent increases in ECG intervals (eg, PR, QRS duration, QT/QT$_c$, JT), usually occurring 1-2 hours after I.V. administration. In general, these changes are not clinically relevant, however, when used in conjunction with other agents that prolong these intervals, arrhythmia may occur. When used with agents that prolong the QT interval (eg, Class I and III antiarrhythmics), clinically relevant QT interval prolongation may occur resulting in torsade de pointes. A number of trials have shown that 5-HT$_3$ antagonists produce QT interval prolongation to variable degrees. Use with caution in patients at risk of QT prolongation and/or ventricular arrhythmia. Reduction in heart rate may also occur with the 5-HT$_3$ antagonists. I.V. formulations of 5-HT$_3$ antagonists have more association with ECG interval changes, compared to oral formulations.

Disease-related concerns:

- Long QT syndrome: Use with caution in patients with congenital long QT syndrome or other risk factors for QT prolongation (eg, medications known to prolong QT interval, electrolyte abnormalities [hypokalemia or hypomagnesemia], and cumulative high-dose anthracycline therapy).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <1 month of age.

Dosage form specific issues:

- Phenylalanine: Orally-disintegrating tablets contain phenylalanine.

Other warnings/precautions:

- Chemotherapy-related emesis: **For chemotherapy, should be used on a scheduled basis, not on an "as needed" (PRN) basis,** since data support the use of this drug only in the prevention of nausea and vomiting (due to antineoplastic therapy) and not in the rescue of nausea and vomiting. Should only be used in the first 24-48 hours of chemotherapy. Data does not support any increased efficacy in delayed nausea and vomiting.
- Ileus or gastric distention: Does not stimulate gastric or intestinal peristalsis; may mask progressive ileus and/or gastric distension.

Geriatric ConsiderationsElderly have a slightly decreased hepatic clearance rate. This does not, however, require a dose adjustment.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; however, there are no adequate and well-controlled studies in pregnant women. Use of ondansetron for the treatment of nausea and vomiting of pregnancy (NVP) has been evaluated. Additional studies are needed to determine safety to the fetus, particularly during the first trimester. Based on preliminary data, use is generally reserved for severe NVP (hyperemesis gravidarum) or when conventional treatments are not effective.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**Note:** Percentages reported in adult patients.

>10%:

Central nervous system: Headache (9% to 27%), malaise/fatigue (9% to 13%)

Gastrointestinal: Constipation (6% to 11%)

1% to 10%:

Central nervous system: Drowsiness (8%), fever (2% to 8%), dizziness (4% to 7%), anxiety (6%), cold sensation (2%)

Dermatologic: Pruritus (2% to 5%), rash (1%)

Gastrointestinal: Diarrhea (2% to 7%)

Genitourinary: Gynecological disorder (7%), urinary retention (5%)

Hepatic: ALT increased (1% to 5%), AST increased (1% to 5%)

Local: Injection site reaction (4%; pain, redness, burning)

Neuromuscular & skeletal: Paresthesia (2%)

Respiratory: Hypoxia (9%)

<1%: Anaphylaxis, angina, bronchospasm, ECG changes, extrapyramidal symptoms, grand mal seizure, hypokalemia, tachycardia, vascular occlusive events

Postmarketing and/or case reports: Anaphylactoid reactions, angioedema, arrhythmia, blindness (transient/following infusion; lasting ≤48 hours), blurred vision (transient/following infusion), bradycardia, cardiopulmonary arrest, dyspnea, dystonic reaction, electrocardiographic alterations (second-degree heart block and ST-segment depression), flushing, hiccups, hypersensitivity reaction, hypotension, laryngeal edema, laryngospasm, oculogyric crisis, palpitation, premature ventricular contractions (PVC), QT interval increased, shock, stridor, supraventricular tachycardia, syncope, urticaria, ventricular arrhythmia

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2C9 (minor), 2D6 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2D6 (weak)

Drug Interactions

Apomorphine: Antiemetics (5HT3 Antagonists) may enhance the hypotensive effect of Apomorphine. *Risk X: Avoid combination*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Antiemetics (5HT3 Antagonists). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Food increases the extent of absorption. The C_{max} and T_{max} do not change much.

Herb/Nutraceutical: St John's wort may decrease ondansetron levels.

Monitoring ParametersClosely monitor patients <4 months of age

Nursing: Physical Assessment/MonitoringAssess allergy history (selective 5-HT_3 receptor antagonists) prior to administering. Use with caution in presence of, or potential for, cardiac conduction abnormalities (eg, QT prolongation, medication known to prolong QT interval, electrolyte abnormalities). Follow specific administration specifics according to formulation. **Note:** Oral and I.V. doses have different schedules and should not be administered on "PRN" basis. Assess therapeutic effectiveness and adverse reactions on a regular basis. Teach patient possible side effects and adverse symptoms to report.

Patient EducationThis drug is given to reduce the incidence of nausea and vomiting. Do not take any other medication for nausea and vomiting with this medication unless approved by prescriber. If this medication is given by intravenous infusion you will be monitored during infusion. Report immediately any chest pain, respiratory difficulty, pain or itching at infusion site. Self-administered oral doses must be taken exactly as directed. If self-administered, take as directed. May cause headache, drowsiness, or dizziness (request assistance when getting up or changing position and do not perform activities requiring alertness [including driving] until response to drug is known). Report chest pain or palpitations; persistent headache; excessive drowsiness; fever; or changes in elimination patterns (constipation or diarrhea) or other adverse effects. **Breast-feeding precaution:** Consult prescriber if you are or intend to breast-feed.

Orally-disintegrating tablets: Do not remove from blister until needed. Peel backing off the blister, do not push tablet through. Using dry hands, place tablet on tongue and allow to dissolve. Swallow with saliva.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Infusion, premixed in D_5 [preservative free]: 32 mg (50 mL)

Zofran®: 32 mg (50 mL) [DSC]

Injection, solution: 2 mg/mL (2 mL, 20 mL)

Zofran®: 2 mg/mL (2 mL, 20 mL)

Injection, solution [preservative free]: 2 mg/mL (2 mL)

Solution, oral: 4 mg/5 mL (50 mL)

Zofran®: 4 mg/5 mL (50 mL) [contains sodium benzoate; strawberry flavor]

Tablet: 4 mg; 8 mg

Zofran®: 4 mg; 8 mg

Tablet, orally disintegrating: 4 mg; 8 mg

Zofran® ODT: 4 mg, 8 mg [each strength contains phenylalanine <0.03 mg/tablet; strawberry flavor]

Generic AvailableYes

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Tablet, orally-disintegrating (Ondansetron)

4 mg (30): $549.00

Tablet, orally-disintegrating (Zofran ODT)

4 mg (30): $659.95

Tablets (Ondansetron HCl)

4 mg (30): $569.96

8 mg (30): $1048.95

Tablets (Zofran)

4 mg (10): $244.63

8 mg (30): $1169.97

24 mg (10): $1008.41

Mechanism of ActionSelective 5-HT$_3$-receptor antagonist, blocking serotonin, both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone

Pharmacodynamics/Kinetics

Onset of action: ~30 minutes

Distribution: V$_d$: Children: 1.7-3.7 L/kg; Adults: 2.2-2.5 L/kg

Protein binding, plasma: 70% to 76%

Metabolism: Extensively hepatic via hydroxylation, followed by glucuronide or sulfate conjugation; CYP1A2, CYP2D6, and CYP3A4 substrate; some demethylation occurs

Bioavailability: Oral: 56% to 71%; Rectal: 58% to 74%

Half-life elimination: Children <15 years: 2-7 hours; Adults: 3-6 hours

Mild-to-moderate hepatic impairment: Adults: 12 hours

Severe hepatic impairment (Child-Pugh C): Adults: 20 hours

Time to peak: Oral: ~2 hours

Excretion: Urine (44% to 60% as metabolites, 5% to 10% as unchanged drug); feces (~25%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may increase the metabolism of ondansetron; monitor for diminished effects

Index TermsGR38032R; Ondansetron Hydrochloride

References

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Kris MG, Hesketh PJ, Somerfield MR, et al, “American Society of Clinical Oncology Guideline for Antiemetics in Oncology: Update 2006,” *J Clin Oncol*, 2006, 24(18):2932-47. [PubMed 16717289]

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Navari RM and Koeller JM, “Electrocardiographic and Cardiovascular Effects of the 5-Hydroxytryptamine$_3$ Receptor Antagonists,” *Ann Pharmacother*, 2003, 37(9):1276-86.[PubMed 12921512]

Roila F and Del Favero A, “Ondansetron Clinical Pharmacokinetics,” *Clin Pharmacokinet*, 1995, 29(2):95-109. [PubMed 7586904]

Siu SS, Yip SK, Cheung CW, et al, “Treatment of Intractable Hyperemesis Gravidarum by Ondansetron,” *Eur J Obstet Gynecol Reprod Biol*, 2002, 105(1):73-4.[PubMed 12270570]

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Wilde MI and Markham A, “Ondansetron. A Review of Its Pharmacology and Preliminary Clinical Findings in Novel Application,” *Drugs*, 1996, 52(5):773-94.[PubMed 9118822]

International Brand NamesAtossa (PL); Avessa (LU); Cedantron (ID); Cetron (AR); Danac (MX); Dantron (TH, ZA); Danzetron (AU); Emeset (IN, TH); Emetron (HU, PL); Emodan (PH); Frazon (ID); Invomit (ID); Izofran (CN, UY); Lartron (MX); Narfoz (ID); Nausedron (BR); Ondak (CO); Ondant (KP); Ondavell (ID); Ondaz (AU); Onetic (ID); Onsia (TH); Onzod (TW); Osetron (MY); Setronon (PL); Vomceran (ID); Vometron (ID); Vomiof (IN); Vomiz (TW); Zetron (TH); Zofran (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CO, CY, CZ, DE, DK, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PH, PK, PL, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Zofran Zydis (CR, DO, GT, HN, KP, NI, NZ, PA, SV, TH); Zofron (GR); Zophren (FR)

OPA

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, Hodgkin's Disease

Regimen UseLymphoma, Hodgkin's disease

Regimen

Vincristine: I.V.: 1.5 mg/m^2/day (maximum 2 mg) days 1, 8, and 15

[total dose/cycle = 4.5 mg/m^2]

Prednisone: Oral: 60 mg/m^2/day days 1 to 15 in 3 divided doses

[total dose/cycle = 900 mg/m^2]

Doxorubicin: I.V.: 40 mg/m^2/day days 1 and 15

[total dose/cycle = 80 mg/m^2]

Second cycle may be given based on individual response; time between cycles not specified

References

Schellong G, Riepenhausen M, Creutzig U, et al, âLow Risk of Secondary Leukemias After Chemotherapy Without Mechlorethamine in Childhood Hodgkin's Disease. German-Austrian Pediatric Hodgkin's Disease Group,â *J Clin Oncol*, 1997, 15(6):2247-53.[PubMed 9196137]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Neuroblastoma

Regimen UseNeuroblastoma

Regimen

Vincristine: I.V.: 1.5 mg/m^2 day 1

[total dose/cycle = 1.5 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Doxorubicin: I.V.: 40 mg/m^2 day 1

[total dose/cycle = 40 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 2

[total dose/cycle = 100 mg/m^2]

Teniposide: I.V.: 150 mg/m^2 day 4

[total dose/cycle = 150 mg/m^2]

Repeat cycle every 21 days

References

Shafford EA, Rogers DW, Pritchard J, et al, âAdvanced Neuroblastoma: Improved Response Rate Using a Multiagent Regimen (OPEC) Including Sequential Cisplatin and VM-26,â *J Clin Oncol*, 1984, 2(7):742-7.[PubMed 6539811]

OPEC

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Neuroblastoma

Regimen UseNeuroblastoma

Regimen

Vincristine: I.V.: 1.5 mg/m^2 day 1

[total dose/cycle = 1.5 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 2

[total dose/cycle = 100 mg/m^2]

Teniposide: I.V.: 150 mg/m^2 day 4

[total dose/cycle = 150 mg/m^2]

Repeat cycle every 21 days

References

Shafford EA, Rogers DW, Pritchard J, et al, âAdvanced Neuroblastoma: Improved Response Rate Using a Multiagent Regimen (OPEC) Including Sequential Cisplatin and VM-26,â *J Clin Oncol*, 1984, 2(7):742-7.[PubMed 6539811]

Opium Tincture

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Opium tincture may be confused with camphorated tincture of opium (paregoric)

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Use care when prescribing opium tincture; each mL contains the equivalent of morphine 10 mg; paregoric contains the equivalent of morphine 0.4 mg/mL

DTO is an error-prone abbreviation (mistaken as Diluted Tincture of Opium; dose equivalency of paregoric)

Pronunciation(OH pee um TING chur)

Pharmacologic Category[Analgesic, Opioid](); [Antidiarrheal]()

Use: Labeled IndicationsTreatment of diarrhea or relief of pain

Dosing: Adults**Note:** Opium tincture 10% contains morphine 10 mg/mL. Use caution in ordering, dispensing, and/or administering.

Diarrhea: Oral: 0.3-1 mL/dose every 2-6 hours to maximum of 6 mL/24 hours

Analgesia: Oral: 0.6-1.5 mL/dose every 3-4 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Opium tincture 10% contains morphine 10 mg/mL. Use caution in ordering, dispensing, and/or administering.

Diarrhea: Oral: Children: 0.005-0.01 mL/kg/dose every 3-4 hours for a maximum of 6 doses/24 hours

Analgesia: Oral: Children: 0.01-0.02 mL/kg/dose every 3-4 hours

StorageProtect from light.

RestrictionsC-II

ContraindicationsHypersensitivity to morphine sulfate or any component of the formulation; increased intracranial pressure; severe respiratory depression; severe hepatic or renal insufficiency; pregnancy (prolonged use or high dosages near term)

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or with drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with severe hepatic dysfunction.

- Obesity: Use with caution in patients who are morbidly obese.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorders which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Infants <3 months of age are more susceptible to respiratory depression; use with caution and generally in reduced doses in this age group.

Dosage form specific issues:

- Sulfites: Some preparations contain sulfites which may cause allergic reactions.

Other warnings/precautions:

- Not paregoric: This is **not** paregoric, dose accordingly.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Pregnancy Risk FactorB/D (prolonged use or high doses at term)
LactationEnters breast milk/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation, hypotension, bradycardia, peripheral vasodilation

Central nervous system: Drowsiness, dizziness, restlessness, headache, malaise, CNS depression, intracranial pressure increased, insomnia, mental depression

Gastrointestinal: Nausea, vomiting, constipation, anorexia, stomach cramps, biliary tract spasm

Genitourinary: Urination decreased, urinary tract spasm

Neuromuscular & skeletal: Weakness

Ocular: Miosis

Respiratory: Respiratory depression

Miscellaneous: Histamine release, physical and psychological dependence

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Test InteractionsIncreased aminotransferase [ALT/AST] (S)

Monitoring ParametersObserve patient for excessive sedation, respiratory depression, implement safety measures, assist with ambulation

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for additive or adverse interactions. Monitor vital signs, effectiveness of pain relief, adverse reactions, and signs of overdose at beginning of therapy and at regular intervals with long-term use. May cause physical and/or psychological dependence. For inpatients, implement safety measures. Assess knowledge/teach patient appropriate use (if self-administered). Teach patient to monitor for adverse reactions, adverse reactions to report, and appropriate interventions to reduce side effects. Discontinue slowly after prolonged use.

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids). May cause hypotension, dizziness, drowsiness, impaired coordination, or blurred vision (use caution when driving, climbing stairs, or changing position - rising from sitting or lying to standing, or when engaging in tasks requiring alertness until response to drug is known); or dry mouth (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help). Report slow or rapid heartbeat, acute dizziness, or persistent headache; changes in mental status; swelling of extremities or unusual weight gain; changes in urinary elimination or pain on urination; acute headache; trembling or muscle spasms; blurred vision; skin rash; or shortness of breath. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid: 10% (120 mL, 480 mL) [0.6 mL equivalent to morphine 6 mg; contains alcohol 19%]

Generic AvailableYes

Mechanism of ActionContains many narcotic alkaloids including morphine; its mechanism for gastric motility inhibition is primarily due to this morphine content; it results in a decrease in digestive secretions, an increase in GI muscle tone, and therefore a reduction in GI propulsion

Pharmacodynamics/Kinetics

Duration: 4-5 hours

Absorption: Variable

Metabolism: Hepatic

Excretion: Urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and drowsiness are common; may cause restlessness; may rarely cause insomnia or depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may alter the analgesic effects of opioids; monitor for altered response

Index TermsDTO (error-prone abbreviation); Opium Tincture, Deodorized

References

Kraus DM and Hatzopoulos FK, “Neonatal Therapy,” *Applied Therapeutics: The Clinical Use of Drugs*, 6th ed, Young LY and Koda-Kimble MA, eds, Vancouver, WA: Applied Therapeutics, Inc, 1995.

Levy M and Spino M, “Neonatal Withdrawal Syndrome: Associated Drugs and Pharmacologic Management,” *Pharmacotherapy*, 1993, 13(3):202-11. [PubMed 8321734]

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

OPPA

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, Hodgkin's Disease
Regimen UseLymphoma, Hodgkin's disease
Regimen

Vincristine: I.V.: 1.5 mg/m^2/day (maximum 2 mg) days 1, 8, and 15

[total dose/cycle = 4.5 mg/m^2]

Prednisone: Oral: 60 mg/m^2/day days 1 to 15 in 3 divided doses

[total dose/cycle = 900 mg/m^2]

Doxorubicin: I.V.: 40 mg/m^2/day days 1 and 15

[total dose/cycle = 80 mg/m^2]

Procarbazine: Oral: 100 mg/m^2/day days 1 to 15 in 2 or 3 divided doses

[total dose/cycle = 1500 mg/m^2]

Second cycle may be given based on individual response; time between cycles not specified

References

Schellong G, Riepenhausen M, Creutzig U, et al, âLow Risk of Secondary Leukemias After Chemotherapy Without Mechlorethamine in Childhood Hodgkin's Disease. German-Austrian Pediatric Hodgkin's Disease Group,â *J Clin Oncol*, 1997, 15(6):2247-53.[PubMed 9196137]

Oprelvekin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Oprelvekin may be confused with aldesleukin, Proleukin®

Neumega® may be confused with Neulasta®, Neupogen®

Pronunciation(oh PREL ve kin)

U.S. Brand NamesNeumega®

Pharmacologic CategoryBiological Response Modulator; Human Growth Factor

Use: Labeled IndicationsPrevention of severe thrombocytopenia; reduce the need for platelet transfusions following myelosuppressive chemotherapy

Dosing: Adults

Prevention of thrombocytopenia: SubQ: 50 mcg/kg once daily for ~10-21 days (until postnadir platelet count ≥50,000 cells/µL)

Administer first dose ~6-24 hours after the end of chemotherapy. Discontinue at least 48 hours before beginning the next cycle of chemotherapy.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Prevention of thrombocytopenia (unlabeled use): SubQ: 75-100 mcg/kg once daily for 10-21 days (until postnadir platelet count ≥50,000 cells/µL). **Note:** A safe and effective dose for use in children has not been established by the manufacturer.

Administer first dose ~6-24 hours after the end of chemotherapy. Discontinue at least 48 hours before beginning the next cycle of chemotherapy.

Administration: I.V. DetailpH: 7

Administration: OtherSubcutaneously in the abdomen, thigh, hip, or upper arm.

StorageStore vials under refrigeration between 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Use reconstituted oprelvekin within 3 hours of reconstitution and store in the vial at either 2°C to 8°C (36°F to 46°F) or room temperature of ≤25°C (77°F). Do not freeze or shake reconstituted solution.

ReconstitutionReconstitute to a final concentration of 5 mg/mL with SWFI; swirl gently, do not shake.

ContraindicationsHypersensitivity to oprelvekin or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Anaphylactoid/hypersensitivity reactions: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: **[U.S. Boxed Warning]: Allergic or hypersensitivity reactions, including anaphylaxis have been reported. May occur with the first or with subsequent doses. Permanently discontinue in any patient developing an allergic reaction.**

- Cardiovascular effects: Arrhythmia, pulmonary edema, and cardiac arrest have been reported; use in patients with a history of atrial arrhythmia only if the potential benefit exceeds possible risks. Patients experiencing arrhythmia may be at risk for stroke; use caution in patients with a history of transient ischemic attack or stroke. Ventricular arrhythmia has also been reported, occurring within 2-7 days of treatment initiation; use with caution in patients with conduction defects.

- Fluid retention: May cause serious fluid retention; use cautiously in patients with conditions where expansion of plasma volume should be avoided (eg, left ventricular dysfunction, HF, hypertension).

- Papilledema: Dose limiting papilledema, more frequently associated with use in children, has occurred; use with caution in patients with pre-existing papilledema or with tumors involving the central nervous system. Patients experiencing oprelvekin-related papilledema may be at risk for visual acuity changes, including blurred vision or blindness.

Disease-related concerns:

- Ascites/pericardial effusion: Use with caution in patients with pre-existing pericardial effusions or ascites.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.
- Thromboembolic disease: Use with caution in patients with a history of stroke or thromboembolic problems.

Concurrent drug therapy issues:

- Chemotherapy regimens: Efficacy has not been established with chemotherapy regimens >5 days duration or with regimens associated with delayed myelosuppression (eg, nitrosoureas, mitomycin C). Not indicated following myeloablative chemotherapy; increased toxicities were reported when used following myeloablative therapy.
- Diuretics: Closely monitor fluid and electrolytes in patient on chronic diuretic therapy; severe hypokalemia contributing to sudden death have been reported in these patients.

Special populations:

- Pediatrics: Although used in children in clinical trials, safety and efficacy have not been established in children.

Other warnings/precautions:

- Chronic administration: Safety and efficacy have not been established with chronic administration.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have demonstrated adverse fetal effects. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefits outweigh the potential risk to the fetus.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

>10%:

Cardiovascular: Tachycardia (children 84%; adults 20%), edema (59%), palpitation (14%), cardiomegaly (children 21%), vasodilation (19%), syncope (13%), atrial arrhythmia (12%)

Central nervous system: Headache (41%), dizziness (38%), fever (36%), insomnia (33%), fatigue (30%)

Dermatologic: Rash (25%)

Endocrine & metabolic: Fluid retention

Gastrointestinal: Nausea/vomiting (77%), diarrhea (43%), oral moniliasis (14%)

Hematologic: Anemia (dilutional); appears within 3 days of initiation of therapy, resolves in about 1 week after cessation of oprelvekin

Neuromuscular & skeletal: Weakness (severe 14%), arthralgia, periostitis (children 11%)

Ocular: Conjunctival injection/redness/swelling (children 57%; adults 19%), papilledema (children 16%; adults 1%)

Respiratory: Dyspnea (48%), rhinitis (42%), cough (29%), pharyngitis (25%)

1% to 10%:

Gastrointestinal: Weight gain (5%)

Respiratory: Pleural effusion (10%)

Postmarketing and/or case reports: Allergic reaction, amblyopia, anaphylaxis/anaphylactoid reactions, blindness, blurred vision, capillary leak syndrome, CHF, dehydration, exfoliative dermatitis, eye hemorrhage, facial edema, fibrinogen increased, fluid overload, hypoalbuminemia, hypocalcemia, hypotension, injection site reactions (dermatitis, pain, discoloration), optic neuropathy, paresthesia, pericardial effusion, pulmonary edema, renal failure, skin discoloration, stroke, ventricular arrhythmia

Oncology: VesicantNo

Oncology: Emetic PotentialModerate (30% to 60%)

Drug InteractionsThere are no known significant interactions.

Test InteractionsDecrease in hemoglobin concentration, serum concentration of albumin and other proteins (result of expansion of plasma volume)

Monitoring ParametersMonitor electrolytes and fluid balance during therapy; obtain a CBC at regular intervals during therapy; monitor platelet counts until adequate recovery has occurred

Monitoring: Lab TestsMonitor electrolytes and fluid balance during therapy; obtain a CBC at regular intervals during therapy; monitor platelet counts until adequate recovery has occurred

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Neumega®: 5 mg [packaged with diluent]

Generic AvailableNo

ManufacturerGenetics Institute

Mechanism of ActionOprelvekin is a growth factor which stimulates multiple stages of megakaryocytopoiesis and thrombopoiesis, resulting in proliferation of megakaryocyte progenitors and megakaryocyte maturation, or increased platelet production.

Pharmacodynamics/Kinetics

Bioavailability: >80%

Half-life elimination: Terminal: 5-9 hours

Time to peak, serum: 1-6 hours

Excretion: Urine (primarily as metabolites)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral moniliasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness, insomnia, and fatigue are common

Mental Health: Effects on Psychiatric TreatmentAnemia is common; use caution with clozapine and carbamazepine

Index TermsIL-11; Interleukin-11; NSC-722848; Recombinant Human Interleukin-11; Recombinant Interleukin-11; rhIL-11; rIL-11

References

Du X and Williams DA, “Interleukin-11: Review of Molecular, Cell Biology, and Clinical Use,” *Blood*, 1997, 89(11):3897-908.

Gordon MS, “Thrombopoietic Activity of Recombinant Human Interleukin 11 in Cancer Patients Receiving Chemotherapy,” *Cancer Chemother Pharmacol*, 1996, 38 (Suppl):96-8.

Sitaraman SV and Gewirtz AT, “Oprelvekin. Genetics Institute,” *Curr Opin Investig Drugs*, 2001, 2(10):1395-400.[PubMed 11890354]

Tepler I, Elias L, Smith JW 2d, et al, “A Randomized Placebo-Controlled Trial of Recombinant Human Interleukin-11 in Cancer Patients With Severe Thrombocytopenia Due to Chemotherapy,” *Blood*, 1996, 87(9):3607-14. [PubMed 8611684]

Teramura M, Kobayashi S, Yoshinaga K, et al, “Effect of Interleukin 11 on Normal and Pathological Thrombopoiesis,” *Cancer Chemother Pharmacol*, 1996, 38 (Suppl):99-102.

International Brand NamesNeumega (BR, CO, IL, MX)

Orlistat

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Xenical® may be confused with Xeloda®

Pronunciation(OR li stat)

U.S. Brand NamesAlli™ [OTC]; Xenical®

Canadian Brand NamesXenical®

Pharmacologic CategoryLipase Inhibitor

Use: Labeled IndicationsManagement of obesity, including weight loss and weight management, when used in conjunction with a reduced-calorie and low-fat diet; reduce the risk of weight regain after prior weight loss; indicated for obese patients with an initial body mass index (BMI) ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of other risk factors

Dosing: Adults**Obesity:** Oral:

Xenical®: 120 mg 3 times/day with each main meal containing fat (during or up to 1 hour after the meal); omit dose if meal is occasionally missed or contains no fat.

Alli™: OTC labeling: 60 mg 3 times/day with each main meal containing fat

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Obesity (Xenical®):** Children ≥12 years: Refer to adult dosing.

Dietary ConsiderationsMultivitamin supplements that contain fat-soluble vitamins should be taken once daily at least 2 hours before or after the administration of orlistat (ie, bedtime). Distribute the daily intake of fat over 3 main meals. Gastrointestinal effects of orlistat may increase if taken with any 1 meal very high in fat.

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to orlistat or any component of the formulation; chronic malabsorption syndrome or cholestasis

Warnings/Precautions

Concerns related to adverse effects:

- Increased urinary oxalate: Some patients may develop increased levels of urinary oxalate following treatment; caution should be exercised when prescribing it to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Dietary guidelines: Patients should be advised to adhere to dietary guidelines; gastrointestinal adverse events may increase if taken with a diet high in fat (>30% total daily calories from fat). The daily intake of fat should be distributed over three main meals. If taken with any one meal very high in fat, the possibility of gastrointestinal effects increases. Patients should be counseled to take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate nutrition because orlistat has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene.

- OTC labeling: Prior to use, patients should contact their healthcare provider if they have ever had kidney stones, gall bladder disease, or pancreatitis. Patients taking medications for diabetes or thyroid disease, anticoagulants, or other weight-loss products should consult their healthcare provider or pharmacist. Patients who have had an organ transplant should not use orlistat. If severe and/or continuous abdominal pain occurs, use should be discontinued and healthcare provider consulted.

- Long-term therapy: Safety and efficacy have not been established with use >4 years.

- Potential for misuse: As with any weight-loss agent, the potential exists for misuse in appropriate patient populations (eg, patients with anorexia nervosa or bulimia).

Pregnancy Risk FactorB

Pregnancy ConsiderationsThere are no adequate and well-controlled studies of orlistat in pregnant women. Because animal reproductive studies are not always predictive of human response, orlistat is not recommended for use during pregnancy. Teratogenicity studies were conducted in rats and rabbits at doses up to 800 mg/kg/day. Neither study showed embryotoxicity or teratogenicity. This dose is 23 and 47 times the daily human dose calculated on a body surface area basis for rats and rabbits, respectively.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Central nervous system: Headache (31%)

Gastrointestinal: Oily spotting (27%), abdominal pain/discomfort (26%), flatus with discharge (24%), fecal urgency (22%), fatty/oily stool (20%), oily evacuation (12%), defecation increased (11%)

Neuromuscular & skeletal: Back pain (14%)

Respiratory: Upper respiratory infection (38%)

1% to 10%:

Central nervous system: Fatigue (7%), anxiety (5%), sleep disorder (4%)

Dermatologic: Dry skin (2%)

Endocrine & metabolic: Menstrual irregularities (10%)

Gastrointestinal: Fecal incontinence (8%), nausea (8%), infectious diarrhea (5%), rectal pain/discomfort (5%), vomiting (4%)

Neuromuscular & skeletal: Arthritis (5%), myalgia (4%)

Otic: Otitis (4%)

<1%: Abdominal distension, allergic reactions, anaphylaxis, angioedema, bronchitis, bronchospasm, bullous eruption, cholelithiasis (may be caused by weight loss), hepatitis (causal relationship not established), hypoglycemia (in patients with diabetes), pancreatitis, pruritus, rash, transaminases increased, urticaria

Drug Interactions

Amiodarone: Orlistat may decrease the absorption of Amiodarone. *Risk C: Monitor therapy*

Levothyroxine: Orlistat may decrease the serum concentration of Levothyroxine. *Risk C: Monitor therapy*

Warfarin: Orlistat may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Fat-soluble vitamins: Absorption of vitamins A, D, E, and K may be decreased by orlistat. A multivitamin containing the fat-soluble vitamins (A, D, E, and K) should be administered once daily at least 2 hours before or after orlistat.

Nursing: Physical Assessment/MonitoringAssess effectiveness of other medications patient may be taking (especially anticoagulants). Monitor effectiveness of therapy, laboratory results, and adverse reactions at beginning of therapy and periodically during therapy. Assess knowledge/teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationTake this medication exactly as ordered; do not alter prescribed dose without consulting prescriber. Maintain prescribed diet (ideally, low-fat diet; high-fat meals may result in GI distress), exercise regimen, and vitamin supplements as prescribed. You may experience dizziness or lightheadedness (use caution when driving or engaging in tasks requiring alertness until response to drug is known) or increased flatus and fecal urgency (this may lessen with continued use). Report persistent back, muscle, or joint pain; signs of respiratory tract infection or flu-like symptoms; skin rash or irritation; or other reactions. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Alli™: 60 mg

Xenical®: 120 mg

Generic AvailableNo

ManufacturerRoche Laboratories Inc

Pricing: U.S. (www.drugstore.com)

Capsules (Xenical)

120 mg (90): $258.72

Mechanism of ActionA reversible inhibitor of gastric and pancreatic lipases, thus inhibiting absorption of dietary fats by 30% (at doses of 120 mg 3 times/day).

Pharmacodynamics/Kinetics

Onset of action: 24-48 hours

Duration: 48-72 hours

Absorption: Minimal

Metabolism: Metabolized within the gastrointestinal wall; forms inactive metabolites

Excretion: Feces (97%, 83% as unchanged drug); urine (<2%)

Related Information

- Obesity Treatment Guidelines for Adults

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, fatigue, and sleep disorders

Mental Health: Effects on Psychiatric TreatmentNone reported; be vigilant for abuse in patients with anorexia nervosa or bulimia

Cardiovascular ConsiderationsObesity is a modifiable risk factor for cardiovascular disease. When combined with dietary measures, orlistat may decrease weight by 3-4 kg. Orlistat and dietary measures resulted in a greater reduction in the incidence of type 2 diabetes mellitus (noninsulin dependent, NIDDM) over 4 years in obese patients with impaired glucose tolerance (Torgerson, 2004).

References

Davidson MH, Hauptman J, DiGirolamo M, et al, “Weight Control and Risk Factor Reduction in Obese Subjects Treated for 2 Years With Orlistat: A Randomized Controlled Trial,” *JAMA*, 1999, 281(3):235-42. [PubMed 9918478]

Heymsfield SB, Segal KR, Hauptman J, et al, “Effects of Weight Loss With Orlistat on Glucose Tolerance and Progression to Type 2 Diabetes in Obese Adults,” *Arch Intern Med*, 2000, 160(9):1321-6. [PubMed 10809036]

Hollander PA, Elbein SC, Hirsch IB, et al, “Role of Orlistat in the Treatment of Obese Patients With Type 2 Diabetes. A 1-year Randomized Double-Blind Study,” *Diabetes Care*, 1998, 21(8):1288-94. [PubMed 9702435]

McTigue KM, Harris R, Hemphill B, et al, “Screening and Interventions for Obesity in Adults: Summary of the Evidence for the U.S. Preventive Services Task Force,” *Ann Intern Med*, 2003, 139(11):933-49.[PubMed 14644897]

National Heart, Lung, and Blood Institute Obesity Education Initiative, “Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report,” *NIH Publication* No. 98-4083. Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, 1998.

Snow V, Barry P, Fitterman N, et al, “Pharmacologic and Surgical Management of Obesity in Primary Care: A Clinical Practice Guideline From the American College of Physicians,” *Ann Intern Med*, 2005, 142(7):525-31.[PubMed 15809464]

Torgenson JS, Pauptman J, Boldrin MN, et al, “XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study: A Randomized Study of Orlistat as an Adjunct to Lifestyle Changes for the Prevention of Type 2 Diabetes in Obese Patients,” *Diabetes Care*, 2004, 27(1):155-61.[PubMed 14693982]

International Brand NamesLesofat (PH); Xenical (AR, AT, AU, BB, BE, BF, BG, BJ, BM, BO, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CZ, DE, DK, DO, EC, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HU, ID, IE, IL, IT, JM, KE, KP, LR, MA, ML, MR, MU, MW, MX, NE, NG, NI, NL, NO, PA, PE, PH, PL, PR, PT, PY, RU, SC, SD, SE, SG, SL, SN, SR, SV, TH, TN, TR, TT, TZ, UG, UY, VE, ZA, ZM, ZW)

Orphenadrine, Aspirin, and Caffeine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Norgesic™ Forte may be confused with Norgesic 40®

Pronunciation(or FEN a dreen, AS pir in, & KAF een)

U.S. Brand NamesNorgesic™ Forte [DSC]; Norgesic™ [DSC]; Orphengesic Forte [DSC]; Orphengesic [DSC]

Canadian Brand NamesNorgesic™; Norgesic™ Forte

Pharmacologic CategorySkeletal Muscle Relaxant

Use: Labeled IndicationsRelief of discomfort associated with skeletal muscular conditions

Dosing: Adults**Muscular pain/spasms:** Oral: 1-2 tablets 3-4 times/day

Dosing: ElderlyNot recommended for use in the elderly; see individual agents

ContraindicationsHypersensitivity to any component of the formulation; glaucoma; pyloric obstruction; duodenal obstruction; achalasia; prostatic hyperplasia; bladder obstruction; myasthenia gravis

Allergy Considerations

- Salicylate Allergy/Sensitivity

Pregnancy Risk FactorD

LactationEnters breast milk/use caution due to aspirin content

Metabolism/Transport Effects

Orphenadrine: **Substrate** (minor) of CYP1A2, 2B6, 2D6, 3A4; **Inhibits** CYP1A2 (weak), 2A6 (weak), 2B6 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak), 3A4 (weak)

Aspirin: **Substrate** of CYP2C9 (minor)

Caffeine: **Substrate** of CYP1A2 (major), 2C9 (minor), 2D6 (minor), 2E1 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 3A4 (moderate)

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: May decrease the metabolism of Caffeine. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Ofloxacin; Sparfloxacin; Trovafloxacin. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Regadenoson: Caffeine may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: Orphenadrine citrate 25 mg, aspirin 385 mg, and caffeine 30 mg; orphenadrine citrate 50 mg, aspirin 770 mg, and caffeine 60 mg

Norgesic™, Orphengesic: Orphenadrine citrate 25 mg, aspirin 385 mg, and caffeine 30 mg [DSC]

Norgesic™ Forte, Orphengesic Forte: Orphenadrine citrate 50 mg, aspirin 770 mg, and caffeine 60 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Norgesic)

25-385-30 mg (30): $35.99

Tablets (Orphenadrine Compound-DS)

50-770-60 mg (30): $73.48

Tablets (Orphenadrine-Aspirin-Caffeine)

25-385-30 mg (30): $39.99

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Aspirin
- Orphenadrine

Dental Health Professional ConsiderationsThere is no scientific evidence to warrant discontinuance of aspirin prior to dental surgery. Patients taking one aspirin tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with the physician before removal of the aspirin relative to prevention of postoperative bleeding.

The Food and Drug Administration (FDA), has issued a letter updating information and considerations regarding the use of ibuprofen (400 mg doses) in patients who are taking low dose aspirin (81 mg, immediate release; not enteric coated) for cardioprotection and stroke prevention. Ibuprofen, at these doses, may interfere with aspirin's antiplatelet effect depending upon when it is administered. Patients initiated on aspirin first (for ~1 week) then ibuprofen (400 mg 3 times/day for 10 days) seem to maintain aspirin's platelet effect (Cryer B, 2005). Ibuprofen has the greatest impact on aspirin if administered less than 8 hours before aspirin (Catella-Lawson F, 2001).

Patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. With occasional use of ibuprofen, a clinically-significant interaction with aspirin in unlikely. To avoid interference during chronic dosing, a single dose of ibuprofen should be taken 30-120 minutes after aspirin ingestion or at least 8 hours should elapse after ibuprofen dosing before giving aspirin (FDA, 2006; Catella-Lawson F, 2001).

The clinical implications of the interaction are unclear. There have not been any clinical endpoint studies conducted at this time. Avoidance of this interaction is potentially important because aspirin's vascular protection could be decreased or negated.

Other nonselective NSAIDs may have potential for a similar interaction with aspirin. Such has been described with naproxen (Capone ML, 2005). Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin. Other clinical scenarios (use of smaller ibuprofen doses, other aspirin products, other doses of aspirin) have not been evaluated.

Additional information is available at: http://www.fda.gov/cder/drug/infopage/aspirin/default.htm

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: The peripheral anticholinergic effects of orphenadrine may decrease or inhibit salivary flow; normal salivation will return with cessation of drug therapy.

Aspirin: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity (see Dental Comment).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and dizziness are common; may rarely cause hallucinations

Mental Health: Effects on Psychiatric TreatmentMay rarely cause aplastic anemia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation

Index TermsAspirin, Orphenadrine, and Caffeine; Caffeine, Orphenadrine, and Aspirin

References

Capone ML, Sciulli MG, Tacconelli S, et al, "Pharmacodynamic Interaction of Naproxen With Low-Dose Aspirin in Healthy Subjects," *J Am Coll Cardiol*, 2005, 45(8):1295-1301.[PubMed 15837265]

Catella-Lawson F, Reilly MP, Kapoor SC, et al, "Cyclooxygenase Inhibitors and the Antiplatelet Effects of Aspirin," *N Engl J Med*, 2001, 345(25):1809-17.[PubMed 11752357]

Cryer B, Verlin RG, Cooper SA, et al, "Double-Blind, Randomized, Parallel, Placebo-Controlled Study of Ibuprofen Effects on Thromboxane B2 Concentrations in Aspirin-Treated Healthy Adult Volunteers," *Clin Ther*, 2005, 27(2):185-191.[PubMed 15811481]

International Brand NamesNorgesic Forte (DO, GT, HN, NI, PA, SV); Norgesic® (CA); Norgesic® Forte (CA)

Orphenadrine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Norflex™ may be confused with norfloxacin, Noroxin®

International issues:

Flexin® [Israel] may be confused with Floxin® which is a brand name for ofloxacin in the U.S.

Flexin® [Israel]: Brand name for indomethacin in Great Britain

Pronunciation(or FEN a dreen)
U.S. Brand NamesNorflex™
Canadian Brand NamesNorflex™; Orphenace®; Rhoxal-orphendrine
Pharmacologic CategoryAnti-Parkinson's Agent, Anticholinergic; Skeletal Muscle Relaxant
Use: Labeled IndicationsTreatment of muscle spasm associated with acute painful musculoskeletal conditions
Dosing: Adults**Muscle spasms:**

Oral: 100 mg twice daily

I.M., I.V.: 60 mg every 12 hours

Dosing: ElderlyUse caution; generally not recommended for use in the elderly (see Geriatric Considerations).
Administration: OralDo not crush sustained release drug product.
StorageStore at 15°C to 30°C (59°F to 86°F). Protect injection solution from light.
ContraindicationsHypersensitivity to orphenadrine or any component of the formulation; glaucoma; GI obstruction, stenosing peptic ulcer; prostatic hypertrophy, bladder neck obstruction; cardiospasm; myasthenia gravis
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with HF, cardiac decompensation, coronary insufficiency, tachycardia, or cardiac arrhythmias.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for abuse exists.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Sulfites: Injection contains sodium bisulfite which may cause allergic reaction in some individuals.

Other warnings/precautions:

- Long-term use: Has not been evaluated for continuous long-term use; monitor closely.

Geriatric ConsiderationsBecause of its anticholinergic side effects (eg, constipation, urinary retention, confusion), orphenadrine is not a drug of choice in the elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation, tachycardia

Central nervous system: Agitation, drowsiness, dizziness, euphoria, hallucination, headache, mental confusion

Dermatologic: Pruritus, urticaria

Gastrointestinal: Constipation, gastric irritation, nausea, vomiting, xerostomia

Genitourinary: Urination hesitancy, urinary retention

Hematologic: Aplastic anemia (rare)

Neuromuscular & skeletal: Tremor, weakness

Ocular: Blurred vision, intraocular pressure increased, nystagmus, pupil dilation

Respiratory: Nasal congestion

Miscellaneous: Anaphylactic reaction (injection, rare), hypersensitivity

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 2B6, 2D6, 3A4; **Inhibits** CYP1A2 (weak), 2A6 (weak), 2B6 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Nursing: Physical Assessment/MonitoringMonitor effectiveness of therapy (according to rationale for therapy) and adverse reactions at beginning of therapy and periodically with long-term use. Do not discontinue abruptly; taper dosage slowly. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed. Do not increase dose or discontinue without consulting prescriber. Do not chew or crush sustained release tablets. Do not use alcohol, prescriptive or OTC antidepressants, sedatives, or pain medications without consulting prescriber. You may experience drowsiness, dizziness, lightheadedness (avoid driving or engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, or sucking hard candy may help); constipation (increased exercise, fluids, fruit, or fibers may help); or decreased urination (void before taking medication). Report excessive drowsiness or mental agitation, chest pain, skin rash, swelling of mouth/face, difficulty speaking, or vision changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as citrate: 30 mg/mL (2 mL)

Norflex™: 30 mg/mL (2 mL) [contains sodium bisulfite]

Tablet, extended release, as citrate: 100 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, 12-hour (Orphenadrine Citrate CR)

100 mg (30): $49.00

Mechanism of ActionIndirect skeletal muscle relaxant thought to work by central atropine-like effects; has some euphorigenic and analgesic properties

Pharmacodynamics/Kinetics

Onset of effect: Peak effect: Oral: 2-4 hours

Duration: 4-6 hours

Protein binding: 20%

Metabolism: Extensively hepatic

Half-life elimination: 14-16 hours

Excretion: Primarily urine (8% as unchanged drug)

Dental Health: Effects on Dental Treatment The peripheral anticholinergic effects of orphenadrine may decrease or inhibit salivary flow; normal salivation will return with cessation of drug therapy.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Drowsiness and dizziness are common; may rarely cause hallucinations

Mental Health: Effects on Psychiatric Treatment May rarely cause aplastic anemia; use caution with clozapine and carbamazepine; has been used to treat tardive dyskinesia and augment typical antipsychotics; clozapine is a better option; concurrent use with psychotropics may produce additive sedation

Index Terms Orphenadrine Citrate

References

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Clarke B, Mair J, and Rudolf M, “Acute Poisoning With Orphenadrine,” *Lancet*, 1985, 1(8442):1386.

International Brand Names Biorphen (GB); Disipal (CH, CZ, DK, IE, IT, LU, NO); Erilax (KP); Flexen (PE); Lysantin (DK); Mefeamina (ES); Mioflex (IT); Neekxin (KP); Norflex (AE, AU, BB, BE, BH, BM, BS, BZ, CH, CR, CY, DE, DK, DO, EG, FI, GT, GY, HK, HN, IE, IL, IQ, IR, JM, JO, KE, KW, LB, LU, LY, MU, MX, MY, NG, NL, OM, PA, PE, PK, PT, QA, SA, SE, SR, SV, SY, TH, TT, TW, UY, VE, YE, ZA); Opheraxcin (KP); Opheryl (KP); Orfen (FI); Orpherin (KP); Orphipal (IN); Plenactol (CN); Relaflex (GT, HN, NI, SV); Slaxin (KP); Terilax XL (KP)

Oseltamivir

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

CDC Interim Recommendations Concerning Use of Antivirals During 2008-09 Influenza Season - December 2008

The Centers for Disease Control (CDC) has issued a Health Advisory with interim recommendations for chemoprophylaxis or influenza treatment with the following antiviral agents: Oseltamivir (Tamiflu®), zanamivir (Relenza®), rimantadine (Flumadine®), amantadine (Symmetrel®).

The recommendations were prompted by preliminary data in a limited number of states indicating a high prevalence of the oseltamivir-resistant influenza A (H1N1) strain. Influenza activity remains low at the present time, but of the 50 H1N1 isolates from 12 states tested between October 1 and December 19, 2008, 49 (98%) were resistant to oseltamivir. The CDC is unable to make any accurate predictions of which influenza virus types (A or B) or subtypes of influenza A (H1N1 or H3N2) will predominate during the 2008-09 season, but based on the current findings, the following recommendations have been made:

- Patients testing positive for influenza type B: If treatment is indicated, patients may receive either oseltamivir or zanamivir (no preference).

- Patients testing positive for influenza type A (or patients testing negative for influenza, but likelihood of influenza infection is high): If treatment is indicated, patient may receive zanamivir. If zanamivir therapy is inappropriate (eg, patients with chronic respiratory disease, patients <7 years of age) or zanamivir is unavailable, combination treatment with oseltamivir and rimantadine is acceptable (if rimantadine is unavailable, amantadine may be substituted). Oseltamivir monotherapy should only be used if local surveillance indicates that influenza A (H3N2) or influenza type B viruses are likely.

- If confirmatory diagnostic testing to distinguish between subtypes of influenza A (H1N1 or H3N2) is available, and treatment is indicated:

    Patients testing positive for influenza A (H3N2): Use oseltamivir or zanamivir (no preference)

    Patients testing positive for influenza A (H1N1): Use zanamivir (or combination treatment with oseltamivir and rimantadine as an alternative)

Patients requiring chemoprophylaxis due to potential exposure with laboratory-confirmed influenza A (H3N2) or influenza B should receive oseltamivir or zanamivir. Patients requiring chemoprophylaxis due to influenza A (H1N1) virus should receive zanamivir (or rimantadine, if zanamivir use contraindicated).

The CDC is reminding clinicians to continue to vaccinate patients using the influenza vaccine, which is expected to be effective against all circulating influenza vaccines, including the oseltamivir-resistant strain.

For additional information, including the CDC Health Advisory, please refer to http://www2a.cdc.gov/HAN/ArchiveSys/ViewMsgV.asp?AlertNum=00279

Neuropsychiatric Events Associated With Tamiflu® (Oseltamivir) - March 4, 2008

Roche Laboratories, in conjunction with the U.S. Food and Drug Administration (FDA), has issued a Dear Healthcare Professional letter concerning postmarketing reports of neuropsychiatric events in patients receiving Tamiflu® (oseltamivir). These events include hallucination, delirium, and abnormal behavior, which in some cases have led to injury (with fatalities). Although the role of oseltamivir in the development of these events has not been established, the prescribing information has been revised to acknowledge their occurrence. The reported events primarily occurred in pediatric patients from Japan and often had a sudden onset with rapid resolution.

Patients with influenza (particularly pediatric patients) may be more susceptible to the development of adverse events (seizures, confusion, abnormal behavior) early in the course of their illness regardless of whether oseltamivir therapy has been initiated. Additionally, adverse events may occur in the presence of encephalitis or encephalopathy, or in the absence of marked disease. Patients receiving oseltamivir should be closely monitored for any unusual behavior and healthcare professionals should be notified immediately if such signs occur.

Additional information can be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Tamiflu.

Medication Safety Issues

Sound-alike/look-alike issues:

Tamiflu® may be confused with Thera-Flu®

Pronunciation(oh sel TAM i vir)

U.S. Brand NamesTamiflu®

Canadian Brand NamesTamiflu®

Pharmacologic CategoryAntiviral Agent; Neuraminidase Inhibitor

Use: Labeled IndicationsTreatment of uncomplicated acute illness due to influenza (A or B) infection in children ≥1 year of age and adults who have been symptomatic for no more than 2 days; prophylaxis against influenza (A or B) infection in children ≥1 year of age and adults

The Advisory Committee on Immunization Practices (ACIP) recommends that **treatment** be considered for the following:

- Persons hospitalized with laboratory confirmed influenza (may also have benefit if started >48 hours after onset of illness).
- Persons with laboratory confirmed influenza pneumonia.
- Persons with laboratory confirmed influenza and bacterial infections.
- Persons with laboratory confirmed influenza and who are at higher risk for influenza complications.
- Persons presenting for care within 48 hours of laboratory confirmed influenza onset and who want to decrease duration and/or severity of their symptoms or decrease the risk of transmission to those at high risk for complications.

The ACIP recommends that **prophylaxis** be considered for the following:

- Persons at high risk for influenza infection during the first 2 weeks following vaccination (eg, children <9 years and not previously vaccinated) if the virus is circulating in the community.
- Persons at high risk for influenza infection, but the vaccination is contraindicated.
- Unvaccinated family members or healthcare providers with prolonged exposure to or close contact with high-risk persons, unvaccinated persons, or infants <6 months of age.
- Persons at high risk for influenza infection, their family members and close contacts, and healthcare workers when the circulating strain of influenza is not matched with the vaccine.
- Persons with immune deficiency or those who may not respond to vaccination.
- Unvaccinated staff and persons during response to an outbreak in a closed institutional setting that has patients at high risk for infection (eg, extended care facilities).

Dosing: Adults

Influenza prophylaxis: Oral: 75 mg once daily; initiate treatment within 2 days of contact with an infected individual; duration of treatment: 10 days. During community outbreaks, dosing is 75 mg once daily. May be used for up to 6 weeks; duration of protection lasts for length of dosing period.

Influenza treatment: Oral: 75 mg twice daily initiated within 2 days of onset of symptoms; duration of treatment: 5 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Influenza prophylaxis: Oral: Initiate treatment within 2 days of contact with an infected individual; duration of treatment: 10 days:

Children: 1-12 years:

≤15 kg: 30 mg once daily

>15 kg to ≤23 kg: 45 mg once daily

>23 kg to ≤40 kg: 60 mg once daily

>40 kg: 75 mg once daily

Influenza treatment: Oral: Initiate treatment within 2 days of onset of symptoms; duration of treatment: 5 days:

Children: 1-12 years:

≤15 kg: 30 mg twice daily

>15 kg - ≤23 kg: 45 mg twice daily

>23 kg - ≤40 kg: 60 mg twice daily

>40 kg: 75 mg twice daily

Adolescents ≥13 years: Refer to adult dosing.

Dosing: Renal ImpairmentAdults:

Cl_{cr} 10-30 mL/minute:

Treatment: Reduce dose to 75 mg once daily for 5 days.

Prophylaxis: Administer 75 mg every other day or 30 mg once daily.

CAPD (unlabeled dose): 30 mg once weekly (Robson, 2006)

Hemodialysis (unlabeled dose): 30 mg after every other session (Robson, 2006)

Dosing: Hepatic ImpairmentNo adjustment required in mild-to-moderate hepatic impairment. Safety and kinetics in patients with severe hepatic impairment have not been evaluated.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralCapsules may be opened and mixed with sweetened liquid (eg, chocolate syrup).

Dietary ConsiderationsTake with or without food; take with food to improve tolerance.

Storage

Capsules: Store at 25°C (77°F).

Oral suspension: Store powder for suspension at 25°C (77°F). Once reconstituted, store suspension under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Use within 10 days of preparation.

ReconstitutionOral suspension: Reconstitute with 23 mL of water (to make 25 mL total suspension).

Extemporaneously Prepared

If the commercially prepared oral suspension is not available, the manufacturer provides the following compounding information to prepare a **15 mg/mL** suspension in emergency situations. **Note:** The strength and dosing instructions differ from that of the commercially prepared product (see chart below).

1. Calculate the total volume needed by patient weight (refer to chart below).
2. Calculate the number of capsules and required volume of vehicle (refer to chart below). **Note:** Acceptable vehicles are cherry syrup or Ora-Sweet® SF.
3. Transfer contents of capsules into mortar and triturate granules into a fine powder.
4. Add ~$^{1}/_{3}$ of vehicle and triturate into a uniform suspension.
5. Add another $^{1}/_{3}$ of vehicle and triturate, transfer to amber prescription bottle.
6. Add remaining vehicle to prescription bottle; shake well.

Suspension is stable for 35 days under refrigeration at 2°C to 8°C (36°F to 46°F) or 5 days at room temperature of 25°C (77°F). Shake gently prior to use. Do **not** dispense with dosing device provided with commercially-available product.

Preparation of Oseltamivir 15 mg/mL Suspension

Body Weight	**Total Volume per Patient**[1]	**# of 75 mg Capsules**[2]	**Required Volume of Vehicle**[2,3]	**Treatment Dose (wt based)**[4]	**Prophylactic Dose (wt based)**[4]
≤15 kg	30 mL	6	29 mL	2 mL (30 mg) twice daily for 5 days	2 mL (30 mg) once daily for 10 days
16-23 kg	40 mL	8	38.5 mL	3 mL (45 mg) twice daily for 5 days	3 mL (45 mg) once daily for 10 days
24-40 kg	50 mL	10	48 mL	4 mL (60 mg) twice daily for 5 days	4 mL (60 mg) once daily for 10 days
≥41 kg	60 mL	12	57 mL	5 mL (75 mg) twice daily for 5 days	5 mL (75 mg) once daily for 10 days

[1] Entire course of therapy.

[2] Based on total volume per patient.

[3] Acceptable vehicles are cherry syrup or Ora-Sweet® SF.

[4] Using 15 mg/mL suspension.

ContraindicationsHypersensitivity to oseltamivir or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity: Rare but severe hypersensitivity reactions (anaphylaxis, severe dermatologic reactions) have been associated with use.
- Neuropsychiatric events: Rare occurrences of neuropsychiatric events (including confusion, delirium, hallucinations, and/or self-injury) have been reported from postmarketing surveillance; direct causation is difficult to establish (influenza infection may also be associated with behavioral and neurologic changes).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with chronic cardiac disease; efficacy has not been established.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment; safety and efficacy have not been established.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment is required for creatinine clearance <30 mL/minute.
- Respiratory disease: Use with caution in patients with respiratory disease; efficacy has not been established.

Special populations:

- Immunocompromised patients: Use with caution in immunocompromised patients; safety and efficacy for treatment or prophylaxis in immunocompromised patients have not been established.
- Pediatrics: Rare occurrences of neuropsychiatric events (including confusion, delirium, hallucinations, and/or self-injury) have been reported primarily in pediatric patients from postmarketing surveillance; monitor closely for signs of any unusual behavior. Safety and efficacy have not been established in children <1 year of age.

Other warnings/precautions:

- Appropriate use: Oseltamivir is not a substitute for the influenza virus vaccine. Also consider primary or concomitant bacterial infections. Efficacy has not been established if treatment begins >40 hours after the onset of symptoms.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are insufficient human data to determine the risk to a pregnant woman or developing fetus. Studies evaluating the effects on embryo-fetal development in rats and rabbits showed a dose-dependent increase in the rates of minor skeleton abnormalities in exposed offspring. The rate of each abnormality remained within the background rate of occurrence in the species studied.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsOseltamavir and its carboxylate metabolite have been detected in breast milk. Breast milk samples were obtained from a single patient (~9 months post-partum) over the course of 5 days of treatment. The maximum total concentration of oseltamavir (expressed as parent drug and metabolite) was 81.6 ng/mL. Using a milk concentration of 81.6 ng/mL, the estimated exposure to the breastfeeding infant would be ~0.5% of the weight adjusted maternal dose (in a 60 kg woman).

Adverse Reactions

>10%: Gastrointestinal: Vomiting (2% to 15%)

1% to 10%: Gastrointestinal: Nausea (3% to 10%), abdominal pain (2% to 5%)

<1%: Anemia, angina, fracture, peritonsillar abscess, pneumonia, pseudomembranous colitis, pyrexia

Postmarketing and/or case reports: Allergy, anaphylactic/anaphylactoid reaction, arrhythmia, confusion, dermatitis, diabetes aggravation, eczema, erythema multiforme, hepatitis, liver function tests abnormal, neuropsychiatric events (self-injury, confusion, delirium), rash, seizure, Stevens-Johnson syndrome, swelling of face or tongue, toxic epidermal necrolysis, urticaria

Drug Interactions

Influenza Virus Vaccine: Antiviral Agents (Influenza A and B) may diminish the therapeutic effect of Influenza Virus Vaccine. This only pertains to live, attentuated influenza virus vaccine. *Risk D: Consider therapy modification*

Monitoring ParametersSigns or symptoms of unusual behavior, including attempts at self-injury, confusion, and/or delirium

Nursing: Physical Assessment/MonitoringTeach patient appropriate use, interventions to reduce side effects, and adverse reactions to report.

Patient EducationThis is not a substitute for the flu shot. Must be taken within 2 days of contact with an infected individual or onset of flu symptoms (eg, fever, cough, headache, fatigue, muscular weakness, and sore throat). Take as directed; do not increase dose or frequency, and do not miss a dose. You may experience nausea or vomiting (small frequent meals, good mouth care, chewing gum, or sucking hard candy may help). Report hallucinations or unusual behavior or significant adverse effects to your prescriber. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as phosphate:

Tamiflu®: 30 mg, 45 mg, 75 mg

Powder for oral suspension:

Tamiflu®: 12 mg/mL (25 mL) [contains sodium benzoate; tutti-frutti flavor]

Generic AvailableNo

ManufacturerRoche Laboratories Inc

Pricing: U.S. (www.drugstore.com)

Capsules (Tamiflu)

30 mg (10): $92.99

45 mg (10): $92.99

75 mg (10): $92.99

Suspension (reconstituted) (Tamiflu)

12 mg/mL (25): $50.99

Mechanism of ActionOseltamivir, a prodrug, is hydrolyzed to the active form, oseltamivir carboxylate (OC). OC inhibits influenza virus neuraminidase, an enzyme known to cleave the budding viral progeny from its cellular envelope attachment point (neuraminic acid) just prior to release.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: V_d: 23-26 L (oseltamivir carboxylate)

Protein binding, plasma: Oseltamivir carboxylate: 3%; Oseltamivir: 42%

Metabolism: Hepatic (90%) to oseltamivir carboxylate; neither the parent drug nor active metabolite has any effect on the cytochrome P450 system

Bioavailability: 75% as oseltamivir carboxylate

Half-life elimination: Oseltamivir: 1-3 hours; Oseltamivir carboxylate: 6-10 hours

Excretion: Urine (>90% as oseltamivir carboxylate); feces

Related Information

- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsIn clinical studies of the influenza virus, 1.3% of post-treatment isolates in adults and adolescents and 8.6% of isolates in children had decreased neuraminidase susceptibility *in vitro* to oseltamivir carboxylate.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

References

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Wentges-van Holthe N, van Eijkeren M, and van der Laan JW, “Oseltamivir and Breastfeeding,” *Int J Infect Dis*, 2008, 12(4):451.[PubMed 18243025]

International Brand Names Fluhalt (MY); Tamiflu (AR, AT, AU, BE, BG, BR, CH, CL, CN, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, HU, IE, IL, IT, JP, KP, MX, NL, NO, PE, PH, PL, PT, PY, RU, SE, SG, TH, TR, UY)

Oxacillin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(oks a SIL in)

Pharmacologic Category[Antibiotic, Penicillin]

Use: Labeled IndicationsTreatment of infections such as osteomyelitis, septicemia, endocarditis, and CNS infections caused by susceptible strains of *Staphylococcus*

Dosing: Adults

Endocarditis: I.V.: 2 g every 4 hours with gentamicin

Mild-to-moderate infections: I.M., I.V.: 250-500 mg every 4-6 hours

Prosthetic joint infection: I.V.: 2 g every 4 hours with rifampin

Severe infections: I.M., I.V.: 1-2 g every 4-6 hours

Staphylococcus aureus,**methicillin-susceptible infections, including brain abscess, bursitis, erysipelas, mastitis, mastoiditis, osteomyelitis, perinephric abscess, pneumonia, pyomyositis, scalded skin syndrome, toxic shock syndrome:** I.V.: 2 g every 4 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Arthritis (septic): I.V.: 37 mg/kg every 6 hours

Epiglottitis: I.V.: 150-200 mg/kg/day divided every 6 hours

Mild-to-moderate infections: I.M., I.V.: 100-150 mg/kg/day in divided doses every 6 hours (maximum: 4 g/day)

Severe infections: I.M., I.V.: 150-200 mg/kg/day in divided doses every 6 hours (maximum: 12 g/day)

Staphylococcal scalded-skin syndrome: I.V.: 150 mg/kg/day divided every 6 hours for 5-7 days

Dosing: Renal Impairment

Cl_{cr} <10 mL/minute: Clinical practice varies; some clinicians recommend adjustment to the lower range of the usual dosage as based on severity of infection.

Not dialyzable (0% to 5%)

Administration: I.V.Administer around-the-clock to promote less variation in peak and trough serum levels. Administer IVP over 10 minutes. Administer IVPB over 30 minutes.

Administration: I.V. DetailRapid administration may result in seizures.

Dietary ConsiderationsSodium content of 1 g: 92.4 mg (4.02 mEq)

StorageReconstituted parenteral solution is stable for 3 days at room temperature and 7 days when refrigerated. For I.V. infusion in NS or D_5W, solution is stable for 6 hours at room temperature.

CompatibilityStable in dextran 70 6% in dextrose, dextran 40 10% in dextrose, D_5LR, $D_{10}W$, hetastarch 6%, LR; **variable stability (consult detailed reference)** in D_5NS, D_5W, NS.

Y-site administration: Compatible: Acyclovir, cyclophosphamide, diltiazem, famotidine, fluconazole, foscarnet, heparin, hydrocortisone sodium succinate, hydromorphone, labetalol, levofloxacin, magnesium sulfate, meperidine, methotrexate, morphine, perphenazine, potassium chloride, tacrolimus, vitamin B complex with C, zidovudine. **Incompatible:** Sodium bicarbonate, verapamil.

Compatibility when admixed: Compatible: Chloramphenicol, dopamine, potassium chloride, sodium bicarbonate. **Incompatible:** Cytarabine. **Variable (consult detailed reference):** Amikacin, verapamil.

ContraindicationsHypersensitivity to oxacillin or other penicillins or any component of the formulation

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and

pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Special populations:

- Elderly: Use with caution in the elderly; dosage adjustment recommended.
- Neonates: Use with caution in neonates; elimination of drug is slow.

Geriatric ConsiderationsOxacillin has not been studied in the elderly. Dosing adjustments are not necessary except in renal failure (eg, Cl_{cr} <10 mL/minute). Consider sodium content in patients who may be sensitive to volume expansion (ie, CHF).

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, oxacillin is classified as pregnancy category B. Oxacillin is distributed into the amniotic fluid and is detected in cord blood. There was not an increased risk of teratogenic effects with oxacillin observed in an epidemiologic study.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsLow levels of oxacillin are found in breast milk. The manufacturer recommends that caution be exercised when administering oxacillin to nursing women. Other penicillins distribute into human milk and are considered safe for use during breast-feeding. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Oxacillin in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Fever

Dermatologic: Rash

Gastrointestinal: Diarrhea, nausea, vomiting

Hematologic: Agranulocytosis, eosinophilia, leukopenia, neutropenia, thrombocytopenia

Hepatic: AST increased, hepatotoxicity

Renal: Acute interstitial nephritis, hematuria

Miscellaneous: Serum sickness-like reactions

Drug Interactions

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Test InteractionsMay interfere with urinary glucose tests using cupric sulfate (Benedict's solution, Clinitest®); may inactivate aminoglycosides *in vitro*; false-positive urinary and serum proteins

Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose; monitor periodic CBC, urinalysis, BUN, serum creatinine, AST and ALT

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's allergy history prior to beginning therapy. See Administration for I.V. specifics (rapid administration may result in seizures). Patient should be monitored closely with first infusion/injection (anaphylactic reaction). Evaluate results of laboratory tests, therapeutic effectiveness (resolution of infection; if no response, therapy should be reevaluated), and adverse reactions (hypersensitivity, opportunistic infection, hepatotoxicity, renal toxicity, gastrointestinal upset) at regular intervals during treatment. Caution patients with diabetes about using Clinitest® (may interfere with accuracy). Teach patient possible side effects/appropriate interventions and symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity studies prior to initiating therapy; monitor periodic CBC, urinalysis, BUN, serum creatinine, AST and ALT

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by infusion or injection. Report immediately any redness, swelling, burning, or pain at injection/infusion site; respiratory difficulty or swallowing; chest pain; or rash. May cause nausea (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report signs of opportunistic infection (eg, fever, chills, sore throat, burning urination, fatigue); changes in urinary elimination; yellowing of skin or sclera, dark urine, or pale stool; persistent diarrhea; rash or other persistent side effects; or if condition does not respond to treatment.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed iso-osmotic dextrose solution]: 1 g (50 mL); 2 g (50 mL)

Injection, powder for reconstitution: 1 g, 2 g, 10 g

Generic AvailableYes

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs); which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Distribution: Into bile, synovial and pleural fluids, bronchial secretions; also distributes to peritoneal and pericardial fluids; penetrates the blood-brain barrier only when meninges are inflamed

Protein binding: ~94%

Metabolism: Hepatic to active metabolites

Half-life elimination: Children 1 week to 2 years: 0.9-1.8 hours; Adults: 23-60 minutes; prolonged in neonates and with renal impairment

Time to peak, serum: I.M.: 30-60 minutes

Excretion: Urine and feces (small amounts as unchanged drug and metabolites)

Related Information

- Antibiotic Treatment of Adults With Infective Endocarditis
- Community-Acquired Pneumonia in Adults

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Prolonged use of penicillins may lead to development of oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusPenicillins reported to cause apprehension, illusions, hallucinations, depersonalization, agitation, insomnia, and encephalopathy

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine

Index TermsMethylphenyl Isoxazolyl Penicillin; Oxacillin Sodium

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International Brand NamesBristopen (FR); Dicloxalox (PE); Oxacil (BR); Oxacilina (CO); Oxacillin (PL); Oxapen (PH); Panadox (PH); Penstapho (BE, IT); Prostafilina (VE); Prostaphlin (EE, HN, PH, TW); Stafcil (PH); Staficilin-N (BR); Stapenor (AT); Syntarpen (PL); Wydox (PH)

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Oxaliplatin may be confused with Aloxi®, carboplatin

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ox AL i pla tin)

U.S. Brand NamesEloxatin®

Canadian Brand NamesEloxatin®

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent; Antineoplastic Agent, Platinum Analog

Use: Labeled IndicationsTreatment of stage III colon cancer and advanced colorectal cancer

Use: Unlabeled/InvestigationalTreatment of esophageal cancer, gastric cancer, head and neck cancer, non-Hodgkin's lymphoma, ovarian cancer, pancreatic cancer

Dosing: AdultsDetails concerning dosing in combination regimens should also be consulted.

Stage III colon cancer and colorectal cancer: I.V.:

85 mg/m^2 every 2 weeks **or**

Unlabeled doses:

20-25 mg/m^2 days 1-5 every 3 weeks **or**

100-130 mg/m^2 every 2-3 weeks

Dosing: ElderlyNo dosing adjustment recommended.

Dosing: Renal ImpairmentThe FDA-approved labeling does not contain renal dosing adjustment guidelines. Oxaliplatin is primarily eliminated renally; in patients with Cl_{cr} <30 mL/minute, the AUC is increased ~190%. Oxaliplatin use has been studied in 25 patients with renal dysfunction; treatment was well-tolerated in patients with mild-to-moderate impairment (Cl_{cr} 20-59 mL/minute), suggesting that dose reduction is not necessary in this patient population (Takimoto, 2003). Patients with severe renal impairment (Cl_{cr} <20 mL/minute) have not been adequately studied; consider omitting dose or changing chemotherapy regimen if Cl_{cr} <20 mL/minute.

Note: Canadian labeling: Use in patients with Cl_{cr} <30 mL/minute is contraindicated in Canadian labeling.

Dosing: Hepatic ImpairmentMild, moderate, or severe hepatic impairment: Dosage adjustment not necessary (Synold, 2007; Doroshow, 2003).

Dosing: Adjustment for Toxicity Acute toxicities: Longer infusion times may mitigate acute toxicities.

Neurosensory events:

Persistent (>7 days) grade 2 neurosensory events: Consider oxaliplatin dose reduction if symptoms do not resolve:

Stage III colon cancer: Reduce dose to 75 mg/m^2

Advanced colorectal cancer: Reduce dose to 65 mg/m^2

Consider withholding oxaliplatin for grade 2 neuropathy lasting >7 days despite dose reduction.

Persistent grade 3 neurosensory events: Consider discontinuing oxaliplatin

Other toxicities (grade 3/4 gastrointestinal toxicity, grade 4 neutropenia, or grade 3/4 thrombocytopenia): After recovery from toxicity, oxaliplatin dose reductions are recommended:

Stage III colon cancer: Reduce dose to 75 mg/m^2 ; delay next dose until neutrophils recover to ≥1500/mm^3 and platelets recover to ≥75,000/mm^3

Advanced colorectal cancer: Reduce dose to 65 mg/m^2; delay next dose until neutrophils recover to ≥1500/mm^3 and platelets recover to ≥75,000/mm^3

Dosing: Combination Regimens

Biliary adenocarcinoma: GEMOX

Colorectal cancer:

- Bevacizumab-Oxaliplatin-Fluorouracil-Leucovorin
- Cetuximab-FOLFOX4
- FLOX (Nordic FLOX)
- FOIL
- FOLFOX 1
- FOLFOX 2
- FOLFOX 3
- FOLFOX 4
- FOLFOX 6
- FOLFOX 7
- XelOx (Colorectal Cancer)

Esophageal cancer:

- Epirubicin-Oxaliplatin-Capecitabine
- Epirubicin-Oxaliplatin-Fluorouracil (Esophageal Cancer) Cancer)

Gastric cancer: Epirubicin-Oxaliplatin-Capecitabine

Lymphoma, non-Hodgkin's: DHAP

Lymphoma, non-Hodgkin's: DHAP

Pancreatic cancer: Gemcitabine-Oxaliplatin

Calculations

- Body Surface Area: Adults
- Creatinine Clearance: Adults

Administration: I.V.Administer as I.V. infusion over 2-6 hours. Flush infusion line with D_5W prior to administration of any concomitant medication. Patients should receive an antiemetic premedication regimen. Avoid mucositis prophylaxis with ice chips during oxaliplatin infusion.

StorageStore intact vials at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F); do not freeze. Protect concentrated solution from light (store in original outer carton). According to the manufacturer, solutions diluted for infusion are stable up to 6 hours at room temperature of 20°C to 25°C (68°F to 77°F) or up to 24 hours under refrigeration at 2°C to 8°C (36°F to 46°F). Oxaliplatin solution diluted with D_5W to a final concentration of 0.7 mg/mL (polyolefin container) has been shown to retain >90% of it's original concentration for up to 30 days when stored at room temperature or refrigerated; artificial light did not affect the concentration (Andre, 2007). As this study did not examine sterility, refrigeration would be preferred to limit microbial growth.

Reconstitution

Aqueous solution: **Do not prepare using a chloride-containing solution (eg, NaCl).** Dilution with D_5W (250 or 500 mL) is required prior to administration. Infusion solutions do not require protection from light. Use appropriate precautions for handling and disposal.

Lyophilized powder [CAN; not available in U.S.]: **Do not prepare using a chloride-containing solution (eg, NaCl).** Use only water for injection or D_5W to reconstitute powder. To obtain final concentration of 5 mg/mL add 10 mL of diluent to 50 mg vial or 20 mL diluent to 100 mg vial. Gently swirl vial to dissolve powder. Dilution with D_5W (250 or 500 mL) is required prior to administration. Infusion solutions do not require protection from light. Discard unused portion of vial. Use appropriate precautions for handling and disposal.

Compatibility**Incompatible** with alkaline solutions (eg, fluorouracil) and chloride-containing solutions. Flush infusion line with D_5W prior to, and following, administration of concomitant medications via same I.V. line.

Y-site administration: Compatible: Allopurinol, aminophylline, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, chlorpromazine, cimetidine, cyclophosphamide, dexamethasone, diphenhydramine, dobutamine, docetaxel, dolasetron, dopamine, doxorubicin, droperidol, enalaprilat, epirubicin, etoposide phosphate, famotidine, fentanyl, furosemide, gemcitabine, granisetron, haloperidol lactate, heparin, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, ifosfamide, irinotecan, leucovorin calcium, lorazepam, magnesium sulfate, mannitol, meperidine, mesna, methotrexate, methylprednisolone sodium succinate, metoclopramide, mitoxantrone, morphine, nalbuphine, ondansetron, paclitaxel, palonosetron, potassium chloride, prochlorperazine, promethazine, ranitidine, sodium bicarbonate, theophylline, topotecan, verapamil, vincristine, vinorelbine. **Incompatible:** Diazepam.

ContraindicationsHypersensitivity to oxaliplatin, other platinum-containing compounds, or any component of the formulation

Canadian labeling: Additional contraindications (not in U.S. labeling): Pregnancy, breast-feeding; severe renal impairment (Cl_{cr} <30 mL/minute)

Allergy Considerations

- [Platinum Derivative Allergy]

Warnings/Precautions

Boxed warnings:

- Anaphylaxis: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Anaphylaxis: **[U.S. Boxed Warning]: Anaphylactic/anaphylactoid reactions may occur within minutes of oxaliplatin administration; symptoms may be managed with epinephrine, corticosteroids, and antihistamines.** Allergic reactions may occur with any cycle and may include bronchospasm (rare), erythema, hypotension (rare), pruritus, rash, and/or urticaria.

- Neuropathy: Two different types of peripheral sensory neuropathy may occur: First, an acute (within first 2 days), reversible (resolves within 14 days), with primarily peripheral symptoms that are often exacerbated by cold (may include pharyngolaryngeal dysesthesia); avoid mucositis prophylaxis with ice chips during oxaliplatin infusion; may recur with subsequent doses. Secondly, a more persistent (>14 days) presentation that often interferes with daily activities (eg, writing, buttoning, swallowing), these symptoms may improve upon discontinuing treatment.

- Hepatotoxicity: Hepatotoxicity (including hepatic failure and hepatitis) has been reported. The presence of hepatic vascular disorders (including veno-occlusive disease) should be considered, especially in individuals developing portal hypertension or who present with increased liver function tests.

- Pulmonary fibrosis: May cause pulmonary fibrosis; withhold treatment for unexplained pulmonary symptoms (eg, crackles, dyspnea, nonproductive cough, pulmonary infiltrates) until interstitial lung disease or pulmonary fibrosis are excluded.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; increased toxicity may occur.

Concurrent drug therapy issues:

- Fluorouracil (5-FU): Risk of adverse hematologic effects or adverse GI effects associated with severe diarrhea/emesis (eg, dehydration, hypokalemia, ileus) may be increased with concomitant use of 5-FU.

- Taxane derivatives: When administered as sequential infusions, taxane derivatives (docetaxel, paclitaxel) should be administered before platinum derivatives (carboplatin, cisplatin, oxaliplatin) to limit myelosuppression and enhance efficacy.

Special populations:

- Elderly: Elderly patients are more sensitive to adverse events, particularly diarrhea, dehydration, hypokalemia, leukopenia, fatigue, and syncope.

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorD

Pregnancy ConsiderationsDecreased fetal weight, decreased ossification, and increased fetal deaths were observed in animal studies at one-tenth the equivalent human dose. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid pregnancy and use effective contraception during treatment.

Canadian labeling: Use in pregnant women is contraindicated in the Canadian labeling. Males should be advised not to father children during and for up to 6 months following therapy. May cause permanent infertility in males. Prior to initiating therapy, advise males desiring to father children, to seek counseling on sperm storage.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse ReactionsPercentages reported with monotherapy.

>10%:

Central nervous system: Fatigue (61%), fever (25%), pain (14%), headache (13%), insomnia (11%)

Gastrointestinal: Nausea (64%), diarrhea (46%), vomiting (37%), abdominal pain (31%), constipation (31%), anorexia (20%), stomatitis (14%)

Hematologic: Anemia (64%; grades 3/4: 1%), thrombocytopenia (30%; grades 3/4: 3%), leukopenia (13%)

Hepatic: AST increased (54%; grades 3/4: 4%), ALT increased (36%; grades 3/4: 1%), total bilirubin increased (13%; grades 3/4: 5%)

Neuromuscular & skeletal: Peripheral neuropathy (may be dose limiting; 76%; acute 65%; grades 3/4: 5%; persistent 43%; grades 3/4: 3%), back pain (11%)

Respiratory: Dyspnea (13%), cough (11%)

1% to 10%:

Cardiovascular: Edema (10%), chest pain (5%), peripheral edema (5%), flushing (3%), thromboembolism (2%)

Central nervous system: Dizziness (7%)

Dermatologic: Rash (5%), alopecia (3%), hand-foot syndrome (1%)

Endocrine & metabolic: Dehydration (5%), hypokalemia (3%)

Gastrointestinal: Dyspepsia (7%), taste perversion (5%), flatulence (3%), mucositis (2%), gastroesophageal reflux (1%), dysphagia (acute 1% to 2%)

Genitourinary: Dysuria (1%)

Hematologic: Neutropenia (7%)

Local: Injection site reaction (9%; redness/swelling/pain)

Neuromuscular & skeletal: Rigors (9%), arthralgia (7%)

Ocular: Abnormal lacrimation (1%)

Renal: Serum creatinine increased (5% to 10%)

Respiratory: URI (7%), rhinitis (6%), epistaxis (2%), pharyngitis (2%), pharyngolaryngeal dysesthesia (grades 3/4: 1% to 2%)

Miscellaneous: Allergic reactions (3%); hypersensitivity (includes urticaria, pruritus, facial flushing, shortness of breath, bronchospasm, diaphoresis, hypotension, syncope: grades 3/4: 2% to 3%); hiccup (2%)

<1%, postmarketing, and/or case reports (reported with mono- and combination therapy): Acute renal failure, alkaline phosphatase increased, anaphylactic/anaphylactoid reactions, anaphylactic shock, angioedema, aphonia, ataxia, colitis, cranial nerve palsies, deep tendon reflex loss, deafness, diplopia, dysarthria, dysphonia, eosinophilic pneumonia, extravasation (including necrosis), fasciculations, gait abnormal, hemolysis, hemolytic anemia (immuno-allergic), hemolytic uremia syndrome, hepatic failure, hepatitis, hepatotoxicity, hypertension, hypomagnesemia, ileus, INR increased, interstitial lung diseases, interstitial nephritis (acute), intestinal obstruction, Lhermittes' sign, metabolic acidosis, muscle spasm, myoclonus, necrosis (following extravasation), neutropenic fever, optic neuritis, pancreatitis, perisinusoidal fibrosis, prothrombin time increased, ptosis, pulmonary fibrosis, rhabdomyolysis, seizure, thrombocytopenia (immuno-allergic), trigeminal neuralgia, tubular necrosis (acute), veno-occlusive liver disease (sinusoidal obstruction syndrome and perisinusoidal fibrosis), visual acuity decreased, visual field disturbance

Oncology: VesicantIrritant; cases of extravasation have reported necrosis.

Cool compress may be used for immediate management of extravasation, with consideration of potential for peripheral neuropathy exacerbated by cold. Warm compresses will avoid peripheral neuropathy, however, while possibly increasing drug removal through local vasodilation, may increase cellular uptake and injury.

Oncology: Emetic PotentialModerate-to-high (30% to 90%)

Drug Interactions

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Taxane Derivatives: Platinum Derivatives may enhance the myelosuppressive effect of Taxane Derivatives. Administer Taxane derivative before Platinum derivative when given as sequential infusions to limit toxicity. *Risk D: Consider therapy modification*

Topotecan: Platinum Derivatives may enhance the adverse/toxic effect of Topotecan. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Monitoring ParametersCBC with differential, serum creatinine, liver function tests (including ALT, AST and bilirubin); INR and prothrombin time (in patients on oral anticoagulant therapy); signs of neuropathy, hypersensitivity, and/or respiratory effects; delay dosage until recovery of neutrophils ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L

Nursing: Physical Assessment/MonitoringShould only be administered under the supervision of an experienced cancer chemotherapy physician. Assess potential for interactions with other pharmacological agents. See Administration for infusion specifics. Patient must be observed closely for anaphylactic-like reactions (can occur within minutes of administration; appropriate medications for the treatment of hypersensitivity reactions should be available). Assess for adverse reactions during and between each infusion (eg, pulmonary and hepatic toxicity, neuropathy [acute or persistent], GI disturbance, anemia, chest pain, thromboembolism). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, serum creatinine, liver function tests (including ALT, AST and bilirubin); INR and prothrombin time (in patients on oral anticoagulant therapy); delay dosage until recovery of neutrophils ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L

Patient EducationDo not take any new medication during therapy without consulting prescriber. This medication can only be administered by infusion; you will be monitored closely during and following infusion. Report immediately any pain, burning, or swelling at infusion site or any signs of allergic reaction (eg, respiratory difficulty or swallowing, back pain, chest tightness, rash, hives, swelling of lips or mouth). It is important that you maintain adequate nutrition (small, frequent meals may help) and adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause fatigue, headache, insomnia (use caution when driving or engaging in tasks requiring alertness until response to drug in known); nausea, vomiting, loss of appetite, or taste perversion (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help - if nausea/vomiting is unresolved, consult prescriber for approved antiemetic); mouth sores (use soft toothbrush or cotton swabs for mouth care); diarrhea (boiled milk, buttermilk, or yogurt may help); constipation (increased dietary fluid and fiber may help); or loss of hair (reversible). Report any numbness, pain, tingling, or loss of sensation of extremities; chest pain or palpitations; swelling, pain, or hot areas in legs; unusual fatigue; unusual bruising or bleeding; cough, sore throat, or respiratory difficulty; muscle cramps or twitching; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian availability; not available in U.S.

Injection, solution [preservative free]:

Eloxatin®: 5 mg/mL (10 mL, 20 mL, 40 mL)

Injection, powder for reconstitution [preservative free]:

Eloxatin® [CAN]: 50 mg [contains lactose], 100 mg [contains lactose] [not available in U.S.]

Generic AvailableNo

ManufacturerSanofi-Aventis

Mechanism of ActionOxaliplatin, a platinum derivative, is an alkylating agent. Following intracellular hydrolysis, the platinum compound binds to DNA forming cross-links which inhibit DNA replication and transcription, resulting in cell death. Cytotoxicity is cell-cycle nonspecific.

Pharmacodynamics/Kinetics

Distribution: V_d: 440 L

Protein binding: >90% primarily albumin and gamma globulin (irreversible binding to platinum)

Metabolism: Nonenzymatic (rapid and extensive), forms active and inactive derivatives

Half-life elimination: Terminal: 391 hours; Distribution: Alpha phase: 0.4 hours, Beta phase: 16.8 hours

Excretion: Primarily urine (~54%); feces (~2%)

Pharmacotherapy PearlsCold temperature may exacerbate acute neuropathy. Do not use ice for mucositis prophylaxis.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, dysphagia, mucositis, and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusFatigue is common; may cause insomnia and dizziness

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; use caution with SSRIs. Hematologic side effects are common; use caution with clozapine, carbamazepine, and valproic acid

Index TermsDiaminocyclohexane Oxalatoplatinum; L-OHP; NSC-266046

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International Brand NamesCrisapla (UY); Dacotin (IN); Dacplat (AR); Eloxatin (AU, BE, BG, BR, CH, CL, CN, CR, CZ, DE, DK, DO, EC, EE, ES, FI, GB, GT, HK, HN, ID, IE, IL, IT, KP, MX, MY, NI, NL, NO, PA, PE, PH, SE, SG, SV, TH); Eloxatine (FR, VE); Entia (TH); Henplatin (PH); Liplatin (KP); Olipcis (MX); Oxalip (TH); Oxaltic (AR); Oxaltie (PK); Oxapla (KP); Oxerin (CO); Oxitan (TH); Oxitel (PH); OXP (KP); Rexta (ID); Riptam (MX); Xaliplat (AU, PY)

Oxandrolone

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(oks AN droe lone)

U.S. Brand NamesOxandrin®

Pharmacologic CategoryAndrogen

Use: Labeled IndicationsAdjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who, without definite pathophysiologic reasons, fail to gain or to maintain normal weight; to offset protein catabolism with prolonged corticosteroid administration; relief of bone pain associated with osteoporosis

Dosing: Adults**Weight gain (adjunct):** Oral: 2.5-20 mg in divided doses 2-4 times/day based on individual response; a course of therapy of 2-4 weeks is usually adequate. This may be repeated intermittently as needed.

Dosing: Elderly5 mg twice daily

Dosing: Pediatric**Weight gain (adjunct):** Oral: Children: Total daily dose: ≤0.1 mg/kg **or** ≤0.045 mg/lb

Dosing: Renal ImpairmentCaution is recommended because of the propensity of oxandrolone to cause edema and water retention.

Dosing: Hepatic ImpairmentCaution is advised but there are not specific guidelines for dosage reduction.

RestrictionsC-III

ContraindicationsHypersensitivity to oxandrolone or any component of the formulation; nephrosis; carcinoma of breast or prostate; hypercalcemia; pregnancy

Allergy Considerations

- Androgen Allergy

Warnings/Precautions

Boxed warnings:

- Blood lipid changes: See "Concerns related to adverse effects" below.
- Hepatic effects: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Blood lipid changes: **[U.S. Boxed Warning]: May cause blood lipid changes with increased risk of arteriosclerosis.**
- Hepatic effects: **[U.S. Boxed Warning]: Anabolic steroids may cause peliosis hepatis or liver cell tumors which may not be apparent until liver failure or intra-abdominal hemorrhage develops.** Discontinue in case of cholestatic hepatitis with jaundice or abnormal liver function tests.

Disease-related concerns:

- Breast cancer: Use with caution in patients with breast cancer; may cause hypercalcemia by stimulating osteolysis.
- COPD: Use with caution in patients with COPD.
- Diabetes: Use with caution in patients with diabetes mellitus; monitor carefully.
- Edematous conditions: Use with caution in patients with conditions influenced by edema (eg, cardiovascular disease, migraine, seizure disorder, renal impairment); may cause fluid retention.
- Hepatic impairment: Use with caution in patients with hepatic impairment.

Concurrent drug therapy issues:

- Warfarin: Use caution with concomitant warfarin therapy; warfarin dose may need significantly decreased.

Special populations:

- Elderly: Use with caution in elderly patients, they may be at greater risk for prostatic hyperplasia, fluid retention, and transaminase elevations.
- Pediatrics: May accelerate bone maturation without producing compensatory gain in linear growth in children; in prepubertal children perform radiographic examination of the hand and wrist every 6 months to determine the rate of bone maturation and to assess the effect of treatment on the epiphyseal centers.
- Women: Discontinue with evidence of mild virilization in women.

Pregnancy Risk FactorX

Pregnancy ConsiderationsMasculinization of the fetus has been reported.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Edema

Central nervous system: Depression, excitation, insomnia

Dermatologic: Acne (females and prepubertal males)

Also reported in females: Hirsutism, male-pattern baldness

Endocrine & metabolic: Electrolyte imbalances, glucose intolerance, gonadotropin secretion inhibited, gynecomastia, HDL decreased, LDL increased

Also reported in females: Clitoral enlargement, menstrual irregularities

Genitourinary:

Prepubertal males: Increased or persistent erections, penile enlargement

Postpubertal males: Bladder irritation, epididymitis, impotence, oligospermia, priapism (chronic), testicular atrophy, testicular function inhibited

Hepatic: Alkaline phosphatase increased, ALT increased, AST increased, bilirubin increased, cholestatic jaundice, hepatic necrosis (rare), hepatocellular neoplasms, peliosis hepatis (with long-term therapy)

Neuromuscular & skeletal: CPK increased, premature closure of epiphyses (in children)

Renal: Creatinine excretion increased

Miscellaneous: Bromsulfophthalein retention, habituation, voice alteration (deepening, in females)

Drug Interactions

CycloSPORINE: Androgens may enhance the hepatotoxic effect of CycloSPORINE. Androgens may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Androgens may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Test InteractionsMay suppress factors II, V, VII, and X; may increase PT; may decrease thyroxine-binding globulin and radioactive iodine uptake

Monitoring ParametersLiver function tests, cholesterol profile, hemoglobin/hematocrit; INR/PT in patients on anticoagulant therapy

Children: Radiographs of left wrist every 6 months (to assess bone maturation)

Adult females: Signs of virilization (deepening voice, hirsutism, acne, clitoromegaly); urine and serum calcium in women with breast cancer

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 2.5 mg, 10 mg

Oxandrin®: 2.5 mg, 10 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Oxandrin)

2.5 mg (30): $187.50

10 mg (30): $621.65

Tablets (Oxandrolone)

10 mg (30): $329.97

Mechanism of ActionSynthetic testosterone derivative with similar androgenic and anabolic actions

Pharmacodynamics/KineticsHalf-life elimination: 10-13 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesKicker (KP); Oxandrin (AU); Oxandrolone SPA (IT); Vasorome (JP)

Oxaprozin

Lexi-Drugs Online

English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Daypro® may be confused with Diupres®

Oxaprozin may be confused with oxazepam

Pronunciation(oks a PROE zin)

U.S. Brand NamesDaypro®

Canadian Brand NamesApo-Oxaprozin®; Daypro®

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsAcute and long-term use in the management of signs and symptoms of osteoarthritis and rheumatoid arthritis; juvenile rheumatoid arthritis

Dosing: Adults

Osteoarthritis: Oral: 600-1200 mg once daily; patients should be titrated to lowest dose possible; patients with low body weight should start with 600 mg daily

Rheumatoid arthritis: Oral: 1200 mg once daily; a one-time loading dose of up to 1800 mg/day or 26 mg/kg (whichever is lower) may be given

Maximum doses:

Patient <50 kg: Maximum: 1200 mg/day

Patient >50 kg with normal renal/hepatic function and low risk of peptic ulcer: Maximum: 1800 mg or 26 mg/kg (whichever is lower) in divided doses

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Juvenile rheumatoid arthritis: Oral:

Note: Individualize to lowest effective dose.

Children 6-16 years:

22-31 kg: 600 mg once daily

32-54 kg: 900 mg once daily

≥55 kg: 1200 mg once daily

Dosing: Renal ImpairmentIn general, NSAIDs are not recommended for use in patients with advanced renal disease but the manufacturer of oxaprozin does provide some guidelines for adjustment in renal dysfunction.

Severe renal impairment or on dialysis: 600 mg once daily; may increase cautiously to 1200 mg/day with close monitoring.

Dosing: Hepatic ImpairmentUse caution in patients with severe dysfunction.

StorageStore at 25°C (77°F). Protect from light; keep bottle tightly closed.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to oxaprozin, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.

- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure, anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.

- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.

- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events. Alternate therapies should be considered for patients at high risk.

- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers); concurrent therapy with aspirin, anticoagulants, and/or corticosteroids; smoking; use of alcohol; and the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events. Alternate therapies should be considered for patients at high risk.

- Photosensitivity reactions: May cause mild photosensitivity reactions.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs, even at low doses.

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of the elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not generally effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects, such as confusion, agitation, and hallucination, are generally seen in overdose or high dose situations, but the elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (3rd trimester)

Pregnancy ConsiderationsSafety and efficacy in pregnant women have not been established. Exposure late in pregnancy may lead to premature closure of the ductus arteriosus and may inhibit uterine contractions.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

1% to 10%:

Cardiovascular: Edema

Central nervous system: Confusion, depression, dizziness, headache, sedation, sleep disturbance, somnolence

Dermatologic: Pruritus, rash

Gastrointestinal: Abdominal distress, abdominal pain, anorexia, constipation, diarrhea, flatulence, gastrointestinal ulcer, gross bleeding with perforation, heartburn, nausea, vomiting

Hematologic: Anemia, bleeding time increased

Hepatic: Liver enzyme elevation

Otic: Tinnitus

Renal: Dysuria, renal function abnormal, urinary frequency

<1% (effects reported with oxaprozin or other NSAIDs): Acute interstitial nephritis, acute renal failure, agranulocytosis, alopecia, anaphylaxis, angioedema, anxiety, asthma, blurred vision, bruising, CHF, conjunctivitis, cystitis, dream abnormalities, drowsiness, dyspnea, eosinophilia, erythema multiforme, esophagitis, exfoliative dermatitis, fever, gastritis, GI bleeding, glossitis, hearing decreased, hematemesis, hematuria, hemorrhoidal bleeding, hepatitis, hypersensitivity reaction, hypertension, infection, insomnia, jaundice, leukopenia, liver function abnormalities, malaise, melena, menstrual flow increased/decreased, nephrotic syndrome, nervousness, oliguria, palpitation, pancreatitis, pancytopenia, paresthesia, peptic ulcer, photosensitivity, pneumonia, polyuria, proteinuria, pseudoporphyria, pulmonary infection, purpura, rectal bleeding, renal insufficiency, respiratory depression, sepsis, serum sickness, sinusitis, Stevens-Johnson syndrome, stomatitis, syncope, tachycardia,taste alteration, thrombocytopenia, toxic epidermal necrolysis, tremor, upper respiratory tract infection, vertigo, weakness, weight changes, xerostomia

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Test InteractionsFalse-positive urine immunoassay screening tests for benzodiazepines have been reported and may occur several days after discontinuing oxaprozin.

Monitoring ParametersMonitor CBC; hepatic, renal, and ocular function

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess effectiveness and interactions of other medications patient may be taking. Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically throughout therapy. Schedule ophthalmic evaluations for patients who develop eye complaints during long-term NSAID therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC; hepatic, renal function

Patient EducationTake this medication exactly as directed; do not increase dose without consulting prescriber. Do not crush tablets. Take with food or milk to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol, aspirin or aspirin-containing medication, or any other anti-inflammatory medications without consulting prescriber. You may experience drowsiness, dizziness, or nervousness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); anorexia, nausea, vomiting, or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). GI bleeding, ulceration, or perforation can occur with or without pain. Discontinue medication and contact prescriber if persistent abdominal pain, cramping, or blood in stool occurs. Report vaginal bleeding; breathlessness, respiratory difficulty, or unusual cough; chest pain, rapid heartbeat, palpitations; unusual bruising or bleeding (blood in urine, mouth, or vomitus); swollen extremities; skin rash or itching; acute fatigue; or swelling of face, lips, tongue, or throat. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 600 mg

Generic AvailableYes

ManufacturerSearle

Pricing: U.S. (www.drugstore.com)

Tablets (Daypro)

600 mg (60): $142.76

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Absorption: Almost complete

Protein binding: >99%

Metabolism: Hepatic via oxidation and glucuronidation; no active metabolites

Half-life elimination: 40-50 hours

Time to peak: 2-4 hours

Excretion: Urine (5% unchanged, 65% as metabolites); feces (35% as metabolites)

Related Information

- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness; may rarely cause drowsiness, confusion, insomnia, or depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A meta-analysis (Pope, 1993) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 Heart Failure Guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin's inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

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International Brand NamesDaypro (PK); Dayrun (BG, CZ, EE); Deflam (ZA); Duraprox (BE, CN)

Oxazepam

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Oxazepam may be confused with oxaprozin, quazepam

Serax® may be confused with Eurax®, Urex®, Zyrtec®

International issues:

Murelax® [Australia] may be confused with Miralax™ which is a brand name for polyethylene glycol 3350 in the U.S.

Pronunciation(oks A ze pam)
U.S. Brand NamesSerax®
Canadian Brand NamesApo-Oxazepam®; Bio-Oxazepam; Novoxapram®; Oxpam®; Oxpram®; PMS-Oxazepam; Riva-Oxazepam
Pharmacologic CategoryBenzodiazepine
Use: Labeled IndicationsTreatment of anxiety; management of ethanol withdrawal
Use: Unlabeled/InvestigationalAnticonvulsant in management of simple partial seizures; hypnotic
Dosing: Adults

Anxiety: Oral: 10-30 mg 3-4 times/day

Ethanol withdrawal: Oral: 15-30 mg 3-4 times/day

Hypnotic: Oral: 15-30 mg

Dosing: ElderlyOral: Anxiety: 10 mg 2-3 times/day; increase gradually as needed to a total of 30-45 mg/day. Dose titration should be slow to evaluate sensitivity.
Dosing: Renal ImpairmentNot dialyzable (0% to 5%)
Administration: OralGive orally in divided doses
RestrictionsC-IV
ContraindicationsHypersensitivity to oxazepam or any component of the formulation (cross-sensitivity with other benzodiazepines may exist); narrow-angle glaucoma (not in product labeling, however, benzodiazepines are contraindicated); not indicated for use in the treatment of psychosis; pregnancy
Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension (rare); use with caution in patients with cardiovascular or cerebrovascular disease, or in patients who would not tolerate transient decreases in blood pressure.
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.
- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury.
- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.
- Pediatrics: Safety and efficacy in established in pediatric patients <6 years of age; dose has not been established between 6-12 years of age.

Dosage form specific issues:

- Tartrazine: Serax® 15 mg tablet contains tartrazine.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.
- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsBecause of its relatively short half-life and its lack of active metabolites, oxazepam is recommended for use in the elderly when a benzodiazepine is indicated.
Pregnancy Risk FactorD
LactationEnters breast milk/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Syncope (rare), edema

Central nervous system: Drowsiness, ataxia, dizziness, vertigo, memory impairment, headache, paradoxical reactions (excitement, stimulation of effect), lethargy, amnesia, euphoria

Dermatologic: Rash

Endocrine & metabolic: Decreased libido, menstrual irregularities

Genitourinary: Incontinence

Hematologic: Leukopenia, blood dyscrasias

Hepatic: Jaundice

Neuromuscular & skeletal: Dysarthria, tremor, reflex slowing

Ocular: Blurred vision, diplopia

Miscellaneous: Drug dependence

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Yohimbine: May diminish the therapeutic effect of Antianxiety Agents. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersRespiratory and cardiovascular status
Reference RangeTherapeutic: 0.2-1.4 mcg/mL (SI: 0.7-4.9 µmol/L)
Nursing: Physical Assessment/MonitoringAssess other medications the patient may be taking for effectiveness and interactions. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance; periodically evaluate need for continued use. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and

adverse reactions at beginning of therapy and periodically with long-term use. Can cause CNS depression (dose-related); monitor for sedation, dizziness, confusion, or ataxia which may impair physical and mental capabilities. Be alert to the possibility of suicide ideation. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results. Drug may cause physical and/or psychological dependence. Do not use alcohol or other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); altered sexual drive or ability (reversible); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report persistent CNS effects (eg, confusion, depression, thoughts of suicide, increased sedation, excitation, headache, agitation, insomnia or nightmares, dizziness, fatigue, impaired coordination, changes in personality, or changes in cognition); changes in urinary pattern; muscle cramping, weakness, tremors, or rigidity; ringing in ears or visual disturbances; chest pain, palpitations, or rapid heartbeat; excessive perspiration, excessive GI symptoms (cramping, constipation, vomiting, anorexia); or worsening of condition. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 10 mg, 15 mg, 30 mg

Tablet: 15 mg [contains tartrazine]

Generic AvailableYes: Capsule

Pricing: U.S. (www.drugstore.com)

Capsules (Oxazepam)

10 mg (30): $17.99

15 mg (30): $21.99

30 mg (30): $35.99

Capsules (Serax)

10 mg (30): $32.99

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Absorption: Almost complete

Protein binding: 86% to 99%

Metabolism: Hepatic to inactive compounds (primarily as glucuronides)

Half-life elimination: 2.8-5.7 hours

Time to peak, serum: 2-4 hours

Excretion: Urine (as unchanged drug (50%) and metabolites)

Related Information

- Benzodiazepines
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsNot intended for management of anxieties and minor distresses associated with everyday life. Treatment longer than 4 months should be re-evaluated to determine the patient's need for the drug. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Oxazepam is a short half-life benzodiazepine. Duration of action after a single dose is determined by redistribution rather than metabolism.

Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include personal or family history of substance abuse and personality disorder. Oxazepam undergoes phase II metabolism and, therefore, is less likely to be affected in patients with hepatic dysfunction.

Anesthesia and Critical Care Concerns/Other Considerations Not intended for management of anxieties and minor distresses associated with everyday life; treatment >4 months should be re-evaluated to determine the patient's need for the drug. Chronic use of this agent may increase the perioperative benzodiazepine dose needed to achieve desired effect. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

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International Brand Names Adumbran (AT, DE, GR); Alepam (AU, TW); Alopam (DK, NO); Anastil (VE); Anxiolit (AT, CH, GR); Anxiolit Retard (CH); Durazepam (DE); Enidrel (AR); Medopam (ZA); Murelax (AU); Nesontil (AR); Noripam (ZA); Oksazepam (HR, PL); Opamox (FI); Ox-Pam (NZ); Oxapam (IT); Oxazepam (PL); Oxazepam Efeka (LU); Oxazepam-Eurogenerics (LU); Oxazepam-ratiopharm (LU); Praxiten (AT, GR, HR); Propax (PT); Purata (ZA); Selars (TW); Serefar (UY); Serenal (PT); Serepax (AU, CN, GR, IN, NZ, ZA); Seresta (BE, CH, FR, LU, NL); Simazepan (PY); Sobril (NO, SE); Suxidina (ES); Tranquo (LU); Vaben (IL); Youfei (CL)

OXcarbazepine

Lexi-Drugs Online

English English

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Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

OXcarbazepine may be confused with carBAMazepine

Trileptal® may be confused with TriLipix™

Pronunciation(ox car BAZ e peen)

U.S. Brand NamesTrileptal®

Canadian Brand NamesTrileptal®

Pharmacologic CategoryAnticonvulsant, Miscellaneous

Use: Labeled IndicationsMonotherapy or adjunctive therapy in the treatment of partial seizures in adults and children ≥4 years of age with epilepsy; adjunctive therapy in the treatment of partial seizures in children ≥2 years of age with epilepsy

Use: Unlabeled/InvestigationalBipolar disorder; treatment of neuropathic pain

Dosing: Adults

Adjunctive therapy, partial seizures (epilepsy): Oral: Initial: 300 mg twice daily; dosage may be increased by 600 mg/day at approximate weekly intervals. Recommended daily dose is 1200 mg/day in 2 divided doses. Although daily doses >1200 mg/day were somewhat more efficacious, most patients were unable to tolerate 2400 mg/day (due to CNS effects).

Conversion to monotherapy, partial seizures (epilepsy): Oral: Patients receiving concomitant antiepileptic drugs (AEDs): Initial: 300 mg twice daily while simultaneously reducing the dose of concomitant AEDs. Withdraw concomitant AEDs completely over 3-6 weeks, while increasing the oxcarbazine dose in increments of 600 mg/day at weekly intervals, reaching the maximum oxcarbazine dose (2400 mg/day) in about 2-4 weeks (lower doses have been effective in patients in whom monotherapy has been initiated).

Initiation of monotherapy, partial seizures (epilepsy): Oral: Patients not receiving prior AEDs: 300 mg twice daily (total dose 600 mg/day). Increase dose by 300 mg/day every third day to a dose of 1200 mg/day. Higher dosages (2400 mg/day) have been shown to be effective in patients converted to monotherapy from other AEDs.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Adjunctive treatment, partial seizures (epilepsy): Oral: Children 2-3 years:

Initial: 8-10 mg/kg/day (not to exceed 600 mg/day) given in a twice daily regimen.

Maintenance: The target maintenance dose should be achieved over 2 weeks, and depends on weight of the child:

<20 kg: 600 mg/day in 2 divided doses; consider initiating dose at 16-20 mg/kg/day; maximum maintenance dose should be achieved over 2-4 weeks and should not exceed 60 mg/kg/day

Adjunctive treatment, partial seizures (epilepsy): Oral: Children 4-16 years:

Initial: 8-10 mg/kg/day (not to exceed 600 mg/day) given in a twice daily regimen.

Maintenance: The target maintenance dose should be achieved over 2 weeks, and depends on weight of the child:

20-29 kg: 900 mg/day in 2 divided doses

29.1-39 kg: 1200 mg/day in 2 divided doses

>39 kg: 1800 mg/day in 2 divided doses

Conversion to monotherapy: Children 4-16 years: Oxcarbazepine 8-10 mg/kg/day in twice daily divided doses, while simultaneously initiating the reduction of the dose of the concomitant antiepileptic drug; the concomitant drug should be withdrawn over 3-6 weeks. Oxcarbazepine dose may be increased by a maximum of 10 mg/kg/day at weekly intervals. See below for recommended total daily dose by weight.

Initiation of monotherapy: Children 4-16 years: Oxcarbazepine should be initiated at 8-10 mg/kg/day in twice daily divided doses; doses may be titrated by 5 mg/kg/day every third day. See below for recommended total daily dose by weight.

Range of maintenance doses by weight during monotherapy:

20 kg: 600-900 mg/day

25-30 kg: 900-1200 mg/day

35-40 kg: 900-1500 mg/day

45 kg: 1200-1500 mg/day

50-55 kg: 1200-1800 mg/day

60-65 kg: 1200-2100 mg/day

70 kg: 1500-2100 mg/day

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute: Therapy should be initiated at one-half the usual starting dose (300 mg/day in adults) and increased slowly to achieve the desired clinical response

Dosing: Hepatic ImpairmentAdjustment not needed for mild-to-moderate impairment. No data in patients with severe impairment.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralSuspension: Prior to using for the first time, firmly insert the plastic adapter provided with the bottle. Cover adapter with child-resistant cap when not in use. Shake bottle for at least 10 seconds, remove child-resistant cap, and insert the oral dosing syringe provided to withdraw appropriate dose. Dose may be taken directly from oral syringe or may be mixed in a small glass of water immediately prior to swallowing. Rinse syringe with warm water after use and allow to dry thoroughly. Discard any unused portion after 7 weeks of first opening bottle.

Dietary ConsiderationsMay be taken with or without food.

StorageStore tablets and suspension at 25°C (77°F). Use suspension within 7 weeks of first opening container.

ContraindicationsHypersensitivity to oxcarbazepine or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Use has been associated with CNS-related adverse events, most significant of these were cognitive symptoms including psychomotor slowing, difficulty with concentration, and speech or language problems, somnolence or fatigue, and coordination abnormalities, including ataxia and gait disturbances. Caution patients about performing tasks which require mental alertness (eg, operating machinery or driving).

- Dermatologic reactions: Potentially serious, sometimes fatal, dermatologic reactions (eg, Stevens-Johnson, toxic epidermal necrolysis) have been reported in adults and children; monitor for signs and symptoms of skin reactions; discontinuation and conversion to alternate therapy may be required.

- Hypersensitivity reactions: Rare cases of anaphylaxis and angioedema have been reported, even after initial dosing; permanently discontinue should symptoms occur. Use caution in patients with previous hypersensitivity to carbamazepine (cross-sensitivity occurs in 25% to 30%). Potentially serious, sometimes fatal multiorgan hypersensitivity reactions have also been reported; monitor for signs and symptoms of possible disparate manifestations associated with lymphatic, hepatic, renal, and/or hematologic organ systems; discontinuation and conversion to alternate therapy may be required.

- Hyponatremia: Clinically-significant hyponatremia (sodium <125 mmol/L) can develop during use; monitor serum sodium, particularly during the first 3 months of therapy or in patients at risk for hyponatremia.

Disease-related concerns:

Renal impairment: Single-dose studies show that half-life of the primary active metabolite is prolonged 3-4 fold and AUC is doubled in patients with Cl_{cr} <30 mL/minute; dose adjustment required in these patients.

Concurrent drug therapy issues:

- Oral contraceptives: May reduce the efficacy of oral contraceptives; nonhormonal contraceptive measures are recommended.

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Pediatric: Safety and efficacy in children <2 years of age have not been established.

Other warnings/precautions:

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsStudies in elderly volunteers (60-82 years of age) with both single dose (300 mg) and multiple doses (600 mg/day) reported maximum plasma concentrations and AUC as being 30% to 60% higher than younger volunteers (18-32 years of age). These results were due to differences in creatinine clearance between the two groups. Since elderly may have Cl_{cr} <30 mL/minute, dose reductions may be needed.

Pregnancy Risk FactorC

Pregnancy ConsiderationsOxcarbazepine crosses the human placenta. Teratogenic effects have been observed in animal studies. There are no adequate and well-controlled studies in pregnant women; however, oxcarbazepine is structurally related to carbamazepine (teratogenic in humans); use during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus. Nonhormonal forms of contraception should be used during therapy.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsOxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. A milk-to-plasma concentration ratio of 0.5 was found for both. Because of the potential for serious adverse reactions to oxcarbazepine in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug in nursing women.

Adverse ReactionsAs reported in adults with doses of up to 2400 mg/day (includes patients on monotherapy, adjunctive therapy, and those not previously on AEDs); incidence in children was similar.

>10%:

Central nervous system: Dizziness (22% to 49%), somnolence (20% to 36%), headache (13% to 32%), ataxia (5% to 31%), fatigue (12% to 15%), vertigo (6% to 15%)

Gastrointestinal: Vomiting (7% to 36%), nausea (15% to 29%), abdominal pain (10% to 13%)

Neuromuscular & skeletal: Abnormal gait (5% to 17%), tremor (3% to 16%)

Ocular: Diplopia (14% to 40%), nystagmus (7% to 26%), abnormal vision (4% to 14%)

1% to 10%:

Cardiovascular: Hypotension (1% to 2%), leg edema (1% to 2%)

Central nervous system: Nervousness (2% to 5%), amnesia (4%), abnormal thinking (2% to 4%), insomnia (2% to 4%), speech disorder (1% to 3%), EEG abnormalities (2%), abnormal feelings (1% to 2%), agitation (1% to 2%), confusion (1% to 2%)

Dermatologic: Rash (4%), acne (1% to 2%)

Endocrine & metabolic: Hyponatremia (1% to 3%)

Gastrointestinal: Diarrhea (5% to 7%), dyspepsia (5% to 6%), constipation (2% to 6%), gastritis (1% to 2%), weight gain (1% to 2%)

Neuromuscular & skeletal: Weakness (3% to 6%), back pain (4%), falling down (4%), abnormal coordination (1% to 4%), dysmetria (1% to 3%), sprains/strains (2%), muscle weakness (1% to 2%)

Ocular: Abnormal accommodation (2%)

Respiratory: Upper respiratory tract infection (7%), rhinitis (2% to 5%), chest infection (4%), epistaxis (4%), sinusitis (4%)

Postmarketing and/or case reports (limited to important or life-threatening): Aggressive reaction, amylase increased, anaphylaxis, angioedema, aphasia, asthma, aura, biliary pain, blood in stool, bradycardia, bruising, cardiac failure, cataract, cerebral hemorrhage, chest pain, cholelithiasis, colitis, conjunctival hemorrhage, consciousness decreased, convulsions aggravated, delirium, delusion, duodenal ulcer, dysphagia, dysphonia, dyspnea, dystonia, dysuria, emotional lability, enteritis, erythema multiforme, erythematosus rash, esophagitis, eye edema, extrapyramidal disorder, facial rash, gastric ulcer, GGT increased, gingival bleeding, hematuria, hemianopia, hemiplegia, hematemesis, hot flushes, hyper-/hypoglycemia, hyper-/hypokinesia, hyper-/hyporeflexia, hypersensitivity reaction, hyper-/hypotonia, hypertension, hypocalcemia, hypochondrium pain, hypoesthesia, hypokalemia, hysteria, intermenstrual bleeding, laryngismus, leukopenia, leukorrhea, lipase increased, liver enzymes elevated, maculopapular rash, manic reaction, migraine, menorrhagia, multiorgan hypersensitivity (eosinophilia, arthralgia, rash, fever, lymphadenopathy), muscle contractions (involuntary), mydriasis, neuralgia, oculogyric crisis, otitis externa, palpitation, pancreatitis, panic disorder, paralysis, paroniria, photophobia, photosensitivity reaction, pleurisy, postural hypotension, priapism, purpura, psychosis, ptosis, rectal hemorrhage, renal calculus, renal pain, rigors, scotoma, sialoadenitis, Stevens-Johnson syndrome, stupor, suicidal behavior/ideation, syncope, systemic lupus erythematosus, tachycardia, tetany, thrombocytopenia, toxic epidermal necrolysis, ulcerative stomatitis, urinary tract pain, urticaria, vitiligo, weight loss, xerophthalmia

Metabolism/Transport Effects**Inhibits** CYP2C19 (weak); **Induces** CYP3A4 (strong)

Drug Interactions

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): OXcarbazepine may decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Oral Contraceptive (Progestins): OXcarbazepine may decrease the serum concentration of Oral Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

PHENobarbital: May decrease the serum concentration of OXcarbazepine. *Risk C: Monitor therapy*

Phenytoin: May decrease the serum concentration of OXcarbazepine. OXcarbazepine may increase the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the serum concentration of OXcarbazepine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: St John's wort may decrease oxcarbazepine levels. Avoid evening primrose (seizure threshold decreased). Avoid valerian, St John's wort, kava kava, gotu kola.

Test InteractionsThyroid function tests may depress serum T_4 without affecting T_3 levels or TSH.

Monitoring ParametersSeizure frequency, serum sodium (particularly during first 3 months of therapy), symptoms of CNS depression (dizziness, headache, somnolence). Additional serum sodium monitoring recommended during maintenance treatment in patients receiving other medications known to decrease sodium levels, in patients with signs/symptoms of hyponatremia, and in patients with an increase in seizure frequency or severity.

Nursing: Physical Assessment/MonitoringAssess complete allergy history (carbamazepine). Assess effectiveness and interactions of other medications. Monitor therapeutic effectiveness (seizure activity, frequency, duration, type), laboratory results, and adverse reactions (eg, sedation, CNS changes, visual changes). Monitor for skin reactions. Dosage should be tapered when discontinuing to reduce risk of increased seizures. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse reactions to report. **Note:** Oxcarbazepine may reduce the effectiveness of oral contraceptives; nonhormonal contraception is recommended.

Monitoring: Lab TestsSerum sodium (particularly during first 3 months of therapy); additional serum sodium monitoring is recommended during maintenance treatment in patients receiving other medications known to decrease sodium levels, in patients with signs/symptoms of hyponatremia, and in patients with an increase in seizure frequency or severity.

Patient EducationDo not increase dose or frequency or discontinue without consulting prescriber. While using the medication, do not use alcohol and other prescription or OTC medications (especially medications to relieve pain, induce sleep, reduce anxiety, treat or prevent cold, coughs, or allergies) unless approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (small frequent meals, good mouth care, chewing gum, or sucking hard candy may help, or contact prescriber). Report CNS changes, increase in seizure frequency or severity, mentation changes, suicidal ideation, depression, changes in cognition or memory, persistent fever, acute fatigue or weakness, or insomnia; muscle cramping, weakness, or abdominal pain; rash or skin irritations; unusual bruising or bleeding (mouth, urine, stool); swelling of extremities; or other adverse response. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. **Note:** Oxcarbazepine may reduce the effectiveness of oral contraceptives; nonhormonal contraception is recommended. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, oral:

Trileptal®: 300 mg/5 mL (250 mL) [contains ethanol; packaged with oral syringe]

Tablet: 150 mg, 300 mg, 600 mg

Trileptal®: 150 mg, 300 mg, 600 mg

Generic AvailableYes: Tablet

ManufacturerNovartis Pharmaceuticals Corp

Pricing: U.S. (www.drugstore.com)

Suspension (Trileptal)

300 mg/5 mL (250): $155.23

Tablets (Oxcarbazepine)

150 mg (30): $45.99

300 mg (60): $129.99

600 mg (60): $259.98

Tablets (Trileptal)

150 mg (60): $98.74

300 mg (60): $175.98

600 mg (60): $329.96

Mechanism of ActionPharmacological activity results from both oxcarbazepine and its monohydroxy metabolite (MHD). Precise mechanism of anticonvulsant effect has not been defined. Oxcarbazepine and MHD block voltage-sensitive sodium channels, stabilizing hyperexcited neuronal membranes, inhibiting repetitive firing, and decreasing the propagation of synaptic impulses. These actions are believed to prevent the spread of seizures. Oxcarbazepine and MHD also increase potassium conductance and modulate the activity of high-voltage activated calcium channels.

Pharmacodynamics/Kinetics

Absorption: Complete; food has no affect on rate or extent

Distribution: MHD: V_d: 49 L

Protein binding, serum: MHD: 40%

Metabolism: Hepatic to 10-monohydroxy metabolite (MHD; active); MHD is further glucuronidated or oxidized to a 10,11-dihydroxy metabolite (DHD; inactive)

Bioavailability: Decreased in children <8 years; increased in elderly >60 years

Half-life elimination: Parent drug: 2 hours; MHD: 9 hours; renal impairment (Cl_{cr} 30 mL/minute): MHD: 19 hours

Clearance of MHD is increased in younger children (~80% in children 2-4 years of age) and approaches that of adults by ~13 years of age

Time to peak, serum (median): Tablets: 4.5 hours; oral suspension: 6 hours

Excretion: Urine (95%, <1% as unchanged oxcarbazepine, 27% as unchanged MHD, 49% as MHD glucuronides); feces (<4%)

Related Information

- Anticonvulsants by Seizure Type

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health Comment Oxcarbazepine has been associated with psychomotor slowing, difficulty with concentration, speech or language problems, sedation, ataxia, and gait disturbances. Because this agent is the 10-keto analog of carbamazepine, it is often considered useful for the management of bipolar disorder. However, there is a paucity of research data supporting this usage.

Index TermsGP 47680; OCBZ

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International Brand Names Actinium (MX); Apydan (PL); Deprectal (MX); Lonazet (CO); Neurtrol (TW); Oxetol (MX); Oxrate (IN); Prolepsi (ID); Timox (DE); Trexapin (IL); Trileptal (AE, AR, AT, AU, BE, BG, BH, BO, BR, CH, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EE, EG, ES, FI, GB, GR, GT, HK, HN, ID, IE, IL, IQ, IR, IT, JO, KW, LB, LY, MX, MY, NI, NL, NO, OM, PA, PE, PH, PL, PR, PY, QA, SA, SE, SV, SY, TH, TW, UY, VE, YE); Trileptin (IL)

Oxiconazole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(oks i KON a zole)
U.S. Brand NamesOxistat®
Canadian Brand NamesOxistat®
Pharmacologic CategoryAntifungal Agent, Topical
Use: Labeled IndicationsTreatment of tinea pedis (athlete's foot), tinea cruris (jock itch), tinea corporis (ringworm), and tinea (pityriasis) versicolor
Dosing: Adults

Tinea corporis/tinea cruris: Topical: Cream, lotion: Apply to affected areas 1-2 times daily for 2 weeks

Tinea pedis: Topical: Cream, lotion: Apply to affected areas 1-2 times daily for 1 month

Tinea versicolor: Topical: Cream: Apply to affected areas once daily for 2 weeks

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Tinea corporis, tinea cruris, tinea pedis, tinea versicolor:** Topical: Cream, lotion: Refer to adult dosing.
StorageStore between 15°C to 30°C (59°F to 86°F). Shake lotion well before use.
ContraindicationsHypersensitivity to oxiconazole or any component of the formulation
Allergy Considerations

- Azole Antifungal Allergy

Warnings/Precautions

Concerns related to adverse effects:

• Irritation: Discontinue if sensitivity or irritation occurs

Special population:

Pediatrics: Efficacy has been established in children, however, the occurrence of the approved indications in children <12 years of age is rare

Other warnings/precautions:

• Appropriate use: For topical use only; avoid contact with eyes or vagina

Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate or well-controlled studies in pregnant women.
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsSystemic absorption is low, however, the manufacturer reports that oxiconazole is excreted in breast milk.
Adverse Reactions

1% to 10%:

Dermatologic: Pruritus (<2%)

Local: Burning (≤1%)

<1%: Allergic contact dermatitis, dyshidrotic eczema, erythema, fissure, folliculitis, irritation, maceration, nodules, pain, papules, rash, scaling, stinging, tingling

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream:

Oxistat®: 1% (15 g, 30 g, 60 g) [contains benzoic acid]

Lotion:

Oxistat®: 1% (30 mL) [contains benzoic acid]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Cream (Oxistat)

1% (15): $38.99

1% (30): $62.99

1% (60): $88.99

Lotion (Oxistat)

1% (30): $63.49

Mechanism of ActionThe cytoplasmic membrane integrity of fungi is destroyed by oxiconazole which exerts a fungicidal activity through inhibition of ergosterol synthesis. Effective for treatment of tinea pedis, tinea cruris, tinea corporis, and tinea versicolor. Active against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton violaceum*, *Microsporum canis*, *Microsporum audouinii*, *Microsporum gypseum*, *Epidermophyton floccosum*, *Candida albicans*, and *Malassezia furfur*.

Pharmacodynamics/Kinetics

Absorption: In each layer of the dermis; very little systemically after one topical dose

Distribution: To each layer of the dermis

Excretion: Urine (<0.3%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsOxiconazole Nitrate

International Brand NamesDerimine (JP); Myfungar (DE, MX); Oceral (CH); Okinazole (JP); Oxicone (TW); Oxistat (AR, MX); Oxitrat (BR); Oxizole (TW); Salongo (ES); Zoderm (IN)

Oxprenolol

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English

Jump To Field (Select Field Name)

Pronunciation(ox PREN oh lole)
Canadian Brand NamesTrasicor®
Pharmacologic Category[Beta Blocker, Nonselective]
Use: Labeled IndicationsTreatment of mild or moderate hypertension
Use: Unlabeled/InvestigationalTreatment of nonsevere hypertension in pregnancy (second-line agent)
Dosing: Adults**Hypertension:** Oral:

Initial: 20 mg 3 times/day (regular-release formulation); increase by 60 mg/day (in 3 divided doses) at 1- to 2-week intervals until adequate control is obtained.

Maintenance: 120-320 mg/day; do not exceed 480 mg

Dosing: ElderlyRefer to adult dosing.
StorageStore at 30°C (86°F). Protect from heat.
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to oxprenolol or any component of the formulation; history of allergic rhinitis, asthma, or allergic bronchospasm; sinus bradycardia; greater that first degree AV block; sick sinus syndrome; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; cardiogenic shock; anesthesia with agents that produce myocardial depression; pregnancy (similar agents); breast-feeding
Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Concerns related to adverse events:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.
- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.
- Heart failure (HF): Use with caution in patients with compensated heart failure and monitor for a worsening of the condition.
- Hepatic impairment: Use with caution in patients with severe hepatic insufficiency or inflammatory diseases; increased serum concentrations have been noted.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis.
- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).
- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.
- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.

Pregnancy Risk FactorNot assigned (similar agents rated C/D)
Pregnancy ConsiderationsOxprenolol crosses the placental barrier and may cause bradycardia in the fetus and newborn infants.
LactationEnters breast milk/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: CHF, pulmonary edema, cardiac enlargement, postural hypotension, severe bradycardia, lengthening of PR interval, second-

and third-degree AV block, sinus arrest, palpitation, chest pain; peripheral vascular disorders, Raynaud's phenomenon, claudication, hot flashes, syncope

Central nervous system: Vertigo, lightheadedness, headache, dizziness, anxiety, mental depression, nervousness, irritability, hallucinations, sleep disturbances, nightmares, insomnia, sedation, vivid dreams, slurred speech

Dermatological: Dry skin, rash, pruritus

Endocrine & metabolic: Libido decreased, impotence, weight gain, hypoglycemia

Gastrointestinal: Diarrhea, constipation, flatulence, heartburn, anorexia, nausea, vomiting, abdominal pain, dry mouth

Hematological: Thrombocytopenia, leukopenia

Hepatic: Alkaline phosphatase increased, bilirubin increased, transaminases increased

Neuromuscular & skeletal: Paresthesia, weakness

Ocular: Keratoconjunctivitis, dry eyes, itching eyes, blurred vision

Otic: Tinnitus

Renal: BUN increased

Respiratory: Dyspnea, wheezing, bronchospasm, nasal congestion, status asthmaticus

Miscellaneous: Diaphoresis, exertional tiredness

Metabolism/Transport Effects **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension).

Monitoring ParametersBlood pressure, heart rate; monitor weight and fluid balance; monitor blood glucose closely in patients with diabetes

Monitoring: Lab TestsMonitor blood glucose in patients with diabetes.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet (Trasicor®): 40 mg, 80 mg

Generic AvailableNo

ManufacturerNovartis (Canada)

Mechanism of ActionOxprenolol has a competitive ability to antagonize catecholamine-induced tachycardia at the beta-receptor sites in the heart, thus decreasing cardiac output; inhibits of renin release by the kidneys, and inhibits the vasomotor centers.

Pharmacodynamics/Kinetics

Duration of beta-blocking effects: Immediate-release tablet: 8-12 hours

Absorption: 20% to 70%

Distribution: 1.3 L/kg

Protein binding: 80%

Metabolism: Hepatic first-pass effect

Half-life elimination: 1.3-1.5 hours

Time to peak, serum: Immediate-release tablet: 0.5-1.5 hours

Excretion: Urine (as inactive metabolites, <5% as unchanged drug); major metabolite is glucuronide

Pharmacotherapy PearlsNot available in U.S.

Dental Health: Effects on Dental TreatmentNonselective beta-blockers may enhance the pressor response to epinephrine, resulting in hypertension and bradycardia. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, dizziness, depression, nervousness, irritability, insomnia, hallucinations, sedation, or vivid dreams

Mental Health: Effects on Psychiatric TreatmentConcomitant use with psychotropic agents may produce additive sedative effects

Index TermsOxprenolol Hydrochloride

References

Lang DM, "Anaphylactoid and Anaphylactic Reactions. Hazards of Beta-Blockers," *Drug Saf*, 1995, 12(5):299-304.[PubMed 7669259]

Mokhlesi B, Leikin JB, Murray P, et al, "Adult Toxicology in Critical Care: Part II: Specific Poisonings," *Chest*, 2003, 123(3):897-922. [PubMed

12628894]

Rey E, LeLorier J, Burgess E, et al, "Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic Treatment of Hypertensive Disorders in Pregnancy," *CMAJ*, 1997, 157(9):1245-54. [PubMed 9361646]

Trasicor® product monograph, Novartis Pharmaceuticals Canada Inc, Quebec, 1984 (Rev. March 31, 1999).

International Brand Names Apsolox (GB); Corbeton (AU); Coretal (PL); Paritane (GB); Slow-Trasicor (GB, NZ); Tevacor (IL); Trasicor (AT, BE, CH, DE, DK, ES, FR, GB, HN, HR, HU, IN, IT, LU, NL, NO); Vrachor (GR)

Oxybutynin

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Medication Safety Issues

Sound-alike/look-alike issues:

Oxybutynin may be confused with OxyContin®

Ditropan® may be confused with Detrol®, diazepam, Diprivan®, dithranol

Transdermal patch may contain conducting metal (eg, aluminum); remove patch prior to MRI.

Pronunciation(oks i BYOO ti nin)
U.S. Brand NamesDitropan®; Ditropan® XL; Gelnique™; Oxytrol®
Canadian Brand NamesApo-Oxybutynin®; Ditropan®; Ditropan® XL; Gen-Oxybutynin; Novo-Oxybutynin; Nu-Oxybutyn; Oxytrol®; PMS-Oxybutynin; Riva-Oxybutynin; Uromax®
Pharmacologic CategoryAntispasmodic Agent, Urinary
Use: Labeled IndicationsAntispasmodic for neurogenic bladder (urgency, frequency, urge incontinence)
Dosing: Adults

Bladder spasms:

Oral:

Regular release: 5 mg 2-3 times/day up to maximum of 5 mg 4 times/day

Extended release: Initial: 5-10 mg once daily, adjust dose in 5 mg increments at weekly intervals; maximum: 30 mg daily

Transdermal: Apply one 3.9 mg/day patch twice weekly (every 3-4 days)

Note: Should be discontinued periodically to determine whether the patient can manage without the drug and to minimize resistance to the drug.

Dosing: Elderly

Oral: Regular release: Initial dose: 2.5 mg 2-3 times/day; increase as needed to 5 mg 2-3 times/day

Transdermal: Refer to adult dosing. **Note:** Should be discontinued periodically to determine whether the patient can manage without the drug and to minimize resistance to the drug.

Dosing: Pediatric

Bladder spasms: Oral: Children:

1-5 years (unlabeled use): 0.2 mg/kg/dose 2-4 times/day

>5 years: 5 mg twice daily, up to 5 mg 3 times/day maximum

>6 years: Extended release: 5 mg once daily; adjust dose in 5 mg increments; maximum dose: 20 mg/day

Administration: OralImmediate release tablets and solution should be administered on an empty stomach with water. Extended release tablets may be taken with or without food and must be swallowed whole; do not crush, divide, or chew.
Administration: OtherTransdermal: Apply to clean, dry skin on abdomen, hip, or buttock. Select a new site for each new system (avoid reapplication to same site within 7 days).
Dietary ConsiderationsFood causes a slight delay in the absorption of the oral solution and bioavailability is increased by ~25%. Absorption of the extended release tablet is not affected by food.
StorageStore at controlled room temperature. Protect syrup from light. Keep transdermal patch in sealed pouch.
ContraindicationsHypersensitivity to oxybutynin or any component of the formulation; untreated glaucoma; urinary retention; gastric retention or conditions with severely decreased GI motility
Warnings/Precautions

Concerns related to adverse effects:

- Anticholinergic effects: May cause anticholinergic effects (eg, agitation, confusion, hallucinations, somnolence) which may require dose reduction or discontinuation of therapy.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Heat prostration: May increase the risk of heat prostration.

Disease-related concerns:

- Autonomic neuropathy: Use with caution in patients with autonomic neuropathy; may exacerbate condition.
- Cardiovascular disease: Use with caution in patients with CAD, heart failure, hypertension, and/or cardiac arrhythmias; may exacerbate condition.
- Dementia: Use with caution in patients with dementia; may aggravate symptoms of disease.
- Gastrointestinal disorders: Use with caution in patients with ulcerative colitis, intestinal atony, gastroesophageal reflux or with medications that may exacerbate esophagitis (eg, bisphosphonates). May decrease GI motility; in patients with ulcerative colitis, use may increase risk of paralytic ileus or toxic megacolon.
- Glaucoma: Use with caution in patients with treated angle-closure glaucoma; may exacerbate condition; use is contraindicated with untreated glaucoma.
- Hepatic impairment: Use with caution in patients with hepatic impairment; due to limited experience.
- Hiatal hernia: Use with caution in patients with hiatal hernia.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism; may exacerbate condition.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; may exacerbate condition.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture; may cause urinary retention.
- Renal impairment: Use with caution in patients with renal impairment; due to limited experience. Use caution with bladder outflow obstruction; may increase risk of urinary retention.

Special populations:

- Elderly: Use with caution in the elderly due to anticholinergic activity (eg, confusion, constipation, blurred vision, and tachycardia).

Dosage form specific issues:

- Extended release formulation: The extended release formulation consists of drug within a nondeformable matrix; following drug release/absorption, the matrix/shell is expelled in the stool. The use of nondeformable products in patients with known stricture/narrowing of the GI tract has been associated with symptoms of obstruction.
- Transdermal patch: May contain conducting metal (eg, aluminum); remove patch prior to MRI.

Geriatric ConsiderationsCaution should be used in the elderly due to anticholinergic activity (eg, confusion, constipation, blurred vision, and tachycardia). Start with lower doses. Transdermal dosage form may have less potential for these effects. Oxybutynin may cause memory problems in the elderly. A study of 12 healthy volunteers with an average age of 69 showed cognitive decline while taking the drug (*J Am Geriatr Soc*, 1998, L46:8-13). Studies using transdermal dosage form did not reveal any differences in safety or efficacy between elderly and younger adults.
Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women; use during pregnancy only if clearly needed.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsSuppression of lactation has been reported.
Adverse Reactions

Oral:

>10%:

Central nervous system: Dizziness (4% to 17%), somnolence (2% to 14%)

Gastrointestinal: Xerostomia (29% to 71%; dose related), constipation (7% to 15%), nausea (2% to 12%)

5% to 10%:

Central nervous system: Headache (6% to 10%), pain (4% to 7%), nervousness (1% to 7%), insomnia (1% to 6%)

Gastrointestinal: Diarrhea (7% to 9%), dyspepsia (6% to 7%)

Genitourinary: Urinary hesitation (9%), urinary tract infection (5% to 7%), urinary retention (6%)

Neuromuscular & skeletal: Weakness (3% to 7%)

Ocular: Blurred vision (1% to 10%), dry eyes (3% to 6%)

Respiratory: Rhinitis (2% to 6%)

1% to <5%: Abdominal pain, aptyalism, arrhythmia, arthralgia, asthma, back pain, bronchitis, confusion, convulsion, cough, cystitis, depression, dry skin, dry throat, dysgeusia, dysphagia, dysuria, edema, eructation, extremity pain, eye irritation, fatigue, flank pain, flatulence, fluid retention, flushing, fungal infection, gastrointestinal reflux disease, hoarseness, hyperglycemia, hyper-/hypotension, keratoconjunctivitis sicca, loose stools, nasal congestion, nasal dryness, nasopharyngitis, pain, palpitation, pharyngolaryngeal pain, pollakiuria, pruritus, sinus congestion, sinus headache, thirst, tongue coated, upper respiratory tract infection, vomiting

Postmarketing and/or case reports: Agitation, convulsion, cycloplegia, GI motility decreased, hallucination, impotence, mydriasis, psychotic disorder, rash, sweating decreased, tachycardia

Transdermal:

>10%: Local: Application site reaction (17%), pruritus (14%)

1% to 10%:

Gastrointestinal: Xerostomia (4% to 10%), diarrhea (3%), constipation (3%)

Genitourinary: Dysuria (2%)

Local: Erythema (6% to 8%), vesicles (3%), rash (3%)

Ocular: Vision changes (3%)

Postmarketing and/or case reports: Cardiac arrhythmia, cycloplegia, hallucinations, lactation suppressed, myocarditis, impotence, seizure, sweating decreased, tachycardia

Metabolism/Transport Effects **Substrate** of CYP3A4 (minor); **Inhibits** CYP2C8 (weak), 2D6 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions Ethanol: Use ethanol with caution (may increase CNS depression and toxicity). Watch for sedation.

Test Interactions May suppress the wheal and flare reactions to skin test antigens.

Monitoring Parameters Incontinence episodes, postvoid residual (PVR)

Nursing: Physical Assessment/Monitoring Assess other prescriptions, OTC medications, or herbal products patient may be taking for interactions. Assess voiding pattern, incontinent episodes, frequency, urgency, distention, and urinary retention prior to beginning therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, possible side effects, and symptoms to report.

Patient Education Take prescribed oral dose preferably on an empty stomach, 1 hour before or 2 hours after meals. Swallow extended-release tablets whole; do not chew or crush. You may experience dizziness, lightheadedness, or drowsiness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); dry mouth or changes in appetite (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); constipation (increased exercise, fluids, fruit, fiber, or stool softener may help); decreased sexual ability (reversible with discontinuance of drug); or decreased sweating (use caution in hot weather, avoid extreme exercise or activity). Use alcohol with caution; may increase drowsiness. Report rapid heartbeat, palpitations, or chest pain; difficulty voiding; or vision changes. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Product Availability

Gelnique™: FDA approved January 2009; anticipated availability in second quarter 2009

Gelnique™ is a topical gel for the treatment of overactive bladder.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Syrup, as chloride: 5 mg/5 mL (473 mL)

Ditropan®: 5 mg/5 mL (473 mL)

Tablet, as chloride: 5 mg

Ditropan®: 5 mg

Tablet, extended release, as chloride: 5 mg, 10 mg, 15 mg

Ditropan® XL: 5 mg, 10 mg, 15 mg

Transdermal system:

Oxytrol®: 3.9 mg/day (8s) [39 cm^2; total oxybutynin 36 mg]

Generic Available Yes: Excludes transdermal patch

Pricing: U.S. (www.drugstore.com)

Patch, twice-weekly (Oxytrol)

3.9 mg/24 hrs (8): $123.01

Syrup (Ditropan)

5 mg/5 mL (300): $70.98

Syrup (Oxybutynin Chloride)

5 mg/5 mL (120): $24.99

Tablet, 24-hour (Ditropan XL)

5 mg (30): $112.23

10 mg (30): $109.99

15 mg (30): $115.84

Tablet, 24-hour (Oxybutynin Chloride)

5 mg (100): $289.98

10 mg (100): $292.00

15 mg (100): $299.99

Tablets (Ditropan)

5 mg (60): $62.99

Tablets (Oxybutynin Chloride)

5 mg (60): $13.45

Mechanism of ActionDirect antispasmodic effect on smooth muscle, also inhibits the action of acetylcholine on smooth muscle (exhibits $^1/_5$ the anticholinergic activity of atropine, but is 4-10 times the antispasmodic activity); does not block effects at skeletal muscle or at autonomic ganglia; increases bladder capacity, decreases uninhibited contractions, and delays desire to void, therefore, decreases urgency and frequency

Pharmacodynamics/Kinetics

Onset of action: Oral: 30-60 minutes

Peak effect: 3-6 hours

Duration: 6-10 hours (up to 24 hours for extended release oral formulation)

Absorption: Oral: Rapid and well absorbed; Transdermal: High

Distribution: I.V.: V_d: 193 L

Metabolism: Hepatic via CYP3A4; Oral: High first-pass metabolism (not with I.V. or transdermal use); forms active and inactive metabolites

Bioavailability: Oral: ~6%

Half-life elimination: I.V.: ~2 hours (parent drug), 7-8 hours (metabolites)

Time to peak, serum: Oral: ~60 minutes; Transdermal: 24-48 hours

Excretion: Urine, as metabolites and unchanged drug (<0.1%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause insomnia or dizziness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation and anticholinergic side effects (dry mouth)

Index TermsOxybutynin Chloride

International Brand NamesButyn (PK); Cystrin (GB, PL); Ditropan (AR, AT, AU, BE, CH, CZ, FI, FR, GB, GR, HN, HU, IT, LU, PL, PT, SE, TW); Diutropin (TH); Dridase (DE, NL); Driptane (BG, EE, PH, PL); Frenurin (BR); Gradual (UY); Iliaden (PE); Inprax (MX); Kentera (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Kentera Patch (GB, IE); Lenditro (ZA); Lyrinel (IL, MX, TH); Lyrinel Oros SR (KP); Lyrinel XL (GB); Mutum (EC); Mutum CR (CO, EC); Nefryl (MX); Novitropan (IL); Obutin (SG); Odranal (CN); Oxyban (TW); Oxytrol (NZ); Pollakisu (JP); Reteven (VE); Tavor (MX); Tropan (IN); Urihexal (ZA); Uroflax (PY); Uroxal (HU)

Oxychlorosene

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English

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Pronunciation(oks i KLOR oh seen)

U.S. Brand NamesClorpactin速 WCS-90 [OTC]

Pharmacologic CategoryAntibiotic, Topical

Use: Labeled IndicationsTreatment of localized infections

Dosing: AdultsLocal infections: Topical (0.1% to 0.5% solutions): Apply by irrigation, instillation, spray, soaks, or wet compresses

Dosing: ElderlyRefer to adult dosing.

StorageRefrigerate

ContraindicationsHypersensitivity to oxychlorosene or any component of the formulation; site of infection not exposed to direct contact with the solution

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for solution, as sodium: 2 g

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsOxychlorosene Sodium

Oxycodone and Acetaminophen

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Endocet® may be confused with Indocid®

Percocet® may be confused with Fioricet®, Percodan®

Roxicet™ may be confused with Roxanol™

Tylox® may be confused with Trimox®, Tylenol®, Wymox®, Xanax®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(oks i KOE done & a seet a MIN oh fen)

U.S. Brand NamesEndocet®; Magnacet™; Percocet®; Primalev™; Roxicet™; Roxicet™ 5/500; Tylox®

Canadian Brand NamesEndocet®; Oxycocet®; Percocet®; Percocet®-Demi; PMS-Oxycodone-Acetaminophen

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled IndicationsManagement of moderate-to-severe pain

Use: DentalTreatment of postoperative pain

Dosing: Adults

Note: Initial dose is based on the **oxycodone** content; however, the maximum daily dose is based on the **acetaminophen** content.

Management of pain: Doses should be given every 4-6 hours as needed and titrated to appropriate analgesic effects.

Maximum daily dose, based on acetaminophen content: Oral: 4 g/day.

Mild-to-moderate pain: Oral: Initial dose, **based on oxycodone content:** 2.5-5 mg

Severe pain: Oral: Initial dose, **based on oxycodone content:** 10-30 mg

Dosing: ElderlyDoses should be titrated to appropriate analgesic effects: Oral: Initial dose, **based on oxycodone content:** 2.5-5 mg every 6 hours. Do not exceed 4 g/day of acetaminophen.

Dosing: Pediatric

Note: Initial dose is based on the **oxycodone** content; however, the maximum daily dose is based on the **acetaminophen** content.

Management of pain: Doses should be given every 4-6 hours as needed and titrated to appropriate analgesic effects.

Mild-to-moderate pain: Oral: Initial dose, **based on oxycodone content:** 0.05-0.1 mg/kg/dose

Severe pain: Oral: Initial dose, **based on oxycodone content:** 0.3 mg/kg/dose

Maximum dose, based on acetaminophen content: Oral: Children <45 kg: 90 mg/kg/day; children >45 kg: 4 g/day

Dosing: Hepatic ImpairmentDose should be reduced in patients with severe liver disease.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from moisture.

RestrictionsC-II

ContraindicationsHypersensitivity to oxycodone, acetaminophen, or any component of the formulation; severe respiratory depression (in absence of resuscitative equipment or ventilatory support); pregnancy (prolonged periods or high doses at term)

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Hepatotoxicity: May cause severe hepatic toxicity on acute overdose; in addition, chronic daily dosing in adults has resulted in liver damage in some patients.

- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydrocodone, hydromorphone, levorphanol, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.

- Biliary tract impairment: Use hydrocodone with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.

- CNS depression/coma: Use with caution in patients with CNS depression or coma.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.

- G6PD deficiency: Use with caution in patients with known G6PD deficiency.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Obesity: Use with caution in patients who are morbidly obese.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Psychosis: Use with caution in patients with toxic psychosis.

- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use hydrocodone with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

- Seizures: Use with caution in patients with a history of seizure disorders.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

Dosage form specific issues:

- Sulfites: Some preparations contain sulfites which may cause allergic reactions.

Other warnings/precautions:

- Dosage limit: Limit acetaminophen dose to <4 g/day.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsEnhanced analgesia has been seen in elderly patients on therapeutic doses of narcotics; duration of action may be increased in the elderly. Elderly may be particularly susceptible to the CNS depressant and constipating effects of narcotics. If 1 tablet/dose is used, it may be useful to add an additional 325 mg of acetaminophen to maximize analgesic effect.

Pregnancy Risk FactorC/D (prolonged periods or high doses at term)

Pregnancy ConsiderationsUse of narcotics during pregnancy may produce physical dependence in the neonate; respiratory depression may occur in the newborn if narcotics are used prior to delivery (especially high doses).

LactationEnters breast milk/use caution

Breast-Feeding Considerations

Oxycodone: Excreted in breast milk. If occasional doses are used during breast-feeding, monitor infant for sedation, GI effects, and changes in feeding pattern.

Acetaminophen: May be taken while breast-feeding.

Adverse ReactionsFrequency not defined (also see individual agents): Allergic reaction, constipation, dizziness, dysphoria, euphoria, lightheadedness, nausea, pruritus, respiratory depression, sedation, skin rash, vomiting
Metabolism/Transport Effects

Oxycodone: **Substrate** (minor) of CYP2D6, 3A

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: May have additive CNS depression. In addition, excessive intake of ethanol may increase the risk of acetaminophen-induced hepatotoxicity. Avoid ethanol or limit to <3 drinks/day.
Monitoring ParametersMonitor for pain relief, respiratory and mental status, blood pressure, constipation
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet:

Roxicet™ 5/500: Oxycodone hydrochloride 5 mg and acetaminophen 500 mg

Capsule: 5/500: Oxycodone hydrochloride 5 mg and acetaminophen 500 mg

Tylox®: 5/500: Oxycodone hydrochloride 5 mg and acetaminophen 500 mg [contains sodium benzoate and sodium metabisulfite]

Solution, oral:

Roxicet™: Oxycodone hydrochloride 5 mg and acetaminophen 325 mg per 5 mL (5 mL, 500 mL) [contains alcohol <0.5%]

Tablet: 2.5/325: Oxycodone hydrochloride 2.5 mg and acetaminophen 325 mg; 5/325: Oxycodone hydrochloride 5 mg and acetaminophen 325 mg; 7.5/325: Oxycodone hydrochloride 7.5 mg and acetaminophen 325 mg; 7.5/500: Oxycodone hydrochloride 7.5 mg and acetaminophen 500 mg; 10/325: Oxycodone hydrochloride 10 mg and acetaminophen 325 mg; 10/650: Oxycodone hydrochloride 10 mg and acetaminophen 650 mg

Endocet® 5/325 [scored]: Oxycodone hydrochloride 5 mg and acetaminophen 325 mg

Endocet® 7.5/325: Oxycodone hydrochloride 7.5 mg and acetaminophen 325 mg

Endocet® 7.5/500: Oxycodone hydrochloride 7.5 mg and acetaminophen 500 mg

Endocet® 10/325: Oxycodone hydrochloride 10 mg and acetaminophen 325 mg

Endocet® 10/650: Oxycodone hydrochloride 10 mg and acetaminophen 650 mg

Magnacet™ 2.5/400: Oxycodone hydrochloride 2.5 mg and acetaminophen 400 mg

Magnacet™ 5/400: Oxycodone hydrochloride 5 mg and acetaminophen 400 mg

Magnacet™ 7.5/400: Oxycodone hydrochloride 7.5 mg and acetaminophen 400 mg

Magnacet™ 10/400: Oxycodone hydrochloride 10 mg and acetaminophen 400 mg

Percocet® 2.5/325: Oxycodone hydrochloride 2.5 mg and acetaminophen 325 mg

Percocet® 5/325 [scored]: Oxycodone hydrochloride 5 mg and acetaminophen 325 mg

Percocet® 7.5/325: Oxycodone hydrochloride 7.5 mg and acetaminophen 325 mg

Percocet® 7.5/500: Oxycodone hydrochloride 7.5 mg and acetaminophen 500 mg

Percocet® 10/325: Oxycodone hydrochloride 10 mg and acetaminophen 325 mg

Percocet® 10/650: Oxycodone hydrochloride 10 mg and acetaminophen 650 mg

Primalev™ 2.5/300: Oxycodone hydrochloride 2.5 mg and acetaminophen 300 mg

Primalev™ 5/300: Oxycodone hydrochloride 5 mg and acetaminophen 300 mg

Primalev™ 7.5/300: Oxycodone hydrochloride 7.5 mg and acetaminophen 300 mg

Primalev™ 10/300: Oxycodone hydrochloride 10 mg and acetaminophen 300 mg

Roxicet™ [scored]: Oxycodone hydrochloride 5 mg and acetaminophen 325 mg

Generic AvailableYes: Excludes caplet and solution
Pricing: U.S. (www.drugstore.com)

Capsules (Oxycodone-Acetaminophen)

5-500 mg (20): $15.99

5-500 mg (30): $21.00

Capsules (Tylox)

5-500 mg (20): $41.94

Solution (Roxicet)

5-325 mg/5 mL (470): $43.43

Tablets (Endocet)

5-325 mg (30): $17.99

7.5-325 mg (20): $26.66

7.5-500 mg (20): $26.66

10-325 mg (20): $33.33

10-650 mg (20): $26.66

Tablets (Oxycodone-Acetaminophen)

5-325 mg (20): $11.99

7.5-325 mg (20): $31.99

10-325 mg (20): $40.66

10-650 mg (20): $33.33

Tablets (Percocet)

2.5-325 mg (30): $65.93

5-325 mg (20): $63.00

7.5-325 mg (20): $65.93

7.5-500 mg (20): $73.26

10-325 mg (20): $87.91

10-650 mg (20): $95.24

Tablets (Roxicet)

5-325 mg (20): $9.99

Mechanism of Action

Oxycodone, as with other narcotic (opiate) analgesics, blocks pain perception in the cerebral cortex by binding to specific receptor molecules (opiate receptors) within the neuronal membranes of synapses. This binding results in a decreased synaptic chemical transmission throughout the CNS thus inhibiting the flow of pain sensations into the higher centers. Mu and kappa are the two subtypes of the opiate receptor to which oxycodone binds to cause analgesia.

Acetaminophen inhibits the synthesis of prostaglandins in the CNS and peripherally blocks pain impulse generation; produces antipyresis from inhibition of hypothalamic heat-regulating center.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Acetaminophen
- Narcotic / Opioid Analgesics
- OxyCODONE

Dental Health Professional ConsiderationsOxycodone, as with other narcotic analgesics, is recommended only for limited acute dosing (ie, 3 days or less). Oxycodone has an addictive liability, especially when given long-term. The acetaminophen component requires use with caution in patients with alcoholic liver disease.

Acetaminophen: A study by Hylek, et al, suggested that the combination of acetaminophen with warfarin (Coumadin®) may cause enhanced anticoagulation. The following recommendations have been made by Hylek, et al, and supported by an editorial in *JAMA* by Bell.

Dose and duration of acetaminophen should be as low as possible, individualized and monitored.

For patients who reported taking the equivalent of at least 4 regular strength (325 mg) tablets for longer than a week, the odds of having an INR >6.0 were increased 10-fold above those not taking acetaminophen. Risk decreased with lower intakes of acetaminophen reaching a background level of risk at a dose of 6 or fewer 325 mg tablets per week.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Nausea, sedation, constipation, and xerostomia (normal salivary flow resumes upon discontinuation). See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and fatigue are common. May cause restlessness, nervousness, or confusion; may rarely cause hallucinations, depression, or paradoxical CNS stimulation.

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may cause additive sedation; use lower doses of both agents. Oxycodone may cause severe hypotension after concurrent administration with drugs which compromise vasomotor tone (eg, phenothiazines); monitor blood pressure.

Cardiovascular ConsiderationsOxycodone may cause constipation which may be problematic in patients with unstable angina, and patients after myocardial infarction. The hemodynamic responses to valsalva-like maneuvers due to straining may have adverse cardiovascular consequences in patients with critical coronary artery disease.

Index TermsAcetaminophen and Oxycodone

References

American Pain Society, *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain*, 4th ed, Skokie, IL: American Pain Society, 1999.

Cooper SA, Precheur H, Rauch D, et al, “Evaluation of Oxycodone and Acetaminophen in Treatment of Postoperative Pain,” *Oral Surg Oral Med Oral Pathol*, 1980, 50(6):496-501. [PubMed 7005804]

Dionne RA, “New Approaches to Preventing and Treating Postoperative Pain,” *J Am Dent Assoc*, 1992, 123(6):26-34.

Gobetti JP, “Controlling Dental Pain,” *J Am Dent Assoc*, 1992, 123(6):47-52.

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

Olkkola KT, Hamunen K, and Maunuksela EL, “Clinical Pharmacokinetics and Pharmacodynamics of Opioid Analgesics in Infants and Children,” *Clin Pharmacokinet*, 1995, 28(5):385-404. [PubMed 7614777]

Sinatra RS and Harrison DM, “Oxymorphone in Patient-Controlled Analgesia,” *Clin Pharm*, 1989, 8(8):541, 544. [PubMed 2475287]

“The Management of Chronic Pain in Older Persons. AGS Panel on Chronic Pain in Older Persons, American Geriatric Society,” *Geriatrics*, 1998, 53(Suppl 3):8-24.

International Brand NamesPercocet-5 (IL); Tylenol Oxy (KP)

Oxycodone and Aspirin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Percodan® may be confused with Decadron®, Percocet®, Percogesic®, Periactin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(oks i KOE done & AS pir in)

U.S. Brand NamesEndodan®; Percodan®

Canadian Brand NamesEndodan®; Oxycodan®; Percodan®

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled IndicationsManagement of moderate-to-severe pain

Use: DentalTreatment of postoperative pain

Dosing: Adults**Analgesic:** Oral (based on oxycodone combined salts): Percodan®: 1 tablet every 6 hours as needed for pain; maximum aspirin dose should not exceed 4 g/day.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Analgesic:** Oral (based on oxycodone combined salts): Maximum oxycodone: 5 mg/dose; maximum aspirin dose should not exceed 4 g/day. Doses should be given every 6 hours as needed.

Mild-to-moderate pain: Initial dose, **based on oxycodone content:** 0.05-0.1 mg/kg/dose

Severe pain: Initial dose, **based on oxycodone content:** 0.3 mg/kg/dose

Dosing: Hepatic ImpairmentDose should be reduced in patients with severe liver disease.

Dietary ConsiderationsMay be taken with food or water.

RestrictionsC-II

ContraindicationsHypersensitivity to oxycodone, salicylates, other NSAIDs, or any component of the formulation; patients with the syndrome of asthma, rhinitis, and nasal polyps; inherited or acquired bleeding disorders (including factor VII and factor IX deficiency); do not use in children (<16 years of age) in the presence of viral infections (chickenpox or flu symptoms), with or without fever, due to a potential association with Reye's syndrome; significant respiratory depression; hypercarbia; known or suspected paralytic ileus; acute or severe bronchial asthma; pregnancy (3rd trimester)

Allergy Considerations

- Opioid Allergy/Hypersensitivity
- Salicylate Allergy/Sensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydrocodone, hydromorphone, levorphanol, oxymorphone).
- Salicylate sensitivity: Patients with sensitivity to tartrazine dyes, nasal polyps, and asthma may have an increased risk of salicylate sensitivity.
- Tinnitus: Discontinue use if tinnitus or impaired hearing occurs.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- Bleeding disorders: Use with caution in patients with platelet and bleeding disorders.

- CNS depression/coma: Use with caution in patients with CNS depression or coma.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Ethanol use: Heavy ethanol use (>3 drinks/day) can increase bleeding risks.

- Gastrointestinal disease: Use with caution in patients with erosive gastritis or peptic ulcer disease.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Obesity: Use with caution in patients who are morbidly obese.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Psychosis: Use with caution in patients with toxic psychosis.

- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use hydrocodone with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

- Seizures: Use with caution in patients with a history of seizure disorders.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Surgical patients: ASA should be avoided (if possible) in surgical patients for 1-2 weeks prior to surgery, to reduce the risk of excessive bleeding (except in patients with cardiac stents that have not completed their full course of dual antiplatelet therapy [aspirin, clopidogrel]; patient specific situations need to be discussed with cardiologist; AHA/ACC/SCAI/ACS/ADA Science Advisory provides recommendations).

Other warnings/precautions:

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsEnhanced analgesia has been seen in the elderly patients on therapeutic doses of narcotics; duration of action may be increased. Elderly may be particularly susceptible to the CNS depressant and constipating effects of narcotics. If 1 tablet/dose is used, it may be useful to add an additional 325 mg of aspirin to maximize analgesic effect.

Pregnancy Risk FactorD

Pregnancy ConsiderationsSee individual agents.

LactationEnters breast milk/use caution

Breast-Feeding Considerations

Aspirin: Caution is suggested due to potential adverse effects in nursing infants.

Oxycodone: No data reported.

Adverse Reactions**Note:** Also refer to individual agents

Common (frequency not defined):

Central nervous system: Dizziness, drowsiness, lightheadedness, sedation

Dermatologic: Pruritus

Gastrointestinal: Nausea, vomiting, constipation

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Allergic reaction, anaphylaxis, anaphylactoid reaction, angioedema, apnea, asthma, bradycardia, bronchospasm, circulatory depression, confusion, duodenal ulcer, dysphoria, dyspnea, ecchymosis, euphoria, gastric ulcer, gastrointestinal bleeding, hallucination, hemorrhage, hepatitis, hepatotoxicity, hypotension, hypoglycemia, hyperglycemia, ileus, interstitial nephritis, intestinal obstruction, laryngeal edema, metabolic acidosis, pancreatitis, papillary necrosis, paresthesia, purpura, pulmonary edema, proteinuria, rash, renal failure, respiratory alkalosis, respiratory depression, Reye syndrome, rhabdomyolysis, seizure, shock, thrombocytopenia, tinnitus

Metabolism/Transport Effects

Oxycodone: **Substrate** (minor) of CYP2D6, 3A

Aspirin: **Substrate** of CYP2C9 (minor)

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Test InteractionsMay cross-react with urine tests for cocaine or marijuana.

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Oxycodone hydrochloride 4.5 mg, oxycodone terephthalate 0.38 mg, and aspirin 325 mg

Endodan®, Percodan®: Oxycodone hydrochloride 4.8355 mg and aspirin 325 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Endodan)

4.5-0.38-325 mg (30): $18.99

Tablets (Oxycodone-Aspirin)

4.5-0.38-325 mg (20): $26.66

Tablets (Percodan)

4.5-0.38-325 mg (20): $35.99

Mechanism of Action

Oxycodone, as with other narcotic (opiate) analgesics, blocks pain perception in the cerebral cortex by binding to specific receptor molecules (opiate receptors) within the neuronal membranes of synapses. This binding results in a decreased synaptic chemical transmission throughout the CNS, thus inhibiting the flow of pain sensations into the higher centers. Mu and kappa are the two subtypes of the opiate receptor to which oxycodone binds to cause analgesia.

Aspirin inhibits prostaglandin synthesis by decreasing the activity of the enzyme, cyclooxygenase, which results in decreased formation of prostaglandin precursors, acts on the hypothalamic heat-regulating center to reduce fever, blocks thromboxane synthetase action which prevents formation of the platelet-aggregating substance thromboxane A_2

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Aspirin
- Narcotic / Opioid Analgesics
- OxyCODONE

Dental Health Professional ConsiderationsOxycodone, as with other narcotic analgesics, is recommended only for limited acute dosing (ie, 3 days or less). Oxycodone has an addictive liability, especially when given long-term. The oxycodone with aspirin could have anticoagulant effects and could possibly affect bleeding times.

There is no scientific evidence to warrant discontinuance of aspirin prior to dental surgery. Patients taking one aspirin tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with the physician before removal of the aspirin relative to prevention of postoperative bleeding.

The Food and Drug Administration (FDA), has issued a letter updating information and considerations regarding the use of ibuprofen (400 mg doses) in patients who are taking low dose aspirin (81 mg, immediate release; not enteric coated) for cardioprotection and stroke prevention. Ibuprofen, at these doses, may interfere with aspirin's antiplatelet effect depending upon when it is administered. Patients initiated on aspirin first (for ~1 week) then ibuprofen (400 mg 3 times/day for 10 days) seem to maintain aspirin's platelet effect (Cryer B, 2005). Ibuprofen has the greatest impact on aspirin if administered less than 8 hours before aspirin (Catella-Lawson F, 2001).

Patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. With occasional use of ibuprofen, a clinically-significant interaction with aspirin in unlikely. To avoid interference during chronic dosing, a single dose of ibuprofen should be taken 30-120 minutes after aspirin ingestion or at least 8 hours should elapse after ibuprofen dosing before giving aspirin (FDA, 2006; Catella-Lawson F, 2001).

The clinical implications of the interaction are unclear. There have not been any clinical endpoint studies conducted at this time. Avoidance of this interaction is potentially important because aspirin's vascular protection could be decreased or negated.

Other nonselective NSAIDs may have potential for a similar interaction with aspirin. Such has been described with naproxen (Capone ML, 2005). Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin. Other clinical scenarios (use of smaller ibuprofen doses, other aspirin products, other doses of aspirin) have not been evaluated.

Additional information is available at: http://www.fda.gov/cder/drug/infopage/aspirin/default.htm

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Nausea, sedation, constipation, and xerostomia (normal salivary flow resumes upon discontinuation). May have anticoagulant effects which may affect bleeding time. The elderly are a high-risk population for adverse effects from NSAIDs. As many as 60% of elderly patients with GI complications from NSAIDs can develop peptic ulceration and/or hemorrhage asymptomatically. Concomitant disease and drug use contribute to the risk of GI adverse effects. Enhanced analgesia has been seen with therapeutic doses of narcotics; duration of action may be increased. Elderly may also be particularly susceptible to the CNS depressant effects of narcotics. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and fatigue are common. May cause agitation, anxiety, lethargy, mental impairment, restlessness, nervousness, or confusion; may rarely cause hallucinations, depression, or paradoxical CNS stimulation.

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may cause additive sedation; use lower doses of both agents. Oxycodone may cause severe hypotension after concurrent administration with drugs which compromise vasomotor tone (eg, phenothiazines); monitor blood pressure. May cause GI side effects which may be further exacerbated with concurrent SSRI, lithium, or valproic acid use; monitor. May cause platelet abnormalities which may be further exacerbated with concurrent SSRI use; monitor. Salicylate can displace phenytoin and valproic acid leading to a decrease in phenytoin and an increase in valproic acid levels; monitor.

Index TermsAspirin and Oxycodone

References

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Mokhlesi B, Leikin JB, Murray P, et al, "Adult Toxicology in Critical Care: Part II: Specific Poisonings," *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

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International Brand NamesPercodan (IL)

Oxycodone and Ibuprofen

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(oks i KOE done & eye byoo PROE fen)

U.S. Brand NamesCombunox™

Pharmacologic CategoryAnalgesic, Opioid; Nonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsShort-term (≤7 days) management of acute, moderate-to-severe pain

Use: DentalShort-term (≤3-5 days) management of acute, moderate-to-severe pain

Dosing: Adults**Pain:** Oral: Take 1 tablet every 6 hours as needed (maximum: 4 tablets/24 hours); do not take for longer than 7 days

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsTake with or without food.

StorageStore between 15°C to 30°C (59°F to 86°F).

RestrictionsC-II

A medication guide should be dispensed with each prescription for oral administration. A template for the required MedGuide can be found on the FDA website at http://www.fda.gov/cder/drug/infopage/COX2/NSAIDmedguide.htm

ContraindicationsHypersensitivity to oxycodone, ibuprofen, aspirin, other NSAIDs, or any component of the formulation; patients with suspected paralytic ileus; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery; significant respiratory depression, hypercarbia, acute/severe bronchial asthma

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See "Concerns related to adverse effects" below.
- Coronary artery bypass graft surgery: See "Disease-related concerns" below.
- Gastrointestinal events: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Aseptic meningitis: May increase the risk of aseptic meningitis, especially in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin's cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydrocodone, hydromorphone, levorphanol, oxymorphone).
- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Asthma: Do not administer NSAIDs to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use with caution in patients with other forms of asthma.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure (ICP); exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.
- Obesity: Use with caution in patients who are morbidly obese.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Psychosis: Use with caution in patients with toxic psychosis.
- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.
- Respiratory disease: Use hydrocodone with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages. Opioids may suppress cough reflex; use with caution during postoperative period and in patients with pulmonary disease.
- Seizures: Use with caution in patients with a history of seizure disorders.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) even at low doses.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.
- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsThe elderly are at increased risk for adverse effects from NSAIDs. As many as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. CNS adverse effects, such as confusion, agitation, and hallucination, are generally seen in overdose or high-dose situations; however, elderly patients may demonstrate these adverse effects at lower doses than younger adults. The elderly are also at increased risk of renal toxicity.

Pregnancy Risk FactorC/D (3rd trimester)

Pregnancy Considerations As with other NSAID-containing products, this agent should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus.

Lactation Enters breast milk/contraindicated

Breast-Feeding Considerations Ibuprofen is not transferred to milk in significant quantities and is considered compatible with breast-feeding by AAP. Oxycodone, however, is excreted in breast milk and withdrawal may occur in breast-fed infants when maternal opioid administration is discontinued. Discontinuation of either the opioid-containing medication (Combunox™) or breast-feeding is recommended.

Adverse Reactions

>10%:

Central nervous system: Dizziness (5% to 19%), somnolence (7% to 17%)

Gastrointestinal: Nausea (9% to 25%)

2% to 10%:

Cardiovascular: Vasodilation (<1% to 3%)

Central nervous system: Headache (10%), fever (3%)

Gastrointestinal: Constipation (<1% to 5%), vomiting (5%), diarrhea (2%), dyspepsia (<1% to 2%), flatulence (1%)

Neuromuscular & skeletal: Weakness (3%)

Miscellaneous: Diaphoresis (2%)

<2% (Limited to important or life-threatening): Abdominal enlargement/pain, anemia, amblyopia, anxiety, arthritis, back pain, chest pain, chills, edema, euphoria, hyperkinesias, hypertonia, hypokalemia, hypotension, hypoxia, ileus, infection, LFTs increased, lung disorder, pharyngitis, syncope, rash, tachycardia, taste perversion, thrombophlebitis, urinary retention

Metabolism/Transport Effects

Oxycodone: **Substrate** (minor) of CYP2D6, 3A

Ibuprofen: **Substrate** (minor) of CYP2C9, 2C19; **Inhibits** CYP2C9 (strong)

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy*

modification

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Based on **oxycodone** component:

Ethanol: Avoid or limit ethanol (may increase CNS depression). Watch for sedation.

Based on **ibuprofen** component:

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Food or milk are recommended to decrease gastric irritation.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Monitoring ParametersRespiratory function

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Oxycodone 5 mg and ibuprofen 400 mg

Combunox™: 5/400: Oxycodone 5 mg and ibuprofen 400 mg

Generic AvailableYes

ManufacturerForest Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Combunox)

5-400 mg (20): $39.51

Tablets (Oxycodone-Ibuprofen)

5-400 mg (20): $33.33

Mechanism of Action

Oxycodone: Binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression

Ibuprofen: Reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/KineticsAlso see individual agents.

Absorption: Ibuprofen, oxycodone: rapidly absorbed

Protein binding: Ibuprofen: 99%; Oxycodone: 45%

Metabolism: Oxycodone: Hepatic to metabolites, noroxycodone (major), and oxymorphone (minor)

Bioavailability: Oxycodone: increased with food (25%)

Half-life elimination: Ibuprofen: 1.8-2.6 hours; Oxycodone: 3.1-3.7 hours

Time to peak, serum: Ibuprofen: 1.6-3.1 hours; Oxycodone 1.3-2.1 hours

Excretion: Ibuprofen: Urine (<0.2% unchanged); Oxycodone: Urine (~4 % unchanged)

Dental Health Professional ConsiderationsThe combination of oxycodone and ibuprofen in this dose form is appropriate for the management of moderate-to-severe pain when the concomitant anti-inflammatory action of ibuprofen is desired. Oxycodone is recommended only for limited acute dosing (ie, ≤3 days). Oxycodone has an addictive liability, especially when given long term.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Nausea, sedation, dizziness. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and sedation are common; may cause anxiety or euphoria

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedative effects. Oxycodone may cause severe hypotension after concurrent administration with drugs which compromise vasomotor tone, such as phenothiazines; monitor blood pressure. May cause GI side effects; concomitant use with SSRIs, lithium, valproic acid may produce additive effects; monitor. May cause platelet abnormalities which may be potentiated with concurrent SSRI use; monitor. Ibuprofen component may decrease lithium clearance resulting in an increase in serum lithium levels and potentially lithium toxicity; monitor serum lithium levels.

Index TermsIbuprofen and Oxycodone

OxyCODONE

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

OxyCODONE may be confused with HYDROcodone, OxyContin®, oxymorphone

OxyContin® may be confused with MS Contin®, oxybutynin

OxyFast® may be confused with Roxanol™

Roxicodone® may be confused with Roxanol™

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(oks i KOE done)

U.S. Brand NamesETH-Oxydose™; OxyContin®; OxyFast®; OxyIR®; Roxicodone®

Canadian Brand NamesOxy.IR®; OxyContin®; PMS-Oxycodone; Supeudol®

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled IndicationsManagement of moderate-to-severe pain, normally used in combination with nonopioid analgesics

OxyContin® is indicated for around-the-clock management of moderate-to-severe pain when an analgesic is needed for an extended period of time.

Use: DentalTreatment of postoperative pain

Dosing: Adults**Management of pain:** Oral:

Regular or immediate release formulations: 2.5-5 mg every 6 hours as needed

Controlled release:

Opioid naive: 10 mg every 12 hours

Concurrent CNS depressants: Reduce usual dose by $^{1}/_{3}$ to $^{1}/_{2}$

Conversion from transdermal fentanyl: For each 25 mcg/hour transdermal dose, substitute 10 mg controlled release oxycodone every 12 hours; should be initiated 18 hours after the removal of the transdermal fentanyl patch

Currently on opioids: Use standard conversion chart to convert daily dose to oxycodone equivalent. Divide daily dose in 2 (for twice-daily dosing, usually every 12 hours) and round down to nearest dosage form.

Note: 60 mg, 80 mg, or 160 mg tablets are for use **only** in opioid-tolerant patients. Special safety considerations must be addressed when converting to OxyContin® doses ≥160 mg every 12 hours. Dietary caution must be taken when patients are initially titrated to 160 mg tablets. Using different strengths to obtain the same daily dose is equivalent (eg, four 40 mg tablets, two 80 mg tablets, one 160 mg tablet); all produce similar blood levels.

Multiplication factors for converting the daily dose of current oral opioid to the daily dose of oral oxycodone:

Current opioid mg/day dose x factor = Oxycodone mg/day dose

Codeine mg/day oral dose **x** 0.15 = Oxycodone mg/day dose

Hydrocodone mg/day oral dose **x** 0.9 = Oxycodone mg/day dose

Hydromorphone mg/day oral dose **x** 4 = Oxycodone mg/day dose

Levorphanol mg/day oral dose **x** 7.5 = Oxycodone mg/day dose

Meperidine mg/day oral dose **x** 0.1 = Oxycodone mg/day dose

Methadone mg/day oral dose **x** 1.5 = Oxycodone mg/day dose

Morphine mg/day oral dose **x** 0.5 = Oxycodone mg/day dose

Note: Divide the oxycodone mg/day dose into the appropriate dosing interval for the specific form being used.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricOral: Regular or immediate release formulations:

6-12 years: 1.25 mg every 6 hours as needed

>12 years: 2.5 mg every 6 hours as needed

Dosing: Hepatic ImpairmentReduce dosage in patients with severe liver disease.
Calculations

- Fentanyl Transdermal Conversion
- Opioid Agonist Conversion

Administration: OralDo not crush, break, or chew controlled-release tablets; 60 mg, 80 mg, and 160 mg tablets are for use **only** in opioid-tolerant patients. Do not administer OxyContin® 160 mg tablet with a high-fat meal. Controlled release tablets are not indicated for rectal administration; increased risk of adverse events due to better rectal absorption.
Dietary ConsiderationsInstruct patient to avoid high-fat meals when taking OxyContin® 160 mg tablets.
StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light.
RestrictionsC-II
ContraindicationsHypersensitivity to oxycodone or any component of the formulation; significant respiratory depression; hypercarbia; acute or severe bronchial asthma; OxyContin® is also contraindicated in paralytic ileus (known or suspected); pregnancy (prolonged use or high doses at term)
Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Abuse/misuse/diversion: See "Other warnings/precautions" below.
- Controlled-release tablets: See "Dosage form specific issues" below.

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene-derivative opioid agonists (codeine, hydrocodone, hydromorphone, levorphanol, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenocortical insufficiency: Use with caution in patients with adrenocortical insufficiency, including Addison's disease.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with severe hepatic dysfunction.
- Obesity: Use with caution in patients who are morbidly obese.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Psychosis: Use with caution in patients with toxic psychosis.
- Renal impairment: Use with caution in patients with severe renal dysfunction.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.
- Seizures: Use with caution in patients with a history of seizure disorders.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

Dosage form specific issues:

- Controlled-release tablets: **[U.S. Boxed Warning]: OxyContin® is not intended for use as an "as needed" analgesic or for immediately-postoperative pain management** (should be used postoperatively only if the patient has received it prior to surgery or if severe, persistent pain is anticipated). **[U.S. Boxed Warning]: Do NOT crush, break, or chew controlled-release tablets;** 60 mg, 80 mg, and 160 mg strengths are for use only in opioid-tolerant patients.

- Latex sensitivity: Use the oral concentrate formulation with caution in patients with latex sensitivity; dropper dispenser contains dry, natural rubber.

Other warnings/precautions:

- Abuse/misuse/diversion: **[U.S. Boxed Warning]: Healthcare provider should be alert to problems of abuse, misuse, and diversion.**

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsThe elderly may be particularly susceptible to the CNS depressant and constipating effects of narcotics. Prophylactic use of a laxative should be considered. Serum levels at a given dose may also be increased relative to concentrations in younger patients.

Pregnancy Risk FactorB/D (prolonged use or high doses at term)

Pregnancy ConsiderationsShould be used in pregnancy only if clearly needed. Use of narcotics during pregnancy may produce physical dependence in the neonate; respiratory depression may occur in the newborn if narcotics are used prior to delivery (especially high doses).

LactationEnters breast milk/use caution

Adverse Reactions

>10%:

Central nervous system: Somnolence (23% to 24%), dizziness (13% to 16%)

Dermatologic: Pruritus (12% to 13%)

Gastrointestinal: Nausea (23% to 27%), constipation (23% to 26%), vomiting (12% to 14%)

1% to 10%:

Cardiovascular: Postural hypotension (1% to 5%)

Central nervous system: Headache (7% to 8%), abnormal dreams (1% to 5%), anxiety (1% to 5%), chills (1% to 5%), confusion (1% to 5%), euphoria (1% to 5%), fever (1% to 5%), insomnia (1% to 5%), nervousness (1% to 5%), thought abnormalities (1% to 5%)

Dermatologic: Rash (1% to 5%)

Gastrointestinal: Xerostomia (6% to 7%), abdominal pain (1% to 5%), anorexia (1% to 5%), diarrhea (1% to 5%), dyspepsia (1% to 5%), gastritis (1% to 5%)

Neuromuscular & skeletal: Weakness (6% to 7%), twitching (1% to 5%)

Respiratory: Dyspnea (1% to 5%), hiccups (1% to 5%)

Miscellaneous: Diaphoresis (5% to 6%)

<1% (Limited to important or life-threatening): Agitation, amenorrhea, amnesia, anaphylaxis, anaphylactoid reaction, appetite increased, chest pain, cough, dehydration, depression, dysphagia, dysuria, edema, emotional lability, eructation, exfoliative dermatitis, facial edema, hallucinations, hematuria, histamine release, hyperkinesia, hypoesthesia, hyponatremia, hypotonia, ileus, impotence, intracranial pressure increased, libido decreased, malaise, migraine, paradoxical CNS stimulation, paralytic ileus, paresthesia, pharyngitis, physical dependence, polyuria, psychological dependence, seizure, SIADH, speech disorder, ST segment depression, stomatitis, stupor, syncope, tablet in stool (OxyCodone®), taste perversion, thirst, tinnitus, tremor, urinary retention, urticaria, vasodilation, vertigo, vision change, voice alteration, withdrawal syndrome

Metabolism/Transport Effects**Substrate** (minor) of CYP2D6, 3A

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: When taken with a high-fat meal, peak concentration is 25% greater following a single OxyContin® 160 mg tablet as compared to two 80 mg tablets.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsSome quinolones may produce a false-positive urine screening result for opiates using commercially-available immunoassay kits. This has been demonstrated most consistently for levofloxacin and ofloxacin, but other quinolones have shown cross-reactivity in certain assay kits. Confirmation of positive opiate screens by more specific methods should be considered.

Monitoring ParametersPain relief, respiratory and mental status, blood pressure

Reference RangeBlood level of 5 mg/L associated with fatality

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for additive or adverse interactions. Monitor for effectiveness of pain relief and monitor for signs of overdose. Monitor vital signs, CNS and respiratory status, and degree of sedation at beginning of therapy and at regular intervals with long-term use. May cause physical and/or psychological dependence. For inpatients, implement safety measures. Assess knowledge/teach patient appropriate use (if self-administered). Teach patient to monitor for adverse reactions, adverse reactions to report, and appropriate interventions to reduce side effects.

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. Do not crush or chew controlled-release tablets. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause hypotension, dizziness, drowsiness, impaired coordination, or blurred vision (use caution when driving, climbing stairs, or changing position - rising from sitting or lying to standing, or when engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or dry mouth (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help; if unresolved, consult prescriber about use of stool softeners). The wax matrix from OxyContin® tablets may appear in stool. Report persistent dizziness or headache; excessive fatigue or sedation; changes in mental status; changes in urinary elimination or pain on urination; weakness or trembling; blurred vision; or shortness of breath. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. If you are breast-feeding, take medication immediately after breast-feeding or 3-4 hours prior to next feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, immediate release, as hydrochloride: 5 mg

OxyIR®: 5 mg

Liquid, oral, as hydrochloride [concentrate]:

Roxicodone®: 20 mg/mL (30 mL) [contains sodium benzoate]

Solution, oral, as hydrochloride: 5 mg/5 mL (500 mL)

Roxicodone®: 5 mg/5 mL (5 mL, 500 mL) [contains ethanol]

Solution, oral, as hydrochloride [concentrate]: 20 mg/mL (30 mL)

ETH-Oxydose™: 20 mg/mL (1 mL, 30 mL) [contains sodium benzoate; berry flavor]

OxyFast®: 20 mg/mL (30 mL) [contains natural rubber/natural latex in packaging and sodium benzoate]

Tablet, as hydrochloride: 5 mg, 10 mg, 15 mg, 20 mg, 30 mg

Roxicodone®: 5 mg, 15 mg, 30 mg

Tablet, controlled release, as hydrochloride:

OxyContin®: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 160 mg

Tablet, extended release, as hydrochloride: 10 mg, 20 mg, 40 mg, 80 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Oxycodone HCl)

5 mg (20): $11.99

Capsules (OxyIR)

5 mg (20): $16.66

Concentrate (Oxycodone HCl)

20 mg/mL (20): $22.66

Concentrate (Oxyfast)

20 mg/mL (30): $46.25

Solution (Roxicodone)

5 mg/5 mL (430): $39.99

Tablet, 12-hour (Oxycodone HCl)

10 mg (20): $31.99

20 mg (20): $53.33

80 mg (20): $166.68

Tablet, 12-hour (OxyContin)

10 mg (20): $45.47

20 mg (20): $76.67

40 mg (20): $137.91

80 mg (20): $257.93

Tablets (Oxycodone HCl)

5 mg (20): $16.66

15 mg (20): $17.99

30 mg (20): $24.66

Tablets (Roxicodone)

15 mg (20): $31.60

30 mg (20): $49.99

Mechanism of ActionBinds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression

Pharmacodynamics/Kinetics

Onset of action: Pain relief: 10-15 minutes

Peak effect: 0.5-1 hour

Duration: Immediate release: 3-6 hours; Controlled release: ≤12 hours

Distribution: V_d: 2.6 L/kg; distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, brain, and breast milk

Protein binding: ~45%

Metabolism: Hepatically via CYP3A4 to noroxycodone (has weak analgesic), noroxymorphone, and alpha- and beta-noroxycodol. CYP2D6 mediated metabolism produces oxymorphone (has analgesic activity; low plasma concentrations), alpha- and beta-oxymorphol.

Bioavailability: Controlled release, immediate release: 60% to 87%

Half-life elimination: Immediate release: 2-3 hours; controlled release: ~5 hours

Excretion: Urine (~19% as parent; > 64% as metabolites)

Pharmacotherapy PearlsProphylactic use of a laxative should be considered. OxyContin® 60 mg, 80 mg, and 160 mg tablets are for use in opioid-tolerant patients only.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and dizziness are common; may cause agitation, confusion, amnesia, depression, emotional lability, hallucinations, and malaise

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may cause additive sedation; use lower doses of both agents. Oxycodone may cause severe hypotension after concurrent administration with drugs which compromise vasomotor tone (eg, phenothiazines); monitor blood pressure.

Cardiovascular ConsiderationsOxycodone may cause constipation which may be problematic in patients with unstable angina, and patients after myocardial infarction. The hemodynamic responses to valsalva-like maneuvers due to straining may have adverse cardiovascular consequences in patients with critical coronary artery disease.

Index Terms Dihydrohydroxycodeinone; Oxycodone Hydrochloride

References

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Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

Turturro MA and O'Toole KS, “Oxycodone-Induced Pulmonary Edema,” *Am J Emerg Med*, 1991, 9(2):201-3.[PubMed 1994955]

Zacher JL and Givone DM, “False-Positive Urine Opiate Screening Associated With Fluoroquinolone Use,” *Ann Pharmacother*, 2004, 38:1525-28.[PubMed 15252190]

International Brand Names Endone (AU); Ircodon (KP); Oxicontin (CO); Oxycod (IL); OxyContin (AR, AU, BR, CH, CL, CN, CZ, DK, EC, EE, ES, FI, GB, HN, IE, IL, MY, NL, NO, PE, PY, SE, SG, VE); Oxycontin CR (KP); Oxycontin LP (FR); Oxygesic (DE); Oxynorm (AU, CH, DK, ES, FR, GB, NO, PH, SE, SG); Plexicodim (MX)

Oxygen

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Jump To Field (Select Field Name)

Pronunciation(OKS i jen)

Pharmacologic CategoryDental Gases

Use: Labeled IndicationsTreatment of various clinical disorders, both respiratory and nonrespiratory; relief of arterial hypoxia and secondary complications; treatment of pulmonary hypertension, polycythemia secondary to hypoxemia, chronic disease states complicated by anemia, cancer, migraine headaches, coronary artery disease, seizure disorders, sickle-cell crisis, and sleep apnea

Use: DentalAdministered as a supplement with nitrous oxide to ensure adequate ventilation during sedation; a resuscitative agent for medical emergencies in dental office

Dosing: AdultsChildren and Adults: Average rate of 2 L/minute

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

ContraindicationsNo data reported

Warnings/Precautions

Concerns related to adverse effects:

- Hypoventilation: Oxygen-induced hypoventilation is the greatest potential hazard of oxygen therapy. In patients with severe COPD, the respiratory drive results from hypoxic stimulation of the carotid chemoreceptors. If this hypoxic drive is diminished by excessive oxygen therapy, hypoventilation may occur and further carbon dioxide retention with possible cessation of ventilation.

- Pulmonary fibrosis: Extended exposure to higher O_2 concentrations has been associated with pulmonary fibrosis.

Pregnancy Risk FactorNo data reported

Adverse ReactionsNo data reported

Drug InteractionsNo data reported

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid system with large reservoir holding 75-100 lb of liquid oxygen; compressed gas system consisting of high-pressure tank; tank sizes are "H" (6900 L of oxygen), "E" (622 L of oxygen) and "D" (356 L of oxygen)

Generic AvailableYes

Mechanism of ActionIncreased oxygen in tidal volume and oxygenation of tissues at molecular level

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsLow levels of oxygen may hold promise in the management of patients with heart failure and Cheyne-Stokes breathing.

International Brand NamesOxygenium (PL)

Oxymetazoline

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English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Oxymetazoline may be confused with oxymetholone

Afrin® may be confused with aspirin

Visine® may be confused with Visken®

Pronunciation(oks i met AZ oh leen)
U.S. Brand Names4-Way® 12 Hour [OTC]; Afrin® Extra Moisturizing [OTC]; Afrin® Original [OTC]; Afrin® Severe Congestion [OTC]; Afrin® Sinus [OTC]; Dristan™ 12-Hour [OTC]; Duramist® Plus [OTC]; Duration® [OTC] [DSC]; Genasal [OTC]; Mucinex® Full force™ [OTC]; Mucinex® moisture smart™ [OTC]; Neo-Synephrine® 12 Hour Extra Moisturizing [OTC]; Neo-Synephrine® 12 Hour [OTC]; NRS® [OTC]; Nōstrilla® [OTC]; Vicks Sinex® 12 Hour Ultrafine Mist [OTC]; Vicks Sinex® 12 Hour [OTC]; Vicks® Early Defense™ [OTC]; Visine® L.R. [OTC]
Canadian Brand NamesClaritin® Allergic Decongestant; Dristan® Long Lasting Nasal; Drixoral® Nasal
Pharmacologic CategoryAdrenergic Agonist Agent; Imidazoline Derivative; Vasoconstrictor
Use: Labeled IndicationsAdjunctive therapy of middle ear infections, associated with acute or chronic rhinitis, the common cold, sinusitis, hay fever, or other allergies

Ophthalmic: Relief of redness of eye due to minor eye irritations

Use: DentalSymptomatic relief of nasal mucosal congestion
Dosing: Adults

Nasal congestion: Intranasal (therapy should not exceed 3 days): 0.05% solution: Instill 2-3 sprays into each nostril twice daily

Relief of eye redness: Ophthalmic: 0.025% solution: Instill 1-2 drops in affected eye(s) every 6 hours as needed or as directed by healthcare provider

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Nasal congestion: Intranasal: Children ≥6 years: Refer to adult dosing.

Relief of eye redness: Ophthalmic: Children ≥6 years: 0.025% solution: Instill 1-2 drops in affected eye(s) every 6 hours as needed or as directed by healthcare provider

StorageStore at room temperature.
ContraindicationsHypersensitivity to oxymetazoline or any component of the formulation
Warnings/Precautions

Dosage form specific issues:

- Nasal: Rebound congestion may occur with extended use (>3 days). Prior to self-medication (OTC use), contact healthcare provider in the presence of hypertension, diabetes, hyperthyroidism, heart disease, coronary artery disease, cerebral arteriosclerosis, or long-standing bronchial asthma.

- Ophthalmic: Prior to OTC use, contact healthcare provider in the presence of glaucoma or if needed for >72 hours.

Geriatric ConsiderationsEvaluate the patient's ability to self-administer. Use with caution in patients with cardiovascular disease.
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypertension, palpitation

Local: Transient burning, stinging

Respiratory: Dryness of the nasal mucosa, rebound congestion with prolonged use, sneezing

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Gel, intranasal, as hydrochloride [spray]:

Vicks® Early Defense™: 0.05% (14.7 mL) [microgel; contains benzyl alcohol and menthol]

Solution, intranasal, as hydrochloride [spray]: 0.05% (15 mL, 30 mL)

Afrin® Extra Moisturizing: 0.05% (15 mL) [contains benzyl alcohol and glycerin; regular or no drip formula]

Afrin® Original: 0.05% (15 mL, 30 mL) [contains benzalkonium chloride]

Afrin® Original: 0.05% (15 mL) [contains benzyl alcohol and benzalkonium chloride; no drip formula]

Afrin® Severe Congestion: 0.05% (15 mL) [contains benzyl alcohol and menthol; regular or no drip formula]

Afrin® Sinus: 0.05% (15 mL) [contains benzyl alcohol, benzalkonium chloride, camphor, phenol; regular or no drip formula]

Dristan™ 12-Hour: 0.05% (15 mL) [contains benzyl alcohol and benzalkonium chloride]

Duramist® Plus, Neo-Synephrine® 12 Hour, Nōstrilla®, Vicks Sinex® 12 Hour Ultrafine Mist, Vicks Sinex® 12 Hour, 4-Way® 12 Hour: 0.05% (15 mL) [contains benzalkonium chloride]

Duration®: 0.05% (30 mL) [contains benzalkonium chloride] [DSC]

Genasal, NRS®: 0.05% (15 mL, 30 mL) [contains benzalkonium chloride]

Mucinex® Full force™: 0.05% (22 mL) [contains benzalkonium chloride, camphor, and menthol]

Mucinex® moisture smart™: 0.05% (22 mL) [contains benzalkonium chloride and glycerin]

Neo-Synephrine® 12 Hour Extra Moisturizing: 0.05% (15 mL) [contains glycerin]

Solution, ophthalmic, as hydrochloride:

Visine® L.R.: 0.025% (15 mL, 30 mL) [contains benzalkonium chloride]

Generic AvailableYes: Nasal spray
Mechanism of ActionStimulates alpha-adrenergic receptors in the arterioles of the nasal mucosa to produce vasoconstriction
Pharmacodynamics/Kinetics

Onset of action: Intranasal: 5-10 minutes

Duration: 5-6 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentMay increase toxicity if used with MAO inhibitors (hypertension)
Index TermsOxymetazoline Hydrochloride
International Brand NamesAcatar (PL); Afrazine (GB); Afrin (CO, HK, ID, MX, PE, PL, SG, VE); Alerfrin (ES); Alrin (IL); Aturgyl (FR); Collifrin (MX); Corilisina (ES); Descongestan (ES); Dimetapp 12 Hour Decongestant Spray (AU); Dristan (FI); Dristan Nasal (AR); Drixine (AU, KP, PH); Egarone (ES); Humoxal (ES); Idasal (ES); Iliadin (CL, CN, DK, HK, ID, MX, NO, PE, SE, SG, TH, ZA); Inalintra (ES); Isly (AR); Lidil (AR, UY); Nasavin (PK); Nasex (PT); Nasin (VE); Nasivin (AT, BR, CH, CZ, DE, EC, HN, HU, IT, LU, NL, PL); Nasivion (IN); Nasolina (ES); Nasovalda (ES); Nebulicina (ES); Nesivine (BE); Nezeril (FI, SE); Nosox (PL); Oftinal (ES); Operil (HR); Oxalin (PL); Oximetazolina (MX); Oxylin Liquifilm (MX); Oxymet (TH); Resoxym (BG, PL); Respibien (ES); Respir (ES); Rhinoclir (IL); Rinerge (PK); Rinocorin (ES); Rinodif (ES); Sindecon (TW); Sinex (PL); Tabcin (AR); Utabon (CR, DO, ES, GT, NI, PA, SV); Vicks Sinex (BE, FI, IT, LU); Visine A. D. (MX)

Oxymetholone

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Oxymetholone may be confused with oxymetazoline, oxymorphone

Pronunciation(oks i METH oh lone)

U.S. Brand NamesAnadrol®-50

Pharmacologic CategoryAnabolic Steroid

Use: Labeled IndicationsTreatment of anemias caused by deficient red cell production

Dosing: Adults**Erythropoietic effects:** Oral: 1-5 mg/kg/day in 1 daily dose; maximum: 100 mg/day; give for a minimum trial of 3-6 months because response may be delayed

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Dosing: Hepatic Impairment

Mild-to-moderate hepatic impairment: Oxymetholone should be used with caution in patients with liver dysfunction because of its hepatotoxic potential.

Severe hepatic impairment: Oxymetholone should **not** be used.

StorageStore at 15°C to 30°C (59°F to 86°F).

RestrictionsC-III

ContraindicationsHypersensitivity to oxymetholone or any component of the formulation; breast cancer in men; breast cancer in women with hypercalcemia; prostate cancer; severe liver dysfunction; nephrosis; pregnancy

Allergy Considerations

- Androgen Allergy

Warnings/Precautions

Boxed warnings:

- Blood lipid changes: See “Concerns related to adverse effects” below.
- Hepatic effects: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Blood lipid changes: **[U.S. Boxed Warning]: Anabolic steroids may cause blood lipid changes with increased risk of arteriosclerosis.**
- Hepatic effects: **[U.S. Boxed Warning]: Anabolic steroids may cause peliosis hepatis or liver cell tumors which may not be apparent until liver failure or intra-abdominal hemorrhage develops.**

Disease-related concerns:

- Breast cancer: Use with caution in patients with breast cancer; may cause hypercalcemia by stimulating osteolysis.
- Diabetes: Use with caution in patients with diabetes mellitus; monitor carefully.
- Edematous conditions: Use with caution in patients with conditions influenced by edema (eg, cardiovascular disease, migraine, seizure disorder, renal impairment); may cause fluid retention.
- Hepatic impairment: Use with caution in patients with hepatic disease.

Special populations:

- Elderly: Use with caution in elderly patients, they may be at greater risk for prostatic hyperplasia, fluid retention, and transaminase elevations.
- Pediatrics: May accelerate bone maturation without producing compensatory gain in linear growth in children; in prepubertal children perform radiographic examination of the hand and wrist every 6 months to determine the rate of bone maturation and to assess the effect of treatment on the epiphyseal centers.
- Women: Discontinue with evidence of mild virilization in women.

Geriatric ConsiderationsTheoretically, androgens may increase the risk of prostatic hyperplasia.

Pregnancy Risk FactorX

Pregnancy ConsiderationsOligospermia or amenorrhea may occur resulting in an impairment of fertility.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Coronary artery disease, peripheral edema

Central nervous system: Excitation, insomnia

Dermatologic: Acne (prepubertal males, women), hirsutism (women), hypercalcemia, hyperchloremia, hyperkalemia, hyperphosphatemia, hyperpigmentation, male-pattern baldness (postpubertal males, women)

Endocrine & metabolic: Amenorrhea, cholesterol increased, clitoromegaly, creatinine phosphokinase increased, glucose tolerance decreased, gynecomastia, HDL-cholesterol decreased, hoarseness (women), hypernatremia, impotence (postpubertal males), LDL-cholesterol decreased, libido increased/decreased, menstrual irregularities, oligospermia, phallic enlargement (prepubertal males), priapism (postpubertal males), testicular atrophy (postpubertal males), testicular dysfunction (postpubertal males); virilism (women, high dose); voice deepening (women)

Gastrointestinal: Diarrhea, nausea, vomiting

Genitourinary: Bladder irritability (postpubertal males), epididymitis (postpubertal males), prostatic hyperplasia (elderly males), seminal volume decreased (postpubertal males)

Hematologic: Iron-deficiency anemia, polycythemia, suppression of clotting factors

Hepatic: Cholestatic hepatitis, hepatic necrosis, hepatocellular carcinoma jaundice, liver cell tumors, peliosis hepatis, transaminases increased

Neuromuscular & skeletal: Premature closure of epiphysis (children)

Drug Interactions

CycloSPORINE: Androgens may enhance the hepatotoxic effect of CycloSPORINE. Androgens may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Androgens may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Test InteractionsDecreased thyroxine-binding globulin, T_4; increased resin uptake of T_3 and T_4

Monitoring ParametersLiver function, blood sugars, lipid profile, iron studies, hemoglobin/hematocrit, x-ray of bones every 6 months (prepubertal patients); signs of virilization (females)

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness (according to purpose of use), and adverse response. Caution patients with diabetes to monitor serum glucose closely (may increase the effect of oral hypoglycemic agents). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, adverse reactions may differ according to age/gender of patient). **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to females of childbearing age unless patient is capable of complying with contraceptive use.

Monitoring: Lab TestsLiver function, blood sugars, lipid profile, iron studies, hemoglobin/hematocrit

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Do not donate blood during or for 1 month following therapy. Take as directed. If you have diabetes, monitor serum glucose closely and notify prescriber of significant changes; medication may increase the effect of insulin and oral hypoglycemic agents. May cause nausea or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help) or diarrhea (buttermilk, boiled milk, or yogurt may help). **Males:** Acne, swelling of breasts, loss of libido, impotence. **Females:** Virilism, menstrual irregularity (usually reversible). Report changes in menstrual pattern; enlarged or painful breasts; deepening of voice or unusual growth of body hair; fluid retention (eg, swelling of ankles, feet, or hands, respiratory difficulty, or sudden weight gain); bladder irritability; unresolved CNS changes (eg, nervousness, chills, insomnia); change in color of urine or stool; yellowing of eyes or skin; unusual bruising or bleeding; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. This drug may cause severe fetal defects. Consult prescriber for instruction on appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Anadrol®-50: 50 mg

Generic AvailableNo

Mechanism of ActionEnhances the production and urinary excretion of erythropoietin in patients with anemias due to bone marrow failure; stimulates erythropoiesis in anemias due to deficient red cell production.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesAdroyd (IN); Anapolon (PL); Anasteronal (ES); Androlic (TH); Hemogenin (BR); Oxitosona (ES); Roboral (IL); Synasteron (BE); Zenalosyn (NL)

Oxymorphone

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Oxymorphone may be confused with oxycodone, oxymetholone

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(oks i MOR fone)

U.S. Brand NamesOpana®; Opana® ER

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled Indications

Parenteral: Management of moderate-to-severe pain and preoperatively as a sedative and/or supplement to anesthesia

Oral, regular release: Management of moderate-to-severe pain

Oral, extended release: Management of moderate-to-severe pain in patients requiring around-the-clock opioid treatment for an extended period of time

Dosing: AdultsAnalgesia: **Note:** Dosage must be individualized.

I.M., SubQ: Initial: 1-1.5 mg; may repeat every 4-6 hours as needed

Labor analgesia: I.M.: 0.5-1 mg

I.V.: Initial: 0.5 mg

Oral:

Immediate release:

Opioid-naive: 10-20 mg every 4-6 hours as needed. Initial dosages as low as 5 mg may be considered in selected patients and/or patients with renal impairment. Dosage adjustment should be based on level of analgesia, side effects, and pain intensity. Initiation of therapy with initial dose >20 mg is **not** recommended.

Currently on stable dose of parenteral oxymorphone: ~10 times the daily parenteral requirement. The calculated amount should be divided and given in 4-6 equal doses.

Currently on other opioids: Use standard conversion chart to convert daily dose to oxymorphone equivalent. Generally start with $^1/_2$ the calculated daily oxymorphone dosage and administered in divided doses every 4-6 hours.

Extended release (Opana® ER):

Opioid-naive: Initial: 5 mg every 12 hours. Supplemental doses of immediate-release oxymorphone may be used as “rescue” medication as dosage is titrated.

Note: Continued requirement for supplemental dosing may be used to titrate the dose of extended-release continuous therapy. Adjust therapy incrementally, by 5-10 mg every 12 hours at intervals of every 3-7 days. Ideally, basal dosage may be titrated to generally mild pain or no pain with the regular use of fewer than 2 supplemental doses per 24 hours.

Currently on stable dose of parenteral oxymorphone: Approximately 10 times the daily parenteral requirement. The calculated amount should be given in 2 divided doses (every 12 hours).

Currently on opioids: Use conversion chart (see Note below) to convert daily dose to oxymorphone equivalent. Generally start with $^1/_2$ the calculated daily oxymorphone dosage. Divide daily dose in 2 (for every 12-hour dosing) and round down to nearest dosage form. **Note:** Per manufacturer, the following approximate oral dosages are equivalent to oxymorphone 10 mg:

Hydrocodone 20 mg

Oxycodone 20 mg

Methadone 20 mg

Morphine 30 mg

Conversion of stable dose of immediate-release oxymorphone to extended-release oxymorphone: Administer $^1/_2$ of the daily dose of immediate-release oxymorphone (Opana®) as the extended-release formulation (Opana® ER) every 12 hours

Dosing: ElderlyRefer to adult dosing. **Note:** Initiate dosing at the lower end of the dosage range.

Dosing: Renal ImpairmentCl_{cr} <50 mL/minute: Reduce initial dosage of oral formulations (bioavailability increased 57% to 65%). Begin therapy at lowest dose and titrate carefully.

Dosing: Hepatic ImpairmentGenerally, contraindicated for use in patients with moderate-to-severe liver disease. Initiate with lowest possible dose and titrate slowly in mild impairment.

Administration: I.V. DetailpH: 2.7-4.5

Administration: OralAdminister immediate release and extended release tablets 1 hour before or 2 hours after eating. Opana® ER tablet should be swallowed; do not break, crush, or chew.

Dietary ConsiderationsImmediate release and extended release tablets should be taken 1 hour before or 2 hours after eating.

StorageInjection solution, tablet: Store at 15°C to 30°C (59°F to 86°F).

Compatibility**Compatibility in syringe: Compatible:** Glycopyrrolate, hydroxyzine, ranitidine.

RestrictionsC-II

ContraindicationsHypersensitivity to oxymorphone, other morphine analogs (phenanthrene derivatives), or any component of the formulation; paralytic ileus (known or suspected); increased intracranial pressure; moderate-to-severe hepatic impairment; severe respiratory depression (unless in monitored setting with resuscitative equipment); acute/severe bronchial asthma; hypercarbia; pregnancy (prolonged use or high doses at term).

Note: Injection formulation is also contraindicated in the treatment of upper airway obstruction and pulmonary edema due to a chemical respiratory irritant.

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Abuse/misuse/diversion: See “Other warnings/precautions” below.
- Opana® ER: See “Dosage form specific issues” below.

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or with drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene-derivative opioid agonists (codeine, hydrocodone, hydromorphone, levorphanol, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with mild hepatic dysfunction; use is contraindicated in moderate-to-severe impairment.
- Obesity: Use with caution in patients who are morbidly obese.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Opana® ER: **[U.S. Boxed Warnings]: Opana® ER is an extended release oral formulation of oxymorphone and is not suitable for use as an "as needed" analgesic. Tablets should not be broken, chewed, dissolved, or crushed; tablets should be swallowed whole.** Opana® ER is intended for use in long-term, continuous management of moderate-to-severe chronic pain. It is not indicated for use in the immediate postoperative period (12-24 hours). **[U.S. Boxed Warning]: The coingestion of ethanol or ethanol-containing medications with Opana® ER may result in accelerated release of drug from the dosage form, abruptly increasing plasma levels, which may have fatal consequences.**

Other warnings/precautions:

- Abuse/misuse/diversion: **[U.S. Boxed Warning]: Healthcare provider should be alert to problems of abuse, misuse, and diversion.**

- Optimal regimen: An opioid-containing analgesic regimen should be tailored to each patient's needs and based upon the type of pain being treated (acute versus chronic), the route of administration, degree of tolerance for opioids (naive versus chronic user), age, weight, and medical condition. The optimal analgesic dose varies widely among patients; doses should be titrated to pain relief/prevention.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsElderly may be particularly susceptible to the CNS depressant and constipating effects of narcotics. Plasma levels of oxymorphone were about 40% higher in elderly patients as compared to younger patients.

Pregnancy Risk FactorC/D (prolonged use or high doses at term)

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies, however, decreased fetal weight, decreased litter size, increased stillbirths, and increased neonatal death were noted. Chronic opioid use during pregnancy may lead to a withdrawal syndrome in the neonate. Symptoms include irritability, hyperactivity, loss of sleep pattern, abnormal crying, tremor, vomiting, diarrhea, weight loss, or failure to gain weight. Opioid analgesics are considered pregnancy risk factor D if used for prolonged periods or in larger doses near term.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, cardiac shock, flushing, hypotension, orthostatic hypotension, palpitation, peripheral vasodilation, shock, tachycardia

Central nervous system: Agitation, amnesia, anorexia, anxiety, CNS depression, coma, confusion, convulsion, dizziness, drowsiness, dysphoria, euphoria, fatigue, fever, hallucinations, headache, insomnia, intracranial pressure increased, malaise, mental depression, mental impairment, nervousness, restlessness, paradoxical CNS stimulation

Dermatologic: Pruritus, urticaria, rash

Endocrine & metabolic: Antidiuretic hormone release, weight loss

Gastrointestinal: Abdominal pain, appetite depression, biliary tract spasm, constipation, dehydration, dry mouth, dyspepsia, flatulence, nausea, paralytic ileus, stomach cramps, vomiting, xerostomia

Genitourinary: Urination decreased, urinary retention, urinary tract spasm

Local: Pain/reaction at injection site

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision, diplopia, miosis

Renal: Oliguria

Respiratory: Apnea, bronchospasm, cyanosis, dyspnea, hypoventilation, laryngeal edema, laryngeal spasm, respiratory depression

Miscellaneous: Diaphoresis, histamine release, physical and psychological dependence

Oncology: VesicantNo

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression). Ethanol ingestion with extended-release tablets is specifically contraindicated due to possible accelerated release and potentially fatal overdose.

Food: When taken orally with a high-fat meal, peak concentration is 38% to 50% greater. Both immediate-release and extended-release tablets should be taken 1 hour before or 2 hours after eating.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsSome quinolones may produce a false-positive urine screening result for opiates using commercially-available immunoassay kits. This has been demonstrated most consistently for levofloxacin and ofloxacin, but other quinolones have shown cross-reactivity in certain assay kits. Confirmation of positive opiate screens by more specific methods should be considered. May cause elevation in amylase (due to constriction of the sphincter of Oddi).

Monitoring ParametersRespiratory rate, heart rate, blood pressure, CNS activity

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for additive or adverse interactions. Monitor therapeutic effectiveness, adverse reactions, and signs of overdose at beginning of therapy and at regular intervals with long-term use. Monitor blood pressure, CNS and respiratory status, and degree of sedation. May cause physical and/or psychological dependence. For inpatients, implement safety measures. Assess knowledge/teach patient appropriate use (if self-administered). Teach patient to monitor for adverse reactions, adverse reactions to report, and appropriate interventions to reduce side effects.

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency or discontinue this medicine without consulting prescriber. Drug may cause physical and/or psychological dependence. Do not break, chew, dissolve, or crush extended release tablets. Swallow whole. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause hypotension, dizziness, drowsiness, impaired coordination, or blurred vision (use caution when driving, climbing stairs, or changing position - rising from sitting or lying to standing, or when engaging in tasks requiring alertness until response to drug is known); nausea, vomiting or dry mouth (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help; if unresolved, consult prescriber about use of stool softeners). Report persistent dizziness or headache; excessive fatigue or sedation; changes in mental status; changes in urinary elimination or pain on urination; weakness or trembling; blurred vision; or shortness of breath. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride:

Opana®: 1 mg/mL (1 mL)

Tablet, as hydrochloride:

Opana®: 5 mg, 10 mg

Tablet, extended release, as hydrochloride:

Opana®: ER: 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablet, 12-hour (Opana ER)

5 mg (20): $39.99

7.5 mg (20): $49.99

10 mg (20): $69.33

15 mg (20): $89.99

20 mg (20): $124.79

30 mg (20): $169.99

Tablets (Opana)

5 mg (20): $61.53

Mechanism of ActionOxymorphone hydrochloride (Numorphan®) is a potent narcotic analgesic with uses similar to those of morphine. The drug is a semisynthetic derivative of morphine (phenanthrene derivative) and is closely related to hydromorphone chemically (Dilaudid®).

Pharmacodynamics/Kinetics

Onset of action: Parenteral: 5-10 minutes

Duration: Analgesic: Parenteral: 3-6 hours

Distribution: V_d: I.V.: 1.94-4.22 L/kg

Protein binding: 10% to 12%

Metabolism: Hepatic via glucuronidation to active and inactive metabolites

Bioavailability: Oral: 10%

Half-life elimination: Oral: Immediate release: 7-9 hours; Extended release: 9-11 hours

Excretion: Urine (<1% as unchanged drug); feces

Related Information

- Narcotic / Opioid Analgesics

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Anticholinergic side effects can cause a reduction of saliva production or secretion, contributing to discomfort and dental disease (ie, caries, oral candidiasis, and periodontal disease).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and dizziness are common; may cause nervousness, restlessness or confusion; may rarely cause depression or hallucinations

Mental Health: Effects on Psychiatric TreatmentPsychotropics may alter the analgesic effects of opioids; monitor for change in pain relief

Cardiovascular ConsiderationsOxymorphone may cause constipation which may be problematic in patients with unstable angina, and patients after myocardial infarction. The hemodynamic responses to valsalva-like maneuvers due to straining may have adverse cardiovascular consequences in patients with critical coronary artery disease.

Index TermsOxymorphone Hydrochloride

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Oxytocin

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Pitocin® may be confused with Pitressin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(oks i TOE sin)

U.S. Brand NamesPitocin®

Canadian Brand NamesPitocin®; Syntocinon®

Pharmacologic CategoryOxytocic Agent

Use: Labeled IndicationsInduction of labor at term; control of postpartum bleeding; adjunctive therapy in management of abortion

Dosing: Adults**Note:** I.V. administration requires the use of an infusion pump.

Induction of labor: I.V.: 0.5-1 milliunits/minute; gradually increase dose in increments of 1-2 milliunits/minute until desired contraction pattern is established; dose may be decreased after desired frequency of contractions is reached and labor has progressed to 5-6 cm dilation. Infusion rates of 6 milliunits/minute provide oxytocin levels similar to those at spontaneous labor; rates >9-10 milliunits/minute are rarely required.

Postpartum bleeding:

I.M.: Total dose of 10 units after delivery

I.V.: 10-40 units by I.V. infusion in 1000 mL of intravenous fluid at a rate sufficient to control uterine atony

Adjunctive treatment of abortion: I.V.: 10-20 milliunits/minute; maximum total dose: 30 units/12 hours

Administration: I.V.Refer to Reconstitution for dilution information. An infusion pump is required for administration.

StorageStore oxytocin at 2°C to 8°C (36°F to 46°F); do not freeze. Pitocin® may also be stored at 15°C to 25°C (59°F to 77°F) for up to 30 days.

ReconstitutionI.V.

Induction or stimulation of labor: Add oxytocin 10 units to NS or LR 1000 mL to yield a solution containing oxytocin 10 milliunits/mL. Rotate solution to mix.

Postpartum uterine bleeding: Add oxytocin 10-40 units to running I.V. infusion; maximum: 40 units/1000 mL.

Adjunctive management of abortion: Add oxytocin 10 units to 500 mL of a physiologic saline solution or D_5W.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, ${}^1/_2NS$, NS.

Y-site administration: Compatible: Heparin, hydrocortisone sodium succinate, insulin (regular), meperidine, morphine, potassium chloride, vitamin B complex with C, warfarin.

Compatibility when admixed: Compatible: Chloramphenicol, metaraminol, sodium bicarbonate, thiopental, verapamil. **Incompatible:** Fibrinolysin (human), norepinephrine, prochlorperazine edisylate, warfarin. **Variable (consult detailed reference):** Phytonadione.

ContraindicationsHypersensitivity to oxytocin or any component of the formulation; significant cephalopelvic disproportion; unfavorable fetal positions; fetal distress; hypertonic or hyperactive uterus; contraindicated vaginal delivery (invasive cervical cancer, active genital herpes, prolapse of the cord, cord presentation, total placenta previa, or vasa previa)

Warnings/Precautions

Boxed warnings:

- Appropriate use: See "Other warnings/precautions" below.

Concerns related to adverse effects:

- Antidiuretic effect: May produce antidiuretic effect (ie, water intoxication and excess uterine contractions).

- Uterine effects: High doses or hypersensitivity to oxytocin may cause uterine hypertonicity, spasm, tetanic contraction, or rupture of the uterus.

- Water intoxication: Severe water intoxication with convulsions, coma, and death is associated with a slow oxytocin infusion over 24 hours.

Other warnings/precautions:

- Appropriate use: **[U.S. Boxed Warning]: To be used for medical rather than elective induction of labor.**

Pregnancy Risk FactorX

Pregnancy Considerations**[U.S. Boxed Warning]: To be used for medical rather than elective induction of labor.** Reproduction studies have not been conducted. When used as indicated, teratogenic effects would not be expected. Nonteratogenic adverse reactions are reported in the neonate as well as the mother.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsEndogenous levels of oxytocin naturally increase during breast-feeding.

Adverse ReactionsFrequency not defined.

Fetus or neonate:

Cardiovascular: Arrhythmias (including premature ventricular contractions), bradycardia

Central nervous system: Brain or CNS damage (permanent), neonatal seizure

Hepatic: Neonatal jaundice

Ocular: Neonatal retinal hemorrhage

Miscellaneous: Fetal death, low Apgar score (5 minute)

Mother:

Cardiovascular: Arrhythmias, hypertensive episodes, premature ventricular contractions

Gastrointestinal: Nausea, vomiting

Genitourinary: Pelvic hematoma, postpartum hemorrhage, uterine hypertonicity, tetanic contraction of the uterus, uterine rupture, uterine spasm

Hematologic: Afibrinogenemia (fatal)

Miscellaneous: Anaphylactic reaction, subarachnoid hemorrhage

Drug Interactions

Dinoprostone: May enhance the therapeutic effect of Oxytocin. *Risk D: Consider therapy modification*

Misoprostol: May enhance the therapeutic effect of Oxytocin. *Risk D: Consider therapy modification*

Monitoring ParametersFluid intake and output during administration; fetal monitoring

Nursing: Physical Assessment/MonitoringMonitor blood pressure, fluid intake and output, and labor closely if using oxytocin for induction; fetal monitoring is strongly recommended. **Pregnancy risk factor X.**

Patient EducationI.V./I.M.: Generally used in emergency situations. Drug teaching should be incorporated in other situational teaching. **Pregnancy/breast-feeding precautions:** Consult prescriber if you suspect you might be pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Use caution if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 10 units/mL (1 mL, 10 mL, 30 mL)

Pitocin®: 10 units/mL (1 mL, 10 mL)

Generic AvailableYes

Mechanism of ActionProduces the rhythmic uterine contractions characteristic to delivery

Pharmacodynamics/Kinetics

Onset of action: Uterine contractions: I.M.: 3-5 minutes; I.V.: ~1 minute

Duration: I.M.: 2-3 hour; I.V.: 1 hour

Metabolism: Rapidly hepatic and via plasma (by oxytocinase) and to a smaller degree the mammary gland

Half-life elimination: 1-5 minutes

Excretion: Urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPit

References

de Groot AN, van Dongen PW, Vree TB, et al, “Ergot Alkaloids. Current Status and Review of Clinical Pharmacology and Therapeutic Use Compared With Other Oxytocics in Obstetrics and Gynaecology,” *Drugs*, 1998, 56(4):523-35.[PubMed 9806101]

International Brand NamesEstima (PH); Evatocin (PH); Fetusin (PH); Indoxin (ID); NeOxyn (PH); Octocin (TH); Oksitocins (EE); Otoxin (PH); Oxitone (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PH, QA, SA, SY, YE); Oxytocin (PL); Partocon INJ (FI); Pitocin (EC); Pitocin INJ (IN); Pitogin (ID); Piton S (ID); Piton S INJ (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, NL, OM, QA, SA, SY, TW, YE); Sandopart (PL); Solvoxine (PH); Synthetic Oxytocin INJ (IN); Syntocinon (DK, HR, IT, LU, PL, PT); Syntocinon INJ (AR, AT, AU, BE, BF, BJ, BR, CH, CI, CN, DE, ES, ET, FI, FR, GB, GH, GM, GN, HK, ID, IE, KE, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, PE, PH, PK, PY, SC, SD, SE, SL, SN, TN, TZ, UG, UY, VE, ZA, ZM, ZW); Syntocinon Spray (AT, CH, NO, SE); Tiacinon (ID); Tranoxy (PH); Xitocin (MX)

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Hepatoblastoma

Regimen Use Hepatoblastoma

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Cisplatin: I.V.: 90 mg/m^2 day 1

[total dose/cycle = 90 mg/m^2]

Doxorubicin: I.V.: 20 mg/m^2/day continuous infusion days 2 to 5

[total dose/cycle = 80 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 4

[total dose/cycle = 80 mg/m^2]

Doxorubicin: I.V.: 100 mg/m^2 continuous infusion day 1

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21-28 days

References

Variation 1:

Ortega JA, Douglass EC, Feusner JH, et al, “Randomized Comparison of Cisplatin/Vincristine/Fluorouracil and Cisplatin/Continuous Infusion Doxorubicin for Treatment of Pediatric Hepatoblastoma: A Report From the Children's Cancer Group and the Pediatric Oncology Group,” *J Clin Oncol*, 2000, 18(14):2665-75. [PubMed 10894865]

Variation 2:

Ortega JA, Krailo MD, Haas JE, et al, “Effective Treatment of Unresectable or Metastatic Hepatoblastoma With Cisplatin and Continuous Infusion Doxorubicin Chemotherapy: A Report From the Childrens Cancer Study Group,” *J Clin Oncol*, 1991, 9(12):2167-76.[PubMed 1720452]

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Ovarian Cancer

Regimen Use Ovarian cancer

Regimen

Cisplatin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Cyclophosphamide: I.V.: 1000 mg/m^2 day 1

[total dose/cycle = 1000 mg/m^2]

Repeat cycle every 21 days for 8 cycles

References

Omura GA, Bundy BN, Berek JS, et al, âRandomized Trial of Cyclophosphamide Plus Cisplatin With or Without Doxorubicin in Ovarian Carcinoma: A Gynecologic Oncology Group Study,â *J Clin Oncol*, 1989, 7(4):457-65.[PubMed 2926470]

Paclitaxel (Protein Bound)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Paclitaxel (protein bound) may be confused with paclitaxel (conventional)

Abraxane® may be confused with Paxil®, Taxol®, Taxotere®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(pac li TAKS el PROE teen bownd)

U.S. Brand NamesAbraxane®

Pharmacologic CategoryAntineoplastic Agent, Antimicrotubular; Antineoplastic Agent, Natural Source (Plant) Derivative; Antineoplastic Agent, Taxane Derivative

Use: Labeled IndicationsTreatment of relapsed or refractory breast cancer

Dosing: Adults**Breast cancer:** I.V.: 260 mg/m^2 every 3 weeks **or** alternate weekly schedule (unlabeled): 100-150 mg/m^2 on days 1, 8, and 15 of a 28-day cycle

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentSafety not established for serum creatinine >2 mg/dL; use with caution.

Dosing: Hepatic ImpairmentEffects of hepatic dysfunction (serum bilirubin >1.5 mg/dL) unknown; dosage adjustment recommendations are not available.

Dosing: Adjustment for Toxicity

Severe neutropenia (<500 cells/mm^3) ≥1 week: Reduce dose to 220 mg/m^2 for subsequent courses

Recurrent severe neutropenia: Reduce dose to 180 mg/m^2

Sensory neuropathy, grade 3: Hold treatment until resolved to grade 1 or 2, then resume with reduced dose

Severe sensory neuropathy: Reduce dose to 220 mg/m^2 for subsequent courses

Recurrent severe sensory neuropathy: Reduce dose to 180 mg/m^2

Calculations

- Body Surface Area: Adults

Administration: I.V.Administer over 30 minutes. Do not use an in-line filter. Avoid extravasation.

StorageStore intact vial at room temperature of 20°C to 25°C (68°F to 77°F) and protect from bright light. Reconstituted solution may be stored under refrigeration 2°C to 8°C (36°F to 46°F) for up to 8 hours. The solution for administration is stable for up to 8 hours at room temperature and ambient light.

ReconstitutionUse appropriate precautions for handling and disposal. Reconstitute vial with 20 mL NS to a concentration of 5 mg/mL. Add NS slowly, directing it along inside vial wall; allow vial to sit for 5 minutes, then gently swirl for 2 minutes; avoid foaming. Place dose without further dilution into an empty sterile container. **Note:** Use of DEHP-free containers or administration sets is not necessary. **Do not use an in-line filter.**

CompatibilityStable in NS. Formulation contains albumin; do not mix with other drugs.

ContraindicationsPatients with baseline neutrophils <1500/mm^3

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Do not interchange: See “Other warnings/precautions” below.
- Experienced physician: See “Other warnings/precautions” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: Baseline neutrophils should be ≥1500/mm^3 for administration;** neutrophils should recover to >1500/mm^3 and platelets should recover to >100,000/mm^3 prior to the next treatment cycle. Dose-dependent bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity. For severe neutropenia, dose reductions may be recommended for subsequent cycles. When administered as sequential infusions, taxane derivatives (docetaxel, paclitaxel) should be administered before platinum derivatives (carboplatin, cisplatin) to limit myelosuppression.

- Hypersensitivity: Rare postmarketing cases of severe hypersensitivity have been reported; do not rechallenge after severe hypersensitivity reaction. Use has not been studied in patients with a prior hypersensitivity reaction to conventional paclitaxel or albumin.

- Neuropathy: Dose-related sensory neuropathy is common; severe sensory neuropathy may occur.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; not studied in patients with serum bilirubin >1.5 mg/dL.

- Renal impairment: Use with caution in patients with renal impairment; not studied in patients with serum creatinine >2 mg/dL.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Albumin: Product contains albumin, which confers a theoretical risk of transmission of viral disease or Creutzfeldt-Jakob disease.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

- Do not interchange: **[U.S. Boxed Warning]: Paclitaxel (protein-bound) is not interchangeable with other forms of paclitaxel, including Cremophor®-based or unbound paclitaxel.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenic effects and fetal mortality have been observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant during therapy. Additionally, testicular atrophy/degeneration was observed in animal studies; males should be advised to not father a child during therapy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends that nursing be discontinued during therapy.

Adverse Reactions

>10%:

Cardiovascular: ECG abnormal (60%)

Dermatologic: Alopecia (90%)

Gastrointestinal: Nausea (30%; grades 3/4: 3%), diarrhea (27%; grades 3/4: <1%), vomiting (18%; grades 3/4: 4%)

Hematologic: Neutropenia (80%; grade 4: 9%), anemia (33%; grades 3/4: 1%)

Hepatic: AST increased (39%), alkaline phosphatase increased (36%), GGT increased (grades 3/4: 14%)

Neuromuscular & skeletal: Sensory neuropathy (71%; grades 3/4: 10%; dose dependent; may be cumulative), weakness (47%), myalgia/arthralgia (44%)

Ocular: Vision disturbance (13%; severe [keratitis, blurred vision]: 1%)

Renal: Creatinine increased (11%; severe 1%)

Respiratory: Dyspnea (12%)

Miscellaneous: Infection (24%; primarily included oral candidiasis, respiratory tract infection, and pneumonia)

1% to 10%:

Cardiovascular: Edema (10%), hypotension (5%), cardiovascular events (grades 3/4: 3%; included chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension)

Gastrointestinal: Mucositis (7%; grades 3/4: <1%)

Hematologic: Bleeding (2%), neutropenic fever (2%), thrombocytopenia (2%; grades 3/4: <1%)

Hepatic: Bilirubin increased (7%)

Neuromuscular & skeletal: Peripheral neuropathy (grade 3: 10%)

Respiratory: Cough (7%)

Miscellaneous: Hypersensitivity reaction (4%, includes chest pain, dyspnea, flushing, hypotension; severe: <1%)

<1%, postmarketing, and/or case reports: Arrhythmia, bradycardia, cardiac ischemia, cerebrovascular attack, cranial nerve palsies, embolism, erythema, hand-foot syndrome (in patients previously exposed to capecitabine), injection site reaction, maculopapular rash, MI, motor neuropathy, nail discoloration, nail pigmentation changes, photosensitivity reaction, pneumothorax, pruritus, radiation recall, stroke, thrombosis, transient ischemic attack

Adverse reactions reported with paclitaxel, which may occur with paclitaxel (protein bound): Autonomic neuropathy, cellulitis, conjunctivitis, extravasation recall, hepatic encephalopathy, hepatic necrosis, induration, intestinal obstruction, intestinal perforation, interstitial pneumonia, ischemic colitis, lacrimation increased, lung fibrosis, neutropenic enterocolitis (typhlitis), optic nerve damage (persistent), pancreatitis, paralytic ileus, phlebitis, pulmonary embolism, radiation pneumonitis with concurrent radiation therapy, skin exfoliation, skin fibrosis, skin necrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Oncology: VesicantNo
Oncology: Emetic PotentialLow (10% to 30%)
Metabolism/Transport Effects**Substrate** (major) of CYP2C8, 2C9, 3A4; **Induces** CYP3A4 (weak)
Drug Interactions

Antineoplastic Agents (Anthracycline): Taxane Derivatives may enhance the adverse/toxic effect of Antineoplastic Agents (Anthracycline). Taxane Derivatives may increase the serum concentration of Antineoplastic Agents (Anthracycline). Taxane Derivatives may also increase the formation of toxic anthracycline metabolites in heart tissue. *Risk D: Consider therapy modification*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

CYP2C8 Inducers (Highly Effective): May increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Moderate): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Strong): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

DOXOrubicin: Taxane Derivatives may decrease the metabolism of DOXOrubicin. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Platinum Derivatives: May enhance the myelosuppressive effect of Taxane Derivatives. Administer Taxane derivative before Platinum derivative when given as sequential infusions to limit toxicity. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vinorelbine: Paclitaxel (Protein Bound) may enhance the neurotoxic effect of Vinorelbine. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid St John's wort (may decrease paclitaxel levels). Avoid echinacea. Avoid black cohosh, dong quai in estrogen-dependent tumors.
Monitoring ParametersCBC, BP (during infusion), baseline ECG; hepatic function; monitor infusion site
Nursing: Physical Assessment/MonitoringPaclitaxel (protein bound) is not interchangeable with paclitaxel. Taxane derivatives should be administered before platinum derivatives to limit myelosuppression. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, risk of increased or decrease levels/effects of paclitaxel). See Administration for specific infusion directions. Evaluate results of laboratory adverse response prior to, during, and between each infusion (eg, cardiovascular abnormalities; sensory neuropathy [numbness, tingling, burning pain], myelosuppression [anemia, opportunistic infection], GI irritation [nausea, vomiting, mucositis, stomatitis]). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC, BP (during infusion); hepatic function

Patient EducationThis drug can only be administered by intravenous infusion; you will be monitored closely during and following infusions. Immediately report any burning, pain, or swelling at infusion site; any unusual chest pain or tightness, rapid heartbeat or palpitations; difficulty breathing; difficulty swallowing; nausea or vomiting; or other adverse symptoms during infusion. Do not take any new medications during therapy without consulting prescriber. You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations unless approved by prescriber). It is important that you maintain adequate nutrition and fluid intake (2-3 L/day of fluids, unless instructed to restrict fluid intake). May cause nausea or vomiting (small frequent meals, and frequent mouth care may help); mouth sores (sucking ice chip may be beneficial, use good mouth care with a soft toothbrush and waxed dental floss; if severe or infection occurs consult prescriber for appropriate treatment); diarrhea (buttermilk or yogurt may help); loss of hair (will grow back after therapy). Report chest pain, palpitations, swelling of extremities; difficult breathing; pain or decreased sensation in extremities; unusual sign of weakness, fatigue, lethargy, persistent gastrointestinal disturbances (nausea, vomiting, diarrhea); or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Females should not get pregnant while taking this medication and males should not father a child while receiving treatment. This drug may cause fetal deformities or loss of pregnancy; consult prescriber for appropriate contraceptives. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Abraxane®: 100 mg [contains albumin (human)]

Generic AvailableNo

ManufacturerAbraxis Bioscience Inc

Mechanism of ActionPaclitaxel promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G_2 mitotic phase, and inhibiting cell replication. May also distort mitotic spindles, resulting in the breakage of chromosomes. Paclitaxel may also suppress cell proliferation and modulate immune response.

Pharmacodynamics/Kinetics

Distribution: V_d: 632 L/m^2

Protein binding: 89% to 98%

Metabolism: Hepatic via CYP3A4 (to minor metabolites) and 2C8 (primarily to 6-alpha-hydroxypaclitaxel)

Half-life elimination: Terminal: 27 hours

Excretion: Feces (20%); urine (4% as unchanged drug, <1% as metabolites)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentECG abnormalities are common; avoid use with ziprasidone, pimozide, thioridazine, and mesoridazine. GI side effects are common; concomitant use with SSRIs, lithium, or valproic acid may produce additive effects. Neutropenia is common; use caution with clozapine, carbamazepine, and valproic acid. Carbamazepine, phenobarbital, and phenytoin may reduce the effects of paclitaxel.

Oncology: Bone Marrow CommentsGlutamine may decrease mucositis.

Index TermsABI-007; Albumin-Bound Paclitaxel; nab-Paclitaxel; NSC-736631; Protein-Bound Paclitaxel

References

Baker AF and Dorr RT, “Drug Interactions With the Taxanes: Clinical Implications,” *Cancer Treat Rev*, 2001, 27(4):221-33.[PubMed 11545542]

Gradishar WJ, Krasnojon S, Cheporov A, et al, “Randomized Comparison of Weekly or Every-3-Week (q3w) Nab-Paclitaxel Compared to q3w Docetaxel as First-Line Therapy in Patients (pts) With Metastatic Breast Cancer (MBC),” *J Clin Oncol*, 2007, 25(18S): 1032. [abstract from 2007 ASCO Annual Meeting, Part 1]

Gradishar WJ, Tjulandin S, Davidson N, et al, “Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel Compared With Polyethylated Castor Oil-Based Paclitaxel in Women With Breast Cancer,” *J Clin Oncol*, 2005, 23(31):7794-803.[PubMed 16172456]

Ibrahim NK, Samuels B, Page R, et al, “Multicenter Phase II Trial of ABI-007, an Albumin-Bound Paclitaxel, in Women With Metastatic Breast Cancer,” *J Clin Oncol*, 2005, 23(25):6019-26.[PubMed 16135470]

Nyman DW, Campbell KJ, Hersh E, et al, “Phase I and Pharmacokinetics Trial of ABI-007, a Novel Nanoparticle Formulation of Paclitaxel in Patients With Advanced Nonhematologic Malignancies,” *J Clin Oncol*, 2005, 23(31):7785-93.[PubMed 16258082]

International Brand NamesAbraxane (CZ)

Paclitaxel + Estramustine + Carboplatin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer

Regimen UseProstate cancer

Regimen

Paclitaxel: I.V.: 100 mg/m^2 day 3 each week

[total dose/cycle = 400 mg/m^2]

Estramustine: Oral: 10 mg/kg/day days 1 to 5 each week

[total dose/cycle = 200 mg/kg]

Carboplatin: I.V.: Target AUC 6 day 3

[total dose/cycle = AUC = 6]

Repeat cycle every 28 days

References

Kelly WK, Curley T, Slovin S, et al, âPaclitaxel, Estramustine Phosphate, and Carboplatin in Patients With Advanced Prostate Cancer,â *J Clin Oncol*, 2001, 19(1):44-53.[PubMed 11134194]

Paclitaxel + Estramustine + Etoposide

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Prostate Cancer

Regimen UseProstate cancer

Regimen

Paclitaxel: I.V.: 135 mg/m^2 day 2

[total dose/cycle = 135 mg/m^2]

Estramustine: Oral: 280 mg 3 times/day days 1 to 14

[total dose/cycle = 11,760 mg]

Etoposide: Oral: 100 mg/day days 1 to 14

[total dose/cycle = 1400 mg]

Repeat cycle every 21 days

References

Smith DC, Esper P, Strawderman M, et al, âPhase II Trial of Oral Estramustine, Oral Etoposide, and Intravenous Paclitaxel in Hormone-Refractory Prostate Cancer,â *J Clin Oncol*, 1999, 17(6):1664-71.[PubMed 10561202]

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer
Regimen Use Breast cancer
Index Terms Bevacizumab-Paclitaxel
Regimen

Paclitaxel: I.V.: 90 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 270 mg/m^2]

Bevacizumab: I.V.: 10 mg/kg/day days 1 and 15

[total dose/cycle = 20 mg/kg]

Repeat cycle every 28 days

References

Miller KD, “E2100: A Phase III Trial of Paclitaxel Versus Paclitaxel/Bevacizumab for Metastatic Breast Cancer,” *Clin Breast Cancer*, 2003, 3(6):421-2. [PubMed 12636887]

Miller K, Wang M, Gralow J, et al, “Paclitaxel Plus Bevacizumab Versus Paclitaxel Alone for Metastatic Breast Cancer,” *N Engl J Med*, 2007, 357(26):2666-76. [PubMed 18160686]

Paclitaxel-Carboplatin (Bladder Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Bladder Cancer
Regimen UseBladder cancer
Index TermsCarboplatin-Paclitaxel (Bladder Cancer); PC (Bladder Cancer)
Regimen

Paclitaxel: I.V.: 200 mg/m^2 or 225 mg/m^2 day 1

[total dose/cycle = 200 or 225 mg/m^2]

Carboplatin: I.V.: AUC 5-6 day 1

[total dose/cycle = AUC = 5-6]

Repeat cycle every 21 days

References

Vaughn DJ, Malkowicz SB, Zoltick B, et al, âPaclitaxel Plus Carboplatin in Advanced Carcinoma of the Urothelium: An Active and Tolerable Outpatient Regimen,â *J Clin Oncol*, 1998, 16(1):255-60.[PubMed 9440750]

Paclitaxel-Carboplatin (Cervical Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Cervical Cancer

Regimen Use Cervical cancer

Index Terms Carboplatin-Paclitaxel (Cervical Cancer)

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Paclitaxel: I.V.: 175 mg/m^2 over 3 hours day 1

[total dose/cycle = 175 mg/m^2]

Carboplatin: I.V.: AUC 5 or 6 day 1

[total dose/cycle = AUC = 5 or 6]

Repeat cycle every 28 days for 6-9 cycles

Variation 2 (if patient has received prior pelvic radiation):

Paclitaxel: I.V.: 155 mg/m^2 over 3 hours day 1

[total dose/cycle = 155 mg/m^2]

Carboplatin: I.V.: AUC 5 or 6 day 1

[total dose/cycle = AUC = 5 or 6]

Repeat cycle every 28 days for 6-9 cycles

References

Tinker AV, Bhagat K, Swenerton KD, et al, "Carboplatin and Paclitaxel for Advanced and Recurrent Cervical Carcinoma: The British Columbia Cancer Agency Experience," *Gynecol Oncol*, 2005, 98(1):54-8.[PubMed 15904950]

Paclitaxel-Carboplatin-Bevacizumab

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lung Cancer (Nonsmall Cell)

Regimen Use Lung cancer, nonsquamous, nonsmall cell

Index Terms Bevacizumab-Paclitaxel-Carboplatin

Regimen

Paclitaxel: I.V.: 200 mg/m^2 infused over 3 hours day 1

[total dose/cycle = 200 mg/m^2]

followed by

Carboplatin: I.V.: Target AUC 6 day 1

[total dose/cycle = AUC = 6]

followed by

Bevacizumab: I.V.: 15 mg/kg day 1

[total dose/cycle = 15 mg/kg]

Repeat cycle every 21 days for 6 cycles

References

Johnson DH, Fehrenbacher L, Novotny WF, “Randomized Phase II Trial Comparing Bevacizumab Plus Carboplatin and Paclitaxel With Carboplatin and Paclitaxel Alone in Previously Untreated Locally Advanced or Metastatic Nonsmall-Cell Lung Cancer,” *J Clin Oncol*, 2004, 22(11):2184-91. [PubMed 15169807]

Sandler A, Gray R, Perry MC, et al, “Paclitaxel-Carboplatin Alone or With Bevacizumab for Nonsmall-Cell Lung Cancer,” *N Engl J Med*, 2006, 355(24):2542-50.[PubMed 17167137]

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Adenocarcinoma (Unknown Primary)]

Regimen UseAdenocarcinoma, unknown primary

Regimen

Paclitaxel: I.V.: 200 mg/m^2 infused over 1 hour day 1

[total dose/cycle = 200 mg/m^2]

followed by

Carboplatin: I.V.: Target AUC 6

[total dose = AUC = 6]

Etoposide: Oral: 50 mg/day days 1, 3, 5, 7, and 9

and Oral: 100 mg/day days 2, 4, 6, 8, and 10

[total dose/cycle = 750 mg]

Repeat cycle every 21 days

References

Hainsworth JD, Erland JB, Kalman LA, et al, âCarcinoma of Unknown Primary Site: Treatment With 1-Hour Paclitaxel, Carboplatin, and Extended-Schedule Etoposide,â *J Clin Oncol*, 1997, 15(6):2385-93.

Paclitaxel-Carboplatin-Gemcitabine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Bladder Cancer]

Regimen UseBladder cancer

Regimen

Paclitaxel: I.V.: 200 mg/m^2 day 1

[total dose/cycle = 200 mg/m^2]

Gemcitabine: I.V.: 1000 mg/m^2/day days 1 and 8

[total dose/cycle = 2000 mg/m^2]

Carboplatin: I.V.: AUC 5 day 1

[total dose/cycle = AUC = 5]

Repeat cycle every 21 days

References

Hainsworth JD, Meluch AA, Litchy S, et al, âPaclitaxel, Carboplatin, and Gemcitabine in the Treatment of Patients With Advanced Transitional Cell Carcinoma of the Urothelium,â *Cancer*, 2005, 103(11):2298-303[PubMed 15856431]

Paclitaxel-Cetuximab

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Head and Neck Cancer

Regimen Use Head and neck cancer

Index Terms Cetuximab-Paclitaxel

Regimen

Week 1:

Paclitaxel: I.V.: 80 mg/m^2 day 1

[total dose/week 1 = 80 mg/m^2]

Cetuximab: I.V.: 400 mg/m^2 (loading dose) day 1 (week 1 only)

[total loading dose (week 1) = 400 mg/m^2]

Subsequent weeks:

Paclitaxel: I.V.: 80 mg/m^2 day 1

[total dose/week = 80 mg/m^2]

Cetuximab: I.V.: 250 mg/m^2 day 1

[total dose/week = 250 mg/m^2]

References

Hitt R, Irigoyen H, Nunez J, et al, "Phase II Study of Combination Cetuximab and Weekly Paclitaxel in Patients With Metastatic/Recurrent Squamous Cell Carcinama of Head and Neck (SCCHN): Spanish Head and Neck Cancer Group (TTCC)," *J Clin Oncol*, 2007, 25(18S) [abstract 6012 from 2007 ASCO Annual Meeting].

Paclitaxel-Cisplatin (Cervical Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Cervical Cancer

Regimen Use Cervical cancer

Index Terms Cisplatin-Paclitaxel (Cervical Cancer)

Regimen

Paclitaxel: I.V.: 135 mg/m^2 continuous infusion over 24 hours day 1

[total dose/cycle = 135 mg/m^2]

Cisplatin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Repeat cycle every 21 days for 6 cycles

References

Moore DH, Blessing JA, McQuellon RP, et al, "Phase III Study of Cisplatin With or Without Paclitaxel in Stage IVB, Recurrent, or Persistent Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study," *J Clin Oncol*, 2004, 22(15):3113-9. [PubMed 15284262]

Paclitaxel-Cisplatin-Fluorouracil (Esophageal Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Esophageal Cancer

Regimen Use Esophageal cancer

Index Terms Paclitaxel-Fluorouracil-Cisplatin (Esophageal Cancer); TCF (Esophageal Cancer)

Regimen

Paclitaxel: I.V.: 175 mg/m^2 over 3 hours day 1

[total dose/cycle = 175 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5 for Cycles 1, 2, and 3

[total dose/cycle = 100 mg/m^2]

then 15 mg/m^2/day days 1 to 5

[total dose/cycle = 75 mg/m^2]

Fluorouracil: I.V.: 750 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 3750 mg/m^2]

Repeat cycle every 28 days

References

Ilson DH, Ajani J, Bhalla K, et al, âPhase II Trial of Paclitaxel, Fluorouracil, and Cisplatin in Patients With Advanced Carcinoma of the Esophagus,â *J Clin Oncol*, 1998, 16(5):1826-34.[PubMed 9586897]

Paclitaxel-Gemcitabine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Bladder Cancer
Regimen Use Bladder cancer
Index Terms Gemcitabine-Paclitaxel

Regimen

Paclitaxel: I.V.: 200 mg/m^2 day 1

[total dose/cycle = 200 mg/m^2]

Gemcitabine: I.V.: 1000 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 3000 mg/m^2]

Repeat cycle every 21 days for a maximum of 6 cycles

References

Meluch AA, Greco FA, Burris HA 3rd, et al, "Paclitaxel and Gemcitabine Chemotherapy for Advanced Transitional-Cell Carcinoma of the Urothelial Tract: A Phase II Trial of the Minnie Pearl Cancer Research Network," *J Clin Oncol*, 2001, 19(12):3018-24.[PubMed 11408496]

Paclitaxel-Ifosfamide-Cisplatin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Testicular Cancer]

Regimen UseTesticular cancer

Index TermsCisplatin-Ifosfamide-Paclitaxel

Regimen

Paclitaxel: I.V.: 250 mg/m^2 continuous infusion day 1

[total dose/cycle = 250 mg/m^2]

Ifosfamide: I.V.: 1500 mg/m^2/day days 2 to 5

[total dose/cycle = 6000 mg/m^2]

Cisplatin: I.V.: 25 mg/m^2/day days 2 to 5

[total dose/cycle = 100 mg/m^2]

Mesna: I.V.: 500 mg/m^2 prior to ifosfamide and every 4 hours for 2 doses, days 2 to 5

[total dose/cycle = 6000 mg/m^2]

Repeat cycle every 21 days for 4 cycles

References

Kondagunta GV, Bacik J, Donadio A, et al, âCombination of Paclitaxel, Ifosfamide, and Cisplatin is an Effective Second-Line Therapy for Patients With Relapsed Testicular Germ Cell Tumors,â *J Clin Oncol*, 2005, 23(27):6549-55.[PubMed 16170162]

Paclitaxel-Vinorelbine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Breast Cancer]

Regimen UseBreast cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Paclitaxel: I.V.: 135 mg/m^2 day 1

[total dose/cycle = 135 mg/m^2]

Vinorelbine: I.V.: 30 mg/m^2 day 1

[total dose/cycle = 30 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Paclitaxel: I.V.: 150 mg/m^2 day 1

[total dose/cycle = 150 mg/m^2]

Vinorelbine: I.V.: 25 mg/m^2 day 1

[total dose/cycle = 25 mg/m^2]

Repeat cycle every 21 days

Variation 3:

Paclitaxel: I.V.: 135 mg/m^2 day 1

[total dose/cycle = 135 mg/m^2]

Vinorelbine: I.V.: 30 mg/m^2/day days 1 and 8

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 28 days

References

Variation 1:

Martin M, Lluch A, Casado A, et al, "Paclitaxel Plus Vinorelbine: An Active Regimen in Metastatic Breast Cancer Patients With Prior Anthracycline Exposure," *Ann Oncol*, 2000, 11(1):85-9. [PubMed 10690393]

Variation 2:

Vici P, Amodio A, Di Lauro L, et al, "First-Line Chemotherapy With Vinorelbine and Paclitaxel As Simultaneous Infusion in Advanced Breast Cancer," *Oncology*, 2000, 58(1):3-7.[PubMed 10644933]

Variation 3:

Romero Acuna LR, Langhi M, Perez J, et al, "Vinorelbine and Paclitaxel as First-Line Chemotherapy in Metastatic Breast Cancer," *J Clin Oncol*, 1999, 17(1):74-81.[PubMed 10458220]

Paclitaxel

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Paclitaxel may be confused with paroxetine, Paxil®

Paclitaxel (conventional) may be confused with paclitaxel (protein-bound)

Taxol® may be confused with Abraxane®, Paxil®, Taxotere®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(pac li TAKS el)

U.S. Brand NamesOnxol® ; Taxol®

Canadian Brand NamesAbraxane® For Injectable Suspension; Apo-Paclitaxel®; Taxol®

Pharmacologic CategoryAntineoplastic Agent, Antimicrotubular; Antineoplastic Agent, Natural Source (Plant) Derivative; Antineoplastic Agent, Taxane Derivative

Use: Labeled IndicationsTreatment of breast, nonsmall cell lung, and ovarian cancers; treatment of AIDS-related Kaposi's sarcoma (KS)

Use: Unlabeled/InvestigationalTreatment of bladder, cervical, prostate, small cell lung, and head and neck cancers; treatment of (unknown primary) adenocarcinoma

Dosing: Adults**Note:** Premedication with dexamethasone (20 mg orally or I.V. at 12 and 6 hours **or** 14 and 7 hours before the dose; reduce dexamethasone dose to 10 mg orally with advanced HIV disease), diphenhydramine (50 mg I.V. 30-60 minutes prior to the dose), and cimetidine, famotidine, or ranitidine (I.V. 30-60 minutes prior to the dose) is recommended.

Ovarian carcinoma:

I.V.: 135-175 mg/m^2 over 3 hours every 3 weeks **or**

135 mg/m^2 over 24 hours every 3 weeks **or**

50-80 mg/m^2 over 1-3 hours weekly **or**

1.4-4 mg/m^2/day continuous infusion for 14 days every 4 weeks

Intraperitoneal (unlabeled route): 60 mg/m^2 on day 8 of a 21-day treatment cycle for 6 cycles, in combination with I.V. paclitaxel and intraperitoneal cisplatin. **Note:** Administration of intraperitoneal paclitaxel should include the standard paclitaxel premedication regimen.

Metastatic breast cancer: I.V.: 175-250 mg/m^2 over 3 hours every 3 weeks **or**

50-80 mg/m^2 weekly **or**

1.4-4 mg/m^2/day continuous infusion for 14 days every 4 weeks

Nonsmall cell lung carcinoma: I.V.: 135 mg/m^2 over 24 hours every 3 weeks

AIDS-related Kaposi's sarcoma: I.V.: 135 mg/m^2 over 3 hours every 3 weeks

or 100 mg/m^2 over 3 hours every 2 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentThere are no FDA-approved labeling guidelines for dosage adjustment in patients with renal impairment. Arnoff (2007) recommends no dosage adjustment necessary for adults with Cl_{cr} <50 mL/minute.

Dosing: Hepatic Impairment**Note:** The FDA-approved labeling recommendations are based upon the patient's first course of therapy where the usual dose would be 135 mg/m^2 dose over 24 hours or the 175 mg/m^2 dose over 3 hours in patients with normal hepatic function. Dosage in subsequent courses should be based upon individual tolerance. Adjustments for other regimens are not available.

24-hour infusion:

Transaminases <2 times upper limit of normal (ULN) and bilirubin level ≤1.5 mg/dL: 135 mg/m^2

Transaminases 2-<10 times ULN and bilirubin level ≤1.5 mg/dL: 100 mg/m^2

Transaminases <10 times ULN and bilirubin level 1.6-7.5 mg/dL: 50 mg/m^2

Transaminases ≥10 times ULN or bilirubin level >7.5 mg/dL: Avoid use

3-hour infusion:

Transaminases <10 times ULN and bilirubin level ≤1.25 times ULN: 175 mg/m^2

Transaminases <10 times ULN and bilirubin level 1.26-2 times ULN: 135 mg/m^2

Transaminases <10 times ULN and bilirubin level 2.01-5 times ULN: 90 mg/m^2

Transaminases ≥10 times ULN or bilirubin level >5 times ULN: Avoid use

Dosing: Adjustment for Toxicity

Dosage modification for toxicity (solid tumors, including ovary, breast, and lung carcinoma): Courses of paclitaxel should not be repeated until the neutrophil count is ≥1500 cells/mm^3 and the platelet count is ≥100,000 cells/mm^3; reduce dosage by 20% for patients experiencing severe peripheral neuropathy or severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer)

Dosage modification for immunosuppression in advanced HIV disease: Paclitaxel should not be given to patients with HIV if the baseline or subsequent neutrophil count is <1000 cells/mm^3. Additional modifications include: Reduce dosage of dexamethasone in premedication to 10 mg orally; reduce dosage by 20% in patients experiencing severe peripheral neuropathy or severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer); initiate concurrent hematopoietic growth factor (G-CSF) as clinically indicated

Dosing: Combination Regimens

Adenocarcinoma, unknown primary:

Carbo-Tax (Adenocarcinoma)

Paclitaxel-Carboplatin-Etoposide

PCE

Bladder cancer:

Paclitaxel-Carboplatin (Bladder Cancer)

Paclitaxel-Carboplatin-Gemcitabine

Paclitaxel-Gemcitabine

Breast cancer:

AC/Paclitaxel (Sequential)

AC-Paclitaxel-Trastuzumab

ICE-T

Paclitaxel-Bevacizumab

Paclitaxel-Vinorelbine

Trastuzumab-Paclitaxel

Trastuzumab-Paclitaxel-Carboplatin

Trastuzumab-Paclitaxel (Weekly)

Cervical cancer:

Paclitaxel-Carboplatin (Cervical Cancer)

Paclitaxel-Cisplatin (Cervical Cancer)

Esophageal cancer:

Paclitaxel-Cisplatin-Fluorouracil (Esophageal Cancer)

TIP

Head and neck cancer:

FU HURT

Paclitaxel-Cetuximab

TIP

Lung cancer (nonsmall cell):

Carbo-Tax (NSCLC)

CaT (NSCLC)

Paclitaxel-Carboplatin-Bevacizumab

PC (NSCLC)

Ovarian cancer:

Carbo-Tax (Ovarian Cancer)

CaT (Ovarian Cancer)

Cisplatin-Paclitaxel (Intraperitoneal Regimen)

CT

Gemcitabine-Paclitaxel

Prostate cancer:

Estramustine-Paclitaxel

Paclitaxel + Estramustine + Carboplatin

Paclitaxel + Estramustine + Etoposide

Sarcoma, soft tissue: ICE-T

Testicular cancer: Paclitaxel-Ifosfamide-Cisplatin

Oncology: Bone Marrow - High DoseI.V.: 250-775 mg/m^2; generally combined with other high-dose chemotherapy; maximum dose as single agent: 825 mg/m^2

Calculations

- Body Surface Area: Adults

Administration: I.V.Infuse over 1-96 hours. When administered as sequential infusions, taxane derivatives should be administered before platinum derivatives (cisplatin, carboplatin) to limit myelosuppression and to enhance efficacy.

Premedication with dexamethasone (20 mg orally or I.V. at 12 and 6 hours **or** 14 and 7 hours before the dose; reduce to 10 mg with advanced HIV disease), diphenhydramine (50 mg I.V. 30-60 minutes prior to the dose), and cimetidine 300 mg, famotidine 20 mg, or ranitidine 50 mg (I.V. 30-60 minutes prior to the dose) is recommended.

Administer I.V. infusion over 1-24 hours; infuse through a 0.22 micron in-line filter and nonsorbing administration set.

Administration: I.V. DetailpH: 4.4-5.6

Administration: OtherIntraperitoneal: 1-2 hour infusion

StorageStore intact vials at room temperature of 20°C to 25°C (68°F to 77°F). Protect from light. Solutions in D_5W and NS are stable for up to 3 days at room temperature (25°C).

Paclitaxel should be dispensed in either glass or non-PVC containers (eg, Excel™/PAB™). Use **nonpolyvinyl** (non-PVC) tubing (eg, polyethylene) to minimize leaching. Formulated in a vehicle known as Cremophor® EL (polyoxyethylated castor oil). Cremophor® EL has been found to leach the plasticizer DEHP from polyvinyl chloride infusion bags or administration sets. Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices is not recommended.

ReconstitutionDilute in 250-1000 mL D_5W, D_5LR, D_5NS, or NS to a concentration of 0.3-1.2 mg/mL. Chemotherapy dispensing devices (eg, Chemo Dispensing Pin™) should not be used to withdraw paclitaxel from the vial.

CompatibilityStable in D_5W, D_5LR, D_5NS, NS.

Y-site administration: Compatible: Acyclovir, amikacin, aminophylline, ampicillin/sulbactam, bleomycin, butorphanol, calcium chloride, carboplatin, cefepime, cefotetan, ceftazidime, ceftriaxone, cimetidine, cisplatin, cladribine, cyclophosphamide, cytarabine, dacarbazine, dexamethasone sodium phosphate, diphenhydramine, doxorubicin, droperidol, etoposide, etoposide phosphate, famotidine, floxuridine, fluconazole, fluorouracil, furosemide, ganciclovir, gatifloxacin, gemcitabine, gentamicin, granisetron, haloperidol, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, ifosfamide, linezolid, lorazepam, magnesium sulfate, mannitol, meperidine, mesna, methotrexate, metoclopramide, morphine, nalbuphine, ondansetron, ondansetron with ranitidine, pentostatin, potassium chloride, prochlorperazine edisylate, propofol, ranitidine, sodium bicarbonate, thiotepa, topotecan, vancomycin, vinblastine, vincristine, zidovudine. **Incompatible:** Amphotericin B, amphotericin B cholesteryl sulfate complex, chlorpromazine, doxorubicin liposome, hydroxyzine, methylprednisolone sodium succinate, mitoxantrone.

Compatibility when admixed: Compatible: Carboplatin, doxorubicin. **Variable (consult detailed reference):** Cisplatin.

ContraindicationsHypersensitivity to paclitaxel, Cremophor® EL (polyoxyethylated castor oil), or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.

- Experienced physician: See “Other warnings/precautions” below.

- Hypersensitivity reactions: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: Bone marrow suppression is the dose-limiting toxicity; do not administer if baseline absolute neutrophil count (ANC) is <1500 cells/mm^3 (<1000 cells/mm^3 for patients with AIDS-related KS);** reduce future doses by 20% for severe neutropenia (<500 cells/mm^3 for 7 days or more) and consider the use of supportive therapy, including growth factor treatment. When administered as sequential infusions, taxane derivatives (docetaxel, paclitaxel) should be administered before platinum derivatives (carboplatin, cisplatin) to limit myelosuppression.

- Cardiovascular effects: Infusion-related hypotension, bradycardia, and/or hypertension may occur; frequent monitoring of vital signs is recommended, especially during the first hour of the infusion. Rare but severe conduction abnormalities have been reported; conduct cardiac monitoring during subsequent infusions for these patients.

- Hypersensitivity reactions: **[U.S. Boxed Warning]: Severe hypersensitivity reactions have been reported;** premedication may minimize this effect. Stop infusion and do not rechallenge for severe hypersensitivity reactions (hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, urticaria). Minor hypersensitivity reactions (flushing, skin reactions, dyspnea, hypotension, or tachycardia) do not require interruption of treatment.

- Peripheral neuropathy: With use, peripheral neuropathy may occur; patients with pre-existing neuropathies from chemotherapy or coexisting conditions (eg, diabetes mellitus) may be at a higher risk; reduce dose by 20% for severe neuropathy.

Disease-related concerns:

- Hepatic impairment: Use with extreme caution in patients with hepatic dysfunction (myelotoxicity may be worsened); dose reductions are recommended.

Special populations:

- Elderly: Use with caution in the elderly; increased risk of toxicity (neutropenia, neuropathy).

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Dehydrated alcohol: Formulations contain dehydrated alcohol; may cause adverse CNS effects.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Geriatric ConsiderationsElderly patients may have a higher incidence of severe neuropathy, severe myelosuppression, or cardiovascular events as compared to younger patients.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated embryotoxicity, fetal toxicity, and maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions, breast-feeding is contraindicated.

Adverse ReactionsPercentages reported with single-agent therapy. **Note:** Myelosuppression is dose related, schedule related, and infusion-rate dependent (increased incidences with higher doses, more frequent doses, and longer infusion times) and, in general, rapidly reversible upon discontinuation.

>10%:

Cardiovascular: Flushing (28%), ECG abnormal (14% to 23%), edema (21%), hypotension (4% to 12%)

Dermatologic: Alopecia (87%), rash (12%)

Gastrointestinal: Nausea/vomiting (52%), diarrhea (38%), mucositis (17% to 35%; grades 3/4: up to 3%), stomatitis (15%; most common at doses >390 mg/m^2), abdominal pain (with intraperitoneal paclitaxel)

Hematologic: Neutropenia (78% to 98%; grade 4: 14% to 75%; onset 8-10 days, median nadir 11 days, recovery 15-21 days), leukopenia (90%; grade 4: 17%), anemia (47% to 90%; grades 3/4: 2% to 16%), thrombocytopenia (4% to 20%; grades 3/4: 1% to 7%), bleeding (14%)

Hepatic: Alkaline phosphatase increased (22%), AST increased (19%)

Local: Injection site reaction (erythema, tenderness, skin discoloration, swelling: 13%)

Neuromuscular & skeletal: Peripheral neuropathy (42% to 70%; grades 3/4: up to 7%), arthralgia/myalgia (60%), weakness (17%)

Renal: Creatinine increased (observed in KS patients only: 18% to 34%; severe: 5% to 7%)

Miscellaneous: Hypersensitivity reaction (31% to 45%; grades 3/4: up to 2%), infection (15% to 30%)

1% to 10%:

Cardiovascular: Bradycardia (3%), tachycardia (2%), hypertension (1%), rhythm abnormalities (1%), syncope (1%), venous thrombosis (1%)

Dermatologic: Nail changes (2%)

Hematologic: Febrile neutropenia (2%)

Hepatic: Bilirubin increased (7%)

Respiratory: Dyspnea (2%)

<1%, postmarketing, and/or case reports: Anaphylaxis, ataxia, atrial fibrillation, AV block, back pain, cardiac conduction abnormalities, cellulitis, CHF, chills, conjunctivitis, dehydration, enterocolitis, extravasation recall, hepatic encephalopathy, hepatic necrosis, induration, intestinal obstruction, intestinal perforation, interstitial pneumonia, ischemic colitis, lacrimation increased, maculopapular rash, malaise, MI, necrotic changes and ulceration following extravasation, neuroencephalopathy, neutropenic enterocolitis, ototoxicity (tinnitus and hearing loss), pancreatitis, paralytic ileus, phlebitis, pruritus, pulmonary embolism, pulmonary fibrosis, radiation recall, radiation pneumonitis, pruritus, renal insufficiency, seizure, skin exfoliation, skin fibrosis, skin necrosis, Stevens-Johnson syndrome, supraventricular tachycardia, toxic epidermal necrolysis, ventricular tachycardia (asymptomatic), visual disturbances (scintillating scotomata)

Oncology: VesicantNo; the drug is an irritant. See Management of Drug Extravasations.
Oncology: Emetic PotentialLow (10% to 30%)
Metabolism/Transport Effects**Substrate** (major) of CYP2C8, 3A4; **Induces** CYP3A4 (weak)
Drug Interactions

Antineoplastic Agents (Anthracycline): Taxane Derivatives may enhance the adverse/toxic effect of Antineoplastic Agents (Anthracycline). Taxane Derivatives may increase the serum concentration of Antineoplastic Agents (Anthracycline). Taxane Derivatives may also increase the formation of toxic anthracycline metabolites in heart tissue. *Risk D: Consider therapy modification*

CYP2C8 Inducers (Highly Effective): May increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Moderate): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Strong): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

DOXOrubicin: Taxane Derivatives may decrease the metabolism of DOXOrubicin. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Platinum Derivatives: May enhance the myelosuppressive effect of Taxane Derivatives. Administer Taxane derivative before Platinum derivative when given as sequential infusions to limit toxicity. *Risk D: Consider therapy modification*

Trastuzumab: May decrease the serum concentration of Paclitaxel. Paclitaxel may increase the serum concentration of Trastuzumab. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vinorelbine: Paclitaxel may enhance the neurotoxic effect of Vinorelbine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid black cohosh, dong quai in estrogen-dependent tumors. Avoid valerian, St John's wort (may decrease paclitaxel levels), kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersCBC with differential; monitor for hypersensitivity reactions, vital signs (frequently during the first hour of infusion), continuous cardiac monitoring (patients with conduction abnormalities)

Reference RangeMean maximum serum concentrations: 435-802 ng/mL following 24-hour infusions of 200-275 mg/m^2 and were approximately 10% to 30% of those following 6-hour infusions of equivalent doses

Nursing: Physical Assessment/MonitoringShould only be administered under the supervision of an experienced cancer chemotherapy physician. Paclitaxel (protein bound) is not interchangeable with paclitaxel (conventional). Assess patient carefully for cautious use indications and contraindications. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, risk of increased or decreased levels/effects of paclitaxel). See Administration for specific infusion directions. Infusion site must be monitored closely to avoid extravasation. Evaluate results of laboratory tests and adverse response prior to, during, and between each infusion (eg, hypersensitivity reaction, cardiovascular abnormalities, sensory neuropathy, myelosuppression, GI irritation). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelet count, liver and kidney function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug can only be given by infusion. Report immediately any redness, swelling, burning, pain at infusion site or signs of allergic reaction (eg, respiratory difficulty or swallowing, chest tightness, rash, hives, swelling of lips or mouth). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition. You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause loss of hair (will grow back after therapy); experience nausea or vomiting (consult prescriber for approved antiemetic); feel weak or lethargic (use caution when driving or engaging in tasks that require alertness until response to drug is known); or mouth sores (sucking ice chips may help; use good oral care with soft toothbrush and waxed dental floss; consult prescriber if severe or infection developes). Report numbness or tingling in fingers or toes (use care to prevent injury); signs of opportunistic infection (fever, chills, sore throat, burning urination, fatigue); unusual bleeding (tarry stools, easy bruising, or blood in stool, urine, or mouth); unresolved mouth sores; nausea or vomiting; or skin rash or itching. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate barrier contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 6 mg/mL (5 mL, 16.7 mL, 25 mL, 50 mL) [contains ethanol and purified Cremophor® EL (polyoxyethylated castor oil)]

Onxol® : 6 mg/mL (5 mL, 25 mL, 50 mL) [contains ethanol and purified Cremophor® EL (polyoxyethylated castor oil)]

Taxol®: 6 mg/mL (5 mL [DSC], 16.7 mL, 50 mL) [contains ethanol and purified Cremophor® EL (polyoxyethylated castor oil)]

Generic AvailableYes

Mechanism of ActionPaclitaxel promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G_2 mitotic phase, and inhibiting cell replication. In addition, the drug can distort mitotic spindles, resulting in the breakage of chromosomes. Paclitaxel may also suppress cell proliferation and modulate immune response.

Pharmacodynamics/Kinetics

Distribution:

V_d: Widely distributed into body fluids and tissues; affected by dose and duration of infusion

V_{dss}:

1- to 6-hour infusion: 67.1 L/m^2

24-hour infusion: 227-688 L/m^2

Protein binding: 89% to 98%

Metabolism: Hepatic via CYP2C8 and 3A4; forms metabolites (primarily 6α-hydroxypaclitaxel)

Half-life elimination:

1- to 6-hour infusion: Mean (beta): 6.4 hours

3-hour infusion: Mean (terminal): 13.1-20.2 hours

24-hour infusion: Mean (terminal): 15.7-52.7 hours

Excretion: Feces (~70%, 5% as unchanged drug); urine (14%)

Clearance: Mean: Total body: After 1- and 6-hour infusions: 5.8-16.3 L/hour/m^2; After 24-hour infusions: 14.2-17.2 L/hour/m^2

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsSensory neuropathy is almost universal at doses >250 mg/m^2; motor neuropathy is uncommon at doses <250 mg/m^2. Myopathic effects are common with doses >200 mg/m^2, generally occur within 2-3 days of treatment, and resolve over 5-6 days. Intraperitoneal administration of paclitaxel is associated with a higher incidence of chemotherapy related toxicity.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Severe, potentially dose-limiting mucositis and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine

Oncology: Bone Marrow CommentsGlutamine may decrease mucositis

Index TermsNSC-125973; NSC-673089

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Spencer CM and Faulds D, “Paclitaxel. A Review of Its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Potential in the Treatment of Cancer,” *Drugs*, 1994, 48(5):794-847.[PubMed 7530632]

International Brand NamesAclixel (MX); Anzatac (ID); Anzatax (AU, BR, HK, MY, SG, TH, TW); Asotax (AR, MX); Biotax (IL); Bristaxol (CO, MX); Britaxol (CN); Clitaxel (VE); Cryoxet (MX); Ebetaxel (HK, ID, IL); Formoxol (MY); Genaxol (TW); Genexol (KP); Intaxel (HK, IN, TH); Mitotax (MY); Neotax (KP); Oncotaxel (TH); Paclitaxin (TH); Pacxel (KP); Padexol (KP); Panataxel (EC); Parexel (PY); Paxene (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Paxenor (PL); Paxus (ID); Poltaxel (PL); Praxel (CN, MX, TH); Sindaxel (PL); Taxocris (UY); Taxol (AR, BE, BG, CH, CL, CZ, DE, DK, EE, ES, FI, GR, HK, HN, ID, IT, KP, MY, NL, NO, NZ, PH, PK, PL, SE, TH, ZA); Taycovit (PE)

Palifermin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(pal ee FER min)
U.S. Brand NamesKepivance®
Pharmacologic CategoryKeratinocyte Growth Factor
Use: Labeled IndicationsDecrease the incidence and severity of severe oral mucositis associated with hematologic malignancies in patients receiving myelotoxic therapy requiring hematopoietic stem cell support
Use: DentalDecrease the incidence and severity of severe oral mucositis associated with hematologic malignancies in patients receiving myelotoxic therapy requiring hematopoietic stem cell support
Dosing: Adults**Oral mucositis:** I.V.: 60 mcg/kg/day for 3 consecutive days before and after myelotoxic therapy; total of 6 doses

Note: Administer first 3 doses prior to myelotoxic therapy, with the 3rd dose given 24-48 hours before therapy begins. The last 3 doses should be administered after myelotoxic therapy, with the first of these doses after but on the same day as hematopoietic stem cell infusion and at least 4 days after the most recent dose of palifermin.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo adjustment necessary.
Administration: I.V.Administer by I.V. bolus. If heparin is used to maintain the patency of the I.V. line, flush line with saline prior to and after palifermin administration. Do not administer palifermin during or within 24 hours before or after chemotherapy. Allow solution to reach room temperature prior to administration; do not use if at room temperature >1 hour. Do not filter.
Administration: I.V. DetailpH 6.5
StorageStore intact vials under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light. Reconstituted vials are stable for up to 72 hours refrigerated and should not be used if left at room temperature >2 hours (data on file). The product labeling, however, indicates that reconstituted vials are stable for up to 24 hours refrigerated and should not be used if left at room temperature >1 hour. Protect reconstituted solution from light. Do not freeze reconstituted product.
ReconstitutionTo reconstitute, slowly add 1.2 mL SWFI, to a final concentration of 5 mg/mL. Swirl gently; do not shake or vigorously agitate. Do not filter during preparation or administration.
Compatibility**Incompatible:** Heparin.
ContraindicationsHypersensitivity to palifermin, *E. coli*-derived proteins, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Mucocutaneous effects: Edema, erythema, pruritus, rash, oral/perioral dysesthesia, taste alteration, tongue discoloration, and tongue thickening may occur; instruct patients to report mucocutaneous effects.
- Mucositis: If administered within 24 hours of chemotherapy, palifermin may increase the severity and duration of mucositis due to the increased sensitivity of rapidly-dividing epithelial cells. Palifermin should be administered prior to and following, but not during or within 24 hours of (before or after) chemotherapy.

Disease-related concerns:

- Nonhematologic malignancies: Safety and efficacy have not been established with nonhematologic malignancies; effect on the growth of nonhematopoietic human tumors is not known.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Tumor growth: Palifermin has been shown to enhance epithelial tumor cell lines *in vitro*.

Pregnancy Risk FactorC
Pregnancy ConsiderationsPalifermin has been shown to be embryotoxic in animal studies at doses also associated with maternal toxicity. There are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%:

Cardiovascular: Edema (28%), hypertension (7% to 14%)

Central nervous system: Fever (39%); pain (16%); dysesthesia (oral hyperesthesia, hypoesthesia, and paresthesia 12%)

Dermatologic: Rash (62%; grade 3: 3%), pruritus (35%), erythema (32%)

Gastrointestinal: Serum amylase increased (grades 3/4: 38%), mouth/tongue discoloration or thickness (17%), taste alteration (16%), serum lipase increased (grades 3/4: 11%)

Renal: Proteinuria (17%)

Respiratory: Cough (32%), rhinitis (16%)

1% to 10%:

Neuromuscular & skeletal: Arthralgia (10%)

Miscellaneous: Antibody formation (2%)

<1%, postmarketing, and/or case reports: Flexural hyperpigmentation

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringTeach patient/caregiver reason for use, possible side effects, appropriate interventions, adverse symptoms to report, and pregnancy precautions (see Patient Education).

Patient EducationThis drug can only be administered by intravenous infusion; you will be monitored during and after infusion. Report any pain, redness, or swelling at infusion site. This drug may help reduce the incidence of mouth sores; however, good mouth care with soft swabs and nonirritating mouth wash is very important. May cause some mouth/tongue discoloration or thickness and some taste alteration (frequent mouth care or sucking lozenges may help). Report any swelling or loss of sensation in extremities; usual joint or muscle pain; fever; skin rash or redness; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Kepivance®: 6.25 mg [contains mannitol 50 mg, sucrose 25 mg]

Generic AvailableNo

ManufacturerAmgen Inc

Mechanism of ActionPalifermin is a recombinant keratinocyte growth factor (KGF) produced in *E. coli*. Endogenous KGF is produced by mesenchymal cells in response to epithelial tissue injury. KGF binds to the KGF receptor resulting in proliferation, differentiation and migration of epithelial cells in multiple tissues, including (but not limited to) the tongue, buccal mucosa, esophagus, and salivary gland.

Pharmacodynamics/Kinetics

Onset of action: Epithelial cell proliferation (dose-dependent): 48 hours

Half-life elimination: 4.5 hours (range: 3.3-5.7 hours)

Pharmacotherapy Pearls**Oncology Comment:** The Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) guidelines for the prevention and treatment of mucositis recommend palifermin (at the FDA-approved dose) for the prevention of oral mucositis in patients with hematologic malignancies who are receiving high-dose chemotherapy and total body irradiation with autologous stem cell transplantation (Keefe, 2007).

Guidelines from the American Society of Clinical Oncology (ASCO) for the use of chemotherapy and radiotherapy protectants (Hensley, 2008) recommend the use of palifermin to decrease the incidence of severe mucositis in patients undergoing autologous stem-cell transplantation with a total body irradiation (TBI) conditioning regimen. According to the ASCO guidelines, data are insufficient to recommend palifermin when the conditioning regimen is chemotherapy only. Palifermin may be considered in patients undergoing myeloablative allogeneic stem-cell transplantation with a TBI conditioning regimen, however data are again insufficient to recommend palifermin when the conditioning regimen is chemotherapy only. Due to a lack of appropriate data, the guidelines also do not recommend palifermin use in non-stem-cell transplantation treatment regimens or for use when treating solid tumors.

Dental Health Professional ConsiderationsPalifermin works at the cellular level by protecting the epithelial cells lining the mouth and throat from damage caused by chemotherapy and radiation and by stimulating the growth and development of new epithelial cells to build up the mucosal barrier.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste alteration, mouth/tongue discoloration or thickness. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentEdema is common; rule out lithium as a cause. Rash is common; monitor, especially if receiving lamotrigine.

Index TermsAMJ 9701; rhKGF; rhu Keratinocyte Growth Factor; rHu-KGF

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International Brand NamesKepivance (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Paliperidone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

Gill SS, Bronskill SE, Normand SL, et al, “Antipsychotic Drug Use and Mortality in Older Adults With Dementia,” *Ann Intern Med*, 2007, 146(11):775-86.[PubMed 17548409]

Schneeweiss S, Setoguchi S, Brookhart A, et al, “Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients,” *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Pronunciation(pal ee PER i done)

U.S. Brand NamesInvega®

Canadian Brand NamesInvega®

Pharmacologic CategoryAntipsychotic Agent, Atypical

Use: Labeled IndicationsTreatment of schizophrenia

Use: Unlabeled/InvestigationalPsychosis/agitation related to Alzheimer's dementia

Dosing: Adults**Schizophrenia:** Oral: Usual: 6 mg once daily in the morning; titration not required, though some may benefit from higher or lower doses. If exceeding 6 mg/day, increases of 3 mg/day are recommended no more frequently than every 5 days, up to a maximum of 12 mg/day. Some patients may require only 3 mg/day.

Dosing: ElderlyRefer to adult dosing. Additional monitoring of renal function and orthostatic blood pressure may be warranted.

Dosing: Renal Impairment

Mild impairment (Cl_{cr} 50 to <80 mL/minute): Initial: 3 mg once daily; may increase to maximal dose of 6 mg/day if needed

Moderate-to-severe impairment (Cl_{cr} 10-49 mL/minute): Initial: 1.5 mg once daily; may increase to maximal dose of 3 mg/day if needed

Severe impairment (Cl_{cr} <10 mL/minute): Has not been studies; not recommended

Dosing: Hepatic ImpairmentNo adjustment necessary for mild-to-moderate (Child-Pugh class A and B) impairment. Not studied in severe impairment.

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered with or without food. Extended release tablets should be swallowed whole with liquids; do not crush, chew, or divide.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at controlled room temperature of ≤25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture.

ContraindicationsHypersensitivity to paliperidone, risperidone, or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Dementia: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction and prolong the QT_c interval; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics. Risk may be increased by conditions or concomitant medications which cause bradycardia, hypokalemia, and/or hypomagnesemia. Avoid use in combination with QT_c-prolonging drugs. Avoid use in patients with congenital long-QT syndrome and in patients with history of cardiac arrhythmia.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (eg, Alzheimer's disease). Do not use in patients unable to swallow the tablet whole.

- Extrapyramidal symptoms: May cause extrapyramidal symptoms (EPS), including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is generally much lower relative to typical/conventional antipsychotics). Risk of tardive dyskinesia may be increased in the elderly, particularly women. Symptoms may be masked by antipsychotic treatment. Risk of dystonia (and probably other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Hyperglycemia: Atypical antipsychotics have been associated with development of hyperglycemia; in some cases, may be extreme and associated with ketoacidosis, hyperosmolar coma, or death. Use with caution in patients with diabetes (or risk factors) or other disorders of glucose regulation; monitor for worsening of glucose control.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May be low to moderately sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Suicidal ideation: The possibility of a suicide attempt is inherent in psychotic illness or bipolar disorder; use with caution in high-risk patients during initiation of therapy. Prescriptions should be written for the smallest quantity consistent with good patient care.

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

- Weight gain: Significant weight gain has been observed with antipsychotic therapy; incidence varies with product. Monitor waist circumference and BMI.

Disease-related concerns:

- Dementia: **[U.S. Boxed Warning]: Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo.** An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Paliperidone has not been studied in this clinical population and is not approved for the treatment of dementia-related psychosis.

- Gastrointestinal disorders: Use is not recommended in patients with pre-existing severe gastrointestinal narrowing disorders. Patients with upper GI tract alterations in transit time may have increased or decreased bioavailability of paliperidone.

- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors (elevates prolactin levels); galactorrhea, amenorrhea, gynecomastia, impotence, and decreased bone density are associated with prolactin-elevating medications.

- Renal impairment: Use with caution in patients with renal disease; dosage reduction is recommended.

- Seizures: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold. Elderly patients may be at increased risk of seizures due to an increased prevalence of predisposing factors.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

Dosage form specific issues:

- Extended-release tablet: Formulation consists of drug within a nonabsorbable shell; following drug release/absorption, the shell is expelled in the stool.

Geriatric ConsiderationsAny changes in disease status in any organ system can result in behavior changes. Extrapyramidal syndrome symptoms occur less with this agent when total daily dose remains ≤6 mg as compared with phenothiazines and butyrophenone classes of antipsychotics.

In the treatment of agitated, demented, elderly patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control. In light of significant risks and adverse effects in elderly population compared with limited data demonstrating efficacy in the treatment of dementia related psychosis, aggression, and agitation, an extensive risk:benefit analysis should be performed prior to use.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies with risperidone indicate an increase in fetal mortality. There are no adequate and well-controlled studies in pregnant women. Reversible EPS symptoms were noted in neonates following maternal use of risperidone during the last trimester. Healthcare providers are encouraged to enroll women 18-45 years of age exposed to paliperidone during pregnancy in the Atypical Antipsychotics Pregnancy Registry (1-866-961-2388).

LactationEnters breast milk/use caution

Adverse Reactions

>10%:

Cardiovascular: Tachycardia (12% to 14%)

Central nervous system: Headache (11% to 14%), somnolence (6% to 11% dose dependent)

1% to 10%:

Cardiovascular: Orthostatic hypotension (1% to 4% dose dependent), bundle branch block (<1% to 3%), AV block (first degree ≤2%), arrhythmia (≤2%)

Central nervous system: Akathisia (3% to 10% dose dependent), EPS (2% to 7% dose dependent), parkinsonism (≤7% dose dependent), dizziness (4% to 6%), dystonia (1% to 5% dose dependent), hypertonia (1% to 4% dose dependent), fatigue (1% to 2%)

Endocrine & metabolic: Weight gain (6% to 9% dose dependent)

Gastrointestinal: Salivation increased (≤4% dose dependent), xerostomia (1% to 3%), abdominal pain (1% to 3%)

Neuromuscular & skeletal: Hyperkinesia (3% to 10% dose dependent), dyskinesia (3% to 9% dose dependent), tremor (3% to 4%), weakness (≤2%)

<1%, postmarketing, and/or case reports: Anaphylactic reaction, bradycardia, edema, hyperglycemia, ischemia, neuroleptic malignant syndrome, palpitation, prolactin increased, QT_c interval prolongation, sedation, seizure, syncope, tardive dyskinesia, tongue swelling

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Atypical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

CarBAMazepine: May decrease the serum concentration of Paliperidone. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Itraconazole: May decrease the metabolism of Paliperidone. *Risk C: Monitor therapy*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Monitoring ParametersVital signs; fasting lipid profile and fasting blood glucose/Hgb A_{1c} (prior to treatment, at 3 months, then annually), prolactin levels; BMI, personal/family history of obesity, diabetes, waist circumference; blood pressure; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms; orthostatic blood pressure changes for 3-5 days after starting or increasing dose. Weight should be assessed prior to treatment, at 4 weeks, 8 weeks, 12 weeks, and then at quarterly intervals. Consider titrating to a different antipsychotic agent for a weight gain ≥5% of the initial weight.

Nursing: Physical Assessment/MonitoringUse with caution in presence of renal disease, cardiovascular disease, hypovolemia, or dehydration. Assess potential for interactions (eg, cumulative CNS depression, hypotension) with other pharmacological agents or herbal products patient may be taking. Assess results of laboratory tests prior to treatment, at 3 months, and annually with long-term therapy. Instruct patients with diabetes to monitor serum glucose closely (may seriously affect glucose control). Assess therapeutic effectiveness (according to purpose for treatment) and adverse reactions (weight gain, cardiovascular changes, extrapyramidal effects, neuroleptic syndrome, CNS changes) regularly during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsFasting lipid profile and fasting blood glucose/Hgb A_{1c} (prior to treatment, at 3 months, then annually), prolactin levels

Patient EducationDo not take any new prescription or over-the-counter medications or herbal products without consulting prescriber. Take exactly as directed with liquids. Do not chew, crush, or break tablet; swallow whole with liquids. Do not increase dose or frequency or discontinue without consulting prescriber; may take several weeks to achieve desired results. Avoid alcohol or stimulants unless approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, you should monitor glucose levels closely; this medication may affect glucose control (notify prescriber of any change in glucose levels). This medication comes in a nonabsorbable shell, after release of the drug the shell is expelled and may be visible in the stool (normal). You may experience fatigue, dizziness, restlessness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug in known); orthostatic hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); nausea, abdominal pain, dry or sore mouth (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); difficulty on urination (void before taking medication). Report immediately any chest pain, rapid or irregular heart beat; difficulty breathing; weight gain >5 pounds; muscle or bone pain, tremors, or unusual movements; altered gait or balance; CNS changes (unusual anxiety or nervousness, abnormal thoughts, excessive sleepiness, dizziness, confusion, or suicidal ideation); or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian availability; not available in U.S.

Tablet, extended-release:

Invega®: 1.5 mg, 3 mg, 6 mg, 9 mg [osmotic controlled release]

Invega® [CAN]: 12 mg [osmotic controlled release, not available in the U.S.]

Generic AvailableNo

ManufacturerALZA Corporation

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Invega)

3 mg (100): $1093.03

6 mg (100): $1093.03

9 mg (100): $1638.97

Mechanism of ActionPaliperidone is considered a benzisoxazole atypical antipsychotic as it is the primary active metabolite of risperidone. As with other atypical antipsychotics, it’s therapeutic efficacy is believed to result from mixed central serotonergic and dopaminergic antagonism. The addition of serotonin antagonism to dopamine antagonism (classic neuroleptic mechanism) is thought to improve negative symptoms of psychoses and reduce the incidence of extrapyramidal side effects. Similar to risperidone, paliperidone demonstrates high affinity to α_1, D_2, H_1, and 5-HT_{2C} receptors, and low affinity for muscarinic and 5-HT_{1A} receptors. In contrast to risperidone, paliperidone displays nearly 10-fold lower affinity for α_2 and 5-HT_{2A} receptors, and nearly three- to fivefold less affinity for 5-HT_{1A} and 5-HT_{1D}, respectively.

Pharmacodynamics/Kinetics

Distribution: V_d: 487 L

Protein binding: 74%

Metabolism: Hepatic via CYP2D6 and 3A4 (limited role in elimination); minor metabolism (<10% each) via dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission

Bioavailability: 28%

Half-life elimination: 23 hours; 24-51 hours with renal impairment (Cl_{cr} <80 mL/minute)

Time to peak, plasma: ~24 hours

Excretion: Urine (80%); feces (11%)

Related Information

- Antipsychotic Agents
- Antipsychotic Receptor Profile
- Atypical Antipsychotics
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsInvega® is an extended release tablet based on the OROS® osmotic delivery system. Water from the GI tract enters through a semipermeable membrane coating the tablet, solubilizing the drug into a gelatinous form which, through hydrophilic expansion, is then expelled through laser-drilled holes in the coating.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentPaliperidone is an antipsychotic agent of a class often referred to as atypical. It should be noted that the definition of the term “atypical” is not universally agreed upon. Some prefer to describe antipsychotics based on their pharmacological properties. A common feature of all definitions used to describe “atypical” antipsychotics is the lack of significant acute or subacute EPS, at dosages generally associated with antipsychotic actions. Other experts have included definitions of atypicality that include a) failure to increase serum prolactin levels; b) superior efficacy for positive, negative, and cognitive symptoms; and c) lack of evidence of tardive dyskinesia or dystonia following chronic administration. Paliperidone is associated with a dose dependent increase in EPS; however, there was no difference compared with placebo in the incidence of any EPS symptoms at doses ≤6 mg/day.

Tardive dyskinesia (TD) secondary to **typical** antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. The incidence of TD associated with the atypical antipsychotics is estimated to be 0.5% to 1%. It is not clear if this estimate represents a risk associated with mental illness or to what extent drug therapy can be implicated. Atypical antipsychotics appear less likely to cause tardive dyskinesia than typical antipsychotics (fluphenazine, haloperidol).

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Cardiovascular ConsiderationsPaliperidone may cause orthostatic hypotension and tachycardia but to a degree which may be less than is seen with other agents (eg, phenothiazines [chlorpromazine, thioridazine]). Paliperidone may also prolong the QT interval. For these reasons, patient's with cardiovascular disease should be monitored closely while on therapy.

Anesthesia and Critical Care Concerns/Other ConsiderationsPaliperidone may cause orthostatic hypotension and tachycardia but to a degree which may be less than is seen with other agents (eg, phenothiazines [chlorpromazine, thioridazine]). Paliperidone may also prolong the QT interval. For these reasons, patient's with cardiovascular disease should be monitored closely while on therapy.

Index Terms9-hydroxy-risperidone; 9-OH-risperidone

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International Brand NamesInvega (AR, CH, CZ, DE, DK, EE, GB, HK, IE, KP, MY, SE, SG, TW)

Palivizumab

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Synagis® may be confused with Synalgos®-DC, Synvisc®

Pronunciation(pah li VIZ u mab)
U.S. Brand NamesSynagis®
Canadian Brand NamesSynagis®
Pharmacologic CategoryMonoclonal Antibody
Use: Labeled IndicationsPrevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in infants and children at high risk of RSV disease
Dosing: Pediatric

Prevention of RSV: I.M.: Infants and Children <2 years: 15 mg/kg of body weight, monthly throughout RSV season (first dose administered prior to commencement of RSV season)

Note:*Cardiopulmonary bypass patients:* I.M.: Administer a dose as soon as possible after cardiopulmonary bypass procedure, even if <1 month from previous dose.

Administration: I.M.Injection should (preferably) be in the anterolateral aspect of the thigh; gluteal muscle should not be used routinely; injection volume over 1 mL should be given as divided doses
StorageStore in refrigerator at a temperature between 2°C to 8°C (35.6°F to 46.4°F) in original container; do not freeze. Do not shake, vigorously agitate or dilute the solution.
ContraindicationsHistory of severe prior reaction to palivizumab or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Very rare cases of anaphylaxis have been observed; rare cases of severe acute hypersensitivity reactions have also been reported. Use with caution after mild hypersensitivity reaction; permanently discontinue for severe hypersensitivity reaction.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia); bleeding/hematoma may occur from I.M. administration.

- Respiratory syncytial virus (RSV): Safety and efficacy have not been demonstrated in the treatment of established RSV disease.

Special populations:

- Pediatrics: Safety and efficacy have been established in infants with chronic lung disease, infants with a history of premature birth (≤35 weeks gestational age), and children with hemodynamically-significant congenital heart disease (CHD).

Pregnancy Risk FactorC
Pregnancy ConsiderationsNot for adult use; reproduction studies have not been conducted
Adverse ReactionsThe incidence of adverse events was similar between the palivizumab and placebo groups.
>1%:

Cardiovascular: Arrhythmia, cyanosis

Central nervous system: Fever, nervousness

Dermatologic: Rash

Gastrointestinal: Diarrhea, gastroenteritis, vomiting

Hepatic: ALT increase

Otic: Otitis media

Respiratory: Cough, rhinitis, upper respiratory infection, wheezing

<1%, postmarketing, and/or case reports: Anaphylaxis (very rare - includes angioedema, dyspnea, hypotonia, pruritus, respiratory failure, unresponsiveness, urticaria); antibody development, hypersensitivity reactions, injection site reactions, thrombocytopenia

Drug Interactions

Abciximab: May enhance the potential for allergic or hypersensitivity reactions to Monoclonal Antibodies. Also may cause thrombocytopenia or diminished therapeutic effects. *Risk C: Monitor therapy*

Monitoring ParametersMonitor for anaphylaxis or acute hypersensitivity reactions

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Synagis®: 100 mg/mL (0.5 mL, 1 mL)

Generic AvailableNo

ManufacturerMedImmune, Inc

Mechanism of ActionExhibits neutralizing and fusion-inhibitory activity against RSV; these activities inhibit RSV replication in laboratory and clinical studies

Pharmacodynamics/Kinetics

Half-life elimination: Children <24 months: 20 days

Time to peak, serum: 48 hours

Pharmacotherapy PearlsRSV prophylaxis should be initiated at the onset of the RSV season. In most areas of the United States, onset of RSV outbreaks is October to December, and termination is March to May, but regional differences occur.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause nervousness

Mental Health: Effects on Psychiatric TreatmentMay cause anemia; use caution with clozapine and carbamazepine

References

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International Brand NamesAbbosynagis (IL); Synagis (AE, AR, AT, AU, BE, BG, BH, BO, BR, CH, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, FI, FR, GB, GR, GT, HK, HN, IE, IL, IQ, IR, IT, JO, JP, KP, KW, LB, LY, MX, MY, NI, NL, NO, OM, PA, PE, PL, PR, PT, PY, QA, RU, SA, SE, SV, SY, TR, TW, UY, VE, YE)

Palonosetron

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Aloxi® may be confused with Eloxatin®, oxaliplatin

Palonosetron may be confused with dolasetron, granisetron, ondansetron

Pronunciation(pal oh NOE se tron)

U.S. Brand NamesAloxi®

Pharmacologic CategoryAntiemetic; Selective 5-HT_3 Receptor Antagonist

Use: Labeled Indications

I.V.: Prevention of chemotherapy-associated nausea and vomiting; indicated for prevention of acute (highly-emetogenic therapy) as well as acute and delayed (moderately-emetogenic therapy) nausea and vomiting; prevention of postoperative nausea and vomiting (PONV)

Oral: Prevention of chemotherapy-associated nausea and vomiting (moderately-emetogenic therapy)

Dosing: Adults

Chemotherapy-associated nausea and vomiting:

I.V.: 0.25 mg 30 minutes prior to the start of chemotherapy administration, day 1 of each cycle

Oral: 0.5 mg 1 hour prior to the start of chemotherapy

Breakthrough: Palonosetron has not been shown to be effective in terminating nausea or vomiting once it occurs and should not be used for this purpose.

PONV: I.V.: 0.075 mg immediately prior to anesthesia induction

Dosing: ElderlyNo dosage adjustment necessary.

Dosing: Renal ImpairmentNo dosage adjustment necessary.

Dosing: Hepatic ImpairmentNo dosage adjustment necessary.

Administration: I.V.Flush I.V. line with NS prior to and following administration.

Chemotherapy-associated nausea and vomiting: Infuse over 30 seconds, 30 minutes prior to the start of chemotherapy

PONV: Infuse over 10 seconds immediately prior to anesthesia induction

Administration: I.V. DetailpH: 4.5-5.5

Administration: OralMay administer with or without meals.

Dietary ConsiderationsCapsule: May be taken with or without meals.

Storage

Capsule: Store at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.

Injection: Store intact vials at room temperature of 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F); do not freeze. Protect from light. Solutions of 5 mcg/mL and 30 mcg/mL in NS, D_5W, $D_5$1/2NS, and D_5LR injection are stable for 48 hours at room temperature and 14 days under refrigeration.

CompatibilityStable in D_5W, NS, $D_5$1/2NS, and D_5LR.

Y-site administration: Compatible: Atropine, carboplatin, cisplatin, cyclophosphamide, dacarbazine, docetaxel, doxorubicin, epirubicin, famotidine, fentanyl, fluorouracil, gemcitabline, heparin, hydromorphone, ifosfamide, irinotecan, lidocaine, lorazepam, meperidine, metoclopramide, midazolam, morphine, oxaliplatin, paclitaxel, potassium chloride, promethazine, sufentanil, topotecan. **Incompatible:** Methylprednisolone

Compatibility in syringe: Compatible: Dexamethasone

Compatibility when admixed: Compatible: Dexamethasone

ContraindicationsHypersensitivity to palonosetron or any component of the formulation

Allergy Considerations

- Serotonin 5-HT_3 Antagonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Hypersensitivity has been observed rarely with I.V. palonosetron. Use with caution in patients allergic to other 5-HT$_3$ receptor antagonists; cross-reactivity has been reported.

- ECG effects: Some selective 5-HT$_3$ receptor antagonists have been associated with dose-dependent increases in ECG intervals (eg, PR, QRS duration, QT/QT$_c$, JT), usually occurring 1-2 hours after I.V. administration. In general, these changes are not clinically relevant, however, when these agents are used in conjunction with other agents that prolong these intervals, arrhythmia may occur. When used with agents that prolong the QT interval (eg, Class I and III antiarrhythmics), clinically relevant QT interval prolongation could result in torsade de pointes. A number of trials have shown that 5-HT$_3$ antagonists produce QT interval prolongation to variable degrees. Use with caution in patients at risk of QT prolongation and/or ventricular arrhythmia. Reduction in heart rate may also occur with the 5-HT$_3$ antagonists.

Disease-related concerns:

- Long QT syndrome: Use with caution in patients with congenital long QT syndrome or other risk factors for QT prolongation (eg, medications known to prolong QT interval, electrolyte abnormalities [hypokalemia or hypomagnesemia], and cumulative high-dose anthracycline therapy).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Chemotherapy-associated emesis: **For chemotherapy, should be used on a scheduled basis, not on an "as needed" (PRN) basis,** since data support the use of this drug only in the prevention of nausea and vomiting (due to antineoplastic therapy) and not in the rescue of nausea and vomiting. Not intended for treatment of nausea and vomiting or for chronic continuous therapy.

- PONV: Use is not recommended if there is little expectation of PONV; may use for low expectation of PONV if it is essential to avoid nausea and vomiting in the postoperative period.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women; use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsThe extent to which palonosetron is excreted in breast milk, if at all, is unknown. Due to the potential for adverse effects in the nursing infant, breast-feeding is not recommended.

Adverse ReactionsAdverse events may vary according to indication. In general, adverse reactions similar between I.V. and oral dosage forms.

1% to 10%:

Cardiovascular: QT prolongation (chemotherapy-associated <1%; PONV 1% to 5%), bradycardia (chemotherapy-associated 1%; PONV 4%), hypotension (≤1%), sinus bradycardia (≤1%), tachycardia (nonsustained) (≤1%)

Central nervous system: Headache (chemotherapy-associated 4% to 9%; PONV 3%), anxiety (1%), dizziness (≤1%), fatigue (≤1%)

Dermatologic: Pruritus (≤1%)

Endocrine & metabolic: Hyperkalemia (1%)

Gastrointestinal: Constipation (1% to 5%), diarrhea (≤1%), flatulence (≤1%)

Genitourinary: Urinary retention (≤1%)

Hepatic: ALT increased (≤1%; transient), AST increased (≤1%; transient)

Neuromuscular & skeletal: Weakness (1%)

<1%, postmarketing, and/or case reports: Abdominal pain, abnormal taste, allergic dermatitis, alopecia, amblyopia, anemia, anorexia, appetite decreased, arrhythmia, arthralgia, atrioventricular block (first and second degree), bilirubin increased (transient), chills, dyspepsia, dyspnea, edema (generalized), electrolyte fluctuations, epistaxis, erythema, euphoric mood, extrasystoles, eye irritation/edema, fever, flu-like syndrome, gastritis, glycosuria, hiccups, hot flash, hyperglycemia, hypersensitivity (rare), hypersomnia, hypertension, hypokalemia, hypoventilation, injection site reactions (burning/discomfort/induration/pain; rare), insomnia, intestinal hypomotility, joint stiffness, laryngospasm, metabolic acidosis, motion sickness, myalgia, myocardial ischemia, pain in extremities, paresthesia, platelets decreased, rash, salivation increased, sinus arrhythmia, sinus tachycardia, sinusitis, somnolence, supraventricular extrasystoles, tinnitus, T-wave amplitude decreased, vein discoloration, vein distention, ventricular extrasystoles, xerostomia

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 2D6, 3A4

Drug Interactions

Apomorphine: Antiemetics (5HT3 Antagonists) may enhance the hypotensive effect of Apomorphine. *Risk X: Avoid combination*

Nursing: Physical Assessment/MonitoringAssess allergy history (selective 5-HT$_3$ receptor antagonists) prior to administering. Use with caution in presence of, or potential for, cardiac conduction abnormalities (eg, QT prolongation, medication known to prolong QT interval, electrolyte abnormalities). To be used on a scheduled basis (not on a "PRN" basis) for prevention of nausea and vomiting associated with moderately to highly emetogenic cancer chemotherapy; not recommended for treatment of existing chemotherapy-induced emesis. Follow infusion specifics. Assess patient response and adverse reactions at beginning and periodically during therapy. Teach patient possible side effects and adverse symptoms to report.

Patient EducationThis drug is given to reduce the incidence of nausea and vomiting. Do not take any other medication for nausea and vomiting with this medication unless approved by prescriber. This medication can only be given by intravenous infusion and you will be monitored during infusion. Report immediately any chest pain, respiratory difficulty, pain or itching at infusion site. May cause headache, drowsiness, or dizziness (request assistance when getting up or changing position and do not perform activities requiring alertness until response to drug is known). Report chest pain or palpitations; persistent headache; excessive drowsiness; fever; or changes in elimination patterns (constipation or diarrhea) or other adverse effects. **Breast-feeding precaution:** Consult prescriber if you are or intend to breast-feed.

Product AvailabilityAloxi® capsules: FDA approved August 2008; availability anticipated in the first quarter of 2009

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Aloxi®: 0.5 mg

Injection, solution:

Aloxi®: 0.05 mg/mL (1.5 mL, 5 mL) [contains edetate disodium]

Generic AvailableNo

ManufacturerEisai, Inc

Pricing: U.S. (www.drugstore.com)

Solution (Aloxi)

0.25 mg/5 mL (5): $394.25

Mechanism of ActionSelective 5-HT$_3$ receptor antagonist, blocking serotonin, both on vagal nerve terminals in the periphery and centrally in the chemoreceptor trigger zone

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: V$_d$: 8.3 ± 2.5 L/kg

Protein binding: ~62%

Metabolism: ~50% metabolized via CYP enzymes (and likely other pathways) to relatively inactive metabolites (N-oxide-palonosetron and 6-S-hydroxy-palonosetron); CYP1A2, 2D6, and 3A4 contribute to its metabolism

Bioavailability: Oral: 97%

Half-life elimination: I.V.: Terminal: ~40 hours; Oral: 29-45 hours (healthy patients), 38-62 hours (cancer patients)

Time to peak, plasma: Oral: 3-7 hours (healthy patients); ~5 hours (cancer patients)

Excretion: Urine (80% to 93%, 40% as unchanged drug); feces (5% to 8%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety and dizziness; may rarely cause euphoria, insomnia, or sedation

Mental Health: Effects on Psychiatric TreatmentUse caution with thioridazine and ziprasidone; combined use may cause QT prolongation

Index TermsPalonosetron Hydrochloride; RS-25259; RS-25259-197

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International Brand NamesAloxi (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Onicit (BR, CN, CO, DO, GT, HN, MX, NI, PE, SV, VE); Paloxi (ID, IL, KP); Palzen (IN)

Special Alerts

Bisphosphonates: Safety Update Regarding Possible Association With Atrial Fibrillation - November 2008

The Food and Drug Administration (FDA) has been reviewing placebo-controlled trials of the 7 bisphosphonates currently marketed in the US. This review is in response to study results associating an increased incidence of atrial fibrillation (AF) with alendronate or zoledronic acid use in women (65-89 years of age) with osteoporosis.

The FDA reviewed all the submitted data (19,687 bisphosphonate-treated patients and 18,358 placebo-treated patients) from these studies. Overall, the occurrence of AF was rare in each study with an absolute difference in event rates between each of the bisphosphonate and placebo arms of 0-3 per 1000. A zoledronic acid study showed a statistically significant increase in the rate of AF in the active treatment arm. However, no clear association between bisphosphonate use and AF could be established. In this study, AF events were diagnosed more than 30 days after receiving zoledronic acid in 47 of the 50 patients diagnosed with AF. According to the FDA, healthcare providers should not alter their prescribing patterns for bisphosphonates and patients should not stop taking their medication.

The FDA will continue monitoring the safety of bisphosphonates through postmarketing reports and is assessing the need for additional epidemiologic studies.

Further information is available at http://www.fda.gov/cder/drug/early_comm/bisphosphonates_update_200811.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Aredia® may be confused with Adriamycin, Meridia®

International issues:

Linoten® [Spain] may be confused with Lidopen® which is a brand name for lidocaine in the U.S.

Pronunciation(pa mi DROE nate)

U.S. Brand NamesAredia®

Canadian Brand NamesAredia®; Pamidronate Disodium®; Rhoxal-pamidronate

Pharmacologic CategoryAntidote; Bisphosphonate Derivative

Use: Labeled IndicationsTreatment of hypercalcemia associated with malignancy; treatment of osteolytic bone lesions associated with multiple myeloma or metastatic breast cancer; moderate to severe Paget's disease of bone

Use: Unlabeled/InvestigationalTreatment of pediatric osteoporosis, treatment of osteogenesis imperfecta

Dosing: AdultsDilute prior to administration and infuse intravenously slowly over at least 2 hours. Single doses should not exceed 90 mg.

Hypercalcemia of malignancy: I.V.:

Moderate cancer-related hypercalcemia (corrected serum calcium: 12-13.5 mg/dL): 60-90 mg, as a single dose over 2-24 hours

Severe cancer-related hypercalcemia (corrected serum calcium: >13.5 mg/dL): 90 mg, as a single dose over 2-24 hours

Repeat dosing: A period of 7 days should elapse before the use of second course; repeat infusions every 2-3 weeks have been suggested, however, could be administered every 2-3 months according to the degree and of severity of hypercalcemia and/or the type of malignancy.

Osteolytic bone lesions with multiple myeloma: 90 mg over 2-4 hours monthly

Osteolytic bone lesions with metastatic breast cancer: 90 mg over 2 hours repeated every 3-4 weeks

Paget's disease: 30 mg over 4 hours daily for 3 consecutive days

Dosing: ElderlyRefer to adult dosing. Begin at lower end of adult dosing range.

Dosing: Renal Impairment Safety and efficacy have not been established in patients with serum creatinine >5 mg/dL; studies are limited in multiple myeloma patients with serum creatinine ≥3 mg/dL

The manufacturer recommends the following guidelines:

Treatment of bone metastases: Use is not recommended in patients with severe renal impairment.

Renal impairment in indications other than bone metastases: Use clinical judgment to determine if benefits outweigh potential risks.

American Society of Clinical Oncology (ASCO) guidelines for bisphosphonate use in multiple myeloma (Kyle, 2007) recommend considering a reduced initial dose in patients with pre-existing renal impairment.

Dosing adjustment in renal toxicity: In patients with bone metastases, treatment should be withheld for deterioration in renal function (increase of serum creatinine ≥0.5 mg/dL in patients with normal baseline or ≥1.0 mg/dL in patients with abnormal baseline). Resumption of therapy may be considered when serum creatinine returns to within 10% of baseline.

Dosing: Hepatic ImpairmentNo adjustment required in patients with mild-to-moderate hepatic impairment; not studied in patients with severe hepatic impairment.

Calculations

- Calcium Correction

Administration: I.V.I.V. infusion over 2-24 hours. Longer infusion times (>2 hours) may reduce the risk for renal toxicity, especially in patients with pre-existing renal insufficiency. The manufacturer recommends infusing over 2-24 hours for hypercalcemia of malignancy; over 2 hours for osteolytic bone lesions with metastatic breast cancer; and over 4 hours for Paget's disease and for osteolytic bone lesions with multiple myeloma. The ASCO guidelines for bisphosphonate use in multiple myeloma recommend infusing pamidronate over at least 2 hours; if therapy is withheld due to renal toxicity, infuse over at least 4 hours upon reintroduction of treatment after renal recovery.

Administration: I.V. DetailpH: 6-7.4

Dietary ConsiderationsMultiple myeloma or metastatic bone lesions from solid tumors or Paget's disease: Take adequate daily calcium and vitamin D supplement

Storage

Powder for reconstitution: Store below 30°C (86°F). The reconstituted solution is stable for 24 hours stored under refrigeration at 2°C to 8°C (36°F to 46°F).

Solution for injection: Store at 20°C to 25°C (68°f to 77°F).

Pamidronate solution for infusion is stable at room temperature for up to 24 hours.

ReconstitutionPowder for injection: Reconstitute by adding 10 mL of SWFI to each vial of lyophilized pamidronate disodium powder, the resulting solution will be 30 mg/10 mL or 90 mg/10 mL.

Pamidronate may be further diluted in 250-1000 mL of 0.45% or 0.9% sodium chloride or 5% dextrose. (The manufacturer recommends dilution in 1000 mL for hypercalcemia of malignancy, 500 mL for Paget's disease and bone metastases of myeloma, and 250 mL for bone metastases of breast cancer.)

Compatibility**Incompatible** with calcium-containing infusion solutions such as Ringer's injection.

ContraindicationsHypersensitivity to pamidronate, other bisphosphonates, or any component of the formulation

Allergy Considerations

- Bisphosphonate Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bone/joint/muscle pain: Infrequently, severe (and occasionally debilitating) bone, joint, and/or muscle pain have been reported during bisphosphonate treatment. The onset of pain ranged from a single day to several months. Symptoms usually resolve upon discontinuation. Some patients experienced recurrence when rechallenged with same drug or another bisphosphonate; avoid use in patients with a history of these symptoms in association with bisphosphonate therapy.

- Electrolyte abnormalities: Use has been associated with asymptomatic electrolyte abnormalities (including hypophosphatemia, hypokalemia, hypomagnesemia, and hypocalcemia). Rare cases of symptomatic hypocalcemia, including tetany have been reported.

- Leukopenia: Oral therapy has been associated with leukopenia and monitoring of white blood cell counts is suggested. Patients with pre-existing anemia, leukopenia, or thrombocytopenia should be closely monitored during the first 2 weeks of treatment.

- Osteonecrosis of the jaw: Bisphosphonate therapy has been associated with osteonecrosis, primarily of the jaw; this has been observed mostly in cancer patients, but also in patients with postmenopausal osteoporosis and other diagnoses. Risk factors include a diagnosis of cancer, with concomitant chemotherapy, radiotherapy, or corticosteroids; anemia, coagulopathy, infection, or pre-existing dental disease. Symptoms included nonhealing extraction socket or an exposed jawbone. There are no data addressing whether discontinuation of therapy reduces the risk of developing osteonecrosis; however, as a precautionary measure, dental exams and preventative dentistry should be performed prior to placing patients with risk factors on chronic bisphosphonate therapy. Invasive dental procedures should be avoided during treatment.

- Renal deterioration: Single pamidronate doses should not exceed 90 mg. Initial or single doses have been associated with renal deterioration, progressing to renal failure and dialysis. Glomerulosclerosis (focal segmental) with or without nephrotic syndrome has also been reported. Longer infusion times (>2 hours) may reduce the risk for renal toxicity, especially in patients with pre-existing renal insufficiency. Withhold pamidronate treatment (until renal function returns to baseline) in patients with evidence of renal deterioration.

- Thrombophlebitis: Vein irritation and thrombophlebitis may occur with infusions.

Disease-related concerns:

- Hypercalcemia of malignancy: Adequate hydration is required during treatment (urine output ~2 L/day); avoid overhydration, especially in patients with heart failure.

- Hypoparathyroidism: Use caution with a history of thyroid surgery; patients may have relative hypoparathyroidism, predisposing them to pamidronate-related hypocalcemia.

- Renal impairment: Patients with serum creatinine >3 mg/dL were not studied in clinical trials; limited data is available in patients with Cl_{cr} <30 mL/minute. Evaluate serum creatinine prior to each treatment. For the treatment of bone metastases, use is not recommended in patients with severe renal impairment. With indications other than bone metastases, use clinical judgment to determine if benefits outweigh potential risks in patients with renal impairment.

Special populations:

- Women of childbearing potential: Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant during therapy.

Geriatric ConsiderationsOf the studies done with this drug, approximately 20% of the patients were ≥65 years of age with 15% ≥75 years. No differences were noted between elderly and younger adults. Dosing should be initiated with lowest recommended dose in elderly. Monitor serum electrolytes periodically since the elderly are often receiving diuretics which can result in decreases in serum calcium, potassium, and magnesium.

Pregnancy Risk FactorD

Pregnancy ConsiderationsPamidronate has been shown to cross the placenta and cause nonteratogenic embryo/fetal effects in animals. There are no adequate and well-controlled studies in pregnant women; manufacturer states pamidronate should not be used in pregnancy. Based on limited case reports, serum calcium levels in the newborn may be altered if pamidronate is administered during pregnancy. Bisphosphonates are incorporated into the bone matrix and gradually released over time. Theoretically, there may be a risk of fetal harm when pregnancy follows the completion of therapy. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant during therapy.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**Note:** Actual percentages may vary by indication; treatment for multiple myeloma is associated with higher percentage.

>10%:

Central nervous system: Fatigue (≤37%), fever (18% to 39%), headache (≤26%), insomnia (≤22%)

Endocrine & metabolic: Hypophosphatemia (≤18%), hypokalemia (4% to 18%), hypomagnesemia (4% to 12%), hypocalcemia (≤12%)

Gastrointestinal: Nausea (≤54%), vomiting (≤36%), anorexia (≤26%), abdominal pain (≤23%), dyspepsia (≤23%)

Genitourinary: Urinary tract infection (≤19%)

Hematologic: Anemia (≤43%), granulocytopenia (≤20%)

Local: Infusion site reaction (≤18%; includes induration, pain, redness and swelling)

Neuromuscular & skeletal: Weakness (≤22%), myalgia (≤26%), arthralgia (≤14%), osteonecrosis of the jaw (cancer patients: 1% to 11%)

Renal: Serum creatinine increased (≤19%)

Respiratory: Dyspnea (≤30%), cough (≤26%), upper respiratory tract infection (≤24%), sinusitis (≤16%), pleural effusion (≤11%)

1% to 10%:

Cardiovascular: Atrial fibrillation (≤6%), hypertension (≤6%), syncope (≤6%), tachycardia (≤6%), atrial flutter (≤1%), cardiac failure (≤1%), edema (≤1%)

Central nervous system: Somnolence (≤6%), psychosis (≤4%)

Endocrine & metabolic: Hypothyroidism (≤6%)

Gastrointestinal: Constipation (≤6%), gastrointestinal hemorrhage (≤6%), diarrhea (≤1%), stomatitis (≤1%)

Hematologic: Leukopenia (≤4%), neutropenia (≤1%), thrombocytopenia (≤1%)

Neuromuscular & skeletal: Back pain (≤5%), bone pain (≤5%)

Renal: Uremia (≤4%)

Respiratory: Rales (≤6%), rhinitis (≤6%)

Miscellaneous: Moniliasis (≤6%)

<1%, postmarketing, and/or case reports: Acute renal failure, adult respiratory distress syndrome, allergic reaction, anaphylactic shock, angioedema, bronchospasm, CHF, confusion, conjunctivitis, electrolyte/mineral abnormality, episcleritis, fluid overload, flu-like syndrome, focal segmental glomerulosclerosis (including collapsing variant), hallucinations (visual), hematuria, herpes virus reactivation, hyperkalemia, hypernatremia, hypotension, injection site phlebitis/thrombophlebitis, interstitial pneumonitis, iridocyclitis, iritis, joint and/or muscle pain (sometimes severe and/or incapacitating), left ventricular failure, lymphocytopenia, malaise, nephrotic syndrome, osteonecrosis (other than jaw), paresthesia, pruritus, rash, renal deterioration, scleritis, seizure, tetany, uveitis, xanthopsia

Oncology: VesicantNo

Oncology: Emetic PotentialLow

Drug Interactions

Aminoglycosides: May enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Phosphate Supplements: Bisphosphonate Derivatives may enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Thalidomide: May enhance the nephrotoxic effect of Pamidronate. *Risk C: Monitor therapy*

Test InteractionsBisphosphonates may interfere with diagnostic imaging agents such as technetium-99m-diphosphonate in bone scans.

Monitoring ParametersSerum creatinine (prior to each treatment); serum electrolytes, including calcium, phosphate, magnesium and potassium; CBC with differential; monitor for hypocalcemia for at least 2 weeks after therapy; dental exam and preventative dentistry for patients at risk for osteonecrosis; patients with pre-existing anemia, leukopenia, or thrombocytopenia should be closely monitored during the first 2 weeks of treatment

Reference RangeCalcium (total): Adults: 9.0-11.0 mg/dL (SI: 2.05-2.54 mmol/L), may slightly decrease with aging; Phosphorus: 2.5-4.5 mg/dL (SI: 0.81-1.45 mmol/L)

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests, therapeutic effectiveness and adverse reactions. Monitor for signs of hypocalcemia or renal failure. Teach patient lifestyle and dietary changes that will be beneficial, possible side effects, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsSerum creatinine (prior to each treatment); serum electrolytes, including calcium, phosphate, magnesium and potassium; CBC with differential; monitor for hypocalcemia for at least 2 weeks after therapy; patients with pre-existing anemia, leukopenia, or thrombocytopenia should be closely monitored during the first 2 weeks of treatment

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered intravenously; report immediately any difficulty breathing, chest tightness, difficulty swallowing, redness, swelling, or pain at infusion site. You may experience nausea or vomiting (small frequent meals and good mouth care may help); loss of appetite; abdominal pain; heartburn; recurrent bone pain (consult prescriber for analgesic); fever; headache; anxiety; insomnia; increased fatigue (adequate rest is important); dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report palpitations or rapid heart beat, unusual muscle twitching or spasms, persistent diarrhea/constipation, unusual weight gain, decreased urine output, swelling of extremeties, acute bone pain, respiratory difficulty, or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not get pregnant during therapy. Consult prescriber for instructions on appropriate contraceptive measures. This drug may cause fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as disodium: 30 mg, 90 mg

Aredia®: 30 mg, 90 mg

Injection, solution: 3 mg/mL (10 mL); 6 mg/mL (10 mL); 9 mg/mL (10 mL)

Generic AvailableYes

Mechanism of ActionA bisphosphonate which inhibits bone resorption via actions on osteoclasts or on osteoclast precursors. Does not appear to produce any significant effects on renal tubular calcium handling and is poorly absorbed following oral administration (high oral doses have been reported effective); therefore, I.V. therapy is preferred.

Pharmacodynamics/Kinetics

Onset of action: 24-48 hours

Peak effect: Maximum: 5-7 days

Absorption: Poor; pharmacokinetic studies lacking

Metabolism: Not metabolized

Half-life elimination: 21-35 hours

Excretion: Biphasic; urine (30% to 62% as unchanged drug; lower in patients with renal dysfunction) within 120 hours

Dental Health Professional ConsiderationsNovartis Pharmaceuticals Corporation has notified dental health professionals of the risk of **osteonecrosis of the jaw (ONJ)** and the use of the intravenous bisphosphonates, pamidronate (Zometa®) and zoledronic acid (Aredia®): *"Dear Dental Health Professional" Letter Issued for Intravenous Bisphosphonates, Pamidronate and Zoledronic Acid, Regarding the Risk of Osteonecrosis of the Jaw (ONJ) in Cancer Patients* – May 2005.

Often observed in patients receiving chemotherapy and corticosteroids, reports of ONJ (the majority being associated with dental procedures) have been documented in cancer patients. Dental exams and preventative dentistry should be performed prior to placing patients with risk factors (chemotherapy, corticosteroids, poor oral hygiene) on intravenous bisphosphonate therapy. Additionally, invasive dental procedures should be avoided during therapy; patients developing ONJ while on bisphosphonate therapy should not have invasive dental procedures because the condition may be exacerbated. It has not been determined whether the discontinuation of bisphosphonate therapy in patients requiring dental surgery decreases the risk of ONJ. The treating healthcare professional is encouraged to assess the benefits and risks.

Bisphosphonates are widely used in the management of metastatic bone disease to treat hypercalcemia associated with malignancies and to treat osteoporosis. It is suggested that because of the trend in the use of chronic bisphosphonate therapy, the observation of an associated risk of osteonecrosis of the jaw should alert practitioners to monitor for this previously unrecognized potential complication.

Additional information is available at http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#zometa2, or by contacting Novartis Oncology Medical Services at 1-888-669-6682.

Estimates of Percent Incidence of ONJ in Treated Cancer Patients

Two reports have attempted to assess the percent of cancer patients developing ONJ after bisphosphonate treatment. Maerevoet et al, reported that among 194 patients treated with Zometa® every 3-4 weeks, nine developed ONJ. Before receiving Zometa®, six had received Aredia® 90 mg every 3-4 weeks. The median duration of treatment with Aredia® was 39 months and for Zometa® 18 months. The incidence of ONJ in these patients was calculated to be 4.6%. Durie et al, described the results of a survey by the International Myeloma Foundation in 2004 to assess the risk factors of ONJ. Out of 1203 respondents, 904 had myeloma and 299 breast cancer. Of the myeloma patients, 62 developed ONJ and 54 had suspicious findings. Of the breast cancer patients, 13 had ONJ and 23 had suspicious findings. The total number of cases of either ONJ or suspicious findings was 152. ONJ developed in 10% of 211 patients receiving Zometa® compared to 4% of 413 receiving Aredia®. The mean time to onset of ONJ among patients taking Zometa® was 18 months; the mean time to onset after Aredia® was 6 years. It should be noted that an early report by authors from Novartis Pharmaceuticals Corporation (Tarassoff, 2003) stressed that Aredia® and Zometa® had been used in 2.5 million patients world wide and reports of ONJ during their extensive use had been rare. In addition, these authors stated that review of the reported cases revealed multiple risk factors for avascular necrosis. McMahon et al, followed up with a report that, along with other factors, bisphosphonates are additional stressors of bone health that can tip the balance to osteonecrosis. They suggested that the prevention of ONJ should be stressed such as the elimination of chronic dental infections prior to chemotherapy and bisphosphonate use in cancer patients.

Dental Health: Effects on Dental TreatmentOsteonecrosis of the jaw (ONJ), generally associated with local infection and/or tooth extraction and often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates. However, some have occurred in patients with postmenopausal osteoporosis taking oral bisphosphonates. Dental surgery may exacerbate ONJ. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentMay rarely cause leukopenia; use caution with clozapine and carbamazepine. Bisphosphonates, including pamidronate, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. Use caution in patients receiving lithium.

Index TermsPamidronate Disodium

References

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International Brand NamesAminomux (AR, PY, UY, VE); Aredia (AE, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CY, CZ, DE, DK, EG, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, NO, OM, PE, PH, PK, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Pamifos (PL); Pamired (MY); Pamisol (AU, MX, MY, SG); Pamitor (PL); Panolin (KP); Panorin (KP)

Pancreatin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Pancreatin may be confused with Panretin®

Pronunciation(PAN kree a tin)
U.S. Brand NamesDygase [DSC]; Hi-Vegi-Lip [OTC]; ku-zyme® [DSC]; kutrase® [DSC]; Lapase [DSC]; Pan-2400™ [OTC]; Veg-Pancreatin 4X [OTC]
Pharmacologic CategoryEnzyme
Use: Labeled IndicationsRelief of functional indigestion due to enzyme deficiency or imbalance
Dosing: AdultsActual dose varies with condition of patient and is usually given with each meal or snack.

Malabsorption: Oral:

ku-zyme®: 1-2 capsules with each meal or snack

kutrase®: 1 capsule with each meal or snack

Dosing: ElderlyRefer to adult dosing.
Administration: OralSwallow capsules/tablets whole; retention in the mouth before swallowing may cause mucosal irritation and stomatitis. Capsules may also be opened and sprinkled on soft food (do not chew).
Dietary ConsiderationsShould be taken with a meal or snack. Capsules may be opened and sprinkled on soft food.
StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from humidity.
ContraindicationsHypersensitivity to pork protein or any component of the formulation; acute pancreatitis or acute exacerbations of chronic pancreatic disease
Warnings/Precautions

Dosage form specific issues:

- Pork: Some products are made from pork protein and should not be used if allergic to pork.

Geriatric ConsiderationsNo special considerations necessary since drug is dosed to response; however, drug-induced diarrhea can result in unwanted side effects (confusion, hypotension, lethargy, fluid electrolyte loss).
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsSystemic absorption and concentration in the breast milk is unlikely, but unknown.
Adverse ReactionsFrequency not defined.

Gastrointestinal: Loose stools (decrease dose)

Respiratory: Mucous membrane irritation or precipitation of asthma attack (due to inhalation of airborne powder)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule: Lipase 8500 units, protease 50,000 units, amylase 50,000 units [pancreatin 500 mg]

Dygase, kutrase®: Lipase 2400 units, protease 30,000 units, amylase 30,000 units [DSC]

ku-zyme®: Lipase 1200 units, protease 15,000 units, amylase 15,000 units [DSC]

Lapase: Lipase 1200 units, protease 15,000 units, and amylase 15,000 units [contains tartrazine] [DSC]

Pan-2400™: Lipase 9816 units, protease 60,214 units, amylase 75,900 units [pancreatin 2400 mg]

Tablet: Lipase 565 units, protease 8200 units, amylase 8200 units [pancreatin 325 mg]; lipase 2400 units, protease 30,000 units, amylase 30,000 units [pancreatin 1200 mg]

Hi-Vegi-Lip: Lipase 4800 units, protease 60,000 units, amylase 60,000 units [pancreatin 2400 mg; vegetable source]

Veg-Pancreatin 4X: Lipase 5500 units, protease 69,000 units, amylase 69,000 units [pancreatin 690 mg; vegetable source]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsules (Dygase)

30-2.4-30 units (100): $69.99

Mechanism of ActionAn enzyme supplement, not a replacement, which contains a combination of lipase, amylase and protease. Enhances the digestion of proteins, starch and fat in the stomach and intestines.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesBilipeptal mono (DE); Carzodelan (DE); Cholspasminase (DE); Combizym (CH, IT, LU, NL, NO, PL, SE); Cotazym (DE); Creon (AR, BE, CH, FR, GB, IE, LU, MX, NL, ZA); Dichronase (DE); Digest Merz (DE); Enzyflat (AT); Enzym-Lefax (DE); Enzymed (DE); Euflat-E (DE); Eurobiol (AR, CH, FR); Festal (AT, DE, IN, IT); Helopanzym (AT, DE); Hepa-Merz (LU); Hevertozym (DE); Kreon (AT, CZ, DE, ES, HR, HU, PL, PT); Licrease (FR); Lipazym (DE); Lyopase (BE); Meteophyt (DE); Meteozym (DE); Mezym (DE); Neo-Pancreatinum (PL); Neo-Panpur (HU); Nutrizym (AT, DE, GB, IE); Optifree (AT, FR); Ozym (DE); Pancreal Kirchner (FR); Pancrease (BE, CZ, ES, GB, IE, NL, NO); Pancrecura (AR); Pancreolan (CZ); Pancreon (IT); Pancrex (GB); Pancrin (AT, IT); Pancrotanon (IT); Pangrol (CZ, DE, PL); Pankreatan (DE); Pankreatin Laves (DE); Pankreatin Mikro-ratiopharm (DE); pankreatin OPT (DE); Pankreatin Rosco (DK, SE); Pankreatin Stada (DE); Pankreon (AT, BR, DE, DK, ES, FI, NO, SE); Pankreozym (AR); Pankrotanon (CH); Panpeptal (DE); Panpur (DE); Panzynorm (AT, CZ, DE, IN); Panzytrat (CH, DE, HU, IE, LU, NL, PL); Polyzym (AT, BR, FR); Trepetan (MX); Tryptoferm (DE); Unexym (DE); Viokase (AU, LU)

Pancrelipase

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(pan kre LYE pase)

U.S. Brand NamesCreon®; ku-zyme® HP [DSC]; Lipram 4500 [DSC]; Lipram-CR [DSC]; Lipram-PN [DSC]; Lipram-UL [DSC]; Palcaps [DSC]; Pancrease® MT; Pancrecarb MS®; Pangestyme™ CN; Pangestyme™ EC; Pangestyme™ MT; Pangestyme™ UL; Panocaps MT [DSC]; Panocaps [DSC]; Panokase® 16 [DSC]; Panokase® [DSC]; Plaretase® 8000; Ultracaps MT [DSC]; Ultrase®; Ultrase® MT; Viokase®

Canadian Brand NamesCotazym®; Creon®; Pancrease®; Pancrease® MT; Ultrase®; Ultrase® MT; Viokase®

Pharmacologic CategoryEnzyme

Use: Labeled IndicationsReplacement therapy in symptomatic treatment of malabsorption syndrome caused by pancreatic insufficiency

Use: Unlabeled/InvestigationalTreatment of occluded feeding tubes

Dosing: Adults

Malabsorption: Oral:

Powder: Actual dose depends on the condition being treated and the digestive requirements of the patient: 0.7 g ($^{1}/_{4}$ teaspoonful) with meals

Capsules/tablets: The following dosage recommendations are only an approximation for initial dosages. The actual dosage will depend on the condition being treated and the digestive requirements of the individual patient.

Note: Dosage adjustment: Adjust dose based on body weight and stool fat content. Total daily dose reflects ~3 meals/day and 2-3 snacks/day, with half the mealtime dose given with a snack. Older patients may need less units/kg due to increased weight, but decreased ingestion of fat/kg. Maximum dose: 2500 units of lipase/kg/meal (10,000 units of lipase/kg/day): 4000-48,000 units of lipase with meals and with snacks

Occluded feeding tubes (unlabeled use): One tablet of Viokase® crushed with one 325 mg tablet of sodium bicarbonate (to activate the Viokase®) in 5 mL of water can be instilled into the nasogastric tube and clamped for 5 minutes; then, flushed with 50 mL of tap water

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Malabsorption: Oral:

Powder: Actual dose depends on the condition being treated and the digestive requirements of the patient: Children <1 year: Start with $^{1}/_{8}$ teaspoonful with feedings

Capsules/tablets: Children: Approximate initial dosages; actual dosage will depend on the condition being treated and the digestive requirements of the individual patient.

<1 year: 2000 units of lipase with meals

1-6 years: 4000-8000 units of lipase with meals and 4000 units with snacks

7-12 years: 4000-12,000 units of lipase with meals and snacks

Note: Dosage adjustment: Adjust dose based on body weight and stool fat content. Total daily dose reflects ~3 meals/day and 2-3 snacks/day, with half the mealtime dose given with a snack.

Administration: OralOral: Administer with meals or snacks and swallow whole with a generous amount of liquid. Do not crush or chew; retention in the mouth before swallowing may cause mucosal irritation and stomatitis. Delayed-release capsules containing enteric-coated microspheres or microtablets may also be opened and the contents sprinkled on soft food with a low pH that does not require chewing, such as applesauce, gelatin; apricot, banana, or sweet potato baby food; baby formula. Dairy products such as milk, custard, or ice cream may have a high pH and should be avoided. Avoid inhalation of powder, may cause nasal and respiratory tract irritation.

Dietary ConsiderationsShould be used as part of a high-calorie diet, appropriate for age and clinical status. Administer with meals or snacks and swallow whole with a generous amount of liquid. Do not crush or chew. Delayed-release capsules containing enteric coated microspheres or microtablets may also be opened and the contents sprinkled on soft food with a low pH such as applesauce, gelatin; apricot, banana, or sweet potato baby food; baby formula. Dairy products such as milk, custard or ice cream may have a high pH and should be avoided.

StorageStore between 15°C to 25°C (59°F to 77°F); do not refrigerate. Keep in a dry place.

ContraindicationsHypersensitivity to pork protein or any component of the formulation; acute pancreatitis or acute exacerbations of chronic pancreatic disease

Warnings/Precautions

Concerns related to adverse effects:

- Fibrotic strictures: In the colon, fibrotic strictures (some requiring surgery) have been reported with high doses; use caution, especially in children with cystic fibrosis.

Dosage form specific issues:

- Brand interchangeability: Use caution when adjusting doses or changing brands.
- Capsules: Pancrelipase is inactivated by acids; do not crush or chew, some capsules may be opened and sprinkled on food.
- Powder: Avoid inhalation of powder; may cause nasal and respiratory tract irritation.

Geriatric ConsiderationsNo special considerations are necessary since drug is dosed to response; however, drug-induced diarrhea can result in unwanted side effects (eg, confusion, hypotension, lethargy, fluid and electrolyte loss).

Pregnancy Risk FactorB/C (product specific)

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsSystemic absorption and concentration in the breast milk is unlikely, but unknown.

Adverse ReactionsFrequency not defined; occurrence of events may be dose related.

Central nervous system: Pain

Dermatologic: Rash

Endocrine & metabolic: Hyperuricemia

Gastrointestinal: Nausea, cramps, constipation, diarrhea, perianal irritation/inflammation (large doses), irritation of the mouth, abdominal pain, intestinal obstruction, vomiting, flatulence, melena, weight loss, fibrotic strictures, greasy stools

Ocular: Lacrimation

Renal: Hyperuricosuria

Respiratory: Sneezing, dyspnea, bronchospasm

Miscellaneous: Allergic reactions

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsFood: Avoid placing contents of opened capsules on alkaline food (pH >5.5); pancrelipase may impair absorption of oral iron and folic acid.

Monitoring ParametersAbdominal symptoms, nutritional intake, growth (in children), stool character, fecal fat

Nursing: Physical Assessment/MonitoringDosing and administration depends on purpose for use. Use caution preparing powder. If powder spills on skin, wash off immediately. Do not inhale powder. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take right before or with foods and swallow whole with a generous amount of liquid. Dairy products, such as milk, custard, or ice cream, may have a high pH and should not taken together with this medication. Do not crush or chew tablets or regular capsules. Delayed-release capsules containing enteric coated microspheres or microtablets may be opened and the contents sprinkled on soft food with a low pH such as applesauce, gelatin, apricot, banana, or sweet potato baby food. **Powder:** If powder spills on skin, wash off immediately, do not inhale powder when preparing. You may experience some gastric discomfort. Report unusual rash, persistent GI upset; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

ku-zyme® HP: Lipase 8000 units, protease 30,000 units, and amylase 30,000 units [DSC]

Capsule, delayed release, enteric coated granules:

Pangestyme™ CN-10: Lipase 10,000 units, protease 37,500 units, amylase 33,200 units

Pangestyme™ CN-20: Lipase 20,000 units, protease 75,000 units, amylase 66,400 units

Pangestyme™ EC: Lipase 4500 units, protease 25,000 units, and amylase 20,000 units

Pangestyme™ MT16: Lipase 16,000 units, protease 48,000 units, and amylase 48,000 units

Pangestyme™ UL 12: Lipase 12,000 units, protease 39,000 units, and amylase 39,000 units

Pangestyme™ UL 18: Lipase 18,000 units, protease 58,500 units, and amylase 58,500 units

Pangestyme™ UL 20: Lipase 20,000 units, protease 65,000 units, and amylase 65,000 units

Capsule, delayed release, enteric coated microspheres: Lipase 4500 units, protease 25,000 units, and amylase 20,000 units

Creon® 5: Lipase 5000 units, protease 18,750 units, and amylase 16,600 units

Creon® 10, Palcaps 10: Lipase 10,000 units, protease 37,500 units, and amylase 33,200 units

Creon® 20, Palcaps 20: Lipase 20,000 units, protease 75,000 units, and amylase 66,400 units

Lipram 4500, Panocaps: Lipase 4500 units, protease 25,000 units, and amylase 20,000 units [DSC]

Lipram-CR10: Lipase 10,000 units, protease 37,500 units, and amylase 33,200 units [DSC]

Lipram-CR20: Lipase 20,000 units, protease 75,000 units, and amylase 66,400 units [DSC]

Lipram-PN10: Lipase 10,000 units, protease 30,000 units, and amylase 30,000 units [DSC]

Lipram-PN16, Panocap MT 16: Lipase 16,000 units, protease 48,000 units, and amylase 48,000 units [DSC]

Lipram-PN20, Panocap MT 20: Lipase 20,000 units, protease 44,000 units, and amylase 56,000 units [DSC]

Lipram-UL20, Ultracaps MT 20: Lipase 20,000 units, protease 65,000 units, and amylase 65,000 units [DSC]

Pancrecarb MS-4®: Lipase 4000 units, protease 25,000 units, and amylase 25,000 units [buffered]

Pancrecarb MS-8®: Lipase 8000 units, protease 45,000 units, and amylase 40,000 units [buffered]

Pancrecarb MS-16® Lipase 16,000 units, protease 52,000 units, and amylase 52,000 units [buffered]

Capsule, enteric coated microspheres:

Ultrase®: Lipase 4500 units, protease 25,000 units, and amylase 20,000 units

Capsule, enteric coated microtablets:

Pancrease® MT 4: Lipase 4000 units, protease 12,000 units, and amylase 12,000 units

Pancrease® MT 10: Lipase 10,000 units, protease 30,000 units, and amylase 30,000 units

Pancrease® MT 16: Lipase 16,000 units, protease 48,000 units, and amylase 48,000 units

Pancrease® MT 20: Lipase 20,000 units, protease 44,000 units, and amylase 56,000 units

Capsule, enteric coated minitablets:

Ultrase® MT12: Lipase 12,000 units, protease 39,000 units, and amylase 39,000 units

Ultrase® MT18: Lipase 18,000 units, protease 58,500 units, and amylase 58,500 units

Ultrase® MT20: Lipase 20,000 units, protease 65,000 units, and amylase 65,000 units

Powder (Viokase®): Lipase 16,800 units, protease 70,000 units, and amylase 70,000 units per 0.7 g (227 g)

Tablet: Lipase 8000 units, protease 30,000 units, and amylase 30,000 units

Panokase®: Lipase 8000 units, protease 30,000 units, and amylase 30,000 units [DSC]

Panokase® 16: Lipase 16,000 units, protease 60,000 units, and amylase 60,000 units [DSC]

Plaretase™ 8000: Lipase 8000 units, protease 30,000 units, and amylase 30,000 units

Viokase® 8: Lipase 8000 units, protease 30,000 units, and amylase 30,000 units

Viokase® 16: Lipase 16,000 units, protease 60,000 units, and amylase 60,000 units

Generic AvailableYes: Excludes powder
Pricing: U.S. (www.drugstore.com)

Capsule, enteric pellets (Creon 10)

33.2-10-37.5 units (100): $134.93

Capsule, enteric pellets (Creon 20)

66.4-20-75 units (100): $243.78

Capsule, enteric pellets (Creon 5)

16.6-5-18.75 units (100): $86.14

Capsule, enteric pellets (Lipram-CR10)

33.2-10-37.5 units (30): $36.23

Capsule, enteric pellets (Lipram-CR20)

66.4-20-75 units (90): $155.93

Capsule, enteric pellets (Lipram-UL12)

39-12-39 units (30): $22.98

Capsule, enteric pellets (Lipram-UL20)

65-20-65 units (100): $124.99

Capsule, enteric pellets (Pancrease)

4500 unit (30): $17.97

Capsule, enteric pellets (Pancrease MT 10)

30-10-30 units (100): $112.22

Capsule, enteric pellets (Pancrease MT 16)

48-16-48 units (30): $53.68

Capsule, enteric pellets (Pancrease MT 20)

56-20-44 units (30): $66.86

Capsule, enteric pellets (Pangestyme CN 10)

33.2-10-37.5 units (100): $56.83

Capsule, enteric pellets (Pangestyme CN 20)

66.4-20-75 units (100): $173.53

Capsule, enteric pellets (Pangestyme EC)

4500 unit (100): $43.08

4500 unit (250): $85.33

Capsule, enteric pellets (Pangestyme MT 16)

48-16-48 units (30): $37.01

Capsule, enteric pellets (Ultrase)

4500 unit (100): $70.70

Capsule, enteric pellets (Ultrase MT 12)

39-12-39 units (100): $145.75

Capsule, enteric pellets (Ultrase MT 18)

58.5-18-58.5 units (100): $234.02

Capsule, enteric pellets (Ultrase MT 20)

65-20-65 units (100): $258.76

Powder (Viokase)

70-16.8-70 units (227): $259.64

Tablets (Pancrelipase)

30-8-30 units (100): $35.56

Tablets (Panokase)

30-8-30 units (100): $34.50

Tablets (Plaretase 8000)

30-8-30 units (500): $155.65

Tablets (Viokase 16)

60-16-60 units (30): $49.91

Tablets (Viokase 8)

30-8-30 units (100): $72.12

Mechanism of ActionPancrelipase is a natural product harvested from the hog pancreas. It contains a combination of lipase, amylase, and protease. Products are formulated to dissolve in the more basic pH of the duodenum so that they may act locally to break down fats, protein, and starch.

Pharmacodynamics/Kinetics

Absorption: None; acts locally in GI tract

Excretion: Feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms Lipancreatin

References

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Pettei MJ, Leonidas JC, Levinne JJ, et al, “Pancolonic Disease in Cystic Fibrosis and High-Dose Pancreatic Enzyme Therapy,” *J Pediatr*, 1994, 125(4):587-9. [PubMed 7931879]

Taylor CG, “Colonic Strictures in Cystic Fibrosis,” *Lancet*, 1994, 343(8898):615-6.[PubMed 7906805]

International Brand Names Alipase (FR); Cotazym-S (AU); Cotazym-S Forte (AU); Krebsilasi (IT); Lipancrea (PL); Pancrease (BE, DK, ES, FI, IT, NL, NO, NZ, SE); Pancrease HL (GB); Pancrex (IT); Panzytrat (AU); Prolipase (AT, CH, CZ, HR)

Pancuronium

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Pancuronium may be confused with pipecuronium

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(pan kyoo ROE nee um)

Canadian Brand NamesPancuronium Bromide®

Pharmacologic CategoryNeuromuscular Blocker Agent, Nondepolarizing

Use: Labeled IndicationsAdjunct to general anesthesia to facilitate endotracheal intubation and to relax skeletal muscles during surgery; to facilitate mechanical ventilation in ICU patients; does not relieve pain or produce sedation

Drug of choice for neuromuscular blockade except in patients with renal failure, hepatic failure, or cardiovascular instability or in situations not suited for pancuronium's long duration of action

Dosing: AdultsAdminister I.V.; dose to effect; doses will vary due to interpatient variability; use ideal body weight for obese patients

Neuromuscular blockade: Initial: 0.06-0.1 mg/kg or 0.05 mg/kg after initial dose of succinylcholine for intubation; maintenance dose: 0.01 mg/kg 60-100 minutes after initial dose and then 0.01 mg/kg every 25-60 minutes

Pretreatment/priming: 10% of intubating dose given 3-5 minutes before initial dose

Neuromuscular blockade in the ICU: 0.05-0.1 mg/kg bolus followed by 0.8-1.7 mcg/kg/minute once initial recovery from bolus observed or 0.1-0.2 mg/kg every 1-3 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricInfants >1 month and Children: Refer to adult dosing.

Dosing: Renal ImpairmentElimination half-life is doubled, plasma clearance is reduced, and rate of recovery is sometimes much slower.

Cl_{cr} 10-50 mL/minute: Administer 50% of normal dose.

Cl_{cr} <10 mL/minute: Do not use.

Dosing: Hepatic ImpairmentElimination half-life is doubled, plasma clearance is doubled, recovery time is prolonged, volume of distribution is increased (50%) and results in a slower onset, higher total dosage, and prolongation of neuromuscular blockade. Patients with liver disease may develop slow resistance to nondepolarizing muscle relaxant. Large doses may be required and problems may arise in antagonism.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.May be administered undiluted by rapid I.V. injection.

Administration: I.V. DetailpH: 4 (adjusted)

StorageRefrigerate; however, stable for up to 6 months at room temperature.

CompatibilityStable in D_5NS, D_5W, LR, NS.

Y-site administration: Compatible: Aminophylline, cefazolin, cefuroxime, cimetidine, dobutamine, dopamine, epinephrine, esmolol, etomidate, fentanyl, fluconazole, gentamicin, heparin, hydrocortisone sodium succinate, isoproterenol, levofloxacin, lorazepam, midazolam, milrinone, morphine, nitroglycerin, ranitidine, sodium nitroprusside, trimethoprim/sulfamethoxazole, vancomycin. **Incompatible** Diazepam, thiopental. **Variable (consult detailed reference):** Propofol.

Compatibility in syringe: Compatible: Alcuronium, gallamine, heparin, hydrocortisone, meperidine, methohexital, neostigmine, opium alkaloids, promethazine, succinylcholine, thiopental, tubocurarine.

Compatibility when admixed: Compatible: Verapamil.

ContraindicationsHypersensitivity to pancuronium, bromide, or any component of the formulation

Allergy Considerations

- Neuromuscular-Blocking Agent Allergy

Warnings/Precautions

Boxed warnings:

- Experienced personnel: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Neuromuscular cross-sensitivity: Cross-sensitivity with other neuromuscular-blocking agents may occur; use extreme caution in patients with previous anaphylactic reactions.

Disease-related concerns:

- Burn injury: Resistance may occur in burn patients (>30% of body) for period of 5-70 days postinjury.

- Conditions which may antagonize neuromuscular blockade: Alkalosis, hypercalcemia, demyelinating lesions, peripheral neuropathies, denervation, infection, muscle trauma, and diabetes mellitus may result in antagonism of neuromuscular blockade.

- Conditions which may potentiate neuromuscular blockade: Electrolyte abnormalities, severe hyponatremia, severe hypocalcemia, severe hypokalemia, hypermagnesemia, neuromuscular diseases, acidosis, acute intermittent porphyria, Eaton-Lambert syndrome, myasthenia gravis, renal failure, and hepatic failure may result in potentiation of neuromuscular blockade.

- Hepatic impairment: Use with caution in patients with hepatic impairment; adjust dose appropriately.

- Renal impairment: Use with caution in patients with renal impairment; adjust dose appropriately.

Special populations:

- Elderly: Use with caution in the elderly, effects and duration are more variable.

- Immobilized patients: Resistance may occur in patients who are immobilized.

Other warnings/precautions:

- Appropriate use: Maintenance of an adequate airway and respiratory support is critical.

- Experienced personnel: **[U.S. Boxed Warning]: Should be administered by adequately trained individuals familiar with its use.**

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Elevation in pulse rate, elevated blood pressure and cardiac output, tachycardia, edema, skin flushing, circulatory collapse

Dermatologic: Rash, itching, erythema, burning sensation along the vein

Gastrointestinal: Excessive salivation

Neuromuscular & skeletal: Profound muscle weakness

Respiratory: Wheezing, bronchospasm

Miscellaneous: Hypersensitivity reaction

Postmarketing and/or case reports: Acute quadriplegic myopathy syndrome (prolonged use), myositis ossificans (prolonged use)

Causes of prolonged neuromuscular blockade: Excessive drug administration; cumulative drug effect, decreased metabolism/excretion (hepatic and/or renal impairment); accumulation of active metabolites; electrolyte imbalance (hypokalemia, hypocalcemia, hypermagnesemia, hypernatremia); hypothermia; drug interactions; increased sensitivity to muscle relaxants (eg, neuromuscular disorders such as myasthenia gravis or polymyositis)

Drug Interactions

Acetylcholinesterase Inhibitors: May diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Aminoglycosides: May enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Neuromuscular-Blocking Agents may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Neuromuscular-Blocking Agents may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Calcium Channel Blockers: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Cardiac Glycosides: Neuromuscular-Blocking Agents may enhance the arrhythmogenic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Colistimethate: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Neuromuscular-Blocking Agents (Nondepolarizing) may enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

Inhalational Anesthetics: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Neuromuscular-Blocking Agents (Nondepolarizing). Specifically, episodes of apnea have been reported in patients using this combination. *Risk C: Monitor therapy*

Lincosamide Antibiotics: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Lithium: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Loop Diuretics: May diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Loop Diuretics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Magnesium Salts: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Polymyxin B: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Procainamide: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

QuiNIDine: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Tetracycline Derivatives: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Vancomycin: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Monitoring ParametersHeart rate, blood pressure, assisted ventilation status; cardiac monitor, blood pressure monitor, and ventilator required

Nursing: Physical Assessment/MonitoringOnly clinicians experienced in the use of neuromuscular blocking drugs should administer and/or manage the use of pancuronium. Dosage and rate of administration should be individualized and titrated to the desired effect, according to relevant clinical factors, premedication, concomitant medications, age, and general condition of the patient. Ventilatory support must be instituted and maintained until adequate respiratory muscle function and/or airway protection are assured. Assess other medications for effectiveness and safety. Other drugs that affect neuromuscular activity may increase/decrease neuromuscular block induced by pancuronium. This drug does not cause anesthesia or analgesia; pain must be treated with appropriate analgesic agents. Continuous monitoring of vital signs, cardiac status, respiratory status, and degree of neuromuscular block (objective assessment with peripheral external nerve stimulator) is mandatory and until full muscle tone has returned. Muscle tone returns in a predictable pattern, starting with diaphragm, abdomen, chest, limbs, and finally muscles of the neck, face, and eyes. Safety precautions must be maintained until full muscle tone has returned. **Note:** It may take longer for return of muscle tone in obese or elderly patients or patients with renal or hepatic disease, myasthenia gravis, myopathy, other neuromuscular disease, dehydration, electrolyte imbalance, or severe acid/base imbalance. Provide appropriate patient teaching/support prior to and following administration.

Long-term use: Monitor level of neuromuscular blockade, skeletal muscle movement, and respiratory effort. Reposition patient and provide appropriate skin care, mouth care, and care of patient's eyes every 2-3 hours while sedated. Provide appropriate emotional and sensory support (auditory and environmental).

Patient EducationPatient will usually be unconscious prior to administration. Patient education should be appropriate to individual situation. Reassurance of constant monitoring and emotional support to reduce fear and anxiety should precede and follow administration. Following return of muscle tone, do not attempt to change position or rise from bed without assistance. Report immediately any skin rash or hives, pounding heartbeat, respiratory difficulty, or muscle tremors. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as bromide: 1 mg/mL (10 mL); 2 mg/mL (2 mL, 5 mL) [may contain benzyl alcohol]

Generic AvailableYes

Mechanism of ActionBlocks neural transmission at the myoneural junction by binding with cholinergic receptor sites

Pharmacodynamics/Kinetics

Onset of effect: Peak effect: I.V.: 2-3 minutes

Duration (dose dependent): 60-100 minutes

Metabolism: Hepatic (30% to 45%); active metabolite 3-hydroxypancuronium ($^{1}/_{3}$ to $^{1}/_{2}$ the activity of parent drug)

Half-life elimination: 110 minutes

Excretion: Urine (55% to 70% as unchanged drug)

Related Information

- Neuromuscular-Blocking Agents

Pharmacotherapy PearlsPancuronium is classified as a long-duration neuromuscular-blocking agent. Neuromuscular blockade will be prolonged in patients with decreased renal function. Pancuronium does not relieve pain or produce sedation. It may produce cumulative effect on duration of blockade. It produces tachycardia secondary to vagolytic activity and sympathetic stimulation.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other ConsiderationsClassified as a long duration neuromuscular-blocking agent; neuromuscular blockade will be prolonged in patients with decreased renal function; may produce cumulative effect on duration of blockade; produces tachycardia secondary to vagolytic activity and sympathetic stimulation.

Critically-Ill Adult Patients:

The 2008 Surviving Sepsis Campaign guidelines recommend avoiding use of neuromuscular blockers if at all possible in the septic patient due to the risk of prolonged neuromuscular blockade following discontinuation. If one is required, monitor the depth of blockade (Grade 1B).

The 2002 ACCM/SCCM/ASHP clinical practice guidelines for sustained neuromuscular blockade in the adult critically-ill patient recommend:

Optimize sedatives and analgesics prior to initiation and monitor and adjust accordingly during course. Neuromuscular blockers do not relieve pain or produce sedation.

Protect patient's eyes from development of keratitis and corneal abrasion by administering ophthalmic ointment and taping eyelids closed or using eye patches. Reposition patient routinely to protect pressure points from breakdown. Address DVT prophylaxis.

Concurrent use of a neuromuscular blocker and corticosteroids appear to increase the risk of certain ICU myopathies; avoid or administer the corticosteroid at the lowest dose possible. Reassess need for neuromuscular blocker daily.

Using daily drug holidays (stopping neuromuscular-blocking agent until patient requires it again) may decrease the incidence of acute quadriplegic myopathy syndrome.

Tachyphylaxis can develop; switch to another neuromuscular blocker (taking into consideration the patient's organ function) if paralysis is still necessary.

Atracurium or cisatracurium is recommended for patients with significant hepatic or renal disease, due to organ-independent Hofmann elimination.

Monitor patients clinically and via “Train of Four” (TOF) testing with a goal of adjusting the degree of blockade to 1-2 twitches or based upon the patient's clinical condition.

Index TermsPancuronium Bromide; Pavulon [DSC]

References

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Murray MJ, Cowen J, DeBlock H, et al, “Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient. Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists, American College of Chest Physicians,” *Crit Care Med*, 2002, 30(1):142-56. Available at: http://www.sccm.org/pdf/NeuromuscularBlockade.pdf. Accessed August 6, 2003.[PubMed 11902255]

International Brand NamesAlpax (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Bromurex (CO); Curon-B (ZA); Pancuron (PY); Pancuronio (CO); Pancuronium (PL); Pancuronium Bromide (AU); Pavulon (AE, AR, AT, AU, BD, BE, BG, BH, BR, CH, CL, CN, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JO, JP, KP, KW, LB, LU, LY, MY, NL, NO, OM, PH, PK, PL, PT, QA, RU, SA, SE, SG, SY, TH, TR, TW, VE, YE); Pavulone (IL)

Panitumumab

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(pan i TOOM yoo mab)

U.S. Brand NamesVectibix®

Canadian Brand NamesVectibix®

Pharmacologic CategoryAntineoplastic Agent, Monoclonal Antibody; Epidermal Growth Factor Receptor (EGFR) Inhibitor

Use: Labeled IndicationsMonotherapy in treatment of refractory metastatic colorectal cancer

Dosing: Adults**Metastatic colorectal cancer:** I.V.: 6 mg/kg every 2 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentHas not been studied

Dosing: Hepatic ImpairmentHas not been studied

Dosing: Adjustment for Toxicity

Infusion reactions, mild-to-moderate (grade 1 or 2): Reduce the infusion rate by 50% for the duration of infusion

Infusion reactions, severe (grade 3 or 4): Immediately and permanently discontinue treatment

Dermatologic toxicity (grade 3 or 4, or intolerable): Withhold treatment; if skin toxicity does not improve to ≤ grade 2 within 1 month, permanently discontinue. If skin toxicity improves to ≤ grade 2 within 1 month (with patient missing ≤2 doses), resume treatment at 50% of the original dose. Dose may be increased in increments of 25% of the original dose (up to 6 mg/kg) if skin toxicities do not recur. For recurrent skin toxicity, permanently discontinue.

Administration: I.V.Doses ≤1000 mg, infuse over 1 hour; doses >1000 mg, infuse over 90 minutes; reduce infusion rate by 50% for mild-to-moderate infusion reactions; discontinue for severe infusion reactions. Administer through a low protein-binding 0.2 or 0.22 micrometer in-line filter. Flush with NS before and after infusion.

Administration: I.V. DetailpH: 5.6-6; may contain a small amount of visible transparent or white, amorphous panitumumab particles

StorageStore unopened vials under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze; do not shake; protect from light. Preparations in infusion containers are stable for 24 hours under refrigeration at 2°C to 8°C (36°F to 46°F) or for 6 hours at room temperature (do not freeze).

Reconstitution Dilute in 100-150 mL of normal saline to a final concentration of ≤10 mg/mL. Do not shake, invert gently to mix.

ContraindicationsThere are no contraindications listed in manufacturer's labeling.

Warnings/Precautions

Boxed warnings:

- Dermatologic toxicity: See “Concerns related to adverse effects” below.

- Infusion reactions: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Dermatologic toxicity: **[U.S. Boxed Warning]: Dermatologic toxicities have been reported in ~90% of patients (severe in 12% of patients);** may include dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin and skin fissures. Severe skin toxicities may be complicated by infection, sepsis, or abscesses. The median time to development of skin (or ocular) toxicity was 2 weeks, with resolution ~7 weeks after discontinuation. The severity of dermatologic toxicity is predictive for response; grades 2-4 skin toxicity correlates with improved progression free survival and overall survival, compared to grade 1 skin toxicity (Van Cutsem, 2007). Withhold treatment (and monitor) for severe or life-threatening dermatologic toxicities; may require dose reduction or permanent discontinuation. Patients should minimize sunlight exposure; may exacerbate skin reactions. Gastric mucosal, ocular and nail toxicities have also been reported.

- Diarrhea: May cause diarrhea; the incidence and severity of chemotherapy-induced diarrhea is increased with combination chemotherapy. Due to the potential for severe diarrhea and other toxicities, use with combination chemotherapy regimens is not recommended.

- Electrolyte depletion: May occur during treatment and after treatment is discontinued; monitor for hypomagnesemia and hypocalcemia.

- Infusion reactions: **[U.S. Boxed Warning]: Severe infusion reactions (anaphylactic reaction, bronchospasm, fever, chills, and hypotension) have been reported in ~1% of patients.** Discontinue infusion for severe reactions; permanently discontinue in patients with persistent severe infusion reactions. Appropriate medical support for the management of infusion reactions should be readily available. Mild to moderate infusion reactions are managed by slowing the infusion rate.

- Pulmonary fibrosis: Has been reported (rarely); permanently discontinue treatment if interstitial lung disease, pneumonitis or lung infiltrates develop. Use caution with lung disease; patients with underlying lung disease were excluded from clinical trials.

Concurrent drug therapy issues:

- Combination chemotherapy: Studies using panitumumab in combination with chemotherapy (with or without bevacizumab) resulted in decreased progression-free survival and significantly increased toxicity compared to regimens without panitumumab. Toxicities included rash, diarrhea/dehydration, electrolyte disturbances, stomatitis, and an increased incidence of pulmonary embolism. Panitumumab is not indicated for use in combination with chemotherapy.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproductive studies have demonstrated adverse fetal effects. Based on animal studies, panitumumab may disrupt normal menstrual cycles. There are no adequate and well-controlled studies in pregnant women. IgG is known to cross the placenta; therefore, it is possible the developing fetus may be exposed to panitumumab. Because panitumumab inhibits epidermal growth factor (EGF), a component of fetal development, adverse effects on pregnancy would be expected. Panitumumab should only be given to a pregnant woman if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential should use effective contraception during and for 6 months after treatment. Women who become pregnant during panitumumab treatment are encouraged to enroll in Amgen’s Pregnancy Surveillance Program (1-800-772-6436).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsBreast-feeding should be discontinued during treatment and for 2 months following the last dose.

Adverse Reactions

>10%:

Cardiovascular: Peripheral edema (12%)

Central nervous system: Fatigue (26%)

Dermatologic: Skin toxicity (90%; grades 3/4: 16%), erythema (65%; grades 3/4: 5%), acneiform rash (57%; grades 3/4: 7%), pruritus (57%; grades 3/4: 2%), exfoliation (25%; grades 3/4: 2%), paronychia (25%), rash (22%; grades 3/4: 1%), fissures (20%; grades 3/4: 1%), acne (13%; grades 3/4: 1%)

Endocrine & metabolic: Hypomagnesemia (38%; grades 3/4: 4%)

Gastrointestinal: Abdominal pain (25%), nausea (23%), diarrhea (21%; grades 3/4: 2%), constipation (21%), vomiting (19%)

Respiratory: Cough (14%)

1% to 10%:

Dermatologic: Dry skin (10%), nail disorder (other than paronychia: 9%)

Gastrointestinal: Stomatitis (7%), mucositis (6%)

Ocular: Eyelash growth (6%), conjunctivitis (4%), ocular hyperemia (3%), lacrimation increased (2%), eye/eye lid irritation (1%)

Miscellaneous: Antibody formation (≤5%), infusion reactions (3%; grades 3/4: 1%)

<1%, postmarketing, and/or case reports: Allergic reaction, anaphylactoid reaction, chills, dyspnea, fever, hypocalcemia, hypoxia, pulmonary embolism, pulmonary fibrosis, pulmonary infiltrate

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersKRAS genotyping of tumor tissue. Monitor serum electrolytes, including magnesium and calcium (periodically during and for at least 8 weeks after therapy). Monitor vital signs and temperature before, during, and after infusion. Monitor for skin toxicity.

Nursing: Physical Assessment/MonitoringPatient must be monitored closely during and following infusion for infusion reaction (appropriate medical support for the management of infusion reactions should be readily available). Assess results of laboratory tests, therapeutic effectiveness, and adverse response (severe skin reactions can occur 2-7 weeks [may necessitate dose reduction]; peripheral edema; gastrointestinal upset [pain, nausea, diarrhea, constipation, vomiting]) at each infusion and throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsKRAS genotyping of tumor tissue. Monitor serum electrolytes, including magnesium and calcium (periodically during and for at least 8 weeks after therapy).

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by infusion; you will be closely monitored during infusion; report immediately unusual back or abdominal pain, acute headache, difficulty breathing or chest tightness, difficulty swallowing, itching or rash, redness, swelling, or pain at infusion site. Maintain adequate hydration (2-3 L/day of fluids, unless instructed to restrict fluid intake) and nutrition (small, frequent meals). You may experience nausea or vomiting (frequent oral care, sucking lozenges, or chewing gum may help); or diarrhea (buttermilk, boiled milk, or yogurt may help); constipation (increased dietary fiber may help). Report immediately any skin rash, redness, or infection; any unusual swelling of extremities or weight gain (>5 pounds in any week); unremitting abdominal pain, vomiting, diarrhea, or constipation; any changes in vision; unusual infection (respiratory or wound), or any other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for use appropriate contraceptive measures (may cause fetal defects). Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Vectibix®: 20 mg/mL (5 mL, 10 mL, 20 mL)

Generic AvailableNo

ManufacturerAmgen, Inc

Pricing: U.S. (www.drugstore.com)

Solution (Vectibix)

100 mg/5 mL (5): $926.90

200 mg/10 mL (10): $1853.79

400 mg/20 mL (20): $4222.59

Mechanism of ActionRecombinant human IgG2 monoclonal antibody which binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands. Binding to the EGFR blocks phosphorylation and activation of intracellular tyrosine kinases, resulting in inhibition of cell survival, growth, proliferation and transformation.

Pharmacodynamics/KineticsHalf-life elimination: ~7.5 days (range: 4-11 days)

Pharmacotherapy Pearls**Oncology Comment:** The National Comprehensive Cancer Network® (NCCN) guidelines for colon cancer (v.4.2008) recommend genotyping tumor tissue for KRAS mutation in all patients with metastatic colorectal cancer (genotyping may be done on archived specimens). Patients with known codon 12 or 13 KRAS gene mutations are unlikely to respond to EGFR inhibitors and should not receive panitumumab. Favorable progression-free survival and higher response rates have been demonstrated with panitumumab in patients with KRAS wild-type; patients with the KRAS mutation did not respond to panitumumab (Amado, 2008). Because EGFR testing in colorectal tumors does not correlate with response, the NCCN guidelines do not recommend routine EGFR testing in colorectal cancer. Severity of dermatologic toxicity associated with panitumumab is predictive for response; grades 2-4 skin toxicity correlates with improved progression free survival and overall survival, compared to patients with grade 1 skin toxicity (Van Cutsem, 2007). The NCCN guidelines do not recommend the use of panitumumab after failure of cetuximab therapy.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis and mucositis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusFatigue is common

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with lithium, valproic acid, carbamazepine, and SSRIs may produce additive effects

Index TermsABX-EGF; NSC-742319; rHuMAb-EGFr

References

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National Comprehensive Cancer Network (NCCN), "Clinical Practice Guidelines in Oncology™: Colon Cancer," Version 4, 2008. Accessible at http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf

Rowinsky EK, Schwartz GH, Gollob JA, et al, "Safety, Pharmacokinetics, and Activity of ABX-EGF, a Fully Human Anti-Epidermal Growth Factor Receptor Monoclonal Antibody in Patients with Metastatic Renal Cell Cancer," *J Clin Oncol*, 2004, 22(15):3003-15.[PubMed 15210739]

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Van Cutsem E, Peeters M, Siena S, et al, "Open-Label Phase III Trial of Panitumumab Plus Best Supportive Care Compared With Best Supportive Care Alone in Patients With Chemotherapy-Refractory Metastatic Colorectal Cancer," *J Clin Oncol*, 2007, 25(13): 1658-64.

International Brand NamesVectibix (CZ, DE, DK, EE, GB, NO, SE)

Pantoprazole

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Clopidogrel (Plavix®) and Proton Pump Inhibitors (PPIs): Ongoing Safety Review - January 2009

The U.S. Food and Drug Administration (FDA) is communicating important information regarding an ongoing safety review of clopidogrel and its effectiveness when used with proton pump inhibitors (PPIs).

Clopidogrel is a prodrug requiring hepatic conversion via CYP3A4 and/or CYP2C19 to its active metabolite. Impaired clopidogrel conversion to its active metabolite may be due to either CYP450 polymorphisms or drug-drug interactions resulting in suboptimal antiplatelet activity.

A PPI is often prescribed with the combination of aspirin and clopidogrel to prevent gastrointestinal bleeding. A number of PPIs are available and include esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. Several studies have reported greater clinical event rates (eg, myocardial infarction, death) or greater platelet reactivity associated with concurrent use of clopidogrel and a PPI (Ho, 2008; Pezella, 2008; Gilard, 2006). Similarly, a prospective, randomized, double-blind trial demonstrated a reduction in antiplatelet activity when omeprazole and clopidogrel are used concurrently (Gilard, 2008). Another controlled trial with the PPI lansoprazole also found evidence of a possible interaction resulting in less antiplatelet activity (Small, 2008). This interaction is thought to result from competitive inhibition of the CYP2C19-mediated activation of clopidogrel by omeprazole and other PPIs, which are all metabolized to at least some degree by CYP2C19. In contrast, one study with esomeprazole and pantoprazole did not find evidence of reduced antiplatelet activity when administered with clopidogrel (Siller-Matula, 2009), highlighting the need for additional studies to determine the degree to which individual PPIs may differ in their potential for interacting with clopidogrel.

The manufacturer of Plavix® has agreed to conduct further studies to better understand the effect of other drugs (including PPIs) and genetic factors on the effectiveness of clopidogrel. The FDA is recommending that healthcare providers continue to prescribe clopidogrel while reevaluating the need for prescription or over-the-counter (OTC) PPIs in patients taking clopidogrel. Patients should continue taking clopidogrel as directed. If taking a PPI with clopidogrel, patients should consult with their healthcare provider.

For more information, healthcare professionals may refer to the following FDA website: http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm

References:

Ho PM, Maddox TM, Wang L, et al, "Proton Pump Inhibitors May Attenuate the Benefits of Clopidogrel Among ACS Patients: Using Registry Data to Address Medication Effectiveness," United States Department of Veterans Affairs, 2008 QUERI National Meeting Abstract. Available at http://www.hsrd.research.va.gov/meetings/QUERI08/display_abstract.cfm?RecordID=118; accessed October 30, 2008).

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Siller-Matula JM, Spiel AO, Lang IM, et al, "Effects of Pantoprazole and Esomeprazole on Platelet Inhibition by Clopidogrel," *Am Heart J*, 2009, 157(1): 148.e1-5.

Small DS, Farid NA, Payne CD, et al, "Effects of the Proton Pump Inhibitor Lansoprazole on the Pharmacokinetics and Pharmacodynamics of Prasugrel and Clopidogrel," *J Clin Pharmacol*, 2008, 48(4):475-84.

Medication Safety Issues

Sound-alike/look-alike issues:

Protonix® may be confused with Lotronex®, Lovenox®, protamine

Vials containing Protonix® I.V. for injection are not recommended for use with spiked I.V. system adaptors. Nurses and pharmacists have reported breakage of the glass vials during attempts to connect spiked I.V. system adaptors, which may potentially result in injury to healthcare professionals.

International issues:

Protonix® may be confused with Pretanix® which is a brand name for indapamide in Hungary

Pronunciation(pan TOE pra zole)

U.S. Brand NamesProtonix®

Canadian Brand NamesApo-Pantoprazole; Co-Pantoprazole; Gen-Pantoprazole; Novo-Pantoprazole; Pantoloc®; Pantoloc® M; Panto™ I.V.; PMS-Pantoprazole; Protonix®; Ran-Pantoprazole; Ratio-Pantoprazole; Riva-Pantoprazole; Sandoz-Pantoprazole; Tecta™

Pharmacologic CategoryProton Pump Inhibitor; Substituted Benzimidazole

Use: Labeled Indications

Oral: Treatment and maintenance of healing of erosive esophagitis associated with GERD; reduction in relapse rates of daytime and nighttime heartburn symptoms in GERD; hypersecretory disorders associated with Zollinger-Ellison syndrome or other GI hypersecretory disorders

I.V.: Short-term treatment (7-10 days) of patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis; hypersecretory disorders associated with Zollinger-Ellison syndrome or other neoplastic disorders

Use: Unlabeled/InvestigationalPeptic ulcer disease, active ulcer bleeding (parenteral formulation); adjunct treatment with antibiotics for *Helicobacter pylori* eradication; stress-ulcer prophylaxis in the critically-ill

Dosing: Adults

Erosive esophagitis associated with GERD:

Oral:

Treatment: 40 mg once daily for up to 8 weeks; an additional 8 weeks may be used in patients who have not healed after an 8-week course

Maintenance of healing: 40 mg once daily

Note: Lower doses (20 mg once daily) have been used successfully in mild GERD treatment and maintenance of healing

I.V.: 40 mg once daily for 7-10 days

Peptic ulcer disease: Eradication of *Helicobacter pylori* (unlabeled use): Oral: Doses up to 40 mg twice daily have been used as part of combination therapy

Hypersecretory disorders (including Zollinger-Ellison):

Oral: Initial: 40 mg twice daily; adjust dose based on patient needs; doses up to 240 mg/day have been administered

I.V.: 80 mg twice daily; adjust dose based on acid output measurements; 160-240 mg/day in divided doses has been used for a limited period (up to 7 days)

Prevention of rebleeding in peptic ulcer bleed (unlabeled use): I.V.: 80 mg, followed by 8 mg/hour infusion for 72 hours. **Note:** A daily infusion of 40 mg does not raise gastric pH sufficiently to enhance coagulation in active GI bleeds.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**GERD, erosive esophagitis associated with GERD:**

Oral:

Children <5 years: Dosage not established.

Children ≥5 years (unlabeled use): 20-40 mg once daily

I.V.: Dosage not established

Dosing: Renal ImpairmentNo adjustment is required. Pantoprazole is not removed by hemodialysis.

Dosing: Hepatic ImpairmentNo adjustment is required.

Administration: I.V.Flush I.V. line before and after administration. In-line filter not required.

2-minute infusion: The volume of reconstituted solution (4 mg/mL) to be injected may be administered intravenously over at least 2 minutes.

15-minute infusion: Infuse over 15 minutes at a rate not to exceed 7 mL/minute (3 mg/minute).

Administration: Oral

Tablet: Should be swallowed whole, do not crush or chew. Best if taken before breakfast.

Delayed-release oral suspension: Should only be administered in apple juice or applesauce and taken ~30 minutes before a meal. Do not administer with any other liquid (eg, water) or foods.

Oral administration in **applesauce**: Sprinkle intact granules on 1 tablespoon of applesauce and swallow within 10 minutes of preparation.

Oral administration in **apple juice**: Empty intact granules into 5 mL of apple juice (~1 teaspoonful), stir for 5 seconds, and swallow immediately after preparation. Rinse container once or twice with apple juice and swallow immediately.

Nasogastric tube administration: Separate the plunger from the barrel of a 60 mL catheter tip syringe and connect to a ≥16 French nasogastric tube. Holding the syringe attached to the tubing as high as possible, empty the contents of the packet into barrel of the syringe, add 10 mL of apple juice and gently tap/shake the barrel of the syringe to help empty the syringe. Add an additional 10 mL of apple juice and gently tap/shake the barrel to help rinse. Repeat rinse with at least 2 -10 mL aliquots of apple juice. No granules should remain in the syringe.

Dietary Considerations

Oral: May be taken with or without food; best if taken before breakfast.

I.V.: Due to EDTA in preparation, zinc supplementation may be needed in patients prone to zinc deficiency.

Storage

Oral: Store tablet and oral suspension at controlled room temperature of 20°C to 25°C (68°F to 77°F).

I.V.: Prior to reconstitution, store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light. When reconstituted, solution is stable up to 96 hours at room temperature (Johnson, 2005). The preparation should be stored at 3°C to 5°C (37°F to 41°F) if it is stored beyond 48 hours to minimize discoloration. If further diluting in 100 mL of D_5W, LR, or NS, dilute within 6 hours of reconstitution. Diluted solution is stable at room temperature for up to 24 hours from the time of initial reconstitution; protection from light is not required.

ReconstitutionReconstitute with 10 mL NS (final concentration 4 mg/mL). Reconstituted solution may be given intravenously (over 2 minutes) or may be added to 100 mL D_5W, NS, or LR (for 15-minute infusion).

CompatibilityStable in D_5W, LR, NS.

Y-site administration: Incompatible: Midazolam, zinc.

Extemporaneously PreparedA 2 mg/mL pantoprazole oral liquid can be prepared with twenty pantoprazole 40 mg tablets, 340 mL sterile water, and 33.6 g of sodium bicarbonate powder. Remove the Protonix® imprint from each of the tablets on a paper towel dampened with ethanol (improves the look of product). Let tablets air dry. Grind the tablets into a coarse powder, transfer to a 600 mL beaker and add 340 mL of sterile water for irrigation and place beaker on a magnetic stirrer. Add 16.8 g of sodium bicarbonate powder and stir for about 20 minutes until the tablet remnants have disintegrated. While stirring, add another 16.8 g of sodium bicarbonate powder and stir for about 5 minutes until powder has dissolved. Add enough sterile water for irrigation to bring the final volume to 400 mL. Mix well. Transfer to amber-colored bottle. Stable for 62 days under refrigeration. Shake well before use.

Dentinger PJ, Swenson CF, and Anaizi NH, "Stability of Pantoprazole in an Extemporaneously Compounded Oral Liquid," *Am J Health Syst Pharm*, 2002, 59:953-6.

ContraindicationsHypersensitivity to pantoprazole, substituted benzamidazoles (eg, esomeprazole, lansoprazole, omeprazole, rabeprazole), or any component of the formulation

Allergy Considerations

- Proton Pump Inhibitor, Benzimidazole Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Atrophic gastritis: Long-term pantoprazole therapy (especially in patients who were *H. pylori* positive) has caused biopsy-proven atrophic gastritis.
- Carcinoma: No occurrences of enterochromaffin-like (ECL) cell carcinoids, dysplasia, or neoplasia, such as those seen in rodent studies, have been reported in humans.
- Vitamin B_{12} malabsorption: Prolonged treatment (typically >3 years) may lead to vitamin B_{12} malabsorption and subsequent deficiency.

Disease-related concerns:

- Gastric malignancy: Relief of symptoms does not preclude the presence of a gastric malignancy.
- Gastrointestinal infection (eg, *Salmonella, Campylobacter*): Use of proton pump inhibitors may increase risk of these infections.

Dosage form specific issues:

- Edetate sodium (EDTA): Intravenous preparation contains edetate sodium; use caution in patients who are at risk for zinc deficiency if other EDTA-containing solutions are coadministered.

Geriatric ConsiderationsDosage adjustment not required.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use in pregnancy only if clearly needed.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsNot recommended due to carcinogenicity in animal studies.

Adverse Reactions

≥1%:

Cardiovascular: Chest pain

Central nervous system: Headache (2% to 9%), insomnia (≤1%), anxiety, dizziness, migraine

Dermatologic: Rash (≤2%)

Endocrine & metabolic: Hyperglycemia (≤1%), hyperlipidemia

Gastrointestinal: Diarrhea (2% to 6%), flatulence (2% to 4%), abdominal pain (1% to 4%), nausea (≤2%), vomiting (≤2%), eructation (≤1%), constipation, dyspepsia, gastroenteritis, rectal disorder

Genitourinary: Urinary frequency, UTI

Hepatic: Liver function tests abnormal (≤2%)

Local: Injection site reaction (includes thrombophlebitis and abscess)

Neuromuscular & skeletal: Arthralgia, back pain, hypertonia, neck pain, weakness

Respiratory: Bronchitis, cough, dyspnea, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection

Miscellaneous: Flu syndrome, infection, pain

<1%, postmarketing, and/or case reports: Abnormal dreams, acne, albuminuria, alkaline phosphatase increased, allergic reaction, alopecia, anaphylaxis, anemia, angioedema, angina pectoris, anorexia, aphthous stomatitis, appetite increased, arrhythmia, asthma exacerbation, atrial fibrillation/flutter, atrophic gastritis, balanitis, biliary pain, blurred vision, bone pain, breast pain, bursitis, cataract, CHF, chills, cholecystitis, cholelithiasis, CPK increased, colitis, confusion, contact dermatitis, creatinine increased, cystitis, deafness, decreased reflexes, dehydration, depression, diabetes mellitus, diaphoresis, diplopia, duodenitis, dysarthria, dysmenorrhea, dysphagia, dysuria, ecchymosis, ECG abnormality, eczema, eosinophilia, epididymitis, epistaxis, erythema multiforme, esophagitis, extraocular palsy, facial edema, fever, fungal dermatitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, generalized edema, GGT increased, gingivitis, glaucoma, glossitis, glycosuria, goiter, gout, halitosis, hallucinations, heat stroke, hematemesis, hematuria, hemorrhage, hepatic failure, hepatitis, hernia, herpes simplex, herpes zoster, hiccup, hyperbilirubinemia, hyperesthesia, hyper-/hypotension, hyperkinesia, hyperuricemia, hypokinesia, impaired urination, impotence, interstitial nephritis, jaundice, kidney calculus, kidney pain, laryngitis, leg cramps, leukocytosis, leukopenia, libido decreased, lichenoid dermatitis, maculopapular rash, malaise, melena, mouth ulceration, myalgia, myocardial infarction, myocardial ischemia, neoplasm, nervousness, neuralgia, neuritis, nocturia, optic neuropathy (including anterior ischemic), otitis externa, palpitation, pancreatitis, pancytopenia, paresthesia, periodontal abscess, periodontitis, photosensitivity, pneumonia, pruritus, pyelonephritis, rectal hemorrhage, retinal vascular disorder, rhabdomyolysis, salivation increased, scrotal edema, seizure, skin ulcer, somnolence, Stevens-Johnson syndrome, stomach ulcer, stomatitis, syncope, tachycardia, taste perversion, tenosynovitis, thrombocytopenia, thrombosis, tinnitus, tongue discoloration, toxic epidermal necrolysis, tremor, urethral pain, urethritis, urticaria, vaginitis, vasodilation, vertigo, vision abnormal, weight changes, xerostomia

Metabolism/Transport Effects**Substrate** of CYP2C19 (major), 2C9 (minor), 2D6 (minor), 3A4 (minor); **Inhibits** 2C9 (weak); **Induces** CYP1A2 (weak), 3A4 (weak)

Drug Interactions

Atazanavir: Proton Pump Inhibitors may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Clopidogrel: Proton Pump Inhibitors may diminish the therapeutic effect of Clopidogrel. This appears to be due to reduced formation of the active clopidogrel metabolite. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: Proton Pump Inhibitors may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Proton Pump Inhibitors may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Erlotinib: Proton Pump Inhibitors may decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Fluconazole: May increase the serum concentration of Proton Pump Inhibitors. *Risk C: Monitor therapy*

Indinavir: Proton Pump Inhibitors may decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Iron Salts: Proton Pump Inhibitors may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk C: Monitor therapy*

Itraconazole: Proton Pump Inhibitors may decrease the serum concentration of Itraconazole. *Risk D: Consider therapy modification*

Ketoconazole: Proton Pump Inhibitors may decrease the serum concentration of Ketoconazole. Ketoconazole may increase the serum concentration of Proton Pump Inhibitors. *Risk D: Consider therapy modification*

Mesalamine: Proton Pump Inhibitors may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids; proton pump inhibitors would be expected to interact in a similar manner. *Risk X: Avoid combination*

Methotrexate: Proton Pump Inhibitors may decrease the excretion of Methotrexate. Antirheumatic doses of methotrexate probably hold minimal risk. *Risk C: Monitor therapy*

Mycophenolate: Proton Pump Inhibitors may decrease the serum concentration of Mycophenolate. Specifically, concentrations of the active mycophenolic acid may be reduced. *Risk C: Monitor therapy*

Nelfinavir: Proton Pump Inhibitors may decrease serum concentrations of the active metabolite(s) of Nelfinavir. Proton Pump Inhibitors may decrease the serum concentration of Nelfinavir. *Risk X: Avoid combination*

Saquinavir: Proton Pump Inhibitors may increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

Tipranavir: May decrease the serum concentration of Proton Pump Inhibitors. These data are derived from studies with Ritonavir-boosted Tipranavir. *Risk C: Monitor therapy*

Topotecan: BCRP/ABCG2 Inhibitors may increase the serum concentration of Topotecan. *Risk D: Consider therapy modification*

Voriconazole: Proton Pump Inhibitors may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause gastric mucosal irritation).

Herb/Nutraceutical: Prolonged treatment (typically >3 years) may lead to vitamin B_{12} malabsorption and subsequent deficiency.

Test InteractionsFalse-positive urine screening tests for tetrahydrocannabinol (THC) have been noted in patients receiving proton pump inhibitors, including pantoprazole.

Monitoring ParametersHypersecretory disorders: Acid output measurements, target level <10 mEq/hour (<5 mEq/hour if prior gastric acid-reducing surgery)

Nursing: Physical Assessment/MonitoringAssess other medications for effectiveness and interactions (cytochrome P450 enzyme substrate), especially those drugs where absorption is determined by an acidic gastric pH. Monitor therapeutic effectiveness and adverse effects at beginning of therapy and regularly with long-term use. Assess knowledge/teach patient appropriate use, possible side effects/interventions, and adverse symptoms to report.

Patient EducationTake as directed; do not alter dosage without consulting prescriber. Take at similar time each day. Swallow tablet whole (do not crush or chew). Avoid alcohol. You may experience dizziness, headache, or anxiety (use caution when driving or engaging in dangerous activities until response to medication is known); vomiting or loss of appetite (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (boiled milk, yogurt, or buttermilk may help). Report persistent abdominal discomfort; chest pain or palpitations; acute headache; unresolved diarrhea; excessive fatigue; increased muscle, joint, or body pain; shortness of breath or wheezing; cold or flu symptoms; changes in urinary pattern; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Note: Strength expressed as base

Granules for suspension, delayed release, enteric coated, as sodium, oral:

Protonix®: 40 mg/packet (30s)

Injection, powder for reconstitution, as sodium:

Protonix®: 40 mg [contains edetate sodium 1 mg]

Tablet, delayed release, as sodium: 20 mg, 40 mg

Protonix®: 20 mg, 40 mg

Tablet, enteric coated, as magnesium:

Pantoloc® M [CAN]: 40 mg [not available in the U.S.]

Generic AvailableYes: Delayed release tablet

ManufacturerWyeth-Ayerst Laboratories

Pricing: U.S. (www.drugstore.com)

Tablet, EC (Pantoprazole Sodium)

20 mg (30): $109.99

40 mg (90): $324.98

Tablet, EC (Protonix)

20 mg (30): $134.03

40 mg (30): $132.03

Mechanism of ActionSuppresses gastric acid secretion by inhibiting the parietal cell H^+/K^+ ATP pump

Pharmacodynamics/Kinetics

Absorption: Rapid, well absorbed

Distribution: V_d: 11-24 L

Protein binding: 98%, primarily to albumin

Metabolism: Extensively hepatic; CYP2C19 (demethylation), CYP3A4; no evidence that metabolites have pharmacologic activity

Bioavailability: 77%

Half-life elimination: 1 hour; increased to 3.5-10 hours with CYP2C19 deficiency

Time to peak: Oral: 2.5 hours

Excretion: Urine (71%); feces (18%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety or dizziness; may rarely produce confusion, depression, dysarthria, hallucinations, nervousness, or somnolence

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other Considerations

Evidence-Based Information:

Acute ulcer: Pre-endoscopy therapy: Lau and associates (2007) evaluated the effects of preemptive infusion of omeprazole before endoscopy in upper gastrointestinal bleeding. Consecutive patients (n=638) were stabilized and then randomly assigned to intravenous omeprazole (80 mg bolus followed by a continuous infusion of 8 mg/hour) or placebo infusion before endoscopy the next morning. The primary endpoint was the need for endoscopic therapy (eg, epinephrine, thermocoagulation). Seven patients were excluded from the analysis. The need for endoscopic treatment was significantly lower in the omeprazole group (60/314 patients; 19%) than in the placebo group (90/317; 28%). The active treatment group had a significantly shorter hospital stay. Duration of infusion before endoscopy was similar in both groups (~8-21 hours).

Acute ulcer: Postendoscopy therapy: Intravenous omeprazole has been studied in prevention of rebleeding in ulcer patients who are at high risk for rebleeding (endoscopic findings of active bleeding or nonbleeding visible vessel) after successful hemostasis (Lin, 1998; Lau, 2000). Lin and his group treated 100 ulcer patients (actively bleeding ulcers or ulcers with nonbleeding visible vessels) endoscopically and then randomized them to cimetidine (300 mg bolus followed by 50 mg/hour infusion) or omeprazole (40 mg bolus, ~7 mg/hour infusion) for 72 hours. Patients were discharged on the oral form of the drug arm they were assigned to. The omeprazole group maintained an intragastric pH >6 for about 84% of the infusion duration, while the cimetidine group maintained their pH >6 only about 50% of the time. Rebleeding occurred significantly more often in the cimetidine group.

Lau and his colleagues treated patients with actively bleeding ulcers or ulcers with nonbleeding visible vessels with an epinephrine infusion followed by thermocoagulation. They were then randomized to omeprazole (80 mg bolus followed by a continuous infusion of 8 mg/hour for 72 hours) or placebo. All patients were discharged on oral omeprazole (20 mg/day) for 8 weeks and received *H. pylori* treatment if indicated. The primary goal was to evaluate the rate of rebleeding during the first 30 days after endoscopy. Two hundred and forty patients were enrolled with randomization of 120 into each group. Bleeding recurred in significantly more patients receiving placebo than omeprazole infusion. The authors concluded that after endoscopic therapy, omeprazole reduces the risk of rebleeding in patients with actively bleeding ulcers or ulcers with nonbleeding visible vessels.

Stress ulcer prophylaxis: The 2008 Surviving Sepsis Campaign guidelines recommend that stress ulcer prophylaxis using an H_2 blocker (Grade 1A) or proton pump inhibitor (Grade 1B) be given to patients with severe sepsis to prevent upper GI bleed. Benefit of prevention of upper GI bleed must be weighed against potential effect of increased stomach pH on development of ventilator-associated pneumonia.

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International Brand NamesAnagastra (ES); Branzol (UY); Ciproton (MX); Controloc (BG, EE, EG, HN, HR, HU, IL, IR, JO, MY, PK, PL, SG, TH, ZA); Eupantol (FR); Inipomp (FR); Kuppam (MX); Leminter (MX); Pantec (IN); Pantecta (CR, DO, ES, GT, HN, IT, NI, PA, SV); Panto-Byk (LU); Pantoc (PT); Pantocar (PH); Pantodac (IN); Pantodar (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Pantoloc (AT, CL, DK, HK, KP, PH, SE, TW); Pantomed (KP); Pantop (AR, VE); Pantozol (AE, BH, CH, CY, DE, EG, ID, IL, IQ, IR, JO, KW, LB, LU, LY, MX, NL, OM, QA, SA, SY, YE); Pauly (MX); Peptazol (SG); Pepticus (PY); Peucetol (MX); Protium (GB, IE); Prozolan (MX); Regad (MX); Rifun 40 (DE); Somac (AU, FI, NO); Tecta (MX); Ulcepraz (PH); Unigastrozol (MX); Ziprol (BR); Zolpra (MX); Zurcal (AT, CH, CN, CO, EC, MX, PE, PT); Zurcale (BE); Zurcazol (GR)

Pantothenic Acid

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(pan toe THEN ik AS id)
U.S. Brand NamesPanto-250
Pharmacologic CategoryVitamin, Water Soluble
Use: Labeled IndicationsPantothenic acid deficiency
Dosing: Adults**Dietary deficiency:** Oral: Recommended daily dose 4-7 mg/day
Dosing: ElderlyRefer to adult dosing.
Pregnancy Risk FactorA/C (dose exceeding RDA recommendation)
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Panto-250: 250 mg [contains calcium 23 mg]

Liquid: 200 mg/5 mL (240 mL)

Tablet: 100 mg, 200 mg, 250 mg, 500 mg

Tablet, sustained release: 500 mg

Generic AvailableYes
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsCalcium Pantothenate; Vitamin B_5
International Brand NamesCalcium Pantothenicum (PL); Kerato Biciron (DE); Pantothen Streuli (CH)

Papain and Urea

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English

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Special Alerts

Papain-Containing Topical Products: FDA Enforcement Action - November 2008

In September 2008, the U.S. Food and Drug Administration (FDA) ordered companies to discontinue manufacturing papain-containing topical products by November 24, 2008, and to cease shipping of these products by January 21, 2009. At present, all topical products containing papain (~35 products under various trade names) lack FDA approval. Safety concerns have also been raised from reports of serious hypersensitivity reactions, including anaphylaxis, associated with papain use. Hypotension and tachycardia has also been observed in association with these hypersensitivity reactions. In addition, the medical literature also suggests that patients with latex hypersensitivity may also be allergic to papaya, the source of papain.

Papain-containing topical products manufactured prior to the ordered stop date may still be found on pharmacy shelves for a short period of time. However, healthcare providers are reminded that alternative products with FDA approval for the management of wounds are available.

Additional information may be found at http://www.fda.gov/cder/news/papain/qa.htm

Pronunciation(pa PAY in & yoor EE a)

U.S. Brand NamesAccuzyme®; Accuzyme® SE; AllanEnzyme; Ethezyme™ 650 [DSC]; Ethezyme™ 830 [DSC]; Ethezyme™ [DSC]; Kovia®; Paptase™

Pharmacologic CategoryEnzyme, Topical Debridement

Use: Labeled IndicationsDebridement of necrotic tissue and liquefaction of slough in acute and chronic lesions such as pressure ulcers, varicose and diabetic ulcers, burns, postoperative wounds, pilonidal cyst wounds, carbuncles, and miscellaneous traumatic or infected wounds

Dosing: AdultsTopical: Apply with each dressing change. Daily or twice daily dressing changes are preferred, but may be every 2-3 days. Cover with dressing following application.

Ointment: Apply $^1/_8$-inch thickness over the wound with clean applicator.

Spray: Completely cover the wound site so that the wound is not visible.

Dosing: ElderlyRefer to adult dosing.

Administration: Topical**Note:** If eschar is present it may be necessary to consult qualified practitioner to cross-hatch the eschar prior to application. The wound should be completely covered by application.

Ointment, spray: Cleanse wound prior to application. May apply under pressure dressings. Initially may require more frequent dressing changes to decrease irritation from enzymatic activity. Avoid cleansing with hydrogen peroxide solution. Avoid using heavy metal-containing solutions (eg, lead, mercury, silver). Do not use in or around the eyes.

Spray: Cleanse wound prior to application. Shake well before use; tap bottom of bottle on solid surface several times to loosen liquid from inside walls. Prime pump (initial use only): Hold spray upright directly above the wound and prime the pump 10-14 times. Normal use: Allow a distance of 1-2 inches between the spray container and the wound; may hold spray at an angle or upright.

Storage

Ointment: Store in a cool place; do not refrigerate.

Spray: Store upright in a cool place at 8°C to 15°C (46°F to 59°F); do not refrigerate.

ContraindicationsHypersensitivity to papain, urea, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Anaphylaxis and severe hypersensitivity reactions have occurred with papain use. Tachycardia and hypotension, in association with some hypersensitivity reactions, have also been observed.

- Latex hypersensitivity: Inconclusive data suggests a possible cross-sensitivity may exist between patients with natural rubber latex hypersensitivity and papaya, the source of papain.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Administration: For external use only; not for use in the eyes.

Geriatric ConsiderationsPreventive skin care should be instituted in all older patients at high risk for pressure ulcers.
Adverse ReactionsFrequency not defined: Local: Burning sensation, skin irritation

Postmarketing and/or case reports: Anaphylaxis, hypersensitivity reactions

Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringSee individual agent for Urea.
Patient EducationSee individual agent for Urea.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol, topical:

Paptase™: Papain 8.3 x 10^5 units/g and urea 10% (45 g)

Emulsion, topical [spray]:

Accuzyme® SE: Papain 8.3 x 10^5 units/g and urea 10% (34 mL)

Ointment, topical:

Accuzyme®: Papain 8.3 x 10^5 units/g and urea 10% (6 g, 30 g)

AllanEnzyme: Papain 8.3 x 10^5 units/g and urea 10% (30 g)

Ethezyme™: Papain 1.1 x 10^6 units and urea 10% (30 g) [DSC]

Ethezyme™ 650: Papain 6.5 x 10^5 units/g and urea 10% (30 g) [DSC]

Ethezyme™ 830: Papain 8.3 x 10^5 units/g and urea 10% (30 g) [DSC]

Kovia®: Papain 8.3 x 10^5 units/g and urea 10% (3.5 g) [single-dose packet]; 30 g

Solution, topical [spray]:

AllanEnzyme: Papain 8.3 x 10^5 units/g and urea 10% (33 mL)

Generic AvailableYes: Ointment
Pricing: U.S. (www.drugstore.com)

Emulsion (Accuzyme SE)

830000-10 units/g-% (34): $49.99

Ointment (Accuzyme)

830000-100unit-mg/gm (30): $54.55

Mechanism of Action

Papain: Potent digestant of nonviable protein matter; harmless to viable tissue. Requires activation to exert its function.

Urea: Exposes papain activators (sulfhydryl groups) and denatures nonviable protein matter making it more susceptible to enzymatic digestion.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
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Papaverine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(pa PAV er een)

U.S. Brand NamesPara-Time SR®

Pharmacologic CategoryVasodilator

Use: Labeled IndicationsOral: Relief of peripheral and cerebral ischemia associated with arterial spasm and myocardial ischemia complicated by arrhythmias

Use: Unlabeled/InvestigationalInvestigational: Parenteral: Various vascular spasms associated with muscle spasms as in myocardial infarction, angina, peripheral and pulmonary embolism, peripheral vascular disease, angiospastic states, and visceral spasm (ureteral, biliary, and GI colic); testing for impotence

Dosing: Adults**Arterial spasm:**

Oral, sustained release: 150-300 mg every 12 hours; in difficult cases: 150 mg every 8 hours

I.M., I.V.: 30-65 mg (rarely up to 120 mg); may repeat every 3 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Arterial spasm:** I.M., I.V.: 6 mg/kg/day in 4 divided doses

Administration: I.V.Rapid I.V. administration may result in arrhythmias and fatal apnea; administer no faster than over 1-2 minutes.

Administration: I.V. DetailpH: Not <3; 3-4 (2% solution in water)

Dietary ConsiderationsMay be taken with food.

StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light.

ReconstitutionSolutions should be clear to pale yellow. Precipitates with lactated Ringer's.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, ${}^1/_2NS$, NS; **incompatible** with LR.

Compatibility in syringe: Compatible: Iohexol 64.7%, iopamidol 61%, iothalamate sodium 60%, metrizamide 48.25%, phentolamine. **Incompatible:** Diatrizoate meglumine 52%, diatrizoate sodium 8%. **Variable (consult detailed reference):** Diatrizoate meglumine 66%, diatrizoate sodium 10%, diatrizoate sodium 60%, ioxaglate meglumine 39.3%, ioxaglate sodium 19.6%.

Compatibility when admixed: Compatible: Theophylline. **Incompatible:** Aminophylline with trimecaine.

ContraindicationsHypersensitivity to papaverine or any component of the formulation

Allergy Considerations

- Benzylisoquinoline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Arrhythmias: May (in large doses or with rapid infusion) depress AV and intraventricular cardiac conduction leading to serious arrhythmias (eg, premature beats, paroxysmal tachycardia).

- Hepatitis: May cause hepatic hypersensitivity (eosinophilia with abnormal LFTs.

Disease-related concerns:

- Glaucoma: Use with caution in patients with glaucoma.

Other warnings/precautions:

- I.V. administration: Administer I.V. cautiously since apnea and arrhythmias may result.

Geriatric ConsiderationsVasodilators have been used to treat dementia upon the premise that dementia is secondary to a cerebral blood flow insufficiency. The hypothesis is that if blood flow could be increased, cognitive function would be increased. This hypothesis is no longer valid. The use of vasodilators for cognitive dysfunction is not recommended or proven by appropriate scientific study.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias (with rapid I.V. use), flushing of the face, mild hypertension, tachycardia

Central nervous system: Drowsiness, headache, lethargy, sedation, vertigo

Gastrointestinal: Abdominal distress, anorexia, constipation, diarrhea, nausea

Hepatic: Chronic hepatitis, hepatic hypersensitivity

Respiratory: Apnea (with rapid I.V. use)

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Nursing: Physical Assessment/MonitoringUse caution in presence of glaucoma. **I.V., I.M.:** Blood pressure and heart rate should be monitored. **I.V.:** Should be administered slowly (over 1-2 minutes) to avoid apnea or arrhythmias. **Oral:** Blood pressure and heart rate should be monitored prior to therapy and at frequent intervals thereafter. Assess therapeutic effectiveness and adverse response (eg, arrhythmias, tachycardia, hypertension, GI disturbance). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed; do not alter dose or discontinue without consulting prescriber. Swallow extended release capsules whole; do not chew, crush, or dissolve. May cause dizziness, confusion, or blurred vision (avoid driving or engaging in tasks that require alertness until response to drug is known); or constipation (increased exercise, fluids, fruit, or fiber may help). Report rapid heartbeat or palpitations and CNS changes (eg, depression, persistent sedation or lethargy, or acute headache). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, sustained release, as hydrochloride: 150 mg

Para-Time SR®: 150 mg

Injection, solution, as hydrochloride: 30 mg/mL (2 mL, 10 mL)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsule, controlled release (Papaverine HCl CR)

150 mg (60): $19.98

Solution (Papaverine HCl)

30 mg/mL (10): $25.99

Mechanism of ActionSmooth muscle spasmolytic producing a generalized smooth muscle relaxation including: vasodilatation, gastrointestinal sphincter relaxation, bronchiolar muscle relaxation, and potentially a depressed myocardium (with large doses); muscle relaxation may occur due to inhibition or cyclic nucleotide phosphodiesterase, increasing cyclic AMP; muscle relaxation is unrelated to nerve innervation; papaverine increases cerebral blood flow in normal subjects; oxygen uptake is unaltered

Pharmacodynamics/Kinetics

Onset of action: Oral: Rapid

Protein binding: 90%

Metabolism: Rapidly hepatic

Half-life elimination: 0.5-1.5 hours

Excretion: Primarily urine (as metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness

Mental Health: Effects on Psychiatric TreatmentMay decrease the effects of levodopa

Anesthesia and Critical Care Concerns/Other ConsiderationsThe use of vasodilators for cognitive dysfunction is **not** recommended.

Index TermsPapaverine Hydrochloride; Pavabid [DSC]

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International Brand NamesPapaverini (ID); Papaverinum Hydrochloricum (PL)

Papillomavirus (Types 6, 11, 16, 18) Vaccine (Human, Recombinant)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation

(pap ih LO ma VYE rus typs six e LEV en SIX teen AYE teen vak SEEN YU man ree KOM be nant)

U.S. Brand NamesGardasil®

Canadian Brand NamesGardasil®

Pharmacologic CategoryVaccine, Inactivated (Viral)

Use: Labeled IndicationsFemales: Prevention of cervical, vulvar, and vaginal cancer, genital warts, cervical adenocarcinoma *in situ*, and vulvar, vaginal, or cervical intraepithelial neoplasia caused by human papillomavirus (HPV) types 6, 11, 16, 18

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for females 11-12 years of age; catch-up vaccination is recommended for females 13-26 years of age

Dosing: Adults**Immunization regimen:** I.M.: Females: Children ≥9 years and Adults ≤26 years: 0.5 mL followed by 0.5 mL at 2 and 6 months after initial dose

CDC recommended immunization schedule: Administer first dose to females at age 11-12 years; begin series in females aged 13-26 years if not previously vaccinated. Minimum interval between first and second doses is 4 weeks; the minimum interval between first and third doses is 24 weeks.

Dosing: Pediatric**Immunization regimen:** Females: Children ≥9 years: Refer to adult dosing.

Administration: I.M.Shake suspension well before use. Inject I.M. into the deltoid region of the upper arm or higher anterolateral thigh area. Observe for syncope for 15 minutes following administration.

Administration with other vaccines:

Papillomavirus (Types 6, 11, 16, 18) Recombinant vaccine with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Papillomavirus (Types 6, 11, 16, 18) Recombinant vaccine with live vaccines: May be given simultaneously or at any interval between doses

Vaccine administration with antibody-containing products: Papillomavirus (Types 6, 11, 16, 18) Recombinant vaccine may be given simultaneously at different sites or at any interval between doses. Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends "it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection."

StorageStore at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light.

ContraindicationsHypersensitivity to papillomavirus recombinant vaccine or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.
- Syncope: Syncope may occur following vaccination; observe for 15 minutes following administration.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).
- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.
- Human papillomavirus (HPV) infection: There is no evidence that individuals already infected with HPV will be protected; those already infected with 1 or more HPV types were protected from disease in the remaining HPV types. Not for the treatment of active disease; will not protect against diseases not caused by HPV vaccine types 6, 11, 16, and 18.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination.

- Males: Safety and efficacy have not been established in males.

- Pediatrics: Safety and efficacy have not been established in girls <9 years of age.

- Pregnancy: Not recommended for use during pregnancy.

- Women: Safety and efficacy have not been established in women >26 years of age.

Dosage form specific issues:

- Yeast: Product may contain yeast.

Other warnings/precautions:

- Maximum efficacy: The entire 3-dose regimen should be completed for maximum efficacy.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Administration of the vaccine in pregnancy is not recommended. In clinical trials, women who were found to be pregnant before the completion of the 3-dose regimen were instructed to defer any remaining dose until pregnancy resolution. Pregnancies detected within 30 days of vaccination had a higher rate of congenital anomalies (pyloric stenosis, congenital megacolon, congenital hydronephrosis, hip dysplasia, club foot) than the placebo group. Pregnancies with onset beyond 30 days of vaccination had a rate of congenital anomalies consistent with the general population. Overall, the type of teratogenic events were the same as those generally observed for this age group. A registry has been established for women exposed to the HPV vaccine during pregnancy (1-800-986-8999).

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsInfants had a higher incidence of acute respiratory illness when breast-fed by mothers within 30 days postvaccination. Lactating women may receive vaccine.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

>10%:

Central nervous system: Fever (13%)

Local: Injection site: Pain (84%), swelling (25%), erythema (25%)

1% to 10%:

Central nervous system: Dizziness (4%), malaise (1%), insomnia (1%)

Gastrointestinal: Nausea (7%), diarrhea (4%), vomiting (2%), toothache (2%)

Local: Injection site: Bruising (3%), pruritus (3%)

Neuromuscular & skeletal: Arthralgia (1%)

Respiratory: Cough (2%), nasal congestion (1%)

<1%, postmarketing, and/or case reports: Anaphylactic/anaphylactoid reaction, appendicitis, arrhythmia, arthritis, asthma, autoimmune hemolytic anemia, bronchospasm, DVT, fatigue, gastroenteritis, Guillain-Barré syndrome, headache, hypersensitivity reaction, hyperthyroidism, JRA, lymphadenopathy, motor neuron disease, myalgia, pancreatitis, paralysis, pelvic inflammatory disease, pulmonary embolus, RA, renal failure (acute), seizure, sepsis, syncope, transverse myelitis, urticaria, weakness

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Monitoring ParametersGynecologic screening exam, papillomavirus test; observe for syncope/fainting for ~15 minutes after administration of vaccine

Nursing: Physical Assessment/MonitoringNot for treatment of active disease. Assess for impaired immune responsiveness; may have reduced antibody response to immunizations. Treatment for anaphylactic/anaphylactoid reaction should be available during vaccine use; if there is a hypersensitivity response after receiving a dose of Gardasil®, patient should not receive further doses. **Note:** All serious adverse reactions must be reported to the U.S. DHHS. Federal law requires that date of administration, name of manufacturer, lot number, administering person's name, title, and address be recorded in patient's permanent medical record. All patients should be informed that the vaccine is not a treatment for active disease and is not a substitute for regular, routine cervical screening. Teach patient appropriate use (necessity for 3 doses), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis vaccine is not a treatment for active disease and does not substitute for regular, routine cervical cancer screening. Three doses will be required for effective immunity; consult prescriber for appropriate schedule of vaccinations. May cause drowsiness, malaise, or insomnia (do not drive or engage in activities that require alertness and coordination until response to drug is known); diarrhea (buttermilk, boiled milk, or yogurt may help); or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). May cause some redness, pain, or swelling at injection site; consult prescriber if excessive or persistent. Notify prescriber immediately of any acute reaction (eg, difficulty breathing, chest pain, acute headache, rash, difficulty swallowing). **Breast-feeding precaution:** Inform prescriber if you are or intend to breast-feed.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension [preservative free]:

Gardasil®: HPV 6 L1 protein 20 mcg, HPV 11 L1 protein 40 mcg, HPV 16 L1 protein 40 mcg, and HPV 18 L1 protein 20 mcg per 0.5 mL (0.5 mL) [contains aluminum, polysorbate 80; manufactured using *S. cerevisiae* (baker's yeast)]

Generic Available No
Manufacturer Merck & Co, Inc
Pricing: U.S. (www.drugstore.com)

Suspension (Gardasil)

(0.5): $149.73

(3): $842.04

(5): $1351.67

Mechanism of Action Contains inactive human papillomavirus (HPV) proteins HPV 6 L1, HPV 11 L1, HPV 16 L1, and HPV 18 L1 which produce neutralizing antibodies to prevent cervical cancer, cervical adenocarcinoma, cervical, vaginal and vulvar neoplasia and genital warts caused by HPV.
Related Information

- Immunization Recommendations

Pharmacotherapy Pearls Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title and address be entered into the patient's permanent medical record. Ideally, administration of vaccine should occur prior to potential HPV exposure. Benefits of vaccine decrease once infected with ≥1 of the HPV vaccine types.
Dental Health: Effects on Dental Treatment No significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions
Index Terms HPV Vaccine ; Human Papillomavirus Vaccine; Papillomavirus Vaccine, Recombinant; Quadrivalent Human Papillomavirus Vaccine
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International Brand Names Gardasil (AR, AT, AU, BE, BG, CH, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, MY, NL, NO, NZ, PH, PT, RU, SE, SG, TH, TR, TW)

Paregoric

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Camphorated tincture of opium is an error-prone synonym (mistaken as opium tincture)

Paregoric may be confused with Percogesic®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Use care when prescribing opium tincture; each mL contains the equivalent of morphine 10 mg; paregoric contains the equivalent of morphine 0.4 mg/mL

Pronunciation(par e GOR ik)

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled IndicationsTreatment of diarrhea or relief of pain; neonatal opiate withdrawal

Dosing: Adults**Diarrhea:** Oral: 5-10 mL 1-4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Neonatal opiate withdrawal: Oral: 3-6 drops every 3-6 hours as needed, or initially 0.2 mL every 3 hours; increase dosage by approximately 0.05 mL every 3 hours until withdrawal symptoms are controlled; it is rare to exceed 0.7 mL/dose. Stabilize withdrawal symptoms for 3-5 days, then gradually decrease dosage over a 2- to 4-week period.

Diarrhea: Oral: Children: 0.25-0.5 mL/kg 1-4 times/day

StorageStore in light-resistant, tightly-closed container.

RestrictionsC-III

ContraindicationsHypersensitivity to opium or any component of the formulation; diarrhea caused by poisoning until the toxic material has been removed; pregnancy (prolonged use or high doses)

Allergy Considerations

- Belladonna Alkaloid Allergy
- Benzylisoquinoline Allergy
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).
- Opioid agonist toxicities: Opium shares the toxic potentials of opiate agonists, and precautions of opiate agonist therapy should be observed.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Hepatic impairment: Use with caution in patients with hepatic dysfunction.

- Obesity: Use with caution in patients who are morbidly obese.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Renal impairment: Use with caution in patients with renal dysfunction.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

- Seizures: Use with caution in patients with a history of seizure disorders.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Dosage form specific issues:

- Sulfites: Some preparations contain sulfites which may cause allergic reactions

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Infants <3 months of age are more susceptible to respiratory depression; use with caution and generally in reduced doses in this age group.

Other warnings/precautions:

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Pregnancy Risk FactorB/D (prolonged use or high doses)
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsInformation regarding use while breast-feeding is based on experience with morphine. Probably safe with low doses and by administering dose after breast-feeding to further minimize exposure to the drug. Monitor the infant for possible side effects related to opiates.
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension, peripheral vasodilation

Central nervous system: Drowsiness, dizziness, insomnia, CNS depression, mental depression, increased intracranial pressure, restlessness, headache, malaise

Gastrointestinal: Constipation, anorexia, stomach cramps, nausea, vomiting, biliary tract spasm

Genitourinary: Ureteral spasms, decreased urination, urinary tract spasm

Hepatic: Increased liver function tests

Neuromuscular & skeletal: Weakness

Ocular: Miosis

Respiratory: Respiratory depression

Miscellaneous: Physical and psychological dependence, histamine release

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Nursing: Physical Assessment/MonitoringMonitor for excessive sedation, respiratory depression, or hypotension. For inpatients, implement safety measures (eg, side rails up, call light within reach, patient instructions to call for assistance). Has potential for psychological or physiological dependence

Patient EducationTake exactly as directed; do not increase dosage. May cause dependence with prolonged or excessive use. Avoid alcohol or any other prescription and OTC medications that may cause sedation (sleeping medications, some cough/cold remedies, antihistamines, etc). You may experience drowsiness, dizziness, or impaired judgment (use caution when driving or engaging in tasks that require alertness until response to drug is known) or postural hypotension (use caution when rising from sitting or lying position or when climbing stairs). You may experience nausea or loss of appetite (small frequent meals may help) or constipation (a laxative may be necessary). Report unresolved nausea, vomiting, respiratory difficulty (shortness of breath or decreased respirations), chest pain, or palpitations. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. If breast-feeding, take immediately after feeding or 4-6 hour before next feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, oral: Morphine equivalent 2 mg/5 mL (473 mL) [equivalent to opium 20 mg powder; contains alcohol 45% and benzoic acid]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tincture (Paregoric)

2 mg/5 mL (240): $69.98

Mechanism of ActionIncreases smooth muscle tone in GI tract, decreases motility and peristalsis, diminishes digestive secretions

Pharmacodynamics/KineticsIn terms of opium:

Metabolism: Hepatic

Excretion: Urine (primarily as morphine glucuronide conjugates and unchanged drug - morphine, codeine, papaverine, etc)

Pharmacotherapy PearlsContains morphine 0.4 mg/mL and alcohol 45%. Do **not** confuse this product with opium tincture which is 25 times **more** potent; each 5 mL of paregoric contains 2 mg morphine equivalent, 0.02 mL anise oil, 20 mg benzoic acid, 20 mg camphor, 0.2 mL glycerin and alcohol; final alcohol content 45%; paregoric also contains papaverine and noscapine; because all of these additives may be harmful to neonates, **a 25-fold dilution of opium tincture** is often preferred for treatment of neonatal abstinence syndrome (opiate withdrawal).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and dizziness are common; may cause restlessness; may rarely cause insomnia or depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation

Index TermsCamphorated Tincture of Opium (error-prone synonym)

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Paricalcitol

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(pah ri KAL si tole)

U.S. Brand NamesZemplar®

Canadian Brand NamesZemplar®

Pharmacologic CategoryVitamin D Analog

Use: Labeled Indications

I.V.: Prevention and treatment of secondary hyperparathyroidism associated with stage 5 chronic kidney disease (CKD)

Oral: Prevention and treatment of secondary hyperparathyroidism associated with stage 3 and 4 CKD

Dosing: Adults**Note:** If hypercalcemia or Ca x P >75 is observed, reduce or interrupt dosing until parameters are normalized.

Secondary hyperparathyroidism associated with chronic renal failure (stage 5 CKD): Children ≥5 years and Adults: I.V.: 0.04-0.1 mcg/kg (2.8-7 mcg) given as a bolus dose no more frequently than every other day at any time during dialysis; dose may be increased by 2-4 mcg every 2-4 weeks; doses as high as 0.24 mcg/kg (16.8 mcg) have been administered safely; the dose of paricalcitol should be adjusted based on serum intact PTH (iPTH) levels, as follows:

Same or increasing iPTH level: Increase paricalcitol dose

iPTH level decreased by <30%: Increase paricalcitol dose

iPTH level decreased by >30% and <60%: Maintain paricalcitol dose

iPTH level decrease by >60%: Decrease paricalcitol dose

iPTH level 1.5-3 times upper limit of normal: Maintain paricalcitol dose

Secondary hyperparathyroidism associated with stage 3 and 4 CKD: Adults: Oral: Initial dose based on baseline serum iPTH:

iPTH ≤500 pg/mL: 1 mcg/day or 2 mcg 3 times/week

iPTH >500 pg/mL: 2 mcg/day or 4 mcg 3 times/week

Dosage adjustment based on iPTH level relative to baseline, adjust dose at 2-4 week intervals:

iPTH same or increased: Increase paricalcitol dose by 1 mcg/day or 2 mcg 3 times/week

iPTH decreased by <30%: Increase paricalcitol dose by 1 mcg/day or 2 mcg 3 times//week

iPTH decreased by ≥30% or ≤60%: Maintain paricalcitol dose

iPTH decreased by >60%: Decrease paricalcitol dose by 1 mcg/day* or 2 mcg 3 times/week

iPTH <60 pg/mL: Decrease paricalcitol dose by 1 mcg/day* or 2 mcg 3 times/week

*If patient is taking the lowest dose on a once-daily regimen, but further dose reduction is needed, decrease dose to 1 mcg 3 times/week. If further dose reduction is required, withhold drug as needed and restart at a lower dose. If applicable, calcium-phosphate binder dosing may also be adjusted or withheld, or switch to noncalcium-based binder.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Secondary hyperparathyroidism associated with chronic renal failure (stage 5 CKD):** I.V.: Children ≥5 years: Refer to adult dosing.

Dosing: Renal ImpairmentRefer to adult dosing.

Dosing: Hepatic ImpairmentAdjustment not needed for mild-to-moderate impairment. Paricalcitol has not been evaluated in severe hepatic impairment.

Administration: I.V.Administered as a bolus dose at anytime during dialysis. Doses should not be administered more often than every other day.

Administration: OralMay be administered with or without food. With the 3 times/week dosing schedule, doses should not be given more frequently than every other day.

Dietary Considerations

The capsules may contain coconut or palm kernel oil.

ContraindicationsHypersensitivity to paricalcitol or any component of the formulation; patients with evidence of vitamin D toxicity; hypercalcemia

Warnings/Precautions

Concerns related to adverse effects:

- Excessive vitamin D: Excessive vitamin D administration may lead to over suppression of PTH, progressive or acute hypercalcemia, hypercalciuria, hyperphosphatemia and adynamic bone disease.

- Hypercalcemia: Progressive and/or acute hypercalcemia may increase risk of cardiac arrhythmias and seizures; chronic hypercalcemia may lead to generalized vascular and other soft-tissue calcification. Phosphate and vitamin D (and its derivatives) should be withheld during therapy to avoid hypercalcemia.

Concurrent drug therapy issues:

- Cardiac glycosides: Use with caution in patients taking cardiac glycosides; digitalis toxicity is potentiated by hypocalcemia.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children for the oral formulation or in children <5 years of age for the I.V. formulation.

Geriatric ConsiderationsNo specific dose changes necessary. Monitor closely. It may be advised to obtain baseline electrolytes, calcium, phosphorous, and digoxin serum concentrations, if applicable.
Pregnancy Risk FactorC
Pregnancy Considerations

Teratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%: Gastrointestinal: Nausea (6% to 13%)

1% to 10%:

Cardiovascular: Edema (7%), hypertension (7%), hypotension (5%), palpitation (3%), chest pain (3%), syncope (3%), cardiomyopathy (2%), MI (2%), postural hypotension (2%)

Central nervous system: Pain (8%), chills (5%), dizziness (5%), headache (5%), lightheadedness (5%), vertigo (5%), fever (3% to 5%), depression (3%), insomnia (2%)

Dermatologic: Rash (2% to 6%), skin ulcer (3%), pruritus (3%), skin hypertrophy (2%)

Endocrine & metabolic: Dehydration (3%), acidosis (2%), hypokalemia (2%)

Gastrointestinal: Vomiting (6% to 8%), diarrhea (7%), GI bleeding (5%), abdominal pain (4%), xerostomia (3%), constipation (4%), gastroenteritis (3%), dyspepsia (2%), gastritis (2%), rectal disorder (2%)

Genitourinary: Urinary tract infection (3%), kidney function abnormal (2%)

Neuromuscular & skeletal: Arthritis (5%), back pain (4%), leg cramps (3%), weakness (3%), neuropathy (2%)

Ocular: Amblyopia (2%), retinal disorder (2%)

Respiratory: Pneumonia (2% to 5%), rhinitis (5%), sinusitis (3%), bronchitis (3%), cough (3%), epistaxis (2%)

Miscellaneous: Infection (bacterial, fungal, viral: 2% to 8%); allergic reaction (6%), flu-like syndrome (2% to 5%), sepsis (5%), cyst (2%)

Postmarketing and/or case reports: Facial edema, oral edema, taste perversion (metallic), urticaria

Metabolism/Transport Effects

Substrate of CYP3A4 (major)

Drug InteractionsThere are no known significant interactions.
Monitoring Parameters

Signs and symptoms of vitamin D intoxication

Serum calcium and phosphorus:

I.V.: Twice weekly during initial phase, then at least monthly once dose established

Oral: At least every 2 weeks for 3 months or following dose adjustment, then monthly for 3 months, then every 3 months

Serum or plasma intact PTH (iPTH):

I.V.: Every 3 months

Oral: At least every 2 weeks for 3 months or following dose adjustment, then monthly for 3 months, then every 3 months

In trials, a mean PTH level reduction of 30% was achieved within 6 weeks with I.V. administration

Reference Range

CKD (definition of stages; chronic disease is kidney damage or GFR <60 mL/minute/1.73 m^2 for ≥3 months)

- Stage 3: GFR 30-59 mL/minute/1.73 m^2 (moderate decrease GFR)
- Stage 4: GFR 15-29 mL/minute/1.73 m^2 (severe decreased GFR)
- Stage 5: GFR <15 mL/minute/1.73 m^2 or dialysis (kidney failure)

Target range for iPTH:

- Stage 3 CKD: 35-70 pg/mL
- Stage 4 CKD: 70-110 pg/mL
- Stage 5 CKD: 150-300 pg/mL

Serum phosphorous:

- Stage 3 and 4 CKD: ≥2.7 to <4.6 mg/dL
- Stage 5 CKD: 3.5-5.5 mg/dL

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests. Monitor patient response and adverse effects. Monitor for signs and symptoms of vitamin D intoxication and hypercalcemia. Assess knowledge/instruct patient on safe and appropriate use of paricalcitol and dietary requirements.

Monitoring: Lab TestsSerum calcium and phosphorus should be monitored closely (eg, twice weekly) during dose titration. Monitor serum PTH. In trials, a mean PTH level reduction of 30% was achieved within 6 weeks.

Patient EducationTake as directed; do not increase dosage without consulting prescriber. Adhere to diet as recommended (do not take any other phosphate or vitamin D related compounds while taking paricalcitol). You may experience nausea or vomiting (small frequent meals, frequent mouth care, chewing gums, or sucking lozenges may help); swelling of extremities (elevate feet when sitting); or lightheadedness or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Report persistent fever, gastric disturbances, abdominal pain or blood in stool, chest pain or palpitations, bone pain, irritability, muscular twitching, weakness, or signs of respiratory infection or flu. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, gelatin: 1 mcg, 2 mcg, 4 mcg [contains alcohol and coconut or palm kernel oil]

Injection, solution: 2 mcg/mL (1 mL); 5 mcg/mL (1 mL, 2 mL) [contains alcohol 20% v/v and propylene glycol 30% v/v]

Generic AvailableNo

ManufacturerAbbott Laboratories (Pharmaceutical Product Division)

Pricing: U.S. (www.drugstore.com)

Capsules (Zemplar)

- 1 mcg (30): $226.67
- 4 mcg (30): $915.98

Mechanism of ActionDecreased renal conversion of vitamin D to its primary active metabolite (1,25-hydroxyvitamin D) in chronic renal failure leads to reduced activation of vitamin D receptor (VDR), which subsequently removes inhibitory suppression of parathyroid hormone (PTH) release; increased serum PTH (secondary hyperparathyroidism) reduces calcium excretion and enhances bone resorption. Paricalcitol is a synthetic vitamin D analog which binds to and activates the VDR in kidney, parathyroid gland, intestine and bone, thus reducing PTH levels and improving calcium and phosphate homeostasis.

Pharmacodynamics/Kinetics

Distribution: V_d:

- Healthy subjects: Oral: 34 L; I.V.: 24 L
- Stage 3 and 4 CKD: Oral: 44-46 L
- Stage 5 CKD: I.V.: 31-35 L

Protein binding: >99%

Metabolism: Hydroxylation and glucuronidation via hepatic and nonhepatic enzymes, including CYP24, CYP3A4, UGT1A4; forms metabolites (at least one active)

Bioavailability: Oral: ~72% in healthy subjects

Half-life elimination:

- Healthy subjects: Oral: 4-6 hours
- Stage 3 and 4 CKD: Oral: 17-20 hours
- Stage 5 CKD: I.V.: 14-15 hours

Excretion: Healthy subjects: Feces (oral: 70% to 74%; I.V.: 63%); urine (oral: 16% to 18%, I.V.: 19%); 51% to 59% as metabolites

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

References

"K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Guideline 1. Evaluation of Calcium and Phosphorus Metabolism," *Am J Kidney Dis*, 2003, 42(4 Suppl 3):52-7.

"K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Guideline 3. Evaluation of Serum Phosphorus Levels," *Am J Kidney Dis*, 2003, 42(4 Suppl 3):62-3.[PubMed 12830457]

"K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification, Part 4. Definition and Classification of Stages of Chronic Kidney Disease," *Am J Kidney Dis*, 2002, 39(2 Suppl 1):46-75.

International Brand NamesZemplar (AR, CH, CN, CO, CZ, DE, DK, EE, FI, GB, HK, HN, IE, IL, KP, MX, MY, SE, SG, TW, UY, VE)

Paromomycin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(par oh moe MYE sin)

U.S. Brand NamesHumatin® [DSC]

Canadian Brand NamesHumatin®

Pharmacologic Category[Amebicide]

Use: Labeled IndicationsTreatment of acute and chronic intestinal amebiasis; hepatic coma

Use: Unlabeled/InvestigationalTreatment of cryptosporidiosis

Dosing: Adults

Intestinal amebiasis: Oral: 25-35 mg/kg/day in 3 divided doses for 5-10 days

Infection by*Dientamoeba fragilis*: Oral: 25-30 mg/kg/day in 3 divided doses for 7 days

Infection by*Cryptosporidium*(unlabeled use): Oral: Adults with AIDS: 1.5-2.25 g/day in 3-6 divided doses for 10-14 days (occasionally courses of up to 4-8 weeks may be needed)

Tapeworm (fish, dog, bovine, porcine): Oral: 1 g every 15 minutes for 4 doses

Hepatic coma: Oral: 4 g/day in 2-4 divided doses for 5-6 days

Dwarf tapeworm: Oral: 45 mg/kg/dose every day for 5-7 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Intestinal amebiasis: Children: Refer to adult dosing.

Infection by*Dientamoeba fragilis*: Children: Refer to adult dosing.

Tapeworm (fish, dog, bovine, porcine): Oral: Children: 11 mg/kg every 15 minutes for 4 doses

Dwarf tapeworm: Children: Refer to adult dosing.

ContraindicationsHypersensitivity to paromomycin or any component of the formulation; intestinal obstruction

Warnings/Precautions

Concerns related to adverse effects:

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment.
- Ulcerative bowel lesions: Use with caution in patients with possible or proven ulcerative bowel lesions.

Pregnancy Risk FactorC

LactationDoes not enter breast milk/compatible

Breast-Feeding ConsiderationsParomomycin is not expected to be excreted in breast milk since the drug is not systemically available after oral ingestion.

Adverse Reactions

1% to 10%: Gastrointestinal: Diarrhea, abdominal cramps, nausea, vomiting, heartburn

<1%: Headache, vertigo, exanthema, rash, pruritus, steatorrhea, secondary enterocolitis, eosinophilia, ototoxicity

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsFood: Paromomycin may cause malabsorption of xylose, sucrose, and fats.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule: 250 mg

Humatin®: 250 mg [DSC]

Generic AvailableYes

Mechanism of ActionActs directly on ameba; has antibacterial activity against normal and pathogenic organisms in the GI tract; interferes with bacterial protein synthesis by binding to 30S ribosomal subunits

Pharmacodynamics/Kinetics

Absorption: None

Excretion: Feces (100% as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsParomomycin Sulfate

References

Danziger LH, Kanyok TP, and Novak RM, “Treatment of Cryptosporidial Diarrhea in an AIDS Patient With Paromomycin,” *Ann Pharmacother*, 1993, 27(12):1460-2. [PubMed 8305777]

“Drugs for Parasitic Infections,” *Med Lett Drugs Ther*, 1998, 40(1017):1-12. [PubMed 9442765]

Liu LX and Weller PF, “Antiparasitic Drugs,” *N Engl J Med*, 1996, 334(18):1178-84.[PubMed 8602186]

International Brand NamesAminosidine (JP); Gabbroral (BE, IT, LU); Humagel (FR); Humatin (AT, CH, DE, ES, IT)

PARoxetine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

PARoxetine may be confused with FLUoxetine, paclitaxel, pyridoxine

Paxil® may be confused with Doxil®, paclitaxel, Plavix®, Taxol®

Pronunciation(pa ROKS e teen)

U.S. Brand NamesPaxil CR®; Paxil®; Pexeva®

Canadian Brand NamesApo-Paroxetine®; CO Paroxetine; Gen-Paroxetine; Novo-Paroxetine; Paxil CR®; Paxil®; PMS-Paroxetine; ratio-Paroxetine; Rhoxal-paroxetine; Sandoz-Paroxetine

Pharmacologic CategoryAntidepressant, Selective Serotonin Reuptake Inhibitor

Use: Labeled IndicationsTreatment of major depressive disorder (MDD); treatment of panic disorder with or without agoraphobia; obsessive-compulsive disorder (OCD); social anxiety disorder (social phobia); generalized anxiety disorder (GAD); post-traumatic stress disorder (PTSD); premenstrual dysphoric disorder (PMDD)

Use: Unlabeled/InvestigationalMay be useful in eating disorders, impulse control disorders, self-injurious behavior; vasomotor symptoms of menopause; treatment of depression and obsessive-compulsive disorder (OCD) in children; treatment of mild dementia-associated agitation in nonpsychotic patients

Dosing: Adults

Major depressive disorder: Oral:

Paxil®, Pexeva®: Initial: 20 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least 1 week; maximum dose: 50 mg/day

Paxil CR®: Initial: 25 mg once daily; increase if needed by 12.5 mg/day increments at intervals of at least 1 week; maximum dose: 62.5 mg/day

Generalized anxiety disorder (Paxil®, Pexeva®): Oral: Initial: 20 mg once daily, preferably in the morning (if dose is increased, adjust in increments of 10 mg/day at 1-week intervals); doses of 20-50 mg/day were used in clinical trials, however, no greater benefit was seen with doses >20 mg.

Obsessive-compulsive disorder (Paxil®, Pexeva®): Oral: Initial: 20 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least 1 week; recommended dose: 40 mg/day; range: 20-60 mg/day; maximum dose: 60 mg/day

Panic disorder: Oral:

Paxil®, Pexeva®: Initial: 10 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least 1 week; recommended dose: 40 mg/day; range: 10-60 mg/day; maximum dose: 60 mg/day

Paxil CR®: Initial: 12.5 mg once daily; increase if needed by 12.5 mg/day at intervals of at least 1 week; maximum dose: 75 mg/day

Premenstrual dysphoric disorder (Paxil CR®): Oral: Initial: 12.5 mg once daily in the morning; may be increased to 25 mg/day; dosing changes should occur at intervals of at least 1 week. May be given daily throughout the menstrual cycle or limited to the luteal phase.

Post-traumatic stress disorder (Paxil®): Oral: Initial: 20 mg once daily, preferably in the morning; increase if needed by 10 mg/day increments at intervals of at least 1 week; range: 20-50 mg. Limited data suggest doses of 40 mg/day were not more efficacious than 20 mg/day.

Social anxiety disorder: Oral:

Paxil®: Initial: 20 mg once daily, preferably in the morning; recommended dose: 20 mg/day; range: 20-60 mg/day; doses >20 mg may not have additional benefit

Paxil CR®: Initial: 12.5 mg once daily, preferably in the morning; may be increased by 12.5 mg/day at intervals of at least 1 week; maximum dose: 37.5 mg/day

Menopause-associated vasomotor symptoms (unlabeled use, Paxil CR®): Oral: 12.5-25 mg/day

Note: Upon discontinuation of paroxetine therapy, gradually taper dose:

Paxil®, Pexeva®: 10 mg/day at weekly intervals; when 20 mg/day dose is reached, continue for 1 week before treatment is discontinued. Some patients may need to be titrated to 10 mg/day for 1 week before discontinuation.

Paxil CR®: Patients receiving 37.5 mg/day in clinical trials had their dose decreased by 12.5 mg/day to a dose of 25 mg/day and remained at a dose of 25 mg/day for 1 week before treatment was discontinued.

Dosing: Elderly

Major depressive disorder, obsessive compulsive disorder, panic attack, social anxiety disorder:

Paxil®, Pexeva®: Oral: Initial: 10 mg/day; increase if needed by 10 mg/day increments at intervals of at least 1 week; maximum dose: 40 mg/day

Paxil CR®: Initial: 12.5 mg/day; increase if needed by 12.5 mg/day increments at intervals of at least 1 week; maximum dose: 50 mg/day

Note: Upon discontinuation of paroxetine therapy, gradually taper dose:

Paxil®, Pexeva®: 10 mg/day at weekly intervals; when 20 mg/day dose is reached, continue for 1 week before treatment is discontinued. Some patients may need to be titrated to 10 mg/day for 1 week before discontinuation.

Paxil CR®: Patients receiving 37.5 mg/day in clinical trials had their dose decreased by 12.5 mg/day to a dose of 25 mg/day and remained at a dose of 25 mg/day for 1 week before treatment was discontinued.

Dosing: Pediatric

Depression (unlabeled use; not recommended by FDA): Oral: Initial: 10 mg/day and adjusted upward on an individual basis to 20 mg/day

Obsessive-compulsive disorder (unlabeled use): Oral: Initial: 10 mg/day and titrate up as necessary to 60 mg/day

Self-injurious behavior (unlabeled use): Oral: 20 mg/day

Social anxiety disorder (unlabeled use): Oral: 2.5-15 mg/day

Dosing: Renal Impairment

Cl_{cr} <30 mL/minute: Mean plasma concentrations ~4 times that seen in normal function.

Cl_{cr} 30-60 mL/minute: Plasma concentrations 2 times that seen in normal function.

Paxil®, Pexeva®: Adults: Initial: 10 mg/day; increase if needed by 10 mg/day increments at intervals of at least 1 week; maximum dose: 40 mg/day

Paxil CR®: Initial: 12.5 mg/day; increase if needed by 12.5 mg/day increments at intervals of at least 1 week; maximum dose: 50 mg/day

Dosing: Hepatic Impairment

In hepatic dysfunction, plasma concentration is 2 times that seen in normal function.

Paxil®, Pexeva®: Initial: 10 mg/day; increase if needed by 10 mg/day increments at intervals of at least 1 week; maximum dose: 40 mg/day

Paxil CR®: Initial: 12.5 mg/day; increase if needed by 12.5 mg/day increments at intervals of at least 1 week; maximum dose: 50 mg/day

Calculations

- Creatinine Clearance: Adults

Administration: Oral

May be administered with or without food. Do not crush, break, or chew controlled release tablets.

Dietary Considerations

May be taken with or without food.

Storage

Suspension: Store at ≤25°C (≤77°F).

Tablet: Store at 15°C to 30°C (59°F to 86°F).

Restrictions

An FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

Contraindications

Hypersensitivity to paroxetine or any component of the formulation; use with or within 14 days of MAO inhibitors; concurrent use with thioridazine or pimozide

Allergy Considerations

- Selective Serotonin Reuptake Inhibitor (SSRI) Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Paroxetine is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants (for any indication) should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Paroxetine is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Akathisia: Inability to remain still due to feelings of agitation or restlessness has been observed with paroxetine and other SSRIs. Usually occurs within the first few weeks of therapy.

- Anticholinergic effects: Has low potential for sedation and anticholinergic effects relative to cyclic antidepressants; however among the SSRI class these effects are relatively higher.

- Bleeding risk: May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin, NSAIDs, warfarin or other anticoagulants. Bleeding related to SSRI use has been reported to range from relatively minor bruising and epistaxis to life-threatening hemorrhage.

- CNS depression: Has a low potential to impair cognitive or motor performance; caution operating hazardous machinery or driving.

- Sexual dysfunction: May cause or exacerbate sexual dysfunction.

- SIADH and hyponatremia: SSRIs and SNRIs have been associated with the development of SIADH; hyponatremia has been reported rarely (including severe cases with serum sodium <110 mmol/L), predominately in the elderly. Volume depletion and/or concurrent use of diuretics likely increases risk.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; paroxetine has not been systemically evaluated in patients with a recent history of MI or unstable heart disease.

- Hepatic impairment: Use with caution in patients with hepatic impairment; clearance is decreased and plasma concentrations are increased; a lower dosage may be needed.

- Narrow-angle glaucoma: May cause mydriasis which can exacerbate narrow angle glaucoma.

- Renal impairment: Use with caution in patients with renal impairment; clearance is decreased and plasma concentrations are increased; a lower dosage may be needed.

- Seizure disorder: Use with caution in patients with a previous seizure disorder or condition predisposing to seizures such as brain damage or alcoholism.

Concurrent drug therapy issues:

- Agents which lower seizure threshold: Concurrent therapy of paroxetine with these drugs may increase the risk of seizure.

- Anticoagulants/Antiplatelets: Use caution with concomitant use of NSAIDs, ASA, or other drugs that affect coagulation; the risk of bleeding may be potentiated.

- CNS depressants: Use caution with concomitant therapy.

- MAO inhibitors: Potential for severe reaction when used with MAO inhibitors; autonomic instability, coma, death, delirium, diaphoresis, hyperthermia, mental status changes/agitation, muscular rigidity, myoclonus, neuroleptic malignant syndrome features, and seizures may occur. Concurrent use with paroxetine is contraindicated.

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (eg, SSRIs, SNRIs, triptans) or agents which reduce paroxetine's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

- Thioridazine and pimozide: Potential for QT_c prolongation and arrhythmia; concurrent use of paroxetine with either of these agents is contraindicated.

Special populations:

- Elderly: Use caution in elderly patients; risk of hyponatremia and other adverse events may be increased.

- Pediatrics: Safety and efficacy in children have not been established.

- Pregnancy: Avoid use in the first trimester.

Other warnings/precautions:

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

- Withdrawal syndrome: May cause dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Upon discontinuation of paroxetine therapy, gradually taper dose. If intolerable symptoms occur following a decrease in dosage or upon discontinuation of therapy, then resuming the previous dose with a more gradual taper should be considered.

Geriatric ConsiderationsParoxetine is the most sedating and anticholinergic of the selective serotonin reuptake inhibitors. Paroxetine has been shown to be an equally effective antidepressant compared to nortriptyline in patients with ischemic heart disease. However, nortriptyline was associated with a significantly higher rate of adverse cardiac events (sustained increase in heart rate, sinus tachycardia, and asymptomatic increase in ventricular ectopy) compared to placebo. The elderly are more prone to SSRI/SNRI-induced hyponatremia.

Pregnancy Risk FactorD

Pregnancy ConsiderationsDue to adverse events observed in human studies, paroxetine is classified as pregnancy category D. Paroxetine crosses the placenta. The risk of cardiovascular and other congenital malformations may be higher with paroxetine than with other antidepressants. Nonteratogenic effects in the newborn following SSRI exposure late in the third trimester include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypo- or hypertonia, hyper-reflexia, jitteriness, irritability, constant crying, and tremor. An increased risk of low birth weight, lower APGAR scores, and blunted behavioral response to pain for a prolonged period after delivery has also been reported. Exposure to SSRIs after the twentieth week of gestation has been associated with persistent pulmonary hypertension of the newborn (PPHN). Adverse effects may be due to toxic effects of the SSRI or drug withdrawal due to discontinuation. The long-term effects of *in utero* SSRI exposure on infant development and behavior are not known.

Due to pregnancy-induced physiologic changes, women who are pregnant may require increased doses of paroxetine to achieve euthymia. Women treated for major depression and who are euthymic prior to pregnancy are more likely to experience a relapse when medication is discontinued as compared to pregnant women who continue taking antidepressant medications. The ACOG recommends that therapy with SSRIs or SNRIs during pregnancy be individualized; treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary healthcare provider, and pediatrician (ACOG, 2007). The ACOG also recommend that therapy with paroxetine be avoided during pregnancy if possible and that fetuses exposed in early pregnancy be assessed with a fetal echocardiography. If treatment during pregnancy is required, consider tapering therapy during the third trimester in order to prevent withdrawal symptoms in the infant. If this is done and the woman is considered to be at risk from her major depressive disorder, the medication can be restarted following delivery, although the dose should be readjusted to that required before pregnancy.

LactationEnters breast milk/use caution (AAP rates “of concern”)

Breast-Feeding ConsiderationsParoxetine is excreted in breast milk and concentrations in the hindmilk are higher than in foremilk. Paroxetine has not been detected in the serum of nursing infants and adverse events have not been reported. The AAP considers paroxetine to be a "drug for which the effect on the nursing infant is unknown but may be of concern." The manufacturer recommends that caution be exercised when administering paroxetine to nursing women.

The long-term effects on development and behavior have not been studied; therefore, one should prescribe paroxetine to a mother who is breast-feeding only when the benefits outweigh the potential risks.

Adverse ReactionsFrequency varies by dose and indication. Adverse reactions reported as a composite of all indications.

>10%:

Central nervous system: Somnolence (15% to 24%), insomnia (11% to 24%), headache (17% to 18%), dizziness (6% to 14%)

Endocrine & metabolic: Libido decreased (3% to 15%)

Gastrointestinal: Nausea (19% to 26%), xerostomia (9% to 18%), constipation (5% to 16%), diarrhea (9% to 12%)

Genitourinary: Ejaculatory disturbances (10% to 28%)

Neuromuscular & skeletal: Weakness (12% to 22%), tremor (4% to 11%)

Miscellaneous: Diaphoresis (5% to 14%)

1% to 10%:

Cardiovascular: Vasodilation (2% to 4%), chest pain (3%), palpitation (2% to 3%), hypertension (≥1%), tachycardia (≥1%)

Central nervous system: Nervousness (4% to 9%), anxiety (5%), agitation (3% to 5%), abnormal dreams (3% to 4%), concentration impaired (3% to 4%), yawning (2% to 4%), depersonalization (up to 3%), amnesia (2%), emotional lability (≥1%), vertigo (≥1%), confusion (1%), chills (2%)

Dermatologic: Rash (2% to 3%), pruritus (≥1%)

Endocrine & metabolic: Orgasmic disturbance (2% to 9%), dysmenorrhea (5%)

Gastrointestinal: Anorexia, appetite decreased (5% to 9%), dyspepsia (2% to 5%), flatulence (4%), abdominal pain (4%), appetite increased (2% to 4%), vomiting (2% to 3%), taste perversion (2%), weight gain (≥1%)

Genitourinary: Impotence (2% to 9%), genital disorder (female 2% to 9%), urinary frequency (2% to 3%), urinary tract infection (2%)

Neuromuscular & skeletal: Paresthesia (4%), myalgia (2% to 4%), back pain (3%), myoclonus (2% to 3%), myopathy (2%), myasthenia (1%), arthralgia (≥1%)

Ocular: Blurred vision (4%), abnormal vision (2% to 4%)

Otic: Tinnitus (≥1%)

Respiratory: Respiratory disorder (up to 7%), pharyngitis (4%), sinusitis (up to 4%), rhinitis (3%)

Miscellaneous: Infection (5% to 6%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Acute renal failure, adrenergic syndrome, akinesia, alkaline phosphatase increased, allergic reaction, anaphylaxis, anemias (various), angina pectoris, angioedema, aphasia, aphthous stomatitis, arrhythmias (atrial and ventricular), arthrosis, asthma, behavioral disturbances (various), bilirubinemia, bleeding time increased, blood dyscrasias, bloody diarrhea, bradycardia, bronchitis, bulimia, BUN increased, bundle branch block, cardiospasm, cataract, cellulitis, cerebral ischemia, cerebrovascular accident, cholelithiasis, colitis, congestive heart failure, creatinine phosphokinase increased, deafness, dehydration, delirium, diabetes mellitus, drug dependence, dyskinesia, dysphagia, dyspnea, dystonia, ecchymosis, eclampsia, electrolyte abnormalities, emphysema, erythema, exfoliative dermatitis, extrapyramidal syndrome, fecal impactions, fungal dermatitis, gamma globulins increased, gastroenteritis, glaucoma, goiter, Guillain-Barré syndrome, hallucinations, hematemesis, hematoma, hemorrhage, hemoptysis, hepatic necrosis, hepatitis, hypercholesteremia, hyper-/hypoglycemia, hyper-/hypothyroidism, hypotension, ileus, intestinal obstruction, jaundice, ketosis, lactic dehydrogenase increased, liver function tests abnormal, low cardiac output, lung fibrosis, lymphadenopathy, meningitis, MI, migraine, myelitis, myocardial ischemia, neuroleptic malignant syndrome, neuropathy, osteoporosis, pancreatitis, pancytopenia, peptic ulcer, peritonitis, phlebitis, pneumonia, platelet count abnormalities, pulmonary edema, pulmonary embolus, pulmonary hypertension, seizure, sepsis, serotonin syndrome, status epilepticus, suicidal tendencies, syncope, tetany, thrombophlebitis, thrombosis, tongue edema, torsade de pointes, toxic epidermal necrolysis, vasculitic syndrome

Metabolism/Transport Effects **Substrate** of CYP2D6 (major); **Inhibits** CYP1A2 (weak), 2B6 (moderate), 2C9 (weak), 2C19 (weak), 2D6 (strong), 3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha-/Beta-Blockers: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Alpha-/Beta-Blockers. *Risk C: Monitor therapy*

Amprenavir: May decrease the serum concentration of PARoxetine. *Risk C: Monitor therapy*

Analgesics (Opioid): May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin Reuptake Inhibitor/Antagonist): Selective Serotonin Reuptake Inhibitors may enhance the serotonergic effect of Antidepressants (Serotonin Reuptake Inhibitor/Antagonist). This may cause serotonin syndrome. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Aspirin: Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Atomoxetine: PARoxetine may decrease the metabolism of Atomoxetine. *Risk D: Consider therapy modification*

Beta-Blockers: Selective Serotonin Reuptake Inhibitors may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Acebutolol; Atenolol; Carteolol; Esmolol; Levobunolol; Metipranolol; Nadolol; Penbutolol. *Risk C: Monitor therapy*

BusPIRone: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. Selective Serotonin Reuptake Inhibitors may decrease the metabolism of BusPIRone. *Risk C: Monitor therapy*

CarBAMazepine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of CarBAMazepine. Specifically those SSRIs that inhibit CYP3A4 isoenzymes. CarBAMazepine may increase the metabolism of Selective Serotonin Reuptake Inhibitors. Specifically those agents metabolized via CYP1A2, 2C, and/or 3A4 isoenzymes. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Selective Serotonin Reuptake Inhibitors. *Risk D: Consider therapy modification*

Clozapine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inhibitors (Moderate) may decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Strong) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk D: Consider therapy modification*

Cyproheptadine: May diminish the therapeutic effect of Selective Serotonin Reuptake Inhibitors. *Risk C: Monitor therapy*

Darunavir: May decrease the serum concentration of PARoxetine. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Desmopressin: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dextromethorphan: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Dextromethorphan. *Risk D: Consider therapy modification*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

DULoxetine: PARoxetine may decrease the metabolism of DULoxetine. *Risk C: Monitor therapy*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Fosamprenavir: May decrease the serum concentration of PARoxetine. The active metabolite amprenavir is likely responsible for this effect. *Risk C: Monitor therapy*

Galantamine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Galantamine. *Risk C: Monitor therapy*

Haloperidol: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Haloperidol. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Iobenguane I 123: Selective Serotonin Reuptake Inhibitors may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methadone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Methadone. Fluvoxamine appears to be the only interacting SSRI. *Risk D: Consider therapy modification*

Mexiletine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Mexiletine. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk D: Consider therapy modification*

NSAID (Nonselective): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Pimozide: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Pimozide. *Risk X: Avoid combination*

Propafenone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Propafenone. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Risperidone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Risperidone. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tamoxifen: CYP2D6 Inhibitors (Strong) may decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

Tetrabenazine: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Tetrabenazine. Specifically, concentrations of the active alpha- and beta-dihydrotetrabenazine metabolites may be increased. Management: Tetrabenazine dose should be reduced by 50% when starting a strong CYP2D6 inhibitor. Maximum tetrabenazine dose is 50mg/day when used with a strong CYP2D6 inhibitor. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

TraMADol: Selective Serotonin Reuptake Inhibitors may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. TraMADol may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tryptophan: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Selective Serotonin Reuptake Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Peak concentration is increased, but bioavailability is not significantly altered by food.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava.

Monitoring ParametersMental status for depression, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased), anxiety, social functioning, mania, panic attacks; akathisia

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescription or OTC medications or herbal products patient may be taking. Assess results of laboratory tests. Assess therapeutic effectiveness (according to rationale for prescribing), and adverse reactions at beginning of therapy and frequently with long-term use. Monitor for clinical worsening and suicidal ideation. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report

Monitoring: Lab TestsHepatic and renal function

Patient EducationTake exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. It may take 2-3 weeks to achieve desired results. Take in the morning to reduce the incidence of insomnia (may be taken with or without food). Do not crush, break, or chew controlled release (Paxil CR®) tablets. Avoid alcohol, caffeine, and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or lightheadedness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, anorexia, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or orthostatic hypotension (use caution when climbing stairs or changing position from lying or sitting to standing). Report persistent insomnia or excessive daytime sedation; muscle cramping, tremors, weakness, or change in gait; chest pain, palpitations, or rapid heartbeat; vision changes or eye pain; respiratory difficulty or breathlessness; abdominal pain or blood in stool; change in affect or thought processes, unusual agitation, or abnormal dreams; worsening of condition; or suicidal ideation. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: Strength expressed as base:

Suspension, oral, as hydrochloride: 10 mg/5 mL (250 mL)

  Paxil®: 10 mg/5 mL (250 mL) [orange flavor]

Tablet, as hydrochloride: 10 mg, 20 mg, 30 mg, 40 mg

  Paxil®: 10 mg, 20 mg, 30 mg, 40 mg

Tablet, as mesylate:

  Pexeva®: 10 mg, 20 mg, 30 mg, 40 mg

Tablet, controlled release, as hydrochloride: 37.5 mg

  Paxil CR®: 12.5 mg, 25 mg, 37.5 mg

Tablet, extended release, as hydrochloride: 12.5 mg, 25 mg

Generic AvailableYes

ManufacturerSmithKline Beecham Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Suspension (Paxil)

  10 mg/5 mL (250): $166.90

Tablet, 24-hour (Paroxetine HCl)

  12.5 mg (30): $96.99

  25 mg (30): $99.99

  37.5 mg (30): $101.99

Tablet, 24-hour (Paxil CR)

  12.5 mg (30): $105.99

  25 mg (30): $106.99

  37.5 mg (30): $115.99

Tablets (Paroxetine HCl)

  10 mg (30): $30.99

  20 mg (30): $13.99

  30 mg (30): $35.99

  40 mg (30): $31.99

Tablets (Paxil)

10 mg (30): $99.99

20 mg (30): $103.98

30 mg (30): $113.99

40 mg (30): $115.99

Tablets (Pexeva)

20 mg (30): $155.01

30 mg (30): $163.49

40 mg (30): $166.94

Mechanism of ActionParoxetine is a selective serotonin reuptake inhibitor, chemically unrelated to tricyclic, tetracyclic, or other antidepressants; presumably, the inhibition of serotonin reuptake from brain synapse stimulated serotonin activity in the brain

Pharmacodynamics/Kinetics

Onset of action: Depression: The onset of action is within a week; however, individual response varies greatly and full response may not be seen until 8-12 weeks after initiation of treatment.

Absorption: Completely absorbed following oral administration

Distribution: V_d: 8.7 L/kg (3-28 L/kg)

Protein binding: 93% to 95%

Metabolism: Extensively hepatic via CYP2D6 enzymes; primary metabolites are formed via oxidation and methylation of parent drug, with subsequent glucuronide/sulfate conjugation; nonlinear pharmacokinetics (via 2D6 saturation) may be seen with higher doses and longer duration of therapy. Metabolites exhibit ~2% potency of parent compound. C_{min} concentrations are 70% to 80% greater in the elderly compared to nonelderly patients; clearance is also decreased.

Half-life elimination: 21 hours (3-65 hours)

Time to peak: Immediate release: 5.2 hours; controlled release: 6-10 hours

Excretion: Urine (64%, 2% as unchanged drug); feces (36% primarily via bile, <1% as unchanged drug)

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Selective Serotonin Reuptake Inhibitors (SSRIs) CYP Profile
- Selective Serotonin Reuptake Inhibitors (SSRIs) FDA-Approved Indications
- Selective Serotonin Reuptake Inhibitors (SSRIs) Pharmacokinetics
- Selective Serotonin Reuptake Inhibitors (SSRIs) Receptor Profile
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsPaxil CR® incorporates a degradable polymeric matrix (Geomatrix™) to control dissolution rate over a period of 4-5 hours. An enteric coating delays the start of drug release until tablets have left the stomach.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), postural hypotension, and abnormal taste. Problems with SSRI-induced bruxism have been reported and may preclude their use; clinicians attempting to evaluate any patient with bruxism or involuntary muscle movement, who is simultaneously being treated with an SSRI drug, should be aware of the potential association. Prolonged use may decrease or inhibit salivary flow; normal salivation resumes upon discontinuation.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAlthough caution should be used in patients taking tricyclic antidepressants, no interactions have been reported with vasoconstrictor and paroxetine, a nontricyclic antidepressant which acts to increase serotonin; no precautions appear to be needed

Mental Health: Child/Adolescent Considerations

Depression: Paroxetine was shown to be effective and generally well tolerated in a recent randomized, double-blind, placebo-controlled parallel-design study; 275 adolescents (12-18 years of age) with major depression were randomized to receive paroxetine, imipramine, or placebo; 93 patients (mean age: 14.8 ± 1.6 years) received paroxetine at initial doses of 20 mg/day given in the morning; doses were increased if needed at week 5 to 30 mg/day (given in divided doses) and at weeks 6-8 to 40 mg/day (given in divided doses); 48% of patients remained at the initial starting dose of 20 mg/day; mean optimal daily dose: 28 ± 8.54 mg (Keller, 2001). Paroxetine was shown to be effective and well tolerated in an open label clinical trial in 45 children <14 years of age (mean: 10.7 ± 2 years) with major depression (Rey-Sanchoz, 1997). Doses were initiated at 10 mg/day and adjusted upward on an individual basis with a mean dose of 16.2 mg/day used for an average of 8.4 months. Further studies are needed.

Obsessive-compulsive disorder (OCD): Twenty OCD outpatients 8-17 years of age were treated with daily doses ranging from 10-60 mg/day for 12 weeks (Rosenberg, 1999). A randomized, double-blind, placebo-controlled trial with paroxetine was conducted in 207 pediatric patients (aged 7-17 years) meeting DSM-IV criteria for OCD (Geller et al, 2004). Patients received 10-50 mg/day paroxetine or placebo for 10 weeks and change from baseline of the Children's Yale-Brown Obsessive-Compulsive Scale was assessed as the primary endpoint. In the intent-to-treat population, paroxetine was associated with a significant adjusted mean difference improvement (-3.45; 95% CI: -5.6 to -1.29, p =0.002) compared to placebo. Side effects were generally mild to moderate, with 10% and 3% of paroxetine- and placebo-receiving patients, respectively, discontinuing due to adverse events.

Self-injurious behavior: A 15-year old autistic male with self-injurious behavior was successfully treated with 20 mg/day (Snead, 1994). Further studies are needed.

Social anxiety disorder: A small case series reported the effective use of paroxetine in 5 pediatric patients with social phobia [2 children (7 and 11 years of age) and 3 adolescents (16, 17, and 18 years of age)]; comorbid diagnoses (obsessive compulsive disorder and/or dysthymia) existed in 3 patients; doses were adjusted on an individual basis; the 7-year old was started on 2.5 mg/day and increased to 5 mg/day after 4 weeks; the 11-year old was started on 5 mg/day and the dose was titrated upwards by 5 mg/day increments every 3-4 weeks to 15 mg/day; adolescents were started on 20 mg/day (Mancini, 1999); further studies are needed. In a 16-week trial of pediatric patients (aged 8-17 years) presenting with social anxiety disorder, 163 were randomized to receive paroxetine (10-50 mg/day) and 156 to receive placebo (Wagner et al, 2004). From the intent-to-treat analysis, 77.6% of paroxetine patients responded (achievement of Clinical Global Impression-Improvement score of 1 or 2) compared to 38.3% of placebo patients (odds ratio: 7.02, $p < 0.001$). Adverse events occurred in 5% of paroxetine-receiving patients (twice the placebo rate) and consisted mainly of insomnia, decreased appetite and vomiting.

A recent report described the SSRI discontinuation syndrome in 6 children; the syndrome was similar to that reported in adults (Diler, 2002).

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Wagner KD, Berard R, Stein MB, et al, “A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Paroxetine in Children and Adolescents With Social Anxiety Disorder,” *Arch Gen Psychiatry*, 2004, 61(11):1153-62.

Mental Health CommentThe SSRIs as a class are generally considered to be safe and equally effective. For the management of depression, these drugs display a flat dose-response curve. Allow sufficient dose-response time (6-12 weeks). Differences lie in approved indications, receptor profiles, pharmacokinetics, and cytochrome P450 activity profile. Subtle differences exist in adverse effect profiles. All SSRIs have the potential to cause sexual dysfunction. Among the SSRIs, paroxetine is felt to be the most sedating and anticholinergic. Discontinuation syndromes may be more severe with paroxetine compared to other SSRIs. It also has been associated with more long-term weight gain (Marks, 2008).

Marks DM, Park MH, Ham BJ, et al, "Paroxetine: Safety and Tolerability Issues," *Expert Opin Drug Saf*, 2008, 7(6):783-94.

Index TermsParoxetine Hydrochloride; Paroxetine Mesylate

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International Brand NamesAropax (LU, MX); Aropax 20 (AR, AU, BE, BR, PY, UY, ZA); Aroxat (CN); Deroxat (CH, FR); Divarius (FR); Euplix (DE); Extine (AU); Loxamine (AU, NZ); PARI CR (IN); Parosenin (KP); Parotin (HK); Parox (KP); Paxan (CO); Paxetil (KP); Paxil (BB, BM, BS, BZ, CR, DO, EC, GT, GY, HN, JM, MX, NI, NL, PA, SR, SV, TT, VE); Paxil CR (BB, BM, BS, BZ, CR, DO, GT, GY, HN, JM, KP, NI, NL, PA, SR, SV, TT); Paxtine (AU); Paxxet (IL); Rexetin (PL); Seroxat (AE, AT, BD, BF, BG, BH, BJ, CI, CL, CO, CY, CZ, DE, DK, EE, EG, ES, ET, FI, GB, GH, GM, GN, HK, HN, HU, ID, IE, IL, IN, IQ, IR, IT, JO, JP, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PE, PH, PK, PL, PT, QA, SA, SC, SD, SE, SG, SL, SN, SY, TH, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Seroxat CR (SG); Setine (TW); Tagonis (DE); Xetine-P (TW)

PC (NSCLC)

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Lung Cancer (Nonsmall Cell)]

Regimen UseLung cancer, nonsmall cell

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Paclitaxel: I.V.: 175-225 mg/m^2 day 1

[total dose/cycle = 175-225 mg/m^2]

Carboplatin: I.V.: Target AUC 5-7 day 1

[total dose/cycle = AUC = 5-7]

Repeat cycle every 21 days for 2-8 cycles

Variation 2:

Paclitaxel: I.V.: 175 mg/m^2 day 1

[total dose/cycle = 175 mg/m^2]

Cisplatin: I.V.: 80 mg/m^2 day 1

[total dose/cycle = 80 mg/m^2]

Repeat cycle every 21 days

Variation 3:

Paclitaxel: I.V.: 135 mg/m^2 continuous infusion day 1

[total dose/cycle = 135 mg/m^2]

Carboplatin: I.V.: AUC 7.5 day 2

[total dose/cycle = AUC = 7.5]

Repeat cycle every 21 days

Variation 4:

Paclitaxel: I.V.: 135 mg/m^2 continuous infusion day 1

[total dose/cycle = 135 mg/m^2]

Cisplatin: I.V.: 75 mg/m^2 day 2

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 21 days

References

Variation 1:

Hainsworth JD, Urba WJ, Hon JK, et al, “One-Hour Paclitaxel Plus Carboplatin in the Treatment of Advanced Nonsmall-Cell Lung Cancer: Results of a Multicentre, Phase II Trial,” *Eur J Cancer*, 1998, 34(5):654-8. [PubMed 9713269]

Helsing M, Thaning L, Sederholm C, et al, “Treatment With Paclitaxel 1-h Infusion and Carboplatin of Patients With Advanced Nonsmall-Cell Lung Cancer: A Phase II Multicentre Trial. Joint Lung Cancer Study Group,” *Lung Cancer*, 1999, 24(2):107-13. [PubMed 10444061]

Kosmidis PA, Mylonakis N, Fountzilas G, et al, “Paclitaxel and Carboplatin in Inoperable Nonsmall-Cell Lung Cancer: A Phase II Study,” *Ann Oncol*, 1997, 8(7):697-9. [PubMed 9296226]

Laohavinij S, Maoleekoonpairoj S, Cheirsilpa A, et al, “Phase II Study of Paclitaxel and Carboplatin for Advanced Nonsmall-Cell Lung Cancer,” *Lung Cancer*, 1999, 26(3):175-85. [PubMed 10598928]

Variation 2:

Giaccone G, Splinter TA, Debruyne C, et al, “Randomized Study of Paclitaxel-Cisplatin Versus Cisplatin-Teniposide in Patients With Advanced Nonsmall-Cell Lung Cancer. The European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group,” *J Clin Oncol*, 1998, 16(6):2133-41. [PubMed 9626213]

Variation 3:

Langer CJ, Leighton JC, Comis RL, et al, “Paclitaxel by 24- or 1-Hour Infusion in Combination With Carboplatin in Advanced Nonsmall Cell Lung Cancer: The Fox Chase Cancer Center Experience,” *Semin Oncol*, 1995, 22(4 Suppl 9):18-29. [PubMed 7544025]

Variation 4:

Schiller JH, Harrington D, Belani CP, et al, “Comparison of Four Chemotherapy Regimens for Advanced Nonsmall-Cell Lung Cancer,” *N Engl J Med*, 2002, 346(2):92-8.[PubMed 11784875]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Adenocarcinoma (Unknown Primary)

Regimen UseAdenocarcinoma, unknown primary

Regimen

Paclitaxel: I.V.: 200 mg/m^2 day 1

[total dose/cycle = 200 mg/m^2]

Carboplatin: I.V.: AUC = 6 day 1

[total dose/cycle = AUC = 6]

Etoposide: Oral: 50 mg/day days 1, 3, 5, 7, and 9

and Oral: 100 mg/day days 2, 4, 6, 8, and 10

[total dose/cycle = 750 mg]

Repeat cycle every 3 weeks

References

Greco FA, Burris HA 3rd, Erland JB, et al, âCarcinoma of Unknown Primary Site,â *Cancer*, 2000, 89(12):2655-60.[PubMed 11135228]

PCR

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Leukemia, Chronic Lymphocytic]

Regimen UseLeukemia, chronic lymphocytic

Index TermsPentostatin-Cyclophosphamide-Rituximab

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cycle 1:

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Pentostatin: I.V.: 4 mg/m^2 day 1

[total dose/cycle = 4 mg/m^2]

Treatment cycle is 3 weeks

Cycles 2-6:

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Pentostatin: I.V.: 4 mg/m^2 day 1

[total dose/cycle = 4 mg/m^2]

Rituximab: I.V.: 375 mg/m^2 day 1

[total dose/cycle = 375 mg/m^2]

Repeat cycle every 3 weeks

Variation 2:

Cycle 1:

Pentostatin: I.V.: 2 mg/m^2 day 1

[total dose/cycle = 2 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Rituximab: I.V.: 100 mg/m^2 day 1 only

followed by I.V.: 375 mg/m^2/day days 3 and 5 only

[total dose/cycle 1 = 850 mg/m^2]

Treatment cycle is 3 weeks

Cycles 2-6:

Pentostatin: I.V.: 2 mg/m^2 day 1

[total dose/cycle = 2 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Rituximab: I.V.: 375 mg/m^2 day 1

[total dose/cycle = 375 mg/m^2]

Repeat cycle every 3 weeks

References

Variation 1:

Lamanna N, Kalaycio M, Maslak P, et al, "Pentostatin, Cyclophosphamide, and Rituximab Is an Active, Well-Tolerated Regimen for Patients With Previously Treated Chronic Lymphocytic Leukemia," *J Clin Oncol*, 2006, 24(10):1575-81.[PubMed 16520464]

Variation 2:

Kay NE, Geyer SM, Call TG, et al, "Combination Chemoimmunotherapy With Pentostatin, Cyclophosphamide, and Rituximab Shows Significant Clinical Activity With Low Accompanying Toxicity in Previously Untreated B Chronic Lymphocytic Leukemia," *Blood*, 2007, 109(2):405-11.[PubMed 17008537]

Pharmacologic CategoryChemotherapy Regimen, Brain Tumors

Regimen UseBrain tumors

Regimen

Lomustine: Oral: 110 mg/m^2 day 1

[total dose/cycle = 110 mg/m^2]

Procarbazine: Oral: 60 mg/m^2/day days 8 to 21

[total dose/cycle = 840 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day (maximum 2 mg) days 8 and 29

[total dose/cycle = 2.8 mg/m^2; maximum 4 mg]

Repeat cycle every 6-8 weeks

References

Levin VA, Silver P, Hannigan J, et al, “Superiority of Postradiotherapy Adjuvant Chemotherapy With CCNU, Procarbazine, and Vincristine (PCV) Over BCNU for Anaplastic Gliomas: NCOG 6G61 Final Report,” *Int J Radiat Oncol Biol Phys*, 1990, 18(2):321-4.[PubMed 2154418]

van den Bent MJ, Carpentier AF, Brandes AA, et al, “Adjuvant Procarbazine, Lomustine, and Vincristine Improves Progression-Free Survival but not Overall Survival in Newly Diagnosed Anaplastic Oligodendrogliomas and Oligoastrocytomas: A Randomized European Organisation for Research and Treatment of Cancer Phase III Trial,” *J Clin Oncol*, 2006, 24(18):2715-22.[PubMed 16782911]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Neuroblastoma

Regimen UseNeuroblastoma

Regimen

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Teniposide: I.V.: 160 mg/m^2 day 3

[total dose/cycle = 160 mg/m^2]

alternating with

Cyclophosphamide: I.V.: 300 mg/m^2/day days 1 to 5

[total dose/cycle = 1500 mg/m^2]

Doxorubicin: I.V.: 60 mg/m^2 day 5

[total dose/cycle = 60 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2/day days 1 and 5

[total dose/cycle = 3 mg/m^2]

Repeat cycle every 21 days

References

Bernard JL, Philip T, Zucker JM, et al, âSequential Cisplatin/VM-26 and Vincristine/Cyclophosphamide/Doxorubicin in Metastatic Neuroblastoma: An Effective Alternating Non-Cross-Resistant Regimen?â *J Clin Oncol*, 1987, 5(12):1952-9.[PubMed 3681378]

Pegademase Bovine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(peg A de mase BOE vine)

U.S. Brand NamesAdagen®

Canadian Brand NamesAdagen®

Pharmacologic CategoryEnzyme

Use: Labeled IndicationsEnzyme replacement therapy for adenosine deaminase (ADA) deficiency in patients with severe combined immunodeficiency disease (SCID) who are not candidates for or who have failed bone marrow transplant

Dosing: Pediatric**Note:** Dose should be individualized based on monitoring of plasma ADA activity levels and dATP content.

Adenosine deaminase deficiency (enzyme replacement therapy): I.M.: Infants and Children: Dose given every 7 days, 10 units/kg the first dose, 15 units/kg the second dose, and 20 units/kg the third dose; maintenance dose: 20 units/kg/week is recommended depending on patient's ADA level; maximum single dose: 30 units/kg

Administration: I.M.Administer intramuscularly; do not dilute or mix with other medications prior to administration.

StorageRefrigerate at 2°C to 8°C (36°F to 46°F); do not freeze. Discard unused portions; do not save for further use. Do not use if previously frozen.

ContraindicationsNot to be used as preparatory or support therapy for bone marrow transplantation; severe thrombocytopenia

Warnings/Precautions

Concerns related to adverse effects:

- Antibody formation: Development of antibodies has been reported in patients resulting in more rapid clearance of pegademase bovine. In patients who experience a persistent decrease in preinjection levels of plasma ADA to <10 micromole/hour/mL and have had other causes ruled out (eg, improper storage of vials, improper handling of plasma sample), antibody formation should be considered and a specific assay for antibody ADA should be performed. Dosage adjustments may be required in patients developing antibodies.

Disease-related concerns:

- Immune status: Failure to maintain adequate levels of plasma ADA activity will increase patients risk for infection.

- Thrombocytopenia: Use with caution in patients with thrombocytopenia; should not be used in patients with severe thrombocytopenia.

Other warnings/precautions:

- Appropriate use: Not a substitute for bone marrow transplant; should be used in conjunction with continued close monitoring and appropriate diagnostic tests and therapy. Therapy is not a cure for SCID and must be continued.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have not been conducted. There are no adequate and well-controlled studies in pregnant women. The benefits versus risks should be considered carefully before initiating pegademase bovine therapy in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

<1%: Headache, pain at injection site

Postmarketing and/or case reports: Autoimmune hemolytic anemia, erythema (injection site), hemolytic anemia, thrombocythemia, urticaria

Drug Interactions

Pentostatin: Pegademase Bovine may diminish the therapeutic effect of Pentostatin. Pentostatin may diminish the therapeutic effect of Pegademase Bovine. *Risk X: Avoid combination*

Monitoring Parameters

Plasma ADA activity prior to treatment, then a preinjection level every 1-2 weeks for the first 8-12 weeks, then twice a month for the next 3-9 months, then monthly until after 18-24 months. After 24 months monitor level every 2-4 months. If therapy is interrupted, more frequent monitoring is required.

Monitor red cell dATP prior to treatment and until levels have decreased adequately (usually after 2 months of maintenance therapy), then monitor 2-4 times a year for first year and 2-3 times a year thereafter. If therapy is interrupted, more frequent monitoring is required.

Monitor immune function and clinical status.

Reference Range

Plasma ADA activity: Recommended maintenance trough level: 15-35 micromole/hour/mL

Red cell dATP: After 2 months of maintenance therapy, levels should decrease to ≤0.005-0.015 micromole/mL (normal dATP value: <0.001

micromole/mL) or ≤1% of total erythrocyte adenine nucleotide (ATP + dATP) content with a normal ATP level

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Adagen®: 250 units/mL (1.5 mL)

Generic AvailableNo

Mechanism of ActionAdenosine deaminase is an enzyme that catalyzes the deamination of both adenosine and deoxyadenosine. Hereditary lack of adenosine deaminase activity results in severe combined immunodeficiency disease, a fatal disorder of infancy characterized by profound defects of both cellular and humoral immunity. It is estimated that 25% of patients with the autosomal recessive form of severe combined immunodeficiency lack adenosine deaminase. Pegademase bovine is a (modified) enzyme replacement for adenosine deaminase deficiency.

Pharmacodynamics/Kinetics

Absorption: Rapid

Half-life elimination: Plasma ADA half-life (following administration): Range: 3 to >6 days

Time to peak: Plasma adenosine deaminase activity: 2-3 days

Pharmacotherapy Pearls

Any indication (laboratory or clinical) of a decrease in potency of Adagen® should be reported to Enzon Pharmaceuticals (866-792-5172).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesAdagen (CA)

Pegaptanib

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(peg AP ta nib)

U.S. Brand NamesMacugen®

Canadian Brand NamesMacugen®

Pharmacologic CategoryOphthalmic Agent; Vascular Endothelial Growth Factor (VEGF) Inhibitor

Use: Labeled IndicationsTreatment of neovascular (wet) age-related macular degeneration (AMD)

Dosing: Adults**AMD:** Intravitreous injection: 0.3 mg into affected eye every 6 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentAdjustment not required with renal impairment; information not available for patients requiring hemodialysis.

Administration: OtherFor intravitreous injection only. Adequate anesthesia and a broad spectrum antibiotic should be administered prior to injection. pH: 6-7

StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Do not shake vigorously.

ContraindicationsHypersensitivity to pegaptanib or any component of the formulation; ocular or periocular infection

Warnings/Precautions

Concerns related to adverse effects:

- Endophthalmitis: Intravitreous injections may be associated with endophthalmitis; patients should be instructed to report any signs of infection immediately.
- Hypersensitivity reactions: Rare hypersensitivity reactions (including anaphylaxis) have been associated with use, occurring within several hours of use; monitor closely. Equipment and appropriate personnel should be available for monitoring and treatment of anaphylaxis.
- Increased intraocular pressure: Following injection, intraocular pressure may increased.

Disease-related concerns:

- Hepatic impairment: Safety and efficacy have not been established with hepatic impairment.
- Renal impairment: Safety and efficacy have not been established in patients requiring hemodialysis.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Concurrent administration in both eyes: Safety and efficacy for administration into both eyes concurrently have not been studied.

Geriatric ConsiderationsIn studies, 94% of patients treated with pegaptanib were ≥65 years of age. No difference in efficacy was seen as compared to younger adults.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not reported in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

10% to 40%:

Cardiovascular: Hypertension

Ocular: Anterior chamber inflammation, blurred vision, cataract, conjunctival hemorrhage, corneal edema, eye discharge, eye irritation, eye pain, intraocular pressure increased, ocular discomfort, punctate keratitis, visual acuity decreased, visual disturbance, vitreous floaters, vitreous opacities

1% to 10%:

Cardiovascular: Carotid artery occlusion (1% to 5%), cerebrovascular accident (1% to 5%), chest pain (1% to 5%), transient ischemic attack (1% to 5%)

Central nervous system: Dizziness (6% to 10%), headache (6% to 10%), vertigo (1% to 5%)

Dermatologic: Contact dermatitis (1% to 5%)

Endocrine & metabolic: Diabetes mellitus (1% to 5%)

Gastrointestinal: Diarrhea (6% to 10%), nausea (6% to 10%), dyspepsia (1% to 5%), vomiting (1% to 5%)

Genitourinary: Urinary retention (1% to 5%)

Neuromuscular & skeletal: Arthritis (1% to 5%), bone spur (1% to 5%)

Ocular: Blepharitis (6% to 10%), conjunctivitis (6% to 10%), photopsia (6% to 10%), vitreous disorder (6% to 10%), allergic conjunctivitis (1% to 5%), conjunctival edema (1% to 5%), corneal abrasion (1% to 5%), corneal deposits (1% to 5%), corneal epithelium disorder (1% to 5%), endophthalmitis (1% to 5%), eye inflammation (1% to 5%), eye swelling (1% to 5%), eyelid irritation (1% to 5%), meibomianitis (1% to 5%), mydriasis (1% to 5%), periorbital hematoma (1% to 5%), retinal edema (1% to 5%), vitreous hemorrhage (1% to 5%)

Otic: Hearing loss (1% to 5%)

Renal: Urinary tract infection (6% to 10%)

Respiratory: Bronchitis (6% to 10%), pleural effusion (1% to 5%)

Miscellaneous: Contusion (1% to 5%)

<1%: Iatrogenic traumatic cataract, endophthalmitis, retinal detachment

Postmarketing and/or case reports: Anaphylaxis, anaphylactoid reaction, angioedema, hypersensitivity

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersIntraocular pressure (within 30 minutes and 2-7 days after injection); endophthalmitis

Nursing: Physical Assessment/MonitoringAssess allergy history before beginning therapy. Assess visual acuity and intraocular pressure prior to beginning treatment and periodically during treatment. Adequate anesthesia and broad spectrum antibiotic should be administered prior to intravitreous injection. Rare hypersensitivity reactions, including anaphylaxis, can occur within several hours of use; patient should be monitored closely following injection and appropriate emergency equipment should be immediately available. Teach patient/caregiver possible side effects/appropriate interventions and adverse symptoms to report (eg, any signs of infection, intraocular discomfort, or visual disturbances).

Patient EducationThis treatment will not reverse vision loss, but may decrease further loss. Do not rub eyes or use any ocular products unless recommended by prescriber. You may experience dizziness or headache (use caution when driving or engaged in tasks that require alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, or sucking lozenges may help); diarrhea (buttermilk, boiled milk, or yogurt may help). Notify prescriber immediately at any sign of infection (redness, drainage, eye pain, itching sensitivity to light, swelling, or change in vision); unusual chest pain or loss of consciousness; acute headache or persistent dizziness; or other persistent adverse effects.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 0.3 mg/90 µL (90 µL) [prefilled syringe]

Generic AvailableNo

ManufacturerEyetech Pharmaceuticals; Pfizer Inc

Mechanism of ActionPegaptanib is an apatamer, an oligonucleotide covalently bound to polyethylene glycol, which can adopt a three-dimensional shape and bind to vascular endothelial growth factor (VEGF). Pegaptanib binds to extracellular VEGF, inhibiting VEGF from binding to its receptors and thereby suppressing neovascularization and slowing vision loss.

Pharmacodynamics/Kinetics

Absorption: Slow systemic absorption following intravitreous injection

Metabolism: Metabolized by endo- and exonucleases

Half-life elimination: Plasma: 6-14 days

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentBlurred vision and GI side effects are common. Concomitant use with psychotropics with high anticholinergic load may produce additive effects; monitor. Concomitant use with SSRIs, lithium, or valproic acid may produce additive effects; monitor.

Index TermsEYE001; Pegaptanib Sodium

References

Gragoudas ES, Adamis AP, Cunningham ET, et al, “Pegaptanib for Neovascular Age-Related Macular Degeneration,” *N Engl J Med*, 2004, 351(27):2805-16.[PubMed 15625332]

International Brand NamesMacugen (AT, BE, BG, BR, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IL, IT, NL, NO, PE, PH, PT, RU, SE, SG, TH, TR)

Pegaspargase

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Pegaspargase may be confused with asparaginase

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(peg AS par jase)

U.S. Brand NamesOncaspar®

Pharmacologic CategoryAntineoplastic Agent, Miscellaneous

Use: Labeled IndicationsTreatment of acute lymphocytic leukemia (ALL); treatment of ALL with previous hypersensitivity to native L-asparaginase

Dosing: AdultsUsually administered as part of a combination chemotherapy regimen.

I.M. administration is **preferred** over I.V. administration due to lower incidence of hepatotoxicity, coagulopathy, gastrointestinal and renal disorders with I.M. administration.

Acute lymphoblastic leukemia (ALL): I.M., I.V.: 2500 int. units/m^2 every 14 days

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricUsually administered as part of a combination chemotherapy regimen.

I.M. administration is **preferred** over I.V. administration due to lower incidence of hepatotoxicity, coagulopathy, gastrointestinal and renal disorders with I.M. administration.

Acute lymphoblastic leukemia: I.M., I.V.:

Body surface area <0.6 m^2: 82.5 int. units/kg every 14 days

Body surface area ≥0.6 m^2: 2500 int. units/m^2 every 14 days

Dosing: Combination Regimens

Leukemia (acute lymphocytic): Hyper-CVAD (Leukemia, Acute Lymphocytic)

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.M.Must only be administered as a deep intramuscular injection into a large muscle; if I.M. injection volume is >2 mL, use multiple injection sites.

Administration: I.V.May be administered as a 1- to 2-hour I.V. infusion; **do not administer I.V. push**.

Administration: I.V. DetailDo not filter solution. Have available appropriate agents for maintenance of an adequate airway and treatment of a hypersensitivity reaction (antihistamine, epinephrine, oxygen, I.V. corticosteroids). Be prepared to treat anaphylaxis at each administration. Administer through an infusion that is already running.

pH: 7.3

StorageRefrigerate at 2°C to 8°C (36°F to 46°F); do not freeze. Do not use product if it is known to have been frozen. Do not use if stored at room temperature for >48 hours. Avoid excessive agitation; do not shake. Do not use if cloudy or if precipitate is present.

Reconstitution

Standard I.M. dilution: Do not exceed 2 mL volume per injection site.

Standard I.V. dilution: Dilute in 100 mL NS or D_5W; stable for 48 hours at room temperature.

CompatibilityStable in NS, D_5W.

ContraindicationsHypersensitivity to pegaspargase or any component of the formulation; history of serious thrombosis with previous L-asparaginase treatment; pancreatitis or a history of pancreatitis; previous serious allergic reactions (urticaria, bronchospasm, laryngeal edema, hypotension) or other unacceptable adverse reactions to pegaspargase; previous hemorrhagic event with L-asparaginase

Allergy Considerations

- Asparaginase Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Allergic reactions: Monitor for severe allergic reactions; may be used cautiously in patients who have had hypersensitivity reactions to *E. coli* asparaginase; however, up to 32% of patients who have an allergic reaction to *E. coli* asparaginase will also react to pegaspargase; immediate treatment for hypersensitivity reactions should be available during administration.

- Coagulopathy: Has been reported; monitor coagulation parameters. Use cautiously in patients with an underlying coagulopathy or previous hematologic complications from asparaginase.

- Glucose intolerance: May cause (possibly irreversible) glucose intolerance; use with caution in patients with hyperglycemia.

- Pancreatitis: Discontinue if pancreatitis occurs during treatment.

- Thrombotic events: May occur; discontinue with serious thrombotic event.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

Concurrent drug therapy issues:

- Hepatotoxic medications: Use with caution in patients on concomitant hepatotoxic medications.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with pegaspargase.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse ReactionsIn general, pegaspargase toxicities tend to be less frequent and appear somewhat later than comparable toxicities of asparaginase. Intramuscular rather than intravenous injection may decrease the incidence of coagulopathy; GI, hepatic, and renal toxicity. Except for hypersensitivity reactions, adults tend to have a higher incidence than children.

>5%:

Cardiovascular: Edema

Central nervous system: Fever, malaise

Dermatologic: Rash (1% to >5%)

Gastrointestinal: Nausea, vomiting

Hematologic: Coagulopathy (7%; grades 3/4: 2%)

Hepatic: Transaminases increased (11%; grades 3/4: 3%), ALT increased

Miscellaneous: Allergic reactions (including bronchospasm, chills, dyspnea, edema, erythema, fever, rash, urticaria: 1% to 10%; 32% in patients with prior hypersensitivity to asparaginase products)

1% to 5%:

Cardiovascular: Hypotension, peripheral edema, tachycardia, thrombosis (4%)

Central nervous system: Chills, CNS thrombosis/hemorrhage (2%), headache, seizure

Dermatologic: Lip edema, urticaria

Endocrine & metabolic: Hyperglycemia (3% to 5%), hyperuricemia, hypoglycemia, hypoproteinemia

Gastrointestinal: Abdominal pain, anorexia, diarrhea, pancreatitis (1% to 2%; grades 3/4: 2%)

Hematologic: Anticoagulant effect decreased, disseminated intravascular coagulation (DIC), fibrinogen decreased, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, thromboplastin increased, myelosuppression (mild to moderate; onset: 7 days; nadir: 14 days; recovery: 21 days)

Hepatic: Liver function tests abnormal (5%), hyperbilirubinemia, jaundice, AST increased

Local: Injection site hypersensitivity, pain or reaction

Neuromuscular & skeletal: Arthralgia, limb pain, myalgia, paresthesia

Respiratory: Dyspnea

Miscellaneous: Anaphylactic reactions, night sweats

<1%, postmarketing, and/or case reports: Abnormal renal function, alopecia, amylase increased, anemia, antithrombin III decreased, appetite increased, ascites, bone pain, bronchospasm, bruising, BUN increased, chest pain, coagulation disorder, coagulation time increased, colitis, coma, confusion, constipation, cough, creatinine increased, dizziness, DVT, emotional lability, endocarditis, epistaxis, erythema, excessive thirst, face edema, fatigue, fatty liver deposits, flatulence, gastrointestional pain, glucose intolerance, hematuria, hemorrhagic cystitis, hepatomegaly, hyperammonemia, hypertension, hypoalbuminemia, hyponatremia, joint disorder, lesional edema, lipase increased, liver failure, metabolic acidosis, mucositis, petechial rash, polyuria, proteinuria, prothrombin time increased, pruritus, purpura, renal failure, sagittal sinus thrombosis, sepsis, septic shock, somnolence, subacute bacterial endocarditis, superficial venous thrombosis, thirst, upper respiratory infection, uric acid nephropathy, urinary frequency, weight loss

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersVital signs during administration, CBC with differential, platelets, amylase, liver enzymes, fibrinogen, PT, PTT, renal function tests, urine dipstick for glucose, blood glucose; monitor for onset of abdominal pain and mental status changes

Nursing: Physical Assessment/MonitoringIdentify patient's allergy history with L-asparaginase before beginning therapy. I.V.: See Administration for infusion specifics and anaphylactic precautions (have a freely-running I.V. in place and emergency medications at hand). Patient must be monitored closely during and for 1 hour following each infusion (anaphylactic reactions can occur with each dose). Assess results of laboratory tests and patient response with each dose (eg, GI disturbance, nausea, vomiting; depression of clotting factors; hypotension). **Note:** I.M. rather than I.V. administration may decrease the incidence of coagulopathy and GI, hepatic, and renal toxicity. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, platelets, amylase, liver enzymes, fibrinogen, PT, PTT, renal function tests, urine dipstick for glucose, blood glucose

Patient EducationThis drug is given by infusion or injection; report immediately any redness, swelling, burning, or pain at infusion/injection site or any signs of allergic reaction (eg, respiratory difficulty or swallowing, chest tightness, rash, hives, swelling of lips or mouth). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake and nutrition (small frequent meals will help). You may be more susceptible to infection (avoid crowds and exposure to infection and do not have vaccinations without consulting prescriber). May cause nausea, vomiting, or loss of appetite (frequent mouth care, chewing gum, or sucking lozenges may help); mouth sores (use soft toothbrush, waxed dental floss, and frequent mouth rinses); diarrhea (buttermilk, boiled milk, or yogurt may help); dizziness, drowsiness, syncope, or blurred vision (use caution when driving or engaging in tasks that require alertness until response to drug is known); increased sweating; decreased sexual drive; or cough. Report immediately any unusual bleeding or bruising, nosebleeds, bleeding gums, black tarry stools, blood in urine or stool, pinpoint red spots on your skin; persistent nausea or vomiting; allergic reaction (fever, rash, swelling around mouth, chest pain, rapid heart beat); weakness or fatigue, edema (swelling of extremities or sudden weight gain); or other adverse reactions.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Oncaspar®: 750 units/mL (5 mL)

Generic AvailableNo

Mechanism of ActionPegaspargase is a modified version of asparaginase. Leukemic cells, especially lymphoblasts, require exogenous asparagine; normal cells can synthesize asparagine. Asparaginase contains L-asparaginase amidohydrolase type EC-2 which inhibits protein synthesis by deaminating asparagine to aspartic acid and ammonia in the plasma and extracellular fluid and therefore deprives tumor cells of the amino acid for protein synthesis. Asparaginase is cycle-specific for the G_1 phase of the cell cycle.

Pharmacodynamics/Kinetics

Duration: Asparaginase was measurable for at least 20 days following initial treatment with pegaspargase

Distribution: V_d: 4-5 L/kg; 70% to 80% of plasma volume; does not penetrate the CSF

Metabolism: Systemically degraded

Half-life elimination: 5.8 days; unaffected by age, renal or hepatic function; half life decreased to 3.2 days in patients with previous hypersensitivity to native L-asparaginase

Excretion: Urine (trace amounts)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common

Mental Health: Effects on Psychiatric TreatmentMay cause pancytopenia; use caution with clozapine and carbamazepine

Index TermsNSC-644954; PEG-L-asparaginase

References

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Patel SS and Benfield P, “Pegaspargase (Polyethylene Glycol-L-Asparaginase),” *Clin Immunother*, 1996, 5:490-6.

International Brand NamesOncaspar (DE, PL)

Pegfilgrastim

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Neulasta® may be confused with Neumega® and Lunesta™

Pronunciation(peg fil GRA stim)
U.S. Brand NamesNeulasta®
Canadian Brand NamesNeulasta®
Pharmacologic CategoryColony Stimulating Factor
Use: Labeled IndicationsTo decrease the incidence of infection, by stimulation of granulocyte production, in patients with nonmyeloid malignancies receiving myelosuppressive therapy associated with a significant risk of febrile neutropenia
Dosing: Adults**Myelosuppressive therapy:** SubQ: 6 mg once per chemotherapy cycle; do not administer in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricAdolescents >45 kg: Refer to adult dosing.
Dosing: Renal ImpairmentNo adjustment necessary.
Administration: OtherDo not use 6 mg fixed dose in infants, children, or adolescents <45 kg. Engage/activate needle guard following use to prevent accidental needlesticks.
StorageStore under refrigeration 2°C to 8°C (36°F to 46°F); do not freeze. If inadvertently frozen, allow to thaw in refrigerator; discard if frozen more than one time. Protect from light. Do not shake. Allow to reach room temperature prior to injection. May be kept at room temperature for up to 48 hours.
ContraindicationsHypersensitivity to pegfilgrastim, filgrastim, *E. coli*-derived proteins, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Allergic reactions: Anaphylaxis, skin rash, erythema, and urticaria have occurred primarily with the initial dose and may recur after discontinuation; close follow up for several days and permanent discontinuation are recommended for severe reactions.
- Respiratory distress syndrome: Acute respiratory distress syndrome (ARDS) has been reported with use; evaluate patients with pulmonary symptoms such as fever, lung infiltrates, or respiratory distress; withhold or discontinue pegfilgrastim if ARDS occurs.
- Splenic rupture: Rare cases of splenic rupture have been reported; patients must be instructed to report left upper quadrant pain or shoulder tip pain.

Disease-related concerns:

- Sickle cell disease: May precipitate sickle cell crises in patients with sickle cell disease; carefully evaluate potential risks and benefits.

Concurrent drug therapy issues:

- Cytotoxic chemotherapy: Do not use pegfilgrastim in the period 14 days before to 24 hours after administration of cytotoxic chemotherapy because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy.

Special populations:

- Adolescents: The 6 mg fixed dose should not be used in adolescents weighing <45 kg.
- Delayed myelosuppression: Use has not been evaluated with patients receiving chemotherapy associated with delayed myelosuppression (eg, nitrosoureas, mitomycin C).
- Pediatrics: Safety and efficacy in pediatric patients have not been established.
- Radiation therapy recipients: Use has not been evaluated for peripheral blood progenitor cell (PBPC) mobilization with patients receiving radiation therapy.
- Stem cell mobilization: Safety and efficacy have not been evaluated for peripheral blood progenitor cell (PBPC) mobilization.

Dosage form specific issues:

- Latex: The packaging (needle cover) contains latex.

Other warnings/precautions:

- Tumor growth factor: May potentially act as a growth factor for any tumor type, particularly myeloid malignancies; caution should be exercised when using in any malignancy with myeloid characteristics. Tumors of nonhematopoietic origin may have surface receptors for pegfilgrastim.

Geriatric ConsiderationsNot for patients <45 kg.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies have demonstrated adverse effects and fetal loss. There are no adequate and well-controlled studies in pregnant women; use only if potential benefit to mother justifies the potential risk to the fetus.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%:

Cardiovascular: Peripheral edema (12%)

Central nervous system: Headache (16%)

Gastrointestinal: Vomiting (13%)

Neuromuscular & skeletal: Bone pain (31% to 57%), myalgia (21%), arthralgia (16%), weakness (13%)

1% to 10%: Gastrointestinal: Constipation (10%)

<1%, postmarketing, and/or case reports: Acute respiratory distress syndrome (ARDS), allergic reaction, anaphylaxis, erythema, fever, flushing, hyperleukocytosis, hypoxia, injection site pain, leukocytosis, rash, sickle cell crisis, splenic rupture, Sweet's syndrome (acute febrile dermatosis), urticaria. Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors.

Drug InteractionsThere are no known significant interactions.
Test InteractionsMay interfere with bone imaging studies; increased hematopoietic activity of the bone marrow may appear as transient positive bone imaging changes
Monitoring ParametersComplete blood count (with differential) and platelet count should be obtained prior to chemotherapy. Leukocytosis (white blood cell counts 100,000/mm^3) has been observed in <1% of patients receiving pegfilgrastim. Monitor platelets and hematocrit regularly. Evaluate fever, pulmonary infiltrates, and respiratory distress; evaluate for left upper abdominal pain, shoulder tip pain, or splenomegaly. Monitor for sickle cell crisis (in patients with sickle cell anemia).
Monitoring: Lab TestsComplete blood count (with differential) and platelet count should be obtained prior to chemotherapy. Leukocytosis (white blood cell counts 100,000/mm^3) has been observed in <1% of patients receiving pegfilgrastim. Monitor platelets and hematocrit regularly.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Neulasta®: 10 mg/mL (0.6 mL) [prefilled syringe; needle cover contains latex]

Generic AvailableNo
ManufacturerAmgen Inc
Pricing: U.S. (www.drugstore.com)

Solution (Neulasta)

6 mg/0.6 mL (0.6): $3331.13

Mechanism of ActionStimulates the production, maturation, and activation of neutrophils, pegfilgrastim activates neutrophils to increase both their migration and cytotoxicity. Pegfilgrastim has a prolonged duration of effect relative to filgrastim and a reduced renal clearance.
Pharmacodynamics/KineticsHalf-life elimination: SubQ: 15-80 hours
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentLithium may potentiate release of neutrophils from bone marrow
Index TermsG-CSF (PEG Conjugate); Granulocyte Colony Stimulating Factor (PEG Conjugate); NSC-725961; SD/01
References

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Wolff AC, Jones RJ, Davidson NE, et al, "Myeloid Toxicity in Breast Cancer in Patients Receiving Adjuvant Chemotherapy With Pegfilgrastim Support," *J Clin Oncol*, 2006, 24(15):2392-4.

International Brand NamesNeulasta (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Neulastim (CN, CO, EC, HK, IL, NZ, SG, TH); Neulastyl (PH); Neupopeg (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Peginterferon Alfa-2a

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(peg in ter FEER on AL fa too aye)

U.S. Brand NamesPegasys®

Canadian Brand NamesPegasys®

Pharmacologic CategoryInterferon

Use: Labeled IndicationsTreatment of chronic hepatitis C (CHC), alone or in combination with ribavirin, in patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A) and patients with clinically-stable HIV disease; treatment of patients with HBeAg positive and HBeAg negative chronic hepatitis B with compensated liver disease and evidence of viral replication and liver inflammation

Dosing: Adults

Chronic hepatitis C (monoinfection or coinfection with HIV): SubQ:

Monotherapy: 180 mcg once weekly for 48 weeks

Combination therapy with ribavirin: Recommended dosage: 180 mcg once/week with ribavirin (Copegus®)

Duration of therapy: Monoinfection (based on genotype):

Genotype 1,4: 48 weeks

Genotype 2,3: 24 weeks

Duration of therapy: Coinfection: 48 weeks

Chronic hepatitis B: SubQ: 180 mcg once weekly for 48 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} <50 mL/minute: Use caution; monitor for toxicity

End-stage renal disease requiring hemodialysis: 135 mcg/week; monitor for toxicity

Dosing: Hepatic Impairment

HCV: ALT progressively rising above baseline: Decrease dose to 135 mcg/week. If ALT continues to rise or is accompanied by increased bilirubin or hepatic decompensation, discontinue therapy immediately.

HBV:

ALT >5 x ULN: Monitor LFTs more frequently; consider decreasing dose to 135 mcg/week or temporarily discontinuing (may resume after ALT flare subsides).

ALT >10 x ULN: Consider discontinuing.

Dosing: Adjustment for Toxicity

Dose modifications for adverse events/toxicity:

For moderate to severe adverse reactions: Initial: 135 mcg/week; may need decreased to 90 mcg/week in some cases

Based on hematologic parameters:

ANC <750/mm^3: 135 mcg/week

ANC <500/mm^3: Suspend therapy until >1000/mm^3, then restart at 90 mcg/week; monitor ANC

Platelet count <50,000/mm^3: 90 mcg/week

Platelet count <25,000/mm^3: Discontinue therapy

Depression (severity based on DSM-IV criteria):

Mild depression: No dosage adjustment required; evaluate once weekly by visit/phone call. If depression remains stable, continue weekly visits. If depression improves, resume normal visit schedule

Moderate depression: Decrease interferon dose to 90-135 mcg once/week; evaluate once weekly with an office visit at least every other week. If depression remains stable, consider psychiatric evaluation and continue with reduced dosing. If symptoms improve and remain stable for 4 weeks, resume normal visit schedule; continue reduced dosing or return to normal dose.

Severe depression: Discontinue interferon permanently. Obtain immediate psychiatric consultation. Discontinue ribavirin if using concurrently.

Administration: OtherSubQ: Administer in the abdomen or thigh. Rotate injection site. Do not use if solution contains particulate matter or is discolored. Discard unused solution. Administration should be done on the same day and at approximately the same time each week.

Dietary ConsiderationsAvoid ethanol use in patients with hepatitis C virus.

StorageStore in refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light. Discard unused solution.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to polyethylene glycol (PEG), interferon alfa, or any component of the formulation; autoimmune hepatitis; decompensated liver disease in cirrhotic patients (Child-Pugh score >6); decompensated liver disease (Child-Pugh score ≥6, class B and C) in CHC coinfected with HIV; neonates and infants

Warnings/Precautions

Boxed warnings:

- Autoimmune disease: See “Disease-related concerns” below.

- Combination therapy with ribavirin: See “Concurrent drug therapy issues” below.

- Infectious disorders: See “Disease-related concerns” below.

- Ischemic disorders: See “Disease-related concerns” below.

- Neuropsychiatric disorders: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related t o adverse effects:

- Bone marrow suppression: May cause myelosuppression (including neutropenia, thrombocytopenia, lymphopenia, aplastic anemia). Use caution with baseline neutrophil count <1500/mm^3, platelet count <90,000/mm^3 or hemoglobin <10 g/dL. Discontinue therapy (at least temporarily) if ANC <500/mm^3 or platelet count <25,000/mm^3.

- CNS effects: Patients who experience dizziness, confusion, somnolence, or fatigue should use caution when performing tasks which require mental alertness (eg, operating machinery or driving).

- Dermatologic effects: Serious cutaneous reactions, including vesiculobullous eruptions, Stevens-Johnson syndrome, and exfoliative dermatitis, have been reported (rarely) with use, with or without ribavirin therapy; discontinue with signs or symptoms of severe skin reactions.

- Flu-like symptoms: Commonly associated with flu-like symptoms, including fever; rule out other causes/infection with persistent or high fever.

- Gastrointestinal effects: Gastrointestinal hemorrhage, ulcerative and hemorrhagic/ischemic colitis have been observed with interferon alfa treatment; may be severe and/or life-threatening; discontinue if symptoms of colitis (eg, abdominal pain, bloody diarrhea, and/or fever) develop.

- Hepatic effects: Hepatic decompensation and death have been associated with the use of alpha interferons including Pegasys®, in cirrhotic chronic hepatitis C patients; patients coinfected with HIV and receiving highly active antiretroviral therapy have shown an increased risk. Monitor hepatic function; discontinue if decompensation occurs (Child-Pugh score >6) in monoinfected patients and (Child-Pugh score ≥6, class B and C) in patients coinfected with HIV.

- Hypersensitivity reactions: Severe acute hypersensitivity reactions have occurred rarely; prompt discontinuation is advised.

- Infections: Serious and severe infections (bacterial, viral, and fungal) have been reported with treatment.

- Neuropsychiatric disorders: **[U.S. Boxed Warning]: Discontinue treatment with worsening or persistently severe signs/symptoms of neuropsychiatric disorders.** Severe psychiatric adverse effects (including depression, suicidal ideation, and suicide attempt) may occur. Avoid use in severe psychiatric disorders; use with extreme caution in patients with a history of depression.

- Ocular effects: Discontinue if new or worsening ophthalmologic disorders occur including retinal hemorrhages, cotton wool spots, and retinal artery or vein obstruction; visual exams are recommended in these instances, at the initiation of therapy, and periodically during therapy.

- Pancreatitis: Discontinue therapy if known or suspected pancreatitis develops.

- Pulmonary effects: Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonia, and sarcoidosis, resulting in potentially fatal respiratory failure may occur with treatment. Discontinue with unexplained pulmonary infiltrates or evidence of impaired pulmonary function. Use with caution in patients with pulmonary dysfunction or a history of pulmonary disease.

Disease-related concerns:

- Anemia: Use with caution in patients with an increased risk for severe anemia (eg, spherocytosis, history of GI bleeding).

- Autoimmune disease: **[U.S. Boxed Warning]: Discontinue treatment with worsening or persistently severe signs/symptoms of autoimmune disorders;** use with caution in patients with autoimmune disease.

- Cardiovascular disease: Use with caution in patients with prior cardiovascular disease; hypertension, arrhythmia, chest pain, and MI have been observed with treatment.

- Diabetes: Use with caution in patients with diabetes mellitus; hyper/hypoglycemia have been reported; may require adjustments in antidiabetic medications; discontinue peginterferon alfa 2-a if unable to effectively manage diabetes with medication.

- Hepatitis B: In hepatitis B patients, flares (transient and potentially severe increases in serum ALT) may occur during or after treatment; more frequent monitoring of LFTs and a dose reduction are recommended. Discontinue if ALT elevation continues despite dose reduction or if increased bilirubin or hepatic decompensation occur.

- Infectious disorders: **[U.S. Boxed Warning]: Discontinue treatment in patients with worsening or persistently severe signs/symptoms of infectious disorders.**

- Ischemic disorders: **[U.S. Boxed Warning]: Discontinue treatment in patients with worsening or persistently severe signs/symptoms of ischemic (including radiographic changes or worsening hepatic function) disorders.**

- Renal impairment: Use with caution in patients with renal dysfunction (Cl_{cr} <50 mL/minute); monitor for signs/symptoms of toxicity (dosage adjustment required if toxicity occurs).

- Thyroid disorders: Use with caution in patients with pre-existing thyroid disease; thyroid disorders (hyper- or hypothyroidism) or exacerbations have been reported; discontinue peginterferon alfa 2-a if unable to effectively manage with medication.

Concurrent drug therapy issues:

Combination therapy with ribavirin: **[U.S. Boxed Warning]: Combination treatment with ribavirin may cause birth defects and/or fetal mortality; hemolytic anemia (which may worsen cardiac disease), genotoxicity, mutagenicity, and may possibly be carcinogenic.**

Special populations:

- Elderly: Use with caution in the elderly.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Product variability: **Due to differences in dosage, patients should not change brands of interferon without the concurrence of their healthcare provider.**

Other warnings/precautions:

- Appropriate use: Safety and efficacy have not been established in patients who have failed other alpha interferon therapy, received organ transplants, been coinfected with HBV and HCV or HIV; or with HCV and HIV with a $CD4^+$ cell count <100 cells/microL, or been treated for >48 weeks.

Pregnancy Risk FactorC / X in combination with ribavirin

Pregnancy ConsiderationsReproduction studies with pegylated interferon alfa have not been conducted. Animal studies with nonpegylated interferon alfa-2b have demonstrated abortifacient effects. Disruption of the normal menstrual cycle was also observed in animal studies; therefore, the manufacturer recommends that reliable contraception is used in women of childbearing potential. Alfa interferon is endogenous to normal amniotic fluid. *In vitro* administration studies have reported that when administered to the mother, it does not cross the placenta. Case reports of use in pregnant women are limited. The Perinatal HIV Guidelines Working Group does not recommend that peginterferon-alfa be used during pregnancy. Peginterferon monotherapy should only be used in pregnancy when the potential benefit to the mother justifies the possible risk to the fetus. Combination therapy with ribavirin is contraindicated in pregnancy (refer to Ribavirin monograph); a pregnancy registry has been established for women inadvertently exposed to ribavirin while pregnant (800-593-2214).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsBreast milk samples obtained from a lactating mother prior to and after administration of interferon alfa-2b showed that interferon alfa is present in breast milk and administration of the medication did not significantly affect endogenous levels. The AAP considers interferon alfa to be “usually compatible with breastfeeding”. Breast-feeding is not linked to the spread of hepatitis C virus; however, if nipples are cracked or bleeding, breast-feeding is not recommended. Mothers co-infected with HIV are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse Reactions**Note:** Percentages are reported for peginterferon alfa-2a in chronic hepatitis C (CHC) patients. Other percentages indicated as “with ribavirin” or “in HIV/CHC” or "in hepatitis B" are those which significantly exceed incidence reported for peginterferon monotherapy in CHC patients.

>10%:

Central nervous system: Headache (54%), fatigue (56%), pyrexia (37%; 41% with ribavirin; 54% in hepatitis B), insomnia (19%; 30% with ribavirin), depression (18%), dizziness (16%), irritability/anxiety/nervousness (19%; 33% with ribavirin), pain (11%)

Dermatologic: Alopecia (23%; 28% with ribavirin), pruritus (12%; 19% with ribavirin), dermatitis (16% with ribavirin)

Gastrointestinal: Nausea/vomiting (24%), anorexia (17%; 24% with ribavirin), diarrhea (16%), weight loss (16% in HIV/CHC), abdominal pain (15%)

Hematologic: Neutropenia (21%; 27% with ribavirin; 40% in HIV/CHC), lymphopenia (14% with ribavirin), anemia (11% with ribavirin; 14% in HIV/CHC)

Hepatic: ALT increases 5-10 x ULN during treatment (25% to 27% in hepatitis B); ALT increases >10 x ULN during treatment (12% to 18% in hepatitis B); ALT increases 5-10 x ULN after treatment (13% to 16% in hepatitis B); ALT increases >10 x ULN after treatment (7% to 12% in hepatitis B)

Local: Injection site reaction (22%)

Neuromuscular & skeletal: Weakness (56%; 65% with ribavirin), myalgia (37%), rigors (35%; 25% to 27% in hepatitis B), arthralgia (28%)

Respiratory: Dyspnea (13% with ribavirin)

1% to 10%:

Central nervous system: Concentration impaired (8%), memory impaired (5%), mood alteration (3%; 9% in HIV/CHC)

Dermatologic: Dermatitis (8%), rash (5%), dry skin (4%; 10% with ribavirin), eczema (1%; 5% with ribavirin)

Endocrine & metabolic: Hypothyroidism (3% to 4%), hyperthyroidism (≤1%)

Gastrointestinal: Xerostomia (6%), dyspepsia (<1%; 6% with ribavirin), weight loss (4%; 10% with ribavirin)

Hematologic: Thrombocytopenia (5%; 8% in HIV/CHC), lymphopenia (3%), anemia (2%)

Hepatic: Hepatic decompensation (2% in CHC/HIV)

Neuromuscular & skeletal: Back pain (9%)

Ocular: Blurred vision (4%)

Respiratory: Cough (4%; 10% with ribavirin), dyspnea (4%), exertional dyspnea (4% with ribavirin)

Miscellaneous: Diaphoresis (6%), bacterial infection (3%; 5% in HIV/CHC)

≤1%, postmarketing, and/or case reports: Aggression, anaphylaxis, angioedema, angina, aplastic anemia, arrhythmia, autoimmune disorders, bronchiolitis obliterans, bronchoconstriction, cerebral hemorrhage, chest pain, cholangitis, colitis, coma, corneal ulcer, cotton wool spots, diabetes mellitus, endocarditis, erythema multiforme major, exertional dyspnea, exfoliative dermatitis, fatty liver, gastrointestinal bleeding, hallucination, hearing impairment, hearing loss, hemoglobin decreased, hematocrit decreased, hepatic dysfunction, hepatic decompensation, hyper-/hypoglycemia, hypersensitivity reactions, hypertension, influenza, interstitial pneumonitis, MI, myositis, optic neuritis, papilledema, pancreatitis, peptic ulcer, peripheral neuropathy, pneumonia, psychiatric disorder, psychosis, pulmonary embolism, pulmonary infiltrates, retinal hemorrhage, retinopathy, rheumatoid arthritis, sarcoidosis, Stevens-Johnson syndrome, substance overdose, suicidal ideation, suicide, supraventricular arrhythmia, systemic lupus erythematosus, thrombotic thrombocytopenic purpura, urticaria, vesiculobullous eruptions, vision decreased/loss

Metabolism/Transport Effects **Inhibits** CYP1A2 (weak)

Drug Interactions

Aldesleukin: Interferons (Alfa) may enhance the adverse/toxic effect of Aldesleukin. In particular, risks of myocardial and renal toxicity may be increased by this combination. *Risk D: Consider therapy modification*

Ribavirin: Interferons (Alfa) may enhance the adverse/toxic effect of Ribavirin. Hemolytic anemia has been observed. *Risk C: Monitor therapy*

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions Ethanol: Avoid use in patients with hepatitis C virus.

Monitoring Parameters Prior to treatment, pregnancy screening should occur for women of childbearing age who are receiving treatment or who have male partners who are receiving treatment. In combination therapy with ribavirin, pregnancy tests should continue monthly up to 6 months after discontinuation of therapy. Standard hematological tests should be performed prior to therapy, at week 2, and periodically. Standard biochemical tests should be performed prior to therapy, at week 4, and periodically. Evaluate for depression and other psychiatric symptoms before and during therapy; baseline eye examination and periodically in patients with baseline disorders; baseline echocardiogram in patients with cardiac disease; serum HCV RNA levels after 12 weeks of treatment. Consider discontinuing treatment if virologic tests indicate no response by week 12.

Clinical studies tested as follows: CBC (including hemoglobin, WBC, and platelets) and chemistries (including liver function tests and uric acid) measured at weeks 1, 2, 4, 6, and 8, and then every 4-6 weeks (more frequently if abnormal) weeks; TSH measured every 12 weeks

In addition, the following baseline values were used as entrance criteria:

Platelet count ≥90,000/mm^3 (as low as 75,000/mm^3 in patients with cirrhosis or transition to cirrhosis)

ANC ≥1500/mm^3

Serum creatinine <1.5 times ULN

TSH and T$_4$ within normal limits or adequately controlled

CD4$^+$ cell count ≥200 cells/microL or CD4$^+$ cell count ≥100 cells/ microL, but <200 cells/ microL and HIV-1 RNA <5000 copies/mL in CHC patients coinfected with HIV

Hemoglobin ≥12 g/dL for women and ≥13 g/dL for men in CHC monoinfected patients

Hemoglobin ≥11 g/dL for women and ≥12 g/dL for men in CHC patients coinfected with HIV

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests prior to and periodically during therapy. Evaluate for depression and other psychiatric symptoms before and during therapy; baseline eye examination and periodically in patients with baseline disorders; baseline echocardiogram in patients with cardiac disease; assess therapeutic effectiveness and adverse response at beginning of and at regular intervals during therapy. Teach patient proper use if self-administered (appropriate injection technique and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsStandard hematological tests should be performed prior to therapy, at week 2, and periodically. Standard biochemical tests should be performed prior to therapy, at week 4, and periodically. Baseline eye examination and periodically in patients with baseline disorders; baseline echocardiogram in patients with cardiac disease; serum HCV RNA levels after 12 weeks of treatment

Clinical studies tested as follows: CBC (including hemoglobin, WBC, and platelets) and chemistries (including liver function tests and uric acid) measured at weeks 1, 2, 4, 6, and 8, and then every 4 weeks; TSH measured every 12 weeks

In addition, the following baseline values were used as entrance criteria:

Platelet count ≥ 90,000/mm^3 (as low as 75,000/mm^3 in patients with cirrhosis or transition to cirrhosis)

ANC ≥ 1500/mm^3

Serum creatinine <1.5 times ULN

TSH and T_4 within normal limits or adequately controlled

Consider discontinuing treatment if virologic tests indicate no response by week 12.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy without consulting prescriber. This medication must be given by injection; if self-administered, follow exact instructions for injection and syringe/needle disposal. Avoid alcohol. You will need laboratory tests and ophthalmic exams prior to and during therapy. May cause headache, insomnia, dizziness (use caution when driving or engaging in potentially hazardous tasks until response to drug is known); loss of hair (will grow back after therapy); nausea or anorexia (small frequent meals or frequent mouth care may help); diarrhea (boiled milk, buttermilk, or yogurt may help); weakness, fatigue; muscle, skeletal, or joint pain; or increased perspiration. Report any severe or persistent adverse effects, including nausea, vomiting, or abdominal or back pain; severe depression, anxiety, or suicidal ideation; skin rash; pain, redness, or swelling at injection site; signs of infection; unusual bleeding or bruising; changes in vision; severe shivering (rigors); or chest pain, palpitations, or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber for appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection solution:

Pegasys®

180 mcg/0.5 mL (0.5 mL) [prefilled syringe; contains benzyl alcohol and polysorbate 80; packaged with needles and alcohol swabs]

180 mcg/mL (1 mL) [vial; contains benzyl alcohol and polysorbate 80]

Generic AvailableNo

ManufacturerRoche Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Kit (Pegasys)

180 mcg/0.5 mL (1): $2017.16

Solution (Pegasys)

180 mcg/mL (1): $564.17

Mechanism of ActionAlpha interferons are a family of proteins, produced by nucleated cells, that have antiviral, antiproliferative, and immune-regulating activity. There are 16 known subtypes of alpha interferons. Interferons interact with cells through high affinity cell surface receptors. Following activation, multiple effects can be detected including induction of gene transcription. Inhibits cellular growth, alters the state of cellular differentiation, interferes with oncogene expression, alters cell surface antigen expression, increases phagocytic activity of macrophages, and augments cytotoxicity of lymphocytes for target cells.

Pharmacodynamics/Kinetics

Half-life elimination: Terminal: 50-160 hours; increased with renal dysfunction

Time to peak, serum: 72-96 hours

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSevere psychiatric adverse effects (including depression, suicidal ideation, and suicide attempt) may occur. May also cause sedation, anxiety, emotional lability, irritability, insomnia, dizziness, and impaired concentration.

Mental Health: Effects on Psychiatric TreatmentContraindicated in those with severe psychiatric disorder. Gastrointestinal side effects are common; use caution with SSRIs, valproic acid, and lithium. Flu-like symptoms are common; take this into consideration if also concerned about SSRI discontinuation syndrome. A case of agranulocytosis has been reported with concurrent use of clozapine; monitor.

Index TermsInterferon Alfa-2a (PEG Conjugate); Pegylated Interferon Alfa-2a

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International Brand NamesPegasys (AR, AT, AU, BE, BG, BR, CH, CL, CN, CO, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IT, MX, NL, NO, PE, PH, PK, PL, PT, PY, RU, SE, SG, TH, TR, TW, UY, VE); Pegasys PFS (KP)

Peginterferon Alfa-2b and Ribavirin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(peg in ter FEER on AL fa too bee & rye ba VYE rin)
Canadian Brand NamesPegasys; Pegasys® RBV; Pegetron™
Pharmacologic CategoryAntiviral Agent; Interferon
Use: Labeled IndicationsCombination therapy for the treatment of chronic hepatitis C in patients with compensated liver disease
Dosing: Adults

Chronic hepatitis C: Recommended dosage of combination therapy:

Intron® A: SubQ: 1.5 mcg/kg/week

and

Rebetol®: Oral:

≤64 kg: 800 mg/day (two 200 mg capsules in the morning and two 200 mg capsules in the evening)

64-84 kg: 1000 mg/day (two 200 mg capsules in the morning and three 200 mg capsules in the evening)

≥85 kg: 1200 mg/day (three 200 mg capsules in the morning and three 200 mg capsules in the evening)

Note: Treatment duration may vary. Consult current guidelines and literature.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentAvoid use in patients with Cl_{cr} <50 mL/minute. Permanently discontinue therapy in any patient with a serum creatinine >2 mg/dL.
Dosing: Hepatic ImpairmentNot for use in patients with severe hepatic impairment. Reduce ribavirin dose to 600 mg/day in any patient with a indirect bilirubin >5 mg/dL. Permanently discontinue therapy in any patient with a direct bilirubin >2.5 times ULN or indirect bilirubin >4 mg/dL (for >4 weeks); AST/ALT 2 times baseline **and** 10 times ULN.
Dosing: Adjustment for Toxicity

Hemoglobin:

Hemoglobin <10 g/dL: Continue current peginterferon alfa-2b dose; decrease ribavirin dose by 200 mg/day

Hemoglobin <8.5 g/dL: Permanently discontinue peginterferon alfa-2b and ribavirin

Hemoglobin decrease >2 g/dL in any 4-week period and stable cardiac disease: Decrease peginterferon alfa-2b dose by half; decrease ribavirin dose by 200 mg per day. Hemoglobin <12 g/dL after ribavirin dose is decreased: Permanently discontinue both peginterferon alfa-2b and ribavirin.

White blood cells:

WBC <1.5 x 10^9/L: Decrease peginterferon alfa-2b dose by half

WBC <1.0 x 10^9/L: Permanently discontinue peginterferon alfa-2b and ribavirin

Neutrophils:

Neutrophils <0.75 x 10^9/L: Decrease peginterferon alfa-2b dose by half

Neutrophils <0.5 x 10^9/L: Permanently discontinue peginterferon alfa-2b and ribavirin

Platelets:

Platelet count <50 x 10^9/L: Decrease peginterferon alfa-2b dose by half

Platelet count <25 x 10^9/L: Permanently discontinue peginterferon alfa-2b and ribavirin

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralCapsule should not be opened, crushed, chewed, or broken.
Administration: OtherSee individual agents.
Dietary ConsiderationsTake oral formulation without regard to food, but always in a consistent manner with respect to food intake (ie, always take with food or always take on an empty stomach).

Storage

Rebetol® capsule/Intron® A injection combination package: Store under refrigeration between 2°C and 8°C (36°F and 46°F). When the package is separated:

Rebetol® capsules: Store under refrigeration between 2°C and 8°C (36°F and 46°F) or at 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F).

Peginterferon injection: Store vial/carton under refrigeration between 2°C and 8°C (36°F and 46°F).

Reconstitution Peginterferon alpha-2b powder for injection should be reconstituted with 0.7 mL of diluent (provided). Roll gentle to form solution; do not shake. Vials are calibrated to provide appropriate dose in a volume of 0.5 mL of resulting solution. Use within 3 hours of reconstitution.

Restrictions Not available in U.S.

Contraindications Hypersensitivity to polyethylene glycol (PEG), interferon alfa, ribavirin, or any component of the formulation; autoimmune hepatitis; decompensated liver disease; previous treatment with interferon; severe psychiatric disorder; males with a pregnant female partner; pregnancy

Allergy Considerations

- Interferon Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bone marrow suppression: Anemia has been observed in patients receiving the interferon/ribavirin combination.
- Colitis: Discontinue ribavirin therapy in suspected/confirmed colitis.
- Dental/periodontal disorders: Have been reported with ribavirin and interferon therapy; patients should be instructed to brush teeth twice daily and have regular dental exams.
- Hemolytic anemia: Hemolytic anemia is a significant toxicity, usually occurring within 1-2 weeks, and may worsen underlying cardiac disease; use caution and assess cardiac disease before initiation. Patients with renal dysfunction and/or those >50 years of age should be carefully assessed for development of anemia. If any deterioration in cardiovascular status occurs, discontinue therapy.
- Neuropsychiatric disorders: Interferon alfa-2b may cause severe psychiatric adverse events (psychosis, mania, depression, suicidal behavior/ideation) in patients with and without previous psychiatric symptoms, avoid use in severe psychiatric disorders or in patients with a history of depression; careful neuropsychiatric monitoring is required during therapy. Suicidal ideation or attempts may occur more frequently in pediatric patients when compared to adults. Severe psychiatric events have also occurred with ribavirin.
- Ocular effects: Ophthalmologic disorders (including retinal hemorrhages, cotton wool spots, and retinal artery or vein obstruction) have occurred in patients using other alpha interferons. Prior to start of therapy, visual exams are recommended for patients with diabetes mellitus or hypertension.
- Pancreatitis: Discontinue ribavirin therapy in suspected/confirmed pancreatitis.
- Rash: Transient rashes do not necessitate interruption of therapy.

Disease-related concerns:

- Autoimmune disease: Peginterferon alfa-2b may cause or aggravate fatal or life-threatening autoimmune disorders; treatment should be discontinued in patients with worsening or persistently severe signs/symptoms.
- Bone marrow suppression: Use peginterferon alfa-2b with caution in patients with low peripheral blood counts or myelosuppression, including concurrent use of myelosuppressive therapy. Discontinue therapy when significant decreases in neutrophil ($<0.5 \times 10^9$/L) or platelet counts ($<50{,}000/\text{mm}^3$)
- Cardiovascular disease: Use peginterferon alfa-2b with caution in patients with cardiac disease (ischemic or thromboembolic), hypertension or arrhythmias.
- Endocrine disorders: Use peginterferon alfa-2b with caution in patients with endocrine disorders.
- Hepatic impairment: Interferon alfa-2b treatment should be discontinued in patients who develop worsening of hepatic function; use with caution in patients with hepatic impairment. Safety and efficacy of ribavirin have not been established in patients with decompensated liver disease.
- Hepatitis: Safety and efficacy of ribavirin have not been established in patients with concurrent hepatitis B virus.
- HIV: Safety and efficacy of ribavirin have not been established in patients with HIV exposure.
- Infectious disorders: Peginterferon alfa-2b may cause or aggravate fatal or life-threatening infectious disorders; discontinue if signs and symptoms occur.
- Ischemic disorders: Peginterferon alfa-2b may cause or aggravate fatal or life-threatening ischemic disorders.
- Renal impairment: Use peginterferon alfa-2b with caution in patients with renal impairment; use is not recommended if $Cl_{cr}<50$ mL/minute; monitor for signs/symptoms of toxicity (dosage adjustment required if toxicity occurs).
- Respiratory disease: Use with caution in patients with pulmonary disease; pulmonary symptoms have been associated with administration.

- Sarcoidosis: Use ribavirin with caution in patients with sarcoidosis (exacerbation reported).

Concurrent drug therapy issues:

- Medications causing lactic acidosis: Use with caution in patient receiving medications which may cause lactic acidosis (eg, nucleoside analogues).

Special populations:

- Elderly: Use with caution in elderly patients; higher frequency of anemia; take renal function into consideration before initiating.

- Organ transplant recipients: Safety and efficacy of ribavirin have not been established in organ transplant patients.

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: Avoid pregnancy in female patients and female partners of patients during ribavirin therapy by using two effective forms of contraception; continue contraceptive measures for at least 6 months after completion of therapy. If patient or female partner becomes pregnant during treatment, she should be counseled about potential risks of exposure. Negative pregnancy test is required before initiation and monthly thereafter.

Dosage form specific issues:

- Product variability: **Due to differences in dosage, patients should not change brands of interferons.**

Other warnings/precautions:

- Appropriate use: Safety and efficacy have not been established in patients who have failed other alpha interferon (including peginterferon alfa-2b) therapy, have received organ transplants, have been infected with HIV or hepatitis B, or have received treatment for >48 weeks.

Pregnancy Risk FactorX

Pregnancy ConsiderationsAbortifacient and teratogenic effects have been reported in women receiving interferons. Women of childbearing potential should not be treated unless two reliable forms of contraception are used. In addition, male patients and their female partners must also use two reliable forms of contraception. Pregnancy must be avoided during treatment and for 6 months following therapy.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions**Note:** Adverse reactions listed are specific to combination regimen in previously untreated hepatitis patients. See individual agents for additional adverse reactions reported with each agent during therapy for other diseases.

>10%:

Central nervous system: Fatigue (62% to 64%), headache (58% to 62%), fever (44% to 46%), rigors (45% to 48%), insomnia (40%), irritability (34% to 35%), depression (29% to 34%), impaired concentration (16% to 17%), anxiety (15%), emotional lability (11%)

Dermatologic: Alopecia (29% to 36%), pruritus (26% to 29%), rash (22% to 24%), dry skin (18% to 24%)

Endocrine & metabolic: Weight loss (17% to 29%)

Gastrointestinal: Nausea (36% to 43%), anorexia (29% to 32%), diarrhea (16% to 22%), vomiting (14%), abdominal pain (12% to 13%), xerostomia (8% to 12%)

Local: Injection site reaction (58% to 59%), injection site inflammation (25% to 27%)

Neuromuscular & skeletal: Myalgia (48% to 56%), arthralgia (34%), musculoskeletal pain (17% to 21%), weakness (16% to 18%)

Respiratory: Dyspnea (23% to 26%), cough (15% to 17%), pharyngitis (11% to 12%)

Miscellaneous: Flu-like syndrome (24% to 27%)

1% to 10%:

Cardiovascular: Chest pain, tachycardia

Central nervous system: Agitation, nervousness; suicidal ideation and suicide attempt have been reported in up to 1.2% of patients

Endocrine & metabolic: Thyroid abnormalities (hyper-/hypothyroidism), menstrual disorder

Gastrointestinal: Constipation, dyspepsia, right upper quadrant pain, taste perversion

Local: Injection site pain

Respiratory: Nonproductive cough, rhinitis

<1% (reported with other interferon preparations and/or ribavirin; limited to important or life-threatening): Acute hypersensitivity reactions, anaphylaxis, angioedema, aplastic anemia (very rare), arrhythmia, bronchoconstriction, cardiomyopathy, cotton wool spots, diabetes, hearing loss, hepatotoxic reactions, hypotension, MI, pneumonia, pneumonitis, retinal hemorrhages, retinal artery or vein obstruction, severe psychiatric reactions, suicidal behavior, suicidal ideation, tinnitus, urticaria; rare cases of autoimmune diseases including vasculitis, polyarteritis reaction, rheumatoid arthritis, lupus erythematosus, and Raynaud's phenomenon

Postmarketing and/or case reports: Dental disorders, hypertriglyceridemia, nephrotic syndrome, pancreatitis, periodontal disorders, hallucinations, renal failure, sarcoidosis (including exacerbations of sarcoidosis)

Metabolism/Transport EffectsPeginterferon Alfa-2a: **Inhibits** CYP1A2 (weak)

Drug Interactions

Aldesleukin: Interferons (Alfa) may enhance the adverse/toxic effect of Aldesleukin. In particular, risks of myocardial and renal toxicity may be increased by this combination. *Risk D: Consider therapy modification*

Influenza Virus Vaccine: Antiviral Agents (Influenza A and B) may diminish the therapeutic effect of Influenza Virus Vaccine. This only pertains to live, attentuated influenza virus vaccine. *Risk D: Consider therapy modification*

Interferons (Alfa): May enhance the adverse/toxic effect of Ribavirin. Hemolytic anemia has been observed. *Risk C: Monitor therapy*

Reverse Transcriptase Inhibitors (Nucleoside): Ribavirin may enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Ribavirin: Interferons (Alfa) may enhance the adverse/toxic effect of Ribavirin. Hemolytic anemia has been observed. *Risk C: Monitor therapy*

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Monitoring ParametersObtain pretreatment CBC, liver function tests, TSH, and electrolytes, then monitor routinely throughout therapy (at 2- and 4 weeks, more frequently if indicated); discontinue if WBC <1.0 x 10^9/L, neutrophils <0.5 x 10^9/L, platelets <25 x 10^9/L, or if hemoglobin <8.5 g/dL (in cardiac patients, discontinue if hemoglobin <12 g/dL after 4 weeks of dosage reduction). Pretreatment and monthly pregnancy test for women of childbearing age. Baseline chest x-ray, ECG, weight; patients with pre-existing cardiac abnormalities, or in advanced stages of cancer should have ECGs taken before and during treatment; reticulocyte count, I & O; dental exams

Reference RangePeak serum level after I.V. infusion of 10 million units: 546 units/mL

Early viral response (EVR): >2 log decrease in HCV RNA after 12 weeks of treatment

End of treatment response (ETR): Absence of detectable HCV RNA at end of the recommended treatment period

Sustained treatment response (STR): Absence of HCV RNA in the serum 6 months following completion of full treatment course

Monitoring: Lab TestsObtain pretreatment CBC, liver function tests, TSH, and electrolytes, then monitor routinely throughout therapy (at 2- and 4 weeks, more frequently if indicated); discontinue if WBC <1.0 x 10^9/L, neutrophils <0.5 x 10^9/L, platelets <25 x 10^9/L, or if hemoglobin <8.5 g/dL (in cardiac patients, discontinue if hemoglobin <12 g/dL after 4 weeks of dosage reduction). Pretreatment and monthly pregnancy test for women of childbearing age. Baseline chest x-ray, ECG, weight; patients with pre-existing cardiac abnormalities, or in advanced stages of cancer should have ECGs taken before and during treatment; reticulocyte count, I & O

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Combination package:

Injection, powder for reconstitution (Peginterferon alfa-2b): 50 mcg/0.5 mL

Capsules: Ribavirin (Rebetol®): 200 mg (56s)

Injection, powder for reconstitution (Peginterferon alfa-2b): 80 mcg/0.5 mL

Capsules: Ribavirin (Rebetol®): 200 mg (56s)

Injection, powder for reconstitution (Peginterferon alfa-2b): 100 mcg/0.5 mL

Capsules: Ribavirin (Rebetol®): 200 mg (70s)

Injection, powder for reconstitution (Peginterferon alfa-2b): 120 mcg/0.5 mL

Capsules: Ribavirin (Rebetol®): 200 mg (70s)

Injection, powder for reconstitution (Peginterferon alfa-2b): 150 mcg/0.5 mL

Capsules: Ribavirin (Rebetol®): 200 mg (84s)

Mechanism of Action

Peginterferon Alfa-2b: Alpha interferons are a family of proteins, produced by nucleated cells, that have antiviral, antiproliferative, and immune-regulating activity. There are 16 known subtypes of alpha interferons. Interferons interact with cells through high affinity cell surface receptors. Following activation, multiple effects can be detected including induction of gene transcription. Inhibits cellular growth, alters the state of cellular differentiation, interferes with oncogene expression, alters cell surface antigen expression, increases phagocytic activity of macrophages, and augments cytotoxicity of lymphocytes for target cells.

Ribavirin: Inhibits replication of RNA and DNA viruses; inhibits influenza virus RNA polymerase activity and inhibits the initiation and elongation of RNA fragments resulting in inhibition of viral protein synthesis.

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and metallic taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSevere psychiatric disorders, including depression and suicidal behavior, have been associated with interferon use. Careful neuropsychiatric monitoring is recommended.

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsRibavirin and Peginterferon Alfa-2b

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International Brand NamesPegatron Combination Therapy (NZ)

Peginterferon Alfa-2b

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Peginterferon alfa-2b may be confused with interferon alfa-2a, interferon alfa-2b, interferon alfa-n3, peginterferon alfa-2a

PegIntron™ may be confused with Intron® A

International issues:

Peginterferon alfa-2b may be confused with interferon alpha multi-subtype which is available in international markets

Pronunciation(peg in ter FEER on AL fa too bee)

U.S. Brand NamesPegIntron™

Canadian Brand NamesPegIntron™

Pharmacologic CategoryInterferon

Use: Labeled IndicationsTreatment of chronic hepatitis C (in combination with ribavirin) in patients who have never received alfa interferons and have compensated liver disease; treatment of chronic hepatitis C (as monotherapy) in adult patients who have never received alfa interferons

Use: Unlabeled/InvestigationalTreatment of advanced melanoma

Dosing: Adults

Chronic hepatitis C: SubQ: Administer dose once weekly; **Note:** Treatment duration may vary. Consult current guidelines and literature. Discontinue after 6 months of treatment if HCV viral levels remain detectable.

Monotherapy: Initial: 1 mcg/kg/week

- ≤45 kg: 40 mcg once weekly
- 46-56 kg: 50 mcg once weekly
- 57-72 kg: 64 mcg once weekly
- 73-88 kg: 80 mcg once weekly
- 89-106 kg: 96 mcg once weekly
- 107-136 kg: 120 mcg once weekly
- 137-160 kg: 150 mcg once weekly

Combination therapy with ribavirin: Initial: 1.5 mcg/kg/week

- <40 kg: 50 mcg once weekly (with ribavirin 800 mg/day)
- 40-50 kg: 64 mcg once weekly (with ribavirin 800 mg/day)
- 51-60 kg: 80 mcg once weekly (with ribavirin 800 mg/day)
- 61-65 kg: 96 mcg once weekly (with ribavirin 800 mg/day)
- 66-75 kg: 96 mcg once weekly (with ribavirin 1000 mg/day)
- 76-85 kg: 120 mcg once weekly (with ribavirin 1000 mg/day)
- 86-105 kg: 150 mcg once weekly (with ribavirin 1200 mg/day)
- >105 kg: 150 mcg once weekly (with ribavirin 1400 mg/day)

Advanced melanoma (unlabeled use): 6 mcg/kg weekly for 8 weeks, followed by 3 mcg/kg weekly for a total of 5 years (Eggermont, 2008).

Dosing: ElderlyMay require dosage reduction based upon renal dysfunction, but no established guidelines are available.

Dosing: Pediatric**Chronic hepatitis C:** Children ≥3 years: SubQ: Combination therapy with ribavirin: 60 mcg/m^2 once weekly (in combination with ribavirin 15 mg/kg/day in 2 divided doses); **Note:** Children who reach their 18th birthday during treatment should remain on the pediatric regimen. Discontinue combination therapy at 12 weeks if HCV-RNA decreases <2 $\log_{10}$ (compared to pretreatment) or if detectable HCV-RNA at 24 weeks.

Dosing: Renal Impairment
Peginterferon alfa-2b monotherapy:

Cl_{cr} 30-50 mL/minute: Reduce dose by 25%

Cl_{cr} 10-29 mL/minute: Reduce dose by 50%

Hemodialysis: Reduce dose by 50%

Discontinue use if renal function declines during treatment.

Peginterferon alfa-2b combination with ribavirin:

Children: Serum creatinine >2 mg/dL: Discontinue treatment.

Adults: Cl_{cr} <50 mL/minute: Combination therapy with ribavirin is not recommended.

Dosing: Hepatic ImpairmentContraindicated in decompensated liver disease

Dosing: Adjustment for ToxicityFor serious adverse reaction during treatment, modify dosage or discontinue; discontinue for persistent serious adverse reaction:

Dosage adjustment for depression (severity based upon DSM-IV criteria):

Mild depression: No dosage adjustment required; evaluate once weekly by visit/phone call. If depression remains stable, continue weekly visits. If depression improves, resume normal visit schedule.

Moderate depression: Adults: Decrease peginterferon alfa-2b dose by 50%; Children: Decrease peginterferon alfa-2b dose to 40 mcg/m^2/week, may further decrease to 20 mcg/m^2/week if needed. Evaluate once weekly with an office visit at least every other week. If depression remains stable, consider psychiatric evaluation and continue with reduced dosing. If symptoms improve and remain stable for 4 weeks, resume normal visit schedule; continue reduced dosing or return to normal dose.

Severe depression: Discontinue peginterferon alfa-2b and ribavirin permanently. Obtain immediate psychiatric consultation.

Dosage adjustment in hematologic toxicity:

Children:

Hemoglobin decrease ≥2 g/dL in any 4-week period in patients with pre-existing cardiac disease: Monitor and evaluate weekly.

Hemoglobin <10 g/dL: Decrease ribavirin dose to 12 mg/kg/day; may further reduce to 8 mg/kg/day.

WBC <1.5 x 10^9/L, neutrophils <0.75 x 10^9/L, or platelets <70 x 10^9/L: Reduce peginterferon alfa-2b dose to 40 mcg/m^2/week; may further reduce to 20 mcg/m^2/week.

Hemoglobin <8.5 g/dL, WBC <1.0 x 10^9/L, neutrophils <0.5 x 10^9/L, or platelets <50 x 10^9/L: Permanently discontinue peginterferon alfa-2b and ribavirin.

Adults:

Hemoglobin decrease >2 g/dL in any 4-week period and stable cardiac disease: Decrease peginterferon alfa-2b dose by 50%; decrease ribavirin dose by 200 mg/day. Hemoglobin <12 g/dL after dose reductions: Permanently discontinue both peginterferon alfa-2b and ribavirin.

Hemoglobin <10 g/dL in patients with cardiac disease: Reduce peginterferon alfa-2b dose by 50%; decrease ribavirin dose by 200 mg/day.

WBC <1.5 x 10^9/L, neutrophils <0.75 x 10^9/L, or platelets <80 x 10^9/L: Reduce peginterferon alfa-2b dose by 50%.

Hemoglobin <8.5 g/dL, WBC <1.0 x 10^9/L, neutrophils <0.5 x 10^9/L, or platelets <50 x 10^9/L: Permanently discontinue peginterferon alfa-2b and ribavirin.

Administration: OtherFor SubQ administration; rotate injection site; thigh, outer surface of upper arm, and abdomen are preferred injection sites; do not inject near navel or waistline; patients who are thin should only use thigh or upper arm. Do not inject into bruised, infected, irritated, red, or scarred skin.

StoragePrior to reconstitution, store Redipen™ at 2°C to 8°C (36°F to 46°F). Store vials at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Once reconstituted each product should be used immediately or may be stored for ≤24 hours at 2°C to 8°C (36°F to 46°F); do not freeze. Products do not contain preservative.

Reconstitution

Redipen™: Hold cartridge upright and press the two halves together until there is a "click". Gently invert to mix; do not shake.

Vial: Add 0.7 mL of sterile water for injection, USP (supplied diluent) to the vial. Gently swirl. Do not re-enter vial after dose removed. Discard unused portion.

CompatibilityDo not mix with any other medicines.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity (including urticaria, angioedema, bronchoconstriction, anaphylaxis, Stevens Johnson syndrome and toxic epidermal necrolysis) to interferons, or any component of the formulation; autoimmune hepatitis; decompensated liver disease (Child-Pugh score >6, classes B and C) in cirrhotic chronic hepatitis C (prior to or during treatment)

Combination therapy with peginterferon alfa-2b and ribavirin is also contraindicated in pregnancy, women who may become pregnant, males with pregnant partners; hemoglobinopathies (eg, thalassemia major, sickle-cell anemia); renal dysfunction (Cl_{cr} <50 mL/minute)

Warnings/Precautions

Boxed warnings:

- Autoimmune disease: See "Disease-related concerns" below.
- Combination therapy with ribavirin: See "Concurrent drug therapy issues" below.
- Infectious disorders: See "Disease-related concerns" below.
- Ischemic disorders: See "Disease-related concerns" below.
- Neuropsychiatric disorders: See "Concerns related to adverse effects" below.
- Pregnancy: See "Special populations" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Causes bone marrow suppression, including potentially severe cytopenias; alfa interferons may (rarely) cause aplastic anemia. Use with caution in patients who are chronically immunosuppressed, with low peripheral blood counts or myelosuppression, including concurrent use of myelosuppressive therapy. Dosage modification may be necessary for hematologic toxicity. Combination therapy with ribavirin may potentiate the neutropenic effects of alfa interferons. When used in combination with ribavirin, an increased incidence of anemia was observed when using ribavirin weight-based dosing, as compared to flat-dose ribavirin.
- Colitis: Ulcerative or hemorrhagic/ischemic colitis has been observed with alfa interferons; discontinue therapy if signs of colitis (abdominal pain, bloody diarrhea, fever) develop.
- Dental/periodontal disorders: Have been reported with combination therapy; dry mouth may affect teeth and mucous membranes. Instruct patients to brush teeth twice daily; encourage regular dental exams.
- Hypersensitivity: Acute hypersensitivity reactions and cutaneous reactions have been reported (rarely) with alfa interferons; prompt discontinuation is recommended. Transient rashes do not require interruption of therapy.
- Hypertriglyceridemia: Has been reported; monitor; discontinue if severe (triglycerides >1000 mg/dL), particularly if combined with symptoms of pancreatitis.
- Neuropsychiatric disorders: **[U.S. Boxed Warning]: May cause or aggravate severe neuropsychiatric adverse events in patients with and without a history of psychiatric disorder;** addiction relapse, aggression, depression, homicidal ideation and suicidal behavior/ideation have been observed with peginterferon alfa-2b; bipolar disorder, hallucinations, mania, and psychosis have been observed with other alfa interferons. Use with extreme caution in patients with a history of psychiatric disorders, including depression. Monitor all patients for evidence of depression; patients who develop psychiatric disorders should be monitored during and for 6 months after completion of therapy; discontinue treatment if psychiatric symptoms persist, worsen or if suicidal behavior develops. Higher doses may be associated with the development of encephalopathy (higher risk in elderly patients).
- Ophthalmic effects: Ophthalmologic disorders (including decreased/loss of vision, macular edema, retinal hemorrhages, optic neuritis, papilledema, cotton wool spots, and retinal artery or vein thrombosis) have occurred with peginterferon alfa-2b and/or with other alfa interferons. Prior to start of therapy, ophthalmic exams are recommended for all patients; patients with diabetic or hypertensive retinopathy should have periodic ophthalmic exams during treatment. Discontinue treatment with new or worsening ophthalmic disorder.
- Pancreatitis: Pancreatitis has been observed with alfa interferon therapy; discontinue therapy if known or suspected pancreatitis develops.
- Pulmonary effects: May cause or aggravate dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, and sarcoidosis which may result in respiratory failure; may recur upon rechallenge with treatment; monitor closely.

Disease-related concerns:

- Autoimmune disease: **[U.S. Boxed Warning]: May cause or exacerbate autoimmune disorders; monitor closely; discontinue treatment in patients with worsening or persistently severe signs/symptoms of autoimmune disease.** Thyroiditis, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, rheumatoid arthritis, interstitial nephritis, systemic lupus erythematosus, and psoriasis have been reported with therapy; use with caution in patients with autoimmune disorders.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease or a history of cardiovascular disease; hypotension, arrhythmia, tachycardia, cardiomyopathy, angina pectoris and MI have been observed with treatment. Patients with pre-existing cardiac abnormalities should have baseline ECGs prior to combination treatment with ribavirin; patients with a history of significant or unstable cardiac disease should not receive combination treatment with ribavirin.
- Diabetes: Diabetes mellitus and hyperglycemia have been reported; discontinue if diabetes cannot be effectively managed with medication. Use caution in patients with a history of diabetes mellitus, particularly if prone to DKA.

- Hepatic effects: Discontinue treatment immediately with hepatic decompensation (Child Pugh score >6). Patients with chronic hepatitis C (CHC) with cirrhosis and patients coinfected with human immunodeficiency virus (HIV) receiving highly-active antiretroviral therapy (HAART) are at increased risk for hepatic decompensation; monitor closely. A transient increase in ALT (2-5 times above baseline) which is not associated with liver dysfunction may occur with peginterferon alfa-2b use; may continue treatment with close monitoring.

- Infectious disorders: **[U.S. Boxed Warning]: May cause or aggravate infectious disorders; monitor closely; discontinue treatment in patients with worsening or persistently severe signs/symptoms of infectious disorders.** Interferon therapy is commonly associated with flu-like symptoms, including fever; rule out other causes/infection with persistent or high fever.

- Ischemic disorders: **[U.S. Boxed Warning]: May cause or aggravate ischemic disorders and hemorrhagic cerebrovascular events; monitor closely; discontinue treatment in patients with worsening or persistent ischemia** (including radiographic changes or worsening hepatic function). Has been reported in patients without risk factors for stroke.

- Renal impairment: Use with caution in patients with renal impairment (Cl_{cr} <50 mL/minute); monitor closely; dosage adjustments are recommended with monotherapy in patients with moderate-to-severe impairment. Do not use combination therapy with ribavirin in adults with renal dysfunction (Cl_{cr} <50 mL/minute); discontinue if serum creatinine >2 mg/dL in children. Serum creatinine increases have been reported in patients with renal insufficiency.

- Thyroid disorders: Use with caution in patients with thyroid disorders; may cause or aggravate hyper- or hypothyroidism. Discontinue use in patients with thyroid disease who cannot be controlled with medication.

Concurrent drug therapy issues:

- Combination therapy with ribavirin: **[U.S. Boxed Warning]: Combination treatment with ribavirin may cause birth defects and/or fetal mortality; hemolytic anemia (which may worsen cardiac disease), genotoxicity, mutagenicity, and may possibly be carcinogenic.**

Special populations:

- Elderly: Use with caution in the elderly; the potential adverse effects may be more pronounced in the elderly.

- Pediatrics: Growth velocity (height and weight) was decreased in children on combination treatment, particularly during the first 6 months of treatment. Safety and efficacy have not been established in children <3 years of age.

- Pregnancy: **[U.S. Boxed Warning]: Combination therapy with ribavirin may cause birth defects; avoid pregnancy in females and female partners of male patients.** Combination therapy with ribavirin is contraindicated in pregnancy.

Dosage form specific issues:

- Product variability: **Due to differences in dosage, patients should not change brands of interferon.**

Other warnings/precautions:

- Appropriate use: Combination therapy with ribavirin is preferred over monotherapy for the treatment of chronic hepatitis C. Safety and efficacy have not been established in patients who have failed other alfa interferon therapy, received organ transplants, coinfected with HIV or hepatitis B, or received treatment for >1 year.

Geriatric Considerations May require dosage reduction based upon renal dysfunction, but no established guidelines are available. Geriatric patients often have Cl_{cr} <50 mL/minute, as well as, many diseases that put them at risk for adverse effects with this agent. Calculation and measuring creatinine clearance must be done prior to initiating this drug.

Pregnancy Risk Factor C / X in combination with ribavirin

Pregnancy Considerations Reproduction studies with pegylated interferon alfa have not been conducted. Animal studies with nonpegylated interferon alfa-2b have demonstrated abortifacient effects. Disruption of the normal menstrual cycle was also observed in animal studies; therefore, the manufacturer recommends that reliable contraception is used in women of childbearing potential. Alfa interferon is endogenous to normal amniotic fluid. *In vitro* administration studies have reported that when administered to the mother, it does not cross the placenta. Case reports of use in pregnant women are limited. The Perinatal HIV Guidelines Working Group does not recommend that peginterferon-alfa be used during pregnancy. Peginterferon alfa-2b monotherapy should only be used in pregnancy when the potential benefit to the mother justifies the possible risk to the fetus. **[U.S. Boxed Warning]: Combination therapy with ribavirin may cause birth defects; avoid pregnancy in females and female partners of male patients;** combination therapy with ribavirin is contraindicated in pregnancy. A pregnancy registry has been established for women inadvertently exposed to ribavirin while pregnant (800-593-2214).

Lactation Excretion in breast milk unknown/not recommended

Breast-Feeding Considerations Breast milk samples obtained from a lactating mother prior to and after administration of interferon alfa-2b showed that interferon alfa is present in breast milk and administration of the medication did not significantly affect endogenous levels. The AAP considers interferon alfa to be “usually compatible with breast-feeding.” Breast-feeding is not linked to the spread of hepatitis C virus; however, if nipples are cracked or bleeding, breast-feeding is not recommended. Mothers coinfected with HIV are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse Reactions **Note:** Percentages reported for adults receiving monotherapy unless noted:

>10%:

Central nervous system: Headache (56%), fatigue (52%), depression (16% to 29%; may be severe), anxiety/emotional liability/irritability (28%), insomnia (23%), fever (22%), dizziness (12%)

Dermatologic: Alopecia (22%), pruritus (12%), dry skin (11%)

Gastrointestinal: Nausea (26%), anorexia (20%), diarrhea (18%), abdominal pain (8% to 15%), weight loss (11%)

Hematologic: Neutropenia (6% to 70%; grade 4: 1%), thrombocytopenia (7% to 20%; grades 3/4: <4%), anemia (in combination with ribavirin: 12% to 47%)

Local: Injection site inflammation/reaction (23% to 47%)

Neuromuscular & skeletal: Myalgia (54%), weakness (52%), musculoskeletal pain (28%), arthralgia (23%), rigors (23%)

Miscellaneous: Viral infection (11%)

>1% to 10%:

Cardiovascular: Chest pain (6%), flushing (6%)

Central nervous system: Concentration impaired (10%), malaise (7%), nervousness (4%), agitation (2%), suicidal behavior (ideation/attempt/suicide ≤2%)

Dermatologic: Rash (6%)

Endocrine & metabolic: Hypothyroidism (5%), menstrual disorder (4%), hyperthyroidism (3%)

Gastrointestinal: Vomiting (7%), dyspepsia (6%), xerostomia (6%), constipation (1%)

Hepatic: Transaminases increased (10%; transient), hepatomegaly (6%)

Local: Injection site pain (2% to 3%)

Ocular: Conjunctivitis (4%), blurred vision (2%)

Respiratory: Pharyngitis (10%), cough (8%), sinusitis (7%), dyspnea (4%), rhinitis (2%)

Miscellaneous: Diaphoresis (6%), neutralizing antibodies (2%)

≤1%, postmarketing, and/or case reports (limited to important or life-threatening): Abscess, addiction (drug) relapse, aggressive behavior, anaphylaxis, angina, angioedema, aphthous stomatitis, aplastic anemia, arrhythmia, autoimmune thrombocytopenia (with or without purpura), bronchiolitis obliterans, bronchoconstriction, cardiomyopathy, cellulitis, cerebral hemorrhage, cerebral ischemia, cotton wool spots, cytopenia, diabetes mellitus, drug overdose, emphysema, encephalopathy, erythema multiforme, fungal infection, gastroenteritis, gout, hallucinations, hearing impairment/loss, hemorrhagic colitis, homicidal ideation, hyperglycemia, hypersensitivity reactions, hypertriglyceridemia, hypotension, injection site necrosis, interstitial nephritis, interstitial pneumonia, ischemic colitis, leukopenia, loss of consciousness, lupus-like syndrome, macular edema, memory loss, MI, migraine, myositis, nerve palsy (facial/oculomotor), optic neuritis, pancreatitis, papilledema, pericardial effusion, peripheral neuropathy, phototoxicity, pleural effusion, pneumonia, pneumonitis, polyneuropathy, psoriasis, psychosis, pulmonary infiltrates, pure red cell aplasia, renal insufficiency, renal failure, retinal artery or vein thrombosis, retinal hemorrhage, retinal ischemia, rhabdomyolysis, rheumatoid arthritis, sarcoidosis, seizure, sepsis, serum creatinine increased, Stevens-Johnson syndrome, supraventricular arrhythmia, tachycardia, thrombotic thrombocytopenic purpura, thyroiditis, toxic epidermal necrolysis, transient ischemic attack, ulcerative colitis, urticaria, vasculitis, vertigo, vision decrease/loss, visual acuity decreased

Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Inhibits** CYP1A2 (weak)
Drug Interactions

Aldesleukin: Interferons (Alfa) may enhance the adverse/toxic effect of Aldesleukin. In particular, risks of myocardial and renal toxicity may be increased by this combination. *Risk D: Consider therapy modification*

Ribavirin: Interferons (Alfa) may enhance the adverse/toxic effect of Ribavirin. Hemolytic anemia has been observed. *Risk C: Monitor therapy*

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid use in patients with hepatitis C virus.
Monitoring ParametersBaseline and periodic TSH, hematology (including CBC with differential, platelets), chemistry (including LFTs) testing, renal function, triglycerides. Evaluate for depression and other psychiatric symptoms before and after initiation of therapy; baseline ophthalmic eye examination; periodic ophthalmic exam in patients with diabetic or hypertensive retinopathy; baseline echocardiogram in patients with cardiac disease; serum HCV RNA levels, serum glucose or Hb A_{1c} (for patients with diabetes mellitus).

In combination therapy with ribavirin, pregnancy tests (for women of childbearing age who are receiving treatment or who have male partners who are receiving treatment), continue monthly up to 6 months after discontinuation of therapy.

Reference Range

Early viral response (EVR): >2 log decrease in HCV RNA after 12 weeks of treatment

End of treatment response (ETR): Absence of detectable HCV RNA at end of the recommended treatment period

Sustained treatment response (STR): Absence of HCV RNA in the serum 6 months following completion of full treatment course

Monitoring: Lab TestsBaseline and periodic TSH, hematology (including CBC with differential, platelets). chemistry (including LFTs) testing, renal function, triglycerides; serum HCV RNA levels, serum glucose or Hb A_{1c} (for patients with diabetes mellitus)

In combination therapy with ribavirin, pregnancy tests (for women of childbearing age who are receiving treatment or who have male partners who are receiving treatment), continue monthly up to 6 months after discontinuation of therapy.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

PegIntron™: 50 mcg, 80 mcg, 120 mcg, 150 mcg [contains polysorbate 80 and sucrose]

PegIntron™ Redipen®: 50 mcg, 80 mcg, 120 mcg, 150 mcg [contains polysorbate 80 and sucrose]

Generic AvailableNo
ManufacturerSchering-Plough
Pricing: U.S. (www.drugstore.com)

Kit (Peg-Intron)

50 mcg/0.5 mL (1): $443.95

80 mcg/0.5 mL (1): $465.70

120 mcg/0.5 mL (1): $489.44

150 mcg/0.5 mL (1): $513.92

Kit (Peg-Intron Redipen)

80 mcg/0.5 mL (1): $465.54

120 mcg/0.5 mL (1): $483.37

150 mcg/0.5 mL (1): $504.05

Kit (Peg-Intron Redipen Pak 4)

50 mcg/0.5 mL (4): $1747.09

Mechanism of ActionAlpha interferons are a family of proteins, produced by nucleated cells, that have antiviral, antiproliferative, and immune-regulating activity. There are 16 known subtypes of alpha interferons. Interferons interact with cells through high affinity cell surface receptors. Following activation, multiple effects can be detected including induction of gene transcription. Inhibits cellular growth, alters the state of cellular differentiation, interferes with oncogene expression, alters cell surface antigen expression, increases phagocytic activity of macrophages, and augments cytotoxicity of lymphocytes for target cells.
Pharmacodynamics/Kinetics

Bioavailability: Increases with chronic dosing

Half-life elimination: ~40 hours (range: 22-60 hours)

Time to peak: 15-44 hours

Excretion: Urine (30%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusSevere psychiatric adverse effects (including depression, suicidal ideation, and suicide attempt) may occur. May also cause sedation, anxiety, emotional lability, irritability, insomnia, dizziness, and impaired concentration.
Mental Health: Effects on Psychiatric TreatmentContraindicated in those with severe psychiatric disorder. Gastrointestinal side effects are common; use caution with SSRIs, valproic acid, and lithium. Flu-like symptoms are common; take this into consideration if also concerned about SSRI discontinuation syndrome. A case of agranulocytosis has been reported with concurrent use of clozapine; monitor.
Index TermsInterferon Alfa-2b (PEG Conjugate); Pegylated Interferon Alfa-2b
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International Brand NamesPEG-Intron (AT, AU, BE, BG, BR, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, HN, ID, IE, IL, IT, KP, MY, NI, NL, NO, NZ, PA, PE, PK, PT, RU, SE, SG, SV, TH, TR, VE); Pegintron (PL); Pegtron (MX); ViraFeronPEG (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Pegvisomant

Lexi-Drugs Online

English

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Special Alerts

Pegvisomant: Increased Risks of Hepatotoxicity - June 2008

Pfizer Canada, in conjunction with Health Canada, has issued a “Dear Healthcare Professional” letter regarding upcoming labeling changes for pegvisomant (Somavert®) concerning an increased risk of markedly elevated hepatic enzymes associated with its use in combination with a somatostatin analogue (octreotide acetate).

Elevated hepatic transaminase levels >10 times the upper limit of normal (ULN) have been reported in two postmarketing studies of patients receiving pegvisomant concomitantly with octreotide, and in some patients the changes were observed within 3 months of initiating therapy. Some of the affected patients had been receiving supratherapeutic doses of octreotide. In one of the studies, enzyme levels returned to normal upon discontinuation of therapy.

It is recommended that prior to initiating pegvisomant therapy, baseline levels of transaminases, total bilirubin (TBIL), and alkaline phosphatase be obtained and then routinely monitored during therapy. A comprehensive hepatic workup is recommended for any patient with elevated hepatic enzymes ≥3 times ULN during therapy. Therapy should be discontinued immediately if at any time a patient displays signs/symptoms of hepatitis or other hepatic injury (eg, jaundice, bilirubinuria). Discontinue therapy permanently if hepatic injury is confirmed.

Patients with enzyme levels ≥3 but <5 times ULN and without signs/symptoms of hepatic injury or an increase in serum TBIL may continue with therapy, but with more frequent (weekly) monitoring of hepatic function.

Patients with transaminase levels ≥5 times ULN or transaminase levels ≥3 times ULN associated with any increase in TBIL (with or without signs/symptoms of hepatitis or other hepatic injury) should discontinue pegvisomant therapy immediately. Cautious reinitiation of therapy with more frequent monitoring of hepatic function may be considered with normalization of hepatic enzymes and function.

Further information may be found at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2008/index-eng.php

Pronunciation(peg VI soe mant)

U.S. Brand NamesSomavert®

Canadian Brand NamesSomavert®

Pharmacologic CategoryGrowth Hormone Receptor Antagonist

Use: Labeled IndicationsTreatment of acromegaly in patients resistant to or unable to tolerate other therapies

Dosing: Adults**Acromegaly:** SubQ: Initial loading dose: 40 mg; maintenance dose: 10 mg once daily; doses may be adjusted by 5 mg increments in 4- to 6-week intervals based on IGF-I concentrations (maximum maintenance dose: 30 mg/day)

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic Impairment

At initiation of therapy:

Normal liver function test (LFT): Initiate therapy; monitor LFT monthly for first 6 months, quarterly for next 6 months, then biannually the following year.

Baseline LFT elevated but ≤3 x ULN: May initiate therapy with monthly evaluation of LFT for 1 year then biannually the following year.

Baseline LFT >3 times ULN: Do not initiate treatment without comprehensive work-up to determine cause; monitor closely if treatment is started.

With ongoing therapy:

LFT ≥3 x but <5 x ULN without signs/symptoms of hepatitis, hepatic injury, or increase in total bilirubin: Continue treatment, but monitor LFT weekly for further increases; perform comprehensive hepatic work-up to rule out alternative cause of hepatic dysfunction

LFT ≥5 x ULN or transaminase ≥3 x ULN associated with any increase in total bilirubin: Discontinue immediately and perform comprehensive hepatic work-up. If LFTs return to normal, may cautiously consider restarting therapy with frequent LFT monitoring.

Signs or symptoms of hepatitis or hepatic injury: Discontinue therapy immediately and perform comprehensive hepatic work-up; discontinue permanently if liver injury is confirmed.

Administration: OtherFor SubQ administration only; to minimize the risk for lipohypertrophy, rotate injection site daily; may administer in upper arm, thigh, abdomen, or buttocks; do not rub injection site. The manufacturer recommends the initial dose be administered under the supervision of prescribing healthcare provider.

StorageStore intact vials under refrigeration at 2°C to 8°C (36°F to 46°F); protect from freezing. Following reconstitution, use within 6 hours. Do not use solution if cloudy.

ReconstitutionReconstitute each vial with 1 mL SWFI. Aim diluent along glass wall of vial. Gently roll in order to dissolve powder; do not shake.

ContraindicationsHypersensitivity to pegvisomant, polyethylene glycol, latex, or any other component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Growth hormone (GH) deficiency: Use may be associated with functional GH deficiency in spite of elevated serum GH levels; monitor closely for signs/symptoms of GH deficiency (eg, decreased muscle or bone mass, decreased strength); dose adjustments may be needed to maintain insulin-like growth factor 1 (IGF-1) within age-adjusted normal levels.

- Hepatic effects: May increase liver function tests; transient but marked elevations (≤15 x upper limit of normal [ULN]) in transaminase levels, usually without accompanying hyperbilirubinemia, have been reported with use; transaminase levels often normalized following interruption of therapy; use with caution in patients with hepatic impairment; monitor hepatic function periodically during therapy; discontinue use immediately with signs/symptoms of jaundice.

- Lipohypertrophy: May occur following administration; daily rotation of injection site may prevent or reduce incidence.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; may affect glucose metabolism; monitor closely; dosage adjustments of antidiabetic therapy may be necessary.

- Growth hormone (GH)-secreting tumors: Pegvisomant may expand GH-secreting tumors causing serious complications; carefully monitor patients with periodic imaging scans of the sella turcica.

- Renal impairment: Use in patients with renal impairment has not been studied.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific:

- Latex: Vial stopper contains latex

Other warnings/precautions:

- Administration: The manufacturer recommends the initial dose be administered under the supervision of prescribing healthcare provider.

- Monitoring: Interferes with commercially available GH assays; do not make dose adjustments based on serum GH concentrations reported from assays; use insulin-like growth factor I (IGF-I) levels to adjust therapy.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women; use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Pain (4% to 14%)

Gastrointestinal: Diarrhea (≤14%), nausea (≤14%)

Hepatic: Liver function tests abnormal (4% to 12%; >10 x ULN: 1%)

Local: Injection site reaction (4% to 11%)

Miscellaneous: Infection (≤23%), non-neutralizing anti-GH antibodies (17%; relevance unknown), flu-like syndrome (4% to 12%)

1% to 10%:

Cardiovascular: Hypertension (≤8%), chest pain (≤8%), peripheral edema (≤8%)

Central nervous system: Dizziness (4% to 8%)

Neuromuscular & skeletal: Back pain (≤8%), paresthesia (≤7%)

Respiratory: Sinusitis (≤8%)

Postmarketing and/or case reports: Alkaline phosphatase increased, hepatic transaminases increased ≤15 times ULN, lipohypertrophy, progressive tumor growth

Drug Interactions

Analgesics (Opioid): May diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Antidiabetic Agents: Pegvisomant may enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Somatostatin Analogs: May enhance the adverse/toxic effect of Pegvisomant. Specifically, this combination may increase the risk for significant elevations of liver enzymes. *Risk C: Monitor therapy*

Test InteractionsInterferes with measurement of serum GH concentrations by available GH assays; commercially available GH assays will overestimate true GH levels

Monitoring ParametersGH-secreting tumor size, serum glucose, signs and symptoms of growth hormone deficiency, serum IGF-I (every 4-6 weeks after initial dose and dosage change, every 6 months when normalized)

Liver function tests (ALT, AST, total bilirubin, and alkaline phosphatase levels):

- Baseline:
  - Normal: Monthly for first 6 months, quarterly for next 6 months, biannually for the next year
  - Elevated, but ≤3 x ULN: Monitor monthly for at least 1 year, then biannually the next year
  - >3 x ULN: Withhold treatment; perform comprehensive liver function evaluation (rule out cholelithiasis or choledocholithiasis); if appropriate for treatment, closely monitor hepatic function and clinical status.
- During therapy:
  - ≥3 x but <5 x ULN without signs/symptoms of hepatitis, hepatic injury or increase in total bilirubin: monitor weekly for further increases; perform comprehensive hepatic work-up
  - ≥5 x ULN or transaminase ≥3 x ULN associated with any increase in total bilirubin: Comprehensive hepatic work-up. If appropriate for treatment monitor closely

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, and herbal products patient may be taking. Closely assess results of all laboratory tests at beginning and periodically during therapy. **Note:** First dose should be administered under supervision of prescriber. Assess therapeutic effectiveness and adverse reactions. Teach patient proper use (storage, reconstitution, injection technique, site rotation, and disposal of syringes/needles), possible side effects/appropriate interventions, and adverse symptoms to report. Instruct patients with diabetes on need to monitor glucose levels regularly; dose adjustment of hypoglycemic agent may be needed.

Monitoring: Lab TestsSerum glucose, serum IGF-I (every 4-6 weeks after initial dose and dosage change, every 6 months when normalized)

Liver function tests (ALT, AST, total bilirubin, and alkaline phosphatase levels):

- Baseline:
  - Normal: Monthly for first 6 months, quarterly for next 6 months, biannually for the next year
  - Elevated, but ≤3 x ULN: Monitor monthly for at least 1 year, then biannually the next year
  - >3 x ULN: Withhold treatment; perform comprehensive liver function evaluation (rule out cholelithiasis or choledocholithiasis); if appropriate for treatment, closely monitor hepatic function and clinical status.
- During therapy:
  - ≥3 x but <5 x ULN without signs/symptoms of hepatitis, hepatic injury or increase in total bilirubin: monitor weekly for further increases; perform comprehensive hepatic work-up
  - ≥5 x ULN or transaminase ≥3 x ULN associated with any increase in total bilirubin: Comprehensive hepatic work-up. If appropriate for treatment monitor closely

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. This medication may only be administered by injection. If instructed in self-injection, follow instructions exactly. Report immediately any reaction at injection site (redness, swelling, itching). May cause diarrhea (buttermilk, boiled milk, or yogurt may help); nausea (frequent small meals and good mouth care may help); or signs of allergic response (chest pain, respiratory difficulty, skin rash). **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

- Somavert®: 10 mg, 15 mg, 20 mg [vial stopper contains latex; packaged with SWFI]

Generic AvailableNo

ManufacturerPharmacia

Mechanism of ActionAn analogue of human growth hormone, pegvisomant selectively binds to growth hormone (GH) receptors, blocking the binding of endogenous GH, leading to decreased serum concentrations of insulin-like growth factor-1 (IGF-I) and other GH-responsive proteins. Pegvisomant is made up of a recombinant DNA protein covalently bound to polyethylene glycol (PEG) polymers.

Pharmacodynamics/Kinetics

Absorption: SubQ: 57%

Distribution: 7 L

Half-life elimination: ~6 days

Time to peak, serum: 33-77 hours

Excretion: Urine (<1%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; use caution with SSRIs. Increased dose of pegvisomant may be needed in patients receiving opioids.

Index TermsB2036-PEG

International Brand NamesSomavert (AR, AT, BE, BG, BR, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, NL, NO, PE, PT, RU, SE, TR)

Pemetrexed (Bladder Cancer Regimen)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Bladder Cancer]

Regimen UseBladder cancer

Regimen

Pemetrexed: I.V.: 500 mg/m^2 infused over 10 minutes day 1

[total dose/cycle = 500 mg/m^2]

Repeat cycle every 21 days

References

Sweeney CJ, Roth BJ, Kabbinavar FF, et al, "Phase II Study of Pemetrexed for Second-Line Treatment of Transitional Cell Cancer of the Urothelium," *J Clin Oncol*, 2006, 24(21):3451-7.[PubMed 16849761]

Pemetrexed-Carboplatin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Malignant Pleural Mesothelioma

Regimen Use Malignant pleural mesothelioma

Index Terms Carboplatin-Pemetrexed

Regimen

Pemetrexed: I.V.: 500 mg/m^2 infused over 10 minutes day 1

> [total dose/cycle = 500 mg/m^2]

Carboplatin: I.V.: AUC 5 infused over 30 minutes day 1 (start 30 minutes after pemetrexed)

> [total dose/cycle = AUC = 5]

Repeat cycle every 21 days

References

Ceresoli GL, Zucali PA, Favaretto AG, et al, "Phase II Study of Pemetrexed Plus Carboplatin in Malignant Pleural Mesothelioma," *J Clin Oncol*, 2006, 24(9):1443-8.[PubMed 16549838]

Pemetrexed-Cisplatin (NSCLC)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Lung Cancer (Nonsmall Cell)]

Regimen UseLung cancer, nonsmall cell

Index TermsCisplatin-Pemetrexed (NSCLC)

Regimen

Pemetrexed: I.V.: 500 mg/m^2/dose day 1

[total dose/cycle = 500 mg/m^2]

Cisplatin: I.V.: 75 mg/m^2/dose day 1

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 21 days for up to 6 cycles

References

Scagliotti GV, Parikh P, von Pawel J, et al, "Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non-Small-Cell Lung Cancer," *J Clin Oncol*, 2008, 26(21):3543-51.[PubMed 18506025]

Pemetrexed

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(pem e TREKS ed)

U.S. Brand NamesAlimta®

Canadian Brand NamesAlimta®

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite; Antineoplastic Agent, Antimetabolite (Antifolate)

Use: Labeled IndicationsTreatment of malignant pleural mesothelioma; treatment of locally advanced or metastatic nonsquamous nonsmall cell lung cancer (NSCLC)

Use: Unlabeled/InvestigationalTreatment of bladder cancer

Dosing: AdultsDetails concerning dosing in combination regimens should also be consulted. **Note:** Start vitamin supplements 1 week before initial dose of pemetrexed: Folic acid 350-1000 mcg/day orally (must be taken at least 5 out of 7 days prior to treatment initiation; continue for 21 days after last pemetrexed dose) and vitamin B_{12} 1000 mcg I.M. during the week prior to treatment initiation and then every 3 cycles. Give dexamethasone 4 mg orally twice daily for 3 days, beginning the day before treatment to minimize cutaneous reactions. New treatment cycles should not begin unless ANC ≥1500/mm^3, platelets ≥100,000/mm^3, and Cl_{cr} ≥45 mL/minute.

Nonsmall cell lung cancer: I.V: 500 mg/m^2 on day 1 of each 21-day cycle (in combination with cisplatin for initial treatment; monotherapy in patients who have received prior treatment)

Malignant pleural mesothelioma: I.V.: 500 mg/m^2 on day 1 of each 21-day cycle (in combination with cisplatin)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} ≥45 mL/minute: No dosage adjustment required.

Cl_{cr} <45 mL/minute: No dosage adjustment guidelines are available; manufacturer recommends not using the drug.

Dosing: Hepatic ImpairmentGrade 4 transaminase elevation (>20 times ULN): Reduce dose to 75% of previous dose

Dosing: Adjustment for Toxicity

Toxicity: Discontinue if patient develops grade 3 or 4 toxicity after two dose reductions (except grade 3 transaminase elevations) or immediately if grade 3 or 4 neurotoxicity develops

Hematologic toxicity: Upon recovery, reinitiate therapy

Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3: Reduce dose to 75% of previous dose of pemetrexed (and cisplatin)

Nadir platelets <50,000/mm^3**without bleeding** (regardless of nadir ANC): Reduce dose to 75% of previous dose of pemetrexed (and cisplatin)

Nadir platelets <50,000/mm^3**with bleeding** (regardless of nadir ANC): Reduce dose to 50% of previous dose of pemetrexed (and cisplatin)

Nonhematologic toxicity (excluding neurotoxicity or grade 3 transaminase elevations): Withhold treatment until recovery to baseline; upon recovery, reinitiate therapy as follows:

Grade 3 or 4 toxicity (excluding mucositis or grade 3 transaminase elevations): Reduce dose to 75% of previous dose of pemetrexed (and cisplatin)

Grade 3 or 4 diarrhea or any diarrhea requiring hospitalization: Reduce dose to 75% of previous dose of pemetrexed (and cisplatin)

Grade 3 or 4 mucositis: Reduce pemetrexed dose to 50% of previous dose (continue cisplatin at 100% of previous dose)

Neurotoxicity:

Common Toxicity Criteria (CTC) Grade 0-1: Continue at 100% of previous dose of pemetrexed (and cisplatin)

CTC Grade 2: Continue pemetrexed at previous dose; reduce cisplatin dose to 50% of previous dose

Dosing: Combination Regimens

Bladder cancer: Pemetrexed (Bladder Cancer Regimen)

Lung cancer (nonsmall cell): Pemetrexed-Cisplatin (NSCLC)

Malignant pleural mesothelioma:

Cisplatin-Pemetrexed (Mesothelioma)

Pemetrexed-Carboplatin

Calculations

- ANC: Absolute Neutrophil Count
- Body Surface Area: Adults
- Creatinine Clearance: Adults

Administration: I.V.Infuse over 10 minutes.

Administration: I.V. DetailpH: 6.6-7.8

Dietary ConsiderationsInitiate folic acid supplementation 1 week before first dose of pemetrexed, continue for full course of therapy, and for 21 days after last dose. Institute vitamin B_{12} 1 week before the first dose; administer every 9 weeks thereafter.

StorageStore intact vials at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Reconstituted and infusion solutions are stable for 24 hours when refrigerated at 2°C to 8°C (36°F to 46°F) or stored at room temperature of 15°C to 30°C (59°F to 86°F). Concentrations at 25 mg/mL are stable in polypropylene syringes for 2 days at room temperature (23°C) (Zhang, 2005).

ReconstitutionReconstitute with NS (preservative free); add 4.2 mL to the 100 mg vial and 20 mL to the 500 mg vial, resulting in a 25 mg/mL concentration. Gently swirl. Solution may be colorless to green-yellow. Further dilute in 100 mL NS for infusion. Use appropriate precautions for handling and disposal.

CompatibilityStable in NS; physically **incompatible** with calcium-containing products, including Ringer's and lactated Ringer's injection.

Y-site administration: Compatible: Acyclovir, amifostine, amikacin sulfate, aminophylline, ampicillin sodium, ampicillin sodium-sulbactam sodium, aztreonam, bumetanide, buprenorphine hydrochloride, butorphanol tartrate, carboplatin, ceftizoxime sodium, ceftriaxone sodium, cefuroxime sodium, cimetidine hydrochloride, cisplatin, clindamycin phosphate, co-trimoxazole, cyclophosphamide, cytarabine, dexamethasone sodium phosphate, dexrazoxane, diphenhydramine hydrochloride, docetaxel, dopamine hydrochloride, enalaprilat, famotidine, fluconazole, fluorouracil, ganciclovir sodium, granisetron hydrochloride, haloperidol lactate, heparin sodium, hydromorphone hydrochloride, hydroxyzine hydrochloride, ifosfamide, leucovorin calcium, lorazepam, mannitol, meperidine hydrochloride, mesna, methylprednisolone sodium succinate, metoclopramide hydrochloride, morphine sulfate, paclitaxel, potassium chloride, promethazine hydrochloride, ranitidine hydrochloride, sodium bicarbonate, ticarcillin disodium, ticarcillin disodium-clavulanate potassium, vancomycin hydrochloride, vinblastine sulfate, vincristine sulfate, zidovudine. **Incompatible:** Amphotericin B, calcium gluconate, cefazolin sodium, cefotaxime sodium, cefotetan disodium, cefoxitin sodium, ceftazidime, chlorpromazine hydrochloride, ciprofloxacin, dobutamine hydrochloride, doxorubicin hydrochloride, doxycycline hyclate, droperidol, gemcitabine hydrochloride, gentamicin sulfate, irinotecan hydrochloride, metronidazole, minocycline hydrochloride, mitoxantrone hydrochloride, nalbuphine hydrochloride, ondansetron hydrochloride, prochlorperazine edisylate, tobramycin sulfate, topotecan hydrochloride.

ContraindicationsSevere hypersensitivity to pemetrexed or any component of the formulation

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Use may cause anemia, neutropenia, thrombocytopenia and/or pancytopenia; may require dose reductions in subsequent cycles. Prophylactic folic acid and vitamin B_{12} supplements are necessary to reduce hematologic toxicity and should be started 1 week before the first dose of pemetrexed.

- Cutaneous reactions: May occur; pretreatment with corticosteroids reduces the incidence and severity of cutaneous reactions.

- Gastrointestinal toxicity: May occur; prophylactic folic acid and vitamin B_{12} supplements are necessary to reduce gastrointestinal toxicity and should be started 1 week before the first dose of pemetrexed.

Disease-related concerns:

- Ascites/pleural effusions: Effects of third space fluid on drug disposition unknown; consider draining effusion(s) prior to treatment.

- Hepatic impairment: Use caution with hepatic impairment not due to metastases; may require dose adjustment.

- Renal impairment: Decreased renal function results in increased toxicity. The manufacturer does not recommend use if Cl_{cr} <45 mL/minute. Use caution in patients receiving concurrent nephrotoxins; may result in delayed pemetrexed clearance.

Concurrent drug therapy issues:

- NSAIDs: NSAIDs may reduce the clearance of pemetrexed. Patients with Cl_{cr} 45-79 mL/minute should avoid NSAIDs with short elimination half-lives (eg, ibuprofen, indomethacin, ketoprofen, ketorolac) for 2 days before, the day of, and 2 days following a dose of pemetrexed. All patients should avoid NSAIDs with long half-lives (eg, nabumetone, naproxen, oxaprozin, piroxicam) for 5 days before, the day of, and 2 days following a dose of pemetrexed.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAdverse events were observed in animal reproduction studies. There are no adequate and well-controlled trials in pregnant women. Women of childbearing potential should avoid becoming pregnant during treatment.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.
Adverse Reactions**Note:** Reported for monotherapy in patients who received folate and B_{12} supplementation.

>10%:

Central nervous system: Fatigue (34%; dose-limiting)

Dermatologic: Rash/desquamation (14%)

Gastrointestinal: Nausea (31%), anorexia (22%), vomiting (16%), stomatitis (15%), diarrhea (13%)

Hematologic: Anemia (19%; grades 3/4: 4%), leukopenia (12%; grades 3/4: 4%), neutropenia (11%; grades 3/4: 5%; nadir: 8-10 days; recovery: 12-17 days; dose-limiting)

Respiratory: Pharyngitis (15%)

1% to 10%:

Cardiovascular: Edema (5%)

Central nervous system: Fever (8%)

Dermatologic: Pruritus (7%), alopecia (6%), erythema multiforme

Gastrointestinal: Constipation (6%), weight loss (1%), abdominal pain

Hematologic: Thrombocytopenia (8%; grades 3/4: 2%; dose-limiting), febrile neutropenia (grades 3/4: 2%)

Hepatic: ALT increased (8%; grades 3/4: 2%), AST increased (7%; grades 3/4: 1%)

Neuromuscular & skeletal: Neuropathy (sensory and motor)

Renal: Creatinine increased

Miscellaneous: Allergic reaction/hypersensitivity, infection

<1%, postmarketing, and/or case reports (mono- or combination therapy): Colitis, interstitial pneumonitis, pancytopenia, radiation recall (median onset: 6 days; range: 1-35 days), renal failure, supraventricular arrhythmia

Oncology: VesicantNo
Oncology: Emetic PotentialLow (10% to 30%)
Drug Interactions

NSAID (Nonselective): May decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsLower ANC nadirs occur in patients with elevated baseline cystathionine or homocysteine concentrations. Levels of these substances can be reduced by folic acid and vitamin B_{12} supplementation.
Monitoring ParametersCBC with differential and platelets (before each dose); serum creatinine, total bilirubin, ALT, AST (day 1 of each, or every other, cycle)
Nursing: Physical Assessment/MonitoringSee premedication requirements (eg, start folic acid and vitamin B_{12} one week before first dose of pemetrexed). Corticosteroids may be used to reduce cutaneous reactions. Assess potential for interactions with other pharmacological agents (eg, NSAIDs and other agents with nephrotoxic potential). Evaluate results of laboratory tests on a regular schedule and assess adverse response at frequent intervals during treatment (eg, chest pain, hypertension, CNS changes, GI upset [nausea, vomiting, diarrhea, constipation], anemia, neuropathy, rash, infection). Teach patient appropriate interventions to reduce side effects and adverse symptoms to report.
Monitoring: Lab TestsCBC with differential and platelets (before each dose); serum creatinine, total bilirubin, ALT, AST (day 1 of each, or every other, cycle)
Patient EducationThis medication is only administered intravenously. Report immediately any burning, pain, itching, or redness at infusion site or any sudden feelings of anxiety, difficulty breathing, chest or back pain. It is important that you maintain adequate hydration (2-3 L/day of fluids, unless instructed to restrict fluid intake) and adequate nutrition (frequent small meals may help). Maintain regularly scheduled dietary supplements (vitamin B_{12} and folic acid) as prescribed. May cause severe nausea, vomiting, constipation or diarrhea (small frequent meals, and good mouth care are important; if persistent, consult prescriber for medication); mouth sores (use soft toothbrush or cotton swabs for mouth care). Report promptly any chest pain, swelling of extremities or unusual weight gain; rash; tingling or loss of sensation in extremities; difficulty breathing; fever, chills; unusual or persistent fatigue, or any other unusual symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Alimta®: 100 mg, 500 mg

Generic AvailableNo
ManufacturerLilly
Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Alimta)

500 mg (1): $2644.11

Mechanism of ActionInhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT), and aminoimidazole carboxamide ribonucleotide formyltransferase (AICARFT), the enzymes involved in folate metabolism and DNA synthesis, resulting in inhibition of purine and thymidine nucleotide and protein synthesis.

Pharmacodynamics/Kinetics

Duration: V_{dss}: 16.1 L

Protein binding: ~73% to 81%

Metabolism: Minimal

Half-life elimination: Normal renal function: 3.5 hours; Cl_{cr} 40-59 mL/minute: 5.3-5.8 hours

Excretion: Urine (70% to 90% as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dysphagia, esophagitis, odynophagia, and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusFatigue and depression are common

Mental Health: Effects on Psychiatric TreatmentGastrointestinal side effects are common; these effects may be additive with concurrent use of SSRIs, acetylcholinesterase inhibitors, aripiprazole, or ziprasidone. Hematologic adverse effects are common; use caution with clozapine, carbamazepine, valproate, mirtazapine. Sedation is common; concurrent use with psychotropics may produce additive effects.

Index TermsLY231514; Multitargeted Antifolate; NSC-698037; Pemetrexed Disodium

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International Brand NamesAlimta (AR, AT, AU, BE, BG, BR, CH, CL, CN, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, MX, MY, NL, NO, PE, PH, PT, RU, SE, SG, TH, TR, TW)

Pemirolast

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(pe MIR oh last)
U.S. Brand NamesAlamast®
Canadian Brand NamesAlamast®
Pharmacologic CategoryMast Cell Stabilizer; Ophthalmic Agent, Miscellaneous
Use: Labeled IndicationsPrevention of itching of the eye due to allergic conjunctivitis
Dosing: Adults**Allergic conjunctivitis:** Ophthalmic: 1-2 drops instilled in affected eye(s) 4 times/day
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren >3 years: Refer to adult dosing.
StorageStore at room temperature of 15°C to 25°C (59°F to 77°F).
ContraindicationsHypersensitivity to pemirolast or any component of the formulation
Warnings/Precautions

Special populations:

- Contact lens wearers: Not for use to treat contact lens-related irritation. Do not wear soft contact lens if eyes are red. Contains benzalkonium chloride (a preservative in Alamast®) which may be absorbed by contact lenses; remove contact lens prior to administration and wait 10 minutes before reinserting.

- Pediatrics: Safety and efficacy have not been established in children <3 years of age.

Other warnings/precautions:

- Appropriate use: For ophthalmic use only; not for injection or oral use.

Pregnancy Risk FactorC
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Should only be used during pregnancy if the benefit outweighs the risk to the fetus.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%:

Central nervous system: Headache (10% to 25%)

Respiratory: Rhinitis (10% to 25%)

Miscellaneous: Cold/flu symptoms (10% to 25%)

<5%:

Central nervous system: Fever

Endocrine & metabolic: Dysmenorrhea

Neuromuscular & skeletal: Back pain

Ocular: Burning eyes, dry eyes, foreign body sensation, ocular discomfort

Respiratory: Bronchitis, cough, sinusitis, sneezing/nasal congestion

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic, as potassium: 0.1% (10 mL) [contains lauralkonium chloride]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Solution (Alamast)

0.1% (10): $97.52

Mechanism of ActionMast cell stabilizer that inhibits the *in vivo* type I immediate hypersensitivity reaction; in addition, inhibits chemotaxis of eosinophils into the ocular tissue and blocks their release of mediators; also reported to prevent calcium influx into mast cells following antigen stimulation
Pharmacodynamics/Kinetics

Onset of action: A few days

Peak effect: 4 weeks

Absorption: Systemic

Half-life elimination: 4.5 hours

Excretion: Urine (10% to 15%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesAlegysal (CL, ID, JP, PH, TW); Pemirox (HK, TH)

Penbutolol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Levatol® may be confused with Lipitor®

International issues:

Levatol® may be confused with Lovacol® which is a brand name for lovastatin in Chile, Finland, and France

Pronunciation(pen BYOO toe lole)
U.S. Brand NamesLevatol®
Canadian Brand NamesLevatol®
Pharmacologic CategoryBeta Blocker With Intrinsic Sympathomimetic Activity
Use: Labeled IndicationsTreatment of mild to moderate arterial hypertension
Dosing: Adults**Hypertension:** Oral: Initial: 20 mg once daily, full effect of a 20 or 40 mg dose is seen by the end of a 2-week period, doses of 40-80 mg have been tolerated but have shown little additional antihypertensive effects; usual dose range (JNC 7): 10-40 mg once daily
Dosing: ElderlyRefer to adult dosing.
ContraindicationsHypersensitivity to penbutolol or any component of the formulation; uncompensated congestive heart failure; cardiogenic shock; bradycardia or heart block (except in patients with a functioning artificial pacemaker); sinus node dysfunction; asthma; bronchospastic disease; COPD; pulmonary edema; pregnancy (2nd and 3rd trimester)
Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Concerns related to adverse events:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.
- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.
- Heart failure (HF): Use with caution in patients with compensated heart failure and monitor for a worsening of the condition (beta-blockers with intrinsic sympathomimetic activity have not been demonstrated to be of value in HF).
- Myasthenia gravis: Use with caution in patients with myasthenia gravis.
- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).
- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.
- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents which decrease myocardial function.
- Calcium channel blockers: Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.

Geriatric ConsiderationsDue to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (ie, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20% to 50% in elderly populations. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults.

Pregnancy Risk FactorC (manufacturer); D (2nd and 3rd trimester - expert analysis)

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsIt is recommended that the infant be monitored for signs or symptoms of beta-blockade (hypotension, bradycardia, etc) with long-term use.

Adverse Reactions

1% to 10%:

Cardiovascular: CHF, arrhythmia

Central nervous system: Mental depression, headache, dizziness, fatigue

Gastrointestinal: Nausea, diarrhea, dyspepsia

Neuromuscular & skeletal: Arthralgia

<1% (Limited to important or life-threatening): AV block, bradycardia, bronchospasm, cold extremities, confusion, cough, edema, hypoglycemia, hypotension, insomnia, lethargy, ischemic colitis, mesenteric arterial thrombosis, nightmares, purpura, Raynaud's phenomena, thrombocytopenia

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as sulfate: 20 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Levatol)

20 mg (30): $67.03

Mechanism of ActionBlocks both beta$_1$- and beta$_2$-receptors and has mild intrinsic sympathomimetic activity; has negative inotropic and chronotropic effects and can significantly slow AV nodal conduction

Pharmacodynamics/Kinetics

Absorption: ~100%

Protein binding: 80% to 98%

Metabolism: Extensively hepatic (oxidation and conjugation)

Bioavailability: ~100%

Half-life elimination: 5 hours

Excretion: Urine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Penbutolol is a nonselective beta-blocker and may enhance the pressor response to epinephrine, resulting in hypertension and bradycardia. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or depression; may rarely cause insomnia, confusion, or nightmares

Mental Health: Effects on Psychiatric TreatmentConcurrent use with phenothiazines may potentiate hypotensive effects of penbutolol

Cardiovascular ConsiderationsThis drug possesses intrinsic sympathomimetic activity. While beta-blockers with intrinsic sympathomimetic activity induce fewer side effects, the cardiovascular benefits when used in patients with hypertension or heart failure are less clear than for beta-blockers without intrinsic sympathomimetic activity.

Hypertension: Beta-blocker therapy in the treatment of hypertension has been associated with improved cardiovascular outcomes. This class of drug is beneficial for elderly patients with hypertension. A recent UKPDS study showed that beta-blocker therapy (atenolol) was as effective as an ACE inhibitor in reducing cardiovascular events and that the benefits of therapy were related more to the degree of antihypertensive efficacy rather than the class of drug used.

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia and hypertension.

Anesthesia and Critical Care Concerns/Other ConsiderationsPenbutolol possesses intrinsic sympathomimetic activity. While beta-blockers with intrinsic sympathomimetic activity induce fewer side effects, the cardiovascular benefits are less clear.

Index TermsPenbutolol Sulfate

References

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Gibbons RJ, Abrams J, Chatterjee K, et al, “ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina - Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina),” *J Am Coll Cardiol*, 2003, 41(1):159-68. [PubMed 12570960]

Lang DM, “Anaphylactoid and Anaphylactic Reactions. Hazards of Beta-Blockers,” *Drug Saf*, 1995, 12(5):299-304.[PubMed 7669259]

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

International Brand NamesBetapressin (AT, CH, CZ, DE, FR, IT); Betapressine (FR); Hostabloc (AR)

Penciclovir

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Denavir® may be confused with indinavir

Pronunciation(pen SYE kloe veer)
U.S. Brand NamesDenavir®
Pharmacologic CategoryAntiviral Agent
Use: Labeled IndicationsTopical treatment of herpes simplex labialis (cold sores)
Use: DentalTopical treatment of herpes simplex labialis (cold sores)
Dosing: Adults**Herpes simplex labialis (cold sores):** Topical: Apply cream at the first sign or symptom of cold sore (eg, tingling, swelling); apply every 2 hours during waking hours for 4 days.
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Herpes simplex labialis (cold sores):** Children ≥12 years: Refer to adult dosing.
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).
ContraindicationsHypersensitivity to the penciclovir or any component of the formulation; previous and significant adverse reactions to famciclovir
Allergy Considerations

- Antiviral Acyclic Guanine Derivative Allergy

Warnings/Precautions

Special populations:

- Immunocompromised patients: The effect of penciclovir has not been established in immunocompromised patients.
- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Appropriate use: Should only be used on herpes labialis on the lips and face; because no data are available, application to mucous membranes is not recommended. Avoid application in or near eyes since it may cause irritation.

Pregnancy Risk FactorB
LactationExcretion in breast milk unknown
Adverse Reactions

>10%: Dermatologic: Mild erythema (50%)

1% to 10%: Central nervous system: Headache (5.3%)

<1%: Local anesthesia (0.9%)

Postmarketing and/or case reports: Application site reaction, local edema, urticaria, pain, pruritus, paresthesia, skin discoloration, erythematous rash, oropharyngeal edema, parosmia

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersReduction in virus shedding, negative cultures for herpesvirus; resolution of pain and healing of cold sore lesion
Nursing: Physical Assessment/MonitoringAssess for effectiveness of therapy. Teach patient appropriate application and use and adverse symptoms to report.
Patient EducationThis is not a cure for herpes (recurrences tend to appear within 3 months of original infection), nor will this medication reduce the risk of transmission to others when lesions are present. For external use only. Wash hands before and after application. Apply this film over affected areas at first sign of cold sore. Avoid use of other topical creams, lotions, or ointments unless approved by prescriber. You may experience headache, mild rash, or taste disturbances. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream: 1% (1.5 g)

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Cream (Denavir)

1% (1.5): $43.18

Mechanism of ActionIn cells infected with HSV-1 or HSV-2, viral thymidine kinase phosphorylates penciclovir to a monophosphate form which, in turn, is converted to penciclovir triphosphate by cellular kinases. Penciclovir triphosphate inhibits HSV polymerase competitively with deoxyguanosine triphosphate. Consequently, herpes viral DNA synthesis and, therefore, replication are selectively inhibited

Pharmacodynamics/KineticsAbsorption: Topical: None

Pharmacotherapy PearlsPenciclovir is the active metabolite of the prodrug famciclovir. Penciclovir is an alternative to topical acyclovir for HSV-1 and HSV-2 infections. Neither drug will prevent recurring HSV attacks.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Alrabiah FA and Sacks SL, “New Antiherpesvirus Agents. Their Targets and Therapeutic Potential,” *Drugs*, 1996, 52(1):17-32.[PubMed 8799682]

International Brand NamesFamvir[extern.] (CH); Vectavir (AT, AU, BB, BE, BG, BM, BS, BZ, CZ, DE, DK, EE, ES, FI, GB, GY, HN, IE, IT, JM, NL, NO, PL, SE, SR, TT)

Penicillamine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Penicillamine may be confused with penicillin

Depen® may be confused with Endal®

International issues:

Depen® may be confused with Depon® which is a brand name for acetaminophen in Greece

Depen® may be confused with Dipen® which is a brand name for diltiazem in Greece

Pemine® [Italy] may be confused with Pamine® which is a brand name for methscopolamine in the U.S.

Pronunciation(pen i SIL a meen)

U.S. Brand NamesCuprimine®; Depen®

Canadian Brand NamesCuprimine®; Depen®

Pharmacologic CategoryChelating Agent

Use: Labeled IndicationsTreatment of Wilson's disease, cystinuria; adjunctive treatment of rheumatoid arthritis

Use: Unlabeled/InvestigationalChelation therapy for the treatment of lead poisoning (third-line agent); treatment of arsenic poisoning

Dosing: Adults

Rheumatoid arthritis: Oral: 125-250 mg/day, may increase dose at 1- to 3-month intervals up to 1-1.5 g/day (maximum in older adults: 750 mg/day)

Wilson's disease: Oral: 250 mg 4 times/day (maximum in older adults: 750 mg/day). **Note:** Dose titrated to maintain urinary copper excretion >2 mg/day; decrease dose for surgery and during last trimester of pregnancy

Cystinuria:Note: Adjust dose to limit cystine excretion to 100-200 mg/day (<100 mg/day with history of stone formation): Oral: 1-4 g/day in divided doses every 6 hours; usual dose: 2 g/day

Arsenic poisoning (unlabeled use): Oral: 500 mg 4 times/day for 5 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Rheumatoid arthritis (unlabeled use): Oral: Initial: 3 mg/kg/day (≤250 mg/day) for 3 months, then 6 mg/kg/day (≤500 mg/day) in divided doses twice daily for 3 months to a maximum of 10 mg/kg/day in 3-4 divided doses; maximum dose: 750 mg/day

Wilson's disease: Oral: **Note:** Doses titrated to maintain urinary copper excretion >2 mg/day (decrease dose for surgery): Children <12 years: 20 mg/kg/day in 2-3 divided doses, round off to the nearest 250 mg dose; maximum 1 g/day

Cystinuria: Children: 30 mg/kg/day in 4 divided doses. **Note:** Adjust dose to limit cystine excretion to 100-200 mg/day (<100 mg/day with history of stone formation).

Lead poisoning (unlabeled use): Oral: 20-30 mg/kg/day, administered in 3-4 divided doses; initiating treatment at 25% of this dose and gradually increasing to the full dose over 2-3 weeks may minimize adverse reactions. Doses of 15 mg/kg/day may also be effective and have less adverse effects (Shannon 2000). **Note:** For the treatment of high blood lead levels in children, the CDC recommends chelation treatment when blood lead levels are >45 mcg/dL (CDC, 2002). Children with blood lead levels >70 mcg/dL or symptomatic lead poisoning should be treated with parenteral agents (AAP, 2005).

Arsenic poisoning (unlabeled use): Oral: Children: 100 mg/kg/day in divided doses every 6 hours for 5 days; maximum: 1 g/day

Dosing: Renal ImpairmentCl_{cr} <50 mL/minute: Avoid use.

Hemodialysis: Dialyzable; a dosing decrease from 250 mg/day to 250 mg 3 times/week after dialysis has been suggested in the treatment of rheumatoid arthritis.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralFor patients who cannot swallow, contents of capsules may be administered in 15-30 mL of chilled puréed fruit or fruit juice. Give on an empty stomach (1 hour before meals and at bedtime).

Cystinuria: If administering 4 equal doses is not feasible, administer the larger dose at bedtime.

Rheumatoid arthritis: Doses ≤500 mg/day may be given as a single dose; >500 mg administer in divided doses

Dietary ConsiderationsShould be taken at least 1 hour before a meal on an empty stomach. Iron may decrease drug action. Patients with Wilson's disease or cystinuria should receive pyridoxine supplementation 25 mg/day. For Wilson's disease, decrease copper in diet to <1-2 mg/day and omit chocolate, nuts, shellfish, mushrooms, liver, raisins, broccoli, copper-enriched cereal, multivitamins with copper, and molasses. For lead poisoning, decrease calcium in diet. For cystinuria, increase daily fluid intake including 1 pint of fluid prior to bedtime and 1 additional pint during the night.

StorageStore in tight, well-closed containers.

Extemporaneously PreparedA 50 mg/mL suspension may be made by mixing twenty 250 mg capsules with 1 g carboxymethylcellulose, 50 g sucrose, 100 mg citric acid, parabens, and purified water to a total volume of 100 mL; cherry flavor may be added. Stability is 30 days refrigerated.

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, 1st ed, Cincinnati, OH: Harvey Whitney Books Co, 1990.

ContraindicationsHypersensitivity to penicillamine or any component of the formulation; renal insufficiency (in patients with rheumatoid arthritis); patients with previous penicillamine-related aplastic anemia or agranulocytosis; breast-feeding; pregnancy (in patients with rheumatoid arthritis)

Warnings/Precautions

Boxed warnings:

- Experienced physician: See "Other warnings/precautions" below.
- Toxicity symptoms: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Allergic reactions: Approximately 33% of patients will experience an allergic reaction.
- Goodpasture's syndrome: Penicillamine has been associated with fatalities due to Goodpasture's syndrome.
- Hematologic toxicities: Penicillamine has been associated with fatalities due to agranulocytosis, aplastic anemia, and thrombocytopenia.
- Hepatotoxicity: Monitor liver function tests periodically due to rare reports of intrahepatic cholestasis or toxic hepatitis.
- Penicillin cross-sensitivity: Patients with a penicillin allergy may theoretically have cross-sensitivity to penicillamine; however, the possibility has been eliminated now that penicillamine is produced synthetically and no longer contains trace amounts of penicillin.
- Proteinuria/hematuria: Proteinuria or hematuria may develop; monitor for membranous glomerulopathy which can lead to nephrotic syndrome. In rheumatoid arthritis patients, discontinue if gross hematuria or persistent microscopic hematuria develop.
- Myasthenia gravis: Penicillamine has been associated with fatalities due to myasthenia gravis.
- Toxicity symptoms: **[U.S. Boxed Warning]: Patients should be warned to report promptly any symptoms suggesting toxicity (fever, sore throat, chills, bruising, or bleeding);** toxicity may be dose related.

Disease-related concerns:

- Cystinuria: Once instituted for cystinuria, continue treatment on a daily basis; interruptions of even a few days have been followed by hypersensitivity with reinstitution of therapy.
- Lead poisoning: Investigate, identify, and remove sources of lead exposure prior to treatment. Penicillamine is considered to be a third-line agent for the treatment of lead poisoning in children due to the overall toxicity associated with its use; penicillamine should only be used when unacceptable reactions have occurred with edetate CALCIUM disodium and succimer. Primary care providers should consult experts in chemotherapy of lead toxicity before using chelation drug therapy.
- Wilson's disease: Once instituted for Wilson's disease, continue treatment on a daily basis; interruptions of even a few days have been followed by hypersensitivity with reinstitution of therapy.

Concurrent drug therapy issues:

- Hematopoietic-depressant drugs: Use with caution in patients on other hematopoietic-depressant drugs (eg, gold, immunosuppressants, antimalarials, phenylbutazone); hematologic and renal adverse reactions are similar.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the close supervision of a physician familiar with the toxicity and dosage considerations.**

Geriatric ConsiderationsClose monitoring of elderly is necessary; since steady-state serum/tissue concentrations rise slowly, "go slow" with dose increase intervals; steady-state concentrations decline slowly after discontinuation suggesting extensive tissue distribution. Skin rashes and taste abnormalities occur more frequently in the elderly than in young adults; leukopenia, thrombocytopenia, and proteinuria occur with equal frequency in both younger adults and elderly. Since toxicity may be dose related, it is recommended not to exceed 750 mg/day in the elderly.

Pregnancy Risk FactorD

Pregnancy ConsiderationsBirth defects, including congenital cutix laxa and associated defects, have been reported in infants following penicillamine exposure during pregnancy. Use for the treatment of rheumatoid arthritis during pregnancy is contraindicated. Use for the treatment of cystinuria only if the possible benefits to the mother outweigh the potential risks to the fetus. Continued treatment of Wilson's disease during pregnancy protects the mother against relapse. Discontinuation has detrimental maternal and fetal effects. Daily dosage should be limited to 750 mg. For planned cesarean section, reduce dose to 250 mg/day for the last 6 weeks of pregnancy, and continue at this dosage until wound healing is complete.

LactationExcretion in breast milk unknown/contraindicated

Adverse ReactionsFrequency not defined, may vary by indication. Adverse effects requiring discontinuation of treatment have been reported in 20% to 30% of patients with Wilson's disease.

Cardiovascular: Vasculitis

Central nervous system: Anxiety, agitation, fever, hyperpyrexia, psychiatric disturbances; worsening neurologic symptoms (10% to 50% patients with Wilson's disease)

Dermatologic: Alopecia, cheilosis, dermatomyositis, exfoliative dermatitis, lichen planus, rash (early and late 5%), pemphigus, pruritus, skin friability increased, toxic epidermal necrolysis, urticaria, wrinkling (excessive), yellow nail syndrome

Endocrine & metabolic: Hypoglycemia, thyroiditis

Gastrointestinal: Anorexia, diarrhea (17%), epigastric pain, gingivostomatitis, glossitis, nausea, oral ulcerations, pancreatitis, peptic ulcer reactivation, taste alteration (12%), vomiting

Hematologic: Eosinophilia, hemolytic anemia, leukocytosis, leukopenia (2% to 5%), monocytosis, red cell aplasia, thrombocytopenia (4% to 5%), thrombotic thrombocytopenia purpura, thrombocytosis

Hepatic: Alkaline phosphatase increased, hepatic failure, intrahepatic cholestasis, toxic hepatitis

Local: Thrombophlebitis, white papules at venipuncture and surgical sites

Neuromuscular & skeletal: Arthralgia, dystonia, myasthenia gravis, muscle weakness, neuropathies, polyarthralgia (migratory, often with objective synovitis), polymyositis

Ocular: Diplopia, extraocular muscle weakness, optic neuritis, ptosis, visual disturbances

Otic: Tinnitus

Renal: Goodpasture's syndrome, hematuria, nephrotic syndrome, proteinuria (6%), renal failure, renal vasculitis

Respiratory: Asthma, interstitial pneumonitis, pulmonary fibrosis, obliterative bronchiolitis

Miscellaneous: Allergic alveolitis, anetoderma, elastosis perforans serpiginosa, lupus-like syndrome, lactic dehydrogenase increased, lymphadenopathy, mammary hyperplasia, positive ANA test

Drug Interactions

Antacids: May decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Digoxin: Penicillamine may decrease the serum concentration of Digoxin. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Penicillamine. Only oral iron salts are a concern. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol.

Food: Penicillamine serum levels may be decreased if taken with food. Do not administer with milk.

Monitoring ParametersUrinalysis, CBC with differential, platelet count, skin, lymph nodes, and body temperature twice weekly during the first month of therapy, then every 2 weeks for 5 months, then monthly; LFTs every 6 months

Cystinuria: Urinary cystine, annual X-ray for renal stones

Lead poisoning: Serum lead concentration (baseline and 7-21 days after completing chelation therapy); hemoglobin or hematocrit, iron status, free erythrocyte protoporphyrin or zinc protoporphyrin; neurodevelopmental changes

Wilson's disease: Serum copper, 24-hour urinary copper excretion, LFTs every 3 months during the first year of treatment

CBC: WBC <3500/mm^3, neutrophils <2000/mm^3, or monocytes >500/mm^3 indicate need to stop therapy immediately; platelet counts <100,000/mm^3 indicate need to stop therapy until numbers of platelets increase

Urinalysis: Monitor for proteinuria and hematuria. A quantitative 24-hour urine protein at 1- to 2-week intervals initially (first 2-3 months) is recommended if proteinuria develops; in patients with rheumatoid arthritis, discontinue or decrease dose with proteinuria >1 g/24 hours, progressively increasing proteinuria or hematuria.

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess results of laboratory tests, therapeutic effectiveness (dependent on purpose of therapy), and adverse reactions at beginning of therapy and periodically throughout therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse

symptoms to report.
Monitoring: Lab TestsUrinalysis, CBC with differential, platelet count (twice weekly); weekly measurements of urinary and blood concentration of the intoxicating metal is indicated.

Cystinuria: Urinary cystine, annual X-ray for renal stones

Lead poisoning: Serum lead concentration (baseline and 7-21 days after completing chelation therapy); hemoglobin or hematocrit, iron status, free erythrocyte protoporphyrin or zinc protoporphyrin

Wilson's disease: Serum copper, 24-hour urinary copper excretion, LFTs every 3 months during the first year of treatment

CBC: WBC <3500/mm^3, neutrophils <2000/mm^3, or monocytes >500/mm^3 indicate need to stop therapy immediately. Quantitative 24-hour urine protein at 1- to 2-week intervals initially (first 2-3 months); urinalysis, LFTs occasionally; platelet counts <100,000/mm^3 indicate need to stop therapy until numbers of platelets increase.

Patient EducationTake this medication exactly as directed; do not increase dose without consulting prescriber. Capsules may be opened and contents mixed in 15-30 mL of chilled fruit juice or puree; do not take with milk or milk products. Avoid or limit alcohol and excess intake of vitamin A. It is preferable to take penicillamine on empty stomach, 1 hour before or 2 hours after meals. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake.

Wilson's disease: Avoid chocolate, shellfish, nuts, mushrooms, liver, broccoli, molasses.

Lead poisoning: Decrease dietary calcium.

Cystinuria: Take with large amounts of water

You may experience anorexia, nausea, vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report persistent fever or chills, unhealed sores, white spots or sores in mouth or vaginal area, extreme fatigue, or signs of infection; breathlessness, respiratory difficulty, or unusual cough; unusual bruising/bleeding; blood in urine, stool, mouth, or vomitus; swollen face or extremities; skin rash or itching; muscle pain or cramping; or pain on urination. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptives. Do not breast-feed

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Cuprimine®: 250 mg

Tablet:

Depen®: 250 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Depen Titratabs)

250 mg (30): $121.97

Mechanism of ActionChelates with lead, copper, mercury and other heavy metals to form stable, soluble complexes that are excreted in urine; depresses circulating IgM rheumatoid factor, depresses T-cell but not B-cell activity; combines with cystine to form a compound which is more soluble, thus cystine calculi are prevented
Pharmacodynamics/Kinetics

Onset of action: Rheumatoid arthritis: 2-3 months; Wilson's disease: 1-3 months

Absorption: 40% to 70%

Protein binding: 80% to albumin and ceruloplasmin

Metabolism: Hepatic (small amounts metabolized to s-methyl-d-penicillamine)

Half-life elimination: 1.7-3.2 hours

Time to peak, serum: ~2 hours

Excretion: Urine (30% to 60% as unchanged drug)

Related Information

- Antacid Drug Interactions

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral ulcerations, glossitis, gingivostomatitis, and taste alteration.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause anxiety, agitation, visual and psychic disturbances

Mental Health: Effects on Psychiatric Treatment May cause aplastic anemia; use caution with clozapine and carbamazepine. May cause dystonia. May cause thrombocytopenia; monitor in patients receiving valproate.

Index Terms D-3-Mercaptovaline; D-Penicillamine; β,β-Dimethylcysteine

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International Brand Names Adalken (MX); Artamin (AT, CY, KP, MY, PL); Atamir (DK); Byanodine (HU); Cilamin (IN); Cuprenil (BG, HN, PL); Cuprimine (MY, NL, NO, TH, TW); Cuprimune (AR, BR); Cupripen (CO, ES, UY); D-Penamine (AU); D-Penicillamine (AU); D-Penil (PE); Distamine (GB, IE, NL); Gerodyl (DK); Kelatin (BE, LU, NL); Kelatine (PT); Mercaptyl (CH); Metalcaptase (DE, HR, JP, LU); Metalcaptase[inj.] (CZ, HR); Pemine (IT); Penicilamin (CZ); Penicilamina (CN); Penicillamin (FI, SE); Reumacillin (FI); Rhumantin (DK); Sufortanon (ES); Trisorcin (HR); Trolovol (FR, HR); Vistamin (PK)

Penicillin G (Parenteral/Aqueous)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Penicillin may be confused with penicillamine

Pronunciation(pen i SIL in jee, pa REN ter al, AYE kwee us)

U.S. Brand NamesPfizerpen®

Canadian Brand NamesCrystapen®

Pharmacologic CategoryAntibiotic, Penicillin

Use: Labeled IndicationsTreatment of infections (including sepsis, pneumonia, pericarditis, endocarditis, meningitis, anthrax) caused by susceptible organisms; active against some gram-positive organisms, generally not *Staphylococcus aureus*; some gram-negative organisms such as *Neisseria gonorrhoeae*, and some anaerobes and spirochetes

Dosing: Adults

***Actinomyces*species:** I.V.: 10-20 million units/day divided every 4-6 hours for 4-6 weeks

Clostridium perfringens: I.V.: 24 million units/day divided every 4-6 hours with clindamycin

Corynebacterium diptheriae: I.V.: 2-3 million units/day in divided doses every 4-6 hours for 10-12 days

Erysipelas: I.V.: 1-2 million units every 4-6 hours

Erysipelothrix: I.V.: 2-4 million units every 4 hours

Fascial space infections: I.V.: 2-4 million units every 4-6 hours with metronidazole

Leptospirosis: I.V.: 1.5 million units every 6 hours for 7 days

Listeria: I.V.: 15-20 million units/day in divided doses every 4-6 hours for 2 weeks (meningitis) or 4 weeks (endocarditis)

Lyme disease (meningitis): I.V.: 20 million units/day in divided doses

Neurosyphilis: I.V.: 18-24 million units/day in divided doses every 4 hours (or by continuous infusion) for 10-14 days

Streptococcus:

Brain abscess: I.V.: 18-24 million units/day in divided doses every 4 hours with metronidazole

Endocarditis or osteomyelitis: I.V.: 3-4 million units every 4 hours for at least 4 weeks

Pregnancy (prophylaxis GBS): I.V.: 5 million units x 1 dose, then 2.5 million units every 4 hours until delivery (ACOG, 2002; CDC, 2002)

Skin and soft tissue: I.V.: 3-4 million units every 4 hours for 10 days

Toxic shock: I.V.: 24 million units/day in divided doses with clindamycin

Streptococcal pneumonia: I.V.: 2-3 million units every 4 hours

Whipple's disease: I.V.: 2 million units every 4 hours for 2 weeks, followed by oral trimethoprim/sulfamethoxazole or doxycycline for 1 year

Relapse or CNS involvement: 4 million units every 4 hours for 4 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Susceptible infections: I.M., I.V.:

Infants >1 month and Children: I.M., I.V.: 100,000-400,000 units/kg/day in divided doses every 4-6 hours (maximum dose: 24 million units/day)

***Meningitis*(gonococcal):** I.V.: 250,000 units/kg/day in 4 divided doses

Moderate infections: I.M., I.V.: 100,000-250,000 units/kg/day in 4 divided doses

Severe infections: I.M., I.V.: 250,000-400,000 units/kg/day in divided doses every 4-6 hours (maximum dose: 24 million units/day)

Syphilis (congenital): Infants: I.V.: 50,000 units/kg every 4-6 hours for 10 days

Dosing: Renal ImpairmentDosage modification is required in patients with renal insufficiency.

Uremic patients with Cl_{cr} >10 mL/minute/1.73 m^2: Administer full loading dose followed by $^1/_2$ of the loading dose given every 4-5 hours

Cl_{cr} <10 mL/minute/1.73 m^2: Administer full loading dose followed by $^1/_2$ of the loading dose given every 8-10 hours

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Administer I.M. by deep injection in the upper outer quadrant of the buttock. Administer injection around-the-clock to promote less variation in peak and trough levels.

Administration: I.V.Usually administered by intermittent infusion. In some centers, large doses may be administered by continuous I.V. infusion.

Administration: I.V. DetailpH: 6-7.5

Dietary Considerations

Injection powder for reconstitution as potassium contains sodium 6.8 mg (0.3 mEq) and potassium 65.6 mg (1.68 mEq) per 1 million units

Injection solution (premixed) as a potassium contains sodium 23.5 mg (1.02 mEq) and potassium 66.5 mg (1.7 mEq) per 1 million units

Storage

Penicillin G potassium powder for injection should be stored below 86°F (30°C). Following reconstitution, solution may be stored for up to 7 days under refrigeration. Premixed bags for infusion should be stored in the freezer (-20°C to -4°F); frozen bags may be thawed at room temperature or in refrigerator. Once thawed, solution is stable for 14 days if stored in refrigerator or for 24 hours when stored at room temperature. Do not refreeze once thawed.

Penicillin G sodium powder for injection should be stored at controlled room temperature. Reconstituted solution may be stored under refrigeration for up to 3 days.

CompatibilityInactivated in acidic or alkaline solutions.

Penicillin G potassium:

Stable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4$NS, $D_5{}^1/_2$NS, D_5NS, D_5W, D_{10}W, LR, $^1/_2$NS, NS, hetastarch 6%; **incompatible** with dextran 70 6% in dextrose, dextran 40 10% in dextrose; **variable stability (consult detailed reference)** in fat emulsion 10%, peritoneal dialysis solutions.

Y-site administration: Compatible: Acyclovir, amiodarone, cyclophosphamide, diltiazem, enalaprilat, esmolol, fluconazole, foscarnet, heparin, heparin with hydrocortisone sodium succinate, hydromorphone, labetalol, magnesium sulfate, meperidine, morphine, nicardipine, perphenazine, potassium chloride, tacrolimus, theophylline, verapamil, vitamin B complex with C.

Compatibility in syringe: Compatible: Caffeine citrate, heparin. **Incompatible:** Metoclopramide.

Compatibility when admixed: Compatible: Ascorbic acid injection, calcium chloride, calcium gluconate, chloramphenicol, cimetidine, clindamycin, colistimethate, corticotropin, dimenhydrinate, diphenhydramine, ephedrine, erythromycin lactobionate, furosemide, hydrocortisone sodium succinate, kanamycin, lidocaine, magnesium sulfate, methylprednisolone sodium succinate, metronidazole, metronidazole with sodium bicarbonate, polymyxin B sulfate, potassium chloride, potassium chloride with vitamin B complex with C, procaine, prochlorperazine edisylate, ranitidine, verapamil. **Incompatible:** Aminophylline, amphotericin B, chlorpromazine, dopamine, floxacillin, hydroxyzine, metaraminol, pentobarbital, phenytoin, prochlorperazine mesylate, promazine, thiopental, vancomycin, vitamin B complex with C with oxytetracycline. **Variable (consult detailed reference):** Amikacin, heparin, lincomycin, promethazine, sodium bicarbonate, vitamin B complex with C.

Penicillin G sodium:

Stable in dextran 40 10%; **incompatible** with fat emulsion 10%; **variable stability (consult detailed reference)** in D_5W, NS, peritoneal dialysis solution.

Y-site administration: Compatible: Clarithromycin, levofloxacin.

Compatibility in syringe: Compatible: Caffeine citrate, chloramphenicol, cimetidine, colistimethate, dimenhydramine, gentamicin, heparin, kanamycin, lincomycin, pantoprazole, polymyxin B sulfate, streptomycin.

Compatibility when admixed: Compatible: Calcium chloride, calcium gluconate, chloramphenicol, clindamycin, colistimethate, diphenhydramine, erythromycin lactobionate, furosemide, gentamicin, hydrocortisone sodium succinate, kanamycin, polymyxin B sulfate, procaine, ranitidine, verapamil, vitamin B complex with C. **Incompatible:** Amphotericin B, bleomycin, chlorpromazine, cytarabine, floxacillin, hydroxyzine, methylprednisolone sodium succinate, prochlorperazine mesylate, promethazine, vancomycin. **Variable (consult detailed reference):** Heparin, lincomycin, potassium chloride.

ContraindicationsHypersensitivity to penicillin or any component of the formulation

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- Neurovascular damage: Avoid intra-arterial administration or injection into or near major peripheral nerves or blood vessels since such injections may cause severe and/or permanent neurovascular damage.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended. In the presence of concomitant hepatic impairment, further dosage adjustment may be needed.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures.

Special populations:

- Pediatrics: Neonates may have decreased renal clearance of penicillin and require frequent dosage adjustments depending on age.

Other warnings/precautions:

- Electrolyte imbalance: Product contains sodium and potassium; high doses of I.V. therapy may alter serum levels.

- Prolonged use: Extended duration of therapy or use associated with high serum concentrations (eg, in renal insufficiency) may be associated with an increased risk for some adverse reactions (neutropenia, hemolytic anemia, serum sickness).

Geriatric ConsiderationsDespite a reported prolonged half-life, it is usually not necessary to adjust the dose of penicillin G or VK in elderly to account for renal function changes with age, however, it is advised to calculate an estimated creatinine clearance and adjust dose accordingly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, penicillin G is classified as pregnancy category B. Penicillin crosses the placenta and distributes into amniotic fluid. There is no evidence of adverse fetal effects after penicillin use during pregnancy in humans. Penicillin G is the drug of choice for treatment of syphilis during pregnancy and penicillin G (parenteral/aqueous) is the drug of choice for the prevention of early-onset Group B Streptococcal (GBS) disease in newborns.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsVery small amounts of penicillin G transfer into breast milk. Peak milk concentrations occur at approximately 1 hour after an IM dose and are higher if multiple doses are given. The manufacturer recommends that caution be exercised when administering penicillin to nursing women. Nondose-related effects could include modification of bowel flora and allergic sensitization.

Pregnancy & Lactation, In-Depth

- Penicillin G (Parenteral/Aqueous) in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Coma (high doses), hyperreflexia (high doses), seizures (high doses)

Dermatologic: Contact dermatitis, rash

Endocrine & metabolic: Electrolyte imbalance (high doses)

Gastrointestinal: Pseudomembranous colitis

Hematologic: Neutropenia, positive Coombs' hemolytic anemia (rare, high doses)

Local: Injection site reaction, phlebitis, thrombophlebitis

Neuromuscular & skeletal: Myoclonus (high doses)

Renal: Acute interstitial nephritis (high doses), renal tubular damage (high doses)

Miscellaneous: Anaphylaxis, hypersensitivity reactions (immediate and delayed), Jarisch-Herxheimer reaction, serum sickness

Drug Interactions

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Test InteractionsFalse-positive or negative urinary glucose determination using Clinitest®; positive Coombs' [direct]; false-positive urinary and/or serum proteins

Monitoring ParametersPeriodic electrolyte, hepatic, renal, cardiac and hematologic function tests during prolonged/high-dose therapy; observe for signs and symptoms of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient’s allergy history prior to starting therapy. Use with caution and monitor closely in presence of renal impairment or seizure disorder. Assess potential for interactions with other pharmacological agents (eg, decreased or increased levels/effects of penicillin G). Avoid intravascular or intra-arterial administration or injection into or near major peripheral nerves or blood vessels; may cause severe and/or permanent neurovascular damage. Advise patients with diabetes about use of Clinitest®; may cause false positive or negative. Assess effectiveness (resolution of infections) and adverse reactions (eg, hypersensitivity reactions, opportunistic infection [fever, chills, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge, fatigue], CNS changes, thrombophlebitis). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity before administering first dose; periodic electrolyte, hepatic, renal, cardiac and hematologic function tests during prolonged/high-dose therapy

Patient EducationThis drug can only be given by injection or infusion. Report immediately any redness, swelling, burning, or pain at infusion site or any signs of allergic reaction (eg, respiratory or swallowing difficulty, chest tightness, rash, hives, swelling of lips or mouth). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If being treated for sexually-transmitted disease, partner will also need to be treated. If you have diabetes, drug may cause false test results with Clinitest®, consult prescriber for alternative method of glucose monitoring. May cause confusion or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report persistent adverse effects or signs of opportunistic infection (eg, fever, chills, diarrhea, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge, fatigue).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion, as potassium [premixed iso-osmotic dextrose solution, frozen]: 1 million units (50 mL), 2 million units (50 mL), 3 million units (50 mL) [contains sodium 1.02 mEq and potassium 1.7 mEq per 1 million units]

Injection, powder for reconstitution, as potassium (Pfizerpen®): 5 million units, 20 million units [contains sodium 6.8 mg (0.3 mEq) and potassium 65.6 mg (1.68 mEq) per 1 million units]

Injection, powder for reconstitution, as sodium: 5 million units [contains sodium 1.68 mEq per 1 million units]

Generic AvailableYes

Mechanism of ActionInterferes with bacterial cell wall synthesis during active multiplication, causing cell wall death and resultant bactericidal activity against susceptible bacteria

Pharmacodynamics/Kinetics

Distribution: Poor penetration across blood-brain barrier, despite inflamed meninges

Relative diffusion from blood into CSF: Poor unless meninges inflamed (exceeds usual MICs)

CSF:blood level ratio: Normal meninges: <1%; Inflamed meninges: 2% to 6%

Protein binding: 65%

Metabolism: Hepatic (30%) to penicilloic acid

Half-life elimination:

Neonates: <6 days old: 3.2-3.4 hours; 7-13 days old: 1.2-2.2 hours; >14 days old: 0.9-1.9 hours

Children and Adults: Normal renal function: 30-50 minutes

End-stage renal disease: 3.3-5.1 hours

Time to peak, serum: I.M.: ~30 minutes; I.V.: ~1 hour

Excretion: Urine (58% to 85% as unchanged drug)

Related Information

- Antibiotic Treatment of Adults With Infective Endocarditis
- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Desensitization Protocols
- Treatment of Sexually-Transmitted Infections

Pharmacotherapy Pearls1 million units is approximately equal to 625 mg.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause drowsiness or confusion

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: One million units is approximately equal to 625 mg.

Index TermsBenzylpenicillin Potassium; Benzylpenicillin Sodium; Crystalline Penicillin; Penicillin G Potassium; Penicillin G Sodium

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International Brand NamesBenpen (AU); Broncobiot (PE); Celinex (PH); Lascacilin (PY); Pencarv (PH); Pengesod (MX); Penicilina Northia (AR); Penicillin G (BG); Penicillin G- Natrium (AT); Pisacilina (CO); Sodipen (MX)

Penicillin G Benzathine and Penicillin G Procaine

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Bicillin® C-R (penicillin G benzathine and penicillin G procaine) may be confused with Bicillin® L-A (penicillin G benzathine). Penicillin G benzathine is the only product currently approved for the treatment of syphilis. Administration of penicillin G benzathine and penicillin G procaine combination instead of Bicillin® L-A may result in inadequate treatment response.

Penicillin G benzathine may only be administered by deep intramuscular injection; intravenous administration of penicillin G benzathine has been associated with cardiopulmonary arrest and death.

Sound-alike/look-alike issues:

Penicillin may be confused with penicillamine

Bicillin® may be confused with Wycillin®

Pronunciation(pen i SIL in jee BENZ a theen & pen i SIL in jee PROE kane)

U.S. Brand NamesBicillin® C-R; Bicillin® C-R 900/300

Pharmacologic CategoryAntibiotic, Penicillin

Use: Labeled IndicationsMay be used in specific situations in the treatment of streptococcal infections

Dosing: AdultsStreptococcal infections: I.M.: 2.4 million units in a single dose

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricStreptococcal infections: I.M.:

Children:

<14 kg: 600,000 units in a single dose

14-27 kg: 900,000 units to 1.2 million units in a single dose

Children >27 kg: Refer to adult dosing.

StorageRefrigerate

ContraindicationsHypersensitivity to penicillin or any component of the formulation

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Boxed warnings:

- Intravenous administration: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment.

Other warnings/precautions:

- Intravenous administration: **[U.S. Boxed Warning]: Not for intravenous use; cardiopulmonary arrest and death have occurred from inadvertent I.V. administration.**

- Prolonged use: Extended duration of therapy or use associated with high serum concentrations (eg, in renal insufficiency) may be associated with an increased risk for some adverse reactions (neutropenia, hemolytic anemia, serum sickness).

Geriatric ConsiderationsNo adjustment for renal function or age is necessary.

Pregnancy Risk FactorB

Pregnancy ConsiderationsSee individual agents.

Breast-Feeding ConsiderationsSee individual agents.

Pregnancy & Lactation, In-Depth

- Penicillin G Benzathine in Pregnancy & Lactation
- Penicillin G Procaine in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: CNS toxicity (convulsions, confusion, drowsiness, myoclonus)

Hematologic: Positive Coombs' reaction, hemolytic anemia

Renal: Interstitial nephritis

Miscellaneous: Hypersensitivity reactions, Jarisch-Herxheimer reaction

Drug Interactions

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Test InteractionsMay interfere with urinary glucose tests using cupric sulfate (Benedict's solution, Clinitest®); may inactivate aminoglycosides *in vitro*; positive Coombs' [direct], increased protein

Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose

Patient Education

Report persistent diarrhea.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, suspension [prefilled syringe]:

Bicillin® C-R:

600,000 units: Penicillin G benzathine 300,000 units and penicillin G procaine 300,000 units per 1 mL (1 mL) [DSC]

1,200,000 units: Penicillin G benzathine 600,000 units and penicillin G procaine 600,000 units per 2 mL (2 mL)

2,400,000 units: Penicillin G benzathine 1,200,000 units and penicillin G procaine 1,200,000 units per 4 mL (4 mL) [DSC]

Bicillin® C-R 900/300: 1,200,000 units: Penicillin G benzathine 900,000 units and penicillin G procaine 300,000 units per 2 mL (2 mL)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Suspension (Bicillin C-R (1200000))

300000-300000 units/mL (20): $429.99

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs); which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause drowsiness or confusion

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPenicillin G Procaine and Benzathine Combined

Penicillin G Benzathine

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Medication Safety Issues

Sound-alike/look-alike issues:

Penicillin may be confused with penicillamine

Bicillin® may be confused with Wycillin®

Bicillin® C-R (penicillin G benzathine and penicillin G procaine) may be confused with Bicillin® L-A (penicillin G benzathine). Penicillin G benzathine is the only product currently approved for the treatment of syphilis. Administration of penicillin G benzathine and penicillin G procaine combination instead of Bicillin® L-A may result in inadequate treatment response.

Penicillin G benzathine may only be administered by deep intramuscular injection; intravenous administration of penicillin G benzathine has been associated with cardiopulmonary arrest and death.

Pronunciation(pen i SIL in jee BENZ a theen)

U.S. Brand NamesBicillin® L-A

Canadian Brand NamesBicillin® L-A

Pharmacologic CategoryAntibiotic, Penicillin

Use: Labeled IndicationsActive against some gram-positive organisms, few gram-negative organisms such as *Neisseria gonorrhoeae*, and some anaerobes and spirochetes; used in the treatment of syphilis; used only for the treatment of mild to moderately severe infections caused by organisms susceptible to low concentrations of penicillin G or for prophylaxis of infections caused by these organisms

Dosing: Adults**Note:** Not indicated as single drug therapy for neurosyphilis, but may be given 1 time/week for 3 weeks following I.V. treatment (refer to Penicillin G monograph for dosing)

Group A streptococcal upper respiratory infection: I.M.: 1.2 million units as a single dose

Prophylaxis of recurrent rheumatic fever: I.M.: 1.2 million units every 3-4 weeks or 600,000 units twice monthly

Syphilis:

Early: I.M.: 2.4 million units as a single dose in 2 injection sites

More than 1-year duration: I.M.: 2.4 million units in 2 injection sites once weekly for 3 doses

Neurosyphilis: Not indicated as single-drug therapy, but may be given once weekly for 3 weeks following I.V. treatment; refer to Penicillin G Parenteral/Aqueous monograph for dosing

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Congenital syphilis (asymptomatic): I.M.: Neonates >1200 g: 50,000 units/kg as a single dose

Group A streptococcal upper respiratory infection: I.M.: Infants and Children: 25,000-50,000 units/kg as a single dose (maximum: 1.2 million units)

Prophylaxis of recurrent rheumatic fever: I.M.: Infants and Children: 25,000-50,000 units/kg every 3-4 weeks (maximum: 1.2 million units/dose)

Syphilis:

Early: I.M.: Infants and Children: 50,000 units/kg as a single injection (maximum: 2.4 million units)

More than 1-year duration: I.M.: Infants and Children: 50,000 units/kg every week for 3 doses (maximum: 2.4 million units/dose)

Administration: I.M.Administer by deep I.M. injection in the upper outer quadrant of the buttock. Do **not** give I.V., intra-arterially, or SubQ. When doses are repeated, rotate the injection site.

StorageRefrigerate

ContraindicationsHypersensitivity to penicillin or any component of the formulation

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment.
- Seizure disorders: Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures.
- Syphilis/neurosyphilis use: CDC and AAP do not currently recommend the use of penicillin G benzathine to treat congenital syphilis or neurosyphilis due to reported treatment failures and lack of published clinical data on its efficacy.

Other warnings/precautions:

- Prolonged use: Extended duration of therapy or use associated with high serum concentrations (eg, in renal insufficiency) may be associated with an increased risk for some adverse reactions (neutropenia, hemolytic anemia, serum sickness).

Geriatric ConsiderationsNot indicated as single drug therapy for neurosyphilis, but may be given 1 time/week for 3 weeks following I.V. treatment with Penicillin G (Parenteral/Aqueous). No adjustment for renal function or age is necessary.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, penicillin G is classified as pregnancy category B. Penicillin crosses the placenta and distributes into amniotic fluid. There is no evidence of adverse fetal effects after penicillin use during pregnancy in humans. Penicillin G is the drug of choice for treatment of syphilis during pregnancy.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsPenicillins are excreted in breast milk. The manufacturer recommends that caution be exercised when administering penicillin to nursing women. Nondose-related effects could include modification of bowel flora and allergic sensitization.

Pregnancy & Lactation, In-Depth

- Penicillin G Benzathine in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Convulsions, confusion, drowsiness, myoclonus, fever

Dermatologic: Rash

Endocrine & metabolic: Electrolyte imbalance

Hematologic: Positive Coombs' reaction, hemolytic anemia

Local: Pain, thrombophlebitis

Renal: Acute interstitial nephritis

Miscellaneous: Anaphylaxis, hypersensitivity reactions, Jarisch-Herxheimer reaction

Drug Interactions

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Test InteractionsPositive Coombs' [direct], false-positive urinary and/or serum proteins; false-positive or negative urinary glucose using Clinitest®

Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient’s allergy history prior to starting therapy. Use with caution in presence of impaired renal function or history of seizures. Assess potential for interactions with other pharmacological agents patient may be taking (eg, increase or decrease levels/effect of penicillin). Advise patients with diabetes about use of Clinitest®; may cause false readings. Assess for therapeutic effectiveness (resolution of infection) and adverse reactions (eg, hypersensitivity reactions, opportunistic infection). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity before administering first dose.

Patient EducationThis drug can only be given by injection. Report immediately any redness, swelling, burning, or pain at injection site or any signs of allergic reaction (eg, respiratory difficulty or swallowing, chest tightness, rash, hives, swelling of lips or mouth). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If being treated for sexually-transmitted disease, partner will also need to be treated. If you have diabetes, drug may cause false test results with Clinitest®; consult prescriber for alternative method of glucose monitoring. May cause confusion or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report persistent adverse effects or signs of opportunistic infection (eg, fever, chills, diarrhea, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge, fatigue).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension [prefilled syringe]: 600,000 units/mL (1 mL, 2 mL, 4 mL)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Suspension (Bicillin L-A)

2400000 units/4 mL (4): $89.99

Mechanism of ActionInterferes with bacterial cell wall synthesis during active multiplication, causing cell wall death and resultant bactericidal activity against susceptible bacteria

Pharmacodynamics/Kinetics

Duration: 1-4 weeks (dose dependent); larger doses result in more sustained levels

Distribution: Highest levels in the kidney; lesser amounts in liver, skin, intestines

Protein Binding: ~60%

Absorption: I.M.: Slow

Time to peak, serum: 12-24 hours

Related Information

- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause drowsiness or confusion; penicillins reported to cause apprehension, illusions, hallucinations, depersonalization, agitation, insomnia, and encephalopathy

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBenzathine Benzylpenicillin; Benzathine Penicillin G; Benzylpenicillin Benzathine

References

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WHO Study Group, "Rheumatic Fever and Rheumatic Heart Disease," *World Health Organ Tech Rep Ser*, 1988, 764:1-58. [PubMed 3131967]

Wright AJ, "The Penicillins," *Mayo Clin Proc*, 1999, 74(3):290-307.[PubMed 10090000]

International Brand NamesBenzetacil (BR, EC, ES, MX); Benzetacil L.A. (AR, CO, PE, PY, UY, VE); Bicillin L-A (AU, NZ); Bicillin LA 1.2 (ZA); Bicillin LA 2.4 (ZA); Biconcilina BZ (EC); Brevicilina (ES); Cepacilina (ES); Debecylina (PL); Diaminocillina (IT); Extencilline (FR, HR); Lentocilin-S (PT); Leomypen (DK); LPG (AU); Lutecilina (CO); Pen Di Ben (AR); Penadur (CH, LU); Penadur - LA (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Penadur L.A. (BE, GR, PT); Penadur LA (BF, BJ, CI, ET, GH, GM, GN, HK, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, PH, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Pendepon (CZ); Pendysin (DE); Penidural (NL); Penidure LA 12 (IN); Penidure LA 24 (IN); Penidure LA 6 (IN); Penilente (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Peniroger Retard (ES); Penretard (BR); Provipen Benzatina (ES); Retarpen (AE, AT, BH, CY, CZ, EG, HR, IL, IQ, IR, JO, KW, LB, LY, MY, OM, PL, QA, SA, SG, SY, YE); Tardocillin (DE); Taropen (PL); Wycillina A P (IT); Zalpen (PH)

Penicillin G Procaine

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Penicillin G procaine may be confused with penicillin V potassium

Wycillin® may be confused with Bicillin®

Pronunciation(pen i SIL in jee PROE kane)

Canadian Brand NamesPfizerpen-AS®; Wycillin®

Pharmacologic CategoryAntibiotic, Penicillin

Use: Labeled IndicationsTreatment of moderately-severe infections due to *Treponema pallidum* and other penicillin G-sensitive microorganisms that are susceptible to low, but prolonged serum penicillin concentrations; anthrax due to *Bacillus anthracis* (postexposure) to reduce the incidence or progression of disease following exposure to aerolized *Bacillus anthracis*

Dosing: Adults

Anthrax:

Inhalational (postexposure prophylaxis): I.M.: 1,200,000 units every 12 hours

Note: Overall treatment duration should be 60 days. Available safety data suggest continued administration of penicillin G procaine for longer than 2 weeks may incur additional risk of adverse reactions. Clinicians may consider switching to effective alternative treatment for completion of therapy beyond 2 weeks.

Cutaneous (treatment): I.M.: 600,000-1,200,000 units/day; alternative therapy is recommended in severe cutaneous or other forms of anthrax infection

Endocarditis caused by susceptible viridans*Streptococcus*(when used in conjunction with an aminoglycoside): I.M.: 1.2 million units every 6 hours for 2-4 weeks

Gonorrhea (uncomplicated): 4.8 million units as a single dose divided in 2 sites given 30 minutes after probenecid 1 g orally

Neurosyphilis: I.M.: 2.4 million units/day with 500 mg probenecid by mouth 4 times/day for 10-14 days; **penicillin G aqueous I.V. is the preferred agent**

Whipple's disease: I.M.: 1.2 million units/day (with streptomycin) for 10-14 days, followed by oral trimethoprim/sulfamethoxazole or doxycycline for 1 year

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Susceptible infections: I.M.: Infants and Children: 25,000-50,000 units/kg/day in divided doses 1-2 times/day; not to exceed 4.8 million units/24 hours

Anthrax, inhalational (postexposure prophylaxis): I.M.: 25,000 units/kg every 12 hours (maximum: 1,200,000 units every 12 hours).

Note: Overall treatment duration should be 60 days. Available safety data suggest continued administration of penicillin G procaine for longer than 2 weeks may incur additional risk for adverse reactions. Clinicians may consider switching to effective alternative treatment for completion of therapy beyond 2 weeks.

Syphilis (congenital): I.M.: 50,000 units/kg/day once daily for 10 days; if more than 1 day of therapy is missed, the entire course should be restarted

Dosing: Renal Impairment

Cl_{cr} 10-30 mL/minute: Administer every 8-12 hours.

Cl_{cr} <10 mL/minute: Administer every 12-18 hours.

Moderately dialyzable (20% to 50%)

Administration: I.M.Procaine suspension is for deep I.M. injection only. Rotate the injection site. Do not inject in gluteal muscle in children <2 years of age.

StorageRefrigerate

ContraindicationsHypersensitivity to penicillin, procaine, or any component of the formulation

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- Neurovascular damage: Avoid I.V., intravascular, or intra-arterial administration since severe and/or permanent neurovascular damage may occur.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with severe renal impairment; dosage adjustment recommended.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures.

Other warnings/precautions:

- Prolonged use: Extended duration of therapy or use associated with high serum concentrations (eg, in renal insufficiency) may be associated with an increased risk for some adverse reactions (neutropenia, hemolytic anemia, serum sickness).

Geriatric ConsiderationsDosage does not usually need to be adjusted in the elderly, however, if multiple doses are to be given, adjust dose for renal function.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, penicillin G is classified as pregnancy category B. Penicillin crosses the placenta and distributes into amniotic fluid. There is no evidence of adverse fetal effects after penicillin use during pregnancy in humans.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsPenicillins are excreted in breast milk. The manufacturer recommends that caution be exercised when administering penicillin to nursing women. Nondose-related effects could include modification of bowel flora and allergic sensitization.

Pregnancy & Lactation, In-Depth

- Penicillin G Procaine in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Cardiovascular: Myocardial depression, vasodilation, conduction disturbances

Central nervous system: Confusion, drowsiness, myoclonus, CNS stimulation, seizure

Hematologic: Positive Coombs' reaction, hemolytic anemia, neutropenia

Local: Pain at injection site, thrombophlebitis, sterile abscess at injection site

Renal: Interstitial nephritis

Miscellaneous: Pseudoanaphylactic reactions, hypersensitivity reactions, Jarisch-Herxheimer reaction, serum sickness

Drug Interactions

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Test InteractionsPositive Coombs' [direct], false-positive urinary and/or serum proteins

Monitoring ParametersPeriodic renal and hematologic function tests with prolonged therapy; fever, mental status, WBC count

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's allergy history prior to starting therapy. Use with caution and monitor closely in presence of renal impairment or seizure disorder. Assess potential for interactions with other pharmacological agents (eg, decreased or increased levels/effects of penicillin G). Avoid intravascular or intra-arterial administration or injection into or near major peripheral nerves or blood vessels; may cause severe and/or permanent neurovascular damage. Advise patients with diabetes about use of Clinitest®; may cause false positive or negative. Assess effectiveness (resolution of infections) and adverse reactions (eg, hypersensitivity reactions, opportunistic infection [fever, chills, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge, fatigue], CNS changes, thrombophlebitis). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsPeriodic renal and hematologic function with prolonged therapy; WBC count; perform culture and sensitivity before administering first dose.

Patient EducationThis drug can only be given by injection. Report immediately any redness, swelling, burning, or pain at injection site or any signs of allergic reaction (eg, respiratory or swallowing difficulty, chest tightness, rash, hives, swelling of lips or mouth). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If being treated for sexually-transmitted disease, partner will also need to be treated. If you have diabetes, drug may cause false test results with Clinitest®, consult prescriber for alternative method of glucose monitoring. May cause confusion or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report persistent adverse effects or signs of opportunistic infection (eg, fever, chills, diarrhea, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge, fatigue).

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension: 600,000 units/mL (1 mL, 2 mL)

Generic Available Yes

Mechanism of Action Inhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs); which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Duration: Therapeutic: 15-24 hours

Absorption: I.M.: Slow

Distribution: Penetration across the blood-brain barrier is poor, despite inflamed meninges

Protein binding: 65%

Metabolism: ~30% hepatically inactivated

Time to peak, serum: 1-4 hours

Excretion: Urine (60% to 90% as unchanged drug)

Clearance: Renal: Delayed in neonates, young infants, and with impaired renal function

Related Information

- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May rarely cause drowsiness, confusion, or CNS stimulation

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms APPG; Aqueous Procaine Penicillin G; Procaine Benzylpenicillin; Procaine Penicillin G; Wycillin [DSC]

References

Donowitz GR and Mandell GL, “Beta-Lactam Antibiotics,” *N Engl J Med*, 1988, 318(7):419-26 and 318(8):490-500. [PubMed 3277054]

Paryani SG, Vaughn AJ, Crosby M, et al, “Treatment of Asymptomatic Congenital Syphilis: Benzathine Versus Procaine Penicillin G Therapy,” *J Pediatr*, 1994, 125(3):471-5. [PubMed 8071762]

Wright AJ, “The Penicillins,” *Mayo Clin Proc*, 1999, 74(3):290-307. [PubMed 10090000]

Yoshikawa TT, “Antimicrobial Therapy for the Elderly Patient,” *J Am Geriatr Soc*, 1990, 38(12):1353-72.[PubMed 2254575]

International Brand Names Aquacaine (AU); Aqucilina (ES); Benzetacil (MX); Cidan-Cilina 900 (ES); Cilicaine Syringe (AU); Farmaproina (ES); Fradicilina (ES); Hidrociclina (MX); Intrasept (CH); Jenacillin O (DE); Klaricina (ES); Mudapenil (AR); Pam (NL); Penicillinum procainicum (PL); Peniern (ES); Penifasa 900 (ES); Peniroger Procain (ES); Procain-Penicillin Streuli (CH); Procaine Penicillin. G (FI); Procapen (FI); Provipen Procaina (ES); Retardillin (HU); Servipen-G Forte (CH)

Penicillin V Potassium

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Medication Safety Issues

Sound-alike/look-alike issues:

Penicillin V procaine may be confused with penicillin G potassium

Pronunciation(pen i SIL in vee poe TASS ee um)
Canadian Brand NamesApo-Pen VK®; Novo-Pen-VK; Nu-Pen-VK
Pharmacologic CategoryAntibiotic, Penicillin
Use: Labeled IndicationsTreatment of infections caused by susceptible organisms involving the respiratory tract, otitis media, sinusitis, skin, and urinary tract; prophylaxis in rheumatic fever
Use: DentalAntibiotic of first choice in treatment of common orofacial infections caused by aerobic gram-positive cocci and anaerobes. These orofacial infections include cellulitis, periapical abscess, periodontal abscess, acute suppurative pulpitis, oronasal fistula, pericoronitis, osteitis, osteomyelitis, postsurgical and post-traumatic infection. **Note: This agent is no longer recommended for dental procedure prophylaxis.**
Dosing: Adults

Acintomycosis:

Mild: 2-4 g/day in 4 divided doses for 8 weeks

Surgical: 2-4 g/day in 4 divided doses for 6-12 months (after I.V. penicillin G therapy of 4-6 weeks)

Erysipelas: 500 mg 4 times/day

Pharyngitis (streptococcal): 500 mg 3-4 times/day for 10 days

Prophylaxis of pneumococcal or recurrent rheumatic fever infections: 250 mg twice daily

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Pharyngitis (streptococcal): 250 mg 2-3 times/day for 10 days

Prophylaxis of pneumococcal infections:

Children <5 years: 125 mg twice daily

Children ≥5 years: 250 mg twice daily

Prophylaxis of recurrent rheumatic fever:

Children <5 years: 125 mg twice daily

Children ≥5 years: 250 mg twice daily

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer every 8-12 hours.

Cl_{cr} <10 mL/minute: Administer every 12-16 hours.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V. DetailpH: 6.0-8.5
Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels. Take on an empty stomach 1 hour before or 2 hours after meals, to enhance absorption, take until gone, do not skip doses.
Dietary ConsiderationsTake on an empty stomach 1 hour before or 2 hours after meals.
StorageRefrigerate suspension after reconstitution; discard after 14 days.
ContraindicationsHypersensitivity to penicillin or any component of the formulation
Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with severe renal impairment; dosage adjustment recommended.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures.

Other warnings/precautions:

- Prolonged use: Extended duration of therapy or use associated with high serum concentrations (eg, in renal insufficiency) may be associated with an increased risk for some adverse reactions (neutropenia, hemolytic anemia, serum sickness).

Geriatric ConsiderationsDosage adjustment in the elderly is usually not necessary.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, penicillin V is classified as pregnancy category B. Penicillin crosses the placenta and distributes into amniotic fluid. There is no evidence of adverse fetal effects after penicillin use during pregnancy in humans. Due to pregnancy-induced physiologic changes, some pharmacokinetic parameters of penicillin V may be altered in the second and third trimester. Higher doses or increased dosing frequency may be required.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsPenicillins are excreted in breast milk. The manufacturer recommends that caution be exercised when administering penicillin to nursing women. Nondose-related effects could include modification of bowel flora and allergic sensitization.

Pregnancy & Lactation, In-Depth

- Penicillin V Potassium in Pregnancy & Lactation

Adverse Reactions

>10%: Gastrointestinal: Mild diarrhea, vomiting, nausea, oral candidiasis

<1%: Convulsions, fever, hemolytic anemia, positive Coombs' reaction, acute interstitial nephritis, hypersensitivity reactions, anaphylaxis

Drug Interactions

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Decreases drug absorption rate; decreases drug serum concentration.

Test InteractionsFalse-positive or negative urinary glucose determination using Clinitest®; positive Coombs' [direct]; false-positive urinary and/or serum proteins

Monitoring ParametersPeriodic renal and hematologic function tests during prolonged therapy; monitor for signs of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient’s allergy history prior to starting therapy. Use with caution in presence of renal impairment. Assess potential for interactions with other pharmacological agents (eg, decreased or increased levels/effects of penicillin V). Assess results of laboratory tests, effectiveness (resolution of infection), and adverse reactions (eg, hypersensitivity reactions, opportunistic infection [fever, chills, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge, fatigue]). Advise patients with diabetes about use of Clinitest®; may cause false readings. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsPeriodic renal and hematologic function during prolonged therapy; perform culture and sensitivity before administering first dose.

Patient EducationTake as directed at intervals around-the-clock, preferable on an empty stomach (1 hour before or 2 hours after a meal). Take entire prescription; do not skip doses or discontinue without consulting prescriber. Take a missed dose as soon as possible. If almost time for next dose, skip the missed dose and return to your regular schedule. Do not take a double dose. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, drug may cause false test results with Clinitest®, consult prescriber for alternative method of glucose monitoring. May cause nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report persistent adverse effects; signs of opportunistic infection (eg, fever, chills, diarrhea, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge, fatigue); or signs of hypersensitivity reaction (rash, hives, itching, swelling of lips, tongue, mouth, or throat).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: 250 mg = 400,000 units

Powder for oral solution: 125 mg/5 mL (100 mL, 200 mL); 250 mg/5 mL (100 mL, 200 mL)

Tablet: 250 mg, 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Penicillin V Potassium)

250 mg/5 mL (100): $12.99

Tablets (Penicillin V Potassium)

250 mg (30): $12.99

500 mg (30): $22.99

Tablets (Veetids)

500 mg (30): $13.99

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs); which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Absorption: 60% to 73%

Distribution: Widely distributed to kidneys, liver, skin, tonsils, and into synovial, pleural, and pericardial fluids

Protein binding, plasma: 80%

Half-life elimination: 30 minutes; prolonged with renal impairment

Time to peak, serum: 0.5-1 hour

Excretion: Urine (as unchanged drug and metabolites)

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Desensitization Protocols

Pharmacotherapy Pearls0.7 mEq of potassium per 250 mg penicillin V; 250 mg equals 400,000 units of penicillin

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral candidiasis (prolonged use).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusPenicillins reported to cause apprehension, illusions, hallucinations, depersonalization, agitation, insomnia, and encephalopathy

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPen VK; Phenoxymethyl Penicillin

References

Dajani AS, Bisno AL, Chung KJ, et al, “Prevention of Rheumatic Fever. A Statement for Health Professionals by the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, The American Heart Association,” *Pediatr Infect Dis J*, 1989, 8(5):263-6. [PubMed 2726321]

Slots J, Research, Science and Therapy Committee, "Systemic Antibiotics in Periodontics," *J Periodontol*, 2004, 75(11):1553-65.[PubMed 15633334]

Wynn RL and Bergman SA, “Antibiotics and Their Use in the Treatment of Orofacial Infections, Part I and Part II,” *Gen Dent*, 1994, 42(5):398-402, 498-502.[PubMed 7489869]

International Brand NamesAbbocillin VK (AU); Anapenil (MX); Beapen (MY); Cilicaine VK (AU); Fenocin (ID); Kaypen (IN); L.P.V. (AU); Len V.K. (ZA); Megacilina Oral (PE); Milcopen (FI); Oracillin VK (ZA); Orvek (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ospa-V (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ospen (FR, MY, SG, UY, VE); Ospen 250 (AT); Pen V (HK); Pen-Vi-K (MX); Penilevel (ES); Penoxil (MY); Pentranex (PH); Pota-Vi-Kin (MX); Prevecilina (CO); Rafapen V-K (IL); Robicillin VK (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Servipen-V (TH); V-Cil-K (BB, BF, BJ, BM, BS, BZ, CI, ET, GH, GM, GN, GY, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, PR, SC, SD, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); V-Cillin K (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW)

Pentafluoropropane and Tetrafluoroethane

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English

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Pronunciation

(pen ta flure oh PRO pane & tet ra flure oh ETH ane)

U.S. Brand NamesGebauer's Instant Ice™ [OTC]; Gebauer's Pain Ease®; Gebauer's Spray and Stretch®

Pharmacologic CategoryAnesthetic, Topical

Use: Labeled Indications

Treatment of myofascial pain, restricted motion due to muscle tension, muscle spasm and minor sports injuries (eg, bruises, contusions, swelling, minor sprains); pain associated with injections or minor surgical procedures

Dosing: Adults

Myofascial pain, restricted motion, muscle tension: Topical: Spray over affected muscle at a rate of ~4 inches/second (10 cm/second), including muscle attachment, trigger point, and reference zone; may repeat if necessary. **Note:** Passively stretch the muscle during application.

Temporary relief of minor sports injury, preinjection anesthesia, anesthetic in minor surgery: Topical: Dosage varies with duration of application. Spray over affected area for 4-10 seconds from a distance of 3-7 inches (8-18 cm); spray until skin begins to turn white; do not frost the skin. Reapply as needed.

Dosing: ElderlyRefer to adult dosing.

Administration: Topical

For external use only. Discontinue if skin becomes irritated. Do not use near face, open wounds, or abraded skin. Adjacent skin areas may be protected with petroleum.

Myofascial pain: Aim the spray so it meets the skin at an acute angle. Direct in parallel sweeps 0.5-1 inches apart at the rate of 4 inches/second. Passively stretch the muscle during application; increase the force of the stretch with successive sweeps. As the muscle relaxes, establish a new stretch length. For complete pain relief, the full, normal length of the muscle must be reached. Apply moist heat for 10-15 minutes after treatment. Avoid use on unaffected area.

Sports injuries: Spray until the skin begins to turn white. Avoid use on unaffected areas.

StorageStore at room temperature. Avoid exposure to temperatures ≥49°C (≥120°F). Do not puncture or incinerate container.

Contraindications

Hypersensitivity to pentafluoropropane, tetrafluoroethane, or any other component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Skin irritation: Discontinue if skin becomes irritated.
- Skin pigmentation: Overuse may alter skin pigmentation.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus.
- Poor circulation: Use with caution in patients with poor circulation.

Other warnings/precautions:

- Appropriate use: For external use only; do not use on large areas of damaged skin, puncture wounds, animal bites, serious wounds, or genital mucous membranes. Provides temporary relief (<1 minute) in sports injuries; initiate other therapy as soon as possible.
- OTC labeling: Do not spray near face, on open wounds, or abraded skin.

Pregnancy ConsiderationsTeratogenic effects were not noted in animal studies.

Adverse Reactions

Frequency not defined.

Dermatologic: Skin irritation, skin pigmentation change, frostbite

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol, topical spray:

Gebauer's Spray and Stretch®: Pentafluoropropane 95% and tetrafluoroethane 5% (103.5 mL) [available in fine stream spray]

Gebauer's Pain Ease®: Pentafluoropropane 95% and tetrafluoroethane 5% (103.5 mL) [available in mist spray or medium stream spray]

Gebauer's Instant Ice™ [OTC]: Pentafluoropropane 95% and tetrafluoroethane 5% (103.5 mL) [available in mist spray or stream spray]

Generic AvailableNo

Mechanism of Action

Vapocoolant and counterirritant

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsTetrafluoroethane and Pentafluoropropane

Pentamidine

Lexi-Drugs Online

English English

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Pronunciation(pen TAM i deen)

U.S. Brand NamesNebuPent®; Pentam-300®

Canadian Brand NamesPentamidine Isetionate for Injection

Pharmacologic CategoryAntibiotic, Miscellaneous

Use: Labeled IndicationsTreatment and prevention of pneumonia caused by *Pneumocystis carinii* (PCP)

Use: Unlabeled/InvestigationalTreatment of trypanosomiasis and visceral leishmaniasis

Dosing: Adults

Treatment of PCP pneumonia: I.M., I.V. (I.V. preferred): 4 mg/kg/day once daily for 14 days

Prevention of PCP pneumonia: Inhalation: 300 mg every 4 weeks via Respirgard® II nebulizer

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Treatment of PCP pneumonia: I.M., I.V. (I.V. preferred): Children: 4 mg/kg/day once daily for 10-14 days

Prevention of PCP pneumonia: Children:

> *I.M., I.V.:* 4 mg/kg monthly or every 2 weeks
>
> *Inhalation (aerosolized pentamidine in children ≥5 years):* 300 mg/dose given every 3-4 weeks via Respirgard® II inhaler (8 mg/kg dose has also been used in children <5 years)

Treatment of trypanosomiasis (unlabeled use): I.V.: 4 mg/kg/day once daily for 10 days

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer dose every 24-36 hours.

Cl_{cr} <10 mL/minute: Administer dose every 48 hours.

Not removed by hemo- or peritoneal dialysis or continuous arteriovenous or venovenous hemofiltration. Supplemental dose is not necessary.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Deep I.M.

Administration: I.V.Do not use NS as a diluent. Infuse I.V. slowly over a period of at least 60 minutes or administer deep I.M.

Administration: I.V. DetailpH: 5.4 (sterile water); 4.09-4.38 (D_5W)

Administration: InhalationDeliver until nebulizer is gone (30-45 minutes). Virtually undetectable amounts are transferred to healthcare personnel during aerosol administration.

StorageStore intact vials at controlled room temperature and protect from light. Do not refrigerate due to the possibility of crystallization. Reconstituted solutions (60-100 mg/mL) are stable for 48 hours at room temperature and do not require light protection. Diluted solutions for injection (1-2.5 mg/mL) in D_5W are stable for at least 24 hours at room temperature. The manufacturer recommends D_5W, however stability in NS has also been documented; in addition, light protection is recommended by the manufacturer, but stability has been documented without protection from light.

ReconstitutionPowder for inhalation should be reconstituted with SWFI. Powder for injection may be reconstituted with SWFI or D_5W. Precipitation may occur if products are reconstituted with NS.

CompatibilitySolutions for injection (1-2.5 mg/mL) in D_5W are stable for at least 24 hours at room temperature. The manufacturer's labeling recommends D_5W, however stability in NS has also been documented.

Y-site administration: Compatible: Diltiazem, gatifloxacin, zidovudine. **Incompatible:** Aldesleukin, cefazolin, cefoperazone, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, fluconazole, foscarnet, linezolid.

ContraindicationsHypersensitivity to pentamidine isethionate or any component of the formulation (inhalation and injection)

Warnings/Precautions

Concerns related to adverse effects:

- Hypotension: Severe hypotension (some fatalities) has been observed, even after a single dose; more common with rapid I.V. administration.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Asthma: Use with caution in patients with asthma.

- Cardiovascular disease: Use with caution in patients with pre-existing cardiovascular disease; hyper-/hypotension and arrhythmia, including ventricular tachycardia have been reported.

- Diabetes: Use with caution in patients with diabetes mellitus; hyper-/hypoglycemia and pancreatic islet cell necrosis with hyperinsulinemia has been reported. Symptoms may occur months after therapy; monitor blood glucose daily on therapy and periodically thereafter.

- Hematologic disorders: Use with caution in patients with current evidence and/or prior history of hematologic disorders; anemia, leukopenia and/or thrombocytopenia have been reported.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Pancreatitis: Use with caution in patients with a history of pancreatic disease or elevated amylase/lipase levels; acute pancreatitis has been reported.

- Renal impairment: Use with caution in patients with renal impairment.

Other warnings/precautions:

- Extravasation: May cause tissue ulceration and/or necrosis. Treat symptomatically.

Geriatric ConsiderationsTen percent of acquired immunodeficiency syndrome (AIDS) cases are in the elderly and this figure is expected to increase. Pentamidine has not as yet been studied exclusively in this population. Adjust dose for renal function.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/contraindicated
Adverse ReactionsInjection (I); Aerosol (A)

>10%:

Cardiovascular: Chest pain (A - 10% to 23%)

Central nervous system: Fatigue (A - 50% to 70%); dizziness (A - 31% to 47%)

Dermatologic: Rash (31% to 47%)

Endocrine & metabolic: Hyperkalemia

Gastrointestinal: Anorexia (A - 50% to 70%), nausea (A - 10% to 23%)

Local: Local reactions at injection site

Renal: Increased creatinine (I - 23%)

Respiratory: Wheezing (A - 10% to 23%), dyspnea (A - 50% to 70%), cough (A - 31% to 47%), pharyngitis (10% to 23%)

1% to 10%:

Cardiovascular: Hypotension (I - 4%)

Central nervous system: Confusion/hallucinations (1% to 2%), headache (A - 1% to 5%)

Dermatologic: Rash (I - 3.3%)

Endocrine & metabolic: Hypoglycemia <25 mg/dL (I - 2.4%)

Gastrointestinal: Nausea/anorexia (I - 6%), diarrhea (A - 1% to 5%), vomiting

Hematologic: Severe leukopenia (I - 2.8%), thrombocytopenia <20,000/mm^3 (I - 1.7%), anemia (A - 1% to 5%)

Hepatic: Increased LFTs (I - 8.7%)

<1%: Hypotension <60 mm Hg systolic (I - 0.9%), tachycardia, arrhythmia, dizziness (I), fever, fatigue (I), hyperglycemia or hypoglycemia, hypocalcemia, pancreatitis, megaloblastic anemia, granulocytopenia, leukopenia, renal insufficiency, extrapulmonary pneumocystosis, irritation of the airway, pneumothorax, Jarisch-Herxheimer-like reaction, mild renal or hepatic injury

Oncology: VesicantNo
Metabolism/Transport Effects**Substrate** of CYP2C19 (major); **Inhibits** CYP2C8/9 (weak), 2C19 (weak), 2D6 (weak), 3A4 (weak)
Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression or aggravate hypoglycemia).

Monitoring ParametersLiver function tests, renal function tests, blood glucose, serum potassium and calcium, ECG, blood pressure

Nursing: Physical Assessment/MonitoringAssess patient for cautious use conditions and previous allergy history. Assess potential for interactions with other pharmacological agents patient may be taking (eg, increase or decrease levels/effects of pentamidine). **I.V., I.M.:** Patients should be lying down. Blood pressure, cardiac status, and respiratory function should be monitored closely during I.V. administration or following I.M. injection. Evaluate results of laboratory tests, therapeutic response, and adverse reactions (eg, chest pain, hypotension, rash, confusion, hallucinations, hypoglycemia, dyspnea, cough). Teach patient proper use (eg, nebulizer use if self-administered), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsLiver and renal function, blood glucose, serum potassium and calcium, ECG, CBC with platelets

Patient EducationDo not take any new medication during therapy without consulting prescriber. I.V. or I.M. preparations must be given every day (if I.M. is self-administered follow exact directions for injection and disposal of syringe/needle). Inhalant drug must be prepared and used with a nebulizer exactly as directed once every 4 weeks. Frequent blood tests and blood pressure checks will be required while using this drug. PCP pneumonia may still occur despite pentamidine use. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid excessive alcohol (may exacerbate adverse effects). If you have diabetes, monitor glucose levels closely and frequently. May cause hypotension (use caution when rising from sitting or lying position or when climbing stairs); or metallic taste, nausea, vomiting, or anorexia (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report chest pain or irregular heartbeat; unusual confusion or hallucinations; rash; or unusual wheezing, coughing, or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as isethionate [preservative free]:

Pentam-300®: 300 mg

Powder for solution, for nebulization, as isethionate [preservative free]:

NebuPent®: 300 mg

Generic AvailableNo

Mechanism of ActionInterferes with RNA/DNA, phospholipids and protein synthesis, through inhibition of oxidative phosphorylation and/or interference with incorporation of nucleotides and nucleic acids into RNA and DNA, in protozoa

Pharmacodynamics/Kinetics

Absorption: I.M.: Well absorbed; Inhalation: Limited systemic absorption

Half-life elimination: Terminal: 6.4-9.4 hours; may be prolonged with severe renal impairment

Excretion: Urine (33% to 66% as unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsVirtually undetectable amounts are transferred to healthcare personnel during aerosol administration.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsPentamidine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusSedation and dizziness are common; may cause confusion or hallucinations

Mental Health: Effects on Psychiatric TreatmentContraindicated with ziprasidone. May cause leukopenia; use caution with clozapine and carbamazepine.

Index TermsPentamidine Isethionate

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International Brand Names Pentacarinat (AT, BB, BE, BG, BM, BS, BZ, CH, CZ, DE, DK, ES, FI, FR, GB, GR, GY, HK, HN, IE, IT, JM, NL, NO, NZ, PR, PT, RU, SE, SR, TH, TR, TT); Pentam 300 (MX)

Pentastarch

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(PEN ta starch)
U.S. Brand NamesPentaspan速
Canadian Brand NamesPentaspan速
Pharmacologic CategoryBlood Modifiers
Use: Labeled Indications**Orphan drug:** Adjunct in leukapheresis to improve harvesting and increase yield of leukocytes by centrifugal means
Dosing: Adults**Leukapheresis:** 250-700 mL to which citrate anticoagulant has been added is administered by adding to the input line of the centrifugation apparatus at a ratio of 1:8-1:13 to venous whole blood
Dosing: ElderlyRefer to adult dosing.
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed in NS]: 10% (500 mL)

Generic AvailableNo
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesHAES-steril (GB, NO)

Pentazocine and Acetaminophen

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Talacen® may be confused with Tegison®, Timoptic®, Tinactin®

International issues:

Talacen® may be confused with Talliton® which is a brand name for carvedilol in Hungary

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(pen TAZ oh seen & a seet a MIN oh fen)
U.S. Brand NamesTalacen®
Pharmacologic CategoryAnalgesic Combination (Opioid)
Use: Labeled IndicationsRelief of mild to moderate pain
Use: DentalRelief of mild to moderate pain
Dosing: Adults**Analgesic:** Oral: 1 caplet every 4 hours (maximum: 6 caplets/day)
Dosing: ElderlyRefer to adult dosing. Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.
StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
RestrictionsC-IV
ContraindicationsHypersensitivity to pentazocine, acetaminophen, or any component of the formulation
Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hepatotoxicity: May cause severe hepatic toxicity on acute overdose; in addition, chronic daily dosing in adults has resulted in liver damage in some patients.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.
- G6PD deficiency: Use with caution in patients with known G6PD deficiency.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic dysfunction.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Renal impairment: Use with caution in patients with renal dysfunction.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

- Seizures: Use with caution in patients with a history of seizure disorders.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

Dosage form specific issues:

- Sodium metabisulfite: May contain sodium metabisulfite; may cause allergic-type reactions

Other warnings/precautions:

- Dosage limit: Limit acetaminophen dose to <4 g/day.

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms; taper dose to decrease risk of withdrawal symptoms.

Pregnancy Risk FactorC/D (prolonged use or high doses at term)
Pregnancy ConsiderationsPentazocine was not found to be teratogenic in animal studies. Pentazocine and acetaminophen cross the placenta in humans. Use should be avoided during labor and delivery of premature infants. Abstinence syndromes in the newborn have been reported after long-term use of pentazocine during pregnancy. Other adverse effects in the newborn have been reported following abuse of pentazocine during pregnancy; these effects may be due to pentazocine, other drugs abused, the mother's lifestyle, or a combination of all factors.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsExcretion of pentazocine in breast milk is unknown; acetaminophen is excreted in breast milk
Adverse ReactionsAdverse reactions attributed to pentazocine 50 mg. Frequency not defined.

Cardiovascular: Flushing, hypotension, syncope, tachycardia

Central nervous system: Chills, confusion, depression, disorientation, dizziness, drowsiness, euphoria, excitement, hallucinations, headache, insomnia, irritability, lightheadedness, sedation

Dermatologic: Erythema multiforme, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Gastrointestinal: Abdominal distress, anorexia, biliary spasm, constipation, diarrhea, nausea, vomiting

Genitourinary: Urinary retention

Hematologic: Agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenic purpura, WBCs decreased

Neuromuscular & skeletal: Paresthesia, tremor, weakness

Ocular: Blurred vision

Otic: Tinnitus

Respiratory: Respiratory depression

Miscellaneous: Anaphylaxis, diaphoresis, facial edema

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet:

Talacen®: Pentazocine 25 mg and acetaminophen 650 mg [contains sodium metabisulfite]

Tablet: Pentazocine 25 mg and acetaminophen 650 mg

Generic AvailableYes
ManufacturerSanofi-Aventis U.S. LLC
Pricing: U.S. (www.drugstore.com)

Tablets (Pentazocine-APAP)

25-650 mg (30): $39.99

Mechanism of Action

Pentazocine: Binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression; partial agonist-antagonist

Acetaminophen: Inhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation

Pharmacodynamics/KineticsSee individual agents.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Index TermsAcetaminophen and Pentazocine; Pentazocine Hydrochloride and Acetaminophen

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Pentazocine

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English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(pen TAZ oh seen)

U.S. Brand NamesTalwin®; Talwin® Nx

Canadian Brand NamesTalwin®

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled Indications

Talwin®: Relief of moderate-to-severe pain; has also been used as a sedative prior to surgery and as a supplement to surgical anesthesia

Talwin® Nx: Relief of moderate-to-severe pain; indicated for oral use only

Dosing: Adults**Analgesic:**

Oral: 50 mg every 3-4 hours; may increase to 100 mg/dose if needed, but should not exceed 600 mg/day (maximum: 12 tablets/day)

I.M., SubQ: 30-60 mg every 3-4 hours; do **not** exceed 60 mg/dose (maximum: 360 mg/day)

I.V.: 30 mg every 3-4 hours; do **not** exceed 30 mg/dose (maximum: 360 mg/day)

Dosing: ElderlyUse with caution; may be more sensitive to analgesic and sedative effects; decrease initial dose and monitor closely

Dosing: Pediatric

Analgesia:

I.M.: Children:

5-8 years: 15 mg

8-14 years: 30 mg

Oral: Children >12 years: Refer to adult dosing.

Preoperative/preanesthetic: Children 1-16 years: I.M.: 0.5 mg/kg

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer 75% of normal dose.

Cl_{cr} <10 mL/minute: Administer 50% of normal dose.

Dosing: Hepatic ImpairmentReduce dose or avoid use in patients with liver disease.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Opioid Agonist Conversion

Administration: I.M.Rotate injection site; avoid intra-arterial injection

Administration: I.V. DetailpH: 4-5 (adjusted with lactic acid or sodium hydroxide)

Administration: OtherRotate injection site; avoid SubQ use unless absolutely necessary (may cause tissue damage); avoid intra-arterial injection

Storage

Injection: Store at 20°C to 25°C (68°F to 77°F); do not freeze. Protect from heat.

Tablet: Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

Compatibility

Y-site administration: Compatible: Heparin, hydrocortisone sodium succinate, potassium chloride, vitamin B complex with C. **Incompatible:** Nafcillin.

Compatibility in syringe: Compatible: Atropine, butorphanol, chlorpromazine, cimetidine, dimenhydrinate, diphenhydramine, droperidol, fentanyl, hydromorphone, hydroxyzine, meperidine, meperidine with perphenazine, metoclopramide, morphine, perphenazine, prochlorperazine edisylate, promazine, promethazine, propiomazine, ranitidine, scopolamine. **Incompatible:** Glycopyrrolate, heparin, pentobarbital.

Compatibility when admixed: Incompatible: Aminophylline, amobarbital, pentobarbital, phenobarbital, sodium bicarbonate.

RestrictionsC-IV

ContraindicationsHypersensitivity to pentazocine, naloxone, or any component of the formulation

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Talwin® Nx: See "Dosage form specific issues" below.

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Injection-site reactions: Severe sclerosis has occurred at the injection-site following multiple injections; avoid SubQ use unless absolutely necessary; rotate sites of injection.
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Ethanol use: Use with caution due to the potential for increased risk of CNS depressant effects.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic dysfunction.
- Obesity: Use with caution in patients who are morbidly obese.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Renal impairment: Use with caution in patients with renal dysfunction.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.
- Seizures: Use with caution in patients with a history of seizure disorders.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.
- Pediatrics: Safety and efficacy have not been established in children <1 year of age (Talwin®) and <12 years of age (Talwin® Nx).

Dosage form specific issues:

- Sulfites: Injection may contain sulfites which may cause allergic reaction.
- Talwin® Nx: **[U.S. Boxed Warning]: Talwin® Nx is intended for oral administration only - severe vascular reactions have resulted from misuse by injection.**

Other warnings/precautions:

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms; taper dose to decrease risk of withdrawal symptoms.

Geriatric ConsiderationsPentazocine is not recommended for use in the elderly because of its propensity to cause delirium and agitation. If pentazocine must be used, be sure to adjust dose for renal function.

Pregnancy Risk FactorC/D (prolonged use or high doses at term)

Pregnancy ConsiderationsPentazocine was not found to be teratogenic in animal studies. Pentazocine and naloxone have been shown to cross the human placenta. Use should be avoided during labor and delivery of premature infants. Abstinence syndromes in the newborn have been reported after long-term use of pentazocine during pregnancy. Other adverse effects in the newborn have been reported following abuse of pentazocine during pregnancy; these effects may be due to pentazocine, other drugs abused, the mother's lifestyle, or a combination of all factors.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsExcretion of pentazocine in breast milk is unknown; no data available for naloxone

Adverse ReactionsFrequency not defined.

Cardiovascular: Circulatory depression, facial edema, flushing, hypotension, shock, syncope, tachycardia

Central nervous system: Chills, CNS depression, confusion, disorientation, dizziness, drowsiness, euphoria, excitement, hallucinations, headache, insomnia, irritability, lightheadedness, malaise, nightmares, sedation

Dermatologic: Dermatitis, erythema multiforme, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Gastrointestinal: Abdominal distress, anorexia, constipation, diarrhea, nausea, vomiting, xerostomia

Genitourinary: Urinary retention

Hematologic: Decreased WBCs, eosinophilia

Local: Tissue damage and irritation with I.M./SubQ use

Neuromuscular & skeletal: Paresthesia, tremor, weakness

Ocular: Blurred vision, miosis

Otic: Tinnitus

Respiratory: Dyspnea, respiratory depression (rare)

Miscellaneous: Anaphylaxis, diaphoresis, physical and psychological dependence

Oncology: VesicantLocal effects (stinging, induration, ulceration, thrombosis) have been associated with chronic use of pentazocine. I.M. injections are reported to cause less local tissue damage than SubQ injections.

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersRelief of pain, respiratory and mental status, blood pressure

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for additive or adverse interactions. Monitor therapeutic effectiveness, adverse reactions, and overdose at beginning of therapy and at regular intervals with long-term use. May cause physical and/or psychological dependence. For inpatients, implement safety measures. Assess knowledge/teach patient appropriate use (if self-administered), adverse reactions to report and appropriate interventions to reduce side effects..

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially sedatives, tranquilizers, antihistamines, or pain medications) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause hypotension, dizziness, drowsiness, impaired coordination, or blurred vision (use caution when driving, climbing stairs, or changing position - rising from sitting or lying to standing, or when engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, loss of appetite, or dry mouth (frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help; if unresolved, consult prescriber about use of stool softeners). Report persistent dizziness or headache; excessive fatigue or sedation; changes in mental status; changes in urinary elimination or pain on urination; weakness or trembling; blurred vision; or shortness of breath. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Talwin®: 30 mg/mL (1 mL, 10 mL) [10 mL size contains sodium bisulfite]

Tablet: Pentazocine 50 mg and naloxone 0.5 mg

Talwin® Nx: Pentazocine 50 mg and naloxone 0.5 mg

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Solution (Talwin)

30 mg/mL (10): $74.42

Tablets (Pentazocine-Naloxone HCl)

50-0.5 mg (30): $40.22

Tablets (Talwin NX)

50-0.5 mg (30): $65.09

Mechanism of Action

Pentazocine: Binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression; partial agonist-antagonist

Naloxone: Pure opioid antagonist that competes for and displaces narcotics at opioid receptor sites in CNS

Pharmacodynamics/Kinetics

Onset of action: Oral, I.M., SubQ: 15-20 minutes; I.V.: 2-3 minutes

Duration: Oral: 4-5 hours; Parenteral: 2-3 hours

Protein binding: 60%

Metabolism: Hepatic via oxidative and glucuronide conjugation pathways; extensive first-pass effect

Bioavailability: Oral: ~20%; increased to 60% to 70% with cirrhosis

Half-life elimination: 2-3 hours; prolonged with hepatic impairment

Excretion: Urine (small amounts as unchanged drug)

Related Information

- Depression
- Narcotic / Opioid Analgesics

Pharmacotherapy PearlsTalwin® Nx: If tablet misused as an injection, the naloxone component will prevent the effect of pentazocine.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness and euphoria are common; may cause restlessness or nightmares; may rarely cause confusion, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive effects or toxicity; may cause withdrawal in patients currently dependent on narcotics

Index TermsNaloxone Hydrochloride and Pentazocine Hydrochloride; Pentazocine Hydrochloride; Pentazocine Hydrochloride and Naloxone Hydrochloride; Pentazocine Lactate

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Rita L, Seleny FL, and Levin RM, “A Comparison of Pentazocine and Morphine for Pediatric Premedication,” *Anesth Analg*, 1970, 49(3):377-82. [PubMed 5534413]

Waterworth TA, “Pentazocine (Fortal) as Postoperative Analgesic in Children,” *Arch Dis Child*, 1974, 49(6):488-90.[PubMed 4604887]

International Brand NamesDolapent (FI, PL); Fortal (BE, LU); Fortalgesic[inj.] (CH); Fortalgesic[Suppos.] (CH); Fortalgesic[Tab.] (CH); Fortral (AT, AU, BG, CZ, DE, DK, FR, GB, HR, IE, NL, NZ, PL); Fortralin (FI, NO); Fortralin[inj./rect.] (NO); Fortralin[inj.] (FI, NO); Fortwin (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Ospronim (ZA); Peltazon (JP); Pentagin (JP); Pentajin (JP); Pentawin (IN); Pentazocina[inj.] (ES); Pentazocinum (PL); Sosegon (AE, BF, BH, BJ, CI, CY, EC, EG, ES, ET, GH, GM, GN, IL, IQ, IR, JO, JP, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PK, PT, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Sosegon[inj./rect.] (ES, JP); Talwin Lactate (IT, PE)

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

PENTobarbital may be confused with PHENobarbital

Nembutal® may be confused with Myambutol®

Pronunciation(pen toe BAR bi tal)

U.S. Brand NamesNembutal®

Canadian Brand NamesNembutal® Sodium

Pharmacologic CategoryAnticonvulsant, Barbiturate; Barbiturate

Use: Labeled IndicationsSedative/hypnotic; preanesthetic; high-dose barbiturate coma for treatment of increased intracranial pressure or status epilepticus unresponsive to other therapy

Dosing: Adults

Hypnotic:

I.M.: 150-200 mg

I.V.: Initial: 100 mg, may repeat every 1-3 minutes up to 200-500 mg total dose

Preoperative sedation: I.M.: 150-200 mg

Barbiturate coma in head injury patients or status epilepticus: I.V.: Loading dose: 5-10 mg/kg given slowly over 1-2 hours; monitor blood pressure and respiratory rate; maintenance infusion: initial: 1 mg/kg/hour; may increase to 2-3 mg/kg/hour; maintain burst suppression on EEG

Status epilepticus: I.V.: Loading dose: 10-20 mg/kg given slowly over 1-2 hours; maintenance infusion: 0.5-3 mg/kg/hour. **Note**: Intubation required; monitor hemodynamics

Dosing: ElderlyNot recommended for use in the elderly (see Geriatric Considerations).

Dosing: Pediatric

Hypnotic: I.M.: 2-6 mg/kg; maximum: 100 mg/dose

Preoperative/preprocedure sedation: ≥6 months:

Note: Limited information is available for infants <6 months of age.

I.M.: 2-6 mg/kg; maximum: 100 mg/dose

I.V.: 1-3 mg/kg to a maximum of 100 mg until asleep

Conscious sedation prior to a procedure: I.V.:

Children 5-12 years: I.V.: 2 mg/kg 5-10 minutes before procedures, may repeat one time

Adolescents: 100 mg prior to a procedure

Barbiturate coma in head injury patients: I.V.: Loading dose: 5-10 mg/kg given slowly over 1-2 hours; monitor blood pressure and respiratory rate; Maintenance infusion: Initial: 1 mg/kg/hour; may increase to 2-3 mg/kg/hour; maintain burst suppression on EEG

Status epilepticus: I.V.: **Note**: Intubation required; monitor hemodynamics: Loading dose: 5-15 mg/kg given slowly over 1-2 hours; maintenance infusion: 0.5-5 mg/kg/hour

Dosing: Hepatic ImpairmentReduce dosage in patients with severe liver dysfunction.

Administration: I.M.Pentobarbital may be administered by deep I.M.: No more than 5 mL (250 mg) should be injected at any one site because of possible tissue irritation.

Administration: I.V.Pentobarbital must be administered by slow I.V. injection. I.V. push doses can be given undiluted, but should be administered no faster than 50 mg/minute. Avoid intra-arterial injection. Has many incompatibilities when given I.V.

Administration: I.V. DetailAvoid extravasation. Institute safety measures to avoid injuries. Parenteral solutions are highly alkaline. Avoid rapid I.V. administration >50 mg/minute.

pH: 9.5

StorageProtect from freezing. Aqueous solutions are not stable; a commercially available vehicle (containing propylene glycol) is more stable. When mixed with an acidic solution, precipitate may form. Use only clear solution.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4$NS, $D_5{}^1/_2$NS, D_5NS, D_{10}W, LR, $^1/_2$NS; **variable stability (consult detailed reference)** in D_5W, NS.

Y-site administration: Compatible: Acyclovir, gatifloxacin, insulin (regular), linezolid, propofol. **Incompatible:** Amphotericin B cholesteryl sulfate complex.

Compatibility in syringe: Compatible: Aminophylline, ephedrine, hyaluronidase, hydromorphone, neostigmine, scopolamine, sodium bicarbonate, thiopental. **Incompatible:** Atropine with cimetidine, butorphanol, chlorpromazine, cimetidine, dimenhydrinate, diphenhydramine, droperidol, fentanyl, glycopyrrolate, hydroxyzine, meperidine, midazolam, nalbuphine, pentazocine, perphenazine, prochlorperazine edisylate, promazine, promethazine, ranitidine. **Variable (consult detailed reference):** Atropine, morphine.

Compatibility when admixed: Compatible: Amikacin, aminophylline, calcium chloride, chloramphenicol, dimenhydrinate, erythromycin lactobionate, lidocaine, thiopental, verapamil. **Incompatible:** Cefazolin, chlorpheniramine, cimetidine, clindamycin, droperidol, ephedrine, fentanyl, hydrocortisone sodium succinate, hydroxyzine, insulin (regular), levorphanol, norepinephrine, pancuronium, penicillin G potassium, pentazocine, phenytoin, promazine, promethazine, streptomycin, triflupromazine, vancomycin. **Variable (consult detailed reference):** Chlorpromazine, isoproterenol, metaraminol, methyldopate, norepinephrine, sodium bicarbonate, succinylcholine.

RestrictionsC-II

ContraindicationsHypersensitivity to barbiturates or any component of the formulation; marked hepatic impairment; dyspnea or airway obstruction; porphyria; pregnancy

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypotension: May cause hypotension particularly when administered intravenously; use with caution in hemodynamically unstable patients (hypotension or shock). High doses (loading doses of 15-35 mg/kg given over 1-2 hours) have been utilized to induce pentobarbital coma, but these higher doses often cause hypotension requiring vasopressor therapy.
- Paradoxical stimulatory response: May cause paradoxical responses, including agitation and hyperactivity, particularly in acute pain and pediatric patients.
- Respiratory depression: May cause respiratory depression particularly when administered intravenously; use with caution patients with respiratory disease.

Disease-related concerns:

- Depression: Use with caution in patients with depression or suicidal tendencies.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Substance abuse: Use with caution in patients with a history of drug abuse; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in patients who are debilitated.
- Elderly: Use with caution in the elderly; use of this agent as a hypnotic in the elderly is not recommended due to its long half-life and potential for physical and psychological dependence.
- Pediatrics: Use with caution in children.

Other warnings/precautions:

- Acute pain: Do not administer to patients in acute pain.
- Insomnia use: Tolerance to hypnotic effect can occur; do not use for >2 weeks to treat insomnia.
- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsUse of this agent as a hypnotic in the elderly is not recommended due to its long half-life and addiction potential.

Pregnancy Risk FactorD

LactationEnters breast milk/contraindicated

Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, hypotension, syncope

Central nervous system: Drowsiness, lethargy, CNS excitation or depression, impaired judgment, “hangover” effect, confusion, somnolence, agitation, hyperkinesia, ataxia, nervousness, headache, insomnia, nightmares, hallucinations, anxiety, dizziness

Dermatologic: Rash, exfoliative dermatitis, Stevens-Johnson syndrome

Gastrointestinal: Nausea, vomiting, constipation

Hematologic: Agranulocytosis, thrombocytopenia, megaloblastic anemia

Local: Pain at injection site, thrombophlebitis with I.V. use

Renal: Oliguria

Respiratory: Laryngospasm, respiratory depression, apnea (especially with rapid I.V. use), hypoventilation

Miscellaneous: Gangrene with inadvertent intra-arterial injection

Metabolism/Transport Effects **Induces** CYP2A6 (strong), 3A4 (strong)

Drug Interactions

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Carbonic Anhydrase Inhibitors: May enhance the adverse/toxic effect of Anticonvulsants (Barbiturate). Specifically, osteomalacia and rickets. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2A6 Substrates: CYP2A6 Inducers (Strong) may increase the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

Griseofulvin: Barbiturates may decrease the absorption of Griseofulvin. *Risk D: Consider therapy modification*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersRespiratory status (for conscious sedation, includes pulse oximetry), cardiovascular status, CNS status; cardiac monitor and blood pressure monitor required

Reference Range

Therapeutic:

Hypnotic: 1-5 mcg/mL (SI: 4-22 µmol/L)

Coma: 10-50 mcg/mL (SI: 88-221 µmol/L)

Toxic: >10 mcg/mL (SI: >44 µmol/L)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance. Periodically evaluate the need for continued use. **I.V.:** Keep patient under observation. Monitor cardio/respiratory status and institute patient safety precautions. Monitor effectiveness of therapy and adverse reactions.

Patient EducationPatient instructions and information are determined by patient condition and therapeutic purpose. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help). Report skin rash or irritation; CNS changes (confusion, depression, increased sedation, excitation, headache, insomnia, or nightmares); respiratory difficulty or shortness of breath; changes in urinary pattern or menstrual pattern; muscle weakness or tremors; or difficulty swallowing or feeling of tightness in throat. **Pregnancy/breast-feeding precautions:** Do not get pregnant; use appropriate contraceptive measures to prevent possible harm to the fetus. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sodium: 50 mg/mL (20 mL, 50 mL) [contains alcohol 10% and propylene glycol 40%]

Generic AvailableNo

ManufacturerOvation Pharmaceuticals

Mechanism of ActionShort-acting barbiturate with sedative, hypnotic, and anticonvulsant properties. Barbiturates depress the sensory cortex, decrease motor activity, alter cerebellar function, and produce drowsiness, sedation, and hypnosis. In high doses, barbiturates exhibit anticonvulsant activity; barbiturates produce dose-dependent respiratory depression.

Pharmacodynamics/Kinetics

Onset of action: I.M.: 10-15 minutes; I.V.: ~1 minute

Duration: I.V.: 15 minutes

Distribution: V_d: Children: 0.8 L/kg; Adults: 1 L/kg

Protein binding: 35% to 55%

Metabolism: Extensively hepatic via hydroxylation and oxidation pathways

Half-life elimination: Terminal: Children: 25 hours; Adults: Healthy: 22 hours (range: 15-50 hours)

Excretion: Urine (<1% as unchanged drug)

Related Information

- Status Epilepticus

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Anesthesia and Critical Care Concerns/Other Considerations Pentobarbital 50 mg/mL contains propylene glycol 414.4 mg/mL (40% v/v).

Pentobarbital is one of the standard choices for refractory status epilepticus. Most patients will require systemic and pulmonary arterial catheterization with fluid and vasoactive therapy to maintain blood pressure. High-dose pentobarbital generally produces poikilothermia. Maintenance anticonvulsant treatment may be substantial in order to wean pentobarbital. High doses of barbiturates are potentially immunosuppressive; guard against infection.

Index Terms Pentobarbital Sodium

References

Chapman MG, Smith M, and Hirsch NP, “Status Epilepticus,” *Anaesthesia*, 2001, 56(7):648-59. [PubMed 11437765]

Fischer JH and Raineri DL, “Pentobarbital Anesthesia for Status Epilepticus,” *Clin Pharm*, 1987, 6(8):601-2. [PubMed 3691007]

Hubbard AM, Markowitz RI, Kimmel B, et al, “Sedation for Pediatric Patients Undergoing CT and MRI,” *J Comput Assist Tomogr*, 1992, 16(1):3-6. [PubMed 1729302]

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Meierkord H, Boon P, Engelsen B, et al, “EFNS Guideline on the Management of Status Epilepticus,” *Eur J Neurol*, 2006, 13(5):445-50.[PubMed 16722966]

Pereira JK, Burrows PE, Richards HM, et al, “Comparison of Sedation Regimens for Pediatric Outpatient CT,” *Pediatr Radiol*, 1993, 23(5):341-4. [PubMed 8233681]

Schaible DH, Cupit GC, Swedlow DB, et al, “High-Dose Pentobarbital Pharmacokinetics in Hypothermic Brain-Injured Children,” *J Pediatr*, 1982, 100(4):655-60. [PubMed 7062221]

Tobias JD, Deshpande JK, Pietsch JB, et al, “Pentobarbital Sedation for Patients in the Pediatric Intensive Care Unit,” *South Med J*, 1995, 88(3):290-4. [PubMed 7886524]

Wermeling D, Record K, Bell R, et al, “Hemodialysis Clearance of Pentobarbital During Continuous Infusion,” *Ther Drug Monit*, 1985, 7(4):485-7. [PubMed 4082247]

Zeltzer LK, Altman A, Cohen D, et al, “American Academy of Pediatrics Report of the Subcommittee on the Management of Pain Associated With Procedures in Children With Cancer,” *Pediatrics*, 1990, 86(5 Pt 2):826-31.[PubMed 2216645]

International Brand Names Dormital (UY); Mebumal (DK); Medinox Mono (DE); Nembutal (AT); Pentone (AU); Praecicalm (DE); Prodormol (IL); Sombutol (FI); Sopental (ZA)

Medication Safety Issues

Sound-alike/look-alike issues:

Pentosan may be confused with pentostatin

Elmiron® may be confused with Imuran®

Pronunciation(PEN toe san pol i SUL fate SOW dee um)
U.S. Brand NamesElmiron®
Canadian Brand NamesElmiron®
Pharmacologic CategoryAnalgesic, Urinary
Use: Labeled Indications**Orphan drug:** Relief of bladder pain or discomfort due to interstitial cystitis
Dosing: Adults**Interstitial cystitis:** Oral: 100 mg 3 times/day taken with water 1 hour before or 2 hours after meals

Note: Patients should be evaluated at 3 months and may be continued an additional 3 months if there has been no improvement and if there are no therapy-limiting side effects. **The risks and benefits of continued use beyond 6 months in patients who have not responded is not yet known**.

Dosing: ElderlyRefer to adult dosing.
Administration: OralShould be administered with water 1 hour before or 2 hours after meals.
StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to pentosan polysulfate sodium, related compounds (LMWHs or heparin), or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: Pentosan polysulfate is a low-molecular weight heparin-like compound with anticoagulant and fibrinolytic effects, therefore, bleeding complications such as ecchymosis, epistaxis and gum bleeding, may occur. Patients undergoing invasive procedures or having signs or symptoms of underlying coagulopathies or other increased risk of bleeding (eg, receiving heparin, warfarin, thrombolytics, NSAIDs, or high dose aspirin) should be evaluated prior to use.

Disease-related concerns:

- Aneurysm: Carefully evaluate patients with aneurysm before initiating therapy.

- Bleeding disorders: Carefully evaluate patients with hemophilia and/or thrombocytopenia before initiating therapy.

- Gastrointestinal disease: Carefully evaluate patients with gastrointestinal ulcerations, polyps, and/or diverticula before initiating therapy.

- Heparin-induced thrombocytopenia: Use with caution in patients with a history of heparin-induced thrombocytopenia.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <16 years of age.

Pregnancy Risk FactorB
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use with caution and only if clearly needed during pregnancy. Based on limited data, pentosanpolysulfate does not appear to cross the placenta.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

1% to 10%:

Central nervous system: Headache (3%), dizziness (1%)

Dermatologic: Alopecia (4%), rash (3%)

Gastrointestinal: Rectal hemorrhage (6%), diarrhea (4%), nausea (4%), dyspepsia (2%), abdominal pain (2%)

Hepatic: Liver function test abnormalities (1%)

<1%: Allergic reactions, amblyopia, anemia, anorexia, colitis, conjunctivitis, constipation, depression, dyspnea, ecchymosis, epistaxis, esophagitis, flatulence, gastritis, gum bleeding, hyperkinesia, increased partial thromboplastin time, insomnia, leukopenia, mouth ulcer,

nystagmus, optic neuritis, pharyngitis, photosensitivity, prolonged PT, pruritus, retinal hemorrhage, rhinitis, thrombocytopenia, tinnitus, urticaria, vaginitis

Drug Interactions

Anticoagulants: Pentosan Polysulfate Sodium may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: Pentosan Polysulfate Sodium may enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 100 mg

Generic Available No

Pricing: U.S. (www.drugstore.com)

Capsules (Elmiron)

100 mg (90): $281.38

Mechanism of Action Although pentosan polysulfate sodium is a low-molecular weight heparinoid, it is not known whether these properties play a role in its mechanism of action in treating interstitial cystitis; the drug appears to adhere to the bladder wall mucosa where it may act as a buffer to protect the tissues from irritating substances in the urine.

Pharmacodynamics/Kinetics

Absorption: ~3%

Metabolism: Hepatic and via spleen; some metabolism occurs in renal parenchyma

Half-life elimination: 4.8 hours

Excretion: Urine (3% as unchanged drug)

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness

Mental Health: Effects on Psychiatric Treatment May cause anemia and leukopenia; use caution with clozapine and carbamazepine

Index TermsPPS

References

Forestier F, Fischer AM, Daffos F, et al, "Absence of Transplacental Passage of Pentosan Polysulfate During Mid Trimester of Pregnancy," *Thromb Haemost*, 1986, 15;56(3):247-9.[PubMed 2436327]

International Brand Names Elmiron (AR, AU, HK, KP, PE, TW); Fibrase (IT); Fibrezym (DE); Fibrocid (ES); Fibrocide (PT); Hemoclar (FR); Pentosanpolysulfat SP 54 (DE); Polyanion (AT); SP54 (HU, MY); Tavan-SP (ZA); Thrombocid (CH, DE, ES, PT)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Chronic Lymphocytic

Regimen UseLeukemia, chronic lymphocytic

Regimen

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Pentostatin: I.V.: 4 mg/m^2 day 1

[total dose/cycle = 4 mg/m^2]

Repeat cycle every 3 weeks for up to 6 cycles

References

Weiss MA, Maslak PG, Jurcic JG, et al, "Pentostatin and Cyclophosphamide: An Effective New Regimen in Previously Treated Patients With Chronic Lymphocytic Leukemia," *J Clin Oncol*, 2003, 21(7):1278-84.[PubMed 12663715]

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Pentostatin may be confused with pentamidine, pentosan

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

International issues:

Nipent® may be confused with Nipin® which is a brand name for nifedipine in Italy and Singapore

Pronunciation(pen toe STAT in)

U.S. Brand NamesNipent®

Canadian Brand NamesNipent®

Pharmacologic CategoryAntineoplastic Agent, Antibiotic; Antineoplastic Agent, Antimetabolite (Purine Antagonist)

Use: Labeled IndicationsTreatment of hairy cell leukemia

Use: Unlabeled/InvestigationalTreatment of cutaneous T-cell lymphoma, chronic lymphocytic leukemia (CLL), and acute and chronic graft-versus-host-disease (GVHD)

Dosing: AdultsRefer to individual protocols.

Hairy cell leukemia: I.V.: 4 mg/m^2 every 2 weeks

CLL (unlabeled use): I.V.: 4 mg/m^2 weekly for 3 weeks, then every 2 weeks

Cutaneous T-cell lymphoma (unlabeled use): I.V.: 3.75-5 mg/m^2 daily for 3 days every 3 weeks

Acute GVHD (unlabeled use): I.V.: 1.5 mg/m^2 daily for 3 days; may repeat after 2 weeks if needed

Chronic GVHD (unlabeled use): I.V.: 4 mg/m^2 every 2 weeks for 12 doses; then 4 mg/m^2 every 3-4 weeks (if still improving)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentThe FDA-approved labeling does not contain renal dosage adjustment guidelines; use with caution in patients with Cl_{cr} <60 mL/minute. Two patients with Cl_{cr} 50-60 mL/minute achieved responses when treated with 2 mg/m^2/dose. The following guidelines have been used by some clinicians:

Kintzel, 1995:

Cl_{cr} 46-60 mL/minute: Administer 70% of dose

Cl_{cr} 31-45 mL/minute: Administer 60% of dose

Cl_{cr} <30 mL/minute: Consider use of alternative drug

Lathia, 2002:

Cl_{cr} 40-59 mL/minute: Administer 3 mg/m^2/dose

Cl_{cr} 20-39 mL/minute: Administer 2 mg/m^2/dose

Dosing: Combination Regimens

Leukemia, chronic lymphocytic:

PCR

Pentostatin-Cyclophosphamide

Calculations

- Body Surface Area: Adults

- Creatinine Clearance: Adults

Administration: I.V.Administer I.V. 20- to 30-minute infusion or I.V. bolus over 5 minutes. Hydrate with 500-1000 mL fluid prior to infusion and 500 mL after infusion.

Administration: I.V. DetailpH: 7.0-8.5

StorageStore intact vials under refrigeration at 2°C to 8°C (36°F to 46°F); reconstituted vials, or further dilutions, are stable at room temperature for 8 hours in D_5W or 48 hours in NS.

ReconstitutionReconstitute with 5 mL SWFI to a concentration of 2 mg/mL. The solution may be further diluted in 25-50 mL NS or D_5W for infusion.

CompatibilityStable in LR, NS; **variable stability (consult detailed reference)** in D_5W.

Y-site administration: Compatible: Fludarabine, melphalan, ondansetron, paclitaxel, sargramostim.

ContraindicationsHypersensitivity to pentostatin or any component of the formulation

Warnings/Precautions

Boxed warnings:

- CNS toxicity: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.
- Hepatotoxicity: See “Concerns related to adverse effects” below.
- Pulmonary toxicity: See “Concerns related to adverse effects” below.
- Renal toxicity: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: May occur, primarily early in treatment; if neutropenia persists beyond early cycles, evaluate for disease status.
- CNS toxicity: **[U.S. Boxed Warnings]: Severe CNS toxicities have occurred with doses higher than recommended; do not exceed the recommended dose.** Withhold treatment for CNS toxicity.
- Hepatotoxicity: **[U.S. Boxed Warnings]: Severe liver toxicities have occurred with doses higher than recommended; do not exceed the recommended dose.** May cause elevations (reversible) in liver function tests.
- Pulmonary toxicity: **[U.S. Boxed Warnings]: Severe pulmonary toxicities have occurred with doses higher than recommended; do not exceed the recommended dose. Do not administer concurrently with fludarabine; concomitant use has resulted in serious or fatal pulmonary toxicity.**
- Rash: Severe rashes may occur and worsen with therapy continuation; may require withholding of treatment or discontinuation.
- Renal toxicity: **[U.S. Boxed Warnings]: Severe renal toxicities have occurred with doses higher than recommended; do not exceed the recommended dose.**

Disease-related concerns:

- Infections: In patients who present with infections prior to treatment, infections should be resolved, if possible, prior to initiation of treatment. Treatment should be temporarily withheld for active infections during therapy.
- Renal impairment: Use with caution in patients with renal dysfunction (Cl_{cr} <60 mL/minute); the terminal half-life is prolonged; appropriate dosing guidelines in renal insufficiency have not been determined.

Concurrent drug therapy issues:

- Carmustine/etoposide/cyclophosphamide: Fatal pulmonary edema and hypotension have been reported in patients treated with pentostatin in combination with carmustine, etoposide, or high-dose cyclophosphamide as part of a myeloablative regimen for bone marrow transplant.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenicity, maternal toxicity, and fetal loss. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in nursing the infant, breast-feeding is not recommended.

Adverse Reactions

>10%:

Central nervous system: Fever (42% to 46%), fatigue (29% to 42%), pain (8% to 20%), chills (11% to 19%), headache (13% to 17%), CNS toxicity (1% to 11%)

Dermatologic: Rash (26% to 43%), pruritus (10% to 21%), skin disorder (4% to 17%)

Gastrointestinal: Nausea/vomiting (22% to 63%), diarrhea (15% to 17%), anorexia (13% to 16%), abdominal pain (4% to 16%), stomatitis (5% to 12%)

Hematologic: Myelosuppression (nadir: 7 days; recovery: 10-14 days), leukopenia (22% to 60%), anemia (8% to 35%), thrombocytopenia (6% to 32%)

Hepatic: Transaminases increased (2% to 19%)

Neuromuscular & skeletal: Myalgia (11% to 19%), weakness (10% to 12%)

Respiratory: Cough (17% to 20%), upper respiratory infection (13% to 16%), rhinitis (10% to 11%), dyspnea (8% to 11%)

Miscellaneous: Infection (7% to 36%), allergic reaction (2% to 11%)

1% to 10%:

Cardiovascular: Chest pain (3% to 10%), facial edema (3% to 10%), hypotension (3% to 10%), peripheral edema (3% to 10%), angina (<3%), arrhythmia (<3%), AV block (<3%), bradycardia (<3%), cardiac arrest (<3%), deep thrombophlebitis (<3%), heart failure (<3%), hypertension (<3%), pericardial effusion (<3%), sinus arrest (<3%), syncope (<3%), tachycardia (<3%), vasculitis (<3%), ventricular extrasystoles (<3%)

Central nervous system: Anxiety (3% to 10%), confusion (3% to 10%), depression (3% to 10%), dizziness (3% to 10%), insomnia (3% to 10%), nervousness (3% to 10%), somnolence (3% to 10%), abnormal dreams/thinking (<3%), amnesia (<3%), ataxia (<3%), emotional lability (<3%), encephalitis (<3%), hallucination (<3%), hostility (<3%), meningism (<3%), neuritis (<3%), neurosis (<3%), seizure (<3%), vertigo (<3%)

Dermatologic: Cellulitis (6%), furunculosis (4%), dry skin (3% to 10%), urticaria (3% to 10%), acne (<3%), alopecia (<3%), eczema (<3%), petechial rash (<3%), photosensitivity (<3%), abscess (2%)

Endocrine & metabolic: Amenorrhea (<3%), hypercalcemia (<3%), hyponatremia (<3%), gout (<3%), libido decreased/loss (<3%)

Gastrointestinal: Dyspepsia (3% to 10%) flatulence (3% to 10%), gingivitis (3% to 10%), constipation (<3%), dysphagia (<3%), glossitis (<3%), ileus (<3%), taste perversion (<3%), oral moniliasis (2%)

Genitourinary: Urinary tract infection (3%), impotence (<3%)

Hematologic: Agranulocytosis (3% to 10%), hemorrhage (3% to 10%), acute leukemia (<3%), aplastic anemia (<3%), hemolytic anemia (<3%)

Local: Phlebitis (<3%)

Neuromuscular & skeletal: Arthralgia (3% to 10%), paresthesia (3% to 10%), arthritis (<3%), dysarthria (<3%), hyperkinesia (<3%), neuralgia (<3%), neuropathy (<3%), paralysis (<3%), twitching (<3%), osteomyelitis (1%)

Ocular: Conjunctivitis (4%), amblyopia (<3%), eyes nonreactive (<3%), lacrimation disorder (<3%), photophobia (<3%), retinopathy (<3%), vision abnormal (<3%), watery eyes (<3%), xerophthalmia (<3%)

Otic: Deafness (<3%), earache (<3%), labyrinthitis (<3%), tinnitus (<3%)

Renal: Creatinine increased (3% to 10%), nephropathy (<3%), renal failure (<3%), renal insufficiency (<3%), renal function abnormal (<3%), renal stone (<3%)

Respiratory: Pharyngitis (8% to 10%), sinusitis (6%), pneumonia (5%), asthma (3% to 10%), bronchitis (3%), bronchospasm (<3%), laryngeal edema (<3%), pulmonary embolus (<3%)

Miscellaneous: Diaphoresis (8% to 10%), herpes zoster (8%), viral infection (≤8%), bacterial infection (5%), herpes simplex (4%), sepsis (3%), flu-like syndrome (<3%)

<1%, postmarketing, and/or case reports: Dysuria, fungal infection (skin), hematuria, lethargy, pulmonary edema, pulmonary toxicity (fatal; in combination with fludarabine), uveitis/vision loss

Oncology: VesicantNo

Oncology: Emetic PotentialModerate (30% to 60%)

Drug Interactions

Cyclophosphamide: Pentostatin may enhance the cardiotoxic effect of Cyclophosphamide. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fludarabine: May enhance the adverse/toxic effect of Pentostatin. Pulmonary toxicity is of specific concern. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Pegademase Bovine: May diminish the therapeutic effect of Pentostatin. Pentostatin may diminish the therapeutic effect of Pegademase Bovine. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersCBC with differential, platelet count, liver function, serum uric acid, renal function (creatinine clearance), bone marrow evaluation

Nursing: Physical Assessment/MonitoringUse caution in the presence of renal insufficiency, fever, infection, or renal dysfunction. Assess other pharmacological products patient may be taking for potential adverse interactions. See Administration for infusion specifics. Assess results of laboratory tests prior to treatment and on a regular basis throughout therapy. Evaluate patient response closely (CNS, hematological and neuromuscular effects). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, platelet count, liver function, serum uric acid, renal function (creatinine clearance), bone marrow evaluation

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug is administered by infusion; report any burning, pain, redness, or swelling at infusion site. It is important to maintain adequate hydration (2-3 L/day of fluids unless instructed to restrict fluid intake) and nutrition (small, frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause mild nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); loss of hair (reversible); diarrhea (buttermilk, boiled milk, or yogurt may help); or mouth sores (use soft toothbrush or cotton swabs for oral care). Report extreme fatigue; pain or numbness in extremities; severe GI upset or diarrhea; bleeding or bruising; fever, chills, or sore throat; vaginal discharge; difficulty or pain on urination; muscle pain or weakness; unusual cough or respiratory difficulty; or other unusual side effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate barrier contraceptives. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]: 10 mg [contains mannitol 50 mg]

Nipent®: 10 mg [contains mannitol 50 mg]

Generic AvailableYes

Mechanism of ActionPentostatin is a purine antimetabolite that inhibits adenosine deaminase, preventing the deamination of adenosine to inosine. Accumulation of deoxyadenosine (dAdo) and deoxyadenosine 5′-triphosphate (dATP) results in a reduction of purine metabolism and DNA synthesis and cell death.

Pharmacodynamics/Kinetics

Distribution: I.V.: V_d: 36.1 L (20.1 L/m^2); rapidly to body tissues

Protein binding: ~4%

Half-life elimination: Distribution half-life: 11-85 minutes; Terminal: 3-7 hours; renal impairment (Cl_{cr} <50 mL/minute): 4-18 hours

Excretion: Urine (~50% to 96%) within 24 hours (30% to 90% as unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause anxiety, confusion, insomnia, depression

Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; avoid clozapine and carbamazepine

Index Terms2′-Deoxycoformycin; Co-Vidarabine; dCF; Deoxycoformycin; NSC-218321

References

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International Brand NamesNipent (BE, DE, ES, FR, GB, IT, NL)

Pentoxifylline

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Pentoxifylline may be confused with tamoxifen

Trental® may be confused with Bentyl®, Tegretol®, Trandate®

Pronunciation(pen toks IF i lin)

U.S. Brand NamesPentoxil®; Trental®

Canadian Brand NamesAlbert® Pentoxifylline; Apo-Pentoxifylline SR®; Nu-Pentoxifylline SR; ratio-Pentoxifylline; Trental®

Pharmacologic CategoryBlood Viscosity Reducer Agent

Use: Labeled IndicationsTreatment of intermittent claudication on the basis of chronic occlusive arterial disease of the limbs; may improve function and symptoms, but not intended to replace more definitive therapy

Use: Unlabeled/InvestigationalAIDS patients with increased TNF, CVA, cerebrovascular diseases, diabetic atherosclerosis, diabetic neuropathy, gangrene, hemodialysis shunt thrombosis, vascular impotence, cerebral malaria, septic shock, sickle cell syndromes, vasculitis, and venous leg ulcers

Dosing: Adults**Peripheral vascular disease:** Oral: 400 mg 3 times/day with meals; maximal therapeutic benefit may take 2-4 weeks to develop; recommended to maintain therapy for at least 8 weeks. May reduce to 400 mg twice daily if GI or CNS side effects occur.

Dosing: ElderlyRefer to adult dosing.

Administration: OralTablets should be swallowed whole; do not chew, break, or crush.

Dietary ConsiderationsMay be taken with meals or food.

StorageStore between 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to pentoxifylline, xanthines (eg, caffeine, theophylline), or any component of the formulation; recent cerebral and/or retinal hemorrhage

Warnings/Precautions

Special populations:

- Elderly: Use with caution in the elderly; start with lower doses.
- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsPentoxifylline's value in the treatment of intermittent claudication is controversial. Walking distance improved statistically in some clinical trials, but the actual distance was minimal when applied to improving physical activity.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationEnters breast milk/not recommended

Adverse Reactions

1% to 10%: Gastrointestinal: Nausea (2%), vomiting (1%)

<1%, postmarketing, and/or case reports: Anaphylactoid reaction, angioedema, angina, anorexia, anxiety, aplastic anemia, arrhythmia, aseptic meningitis, bloating, blurred vision, brittle fingernails, chest pain, cholecystitis, confusion, conjunctivitis, constipation, depression, dyspnea, earache, edema, epistaxis, eructation, fibrinogen decreased (serum), flatus, flu-like syndrome, hallucinations, hepatitis, hypotension, jaundice, laryngitis, leukemia, leukopenia, liver enzymes increased, malaise, nasal congestion, pancytopenia, pruritus, purpura, rash, scotoma, seizure, sialism, sore throat, taste perversion, tachycardia, thrombocytopenia, tremor, urticaria, weight change, xerostomia

Metabolism/Transport Effects**Inhibits** CYP1A2 (weak)

Drug Interactions

Ciprofloxacin: May enhance the adverse/toxic effect of Pentoxifylline. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Pentoxifylline. Specifically, the risk of bleeding may be increased with this combination. *Risk X: Avoid combination*

Theophylline Derivatives: Pentoxifylline may increase the serum concentration of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Food may decrease rate but not extent of absorption. Pentoxifylline peak serum levels may be decreased if taken with food.

Test InteractionsDecreased calcium (S), magnesium (S); false-positive theophylline levels

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic effectiveness, and adverse reactions at regular intervals during therapy (eg, cardiac status and blood pressure). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This may relieve pain of claudication, but additional therapy may be recommended. Take as prescribed for full length of prescription. May cause dizziness (use caution when driving or engaging in tasks that are potentially hazardous until response to drug is known); or heartburn, nausea, or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report chest pain; swelling of lips, mouth, or tongue; persistent headache; respiratory difficulty; rash; or unrelieved nausea or vomiting. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, controlled release:

Trental®: 400 mg

Tablet, extended release: 400 mg

Pentoxil®: 400 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, controlled release (Pentoxifylline CR)

400 mg (100): $23.33

Tablet, controlled release (Pentoxil)

400 mg (100): $25.99

Tablet, controlled release (Trental)

400 mg (60): $71.60

Mechanism of ActionReduces blood viscosity via increased leukocyte and erythrocyte deformability and decreased neutrophil adhesion/activation; improves peripheral tissue oxygenation presumably through enhanced blood flow.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Metabolism: Hepatic and via erythrocytes; extensive first-pass effect

Half-life elimination: Parent drug: 24-48 minutes; Metabolites: 60-96 minutes

Time to peak, serum: 2-4 hours

Excretion: Primarily urine (active metabolites); feces (4%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, confusion, depression, dizziness, or rarely agitation

Mental Health: Effects on Psychiatric TreatmentMay cause seizures; use with caution with concomitant use of clozapine, which is associated with dose-dependent risk of seizures

Cardiovascular ConsiderationsPentoxifylline may be used in the treatment of peripheral vascular disease; however, its efficacy is not fully established. The role of cytokine modulation with pentoxifylline in patients with heart failure is under investigation.

Anesthesia and Critical Care Concerns/Other ConsiderationsPentoxifylline may be used in the treatment of peripheral vascular disease, however, its efficacy is not fully established. Therapeutic effects may be seen after 2-4 weeks.

Index TermsOxpentifylline

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International Brand NamesAgapurin (HU, PK, PL, TH); Angiopurin (HU); Apo-Pentox (PL); Artal (FI); Artelife (MX); Azupentat (PL); Cerator (TH); Ceretal (TW); Chinotal (HU); Dartelin (HR, PL); Duplat (MX); Elorgan (ES); Erytral (ID); Fixoten (MX); Flexital CR (TH); Fylin (TW); Grofilina (PL); Harin (KP); Hemovas (ES); Ipentol (TW); Kentadin (MX); Oxopurin 400 SR (IL); Penphylline (TW); Pentamon (HR); Pentilin (HR, PL); Pentohexal (PL); Pentox (PH); Pentox von ct (LU); Pentoxi (CH); Pentoxifilin (CO); Pentoxifyllin AL (HU); Pentoxifyllin Pharmavit (HU); Pentoxifyllin-B (HU); Pentoxifyllin-ratiopharm (LU); Pentoxin SR (KP); Pentyllin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Perencal (KP); Peridane (MX); Pexal (BB, BM, BS, BZ, GY, JM, SR, TT); Pexol (PE); Polfilin (PL); Profiben (MX); Qiquan (CL); Ralofekt (PL); Rentylin (LU); Sufisal (MX); Tarontal (GR, ID); Torental (BE, FR, LU); Toxipen (PH); Trenfyl (ID); Trenlin (HK); Trenlin SR (SG); Trental (AE, AR, AT, AU, BB, BD, BE, BG, BH, BM, BO, BR, BS, BZ, CH, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, FI, FR, GB, GR, GT, GY, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, JP, KP, KW, LB, LY, MX, MY, NI, NL, NO, NZ, OM, PA, PE, PH, PK, PL, PR, PT, PY, QA, RU, SA, SE, SG, SR, SV, SY, TH, TR, TW, UY, VE, YE); Trepal-400 (TH); Vantoxyl (MX); Vasopentox (PE); Vazofen (PH); Xipen (MX)

Perflutren Lipid Microspheres

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Perflutren Lipid Microsphere (Definity®): Revised Contraindications - May 2008; updated July 2008

Lantheus Medical Imaging, in conjunction with the Food and Drug Administration (FDA), has revised the contraindications of perflutren lipid microsphere. Perflutren lipid microsphere is no longer contraindicated in patients with serious ventricular arrhythmias, at high risk for ventricular arrhythmias due to QT prolongation, pulmonary arterial vascular compromise (eg, pulmonary embolism, pulmonary hypertension, severe emphysema), or an unstable cardiopulmonary status (eg, unstable angina, acute MI, respiratory failure, recent worsening or clinically unstable HF).

Updated U.S. labeled contraindications now include only those patients with hypersensitivity to perflutren and right-to-left, bidirectional, or transient right-to-left cardiac shunt.

In July 2008, the FDA issued a Medwatch alert to inform healthcare professionals of the labeling changes, including revisions to the boxed warnings and warnings emphasizing the risk of cardiopulmonary reactions. These product labeling changes have previously been incorporated into the perflutren lipid microsphere Lexi-Comp monograph.

For more information, U.S. healthcare professionals may refer to the following websites:

http://www.lantheus.com/News.html

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Microbubble

Pronunciation(per FLOO tren LIPid MI kro SFIRS)

U.S. Brand NamesDefinity®

Canadian Brand NamesDefinity®

Pharmacologic CategoryDiagnostic Agent

Use: Labeled IndicationsOpacification of left ventricular chamber and improvement of delineation of the left ventricular endocardial border in patients with suboptimal echocardiograms

Dosing: AdultsDose should be given following baseline noncontrast echocardiography. Imaging should begin immediately following dose and compared to noncontrast image. Mechanical index for the ultrasound device should be set at ≤0.8. **Note:** Maximum dose is either two I.V. bolus doses or one single I.V. infusion.

I.V. bolus: 10 microliters (µL)/kg of activated product, followed by 10 mL saline flush; may repeat in 30 minutes if needed

I.V. infusion: Initial: 4 mL/minute (or 240 mL/hour) of prepared infusion; titrate to achieve optimal image; maximum rate: 10 mL/minute (or 600 mL/hour)

Dosing: ElderlyRefer to adult dosing.

Administration: I.V.

I.V. bolus: Administer over 30-60 seconds, follow with 10 mL saline flush

I.V. infusion rate: 4 mL/minute (or 240 mL/hour) to 10 mL/minute (or 600 mL/hour)

StoragePrior to activation, store under refrigeration, 2°C to 8°C (36°F to 46°F). Following activation, store at room temperature.

ReconstitutionPrior to administration, product must be activated. To activate, first bring vial to room temperature. Vial should then be shaken for 45 seconds using the Vialmix™ apparatus (which should be obtained from the manufacturer). Do **not** use if the 45 second activation cycle has not been completed. Following activation, the product will appear milky and may be used immediately. Activated product must be used within 12 hours. If not used within 5 minutes of activation, resuspend using hand agitation for 10 seconds. To withdraw product, invert vial and aseptically position needle (18 or 20 gauge) or dispensing pin in center of liquid; do **not** inject air. Once withdrawn from vial into a syringe, use immediately. Do **not** allow product to stand in syringe. Product does not contain bacterial preservative. Vial is for single use only.

To prepare I.V. infusion, add 1.3 mL activated product to 50 mL preservative free saline.

ContraindicationsHypersensitivity to perflutren, octafluoropropane (OFP) or any component of the formulation; right-to-left, bidirectional, or transient right-to-left cardiac shunt; administration by intra-arterial injection

Warnings/Precautions

Boxed warning:

- Serious cardiopulmonary reactions: See “Concerns related to adverse effects” below

Concerns related to adverse effects:

- Anaphylactoid reactions: Postmarketing reports of anaphylactoid reactions (eg, shock, bronchospasm, upper airway swelling, loss of consciousness, urticaria and pruritus) have been reported in patients with no prior exposure. Monitor for signs and symptoms of anaphylactoid reactions. Immediate treatment (including epinephrine 1:1000) should be available.

- Serious cardiopulmonary reactions: **[U.S. Boxed Warning]: Serious cardiopulmonary reactions (some fatal) have occurred during or within 30 minutes following administration. Ensure patient does not have any contraindications for use. Equipment for resuscitation and trained personnel experienced in handling medical emergencies should always be immediately available.** In patients with pulmonary hypertension or unstable cardiopulmonary conditions (eg, unstable angina, acute MI, respiratory failure, patients receiving mechanical ventilation, recent worsening or unstable HF, serious ventricular arrhythmias), monitor (eg, vital signs, cardiac rhythm, and oxygen saturation) during and for at least 30 minutes following administration.

- QT_c prolongation: Transient QT_c prolongation (>30 msec) has been observed, some with associated cardiac rhythm changes; malignant symptomatology was not observed in clinical trials. The effects of concomitant drugs have not been evaluated. Monitor patients at high risk for ventricular arrhythmias due to QT_c prolongation.

- Ventricular arrhythmias: High ultrasound mechanical indices with or without end-systolic triggering may cause ventricular arrhythmias. Safety of activated perflutren lipid microspheres with mechanical indices >0.8 or end-systolic triggering has not been established.

Disease-related concerns:

- Cardiac shunts: Patients with right-to-left, bidirectional, or transient right-to-left cardiac shunts should not receive perflutren lipid microsphere. Use of phospholipid encapsulated microspheres will result in microvascular occlusion and ischemia since the pulmonary particle-filtering mechanism will be bypassed resulting in a direct transfer from venous to arterial circulation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Product must be activated prior to use.

- Cardiac stress testing: Safety and efficacy with exercise stress or pharmacologic stress testing have not been established.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAnimal studies have not shown adverse to the fetus, however, reproduction studies have not been performed in humans. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Cardiovascular: QT_c prolongation (>30 msec, 29%)

1% to 10%:

Cardiovascular: Arrhythmia (secondary to QT prolongation, 8%); flushing (1%)

Central nervous system: Headache (2%)

Gastrointestinal: Nausea (1%)

Neuromuscular & skeletal: Back pain (1%)

Renal: Renal pain (1%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Abdominal pain, albuminuria, anaphylactoid reactions, arthralgia, atrial fibrillation, bradycardia, bronchospasm, cardiac arrest, chest pain, conjunctivitis, convulsions, cough, diarrhea, dizziness, diaphoresis, dyspnea, dyspepsia, ECG abnormal, eosinophilia, erythematous rash, fatigue, fever, granulocytosis, hearing impairment, hematoma, hot flashes, hyper-/hypotension, hypersensitivity reaction, hypertonia, hypoxia, injection site reactions, leg cramps, leukocytosis, leukopenia, loss of consciousness, lymphadenopathy, monocytosis, myocardial ischemia, oxygenation decreased, pain, palpitation, paresthesia, pharyngitis, pruritus, rash, respiratory arrest, respiratory distress, rhinitis, rigors, supraventricular tachycardia, syncope, tachycardia, taste perversion, upper respiratory tract edema, urine abnormal, urticaria, ventricular fibrillation, ventricular tachycardia, vertigo, visual abnormalities, vomiting, xerostomia

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Monitoring Parameters Cardiopulmonary reactions in all patients; in high-risk patients, closely monitor blood pressure, heart rate, oxygen saturation, cardiac rhythm monitoring (during and for 30 minutes following infusion)

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: OFP 6.52 mg/mL and lipid blend 0.75 mg/mL (2 mL) [following activation, forms a suspension containing perflutren lipid microspheres 1.2 x 10^{10}/mL and OFP 1.1 mg/mL]

Generic Available No

ManufacturerLantheus Medical Imaging

Mechanism of Action Activated perflutren lipid microspheres provide contrast enhancement of the endocardial borders during echocardiography.

Pharmacodynamics/Kinetics

Onset of action: Immediate

Duration: I.V. bolus: 3.4 minutes; I.V. infusion: 7.1 minutes

Metabolism: OFP: not metabolized; Phospholipid component: Free fatty acids

Half-life elimination: OFP: 1.3 minutes (healthy patients); 1.9 minutes (patients with COPD)

Pharmacotherapy Pearls Following activation, a suspension is formed containing perflutren lipid microspheres. The perflutren lipid microspheres are composed of octafluoropropane (OFP) encapsulated in a phospholipid outer shell.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

References

Herzog CA, "Incidence of Adverse Events Associated With Use of Perflutren Contrast Agents for Echocardiography," *JAMA* , 2008, 299(17):2023-5.[PubMed 18460662]

Kusnetzky LL, Kalid A, Khumri TM, et al, "Acute Mortality in Hospitalized Patients Undergoing Echocardiography With and Without an Ultrasound Contrast Agent: Results in 18,671 Consecutive Studies," *J Am Coll Cardiol*, 2008, 51(17):1704-6.[PubMed 18436124]

International Brand Names Definity (CN, NZ); Luminity (CZ, IE, SE)

Perflutren Protein Type A

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Perflutren Lipid Microsphere (Definity®) and Perflutren Protein Type A Microsphere (Optison™): Revised Boxed Warnings, Warnings, and Contraindications - July 2008

The Food and Drug Administration (FDA) has revised the contraindications, boxed warnings, and warnings for microbubble contrast agents (perflutren lipid microsphere and perflutren protein type A microspheres). Perflutren protein type A microspheres (Optison™) is no longer contraindicated in patients with serious ventricular arrhythmias, at high risk for ventricular arrhythmias due to QT prolongation, pulmonary arterial vascular compromise (eg, pulmonary embolism, pulmonary hypertension, severe emphysema), or an unstable cardiopulmonary status (eg, unstable angina, acute MI, respiratory failure, recent worsening or clinically unstable HF). The FDA has determined that the diagnostic benefits derived from use in some patients may outweigh the risk for serous cardiopulmonary reactions. Updated U.S. labeled contraindications now include only those patients with hypersensitivity to perflutren and right-to-left, bidirectional, or transient right-to-left cardiac shunt.

Revisions to the boxed warnings and warnings emphasize the risk of cardiopulmonary reactions that can occur during or within 30 minutes following administration. Patients with pulmonary hypertension or unstable cardiopulmonary conditions (eg, unstable angina, acute MI, respiratory failure, patients receiving mechanical ventilation, recent worsening or unstable HF, serious ventricular arrhythmias) should be monitored closely (eg, vital signs, cardiac rhythm, and oxygen saturation) during and for at least 30 minutes following administration.

The FDA MedWatch alert can be found at:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Microbubble

Pronunciation(per FLOO tren PRO teen typ aye)

U.S. Brand NamesOptison™

Pharmacologic CategoryDiagnostic Agent

Use: Labeled IndicationsOpacification of left ventricular chamber and improvement of delineation of the left ventricular endocardial border in patients with suboptimal echocardiograms

Dosing: Adults

I.V.: 0.5 mL via peripheral vein; flush with D_5W or NS following dose; may repeat in increments of 0.5 mL up to 5 mL cumulatively in 10 minutes (maximum total dose: 8.7 mL in any one patient study)

Dosing: ElderlyRefer to adult dosing.

Administration: I.V.

While allowing the vial to come to room temperature, it should be inverted and gently rotated to resuspend the microspheres; the solution should appear milky-white. Do **not** use if solution is clear. The vial should then be vented with a sterile vent spike or 18-gauge needle. Air should **not** be injected into the vial. The dose should be removed from the vial and injected at a rate ≤1 mL/second into a peripheral vein within 1 minute of resuspension. Resuspension should be repeated prior to injection if more than 1 minute elapses. Flush line with D_5W or NS immediately after injection.

Administration: I.V. Detail

pH: 6.4-7.4

StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Discard unused portion.

ContraindicationsHypersensitivity to perflutren or any component of the formulation, blood, blood products, or albumin; right-to-left, bidirectional, or transient right-to-left cardiac shunt; administration by intra-arterial injection

Warnings/Precautions

Boxed warning:

- Serious cardiopulmonary reactions: See “Concerns related to adverse effects” below

Concerns related to adverse effects:

- Anaphylactoid reactions: Postmarketing reports of anaphylactoid reactions (eg, shock, bronchospasm, upper airway swelling, loss of consciousness, urticaria and pruritus) have been reported in patients with no prior exposure. Monitor for signs and symptoms of anaphylactoid reactions. Immediate treatment (including epinephrine 1:1000) should be available.

- Serious cardiopulmonary reactions: **[U.S. Boxed Warning]: Serious cardiopulmonary reactions (some fatal) have occurred during or within 30 minutes following administration. Ensure patient does not have any contraindications for use. Equipment for resuscitation and trained personnel experienced in handling medical emergencies should always be immediately available.** In patients with pulmonary hypertension or unstable cardiopulmonary conditions (eg, unstable angina, acute MI, respiratory failure, patients receiving mechanical ventilation, recent worsening or unstable HF, serious ventricular arrhythmias), monitor (eg, vital signs, cardiac rhythm, and oxygen saturation) during and for at least 30 minutes following administration.

- QT_c prolongation: Transient QT_c prolongation (>30 msec) has been observed with another microbubble contrast agent (perflutren lipid microsphere), some with associated cardiac rhythm changes; malignant symptomatology was not observed in clinical trials. Clinical trials evaluating the effects of perflutren protein-type A microspheres on the QT interval have not been conducted; however, effects on the QT interval are expected to be similar. Monitor patients at high risk of arrhythmias due to QT_c prolongation.

- Ventricular arrhythmias: High ultrasound mechanical indices with or without end-systolic triggering may cause ventricular arrhythmias. Safety of perflutren protein-type A microspheres with mechanical indices >0.8 or end-systolic triggering has not been established.

Disease-related concerns:

- Cardiac shunts: Patients with right-to-left, bidirectional, or transient right-to-left cardiac shunts should **not** receive perflutren protein-type A microspheres. Use of phospholipid encapsulated microspheres will result in microvascular occlusion and ischemia since the pulmonary particle-filtering mechanism will be bypassed resulting in a direct transfer from venous to arterial circulation.

- Congenital heart defects: Extreme caution should be used in patients with congenital heart defects. Safety and efficacy have not been established in this population.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Albumin: Product contains albumin; may carry a remote risk of virus transmission or hypersensitivity reaction.

Other warnings/precautions:

- Cardiac stress testing: Safety and efficacy with exercise stress or pharmacologic stress testing have not been established.

Pregnancy Risk FactorC

Pregnancy ConsiderationsEmbryotoxic, fetotoxic, and teratogenic effects were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use only when potential benefits outweigh the potential hazards to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Cardiovascular: Flushing (4%), chest pain (1%)

Central nervous system: Headache (5%), dizziness (3%), chills/fever (1%), malaise/weakness/fatigue (1%)

Gastrointestinal: Nausea/vomiting (4%), altered taste (2%)

Local: Injection site discomfort (1%)

Respiratory: Dyspnea (1%)

Miscellaneous: Flu-like syndrome (1%)

<1%, postmarketing, and/or case reports: Anaphylactoid reaction, arthralgia, back pain, body or muscle aches, bronchospasm, burning sensation in the eyes, cardiac arrest, cardiopulmonary reaction, cough, discoloration at the injection site, eosinophilia, erythema, eye irritation, hypersensitivity, hypotension, induration, irritability, loss of consciousness, oxygen desaturation, palpitation, paresthesia, photophobia, premature ventricular contraction, pruritus, rash, respiratory arrest, respiratory distress, seizure, supraventricular fibrillation, supraventricular tachycardia, tinnitus, tremor, upper airway swelling, urticaria, ventricular fibrillation, ventricular tachycardia, visual blurring, wheezing, xerostomia

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersCardiopulmonary reactions in all patients; in high-risk patients, closely monitor blood pressure, heart rate, oxygen saturation, cardiac rhythm (during and for 30 minutes following infusion)

Nursing: Physical Assessment/MonitoringThis medication is administered I.V. and is used short term for increased visualization during an echocardiogram. Monitor patient for allergic response.

Patient EducationThis medication is administered to increase visualization during an echocardiogram. You may experience headache, nausea, dizziness, or flushing. Report immediately any chest pain or difficulty breathing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension [preservative free]:

Optison™: Perflutren 0.11-0.33 mg and protein-type A microspheres 5-8 x 10^8 per mL (3 mL) [contains human albumin 10 mg/mL]

Generic AvailableNo

ManufacturerMallinckrodt Inc

Mechanism of ActionPerflutren is a stable gas that provides an echogenic contrast effect in the blood and allows for improved delineation of the left ventricular endocardial border.

Pharmacodynamics/Kinetics

Duration: Contrast enhancement: Dose dependent: 1 minute (0.2 mL) to 5 minutes (5 mL)

Metabolism: Perflutren: Not metabolized

Half-life elimination: 0.6-2 minutes

Excretion: Perflutren: Lungs

Mental Health: Effects on Mental StatusMay cause dizziness or fatigue

Mental Health: Effects on Psychiatric TreatmentNone reported

Periciazine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(per ee CYE ah zeen)

Canadian Brand NamesNeuleptil®

Pharmacologic CategoryAntipsychotic Agent, Typical, Phenothiazine, Piperidine

Use: Labeled IndicationsAdjunctive therapy in selected psychotic patients to control prevailing hostility, impulsivity, or aggression

Dosing: Adults

Oral: 5-20 mg in the morning, followed by 10-40 mg in the evening. In dividing doses, it is suggested that the larger dose should be administered in the evening. In general, lower dosage should be used on initiation and gradually increased based on effect and tolerance.

Dosing: Elderly

Initial daily dose should be ~5 mg/day. May be increased gradually based on effect and tolerance. Refer to adult dosing.

Dosing: Pediatric

Children >5 years: Oral: 2.5-10 mg in the morning, followed by 5-30 mg in the evening. In general, lower dosage should be used on initiation and gradually increased based on effect and tolerance.

Dosing: Renal ImpairmentNo adjustment required.

StorageStore at room temperature of 20°C to 25°C (68°F to 77°F). Protect from light.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to periciazine, phenothiazine derivatives, or any component of the formulation; severe CNS depression including acute intoxication with CNS depressant medications; subcortical brain damage; hepatic dysfunction; circulatory collapse; severely-depressed patients; bone marrow suppression; blood dyscrasias; coma; patients receiving spinal or regional anesthesia

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines); relative risk with periciazine has not been established, although rare cases of QT_c prolongation have been reported.
- Anticholinergic effects: Phenothiazines may cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems.
- Blood dyscrasias: Check blood counts periodically and discontinue at first signs of blood dyscrasias; use is contraindicated in patients with bone marrow suppression.
- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).
- Extrapyramidal symptoms: May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia.
- Neuroleptic malignant syndrome (NMS): May be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).
- Pigmentary retinopathy: Prolonged therapy may cause pigmentary retinopathy, corneal deposits, and/or changes in skin pigmentation.
- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.
- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Mitral valve prolapse: Use with caution in patients with mitral valve prolapse; may worsen.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Pheochromocytoma: Use with caution in patients with pheochromocytoma; may worsen.

- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Respiratory disease: Use with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for developing tardive dyskinesia.

Pregnancy ConsiderationsTeratogenic effects were observed in some animal studies. Safety and efficacy have not been established in pregnant women.

Adverse ReactionsFrequency not defined; listing includes adverse reactions reported with other agents from the phenothiazine class.

Cardiovascular: AV block, cardiac arrest, ECG changes, edema, hypotension, paroxysmal atrial tachycardia, QT_c prolongation, syncope, tachycardia

Central nervous system; Aggressive behavior, agitation, anxiety, bizarre dreams, cerebral edema, depression, dizziness, drowsiness, EEG changes, excitement; extrapyramidal symptoms (tremor, akathisia, dystonia, dyskinesia, oculogyric, opisthotonos, hyper-reflexia, pseudo-Parkinsonism, rigidity, sialorrhea); fatigue, fever, headache, insomnia, paradoxical psychosis, restlessness, seizure, sleep disturbance, tardive dyskinesia

Dermatologic: Angioedema, dermatitis, eczema, epithelial keratopathy, erythema, exfoliative dermatitis, photosensitivity, pruritus, rash, seborrhea, skin pigmentation (prolonged therapy), urticaria

Endocrine & metabolic: Anorexia, appetite increased, delayed ovulation, galactorrhea, gynecomastia, libido changes, menstrual irregularities, thirst, weight changes

Gastrointestinal: Adynamic ileus, constipation, fecal impaction, nausea, salivation, vomiting, xerostomia

Genitourinary: Bladder paralysis, impotence, incontinence, polyuria, urinary retention

Hematologic: Agranulocytosis, anemia, eosinophilia, leukopenia, pancytopenia, thrombocytopenia

Hepatic: Cholestasis, cholestatic jaundice, jaundice

Ocular: Blurred vision, corneal deposits (prolonged therapy), glaucoma, lenticular deposits, pigmentary retinopathy (prolonged therapy)

Respiratory: Nasal congestion, pneumonia, pneumonitis

Miscellaneous: Diaphoresis increased, lupus-like syndrome

Metabolism/Transport EffectsNo published data on CYP metabolism. Based on structural analysis, may be a substrate of CYP2D6 and 3A4.

Drug InteractionsNo published data on CYP metabolism. Based on structural analysis, may be a substrate of CYP2D6 and 3A4.

Aluminum salts: May decrease the absorption of phenothiazines; monitor.

Amphetamines: Efficacy may be diminished by antipsychotics; in addition, amphetamines may increase psychotic symptoms; avoid concurrent use.

Anticholinergics: May inhibit the therapeutic response to phenothiazines and excess anticholinergic effects may occur; includes benztropine, trihexyphenidyl, biperiden, and drugs with significant anticholinergic activity (TCAs, antihistamines, disopyramide).

Antihypertensives: Concurrent use of phenothiazines with an antihypertensive may produce additive hypotensive effects (particularly orthostasis).

Beta-blockers: May increase the risk of arrhythmia; serum concentrations of phenothiazines may be increased; propranolol also increases phenothiazine concentrations; may also occur with pindolol. Propranolol and pindolol are contraindicated.

Bromocriptine: Phenothiazines inhibit the ability of bromocriptine to lower serum prolactin concentrations.

Carvedilol: Serum concentrations may be increased, leading to hypotension and bradycardia; avoid concurrent use.

CNS depressants: Sedative effects may be additive with phenothiazines; monitor for increased effect; includes barbiturates, benzodiazepines, opioid analgesics, ethanol, and other sedative agents.

CYP2D6 inhibitors: May increase the levels/effects of Periciazine. Example inhibitors include chlorpromazine, delavirdine, fluoxetine, miconazole, paroxetine, pergolide, quinidine, quinine, ritonavir, and ropinirole. Other piperidine phenothiazines (thioridazine) are contraindicated with inhibitors of this enzyme.

CYP3A4 inhibitors: May increase the levels/effects of Periciazine. Example inhibitors include azole antifungals, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, nefazodone, nicardipine, propofol, protease inhibitors, quinidine,telithromycin, and verapamil.

Epinephrine: Low potency antipsychotics may diminish the pressor effects of epinephrine.

Guanethidine and guanadrel: Antihypertensive effects may be inhibited by phenothiazines.

Levodopa: Phenothiazines may inhibit the antiparkinsonian effect of levodopa; avoid this combination.

Lithium: Phenothiazines may produce neurotoxicity with lithium; this is a rare effect.

Metoclopramide: May increase extrapyramidal symptoms (EPS) or risk.

Phenytoin: May reduce serum levels of phenothiazines; phenothiazines may increase phenytoin serum levels.

Polypeptide antibiotics (eg, bacitracin): Rare cases of respiratory paralysis have been reported with concurrent use of phenothiazines.

Potassium-depleting agents: May increase the risk of serious arrhythmias with phenothiazines; includes many diuretics, aminoglycosides, and amphotericin; monitor serum potassium closely.

QT_c-prolonging agents: Effects on QT_c interval may be additive with phenothiazines, increasing the risk of malignant arrhythmias; includes type Ia antiarrhythmics, TCAs, and some quinolone antibiotics (moxifloxacin). These agents are contraindicated with other piperidine phenothiazines (thioridazine).

Sulfadoxine-pyrimethamine: May increase phenothiazine concentrations.

Trazodone: Phenothiazines and trazodone may produce additive hypotensive effects.

Tricyclic antidepressants: Concurrent use may produce increased toxicity or altered therapeutic response.

Valproic acid: Serum levels may be increased by phenothiazines.

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid kava kava, valerian, St John's wort, gotu kola (may increase CNS depression). Avoid dong quai, St John's wort (may also cause photosensitization). Cigarette smoking may decrease the serum concentrations of periciazine.

Test InteractionsPhenothiazines have been reported to cause false-positive pregnancy tests.

Monitoring ParametersVital signs; serum potassium and magnesium, lipid profile, waist circumference, fasting blood glucose/Hgb A_{1c}; BMI; mental status, abnormal involuntary movement scale (AIMS); periodic eye exam and evaluation of renal and liver function tests (long-term therapy).

Based on experience with other piperidine phenothiazines: Consider baseline and periodic ECG; do not initiate if QT_c >450 msec.

Nursing: Physical Assessment/MonitoringAssess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Monitor pulse and blood pressure at beginning and periodically during therapy. Monitor cardiac status. Observe for fluid retention. Monitor weight. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Monitoring: Lab TestsSerum potassium and magnesium, lipid profile, fasting blood glucose/Hgb A_{1c}; evaluation of renal and liver function tests (long-term therapy).

Based on experience with other piperidine phenothiazines: Consider baseline and periodic ECG; do not initiate if QT_c >450 msec.

Patient EducationInform prescriber of all prescription medications, OTC medications, or herbal products you are taking. Avoid alcohol; may increase drowsiness. Maintain adequate hydration (2-3 L/day) unless instructed to restrict intake by prescriber. May cause CNS changes (eg, confusion, depression, increased sedation, excitation, headache, agitation, insomnia or nightmares, dizziness, fatigue, impaired coordination, changes in personality, or changes in cognition). Use caution when driving or engaging in activities requiring alertness until response to drug is known. May also cause orthostatic hypotension (use caution when changing position from lying or sitting to standing). Report rapid or irregular pulse, fainting, sudden weight gain >5 lbs per week, shortness of breath, chest pain, or swelling of the extremities.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Capsule:

Neuleptil® [CAN]: 5 mg, 10 mg, 20 mg [not available in the U.S.]

Solution, oral drops:

Neuleptil® [CAN]: 10 mg/mL (100 mL) [contains ethanol 12% and sucrose 250 mg/mL [not available in the U.S.]

ManufacturerErfa Canada Inc

Mechanism of ActionBlocks postsynaptic mesolimbic dopaminergic receptors in the brain; depresses the release of hypothalamic and hypophyseal hormones.

Dental Health Professional ConsiderationsThis drug is known to prolong the QT interval. The QT interval is measured as the time and distance between the Q point of the QRS complex and the end of the T wave in the ECG tracing. After adjustment for heart rate, the QT interval is defined as prolonged if it is more than 450 msec in men and 460 msec in women. A long QT syndrome was first described in the 1950s and 60s as a congenital syndrome involving QT interval prolongation and syncope and sudden death. Some of the congenital long QT syndromes were characterized by a peculiar electrocardiographic appearance of the QRS complex involving a premature atria beat followed by a pause, then a subsequent sinus beat showing marked QT prolongation and deformity. This type of cardiac arrhythmia was originally termed “torsade de pointes” (translated from the French as “twisting of the points”).

Prolongation of the QT interval is thought to result from delayed ventricular repolarization. The repolarization process within the myocardial cell is due to the efflux of intracellular potassium. The channels associated with this current can be blocked by many drugs and predispose the electrical propagation cycle to torsade de pointes.

Periciazine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Significant hypotension may occur, especially when the drug is administered parenterally. Orthostatic hypotension is due to alpha-receptor blockade; elderly are at greater risk.

Tardive dyskinesia: Prevalence rate may be 40% in elderly; development of the syndrome and the irreversible nature are proportional to duration and total cumulative dose over time. Extrapyramidal reactions are more common in elderly with up to 50% developing these reactions after 60 years of age. Drug-induced Parkinson's syndrome occurs often; akathisia is the most common extrapyramidal reaction in elderly.

Increased confusion, memory loss, psychotic behavior, and agitation frequently occur as a consequence of anticholinergic effects. Antipsychotic-associated sedation in nonpsychotic patients is extremely unpleasant due to feelings of depersonalization, derealization, and dysphoria.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsMost pharmacology textbooks state that in presence of phenothiazines, systemic doses of epinephrine paradoxically decrease the blood pressure. This is the so called “epinephrine reversal” phenomenon. This has never been observed when epinephrine is given by infiltration as part of the anesthesia procedure. See Dental Comment.

Mental Health CommentIn 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Index TermsPericyazine

References

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International Brand NamesNeulactil (AU, DK, FI, GB, HK, NO, ZA); Neuleptil (AR, AT, BG, BR, CN, GR, IL, IT, NL, PE, PT, PY, UY, VE); Neuperil (FI)

Perindopril Erbumine and Indapamide

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English

Jump To Field (Select Field Name)

Pronunciation(per IN doe pril er BYOO meen & in DAP a mide)

Canadian Brand NamesCoversyl® Plus

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Diuretic, Thiazide-Related

Use: Labeled IndicationsTreatment of hypertension; not indicated for initial treatment of hypertension

Dosing: Adults**Note: Not for initial therapy. Titration of individual components to an appropriate clinical response is required prior to converting to an equivalent dose of the combination product.**

Hypertension: Oral: Usual maintenance dose: Perindopril 4 mg/indapamide 1.25 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} ≥30-60 mL/minute: Use with caution due to perindopril component. No specific dosing guidelines for the combination product provided with approved labeling.

Cl_{cr} <30 mL/minute: Use not recommended.

Dosing: Hepatic ImpairmentNo specific dosing available. Contraindicated in patients with hepatic coma.

Administration: OralAdminister early in the day to avoid nocturia. Food may decrease the bioavailability of perindoprilat (active metabolite of perindopril).

Dietary ConsiderationsTake without food.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to perindopril, indapamide, any other component of the formulation, or sulfonamide-derived drugs; angioedema related to previous treatment with an ACE inhibitor; progressive, severe oliguria; anuria; hepatic coma

Warnings/Precautions

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose), angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema or previous angioedema associated with ACE inhibitor therapy may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs. Consider discontinuing therapy if symptoms of hepatic dysfunction (eg, fever, malaise, muscle pain, rash) present within the first weeks to months of therapy.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Dermatologic reactions: Severe reactions (eg, Stevens-Johnson syndrome, erythema multiforme) rarely have been observed with indapamide use in postmarketing studies.

- Electrolyte disturbances: Hyperkalemia may occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Indapamide may cause hypokalemia, hypochloremic alkalosis, and hyponatremia. Measure potassium levels during the first week of therapy.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement if needed may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use perindopril with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity. Indapamide can cause systemic lupus erythematosus (SLE) exacerbation or activation.

- Diabetes: Use indapamide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: Hyperuricemia has been observed with indapamide use. In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by indapamide.

- Hepatic impairment: Use with caution in patients with prior hepatic dysfunction. Prior to initiation of therapy obtain baseline transaminase and bilirubin levels. In cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy. Contraindicated in patients with hepatic coma.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with indapamide.

- Renal artery stenosis: Use perindopril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment. Patients with renal impairment may be at increased risk for hematologic toxicity. Use is contraindicated in patients with progressive or severe oliguria or anuria.

Concurrent drug therapy issues:

- Drugs with QT prolongation potential: Indapamide may prolong QT interval; Concurrent use with other non-antiarrhythmic drugs known to prolong QT interval is not recommended. Use caution in patients at risk for QT prolongation, including patients with pre-existing QT interval prolongation; patients taking antiarrhythmic medications or other medications that lead to QT prolongation or other potassium-wasting medications.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **ACEIs can cause injury and death to the developing fetus when used in pregnancy. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsSee individual agents.

Pregnancy Considerations**ACEIs can cause injury and death to the developing fetus when used in pregnancy. ACEIs should be discontinued as soon as possible once pregnancy is detected.** See individual agents.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions**Note:** Observed with perindopril/indapamide; also see individual agents.

1% to 10%:

Central nervous system: Dizziness (1% to 2%)

Endocrine & metabolic: Hypokalemia (4%), hyperkalemia (1%)

Gastrointestinal: Nausea (2%), vomiting (2%), dyspepsia (1%)

Respiratory: Cough (3%), upper respiratory infection (2%)

<1%, postmarketing, and/or case reports (limited to significant or life-threatening): Abdominal pain, agranulocytosis, angioedema, angina,

anxiety, arrhythmias, asthma, BUN increased, chest pain, colitis, constipation, creatinine increased, dermatitis, diarrhea, depression, drowsiness, dysuria, ECG abnormal, edema, epidermal necrolysis, epistaxis, erythema multiforme, esophagitis, fever, flushing, gout, hemoglobin decreased, hepatitis, hyperbilirubinemia, hyper-/hypotension, impotence, laryngitis, limb pain, migraine, neutropenia, oliguria, orthostatic hypotension, palpitation, polyuria, pruritus, rash, renal impairment, respiratory insufficiency, rhinitis, sinusitis, somnolence, Stevens-Johnson syndrome, syncope, tachycardia, tetany, tinnitus, transaminases increased, uric acid increased, visual disturbance

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: Bioavailability of perindoprilat (active metabolite of perindopril) is reduced ~35% by food.

Monitoring ParametersBlood pressure; BUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsBUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet:

Coversyl® Plus [CAN]: Perindopril erbumine 4 mg and indapamide 1.25 mg [not available in the U.S.]

Generic AvailableNo

ManufacturerServier Canada Inc

Mechanism of ActionSee individual agents.

Pharmacodynamics/KineticsSee individual agents.

Pharmacotherapy PearlsHealth Canada issued a Notice of Compliance, March 2007, concerning the name change of Preterax® to Coversyl® Plus LD. The new labeling and packaging is to be released at a later date.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Indapamide: Orthostatic hypotension, palpitations, flushing, rhinorrhea, and xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index TermsIndapamide and Perindopril Erbumine; Perindopril and Indapamide

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International Brand NamesAcertil Plus (KP); Biprel (CL); BiPreterax (AR, BB, BM, BS, BZ, CO, CR, DE, DO, GT, GY, HN, IE, JM, NI, NL, PA, PE, PH, PK, SR, SV, TT, TW, VE); Coversum Combi (DE); Coversyl Comp (DK, SE); Coversyl Plus (AU, BE, BR, GB, ID, IN, MY, SG, UY); Noliprel (BG, CZ, EE); Predonium (HK, NZ); Predonium DS (NZ); Prestarium (EE); Preterax (AR, BB, BM, BS, BZ, CH, CO, CR, DO, GT, GY, HN, JM, MX, NI, NL, PA, PE, PH, PK, PY, SG, SR, SV, TT, TW, VE); Preterax Forte (CH)

Perindopril Erbumine

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English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(per IN doe pril er BYOO meen)

U.S. Brand NamesAceon®

Canadian Brand NamesApo-Perindopril®; Coversyl®

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor

Use: Labeled IndicationsTreatment of hypertension; reduction of cardiovascular mortality or nonfatal myocardial infarction in patients with stable coronary artery disease

Use: Unlabeled/InvestigationalTo delay the progression of nephropathy and reduce risks of cardiovascular events in hypertensive patients with type 1 or 2 diabetes mellitus

Dosing: Adults

Hypertension: Oral: Initial: 4 mg/day but may be titrated to response; usual range: 4-8 mg/day (may be given in 2 divided doses); increase at 1- to 2-week intervals (maximum: 16 mg/day)

Concomitant therapy with diuretics: To reduce the risk of hypotension, discontinue diuretic, if possible, 2-3 days prior to initiating perindopril. If unable to stop diuretic, initiate perindopril at 2-4 mg/day and monitor blood pressure closely for the first 2 weeks of therapy, and after any dose adjustment of perindopril or diuretic.

Stable coronary artery disease: Oral: Initial: 4 mg once daily for 2 weeks; increase as tolerated to 8 mg once daily.

Heart failure (unlabeled use): Oral: Initial: 2 mg once daily; increase at 1- to 2-week intervals; target dose: 8-16 mg once daily (ACC/AHA 2005 Heart Failure Guidelines)

Dosing: Elderly

Hypertension: >65 years of age: Initial: 4 mg/day; maintenance: 8 mg/day; experience with doses >8 mg/day is limited.

Stable coronary artery disease: >70 years of age: Initial: 2 mg/day for 1 week; increase as tolerated to 4 mg/day for 1 week; then increase as tolerated to 8 mg/day; experience with doses >8 mg/day is limited.

Dosing: Renal Impairment

Cl_{cr} >30 mL/minute: Initial: 2 mg/day; maintenance dosing not to exceed 8 mg/day

Cl_{cr} <30 mL/minute: Safety and efficacy not established.

Hemodialysis: Perindopril and its metabolites are dialyzable

Dosing: Hepatic ImpairmentNo adjustment necessary.

Calculations

- Creatinine Clearance: Adults

StorageStore at room temperature of 20°C to 25°C (68°F to 77°F). Protect from moisture.

ContraindicationsHypersensitivity to perindopril, any other ACE inhibitor, or any component of the formulation; angioedema related to previous treatment with an ACE inhibitor

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose), angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss, or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsDue to frequent decreases in glomerular filtration (also creatinine clearance) with aging, elderly patients may have exaggerated responses to ACE inhibitors; differences in clinical response due to hepatic changes are not observed. ACE inhibitors may be preferred agents in elderly patients with congestive heart failure and diabetes mellitus. Diabetic proteinuria is reduced and insulin sensitivity is enhanced. In general, the side effect profile is favorable in elderly and causes little or no CNS confusion; use lowest dose recommendations initially. Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.

Pregnancy Risk FactorD

Pregnancy ConsiderationsDue to adverse events observed in humans, perindopril is considered pregnancy category D. Perindopril crosses the placenta. First trimester exposure to ACE inhibitors may cause major congenital malformations. An increased risk of cardiovascular and/or central nervous system malformations was observed in one study; however, an increased risk of teratogenic events was not observed in other studies. Second and third trimester use of an ACE inhibitor is associated with oligohydramnios. Oligohydramnios due to decreased fetal renal function may lead to fetal limb contractures, craniofacial deformation, and hypoplastic lung development. The use of ACE inhibitors during the second and third trimesters is also associated with anuria, hypotension, renal failure (reversible or irreversible), skull hypoplasia, and death in the fetus/neonate. Chronic maternal hypertension itself is also associated with adverse events in the fetus/infant. ACE inhibitors are not recommended during pregnancy to treat maternal hypertension or heart failure. Those who are planning a pregnancy should be considered for other medication options if an ACE inhibitor is currently prescribed or the ACE inhibitor should be discontinued as soon as possible once pregnancy is detected. The exposed fetus should be monitored for fetal growth, amniotic fluid volume, and organ formation. Infants exposed to an ACE inhibitor *in utero*, especially during the second and third trimester, should be monitored for hyperkalemia, hypotension, and oliguria.

[U.S. Boxed Warning]: Based on human data, ACE inhibitors can cause injury and death to the developing fetus. ACE inhibitors should be discontinued as soon as possible once pregnancy is detected.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if perindopril is excreted in human breast milk. The manufacturer recommends that caution be exercised when administering perindopril to nursing women.

Pregnancy & Lactation, In-Depth

- Perindopril Erbumine in Pregnancy & Lactation

Adverse Reactions

>10%:

Central nervous system: Headache (24%)

Respiratory: Cough (incidence is higher in women, 3:1) (12%)

1% to 10%:

Cardiovascular: Edema (4%), chest pain (2%), ECG abnormal (2%), palpitation (1%)

Central nervous system: Dizziness (8%, less than placebo), sleep disorders (3%), depression (2%), fever (2%), nervousness (1%), somnolence (1%)

Dermatologic: Rash (2%)

Endocrine & metabolic: Hyperkalemia (1%, less than placebo), triglycerides increased (1%), menstrual disorder (1%)

Gastrointestinal: Diarrhea (4%), abdominal pain (3%), nausea (2%), vomiting (2%), dyspepsia (2%), flatulence (1%)

Genitourinary: Urinary tract infection (3%), sexual dysfunction (male 1%)

Hepatic: ALT increased (2%)

Neuromuscular & skeletal: Weakness (8%), back pain (6%), lower extremity pain (5%), upper extremity pain (3%), hypertonia (3%), paresthesia (2%), joint pain (1%), myalgia (1%), arthritis (1%), neck pain (1%)

Renal: Proteinuria (2%)

Respiratory: Upper respiratory tract infection (9%), sinusitis (5%), rhinitis (5%), pharyngitis (3%)

Otic: Tinnitus (2%), ear infection (1%)

Miscellaneous: Viral infection (3%), seasonal allergy (2%)

Note: Some reactions occurred at an incidence >1% but ≤ placebo.

<1% (Limited to important or life-threatening): Alkaline phosphatase increased, amnesia, anaphylaxis, angioedema (0.1%), anxiety, appetite increased, arthralgia, AST increased, bronchitis, bruising, cerebral vascular accident (0.2%), chills, cholesterol increased, conduction abnormalities, conjunctivitis, constipation, diaphoresis, dry skin, dyspnea, earache, epistaxis, erythema, facial edema, flank pain, fluid retention, gastroenteritis, gout, hematoma, hematuria, hyperglycemia, hypokalemia, hypotension, leukopenia, malaise, migraine, MI, murmur, nephrolithiasis, neutropenia, orthostatic hypotension, pain, pruritus, psychosexual disorder, pulmonary fibrosis (<0.1%), purpura (0.1%), rhinorrhea, serum creatinine increased, sneezing, syncope, tinea, uric acid increased, urinary frequency, urinary retention, vaginitis, vasodilation, ventricular extrasystole, vertigo, xerostomia

Additional adverse effects that have been reported with **ACE inhibitors** include agranulocytosis (especially in patients with renal impairment or collagen vascular disease), neutropenia, anemia, bullous pemphigoid, cardiac arrest, eosinophilic pneumonitis, exfoliative dermatitis, falls, hepatic failure, hyponatremia, jaundice, pancreatitis (acute), pancytopenia, pemphigus, psoriasis, thrombocytopenia; decreases in creatinine clearance in some elderly hypertensive patients or those with chronic renal failure, and worsening of renal function in patients with bilateral renal artery stenosis or hypovolemic patients (diuretic therapy). In addition, a syndrome which may include fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash, eosinophilia and positive ANA, and elevated ESR has been reported with ACE inhibitors.

Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Perindopril active metabolite concentrations may be lowered if taken with food.

Herb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure; serum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringUse with caution and monitor closely in presence of with renal impairment, hypovolemia; collagen vascular diseases; valvular stenosis, hyperkalemia; or anesthesia. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, other drugs may effect blood pressure or increase risk of toxicities). It is recommended that first dose is administered in prescriber's office with careful blood pressure monitoring (hypotension can occur, especially with first dose; angioedema can occur at any time during treatment, especially following first dose). Assess results of laboratory tests and patient response at beginning of therapy, when adjusting dose, and periodically with long-term therapy (eg, BP [standing and sitting], cardiac status, and fluid balance). Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take as directed; do not alter dose or discontinue without consulting prescriber. Take first dose at bedtime. Do not take potassium supplements or salt substitutes containing potassium without consulting prescriber. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause increased cough (if persistent or bothersome, contact prescriber); headache (consult prescriber for approved analgesic); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report chest pain, respiratory difficulty or persistent cough, painful muscles or joints, rash, ringing in ears, or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 2 mg, 4 mg, 8 mg

Generic AvailableNo
ManufacturerSolvay Pharmaceuticals
Pricing: U.S. (www.drugstore.com)

Tablets (Aceon)

2 mg (100): $165.98

4 mg (100): $188.85

8 mg (100): $228.86

Mechanism of ActionPerindopril is a prodrug for perindoprilat, which acts as a competitive inhibitor of angiotensin-converting enzyme (ACE); prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor; results in lower levels of angiotensin II which, in turn, causes an increase in plasma renin activity and a reduction in aldosterone secretion
Pharmacodynamics/Kinetics

Onset of action: Peak effect: 1-2 hours

Protein binding: Perindopril: 60%; Perindoprilat: 10% to 20%

Metabolism: Hepatically hydrolyzed to active metabolite, perindoprilat (~17% to 20% of a dose) and other inactive metabolites

Bioavailability: Perindopril: 75%; Perindoprilat ~25% (~16% with food)

Half-life elimination: Parent drug: 1.5-3 hours; Metabolite: Effective: 3-10 hours, Terminal: 30-120 hours

Time to peak: Chronic therapy: Perindopril: 1 hour; Perindoprilat: 3-7 hours (maximum perindoprilat serum levels are 2-3 times higher and T_{max} is shorter following chronic therapy); CHF: Perindoprilat: 6 hours

Excretion: Urine (75%, 4% to 12% as unchanged drug)

Related Information

- Angiotensin Agents
- Heart Failure (Systolic)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness or fatigue; may rarely cause sedation, insomnia, or depression
Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels
Cardiovascular Considerations

Congestive Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines recommend that ACE inhibitors be used in patients with a reduced EF (with or without heart failure symptoms) unless contraindicated. ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. In this situation, they decrease hospitalizations for, and retard progression to, congestive heart failure. When used in patients with heart failure, the target dose should be achieved, if possible. Lower daily doses of ACE inhibitors have demonstrated the same mortality effects as high doses, but have not decreased hospitalizations to the extent that high-dose ACE inhibitors have, as demonstrated in the ATLAS study (Packer M, 1999).

Hypertension: The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) can be beneficial in patients with hypertension and LVH without symptoms of heart failure. JNC 7 suggests that patients can benefit from treatment with an ACE inhibitor if they have hypertension **and** heart failure, acute myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, or history of stroke.

Vascular Disease: The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors can be useful in preventing heart failure in patients who have a history of atherosclerotic vascular disease, diabetes, or hypertension with associated cardiovascular risk factors. The HOPE trial (Heart Outcomes Prevention Evaluation Study Investigators, 2000) investigated the value of an ACE inhibitor (ramipril 5-10 mg daily) versus placebo in patients who had evidence of vascular disease or diabetes (one other cardiovascular risk factor) and were at least 55 years of age. Patients were excluded if they had a low ejection fraction, heart failure, or were on an ACE inhibitor. The primary outcome was a composite of death from cardiovascular cause, myocardial infarction, or stroke; 9297 patients were enrolled and randomized. Ramipril significantly reduced the risk of death from CV causes, MI, or stroke over placebo. New cases of diabetes were also reduced in the ramipril group. In the EUROPA trial, patients with stable coronary artery disease (at low risk for cardiovascular events) received perindopril or placebo and were evaluated for incidence of cardiovascular events after four years of treatment. In this randomized, placebo-controlled, prospective study, 12,218 patients received either perindopril (8 mg/day, n=6110) or placebo (n=6108) and were assessed for the primary endpoint of a cardiovascular event, defined as cardiovascular death, myocardial infarction, or cardiac arrest. The study population was well balanced with respect to baseline demographics and concomitant medication use (including beta-blockers, platelet inhibitors, antihyperlipidemics, calcium channel blockers, nitrates, and diuretics). Intent-to-treat analysis revealed that 603 (10%) of placebo patients experienced the primary endpoint of a cardiovascular event compared to 488 (8%) of perindopril-receiving patients, for a 20% relative risk reduction (p=0.0003). This result was not influenced by presence of other comorbidities (eg, diabetes, hypertension) or concomitant beta-blocker, calcium channel blocker, or lipid-lowering therapies. Withdrawal from the study (postrandomization) due to adverse reactions was similar between treatment groups. Number needed to treat analysis suggests that treatment of 50 patients over a 4-year period will prevent one major cardiovascular event.

Acute Coronary Syndromes: In the treatment of unstable angina/non-ST-segment elevation MI, ACE inhibitors are recommended when hypertension persists despite treatment with nitroglycerin and a beta-blocker in patients with LV systolic dysfunction or CHF and in ischemic patients with diabetes (Class I). ACE inhibitors are also recommended for all post-ACS individuals (Class IIa). According to 2004 ACC/AHA STEMI guidelines, an ACE inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF <0.4, in the absence of hypotension or known contraindications to this class of medicines. In the emergency management of complicated STEMI, a short-acting ACEI (eg, captopril 1-6.25 mg) may be added once the patient's systolic blood pressure is >100 mm Hg and not <30 mm Hg below baseline. The VALIANT trial evaluated the effects of valsartan (target dose: 160 mg twice daily), captopril (target dose: 50 mg twice daily), and the combination (target doses: valsartan 80 mg twice daily and captopril 150 mg once daily) in a randomized, double-blind trial of patients with acute MI (0.5-10 days post-MI) complicated by left ventricular systolic dysfunction, heart failure, or both. Enrollment in the study numbered 14,703 patients and followed for a median of 24.7 months. There was no difference in the primary endpoint (all cause mortality) among the 3 groups. There was no difference in incidence of CV death, recurrent MI, or hospitalization for heart failure either. Hypotension and renal dysfunction occurred significantly more often in the valsartan group than captopril alone. Cough, rash, and taste disturbances occurred more often in the captopril group. The authors (Pfeffer MA, 2003) concluded that valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after MI. Combining valsartan with captopril increased the rate of adverse events without improving survival.

Potential Adverse Events: ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. In those patients experiencing cough on an ACE inhibitor, the ACE inhibitor may be discontinued and, if necessary, ARB therapy instituted. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Drug Interactions: Concomitant indomethacin therapy may blunt the reduction in sitting and 24-hour ambulatory diastolic blood pressure. Use of NSAIDs should be avoided or limited, with monitoring of blood pressure control in this setting. In patients with heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

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International Brand NamesAcerpril (KP); Acertil (CL, HK, KP, TW); Covapril (MY); Coverene (AR); Coverex (BG, HN, HU, PL, SE); Coversum (AT, CH, DE); Coversyl (AE, AU, BB, BE, BM, BR, BS, BZ, CN, CO, CR, DK, DO, ES, FI, FR, GB, GR, GT, GY, HN, IE, IN, IT, JM, JP, KW, LU, MT, MX, MY, NI, NL, PA, PE, PH, PK, PT, PY, SA, SR, SV, TT, UY, VE, ZA); Covinace (MY); Perinace (MY); Peryndopryl Anpharm (PL); Prenessa (EE); Prestarium (HR, PL); Prestoril (IL); Prexum (ID); Provinace (HK)

Permethrin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(per METH rin)
U.S. Brand NamesA200® Lice [OTC]; Acticin®; Elimite®; Nix® [OTC]; Rid® Spray [OTC]
Canadian Brand NamesKwellada-P™; Nix®
Pharmacologic CategoryAntiparasitic Agent, Topical; Scabicidal Agent
Use: Labeled IndicationsSingle-application treatment of infestation with *Pediculus humanus capitis* (head louse) and its nits or *Sarcoptes scabiei* (scabies); indicated for prophylactic use during epidemics of lice
Dosing: Adults

Head lice: Topical: After hair has been washed with shampoo, rinsed with water and towel dried, apply a sufficient volume of creme rinse to saturate the hair and scalp; also apply behind the ears and at the base of the neck; leave on hair for 10 minutes before rinsing off with water; remove remaining nits. May repeat in 1 week if lice or nits still present; in areas of head lice resistance to 1% permethrin, 5% permethrin has been applied to clean, dry hair and left on overnight (8-14 hours) under a shower cap.

Scabies: Topical: Apply cream from head to toe; leave on for 8-14 hours before washing off with water; may reapply in 1 week if live mites appear. Time of application was limited to 6 hours before rinsing with soap and water.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Head lice: Topical: Children >2 months: Refer to adult dosing.

Scabies: Topical: Apply cream from head to toe; leave on for 8-14 hours before washing off with water; for infants, also apply on the hairline, neck, scalp, temple, and forehead; may reapply in 1 week if live mites appear. Permethrin 5% cream was shown to be safe and effective when applied to an infant <1 month of age with neonatal scabies; time of application was limited to 6 hours before rinsing with soap and water.

Administration: TopicalAvoid contact with eyes and mucous membranes during application. Because scabies and lice are so contagious, use caution to avoid spreading or infecting oneself; wear gloves when applying

Cream rinse/lotion: Shake cream rinse well before using. Apply immediately after hair is shampooed, rinsed, and towel-dried. Apply enough to saturate hair and scalp (especially behind ears and on nape of neck). Leave on hair for 10 minutes before rinsing with water. Remove nits with fine-tooth comb. May repeat in 1 week if lice or nits are still present.

Cream: Apply from neck to toes. Bathe to remove drug after 8-14 hours. Repeat in 7 days if lice or nits are still present. Report if condition persists or infection occurs.

ContraindicationsHypersensitivity to pyrethyoid, pyrethrin, chrysanthemums, or any component of the formulation; lotion is contraindicated for use in infants <2 months of age
Warnings/Precautions

Concerns related to adverse effects:

- Skin irritation: Treatment may temporarily exacerbate the symptoms of itching, redness, and swelling.

Special populations:

- Pregnancy: Use during pregnancy only if clearly needed.

Other warnings/precautions:

- Appropriate use: For external use only.

Geriatric ConsiderationsBecause of its minimal absorption, permethrin is a drug of choice and is preferred over lindane.
Pregnancy Risk FactorB
LactationEffect on infant unknown
Adverse Reactions1% to 10%:

Dermatologic: Pruritus, erythema, rash of the scalp

Local: Burning, stinging, tingling, numbness or scalp discomfort, edema

Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringAssess head, hair, and skin surfaces for presence of lice and nits. Assess knowledge/teach patient appropriate application and use and adverse symptoms to report.
Patient EducationFor external use only. Do not apply to face and avoid contact with eyes or mucous membrane. Clothing and bedding must

be washed in hot water or dry cleaned to kill nits. May need to treat all members of household and all sexual contacts concurrently. Wash all combs and brushes with permethrin and thoroughly rinse. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Cream rinse/lotion: Apply immediately after hair is shampooed, rinsed, and towel-dried. Apply enough to saturate hair and scalp (especially behind ears and on nape of neck). Leave on hair for 10 minutes before rinsing with water. Remove nits with fine-tooth comb. May repeat in 1 week if lice or nits are still present.

Cream: Apply from neck to toes. Bathe to remove drug after 8-14 hours. Repeat in 7 days if lice or nits are still present. Report if condition persists or infection occurs.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical (Acticin®, Elimite®): 5% (60 g) [contains coconut oil]

Lotion, topical: 1% (59 mL)

Liquid, topical [creme rinse formulation] (Nix®): 1% (60 mL) [contains isopropyl alcohol 20%]

Solution, spray [for bedding and furniture]:

A200® Lice: 0.5% (180 mL)

Nix®: 0.25% (148 mL)

Rid®: 0.5% (150 mL)

Generic AvailableYes: Excludes spray

Pricing: U.S. (www.drugstore.com)

Cream (Acticin)

5% (60): $18.99

Cream (Elimite)

5% (60): $63.23

Mechanism of ActionInhibits sodium ion influx through nerve cell membrane channels in parasites resulting in delayed repolarization and thus paralysis and death of the pest

Pharmacodynamics/Kinetics

Absorption: <2%

Metabolism: Hepatic via ester hydrolysis to inactive metabolites

Excretion: Urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

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International Brand NamesAssy (AR); Destolit (PE); Dronol (PY); Gamabenceno Plus (CO); Infectopedicul (DE); Klinits (CN); Lice-omite (PK); Lindell (PH); Loxazol (CH, NL); Lyclear (AU, GB, IE); Lyclear Creme Rinse (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Lyclear Dermal Cream (IL); Lyclear Scabies Cream (AU); Lyderm (NZ); Mite-X (IL); Nastizol EX (MX); Nedax Plus (BR); New-Nok (IL); Nittyfor (HU); Nix (BE, DK, EE, FI, IT, NO, PT, SE); Nix Cream (BB, BM, BS, BZ, GY, JM, PR, SR, TT); Nix Creme Rinse (LU); Nix Dermal Cream (BB, BM, BS, BZ, GY, JM, PR, SR, TT); Novo-Herklin 2000 (CR, DO, GT, HN, MX, NI, PA, SV); Parapoux (FR); Permicren (UY); Permite (IN); Piokil Plus (VE); Pyrifoam (AU, PH); Quellada Creme Rinse (AU); Quellada Head Lice Treatment (AU); Sarnol (EC); Scabisan (MX); Scabmite (ID); Zalvor (LU); Zehu-Ze (IL)

Perphenazine

Lexi-Drugs Online

English

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Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

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Schneeweiss S, Setoguchi S, Brookhart A, et al, “Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients,” *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Medication Safety Issues

Sound-alike/look-alike issues:

Trilafon® may be confused with Tri-Levlen®

Pronunciation(per FEN a zeen)
Canadian Brand NamesApo-Perphenazine®
Pharmacologic CategoryAntiemetic; Antipsychotic Agent, Typical, Phenothiazine
Use: Labeled IndicationsTreatment of schizophrenia; severe nausea and vomiting
Use: Unlabeled/InvestigationalEthanol withdrawal; behavioral symptoms associated with dementia (elderly); Tourette's syndrome; Huntington's chorea; spasmodic torticollis; Reye's syndrome; psychosis; psychosis/agitation related to Alzheimer's dementia
Dosing: Adults

Schizophrenia/psychoses:

Nonhospitalized: Initial: 4-8 mg 3 times/day; reduce dose as soon as possible to minimum effective dosage (maximum: 64 mg/day)

Hospitalized: 8-16 mg 2-4 times/day (maximum: 64 mg/day)

Nausea/vomiting: Oral: 8-16 mg/day in divided doses up to 24 mg/day (maximum: 24 mg/day)

Dosing: ElderlyBehavioral symptoms associated with dementia (unlabeled use): Oral: Initial: 2-4 mg 1-2 times/day; increase at 4- to 7-day intervals by 2-4 mg/day. Increase dose intervals (bid, tid, etc) as necessary to control behavior response or side effects. Maximum daily dose: 32 mg; gradual increase (titration) and bedtime administration may prevent some side effects or decrease their severity.

Dosing: Renal ImpairmentNot dialyzable (0% to 5%)

Dosing: Hepatic ImpairmentDosage reductions should be considered in patients with liver disease although no specific guidelines are available.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light.

ContraindicationsHypersensitivity to perphenazine or any component of the formulation (cross-reactivity between phenothiazines may occur); severe CNS depression (comatose or patients receiving large doses of CNS depressants); subcortical brain damage; bone marrow suppression; blood dyscrasias; liver damage

Allergy Considerations

- Phenothiazine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines).
- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to other neuroleptics, perphenazine has a low potency of cholinergic blockade.
- Blood dyscrasias: Check blood counts periodically and discontinue at first signs of blood dyscrasias; use is contraindicated in patients with bone marrow suppression.
- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (eg, Alzheimer's disease).
- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is moderate-high relative to other neuroleptics). Risk of dystonia (and possibly other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.
- Neuroleptic malignant syndrome (NMS): May be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).
- Photosensitivity: May cause photosensitization; avoid prolonged exposure to sunlight.
- Pigmentary retinopathy: May be associated with pigmentary retinopathy.
- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.
- Dementia: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo. An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Perphenazine is not approved for this indication.
- Depression: Use with caution in patients with depression; possibility of increased risk of suicide; limit quantities of drug available until significant remission observed.
- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.
- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment may be required.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.
- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.
- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.
- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for developing tardive dyskinesia.

- Poor metabolizers: Use with caution in patients with reduced functional alleles of CYP2D6. Poor metabolizers may have higher plasma concentrations at usual doses, increasing risk for adverse reactions.

Geriatric ConsiderationsAny changes in disease status in any organ system can result in behavior changes.

Many elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior. Before initiating antipsychotic medication, the clinician should investigate any possible reversible cause; any stress or stress from any disease can cause acute “confusion” or worsening of baseline nonpsychotic behavior. Most commonly acute changes in behavior are due to increases in drug dose or addition of new drug to regimen; fluid electrolyte loss; infections; and changes in environment.

In the treatment of agitated, demented, elderly patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control.

Pregnancy Risk FactorC
LactationEnters breast milk/not recommended (AAP rates “of concern”)
Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, cardiac arrest, ECG changes, hyper-/hypotension, orthostatic hypotension, pallor, peripheral edema, sudden death, tachycardia

Central nervous system: Bizarre dreams, catatonic-like states, cerebral edema, dizziness, drowsiness, extrapyramidal symptoms (pseudoparkinsonism, akathisia, dystonias, tardive dyskinesia), faintness, headache, hyperactivity, hyperpyrexia, impairment of temperature regulation, insomnia, lethargy, neuroleptic malignant syndrome (NMS), nocturnal confusion, paradoxical excitement, paranoid reactions, restlessness, seizure

Dermatologic: Discoloration of skin (blue-gray), photosensitivity, rash

Endocrine & metabolic: Amenorrhea, breast enlargement, hyper-/hypoglycemia, galactorrhea, lactation, libido changes, gynecomastia, menstrual irregularity, parotid swelling (rare), SIADH

Gastrointestinal: Adynamic ileus, anorexia, appetite increased, constipation, diarrhea, fecal impaction, obstipation, nausea, salivation, stomach pain, vomiting, weight gain, xerostomia

Genitourinary: Bladder paralysis, ejaculatory disturbances, incontinence, polyuria, priapism, urinary retention

Hematologic: Agranulocytosis, eosinophilia, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenic purpura

Hepatic: Hepatotoxicity, jaundice

Neuromuscular & skeletal: Muscle weakness, tremor

Ocular: Blurred vision, cornea and lens changes, epithelial keratopathies, glaucoma, mydriasis, myosis, pigmentary photophobia, retinopathy

Renal: Glycosuria

Respiratory: Nasal congestion

Miscellaneous: Allergic reactions, diaphoresis, systemic lupus erythematosus-like syndrome

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2D6 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Analgesics (Opioid): Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antimalarial Agents: May increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Beta-Blockers: Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Monitoring ParametersVital signs; lipid profile, fasting blood glucose/Hgb A_{1c}, baseline liver and kidney function, CBC prior to and periodically during therapy; BMI; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms (EPS)

Reference Range2-6 nmol/L

Nursing: Physical Assessment/MonitoringAssess other medications patient is taking for effectiveness and interactions. Monitor ophthalmic screening, laboratory results, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. Monitor blood pressure; can cause orthostatic hypotension. Initiate at lower doses and taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsBaseline liver and kidney function, CBC prior to and periodically during therapy, lipid profile, fasting blood glucose/Hgb A_{1c}; BMI

Patient EducationUse exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results; do not discontinue without consulting prescriber. Do not take within 2 hours of any antacid. Avoid alcohol or caffeine and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid skin contact with medication; may cause contact dermatitis (wash immediately with warm, soapy water). You may experience excess drowsiness, restlessness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); dry mouth, nausea, vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); urinary retention (void before taking medication); photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); or decreased perspiration (avoid strenuous exercise in hot environments). Report persistent CNS effects (eg, trembling fingers, altered gait or balance, excessive sedation, seizures, unusual movements, anxiety, abnormal thoughts, confusion, personality changes); chest pain, palpitations, rapid heartbeat, severe dizziness; unresolved urinary retention or changes in urinary pattern; menstrual pattern, change in libido, or ejaculatory difficulty; vision changes; skin rash or yellowing of skin; respiratory difficulty; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 2 mg, 4 mg, 8 mg, 16 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Perphenazine)

2 mg (60): $20.99

4 mg (60): $25.99

8 mg (60): $45.99

16 mg (60): $55.49

Mechanism of ActionPerphenazine is a piperazine phenothiazine antipsychotic which blocks postsynaptic mesolimbic dopaminergic receptors in the brain; exhibits alpha-adrenergic blocking effect and depresses the release of hypothalamic and hypophyseal hormones

Pharmacodynamics/Kinetics

Absorption: Oral: Well absorbed

Distribution: Crosses placenta

Metabolism: Extensively hepatic to metabolites via sulfoxidation, hydroxylation, dealkylation, and glucuronidation

Half-life elimination: Perphenazine: 9-12 hours; 7-hydroxyperphenazine: 10-19 hours

Time to peak, serum: Perphenazine: 1-3 hours; 7-hydroxyperphenazine: 2-4 hours

Excretion: Urine and feces

Related Information

- Antipsychotic Agents
- CMS: Long-Term Care Facility Thresholds

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Significant hypotension may occur, especially when the drug is administered parenterally; orthostatic hypotension is due to alpha-receptor blockade, the elderly are at greater risk for orthostatic hypotension.

Tardive dyskinesia: Prevalence rate may be 40% in elderly; development of the syndrome and the irreversible nature are proportional to duration and total cumulative dose over time. Extrapyramidal reactions are more common in elderly with up to 50% developing these reactions after 60 years of age. Drug-induced Parkinson's syndrome occurs often; akathisia is the most common extrapyramidal reaction in elderly.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsMost pharmacology textbooks state that in presence of phenothiazines, systemic doses of epinephrine paradoxically decrease the blood pressure. This is the so called “epinephrine reversal” phenomenon. This has never been observed when epinephrine is given by infiltration as part of the anesthesia procedure.

Mental Health CommentPerphenazine is an intermediate-potency antipsychotic. Older antipsychotic medications (chlorpromazine, haloperidol), which do not meet specific criteria for “atypical” antipsychotics, are often referred to as typical antipsychotics. They are associated with the troubling side effect, EPS. However, it is commonly believed that in order for a drug to treat psychosis, it must block dopamine is some manner.

Common side effects include sedation and neuroleptic effect (reduced initiative, interest in the environment, and display of emotion or affect). All **typical** antipsychotics are considered to be equally effective if given in equipotent doses. An inverse relationship exists between intrinsic antimuscarinic activity and propensity to cause extrapyramidal side effects. If dystonia or pseudoparkinsonism occurs, antiparkinsonian agents should be considered. If akathisia occurs, beta-blockers (eg, propranolol), benzodiazepines, or antiparkinsonian agents should be considered. Tardive dyskinesia (TD) secondary to typical antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. After this time period, the incidence is estimated to be 2% to 3% per year. Prevalence rates are approximately 15% to 20%. Female gender and age constitute risk factors for TD. Indeed, prevalence rates have been reported to be as high as 70% in elderly females. No specific treatment exists for TD, however, patients are often initiated on/switched to an atypical antipsychotic because of their lower incidence to cause TD and hopes of suppression.

Typical antipsychotics are usually only indicated for schizophrenia, but are generally effective for mania and psychosis and/or behavioral syndromes secondary to other mental conditions. Nonpsychiatric uses include Tourette's syndrome, Huntington's disease, and occasionally, intractable hiccups, pruritus, nausea, and vomiting.

These drugs are thought to exert their antipsychotic activity by blocking dopamine D_2 receptors in the mesolimbic dopaminergic pathway. Side effects are often related to their ability to antagonize dopamine receptors in the nigrostriatal and tuberoinfundibular pathways.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Anesthesia and Critical Care Concerns/Other ConsiderationsCoadministration of two or more antipsychotics does not improve clinical response and may increase the potential for adverse effects.

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Peabody CA, Warner MD, Whiteford HA, et al, “Neuroleptics and the Elderly,” *J Am Geriatr Soc*, 1987, 35(3):233-8. [PubMed 2880887]

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Risse SC and Barnes R, “Pharmacologic Treatment of Agitation Associated With Dementia,” *J Am Geriatr Soc*, 1986, 34(5):368-76. [PubMed 2870097]

Saltz BL, Woerner MG, Kane JM, et al, “Prospective Study of Tardive Dyskinesia Incidence in the Elderly,” *JAMA*, 1991, 266(17):2402-6. [PubMed 1681122]

Seifert RD, “Therapeutic Drug Monitoring: Psychotropic Drugs,” *J Pharm Pract*, 1984, 6:403-16.

International Brand NamesAnimin (TW); APO-Perphenazine (MY); Decentan (AT, DE, ES); Fentazin (GB, IE); Leptopsique (MX); Peratsin (FI); Pernamed (TH); Pernazine (TH); Perphenan (IL); Porazine (TH); Trilafon (BE, CH, DK, ID, IT, LU, NL, NO, PL, SE); Trilafon Enanthate (PL); Trilifan Retard[inj.] (FR); Trimin (AE, BH, CY, EG, IL, IQ, IR, JO, KP, KW, LB, LY, OM, QA, SA, SY, YE)

PFL (Colorectal Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Colorectal Cancer]
Regimen UseColorectal cancer
Regimen

Cisplatin: I.V.: 25 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 125 mg/m^2]

Fluorouracil: I.V.: 800 mg/m^2/day continuous infusion days 2 to 5

[total dose/cycle = 3200 mg/m^2]

Leucovorin calcium: I.V.: 500 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 2500 mg/m^2]

Repeat cycle every 28 days

References

Dreyfuss AI, Clark JR, Wright JE, et al, âContinuous Infusion High-Dose Leucovorin With 5-Fluorouracil and Cisplatin for Untreated Stage IV Carcinoma of the Head and Neck,â *Ann Intern Med*, 1990, 112(3):167-72.[PubMed 2297193]

PFL (Head and Neck Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Head and Neck Cancer

Regimen Use Head and neck cancer

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Cisplatin: I.V.: 25 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 125 mg/m^2]

Fluorouracil: I.V.: 800 mg/m^2/day continuous infusion days 2 to 6

[total dose/cycle = 4000 mg/m^2]

Leucovorin: I.V.: 500 mg/m^2/day continuous infusion days 1 to 6

[total dose/cycle = 3000 mg/m^2]

Repeat cycle every 28 days

Variation 2:

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Fluorouracil: I.V.: 600-1000 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 3000-5000 mg/m^2]

Leucovorin: Oral: 50 mg/m^2 every 4-6 hours days 1 to 6

[total dose/cycle = 1200-1800 mg/m^2]

Repeat cycle every 21 days

References

Variation 1:

Dreyfuss AI, Clark JR, Wright JE, et al, “Continuous Infusion High-Dose Leucovorin With 5-Fluorouracil and Cisplatin for Untreated Stage IV Carcinoma of the Head and Neck,” *Ann Intern Med*, 1990, 112(3):167-72. [PubMed 2297193]

Variation 2:

Vokes EE, Schilsky RL, Weichselbaum RR, et al, “Cisplatin, 5-Fluorouracil, and High-Dose Oral Leucovorin for Advanced Head and Neck Cancer,” *Cancer*, 1989, 63(6 Suppl):1048-53.[PubMed 2783881]

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Head and Neck Cancer

Regimen Use Head and neck cancer

Regimen

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Fluorouracil: I.V.: 640 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 3200 mg/m^2]

Leucovorin calcium: Oral: 100 mg every 4 hours days 1 to 5

[total dose/cycle = 3000 mg/m^2]

Interferon alfa-2b: SubQ: 2 x 10^6 units/m^2 days 1 to 6

[total dose/cycle = 12 x 10^6 units/m^2]

References

Brockstein BE, Weichselbaum RW, and Vokes EE, “Concomitant and Rapidly Alternating Chemoradiotherapy for Head and Neck Cancer,” *Advances in Oncology*, 1998, 14:8-15.

Kies MS, Haraf DJ, Athanasiadis I, et al, “Induction Chemotherapy Followed by Concurrent Chemoradiation for Advanced Head and Neck Cancer: Improved Disease Control And Survival,” *J Clin Oncol*, 1998, 16(8):2715-21.[PubMed 9704722]

Phenazopyridine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Phenazopyridine may be confused with phenoxybenzamine

Pyridium® may be confused with Dyrenium®, Perdiem®, pyridoxine, pyrithione

Pronunciation(fen az oh PEER i deen)
U.S. Brand NamesAZO-Gesic® [OTC]; AZO-Standard® Maximum Strength [OTC]; AZO-Standard® [OTC]; Baridium® [OTC]; Prodium® [OTC]; Pyridium®; ReAzo [OTC]; Uristat® [OTC] [DSC]; UTI Relief® [OTC]
Canadian Brand NamesPhenazo™
Pharmacologic CategoryAnalgesic, Urinary
Use: Labeled IndicationsSymptomatic relief of urinary burning, itching, frequency and urgency in association with urinary tract infection or following urologic procedures
Dosing: Adults**Urinary analgesic:** Oral: 100-200 mg 3 times/day after meals for 2 days when used concomitantly with an antibacterial agent
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Urinary analgesic:** Oral: Children: 12 mg/kg/day in 3 divided doses administered after meals for 2 days
Dosing: Renal Impairment

Cl_{cr} 50-80 mL/minute: Administer every 8-16 hours.

Cl_{cr} <50 mL/minute: Avoid use.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Dietary ConsiderationsShould be taken after meals.
ContraindicationsHypersensitivity to phenazopyridine or any component of the formulation; kidney or liver disease; patients with a Cl_{cr} <50 mL/minute
Warnings/Precautions

Concerns related to adverse effects:

• Yellow discoloration: Drug should be discontinued if skin or sclera develop a yellow color.

Disease-related concerns:

• Renal impairment: Use with caution in patients with renal impairment; use is contraindicated in patients with a Cl_{cr} <50 mL/minute.

Special populations:

• Elderly: Use of this agent in the elderly is limited since accumulation can occur in patients with renal insufficiency.

Other warnings/precautions:

• Limitations of use: Does not treat urinary infection, acts only as an analgesic.

Geriatric ConsiderationsUse of this agent in older adults is limited since accumulation of phenazopyridine can occur in patients with renal insufficiency.
Pregnancy Risk FactorB
LactationExcretion in breast milk unknown
Adverse Reactions

1% to 10%:

Central nervous system: Headache, dizziness

Gastrointestinal: Stomach cramps

<1%: Acute renal failure, methemoglobinemia, hemolytic anemia, hepatitis, rash, skin pigmentation, vertigo

Drug InteractionsThere are no known significant interactions.
Test InteractionsPhenazopyridine may cause delayed reactions with glucose oxidase reagents (Clinistix®, Tes-Tape®); occasional false-

positive tests occur with Tes-Tape®; cupric sulfate tests (Clinitest®) are not affected; interference may also occur with urine ketone tests (Acetest®, Ketostix®) and urinary protein tests; tests for urinary steroids and porphyrins may also occur

Nursing: Physical Assessment/MonitoringAssess therapeutic effectiveness (according to rationale for use). Instruct patients with diabetes to use serum glucose monitoring (phenazopyridine may interfere with certain urine testing reagents). Teach patient appropriate use, side effects/appropriate interventions, and adverse symptoms to report..

Patient EducationTake exactly as directed. May discolor urine (orange/yellow); this is normal, but will also stain fabric. If you have diabetes, use serum glucose tests; this medication may interfere with accuracy of urine testing. Report persistent headache, dizziness, or stomach cramping. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, as hydrochloride: 100 mg, 200 mg

AZO-Gesic®, Prodium®, ReAzo; Uristat® [DSC]: 95 mg

AZO-Standard®: 95 mg [gluten free]

AZO Standard® Maximum Strength: 97.5 mg [gluten free]

Baridium®, UTI Relief®: 97.2 mg

Pyridium®: 100 mg, 200 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Phenazopyridine HCl)

100 mg (30): $13.39

Tablets (Pyridium)

100 mg (30): $35.99

200 mg (30): $58.99

Mechanism of ActionAn azo dye which exerts local anesthetic or analgesic action on urinary tract mucosa through an unknown mechanism

Pharmacodynamics/Kinetics

Metabolism: Hepatic and via other tissues

Excretion: Urine (65% as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPhenazopyridine Hydrochloride; Phenylazo Diamino Pyridine Hydrochloride

International Brand NamesAnazo (TH); Azo Cefasabal (PE); Cistalgina (AR); CP-Pyridine (HK); Nefrecil (PL); Phenazo (HK); Phendiridine (TH); Pirimir (MX); Pyredal (NO); Pyridium (AE, BF, BH, BJ, BR, CI, CN, CR, CY, DE, EG, ES, ET, FR, GH, GM, GN, GT, HK, HN, IL, IN, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NI, OM, PA, PE, QA, SA, SC, SD, SL, SN, SV, SY, TN, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Pyronium (BE); Sedural (IL); Tiotal (PY); Urogen (TW); Urogesic (SG); Urogetix (ID); Uroprin (TW); Uropyrin (TW); Uropyrine (BE); Uroxacin (CO)

Phendimetrazine

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Medication Safety Issues

Sound-alike/look-alike issues:

Bontril PDM® may be confused with Bentyl®

Pronunciation(fen dye ME tra zeen)

U.S. Brand NamesBontril PDM®; Bontril® Slow-Release

Canadian Brand NamesBontril®; Plegine®; Statobex®

Pharmacologic CategoryAnorexiant; Sympathomimetic

Use: Labeled IndicationsShort-term (few weeks) adjunct in exogenous obesity

Dosing: Adults**Appetite suppressant (short-term):** Oral:

Capsule: 105 mg once daily in the morning before breakfast

Tablet: 17.5-35 mg 2 or 3 times daily, 1 hour before meals (maximum: 70 mg 3 times/day)

Dosing: ElderlyRefer to adult dosing.

Calculations

- Body Mass Index

Administration: Oral

Capsule: Administer 30-60 minutes before morning meal

Tablet: Administer 1 hour before meals

Dietary ConsiderationsMost effective when combined with a low calorie diet and behavior modification counseling.

RestrictionsC-III

Pharmacotherapy for weight loss is recommended only for obese patients with a body mass index ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of other risk factors such as hypertension, diabetes, and/or dyslipidemia or a high waist circumference; therapy should be used in conjunction with a comprehensive weight management program. Rule out organic causes of obesity (eg, untreated hypothyroidism) prior to use.

Note: Phendimetrazine is not approved for long-term use. The limited usefulness of medications in this class should be weighed against possible risks associated with their use. Consult weight loss guidelines for current pharmacotherapy recommendations.

ContraindicationsHypersensitivity or idiosyncrasy to phendimetrazine or other sympathomimetic amines or any component of the formulation; advanced arteriosclerosis, symptomatic cardiovascular disease; pulmonary hypertension; moderate and severe hypertension; hyperthyroidism; glaucoma; highly nervous or agitated states, history of drug abuse; use with other CNS stimulants; during or within 14 days following MAO inhibitor therapy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Amphetamines may impair the ability to engage in potentially hazardous activities.
- Primary pulmonary hypertension (PPH): A rare, frequently fatal disease of the lungs, PPH has been found to occur with increased frequency in patients receiving some anorexigens.
- Valvular heart disease: The use of some anorexigens has been associated with the development of valvular heart disease. Avoid stimulants in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that could increase the risk of sudden death that these conditions alone carry.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; antidiabetic agent requirements may be altered with anorexigens and concomitant dietary restrictions.
- Hypertension: Use with caution in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases in blood pressure or heart rate.
- Seizure disorders: Use with caution in patients with a history of seizure disorders.
- Tourette's syndrome: Use with caution in patients with Tourette's syndrome; stimulants may unmask tics.

Concurrent drug therapy issues:

- Anorexigens: Safety and efficacy have not been established for use with other weight loss medications, including over-the-counter or herbal products. Not recommended for use in patients who have used other anorectic agents within the past year.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abuse potential: Phendimetrazine is pharmacologically related to the amphetamines, which have a high abuse potential; prolonged use may lead to dependency. Prescriptions should be written for the smallest quantity consistent with good patient care to minimize possibility of overdose.

- Discontinuation of therapy: Discontinue if satisfactory weight loss has not occurred within the first 4 weeks of treatment, or if tolerance develops.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Flushing, hypertension, palpitation, tachycardia

Central nervous system: Agitation, dizziness, headache, insomnia, overstimulation, psychosis, restlessness

Endocrine & metabolic: Changes in libido

Gastrointestinal: Constipation, diarrhea, nausea, stomach pain, xerostomia

Genitourinary: Dysuria, urinary frequency

Neuromuscular & skeletal: Tremor

Ocular: Blurred vision, mydriasis

Miscellaneous: Diaphoresis, tachyphylaxis

Postmarketing and/or case reports: Dilated cardiomyopathy

Drug Interactions

Alkalinizing Agents: May decrease the excretion of Amphetamines. *Risk D: Consider therapy modification*

Ammonium Chloride: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

Analgesics (Opioid): Amphetamines may enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Antihistamines: Amphetamines may diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antipsychotics: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Amphetamines. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Ethosuximide: Amphetamines may diminish the therapeutic effect of Ethosuximide. Amphetamines may decrease the serum concentration of Ethosuximide. *Risk C: Monitor therapy*

Gastrointestinal Acidifying Agents: May decrease the serum concentration of Amphetamines. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Methenamine: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

PHENobarbital: Amphetamines may decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Phenytoin: Amphetamines may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Monitoring ParametersBaseline cardiac evaluation (for preexisting valvular heart disease, pulmonary hypertension); echocardiogram during therapy; weight, waist circumference; blood pressure

Reference Range

Adult classification of weight by BMI (kg/m^2):

- Underweight: <18.5
- Normal: 18.5-24.9
- Overweight: 25-29.9
- Obese, class I: 30-34.9
- Obese, class II: 35-39.9
- Extreme obesity (class III): ≥40

Waist circumference: In adults with a BMI of 25-34.9 kg/m^2, high-risk waist circumference is defined as:

- Men >102 cm (>40 in)
- Women >88 cm (>35 in)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, slow release, as tartrate: 105 mg

- Bontril® Slow Release: 105 mg

Tablet, as tartrate: 35 mg

- Bontril PDM®: 35 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Bontril Slow Release)

- 105 mg (30): $43.99

Capsule, 24-hour (Phendimetrazine Tartrate)

- 105 mg (30): $31.99

Tablets (Bontril PDM)

- 35 mg (30): $25.99

Tablets (Phendimetrazine Tartrate)

- 35 mg (90): $21.99

Mechanism of ActionPhendimetrazine is a sympathomimetic amine with pharmacologic properties similar to the amphetamines. The mechanism of action in reducing appetite appears to be secondary to CNS effects, including stimulation of the hypothalamus to release norepinephrine.

Pharmacodynamics/Kinetics

Metabolism: Forms 2 metabolites

Half-life elimination: Bontril® PDM: ~2 hours; Bontril® Slow Release: ~10 hours

Excretion: Urine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse vasoconstrictor with caution in patients taking phendimetrazine. Phendimetrazine can enhance the sympathomimetic response to epinephrine leading to potential hypertension and cardiotoxicity.

Index TermsPhendimetrazine Tartrate

References

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“U.S. Preventative Services Task Force. Screening for Obesity in Adults: Recommendations and Rationale,” *Ann Intern Med*, 2003, 139(11):933-49[PubMed 14644896]

International Brand Names Adpen (KP); Anoran (BE); Antapentan (AT); Atrazin (KP); Diet (KP); Fendy 35 (KP); Furing (KP); Obesan-X (ZA); Phendirazine (KP); Plegine (IT); Prelu-2 (DE)

Phenelzine

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Phenelzine may be confused with phenytoin

Nardil® may be confused with Norinyl®

Pronunciation(FEN el zeen)

U.S. Brand NamesNardil®

Canadian Brand NamesNardil®

Pharmacologic CategoryAntidepressant, Monoamine Oxidase Inhibitor

Use: Labeled IndicationsSymptomatic treatment of atypical, nonendogenous, or neurotic depression

Use: Unlabeled/InvestigationalSelective mutism

Dosing: Adults**Depression:** Oral: 15 mg 3 times/day; may increase to 60-90 mg/day during early phase of treatment, then reduce dose for maintenance therapy slowly after maximum benefit is obtained. Takes 2-4 weeks for a significant response to occur.

Dosing: ElderlyOral: Initial: 7.5 mg/day; increase by 7.5-15 mg/day every 3-4 days as tolerated; usual therapeutic dose: 15-60 mg/day in 3-4 divided doses.

Dosing: Pediatric**Selective mutism (unlabeled use):** Oral: 30-60 mg/day

StorageProtect from light.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to phenelzine or any component of the formulation; congestive heart failure; pheochromocytoma; abnormal liver function tests or history of hepatic disease; renal disease or severe renal impairment

Concurrent use of sympathomimetics (including amphetamines, cocaine, dopamine, epinephrine, methylphenidate, norepinephrine, or phenylephrine) and related compounds (methyldopa, levodopa, phenylalanine, tryptophan, or tyrosine), as well as ophthalmic alpha$_2$-agonists (apraclonidine, brimonidine); may result in hypertensive reactions

CNS depressants, cyclobenzaprine, dextromethorphan, ethanol, meperidine, bupropion, or buspirone; may result in delirium, excitation, hyperpyrexia, seizures, and coma.

At least 2 weeks should elapse between the discontinuation of serotoninergic agents (including SNRIs, SSRIs, and tricyclics) and other MAO inhibitors and the initiation of phenelzine. At least 5 weeks should elapse between the discontinuation of fluoxetine and the initiation of phenelzine. In all cases, a sufficient amount of time must be allowed for the clearance of the serotoninergic agent and any active metabolites prior to the initiation of phenelzine.

At least 2 weeks should elapse between the discontinuation of phenelzine and the initiation of the following agents: Serotoninergic agents (including SNRIs, SSRIs, fluoxetine, and tricyclics), bupropion, buspirone, and other antidepressants.

General anesthesia, spinal anesthesia (hypotension may be exaggerated). Use caution with local anesthetics containing sympathomimetic agents. Phenelzine should be discontinued ≥10 days prior to elective surgery.

Foods high in tyramine or dopamine content; foods and/or supplements containing tyrosine, phenylalanine, tryptophan, or caffeine; may result in hypertensive reactions

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription.**Phenelzine is not FDA approved for the treatment of depression in children ≤16 years of age.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Phenelzine is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Hypertensive crisis: May occur with foods/supplements high in tyramine, tryptophan, phenylalanine, or tyrosine content; treatment with phentolamine is recommended for hypertensive crisis.

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; sensitization to the effects of insulin may occur, monitor blood glucose closely.

- Glaucoma: Use with caution in patients with glaucoma.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

- Thyroid dysfunction: Use with caution in patients with hyperthyroidism.

Concurrent drug therapy issues:

- High potential for interactions: Do not use with other MAO inhibitors or antidepressants. Avoid products containing sympathomimetic stimulants or dextromethorphan. Concurrent use with antihypertensive agents may lead to exaggeration of hypotensive effects.

Special populations:

- Elderly: The MAO inhibitors are effective and generally well tolerated by older patients. It is the potential interactions with tyramine or tryptophan-containing foods and other drugs, and their effects on blood pressure that have limited their use.

Other warnings/precautions:

- Appropriate use: Phenelzine is not generally considered a first-line agent for the treatment of depression; phenelzine is typically used in patients who have failed to respond to other treatments.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

- Myelography: Discontinue at least 48 hours prior to myelography.

Geriatric ConsiderationsThe MAO inhibitors are effective and generally well tolerated by elderly patients. It is their potential interactions with tyramine or tryptophan-containing food and other drugs and their effects on blood pressure that have limited their use. The MAO inhibitors are usually reserved for patients who do not tolerate or respond to the traditional “cyclic” or “second generation” antidepressants. The brain activity of monoamine oxidase increases with age and even more so in patients with Alzheimer's disease. Therefore, the MAO inhibitors may have an increased role in patients with Alzheimer's disease who are depressed. Phenelzine is less stimulating than tranylcypromine.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Edema, orthostatic hypotension

Central nervous system: Anxiety (acute), ataxia, coma, delirium, dizziness, drowsiness, fatigue, fever, headache, hyper-reflexia, mania, seizure, sleep disturbances, twitching

Dermatologic: Pruritus, rash

Endocrine & metabolic: Decreased sexual ability (anorgasmia, ejaculatory disturbances, impotence), hypermetabolic syndrome, hypernatremia

Gastrointestinal: Constipation, weight gain, xerostomia

Genitourinary: Urinary retention

Hematologic: Leukopenia

Hepatic: Hepatitis, jaundice, necrotizing hepatocellular necrosis (rare)

Neuromuscular & skeletal: Lupus-like syndrome, myoclonia, tremor, weakness

Ocular: Blurred vision, glaucoma

Miscellaneous: Diaphoresis, transient cardiac or respiratory depression (following ECT), withdrawal syndrome (nausea, vomiting, malaise)

Respiratory: Edema (glottis)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): MAO Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists (Indirect-Acting): MAO Inhibitors may enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Alpha1-Agonists: MAO Inhibitors may enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Alpha2-Agonists (Ophthalmic): MAO Inhibitors may enhance the hypertensive effect of Alpha2-Agonists (Ophthalmic). *Risk X: Avoid combination*

Altretamine: May enhance the orthostatic effect of MAO Inhibitors. *Risk C: Monitor therapy*

Amphetamines: MAO Inhibitors may enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Anilidopiperidine Opioids: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. *Risk D: Consider therapy modification*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Atomoxetine: MAO Inhibitors may enhance the neurotoxic (central) effect of Atomoxetine. *Risk X: Avoid combination*

Beta2-Agonists: MAO Inhibitors may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: MAO Inhibitors may enhance the neurotoxic (central) effect of BuPROPion. *Risk X: Avoid combination*

BusPIRone: May enhance the adverse/toxic effect of MAO Inhibitors. Elevated blood pressure has been reported. *Risk X: Avoid combination*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

COMT Inhibitors: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Cyclobenzaprine: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

Dexmethylphenidate: MAO Inhibitors may enhance the hypertensive effect of Dexmethylphenidate. *Risk X: Avoid combination*

Dextromethorphan: MAO Inhibitors may enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

Levodopa: May enhance the adverse/toxic effect of MAO Inhibitors. Of particular concern is the development of hypertensive reactions when levodopa is used with nonselective MAOI. *Risk D: Consider therapy modification*

Linezolid: MAO Inhibitors may enhance the adverse/toxic effect of Linezolid. *Risk X: Avoid combination*

Lithium: MAO Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Maprotiline: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

Meperidine: MAO Inhibitors may enhance the serotonergic effect of Meperidine. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methyldopa: MAO Inhibitors may enhance the adverse/toxic effect of Methyldopa. *Risk X: Avoid combination*

Methylphenidate: MAO Inhibitors may enhance the hypertensive effect of Methylphenidate. *Risk X: Avoid combination*

Mirtazapine: MAO Inhibitors may enhance the neurotoxic (central) effect of Mirtazapine. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the adverse/toxic effect of MAO Inhibitors. Specifically, the risk of serotonin syndrome or other serotonergic adverse events may be increased. *Risk X: Avoid combination*

Rauwolfia Alkaloids: MAO Inhibitors may enhance the adverse/toxic effect of Rauwolfia Alkaloids. Existing MAOI therapy can result in paradoxical effects of added rauwolfia alkaloids (eg, excitation, hypertension). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: MAO Inhibitors may decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. **Exceptions:** Eletriptan; Frovatriptan; Naratriptan. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Succinylcholine: Phenelzine may enhance the neuromuscular-blocking effect of Succinylcholine. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

TraMADol: May enhance the neuroexcitatory and/or seizure-potentiating effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: MAO Inhibitors may enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (based on CNS depressant effects and potential tyramine content)

Food: Concurrent ingestion of foods rich in tyramine may cause sudden and severe high blood pressure (hypertensive crisis). Avoid tyramine-containing foods with MAO-Is. Food's freshness is also an important concern; improperly stored or spoiled food can create an environment where tyramine concentrations may increase.

Herb/Nutraceuticals: Avoid supplements containing caffeine, tyrosine, tryptophan or phenylalanine. Ingestion of large quantities may increase the risk of severe side effects (eg, hypertensive reactions, serotonin syndrome).

Monitoring ParametersBlood pressure, heart rate; diet, weight; mood (if depressive symptoms), suicidal ideation (especially during the initial months of therapy or when doses are increased or decreased)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Monitor blood pressure. Observe for clinical worsening, suicidality, and unusual behavior changes, especially during the initial few months of therapy or during dosage changes. Taper dosage slowly when discontinuing; allow 3-4 weeks between discontinuing phenelzine and starting another antidepressant. Advise patients with diabetes to monitor serum glucose closely (phenelzine may lower glucose level). Assess knowledge/teach patient appropriate use, interventions to reduce side effects (including tyramine-free diet; see Tyramine Contents of Foods list), and adverse symptoms to report.

Patient EducationTake exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results. Avoid alcohol, caffeine, and other prescription or OTC medications not approved by prescriber. Avoid tyramine-containing foods. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience postural hypotension (use caution when climbing stairs or changing position from lying or sitting to standing); drowsiness, lightheadedness, dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); anorexia, dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); or diarrhea (buttermilk, yogurt, or boiled milk may help). If you have diabetes, monitor serum glucose closely (Nardil® may effect glucose levels). Report persistent insomnia; chest pain, palpitations, irregular or rapid heartbeat, or swelling of extremities; muscle cramping, tremors, or altered gait; blurred vision or eye pain; yellowing of eyes or skin; pale stools/dark urine; suicide ideation; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 15 mg

Generic AvailableNo

ManufacturerPfizer Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Nardil)

15 mg (100): $61.99

Mechanism of ActionThought to act by increasing endogenous concentrations of norepinephrine, dopamine, and serotonin through inhibition of the enzyme (monoamine oxidase) responsible for the breakdown of these neurotransmitters

Pharmacodynamics/Kinetics

Onset of action: Therapeutic: 2-4 weeks; geriatric patients receiving an average of 55 mg/day developed a mean platelet MAO activity inhibition of about 85%.

Duration: May continue to have a therapeutic effect and interactions 2 weeks after discontinuing therapy

Absorption: Well absorbed

Metabolism: Oxidized via monoamine oxidase (primary pathway) and acetylation (minor pathway)

Half-life elimination: 11 hours

Excretion: Urine (primarily as metabolites and unchanged drug)

Related Information

- Antidepressant Agents
- Teratogenic Risks of Psychotropic Medications
- Tyramine Content of Foods

Pharmacotherapy PearlsPyridoxine deficiency has occurred; symptoms include numbness and edema of hands; may respond to supplementation.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension, xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation). Avoid use as an analgesic due to toxic reactions with MAO inhibitors.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAttempts should be made to avoid use of vasoconstrictor due to possibility of hypertensive episodes with monoamine oxidase inhibitors

Mental Health: Child/Adolescent ConsiderationsFour children 5.5-7 years of age, diagnosed with selective mutism were treated with 30-60 mg/day for 24-60 weeks (Golwyn, 1999).

Golwyn DH and Sevlie CP, "Phenelzine Treatment of Selective Mutism in Four Prepubertal Children," *J Child Adolesc Psychopharmacol*, 1999, 9(2):109-13.

Mental Health CommentNot commonly used due to a required low tyramine diet and drug-drug interactions. It is estimated that 20 mg of tranylcypromine = 40 mg of isocarboxazid = 45 mg phenelzine. Phenelzine and isocarboxazid are hydrazine MAO inhibitors and tranylcypromine is a nonhydrazine. These drugs produce irreversible inhibition of MAO inhibitors. The half-life for regeneration is 2-3 days. Therefore, a 2-week period is required when switching from an MAO inhibitor to another antidepressant.

While hypertension and hypertensive crisis are risks associated with MAO inhibitor therapy, orthostatic hypotension may also occur. Orthostasis associated with MAO inhibitor therapy is not related to alpha$_1$-adrenergic receptor blockade. The "false transmitter" concept is used to explain this side effect. This concept states that MAO inhibitors promote gradual accumulation in sympathetic nerve ending of amines lacking direct sympathomimetic activity (octopamine) at the expense of the normal synaptic transmitter, norepinephrine. Since octopamine has little ability to activate either alpha- or beta-adrenergic receptors, a functional impairment of sympathetic neurotransmission occurs.

The MAO inhibitors are usually reserved for patients who do not tolerate or respond to other antidepressants. The brain activity of monoamine oxidase increases with age and even more so in patients with Alzheimer's disease. Therefore, the MAO inhibitors may have an increased role in patients with Alzheimer's disease who are depressed. Phenelzine is less stimulating than tranylcypromine.

Anesthesia and Critical Care Concerns/Other ConsiderationsAvoid food containing tyramine. The MAO inhibitors are usually reserved for patients who do not tolerate or respond to other antidepressants.

Index TermsPhenelzine Sulfate

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International Brand Names Nardelzine (BE, ES, LU); Nardil (AU, GB, IE)

Phenindamine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(fen IN dah meen)

U.S. Brand NamesNolahist速 [OTC] [DSC]

Canadian Brand NamesNolahist速

Pharmacologic CategoryHistamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTreatment of perennial and seasonal allergic rhinitis and chronic urticaria

Dosing: Adults**Allergic rhinitis, urticaria:** Oral: 25 mg every 4-6 hours, up to 150 mg/24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Allergic rhinitis, urticaria:** Oral:

Children <6 years: As directed by physician

Children 6 to <12 years: 12.5 mg every 4-6 hours, up to 75 mg/24 hours

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as tartrate: 25 mg [DSC]

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPhenindamine Tartrate

International Brand NamesPernovin (HU); Thephorin (GB, IE)

PHENobarbital

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

PHENobarbital may be confused with PENTobarbital

Luminal® may be confused with Tuinal®

Pronunciation(fee noe BAR bi tal)

U.S. Brand NamesLuminal® Sodium

Canadian Brand NamesPMS-Phenobarbital

Pharmacologic CategoryAnticonvulsant, Barbiturate; Barbiturate

Use: Labeled IndicationsManagement of generalized tonic-clonic (grand mal) and partial seizures; sedative

Use: Unlabeled/InvestigationalFebrile seizures in children; may also be used for prevention and treatment of neonatal hyperbilirubinemia and lowering of bilirubin in chronic cholestasis; neonatal seizures; management of sedative/hypnotic withdrawal

Dosing: Adults

Sedation: Oral, I.M.: 30-120 mg/day in 2-3 divided doses

Hypnotic: Oral, I.M., I.V., SubQ: 100-320 mg at bedtime

Preoperative sedation: I.M.: 100-200 mg 1-1.5 hours before procedure

Anticonvulsant/status epilepticus:

Loading dose: I.V.: 300-800 mg initially followed by 120-240 mg/dose at 20-minute intervals until seizures are controlled or a total dose of 1-2 g

Maintenance dose: Oral, I.V.: 1-3 mg/kg/day in divided doses or 50-100 mg 2-3 times/day

Sedative/hypnotic withdrawal (unlabeled use): Initial daily requirement is determined by substituting phenobarbital 30 mg for every 100 mg pentobarbital used during tolerance testing; then daily requirement is decreased by 10% of initial dose.

Dosing: ElderlyGeriatric patients should be started at the lowest recommended dose. Refer to adult dosing.

Dosing: Pediatric

Sedation: Oral: Children: 2 mg/kg 3 times/day

Hypnotic: I.M., I.V., SubQ: Children: 3-5 mg/kg at bedtime

Preoperative sedation: Oral, I.M., I.V.: Children: 1-3 mg/kg 1-1.5 hours before procedure

Anticonvulsant/Status epilepticus (Loading dose): I.V.: Infants and Children: 10-20 mg/kg in a single or divided dose; in select patients may administer additional 5 mg/kg/dose every 15-30 minutes until seizure is controlled or a total dose of 40 mg/kg is reached

Anticonvulsant maintenance dose: Oral, I.V.:

Infants: 5-8 mg/kg/day in 1-2 divided doses

Children:

1-5 years: 6-8 mg/kg/day in 1-2 divided doses

5-12 years: 4-6 mg/kg/day in 1-2 divided doses

>12 years: 1-3 mg/kg/day in divided doses or 50-100 mg 2-3 times/day

Dosing: Renal Impairment

Cl_{cr} <10 mL/minute: Administer every 12-16 hours.

Moderately dialyzable (20% to 50%)

Dosing: Hepatic ImpairmentIncreased side effects may occur in severe liver disease. Monitor plasma levels and adjust dose accordingly.
Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Avoid rapid I.V. administration >50 mg/minute. Avoid intra-arterial injection.
Administration: I.V. DetailParenteral solutions are highly alkaline. Avoid extravasation.

pH: 9.2-10.2

Dietary ConsiderationsVitamin D: Loss in vitamin D due to malabsorption; increase intake of foods rich in vitamin D. Supplementation of vitamin D and/or calcium may be necessary. Sodium content of injection (65 mg, 1 mL): 6 mg (0.3 mEq).
StorageProtect elixir from light. Not stable in aqueous solutions; use only clear solutions. Do not add to acidic solutions; precipitation may occur.
CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4$NS, $D_5{}^1/_2$NS, D_5NS, D_5W, D_{10}W, LR, ${}^1/_2$NS, NS.

Y-site administration: Compatible: Enalaprilat, fosphenytoin, gatifloxacin, levofloxacin, linezolid, meropenem, propofol, sufentanil. **Incompatible:** Amphotericin B cholesteryl sulfate complex, hydromorphone.

Compatibility in syringe: Compatible: Heparin. **Incompatible:** Hydromorphone, pentazocine, ranitidine, sufentanil.

Compatibility when admixed: Compatible: Amikacin, aminophylline, calcium chloride, calcium gluconate, colistimethate, dimenhydrinate, meropenem, polymyxin B sulfate, sodium bicarbonate, thiopental, verapamil. **Incompatible:** Chlorpromazine, cimetidine, clindamycin, dimenhydrinate, diphenhydramine, droperidol, ephedrine, hydralazine, hydrocortisone sodium succinate, hydroxyzine, insulin (regular), kanamycin, levorphanol, meperidine, morphine, norepinephrine, pancuronium, penicillin G, pentazocine, phenytoin, procaine, prochlorperazine edisylate, prochlorperazine mesylate, promazine, promethazine, streptomycin, succinylcholine, vancomycin. **Variable (consult detailed reference):** Isoproterenol, metaraminol, methyldopate, norepinephrine.

Extemporaneously PreparedAn alcohol-free phenobarbital 10 mg/mL suspension can be prepared as follows: Levigate ten phenobarbital 60 mg tablets in a glass mortar into a fine powder. Mix 30 mL of Ora-Plus® and 30 mL of either Ora-Sweet® or Ora-Sweet® SF; stir vigorously. Add 15 mL of the Ora-Plus®/Ora-Sweet® (or Ora-Sweet® SF) mixture to the powder; triturate well. Transfer to a 2 ounce amber plastic bottle; qs to a final volume of 60 mL, making sure to rinse the mortar with the syrup mixture several times to ensure all drug is removed. Stable for up to 115 days at room temperature. Shake well prior to use.

May mix dose with chocolate syrup (1:1 volume) immediately before administration to mask the bitter aftertaste.

Cober M and Johnson CE, "Stability of an Extemporaneously Prepared Alcohol-Free Phenobarbital Suspension," *Am J Health Syst Pharm*, 2007, 64(6):644-6.

RestrictionsC-IV
ContraindicationsHypersensitivity to barbiturates or any component of the formulation; marked hepatic impairment; dyspnea or airway obstruction; porphyria; pregnancy
Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Concern related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Hypotension: May cause hypotension particularly when administered intravenously; use with caution in hemodynamically unstable patients (hypotension or shock).

- Paradoxical stimulatory response: May cause paradoxical responses, including agitation and hyperactivity, particularly in acute pain and pediatric patients.

- Respiratory depression: May cause respiratory depression particularly when administered intravenously; use with caution patients with respiratory disease.

Disease-related concerns:

- Depression: Use with caution in patients with depression or suicidal tendencies.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Hypoadrenalism: Use with caution in patients with hypoadrenalism.

- Renal impairment: Use with caution in patients with renal impairment.

- Substance abuse: Use with caution in patients with a history of drug abuse; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in patients who are debilitated.

- Elderly: Use with caution in the elderly; due to its long half-life and risk of dependence, phenobarbital is not recommended as a sedative in the elderly.

- Pediatrics: Use with caution in children; has been associated with cognitive deficits.

Other warnings/precautions:

- Acute pain: Do not administer to patients in acute pain.

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsUsing barbiturates in elderly may induce paradoxical stimulation, cause or aggravate depression and confusion. Due to its long half-life and risk of dependence, phenobarbital is not recommended as a sedative or hypnotic in the elderly. Interpretive guidelines from the Centers for Medicare and Medicaid Services (CMS) discourage the use of this agent as a sedative/hypnotic in long-term care residents.

Pregnancy Risk FactorD

Pregnancy ConsiderationsCrosses the placenta. Cardiac defect reported; hemorrhagic disease of newborn due to fetal vitamin K depletion may occur; may induce maternal folic acid deficiency; withdrawal symptoms observed in infant following delivery. Epilepsy itself, number of medications, genetic factors, or a combination of these probably influence the teratogenicity of anticonvulsant therapy. Benefit:risk ratio usually favors continued use during pregnancy and breast-feeding.

LactationEnters breast milk/not recommended (AAP recommends use “with caution”)

Breast-Feeding ConsiderationsSedation has been reported in nursing infants; infantile spasms may occur after weaning from breast milk. AAP recommends USE WITH CAUTION.

Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, hypotension, syncope

Central nervous system: Drowsiness, lethargy, CNS excitation or depression, impaired judgment, “hangover” effect, confusion, somnolence, agitation, hyperkinesia, ataxia, nervousness, headache, insomnia, nightmares, hallucinations, anxiety, dizziness

Dermatologic: Rash, exfoliative dermatitis, Stevens-Johnson syndrome

Gastrointestinal: Nausea, vomiting, constipation

Hematologic: Agranulocytosis, thrombocytopenia, megaloblastic anemia

Local: Pain at injection site, thrombophlebitis with I.V. use

Renal: Oliguria

Respiratory: Laryngospasm, respiratory depression, apnea (especially with rapid I.V. use), hypoventilation

Miscellaneous: Gangrene with inadvertent intra-arterial injection

Metabolism/Transport Effects**Substrate** of CYP2C9 (minor), 2C19 (major), 2E1 (minor); **Induces** CYP1A2 (strong), 2A6 (strong), 2B6 (strong), 2C8 (strong), 2C9 (strong), 3A4 (strong)

Drug Interactions

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Aminocamptothecin: PHENobarbital may decrease the serum concentration of Aminocamptothecin. *Risk C: Monitor therapy*

Amphetamines: May decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inducers (Strong) may decrease the serum concentration of Bendamustine. Concentrations of active metabolites may be increased. *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Carbonic Anhydrase Inhibitors: May enhance the adverse/toxic effect of Anticonvulsants (Barbiturate). Specifically, osteomalacia and rickets. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inducers (Strong) may increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2A6 Substrates: CYP2A6 Inducers (Strong) may increase the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inducers (Strong) may increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inducers (Highly Effective) may increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inducers (Highly Effective) may increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Darunavir: PHENobarbital may decrease the serum concentration of Darunavir. *Risk X: Avoid combination*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Etravirine: PHENobarbital may decrease the serum concentration of Etravirine. Management: The manufacturer of etravirine states these drugs should not be used in combination *Risk X: Avoid combination*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

Folic Acid: May decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Griseofulvin: Barbiturates may decrease the absorption of Griseofulvin. *Risk D: Consider therapy modification*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Lacosamide: PHENobarbital may decrease the serum concentration of Lacosamide. *Risk C: Monitor therapy*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Leucovorin-Levoleucovorin: May decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Methylfolate: May decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

OXcarbazepine: PHENobarbital may decrease the serum concentration of OXcarbazepine. *Risk C: Monitor therapy*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Rufinamide: May increase the serum concentration of PHENobarbital. PHENobarbital may decrease the serum concentration of Rufinamide. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tipranavir: PHENobarbital may decrease the serum concentration of Tipranavir. Tipranavir may decrease the serum concentration of PHENobarbital. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Voriconazole: Barbiturates may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: May cause decrease in vitamin D and calcium.

Herb/Nutraceutical: Avoid evening primrose (seizure threshold decreased). Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsAssay interference of LDH
Monitoring ParametersPhenobarbital serum concentrations, mental status, CBC, LFTs, seizure activity
Reference Range

Therapeutic:

Infants and children: 15-30 mcg/mL (SI: 65-129 µmol/L)

Adults: 20-40 mcg/mL (SI: 86-172 µmol/L)

Toxic: >40 mcg/mL (SI: >172 µmol/L)

Toxic concentration: Slowness, ataxia, nystagmus: 35-80 mcg/mL (SI: 150-344 µmol/L)

Coma with reflexes: 65-117 mcg/mL (SI: 279-502 µmol/L)

Coma without reflexes: >100 mcg/mL (SI: >430 µmol/L)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance; periodically evaluate need for continued use. **I.V.:** Monitor cardio/respiratory and CNS status; use safety precautions. Monitor effectiveness of therapy and adverse reactions. **Oral:** Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, possible side effects, and symptoms to report.
Monitoring: Lab TestsPhenobarbital serum concentrations, CBC, LFTs
Patient EducationI.M./I.V.: Patient instructions and information are determined by patient condition and therapeutic purpose. If self-administered, use exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help). Report skin rash or irritation; CNS changes (confusion, depression, increased sedation, excitation, headache, insomnia, or nightmares); respiratory difficulty or shortness of breath; changes in urinary pattern or menstrual pattern; muscle weakness or tremors; or difficulty swallowing or feeling of tightness in throat. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Elixir: 20 mg/5 mL (5 mL, 7.5 mL, 15 mL, 480 mL) [contains alcohol]

Injection, solution, as sodium: 65 mg/mL (1 mL); 130 mg/mL (1 mL) [contains alcohol and propylene glycol]

Luminal® Sodium: 60 mg/mL (1 mL); 130 mg/mL (1 mL) [contains alcohol 10% and propylene glycol]

Tablet: 15 mg, 30 mg, 60 mg, 100 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Elixir (Phenobarbital)

20 mg/5 mL (473): $16.98

Tablets (Phenobarbital)

16.2 mg (100): $12.99

32.4 mg (100): $10.99

64.8 mg (100): $12.99

97.2 mg (100): $12.99

Mechanism of ActionLong-acting barbiturate with sedative, hypnotic, and anticonvulsant properties. Barbiturates depress the sensory cortex, decrease motor activity, alter cerebellar function, and produce drowsiness, sedation, and hypnosis. In high doses, barbiturates exhibit anticonvulsant activity; barbiturates produce dose-dependent respiratory depression.
Pharmacodynamics/Kinetics

Onset of action: Oral: Hypnosis: 20-60 minutes; I.V.: ~5 minutes

Peak effect: I.V.: ~30 minutes

Duration: Oral: 6-10 hours; I.V.: 4-10 hours

Absorption: Oral: 70% to 90%

Protein binding: 20% to 45%; decreased in neonates

Metabolism: Hepatic via hydroxylation and glucuronide conjugation

Half-life elimination: Neonates: 45-500 hours; Infants: 20-133 hours; Children: 37-73 hours; Adults: 53-140 hours

Time to peak, serum: Oral: 1-6 hours

Excretion: Urine (20% to 50% as unchanged drug)

Related Information

- Status Epilepticus

Pharmacotherapy PearlsInjectable solutions contain propylene glycol.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Anesthesia and Critical Care Concerns/Other ConsiderationsPhenobarbital 65 mg/mL and 130 mg/mL each contains propylene glycol 702.4 mg/mL (67.8% v/v).

Status Epilepticus: A randomized, double-blind trial (Treiman, 1998) evaluated the efficacy of four treatments in overt status epilepticus. Treatment arms were designed based upon accepted practices of North American neurologists. The treatments were: 1) lorazepam 0.1 mg/kg, 2) diazepam 0.15 mg/kg followed by phenytoin 18 mg/kg, 3) phenytoin 18 mg/kg alone, and 4) phenobarbital 15 mg/kg. Treatment was considered successful if the seizures were terminated (clinically and by EEG) within 20 minutes of start of therapy without seizure recurrence within 60 minutes from the start of therapy. Patients who failed the first treatment received a second and a third, if necessary. Patients did not receive randomized treatments after the first one but the treating physician remained blinded. Treatment success: Lorazepam 64.9%, phenobarbital 58.2%, diazepam/phenytoin 55.8%, and phenytoin alone 43.6%. Using an “intention-to-treat” analysis, there was no statistical difference between the groups. Results of subsequent treatments in patients who failed the first therapy indicated that response rate significantly dropped regardless of treatment. Aggregate response rate to the second treatment was 7.0% and third treatment 2.3%.

Index TermsPhenobarbital Sodium; Phenobarbitone; Phenylethylmalonylurea
References

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Amitai Y and Degani Y, “Treatment of Phenobarbital Poisoning With Multiple Dose of Activated Charcoal in an Infant,” *J Emerg Med*, 1990, 8(4):449-50. [PubMed 2212564]

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Lin JL and Jeng LB, “Critical, Acutely Poisoned Patients Treated With Continuous Arteriovenous Hemoperfusion in the Emergency Department,” *Ann Emerg Med*, 1995, 25(1):75-80. [PubMed 7802374]

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Treiman DM, Meyers PD, Walton NY, et al, “A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group,” *N Engl J Med*, 1998, 339(12):792-8.[PubMed 9738086]

International Brand NamesAlepsal (MX); Andral (PH); Aphenylbarbit (CH); Atrofen (DO); Barbilettae (FI); Barbiphenyl (FI); Bialminal (PT); Comizial (IT); Dormital (PY); Edhanol (BR); Fenemal (DK, NO); Fenemal NM Pharma (SE); Fenobarbital (EC, PE); Fenobarbital FNA (NL); Fenobarbitale (IT); Fenobarbitale Sodico (IT); Fenton (PK); Gardenal (BE, BR, CZ, ES, FR, GR, IN, LU, UY, VE, ZA); Gardenal Sodium (GB); Gardenale (ES, IT); Gardenale[inj.] (IT); Gratusminal (ES); Lepinal natrium (PL); Lethyl (ZA); Lumcalcio (ES); Luminal (AR, CH, DE, ES, KP, PH); Luminale (IT); Luminaletas (AR, ES); Luminalette (IT); Luminaletten (DE); Luminale[inj.] (IT); Luminalum (PL); Menobarb (TH); Neurobiol (IT); Pevalon (CY); Phenaemal (EE); Phenobarbiton (HR); Phenobarbiton-natrium (HR); Phenobarbitone (AU); Phenobarbitone Injection (GB); Phenotal (TH); Sevenal (HN, HU); Tridezibarbitur (AT); Uni-Feno (HK)

Phenol

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Cēpastat® may be confused with Capastat®

Pronunciation(FEE nol)
U.S. Brand NamesCastellani Paint Modified [OTC]; Cepastat® Extra Strength [OTC]; Cepastat® [OTC]; Cheracol® [OTC]; Chloraseptic® Gargle [OTC]; Chloraseptic® Mouth Pain [OTC]; Chloraseptic® Pocket Pump [OTC]; Chloraseptic® Spray for Kids [OTC]; Chloraseptic® Spray [OTC]; Pain-A-Lay® [OTC]; Phenaseptic [OTC]; Phenol EZ® [OTC]; Ulcerease® [OTC]; Vicks® Formula 44® Sore Throat [OTC]
Canadian Brand NamesP & S™ Liquid Phenol
Pharmacologic CategoryAnesthetic, Topical
Use: Labeled IndicationsRelief of sore throat pain, mouth, gum, and throat irritations; antiseptic; topical anesthetic
Dosing: Adults

Sore throat: Oral:

Cēpastat® Extra Strength, Cēpastat®: Up to 2 lozenges every 2 hours as needed

Cheracol®, Pain-A-Lay® Spray: Spray directly in throat; rinse for 15 seconds then expectorate; may repeat every 2 hours

Chloraseptic®: Five sprays onto throat or affected area; may repeat every 2 hours

Chloraseptic® Gargle, Chloraseptic® Mouth Pain, Pain-A-Lay® Gargle, Ulcerease®: Gargle or swish for 15 seconds, then expectorate; may repeat every 2 hours

Antiseptic: Topical: Castellani Paint Modified: Apply small amount to affected area 1-3 times/day

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Sore throat:** Oral:

Children 2-12 years:

Chloraseptic®: Three sprays onto throat or affected area; may repeat every 2 hours

Chloraseptic® for Kids: Five sprays onto throat or affected area; may repeat every 2 hours

Children >3 year (Ulcerease®): Refer to adult dosing.

Children 6-12 years:

Cēpastat® Extra Strength: Up to 1 lozenge every 2 hours as needed (maximum: 10 lozenges/24 hours)

Cēpastat®: Up to 1 lozenge every 2 hours as needed (maximum: 18 lozenges/24 hours)

Pain-A-Lay® Gargle: Using gauze pad, apply 10 mL to affected area, or gargle or swish for 15 seconds, then expectorate

Children ≥12 years: Cēpastat® Extra Strength, Cēpastat®,Cheracol®, Pain-A-Lay® (spray/gargle), Chloraseptic® (spray/gargle), Chloraseptic® Mouth Pain: Refer to adult dosing.

Administration: OralAllow to lozenge dissolve slowly in mouth. Spray should be allowed to remain in mouth for ~15 seconds, then expectorate.
Administration: Topical Castellani Paint Modified: May stain skin and clothing; apply to clean area
StorageStore at <86°F (30°C). Protect from humidity.
Warnings/Precautions

Other warnings/precautions:

- OTC labeling: Sore throat: Not for use >7 days or if pain, redness, or irritation continues. If sore throat is severe, not for use >2 days or if followed by fever, headache, rash, nausea, or vomiting. Oral gargles and sprays should not be swallowed.

- OTC labeling: Topical antiseptic: Do not use in eyes, or apply to large areas of the body, deep or puncture wounds, animal bites or burns. Do not use for >7 days; do not bandage affected area.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Lozenge, oral:

Cēpastat®: 14.5 mg (18s) [sugar free; contains menthol; cherry flavor]

Cēpastat® Extra Strength: 29 mg (18s) [sugar free; contains menthol; eucalyptus flavor]

Solution, oral [gargle]:

Chloraseptic®: 1.4% (296 mL) [alcohol and sugar free; cool mint flavor]

Pain-A-Lay®: 1.4% (240 mL, 540 mL) [contains tartrazine]

Ulcerease®: 0.6% (180 mL) [alcohol, dye, and sugar free; contains glycerin]

Solution, oral [spray]: 1.4% (180 mL)

Cheracol®: Phenol 1.4% (180 mL) [alcohol and sugar free; contains tartrazine]

Chloraseptic®: 1.4% (180 mL) [alcohol and sugar free; cherry, cool mint, and menthol flavors]

Chloraseptic® for Kids: 0.5% (177 mL) [grape flavor]

Chloraseptic® Mouth Pain: 1.4% (30 mL) [alcohol and sugar free; cool mint flavors]

Chloraseptic® Pocket Pump: 1.4% (20 mL) [alcohol and sugar free; cherry flavor]

Pain-A-Lay®: 1.4% (180 mL) [contains tartrazine]

Phenaseptic: 1.4% (180 mL) [sugar free; cherry flavor]

Vicks® Formula 44® Sore Throat: 1.4% (180 mL) [contains glycerin; cherry ice and honey lemon ice flavors]

Solution, topical:

Castellani Paint Modified: Phenol 1.5% (30 mL) [contains alcohol 13%, acetone, basic fuchsin, resorcinol]

Castellani Paint Modified [colorless]: Phenol 1.5% (30 mL) [contains alcohol 13%, acetone, and resorcinol]

Swabs, topical:

Phenol EZ®: 89% (30s) [~0.2 mL]

Generic AvailableYes: Oral spray
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Mental Health CommentIn overdose, may cause agitation, confusion, slurred speech, and CNS depression.
Index TermsCarbolic Acid
International Brand NamesPaoscle (JP); Phenolum liquefactum (PL)

Phenoxybenzamine

Lexi-Drugs Online

English

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Phenoxybenzamine may be confused with phenazopyridine

Pronunciation(fen oks ee BEN za meen)

U.S. Brand NamesDibenzyline®

Canadian Brand NamesDibenzyline®

Pharmacologic CategoryAlpha $_1$ Blocker; Antidote

Use: Labeled IndicationsSymptomatic management of pheochromocytoma

Use: Unlabeled/InvestigationalMicturition problems associated with neurogenic bladder, functional outlet obstruction, and partial prostate obstruction; treatment of hypertensive crisis caused by sympathomimetic amines

Dosing: Adults

Pheochromocytoma, hypertension: Oral: Initial: 10 mg twice daily, increase by 10 mg every other day until optimal blood pressure response is achieved; usual range: 20-40 mg 2-3 times/day. Doses up to 240 mg/day have been reported (Kinney, 2000).

Micturition disorders (unlabeled use): Oral: 10-20 mg 1-2 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Pheochromocytoma, hypertension (unlabeled uses):** Oral: Initial: 0.25-1 mg/kg/day (maximum: 10 mg); increase slowly to blood pressure control

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to phenoxybenzamine or any component of the formulation; conditions in which a fall in blood pressure would be undesirable (eg, shock)

Warnings/Precautions

Concerns related to adverse effects:

- Cardiovascular effects: An exaggerated hypotensive response and tachycardia may occur when administered concurrently with compounds that stimulate both alpha- and beta-adrenergic receptors or in the setting of pheochromocytoma. Discontinue if symptoms of severe hypotension or angina occur.

Disease-related concerns:

- Obstructive atherosclerosis: Use with caution in patients with obstructive cerebral or coronary atherosclerosis, since a marked reduction in blood pressure may induce ischemic symptoms.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory tract infection: Can exacerbate symptoms of respiratory tract infections.

Special populations:

- Elderly: Use with caution in the elderly; may be at higher risk of adverse effects.

Other warnings/precautions:

- Long-term use: Not recommended for long-term use due to case reports of cancer in humans.

Geriatric ConsiderationsBecause of the risk of adverse effects, avoid the use of this medication in the elderly if possible.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdequate animal reproduction studies have not been conducted. It is not known whether phenoxybenzamine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Postural hypotension, tachycardia

Central nervous system: Drowsiness, fatigue

Gastrointestinal: GI irritation

Genitourinary: Inhibition of ejaculation

Ocular: Miosis

Respiratory: Nasal congestion

Drug Interactions

Alfuzosin: Alpha1-Blockers may enhance the antihypertensive effect of Alfuzosin. Risk of orthostatic hypotension or syncope may be increased. Alfuzosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Alpha1-Blockers may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: May enhance the hypotensive effect of Alpha1-Blockers. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Silodosin: Alpha1-Blockers may enhance the adverse/toxic effect of Silodosin. Of particular concern are the risk of postural hypotension, syncope, and/or hypotension. Silodosin may enhance the hypotensive effect of Alpha1-Blockers. Of particular concern are the risk of postural hypotension, syncope, and/or hypotension. *Risk X: Avoid combination*

Tamsulosin: Alpha1-Blockers may enhance the antihypertensive effect of Tamsulosin. Risk of orthostatic hypotension or syncope may be increased. Tamsulosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol.

Herb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice, (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure, pulse, urine output, orthostatics

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride:

Dibenzyline®: 10 mg [contains benzyl alcohol]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Dibenzyline)

10 mg (30): $203.94

Mechanism of ActionProduces long-lasting noncompetitive alpha-adrenergic blockade of postganglionic synapses in exocrine glands and smooth muscle; relaxes urethra and increases opening of the bladder

Pharmacodynamics/Kinetics

Duration: I.V.: ≥3 days

Bioavailability: 20% to 30%

Half-life elimination: I.V.: 24 hours

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation, confusion, or dizziness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with low potency antipsychotics, TCAs and MAO inhibitors may produce additive hypotension

Anesthesia and Critical Care Concerns/Other ConsiderationsHypotensive effect may last for a few days after discontinuation.

Index TermsPhenoxybenzamine Hydrochloride

References

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Kinney MA, Narr BJ, and Warner MA, “Perioperative Management of Pheochromocytoma,” *J Cardiothorac Vasc Anesth*, 2002, 16(3):359-69.[PubMed 12073213]

Kinney MA, Warner ME, vanHeerden JA, et al, “Perianesthetic Risks and Outcomes of Pheochromocytoma and Paraganglioma Resection,” *Anesth Analg*, 2000, 91(5):1118-23.[PubMed 11049893]

Te AE, “A Modern Rationale for the Use of Phenoxybenzamine in Urinary Tract Disorders and Other Conditions,” *Clin Ther*, 2002, 24(6):851-61.[PubMed 12117078]

International Brand Names Dibenyline (AE, AU, BE, BF, BH, BJ, CI, CY, EG, ET, GB, GH, GM, GN, HK, IL, IQ, IR, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Dibenzyran (AT, DE); Fenoxene (IN); Seton (TW)

Phentermine

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Phentermine may be confused with phentolamine, phenytoin

Ionamin® may be confused with Imodium®

Pronunciation(FEN ter meen)

U.S. Brand NamesAdipex-P®; Ionamin®

Canadian Brand NamesIonamin®

Pharmacologic CategoryAnorexiant; Sympathomimetic

Use: Labeled IndicationsShort-term (few weeks) adjunct in exogenous obesity

Dosing: Adults**Obesity (short-term adjunct):** Oral: 18.75-37.5 mg/ day (phentermine hydrochloride) **or** 15-30 mg/day (phentermine resin)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren >16 years: Refer to adult dosing.

Calculations

- Body Mass Index

Administration: Oral

Phentermine hydrochloride: Administer before breakfast or 1-2 hours after breakfast. Tablets may be divided in half and dose may be given in 2 divided doses. Avoid late evening administration.

Phentermine resin: Administer before breakfast or 10-14 hours before retiring. Swallow capsules whole.

Dietary ConsiderationsMost effective when combined with a low calorie diet and behavior modification counseling.

RestrictionsC-IV

Pharmacotherapy for weight loss is recommended only for obese patients with a body mass index ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of other risk factors such as hypertension, diabetes, and/or dyslipidemia or a high waist circumference; therapy should be used in conjunction with a comprehensive weight management program. Rule out organic causes of obesity (eg, untreated hypothyroidism) prior to use.

Note: Phentermine is not approved for long-term use. The limited usefulness of medications in this class should be weighed against possible risks associated with their use. Consult weight loss guidelines for current pharmacotherapy recommendations.

ContraindicationsHypersensitivity or idiosyncrasy to phentermine or other sympathomimetic amines or any component of the formulation; advanced arteriosclerosis, cardiovascular disease, moderate-to-severe hypertension; pulmonary hypertension; hyperthyroidism, glaucoma, agitated states, patients with a history of drug abuse; use during or within 14 days following MAO inhibitor therapy

Allergy Considerations

- Amphetamine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Amphetamines may impair the ability to engage in potentially hazardous activities.
- Primary pulmonary hypertension (PPH): A rare, frequently fatal disease of the lungs, PPH has been reported to occur in patients receiving a combination of phentermine and fenfluramine or dexfenfluramine. The possibility of an association between PPH and the use of phentermine alone cannot be ruled out.
- Valvular heart disease: The use of some anorexigens, including phentermine, has been associated with the development of valvular heart disease. Avoid stimulants in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that could increase the risk of sudden death that these conditions alone carry.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; antidiabetic agent requirements may be altered with anorexigens and concomitant dietary restrictions.
- Hypertension: Use with caution in patients with hypertension and other cardiovascular conditions that might be exacerbated by

increases in blood pressure or heart rate.

- Seizure disorders: Use with caution in patients with a history of seizure disorders.

- Tourette's syndrome: Use with caution in patients with Tourette's syndrome; stimulants may unmask tics.

Concurrent drug therapy issues:

- Anorexigens: Safety and efficacy have not been established for use with other weight loss medications, including over-the-counter or herbal products. Not recommended for use in patients who have used other anorectic agents within the past year.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children ≤16 years of age.

Other warnings/precautions:

- Abuse potential: Phentermine is pharmacologically related to the amphetamines, which have a high abuse potential; prolonged use may lead to dependency. Prescriptions should be written for the smallest quantity consistent with good patient care to minimize possibility of overdose.

- Discontinuation of therapy: Discontinue if satisfactory weight loss has not occurred within the first 4 weeks of treatment, or if tolerance develops.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypertension, palpitation, primary pulmonary hypertension and/or regurgitant cardiac valvular disease, tachycardia

Central nervous system: Dizziness, dysphoria, euphoria, headache, insomnia, overstimulation, psychosis, restlessness

Dermatologic: Urticaria

Endocrine & metabolic: Changes in libido

Gastrointestinal: Constipation, diarrhea, unpleasant taste, xerostomia

Genitourinary: Impotence

Neuromuscular & skeletal: Tremor

Drug Interactions

Alkalinizing Agents: May decrease the excretion of Amphetamines. *Risk D: Consider therapy modification*

Ammonium Chloride: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

Analgesics (Opioid): Amphetamines may enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Antihistamines: Amphetamines may diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antipsychotics: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Amphetamines. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Ethosuximide: Amphetamines may diminish the therapeutic effect of Ethosuximide. Amphetamines may decrease the serum concentration of Ethosuximide. *Risk C: Monitor therapy*

Gastrointestinal Acidifying Agents: May decrease the serum concentration of Amphetamines. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Methenamine: May decrease the serum concentration of Amphetamines. This effect is likely due to an enhanced excretion of amphetamines in the urine. *Risk C: Monitor therapy*

PHENobarbital: Amphetamines may decrease the serum concentration of PHENobarbital. *Risk C: Monitor therapy*

Phenytoin: Amphetamines may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Monitoring Parameters Weight, waist circumference; blood pressure

Reference Range

Adult classification of weight by BMI (kg/m^2):

Underweight: <18.5

Normal: 18.5-24.9

Overweight: 25-29.9

Obese, class I: 30-34.9

Obese, class II: 35-39.9

Extreme obesity (class III): ≥40

Waist circumference: In adults with a BMI of 25-34.9 kg/m^2, high-risk waist circumference is defined as:

Men >102 cm (>40 in)

Women >88 cm (>35 in)

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 15 mg, 30 mg, 37.5 mg

Adipex-P®: 37.5 mg

Capsule, resin complex:

Ionamin®: 15 mg

Tablet, as hydrochloride: 37.5 mg

Adipex-P®: 37.5 mg

Generic Available Yes: Capsule (excludes resin complex capsule), tablet

Pricing: U.S. (www.drugstore.com)

Capsules (Adipex-P)

37.5 mg (30): $62.99

Capsules (Phentermine HCl)

15 mg (30): $40.99

30 mg (30): $34.99

37.5 mg (30): $29.99

Capsules (Phentermine Resin Complex)

15 mg (30): $29.99

Tablets (Adipex-P)

37.5 mg (30): $61.94

Tablets (Phentermine HCl)

37.5 mg (30): $29.99

Mechanism of Action Phentermine is a sympathomimetic amine with pharmacologic properties similar to the amphetamines. The mechanism of action in reducing appetite appears to be secondary to CNS effects, including stimulation of the hypothalamus to release norepinephrine.

Pharmacodynamics/Kinetics

Duration: Resin produces more prolonged clinical effects

Absorption: Well absorbed; resin absorbed slower

Excretion: Primarily urine

Related Information

- Obesity Treatment Guidelines for Adults

Dental Health Professional Considerations Many diet physicians have prescribed fenfluramine ("fen") and phentermine ("phen"). When taken together the combination is known as "fen-phen". The diet drug dexfenfluramine (Redux®) is chemically similar to fenfluramine (Pondimin®) and was also used in combination with phentermine called "Redux-phen". While each of the three drugs alone had approval from the FDA for sale in the treatment of obesity, neither combination had an official approval. The use of the combinations in the treatment of obesity was considered an “off-label” use. Reports in medical literature have been accumulating for some years about significant side effects associated with fenfluramine and dexfenfluramine. In 1997, the manufacturers, at the urging of the FDA, agreed to voluntarily withdraw the drugs from the market. The action was based on findings from physicians who evaluated patients taking fenfluramine and dexfenfluramine with echocardiograms. The findings indicated that approximately 30% of patients had abnormal echocardiograms, even though they had no symptoms. This was a much higher than expected percentage of abnormal test results. This conclusion was based on a sample of 291 patients examined by five different physicians. Under normal conditions, fewer than 1% of patients would be expected to show signs of heart valve disease. The findings suggested that fenfluramine and dexfenfluramine were the likely cause of heart valve problems of the type that promoted FDA's earlier warnings concerning “fen-phen”. The earlier warning included the following: The mitral valve and other valves in the heart are damaged by a strange white coating and allow blood to flow back, causing heart muscle damage. In several cases, valve replacement surgery has been done. As a rule, the person must, thereafter for life, be on a blood thinner to prevent clots from the mechanical valve. This type of valve damage had only been seen before in persons who were exposed to large amounts of serotonin. The fenfluramine increases the availability of serotonin.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and unpleasant taste. Up to 10% of patients may present with hypertension. The use of local anesthetic without vasoconstrictor is recommended in these patients. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse vasoconstrictor with caution in patients taking phentermine. Amphetamines enhance the sympathomimetic response of epinephrine and norepinephrine leading to potential hypertension and cardiotoxicity.

Cardiovascular ConsiderationsPhentermine should be avoid in patients with cardiovascular disease. The combination with fenfluramine (Phen-Fen® - no longer available) was associated with mitral valve fibrosis and mitral regurgitation. Primary pulmonary hypertension has also been reported in patients receiving Phen-Fen®.

Index TermsPhentermine Hydrochloride

References

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International Brand NamesAdipex (CH, CZ, KP); Adipex Retard (AT, MY); Dietamin (KP); Duromine (AU, BB, BF, BJ, BM, BS, BZ, CI, CR, CY, DO, ET, GB, GH, GM, GN, GT, GY, HN, IE, JM, KE, KW, LB, LR, MA, ML, MR, MU, MW, NE, NG, NI, NL, PA, PR, SC, SD, SL, SN, SR, SV, TN, TT, TZ, UG, ZA, ZM, ZW); Fastin (KP); Furimin (KP); Hutermin (KP); Ionamin (BE, IE, LU); Ionamine (CH); Mirapront (IT); Normaform (CH); Panbesy (BE, HK, LU, TH); Phenkini (KP); Razin (IL); Retis (KP); Sinpet (MX); Supremin (PH); Umine (NZ); Weltmine (KP)

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Phentolamine may be confused with phentermine, Ventolin®

Pronunciation(fen TOLE a meen)

U.S. Brand NamesOraVerse™

Canadian Brand NamesRegitine®; Rogitine®

Pharmacologic CategoryAlpha $_1$ Blocker

Use: Labeled IndicationsDiagnosis of pheochromocytoma and treatment of hypertension associated with pheochromocytoma or other forms of hypertension caused by excess sympathomimetic amines; as treatment of dermal necrosis after extravasation of drugs with alpha-adrenergic effects (norepinephrine, dopamine, epinephrine)

OraVerse™: Reversal of soft tissue anesthesia and the associated functional deficits resulting from a local dental anesthetic containing a vasoconstrictor

Use: Unlabeled/InvestigationalTreatment of pralidoxime-induced hypertension

Use: DentalReversal of soft tissue anesthesia and the associated functional deficits resulting from a local dental anesthetic containing a vasoconstrictor

Dosing: Adults

Treatment of alpha-adrenergic drug extravasation: SubQ:

Infiltrate area with a small amount (eg, 1 mL) of solution (made by diluting 5-10 mg in 10 mL of NS) within 12 hours of extravasation; do not exceed 0.1-0.2 mg/kg or 5 mg total

If dose is effective, normal skin color should return to the blanched area within 1 hour.

Diagnosis of pheochromocytoma: I.M., I.V.: 5 mg

Surgery for pheochromocytoma: Hypertension: I.M., I.V.: 5 mg given 1-2 hours before procedure and repeated as needed every 2-4 hours

Hypertensive crisis: I.V.: 5-20 mg

Reversal of soft tissue (lip, tongue) anesthesia (OraVerse™): Infiltration or block technique: Submucosal oral injection: **Note:** Dose is based upon the number of cartridges of local anesthetic administered. Infiltration or block injection:

0.2 mg if one-half cartridge of anesthesia was administered

0.4 mg if 1 cartridge of anesthesia was administered

0.8 mg if 2 cartridges of anesthesia were administered

Treatment of pralidoxime-induced hypertension (unlabeled use): I.V.: 5 mg

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Treatment of alpha-adrenergic drug extravasation: SubQ: Infiltrate area with a small amount (eg, 1 mL) of solution (made by diluting 5-10 mg in 10 mL of NS) within 12 hours of extravasation; do not exceed 0.1-0.2 mg/kg or 5 mg total

Diagnosis of pheochromocytoma: I.M., I.V.: 0.05-0.1 mg/kg/dose, maximum single dose: 5 mg

Surgery for pheochromocytoma: Hypertension: I.M., I.V.: 0.05-0.1 mg/kg/dose given 1-2 hours before procedure; repeat as needed every 2-4 hours until hypertension is controlled; maximum single dose: 5 mg.

Treatment of pralidoxime-induced hypertension (unlabeled use): I.V.: 1 mg

Reversal of soft tissue (lip, tongue) anesthesia (OraVerse™): Infiltration or block technique: Submucosal oral injection:

Children: 15-30 kg: 0.2 mg maximum dose

Children >30 kg and <12 years: 0.4 mg maximum dose

Administration: I.V.

Vasoconstrictor (alpha-adrenergic agonist) extravasation: Infiltrate the area of extravasation with multiple small injections using only 27- or

30-gauge needles and changing the needle between each skin entry. Be careful not to cause so much swelling of the extremity or digit that a compartment syndrome occurs. If infiltration is severe, may also need to consult vascular surgeon.

Pheochromocytoma: Inject each 5 mg over 1 minute.

Administration: I.V. DetailpH: 4.5-6.5
StorageReconstituted solution is stable for 48 hours at room temperature and 1 week when refrigerated.

OraVerse™: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

CompatibilityStable in NS.

Y-site administration: Compatible: Amiodarone.

Compatibility in syringe: Compatible: Papaverine.

Compatibility when admixed: Compatible: Dobutamine, verapamil.

ContraindicationsHypersensitivity to phentolamine or any component of the formulation; renal impairment; coronary or cerebral arteriosclerosis; concurrent use with phosphodiesterase-5 (PDE-5) inhibitors including sildenafil (>25 mg), tadalafil, or vardenafil

OraVerse™: There are no contraindications listed in the manufacturer's labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Angina: Discontinue if symptoms of angina occur or worsen.
- Vascular events: Following administration myocardial infarction, cerebrovascular spasm and cerebrovascular occlusion have occurred.

Disease-related concerns:

- Cardiac arrhythmias: Use with caution in patients with tachycardia or a history of cardiac arrhythmias.
- Gastrointestinal disease: Use with caution in patients with gastritis or peptic ulcer disease.

Special populations:

Pediatrics: OraVerse™: Efficacy has not been established in children <6 years of age or <15 kg (33 pounds).

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown
Adverse ReactionsFrequency not always defined.

Cardiovascular: Arrhythmia, flushing, hypertension (OraVerse™), hypotension, orthostatic hypotension, tachycardia (OraVerse™ ≤6%), bradycardia (OraVerse™ ≤4%)

Central nervous system: Dizziness, headache (OraVerse™ ≤6%)

Dermatologic: Pruritus (OraVerse™)

Gastrointestinal: Nausea, vomiting, diarrhea

Local: Injection site pain (OraVerse™ 4% to 6%)

Neuromuscular & skeletal: Paresthesia (OraVerse™), weakness

Respiratory: Nasal congestion

Postmarketing and/or case reports: Pulmonary hypertension

Drug Interactions

Alfuzosin: Alpha1-Blockers may enhance the antihypertensive effect of Alfuzosin. Risk of orthostatic hypotension or syncope may be increased. Alfuzosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Alpha1-Blockers may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: May enhance the hypotensive effect of Alpha1-Blockers. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Silodosin: Alpha1-Blockers may enhance the adverse/toxic effect of Silodosin. Of particular concern are the risk of postural hypotension, syncope, and/or hypotension. Silodosin may enhance the hypotensive effect of Alpha1-Blockers. Of particular concern are the risk of postural hypotension, syncope, and/or hypotension. *Risk X: Avoid combination*

Tamsulosin: Alpha1-Blockers may enhance the antihypertensive effect of Tamsulosin. Risk of orthostatic hypotension or syncope may be increased. Tamsulosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Test InteractionsIncreased LFTs rarely

Monitoring ParametersBlood pressure, heart rate; area of infiltration; monitor patient for orthostasis; assist with ambulation

Nursing: Physical Assessment/MonitoringSee Dosing and Administration for specifics according to purpose for use. When used to treat dermal necrosis after extravasation of drugs with alpha-adrenergic effects, monitor effectiveness of treatment closely. Assess patient response (eg, cardiac status). Teach patient adverse symptoms to report.

Patient EducationThis medication can only be administered by infusion or injection. Report immediately any pain at infusion/injection site. May cause orthostatic hypotension (use caution when changing position or call for assistance). Report dizziness, rapid heartbeat, feelings of weakness, or nausea/vomiting. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as mesylate: 5 mg

Injection, solution, as mesylate [preservative free]:

OraVerse™: 0.4 mg/1.7 mL (1.7 mL) [contains edetate disodium; dental cartridge]

Generic AvailableYes

Mechanism of ActionCompetitively blocks alpha-adrenergic receptors to produce brief antagonism of circulating epinephrine and norepinephrine to reduce hypertension caused by alpha effects of these catecholamines; also has a positive inotropic and chronotropic effect on the heart

OraVerse™: Causes vasodilation and increased blood flow in injection area via alpha-adrenergic blockade to accelerate reversal of soft tissue anesthetic

Pharmacodynamics/Kinetics

Onset of action: I.M.: 15-20 minutes; I.V.: Immediate

Peak effect: OraVerse™: 10-20 minutes

Duration: I.M.: 30-45 minutes; I.V.: 15-30 minutes

Metabolism: Hepatic

Half-life elimination: 19 minutes

Excretion: Urine (10% as unchanged drug)

Related Information

- Hypertension

Dental Health Professional ConsiderationsOraVerse™ (solution for injection/dental cartridge) is administered as a submucosal injection and is not to be confused with phentolamine used as an intramuscular or intravenous injection for the treatment of hypertension associated with pheochromocytoma.

In adolescents >12 years and adults, OraVerse™ reduced the median time to recovery of normal sensation in the lower lip by 85 minutes compared to control. OraVerse™ reduced the median time to recovery of normal sensation in the upper lip by 83 minutes. Within 1 hour after administration, 41% of patients reported normal lower lip sensation as compared to 7% in the control group and 59% of patients given OraVerse™ reported normal upper lip sensation as compared to 12% in the control group.

In children 6-11 years of age, the median time to normal sensation was reduced by 75 minutes after OraVerse™ administration, a 56% acceleration of the time to normal sensation.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: The most common reaction that was greater than controls was injection site pain (~4% to 6%). A few incidences of paresthesia associated with OraVerse™ have been reported. These incidences were mild and transient, and resolved during the same time period. Orthostatic hypotension has also been reported.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAlthough the alpha-adrenergic blocking effects could antagonize epinephrine, there is no information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive hypotension; treatment of choice for hypertensive crisis secondary to MAO inhibitors

Index Terms Phentolamine Mesylate; Regitine [DSC]

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International Brand Names Fentanor (IN); Phentolmin (KP); Regitin (CH, CZ, DK, HN); Regitina (AR, BR, VE); Regitine (AU, BE, CL, HU, IL, LU, NL); Rogitine (GB)

Phenylephrine and Pyrilamine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(fen il EF rin & peer IL a meen)

U.S. Brand NamesAldex®D; AllanVan-S [DSC]; Deconsal® CT; K-Tan 4 [DSC]; K-Tan [DSC]; Pyrilafen Tannate-12™; Ry-T-12; Ryna-12 S®; Ryna®-12; Rynesa 12S; V-Tann™ [DSC]; Viravan® [DSC]

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of nasal congestion and discharge associated with the common cold, sinusitis, allergic rhinitis, and other respiratory tract conditions

Dosing: Adults**Relief of cough, congestion:** Oral:

Aldex® D, Deconsal® CT: 5-10 mL of the suspension or 1-2 tablets every 12 hours

Ryna®-12: 1-2 tablets every 12 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Relief of cough, congestion:** Oral:

Aldex® D, Deconsal® CT:

Children 2-6 years: 2.5 mL of the suspension or $^1/_2$ tablet every 12 hours

Children 6-12 years: 5 mL of the suspension or $^1/_2$ to 1 tablet every 12 hours

Children >12 years: Refer to adult dosing.

Ryna®-12:

Children 6-12 years: $^1/_2$ to 1 tablet every 12 hours

Children >12 years: Refer to adult dosing.

Ryna-12 S®, Rynesa 12S, Ry-T 12:

Children 2-6 years: 2.5-5 mL every 12 hours

Children >6 years: 5-10 mL every 12 hours

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to phenylephrine, pyrilamine, or any component of the formulation; asthma; hypertension or peripheral vascular insufficiency; use with or within 14 days of MAO inhibitors; newborns; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; contraindicated in patients with hypertension.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or urinary obstruction.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination. Phenylephrine may cause fetal anoxia or bradycardia if administered late in pregnancy or during labor. Sympathomimetics may cause minor malformations when used during the first trimester.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsSpecific information for phenylephrine or pyrilamine is not available, however, infants may be more sensitive to the effects of antihistamines.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, hyper-/hypotension, palpitation

Central nervous system: Coordination disturbed, drowsiness, dysphoria, euphoria, headache, insomnia, irritability, nervousness, sedation, seizure

Dermatologic: Photosensitivity, pruritus, rash, urticaria

Gastrointestinal: Anorexia, constipation, diarrhea, epigastric discomfort, nausea, vomiting, xerostomia

Genitourinary: Difficult urination, urinary frequency

Hematologic: Agranulocytosis, hemolytic anemia, thrombocytopenia

Neuromuscular & skeletal: Tremor, weakness

Ocular: Visual disturbances

Respiratory: Shortness of breath, wheezing

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Nursing: Physical Assessment/MonitoringSee individual agent for Phenylephrine.

Patient EducationSee individual agent for Phenylephrine.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Suspension:

Aldex®D: Phenylephrine hydrochloride 5 mg and pyrilamine maleate 16 mg (480 mL) [contains tannic acid to provide a tannate suspension; contains sodium benzoate; grape flavor]

AllanVan-S: Phenylephrine tannate 12.5 mg and pyrilamine tannate 30 mg per 5 mL (120 mL, 480 mL) [contains sodium benzoate; grape flavor] [DSC]

K-Tan 4: Phenylephrine tannate 5 mg and pyrilamine tannate 30 mg per 5 mL (120 mL) [contains benzoic acid; strawberry-currant flavor] [DSC]

Pyrilafen Tannate-12™: Phenylephrine tannate 5 mg and pyrilamine tannate 30 mg per 5 mL (120 mL, 480 mL [DSC]) [strawberry-black currant flavor]

Ryna-12 S®: Phenylephrine tannate 5 mg and pyrilamine tannate 30 mg per 5 mL (120 mL) [contains benzoic acid; strawberry-currant flavor]

Rynesa 12S: Phenylephrine tannate 5 mg and pyrilamine tannate 30 mg per 5 mL (120 mL, 480 mL) [contains sodium benzoate; cherry berry flavor]

Ry-T-12: Phenylephrine tannate 5 mg and pyrilamine tannate 30 mg per 5 mL (120 mL, 480 mL) [contains benzoic acid]

V-Tann™: Phenylephrine tannate 12.5 mg and pyrilamine tannate 30 mg per 5 mL (120 mL, 480 mL) [alcohol free, dye free, gluten free; contains sodium benzoate; grape flavor] [DSC]

Viravan®: Phenylephrine tannate 12.5 mg and pyrilamine tannate 30 mg per 5 mL (120 mL, 480 mL) [contains sodium benzoate; grape flavor] [DSC]

Tablet:

K-Tan [DSC], Ryna®-12: Phenylephrine tannate 25 mg and pyrilamine tannate 60 mg

Tablet, chewable:

Deconsal® CT: Phenylephrine hydrochloride 10 mg and pyrilamine maleate 16 mg [dye free; grape flavor]

Viravan®: Phenylephrine tannate 25 mg and pyrilamine tannate 30 mg [dye free; grape flavor] [DSC]

Generic AvailableYes: Suspension, tablet

Pricing: U.S. (www.drugstore.com)

Suspension (Ryna-12 S)

30-5 mg/5 mL (118): $74.79

Mechanism of Action

Phenylephrine hydrochloride is a sympathomimetic agent (primarily alpha), decongestant.

Pyrilamine is an H_1-receptor antagonist.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause sedation, dysphoria, euphoria, insomnia, anxiety, excitability, nervousness, fatigue, or depression

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors. Concurrent use with psychotropic agents may result in additive sedative and/or anticholinergic effects; monitor. May cause seizures; monitor in patients receiving clozapine. May rarely be associated with agranulocytosis; use caution with clozapine, carbamazepine, and mirtazapine. May cause thrombocytopenia; monitor in patients receiving valproic acid.

Index TermsPyrilamine Tannate and Phenylephrine Tannate

Phenylephrine and Scopolamine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Murocoll-2速 may be confused with Murocel速

Pronunciation(fen il EF rin & skoe POL a meen)

U.S. Brand NamesMurocoll-2速

Pharmacologic CategoryAnticholinergic/Adrenergic Agonist

Use: Labeled IndicationsMydriasis, cycloplegia, and to break posterior synechiae in iritis

Dosing: Adults**Ocular procedures:** Ophthalmic: Instill 1-2 drops into eye(s); repeat in 5 minutes

Dosing: ElderlyRefer to adult dosing.

Contraindications

Based on **phenylephrine** component: Hypersensitivity to phenylephrine, bisulfite (some products contain metabisulfite), or any component of the formulation; hypertension; ventricular tachycardia

Based on **scopolamine** component: Hypersensitivity to scopolamine or any component of the formulation; narrow-angle glaucoma; acute hemorrhage, gastrointestinal or genitourinary obstruction, thyrotoxicosis, tachycardia secondary to cardiac insufficiency, paralytic ileus

Allergy Considerations

- Belladonna Alkaloid Allergy

Pregnancy Risk FactorC

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic: Phenylephrine hydrochloride 10% and scopolamine hydrobromide 0.3% (5 mL) [contains benzalkonium chloride and sodium metabisulfite]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Murocoll-2)

10-0.3% (5): $16.99

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentThis form of phenylephrine will have no effect on dental treatment when given as eye drops.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsScopolamine and Phenylephrine

Phenylephrine and Zinc Sulfate

English

Jump To Field (Select Field Name)

Pronunciation(fen il EF rin & zingk SUL fate)

Canadian Brand NamesZincfrin速

Pharmacologic CategoryAdrenergic Agonist Agent

Use: Labeled IndicationsSoothe, moisturize, and remove redness due to minor eye irritation

Dosing: Adults **Ocular irritation:** Ophthalmic: Instill 1-2 drops in eye(s) 2-4 times/day as needed

Dosing: ElderlyRefer to adult dosing.

RestrictionsNot available in the U.S.

ContraindicationsHypersensitivity to phenylephrine, zinc sulfate, or any component of the formulation

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Quinolone Antibiotics: Zinc Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tetracycline Derivatives: Zinc Salts may decrease the absorption of Tetracycline Derivatives. Only a concern when both products are administered orally. **Exceptions:** Doxycycline. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Zinc Salts. Zinc Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Available in Canada

Solution, ophthalmic:

Zincfrin速 [CAN]: Phenylephrine 0.12% and zinc sulfate 0.25% (15 mL) [not available in the U.S.]

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsZinc Sulfate and Phenylephrine

International Brand NamesExastrin (MX)

Phenylephrine, Hydrocodone, and Chlorpheniramine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(fen il EF rin, hye droe KOE done, & klor fen IR a meen)

U.S. Brand NamesB-Tuss™; Coughtuss; Cytuss HC; De-Chlor HC; DroTuss-CP; ED-TLC; ED-Tuss HC; Histinex® HC; Hydro PC II Plus; Hydro-PC II; Hydron CP; Maxi-Tuss HCX; Maxi-Tuss HC®; Mintuss HC; Mintuss MS; PolyTussin HD; Relacon-HC; Rindal HD Plus; Triant-HC™

Pharmacologic CategoryAlpha/Beta Agonist; Analgesic, Opioid; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of cough and congestion associated with the common cold, sinusitis, or acute upper respiratory tract infections

Dosing: Adults**Cough and congestion:** Oral:

B-Tuss™: 5-10 mL every 6 hours (maximum: 40 mL/24 hours)

Histinex® HC, Cytuss HC: 10 mL every 4 hours (maximum: 40 mL/24 hours)

Maxi-Tuss HC®, Maxi-Tuss HCX: 5 mL every 4 hours (maximum: 30 mL/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Cough and congestion:** Oral:

Children 2-6 years: *B-Tuss™:* 1.25-2.5 mL every 6 hours (maximum: 10 mL/24 hours)

Children 6-12 years:

B-Tuss™: 2.5-5 mL every 6 hours (maximum: 20 mL/24 hours)

Histinex® HC, Cytuss HC: 5 mL every 4 hours (maximum: 20 mL/24 hours)

Maxi-Tuss HC®, Maxi-Tuss HCX: 2.5 mL every 4 hours (maximum: 15 mL/24 hours)

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

RestrictionsC-III

ContraindicationsHypersensitivity to phenylephrine, hydrocodone, chlorpheniramine, codeine, sympathomimetic amines, antihistamines, or any component of the formulation; bronchial asthma, status asthmaticus; severe hypertension, severe coronary artery disease; MAO inhibitor therapy or within 14 days of therapy; narrow-angle glaucoma; urinary retention; peptic ulcer

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydromorphone, levorphanol, morphine, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with pulmonary disease or decrease ventilatory function; dose-related respiratory depression occurs.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children.

Dosage form specific issues:

- Aspartame: Some products may contain aspartame.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Opioid analgesics are considered FDA risk category D if used for prolonged periods or in large doses near term. Withdrawal symptoms may be observed in babies born to mothers taking opioids regularly during pregnancy. Respiratory depression may be observed in the newborn if opioids are given close to delivery.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsHydrocodone is excreted in breast milk; information for chlorpheniramine and phenylephrine is not available. The manufacturers recommend discontinuing the medication or to discontinue nursing during therapy.

Adverse ReactionsSee individual agents.

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May diminish the analgesic effect of Hydrocodone. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsSee individual agents.

Nursing: Physical Assessment/MonitoringSee individual agent for Phenylephrine.

Patient EducationSee individual agent for Phenylephrine. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid:

B-Tuss™: Phenylephrine hydrochloride 5 mg, hydrocodone bitartrate 5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [alcohol free, sugar free; candy apple flavor]

Coughtuss: Phenylephrine hydrochloride 5 mg, hydrocodone bitartrate 5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [alcohol free, sugar free; candy apple flavor]

De-Chlor HC: Phenylephrine hydrochloride 10 mg, hydrocodone bitartrate 2.5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [cherry flavor]

DroTuss-CP: Phenylephrine hydrochloride 5 mg, hydrocodone bitartrate 5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [alcohol free, sugar free; candy apple flavor]

ED-Tuss HC: Phenylephrine hydrochloride 10 mg, hydrocodone bitartrate 3.5 mg, and chlorpheniramine maleate 4 mg per 5 mL (480 mL)

ED-TLC: Phenylephrine hydrochloride 5 mg, hydrocodone bitartrate 1.67 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL)

Hydron CP: Phenylephrine hydrochloride 10 mg, hydrocodone bitartrate 5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [pineapple-orange flavor]

Hydro PC II Plus: Phenylephrine hydrochloride 7.5 mg, hydrocodone bitartrate 3.5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [strawberry flavor]

Maxi-Tuss HCX: Phenylephrine hydrochloride 12 mg, hydrocodone bitartrate 6 mg and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [alcohol free, sugar free; contains aspartame; vanilla bean flavor]

Relacon-HC: Phenylephrine hydrochloride 10 mg, hydrocodone bitartrate 3.5 mg, and chlorpheniramine maleate 2.5 mg per 5 mL (480 mL) [raspberry flavor]

Triant-HC™: Phenylephrine hydrocloride 5 mg, hydrocodone bitartrate 1.67 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [alcohol free, sugar free; strawberry flavor]

Syrup:

Cytuss HC: Phenylephrine hydrochloride 5 mg, hydrocodone bitartrate 2.5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [peach flavor]

Histinex® HC: Phenylephrine hydrochloride 5 mg, hydrocodone bitartrate 2.5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL, 960 mL) [alcohol free, sugar free; contains sodium benzoate]

Hydro-PC II: Phenylephrine hydrochloride 7.5 mg, hydrocodone bitartrate 2 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [strawberry flavor]

Maxi-Tuss HC®: Phenylephrine hydrochloride 10 mg, hydrocodone bitartrate 2.5 mg, and chlorpheniramine maleate 4 mg per 5 mL (480 mL) [orange flavor]

Mintuss HC: Phenylephrine hydrochloride 10 mg, hydrocodone bitartrate 2.5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [alcohol free; contains sodium benzoate; black cherry flavor]

Mintuss MS: Phenylephrine hydrochloride 10 mg, hydrocodone bitartrate 5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [alcohol free; contains sodium benzoate; orange flavor]

PolyTussin HD: Phenylephrine hydrochloride 5 mg, hydrocodone bitartrate 6 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [alcohol free, sugar free]

Rindal HD Plus: Phenylephrine hydrochloride 7.5 mg, hydrocodone bitartrate 3.5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [alcohol free, sugar free; contains sodium benzoate; black raspberry flavor]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Syrup (Hydro-PC II Plus)

7.5-2-3.5 mg/5 mL (473): $36.00

Mechanism of Action

Phenylephrine: Potent, direct-acting alpha-adrenergic stimulator with weak beta-adrenergic activity; causes vasoconstriction of the arterioles of the nasal mucosa and conjunctiva

Hydrocodone: Binds to opiate receptors in the CNS; suppresses cough in medullary center; produces generalized CNS depression

Chlorpheniramine: Competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Chlorpheniramine
- Phenylephrine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause anxiety, restlessness, and sedation; may rarely cause hallucinations

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors; concurrent use with psychotropics may result in additive sedation; may result in loss of pain control if used with fluoxetine or paroxetine

Index Terms Chlorpheniramine, Phenylephrine, and Hydrocodone; Dihydrocodeine Bitartrate, Phenylephrine Hydrochloride, and Chlorpheniramine Maleate; Hydrocodone, Phenylephrine, and Chlorpheniramine; Phenylephrine Hydrochloride, Hydrocodone Bitartrate, and Chlorpheniramine Maleate

References

Anderson PO, Sauberan JB, Lane JR, et al, “Hydrocodone Excretion Into Breast Milk: The First Two Reported Cases,” *Breastfeed Med*, 2007, 2(1):10-4.[PubMed 17661614]

Rathmell JP, Viscomi CM, and Ashburn MA, “Management of Nonobstetric Pain During Pregnancy and Lactation,” *Anesth Analg*, 1997, 85(5):1074-87. [PubMed 9356103]

Phenylephrine, Pyrilamine, and Dextromethorphan

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

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It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(fen il EF rin, peer IL a meen, & deks troe meth OR fan)

U.S. Brand NamesAldex® DM; AllanVan-DM; Codal-DM [OTC]; codimal® DM [OTC]; Codituss DM [OTC]; MyHist-DM; Poly-Hist DM; Tannate-V-DM; Viravan®-DM

Pharmacologic CategoryAlpha/Beta Agonist; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of cough, nasal congestion, and discharge associated with the common cold, sinusitis, allergic rhinitis, and other respiratory tract conditions

Dosing: Adults **Relief of cough, congestion:** Oral:

codimal® DM: 10 mL every 4 hours; maximum: 60 mL/24 hours

Viravan®-DM: 5-10 mL of the suspension or 1-2 tablets every 12 hours

Dosing: Elderly Refer to adult dosing.

Dosing: Pediatric **Relief of cough, congestion:** Oral:

Children 2-6 years (Viravan®-DM): 2.5 mL of the suspension or $^{1}/_{2}$ tablet every 12 hours

Children 6-12 years:

- *codimal® DM:* 5 mL every 4 hours; maximum: 30 mL/24 hours
- *Viravan®-DM:* 5 mL of the suspension or $^{1}/_{2}$ to 1 tablet every 12 hours

Children >12 years: Refer to adult dosing.

Storage Store at controlled room temperature of 20°C to 25°C (68°F to 77°F).

Contraindications Hypersensitivity to phenylephrine, pyrilamine, dextromethorphan, or any component of the formulation; asthma; hypertension or peripheral vascular insufficiency; use with or within 14 days of MAO inhibitors; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; contraindicated in patients with hypertension.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in patients who are sedated, debilitated or confined to a supine position.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Use with caution in atopic children. Antihistamines may cause excitation in young children.

Other warnings/precautions:

- Self-medication (OTC use): When used for self-medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever, rash, or persistent headache. Discontinue and contact healthcare provider if nervousness, dizziness, or sleeplessness occur.

Pregnancy Risk Factor C

Pregnancy Considerations Reproduction studies have not been conducted with this combination. Phenylephrine may cause fetal anoxia or bradycardia if administered late in pregnancy or during labor. Sympathomimetics may cause minor malformations when used during the first trimester.

Lactation Excretion in breast milk unknown/contraindicated

Breast-Feeding Considerations Specific information for phenylephrine or pyrilamine is not available, however, infants may be more sensitive to the effects of antihistamines.

Adverse Reactions Frequency not defined.

Cardiovascular: Arrhythmias, hyper-/hypotension, palpitation

Central nervous system: Coordination disturbances, drowsiness, dysphoria, euphoria, headache, insomnia, irritability, nervousness, sedation, seizure

Dermatologic: Photosensitivity, pruritus, rash, urticaria

Gastrointestinal: Constipation, diarrhea, epigastric discomfort, nausea, vomiting, xerostomia

Genitourinary: Difficult urination, urinary frequency

Hematologic: Agranulocytosis, hemolytic anemia, thrombocytopenia

Neuromuscular & skeletal: Tremor, weakness

Ocular: Visual disturbances

Respiratory: Shortness of breath, wheezing

Metabolism/Transport EffectsDextromethorphan: **Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Nursing: Physical Assessment/MonitoringSee individual agent for Phenylephrine.

Patient EducationSee individual agent for Phenylephrine.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid:

MyHist-DM: Phenylephrine hydrochloride 7.5 mg, pyrilamine maleate 12.5 mg, and dextromethorphan hydrochloride 15 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; grape flavor]

Suspension:

AllanVan-DM, Tannate-V-DM, Viravan®-DM: Phenylephrine tannate 12.5 mg, pyrilamine tannate 30 mg, and dextromethorphan tannate 25 mg per 5 mL (480 mL) [contains sodium benzoate; grape flavor]

Aldex® DM: Phenylephrine hydrochloride 5 mg, pyrilamine maleate 16 mg, and dextromethorphan hydrochloride 15 mg per 5 mL (480 mL) [contains tannic acid to provide a tannate suspension; contains sodium benzoate; grape flavor]

Syrup:

Codal-DM: Phenylephrine hydrochloride 5 mg, pyrilamine maleate 8.33 mg, and dextromethorphan hydrobromide 10 mg (480 mL) [cherry flavor] codimal® DM: Phenylephrine hydrochloride 5 mg, pyrilamine maleate 8.33 mg, and dextromethorphan hydrobromide 10 mg (120 mL, 480 mL) [alcohol free, dye free, sugar free; contains benzoic acid]

Codituss DM: Phenylephrine hydrochloride 5 mg, pyrilamine maleate 8.33 mg, and dextromethorphan hydrobromide 10 mg (120 mL, 480 mL) [alcohol free, dye free, sugar free; cherry punch flavor]

Poly Hist DM: Phenylephrine hydrochloride 7.5 mg, pyrilamine maleate 8.33 mg, and dextromethorphan hydrobromide 10 mg (480 mL) [alcohol free, dye free, sugar free; grape flavor]

Tablet, chewable [scored]:

Deconsal® DM: Phenylephrine hydrochloride 10 mg, pyrilamine maleate 16 mg, and dextromethorphan hydrobromide 15 mg [dye free; grape flavor]

Viravan®-DM: Phenylephrine tannate 25 mg, pyrilamine tannate 30 mg, and dextromethorphan tannate 25 mg [dye free; grape flavor]

Generic AvailableYes: Excludes chewable tablet

Pricing: U.S. (www.drugstore.com)

Syrup (Codal-DM)

5-8.33-10 mg/5 mL (120): $7.99

Mechanism of Action

Phenylephrine hydrochloride is a sympathomimetic agent (primarily alpha), decongestant.

Pyrilamine is an H_1-receptor antagonist.

Dextromethorphan, a non-narcotic antitussive, increases cough threshold by its activity on the medulla oblongata.

Related Information

- Dextromethorphan
- Phenylephrine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusSedation is common; may cause anxiety, excitability, dysphoria, euphoria, insomnia, nervousness, fatigue, or depression

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors. Concurrent use with psychotropic agents may result in additive sedative and/or anticholinergic effects; monitor. May cause seizures; monitor in patients receiving clozapine. May rarely be associated with agranulocytosis; use caution with clozapine, carbamazepine, and mirtazapine. May cause thrombocytopenia; monitor in patients receiving valproic acid.

Index TermsDextromethorphan Tannate, Pyrilamine Tannate, and Phenylephrine Tannate; Pyrilamine Maleate, Dextromethorphan Hydrobromide, and Phenylephrine Hydrochloride

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Pronunciation(fen il EF rin, peer IL a meen, & gwye FEN e sin)
U.S. Brand NamesRyna-12X®
Pharmacologic CategoryAlpha/Beta Agonist; Decongestant; Expectorant; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation
Use: Labeled IndicationsSymptomatic relief of cough, nasal congestion, and discharge associated with the common cold, sinusitis, allergic rhinitis, and other respiratory tract conditions
Dosing: Adults

Relief of cough, congestion: Oral: 1-2 tablets every 12 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Relief of cough, congestion: Oral:

Children 2-6 years: 2.5-5 mL of the suspension every 12 hours

Children 6-11 years: 5-10 mL of the suspension **or** $^1/_2$ to 1 tablet every 12 hours

Children ≥12 years: Refer to adult dosing.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).
ContraindicationsHypersensitivity to phenylephrine, pyrilamine, guaifenesin, or any component of the formulation; severe hypertension or coronary artery disease; use with or within 14 days of MAO inhibitors
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; contraindicated in patients with severe hypertension or coronary artery disease..
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or narrow-angle glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in patients who are sedated, debilitated or confined to a supine position.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children.

Other warnings/precautions:

- Cough control: Use with caution in patients with chronic or persistent coughs due to asthma, emphysema, smoking, or cough accompanied by excessive secretions.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Phenylephrine may cause fetal anoxia or bradycardia if administered late in pregnancy or during labor. Sympathomimetics may cause minor malformations when used during the first trimester.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsSpecific information for phenylephrine or pyrilamine is not available, however, infants may be more sensitive to the effects of antihistamines.

Adverse ReactionsFrequency not defined.

Central nervous system: Dizziness (rare), drowsiness, headache, nervousness, restlessness, sedation

Dermatologic: Rash (rare), urticaria (rare)

Gastrointestinal: Dry mucous membranes, nausea, vomiting

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).
Test InteractionsGuaifenesin: Possible color interference with determination of 5-HIAA and VMA; discontinue for 48 hours prior to test
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension:

Ryna-12X®: Phenylephrine tannate 5 mg, pyrilamine tannate 30 mg, and guaifenesin 100 mg per 5 mL (120 mL) [contains benzoic acid; grape flavor]

Tablet [scored]:

Ryna-12X®: Phenylephrine tannate 25 mg, pyrilamine tannate 60 mg, and guaifenesin 200 mg

Generic AvailableNo
Mechanism of Action

Phenylephrine is a sympathomimetic agent (primarily alpha), decongestant.

Pyrilamine is an H_1-receptor antagonist.

Guaifenesin is an expectorant.

Related Information

- GuaiFENesin
- Phenylephrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Pyrilamine: Prolonged use will cause significant xerostomia (normal salivary flow resumes upon discontinuation).

Phenylephrine: Up to 10% of patients could experience tachycardia, palpitations, and xerostomia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine or mepivacaine and levonordefrin (Carbocaine® 2% with Neo-Cobefrin®) to cause a pressor response.
Mental Health: Effects on Mental StatusMay cause sedation, nervousness, restlessness, or dizziness
Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor treatment. May cause CNS depression, concurrent use with psychotropics may produce additive effects.
Index TermsGuaifenesin, Pyrilamine Tannate, and Phenylephrine Tannate; Pyrilamine Tannate, Guaifenesin, and Phenylephrine Tannate

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Mydfrin® may be confused with Midrin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(fen il EF rin)

U.S. Brand Names4 Way® Fast Acting [OTC]; 4 Way® Menthol [OTC]; 4 Way® No Drip [OTC]; AK-Dilate®; Altafrin; Anu-Med [OTC]; Dimetapp® Toddler's [OTC]; Formulation R™ [OTC]; Little Noses® Decongestant [OTC]; LuSonal™; Medi-Phenyl [OTC]; Medicone® Suppositories [OTC]; Mydfrin®; Nasop12™; Neo-Synephrine® Extra Strength [OTC]; Neo-Synephrine® Injection; Neo-Synephrine® Mild [OTC]; Neo-Synephrine® Regular Strength [OTC]; Neofrin™; NāSop™ [DSC]; OcuNefrin™ [OTC]; Preparation H® [OTC]; Rectacaine [OTC]; Relief® [OTC] [DSC]; Rhinall [OTC]; Sudafed PE™ [OTC]; Triaminic® Infant Thin Strips® Decongestant [OTC] [DSC]; Triaminic® Thin Strips® Cold [OTC]; Tronolane® Suppository [OTC]; Tur-bi-kal® [OTC]; Vicks® Sinex® Nasal Spray [OTC]; Vicks® Sinex® UltraFine Mist [OTC]

Canadian Brand NamesDionephrine®; Mydfrin®; Neo-Synephrine®

Pharmacologic CategoryAlpha/Beta Agonist; Ophthalmic Agent, Antiglaucoma; Ophthalmic Agent, Mydriatic

Use: Labeled IndicationsTreatment of hypotension, vascular failure in shock; as a vasoconstrictor in regional analgesia; as a mydriatic in ophthalmic procedures and treatment of wide-angle glaucoma; supraventricular tachycardia

For OTC use as symptomatic relief of nasal and nasopharyngeal mucosal congestion, treatment of hemorrhoids, relief of redness of the eye due to irritation

Dosing: Adults

Hemorrhoids: Rectal:

Cream/ointment: Apply to clean dry area, up to 4 times/day; may be used externally or inserted rectally using applicator.

Suppository: Insert 1 suppository rectally, up to 4 times/day

Hypotension/shock:

I.V. bolus: 0.1-0.5 mg/dose every 10-15 minutes as needed (initial dose should not exceed 0.5 mg)

I.V. infusion: Initial dose: 100-180 mcg/minute; when blood pressure is stabilized, maintenance rate: 40-60 mcg/minute; rates up to 360 mcg/minute have been reported; dosing range: 0.4-9.1 mcg/kg/minute

Nasal congestion:

Intranasal: Instill 1-2 sprays or instill 1-2 drops every 4 hours of 0.25% to 0.5% solution as needed; 1% solution may be used in adult in cases of extreme nasal congestion; do not use nasal solutions more than 3 days

Oral:

Hydrochloride salt: 10-20 mg every 4 hours

Tannate salt:

NāSop™ suspension: 7.5-15 mg every 12 hours

Nasop12™ chewable tablet: 1-2 tablets (10-20 mg) every 12 hours

Ocular procedures:*Ophthalmic:* Instill 1 drop of 2.5% or 10% solution, may repeat in 10-60 minutes as needed.

Paroxysmal supraventricular tachycardia:*I.V.:* 0.25-0.5 mg/dose over 20-30 seconds

Reduction in ocular redness (OTC formulation):*Ophthalmic:* Instill 1-2 drops 0.12% solution into affected eye, up to 4 times/day; do not use for >72 hours

Dosing: Elderly

Nasal decongestant: Administer 2-3 drops or 1-2 sprays every 4 hours of 0.125% to 0.25% solution as needed; do not use more than 3 days.

Ophthalmic preparations for pupil dilation: Instill 1 drop of 2.5% solution, may repeat in 1 hour if necessary.

Refer to adult dosing for other uses and Geriatric Considerations for cautions on I.V. use.

Dosing: Pediatric

Hemorrhoids: Children >12 years: Refer to adult dosing.

Hypotension/shock: Children:

I.V. bolus: 5-20 mcg/kg/dose every 10-15 minutes as needed

I.V. infusion: 0.1-0.5 mcg/kg/minute

Nasal congestion:

2-6 years:

Intranasal: Instill 1 drop every 2-4 hours of 0.125% solution as needed. (**Note:** Therapy should not exceed 3 continuous days.)

Oral: Tannate salt (NāSop™ suspension): 1.87-3.75 mg every 12 hours

6-12 years:

Intranasal: Instill 1-2 sprays or instill 1-2 drops every 4 hours of 0.25% solution as needed. (**Note:** Therapy should not exceed 3 continuous days.)

Oral:

Hydrochloride salt: 10 mg every 4 hours

Tannate salt:

NāSop™ suspension: 3.75-7.5 mg every 12 hours

Nasop12™ chewable tablet: $^1/_2$ to 1 tablet (5-10 mg) every 12 hours

>12 years: Refer to adult dosing.

Ocular procedures: Ophthalmic:

Infants <1 year: Instill 1 drop of 2.5% 15-30 minutes before procedures

Children: Refer to adult dosing.

Paroxysmal supraventricular tachycardia: I.V.: Children: 5-10 mcg/kg/dose over 20-30 seconds

Calculations

- Phenylephrine
- Phenylephrine, Weight-Based

Administration: I.V. DetailMay cause necrosis or sloughing tissue if extravasation occurs during I.V. administration or SubQ administration.

Extravasation management: Use phentolamine as antidote; mix 5 mg with 9 mL of NS. Inject a small amount of this dilution subcutaneously into extravasated area. Blanching should reverse immediately. Monitor site. If blanching should recur, additional injections of phentolamine may be needed.

pH: 3.0-6.5

Administration: OralChewable tablet: Chew or crush well. May mix crushed tablet with food. Do not swallow whole.

Dietary ConsiderationsNāSop™ contains phenylalanine 4 mg/tablet. LuSonal™ contains phenylalanine. Sudafed PE™ contains phenylalanine 1 mg/strip.

Storage

Solution for injection: Store vials at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from light. Do not use solution if brown or contains a precipitate.

Ophthalmic solution:

0.12%: Store at controlled room temperature. Protect from light and excessive heat.

2.5% and 10%: Refer to product labeling. Some products are labeled to store at room temperature, others should be stored under refrigeration at 2˚C to 8˚C (36˚F to 46˚F). Do not use solution if brown or contains a precipitate.

Tablet, chewable: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

ReconstitutionSolution for injection:

I.V. infusion: May dilute 10 mg in 500 mL NS or D_5W.

I.V. injection: Dilute with SWFI to a concentration of 1 mg/mL.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, $^1/_2NS$, NS, sodium bicarbonate 5%.

Y-site administration: Compatible: Amiodarone, cisatracurium, etomidate, famotidine, haloperidol, inamrinone, levofloxacin, remifentanil, zidovudine. **Incompatible:** Thiopental. **Variable (consult detailed reference):** Propofol.

Compatibility when admixed: Compatible: Chloramphenicol, chloramphenicol with sodium bicarbonate, dobutamine, lidocaine, potassium chloride, sodium bicarbonate.

ContraindicationsHypersensitivity to phenylephrine or any component of the formulation; hypertension; ventricular tachycardia

Oral: Use with or within 14 days of MAO inhibitor therapy

Nasop12™: Additional contraindications: Use in newborns; breast-feeding

Ophthalmic: Narrow-angle glaucoma

Warnings/Precautions

Boxed warnings:

- Trained personnel: See "Other warnings/precautions" below.

Concurrent drug therapy issues:

- Monoamine oxidase inhibitors (MAO-I): Use with extreme caution in patients taking MAO inhibitors; hypertension may result from concurrent use.

Dosage form specific issues:

- Intravenous: Use with caution in the elderly, patients with hyperthyroidism, bradycardia, partial heart block, myocardial disease, or severe CAD. Assure adequate circulatory volume to minimize need for vasoconstrictors. Avoid hypertension; monitor blood pressure closely and adjust infusion rate. Avoid extravasation; infuse into a large vein if possible. Avoid infusion into leg veins. Watch I.V. site closely. If extravasation occurs, infiltrate the area subcutaneously with diluted phentolamine (5-10 mg in 10-15 mL of saline) with a fine hypodermic needle. Phentolamine should be administered as soon as possible after extravasation is noted.

- Nasal: Use with caution in patients with hyperthyroidism, diabetes mellitus, cardiovascular disease, ischemic heart disease, increased intraocular pressure, prostatic hyperplasia or in the elderly. Rebound congestion may occur when nasal products are discontinued after chronic use. When used for self-medication (OTC), notify healthcare provider if symptoms do not improve within 3 days.

- Ophthalmic: When used for self-medication (OTC), notify healthcare provider in case of vision changes, continued redness, or if symptoms worsen or do not improve within 3 days.

- Oral: Use with caution in patients with asthma, bowel obstruction/narrowing, hyperthyroidism, diabetes mellitus, cardiovascular disease, ischemic heart disease, increased intraocular pressure, prostatic hyperplasia or in the elderly. When used for self-medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever. Discontinue and contact healthcare provider if nervousness, dizziness, or sleeplessness occur. Not for OTC use in children <2 years of age.

- Rectal: Use with caution in patients with hyperthyroidism, diabetes mellitus, cardiovascular disease, ischemic heart disease, increased intraocular pressure, prostatic hyperplasia or in the elderly. When used for self-medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or if bleeding occurs.

- Sulfites: Some products contain sulfites which may cause allergic reactions in susceptible individuals.

Other warnings/precautions:

- Trained personnel: **[U.S. Boxed Warning]: Intravenous preparations should be administered by adequately trained individuals familiar with its use.**

Geriatric ConsiderationsElderly are more predisposed to the adverse effects of sympathomimetics since they frequently have cardiovascular disease and diabetes mellitus, and are on multiple medications. Since oral and topical phenylephrine can be obtained OTC, elderly patients should be counseled about their proper use and in what disease states they should be avoided. Phenylephrine I.V. should be used with extreme caution in the elderly. The 10% ophthalmic solution has caused increased blood pressure in elderly patients and its use should, therefore, be avoided.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia (rare), decreased cardiac output, hypertension, pallor, precordial pain or discomfort, reflex bradycardia, severe peripheral and visceral vasoconstriction

Central nervous system: Anxiety, dizziness, excitability, giddiness, headache, insomnia, nervousness, restlessness

Endocrine & metabolic: Metabolic acidosis

Gastrointestinal: Gastric irritation, nausea

Local: I.V.: Extravasation which may lead to necrosis and sloughing of surrounding tissue, blanching of skin

Neuromuscular & skeletal: Paresthesia, pilomotor response, tremor, weakness

Renal: Decreased renal perfusion, reduced urine output

Respiratory: Respiratory distress

Miscellaneous: Hypersensitivity reactions (including rash, urticaria, leukopenia, agranulocytosis, thrombocytopenia)

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid ephedra, yohimbe (may cause CNS stimulation).
Monitoring ParametersBlood pressure, pulse; excitability, irritability, anxiety

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness and adverse reactions according to use. **Parenteral:** Monitor arterial blood gases, vital signs, adverse reactions, and infusion site. **Nasal/ophthalmic:** Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. Systemic absorption from ophthalmic instillation is minimal.

Patient Education

Nasal decongestant: Do not use for more than 3 days in a row. Clear nose as much as possible before use. Tilt head back and instill recommended dose of drops or spray. Do not blow nose for 5-10 minutes. You may experience transient stinging or burning.

Ophthalmic: Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Open eye, look at ceiling, and instill prescribed amount of solution. Close eye and roll eye in all directions, and apply gentle pressure to inner corner of eye for 1-2 minutes after instillation. Temporary stinging or blurred vision may occur. Report persistent pain, burning, double vision, severe headache, or if condition worsens.

Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, rectal, as hydrochloride:

- Formulation R™: 0.25% (54 g) [contains sodium benzoate]

Filmstrip, orally disintegrating, as hydrochloride:

- Sudafed PE™: 10 mg (5s, 10s) [contains phenylalanine 1 mg/strip; cherry menthol flavor]
- Triaminic® Infant Thin Strips® Decongestant: 1.25 mg [mixed berry flavor] [DSC]
- Triaminic® Thin Strips® Cold: 2.5 mg [raspberry flavor]

Injection, solution, as hydrochloride: 1% [10 mg/mL] (1 mL, 5 mL, 10 mL) [may contain sodium metabisulfite]

- Neo-Synephrine®: 1% (1 mL) [contains sodium metabisulfite]

Liquid, oral, as hydrochloride:

- LuSonal™: 7.5 mg/5 mL (480 mL) [contains phenylalanine; strawberry flavor]

Liquid, oral, as hydrochloride [drops]:

- Dimetapp® Toddler's: 1.25 mg/0.8 mL (15 mL) [alcohol free; contains sodium benzoate; grape flavor]

Ointment, rectal, as hydrochloride:

- Formulation R™, Preparation H®: 0.25% (30 g, 60 g) [contains benzoic acid]
- Rectacaine: 0.25% (30 g)

Solution, intranasal, as hydrochloride [drops]:

- Little Noses® Decongestant: 0.125% (15 mL) [contains benzalkonium chloride]
- Neo-Synephrine® Extra Strength: 1% (15 mL) [contains benzalkonium chloride]
- Neo-Synephrine® Regular Strength: 0.5% (15 mL) [contains benzalkonium chloride]
- Rhinall: 0.25% (30 mL) [contains benzalkonium chloride and sodium bisulfite]
- Tur-bi-kal®: 0.17% (30 mL) [contains benzalkonium chloride]

Solution, intranasal, as hydrochloride [spray]:

- 4 Way® Fast Acting: 1% (15 mL, 30 mL) [contains benzalkonium chloride]
- 4 Way® Menthol: 1% (15 mL) [contains benzalkonium chloride and menthol]
- 4 Way® No Drip: 1% (15 mL) [contains benzalkonium chloride]
- Neo-Synephrine® Extra Strength: 1% (15 mL) [contains benzalkonium chloride]
- Neo-Synephrine® Mild: 0.25% (15 mL) [contains benzalkonium chloride]
- Neo-Synephrine® Regular Strength: 0.5% (15 mL) [contains benzalkonium chloride]
- Rhinall: 0.25% (40 mL) [contains benzalkonium chloride and sodium bisulfite]
- Vicks® Sinex®, Vicks® Sinex® UltraFine Mist: 0.5% (15 mL) [contains benzalkonium chloride]

Solution, ophthalmic, as hydrochloride: 2.5% (2 mL, 3 mL, 5 mL, 15 mL) [may contain sodium bisulfite]

- AK-Dilate®: 2.5% (2 mL, 15 mL); 10% (5 mL) [contains benzyl alcohol]

Altrafrin: 0.12% (15 mL) [OTC]; 2.5% (15 mL) [RX; contains benzalkonium chloride]; 10% (5 mL) [RX; contains benzalkonium chloride]

Mydfrin®: 2.5% (3 mL, 5 mL) [contains sodium bisulfite]

Neofrin™: 2.5% (15 mL); 10% (15 mL)

OcuNefrin™: 0.12% (15 mL)

Relief®: 0.12% (15 mL) [contains benzalkonium chloride] [DSC]

Suppository, rectal, as hydrochloride: 0.25% (12s)

Anu-Med: 0.25% (12s)

Formulation R™, Preparation H®: 0.25% (12s, 24s, 48s)

Medicone®, Tronolane®: 0.25% (12s, 24s)

Rectacaine: 0.25% (12s)

Suspension, oral, as tannate:

NāSop™: 7.5 mg/5 mL (120 mL) [orange flavor] [DSC]

Tablet, chewable, as tannate:

Nasop12™: 10 mg [grape flavor]

Tablet, as hydrochloride: 10 mg

Medi-Phenyl: 5 mg

Sudafed PE™: 10 mg

Tablet, orally dissolving, as hydrochloride:

NāSop™: 10 mg [contains phenylalanine 4 mg/tablet; bubble gum flavor] [DSC]

Generic AvailableYes: Excludes chewable tablet, cream, filmstrip, liquid, suspension

Pricing: U.S. (www.drugstore.com)

Solution (Mydfrin)

2.5% (5): $33.57

Solution (Neo-Synephrine)

2.5% (15): $35.99

Mechanism of ActionPotent, direct-acting alpha-adrenergic stimulator with weak beta-adrenergic activity; causes vasoconstriction of the arterioles of the nasal mucosa and conjunctiva; activates the dilator muscle of the pupil to cause contraction; produces vasoconstriction of arterioles in the body; produces systemic arterial vasoconstriction

Pharmacodynamics/Kinetics

Onset of action: I.M., SubQ: 10-15 minutes; I.V.: Immediate; Ophthalmic: 10-15 minutes

Duration: I.M.: 0.5-2 hours; I.V.: 15-30 minutes; SubQ: 1 hour; Ophthalmic: Maximal mydriasis: 1 hour, recover time: 3-6 hours

Metabolism: Hepatic, via intestinal monoamine oxidase to phenolic conjugates

Excretion: Urine (90%)

Related Information

- Hemodynamic Support, Intravenous

Pharmacotherapy PearlsPhenylephrine allows for close titration of blood pressure and should be used in patients with hypotension or shock due to peripheral vasodilation. Phenylephrine should not constitute sole therapy in patients with hypotension due to aortic dysfunction or hypovolemia. An important benefit of this drug is the short half-life, allowing rapid changes in dosage with prompt appropriate blood pressure responses. When administered intravenously, it should be used in intensive care settings or under very close monitoring.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tachycardia, palpitations (use vasoconstrictor with caution), and xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause anxiety or restlessness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with MAO inhibitors may result in hypertensive crisis; avoid combination

Cardiovascular Considerations

Hypotension in Patients With Hypertrophic Obstructive Cardiomyopathy (HOCM): Phenylephrine is the vasopressor of choice in these patients. Phenylephrine is a pure alpha$_1$ agonist that will cause vasoconstriction without increasing heart rate and contractility. This is advantageous in patients with HOCM because increases in both heart rate and contractility may cause the obstruction to become worse, leading to a decrease in cardiac output. Other vasopressors like dopamine, epinephrine, and norepinephrine may increase contractility and/or heart rate.

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Phenylephrine allows for close titration of blood pressure and may be used in patients with hypotension or shock due to peripheral vasodilation; can increase blood pressure in fluid-resuscitated septic shock patients; does not impair cardiac or renal function. May be a good choice when tachyarrhythmias limit use of other vasopressors, although experience in patients with septic shock is limited. An increase in oxygen delivery and consumption may occur in >15% of patients according to one study (Flancbaum, 1997).

Extravasation Management: Antidote for peripheral ischemia caused by phenylephrine extravasation: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 5-10 mg of Regitine® (phentolamine), an adrenergic blocking agent, diluted in 10-15 mL of saline. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted, as phentolamine may be ineffective if given >12 hours after extravasation.

Index TermsPhenylephrine Hydrochloride; Phenylephrine Tannate

References

Bonfiglio MF, Dasta JF, Gregory JS, et al, “High-Dose Phenylephrine Infusion in the Hemodynamic Support of Septic Shock,” *DICP*, 1990, 24(10):936-9. [PubMed 2244407]

Flancbaum L, Dick M, Dasta J, et al, “A Dose-Response Study of Phenylephrine in Critically Ill, Septic Surgical Patients,” *Eur J Clin Pharmacol*, 1997, 51(6):461-5. [PubMed 9112060]

Gregory JS, Bonfiglio MF, Dasta JF, et al, “Experience With Phenylephrine as a Component of the Pharmacologic Support of Septic Shock,” *Crit Care Med*, 1991, 19(11):1395-400.[PubMed 1935160]

International Brand Names Afrinex infantil (MX); Albalon Relief (AU); Analux (PL); Bregamin (MX); Bremagan Flu (MX); Coldaid (MX); Drosin (IN); Efrin-10 (IL); Efrisel (ID); Fenilefrina (BR); Flavit AV (MX); Fluviatol NF (MX); Isonefrine (PK); Isopto Frin (AU, EC); Metaoxedrin (DK, NO); Minims Phenylephrine HCL 10% (ZA); Minims Phenylephrine Hydrochloride (GB, IE); Mydfrin (AE, AR, BG, BH, CN, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, MY, OM, PH, PY, QA, SA, SY, UY, YE); Neo-Synephrine (PL); Neo-Synephrine Ophthalmic (BE, DE); Neosinicin (TW); Neosynephrine Faure 10% (FR); Oftan-Metaoksedrin (FI); Optistin (IT); Phenylephrine (NL); Prefrin (AE, AT, AU, BH, CY, EC, EG, HK, ID, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, TH, YE, ZA)

Phenytoin

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Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Phenytoin and Fosphenytoin: Genetic Susceptibility to Serious Skin Reactions - November 2008

The U.S. Food and Drug Administration (FDA) is notifying healthcare professionals of preliminary information concerning the potential for serious skin reactions in susceptible patients treated with phenytoin (or fosphenytoin). Data suggests that patients testing positive for the human leukocyte antigen (HLA) allele *HLA-B*1502* have an increased risk of developing Stevens-Johnson syndrome (SJS) and/or toxic epidermal necrolysis (TEN). The risk appears to be highest in the early months of therapy initiation. The presence of this genetic variant exists in up to 15% of people of Asian descent in China, Thailand, Malaysia, Indonesia, Taiwan, and the Philippines, and may vary from <1% in Japanese and Koreans, to 2% to 4% of South Asians and Indians. This variant is virtually absent in those of Caucasian, African-American, Hispanic, or European ancestry. Of note, carbamazepine, another antiepileptic with a chemical structure similar to phenytoin, updated its prescribing information (December 2007) to include a warning of an increased risk of SJS and TEN in patients carrying the *HLA-B*1502* allele and a recommendation to screen patients of Asian descent for the allele prior to initiating therapy. In contrast to carbamazepine, the FDA is not recommending testing for the presence of *HLA-B*1502* prior to initiating phenytoin therapy until more information is available. In the interim, the FDA is advising that prescribers avoid phenytoin or fosphenytoin as alternatives to carbamazepine therapy in patients positive for *HLA-B*1502*.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Phenytoin

Medication Safety Issues

Sound-alike/look-alike issues:

Phenytoin may be confused with phenelzine, phentermine

Dilantin® may be confused with Dilaudid®, diltiazem, Dipentum®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V. formulation) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

International issues:

Dilantin® may be confused with Dolantine® which is a brand name for pethidine in Belgium and Switzerland

Pronunciation(FEN i toyn)

U.S. Brand Names Dilantin®; Phenytek®

Canadian Brand Names Dilantin®

Pharmacologic Category Antiarrhythmic Agent, Class Ib; Anticonvulsant, Hydantoin

Use: Labeled Indications Management of generalized tonic-clonic (grand mal), complex partial seizures; prevention of seizures following head trauma/neurosurgery

Dosing: Adults

Status epilepticus: I.V.: Loading dose: Manufacturer recommends 10-15 mg/kg, however, 15-20 mg/kg is generally recommended; maximum rate: 50 mg/minute

Anticonvulsant: Oral: Loading dose: 15-20 mg/kg; based on phenytoin serum concentrations and recent dosing history; administer oral loading dose in 3 divided doses given every 2-4 hours to decrease GI adverse effects and to ensure complete oral absorption; maintenance dose: 300 mg/day or 5-6 mg/kg/day in 3 divided doses or 1-2 divided doses using extended release (range 200-1200 mg/day)

Dosage adjustment in obesity: Loading dose: Use adjusted body weight (ABW) (Abernethy, 1985)

ABW = [(Actual body weight – IBW) x 1.33] + IBW

Maximum loading dose: 2000 mg (Erstad, 2004)

Maintenance doses should be based on ideal body weight, conventional daily doses with adjustments based upon therapeutic drug monitoring and clinical effectiveness. (Abernethy, 1985; Erstad, 2002; Erstad, 2004)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Status epilepticus: I.V.:

Infants and Children: Loading dose: 15-20 mg/kg in a single or divided dose; maintenance dose: Initial: 5 mg/kg/day in 2 divided doses, usual doses:

6 months to 3 years: 8-10 mg/kg/day

4-6 years: 7.5-9 mg/kg/day

7-9 years: 7-8 mg/kg/day

10-16 years: 6-7 mg/kg/day, some patients may require every 8 hours dosing

Anticonvulsant: Children: Oral: Refer to adult dosing.

Dosing: Renal ImpairmentPhenytoin level in serum may be difficult to interpret in renal failure. Monitoring of free (unbound) concentrations or adjustment to allow interpretation is recommended.

Dosing: Hepatic ImpairmentSafe in usual doses in mild liver disease; clearance may be substantially reduced in cirrhosis and plasma level monitoring with dose adjustment advisable. Free phenytoin levels should be monitored closely.

Calculations

- Phenytoin, Corrected Serum

Administration: I.M.Although approved for I.M. use, I.M. administration is not recommended due to erratic absorption and pain on injection. Fosphenytoin may be considered.

Administration: I.V.Vesicant. Fosphenytoin may be considered for loading in patients who are in status epilepticus, hemodynamically unstable or develop hypotension/bradycardia with I.V. administration of phenytoin. Phenytoin may be administered by IVP or IVPB administration. The maximum rate of I.V. administration is 50 mg/minute. Highly sensitive patients (eg, elderly, patients with pre-existing cardiovascular conditions) should receive phenytoin more slowly (eg, 20 mg/minute).

Administration: I.V. DetailAn in-line 0.22-5 micron filter is recommended for IVPB solutions due to the high potential for precipitation of the solution. Avoid extravasation. Following I.V. administration, NS should be injected through the same needle or I.V. catheter to prevent irritation.

pH: 10.0-12.3

Administration: OralSuspension: Shake well prior to use. Absorption is impaired when phenytoin suspension is given concurrently to patients who are receiving continuous nasogastric feedings. A method to resolve this interaction is to divide the daily dose of phenytoin and withhold the administration of nutritional supplements for 1-2 hours before and after each phenytoin dose.

Administration: OtherSubQ administration is not recommended because of the possibility of local tissue damage (due to high pH).

Dietary Considerations

Folic acid: Phenytoin may decrease mucosal uptake of folic acid; to avoid folic acid deficiency and megaloblastic anemia, some clinicians recommend giving patients on anticonvulsants prophylactic doses of folic acid and cyanocobalamin. However, folate supplementation may increase seizures in some patients (dose dependent). Discuss with healthcare provider prior to using any supplements.

Calcium: Hypocalcemia has been reported in patients taking prolonged high-dose therapy with an anticonvulsant. Some clinicians have given an additional 4000 units/week of vitamin D (especially in those receiving poor nutrition and getting no sun exposure) to prevent hypocalcemia.

Vitamin D: Phenytoin interferes with vitamin D metabolism and osteomalacia may result; may need to supplement with vitamin D

Tube feedings: Tube feedings decrease phenytoin absorption. To avoid decreased serum levels with continuous NG feeds, hold feedings for 1-2 hours prior to and 1-2 hours after phenytoin administration, if possible. There is a variety of opinions on how to administer phenytoin with enteral feedings. Be **consistent** throughout therapy.

Sodium content of 1 g injection: 88 mg (3.8 mEq)

Storage

Capsule, tablet: Store below 30°C (86°F). Protect from light and moisture.

Oral suspension: Store at room temperature of 20°C to 25°C (68°F to 77°F); do not freeze. Protect from light.

Solution for injection: Store at room temperature of 15°C to 30°C (59°F to 86°F). Use only clear solutions free of precipitate and haziness; slightly yellow solutions may be used. Precipitation may occur if solution is refrigerated and may dissolve at room temperature.

ReconstitutionI.V.: Further dilution of the solution for I.V. infusion is controversial and no consensus exists as to the optimal concentration and length of stability. Stability is concentration and pH dependent. Based on limited clinical consensus, NS or LR are recommended diluents; dilutions of 1-10 mg/mL have been used and should be administered as soon as possible after preparation (some recommend to discard if not used within 4 hours). Do not refrigerate.

Compatibility**Incompatible** in D_5NS, D_5W, fat emulsion 10%, $^1/_2$NS; **variable stability (consult detailed reference)** in NS

Y-site administration: Compatible: Esmolol, famotidine, fluconazole, foscarnet, tacrolimus. **Incompatible:** Amphotericin B cholesteryl sulfate complex, ciprofloxacin, clarithromycin, diltiazem, enalaprilat, gatifloxacin, heparin, heparin with hydrocortisone sodium succinate, hydromorphone, linezolid, potassium chloride, propofol, sufentanil, theophylline, vitamin B complex with C. **Variable (consult detailed reference):** TPN.

Compatibility in syringe: Incompatible: Hydromorphone, sufentanil.

Compatibility when admixed: Compatible: Bleomycin, sodium bicarbonate, verapamil. **Incompatible:** Amikacin, aminophylline, bretylium, chloramphenicol, dimenhydrinate, diphenhydramine, dobutamine, hydroxyzine, insulin (regular), kanamycin, levorphanol, lidocaine, lincomycin, meperidine, metaraminol, morphine, nitroglycerin, norepinephrine, penicillin G potassium, pentobarbital, phenobarbital, phenylephrine, phytonadione, procainamide, procaine, prochlorperazine edisylate, promazine, promethazine, streptomycin, vancomycin, vitamin B complex with C.

ContraindicationsHypersensitivity to phenytoin, other hydantoins, or any component of the formulation; pregnancy

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Blood dyscrasias: A spectrum of hematologic effects have been reported with use (eg, neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias); patients with a previous history of adverse hematologic reaction to any drug may be at increased risk. Early detection of hematologic change is important; advise patients of early signs and symptoms including fever, sore throat, mouth ulcers, infections, easy bruising, petechial or purpuric hemorrhage.

- Dermatologic reactions: Severe reactions, including toxic epidermal necrolysis and Stevens-Johnson syndromes, although rarely reported, have resulted in fatalities; drug should be discontinued if there are any signs of rash. Data suggests a genetic susceptibility for serious skin reactions in patients of Asian descent (see "Special populations" below).

- Hypersensitivity syndrome: Acute hepatotoxicity associated with a hypersensitivity syndrome characterized by fever, skin eruptions, and lymphadenopathy has been reported to occur within the first 2 months of treatment; discontinue if skin rash or lymphadenopathy occurs.

- Osteomalacia: Has been reported.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with sinus bradycardia, SA block, or AV block.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Hypoalbuminemia: Use with caution in patients with any condition associated with low serum albumin levels, which will increase the free fraction of phenytoin in the serum and, therefore, the pharmacologic response.

- Porphyria: Use with caution in patients with porphyria.

- Seizures: May increase frequency of petit mal seizures.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Asian ancestry: Asian patients with the variant *HLA-B*1502* may be at an increased risk of developing Stevens-Johnson syndrome and/or toxic epidermal necrolysis.

- Debilitated patients: Use with caution in patients who are debilitated.

- Elderly: Use with caution in the elderly.

Dosage form specific issues:

- Injectable: I.V. form may cause hypotension, skin necrosis at I.V. site; avoid I.V. administration in small veins.

Other warnings/precautions:

- Serum levels: Sedation, confusional states, or cerebellar dysfunction (loss of motor coordination) may occur at higher total serum concentrations, or at lower total serum concentrations when the free fraction of phenytoin is increased.

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsElderly may have reduced hepatic clearance due to age decline in phase I metabolism. Elderly may have low albumin which will increase free fraction and, therefore, pharmacologic response. Monitor closely in those who are hypoalbuminemic. Free fraction measurements advised, also elderly may display a higher incidence of adverse effects (cardiovascular) when using the I.V. loading regimen; therefore, recommended to decrease loading I.V. dose to 25 mg/minute.

Pregnancy Risk FactorD

Pregnancy ConsiderationsPhenytoin crosses the placenta. Congenital malformations (including a pattern of malformations termed the “fetal hydantoin syndrome” or “fetal anticonvulsant syndrome”) have been reported in infants. Isolated cases of malignancies (including neuroblastoma) and coagulation defects in the neonate following delivery have also been reported. Epilepsy itself, the number of medications, genetic factors, or a combination of these probably influence the teratogenicity of anticonvulsant therapy.

Total plasma concentrations of phenytoin are decreased by 56% in the mother during pregnancy; unbound plasma (free) concentrations are decreased by 31%. Because protein binding is decreased, monitoring of unbound plasma concentrations is recommended. Concentrations should be monitored through the 8th week postpartum. The use of folic acid throughout pregnancy and vitamin K during the last month of pregnancy is recommended.

A pregnancy registry is available for women exposed to antiepileptic drug (including phenytoin) at the Genetics and Teratology Unit Massachusetts General Hospital, 1-888-233-2334.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsPhenytoin is excreted in breast milk; however, the amount to which the infant is exposed is considered small. The manufacturers of phenytoin do not recommend breast-feeding during therapy, however, the AAP considers it to be usually compatible. Women should be counseled of the possible risks and benefits associated with breast-feeding while on phenytoin.

Adverse ReactionsI.V. effects: Hypotension, bradycardia, cardiac arrhythmia, cardiovascular collapse (especially with rapid I.V. use), venous irritation and pain, thrombophlebitis

Effects not related to plasma phenytoin concentrations: Hypertrichosis, gingival hypertrophy, thickening of facial features, carbohydrate intolerance, folic acid deficiency, peripheral neuropathy, vitamin D deficiency, osteomalacia, systemic lupus erythematosus

Concentration-related effects: Nystagmus, blurred vision, diplopia, ataxia, slurred speech, dizziness, drowsiness, lethargy, coma, rash, fever, nausea, vomiting, gum tenderness, confusion, mood changes, folic acid depletion, osteomalacia, hyperglycemia

Related to elevated concentrations:

>20 mcg/mL: Far lateral nystagmus

>30 mcg/mL: 45° lateral gaze nystagmus and ataxia

>40 mcg/mL: Decreased mentation

>100 mcg/mL: Death

Cardiovascular: Hypotension, bradycardia, cardiac arrhythmia, cardiovascular collapse

Central nervous system: Psychiatric changes, slurred speech, dizziness, drowsiness, headache, insomnia

Dermatologic: Rash

Gastrointestinal: Constipation, nausea, vomiting, gingival hyperplasia, enlargement of lips

Hematologic: Leukopenia, thrombocytopenia, agranulocytosis

Hepatic: Hepatitis

Local: Thrombophlebitis

Neuromuscular & skeletal: Tremor, peripheral neuropathy, paresthesia

Ocular: Diplopia, nystagmus, blurred vision

Rarely seen effects: Blood dyscrasias, coarsening of facial features, dyskinesias, hepatitis, hypertrichosis, lymphadenopathy, lymphoma, pseudolymphoma, SLE-like syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, venous irritation and pain

Metabolism/Transport Effects**Substrate** of CYP2C9 (major), 2C19 (major), 3A4 (minor); **Induces** CYP2B6 (strong), 2C8 (strong), 2C9 (strong), 2C19 (strong), 3A4 (strong)

Drug Interactions

Acetaminophen: Anticonvulsants (Hydantoin) may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Aminocamptothecin: Phenytoin may decrease the serum concentration of Aminocamptothecin. *Risk C: Monitor therapy*

Amiodarone: Phenytoin may increase the metabolism of Amiodarone. Amiodarone may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Amphetamines: May decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Amprenavir: Phenytoin may increase the serum concentration of Amprenavir. Amprenavir may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Phenytoin. Phenytoin may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Benzodiazepines: May increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. **Exceptions:** ALPRAZolam. *Risk C: Monitor therapy*

Calcium Channel Blockers: May decrease the metabolism of Phenytoin. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Capecitabine: May increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Phenytoin. Phenytoin may increase the metabolism of CarBAMazepine. CarBAMazepine may decrease the metabolism of Phenytoin. Possibly by competitive inhibition at sites of metabolism. *Risk D: Consider therapy modification*

Carbonic Anhydrase Inhibitors: May enhance the adverse/toxic effect of Anticonvulsants (Hydantoin). Specifically, osteomalacia and rickets. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Caspofungin: Inducers of Drug Clearance may decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) when coadministered with known inducers of drug clearance. *Risk D: Consider therapy modification*

Chloramphenicol: May decrease the metabolism of Anticonvulsants (Hydantoin). Anticonvulsants (Hydantoin) may decrease the serum concentration of Chloramphenicol. Increased chloramphenicol concentrations have also been seen. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Anticonvulsants (Hydantoin). *Risk D: Consider therapy modification*

Ciprofloxacin: May decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Clozapine: Phenytoin may increase the metabolism of Clozapine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Colesevelam: May decrease the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Contraceptive (Progestins): Phenytoin may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

CycloSPORINE: Phenytoin may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2B6 Substrates: CYP2B6 Inducers (Strong) may increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C19 Substrates: CYP2C19 Inducers (Strong) may increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inducers (Highly Effective) may increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inducers (Highly Effective) may increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Darunavir: Phenytoin may decrease the serum concentration of Darunavir. *Risk X: Avoid combination*

Dexmethylphenidate: May decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Diazoxide: May decrease the serum concentration of Phenytoin. Total phenytoin concentrations may be affected more than free phenytoin concentrations. *Risk C: Monitor therapy*

Disopyramide: Phenytoin may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Disulfiram: May decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Doxycycline: Phenytoin may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Efavirenz: Phenytoin may decrease the serum concentration of Efavirenz. Efavirenz may increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Etoposide: Phenytoin may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Phenytoin may decrease the serum concentration of Etoposide Phosphate. Phenytoin may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Etravirine: Phenytoin may decrease the serum concentration of Etravirine. Management: The manufacturer of etravirine states these drugs should not be used in combination *Risk X: Avoid combination*

Felbamate: Phenytoin may increase the metabolism of Felbamate. Felbamate may increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Floxuridine: May increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Fluconazole: May decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Flunarizine: Phenytoin may decrease the serum concentration of Flunarizine. *Risk C: Monitor therapy*

Fluorouracil: May increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Folic Acid: May decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Fosamprenavir: May decrease the serum concentration of Phenytoin. The active amprenavir metabolite is likely responsible for this effect. Phenytoin may increase the serum concentration of Fosamprenavir. Specifically, phenytoin may increase the concentration of the active metabolite amprenavir. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Phenytoin may increase the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Rosuvastatin. *Risk D: Consider therapy modification*

Irinotecan: Phenytoin may increase the metabolism of Irinotecan. *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Lacosamide: Phenytoin may decrease the serum concentration of Lacosamide. *Risk C: Monitor therapy*

LamoTRIgine: Phenytoin may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Leucovorin-Levoleucovorin: May decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Levodopa: Phenytoin may diminish the therapeutic effect of Levodopa. *Risk C: Monitor therapy*

Lithium: Phenytoin may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Loop Diuretics: Phenytoin may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Lopinavir: Phenytoin may decrease the serum concentration of Lopinavir. Lopinavir may decrease the serum concentration of Phenytoin. Management: The manufacturer of lopinavir/ritonavir recommends avoiding once-daily administration if used together with phenytoin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mebendazole: Phenytoin may decrease the serum concentration of Mebendazole. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Meperidine: Phenytoin may increase the metabolism of Meperidine. *Risk C: Monitor therapy*

Methadone: Phenytoin may increase the metabolism of Methadone. *Risk C: Monitor therapy*

Methylfolate: May decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Methylphenidate: May decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Metyrapone: Phenytoin may increase the metabolism of Metyrapone. The oral metyrapone test would thus be unreliable unless the metapyrone dosage was substantially increased (eg, 750 mg every 2 hours). *Risk D: Consider therapy modification*

Mexiletine: Phenytoin may increase the metabolism of Mexiletine. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Phenytoin may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

OXcarbazepine: Phenytoin may decrease the serum concentration of OXcarbazepine. OXcarbazepine may increase the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Primidone: Phenytoin may increase the metabolism of Primidone. The ratio of primidone:phenobarbital is thus changed. *Risk C: Monitor therapy*

Proton Pump Inhibitors: May increase the serum concentration of Phenytoin. **Exceptions:** Esomeprazole; Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Pyridoxine: May increase the metabolism of Phenytoin. This is most apparent in high pyridoxine doses (eg, 80 mg to 200 mg daily) *Risk C:*

Monitor therapy

QUEtiapine: Phenytoin may increase the metabolism of QUEtiapine. *Risk D: Consider therapy modification*

QuiNIDine: Phenytoin may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Ritonavir: Phenytoin may decrease the serum concentration of Ritonavir. Ritonavir may decrease the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Rufinamide: May increase the serum concentration of Phenytoin. Phenytoin may decrease the serum concentration of Rufinamide. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Phenytoin. **Exceptions:** PARoxetine. *Risk D: Consider therapy modification*

Sirolimus: Phenytoin may increase the metabolism of Sirolimus. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Tacrolimus: Phenytoin may increase the metabolism of Tacrolimus. Tacrolimus may increase the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Temsirolimus: Phenytoin may decrease the serum concentration of Temsirolimus. Concentrations of the active metabolite, sirolimus, are also likely to be decreased (and maybe to an even greater degree). Management: Temsirolimus prescribing information recommends against coadministration with strong CYP3A4 inducers such as phenytoin; however, if concurrent therapy is necessary, an increase in temsirolimus dose to 50 mg/week should be considered. *Risk D: Consider therapy modification*

Teniposide: Phenytoin may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Phenytoin may increase the metabolism of Theophylline Derivatives. Theophylline Derivatives may decrease the serum concentration of Phenytoin. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Thyroid Products: Phenytoin may increase the metabolism of Thyroid Products. Phenytoin may also displace thyroid hormones from protein binding sites. *Risk C: Monitor therapy*

Ticlopidine: May decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Tipranavir: Phenytoin may decrease the serum concentration of Tipranavir. Tipranavir may decrease the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Topiramate: May decrease the metabolism of Phenytoin. Phenytoin may increase the metabolism of Topiramate. *Risk C: Monitor therapy*

Trimethoprim: May decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Valproic Acid: Phenytoin may increase the metabolism of Valproic Acid. A hepatotoxic metabolite of valproic acid may result. Valproic Acid may decrease the serum concentration of Phenytoin. Continued therapy usually yields a normalization (or slight increase) of serum phenytoin concentrations. Free phenytoin concentrations, however, tend to remain relatively stable (possibly increased with continued therapy). *Risk C: Monitor therapy*

Vecuronium: Phenytoin may decrease the serum concentration of Vecuronium. *Risk C: Monitor therapy*

Vigabatrin: May decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Phenytoin may enhance the anticoagulant effect of Vitamin K Antagonists. Vitamin K Antagonists may increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Zonisamide: Phenytoin may increase the metabolism of Zonisamide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol:

Acute use: Avoid or limit ethanol (inhibits metabolism of phenytoin). Watch for sedation.

Chronic use: Avoid or limit ethanol (stimulates metabolism of phenytoin).

Food: Phenytoin serum concentrations may be altered if taken with food. If taken with enteral nutrition, phenytoin serum concentrations may be decreased. Tube feedings decrease bioavailability; hold tube feedings 1-2 hours before and 1-2 hours after phenytoin administration. May decrease calcium, folic acid, and vitamin D levels.

Herb/Nutraceutical: Avoid evening primrose (seizure threshold decreased). Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersBlood pressure, vital signs (with I.V. use); plasma phenytoin level, CBC, liver function. **Note:** If available, free phenytoin concentrations should be obtained in patients with renal impairment and/or hypoalbuminemia. If free phenytoin levels are unavailable, the adjusted total level is based upon equations in adult patients.

Reference RangeTiming of serum samples: Because it is slowly absorbed, peak blood levels may occur 4-8 hours after ingestion of an oral dose. The serum half-life varies with the dosage and the drug follows Michaelis-Menten kinetics. The average adult half-life is about 24 hours. Steady-state concentrations are reached in 5-10 days.

Children and Adults: Toxicity is measured clinically, and some patients require levels outside the suggested therapeutic range

Therapeutic range:

Total phenytoin: 10-20 mcg/mL (children and adults), 8-15 mcg/mL (neonates)

Concentrations of 5-10 mcg/mL may be therapeutic for some patients but concentrations <5 mcg/mL are not likely to be effective

50% of patients show decreased frequency of seizures at concentrations >10 mcg/mL

86% of patients show decreased frequency of seizures at concentrations >15 mcg/mL

Add another anticonvulsant if satisfactory therapeutic response is not achieved with a phenytoin concentration of 20 mcg/mL

Free phenytoin: 1-2.5 mcg/mL

Total phenytoin:

Toxic: >30 mcg/mL (SI: <120-200 µmol/L)

Lethal: >100 mcg/mL (SI: >400 µmol/L)

When to draw levels: This is dependent on the disease state being treated and the clinical condition of the patient

Key points:

Slow absorption of extended capsules and prolonged half-life minimize fluctuations between peak and trough concentrations, timing of sampling not crucial

Trough concentrations are generally recommended for routine monitoring. Daily levels are not necessary and may result in incorrect dosage adjustments. If it is determined essential to monitor free phenytoin concentrations, concomitant monitoring of total phenytoin concentrations is not necessary and expensive.

After a loading dose: If rapid therapeutic levels are needed, initial levels may be drawn after 1 hour (I.V. loading dose) or within 24 hours (oral loading dose) to aid in determining maintenance dose or need to reload.

Rapid achievement: Draw within 2-3 days of therapy initiation to ensure that the patient's metabolism is not remarkably different from that which would be predicted by average literature-derived pharmacokinetic parameters; early levels should be used cautiously in design of new dosing regimens

Second concentration: Draw within 6-7 days with subsequent doses of phenytoin adjusted accordingly

If plasma concentrations have not changed over a 3- to 5-day period, monitoring interval may be increased to once weekly in the acute clinical setting

In stable patients requiring long-term therapy, generally monitor levels at 3- to 12-month intervals

Adjustment of serum concentration: See tables.

Note: Although it is ideal to obtain free phenytoin concentrations to assess serum concentrations in patients with hypoalbuminemia or renal failure (Cl_{cr} ≤10 mL/minute), it may not always be possible. If free phenytoin concentrations are unavailable, the following equations may be utilized in adult patients.

Adjustment of Serum Concentration in Adults With Low Serum Albumin

Measured Total Phenytoin Concentration (mcg/mL)	**Patient's Serum Albumin (g/dL)**			
	3.5	**3**	**2.5**	**2**
	Adjusted Total Phenytoin Concentration (mcg/mL)[1]			
5	6	7	8	10
10	13	14	17	20
15	19	21	25	30

[1] Adjusted concentration = measured total concentration divided by [(0.2 x albumin) + 0.1].

Adjustment of Serum Concentration in Adults With Renal Failure (Cl_{cr} ≤10 mL/min)

Measured Total Phenytoin Concentration (mcg/mL)	Patient's Serum Albumin (g/dL)				
	4	3.5	3	2.5	2
	Adjusted Total Phenytoin Concentration (mcg/mL)[1]				
5	10	11	13	14	17
10	20	22	25	29	33
15	30	33	38	43	50

[1] Adjusted concentration = measured total concentration divided by [(0.1 x albumin) + 0.1].

Nursing: Physical Assessment/MonitoringAssess potential for numerous interactions with other prescriptions, OTC medications, or herbal products patient may be taking (see extensive list of Drug Interactions). Assess results of laboratory tests, therapeutic effectiveness, and adverse response when beginning therapy and at regular intervals during treatment. When discontinuing oral formulation, taper dose gradually; abrupt discontinuance can cause status epilepticus. Teach patient proper use (oral), side effects/appropriate interventions, and adverse symptoms to report. **I.V.:** Monitor blood pressure. Infusion site should be monitored closely (vesicant). Patient should be monitored closely for adverse/toxic results.

Monitoring: Lab TestsPlasma phenytoin level, CBC, liver function. **Note:** If available, free phenytoin concentrations should be obtained in patients with renal impairment and/or hypoalbuminemia. If free phenytoin levels are unavailable, the adjusted total level is based upon equations in adult patients.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take exactly as directed, preferably on an empty stomach. Do not alter dose or discontinue without consulting prescriber. Do not crush, break, or chew extended release capsules. Shake liquid suspension well before using. Follow recommended diet, avoid alcohol, and maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause gum or mouth soreness (use good oral hygiene and have frequent dental exams); drowsiness, dizziness, nervousness, or headache (use caution when driving or engaging in tasks that require alertness until response to drug is known); or nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report chest pain, irregular heartbeat, or palpitations; slurred speech, unsteady gait, coordination difficulties, or change in mentation; skin rash; unresolved nausea, vomiting, or constipation; swollen glands; swollen, sore, or bleeding gums; unusual bruising or bleeding; acute persistent fatigue; vision changes; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Do not get pregnant; use contraceptive measures to prevent possible harm to the fetus (effectiveness of oral contraceptives may be affected by phenytoin). Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release, as sodium: 100 mg

Dilantin®: 30 mg [contains sodium benzoate], 100 mg

Phenytek®: 200 mg, 300 mg

Capsule, prompt release, as sodium: 100 mg

Injection, solution, as sodium: 50 mg/mL (2 mL, 5 mL) [contains alcohol and propylene glycol]

Suspension, oral: 100 mg/4 mL (4 mL); 125 mg/5 mL (240 mL)

Dilantin®: 125 mg/5 mL (240 mL) [contains alcohol <0.6%, sodium benzoate; orange vanilla flavor]

Tablet, chewable:

Dilantin®: 50 mg

Generic AvailableYes: Excludes chewable tablet

Pricing: U.S. (www.drugstore.com)

Capsules (Dilantin)

30 mg (90): $39.99

100 mg (90): $41.99

Capsules (Phenytek)

200 mg (30): $33.62

300 mg (30): $41.98

300 mg (100): $118.60

Capsules (Phenytoin Sodium Extended)

100 mg (90): $31.99

Capsules (Phenytoin Sodium Prompt)

100 mg (100): $25.99

Chewable (Dilantin Infatabs)

50 mg (90): $46.99

Suspension (Dilantin)

125 mg/5 mL (237): $59.99

Suspension (Phenytoin)

125 mg/5 mL (237): $28.99

Mechanism of ActionStabilizes neuronal membranes and decreases seizure activity by increasing efflux or decreasing influx of sodium ions across cell membranes in the motor cortex during generation of nerve impulses; prolongs effective refractory period and suppresses ventricular pacemaker automaticity, shortens action potential in the heart

Pharmacodynamics/Kinetics

Onset of action: I.V.: ~0.5-1 hour

Absorption: Oral: Slow

Distribution: V_d:

Neonates: Premature: 1-1.2 L/kg; Full-term: 0.8-0.9 L/kg

Infants: 0.7-0.8 L/kg

Children: 0.7 L/kg

Adults: 0.6-0.7 L/kg

Protein binding:

Neonates: ≥80% (≤20% free)

Infants: ≥85% (≤15% free)

Adults: 90% to 95%

Others: Decreased protein binding

Disease states resulting in a decrease in serum albumin concentration: Burns, hepatic cirrhosis, nephrotic syndrome, pregnancy, cystic fibrosis

Disease states resulting in an apparent decrease in affinity of phenytoin for serum albumin: Renal failure, jaundice (severe), other drugs (displacers), hyperbilirubinemia (total bilirubin >15 mg/dL), Cl_{cr} <25 mL/minute (unbound fraction is increased two- to threefold in uremia)

Metabolism: Follows dose-dependent capacity-limited (Michaelis-Menten) pharmacokinetics with increased V_{max} in infants >6 months of age and children versus adults; major metabolite (via oxidation), HPPA, undergoes enterohepatic recirculation

Bioavailability: Form dependent

Half-life elimination: Oral: 22 hours (range: 7-42 hours)

Time to peak, serum (form dependent): Oral: Extended-release capsule: 4-12 hours; Immediate release preparation: 2-3 hours

Excretion: Urine (<5% as unchanged drug); as glucuronides

Clearance: Highly variable, dependent upon intrinsic hepatic function and dose administered; increased clearance and decreased serum concentrations with febrile illness

Related Information

- Anticonvulsant Drugs of Choice
- Status Epilepticus

Dental Health: Effects on Dental TreatmentGingival hyperplasia is a common problem observed during the first 6 months of phenytoin therapy appearing as gingivitis or gum inflammation. To minimize severity and growth rate of gingival tissue begin a program of professional cleaning and patient plaque control within 10 days of starting anticonvulsant therapy.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Anesthesia and Critical Care Concerns/Other ConsiderationsBecause phenytoin induces the metabolism of many drugs, it may alter their effective blood concentration.

The vehicle which contains propylene glycol and ethanol may cause hypotension, bradycardia, arrhythmias, or asystole refractory to defibrillation. Phenytoin 50 mg/mL contains propylene glycol 414.4 mg/mL (40% v/v). Rapid intravenous administration may cause hypotension. Infuse at a rate no greater than 50 mg/minute in adults and 25 mg/minute in the elderly.

Patients on chronic phenytoin therapy require larger and more frequent doses of nondepolarizing muscle relaxants to attain the same degree of muscle relaxation. This is probably due to increased levels of alpha$_1$-acid glycoprotein released by the liver (which bind free phenytoin) during hepatic enzyme induction.

Status Epilepticus: A randomized, double-blind trial (Treiman, 1998) evaluated the efficacy of four treatments in overt status epilepticus. Treatment arms were designed based upon accepted practices of North American neurologists. The treatments were: 1) lorazepam 0.1 mg/kg, 2) diazepam 0.15 mg/kg followed by phenytoin 18 mg/kg, 3) phenytoin 18 mg/kg alone, and 4) phenobarbital 15 mg/kg. Treatment was considered successful if the seizures were terminated (clinically and by EEG) within 20 minutes of start of therapy without seizure recurrence within 60 minutes from the start of therapy. Patients who failed the first treatment received a second and a third, if necessary. Patients did not receive randomized treatments after the first one but the treating physician remained blinded. Treatment success: Lorazepam 64.9%, phenobarbital 58.2%, diazepam/phenytoin 55.8%, and phenytoin alone 43.6%. Using an intention to treat analysis, there was no statistical difference between the groups. Results of subsequent treatments in patients who failed the first therapy indicated that response rate significantly dropped regardless of treatment. Aggregate response rate to the second treatment was 7.0% and third treatment 2.3%.

Index Terms Diphenylhydantoin; DPH; Phenytoin Sodium; Phenytoin Sodium, Extended; Phenytoin Sodium, Prompt

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International Brand NamesAleviatin (JP, TW); Antisacer (PT); Aurantin (IT); Clerin (PY); Clerin LR (PY); Cumatil (CO); Di-Hydan (BE, FR, LU); Difetoin (HR); Dilantin (AU, FR, HK, ID, IN, MY, PH, PK, TH, VE); Dintoina (IT); Diphantoine (BE, NL); Diphantoine Z (NL); Diphedan (HU); Ditoin (HK, MY, TH); Ditomed (TH); Epamin (AR, BO, BR, CN, CO, CR, DO, EC, GT, HN, MX, NI, PA, PE, PR, PY, SV, UY, VE); Epanutin (AE, AT, BE, BF, BH, BJ, CI, CY, CZ, DE, EG, ES, ET, FI, GB, GH, GM, GN, GR, HN, HU, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SE, SL, SN, SY, TN, TR, TZ, UG, UY, YE, ZA, ZM, ZW); Epanutin [caps] (PL); Epilan-D (AT, BG, CZ); Epilantin (PH); Epileptin (TW); Epinat (NO); Eptoin (IN); Felantin (PE); Fenatoin NM (SE); Fenidantoin S (MX); Fenitoina (ES); Fenitoina Rubio (ES); Fenitoina Sodica (IT); Fenitron (MX); Fenytoin (DE, DK); Fomiken (MX); Hidanil (CO); Hidantoína (MX); Hydantin (FI, TW); Hydantol (JP); Ikaphen (ID); Kutoin (ID); Lantidin (PH); Lehydan (SE); Movileps (ID); Neosidantoina (ES); Pepsytoin-100 (TH); Phenhydan (AT, CH, DE, EE, HU, LU); Phenilep (ID); Phenytoin KP (TH); Phenytoinum (PL); Pyoredol (AR, FR); Sinergina (ES); Utoin (TH)

Physostigmine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Physostigmine may be confused with Prostigmin®, pyridostigmine

Pronunciation(fye zoe STIG meen)

Canadian Brand NamesEserine®; Isopto® Eserine

Pharmacologic CategoryAcetylcholinesterase Inhibitor

Use: Labeled IndicationsReverse toxic, life-threatening delirium caused by atropine, diphenhydramine, dimenhydrinate, *Atropa belladonna* (deadly nightshade), or jimson weed (*Datura* spp)

Dosing: Adults**Reversal of toxic anticholinergic effects: Note:** Administer slowly over 5 minutes to prevent respiratory distress and seizures. Continuous infusions of physostigmine should never be used.

I.M., I.V.: 0.5-2 mg to start; repeat every 20 minutes until response occurs or adverse effect occurs; repeat 1-4 mg every 30-60 minutes as life-threatening symptoms recur

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Reversal of toxic anticholinergic effects** (reserve for life-threatening situations only): **Note:** Administer slowly over 5 minutes to prevent respiratory distress and seizures. Continuous infusions of physostigmine should never be used.

I.V.: 0.01-0.03 mg/kg/dose. May repeat after 5-10 minutes to a maximum total dose of 2 mg or until response occurs or adverse cholinergic effects occur.

Administration: I.V.Infuse slowly I.V. over 5 minutes. Too rapid administration can cause bradycardia and hypersalivation leading to respiratory distress and seizures.

StorageDo not use solution if cloudy or dark brown.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5W, $D_{10}W$, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, fat emulsion 10%, LR, $^1/_2NS$, NS.

Y-site administration: Compatible: Ampicillin, epinephrine, famotidine, heparin, hydrocortisone sodium succinate, potassium chloride, tolazoline, vitamin B complex with C. **Incompatible:** Dobutamine.

Compatibility in syringe: Compatible: Doxapram.

Compatibility when admixed: Compatible: Amikacin, chloramphenicol, cimetidine, netilmicin, sodium bicarbonate. **Incompatible:** Phenytoin, ranitidine. **Variable (consult detailed reference):** Oxytocin.

ContraindicationsHypersensitivity to physostigmine or any component of the formulation; GI or GU obstruction; asthma; gangrene; diabetes, cardiovascular disease; any vagotonic state; coadministration of choline esters and depolarizing neuromuscular-blocking agents

Allergy Considerations

- Cholinesterase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Arrhythmias: Patient must have a normal QRS interval, as measured by ECG, in order to receive; use caution in poisoning with agents known to prolong intraventricular conduction.
- Cholinergic effects: Discontinue if symptoms of excess cholinergic activity (eg, salivation, sweating, urinary incontinence); overdosage may result in cholinergic crisis, which must be distinguished from myasthenic crisis.
- Hypersensitivity/overdose reactions: Due to the possibility of hypersensitivity or overdose/cholinergic crisis, atropine should be readily available.

Disease-related concerns:

- Anticholinergic toxicity: Not intended as a first-line agent for anticholinergic toxicity.
- Asthma: Use with caution in patients with asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease, including bradycardia.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Gangrene: Use with caution in patients with gangrene.

- Parkinson's disease: Not intended as a first-line agent for Parkinson's disease.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Concurrent drug therapy issues:

- Choline esters: Concomitant administration of choline esters is contraindicated.

- Depolarizing neuromuscular-blocking agents (ie, succinylcholine): Concomitant administration of depolarizing neuromuscular-blocking agents is contraindicated.

Dosage form specific issues:

- Benzyl alcohol: Products may contain benzyl alcohol which has been associated with "gasping syndrome" in neonates.

- Sodium bisulfate: Products may contain sodium bisulfate.

Other warnings/precautions:

- I.V. administration: Administer slowly over 5 minutes to prevent respiratory distress and seizures. Continuous infusions should never be used.

- Tricyclic antidepressant (TCA) poisoning: Asystole and seizures have been reported when physostigmine was administered to TCA poisoned patients. Physostigmine is not recommended in patients with known or suspected TCA intoxication.

Geriatric ConsiderationsSee Warnings/Precautions.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown
Adverse ReactionsFrequency not defined.

Cardiovascular: Asystole, bradycardia, palpitation

Central nervous system: Hallucinations, nervousness, restlessness, seizure

Gastrointestinal: Diarrhea, nausea, salivation, stomach pain

Genitourinary: Urinary frequency

Neuromuscular & skeletal: Twitching

Ocular: Lacrimation, miosis

Respiratory: Bronchospasm, dyspnea, pulmonary edema, respiratory paralysis

Miscellaneous: Diaphoresis

Drug Interactions

Beta-Blockers: Acetylcholinesterase Inhibitors may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Cholinergic Agonists: Acetylcholinesterase Inhibitors may enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Ginkgo Biloba: May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): Acetylcholinesterase Inhibitors may diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Succinylcholine: Acetylcholinesterase Inhibitors may enhance the neuromuscular-blocking effect of Succinylcholine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Ginkgo biloba may enhance the adverse/toxic effect of physostigmine; monitor.
Test InteractionsIncreased aminotransferase [ALT/AST] (S), increased amylase (S)
Monitoring ParametersECG, vital signs
Nursing: Physical Assessment/MonitoringWhen used to reverse neuromuscular block, patient must be monitored closely until full return of neuromuscular functioning. Assess bladder and sphincter adequacy prior to administering medication. Assess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness and adverse reactions (cholinergic crisis). Assess knowledge/teach patient appropriate use of ophthalmic forms, interventions to reduce side effects, and adverse symptoms to report.
Patient EducationMaintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause dizziness, drowsiness, or hypotension (rise slowly from sitting or lying position and use caution when driving or climbing stairs); vomiting or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea (boiled milk, yogurt, or buttermilk may help). Report persistent abdominal discomfort; significantly increased salivation, sweating, tearing, or urination; flushed skin; chest pain or palpitations; acute headache; unresolved diarrhea; excessive fatigue, insomnia, dizziness, or depression; increased muscle, joint, or body pain; vision changes or blurred vision; or shortness of breath or wheezing. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as salicylate: 1 mg/mL (2 mL) [contains benzyl alcohol and sodium metabisulfite]

Generic AvailableYes

Mechanism of ActionInhibits destruction of acetylcholine by acetylcholinesterase which facilitates transmission of impulses across myoneural junction and prolongs the central and peripheral effects of acetylcholine

Pharmacodynamics/Kinetics

Onset of action: ~5 minutes

Duration: 1-2 hours

Absorption: I.M.: Readily absorbed

Distribution: Crosses blood-brain barrier readily and reverses both central and peripheral anticholinergic effects

Metabolism: Hepatic and via hydrolysis by cholinesterases

Half-life elimination: 15-40 minutes

Related Information

- Depression
- Glaucoma Drug Therapy

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Salivation.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause restlessness, nervousness, or hallucinations

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsCholinergic effects of physostigmine include bradycardia and bradydysrhythmias.

Anesthesia and Critical Care Concerns/Other ConsiderationsCholinergic effects of physostigmine include bradycardia and bradydysrhythmias.

Index TermsEserine Salicylate; Physostigmine Salicylate; Physostigmine Sulfate

References

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Lugassy D, Manno R, and Barrueto, Jr F, “Diphenhydramine Overdose Reversed With Aggressive Physostigmine Administration,” *Clin Toxicol (Phila)*, 2006, 44:715.

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Theesen KA, Boyd JA, “Dementia of the Alzheimer's Type: An Update,” *Consult Pharm*, 1990, 5:535-40.

International Brand NamesAnticholium (AT, DE); Fisostigmina Salicilato (IT); Fisostin (IT); Physostigmine Salicylate (AU); Physostigminum Salicylicum (PL)

Phytonadione

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Mephyton® may be confused with melphalan, methadone

Pronunciation(fye toe na DYE one)

U.S. Brand NamesMephyton®

Canadian Brand NamesAquaMEPHYTON®; Konakion; Mephyton®

Pharmacologic CategoryVitamin, Fat Soluble

Use: Labeled IndicationsPrevention and treatment of hypoprothrombinemia caused by coumarin derivative-induced or other drug-induced vitamin K deficiency, hypoprothrombinemia caused by malabsorption or inability to synthesize vitamin K; hemorrhagic disease of the newborn

Use: Unlabeled/InvestigationalTreatment of hypoprothrombinemia caused by anticoagulant rodenticides

Dosing: Adults**Note:** According to the manufacturer, SubQ is the preferred parenteral route; I.M. route should be avoided due to the risk of hematoma formation; I.V. route should be restricted for emergency use only. The American College of Chest Physicians recommends the I.V. route in patients with serious or life-threatening bleeding secondary to use of vitamin K antagonists.

Adequate intake: Males: 120 mcg/day; Females: 90 mcg/day

Hypoprothrombinemia due to drugs (other than coumarin derivatives) or factors limiting absorption or synthesis: Oral, SubQ, I.M., I.V.: Initial: 2.5-25 mg (rarely up to 50 mg)

Vitamin K deficiency (supratherapeutic INR) secondary to coumarin derivative (Ansell, 2008):

If INR above therapeutic range to <5 (no significant bleeding and rapid reversal unnecessary): Lower or hold next dose and monitor frequently; when INR approaches desired range, resume dosing with a lower dose.

If INR ≥5 and <9 (no significant bleeding): If no risk factors for bleeding exist, omit next 1 or 2 doses, monitor INR more frequently, and resume with an appropriately adjusted dose when INR in desired range.

Alternatively, if other risk factors for bleeding exist, omit next dose and administer vitamin K orally 1-2.5 mg; resume with an appropriately adjusted dose when INR in desired range.

If INR ≥5 and <9 (no significant bleeding and rapid reversal required for surgery): Administer vitamin K orally ≤5 mg and hold warfarin. Expect INR to be reduced within 24 hours; if INR still elevated, another 1-2 mg of vitamin K orally may be given.

If INR ≥9 (no significant bleeding): Hold warfarin, administer vitamin K orally 2.5-5 mg, expect INR to be reduced within 24-48 hours, monitor INR more frequently and give additional vitamin K at an appropriate dose if necessary. Resume warfarin at an appropriately adjusted dose when INR is in desired range.

If serious bleeding at any INR elevation: Hold warfarin, administer vitamin K 10 mg by slow I.V. infusion and supplement with FFP, PCC, or rFVIIa depending on the urgency of the situation; I.V. vitamin K may be repeated every 12 hours.

If life-threatening bleeding: Hold warfarin, give FFP, PCC, or rFVIIa supplemented with vitamin K 10 mg slow I.V. infusion; repeat if necessary, depending on INR.

Notes:

If mild-moderate INR elevation without major bleeding occurs, administer vitamin K orally instead of subcutaneously.

Use of high doses of vitamin K (eg, 10-15 mg) may cause warfarin resistance for ≥1 week. During this period of resistance, heparin or low molecular weight heparin may be given until INR responds.

FFP=fresh frozen plasma; PCC=prothrombin complex concentrate; rFVIIa=recombinant factor VIIa

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** According to the manufacturer, SubQ is the preferred parenteral route; I.M. route should be avoided due to the risk of hematoma formation; I.V. route should be restricted for emergency use only. The American College of Chest Physicians recommends the I.V. route in patients with serious or life-threatening bleeding secondary to use of vitamin K antagonists.

Adequate intake:

1-3 years: 30 mcg/day

4-8 years: 55 mcg/day

9-13 years: 60 mcg/day

14-18 years: 75 mcg/day

Hemorrhagic disease of the newborn:

Prophylaxis: I.M.: 0.5-1 mg within 1 hour of birth

Treatment: I.M., SubQ: 1 mg/dose/day; higher doses may be necessary if mother has been receiving oral anticoagulants

Administration: I.V.Infuse slowly; rate of infusion should not exceed 1 mg/minute (3 mg/m^2/minute in children and infants). The injectable route should be used only if the oral route is not feasible or there is a greater urgency to reverse anticoagulation.

Administration: I.V. DetailpH: 3.5-7.0

Administration: OralThe parenteral preparation has been administered orally to neonates.

Storage

Injection: Store at 15°C to 30°C (59°F to 86°F). **Note:** Store Hospira product at 20°C to 25°C (68°F to 77°F).

Oral: Store tablets at 15°C to 30°C (59°F to 86°F). Protect from light.

ReconstitutionDilute injection solution in preservative-free NS, D_5W, or D_5NS.

Extemporaneously PreparedA 1 mg/mL oral suspension was stable for only 3 days when refrigerated when compounded as follows:

Triturate six 5 mg tablets in a mortar, reduce to a fine powder, then add 5 mL each of water and methylcellulose 1% while mixing; then transfer to a graduate and qs to 30 mL with sorbitol

Shake well before using and keep in refrigerator

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, 3rd ed, Cincinnati, OH: Harvey Whitney Books Co, 1997.

ContraindicationsHypersensitivity to phytonadione or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Anaphylaxis/hypersensitivity reactions: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: **[U.S. Boxed Warning]: Severe reactions resembling hypersensitivity (eg, anaphylaxis) reactions have occurred rarely during or immediately after I.V. administration (even with proper dilution and rate of administration).** Allergic reactions have also occurred with I.M. and SubQ injections.

Disease-related concerns:

- Anticoagulant induced hypoprothrombinemia: Administer a dose that will quickly lower the INR into a safe range without causing resistance to warfarin. High phytonadione doses may lead to warfarin resistance for at least one week.

- Liver disease induced hypoprothrombinemia: If initial doses do not reverse coagulopathy, then higher doses are unlikely to have any effect. **Note:** Ineffective in hereditary hypoprothrombinemia.

- Renal impairment: Use with caution in patients with renal impairment (including premature infants).

Special populations:

- Newborns: Use with caution in newborns, especially premature infants; hemolysis, jaundice, and hyperbilirubinemia have been reported with larger than recommended doses.

Dosage form specific issues:

- Aluminum: Injectable products may contain aluminum; may result in toxic levels following prolonged administration.

- Benzyl alcohol: Some dosage forms contain benzyl alcohol which has been associated with "gasping syndrome" in neonates.

Other warnings/precautions:

- Appropriate route: Oral administration is the safest and requires the presence of bile salts for absorption. In obstructive jaundice or with biliary fistulas, concurrent administration of bile salts would be necessary for proper absorption. Manufacturers recommend the SubQ route over other parenteral routes, however, SubQ is less predictable when compared to the oral route, and efficacy may be delayed. The American College of Chest Physicians recommends the I.V. route in patients with serious or life-threatening bleeding secondary to use of vitamin K antagonists such as warfarin. The I.V. route should be restricted to emergency situations only where oral phytonadione cannot be used. Efficacy (eg, control of bleeding, decrease in INR) is delayed regardless of route of administration; patient management may require other treatments in the interim.

Pregnancy Risk FactorC

LactationEnters breast milk/use caution (AAP rates "compatible")

Adverse ReactionsParenteral administration: Frequency not defined.

Cardiovascular: Cyanosis, flushing, hypotension

Central nervous system: Dizziness

Dermatologic: Scleroderma-like lesions

Endocrine & metabolic: Hyperbilirubinemia (newborn; greater than recommended doses)

Gastrointestinal: Abnormal taste

Local: Injection site reactions

Respiratory: Dyspnea

Miscellaneous: Anaphylactoid reactions, diaphoresis, hypersensitivity reactions

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

Vitamin K Antagonists (eg, warfarin): Phytonadione may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Monitoring ParametersPT, INR
Nursing: Physical Assessment/MonitoringNote dosing specifics according to purpose for use. Assess results of laboratory tests and patient response (degree of bleeding). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsPT, INR
Patient EducationDo not take any new medication during therapy (especially any aspirin-containing products or NSAIDs) without consulting prescriber. Oral: Take only as directed; do not take more or more often than prescribed. Consult prescriber for recommended diet. Report bleeding gums; blood in urine, stool, or vomitus; unusual bruising or bleeding; or abdominal cramping. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, aqueous colloidal: 2 mg/mL (0.5 mL); 10 mg/mL (1 mL)

Tablet: 100 mcg [OTC]

Mephyton®: 5 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Mephyton)

5 mg (30): $59.99

Mechanism of ActionPromotes liver synthesis of clotting factors (II, VII, IX, X); however, the exact mechanism as to this stimulation is unknown. Menadiol is a water soluble form of vitamin K; phytonadione has a more rapid and prolonged effect than menadione; menadiol sodium diphosphate (K_4) is half as potent as menadione (K_3).
Pharmacodynamics/Kinetics

Onset of action: Increased coagulation factors: Oral: 6-10 hours; I.V.: 1-2 hours

Peak effect: INR values return to normal: Oral: 24-48 hours; I.V.: 12-14 hours

Absorption: Oral: From intestines in presence of bile; SubQ: Variable

Metabolism: Rapidly hepatic

Excretion: Urine and feces

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Abnormal taste.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay rarely cause dizziness
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsMethylphytyl Napthoquinone; Phylloquinone; Phytomenadione; Vitamin K_1
References

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Watt BE, Proudfoot AT, Bradberry SM, et al, "Anticoagulant Rodenticides," *Toxicol Rev*, 2005, 24(4):259-69.[PubMed 16499407]

Weibert RT, Le DT, Kayser SR, et al, "Correction of Excessive Anticoagulation With Low-Dose Oral Vitamin K1," *Ann Intern Med*, 1997, 126(12):959-62.[PubMed 9182473]

International Brand NamesHaemokion (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Kanakion (PT); Kanavit (CZ); Kenadion (IN); Kona-K (PH); Konakion (10 mg) (AE, AU, BG, BH, CY, DE, EC, EG, GB, GH, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LY, NL, OM, QA, SA, SE, SY, TZ, UG, YE, ZM); Konakion (BE, DK, ES, HR, HU, LU, NO, NZ); Konakion 10 mg (AT, FI, HN); Konakion MM (MX); Konakion MM Paediatric (BB, BM, BS, BZ, GY, JM, SR, TT); Konakion MM Pediatric (AR, AU, BR, CH, CN, CO, PE, PK, PY, UY); Vitacon (PL); Vitak (JP); Vitamin K (HK); Vitamin K1 (KP); Vitamine K!1 Roche (FR)

Pilocarpine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Isopto® Carpine may be confused with Isopto® Carbachol

Salagen® may be confused with Salacid®, selegiline

International issues:

Salagen® may be confused with Poagen® which is a brand name for grass pollen extract in Portugal

Pronunciation(pye loe KAR peen)
U.S. Brand NamesIsopto® Carpine; Pilopine HS®; Salagen®
Canadian Brand NamesDiocarpine; Isopto® Carpine; Pilopine HS®; Salagen®
Pharmacologic CategoryCholinergic Agonist; Ophthalmic Agent, Antiglaucoma; Ophthalmic Agent, Miotic
Use: Labeled Indications

Ophthalmic: Management of chronic simple glaucoma, chronic and acute angle-closure glaucoma

Oral: Symptomatic treatment of xerostomia caused by salivary gland hypofunction resulting from radiotherapy for cancer of the head and neck or Sjögren's syndrome

Use: Unlabeled/InvestigationalCounter effects of cycloplegics
Use: DentalTreatment of xerostomia caused by radiation therapy in patients with head and neck cancer and from Sjögren's syndrome
Dosing: Adults

Glaucoma: Ophthalmic:

Solution: Instill 1-2 drops up to 6 times/day; adjust the concentration and frequency as required to control elevated intraocular pressure.

Gel: Instill 0.5” ribbon into lower conjunctival sac once daily at bedtime.

To counteract the mydriatic effects of sympathomimetic agents (unlabeled use): Ophthalmic solution: Instill 1 drop of a 1% solution in the affected eye.

Xerostomia: Oral:

Following head and neck cancer: 5 mg 3 times/day, titration up to 10 mg 3 times/day may be considered for patients who have not responded adequately; do not exceed 2 tablets/dose

Sjögren's syndrome: 5 mg 4 times/day

Dosing: ElderlyRefer to adult dosing.
Dosing: Hepatic ImpairmentOral: Patients with moderate impairment: 5 mg 2 times/day regardless of indication; adjust dose based on response and tolerability. Do not use with severe impairment (Child-Pugh score 10-15)
Administration: OralAvoid administering with high-fat meal. Fat decreases the rate of absorption, maximum concentration, and increases the time it takes to reach maximum concentration.
Administration: OtherOphthalmic: If both solution and gel are used, the solution should be applied first, then the gel at least 5 minutes later. Following administration of the solution, finger pressure should be applied on the lacrimal sac for 1-2 minutes.
Storage

Gel: Store at room temperature of 2°C to 27°C (36°F to 80°F); do not freeze. Avoid excessive heat.

Tablets: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to pilocarpine or any component of the formulation; acute inflammatory disease of the anterior chamber of the eye; in addition, tablets are also contraindicated in patients with uncontrolled asthma, angle-closure glaucoma, severe hepatic impairment
Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; may have difficulty compensating for transient changes in hemodynamics or rhythm induced by pilocarpine.

Dosage form specific issues:

- Ophthalmic products: May cause decreased visual acuity, especially at night or with reduced lighting.

- Oral tablet: Use caution with controlled asthma, chronic bronchitis or COPD; may increase airway resistance, bronchial smooth muscle tone, and bronchial secretions. Use caution with cholelithiasis, biliary tract disease, nephrolithiasis; adjust dose with moderate hepatic impairment.

Geriatric ConsiderationsAssure the patient or a caregiver can adequately administer ophthalmic medication dosage form.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

Ophthalmic: Frequency not defined:

Cardiovascular: Hypertension, tachycardia

Gastrointestinal: Diarrhea, nausea, salivation, vomiting

Ocular: Burning, ciliary spasm, conjunctival vascular congestion, corneal granularity (gel 10%), lacrimation, lens opacity, myopia, retinal detachment, supraorbital or temporal headache, visual acuity decreased

Respiratory: Bronchial spasm, pulmonary edema

Miscellaneous: Diaphoresis

Oral (frequency varies by indication and dose):

>10%:

Cardiovascular: Flushing (8% to 13%)

Central nervous system: Chills (3% to 15%), dizziness (5% to 12%), headache (11%)

Gastrointestinal: Nausea (6% to 15%)

Genitourinary: Urinary frequency (9% to 12%)

Neuromuscular & skeletal: Weakness (2% to 12%)

Respiratory: Rhinitis (5% to 14%)

Miscellaneous: Diaphoresis (29% to 68%)

1% to 10%:

Cardiovascular: Edema (<1% to 5%), facial edema, hypertension (3%), palpitation, tachycardia

Central nervous system: Pain (4%), fever, somnolence

Dermatologic: Pruritus, rash

Gastrointestinal: Diarrhea (4% to 7%), dyspepsia (7%), vomiting (3% to 4%), constipation, flatulence, glossitis, salivation increased, stomatitis, taste perversion

Genitourinary: Vaginitis, urinary incontinence

Neuromuscular & skeletal: Myalgias, tremor

Ocular: Lacrimation (6%), amblyopia (4%), abnormal vision, blurred vision, conjunctivitis

Otic: Tinnitus

Respiratory: Cough increased, dysphagia, epistaxis, sinusitis

Miscellaneous: Allergic reaction, voice alteration

<1%: Abnormal dreams, abnormal thinking, alopecia, angina pectoris, anorexia, anxiety, aphasia, appetite increased, arrhythmia, arthralgia, arthritis, bilirubinemia, body odor, bone disorder, bradycardia, breast pain, bronchitis, cataract, cholelithiasis, colitis, confusion, contact dermatitis, cyst, deafness, depression, dry eyes, dry mouth, dry skin, dyspnea, dysuria, ear pain, ECG abnormality, eczema, emotional lability, eructation, erythema nodosum, esophagitis, exfoliative dermatitis, eye hemorrhage, eye pain, gastritis, gastroenteritis, gastrointestinal disorder, gingivitis, glaucoma, hematuria, hepatitis, herpes simplex, hiccup, hyperkinesias, hypoesthesia, hypoglycemia, hypotension, hypothermia, insomnia, intracranial hemorrhage, laryngismus, laryngitis, leg cramps, leukopenia, liver function test abnormal, lymphadenopathy, mastitis, melena, menorrhagia, metrorrhagia, migraine, moniliasis, myasthenia, MI, neck pain, photosensitivity reaction, nervousness, ovarian disorder, pancreatitis, paresthesia, parotid gland enlargement, peripheral edema, platelet abnormality, pneumonia, pyuria, salivary gland enlargement, salpingitis, seborrhea, skin ulcer, speech disorder, sputum increased, stridor, syncope, taste loss, tendon disorder, tenosynovitis, thrombocythemia, thrombocytopenia, thrombosis, tongue disorder, twitching, urethral pain, urinary impairment, urinary urgency, vaginal hemorrhage, vaginal moniliasis, vesiculobullous rash, WBC abnormality, yawning

Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Inhibits** CYP2A6 (weak), 2E1 (weak), 3A4 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Avoid administering oral formulation with high-fat meal; fat decreases the rate of absorption, maximum concentration and increases the time it takes to reach maximum concentration.

Monitoring ParametersIntraocular pressure, funduscopic exam, visual field testing

Nursing: Physical Assessment/MonitoringMonitor for adverse effects and response to treatment. Assess results of intraocular pressure testing, fundoscopic exam, and visual field testing on a periodic basis. Teach patient appropriate administration of ophthalmic solution.

Patient EducationUse as often as recommended. Avoid taking oral medication with a high fat meal.

Ophthalmic: Wash hands before using. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Sit or lie down. Open eye, look at ceiling, and instill prescribed amount of solution. Do not blink for 30 seconds, close eye and roll eye in all directions, and apply gentle pressure to inner corner of eye for 1-2 minutes. Temporary stinging or blurred vision may occur. You may experience altered dark adaptation; use caution when driving at night or in poorly lit environments. Report persistent pain, redness, burning, double vision, or severe headache. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel, ophthalmic, as hydrochloride (Pilopine HS®): 4% (4 g) [contains benzalkonium chloride]

Solution, ophthalmic, as hydrochloride: 0.5% (15 mL); 1% (2 mL, 15 mL); 2% (2 mL, 15 mL); 3% (15 mL); 4% (2 mL, 15 mL); 6% (15 mL) [may contain benzalkonium chloride]

Isopto® Carpine: 1% (15 mL); 2% (15 mL); 4% (15 mL) [contains benzalkonium chloride]

Tablet, as hydrochloride: 5 mg, 7.5 mg

Salagen®: 5 mg, 7.5 mg

Generic AvailableYes: Hydrochloride solution, tablet

Pricing: U.S. (www.drugstore.com)

Gel (Pilopine HS)

4% (4): $55.99

Solution (Isopto Carpine)

1% (15): $31.51

2% (15): $31.46

4% (15): $32.51

Solution (Pilocarpine HCl)

0.5% (15): $7.99

1% (15): $12.99

Tablets (Pilocarpine HCl)

5 mg (90): $99.99

Tablets (Salagen)

5 mg (90): $173.62

7.5 mg (100): $249.78

Mechanism of ActionDirectly stimulates cholinergic receptors in the eye causing miosis (by contraction of the iris sphincter), loss of accommodation (by constriction of ciliary muscle), and lowering of intraocular pressure (with decreased resistance to aqueous humor outflow)

Pharmacodynamics/Kinetics

Onset of action:

Ophthalmic: Miosis: 10-30 minutes; Intraocular pressure reduction: 1 hour

Oral: 20 minutes

Duration:

Ophthalmic: Miosis: 4-8 hours; Intraocular pressure reduction: 4-12 hours

Oral: 3-5 hours

Half-life elimination: Oral: 0.76-1.35 hours; increased with hepatic impairment

Excretion: Urine

Related Information

- Glaucoma Drug Therapy

Dental Health Professional ConsiderationsPilocarpine may have potential as a salivary stimulant in individuals suffering from xerostomia induced by antidepressants and other medications. At the present time however, the FDA has not approved pilocarpine for use in drug-induced xerostomia (clinical studies required). In an attempt to discern the efficacy of pilocarpine as a salivary stimulant in patients suffering from Sjögren's syndrome (SS), Rhodus and Schuh studied 9 patients with SS given daily doses of pilocarpine over a 6-week period. A dose of 5 mg daily produced a significant overall increase in both whole unstimulated salivary flow and parotid stimulated salivary flow. These results support the use of pilocarpine to increase salivary flow in patients with SS.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentPilocarpine may antagonize the effects of anticholinergics and produce cardiac conduction abnormalities in patients receiving beta-blockers

Index TermsPilocarpine Hydrochloride

References

Hawthorne M and Sullivan K, "Pilocarpine for Radiation-Induced Xerostomia in Head and Neck Cancer," *Int J Palliat Nurs*, 2000, 6(5):228-32.[PubMed 12419994]

Jacobs CD and van der Pas M, “A Multicenter Maintenance Study of Oral Pilocarpine Tablets for Radiation-Induced Xerostomia,” *Oncology*, 1996, 10(3 Suppl):16-20. [PubMed 8723429]

Johnson JT, Ferretti GA, Nethery WJ, et al, “Oral Pilocarpine for Postirradiation Xerostomia in Patients With Head and Neck Cancer,” *N Engl J Med*, 1993, 329(6):390-5. [PubMed 8326972]

LeVeque FG, Montgomery M, Potter D, et al, “A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Titration Study of Oral Pilocarpine for Treatment of Radiation-Induced Xerostomia in Head and Neck Cancer Patients,” *J Clin Oncol*, 1993, 11(6):1124-31. [PubMed 8501499]

Rieke JW, Hafermann MD, Johnson JT, et al, “Oral Pilocarpine for Radiation-Induced Xerostomia: Integrated Efficacy and Safety Results From Two Prospective Randomized Clinical Trials,” *Int J Radiat Oncol Biol Phys*, 1995, 31(3):661-9. [PubMed 7852133]

Schuller DE, Stevens P, Clausen KP, et al, “Treatment of Radiation Side Effects With Oral Pilocarpine,” *J Surg Oncol*, 1989, 42(4):272-6.[PubMed 2687586]

Taylor SE, "Efficacy and Economic Evaluation of Pilocarpine in Treating Radiation-Induced Xerostomia," *Expert Opin Pharmacother*, 2003, 4(9):1489-97.[PubMed 12943478]

International Brand NamesAntodrel (ES); Asthenopin (LU, PH); Caliprene (MX); Carpinplast (ES); Colircusi Pilocarpina (ES); Colirio Ocul Pilocarpina (ES); Dretinof (MX); Glaucocarpine (IL); Humacarpin (HU); Isopto Carpina (AR, BR, ES, PE, PY, UY, VE); Isopto Carpine (AE, AU, BE, BF, BH, BJ, CI, CY, EE, EG, ET, FI, GH, GM, GN, GR, HK, HN, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PH, QA, SA, SC, SD, SL, SN, SY, TH, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Isopto Pilocarpina (CN); Isopto Pilocarpine (FR); Isopto-carpine (PL); Liocarpina (IT); Locarp (IN); Medicarpine (PK); Minims-Pilocarpinnitrat (AT); Miokar (ID); Nitrate de Pilocarpine-Chauvin (LU); O.P.D. (TW); Ocusert P-20 (JP); Ocusert P-40 (JP); Ocusert Pilo-20 (GB); Ocusert Pilo-40 (GB, NZ); Ocusert Pilocarpine (GB); Oft Cusi Pilocarpina (ES); Oftan-Pilocarpin (FI); P.V. Carpine Liquifilm Ophthalimic Solution (AU); Pil Ofteno (GT, SV); Pilocarcil (PT); Pilocarpin (HU, KP); Pilocarpin Agepha (AT); Pilocarpina Llorens (ES); Pilocarpinum (PL); Pilocarpinum hydrochloricum (PL); Pilocarpinum ophtalmicum (PL); Pilocarpol (AT, DE); Pilogel (AT, CZ, GB, HU, IE, IT, PL, TW); Pilogel HS (CN, SG); Pilokarpin (HR); Pilokarpin Isopto (DK); Pilomann (DE, LU, PL); Pilomann Edo Sine (LU); Pilomin (BG); Pilopine-HS (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Pilopt Eye Drops (AU); Pilotonina (IT); Salagen (AT, CO, HK, HU, KP, NO, PL, TW); Sno Pilo (IE); Solutio pilocarpini hydrochloridi (PL); Spersacarpine (CH, LU, MY, SE, TW); Unguentum pilocarpini (PL); Zhenrui (CL)

Pimecrolimus

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English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(pim e KROE li mus)

U.S. Brand NamesElidel®

Canadian Brand NamesElidel®

Pharmacologic Category[Immunosuppressant Agent](); [Topical Skin Product]()

Use: Labeled IndicationsShort-term and intermittent long-term treatment of mild to moderate atopic dermatitis in patients not responsive to conventional therapy or when conventional therapy is not appropriate

Dosing: Adults

Mild to moderate atopic dermatitis: Topical: Apply thin layer to affected area twice daily; rub in gently and completely. **Note:** Limit application to involved areas. Continue as long as signs and symptoms persist; discontinue if resolution occurs; re-evaluate if symptoms persist >6 weeks.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥2 years: Topical: Refer to adult dosing.

Administration: TopicalDo not use with occlusive dressings. Burning at the application site is most common in first few days; improves as atopic dermatitis improves. Limit application to areas of involvement. Continue as long as signs and symptoms persist; discontinue if resolution occurs; re-evaluate if symptoms persist >6 weeks.

StorageStore at 15°C to 30°C (59°F to 86°F); do not freeze.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to pimecrolimus or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Malignancy: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Local symptoms: May cause local symptoms (eg, burning, soreness, stinging) during first few days of treatment; usually self-resolving.
- Lymphadenopathy: May be associated with development of lymphadenopathy; possible infectious causes should be investigated. Discontinue use in patients with unknown cause of lymphadenopathy or acute infectious mononucleosis.
- Malignancy: **[U.S. Boxed Warning]: Topical calcineurin inhibitors have been associated with rare cases of lymphoma and skin malignancy;** avoid use on malignant or premalignant skin conditions (eg, cutaneous T-cell lymphoma). **Should be used for short-term and intermittent treatment using the minimum amount necessary for the control of symptoms; application should be limited to involved areas.** Safety of intermittent use for >1 year has not been established. **[U.S. Boxed Warning]: The use of Elidel® in children <2 years of age is not recommended,** particularly since the effect on immune system development is unknown.
- Skin papilloma: Papilloma/warts have been observed with use; discontinue pimecrolimus until resolution if worsening or do not respond to conventional treatment.

Disease-related concerns:

- Atopic dermatitis: Diagnosis should be reconfirmed if sign/symptoms do not improve within 6 weeks of treatment. Patients with atopic dermatitis are predisposed to skin infections, and pimecrolimus therapy has been associated with risk of developing eczema herpeticum, varicella zoster, and herpes simplex.
- Erythroderma: Safety not established in patients with generalized erythroderma.
- Skin diseases which may increase systemic absorption: Not recommended for use in patients with Netherton's syndrome or skin conditions which may increase the potential for systemic absorption.

Special populations:

- Immunocompromised patients: Should not be used in immunocompromised patients.
- Pediatrics: Not for use in children <2 years of age.

Other warnings/precautions:

- Appropriate use: Topical calcineurin agents are considered second-line therapies in the treatment of atopic dermatitis/eczema, and should be limited to use in patients who have failed or cannot tolerate treatment with other therapies. Do not apply to areas of active bacterial or viral infection; infections at the treatment site should be cleared prior to therapy.

- Sun exposure: Avoid artificial or natural sunlight exposure, even when Elidel® is not on the skin.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women; use only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

>10%:

Central nervous system: Headache (7% to 25%), fever (1% to 13%)

Local: Burning at application site (2% to 26%; tends to resolve/improve as lesions resolve)

Respiratory: Nasopharyngitis (8% to 27%), cough (2% to 16%), upper respiratory tract infection (4% to 19%), bronchitis (≤11%)

Miscellaneous: Influenza (3% to 13%)

1% to 10%:

Dermatologic: Skin infection (2% to 6%), folliculitis (1% to 6%), impetigo (2% to 4%), skin papilloma (warts) (≤3%), acne (≤2%), herpes simplex dermatitis (≤ 2%), molluscum contagiosum (≤2%), urticaria (≤1%)

Endocrine & metabolic: Dysmenorrhea (1% to 2%)

Gastrointestinal: Diarrhea (1% to 8%), gastroenteritis (≤7%), abdominal pain (≤4%), constipation (≤4%)

Local: Irritation at application site (≤6%), pruritus at application site (1% to 6%), erythema at application site (≤2%)

Ocular: Eye infection (≤1%)

Otic: Ear infection (1% to 6%), otitis media (1% to 3%)

Respiratory: Pharyngitis (1% to 8%), asthma (1% to 4%), asthma aggravated (≤4%), nasal congestion (1% to 3%), sinusitis (1% to 3%), epistaxis (≤3%), dyspnea (≤2%), pneumonia (≤2%), rhinorrhea (≤2%), wheezing (≤1%)

Miscellaneous: Viral infection (≤7%), tonsillitis (≤6%), hypersensitivity (3% to 5%), herpes simplex infection (≤4%), bacterial infection (1% to 2%)

<1%: Eczema herpeticum, lymphadenopathy

Postmarketing and/or case reports: Anaphylaxis, angioneurotic edema, facial edema, flushing (ethanol-associated), ocular irritation (following application near eyes), malignancy (basal cell carcinoma, squamous cell carcinoma, malignant melanoma, lymphoma), skin discoloration

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)

Drug Interactions

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (topical pimecrolimus may increase the potential for experiencing facial flushing following the consumption of alcoholic beverages).

Nursing: Physical Assessment/MonitoringSee Administration directions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationThis medication is for external use only. Avoid alcohol use while using this medication. Do not use for any skin disorder except that for which it was prescribed. Avoid getting any medication in or close to eyes. Apply as often as directed by prescriber, in thin film to affected area. Do not cover with bandages or occlusive dressings. Wash and dry hands thoroughly before and after applying (if affected area is not on hands). Avoid artificial or natural sunlight even when drug not applied to skin. Discontinue therapy after signs and symptoms have disappeared; restart treatment at first sign of recurrence. You may experience burning at site of application, this will usually last less than 5 days, and go away as skin condition improves. You may experience headache, fever, cough, nasal or throat irritation, flu-like symptoms, diarrhea, or constipation; contact prescriber if these persist. Contact prescriber if skin condition worsens or if symptoms persist longer than 6 weeks. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical:

Elidel®: 1% (30 g, 60 g, 100 g)

Generic AvailableNo

ManufacturerNovartis Pharmaceuticals Corp

Pricing: U.S. (www.drugstore.com)

Cream (Elidel)

1% (30): $81.99

1% (60): $152.99

1% (100): $237.98

Mechanism of ActionPenetrates inflamed epidermis to inhibit T cell activation by blocking transcription of proinflammatory cytokine genes such as interleukin-2, interferon gamma (Th1-type), interleukin-4, and interleukin-10 (Th2-type). Pimecrolimus binds to the intracellular protein FKBP-12, inhibiting calcineurin, which blocks cytokine transcription and inhibits T-cell activation. Prevents release of inflammatory cytokines and mediators from mast cells *in vitro* after stimulation by antigen/IgE.

Pharmacodynamics/KineticsAbsorption: Poor when applied to 13% to 62% body surface area in adults for up to a year; detectable blood levels were observed in a higher proportion of children, as compared to adults

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesDouglas Cream (KP); Elidel (AR, AU, BE, BG, BR, CH, CL, CN, CO, CZ, DE, DK, EC, EE, ES, FI, GB, HK, HN, ID, IL, IT, KP, MX, MY, NL, NO, PL, PT, SE, TH, TW, UY, VE); Rizan (ES)

Pimozide

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Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

Gill SS, Bronskill SE, Normand SL, et al, “Antipsychotic Drug Use and Mortality in Older Adults With Dementia,” *Ann Intern Med*, 2007, 146(11):775-86.[PubMed 17548409]

Schneeweiss S, Setoguchi S, Brookhart A, et al, “Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients,” *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Pronunciation(PI moe zide)

U.S. Brand NamesOrap®

Canadian Brand NamesApo-Pimozide®; Orap®

Pharmacologic CategoryAntipsychotic Agent, Typical

Use: Labeled IndicationsSuppression of severe motor and phonic tics in patients with Tourette's disorder who have failed to respond satisfactorily to standard treatment

Use: Unlabeled/InvestigationalPsychosis; reported use in individuals with delusions focused on physical symptoms (ie, preoccupation with parasitic infestation); Huntington's chorea; psychosis/agitation related to Alzheimer's dementia

Dosing: Adults

Tourette's disorder: Oral: Initial: 1-2 mg/day, then increase dosage as needed every other day; range is usually 7-16 mg/day; maximum: 10 mg/day or 0.2 mg/kg/day are not generally recommended.

Note: Sudden unexpected deaths have occurred in patients taking doses >10 mg.

Note: An ECG should be performed baseline and periodically thereafter, especially during dosage adjustment.

Dosing: ElderlyRecommend initial dose of 1 mg/day; periodically attempt gradual reduction of dose to determine if tic persists; follow up for 1-2 weeks before concluding the tic is a persistent disease phenomenon and not a manifestation of drug withdrawal. **Note:** An ECG should be performed baseline and periodically thereafter, especially during dosage adjustment.

Dosing: Pediatric

Tourette's disorder: Oral:

Children ≤12 years: Initial: 0.05 mg/kg preferably once at bedtime; may be increased every third day; usual range: 2-4 mg/day; do not exceed 10 mg/day (0.2 mg/kg/day)

Children >12 years: Refer to adult dosing.

Note: An ECG should be performed baseline and periodically thereafter, especially during dosage adjustment.

Dosing: Hepatic ImpairmentReduced dose is necessary.
ContraindicationsHypersensitivity to pimozide or any component of the formulation; severe CNS depression; coma; history of dysrhythmia; prolonged QT syndrome; concurrent use with QT_c-prolonging agents; hypokalemia or hypomagnesemia; concurrent use of drugs that are inhibitors of CYP3A4, including concurrent use of azole antifungals, fluvoxamine, macrolide antibiotics (such as clarithromycin or erythromycin [**Note:** The manufacturer lists azithromycin and dirithromycin in its list of contraindicated macrolides; however, these drugs do not inhibit CYP3A4 and are not expected to interact with pimozide]), mesoridazine, nefazodone, protease inhibitors (ie, atazanavir, indinavir, nelfinavir, ritonavir, saquinavir), sertraline, thioridazine, zileuton, and ziprasidone; simple tics other than Tourette's
Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics. Avoid use in patients with underlying QT prolongation, in those taking medicines that prolong the QT interval, or cause polymorphic ventricular tachycardia; monitor ECG closely for dose-related QT effects. Sudden unexplained deaths have occurred in patients taking high doses (>10 mg).

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to neuroleptics, pimozide has a moderate potency of cholinergic blockade.

- Blood dyscrasias: Myelosuppression (eg, leukopenia, agranulocytosis) has been observed with antipsychotic use; check blood counts periodically and discontinue at first signs of blood dyscrasias.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is high relative to other neuroleptics). Risk of dystonia (and possibly other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Pigmentary retinopathy: May be associated with pigmentary retinopathy.

- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Dementia: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo. An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Pimozide is not approved for this indication.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

Geriatric ConsiderationsNo specific clinical studies in the use of this drug in elderly; use with extreme caution in elderly due to cardiovascular effects. Consider cardiovascular effects of drugs an elderly patient may be receiving.

In the treatment of agitated, demented, older adult patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown

Adverse Reactions

Frequencies >1% reported in adults (limited data) and/or children with Tourette's disorder:

Cardiovascular: Abnormal ECG (3%)

Central nervous system: Somnolence (up to 28% in children), sedation (14%), akathisia (8%), nervousness (1% to 8%), drowsiness (7%), hyperkinesias (6%), insomnia (2%), depression (2%), headache (1%)

Dermatologic: Rash (8%)

Gastrointestinal: Xerostomia (25%), constipation (20%), increased salivation (14%), diarrhea (5%), thirst (5%), appetite increased (5%), taste disturbance (5%), dysphagia (3%)

Genitourinary: Impotence (15%)

Neuromuscular & skeletal: Weakness (22%), muscle tightness (15%), rigidity (10%), myalgia (3%), torticollis (3%), tremor (3%)

Ocular: Visual disturbance (6% to 20%), accommodation decreased (20%)

Miscellaneous: Speech disorder (10%)

Frequency not established (reported in disorders other than Tourette's disorder): Anorexia, blood dyscrasias, breast edema, chest pain, diaphoresis, dizziness, excitement; extrapyramidal symptoms (akathisia, akinesia, dystonia, pseudoparkinsonism, tardive dyskinesia); facial edema, gingival hyperplasia (case report), hyper-/hypotension, hyponatremia, jaundice, libido decreased, nausea, neuroleptic malignant syndrome, orthostatic hypotension, palpitation, periorbital edema, postural hypotension, QT_c prolongation, seizure, tachycardia, ventricular arrhythmia, vomiting, weight gain/loss

Metabolism/Transport Effects**Substrate** (major) of CYP1A2, 3A4; **Inhibits** CYP2C19 (weak), 2D6 (weak), 2E1 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Pimozide. *Risk X: Avoid combination*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Efavirenz: May enhance the arrhythmogenic effect of Pimozide. *Risk X: Avoid combination*

Fosaprepitant: May increase the serum concentration of Pimozide. The active metabolite aprepitant is likely responsible for this effect. *Risk X: Avoid combination*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Pimozide. QTc prolongation is a risk. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk X: Avoid combination*

Nefazodone: May decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Pimozide. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Pimozide. *Risk X: Avoid combination*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Pimozide serum concentration may be increased when taken with grapefruit juice; avoid concurrent use.

Herb/Nutraceutical: St John's wort may decrease pimozide levels. Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Monitoring ParametersECG should be performed baseline and periodically thereafter, especially during dosage adjustment; vital signs; lipid profile, fasting blood glucose/Hgb A_{1c}; BMI; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms (EPS)

Nursing: Physical Assessment/MonitoringAssess other medications patient is taking for effectiveness and interactions. Assess patient/caregiver knowledge of rationale for therapy and risks involved. Assess results of ophthalmic exam and laboratory tests, blood pressure, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. Conduct baseline ECG and periodically during therapy (especially during dosage adjustment). Initiate at lower doses (see Dosing) and decrease dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsLipid profile, fasting blood glucose/Hgb A_{1c}; BMI

Patient EducationUse exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results; do not discontinue without consulting prescriber. Avoid alcohol or caffeine and other prescription or OTC medications not approved by prescriber. Avoid grapefruit juice. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience excess drowsiness, restlessness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); or constipation, dry mouth, anorexia (increased exercise, fluids, fruit, or fiber may help). Report persistent CNS effects (eg, trembling fingers, altered gait or balance, excessive sedation, seizures, unusual muscle or facial movements, anxiety, abnormal thoughts, confusion, personality changes); unresolved constipation or GI effects; breast swelling (male and female) or decreased sexual ability; vision changes; respiratory difficulty; unusual cough or flu-like symptoms; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 1 mg, 2 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Orap)

1 mg (60): $64.04

2 mg (60): $82.94

Mechanism of ActionPimozide, a diphenylbutylperidine antipsychotic, is a potent centrally-acting dopamine-receptor antagonist resulting in its characteristic neuroleptic effects

Pharmacodynamics/Kinetics

Absorption: 50%

Protein binding: 99%

Metabolism: Hepatic; significant first-pass effect

Half-life elimination: 50 hours

Time to peak, serum: 6-8 hours

Excretion: Urine

Related Information

- Antipsychotic Agents
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsLess sedation, but pimozide is more likely to cause acute extrapyramidal symptoms than chlorpromazine.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tourette's disorder: Xerostomia and increased salivation (normal salivary flow resumes upon discontinuation), taste disturbance, and dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsPimozide is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Child/Adolescent ConsiderationsTwenty-two children 7-16 years of age with Tourette's disorder were treated with a mean dose of 3.4 mg/day (Sallee, 1997). Twenty-four patients with Tourette's disorder were treated with 2.9 mg/day (Bruggeman, 2001).

Bruggeman R, van der Linden C, Buitelaar JK, et al, “Risperidone Versus Pimozide in Tourette's Disorder: A Comparative Double-Blind Parallel-Group Study,” *J Clin Psychiatry*, 2001, 62(1):50-6.

Sallee FR, Nesbitt L, Jackson C, et al, “Relative Efficacy of Haloperidol and Pimozide in Children and Adolescents With Tourette's Disorder,” *Am J Psychiatry*, 1997, 154(8):1057-62.

Mental Health CommentOlder antipsychotic medications (chlorpromazine, haloperidol), which do not meet specific criteria for “atypical antipsychotics”, are often referred to as typical antipsychotics. They are associated with the troubling side effect, EPS. However, it is commonly believed that in order for a drug to treat psychosis, it must block dopamine is some manner.

Common side effects include sedation and neuroleptic effect (reduced initiative, interest in the environment, and display of emotion or affect). All **typical** antipsychotics are considered to be equally effective if given in equipotent doses. An inverse relationship exists between intrinsic antimuscarinic activity and propensity to cause extrapyramidal side effects. If dystonia or pseudoparkinsonism occurs, antiparkinsonian agents should be considered. If akathisia occurs, beta-blockers (eg, propranolol), benzodiazepines, or antiparkinsonian agents should be considered. Tardive dyskinesia (TD) secondary to typical antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. After this time period, the incidence is estimated to be 2% to 3% per year. Prevalence rates are ~15% to 20%. Female gender and age constitute risk factors for TD. No specific treatment exists for TD, however, patients are often initiated on/switched to an atypical antipsychotic because of their lower incidence to cause TD and hopes of suppression.

Typical antipsychotics are usually only indicated for schizophrenia, but are generally effective for mania and psychosis and/or behavioral syndromes secondary to other mental conditions. Nonpsychiatric uses include Tourette's syndrome, Huntington's disease, and occasionally, intractable hiccups, pruritus, nausea, and vomiting.

These drugs are thought to exert their antipsychotic activity by blocking dopamine D_2 receptors in the mesolimbic dopaminergic pathway. Side effects are often related to their ability to antagonize dopamine receptors in the nigrostriatal and tuberoinfundibular pathways.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Anesthesia and Critical Care Concerns/Other ConsiderationsPimozide causes less sedation but is more likely to cause extrapyramidal signs than chlorpromazine.

References

Bruggeman R, van der Linden C, Buitelaar JK, et al, “Risperidone Versus Pimozide in Tourette's Disorder: A Comparative Double-Blind Parallel-Group Study,” *J Clin Psychiatry*, 2001, 62(1):50-6.

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Larkin C, “Epileptogenic Potential of Pimozide,” *Am J Psychiatry*, 1983, 140(3):372-3.

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“Pimozide (Orap) Contraindicated With Clarithromycin (Biaxin™) and Other Macrolide Antibiotics,” *FDA Medical Bulletin*, October 1996, 3.

Rabins PV, Blacker D, Rovner BW, et al, “Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias,” October, 2007. Available at http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm

Risse SC and Barnes R, “Pharmacologic Treatment of Agitation Associated With Dementia,” *J Am Geriatr Soc*, 1986, 34(5):368-76. [PubMed 2870097]

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Saltz BL, Woerner MG, Kane JM, et al, “Prospective Study of Tardive Dyskinesia Incidence in the Elderly,” *JAMA*, 1991, 266(17):2402-6. [PubMed 1681122]

Seifert RD, “Therapeutic Drug Monitoring: Psychotropic Drugs,” *J Pharm Pract*, 1984, 6:403-16.

International Brand NamesOrap (1 mg) (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, HK, ID, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TH, TN, TZ, UG, YE, ZA, ZM, ZW); Orap (4 mg) (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Orap (AR, AT, AU, BE, BR, CH, CZ, DE, DK, ES, FR, GB, HR, IE, IN, IT, JP, LU, NL, NO, PL, VE); Orap Forte (4 mg) (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, HK, ID, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PT, QA, SA, SC, SD, SL, SN, SY, TH, TN, TZ, UG, YE, ZA, ZM, ZW); Pizide (TH); Spimo (TW)

Pinaverium

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(pin ah VEER ee um)
Canadian Brand NamesDicetel®
Pharmacologic CategoryCalcium Channel Blocker
Use: Labeled IndicationsTreatment and relief of symptoms associated with irritable bowel syndrome (IBS); treatment of symptoms related to functional disorders of the biliary tract
Dosing: Adults**IBS, biliary spasm:** Oral: Initial: 50 mg 3 times/day; in exceptional cases, the dosage may be increased up to 100 mg 3 times/day (maximum dose: 300 mg/day). Tablets should be taken with a full glass of water during a meal/snack.
Dosing: ElderlyRefer to adult dosing.
Administration: OralDo not crush tablet. Should be taken with a glass of water during meals or snacks. The tablet should not be swallowed when in the lying position or just before bedtime.
Dietary ConsiderationsShould be taken with a full glass of water during a meal/snack.
StorageStore at 15°C to 30°C (59°F to 86°F).
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to pinaverium or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Angina/MI: Increased angina and/or MI has occurred with initiation or dosage titration of calcium channel blockers.
- Esophageal irritation: May cause esophageal irritation; minimize risk by administering with a full glass of water with a meal/snack (do not crush tablets). Patients must be advised not to take medication when lying down or at bedtime. Avoid use in patients with possible gastroesophageal reflux or hiatal hernia.
- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition.
- Peripheral edema: The most common side effect is peripheral edema; occurs within 2-3 weeks of starting therapy.
- Reflex tachycardia: May occur with use.

Disease-related concerns:

- GI motility: Avoid using to treat motility dysfunction associated with underlying disease states.
- Hepatic impairment: Use with caution in patients with hepatic impairment; may require lower starting dose.
- Idiopathic hypertrophic subaortic stenosis (IHSS): Use with caution in patients with IHSS.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorNot available
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women; use is not recommended.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsManufacturer advises against administration in breast-feeding women.
Adverse Reactions<1%: Abdominal distension, constipation, diarrhea, drowsiness, dyspepsia, epigastric pain, headache, nausea, rash, vertigo, xerostomia
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet:

Dicetel® [CAN]: 50 mg, 100 mg [not available in the U.S.]

Generic AvailableNo
ManufacturerSolvay (Canada)
Mechanism of ActionBlocks influx of calcium via voltage-sensitive channels within smooth muscle cells of the gastrointestinal tract.
Pharmacotherapy PearlsNot available in U.S.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPinaverium Bromide

International Brand NamesDicetel (AR, AT, BE, BR, CH, FR, HU, IT, LU, NL, PT); Eldicet (ES, IN)

Pindolol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Pindolol may be confused with Parlodel®, Plendil®

Visken® may be confused with Visine®

Pronunciation(PIN doe lole)

Canadian Brand NamesApo-Pindol®; Gen-Pindolol; Novo-Pindol; Nu-Pindol; PMS-Pindolol; Visken®

Pharmacologic CategoryBeta Blocker With Intrinsic Sympathomimetic Activity

Use: Labeled IndicationsTreatment of hypertension, alone or in combination with other agents

Use: Unlabeled/InvestigationalPotential augmenting agent for antidepressants; ventricular arrhythmias/tachycardia, antipsychotic-induced akathisia, situational anxiety; aggressive behavior associated with dementia

Dosing: Adults

Hypertension: Oral: Initial: 5 mg twice daily, increase as necessary by 10 mg/day every 3-4 weeks (maximum daily dose: 60 mg); usual dose range (JNC 7): 10-40 mg twice daily.

Antidepressant augmentation (unlabeled use): Oral: 2.5 mg 3 times/day

Dosing: ElderlyOral: Initial: 5 mg once daily; increase as necessary by 5 mg/day every 3-4 weeks.

Dosing: Renal ImpairmentUse with caution. Clearance significantly decreased in uremic patients. Dosage reduction may be necessary.

Dosing: Hepatic ImpairmentUse with caution. Elimination half-life in cirrhotic patients may be 10 times as long compared to normal patients. Dosage reduction is necessary in severely impaired.

Dietary ConsiderationsMay be taken without regard to meals.

StorageStore below 30°C (86°F). Protect from light.

ContraindicationsBronchial asthma; cardiogenic shock; heart block (2nd or 3rd degree) except in patients with a functioning artificial pacemaker; overt cardiac failure; severe bradycardia

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Concerns related to adverse events:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.

- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.

- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.

- Heart failure (HF): Use with caution in patients with compensated HF and monitor for a worsening of the condition. If condition worsens, consider temporary discontinuation or dosage reduction of pindolol. Patients should be stabilized on heart failure regimen prior to initiation of beta-blocker. Beta-blocker therapy should be initiated at very low doses with gradual and very careful titration. Adjustment of other medications (ACE inhibitors and/or diuretics) may be required. Beta-blockers with intrinsic sympathomimetic activity (eg, pindolol) have not been demonstrated to be of value in HF.

- Hepatic impairment: Use with caution in patients with hepatic impairment; pindolol levels may increase significantly with hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis.

- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).

- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.

- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.

- Renal impairment: Use with caution in patients with renal impairment.

- Thyrotoxicosis: Beta-blockade may mask signs of hyperthyroidism (eg, tachycardia). Abrupt discontinuation of beta-blockade may exacerbate symptoms of hyperthyroidism and may also induce thyroid storm.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents which decrease myocardial function (eg, ether, cyclopropane and trichloroethylene).

- Calcium channel blockers (nondihydropyridines): Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block may occur.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered over 1-2 weeks to avoid acute tachycardia, hypertension, and/or ischemia.

Geriatric Considerations Due to alterations in the beta-adrenergic autonomic nervous system, beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (eg, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20% to 50% in elderly populations. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults.

Pregnancy Risk Factor B

Pregnancy Considerations Adverse events were not observed in animal studies. Pindolol crosses the human placenta. Beta-blockers have been associated with bradycardia, hypotension, and IUGR; IUGR is probably related to maternal hypertension. Available evidence suggests beta-blockers are generally safe during pregnancy (JNC 7).

Lactation Enters breast milk/not recommended

Breast-Feeding Considerations There is limited experience with pindolol. Cases of neonatal hypoglycemia have been reported following maternal use of beta-blockers at parturition or during breast-feeding. Monitor breast-fed infant for symptoms of beta-blockade (hypotension, bradycardia, etc) with long-term use.

Adverse Reactions

1% to 10%:

Cardiovascular: Edema (6%), chest pain (3%), bradycardia (≤2%), heart block (≤2%), hypotension (≤2%), syncope (≤2%), tachycardia (≤2%), palpitation (≤1%)

Central nervous system: Insomnia (10%), dizziness (9%), fatigue (8%), nervousness (7%), nightmares/vivid dreams (5%), anxiety (≤2%), lethargy (≤2%)

Dermatologic: Hyperhidrosis (≤2%), pruritus (1%)

Gastrointestinal: Nausea (5%), diarrhea (≤2%), vomiting (≤2%), weight gain (≤2%)

Genitourinary: Impotence (≤2%)

Hematologic: Claudication (≤2%)

Hepatic: ALT increased (7%), AST increased (7%)

Neuromuscular & skeletal: Muscle pain (10%), arthralgia (7%), weakness (4%), paresthesia (3%), muscle cramps (3%)

Ocular: Burning eyes (≤2%), visual disturbances (≤2%), eye discomfort (≤2%)

Renal: Polyuria (≤2%)

Respiratory: Dyspnea (5%), wheezing (≤2%)

Miscellaneous: Cold extremities (≤2%)

<1%, postmarketing, and/or case reports: Alkaline phosphatase increased, hallucination, heart failure, lactic acid dehydrogenase increased, uric acid increased

Other adverse reactions (noted with other beta-adrenergic-blocking agents that should be considered potential adverse events with pindolol): Agranulocytosis, alopecia, catatonia, clouded sensorium, disorientation, emotional lability, fever, intensification of pre-existing AV block, ischemic colitis, laryngospasm, mental depression, mesenteric artery thrombosis, nonthrombocytopenic purpura, Peyronie’s disease, rash (erythematous), respiratory distress, short-term memory loss, thrombocytopenic purpura

Metabolism/Transport Effects **Substrate** of CYP2D6 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, and licorice (may worsen hypertension). Avoid black cohosh, california poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, and shepherd's purse (may increase antihypertensive effect).

Monitoring ParametersBlood pressure, heart rate, respiratory function

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, anything that affects blood pressure or cardiac status). Assess patient response at beginning of therapy, when adjusting dosage, and periodically with long-term therapy (eg, cardiac, respiratory, hemodynamic status). If patient has diabetes, caution patient to monitor serum glucose levels closely (may alter glucose tolerance, potentiate hypoglycemia, or mask symptoms of hypoglycemia). Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed. Do not alter dose or discontinue without consulting prescriber. If you have diabetes, monitor serum glucose closely (drug may alter glucose tolerance or mask signs of hypoglycemia). May cause nervousness, fatigue, dizziness, insomnia, or postural hypotension (use caution when changing position from lying or sitting to standing, when driving, or climbing stairs until response to medication is known); or nausea or abdominal discomfort (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report chest pain or swelling of extremities; unusual weight gain (>5 lb/week); shortness of breath; unusual muscle weakness or pain; or other persistent adverse effects. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 5 mg, 10 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Pindolol)

5 mg (60): $15.99

10 mg (60): $16.99

Mechanism of ActionBlocks both beta$_1$- and beta$_2$-receptors and has mild intrinsic sympathomimetic activity; pindolol has negative inotropic and chronotropic effects and can significantly slow AV nodal conduction. Augmentive action of antidepressants thought to be mediated via a serotonin 1A autoreceptor antagonism.

Pharmacodynamics/Kinetics

Absorption: Rapid, 50% to 95%

Distribution: V$_d$: ~2 L/kg

Protein binding: 40%

Metabolism: Hepatic (60% to 65%) to conjugates

Half-life elimination: 3-4 hours; prolonged with advanced age, and cirrhosis (range: 2.5-30 hours)

Time to peak, serum: ~1 hour

Excretion: Urine (35% to 40% as unchanged drug); feces (6% to 9%)

Related Information

- Beta-Blockers

Dental Health: Effects on Dental TreatmentPindolol is a nonselective beta-blocker and may enhance the pressor response to epinephrine, resulting in hypertension and bradycardia. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution; epinephrine has interacted with nonselective beta-blockers to result in initial hypertensive episode followed by bradycardia

Mental Health: Effects on Mental StatusInsomnia is common; may cause dizziness, fatigue, nervousness, or nightmares; may rarely cause depression or hallucinations

Mental Health: Effects on Psychiatric TreatmentHas been used as an augmentive agent to the SSRIs for the treatment of depression; barbiturates may decrease the effects of beta-blockers

Cardiovascular ConsiderationsThis drug possesses intrinsic sympathomimetic activity. While beta-blockers with intrinsic sympathomimetic activity induce fewer side effects, the cardiovascular benefits listed below are less clear than for beta-blockers without intrinsic sympathomimetic activity.

Atrial Fibrillation: Beta-blocker therapy provides effective rate control in patients with atrial fibrillation (Class IIa recommendation).

Chronic Stable Angina: Beta-blockers are effective in the treatment of angina as monotherapy or when combined with nitrates and/or calcium channel blockers. In patients with severe intractable angina requiring negative cardiac chronotropic medications, pacemaker placement has been carried out to maintain heart rate in the setting of large doses of beta-blockers and/or calcium channel blockers. Beta-blockers are ineffective in the treatment of pure vasospastic (Prinzmetal) angina. It is beneficial to start and continue beta-blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated (Class Ia recommendation).

Heart Failure: Strong evidence supports that beta-blocker therapy, without intrinsic sympathomimetic activity (ISA), should be initiated in select patients with **stable** congestive heart failure (NYHA Class II-III). Pindolol possesses intrinsic sympathomimetic activity and should not be used in the treatment of heart failure. To date, carvedilol, sustained release metoprolol, and bisoprolol have demonstrated a beneficial effect on morbidity and mortality. It is important that beta-blocker therapy be instituted initially at very low doses with gradual and very careful titration.

Hypertension: Beta-blocker therapy in the treatment of hypertension has been associated with improved cardiovascular outcomes. According to the 2003 JNC-VII guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Beta-blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for a beta-blocker include patients with heart failure, post myocardial infarction, high coronary disease risk, or diabetes. In type-2 diabetic patients, a UK Prospective Diabetes Study Group (UKPDS) trial showed that beta-blocker therapy (atenolol) was as effective as an ACE inhibitor in reducing cardiovascular events and that the benefits of therapy were related more to the degree of antihypertensive efficacy rather than the class of drug used.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered over 1-2 weeks to avoid acute tachycardia and hypertension.

Anesthesia and Critical Care Concerns/Other ConsiderationsPindolol possesses intrinsic sympathomimetic activity. While beta-blockers with intrinsic sympathomimetic activity induce fewer side effects, the cardiovascular benefits are less clear than for beta-blockers without intrinsic sympathomimetic activity.

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered over 1-2 weeks to avoid acute tachycardia and hypertension.

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International Brand NamesApo-Pindolol (NZ); Barbloc (AU, TW); Blocklin (TW); Carvisken (JP); Decreten (ID); Dranolis (GR); Hexapindol (DK); Huma-Pindol (HU); Pidol (TW); Pinden (IL); Pindol (NZ); Pindomex (FI); Pinloc (FI); Pyndale (PH); Treparasen (GR); Viskeen (NL); Viskeen Retard (NL); Visken (AT, AU, BE, BF, BG, BJ, BR, CH, CI, CZ, DE, DK, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, HU, IE, IN, IT, KE, LR, LU, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, PH, PL, PT, RU, SC, SD, SE, SL, SN, TN, TR, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Viskene (PT); Vypen (NZ)

Pioglitazone and Glimepiride

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(pye oh GLI ta zone & GLYE me pye ride)

U.S. Brand NamesDuetact™

Pharmacologic CategoryAntidiabetic Agent, Sulfonylurea; Antidiabetic Agent, Thiazolidinedione; Hypoglycemic Agent, Oral

Use: Labeled IndicationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as an adjunct to diet and exercise

Dosing: Adults**Type 2 diabetes mellitus:** Oral: Initial dose should be based on current dose of pioglitazone and/or sulfonylurea.

Patients inadequately controlled on **glimepiride** alone: Initial dose: 30 mg/2 mg or 30 mg/4 mg once daily

Patients inadequately controlled on **pioglitazone** alone: Initial dose: 30 mg/2 mg once daily

Patients with systolic dysfunction (eg, NYHA Class I and II): Initiate only after patient has been safely titrated to 30 mg of pioglitazone. Initial dose: 30 mg/2 mg or 30 mg/4 mg once daily.

Note: No exact dosing relationship exists between glimepiride and other sulfonlyureas. Dosing should be limited to less than or equal to the maximum initial dose of glimepiride (2 mg). When converting patients from other sulfonylureas with longer half lives (eg, chlorpropamide) to glimepiride, observe patient carefully for 1-2 weeks due to overlapping hypoglycemic effects.

Dosing adjustment: Dosage may be increased up to max dose and formulation strengths available; tablet should not be given more than once daily; see individual agents for frequency of adjustments. Dosage adjustments in patients with systolic dysfunction should be done carefully and patient monitored for symptoms of worsening heart failure.

Maximum dose: Pioglitazone 45 mg/glimepiride 8 mg daily

Dosing: ElderlyInitial: Glimepiride 1 mg/day prior to initiating Duetact™; dose titration and maintenance dosing should be conservative to avoid hypoglycemia. Refer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <22 mL/minute: Initial dose should be 1 mg of glimepiride and dosage increments should be based on fasting blood glucose levels.

Dosing: Hepatic ImpairmentDo not initiate treatment with active liver disease or ALT >2.5 times ULN. During treatment, if ALT levels elevate >3 times ULN, the test should be repeated as soon as possible. If ALT levels remain >3 times ULN or if the patient is jaundiced, Duetact™ should be discontinued.

Administration: OralAdminister once daily with the first main meal of the day. To avoid hypoglycemia, patients without oral intake may need to have the dose held.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from moisture and humidity.

ContraindicationsHypersensitivity to glimepiride, pioglitazone, or any component of the formulation; diabetic ketoacidosis (with or without coma); NYHA Class III/IV heart failure (initiation of therapy)

Warnings/Precautions

Boxed warnings:

- Heart failure/cardiac effects: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS) have not supported an association.

- Fractures: Increased incidence of bone fractures in females treated with pioglitazone; majority of fractures occurred in the lower limb and distal upper limb. Consider risk of fracture prior to initiation and during use.

- Heart failure/cardiac effects: **[U.S. Boxed Warning]: Thiazolidinediones, including pioglitazone, may cause or exacerbate heart failure;** closely monitor for signs and symptoms of heart failure (eg, rapid weight gain, dyspnea, edema), particularly after initiation or dose increases. Not recommended for use in any patient with symptomatic heart failure; initiation of therapy is contraindicated in patients with NYHA class III or IV heart failure. If used in patients with NYHA class II (systolic) heart failure, initiate at lowest dosage and monitor closely. Use with caution in patients with edema; may increase plasma volume and/or cause fluid retention. Dose reduction or discontinuation is recommended if heart failure suspected.

- Hematologic effects: May decrease hemoglobin/hematocrit; effects may be related to increased plasma volume.

- Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when ethanol is ingested, or when more than one glucose-lowering drug is used. It is also more likely in elderly patients, malnourished patients and in patients with impaired renal or hepatic function; use with caution.

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

- Weight gain: Dose-related weight gain observed with pioglitazone use; mechanism unknown but likely associated with fluid retention and fat accumulation.

Disease-related concerns:

- Anemia: Use with caution in patients with anemia; may reduce hemoglobin and hematocrit.

- Diabetes, type 1: Mechanism of pioglitazone requires the presence of insulin; therefore, use in type 1 diabetes (insulin dependent, IDDM) or diabetic ketoacidosis is not recommended.

- Hepatic impairment: Use pioglitazone with caution in patients with minor elevations in transaminases (AST or ALT); do not initiate in patients with active liver disease of ALT >2.5 times the upper limit of normal at baseline. During therapy, if ALT >3 times the upper limit of normal, reevaluate levels promptly and discontinue if elevation persists or if jaundice occurs at any time during use. Idiosyncratic hepatotoxicity has been reported with another thiazolidinedione agent (troglitazone); avoid use in patients who previously experienced jaundice during troglitazone therapy.

- Macular edema/diabetic retinopathy: Use pioglitazone with caution in patients with pre-existing macular edema or diabetic retinopathy; postmarketing events of new-onset or worsening diabetic macular edema with decreased visual acuity have been reported.

- Stress-related states: It may be necessary to discontinue therapy and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Premenopausal/anovulatory females: Use pioglitazone with caution in premenopausal, anovulatory women; may result in a resumption of ovulation, increasing the risk of pregnancy.

Geriatric ConsiderationsRapid and prolonged hypoglycemia (>12 hours) despite hypertonic glucose injections have been reported with glimepiride. Age, hepatic impairment, and renal impairment are independent risk factors for hypoglycemia; dosage titration should be made at weekly intervals. How “tightly” a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar of <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well they recognize hypoglycemic or hyperglycemic symptoms, and how to respond to them and their other disease states. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination; therefore, pioglitazone/glimepiride is classified as pregnancy category C. See individual agents.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsSee individual agents.

Pregnancy & Lactation, In-Depth

- Glimepiride in Pregnancy & Lactation
- Pioglitazone in Pregnancy & Lactation

Adverse ReactionsAlso see individual agents.

>10%:

Cardiovascular: Peripheral edema (6% to 12%)

Endocrine & metabolic: Hypoglycemia (13 % to 16%)

Gastrointestinal: Weight gain (9% to 13%)

Respiratory: Upper respiratory tract infection (12% to 15%)

1% to 10%:

Central nervous system: Headache (4% to 7%)

Gastrointestinal: Diarrhea (4% to 6%), nausea (4% to 5%)

Genitourinary: Urinary tract infection (6% to 7%)

Hematologic: Anemia (≤2%)

Neuromuscular & skeletal: Limb pain (4% to 5%)

Metabolism/Transport Effects

Pioglitazone: **Substrate** of CYP2C8 (major), 3A4 (minor); **Inhibits** CYP2C8 (moderate), 2C9 (weak), 2C19 (weak), 2D6 (moderate); **Induces** CYP3A4 (weak)

Glimepiride: **Substrate** of CYP2C9 (major)

Also see individual agents.

Drug Interactions

Alcohol (Ethyl): Sulfonylureas may enhance the adverse/toxic effect of Alcohol (Ethyl). A flushing reaction may occur. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Antidiabetic Agents (Thiazolidinedione). *Risk D: Consider therapy modification*

Chloramphenicol: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Cyclic Antidepressants: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonylureas may increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP2C8 Inducers (Highly Effective): May increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Moderate): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Strong): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Fibric Acid Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Fluconazole: May increase the serum concentration of Sulfonylureas. *Risk C: Monitor therapy*

Gemfibrozil: May decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Insulin: May enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pregabalin: May enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Salicylates: May enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. **Exceptions:** Sulfacetamide. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Trimethoprim: May decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions Also see individual agents.

Monitoring ParametersLiver enzymes and renal function prior to initiation and periodically during treatment. If the ALT is increased to >2.5 times ULN, liver function testing should be performed more frequently until the levels return to normal or pretreatment values. **Note:** If ALT levels elevate >3 times ULN, the test should be repeated as soon as possible. If ALT levels remain >3 times ULN or if the patient is jaundiced, therapy should be discontinued. Also monitor hemoglobin A_{1C}, serum glucose and signs and symptoms of heart failure. Routine ophthalmic exams recommended; patients reporting visual deterioration should have a prompt referral to an ophthalmologist and consideration should be given to discontinuing pioglitazone.

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsHemoglobin A_{1C}, serum glucose; liver enzymes and renal function prior to initiation and periodically during treatment

Note: If the ALT is increased to >2.5 times ULN, liver function testing should be performed more frequently until the levels return to normal or pretreatment values. If ALT levels elevate >3 times ULN, the test should be repeated as soon as possible. If ALT levels remain >3 times ULN or if the patient is jaundiced, therapy should be discontinued. Also monitor hemoglobin A_{1C}, serum glucose

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Duetact™:

30 mg/2 mg: Pioglitazone 30 mg and glimepiride 2 mg

30 mg/4 mg: Pioglitazone 30 mg and glimepiride 4 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Duetact)

30-2 mg (30): $211.74

30-4 mg (30): $211.74

Mechanism of Action

Pioglitazone: A thiazolidinedione that lowers blood glucose by improving target cell response to insulin, without increasing pancreatic insulin secretion. It has a mechanism of action that is dependent on the presence of insulin for activity.

Glimepiride: A sulfonylurea that stimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites.

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentPioglitazone-dependent patients with diabetes (noninsulin dependent, type 2) or glimepiride-dependent patients with diabetes (noninsulin dependent, type 2) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue

Mental Health: Effects on Psychiatric TreatmentWeight gain is common; use caution with atypical antipsychotics. Nefazodone and other CYP3A4 inhibitors may decrease the metabolism of pioglitazone; glucose may need to be checked more frequently. Phenothiazines and TCAs may antagonize hypoglycemic effects of glimepiride; MAO inhibitors and TCAs may enhance hypoglycemic effects.

Index TermsGlimepiride and Pioglitazone; Glimepiride and Pioglitazone Hydrochloride

References

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Yaturu S, Bryant B, Jain SK, "Thiazolidinedione Treatment Decreases Bone Mineral Density in Type 2 Diabetic Men," *Diabetes Care*, 2007, 30(6):1574-76.[PubMed 17363747]

International Brand NamesTandemact (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Pioglitazone and Metformin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(pye oh GLI ta zone & met FOR min)

U.S. Brand NamesActoplus Met™

Pharmacologic CategoryAntidiabetic Agent, Biguanide; Antidiabetic Agent, Thiazolidinedione

Use: Labeled IndicationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM)

Dosing: Adults**Type 2 diabetes mellitus:** Oral: Initial dose should be based on current dose of pioglitazone and/or metformin; daily dose should be divided and given with meals.

Patients inadequately controlled on **metformin alone**: Initial dose: Pioglitazone 15-30 mg/day plus current dose of metformin

Patients inadequately controlled on **pioglitazone alone**: Initial dose: Metformin 1000-1700 mg/day plus current dose of pioglitazone

Note: When switching from combination pioglitazone and metformin as separate tablets: Use current dose.

Dosing adjustment: Doses may be increased as increments of pioglitazone 15 mg and/or metformin 500-850 mg, up to the maximum dose; doses should be titrated gradually. Guidelines for frequency of adjustment (adapted from rosiglitazone/metformin combination labeling):

After a change in the **metformin** dosage, titration can be done after 1-2 weeks

After a change in the **pioglitazone** dosage, titration can be done after 8-12 weeks

Maximum dose: Pioglitazone 45 mg/metformin 2550 mg daily

Dosing: Elderly Refer to adult dosing. The initial and maintenance dosing should be conservative, due to the potential for decreased renal function (monitor). Generally, elderly patients should not be titrated to the maximum; do not use in patients ≥80 years of age unless normal renal function has been established.

Dosing: Renal ImpairmentDo not use with renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females or abnormal clearance).

Dosing: Hepatic ImpairmentDo not initiate treatment with active liver disease or ALT >2.5 times ULN. During treatment if ALT levels elevate >3 times ULN, the test should be repeated as soon as possible. If ALT levels remain >3 times ULN or if the patient is jaundiced, therapy should be discontinued.

Administration: OralAdminister with meals.

Dietary ConsiderationsShould be taken with meals. Avoid ethanol. Dietary modification based on ADA recommendations is a part of therapy. Monitor for signs and symptoms of vitamin B_{12} and/or folic acid deficiency; supplementation may be required.

Storage Store at 15°C to 30°C (59°F to 86°F). Protect from moisture and humidity.

ContraindicationsHypersensitivity to pioglitazone, metformin, or any component of the formulation; NYHA Class III/IV heart failure (initiation of therapy); renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females, or abnormal creatinine clearance which may also result from conditions such as cardiovascular collapse, acute myocardial infarction, and septicemia); acute or chronic metabolic acidosis with or without coma (including diabetic ketoacidosis); concurrent iodinated radiocontrast adminstration (manufacturer recommends temporary discontinuation of metformin)

Warnings/Precautions

Boxed warnings:

- Heart failure/cardiac effects: See “Concerns related to adverse effects” below.
- Lactic acidosis: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Fractures: Increased incidence of bone fractures in females treated with pioglitazone; majority of fractures occurred in the lower limb and distal upper limb. Consider risk of fracture prior to initiation and during use.
- Heart failure/cardiac effects: **[U.S. Boxed Warning]: Thiazolidinediones, including pioglitazone, may cause or exacerbate heart failure;** closely monitor for signs and symptoms of heart failure (eg, rapid weight gain, dyspnea, edema), particularly after initiation or dose increases. Not recommended for use in any patient with symptomatic heart failure; initiation of therapy is contraindicated in patients with NYHA class III or IV heart failure. If used in patients with NYHA class II (systolic) heart failure, initiate at lowest dosage and monitor closely. In addition metformin should be used with caution in patients with heart failure requiring pharmacologic management, particularly in unstable or acute heart failure due to risk of lactic acidosis secondary to hypoperfusion. Use with caution in patients with edema; may increase plasma volume and/or cause fluid retention. Dose reduction or discontinuation is recommended if heart failure suspected.
- Hematologic effects: Pioglitazone may decrease hemoglobin/hematocrit; effects may be related to increased plasma volume. Metformin may impair vitamin B_{12} absorption; monitor for anemia.

- Lactic acidosis: **[U.S. Boxed Warning]: Lactic acidosis is a rare, but potentially severe consequence of therapy with metformin.** Lactic acidosis should be suspected in any patient with diabetes receiving metformin with evidence of acidosis but without evidence of ketoacidosis. Discontinue metformin in clinical situations predisposing to hypoxemia, including conditions such as cardiovascular collapse, respiratory failure, acute myocardial infarction, acute congestive heart failure, and septicemia. The risk of accumulation and lactic acidosis increases with the degree of impairment of renal function.

- Weight gain: Dose-related weight gain observed with pioglitazone use; mechanism unknown but likely associated with fluid retention and fat accumulation.

Disease-related concerns:

- Anemia: Use pioglitazone with caution in patients with anemia; may reduce hemoglobin and hematocrit.

- Diabetes, type 1: Mechanism of pioglitazone requires the presence of insulin; therefore, use in type 1 diabetes (insulin dependent, IDDM) or diabetic ketoacidosis is not recommended.

- Hepatic impairment: Avoid metformin use in patients with impaired liver function due to potential for lactic acidosis. Use pioglitazone with caution in patients with elevated transaminases (AST or ALT); do not initiate in patients with active liver disease of ALT >2.5 times the upper limit of normal at baseline. During therapy, if ALT >3 times the upper limit of normal, reevaluate levels promptly and discontinue if elevation persists or if jaundice occurs at any time during use. Idiosyncratic hepatotoxicity has been reported with another thiazolidinedione agent (troglitazone); avoid use in patients who previously experienced jaundice during troglitazone therapy. Monitoring should include periodic determinations of liver function.

- Macular edema/diabetic retinopathy: Use pioglitazone with caution in patients with pre-existing macular edema or diabetic retinopathy; postmarketing events of new-onset or worsening diabetic macular edema with decreased visual acuity have been reported.

- Renal impairment: Metformin is substantially excreted by the kidney; patients with renal function below the limit of normal for their age should not receive therapy. Use of concomitant medications that may affect renal function (ie, affect tubular secretion) may also affect metformin disposition. Metformin should be withheld in patients with dehydration and/or prerenal azotemia.

- Stress-related states: It may be necessary to discontinue metformin and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Special populations:

- Elderly: Metformin should not be initiated in patients ≥80 years of age unless normal renal function is confirmed.

- Pediatrics: Safety and efficacy have not been established in children.

- Premenopausal/anovulatory females: Use pioglitazone with caution in premenopausal, anovulatory women; may result in a resumption of ovulation, increasing the risk of pregnancy.

Other warnings/precautions:

- Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism.

- Iodinated contrast: Metformin therapy should be temporarily discontinued prior to or at the time of intravascular administration of iodinated contrast media (potential for acute alteration in renal function). Metformin should be withheld for 48 hours after the radiologic study and restarted only after renal function has been confirmed as normal.

- Surgical procedures: Metformin therapy should be suspended for any surgical procedures (resume only after normal intake resumed and normal renal function is verified).

Geriatric ConsiderationsIntensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies were not conducted with this combination; therefore, pioglitazone/metformin is classified as pregnancy category C. See individual agents.

Lactation

Metformin: Enters breast milk/not recommended

Pioglitazone: Excretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsSee individual agents.

Pregnancy & Lactation, In-Depth

- MetFORMIN in Pregnancy & Lactation
- Pioglitazone in Pregnancy & Lactation

Adverse ReactionsAlso see individual agents. Percentages of adverse effects as reported with the combination product.

>10%:

Cardiovascular: Edema (lower limb, 3% to 11%)

Respiratory: Upper respiratory infection (12% to 16%)

1% to 10%:

Central nervous system: Headache (2% to 6%), dizziness (5%)

Endocrine & metabolic: Weight gain (3% to 7%)

Gastrointestinal: Diarrhea (5% to 6%), nausea (4% to 6%)

Genitourinary: Urinary tract infection (5% to 6%)

Hematologic: Anemia (≤2%)

Respiratory: Sinusitis (4% to 5%)

Metabolism/Transport Effects Pioglitazone: **Substrate** of CYP2C8 (major), 3A4 (minor); **Inhibits** CYP2C8 (moderate), 2C9 (weak), 2C19 (weak), 2D6 (moderate); **Induces** CYP3A4 (weak)

Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Antidiabetic Agents (Thiazolidinedione). *Risk D: Consider therapy modification*

Cephalexin: May increase the serum concentration of MetFORMIN. *Risk C: Monitor therapy*

Cimetidine: May decrease the excretion of MetFORMIN. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

CYP2C8 Inducers (Highly Effective): May increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Moderate): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Strong): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Gemfibrozil: May decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Insulin: May enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Iodinated Contrast Agents: May enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pregabalin: May enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Trimethoprim: May decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions See individual agents.

Monitoring ParametersHemoglobin A_{1c}, serum glucose; signs and symptoms of heart failure; liver enzymes prior to initiation and periodically during treatment (per clinician judgment). If the ALT is increased to >2.5 times ULN, liver function testing should be performed more frequently until the levels return to normal or pretreatment values. Patients with an elevation in ALT >3 times ULN should be rechecked as soon as possible. If the ALT levels remain >3 times ULN, therapy with pioglitazone should be discontinued. Initial and periodic monitoring of hematologic parameters (eg, hemoglobin/hematocrit and red blood cell indices) and renal function should performed. Check vitamin B_{12} and folate if anemia is present. Routine ophthalmic exams recommended; patients reporting visual deterioration should have a prompt referral to an ophthalmologist and consideration should be given to discontinuing pioglitazone.

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsHemoglobin A_{1c}, serum glucose; signs and symptoms of heart failure; liver enzymes prior to initiation and periodically during treatment (per clinician judgment). If the ALT is increased to >2.5 times ULN, liver function testing should be performed more frequently until the levels return to normal or pretreatment values. Patients with an elevation in ALT >3 times ULN should be rechecked as soon as possible. If the ALT levels remain >3 times ULN, therapy with pioglitazone should be discontinued. Initial and periodic monitoring of hematologic parameters (eg, hemoglobin/hematocrit and red blood cell indices) and renal function should performed. Check vitamin B_{12} and folate if anemia is present.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Actoplus Met™:

15/500: Pioglitazone 15 mg and metformin hydrochloride 500 mg

15/850: Pioglitazone 15 mg and metformin hydrochloride 850 mg

Generic AvailableNo

ManufacturerTakeda Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Actoplus Met)

15-500 mg (30): $108.01

15-850 mg (30): $106.94

Mechanism of Action

Pioglitazone is a thiazolidinedione antidiabetic agent that lowers blood glucose by improving target cell response to insulin, without increasing pancreatic insulin secretion. It has a mechanism of action that is dependent on the presence of insulin for activity.

Metformin decreases hepatic glucose production, decreasing intestinal absorption of glucose, and improves insulin sensitivity (increases peripheral glucose uptake and utilization).

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentPioglitazone-dependent patients with diabetes (noninsulin dependent, type 2) or metformin-dependent patients with diabetes (noninsulin dependent, type 2) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause weight gain; concomitant use with psychotropic agents may produce additive effects; monitor. May cause GI side effects, which when combined with lithium, SSRIs, valproic acid, or carbamazepine may produce additive effects.

Index TermsMetformin Hydrochloride and Pioglitazone Hydrochloride

References

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Yaturu S, Bryant B, Jain SK, “Thiazolidinedione Treatment Decreases Bone Mineral Density in Type 2 Diabetic Men,” *Diabetes Care*, 2007, 30(6):1574-76.[PubMed 17363747]

International Brand Names Competact (CH, DE, EE, GB, IE, NO, SE); Diavista-M (IN); Pioglit-MF15 (IN); Piomed M-15 (IN)

Pioglitazone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Actos® may be confused with Actidose®, Actonel®

Pronunciation(pye oh GLI ta zone)

U.S. Brand NamesActos®

Canadian Brand NamesActos®; Apo-Pioglitazone; CO Pioglitazone; Gen-Pioglitazone; Novo-Pioglitazone; PMS-Pioglitazone; ratio-Pioglitazone; Sandoz-Pioglitazone; SPEF-Pioglitazone

Pharmacologic CategoryAntidiabetic Agent, Thiazolidinedione

Use: Labeled Indications

Type 2 diabetes mellitus (noninsulin dependent, NIDDM), monotherapy: Adjunct to diet and exercise, to improve glycemic control

Type 2 diabetes mellitus (noninsulin dependent, NIDDM), combination therapy with sulfonylurea, metformin, or insulin: When diet, exercise, and a single agent alone does not result in adequate glycemic control

Use: Unlabeled/Investigational

Polycystic ovary syndrome (PCOS)

Dosing: Adults**Type 2 diabetes:** Oral:

Monotherapy: Initial: 15-30 mg once daily; if response is inadequate, the dosage may be increased in increments up to 45 mg once daily; maximum recommended dose: 45 mg once daily

Combination therapy:

Note: Maximum recommended dose: 45 mg/day

With sulfonylureas: Initial: 15-30 mg once daily; dose of sulfonylurea should be reduced if the patient reports hypoglycemia

With metformin: Initial: 15-30 mg once daily; it is unlikely that the dose of metformin will need to be reduced due to hypoglycemia

With insulin: Initial: 15-30 mg once daily; dose of insulin should be reduced by 10% to 25% if the patient reports hypoglycemia or if the plasma glucose falls to below 100 mg/dL.

Dosage adjustment in patients with CHF (NYHA Class II) in mono- or combination therapy: Oral: Initial: 15 mg once daily; may be increased after several months of treatment, with close attention to heart failure symptoms

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentClearance is significantly lower in hepatic impairment (Child-Pugh Grade B/C). Therapy should not be initiated if the patient exhibits active liver disease or increased transaminases (>2.5 times ULN) at baseline. During treatment if ALT levels elevate >3 times ULN, the test should be repeated as soon as possible. If ALT levels remain >3 times ULN or if the patient is jaundiced, therapy should be discontinued.

Administration: OralMay be administered without regard to meals.

Dietary ConsiderationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM) should include diet control. May be taken without regard to meals.

ContraindicationsHypersensitivity to pioglitazone or any component of the formulation; NYHA Class III/IV heart failure (initiation of therapy)

Allergy Considerations

- Thiazolidinedione Allergy

Warnings/Precautions

Boxed warnings:

• Heart failure/cardiac effects: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

• Fractures: Increased incidence of bone fractures in females treated with pioglitazone; majority of fractures occurred in the lower limb and distal upper limb. Consider risk of fracture prior to initiation and during use.

- Heart failure/cardiac effects: **[U.S. Boxed Warning]: Thiazolidinediones, including pioglitazone, may cause or exacerbate heart failure;** closely monitor for signs and symptoms of heart failure (eg, rapid weight gain, dyspnea, edema), particularly after initiation or dose increases. Not recommended for use in any patient with symptomatic heart failure; initiation of therapy is contraindicated in patients with NYHA class III or IV heart failure. If used in patients with NYHA class II (systolic) heart failure, initiate at lowest dosage and monitor closely. Use with caution in patients with edema; may increase plasma volume and/or cause fluid retention. Dose reduction or discontinuation is recommended if heart failure suspected.

- Hematologic effects: May decrease hemoglobin/hematocrit; effects may be related to increased plasma volume.

- Weight gain: Dose-related weight gain observed with use; mechanism unknown but likely associated with fluid retention and fat accumulation.

Disease-related concerns:

- Anemia: Use with caution in patients with anemia; may reduce hemoglobin and hematocrit.

- Diabetes, type 1: Mechanism requires the presence of insulin; therefore, use in type 1 diabetes (insulin dependent, IDDM) or diabetic ketoacidosis is not recommended.

- Hepatic impairment: Use with caution in patients with elevated transaminases (AST or ALT); do not initiate in patients with active liver disease of ALT >2.5 times the upper limit of normal at baseline. During therapy, if ALT >3 times the upper limit of normal, reevaluate levels promptly and discontinue if elevation persists or if jaundice occurs at any time during use. Idiosyncratic hepatotoxicity has been reported with another thiazolidinedione agent (troglitazone); avoid use in patients who previously experienced jaundice during troglitazone therapy.

- Macular edema/diabetic retinopathy: Use with caution in patients with pre-existing macular edema or diabetic retinopathy; postmarketing events of new-onset or worsening diabetic macular edema with decreased visual acuity have been reported.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Premenopausal/anovulatory females: Use with caution in premenopausal, anovulatory women; may result in a resumption of ovulation, increasing the risk of pregnancy.

Geriatric ConsiderationsNo dosage adjustment is recommended in elderly patients. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsPioglitazone is classified as pregnancy category C due to adverse effects observed in animal studies. The use of pioglitazone in pregnant women is limited to very few case reports where pregnancy occurred during treatment for polycystic ovarian syndrome (PCOS); details concerning fetal outcomes are limited. Thiazolidinediones may cause ovulation in anovulatory premenopausal women, increasing the risk of pregnancy; adequate contraception in premenopausal women is recommended. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if pioglitazone is excreted in breast milk. Breast-feeding is not recommended by the manufacturer.

Pregnancy & Lactation, In-Depth

- Pioglitazone in Pregnancy & Lactation

Adverse Reactions

>10%:

Cardiovascular: Edema (5%; in combination trials with sulfonlyureas or insulin, the incidence of edema was as high as 15%)

Respiratory: Upper respiratory tract infection (13%)

1% to 10%:

Cardiovascular: Heart failure (requiring hospitalization; up to 6% in patients with prior macrovascular disease)

Central nervous system: Headache (9%), fatigue (4%)

Gastrointestinal: Tooth disorder (5%)

Hematologic: Anemia (≤2%)

Neuromuscular & skeletal: Myalgia (5%)

Respiratory: Sinusitis (6%), pharyngitis (5%)

<1%: CPK increased, transaminases increased

Frequency not defined: HDL-cholesterol increased, hematocrit/hemoglobin decreased, hypoglycemia (in combination trials with sulfonylureas or insulin), serum triglycerides decreased, weight gain/loss

Postmarketing and/or case reports: Bladder cancer, blurred vision, dyspnea (associated with weight gain and/or edema), fractures (females; usually in distal upper limbs or distal lower limbs), hepatic failure (very rare), hepatitis, macular edema (new onset or worsening), visual acuity decreased

Metabolism/Transport Effects **Substrate** of CYP2C8 (major), 3A4 (minor); **Inhibits** CYP2C8 (moderate), 2C9 (weak), 2C19 (weak), 2D6 (moderate); **Induces** CYP3A4 (weak)

Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Antidiabetic Agents (Thiazolidinedione). *Risk D: Consider therapy modification*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

CYP2C8 Inducers (Highly Effective): May increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Moderate): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Strong): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Gemfibrozil: May decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Insulin: May enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pregabalin: May enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Trimethoprim: May decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Caution with ethanol (may cause hypoglycemia).

Food: Peak concentrations are delayed when administered with food, but the extent of absorption is not affected. Pioglitazone may be taken without regard to meals.

Herb/Nutraceutical: Caution with alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, and stinging nettle (may cause hypoglycemia).

Monitoring Parameters Hemoglobin A_{1c}, serum glucose; signs and symptoms of heart failure; liver enzymes prior to initiation and periodically during treatment (per clinician judgment). If the ALT is increased to >2.5 times the upper limit of normal, liver function testing should be performed more frequently until the levels return to normal or pretreatment values. Patients with an elevation in ALT >3 times the upper limit of normal should be rechecked as soon as possible. If the ALT levels remain >3 times the upper limit of normal, therapy with pioglitazone should be discontinued. Routine ophthalmic exams are recommended; patients reporting visual deterioration should have a prompt referral to an ophthalmologist and consideration should be given to discontinuing pioglitazone.

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking. Assess results of laboratory tests. and response to therapy frequently until patient is stable. Monitor for signs of heart failure (weight gain, edema, dyspnea). Monitor for adverse response. Assess knowledge/teach risks of hyper-/hypoglycemia, symptoms, and treatment. Refer patient to a diabetic educator, if available.

Monitoring: Lab TestsHemoglobin A_{1c}, serum glucose, liver enzymes prior to initiation and periodically during treatment (per clinician judgment); if the ALT is increased to >2.5 times ULN, liver function testing should be performed more frequently until the levels return to normal or pretreatment values. Patients with an elevation in ALT >3 times ULN should be rechecked as soon as possible. If the ALT levels remain >3 times ULN, therapy with pioglitazone should be discontinued.

Patient EducationUse exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. May be taken without regard to meals. Avoid or use caution with alcohol while taking this medication. If dose is missed, take as soon as possible. If dose is missed completely one day, do not double dose the next day. Follow dietary, exercise, and glucose monitoring instructions of prescriber (more frequent monitoring may be advised in periods of stress, trauma, surgery, increased exercise etc). Report respiratory infection, unusual weight gain, aggravation of hyper-/hypoglycemic condition, unusual swelling of extremities, shortness of breath, fatigue, yellowing of skin or eyes, dark urine, pale stool, nausea/vomiting, abdominal pain, or muscle pain. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Use alternate means of contraception if using oral contraceptives. You may be at increased risk of pregnancy while taking this medication. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Actos®: 15 mg, 30 mg, 45 mg

Generic AvailableNo

ManufacturerTakeda Pharmaceuticals America, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Actos)

15 mg (30): $141.98

30 mg (30): $203.31

45 mg (30): $222.38

Mechanism of ActionThiazolidinedione antidiabetic agent that lowers blood glucose by improving target cell response to insulin, without increasing pancreatic insulin secretion. It has a mechanism of action that is dependent on the presence of insulin for activity. Pioglitazone is a potent and selective agonist for peroxisome proliferator-activated receptor-gamma (PPARgamma). Activation of nuclear PPARgamma receptors influences the production of a number of gene products involved in glucose and lipid metabolism. PPARgamma is abundant in the cells within the renal collecting tubules; fluid retention results from stimulation by thiazolidinediones which increases sodium reabsorption.

Pharmacodynamics/Kinetics

Onset of action: Delayed

Peak effect: Glucose control: Several weeks

Distribution: V_{ss} (apparent): 0.63 L/kg

Protein binding: 99.8%; primarily to albumin

Metabolism: Hepatic (99%) via CYP2C8 and 3A4 to both active and inactive metabolites

Half-life elimination: Parent drug: 3-7 hours; Total: 16-24 hours

Time to peak: ~2 hours; delayed with food

Excretion: Urine (15% to 30%) and feces as metabolites

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tooth disorder. Pioglitazone-dependent diabetics should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue

Mental Health: Effects on Psychiatric TreatmentWeight gain is common; caution with atypical antipsychotics; nefazodone and other CYP3A4 inhibitors may decrease the metabolism of pioglitazone; glucose may need to be checked more frequently

Cardiovascular ConsiderationsThe glitazones are peroxisome proliferator-activated receptor gamma (PPAR gamma) agonists used to treat type 2 diabetes. Their actions ameliorate insulin resistance and could positively affect cardiovascular risk.

The PROACTIVE study is a randomized, double-blind, placebo-controlled study of type 2 diabetes with macrovascular disease (Dormandy JA, 2005). Patients received either placebo or pioglitazone (45 mg/day). The primary endpoint included all-cause mortality, nonfatal MI, stroke, ACS, and a variety of CV interventions. The secondary endpoint was all-cause mortality, nonfatal MI, and stroke. Over 5000 patients were enrolled and followed for a mean of 2.8 years. The secondary endpoint was achieve in 301 (12.3%) of pioglitazone patients and 358 (14.4%) of placebo patients. Pioglitazone significantly reduced (p = 0.02; CI 0.72-0.98) the incidence of all-cause mortality, nonfatal MI, and stroke in this population. The incidence of edema (without heart failure), heart failure, and weight gain were increased in the pioglitazone group.

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International Brand NamesActos (AR, AT, AU, BB, BE, BG, BM, BO, BR, BS, BZ, CH, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, GY, HK, HN, ID, IE, IT, JM, JP, KP, MX, MY, NI, NL, NO, PA, PE, PH, PR, PT, PY, RU, SE, SR, SV, TH, TR, TT, TW, UY, VE); Anxotos (TW); Beitangning (CL); Cereluc (AR); Diabetone (PH); Glita (IN); Glucemin (CO); Glustin (AE, AT, BE, BF, BG, BH, BJ, CH, CI, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HN, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, NO, OM, PT, QA, RU, SA, SC, SD, SE, SL, SN, SY, TN, TR, TZ, UG, YE, ZA, ZM, ZW); Pioglit (IN, PY); Piomed (UY); Piota (TW); Piozone (PH); Prialta (PH); Utmos (TH); Zactos (MX); Zolid (PK); Zypi (PH)

Piperacillin and Tazobactam Sodium

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Zosyn® may be confused with Zofran®, Zyvox®

Pronunciation(pi PER a sil in & ta zoe BAK tam SOW dee um)

U.S. Brand NamesZosyn®

Canadian Brand NamesTazocin®

Pharmacologic CategoryAntibiotic, Penicillin

Use: Labeled IndicationsTreatment of moderate-to-severe infections caused by susceptible organisms, including infections of the lower respiratory tract (community-acquired pneumonia, nosocomial pneumonia); urinary tract; uncomplicated and complicated skin and skin structures; gynecologic (endometritis, pelvic inflammatory disease); bone and joint infections; intra-abdominal infections (appendicitis with rupture/abscess, peritonitis); and septicemia. Tazobactam expands activity of piperacillin to include beta-lactamase producing strains of *S. aureus*, *H. influenzae*, *Bacteroides*, and other gram-negative bacteria.

Dosing: Adults

Diverticulitis, intra-abdominal abscess, peritonitis: I.V.: 3.375 g every 6 hours; **Note:** Some clinicians use 4.5 g every 8 hours for empiric coverage since the %time>MIC is similar between the regimens for most pathogens; however, this regimen is NOT recommended for nosocomial pneumonia or *Pseudomonas* coverage.

Pneumonia (nosocomial): I.V.: 4.5 g every 6 hours for 7-14 days (when used empirically, combination with an aminoglycoside or antipseudomonal fluoroquinolone is recommended; consider discontinuation of additional agent if *P. aeruginosa* is not isolated)

Severe infections: I.V.: 3.375 g every 6 hours for 7-10 days; **Note:** Some clinicians use 4.5 g every 8 hours for empiric coverage since the %time>MIC is similar between the regimens for most pathogens; however, this regimen is NOT recommended for nosocomial pneumonia or *Pseudomonas* coverage.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Usual dosage range:** Children: I.V.:

2-8 months: 80 mg of piperacillin component/kg every 8 hours

≥9 months and ≤40 kg: 100 mg of piperacillin component/kg every 8 hours

Indication-specific dosing: I.V.: **Note:** Dosing based on piperacillin component:

Appendicitis, peritonitis: Children:

2-8 months: 80 mg/kg every 8 hours

≥9 months and ≤40 kg: 100 mg/kg every 8 hours

>40 kg: refer to adult dosing

Cystic fibrosis, pseudomonal infections (unlabeled use): 350-450 mg/kg/day in divided doses

Dosing: Renal Impairment

Cl_{cr} 20-40 mL/minute: Administer 2.25 g every 6 hours (3.375 g every 6 hours for nosocomial pneumonia)

Cl_{cr} <20 mL/minute: Administer 2.25 g every 8 hours (2.25 g every 6 hours for nosocomial pneumonia)

Hemodialysis/CAPD: Administer 2.25 g every 12 hours (2.25 g every 8 hours for nosocomial pneumonia) with an additional dose of 0.75 g after each hemodialysis session

Continuous renal replacement therapy (CRRT): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH: 2.25 g every 6 hours

CVVHD/CVVHDF: 2.25-3.375 g every 6 hours

Note: Higher dose of 3.375 g should be considered when treating resistant pathogens (especially *Pseudomonas*); alternative recommendations suggest dosing of 4.5 g every 8 hours; regardless of regimen, there is some concern of tazobactam (TAZ) accumulation, given its lower clearance relative to piperacillin (PIP). Some clinicians advocate dosing with PIP to alternate with

PIP/TAZ, particularly in CVVH-dependent patients, to lessen this concern.

Dosing: Hepatic ImpairmentHepatic impairment does not affect the kinetics of piperacillin or tazobactam significantly.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Administer by I.V. infusion over 30 minutes.

Some penicillins (eg, carbenicillin, ticarcillin and piperacillin) have been shown to inactivate aminoglycosides *in vitro*. This has been observed to a greater extent with tobramycin and gentamicin, while amikacin has shown greater stability against inactivation. Concurrent use of these agents may pose a risk of reduced antibacterial efficacy *in vivo*, particularly in the setting of profound renal impairment. However, definitive clinical evidence is lacking. If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered. **Note:** Reformulated Zosyn® containing EDTA has been shown to be compatible *in vitro* for Y-site infusion with amikacin and gentamicin, but not compatible with tobramycin.

Dietary Considerations

Infusion, premixed: 2.25 g contains sodium 5.58 mEq (128 mg); 3.375 g contains sodium 8.38 mEq (192 mg); 4.5 g contains sodium 11.17 mEq (256 mg)

Injection, powder for reconstitution: 2.25 g contains sodium 5.58 mEq (128 mg); 3.375 g contains sodium 8.38 mEq (192 mg); 4.5 g contains sodium 11.17 mEq (256 mg); 40.5 g contains sodium 100.4 mEq (2304 mg, bulk pharmacy vial)

Storage

Vials: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F). Use single-dose vials immediately after reconstitution (discard unused portions after 24 hours at room temperature and 48 hours if refrigerated). After reconstitution, vials or solution are stable in NS or D_5W for 24 hours at room temperature and 48 hours (vials) or 7 days (solution) when refrigerated.

Premixed solution: Store frozen at -20°C (-4°F). Thawed solution is stable for 24 hours at room temperature or 14 days under refrigeration; do not refreeze.

ReconstitutionReconstitute with 5 mL of diluent per 1 g of piperacillin and then further dilute.

CompatibilityStable in dextran 6% in NS, D_5W, NS, sterile water for injection; LR (EDTA-formulated product only); **variable stability (consult detailed reference)** in peritoneal dialysis solution.

Y-site administration: Compatible: Amikacin (EDTA formulated product only), aminophylline, aztreonam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, carmustine, cefepime, cimetidine, clindamycin, co-trimoxazole, cyclophosphamide, cytarabine, dexamethasone sodium phosphate, diphenhydramine, docetaxel, dopamine, enalaprilat, etoposide, etoposide phosphate, floxuridine, fluconazole, fludarabine, fluorouracil, furosemide, gentamicin (EDTA formulated product only), granisetron, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, ifosfamide, leucovorin, linezolid, lorazepam, magnesium sulfate, mannitol, meperidine, mesna, methotrexate, methylprednisolone sodium succinate, metoclopramide, metronidazole, morphine, ondansetron, plicamycin, potassium chloride, ranitidine, remifentanil, sargramostim, sodium bicarbonate, thiotepa, vinblastine, vincristine, zidovudine. **Incompatible:** Acyclovir, alatrofloxacin, amphotericin B, amphotericin B cholesteryl sulfate complex, chlorpromazine, cisplatin, dacarbazine, daunorubicin, dobutamine, doxorubicin, doxorubicin liposome, doxycycline, droperidol, famotidine, ganciclovir, gatifloxacin, gemcitabine, haloperidol, hydroxyzine, idarubicin, minocycline, mitomycin, mitoxantrone, nalbuphine, prochlorperazine edisylate, promethazine, streptozocin, tobramycin. **Variable (consult detailed reference):** Cisatracurium, vancomycin.

Compatibility when admixed: Compatible: Potassium chloride. **Incompatible:** Aminoglycosides.

ContraindicationsHypersensitivity to penicillins, beta-lactamase inhibitors, or any component of the formulation

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- Bleeding disorders: Particularly in patients with renal impairment, bleeding disorders have been observed; discontinue if thrombocytopenia or bleeding occurs.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Cystic fibrosis: An increased frequency of fever and rash has been reported in patients with cystic fibrosis.

- Renal impairment: Use with caution in patients with renal impairment or underdeveloped kidneys; due to sodium load and to the adverse effects of high serum concentrations of penicillins. Dosage adjustment recommended.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 months of age.

Geriatric ConsiderationsHas not been studied exclusively in the elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, piperacillin/tazobactam is classified as pregnancy category B. Piperacillin and tazobactam both cross the placenta and are found in the fetal serum, placenta, amniotic fluid, and fetal urine. When used during pregnancy, the clearance and volume of distribution of piperacillin/tazobactam are increased; half-life and AUC are decreased.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsLow concentrations of piperacillin are excreted in breast milk; information for tazobactam is not available. The manufacturer recommends that caution be exercised when administering piperacillin/tazobactam to nursing women. Other pencillins are considered safe for use during breast-feeding. Nondose-related effects could include modification of bowel flora. When given alone in the early postpartum period, some pharmacokinetic parameters of piperacillin may be altered (refer to Piperacillin monograph for details).

Pregnancy & Lactation, In-Depth

- Piperacillin and Tazobactam Sodium in Pregnancy & Lactation

Adverse Reactions

>10%: Gastrointestinal: Diarrhea (7% to 11%)

>1% to 10%:

Cardiovascular: Hypertension (2%)

Central nervous system: Insomnia (7%), headache (8%), fever (2% to 5%), agitation (2%), pain (2%)

Dermatologic: Rash (4%), pruritus (3%)

Gastrointestinal: Constipation (1% to 8%), nausea (7%), vomiting (3% to 4%), dyspepsia (3%), stool changes (2%), abdominal pain (1% to 2%)

Hepatic: Transaminases increased

Local: Local reaction (3%), abscess (2%)

Respiratory: Pharyngitis (2%)

Miscellaneous: Moniliasis (2%), sepsis (2%), infection (2%)

≤1%, postmarketing, and/or case reports: Agranulocytosis, anaphylaxis/anaphylactoid reaction, anemia, anxiety, arrhythmia, arthralgia, atrial fibrillation, back pain, bradycardia, bronchospasm, candidiasis, cardiac arrest, cardiac failure, circulatory failure, chest pain, cholestatic jaundice, confusion, convulsions, coughing, depression, diaphoresis, dizziness, dyspnea, dysuria, edema, epistaxis, erythema multiforme, flatulence, flushing, gastritis, genital pruritus, hallucination, hematuria, hemolytic anemia, hemorrhage, hepatitis, hiccough, hypoglycemia, hypotension, ileus, incontinence, inflammation, injection site reaction, interstitial nephritis, leukorrhea, malaise, mesenteric embolism, myalgia, myocardial infarction, oliguria, pancytopenia, phlebitis, photophobia, pseudomembranous colitis, pulmonary edema, pulmonary embolism, purpura, renal failure, rhinitis, rigors, Stevens-Johnson syndrome, syncope, tachycardia (supraventricular and ventricular), taste perversion, thirst, thrombocytopenia, thrombocytosis, thrombophlebitis, tinnitus, toxic epidermal necrolysis, tremor, ulcerative stomatitis, urinary retention, vaginitis, ventricular fibrillation, vertigo

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Aminoglycosides: Penicillins may decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. *Risk D: Consider therapy modification*

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Test InteractionsPositive Coombs' [direct] test; false positive reaction for urine glucose using copper-reduction method (Clinitest®); may result in false positive results with the Platelia® *Aspergillus* enzyme immunoassay (EIA)

Some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*, leading to a potential underestimation of aminoglycoside serum concentration. **Note:** Reformulated Zosyn® containing EDTA has been shown to be compatible *in vitro* for Y-site infusion with amikacin and gentamicin, but not compatible with tobramycin.

Monitoring ParametersCreatinine, BUN, CBC with differential, PT, PTT; signs of bleeding; monitor for signs of anaphylaxis during first dose

Nursing: Physical Assessment/MonitoringSee individual agent for Piperacillin.

Monitoring: Lab TestsLFTs, creatinine, BUN, CBC with differential, serum electrolytes, urinalysis, PT, PTT; perform culture and sensitivity before administering first dose.

Patient EducationSee individual agent for Piperacillin.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: 8:1 ratio of piperacillin sodium/tazobactam sodium

Infusion [premixed iso-osmotic solution, frozen]:

- 2.25 g: Piperacillin 2 g and tazobactam 0.25 g (50 mL) [contains sodium 5.58 mEq (128 mg) and EDTA]
- 3.375 g: Piperacillin 3 g and tazobactam 0.375 g (50 mL) [contains sodium 8.38 mEq (192 mg) and EDTA]
- 4.5 g: Piperacillin 4 g and tazobactam 0.5 g (50 mL) [contains sodium 11.17 mEq (256 mg) and EDTA]

Injection, powder for reconstitution:

- 2.25 g: Piperacillin 2 g and tazobactam 0.25 g [contains sodium 5.58 mEq (128 mg) and EDTA]
- 3.375 g: Piperacillin 3 g and tazobactam 0.375 g [contains sodium 8.38 mEq (192 mg) and EDTA]
- 4.5 g: Piperacillin 4 g and tazobactam 0.5 g [contains sodium 11.17 mEq (256 mg) and EDTA]
- 40.5 g: Piperacillin 36 g and tazobactam 4.5 g [contains sodium 100.4 mEq (2304 mg) and EDTA; bulk pharmacy vial]

Generic AvailableNo

ManufacturerLederle Laboratories

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Zosyn)

- 2-0.25 g (1): $130.02
- 3-0.375 g (1): $182.99
- 4-0.5 g (1): $229.99
- 36-4.5 g (1): $246.00

Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs); which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested. Tazobactam inhibits many beta-lactamases, including staphylococcal penicillinase and Richmond and Sykes types II, III, IV, and V, including extended spectrum enzymes; it has only limited activity against class I beta-lactamases other than class Ic types.

Pharmacodynamics/KineticsBoth AUC and peak concentrations are dose proportional; hepatic impairment does not affect kinetics

Distribution: Well into lungs, intestinal mucosa, skin, muscle, uterus, ovary, prostate, gallbladder, and bile; penetration into CSF is low in subject with noninflamed meninges

Protein binding: Piperacillin and tazobactam: ~30%

Metabolism:

- Piperacillin: 6% to 9% to desethyl metabolite (weak activity)
- Tazobactam: ~26% to inactive metabolite

Bioavailability:

- Piperacillin: I.M.: 71%
- Tazobactam: I.M.: 84%

Half-life elimination: Piperacillin and tazobactam: 0.7-1.2 hours

Time to peak, plasma: Immediately following infusion of 30 minutes

Excretion: Clearance of both piperacillin and tazobactam are directly proportional to renal function

- Piperacillin: Urine (68% as unchanged drug); feces (10% to 20%)
- Tazobactam: Urine (80% as unchanged drug; remainder as inactive metabolite)

Related Information

- Antimicrobial Drugs of Choice

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Prolonged use of penicillins may lead to development of oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia, dizziness or agitation; may rarely cause confusion; penicillins reported to cause apprehension, illusions, hallucinations, depersonalization, agitation, encephalopathy, and insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPiperacillin Sodium and Tazobactam Sodium; Tazobactam and Piperacillin

References

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International Brand NamesAstaz-P (TH); Piptaz (PH); Tabaxin (KP); Tasovak (MX); Tazobac (CH, DE); Tazobak (PH); Tazocel (ES); Tazocilline (FR); Tazocin (AE, AU, BE, BG, BH, BR, CL, CO, CR, CY, CZ, EC, EE, EG, GB, GT, HK, HN, ID, IE, IL, IQ, IR, IT, JO, KP, KW, LB, LY, MX, MY, NI, NL, NO, OM, PA, PE, PK, QA, SA, SE, SG, SV, SY, TH, TW, YE); Tazocin EF (DO); Tazomax (UY); Tazonam (AR, AT, CN, PY); Tazoperan (KP); Tazopril (VE); Vigocid (PH); Zosyn (IN)

Piperacillin

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English English

Jump To Field (Select Field Name)

Pronunciation(pi PER a sil in)

Canadian Brand NamesPiperacillin for Injection, USP

Pharmacologic CategoryAntibiotic, Penicillin

Use: Labeled IndicationsTreatment of susceptible infections such as septicemia, acute and chronic respiratory tract infections, skin and soft tissue infections, and urinary tract infections due to susceptible strains of *Pseudomonas*, *Proteus*, and *Escherichia coli* and *Enterobacter*; active against some streptococci and some anaerobic bacteria; febrile neutropenia (as part of combination regimen)

Dosing: Adults

Usual dosage range:

I.M.: 2-3 g/dose every 6-12 hours; maximum: 24 g/24 hours

I.V.: 3-4 g/dose every 4-6 hours; maximum: 24 g/24 hours

Burn wound sepsis: I.V.: 4 g every 4 hours with vancomycin and amikacin

Cholangitis, acute: I.V.: 4 g every 6 hours

Keratitis*(Pseudomonas):* Ophthalmic: 6-12 mg/mL every 15-60 minutes around the clock for 24-72 hours, then slow reduction

Malignant otitis externa: I.V.: 4-6 g every 4-6 hours with tobramycin

Moderate infections: I.M., I.V.: 2-3 g/dose every 6-12 hours (maximum: 2 g I.M./site)

Prosthetic joint *(Pseudomonas):* I.V.: 3 g every 6 hours with aminoglycoside

***Pseudomonas* infections:** I.V.: 4 g every 4 hours

Severe infections: I.M., I.V.: 3-4 g/dose every 4-6 hours (maximum: 24 g/24 hours)

Urinary tract infections: I.V.: 2-3 g/dose every 6-12 hours

Uncomplicated gonorrhea: I.M.: 2 g in a single dose accompanied by 1 g probenecid 30 minutes prior to injection

Dosing: ElderlyAdjust dose for renal impairment:

I.M.: 1-2 g every 8-12 hours

I.V.: 2-4 g every 6-8 hours

Dosing: Pediatric

Usual dosage range:

Neonates: I.M., I.V.: 100 mg/kg every 12 hours

Infants and Children: I.M., I.V.: 200-300 mg/kg/day in divided doses every 4-6 hours

Cystic fibrosis: I.M., I.V.: 350-500 mg/kg/day in divided doses every 4-6 hours

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer every 6-8 hours.

Cl_{cr} <10 mL/minute: Administer every 8 hours.

Moderately dialyzable (20% to 50%)

Continuous arteriovenous or venovenous hemofiltration: Dose as for Cl_{cr} 10-50 mL/minute.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.MDo not administer more than 2 g per injection site.

Administration: I.VAdminister around-the-clock to promote less variation in peak and trough serum levels. Give at least 1 hour apart from aminoglycosides. Rapid administration can lead to seizures. Administer direct I.V. over 3-5 minutes. Intermittently infusion over 30 minutes.

Some penicillins (eg, carbenicillin, ticarcillin and piperacillin) have been shown to inactivate aminoglycosides *in vitro*. This has been observed to a greater extent with tobramycin and gentamicin, while amikacin has shown greater stability against inactivation. Concurrent use of these agents may pose a risk of reduced antibacterial efficacy *in vivo*, particularly in the setting of profound renal impairment. However, definitive clinical evidence is lacking. If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered.

Administration: I.V. DetailpH: 5.5-7.5

Dietary ConsiderationsSodium content of 1 g: 1.85 mEq

StorageReconstituted solution is stable (I.V. infusion) in NS or D_5W for 24 hours at room temperature, 7 days when refrigerated, or 4 weeks when frozen. After freezing, thawed solution is stable for 24 hours at room temperature or 48 hours when refrigerated. 40 g bulk vial should **not** be frozen after reconstitution.

CompatibilityStable in dextran 6% in NS, D_5NS, D_5W, LR, NS, sterile water for injection, bacteriostatic water; **variable stability (consult detailed reference)** in peritoneal dialysis solutions.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, aztreonam, ciprofloxacin, cyclophosphamide, diltiazem, docetaxel, doxorubicin liposome, enalaprilat, esmolol, etoposide phosphate, famotidine, fludarabine, foscarnet, granisetron, heparin, hydromorphone, IL-2, labetalol, linezolid, lorazepam, magnesium sulfate, melphalan, meperidine, midazolam, morphine, perphenazine, propofol, ranitidine, remifentanil, tacrolimus, teniposide, theophylline, thiotepa, verapamil, zidovudine. **Incompatible:** Amphotericin B cholesteryl sulfate complex, filgrastim, fluconazole, gatifloxacin, gemcitabine, ondansetron, sargramostim, vinorelbine. **Variable (consult detailed reference):** Cisatracurium, vancomycin.

Compatibility in syringe: Compatible: Heparin.

Compatibility when admixed: Compatible: Ciprofloxacin, clindamycin, flucloxacillin, fluconazole, hydrocortisone sodium succinate, linezolid, ofloxacin, potassium chloride, verapamil. **Incompatible:** Aminoglycosides.

ContraindicationsHypersensitivity to piperacillin, other beta-lactam antibiotics (penicillins or cephalosporins), or any component of the formulation

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- Bleeding disorders: Particularly in patients with renal impairment, bleeding disorders have been observed; discontinue if thrombocytopenia or bleeding occurs.

- Leukopenia/neutropenia: During prolonged use, leukopenia and neutropenia have been reported.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Cystic fibrosis: An increased frequency of fever and rash has been reported in patients with cystic fibrosis.

- Renal impairment: Use with caution in patients with renal impairment, due to sodium load and adverse effects (anemia, neuropsychological changes); dosage adjustment recommended.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures.

Geriatric ConsiderationsAntipseudomonal penicillins should not be used alone and are often combined with an aminoglycoside as empiric therapy for lower respiratory infection and sepsis in which gram-negative (including *Pseudomonas*) and/or anaerobes are of a high probability. Because of piperacillin's lower sodium content, it is preferred over ticarcillin in patients with a history of heart failure and/or renal or hepatic disease. Adjust dose for renal function.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal studies; therefore, piperacillin is classified as pregnancy category B. Piperacillin crosses the placenta and distributes into the amniotic fluid. Due to pregnancy induced physiologic changes, some pharmacokinetic parameters of piperacillin may be altered. At term, the apparent volume of distribution of piperacillin is increased and peak concentrations are significantly lower. Total clearance is normal to increased at term. These changes continue into the early postpartum period.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsSmall amounts of piperacillin are excreted in breast milk. The manufacturer recommends that caution be exercised when administering piperacillin to nursing women. Other penicillins are considered safe for use during breast-feeding. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Piperacillin in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Confusion, convulsions, drowsiness, fever, Jarisch-Herxheimer reaction

Dermatologic: Rash, toxic epidermal necrolysis, urticaria

Endocrine & metabolic: Electrolyte imbalance, hypokalemia

Hematologic: Abnormal platelet aggregation and prolonged PT (high doses), agranulocytosis, Coombs' reaction (positive), hemolytic anemia, pancytopenia

Local: Thrombophlebitis

Neuromuscular & skeletal: Myoclonus

Renal: Acute interstitial nephritis, acute renal failure

Miscellaneous: Anaphylaxis, hypersensitivity reactions

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

Aminoglycosides: Penicillins may decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. *Risk D: Consider therapy modification*

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Test InteractionsMay interfere with urinary glucose tests using cupric sulfate (Benedict's solution, Clinitest®); false-positive urinary and serum proteins, positive Coombs' test [direct]. False-positive Platelia® *Aspergillus* EIA test (Bio-Rad Laboratories) has been reported.

Some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*, leading to a potential underestimation of aminoglycoside serum concentration.

Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose
Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's allergy history prior to starting therapy. Use caution with impaired renal function and history of seizure activity. Assess potential for interactions with other pharmacological agents patient may be taking (eg, increase or decrease levels/effect of penicillin or increase risk of toxicity). See Administration for infusion directions. Evaluate therapeutic effectiveness (resolution of infection) and adverse reactions (eg, hypersensitivity reactions, opportunistic infection [fever, chills, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge, fatigue], confusion, convulsions, rash, thrombophlebitis, renal failure). Advise patients with diabetes about use of Clinitest®; may cause false positive test results. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.
Monitoring: Lab TestsPerform culture and sensitivity before administering first dose.
Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug can only be given by injection or infusion. Report immediately any redness, swelling, burning, or pain at infusion/injection site or any signs of allergic reaction (eg, respiratory difficulty or swallowing, chest tightness, rash, hives, swelling of lips or mouth). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, drug may cause false test results with Clinitest®, consult prescriber for alternative method of glucose monitoring. May cause confusion or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report chest pain, palpitations, or irregular heartbeat; unusual confusion, pain, swelling or heat in legs, changes in urinary pattern, signs of an opportunistic infection (fever, chills, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge, fatigue), persistent diarrhea, or other persistent adverse effects.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 2 g, 3 g, 4 g, 40 g

Generic AvailableYes
ManufacturerLederle Laboratories
Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs); which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.
Pharmacodynamics/Kinetics

Absorption: I.M.: 70% to 80%

Protein binding: ~16%

Bioavailability: Not well absorbed when given orally

Half-life elimination (dose dependent; prolonged with moderately severe renal or hepatic impairment):

Neonates: 1-5 days old: 3.6 hours; >6 days old: 2.1-2.7 hours

Children: 1-6 months: 0.79 hour; 6 months to 12 years: 0.39-0.5 hour

Adults: 36-80 minutes

Time to peak, serum: I.M.: 30-50 minutes

Excretion: Primarily urine; partially feces

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Prolonged use of penicillins may lead to development of oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or confusion; penicillins reported to cause apprehension, illusions, hallucinations, depersonalization, agitation, encephalopathy, and insomnia

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia, neutropenia, pancytopenia, and agranulocytosis; monitor patients receiving clozapine, carbamazepine, or valproic acid therapy.

Index TermsPiperacillin Sodium

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International Brand NamesAvocin (ES, IT); Cypercil (PH); Isipen (CZ, HR, PL); Ivacin (DK, SE); Pentcillin (JP); Peracillin (KP); Peracin (TH); Picillin (IT); Picillina (TW); Pipcil (BE, LU, NL); Piperac (AR); Piperacillin (PL); Piperilline (FR); Piperzam (ES); Pipracil (HK, IN, MY); Pipracin (IL); Pipraks (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Pipril (AT, AU, BG, CH, CZ, DE, ES, FI, GB, GR, HN, HR, HU, IE, PK, PL); Pipril ”Orifarm” (DK); Piprilin (PT)

Piperazine

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Pronunciation(PI per a zeen)

Canadian Brand NamesEntacyl®

Pharmacologic CategoryAnthelmintic

Use: Labeled IndicationsTreatment of pinworm and roundworm infections (used as an alternative to first-line agents, mebendazole, or pyrantel pamoate)

Dosing: Adults

Pinworm eradication: Oral: 65 mg/kg/day (not to exceed 2.5 g/day) as a single daily dose for 7 days; in severe infections, repeat course after a 1-week interval

Roundworm eradication: Oral: 3.5 g/day for 2 days (in severe infections, repeat course, after a 1-week interval)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Pinworm eradication: Oral: Children: 65 mg/kg/day (not to exceed 2.5 g/day) as a single daily dose for 7 days; in severe infections, repeat course after a 1-week interval

Roundworm eradication: Oral: Children: 75 mg/kg/day as a single daily dose for 2 days; maximum: 3.5 g/day

ContraindicationsHypersensitivity to piperazine or any component of the formulation; seizure disorders; liver or kidney impairment

Warnings/Precautions

Disease-related concerns:

- Anemia: Use with caution in patients with anemia.

- Malnutrition: Use with caution in patients with malnutrition.

Other warnings/precautions:

- Prolonged use: Avoid prolonged use especially in children.

Geriatric ConsiderationsNot a drug of choice. Monitor closely in the elderly.

Pregnancy Risk FactorB

Adverse Reactions<1%: Bronchospasms, diarrhea, dizziness, EEG changes, headache, hemolytic anemia, hypersensitivity reactions, nausea, seizure, vertigo, visual impairment, vomiting, weakness

Drug Interactions

Aminoquinolines (Antimalarial): May decrease the serum concentration of Anthelmintics. *Risk C: Monitor therapy*

Monitoring ParametersStool exam for worms and ova

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Piperazine citrate is available from Panorama Pharmacy (1-800-247-9767).

Generic AvailableYes

Mechanism of ActionCauses muscle paralysis of the roundworm by blocking the effects of acetylcholine at the neuromuscular junction

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Time to peak, serum: 1 hour

Excretion: Urine (as unchanged drug and metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause seizures; use caution with high-dose clozapine

Index TermsPiperazine Citrate

References

"Drugs for Parasitic Infections," *Med Lett Drugs Ther*, 1993, 35(911):111-22.[PubMed 8246830]

International Brand NamesAdiver (BE); Antelmina (FR); Anticucs (ES); Ascarobel (BR); Bioxurin (ES); Citroperazin (BR); Citropiperazina (IT);

Combicitrine (ID); Diurazina (IT); Gentiazina (IT); Helman (AT); Helmirazin (CZ); Kihomato (FI); Lombrifher (ES); Lombrimade (ES); Ortovermin (BR); Oxurasin (NO); Pipadox (NL); Pipelmin (BR); Piper-Jodina (IT); Piperazina adipato (IT); Piperazincitrat Richter (AT); Pipermel (PT); Piperoverm (AT); Pipertox (PT); Tasnon (DE); Thelmin (HR); Uvilon (IT); Vermenter (ES); Vermi Quimpe (ES); Vermifuge Sorin (FR); Vermilen (BR)

Pipotiazine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(pip oh TYE a zeen)

Canadian Brand NamesPiportil® L_4

Pharmacologic CategoryAntipsychotic Agent, Typical, Phenothiazine, Piperidine

Use: Labeled IndicationsManagement of schizophrenia

Dosing: Adults**Schizophrenia (maintenance treatment):** I.M.: Initial (dosage must be individualized): 50-100 mg; may be increased in 25 mg increments every 2-3 weeks. Optimal dosage and interval must be determined by individual response. Usual maintenance dose: 75-150 mg every 4 weeks; range: 25-250 mg every 3-4 weeks. A lower dose at a shorter interval (eg, every 3 weeks) may be preferred to higher doses every 4 weeks.

Dosing: Elderly≥50 years: Initial dosage <50 mg is recommended.

Administration: I.M.Administer using at least a 21-gauge needle for injection.

StorageStore at room temperature of 20°C to 25°C (68°F to 77°F). Protect from light.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to pipotiazine, phenothiazine derivatives, or any component of the formulation (cross-reactivity between phenothiazines may occur); severe CNS depression; subcortical brain damage; hepatic or renal dysfunction; circulatory collapse; severe hypotension; severely depressed patients; high doses of hypnotics; bone marrow suppression; blood dyscrasias; coma; pheochromocytoma

Other piperidine phenothiazines (ie, thioridazine) are contraindicated for use in combination with other drugs that are known to prolong the QT_c interval; in patients with congenital long QT syndrome or a history of cardiac arrhythmias. In addition, these drugs are contraindicated with concurrent use with medications that inhibit the metabolism of phenothiazines (fluoxetine, paroxetine, fluvoxamine, propranolol, pindolol), and in patients known to have genetic defect leading to reduced levels of activity of CYP2D6. The metabolism and adverse effect profile of pipotiazine have not been adequately characterized to evaluate whether these contraindications also apply to this drug. They are not labeled contraindications (per Canadian product monograph).

Allergy Considerations

- Phenothiazine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines); relative risk with pericyazine has not been established, although rare cases of QT_c prolongation have been reported.
- Anticholinergic effects: Phenothiazines may cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems.
- Blood dyscrasias: Check blood counts periodically and discontinue at first signs of blood dyscrasias; use is contraindicated in patients with bone marrow suppression.
- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).
- Extrapyramidal symptoms: May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia.
- Neuroleptic malignant syndrome (NMS): May be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).
- Pigmentary retinopathy: Prolonged therapy may cause pigmentary retinopathy, corneal deposits, and/or changes in skin pigmentation.
- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Respiratory disease: Use with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for developing tardive dyskinesia.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Depot injections: Adverse effects of depot injections may be prolonged.

- Sesame oil: Some product may contain sesame oil; use with caution in patients with known allergy to sesame oil or similar compounds.

Pregnancy ConsiderationsSafety and efficacy in pregnant women have not been established.
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Cardiac arrest, ECG changes, edema, hypotension, QT_c prolongation, syncope, tachycardia

Central nervous system: Agitation, anxiety, bizarre dreams, cerebral edema, depression, dizziness, drowsiness, EEG changes, excitement, extrapyramidal symptoms (akathisia, dyskinesia, dystonia, hyper-reflexia, oculogyric crisis, opisthotonos, pseudoparkinsonism, rigidity, sialorrhea, tremor), fatigue, fever, headache, insomnia, paradoxical psychosis, restlessness, seizure, sleep disturbance, tardive dyskinesia

Dermatologic: Angioedema, eczema, epithelial keratopathy erythema, exfoliative dermatitis, dermatitis, photosensitivity, pruritus, rash, seborrhea, skin pigmentation (prolonged therapy), urticaria

Endocrine & metabolic: Anorexia, appetite increased, galactorrhea, gynecomastia, libido (changes in), menstrual irregularities, thirst, weight changes

Gastrointestinal: Adynamic ileus, cholestasis, constipation, fecal impaction, jaundice nausea, salivation, vomiting, xerostomia

Genitourinary: Bladder paralysis, impotence, incontinence, polyuria, urinary retention

Hematologic: Agranulocytosis, anemia, eosinophilia, leukopenia, pancytopenia, thrombocytopenia

Ocular: Blurred vision, corneal deposits (prolonged therapy), glaucoma, lenticular deposits, pigmentary retinopathy (prolonged therapy)

Respiratory: Nasal congestion, pneumonia, pneumonitis

Miscellaneous: Diaphoresis iincreased, lupus-like syndrome

Metabolism/Transport EffectsNo published data on CYP metabolism. Based on structural analysis, pipotiazine may be a substrate of CYP2D6 and 3A4.
Drug Interactions

Analgesics (Opioid): Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Antimalarial Agents: May increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Beta-Blockers: Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid kava kava, valerian, St John's wort, gotu kola (may increase CNS depression). Avoid dong quai, St John's wort (may also cause photosensitization).

Test InteractionsPhenothiazines have been reported to cause false positive pregnancy tests.

Monitoring ParametersVital signs; serum potassium and magnesium, lipid profile evaluation of renal and liver function tests (long-term therapy), fasting blood glucose/Hgb A_{1c}; waist circumference, BMI; mental status, abnormal involuntary movement scale (AIMS); periodic eye exam

Based on experience with other piperidine phenothiazines: consider baseline and periodic ECG, do not initiate if QT_c >450 msec

Monitoring: Lab TestsVital signs; serum potassium and magnesium, lipid profile, fasting blood glucose/Hgb A_{1c}; evaluation of renal and liver function tests (long-term therapy); BMI; periodic eye exam

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, oil:

Piportil® L_4: 25 mg/mL (1 mL) [contains sesame oil]; 50 mg/mL (1 mL, 2 mL) [contains sesame oil]

Generic AvailableNo

ManufacturerAventis Pharma (Canada)

Mechanism of ActionBlocks postsynaptic mesolimbic dopaminergic receptors in the brain; depresses the release of hypothalamic and hypophyseal hormones. Relative to other piperidine phenothiazines, pipotiazine appears to be less sedating, with less potential to potentiate other CNS depressants, and may possess a lower propensity to cause hypotension. However, it has a relatively high propensity for cause extrapyramidal reactions.

Pharmacodynamics/Kinetics

Onset of action: I.M.: 2-3 days

Duration: 3-6 weeks

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentCoadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Index TermsPipotiazine Palmitate

International Brand NamesLongum 4 (NL); Lonseren (ES); Piportil (BR, FR, HN, NO, NZ, PL); Piportil Depot (GB, ZA); Piportil L4 (AR, BR, CN, CO, FR, MX, PE, PL, PY, UY)

Pirbuterol

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(peer BYOO ter ole)

U.S. Brand NamesMaxair™ Autohaler™

Pharmacologic CategoryBeta$_2$ Agonist

Use: Labeled IndicationsPrevention and treatment of reversible bronchospasm including asthma

Dosing: Adults**Bronchospasm:** Inhalation: 2 inhalations every 4-6 hours for prevention; 2 inhalations at an interval of at least 1-3 minutes, followed by a third inhalation in treatment of bronchospasm, not to exceed 12 inhalations/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥12 years: Refer to adult dosing.

Administration: InhalationShake inhaler well before use.

StorageStore between 15°C and 30°C (59°F and 86°F).

ContraindicationsHypersensitivity to pirbuterol, albuterol, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.
- Serious effects/fatalities: Do not exceed recommended dose; serious adverse events, including fatalities, have been associated with excessive use of inhaled sympathomimetics.

Disease-related concerns:

- Asthma: Appropriate use: Optimize anti-inflammatory treatment before initiating maintenance treatment with albuterol. Do not use as a component of chronic therapy without an anti-inflammatory agent. Only the mildest forms of asthma (Step 1 and/or exercise-induced) would not require concurrent use based upon asthma guidelines.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (arrhythmia or hypertension or heart failure); beta-agonists may cause elevation in blood pressure, heart rate and result in CNS stimulation/excitation. Beta$_2$-agonists may also increase risk of arrhythmias.
- Diabetes: Use with caution in patients with diabetes mellitus; beta$_2$-agonists may increase serum glucose.
- Glaucoma: Use with caution in patients with glaucoma; may elevate intraocular pressure.
- Hyperthyroidism: Use with caution in hyperthyroidism; may stimulate thyroid activity.
- Hypokalemia: Use with caution in patients with hypokalemia; beta$_2$-agonists may decrease serum potassium.
- Seizures: Use with caution in patients with seizure disorders; beta-agonists may result in CNS stimulation/excitation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Patient information: Patients must be instructed to seek medical attention in cases where acute symptoms are not relieved or a previous level of response is diminished. The need to increase frequency of use may indicate deterioration of asthma, and treatment must not be delayed. All patients should utilize a spacer device when using a metered-dose inhaler.

Geriatric ConsiderationsElderly patients may find it beneficial to utilize a spacer device when using a metered dose inhaler. Difficulty in using the inhaler often limits its effectiveness. The Maxair™ Autohaler™ may be easier for the elderly to use.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown

Adverse Reactions

>10%:

Central nervous system: Nervousness (7%)

Endocrine & metabolic: Serum glucose increased, serum potassium decreased

Neuromuscular & skeletal: Trembling (6%)

1% to 10%:

Cardiovascular: Palpitation (2%), tachycardia (1%)

Central nervous system: Headache (2%), dizziness (1%)

Gastrointestinal: Nausea (2%)

Respiratory: Cough (1%)

<1%: Abdominal pain/cramps, alopecia, anxiety, bruising, chest pain, confusion, depression, diarrhea, dry mouth, edema, flushing, glossitis, hyperkinesia, hypokalemia, hypotension, insomnia, pruritus, rash, skipped beats, smell/taste changes, sore throat, stomatitis, syncope, vomiting, weakness, numbness in extremities, weight gain

Drug Interactions

Alpha-/Beta-Blockers: May diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Atomoxetine: May enhance the tachycardic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Betahistine: May diminish the therapeutic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Monitoring ParametersRespiratory rate; FEV$_1$, peak flow, and/or other pulmonary function tests; blood pressure, heart rate; CNS stimulation; serum glucose, serum potassium

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. For inpatient care, monitor vital signs and lung sounds prior to and periodically during therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsFEV$_1$, peak flow, and/or other pulmonary function tests; serum potassium, serum glucose (in selected patients)

Patient EducationUse exactly as directed. Do not use more often than recommended. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience nervousness, dizziness, or fatigue (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or dry mouth or stomach upset (small frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help). If you have diabetes, check blood sugar; blood glucose levels may be increased. Report unresolved GI upset; dizziness or fatigue; vision changes; chest pain, rapid heartbeat, or palpitations; nervousness or insomnia; muscle cramping or tremor; or unusual cough. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Aerosol: Store canister upside down; do not freeze. Shake canister before using. Sit when using medication. Close eyes when administering pirbuterol to avoid spray getting into eyes. Exhale slowly and completely through nose; inhale deeply through mouth while administering aerosol. Hold breath for 5-10 seconds after inhalation. Wait at least 1 full minute between inhalations. Wash mouthpiece between use. If more than one inhalation medication is used, use bronchodilator first and wait 5 minutes between medications

Maxair™ Autohaler™: Hold upright. Raise lever so that it stays up and snaps into place. Shake well. Exhale. Seal lips tightly around mouthpiece, inhale deeply. A "click" will be heard and you will feel a soft puff when the medication has been triggered. Continue to take a full, deep breath. Remove inhaler from mouth, hold breath for 10 seconds, then exhale slowly. **Note:** A test-fire slide has been added to the bottom of the Autohaler™ actuator/mouthpiece. The inhaler should be primed prior to using for the first time or if it has not been used in 48 hours. To prime, remove mouthpiece; point mouthpiece away from yourself or others, and push the lever so that it stays up. Push the white test-fire slide located on the bottom of the mouthpiece to release the priming spray. In order to release a second priming spray, push lever to "down" position, then repeat steps. When two priming sprays have been done, return lever to "down" position.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol for oral inhalation, as acetate:

Maxair™ Autohaler™: 200 mcg/actuation (14 g) [400 actuations; contains chlorofluorocarbons]

Generic AvailableNo

Manufacturer3M Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Aerosol (Maxair Autohaler)

200 mcg/INH (14): $115.99

Mechanism of ActionPirbuterol is a beta$_2$-adrenergic agonist with a similar structure to albuterol, specifically a pyridine ring has been substituted for the benzene ring in albuterol. The increased beta$_2$ selectivity of pirbuterol results from the substitution of a tertiary butyl group on the nitrogen of the side chain, which additionally imparts resistance of pirbuterol to degradation by monoamine oxidase and provides a lengthened duration of action in comparison to the less selective previous beta-agonist agents.

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Therapeutic: Oral: 2-3 hours with peak serum concentration of 6.2-9.8 mcg/L; Inhalation: 0.5-1 hour

Half-life elimination: 2-3 hours

Metabolism: Hepatic

Excretion: Urine (10% as unchanged drug)

Related Information

- Bronchodilators
- Inhalant Agents

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and taste changes.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Nervousness and restlessness are common; may cause dizziness; may rarely cause insomnia

Mental Health: Effects on Psychiatric Treatment Concurrent use with TCAs and MAO inhibitors may results in increased toxicity; monitor

Cardiovascular Considerations Beta-agonists will induce increases in heart rate. This should be considered in patients with resting tachycardia. Because of the frequent coexistence of chronic obstructive lung disease and coronary artery disease, many patients are on simultaneous therapy with beta-agonists and beta-blockade. This combination should, for obvious reasons, be avoided. Frequent use of inhaled beta-agonists when used in patients with atrial fibrillation, may counteract pharmacologic interventions directed at rate control. Acute inhaled beta-agonists may be used to treat hyperkalemia in patients with renal failure.

Index Terms Pirbuterol Acetate

References

Expert Panel Report 3, “Guidelines for the Diagnosis and Management of Asthma,” *Clinical Practice Guidelines*, National Institutes of Health, National Heart, Lung, and Blood Institute, NIH Publication No. 08-4051, prepublication 2007. Available at http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

International Brand Names Broncocor (IT); Broncocor[inhal.] (IT); Exirel (AT, GB); Exirel[inhal.] (AT, GB); Maxair (CH); Maxair Autohaler (FR); Spirolair (BE, LU); Zeisin Autohaler (DE)

Piroxicam

Lexi-Drugs Online

English

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

International issues:

Flogene® [Brazil] may be confused with Florone® which is a brand name for diflorasone in the U.S.

Pronunciation(peer OKS i kam)

U.S. Brand NamesFeldene®

Canadian Brand NamesApo-Piroxicam®; Gen-Piroxicam; Novo-Pirocam; Nu-Pirox; Pexicam®

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsSymptomatic treatment of acute and chronic rheumatoid arthritis and osteoarthritis

Use: Unlabeled/InvestigationalAnkylosing spondylitis

Dosing: Adults**Inflammation, rheumatoid arthritis:** Oral: 10-20 mg/day once daily; although associated with increase in GI adverse effects, doses >20 mg/day have been used (ie, 30-40 mg/day); maximum dose: 20 mg/day

Dosing: ElderlyRefer to adult dosing. **Note:** Some clinicians have used 10 mg every other day to initiate therapy in the elderly to help avoid side effects and produce therapeutic effect at minimal dose. Maximum dose: 20 mg/day.

Dosing: PediatricOral: Children (unlabeled use): 0.2-0.3 mg/kg/day once daily; maximum dose: 15 mg/day

Dosing: Renal ImpairmentNot recommended in patients with advanced renal disease.

Dosing: Hepatic ImpairmentReduced dose is necessary.

Dietary ConsiderationsMay be taken with food to decrease GI adverse effect.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to piroxicam, aspirin, other NSAIDs or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin’s cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.
- Serum sickness: A serum sickness-like reaction can rarely occur; watch for arthralgias, pruritus, fever, fatigue, and rash.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not generally effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (3rd trimester)

LactationEnters breast milk (small amounts)/not recommended (AAP rates "compatible")

Adverse Reactions

>10%:

Central nervous system: Dizziness

Dermatologic: Rash

Gastrointestinal: Abdominal cramps, heartburn, indigestion, nausea

1% to 10%:

Central nervous system: Headache, nervousness

Dermatologic: Itching

Endocrine & metabolic: Fluid retention

Gastrointestinal: Vomiting

Otic: Tinnitus

<1%: Acute renal failure, agranulocytosis, allergic rhinitis, anemia, angioedema, arrhythmia, aseptic meningitis, blurred vision, bone marrow suppression, confusion, CHF, conjunctivitis, cystitis, drowsiness, dry eyes, dyspnea, epistaxis, erythema multiforme, gastritis, GI ulceration, hallucinations, hearing decreased, hemolytic anemia, hepatitis, hot flashes, hypertension, insomnia, leukopenia, mental depression, peripheral neuropathy, photosensitivity, polydipsia, polyuria, Stevens-Johnson syndrome, tachycardia, thrombocytopenia, toxic amblyopia, toxic epidermal necrolysis, urticaria

Metabolism/Transport Effects**Substrate** of CYP2C9 (minor); **Inhibits** CYP2C9 (strong)

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor*

therapy

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Onset of effect may be delayed if piroxicam is taken with food.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Test InteractionsIncreased chloride (S), increased sodium (S), increased bleeding time

Monitoring ParametersOccult blood loss, hemoglobin, hematocrit, and periodic renal and hepatic function tests; periodic ophthalmologic exams with chronic use

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess effectiveness and interactions of other medications patient may be taking. Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, GI effects, hepatotoxicity, ototoxicity) at beginning of therapy and periodically throughout therapy. Schedule ophthalmic evaluations for patients who develop eye complaints during long-term NSAID therapy. Advise patients with diabetes to use serum glucose testing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsOccult blood loss, hemoglobin, hematocrit, and periodic renal and hepatic function tests

Patient EducationTake this medication exactly as directed; do not increase dose without consulting prescriber. Do not break capsules. Take with food or milk to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol, aspirin or aspirin-containing medication, or any other anti-inflammatory medications without consulting prescriber. You may experience drowsiness, dizziness, or nervousness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); anorexia, nausea, vomiting, flatulence, or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or fluid retention (weigh yourself weekly and report unusual weight gain [3-5 lb/week]). GI bleeding, ulceration, or perforation can occur with or without pain; discontinue medication and contact prescriber if persistent abdominal pain or cramping, or blood in stool occurs. Report unusual swelling of extremities or unusual weight gain; breathlessness, respiratory difficulty, or unusual cough; chest pain, rapid heartbeat, palpitations; unusual bruising/bleeding; blood in urine, stool, mouth, or vomitus; unusual fatigue; changes in urinary pattern (polyuria or anuria); skin rash or itching; or change in hearing or ringing in ears. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 10 mg, 20 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Feldene)

20 mg (30): $126.47

Capsules (Piroxicam)

10 mg (30): $11.99

20 mg (30): $14.99

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: Analgesic: ~1 hour

Peak effect: 3-5 hours

Protein binding: 99%

Metabolism: Hepatic

Half-life elimination: 45-50 hours

Excretion: Primarily urine and feces (small amounts) as unchanged drug (5%) and metabolites

Related Information

- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness; may rarely cause drowsiness, confusion, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A meta-analysis (Pope, 1993) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 Heart Failure Guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin's inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

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International Brand NamesAntiflog (IT); Apo-Piroxicam (PL); Arpyrox (ID); Artrilase (EC); Atidem (PE); Baxo (JP); Brexic (IN); Brexin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Brucam (MX); Candyl-D (NZ); Dacam (FI); Dolonex (IN); Edecam (MX); Exipan (IL); Facicam (MX); Felden (AT, CH, DK, FI, NO); Feldene (AE, AR, AU, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CI, CN, CR, CY, DO, EC, EE, EG, ET, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, ID, IE, IL, IQ, IR, IT, JM, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, OM, PA, PE, PH, PK, PL, PT, QA, SA, SC, SD, SL, SN, SR, SV, SY, TH, TN, TT, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Feldene Gel (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Felrox (TH); Finalgel Sport (PL); Flamexin (PL); Flamic Gel (TH); Flaxine (PH); Flexirox (FR); Focus (TW); Genoldene (MX); Hotemin (CZ, MY, PL); Improntal (ES); Infeld (ID); Inflamene (BR, ID); Ketazon (AR); Kifadene (ID); Konshien (TW); Leal (UY); Licofel (ID); Macroxam (PH); Manoxicam (TH); Mobilis (AU); Mobilus D (AU); Movon Gel (IN); Movon-20 (IN); Moxicam (TH); Murupe Patch 48 (KP); Palpasin (PH); Parixam (PH); PC-20 (TH); Pemar (CN); Piram (TH); Piram-D (NZ); Pirax (TH); Pirkam (DK); Pirobeta (AU); Pirocutan (DE); Pirocutan Gel (DE); Pirohexal-D (AU); Pirom (DK); Pirox (IN, MX); Piroxedol (CO); Piroxene (PY); Piroxicam (CO, PL); Piroxim (AE, BF, BH, BJ, CI, CO, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Pixicam (ZA); Posedene (TH); Priorheum (DE); Proxalyoc (FR); Proximax (PH); Pyridam (ID); Pyroxy (TH); Raxicam (PH); Reumador (PL); Rexicam (ID); Rheugesic (ZA); Rosiden (KP, SG); Roxicam (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Roxium (TH); Ruvamed (GR); Salvacam Gel (DO, GT, NI, PA, SV); Scandene (ID); Sefdene (HK, SG); Sinalgico (AR); Sofden (ID); Sotilen (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, HK, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Stopen (CO); Toricam Gel (TW); Tropidene (ID); Unicam (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Vitaxicam (SG); Xicalom (ID); Xicam (TH); Xycam (ZA); Zitumex (GR); Zunden (IT); Zuparex (MX)

Pivampicillin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(piv am pi SIL in)

Canadian Brand NamesPondocillin®

Pharmacologic CategoryAntibiotic, Penicillin

Use: Labeled IndicationsTreatment of susceptible bacterial infections (nonbeta-lactamase-producing organisms); susceptible bacterial infections caused by streptococci, pneumococci, nonpenicillinase-producing staphylococci, *H. influenzae*, *N. gonorrhoeae*, *E. coli*, *P. mirabilis*, *Listeria*, *Salmonella*, *Shigella*, *Enterobacter*, and *Klebsiella*

Dosing: Adults

Bacterial infections: Oral: Usual dose: 500 mg (tablet) or 525 mg (suspension) twice daily; dosage may be doubled in severe infections

Gonococcal urethritis: Oral: 1.5 g as a single dose with 1 g probenecid concurrently

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Bacterial infections:** Oral suspension:

Infants <3 months: Use of pivampicillin in this age group should be avoided (see Warnings/Precautions on carnitine)

Infants 3-12 months: Dosage range: 40-60 mg/kg/day in 2 divided doses

Children ≤10 years: Dosage range: 25-35 mg/kg/day, not to exceed recommended daily adult dose of 500 mg twice daily

Children >10 years: Refer to adult dosing.

Alternatively: Children:

1-3 years: 175 mg twice daily

4-6 years: 262.5 mg twice daily

7-10 years: 350 mg twice daily

Dosing: Renal ImpairmentNo adjustment needed unless renal impairment is severe. Specific recommendations are not available.

Administration: OralMay be taken with or without food since absorption is virtually unaffected by taking with food; however, peak serum levels may be reduced and delayed when compared to doses given in fasting state; total bioavailability is not affected.

Storage

Suspension: Store powder at <25°C (77°F); reconstituted suspension may be stored for 7 days at room temperature and for 14 days under refrigeration.

Tablet: Store at <30°C (86°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to ampicillin, pivalic acid, any component of the formulation, or other penicillins or cephalosporins; in secondary infections associated with mononucleosis or lymphatic leukemia; infections due to beta-lactamase-producing bacteria

Warnings/Precautions

Concerns related to adverse effects:

- Decreased carnitine: An increase in carnitine excretion in urine as conjugate with pivalic acid, and thus a decrease in serum carnitine levels, has been seen in patients. Carnitine production begins at birth and in healthy children is fully developed within a few months after birth.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Porphyria: Avoid use in patients with porphyria; use has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Concurrent drug therapy issues:

- Medications liberating pivalic acid: Concurrent treatment with medications liberating pivalic acid (eg, valproate) should be avoided.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <3 months of age; the suspension is not recommended for treatment of severe infections in children.

Pregnancy Risk FactorB (based on ampicillin rating in the U.S.)
Pregnancy ConsiderationsSafety has not been established; ampicillin component crosses the human placenta
LactationAmpicillin enters breast milk. It is not known if pivalic acid component is secreted into breast milk. Use caution.
Breast-Feeding ConsiderationsAdministration to a mother breast-feeding a child >3 months of age should weigh risks to infant versus benefit to mother (see Warnings/Precautions for precaution on carnitine).
Adverse ReactionsFrequency not defined; although some reactions may have not been reported with pivampicillin use, they are considered due to ampicillin component and events reported due to ampicillin, and therefore, may be expected to occur.

Central nervous system: Dizziness

Dermatologic: Erythema multiforme, exfoliative dermatitis, pruritus, rash (erythematous or macropapular), urticaria

Gastrointestinal: Black "hairy" tongue, diarrhea, enterocolitis, flatulence, glossitis, nausea, retrosternal pain, stomatitis, vomiting

Hematologic: Agranulocytosis, anemia, eosinophilia, leukopenia, thrombocytopenia, thrombocytopenic purpura

Hepatic: AST increased (transient)

Miscellaneous: Anaphylaxis

Drug Interactions

Allopurinol: May enhance the potential for allergic or hypersensitivity reactions to Pivampicillin. *Risk C: Monitor therapy*

Aminoglycosides: Penicillins may decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. *Risk D: Consider therapy modification*

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Absorption unaffected by taking with food, however, peak serum levels may be reduced and delayed.
Test InteractionsMay interfere with urinary glucose tests using cupric sulfate: some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*, leading to a potential underestimation of aminoglycoside serum concentration.
Monitoring ParametersWith prolonged therapy, monitor renal, hepatic, and hematologic function periodically; observe signs and symptoms of anaphylaxis during first dose
Nursing: Physical Assessment/MonitoringAssess culture and sensitivity report and patient allergy history prior to starting therapy. Assess potential for interactions with other medications patient may be taking. Caution patients with diabetes about altered response to Clinitest®. Assess for therapeutic effectiveness and adverse reactions (eg, rash, gastrointestinal upset, anaphylaxis, opportunistic infection [fever, chills, unhealed sores, white plaques in mouth or vagina, purulent vaginal discharge] and fatigue). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsWith prolonged therapy, monitor renal, hepatic, and hematologic function periodically
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take entire prescription, even if you are feeling better. Take at equal intervals around-the-clock. Tablets or suspension may be taken with or without food. Suspension may be stored for 7 days at room temperature or 14 days if refrigerated. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, drug may cause false test results with Clinitest® urine glucose monitoring; use of another type of glucose monitoring is preferable. May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report immediately any rash; swelling of face, tongue, mouth, or throat; unusual or persistent diarrhea; vaginal itching, burning, or pain; unresolved vomiting or constipation; fever or chills; abdominal pain; jaundice; unusual bruising or bleeding; or if condition being treated worsens or does not improve by the time prescription is completed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Powder for oral suspension:

Pondocillin® [CAN]: 175 mg/5 mL (100 mL, 150 mL, 200 mL) [banana and vanilla flavors] not available in the U.S.]

Tablet:

Pondocillin® [CAN]: 500 mg [equivalent to 377 mg ampicillin] [not available in the U.S.]

Generic AvailableNo
Manufacturer

Leo Pharma Inc

Mechanism of ActionProdrug converted to microbiologically active component (ampicillin) which inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

Pharmacodynamics/Kinetics

Distribution: Bile, blister, and tissue fluids; penetration into CSF occurs with inflamed meninges only, good only with inflammation (exceeds usual MICs). Normal meninges: NIL; Inflamed meninges: 5% to 10%

Protein binding: 20% as ampicillin

Metabolism: Pivampicillin is converted to ampicillin within 15 minutes of absorption

Bioavailability: Amounts in excess of 99% absorbed

Half-life elimination: Children and Adults: 1-1.8 hours

Time to peak, plasma: 1 hour

Excretion: Urine (>70% as ampicillin); pivalic acid is excreted in urine in form of labile conjugates with glycine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral candidiasis, black "hairy" tongue, glossitis, and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentAvoid use with valproic acid

Index TermsMK-191; Pivampicilin

International Brand NamesPondocillin (DK, NO)

Pizotifen

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(pi ZOE ti fen)

Canadian Brand NamesSandomigran DS®; Sandomigran®

Pharmacologic CategorySerotonin and Histamine Antagonist

Use: Labeled IndicationsMigraine prophylaxis

Dosing: Adults**Migraine prophylaxis:** Oral: Initial: 0.5 mg at bedtime; increase gradually to 0.5 mg 3 times/day. Usual dosage range: 1-6 mg/day.

Note: Therapeutic response may require several weeks of therapy. Do not discontinue abruptly (reduce gradually over 2-week period).

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Migraine prophylaxis:** Oral: Children ≥12 years: Refer to adult dosing.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to pizotifen or any component of the formulation; concurrent use of MAO inhibitors; gastric outlet obstruction (pyloroduodenal obstruction, stenosing pyloric ulcer)

Warnings/Precautions

Concerns related to adverse effects:

- Anticholinergic effects: Although anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention) are limited; use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Use with caution in patients intolerant to anticholinergic agents, including tricyclic antidepressants, phenothiazines, or cyproheptadine.

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.

- Diabetes: Use with caution in patients with diabetes mellitus.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Migraine attacks: Not for use in acute treatment of migraine attacks.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Obesity: Use with caution in obese patients.

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Abrupt discontinuation: Avoid abrupt discontinuation; taper dosage over 2 weeks prior to discontinuation.

- Response to therapy: Therapeutic response may require several weeks of therapy.

- Tolerance: May develop in some patients; consider drug-free period after several months of treatment.

Pregnancy Risk FactorNot available

Pregnancy ConsiderationsUse only if potential benefit to the mother outweighs possible risk to the fetus.

Adverse ReactionsFrequency not defined.

Cardiovascular: Edema, hypotension

Central nervous system: Drowsiness, dizziness, headache, fatigue, confusion, depression, nervousness

Endocrine & metabolic: Increased appetite, weight gain

Gastrointestinal: Nausea, xerostomia, epigastric distress

Genitourinary: Impotence

Neuromuscular & skeletal: Weakness, muscle pain

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersHepatic function tests (prolonged use)

Monitoring: Lab TestsHepatic function tests (prolonged use)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet:

Sandomigran® [CAN]: 0.5 mg [pizotifen malate 0.73 mg]

Tablet, double strength:

Sandomigran® DS [CAN]: 1 mg [pizotifen malate 1.46 mg]

Generic AvailableNo

ManufacturerNovartis (Canada)

Mechanism of ActionSerotonin and histamine antagonist; mechanism of action in migraine prophylaxis has not been fully elucidated

Pharmacodynamics/Kinetics

Onset of action: May require several weeks of therapy

Half-life elimination: 26 hours

Time to peak: 5-7 hours

Pharmacotherapy PearlsNot available in U.S.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index TermsPizotifen Malate

International Brand NamesAnorsia (TH); Lematite (PK); Litec (PH); Lysagor (ID); Mor-Vita (PH); Mosegor (CH, DE, ES, LU, PH, PK, PT); Pizomed (TH); Polomigran (PL); Sandomigran (AR, AT, AU, BE, BR, CZ, DE, ES, FR, GB, HK, HU, IE, IL, IT, LU, MY, NL, VE); Sandomigrin (DK, NO, SE)

Plasma Protein Fraction

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Pronunciation(PLAS mah PROE teen FRAK shun)
U.S. Brand NamesPlasmanate®
Pharmacologic CategoryBlood Product Derivative
Use: Labeled IndicationsPlasma volume expansion and maintenance of cardiac output in the treatment of certain types of shock or impending shock
Dosing: Adults**Volume expansion:** I.V.: Usual minimum dose: 250-500 mL; adjust dose based on response
Dosing: ElderlyRefer to adult dosing.
Administration: I.V.

For I.V. administration. Administration should begin within 4 hours after entering the container; rapid infusion may cause vascular overload. Hypotension may occur when administered at rates >10 mL/minute; decrease rate of infusion if hypotension occurs

Dietary ConsiderationsInjection solution contains sodium 145 mEq/L and potassium 0.25 mEq/L.
Storage

Store at room temperature ≤30°C (≤86°F). Do not freeze. Do not use if solution is turbid or has been frozen. Administration should begin within 4 hours of opening container.

Contraindications

Hypersensitivity to plasma protein fraction or any component of the formulation; patients on cardiopulmonary bypass; severe anemia; congestive heart failure; increased blood volume

Warnings/Precautions

Concerns related to adverse effects:

- Hypotension: Rapid infusions may cause hypotension. Decrease or stop infusion if sudden hypotension occurs.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children. May be useful for initial therapy of shock due to dehydration or infection.

Other warnings/precautions:

- Coagulation disorders: Plasma protein fraction does not contain coagulation factors and does not correct coagulation disorders.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
Adverse ReactionsFrequency not defined.

Cardiovascular: Edema, flushing, hypotension (related to rate of infusion)

Central nervous system: Headache

Dermatologic: Urticaria

Gastrointestinal: Nausea

Neuromuscular & skeletal: Back pain

Respiratory: Pulmonary edema

Drug InteractionsThere are no known significant interactions.
Monitoring Parameters

Blood pressure, pulse, pulmonary exam

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [human; preservative free]:

Plasmanate®: 5% (50 mL, 250 mL) [contains human albumin ~88%, sodium 145 mEq/L and potassium 0.25 mEq/L]

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesPlasma Proteinlosung 5% (AT); Plasma-Protein-Fraktion (DE); Plasmanate (HK, ID, MY); Plasmatein (HK, MY, PH); Protenate (HK, ID, TW)

Plerixafor

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(pler IX a fore)
U.S. Brand NamesMozobil™
Pharmacologic CategoryHematopoietic Stem Cell Mobilizer
Use: Labeled IndicationsMobilization of hematopoietic stem cells (HSC) for collection and subsequent autologous transplantation (in combination with G-CSF) in patients with non-Hodgkin’s lymphoma (NHL) and multiple myeloma (MM)
Dosing: Adults**Note:** Dosing is based on actual body weight. Begin plerixafor after patient has received G-CSF 10 mcg/kg once daily for 4 days; plerixafor, G-CSF and apheresis should be continued daily until sufficient cell collection up to a maximum of 4 days.

HSC mobilization: SubQ: 0.24 mg/kg once daily ~11 hours prior to apheresis for up to 4 consecutive days; maximum dose: 40 mg/day

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal Impairment
Cl_{cr} >50 mL/minute: No adjustment required.

Cl_{cr} ≤50 mL/minute: 0.16 mg/kg; maximum dose: 27 mg/day.

Hemodialysis: Insufficient information for dosing recommendation

Administration: I.V. DetailpH: 6-7.5
Administration: OtherAdminister subcutaneously, ~11 hours prior to initiation of apheresis. In some clinical trials, plerixafor administration began in the evening prior to apheresis. (G-CSF was begun on day 1, plerixafor initiated in the evening on day 4 and apheresis in the morning on day 5; with G-CSF, plerixafor and apheresis then continued daily until sufficient cell collection for autologous transplant.)
StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). The manufacturer recommends discarding unused drug remaining in the vial after use.
ContraindicationsThere are no contraindications listed within the manufacturer’s labeling.
Warnings/Precautions

Concerns related to adverse effects:

- Leukocytosis: Increases circulating leukocytes when used in conjunction with G-CSF; monitor WBC. Use with caution in patients with neutrophil count >50,000/mm^3.
- Thrombocytopenia: Has been observed with use; monitor platelet count.

Disease-related concerns:

- Leukemia: Not intended for mobilization in patients with leukemia; may contaminate apheresis product by mobilizing leukemic cells.
- Renal impairment: Primary route of elimination is urinary; dosage reduction is recommended in patients with moderate-severe renal impairment (Cl_{cr} ≤50 mL/minute).

Concurrent drug therapy issues:

- G-CSF: Splenomegaly and splenic rupture have been reported (rarely) with G-CSF use; instruct patients to report left upper quadrant pain or scapular/shoulder tip pain; promptly evaluate in any patient who report these.
- Nephrotoxic drugs: Medications that may reduce renal function or compete for active tubular secretion may increase serum concentrations of plerixafor.

Special populations:

- Obese patients: Use has not been studied in patients weighing >175% of ideal body weight.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Tumor cell mobilization: When used in combination with G-CSF, tumor cells released from marrow could be collected in leukapheresis product; potential effect of tumor cell reinfusion is unknown.

Pregnancy Risk FactorD
Pregnancy ConsiderationsAdverse effects (including fetal mortality, decreased fetal weights, and teratogenicity) have been reported in animal studies. May cause fetal harm if administered to pregnant women. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should use effective contraceptive measures to avoid becoming pregnant during treatment.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse ReactionsAdverse reactions reported with G-CSF combination therapy.

>10%:

Central nervous system: Fatigue (27%), headache (22%), dizziness (11%)

Gastrointestinal: Diarrhea (37%), nausea (34%)

Local: Injection site reactions (34%, including erythema, hematoma, hemorrhage, induration, inflammation, irritation, pain, paresthesia, pruritus, rash, swelling, urticaria)

Neuromuscular & skeletal: Arthralgia (13%)

5% to 10%:

Central nervous system: Insomnia (7%)

Gastrointestinal: Vomiting (10%), flatulence (7%)

<5%, postmarketing, and/or case reports: Abdominal discomfort, abdominal distension, abdominal pain, constipation, diaphoresis, dyspepsia, dyspnea, erythema, hypesthesia (oral), hypoxia, leukocytes increased, malaise, musculoskeletal pain, orthostatic hypotension, periorbital swelling, syncope, thrombocytopenia, urticaria, vasovagal reaction, xerostomia

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersCBC with differential and platelets

Monitoring: Lab TestsCBC with differential and platelets

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Mozobil™: 20 mg/mL (1.2 mL)

Generic AvailableNo

ManufacturerGenzyme Corporation

Mechanism of ActionReversibly inhibits binding of stromal cell-derived factor-1-alpha (SDF-1α), expressed on bone marrow stromal cells, to the CXC chemokine receptor 4 (CXCR4), resulting in mobilization of hematopoietic stem and progenitor cells from bone marrow into peripheral blood. Plerixafor used in combination with G-CSF results in synergistic increase in CD34+ cell mobilization. Mobilized CD34+ cells are capable of engrafting with extended repopulating capacity.

Pharmacodynamics/Kinetics

Onset of action: Peak CD34+ mobilization: Plerixafor monotherapy: 6-9 hours after administration; Plerixafor + G-CSF: 10-14 hours

Duration: WBC counts return toward baseline at ~24 after administration

Absorption: SubQ: Rapid

Distribution: 0.3L/kg; primarily to extravascular fluid space

Protein binding: ≤58%

Metabolism: Not metabolized

Half-life elimination: Terminal: 3-6 hours

Time to peak, plasma: SubQ: 30-60 minutes

Excretion: Urine (~70%; as parent drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusFatigue, dizziness, and headache are common; may cause insomnia

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with SSRIs, carbamazepine, valproic acid, and lithium may produce additive effects

Index TermsAMD3100; LM3100

References

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Pneumococcal Conjugate Vaccine (7-Valent)

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Prevnar® may be confused with PREVEN®

Pronunciation(noo moe KOK al KON ju gate vak SEEN, seven vay lent)
U.S. Brand NamesPrevnar®
Canadian Brand NamesPrevnar®
Pharmacologic CategoryVaccine, Inactivated (Bacterial)
Use: Labeled Indications

Immunization of infants and toddlers against *Streptococcus pneumoniae* infection caused by serotypes included in the vaccine

Immunization of infant and toddlers against otitis media caused by serotypes included in the vaccine

Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for the following:

All children 2-23 months

Children ≥2-59 months with cochlear implants

Children ages 24-59 months with: Sickle cell disease (including other sickle cell hemoglobinopathies, asplenia, splenic dysfunction), HIV infection, immunocompromising conditions (congenital immunodeficiencies excluding chronic granulomatous disease, renal failure, nephrotic syndrome, diseases associated with immunosuppressive or radiation therapy, solid organ transplant), chronic illnesses (cardiac disease, cerebrospinal fluid leaks, diabetes mellitus, pulmonary disease excluding asthma unless on high dose corticosteroids)

Consider use in all children 24-59 months with priority given to:

Children 24-35 months

Children 24-59 months who are of Alaska native, American Indian, or African-American descent

Children 24-59 months who attend group day care centers

Dosing: AdultsDosing established for infants and toddlers
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Immunization: Infants: 2-6 months: I.M.: 0.5 mL at approximately 2-month intervals for 3 consecutive doses, followed by a fourth dose of 0.5 mL at 12-15 months of age; first dose may be given as young as 6 weeks of age, but is typically given at 2 months of age. In case of a moderate shortage of vaccine, defer the fourth dose until shortage is resolved; in case of a severe shortage of vaccine, defer third and fourth doses until shortage is resolved.

Previously Unvaccinated Older Infants and Children: I.M.:

7-11 months: 0.5 mL for a total of 3 doses; 2 doses at least 4 weeks apart, followed by a third dose after the 1-year birthday (12-15 months), separated from the second dose by at least 2 months. In case of a severe shortage of vaccine, defer the third dose until shortage is resolved.

12-23 months: 0.5 mL for a total of 2 doses, separated by at least 2 months. In case of a severe shortage of vaccine, defer the second dose until shortage is resolved.

24-59 months:

Healthy Children: 0.5 mL as a single dose. In case of a severe shortage of vaccine, defer dosing until shortage is resolved.

Children with sickle cell disease, asplenia, HIV infection, chronic illness or immunocompromising conditions: 0.5 mL for a total of 2 doses, separated by 2 months

Previously Vaccinated with PPSV (ACIP recommendations): I.M.: Children 24-59 months of age at high risk for pneumococcal disease but have already received the PPSV may benefit from the immunologic response induced by PCV. Suggested dosing: Starting ≥2 months after last PPSV dose: One dose of PCV, followed by a second dose ≥2 months later.

Previously Vaccinated with PCV and with a lapse in vaccine administration (ACIP recommendations) : I.M.;

7-11 months: Previously received 1 or 2 doses PCV: 0.5 mL dose at 7-11 months of age, followed by a second dose ≥2 months later at 12-15 months of age

12-23 months:

Previously received 1 dose before 12 months of age: 0.5 mL dose, followed by a second dose ≥2 months later

Previously received 2 doses before age 12 months: 0.5 mL dose ≥2 months after the most recent dose

24-59 months: Any incomplete schedule: 0.5 mL as a single dose; **Note:** Patients with chronic diseases or immunosuppressing conditions should receive 2 doses ≥2 months apart

Administration: I.M.Shake well prior to use. Administer I.M. (deltoid muscle for toddlers and young children or lateral midthigh in infants). Do not inject I.V.; avoid intradermal route.

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

Administration with other vaccines:

PCV with other inactivated vaccines: May be given simultaneously or at any interval between doses.

PCV with live vaccines: May be given simultaneously or at any interval between doses

Vaccine administration with antibody-containing products: PCV and antibody-containing products may be given simultaneously at different sites or at any interval between doses. Examples of antibody containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StorageStore refrigerated at 2°C to 8°C (36°F to 46°F); do not freeze.

ContraindicationsHypersensitivity to pneumococcal vaccine or any component of the formulation, including diphtheria toxoid

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Acute illness: The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and the etiology of the disease. Immunization should be delayed during the course of an acute severe febrile illness; may administer to patients with mild acute illness (with or without fever).

- Asplenia: Use of pneumococcal conjugate vaccine does not replace use of the 23-valent pneumococcal polysaccharide vaccine in children ≥24 months of age with asplenia.

- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.

- Chronic illness: Use of pneumococcal conjugate vaccine does not replace use of the 23-valent pneumococcal polysaccharide vaccine in children ≥24 months of age with chronic illness.

- HIV: Use of pneumococcal conjugate vaccine does not replace use of the 23-valent pneumococcal polysaccharide vaccine in children ≥24 months of age with HIV infection.

- Pneumococcal infections: Not to be used to treat pneumococcal infections or to provide immunity against diphtheria.

- Seizure disorders: Febrile seizures have been reported (rare). Antipyretics should be administered at the time of vaccination to patients at risk for seizures to reduce the risk of postvaccination fever

- Sickle cell disease: Use of pneumococcal conjugate vaccine does not replace use of the 23-valent pneumococcal polysaccharide vaccine in children ≥24 months of age with sickle cell disease.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination. Use of pneumococcal conjugate vaccine does not replace use of the 23-valent pneumococcal polysaccharide vaccine in children ≥24 months of age who are immunocompromised.

- Pediatrics: Safety and efficacy have not been established in children <6 weeks or ≥10 years of age.

Dosage form specific issues:

- Latex: Packaging may contain natural latex rubber.

Pregnancy Risk FactorC

Pregnancy Considerations

Reproduction studies have not been conducted. This product is indicated for use in infants and toddlers.

Lactation

Excretion in breast milk unknown/not recommended

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

>10%:

Central nervous system: Fever, irritability, drowsiness, restlessness

Dermatologic: Erythema

Gastrointestinal: Decreased appetite, vomiting, diarrhea

Local: Induration, tenderness, nodule

1% to 10%: Dermatologic: Rash

Postmarketing and/or case reports: Anaphylactic reaction, anaphylactoid reaction, angioneurotic edema, apnea, bronchospasm, crying, dyspnea, erythema multiforme, facial edema, febrile seizure, hypersensitivity reaction, injection site reaction (eg, dermatitis, lymphadenopathy, pruritus, urticaria), shock

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Monitoring ParametersMonitor for syncope for ≥15 minutes following vaccination.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension:

Prevnar®: 2 mcg of each capsular saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 mcg of serotype 6B [bound to diphtheria CRM$_{197}$ protein ~20 mcg] per 0.5 mL (0.5 mL) [contains aluminum, natural rubber/natural latex in packaging, soy, and yeast]

Generic AvailableNo

Mechanism of ActionPromotes active immunization against invasive disease caused by *S. pneumoniae* capsular serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, all which are individually conjugated to CRM197 protein

Related Information

- Immunization Recommendations

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title and address be entered into the patient's permanent medical record.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusIrritability, drowsiness, and restlessness are common

Mental Health: Effects on Psychiatric TreatmentMay lessen the effects of anxiolytics

Index TermsDiphtheria CRM$_{197}$ Protein; PCV; PCV7; Pneumococcal 7-Valent Conjugate Vaccine

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Reefhuis J, Honein MA, Whitney CG, et al, “Risk of Bacterial Meningitis in Children With Cochlear Implants,” *N Engl J Med*, 2003, 349:435-

45.[PubMed 12890842]

International Brand Names Prevenar (AR, AU, BE, BR, CH, CN, CO, CR, CZ, DE, DK, EE, ES, FI, GB, GT, HN, IE, KP, NI, NL, NO, PA, PE, PH, SE, SV, TW, VE); Prevnar (AT, BE, BG, CH, CZ, DE, DK, DO, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TH, TR)

Pneumococcal Polysaccharide Vaccine (Polyvalent)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(noo moe KOK al pol i SAK a ride vak SEEN, pol i VAY lent)

U.S. Brand NamesPneumovax® 23

Canadian Brand NamesPneumo 23™; Pneumovax® 23

Pharmacologic CategoryVaccine, Inactivated (Bacterial)

Use: Labeled IndicationsImmunization against pneumococcal disease caused by serotypes included in the vaccine. Use is recommended for the following:

Immunocompetent individuals:

Routine vaccination for persons ≥50 years of age

Persons ≥2 years with the following chronic conditions: cardiovascular disease, pulmonary disease, diabetes mellitus, liver disease

Persons ≥2 years with alcoholism, cerebrospinal fluid leaks, functional or anatomic asplenia

Persons ≥2 years in special living environments or social settings

Adults 19-64 years who smoke cigarettes

Immunocompromised individuals: Persons ≥2 years with HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure, nephritic syndrome, chronic immunosuppressive therapy (including corticosteroids), persons who received an organ or bone marrow transplant

In addition, the Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for all immunocompetent persons ≥65 years of age and persons aged 2-64 years with cochlear implants. Routine vaccination is not recommended for Alaska Natives or American Indian persons unless they have underlying conditions which are indications for vaccination; in special situations, vaccination may be recommended when living in an area at increased risk of invasive pneumococcal disease.

Dosing: Adults**Immunization:** I.M., SubQ: 0.5 mL

Revaccination:

Immunocompetent individuals: Revaccination generally not recommended

Children ≥2 years and Adults at highest risk for infection: One revaccination ≥5 years after first dose of PPSV. May consider giving the revaccination dose ≥3 years after first dose of PPSV in children who will be ≤10 years of age at the time of revaccination. Patients at highest risk for infection include those with asplenia, sickle cell anemia, HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, conditions associated with immunosuppression, and patients on immunosuppressive therapy (including corticosteroids)

Elderly (≥65 years): One revaccination if ≥5 years after first dose of PPSV and if <65 years of age of initial vaccination.

Previously vaccinated with PCV vaccine: Children ≥2 years and Adults (ACIP recommendations):

With sickle cell disease, asplenia, immunocompromised or HIV infection: 0.5 mL at ≥2 years of age and ≥2 months after last dose of PCV; one revaccination with PPSV should be given ≥5 years for children >10 years of age and after 3-5 years for children ≤10 years of age; revaccination should not be administered <3 years after the previous PPSV dose

With chronic illness: 0.5 mL at ≥2 years of age and ≥2 months after last dose of PCV; revaccination with PPSV is not recommended

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥2 years: Refer to adult dosing.

Administration: I.M.Do not inject I.V., avoid intradermal (may cause severe local reactions); administer SubQ or I.M. (deltoid muscle or lateral midthigh)

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends "it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection."

Administration with other vaccines:

PPSV with other inactivated vaccines: May be given simultaneously or at any interval between doses.

PPSV with live vaccines: May be given simultaneously or at any interval between doses

Vaccine administration with antibody-containing products: PPSV and antibody-containing products may be given simultaneously at different sites or at any interval between doses. Examples of antibody containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F).
ContraindicationsHypersensitivity to pneumococcal vaccine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Acute illness: The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and the etiology of the disease. Immunization should be delayed during the course of an acute febrile illness.

- Cardiovascular disease: Use with caution in patients with severe cardiovascular where a systemic reaction may pose a significant risk.

- HIV: Patients with HIV should be vaccinated as soon as possible (following confirmation of the diagnosis).

- Respiratory disease: Use with caution in patients with severe pulmonary disease where a systemic reaction may pose a significant risk.

- Splenectomy: Patients who will undergo splenectomy should also be vaccinated 2 weeks prior to surgery, if possible.

- Thrombocytopenia purpura: May cause relapse in patients with stable idiopathic thrombocytopenia purpura.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist. If a person has not received any pneumococcal vaccine or if pneumococcal vaccination status is unknown, PPSV should be administered as indicated.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients; patients who will be receiving immunosuppressive therapy (including Hodgkin's disease, cancer chemotherapy, or transplantation) should be vaccinated at least 2 weeks prior to the initiation of therapy. Immune responses may be impaired for several months following intensive immunosuppressive therapy (up to 2 years in Hodgkin's disease patients).

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Geriatric ConsiderationsElderly have ~3 times the incidence of pneumococcal pneumonia than younger adults and 30% of all pneumococcal meningitis occurs in persons >50 years of age with a 20% mortality. Limited data on the elderly; however, elderly, compared to young adults, develop slightly lower antibody titers; provides 60% to 70% protection for bacterial pneumonia. 90% protection for pneumococcal pneumonia strains; 20% of the elderly with pneumococcal pneumonia have an associated bacteremia with a 17% to 40% fatality. All persons ≥65 years of age should receive the pneumococcal vaccine including previously unvaccinated persons and persons who have not been vaccinated within 5 years. All persons of unknown vaccination status should receive once dose of vaccine.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Vaccination should be considered in pregnant women at high risk for infection.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Frequency not defined.

Central nervous system: Chills, Guillain-Barré syndrome, fever ≤102˚F*, fever >102˚F, headache, malaise, pain, radiculoneuropathy, seizure (febrile)

Dermatologic: Angioneurotic edema, cellulitis, rash, urticaria

Gastrointestinal: Nausea, vomiting

Hematologic: Hemolytic anemia (in patients with other hematologic disorders), leukocytosis, thrombocytopenia (in patients with stabilized ITP)

Local: Injection site reaction* (erythema, induration, swelling, soreness, warmth); peripheral edema in injected extremity

Neuromuscular & skeletal: Arthralgia, arthritis, limb mobility decreased, myalgia, paresthesia, weakness

Miscellaneous: Anaphylactoid reaction, C-reactive protein increased, lymphadenitis, serum sickness

*Reactions most commonly reported in clinical trials.

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Monitoring ParametersMonitor for syncope for ≥15 minutes following vaccination.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Pneumovax® 23: 25 mcg each of 23 capsular polysaccharide isolates/0.5 mL (0.5 mL, 2.5 mL)

Generic AvailableNo
Mechanism of ActionAlthough there are more than 80 known pneumococcal capsular types, pneumococcal disease is mainly caused by only a few types of pneumococci. Pneumococcal vaccine contains capsular polysaccharides of 23 pneumococcal types of *Streptococcal pneumoniae* which represent at least 85% to 90% of pneumococcal disease isolates in the United States. The pneumococcal vaccine with 23 pneumococcal capsular polysaccharide types became available in 1983. The 23 capsular pneumococcal vaccine contains purified capsular polysaccharides of pneumococcal types 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. These are the main pneumococcal types associated with serious infections in the United States.
Related Information

- Immunization Recommendations
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause malaise
Mental Health: Effects on Psychiatric TreatmentNone reported
Index Terms23-Valent Pneumococcal Polysaccharide Vaccine; 23PS; PPSV; PPV23
References

ACIP Provisional Recommendations for Use of Pneumococcal Vaccines, available at http://www.cdc.gov/vaccines/recs/provisional/downloads/pneumo-oct-2008-508.pdf

Advisory Committee on Immunization Practices (ACIP), "Pneumococcal Vaccination for Cochlear Implant Recipients," *MMWR*, 2002, 51(41):931. [PubMed 12408148]

Centers for Disease Control and Prevention, "Prevention of Pneumococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP)," *MMWR Recomm Rep*, 1997, 46(RR-8):1-24.

Centers for Disease Control and Prevention (CDC), "Syncope After Vaccination -- United States, January 2005-July 2007," *MMWR Morb Mortal Wkly Rep*, 2008, 57(17):457-60.[PubMed 18451756]

Centers for Disease Control, "Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization," *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.[PubMed 17136024]

Davidson M, Bulkow LR, Grabman J, et al, "Immunogenicity of Pneumococcal Revaccination in Patients With Chronic Disease," *Arch Intern Med*, 1994, 154(19):2209-14. [PubMed 7944842]

Gardner P and Schaffner W, "Immunization of Adults," *N Engl J Med*, 1993, 328(17):1252-8. [PubMed 8464436]

"Preventing Pneumococcal Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention," *MMWR Recomm Rep*, 2000, 49(RR-9):1-35.

International Brand NamesMoniarix (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Pneumo 23 (AR, BE, BG, BR, CL, CN, CO, CR, CZ, DO, EE, ES, FR, GT, HK, HN, IN, IT, MY, NZ, PA, PE, PH, PK, PY, SE, SG, SV, TH, TW, UY); Pneumo 23 Imovax (IL); Pneumo Novum (DK); Pneumovax (CL, JP, SE, SG); Pneumovax 23 (AR, AU, CH, HK, NL, TW); Pneumovax II (GB, IE); Pnu-Imune 23 (GR); Pnu-imune 23 (PL); Prevenar (PL)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Brain Tumors

Regimen UseBrain tumors

Regimen

Prednisone: Oral: 40 mg/m^2/day days 1 to 14

[total dose/cycle = 560 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2/day (maximum 2 mg) days 1, 8, and 15

[total dose/cycle = 4.5 mg/m^2]

Lomustine: Oral: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 6 weeks

References

Finlay JL, Boyett JM, Yates AJ, et al, âRandomized Phase III Trial in Childhood High-Grade Astrocytoma Comparing Vincristine, Lomustine, and Prednisone With the Eight-Drugs-In-1-Day Regimen. Childrens Cancer Group,â *J Clin Oncol*, 1995, 13(1):112-23.[PubMed 7799011]

Podofilox

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(poe DOF il oks)
U.S. Brand NamesCondylox®
Canadian Brand NamesCondyline™; Wartec®
Pharmacologic CategoryKeratolytic Agent; Topical Skin Product
Use: Labeled IndicationsTreatment of external genital warts
Dosing: Adults**Genital warts:** Topical: Apply twice daily (morning and evening) for 3 consecutive days, then withhold use for 4 consecutive days; this cycle may be repeated up to 4 times until there is no visible wart tissue
Dosing: ElderlyRefer to adult dosing.
Pregnancy Risk FactorC
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel: 0.5% (3.5 g) [contains alcohol]

Solution, topical: 0.5% (3.5 mL) [contains alcohol]

Generic AvailableYes: Topical solution
Pricing: U.S. (www.drugstore.com)

Gel (Condylox)

0.5% (3.5): $215.99

Solution (Condylox)

0.5% (3.5): $121.41

Solution (Podofilox)

0.5% (3.5): $105.99

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesCondyline (BG, CH, DK, FI, FR, GB, HN, IE, IN, IT, NL, NO, PT, SE); Condyline Liquid (NZ); Condyline Paint (AU); Condylox (AT, CL, DE, IL); Podofilox (GR); Podoxin (AR, UY); Warix (CH); Wartec (AU, BE, DE, DK, EE, FI, GR, HK, NO, PE, PK, SE, ZA); Warticon (GB, IE)

Podophyllum Resin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(po DOF fil um REZ in)

U.S. Brand NamesPodocon-25®

Canadian Brand NamesPodofilm®

Pharmacologic CategoryKeratolytic Agent

Use: Labeled IndicationsTopical treatment of benign growths including external genital and perianal warts, papillomas, fibroids; compound benzoin tincture generally is used as the medium for topical application

Dosing: Adults**Treatment of benign growths (warts, papillomas, fibroids):** Topical: 10% to 25% solution in compound benzoin tincture; apply drug to dry surface, use 1 drop at a time allowing drying between drops until area is covered. Total volume should be limited to <0.5 mL per treatment session.

Condylomata acuminatum: 25% solution is applied daily. Use a 10% solution when applied to or near mucous membranes.

Verrucae: 25% solution is applied 3-5 times/day directly to the wart.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: TopicalShake well before using. **Only to be applied by physician.** Solution should be washed off within 1-4 hours for genital and perianal warts and within 1-2 hours for accessible meatal warts. Use protective occlusive dressing around warts to prevent contact with unaffected skin. For external use only.

ContraindicationsNot to be used on birthmarks, moles, or warts with hair growth; cervical, urethral, oral warts; not to be used by patient with diabetes or patient with poor circulation; pregnancy

Warnings/Precautions

Dosage form specific issues:

- 25% solution: Should not be applied to or near mucous membranes.

Other warnings/precautions:

- Appropriate use: Use of large amounts of drug should be avoided. For external use only; avoid contact with the eyes as it can cause severe corneal damage; do not apply to moles, birthmarks, or unusual warts. To be applied by a physician only.

Pregnancy Risk FactorX

LactationEnters breast milk/contraindicated

Adverse Reactions

1% to 10%:

Dermatologic: Pruritus

Gastrointestinal: Nausea, vomiting, abdominal pain, diarrhea

<1%: Confusion, hallucinations, hepatotoxicity, lethargy, leukopenia, peripheral neuropathy, renal failure, thrombocytopenia

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/Monitoring**Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to sexually-active female patients unless capable of complying with contraceptive use. Breast-feeding is contraindicated.

Patient EducationCover with occlusive dressing to prevent contact with unaffected skin. Wash off medication as instructed by professional who applied the treatment. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, topical: 25% (15 mL) [in benzoin tincture]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Podocon)

25% (15): $84.49

Mechanism of ActionDirectly affects epithelial cell metabolism by arresting mitosis through binding to a protein subunit of spindle microtubules (tubulin)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment May rarely cause leukopenia, use caution with clozapine and carbamazepine

Index Terms Mandrake; May Apple; Podophyllin

References

“1993 Sexually Transmitted Diseases Treatment Guidelines,” *MMWR Recomm Rep*, 1993, 42(RR-14):1-102.

Goldfarb MT, Gupta AK, Gupta MA, et al, “Office Therapy for Human Papillomavirus Infection in Nongenital Sites,” *Dermatol Clin*, 1991, 9(2):287-96.[PubMed 1711941]

International Brand Names Podofilia No. 2 (MX)

POG-8651

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Osteosarcoma

Regimen Use Osteosarcoma

Regimen

(Surgery at week 10)

Methotrexate: I.V.: 12 g/m^2 weeks 0, 1, 5, 6, 13, 14, 18, 19, 23, 24, 37, and 38

[total dose/cycle = 144 g/m^2]

Leucovorin: (route not specified): 15 mg every 6 hours for 10 doses, weeks 0, 1, 5, 6, 13, 14, 18, 19, 23, 24, 37, and 38

[total dose/cycle = 1800 mg]

Doxorubicin: I.V.: 37.5 mg/m^2/day days 1 and weeks 2, 7, 25, and 28 and 30 mg/m^2 days 1, 2, and 3, week 20

[total dose/cycle = 390 mg/m^2]

Cisplatin: I.V.: 60 mg/m^2/day days 1 and 2, weeks 2, 7, 25, and 28

[total dose/cycle = 480 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2/day days 1, 2, and 3, weeks 15, 31, 34, 39, and 42

[total dose/cycle = 9000 mg/m^2]

Bleomycin: I.V.: 15 units/m^2/day days 1, 2, and 3, weeks 15, 31, 34, 39, and 42

[total dose/cycle = 225 units/m^2]

Dactinomycin: I.V.: 0.6 mg/m^2/day days 1, 2, and 3, weeks 15, 31, 34, 39, and 42

[total dose/cycle = 9 mg/m^2]

or

(Surgery at week 0)

Methotrexate: 12 g/m^2 weeks 3, 4, 8, 9, 13, 14, 18, 19, 23, 24, 37, and 38

[total dose/cycle = 144 g/m^2]

Leucovorin: (route not specified): 15 mg every 6 hours for 10 doses, weeks 3, 4, 8, 9, 13, 14, 18, 19, 23, 24, 37, and 38

[total dose/cycle = 1800 mg]

Doxorubicin: I.V.: 37.5 mg/m^2/day days 1 and 2, weeks 5, 10, 25, and 28 and 30 mg/m^2 days 1, 2, and 3, week 20

[total dose/cycle = 390 mg/m^2]

Cisplatin: I.V.: 60 mg/m^2/day days 1 and 2, weeks 5, 10, 25, and 28

[total dose/cycle = 480 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2/day days 1, 2, and 3, weeks 15, 31, 34, 39, and 42

[total dose/cycle = 9000 mg/m^2]

Bleomycin: I.V.: 15 units/m^2/day days 1, 2, and 3, weeks 15, 31, 34, 39, and 42

[total dose/cycle = 225 units/m^2]

Dactinomycin: I.V.: 0.6 mg/m^2/day days 1, 2, and 3, weeks 15, 31, 34, 39, and 42

[total dose/cycle = 9 mg/m^2]

References

Goorin AM, Schwartzentruber DJ, Devidas M, et al, âPresurgical Chemotherapy Compared With Immediate Surgery and Adjuvant Chemotherapy for Nonmetastatic Osteosarcoma: Pediatric Oncology Group Study POG-8651,â *J Clin Oncol*, 2003, 21(8):1574-80.[PubMed 12697883]

Poliovirus Vaccine (Inactivated)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(POE lee oh VYE rus vak SEEN, in ak ti VAY ted)

U.S. Brand NamesIPOL®

Canadian Brand NamesIPOL®

Pharmacologic CategoryVaccine

Use: Labeled IndicationsActive immunization against poliomyelitis caused by poliovirus types 1, 2 and 3. Routine immunization of adults in the United States is generally not recommended. Adults with previous wild poliovirus disease, who have never been immunized, or those who are incompletely immunized may receive inactivated poliovirus vaccine if they fall into one of the following categories:

- Travelers to regions or countries where poliomyelitis is endemic or epidemic
- Healthcare workers in close contact with patients who may be excreting poliovirus
- Laboratory workers handling specimens that may contain poliovirus
- Members of communities or specific population groups with diseases caused by wild poliovirus
- Incompletely vaccinated or unvaccinated adults in a household or with other close contact with children receiving oral poliovirus (may be at increased risk of vaccine associated paralytic poliomyelitis)

Dosing: Adults**Immunization:** I.M., SubQ:

Previously unvaccinated: Two 0.5 mL doses administered at 1- to 2-month intervals, followed by a third dose 6-12 months later. If <3 months, but at least 2 months are available before protection is needed, 3 doses may be administered at least 1 month apart. If administration must be completed within 1-2 months, give 2 doses at least 1 month apart. If <1 month is available, give 1 dose.

Incompletely vaccinated: Adults with at least 1 previous dose of OPV, <3 doses of IPV, or a combination of OPV and IPV equaling <3 doses, administer at least one 0.5 mL dose of IPV. Additional doses to complete the series may be given if time permits.

Completely vaccinated: One 0.5 mL dose

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Immunization:** I.M., SubQ: Primary immunization: Administer three 0.5 mL doses, preferably 8 or more weeks apart at 2, 4, and 6-18 months of age. Booster dose: 0.5 mL at 4-6 years of age.

Administration: I.M.Administer to midlateral aspect of the thigh in infants and small children. Administer in the deltoid area to adults or older children.

Administration: I.V.Do not administer I.V.

Administration: OtherSubQ: Administer to midlateral aspect of the thigh in infants and small children. Administer in the deltoid area to adults or older children.

StorageStore under refrigeration 2°C to 8°C (35°F to 46°F); do not freeze.

ContraindicationsHypersensitivity to any component of the vaccine

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).
- Polio infection: Patients with prior clinical poliomyelitis or incomplete immunization with oral poliovirus vaccine (OPV) may receive inactivated poliovirus vaccine (IPV).

Concurrent drug therapy issues:

- Immune globulin: Immune response may be decreased in patients receiving immune globulin.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients; patients with HIV infection, severe combined immunodeficiency, hypogammaglobulinemia, agammaglobulinemia, or altered immunity (due to corticosteroids, alkylating agents, antimetabolites or radiation) may receive inactivated poliovirus vaccine (IPV).
- Pediatrics: Safety and efficacy have not been established in children <6 weeks of age.

Dosage form specific issues:

- 2-phenoxyethanol: Products may contain 2-phenoxyethanol.
- Calf serum protein: Products may contain calf serum protein.
- Formaldehyde: Products may contain formaldehyde.
- Latex: Packaging may contain natural latex rubber.
- Neomycin: Products may contain neomycin.
- Polymyxin B: Products may contain polymyxin B.
- Streptomycin: Products may contain streptomycin.

Geriatric ConsiderationsFor the elderly who cannot document a primary immunization series or at risk due to contact or travel, administer the initial series. Boosters may be necessary for travel since antibody titers may diminish with age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Although adverse effects of IPV have not been documented in pregnant women or their fetuses, vaccination of pregnant women should be avoided on theoretical grounds. Pregnant women at increased risk for infection and requiring immediate protection against polio may be administered the vaccine.

LactationExcretion into breast milk unknown/use caution

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Percentages noted with concomitant administration of DTP or DTaP vaccine and observed within 48 hours of injection.

>10%:

Central nervous system: Irritability (7% to 65%), tiredness (4% to 61%), fever ≥39°C (≤38%)

Gastrointestinal: Anorexia (1% to 17%)

Local: Injection Site: Tenderness (≤29%), pain (13%), swelling (≤11%)

1% to 10%:

Gastrointestinal: Vomiting (1% to 3%)

Local: Injection site: Erythema (≤3%), induration (1%)

Miscellaneous: Persistent crying (up to 1% reported within 72 hours)

Postmarketing and/or case reports: Guillain-Barré syndrome has been temporally related to another inactivated poliovirus vaccine

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension:

IPOL®: Type 1 poliovirus 40 D-antigen units, type 2 poliovirus 8 D-antigen units, and type 3 poliovirus 32 D-antigen units per 0.5 mL (0.5 mL, 5 mL) [contains 2-phenoxyethanol, formaldehyde, calf serum protein, neomycin (may have trace amounts), streptomycin (may have trace amounts), and polymyxin B (may have trace amounts)]

Generic AvailableNo

Related Information

- Immunization Recommendations

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

As the global eradication of poliomyelitis continues, the risk for importation of wild-type poliovirus into the United States decreases dramatically. To eliminate the risk for vaccine-associated paralytic poliomyelitis (VAPP), an all-IPV schedule is recommended for routine childhood vaccination in the United States. Oral poliovirus vaccine (OPV), is not commercially available in the United States, but has been stockpiled for use in the following special circumstances:

Mass vaccination campaigns to control outbreaks of paralytic polio

Unvaccinated children who will be traveling within 4 weeks to areas where polio is endemic or epidemic

Children of parents who do not accept the recommended number of vaccine injections; these children may receive OPV only for the third or fourth dose or both. In this situation, healthcare providers should administer OPV only after discussing the risk for VAPP with parents or caregivers.

Currently, the primary risk for paralytic polio in U.S. residents is through travel to countries where polio remains endemic or where polio outbreaks are occurring. Unvaccinated persons traveling to countries that use OPV should be aware of the risk caused by OPV and should consider polio vaccination prior to travel.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsEnhanced-potency Inactivated Poliovirus Vaccine; IPV; Salk Vaccine
References

Centers for Disease Control and Prevention, “Imported Vaccine-Associated Paralytic Poliomyelitis -- United States,” *MMWR Recomm Rep*, 2005, 55(RR 4);97-9.

Centers for Disease Control and Prevention, “Poliomyelitis Prevention in the United States: Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP),” *MMWR Recomm Rep*, 2000, 49(RR-5):14.

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 1994, 43(RR-1):23.

Gardner P and Schaffner W, “Immunization of Adults,” *N Engl J Med*, 1993, 328(17):1252-8.[PubMed 8464436]

International Brand NamesImovax Polio (AR, BE, BG, CZ, EE, FI, HK, HN, IL, IT, KP, NO, PE, PK, PY, TW, UY); Ipol (NZ); Opvero (TH); Polio Salk "Sero" (AT)

Poly-L-Lactic Acid

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(POL i el LAK tik AS id)
U.S. Brand NamesSculptra®
Pharmacologic CategoryCosmetic Agent, Implant
Use: Labeled IndicationsRestoration and/or correction of facial lipoatrophy in patients with HIV
Dosing: Adults **Lipoatrophy:** Intradermal or SubQ: ~0.05-0.2 mL per individual injection depending on technique used; ~20 injections may be needed per cheek. Treatment should be individualized. Separate treatments by ≥2 weeks. Typical course involves 3-6 treatments. Supplemental injections may be needed. Do not overfill contour deficiency. For patients with severe facial fat loss, the average treatment requires ~1 vial per cheek area per treatment.
Dosing: ElderlyRefer to adult dosing.
Administration: OtherFor injection into deep dermis or subcutaneous layer. Avoid intravenous injection. Administer using 26 gauge needle; do not bend needle. Massage treatment area periodically during session to evenly distribute.
StoragePrior to and following reconstitution, store at room temperature.
ReconstitutionSlowly add 3-5 mL SWFI to vial and allow to stand for 2 hours to hydrate. **Do not shake.** After 2 hours, agitate vial until a uniform suspension is formed. Use within 72 hours.
ContraindicationsHypersensitivity to poly-L-lactic acid or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Photosensitivity: Patients should be instructed to limit exposure to excessive sunlight or UV lamps until any swelling or redness is resolved.

Concurrent drug therapy issues:

- Anticoagulants/antiplatelets: Use with caution in patients on anticoagulants or antiplatelet medications.

Special populations:

- Non-Caucasians: Safety and efficacy in non-Caucasians are limited.
- Pediatrics: Safety and efficacy have not been established in children.
- Women: Safety and efficacy are limited in women with HIV.

Other warnings/precautions:

- Administration: Avoid IV injection; may lead to occlusion, infarction, or embolism.
- Appropriate use: Not for use if skin inflammation or infection exists in or near the treatment area; control inflammation or infection before use. Avoid use with implants. Avoid overcorrection of contour deficit; improvement occurs over weeks of treatment. Safety and efficacy have not been established for use in the periorbital area.

Pregnancy ConsiderationsSafety for use during pregnancy has not been established.
Breast-Feeding ConsiderationsSafety for use during breast-feeding has not been established. HIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.
Adverse Reactions

>10%:

Dermatologic: Bruising (1% to 38%)

Hematologic: Hematoma (up to 28%)

Local: Injection site: Papules (6% to 52%), edema (3% to 17%)

Miscellaneous: Discomfort (up to 19%)

1% to 10%:

Central nervous system: Fever (<5%)

Local: erythema (up to 10%), injection site reactions (<5%)

Postmarketing/case reports: Allergic reaction, angioedema, brittle nails, colitis, ectropion, fatigue, hair breakage, hypersensitivity reaction, hypertrophy, joint aches, malaise, photosensitivity, Quicke's edema, rash, skin roughness, telangiectasia, visible nodules

Injection site reactions: Abscess, atrophy, discharge, fat atrophy, granuloma

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for suspension:

Sculptra®: Poly-L-lactic acid USP

Generic AvailableNo

ManufacturerDermik Laboratories

Mechanism of ActionPoly-L-lactic acid is an immunologically inert synthetic polymer. It increases dermal thickness by causing a local reaction leading to an increase in collagen deposits. It is eventually degraded and undergoes resorption.

Pharmacodynamics/Kinetics

Onset of action: Weeks to months for full effect of treatment

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue and malaise

Mental Health: Effects on Psychiatric TreatmentMay cause photosensitivity; monitor concurrent use with psychotropics that also cause photosensitivity

Index TermsNew-Fill®; PLA

References

Moyle GJ, Lysakova L, Brown S, et al, “A Randomized Open-Label Study of Immediate Versus Delayed Polylactic Acid Injections for the Cosmetic Management of Facial Lipoatrophy in Persons With HIV Infection,” *HIV Med*, 2004, 5(2):82-7. [PubMed 15012646]

Valantin MA, Aubron-Olivier C, Ghosn J, et al, Polylactic Acid Implants (New-Fill) to Correct Facial Lipoatrophy in HIV-Infected Patients: Results of the Open-Label Study VEGA,” *AIDS*, 2003, 17(17):2471-7.

Polycarbophil

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(pol i KAR boe fil)

U.S. Brand NamesEqualactin® [OTC]; Fiber-Lax® [OTC]; Fiber-Tabs™ [OTC]; FiberCon® [OTC]; Konsyl® Fiber Caplets [OTC]

Pharmacologic CategoryAntidiarrheal; Laxative, Bulk-Producing

Use: Labeled IndicationsTreatment of constipation or diarrhea

Dosing: Adults**Constipation or diarrhea:** General dosing guidelines (OTC labeling): Oral: 1250 mg calcium polycarbophil 1-4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricConstipation or diarrhea: General dosing guidelines (OTC labeling): Oral:

Children 6-12 years: 625 mg calcium polycarbophil 1-4 times/day

Children ≥12 years: Refer to adult dosing.

Administration: OralPatient should drink adequate fluids (8 oz of water or other fluids) with each dose.

Dietary ConsiderationsFiberCon® contains calcium 122 mg/caplet. Fiber-Lax® contains calcium 170 mg/captab. Konsyl® Fiber contains calcium 125 mg/tablet.

Warnings/Precautions

Other warnings/precautions:

- Administration: Taking products without adequate fluid may cause it to swell and block throat or esophagus; use with caution in patients who have difficulty swallowing.

Geriatric ConsiderationsElderly may have insufficient fluid intake which may predispose them to fecal impaction and bowel obstruction. Bloating and flatulence may be a problem when used short-term. Use cautiously in patients with a history of bowel impaction/obstruction.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined: Gastrointestinal: Abdominal fullness

Drug Interactions

Bisphosphonate Derivatives: Calcium Salts may decrease the absorption of Bisphosphonate Derivatives. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Calcium Salts may diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

DOBUTamine: Calcium Salts may diminish the therapeutic effect of DOBUTamine. *Risk C: Monitor therapy*

Eltrombopag: Calcium Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., calcium-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

Estramustine: Calcium Salts may decrease the absorption of Estramustine. *Risk D: Consider therapy modification*

Phosphate Supplements: Calcium Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Calcium Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. **Exceptions:** Moxifloxacin. *Risk D: Consider therapy modification*

Thiazide Diuretics: May decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Trientine: Calcium Salts may decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet: Calcium polycarbophil 625 mg [equivalent to polycarbophil 500 mg]

FiberCon®: Calcium polycarbophil 625 mg [equivalent to polycarbophil 500 mg; contains calcium 122 mg/caplet]

Konsyl® Fiber: Calcium polycarbophil 625 mg [equivalent to polycarbophil 500 mg; contains calcium 125 mg/caplet]

Captab:

Fiber-Lax®: Calcium polycarbophil 625 mg [equivalent to polycarbophil 500 mg; contains calcium 170 mg/captab]

Tablet: Calcium polycarbophil 625 mg [equivalent to polycarbophil 500 mg]

Fiber-Tabs™: Calcium polycarbophil 625 mg [equivalent to polycarbophil 500 mg]

Tablet, chewable:

Equalactin®: Calcium polycarbophil 625 mg [equivalent to polycarbophil 500 mg; citrus flavor]

Generic AvailableYes

Mechanism of ActionRestoring a more normal moisture level and providing bulk in the patient's intestinal tract

Dental Health: Effects on Dental TreatmentOral medication should be given at least 1 hour prior to taking the bulk-producing laxative in order to prevent decreased absorption of medication.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Polyethylene Glycol 3350

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

MiraLax™ may be confused with Mirapex®

International issues:

MiraLax™ may be confused with Murelax® which is a brand name for oxazepam in Australia

Pronunciation(pol i ETH i leen GLY kol 3350)
U.S. Brand NamesGlycoLax®; MiraLax® [OTC]
Pharmacologic CategoryLaxative, Osmotic
Use: Labeled IndicationsTreatment of occasional constipation in adults
Use: Unlabeled/InvestigationalTreatment of constipation in children
Dosing: Adults**Occasional constipation:** Oral: 17 g of powder (~1 heaping tablespoon) dissolved in 8 oz of water, once daily; do not use for >2 weeks.
Dosing: ElderlyRefer to adult dosing.
StorageStore at room temperature of 15°C to 30°C (59°F to 86°F) before reconstitution.
ReconstitutionDissolve powder in 8 ounces of water, juice, cola, or tea.
ContraindicationsHypersensitivity to polyethylene glycol or any component of the formulation; gastrointestinal obstruction
Warnings/Precautions

Special populations:

- Pediatrics: Safety and efficacy have not been established in children ≤16 years of age.

Other warnings/precautions:

- Appropriate use: Evaluate patients with symptoms of bowel obstruction (nausea, vomiting, abdominal pain or distension) prior to use. Not intended for use as a bowel evacuant prior to GI examination.

- Duration of therapy: Do not use for longer than 2 weeks; 2-4 days may be required to produce bowel movement.

Geriatric ConsiderationsElderly are more likely to show CNS signs of dehydration and electrolyte loss than younger adults. Therefore, monitor closely for fluid and electrolyte loss with chronic use.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted in animals or in humans.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Dermatologic: Urticaria

Gastrointestinal: Abdominal bloating, cramping, diarrhea, flatulence, nausea

Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringAssess patient for symptoms of bowel obstruction prior to treatment. Instruct patient in appropriate use (not to be used for longer than 2 weeks), possible side effects/appropriate interventions, and adverse symptoms to report.
Patient EducationFollow instructions exactly. Do not use for longer than prescribed. Mix one heaping tablespoon of powder in 8 ounces of water and drink immediately. May take 2-4 days to produce bowel movement. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. May cause some gastrointestinal discomfort (mild bloating, cramping, flatulence, nausea, diarrhea). Stop taking and report any signs of blood in urine or stool, excessive vomiting, or cramping. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Powder, for oral solution: PEG 3350 17 g/packet (12s); PEG 3350 255 g (14 oz); PEG 3350 527 g (26 oz)

GlycoLax®: PEG 3350 17 g/packet (14s) [DSC]; PEG 3350 255 g (16 oz) [DSC]; PEG 3350 527 g (24 oz)

MiraLax®: PEG 3350 17 g/packet (12s) [DSC]; PEG 3350 255 g (14 oz); PEG 3350 527 g (26 oz) [DSC]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Powder (Polyethylene Glycol 3350)

(527): $39.00

Solution (reconstituted) (Colyte-Flavored)

240 g (3785): $18.17

Mechanism of ActionAn osmotic agent, polyethylene glycol 3350 causes water retention in the stool; increases stool frequency and consistency

Pharmacodynamics/KineticsOnset of action: Oral: 48-96 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPEG

References

Bell EA and Wall GC, "Pediatric Constipation Therapy Using Guidelines and Polyethylene Glycol 3350," *Ann Pharmacother*, 2004, 38(4):686-93.[PubMed 14990783]

Loening-Baucke V, Krishna R, and Pashankar DS, "Polyethylene Glycol 3350 Without Electrolytes for the Treatment of Functional Constipation in Infants and Toddlers," *J Pediatr Gastroenterol Nutr*, 2004, 39(5):536-9.[PubMed 15572895]

Pashankar DS, Loening-Baucke V, and Bishop WP, "Safety of Polyethylene Glycol 3350 for the Treatment of Chronic Constipation in Children," *Arch Pediatr Adolesc Med*, 2003, 157(7):661-4.[PubMed 12860787]

Polyethylene Glycol-Electrolyte Solution and Bisacodyl

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(pol i ETH i leen GLY kol ee LEK troe lite soe LOO shun & bis a KOE dil)
U.S. Brand NamesHalfLytely® and Bisacodyl
Pharmacologic CategoryLaxative, Bowel Evacuant; Laxative, Stimulant
Use: Labeled IndicationsBowel cleansing prior to colonoscopy
Dosing: Adults**Bowel cleansing:** Oral:

Bisacodyl: 2 tablets as a single dose. After bowel movement or 6 hours (whichever occurs first), initiate polyethylene glycol-electrolyte solution

Polyethylene glycol-electrolyte solution: 8 ounces every 10 minutes until 2 L are consumed

Dosing: ElderlyRefer to adult dosing.
Administration: OralDo not chew or crush bisacodyl tablets. Rapidly drinking the polyethylene glycol-electrolyte solution is preferred to drinking small amount continuously. If severe bloating, distention, or abdominal pain occurs, administration should be slowed or temporarily discontinued until symptoms resolve.
Dietary ConsiderationsDrink only clear liquids during bowel preparation; after consuming the solution, avoid drinking large quantities of clear liquids until colonoscopy.
StoragePolyethylene glycol-electrolyte solution: Store at 15°C to 30°C (59°F to 86°F). When reconstituted, may refrigerate. Use within 48 hours.
ReconstitutionFill the container with water to the fill mark. Shake well.
ContraindicationsHypersensitivity to bisacodyl, polyethylene glycol or any component of the formulation, gastrointestinal obstruction, bowel perforation, toxic colitis, or toxic megacolon
Warnings/Precautions

Concerns related to adverse effects:

- Ischemic colitis: Cases of ischemic colitis have been reported; development of severe abdominal pain or rectal bleeding should prompt further evaluation.
- Seizures: Generalized tonic-clonic seizures have occurred in patients with no prior history of seizures when using the large volume (4 L) preparation. Seizures resolved with the correction of fluid and electrolyte abnormalities. Use caution in patients taking medications which increase the risk for electrolyte abnormalities (eg, diuretics) and/or patients with pre-existing electrolyte abnormalities. Evaluation of electrolytes pre- and post-colonoscopy is warranted in this population.

Disease-related concerns:

- Gastric retention: Use caution in patients with gastric retention.
- Ileus: Use caution in patients with ileus.
- Impaired gag reflux: Observe unconscious or semiconscious patients with impaired gag reflex or those who are otherwise prone to regurgitation or aspiration during administration.
- Renal impairment: Patients with impaired renal function who develop severe vomiting should be closely monitored including measurement of electrolytes.
- Ulcerative colitis: Use with caution in patients with severe ulcerative colitis.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: No additional ingredients or flavors (other than the flavor packs provided) should be added to the polyethylene glycol-electrolyte solution.

Geriatric ConsiderationsStudies of this combination preparation drug included 28% of patients >65 years of age with 9.1% being >75 years. No differences in safety or efficacy were observed. No adjustments in dose are necessary.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproductive studies have not been conducted with this combination.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%:

Gastrointestinal: Nausea (13%), fullness (11%)

Miscellaneous: Overall discomfort (14%)

1% to 10%: Gastrointestinal: Cramping (7%), vomiting (5%)

Postmarketing and/or case reports: Anaphylaxis, aspiration, asystole, dermatitis, dizziness, dyspnea, esophageal perforation, hypersensitivity, ischemic colitis, Mallory-Weiss syndrome, pulmonary edema, rhinorrhea, seizure (using the 4 L preparation), syncope, urticaria

Drug Interactions

Antacids: May diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Take clear liquid diet during bowel preparation; after consuming the solution, avoid drinking large quantities of clear liquids until colonoscopy.

Monitoring ParametersBowel movements; electrolytes, renal function

Nursing: Physical Assessment/MonitoringSee individual agent for Polyethylene Glycol-Electrolyte Solution.

Monitoring: Lab TestsElectrolytes, renal function

Patient EducationSee individual agent for Polyethylene Glycol-Electrolyte Solution.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Kit [each kit contains]:

HalfLytely® and Bisacodyl:

Powder for oral solution (HalfLytely®): PEG 3350 210 g, sodium bicarbonate 2.86 g, sodium chloride 5.6 g, potassium chloride 0.74 g (2000 mL) [sulfate-free; cherry, lemon-lime, orange flavor]

Tablet, delayed release (Bisacodyl): 5 mg (2s)

Generic AvailableNo

ManufacturerBraintree Laboratories, Inc

Pricing: U.S. (www.drugstore.com)

Kit (HalfLytely Bowel Prep)

5-210 mg-g (1): $57.77

Mechanism of ActionBisacodyl acts on the colonic mucosa to increase peristalsis throughout the large intestine. Polyethylene glycol-electrolyte solution induces catharsis through strong electrolyte and osmotic effects.

Pharmacodynamics/KineticsSee individual agents.

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Mental Health Comment

Oral medications should not be administered within 1 hour of start of therapy

Index TermsElectrolyte Lavage Solution

References

DiPalma JA, McGowan J, and Cleveland M, “Clinical Trial: An Efficacy Evaluation of Reduced Bisacodyl Given as Part of a Polyethylene Glycol Electrolyte Solution Preparation Prior to Colonoscopy,” *Aliment Pharmacol Ther*, 2007, 26(8):113-9.[PubMed 17894653]

DiPalma JA, Wolff BG, Meagher A, et al, “Comparison of Reduced Volume Versus Four Liters Sulfate-Free Electrolyte Lavage Solutions for Colonoscopy Colon Cleansing,” *Am J Gastroenterol*, 2003, 98(10):2187-91.[PubMed 14572566]

Polyethylene Glycol-Electrolyte Solution

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

GoLYTELY® may be confused with NuLYTELY®

NuLYTELY® may be confused with GoLYTELY®

TriLyte® may be confused with TriLipix™

Pronunciation(pol i ETH i leen GLY kol ee LEK troe lite soe LOO shun)
U.S. Brand NamesColyte®; GoLYTELY®; MoviPrep®; NuLYTELY®; TriLyte®
Canadian Brand NamesColyte™; Klean-Prep®; PegLyte®
Pharmacologic CategoryLaxative, Osmotic
Use: Labeled IndicationsBowel cleansing prior to GI examination
Use: Unlabeled/InvestigationalWhole bowel irrigation (WBI) in the following toxic ingestions: Packets of illicit drugs (body packers, body stuffers), potentially toxic sustained-release or enteric-coated agents, substantial amounts of iron (AACT, 2004)
Dosing: Adults

Bowel cleansing prior to GI exam:

Oral:

CoLyte®, GoLYTELY®, NuLYTELY®, TriLyte®: 240 mL (8 oz) every 10 minutes, until 4 L are consumed or the rectal effluent is clear; rapid drinking of each portion is preferred to drinking small amounts continuously. **Note:** The solution may be given via nasogastric tube to patients who are unwilling or unable to drink the solution.

MoviPrep®: Administer 2 L total with an additional 2 L of clear fluid prior to colonoscopy as follows:

Split dose: Evening before colonoscopy: 240 mL (8 oz) every 15 minutes until 1 L is consumed. Then drink 16 oz of clear liquid. On the morning of the colonoscopy, repeat process with second liter over 1 hour and then drink 16 oz of clear liquid at least 1 hour before the procedure.

Full dose: Evening before colonoscopy (~6 PM): 240 mL (8 oz every 15 minutes) until 1 L is consumed; 90 minutes later (~7:30 PM), repeat dose. Then drink 32 oz of clear liquid.

Nasogastric tube: 20-30 mL/minute (1.2-1.8 L/hour); the first bowel movement should occur ~1 hour after the start of administration.

Toxic ingestion (unlabeled use; AACT, 2004):*Nasogastric tube:* 1500-2000 mL/hour until rectal effluent is clear. **Note:** May take several hours for the rectal effluent to become clear. Duration may be extended if evidence of continued presence of toxins in GI tract (eg, radiographic evidence or ongoing elimination of toxins)

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Bowel cleansing prior to GI exam: (CoLyte®, GoLYTELY®, NuLYTELY®, TriLyte®):

Oral: 25 mL/kg/hour (some studies have used up to 40 mL/kg/hour) for 4-10 hours until rectal effluent is clear (maximum total dose: 4 L)

Nasogastric tube: 25 mL/kg/hour until rectal effluent is clear

Toxic ingestion (unlabeled use; AACT, 2004):*Nasogastric tube:*

Children ≥9 months to 6 years: 500 mL/hour until rectal effluent is clear

Children 6-12 years: 1000 mL/hour until rectal effluent is clear

Adolescents: 1500-2000 mL/hour until rectal effluent is clear

Note: May take several hours for the rectal effluent to become clear. Duration may be extended if evidence of continued presence of toxins in GI tract (eg, radiographic evidence or ongoing elimination of toxins)

Administration: OralRapid drinking of each portion is preferred to drinking small amounts continuously. Do not add flavorings, unless provided by the manufacturer, as additional ingredients before use. Chilled solution often more palatable. Oral medications should not be administered within 1 hour of start of therapy.
Dietary Considerations

CoLyte®, GoLYTELY®, NuLYTELY®, TriLyte®: Ideally, the patient should fast for ~3-4 hours prior to administration, but in no case should solid food be given for at least 2 hours before the solution is given. Some products contain aspartame which is metabolized to phenylalanine.

MoviPrep®: Patient should not eat solid food from start of solution administration until after colonoscopy. Patient may have clear liquid soup/plain yogurt for dinner; finish at least 1 hour before start of colon prep.

Storage

CoLyte®, GoLYTELY®, NuLYTELY®, TriLyte®: Store at controlled room temperature of 25°C (77°F) before reconstitution. Refrigerate reconstituted solution. Use within 48 hours of preparation.

MoviPrep®: Store at controlled room temperature of 25°C (77°F) before reconstitution. Refrigerate reconstituted solution. Use within 24 hours of preparation.

Reconstitution

CoLyte®, GoLYTELY®, NuLYTELY®, TriLyte®: Tap water may be used for preparation of the solution; shake container vigorously several times to ensure dissolution of powder.

MoviPrep®: Mix the contents of pouch A and pouch B (one each) in container provided. Add 1 L of lukewarm water; mix the solution until dissolved. Repeat mixing procedure if second liter is needed. Refrigerate reconstituted solution.

ContraindicationsHypersensitivity to polyethylene glycol or any component of the formulation; ileus, gastrointestinal obstruction, gastric retention, bowel perforation, toxic colitis, toxic megacolon

Warnings/Precautions

Concerns related to adverse effects:

- Seizures: Seizures associated with electrolyte abnormalities (eg, hyponatremia, hypokalemia) have occurred. Use with caution in patients with underlying hyponatremia or with concomitant administration of medications that alter electrolyte balance.

Disease-related concerns:

- Impaired gag reflux: Observe unconscious or semiconscious patients with impaired gag reflex or those who are otherwise prone to regurgitation or aspiration during administration.

- Ulcerative colitis: Use with caution in patients with severe ulcerative colitis.

Dosage form specific issues:

- MoviPrep®: May be safer to use in patients who cannot tolerate fluid load (eg, heart failure, renal insufficiency, ascites); not significantly absorbed. Use cautiously in patients with G6PD deficiency; contains ascorbic acid. Contains phenylalanine.

Other warnings/precautions:

- Appropriate use: Evaluate patients with symptoms of bowel obstruction (nausea, vomiting, abdominal pain or distension) prior to use. Do not add flavorings, unless provided by the manufacturer, as additional ingredients before use.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted in animals or in humans.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsSignificant changes in the mother's fluid or electrolyte balance would not be expected.

Adverse Reactions

>10%:

Central nervous system: Malaise (18% to 27%)

Gastrointestinal: Abdominal distension (<60%), anal irritation (<52%), nausea (14% to 47%), abdominal pain (13% to 39%), vomiting (7% to 12%)

Neuromuscular & skeletal: Rigors (34%)

Miscellaneous: Thirst (<47%)

1% to 10%:

Central nervous system: Dizziness (7%), headache (2%)

Gastrointestinal: Dyspepsia (1% to 3%)

Frequency not defined, postmarketing, and/or case reports: Abdominal cramps, abdominal fullness, allergic reactions, anaphylaxis, aspiration, asystole, bloating, chest tightness, dehydration (children), dermatitis, dyspnea (acute), esophageal perforation, facial edema, flatulence, hypersensitivity reactions, hypokalemia (children), Mallory-Weiss tear, pulmonary edema, rash, rhinorrhea, seizure, throat tightness, upper GI bleeding, urticaria

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersElectrolytes, serum glucose, BUN, urine osmolality; children <2 years of age should be monitored for hypoglycemia, dehydration, hypokalemia

Nursing: Physical Assessment/MonitoringInstruct patient in appropriate use according to formulation and purpose for use.

Monitoring: Lab TestsElectrolytes, serum glucose, BUN, urine osmolality

Patient EducationFollow instructions exactly; directions will differ according to the formulation and the purpose for which this medication is taken. Do not eat any solid foods for at least 2 -3 hours before taking and do not take any other oral medication for 1 hour before taking. For bowel cleansing prior to GI exam, take 240 mL (8 oz) every 10 minutes, until 4 L is consumed or the rectal effluent is clear. Rapid drinking of each portion is preferred to drinking small amounts continuously. The first bowel movement should occur approximately 1 hour after the start of administration. May cause abdominal bloating and distention before bowel starts to move. If severe discomfort or distention occurs, stop drinking temporarily or drink each portion at longer intervals until these symptoms disappear. Continue drinking until the watery stool is clear and free of solid matter. This usually requires at least 3 L. It is best to drink all of the solutions. Discard any unused portion. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder, for oral solution: PEG 3350 240 g, sodium sulfate 22.72 g, sodium bicarbonate 6.72 g, sodium chloride 5.84 g, and potassium chloride 2.98 g (4000 mL)

Colyte®: PEG 3350 240 g, sodium sulfate 22.72 g, sodium bicarbonate 6.72 g, sodium chloride 5.84 g, and potassium chloride 2.98 g (4000 mL) [available with citrus berry, lemon lime, cherry, orange, and pineapple flavor packets]

GoLYTELY®:

PEG 3350 236 g, sodium sulfate 22.74 g, sodium bicarbonate 6.74 g, sodium chloride 5.86 g, and potassium chloride 2.97 g (4000 mL) [regular and pineapple flavor]

PEG 3350 227.1 g, sodium sulfate 21.5 g, sodium bicarbonate 6.36 g, sodium chloride 5.53 g, and potassium chloride 2.82 g per packet (1s) [regular flavor; makes 1 gallon of solution after mixing]

MoviPrep®: Pouch A: PEG 3350 100g, sodium sulfate 7.5 g, sodium chloride 2.69 g, potassium chloride 1.015 g; Pouch B: Ascorbic acid 4.7 g, sodium ascorbate 5.9 g (1000 mL) [contains phenylalanine 2.33 mg/treatment; lemon flavor; packaged with 2 of Pouch A and 2 of Pouch B in carton and a disposable reconstitution container]

NuLYTELY®: PEG 3350 420 g, sodium bicarbonate 5.72 g, sodium chloride 11.2 g, and potassium chloride 1.48 (4000 mL) [cherry, lemon-lime, orange, and pineapple flavors]

TriLyte®: PEG 3350 420 g, sodium bicarbonate 5.72 g, sodium chloride 11.2 g, and potassium chloride 1.48 g (4000 mL) [supplied with flavor packets]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Powder (MoviPrep)

100 g (1): $64.10

Solution (reconstituted) (Colyte)

240 g (4000): $26.00

Solution (reconstituted) (Colyte with Flavor Packs)

240 g (4000): $30.00

Solution (reconstituted) (Golytely)

227.1 g (1): $15.25

236 g (4000): $25.20

Solution (reconstituted) (Nulytely Cherry)

420 g (4000): $30.00

Solution (reconstituted) (PEG 3350/Electrolytes)

240 g (4000): $16.00

Solution (reconstituted) (TriLyte)

420 g (4000): $26.40

Mechanism of ActionInduces catharsis by strong electrolyte and osmotic effects

Pharmacodynamics/KineticsOnset of effect: Oral: ~1-2 hours

Related Information

- Laxatives, Classification and Properties

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentOral medications should not be administered within 1 hour of start of therapy

Index TermsElectrolyte Lavage Solution

References

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Polymyxin B

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (intrathecal administration) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(pol i MIKS in bee)

U.S. Brand NamesPoly-Rx

Pharmacologic CategoryAntibiotic, Irrigation; Antibiotic, Miscellaneous

Use: Labeled IndicationsTreatment of acute infections caused by susceptible strains of *Pseudomonas aeruginosa*; used occasionally for gut decontamination; parenteral use of polymyxin B has mainly been replaced by less toxic antibiotics, reserved for life-threatening infections caused by organisms resistant to the preferred drugs (eg, pseudomonal meningitis - intrathecal administration)

Dosing: Adults

Ear canal infections (external): Otic (in combination with other drugs): Instill 1-2 drops, 3-4 times/day; should be used sparingly to avoid accumulation of excess debris.

Systemic infections:

I.M.: 25,000-30,000 units/kg/day divided every 4-6 hours

I.V.: 15,000-25,000 units/kg/day divided every 12 hours

Intrathecal: 50,000 units/day for 3-4 days, then every other day for at least 2 weeks

Note: Total daily dose should not exceed 2,000,000 units/day.

Bladder irrigation (in combination with 57 mg neomycin sulfate): Continuous irrigant or rinse in the urinary bladder for up to 10 days using 20 mg (equal to 200,000 units) added to 1 L of normal saline; usually no more than 1 L of irrigant is used per day unless urine flow rate is high; administration rate is adjusted to patient's urine output.

Topical irrigation or topical solution: 500,000 units/L of normal saline; topical irrigation should not exceed 2 million units/day in adults.

Ocular infections: Ophthalmic: A concentration of 0.1% to 0.25% is administered as 1-3 drops every hour, then increasing the interval as response indicates to 1-2 drops 4-6 times/day.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Ear canal infections (external): Otic (in combination with other drugs): 1-2 drops, 3-4 times/day; should be used sparingly to avoid accumulation of excess debris

Systemic infections: Infants <2 years:

I.M.: Up to 40,000 units/kg/day divided every 6 hours (not routinely recommended due to pain at injection sites)

I.V.: Up to 40,000 units/kg/day divided every 12 hours

Intrathecal: 20,000 units/day for 3-4 days, then 25,000 units every other day for at least 2 weeks after CSF cultures are negative and CSF (glucose) has returned to within normal limits

Children ≥2 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 20-50 mL/minute: Administer 75% to 100% of normal daily dose given in divided doses every 12 hours.

Cl_{cr} 5-20 mL/minute: Administer 50% of normal daily dose given in divided doses every 12 hours.

Cl_{cr} <5 mL/minute: Administer 15% of normal daily dose given in divided doses every 12 hours.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Administer into upper outer quadrant of gluteal muscle; however, I.M. route is not recommended due to severe pain at injection site.

Administration: I.V.Infuse over 60-90 minutes.

Administration: I.V. Detail**Extravasation management:** Monitor I.V. site closely; extravasation may cause serious injury with possible necrosis and tissue sloughing. Rotate infusion site frequently.

pH: 5.0-7.5

StoragePrior to reconstitution, store at room temperature of 15°C to 30°C (59°F to 86°F) and protect from light. After reconstitution, store under refrigeration at 2°C to 8°C (36°F to 46°F). Discard any unused solution after 72 hours.

Compatibility

Y-site administration: Compatible: Esmolol.

Compatibility in syringe: Compatible: Penicillin G sodium. **Variable (consult detailed reference):** Ampicillin.

Compatibility when admixed: Compatible: Amikacin, ascorbic acid injection, colistimethate, diphenhydramine, erythromycin lactobionate, hydrocortisone sodium succinate, kanamycin, lincomycin, penicillin G potassium, penicillin G sodium, phenobarbital, ranitidine, vitamin B complex with C. **Incompatible:** Amphotericin B, calcium chloride, calcium gluconate, cefazolin, chloramphenicol, chlorothiazide, heparin, magnesium sulfate.

ContraindicationsHypersensitivity to polymyxin B or any component of the formulation; concurrent use of neuromuscular blockers

Warnings/Precautions

Boxed warnings:

- I.M./I.T. administration: See “Other warnings/precautions” below.
- Nephrotoxicity: See “Concerns related to adverse effects” below.
- Neurotoxicity: See “Concerns related to adverse effects” below.
- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Nephrotoxicity: **[U.S. Boxed Warning]: May cause nephrotoxicity; avoid concurrent or sequential use of other nephrotoxic drugs (eg, aminoglycosides).** Usual risk factors include pre-existing renal impairment, advanced age and dehydration. Polymyxin B-induced nephrotoxicity may be manifested by albuminuria, cellular casts, and azotemia; discontinue therapy with decreasing urinary output and increasing BUN.
- Neurotoxicity: **[U.S. Boxed Warning]: May cause neurotoxicity, which can also result in respiratory paralysis from neuromuscular blockade especially when the drug is given soon after anesthesia or muscle relaxants. Avoid concurrent or sequential use of other neurotoxic drugs.** Neurotoxic reactions are usually associated with high serum levels, often in patients with renal dysfunction.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with impaired renal function; modify dosage.

Special populations:

- Pregnancy: **[U.S. Boxed Warning]: Safety in pregnant women not established.**

Other warnings/precautions:

- I.M./I.T. administration: **[U.S. Boxed Warning]: Intramuscular/intrathecal administration only to hospitalized patients.**
- Parenteral administration: Polymyxin B sulfate is most toxic when given parenterally; avoid parenteral use whenever possible.

Pregnancy Risk FactorB (per expert opinion)

Pregnancy Considerations**[U.S. Boxed Warning]: Safety in pregnant women has not been established.**

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Facial flushing

Central nervous system: Neurotoxicity (irritability, drowsiness, ataxia, perioral paresthesia, numbness of the extremities, and blurred vision); dizziness, drug fever, meningeal irritation with intrathecal administration

Dermatologic: Urticarial rash

Endocrine & metabolic: Hypocalcemia, hyponatremia, hypokalemia, hypochloremia

Local: Pain at injection site

Neuromuscular & skeletal: Neuromuscular blockade, weakness

Renal: Nephrotoxicity

Respiratory: Respiratory arrest

Miscellaneous: Anaphylactoid reaction

Drug Interactions

Capreomycin: May enhance the neuromuscular-blocking effect of Polymyxin B. *Risk C: Monitor therapy*

Colistimethate: Polymyxin B may enhance the neuromuscular-blocking effect of Colistimethate. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Polymyxin B may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Monitoring ParametersNeurologic symptoms and signs of superinfection; renal function (decreasing urine output and increasing BUN may require discontinuance of therapy)

Reference RangeSerum concentrations >5 mcg/mL are toxic in adults

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's allergy history prior to starting therapy. Use caution with impaired renal function. Assess potential for interactions with other pharmacological agents patient may be taking (eg, nephrotoxic and neurotoxic drugs, neuromuscular blocking agents). See Adminstration for I.V. and I.M. specifics. Infusion site must be monitored closely to prevent extravasation; extravasation may cause serious injury with possible necrosis and tissue sloughing (rotate infusion site, should be rotated frequently). Assess therapeutic effectiveness (resolution of infection) and adverse reactions (eg, renal function, neurotoxicity [irritability, drowsiness, ataxia, perioral paresthesia, numbness of the extremities, and blurring of vision]; neuromuscular blockade, rash, respiratory paralysis, ototoxicity). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity prior to beginning therapy. Establish baseline renal function prior to initiating therapy. Monitor renal function closely.

Patient EducationWound irrigation/bladder irrigation/gut sterilization/I.V.: Immediately report numbness or tingling of mouth, tongue, or extremities; constant blurring of vision; increased nervousness or irritability; excessive drowsiness; or respiratory difficulty. For I.V. immediately report swelling, redness, burning, or pain at infusion site.

Ophthalmic: Tilt head back, place medication into eyes (as frequently as prescribed), close eyes, apply light pressure over inside corner of the eye for 1 minute. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). You may experience some stinging or burning or temporary blurring of vision; use caution driving or when engaging in hazardous tasks until vision clears. Report any adverse effects including respiratory difficulty or unusual numbness or tingling of mouth or tongue, increased nervousness or irritability, or excessive drowsiness.

Pregnancy/breast-feeding precautions: Consult prescriber if you suspect you might be pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 500,000 units

Powder [for prescription compounding]:

Poly-Rx: 100 million units (13 g)

Generic AvailableYes

Mechanism of ActionBinds to phospholipids, alters permeability, and damages the bacterial cytoplasmic membrane permitting leakage of intracellular constituents

Pharmacodynamics/Kinetics

Absorption: Well absorbed from peritoneum; minimal from GI tract (except in neonates) from mucous membranes or intact skin

Distribution: Minimal into CSF; does not cross placenta

Half-life elimination: 4.5-6 hours; prolonged with renal impairment

Time to peak, serum: I.M.: ~2 hours

Excretion: Urine (>60% primarily as unchanged drug)

Pharmacotherapy Pearls1 mg = 10,000 units

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause irritability, drowsiness, or ataxia

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPolymyxin B Sulfate

International Brand NamesAerosporin (IN); Alosol (MX); Biodexan Ofteno (MX); Cortisporin Otico (MX); Dexsul (MX); Glubacida (MX); Isopto-Biotic (SE); Maxitrol (MX); Neobacigrin (MX); Neosporin (MX); Polixin (MX); Polymyxin B Pfizer (DE); Polymyxine B FNA (NL); Septilisin (MX); Synalar (MX); Syntex (MX); Tribiot (MX); Trioftín (MX)

Polysaccharide-Iron Complex

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Niferex® may be confused with Nephrox®

Pronunciation(pol i SAK a ride-EYE ern KOM pleks)
U.S. Brand NamesFerrex 150 [OTC]; Niferex® [OTC]; Nu-Iron® 150 [OTC]; Poly-Iron 150 [OTC]; ProFe [OTC]
Pharmacologic CategoryIron Salt
Use: Labeled IndicationsPrevention and treatment of iron-deficiency anemias
Dosing: Adults
Dietary Reference Intake: Dose is RDA presented as elemental iron unless otherwise noted:

19-50 years: Male: 8 mg/day; Female: 18 mg/day; Pregnant female: 27 mg/day; Lactating female: 9 mg/day

≥50 years: 8 mg/day

Iron deficiency (prevention/treatment): Oral:

Elixir: 50-100 mg twice daily

Capsules: 150-300 mg/day

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric
Dietary Reference Intake: Dose is RDA presented as elemental iron unless otherwise noted:

0-6 months: 0.27 mg/day (adequate intake)

7-12 months: 11 mg/day

1-3 years: 7 mg/day

4-8 years: 10 mg/day

9-13 years: 8 mg/day

14-18 years: Male: 11 mg/day; Female: 15 mg/day; Pregnant female: 27 mg/day; Lactating female: 10 mg/day

Iron deficiency (prevention/treatment): Oral: Children ≥6 years: Tablets/elixir: 50-100 mg/day; may be given in divided doses

Dietary ConsiderationsDietary sources of iron include beans, cereal (enriched), clams, beef, lentils, liver, oysters, shrimp, and turkey. Foods that enhance dietary absorption of iron include broccoli, grapefruit, orange juice, peppers and strawberries. Foods that decrease dietary absorption of iron include coffee, dairy products, soy products, spinach, and tea.
Allergy Considerations

- Iron Salt Allergy

Pregnancy ConsiderationsIt is recommended that pregnant women meet the dietary requirements of iron with diet and/or supplements in order to prevent adverse events associated with iron deficiency anemia in pregnancy. Treatment of iron deficiency anemia in pregnant women is the same as in nonpregnant women and in most cases, oral iron preparations may be used. Except in severe cases of maternal anemia, the fetus achieves normal iron stores regardless of maternal concentrations.
LactationEnters breast milk
Breast-Feeding ConsiderationsIron is normally found in breast milk. Breast milk or iron fortified formulas generally provide enough iron to meet the recommended dietary requirements of infants. The amount of iron in breast milk is generally not influenced by maternal iron status.
Adverse Reactions

>10%: Gastrointestinal: Stomach cramping, constipation, nausea, vomiting, dark stools, GI irritation, epigastric pain

1% to 10%:

Gastrointestinal: Diarrhea, heartburn

Genitourinary: Discolored urine

Miscellaneous: Staining of teeth

<1%: Contact irritation

Drug Interactions

Antacids: May decrease the absorption of Iron Salts. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Iron Salts may decrease the absorption of Bisphosphonate Derivatives. Only oral iron salts are of concern. **Exceptions:** Pamidronate; Zoledronic Acid. *Risk D: Consider therapy modification*

Cefdinir: Iron Salts may decrease the serum concentration of Cefdinir. Red-appearing, non-bloody stools may also develop due to the formation of an insoluble iron-cefdinir complex. Management: Avoid concurrent cefdinir and iron when possible. Separating doses by several hours may minimize interaction. Iron-containing infant formulas do not appear to interact with cefdinir. *Risk D: Consider therapy modification*

Dimercaprol: May enhance the nephrotoxic effect of Iron Salts. *Risk X: Avoid combination*

Eltrombopag: Iron Salts may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., iron-containing products) by at least 4 hours. *Risk D: Consider therapy modification*

H2-Antagonists: May decrease the absorption of Iron Salts. *Risk C: Monitor therapy*

Levodopa: Iron Salts may decrease the absorption of Levodopa. Only applies to oral iron preparations. *Risk D: Consider therapy modification*

Methyldopa: Iron Salts may decrease the absorption of Methyldopa. Only oral iron salts are of concern. *Risk D: Consider therapy modification*

Penicillamine: Iron Salts may decrease the absorption of Penicillamine. Only oral iron salts are a concern. *Risk D: Consider therapy modification*

Phosphate Supplements: Iron Salts may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May decrease the absorption of Iron Salts. *Risk C: Monitor therapy*

Quinolone Antibiotics: Iron Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Iron Salts may decrease the absorption of Tetracycline Derivatives. Only a concern with orally administered products. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Iron Salts. Iron Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: Elemental iron 150 mg

Ferrex 150, Nu-Iron® 150: Elemental iron 150 mg

Niferex®: Elemental iron 60 mg

Poly-Iron 150: Elemental iron 150 mg [contains tartrazine]

ProFe: Elemental iron 180 mg

Elixir:

Niferex®: Elemental iron 100 mg/5 mL (240 mL) [contains alcohol 10%; dye free, sugar free]

Generic AvailableYes: Capsule

Pricing: U.S. (www.drugstore.com)

Capsules (Ferrex 150)

150 mg (100): $19.99

Capsules (Niferex)

40-20 mg (100): $73.50

Capsules (Nu-Iron)

150 mg (100): $53.99

Capsules (Poly-Iron 150)

150 mg (90): $25.99

Elixir (Niferex)

100 mg/5 mL (236): $80.55

Pharmacotherapy Pearls100% elemental iron

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentConstipation is common, concurrent use with psychotropic may produce additive effects

Index TermsIron-Polysaccharide Complex

References

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“Nutrition During Lactation.” Subcommittee on Nutrition During Lactation, Committee on Nutritional Status During Pregnancy and Lactation, Food and Nutrition Board Institute of Medicine, National Academy of Sciences Washington, DC: National Academy Press, 1991. Available at http://www.nap.edu.

“Recommendations to Prevent and Control Iron Deficiency in the United States. Centers for Disease Control and Prevention,” *MMWR Recomm Rep*, 1998, 47(RR-3):1-29.[PubMed 9563847]

“Routine Iron Supplementation During Pregnancy. Review Article. US Preventive Services Task Force,” *JAMA*, 1993, 270(23):2848-54.[PubMed 8133626]

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Leukemia, Acute Lymphocytic]

Regimen UseLeukemia, acute lymphocytic

RegimenMaintenance:

Mercaptopurine: Oral: 50 mg 3 times/day

[total dose/cycle = 4200-4650 mg]

Methotrexate: Oral: 20 mg/m^2 once weekly

[total dose/cycle = 80 mg/m^2]

Vincristine: I.V.: 2 mg day 1

[total dose/cycle = 2 mg]

Prednisone: Oral: 200 mg/day days 1 to 5

[total dose/cycle = 1000 mg]

Repeat cycle monthly for 2 years

References

Kantarjian HM, O'Brien S, Smith TL, et al, âResults of Treatment With Hyper-CVAD, a Dose-Intensive Regimen, in Adult Acute Lymphocytic Leukemia,â *J Clin Oncol*, 2000, 18(3):547-61.[PubMed 10653870]

Poractant Alfa

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Pronunciation(por AKT ant AL fa)

U.S. Brand NamesCurosurf®

Canadian Brand NamesCurosurf®

Pharmacologic CategoryLung Surfactant

Use: Labeled IndicationsTreatment of respiratory distress syndrome (RDS) in premature infants

Dosing: Pediatric**Premature infant with RDS:** Initial dose is 2.5 mL/kg of birth weight. Up to 2 subsequent doses of 1.25 mL/kg birth weight can be administered at 12-hour intervals if needed in infants who continue to require mechanical ventilation and supplemental oxygen. Maximum total dose: 5 mL/kg. **Note:** For intratracheal use **only**

Administration: OtherTake from refrigerator and warm to room temperature. Inspect for discoloration. The color should be white to creamy white. Gently turn the vial upside down to get a uniform suspension. Do not shake. Slowly withdraw the entire contents into a 3 mL or 5 mL plastic syringe through a large gauge needle (at least 20 gauge). Attach the catheter to the syringe. Fill the catheter with poractant alfa. Discard the excess through the catheter so that only the total dose to be given remains in the syringe.

Before administering, assure proper placement and patency of the endotracheal tube. The endotracheal tube may be suctioned before administering the poractant alpha. The drug is administered intratracheally through a 5-French end-hole catheter cut to a standard length of 8 cm **or** through a secondary lumen of a dual-lumen endotracheal tube (without interrupting mechanical ventilation). Up to 2 repeated doses may be administered, using the same technique at 12-hour intervals.

Administration using a 5-French end-hole catheter: The infant should be stable before proceeding with dosing. The infant's ventilator settings should be changed to a rate of 40-60 breaths/minute, inspiratory time 0.5 seconds, and supplemental oxygen to maintain SaO_2 >92%. Keep the head and body of the infant in alignment without inclination. Briefly disconnect the endotracheal tube from the ventilator, insert the 5-French catheter. This catheter is inserted into the infant's endotracheal tube with the tip positioned distally in the endotracheal tube. The catheter tip should not extend beyond the distal tip of the endotracheal tube. Each dose should be administered in two aliquots with each aliquot administered into one of the two main bronchi by positioning the infant with either the right or left side dependent.

Insert the first aliquot (1.25 mL/kg birth weight) and position the infant so that either the right or left side is dependent for the aliquot. Remove the catheter and manually ventilate the infant with 100% oxygen at a rate of 40-60 breaths/minute for 1 minute. When the infant is stable, reposition the infant such that the other side is dependent and administer the remaining aliquot using the same technique. Remove the catheter without flushing. Do not suction the airways for 1 hour after instillation unless signs of significant airway obstruction occur. Resume ventilator management and clinical care.

Administration using the secondary lumen of a dual-lumen endotracheal tube: Slowly withdraw the entire vial content into a 3 mL or 5 mL plastic syringe through a large gauge needle (at least 20 gauge). Keep infant in neutral position and administer poractant through the proximal end of the secondary lumen of the endotracheal tube as a single dose over 1 minute (without interrupting mechanical ventilation); transient increases in F_1O_2, ventilatory rate, or peak inspiratory pressure (PIP) may be required.

pH: 6.2 (5.5-6.5; adjusted as required with sodium bicarbonate)

StorageStore under refrigeration at defined temperature of 2°C to 8°C (36°F to 46°F). Unopened, unused vials that have been warmed to room temperature can be returned to refrigerator storage within 24 hours for future use. Do not warm and then refrigerate more than once. Vials are for single use only. Protect from light. Do not shake.

ContraindicationsNo known contraindications

Warnings/Precautions

Concerns related to adverse effects:

- Pulmonary hemorrhage: Pulmonary hemorrhage is a known complication of premature birth and very low birth-weight. It has been reported in both clinical trials and postmarketing reports in infants who have received poractant.
- Transient adverse effects: Transient episodes of bradycardia, decreased oxygen saturation, hypotension, or endotracheal tube blockage may occur. Discontinue dosing procedure and initiate measures to alleviate the condition; may reinstitute after the patient is stable.

Other warnings/precautions:

- Administration: For intratracheal administration only.
- Appropriate use: Correct acidosis, hypotension, anemia, hypoglycemia, and hypothermia before use.
- Monitoring: Produces rapid improvements in lung oxygenation and compliance; may require frequent adjustments to oxygen delivery and ventilator settings.
- Trained personnel: Rapidly affects oxygenation and lung compliance; restrict use to a highly-supervised clinical setting with immediate availability of clinicians experienced in intubation and ventilatory management of premature infants.

Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, hypotension

Respiratory: Endotracheal tube blockage, oxygen desaturation

Postmarketing and/or case reports: Pulmonary hemorrhage

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersArterial blood gases, ventilator measurement assessment
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, intratracheal [preservative free; porcine derived]:

Curosurf®: 80 mg/mL (1.5 mL, 3 mL)

Generic AvailableNo
ManufacturerDey
Mechanism of ActionEndogenous pulmonary surfactant reduces surface tension at the air-liquid interface of the alveoli during ventilation and stabilizes the alveoli against collapse at resting transpulmonary pressures. A deficiency of pulmonary surfactant in preterm infants results in respiratory distress syndrome characterized by poor lung expansion, inadequate gas exchange, and atelectasis. Poractant alpha compensates for the surfactant deficiency and restores surface activity to the infant's lungs. It reduces mortality and pneumothoraces associated with RDS.
Pharmacodynamics/KineticsInformation limited to animal models. No human pharmacokinetic information is available.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
References

Ainsworth SB, Beresford MW, Milligan DW, et al, “Pumactant and Poractant Alfa for Treatment of Respiratory Distress Syndrome in Neonates Born at 25-29 Weeks' Gestation: A Randomised Trial, *Lancet*, 2000, 355(9213):1387-92.

International Brand NamesCurosurf (AE, AT, AU, BG, BH, BR, CH, CY, CZ, DE, DK, EE, EG, ES, FI, FR, GB, GR, HN, HU, IE, IL, IQ, IR, IT, JO, KP, KW, LB, LU, LY, NL, NO, OM, PL, PT, QA, SA, SE, SY, YE)

Porfimer

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(POR fi mer)
U.S. Brand NamesPhotofrin®
Canadian Brand NamesPhotofrin®
Pharmacologic CategoryAntineoplastic Agent, Miscellaneous
Use: Labeled IndicationsPalliation in patients with obstructing (partial or complete) esophageal cancer; treatment of microinvasive endobronchial nonsmall cell lung cancer (NSCLC); reduction of obstruction and palliation in patients with obstructing (partial or complete) NSCLC; ablation of high-grade dysplasia in Barrett's esophagus
Use: Unlabeled/InvestigationalTreatment of gastric cancer (obstruction); treatment of actinic keratoses and low-risk basal and squamous cell skin cancers
Dosing: Adults**Cancer photodynamic therapy:** I.V.: 2 mg/kg, followed by exposure to the appropriate laser light; repeat courses must be separated by at least 30 days (esophageal or endobronchial cancer) or 90 days (Barrett’s esophagus; delay subsequent treatment for insufficient healing) for a maximum of 3 courses
Dosing: ElderlyRefer to adult dosing.
Administration: I.V.Administer slow I.V. injection over 3-5 minutes. Avoid contact with skin during administration.
Administration: I.V. DetailAvoid extravasation.

pH: 7-8

StorageStore intact vials at controlled room temperature of 20°C to 25°C (68°F to 77°F). Reconstituted solutions should be protected from light and used immediately after preparation.
ReconstitutionReconstitute each vial of porfimer with 31.8 mL of either D_5W or NS injection resulting in a final concentration of 2.5 mg/mL. Shake well until dissolved. Protect the reconstituted product from bright light and use immediately. Use appropriate precautions for handling and disposal.
CompatibilityDo not mix porfimer with other drugs in the same solution.
ContraindicationsPorphyria

Photodynamic therapy (PDT) is contraindicated in patients with tracheoesophageal or bronchoesophageal fistula; tumors eroding into a major blood vessel; severe acute respiratory distress when caused by endobronchial lesion; esophageal or gastric varices; esophageal ulcers >1 cm in diameter

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Chest pain: Inflammatory responses within the treatment area may result in substernal chest pain.
- Ocular photosensitivity: Ocular discomfort has been reported; for at least 30 days, when outdoors, patients should wear dark sunglasses which have an average white light transmittance of <4%. Patients should be educated to test for residual photosensitivity before resuming exposure to sunlight.
- Photosensitivity: In patients who are exposed to direct sunlight or bright indoor light (eg fluorescent lights, unshaded light bulbs, examination/operating lights), photosensitivity reactions are common. Conventional ultraviolet (UV) sunscreens are **not** protective against photosensitivity reactions caused by visible light. Photosensitivity may last 30-90 days. Encourage exposure to ambient indoor light (aids in gradually inactivating residual porfimer).

Disease-related concerns:

- Barrett's esophagus: In patients with Barrett's esophagus, conduct rigorous surveillance (endoscopic biopsy every 3 months until 4 consecutive negative results for high-grade dysplasia followed by further follow-up per physician judgement). Esophageal strictures are common adverse events associated with photodynamic therapy of Barrett's esophagus; esophageal dilation may be required.
- Endobronchial tumors: When treating endobronchial tumors, use caution if treatment-induced inflammation may obstruct airway. Assess patient for possibility of tumor erosion into a pulmonary blood vessel (contraindication); fatal massive pulmonary hemoptysis (FMH) may occur. Risk factors for FMH include large, centrally-located tumors, cavitating tumors, or extensive tumor extrinsic to the bronchus. Fistula formation may occur after resolution of tumors with deep bronchial wall invasion.
- Esophageal/gastric varices: Generally not suited for treatment of patients with esophageal or gastric varices; if used in esophageal

varices, extreme caution is warranted and light exposure to the varices should be avoided.

- Esophageal tumors: Porfimer treatment for tumors which erode into the trachea or bronchial tree are likely to cause fistula; use in not recommended. Use is contraindicated in patients with existing tracheoesophageal or bronchoesophageal fistula.

- Hepatic impairment: Elimination may be prolonged in hepatic impairment; toxicities may be increased. Photosensitivity may be increased beyond 90 days in patients with mild-to-severe hepatic impairment.

- Renal impairment: Elimination may be prolonged in renal impairment; toxicities may be increased. Photosensitivity may be increased beyond 90 days in patients with severe renal impairment.

Concurrent drug therapy issues:

- Photosensitizing drugs: Concurrent use with other photosensitizing agents may increase the risk for photosensitivity reactions.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Radiation therapy recipients: Allow 2-4 weeks to elapse after phototherapy prior to initiating radiation therapy; 4 weeks should elapse after radiation therapy prior to initiating phototherapy.

Other warnings/precautions:

- Extravasation: Avoid extravasation. If extravasation occurs, protect affected area from light.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have shown maternal and fetal toxicity, but no major malformations. Effective contraception is recommended for women of childbearing potential.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Cardiovascular: Chest pain (7% to 31%; substernal: 5%), edema (5% to 18%)

Central nervous system: Fever (8% to 31%), pain (1% to 22%), insomnia (5% to 14%)

Dermatologic: Photosensitivity reaction (19% to 22% in cancer patients; 37% to 69% in Barrett’s esophagus patients; severe: 10%)

Gastrointestinal: Esophageal stricture/stenosis (6% in esophageal cancer patients; 30% to 36% in Barrett's esophagus patients), nausea (24% to 37%), vomiting (17% to 31%), constipation (5% to 24%), dysphagia (10% to 24%), mucositis (20% in superficial endobronchial cancer), abdominal pain (5% to 20%)

Hematologic: Anemia (32% in esophageal cancer patients)

Neuromuscular & skeletal: Back pain (3% to 11%)

Respiratory: Pleural effusion (32% in esophageal cancer patients; 12% in Barrett's esophagus patients; ≤5% in endobronchial cancer patients), dyspnea (7% to 30%), bronchial obstruction/mucus plug (21%), pneumonia (6% to 18%), hemoptysis (7% to 16%), cough (5% to 15%), bronchostenosis (11%), pharyngitis (11%)

5% to 10%:

Cardiovascular: Atrial fibrillation (10%), hypotension (7%), cardiac failure (7% in esophageal cancer), hypertension (6%), tachycardia (6%)

Central nervous system: Anxiety (3% to 7%), dysphonia (3% to 5%)

Endocrine & metabolic: Dehydration (7% to 10%)

Gastrointestinal: Weight loss (5% to 9%), anorexia (8%), esophageal edema (8%), hematemesis (8%), esophageal pain (7%), dyspepsia (1% to 6%), diarrhea (5%), eructation (5%), esophagitis (5%), melena (5%), odynophagia (5%)

Genitourinary: Urinary tract infection (7%)

Respiratory: Respiratory insufficiency (≤10%), bronchitis (10%), bronchial ulceration (9%), tracheoesophageal fistula (6%), fatal massive hemoptysis (≤5%)

Miscellaneous: Moniliasis (9%), tumor hemorrhage (8%), hiccups (5%), surgical complication (5% in esophageal cancer patients)

<5%, postmarketing, and/or case reports (limited to important or life-threatening): Abnormal vision, angina, bradycardia, bronchospasm, cataracts, diplopia, erythema, esophageal perforation, eye pain, fluid imbalance, gastric ulcer, hair growth increased, ileus, jaundice, laryngotracheal edema, lung abscess, MI, ocular sensitivity, peritonitis, photophobia, pneumonitis, pruritus, pseudoporphyria state, pulmonary edema, pulmonary embolism, pulmonary hemorrhage, pulmonary thrombosis, respiratory failure, sepsis, sick sinus syndrome, skin blistering, skin discoloration, skin fragility, skin nodules, skin wrinkles, stridor, supraventricular tachycardia

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringEvaluate for renal or hepatic impairment prior to beginning therapy. Assess other pharmacological agents or herbal products patient may be taking that may increase photosensitivity reaction. Infusion site must be monitored closely to prevent extravasation; if extravasation occurs, site should be protected from light. Patients will be photosensitive and must be protected from direct sunlight or bright indoor light for 30–60 days after treatment. However, ambient indoor light is beneficial (should not stay in dark rooms). Assess patient response (eg, atrial fibrillation, hyper-/hypotension, hyperthermia, GI pain or upset, anemia, dyspnea, respiratory insufficiency, dehydration). Teach patient (caregiver) possible side effects/appropriate interventions (light exposure) and adverse symptoms to report.

Patient EducationThis drug can only be given by injection or infusion. Report immediately any redness, swelling, burning, or pain at infusion site. The infusion will be followed by laser light therapy. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will be highly sensitive to bright light. Avoid exposure to sunlight or bright indoor light for at least 30 days following treatment (cover skin with protective clothing and wear dark sunglasses with light transmittance <4% when outdoors - severe blistering, burning, and skin/eye damage can result). Conventional sunscreens do not protect against photosensitization. After 30 days, test small area of skin (not face) for remaining sensitivity. Retest sensitivity if traveling to a different geographic area with greater sunshine. Exposure to indoor normal light is beneficial since it will help dissipate photosensitivity gradually. May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or constipation (increased exercise, fluids, fruit, or fiber may help). Report rapid heart rate, chest pain or palpitations, respiratory difficulty or air hunger, persistent fever or chills, foul-smelling urine or burning on urination, swelling of extremities, increased anxiety, confusion, or hallucination. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as sodium:

Photofrin®: 75 mg

Generic AvailableNo

ManufacturerAxcan Pharma Inc

Mechanism of ActionPorfimer's cytotoxic activity is dependent on light and oxygen. Following administration, the drug is selectively retained in neoplastic tissues. Exposure of the drug to laser light at wavelengths >630 nm results in the production of oxygen free-radicals. Release of thromboxane A_2, leading to vascular occlusion and ischemic necrosis, may also occur.

Pharmacodynamics/Kinetics

Distribution: V_{dss}: 0.49 L/kg

Protein binding, plasma: ~90%

Half-life elimination: Mean: 17 days (range: 13-21 days)

Time to peak, serum: Adults: Females: ~90 minutes; Males: ~10 minutes

Excretion: Feces; Clearance: Plasma: Total: 0.051 mL/minute/kg

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia is common; may cause anxiety or confusion

Mental Health: Effects on Psychiatric TreatmentMay cause anemia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may increase the risk of photosensitivity reactions

Index TermsCL-184116; Dihematoporphyrin Ether; Porfimer Sodium

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International Brand NamesPhotobarr (EE); Photofrin (BG, DE, FI, FR, HN, IL, JP, NL, PL, SE, TW)

Posaconazole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Noxafil® may be confused with minoxidil

International issues:

Noxafil® may be confused with Noxidil® which is a brand name for minoxidil in Thailand

Pronunciation(poe sa KON a zole)

U.S. Brand NamesNoxafil®

Canadian Brand NamesPosanol™

Pharmacologic CategoryAntifungal Agent, Oral

Use: Labeled IndicationsProphylaxis of invasive *Aspergillus* and *Candida* infections in severely-immunocompromised patients [eg, hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with prolonged neutropenia secondary to chemotherapy for hematologic malignancies]; treatment of oropharyngeal candidiasis (including patients refractory to itraconazole and/or fluconazole)

Use: Unlabeled/InvestigationalSalvage therapy of refractory invasive fungal infections; mucormycosis

Use: DentalTreatment of oropharyngeal candidiasis (including patients refractory to itraconazole and/or fluconazole)

Dosing: Adults

Aspergillosis, invasive: Oral:

Prophylaxis: 200 mg 3 times/day

Treatment of refractory infection (unlabeled use): 200 mg 4 times/day initially; after disease stabilization may decrease frequency to 400 mg twice daily in divided doses. **Note:** Duration of therapy should be a minimum of 6-12 weeks or throughout period of immunosuppression.

Candidal infections: Oral:

Prophylaxis: 200 mg 3 times/day

Treatment of oropharyngeal infection: Initial: 100 mg twice daily for 1 day; maintenance: 100 mg once daily for 13 days

Treatment of refractory oropharyngeal infection: 400 mg twice daily

Mucormycosis (unlabeled use): 800 mg/day in 2 or 4 divided doses

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Aspergillosis, invasive: Oral: Children ≥13 years: Refer to adult dosing.

Candidal infections: Oral: Children ≥13 years: Refer to adult dosing.

Mucormycosis (unlabeled use): Oral: Children ≥13 years: Refer to adult dosing.

Dosing: Renal ImpairmentNo adjustment necessary; use caution in severe renal impairment and monitor for breakthrough fungal infections. Variability in posaconazole exposure observed with Cl_{cr}<20 mL/minute.

Dosing: Hepatic ImpairmentNo adjustment necessary; use with caution.

Administration: OralShake well before use. Must be administered with a full meal or an oral liquid nutritional supplement. Administer oral suspension using dosing spoon provided by the manufacturer; spoon should be rinsed clean with water after each use and before storage.

Dietary ConsiderationsGive with meals. If alternative antifungal therapy can not be given to patients without food intake or severe diarrhea/vomiting, close monitoring for breakthrough fungal infections must be performed. Adequate posaconazole absorption from GI tract and subsequent plasma concentrations are dependent on food for efficacy. Lower average plasma concentrations have been associated with an increased risk of treatment failure.

StorageStore at controlled room temperature of 25°C (77°F); do not freeze.

ContraindicationsHypersensitivity to posaconazole or any component of the formulation; coadministration of cisapride, ergot alkaloids, pimozide, quinidine, or sirolimus

Warnings/Precautions

Concerns related to adverse effects:

- Azole hypersensitivity: Use with caution in patients with hypersensitivity to other azole antifungal agents; cross-reaction may occur, but has not been established.

- Hepatic effects: Hepatic dysfunction has occurred, ranging from mild/moderate increases of ALT/AST, alkaline phosphatase, and/or clinical hepatitis to severe reactions (cholestasis, hepatic failure including death); use with caution in patients with hepatic impairment.

Disease-related concerns:

- Arrhythmias: Use caution in patients with an increased risk of arrhythmia (concurrent QT_c-prolonging drugs, hypokalemia). Correct electrolyte abnormalities (eg, potassium, magnesium, and calcium) before initiating therapy.

- GI disturbances: Monitor closely for breakthrough fungal infections in patients with severe diarrhea or vomiting.

- Renal impairment: Use caution in patients with severe renal impairment due to variability in exposure; monitor for breakthrough fungal infections.

Concurrent drug therapy issues:

- Cyclosporine: Concurrent use may significantly increase cyclosporine levels and may result in rare serious adverse events (eg, nephrotoxicity, leukoencephalopathy, and death); dose reduction and close monitoring are recommended with initiation of posaconazole therapy.

- High potential for interactions: Consider alternative therapy or closely monitor for breakthrough fungal infections in patients receiving drugs that decrease absorption or increase the metabolism of posaconazole.

Special populations:

- Patients unable to take or tolerate nutritional supplements: Consider alternative antifungal therapy or closely monitor for breakthrough fungal infections in any patient unable to eat or tolerate an oral liquid nutritional supplement.

- Pediatrics: Safety and efficacy have not been established in children <13 years of age.

Geriatric ConsiderationsDosage adjustment not necessary.
Pregnancy Risk FactorC
Pregnancy ConsiderationsPosaconazole has been shown to be teratogenic in animal studies. There are no adequate and well-controlled studies in pregnant women. Use only if the benefit to the mother justifies potential risk to the fetus.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsExcretion in breast milk has not been investigated; use only if the benefit to the mother justifies potential risk to the fetus.
Adverse Reactions**Note:** A higher frequency of adverse reactions was observed in studies with refractory oropharyngeal candidiasis patients and percentages are included below.

>10%: Gastrointestinal: Diarrhea (3% to 11%)

1% to 10%:

Cardiovascular: QT_c prolongation (4%), hypertension (1%)

Central nervous system: Headache (1% to 8%), dizziness (1% to 3%), fatigue (1% to 3%), insomnia (1% to 3%), fever (up to 3%), somnolence (1%)

Dermatologic: Rash (1% to 4%), pruritus (1% to 2%)

Endocrine & metabolic: Hypokalemia (3%)

Gastrointestinal: Nausea (5% to 8%), vomiting (4% to 7%), abdominal pain (1% to 5%), flatulence (1% to 5%), anorexia (1% to 3%), mucositis (2%), dyspepsia (1% to 2%), xerostomia (1% to 2%), taste perversion (1%), constipation (up to 1%)

Hematologic: Neutropenia (2% to 8%), anemia (up to 3%), thrombocytopenia (up to 2%)

Hepatic: Bilirubin increased (2% to 3%), ALT increased (2% to 3%), AST increased (2% to 3%), GGT increased (2% to 3%), alkaline phosphatase increased (1% to 2%), hepatocellular damage (1%)

Neuromuscular & skeletal: Weakness (1% to 3%), myalgia (up to 2%), tremor (1%)

Ocular: Blurred vision (1%)

Renal: Serum creatinine increased (2%)

<1%, postmarketing, and/or case reports: Adrenal insufficiency, allergic/hypersensitivity reactions, cholestasis, hemolytic uremic syndrome, hepatic failure, hepatitis, pulmonary embolus, thrombotic thrombocytopenic purpura, torsade de pointes

Metabolism/Transport Effects**Inhibits** CYP3A4 (strong)
Drug Interactions

Alfentanil: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amphotericin B: Antifungal Agents (Azole Derivatives, Systemic) may diminish the therapeutic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Aprepitant: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Aprepitant. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Quazepam. *Risk D: Consider therapy modification*

Bosentan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Bosentan. *Risk C: Monitor therapy*

BusPIRone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Busulfan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Busulfan. *Risk C: Monitor therapy*

Calcium Channel Blockers: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CarBAMazepine. *Risk C: Monitor therapy*

Cardiac Glycosides: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cilostazol: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Cinacalcet: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Cinacalcet. *Risk C: Monitor therapy*

Cisapride: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Cisapride. *Risk X: Avoid combination*

Conivaptan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Conivaptan. *Risk X: Avoid combination*

Corticosteroids (Orally Inhaled): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Didanosine: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). Enteric coated didanosine capsules are not expected to affect these antifungals. *Risk D: Consider therapy modification*

Docetaxel: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Docetaxel. *Risk D: Consider therapy modification*

Dofetilide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Dofetilide. *Risk X: Avoid combination*

Efavirenz: May decrease the serum concentration of Posaconazole. *Risk X: Avoid combination*

Eletriptan: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Eletriptan. *Risk D: Consider therapy modification*

Eplerenone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eplerenone. *Risk D: Consider therapy modification*

Ergot Derivatives: Posaconazole may increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Erlotinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Erlotinib. *Risk C: Monitor therapy*

Eszopiclone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eszopiclone. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fosaprepitant: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Fosaprepitant. Specifically, concentrations of aprepitant are likely to be increased. *Risk C: Monitor therapy*

Gefitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Gefitinib. *Risk C: Monitor therapy*

Grapefruit Juice: May increase the metabolism of Antifungal Agents (Azole Derivatives, Systemic). This specifically applies to oral antifungal administration. *Risk D: Consider therapy modification*

H2-Antagonists: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Imatinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Imatinib. *Risk C: Monitor therapy*

Irinotecan: Antifungal Agents (Azole Derivatives, Systemic) may enhance the adverse/toxic effect of Irinotecan. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Losartan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Losartan. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Antifungal Agents (Azole Derivatives, Systemic). Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Macrolide Antibiotics. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Methadone. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Phenytoin: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Phenytoin. Phenytoin may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Phosphodiesterase 5 Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Protease Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. *Risk D: Consider therapy modification*

QuiNIDine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of QuiNIDine. Management: Itraconazole, voriconazole, and posaconazole are specifically contraindicated with quinidine. Use of quinidine with any azole antifungal may require quinidine dose adjustment and should be done with caution and close monitoring. *Risk X: Avoid combination*

Ramelteon: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ranolazine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Repaglinide. Management: Concurrent use of an azole antifungal with both repaglinide and gemfibrozil should be avoided. *Risk C: Monitor therapy*

Rifamycin Derivatives: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Rifamycin Derivatives. Only rifabutin appears to be affected. Rifamycin Derivatives may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Sirolimus. Management: Sirolimus dose reductions of up to 50-90% may be necessary when starting an azole antifungal. Use of sirolimus with the azole antifungals voriconazole and posaconazole is contraindicated. *Risk D: Consider therapy modification*

Solifenacin: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Solifenacin. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Sucralfate: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk C: Monitor therapy*

Sunitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Tacrolimus: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Temsirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Temsirolimus. Concentrations of the active metabolite, sirolimus, are likely to be increased more substantially than those of the parent temsirolimus. *Risk D: Consider therapy modification*

Tolterodine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Tolterodine. This is likely only of concern in CYP2D6-deficient patients (ie, "poor metabolizers") *Risk D: Consider therapy modification*

VinCRIStine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of VinCRIStine. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Posaconazole may increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ziprasidone. *Risk C: Monitor therapy*

Zolpidem: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Zolpidem. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Bioavailability increased ~3-4 times when posaconazole administered with a meal or an oral liquid nutritional supplement. Grapefruit juice may decrease the levels/effects of posaconazole; concurrent use should be avoided.

Monitoring ParametersHepatic function (eg, AST/ALT, alkaline phosphatase and bilirubin) prior to initiation and during treatment; renal function; electrolyte disturbances (eg, calcium, magnesium, potassium); CBC

Nursing: Physical Assessment/MonitoringAssess hepatic and renal function, allergy history, and ability to eat or tolerate an oral liquid nutritional supplement prior to beginning therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions. Assess results of laboratory tests, therapeutic effectiveness (resolution of fungal infection), and adverse response (eg, gastrointestinal disturbance, vision changes, hepatic toxicity [increased liver enzymes, jaundice], CNS changes) on a regular basis during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsHepatic function (eg, AST/ALT, alkaline phosphatase and bilirubin) prior to initiation and during treatment; renal function; electrolyte disturbances (eg, calcium, magnesium, potassium); CBC

Patient EducationDo not take any new prescription or OTC medications, or herbal products during therapy without consulting prescriber. Take exactly as directed. Take full course of medication as ordered; do not discontinue without consulting prescriber (fungal infections may take weeks or months of therapy). Must be taken with full meal or liquid nutritional supplement. Maintain adequate hydration (2-3 L/day of fluids, unless instructed to restrict fluid intake). You may experience diarrhea (buttermilk, boiled milk, or yogurt may help); nausea, vomiting, abdominal pain, or loss of appetite (frequent oral care, sucking lozenges, or chewing gum may help); or constipation (increased dietary fiber, liquids, or exercise may help); headache, dizziness, blurred vision, or insomnia (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report immediately chest pain or palpitations; unusual muscle pain or weakness; unresolved or persistent gastrointestinal upset; urinary pattern changes; yellowing of skin or eyes; changes in color of stool or urine; or any other persistent side effects. **Pregnancy/breast-feeding precautions:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, oral:

Noxafil®: 40 mg/mL (123 mL) [contains sodium benzoate; delivers 105 mL of suspension; cherry flavor; packaged with calibrated dosing spoon]

Generic AvailableNo

ManufacturerSchering-Plough

Mechanism of ActionInterferes with fungal cytochrome P450 (latosterol-14α-demethylase) activity, decreasing ergosterol synthesis (principal sterol in fungal cell membrane) and inhibiting fungal cell membrane formation.

Pharmacodynamics/Kinetics

Absorption: Food and/or liquid nutritional supplements increase absorption; fasting states do not provide sufficient absorption to ensure adequate plasma concentrations

Distribution: V_d: 465-1774 L

Protein binding: ≥97%; predominantly bound to albumin

Metabolism: Not significantly metabolized; ~15% to 17% undergoes non-CYP-mediated metabolism, primarily via hepatic glucuronidation into metabolites

Half-life elimination: 35 hours (range: 20-66 hours)

Time to peak, plasma: ~3-5 hours

Excretion: Feces 71% to 77% (~66% as unchanged drug); urine 13% to 14% (<0.2% as unchanged drug)

Dental Health Professional ConsiderationsThis drug is known to prolong the QT interval. The QT interval is measured as the time and distance between the Q point of the QRS complex and the end of the T wave in the ECG tracing. After adjustment for heart rate, the QT interval is defined as prolonged if it is more than 450 msec in men and 460 msec in women. A long QT syndrome was first described in the 1950s and 60s as a congenital syndrome involving QT interval prolongation and syncope and sudden death. Some of the congenital long QT syndromes were characterized by a peculiar electrocardiographic appearance of the QRS complex involving a premature atria beat followed by a pause, then a subsequent sinus beat showing marked QT prolongation and deformity. This type of cardiac arrhythmia was originally termed “torsade de pointes” (translated from the French as “twisting of the points”).

Prolongation of the QT interval is thought to result from delayed ventricular repolarization. The repolarization process within the myocardial cell is due to the efflux of intracellular potassium. The channels associated with this current can be blocked by many drugs and predispose the electrical propagation cycle to torsade de pointes.

Posaconazole is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), abnormal taste, mucositis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, fatigue, or insomnia

Mental Health: Effects on Psychiatric TreatmentContraindicated with pimozide and ergot alkaloids. Diarrhea and other GI side effects are common and may be worse with combined use of lithium, valproic acid, carbamazepine, or SSRIs. May cause neutropenia; use caution with clozapine. May cause thrombocytopenia; use caution with valproic acid. May increase level of some benzodiazepines, mirtazapine, nefazodone, or venlafaxine; monitor for increased effects and/or toxicity.

Index TermsSCH 56592

References

Greenberg RN, Mullane K, van Burik JA, et al, “Posaconazole as Salvage Therapy for Zygomycosis,” *Antimicrob Agents Chemother*, 2006, 50(1):126-33.[PubMed 16377677]

Herbrecht R, “Posaconazole: A Potent, Extended-Spectrum Triazole Anti-Fungal for the Treatment of Serious Fungal Infections,” *Int J Clin Pract*, 2004, 58(6): 612-24.

Keating G, “Posaconazole,” *Drugs*, 2005, 65(11):1553-67.[PubMed 16033292]

Krieter P, Flannery B, Musick T, et al, “Disposition of Posaconazole Following Single-Dose Oral Administration in Healthy Subjects,” *Antimicrob Agents Chemother*, 2004, 48(9):3543-51.[PubMed 15328123]

Raad II, Graybill JR, Bustamante AB, “Safety of Long-Term Oral Posaconazole Use in the Treatment of Refractory Invasive Fungal Infections,” *Clin Infect Dis*, 2006, 42(12):1726-34.[PubMed 16705579]

Walsh TJ, Anaissie EJ, Denning DW, et al, “Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America,” *Clin Infect Dis*, 2008, 46(3):327-60.[PubMed 18177225]

International Brand NamesNoxafil (AU, BE, CH, CZ, DE, DK, EE, ES, FR, GB, IE, NO, NZ, SE)

Potassium Acetate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Consider special storage requirements for intravenous potassium salts; I.V. potassium salts have been administered IVP in error, leading to fatal outcomes.

Pronunciation(poe TASS ee um AS e tate)
Pharmacologic CategoryElectrolyte Supplement, Parenteral
Use: Labeled IndicationsPotassium deficiency; to avoid chloride when high concentration of potassium is needed, source of bicarbonate
Dosing: AdultsI.V. doses should be incorporated into the patient's maintenance I.V. fluids, intermittent I.V. potassium administration should be reserved for severe depletion situations and requires ECG monitoring; doses listed as mEq of potassium

Treatment of hypokalemia: I.V.: 40-100 mEq/day

I.V. intermittent infusion (must be diluted prior to administration):

5-10 mEq/dose (maximum: 40 mEq/dose) to infuse over 2-3 hours (maximum: 40 mEq over 1 hour)

Note: Continuous cardiac monitor recommended for rates >0.5 mEq/hour

Potassium dosage/rate of infusion guidelines:

Serum potassium >2.5 mEq/L: Maximum infusion rate: 10 mEq/hour; maximum concentration: 40 mEq/L; maximum 24-hour dose: 200 mEq

Serum potassium <2.5 mEq/L: Maximum infusion rate: 40 mEq/hour; maximum concentration: 80 mEq/L; maximum 24-hour dose: 400 mEq

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricI.V. doses should be incorporated into the patient's maintenance I.V. fluids, intermittent I.V. potassium administration should be reserved for severe depletion situations and requires ECG monitoring; doses listed as mEq of potassium.

Note: Use caution in premature neonates; potassium acetate for injection contains aluminum.

Treatment of hypokalemia: I.V.: 2-5 mEq/kg/day

I.V. intermittent infusion (must be diluted prior to administration): 0.5-1 mEq/kg/dose (maximum: 30 mEq/dose) to infuse at 0.3-0.5 mEq/kg/hour (maximum: 1 mEq/kg/hour)

Note: Continuous cardiac monitor recommended for rates >0.5 mEq/hour

Potassium dosage/rate of infusion guidelines:

Serum potassium >2.5 mEq/L: Maximum infusion rate: 10 mEq/hour; maximum concentration: 40 mEq/L; maximum 24-hour dose: 200 mEq

Serum potassium <2.5 mEq/L: Maximum infusion rate: 40 mEq/hour; maximum concentration: 80 mEq/L; maximum 24-hour dose: 400 mEq

Dosing: Renal ImpairmentUse caution; potassium acetate injection contains aluminum.
Administration: I.V. DetailPotassium must be diluted prior to parenteral administration; maximum recommended concentration (peripheral line): 80 mEq/L; maximum recommended concentration (central line): 150 mEq/L or 15 mEq/100 mL; in severely fluid-restricted patients (with central lines): 200 mEq/L or 20 mEq/100 mL has been used; maximum rate of infusion, see Dosage, I.V. intermittent infusion
Compatibility

Y-site administration: Compatible: Ciprofloxacin.

Compatibility when admixed: Compatible: Metoclopramide.

ContraindicationsSevere renal impairment; hyperkalemia
Warnings/Precautions

Concerns related to adverse effects:

- Hyperkalemia: Close monitoring of serum potassium concentrations is needed to avoid hyperkalemia; severe hyperkalemia may lead to muscle weakness/paralysis and cardiac conduction abnormalities (eg, heart block, ventricular arrhythmias, asystole).

Disease-related concerns:

- Acid/base disorders: Use with caution in patients with acid/base alterations; changes in serum potassium concentrations can occur during acid/base correction, monitor closely.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (eg, heart failure, cardiac arrhythmias); patients may be more susceptible to life-threatening cardiac effects associated with hyper/hypokalemia.

- Potassium-altering conditions/disorders: Use with caution in patients with disorders or conditions likely to contribute to altered serum potassium and hyperkalemia (eg, untreated Addison's disease, heat cramps, severe tissue breakdown from trauma or burns).

- Renal impairment: Use with caution in patients with renal impairment; monitor serum potassium concentrations closely. Contraindicated with severe impairment.

Concurrent drug therapy issues:

- Digitalis: Use with caution in digitalized patients; may be more susceptible to potentially life-threatening cardiac effects with rapid changes in serum potassium concentrations.

- Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (eg, ACEIs, potassium-sparing diuretics, potassium containing salt substitutes).

Dosage form specific issues:

- Aluminum: Solution for injection contains aluminum; use with caution in patients with impaired renal function and in premature infants.

Other warnings/precautions:

- Parenteral administration: Use extreme caution with parenteral administration and monitor serum potassium concentrations closely. Evaluate renal function, cardiac and fluid status, and any factors contributing to altered potassium concentrations (eg, acidosis, alkalosis) prior to therapy. Do **NOT** administer undiluted or I.V. push; inappropriate parenteral administration may be fatal. Always administer potassium further diluted; refer to appropriate dilution and administration rate recommendations. Pain and phlebitis may occur during parenteral infusion requiring a decrease in infusion rate or potassium concentration.

Pregnancy Risk FactorC

Adverse Reactions

1% to 10%:

Cardiovascular: Bradycardia

Endocrine & metabolic: Hyperkalemia

Neuromuscular & skeletal: Weakness

Respiratory: Dyspnea

Local: Local tissue necrosis with extravasation

<1%: Abdominal pain, alkalosis, chest pain, mental confusion, paralysis, paresthesia, phlebitis, throat pain

Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Monitoring: Lab TestsSerum potassium

Patient EducationThis form of potassium may only be given I.V. Report immediately any burning or pain at infusion site, chest pain, palpitations, unusual weakness in muscles, tarry stools, or easy bruising.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 2 mEq/mL (20 mL, 50 mL, 100 mL) [contains aluminum]

Injection, solution [concentrate]: 4 mEq/mL (50 mL) [contains aluminum]

Generic AvailableYes

Mechanism of ActionPotassium is the major cation of intracellular fluid and is essential for the conduction of nerve impulses in heart, brain, and skeletal muscle; contraction of cardiac, skeletal and smooth muscles; maintenance of normal renal function, acid-base balance, carbohydrate metabolism, and gastric secretion

Pharmacodynamics/Kinetics

Distribution: Enters cells via active transport from extracellular fluid

Excretion: Primarily urine; skin and feces (small amounts); most intestinal potassium reabsorbed

Pharmacotherapy Pearls1 mEq of acetate is equivalent to the alkalinizing effect of 1 mEq of bicarbonate.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Mental Health CommentHypokalemia is associated with an increased risk of ventricular dysrhythmias; use antipsychotics with caution (especially ziprasidone).

Cardiovascular ConsiderationsHypokalemia is highly arrhythmogenic, particularly in the setting of ischemia or digitalis toxicity. ECG evidence of hypokalemia includes flattening of the T wave. As the T wave shrinks, U waves may appear. There is no prolongation of the QT interval. Hyperkalemia may present as tall peaked symmetrical T waves. S-T elevation may present in severe hyperkalemia. QRS complex progressively widens with eventual apparent sine waves on the ECG. Hyperkalemia will also induce cardiac slowing and AV conduction abnormalities.

References

Hamill RJ, Robinson LM, Wexler HR, et al, “Efficacy and Safety of Potassium Infusion Therapy in Hypokalemic Critically Ill Patients,” *Crit Care Med*, 1991, 19(5):694-9. [PubMed 2026032]

Khilnani P, “Electrolyte Abnormalities in Critically Ill Children,” *Crit Care Med*, 1992, 20(2):241-50.[PubMed 1737458]

Potassium Acid Phosphate

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(poe TASS ee um AS id FOS fate)

U.S. Brand NamesK-Phos® Original

Pharmacologic CategoryUrinary Acidifying Agent

Use: Labeled IndicationsAcidifies urine and lowers urinary calcium concentration; reduces odor and rash caused by ammoniacal urine; increases the antibacterial activity of methenamine

Dosing: Adults**Urine acidification:** Oral: 1000 mg dissolved in 6-8 oz of water 4 times/day with meals and at bedtime; for best results, soak tablets in water for 2-5 minutes, then stir and swallow

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsMay be taken with meals.

ContraindicationsSevere renal impairment; hyperkalemia, hyperphosphatemia; infected magnesium ammonium phosphate stones

Warnings/Precautions

Concerns related to adverse effects:

- GI effects: May cause GI upset (eg, nausea, vomiting, diarrhea, abdominal pain, discomfort) and lead to GI ulceration, bleeding, perforation and/or obstruction.
- Hyperkalemia: Close monitoring of serum potassium concentrations is needed to avoid hyperkalemia; severe hyperkalemia may lead to muscle weakness/paralysis and cardiac conduction abnormalities (eg, heart block, ventricular arrhythmias, asystole).

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; monitor serum potassium concentrations closely. Contraindicated with severe impairment.
- Tissue breakdown: Use with caution in patients with severe tissue breakdown (eg, chemotherapy or hemodialysis).

Concurrent drug therapy issues:

- Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (eg, ACEI, potassium-sparing diuretics, potassium containing salt substitutes).

Geriatric ConsiderationsA complete drug history should be taken to rule out potential drug interactions since the elderly frequently may be taking potassium and potassium-sparing diuretics, salicylates, or antacids. Use with caution in renal impairment (low Cl_{cr}).

Pregnancy Risk FactorC

Adverse Reactions

>10%: Gastrointestinal: Diarrhea, nausea, stomach pain, flatulence, vomiting

1% to 10%:

Cardiovascular: Bradycardia

Endocrine & metabolic: Hyperkalemia

Local: Local tissue necrosis with extravasation

Neuromuscular & skeletal: Weakness

Respiratory: Dyspnea

<1%: Abdominal pain, alkalosis, arrhythmia, arthralgia, bone pain, chest pain, decreased urine output, dyspnea, edema, weight gain, hyperphosphatemia, hypocalcemia, mental confusion, pain of extremities, paralysis, paresthesia, phlebitis, tetany, thirst, throat pain, weakness of extremities

Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Test InteractionsDecreased ammonia (B)
Monitoring ParametersSerum potassium, sodium, phosphate, calcium; serum salicylates (if taking salicylates)
Monitoring: Lab TestsSerum potassium
Patient EducationDissolve tablets completely before drinking. Avoid taking magnesium, calcium, or aluminum antacids at the same time. Patients may pass old kidney stones when starting therapy. Notify prescriber if experiencing nausea, vomiting, or abdominal pain.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet [scored]: 500 mg [phosphorus 114 mg and potassium 144 mg (3.7 mEq) per tablet; sodium free]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (K-Phos)

500 mg (30): $16.99

Mechanism of ActionThe principal intracellular cation; involved in transmission of nerve impulses, muscle contractions, enzyme activity, and glucose utilization
Pharmacodynamics/Kinetics

Absorption: Well absorbed from upper GI tract

Distribution: Enters cells via active transport from extracellular fluid

Excretion: Primarily urine; skin and feces (small amounts); most intestinal potassium reabsorbed

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric Treatment

GI side effects are common; use caution with SSRIs, lithium, and valproic acid

Mental Health CommentHypokalemia is associated with an increased risk of ventricular dysrhythmias; use antipsychotics with caution (especially ziprasidone).
Cardiovascular ConsiderationsHypokalemia is highly arrhythmogenic, particularly in the setting of ischemia or digitalis toxicity. ECG evidence of hypokalemia includes flattening of the T wave. As the T wave shrinks, U waves may appear. There is no prolongation of the QT interval. Hyperkalemia may present as tall peaked symmetrical T waves. S-T elevation may present in severe hyperkalemia. QRS complex progressively widens with eventual apparent sine waves on the ECG. Hyperkalemia will also induce cardiac slowing and AV conduction abnormalities.

Potassium Bicarbonate and Potassium Chloride

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(poe TASS ee um bye KAR bun ate & poe TASS ee um KLOR ide)
U.S. Brand NamesK-Lyte/Cl® [DSC]
Pharmacologic CategoryElectrolyte Supplement, Oral
Use: Labeled IndicationsTreatment or prevention of hypokalemia
Dosing: Adults**Hypokalemia:** Oral:

Prevention: 16-24 mEq/day in 2-4 divided doses

Treatment: 40-100 mEq/day in 2-4 divided doses

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Oral: 1-4 mEq/kg/24 hours in divided doses as required to maintain normal serum potassium

Administration: OralAdminister with meals; solution should be sipped slowly, over 5-10 minutes
Dietary ConsiderationsShould be taken with meals.
StorageStore below 30°C (86°F).
ReconstitutionTablet for oral solution: 25 mEq: Dissolve in 3-4 ounces of cold water.
ContraindicationsHypersensitivity to any component of the formulation; hyperkalemia
Warnings/Precautions

Concerns related to adverse effects:

- GI effects: May cause GI upset (eg, nausea, vomiting, diarrhea, abdominal pain, discomfort) and lead to GI ulceration, bleeding, perforation and/or obstruction.
- Hyperkalemia: Close monitoring of serum potassium concentrations is needed to avoid hyperkalemia; severe hyperkalemia may lead to muscle weakness/paralysis and cardiac conduction abnormalities (eg, heart block, ventricular arrhythmias, asystole).

Disease-related concerns:

- Acid/base disorders: Use with caution in patients with acid/base alterations; changes in serum potassium concentrations can occur during acid/base correction, monitor closely.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (eg, heart failure, cardiac arrhythmias); patients may be more susceptible to life-threatening cardiac effects associated with hyper/hypokalemia.
- Potassium-altering conditions/disorders: Use with caution in patients with disorders or conditions likely to contribute to altered serum potassium and hyperkalemia (eg, untreated Addison's disease, heat cramps, severe tissue breakdown from trauma or burns).
- Renal impairment: Use with caution in patients with renal impairment; monitor serum potassium concentrations closely with severe impairment.

Concurrent drug therapy issues:

- Digitalis: Use with caution in digitalized patients; may be more susceptible to potentially life-threatening cardiac effects with rapid changes in serum potassium concentrations.
- Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (eg, ACEI, potassium-sparing diuretics, potassium containing salt substitutes).

Pregnancy Risk FactorC
LactationEnters breast milk/compatible
Adverse ReactionsFrequency not defined: Gastrointestinal: Abdominal discomfort, diarrhea, nausea, vomiting
Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Anticholinergic Agents: May enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Monitoring ParametersSerum potassium
Nursing: Physical Assessment/MonitoringSee individual agents.
Monitoring: Lab TestsSerum potassium, serum bicarbonate
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet for solution, oral [effervescent]: Potassium chloride 25 mEq [potassium bicarbonate 0.5 g and potassium chloride 1.5 g]

K-Lyte/Cl®: Potassium chloride 25 mEq [potassium bicarbonate 0.5 g and potassium chloride 1.5 g; citrus or fruit punch flavor] [DSC]

Generic AvailableYes
ManufacturerBristol-Myers Squibb
Pricing: U.S. (www.drugstore.com)

Tablet, effervescent (K-Lyte/Cl 25)

25 mEq (30): $42.99

Tablet, effervescent (K-Lyte/Cl 50)

50 mEq (30): $73.99

Related Information

- Potassium Bicarbonate
- Potassium Chloride

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental Status

None reported

Mental Health: Effects on Psychiatric Treatment

GI side effects are common; use caution with SSRIs, lithium, and valproic acid

Mental Health CommentHypokalemia is associated with an increased risk of ventricular dysrhythmias; use antipsychotics with caution (especially ziprasidone). In overdose, may cause anxiety, confusion, unusual tiredness, or weakness.
Cardiovascular ConsiderationsHypokalemia is highly arrhythmogenic, particularly in the setting of ischemia or digitalis toxicity. ECG evidence of hypokalemia includes flattening of the T wave. As the T wave shrinks, U waves may appear. There is no prolongation of the QT interval. Hyperkalemia may present as tall peaked symmetrical T waves. S-T elevation may present in severe hyperkalemia. QRS complex progressively widens with eventual apparent sine waves on the ECG. Hyperkalemia will also induce cardiac slowing and AV conduction abnormalities.
Index TermsPotassium Bicarbonate and Potassium Chloride (Effervescent)
International Brand NamesCorpotasin CL (MX); Sando-K (GB)

Potassium Bicarbonate and Potassium Citrate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Klor-Con® may be confused with Klaron®, K-Lor®

Pronunciation(poe TASS ee um bye KAR bun ate & poe TASS ee um SIT rate)
U.S. Brand NamesEffer-K™; K-Lyte®; K-Lyte® DS; Klor-Con®/EF
Pharmacologic CategoryElectrolyte Supplement, Oral
Use: Labeled IndicationsTreatment or prevention of hypokalemia
Dosing: Adults**Hypokalemia:** Oral:

Prevention: 16-24 mEq/day in 2-4 divided doses

Treatment: 40-100 mEq/day in 2-4 divided doses

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Hypokalemia:** Oral: Children: 1-4 mEq/kg/24 hours in divided doses as required to maintain normal serum potassium
ContraindicationsSevere renal impairment, hyperkalemia
Warnings/Precautions

Concerns related to adverse effects:

- GI effects: May cause GI upset (eg, nausea, vomiting, diarrhea, abdominal pain, discomfort) and lead to GI ulceration, bleeding, perforation and/or obstruction.
- Hyperkalemia: Close monitoring of serum potassium concentrations is needed to avoid hyperkalemia; severe hyperkalemia may lead to muscle weakness/paralysis and cardiac conduction abnormalities (eg, heart block, ventricular arrhythmias, asystole).

Disease-related concerns:

- Acid/base disorders: Use with caution in patients with acid/base alterations; changes in serum potassium concentrations can occur during acid/base correction, monitor closely.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (eg, heart failure, cardiac arrhythmias); patients may be more susceptible to life-threatening cardiac effects associated with hyper/hypokalemia.
- Potassium-altering conditions/disorders: Use with caution in patients with disorders or conditions likely to contribute to altered serum potassium and hyperkalemia (eg, untreated Addison's disease, heat cramps, severe tissue breakdown from trauma or burns).
- Renal impairment: Use with caution in patients with renal impairment; monitor serum potassium concentrations closely. Contraindicated with severe impairment.

Concurrent drug therapy issues:

- Digitalis: Use with caution in digitalized patients; may be more susceptible to potentially life-threatening cardiac effects with rapid changes in serum potassium concentrations.
- Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (eg, ACEI, potassium-sparing diuretics, potassium containing salt substitutes).

Pregnancy Risk FactorC
Adverse Reactions

>10%: Gastrointestinal: Diarrhea, nausea, stomach pain, flatulence, vomiting

1% to 10%:

Cardiovascular: Bradycardia

Endocrine & metabolic: Hyperkalemia

Local: Local tissue necrosis with extravasation

Neuromuscular & skeletal: Weakness

Respiratory: Dyspnea

<1%: Abdominal pain, alkalosis, chest pain, mental confusion, paralysis, paresthesia, phlebitis, throat pain

Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aluminum Hydroxide: Citric Acid Derivatives may increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Test InteractionsDecreased ammonia (B)
Monitoring ParametersSerum potassium
Nursing: Physical Assessment/MonitoringSee individual agents.
Monitoring: Lab TestsSerum potassium, serum bicarbonate
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, effervescent:

Effer-K™: Potassium 25 mEq [cherry berry, lemon citrus, orange, or unflavored]

Klor-Con®/EF: Potassium 25 mEq [sugar free; orange flavor]

K-Lyte®: Potassium 25 mEq [orange flavor]

K-Lyte® DS: Potassium 50 mEq [orange flavor]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablet, effervescent (Klor-Con/EF)

25 mEq (30): $15.99

Mechanism of ActionNeeded for the conduction of nerve impulses in heart, brain, and skeletal muscle; contraction of cardiac, skeletal and smooth muscles; maintenance of normal renal function
Pharmacodynamics/Kinetics

Absorption: Well absorbed from upper GI tract

Distribution: Enters cells via active transport from extracellular fluid

Excretion: Primarily urine; skin and feces (small amounts); most intestinal potassium reabsorbed

Related Information

- Potassium Bicarbonate
- Potassium Citrate

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay rarely cause confusion
Mental Health: Effects on Psychiatric TreatmentNone reported
Cardiovascular ConsiderationsHypokalemia is highly arrhythmogenic, particularly in the setting of ischemia or digitalis toxicity. ECG evidence of hypokalemia includes flattening of the T wave. As the T wave shrinks, U waves may appear. There is no prolongation of the QT interval. Hyperkalemia may present as tall peaked symmetrical T waves. S-T elevation may present in severe hyperkalemia. QRS complex progressively widens with eventual apparent sine waves on the ECG. Hyperkalemia will also induce cardiac slowing and AV conduction abnormalities.
Index TermsPotassium Bicarbonate and Potassium Citrate (Effervescent)

Potassium Bicarbonate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(poe TASS ee um bye KAR bun ate)
Pharmacologic CategoryElectrolyte Supplement, Oral
Use: Labeled IndicationsPotassium deficiency, hypokalemia
Dosing: Adults**Hypokalemia:** Oral: 25 mEq 2-4 times/day
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Hypokalemia**: Oral: Children: 1-4 mEq/kg/day
Warnings/Precautions

Concerns related to adverse effects:

- GI effects: May cause GI upset (eg, nausea, vomiting, diarrhea, abdominal pain, discomfort) and lead to GI ulceration, bleeding, perforation and/or obstruction.
- Hyperkalemia: Close monitoring of serum potassium concentrations is needed to avoid hyperkalemia; severe hyperkalemia may lead to muscle weakness/paralysis and cardiac conduction abnormalities (eg, heart block, ventricular arrhythmias, asystole).

Disease-related concerns:

- Acid/base disorders: Use with caution in patients with acid/base alterations; changes in serum potassium concentrations can occur during acid/base correction, monitor closely.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (eg, heart failure, cardiac arrhythmias); patients may be more susceptible to life-threatening cardiac effects associated with hyper/hypokalemia.
- Potassium-altering conditions/disorders: Use with caution in patients with disorders or conditions likely to contribute to altered serum potassium and hyperkalemia (eg, untreated Addison's disease, heat cramps, severe tissue breakdown from trauma or burns).
- Renal impairment: Use with caution in patients with renal impairment; monitor serum potassium concentrations closely with severe impairment.

Concurrent drug therapy issues:

- Digitalis: Use with caution in digitalized patients; may be more susceptible to potentially life-threatening cardiac effects with rapid changes in serum potassium concentrations.
- Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (eg, ACEI, potassium-sparing diuretics, potassium containing salt substitutes).

Pregnancy Risk FactorC
Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Monitoring: Lab TestsSerum potassium, serum bicarbonate
Patient EducationDissolve completely in 3-8 oz cold water, juice, or other suitable beverage and drink slowly.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet for oral solution, effervescent: Potassium 25 mEq

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablet, effervescent (K-Vescent)

25 mEq (100): $25.99

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Mental Health CommentHypokalemia is associated with an increased risk of ventricular dysrhythmias; use antipsychotics with caution (especially ziprasidone).

Cardiovascular ConsiderationsHypokalemia is highly arrhythmogenic, particularly in the setting of ischemia or digitalis toxicity. ECG evidence of hypokalemia includes flattening of the T wave. As the T wave shrinks, U waves may appear. There is no prolongation of the QT interval. Hyperkalemia may present as tall peaked symmetrical T waves. S-T elevation may present in severe hyperkalemia. QRS complex progressively widens with eventual apparent sine waves on the ECG. Hyperkalemia will also induce cardiac slowing and AV conduction abnormalities.

International Brand NamesKaldyum (PL); Kalimat prolongatum (PL); Kalipoz prolongatum (PL); Kalitrans (DE); Kalium (PL); Kalium Chloratum (PL); Kalium Gluconicum (PL)

Potassium Chloride

Lexi-Drugs Online

English

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Kaon-Cl-10® may be confused with kaolin

KCl may be confused with HCl

K-Lor® may be confused with Klor-Con®

Klor-Con® may be confused with Klaron®, K-Lor®

microK® may be confused with Micronase®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V. formulation) among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Per JCAHO recommendations, concentrated electrolyte solutions should not be available in patient care areas.

Consider special storage requirements for intravenous potassium salts; I.V. potassium salts have been administered IVP in error, leading to fatal outcomes.

Pronunciation(poe TASS ee um KLOR ide)

U.S. Brand NamesK-Lor®; K-Tab®; Kaon-Cl-10®; Kay Ciel® [DSC]; Klor-Con®; Klor-Con® 10; Klor-Con® 8; Klor-Con® M; Klor-Con®/25; microK®; microK® 10

Canadian Brand NamesApo-K®; K-10®; K-Dur®; K-Lor®; K-Lyte®/Cl; Micro-K Extencaps®; Roychlor®; Slo-Pot; Slow-K®

Pharmacologic CategoryElectrolyte Supplement, Oral; Electrolyte Supplement, Parenteral

Use: Labeled IndicationsTreatment or prevention of hypokalemia

Dosing: AdultsI.V. doses should be incorporated into the patient's maintenance I.V. fluids; intermittent I.V. potassium administration should be reserved for severe depletion situations in patients undergoing ECG monitoring. Doses expressed as mEq of potassium.

Normal daily requirements:*Oral, I.V.:* 40-80 mEq/day

Prevention of hypokalemia:*Oral:* 20-40 mEq/day in 1-2 divided doses

Treatment of hypokalemia:

Oral:

Asymptomatic, mild hypokalemia: Usual dosage range: 40-100 mEq/day divided in 2-5 doses; generally recommended to limit doses to 20-25 mEq/dose to avoid GI discomfort.

Mild-to-moderate hypokalemia: Some clinicians may administer up to 120-240 mEq/day divided in 3-4 doses; limit doses to 40-60 mEq/dose. If deficits are severe or ongoing losses are great, I.V. route should be considered.

I.V. intermittent infusion: Peripheral or central line: ≤10 mEq/hour; repeat as needed based on frequently obtained lab values; central line infusion and continuous ECG monitoring highly recommended for infusions >10 mEq/hour.

Potassium dosage/rate of infusion general guidelines (per product labeling): **Note:** High variability exists in dosing/infusion rate recommendations; therapy guided by patient condition and specific institutional guidelines.

Serum potassium >2.5 mEq/L: Maximum infusion rate: 10 mEq/hour; maximum concentration: 40 mEq/L; maximum 24-hour dose: 200 mEq

Serum potassium <2 mEq/L and symptomatic (excluding emergency treatment of cardiac arrest): Maximum infusion rate (central line only): 40 mEq/hour in presence of continuous ECG monitoring and frequent lab monitoring; In selected situations, patients may require up to 400 mEq/24 hours.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricI.V. doses should be incorporated into the patient's maintenance I.V. fluids; intermittent I.V. potassium administration should be reserved for severe depletion situations in patients undergoing ECG monitoring. Doses expressed as mEq of potassium.

Normal daily requirements:*Oral, I.V.:* 1-2 mEq/kg/day

Prevention of hypokalemia: *Oral:* 1-2 mEq/kg/day in 1-2 divided doses

Treatment of hypokalemia:

Oral: 1-2 mEq/kg initially, then as needed based on frequently obtained lab values. If deficits are severe or ongoing losses are great, I.V. route should be considered.

I.V. intermittent infusion: 0.5-1 mEq/kg/dose (maximum dose: 40 mEq). If infusion exceeds 0.5 mEq/kg/hour, physician should be at bedside and patient should have continuous ECG monitoring; repeat as needed based on frequently obtained lab values.

Administration: I.V.Potassium must be diluted prior to parenteral administration. Do not administer I.V. push. In general, the dose, concentration of infusion and rate of administration may be dependant on patient condition and specific institution policy. Some clinicians recommend that the maximum concentration for peripheral infusion is 10 mEq/100 mL and maximum rate of administration for peripheral infusion is 10 mEq/hour. ECG monitoring is recommended for peripheral or central infusions >10 mEq/hour in adults. Concentrations and rates of infusion may be greater with central line administration. Some clinicians recommend that the maximum concentration for central infusion is 20-40 mEq/100 mL and maximum rate of administration for central infusion is 40 mEq/hour.

Administration: OralOral dosage forms should be taken with meals and a full glass of water or other liquid.

Capsule: MicroK®: Swallow whole, do not chew. Capsules may also be opened and contents sprinkled on a spoonful of applesauce or pudding and should be swallowed immediately without chewing. No more than 20 mEq should be given as a single dose.

Powder: Klor-Con®: Dissolve in 4-5 ounces of water or other beverage prior to administration.

Tablet: K-Tab®, Kaon-Cl®, Klor-Con®: Swallow tablets whole; do not crush, chew or suck on tablet. No more than 20 mEq should be given as a single dose.

Klor-Con® M: Tablet may also be broken in half and each half swallowed separately; the whole tablet may be dissolved in ~4 ounces of water (allow ~2 minutes to dissolve, stir well and drink immediately)

Dietary ConsiderationsAdminister with plenty of fluid to decrease stomach irritation and discomfort. Some dietary sources of potassium include leafy green vegetables (eg, spinach, cabbage), tomatoes, cucumbers, zucchini, fruits (eg, apples, oranges, and bananas), root vegetables (eg, carrots, radishes), beans, and peas.

Storage

Capsule: MicroK®: Store between 20°C to 25°C (68°F to 77°F).

Powder for oral solution: Klor-Con®: Store at room temperature of 15°C to 30°C (59°F to 86°F).

Solution for injection: Store at room temperature; do not freeze. Use only clear solutions. Use admixtures within 24 hours.

Tablet: K-Tab®: Store below 30°C (86°F).

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, $D_{20}W$, LR, ${}^1/_2NS$, NS, sodium chloride 3%; **variable compatibility (consult detailed reference)** in fat emulsion 10%, mannitol.

Y-site administration: Compatible: Acyclovir, alatrofloxacin, aldesleukin, allopurinol, amifostine, aminophylline, amiodarone, ampicillin, atropine, aztreonam, betamethasone sodium phosphate, calcium gluconate, chlordiazepoxide, chlorpromazine, ciprofloxacin, cisatracurium, cladribine, clarithromycin, cyanocobalamin, dexamethasone sodium phosphate, digoxin, diltiazem, diphenhydramine, dobutamine, docetaxel, dopamine, doxorubicin liposome, droperidol, edrophonium, enalaprilat, epinephrine, esmolol, estrogens (conjugated), ethacrynate, etoposide, famotidine, fentanyl, fentanyl and droperidol, filgrastim, fludarabine, fluorouracil, furosemide, gatifloxacin, gemcitabine, granisetron, heparin, hydralazine, idarubicin, inamrinone, indomethacin, insulin (regular), isoproterenol, kanamycin, labetalol, lidocaine, linezolid, lorazepam, magnesium sulfate, melphalan, menadiol, meperidine, methoxamine, methylergonovine, midazolam, milrinone, minocycline, morphine, neostigmine, norepinephrine, ondansetron, oxacillin, oxytocin, paclitaxel, penicillin G potassium, pentazocine, phytonadione, piperacillin/tazobactam, procainamide, prochlorperazine edisylate, propofol, propranolol, pyridostigmine, remifentanil, sargramostim, scopolamine, sodium bicarbonate, succinylcholine, tacrolimus, teniposide, theophylline, thiotepa, tirofiban, trimethaphan, trimethobenzamide, vinorelbine, warfarin, zidovudine. **Incompatible:** Amphotericin B cholesteryl sulfate complex, diazepam, ergotamine, phenytoin. **Variable (consult detailed reference):** Methylprednisolone sodium succinate, promethazine.

Compatibility when admixed: Compatible: Aminophylline, amiodarone, atracurium, bretylium, calcium gluconate, cefepime, ceftazidime, chloramphenicol, cimetidine, ciprofloxacin, clindamycin, corticotropin, cytarabine, dimenhydrinate, dopamine, enalaprilat, erythromycin lactobionate, floxacillin, fluconazole, foscarnet, fosphenytoin, furosemide, heparin, hydrocortisone sodium succinate, hydrocortisone sodium succinate with isoproterenol, lidocaine, metaraminol, methyldopate, metoclopramide, mitoxantrone, nafcillin, norepinephrine, oxacillin, penicillin G potassium, penicillin G potassium with vitamin B complex with C, phenylephrine, piperacillin, propafenone, ranitidine, sodium bicarbonate, thiopental, vancomycin, verapamil, vitamin B complex with C. **Incompatible:** Amphotericin B. **Variable (consult detailed reference):** Amikacin, dobutamine, etoposide with cisplatin and mannitol, penicillin G sodium.

ContraindicationsHypersensitivity to any component of the formulation; hyperkalemia. In addition, solid oral dosage forms are contraindicated in patients in whom there is a structural, pathological, and/or pharmacologic cause for delay or arrest in passage through the GI tract.

Warnings/Precautions

Concerns related to adverse effects:

- Hyperkalemia: Close monitoring of serum potassium concentrations is needed to avoid hyperkalemia; severe hyperkalemia may lead to muscle weakness/paralysis and cardiac conduction abnormalities (eg, heart block, ventricular arrhythmias, asystole).

Disease-related concerns:

- Acid/base disorders: Use with caution in patients with acid/base alterations; changes in serum potassium concentrations can occur during acid/base correction, monitor closely.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (eg, heart failure, cardiac arrhythmias); patients may be more susceptible to life-threatening cardiac effects associated with hyper/hypokalemia.

- Potassium-altering conditions/disorders: Use with caution in patients with disorders or conditions likely to contribute to altered serum potassium and hyperkalemia (eg, untreated Addison's disease, heat cramps, severe tissue breakdown from trauma or burns).
- Renal impairment: Use with caution in patients with renal impairment; monitor serum potassium concentrations closely. Contraindicated with severe impairment.

Concurrent drug therapy issues:

- Digitalis: Use with caution in digitalized patients; may be more susceptible to potentially life-threatening cardiac effects with rapid changes in serum potassium concentrations.
- Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (eg, ACEI, potassium-sparing diuretics, potassium containing salt substitutes).

Dosage form specific issues:

- Oral formulations: May cause GI upset (eg, nausea, vomiting, diarrhea, abdominal pain, discomfort) and lead to GI ulceration, bleeding, perforation and/or obstruction. Oral liquid preparations (not solid) should be used in patients with esophageal compression or delayed gastric emptying.

Other warnings/precautions:

- Parenteral administration: Use extreme caution with parenteral administration and monitor serum potassium concentrations closely. Evaluate renal function, cardiac and fluid status, and any factors contributing to altered potassium concentrations (eg, acidosis, alkalosis) prior to therapy. Do **NOT** administer undiluted or I.V. push; inappropriate parenteral administration may be fatal. Always administer potassium further diluted; refer to appropriate dilution and administration rate recommendations. Pain and phlebitis may occur during parenteral infusion requiring a decrease in infusion rate or potassium concentration. Avoid administering potassium diluted in dextrose solutions during initial therapy; potential for transient decreases in serum potassium due to intracellular shift of potassium from dextrose-stimulated insulin release.

Geriatric ConsiderationsElderly may require less potassium than younger adults due to decreased renal function. For the elderly who do not respond to replacement therapy, check serum magnesium. Long-term use of diuretics may result in hypomagnesemic.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. Potassium supplementation (that does not cause maternal hyperkalemia) would not be expected to cause adverse fetal events.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsThe normal content of potassium in human milk is ~13 mEq/L. Supplementation (that does not cause maternal hyperkalemia) would not be expected to affect normal levels.

Adverse ReactionsFrequency not defined.

Dermatologic: Rash

Endocrine & metabolic: Hyperkalemia

Gastrointestinal: Abdominal pain/discomfort, diarrhea, flatulence, GI bleeding (oral), GI obstruction (oral), GI perforation (oral), nausea, vomiting

Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Anticholinergic Agents: May enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Monitoring ParametersSerum potassium, glucose, chloride, pH, urine output (if indicated), cardiac monitor (if intermittent infusion or potassium infusion rates 0.5 mEq/kg/hour in children or >10 mEq/hour in adults)

Nursing: Physical Assessment/MonitoringAssess therapeutic response and adverse effects.

Monitoring: Lab TestsSerum potassium, glucose, chloride

Patient EducationLong-acting and wax matrix tablets should be swallowed whole; do not crush or chew. Powder must be dissolved in water before use. Liquid can be diluted or dissolved in water or juice. Take with food to avoid GI irritation and upset. Report abdominal pain, vomiting, blood in urine or stool, or persistent nausea or vomiting. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, extended release, microencapsulated: 8 mEq [600 mg]; 10 mEq [750 mg]

microK®: 8 mEq [600 mg]

microK® 10: 10 mEq [750 mg]

Infusion [premixed in D_5W]: 20 mEq (1000 mL); 30 mEq (1000 mL); 40 mEq (1000 mL)

Infusion [premixed in D_5W and LR]: 20 mEq (1000 mL); 30 mEq (1000 mL); 40 mEq (1000 mL)

Infusion [premixed in D_5W and sodium chloride 0.2%]: 5 mEq (250 mL); 10 mEq (500 mL, 1000 mL); 20 mEq (1000 mL); 30 mEq (1000 mL); 40 mEq (1000 mL)

Infusion [premixed in D_5W and sodium chloride 0.225%: 10 mEq (500 mL, 1000 mL); 20 mEq (1000 mL); 30 mEq (1000 mL); 40 mEq (1000 mL)

Infusion [premixed in D_5W and sodium chloride 0.3%]: 10 mEq (500 mL); 20 mEq (1000 mL)

Infusion [premixed in D_5W and sodium chloride 0.33%]: 10 mEq (500 mL); 20 mEq (1000 mL)

Infusion [premixed in D_5W and sodium chloride 0.45%]: 10 mEq (500 mL, 1000 mL); 20 mEq (1000 mL); 30 mEq (1000 mL); 40 mEq (1000 mL)

Infusion [premixed in D_5W and NS]: 20 mEq (1000 mL); 40 mEq (1000 mL)

Infusion [premixed in $D_{10}W$ and sodium chloride 0.2%]: 5 mEq (250 mL)

Infusion [premixed in sodium chloride 0.45%]: 20 mEq (1000 mL); 40 mEq (1000 mL)

Infusion [premixed in NS]: 20 mEq (1000 mL); 40 mEq (1000 mL)

Infusion [premixed in SWFI; highly concentrated]: 10 mEq (50 mL, 100 mL); 20 mEq (50 mL, 100 mL); 30 mEq (100 mL); 40 mEq (100 mL)

Injection, solution [concentrate]: 2 mEq/mL (5 mL, 10 mL, 15 mL, 20 mL, 30 mL, 250 mL, 500 mL)

Powder, for oral solution: 20 mEq/packet (30s, 100s, 1000s)

K-Lor™: 20 mEq/packet (30s, 100s) [fruit flavor]

Kay Ciel® 10%: 20 mEq/packet (30s, 100s) [sugar free] [DSC]

Klor-Con®: 20 mEq/packet (30s, 100s) [sugar free; fruit flavor]

Klor-Con®/25: 25 mEq/packet (30s, 100s) [sugar free; fruit flavor]

Solution, oral: 20 mEq/15 mL (15 mL, 30 mL, 480 mL, 3840 mL); 40 mEq/15 mL (15 mL, 480 mL)

Tablet, extended release: 8 mEq [600 mg]; 10 mEq [750 mg]; 20 mEq [1500 mg]

K-Tab®: 10 mEq [750 mg]

Kaon-Cl® 10: 10 mEq [750 mg]

Tablet, extended release, microencapsulated: 10 mEq, 20 mEq

Klor-Con® M10: 10 mEq [750 mg]

Klor-Con® M15: 15 mEq [1125 mg; scored]

Klor-Con® M20: 20 mEq [1500 mg; scored]

Tablet, extended release, wax matrix: 8 mEq, 10 mEq

Klor-Con® 8: 8 mEq [600 mg]

Clor-Con® 10: 10 mEq [750 mg]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsule, controlled release (Micro-K)

8 mEq (30): $36.35

10 mEq (30): $41.95

Capsule, controlled release (Potassium Chloride CR)

10 mEq (30): $26.27

Liquid (Kaon-Cl)

40 MEQ/15ML (20%) (480): $49.01

Liquid (Potassium Chloride)

20 MEQ/15ML (10%) (473): $11.99

40 MEQ/15ML (20%) (240): $12.00

Liquid (Rum-K-SF)

15% (480): $46.99

Pack (K-Lor)

20 mEq (30): $54.99

Pack (Kay Ciel)

20 mEq (30): $58.99

Pack (Klor-Con)

20 mEq (100): $22.99

25 mEq (30): $15.99

Tablet, controlled release (K-Dur)

10 mEq (100): $38.96

Tablet, controlled release (K-Tabs)

10 mEq (100): $63.84

Tablet, controlled release (Kaon-Cl-10)

10 mEq (100): $25.99

Tablet, controlled release (Klor-Con)

8 mEq (30): $12.99

Tablet, controlled release (Klor-Con M15)

15 mEq (30): $13.40

Tablet, controlled release (Klor-Con M20)

20 mEq (100): $43.99

Tablet, controlled release (Klotrix)

10 mEq (100): $34.99

Tablet, controlled release (Potassium Chloride CR)

10 mEq (100): $24.99

Tablet, controlled release (Potassium Chloride Crys CR)

10 mEq (100): $24.99

20 mEq (30): $11.99

Mechanism of ActionPotassium is the major cation of intracellular fluid and is essential for the conduction of nerve impulses in heart, brain, and skeletal muscle; contraction of cardiac, skeletal and smooth muscles; maintenance of normal renal function, acid-base balance, carbohydrate metabolism, and gastric secretion

Pharmacodynamics/Kinetics

Absorption: Well absorbed from upper GI tract

Distribution: Enters cells via active transport from extracellular fluid

Excretion: Primarily urine; skin and feces (small amounts); most intestinal potassium reabsorbed

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause GI side effects; concomitant use with SSRIs, carbamazepine, valproic acid, and lithium may produce additive effects. Anticholinergic agents (many psychotropics possess anticholinergic activity) may enhance the ulcerogenic effects of potassium chloride.

Cardiovascular ConsiderationsHypokalemia is highly arrhythmogenic, particularly in the setting of ischemia or digitalis toxicity. ECG evidence of hypokalemia includes flattening of the T wave. As the T wave shrinks, U waves may appear. There is no prolongation of the QT interval. Hyperkalemia may present as tall peaked symmetrical T waves. S-T elevation may present in severe hyperkalemia. QRS complex progressively widens with eventual apparent sine waves on the ECG. Hyperkalemia will also induce cardiac slowing and AV conduction abnormalities.

Index TermsKCl

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International Brand NamesAcronitol (GR); Addi-K (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SL, SN, TN, TW, TZ, UG, ZA, ZM, ZW); Apo-K (MY); Beacon K SR (MY); Chloropotassuril (BE); Corpotasin (MX); Diffu-K (FR); Durekal (FI); Duro-K 600 (AU); K-Contin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); K-Contin Continus (KP); K-Dur (MX); K-Tab (BB, BM, BS, BZ, GY, JM, NL, PK, PR, SR, TT); Kaldyum (PL); Kaleorid (DK, FR, NO, SE); Kalimat prolongatum (PL); Kalinor-Retard P (DE); Kalinorm (FI); Kalipoz prolongatum (PL); Kalium (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, PH, PL, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Kalium chloratum (PL); Kalium-Durettes (NL); Kalium-R (CH, HN); Kay-Cee-L (GB, IE); KCL Retard (AE, AT, BH, CY, CZ, EG, GR, HN, IL, IQ, IR, IT, JO, KW, LB, LY, OM, QA, SA, SY, YE); Kelefusin (MX); Keylyte (IN); KSR (ID); KSR 600 (AU); Lento-Kalium (IT); Micro-K Extentcaps (BB, BM, BS, BZ, GY, JM, NL, PR, SR, TT); Micro-Kalium Retard (AT); Nu-K (IE); Perennum (PY); Rekawan (DE); Rekawan Retard (AT); Sando-K (GB); Slow-K (AE, AR, AU, BB, BF, BH, BJ, BM, BS, BZ, CI, CN, CY, EG, ET, GB, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Span-K (AU, MY)

Potassium Citrate and Citric Acid

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(poe TASS ee um SIT rate & SI trik AS id)
U.S. Brand NamesCytra-K; Polycitra®-K
Pharmacologic CategoryAlkalinizing Agent, Oral
Use: Labeled IndicationsTreatment of metabolic acidosis; alkalinizing agent in conditions where long-term maintenance of an alkaline urine is desirable
Dosing: Adults**Urine alkalizing agent:** Oral:

Powder: One packet dissolved in water after meals and at bedtime; adjust dose to urinary pH

Solution: 15-30 mL after meals and at bedtime; adjust dose based on urinary pH

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Urine alkalizing agent:** Oral: Solution: 5-15 mL after meals and at bedtime; adjust dose based on urinary pH
Administration: OralDilute with water prior to administration; doses may be chilled to improve palatability. Follow dose with additional water or juice.
StorageStore at controlled room temperature. Protect from excessive heat or freezing. Diluted formulations may be refrigerated to improve palatability.
Reconstitution

Powder: Dilute contents of each packet with at least 6 ounces of water.

Solution: Dilute each dose with water (at least 6 ounces for adults doses).

ContraindicationsSevere renal insufficiency, oliguria, or azotemia; potassium-restricted diet; untreated Addison's disease; adynamia episodica hereditaria; acute dehydration; heat cramps; anuria; severe myocardial damage; hyperkalemia from any cause
Warnings/Precautions

Concerns related to adverse effects:

- GI effects: May cause GI upset (eg, nausea, vomiting, diarrhea, abdominal pain, discomfort) and lead to GI ulceration, bleeding, perforation and/or obstruction.
- Hyperkalemia: Close monitoring of serum potassium concentrations is needed to avoid hyperkalemia; severe hyperkalemia may lead to muscle weakness/paralysis and cardiac conduction abnormalities (eg, heart block, ventricular arrhythmias, asystole).

Disease-related concerns:

- Acid/base disorders: Use with caution in patients with acid/base alterations; changes in serum potassium concentrations can occur during acid/base correction, monitor closely.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (eg, heart failure, cardiac arrhythmias); patients may be more susceptible to life-threatening cardiac effects associated with hyper/hypokalemia.
- Hepatic impairment: Citrate is converted to bicarbonate in the liver; this conversion may be blocked in patients in hepatic failure.
- Potassium-altering conditions/disorders: Use with caution in patients with disorders or conditions likely to contribute to altered serum potassium and hyperkalemia (eg, untreated Addison's disease, heat cramps, severe tissue breakdown from trauma or burns).
- Renal impairment: Use with caution in patients with renal impairment; monitor serum potassium concentrations closely. Contraindicated with severe impairment.
- Severely ill: Citrate is converted to bicarbonate in the liver; this conversion may be blocked in patients who are severely ill or in shock.

Concurrent drug therapy issues:

- Digitalis: Use with caution in digitalized patients; may be more susceptible to potentially life-threatening cardiac effects with rapid changes in serum potassium concentrations.
- Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (eg, ACEI, potassium-sparing diuretics, potassium containing salt substitutes).

Pregnancy Risk FactorA
LactationExcretion in breast milk unknown/compatible
Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aluminum Hydroxide: Citric Acid Derivatives may increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/Monitoring

See individual agent for Potassium Citrate.

Monitoring: Lab TestsSerum potassium, serum bicarbonate

Patient Education

See individual agent for Potassium Citrate.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: Equivalent to potassium 2 mEq/mL and bicarbonate 2 mEq/mL

Powder for solution, oral:

Cytra-K: Potassium citrate monohydrate 3300 mg and citric acid 1002 mg per packet (100s) [sugar free; fruit flavor]

Polycitra®-K: Potassium citrate monohydrate 3300 mg and citric acid 1002 mg per packet (100s) [sugar free]

Solution:

Cytra-K: Potassium citrate monohydrate 1100 mg and citric acid monohydrate 334 mg per 5 mL (480 mL) [alcohol free, sugar free; contains sodium benzoate; berry citrus flavor]

Polycitra®-K: Potassium citrate monohydrate 1100 mg and citric acid monohydrate 334 mg per 5 mL (480 mL) [alcohol free, sugar free]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Pack (Cytra K Crystals)

1002-3300 mg (100): $85.50

Solution (Cytra-K)

1100-334 mg/5 mL (473): $21.00

Solution (Polycitra-K)

1100-334 mg/5 mL (473): $45.98

Pharmacodynamics/Kinetics

Metabolism: To potassium bicarbonate; citric acid is metabolized to CO_2 and H_2O

Excretion: Urine

Related Information

- Potassium Citrate

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Mental Health CommentHypokalemia is associated with an increased risk of ventricular dysrhythmias; use antipsychotics with caution (especially ziprasidone).

Cardiovascular ConsiderationsHypokalemia is highly arrhythmogenic, particularly in the setting of ischemia or digitalis toxicity. ECG evidence of hypokalemia includes flattening of the T wave. As the T wave shrinks, U waves may appear. There is no prolongation of the QT interval. Hyperkalemia may present as tall peaked symmetrical T waves. S-T elevation may present in severe hyperkalemia. QRS complex progressively widens with eventual apparent sine waves on the ECG. Hyperkalemia will also induce cardiac slowing and AV conduction abnormalities.

Index TermsCitric Acid and Potassium Citrate

Potassium Citrate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Urocit®-K may be confused with Urised®

Pronunciation(poe TASS ee um SIT rate)
U.S. Brand NamesUrocit®-K
Canadian Brand NamesK-Citra®; K-Lyte®; Polycitra®-K
Pharmacologic CategoryAlkalinizing Agent
Use: Labeled IndicationsPrevention of uric acid nephrolithiasis; prevention of calcium renal stones in patients with hypocitraturia; urinary alkalinizer when sodium citrate is contraindicated
Dosing: Adults**Alkalinizer, bicarbonate precursor:** Oral: 10-20 mEq 3 times/day with meals up to 100 mEq/day
Dosing: ElderlyRefer to adult dosing.
Administration: OralSwallow tablets whole with a full glass of water.
Dietary ConsiderationsMay be taken with meals.
StorageStore in a cool, dry place.
ContraindicationsSevere renal insufficiency; sodium-restricted diet (sodium citrate); untreated Addison's disease; severe myocardial damage; acute dehydration; patients with hyperkalemia; patients with delayed gastric emptying, esophageal compression, intestinal obstruction or stricture, or those taking anticholinergic medication; patients with active urinary tract infection
Warnings/Precautions

Concerns related to adverse effects:

- GI effects: May cause GI upset (eg, nausea, vomiting, diarrhea, abdominal pain, discomfort) and lead to GI ulceration, bleeding, perforation and/or obstruction. Oral liquid preparations (not solid) should be used in patients with esophageal compression or delayed gastric emptying.

- Hyperkalemia: Close monitoring of serum potassium concentrations is needed to avoid hyperkalemia; severe hyperkalemia may lead to muscle weakness/paralysis and cardiac conduction abnormalities (eg, heart block, ventricular arrhythmias, asystole).

Disease-related concerns:

- Acid/base disorders: Use with caution in patients with acid/base alterations; changes in serum potassium concentrations can occur during acid/base correction, monitor closely.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (eg, heart failure, cardiac arrhythmias); patients may be more susceptible to life-threatening cardiac effects associated with hyper/hypokalemia.

- Hepatic impairment: Citrate is converted to bicarbonate in the liver; this conversion may be blocked in patients in hepatic failure.

- Potassium-altering conditions/disorders: Use with caution in patients with disorders or conditions likely to contribute to altered serum potassium and hyperkalemia (eg, untreated Addison's disease, heat cramps, severe tissue breakdown from trauma or burns).

- Renal impairment: Use with caution in patients with renal impairment; monitor serum potassium concentrations closely. Contraindicated with severe impairment.

- Severely ill: Citrate is converted to bicarbonate in the liver; this conversion may be blocked in patients who are severely ill or in shock.

Concurrent drug therapy issues:

- Digitalis: Use with caution in digitalized patients; may be more susceptible to potentially life-threatening cardiac effects with rapid changes in serum potassium concentrations.

- Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (eg, ACEI, potassium-sparing diuretics, potassium containing salt substitutes).

Pregnancy Risk FactorNot available
LactationEnters breast milk/compatible
Adverse Reactions

>10%: Gastrointestinal: Diarrhea, nausea, stomach pain, flatulence, vomiting (oral)

1% to 10%:

Cardiovascular: Bradycardia

Endocrine & metabolic: Hyperkalemia, metabolic alkalosis in patients with severe renal failure

Neuromuscular & skeletal: Weakness

Respiratory: Dyspnea

<1% (Limited to important or life-threatening): Arrhythmias, chest pain, heart block, hypotension

Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aluminum Hydroxide: Citric Acid Derivatives may increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/Monitoring Assess effectiveness and interactions of other medications patient may be taking. Assess kidney function prior to starting therapy. Monitor cardiac status and serum potassium at beginning of therapy and at regular intervals with long-term therapy. Assess knowledge/teach patient appropriate use, recommended diet, and adverse symptoms to report.

Monitoring: Lab Tests Serum potassium, serum bicarbonate

Patient Education Take as directed; do not take more than directed. Swallow tablet whole with full glass of water or juice and stir before sipping slowly, with or after meals (do not take on an empty stomach). Take any antacids 2 hours before or after potassium. Consult prescriber about advisability of increasing dietary potassium. Report tingling of hands or feet; unresolved nausea or vomiting; chest pain or palpitations; persistent abdominal pain; feelings of weakness, dizziness, listlessness, confusion; acute muscle weakness or cramping; blood in stool or tarry stools; or easy bruising or unusual bleeding.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 540 mg [5 mEq]; 1080 mg [10 mEq]

Urocit®-K: 540 mg [5 mEq]; 1080 mg [10 mEq]

Tablet, extended release: 540 mg [5 mEq]; 1080 mg [10 mEq]

Generic Available Yes

Pricing: U.S. (www.drugstore.com)

Tablet, controlled release (Potassium Citrate)

540 mg (100): $28.99

1080 mg (90): $34.99

Tablet, controlled release (Urocit-K 10)

1080 mg (100): $57.99

Tablet, controlled release (Urocit-K 5)

540 mg (100): $43.99

Pharmacodynamics/Kinetics Metabolism: Hepatic to bicarbonate

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment Contraindicated in patients receiving anticholinergic medications. GI side effects are common; use caution with SSRIs, lithium, and valproic acid.

Mental Health Comment Hypokalemia is associated with an increased risk of ventricular dysrhythmias; use antipsychotics with caution (especially ziprasidone).

Cardiovascular Considerations Hypokalemia is highly arrhythmogenic, particularly in the setting of ischemia or digitalis toxicity. ECG evidence of hypokalemia includes flattening of the T wave. As the T wave shrinks, U waves may appear. There is no prolongation of the QT interval. Hyperkalemia may present as tall peaked symmetrical T waves. S-T elevation may present in severe hyperkalemia. QRS complex progressively widens with eventual apparent sine waves on the ECG. Hyperkalemia will also induce cardiac slowing and AV conduction abnormalities.

International Brand Names Acelka (TH); Kajos (NO, SE); Kalium granulat bezcukrowy (PL); Kation (IT); Litocid (PL); Urocit-K (AU, BR, HK, MY, TW)

Potassium Gluconate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(poe TASS ee um GLOO coe nate)

Pharmacologic CategoryElectrolyte Supplement, Oral

Use: Labeled IndicationsTreatment or prevention of hypokalemia

Dosing: Adults**Note:** Doses listed as mEq of potassium:

Normal daily requirement: Oral: 40-80 mEq/day

Prevention of hypokalemia during diuretic therapy: Oral: 16-24 mEq/day in 1-2 divided doses

Treatment of hypokalemia: Oral: 40-100 mEq/day in 2-4 divided doses

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** Doses listed as mEq of potassium:

Normal daily requirement: Oral: 2-3 mEq/kg/day

Prevention of hypokalemia during diuretic therapy: Oral: 1-2 mEq/kg/day in 1-2 divided doses

Treatment of hypokalemia: Oral: 2-5 mEq/kg/day in 2-4 divided doses

StorageStore at room temperature.

ContraindicationsSevere renal impairment, untreated Addison's disease, heat cramps, hyperkalemia, severe tissue trauma; solid oral dosage forms are contraindicated in patients in whom there is a structural, pathological, and/or pharmacologic cause for delay or arrest in passage through the GI tract

Warnings/Precautions

Concerns related to adverse effects:

- GI effects: May cause GI upset (eg, nausea, vomiting, diarrhea, abdominal pain, discomfort) and lead to GI ulceration, bleeding, perforation and/or obstruction. Oral liquid preparations (not solid) should be used in patients with esophageal compression or delayed gastric emptying.

- Hyperkalemia: Close monitoring of serum potassium concentrations is needed to avoid hyperkalemia; severe hyperkalemia may lead to muscle weakness/paralysis and cardiac conduction abnormalities (eg, heart block, ventricular arrhythmias, asystole).

Disease-related concerns:

- Acid/base disorders: Use with caution in patients with acid/base alterations; changes in serum potassium concentrations can occur during acid/base correction, monitor closely.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (eg, heart failure, cardiac arrhythmias); patients may be more susceptible to life-threatening cardiac effects associated with hyper/hypokalemia.

- Potassium-altering conditions/disorders: Use with caution in patients with disorders or conditions likely to contribute to altered serum potassium and hyperkalemia (eg, untreated Addison's disease, heat cramps, severe tissue breakdown from trauma or burns).

- Renal impairment: Use with caution in patients with renal impairment; monitor serum potassium concentrations closely. Contraindicated with severe impairment.

Concurrent drug therapy issues:

- Digitalis: Use with caution in digitalized patients; may be more susceptible to potentially life-threatening cardiac effects with rapid changes in serum potassium concentrations.

- Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (eg, ACEI, potassium-sparing diuretics, potassium containing salt substitutes).

Geriatric ConsiderationsElderly may require less potassium than younger adults due to decreased renal function. For the elderly who do not respond to replacement therapy, check serum magnesium. Long-term use of diuretics may result in hypomagnesemia.

Pregnancy Risk FactorA

Adverse Reactions

>10%: Gastrointestinal: Diarrhea, nausea, stomach pain, flatulence, vomiting (oral)

1% to 10%:

Cardiovascular: Bradycardia

Endocrine & metabolic: Hyperkalemia

Neuromuscular & skeletal: Weakness

Respiratory: Dyspnea

<1%: Alkalosis, chest pain, mental confusion, paralysis, paresthesia, phlebitis, throat pain

Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Test Interactions Decreased ammonia (B)

Monitoring Parameters Serum potassium, chloride, glucose, pH, urine output (if indicated)

Monitoring: Lab Tests Serum potassium

Patient Education Take with food, water, or fruit juice. Swallow tablets whole; do not crush or chew.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet: 595 mg [equivalent to potassium 99 mg]

Capsule: 99 mg [strength expressed as base]

Tablet: 99 mg [strength expressed as base]; 550 mg [equivalent to potassium 90 mg]; 595 mg [equivalent to potassium 99 mg]

Tablet, timed release: 95 mg [strength expressed as base]

Generic Available Yes

Mechanism of Action Potassium is the major cation of intracellular fluid and is essential for the conduction of nerve impulses in heart, brain, and skeletal muscle; contraction of cardiac, skeletal and smooth muscles; maintenance of normal renal function, acid-base balance, carbohydrate metabolism, and gastric secretion

Pharmacodynamics/Kinetics

Absorption: Well absorbed from upper GI tract

Distribution: Enters cells via active transport from extracellular fluid

Excretion: Primarily urine; skin and feces (small amounts); most intestinal potassium reabsorbed

Pharmacotherapy Pearls9.4 g potassium gluconate is approximately equal to 40 mEq potassium (4.3 mEq potassium/g potassium gluconate).

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Cardiovascular Considerations Hypokalemia is highly arrhythmogenic, particularly in the setting of ischemia or digitalis toxicity. ECG evidence of hypokalemia includes flattening of the T wave. As the T wave shrinks, U waves may appear. There is no prolongation of the QT interval. Hyperkalemia may present as tall peaked symmetrical T waves. S-T elevation may present in severe hyperkalemia. QRS complex progressively widens with eventual apparent sine waves on the ECG. Hyperkalemia will also induce cardiac slowing and AV conduction abnormalities.

International Brand Names Ion-K (CO); Kalium gluconicum (PL); Ultra-K (BE)

Potassium Iodide and Iodine

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Jump To Field (Select Field Name)

Medication Safety Issues
Sound-alike/look-alike issues:

Potassium iodide and iodine (Strong Iodide Solution or Lugol's solution) may be confused with potassium iodide products, including saturated solution of potassium iodide (SSKI®)

Pronunciation(poe TASS ee um EYE oh dide & EYE oh dine)
Pharmacologic CategoryAntithyroid Agent
Use: Labeled IndicationsReduce thyroid vascularity prior to thyroidectomy and management of thyrotoxic crisis; block thyroidal uptake of radioactive isotopes of iodine in a radiation emergency or other exposure to radioactive iodine
Dosing: Adults**RDA**, Adults: 150 mcg (iodine)
Preoperative thyroidectomy: Oral: 0.1-0.3 mL (3-5 drops) of strong iodine (Lugol's solution) 3 times/day; administer for 10 days before surgery

Thyrotoxic crisis: Oral: 1 mL strong iodine (Lugol's solution) 3 times/day

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Refer to adult dosing.

StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light and keep container tightly closed.
ContraindicationsHypersensitivity to iodine or any component of the formulation; hyperkalemia; pulmonary edema; impaired renal function; hyperthyroidism; iodine-induced goiter; dermatitis herpetiformis; hypocomplementemic vasculitis
Warnings/Precautions

Concerns related to adverse effects:

- Hypothyroidism: Prolonged use can lead to hypothyroidism.

- Skin reactions: Can cause acne flare-ups and/ or dermatitis.

Disease-related concerns:

- Adrenal insufficiency: Use with caution in patients with Addison's disease.

- Bronchitis: Use with caution in patients with acute bronchitis.

- Cardiac disease: Use with caution in patients with cardiac disease.

- Cystic fibrosis: May have an exaggerated response.

- Myotonia congenita: Use with caution in patients with myotonia congenita.

- Thyroid disease: Use with caution in patients with a history of thyroid disease.

- Tuberculosis: Use with caution in patients with tuberculosis.

Concurrent drug therapy issues:

- Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (eg, ACEI, potassium-sparing diuretics, potassium containing salt substitutes).

Geriatric ConsiderationsElderly may have reduced renal function and require close monitoring of serum potassium. May be also recommended to check serum magnesium.
Pregnancy Risk FactorD (potassium iodide)
Pregnancy ConsiderationsIodide crosses the placenta (may cause hypothyroidism and goiter in fetus/newborn). Use for protection against thyroid cancer secondary to radioactive iodine exposure is considered acceptable based upon risk/benefit, keeping in mind the dose and duration. Repeat dosing should be avoided if possible. Refer to Iodine for additional information.
LactationEnters breast milk/use caution (AAP rates “compatible”)
Breast-Feeding ConsiderationsAAP considers this drug "compatible," but recommends avoiding breast-feeding following radioactive iodine exposure unless no alternative is available. Skin rash in the nursing infant has been reported with maternal intake of potassium iodide. Refer to Iodine monograph for additional information.
Adverse ReactionsFrequency not defined.
Cardiovascular: Irregular heart beat

Central nervous system: Confusion, tiredness, fever

Dermatologic: Skin rash

Endocrine & metabolic: Goiter, salivary gland swelling/tenderness, thyroid adenoma, swelling of neck/throat, myxedema, lymph node swelling, hyper-/hypothyroidism

Gastrointestinal: Diarrhea, gastrointestinal bleeding, metallic taste, nausea, stomach pain, stomach upset, vomiting

Neuromuscular & skeletal: Numbness, tingling, weakness, joint pain

Miscellaneous: Chronic iodine poisoning (with prolonged treatment/high doses); iodism, hypersensitivity reactions (angioedema, cutaneous and mucosal hemorrhage, serum sickness-like symptoms)

Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Lithium: Potassium Iodide may enhance the adverse/toxic effect of Lithium. Specifically the hypothyroid/goiter-potentiating effects. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Sodium Iodide I131: Antithyroid Agents may diminish the therapeutic effect of Sodium Iodide I131. Management: Discontinue antithyroid therapy 3-4 days prior to sodium iodide I-131 administration. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antithyroid Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Test InteractionsMay alter thyroid function tests.

Monitoring Parameters

Thyroid function tests, signs/symptoms of hyperthyroidism; thyroid function should be monitored in pregnant women, neonates, and young infants if repeat doses are required following radioactive iodine exposure

Nursing: Physical Assessment/MonitoringUse caution in presence of history of thyroid disease, Addison's disease, cardiac disease, myotonia congenital, tuberculosis, or acute bronchitis. Assess potential for interactions with other pharmacological agents or herbal products patient is taking that may increase risk of hyperkalemia, hypokalemia., or additive hypothyroid effects. Assess need for laboratory monitoring, therapeutic effects (according to purpose for use), and adverse reactions. Teach patient or caregiver purpose for use, necessity for contraception for sexually active female patients, possible side effects/appropriate interventions, and adverse symptoms to report (refer to Patient Education).

Patient EducationTake this medication exactly as directed; do not exceed recommended dosage. May cause metallic taste, nausea, or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); soreness of teeth, gums, or glands (use soft toothbrush and frequent mouth rinses; fever, headache or sore joints (consult prescriber for approved analgesic); confusion or tiredness (use caution when driving or engaged in potential hazardous tasks until response to medication is known). Report immediately any swelling of lips, mouth, or tongue; difficulty swallowing; chest pain or irregular heartbeat; muscle weakness; eye irritation or eyelid swelling; skin rash or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause fetal defects. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral: Potassium iodide 100 mg/mL and iodine 50 mg/mL (480 mL)

Solution, topical: Potassium iodide 100 mg/mL and iodine 50 mg/mL (8 mL)

Generic AvailableYes

Mechanism of ActionInhibits secretion of thyroid hormone, fosters colloid accumulation in thyroid follicles. Following radioactive iodine exposure, potassium iodide blocks uptake of radioiodine by the thyroid, reducing the risk of thyroid cancer.

Pharmacodynamics/Kinetics

Onset of action: Hyperthyroidism: 24-48 hours

Peak effect: 10-15 days after continuous therapy

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Metallic taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or confusion

Mental Health: Effects on Psychiatric TreatmentConcurrent use with lithium may produce additive hypothyroid effects

Index TermsLugol's Solution; Strong Iodine Solution

Potassium Iodide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Potassium iodide products, including saturated solution of potassium iodide (SSKI®) may be confused with potassium iodide and iodine (Strong Iodide Solution or Lugol's solution)

Pronunciation(poe TASS ee um EYE oh dide)
U.S. Brand NamesIosat™ [OTC]; SSKI®; ThyroSafe™ [OTC]; ThyroShield™ [OTC]
Pharmacologic CategoryAntithyroid Agent; Expectorant
Use: Labeled IndicationsExpectorant for the symptomatic treatment of chronic pulmonary diseases complicated by mucous; reduce thyroid vascularity prior to thyroidectomy and management of thyrotoxic crisis; block thyroidal uptake of radioactive isotopes of iodine in a radiation emergency or other exposure to radioactive iodine
Use: Unlabeled/InvestigationalLymphocutaneous and cutaneous sporotrichosis
Dosing: Adults

RDA: 150 mcg (iodine)

Expectorant: Oral: *SSKI®:* 300-600 mg 3-4 times/day

Preoperative thyroidectomy: Oral: 50-250 mg (1-5 drops SSKI®) 3 times/day; administer for 10 days before surgery

To reduce risk of thyroid cancer following nuclear accident (Iosat™, ThyroSafe™, ThyroShield™): Oral: Children >68 kg and Adults (including pregnant/lactating women): Oral: 130 mg once daily. **Note:** Dosing should continue until risk of exposure has passed or other measures have are implemented.

Thyrotoxic crisis: Oral: 300-500 mg (6-10 drops SSKI®) 3 times/day

Sporotrichosis (cutaneous, lymphocutaneous; unlabeled use): Oral: Initial: 5 drops (SSKI®) 3 times/day; increase to 40-50 drops (SSKI®) 3 times/day as tolerated for 3-6 months

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Preoperative thyroidectomy: Refer to adult dosing.

To reduce risk of thyroid cancer following nuclear accident (Iosat™, ThyroSafe™, ThyroShield™): Oral:

Infants <1 month: 16.25 mg once daily

Children 1 month to 3 years: 32.5 mg once daily

Children 3-18 years: 65 mg once daily

Children >68 kg: Refer to adult dosing

Note: Dosing should continue until risk of exposure has passed or other measures are implemented.

Thyrotoxic crisis: Oral:

Infants <1 year: 150-250 mg (3-5 drops SSKI®) 3 times/day

Children: Refer to adult dosing.

Administration: OralSSKI®: Dilute in a glassful of water, fruit juice or milk. Take with food to decrease gastric irritation
Dietary ConsiderationsSSKI®: Take with food to decrease gastric irritation.
StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light. Keep tightly closed.

SSKI®: If exposed to cold, crystallization may occur. Warm and shake to redissolve. If solution becomes brown/yellow, it should be discarded.

Reconstitution

SSKI®: May be mixed in water, fruit juice, or milk.

Preparation of oral solution:

Concentration of 16.25 mg/5 mL oral solution: Crush one 130 mg tablet into a fine powder. Add 20 mL of water and mix until powder is dissolved. Add an additional 20 mL of low-fat milk (white or chocolate), orange juice, flat soda, raspberry syrup or infant formula. Final concentration will be 16.25 mg/5 mL. Stable for 7 days under refrigeration.

Concentration of 8.125 mg/5 mL oral solution: Crush one 65 mg tablet into a fine powder. Add 20 mL of water and mix until powder is dissolved. Add an additional 20 mL of low-fat milk (white or chocolate), orange juice, flat soda, raspberry syrup, or infant formula. Final concentration will be 8.125 mg/5 mL. Stable for 7 days under refrigeration.

Extemporaneously PreparedPreparation of oral solution:

Concentration of 16.25 mg/5 mL oral solution: Crush one 130 mg tablet into a fine powder. Add 20 mL of water and mix until powder is dissolved. Add an additional 20 mL of low-fat milk (white or chocolate), orange juice, flat soda, raspberry syrup or infant formula. Final concentration will be 16.25 mg/5 mL.

Concentration of 8.125 mg/5 mL oral solution: Crush one 65 mg tablet into a fine powder. Add 20 mL of water and mix until powder is dissolved. Add an additional 20 mL of low-fat milk (white or chocolate), orange juice, flat soda, raspberry syrup, or infant formula. Final concentration will be 8.125 mg/5 mL.

ContraindicationsHypersensitivity to iodine or any component of the formulation; hyperkalemia; pulmonary edema; impaired renal function; hyperthyroidism; iodine-induced goiter; dermatitis herpetiformis; hypocomplementemic vasculitis

Warnings/Precautions

Concerns related to adverse effects:

- Hypothyroidism: Prolonged use can lead to hypothyroidism.

- Skin reactions: Can cause acne flare-ups and/ or dermatitis.

Disease-related concerns:

- Adrenal insufficiency: Use with caution in patients with Addison's disease.

- Bronchitis: Use with caution in patients with acute bronchitis.

- Cardiac disease: Use with caution in patients with cardiac disease.

- Cystic fibrosis: May have an exaggerated response.

- Myotonia congenita: Use with caution in patients with myotonia congenita.

- Thyroid disease: Use with caution in patients with a history of thyroid disease.

- Tuberculosis: Use with caution in patients with tuberculosis.

Concurrent drug therapy issues:

- Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (eg, ACEI, potassium-sparing diuretics, potassium containing salt substitutes).

Pregnancy Risk FactorD

Pregnancy ConsiderationsIodide crosses the placenta (may cause hypothyroidism and goiter in fetus/newborn). Use as an expectorant during pregnancy is contraindicated by the AAP. Use for protection against thyroid cancer secondary to radioactive iodine exposure is considered acceptable based upon risk/benefit, keeping in mind the dose and duration. Repeat dosing should be avoided if possible. Refer to Iodine for additional information.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsAAP considers this drug compatible, but recommends avoiding breast-feeding following radioactive iodine exposure unless no alternative is available. May cause skin rash in nursing infant. Refer to Iodine for additional information.

Adverse ReactionsFrequency not defined.

Cardiovascular: Irregular heart beat

Central nervous system: Confusion, tiredness, fever

Dermatologic: Skin rash

Endocrine & metabolic: Goiter, salivary gland swelling/tenderness, thyroid adenoma, swelling of neck/throat, myxedema, lymph node swelling, hyper-/hypothyroidism

Gastrointestinal: Diarrhea, gastrointestinal bleeding, metallic taste, nausea, stomach pain, stomach upset, vomiting

Neuromuscular & skeletal: Numbness, tingling, weakness, joint pain

Miscellaneous: Chronic iodine poisoning (with prolonged treatment/high doses); iodism, hypersensitivity reactions (angioedema, cutaneous and mucosal hemorrhage, serum sickness-like symptoms)

Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Lithium: Potassium Iodide may enhance the adverse/toxic effect of Lithium. Specifically the hypothyroid/goiter-potentiating effects. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Sodium Iodide I131: Antithyroid Agents may diminish the therapeutic effect of Sodium Iodide I131. Management: Discontinue antithyroid therapy 3-4 days prior to sodium iodide I-131 administration. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antithyroid Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Test InteractionsMay alter thyroid function tests.

Monitoring ParametersThyroid function tests, signs/symptoms of hyperthyroidism; thyroid function should be monitored in pregnant women, neonates, and young infants if repeat doses are required following radioactive iodine exposure

Nursing: Physical Assessment/MonitoringUse with caution in presence of history of thyroid disease, Addison's disease, cardiac disease, myotonia congenital, tuberculosis, or acute bronchitis. Assess potential for interactions with other pharmacological agents or herbal products patient is taking that may increase risk of hyperkalemia, hypokalemia, or additive hypothyroid effects. Assess need for laboratory monitoring, therapeutic effects (according to purpose for use), and adverse reactions. Teach patient purpose for use, necessity for contraception, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsThyroid function

Patient EducationTake this medication exactly as directed; do not exceed recommended dosage. Dilute SSKI® in glassful of water, fruit juice, or milk with meals to reduce gastric irritation. May cause metallic taste, nausea, or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); soreness of teeth, gums, or glands (use soft toothbrush and frequent mouth rinses); fever, headache or sore joints (consult prescriber for approved analgesic); confusion or tiredness (use caution when driving or engaged in potential hazardous tasks until response to medication is known). Discontinue and report any swelling of lips, mouth, or tongue; difficulty swallowing; chest pain or irregular heartbeat; unusual muscle weakness; eye irritation or eyelid swelling; skin rash or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause fetal defects. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral:

SSKI®: 1 g/mL (30 mL, 240 mL) [contains sodium thiosulfate]

ThyroShield™: 65 mg/mL (30 mL) [black raspberry flavor]

Tablet:

Iosat™: 130 mg

ThyroSafe™: 65 mg [equivalent to iodine 50 mg]

Pricing: U.S. (www.drugstore.com)

Solution (SSKI)

1 g/mL (237): $55.98

Mechanism of ActionReduces viscosity of mucus by increasing respiratory tract secretions; inhibits secretion of thyroid hormone, fosters colloid accumulation in thyroid follicles. Following radioactive iodine exposure, potassium iodide blocks uptake of radioiodine by the thyroid, reducing the risk of thyroid cancer.

Pharmacodynamics/Kinetics

Onset of action: Hyperthyroidism: 24-48 hours

Peak effect: 10-15 days after continuous therapy

Duration: Radioactive iodine exposure: ~24 hours

Pharmacotherapy Pearls10 drops of SSKI® = potassium iodide 500 mg

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Metallic taste.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentConcurrent use with lithium may produce additive hypothyroid effects

Cardiovascular ConsiderationsHypokalemia is highly arrhythmogenic, particularly in the setting of ischemia or digitalis toxicity. ECG evidence of hypokalemia includes flattening of the T wave. As the T wave shrinks, U waves may appear. There is no prolongation of the QT interval. Hyperkalemia may present as tall peaked symmetrical T waves. S-T elevation may present in severe hyperkalemia. QRS complex progressively widens with eventual apparent sine waves on the ECG. Hyperkalemia will also induce cardiac slowing and AV conduction abnormalities.

Index TermsKI

References

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"Potassium Iodide as a Thyroid Blocking Agent in a Radiation Emergency: Final Recommendations on Use," Washington DC, Bureau of Radiological Health and Bureau of Drugs, Food and Drug Administration, 1982.

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International Brand NamesCato-Bell (IN); Iodid (BE); Iodure de Potassium (FR); Ioduro Potasico Rovi (ES); Jodam (PL); Jodetten Henning (DE); Jodgamma (DE); Jodid (DE, HU, LU, PL); Jodid Merck (AT); Jodid Verla (DE); Jodid-ratiopharm (DE); Jodix (FI); Jodostin (PL); Jodox (PL); Kalium jodatum (DE); Kaliumiodid (CH); Kaliumiodid BC (DE); Kaliumjodid Lannacher (AT); Kaliumjodid Recip (SE); Kaliumjodid "Dak" (DK); Mono-Jod (DE); Tarjod (PL); Thyroprotect (DE)

Potassium P-Aminobenzoate

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(poe TASS ee um pe a mee noe BEN zoe ate)
U.S. Brand NamesPotaba®
Pharmacologic CategoryVitamin, Water Soluble
Use: Labeled IndicationsPresently, all indications are classified by the FDA as “possibly effective.”

Treatment of scleroderma, dermatomyositis, morphea, linear scleroderma, pemphigus, Peyronie's disease

Dosing: AdultsOral: Average dose: 12 g/day in 4-6 divided doses
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricOral: 1 g/10 pounds of weight/day; administer in divided doses
Administration: OralAll forms should be administered after meals or with a snack.

Capsule: Take with a glass of water.

Powder: Mix in glass of chilled water or juice; stir and drink.

Tablet: Crush and add to glass of chilled water or juice; stir and drink.

Dietary ConsiderationsTake with food to avoid stomach upset.
ContraindicationsHypersensitivity to potassium p-aminobenzoate or any component of the formulation; concurrent use of sulfonamides
Warnings/Precautions

Concerns related to adverse effects:

- Anorexia: Interrupt therapy if anorexia occurs; may reinstitute once patient improves.

- Nausea: Interrupt therapy if nausea occurs; may reinstitute once patient improves.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus or a history of hypoglycemia.

- Renal impairment: Use with caution in patients with renal impairment.

Pregnancy ConsiderationsSafety for use in pregnancy has not been established.
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Central nervous system: Fever

Dermatologic: Rash

Gastrointestinal: Anorexia, nausea

Miscellaneous: Hypersensitivity reaction

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 0.5 g

Potaba®: 0.5 g

Powder, for solution, oral: 2 g/packet (50s)

Potaba®: 2 g/packet (50s)

Tablet:

Potaba®: 0.5 g

Generic AvailableYes: Excludes tablet
Pricing: U.S. (www.drugstore.com)

Capsules (Aminobenzoate Potassium)

500 mg (250): $100.58

Capsules (Potaba)

500 mg (60): $41.99

Pack (Potaba)

2 g (50): $115.26

Tablets (Potaba)

500 mg (60): $43.42

Mechanism of ActionP-aminobenzoate is a member of the vitamin B complex family. It may have an antifibrotic effect due to increased oxygen uptake at the tissue level.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Potassium Perchlorate

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(poe TASS ee um per KLOR ate)
U.S. Brand NamesPerchloracap® [DSC]
Pharmacologic CategoryDiagnostic Agent
Use: Labeled IndicationsMinimizes accumulation of pertechnetate Tc 99m in imaging studies
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Avoid high humidity.
Pregnancy Risk FactorC
Pregnancy ConsiderationsPotassium perchlorate was shown to cause fetal goiter in animal studies. Elective examinations in women of childbearing potential are suggested during the first 10 days following onset of menses.
LactationExcretion in breast milk unknown/use caution
Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 200 mg [DSC]

Generic AvailableNo
ManufacturerMallinckrodt
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported

Potassium Phosphate and Sodium Phosphate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

K-Phos® Neutral may be confused with Neutra-Phos-K®

Pronunciation(poe TASS ee um FOS fate & SOW dee um FOS fate)
U.S. Brand NamesK-Phos® MF; K-Phos® Neutral; K-Phos® No. 2; Neutra-Phos® [OTC] [DSC]; Phos-NaK; Phospha 250™ Neutral; Uro-KP-Neutral®
Pharmacologic CategoryElectrolyte Supplement, Oral
Use: Labeled IndicationsTreatment of conditions associated with excessive renal phosphate loss or inadequate GI absorption of phosphate; to acidify the urine to lower calcium concentrations; to increase the antibacterial activity of methenamine; reduce odor and rash caused by ammonia in urine
Dosing: Adults**Phosphate supplement:** Oral: Elemental phosphorus 250-500 mg 4 times/day after meals and at bedtime
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Phosphate supplement:** Oral: Children ≥4 years: Elemental phosphorus 250 mg 4 times/day after meals and at bedtime
Administration: OralAdminister with food to reduce risk of diarrhea.

Caplet, tablet: Should be taken with a full glass of water.

Powder: Phos-NaK: Contents of 1 packet should be diluted in 75 mL water before administration. Following dilution of powder, solution may be chilled to increase palatability.

Dietary ConsiderationsShould be taken after meals. In addition to phosphate, products contain potassium and sodium.
ContraindicationsAddison's disease, hyperkalemia, hyperphosphatemia, infected urolithiasis or struvite stone formation, patients with severely impaired renal function
Warnings/Precautions

Disease-related concerns:

- Cardiac disease: Use with caution in patients with cardiac disease, including hypotension.
- Dehydration: Use with caution in patients with acute dehydration.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hypernatremia: Use with caution in patients with hypernatremia.
- Metabolic alkalosis: Use with caution in patients with metabolic alkalosis.
- Renal impairment: Use with caution in patients with renal impairment.

Geriatric ConsiderationsA complete drug history should be taken to rule out potential drug interactions since elderly frequently may be taking potassium and potassium-sparing diuretics or salicylates as antacids. Elderly may require less potassium than younger adults due to decreased renal function. Elderly who do not respond to replacement therapy, check serum magnesium. Long-term use of diuretics may result in hypomagnesemia.
Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, arrhythmia, chest pain, edema, tachycardia

Central nervous system: Mental confusion, tetany (with large doses of phosphate), headache, dizziness, seizure

Endocrine & metabolic: Hyperkalemia, alkalosis

Gastrointestinal: Diarrhea, nausea, stomach pain, flatulence, vomiting, throat pain, weight gain

Genitourinary: Urine output decreased

Local: Phlebitis

Neuromuscular & skeletal: Weakness, arthralgia, bone pain, paralysis, paresthesia, pain/weakness of extremities, muscle cramps

Renal: Acute renal failure

Respiratory: Dyspnea

Miscellaneous: Thirst

Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: May enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Calcium Salts: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Monitoring ParametersSerum potassium, sodium, calcium, phosphate, ECG

Nursing: Physical Assessment/MonitoringSee individual agent for Potassium Phosphate.

Monitoring: Lab TestsSerum potassium, phosphate

Patient EducationSee individual agent for Potassium Phosphate.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet:

Uro-KP-Neutral®: Dipotassium phosphate, disodium phosphate, and monobasic sodium phosphate [equivalent to elemental phosphorus 258 mg, sodium 262.4 mg (10.8 mEq), and potassium 49.4 mg (1.3 mEq)]

Powder, for oral solution:

Neutra-Phos®: Dibasic potassium phosphate, monobasic potassium phosphate, dibasic sodium phosphate, and monosodium phosphate per packet (100s) [equivalent to elemental phosphorus 250 mg (14.25 mEq), sodium 164 mg (7.1 mEq), and potassium 278 mg (7.1 mEq) per packet] [DSC]

Phos-NaK: Dibasic potassium phosphate, monobasic potassium phosphate, dibasic sodium phosphate, and monosodium phosphate per packet (100s) [sugar free; equivalent to elemental phosphorus 250 mg, sodium 160 mg (6.9 mEq), and potassium 280 mg (7.1 mEq) per packet; fruit flavor]

Tablet:

K-Phos® MF: Potassium acid phosphate 155 mg and sodium acid phosphate 350 mg [equivalent to elemental phosphorus 125.6 mg, sodium 67 mg (2.9 mEq), and potassium 44.5 mg (1.1 mEq)]

K-Phos® Neutral: Monobasic potassium phosphate 155 mg, dibasic sodium phosphate 852 mg, and monobasic sodium phosphate 130 mg [equivalent to elemental phosphorus 250 mg, sodium 298 mg (13 mEq), and potassium 45 mg (1.1 mEq)]

K-Phos® No. 2: Potassium acid phosphate 305 mg and sodium acid phosphate 700 mg [equivalent to elemental phosphorus 250 mg, sodium 134 mg (5.8 mEq), and potassium 88 mg (2.3 mEq)]

Phospha 250™ Neutral: Monobasic potassium phosphate 155 mg, dibasic sodium phosphate 852 mg, and monobasic sodium phosphate 130 mg [equivalent to elemental phosphorus 250 mg, sodium 298 mg (13 mEq), and potassium 45 mg (1.1 mEq)]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Pack (Neutra-Phos)

278-164-250 mg (100): $59.99

Pack (Phos-NaK)

278-164-250 mg (100): $35.99

Tablets (K-Phos No 2)

305-700 mg (30): $8.99

Tablets (K-Phos-Neutral)

155-852-130 mg (30): $16.99

Pharmacodynamics/KineticsExcretion: Urine

Pharmacotherapy PearlsAdditional terminology for the potassium and sodium salts:

Sodium phosphate monobasic = Sodium acid phosphate

Sodium phosphate dibasic = Disodium phosphate

Potassium phosphate monobasic = Potassium acid phosphate

Potassium phosphate dibasic = Dipotassium phosphate

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsHypokalemia is highly arrhythmogenic, particularly in the setting of ischemia or digitalis toxicity. ECG evidence of hypokalemia includes flattening of the T wave. As the T wave shrinks, U waves may appear. There is no prolongation of the QT interval. Hyperkalemia may present as tall peaked symmetrical T waves. S-T elevation may present in severe hyperkalemia. QRS complex progressively widens with eventual apparent sine waves on the ECG. Hyperkalemia will also induce cardiac slowing and AV conduction abnormalities.

Index TermsSodium Phosphate and Potassium Phosphate

Potassium Phosphate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Neutra-Phos®-K may be confused with K-Phos Neutral®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V. formulation) among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Per JCAHO recommendations, concentrated electrolyte solutions should not be available in patient care areas.

Consider special storage requirements for intravenous potassium salts; I.V. potassium salts have been administered IVP in error, leading to fatal outcomes.

Safe Prescribing: Because inorganic phosphate exists as monobasic and dibasic anions, with the mixture of valences dependent on pH, ordering by mEq amounts is unreliable and may lead to large dosing errors. In addition, I.V. phosphate is available in the sodium and potassium salt; therefore, the content of these cations must be considered when ordering phosphate. The most reliable method of ordering I.V. phosphate is by millimoles, then specifying the potassium or sodium salt. For example, an order for 15 mmol of phosphate as potassium phosphate in one liter of normal saline. The dosing of phosphate should be 0.2-0.3 mmol/kg with a usual daily requirement of 30-60 mmol/day or 15 mmol of phosphate per liter of TPN or 15 mmol phosphate per 1000 calories of dextrose. Would also provide 22 mEq of potassium.

Pronunciation(poe TASS ee um FOS fate)

U.S. Brand NamesNeutra-Phos®-K [OTC] [DSC]

Pharmacologic CategoryElectrolyte Supplement, Oral; Electrolyte Supplement, Parenteral

Use: Labeled IndicationsTreatment and prevention of hypophosphatemia; **Note:** The concomitant amount of potassium must be calculated into the total electrolyte content. For each 1 mmol of phosphate, ~1.5 mEq of potassium will be administered. Therefore, if ordering 30 mmol of potassium phosphate, the patient will receive ~45 mEq of potassium.

Dosing: Adults

Normal requirements elemental phosphorus: Oral:

Pregnancy lactation: Additional 400 mg/day

Adults: 800 mg

I.V.: **Caution: The concomitant amount of potassium must be calculated into the total electrolyte content. For each 1 mmol of phosphate, ~1.5 mEq of potassium will be administered. Therefore, if ordering 30 mmol of potassium phosphate, the patient will receive ~45 mEq of potassium. With orders for I.V. phosphate, there is considerable confusion associated with the use of millimoles (mmol) versus milliequivalents (mEq) to express the phosphate requirement.** The most reliable method of ordering I.V. phosphate is by millimoles, then specifying the potassium or sodium salt (see Medication Safety Issues). Doses listed as mmol of phosphate.

Acute treatment of hypophosphatemia: It is recommended that repletion of severe hypophosphatemia be done I.V. because large doses of oral phosphate may cause diarrhea and intestinal absorption may be unreliable. Intermittent I.V. infusion should be reserved for severe depletion situations; requires continuous cardiac monitoring. Guidelines differ based on degree of illness, need/use of TPN, and severity of hypophosphatemia. If potassium >4.0 mEq/L consider phosphate replacement strategy without potassium (eg, sodium phosphates). Obese patients and/or severe renal impairment were excluded from phosphate supplement trials.

General replacement guidelines (Lentz, 1978):

Low dose: 0.08 mmol/kg over 6 hours; use if losses are recent and uncomplicated

Intermediate dose: 0.16-0.24 mmol/kg over 4-6 hours; use if serum phosphorus level 0.5-1 mg/dL (0.16-0.32 mmoles/L)

Note: The initial dose may be increased by 25% to 50% if the patient is symptomatic secondary to hypophosphatemia and lowered by 25% to 50% if the patient is hypercalcemic.

Patients receiving TPN; supplemental dose (Clark, 1995):

Low dose: 0.16 mmol/kg over 4-6 hours; use if serum phosphorus level 2.3-3 mg/dL (0.73-0.96 mmoles/L)

Intermediate dose: 0.32 mmol/kg over 4-6 hours; use if serum phosphorus level 1.6-2.2 mg/dL (0.51-0.72 mmoles/L)

High dose: 0.64 mmol/kg over 8-12 hours; use if serum phosphorus <1.5 mg/dL (<0.5 mmoles/L)

Critically-ill adult trauma patients receiving TPN (Brown, 2006):

Low dose: 0.32 mmol/kg over 4-6 hours; use if serum phosphorus level 2.3-3 mg/dL (0.73-0.96 mmoles/L)

Intermediate dose: 0.64 mmol/kg over 4-6 hours; use if serum phosphorus level 1.6-2.2 mg/dL (0.51-0.72 mmoles/L)

High dose: 1 mmol/kg over 8-12 hours; use if serum phosphorus <1.5 mg/dL (<0.5 mmoles/L)

Maintenance:

I.V. solutions: 15-30 mmol/24 hours I.V. or 50-150 mmol/24 hours orally in divided doses

Oral: 1-2 capsules (250-500 mg phosphorus/8-16 mmol) 4 times/day; dilute as instructed

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricI.V. doses should be incorporated into the patient's maintenance I.V. fluids. Intermittent I.V. infusion should be reserved for severe depletion situations; requires continuous cardiac monitoring. It is difficult to determine total body phosphorus deficit; the following are empiric guidelines.

Note: Refer to notes under adult dosing

Normal requirements elemental phosphorus: Oral:

0-6 months: 240 mg

6-12 months: 360 mg

1-10 years: 800 mg

>10 years: 1200 mg

Pediatric I.V. phosphate repletion: Children: 0.25-0.5 mmol/kg **administer over 4-6 hours and repeat if symptomatic hypophosphatemia persists**; to assess the need for further phosphate administration, obtain serum inorganic phosphate after administration of the first dose and base further doses on serum levels and clinical status

Maintenance:

I.V. solutions: Children: 0.5-1.5 mmol/kg/24 hours I.V. or 2-3 mmol/kg/24 hours orally in divided doses

Oral:

Children <4 years: 1 capsule (250 mg phosphorus/8 mmol) 4 times/day; dilute as instructed

Children >4 years: Refer to adult dosing.

StorageStore at room temperature; do not freeze. Use only clear solutions. Up to 10-15 mEq of calcium may be added per liter before precipitate may occur.

Stability of parenteral admixture at room temperature (25°C) is 24 hours.

Phosphate salts may precipitate when mixed with calcium salts. Solubility is improved in amino acid parenteral nutrition solutions. Check with a pharmacist to determine compatibility.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_{10}LR, $D_5{}^1/_4$NS, $D_5{}^1/_2$NS, D_5NS, D_5W, D_{10}W, $^1/_2$NS, NS; **incompatible** with D_5LR, D_{10}NS, LR; **variable stability (consult detailed reference)** in TPN.

Y-site administration: Compatible: Ciprofloxacin, diltiazem, enalaprilat, esmolol, famotidine, labetalol. **Incompatible:** Gatifloxacin. **Variable (consult detailed reference):** TPN.

Compatibility when admixed: Compatible: Magnesium sulfate, metoclopramide, verapamil. **Incompatible:** Dobutamine. **Variable (consult detailed reference):** Calcium chloride, calcium gluconate, ciprofloxacin.

ContraindicationsHyperphosphatemia, hyperkalemia, hypocalcemia, hypomagnesemia, renal failure

Warnings/Precautions

Concerns related to adverse effects:

- Hyperkalemia: Close monitoring of serum potassium concentrations is needed to avoid hyperkalemia; severe hyperkalemia may lead to muscle weakness/paralysis and cardiac conduction abnormalities (eg, heart block, ventricular arrhythmias, asystole).

Disease-related concerns:

- Acid/base disorders: Use with caution in patients with acid/base alterations; changes in serum potassium concentrations can occur during acid/base correction, monitor closely.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (eg, heart failure, cardiac arrhythmias); patients may be more susceptible to life-threatening cardiac effects associated with hyper/hypokalemia.

- Renal impairment: Use with caution in patients with renal impairment; renal impairment requires close monitoring of serum potassium and phosphorus concentrations to avoid hyperkalemia and/or hyperphosphatemia.

Concurrent drug therapy issues:

- Digitalis: Use with caution in digitalized patients; may be more susceptible to potentially life-threatening cardiac effects with rapid changes in serum potassium concentrations.

- Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (eg, ACEI, potassium-sparing diuretics, potassium containing salt substitutes).

Dosage form specific issues:

- Oral formulations: May cause GI upset (eg, nausea, vomiting, diarrhea, abdominal pain, discomfort) and lead to GI ulceration, bleeding, perforation and/or obstruction. Oral liquid preparations (not solid) should be used in patients with esophageal compression or delayed gastric emptying.

Other warnings/precautions:

- Calcium/phosphate compatibility: Admixture of phosphate and calcium in I.V. fluids can result in calcium phosphate precipitation.

- Parenteral administration: Use extreme caution when administering potassium phosphate parenterally; evaluate patient's renal function, cardiac and fluid status, and any factors contributing to altered potassium concentrations (eg, acidosis, alkalosis) prior to therapy. Closely monitor potassium and phosphate concentrations and response to therapy. Parenteral potassium may cause pain and phlebitis, requiring a decrease in infusion rate or potassium concentration.

Geriatric ConsiderationsA complete drug history should be taken to rule out potential drug interactions since elderly frequently may be taking potassium and potassium-sparing diuretics or salicylates as antacids. Elderly may require less potassium than younger adults due to decreased renal function. Elderly who do not respond to replacement therapy, check serum magnesium. Long-term use of diuretics may result in hypomagnesemia. Monitor closely in elderly with Cl_{cr} <30 mL/minute.
Pregnancy Risk FactorC
Adverse Reactions

>10%: Gastrointestinal: Diarrhea, nausea, stomach pain, flatulence, vomiting

1% to 10%:

Cardiovascular: Bradycardia

Endocrine & metabolic: Hyperkalemia

Neuromuscular & skeletal: Weakness

Respiratory: Dyspnea

<1%: Abdominal pain, acute renal failure, alkalosis, chest pain, hypocalcemia tetany (with large doses of phosphate), mental confusion, paralysis, paresthesia, phlebitis, throat pain

Drug Interactions

ACE Inhibitors: Potassium Salts may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Potassium Salts may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: May enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Calcium Salts: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of Potassium Salts. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Potassium-Sparing Diuretics: Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Avoid administering with oxalate (berries, nuts, chocolate, beans, celery, tomato) or phytate-containing foods (bran, whole wheat).
Test InteractionsDecreased ammonia (B)
Monitoring ParametersSerum potassium, calcium, phosphate, sodium, cardiac monitor (when intermittent infusion or high-dose I.V. replacement needed)
Nursing: Physical Assessment/MonitoringAssess therapeutic response and adverse effects.
Monitoring: Lab TestsSerum potassium, phosphate
Patient EducationEmpty contents of packet into 3-4 oz of water. Take with food to reduce the risk of diarrhea. Report excessive nausea, stomach pain, or vomiting. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution: Potassium 4.4 mEq and phosphorus 3 mmol per mL (5 mL, 15 mL, 50 mL) [equivalent to potassium 170 mg and elemental phosphorus 93 mg per mL]

Powder for oral solution:

Neutra-Phos®-K: Monobasic potassium phosphate and dibasic potassium phosphate per packet (100s) [equivalent to elemental potassium 556 mg (14.25 mEq) and phosphorus 250 mg (14.25 mEq) per packet; sodium and sugar free; fruit flavor] [DSC]

Generic AvailableYes: Injection

Pricing: U.S. (www.drugstore.com)

Pack (Neutra-Phos-K)

250-556 mg (100): $69.99

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsHypokalemia is highly arrhythmogenic, particularly in the setting of ischemia or digitalis toxicity. ECG evidence of hypokalemia includes flattening of the T wave. As the T wave shrinks, U waves may appear. There is no prolongation of the QT interval. Hyperkalemia may present as tall peaked symmetrical T waves. S-T elevation may present in severe hyperkalemia. QRS complex progressively widens with eventual apparent sine waves on the ECG. Hyperkalemia will also induce cardiac slowing and AV conduction abnormalities.

Index TermsPhosphate, Potassium

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Povidone-Iodine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Betadine® may be confused with Betagan®, betaine

International issues:

Alphadine®: Brand name for ranitidine in Greece

Oralon® [Japan] may be confused with Oralone® which is a brand name for triamcinolone in the U.S.

Pronunciation(POE vi done EYE oh dyne)

U.S. Brand NamesBetadine®; Operand® [OTC]; Povidine™ [OTC]; Summer's Eve® Medicated Douche [OTC]; Vagi-Gard® [OTC]

Canadian Brand NamesBetadine®; Proviodine

Pharmacologic CategoryAntiseptic, Ophthalmic; Antiseptic, Topical; Antiseptic, Vaginal; Topical Skin Product

Use: Labeled IndicationsExternal antiseptic with broad microbicidal spectrum for the prevention or treatment of topical infections associated with surgery, burns, minor cuts/scrapes; relief of minor vaginal irritation

Dosing: Adults

Antiseptic: Topical: Apply to affected area as needed. Ophthalmic solution may be used to irrigate the eye or applied to area around the eye such as skin, eyelashes, or lid margins.

Surgical scrub: Topical: Apply solution to wet skin or hands, scrub for ~5 minutes, rinse; refer to product labeling for specific procedure-related instructions.

Vaginal irritation: Douche: Insert 0.3% solution vaginally once daily for 5-7 days

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to iodine or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Toxicity: May occur following application of large or prolonged quantities.

Disease-related concerns:

- Burns: Use with caution in patients with burns.
- Renal impairment: Use with caution in patients with renal impairment.
- Thyroid dysfunction: Use with caution in patients with thyroid disorders.

Special populations:

- Pediatrics: Use with caution in children.

Other warnings/precautions:

- Self-medication (OTC use): When used for self-medication (OTC use) do not apply to deep puncture wounds or serious burns; discontinue in case of redness, swelling, irritation or pain; do not use for longer than 1 week.

Pregnancy Risk FactorC (ophthalmic)

Pregnancy ConsiderationsReproduction studies have not been conducted. Vaginal products should not be used during pregnancy. Absorbed systemically as iodine. Transient hypothyroidism in the newborn has been reported following topical or vaginal use prior to delivery. Refer to Iodine for additional information.

LactationEnters breast milk/use caution (AAP rates "compatible")

Breast-Feeding ConsiderationsRefer to Iodine monograph.

Adverse ReactionsFrequency not defined. Also refer to Iodine.

Local: Edema, irritation, pruritus, rash

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Gel, topical: 10% (120 g)

Operand®: 10% (120 g)

Liquid, topical [prep-swab ampul]: 10% (0.65 mL)

Ointment, topical: 10% (1 g)

Povidine™: 10% (30 g)

Pad [prep pads]: 10% (200s)

Betadine® SwabAids: 10% (100s)

Solution, ophthalmic:

Betadine®: 5% (30 mL)

Solution, perineal [concentrate]:

Operand®: 10% (240 mL)

Solution, topical: 10% (22 mL, 60 mL, 90 mL, 240 mL, 480 mL, 3840 mL)

Betadine®: 10% (15 mL, 120 mL, 240 mL, 480 mL, 960 mL, 3840 mL)

Operand®: 10% (60 mL, 120 mL, 240 mL, 480 mL, 960 mL, 3840 mL)

Povidine™: 10% (240 mL)

Solution, topical [cleanser]:

Betadine® Skin Cleanser: 7.5% (120 mL)

Solution, topical [paint sponge]: 10% (50s)

Solution, topical [paint]: 10% (60 mL, 90 mL, 120 mL)

Solution, topical [surgical scrub]: 7.5% (60 mL, 120 mL)

Betadine® Surgical Scrub: 7.5% (120 mL, 480 mL, 960 mL, 3840 mL)

Operand®: 7.5% (60 mL, 120 mL, 240 mL, 480 mL, 960 mL, 3840 mL)

Solution, topical [spray]: 10% (60 mL)

Betadine®: 5% (90 mL) [CFC free; contains dry natural rubber]

Operand®: 10% (59 mL)

Solution, topical [surgical scrub sponge]: 10% (50s)

Solution, vaginal [concentrate, douche]:

Operand®: 10% (240 mL)

Vagi-Gard®: 10% (180 mL, 240 mL)

Solution, vaginal [douche]:

Summer's Eve® Medicated Douche: 0.3% (135 mL) [contains sodium benzoate]

Solution [concentrate, whirlpool]:

Operand®: 10% (3840 mL)

Swabsticks: 10% (25s, 50s, 1000s)

Betadine®: 10% (50s, 200s)

Swabsticks [gel saturated]: 10% (50s)

Swabsticks, topical [surgical scrub]: 7.5% (25s, 50s, 1000s)

Generic AvailableYes

Mechanism of ActionPovidone-iodine is known to be a powerful broad spectrum germicidal agent effective against a wide range of bacteria, viruses, fungi, protozoa, and spores.

Pharmacodynamics/KineticsAbsorption: Topical: Absorbed systemically as iodine; amount depends upon concentration, route of administration, characteristics of skin

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms Polyvinylpyrrolidone with Iodine; PVP-I

References

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International Brand Names Abodine (PK); Asepta (ID); Bacterodine (DO); Bactroderm (CO); Betadine (AU, BG, CH, CZ, ES, FI, FR, GB, GR, HK, HR, HU, ID, IE, IN, IT, KP, MY, NL, PH, PK, PL, PT, TH, VE, ZA); Betaisodona (AT, DE); Betaisodona Loesung (PL); Betascrub (KP); Betatul (ES); Better-Iodine (TW); Braunoderm (ES, IE, LU); Braunol (BE, BG, CH, DE, ES, IE, LU); Braunosan (CH, IE, LU); Braunovidon (AT, EE, HN, IE, PL); Difexon (CN); E.D.P. (AU); Favol (PY); Gyneiod (HU); Igiol (GR); Inadine (IE, LU); Iodep (AR); Iodex (LU); Iodicare (IL); Iodina (ES); Iodo-Vit (IL); Iodofon (UY); Iop (PY); Iso-Betadine (LU); Isodine (AU, CO, MX, PE, PT); Jodi gel (PL); Jodoseptic (HU); Kaput (ES); Marcodine (BR); Meniodina (ES); Minidine (AU); Neojodin (JP); Orto Dermo P (ES); Podine (ZA); Polividona Yodada Cuve (ES); Polividona Yodada Neusc (ES); Polodina-R (PL); Polseptol (PL); Polydine (IL); Povadine (TH); Povadyne (CY); Povibac (AR); Povidine (IN); Povidona Iodada Spa (ES); Povidyn (EC); PV Jod (PL); PVP-Iodine (PL); Sabofen (BR); Topionic (ES); Viodine (AU); Yodine (MX); Yovidona (CO)

Pralidoxime

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Pralidoxime may be confused with pramoxine, pyridoxine

Protopam® may be confused with Proloprim®, protamine, Protropin®

Pronunciation(pra li DOKS eem)

U.S. Brand NamesProtopam®

Canadian Brand NamesProtopam®

Pharmacologic CategoryAntidote

Use: Labeled IndicationsReverse muscle paralysis caused by toxic exposure to organophosphate anticholinesterase pesticides and chemicals; control of overdose of anticholinesterase medications used to treat myasthenia gravis (ambenonium, neostigmine, pyridostigmine)

Use: Unlabeled/InvestigationalTreatment of nerve agent toxicity (chemical warfare) in combination with atropine

Dosing: Adults

Organic phosphorus poisoning (use in conjunction with atropine; atropine effects should be established before pralidoxime is administered): I.V. (may be given I.M. or SubQ if I.V. is not feasible): Initial: 30 mg/kg over 20 minutes, maintenance: I.V. infusion: 4-8 mg/kg/hour

Treatment of acetylcholinesterase inhibitor toxicity: I.V.: Initial: 1-2 g followed by increments of 250 mg every 5 minutes until response is observed

Nerve agent toxicity management (unlabeled use):

Note: Atropine is a component of the management of nerve agent toxicity; consult atropine monograph for specific route and dose. To be effective, pralidoxime must be administered within minutes to a few hours following exposure (depending on the nerve agent).

Prehospital ("in the field"): Mild-to-moderate symptoms: I.M.: 600 mg; severe symptoms: 1800 mg

Hospital/emergency department: Mild-to-severe symptoms: I.V.: 15 mg/kg (up to 1 g)

Dosing: ElderlyRefer to adult dosing. Dosing should be cautious, considering possibility of decreased hepatic, renal, or cardiac function.

Nerve agent toxicity management (unlabeled use): To be effective, pralidoxime must be administered within minutes to a few hours following exposure (depending on the nerve agent). Also see **"Note"** in adult dosing.

Frail patients, elderly:

Prehospital ("in the field"): Mild-to-moderate symptoms: I.M.: 10 mg/kg; severe symptoms: 25 mg/kg

Hospital/emergency department: Mild-to-severe symptoms: I.V.: 5-10 mg/kg

Dosing: Pediatric

Organic phosphorus poisoning: I.V. (may be given I.M. or SubQ if I.V. is not feasible): 20-50 mg/kg/dose; repeat in 1-2 hours if muscle weakness has not been relieved, then at 8- to 12-hour intervals if cholinergic signs recur

Note: Use in conjunction with atropine; atropine effects should be established before pralidoxime is administered

Nerve agent toxicity management (unlabeled use): To be effective, pralidoxime must be administered within minutes to a few hours following exposure (depending on the nerve agent). Also see **"Note"** in adult dosing.

Infants and Children:

Prehospital ("in the field"): Mild-to-moderate symptoms: I.M.: 15 mg/kg; severe symptoms: 25 mg/kg

Hospital/emergency department: Mild-to-severe symptoms: I.V.: 15 mg/kg (up to 1 g)

Dosing: Renal ImpairmentDose should be reduced.

Administration: I.V.I.V.: Infuse over 15-30 minutes at a rate not to exceed 200 mg/minute; may administer I.M. or SubQ if I.V. is not accessible. If a more concentrated 5% solution is used, infuse over at least 5 minutes.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).

ReconstitutionFor I.V. administration, dilute 1 g with 20 mL SWI. Solution should be further diluted and administered as 1-2 g in 100 mL NS. If not practical or in cases of fluid overload, may prepare as a 5% solution.

ContraindicationsHypersensitivity to pralidoxime or any component of the formulation; poisonings due to phosphorus, inorganic phosphates, or organic phosphates without anticholinesterase activity; poisonings due to pesticides of carbamate class (may increase toxicity of carbaryl)

Warnings/Precautions

Disease-related concerns:

- Myasthenia gravis: Use with caution in patients with myasthenia gravis.
- Renal impairment: Use with caution in patients with renal impairment; dosage modification required.

Other warnings/precautions:

- Appropriate use: Clinical symptoms consistent with highly-suspected organophosphorous poisoning should be treated with antidote immediately; administration should not be delayed for confirmatory laboratory tests. Treatment should always include proper evacuation and decontamination procedures; medical personnel should protect themselves from inadvertent contamination. Antidotal administration is intended only for initial management; definitive and more extensive medical care is required following administration. Individuals should not rely solely on antidote for treatment, as other supportive measures (eg, artificial respiration) may still be required.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypertension, tachycardia

Central nervous system: Dizziness, drowsiness, headache

Dermatologic: Rash

Gastrointestinal: Nausea

Hepatic: ALT increased (transient), AST increased (transient)

Local: Pain at injection site after I.M. administration

Neuromuscular & skeletal: Muscle rigidity, weakness

Ocular: Accommodation impaired, blurred vision, diplopia

Renal: Renal function decreased

Respiratory: Hyperventilation, laryngospasm

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersHeart rate, respiratory rate, blood pressure, continuous ECG; cardiac monitor and blood pressure monitor required for I.V. administration

Reference RangeMinimum therapeutic concentration: 4 mcg/mL

Nursing: Physical Assessment/MonitoringMonitor vital signs, blood pressure, and respiratory status on a frequent basis. Continuous ECG and hemodynamic monitoring. Monitor fluid balance throughout therapy (oliguria). With organophosphate poisoning or anticholinesterase overdose, monitor closely for muscle weakness or twitching, reduction in respiratory function, or altered consciousness. Keep under observation for 48-72 hours.

Patient EducationWhen administered in emergency situation, patient education and instruction should be appropriate to patient condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as chloride:

Protopam®: 1 g

Injection, solution: 300 mg/mL (2 mL) [contains benzyl alcohol; prefilled auto injector]

Generic AvailableNo

ManufacturerWyeth

Mechanism of ActionReactivates cholinesterase that had been inactivated by phosphorylation due to exposure to organophosphate pesticides by displacing the enzyme from its receptor sites; removes the phosphoryl group from the active site of the inactivated enzyme

Pharmacodynamics/Kinetics

Protein binding: None

Metabolism: Hepatic

Half-life elimination: 74-77 minutes

Time to peak, serum: I.V.: 5-15 minutes

Excretion: Urine (80% to 90% as metabolites and unchanged drug)

Pharmacotherapy PearlsPralidoxime is most effective when given immediately after poisoning. If the poison has been ingested, exposure may continue due to slow absorption from the lower bowel; relapses may occur after initial improvement and treatment may need continued for several days in these patients. In cases of dermal exposure to organophosphate poisoning, clothing should be removed and hair and skin washed with sodium bicarbonate or alcohol as soon as possible.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness

Mental Health: Effects on Psychiatric TreatmentAvoid with phenothiazines; effects of barbiturates may be increased

Cardiovascular ConsiderationsUse I.V. phentolamine for treatment of pralidoxime-induced hypertension (children: 1 mg; adults: 5 mg).

Anesthesia and Critical Care Concerns/Other ConsiderationsUse I.V. phentolamine for treatment of pralidoxime-induced hypertension (children: 1 mg; adults: 5 mg).

Index Terms2-PAM; 2-Pyridine Aldoxime Methochloride; Pralidoxime Chloride

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International Brand NamesAldopam (IN); Contrathion (AR, BR, FR, IT); PAM (NZ); Pamcl (TW); Pampara (MY, TW); Pralidoxime Iodide (AU)

Pramipexole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Mirapex® may be confused with Mifeprex®, MiraLax™

Pronunciation(pra mi PEKS ole)
U.S. Brand NamesMirapex®
Canadian Brand NamesApo-Pramipexole; Mirapex®; Novo-Pramipexole; PMS-Pramipexole; SANDOZ-Pramipexole
Pharmacologic CategoryAnti-Parkinson's Agent, Dopamine Agonist
Use: Labeled IndicationsTreatment of the signs and symptoms of idiopathic Parkinson's disease; treatment of moderate-to-severe primary Restless Legs Syndrome (RLS)
Use: Unlabeled/InvestigationalTreatment of depression
Dosing: Adults

Parkinson's disease: Oral: Initial: 0.375 mg/day given in 3 divided doses; increase gradually by 0.125 mg/dose every 5-7 days; range: 1.5-4.5 mg/day.

Restless legs syndrome: Oral: Initial: 0.125 mg once daily 2-3 hours before bedtime. Dose may be doubled every 4-7 days up to 0.5 mg/day. Maximum dose: 0.5 mg/day (manufacturer's recommendation).

Note: Most patients require <0.5 mg/day, but higher doses have been used (2 mg/day). If augmentation occurs, dose earlier in the day.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentUse caution; renally-eliminated

Parkinson's disease:

Cl_{cr} 35-59 mL/minute: Initial: 0.125 mg twice daily (maximum dose: 1.5 mg twice daily)

Cl_{cr} 15-34 mL/minute: Initial: 0.125 mg once daily (maximum dose: 1.5 mg once daily)

Cl_{cr} <15 mL/minute (or hemodialysis patients): Not adequately studied.

Restless legs syndrome:

Cl_{cr} 20-60 mL/minute: Duration between titration should be increased to 14 days

Cl_{cr} <20 mL/minute: Not adequately studied

Calculations

- Creatinine Clearance: Adults

Administration: OralDoses should be titrated gradually in all patients to avoid the onset of intolerable side effects. The dosage should be increased to achieve a maximum therapeutic effect, balanced against the side effects of dyskinesia, hallucinations, somnolence, and dry mouth.
Dietary ConsiderationsMay be taken with food to decrease nausea.
StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light.
ContraindicationsHypersensitivity to pramipexole or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Hallucinations: May cause hallucinations, particularly in older patients.

- Impulsive control disorders: Dopamine agonists used for Parkinson's disease or restless legs syndrome have been associated with compulsive behaviors and/or loss of impulse control, which has manifested as pathological gambling, libido increases (hypersexuality), and/or binge eating. Causality has not been established, and controversy exists as to whether this phenomenon is related to the underlying disease, prior behaviors/addictions and/or drug therapy. Dose reduction or discontinuation of therapy has been reported to reverse these behaviors in some, but not all cases.

- Orthostatic hypotension: May cause orthostatic hypotension; Parkinson's disease patients appear to have an impaired capacity to respond to a postural challenge. Use with caution in patients at risk of hypotension (such as those receiving antihypertensive drugs) or where transient hypotensive episodes would be poorly tolerated (cardiovascular disease or cerebrovascular disease). Parkinson's patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation, and should be informed of this risk.

- Pleural/retroperitoneal fibrosis: Ergot-derived dopamine agonists have also been associated with fibrotic complications (eg, retroperitoneal fibrosis, pleural thickening, and pulmonary infiltrates). Although pramipexole is not an ergot, there have been postmarketing reports of possible fibrotic complications with pramipexole; monitor closely for signs and symptoms of fibrosis.

- Retinal changes: Pathologic degenerative changes were observed in the retinas of albino rats during studies with this agent, but were not observed in the retinas of albino mice or in other species. The significance of these data for humans remains uncertain.

- Somnolence: Patients have reported falling asleep while engaging in activities of daily living; this has been reported to occur without significant warning signs. Monitor for daytime somnolence or pre-existing sleep disorder; caution with concomitant sedating medication; discontinue if significant daytime sleepiness or episodes of falling asleep occur. Patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). Use with caution in patients receiving other CNS depressants or psychoactive agents. Effects with other sedative drugs or ethanol may be potentiated. Pramipexole has been associated with somnolence, particularly at higher dosages (>1.5 mg/day).

Disease-related concerns:

- Dyskinesias: Use with caution in patients with pre-existing dyskinesias; may be exacerbated.

- Renal impairment: Use with caution in patients with renal impairment; dose adjustment necessary.

- Restless legs syndrome (RLS): Augmentation (earlier onset of symptoms in the evening/afternoon, increase and/or spread of symptoms to other extremities) or rebound (shifting of symptoms to early morning hours) may occur in some RLS patients.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Discontinuation of therapy: Dopaminergic agents have been associated with a syndrome resembling neuroleptic malignant syndrome on abrupt withdrawal or significant dosage reduction after long-term use.

Pregnancy Risk FactorC
Pregnancy ConsiderationsEarly embryonic loss and postnatal growth inhibition were observed in animal studies. There are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsProlactin secretion may be inhibited.
Adverse Reactions Parkinson’s disease (PD) unless identified as RLS:

>10%:

Cardiovascular: Postural hypotension (dose related; PD 53%)

Central nervous system: Dizziness (PD 25%), headache (RLS 16%), somnolence (dose related; RLS 6%; PD 9% to 22%), insomnia (RLS 13%; PD 17% to 27%), hallucinations (PD 9% to 17%), abnormal dreams (RLS up to 8%)

Gastrointestinal: Nausea (dose related; RLS: 5% to 27%; PD 28%), constipation (dose related; RLS: 4%; PD 10% to 14%)

Neuromuscular & skeletal: Weakness (PD 10% to 14%), dyskinesia (PD 47%), EPS

1% to 10%:

Cardiovascular: Edema, syncope, tachycardia, chest pain

Central nervous system: Malaise, confusion (PD 4% to 10%), amnesia (dose related), dystonias, akathisia, thinking abnormalities, myoclonus, hyperesthesia, paranoia, fever

Endocrine & metabolic: Decreased libido

Gastrointestinal: Anorexia, diarrhea (RLS 3% to7%), dysphagia, weight loss, xerostomia (up to 7%)

Genitourinary: Urinary frequency (PD 6%), impotence, urinary incontinence

Neuromuscular & skeletal: Muscle twitching, leg cramps, arthritis, bursitis, myasthenia, gait abnormalities, hypertonia

Ocular: Vision abnormalities

Respiratory: Dyspnea, nasal congestion (RLS up to 6%), rhinitis

Miscellaneous: Influenza (RLS 3%)

<1%: Liver transaminases increased

Postmarketing and/or case reports: Augmentation (RLS ~20% but similar to placebo), compulsive gambling, rebound (RLS), rhabdomyolysis, tolerance (RLS)

Reported with dopamine agonists: Impulsive/compulsive behaviors (eg, pathological gambling, hypersexuality, binge eating)

Frequency not defined, dose related: Falling asleep during activities of daily living

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antipsychotics (Atypical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Antipsychotics (Typical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Metoclopramide: May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Food intake does not affect the extent of drug absorption, although the time to maximal plasma concentration is delayed by 60 minutes when taken with a meal.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava (may increase risk of serotonin syndrome and/or excessive sedation).

Monitoring ParametersMonitor for improvement in symptoms of Parkinson's disease (eg, mentation, behavior, daily living activities, motor examinations), blood pressure, body weight changes, and heart rate

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Monitor blood pressure. Assess degree of somnolence. Assess for therapeutic effectiveness (improvement of symptoms) and adverse response. Teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed. Avoid alcohol. May cause drowsiness and extreme sedation or somnolence (use caution when driving or engaging in hazardous activities until response to drug is known); loss of impulse control (possibly manifested as pathological gambling, libido increases, and/or binge eating); postural hypotension (use caution when changing position - rise slowly from sitting or lying position to standing and use caution when climbing stairs); weakness, headache, nausea, abnormal dreams, dry mouth, nausea, hallucinations, or new or increased occurrence of involuntary purposeless movements; constipation (increased exercise, fluids, fruit, or fiber may help); or urinary frequency. Consult prescriber about persistent adverse effects. Report to prescriber hallucinations; suicide ideation; or difficulty performing or controlling voluntary movements. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian product

Tablet, as dihydrochloride monohydrate: 0.25 mg [CAN; generic not available in U.S.], 0.5 mg [CAN; generic not available in U.S.], 1 mg [CAN; generic not available in U.S.], 1.5 mg [CAN; generic not available in U.S.]

Mirapex®: 0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg

Generic AvailableNo

ManufacturerPharmacia & Upjohn

Pricing: U.S. (www.drugstore.com)

Tablets (Mirapex)

0.125 mg (30): $92.18

0.25 mg (90): $244.19

0.5 mg (90): $227.10

1 mg (90): $225.74

1.5 mg (90): $238.11

Mechanism of ActionPramipexole is a nonergot dopamine agonist with specificity for the D_2 subfamily dopamine receptor, and has also been shown to bind to D_3 and D_4 receptors. By binding to these receptors, it is thought that pramipexole can stimulate dopamine activity on the nerves of the striatum and substantia nigra.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: V_d: 500 L

Protein binding: 15%

Bioavailability: >90%

Half-life elimination: ~8 hours; Elderly: 12-14 hours

Time to peak, serum: ~2 hours

Excretion: Urine (90% as unchanged drug)

Related Information

- Antiparkinsonian Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

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International Brand NamesMirapex (AR, BR, CN, KP, TW, VE); Mirapexin (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PL, PT, RU, SE, TR); Pexola (CO, UY); Sifrol (AE, AR, AT, BE, BG, BH, BR, CH, CL, CN, CY, CZ, DE, DK, EG, FI, FR, GB, GR, HN, ID, IE, IL, IQ, IR, IT, JO, KW, LB, LY, MX, MY, NL, NO, OM, PE, PH, PT, PY, QA, RU, SA, SE, SG, SY, TR, VE, YE)

Pramlintide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Dosing: The concentration of this product is 600 micrograms (mcg)/mL. Manufacturer recommended dosing ranges from 15 mcg to 120 mcg, which corresponds to injectable volumes of 0.025 mL to 0.2 mL. Patients and healthcare providers should exercise caution when administering this product to avoid inadvertent calculation of the dose based on "units," which could result in a sixfold overdose.

Pronunciation(PRAM lin tide)

U.S. Brand NamesSymlin®

Pharmacologic CategoryAmylinomimetic; Antidiabetic Agent

Use: Labeled Indications

Adjunctive treatment with mealtime insulin in type 1 diabetes mellitus (insulin dependent, IDDM) patients who have failed to achieve desired glucose control despite optimal insulin therapy

Adjunctive treatment with mealtime insulin in type 2 diabetes mellitus (noninsulin dependent, NIDDM) patients who have failed to achieve desired glucose control despite optimal insulin therapy, with or without concurrent sulfonylurea and/or metformin

Dosing: Adults**Note:** When initiating pramlintide, reduce current insulin dose (including rapidly- and mixed-acting preparations) by 50% to avoid hypoglycemia. If pramlintide is discontinued for any reason, restart therapy with same initial titration protocol.

Type 1 diabetes mellitus (insulin dependent, IDDM): SubQ: Initial: 15 mcg immediately prior to meals; titrate in 15 mcg increments every 3 days (if no significant nausea occurs) to target dose of 30-60 mcg (consider discontinuation if intolerant of 30 mcg dose)

Type 2 diabetes mellitus (noninsulin dependent, NIDDM): SubQ: Initial: 60 mcg immediately prior to meals; after 3-7 days, increase to 120 mcg prior to meals if no significant nausea occurs (if nausea occurs at 120 mcg dose, reduce to 60 mcg)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment required; not evaluated in dialysis patients

Administration: OtherDo not mix with other insulins; administer subcutaneously into abdominal or thigh areas at sites distinct from concomitant insulin injections (do not administer into arm due to variable absorption); rotate injection sites frequently. Allow solution to reach room temperature before administering; may reduce injection site reactions. For oral medications in which a rapid onset of action is desired, administer 1 hour before, or 2 hours after pramlintide, if possible. When using the pen-injector, do not transfer drug to a syringe; dosing errors could occur.

Dietary ConsiderationsDietary modification based on ADA recommendations is a part of therapy; pramlintide to be administered prior to major meals consisting of ≥250 Kcal or ≥30 g carbohydrates

StorageStore unopened vials at 2°C to 8°C (36°F to 46°F); do not freeze. Opened vials may be kept refrigerated or at room temperature ≤30°C (≤86°F). Discard opened vial after 30 days. Protect from light.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to pramlintide or any component of the formulation; confirmed diagnosis of gastroparesis; hypoglycemia unawareness

Warnings/Precautions

Boxed warnings:

- Insulin/glucose-lowering agents: See “Concurrent drug therapy issues” below.

Disease-related concerns:

- Gastroparesis: Avoid use in patients with conditions or concurrent medications likely to impair gastric motility (eg, anticholinergics); do not use in patients requiring medication(s) to stimulate gastric emptying.

- Nausea: Use with caution in patients with a history of nausea.

- Neuropathic conditions: Use with caution in patients with neuropathic conditions which may mask signs/symptoms of hypoglycemia.

Concurrent drug therapy issues:

- Antihypertensives: Use caution with certain antihypertensive agents (eg, beta-adrenergic blockers) which may mask signs/symptoms of hypoglycemia.

- Insulin/glucose-lowering agents: **[U.S. Boxed Warning]: Coadministration with insulin may induce severe hypoglycemia (usually within 3 hours following administration);** coadministration with insulin therapy is an approved indication, but does require an initial dosage reduction of insulin and frequent pre- and post-blood glucose monitoring to reduce risk of severe hypoglycemia. Concurrent use of other glucose-lowering agents may increase risk of hypoglycemia.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Avoid use in patients with poor compliance with their insulin regimen and/or blood glucose monitoring. Do not use in patients with Hb A_{1c} levels >9% or recent, recurrent episodes of hypoglycemia; obtain detailed history of glucose control (eg, Hb A_{1c}, incidence of hypoglycemia, glucose monitoring, and medication compliance) and body weight before initiating therapy. Use caution in patients with visual or dexterity impairment. Patients should use caution when driving or operating heavy machinery until effects on blood sugar are known.

Geriatric ConsiderationsPatients must be able to adhere to their insulin regimen and self-monitor their blood glucose. In premarketing studies, the change in the Hb A_{1c} values and hypoglycemia frequencies did not differ by age. Monitor regimen closely.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDue to adverse events observed in some animal studies, pramlintide is classified as pregnancy category C. Based on *in vitro* data, pramlintide has a low potential to cross the placenta. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of pramlintide is generally not recommended in the routine management of diabetes mellitus during pregnancy. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if pramlintide is present in breast milk. The manufacturer recommends that pramlintide be used in nursing women only when the potential benefit to the mother outweighs the possible risk to the infant.

Pregnancy & Lactation, In-Depth

- Pramlintide in Pregnancy & Lactation

Adverse Reactions

>10%:

Central nervous system: Headache (5% to 13%)

Gastrointestinal: Nausea (28% to 48%), anorexia (≤17%), vomiting (7% to 11%)

Endocrine & metabolic: Severe hypoglycemia (type 1 diabetes ≤17%)

Miscellaneous: Inflicted injury (8% to 14%)

1% to 10%:

Central nervous system: Fatigue (3% to 7%), dizziness (2% to 6%)

Endocrine & metabolic: Severe hypoglycemia (type 2 diabetes ≤8%)

Gastrointestinal: Abdominal pain (2% to 8%)

Respiratory: Cough (2% to 6%), pharyngitis (3% to 5%)

Neuromuscular & skeletal: Arthralgia (2% to 7%)

Miscellaneous: Allergic reaction (≤6%)

Postmarketing and/or case reports: Injection site reactions

Drug Interactions

Anticholinergics: Pramlintide may enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. **Exceptions:** Paliperidone. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Use caution with ethanol (may increase hypoglycemia).

Herb/Nutraceutical: Use caution with garlic, chromium, gymnema (may increase hypoglycemia).

Monitoring ParametersPrior to initiating therapy: Hb A_{1c}, hypoglycemic history, body weight. During therapy: urine sugar and acetone, pre- and postprandial and bedtime serum glucose, electrolytes, Hb A_{1c}, lipid profile

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Monitor laboratory tests, adverse reactions (eg, hypoglycemia), and therapeutic response. Teach patient proper use, including appropriate injection techniques and syringe/needle disposal, and monitoring requirements (or refer to diabetic education), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medications without consulting prescriber. This medication is used to control diabetes; it is not a cure. It is imperative to follow other components of prescribed treatment (eg, diet and exercise regimen). Take exactly as directed. Do not change dose or discontinue unless advised by prescriber. This medication cannot be mixed with insulin. Use a different syringe for each medication. If you experience hypoglycemic reaction, contact prescriber immediately. Always carry quick source of sugar with you. Monitor glucose levels as directed by prescriber. You may experience nausea (small, frequent meals, frequent oral care, sucking lozenges, or chewing gum may help). You may experience headache, fatigue, or dizziness (use caution when driving or engaging in activities requiring alertness until response to drug is known). Report unresolved nausea or vomiting and hypoglycemic reactions. **Pregnancy/breast-feeding precaution:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as acetate:

Symlin®: 600 mcg/mL (5 mL); 1000 mcg/mL (1.5 mL) [60 pen-injector]; 1000 mcg/mL (2.7 mL) [120 pen-injector]

Generic AvailableNo

ManufacturerAmylin Pharmaceutical, Inc

Pricing: U.S. (www.drugstore.com)

Solution (Symlin)

600 mcg/mL (5): $143.35

Solution (SymlinPen 120)

1000 mcg/mL (5.4): $259.20

Mechanism of ActionSynthetic analog of human amylin cosecreted with insulin by pancreatic beta cells; reduces postprandial glucose increases via the following mechanisms: 1) prolongation of gastric emptying time, 2) reduction of postprandial glucagon secretion, and 3) reduction of caloric intake through centrally-mediated appetite suppression

Pharmacodynamics/Kinetics

Duration: 3 hours

Protein binding: ~60%

Metabolism: Primarily renal to des-lys^1 pramlintide (active metabolite)

Bioavailability: ~30% to 40%

Half-life elimination: ~48 minutes

Time to peak, plasma: 20 minutes

Excretion: Primarily urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or fatigue

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with SSRIs, lithium, and valproic acid may produce additive effects. Psychotropics with anticholinergic properties may produce synergistic impairment of gastric motility if used with pramlintide.

Index TermsPramlintide Acetate

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Pramosone® may be confused with predniSONE

Zone-A Forte® may be confused with Zonalon®

Pronunciation(pra MOKS een & hye droe KOR ti sone)
U.S. Brand NamesAnalpram-HC®; Epifoam®; Pramosone®; ProctoFoam®-HC
Canadian Brand NamesPramox® HC; Proctofoam™-HC
Pharmacologic CategoryAnesthetic/Corticosteroid
Use: Labeled IndicationsRelief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses
Dosing: Adults**Inflammatory conditions:** Topical/rectal: Apply to affected areas 3-4 times/day
Dosing: ElderlyRefer to adult dosing.
Administration: OtherWhen using rectally, the special applicator should be used, the aerosol container should not be placed in the rectum; for local application the foam can be placed on a tissue first.
StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to pramoxine, hydrocortisone, or any component of the formulation
Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Special populations:

- Pediatrics: Chronic use of corticosteroids in children may interfere with growth and development.

Pregnancy Risk FactorC
Pregnancy ConsiderationsRefer to Hydrocortisone monograph.
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsHydrocortisone: **Substrate** of CYP3A4 (minor); **Induces** CYP3A4 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical:

Analpram-HC®: Pramoxine hydrochloride 1% and hydrocortisone acetate 1% (4 g, 30 g); pramoxine hydrochloride 1% and hydrocortisone acetate 2.5% (4 g, 30 g)

Pramosone®: Pramoxine hydrochloride 1% and hydrocortisone acetate 1% (30 g, 60 g); pramoxine hydrochloride 1% and hydrocortisone acetate 2.5% (30 g, 60 g)

Foam, rectal (ProctoFoam®-HC): Pramoxine hydrochloride 1% and hydrocortisone acetate 1% (10 g)

Foam, topical (Epifoam®): Pramoxine hydrochloride 1% and hydrocortisone acetate 1% (10 g)

Lotion, topical:

Analpram-HC®: Pramoxine hydrochloride 1% and hydrocortisone acetate 2.5% (60 mL)

Pramosone®: Pramoxine hydrochloride 1% and hydrocortisone acetate 1% (60 mL, 120 mL, 240 mL); pramoxine hydrochloride 1% and hydrocortisone acetate 2.5% (60 mL, 120 mL)

Ointment, topical (Pramosone®): Pramoxine hydrochloride 1% and hydrocortisone acetate 1% (30 g); pramoxine hydrochloride 1% and hydrocortisone acetate 2.5% (30 g)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Cream (Analpram-HC)

1-1% (30): $68.99

1-2.5% (30): $68.99

Cream (Analpram-HC Singles)

1-2.5% (4): $15.99

Cream (HC Pramoxine)

2.5-1% (28): $38.13

Cream (Pramosone)

1-1% (28.4): $62.13

1-2.5% (28.4): $60.40

1-2.5% (57): $76.27

Foam (Epifoam)

1-1% (10): $43.99

Foam (Proctofoam HC)

1-1% (10): $68.18

Lotion (Analpram-HC)

1-2.5% (59): $76.98

Lotion (Pramosone)

1-1% (118): $107.76

1-1% (236): $136.76

1-2.5% (59): $74.99

1-2.5% (118): $111.52

Ointment (Pramosone)

1-1% (28.4): $62.99

1-2.5% (28.4): $63.59

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Hydrocortisone
- Pramoxine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsHydrocortisone and Pramoxine; Pramoxine Hydrochloride and Hydrocortisone Acetate

References

Goedert JJ, Vitale F, Lauria C, et al, "Risk Factors for Classical Kaposi's Sarcoma," *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

International Brand NamesEpifoam (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Prasone (TW); Proctofoam (GB); Proctofoam HC (IL)

Pramoxine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Pramoxine may be confused with pralidoxime

Anusol® may be confused with Anusol-HC®, Aplisol®, Aquasol®

Pronunciation(pra MOKS een)

U.S. Brand NamesAnusol® Ointment [OTC]; Caladryl® Clear [OTC]; CalaMycin® Cool and Clear [OTC]; Callergy Clear [OTC]; Curasore® [OTC]; Itch-X® [OTC]; Prax® [OTC]; ProctoFoam® NS [OTC]; Sarna® Sensitive [OTC]; Soothing Care™ Itch Relief [OTC]; Summer's Eve® Anti-Itch Maximum Strength [OTC]; Tronolane® Cream [OTC]; Tucks® Hemorrhoidal [OTC]

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsTemporary relief of pain and itching associated with anogenital pruritus or irritation; dermatosis, minor burns, or hemorrhoids

Dosing: Adults**Anogenital pruritus, dermatosis, minor burns, or hemorrhoids:** Topical: Apply as directed, usually every 3-4 hours to affected area (maximum adult dose: 200 mg)

Dosing: ElderlyRefer to adult dosing.

Pregnancy Risk FactorC

Adverse Reactions

1% to 10%:

Dermatologic: Angioedema

Local: Contact dermatitis, burning, stinging

<1%: Edema, methemoglobinemia in infants, urethritis, urticaria, tenderness

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol, topical, as hydrochloride [foam]: 1% (15 g)

ProctoFoam® NS: 1% (15 g)

Cloth:

Summer's Eve® Anti-Itch Maximum Strength: 1% (12s)

Cream, topical, as hydrochloride:

Tronolane®: 1% (30 g, 60 g) [contains zinc oxide 5%]

Gel, topical, as hydrochloride:

Itch-X®: 1% (35.4 g) [contains benzyl alcohol]

Summer's Eve® Anti-Itch Maximum Strength: 1% (30 mL) [contains glycerin 39%]

Liquid, topical, as hydrochloride:

Curasore®: 1% (15 mL) [contains ethyl alcohol; packaged with cotton applicators]

Lotion, topical, as hydrochloride:

Caladryl® Clear: 1% (177 mL) [contains zinc acetate 0.1%]

Callergy Clear: 1% (180 mL) [contains zinc acetate 0.1%]

Prax®: 1% (15 mL, 120 mL, 240 mL)

Sarna® Sensitive: 1% (222 mL)

Ointment, rectal, as hydrochloride:

Anusol®, Tucks® Hemorrhoidal: 1% (30 g) [contains zinc oxide 12.5% and mineral oil; Anusol® Ointment renamed Tucks® Hemorrhoidal]

Solution, topical, as hydrochloride [spray]:

CalaMycin® Cool and Clear: 1% (60 mL) [contains zinc acetate 0.1%]

Itch-X®: 1% (60 mL) [contains benzyl alcohol]

Soothing Care™ Itch Relief: 1% (74 mL)

Generic AvailableYes: Aerosol, lotion

Pricing: U.S. (www.drugstore.com)

Foam (Proctofoam)

1% (15): $43.99

Mechanism of ActionPramoxine, like other anesthetics, decreases the neuronal membrane's permeability to sodium ions; both initiation and conduction of nerve impulses are blocked, thus depolarization of the neuron is inhibited

Pharmacodynamics/Kinetics

Onset of action: Therapeutic: 2-5 minutes

Peak effect: 3-5 minutes

Duration: Several days

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPramoxine Hydrochloride

International Brand NamesAnugesic (ZA); Nestosyl (NL); Primoly Gel (TH); Sarmed (IL); Tronotene (IT); Tronothane (FR)

Pravastatin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

HMG-CoA Reductase Inhibitors: Evidence Does Not Suggest Increased Incidence of Amyotrophic Lateral Sclerosis (ALS) - Results of FDA Analysis - September 30, 2008

The U.S. Food and Drug Administration's (FDA) review of 41 long-term controlled clinical trials of HMG-CoA reductase inhibitors finds no evidence of an increased incidence of ALS (also known as Lou Gehrig's disease) related to these medications. This analysis occurred after the FDA had received notice of numerous adverse events of which 109 of these reports mentioned ALS, Lou Gehrig's disease, or motor neurone disease. The clinical trials included in the analysis had a median duration of treatment of 3.3 years (range of duration: 6 months to 5 years) and involved 120,964 patients. The analysis identified a total of 19 cases of ALS – 9 cases per 64,602 patients (0.014%) with statin therapy and 10 cases per 56,362 patients (0.017%) with placebo. The incidence rates, based on approximately 400,000 person-years, were 4.2 per 100,000 person-years in the statin-treated group and 5 per 100,000 person-years in the placebo-treated group.

The FDA recommends that health care providers continue to prescribe, and patients continue to use these products as described within their labeling.

For more information, healthcare professionals may refer to the following:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Statin

Colman E, Szarfman A, Wyeth J, et al, "An Evaluation of a Data Mining Signal for Amyotrophic Lateral Sclerosis and Statins Detected in FDA's Spontaneous Adverse Event Reporting System," *Pharmacoepidemiol Drug Saf*, 2008 (epub ahead of print)

Medication Safety Issues

Sound-alike/look-alike issues:

Pravachol® may be confused with Prevacid®, Prinivil®, propranolol

Pronunciation(prav a STAT in)

U.S. Brand NamesPravachol®

Canadian Brand NamesApo-Pravastatin®; CO Pravastatin; DOM-Pravastatin; GEN-Pravastatin; Novo-Pravastatin; NU-Pravastatin; PHL-Pravastatin; PMS-Pravastatin; Pravachol®; RAN-Pravastatin; ratio-Pravastatin; Riva-Pravastatin; Sandoz-Pravastatin

Pharmacologic CategoryAntilipemic Agent, HMG-CoA Reductase Inhibitor

Use: Labeled IndicationsUse with dietary therapy for the following:

Primary prevention of coronary events: In hypercholesterolemic patients without established coronary heart disease to reduce cardiovascular morbidity (myocardial infarction, coronary revascularization procedures) and mortality.

Secondary prevention of cardiovascular events in patients with established coronary heart disease: To slow the progression of coronary atherosclerosis; to reduce cardiovascular morbidity (myocardial infarction, coronary vascular procedures) and to reduce mortality; to reduce the risk of stroke and transient ischemic attacks

Hyperlipidemias: Reduce elevations in total cholesterol, LDL-C, apolipoprotein B, and triglycerides (elevations of 1 or more components are present in Fredrickson type IIa, IIb, III, and IV hyperlipidemias)

Heterozygous familial hypercholesterolemia (HeFH): In pediatric patients, 8-18 years of age, with HeFH having LDL-C ≥190 mg/dL **or** LDL ≥160 mg/dL with positive family history of premature cardiovascular disease (CVD) or 2 or more CVD risk factors in the pediatric patient

Dosing: Adults

Hyperlipidemias, primary prevention of coronary events, secondary prevention of cardiovascular events: Oral: Initial: 40 mg once daily; titrate dosage to response (usual range: 10-80 mg) (maximum dose: 80 mg once daily)

Dosage adjustment based on concomitant cyclosporine: Oral: Initial: 10 mg/day, titrate with caution (maximum dose: 20 mg/day)

Note: Doses should be individualized according to the baseline LDL-cholesterol levels, the recommended goal of therapy, and patient response; adjustments should be made at intervals of 4 weeks or more; doses may need adjusted based on concomitant medications

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Heterozygous familial hypercholesterolemia (HeFH): Oral: Children:

8-13 years: 20 mg/day

14-18 years: 40 mg/day

Dosage adjustment based on concomitant cyclosporine: Refer to adult dosing.

Note: Doses should be individualized according to the baseline LDL-cholesterol levels, the recommended goal of therapy, and patient response; adjustments should be made at intervals of 4 weeks or more; doses may need adjusted based on concomitant medications

Dosing: Renal ImpairmentInitial: 10 mg/day
Dosing: Hepatic ImpairmentInitial: 10 mg/day
Administration: OralMay be taken without regard to meals.
Dietary ConsiderationsMay be taken without regard to meals. Before initiation of therapy, patients should be placed on a standard cholesterol-lowering diet for 6 weeks and the diet should be continued during drug therapy. Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.
StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture and light.
ContraindicationsHypersensitivity to pravastatin or any component of the formulation; active liver disease; unexplained persistent elevations of serum transaminases; pregnancy; breast-feeding
Allergy Considerations

- HMG-CoA Reductase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Myopathy/rhabdomyolysis: Patients receiving HMG-CoA reductase inhibitors have developed rhabdomyolysis with acute renal failure and/or myopathy; patients should be monitored closely. This risk is dose-related and is increased with concurrent use of other lipid lowering medications. Temporarily discontinue for elective major surgery, acute medical or surgical conditions, or in any patient experiencing an acute or serious condition predisposing to renal failure (eg, sepsis, hypotension, trauma, uncontrolled seizures). Based upon current evidence, HMG-CoA reductase inhibitor therapy should be continued in the perioperative period unless risk outweighs cardioprotective benefit. Use caution in patients with renal impairment, inadequately treated hypothyroidism, and those taking other drugs associated with myopathy (eg, colchicine); these patients are predisposed to myopathy. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine.

Disease-related concerns:

- Hepatic impairment and/or ethanol use: Use with caution in patients who consume large amounts of ethanol or have a history of liver disease.

Special Populations:

- Elderly: Use with caution in patients with advanced age, these patients are predisposed to myopathy.

- Pediatrics: Treatment is not recommended in patients <8 years of age.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

- Liver function tests: Must be monitored by periodic laboratory assessment.

Geriatric ConsiderationsEffective and well tolerated in the elderly. No specific dosage recommendations. Clearance is reduced in elderly, resulting in an increase in AUC between 25% to 50%. However, substantial accumulation is not expected.

The definition of and, therefore, when to treat hyperlipidemia in elderly is a controversial issue. The National Cholesterol Education Program recommends that all adults maintain a plasma cholesterol <160 mg/dL. Elderly with one additional risk factor, goal LDL would be <130 mg/dL. It is the authors' belief that pharmacologic treatment be reserved for those who are unable to obtain a desirable plasma cholesterol concentration by diet alone and for whom the benefits of treatment are believed to outweigh the potential adverse effects, drug interactions, and cost of treatment.

Pregnancy Risk FactorX
Pregnancy ConsiderationsCholesterol biosynthesis may be important in fetal development. Contraindicated in pregnancy. Administer to women of childbearing potential only when conception is highly unlikely and patients have been informed of potential hazards.
LactationEnters breast milk/contraindicated
Adverse ReactionsAs reported in short-term trials; safety and tolerability with long-term use were similar to placebo

1% to 10%:

Cardiovascular: Chest pain (4%)

Central nervous system: Headache (2% to 6%), fatigue (4%), dizziness (1% to 3%)

Dermatologic: Rash (4%)

Gastrointestinal: Nausea/vomiting (7%), diarrhea (6%), heartburn (3%)

Hepatic: Transaminases increased (>3x normal on two occasions - 1%)

Neuromuscular & skeletal: Myalgia (2%)

Respiratory: Cough (3%)

Miscellaneous: Influenza (2%)

<1%: Allergy, alopecia, appetite decreased, dermatitis, dry skin, edema, fever, flushing, insomnia, lens opacity, libido change, memory impairment, muscle weakness, neuropathy, paresthesia, pruritus, sexual dysfunction, taste disturbance, tremor, urticaria, vertigo

Postmarketing and/or case reports: Anaphylaxis, angioedema, cholestatic jaundice, cirrhosis, cranial nerve dysfunction, dermatomyositis, erythema multiforme, ESR increase, fulminant hepatic necrosis, gynecomastia, hemolytic anemia, hepatitis, hepatoma, lupus erythematosus-like syndrome, myopathy, pancreatitis, peripheral nerve palsy, polymyalgia rheumatica, positive ANA, purpura, rhabdomyolysis, Stevens-Johnson syndrome, vasculitis

Additional class-related events or case reports (not necessarily reported with pravastatin therapy): Angioedema, cataracts, depression, dyspnea, eosinophilia, erectile dysfunction, facial paresis, hypersensitivity reaction, impaired extraocular muscle movement, impotence, leukopenia, malaise, memory loss, ophthalmoplegia, paresthesia, peripheral neuropathy, photosensitivity, psychic disturbance, skin discoloration, thrombocytopenia, thyroid dysfunction, toxic epidermal necrolysis, transaminases increased, vomiting

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor); **Inhibits** CYP2C9 (weak), 2D6 (weak), 3A4 (weak)

Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Colchicine: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CycloSPORINE: May increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

DAPTOmycin: HMG-CoA Reductase Inhibitors may enhance the adverse/toxic effect of DAPTOmycin. Specifically, the risk of skeletal muscle toxicity may be increased. Management: Consider temporarily stopping HMG-CoA reductase inhibitor therapy prior to daptomycin. If used together, regular (i.e., at least weekly) monitoring of CPK concentrations is recommended. *Risk D: Consider therapy modification*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Fenofibrate: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fenofibric Acid: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Gemfibrozil: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Gemfibrozil may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Niacin: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Niacinamide: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Protease Inhibitors: May increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): HMG-CoA Reductase Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Consumption of large amounts of ethanol may increase the risk of liver damage with HMG-CoA reductase inhibitors.

Food: Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.

Herb/Nutraceutical: St John's wort may decrease pravastatin levels.

Monitoring ParametersObtain baseline LFTs and total cholesterol profile; creatine phosphokinase due to possibility of myopathy. Repeat LFTs prior to elevation of dose. May be measured when clinically indicated and/or periodically thereafter.

Nursing: Physical Assessment/MonitoringUse caution with history of hepatic disease. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, other lipid-lowering agents may increase risk of myopathy or rhabdomyolysis). Evaluate results of laboratory tests (LFTs and lipid profile) at baseline and periodically. Assess patient response on a regular basis throughout therapy (eg, rash, myalgia, gastrointestinal effects). Teach patient proper use (as adjunct to diet and exercise program), possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to women of childbearing age unless they are capable of complying with effective contraceptive use. Instruct patient in appropriate contraceptive measures.

Monitoring: Lab TestsObtain baseline LFTs and total cholesterol profile; creatine phosphokinase due to possibility of myopathy. Repeat

LFTs prior to elevation of dose. May be measured when clinically indicated and/or periodically thereafter.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take at same time each day with or without food. Follow cholesterol-lowering diet and exercise regimen as prescribed. Avoid excess alcohol. You will have periodic blood tests to assess effectiveness. You may experience mild nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea (buttermilk, boiled milk, or yogurt may help); constipation (increased exercise, fruit, fluids, or fiber may help); or headache, dizziness, or insomnia (use caution when driving or engaged in potentially hazardous tasks until response to drug in known). Contact prescriber immediately with persistent muscle pain or cramping, skeletal or joint pain, or numbness. Report other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber for appropriate barrier contraceptive measures to use during and for 1 month following therapy. This drug may cause severe fetal defects. Do not donate blood during or for 1 month following therapy. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as sodium: 10 mg, 20 mg, 40 mg, 80 mg

Pravachol®: 10 mg; 20 mg [DSC]; 40 mg, 80 mg

Generic AvailableYes

ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)

Pricing: U.S. (www.drugstore.com)

Tablets (Pravachol)

10 mg (30): $119.99

20 mg (30): $114.99

40 mg (30): $169.98

80 mg (30): $191.66

Tablets (Pravastatin Sodium)

10 mg (30): $18.99

20 mg (30): $27.00

40 mg (30): $25.99

80 mg (30): $119.99

Mechanism of ActionPravastatin is a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the rate-limiting enzyme involved in *de novo* cholesterol synthesis.

Pharmacodynamics/Kinetics

Onset of action: Several days

Peak effect: 4 weeks

Absorption: Rapidly absorbed; average absorption 34%

Protein binding: 50%

Metabolism: Hepatic to at least two metabolites

Bioavailability: 17%

Half-life elimination: ~2-3 hours

Time to peak, serum: 1-1.5 hours

Excretion: Feces (70%); urine (≤20%, 8% as unchanged drug)

Related Information

- Hyperlipidemia Management
- Lipid-Lowering Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular Considerations

Primary Prevention: HMG-CoA reductase inhibitors are effective in primary and secondary prevention of cardiovascular events in patients with hyperlipidemia. For primary prevention, a patient's major risk factors (cigarette smoking, hypertension or currently taking antihypertensives, low HDL-C, family history, age, gender) should be evaluated. Patients with multiple risk factors (≥2) require more intensive therapy guided by the calculation of a 10-year absolute CHD risk (eg, the percent probability of having a CHD event in next 10 years). An individual's 10-year absolute CHD risk can be calculated at www.med-decisions.com/cvtool/phys/phys.html. LDL cholesterol goals, therapeutic lifestyle changes, and drug therapy are determined based upon a patient's risk factor profile.

Primary prevention trials show that cholesterol-lowering drugs reduce the risk of major coronary events, coronary death, and cerebrovascular events even in the first 6-12 months of use. The WOSCOP trial suggested a trend towards enhanced survival using pravastatin in their patients (mean LDL-cholesterol of 192 mg/dL and no history of MI). In a recent trial (Sever, 2003), patients with HTN and at least three other risk factors were randomized to 10 mg daily of atorvastatin or placebo. These patients had a total nonfasting cholesterol <250 mg/dL before treatment. LDL-C levels were 132 mg/dL before treatment and fell to an average of 90 mg/dL in the atorvastatin-treated group. There was a significant reduction in stroke, cardiovascular events, and coronary events in the atorvastatin-treated group as compared to the placebo group. There was no difference in mortality between the groups.

HMG-CoA reductase inhibitors decrease C-reactive protein (CRP), an inflammatory marker and an acute phase reactant. Elevated levels of high sensitive CRP (hsCRP), which detects CRP levels as low as 0.175 mg/L, have been shown to be associated with an increased risk of cardiovascular events. Recently, the JUPITER trial demonstrated that the use of rosuvastatin in healthy patients (men ≥ 50 years and women ≥ 60 years) without a history of cardiovascular disease with LDL <130 mg/dL and a hsCRP level ≥ 2 mg/L reduced the risk of major cardiovascular events (eg, nonfatal MI, stroke, death from cardiovascular causes), The number needed to treat over 5 years to prevent 1 cardiovascular event is 25. Current guidelines do not recommend drug treatment for patients with an LDL <130 mg/dL. However, identification of the patient at higher risk of cardiovascular events within this subgroup using hsCRP is now important given that statins may prevent the occurrence of these serious cardiovascular events (Ridker, 2008).

Secondary Prevention: Secondary prevention trials indicate that “statin” therapy reduces mortality, major coronary events, coronary artery procedures, and stroke. The Heart Protection Study proved that lowering serum cholesterol levels reduces the rate of major vascular events among high-risk individuals with documented vascular disease (CHD, cerebrovascular, peripheral vascular) or diabetes regardless of initial cholesterol concentrations. PROVE IT is a randomized, double-blind trial evaluating hospitalized patients with acute coronary syndrome to determine the effects of intense LDL-C lowering therapy. Four thousand patients with an LDL-C levels of 106 mg/dL were randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily. After 2 years, the combined cardiovascular endpoint (death, MI, unstable angina requiring hospitalization, revascularization and stroke) was ~26% in the pravastatin patients (median LDL-C 95 mg/dL) and ~22% in the atorvastatin treated patients (median LDL-C 62 mg/dL).

LaRosa and colleagues assessed the efficacy and safety of lowering LDL cholesterol <100 mg/dL in patients with stable coronary heart disease (LaRosa, 2005). Ten thousand and one patients with baseline LDL levels <130 mg/dL were randomized to atorvastatin 10 mg or 80 mg daily and followed for a median of 4.9 years. The primary endpoint was the occurrence of the first major cardiovascular event (death from CVD, MI, resuscitation after cardiac arrest, or stroke). A primary event occurred in 434 patients (8.7%) receiving 80 mg daily (mean LDL 77 mg/dL) and 548 patients (10.9%) receiving 10 mg dose (mean LDL 101 mg/dL) (95% CI, 0.69-0.89; $p <0.001$). There was no mortality difference between the two treatment groups.

In addition to the ability of HMG-CoA reductase inhibitors to decrease levels of high-sensitivity C-reactive protein (hs-CRP), they also possess pleiotropic properties including improved endothelial function, reduced inflammation at the site of the coronary plaque, inhibition of platelet aggregation, and anticoagulant effects. These nonlipid effects may be beneficial when HMG-CoA reductase inhibitors are introduced early in the management of acute coronary syndromes (de Denus, 2002).

Myopathy: Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years of age), women more frequently than men, small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, drug interactions (use with caution or avoid). The combination of a HMG-CoA reductase inhibitor plus nicotinic acid seems to carry a lower risk of myopathy than does a HMG-CoA reductase inhibitor plus a fibrate. Other medications, when used concurrently, may enhance the risk of myopathy associated with statins; these include drugs that inhibit CYP3A4 isoenzymes (lovastatin, simvastatin, atorvastatin) or CYP2C9 isoenzymes (fluvastatin). HMG-CoA reductase inhibitors may exacerbate exercise-induced skeletal muscle injury. Many experts favor getting a baseline creatine kinase (CK) measurement before initiating therapy (asymptomatic CK elevations are common). Obtain a CK measurement if patient complains of muscle soreness, tenderness, or pain.

Anesthesia and Critical Care Concerns/Other Considerations**Myopathy:** Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years), gender (occurs in women more frequently than men), small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, and drug interactions (use with caution or avoid).

Based on current research, HMG-CoA reductase inhibitors should be continued in the perioperative period. Postoperative discontinuation of statin therapy is associated with an increased risk of cardiac morbidity and mortality.

Index TermsPravastatin Sodium

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International Brand NamesAstin (MX); Brakhor (MX); Bristacol (ES); Brufincol (MX); Cholespar (ID); Cholstat (AU); Col-Alphar (MX); Colpradin (MX); Elisor (FR); Emipastin (MX); Genoestatina (MX); Kenstatin (MX); Koloskol (ID); Lipemol (ES); Liplat (ES); Lipostat (AU, BG, CZ, EE, GB, HN, HU, IE, NZ, PH, PL); Liprachol (AU); Liprevil (DE); Loretsin (MX); Mevachol (ID); Mevalotin (CL, DE, ID, JP, KP, TH); Novales (ID); Novina (MX); Prastan (KP); Pratin (TW); Prava (ZA); Pravachol (AT, AU, BB, BM, BS, BZ, CO, DK, FI, GR, GY, HK, ID, JM, MY, NO, PE, PK, PL, SE, SR, TT, VE); Pravacol (AR, BR, CN, EC, MX, PE, PT); Pravalip (IL); Pravaselect (IT); Pravasin (DE, LU); Pravasine (BE); Pravator (IN); Pravyl (CO); Ravasta (KP); Sanaprav (AT, IT); Selectin (IT); Selektine (NL); Selipran (AT, CH); Tissulest (MX); Vasten (FR)

Praziquantel

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(pray zi KWON tel)
U.S. Brand NamesBiltricide®
Canadian Brand NamesBiltricide®
Pharmacologic CategoryAnthelmintic
Use: Labeled IndicationsAll stages of schistosomiasis caused by all *Schistosoma* species pathogenic to humans; clonorchiasis and opisthorchiasis
Use: Unlabeled/InvestigationalCysticercosis and many intestinal tapeworms
Dosing: Adults

Schistosomiasis: Oral: 20 mg/kg/dose 2-3 times/day for 1 day at 4- to 6-hour intervals

Flukes (unlabeled use): Oral: 25 mg/kg/dose every 8 hours for 1-2 days

Cysticercosis (unlabeled use): Oral: 50 mg/kg/day divided every 8 hours for 14 days

Tapeworms (unlabeled use): Oral: 10-20 mg/kg as a single dose (25 mg/kg for *Hymenolepis nana*)

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren >4 years: Refer to adult dosing.
Administration: OralTablets may be halved or quartered.
ContraindicationsHypersensitivity to praziquantel or any component of the formulation; ocular cysticercosis
Warnings/Precautions

Disease-related concerns:

- Cerebral cysticercosis: Patients with cerebral cysticercosis require hospitalization.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

Concurrent drug therapy issues:

- Strong inducers of cytochrome P450: Use caution with concurrent administration of strong inducers of cytochrome P450; therapeutic levels of praziquantel may not be achieved.

Pregnancy Risk FactorB
LactationEnters breast milk
Adverse Reactions

1% to 10%:

Central nervous system: Dizziness, drowsiness, headache, malaise, CSF reaction syndrome in patients being treated for neurocysticercosis

Gastrointestinal: Abdominal pain, loss of appetite, nausea, vomiting

Miscellaneous: Diaphoresis

<1%: Diarrhea, fever, itching, rash, urticaria

Metabolism/Transport Effects**Inhibits** CYP2D6 (weak)
Drug Interactions

Aminoquinolines (Antimalarial): May decrease the serum concentration of Anthelmintics. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Praziquantel. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ketoconazole: May increase the serum concentration of Praziquantel. Management: Praziquantel dose may need to be reduced when used with ketoconazole. *Risk D: Consider therapy modification*

Rifampin: May decrease the serum concentration of Praziquantel. *Risk X: Avoid combination*

Nursing: Physical Assessment/MonitoringSee Warnings/Precautions and Contraindications for use cautions. Worm infestations are easily transmitted, all close family members should be treated. Instruct patient/caregiver on appropriate use, transmission prevention, possible side effects/appropriate interventions, and adverse symptoms to report (see Patient Education).

Monitoring: Lab TestsCulture urine or feces for ova prior to instituting therapy.

Patient EducationTake exactly as directed for full course of medication. Tablets may be chewed, swallowed whole, or crushed and mixed with food. Increase dietary intake of fruit juices. All family members and close friends should also be treated. To reduce possibility of reinfection, wash hands and scrub nails carefully with soap and hot water before handling food, before eating, and before and after toileting. Keep hands out of mouth. Disinfect toilet daily and launder bed linens, undergarments, and nightclothes daily with hot water and soap. Do not go barefoot and do not sit directly on grass or ground. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); or abdominal pain, nausea, or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report unusual fatigue, persistent dizziness, CNS changes, change in color of urine or stool, or easy bruising or unusual bleeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet [tri-scored]: 600 mg

Generic AvailableNo

ManufacturerBayer Corp (Biological and Pharmaceutical Division)

Pricing: U.S. (www.drugstore.com)

Tablets (Biltricide)

600 mg (6): $77.70

Mechanism of ActionIncreases the cell permeability to calcium in schistosomes, causing strong contractions and paralysis of worm musculature leading to detachment of suckers from the blood vessel walls and to dislodgment

Pharmacodynamics/Kinetics

Absorption: Oral: ~80%

Distribution: CSF concentration is 14% to 20% of plasma concentration; enters breast milk

Protein binding: ~80%

Metabolism: Extensive first-pass effect

Half-life elimination: Parent drug: 0.8-1.5 hours; Metabolites: 4.5 hours

Time to peak, serum: 1-3 hours

Excretion: Urine (99% as metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

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International Brand NamesBiltricide (AE, AU, BF, BH, BJ, CI, CY, EG, ET, FR, GH, GM, GN, HK, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Cesol (DE, MX, PL); Cisticid (BR, CN, MX, PE, VE); Distocide (AE, BH, CY, EG, IL, IQ, IR, JO, KP, KW, LB, LY, OM, QA, SA, SY, YE); Droncit Vet (NO); Kalcide (TW); Mycotricide (TH); Opticide (TH); Prazine (IN); Praziquin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Prazite (TH); Prazitral (AR); Vermaqpharma Vet (NO); Wormicide (TH)

Prazosin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Prazosin may be confused with predniSONE

International issues:

Prazac® [Denmark] may be confused with Prozac® which is a brand name for fluoxetine in the U.S.

Prazepam [multiple international markets] may be confused with prazosin.

Pronunciation(PRAZ oh sin)

U.S. Brand NamesMinipress®

Canadian Brand NamesApo-Prazo®; Minipress®; Novo-Prazin; Nu-Prazo

Pharmacologic CategoryAlpha$_1$ Blocker

Use: Labeled IndicationsTreatment of hypertension

Use: Unlabeled/InvestigationalPost-traumatic stress disorder (PTSD); benign prostatic hyperplasia; Raynaud's syndrome

Dosing: Adults

Hypertension: Oral: Initial: 1 mg/dose 2-3 times/day; usual maintenance dose: 3-15 mg/day in divided doses 2-4 times/day; maximum daily dose: 20 mg

Hypertensive urgency: Oral: 10-20 mg once, may repeat in 30 minutes

PTSD (unlabeled use): Initial: 2 mg at bedtime; titrate as tolerated to 10-15 mg at bedtime

Raynaud's (unlabeled use): Oral: 0.5-3 mg twice daily

Benign prostatic hyperplasia (unlabeled use): Oral: 2 mg twice daily

Dosing: ElderlyOral (first dose given at bedtime): Initial: 1 mg 1-2 times/day

Dosing: PediatricOral: Children (unlabeled use): Initial: 0.05-0.1 mg/kg/day in 3 divided doses; maximum: 0.5 mg/kg/day

StorageStore in airtight container. Protect from light.

ContraindicationsHypersensitivity to quinazolines (doxazosin, prazosin, terazosin) or any component of the formulation; concurrent use with phosphodiesterase-5 (PDE-5) inhibitors including sildenafil (>25 mg), tadalafil, or vardenafil

Allergy Considerations

- Alpha-Blocker, Piperazinyl Quinazoline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Angina: Discontinue if symptoms of angina occur or worsen.
- Orthostatic hypotension/syncope: May cause significant orthostatic hypotension and syncope, especially with first dose; anticipate a similar effect if therapy is interrupted for a few days, if dosage is rapidly increased, or if another antihypertensive drug (particularly vasodilators) or a PDE-5 inhibitor is introduced. Patients should be cautioned about performing hazardous tasks when starting new therapy or adjusting dosage upward.

Disease-related concerns:

- Prostate cancer: Should rule out prostatic carcinoma before beginning therapy.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsAdverse effects such as dry mouth and urinary problems can be particularly bothersome in elderly.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Central nervous system: Dizziness (10%)

1% to 10%:

Cardiovascular: Palpitation (5%), edema, orthostatic hypotension, syncope (1%)

Central nervous system: Headache (8%), drowsiness (8%), vertigo, depression, nervousness

Dermatologic: Rash (1% to 4%)

Endocrine & metabolic: Decreased energy (7%)

Gastrointestinal: Nausea (5%), vomiting, diarrhea, constipation

Genitourinary: Urinary frequency (1% to 5%)

Neuromuscular & skeletal: Weakness (7%)

Ocular: Blurred vision, reddened sclera, xerostomia

Respiratory: Dyspnea, epistaxis, nasal congestion

<1% (Limited to important or life-threatening): Abdominal discomfort, alopecia, angina, bradycardia, cataracts (both development and disappearance have been reported), hallucinations, impotence, incontinence, lichen planus, liver function abnormalities, MI, narcolepsy (worsened), pancreatitis, paresthesia, pigmentary mottling and serous retinopathy, priapism, pruritus, tachycardia, tinnitus

Postmarketing and/or case reports: Allergic reaction, cataplexy, enuresis, eye pain, gynecomastia, leukopenia, systemic lupus erythematosus, urticaria, vasculitis

Drug Interactions

Alfuzosin: Alpha1-Blockers may enhance the antihypertensive effect of Alfuzosin. Risk of orthostatic hypotension or syncope may be increased. Alfuzosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Alpha1-Blockers may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: May enhance the hypotensive effect of Alpha1-Blockers. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Silodosin: Alpha1-Blockers may enhance the adverse/toxic effect of Silodosin. Of particular concern are the risk of postural hypotension, syncope, and/or hypotension. Silodosin may enhance the hypotensive effect of Alpha1-Blockers. Of particular concern are the risk of postural hypotension, syncope, and/or hypotension. *Risk X: Avoid combination*

Tamsulosin: Alpha1-Blockers may enhance the antihypertensive effect of Tamsulosin. Risk of orthostatic hypotension or syncope may be increased. Tamsulosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase vasodilation).

Food: Food has variable effects on absorption.

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid saw palmetto (due to limited experience with this combination). Avoid garlic (may have increased antihypertensive effect).

Test InteractionsIncreased urinary VMA 17%, norepinephrine metabolite 42%

Monitoring ParametersBlood pressure, standing and sitting/supine

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, anything that may affect blood pressure [beta-blockers, diuretics, ACE inhibitors, calcium channel blockers, dong quai] and any PDE-5 inhibitors [sildenafil, tadalafil, vardenafil]). Evaluate therapeutic effectiveness (cardiac status and blood pressure) and adverse reactions (eg, orthostatic hypotension, rash, drowsiness, nausea, vomiting) at beginning of therapy and on a regular basis with long-term therapy. When discontinuing, monitor blood pressure and taper dose slowly over 1 week or more. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. Do not take any new medication during therapy unless approved by prescriber. Take as directed, at same time each day, with or without meals; do not skip dose or discontinue without consulting prescriber. Avoid alcohol. Follow recommended diet and exercise program. May cause drowsiness, dizziness, or impaired judgment (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from sitting or lying position or when climbing stairs); or dry mouth or nausea (frequent mouth care or sucking lozenges may help). Report increased nervousness or depression; sudden weight gain (weigh yourself in the same clothes at the same time of day once a week); palpitations or rapid heartbeat; respiratory difficulty; muscle weakness, fatigue, or pain; vision changes or hearing; rash; changes in urinary pattern (void before taking medications); or other persistent side effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 1 mg, 2 mg, 5 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Minipress)

1 mg (60): $29.99

2 mg (60): $60.42

5 mg (60): $101.17

Capsules (Prazosin HCl)

1 mg (60): $17.99

2 mg (60): $22.99

5 mg (60): $33.99

Mechanism of ActionCompetitively inhibits postsynaptic alpha-adrenergic receptors which results in vasodilation of veins and arterioles and a decrease in total peripheral resistance and blood pressure

Pharmacodynamics/Kinetics

Onset of action: BP reduction: ~2 hours

Maximum decrease: 2-4 hours

Duration: 10-24 hours

Distribution: Hypertensive adults: V_d: 0.5 L/kg

Protein binding: 92% to 97%

Metabolism: Extensively hepatic

Bioavailability: 43% to 82%

Half-life elimination: 2-4 hours; prolonged with congestive heart failure

Excretion: Urine (6% to 10% as unchanged drug)

Related Information

- Depression

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation). Significant orthostatic hypotension is a possibility; monitor patient when getting out of dental chair.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause drowsiness or nervousness; may rarely cause nightmares

Mental Health: Effects on Psychiatric TreatmentConcurrent use with low potency antipsychotics and TCAs may increase risk of postural hypotension

Cardiovascular ConsiderationsAn alpha$_1$ blocker may be used in combination with other agents for the treatment of hypertension or alone in select patients who fail to respond or have contraindications to other agents. Patients with BPH may derive an extra benefit from therapy. Recently, the doxazosin treatment arm of ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) was prematurely stopped due to a significantly higher incidence (25%) of cardiovascular events, particularly heart failure events, compared to the diuretic (chlorthalidone) treatment arm. This unfavorable difference was also present when doxazosin was compared to the amlodipine and lisinopril treatment arms. This study does not address cardiovascular outcomes when doxazosin is combined with other antihypertensive medications. Consideration should be given to the ALLHAT results when considering the use of an alpha$_1$ blocker for treatment of hypertension.

Anesthesia and Critical Care Concerns/Other ConsiderationsAlpha$_1$ blockers do not affect renal blood flow or glomerular filtration. Orthostatic hypotension, compared to newer alpha-blockers, is more of a concern.

Index TermsFurazosin; Prazosin Hydrochloride

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Raskind MA, Peskind ER, Kanter ED, et al, "Reduction of Nightmares and Other PTSD Symptoms in Combat Veterans by Prazosin: A Placebo-Controlled Study," *Am J Psychiatry*, 2003, 160(2):371-3.[PubMed 12562588]

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Raskind MA, Peskind ER, Hoff DJ, et al, "A Parallel Group Placebo Controlled Study of Prazosin for Trauma Nightmares and Sleep Disturbance in Combat Veterans With Post-traumatic Stress Disorder," *Biol Psychiatry*, 2007, 61(8):928-34.[PubMed 17069768]

International Brand NamesAtodel (MY, PH); Decliten (AR); Deprazolin (CZ); Hypotens (IL); Hypovase (GB, IE); Hyprosin (NZ, TW); Lopress (TH); Minipres (AR, BZ, CR, ES, GT, MX, NI, PA, SV, VE); Minipres Retard (AR); Minipres SR (CO); Minipress (AE, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, FR, GH, GM, GN, GR, GY, HK, HN, ID, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PK, PL, QA, SA, SC, SD, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Minipress SR (BR); Minipress XL (IN); Minison (MY); Peripress (FI); Polpressin (PL); Polypress (TH); Pratisol (NZ, TW, ZA); Pratsiol (BG, FI); Praxin (PY, UY); Prazohexal (AU); Prazopress (IN); Pressin (AU)

Prednicarbate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Dermatop® may be confused with Dimetapp®

Pronunciation(pred ni KAR bate)

U.S. Brand NamesDermatop®

Canadian Brand NamesDermatop®

Pharmacologic CategoryCorticosteroid, Topical

Use: Labeled IndicationsRelief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (medium potency topical corticosteroid)

Dosing: Adults**Steroid-responsive dermatoses:** Topical: Apply a thin film to affected area twice daily. Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to prednicarbate or any component of the formulation; fungal, viral, or tubercular skin lesions, herpes simplex or zoster

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: Systemic absorption of topical corticosteroids may cause hypothalamic-pituitary-adrenal (HPA) axis suppression (reversible) particularly in younger children. HPA axis suppression may lead to adrenal crisis. Risk is increased when used over large surface areas, for prolonged periods, or with occlusive dressings.
- Contact dermatitis: Allergic contact dermatitis can occur, it is usually diagnosed by failure to heal rather than clinical exacerbation.
- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.
- Systemic effects: Adverse systemic effects including hyperglycemia, glycosuria, fluid and electrolyte changes, and HPA suppression may occur when used on large surface areas, for prolonged periods, or with an occlusive dressing.

Disease-related concerns:

- Diaper dermatitis: Do not use for diaper dermatitis.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <1 year of age. Chronic use of corticosteroids in children may interfere with growth and development.

Geriatric ConsiderationsDue to age-related changes in skin, limit use of topical corticosteroids.

Pregnancy Risk FactorC

Adverse Reactions

1% to 10%: Dermatologic: Skin atrophy, shininess, thinness, mild telangiectasia

<1%: Pruritus, edema, urticaria, burning, allergic contact dermatitis and rash, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, secondary infection, striae, miliaria, paresthesia

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Monitoring ParametersRelief of symptoms

Patient EducationUse only as prescribed and for no longer than the period prescribed. Apply sparingly in a thin film and rub in lightly. Avoid contact with eyes. Do not apply to the face, underarms, or groin areas. Notify prescriber if condition persists or worsens.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream: 0.1% (15 g, 60 g)

Dermatop®: 0.1% (15 g [DSC], 60 g)

Ointment: 0.1% (15 g, 60 g)

Dermatop®: 0.1% (15 g [DSC], 60 g)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Cream (Dermatop)

0.1% (60): $75.20

Cream (Prednicarbate)

0.1% (60): $57.99

Ointment (Dermatop)

0.1% (15): $21.99

0.1% (60): $43.99

Ointment (Prednicarbate)

0.1% (15): $27.97

0.1% (60): $54.99

Mechanism of ActionTopical corticosteroids have anti-inflammatory, antipruritic, vasoconstrictive, and antiproliferative actions

Pharmacotherapy PearlsHas been shown that the atrophic activity of prednicarbate is many times less than agents with similar clinical potency, nevertheless, avoid use on the face.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Goedert JJ, Vitale F, Lauria C, et al, “Risk Factors for Classical Kaposi's Sarcoma,” *J Natl Cancer Inst*, 2002, 94(22):1712-8.[PubMed 12441327]

Rumbaugh MM, “High Potency Topical Corticosteroids,” *US Pharm*, 1993, 18(6):30-41.

International Brand NamesBatmen (ES); Dermatop (BR, CZ, DE, HR, IT); Dermotop (HR); Peitel (ES); Prednitop (CH); Primaderm (AR)

Prednisolone and Gentamicin

English

English

Jump To Field (Select Field Name)

Pronunciation(pred NIS oh lone & jen ta MYE sin)

U.S. Brand NamesPred-G®

Pharmacologic Category[Antibiotic/Corticosteroid, Ophthalmic]

Use: Labeled IndicationsTreatment of steroid responsive inflammatory conditions and superficial ocular infections due to microorganisms susceptible to gentamicin

Dosing: Adults**Inflammatory conditions and superficial ocular infections:** Ophthalmic:

Ointment: Apply $^{1}/_{2}$ inch ribbon in the conjunctival sac 1-3 times/day

Suspension: 1 drop 2-4 times/day; during the initial 24-48 hours, the dosing frequency may be increased if necessary up to 1 drop every hour

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: OtherOphthalmic:

Ointment: For topical application into the conjunctival sac

Suspension: For topical application to the eye only; shake suspension well before using; do not inject subconjunctivally or introduce into the anterior chamber of the eye

ContraindicationsHypersensitivity to gentamicin, prednisolone, other aminoglycosides or corticosteroids, or any component of the formulation; viral disease of the cornea and conjunctiva (including epithelia herpes simplex keratitis, vaccinia, varicella); mycobacterial or fungal infection of the eye; uncomplicated removal of a corneal foreign body

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Infection: Steroids may mask infection or enhance existing ocular infection; prolonged use may result in secondary infections due to immunosuppression.
- Ocular effects: Prolonged use of corticosteroids may result in glaucoma; damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation may occur.

Special populations:

- Cataract surgery patients: Use following cataract surgery may delay healing or increase the incidence of bleb formation.

Other warnings/precautions:

- Appropriate use: For ophthalmic use only. A maximum of 20 mL of suspension should be prescribed initially; patients should be evaluated prior to additional refills. Prescriptions extending beyond 14 days should include exams using magnification.

Geriatric ConsiderationsNo specific recommendations for use in the elderly necessary.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is unknown if topical use results in sufficient absorption to produce detectable quantities in breast milk.

Adverse ReactionsFrequency not defined.

Dermatologic: Delayed wound healing

Local: Burning, stinging

Ocular: Intraocular pressure increased, glaucoma, superficial punctate keratitis, optic nerve damage (infrequent), posterior subcapsular cataract formation

Miscellaneous: Secondary infection

Metabolism/Transport EffectsPrednisolone: **Substrate** of CYP3A4 (minor); **Inhibits** CYP3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Ointment, ophthalmic:

Pred-G®: Prednisolone acetate 0.6% and gentamicin sulfate 0.3% (3.5 g)

Suspension, ophthalmic:

Pred-G®: Prednisolone acetate 1% and gentamicin sulfate 0.3% (5 mL, 10 mL) [contains benzalkonium chloride]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Suspension (Pred-G)

0.3-1% (2): $13.99

0.3-1% (5): $31.99

0.3-1% (10): $55.99

Pharmacodynamics/KineticsSee individual agents.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsGentamicin and Prednisolone
References

Samples JR and Meyer SM, “Use of Ophthalmic Medications in Pregnant and Nursing Women,” *Am J Ophthalmol*, 1988, 106(5):616-23.[PubMed 2903673]

PrednisoLONE

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

PrednisoLONE may be confused with predniSONE

Pediapred® may be confused with Pediazole®

Pronunciation(pred NISS oh lone)
U.S. Brand NamesEconopred® Plus [DSC]; Millipred™; Omnipred™; Orapred ODT™; Orapred®; Pediapred®; Pred Forte®; Pred Mild®; Prelone®
Canadian Brand NamesDiopred®; Hydeltra T.B.A.®; Inflamase® Mild; Novo-Prednisolone; Ophtho-Tate®; Pediapred®; Pred Forte®; Pred Mild®; Sab-Prenase
Pharmacologic CategoryCorticosteroid, Ophthalmic; Corticosteroid, Systemic
Use: Labeled IndicationsTreatment of palpebral and bulbar conjunctivitis; corneal injury from chemical, radiation, thermal burns, or foreign body penetration; endocrine disorders, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, respiratory diseases, hematologic disorders, neoplastic diseases, edematous states, and gastrointestinal diseases; resolution of acute exacerbations of multiple sclerosis; management of fulminating or disseminated tuberculosis and trichinosis; acute or chronic solid organ rejection
Use: DentalTreatment of a variety of oral diseases of allergic, inflammatory, or autoimmune origin
Dosing: AdultsDose depends upon condition being treated and response of patient. Oral dosage expressed in terms of prednisolone base. Consider alternate day therapy for long-term therapy. Discontinuation of long-term therapy requires gradual withdrawal by tapering the dose. Patients undergoing unusual stress while receiving corticosteroids, should receive increased doses prior to, during, and after the stressful situation.

Usual dose (range): Oral: 5-60 mg/day

Rheumatoid arthritis: Oral: Initial: 5-7.5 mg/day, adjust dose as necessary

Multiple sclerosis: Oral: 200 mg/day for 1 week followed by 80 mg every other day for 1 month

Conjunctivitis: Ophthalmic (suspension/solution): Instill 1-2 drops into conjunctival sac every hour during day, every 2 hours at night until favorable response is obtained, then use 1 drop every 4 hours.

Dosing adjustment in hyperthyroidism: Prednisolone dose may need to be increased to achieve adequate therapeutic effects.

Dosing: ElderlyUse lowest effective adult dose. Dose depends upon condition being treated and response of patient; alternate day dosing may be attempted in some disease states.
Dosing: PediatricDose depends upon condition being treated and response of patient; dosage for infants and children should be based on severity of the disease and response of the patient rather than on strict adherence to dosage indicated by age, weight, or body surface area. Oral dosage expressed in terms of prednisolone base. Consider alternate day therapy for long-term therapy. Discontinuation of long-term therapy requires gradual withdrawal by tapering the dose. Patients undergoing unusual stress while receiving corticosteroids, should receive increased doses prior to, during, and after the stressful situation.

Acute asthma: Oral: 1-2 mg/kg/day in divided doses 1-2 times/day for 3-5 days

Anti-inflammatory or immunosuppressive dose: Oral: 0.1-2 mg/kg/day in divided doses 1-4 times/day

Nephrotic syndrome: Oral:

Initial (first 3 episodes): 2 mg/kg/day **or** 60 mg/m^2/day (maximum: 80 mg/day) in divided doses 3-4 times/day until urine is protein free for 3 consecutive days (maximum: 28 days); followed by 1-1.5 mg/kg/dose **or** 40 mg/m^2/dose given every other day for 4 weeks

Maintenance (for frequent relapses): 0.5-1 mg/kg/dose given every other day for 3-6 months

Conjunctivitis: Ophthalmic (suspension/solution): Children: Refer to adult dosing.

Dosing adjustment in hyperthyroidism: Refer to adult dosing.

Dosing: Renal ImpairmentSlightly dialyzable (5% to 20%)
Dosing: Combination Regimens

Lymphoma, Hodgkin's:

LOPP

MOPP

Calculations

- Corticosteroid Conversion

Administration: OralAdminister oral formulation with food or milk to decrease GI effects.

Orapred ODT™: Do not break or use partial tablet. Remove tablet from blister pack just prior to use. May swallow whole or allow to dissolve on tongue.

Dietary ConsiderationsShould be taken after meals or with food or milk to decrease GI effects; increase dietary intake of pyridoxine, vitamin C, vitamin D, folate, calcium, and phosphorus.

StorageStore Orapred ODT™ at 20°C to 25°C (68°F to 77°F) in blister pack. Protect from moisture.

ContraindicationsHypersensitivity to prednisolone or any component of the formulation; acute superficial herpes simplex keratitis; live or attenuated virus vaccines (with immunosuppressive doses of corticosteroids); systemic fungal infections; varicella

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections) or prolong or exacerbate viral infections. Exposure to chickenpox should be avoided; corticosteroids should not be used to treat ocular herpes simplex. Corticosteroids should not be used for cerebral malaria or viral hepatitis. Use with caution in patients with tuberculosis.

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Myopathy: Acute myopathy has been reported with high dose corticosteroids, usually in patients with neuromuscular transmission disorders; may involve ocular and/or respiratory muscles; monitor creatine kinase; recovery may be delayed.

- Ocular effects: Prolonged use of corticosteroids may result in glaucoma; damage to the optic nerve (not indicated for treatment of optic neuritis), defects in visual acuity and fields of vision, and posterior subcapsular cataract formation may occur. Use following cataract surgery may delay healing or increase the incidence of bleb formation.

- Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with HF; long-term use has been associated with fluid retention and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.

- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids.

- Myocardial infarction (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Elderly: Because of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly in the smallest possible effective dose for the shortest duration.

- Pediatrics: May affect growth velocity; growth should be routinely monitored in pediatric patients.

Other warnings/precautions:

- Discontinuation of therapy: Withdraw therapy with gradual tapering of dose.

Geriatric ConsiderationsUseful in patients with inability to activate prednisone (liver disease). Because of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly, in the smallest possible dose, and for the shortest possible time. For long-term use, monitor bone mineral density and institute fracture prevention strategies.

Pregnancy Risk FactorC

Pregnancy ConsiderationsOphthalmic prednisolone was shown to be teratogenic in animal studies and adverse events have been observed with corticosteroids in animal reproduction studies. Prednisolone crosses the placenta; prior to reaching the fetus, prednisolone is converted by placental enzymes to prednisone. As a result, the amount of prednisolone reaching the fetus is ~8-10 times lower than the maternal serum concentration (healthy women at term; similar results observed with preterm pregnancies complicated by HELLP syndrome). Some studies have shown an association between first trimester corticosteroid use and oral clefts; adverse events in the fetus/neonate have been noted in case reports following large doses of systemic corticosteroids during pregnancy. Women exposed to prednisolone during pregnancy for the treatment of an autoimmune disease may contact the OTIS Autoimmune Diseases Study at 877-311-8972.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsPrednisolone is excreted into breast milk with peak concentrations occurring ~1 hour after the maternal dose. The milk/plasma ratio was found to be 0.2 with doses ≥30 mg/day and 0.1 with doses <30 mg/day. Following a maternal dose of prednisolone 80 mg/day, a breast-feeding infant would ingest <0.1% of the dose.

Adverse ReactionsFrequency not defined.

Ophthalmic formulation:

Endocrine & metabolic: Hypercorticoidism (rare)

Ocular: Conjunctival hyperemia, conjunctivitis, corneal ulcers, delayed wound healing, glaucoma, intraocular pressure increased, keratitis, loss of accommodation, optic nerve damage, mydriasis, posterior subcapsular cataract formation, ptosis, secondary ocular infection

Oral formulation:

Cardiovascular: Cardiomyopathy, CHF, edema, facial edema, hypertension

Central nervous system: Convulsions, headache, insomnia, malaise, nervousness, pseudotumor cerebri, psychic disorders, vertigo

Dermatologic: Bruising, facial erythema, hirsutism, petechiae, skin test reaction suppression, thin fragile skin, urticaria

Endocrine & metabolic: Carbohydrate tolerance decreased, Cushing's syndrome, diabetes mellitus, growth suppression, hyperglycemia, hypernatremia, hypokalemia, hypokalemic alkalosis, menstrual irregularities, negative nitrogen balance, pituitary adrenal axis suppression

Gastrointestinal: Abdominal distention, increased appetite, indigestion, nausea, pancreatitis, peptic ulcer, ulcerative esophagitis, weight gain

Hepatic: LFTs increased (usually reversible)

Neuromuscular & skeletal: Arthralgia, aseptic necrosis (humeral/femoral heads), fractures, muscle mass decreased, muscle weakness, osteoporosis, steroid myopathy, tendon rupture, weakness

Ocular: Cataracts, exophthalmus, eyelid edema, glaucoma, intraocular pressure increased, irritation

Respiratory: Epistaxis

Miscellaneous: Diaphoresis increased, impaired wound healing

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor); **Inhibits** CYP3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase gastric mucosal irritation).

Food: Prednisolone interferes with calcium absorption. Limit caffeine.

Herb/Nutraceutical: St John's wort may decrease prednisolone levels. Avoid cat's claw, echinacea (have immunostimulant properties).

Test InteractionsResponse to skin tests

Monitoring ParametersBlood pressure; blood glucose, electrolytes; intraocular pressure (use >6 weeks); bone mineral density

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effectiveness, and adverse effects according to indications for therapy, dose, route, and duration of therapy. With systemic administration, patients with diabetes should monitor glucose levels closely. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. When used for long-term therapy (>10-14 days), do not discontinue abruptly; decrease dosage incrementally.

Monitoring: Lab TestsBlood glucose, electrolytes

Patient EducationTake exactly as directed; do not increase dose or discontinue abruptly without consulting prescriber. Avoid alcohol. Limit intake of caffeine or stimulants. Prescriber may recommend increased dietary vitamins, minerals, or iron. If you have diabetes, monitor glucose levels closely (antidiabetic medication may need to be adjusted). Inform prescriber if you are experiencing greater-than-normal levels of stress (medication may need adjustment). Some forms of this medication may cause GI upset (oral medication should be taken with meals to reduce GI upset; small frequent meals and frequent mouth care may reduce GI upset). You may be more susceptible to infection (avoid crowds and exposure to infection). Report promptly excessive nervousness or sleep disturbances; any signs of infection (sore throat, unhealed injuries); excessive growth of body hair or loss of skin color; vision changes; excessive or sudden weight gain (>3 lb/week); swelling of face or extremities; respiratory difficulty; muscle weakness; change in color of stools (black or tarry) or persistent abdominal pain; or worsening of condition or failure to improve. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Ophthalmic: For ophthalmic use only. Wash hands before using. Tilt head back and look upward. Put drops of suspension inside lower eyelid. Close eye and roll eyeball in all directions. Do not blink for 1/2 minute. Apply gentle pressure to inner corner of eye for 30 seconds. Do not use any other eye preparation for at least 10 minutes. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Do not share medication with anyone else. Wear sunglasses when in sunlight; you may be more sensitive to bright light. Inform prescriber if condition worsens or fails to improve or if you experience eye pain, disturbances of vision, or other adverse eye response.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, ophthalmic, as sodium phosphate: 1% (5 mL, 10 mL, 15 mL) [contains benzalkonium chloride]

Solution, oral, as base: Prednisolone 15 mg/5 mL (240 mL, 480 mL)

Solution, oral, as sodium phosphate: Prednisolone base 5 mg/5 mL (120 mL, 240 mL); prednisolone base 15 mg/5 mL (240 mL)

Millipred™: 13.4 mg/5 mL (237 mL) [equivalent to prednisolone base 10 mg/5 mL; dye free; grape flavor]

Orapred®: 20 mg/5 mL (20 mL, 240 mL) [equivalent to prednisolone base 15 mg/5 mL; dye free; contains alcohol 2%, sodium benzoate; grape flavor]

Pediapred®: 6.7 mg/5 mL (120 mL) [equivalent to prednisolone base 5 mg/5 mL; dye free; raspberry flavor]

Suspension, ophthalmic, as acetate: 1% (5 mL, 10 mL, 15 mL)

Econopred® Plus [DSC], Omnipred™: 1% (5 mL, 10 mL) [contains benzalkonium chloride]

Pred Forte®: 1% (1 mL, 5 mL, 10 mL, 15 mL) [contains benzalkonium chloride and sodium bisulfite]

Pred Mild®: 0.12% (5 mL, 10 mL) [contains benzalkonium chloride and sodium bisulfite]

Syrup, as base: 5 mg/5 mL (120 mL); 15 mg/5 mL (5 mL [DSC], 240 mL, 480 mL)

Prelone®: 15 mg/5 mL (240 mL, 480 mL) [contains alcohol 5%, benzoic acid; cherry flavor]

Tablet, as base: 5 mg

Tablet, orally disintegrating, as sodium phosphate [strength expressed as base]:

Orapred ODT™: 10 mg, 15 mg, 30 mg [grape flavor]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Pediapred)

6.7 mg/5 mL (120): $42.38

Solution (PrednisoLONE Sodium Phosphate)

1% (5): $19.99

1% (10): $23.99

1% (15): $29.99

5 mg/5 mL (118): $26.99

15 mg/5 mL (237): $99.99

Suspension (Econopred Plus)

1% (5): $40.99

1% (10): $57.99

Suspension (Omnipred)

1% (10): $63.99

Suspension (Pred Forte)

1% (5): $31.49

1% (10): $57.74

1% (15): $82.94

Suspension (Pred Mild)

0.12% (10): $39.99

Suspension (PrednisoLONE Acetate)

1% (5): $15.99

1% (10): $20.99

1% (15): $33.99

Syrup (PrednisoLONE)

15 mg/5 mL (120): $52.00

Tablet, orally-disintegrating (Orapred ODT)

15 mg (48): $257.22

Mechanism of ActionDecreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability; suppresses the immune system by reducing activity and volume of the lymphatic system

Pharmacodynamics/Kinetics

Duration: 18-36 hours

Protein binding (concentration dependent): 65% to 91%; decreased in elderly

Metabolism: Primarily hepatic, but also metabolized in most tissues, to inactive compounds

Half-life elimination: 3.6 hours; End-stage renal disease: 3-5 hours

Excretion: Primarily urine (as glucuronides, sulfates, and unconjugated metabolites)

Related Information

- Corticosteroids

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Ulcerative esophagitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNervousness and insomnia are common; may rarely cause delirium, mood swings, euphoria, and hallucinations

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may decrease corticosteroid effectiveness

Cardiovascular ConsiderationsLong-term steroid therapy is associated with fluid retention and hypertension. Glucocorticoid agents have some mineralocorticoid activity with consequent hemodynamic effects. Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. In discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that the steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia.

Steroid therapy in patients with heart failure should be administered cautiously with special attention given to signs and symptoms of fluid retention.

Anesthesia and Critical Care Concerns/Other Considerations

Evidence-Based Information:

Neuromuscular Effects: ICU-acquired paresis was recently studied in five ICUs (three medical and two surgical ICUs) at four French hospitals. All ICU patients without pre-existing neuromuscular disease admitted from March 1999 through June 2000 were evaluated (de Jonghe, 2002). Each patient had to be mechanically-ventilated for ≥ 7 days and was screened daily for awakening. The first day the patient was considered awake was Study Day 1. Patients with severe muscle weakness on Study Day 7 were considered to have ICU-acquired paresis. Among the 95 patients who were evaluated, about 25% developed ICU-acquired paresis. Independent predictors included female gender, the number of days with ≥ 2 organ dysfunction, and administration of corticosteroids. Further studies may be required to verify and characterize the association between the development of ICU-acquired paresis and use of corticosteroids. Concurrent use of a corticosteroid and muscle relaxant appears to increase the risk of certain ICU myopathies; avoid or administer the corticosteroid at the lowest dose possible.

Adrenal Insufficiency: Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. When discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that the steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia. Patients on long-term steroid supplementation will require higher corticosteroid doses when subject to stress (eg, trauma, surgery, severe infection). Guidelines for glucocorticoid replacement during various surgical procedures have been published (Coursin, 2002; Salem, 1994).

Index TermsDeltahydrocortisone; Metacortandralone; Prednisolone Acetate; Prednisolone Acetate, Ophthalmic; Prednisolone Sodium Phosphate; Prednisolone Sodium Phosphate, Ophthalmic

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International Brand NamesAdelcort (GR); Aprednislon (AT); Caberdelta (IT); Cortisolone (IT); Dacortin H (ES); Decortin H (BG, PL); Delcortol (DK); Delta Phorical (BB, BM, BS, BZ, GY, JM, SR, TT); Deltacortril (LU, PK); Deltidrosol (IT); Domucortone (IT); Econopred Plus (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SG, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Encortolon (PL); Fenicort (PL); Fisopred (MX); Hydrocortancyl (FR); Inflanefran (DE); Klismacort (HU); Linola P (PL); Linola-H N (CZ); Liquipred (FR); Meticortelon (HR); Meticortelone (IT, MX); Normonsona (ES); Optilon (KP); Pred Forte (BE, BR, CN, GB, HK, IE, IL, KP, MY, NL, NZ, PH, TH, TW, ZA); Pred Mild (BR, CN, HK, MY, NZ, PH, TH, ZA); Pred Un (MX); Pred-NF (MX); Predartrina (IT); Predmet (IN); Predmix Oral Solution (AU); Prednefrin (CO, PE); Prednefrin Forte (EC, PE); Prednefrin SF (MX); Predni-Ophtal (DE); Prednicortelone (LU); Prednisolon (FI, HU, NO); Prednisolon Galepharm (CH); Prednisolon Streuli[Tab.] (CH); Prednisolon ”Dak” (DK); Prednisolon ”DuraScan” (DK); Prednisolone Ratiopharm (LU); Prednisolonum (PL); Predon (MY); Predsol-Forte (DO, HN); Prezolon (GR); Redipred (AU); Scherisolona (UY); Solupred (FR); Sophipren Ofteno (CR, DO, GT, HN, MX, NI, PA, SV); Spiricort (CH); Ultracortenol (AR, PY, SE, TW); Vistapred (PH)

PredniSONE

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

PredniSONE may be confused with methylPREDNISolone, Pramosone®, prazosin, prednisoLONE, Prilosec®, primidone, promethazine

Pronunciation(PRED ni sone)
U.S. Brand NamesPredniSONE Intensol™; Sterapred®; Sterapred® DS
Canadian Brand NamesApo-Prednisone®; Novo-Prednisone; Winpred™
Pharmacologic CategoryCorticosteroid, Systemic
Use: Labeled IndicationsTreatment of a variety of diseases, including:

Allergic states (including adjunctive treatment of anaphylaxis)

Autoimmune disorders (including systemic lupus erythematosus [SLE])

Collagen diseases

Dermatologic conditions/diseases

Edematous states (including nephrotic syndrome)

Endocrine disorders

Gastrointestinal diseases

Hematologic disorders (including idiopathic thrombocytopenia purpura [ITP])

Multiple sclerosis exacerbations

Neoplastic diseases

Ophthalmic diseases

Respiratory diseases (including acute asthma exacerbation)

Rheumatic disorders (including rheumatoid arthritis)

Trichinosis with neurologic or myocardial involvement

Tuberculous meningitis

Use: Unlabeled/InvestigationalAdjunctive therapy for *Pneumocystis jiroveci* (formerly *carinni*) pneumonia (PCP); autoimmune hepatitis; adjunctive therapy for pain management in immunocompetent patients with herpes zoster; tuberculosis (severe, paradoxical reactions)
Use: DentalTreatment of a variety of oral diseases of allergic, inflammatory, or autoimmune origin
Dosing: Adults**General dosing range:** Oral: Initial: 5-60 mg/day: **Note:** Dose depends upon condition being treated and response of patient; dosage for infants and children should be based on severity of the disease and response of the patient rather than on strict adherence to dosage indicated by age, weight, or body surface area. Consider alternate day therapy for long-term therapy. Discontinuation of long-term therapy requires gradual withdrawal by tapering the dose.

Prednisone taper (other regimens also available):

Day 1: 30 mg divided as 10 mg before breakfast, 5 mg at lunch, 5 mg at dinner, 10 mg at bedtime

Day 2: 5 mg at breakfast, 5 mg at lunch, 5 mg at dinner, 10 mg at bedtime

Day 3: 5 mg 4 times/day (with meals and at bedtime)

Day 4: 5 mg 3 times/day (breakfast, lunch, bedtime)

Day 5: 5 mg 2 times/day (breakfast, bedtime)

Day 6: 5 mg before breakfast

Indication-specific dosing:

Acute asthma (NIH guidelines, 2007): Oral: 40-60 mg per day for 3-10 days; administer as single or 2divided doses

Anaphylaxis, adjunctive treatment (Lieberman 2005): Oral: 0.5 mg/kg

Antineoplastic: Oral: Usual range: 10 mg/day to 100 mg/m^2/day (depending on indication). **Note:** Details concerning dosing in combination regimens should also be consulted.

Autoimmune hepatitis (unlabeled use; Czaja 2002): Oral: Initial treatment: 60 mg/day for 1 week, *followed by* 40 mg/day for 1 week, *then* 30 mg/day for 2 weeks, *then* 20 mg/day. Half this dose should be given when used in combination with azathioprine

Herpes zoster (unlabeled use; Dworkin 2007): Oral: 60 mg/day for 7 days, *followed by* 30 mg/day for 7 days, *then* 15 mg/day for 7 days

Idiopathic thrombocytopenia purpura (American Society of Hematology 1997): Oral: 1-2 mg/kg/day

PCP pneumonia (AIDSinfo guidelines, 2008):Note: Begin within 72 hours of PCP therapy: 40 mg twice daily for 5 days, *followed by* 40 mg once daily for 5 days, *followed by* 20 mg once daily for 11 days or until antimicrobial regimen is completed

Rheumatoid arthritis (American College of Rheumatology 2002): Oral: ≤10 mg/day

Systemic lupus erythematosus (American College of Rheumatology 1999): Oral:

Mild SLE: ≤10 mg/day

Refractory or severe organ-threatening disease: 20-60 mg/day

Thyrotoxicosis (type II amiodarone induced; unlabeled use): Oral: 30-40 mg/day for 7-14 days, gradually taper over 3 months

Tuberculosis, severe, paradoxical reactions (unlabeled use, AIDS info guidelines 2008): Oral: 1 mg/kg/day, gradually reduce after 1-2 weeks

Dosing: ElderlyRefer to adult dosing; use the lowest effective dose. Oral dose depends upon condition being treated and response of patient. Alternate day dosing may be attempted.

Dosing: Pediatric

General dosing range: Oral: Refer to adult dosing. **Note:** Dose depends upon condition being treated and response of patient; dosage for infants and children should be based on severity of the disease and response of the patient rather than on strict adherence to dosage indicated by age, weight, or body surface area. Consider alternate day therapy for long-term therapy. Discontinuation of long-term therapy requires gradual withdrawal by tapering the dose.

Indication-specific dosing:

Acute asthma (NIH guidelines, 2007): Oral:

0-11 years 1-2 mg/kg/day for 3-10 days (maximum: 60 mg/day)

≥12 years: Refer to Adults dosing

Autoimmune hepatitis (unlabeled use; Czaja 2002): Oral: Initial treatment: 2 mg/kg/day for 2 weeks (maximum: 60 mg/day), followed by a taper over 6-8 weeks to a dose of 0.1-0.2 mg/kg/day or 5 mg/day

Nephrotic syndrome (Pediatric Nephrology Panel recommendations [Hogg, 2000]): Oral: Initial: 2 mg/kg/day or 60 mg/m^2/day given every day in 1-3 divided doses (maximum: 80 mg/day) until urine is protein free or for 4-6 weeks; followed by maintenance dose: 2 mg/kg/dose or 40 mg/m^2/dose given every other day in the morning; gradually taper and discontinue after 4-6 weeks. **Note:** No definitive treatment guidelines exist. Dosing is dependant on institution protocols and individual response.

PCP pneumonia (AIDSinfo guidelines, 2008): Oral:

Children: 1 mg/kg twice daily for 5 days, *followed by* 0.5-1 mg/kg twice daily for 5 days, *followed by* 0.5 mg/kg once daily for 11-21 days

Adolescents: Refer to adult dosing.

Dosing: Renal ImpairmentHemodialysis effects: Supplemental dose is not necessary.

Dosing: Combination Regimens**Note:** In the U.S., prednisone is the preferred corticosteroid. However, in the British literature, prednisolone is often used. The oral doses of these two agents are equivalent (ie, 1 mg prednisone = 1 mg prednisolone). Also, early clinical trials gave prednisone only with the first and fourth cycles. Some clinicians give prednisone with every cycle.

Brain tumors:

MOPP (Medulloblastoma)

POC

Breast cancer:

CFP

CMFP

CMFVP (Cooper Regimen, VPCMF)

Leukemia, acute lymphocytic:

DVP

Hyper-CVAD + Imatinib

Hyper-CVAD (Leukemia, Acute Lymphocytic)

- Larson Regimen
- Linker Protocol
- MTX/6-MP/VP (Maintenance)
- POMP
- PVA (POG 8602)
- PVDA

Leukemia, chronic lymphocytic:

- CHL + PRED
- CP (Leukemia)
- CVP (Leukemia)

Lymphoma, Hodgkin's:

- BEACOPP
- CAD/MOPP/ABV
- ChIVPP
- COMP
- LOPP
- MOPP (Lymphoma, Hodgkin's Disease)
- MOPP/ABV Hybrid
- MOPP/ABVD
- MVPP
- OPA
- OPPA
- Stanford V Regimen

Lymphoma, non-Hodgkin's:

- CEPP(B)
- CHOP
- CNOP
- COP-BLAM
- COPP
- CVP (Lymphoma, non-Hodgkin's)
- EPOCH
- MACOP-B
- Pro-MACE-CytaBOM
- Rituximab-CHOP
- R-CVP

Multiple myeloma:

- Bortezomib-Melphalan-Prednisone
- Bortezomib-Melphalan-Prednisone-Thalidomide
- M-2
- Melphalan-Prednisone-Thalidomide
- MP (Multiple Myeloma)
- VBAP
- VBMCP

VCAP

Prostate cancer:

Docetaxel-Prednisone

Estramustine + Docetaxel + Prednisone

MP (Prostate Cancer)

Calculations

- Corticosteroid Conversion

Administration: OralAdminister with food to decrease GI upset.

Dietary ConsiderationsShould be taken after meals or with food or milk; may require increased dietary intake of pyridoxine, vitamin C, vitamin D, folate, calcium, and phosphorus; may require decreased dietary intake of sodium

ContraindicationsHypersensitivity to any component of the formulation; systemic fungal infections; administration of live or live attenuated vaccines with immunosuppressive doses of prednisone

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections.

- Immunosuppression: Prolonged use of corticosteroids may increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox should be avoided. Corticosteroids should not be used to treat ocular herpes simplex or cerebral malaria. Close observation is required in patients with latent tuberculosis and/or TB reactivity; restrict use in active TB (only in conjunction with antituberculosis treatment).

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Myopathy: Acute myopathy has been reported with high dose corticosteroids, usually in patients with neuromuscular transmission disorders; may involve ocular and/or respiratory muscles; monitor creatine kinase; recovery may be delayed.

- Ocular effects: Prolonged use may cause posterior subcapsular cataracts, glaucoma (with possible nerve damage) and may increase the risk for ocular infections.

- Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with HF; long-term use has been associated with fluid retention and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.

- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; effects may be enhanced.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids.

- Myocardial infarction (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Osteoporosis: Use with caution in patients with or who are at risk for osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

Special populations:

- Pediatrics: May affect growth velocity; growth should be routinely monitored in pediatric patients.

Other warnings/precautions:

- Appropriate use: Prior to use, the dose and duration of treatment should be based on the risk versus benefit for each individual patient. In general, use the smallest effective dose for the shortest duration of time to minimize adverse events. A gradual tapering of dose may be required prior to discontinuing therapy.

Geriatric ConsiderationsBecause of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly, in the smallest possible dose, and for the shortest possible time.

Pregnancy ConsiderationsAdverse events have been observed with corticosteroids in animal reproduction studies. Prednisone and prednisolone cross the human placenta. In the mother, prednisone is converted to the active metabolite prednisolone by the liver. Prior to reaching the fetus, prednisolone is converted by placental enzymes back to prednisone. As a result, the level of prednisone remaining in the maternal serum and reaching the fetus are similar, however, the amount of prednisolone reaching the fetus is ~8-10 times lower than the maternal serum concentration (healthy women at term). Some studies have shown an association between first trimester prednisone use and oral clefts; adverse events in the fetus/neonate have been noted in case reports following large doses of systemic corticosteroids during pregnancy. Pregnant women exposed to prednisone for antirejection therapy following a transplant may contact the National Transplantation Pregnancy Registry (NTPR) at 215-955-4820. Women exposed to prednisone during pregnancy for the treatment of an autoimmune disease (eg, rheumatoid arthritis) may contact the OTIS Autoimmune Diseases Study at 877-311-8972.

LactationEnters breast milk/AAP rates "compatible"

Breast-Feeding ConsiderationsPrednisone and its metabolite prednisolone are found in low concentrations in breast milk. Peak milk concentrations of both were found ~2 hours after the maternal dose in one case report. In a study which included 6 mother/infant pairs, adverse events were not observed in nursing infants (maternal prednisone dose not provided).

Adverse Reactions

Frequency not defined.

Cardiovascular: Congestive heart failure (in susceptible patients), hypertension

Central nervous system: Emotional instability, headache, intracranial pressure increased (with papilledema), psychic derangements (including euphoria, insomnia, mood swings, personality changes, severe depression), seizure, vertigo

Dermatologic: Bruising, facial erythema, petechiae, thin fragile skin, urticaria, wound healing impaired

Endocrine & metabolic: Adrenocortical and pituitary unresponsiveness (in times of stress), carbohydrate intolerance, Cushing's syndrome, diabetes mellitus, fluid retention, growth suppression (in children), hypokalemic alkalosis, hypothyroidism enhanced, menstrual irregularities, negative nitrogen balance due to protein catabolism, potassium loss, sodium retention

Gastrointestinal: Abdominal distension, pancreatitis, peptic ulcer (with possible perforation and hemorrhage), ulcerative esophagitis

Hepatic: ALT increased, AST increased, alkaline phosphatase increased

Neuromuscular & skeletal: Aseptic necrosis of femoral and humeral heads, muscle mass loss, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture (particularly Achilles tendon), vertebral compression fractures

Ocular: Exophthalmos, glaucoma, intraocular pressure increased, posterior subcapsular cataracts

Miscellaneous: Allergic reactions, anaphylactic reactions, diaphoresis, hypersensitivity reactions, infections, Kaposi's sarcoma

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor); **Induces** CYP2C19 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Somatropin: May diminish the therapeutic effect of PredniSONE. Growth hormone may reduce the conversion of prednisone to the active prednisolone metabolite. *Risk D: Consider therapy modification*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase gastric mucosal irritation)

Food: Prednisone interferes with calcium absorption. Limit caffeine.

Herb/Nutraceutical: St John's wort may decrease prednisone levels. Avoid cat's claw, echinacea (have immunostimulant properties).

Test InteractionsDecreased response to skin tests

Monitoring ParametersBlood pressure, blood glucose, electrolytes

Following prolonged use: Bone mass density, growth in children, signs and symptoms of infection, cataract formation

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor for effectiveness of therapy and adverse reactions according to dose and length of therapy. Assess knowledge/teach patient appropriate use, possible side effects/interventions, and adverse symptoms to report (ie, opportunistic infection, adrenal suppression). Instruct patients with diabetes to monitor serum glucose levels closely; corticosteroids can alter glucose tolerance. Monitor growth with long-term use in pediatric patients. Dose may need to be increased if patient is experiencing higher than normal levels of stress. When discontinuing, taper dose and frequency slowly.

Monitoring: Lab TestsBlood glucose, electrolytes

Patient EducationTake exactly as directed. Do not take more than prescribed dose and do not discontinue abruptly; consult prescriber. Take with or after meals. Take once-a-day dose with food in the morning. Avoid alcohol. Limit intake of caffeine or stimulants. Maintain adequate nutrition; consult prescriber for possibility of special dietary recommendations. If you have diabetes, monitor serum glucose closely and notify prescriber of changes; this medication can alter glycemic response. Notify prescriber if you are experiencing higher than normal levels of stress; medication may need adjustment. Periodic ophthalmic examinations will be necessary with long-term use. You will be susceptible to infection (avoid crowds and exposure to infection). You may experience insomnia or nervousness; use caution when driving or engaging in tasks requiring alertness until response to drug is known. Report weakness, change in menstrual pattern, vision changes, signs of hyperglycemia, signs of infection (eg, fever, chills, mouth sores, perianal itching, vaginal discharge), other persistent side effects, or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral: 1 mg/mL (5 mL, 120 mL, 500 mL) [contains alcohol 5%, sodium benzoate; peppermint vanilla flavor]

Solution, oral [concentrate]:

PredniSONE Intensol™: 5 mg/mL (30 mL) [contains alcohol 30%]

Tablet: 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 50 mg

Sterapred®: 5 mg [supplied as 21 tablet 6-day unit-dose package or 48 tablet 12-day unit-dose package]

Sterapred® DS: 10 mg [supplied as 21 tablet 6-day unit-dose package or 48 tablet 12-day unit-dose package]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (PredniSONE)

2.5 mg (30): $12.99

5 mg (100): $11.99

10 mg (30): $11.99

20 mg (30): $11.99

50 mg (30): $17.99

Tablets (PredniSONE (Pak))

10 mg (21): $15.99

10 mg (48): $17.99

Tablets (Sterapred DS)

10 mg (21): $59.98

Tablets (Sterapred DS 12 Day)

10 mg (48): $74.36

Mechanism of ActionDecreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability; suppresses the immune system by reducing activity and volume of the lymphatic system; suppresses adrenal function at high doses. Antitumor effects may be related to inhibition of glucose transport, phosphorylation, or induction of cell death in immature lymphocytes. Antiemetic effects are thought to occur due to blockade of cerebral innervation of the emetic center via inhibition of prostaglandin synthesis.

Pharmacodynamics/Kinetics

Absorption: 50% to 90% (may be altered in IBS or hyperthyroidism)

Protein binding (concentration dependent): 65% to 91%

Metabolism: Hepatically converted from prednisone (inactive) to prednisolone (active); may be impaired with hepatic dysfunction

Half-life elimination: Normal renal function: ~3.5 hours

Excretion: Urine (small portion)

Related Information

- Contrast Media Reactions, Premedication for Prophylaxis
- Corticosteroids

Pharmacotherapy PearlsTapering of corticosteroids after a short course of therapy (<7-10 days) is generally not required unless the disease/inflammatory process is slow to respond. Tapering after prolonged exposure is dependent upon the individual patient, duration of corticosteroid treatments, and size of steroid dose. Recovery of the HPA axis may require several months. Subtle but important HPA axis suppression may be present for as long as several months after a course of as few as 10-14 days duration. Testing of HPA axis (cosyntropin) may be required, and signs/symptoms of adrenal insufficiency should be monitored in patients with a history of use.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNervousness and insomnia are common; may rarely cause delirium, mood swings, euphoria, and hallucinations

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may decrease corticosteroid effectiveness

Cardiovascular ConsiderationsLong-term steroid therapy is associated with fluid retention and hypertension. Glucocorticoid agents have some mineralocorticoid activity with consequent hemodynamic effects. Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. In discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that the steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia.

Oral and intravenous steroid therapy in patients with heart failure should be administered cautiously with special attention given to signs and symptoms of fluid retention.

Although glucocorticoids can provide relief from pericarditis postmyocardial infarctions, these drugs may cause thinning of the developing scar and myocardial rupture.

Anesthesia and Critical Care Concerns/Other Considerations

Evidence-Based Information:

Neuromuscular Effects: ICU-acquired paresis was recently studied in 5 ICUs (3 medical and 2 surgical ICUs) at 4 French hospitals. All ICU patients without pre-existing neuromuscular disease admitted from March 1999 through June 2000 were evaluated (De Jonghe, 2002). Each patient had to be mechanically ventilated for ≥7 days and was screened daily for awakening. The first day the patient was considered awake was Study Day 1. Patients with severe muscle weakness on Study Day 7 were considered to have ICU-acquired paresis. Among the 95 patients who were evaluated, about 25% developed ICU-acquired paresis. Independent predictors included female gender, the number of days with ≥2 organ dysfunction, and administration of corticosteroids. Further studies may be required to verify and characterize the association between the development of ICU-acquired paresis and use of corticosteroids. Concurrent use of a corticosteroid and muscle relaxant appears to increase the risk of certain ICU myopathies; avoid or administer the corticosteroid at the lowest dose possible.

Adrenal Insufficiency: Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. When discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that the steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia. Patients on long-term steroid supplementation will require higher corticosteroid doses when subject to stress (ie, trauma, surgery, severe infection). Guidelines for glucocorticoid replacement during various surgical procedures have been published (Coursin, 2002; Salem, 1994).

Index Terms Deltacortisone; Deltadehydrocortisone

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International Brand NamesAlfacort (UY); Apo-Prednisone (NZ); Bioster (PH); Cortancyl (FR); Cortiol (PT); Cortiprex (CN, PE); Cutason (DE); Dacortin (CH, ES); Decortin (BG, DE, HR, PL); Decortisyl (IE); Delcortin (DK); Deltacortene (IT); Deltasone (HK); Deltison (SE); Drazone (PH); Ednapron (MX); Encorton (PL); Hostacortin (ID); Inflason (ID); Me-Korti (FI); Meticorten (AR, BR, CN, EC, MX, PE, PT, VE); Nisona (PE); Nizon (HR); Norapred (MX); Nurison (NL); Panafcort (AU, ZA); Parmenison (AT); Predicorten (BR); Prednicort (BE, LU, PY); Prednidib (MX); Predniment (NL); Prednimut (NL); Prednison (FI, NO); Prednison Galepharm (CH); Prednison Streuli (CH); Prednison "Dak" (DK); Prednisone (CY); Prolix 20 (PH); Pulmison (ZA); Qualisone (PH); Rectodelt (HU); Sone (AU)

Pregabalin

Lexi-Drugs Online

English

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Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

Lyrica® may be confused with Lopressor®

Pronunciation(pre GAB a lin)

U.S. Brand NamesLyrica®

Canadian Brand NamesLyrica®

Pharmacologic CategoryAnalgesic, Miscellaneous; Anticonvulsant, Miscellaneous

Use: Labeled IndicationsManagement of pain associated with diabetic peripheral neuropathy; management of postherpetic neuralgia; adjunctive therapy for partial-onset seizure disorder in adults; management of fibromyalgia

Dosing: Adults

Fibromyalgia: Oral: Initial: 150 mg/day in divided doses (75 mg 2 times/day); may be increased to 300 mg/day (150 mg 2 times/day) within 1 week based on tolerability and effect; may be further increased to 450 mg/day (225 mg 2 times/day). Maximum dose: 450 mg/day (dosages up to 600 mg/day were evaluated with no significant additional benefit and an increase in adverse effects)

Neuropathic pain (diabetes-associated): Oral: Initial: 150 mg/day in divided doses (50 mg 3 times/day); may be increased within 1 week based on tolerability and effect; maximum dose: 300 mg/day (dosages up to 600 mg/day were evaluated with no significant additional benefit and an increase in adverse effects)

Postherpetic neuralgia: Oral: Initial: 150 mg/day in divided doses (75 mg 2 times/day or 50 mg 3 times/day); may be increased to 300 mg/day within 1 week based on tolerability and effect; further titration (to 600 mg/day) after 2-4 weeks may be considered in patients who do not experience sufficient relief of pain provided they are able to tolerate pregabalin. Maximum dose: 600 mg/day

Partial onset seizures (adjunctive therapy): Oral: Initial: 150 mg per day in divided doses (75 mg 2 times/day or 50 mg 3 times/day); may be increased based on tolerability and effect (optimal titration schedule has not been defined). Maximum dose: 600 mg/day

Note: Discontinuing therapy: Pregabalin should not be abruptly discontinued; taper dosage over at least 1 week

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Pregabalin Renal Impairment Dosing

Cl_{cr} (mL/minute)	Total Pregabalin Daily Dose (mg/day)				Dosing Frequency
≥60	150	300	450	600	2-3 divided doses
30-60	75	150	225	300	2-3 divided doses
15-30	25-50	75	100-150	150	1-2 divided doses
<15	25	25-50	50-75	75	Single daily dose

Posthemodialysis supplementary dosage (as a single additional dose):

25 mg/day schedule: Single supplementary dose of 25 mg **or** 50 mg

25-50 mg/day schedule: Single supplementary dose of 50 mg **or** 75 mg

50-75 mg/day schedule: Single supplementary dose of 75 mg **or** 100 mg

75 mg/day schedule: Single supplementary dose of 100 mg **or** 150 mg

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered with or without food.
Dietary ConsiderationsMay be taken with or without food.
StorageStore at 15°C to 30°C (59°F to 86°F).
RestrictionsC-V
ContraindicationsHypersensitivity to pregabalin or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Angioedema: Angioedema has been reported; may be life-threatening; use with caution in patients with a history of angioedema episodes. Concurrent use with other drugs known to cause angioedema (eg, ACE inhibitors) may increase risk.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypersensitivity: Hypersensitivity reactions, including skin redness, blistering, hives, rash, dyspnea, and wheezing have been reported; discontinue treatment of hypersensitivity occurs.
- Platelet count: May decrease platelet count .
- PR interval: May cause mild prolongation of PR interval. Clinical significance unknown, but use with caution in patients with underlying AV block.
- Rhabdomyolysis: Has been associated with increases in CPK and rare cases of rhabdomyolysis; patients should be instructed to notify their prescriber if unexplained muscle pain, tenderness, or weakness, particularly if fever and/or malaise are associated with these symptoms.
- Visual disturbances: Blurred vision, decreased acuity and visual field changes have been associated with therapy; patients should be instructed to notify their physician if these effects are noted.
- Weight gain: Use may be associated with weight gain and peripheral edema; effect on weight gain/edema may be additive to thiazolidinedione antidiabetic agent particularly in patients with prior cardiovascular disease.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with congestive heart failure, hypertension, or diabetes; weight gain and/or peripheral edema may occur.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Tumorigenic potential: Increased incidence of hemangiosarcoma noted in animal studies; significance of these findings in humans is unknown.
- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal. Tapering over at least 1 week is recommended.

Geriatric ConsiderationsIn clinical studies, no differences in safety and efficacy were noted between elderly. Since pregabalin is primarily excreted renally, dosage adjustment, based on Cl_{cr}, is necessary.
Pregnancy Risk FactorC
Pregnancy ConsiderationsIncreased incidence of fetal abnormalities, particularly skeletal malformations, were observed in animal studies. Male-mediated teratogenicity has been observed in animal studies; implications in humans are not defined. Impaired male and female fertility has been noted in animal studies. There are no adequate and well-controlled studies in pregnant women. Use only when potential benefit to the mother outweighs possible risk to the fetus.
LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

Note: Frequency of adverse effects may be influenced by dose or concurrent therapy. In add-on trials in epilepsy, frequency of CNS and visual adverse effects were higher than those reported in pain management trials. Range noted below is inclusive of all trials.

>10%:

Cardiovascular: Peripheral edema (up to 16%)

Central nervous system: Dizziness (8% to 45%), somnolence (4% to 28%), ataxia (up to 20%), headache (up to 14%)

Gastrointestinal: Weight gain (up to 16%), xerostomia (1% to 15%)

Neuromuscular & skeletal: Tremor (up to 11%)

Ocular: Blurred vision (1% to 12%), diplopia (up to 12%)

Miscellaneous: Infection (up to 14%), accidental injury (2% to 11%)

1% to 10%:

Cardiovascular: Chest pain (up to 4%), edema (up to 6%)

Central nervous system: Neuropathy (up to 9%), thinking abnormal (up to 9%), fatigue (up to 8%), confusion (up to 7%), euphoria (up to 7%), speech disorder (up to 7%), attention disturbance (up to 6%), incoordination (up to 6%), amnesia (up to 6%), pain (up to 5%), memory impaired (up to 4%), vertigo (up to 4%), feeling abnormal (up to 3%), hypoesthesia (up to 3%), anxiety (up to 2%), depression (up to 2%), disorientation (up to 2%), lethargy (up to 2%), fever (≥1%), depersonalization (≥1%), hypertonia (≥1%), stupor (≥1%), nervousness (up to 1%)

Dermatologic: Facial edema (up to 3%), bruising (≥1%), pruritus (≥1%)

Endocrine & metabolic: Fluid retention (up to 3%), hypoglycemia (up to 3%), libido decreased (≥1%)

Gastrointestinal: Constipation (up to 10%), appetite increased (up to 7%), flatulence (up to 3%), vomiting (up to 3%), abdominal distension (up to 2%), abdominal pain (≥1%), gastroenteritis (≥1%)

Genitourinary: Incontinence (up to 2%), anorgasmia (≥1%), impotence (≥1%), urinary frequency (≥1%)

Hematologic: Thrombocytopenia (3%)

Neuromuscular & skeletal: Balance disorder (up to 9%), abnormal gait (up to 8%), weakness (up to 7%), arthralgia (up to 6%), twitching (up to 5%), back pain (up to 4%), muscle spasm (up to 4%), myoclonus (up to 4%), paresthesia (>2%), CPK increased (2%), leg cramps (≥1%), myalgia (≥1%), myasthenia (up to 1%)

Ocular: Visual abnormalities (up to 5%), visual field defect (≥2%), eye disorder (up to 2%), nystagmus (>2%), conjunctivitis (≥1%)

Otic: Otitis media (≥1%), tinnitus (≥1%)

Respiratory: Sinusitis (up to 7%), dyspnea (up to 3%), bronchitis (up to 3%), pharyngolaryngeal pain (up to 3%)

Miscellaneous: Flu-like syndrome (up to 2%), allergic reaction (≥1%)

<1% (Limited to important or life-threatening): Abscess, acute renal failure, addiction (rare), agitation, albuminuria, anaphylactoid reaction, anemia, angioedema, aphasia, aphthous stomatitis, apnea, ascites, atelectasis, blepharitis, blindness, bronchiolitis, cellulitis, cerebellar syndrome, cervicitis, chills, cholecystitis, cholelithiasis, chondrodystrophy, circumoral paresthesia, cogwheel rigidity, colitis, coma, corneal ulcer, crystalluria (urate), delirium, delusions, diarrhea, dysarthria, dysautonomia, dyskinesia, dysphagia, dystonia, dysuria, encephalopathy, eosinophilia, esophageal ulcer, esophagitis, exfoliative dermatitis, extraocular palsy, extrapyramidal syndrome, gastritis, GI hemorrhage, glomerulitis, glucose tolerance decreased, granuloma, Guillain-Barré syndrome, hallucinations, heart failure, hematuria, hostility, hyper-/hypokinesia; hypersensitivity (including skin redness, blistering, hives, rash, dyspnea, and wheezing); hypotension, hypotonia, intracranial hypertension, laryngismus, leukopenia, leukorrhea, leukocytosis, lymphadenopathy, manic reaction, melena, myelofibrosis, nausea, nephritis, neuralgia, ocular hemorrhage, oliguria, optic atrophy, pancreatitis, papilledema, paranoid reaction, pelvic pain, periodontal abscess, peripheral neuritis, polycythemia, postural hypotension, prothrombin decreased, psychotic depression, ptosis, pulmonary edema, pulmonary fibrosis, purpura, pyelonephritis, rectal hemorrhage, renal calculus, retinal edema, retinal vascular disorder, retroperitoneal fibrosis, rhabdomyolysis, schizophrenic reaction, shock, skin necrosis, skin ulcer, spasm (generalized), ST depression, Stevens-Johnson syndrome, subcutaneous nodule, suicide, suicide attempt, syncope, thrombocythemia, thrombophlebitis, tongue edema, torticollis, trismus, uveitis, ventricular fibrillation

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antidiabetic Agents (Thiazolidinedione): Pregabalin may enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersMeasures of efficacy (pain intensity/seizure frequency); degree of sedation; symptoms of myopathy or ocular disturbance; weight gain/edema; CPK; skin integrity (in patients with diabetes).

Nursing: Physical Assessment/MonitoringMonitor therapeutic response and adverse reactions at the beginning and periodically throughout therapy. Monitor weight. Assess for signs of fluid retention. Taper dosage over at least one week when discontinuing. Do not discontinue abruptly. Assess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Monitoring: Lab TestsCPK

Patient EducationInform prescriber of all prescription medications, OTC medications, or herbal products you are taking. Avoid alcohol; may increase drowsiness/CNS depression. Taper dosage slowly when discontinuing. Do not discontinue abruptly. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake by prescriber. May cause CNS depression and/or dizziness (use caution when driving or engaging in activities requiring alertness until response to drug is known), headache, weight gain, or fluid retention. Report immediately any visual disturbances, suicidal ideation, or depression. Report unexplained muscle pain, tenderness, or weakness, especially if accompanied by unexplained fever and malaise, dizziness, confusion or abnormal thinking, shortness of breath, weight gain >5 lbs/week, swelling of extremities, problems with coordination, tremor, facial swelling, excessively dry mouth, and excessive drowsiness.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Lyrica®: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg

Generic AvailableNo

Manufacturer

Pfizer

Pricing: U.S. (www.drugstore.com)

Capsules (Lyrica)

25 mg (30): $72.44

50 mg (30): $73.49

75 mg (30): $72.44

100 mg (30): $73.49

150 mg (30): $73.49

200 mg (30): $73.49

225 mg (30): $73.49

300 mg (30): $73.49

Mechanism of ActionBinds to alpha$_2$-delta subunit of voltage-gated calcium channels within the CNS, inhibiting excitatory neurotransmitter release. Although structurally related to GABA, it does not bind to GABA or benzodiazepine receptors. Exerts antinociceptive and anticonvulsant activity. Decreases symptoms of painful peripheral neuropathies and, as adjunctive therapy in partial seizures, decreases the frequency of seizures.

Pharmacodynamics/Kinetics

Onset of action: Pain management: Effects may be noted as early as the first week of therapy.

Distribution: V_d: 0.5 L/kg

Protein binding: 0%

Metabolism: Negligible

Bioavailability: >90%

Half-life elimination: 6.3 hours

Time to peak, plasma: 1.5 hours (3 hours with food)

Excretion: Urine (90% as unchanged drug; minor metabolites)

Related Information

- Anticonvulsant Drugs of Choice

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index Terms CI-1008; S-(+)-3-isobutylgaba

References

Hill CM, Balkenohl M, Thomas DW, et al, "Pregabalin in Patients With Postoperative Dental Pain," *Eur J Pain*, 2001, 5(2):119-24.[PubMed 11465977]

International Brand Names Lyrica (AR, AT, AU, BE, BG, CH, CN, CO, CR, CZ, DE, DK, EC, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IL, IT, KP, MX, NI, NL, NO, PA, PE, PH, PL, PT, RU, SE, SG, SV, TH, TR, UY, VE)

Prilocaine and Epinephrine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(PRIL oh kane & ep i NEF rin)

U.S. Brand NamesCitanest® Forte Dental

Canadian Brand NamesCitanest® Forte

Pharmacologic CategoryLocal Anesthetic

Use: DentalAmide-type anesthetic used for local infiltration anesthesia; injection near nerve trunks to produce nerve block

Dosing: Adults

Dental anesthesia, infiltration, or conduction block:

Children >10 years and Adults: Initial: 40-80 mg (1-2 mL) of prilocaine hydrochloride as a 4% solution with epinephrine 1:200,000; up to a maximum of 400 mg (10 mL) of prilocaine hydrochloride within a 2-hour period. The effective anesthetic dose varies with procedure, intensity of anesthesia needed, duration of anesthesia required, and physical condition of the patient. Always use the lowest effective dose along with careful aspiration.

Note: Adult and children doses of prilocaine hydrochloride with epinephrine cited from USP Dispensing Information (USP DI), 17th ed, The United States Pharmacopeial Convention, Inc, Rockville, MD, 1997, 140.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Dental anesthesia, infiltration, or conduction block:**

Children <10 years: Doses >40 mg (1 mL) of prilocaine hydrochloride as a 4% solution with epinephrine 1:200,000 are rarely needed.

Children >10 years: Refer to adult dosing.

Note: Adult and pediatric doses of prilocaine hydrochloride with epinephrine cited from USP Dispensing Information (USP DI), 17th ed, The United States Pharmacopeial Convention, Inc, Rockville, MD, 1997, 140.

ContraindicationsHypersensitivity to local anesthetics of the amide-type or any component of the formulation

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS toxicity: Careful and constant monitoring of the patient's state of consciousness should be done following each local anesthetic injection; at such times, restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of CNS toxicity. Treatment is primarily symptomatic and supportive.
- Methemoglobinemia: Has been reported with prilocaine.
- Respiratory arrest: Local anesthetics have been associated with rare occurrences of sudden respiratory arrest.
- Seizures: Convulsions due to systemic toxicity leading to cardiac arrest have also been reported, presumably following unintentional intravascular injection.

Disease-related concerns:

- Cardiovascular disease: Should be used in minimal amounts in patients with significant cardiovascular problems (because of epinephrine component).
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hyperthyroidism: Should be avoided in patients with uncontrolled hyperthyroidism.

Special populations:

- Acutely ill patients: Use with caution in acutely ill; reduce dose consistent with age and physical status.
- Debilitated patients: Use with caution in debilitated patients; reduce dose consistent with age and physical status.
- Elderly: Use with caution in the elderly; reduce dose consistent with age and physical status.
- Pediatrics: Use with caution in children; reduce dose consistent with age and physical status.

Dosage form specific issues:

- Sodium metabisulfite: May contain sodium metabisulfite; use caution in patients with a sulfite allergy.

Other warnings/precautions:

- Administration: Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

- Trained personnel: Dental practitioners using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorC

Breast-Feeding ConsiderationsUsual infiltration doses of prilocaine with epinephrine given to nursing mothers has not been shown to affect the health of the nursing infant.

Adverse ReactionsDegree of adverse effects in the CNS and cardiovascular system are directly related to the blood levels of prilocaine. The effects below are more likely to occur after systemic administration rather than infiltration.

Cardiovascular: Myocardial effects include a decrease in contraction force as well as a decrease in electrical excitability and myocardial conduction rate resulting in bradycardia and reduction in cardiac output.

Central nervous system: High blood levels result in anxiety, restlessness, disorientation, confusion, dizziness, tremor and seizure. This is followed by depression of CNS resulting in somnolence, unconsciousness and possible respiratory arrest. Nausea and vomiting may also occur. In some cases, symptoms of CNS stimulation may be absent and the primary CNS effects are somnolence and unconsciousness.

Hypersensitivity reactions: Extremely rare, but may be manifest as dermatologic reactions and edema at injection site. Asthmatic syndromes have occurred. Patients may exhibit hypersensitivity to bisulfites contained in local anesthetic solution to prevent oxidation of epinephrine. In general, patients reacting to bisulfites have a history of asthma and their airways are hyper-reactive to asthmatic syndrome.

Psychogenic reactions: It is common to misinterpret psychogenic responses to local anesthetic injection as an allergic reaction. Intraoral injections are perceived by many patients as a stressful procedure in dentistry. Common symptoms to this stress are diaphoresis, palpitation, hyperventilation, generalized pallor, and a fainting feeling.

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Beta-Blockers: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. *Risk D: Consider therapy modification*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

COMT Inhibitors: May decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

Inhalational Anesthetics: May enhance the arrhythmogenic effect of EPINEPHrine. *Risk D: Consider therapy modification*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Citanest® Forte Dental: Prilocaine hydrochloride 4% and epinephrine bitartrate 1:200,000 (1.8 mL) [contains sodium metabisulfite; prefilled cartridge]

Generic AvailableNo

Mechanism of ActionLocal anesthetics bind selectively to the intracellular surface of sodium channels to block influx of sodium into the axon. As a result, depolarization necessary for action potential propagation and subsequent nerve function is prevented. The block at the sodium channel is reversible. When drug diffuses away from the axon, sodium channel function is restored and nerve propagation returns.

Epinephrine prolongs the duration of the anesthetic actions of prilocaine by causing vasoconstriction (alpha-adrenergic receptor agonist) of the vasculature surrounding the nerve axons. This prevents the diffusion of prilocaine away from the nerves resulting in a longer retention in the axon.

Pharmacodynamics/Kinetics

Onset of action: Infiltration: <2 minutes; Inferior alveolar nerve block: <3 minutes

Duration: Infiltration: 2.25 hours; Inferior alveolar nerve block: 3 hours

Dental Health: Effects on Dental TreatmentIt is common to misinterpret psychogenic responses to local anesthetic injection as an allergic reaction. Intraoral injections are perceived by many patients as a stressful procedure in dentistry. Common symptoms to this stress are diaphoresis, palpitations, hyperventilation, generalized pallor and a fainting feeling. Patients may exhibit hypersensitivity to bisulfites contained in local anesthetic solution to prevent oxidation of epinephrine. In general, patients reacting to bisulfites have a history of asthma and their airways are hyper-reactive to asthmatic syndrome.

Degree of adverse effects in the CNS and cardiovascular system is directly related to blood levels of prilocaine (frequency not defined; more likely to occur after systemic administration rather than infiltration): Bradycardia and reduction in cardiac output, hypersensitivity reactions (extremely rare; may be manifest as dermatologic reactions and edema at injection site), asthmatic syndromes

High blood levels: Anxiety, restlessness, disorientation, confusion, dizziness, tremors, and seizures, followed by CNS depression, resulting in somnolence, unconsciousness and possible respiratory arrest; nausea and vomiting

In some cases, symptoms of CNS stimulation may be absent and the primary CNS effects are somnolence and unconsciousness.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusHigh blood levels result in anxiety, confusion, restlessness, disorientation, and dizziness. This is followed by CNS depression, resulting in somnolence, unconsciousness, and possible respiratory arrest. Symptoms of CNS stimulation may be absent and the primary CNS effects are somnolence and unconsciousness.

Mental Health: Effects on Psychiatric TreatmentConcurrent use with propranolol or MAO inhibitors may produce severe hypertension.

Mental Health CommentIt is common to misinterpret psychogenic responses to local anesthetic injection as an allergic reaction.

Index TermsEpinephrine and Prilocaine (Dental)

References

Ayoub ST and Coleman AE, “A Review of Local Anesthetics,” *Gen Dent*, 1992, 40(4):285-7, 289-90. [PubMed 1397990]

Blanton PL and Roda RS, “The Anatomy of Local Anesthesia,” *J Calif Dent Assoc*, 1995, 23(4):55-65.

Jastak JT and Yagiela JA, “Vasoconstrictors and Local Anesthesia: A Review and Rationale for Use,” *J Am Dent Assoc*, 1983, 107(4):623-30. [PubMed 6355236]

MacKenzie TA and Young ER, “Local Anesthetic Update,” *Anesth Prog*, 1993, 40(2):29-34. [PubMed 8185087]

Wynn RL, “Epinephrine Interactions With Beta-Blockers,” *Gen Dent*, 1994, 42(1):16, 18. [PubMed 7911769]

Yagiela JA, “Local Anesthetics,” *Anesth Prog*, 1991, 38(4-5):128-41. [PubMed 1819966]

Yagiela JA, “Vasoconstrictor Agents for Local Anesthesia,” *Anesth Prog*, 1995, 42(3-4):116-20.[PubMed 8934977]

International Brand NamesCitanest Adrenalin (FI, SE); Citanest Forte (CA)

Prilocaine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Prilocaine may be confused with Polocaine®, Prilosec®

Pronunciation(PRIL oh kane)

U.S. Brand NamesCitanest® Plain Dental

Canadian Brand NamesCitanest® Plain

Pharmacologic CategoryLocal Anesthetic

Use: DentalAmide-type anesthetic used for local infiltration anesthesia; injection near nerve trunks to produce nerve block

Dosing: Adults

Dental anesthesia: Infiltration, or conduction block: Initial: 40-80 mg (1-2 mL) as a 4% solution; up to a maximum of 400 mg (10 mL) as a 4% solution within a 2-hour period. Manufacturer's maximum recommended dose is not more than 600 mg to normal healthy adults. The effective anesthetic dose varies with procedure, intensity of anesthesia needed, duration of anesthesia required and physical condition of the patient. Always use the lowest effective dose along with careful aspiration.

Note: Adult and children doses of prilocaine hydrochloride cited from USP Dispensing Information (USP DI), 17th ed, The United States Pharmacopeial Convention, Inc, Rockville, MD, 1997, 139.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Dental anesthesia: Infiltration, or conduction block:

Children <10 years: Doses >40 mg (1 mL) as a 4% solution per procedure rarely needed

Children >10 years and Adults: Initial: 40-80 mg (1-2 mL) as a 4% solution; up to a maximum of 400 mg (10 mL) as a 4% solution within a 2-hour period. Manufacturer's maximum recommended dose is not more than 600 mg to normal healthy adults. The effective anesthetic dose varies with procedure, intensity of anesthesia needed, duration of anesthesia required and physical condition of the patient. Always use the lowest effective dose along with careful aspiration.

Note: Adult and children doses of prilocaine hydrochloride cited from USP Dispensing Information (USP DI), 17th ed, The United States Pharmacopeial Convention, Inc, Rockville, MD, 1997, 139.

ContraindicationsHypersensitivity to local anesthetics of the amide type or any component of the formulation

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS toxicity: Careful and constant monitoring of the patient's state of consciousness should be done following each local anesthetic injection; at such times, restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of CNS toxicity. Treatment is primarily symptomatic and supportive.
- Methemoglobinemia: Has been reported with prilocaine.
- Respiratory arrest: Local anesthetics have been associated with rare occurrences of sudden respiratory arrest.
- Seizures: Convulsions due to systemic toxicity leading to cardiac arrest have also been reported, presumably following unintentional intravascular injection.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Hepatic impairment: Use with caution in patients with hepatic impairment.

Special populations:

- Acutely ill patients: Use with caution in acutely ill; reduce dose consistent with age and physical status.
- Debilitated patients: Use with caution in debilitated patients; reduce dose consistent with age and physical status.

- Elderly: Use with caution in the elderly; reduce dose consistent with age and physical status.
- Pediatrics: Use with caution in children; reduce dose consistent with age and physical status.

Other warnings/precautions:

- Administration: Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided.
- Trained personnel: Dental practitioners using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorB

Breast-Feeding ConsiderationsUsual infiltration doses of prilocaine given to nursing mothers has not been shown to affect the health of the nursing infant.

Adverse ReactionsDegree of adverse effects in the central nervous system and cardiovascular system are directly related to the blood levels of local anesthetic. The effects below are more likely to occur after systemic administration rather than infiltration.

Cardiovascular: Myocardial effects include a decrease in contraction force as well as a decrease in electrical excitability and myocardial conduction rate resulting in bradycardia and reduction in cardiac output.

Central nervous system: High blood levels result in anxiety, restlessness, disorientation, confusion, dizziness, tremor, and seizure. This is followed by depression of CNS resulting in somnolence, unconsciousness and possible respiratory arrest. Nausea and vomiting may also occur. In some cases, symptoms of CNS stimulation may be absent and the primary CNS effects are somnolence and unconsciousness.

Hypersensitivity reactions: May be manifest as dermatologic reactions and edema at injection site. Asthmatic syndromes have occurred.

Psychogenic reactions: It is common to misinterpret psychogenic responses to local anesthetic injection as an allergic reaction. Intraoral injections are perceived by many patients as a stressful procedure in dentistry. Common symptoms to this stress are diaphoresis, palpitation, hyperventilation, generalized pallor and a fainting feeling

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Citanest® Plain Dental: Prilocaine hydrochloride 4% (1.8 mL) [prefilled cartridge]

Generic AvailableNo

Mechanism of ActionLocal anesthetics bind selectively to the intracellular surface of sodium channels to block influx of sodium into the axon. As a result, depolarization necessary for action potential propagation and subsequent nerve function is prevented. The block at the sodium channel is reversible. When drug diffuses away from the axon, sodium channel function is restored and nerve propagation returns.

Pharmacodynamics/Kinetics

Onset of action: Infiltration: ~2 minutes; Inferior alveolar nerve block: ~3 minutes

Duration: Infiltration: Complete anesthesia for procedures lasting 20 minutes; Inferior alveolar nerve block: ~2.5 hours

Distribution: V_d: 0.7-4.4 L/kg; crosses blood-brain barrier

Protein binding: 55%

Metabolism: Hepatic and renal

Half-life elimination: 10-150 minutes; prolonged with hepatic or renal impairment

Dental Health: Effects on Dental TreatmentIt is common to misinterpret psychogenic responses to local anesthetic injection as an allergic reaction. Intraoral injections are perceived by many patients as a stressful procedure in dentistry. Common symptoms to this stress are diaphoresis, palpitations, hyperventilation, generalized pallor and a fainting feeling.

Degree of adverse effects in the CNS and cardiovascular system is directly related to blood levels of prilocaine (frequency not defined; more likely to occur after systemic administration rather than infiltration): Bradycardia and reduction in cardiac output, hypersensitivity reactions (may be manifest as dermatologic reactions and edema at injection site), asthmatic syndromes

High blood levels: Anxiety, restlessness, disorientation, confusion, dizziness, tremors, and seizures, followed by CNS depression, resulting in somnolence, unconsciousness and possible respiratory arrest; nausea and vomiting

In some cases, symptoms of CNS stimulation may be absent and the primary CNS effects are somnolence and unconsciousness.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusHigh blood levels result in anxiety, confusion, restlessness, disorientation, and dizziness. This is followed by CNS depression, resulting in somnolence, unconsciousness, and possible respiratory arrest. Symptoms of CNS stimulation may be absent and the primary CNS effects are somnolence and unconsciousness.

Mental Health: Effects on Psychiatric TreatmentNone reported

Mental Health Comment

It is common to misinterpret psychogenic responses to local anesthetic injection as an allergic reaction.

Anesthesia and Critical Care Concerns/Other Considerations Addition of sodium bicarbonate to local anesthetic solution can increase onset and potency. Only preservative-free solutions should be used for epidural administration. The metabolite *o*-toluidine can cause methemoglobinemia when large doses of prilocaine >600 mg are administered.

References

Jastak JT and Yagiela JA, “Vasoconstrictors and Local Anesthesia: A Review and Rationale for Use,” *J Am Dent Assoc*, 1983, 107(4):623-30. [PubMed 6355236]

MacKenzie TA and Young ER, “Local Anesthetic Update,” *Anesth Prog*, 1993, 40(2):29-34. [PubMed 8185087]

Wynn RL, “Epinephrine Interactions With Beta-Blockers,” *Gen Dent*, 1994, 42(1):16, 18. [PubMed 7911769]

Yagiela JA, “Local Anesthetics,” *Anesth Prog*, 1991, 38(4-5):128-41.[PubMed 1819966]

International Brand Names Citanest (BE, ES, FI, GB, LU, NL, NO, NZ, SE); Citanest Dental (AU); Xylonest (CH, DE)

Primaquine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Primaquine may be confused with primidone

Pronunciation(PRIM a kween)

Pharmacologic CategoryAminoquinoline (Antimalarial)

Use: Labeled IndicationsPrevention of relapse of *P. vivax* malaria

Use: Unlabeled/InvestigationalPrevention of relapse of *P. ovale* malaria; treatment of *Pneumocystis jiroveci* pneumonia (PCP); prevention of chloroquine-resistant malaria

Dosing: Adults**Note:** The CDC recommends screening for G6PD deficiency prior to initiating treatment with primaquine. Dosage expressed as mg of base (15 mg base = 26.3 mg primaquine phosphate).

Relapse prevention of *P. vivax* malaria: CDC recommendations: Uncomplicated malaria (***P. vivax*** and ***P. ovale***): Oral: 30 mg once daily for 14 days; alternative regimen (recommended for mild G6PD deficiency): 45 mg once weekly for 8 weeks

Prevention of chloroquine-resistant malaria (unlabeled use; CDC guidelines): Oral: Initiate 1-2 days prior to travel and continue for 7 days after departure from malaria-endemic area: 30 mg once daily

***Pneumocystis jiroveci*pneumonia treatment (unlabeled use):** Oral: CDC recommendation (as alternative): 30 mg once daily for 21 days (in combination with clindamycin)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** The CDC recommends screening for G6PD deficiency prior to initiating treatment with primaquine. Dosage expressed as mg of base (15 mg base = 26.3 mg primaquine phosphate).

Relapse prevention of *P. vivax* malaria: CDC recommendations: Uncomplicated malaria (***P. vivax*** and ***P. ovale***): Oral: 0.5 mg/kg once daily for 14 days (maximum dose: 30 mg/day); alternative regimen (recommended for mild G6PD deficiency): 45 mg once weekly for 8 weeks

Prevention of chloroquine-resistant malaria (unlabeled use; CDC guidelines): Oral: Initiate 1-2 days prior to travel and continue for 7 days after departure from malaria-endemic area: 0.5 mg/kg once daily

***Pneumocystis jiroveci*pneumonia treatment (unlabeled use):** Oral: CDC recommendation (as alternative): 0.3 mg/kg once daily for 21 days (in combination with clindamycin)

Administration: OralTake with meals to decrease adverse GI effects. Drug has a bitter taste.

ContraindicationsUse in acutely-ill patients who have a tendency to develop granulocytopenia (eg, rheumatoid arthritis, SLE); concurrent use with other medications causing hemolytic anemia or myeloid bone marrow suppression; concurrent use with or recent use of quinacrine

Allergy Considerations

- QuiNIDine/QuiNINE Derivative Allergy

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Hemolytic anemia: Promptly discontinue with signs of hemolytic anemia (darkening of urine, marked fall in hemoglobin or erythrocyte count). Moderate-to-severe hemolytic reactions may occur in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency and personal or familial history of favism. Geographic regions with a high prevalence of G6PD deficiency (eg, Africa, southern Europe, Mediterranean region, Middle East, southeast Asia, Oceania) are associated with a higher incidence of hemolytic anemia.

- Other hematologic effects: Anemia, methemoglobinemia, and leukopenia have been associated with primaquine use; monitor during treatment; do not exceed recommended dosage and duration.

Disease-related concerns:

- G6PD deficiency: Use with caution in patients with known G6PD; use of aminoquinolines has been associated with hemolysis. The CDC recommends screening for G6PD deficiency prior to therapy initiation.

- NADH methemoglobin reductase deficiency: Use with caution in patients with NADH methemoglobin reductase deficiency; methemoglobinemia may occur.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be prescribed by physicians familiar with its use.**

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias (rare)

Central nervous system: Headache

Dermatologic: Pruritus

Gastrointestinal: Abdominal cramps, dyspepsia, nausea, vomiting

Hematologic: Agranulocytosis, anemia, hemolytic anemia (in patients with G6PD deficiency), leukopenia, leukocytosis, methemoglobinemia (in NADH-methemoglobin reductase-deficient individuals)

Ocular: Interference with visual accommodation

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (strong), 2D6 (weak), 3A4 (weak); **Induces** CYP1A2 (weak)

Drug Interactions

Anthelmintics: Aminoquinolines (Antimalarial) may decrease the serum concentration of Anthelmintics. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): Antimalarial Agents may increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. *Risk C: Monitor therapy*

Beta-Blockers: Aminoquinolines (Antimalarial) may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Carteolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Cardiac Glycosides: Aminoquinolines (Antimalarial) may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inhibitors (Strong) may decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Mefloquine: Aminoquinolines (Antimalarial) may enhance the adverse/toxic effect of Mefloquine. Specifically, the risk for QTc-prolongation and the risk for convulsions may be increased. Mefloquine may increase the serum concentration of Aminoquinolines (Antimalarial). Management: Avoid concurrent use, and delay administration of mefloquine until at least 12 hours after the last dose of an aminoquinoline antimalarial when possible. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to GI irritation).

Monitoring ParametersPeriodic CBC, visual color check of urine, glucose, electrolytes; if hemolysis suspected, monitor CBC, haptoglobin, peripheral smear, urinalysis dipstick for occult blood, G6PD deficiency screening (prior to initiating treatment; CDC recommendation)

Nursing: Physical Assessment/MonitoringScreen for G6PD deficiency prior to beginning therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions or toxicity. Evaluate results of laboratory tests, therapeutic effects (according to purpose for use), and adverse reactions (eg, arrhythmias, pruritus, gastrointestinal upset, hematological changes) on a regular basis throughout therapy. Teach patient proper use, possible side effects/appropriate interventions (eg, importance of adequate hydration and periodic ophthalmic examinations with long-term therapy), and adverse symptoms to report.

Monitoring: Lab TestsPeriodic CBC, visual color check of urine, glucose, electrolytes; if hemolysis suspected - CBC, haptoglobin, peripheral smear, urinalysis dipstick for occult blood, G6PD deficiency screening (prior to initiating treatment; CDC recommendation)

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. It is important to complete full course of therapy for full effect. May be taken with meals to decrease GI upset and bitter aftertaste. Avoid excessive alcohol intake. You should have regular ophthalmic exams (every 4-6 months) if using this medication over extended periods. May cause nausea, vomiting, or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report persistent GI disturbance, chest pain or palpitation, unusual fatigue, easy bruising or bleeding, visual or hearing disturbances, changes in urine (darkening, tinged with red, decreased volume), or any other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as phosphate: 26.3 mg [15 mg base]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Primaquine Phosphate)

26.3 mg (14): $25.99

Mechanism of ActionEliminates the primary tissue exoerythrocytic forms of *P. falciparum*; disrupts mitochondria and binds to DNA

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Metabolism: Hepatic to carboxyprimaquine (active)

Half-life elimination: 3.7-9.6 hours

Time to peak, serum: 1-2 hours

Excretion: Urine (small amounts as unchanged drug)

Related Information

- Immunization Recommendations
- Malaria Treatment

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentContraindicated in patients receiving clozapine or carbamazepine
Index TermsPrimaquine Phosphate; Prymaccone
References

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Centers for Disease Control and Prevention, “*Pneumocystis jiroveci* (formerly *carinii*) Pneumonia (PCP),” available at http://www.dpd.cdc.gov/DPDx/HTML/PDF_Files/MedLetter/Pneumocystis%20jiroveci.pdf; last accessed August 29, 2008.

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Panisko DM and Keystone JS, “Treatment of Malaria - 1990,” *Drugs*, 1990, 39(2):160-89. [PubMed 2183998]

White NJ, “The Treatment of Malaria,” *N Engl J Med*, 1996, 335(11):800-6. [PubMed 8703186]

Wyler DJ, “Malaria Chemoprophylaxis for the Traveler,” *N Engl J Med*, 1993, 329(1):31-7.[PubMed 8505942]

International Brand NamesMalafree (KP); Malirid (IN); PMQ-INGA (IN); Primachina fosfato (IT); Primacin (AU)

Primidone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

Primidone may be confused with predniSONE, primaquine

Pronunciation(PRI mi done)

U.S. Brand NamesMysoline®

Canadian Brand NamesApo-Primidone®

Pharmacologic CategoryAnticonvulsant, Miscellaneous; Barbiturate

Use: Labeled IndicationsManagement of grand mal, psychomotor, and focal seizures

Use: Unlabeled/InvestigationalBenign familial tremor (essential tremor)

Dosing: Adults

Essential tremor (unlabeled use): 750 mg early in divided doses

Seizure disorders (grand mal, psychomotor, and focal): Oral: Initial: 125-250 mg/day at bedtime; increase by 125-250 mg/day every 3-7 days; usual dose: 750-1500 mg/day in divided doses 3-4 times/day with maximum dosage of 2 g/day.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricSeizure disorders (grand mal, psychomotor, and focal): Oral:

Children <8 years: Initial: 50-125 mg/day given at bedtime; increase by 50-125 mg/day increments every 3-7 days; usual dose: 10-25 mg/kg/day in divided doses 3-4 times/day.

Children ≥8 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 50-80 mL/minute: Administer every 8 hours.

Cl_{cr} 10-50 mL/minute: Administer every 8-12 hours.

Cl_{cr} <10 mL/minute: Administer every 12-24 hours.

Moderately dialyzable (20% to 50%)

Administer dose postdialysis or administer supplemental 30% dose.

Dosing: Hepatic ImpairmentIncreased side effects may occur in severe liver disease. Monitor plasma levels and adjust dose accordingly.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Dietary ConsiderationsFolic acid: Low erythrocyte and CSF folate concentrations. Megaloblastic anemia has been reported. To avoid folic acid deficiency and megaloblastic anemia, some clinicians recommend giving patients on anticonvulsants prophylactic doses of folic acid and cyanocobalamin.

StorageProtect from light.

ContraindicationsHypersensitivity to primidone, phenobarbital, or any component of the formulation; porphyria; pregnancy

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Depression: Use with caution in patients with depression or suicidal tendencies.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hypoadrenalism: Use with caution in patients with hypoadrenalism.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.
- Substance abuse: Use with caution in patients with a history of drug abuse; potential for drug dependency exists. Tolerance or psychological and physical dependence may occur with prolonged use.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in patients who are debilitated; may cause paradoxical responses.
- Elderly: Use with caution in the elderly; may cause paradoxical responses.
- Pediatrics: Use with caution in children; may cause paradoxical responses. Primidone's metabolite, phenobarbital, has been associated with cognitive deficits in children.

Other warnings/precautions:

- Acute pain: Do not administer to patients in acute pain.
- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsDue to CNS effects, monitor closely when initiating drug in elderly. Monitor CBC at 6-month intervals to compare with baseline obtained at start of therapy. Since elderly metabolize phenobarbital at a slower rate than younger adults, it is suggested to measure both primidone and phenobarbital serum concentrations together. Adjust dose for renal function in elderly when initiating or changing dose.

Pregnancy Risk FactorD

Pregnancy ConsiderationsCrosses the placenta. Dysmorphic facial features; hemorrhagic disease of newborn due to fetal vitamin K depletion, maternal folic acid deficiency may occur. Epilepsy itself, number of medications, genetic factors, or a combination of these probably influence the teratogenicity of anticonvulsant therapy. Benefit:risk ratio usually favors continued use during pregnancy.

LactationEnters breast milk/not recommended (AAP recommends use "with caution")

Breast-Feeding ConsiderationsSedation and feeding problems may occur in nursing infants. AAP recommends USE WITH CAUTION.

Adverse ReactionsFrequency not defined.

Central nervous system: Drowsiness, vertigo, ataxia, lethargy, behavior change, fatigue, hyperirritability

Dermatologic: Rash

Gastrointestinal: Nausea, vomiting, anorexia

Genitourinary: Impotence

Hematologic: Agranulocytopenia, agranulocytosis, anemia

Ocular: Diplopia, nystagmus

Metabolism/Transport EffectsMetabolized to phenobarbital; **Induces** CYP1A2 (strong), 2B6 (strong), 2C8 (strong), 2C9 (strong), 3A4 (strong)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Barbiturates: Primidone may enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inducers (Strong) may decrease the serum concentration of Bendamustine. Concentrations of active metabolites may be increased. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May enhance the adverse/toxic effect of Primidone. Specifically, osteomalacia and rickets. Carbonic Anhydrase Inhibitors may decrease the serum concentration of Primidone. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Primidone may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inducers (Strong) may increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inducers (Strong) may increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inducers (Highly Effective) may increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inducers (Highly Effective) may increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Primidone. Specifically, the concentration of its metabolite, phenobarbital. *Risk C: Monitor therapy*

Folic Acid: May decrease the serum concentration of Primidone. Additionally, folic acid may decrease concentrations of active metabolites of primidone (e.g., phenobarbital). *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

LamoTRIgine: Primidone may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Leucovorin-Levoleucovorin: May decrease the serum concentration of Primidone. Additionally, leucovorin/levoleucovorin may decrease concentrations of active metabolites of primidone (e.g., phenobarbital). *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Methylfolate: May decrease the serum concentration of Primidone. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Phenytoin: May increase the metabolism of Primidone. The ratio of primidone:phenobarbital is thus changed. *Risk C: Monitor therapy*

QuiNIDine: Primidone may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rufinamide: Primidone may decrease the serum concentration of Rufinamide. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Primidone. More specifically, the metabolism of phenobarbital, primidone's primary active metabolite, would be decreased. Primidone may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Protein-deficient diets increase duration of action of primidone.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersSerum primidone and phenobarbital concentration, CBC, neurological status. Due to CNS effects, monitor closely when initiating drug in elderly. Monitor CBC at 6-month intervals to compare with baseline obtained at start of therapy. Since elderly metabolize phenobarbital at a slower rate than younger adults, it is suggested to measure both primidone and phenobarbital levels together.

Reference RangeTherapeutic: Children <5 years: 7-10 mcg/mL (SI: 32-46 µmol/L); Adults: 5-12 mcg/mL (SI: 23-55 µmol/L); toxic effects rarely present with levels <10 mcg/mL (SI: 46 µmol/L) if phenobarbital concentrations are low. Dosage of primidone is adjusted with reference mostly to the phenobarbital level; Toxic: >15 mcg/mL (SI: >69 µmol/L)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness, laboratory values, and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use and seizure precautions, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsSerum primidone and phenobarbital concentration, CBC. Monitor CBC at 6-month intervals to compare with baseline obtained at start of therapy. Since elderly patients metabolize phenobarbital at a slower rate than younger adults, it is suggested to measure both primidone and phenobarbital levels together.

Patient EducationTake exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day

of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or impotence (reversible). Wear identification of epileptic status and medications. Report behavioral or CNS changes (confusion, depression, increased sedation, excitation, headache, insomnia, or lethargy); muscle weakness, or tremors; unusual bruising or bleeding (mouth, urine, stool); or worsening of seizure activity or loss of seizure control. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this drug; use appropriate contraceptive measures. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 50 mg, 250 mg [generic tablet may contain sodium benzoate]

Dosage forms available in Canada: Tablet: 125 mg, 250 mg. **Note:** 50 mg tablet is **not** available in Canada.

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Mysoline)

50 mg (90): $158.99

250 mg (30): $132.98

Tablets (Primidone)

250 mg (90): $69.99

Mechanism of ActionDecreases neuron excitability, raises seizure threshold similar to phenobarbital; primidone has two active metabolites, phenobarbital and phenylethylmalonamide (PEMA); PEMA may enhance the activity of phenobarbital
Pharmacodynamics/Kinetics

Absorption: 60% to 80%

Distribution: Adults: V_d: 0.6 L/kg

Protein binding: 30%

Metabolism: Hepatic to phenobarbital (active) by oxidation and to phenylethylmalonamide (PEMA; active) by scission of the heterocyclic ring

Half-life elimination (age dependent): Primidone: Mean: 5-15 hours (variable); PEMA: 16 hours (variable)

Time to peak, serum: ~3 hours (variable)

Excretion: Urine (40% as unchanged drug; the remainder is unconjugated PEMA, phenobarbital and its metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Index TermsDesoxyphenobarbital; Primaclone
References

"American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk," *Pediatrics*, 2001, 108(3):776-89. [PubMed 11533352]

Lane GP, Lewis CG, and Zail SC, "Macroscopic Crystalluria After Primidone Overdosage," *Med J Aust*, 1987, 147(11-12):624-5. [PubMed 3696053]

McNamara JO, "Drugs Effective in the Therapy of the Epilepsies," Gardman JG, Limbird LE, eds, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th ed, New York, NY: McGraw-Hill, 2001:532.

Porter RJ, Meldrum BD, "Antiepileptic Drugs," Katzung BG, ed, *Basic & Clinical Pharmacology*, 6th ed, East Norwalk, CT: Appleton & Lange, 1995:369.

Schwankhaus JD, Kattah JC, Lux WE, et al, "Primidone/Phenobarbital-Induced Periodic Alternating Nystagmus," *Ann Ophthalmol*, 1989, 21(6):230-2.[PubMed 2764437]

International Brand NamesApo-Primidone (NZ); Cyral (AT); Liskantin (BG, DE, EE, LU); Majsolin (HR); Mizodin (PL); Mutigan (VE); Mylepsinum (DE); Mysoline (AE, AR, AT, AU, BE, BF, BG, BH, BJ, BR, CH, CI, CN, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, IE, IL, IN, IQ, IR, IT, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SY, TN, TR, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Primidon (HR); Prysoline (IL); Sertan (HN, HU)

Pro-MACE-CytaBOM

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's

Regimen

Prednisone: Oral: 60 mg/m^2/day days 1 to 14

[total dose/cycle = 840 mg/m^2]

Doxorubicin: I.V.: 25 mg/m^2 day 1

[total dose/cycle = 25 mg/m^2]

Cyclophosphamide: I.V.: 650 mg/m^2 day 1

[total dose/cycle = 650 mg/m^2]

Etoposide: I.V.: 120 mg/m^2 day 1

[total dose/cycle = 120 mg/m^2]

Cytarabine: I.V.: 300 mg/m^2 day 8

[total dose/cycle = 300 mg/m^2]

Bleomycin: I.V.: 5 units/m^2 day 8

[total dose/cycle = 5 units/m^2]

Vincristine: I.V.: 1.4 mg/m^2 (maximum 2 mg) day 8

[total dose/cycle = 1.4 mg/m^2]

Methotrexate: I.V.: 120 mg/m^2 day 8

[total dose/cycle = 120 mg/m^2]

Leucovorin: Oral: 25 mg/m^2 every 6 hours for 4 doses (start 24 hours after methotrexate dose) day 9

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21 days

References

Longo DL, DeVita VT Jr, Duffey PL, et al, âSuperiority of ProMACE-CytaBOM Over ProMACE-MOPP in the Treatment of Advanced Diffuse Aggressive Lymphoma: Results of a Prospective Randomized Trial,â *J Clin Oncol*, 1991, 9(1):25-38.[PubMed 1702144]

Probenecid

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Probenecid may be confused with Procanbid®

Pronunciation(proe BEN e sid)

Canadian Brand NamesBenuryl™

Pharmacologic CategoryUricosuric Agent

Use: Labeled IndicationsPrevention of hyperuricemia associated with gout or gouty arthritis; prolongation and elevation of beta-lactam plasma levels

Dosing: Adults

Hyperuricemia with gout: Oral: 250 mg twice daily for 1 week; increase to 250-500 mg/day; may increase by 500 mg/month, if needed, to maximum of 2-3 g/day (dosages may be increased by 500 mg every 6 months if serum urate concentrations are controlled)

Prolong penicillin serum levels: Oral: 500 mg 4 times/day

Gonorrhea: CDC guidelines (alternative regimen): Probenecid 1 g orally with cefoxitin 2 g I.M.

Pelvic inflammatory disease: CDC guidelines: Cefoxitin 2 g I.M. plus probenecid 1 g orally as a single dose

Neurosyphilis: CDC guidelines (alternative regimen): Procaine penicillin 2.4 million units/day I.M. plus probenecid 500 mg orally 4 times/day; both administered for 10-14 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Note: Contraindicated in children <2 years of age.

Prolong penicillin serum levels: Oral: Children 2-14 years: Initial: 25 mg/kg, then 40 mg/kg/day given 4 times/day (maximum: 500 mg/dose)

Treatment of gonorrhea: >45 kg: Refer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute: Avoid use.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Dietary ConsiderationsDrug may cause GI upset; take with food if GI upset. Drink plenty of fluids.

ContraindicationsHypersensitivity to probenecid or any component of the formulation; high-dose aspirin therapy; blood dyscrasias; uric acid kidney stones; children <2 years of age

Warnings/Precautions

Concerns related to adverse effects:

- Gout: May cause exacerbation of acute gouty attack.

Disease-related concerns:

- Peptic ulcer disease: Use with caution in patients with peptic ulcer disease.

- Renal impairment: Monotherapy may not be effective in patients with a creatinine clearance <30 mL/minute.

Concurrent drug therapy issues:

- Penicillin: Use of probenecid with penicillin in patients with renal insufficiency is not recommended.

- Salicylates: Salicylates may diminish the therapeutic effect of probenecid; this effect may be more pronounced with high, chronic doses, however, the manufacturer recommends the use of an alternative analgesic even in place of small doses of aspirin.

Geriatric ConsiderationsSince probenecid loses its effectiveness when the Cl_{cr} is <30 mL/minute, its usefulness in the elderly is limited.

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined.

Cardiovascular: Flushing

Central nervous system: Dizziness, fever, headache

Dermatologic: Alopecia, dermatitis, pruritus, rash

Gastrointestinal: Anorexia, nausea, sore gums, vomiting

Genitourinary: Hematuria, polyuria

Hematologic: Anemia, aplastic anemia, hemolytic anemia, leukopenia

Hepatic: Hepatic necrosis

Neuromuscular & skeletal: Costovertebral pain, gouty arthritis (acute)

Renal: Nephrotic syndrome, renal colic

Miscellaneous: Anaphylaxis, hypersensitivity

Metabolism/Transport Effects**Inhibits** CYP2C19 (weak)

Drug Interactions

Carbapenems: Uricosuric Agents may decrease the excretion of Carbapenems. Management: Avoid concomitant use of doripenem and probenecid. *Risk C: Monitor therapy*

Cephalosporins: Uricosuric Agents may decrease the excretion of Cephalosporins. **Exceptions:** Ceftobiprole. *Risk C: Monitor therapy*

Dapsone: Uricosuric Agents may decrease the excretion of Dapsone. *Risk C: Monitor therapy*

Doripenem: Probenecid may increase the serum concentration of Doripenem. This effect is due to probenecid's ability to decrease the active tubular secretion of doripenem. *Risk D: Consider therapy modification*

Gemifloxacin: Probenecid may decrease the excretion of Gemifloxacin. *Risk C: Monitor therapy*

Ketoprofen: Probenecid may increase the serum concentration of Ketoprofen. *Risk C: Monitor therapy*

Ketorolac: Probenecid may increase the serum concentration of Ketorolac. *Risk X: Avoid combination*

LORazepam: Probenecid may decrease the metabolism of LORazepam. *Risk D: Consider therapy modification*

Methotrexate: Uricosuric Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Mycophenolate: Probenecid may increase the serum concentration of Mycophenolate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: Probenecid may increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Penicillins: Uricosuric Agents may decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Quinolone Antibiotics: Probenecid may increase the serum concentration of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: May diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Sodium Benzoate: Probenecid may increase the serum concentration of Sodium Benzoate. Specifically, probenecid may inhibit the renal transport of the hippuric acid metabolite of sodium benzoate. *Risk C: Monitor therapy*

Sodium Phenylacetate: Probenecid may increase the serum concentration of Sodium Phenylacetate. Specifically, probenecid may inhibit the renal transport of the phenylacetylglutamine metabolite of sodium phenylacetate. *Risk C: Monitor therapy*

Theophylline Derivatives: Uricosuric Agents may decrease the excretion of Theophylline Derivatives. **Exceptions:** Aminophylline; Theophylline. *Risk C: Monitor therapy*

Zidovudine: Probenecid may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Test InteractionsFalse-positive glucosuria with Clinitest®, a falsely high determination of theophylline has occurred and the renal excretion of phenolsulfonphthalein 17-ketosteroids and bromsulfophthalein (BSP) may be inhibited

Monitoring ParametersUric acid, renal function, CBC

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness, laboratory values, and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsUric acid, renal function, CBC

Patient EducationTake as directed; do not discontinue without consulting prescriber. May take 6-12 months to reduce gouty attacks (attacks may increase in frequency and severity for first few months of therapy). Take with food or antacids or alkaline ash foods (milk, nuts, beets, spinach, turnip greens). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid aspirin or aspirin-containing substances. If you have diabetes, use serum glucose monitoring. If you experience severe headache, contact prescriber for medication. You may experience dizziness or lightheadedness (use caution when driving, changing position, or engaging in tasks requiring alertness until response to drug is known); or nausea, vomiting, indigestion, or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report skin rash or itching, persistent headache, blood in urine or painful urination, excessive tiredness or easy bruising or bleeding, or sore gums. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 500 mg

Generic Available Yes

Pricing: U.S. (www.drugstore.com)

Tablets (Probenecid)

500 mg (60): $34.99

Mechanism of Action Competitively inhibits the reabsorption of uric acid at the proximal convoluted tubule, thereby promoting its excretion and reducing serum uric acid levels; increases plasma levels of weak organic acids (penicillins, cephalosporins, or other beta-lactam antibiotics) by competitively inhibiting their renal tubular secretion

Pharmacodynamics/Kinetics

Onset of action: Effect on penicillin levels: 2 hours

Absorption: Rapid and complete

Metabolism: Hepatic

Half-life elimination (dose dependent): Normal renal function: 6-12 hours

Time to peak, serum: 2-4 hours

Excretion: Urine

Related Information

- Treatment of Sexually-Transmitted Infections

Pharmacotherapy Pearls Avoid fluctuation in uric acid (increase or decrease); may precipitate gout attack. Use of sodium bicarbonate or potassium citrate is suggested until serum uric acid normalizes and tophaceous deposits disappear.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Sore gums.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness

Mental Health: Effects on Psychiatric Treatment May rarely cause leukopenia; use caution with clozapine and carbamazepine

Index Terms Benemid [DSC]

References

Centers for Disease Control and Prevention, "Sexually Transmitted Diseases Treatment Guidelines 2002," *MMWR Recomm Rep*, 2002, 51(RR-6):1-84.

International Brand Names Bencid (IN, TH); Benecid Valdecasas (MX); Benemid (GB, IE, NL); Benemide (FR); Benuryl (IL); Brucid (TW); Gonocilin (BR); Pro-Cid (AU); Probecid (FI, NO, SE); Probecilin (BR); Probenecid Weimer (DE); Probenecid ”Dak” (DK); Probenecid ”Medic” (DK); Procid (TW); Pronid (TW); Santuril (CH)

Probucol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(PROE byoo kole)
Canadian Brand NamesLorelco速
Pharmacologic CategoryAntilipemic Agent, Miscellaneous
Use: Labeled IndicationsAdjunct to dietary therapy to decrease elevated serum total and LDL-cholesterol concentrations in primary hypercholesterolemia
Dosing: Adults**Dyslipidemia:** Oral: 500 mg twice daily administered with the morning and evening meals
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Dyslipidemia:** Oral: Children:

<27 kg: 250 mg twice daily with meals

>27 kg: 500 mg twice daily with meals

RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to probucol or any component of the formulation; ventricular arrhythmias
Pregnancy Risk FactorB
Adverse ReactionsFrequency not defined.

Cardiovascular: QT prolongation, serious arrhythmia

Central nervous system: Dizziness, headache, numbness of extremities

Gastrointestinal: Bloating, diarrhea, stomach pain, nausea, vomiting

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CycloSPORINE: Probucol may decrease the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 250 mg, 500 mg [not available in the U.S.]

Generic AvailableNo
Mechanism of ActionIncreases the fecal loss of bile acid-bound low density lipoprotein cholesterol, decreases the synthesis of cholesterol and inhibits enteral cholesterol absorption
Pharmacotherapy PearlsNot available in U.S.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsProbucol is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine速 2% with Neo-Cobefrin速]) be used with caution.
Mental Health: Effects on Mental StatusMay cause dizziness
Mental Health: Effects on Psychiatric TreatmentConcurrent use with phenothiazines, TCAs, or beta-blockers may produce AV block
Index TermsBiphenabid
International Brand NamesAlcolex (HU); Bifenabid (ES); Lesterol (BR); Lisosterol (PT); Lodeco (KP); Lurselle (AT, AU, CH, FR, IE, IT, PL);

Panesclerina (ES); Procol (TW); Sinlestal (JP); Superlipid (ES); Zhile (CL)

Procainamide

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Procanbid® may be confused with probenecid

Pronestyl® may be confused with Ponstel®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

PCA is an error-prone abbreviation (mistaken as patient controlled analgesia)

Pronunciation(pro KANE a mide)

U.S. Brand NamesProcanbid® [DSC]

Canadian Brand NamesApo-Procainamide®; Procainamide Hydrochloride Injection, USP ; Procan® SR; Pronestyl®-SR

Pharmacologic CategoryAntiarrhythmic Agent, Class Ia

Use: Labeled IndicationsTreatment of ventricular tachycardia (VT), premature ventricular contractions, paroxysmal atrial tachycardia (PSVT), and atrial fibrillation (AF); prevent recurrence of ventricular tachycardia, paroxysmal supraventricular tachycardia, atrial fibrillation or flutter

Use: Unlabeled/Investigational

ACLS guidelines:

Stable monomorphic VT (EF >40%, no CHF)

Stable wide complex tachycardia, likely VT (EF >40%, no CHF, patient stable)

Atrial fibrillation or flutter, including pre-excitation syndrome (EF >40%, no CHF)

AV reentrant, narrow complex tachycardia (eg, reentrant SVT) [preserved ventricular function]

PALS guidelines: Tachycardia with pulses and poor perfusion (possible VT)

Dosing: AdultsDose must be titrated to patient's response.

Antiarrhythmic:

Oral: Usual dose: 50 mg/kg/24 hours: maximum: 5 g/24 hours (**Note:** Twice-daily dosing approved for Procanbid®.)

Immediate release formulation: 250-500 mg/dose every 3-6 hours

Extended release formulation: 500 mg to 1 g every 6 hours; Procanbid®: 1000-2500 mg every 12 hours

I.M.: 0.5-1 g every 4-8 hours until oral therapy is possible

I.V. (infusion requires use of an infusion pump):

Loading dose: 15-18 mg/kg administered as slow infusion over 25-30 minutes **or** 100-200 mg/dose repeated every 5 minutes as needed to a total dose of 1 g. Reduce loading dose to 12 mg/kg in severe renal or cardiac impairment.

Maintenance dose: 1-4 mg/minute by continuous infusion. Maintenance infusions should be reduced by one-third in patients with moderate renal or cardiac impairment and by two-thirds in patients with severe renal or cardiac impairment.

ACLS guidelines: Infuse 20 mg/minute until arrhythmia is controlled, hypotension occurs, QRS complex widens by 50% of its original width, or total of 17 mg/kg is given.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricMust be titrated to patient's response:

Arrhythmias:

Oral: 15-50 mg/kg/24 hours divided every 3-6 hours

I.M.: 50 mg/kg/24 hours divided into doses of $^1/_8$ to $^1/_4$ every 3-6 hours in divided doses until oral therapy is possible

I.V. (infusion requires use of an infusion pump):

Load: 3-6 mg/kg/dose over 5 minutes not to exceed 100 mg/dose; may repeat every 5-10 minutes to maximum of 15 mg/kg/load

Maintenance as continuous I.V. infusion: 20-80 mcg/kg/minute; maximum: 2 g/24 hours

Possible VT (pulses and poor perfusion) [PALS 2005 Guidelines]: I.V.; I.O.: 15 mg/kg over 30-60 minutes

Dosing: Renal Impairment

Oral:

Cl_{cr} 10-50 mL/minute: Administer every 6-12 hours.

Cl_{cr} <10 mL/minute: Administer every 8-24 hours.

I.V.:

Loading dose: Reduce dose to 12 mg/kg in severe renal impairment.

Maintenance infusion: Reduce dose by one-third in patients with mild renal impairment. Reduce dose by two-thirds in patients with severe renal impairment.

Dialysis:

Procainamide: Moderately hemodialyzable (20% to 50%): 200 mg supplemental dose posthemodialysis is recommended.

N-acetylprocainamide: Not dialyzable (0% to 5%)

Procainamide/N-acetylprocainamide: Not peritoneal dialyzable (0% to 5%)

Procainamide/N-acetylprocainamide: Replace by blood level during continuous arteriovenous or venovenous hemofiltration

Dosing: Hepatic ImpairmentReduce dose by 50%.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Procainamide

Administration: I.V.Must dilute prior to I.V. administration; maximum rate: 50 mg/minute; give around-the-clock to promote less variation in peak and trough serum levels.

Infusion rate: **2 g/250 mL** (I.V. infusion requires use of an infusion pump):

1 mg/minute: 7.5 mL/hour

2 mg/minute: 15 mL/hour

3 mg/minute: 22.5 mL/hour

4 mg/minute: 30 mL/hour

5 mg/minute: 37.5 mL/hour

6 mg/minute: 45 mL/hour

Administration: I.V. DetailpH: 4-6

Administration: OralDo **not** crush or chew extended release drug products.

Dietary ConsiderationsShould be taken with water on an empty stomach.

StorageProcainamide may be stored at room temperature up to 27°C; however, refrigeration retards oxidation, which causes color formation. The solution is initially colorless but may turn slightly yellow on standing. Injection of air into the vial causes the solution to darken. Solutions darker than a light amber should be discarded. Stability of admixture at room temperature in D_5W or NS: 24 hours.

ReconstitutionMinimum volume: 1 g/250 mL NS/D_5W .

Some information indicates that procainamide may be subject to greater decomposition in D_5W unless the admixture is refrigerated or the pH is adjusted. Procainamide is believed to form an association complex with dextrose - the bioavailability of procainamide in this complex is not known and the complex formation is reversible.

CompatibilityStable in $^1/_2$NS, NS, sterile water for injection; **variable stability (consult detailed reference)** in D_5NS, D_5W.

Y-site administration: Compatible: Amiodarone, cisatracurium, famotidine, heparin, hydrocortisone sodium succinate, potassium chloride, ranitidine, remifentanil, vitamin B complex with C. **Incompatible** Milrinone. **Variable (consult detailed reference):** Diltiazem, inamrinone.

Compatibility when admixed: Compatible: Amiodarone, atracurium, dobutamine, flumazenil, lidocaine, verapamil. **Incompatible:** Esmolol, ethacrynate, milrinone, phenytoin. **Variable (consult detailed reference):** Bretylium.

Extemporaneously Prepared**Note:** Several formulations have been described, some being more complex; for all formulations, the pH must be 4-6 to prevent degradation; some preparations require adjustment of pH; shake well before use

A suspension of 50 mg/mL can be made with the capsules, distilled water, and a 2:1 simple syrup/cherry syrup mixture; stability 2 weeks under refrigeration (ASHP, 1987)

Concentrations of 5, 50, and 100 mg/mL oral liquid preparations (made with the capsules, sterile water for irrigation and cherry syrup) stored at 4°C to 6°C (pH 6) were stable for at least 6 months (Metras, 1992).

A sucrose-based syrup (procainamide 50 mg/mL) made with capsules, distilled water, simple syrup, parabens, and cherry flavoring had a calculated stability of 456 days at 25°C and measured stability of 42 days at 40°C (pH ~5) while a maltitol-based syrup (procainamide 50 mg/mL) made with capsules, distilled water, Lycasin® (a syrup vehicle with 75% w/w maltitol), parabens, sodium bisulfate, saccharin, sodium acetate, pineapple and apricot flavoring, FD & C yellow number 6 (pH adjusted to 5 with glacial acetic acid) had a calculated stability of 97 days at 25°C and a measured stability of 94 days at 40°C. The maltitol-based syrup was more stable than the sucrose-based syrup when temperature was >37°C, but the sucrose-based syrup was more stable at temperatures <37°C (Alexander, 1993).

Alexander KS, Pudipeddi M, and Parker GA, “Stability of Procainamide Hydrochloride Syrups Compounded From Capsules,” *Am J Hosp Pharm*, 1993, 50(4):693-8.

Handbook in Extemporaneous Formulations, Bethesda, MD: American Society of Hospital Pharmacists, 1987.

Metras JI, Swenson CF, and MacDermott MP, “Stability of Procainamide Hydrochloride in an Extemporaneously Compounded Oral Liquid,” *Am J Hosp Pharm*, 1992, 49(7):1720-4.

Swenson CF, “Importance of Following Instructions When Compounding,” *Am J Hosp Pharm*, 1993, 50(2):261.

Contraindications

Hypersensitivity to procaine, other ester-type local anesthetics, or any component of the formulation; complete heart block (except in patients with a functioning artificial pacemaker); second-degree AV block (without a functional pacemaker); various types of hemiblock (without a functional pacemaker); SLE; torsade de pointes; concurrent cisapride use; QT prolongation

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Boxed warnings:

- Blood dyscrasias: See “Other warnings/precautions” below.
- CAST trial: See “Other warnings/precautions” below.
- Drug-induced lupus erythematosus-like syndrome: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Blood dyscrasias: **[U.S. Boxed Warning]: Potentially fatal blood dyscrasias have occurred with therapeutic doses;** close monitoring is recommended during the first 3 months of therapy.
- Conduction disturbances: Reduce dose if first-degree heart block occurs.
- Drug-induced lupus erythematosus-like syndrome: **[U.S. Boxed Warning]: Long-term administration leads to the development of a positive antinuclear antibody (ANA) test in 50% of patients which may result in a drug-induced lupus erythematosus-like syndrome (in 20% to 30% of patients);** discontinue procainamide with SLE symptoms and choose an alternative agent.
- Hypersensitivity reaction: With use, hypersensitivity reactions can occur.
- Proarrhythmic effects: Watch for proarrhythmic effects; monitor and adjust dose to prevent QT_c prolongation.

Disease-related concerns:

- Atrial fibrillation/flutter: May increase ventricular response rate in patients with atrial fibrillation or flutter; control AV conduction before initiating.
- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.
- Heart failure (HF): Use with caution in patients with HF; may precipitate or exacerbate condition.
- Myasthenia gravis: Avoid use in myasthenia gravis; may worsen condition.
- Renal impairment: Use with caution in patients with renal impairment; dosage reduction recommended.

Concurrent drug therapy issues:

- Antiarrhythmics: Use caution with concurrent use of other antiarrhythmics.

Dosage form specific issues:

- Bisulfite: Injection may contain bisulfite (allergens).
- Tartrazine: Some tablets contain tartrazine.

Other warnings/precautions:

- CAST trial: **[U.S. Boxed Warning] In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, non-life-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide.** An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. Antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Geriatric ConsiderationsMonitor closely since clearance is reduced in those >60 years of age. If clinically possible, start doses at lowest recommended dose. Also, elderly frequently have drug therapy which may interfere with the use of procainamide. Adjust dose for renal function in the elderly.

Pregnancy Risk FactorC

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsConsidered compatible by the AAP. However, the AAP stated concern regarding long-term effects and potential for infant toxicity. Use caution and monitor closely if continuing to breast-feed while taking procainamide.

Adverse Reactions

>1%:

Cardiovascular: Hypotension (I.V. up to 5%)

Dermatologic: Rash

Gastrointestinal: Diarrhea (3% to 4%), nausea, vomiting, taste disorder, GI complaints (3% to 4%)

<1% (Limited to important or life-threatening): New or worsened arrhythmia (proarrhythmic effect), tachycardia, QT prolongation (excessive), second-degree heart block, torsade de pointes, ventricular arrhythmia, depressed myocardial contractility, paradoxical increase in ventricular rate in atrial fibrillation/flutter, dizziness, lightheadedness, confusion, hallucinations, mental depression, disorientation, fever, drug fever, rash, urticaria, pruritus, angioneurotic edema, flushing, maculopapular rash, hemolytic anemia, agranulocytosis, neutropenia, thrombocytopenia (0.5%), positive Coombs' test, bone marrow suppression, hypoplastic anemia, leukopenia, pancytopenia, aplastic anemia, transaminases increased, alkaline phosphatase increased, hyperbilirubinemia, hepatic failure,granulomatous hepatitis, intrahepatic cholestasis, arthralgia, myalgia (<0.5%), worsening of myasthenia gravis, neuromuscular blockade, weakness, peripheral/polyneuropathy, myopathy, pleural effusion, SLE-like syndrome (increased incidence with long-term therapy and includes abdominal pain, arthralgia, pleural effusion, pericarditis, fever, chills, myalgia, rash); positive ANA

Postmarketing and/or case reports: Pancreatitis, pseudo-obstruction, tremor, mania, myocarditis, vasculitis, psychosis, cerebellar ataxia, demyelinating polyradiculoneuropathy, respiratory failure due to myopathy, pulmonary embolism, myopathy

Metabolism/Transport Effects**Substrate** of CYP2D6 (major)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amiodarone: Antiarrhythmic Agents (Class Ia) may enhance the QTc-prolonging effect of Amiodarone. Amiodarone may increase the metabolism of Antiarrhythmic Agents (Class Ia). *Risk D: Consider therapy modification*

Cimetidine: May decrease the excretion of Procainamide. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Procainamide may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Trimethoprim: May decrease the excretion of Procainamide. *Risk D: Consider therapy modification*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (acute ethanol administration reduces procainamide serum concentrations).

Herb/Nutraceutical: Avoid ephedra (may worsen arrhythmia).

Monitoring ParametersECG, blood pressure, CBC with differential, platelet count; cardiac monitor and blood pressure monitor required during I.V. administration; blood levels in patients with renal failure or receiving constant infusion >3 mg/minute for longer than 24 hours

Reference Range

Timing of serum samples: Draw trough just before next oral dose; draw 6-12 hours after I.V. infusion has started; half-life is 2.5-5 hours

Therapeutic levels: Procainamide: 4-10 mcg/mL; NAPA 15-25 mcg/mL; Combined: 10-30 mcg/mL

Toxic concentration: Procainamide: >10-12 mcg/mL

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. I.V. requires use of infusion pump and continuous cardiac and hemodynamic monitoring. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy, when titrating dosage, and on a regular basis with long-term therapy. **Note:** Procainamide has a low TI and overdose may easily produce severe and life-threatening reactions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, platelet count

Patient EducationOral: Take exactly as directed; do not take additional doses or discontinue without consulting prescriber. Avoid alcohol. You will need regular cardiac checkups and blood tests while taking this medication. You may experience dizziness, lightheadedness, or visual changes (use caution when driving or engaging in tasks requiring alertness until response to drug is known); loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); headaches (prescriber may recommend mild analgesic); or diarrhea (yogurt or boiled milk may help; if persistent consult prescriber). Report chest pain, palpitation, or erratic heartbeat; increased weight or swelling of hands or feet; shortness of breath; acute diarrhea; or unusual fatigue and tiredness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, as hydrochloride: 250 mg, 500 mg [DSC]

Injection, solution, as hydrochloride: 100 mg/mL (10 mL); 500 mg/mL (2 mL) [contains sodium metabisulfite]

Tablet, extended release, as hydrochloride: 750 mg [DSC]

Procanbid®: 500 mg, 1000 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Procainamide HCl)

250 mg (60): $37.99

500 mg (100): $79.99

Capsules (Pronestyl)

250 mg (120): $88.99

Mechanism of ActionDecreases myocardial excitability and conduction velocity and may depress myocardial contractility, by increasing the electrical stimulation threshold of ventricle, His-Purkinje system and through direct cardiac effects

Pharmacodynamics/Kinetics

Onset of action: I.M. 10-30 minutes

Distribution: V_d: Children: 2.2 L/kg; Adults: 2 L/kg; Congestive heart failure or shock: Decreased V_d

Protein binding: 15% to 20%

Metabolism: Hepatic via acetylation to produce N-acetyl procainamide (NAPA) (active metabolite)

Bioavailability: Oral: 75% to 95%

Half-life elimination:

Procainamide (hepatic acetylator, phenotype, cardiac and renal function dependent):

Children: 1.7 hours; Adults: 2.5-4.7 hours; Anephric: 11 hours

NAPA (dependent upon renal function):

Children: 6 hours; Adults: 6-8 hours; Anephric: 42 hours

Time to peak, serum: Capsule: 45 minutes to 2.5 hours; I.M.: 15-60 minutes

Excretion: Urine (25% as NAPA)

Related Information

- Antiarrhythmic Drugs
- Depression

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste disorder.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsProcainamide is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay cause dizziness, confusion, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentContraindicated with ziprasidone. May rarely cause agranulocytosis; use caution with clozapine and carbamazepine. Concurrent use with phenothiazines, TCAs, or beta-blockers may produce AV block.

Cardiovascular ConsiderationsIn patients with pre-existing cardiovascular disease, the incidence of proarrhythmia and mortality may be increased with Class Ia antiarrhythmic agents. Procainamide may be used to pharmacologically convert atrial fibrillation to normal sinus rhythm. In this setting, it is important that AV nodal conduction be controlled (digoxin, beta-blocker, calcium channel blocker) prior to cardioversion to inhibit procainamide-induced increases in ventricular response. Patients should be monitored (ECG) in a controlled setting when initiating therapy. Therapy should be discontinued or the dose reduced if the QT interval increases ≥25% from baseline.

Anesthesia and Critical Care Concerns/Other ConsiderationsIn patients with pre-existing cardiovascular disease, the incidence of proarrhythmia and mortality may be increased with Class Ia antiarrhythmic agents.

Procainamide may be used to pharmacologically convert atrial fibrillation to normal sinus rhythm. In this setting, it is important that AV nodal conduction be controlled (eg, digoxin, beta-blocker, calcium channel blocker) prior to cardioversion to inhibit procainamide-induced increases in ventricular response. Patients should be monitored (ECG and BP) in a controlled setting when initiating therapy.

Index TermsPCA (error-prone abbreviation); Procainamide Hydrochloride; Procaine Amide Hydrochloride

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International Brand NamesBiocoryl (ES); Cardiorytmin (FI); Gima (ID); Medaject[inj.] (DE); Pasconeural-Injektopas (DE); Procainamid (PL); Procainamid Duriles (DE); Procainamide Cloridrato (IT); Procainamide Durules (NZ); Procainamidum (PL); Procamid depot (FI); Procamide (BR, IT); Pronestyl (AU, BE, CH, CL, ET, GB, IE, IN, KE, LU, MY, NL, NO, TW, TZ, UG, ZA)

Procaine

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (epidural administration) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(PROE kane)
U.S. Brand NamesNovocain®
Pharmacologic CategoryLocal Anesthetic
Use: Labeled IndicationsProduces spinal anesthesia
Dosing: Adults**Spinal analgesia:** Extent of anesthesia:

Perineum: Total dose: 50 mg; Procaine 10%: 0.5 mL with 0.5 mL diluent

Perineum and lower extremities: Total dose: 100 mg; Procaine 10%: 1 mL with 1 mL diluent

Up to costal margin: Total dose: 200 mg; Procaine 10%: 2 mL with 1 mL diluent

Dosing: ElderlyRefer to adult dosing.
CompatibilityStable in NS, sterile distilled water, spinal fluid, sterile dextrose solution (for hyperbaric technique).
ContraindicationsHypersensitivity to procaine, PABA, parabens, other ester local anesthetics, or any component of the formulation; septicemia; infection at the injection site; cerebrospinal system infections (eg, meningitis, syphilis)
Warnings/Precautions

Concerns related to adverse effects:

- CNS toxicity: Careful and constant monitoring of the patient's state of consciousness should be done following each local anesthetic injection; at such times, restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of CNS toxicity. Treatment is primarily symptomatic and supportive.

- Respiratory arrest: Local anesthetics have been associated with rare occurrences of sudden respiratory arrest.

- Seizures: Convulsions due to systemic toxicity leading to cardiac arrest have also been reported, presumably following unintentional intravascular injection.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; may be more susceptible to toxic effects of local anesthetics.

- Endocrine disease: Use with caution in patients with endocrine disease; may be more susceptible to toxic effects of local anesthetics.

- Hyperthyroidism: Use with caution in patients with hyperthyroidism; may be more susceptible to toxic effects of local anesthetics.

Special populations:

- Acutely ill patients: Use with caution in acutely ill; reduce dose consistent with age and physical status.

- Debilitated patients: Use with caution in debilitated patients; reduce dose consistent with age and physical status.

- Elderly: Use with caution in the elderly; reduce dose consistent with age and physical status.

- Pediatrics: Use with caution in children; reduce dose consistent with age and physical status.

Dosage form specific issues:

- Sodium metabisulfite: May contain sodium metabisulfite; use caution in patients with a sulfite allergy.

Other warnings/precautions:

- Administration: Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

- Trained personnel: Clinicians using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. Local anesthetics cross the placenta; effects to the fetus depend on procedure and type of administration.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, cardiac arrest, edema, hyper-/hypotension

Central nervous system: Dizziness, drowsiness, nervousness, seizure, tremor

Dermatologic: Cutaneous lesions (onset may be delayed), urticaria

Ocular: Blurred vision

Respiratory: Respiratory arrest

Miscellaneous: Allergic reactions

Drug Interactions

Sulfonamide Derivatives: Procaine may diminish the therapeutic effect of Sulfonamide Derivatives. *Risk X: Avoid combination*

Nursing: Physical Assessment/MonitoringMonitor response, degree of pain sensation, and injection site. **Epidural:** Monitor CNS status.
Patient EducationThe purpose of this medication is to reduce pain sensation. Report local burning or pain at injection site. Report persistent diarrhea. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride:

Novocain®: 10% (2 mL) [contains sodium bisulfite]

Generic AvailableNo
Mechanism of ActionBlocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction
Pharmacodynamics/Kinetics

Onset of action: 2-5 minutes

Duration (patient, type of block, concentration, and method of anesthesia dependent); 0.5-1.5 hours

Metabolism: Rapidly hydrolyzed by plasma enzymes to PABA and diethylaminoethanol (80% conjugated before elimination)

Half-life elimination: 7.7 minutes

Excretion: Urine (as metabolites and some unchanged drug)

Dental Health: Effects on Dental TreatmentThis is no longer a useful anesthetic in dentistry due to high incidence of allergic reactions.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentIf used with a vasoconstrictor, the effects of MAO inhibitors may be enhanced
Index TermsProcaine Hydrochloride
References

Hart D, “Psychotic Reaction to Procaine,” *J Emerg Nurs*, 1984, 10(1):9-10. [PubMed 6366319]

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International Brand NamesClorhidrato de procaina Biocrom (AR); Endocaina (AR); Fadacaina (AR); Gero (FR); Gero H3 Aslan (AR); Gerovital H3 (BE, NL); Hewedolor-Procain (DE); Hillcain (IL); Inj. Polocaini Hydrochlorici (PL); Injectio Polocaini (PL); Lenident (IT); Lophakomp-Procain N (DE); Novanaest purum 1% (AT); Novanaest purum 2% (AT); Novocain (DE); Procain Braun (DE); Procain curasan (DE); Procain Injektopas (DE); Procain Jenapharm (DE); Procain Rodler (DE); Procain Steigerwald (DE); Procain-HCl (DE); procain-loges (DE); Procaina (ES); Procaine Aguettant (FR); Procaine Biostabilex (FR); Procaine chlorhydrate Lavoisier (FR); Procaine Hydrochloride Inj (AU); Procainhydrochlorid (DE); Prokain (HU); Recorcaina (IT); Rowo Procain (DE); Syntocaine (CH); Venocaina Miro (ES)

Procarbazine

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Procarbazine may be confused with dacarbazine

Matulane® may be confused with Modane®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(proe KAR ba zeen)

U.S. Brand NamesMatulane®

Canadian Brand NamesMatulane®; Natulan®

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent

Use: Labeled IndicationsTreatment of Hodgkin's disease

Use: Unlabeled/InvestigationalTreatment of non-Hodgkin's lymphoma, brain tumors, melanoma, lung cancer, multiple myeloma

Dosing: AdultsRefer to individual protocols.

Chemotherapy: Oral: Initial: 2-4 mg/kg/day in single or divided doses for 7 days then increase dose to 4-6 mg/kg/day until response is obtained or leukocyte count decreased <4000/mm^3 or the platelet count decreased <100,000/mm^3; maintenance: 1-2 mg/kg/day

Dosing: ElderlyRefer to adult dosing; use with caution. Adjust for renal impairment.

Dosing: PediatricRefer to individual protocols. Manufacturer states that the dose is based on patient's ideal weight if the patient is obese or has abnormal fluid retention. Other studies suggest that ideal body weight may not be necessary. Oral (may be given as a single daily dose or in 2-3 divided doses): Children:

BMT aplastic anemia conditioning regimen: 12.5 mg/kg/day every other day for 4 doses

Hodgkin's disease: MOPP/IC-MOPP regimens: 100 mg/m^2/day for 14 days and repeated every 4 weeks

Neuroblastoma and medulloblastoma: Doses as high as 100-200 mg/m^2/day once daily have been used.

Dosing: Renal ImpairmentThe FDA-approved labeling does not contain dosing adjustment guidelines; use with caution; may result in increased toxicity.

Dosing: Hepatic ImpairmentThe FDA-approved labeling does not contain dosing adjustment guidelines; use with caution; may result in increased toxicity. The following guidelines have been used by some clinicians:

Floyd, 2006:

Transaminases 1.6-6 times ULN: Administer 75% of dose

Transaminases >6 times ULN: Use clinical judgment

Serum bilirubin >5 mg/dL or transaminases >3 times ULN: Avoid use

King, 2001: Serum bilirubin >5 mg/dL or transaminases >180 units/L: Avoid use

Dosing: Combination Regimens

Brain tumors:

8 in 1 (Brain tumors)

MOP

MOPP (Medulloblastoma)

PCV

Lymphoma, Hodgkin's:

BEACOPP

CAD/MOPP/ABV

ChlVPP

LOPP

MOPP (Lymphoma, Hodgkin's Disease)

MOPP/ABV Hybrid

MOPP/ABVD

MVPP

OPPA

Lymphoma, non-Hodgkin's:

CEPP(B)

COP-BLAM

COPP

Retinoblastoma: 8 in 1 (Retinoblastoma)

Calculations

- Body Surface Area: Pediatrics

Administration: OralMay be given as a single daily dose or in 2-3 divided doses.

Dietary ConsiderationsAvoid tyramine-containing foods/beverages. Some examples include aged or matured cheese, air-dried or cured meats (including sausages and salamis), fava or broad bean pods, tap/draft beers, Marmite concentrate, sauerkraut, soy sauce and other soybean condiments.

StorageProtect from light.

ContraindicationsHypersensitivity to procarbazine or any component of the formulation; pre-existing bone marrow aplasia; ethanol ingestion; pregnancy

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: May occur 2-8 weeks after treatment initiation; allow ≥1 month interval between radiation therapy or myelosuppressive chemotherapy and initiation of treatment. Withhold treatment for leukopenia (WBC <4000/mm^3) or thrombocytopenia (platelets <100,000/mm^3).
- CNS toxicity: Withhold treatment for CNS toxicity.
- Diarrhea: Withhold treatment for diarrhea.
- Disulfiram-like reaction: Avoid ethanol consumption, may cause disulfiram-like reaction.
- Hemolysis: May cause hemolysis and/or presence of Heinz inclusion bodies in erythrocytes.
- Hemorrhage: Withhold treatment for hemorrhage.
- Hypersensitivity: Withhold treatment for hypersensitivity.
- Infertility: May cause infertility.
- Secondary malignancies: Possibly carcinogenic; acute leukemia and lung cancer have been reported following use.
- Stomatitis: Withhold treatment for stomatitis.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**
- MAO inhibitor activity: Possesses MAO inhibitor activity and has potential for severe drug and food interactions; follow MAO-I diet.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenic effects. There are no adequate and well-controlled studies in pregnant women. There are, however, case reports of fetal malformations in the offspring of pregnant women exposed to procarbazine as part of a combination chemotherapy regimen. Women of childbearing potential should avoid becoming pregnant during treatment.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsMost frequencies not defined.

Cardiovascular: Edema, flushing, hypotension, syncope, tachycardia

Central nervous system: Apprehension, ataxia, chills, coma, confusion, depression, dizziness, drowsiness, fatigue, fever, hallucination, headache, insomnia, lethargy, nervousness, nightmares, pain, seizure, slurred speech

Dermatologic: Alopecia, dermatitis, hyperpigmentation, petechiae, pruritus, purpura, rash, urticaria

Endocrine & metabolic: Gynecomastia (in prepubertal and early pubertal males)

Hematologic: Eosinophilia; hemolysis (in patients with G6PD deficiency); hemolytic anemia; myelosuppression (leukopenia, anemia, thrombocytopenia); pancytopenia

Gastrointestinal: Abdominal pain, anorexia, constipation, diarrhea, dysphagia, hematemesis, melena; nausea and vomiting ([60% to 90%], increasing the dose in a stepwise fashion over several days may minimize); stomatitis, xerostomia

Genitourinary: Azoospermia (reported with combination chemotherapy), hematuria, nocturia, polyuria, reproductive dysfunction (>10%)

Hepatic: Hepatic dysfunction, jaundice

Neuromuscular & skeletal: Arthralgia, falling, foot drop, myalgia, neuropathy, paresthesia, reflex diminished, tremor, unsteadiness, weakness

Ocular: Diplopia, inability to focus, nystagmus, papilledema, photophobia, retinal hemorrhage

Otic: Hearing loss

Respiratory: Cough, epistaxis, hemoptysis, hoarseness, pleural effusion, pneumonitis, pulmonary toxicity (<1%)

Miscellaneous: Allergic reaction, diaphoresis, herpes, infection, secondary malignancies (2% to 15%; reported with combination therapy)

Oncology: Emetic PotentialModerately high (60% to 90%)

Drug Interactions

Alpha-/Beta-Agonists (Direct-Acting): MAO Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists (Indirect-Acting): MAO Inhibitors may enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Alpha1-Agonists: MAO Inhibitors may enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Alpha2-Agonists (Ophthalmic): MAO Inhibitors may enhance the hypertensive effect of Alpha2-Agonists (Ophthalmic). *Risk X: Avoid combination*

Altretamine: May enhance the orthostatic effect of MAO Inhibitors. *Risk C: Monitor therapy*

Amphetamines: MAO Inhibitors may enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Anilidopiperidine Opioids: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. *Risk D: Consider therapy modification*

Atomoxetine: MAO Inhibitors may enhance the neurotoxic (central) effect of Atomoxetine. *Risk X: Avoid combination*

Beta2-Agonists: MAO Inhibitors may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: MAO Inhibitors may enhance the neurotoxic (central) effect of BuPROPion. *Risk X: Avoid combination*

BusPIRone: May enhance the adverse/toxic effect of MAO Inhibitors. Elevated blood pressure has been reported. *Risk X: Avoid combination*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

COMT Inhibitors: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Cyclobenzaprine: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

Dexmethylphenidate: MAO Inhibitors may enhance the hypertensive effect of Dexmethylphenidate. *Risk X: Avoid combination*

Dextromethorphan: MAO Inhibitors may enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Levodopa: May enhance the adverse/toxic effect of MAO Inhibitors. Of particular concern is the development of hypertensive reactions when levodopa is used with nonselective MAOI. *Risk D: Consider therapy modification*

Linezolid: MAO Inhibitors may enhance the adverse/toxic effect of Linezolid. *Risk X: Avoid combination*

Lithium: MAO Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Maprotiline: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

Meperidine: MAO Inhibitors may enhance the serotonergic effect of Meperidine. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methyldopa: MAO Inhibitors may enhance the adverse/toxic effect of Methyldopa. *Risk X: Avoid combination*

Methylphenidate: MAO Inhibitors may enhance the hypertensive effect of Methylphenidate. *Risk X: Avoid combination*

Mirtazapine: MAO Inhibitors may enhance the neurotoxic (central) effect of Mirtazapine. *Risk X: Avoid combination*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Propoxyphene: May enhance the adverse/toxic effect of MAO Inhibitors. Specifically, the risk of serotonin syndrome or other serotonergic adverse events may be increased. *Risk X: Avoid combination*

Rauwolfia Alkaloids: MAO Inhibitors may enhance the adverse/toxic effect of Rauwolfia Alkaloids. Existing MAOI therapy can result in paradoxical effects of added rauwolfia alkaloids (eg, excitation, hypertension). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: MAO Inhibitors may decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. **Exceptions:** Eletriptan; Frovatriptan; Naratriptan. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tetrabenazine: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

TraMADol: May enhance the neuroexcitatory and/or seizure-potentiating effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Tricyclic Antidepressants: MAO Inhibitors may enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: May enhance the adverse/toxic effects of procarbazine; concurrent use not recommended.

Food: Concurrent ingestion of foods rich in tyramine may cause sudden and severe high blood pressure (hypertensive crisis). Avoid tyramine-containing foods with MAO-Is. Food's freshness is also an important concern; improperly stored or spoiled food can create an environment where tyramine concentrations may increase.

Herb/Nutraceuticals: Avoid supplements containing caffeine, tyrosine, tryptophan, or phenylalanine. Ingestion of large quantities may increase the risk of severe side effects (eg, hypertensive reactions, serotonin syndrome).

Monitoring ParametersCBC with differential, platelet and reticulocyte count, urinalysis, liver function test, renal function test.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking (eg, CNS depressants increase risk of adverse reactions). Emetic potential is high; antiemetic is generally required. Assess results of laboratory tests and patient response frequently (eg, neurotoxicity, nausea and vomiting, pneumonitis, arthralgia, paresthesia). Instruct patient about dietary and alcohol cautions (procarbazine has some MAO inhibitory effects, can result in life-threatening hypertension with tyramine [see Tyramine Content of Foods]; alcohol may cause disulfiram like reaction). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, platelet and reticulocyte count, urinalysis, liver and renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed. Avoid alcohol; may cause acute disulfiram reaction (headache, respiratory difficulties, nausea, vomiting, sweating, thirst, hypotension, and flushing). Avoid tobacco. Avoid tyramine-containing foods; could cause serious hypertensive effects. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will be more sensitive to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause considerable nausea or vomiting (consult prescriber for approved antiemetic); mental depression, nervousness, insomnia, nightmares, dizziness, confusion, or lethargy (use caution when driving or engaging in tasks that require alertness until response to drug is known); rash, hair loss, or hyperpigmentation (reversible), loss of libido, sterility, or amenorrhea. Report persistent fever, chills, sore throat; unusual bleeding; blood in urine, stool (black stool), or vomitus; unresolved depression; mania; hallucinations; nightmares; disorientation; seizures; chest pain or palpitations; respiratory difficulty; or vision changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Male: Do not cause a female to become pregnant. Male/female: Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride:

Matulane®: 50 mg

Generic AvailableNo

Mechanism of ActionMechanism of action is not clear, methylating of nucleic acids; inhibits DNA, RNA, and protein synthesis; may damage DNA directly and suppresses mitosis; metabolic activation required by host

Pharmacodynamics/Kinetics

Absorption: Rapid and complete

Distribution: Crosses blood-brain barrier; equilibrates between plasma and CSF

Metabolism: Hepatic and renal

Half-life elimination: 1 hour

Time to peak, plasma: 1 hour

Excretion: Urine and respiratory tract (<5% as unchanged drug, 70% as metabolites)

Related Information

- Safe Handling of Hazardous Drugs
- Tyramine Content of Foods

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), stomatitis, and dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness, nervousness, insomnia, confusion, mania, depression, and hallucinations are common

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine; procarbazine possesses MAO inhibitor activity; avoid with antidepressants, narcotics, phenothiazines, and foods containing tyramine

Index TermsBenzmethyzin; N-Methylhydrazine; NSC-77213; Procarbazine Hydrochloride

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International Brand NamesIndicarb (IN); Matulane (PH); Natulan (AE, AR, AT, AU, BE, BG, BH, CH, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GH, GR, HN, HR, HU, IE, IL, IQ, IR, IT, JO, KW, LB, LU, LY, MY, NL, NO, OM, PK, PL, PT, QA, RU, SA, SE, SY, TR, TZ, UG, YE, ZM); Natulanar (BR)

Prochlorperazine

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Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

Gill SS, Bronskill SE, Normand SL, et al, “Antipsychotic Drug Use and Mortality in Older Adults With Dementia,” *Ann Intern Med*, 2007, 146(11):775-86.[PubMed 17548409]

Schneeweiss S, Setoguchi S, Brookhart A, et al, “Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients,” *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Medication Safety Issues

Sound-alike/look-alike issues:

Prochlorperazine may be confused with chlorproMAZINE

Compazine® may be confused with Copaxone®, Coumadin®

CPZ (occasional abbreviation for Compazine®) is an error-prone abbreviation (mistaken as chlorpromazine)

Pronunciation(proe klor PER a zeen)
U.S. Brand Names Compro™
Canadian Brand Names Apo-Prochlorperazine®; Nu-Prochlor; Stemetil®
Pharmacologic Category Antiemetic; Antipsychotic Agent, Typical, Phenothiazine
Use: Labeled Indications Management of nausea and vomiting; psychotic disorders including schizophrenia; anxiety
Use: Unlabeled/Investigational Behavioral syndromes in dementia; psychosis/agitation related to Alzheimer's dementia
Dosing: Adults

Antiemetic:

Oral (tablet): 5-10 mg 3-4 times/day; usual maximum: 40 mg/day; larger doses may rarely be required

I.M. (deep): 5-10 mg every 3-4 hours; usual maximum: 40 mg/day

I.V.: 2.5-10 mg; maximum 10 mg/dose or 40 mg/day; may repeat dose every 3-4 hours as needed

Rectal: 25 mg twice daily

Surgical nausea/vomiting:Note: Should not exceed 40 mg/day

I.M.: 5-10 mg 1-2 hours before induction or to control symptoms during or after surgery; may repeat once if necessary

I.V. (administer slow IVP <5 mg/minute): 5-10 mg 15-30 minutes before induction or to control symptoms during or after surgery; may repeat once if necessary

Rectal (unlabeled use): 25 mg

Antipsychotic:

Oral: 5-10 mg 3-4 times/day; titrate dose slowly every 2-3 days; doses up to 150 mg/day may be required in some patients for treatment of severe disturbances

I.M.: Initial: 10-20 mg; if necessary repeat initial dose every 1-4 hours to gain control; more than 3-4 doses are rarely needed. If parenteral administration is still required; give 10-20 mg every 4-6 hours; change to oral as soon as possible.

Nonpsychotic anxiety: *Oral (tablet):* Usual dose: 15-20 mg/day in divided doses; do not give doses >20 mg/day or for longer than 12 weeks

Dosing: ElderlyDementia behavior (nonpsychotic, unlabeled use): Initial: 2.5-5 mg 1-2 times/day; increase dose at 4- to 7-day intervals by 2.5-5 mg/day. Increase dosing intervals (twice daily, 3 times/day, etc) as necessary to control response or side effects. Maximum daily dose should probably not exceed 75 mg in the elderly. Gradual increases (titration) may prevent some side effects or decrease their severity. See Geriatric Considerations.

Dosing: PediatricNot recommended in children <10 kg or <2 years.

Antiemetic:

Oral, rectal: >9 kg: 0.4 mg/kg/24 hours in 3-4 divided doses; **or**

9-13 kg: 2.5 mg every 12-24 hours as needed; maximum: 7.5 mg/day

13.1-17 kg: 2.5 mg every 8-12 hours as needed; maximum: 10 mg/day

17.1-37 kg: 2.5 mg every 8 hours or 5 mg every 12 hours as needed; maximum: 15 mg/day

I.M.: 0.13 mg/kg/dose; change to oral as soon as possible

Antipsychotic: Children 2-12 years (not recommended in children <9 kg or <2 years):

Oral, rectal: 2.5 mg 2-3 times/day; do not give more than 10 mg the first day; increase dosage as needed to maximum daily dose of 20 mg for 2-5 years and 25 mg for 6-12 years

I.M.: 0.13 mg/kg/dose; change to oral as soon as possible

Administration: I.M.Inject by deep IM into outer quadrant of buttocks.

Administration: I.V.Doses should be given as a short (~30 minute) infusion to avoid orthostatic hypotension; administer at ≤5 mg/minute

Administration: I.V. DetailDo not dilute with any diluent containing parabens as a preservative. Avoid skin contact with injection solution, contact dermatitis has occurred. I.V. may be administered IVP or IVPB.

pH: 4.2-6.2

Dietary ConsiderationsIncrease dietary intake of riboflavin; should be administered with food or water. Rectal suppositories may contain coconut and palm oil.

Storage

Injection: Store at <30°C (<86°F); do not freeze. Protect from light. Clear or slightly yellow solutions may be used.

I.V. infusion: Injection may be diluted in 50-100 mL NS or D_5W.

Suppository, tablet: Store at 15°C to 30°C (59°F to 86°F). Protect from light.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5W, $D_{10}W$, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, LR, ${}^1/_2NS$, NS.

Y-site administration: Compatible: Amsacrine, calcium gluconate, cisatracurium, cisplatin, cladribine, clarithromycin, cyclophosphamide, cytarabine, docetaxel, doxorubicin, doxorubicin liposome, fluconazole, gatifloxacin, granisetron, heparin, hydrocortisone sodium succinate, linezolid, melphalan, methotrexate, ondansetron, paclitaxel, potassium chloride, propofol, remifentanil, sargramostim, sufentanil, teniposide, thiotepa, topotecan, vinorelbine, vitamin B complex with C. **Incompatible:** Aldesleukin, allopurinol, amifostine, amphotericin B cholesteryl sulfate complex, aztreonam, cefepime, etoposide phosphate, fludarabine, foscarnet, filgrastim, gemcitabine, piperacillin/tazobactam.

Compatibility in syringe: Compatible: Atropine, butorphanol, chlorpromazine, cimetidine, diamorphine, diphenhydramine, droperidol, fentanyl, glycopyrrolate, hydroxyzine, meperidine, metoclopramide, nalbuphine, pentazocine, perphenazine, promazine, promethazine, ranitidine, scopolamine, sufentanil. **Incompatible:** Dimenhydrinate, ketorolac, midazolam, morphine tartrate, pentobarbital, thiopental. **Variable (consult detailed reference):** Hydromorphone, morphine sulfate.

Compatibility when admixed: Compatible: Amikacin, ascorbic acid injection, cephalothin, dexamethasone sodium phosphate, dimenhydrinate, erythromycin lactobionate, ethacrynate, lidocaine, nafcillin, sodium bicarbonate, vitamin B complex with C. **Incompatible:** Aminophylline, amphotericin B, ampicillin, chloramphenicol, chlorothiazide, floxacillin, furosemide, heparin, hydrocortisone sodium succinate, methohexital, penicillin G sodium, phenobarbital, phenytoin, thiopental. **Variable (consult detailed reference):** Calcium gluconate, penicillin G potassium.

ContraindicationsHypersensitivity to prochlorperazine or any component of the formulation (cross-reactivity between phenothiazines may occur); severe CNS depression; coma; pediatric surgery; Reye’s syndrome; should not be used in children <2 years of age or <9 kg

Allergy Considerations

- Phenothiazine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines).
- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems.
- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).
- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia. Risk of dystonia (and possibly other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.
- Hypotension: May occur following administration, particularly when parenteral form is used or in high dosages.
- Neuroleptic malignant syndrome (NMS): May be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).
- Pigmentary retinopathy: May be associated with pigmentary retinopathy.
- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with bone marrow suppression; blood dyscrasias have occurred. Use only if benefits outweigh risk.
- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.
- Dementia: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo. An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Prochlorperazine is not approved for this indication.
- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.
- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.
- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.
- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.
- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for developing tardive dyskinesia.
- Pediatrics: Children with acute illness or dehydration are more susceptible to neuromuscular reactions (eg, dystonias); use cautiously.

Geriatric ConsiderationsDue to side effect profile (dystonias, EPS) this is not a preferred drug in the elderly for antiemetic therapy.

Many elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior. Before initiating antipsychotic medication, the clinician should investigate any possible reversible cause; any stress or stress from any disease can cause acute “confusion” or worsening of baseline nonpsychotic behavior. Most commonly acute changes in behavior are due to increases in drug dose or addition of new drug to regimen, fluid electrolyte loss, infections, and changes in environment.

Any changes in disease status in any organ system can result in behavior changes.

In the treatment of agitated, demented, older adult patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control.

Pregnancy ConsiderationsCrosses the placenta. Isolated reports of congenital anomalies, however, some included exposures to other drugs. Jaundice, extrapyramidal signs, hyper-/hyporeflexes have been noted in newborns. Available evidence with use of occasional low doses suggests safe use during pregnancy.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsOther phenothiazines are excreted in human milk; excretion of prochlorperazine is not known.

Adverse ReactionsReported with prochlorperazine or other phenothiazines. Frequency not defined.

Cardiovascular: Cardiac arrest, hypotension, peripheral edema, Q-wave distortions, T-wave distortions

Central nervous system: Agitation, catatonia, cerebral edema, cough reflex suppressed, dizziness, drowsiness, fever (mild - I.M.), headache, hyperactivity, hyperpyrexia, impairment of temperature regulation, insomnia, neuroleptic malignant syndrome (NMS), paradoxical excitement, restlessness, seizure

Dermatologic: Angioedema, contact dermatitis, discoloration of skin (blue-gray), epithelial keratopathy, erythema, eczema, exfoliative dermatitis (injectable), itching, photosensitivity, rash, skin pigmentation, urticaria

Endocrine & metabolic: Amenorrhea, breast enlargement, galactorrhea, gynecomastia, glucosuria, hyperglycemia, hypoglycemia, lactation, libido (changes in), menstrual irregularity, SIADH

Gastrointestinal: Appetite increased, atonic colon, constipation, ileus, nausea, weight gain, xerostomia

Genitourinary: Ejaculating dysfunction, ejaculatory disturbances, impotence, incontinence, polyuria, priapism, urinary retention, urination difficulty

Hematologic: Agranulocytosis, aplastic anemia, eosinophilia, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenic purpura

Hepatic: Biliary stasis, cholestatic jaundice, hepatotoxicity

Neuromuscular & skeletal: Dystonias (torticollis, opisthotonos, carpopedal spasm, trismus, oculogyric crisis, protusion of tongue); extrapyramidal symptoms (pseudoparkinsonism, akathisia, dystonias, tardive dyskinesia); SLE-like syndrome, tremor

Ocular: blurred vision, cornea and lens changes, lenticular/corneal deposits, miosis, mydriasis, pigmentary retinopathy

Respiratory: Asthma, laryngeal edema, nasal congestion

Miscellaneous: Allergic reactions, diaphoresis

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Analgesics (Opioid): Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antimalarial Agents: May increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Beta-Blockers: Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Limit caffeine.

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization). Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Test InteractionsFalse-positives for phenylketonuria, pregnancy, urinary amylase, uroporphyrins, urobilinogen

Monitoring ParametersVital signs; lipid profile, fasting blood glucose/Hgb A_{1c}; BMI; mental status, abnormal involuntary movement scale (AIMS); periodic ophthalmic exams (if chronically used); extrapyramidal symptoms (EPS)

Nursing: Physical Assessment/MonitoringAssess all other medications patient may be taking. For I.V., continuously monitor blood pressure and heart rate during administration. Monitor blood pressure and heart rate, fluid balance, and dehydration. Monitor for seizures, especially with known seizure disorder. Monitor for excessive sedation, neuromuscular malignant syndrome, autonomic instability (eg, anticholinergic effects), and extrapyramidal symptoms.

Monitoring: Lab TestsBaseline liver and kidney function, CBC prior to and periodically during therapy, lipid profile, fasting blood glucose/Hgb A_{1c}; BMI

Patient EducationTake exact amount as prescribed. Do not change brand names. Do not crush or chew tablets. Do not discontinue without consulting prescriber. Avoid alcohol or other sedatives or sleep-inducing drugs. Avoid skin contact with drug; wash immediately with warm soapy water. You may experience appetite changes; small frequent meals may help. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause dizziness, tremors, or visual disturbance (especially during early therapy); use caution when driving or engaging in tasks that require alertness until response to drug is known. Do not change position rapidly (rise slowly). May cause photosensitivity reaction; use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight. Report immediately any changes in gait or muscular tremors. Report unresolved changes in voiding or elimination (constipation or diarrhea), acute dizziness or unresolved sedation, vision changes, palpitations, yellowing of skin or eyes, or changes in color of urine or stool (pink or red brown urine is expected).
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as edisylate: 5 mg/mL (2 mL, 10 mL) [contains benzyl alcohol]

Suppository, rectal: 25 mg (12s) [may contain coconut and palm oil]

Compro™: 25 mg (12s) [contains coconut and palm oils]

Tablet, as maleate: 5 mg, 10 mg [strength expressed as base]

Generic AvailableYes: Injection, tablet, suppository

Pricing: U.S. (www.drugstore.com)

Suppository (Compro)

25 mg (12): $33.99

Tablets (Prochlorperazine Maleate)

5 mg (30): $12.99

10 mg (30): $13.99

Mechanism of ActionProchlorperazine is a piperazine phenothiazine antipsychotic which blocks postsynaptic mesolimbic dopaminergic D_1 and D_2 receptors in the brain, including the chemoreceptor trigger zone; exhibits a strong alpha-adrenergic and anticholinergic blocking effect and depresses the release of hypothalamic and hypophyseal hormones; believed to depress the reticular activating system, thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone and emesis

Pharmacodynamics/Kinetics

Onset of action: Oral: 30-40 minutes; I.M.: 10-20 minutes; Rectal: ~60 minutes

Peak antiemetic effect: I.V.: 30-60 minutes

Duration: Rectal: 12 hours; Oral: 3-4 hours; I.M., I.V.: Adults: 4-6 hours; I.M.: Children: 12 hours

Distribution: V_d: 1400-1548 L; crosses placenta; enters breast milk

Metabolism: Primarily hepatic; N-desmethyl prochlorperazine (major active metabolite)

Bioavailability: Oral: 12.5%

Half-life elimination: Oral: 3-5 hours; I.V.: ~7 hours

Related Information

- CMS: Long-Term Care Facility Thresholds

Pharmacotherapy PearlsNot recommended as an antipsychotic due to inferior efficacy compared to other phenothiazines.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation). Significant hypotension may occur, especially when the drug is administered parenterally; orthostatic hypotension is due to alpha-receptor blockade, the elderly are at greater risk for orthostatic hypotension.

Tardive dyskinesia: Prevalence rate may be 40% in elderly; development of the syndrome and the irreversible nature are proportional to duration and total cumulative dose over time. Extrapyramidal reactions are more common in elderly with up to 50% developing these reactions after 60 years of age. Drug-induced Parkinson's syndrome occurs often; akathisia is the most common extrapyramidal reaction in elderly.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsMost pharmacology textbooks state that in presence of phenothiazines, systemic doses of epinephrine paradoxically decrease the blood pressure. This is the so called “epinephrine reversal” phenomenon. This has never been observed when epinephrine is given by infiltration as part of the anesthesia procedure.

Mental Health CommentWhile structurally a phenothiazine, this agent has limited antipsychotic activity and should not be used as such.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Anesthesia and Critical Care Concerns/Other ConsiderationsProchlorperazine has a faster onset of action and causes less sedation than promethazine. When compared with ondansetron (4 mg I.V.), prochlorperazine (10 mg I.M.) administered at the end of surgery more effectively reduced postoperative nausea and the need for rescue antiemetics in patients undergoing total hip or knee replacement. In patients undergoing tympanoplasty, prophylactic prochlorperazine (0.02 mg/kg I.M.) administered at the end of surgery was as effective as ondansetron (0.06 mg/kg I.V.) for reducing PONV.

Index TermsChlormeprazine; Compazine; Prochlorperazine Edisylate; Prochlorperazine Maleate

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International Brand NamesAntinaus (NZ); Buccastem 3 (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Chloropernazinum (PL); Dhaperazine (HK, MY); Nautisol (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Prochlor (MY); Proclozine (TH); Seratil (HK); Stemetil (AE, AU, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, DK, EG, ET, FI, GB, GH, GM, GN, GY, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, NO, OM, PK, QA, SA, SC, SD, SE, SG, SL, SN, SR, SY, TH, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Stemzine (AU)

Medication Safety Issues

Sound-alike/look-alike issues:

Kemadrin® may be confused with Coumadin®

Pronunciation(proe SYE kli deen)
U.S. Brand NamesKemadrin® [DSC]
Canadian Brand NamesPMS-Procyclidine
Pharmacologic CategoryAnti-Parkinson's Agent, Anticholinergic; Anticholinergic Agent
Use: Labeled IndicationsRelieves symptoms of parkinsonian syndrome and drug-induced extrapyramidal symptoms
Dosing: Adults**Parkinson's disease or treatment of EPS:** Oral: 2.5 mg 3 times/day after meals; if tolerated, gradually increase dose, to a maximum of 20 mg/day if necessary.
Dosing: ElderlyOral: Initial: 2.5 mg once or twice daily, gradually increasing as necessary. Avoid use if possible (see Geriatric Considerations).
Dosing: Hepatic ImpairmentDecrease dose to a twice daily dosing regimen.
Administration: OralShould be administered after meals to minimize stomach upset.
Dietary ConsiderationsShould be taken after meals to minimize stomach upset.
ContraindicationsHypersensitivity to procyclidine or any component of the formulation; angle-closure glaucoma; myasthenia gravis; safe use in children not established
Warnings/Precautions

Concerns related to adverse effects:

- Anhidrosis/hyperthermia: May cause anhidrosis and hyperthermia, which may be severe; use with caution in hot weather or during exercise. The risk is increased in hot environments, particularly in the elderly, alcoholics, patients with CNS disease, and those with prolonged outdoor exposure.

- CNS effects: May be associated with confusion or hallucinations (generally at higher dosages); intensification of symptoms or toxic psychosis may occur in patients with mental disorders. May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Weakness: When given in large doses or to susceptible patients, may cause weakness and inability to move particular muscle groups.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with tachycardia, cardiac arrhythmias, hypertension, or hypotension.

- GI obstruction: Use with caution in patients with obstructive disease of the GI.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture or retention.

- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Elderly: Frequently develop increased sensitivity and require strict dosage regulation - side effects may be more severe in elderly patients with atherosclerotic changes.

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsAnticholinergic agents are generally not well tolerated in the elderly and their use should be avoided when possible. In the elderly, anticholinergic agents should not be used as prophylaxis against extrapyramidal symptoms. Elderly patients frequently develop increased sensitivity and require strict dosage regulation - side effects may be more severe in elderly patients with atherosclerotic changes.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation, tachycardia

Central nervous system: Ataxia, confusion, drowsiness, fatigue, giddiness, headache, lightheadedness, loss of memory

Dermatologic: Dry skin, photosensitivity, rash

Gastrointestinal: Constipation, dry throat, epigastric distress, nausea, vomiting, xerostomia

Genitourinary: Difficult urination

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision, increased intraocular pain, mydriasis

Respiratory: Dry nose

Miscellaneous: Diaphoresis decreased

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol.

Monitoring ParametersSymptoms of EPS or Parkinson's disease, pulse, anticholinergic effects (ie, CNS, bowel and bladder function)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness, renal function, and adverse reactions (eg, anticholinergic syndrome) at beginning of therapy and periodically throughout therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed (after meals); do not increase, decrease, or discontinue without consulting prescriber. Take at the same time each day. Do not use alcohol, prescription or OTC sedatives, or CNS depressants without consulting prescriber. You may experience drowsiness, dizziness, confusion, and blurred vision (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); increased susceptibility to heat stroke, decreased perspiration (use caution in hot weather, maintain adequate fluids and reduce exercise activity); constipation (increased exercise, fluids, fruit, or fiber may help); or dry skin or nasal passages (consult prescriber for appropriate relief). Report unresolved constipation, chest pain or palpitations, respiratory difficulty, CNS changes (hallucination, loss of memory, nervousness, etc), painful or difficult urination, increased muscle spasticity or rigidity, skin rash, or significant worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, as hydrochloride:

Kemadrin®: 5 mg [scored] [DSC]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Kemadrin)

5 mg (90): $86.10

Mechanism of ActionThought to act by blocking excess acetylcholine at cerebral synapses; many of its effects are due to its pharmacologic similarities with atropine; it exerts an antispasmodic effect on smooth muscle, is a potent mydriatic; inhibits salivation

Pharmacodynamics/Kinetics

Onset of action: 30-40 minutes

Duration: 4-6 hours

Related Information

- Antiparkinsonian Agents
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and dry throat and nose. Prolonged use of antidyskinetics may decrease or inhibit salivary flow, contributing to discomfort and dental disease (ie, caries, oral candidiasis, and periodontal disease).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index TermsProcyclidine Hydrochloride

References

Feinberg M, “The Problems of Anticholinergic Adverse Effects in Older Patients,” *Drugs Aging*, 1993, 3(4):335-48.[PubMed 8369593]

International Brand NamesEmadrin (PK); Kemadrin (AE, AT, AU, BB, BE, BG, BH, BM, BS, BZ, CH, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, GY, HN, HU, IE, IL, IN, IQ, IR, IT, JM, JO, KW, LB, LU, LY, NL, NO, NZ, OM, PT, QA, RU, SA, SE, SR, SY, TR, TT, UY, YE); Osnervan (DE)

Progesterone

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English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(proe JES ter one)

U.S. Brand NamesCrinone®; Endometrin®; First™-Progesterone VGS; Prochieve®; Prometrium®

Canadian Brand NamesCrinone®; Prometrium®

Pharmacologic CategoryProgestin

Use: Labeled Indications

Oral: Prevention of endometrial hyperplasia in nonhysterectomized, postmenopausal women who are receiving conjugated estrogen tablets; secondary amenorrhea

I.M.: Amenorrhea; abnormal uterine bleeding due to hormonal imbalance

Intravaginal gel: Part of assisted reproductive technology (ART) for infertile women with progesterone deficiency; secondary amenorrhea

Vaginal tablet: Part of ART for infertile women with progesterone deficiency

Dosing: AdultsFemales:

Amenorrhea: I.M.: 5-10 mg/day for 6-8 consecutive days

Amenorrhea, secondary:

Intravaginal gel: 45 mg (4% gel) every other day for 6 doses; if response is inadequate, may increase to 90 mg (8% gel) at same schedule

Oral: 400 mg every evening for 10 days

ART in patients who require progesterone supplementation:

Intravaginal gel: 90 mg (8% gel) once daily. If pregnancy occurs, may continue treatment for 10-12 weeks.

Intravaginal tablet: 100 mg 2-3 times daily starting at oocyte retrieval and continuing for up to 10 weeks.

ART in patients with partial or complete ovarian failure:

Intravaginal gel: 90 mg (8% gel) twice daily. If pregnancy occurs, continue treatment for 10-12 weeks.

Endometrial hyperplasia prevention (in postmenopausal women with a uterus who are receiving daily conjugated estrogen tablets): Oral: 200 mg as a single daily dose every evening for 12 days sequentially per 28-day cycle

Functional uterine bleeding: I.M.: 5-10 mg/day for 6 doses

Dosing: ElderlyRefer to adult dosing.

Administration: I.M.Administer deep I.M. only

Administration: Other

Vaginal gel: (A small amount of gel will remain in the applicator following insertion): Administer into the vagina directly from sealed applicator. Remove applicator from wrapper; holding applicator by thickest end, shake down to move contents to thin end; while holding applicator by flat section of thick end, twist off tab; gently insert into vagina and squeeze thick end of applicator.

For use at altitudes above 2500 feet: Remove applicator from wrapper; hold applicator on both sides of bubble in the thick end; using a lancet, make a single puncture in the bubble to relieve air pressure; holding applicator by thickest end, shake down to move contents to thin end; while holding applicator by flat section of thick end, twist off tab; gently insert into vagina and squeeze thick end of applicator.

Vaginal tablet: Insert tablet in vagina using disposable applicator provided.

StorageStore at controlled room temperature.

ContraindicationsHypersensitivity to progesterone or any component of the formulation; undiagnosed abnormal vaginal bleeding; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); known or suspected carcinoma of the breast or genital organs; hepatic dysfunction or disease; missed abortion or ectopic pregnancy; diagnostic test for pregnancy; capsules are also contraindicated for use during pregnancy

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.

- Dementia: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Breast cancer: An increased risk of invasive breast cancer was observed in postmenopausal women using conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA). An increase in abnormal mammograms has also been reported with estrogen and progestin therapy.

- CNS effects: Patients should be warned that progesterone might cause transient dizziness or drowsiness during initial therapy.

- Dementia: **[U.S. Boxed Warning]: The risk of dementia may be increased in postmenopausal women;** increased incidence was observed in women ≥65 years of age taking CEE alone or in combination with MPA.

- Retinal vascular thrombosis: Discontinue pending examination in cases of sudden partial or complete vision loss, sudden onset of proptosis, diplopia, or migraine; discontinue permanently if papilledema or retinal vascular lesions are observed on examination.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Progestins used in combination with estrogen should not be used to prevent coronary heart disease.** Use caution with cardiovascular disease or dysfunction. Progestins used in combination with estrogen may increase the risks of hypertension, myocardial infarction (MI), stroke, pulmonary emboli (PE), and deep vein thrombosis; incidence of these effects was shown to be significantly increased in postmenopausal women using CEE in combination with MPA. Similar risk should be assumed with other progestins.

- Depression: Use with caution in patients with a history of depression.

- Diseases exacerbated by fluid retention: Use with caution in patients with diseases which may be exacerbated by fluid retention, including asthma, epilepsy, migraine, diabetes, or renal dysfunction.

Special populations:

- Pediatrics: Not for use prior to menarche.

- Surgical patients: Whenever possible, progestins in combination with estrogens should be discontinued at least 4 weeks prior to and for 2 weeks following elective surgery associated with an increased risk of thromboembolism or during periods of prolonged immobilization.

Dosage form specific issues:

- Benzyl alcohol: Some products may contain benzyl alcohol.

- Palm oil: Some products may contain palm oil.

- Peanut oil: Some products may contain peanut oil.

- Sesame oil: Some products may contain sesame oil.

Other warnings/precautions:

- Risks vs. benefits: Before prescribing progestin therapy in combination with estrogen to postmenopausal women, the risks and benefits must be weighed for each patient. Women should be informed of these risks and benefits, as well as possible effects of estrogen when added to progestin therapy. Progestins with or without estrogen should be used for shortest duration possible consistent with treatment goals. Conduct periodic risk:benefit assessments.

Geriatric ConsiderationsNot a progestin of choice in the elderly for hormonal cycling.

Pregnancy Risk FactorB (Prometrium®, per manufacturer); none established for vaginal gel, vaginal tablet, or injection

Pregnancy ConsiderationsThere is an increased risk of minor birth defects in children whose mothers take progesterones during the first 4 months of pregnancy. Hypospadias has been reported in male and mild masculinization of the external genitalia has been reported in female babies exposed during the first trimester. Cleft lip, cleft palate, congenital heart disease, patent ductus arteriosus, ventricular septal defect, intrauterine death, and spontaneous abortion have been noted in case reports following use of oral progesterone during pregnancy. High doses of progesterone would be expected to impair fertility. According to the American College of Obstetricians and Gynecologists, additional studies are needed to evaluate the use of progesterone to reduce the risk of preterm birth. If needed, use should be restricted to women with history of previous spontaneous abortion at <37 weeks. The vaginal gel and tablet are indicated for use in ART. The oral capsules are contraindicated for use during pregnancy.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Adverse Reactions

Injection (I.M.):

Cardiovascular: Cerebral edema, cerebral thrombosis, edema

Central nervous system: Depression, fever, insomnia, somnolence

Dermatologic: Acne, allergic rash (rare), alopecia, hirsutism, pruritus, rash, urticaria

Endocrine & metabolic: Amenorrhea, breakthrough bleeding, breast tenderness, galactorrhea, menstrual flow changes, spotting

Gastrointestinal: Nausea, weight gain/loss

Genitourinary: Cervical erosion changes, cervical secretion changes

Hepatic: Cholestatic jaundice

Local: Injection site: Irritation, pain, redness

Ocular: Optic neuritis, retinal thrombosis

Respiratory: Pulmonary embolism

Miscellaneous: Anaphylactoid reactions

Oral capsule (percentages reported when used in combination with or cycled with conjugated estrogens):

>10%:

Central nervous system: Headache (10% to 31%), dizziness (15% to 24%), depression (19%)

Endocrine & metabolic: Breast tenderness (27%), breast pain (6% to 16%)

Gastrointestinal: Abdominal pain (6% to 12%), abdominal bloating (10% to 20%)

Genitourinary: Urinary problems (11%)

Neuromuscular & skeletal: Joint pain (20%), musculoskeletal pain (6% to 12%)

Miscellaneous: Viral infection (7% to 12%)

5% to 10%:

Cardiovascular: Chest pain (7%)

Central nervous system: Fatigue (8% to 9%), emotional lability (6%), irritability (5% to 8%), worry (8%)

Gastrointestinal: Nausea/vomiting (8%), diarrhea (8%)

Respiratory: Upper respiratory tract infection (5%), cough (8%)

Miscellaneous: Night sweats (7%)

<5%: Abscess, accidental injury, acne, angina pectoris, anxiety, arthritis, breast cancer, breast biopsy, bronchitis, cholecystectomy, concentration impaired, confusion, constipation, dyspepsia, earache, edema, fever, fungal vaginitis, gastroenteritis, hemorrhagic rectum, hernia, herpes simplex, hiatus, hypertension, hypertonia, insomnia, leg cramps, leukorrhea, lymphadenopathy, muscle disorder, myalgia, nasal congestion, palpitation, personality disorder, pharyngitis, pneumonitis, sinusitis, somnolence, speech disorder, urinary tract infection, uterine fibroid, vaginal dryness, vaginitis, verruca, vision abnormal, wound debridement, xerostomia

Postmarketing and/or case reports: Aggression, alopecia, ALT increased, anaphylactic reaction, arthralgia, AST increased, asthma, blurred vision, choking, cholestasis, cholestatic hepatitis, circulatory collapse, consciousness depressed/loss, convulsion, depersonalization, diplopia, disorientation, drunk feeling, dysarthria, dysphagia, dyspnea, endometrial carcinoma, facial edema, feeling abnormal, gait abnormal, GGT increased, hepatic enzymes increased, hepatic failure, hepatic necrosis, hepatitis, hyperglycemia, hypersensitivity, hypotension, jaundice, liver function tests increased, menorrhagia, menstrual disorder, metrorrhagia, muscle cramps, ovarian cyst, pancreatitis (acute), paresthesia, pruritus, sedation, stupor, suicidal ideation, syncope, tachycardia, throat tightness, TIA, tinnitus, tongue swelling, urticaria, vertigo, visual disturbance, walking difficulty, weight gain/loss

Vaginal gel (percentages reported with ART); also refer to oral capsule reactions listing for additional effects noted with progesterone:

>10%:

Central nervous system: Somnolence (27%), headache (13% to 17%), nervousness (16%), depression (11%)

Endocrine & metabolic: Breast enlargement (40%), breast pain (13%), libido decreased (11%)

Gastrointestinal: Constipation (27%), nausea (7% to 22%), cramps (15%), abdominal pain (12%)

Genitourinary: Perineal pain (17%), nocturia (13%)

5% to 10%:

Central nervous system: Pain (8%), dizziness (5%)

Gastrointestinal: Diarrhea (8%), bloating (7%), vomiting (5%)

Genitourinary: Vaginal discharge (7%), dyspareunia (6%), genital moniliasis (5%), genital pruritus (5%)

Neuromuscular & skeletal: Arthralgia (8%)

Vaginal tablet (percentages reported with ART); also refer to oral capsule reactions listing for additional effects noted with progesterone:

>10%:

Gastrointestinal: Abdominal pain (12%)

Miscellaneous: Post-oocyte retrieval pain (25% to 28%)

1% to 10%:

Central nervous system: Headache (3% to 4%), fatigue (2% to 3%)

Endocrine & metabolic: Ovarian hyperstimulation syndrome (7%)

Gastrointestinal: Nausea (7% to 8%), abdominal distension (4%), constipation (2% to 3%), vomiting (2% to 3%)

Genitourinary: Uterine spasm (3% to 4%), vaginal bleeding (3%), urinary tract infection (1% to 2%)

<1%: Burning, discomfort, itching, peripheral edema, urticaria, vaginal irritation

Metabolism/Transport Effects **Substrate** of CYP1A2 (minor), 2A6 (minor), 2C9 (minor), 2C19 (major), 2D6 (minor), 3A4 (major); **Inhibits** CYP2C9 (weak), 2C19 (weak), 3A4 (weak)

Drug Interactions

Aminoglutethimide: May increase the metabolism of Progestins. *Risk D: Consider therapy modification*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Progestogenic Properties) (eg, Bloodroot, Yucca): May enhance the adverse/toxic effect of Progestins. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Food increases oral bioavailability.

Herb/Nutraceutical: St John's wort may decrease progesterone levels. Herbs with progestogenic properties may enhance the adverse/toxic effects of progestin; example herbs include bloodroot, chasteberry, damiana, oregano, yucca.

Test Interactions Thyroid function, metyrapone, liver function, coagulation tests, endocrine function tests

Monitoring Parameters Routine physical examination that includes blood pressure and Papanicolaou smear, breast exam, mammogram. Adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding. Signs and symptoms of thromboembolic disorders, vision changes

Nursing: Physical Assessment/Monitoring Assess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic effectiveness and patient response (eg, blood pressure, mammogram, and results of Pap smears and pregnancy tests before beginning treatment and at least annually). Teach patient proper use according to formulation, possible side effects/appropriate interventions (eg, annual physicals, Pap smears, and vision assessment), and adverse symptoms to report.

Patient Education Do not take any new medication during therapy unless approved by prescriber. Use exactly as directed. It is important that you have an annual physical assessment, Pap smear, and vision assessment while taking this medication. May cause temporary dizziness or drowsiness (use caution when driving or engaging in tasks that are potentially hazardous until response to drug is known), headache, joint pain, nausea and/or vomiting, mood swings, or irritability. Report immediately muscle pain or soreness; warmth, swelling, or redness in calves; shortness of breath; chest pain; sudden loss or change in vision; change in menstrual pattern (unusual bleeding, amenorrhea, breakthrough spotting); breast tenderness that does not go away; acute abdominal pain or cramping; signs of vaginal infection (drainage, pain, itching); or CNS changes (eg, blurred vision, confusion, acute anxiety, or unresolved depression).

Vaginal gel: A small amount of gel will remain in the applicator following insertion. Administer into the vagina directly from sealed applicator. Remove applicator from wrapper; holding applicator by thickest end, shake down to move contents to thin end; while holding applicator by flat section of thick end, twist off tab; gently insert into vagina and squeeze thick end of applicator.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Prometrium®: 100 mg, 200 mg [contains peanut oil]

Gel, vaginal:

Crinone®: 8% (1.45 g) [90 mg/dose; contains palm oil; 6 or 18 prefilled applicators]

Prochieve®: 4% (1.45 g) [45 mg/dose; contains palm oil; 6 prefilled applicators]; 8% (1.45 g) [90 mg/dose; contains palm oil; 6 or 18 prefilled applicators]

Injection, oil: 50 mg/mL (10 mL) [contains benzyl alcohol 10%, sesame oil]

Powder, for prescription compounding [micronized]: Progesterone USP (10 g, 25 g, 100 g, 1000 g)

Powder, for prescription compounding [wettable]: Progesterone USP (10 g, 25 g, 100 g, 1000 g)

First™-Progesterone VGS 25: Progesterone USP (0.75 g) [makes 30 progesterone 25 mg vaginal suppositories; kit contains fatty acid base, suppository mold, stirrer, filling tool, guide plate, mold cover with dispensing tool]

First™-Progesterone VGS 50: Progesterone USP (1.5 g) [makes 30 progesterone 50 mg vaginal suppositories; kit contains fatty acid base, suppository mold, stirrer, filling tool, guide plate, mold cover with dispensing tool]

First™-Progesterone VGS 100: Progesterone USP (3 g) [makes 30 progesterone 100 mg vaginal suppositories; kit contains fatty acid base, suppository mold, stirrer, filling tool, guide plate, mold cover with dispensing tool]

First™-Progesterone VGS 200: Progesterone USP (6 g) [makes 30 progesterone 200 mg vaginal suppositories; kit contains fatty acid base, suppository mold, stirrer, filling tool, guide plate, mold cover with dispensing tool]

First™-Progesterone VGS 400: Progesterone USP (12 g) [makes 30 progesterone 400 mg vaginal suppositories; kit contains fatty acid base, suppository mold, stirrer, filling tool, guide plate, mold cover with dispensing tool]

Tablet, vaginal:

Endometrin®: 100 mg (21s) [packaged with applicators]

Generic AvailableYes: Injection, powder

Pricing: U.S. (www.drugstore.com)

Capsules (Prometrium)

100 mg (30): $52.91

200 mg (30): $92.87

Gel (Crinone)

8% (8.7): $79.94

Gel (Prochieve)

4% (26.1): $152.42

8% (26.1): $220.99

Oil (Progesterone)

50 mg/mL (10): $40.99

Mechanism of ActionNatural steroid hormone that induces secretory changes in the endometrium, promotes mammary gland development, relaxes uterine smooth muscle, blocks follicular maturation and ovulation, and maintains pregnancy. When used as part of an ART program in the luteal phase, progesterone supports embryo implantation.

Pharmacodynamics/Kinetics

Absorption: Vaginal gel: Prolonged

Absorption half-life: 25-50 hours

Protein binding: Albumin (50% to 54%) and cortisol-binding protein (43% to 48%)

Metabolism: Hepatic to metabolites

Half-life elimination: Vaginal gel: 5-20 minutes

Time to peak: Oral: Within 3 hours; I.M.: ~8 hours; Vaginal tablet: ~17-24 hours

Excretion: Urine, bile, feces

Related Information

- Depression

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Progestins may predispose the patient to gingival bleeding.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia or depression

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPregnenedione; Progestin

References

"American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk," *Pediatrics*, 2001, 108(3):776-89. [PubMed 11533352]

American College of Obstetricians and Gynecologists, "ACOG Committee Opinion. Use of Progesterone to Reduce Preterm Birth," *Obstet Gynecol*, 2003, 102(5 Pt 1):1115-6.[PubMed 14672496]

Doody K, Shamma N, Paulson R, et al. “Endometrin® for Luteal Phase Support in a Randomized, Controlled, Open-Label, Prospective IVF Clinical Trial Using a Combination of Menopur® and Bravelle®,” *Fertil Steril*, 2007, 87(4 Suppl 2):24 [abstract].[PubMed 17081533]

Ng EH, Chan CC, Tang OS, et al, “A Randomized Comparison of Side Effects and Patient Convenience Between Cyclogest® Suppositories and Endometrin® Tablets Used for Luteal Phase Support in IVF Treatment,” *Eur J Obstet Gynecol Reprod Biol*, 2007, 131(2):182-8.[PubMed 16920249]

International Brand NamesCrinone (AR, AU, BE, CH, DE, DK, ES, FI, GB, GR, HK, ID, IE, IL, IN, IT, KP, MY, NO, PH, SE, SG, TW, UY, VE); Cyclogest (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, MY, OM, QA, SA, SG, SY, YE, ZA); Endometrin (HK, IL); Estima Ge (FR); Gepromi (MX); Geslutin (CO, MX); Geslutin PNM (PE); Glanducorpin (HU); Gynprogest (PY); Luteina (PL); Lutogynestryl Fuerte (PE); Mafel (AR); Naturogest (IN); Progendo (CN); Progering (PE); Progest (IN); Progestan (NL); Progesteronum (PL); Progestine (NL); Progestogel (HK, LU); Utrogestan (AT, BE, BG, BR, CH, CZ, EC, ES, FR, GB, HN, HU, LU, MX, PT, UY)

Promethazine and Codeine

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English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(proe METH a zeen & KOE deen)

Pharmacologic CategoryAnalgesic, Opioid; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporary relief of coughs and upper respiratory symptoms associated with allergy or the common cold

Dosing: Adults **Upper respiratory symptoms:** Oral: 5 mL every 4-6 hours (maximum: 30 mL/24 hours)

Dosing: ElderlyRefer to dosing in individual monographs.

Dosing: Pediatric**Cough and upper respiratory symptoms:** Oral:

Children <2 years: Use of promethazine is contraindicated

Children <16 years: Use of promethazine/codeine combination is contraindicated

Children ≥16 years: Refer to adult dosing.

Dietary ConsiderationsIncrease fluids, fiber intake, and riboflavin in diet.

RestrictionsC-V

ContraindicationsHypersensitivity to promethazine, codeine, or any component of the formulation (cross-reactivity between phenothiazines may occur); children <16 years of age; coma; treatment of lower respiratory tract symptoms, including asthma

Allergy Considerations

- Opioid Allergy/Hypersensitivity
- Phenothiazine Allergy

Warnings/Precautions

Boxed warnings:

- Pediatrics: See “Special populations” below.

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines).
- Anticholinergic effects: Phenothiazines may cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); therefore, they should be used with caution in patients with decreased gastrointestinal motility, urinary retention, BPH, xerostomia, or visual problems.
- Extrapyramidal symptoms: May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia.
- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity and/or autonomic instability.
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).
- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with bone marrow suppression; leukopenia and agranulocytosis have been reported.
- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.
- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with parkinson's disease; may have increased risk of tardive dyskinesia.

- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use with caution in patients with severe respiratory disease (asthma, COPD, sleep apnea); may lead to potentially fatal respiratory depression.

- Seizures: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Pediatrics: **[U.S. Boxed Warning]: The use of this combination in children <16 years of age is contraindicated;** respiratory depression, including fatalities, is associated with concomitant administration of promethazine and other respiratory depressants in children. Fatalities associated with respiratory depression have also been reported with promethazine use in children <2 years of age.

Other warnings/precautions:

- Cough control: Codeine is not recommended for use for cough control in patients with a productive cough. Dose should not be increased if cough does not respond; re-evaluate within 5 days for possible underlying pathology.

Geriatric ConsiderationsElderly may be sensitive to more anticholinergic, sedating, or constipating effects. Initiate at low dosage and increase cautiously.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. See individual agents.
LactationEnters breast milk (codeine)/not recommended
Breast-Feeding ConsiderationsRefer to Codeine monograph.
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsPromethazine: **Substrate** (major) of CYP2B6, 2D6; **Inhibits** CYP2D6 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2B6 Inducers (Strong): May increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Strong): May decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Syrup: Promethazine hydrochloride 6.25 mg and codeine phosphate 10 mg per 5 mL (120 mL, 473 mL) [contains alcohol]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Syrup (Promethazine-Codeine)

6.25-10 mg/5 mL (118): $9.99

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Codeine
- Promethazine

Dental Health: Effects on Dental TreatmentAlthough promethazine is a phenothiazine derivative, extrapyramidal reactions or tardive dyskinesias are not seen with the use of this drug.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness
Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation
Index TermsCodeine and Promethazine

Promethazine and Dextromethorphan

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state "Do not use in children under four years of age." In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, "Infant Deaths Associated with Cough and Cold Medications - Two States, 2005," *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(proe METH a zeen & deks troe meth OR fan)

Pharmacologic CategoryAntitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporary relief of coughs and upper respiratory symptoms associated with allergy or the common cold

Dosing: Adults**Cough and upper respiratory symptoms:** Oral: 5 mL every 4-6 hours, up to 30 mL in 24 hours

Dosing: ElderlyRefer to dosing in individual monographs.
Dosing: Pediatric**Cough and upper respiratory symptoms**: Oral: Children:

<2 years: Use of promethazine is contraindicated

2-6 years: 1.25-2.5 mL every 4-6 hours up to 10 mL in 24 hours

6-12 years: 2.5-5 mL every 4-6 hours up to 20 mL in 24 hours

Dietary ConsiderationsIncrease dietary intake of riboflavin.
ContraindicationsHypersensitivity to promethazine, dextromethorphan, or any component of the formulation (cross-reactivity between phenothiazines may occur); treatment of lower respiratory tract symptoms, including asthma
Allergy Considerations

- Phenothiazine Allergy

Warnings/Precautions

Boxed warnings:

- Pediatrics: See “Special populations” below.

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines).

- Anticholinergic effects: Phenothiazines may cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); therefore, they should be used with caution in patients with decreased gastrointestinal motility, urinary retention, BPH, xerostomia, or visual problems.

- Extrapyramidal symptoms: May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity and/or autonomic instability.

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with bone marrow suppression; leukopenia and agranulocytosis have been reported.

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with parkinson's disease; may have increased risk of tardive dyskinesia.

- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use with caution in patients with severe respiratory disease (asthma, COPD, sleep apnea); may lead to potentially fatal respiratory depression.

- Seizures: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Pediatrics: **[U.S. Boxed Warning]: Safety and efficacy of this combination have not been established in children <2 years of age (use of promethazine is contraindicated). In children ≥2 years, use the lowest possible dose; other drugs with respiratory depressant effects should be avoided.**

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Refer to Promethazine monograph.

LactationExcretion in breast milk unknown/not recommended

Metabolism/Transport Effects

Promethazine: **Substrate** (major) of CYP2B6, 2D6; **Inhibits** CYP2D6 (weak)

Dextromethorphan: **Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

CYP2B6 Inducers (Strong): May increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Strong): May decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Nursing: Physical Assessment/MonitoringSee individual agent for Promethazine.

Patient EducationSee individual agent for Promethazine.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Syrup: Promethazine hydrochloride 6.25 mg and dextromethorphan hydrobromide 15 mg per 5 mL (120 mL, 480 mL) [contains alcohol 7%]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Syrup (Promethazine-DM)

6.25-15 mg/5 mL (118): $8.99

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Dextromethorphan
- Promethazine

Dental Health: Effects on Dental TreatmentAlthough promethazine is a phenothiazine derivative, extrapyramidal reactions or tardive dyskinesias are not seen with the use of this drug.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation

Index TermsDextromethorphan and Promethazine

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(proe METH a zeen & fen il EF rin)

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporary relief of upper respiratory symptoms associated with allergy or the common cold

Dosing: AdultsUpper respiratory symptoms: Oral: 5 mL every 4-6 hours, not to exceed 30 mL in 24 hours

Dosing: ElderlyRefer to dosing in individual monographs.

Dosing: PediatricUpper respiratory symptoms: Oral: Children:

<2 years: Use of promethazine is contraindicated

2-6 years: 1.25-2.5 mL every 4-6 hours, not to exceed 7.5 mL in 24 hours

6-12 years: 2.5-5 mL every 4-6 hours, not to exceed 30 mL in 24 hours

>12 years: Refer to adult dosing.

Dietary ConsiderationsIncrease dietary intake of riboflavin.

ContraindicationsHypersensitivity to promethazine, phenylephrine, or any component of the formulation (cross-reactivity between phenothiazines may occur;) treatment of lower respiratory tract symptoms, including asthma; hypertension; ventricular tachycardia; peripheral vascular insufficiency; use with or within 14 days of MAO inhibitor therapy

Allergy Considerations

- Phenothiazine Allergy

Warnings/Precautions

Boxed warnings:

- Pediatrics: See “Special populations” below.

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines).

- Anticholinergic effects: Phenothiazines may cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); therefore, they should be used with caution in patients with decreased gastrointestinal motility, urinary retention, BPH, xerostomia, or visual problems.

- Extrapyramidal symptoms: May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity and/or autonomic instability.

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with bone marrow suppression; leukopenia and agranulocytosis have been reported.

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Diabetes: Use phenylephrine with caution in patients with diabetes mellitus.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma and/or increased intraocular pressure; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Hyperthyroidism: Use phenylephrine with caution in patients with hyperthyroidism.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with parkinson's disease; may have increased risk of tardive dyskinesia.

- Prostatic hyperplasia: Use phenylephrine with caution in patients with prostatic hyperplasia.

- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use with caution in patients with severe respiratory disease (asthma, COPD, sleep apnea); may lead to potentially fatal respiratory depression.

- Seizures: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use phenylephrine with caution in the elderly.

- Pediatrics: **[U.S. Boxed Warning]: Safety and efficacy of this combination have not been established in children <2 years of age (use of promethazine is contraindicated). In children ≥2 years, use the lowest possible dose; other drugs with respiratory depressant effects should be avoided.**

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. Refer to Promethazine monograph.
LactationExcretion in breast milk unknown/not recommended
Metabolism/Transport EffectsPromethazine: **Substrate** (major) of CYP2B6, 2D6; **Inhibits** CYP2D6 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CYP2B6 Inducers (Strong): May increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Strong): May decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression). Avoid ephedra, yohimbe (may cause CNS stimulation).

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Syrup: Promethazine hydrochloride 6.25 mg and phenylephrine hydrochloride 5 mg per 5 mL (473 mL) [contains alcohol]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Syrup (Promethazine VC)

6.25-5 mg/5 mL (118): $27.99

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Phenylephrine
- Promethazine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Phenylephrine: Tachycardia, palpitations, xerostomia (normal salivary flow resumes upon discontinuation); use vasoconstrictor with caution. Although promethazine is a phenothiazine derivative, extrapyramidal reactions or tardive dyskinesias are not seen with the use of this drug.
Dental Health: Vasoconstrictor/Local Anesthetic Precautions

Phenylephrine: Use with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Promethazine: No information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness
Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation
Index TermsPhenylephrine and Promethazine

Promethazine, Phenylephrine, and Codeine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(proe METH a zeen, fen il EF rin, & KOE deen)

Pharmacologic CategoryAlpha/Beta Agonist; Analgesic, Opioid; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporary relief of coughs and upper respiratory symptoms including nasal congestion associated with allergy or the common cold

Dosing: Adults**Cough and upper respiratory symptoms:** Oral: 5 mL every 4-6 hours, not to exceed 30 mL/24 hours

Dosing: ElderlyRefer to dosing in individual monographs.

Dosing: Pediatric**Cough and upper respiratory symptoms:** Oral:

Children <2 years: Use of promethazine is contraindicated

Children <16 years: Use of promethazine/codeine combination is contraindicated

Children ≥16 years: Refer to adult dosing.

Dietary ConsiderationsMay be taken with food or water to decrease GI upset; increase fiber intake and riboflavin in diet.

RestrictionsC-V

ContraindicationsHypersensitivity to promethazine, phenylephrine, codeine, or any component of the formulation (cross-reactivity between phenothiazines may occur); children <16 years of age; coma; treatment of lower respiratory tract symptoms, including asthma; hypertension; ventricular tachycardia; peripheral vascular insufficiency; use with or within 14 days of MAO inhibitor therapy

Allergy Considerations

- Opioid Allergy/Hypersensitivity
- Phenothiazine Allergy

Warnings/Precautions

Boxed warnings:

- Pediatrics: See “Special populations” below.

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines).
- Anticholinergic effects: Phenothiazines may cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); therefore, they should be used with caution in patients with decreased gastrointestinal motility, urinary retention, BPH, xerostomia, or visual problems.
- Extrapyramidal symptoms: May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia.
- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity and/or autonomic instability.
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).
- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with bone marrow suppression; leukopenia and agranulocytosis have been reported.
- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Diabetes: Use phenylephrine with caution in patients with diabetes mellitus.
- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Hyperthyroidism: Use phenylephrine with caution in patients with hyperthyroidism.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.
- Parkinson's disease: Use with caution in patients with parkinson's disease; may have increased risk of tardive dyskinesia.
- Prostatic hyperplasia: Use phenylephrine with caution in patients with prostatic hyperplasia.
- Renal impairment: Use with caution in patients with severe renal impairment.
- Respiratory disease: Use with caution in patients with severe respiratory disease (asthma, COPD, sleep apnea); may lead to potentially fatal respiratory depression.
- Seizures: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.
- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use phenylephrine with caution in the elderly.
- Pediatrics: **[U.S. Boxed Warning]: The use of this combination in children <16 years of age is contraindicated;** respiratory depression, including fatalities, is associated with concomitant administration of promethazine and other respiratory depressants in children. Fatalities associated with respiratory depression have also been reported with promethazine use in children <2 years of age.

Other warnings/precautions:

- Cough control: Codeine is not recommended for use for cough control in patients with a productive cough. Dose should not be increased if cough does not respond; re-evaluate within 5 days for possible underlying pathology.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted with this combination. See individual agents.
LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsCodeine enters breast milk; excretion of promethazine and phenylephrine is unknown. Also refer to Codeine monograph.
Adverse ReactionsSee individual agents.
Metabolism/Transport Effects

Promethazine: **Substrate** (major) of CYP2B6, 2D6; **Inhibits** CYP2D6 (weak)

Codeine: **Substrate** of CYP2D6 (major), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2B6 Inducers (Strong): May increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Strong): May decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression). Avoid ephedra, yohimbe (may cause CNS stimulation).

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Syrup: Promethazine hydrochloride 6.25 mg, phenylephrine hydrochloride 5 mg, and codeine phosphate 10 mg per 5 mL (480 mL) [contains alcohol and sodium benzoate]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Syrup (Promethazine VC/Codeine)

6.25-5-10 mg/5 mL (118): $26.99

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Codeine
- Phenylephrine
- Promethazine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Phenylephrine: Tachycardia, palpitations, xerostomia (normal salivary flow resumes upon discontinuation); use vasoconstrictor with caution. Although promethazine is a phenothiazine derivative, extrapyramidal reactions or tardive dyskinesias are not seen with the use of this drug.
Dental Health: Vasoconstrictor/Local Anesthetic Precautions

Phenylephrine: Use with caution since phenylephrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Promethazine: No information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness
Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation
Index TermsCodeine, Promethazine, and Phenylephrine; Phenylephrine, Promethazine, and Codeine

Promethazine

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Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Promethazine may be confused with chlorproMAZINE, predniSONE, promazine

Phenergan® may be confused with Phenaphen®, PHENobarbital, Phrenilin®, Theragran®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V. formulation) among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Administration issues:

To prevent or minimize tissue damage during I.V. administration, the Institute for Safe Medication Practices (ISMP) has the following recommendations:

Limit concentration available to the 25 mg/mL product

Consider limiting initial doses to 6.25-12.5 mg

Further dilute the 25 mg/mL strength into 10-20 mL NS

Administer through a large bore vein (not hand or wrist)

Administer via running I.V. line at port furthest from patient's vein

Consider administering over 10-15 minutes

Instruct patients to report immediately signs of pain or burning

Pronunciation(proe METH a zeen)

U.S. Brand NamesPhenadoz™; Phenergan®; Promethegan™

Canadian Brand NamesBioniche Promethazine; Histantil; Phenergan®; PMS-Promethazine

Pharmacologic CategoryAntiemetic; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic treatment of various allergic conditions; antiemetic; motion sickness; sedative; postoperative pain (adjunctive therapy); anesthetic (adjunctive therapy); anaphylactic reactions (adjunctive therapy)

Dosing: Adults

Allergic conditions (including allergic reactions to blood or plasma):

Oral, rectal: 25 mg at bedtime **or** 12.5 mg before meals and at bedtime (range: 6.25-12.5 mg 3 times/day)

I.M., I.V.: 25 mg, may repeat in 2 hours when necessary; switch to oral route as soon as feasible

Antiemetic: Oral, I.M., I.V., rectal: 12.5-25 mg every 4-6 hours as needed

Motion sickness: Oral, rectal: 25 mg 30-60 minutes before departure, then every 12 hours as needed

Sedation: Oral, I.M., I.V., rectal: 12.5-50 mg/dose

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Allergic conditions: Children ≥2 years: Oral, rectal: 0.1 mg/kg/dose (maximum: 12.5 mg) every 6 hours during the day and 0.5 mg/kg/dose (maximum: 25 mg) at bedtime as needed

Antiemetic: Children ≥2 years: Oral, I.M., I.V., rectal: 0.25-1 mg/kg 4-6 times/day as needed (maximum: 25 mg/dose)

Motion sickness: Children ≥2 years: Oral, rectal: 0.5 mg/kg/dose 30 minutes to 1 hour before departure, then every 12 hours as needed (maximum dose: 25 mg twice daily)

Sedation: Children ≥2 years: Oral, I.M., I.V., rectal: 0.5-1 mg/kg/dose every 6 hours as needed (maximum: 50 mg/dose)

Administration: I.M.Preferred route of administration; administer into deep muscle

Administration: I.V.I.V. administration is **not** the preferred route; severe tissue damage may occur. Solution for injection should be administered in a maximum concentration of 25 mg/mL (more dilute solutions are recommended). Administer via running I.V. line at port furthest from patient's vein, or through a large bore vein (not hand or wrist). Consider administering over 10-15 minutes (maximum: 25 mg/minute). Discontinue immediately if burning or pain occurs with administration.

Administration: I.V. DetailRapid I.V. administration may produce a transient fall in blood pressure.

pH: 4.0-5.5

Administration: OtherNot for SubQ or intra-arterial administration.

Dietary ConsiderationsIncrease dietary intake of riboflavin.

Storage

Injection: Prior to dilution, store at room temperature. Protect from light. Solutions in NS or D_5W are stable for 24 hours at room temperature.

Suppositories: Store refrigerated at 2°C to 8°C (36°F to 46°F).

Tablets: Store at room temperature. Protect from light.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5W, $D_{10}W$, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, LR, ${}^1/_2NS$, NS.

Y-site administration: Compatible: Amifostine, amsacrine, aztreonam, ciprofloxacin, cisatracurium, cisplatin, cladribine, cyclophosphamide, cytarabine, docetaxel, doxorubicin, etoposide phosphate, filgrastim, fluconazole, fludarabine, gatifloxacin, gemcitabine, granisetron, linezolid, melphalan, ondansetron, remifentanil, sargramostim, teniposide, thiotepa, vinorelbine. **Incompatible:** Aldesleukin, allopurinol, amphotericin B cholesteryl sulfate complex, cefazolin, cefepime, cefoperazone, cefotetan, doxorubicin liposome, foscarnet, methotrexate, piperacillin/tazobactam. **Variable (consult detailed reference):** Cefazolin, ceftizoxime, heparin, hydrocortisone sodium succinate, potassium chloride, vitamin B complex with C.

Compatibility in syringe: Compatible: Atropine, atropine with meperidine, butorphanol, chlorpromazine, cimetidine, dihydroergotamine, diphenhydramine, droperidol, fentanyl, glycopyrrolate, hydromorphone, hydroxyzine, meperidine, metoclopramide, midazolam, pentazocine, perphenazine, prochlorperazine edisylate, promazine, ranitidine, scopolamine. **Incompatible:** Cefotetan, chloroquine, diatrizoate sodium 75%, diatrizoate meglumine 52% with diatrizoate sodium 8%, diatrizoate meglumine 34.3% with diatrizoate sodium 35%, dimenhydrinate, heparin, iodipamide meglumine 52%, iothalamate meglumine 60%, iothalamate sodium 80%, ketorolac, pentobarbital, thiopental. **Variable (consult detailed reference):** Morphine, nalbuphine.

Compatibility when admixed: Compatible: Amikacin, ascorbic acid injection, buprenorphine, butorphanol, chloroquine, hydromorphone, netilmicin, vitamin B complex with C. **Incompatible:** Aminophylline, chloramphenicol, chlorothiazide, dimenhydrinate, floxacillin, furosemide, heparin, hydrocortisone sodium succinate, methohexital, penicillin G sodium, pentobarbital, phenobarbital, phenytoin, thiopental. **Variable (consult detailed reference):** Penicillin G potassium.

ContraindicationsHypersensitivity to promethazine or any component of the formulation (cross-reactivity between phenothiazines may occur); coma; treatment of lower respiratory tract symptoms, including asthma; children <2 years of age

Allergy Considerations

- Phenothiazine Allergy

Warnings/Precautions

Boxed warnings:

- Pediatrics: See "Special populations" below.

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines).

- Anticholinergic effects: Phenothiazines may cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); therefore, they should be used with caution in patients with decreased gastrointestinal motility, urinary retention, BPH, xerostomia, or visual problems.

- Extrapyramidal symptoms: May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity and/or autonomic instability.

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with bone marrow suppression; leukopenia and agranulocytosis have been reported.

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with parkinson's disease; may have increased risk of tardive dyskinesia.

- Renal impairment: Use with caution in patients with severe renal impairment.

- Respiratory disease: Use with caution in patients with severe respiratory disease (asthma, COPD, sleep apnea); may lead to potentially fatal respiratory depression.

- Seizures: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Pediatrics: **[U.S. Boxed Warning]: Respiratory fatalities have been reported in children <2 years of age. In children ≥2 years, use the lowest possible dose; other drugs with respiratory depressant effects should be avoided.**

Dosage form specific issues:

- Sodium metabisulfite: Injection may contain sodium metabisulfite; may cause allergic reaction.

Other warnings/precautions:

- Appropriate administration: Not for SubQ or intra-arterial administration. I.M. is the preferred route of parenteral administration. I.V. use has been associated with severe tissue damage; discontinue immediately if burning or pain occurs with administration.

Geriatric ConsiderationsBecause promethazine is a phenothiazine (and can, therefore, cause side effects such as extrapyramidal symptoms), it is not considered an antihistamine of choice in the elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Crosses the placenta. Possible respiratory depression if drug is administered near time of delivery; behavioral changes, EEG alterations, impaired platelet aggregation reported with use during labor.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, hypertension, postural hypotension, tachycardia, nonspecific QT changes

Central nervous system: Akathisia, catatonic states, confusion, delirium, disorientation, dizziness, drowsiness, dystonias, euphoria, excitation, extrapyramidal symptoms, fatigue, hallucinations, hysteria, insomnia, lassitude, pseudoparkinsonism, tardive dyskinesia, nervousness, neuroleptic malignant syndrome, nightmares, sedation, seizure, somnolence

Dermatologic: Angioneurotic edema, photosensitivity, dermatitis, skin pigmentation (slate gray), urticaria

Endocrine & metabolic: Lactation, breast engorgement, amenorrhea, gynecomastia, hyper-/hypoglycemia

Gastrointestinal: Xerostomia, constipation, nausea, vomiting

Genitourinary: Urinary retention, ejaculatory disorder, impotence

Hematologic: Agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenia, thrombocytopenic purpura

Hepatic: Jaundice

Local: Venous thrombosis; injection site reactions (burning, erythema, pain, edema)

Neuromuscular & skeletal: Incoordination, tremor

Ocular: Blurred vision, corneal and lenticular changes, diplopia, epithelial keratopathy, pigmentary retinopathy

Otic: Tinnitus

Respiratory: Apnea, asthma, nasal congestion, respiratory depression

Oncology: VesicantNo; may be an irritant
Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Substrate** (major) of CYP2B6, 2D6; **Inhibits** CYP2D6 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central).

Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

CYP2B6 Inducers (Strong): May increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Strong): May decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Test InteractionsAlters the flare response in intradermal allergen tests; hCG-based pregnancy tests may result in false-negatives or false-positives; increased serum glucose may be seen with glucose tolerance tests

Monitoring ParametersRelief of symptoms, mental status

Nursing: Physical Assessment/MonitoringAssess patient carefully for use cautions prior to beginning treatment. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking. Note Administration specifics for I.V. and I.M. use (do not give SubQ or intra-arterially; necrotic lesions may occur). Assess for effectiveness (according to purpose for use) and adverse response (eg, sedation, bradycardia, akathisia, delirium, extrapyramidal symptoms, dermatitis, gastrointestinal upset, urinary retention, blurred vision, respiratory depression). May be sedating and impair physical or mental abilities; use and teach sedation safety measures (eg, side rails up, call light within reach). Teach patient appropriate use (oral), interventions to reduce side effects, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber (especially anything that may cause CNS depression). Take this drug as prescribed; do not increase dosage. Avoid alcohol; may increase CNS depression. May cause dizziness, drowsiness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea, dry mouth, appetite disturbances (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report unusual weight gain, unresolved nausea or diarrhea, chest pain or palpitations, excess sedation or stimulation, or sore throat or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution, as hydrochloride: 25 mg/mL (1 mL); 50 mg/mL (1 mL)

Phenergan®: 25 mg/mL (1 mL); 50 mg/mL (1 mL) [contains sodium metabisulfite]

Suppository, rectal, as hydrochloride: 12.5 mg, 25 mg, 50 mg

Phenadoz™: 12.5 mg, 25 mg

Phenergan®: 25 mg, 50 mg [DSC]

Promethegan™: 12.5 mg, 25 mg, 50 mg

Syrup, as hydrochloride: 6.25 mg/5 mL (120 mL, 480 mL) [contains alcohol]

Tablet, as hydrochloride: 12.5 mg, 25 mg, 50 mg

Phenergan®: 25 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Promethazine HCl)

50 mg/mL (25): $69.99

Suppository (Phenergan)

12.5 mg (12): $47.99

25 mg (12): $54.99

50 mg (12): $69.99

Suppository (Promethazine HCl)

12.5 mg (12): $29.99

50 mg (12): $49.99

Suppository (Promethegan)

25 mg (12): $52.78

50 mg (12): $75.99

Syrup (Promethazine HCl)

6.25 mg/5 mL (118): $12.99

Mechanism of Action

Blocks postsynaptic mesolimbic dopaminergic receptors in the brain; exhibits a strong alpha-adrenergic blocking effect and depresses the release of hypothalamic and hypophyseal hormones; competes with histamine for the H_1-receptor; reduces stimuli to the brainstem reticular system

Pharmacodynamics/Kinetics

Onset of action: I.M.: ~20 minutes; I.V.: 3-5 minutes

Peak effect: C_{max}: 9.04 ng/mL (suppository); 19.3 ng/mL (syrup)

Duration: 2-6 hours

Absorption:

I.M.: Bioavailability may be greater than with oral or rectal administration

Oral: Rapid and complete; large first pass effect limits systemic bioavailability

Distribution: V_d: 171 L

Protein binding: 93%

Metabolism: Hepatic; primarily oxidation; forms metabolites

Half-life elimination: 9-16 hours

Time to maximum serum concentration: 4.4 hours (syrup); 6.7-8.6 hours (suppositories)

Excretion: Primarily urine and feces (as inactive metabolites)

Dental Health: Effects on Dental Treatment

Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Significant hypotension may occur, especially when the drug is administered parenterally; orthostatic hypotension is due to alpha-receptor blockade, the elderly are at greater risk for orthostatic hypotension.

Tardive dyskinesia: Prevalence rate may be 40% in elderly; development of the syndrome and the irreversible nature are proportional to duration and total cumulative dose over time. Extrapyramidal reactions are more common in elderly with up to 50% developing these reactions after 60 years of age. Drug-induced Parkinson's syndrome occurs often; akathisia is the most common extrapyramidal reaction in elderly.

Increased confusion, memory loss, psychotic behavior, and agitation frequently occur as a consequence of anticholinergic effects. Antipsychotic associated sedation in nonpsychotic patients is extremely unpleasant due to feelings of depersonalization, derealization, and dysphoria.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions

Most pharmacology textbooks state that in presence of phenothiazines, systemic doses of epinephrine paradoxically decrease the blood pressure. This is the so called “epinephrine reversal” phenomenon. This has never been observed when epinephrine is given by infiltration as part of the anesthesia procedure.

Index Terms

Promethazine Hydrochloride

References

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2190193]

International Brand NamesAllerfen (IT); Antiallersin (BG); Atosil (DE); Avomine (AU); Diphergan (PL); Duplamin (IT); Fargan (IT); Farganesse (IT); Fenazil (IT); Fenazine (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Fenergan (AR, ES, PE, PT, PY, UY, VE); Frinova (ES); Gold Cross Antihistamine Elixir (AU); Hibechin (JP); Hiberna (JP); Histazin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Insomn-Eze (AU); Lergigan (SE); Meta (TH); Metagon (PH); Phenergan (AE, AT, AU, BB, BE, BF, BH, BJ, BM, BS, BZ, CH, CI, CY, CZ, DK, EG, ET, FI, FR, GB, GH, GM, GN, GR, GY, IE, IL, IN, IQ, IR, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, NZ, OM, PK, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Phenerzin (PH); Pipolphen (HN, HU); Polfergan (PL); Profergan (BR); Prome (ID); Prometazina (IT); Prometazina Cloridrato (IT); Promethazine (PL); Promethazine Hydrochloride BP (AU); Proneurin (DE); Prothazin (AU, PL); Prothiazine (IL); Pyrethia (JP); Sayomol (ES); Zinmet (MY, PH)

Propafenone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Propafenone Tablets: Recall Due to Potential for Oversized Tablets - November 2008

Certain lots of generic propafenone tablets have been recalled due to possibility of oversized tablets. Oversized tablets may contain up to twice the amount of the active ingredient which may result in serious or life-threatening effects.

For more information, including lots involved, please refer to the FDA MedWatch alert: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Ethex

Pronunciation(pro PAF en one)

U.S. Brand NamesRythmol®; Rythmol® SR

Canadian Brand NamesApo-Propafenone®; PMS-Propafenone; Rythmol® Gen-Propafenone

Pharmacologic CategoryAntiarrhythmic Agent, Class Ic

Use: Labeled IndicationsTreatment of life-threatening ventricular arrhythmias

Rythmol® SR: Maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation

Use: Unlabeled/InvestigationalSupraventricular tachycardias, including those patients with Wolff-Parkinson-White syndrome

Dosing: Adults**Note:** Patients who exhibit significant widening of QRS complex or second- or third-degree AV block may need dose reduction.

Ventricular arrhythmias: Oral:

Immediate release tablet: Initial: 150 mg every 8 hours, increase at 3- to 4-day intervals up to 300 mg every 8 hours.

Extended release capsule: Initial: 225 mg every 12 hours; dosage increase may be made at a minimum of 5-day intervals; may increase to 325 mg every 12 hours; if further increase is necessary, may increase to 425 mg every 12 hours

Paroxysmal atrial fibrillation (unlabeled dose): Oral: *Immediate release:* Outpatient: "Pill-in-the-pocket" dose: 450 mg (weight <70 kg); 600 mg (weight ≥70 kg). May not repeat in ≤24 hours. **Note:** An initial inpatient conversion trial should have been successful before sending patient home on this approach. Patient must be taking an AV nodal-blocking agent (eg, beta-blocker, nondihydropyridine calcium channel blocker) prior to initiation of antiarrhythmic.

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic ImpairmentReduction is necessary; however, specific guidelines are not available.

Administration: OralCapsules should be swallowed whole; do not crush or chew.

Dietary Considerations

Capsule: May be taken without regard to food.

Rythmol® SR capsules contain soy lecithin.

Tablet: Should be taken at the same time in relation to meals each day, either always with meals or always between meals.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to propafenone or any component of the formulation; sinoatrial, AV, and intraventricular disorders of impulse generation and/or conduction (except in patients with a functioning artificial pacemaker); sinus bradycardia; cardiogenic shock; uncompensated cardiac failure; hypotension; bronchospastic disorders; uncorrected electrolyte abnormalities; concurrent use of ritonavir (see Drug Interactions)

Warnings/Precautions

Boxed warnings:

- CAST trial: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Conduction disturbances: Can cause or unmask a variety of conduction disturbances.

- Proarrhythmic effects: Watch for proarrhythmic effects; monitor and adjust dose to prevent QT_c prolongation.

Disease-related concerns:

- Bronchospastic disease: Patients with bronchospastic disease should generally not receive this drug.

- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.

- Heart failure (HF): Use with caution in patients with HF; may precipitate or exacerbate condition.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; may exacerbate condition.

Concurrent drug therapy issues:

- Drugs with QT prolongation potential: Use with caution with concurrent use of any drug that can prolong QT interval.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- CAST trial: **[U.S. Boxed Warning]: In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, non-life-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide.** An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. Antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

- Pacemakers: May alter pacing and sensing thresholds of artificial pacemakers.

Geriatric ConsiderationsElderly may have age-related decreases in hepatic Phase I metabolism. Propafenone is dependent upon liver metabolism, therefore, monitor closely in the elderly and adjust dose more gradually during initial treatment. No differences in clearance noted with impaired renal function and, therefore, no adjustment for renal function in the elderly is necessary.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women; use only if potential benefit to the mother justifies potential risk to the fetus.

LactationEnters breast milk/use caution

Adverse Reactions

1% to 10%:

Cardiovascular: New or worsened arrhythmia (proarrhythmic effect) (2% to 10%), angina (2% to 5%), CHF (1% to 4%), ventricular tachycardia (1% to 3%), palpitation (1% to 3%), AV block (first-degree) (1% to 3%), syncope (1% to 2%), increased QRS interval (1% to 2%), chest pain (1% to 2%), PVCs (1% to 2%), bradycardia (1% to 2%), edema (0% to 1%), bundle branch block (0% to 1%), atrial fibrillation (1%), hypotension (0% to 1%), intraventricular conduction delay (0% to 1%)

Central nervous system: Dizziness (4% to 15%), fatigue (2% to 6%), headache (2% to 5%), ataxia (0% to 2%), insomnia (0% to 2%), anxiety (1% to 2%), drowsiness (1%)

Dermatologic: Rash (1% to 3%)

Gastrointestinal: Nausea/vomiting (2% to 11%), unusual taste (3% to 23%), constipation (2% to 7%), dyspepsia (1% to 3%), diarrhea (1% to 3%), xerostomia (1% to 2%), anorexia (1% to 2%), abdominal pain (1% to 2%), flatulence (0% to 1%)

Neuromuscular & skeletal: Tremor (0% to 1%), arthralgia (0% to 1%), weakness (1% to 2%)

Ocular: Blurred vision (1% to 6%)

Respiratory: Dyspnea (2% to 5%)

Miscellaneous: Diaphoresis (1%)

<1% (Limited to important or life-threatening): Agranulocytosis, leukopenia, thrombocytopenia, purpura, granulocytopenia, anemia, increased bleeding time, hepatitis (0.03%), increased serum transaminases (0.2%), prolonged PR interval, sinus node dysfunction, cholestasis (0.1%), gastroenteritis, positive ANA titers (0.7%), lupus erythematosus, AV block (second or third degree), AV dissociation, cardiac arrest, flushing, sinus arrest, abnormal speech, abnormal dreams, abnormal vision, apnea, coma, confusion, depression, memory loss, paresthesia, numbness, psychosis, seizure (0.3%), tinnitus, abnormal smell sensation, vertigo, alopecia, eye irritation, SIADH, hyponatremia, impotence, hyperglycemia, kidney failure, muscle cramps, muscle weakness, nephrotic syndrome, pain, pruritus, CHF, renal failure, nephrotic syndrome

Postmarketing and/or case reports: Peripheral neuropathy, mania, amnesia

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2D6 (major), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2D6 (weak)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Beta-Blockers: Propafenone may decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. **Exceptions:** Atenolol; Carteolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Cardiac Glycosides: Propafenone may increase the serum concentration of Cardiac Glycosides. *Risk C: Monitor therapy*

Cimetidine: May increase the serum concentration of Propafenone. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Ritonavir: May decrease the metabolism of Propafenone. *Risk X: Avoid combination*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Propafenone. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Tipranavir: May increase the serum concentration of Propafenone. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Propafenone may increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Propafenone serum concentrations may be increased if taken with food.

Herb/Nutraceutical: St John's wort may decrease propafenone levels. Avoid ephedra (may worsen arrhythmia).

Monitoring ParametersECG, blood pressure, pulse (particularly at initiation of therapy)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess therapeutic effectiveness, and adverse reactions at beginning of therapy, when titrating dosage, and on a regular basis with long-term therapy. Monitor cardiac status closely. **Note:** Propafenone has a low TI and overdose may easily produce severe and life-threatening reactions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed; do not take additional doses or discontinue without consulting prescriber. You will need regular cardiac checkups. You may experience dizziness, drowsiness, or visual changes (use caution when driving or engaging in tasks requiring alertness until response to drug is known); abnormal taste, nausea or vomiting, or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); headaches (prescriber may recommend mild analgesic); or diarrhea (yogurt or boiled milk may help; if persistent consult prescriber). Report chest pain, palpitation, or erratic heartbeat; respiratory difficulty, increased weight or swelling of hands or feet; acute persistent diarrhea or constipation; or vision changes.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release, as hydrochloride (Rythmol® SR): 225 mg, 325 mg, 425 mg [contains soy lecithin]

Tablet, as hydrochloride (Rythmol®): 150 mg, 225 mg, 300 mg

Generic AvailableYes: Tablet

ManufacturerKnoll Pharmaceutical Company

Pricing: U.S. (www.drugstore.com)

Capsule, 12-hour (Rythmol SR)

225 mg (30): $176.56

325 mg (30): $225.60

425 mg (60): $449.99

Tablets (Propafenone HCl)

150 mg (90): $115.99

225 mg (90): $119.99

300 mg (30): $70.99

Tablets (Rythmol)

225 mg (30): $154.64

Mechanism of ActionPropafenone is a class 1c antiarrhythmic agent which possesses local anesthetic properties, blocks the fast inward sodium current, and slows the rate of increase of the action potential. Prolongs conduction and refractoriness in all areas of the myocardium, with a slightly more pronounced effect on intraventricular conduction; it prolongs effective refractory period, reduces spontaneous automaticity and exhibits some beta-blockade activity.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Metabolism: Hepatic; two genetically determined metabolism groups exist: fast or slow metabolizers; 10% of Caucasians are slow metabolizers; exhibits nonlinear pharmacokinetics; when dose is increased from 300-900 mg/day, serum concentrations increase tenfold; this nonlinearity is thought to be due to saturable first-pass effect

Bioavailability: 150 mg: 3.4%; 300 mg: 10.6%

Half-life elimination: Single dose (100-300 mg): 2-8 hours; Chronic dosing: 10-32 hours

Time to peak: 150 mg dose: 2 hours, 300 mg dose: 3 hours

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Unusual taste and significant xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsIn some patients, propafenone has been reported to induce new or worsened arrhythmias (proarrhythmic effect). It is suggested that vasoconstrictors be used with caution since epinephrine has the potential to stimulate the heart rate when given in the anesthetic regimen. Propafenone is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusDizziness and drowsiness are common; may cause anxiety

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; use TCAs with caution; may cause QT prolongation

Cardiovascular ConsiderationsPropafenone is a class Ic antiarrhythmic with very weak beta-blocking properties. Avoid propafenone use in patients with cardiovascular disease, particularly recent myocardial infarction and heart failure, due to a possible increase in proarrhythmia and mortality.

"Pill-in-the Pocket" administration approach: Patients with a history of palpitations with an abrupt onset, were hemodynamically stable, and had 1-12 episodes of atrial fibrillation within the previous year (and no other cardiac symptoms) were candidates for a clinical trial evaluating flecainide or propafenone for conversion of their rhythm (Alboni P, 2004). Patients had to have minimal, if any, heart disease. Only 12% of all patients evaluated for this trial were eligible for inclusion, thus this type of treatment is only for select patients meeting both inclusion and exclusion criteria. However, patients who had met inclusion criteria and were given either flecainide or propafenone in the hospital phase of the trial and converted to normal sinus rhythm were then enrolled into the ambulatory phase of the trial. Patients in this outpatient trial were to take either flecainide or propafenone at the first onset of palpitations. The doses were as follows: Flecainide 300 mg for patients ≥70 kg and 200 mg for patients <70 kg; propafenone 600 mg for patients ≥70 kg and 450 mg for patients <70 kg. Patients were instructed to sit or lie down after taking either drug until palpitations had stopped or for at least 4 hours. If palpitations had not subsided after 6–8 hours, then the patients were instructed to go to the emergency room. They were not to take more than one dose in a 24-hour period. This treatment regimen demonstrated that 94% of episodes in the 165 patients studied were successfully treated with a mean time to symptom resolution of 113 minutes. Adverse events were reported in 12 patients. One patient developed atrial flutter with a rapid ventricular response that required an emergency room visit. The other 11 patients complained of noncardiac side effects (eg, nausea, weakness, and vertigo). This therapy demonstrated a significant reduction in emergency room visits and hospitalization.

Selected patients with infrequent paroxysmal atrial fibrillation may be candidates for the “Pill-in-the-Pocket” regimen. Many patients may not be appropriate candidates for this regimen, based on previous clinical studies – CAST, CAST 2, CASH; a number of exclusion criteria define the potential harm of these agents.

Anesthesia and Critical Care Concerns/Other ConsiderationsAs with other class 1c agents, avoid use in patients with cardiovascular disease.

Index TermsPropafenone Hydrochloride

References

Alboni P, Botto GL, Baldi N, et al, "Outpatient Treatment of Recent-Onset Atrial Fibrillation With the "Pill-in-the-Pocket" Approach," *N Engl J Med*, 2004, 351(23):2384-91.

“A Randomized, Placebo-Controlled Trial of Propafenone in the Prophylaxis of Paroxysmal Supraventricular Tachycardia and Paroxysmal Atrial Fibrillation. UK Propafenone PSVT Study Group,” *Circulation*, 1995, 92(9):2550-7. [PubMed 7586356]

Boriani G, Capucci A, Lenzi T, et al, “Propafenone for Conversion of Recent-Onset Atrial Fibrillation. A Controlled Comparison Between Oral Loading Dose and Intravenous Administration,” *Chest*, 1995, 108(2):355-8. [PubMed 7634866]

Boriani G, Biffi M, Capucci A, et al, “Oral Propafenone to Convert Recent-Onset Atrial Fibrillation in Patients With and Without Underlying Heart Disease. A Randomized, Controlled Trial,” *Ann Intern Med*, 1997, 126(8):621-5. [PubMed 9103129]

Echt DS, Liebson PR, Mitchell LB, et al, “Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo: The Cardiac Arrhythmia Suppression Trial,” *N Engl J Med*, 1991, 324(12):781-8.[PubMed 1900101]

Fuster V, Ryden LE, Cannom DS, et al, “ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation-Executrive Summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients

With Atrial Fibrillation). Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society," *J Am Coll Cardiol*, 2006, 48(4):854-906.[PubMed 16904574]

International Brand NamesArythmol (GB, IE); Nistaken (MX); Norfenon (MX); Normorytmin (AR); Polfenon (PL); Profex (IL); Prolekofen (PL); Pronon (JP); Propafenon Genericon (HR); Propafenon Pharmavit (HU); Prorynorm (LU); Ritmocor (CN); Ritmonorm (BR, PY); Rythmex (IL); Rythmol (FR, ZA); Rytmocard (PH); Rytmonorm (BE, BG, CH, CL, CO, CZ, DE, DK, EE, ES, FI, GR, HK, HN, HR, HU, ID, IT, JO, KP, LU, NL, NZ, PE, PL, PT, SE, TH, TW, UY, VE); Rytmonorma (AT)

Propantheline

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English English

Jump To Field (Select Field Name)

Pronunciation(proe PAN the leen)
Pharmacologic Category[Anticholinergic Agent]
Use: Labeled IndicationsAdjunctive treatment of peptic ulcer, irritable bowel syndrome, pancreatitis, ureteral and urinary bladder spasm; reduce duodenal motility during diagnostic radiologic procedures
Use: DentalInduce dry field (xerostomia) in oral cavity
Dosing: Adults

Antisecretory: Oral: 15 mg 3 times/day before meals or food and 30 mg at bedtime

Antispasmodic: Oral: 15 mg 3 times/day before meals or food and 30 mg at bedtime

Dosing: ElderlyAntisecretory: 7.5 mg 3 times/day before meals and at bedtime; increase as necessary to a maximum of 30 mg 3 times/day
Dosing: Pediatric

Antisecretory: Oral: Children: 1-2 mg/kg/day in 3-4 divided doses

Antispasmodic: Oral: Children: 2-3 mg/kg/day in divided doses every 4-6 hours and at bedtime

Dietary ConsiderationsShould be taken 30 minutes before meals so that the drug's peak effect occurs at the proper time. The tablet (15 mg) contains lactose 23.2 mg.
ContraindicationsHypersensitivity to propantheline or any component of the formulation; ulcerative colitis, toxic megacolon, obstructive disease of the GI or urinary tract; narrow-angle glaucoma; myasthenia gravis
Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause drowsiness and/or blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Diarrhea: May be a sign of incomplete intestinal obstruction, treatment should be discontinued if this occurs.
- Heat prostration: May occur in the presence of increased environmental temperature; use caution in hot weather and/or exercise.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease, tachyarrhythmias, heart failure, or hypertension; evaluate tachycardia prior to administration.
- Endocrine disease: Use with caution in patients with endocrine diseases.
- Gastrointestinal infections: Use with caution in patients with GI infections.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hiatal hernia: Use with caution in patients with hiatal hernia with reflux esophagitis.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Neuropathy: Use with caution in patients with autonomic neuropathy.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for anticholinergic effects, confusion, and hallucinations.

Geriatric ConsiderationsThe primary use of propantheline in the geriatric population is for treatment of urinary incontinence due to detrusor instability. Even though it does not cross the blood-brain barrier, CNS effects have been reported. Orthostatic hypotension may also occur, therefore, avoid long-term use in the elderly.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown
Breast-Feeding ConsiderationsNo data reported; however, atropine may be taken while breast-feeding.
Adverse ReactionsFrequency not defined.

Dermatologic: Dry skin

Gastrointestinal: Constipation, dry mouth and throat, dysphagia

Respiratory: Dry nose

Miscellaneous: Diaphoresis (decreased)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as bromide: 15 mg [contains lactose 23.2 mg]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Propantheline Bromide)

15 mg (30): $21.99

Mechanism of ActionCompetitively blocks the action of acetylcholine at postganglionic parasympathetic receptor sites

Pharmacodynamics/Kinetics

Onset of action: 30-45 minutes

Duration: 4-6 hours

Half-life elimination, serum: Average: 1.6 hours

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (therapeutic effect; normal salivary flow resumes upon discontinuation), dry throat, nasal dryness, and dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, confusion, amnesia, nervousness, or insomnia

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation or anticholinergic side effects (dry mouth)

Index TermsPropantheline Bromide

International Brand NamesErcoril (DK); Ercotina (SE); Pro-Banthine (AU, BB, BE, BF, BJ, BM, BS, BZ, CI, CY, ET, FR, GB, GH, GM, GN, GY, HK, ID, IE, IN, JM, KE, LR, LU, MA, ML, MR, MU, MW, NE, NG, NL, SC, SD, SL, SN, SR, TN, TT, TW, TZ, UG, ZA, ZM, ZW); Propanline (TW)

Proparacaine and Fluorescein

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Pronunciation(proe PAR a kane & FLURE e seen)
U.S. Brand NamesFlucaine®; Fluoracaine® [DSC]
Pharmacologic CategoryDiagnostic Agent; Local Anesthetic
Use: Labeled IndicationsAnesthesia for tonometry, gonioscopy; suture removal from cornea; removal of corneal foreign body; cataract extraction, glaucoma surgery
Dosing: Adults

Ophthalmic surgery: Instill 1 drop in each eye every 5-10 minutes for 5-7 doses

Tonometry, gonioscopy, suture removal: Instill 1-2 drops in each eye just prior to procedure

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Ophthalmic surgery:** Children: Refer to adult dosing.
StorageStore in tight, light-resistant containers.
ContraindicationsHypersensitivity to proparacaine, fluorescein, any component of the formulation, or ester-type local anesthetics
Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.

- Hyperthyroidism: Use with caution in patients with hyperthyroidism.

Other warnings/precautions:

- Appropriate use: For topical ophthalmic use only; prolonged use not recommended.

Pregnancy Risk FactorC
Adverse Reactions

1% to 10%: Local: Burning, stinging of eye

<1%: Allergic contact dermatitis, irritation, sensitization, erosion of the corneal epithelium, conjunctival congestion and hemorrhage, keratitis, iritis, corneal opacification

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, ophthalmic: Proparacaine hydrochloride 0.5% and fluorescein sodium 0.25% (5 mL)

Flucaine®, Fluoracaine® [DSC]: Proparacaine hydrochloride 0.5% and fluorescein sodium 0.25% (5 mL)

Generic AvailableYes
Mechanism of ActionPrevents initiation and transmission of impulse at the nerve cell membrane by decreasing ion permeability through stabilizing
Pharmacodynamics/Kinetics

Onset of action: ~20 seconds

Duration: 15-20 minutes

Related Information

- Fluorescein
- Proparacaine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsFluorescein and Proparacaine

Proparacaine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Proparacaine may be confused with propoxyphene

Pronunciation(proe PAR a kane)
U.S. Brand NamesAlcaine®; Ophthetic®; Parcaine™
Canadian Brand NamesAlcaine®; Diocaine®
Pharmacologic CategoryLocal Anesthetic, Ophthalmic
Use: Labeled IndicationsAnesthesia for tonometry, gonioscopy; suture removal from cornea; removal of corneal foreign body; cataract extraction, glaucoma surgery; short operative procedure involving the cornea and conjunctiva
Dosing: Adults

Ophthalmic surgery: Ophthalmic: Instill 1 drop of 0.5% solution in eye every 5-10 minutes for 5-7 doses

Tonometry, gonioscopy, suture removal: Ophthalmic: Instill 1-2 drops of 0.5% solution in eye just prior to procedure

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren: Refer to adult dosing
StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light.
ContraindicationsHypersensitivity to proparacaine or any component of the formulation
Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Other warnings/precautions:

• Appropriate use: For topical ophthalmic use only; prolonged use not recommended.

Pregnancy Risk FactorC
Adverse Reactions

1% to 10%: Local: Burning, stinging, redness

<1%: Allergic contact dermatitis, arrhythmia, blurred vision, CNS depression, conjunctival congestion and hemorrhage, corneal opacification, diaphoresis (increased), epithelium, erosion of the corneal iritis, irritation, keratitis, lacrimation, sensitization

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic, as hydrochloride: 0.5% (15 mL) [contains benzalkonium chloride]

Alcaine®: 0.5% (15 mL) [contains benzalkonium chloride]

Ophthetic®: 0.5% (15 mL) [contains benzalkonium chloride]

Parcaine™: 0.5% (15 mL) [contains benzalkonium chloride]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Solution (Ophthetic)

0.5% (15): $17.99

Solution (Proparacaine HCl)

0.5% (15): $14.99

Mechanism of ActionPrevents initiation and transmission of impulse at the nerve cell membrane by decreasing ion permeability through stabilizing
Pharmacodynamics/Kinetics

Onset of action: ~20 seconds

Duration: 15-20 minutes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay rarely produce CNS depression
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsProparacaine Hydrochloride; Proxymetacaine
International Brand NamesAlcaine (AE, AU, BE, BF, BH, BJ, CH, CI, CY, EG, ET, GH, GM, GN, GR, HK, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NO, OM, PK, PL, QA, SA, SC, SD, SL, SN, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Anestalcon (AR, BR, CN); Keracaine (FR, LU); Minims Proxymetacaine Hydrochloride (GB); Miraxil (CO); Ophthaine (GB, IE); Ophthetic (GR); Opthetic (NZ); Poen-Caina (UY); Proparakain-POS (DE); Visonest (BR); Visuanestetico (IT)

Propofol

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Diprivan® may be confused with Diflucan®, Ditropan®

Propofol may be confused with fospropofol

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(PROE po fole)

U.S. Brand NamesDiprivan®

Canadian Brand NamesDiprivan®

Pharmacologic CategoryGeneral Anesthetic

Use: Labeled IndicationsInduction of anesthesia for inpatient or outpatient surgery in patients ≥3 years of age; maintenance of anesthesia for inpatient or outpatient surgery in patients >2 months of age; in adults, for induction and maintenance of monitored anesthesia care sedation during procedures; sedation in intubated, mechanically-ventilated ICU patients

Use: Unlabeled/InvestigationalPostoperative antiemetic; refractory delirium tremens (case reports); moderate sedation (conscious sedation)

Dosing: AdultsDosage must be individualized based on total body weight and titrated to the desired clinical effect. Wait at least 3-5 minutes between dosage adjustments to clinically assess drug effects. Smaller doses are required when used with narcotics. The following are general dosing guidelines (see “Abbreviations” section in front section for explanation of ASA-PS classes):

Induction:

General anesthesia:

Healthy adults, ASA-PS 1 or 2, <55 years: I.V.: 2-2.5 mg/kg (~40 mg every 10 seconds until onset of induction)

Debilitated, ASA-PS 3 or 4: Refer to elderly dosing.

Cardiac anesthesia: I.V.: 0.5-1.5 mg/kg (~20 mg every 10 seconds until onset of induction)

Neurosurgical patients: I.V.: 1-2 mg/kg (~20 mg every 10 seconds until onset of induction)

Maintenance:

General anesthesia:

Healthy adults, ASA-PS 1 or 2, <55 years:

I.V. infusion: Initial: 100-200 mcg/kg/minute for 10-15 minutes; decrease by 30% to 50% during first 30 minutes of maintenance; usual infusion rate: 50-100 mcg/kg/minute to optimize recovery time.

I.V. intermittent bolus: 25-50 mg increments as needed

Debilitated, ASA-PS 3 or 4: I.V. Infusion: Refer to elderly dosing.

Cardiac anesthesia: I.V. infusion:

Low-dose propofol with primary opioid: 50-100 mcg/kg/minute (see manufacturer's labeling)

Primary propofol with secondary opioid: 100-150 mcg/kg/minute

Neurosurgical patients: I.V. infusion: 100-200 mcg/kg/minute

Monitored anesthesia care sedation:

Initiation:

Healthy adults, ASA-PS 1 or 2, <55 years: Slow I.V. infusion: 100-150 mcg/kg/minute for 3-5 minutes **or** slow injection: 0.5 mg/kg over 3-5 minutes

Debilitated, neurosurgical, or ASA-PS 3 or 4 patients: Use 80% of healthy adult dose; **do not use rapid bolus doses (single or repeated)**

Maintenance:

Healthy adults, ASA-PS 1 or 2, <55 years: I.V. infusion using variable rates (preferred over intermittent boluses): 25-75 mcg/kg/minute **or** incremental bolus doses: 10 mg or 20 mg

Debilitated, neurosurgical, or ASA-PS 3 or 4 patients: Use 80% of healthy adult dose; **do not use rapid bolus doses (single or repeated)**

ICU sedation in intubated mechanically-ventilated patients: Avoid rapid bolus injection; individualize dose and titrate to response

Continuous infusion: Initial: 5 mcg/kg/minute; increase by 5-10 mcg/kg/minute every 5-10 minutes until desired sedation level is achieved; usual maintenance (Jacobi, 2002): 5-80 mcg/kg/minute. Elderly, debilitated, or ASA-PS 3 or 4 patients: Refer to elderly dosing. Daily interruption with retitration is recommended to minimize prolonged sedative effects (Jacobi, 2002).

Refractory status epilepticus (unlabeled use): 1-2 mg/kg bolus, then 1.5-10 mg/kg/hour (intubation required)

Dosing: Elderly

General anesthesia:

Induction: Elderly, debilitated, ASA-PS 3 or 4: I.V.: 1-1.5 mg/kg (~20 mg every 10 seconds until onset of induction); **do not use rapid bolus doses (single or repeated)**

Maintenance: Elderly, debilitated, ASA-PS 3 or 4: I.V. infusion: 50-100 mcg/kg/minute

Monitored anesthesia care sedation:

Initiation: Elderly, debilitated, ASA-PS 3 or 4, neurosurgical: I.V.: Use 80% of healthy adult dose; **do not use rapid bolus doses (single or repeated)**

Maintenance: Elderly, debilitated, ASA-PS 3 or 4, neurosurgical: I.V.: Use 80% of healthy adult dose; **do not use rapid bolus doses (single or repeated)**

ICU sedation in intubated mechanically-ventilated patients: Avoid rapid bolus injection; individualize dose and titrate to response: Continuous infusion: Elderly, debilitated, ASA-PS 3 or 4: Use 80% of healthy adult dose; reduce dose after adequate sedation established and adjust to response (eg, evaluate frequently to use minimum dose for sedation). Daily interruption with retitration is recommended to minimize prolonged sedative effects (Jacobi, 2002).

Dosing: PediatricDosage must be individualized based on total body weight and titrated to the desired clinical effect; wait at least 3-5 minutes between dosage adjustments to clinically assess drug effects; smaller doses are required when used with narcotics; the following are general dosing guidelines (see “Abbreviations” section in front section for explanation of ASA-PS classes):

General anesthesia:

Induction: I.V.: Healthy children 3-16 years, ASA-PS 1 or 2: 2.5-3.5 mg/kg over 20-30 seconds; use a lower dose for children ASA-PS 3 or 4

Maintenance: I.V. infusion: Healthy children 2 months to 16 years, ASA-PS 1 or 2: Initial: 200-300 mcg/kg/minute; after 30 minutes, if clinical signs of light anesthesia are absent, decrease the infusion rate; usual infusion rate: 125-150 mcg/kg/minute (range: 125-300 mcg/kg/minute); children ≤5 years may require larger infusion rates compared to older children

Calculations

- Propofol

Administration: I.V. Strict aseptic technique must be maintained in handling although a preservative has been added. Do not use if contamination is suspected. Do not administer through the same I.V. catheter with blood or plasma. Tubing and any unused portions of propofol vials should be discarded after 12 hours.

To reduce pain associated with injection, use larger veins of forearm or antecubital fossa; lidocaine I.V. (1 mL of a 1% solution) may also be used prior to administration or it may be added to propofol immediately before administration in a quantity not to exceed 20 mg lidocaine per 200 mg propofol. Do not use filter <5 micron for administration.

Administration: I.V. DetailpH: 7.0-8.5

Dietary ConsiderationsPropofol is formulated in an oil-in-water emulsion. If on parenteral nutrition, may need to adjust the amount of lipid infused. Propofol emulsion contains 1.1 kcal/mL. Soybean fat emulsion is used as a vehicle for propofol. Formulations also contain egg phosphatide and glycerol.

StorageStore between 4°C to 22°C (40°F to 72°F); refrigeration is not required. Do not freeze. Protect from light. If transferred to a syringe or other container prior to administration, use within 6 hours. If used directly from vial/prefilled syringe, use within 12 hours. Shake well before use. Do not use if there is evidence of separation of phases of emulsion.

ReconstitutionDoes not need to be diluted; however, propofol may be further diluted in 5% dextrose in water to a concentration of ≥2 mg/mL and is stable for 8 hours at room temperature.

CompatibilityStable in D_5W. Do not mix with other therapeutic agents prior to administration.

Y-site administration: Compatible I.V. solutions: D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5W, LR. **Compatible:** Acyclovir, alfentanil, aminophylline, ampicillin, atropine, aztreonam, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, cefazolin, cefoperazone, cefotaxime, cefotetan, cefoxitin, ceftizoxime, ceftriaxone, cefuroxime, chlorpromazine, cimetidine, cisplatin, clindamycin, cyclophosphamide, cyclosporine, cytarabine, dexamethasone sodium phosphate, dexmedetomidine, diphenhydramine, dobutamine, dopamine, doxycycline, droperidol, enalaprilat, ephedrine, epinephrine, esmolol, famotidine, fenoldopam, fentanyl, fluconazole, fluorouracil, furosemide, ganciclovir, glycopyrrolate, granisetron, haloperidol, heparin, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, ifosfamide, imipenem/cilastatin, inamrinone, insulin (regular), isoproterenol, ketamine, labetalol, levorphanol, lorazepam, magnesium sulfate, mannitol, meperidine, midazolam, milrinone, nafcillin, nalbuphine, naloxone, nitroglycerin, norepinephrine, ofloxacin, paclitaxel, pancuronium, pentobarbital, phenobarbital, phenylephrine, piperacillin, potassium chloride, prochlorperazine edisylate, propranolol, ranitidine, scopolamine, sodium bicarbonate, sodium nitroprusside, succinylcholine, sufentanil, thiopental, ticarcillin, ticarcillin/clavulanate potassium, vancomycin, vecuronium. **Incompatible:** Amikacin, amphotericin B, atracurium, calcium chloride, ciprofloxacin, diazepam, digoxin, doripenem, doxacurium, doxorubicin, gentamicin, levofloxacin, methotrexate, methylprednisolone sodium succinate, metoclopramide, minocycline, mitoxantrone, pantoprazole, phenytoin, tobramycin, verapamil. **Variable (consult detailed reference):** Ascorbic acid, ceftazidime, cisatracurium, doxacurium, lidocaine, morphine.

Compatibility in syringe: Compatible: Ondansetron, thiopental. **Note:** Manufacturers recommend that propofol not be mixed with any other therapeutic agents prior to administration.

ContraindicationsHypersensitivity to propofol or any component of the formulation; hypersensitivity to eggs, egg products, soybeans, or soy products

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: May rarely cause hypersensitivity, anaphylaxis, anaphylactoid reactions, angioedema, bronchospasm, and erythema; medications for the treatment of hypersensitivity reactions should be available for immediate use.

- Hypertriglyceridemia: Because propofol is formulated within a 10% fat emulsion, hypertriglyceridemia is an expected side effect. Patients who develop hypertriglyceridemia (eg, >500 mg/dL) are at risk of developing pancreatitis. Serum triglyceride levels should be obtained prior to initiation of therapy and every 3-7 days thereafter. Monitoring of serum triglycerides should especially be considered with therapy >48 hours with doses exceeding 50 mcg/kg/minute (Devlin, 2005). An alternative sedative agent should be employed if significant hypertriglyceridemia occurs. Use with caution in patients with preexisting hyperlipidemia as evidenced by increased serum triglyceride levels or serum turbidity.

- Hypotension: The major cardiovascular effect of propofol is hypotension especially if patient is hypovolemic or if bolus dosing is used. Hypotension may be substantial with a reduction in mean arterial pressure occasionally exceeding 30%. Use with caution in patients who are hemodynamically unstable, hypovolemic, or have abnormally low vascular tone (eg, sepsis).

- Injection-site reaction: Transient local pain may occur during I.V. injection; lidocaine 1% solution may be administered prior to administration or may be added to propofol immediately prior to administration to reduce pain associated with injection (see Administration).

- Myoclonus: Perioperative myoclonus (eg, convulsions and opisthotonos) has occurred with administration.

- Propofol-related infusion syndrome (PRIS): PRIS is a serious side effect with a high mortality rate characterized by dysrhythmia (eg, bradycardia or tachycardia), heart failure, hyperkalemia, lipemia, metabolic acidosis, and/or rhabdomyolysis or myoglobinuria with subsequent renal failure. Risk factors include poor oxygen delivery, sepsis, serious cerebral injury, and the administration of high doses of propofol (usually doses >83 mcg/kg/minute or >5 mg/kg/hour for >48 hours), but has also been reported following large dose, short-term infusions during surgical anesthesia. The onset of the syndrome is rapid, occurring within 4 days of initiation. The mechanism of the syndrome has yet to be determined. Alternate sedative therapy should be considered for patients with escalating doses of vasopressors or inotropes, when cardiac failure occurs during high-dose propofol infusion, when metabolic acidosis is observed, or in whom lengthy and/or high-dose sedation is needed (Jacobi, 2002; Corbett, 2008).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiac disease (ejection fraction <50%) or hypotension; may have more profound adverse cardiovascular responses to propofol.

- Increased intracranial pressure: Use with caution in patients with increased intracranial pressure or impaired cerebral circulation; substantial decreases in mean arterial pressure and subsequent decreases in cerebral perfusion pressure may occur; consider continuous infusion or administer as a slow bolus.

- Infection risk: Propofol vials and prefilled syringes have the potential to support the growth of various microorganisms despite product additives intended to suppress microbial growth. To limit the potential for contamination, strictly adhere to recommendations in product labeling for handling and administering propofol.

- Pancreatitis: Use with caution in patients with preexisting pancreatitis; use of propofol may exacerbate this condition.

- Respiratory disease: Use with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients with a history of epilepsy or seizures; seizure may occur during recovery phase

Concurrent drug therapy issues:

- Opiates: Concomitant use may lead to increased sedative or anesthetic effects of propofol, more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output. Lower doses of propofol may be needed. In addition, fentanyl may cause serious bradycardia when used with propofol in pediatric patients. Alfentanil use with propofol has precipitated seizure activity in patients without any history of epilepsy.

Special populations:

- ASA-PS (American Society of Anesthesiologists - Physical Status) 3/4 patients: Use a lower induction dose, a slower maintenance rate of administration, and avoid rapidly delivered boluses in ASA-PS 3/4 patients to reduce the incidence of unwanted cardiorespiratory depressive events.

- Debilitated patients: Use a lower induction dose, a slower maintenance rate of administration, and avoid rapidly delivered boluses in debilitated patients to reduce the incidence of unwanted cardiorespiratory depressive events.

- Elderly: Use a lower induction dose, a slower maintenance rate of administration, and avoid rapidly delivered boluses in the elderly to reduce the incidence of unwanted cardiorespiratory depressive events.

- Pediatrics: Safety and efficacy have not been established in pediatric intensive care unit patients; concurrent use of fentanyl and propofol in pediatric patients may result in bradycardia.

- Pregnancy: Propofol should only be used in pregnancy if clearly needed. Not recommended for use in obstetrics, including cesarean section deliveries.

Dosage form specific issues:

- Benzyl alcohol: Some products may contain benzyl alcohol which has been associated with the "gasping syndrome" in neonates.

- Edetate disodium: Some formulations contain edetate disodium which may lead to decreased zinc levels in patients with prolonged therapy (>5 days) or a predisposition to zinc deficiency (eg, burns, diarrhea, or sepsis). A holiday from propofol infusion should take place after 5 days of therapy to allow for evaluation and necessary replacement of zinc.

- Sulfites: Some formulations may contain sulfites.

Other warnings/precautions:

- Abrupt discontinuation: Avoid abrupt discontinuation prior to weaning or daily wake up assessments. Abrupt discontinuation can result in rapid awakening, anxiety, agitation, and resistance to mechanical ventilation; wean the infusion rate so the patient awakens slowly. Discontinue opioids and paralytic agents prior to weaning. Long-term infusions can result in some tolerance; taper propofol infusions to prevent withdrawal.

- Analgesic supplementation: Propofol lacks analgesic properties; pain management requires specific use of analgesic agents, at effective dosages, propofol must be titrated separately from the analgesic agent.

- Experienced personnel: Use requires careful patient monitoring, should only be used by experienced personnel who are not actively engaged in the procedure or surgery. If used in a nonintubated and/or nonmechanically-ventilated patient, qualified personnel and appropriate equipment for rapid institution of respiratory and/or cardiovascular support must be immediately available. Use to induce moderate (conscious) sedation in patients warrants monitoring equivalent to that seen with deep anesthesia.

Pregnancy Risk FactorB

Pregnancy ConsiderationsPropofol should only be used in pregnancy if clearly needed. Propofol is not recommended for obstetrics, including cesarean section deliveries. Propofol crosses the placenta and may be associated with neonatal CNS and respiratory depression.

LactationEnters breast milk/not recommended

Adverse Reactions

>10%:

Cardiovascular: Hypotension (children 17%; adults 3% to 26%)

Central nervous system: Movement (children 17%; adults 3% to 10%)

Local: Injection site burning, stinging, or pain (children 10%; adults 18%)

Respiratory: Apnea lasting 30-60 seconds (children 10%; adults 24%), apnea lasting >60 seconds (children 5%; adults 12%)

1% to 10%:

Cardiovascular: Hypertension (children 8%), arrhythmia (1% to 3%), bradycardia (1% to 3%), cardiac output decreased (1% to 3%; concurrent opioid use increases incidence), tachycardia (1% to 3%)

Dermatologic: Pruritus (1% to 3%), rash (children 5%; adults 1% to 3%)

Endocrine & metabolic: Hypertriglyceridemia (3% to 10%)

Respiratory: Respiratory acidosis during weaning (3% to 10%)

<1%, postmarketing, and/or case reports: Agitation, amblyopia, anaphylaxis, anaphylactoid reaction, anticholinergic syndrome, asystole, atrial arrhythmia, bigeminy, cardiac arrest, chills, cough, dizziness, delirium, discoloration (green [urine, hair, or nailbeds]), extremity pain, fever, flushing, hemorrhage, hypersalivation, hypertonia, hypomagnesemia, hypoxia, infusion site reactions (including pain, swelling, blisters and/or tissue necrosis following accidental extravasation); laryngospasm, leukocytosis, lung function decreased, myalgia, myoclonia (rarely including convulsions and opisthotonos), nausea, pancreatitis, paresthesia, phlebitis, postoperative unconsciousness with or without increase in muscle tone, premature atrial contractions, premature ventricular contractions, pulmonary edema, propofol-related infusion syndrome (see Note), rhabdomyolysis, somnolence, syncope, thrombosis, urine cloudy, vision abnormality, wheezing

Note: Propofol-related infusion syndrome (PRIS) is a serious side effect with a high mortality rate characterized by dysrhythmia (eg, bradycardia or tachycardia), heart failure, hyperkalemia, lipemia, metabolic acidosis, and/or rhabdomyolysis or myoglobinuria with subsequent renal failure.

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2A6 (minor), 2B6 (major), 2C9 (major), 2C19 (minor), 2D6 (minor), 2E1 (minor), 3A4 (minor); **Inhibits** CYP1A2 (moderate), 2C9 (weak), 2C19 (moderate), 2D6 (weak), 2E1 (weak), 3A4 (strong)

Drug Interactions

Alfentanil: May enhance the adverse/toxic effect of Propofol. Specifically the development of opisthotonus (severe hyperextension and spasticity resulting in arching or bridging position) and/or grand mal seizures. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Strong): May decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

Ropivacaine: Propofol may increase the serum concentration of Ropivacaine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Edetate disodium, an ingredient of propofol emulsion, may lead to decreased zinc levels in patients on prolonged therapy (>5 days) or those predisposed to deficiency (burns, diarrhea, and/or major sepsis).

Monitoring ParametersCardiac monitor, blood pressure, oxygen saturation (during monitored anesthesia care sedation), arterial blood gas (with prolonged infusions). With prolonged infusions (eg, ICU sedation), monitor for metabolic acidosis, hyperkalemia, rhabdomyolysis or elevated CPK, hepatomegaly, and progression of cardiac and renal failure.

ICU sedation: Assess and adjust sedation according to scoring system; assess CNS function daily. Serum triglyceride levels should be obtained prior to initiation of therapy and every 3-7 days thereafter, especially if receiving for >48 hours with doses exceeding 50 mcg/kg/minute (Devlin, 2005); use intravenous port opposite propofol infusion or temporarily suspend infusion and flush port prior to blood draw.

Diprivan®: Monitor zinc levels in patients predisposed to deficiency (burns, diarrhea, major sepsis) or after 5 days of treatment.

Nursing: Physical Assessment/MonitoringDosage and rate of administration should be individualized and titrated to the desired effect, according to relevant clinical factors, premedication, concomitant medications, age, and general condition of patient. Assess other medications for effectiveness and safety. Other drugs that cause CNS depression may increase CNS depression induced by propofol (monitor and adjust dosage as necessary). Continuous monitoring of vital signs, cardiac and respiratory status, and level of sedation is mandatory during infusion and until full consciousness is regained. Safety precautions must be maintained until patient is fully alert. Propofol is an anesthetic; pain must be treated with appropriate analgesic agents. Do not discontinue abruptly (may result in rapid awakening associated with anxiety, agitation, and resistance to mechanical ventilation). Titrate infusion rate so patient awakes slowly. **Note:** After long-term administration, it will take longer for reduction of propofol levels than if propofol is used for short-term anesthesia. For long-term use, monitor fluid levels (intake and output) during and following infusion (urine will be green). Reposition patient and provide appropriate skin care, mouth care, and care of patient's eyes every 2-3 hours while sedated. Provide appropriate emotional and sensory support (auditory and environmental).

Monitoring: Lab TestsWith prolonged infusions (eg, ICU sedation), arterial blood gases, potassium, CPK, AST and ALT, BUN, creatinine.

Serum triglyceride levels should be obtained prior to initiation of therapy (ICU setting) and every 3-7 days thereafter, especially if receiving for >48 hours with doses exceeding 50 mcg/kg/minute (Devlin, 2005); use intravenous port opposite propofol infusion or temporarily suspend infusion and flush port prior to blood draw.

Diprivan®: Monitor zinc levels in patients predisposed to deficiency (burns, diarrhea, major sepsis) or after 5 days of treatment.

Patient EducationThis is an anesthetic. Patient education should be appropriate to individual situation. With long-term use appropriate emotional and sensory support is strongly recommended. Following return of consciousness, do not attempt to change position or rise from bed without assistance. Flu-like symptoms (chills, fever, body aches) have been reported for up to 3 days following receiving medication; contact prescriber if symptoms occur. Report immediately any pounding or unusual heartbeat, respiratory difficulty, or acute dizziness. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, emulsion: 10 mg/mL (20 mL, 50 mL, 100 mL) [products may contain egg lecithin, and soybean oil; may contain benzyl alcohol, sodium benzoate, or sodium metabisulfite]

Diprivan®: 10 mg/mL (20 mL, 50 mL, 100 mL) [contains egg lecithin, soybean oil, and disodium edetate]

Generic AvailableYes

ManufacturerAstraZeneca Pharmaceuticals LP

Mechanism of ActionPropofol is a sterically hindered, alkyl-phenolic compound with intravenous general anesthetic properties. The drug is unrelated to any of the currently used barbiturate, opioid, benzodiazepine, arylcyclohexylamine, or imidazole intravenous anesthetic agents.

Pharmacodynamics/Kinetics

Onset of action: Anesthetic: Bolus infusion (dose dependent): 9-51 seconds (average 30 seconds)

Duration (dose and rate dependent): 3-10 minutes

Distribution: V_d: 2-10 L/kg; after a 10-day infusion, V_d approaches 60 L/kg; decreased in the elderly

Protein binding: 97% to 99%

Metabolism: Hepatic to water-soluble sulfate and glucuronide conjugates (~50%)

Half-life elimination: Biphasic: Initial: 40 minutes; Terminal: 4-7 hours (after 10-day infusion, may be up to 1-3 days)

Excretion: Urine (~88% as metabolites, 40% as glucuronide metabolite); feces (<2%)

Related Information

- Status Epilepticus

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive CNS depression and respiratory depression; monitor and adjust dosages as needed

Cardiovascular Considerations**Hemodynamic effects:** The major cardiovascular effect of propofol is hypotension especially if patient is hypovolemic or if bolus dosing is used. Hypotension may be substantial with a reduction in mean arterial pressure occasionally exceeding

30%. Propofol may also exert a direct negative inotropic effect in nonfailing and failing myocardium especially with concurrent opioid use (eg, fentanyl). In mechanically ventilated patients, the degree of negative inotropic effects may be exaggerated if positive pressure ventilation is employed. Use caution in patients with ejection fraction (EF) <50%. Bradycardia may also occur with administration especially with concurrent fentanyl administration.

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International Brand NamesAbbofol (PL); Anepol (KP, TH); Anesvan (TH); Dipripol (PL); Diprivan (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HU, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PK, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SR, SV, SY, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Diprofen (TW); Diprofol (IL); Disoprivan (CH, HR); Fresofol (ID, KP, MY, NZ, PH, TW); Fresofol MCT/LCT (MY, TH); Gobbifol (AR); Indofol (MX); IV-Pro (PH); Lipuro (PH); Plofed (PL); Pofol (KP, SG, TH); Propofol (PL); Propofol Fresenius (PL); Propofol-Lipuro (CO); Propovan (PY); Propoven (EE); Provive (KP); Recofol (CH, HU, ID, IL, MX, SG, TH); Safol (ID)

Propoxyphene and Acetaminophen

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Darvocet-N® may be confused with Darvon-N®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Duplicate therapy issues: This product contains acetaminophen, which may be a component of other combination products. Do not exceed the maximum recommended daily dose of acetaminophen.

Pronunciation(proe POKS i feen & a seet a MIN oh fen)

U.S. Brand NamesBalacet 325™; Darvocet A500®; Darvocet-N® 100; Darvocet-N® 50

Canadian Brand NamesDarvocet-N® 100; Darvocet-N® 50

Pharmacologic CategoryAnalgesic Combination (Opioid)

Use: Labeled IndicationsManagement of mild to moderate pain

Use: DentalManagement of postoperative pain

Dosing: Adults

Pain management: Oral:

Darvocet A500®, Darvocet-N® 100: 1 tablet every 4 hours as needed; maximum: 600 mg propoxyphene napsylate/day

Darvocet-N® 50: 1-2 tablets every 4 hours as needed; maximum: 600 mg propoxyphene napsylate/day

Propoxyphene hydrochloride 65 mg and acetaminophen 650 mg: 1 tablet every 4 hours as needed; maximum: 390 mg/day propoxyphene hydrochloride, 4 g/day acetaminophen)

Note: Formulations contain significant amounts of acetaminophen; intake should be limited to <4 g acetaminophen/day (less in patients with hepatic impairment/ethanol abuse)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentSerum concentrations of propoxyphene may be increased or elimination may be delayed; specific dosing recommendations not available.

Dosing: Hepatic ImpairmentSerum concentrations of propoxyphene may be increased or elimination may be delayed; specific dosing recommendations not available.

Administration: OralShould be administered with water on an empty stomach.

Dietary ConsiderationsMay be taken with food if gastrointestinal distress occurs.

StorageStore at controlled room temperature.

RestrictionsC-IV

ContraindicationsHypersensitivity to propoxyphene, acetaminophen, or any component of the formulation

Allergy Considerations

- Acetaminophen Allergy/Hypersensitivity
- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

• Drug-related deaths: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

• CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

• Drug-related deaths: **[U.S. Boxed Warning]: When given in excessive doses, either alone or in combination with other CNS depressants (including alcohol), propoxyphene is a major cause of drug-related deaths; recommended dosage must not be exceeded and alcohol intake should be limited.**

• Hepatotoxicity: Acetaminophen may cause severe hepatic toxicity on acute overdose; in addition, chronic daily dosing in adults has resulted in liver damage in some patients.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Depression: Should not be prescribed in patients who severely depressed or suicidal.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Ethanol use: Use with caution in patients with alcoholic liver disease; consuming ≥3 alcoholic drinks/day may increase the risk of liver damage.
- G6PD deficiency: Use with caution in patients with known G6PD deficiency.
- Hepatic impairment: Use propoxyphene with caution in patients with hepatic impairment; consider dosing adjustment.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Renal impairment: Use propoxyphene with caution in patients with renal impairment; consider dosing adjustment.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Use propoxyphene with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.
- Pediatrics: Safety and efficacy have not been established in children of this combination product.

Other warnings/precautions:

- Dosage limit: Limit acetaminophen dose to <4 g/day.
- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsThe elderly may be particularly susceptible to the CNS depressant and constipating effects of narcotics; do not exceed 4 g/day of acetaminophen. See Warnings/Precautions and Dosage. Propoxyphene is not considered the analgesic of choice in the elderly patient when mild-to-moderate pain requires a narcotic analgesic. This is due to the higher incidence of adverse CNS effects seen in this population group. The addiction potential is also a concern; avoid use, if possible.

Pregnancy Risk FactorC

Pregnancy ConsiderationsWithdrawal symptoms have been reported in the neonate following propoxyphene use during pregnancy. Teratogenic effects have also been noted in case reports. Opioid analgesics are considered pregnancy risk factor D if used for prolonged periods or in large doses near term.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsPropoxyphene, norpropoxyphene and acetaminophen are excreted in breast milk. The AAP considers propoxyphene and acetaminophen to be “compatible” with breast-feeding.

Adverse ReactionsSee individual agents.

Metabolism/Transport Effects

Propoxyphene: **Inhibits** CYP2C9 (weak), 2D6 (weak), 3A4 (weak)

Acetaminophen: **Substrate** (minor) of CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A4; **Inhibits** CYP3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Beta-Blockers: Propoxyphene may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Carteolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

CarBAMazepine: Propoxyphene may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Cholestyramine Resin: May decrease the absorption of Acetaminophen. Effect is minimal if cholestyramine is administered 1 hour after acetaminophen. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Imatinib: May increase the serum concentration of Acetaminophen. *Risk D: Consider therapy modification*

Isoniazid: May enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

MAO Inhibitors: Propoxyphene may enhance the adverse/toxic effect of MAO Inhibitors. Specifically, the risk of serotonin syndrome or other serotonergic adverse events may be increased. *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Tricyclic Antidepressants: Propoxyphene may enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Acetaminophen may enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Propoxyphene may decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Based on **propoxyphene** component:

Ethanol: Avoid or limit ethanol (may increase CNS depression). Watch for sedation.

Food: May decrease rate of absorption, but may slightly increase bioavailability.

Based on **acetaminophen** component:

Ethanol: Excessive intake of ethanol may increase the risk of acetaminophen-induced hepatotoxicity. Avoid ethanol or limit to <3 drinks/day.

Food: Rate of absorption may be decreased when given with food.

Herb/Nutraceutical: St John's wort may decrease acetaminophen levels.

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, 50/325:

Darvocet-N® 50: Propoxyphene napsylate 50 mg and acetaminophen 325 mg

Tablet, 65/650: Propoxyphene hydrochloride 65 mg and acetaminophen 650 mg

Tablet, 100/325:

Balacet 325™: Propoxyphene napsylate 100 mg and acetaminophen 325 mg

Tablet, 100/500: Propoxyphene hydrochloride 100 mg and acetaminophen 500 mg

Darvocet A500®: Propoxyphene napsylate 100 mg and acetaminophen 500 mg

Tablet, 100/650: Propoxyphene napsylate 100 mg and acetaminophen 650 mg

Darvocet-N® 100: Propoxyphene napsylate 100 mg and acetaminophen 650 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Balacet 325)

100-325 mg (30): $86.00

Tablets (Darvocet-N 100)

100-650 mg (30): $59.11

Tablets (Darvocet-N 50)

50-325 mg (30): $21.99

Tablets (Propoxyphene N-APAP)

50-325 mg (30): $31.34

100-500 mg (30): $38.99

100-650 mg (30): $12.99

Tablets (Propoxyphene-APAP)

65-650 mg (30): $16.99

Mechanism of Action

Propoxyphene is a weak narcotic analgesic which acts through binding to opiate receptors to inhibit ascending pain pathways

Propoxyphene, as with other narcotic (opiate) analgesics, blocks pain perception in the cerebral cortex by binding to specific receptor molecules (opiate receptors) within the neuronal membranes of synapses. This binding results in a decreased synaptic chemical transmission throughout the CNS thus inhibiting the flow of pain sensations into the higher centers. Mu and kappa are the two subtypes of the opiate receptor to which propoxyphene binds to cause analgesia.

Acetaminophen inhibits the synthesis of prostaglandins in the CNS and peripherally blocks pain impulse generation; produces antipyresis from inhibition of hypothalamic heat-regulating center

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Acetaminophen
- Propoxyphene

Pharmacotherapy PearlsSome studies have found no significant difference in pain relief between propoxyphene and aspirin or acetaminophen.

Dental Health Professional ConsiderationsPropoxyphene is a narcotic analgesic and shares many properties including addiction liability. The acetaminophen component requires use with caution in patients with alcoholic liver disease.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness, drowsiness, insomnia, and paradoxical excitement are common; may cause nervousness, restlessness, confusion; may rarely cause depression or hallucinations

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation as well as increase their serum levels; monitor for altered clinical response or preferably, use a different analgesic

Index TermsAcetaminophen and Propoxyphene; Propoxyphene Hydrochloride and Acetaminophen; Propoxyphene Napsylate and Acetaminophen

References

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“Drugs for Pain,” *Med Lett Drugs Ther*, 2000, 42(1085):73-8. [PubMed 10951654]

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

Rathmell JP, Viscomi CM, and Ashburn MA, “Management of Nonobstetric Pain During Pregnancy and Lactation,” *Anesth Analg*, 1997, 85(5):1074-87.[PubMed 9356103]

Propoxyphene, Aspirin, and Caffeine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Darvon® may be confused with Devrom®, Diovan®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(proe POKS i feen, AS pir in, & KAF een)

U.S. Brand NamesDarvon® Compound [DSC]

Pharmacologic CategoryAnalgesic Combination (Opioid)

Use: Labeled IndicationsTreatment of mild-to-moderate pain

Use: DentalTreatment of mild-to-moderate pain

Dosing: Adults**Pain:** Oral: One capsule (providing propoxyphene 65 mg) every 4 hours as needed; maximum propoxyphene 390 mg/day. This will also provide aspirin 389 mg and caffeine 32.4 mg per capsule.

Dosing: ElderlyRefer to adult dosing. Consider increasing dosing interval.

Dosing: Renal ImpairmentSerum concentrations of propoxyphene may be increased or elimination may be delayed; specific dosing recommendations not available. Avoid use with Cl_{cr} <10 mL/minute.

Dosing: Hepatic ImpairmentSerum concentrations or propoxyphene may be increased or elimination may be delayed; specific dosing recommendations not available.

Calculations

- Creatinine Clearance: Adults

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

RestrictionsC-IV

ContraindicationsHypersensitivity to propoxyphene, aspirin, caffeine, or any component of the formulation

Allergy Considerations

- Opioid Allergy/Hypersensitivity
- Salicylate Allergy/Sensitivity

Warnings/Precautions

Boxed warnings:

- Drug-related deaths: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Drug-related deaths: **[U.S. Boxed Warning]: When given in excessive doses, either alone or in combination with other CNS depressants (including alcohol), propoxyphene is a major cause of drug-related deaths; recommended dosage must not be exceeded and alcohol intake should be limited.**

- Salicylate sensitivity: Patients with sensitivity to tartrazine dyes, nasal polyps, and asthma may have an increased risk of salicylate sensitivity.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.

- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.

- Bleeding disorders: Use aspirin with caution in patients with platelet and bleeding disorders.

- Depression: Should not be prescribed in patients who severely depressed or suicidal.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Ethanol use: Heavy ethanol use (>3 drinks/day) can increase bleeding risks of aspirin.

- Gastrointestinal disease: Use aspirin with caution in patients with erosive gastritis or peptic ulcer disease.

- Hepatic impairment: Use propoxyphene with caution in patients with hepatic impairment; consider dosing adjustment.

- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.

- Renal impairment: Use propoxyphene with caution in patients with renal impairment; consider dosing adjustment.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use propoxyphene with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.

- Pediatrics: Safety and efficacy have not been established in children of this combination product. Aspirin should be avoided in children (<16 years of age) with viral infections (chickenpox or flu symptoms), with or without fever, due to a potential association with Reye's syndrome.

- Surgical patients: ASA should be avoided (if possible) in surgical patients for 1-2 weeks prior to surgery, to reduce the risk of excessive bleeding.

Other warnings/precautions:

- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Pregnancy Risk FactorC

Pregnancy ConsiderationsWithdrawal symptoms have been reported in the neonate following propoxyphene use during pregnancy. Teratogenic effects have also been noted in case reports. Opioid analgesics are considered pregnancy risk factor D if used for prolonged periods or in large doses near term. Full doses of aspirin during pregnancy may lead to adverse effects in the fetus and mother; exposure late in pregnancy may lead to premature closure of the ductus arteriosus. Moderate amounts of dietary caffeine during pregnancy are not expected to cause harm to the fetus; use of high doses are not recommended.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsPropoxyphene, norpropoxyphene, aspirin, and caffeine are excreted in breast milk. The AAP recommends that aspirin be used “with caution” during breast-feeding; propoxyphene and caffeine (moderate intake) are considered “compatible.”

Adverse ReactionsSee individual agents for Propoxyphene and Aspirin.

Metabolism/Transport EffectsSee individual agents.

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alendronate: Aspirin may enhance the adverse/toxic effect of Alendronate. Specifically gastrointestinal adverse events. *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Beta-Blockers: Propoxyphene may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Carteolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

CarBAMazepine: Propoxyphene may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Heparin: Aspirin may enhance the anticoagulant effect of Heparin. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Ketorolac: May enhance the adverse/toxic effect of Aspirin. *Risk X: Avoid combination*

MAO Inhibitors: Propoxyphene may enhance the adverse/toxic effect of MAO Inhibitors. Specifically, the risk of serotonin syndrome or other serotonergic adverse events may be increased. *Risk X: Avoid combination*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: May decrease the metabolism of Caffeine. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Ofloxacin; Sparfloxacin; Trovafloxacin. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Regadenoson: Caffeine may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Tiludronate: Aspirin may decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Propoxyphene may enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Propoxyphene may decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsBased on **propoxyphene** component:

Ethanol: Avoid or limit ethanol (may increase CNS depression). Watch for sedation.

Food: May decrease rate of absorption, but may slightly increase bioavailability.

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule (Darvon® Compound 65): Propoxyphene hydrochloride 65 mg, aspirin 389 mg, and caffeine 32.4 mg [DSC]

Generic AvailableNo

ManufactureraaiPharma

Mechanism of ActionPropoxyphene is a weak narcotic analgesic which acts through binding to opiate receptors to inhibit ascending pain pathways. Propoxyphene, as with other narcotic (opiate) analgesics, blocks pain perception in the cerebral cortex by binding to specific receptor molecules (opiate receptors) within the neuronal membranes of synapses. This binding results in a decreased synaptic chemical transmission throughout the CNS thus inhibiting the flow of pain sensations into the higher centers. Mu and kappa are the two subtypes of the opiate receptor to which propoxyphene binds to cause analgesia.

Aspirin inhibits prostaglandin synthesis, acts on the hypothalamus heat-regulating center to reduce fever, blocks prostaglandin synthetase action which prevents formation of the platelet-aggregating substance thromboxane A_2.

Caffeine is a CNS stimulant; use with propoxyphene and aspirin increases the level of analgesia provided by each agent.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Aspirin
- Propoxyphene

Dental Health Professional ConsiderationsPropoxyphene is a narcotic analgesic and shares many properties including addiction liability. The aspirin component could have anticoagulant effects and could possibly affect bleeding times.

There is no scientific evidence to warrant discontinuance of aspirin prior to dental surgery. Patients taking one aspirin tablet daily as an antithrombotic and who require dental surgery should be given special consideration in consultation with the physician before removal of the aspirin relative to prevention of postoperative bleeding.

The Food and Drug Administration (FDA), has issued a letter updating information and considerations regarding the use of ibuprofen (400 mg doses) in patients who are taking low dose aspirin (81 mg, immediate release; not enteric coated) for cardioprotection and stroke prevention. Ibuprofen, at these doses, may interfere with aspirin’s antiplatelet effect depending upon when it is administered. Patients initiated on aspirin first (for ~1 week) then ibuprofen (400 mg 3 times/day for 10 days) seem to maintain aspirin’s platelet effect (Cryer B, 2005). Ibuprofen has the greatest impact on aspirin if administered less than 8 hours before aspirin (Catella-Lawson F, 2001).

Patients may require counseling about the appropriate timing of ibuprofen dosing in relationship to aspirin therapy. With occasional use of ibuprofen, a clinically-significant interaction with aspirin in unlikely. To avoid interference during chronic dosing, a single dose of ibuprofen should be taken 30-120 minutes after aspirin ingestion or at least 8 hours should elapse after ibuprofen dosing before giving aspirin (FDA, 2006; Catella-Lawson F, 2001).

The clinical implications of the interaction are unclear. There have not been any clinical endpoint studies conducted at this time. Avoidance of this interaction is potentially important because aspirin's vascular protection could be decreased or negated.

Other nonselective NSAIDs may have potential for a similar interaction with aspirin. Such has been described with naproxen (Capone ML, 2005). Acetaminophen does not appear to interfere with the antiplatelet effect of aspirin. Other clinical scenarios (use of smaller ibuprofen doses, other aspirin products, other doses of aspirin) have not been evaluated.

Additional information is available at: http://www.fda.gov/cder/drug/infopage/aspirin/default.htm

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Aspirin: As with all drugs which may affect hemostasis, bleeding is associated with aspirin. Hemorrhage may occur at virtually any site; risk is dependent on multiple variables including dosage, concurrent use of multiple agents which alter hemostasis, and patient susceptibility. Many adverse effects of aspirin are dose-related, and are rare at low dosages. Other serious reactions are idiosyncratic, related to allergy or individual sensitivity. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness, drowsiness, insomnia, and paradoxical excitement are common; may cause nervousness, restlessness, confusion; may rarely cause depression or hallucinations

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation as well as increase their serum levels; monitor for altered clinical response or preferably, use a different analgesic

Index TermsAspirin, Caffeine, and Propoxyphene; Caffeine, Propoxyphene, and Aspirin; Propoxyphene Hydrochloride, Aspirin, and Caffeine

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Propoxyphene

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Propoxyphene may be confused with proparacaine

Darvon® may be confused with Devrom®, Diovan®

Darvon-N® may be confused with Darvocet-N®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(proe POKS i feen)

U.S. Brand NamesDarvon-N®; Darvon®

Canadian Brand Names642® Tablet; Darvon-N®

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled IndicationsManagement of mild to moderate pain

Dosing: Adults**Pain management:** Oral:

Hydrochloride: 65 mg every 3-4 hours as needed for pain; maximum: 390 mg/day

Napsylate: 100 mg every 4 hours as needed for pain; maximum: 600 mg/day

Dosing: ElderlyPain management: Oral:

Hydrochloride: 65 mg every 4-6 hours as needed for pain

Napsylate: 100 mg every 4-6 hours as needed for pain

Dosing: Pediatric**Pain management:** Oral: Children: Doses for children are not well established; doses of the hydrochloride of 2-3 mg/kg/d divided every 6 hours have been used.

Dosing: Renal ImpairmentSerum concentrations of propoxyphene may be increased or elimination may be delayed. Avoid use in Cl_{cr} <10 mL/minute. Specific dosing recommendations not available for less severe impairment.

Not dialyzable (0% to 5%)

Dosing: Hepatic ImpairmentSerum concentrations of propoxyphene may be increased or elimination may be delayed. Specific dosing recommendations not available.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Opioid Agonist Conversion

Administration: OralShould be administered with glass of water on an empty stomach. Food may decrease rate of absorption, but may slightly increase bioavailability.

Dietary ConsiderationsMay administer with food if gastrointestinal distress occurs.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

RestrictionsC-IV

ContraindicationsHypersensitivity to propoxyphene or any component of the formulation

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

• Drug-related deaths: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

• CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Drug-related deaths: **[U.S. Boxed Warning]: When given in excessive doses, either alone or in combination with other CNS depressants (including alcohol), propoxyphene is a major cause of drug-related deaths; recommended dosage must not be exceeded and alcohol intake should be limited.**
- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Biliary tract impairment: Use with caution in patients with biliary tract dysfunction; acute pancreatitis may cause constriction of sphincter of Oddi.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Depression: Should not be prescribed in patients who severely depressed or suicidal.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment; consider dosing adjustment.
- Obesity: Use with caution in patients who are morbidly obese.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Renal impairment: Use with caution in patients with renal impairment; consider dosing adjustment.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precaution:

- Optimal regimen: An opioid-containing analgesic regimen should be tailored to each patient's needs and based upon the type of pain being treated (acute versus chronic), the route of administration, degree of tolerance for opioids (naive versus chronic user), age, weight, and medical condition. The optimal analgesic dose varies widely among patients; doses should be titrated to pain relief/prevention.
- Withdrawal: Concurrent use of agonist/antagonist analgesics may precipitate withdrawal symptoms and/or reduced analgesic efficacy in patients following prolonged therapy with mu opioid agonists. Abrupt discontinuation following prolonged use may also lead to withdrawal symptoms.

Geriatric ConsiderationsElderly may be particularly susceptible to the CNS depressant and constipating effects of narcotics. Propoxyphene is not considered the analgesic of choice in the elderly when mild to moderate pain requires a narcotic analgesic. This is due to the higher incidence of adverse CNS effects seen in the elderly population. Also a concern is the addiction potential in elderly; avoid use, if possible.

Pregnancy Risk FactorC/D (prolonged use)

Pregnancy ConsiderationsWithdrawal symptoms have been reported in the neonate following propoxyphene use during pregnancy. Teratogenic effects have also been noted in case reports. Opioid analgesics are considered pregnancy risk factor D if used for prolonged periods or in large doses near term.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsPropoxyphene and norpropoxyphene are excreted in breast milk.

Adverse ReactionsFrequency not defined.

Cardiovascular: Bundle branch block, hypotension

Central nervous system: Confusion, dizziness, dysphoria, drowsiness, fatigue, hallucinations, headache, increased intracranial pressure, lightheadedness, malaise, mental depression, nervousness, paradoxical CNS stimulation, paradoxical excitement and insomnia, restlessness, sedation, vertigo

Dermatologic: Rash, urticaria

Endocrine & metabolic: Decreased urinary 17-OHCS, hypoglycemia

Gastrointestinal: Abdominal pain, anorexia, biliary spasm, constipation, nausea, paralytic ileus, stomach cramps, vomiting, xerostomia

Genitourinary: Decreased urination, ureteral spasms

Hepatic: LFTs increased, jaundice

Neuromuscular & skeletal: Weakness

Ocular: Visual disturbances

Respiratory: Dyspnea

Miscellaneous: Histamine release, hypersensitivity reaction psychologic and physical dependence with prolonged use

Metabolism/Transport Effects**Inhibits** CYP2C9 (weak), 2D6 (weak), 3A4 (weak)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Beta-Blockers: Propoxyphene may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Carteolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

CarBAMazepine: Propoxyphene may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

MAO Inhibitors: Propoxyphene may enhance the adverse/toxic effect of MAO Inhibitors. Specifically, the risk of serotonin syndrome or other serotonergic adverse events may be increased. *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Tricyclic Antidepressants: Propoxyphene may enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Propoxyphene may decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol (may increase CNS depression). Watch for sedation.

Food: May decrease rate of absorption, but may slightly increase bioavailability.

Test InteractionsFalse-positive methadone test
Monitoring ParametersPain relief, respiratory and mental status, blood pressure
Reference Range

Therapeutic: Ranges published vary between laboratories and may not correlate with clinical effect

Therapeutic concentration: 0.1-0.4 mcg/mL (SI: 0.3-1.2 µmol/L)

Toxic: >0.5 mcg/mL (SI: >1.5 µmol/L)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness, cardio/respiratory and CNS status, adverse reactions and signs of overdose at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Patient EducationTake as directed; do not take a larger dose or more often than prescribed. Do not use alcohol, other prescription or OTC sedatives, tranquilizers, antihistamines, or pain medications without consulting prescriber. May cause dizziness, drowsiness, or impaired judgment; avoid driving or engaging in tasks requiring alertness until response to drug is known. If you experience vomiting or loss of appetite, frequent mouth care, small frequent meals, chewing gum, or sucking lozenges may help. Increased fluid intake, exercise, fiber in diet may help with constipation (if unresolved consult prescriber). Report unresolved nausea or vomiting, respiratory difficulty or shortness of breath, or unusual weakness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 65 mg

Darvon®: 65 mg

Tablet, as napsylate:

Darvon-N®: 100 mg

Generic AvailableYes: Capsule
Pricing: U.S. (www.drugstore.com)

Capsules (Darvon)

65 mg (30): $43.33

Capsules (Propoxyphene HCl)

65 mg (30): $15.99

Tablets (Darvon-N)

100 mg (30): $60.19

Mechanism of ActionPropoxyphene is a weak narcotic analgesic which acts through binding to opiate receptors to inhibit ascending pain pathways. Propoxyphene, as with other narcotic (opiate) analgesics, blocks pain perception in the cerebral cortex by binding to specific receptor molecules (opiate receptors) within the neuronal membranes of synapses. This binding results in a decreased synaptic chemical transmission throughout the CNS thus inhibiting the flow of pain sensations into the higher centers. Mu and kappa are the two subtypes of the opiate receptor which propoxyphene binds to cause analgesia.
Pharmacodynamics/Kinetics

Onset of action: 0.5-1 hour

Duration: 4-6 hours

Metabolism: Hepatic to active metabolite (norpropoxyphene) and inactive metabolites; first-pass effect

Half-life elimination: Adults: Parent drug: 6-12 hours; Norpropoxyphene: 30-36 hours

Excretion: Urine (primarily as metabolites)

Related Information

- Narcotic / Opioid Analgesics

Pharmacotherapy Pearls100 mg of napsylate = 65 mg of hydrochloride

Propoxyphene hydrochloride: Darvon®

Propoxyphene napsylate: Darvon-N®

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDizziness, drowsiness, insomnia, and paradoxical excitement are common; may cause nervousness, restlessness, confusion; may rarely cause depression or hallucinations
Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation as well as increase their serum levels; monitor for altered clinical response or preferably, use a different analgesic
Anesthesia and Critical Care Concerns/Other ConsiderationsEquivalent dosing: 100 mg of napsylate = 65 mg of hydrochloride
Index TermsDextropropoxyphene; Propoxyphene Hydrochloride; Propoxyphene Napsylate
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International Brand NamesAbalgin (DK, FI); Algifene (DE, PT); Antalvic (FR); Darvon (ES); Deprancol (ES); Depronal (BE, LU, NL); Depronal retard (CH); Develin (DE); Dexofen (SE); Dextropropoxifen ”Dak” (DK); Dextropropoxifeno Bouzen (AR); Distalgesic (SE); Doloxene (AE, AU, BH, CY, DK, EG, GB, IE, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SE, SY, YE); Lentadol (AR); Liberen (IT); Romidon (GR); Zideron (GR)

Propranolol and Hydrochlorothiazide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Inderide® may be confused with Inderal®

Pronunciation(proe PRAN oh lole & hye droe klor oh THYE a zide)
U.S. Brand NamesInderide®
Pharmacologic CategoryBeta Blocker, Nonselective; Diuretic, Thiazide
Use: Labeled IndicationsManagement of hypertension
Dosing: Adults

Hypertension: Oral: Dose is individualized; typical dosages of **hydrochlorothiazide**: 12.5-50 mg/day; initial dose of **propranolol** 80 mg/day

Note: Daily dose of tablet form should be divided into 2 daily doses; may be used to maximum dosage of up to 160 mg of propranolol; higher dosages would result in higher than optimal thiazide dosages.

Dosing: ElderlyRefer to adult dosing.
Allergy Considerations

- Beta-Blocker Allergy
- Thiazide/Thiazide-Related Diuretic Allergy

Geriatric ConsiderationsCombination products are not recommended for first-line therapy and divided doses of diuretics may increase the incidence of nocturia in the elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted for this combination. See individual agents.
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsPropranolol: **Substrate** of CYP1A2 (major), 2C19 (major), 2D6 (major), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2D6 (weak)
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alcohol (Ethyl): May decrease the serum concentration of Propranolol. Alcohol (Ethyl) may increase the serum concentration of Propranolol. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Fluvoxamine: May increase the serum concentration of Propranolol. Management: Use a lower initial propranolol dose and be cautious with propranolol dose titration. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Serotonin 5-HT1D Receptor Agonists: Propranolol may increase the serum concentration of Serotonin 5-HT1D Receptor Agonists. **Exceptions:** Almotriptan; Eletriptan; Frovatriptan; Naratriptan; SUMAtriptan; Zolmitriptan. *Risk D: Consider therapy modification*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Zileuton: May increase the serum concentration of Propranolol. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Propranolol hydrochloride 40 mg and hydrochlorothiazide 25 mg; propranolol hydrochloride 80 mg and hydrochlorothiazide 25 mg

Inderide®: 40/25: Propranolol hydrochloride 40 mg and hydrochlorothiazide 25 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Inderide)

40-25 mg (60): $96.92

80-25 mg (60): $117.80

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Hydrochlorothiazide
- Propranolol

Dental Health: Effects on Dental TreatmentNoncardioselective beta-blockers (ie, propranolol, nadolol) enhance the pressor response to epinephrine, resulting in hypertension and bradycardia. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution; epinephrine has interacted with nonselective beta-blockers to result in initial hypertensive episode followed by bradycardia
Mental Health: Effects on Mental StatusPropranolol may cause fatigue and malaise which are commonly mistaken for depression; may also cause dizziness, confusion, insomnia, or hallucinations
Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropic drugs may produce additive hypotensive effects; monitor blood pressure. May decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels. Cutaneous reactions, including Stevens-Johnson syndrome, have been reported with use of propranolol; use caution with lamotrigine or valproic combination as combined usage with propranolol has been associated with these reactions.
Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for propranolol and hydrochlorothiazide combination therapy may include improved compliance and synergistic reductions in blood pressure with an accompanied reduction in side effects. See Cardiovascular Considerations for individual agents.
Index TermsHydrochlorothiazide and Propranolol
References

Chobanian AV, Bakris GL, Black HR, et al, “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report,” *JAMA*, 2003, 289(19):2560-71. [PubMed 12748199]

Kaplan NM and Sever PS, “Combination Therapy: A Key to Comprehensive Patient Care,” *Am J Hypertens*, 1997, 10(7 Pt 2):127S. [PubMed 9231887]

Moser M and Black HR, “The Role of Combination Therapy in the Treatment of Hypertension,” *Am J Hypertens*, 1998, 11(6 Pt 2):73S-8S, 95S-100S.[PubMed 9655566]

International Brand NamesCiplar-H (IN)

Propranolol

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Propranolol may be confused with Pravachol®, Propulsid®

Inderal® may be confused with Adderall®, Enduron®, Enduronyl®, Imdur®, Imuran®, Inderide®, Isordil®, Toradol®

Inderal® 40 may be confused with Enduronyl® Forte

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Significant differences exist between oral and I.V. dosing. Use caution when converting from one route of administration to another.

International issues:

Inderal® may be confused with Indiaral® which is a brand name for loperamide in France

Pronunciation(proe PRAN oh lole)

U.S. Brand NamesInderal® [DSC]; Inderal® LA; InnoPran XL™

Canadian Brand NamesApo-Propranolol®; Dom-Propranolol; Inderal®; Inderal®-LA; Novo-Pranol; Nu-Propranolol; PMS-Propranolol; Propranolol Hydrochloride Injection, USP

Pharmacologic CategoryAntiarrhythmic Agent, Class II; Beta Blocker, Nonselective

Use: Labeled IndicationsManagement of hypertension; angina pectoris; pheochromocytoma; essential tremor; supraventricular arrhythmias (such as atrial fibrillation and flutter, AV nodal re-entrant tachycardias), ventricular tachycardias (catecholamine-induced arrhythmias, digoxin toxicity); prevention of myocardial infarction; migraine headache prophylaxis; symptomatic treatment of hypertrophic subaortic stenosis (hypertrophic obstructive cardiomyopathy)

Use: Unlabeled/InvestigationalTremor due to Parkinson's disease; ethanol withdrawal; aggressive behavior (not recommended for dementia-associated aggression), anxiety, schizophrenia; antipsychotic-induced akathisia; primary and secondary prophylaxis of variceal hemorrhage; acute panic; thyrotoxicosis; tetralogy of Fallot (TOF) hypercyanotic spells

Dosing: Adults

Akathisia (unlabeled use): Oral: 30-120 mg/day in 2-3 divided doses

Essential tremor: Oral: 40 mg twice daily initially; maintenance doses: Usually 120-320 mg/day

Hypertension: Initial: Oral: 40 mg twice daily; increase dosage every 3-7 days; usual dose: 120-240 mg divided in 2-3 doses/day; maximum daily dose: 640 mg; usual dosage range (JNC 7): 40-160 mg/day in 2 divided doses

Extended release formulations:

Inderal® LA: Initial: 80 mg once daily; usual maintenance: 120-160 mg once daily; maximum daily dose: 640 mg; usual dosage range (JNC 7): 60-180 mg/day once daily

InnoPran XL™: Initial: 80 mg once daily at bedtime; if initial response is inadequate, may be increased at 2-3 week intervals to a maximum dose of 120 mg

Hypertrophic subaortic stenosis: Oral: 20-40 mg 3-4 times/day

Inderal® LA: 80-160 mg once daily

Migraine headache prophylaxis: Oral: Initial: 80 mg/day divided every 6-8 hours; increase by 20-40 mg/dose every 3-4 weeks to a maximum of 160-240 mg/day given in divided doses every 6-8 hours; if satisfactory response not achieved within 6 weeks of starting therapy, drug should be withdrawn gradually over several weeks

Inderal® LA: Initial: 80 mg once daily; effective dose range: 160-240 mg once daily

Pheochromocytoma: Oral: 30-60 mg/day in divided doses

Post-MI mortality reduction: Oral: 180-240 mg/day in 3-4 divided doses

Stable angina: Oral: 80-320 mg/day in doses divided 2-4 times/day

Inderal® LA: Initial: 80 mg once daily; maximum dose: 320 mg once daily

Tachyarrhythmias:

Oral: 10-30 mg/dose every 6-8 hours

I.V.: 1-3 mg/dose slow IVP; repeat every 2-5 minutes up to a total of 5 mg; titrate initial dose to desired response

or

0.1 mg/kg divided into 3 equal doses given at 2-3 minute intervals. May repeat total dose in 2 minutes if necessary (ACLS guidelines, 2005)

Note: Once response achieved or maximum dose administered, additional doses should not be given for at least 4 hours.

Thyrotoxicosis (unlabeled use):

Oral: 10-40 mg/dose every 6 hours

I.V.: 1-3 mg/dose slow IVP as a single dose

Variceal hemorrhage prophylaxis (unlabeled use) (Garcia-Tsao, 2007): *Oral:*

Primary prophylaxis: Initial: 20 mg twice daily; adjust to maximal tolerated dose. **Note:** Risk factors for hemorrhage include Child-Pugh class B/C or variceal red wale markings on endoscopy.

Secondary prophylaxis: Initial: 20 mg twice daily; adjust to maximal tolerated dose

Dosing: Elderly

I.V.: Use caution; initiate at lower end of the dosing range.

Oral: Tachyarrhythmias: Initial: 10 mg twice daily; increase dosage every 3-7 days; usual dose range: 10-320 mg/day given in 1-2 divided doses. Refer to adult dosing for additional uses.

Dosing: Pediatric

Hypertension (unlabeled use):

Oral: Initial: 0.5-1 mg/kg/day in divided doses every 6-12 hours; increase gradually every 5-7 days; maximum: 16 mg/kg/24 hours

Migraine headache prophylaxis (unlabeled use): Oral: Initial: 2-4 mg/kg/day **or**

≤35 kg: 10-20 mg 3 times/day

>35 kg: 20-40 mg 3 times/day

Tachyarrhythmias (unlabeled use):

Oral: Initial: 0.5-1 mg/kg/day in divided doses every 6-8 hours; titrate dosage upward every 3-7 days; usual dose: 2-6 mg/kg/day; higher doses may be needed; do not exceed 16 mg/kg/day or 60 mg/day

I.V.: 0.01-0.1 mg/kg/dose slow IVP over 10 minutes; maximum dose: 1 mg for infants; 3 mg for children

Thyrotoxicosis (unlabeled use): Oral:

2 mg/kg/day, divided every 6-8 hours, titrate to effective dose

Adolescents: Refer to adult dosing.

Hypercyanotic spells (TOF) (unlabeled use):

Oral: Palliation: Initial: 1 mg/kg/day every 6 hours; if ineffective, may increase dose after 1 week by 1 mg/kg/day to a maximum of 5 mg/kg/day, if patient becomes refractory, may increase slowly to a maximum of 10-15 mg/kg/day. Allow 24 hours between dosing changes.

I.V.: 0.01-0.2 mg/kg/dose infused over 10 minutes; maximum dose: 5 mg

Dosing: Renal Impairment

Not dialyzable (0% to 5%); supplemental dose is not necessary.

Peritoneal dialysis effects: Supplemental dose is not necessary.

Dosing: Hepatic ImpairmentMarked slowing of heart rate may occur in chronic liver disease with conventional doses; low initial dose and regular heart rate monitoring.

Administration: I.V.I.V. dose is much smaller than oral dose. When administered acutely for cardiac treatment, monitor ECG and blood pressure. May administer by rapid infusion (I.V. push) at a rate of 1 mg/minute or by slow infusion over ~30 minutes. Necessary monitoring for surgical patients who are unable to take oral beta-blockers (prolonged ileus) has not been defined. Some institutions require monitoring of baseline and postinfusion heart rate and blood pressure when a patient's response to beta-blockade has not been characterized (ie, the patient's initial dose or following a change in dose). Consult individual institutional policies and procedures.

Administration: I.V. DetailpH: 2.8-3.5

Administration: OralDo not crush long-acting forms.

Dietary ConsiderationsTablets (immediate release) should be taken on an empty stomach; capsules (extended release) may be taken with or without food, but should always be taken consistently (with food or on an empty stomach)

Storage

Injection: Store at 20°C to 25°C (68°F to 77°F); protect from freezing or excessive heat. Once diluted, propranolol is stable for 24 hours at room temperature in D_5W or NS. Protect from light. Solution has a maximum stability at pH of 3 and decomposes rapidly in alkaline pH.

Capsule, tablet: Store at 20°C to 25°C (68°F to 77°F); protect from freezing or excessive heat. Protect from light and moisture.

CompatibilityStable in $D_5{}^1/_2NS$, D_5NS, D_5W, LR, ${}^1/_2NS$, NS.

Y-site administration: Compatible: Alteplase, gatifloxacin, heparin, hydrocortisone sodium succinate, inamrinone, linezolid, meperidine, milrinone, morphine, potassium chloride, propofol, tacrolimus, vitamin B complex with C. **Incompatible:** Amphotericin B cholesteryl sulfate complex, lansoprazole.

Compatibility in syringe: Compatible: Inamrinone, milrinone. **Incompatible:** HCO_3 .

Compatibility when admixed: Compatible: Dobutamine, verapamil. **Incompatible:** HCO_3 .

ContraindicationsHypersensitivity to propranolol, beta-blockers, or any component of the formulation; uncompensated congestive heart failure (unless the failure is due to tachyarrhythmias being treated with propranolol), cardiogenic shock, severe sinus bradycardia or heart block (2nd or 3rd degree), severe hyperactive airway disease (asthma or COPD)

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Concerns related to adverse events:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.
- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.
- Heart failure (HF): Use with caution in patients with compensated HF and monitor for a worsening of the condition (efficacy of propranolol in HF has not been demonstrated).
- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment required.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis.
- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).
- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.
- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.
- Renal impairment: Use with caution in patients with renal impairment; may have increased side effects.
- Thyrotoxicosis: Beta-blockade may mask signs of hyperthyroidism (eg, tachycardia). Abrupt discontinuation of beta-blockade may exacerbate symptoms of hyperthyroidism and may also induce thyroid storm. Alterations in thyroid-function tests may be observed.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents which decrease myocardial function (eg, ether, cyclopropane and trichloroethylene); avoid concurrent I.V. use of both agents.
- Calcium channel blockers (nondihydropyridines): Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered over 1-2 weeks to avoid acute tachycardia, hypertension, and/or ischemia.

Geriatric ConsiderationsSince bioavailability increased in about twofold in elderly patients, geriatrics may require lower maintenance doses. Also, as serum and tissue concentrations increase beta$_1$ selectivity diminishes. Beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults due to alterations in the beta-adrenergic autonomic system. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (ie, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20%

to 50% in elderly populations. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults. Due to propranolol's CNS penetration and nonselective action, it may not be the beta-blocker of choice for use in elderly.

Pregnancy Risk FactorC (manufacturer); D (2nd and 3rd trimesters - expert analysis)

Pregnancy ConsiderationsEmbryotoxicity has been observed in some animal studies. Propranolol crosses the placenta. Beta-blockers have been associated with bradycardia, hypotension, and IUGR. IUGR is probably related to maternal hypertension. Available evidence suggests beta-blockers are generally safe during pregnancy (JNC 7). Neonatal hypoglycemia, respiratory depression and congenital abnormalities have been reported following maternal use of beta-blockers.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsPropranolol is excreted in breast milk and breast-feeding is considered compatible by the AAP. It is recommended that the infant be monitored for signs or symptoms of beta-blockade (hypotension, bradycardia, etc) with long-term use.

Adverse ReactionsFrequency not defined.

Cardiovascular: Angina, arterial insufficiency, AV conduction disturbance increased, bradycardia, cardiogenic shock, CHF, hypotension, impaired myocardial contractility, mesenteric arterial thrombosis (rare), Raynaud's syndrome, syncope

Central nervous system: Amnesia, catatonia, cognitive dysfunction, confusion, depression, dizziness, emotional lability, fatigue, hallucinations, hypersomnolence, insomnia, lethargy, lightheadedness, psychosis, vertigo, vivid dreams

Dermatologic: Alopecia, contact dermatitis, cutaneous ulcers, eczematous eruptions, erythema multiforme, exfoliative dermatitis, hyperkeratosis, nail changes, oculomucocutaneous reactions, pruritus, psoriasiform eruptions, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, ulcers, ulcerative lichenoid, urticaria

Endocrine & metabolic: Hyper-/hypoglycemia, hyperkalemia, hyperlipidemia

Gastrointestinal: Anorexia, cramping, constipation, diarrhea, ischemic colitis, nausea, stomach discomfort, vomiting

Genitourinary: Impotence, interstitial nephritis (rare), oliguria (rare), Peyronie's disease, proteinuria (rare)

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenia, thrombocytopenic purpura

Hepatic: Alkaline phosphatase increased, transaminases increased

Neuromuscular & skeletal: Arthropathy, carpal tunnel syndrome (rare), myotonus, paresthesia, polyarthritis, weakness

Ocular: Hyperemia of the conjunctiva, mydriasis, visual acuity decreased, visual disturbances, xerophthalmia

Renal: BUN increased

Respiratory: Bronchospasm, dyspnea, laryngospasm, pharyngitis, pulmonary edema, respiratory distress, wheezing

Miscellaneous: Anaphylactic/anaphylactoid allergic reaction, cold extremities, lupus-like syndrome (rare)

Metabolism/Transport Effects**Substrate** of CYP1A2 (major), 2C19 (minor), 2D6 (major), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alcohol (Ethyl): May decrease the serum concentration of Propranolol. Alcohol (Ethyl) may increase the serum concentration of Propranolol. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C:*

Monitor therapy

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Fluvoxamine: May increase the serum concentration of Propranolol. Management: Use a lower initial propranolol dose and be cautious with propranolol dose titration. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Serotonin 5-HT1D Receptor Agonists: Propranolol may increase the serum concentration of Serotonin 5-HT1D Receptor Agonists. **Exceptions:** Almotriptan; Eletriptan; Frovatriptan; Naratriptan; SUMAtriptan; Zolmitriptan. *Risk D: Consider therapy modification*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Zileuton: May increase the serum concentration of Propranolol. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Ethanol may increase or decrease plasma levels of propranolol. Reports are variable and have shown both enhanced as well as inhibited hepatic metabolism (of propranolol). Caution advised with consumption of alcohol and monitor for heart rate and/or blood pressure changes.

Food: Propranolol serum levels may be increased if taken with food. Protein-rich foods may increase bioavailability; a change in diet from high carbohydrate/low protein to low carbohydrate/high protein may result in increased oral clearance.

Cigarette: Smoking may decrease plasma levels of propranolol by increasing metabolism.

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (american), gotu kola, licorice, yohimbe (may worsen hypertension). Avoid black cohosh, california poppy, coleus, garlic, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (have antihypertensive activity, may cause hypotension).

Monitoring ParametersAcute cardiac treatment: Monitor ECG, heart rate, and blood pressure with I.V. administration; heart rate and blood pressure with oral administration

Reference RangeTherapeutic: 50-100 ng/mL (SI: 190-390 nmol/L) at end of dose interval

Nursing: Physical Assessment/MonitoringAssess potential for adverse interactions with other pharmacological agents or herbal products patient may be taking (eg, cardiac medications, antihypertensives, antimalarials, antipsychotics, or antidiabetic agents). I.V. infusion usually requires hemodynamic monitoring (consult institution protocols). Assess therapeutic effect (according to purpose for use) and adverse reactions when starting or adjusting dosage and on a regular basis. When discontinuing, drug must be tapered gradually over 2 weeks to avoid acute tachycardia, hypertension, and/or ischemia. Caution patients with diabetes to monitor blood glucose levels closely; beta-blockers can mask hypoglycemic symptoms. Teach patient proper use (when self-administered), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy without consulting prescriber. If administered by infusion; report immediately any pain, redness, or swelling at infusion site; any palpitations or chest pain, dizziness, difficulty breathing, or other adverse reactions. **Oral:** Take exactly as directed; do not increase, decrease, or discontinue without consulting prescriber. If you have diabetes, monitor blood sugars carefully; beta-blockers may mask hypoglycemic symptoms. Tablets may be crushed and taken with liquids. Do not crush or chew long-acting forms; swallow whole. You may experience orthostatic hypotension, dizziness, drowsiness, or blurred vision. Use caution when driving, climbing stairs, changing position (rising from sitting or lying to standing), or engaging in tasks requiring alertness until response to drug is know. May cause nausea vomiting, or stomach discomfort (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report chest pain or palpitations; persistent dizziness or lethargy; any CNS symptoms (amnesia, change in cognition, confusion, depression, hallucinations, insomnia, vivid dreams; rash; difficulty breathing or wheezing; weakness, pain, or loss of sensation in extremities or other adverse symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, extended release, as hydrochloride: 60 mg, 80 mg, 120 mg, 160 mg

InnoPran XL™: 80 mg, 120 mg

Capsule, sustained release, as hydrochloride:

Inderal® LA: 60 mg, 80 mg, 120 mg, 160 mg

Injection, solution, as hydrochloride: 1 mg/mL (1 mL)

Inderal®: 1 mg/mL (1 mL) [DSC]

Solution, oral, as hydrochloride: 4 mg/mL (500 mL); 8 mg/mL (500 mL) [strawberry-mint flavor; contains alcohol 0.6%]

Tablet, as hydrochloride: 10 mg, 20 mg, 40 mg, 60 mg, 80 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Inderal LA)

80 mg (30): $132.48

120 mg (30): $157.40

160 mg (30): $194.99

Capsule, 24-hour (InnoPran XL)

80 mg (30): $68.33

120 mg (30): $70.34

Capsule, 24-hour (Propranolol HCl CR)

60 mg (100): $99.99

80 mg (100): $115.99

120 mg (100): $139.98

160 mg (100): $182.98

Solution (Propranolol HCl)

20 mg/5 mL (240): $25.99

Tablets (Propranolol HCl)

10 mg (100): $12.99

20 mg (100): $13.99

40 mg (30): $12.99

60 mg (60): $55.99

80 mg (90): $14.03

Mechanism of ActionNonselective beta-adrenergic blocker (class II antiarrhythmic); competitively blocks response to beta$_1$- and beta$_2$-adrenergic stimulation which results in decreases in heart rate, myocardial contractility, blood pressure, and myocardial oxygen demand. Nonselective beta-adrenergic blockers (propranolol, nadolol) reduce portal pressure by producing splanchnic vasoconstriction (beta$_2$ effect) thereby reducing portal blood flow.

Pharmacodynamics/Kinetics

Onset of action: Beta-blockade: Oral: 1-2 hours

Duration: Immediate release: 6-12 hours; Extended-release formulations: ~24-27 hours

Distribution: V$_d$: 4 L/kg in adults; crosses placenta; small amounts enter breast milk

Protein binding: Newborns: 68%; Adults: 90%

Metabolism: Hepatic to active and inactive compounds; extensive first-pass effect

Bioavailability: 30% to 40%

Half-life elimination: Neonates and Infants: Possible increased half-life; Children: 3.9-6.4 hours; Adults: Immediate release formulation: 3-6 hours; Extended-release formulations: 8-10 hours

Time to peak: Immediate release: 1-4 hours; Extended-release formulations: ~6-14 hours

Excretion: Urine (96% to 99%)

Related Information

- Antiarrhythmic Drugs
- Beta-Blockers
- Depression
- Nonbenzodiazepine Anxiolytics and Hypnotics

Dental Health: Effects on Dental TreatmentPropranolol is a nonselective beta-blocker and may enhance the pressor response to epinephrine, resulting in hypertension and bradycardia. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution; epinephrine has interacted with nonselective beta-blockers to result in initial hypertensive episode followed by bradycardia

Mental Health: Effects on Mental StatusFatigue and malaise are common and often mistaken for depression; may also cause dizziness, confusion, insomnia, or hallucinations

Mental Health: Effects on Psychiatric TreatmentLow-dose propranolol is considered by many to be the drug of choice for akathisia. Concurrent use with psychotropic drugs may produce additive hypotensive effects; monitor blood pressure. Cutaneous reactions, including Stevens-Johnson syndrome, have been reported with use of propranolol; use caution with lamotrigine or valproic combination as combined usage with propranolol has been associated with these reactions.

Cardiovascular Considerations

Atrial Fibrillation: Beta-blocker therapy provides effective rate control in patients with atrial fibrillation.

Chronic Stable Angina: Beta-blockers are effective in the treatment of angina as monotherapy or when combined with nitrates and/or calcium channel blockers. In patients with severe intractable angina requiring negative cardiac chronotropic medications, pacemaker placement has been carried out to maintain heart rate in the setting of large doses of beta-blockers and/or calcium channel blockers. Beta-blockers are ineffective in the treatment of pure vasospastic (Prinzmetal) angina.

Hypertension: Beta-blocker therapy in the treatment of hypertension has been associated with improved cardiovascular outcomes. According to the 2003 JNC-VII guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists that requires the use of other drugs, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Beta-blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for a beta-blocker include patients with heart failure, postmyocardial infarction, high coronary disease risk, or diabetes. In type 2 diabetic patients, a UK Prospective Diabetes Study Group (UKPDS) trial showed that beta-blocker therapy (atenolol) was as effective as an ACE inhibitor in reducing cardiovascular events and that the benefits of therapy were related more to the degree of antihypertensive efficacy rather than the class of drug used.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

ST-Segment Elevation Myocardial Infarction (STEMI): Beta-blockers, without intrinsic sympathomimetic activity (ISA), have been shown to decrease morbidity and mortality when initiated in the acute treatment of STEMI and continued long-term. Oral beta-blockade should be initiated promptly in patients without contraindications (eg, signs of heart failure, evidence of a low output state, risk of cardiogenic shock, or other beta-blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade may be considered and given promptly if the patient is experiencing concomitant hypertension or a tachyarrhythmia (Class IIa recommendation).

Unstable Angina/Non-ST-Segment Elevation MI (UA/NSTEMI): In the treatment of UA/NSTEMI, oral beta-blockade should be initiated within the first 24 hours in patients without contraindications (eg, signs of heart failure, evidence of a low output state, risk of cardiogenic shock, or other beta-blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade should only be considered if the patient is experiencing concomitant hypertension upon presentation (Class IIa recommendation).

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia and hypertension.

Anesthesia and Critical Care Concerns/Other Considerations

Surgery: Based on available evidence, beta-blockers should be started days to weeks before elective surgery in selected patients when possible and titrated to a heart rate <65 beats per minute. Additional data suggest that long acting beta-blockers may be superior to short acting ones (Redelmeier, 2005). The ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery recommend beta-blockers be continued in patients undergoing surgery who are receiving beta-blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA Class I guideline indications (Class I recommendation). The guidelines also recommend that beta-blockers be given to patients undergoing vascular surgery who have myocardial ischemia demonstrated during preoperative testing (Class I recommendation).

The guidelines also state that beta-blockers are probably recommended in patients undergoing intermediate risk (eg, carotid endarterectomy, prostate surgery) or vascular surgery in whom preoperative assessment identifies coronary heart disease or high cardiac risk (Class IIa recommendation). High cardiac risk is defined as having >1 of the following clinical risk factors: History of ischemic heart disease, compensated or prior heart failure, cerebrovascular disease, diabetes mellitus, or renal insufficiency. The use of beta-blockers is uncertain in patients undergoing intermediate risk or vascular surgery with ≤1 clinical risk factor (Class IIb recommendation).

The majority of published trials suggest a benefit of perioperative beta-blocker use during noncardiac surgery especially in high-risk patients; however, more recent clinical trials have not shown a benefit to perioperative beta-blockade for noncardiac surgery (Juul, 2006; Yang, 2006).

Index Terms

Propranolol Hydrochloride

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International Brand NamesAlperol (TH); Angilol (IE, NZ); Angilol LA (NZ); Apsolol (GB); Atensin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Avlocardyl (FR); Bedranol (BB, BF, BJ, BM, BS, BZ, CI, ET, GH, GM, GN, GY, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Berkolol (HK); Beta-Timelets (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Betalol (TH); Betapress (TH); Betascan (TW); Cardiblok (ZA); Cardinol (NZ); Cardinol LA (NZ); Cardispare (ZA); Cardolol (TW); Ciplar (IN); Colliprol (MX); Corbeta (IN); Coriodal (CN); Deralin (AU, IL); Dociton (DE); Duranol (PH); Emforal (TH); Farmadral (ID); Frina (GR); Indenol (KP); Inderal (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CO, CY, DK, EC, EG, ET, GH, GM, GN, GR, GY, HK, HN, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PE, PH, PK, PT, PY, QA, SA, SC, SD, SE, SG, SL, SN, SR, SY, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Inderal LA (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GB, GH, GM, GN, GY, IE, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PE, PT, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Inderalici (MX); Indesol (KP); Indicardin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Inpanol (HK); Laining (TW); MIDDLEEAST (IL); Oposim (AR); Palon (TH); Phanerol (PH); Pranidol (MX); Prestoral (ID); Prolol (IL, TH); Pronol (AU); Propalong (AR); Propayerst (AR); Propra (EE); Propral (FI); Propranolol (PL); Propranolol Eurogenerics (LU); Purbloka (ZA); Rebaten LA (BR); Rexigen (ZA); Sawatal (JP); Slow Deralin (IL); Sumial (ES); Tenomal (GR); Waucoton (GR)

Propylhexedrine

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(proe pil HEKS e dreen)
U.S. Brand NamesBenzedrex® [OTC]
Pharmacologic CategoryAdrenergic Agonist Agent
Use: Labeled IndicationsTopical nasal decongestant
Dosing: Adults**Decongestant:** Nasal: Two inhalations in each nostril, not more frequently than every 2 hours
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren 6-12 years: Refer to adult dosing.
Administration: InhalationFor nasal inhalation only.
StorageStore at 15°C to 30°C (59°F to 86°F). Keep tightly closed. Product effective for at least 3 months after opening.
ContraindicationsHypersensitivity to propylhexedrine or any component of the formulation
Warnings/Precautions

Special populations:

- Pediatrics: Not for OTC use in children <6 years of age.

Dosage form specific issues:

- Nasal: For nasal use only. Do not exceed recommended dosage; do not use for more than 3 days.

Adverse ReactionsFrequency not defined.

Local: Nasal: Burning, stinging

Respiratory: Sneezing, nasal discharge increased

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Inhaler, nasal: 0.4-0.5 mg/inhalation (1s) [total content 250 mg]

Generic AvailableNo
ManufacturerBF Ascher
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported

Propylthiouracil

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Propylthiouracil may be confused with Purinethol®

PTU is an error-prone abbreviation (mistaken as mercaptopurine [Purinethol®; 6-MP])

Pronunciation(proe pil thye oh YOOR a sil)

Canadian Brand NamesPropyl-Thyracil®

Pharmacologic CategoryAntithyroid Agent; Thioamide

Use: Labeled IndicationsPalliative treatment of hyperthyroidism as an adjunct to ameliorate hyperthyroidism in preparation for surgical treatment or radioactive iodine therapy; management of thyrotoxic crisis

Dosing: Adults

Hyperthyroidism: Oral: 300-400 mg/day in divided doses every 6-8 hours. In patients with severe hyperthyroidism, very large goiters, or both, the initial dosage is usually 400 mg/day; an occasional patient will require 600-900 mg/day; maintenance: 100-150 mg/day in divided doses every 8-12 hours

Note: Administer in 3 equally divided doses at approximately 8-hour intervals. Adjust dosage to maintain T_3, T_4, and TSH levels in normal range; elevated T_3 may be sole indicator of inadequate treatment. Elevated TSH indicates excessive antithyroid treatment.

Thyrotoxic crisis: Recommendations vary widely and have not been evaluated in comparative trials: Dosages of 200-300 mg every 4-6 hours have been recommended for short-term initial therapy (until initial response), followed by gradual reduction to a maintenance dosage (100-150 mg/day in divided doses).

Dosing: ElderlyUse lower dose recommendations; adjust for renal impairment.

Initial: 150-300 mg/day in divided doses every 8 hours

Maintenance: 100-150 mg/day in divided doses every 8-12 hours

Dosing: Pediatric

Hyperthyroidism: Oral: Children: Initial: 5-7 mg/kg/day **or** 150-200 mg/m^2/day in divided doses every 8 hours **or**

6-10 years: 50-150 mg/day

>10 years: 150-300 mg/day

Maintenance: Determined by patient response **or** $^1/_3$ to $^2/_3$ of the initial dose in divided doses every 8-12 hours. This usually begins after 2 months on an effective initial dose.

Note: Administer in 3 equally divided doses at approximately 8-hour intervals. Adjust dosage to maintain T_3, T_4, and TSH levels in normal range; elevated T_3 may be sole indicator of inadequate treatment. Elevated TSH indicates excessive antithyroid treatment.

Dosing: Renal ImpairmentAdjustment is not necessary.

Calculations

- Body Surface Area: Pediatrics

Dietary ConsiderationsAdminister at the same time in relation to meals each day, either always with meals or always between meals.

Extemporaneously PreparedA 5 mg/mL oral suspension was stable for 10 days when refrigerated when compounded as follows:

Triturate six 50 mg tablets in a mortar, reduce to a fine powder, add 30 mL of carboxymethylcellulose 1.5%, transfer to a graduate and qs to 60 mL

Shake well before using and keep in refrigerator; protect from light

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, 3rd ed, Cincinnati, OH: Harvey Whitney Books Co, 1997.

ContraindicationsHypersensitivity to propylthiouracil or any component of the formulation; breast-feeding (per manufacturer; however, expert analysis and the AAP state this drug may be used in nursing mothers)

Allergy Considerations

- Thioureylene Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: May cause hypoprothrombinemia and bleeding; use with particular caution in patients >40 years of age.
- Bone marrow suppression: May cause significant bone marrow depression; the most severe manifestation is agranulocytosis. Aplastic anemia, thrombocytopenia, and leukopenia may also occur. Use with caution in patients receiving other drugs known to cause myelosuppression particularly agranulocytosis; discontinue if significant bone marrow suppression occurs, particularly agranulocytosis or aplastic anemia.
- Carcinoma/hyperplasia: Thyroid hyperplasia or carcinoma may occur with prolonged usage (>1 year).
- Dermatitis: Has been associated with rare but severe dermatologic reactions; discontinue in the presence of exfoliative dermatitis.
- Fever: Discontinue in the presence of unexplained fever.
- Hepatic reactions: Rare, severe hepatic reactions (hepatic necrosis, hepatitis) may occur. Symptoms suggestive of hepatic dysfunction should prompt evaluation; discontinue in the presence of hepatitis (transaminase > 3x upper limit of normal).
- Lupus-like syndrome: Has been associated with a variety of autoimmune reactions, including a lupus-like syndrome; discontinuation may be warranted.
- Nephritis: Has been associated with glomerulonephritis and interstitial nephritis with acute renal failure; discontinuation of therapy may be warranted.
- Pneumonitis: Has been associated with rare reports of interstitial pneumonitis. Prompt evaluation is warranted in patients reporting respiratory signs/symptoms consistent with this reaction; discontinuation is warranted in cases or interstitial pneumonitis.
- Vasculitis: Has been associated (rarely) with the development of ANCA-positive vasculitis or leukocytoclastic vasculitis; prompt discontinuation is warranted in patients who develop vasculitis during therapy.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Geriatric ConsiderationsThe use of antithyroid thioamides is as effective in the elderly as they are in younger adults.

Pregnancy Risk FactorD

Pregnancy ConsiderationsPropylthiouracil crosses the placenta and because adverse events may occur in the fetus following maternal use, it is classified as pregnancy category D. The rate of congenital defects does not appear to be increased with maternal propylthiouracil use; however, fetal thyroid function may be transiently suppressed. Untreated hyperthyroidism may also cause adverse events in the mother (eg, heart failure, miscarriage, preeclampsia, thyroid storm), fetus (eg, goiter, growth restriction, hypo/hyperthyroidism, still birth) and neonate (eg, hyper-/hypothyroidism, neuropsychologic damage). The thioamides are treatment of choice for hyperthyroidism during pregnancy. In order to prevent adverse events to the fetus, the lowest effective dose should be used in order to achieve maternal levels of T_4 in the high euthyroid or low hyperthyroid range. Thyroid function should be monitored closely.

LactationEnters breast milk/contraindicated (per manufacturer) (AAP rates “compatible”)

Breast-Feeding ConsiderationsPropylthiouracil is found in breast milk at levels <0.3% of the weight adjusted maternal dose. Although breastfeeding is contraindicated by the manufacturer, the AAP and other expert analysis have concluded that breast-feeding is generally considered safe. Reviews of thionamide use while breast-feeding have not shown that thyroid function of the breast-fed infant is significantly affected.

Adverse ReactionsFrequency not defined.

Cardiovascular: ANCA-positive vasculitis, cutaneous vasculitis, edema, leukocytoclastic vasculitis

Central nervous system: Dizziness, drowsiness, drug fever, fever, headache, neuritis, vertigo

Dermatologic: Alopecia, erythema nodosum, exfoliative dermatitis, pruritus, skin rash, urticaria

Endocrine & metabolic: Goiter, swollen salivary glands, weight gain

Gastrointestinal: Constipation, loss of taste perception, nausea, stomach pain, vomiting

Hematologic: Agranulocytosis, aplastic anemia, bleeding, leukopenia, thrombocytopenia

Hepatic: Cholestatic jaundice, hepatitis

Neuromuscular & skeletal: Arthralgia, paresthesia

Renal: Acute renal failure, glomerulonephritis, nephritis

Respiratory: Alveolar hemorrhage, interstitial pneumonitis

Miscellaneous: SLE-like syndrome

Drug Interactions

Sodium Iodide I131: Antithyroid Agents may diminish the therapeutic effect of Sodium Iodide I131. Management: Discontinue antithyroid therapy 3-4 days prior to sodium iodide I-131 administration. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antithyroid Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Propylthiouracil serum levels may be altered if taken with food.
Monitoring ParametersCBC with differential, prothrombin time, liver function tests, thyroid function tests (TSH, T_3, T_4); periodic blood counts are recommended chronic therapy
Reference RangeNormal laboratory values:

Total T_4: 5-12 mcg/dL

Serum T_3: 90-185 ng/dL

Free thyroxine index (FT_4 I): 6-10.5

TSH: 0.5-4.0 microunits/mL

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, anticoagulant activity increased). Assess results of laboratory tests, therapeutic effectiveness according to use, and adverse response (eg, rash, goiter, nausea, vomiting, leukopenia, agranulocytosis, anemia, jaundice, arthralgia, CNS stimulation or depression). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsCBC with differential, prothrombin time, liver and thyroid function (T_4, T_3, TSH); periodic blood counts are recommended for chronic therapy.
Patient EducationTake as directed, at the same time each day at around-the-clock intervals; at the same time in relation to meals, either always with meals or always between meals. Do not miss doses or make up missed doses. This drug may need to be taken for an extended period of time to achieve appropriate results and you may need periodic blood tests to assess effectiveness of therapy. May cause nausea or vomiting (small, frequent meals may help); constipation (increased exercise, fluids, fruit, or fiber may help); or dizziness or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known). Report rash, skin eruptions, or loss of hair; fever; unusual bleeding or bruising; unusual weight gain (>5 lb/week); unresolved headache or fever; yellowing of eyes or skin; changes in color of urine or feces; or joint or muscle pain or weakness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 50 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Propylthiouracil)

50 mg (90): $17.99

Mechanism of ActionInhibits the synthesis of thyroid hormones by blocking the oxidation of iodine in the thyroid gland; blocks synthesis of thyroxine and triiodothyronine
Pharmacodynamics/Kinetics

Onset of action: Therapeutic: 24-36 hours

Peak effect: Remission: 4 months of continued therapy

Duration: 2-3 hours

Distribution: Concentrated in the thyroid gland

Protein binding: 75% to 80%

Metabolism: Hepatic

Bioavailability: 80% to 95%

Half-life elimination: 1.5-5 hours; End-stage renal disease: 8.5 hours

Time to peak, serum: ~1 hour

Excretion: Urine (35%)

Pharmacotherapy PearlsPreferred over methimazole in thyroid storm due to inhibition of peripheral conversion as well as synthesis of thyroid hormone.
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Loss of taste perception.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness
Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; avoid clozapine and carbamazepine
Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Agranulocytosis, when it occurs, is usually seen during the first several months of therapy.

The use of antithyroid thioamides is as effective in elderly as in younger adults; however, the expense, potential adverse effects, and inconvenience (compliance, monitoring) make them undesirable. The use of radioiodine, due to ease of administration and less concern for long-term side effects and reproduction problems, makes it a more appropriate therapy.

Index TermsPTU (error-prone abbreviation)
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International Brand NamesAntiroid (KP); Bingsaiyou (CL); Peteyu (TH); Procil (TW); Propycil (BG, CH, CZ, DE, HU, PL, PT); Propyl (TH); Propyl-Thiouracil (CH); Propylthiocil (IL); Propylthiouracil (AU); Propylthiouracil ”Dak” (DK); Propylthiouracile (BE); Propyltiouracil ”Medic” (DK); Proracyl (FR); Prothiucil (AT); PTU (IN, UY); Thyrosan (PL); Tiotil (EE, SE); Tirostat (CO); Uracil (TH)

Protamine Sulfate

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Medication Safety Issues

Sound-alike/look-alike issues:

Protamine may be confused with ProAmatine®, Protonix®, Protopam®, Protropin®

Pronunciation(PROE ta meen SUL fate)

Pharmacologic Category[Antidote]

Use: Labeled IndicationsTreatment of heparin overdosage; neutralize heparin during surgery or dialysis procedures

Use: Unlabeled/InvestigationalTreatment of low molecular weight heparin (LMWH) overdose

Dosing: Adults

Heparin neutralization: I.V.: Protamine dosage is determined by the dosage of heparin; 1 mg of protamine neutralizes 90 USP units of heparin (lung) and 115 USP units of heparin (intestinal); maximum dose: 50 mg

Heparin overdosage, following intravenous administration: I.V.: Since blood heparin concentrations decrease rapidly **after** administration, adjust the protamine dosage depending upon the duration of time since heparin administration as follows: See table.

Time Elapsed	Dose of Protamine (mg) to Neutralize 100 units of Heparin
Immediate	1-1.5
30-60 min	0.5-0.75
>2 h	0.25-0.375

Heparin overdosage, following SubQ injection: I.V.: 1-1.5 mg protamine per 100 units heparin; this may be done by a portion of the dose (eg, 25-50 mg) given slowly I.V. followed by the remaining portion as a continuous infusion over 8-16 hours (the expected absorption time of the SubQ heparin dose)

LMWH overdose (unlabeled use):

Enoxaparin: 1 mg protamine for each mg of enoxaparin; if PTT prolonged 2-4 hours after first dose, consider additional dose of 0.5 mg for each mg of enoxaparin.

Dalteparin or tinzaparin: 1 mg protamine for each 100 anti-Xa int. units of dalteparin or tinzaparin; if PTT prolonged 2-4 hours after first dose, consider additional dose of 0.5 mg for each 100 anti-Xa int. units of dalteparin or tinzaparin.

Note: Antifactor Xa activity never completely neutralized (maximum: ~60% to 75%). Excessive protamine doses may worsen bleeding potential.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: I.V.For I.V. use only. Administer slow IVP (50 mg over 10 minutes). Rapid I.V. infusion causes hypotension. Reconstitute vial with 5 mL sterile water. Resulting solution equals 10 mg/mL. Inject without further dilution over 1-3 minutes; maximum of 50 mg in any 10-minute period.

Administration: I.V. DetailpH: 6-7

StorageRefrigerate; do not freeze. Stable for at least 2 weeks at room temperature. Preservative-free formulation does not require refrigeration.

ReconstitutionReconstitute vial with 5 mL sterile water. If using protamine in neonates, reconstitute with preservative-free sterile water for injection; resulting solution equals 10 mg/mL.

CompatibilityStable in D_5W, NS.

Compatibility in syringe: Compatible: Iohexol 64.7%, iopamidol 61%, iothalamate meglumine 60%. **Incompatible:** Diatrizoate meglumine 52%, diatrizoate sodium 8%, diatrizoate sodium 60%, ioxaglate meglumine 39.3%, ioxaglate sodium 19.6%.

Compatibility when admixed: Compatible: Cimetidine, ranitidine, verapamil. **Incompatible:** Cephalosporins, penicillins.

ContraindicationsHypersensitivity to protamine or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Heparin rebound: Heparin rebound associated with anticoagulation and bleeding has been reported to occur occasionally; symptoms typically occur 8-9 hours after protamine administration, but may occur as long as 18 hours later.

- Hypersensitivity reactions: May cause hypersensitivity reaction in patients with a history of allergy to fish (have epinephrine 1:1000 available) and in patients sensitized to protamine (via protamine-containing insulins).

- Infusion reactions: Too rapid administration can cause severe hypotensive and anaphylactoid-like reactions.

Special populations:

- Cardiac surgery patients: May be ineffective in some patients following cardiac surgery despite adequate doses.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown
Adverse ReactionsFrequency not defined.

Cardiovascular: Sudden fall in blood pressure, bradycardia, flushing, hypotension

Central nervous system: Lassitude

Gastrointestinal: Nausea, vomiting

Hematologic: Hemorrhage

Respiratory: Dyspnea, pulmonary hypertension

Miscellaneous: Hypersensitivity reactions

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersCoagulation test, aPTT or ACT, cardiac monitor and blood pressure monitor required during administration
Nursing: Physical Assessment/MonitoringAssess results of laboratory tests and therapeutic effectiveness frequently during therapy. Monitor closely for adverse response. Assess knowledge/teach patient possible side effects and adverse symptoms to report.
Monitoring: Lab TestsCoagulation test, aPTT or ACT
Patient EducationReport any respiratory difficulty, rash or flushing, feeling of warmth, tingling or numbness, dizziness, or disorientation.
Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sulfate [preservative free]: 10 mg/mL (5 mL, 25 mL)

Generic AvailableYes
Mechanism of ActionCombines with strongly acidic heparin to form a stable complex (salt) neutralizing the anticoagulant activity of both drugs
Pharmacodynamics/KineticsOnset of action: I.V.: Heparin neutralization: ~5 minutes
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness
Mental Health: Effects on Psychiatric TreatmentNone reported
Cardiovascular ConsiderationsProtamine is used after coronary artery bypass graft. It is important that very careful monitoring of heart rate and blood pressure be conducted during protamine therapy because of possible acute hypotension. Occasionally, patients may develop heparin rebound with anticoagulation and bleeding, between 8-18 hours after protamine administration. Anaphylaxis or hypersensitivity responses with acute hypotension to protamine may present with its use, especially in patients with allergies to fish, previous exposure to protamine through previous use of protamine or protamine-containing insulin, infertile men, and vasectomized males.

Protamine's reversal of LMWHs is not as complete or predictable as with heparin. Protamine will not reverse the effects of thrombin inhibitors. Excessive protamine dosing (>100 mg) may worsen bleeding by acting as an anticoagulant.

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Monitor vital signs closely during protamine therapy because of possible hypotension during administration.

Anaphylaxis or hypersensitivity responses with acute hypotension to protamine may present with its use, especially in patients with allergies to fish, previous exposure to protamine (through previous use of protamine or protamine-containing insulin), infertile or vasectomized males.

Evidence-Based Information:

Management of Intracerebral Hemorrhage (ICH) Due to Unfractionated Heparin (UFH): Overall management of ICH is similar regardless of cause; however, iatrogenic spontaneous ICH may have specific treatments. According to the 2007 ACC/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage, UFH-related ICH should be treated with I.V. protamine given by slow I.V. injection (not to exceed 5 mg/minute) with a maximum dose of 50 mg (Class I recommendation). Faster infusions of protamine can result in cardiovascular collapse.

Protamine's reversal of LMWHs is not as complete or predictable as with heparin. Protamine neutralizes the antithrombin activity of LMWHs, but the cationic protein neutralizes the antifactor Xa activity incompletely. A recent case illustrates a failure to reverse enoxaparin (Makris, 2000). Protamine will not reverse the effects of thrombin inhibitors such as lepirudin, bivalirudin, or argatroban.

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International Brand NamesDenpru (AR); Prosulf (GB); Protamina (ES); Protamina solfato (IT); Protamine Choay (FR); Protamine Sulfate Injection (AU); Protamine Sulphate (GB); Protamine Sulphate Injection BP (AU); Protamini Sulfas (FI); Protaminsulfat (NO); Protaminsulfat Novo (AT); Protaminsulfat ”Leo” (DE, DK); Protaminum Sulfuricum (PL)

Protein C Concentrate (Human)

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Medication Safety Issues

Sound-alike/look-alike issues:

Ceprotin may be confused with aprotinin, Cipro®

Protein C concentrate (human) may be confused with activated protein C (human, recombinant) which refers to drotrecogin alfa

Pronunciation(PROE teen cee KON suhn trate HYU man)

U.S. Brand NamesCeprotin

Pharmacologic CategoryAnticoagulant; Blood Product Derivative; Enzyme; Protein C

Use: Labeled IndicationsReplacement therapy for severe congenital protein C deficiency for the prevention and/or treatment of venous thromboembolism and purpura fulminans

Dosing: AdultsPatient variables (including age, clinical condition, and plasma levels of protein C) will influence dosing and duration of therapy. Individualize dosing based on protein C activity and patient pharmacokinetic profile. Dosing is dependent on the severity of protein C deficiency, age of patient, clinical condition, and patient's level of protein C. The frequency, duration, and dose should be individualized.

Severe congenital protein C deficiency: I.V.:

Acute episode/short-term prophylaxis: Initial dose: 100-120 int. units/kg (for determination of recovery and half-life)

Subsequent 3 doses: 60-80 int. units/kg every 6 hours (adjust to maintain peak protein C activity of 100%)

Maintenance dose: 45-60 int. units/kg every 6 or 12 hours (adjust to maintain recommended maintenance trough protein C activity levels >25%)

Long-term prophylaxis: Maintenance dose: 45-60 int. units/kg every 12 hours (recommended maintenance trough protein C activity levels >25%)

Note: Maintain target peak protein C activity of 100% during acute episodes and short-term prophylaxis. Maintain trough levels of protein C activity >25%. Higher peak levels of protein C may be necessary in prophylactic therapy of patients at increased risk for thrombosis (eg, infection, trauma, surgical intervention).

Dosing: PediatricPatient variables (including age, clinical condition, and plasma levels of protein C) will influence dosing and duration of therapy. Individualize dosing based on protein C activity and patient pharmacokinetic profile. Dosing is dependent on the severity of protein C deficiency, age of patient, clinical condition, and patient's level of protein C. The frequency, duration, and dose should be individualized.

Severe congenital protein C deficiency: I.V. Refer to adult dosing.

Note: Maintain target peak protein C activity of 100% during acute episodes and short-term prophylaxis. Maintain trough levels of protein C activity >25%. Higher peak levels of protein C may be necessary in prophylactic therapy of patients at increased risk for thrombosis (eg, infection, trauma, surgical intervention).

Administration: I.V.Administer by intravenous injection at a rate not to exceed 2 mL/minute. In children <10 kg, administration should not exceed a rate of 0.2 mL/kg/minute. Administration must be completed within 3 hours of solution preparation.

Dietary ConsiderationsAt maximum daily doses, product formulation contains sodium >200 mg.

StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light.

ReconstitutionAllow Ceprotin and sterile water vial to warm to room temperature. Reconstitute 500 int. units vial with 5 mL and 1000 int. units vial with 10 mL sterile water for injection (resultant concentration ~100 int. units/mL). Gently swirl vial after adding the diluent until powder is completely dissolved. Use provided filter needle to withdraw solution from vial; remove filter needle prior to administration. The resulting solution (which is preservative free) should be administered within 3 hours and any unused portion should be discarded.

ContraindicationsHypersensitivity to protein C or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Heparin-induced thrombocytopenia (HIT): Trace amounts of heparin contained within the formulation may lead to HIT; evaluate platelet counts if HIT is suspected.
- Hypersensitivity reactions: Formulation may contain trace amounts of mouse protein and/or heparin. Discontinue use in the presence of hypersensitivity/allergic reactions.

Disease-related concerns:

- Hepatic impairment: Use caution; not studied in hepatic impairment.
- Renal impairment: Use caution; not studied in patients with renal impairment.

Concurrent drug therapy issues:

- Anticoagulants: An increase risk of bleeding may be seen in patients receiving concomitant anticoagulant therapy including thrombolytic agents, heparin, oral anticoagulants, glycoprotein IIb/IIIa antagonists, platelet aggregation inhibitors, and aspirin.

Special populations:

- Sodium-restricted patients: Use with caution in patients where sodium restriction is necessary.

Other warnings/precautions:

- Infections: Product of human plasma; may potentially contain infectious agents which could transmit disease; screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces this risk. (Consideration should be given for patients to receive appropriate vaccinations during therapy [eg, hepatitis A or B vaccine].)

Geriatric ConsiderationsAccording to the manufacturer, an insufficient number of subjects ≥65 years of age were enrolled in the clinical trials to determine whether elderly patients respond differently than younger ones.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproductive studies have not been performed. It is unknown if administration during pregnancy will result in fetal harm.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsUse in nursing mothers has not been studied.

Adverse ReactionsAs with all drugs which may affect hemostasis, bleeding may be associated with protein C administration. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the concurrent use of multiple agents that alter hemostasis and patient susceptibility. Frequency not defined.

Central nervous system: Lightheadedness

Hematologic: Bleeding

Miscellaneous: Hypersensitivity reactions (itching and rash)

Postmarketing and/or case reports: Fever, hemothorax, hypotension, hyperhidrosis, restlessness

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Recent use/intake of herbs with anticoagulant or antiplatelet activity (including cat's claw, feverfew, garlic, ginkgo, ginseng, and horse chestnut seed) may increase the risk of bleeding.

Monitoring ParametersProtein C activity (chromogenic assay) prior to and during therapy; signs and symptoms of bleeding; hemoglobin/hematocrit, PT/INR, platelet count

Reference RangeMaintain target peak protein C activity of 100% during acute episodes and short-term prophylaxis. Maintain trough levels of protein C activity >25%. Higher peak levels of protein C may be necessary in prophylactic therapy of patients at increased risk for thrombosis (eg, infection, trauma, surgical intervention).

Nursing: Physical Assessment/MonitoringEvaluate any history of hypersensitivity to mouse protein or heparin prior to beginning therapy. Discuss risk/benefit ratio concerning transmission of infectious agents with patient prior to therapy and evaluate need for appropriate vaccinations. Assess other pharmacological or herbal products patient may be taking for potential adverse interactions, specifically any agents that may potentially increase risk of bleeding. See specific administration directions. Treatment for anaphylactic reaction should be immediately available during use. Assess results of laboratory reports prior to and on a regular basis during therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsProtein C activity (chromogenic assay) prior to and during therapy; hemoglobin/hematocrit, PT/INR, platelet count

Patient EducationThis medication can only be administered by intravenous infusion. You will be monitored during and following infusions;

report immediately any difficulty breathing, rash or itching, or difficulty swallowing. If self-administered, follow exact instructions as directed. You may experience lightheadedness (use caution when driving or engaging in tasks that require alertness until response to medication is known). Report immediately any unusual bleeding or bruising, restlessness, difficulty breathing, persistent dizziness, or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage Forms

Injection, powder for reconstitution:

Ceprotin: ~500 int. units [actual potency printed on vial label; contains human albumin and sodium; may contain trace amounts of mouse protein or heparin; packaged with diluent]; ~1000 int. units [actual potency printed on vial label; contains human albumin and sodium; may contain trace amounts of mouse protein or heparin; packaged with diluent]

Generic AvailableNo

ManufacturerBaxter Healthcare Corp

Mechanism of ActionConverted to activated protein C (APC). APC is a serine protease which inactivates factors Va and VIIIa, limiting thrombotic formation. *In vitro* data also suggest inhibition of plasminogen activator inhibitor-1 (PAF-1) resulting in profibrinolytic activity, inhibition of macrophage production of tumor necrosis factor, blocking of leukocyte adhesion, and limitation of thrombin-induced inflammatory responses.

Pharmacodynamics/Kinetics

Distribution: V_d: 0.074L/kg

Metabolism: Activated protein C (APC) inactivated by plasma protease inhibitors

Half-life elimination: Median: 9.8 hours; range 4.9-14.7 hours

Time to peak, plasma: T_{max}: 0.5 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsProtein C

International Brand NamesCeprotin (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Protexel (FR)

Prothrombin Complex (Human) [(Factors II, VII, IX, X), Protein C, and Protein S]

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English

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Pronunciation(PRO throm bin KOM pleks HYU man FAK ters too SEV en nyne ten PROE teen cee & PROE teen ess)

Canadian Brand NamesOctaplex®

Pharmacologic Category[Hemostatic Agent](); [Prothrombin Complex Concentrate (PCC)]()

Use: Labeled IndicationsProphylaxis (perioperative) and treatment of bleeding due to acquired deficiency (eg, overdose of vitamin K antagonist) of one or more of the prothrombin complex coagulation factors II, VII, IX, and X, when rapid correction of factor deficiency is necessary

Dosing: Adults

Dosing should be individualized based on severity of disorder, extent and location of bleeding, and clinical status of patient.

Bleeding/perioperative prophylaxis of bleeding during vitamin K antagonist therapy: I.V.: **Note:** Maximum dose not to exceed 120 mL: Approximate doses required for normalization of INR (≤1.2 within 1 hour):

Initial INR: 2-2.5: Administer 0.9-1.3 mL/kg

2.5-3: Administer 1.3-1.6 mL/kg

3-3.5: Administer 1.6-1.9 mL/kg

>3.5: Administer >1.9 mL/kg

With the correction of vitamin K antagonist-induced impairment of hemostasis in patients who have been treated concomitantly with an appropriate vitamin K dose, repeat dosing with PCC is usually not necessary.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥17 years: Refer to adult dosing.

Administration: I.V.Measure pulse rate before and during infusion. Administer at a rate of 1 mL/minute initially, followed by 2-3 mL/minute. Reduce infusion rate or interrupt infusion if patient's pulse rate increases significantly.

StorageStore 2°C to 8°C (35°F to 46°F); do not freeze. Protect from light.

ReconstitutionAllow diluent (SWFI) and prothrombin complex concentrate vial to warm to room temperature (if using a water bath temperature should not exceed 37°C ([98.6°F]). Aseptically remove protective cover from short end of double-ended needle and insert into diluent vial (needle should be visible in vial). Aseptically remove protective cover from long end of double-ended needle and insert into upright concentrate vials; water is drawn by vacuum into concentrate vial. Remove double-ended needle with empty diluent vial. Gently rotate concentrate vial until contents are completely dissolved. Resulting solution should be colorless to slightly blue. Reconstituted solution should be used immediately. Do not use concentrate if dissolution is incomplete or aggregate forms. Discard any unused portion.

CompatibilityDo not introduce other medications into the same I.V. line.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to any component of the formulation; heparin-induced thrombocytopenia type II or known allergy to heparin; non-life-threatening bleeds in individuals with recent myocardial infarction, high risk of thrombosis, or angina pectoris; untreated disseminated intravascular coagulation (DIC); bleeding associated with hepatic parenchyme disorders, esophageal varices, or major hepatic surgery

Warnings/Precautions

Concerns related to adverse effects:

- Antibody formation: Development of antibodies to one or more of the human prothrombin factors may occur rarely resulting in an inadequate clinical response; monitor for signs of antibody formation.
- Hematologic events: Use has been associated with thrombosis and may be associated with an increased risk of DIC and thromboembolic complications including MI, in patients with acquired or congenital factor deficiency, particularly with repeated dosing or in treatment of isolated factor VII deficiency; use with caution in patients with a history of any condition (eg, MI, coronary artery disease CAD) that increases the risk for thromboembolic events or DIC; monitor closely for signs/symptoms of thrombosis or intravascular coagulation; use with caution in hepatic dysfunction, peri/postoperative patients and neonates; use in DIC and hyperfibrinolysis only after appropriate therapy (eg, heparin, antithrombin, antifibrinolytics) for disruption of the consumptive coagulation process has been administered.
- Hypersensitivity reactions: Prophylactic treatment with antihistamines and/or glucocorticoids may be necessary in patients predisposed to allergies. Glucocorticoids and/or antihistamines also may be used to control mild allergic reactions. Severe hypersensitivity and anaphylactic reactions may rarely occur with use; immediate medical treatment (including epinephrine 1:1000) should be readily available in the event of a severe reaction.

Disease-related concerns:

- Chronic liver disease or transplantation: Monitor antithrombin (AT) levels in patients being treated for bleeding as a result of chronic liver disease or liver transplantation. If AT levels are deficient, AT should be administered concomitantly with PCC. No clinical data is available for use of PCC to treat bleeding due to liver parenchyme disorders, major liver surgery, or esophageal varices; use of PCC for these indications is contraindicated and the preferred method of treatment is fresh frozen plasma (FFP).

- Hypercoagulopathy: Administration of PCC may exacerbate underlying hypercoagulable states in recipients of vitamin K antagonists.

Special populations:

- Pediatrics: Safety and efficacy have not been established in patients <17 years of age.

Dosage form specific issues:

- Heparin: Formulation contains heparin.

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer. Hepatitis B vaccination is recommended for all patients. Hepatitis A vaccination is also recommended for seronegative patients.

Other warnings/precautions:

- Coagulation factor deficiency: Hepatic synthesis of the prothrombin complex (Factors II, VII, IX and X) coagulation factors is vitamin K dependent. Severe hepatic dysfunction, inadequate absorption of vitamin K (eg, pancreatic disorders, diarrhea) or vitamin K antagonist therapy or overdose may lead to coagulation factor deficiencies. In patients with an acquired deficiency of the vitamin K dependent coagulation factors, administer prothrombin complex concentrate (PCC) only if a rapid correction (eg, emergency surgery, major bleeding) is necessary. If not indicated and caused by Vitamin K antagonist therapy, coagulation factor deficiencies may be managed by reducing or discontinuing therapy of the vitamin K antagonist and/or administration of vitamin K.

Pregnancy ConsiderationsModerate-to-significant decreases in fetal body weight have been observed in some animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if clearly needed. Parvovirus B19 or hepatitis A, which may be present in plasma-derived products, may affect a pregnant woman more seriously than a nonpregnant woman.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**Note:** Incidence based on small study population.

1% to 10%:

Cardiovascular: Hypertension (1%)

Central nervous system: Headache (1%)

Hepatic: Transaminases increased (1%)

Local: Injection site burning (1%)

Miscellaneous: Parvovirus B19 seropositive (3%)

Postmarketing and/or case reports: Peripheral ischemia, transient ischemic attack

Test InteractionsaPTT (formulation contains heparin)

Monitoring ParametersCoagulation factor assays, protein C, protein S, aPTT, PT, INR, CBC, AT, D-dimer, fibrinogen; transaminases; development of circulating coagulation factor antibodies (inhibitors); blood pressure, heart rate (before and during administration), temperature (during and following administration)

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products the patient may be taking that may affect coagulation or platelet function. Assess results of laboratory tests (eg, prothrombin time, clotting factor assays) prior to and after therapy. Patient should be monitored continuously during and after therapy (eg, vital signs, cardiac and CNS status). Provide patient education according to patient condition.

Monitoring: Lab TestsCoagulation factor assays, protein C, protein S, aPTT, PT, INR, CBC, AT, D-dimer, fibrinogen; transaminases; development of circulating coagulation factor antibodies (inhibitors); blood pressure, heart rate (before and during administration), temperature (during and following administration)

Patient EducationThis medication can only be administered by infusion; report immediately any swelling, pain, burning, or itching at infusion site. Report acute headache, respiratory difficulty, chills, back pain, dizziness, nausea, or other unusual effects. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Octaplex®: Human coagulation factor II: 11-38 int. units/mL; factor VII: 9-24 int. units/mL; factor IX: 20-31 int. units/mL; factor X: 18-30 int. units/mL: protein C: 7-31 int. units/mL; protein S: 7-32 int. units/mL (20 mL) [contains heparin 4-15.5 int. units/mL, polysorbate 80 ≤50 mcg/mL, sodium citrate 17-27 mmoL/L; packaged with diluent]

Generic AvailableNo

ManufacturerOctapharma Canada, Inc

Mechanism of ActionProthrombin complex concentrate provides an increase in the levels of the vitamin K-dependent coagulation factors (II, VII, IX, and X) with the addition of protein C and protein S. Coagulation factors II, IX, and X are part of the intrinsic coagulation pathway, while factor VII is part of the extrinsic coagulation pathway. In the *extrinsic* pathway, damaged blood vessels release endothelial tissue factor (TF) which complexes with factor VII to form TF-factor VIIa. Within the *intrinsic* pathway, factor IX is converted to IXa. Factor IXa (as well as TF-factor VIIa) converts factor X to factor Xa in the final common pathway of coagulation. Factor Xa activates prothrombin (factor II) into thrombin (IIa) which converts fibrinogen into fibrin resulting in clot formation. Proteins C and S are vitamin K-dependent inhibiting enzymes involved in regulating the coagulation process. Protein S serves as a cofactor for protein C which is converted to activated protein C (APC). APC is a serine protease which inactivates factors Va and VIIIa, limiting thrombotic formation.

Pharmacodynamics/Kinetics

Onset of action: Rapid; significant INR decline within 10 minutes

Duration: ~6-8 hours

Half-life elimination: Factor II: 48–60 hours; Factor VII: 1.5-6 hours; Factor IX: 20-24 hours; Factor X: 24-48 hours; Protein C: 1.5–6 hours; Protein S: 24-48 hours

Note: Half-lives may be significantly reduced in severe hepatocellular damage, DIC, or extended catabolic metabolism.

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other Considerations**Management of intracerebral hemorrhage (ICH) due to warfarin:** Overall management of ICH is similar regardless of cause. However, iatrogenic spontaneous ICH may have specific treatments. Warfarin-related ICH should be treated with IV vitamin K at a dose of 10 mg given slowly (not to exceed 1 mg/minute) (Class I recommendation). It is important to also administer fresh frozen plasma (FFP) since vitamin K may take several hours to normalize INR. Other options besides FFP include prothrombin complex concentrate (PCC) which contains high levels of vitamin K-dependent factors (II, VII, and X) and factor IX complex which contains factors II, VII, IX, and X (Class IIb recommendation). Use of rFVIIa has shown promise for this indication. Advantages to rFVIIa include faster onset of action compared to FFP and vitamin K and a 50% lower volume is required compared to FFP. Disadvantages include a short half-life (~2.6 hours) requiring multiple doses to maintain a normalized INR and an increased risk of thromboembolic complications. Dosing of rFVIIa ranges between 15 and 90 mcg/kg. The use of factor containing products has a risk of thromboembolism.

Index TermsProthrombin Complex Concentrate

References

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Makris M, “Optimization of the Prothrombin Complex Concentrate Dose for Warfarin Reversal,” *Thromb Res*, 2005, 115(6):451-3.[PubMed 15792674]

Protirelin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(proe TYE re lin)
U.S. Brand NamesThyrel® TRH [DSC]
Canadian Brand NamesRelefact® TRH
Pharmacologic CategoryDiagnostic Agent
Use: Labeled IndicationsAdjunct in the diagnostic assessment of thyroid function, and an adjunct to other diagnostic procedures in patients with pituitary or hypothalamic dysfunction; also causes release of prolactin from the pituitary and is used to detect defective control of prolactin secretion
Dosing: Adults**Diagnostic aid:** I.V.: 500 mcg (range 200-500 mcg)
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Diagnostic aid:** I.V.:

Infants and Children <6 years: Experience limited, but doses of 7 mcg/kg have been administered

Children 6-16 years: 7 mcg/kg to a maximum dose of 500 mcg

Administration: I.V.Administer I.V. bolus over 15-30 seconds with patient remaining in supine position; monitor blood pressure frequently during and 15 minutes after administration
ContraindicationsHypersensitivity to protirelin additives or any component of the formulation
Pregnancy Risk FactorC
Adverse Reactions

>10%:

Central nervous system: Headache, lightheadedness

Dermatologic: Flushing of face

Gastrointestinal: Nausea, xerostomia

Genitourinary: Urge to urinate

1% to 10%:

Central nervous system: Anxiety

Endocrine & metabolic: Breast enlargement and leaking in lactating women

Gastrointestinal: Bad taste in mouth, abdominal discomfort

Neuromuscular & skeletal: Tingling

Miscellaneous: Diaphoresis

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 500 mcg/mL (1 mL)

Generic AvailableNo
Mechanism of ActionIncrease release of thyroid stimulating hormone from the anterior pituitary
Pharmacodynamics/Kinetics

Onset of action: Peak effect: TSH: 20-30 minutes

Duration: TSH returns to baseline after ~3 hours

Half-life elimination, serum: Mean plasma: 5 minutes

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and unpleasant taste.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDizziness is common; may cause anxiety
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsLopremone; Thyrotropin Releasing Hormone; TRH
International Brand NamesAntepan (AT, DE); Hirtonin (JP); Irtonin (IT, JP); Probrin (PK); Protiren (AR); Relefact TRH (AT, CH, CZ, DE, GR, KP, NL); Stimu-TSH (FR); Thyroliberin TRH Merck (AT, DE); TRH (CZ, IL, LU, TW); TRH Berlin-Chemie (DE); TRH Ferring (DE); TRH ”UCB” (BE); TRH-Cambridge (GB); Xantium (IT)

Protriptyline

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Vivactil® may be confused with Vyvanse™

Pronunciation(proe TRIP ti leen)

U.S. Brand NamesVivactil®

Pharmacologic CategoryAntidepressant, Tricyclic (Secondary Amine)

Use: Labeled IndicationsTreatment of depression

Dosing: Adults**Depression:** Oral: 15-60 mg/day in 3-4 divided doses

Dosing: ElderlyOral: Initial: 5-10 mg/day; increase every 3-7 days by 5-10 mg; usual dose: 15-20 mg/day

Dosing: Pediatric**Depression:** Oral: Adolescents: 15-20 mg/day

Dietary ConsiderationsMay be taken with food to decrease GI distress.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to protriptyline (cross-reactivity to other cyclic antidepressants may occur) or any component of the formulation; use of MAO inhibitors within 14 days; use of cisapride; use in a patient during the acute recovery phase of MI

Allergy Considerations

- Tricyclic Antidepressant and Related Compounds Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Protriptyline is FDA approved for the treatment of depression in adolescents.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May aggravate aggressive behavior or worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Protriptyline is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. The degree of anticholinergic blockade produced by this agent is moderate relative to other antidepressants.

- Hematologic effects: TCAs may rarely cause bone marrow suppression; monitor for any signs of infection and obtain CBC if symptoms (eg, fever, sore throat) evident.

- Orthostatic hypotension: May cause orthostatic hypotension (risk is moderate relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is low relative to other antidepressants.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk conduction abnormalities with this agent is moderate-high relative to other antidepressants.
- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose regulation.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.
- Thyroid dysfunction: Use with caution in patients with hyperthyroidism or those receiving thyroid supplementation due to concerns of pro-arrhythmogenesis.

Concurrent drug therapy issues:

- Anticholinergic and/or neuroleptic agents: Hyperpyrexia has been observed with TCAs in combination with anticholinergics and/or neuroleptics, particularly during hot weather.
- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Discontinuation of therapy: Recommended to discontinue prior to elective surgery requiring general anesthesia. Therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods.
- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

Geriatric ConsiderationsLittle data on its use in the elderly. Strong anticholinergic properties which may limit its use; more often stimulating rather than sedating. Data from a clinical trial comparing fluoxetine to tricyclics suggest that fluoxetine is significantly less effective than nortriptyline in hospitalized elderly patients with unipolar major affective disorder, especially those with melancholia and concurrent cardiovascular diseases.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, heart block, hyper-/hypotension, MI, palpitation, stroke, tachycardia

Central nervous system: agitation, anxiety, ataxia, confusion, delirium, delusions, dizziness, drowsiness, EPS, exacerbation of psychosis, fatigue, hallucinations, headache, hypomania, incoordination, insomnia, nightmares, panic, restlessness, seizure

Dermatologic: Alopecia, itching, petechiae, photosensitivity, rash, urticaria

Endocrine & metabolic: Breast enlargement, galactorrhea, gynecomastia, increased or decreased libido, syndrome of inappropriate ADH secretion (SIADH)

Gastrointestinal: Anorexia, constipation, decreased lower esophageal sphincter tone may cause GE reflux, diarrhea, heartburn, increased appetite, nausea, trouble with gums, unpleasant taste, vomiting, weight gain/loss, xerostomia

Genitourinary: Difficult urination, impotence, testicular edema

Hematologic: Agranulocytosis, eosinophilia, leukopenia, purpura, thrombocytopenia

Hepatic: Cholestatic jaundice, increased liver enzymes

Neuromuscular & skeletal: Fine muscle tremor, numbness, tingling, tremor, weakness

Ocular: Blurred vision, eye pain, increased intraocular pressure

Otic: Tinnitus

Miscellaneous: Allergic reactions, excessive diaphoresis

Metabolism/Transport Effects**Substrate** of CYP2D6 (major)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Tricyclic Antidepressants may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Agonists: Tricyclic Antidepressants may enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Alpha2-Agonists: Tricyclic Antidepressants may diminish the antihypertensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Altretamine: May enhance the orthostatic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Amphetamines: Tricyclic Antidepressants may enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Beta2-Agonists: Tricyclic Antidepressants may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cinacalcet: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Cisapride: Protriptyline may enhance the arrhythmogenic effect of Cisapride. *Risk X: Avoid combination*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Desmopressin: Tricyclic Antidepressants may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dexmethylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

DULoxetine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Iobenguane I 123: Tricyclic Antidepressants may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May enhance the neurotoxic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Tricyclic Antidepressants may enhance the QTc-prolonging effect of QuiNIDine. QuiNIDine may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

St Johns Wort: May increase the metabolism of Tricyclic Antidepressants. The risk of serotonin syndrome may theoretically be increased. *Risk D: Consider therapy modification*

Sulfonylureas: Cyclic Antidepressants may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Terbinafine: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

TraMADol: Tricyclic Antidepressants may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. *Risk C: Monitor therapy*

Valproic Acid: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Tricyclic Antidepressants may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Yohimbine: Tricyclic Antidepressants may increase the serum concentration of Yohimbine. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Grapefruit juice may inhibit the metabolism of some TCAs and clinical toxicity may result.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava (may increase risk of serotonin syndrome and/or excessive sedation).

Monitoring ParametersMonitor for cardiac abnormalities in elderly patients receiving doses >20 mg; suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased)

Reference RangeTherapeutic: 70-250 ng/mL (SI: 266-950 nmol/L); Toxic: >500 ng/mL (SI: >1900 nmol/L)

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (see extensive list of Drug Interactions). Assess for suicidal tendencies before beginning therapy. May cause physiological or psychological dependence, tolerance, or abuse; periodically evaluate need for continued use. Assess therapeutic effectiveness (mental status, mood, affect) and adverse reactions (eg, suicidal ideation) at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing (allow 3-4 weeks between discontinuing this medication and starting another antidepressant). Caution patients with diabetes to monitor glucose levels closely; may increase or decrease serum glucose levels. Teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed; take once-a-day dose at bedtime. Do not increase dose or frequency; may take 2-3 weeks to achieve desired results. This drug may cause physical and/or psychological dependence. Avoid alcohol and grapefruit juice. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, loss of appetite, or disturbed taste (small frequent meals, good mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); urinary retention (void before taking medication); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); altered sexual drive or ability (reversible); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report chest pain, palpitations, or rapid heartbeat; persistent adverse CNS effects (eg, suicidal ideation, nervousness, restlessness, insomnia, anxiety, excitation, headache, agitation, impaired coordination, changes in cognition); muscle cramping, weakness, tremors, or rigidity; blurred vision or eye pain; breast enlargement or swelling; yellowing of skin or eyes; or worsening of condition.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 5 mg, 10 mg

Vivactil®: 5 mg, 10 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Vivactil)

5 mg (30): $81.61

10 mg (30): $107.26

Mechanism of ActionIncreases the synaptic concentration of serotonin and/or norepinephrine in the central nervous system by inhibition of their reuptake by the presynaptic neuronal membrane

Pharmacodynamics/Kinetics

Distribution: Crosses placenta

Protein binding: 92%

Metabolism: Extensively hepatic via N-oxidation, hydroxylation, and glucuronidation; first-pass effect (10% to 25%)

Half-life elimination: 54-92 hours (average: 74 hours)

Time to peak, serum: 24-30 hours

Excretion: Urine

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), unpleasant taste, and trouble with gums. Long-term treatment with TCAs, such as protriptyline, increases the risk of caries by reducing salivation and salivary buffer capacity.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Use with caution; epinephrine and levonordefrin have been shown to have an increased pressor response in combination with TCAs. Protriptyline is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health Comment Tricyclic antidepressants may be classified as tertiary (amitriptyline, doxepin, clomipramine, imipramine, trimipramine) or secondary amines (nortriptyline, desipramine, protriptyline). The tertiary amines are not recommended to treat depression in the elderly. If a TCA is used in the elderly, it should be a secondary amine. The tertiary amines are commonly used in low dosages for various conditions associated with pain. Toxicity is generally dose dependent. Relatively small overdoses (1-week supply) can be potentially fatal. Protriptyline is thought to have stimulating properties.

Index Terms Protriptyline Hydrochloride

References

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International Brand Names Concordin (DK, GB, IE)

Pseudoephedrine and Codeine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation

(soo doe e FED rin & KOE deen)

U.S. Brand NamesNotuss®-DC; Nucofed® [DSC]
Pharmacologic CategoryAntitussive/Decongestant
Use: Labeled IndicationsTemporary symptomatic relief of congestion and cough due to upper respiratory infections including common cold, bronchitis, sinusitis, and influenza
Dosing: Adults**Relief of congestion and cough:** Oral: One capsule every 6 hours as needed (maximum: 4 capsules/24 hours) **or** 5-10 mL every 4-6 hours as needed (maximum: 40 mL/24 hours)
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Relief of congestion and cough:** Oral:

Children 6-11 years: 2.5-5 mL every 4-6 hours as needed (maximum: 20 mL/24 hours)

Children ≥12 years: Refer to adult dosing.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).
RestrictionsCapsule: C-III; Liquid: C-V
ContraindicationsHypersensitivity to pseudoephedrine, codeine, or any component of the formulation; with or within 14 days of MAO-inhibitor therapy; severe cardiovascular disease (eg, hypertension, CAD, ischemic heart disease); newborns; premature infants; breast-feeding; pregnancy
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.

- Cardiovascular disease: Use with caution in patients with mild-to-moderate cardiovascular disease (including hypertension, CAD, and ischemic heart disease); contraindicated in patients with severe disease.

- Diabetes: Use with caution in patients with diabetes mellitus.

- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or angle-closure glaucoma.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD, or other obstructive pulmonary disease; critical respiratory depression may occur, even at therapeutic dosages.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

- Ulcerative colitis: Use with caution in patients with chronic ulcerative colitis.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- CYP2D6 “ultrarapid metabolizers”: Use codeine with caution in patients with two or more copies of the variant CYP2D6*2 allele; may have extensive conversion to morphine and thus increased opioid-mediated effects.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

Other warnings/precautions:

- Cough control: Not recommended to use for cough control in patients with a chronic cough due to asthma, emphysema, or smoking. Should not be used in patients with excessive secretions.

- Patient education: Patients should notify healthcare provider if symptoms do not improve within 7 days or are accompanied by high fever. Patients should not exceed recommended doses.

Pregnancy Risk FactorC
Pregnancy ConsiderationsRefer to Codeine monograph.
LactationEnters breast milk/contraindicated
Breast-Feeding ConsiderationsRefer to Codeine monograph.
Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, heart rate decreased/increased, hypertension, pallor, palpitation, tightness of chest

Central nervous system: Confusion, coordination impaired, dizziness, drowsiness, euphoria, excitation, fatigue, headache, hysteria, insomnia, irritability, lightheadedness, nervousness, neuritis, restlessness, sedation, seizure, vertigo

Dermatologic: Photosensitivity, pruritus, rash, urticaria

Endocrine & metabolic: Early menses

Gastrointestinal: Abdominal pain, anorexia, constipation, diarrhea, epigastric distress, nausea, vomiting

Genitourinary: Dysuria, polyuria, urinary retention

Neuromuscular & skeletal: Paresthesia, tremor, weakness

Ocular: Blurred vision, diplopia

Otic: Acute labyrinthitis, tinnitus

Respiratory: Dyspnea, nasal congestion, thickening of bronchial secretions, wheezing

Miscellaneous: Diaphoresis

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression); consuming ≥3 alcoholic drinks/day may increase the risk of liver damage

Herb/Nutraceutical: St John's wort may decrease codeine levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression). Avoid ephedra, yohimbe (may cause hypertension).

Test Interactions

Codeine may cause an elevation in serum amylase levels.

Pseudoephedrine interferes with urine detection of amphetamine (false-positive).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

Nucofed®: Pseudoephedrine hydrochloride 60 mg and codeine phosphate 20 mg [DSC]

Liquid, oral:

Notuss®-DC: Pseudoephedrine hydrochloride 30 mg and codeine phosphate 10 mg per 5 mL (473 mL) [dye free, ethanol free, gluten free, sugar free; contains propylene glycol; bubblegum flavor]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Nucofed)

60-20 mg (30): $41.42

Syrup (Nucofed)

20-60 mg/5 mL (120): $25.99

Mechanism of Action

Pseudoephedrine directly stimulates alpha-adrenergic receptors of respiratory mucosa causing vasoconstriction; directly stimulates beta-adrenergic receptors causing bronchial relaxation

Codeine is an antitussive that controls cough by depressing the medullary cough center

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Codeine
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine or mepivacaine and levonordefrin (Carbocaine® 2% with Neo-Cobefrin®) to cause a pressor response.

Mental Health: Effects on Mental StatusMay cause sedation, dizziness, insomnia, nervousness, and restlessness

Mental Health: Effects on Psychiatric TreatmentMay cause CNS depression; concurrent use with psychotropics, valerian, kava kava, and gotu kola may produce additive effects. Codeine may cause psychological and physical dependence; use caution in patients with a history of substance abuse. St John's wort may decrease codeine levels.

Index TermsCodeine and Pseudoephedrine; Codeine Phosphate and Pseudoephedrine Hydrochloride; Pseudoephedrine Hydrochloride and Codeine Phosphate

Pseudoephedrine and Dextromethorphan

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English English

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Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(soo doe e FED rin & deks troe meth OR fan)

U.S. Brand NamesPedia Relief Cough and Cold [OTC]; Pedia Relief Infants [OTC]; PediaCare® Infants' Decongestant & Cough [OTC] [DSC]; Sudafed® Children's Cold & Cough [OTC]; SudoGest Children's [OTC]

Canadian Brand NamesBalminil DM D; Benylin® DM-D; Koffex DM-D; Novahistex® DM Decongestant; Novahistine® DM Decongestant; Robitussin® Childrens Cough & Cold

Pharmacologic CategoryAntitussive/Decongestant

Use: Labeled IndicationsTemporary symptomatic relief of nasal congestion and cough due to common cold, hay fever, upper respiratory allergies

Dosing: Adults**Relief of nasal congestion and cough:**

General dosing guidelines base on pseudoephedrine component: Oral: 60 mg every 4-6 hours (maximum: 240 mg/24 hours)

Product-specific dosing: Oral: Sudafed® Children's Cold & Cough: 20 mL every 4 hours (maximum: 80 mL/24 hours)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Relief of nasal congestion and cough:**

General dosing guidelines base on pseudoephedrine component: Oral:

Children 2-6 years: 15 mg every 4-6 hours (maximum: 60 mg/24 hours)

Children 6-12 years: 30 mg every 4-6 hours (maximum: 120 mg/24 hours)

Children ≥12 years and Adults: 60 mg every 4-6 hours (maximum: 240 mg/24 hours)

Product-specific dosing: Oral:

Children 2-6 years (Sudafed® Children's Cold & Cough): 5 mL every 4 hours (maximum: 20 mL/24 hours)

Children 6-12 years (Sudafed® Children's Cold & Cough): 10 mL every 4 hours (maximum: 40 mL/24 hours)

Children ≥12 years: Refer to adult dosing.

Dietary ConsiderationsTriaminic® Cough contains sodium 20 mg/5 mL. Triaminic® Cough and Nasal Congestion contains sodium 7 mg/5 mL. Vicks® 44D Cough & Head Congestion contains sodium 10.3 mg/5 mL. PediaCare® Children's Long Acting Cough Plus Cold contains phenylalanine 5 mg per tablet.

ContraindicationsHypersensitivity to pseudoephedrine, dextromethorphan, or any component of the formulation; use with or within 14 days of MAO inhibitor therapy

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (hypertension or ischemic heart disease).
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Not for OTC use in children <2 years of age.

Other warnings/precautions:

- Self-medication (OTC use): When used for self-medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever, rash, or persistent headache. Discontinue and contact healthcare provider if nervousness, dizziness, or sleeplessness occur.

Adverse ReactionsSee individual agents.

Metabolism/Transport EffectsDextromethorphan: **Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (minor), 2D6 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

QuiNIDine: May decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the adverse/toxic effect of Dextromethorphan. **Exceptions:** Fluvoxamine. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Liquid:

Sudafed® Children's Cold & Cough: Pseudoephedrine hydrochloride 15 mg and dextromethorphan hydrobromide 5 mg per 5 mL (120 mL) [alcohol free, sugar free; contains sodium benzoate; cherry berry flavor]

Liquid, oral [drops]:

PediaCare® Infants' Decongestant & Cough: Pseudoephedrine hydrochloride 7.5 mg and dextromethorphan hydrobromide 2.5 mg per 0.8 mL (15 mL) [alcohol free; contains sodium benzoate; cherry flavor] [DSC]

Pedia Relief Infants: Pseudoephedrine hydrochloride 7.5 mg and dextromethorphan hydrobromide 2.5 mg per 0.8 mL (15 mL) [cherry flavor]

Syrup:

Pedia Relief Cough and Cold: Pseudoephedrine hydrochloride 15 mg and dextromethorphan hydrobromide 7.5 mg per 5 mL (120 mL) [cherry flavor]

SudoGest Children's: Pseudoephedrine hydrochloride 15 mg and dextromethorphan hydrobromide 5 mg per 5 mL (120 mL)

Generic AvailableYes: Liquid drops, syrup

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Dextromethorphan
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDizziness, drowsiness, nervousness, and insomnia are common; may rarely cause hallucinations

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors

Index TermsDextromethorphan and Pseudoephedrine

International Brand NamesBalminil DM D (CA); Benylin DM-D (CA); Koffex DM-D (CA); Novahistex DM Decongestant (CA); Novahistine DM Decongestant (CA); Robitussin Childrens Cough & Cold (CA)

Pseudoephedrine and Ibuprofen

Lexi-Drugs Online

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- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(soo doe e FED rin & eye byoo PROE fen)
U.S. Brand NamesAdvil® Cold & Sinus [OTC]; Advil® Cold, Children's [OTC] [DSC]; Proprinal® Cold and Sinus [OTC]
Canadian Brand NamesAdvil® Cold & Sinus; Children's Advil® Cold; Sudafed® Sinus Advance
Pharmacologic CategoryDecongestant/Analgesic
Use: Labeled IndicationsFor temporary relief of cold, sinus and flu symptoms (including nasal congestion, sinus pressure, headache, minor body aches and pains, and fever)

Dosing: Adults**Analgesic/decongestant (OTC labeling):** Oral: Ibuprofen 200 mg and pseudoephedrine 30 mg per dose: One dose every 4-6 hours as needed; may increase to 2 doses if necessary (maximum: 6 doses/24 hours). Contact healthcare provider if symptoms have not improved within 7 days when treating cold symptoms or within 3 days when treating fever.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Analgesic/decongestant (OTC labeling):** Oral: Children ≥12 years: Refer to adult dosing.

Administration: OralMay be administered with food or milk if stomach upset occurs.

Dietary ConsiderationsMay be taken with food or milk if stomach upset occurs.

StorageStore at 20°C to 25ºC (68°F to 77°F); avoid excessive heat.

ContraindicationsHypersensitivity to ibuprofen, pseudoephedrine, or any component of the formulation; hypersensitivity to aspirin or other NSAIDs; use with or within 2 weeks of discontinuing MAO inhibitor; immediately prior to or after coronary bypass graft (CABG)

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.

- Aseptic meningitis: May increase the risk of aseptic meningitis, especially in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders.

- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.

- Cardiovascular events: NSAIDs are associated with an increased risk of adverse cardiovascular events, including MI, stroke, and new onset or worsening of pre-existing hypertension. Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin's cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.

- Gastrointestinal events: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation. These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol (≥3 alcoholic beverages/day), the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue at the first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: Use is contraindicated when used immediately prior to or after coronary artery bypass graft (CABG) surgery. Risk of MI and stroke may be increased with use following CABG surgery.

- Diabetes: Use with caution in patients with diabetes mellitus.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or angle-closure glaucoma.

- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or urinary obstruction.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Not for self-medication (OTC use) in children <12 years of age.

Other warnings/precautions:

- Self-medication (OTC use): Prior to self-medication, patients should contact healthcare provider if they have had recurring stomach pain or upset, ulcers, bleeding problems, asthma, high blood pressure, heart or kidney disease, thyroid disease, diabetes, glaucoma, enlarged prostate, other serious medical problems, are currently taking a diuretic, aspirin, anticoagulant, or are ≥60 years of age. Recommended dosages should not be exceeded, due to an increased risk of GI bleeding. Stop use and consult a healthcare provider if symptoms get worse, newly appear, or continue; if an allergic reaction occurs; if nervousness, dizziness, or sleeplessness occurs; or if fever lasts for >3 days, congestion lasts for >7 days, or pain >10 days. Consuming ≥3 alcoholic beverages/day or taking longer than recommended may increase the risk of GI bleeding.

Pregnancy Risk FactorIbuprofen: B/D (3rd trimester)
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsIbuprofen: **Substrate** (minor) of CYP2C9, 2C19; **Inhibits** CYP2C9 (strong)
Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet:

Advil® Cold and Sinus, Proprinal® Cold and Sinus: Pseudoephedrine hydrochloride 30 mg and ibuprofen 200 mg

Capsule, liquid filled:

Advil® Cold and Sinus: Pseudoephedrine hydrochloride 30 mg and ibuprofen 200 mg [solubilized ibuprofen as free acid and potassium salt; contains potassium 20 mg/capsule and coconut oil]

Suspension:

Advil® Cold, Children's: Pseudoephedrine hydrochloride 15 mg and ibuprofen 100 mg per 5 mL (120 mL) [alcohol free; contains sodium 3 mg/5 mL and sodium benzoate; grape flavor] [DSC]

Generic AvailableYes: Caplet

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDizziness, drowsiness, nervousness, and insomnia are common; may rarely cause hallucinations, insomnia, confusion, or depression

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors; may rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Index TermsIbuprofen and Pseudoephedrine

International Brand NamesAdvil Cold & Sinus (IL); Advil Cold-Sinus (EC); Arinac (IN); Brenfed (IN); Dristan Sinus (CO); Nurofen Cold & Flu (ZA); Rhinureflex (FR); Tri-Profen Cold and Flu (AU)

Pseudoephedrine and Methscopolamine

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English

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Pronunciation(soo doe e FED rin & meth skoe POL a meen)
U.S. Brand NamesAlleRx™-D; Amdry-D; Extendryl PSE
Pharmacologic CategoryDecongestant/Anticholingeric Combination
Use: Labeled IndicationsRelief of symptoms of allergic rhinitis, vasomotor rhinitis, sinusitis, and the common cold
Dosing: AdultsOral (Allerx™-D, Amdry-D): One tablet every 12 hours (maximum: 2 tablets/24 hours)
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren ≥12 years: Refer to adult dosing.
StorageStore at controlled room temperature between 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to pseudoephedrine, methscopolamine, or any component of the formulation; severe hypertension; severe coronary artery disease; use with or within 2 weeks of discontinuing MAO inhibitor; narrow-angle glaucoma; urinary retention; peptic ulcer disease; during an asthmatic attack
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression and blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Neuropathy: Use with caution in patients with autonomic neuropathy.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Renal impairment: Use with caution in patients with renal impairment.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.
- Ulcerative colitis: Use with caution in patients with ulcerative colitis.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies with this combination have not been conducted; see individual agents
LactationExcretion in breast milk unknown/ not recommended
Breast-Feeding ConsiderationsPseudoephedrine is excreted in breast milk. Excretion of methscopolamine is unknown. See individual agents.
Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, bradycardia, cardiovascular collapse, flushing, hypotension, pallor, palpitation, tachycardia

Central nervous system: Anxiety, convulsions, CNS depression, dizziness, drowsiness, excitability, fear, giddiness, hallucination, headache, insomnia, irritability, lassitude, nervousness, restlessness

Gastrointestinal: Gastric irritation, nausea, xerostomia

Genitourinary: Dysuria, urinary retention

Neuromuscular & skeletal: Tremor, weakness

Ocular: Blurred vision

Respiratory: Respiratory difficulty

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agent for Pseudoephedrine.

Patient EducationSee individual agent for Pseudoephedrine.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Pseudoephedrine hydrochloride 120 mg and methscopolamine nitrate 2.5 mg

Allerx™-D, Amdry-D: Pseudoephedrine hydrochloride 120 mg and methscopolamine nitrate 2.5 mg

Tablet, extended release:

Extendryl PSE: Pseudoephedrine hydrochloride 120 mg and methscopolamine nitrate 2.5 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, 12-hour (AlleRx-D)

120-2.5 mg (60): $151.79

Mechanism of Action

Pseudoephedrine: Acts as a decongestant in respiratory tract mucous membranes.

Methscopolamine nitrate: Derivative of scopolamine; a peripheral anticholinergic agent

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment:

Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).

Methscopolamine: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), and dry throat and nose. Anticholinergic side effects can cause a reduction of saliva production or secretion, contributing to discomfort and dental disease (ie, caries, oral candidiasis and periodontal disease).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusMay cause sedation, anxiety, dizziness, drowsiness, excitability, hallucinations, insomnia, irritability, nervousness, and restlessness

Mental Health: Effects on Psychiatric TreatmentContraindicated with or within 14 days of MAO inhibitor therapy. Concomitant use with psychotropics may produce additive anticholinergic and sedative effects especially in the elderly.

Index TermsMethscopolamine and Pseudoephedrine; Pseudoephedrine hydrochloride and Methscopolamine Nitrate

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Pseudoephedrine, Dihydrocodeine, and Chlorpheniramine

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English English

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Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(soo doe e FED rin, dye hye droe KOE deen, & klor fen IR a meen)

U.S. Brand NamesColdcough; DiHydro-CP; Hydro-Tussin™ DHC [DSC]; Pancof® [DSC]; Uni-Cof [DSC]

Pharmacologic CategoryAlpha/Beta Agonist; Analgesic, Opioid; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporary relief of cough, congestion, and sneezing due to colds, respiratory infections, or hay fever

Dosing: Adults**Cough and congestion:** Oral: 5-10 mL every 4-6 hours; do not exceed 4 doses in 24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Cough and congestion:** Oral: Children:

2-6 years: 1.25-2.5 mL every 4-6 hours; do not exceed 4 doses in 24 hours

6-12 years: 2.5-5 mL every 4-6 hours; do not exceed 4 doses in 24 hours

>12 years: Refer to adult dosing.

Dietary ConsiderationsSee individual agents.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F).

RestrictionsC-III

ContraindicationsHypersensitivity to pseudoephedrine, dihydrocodeine, codeine, chlorpheniramine (or related substances), or any component of the formulation; narrow-angle glaucoma; severe hypertension, severe cardiovascular disease; during or within 14 days of MAO inhibitor therapy; urinary retention; peptic ulcer; status asthmaticus; severe respiratory depression; infants; pregnancy; breast-feeding

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients not able to maintain blood pressure.
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- CNS depression/coma: Use with caution in patients with CNS depression or coma.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with pulmonary disease or decrease ventilatory function; dose-related respiratory depression occurs.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Antihistamines may cause excitation in young children.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination product. Opioid analgesics are considered FDA risk category D if used for prolonged periods or in large doses near term. Withdrawal symptoms may be observed in babies born to mothers taking opioids regularly during pregnancy. Respiratory depression may be observed in the newborn if opioids are given close to delivery.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsPseudoephedrine enters breast milk (AAP rates “compatible”). Information is not available for hydrocodone; codeine and other opioids are excreted in breast milk and the AAP considers codeine to be “compatible” with breast-feeding. Data is not available for chlorpheniramine. The manufacturers recommend discontinuing the medication or to discontinue nursing during therapy

Adverse ReactionsSee individual agents.

Metabolism/Transport Effects

Dihydrocodeine: **Substrate** of CYP2D6 (minor)

Chlorpheniramine: **Substrate** of CYP2D6 (minor), 3A4 (major); Inhibits CYP2D6 (weak).

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May diminish the analgesic effect of Dihydrocodeine. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Syrup:

Coldcough, Hydro-Tussin™ DHC [DSC], Pancof® [DSC], Uni-Cof [DSC]: Pseudoephedrine hydrochloride 15 mg, dihydrocodeine bitartrate 7.5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; grape flavor]

DiHydro-CP: Pseudoephedrine hydrochloride 15 mg, dihydrocodeine bitartrate 7.5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [grape flavor]

Generic Available Yes

Mechanism of Action

Pseudoephedrine: Directly stimulates alpha-adrenergic receptors of respiratory mucosa causing vasoconstriction; directly stimulates beta-adrenergic receptors causing bronchial relaxation

Dihydrocodeine: Binds to opiate receptors in the CNS; suppresses cough in medullary center

Chlorpheniramine: Competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract

Pharmacodynamics/Kinetics See individual agents.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment:

Chlorpheniramine: Prolonged use will cause significant xerostomia (normal salivary flow resumes upon discontinuation).

Pseudoephedrine: Xerostomia (prolonged use worsens; normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Use with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental Status Sedation is common

Mental Health: Effects on Psychiatric Treatment Contraindicated with or within 14 days of MAO inhibitor therapy. Fluoxetine, paroxetine, and ropinirole may decrease the effects of dihydrocodeine. Nefazodone may increase the effects of chlorpheniramine. Concomitant use with psychotropics may produce additive sedative and anticholinergic effects.

Mental Health Comment May cause paradoxical excitation in some patients. Chlorpheniramine is highly sedative and anticholinergic. Alternative therapy should be considered in the elderly.

Index Terms Chlorpheniramine, Pseudoephedrine, and Dihydrocodeine; Dihydrocodeine Bitartrate, Pseudoephedrine Hydrochloride, and Chlorpheniramine Maleate; Pseudoephedrine, Chlorpheniramine, and Dihydrocodeine

References

"American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk," *Pediatrics*, 2001, 108(3):776-89. [PubMed 11533352]

Rathmell JP, Viscomi CM, and Ashburn MA, "Management of Nonobstetric Pain During Pregnancy and Lactation," *Anesth Analg*, 1997, 85(5):1074-87.[PubMed 9356103]

Pseudoephedrine, Hydrocodone, and Chlorpheniramine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state "Do not use in children under four years of age." In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, "Infant Deaths Associated with Cough and Cold Medications - Two States, 2005," *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Pronunciation(soo doe e FED rin, hye droe KOE done, & klor fen IR a meen)

U.S. Brand NamesAtuss® HD [DSC]; Coldcough HC [DSC]; Detuss [DSC]; Hydron PSC [DSC]; Hyphed [DSC]

Canadian Brand NamesVasophrinic DH

Pharmacologic CategoryAlpha/Beta Agonist; Analgesic, Opioid; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporary relief of cough, congestion, and sneezing due to colds, respiratory infections, or hay fever

Dosing: Adults**Cough and congestion:** Oral:

Histinex® PV, P-V-Tussin®: 10 mL or 1 tablet every 4-6 hours; do not exceed 4 doses in 24 hours

Hydro-Tussin™ HC: 5-10 mL or 1 tablet every 4-6 hours; do not exceed 4 doses in 24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Cough and congestion:** Oral: Children:

2-6 years:

Hydro-Tussin™ HC: 1.25-2.5 mL every 4-6 hours; do not exceed 4 doses in 24 hours

Histinex® PV, P-V-Tussin®: 2.5 mL every 4-6 hours; do not exceed 4 doses in 24 hours

6-12 years:

Histinex® PV, P-V-Tussin®: 5 mL or $^1/_2$ tablet every 4-6 hours; do not exceed 4 doses in 24 hours

Hydro-Tussin™ HC: 2.5-5 mL or $^1/_2$ tablet every 4-6 hours; do not exceed 4 doses in 24 hours

>12 years: Refer to adult dosing.

Dietary ConsiderationsSee individual agents.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

RestrictionsC-III

ContraindicationsHypersensitivity to pseudoephedrine, hydrocodone, chlorpheniramine (or related substances), or any component of the formulation; narrow-angle glaucoma; severe hypertension, severe cardiovascular disease; during or within 14 days of MAO inhibitor therapy; urinary retention; peptic ulcer; status asthmaticus; severe respiratory depression; infants; breast-feeding

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (codeine, hydromorphone, levorphanol, morphine, oxycodone, oxymorphone).

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency, including Addison's disease.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Increased intraocular pressure: Use with caution in patients with increased intraocular pressure.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with pulmonary disease or decrease ventilatory function; dose-related respiratory depression occurs.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

- Pediatrics: Antihistamines may cause excitation in young children.

Other warnings/precautions:

- Cough: Appropriate use: Underlying cause of cough should be determined prior to prescribing.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination product. Opioid analgesics are considered FDA risk category D if used for prolonged periods or in large doses near term. Withdrawal symptoms may be observed in babies born to mothers taking opioids regularly during pregnancy. Respiratory depression may be observed in the newborn if opioids are given close to delivery.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsHydrocodone and pseudoephedrine are excreted in breast milk. Data is not available for chlorpheniramine. Use of this combination is contraindicated by some manufacturers while breast-feeding. Also refer to Pseudoephedrine monograph

Adverse ReactionsSee individual agents.

Metabolism/Transport EffectsHydrocodone: **Substrate** (minor) of CYP2D6, 3A

See individual monographs for Chlorpheniramine and Pseudoephedrine.

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QuiNIDine: May diminish the analgesic effect of Hydrocodone. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsSee individual agents.
Nursing: Physical Assessment/MonitoringSee individual agent for Pseudoephedrine.
Patient EducationSee individual agent for Pseudoephedrine. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, variable release:

Atuss® HD: Pseudoephedrine hydrochloride 30 mg [sustained release], hydrocodone bitartrate 5 mg [immediate release], and chlorpheniramine maleate 2 mg [sustained release] [DSC]

Liquid:

Detuss: Pseudoephedrine hydrochloride 30 mg, hydrocodone bitartrate 5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [alcohol free; vanilla flavor] [DSC]

Hydron PSC: Pseudoephedrine hydrochloride 30 mg, hydrocodone bitartrate 5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [vanilla flavor] [DSC]

Syrup:

Coldcough HC: Pseudoephedrine hydrochloride 15 mg, hydrocodone bitartrate 3 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; grape flavor] [DSC]

Hyphed: Pseudoephedrine hydrochloride 30 mg, hydrocodone bitartrate 2.5 mg, and chlorpheniramine maleate 2 mg per 5 mL (480 mL) [contains alcohol 5%; raspberry flavor] [DSC]

Generic AvailableYes: Excludes capsule, tablet
Pricing: U.S. (www.drugstore.com)

Liquid (Hydron PSC)

30-2-5 mg/5 mL (473): $30.98

Syrup (Hydro-Tussin HC)

15-2-3 mg/5 mL (473): $36.99

Syrup (Q-V Tussin)

30-2-2.5 mg/5 mL (480): $16.99

Tablets (Tussend)

4-5-60 mg (30): $34.99

Mechanism of Action

Pseudoephedrine: Directly stimulates alpha-adrenergic receptors of respiratory mucosa causing vasoconstriction; directly stimulates beta-adrenergic receptors causing bronchial relaxation

Hydrocodone: Binds to opiate receptors in the CNS; suppresses cough in medullary center

Chlorpheniramine: Competes with histamine for H_1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, and respiratory tract

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Chlorpheniramine
- Pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response
Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, nervousness, insomnia, and sedation; may rarely cause hallucinations
Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors; concurrent use with psychotropics may produce additive sedation and dry mouth; may result in loss of pain control if used with fluoxetine and paroxetine
Index TermsChlorpheniramine, Pseudoephedrine, and Hydrocodone; Hydrocodone, Chlorpheniramine, and Pseudoephedrine; Pseudoephedrine Hydrochloride, Hydrocodone Bitartrate, and Chlorpheniramine Maleate
References

"American Academy of Pediatrics Committee on Drugs. The Transfer of Drugs and Other Chemicals Into Human Milk," *Pediatrics*, 2001, 108(3):776-89. [PubMed 11533352]

Anderson PO, Sauberan JB, Lane JR, et al, “Hydrocodone Excretion Into Breast Milk: The First Two Reported Cases,” *Breastfeed Med*, 2007, 2(1):10-4.[PubMed 17661614]

Rathmell JP, Viscomi CM, and Ashburn MA, “Management of Nonobstetric Pain During Pregnancy and Lactation,” *Anesth Analg*, 1997, 85(5):1074-87.[PubMed 9356103]

Pseudoephedrine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Dimetapp® may be confused with Dermatop®, Dimetabs®, Dimetane®

Sudafed® may be confused with Sufenta®

Pronunciation(soo doe e FED rin)

U.S. Brand NamesGenaphed® [OTC]; Kidkare Decongestant [OTC]; Nasofed™; Oranyl [OTC]; Silfedrine Children's [OTC]; Sudafed® 12 Hour [OTC]; Sudafed® 24 Hour [OTC]; Sudafed® Children's [OTC]; Sudafed® Maximum Strength Nasal Decongestant [OTC]; Sudo-Tab® [OTC]; SudoGest [OTC]; Unifed [OTC]

Canadian Brand NamesBalminil Decongestant; Benylin® D for Infants; Contac® Cold 12 Hour Relief Non Drowsy; Drixoral® ND; Eltor®; PMS-Pseudoephedrine; Pseudofrin; Robidrine®; Sudafed® Decongestant

Pharmacologic CategoryAlpha/Beta Agonist

Use: Labeled IndicationsTemporary symptomatic relief of nasal congestion due to common cold, upper respiratory allergies, and sinusitis; also promotes nasal or sinus drainage

Use: DentalTemporary symptomatic relief of nasal congestion due to common cold, upper respiratory allergies, and sinusitis; also promotes nasal or sinus drainage

Dosing: Adults**Nasal congestion:** Oral:

Hydrochloride salt: General dosing guidelines: 30-60 mg every 4-6 hours, sustained release: 120 mg every 12 hours; maximum: 240 mg/24 hours

Tannate salt (Nasofed™ oral suspension): 5-10 mL (50-100 mg) every 12 hours

Dosing: ElderlyNasal congestion: Use caution in this population; initiate using immediate release formulation: Hydrochloride salt: 30-60 mg every 6 hours as needed

Dosing: Pediatric**Nasal congestion:** Oral:

Hydrochloride salt: General dosing guidelines:

Children:

<2 years: 4 mg/kg/day in divided doses every 6 hours

2-5 years: 15 mg every 4-6 hours; maximum: 60 mg/24 hours

6-12 years: 30 mg every 4-6 hours; maximum: 120 mg/24 hours

Tannate salt (Nasofed™ oral suspension):

Children 2-5 years: 1.25-2.5 mL (12.5-25 mg) every 12 hours

Children 6-11 years: 2.5-5 mL (25-50 mg) every 12 hours

Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentConsider reducing dose.

Administration: OralDo not crush extended release drug product, swallow whole.

Dietary ConsiderationsShould be taken with water or milk to decrease GI distress. Nasofed™ oral suspension contains phenylalanine 7 mg/5 mL; Sudafed® Children's chewable tablet contains phenylalanine 0.78 mg/tablet.

ContraindicationsHypersensitivity to pseudoephedrine or any component of the formulation; with or within 14 days of MAO inhibitor therapy; newborns; breast-feeding

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease).
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or angle-closure glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Renal impairment: Use caution in patient with renal impairment; consider dosage adjustments.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.

Dosage form specific issues:

- Phenylalanine: Some products may contain phenylalanine.

Other warnings/precautions:

- Self-medication (OTC use): When used for self-medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever. Discontinue and contact healthcare provider if nervousness, dizziness, or sleeplessness occur. Not for OTC use in children <2 years of age.

Geriatric ConsiderationsElderly patients should be counseled about the proper use of over-the-counter cough and cold preparations. Elderly are more predisposed to adverse effects of sympathomimetics since they frequently have cardiovascular diseases and diabetes mellitus as well as multiple drug therapies. It may be advisable to treat with a short-acting/immediate-release formulation before initiating sustained-release/long-acting formulations.

Pregnancy Risk FactorC

Pregnancy ConsiderationsUse during the 1st trimester may be associated with a possible risk of gastroschisis, small intestinal atresia, and hemifacial microsomia due pseudoephedrine's vasoconstrictive effects. However, additional studies are needed to define the magnitude of risk.

LactationEnters breast milk/use caution (AAP rates "compatible")

Breast-Feeding ConsiderationsPseudoephedrine is excreted in breast milk. Animal reproduction studies have not been conducted. Some manufacturers contraindicate its use; however, the AAP considers it to be "compatible" with breast-feeding.

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, hypotension, palpitation, tachycardia

Central nervous system: Chills, confusion, coordination impaired, dizziness, drowsiness, excitability, fatigue, hallucination, headache, insomnia, nervousness, neuritis, restlessness, seizure, transient stimulation, vertigo

Dermatologic: Photosensitivity, rash, urticaria

Gastrointestinal: Anorexia, constipation, diarrhea, dry throat, nausea, vomiting, xerostomia

Genitourinary: Difficult urination, dysuria, polyuria, urinary retention

Hematologic: Agranulocytosis, hemolytic anemia, thrombocytopenia

Neuromuscular & skeletal: Tremor, weakness

Ocular: Blurred vision, diplopia

Otic: Tinnitus

Respiratory: Chest/throat tightness, dry nose, dyspnea, nasal congestion, thickening of bronchial secretions, wheezing

Miscellaneous: Anaphylaxis, diaphoresis

Drug Interactions

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Onset of effect may be delayed if pseudoephedrine is taken with food.

Herb/Nutraceutical: Avoid ephedra, yohimbe (may cause hypertension).

Test InteractionsInterferes with urine detection of amphetamine (false-positive)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake only as prescribed; do not exceed prescribed dose or frequency. Do not chew or crush timed release forms. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience nervousness, insomnia, dizziness, or drowsiness (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Report persistent CNS changes (dizziness, tremor, agitation, or convulsions); respiratory difficulty; chest pain, palpitations, or rapid heartbeat; muscle tremor; or lack of improvement or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet, extended release, as hydrochloride:

Sudafed® 12 Hour: 120 mg

Liquid, as hydrochloride: 30 mg/5 mL (120 mL)

Silfedrine Children's: 15 mg/5 mL (120 mL, 480 mL) [alcohol and sugar free; grape flavor]

Sudafed® Children's: 15 mg/5 mL (120 mL) [alcohol and sugar free; contains sodium benzoate; grape flavor]

Unifed: 30 mg/5 mL (120 mL, 480 mL, 3840 mL)

Liquid, oral, as hydrochloride [drops]:

Kidkare Decongestant: 7.5 mg/0.8 mL (30 mL) [alcohol free; contains benzoic acid and sodium benzoate; cherry flavor]

Suspension, oral, as tannate:

Nasofed™: 50 mg/5 mL (118 mL) [contains phenylalanine 7 mg/5 mL, propylene glycol; strawberry flavor]

Syrup, as hydrochloride: 30 mg/5 mL (118 mL, 473 mL)

Tablet, as hydrochloride: 30 mg, 60 mg

Genaphed®, Oranyl, Sudafed®, Sudo-Tab®: 30 mg

SudoGest: 30 mg, 60 mg

Tablet, chewable, as hydrochloride:

Sudafed® Children's: 15 mg [sugar free; contains phenylalanine 0.78 mg/tablet; orange flavor]

Tablet, extended release, as hydrochloride:

Sudafed® 24 Hour: 240 mg

Generic AvailableYes: Liquid, tablet

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Sudafed 24 Hour Non-Drowsy)

240 mg (10): $19.87

Tablets (Pseudoephedrine HCl)

60 mg (100): $10.13

Mechanism of ActionDirectly stimulates alpha-adrenergic receptors of respiratory mucosa causing vasoconstriction; directly stimulates beta-adrenergic receptors causing bronchial relaxation, increased heart rate and contractility

Pharmacodynamics/Kinetics

Onset of action: Decongestant: Oral: 15-30 minutes

Duration: Immediate release tablet: 4-6 hours; Extended release: ≤12 hours

Absorption: Rapid

Metabolism: Partially hepatic

Half-life elimination: 9-16 hours

Excretion: Urine (70% to 90% as unchanged drug, 1% to 6% as active norpseudoephedrine); dependent on urine pH and flow rate; alkaline urine decreases renal elimination of pseudoephedrine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDizziness, drowsiness, nervousness, and insomnia are common; may rarely cause hallucinations

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors

Index Terms*d*-Isoephedrine Hydrochloride; Pseudoephedrine Hydrochloride; Pseudoephedrine Sulfate

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International Brand NamesAcunaso (ZA); Afalpi Syrup (IL); Chemists' Own Sinus Relief (AU); Dexan (CN); Dimetapp Sinus Liquid caps (AU); Disofrol (SE); Disudrin (ID); Kopseu (KP); Logicin Plus (HK); Mex 24 (AR); Nasa-12 (LU); Otrinol (CH); Pseudono (TH); Rinafed (CR, GT, HN, PA, SV); Rinomar (BE); Soludril Rhinites (LU); Subulin (TW); Sudafed (AE, AU, BB, BH, BM, BS, BZ, CY, EE, EG, FR, GB, GY, IE, IL, IN, IQ, IR, IT, JM, JO, KP, KW, LB, LY, MX, NL, OM, PL, PT, QA, SA, SR, SY, TT, YE); Sudafed 12h (AU); Sudomyl (NZ); Sudosian (TH); Tiptipot (IL); Vasocedine (BE); Vidadrine (HK)

Psyllium

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English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Fiberall® may be confused with Feverall®

Hydrocil® may be confused with Hydrocet®

Modane® may be confused with Matulane®, Moban®

Pronunciation(SIL i yum)
U.S. Brand NamesBulk-K [OTC]; Fiberall®; Fibro-Lax [OTC]; Fibro-XL [OTC]; Genfiber™ [OTC]; Hydrocil® Instant [OTC]; Konsyl-D™ [OTC]; Konsyl® Easy Mix™ [OTC]; Konsyl® Orange [OTC]; Konsyl® Original [OTC]; Konsyl® [OTC]; Metamucil® Plus Calcium [OTC]; Metamucil® Smooth Texture [OTC]; Metamucil® [OTC]; Natural Fiber Therapy Smooth Texture [OTC]; Natural Fiber Therapy [OTC]; Reguloid [OTC]
Canadian Brand NamesMetamucil®
Pharmacologic CategoryAntidiarrheal; Laxative, Bulk-Producing
Use: Labeled IndicationsOTC labeling: Dietary fiber supplement; treatment of occasional constipation; reduce risk of coronary heart disease (CHD)
Use: Unlabeled/InvestigationalTreatment of diarrhea, chronic constipation, irritable bowel syndrome, inflammatory bowel disease, colon cancer, or diabetes
Dosing: AdultsGeneral dosing guidelines; consult specific product labeling.

Adequate intake for total fiber: Oral: **Note:** The definition of "fiber" varies, however, the soluble fiber in psyllium is only one type of fiber which makes up the daily recommended intake of total fiber.

Adults 19-50 years: Male: 38 g/day; Female: 25 g/day

Adults ≥51 years: Male: 30 g/day; Female: 21 g/day

Pregnancy: 28 g/day

Lactation: 29 g/day

Constipation: Oral: Psyllium: 2.5-30 g per day in divided doses

Reduce risk of CHD: Oral: Soluble fiber ≥7 g (psyllium seed husk ≥10.2 g) per day

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricGeneral dosing guidelines; consult specific product labeling.

Adequate intake for total fiber: Oral: **Note:** The definition of "fiber" varies, however, the soluble fiber in psyllium is only one type of fiber which makes up the daily recommended intake of total fiber.

Children 1-3 years: 19 g/day

Children 4-8 years: 25 g/day

Children 9-13 years: Male: 31 g/day; Female: 26 g/day

Children 14-18 years: Male: 38 g/day; Female: 26 g/day

Constipation: Oral:

Children 6-11 years: Psyllium: 1.25-15 g per day in divided doses

Children ≥12 years: Refer to adult dosing.

Reduce risk of CHD: Oral: Children ≥12 years: Refer to adult dosing.

Administration: OralInhalation of psyllium dust may cause sensitivity to psyllium (eg, runny nose, watery eyes, wheezing). Drink at least 8 ounces of liquid with each dose. Powder must be mixed in a glass of water or juice. Capsules should be swallowed one at a time. When more than one dose is required, they should be divided throughout the day. Separate dose by at least 2 hours from other drug therapies.
Dietary ConsiderationsProducts should be taken with at least 8 ounces of fluids. Some products contain dextrose, sucrose, calcium, potassium, phenylalanine, as well as additional ingredients. Check individual product information for caloric and nutritional value.

When used to reduce the risk of CHD, the amount of **soluble fiber** from psyllium should be ≥7 g/day and it should be used in conjunction with a diet low in saturated fat and cholesterol.

Fiberall® contains phenylalanine.

Metamucil® Smooth Texture orange flavor, sugar free formulation contains phenylalanine 25 mg per teaspoonful. Metamucil® Smooth Texture berry burst flavor contains phenylalanine 16 mg per teaspoonful. Metamucil® Smooth Texture pink lemonade flavor, sugar free formulation contains phenylalanine 19 mg per teaspoonful. Metamucil® wafers contain soy lecithin. Konsyl® Orange sugar free contains calcium 6 mg, phenylalanine 21 mg, potassium 31 mg, and sodium 3 mg per teaspoon.

ContraindicationsHypersensitivity to psyllium or any component of the formulation; fecal impaction; GI obstruction
Warnings/Precautions

Disease-related concerns:

- Coronary heart disease (CHD): To reduce the risk of CHD, the soluble fiber from psyllium should be used in conjunction with a diet low in saturated fat and cholesterol.

- Gastrointestinal disease: Use with caution in patients with esophageal strictures, ulcers, stenosis, or intestinal adhesions or difficulty swallowing

Special populations:

- Elderly: Use with caution in the elderly; may have insufficient fluid intake which may predispose them to fecal impaction and bowel obstruction.

Dosage form specific issues:

- Calcium: Some products may contain calcium.

- Phenylalanine: Some products may contain phenylalanine.

- Potassium: Some products may contain potassium.

- Sodium: Some products may contain sodium.

- Soy lecithin: Some products may contain soy lecithin.

Other warnings/precautions:

- Administration: Products must be taken with at least 8 ounces of fluid in order to prevent choking.

- Self-medication (OTC use): When used for self-medication (OTC), do not use in the presence of abdominal pain, nausea, or vomiting. Notify healthcare provider in case of sudden changes of bowel habits which last >2 weeks or in case of rectal bleeding. Not for self-treatment of constipation lasting >1 week.

Geriatric ConsiderationsElderly may have insufficient fluid intake which may predispose them to fecal impaction and bowel obstruction. Patients should have a 1 month trial, with at least 14 g/day, before effects in bowel function are determined. Bloating and flatulence are mostly a problem in first 4 weeks of therapy. See Warnings/Precautions.
Adverse ReactionsFrequency not defined.

Gastrointestinal: Abdominal cramps, constipation, diarrhea, esophageal or bowel obstruction

Respiratory: Bronchospasm

Miscellaneous: Anaphylaxis upon inhalation in susceptible individuals, rhinoconjunctivitis

Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringTeach patient proper use (according to formulation), possible side effects/appropriate interventions, and adverse symptoms to report.
Patient EducationTake as directed. Powder: Mix in large glass of water or juice (8 oz or more) and drink immediately. Maintain adequate hydration (2-3 L/day of fluids), unless instructed to restrict fluid intake. Mix carefully; do not inhale powder. Separate this medication from other medications by at least 1 hour. Results may begin in 12 hours; full results may take 2-3 days. Do not increase dose. Report persistent constipation; watery diarrhea; difficulty, pain, or choking with swallowing; respiratory difficulty; or unusual coughing.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Fibro XL: 0.675 g [sugar free; provides dietary fiber 3.8 g and soluble fiber 3 g per 7 capsules]

Genfiber™: 0.52 g [provides dietary fiber 3 g and soluble fiber 2 g per 6 capsules]

Konsyl®: 0.52 g [sugar free; contains calcium 8 mg, potassium <11 mg and sodium 1 mg per capsule; provides dietary fiber 3 g and soluble fiber 2 g per 5 capsules]

Metamucil®: 0.52 g [contains potassium 5 mg/capsule; provides dietary fiber 3 g and soluble fiber 2.1 g per 6 capsules]

Metamucil® Plus Calcium: 0.52 g [contains calcium 60 mg and potassium 6 mg per capsule; provides dietary fiber 3 g and soluble fiber 2.1 g per 5 capsules]

Reguloid: 0.52 g [provides dietary fiber 3 g and soluble fiber 2 g per 6 capsules]

Powder:

Bulk-K: 4.7 g/teaspoon (392 g) [provides dietary fiber 3.8 g and soluble fiber 3 g per teaspoon]

Fiberall®: 0.05 g/tablespoon (454 g) [sugar free; contains phenylalanine; psyllium is in combination with other fiber sources providing total dietary fiber 3.5 g and soluble fiber 2 g per tablespoon; also contains vitamins and minerals; orange flavor]

Fibro-Lax: 4.7 g/teaspoon (140 g, 392 g) [provides dietary fiber 3.8 g and soluble fiber 3 g per teaspoon]

Genfiber®:

3.4 g/teaspoon (397 g, 595 g) [contains sodium ≤5 mg teaspoon; provides dietary fiber 3 g and soluble fiber 2 g per teaspoon; natural flavor]

3.4 g/tablespoon (397 g) [contains sodium ≤5 mg tablespoon; provides dietary fiber 3 g and soluble fiber 2 g per tablespoon; orange flavor]

Hydrocil® Instant:

3.5 g/packet (30s, 500s) [sugar free; provides dietary fiber 3 g and soluble fiber 2.4 g per packet]

3.5 g/teaspoon (300 g) [sugar free; provides dietary fiber 3 g and soluble fiber 2.4 g per teaspoon]

Konsyl®: Original:

6 g/packet (30s, 100s, 500s) [sugar free; contains calcium 10 mg, sodium 5 mg, and potassium 55 mg per packet; provides dietary fiber 5 g and soluble fiber 3 g per packet]

6 g/teaspoon (300 g, 450 g) [sugar free; contains calcium 10 mg, sodium 5 mg, and potassium 55 mg per teaspoon; provides dietary fiber 5 g and soluble fiber 3 g per teaspoon]

Konsyl-D™:

3.4 g/packet (100s, 500s) [contains calcium 6 mg, dextrose 3.1 g, potassium 31 mg and sodium 3 mg per packet; provides dietary fiber 3 g and soluble fiber 2 g per packet]

3.4 g/teaspoon (325 g, 397 g, 500 g) [contains calcium 6 mg, dextrose 3.1 g, potassium 31 mg, and sodium 3 mg per teaspoon; provides dietary fiber 3 g and soluble fiber 2 g per teaspoon]

Konsyl® Easy Mix:

6 g/packet (500s) [sugar free; contains calcium 10 mg, potassium 55 mg, and sodium 5 mg per packet; provides dietary fiber 5 g and soluble fiber 3 g per packet]

6 g/teaspoon (250 g) [sugar free; contains calcium 10 mg, potassium 55 mg, and sodium 5 mg per teaspoon; provides dietary fiber 5 g and soluble fiber 3 g per teaspoon]

Konsyl® Orange:

3.4 g/packet (30s) [contains calcium 6 mg, potassium 31 mg, sodium 3 mg, and sucrose 8g per packet; provides dietary fiber 3 g and soluble fiber 2 g per packet; orange flavor]

3.4 g/tablespoon (538 g) [contains calcium 6 mg, potassium 31 mg, sodium 3 mg, and sucrose 8g per tablespoon; provides dietary fiber 3 g and soluble fiber 2 g per tablespoon; orange flavor]

3.4 g/teaspoon (425 g) [sugar free; contains calcium 6 mg, phenylalanine 21 mg, potassium 31 mg, and sodium 3 mg per teaspoon; provides dietary fiber 3 g and soluble fiber 2 g per teaspoon; orange flavor]

Metamucil®:

3.4 g/teaspoon (390 g, 570 g, 870 g) [contains sodium 5 mg and potassium 30 mg per teaspoon; provides dietary fiber 3 g and soluble fiber ~2 g per teaspoon; unflavored]

3.4g/tablespoon (570 g, 870 g, 1254 g) [contains sodium 5 mg and potassium 30 mg per tablespoon; provides dietary fiber 3 g and soluble fiber ~2 g per tablespoon; orange flavor]

Metamucil® Smooth Texture:

3.3 g/teaspoon (288 g, 432 g, 684 g) [sugar free; contains phenylalanine 19 mg, potassium 35 mg, and sodium 5 mg per teaspoon; provides dietary fiber 3 g and soluble fiber ~2 g per teaspoon; pink lemonade flavor]

3.4 g/packet (30s) [contains sodium 5 mg and potassium 30 mg per packet; provides dietary fiber 3 g and soluble fiber ~2 g per packet; orange flavor]

3.4 g/packet (30s) [sugar free; contains phenylalanine 16 mg, sodium 5 mg, and potassium 30 mg per packet; provides dietary fiber 3 g and soluble fiber ~2 g per packet; berry burst flavor]

3.4 g/packet (30s) [sugar free; contains phenylalanine 25 mg, sodium 5 mg, and potassium 30 mg per packet; provides dietary fiber 3 g and soluble fiber ~2 g per packet; orange flavor]

3.4 g/tablespoon (609 g, 912 g, 1368g 1446 g) [contains sodium 5 mg and potassium 30 mg per dose tablespoon; provides dietary fiber 3 g and soluble fiber ~2 g per tablespoon; orange flavor]

3.4 g/teaspoon (300 g, 450 g, 690 g) [sugar free; contains sodium 5 mg and potassium 30 mg per dose teaspoon; provides dietary fiber 3 g and soluble fiber ~2 g per teaspoon; unflavored]

3.4 g/teaspoon (173 g, 300 g, 450 g, 660 g, 1020 g) [sugar free; contains phenylalanine 25 mg, sodium 5 mg, and potassium 30 mg per teaspoon; provides dietary fiber 3 g and soluble fiber ~2 g per teaspoon; orange flavor]

3.4 g/teaspoon (283 g, 425 g, 660 g) [sugar free; contains potassium 30 mg, sodium 5 mg and phenylalanine 16 mg per teaspoon; provides dietary fiber 3 g and soluble fiber ~2 g per teaspoon; berry burst flavor]

Natural Fiber Therapy: 3.4 g/tablespoon (369 g, 539 g) [natural and orange flavors]

Natural Fiber Therapy Smooth Texture: 3.4 g/teaspoon (300 g) [sugar free; orange flavor]

Reguloid®:

3.4 g/teaspoon (284 g, 426 g) [sugar free; contains phenylalanine 30 mg and sodium 6 mg per teaspoon; provides dietary fiber 3 g and soluble fiber 3 g per teaspoon; orange flavor]

3.4 g/teaspoon (284 g, 426 g) [sugar free; contains phenylalanine 6 mg and sodium 2 mg per teaspoon; provides dietary fiber 3 g and soluble fiber 2 g per teaspoon; regular flavor]

3.4 g/tablespoon (369 g, 540 g) [contains sodium 9 mg per tablespoon; provides dietary fiber 3 g and soluble fiber 2 g per tablespoon; orange flavor]

3.4 g/tablespoon (369 g, 540 g) [contains sodium 4 mg per tablespoon; provides dietary fiber 2 g and soluble fiber 2 g per tablespoon; regular flavor]

Wafers:

Metamucil®: 3.4 g/2 wafers (24s) [contains soya lecithin, wheat, sodium 20 mg, and potassium 60 mg per 2 wafers; provides dietary fiber 6 g and soluble fiber 3 g per 2 wafers; apple and cinnamon spice flavors]

Generic AvailableYes: Excludes wafers

Mechanism of ActionPsyllium is a soluble fiber. It absorbs water in the intestine to form a viscous liquid which promotes peristalsis and reduces transit time.

Pharmacodynamics/Kinetics

Onset of action: Relief of constipation: 12-72 hours

Absorption: None; small amounts of grain extracts present in the preparation have been reportedly absorbed following colonic hydrolysis

Related Information

- Laxatives, Classification and Properties

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPlantago Seed; Plantain Seed; Psyllium Husk; Psyllium Hydrophilic Mucilloid

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PVA (POG 8602)

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Pharmacologic Category[Chemotherapy Regimen, Leukemia, Acute Lymphocytic]

Regimen UseLeukemia, acute lymphocytic

Index TermsAlinC 14

Regimen

Induction:

Prednisone: Oral: 40 mg/m^2/day (maximum 60 mg) days 0 to 28 (given in 3 divided doses)

[total dose/cycle = 1160 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2/day (maximum 2 mg) days 0, 7, 14, and 21

[total dose/cycle = 6 mg/m^2; maximum 8 mg]

Asparaginase: I.M.: 6000 units/m^2 3 times per week for 2 weeks

[total dose/cycle = 36,000 units/m^2]

Intrathecal therapy (triple): Days 0 and 22

Leucovorin: route and dose not specified: single dose 24 hours after every intrathecal treatment days 1 and 23

Administer one cycle only

CNS consolidation:

Mercaptopurine: Oral: 75 mg/m^2/day days 29 to 43

[total dose/cycle = 1125 mg/m^2]

Intrathecal therapy (triple): Days 29 and 36

Leucovorin: route and dose not specified: single dose 24 hours after every intrathecal treatment days 30 and 37

Administer one cycle only

Intensification:

Regimen A:

Methotrexate: I.V.: 1000 mg/m^2 continuous infusion over 24 hours day 1

[total dose/cycle = 1000 mg/m^2]

Cytarabine: I.V.: 1000 mg/m^2 continuous infusion over 24 hours day 1 (start 12 hours after start of methotrexate)

[total dose/cycle = 1000 mg/m^2]

Leucovorin: I.M., I.V., or Oral: 30 mg/m^2 at 24 and 36 hours after the start of methotrexate

[total dose/cycle = 60 mg/m^2]

followed by I.M., I.V., or Oral: 3 mg/m^2 at 48, 60, and 72 hours after the start of methotrexate

[total dose/cycle = 9 mg/m^2]

Repeat cycle every 3 weeks for 6 cycles (administered weeks 7, 10, 13, 16, 19, and 22)

Intrathecal therapy (triple): Weeks 9, 12, 15, and 18

Leucovorin: route and dose not specified: single dose 24 hours after every intrathecal treatment weeks 9, 12, 15, and 18

or

Regimen B:

Methotrexate: I.V.: 1000 mg/m^2 continuous infusion over 24 hours day 1

[total dose/cycle = 1000 mg/m^2]

Cytarabine: I.V.: 1000 mg/m^2 continuous infusion over 24 hours day 1 (start 12 hours after methotrexate)

[total dose/cycle = 1000 mg/m^2]

Leucovorin: I.M., I.V., or Oral: 30 mg/m^2 at 24 and 36 hours after the start of methotrexate

[total dose/cycle = 60 mg/m^2]

followed by I.M., I.V., or Oral: 3 mg/m^2 at 48, 60, and 72 hours after the start of methotrexate

[total dose/cycle = 9 mg/m^2]

Repeat cycle every 12 weeks for 6 cycles (administer weeks 7, 19, 31, 43, 55, and 67)

Intrathecal therapy (triple): Weeks 9, 12, 15, and 18

Leucovorin: route and dose not specified: single dose 24 hours after every intrathecal treatment weeks 9, 12, 15, and 18

Maintenance:

Regimen A:

Methotrexate: I.M.: 20 mg/m^2 weekly, weeks 25 to 156

[total dose/cycle = 2640 mg/m^2]

Mercaptopurine: Oral: 75 mg/m^2 daily, weeks 25 to 156

[total dose/cycle = 69,300 mg/m^2]

Intrathecal therapy (triple): Every 8 weeks, weeks 26 through 105

Leucovorin: route and dose not specified: single dose 24 hours after every intrathecal treatment weeks 26 through 105

Prednisone: Oral: 40 mg/m^2/day (maximum 60 mg) days 1 to 7 (given in 3 divided doses), weeks 8, 17, 25, 41, 57, 73, 89, and 105

[total dose/cycle = 2240 mg/m^2; maximum 3360 mg]

Vincristine: I.V.: 1.5 mg/m^2/day (maximum 2 mg) day 1, weeks 8, 9, 17, 18, 25, 26, 41, 42, 57, 58, 73, 74, 89, 90, 105, and 106

[total dose/cycle = 24 mg/m^2; maximum 32 mg]

or

Regimen B:

Methotrexate: I.M.: 20 mg/m^2 weekly, weeks 22-28, 34-40, 46-52, and 58-64

[total dose/cycle = 560 mg/m^2]

Mercaptopurine: Oral: 75 mg/m^2 daily for 7 weeks, weeks 22-28, 34-40, 46-52, and 58-64

[total dose/cycle = 14700 mg/m^2]

followed by

Methotrexate: I.M.: 20 mg/m^2 weekly, weeks 70 to 156

[total dose/cycle = 1720 mg/m^2]

Mercaptopurine: Oral: 75 mg/m^2 daily, weeks 70 to 156

[total dose/cycle = 45,150 mg/m^2]

Intrathecal therapy (triple): Every 8 weeks, weeks 26 through 105

Leucovorin: route and dose not specified: single dose 24 hours after every intrathecal treatment weeks 26 through 105

Prednisone: Oral: 40 mg/m^2/day (maximum 60 mg) days 1 to 7 (given in 3 divided doses), weeks 8, 17, 25, 41, 57, 73, 89, and 105

[total dose/cycle = 2240 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2/day (maximum 2 mg) day 1, weeks 8, 9, 17, 18, 25, 26, 41, 42, 57, 58, 73, 74, 89, 90, 105, and 106

[total dose/cycle = 24 mg/m^2; maximum 32 mg]

References

Land VJ, Shuster JJ, Crist WM, et al, âComparison of Two Schedules of Intermediate-Dose Methotrexate and Cytarabine Consolidation Therapy for Childhood B-Precursor Cell Acute Lymphoblastic Leukemia: A Pediatric Oncology Group Study,â *J Clin Oncol*, 1994, 12(9):1939-45.[PubMed 8083715]

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Testicular Cancer]

Regimen UseTesticular cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Vinblastine: I.V.: 0.2 mg/kg/day days 1 and 2

[total dose/cycle = 0.4 mg/kg]

Bleomycin: I.V.: 30 units/day days 2, 9, and 16

[total dose/cycle = 90 units]

Repeat cycle every 3 weeks

Variation 2:

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Vinblastine: I.V.: 0.15 mg/kg/day days 1 and 2

[total dose/cycle = 0.3 mg/kg]

Bleomycin: I.V.: 30 units/day days 2, 9, and 16

[total dose/cycle = 90 units]

Repeat cycle every 3 weeks

Variation 3:

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Vinblastine: I.V.: 6 mg/m^2/day days 1 and 2

[total dose/cycle = 12 mg/m^2]

Bleomycin: I.M.: 30 units/day days 2, 9, and 16

[total dose/cycle = 90 units]

Repeat cycle every 3 weeks

References

Variation 1:

Einhorn LH and Donohue J, “Cis-Diamminedichloroplatinum, Vinblastine, and Bleomycin Combination Chemotherapy in Disseminated Testicular Cancer,” *Ann Intern Med*, 1977, 87(3):293-8. [PubMed 71004]

Variation 2:

Williams SD, Birch R, Einhorn LH, et al, “Treatment of Disseminated Germ-Cell Tumors With Cisplatin, Bleomycin, and Either Vinblastine or Etoposide,” *N Engl J Med*, 1987, 316(23):1435-40. [PubMed 2437455]

Variation 3:

Bodrogi I, Baki M, Horti J, et al, “Vinblastine, Cisplatin, and Bleomycin Treatment of Advanced Nonseminomatous Testicular Tumors,” *Neoplasma*, 1990, 37(4):445-50.[PubMed 1700311]

PVDA

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Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Leukemia, Acute Lymphocytic]

Regimen UseLeukemia, acute lymphocytic

RegimenInduction:

Prednisone: Oral: 60 mg/m^2/day days 1 to 28

[total dose/cycle = 1680 mg/m^2]

Vincristine: I.V.: 1.5 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 6 mg/m^2]

Daunorubicin: I.V.: 25 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 100 mg/m^2]

Asparaginase: I.M., SubQ, or I.V.: 5000 units/m^2/day days 1 to 14

[total dose/cycle = 70,000 units/m^2]

Administer one cycle only; used in conjunction with intrathecal chemotherapy

References

Hoelzer D, Thiel E, Loffler H, et al, âIntensified Therapy in Acute Lymphoblastic and Acute Undifferentiated Leukemia in Adults,â *Blood*, 1984, 64(1):38-47.[PubMed 6375764]

Pyrantel Pamoate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(pi RAN tel PAM oh ate)

U.S. Brand NamesPin-X® [OTC]; Reese's® Pinworm Medicine [OTC]

Canadian Brand NamesCombantrin™

Pharmacologic CategoryAnthelmintic

Use: Labeled IndicationsTreatment of pinworms (*Enterobius vermicularis*) and roundworms (*Ascaris lumbricoides*)

Use: Unlabeled/InvestigationalTreatment of whipworms (*Trichuris trichiura*) and hookworms (*Ancylostoma duodenale*)

Dosing: Adults**Note:** Dose is expressed as pyrantel base.

Roundworm, pinworm, or trichostrongyliasis: Oral: 11 mg/kg administered as a single dose; maximum dose: 1 g. (**Note:** For pinworm infection, dosage should be repeated in 2 weeks and all family members should be treated).

Hookworm (unlabeled use): Oral: 11 mg/kg administered once daily for 3 days

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

StorageProtect from light.

ContraindicationsHypersensitivity to pyrantel pamoate or any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Anemia: Use with caution in patients with anemia.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Malnutrition: Use with caution in patients with malnutrition.

Special populations:

- Pregnancy: Use with caution in pregnancy.

Other warnings/precautions:

- Household contacts: Since pinworm infections are easily spread to others, treat all family members in close contact with the patient.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Central nervous system: Dizziness, drowsiness, insomnia, headache

Dermatologic: Rash

Gastrointestinal: Abdominal cramps, anorexia, diarrhea, nausea, vomiting, tenesmus

Hepatic: Liver enzymes increased

Neuromuscular & skeletal: Weakness

Drug Interactions

Aminoquinolines (Antimalarial): May decrease the serum concentration of Anthelmintics. *Risk C: Monitor therapy*

Monitoring ParametersStool for presence of eggs, worms, and occult blood, serum AST and ALT

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet, as pamoate:

Reese's® Pinworm Medicine: 180 mg [equivalent to pyrantel base 62.5 mg/tablet]

Suspension, oral as pamoate:

Pin-X®: 144 mg/mL (30 mL, 60 mL) [equivalent to pyrantel base 50 mg/mL; sugar free; contains sodium benzoate; caramel flavor]

Reese's® Pinworm Medicine: 144 mg/mL (30 mL) [equivalent to pyrantel base 50 mg/mL]

Tablet, chewable, as pamoate:

Pin-X®: 720.5 mg [equivalent to pyrantel base 250 mg/tablet; contains aspartame; orange flavor]

Generic AvailableNo

Mechanism of ActionCauses the release of acetylcholine and inhibits cholinesterase; acts as a depolarizing neuromuscular blocker, paralyzing the helminths

Pharmacodynamics/Kinetics

Absorption: Oral: Poor

Metabolism: Partially hepatic

Time to peak, serum: 1-3 hours

Excretion: Feces (50% as unchanged drug); urine (7% as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, or insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

References

"Drugs for Parasitic Infections," *Med Lett Drugs Ther*, 1998, 40(1017):1-12.[PubMed 9442765]

International Brand NamesAnthel (AU, TW); Anthelmin (PK); Ascarical (BR); Aut (AR); Bearantel (SG); Bifantrel (CO); Combantril (CH); Combantrin (AT, BG, CN, EC, FR, GB, GR, IT, PE, PH, PT, VE, ZA); Early Bird (AU); Gelminthic (PH); Helmex (DE); Helmintox (FR); Nemocid (IN); Pirantelina (PY); Piraska (ID); Pyrantelum (PL); Pyrapam (TH); Quantrel (VE); Trilombrin (EC, ES)

Pyrazinamide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(peer a ZIN a mide)
Canadian Brand NamesTebrazid™
Pharmacologic CategoryAntitubercular Agent
Use: Labeled IndicationsAdjunctive treatment of tuberculosis in combination with other antituberculosis agents
Dosing: Adults

Tuberculosis treatment: Oral (dosing is based on lean body weight):

Daily therapy: 15-30 mg/kg/day

40-55 kg: 1000 mg

56-75 kg: 1500 mg

76-90 kg: 2000 mg (maximum dose regardless of weight)

Twice weekly directly observed therapy (DOT): 50 mg/kg

40-55 kg: 2000 mg

56-75 kg: 3000 mg

76-90 kg: 4000 mg (maximum dose regardless of weight)

Three times/week DOT: 25-30 mg/kg (maximum: 2.5 g)

40-55 kg: 1500 mg

56-75 kg: 2500 mg

76-90 kg: 3000 mg (maximum dose regardless of weight)

Note: Used as part of a multidrug regimen. Treatment regimens consist of an initial 2-month phase, followed by a continuation phase of 4 or 7 additional months; frequency of dosing may differ depending on phase of therapy.

Dosing: ElderlyStart with a lower daily dose (15 mg/kg) and increase as tolerated.
Dosing: Pediatric

Tuberculosis treatment: Oral:

Daily therapy: 15-30 mg/kg/day (maximum: 2 g/day)

Twice weekly directly observed therapy (DOT): 50 mg/kg/dose (maximum: 4 g/dose)

See “Note” in adult dosing.

Dosing: Renal Impairment

Cl_{cr} <50 mL/minute: Avoid use or reduce dose to 12-20 mg/kg/day.

Avoid use in hemo- and peritoneal dialysis as well as continuous arteriovenous or venovenous hemofiltration.

Dosing: Hepatic ImpairmentReduce dose.
Calculations

- Adjusted Body Weight
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Ideal Body Weight: Adults

Extemporaneously PreparedPyrazinamide suspension can be compounded with simple syrup or 0.5% methylcellulose with simple syrup at a concentration of 100 mg/mL; the suspension is stable for 2 months at 4°C or 25°C when stored in glass or plastic bottles

To prepare pyrazinamide suspension in 0.5% methylcellulose with simple syrup: Crush 200 pyrazinamide 500 mg tablets and mix with a suspension containing 500 mL of 1% methylcellulose and 500 mL simple syrup. Add to this a suspension containing 140 crushed pyrazinamide tablets in 350 mL of 1% methylcellulose and 350 mL of simple syrup to make 1.7 L of suspension containing pyrazinamide 100 mg/mL in 0.5% methylcellulose with simple syrup.

Nahata MC, Morosco RS, and Peritre SP, "Stability of Pyrazinamide in Two Suspensions," *Am J Health Syst Pharm*, 1995, 52:1558-60.

ContraindicationsHypersensitivity to pyrazinamide or any component of the formulation; acute gout; severe hepatic damage
Warnings/Precautions

Concerns related to adverse effects:

- Hepatotoxicity: Dose-related hepatotoxicity ranging from transient ALT/AST elevations to jaundice, hepatitis and/or liver atrophy (rare) has occurred.

Disease-related concerns:

- Alcoholism: Due to concerns for pre-existing hepatic dysfunction, use with caution in patients with a history of alcoholism (even if ethanol consumption is discontinued during therapy).

- Diabetes: Use with caution in patients with diabetes mellitus.

- Gout: May inhibit uric acid excretion; acute gouty attacks have been reported. Use with caution in patients with chronic gout; contraindicated with acute gout.

- Porphyria: Use with caution in patients with porphyria.

- Renal impairment: Use with caution in patients with renal failure.

Concurrent drug therapy issues:

- Hepatotoxic agents: Use with caution in patients receiving concurrent medications associated with hepatotoxicity (particularly with rifampin).

Geriatric ConsiderationsPyrazinamide is used in the 2-month intensive treatment phase of a 6-month treatment plan. Most elderly acquired their *Mycobacterium tuberculosis* infection before effective chemotherapy was available; however, older persons with new infections (not reactivation), or who are from areas where drug-resistant *M. tuberculosis* is endemic, or who are HIV-infected should receive 3-4 drug therapies including pyrazinamide.
Pregnancy Risk FactorC
LactationEnters breast milk/use caution
Adverse Reactions

1% to 10%:

Central nervous system: Malaise

Gastrointestinal: Anorexia, nausea, vomiting

Neuromuscular & skeletal: Arthralgia, myalgia

<1%: Acne, angioedema (rare), anticoagulant effect, dysuria, fever, gout, hepatotoxicity, interstitial nephritis, itching, photosensitivity, porphyria, rash, sideroblastic anemia, thrombocytopenia, urticaria

Drug Interactions

CycloSPORINE: Pyrazinamide may decrease the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Rifampin: Pyrazinamide may enhance the hepatotoxic effect of Rifampin. Severe (even fatal) liver injury has been reported in patients receiving these 2 drugs as a 2-month treatment regimen for latent TB infection. *Risk D: Consider therapy modification*

Test InteractionsReacts with Acetest® and Ketostix® to produce pinkish-brown color
Monitoring ParametersPeriodic liver function tests, serum uric acid, sputum culture, chest x-ray 2-3 months into treatment and at completion
Nursing: Physical Assessment/MonitoringAssess patient history for use cautions and evaluate any history of alcohol intake prior to beginning treatment. Administer with at least one other effective agent for tuberculosis (other than rifampin). Assess for potential interactions with pharmacological or herbal products patient is taking (especially anything associated with hepatotoxicity). Evaluate results of laboratory tests and chest x-ray regularly, therapeutic effectiveness, and adverse reactions. Teach patient proper use and necessity of scheduled laboratory tests, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsPeriodic liver function, serum uric acid, sputum culture, chest x-ray 2-3 months into treatment and at completion
Patient EducationTake as directed, with food. It is imperative to take for full length of therapy; do not miss doses and do not discontinue without consulting prescriber. You will need regular medical follow-up and laboratory tests while taking this medication. May cause nausea or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report change in color of urine, pale stools, easy bruising or bleeding, blood in urine or difficulty urinating, yellowing of skin or eyes, extreme joint pain, unusual fever, or unresolved nausea or vomiting, **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 500 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Pyrazinamide)

500 mg (30): $35.03

Mechanism of ActionConverted to pyrazinoic acid in susceptible strains of *Mycobacterium* which lowers the pH of the environment; exact mechanism of action has not been elucidated

Pharmacodynamics/KineticsBacteriostatic or bactericidal depending on drug's concentration at infection site

Absorption: Well absorbed

Distribution: Widely into body tissues and fluids including liver, lung, and CSF

Relative diffusion from blood into CSF: Adequate with or without inflammation (exceeds usual MICs)

CSF:blood level ratio: Inflamed meninges: 100%

Protein binding: 50%

Metabolism: Hepatic

Half-life elimination: 9-10 hours

Time to peak, serum: Within 2 hours

Excretion: Urine (4% as unchanged drug)

Related Information

- Antimicrobial Drugs of Choice
- Tuberculosis
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPyrazinoic Acid Amide

References

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American Thoracic Society, “Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection,” *MMWR Recomm Rep*, 2000, 49(RR-6):1-51.

Bass JB Jr, Farer LS, Hopewell PC, et al, “Treatment of Tuberculosis and Tuberculosis Infection in Adults and Children,” *Am J Respir Crit Care Med*, 1994, 149(5):1359-74. [PubMed 8173779]

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“Drugs for Tuberculosis,” *Med Lett Drugs Ther*, 1993, 35(908):99-101. [PubMed 8412982]

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Herlevsen P, Nielsen C, and Pedersen JT, “Convulsions After Treatment With Pyrazinamide,” *Tubercle*, 1987, 68(2):145-6. [PubMed 3499016]

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Lacroix C, Hoang TP, Nouveau J, et al, “Pharmacokinetics of Pyrazinamide and Its Metabolites in Healthy Subjects,” *Eur J Clin Pharmacol*, 1989, 36(4):395-400. [PubMed 2737233]

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Starke JR, “Multidrug Therapy for Tuberculosis in Children,” *Pediatr Infect Dis J*, 1990, 9(11):785-93. [PubMed 2124671]

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Van Scoy RE and Wilkowske CJ, "Antituberculous Agents," *Mayo Clin Proc*, 1992, 67(2):179-87. [PubMed 1347579]

Yoshikawa TT, "Tuberculosis in Aging Adults," *J Am Geriatr Soc*, 1992, 40(2):178-87.[PubMed 1740604]

International Brand NamesBraccopiral (PH); Corsazinmid (ID); Mide (TW); Neotibi (ID); P-Zide (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); P.T.B. (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); P.Z.A. (TW); Piraldina (AE, BG, BH, CY, EG, IL, IN, IQ, IR, IT, JO, KW, LB, LY, OM, QA, SA, SY, YE); Pirazimida (ES); Pirazinamida Prodes (ES); Pirilene (FR); Pramide (PT); Pyrafat (AT, DE, HK); Pyramide (TH); Pyramin (PH); Pyrasol (PH); Pyrazid (PK); Pyrazinamid (HR, HU, PL); Pyrazinamid Lederle (CH); Pyrazinamid "Dak" (DK); Pyrazinamid "Medic" (DK); Pyrazinamide (TH); Pyzamed (PH); PZA (CH); PZA-Ciba (IN, SG); Rifater (MX); Siramid (ID); TBZET (ID); Tebrazid (BE, CH, LU); Tisamid (CZ, FI); TZM (TH); Zapedia (PH); Zcure (PH); Zinamide (AU, GB, IE, NZ)

Pyrethrins and Piperonyl Butoxide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(pye RE thrins & pi PER oh nil byo TOKS ide)

U.S. Brand NamesA-200® Lice Treatment Kit [OTC]; A-200® Maximum Strength [OTC]; Licide® [OTC]; Pronto® Complete Lice Removal System [OTC]; Pronto® Plus Hair and Scalp Masque [OTC] [DSC]; Pronto® Plus Lice Killing Mousse Plus Vitamin E [OTC]; Pronto® Plus Lice Killing Mousse Shampoo Plus Natural Extracts and Oils [OTC]; Pronto® Plus Warm Oil Treatment and Conditioner [OTC]; RID® Maximum Strength [OTC]; Tisit® Blue Gel [OTC]; Tisit® [OTC]

Canadian Brand NamesPronto® Lice Control; R & C™ II; R & C™ Shampoo/Conditioner; RID® Mousse

Pharmacologic CategoryAntiparasitic Agent, Topical; Pediculocide; Shampoo, Pediculocide

Use: Labeled IndicationsTreatment of *Pediculus humanus* infestations (head lice, body lice, pubic lice, and their eggs)

Dosing: Adults**Treatment of *Pediculus humanus* infestations:**

Topical products:

Apply enough solution to completely wet infested area, including hair

Allow to remain on area for 10 minutes

Wash and rinse with large amounts of warm water

Use fine-toothed comb to remove lice and eggs from hair

Shampoo hair to restore body and luster

Treatment may be repeated if necessary once in a 24-hour period

Repeat treatment in 7-10 days to kill newly hatched lice

Note: Keep out of eyes when rinsing hair; protect eyes with a wash cloth or towel.

Solution for furniture, bedding: Spray on entire area to be treated; allow to dry before use. Intended for use on items which cannot be laundered or dry cleaned. **Not for use on humans or animals.**

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Head lice, body lice:** Children: Refer to adult dosing.

Administration: TopicalFor external use only. Avoid touching eyes, mouth, or other mucous membranes.

StorageStore at room temperature of 20°C to 25°C (68°F to 77°F). Do not puncture or incinerate mousse container.

ContraindicationsHypersensitivity to pyrethrins, ragweed, chrysanthemums, or any component of the formulation

Warnings/Precautions

Other warnings/precautions:

- Appropriate use: For external use only; do not use near the eye, in eyelashes or eyebrows. Avoid contact with mucosal tissues (nasal, oral, or genital).

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Dermatologic: Pruritus

Local: Burning, stinging, irritation with repeat use

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, topical:

Pronto® Plus Hair and Scalp Masque: Pyrethrins 0.33% and piperonyl butoxide 4% (60 g) [green cream shampoo; contains coconut and sesame oil; apple herb scent; packaged with nit removal comb] [DSC]

Foam, topical [mousse]:

RID® Maximum Strength: Pyrethrins 0.33% and piperonyl butoxide 4% (156 g) [packaged with nit removal comb] [DSC]

Gel, topical:

Tisit® Blue Gel: Pyrethrins 0.33% and piperonyl butoxide 3% (30 g)

Kit:

- A-200® Lice Treatment Kit:
    - Shampoo: Pyrethrins 0.33% and piperonyl butoxide 4% (120 mL)
    - Solution [spray; for bedding; not for human or animal use]: Permethrin 0.5% (180 mL)
    - [packaged with nit removal comb]
- Pronto® Complete Lice Removal System:
    - Shampoo: Pyrethrins 0.33% and piperonyl butoxide 4% (60 mL)
    - Solution, topical: Benzalkonium chloride 0.1% (60 mL) [lice egg remover antiseptic]
    - [packaged with household furniture spray and nit removal comb]

Liquid, topical:

- Tisit®: Pyrethrins 0.33% and piperonyl butoxide 2% (60 mL, 120 mL) [packaged with nit removal comb]

Oil, topical:

- Pronto® Plus Warm Oil Treatment and Conditioner: Pyrethrins 0.33% and piperonyl butoxide 4% (36 mL) [fruity herbal scent; packaged with nit removal comb]

Shampoo: Pyrethrins 0.33% and piperonyl butoxide 4% (60 mL, 120 mL)

- A-200® Maximum Strength: Pyrethrins 0.33% and piperonyl butoxide 4% (60 mL, 120 mL) [contains benzyl alcohol; packaged with nit removal comb]
- Licide®: Pyrethrins 0.33% and piperonyl butoxide 4% (120 mL) [packaged with nit removal comb; also available in a kit containing shampoo, household spray, and nit removal comb]
- Pronto® Plus Lice Killing Mousse Shampoo Plus Natural Extracts and Oils: Pyrethrins 0.33% and piperonyl butoxide 4% (60 mL) [packaged with nit removal comb]
- Pronto® Plus Lice Killing Mousse Shampoo Plus Vitamin E: Pyrethrins 0.33% and piperonyl butoxide 4% (120 mL) [blue mousse shampoo; contains vitamin E; packaged with nit removal comb]
- RID® Maximum Strength: Pyrethrins 0.33% and piperonyl butoxide 4% (60 mL, 120 mL, 180 mL, 240 mL) [packaged with nit removal comb; also available in a kit containing shampoo, gel, and furniture spray]
- Tisit®: Pyrethrins 0.33% and piperonyl butoxide 3% (60 mL, 120 mL) [also available in a kit containing shampoo, nit removal comb, and furniture spray]

Solution [spray; for furniture, garments, bedding; not for human or animal use]:

- Tisit®: Pyrethrins 0.4% and piperonyl butoxide 2% (150 mL)

Generic Available Yes: Shampoo

Mechanism of Action Pyrethrins are derived from flowers that belong to the chrysanthemum family. The mechanism of action on the neuronal membranes of lice is similar to that of DDT. Piperonyl butoxide is usually added to pyrethrin to enhance the product's activity by decreasing the metabolism of pyrethrins in arthropods.

Pharmacodynamics/Kinetics

Onset of action: ~30 minutes

Absorption: Minimal

Metabolism: Via ester hydrolysis and hydroxylation

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Piperonyl Butoxide and Pyrethrins

References

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International Brand NamesPronto Lice Control (CA); R & C® II (CA); R & C® Shampoo/Conditioner (CA); RID Mousse (CA)

Pyridostigmine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Pyridostigmine may be confused with physostigmine

Mestinon® may be confused with Metatensin®

Regonol® may be confused with Reglan®, Renagel®

Pronunciation(peer id oh STIG meen)

U.S. Brand NamesMestinon®; Mestinon® Timespan®; Regonol®

Canadian Brand NamesMestinon®; Mestinon®-SR

Pharmacologic CategoryAcetylcholinesterase Inhibitor

Use: Labeled IndicationsSymptomatic treatment of myasthenia gravis; antidote for nondepolarizing neuromuscular blockers

Military use: Pretreatment for Soman nerve gas exposure

Dosing: Adults

Myasthenia gravis:

Oral: Highly individualized dosing ranges: 60-1500 mg/day, usually 600 mg/day divided into 5-6 doses, spaced to provide maximum relief

Sustained release formulation: Highly individualized dosing ranges: 180-540 mg once or twice daily (doses separated by at least 6 hours); **Note:** Most clinicians reserve sustained release dosage form for bedtime dose only.

I.M. or slow I.V. Push: To supplement oral dosage pre- and postoperatively during labor and postpartum, during myasthenic crisis, or when oral therapy is impractical): ~1/30th of oral dose; observe patient closely for cholinergic reactions

I.V. infusion: To supplement oral dosage pre- and postoperatively, during labor and postpartum, during myasthenic crisis, or when oral therapy is impractical): Initial: 2 mg/hour with gradual titration in increments of 0.5-1 mg/hour, up to a maximum rate of 4 mg/hour

Pretreatment for Soman nerve gas exposure (military use): Oral: 30 mg every 8 hours beginning several hours prior to exposure; discontinue at first sign of nerve agent exposure, then begin atropine and pralidoxime

Reversal of nondepolarizing muscle relaxants: I.V.: 0.1-0.25 mg/kg/dose; 10-20 mg is usually sufficient (full recovery usually occurs ≤15 minutes, but ≥30 minutes may be required).

Note: Atropine sulfate (0.6-1.2 mg) I.V. immediately prior to pyridostigmine to minimize side effects

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Myasthenia gravis:

Oral: Children: 7 mg/kg/24 hours divided into 5-6 doses. Most clinicians reserve sustained release dosage form for bedtime dose only.

I.M., slow I.V. push: Children: 0.05-0.15 mg/kg/dose

Reversal of nondepolarizing muscle relaxants: I.V.: Children: Dosing range: 0.1-0.25 mg/kg/dose (full recovery usually occurs ≤15 minutes, but ≥30 minutes may be required).

Note: Atropine sulfate (0.6-1.2 mg) I.V. immediately prior to pyridostigmine to minimize side effects:

Dosing: Renal ImpairmentLower dosages may be required due to prolonged elimination; no specific recommendations have been published.

Administration: I.V. DetailpH: 5

Administration: OralDo **not** crush sustained release tablet.

Storage

Injection: Protect from light.

Tablet:

30 mg: Store under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light. Stable at room temperature for up to 3 months.

Mestinon®: Store at 25°C (77°F). Protect from moisture.

Compatibility

Y-site administration: Compatible: Heparin, hydrocortisone sodium succinate, potassium chloride, vitamin B complex with C.

Compatibility in syringe: Compatible: Glycopyrrolate.

ContraindicationsHypersensitivity to pyridostigmine, bromides, or any component of the formulation; GI or GU obstruction
Allergy Considerations

- Cholinesterase Inhibitor Allergy

Warnings/Precautions

Boxed warnings:

- Regonol® injection: See "Dosage form specific issues" below.

Concerns related to adverse effects:

- Anticholinesterase insensitivity: For brief or prolonged periods, anticholinesterase insensitivity can develop.
- Cholinergic effects: Discontinue if symptoms of excess cholinergic activity (eg, salivation, sweating, urinary incontinence); overdosage may result in cholinergic crisis, which must be distinguished from myasthenic crisis.
- Hypersensitivity reactions: Have atropine and epinephrine ready to treat hypersensitivity reactions.

Disease-related concerns:

- Asthma: Use with caution in patients with asthma.
- Cardiovascular disease: Use with caution in patients with bradycardia or cardiac arrhythmias.
- GI disease: Use with caution in patients with GI disease, including peptic ulcer disease.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.
- Myasthenia gravis: Adequate facilities should be available for cardiopulmonary resuscitation when testing and adjusting dose for myasthenia gravis.
- Seizure disorder: Use with caution in patients with a history of seizure disorder.

Dosage form specific issues:

- Regonol® injection: Contains 1% benzyl alcohol as the preservative; not intended for use in newborns. **[U.S. Boxed Warning]: Must be administered by trained personnel.**

Geriatric ConsiderationsMany elderly may have pulmonary or cardiovascular diseases which will require cautious use of pyridostigmine.
Pregnancy Risk FactorB
Pregnancy ConsiderationsSafety has not been established for use during pregnancy. The potential benefit to the mother should outweigh the potential risk to the fetus. When pyridostigmine is needed in myasthenic mothers, giving dose parenterally 1 hour before completion of the second stage of labor may facilitate delivery and protect the neonate during the immediate postnatal state.
LactationEnters breast milk/compatible
Breast-Feeding ConsiderationsNeonates of myasthenia gravis mothers may have difficulty in sucking and swallowing (as well as breathing). Neonatal pyridostigmine may be indicated by symptoms (confirmed by edrophonium test).
Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias (especially bradycardia), AV block, cardiac arrest, decreased carbon monoxide, flushing, hypotension, nodal rhythm, nonspecific ECG changes, syncope, tachycardia

Central nervous system: Convulsions, dizziness, drowsiness, dysphonia, headache, loss of consciousness

Dermatologic: Skin rash, thrombophlebitis (I.V.), urticaria

Gastrointestinal: Abdominal pain, diarrhea, dysphagia, flatulence, hyperperistalsis, nausea, salivation, stomach cramps, vomiting

Genitourinary: Urinary urgency

Neuromuscular & skeletal: Arthralgia, dysarthria, fasciculations, muscle cramps, myalgia, spasms, weakness

Ocular: Amblyopia, lacrimation, small pupils

Respiratory: Bronchial secretions increased, bronchiolar constriction, bronchospasm, dyspnea, laryngospasm, respiratory arrest, respiratory depression, respiratory muscle paralysis

Miscellaneous: Allergic reactions, anaphylaxis, diaphoresis increased

Drug Interactions

Beta-Blockers: Acetylcholinesterase Inhibitors may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Cholinergic Agonists: Acetylcholinesterase Inhibitors may enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Ginkgo Biloba: May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. *Risk C: Monitor therapy*

Methocarbamol: May diminish the therapeutic effect of Pyridostigmine. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): Acetylcholinesterase Inhibitors may diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Succinylcholine: Acetylcholinesterase Inhibitors may enhance the neuromuscular-blocking effect of Succinylcholine. *Risk C: Monitor therapy*

Test InteractionsIncreased aminotransferase [ALT/AST] (S), increased amylase (S)

Monitoring ParametersObserve for cholinergic reactions, particularly when administered I.V.

Nursing: Physical Assessment/MonitoringWhen used to reverse neuromuscular block (anesthesia or excessive acetylcholine), monitor patient safety until full return of neuromuscular functioning. Assess bladder and sphincter adequacy prior to administering medication. Monitor therapeutic effectiveness and adverse reactions (eg, cholinergic crisis). Assess knowledge/teach patient appropriate use (self-injections, oral), interventions to reduce side effects, and adverse symptoms to report.

Patient EducationThis drug will not cure myasthenia gravis, but may help reduce symptoms. Use as directed; do not increase dose or discontinue without consulting prescriber. Take extended release tablets at bedtime; do not chew or crush extended release tablets. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause dizziness, drowsiness, or hypotension (rise slowly from sitting or lying position and use caution when driving or climbing stairs); vomiting or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea (boiled milk, yogurt, or buttermilk may help). Report persistent abdominal discomfort; significantly increased salivation, sweating, tearing, or urination; flushed skin; chest pain or palpitations; acute headache; unresolved diarrhea; excessive fatigue, insomnia, dizziness, or depression; increased muscle, joint, or body pain; vision changes or blurred vision; or shortness of breath or wheezing.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as bromide:

Regonol®: 5 mg/mL (2 mL) [contains benzyl alcohol]

Syrup, as bromide:

Mestinon®: 60 mg/5 mL (480 mL) [raspberry flavor; contains alcohol 5%, sodium benzoate]

Tablet, as bromide: 60 mg

Mestinon®: 60 mg

Tablet, sustained release, as bromide:

Mestinon® Timespan®: 180 mg

Generic AvailableYes: Tablet

ManufacturerICN Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Syrup (Mestinon)

60 mg/5 mL (240): $59.98

Tablet, controlled release (Mestinon)

180 mg (30): $70.37

Tablets (Mestinon)

60 mg (30): $49.19

Tablets (Pyridostigmine Bromide)

60 mg (30): $17.99

Mechanism of ActionInhibits destruction of acetylcholine by acetylcholinesterase which facilitates transmission of impulses across myoneural junction

Pharmacodynamics/Kinetics

Onset of action: Oral, I.M.: 15-30 minutes; I.V. injection: 2-5 minutes

Duration: Oral: Up to 6-8 hours (due to slow absorption); I.V.: 2-3 hours

Absorption: Oral: Very poor

Distribution: 19 ± 12 L

Metabolism: Hepatic

Bioavailability: 10% to 20%

Half-life elimination: 1-2 hours; Renal failure: ≤6 hours

Excretion: Urine (80% to 90% as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dysphagia.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay rarely cause dysphoria or drowsiness
Mental Health: Effects on Psychiatric TreatmentNone reported; but mouth watering is common and may be additive to the sialorrhea associated with clozapine therapy
Anesthesia and Critical Care Concerns/Other ConsiderationsAtropine or glycopyrrolate must be administered in combination with pyridostigmine. Large parenteral doses should be accompanied by parenteral atropine. Ephedrine sulfate and potassium chloride have been used orally (in adult patients) to improve response. Extended release products are preferred for use **only** at bedtime for patients who are very weak upon arising.
Index TermsPyridostigmine Bromide
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International Brand NamesAmygra (PK); Antilon (TW); Brostagin (PL); Distinon (IN); Kalymin (BG, DE, EE); Mestinon (AE, AR, AT, AU, BB, BE, BG, BH, BM, BR, BS, BZ, CH, CN, CO, CR, CY, CZ, DE, DK, DO, EG, ES, FI, FR, GB, GH, GR, GT, GY, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JM, JO, KP, KW, LB, LU, LY, MX, MY, NI, NL, NO, OM, PA, PE, PL, PT, PY, QA, RU, SA, SE, SR, SV, SY, TR, TT, TW, TZ, UG, UY, VE, YE, ZM); Mestinon Retard (NL); Pyrimine (TH); Pyrinol (KP)

Pyridoxine

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Pyridoxine may be confused with paroxetine, pralidoxime, Pyridium®

Pronunciation(peer i DOKS een)

U.S. Brand NamesAminoxin [OTC]; Pyri-500 [OTC]

Pharmacologic Category[Vitamin, Water Soluble]

Use: Labeled IndicationsPrevention and treatment of vitamin B_6 deficiency, pyridoxine-dependent seizures in infants

Use: Unlabeled/InvestigationalTreatment and prophylaxis of neurological toxicities (ie, seizures, coma) associated with isoniazid, hydrazine, and Gyromitrin-containing mushroom (false morel) overdose/toxicity

Dosing: Adults

Recommended daily allowance (RDA):

Male: 1.7-2.0 mg

Female: 1.4-1.6 mg

Dietary deficiency: Oral: 10-20 mg/day for 3 weeks

Drug-induced neuritis (eg, isoniazid, hydralazine, penicillamine, cycloserine): Oral:

Treatment: 100-200 mg/24 hours

Prophylaxis: 25-100 mg/24 hours

Treatment of seizures and/or coma from acute isoniazid toxicity (unlabeled use): I.V.:

Acute ingestion of known amount: A total dose of pyridoxine equal to the amount of isoniazid ingested should be given (ie, if 9 g of isoniazid were ingested, give a total dose of 9 g pyridoxine). Administer at a rate of 1 g/minute if actively seizing; administer over 30 minutes if not actively seizing.

Acute ingestion of unknown amount: 5 g given at a rate of 1 g/minute; repeat doses (every 5-10 minutes) may be needed for persistent seizure activity or CNS toxicity

Treatment of acute hydrazine toxicity (unlabeled use; Nagappan, 2000): I.V.: A total dose of 25 mg/kg should be given over 15-30 minutes

Treatment of seizures from acute Gyromitrin-containing mushroom toxicity (unlabeled use; Diaz, 2005): I.V.: 25 mg/kg over 15-30 minutes; repeat dose as needed to control seizures

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Recommended daily allowance (RDA):

1-3 years: 0.9 mg

4-6 years: 1.3 mg

7-10 years: 1.6 mg

Pyridoxine-dependent Infants:

Oral: 2-100 mg/day

I.M., I.V., SubQ: 10-100 mg

Dietary deficiency: Oral: Children: 5-25 mg/24 hours for 3 weeks, then 1.5-2.5 mg/day in multiple vitamin product

Drug-induced neuritis (eg, isoniazid, hydralazine, penicillamine, cycloserine): Oral: Children:

Treatment: 10-50 mg/24 hours

Prophylaxis: 1-2 mg/kg/24 hours

Treatment of seizures and/or coma from acute isoniazid toxicity (unlabeled use): I.V.: Children:

Acute ingestion of known amount: A total dose of pyridoxine equal to the amount of isoniazid ingested should be given (ie, if 9 g of isoniazid were ingested, give a total dose of 9 g pyridoxine). Administer at a rate of 1 g/minute if actively seizing; administer over 30 minutes if not actively seizing.

Acute ingestion of unknown amount: 5 g given at a rate of 1 g/minute; repeat doses (every 5-10 minutes) may be needed for persistent seizure activity or CNS toxicity

Treatment of seizures from acute Gyromitrin-containing mushroom toxicity (unlabeled use; Diaz, 2005): I.V.: Children: 25 mg/kg over 15-30 minutes; repeat dose as needed to control seizures

Administration: I.M.Burning may occur at the injection site after I.M. or SubQ administration.
Administration: I.V.Seizures have occurred following I.V. administration of very large doses. In patients with active seizures, administer dose at a rate of 1 g/minute; for patients without active seizures, administer dose over 15-30 minutes. If the parenteral formulation is not available, anecdotal reports suggest that pyridoxine tablets may be crushed and made into a slurry and given at the same dose. However, oral administration is not recommended for acutely poisoned patients with seizure activity.
Administration: I.V. DetailpH: 2.0-3.8
StorageProtect from light.
CompatibilityStable in fat emulsion 10%.

Compatibility in syringe: Compatible: Doxapram.

ExtemporaneouslyPreparedA 1 mg/mL oral solution was stable for 30 days when refrigerated when compounded as follows:

Withdraw 100 mg (1 mL of a 100 mg/mL injection) from a vial with a needle and syringe, add to 99 mL of simple syrup in an amber bottle

Keep in refrigerator

Nahata MC and Hipple TF, *Pediatric Drug Formulations*, 3rd ed, Cincinnati, OH: Harvey Whitney Books Co, 1997.

ContraindicationsHypersensitivity to pyridoxine or any component of the formulation
Warnings/Precautions

Warnings related to adverse effects:

- Neuropathy: Severe, permanent peripheral neuropathies have been reported; neurotoxicity is more common with long-term administration of large doses (>2 g/day).

Dosage form specific issues:

- Aluminum: Some parenteral products contain aluminum; use caution in patients with impaired renal function and neonates.

Other warnings/precautions:

- Adequate supplies: High doses may be required to reverse neurological toxicity secondary to isoniazid toxicity. Emergency departments should ensure an adequate supply in the event of an acute isoniazid overdose.

- Dependence/withdrawal: Doses >200 mg/day may cause dependence and withdrawal.

- Vitamin deficiency: Single vitamin deficiency is rare; evaluate for other deficiencies.

Geriatric ConsiderationsUse with caution in patients with Parkinson's disease treated with levodopa.
Pregnancy Risk FactorA/C (dose exceeding RDA recommendation)
Pregnancy ConsiderationsCrosses the placenta; available evidence suggests safe use during pregnancy
LactationEnters breast milk/compatible
Breast-Feeding ConsiderationsCrosses into breast milk; possible inhibition of lactation at doses >600 mg/day. AAP considers **compatible** with breast-feeding.
Adverse ReactionsFrequency not defined.

Central nervous system: Headache, seizure (following very large I.V. doses)

Endocrine & metabolic: Acidosis

Gastrointestinal: Nausea

Hepatic: Increased AST

Neuromuscular & skeletal: Neuropathy, paresthesia

Miscellaneous: Allergic reactions

Drug Interactions

Altretamine: Pyridoxine may diminish the therapeutic effect of Altretamine. Specifically when altretamine is used in combination with Cisplatin the response duration may be diminished. *Risk D: Consider therapy modification*

Barbiturates: Pyridoxine may increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

Levodopa: Pyridoxine may diminish the therapeutic effect of Levodopa. *Risk D: Consider therapy modification*

Phenytoin: Pyridoxine may increase the metabolism of Phenytoin. This is most apparent in high pyridoxine doses (eg, 80 mg to 200 mg daily)

Risk C: Monitor therapy

Test InteractionsUrobilinogen

Monitoring ParametersFor treatment of isoniazid, hydrazine, or Gyromitrin-containing mushroom toxicity, anion gap, arterial blood gases, electrolytes, neurological exam, seizure activity

Reference RangeOver 50 ng/mL (SI: 243 nmol/L) (varies considerably with method). A broad range is ~25-80 ng/mL (SI: 122-389 nmol/L). HPLC method for pyridoxal phosphate has normal range of 3.5-18 ng/mL (SI: 17-88 nmol/L).

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy and adverse effects at beginning of therapy and regularly with long-term use. Assess knowledge/teach patient appropriate use, dietary instructions, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed. Do not take more than recommended. Do not exceed recommended intake of dietary B_6 (eg, red meat, bananas, potatoes, yeast, lima beans, and whole grain cereals). You may experience burning or pain at injection site; notify prescriber if this persists. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 50 mg, 250 mg

Aminoxin: 20 mg

Injection, solution, as hydrochloride: 100 mg/mL (1 mL)

Liquid, oral, as hydrochloride: 200 mg/5 mL (120 mL)

Tablet, as hydrochloride: 25 mg, 50 mg, 100 mg, 250 mg, 500 mg

Tablet, sustained release, as hydrochloride:

Pyri-500: 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Pyridoxine HCl)

100 mg/mL (25): $279.99

Tablets (Vitamin B-6)

100 mg (100): $13.99

Mechanism of ActionPrecursor to pyridoxal, which functions in the metabolism of proteins, carbohydrates, and fats; pyridoxal also aids in the release of liver and muscle-stored glycogen and in the synthesis of GABA (within the central nervous system) and heme

Pharmacodynamics/Kinetics

Absorption: Enteral, parenteral: Well absorbed

Metabolism: Via 4-pyridoxic acid (active form) and other metabolites

Half-life elimination: 15-20 days

Excretion: Urine

Related Information

- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay decrease the effects of levodopa and phenobarbital

Cardiovascular ConsiderationsEpidemiological evidence suggests that total plasma homocysteine level may be an independent cardiovascular risk factor. Plasma homocysteine levels are strongly influenced by genetics and diet (folic acid, pyridoxine/vitamin B_6, and cyanocobalamine/vitamin B_{12}). These vitamins help to break down homocysteine in the body.

Schnyder, et al, studied the effects of homocysteine-lowering therapy (folic acid 1 mg/day, vitamin B_6 10 mg/day, vitamin B_{12} 0.4 mg/day) in patients with coronary artery disease after successful angioplasty in the Swiss Heart Study. This randomized, double-blind, placebo-controlled trial looked at a composite endpoint (death, nonfatal MI, repeat revascularization) 6 months and 1 year after angioplasty. Homocysteine-lowering therapy significantly decreased the incidence of major adverse events, primarily due to a reduced rate of target lesion revascularization. Investigators in the Folate After Coronary Intervention Trial randomized patients who underwent successful coronary stenting procedures to placebo or folic acid (1.2 mg/day), vitamin B_6 (4.8 mg/day), and vitamin B_{12} (0.06 mg/day). Vitamin supplementation was associated with increased restenosis in these PCI patients.

Index TermsPyridoxine Hydrochloride; Vitamin B_6

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Schnyder G, Roffi M, Flammer Y, et al, “Effect of Homocysteine-Lowering Therapy With Folic Acid, Vitamin B12, and Vitamin B6 on Clinical Outcome After Percutaneous Coronary Intervention: The Swiss Heart Study: A Randomized Controlled Trial,” *JAMA*, 2002, 288(8):973-9.[PubMed 12190367]

↑ International Brand NamesAFI-B6 (NO); Alertasa (ES); B(6)-Vicotrat (DE); Becilan (FR); Bedoxine (BE, LU); Bedoyecta (MX); Beesix (ZA); Beglunina (ES); Benadon (AR, AT, CH, ES, GB, IE, IT, PT, SE); Bexivit (GR); Bivit (IT); Bonadon N (DE); Burgerstein Vitamin B!6 (CH); Complement Continus (AE, BH, CH, CY, EG, IE, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Conductasa (ES); Dermo 6 (FR); Dermo Chabre B6 (ES); Dextamina B6 (ES); Dodemina (MX); Dolo Bedoyecta (MX); Dolvifen (MX); Farmobion B6 (IT); Glutarase (IT); Godabion B6 (ES); Heksavit (FI); Hexobion 100 (DE); Hysix (JP); Incremin con hierro (MX); M. V. I. 12 (MX); Memosprint (IT); Natele (MX); Nuro-B (MX); Pharmaton (MX); Pidopidon (JP); Piridoxina Austral (AR); Piriglutina (ES); Plivit B6 (HR); Poly-B con Vitamina C (MX); Pyricontin Continus (IN); Pyridoxin Recip[Tab.] (SE); Pyridoxin ”Dak” (DK); Pyridoxine Aguettant (FR); Pyridoxine Renaudin (FR); Pyridoxine-Labaz (LU); Pyrivitol (AT); Pyroxin (AU); Reisevit (AT); Sechvitan (JP); Serfoxide (ES); Tanvimil B6 (AR); Trineurovita (MX); Vit. B6 Agepha (AT); Vita-B6 (FI); Vitamin B!6 (HU); Vitamin B!6 Streuli (CH); Vitamin B6 (AU); Vitamine B!6 Richard (FR); Vitaminum B6 (PL); Xanturenasi (IT)

Pyrimethamine

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Medication Safety Issues

Sound-alike/look-alike issues:

Daraprim® may be confused with Dantrium®, Daranide®

Pronunciation(peer i METH a meen)
U.S. Brand NamesDaraprim®
Canadian Brand NamesDaraprim®
Pharmacologic CategoryAntimalarial Agent
Use: Labeled IndicationsProphylaxis of malaria due to susceptible strains of plasmodia; used in conjunction with quinine and sulfadiazine for the treatment of uncomplicated attacks of chloroquine-resistant *P. falciparum* malaria; used in conjunction with fast-acting schizonticide to initiate transmission control and suppression cure; synergistic combination with sulfonamide in treatment of toxoplasmosis
Dosing: Adults

Malaria chemoprophylaxis (for areas of chloroquine-resistant*P. falciparum*): Oral: Begin prophylaxis 2 weeks before entering endemic area: 25 mg once weekly. Dosage should be continued for all age groups for at least 6-10 weeks after leaving endemic areas

Chloroquine-resistant*P. falciparum*malaria (when used in conjunction with quinine and sulfadiazine): Oral: 25 mg twice daily for 3 days

Toxoplasmosis: Oral: 50-75 mg/day together with 1-4 g of a sulfonamide for 1-3 weeks depending on patient's tolerance and response, then reduce dose by 50% and continue for 4-5 weeks **or** 25-50 mg/day for 3-4 weeks

Prophylaxis for first episode of*Toxoplasma gondii*: Oral: 50 mg once weekly with dapsone, plus oral folinic acid 25 mg once weekly

Prophylaxis to prevent recurrence of*Toxoplasma gondii*: Oral: 25-50 mg once daily in combination with sulfadiazine or clindamycin, plus oral folinic acid 10-25 mg daily. Atovaquone plus oral folinic acid 10 mg daily has also been used in combination with pyrimethamine.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Malaria chemoprophylaxis (for areas with chloroquine-resistant*P. falciparum*): Oral: Begin prophylaxis 2 weeks before entering endemic area:

Children: 0.5 mg/kg once weekly, not to exceed 25 mg/dose

or

<4 years: 6.25 mg once weekly

4-10 years: 12.5 mg once weekly

Children >10 years: Refer to adult dosing

Note: Dosage should be continued for all age groups for at least 6-10 weeks after leaving endemic areas.

Chloroquine-resistant*P. falciparum*malaria (when used in conjunction with quinine and sulfadiazine): Oral:

Children:

<10 kg: 6.25 mg/day once daily for 3 days

10-20 kg: 12.5 mg/day once daily for 3 days

20-40 kg: 25 mg/day once daily for 3 days

Toxoplasmosis:

Infants (congenital toxoplasmosis): Oral: 1 mg/kg once daily for 6 months with sulfadiazine then every other month with sulfa, alternating with spiramycin.

Children: Loading dose: 2 mg/kg/day divided into 2 equal daily doses for 1-3 days (maximum: 100 mg/day) followed by 1 mg/kg/day divided into 2 doses for 4 weeks; maximum: 25 mg/day

With sulfadiazine or trisulfapyrimidines: 2 mg/kg/day divided every 12 hours for 3 days, followed by 1 mg/kg/day once daily or divided twice daily for 4 weeks given with trisulfapyrimidines or sulfadiazine

Prophylaxis for first episode of*Toxoplasma gondii*: Oral:

Children ≥1 month of age: 1 mg/kg/day once daily with dapsone, plus oral folinic acid 5 mg every 3 days

Adolescents: Refer to adult dosing.

Prophylaxis to prevent recurrence of *Toxoplasma gondii*: Oral:

Children ≥1 month of age: 1 mg/kg/day once daily given with sulfadiazine or clindamycin, plus oral folinic acid 5 mg every 3 days

Adolescents: Refer to adult dosing.

Administration: OralAdminister with meals to minimize GI distress.
StorageStore at 15°C to 25°C (59°F to 77°F). Protect from light.
Extemporaneously PreparedPyrimethamine tablets may be crushed to prepare oral suspensions of the drug in water, cherry syrup or sucrose-containing solutions at a concentration of 1 mg/mL; stable at room temperature for 5-7 days

AHFS Drug Information, McEvoy G, ed, Bethesda, MD: American Society of Health-System Pharmacists, 1996.

ContraindicationsHypersensitivity to pyrimethamine or any component of the formulation; chloroguanide; resistant malaria; megaloblastic anemia secondary to folate deficiency
Warnings/Precautions

Disease-related concerns:

- Folate deficiency: Use caution in patients with possible folate deficiency (eg, malabsorption syndrome, pregnancy, alcoholism).
- G6PD deficiency: Use with caution in patients with possible G6PD deficiency.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Seizure disorders: Use with caution in patients with a history of seizure disorders.

Concurrent drug therapy issues:

- Leucovorin: When used for more than 3-4 days, it may be advisable to administer leucovorin to prevent hematologic complications.

Other warnings/precautions:

- Monitoring: Monitor CBC and platelet counts every 2 weeks.

Pregnancy Risk FactorC
Pregnancy ConsiderationsThere are no adequate or well-controlled studies in pregnant women. Teratogenicity has been reported in animal studies. If administered during pregnancy (ie, for toxoplasmosis), supplementation of folate is strongly recommended. Pregnancy should be avoided during therapy.
LactationEnters breast milk/not recommended (AAP rates “compatible”)
Breast-Feeding ConsiderationsPyrimethamine enters breast milk and may result in significant systemic concentrations in breast-fed infants. AAP rates as “compatible” (although the manufacturer does not recommend its use during breast-feeding). The effect of concurrent therapy with sulfonamide or dapsone (frequently used with pyrimethamine as combination treatment) must be considered.
Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias (large doses)

Central nervous system: Depression, fever, insomnia, lightheadedness, malaise, seizure

Dermatologic: Abnormal skin pigmentation, dermatitis, erythema multiforme, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis

Gastrointestinal: Anorexia, abdominal cramps, atrophic glossitis, diarrhea, vomiting, xerostomia,

Hematologic: Megaloblastic anemia, leukopenia, pancytopenia, thrombocytopenia, pulmonary eosinophilia

Genitourinary: Hematuria

Miscellaneous: Anaphylaxis

Metabolism/Transport Effects**Inhibits** CYP2C9 (moderate), 2D6 (moderate)
Drug Interactions

Antipsychotic Agents (Phenothiazines): Antimalarial Agents may increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Methylfolate: May diminish the therapeutic effect of Pyrimethamine. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Monitoring ParametersCBC, including platelet counts

Nursing: Physical Assessment/MonitoringEvaluate any patient history of renal or hepatic impairment or seizures prior to beginning therapy. When used for more than 3-4 days, it may be advisable to give leucovorin to prevent hematologic complications. Assess potential for interactions with other pharmacological agent patient may be taking (eg, increased potential for toxicities). Evaluate results of laboratory tests, therapeutic effectiveness according to purpose for use, and adverse reactions (eg, arrhythmias, rash, GI disturbance, hematuria, megoblastic anemia) periodically during therapy.. Teach patient appropriate use, possible side effects/interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC, including platelet counts twice weekly; liver and renal function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take with meals. Tablets may be crushed to prepare oral suspensions of the drug in water, cherry syrup, or sucrose-containing solutions at a concentration of 1 mg drug/mL of liquid. It is important to complete full course of therapy for full effect. Regular blood tests will be necessary during therapy. If used for prophylaxis, consult with prescriber in order to begin 2 weeks before traveling to endemic areas, continue during travel period, and for 6-10 weeks following return. May cause GI distress or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); dizziness, lightheadedness, insomnia, or changes in mentation (use caution when driving or with tasks that require alertness until response to drug is known); or changes in skin pigmentation or rash. Report persistent GI disturbance (nausea, vomiting, diarrhea, cramping); chest pain or palpitation; unusual fatigue, easy bruising, bleeding, or bloody emesis; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 25 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Daraprim)

25 mg (30): $25.99

Mechanism of ActionInhibits parasitic dihydrofolate reductase, resulting in inhibition of vital tetrahydrofolic acid synthesis

Pharmacodynamics/Kinetics

Onset of action: ~1 hour

Absorption: Well absorbed

Distribution: Widely, mainly in blood cells, kidneys, lungs, liver, and spleen; crosses into CSF; crosses placenta; enters breast milk

Protein binding: 80% to 87%

Metabolism: Hepatic

Half-life elimination: 80-95 hours

Time to peak, serum: 1.5-8 hours

Excretion: Urine (20% to 30% as unchanged drug)

Related Information

- Immunization Recommendations
- Malaria Treatment
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsLeucovorin may be administered in a dosage of 3-9 mg/day for 3 days or 5 mg every 3 days or as required to reverse symptoms of or to prevent hematologic problems due to folic acid deficiency

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Atrophic glossitis has been reported.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause drowsiness, insomnia, or depression

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; mild hepatotoxicity associated with concurrent usage of lorazepam

References

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International Brand NamesDaraprim (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CN, CY, CZ, DE, EG, ES, ET, GB, GH, GM, GN, GY, IE, IL, IN, IQ, IR, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, OM, PE, PL, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TW, TZ, UG, UY, YE, ZA, ZM, ZW); Daraprin (BR); Malocide (FR); Pyrimen (PL); Tindurin (HN, HU)

Pyrithione Zinc

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Pyrithione may be confused with Pyridium®

International issues:

Skaelud® [Denmark] may be confused with Skelid® which is a brand name for tiludronate in the U.S.

Pronunciation(peer i THYE one zingk)

U.S. Brand NamesBetaMed [OTC]; Denorex® Daily Protection [OTC]; DermaZinc™ [OTC]; DHS™ Zinc [OTC]; Head & Shoulders® Citrus Breeze 2-in-1 [OTC]; Head & Shoulders® Citrus Breeze [OTC]; Head & Shoulders® Classic Clean 2-in-1 [OTC]; Head & Shoulders® Classic Clean [OTC]; Head & Shoulders® Dry Scalp Care 2-in-1 [OTC]; Head & Shoulders® Dry Scalp Care [OTC]; Head & Shoulders® Extra Volume [OTC]; Head & Shoulders® intensive solutions 2-in-1 [OTC]; Head & Shoulders® intensive solutions for dry/damaged hair [OTC]; Head & Shoulders® intensive solutions for fine/oily hair [OTC]; Head & Shoulders® intensive solutions for normal hair [OTC]; Head & Shoulders® Ocean Lift 2-in-1 [OTC]; Head & Shoulders® Ocean Lift [OTC]; Head & Shoulders® Refresh 2-in-1 [OTC]; Head & Shoulders® Refresh [OTC]; Head & Shoulders® Restoring Shine 2-in-1 [OTC]; Head & Shoulders® Restoring Shine [OTC]; Head & Shoulders® Sensitive Care 2-in-1 [OTC]; Head & Shoulders® Sensitive Care [OTC]; Head & Shoulders® Smooth & Silky 2-in-1 [OTC]; Head & Shoulders® Smooth & Silky [OTC]; Selsun® Salon™ 2-in-1 [OTC]; Selsun® Salon™ Classic [OTC]; Selsun® Salon™ Moisturizing [OTC]; Selsun® Salon™ Volumizing [OTC]; Skin Care™ [OTC]; T/Gel® Daily Control 2 in 1 [OTC]; T/Gel® Daily Control [OTC]; Zincon® [OTC]; ZNP® Bar [OTC]

Pharmacologic CategoryTopical Skin Product

Use: Labeled IndicationsRelieves the itching, irritation, and scalp flaking associated with dandruff and/or seborrheal dermatitis

Dosing: Adults**Dandruff/Seborrhea** (Products should be used at least twice weekly for best results, but may be used with each washing): Topical:

Bar: May be used on body and or scalp; wet area, massage in, and rinse.

Shampoo: Should be applied to wet hair and massaged into scalp; rinse. May be followed with conditioner

Dosing: ElderlyRefer to adult dosing.

Administration: TopicalFor topical use only; avoid eyes

ContraindicationsHypersensitivity to pyrithione zinc or any component of the formulation

Warnings/Precautions

Other warnings/precautions:

- Administration: For external use only; avoid contact with the eyes.

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Conditioner, topical:

Head & Shoulders® Classic Clean: 0.5% (400 mL) [contains benzyl alcohol]

Head & Shoulders® Dry Scalp Care: 0.5% (400 mL) [contains benzyl alcohol]

Cream, topical:

DermaZinc™: 0.25% (120 g)

Lotion, topical:

Skin Care™: 0.25% (120 mL) [pump spray]

Shampoo, topical:

BetaMed: 2% (480 mL) [dye free]

Denorex® Daily Protection: 2% (120 mL, 360 mL) [alcohol free]

DermaZinc™: 2% (240 mL)

DHS™ Zinc: 2% (240 mL, 360 mL)

Head & Shoulders® Citrus Breeze: 1% (420 mL, 700 mL) [contains benzyl alcohol]

Head & Shoulders® Classic Clean: 1% (50 mL, 420 mL, 700 mL, 1000 mL, 1200 mL) [contains benzyl alcohol]

Head & Shoulders® Dry Scalp Care: 1% (340 mL, 420 mL, 700 mL, 1200 mL) [contains benzyl alcohol]

Head & Shoulders® Extra Volume: 1% (420 mL, 700 mL) [contains benzyl alcohol]

Head & Shoulders® intensive solutions for dry/damaged hair: 2% (251 mL) [contains benzyl alcohol]

Head & Shoulders® intensive solutions for fine/oily hair: 2% (251 mL) [contains benzyl alcohol]

Head & Shoulders® intensive solutions for normal hair: 2% (251 mL) [contains benzyl alcohol]

Head & Shoulders® Ocean Lift: 1% (420 mL, 700 mL) [contains benzyl alcohol]

Head & Shoulders® Refresh: 1% (420 mL, 700 mL, 1000 mL, 1200 mL) [contains benzyl alcohol]

Head & Shoulders® Restoring Shine: 1% (420 mL, 700 mL) [contains benzyl alcohol]

Head & Shoulders® Sensitive Care: 1% (420 mL, 700 mL) [contains benzyl alcohol]

Head & Shoulders® Smooth & Silky: 1% (420 mL) [contains benzyl alcohol]

Selsun® Salon™ Classic: 1% (384 mL) [contains benzyl alcohol]

Selsun® Salon™ Moisturing: 1% (384 mL) [contains benzyl alcohol]

Selsun® Salon™ Volumizing: 1% (384 mL) [contains benzyl alcohol]

T/Gel® Daily Control: 1% (250 mL) [contains benzyl alcohol]

Zincon®: 1% (120 mL, 240 mL)

Shampoo, topical [with conditioner]:

Head & Shoulders® Citrus Breeze 2-in-1: 1% (420 mL) [contains benzyl alcohol]

Head & Shoulders® Classic Clean 2-in-1: 1% (420 mL, 700 mL) [contains benzyl alcohol]

Head & Shoulders® Dry Scalp Care 2-in-1: 1% (420 mL, 700 mL) [contains benzyl alcohol]

Head & Shoulders® intensive solutions 2-in-1: 2% (251 mL) [contains benzyl alcohol]

Head & Shoulders® Ocean Lift 2-in-1: 1% (420 mL, 700 mL) [contains benzyl alcohol]

Head & Shoulders® Refresh 2-in-1: 2% (420 mL) [contains benzyl alcohol]

Head & Shoulders® Restoring Shine 2-in-1: 1% (420 mL) [contains benzyl alcohol]

Head & Shoulders® Sensitive Care 2-in-1: 1% (420 mL, 700 mL) [contains benzyl alcohol]

Head & Shoulders® Smooth and Silky 2-in-1: 1% (420 mL, 700 mL) [contains benzyl alcohol]

Selsun® Salon™ 2-in-1: 1% (384 mL) [contains benzyl alcohol]

T/Gel® Daily Control 2 in 1: 1% (250 mL) [contains benzyl alcohol]

Soap, topical:

DermaZinc™: 2% (112.5 g) [contains coconut oil]

ZNP®): 2% (119 g) [bar]

Solution, topical [spray/drops]:

DermaZinc™: 0.25% (120 mL)

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesAeroseb (AR); Dan Gard (AU, KP); de-squaman (DE); Desquaman (CH, LU); Dos Ele (AR); Fongitar (ZA); Healing Shampoo (PL); Min-Huil (AR); Pirimed (MX); Skaelud (DK); Stiefel ZNP (PT); Z-P-Dermil (PT); ZN (BR)

Quazepam

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Quazepam may be confused with oxazepam

Pronunciation(KWAZ e pam)

U.S. Brand NamesDoral®

Canadian Brand NamesDoral®

Pharmacologic CategoryBenzodiazepine

Use: Labeled IndicationsTreatment of insomnia

Dosing: Adults**Hypnotic:** Oral: Initial: 15 mg at bedtime; in some patients, the dose may be reduced to 7.5 mg after a few nights

Dosing: ElderlyDosing should be cautious; begin at lower end of dosing range (ie, 7.5 mg)

Dosing: Hepatic ImpairmentDose reduction may be necessary.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).

RestrictionsC-IV

ContraindicationsHypersensitivity to quazepam, other benzodiazepines, or any component of the formulation; sleep apnea; pregnancy

Note: Product labeling does not include narrow-angle glaucoma; however, use in narrow-angle glaucoma is contraindicated with other benzodiazepines.

Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypersensitivity reactions: Postmarketing studies have indicated that the use of hypnotic/sedative agents for sleep has been associated with hypersensitivity reactions including anaphylaxis as well as angioedema.
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.
- Sleep-related activities: An increased risk for hazardous sleep-related activities such as sleep-driving; cooking and eating food, and making phone calls while asleep have also been noted.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.

- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury.

- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.

- Pediatrics: Safety and efficacy have not been established in pediatric patients.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties. Use lowest effective dose.

- Hypnotic: Appropriate use: Should be used only after evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric or medical illness. A worsening of insomnia or the emergence of new abnormalities of thought or behavior may represent unrecognized psychiatric or medical illness and requires immediate and careful evaluation.

- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric Considerations Because of the long half-life of one of its active metabolites, quazepam is not a drug of choice in the elderly. Long-acting benzodiazepines have been associated with falls in the elderly and are not recommended for use in older patients.

Pregnancy Risk Factor X

Pregnancy Considerations Adverse events were observed in animal studies. An increased risk of congenital malformations has been observed with other benzodiazepines following exposure during the 1st trimester. Withdrawal symptoms in the neonate and neonatal flaccidity have been reported following maternal use of benzodiazepines during pregnancy. Use during pregnancy is contraindicated.

Lactation Enters breast milk/not recommended (AAP rates “of concern”)

Breast-Feeding Considerations Approximately 0.1% of the maternal dose is found in breast milk.

Adverse Reactions

>10%: Central nervous system: Daytime drowsiness (12%)

<10%:

Central nervous system: Headache (5%), dizziness (2%), fatigue (2%)

Gastrointestinal: Xerostomia (2%), dyspepsia (1%)

Frequency not defined. **Note:** Asterisked (*) reactions are those reported with benzodiazepines.

Cardiovascular: Palpitation

Central nervous system: Abnormal thinking, agitation, amnesia, anxiety, apathy, ataxia, confusion, depression, dystonia*, euphoria, hallucinations*, hyper-/hypokinesia, incoordination, irritability*, malaise, memory impairment*, nervousness, nightmare, paranoid reaction, sleep disturbances*, slurred speech*, speech disorder, stimulation*

Dermatologic: Dermatitis*, pruritus, rash

Endocrine & metabolic: Libido decreased, menstrual irregularities*

Gastrointestinal: Abdominal pain, abnormal taste perception, anorexia, appetite increased/decreased*, constipation, diarrhea, nausea

Genitourinary: Impotence, incontinence, urinary retention*

Hematologic: Blood dyscrasias

Hepatic: Jaundice*, SGOT increased

Neuromuscular & skeletal: Dysarthria*, muscle cramps*, muscle spasticity*, reflex slowing*, rigidity*, tremor, weakness

Ocular: Abnormal vision, blurred vision*, cataract

Miscellaneous: Drug dependence, withdrawal*

Postmarketing and/or case reports: Anaphylaxis, angioedema, complex sleep-related behavior (sleep-driving, cooking or eating food, making phone calls)

Metabolism/Transport Effects **Substrate** of CYP2C19 (major), and CYP3A4 (major)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Yohimbine: May diminish the therapeutic effect of Antianxiety Agents. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Grapefruit juice may decrease the metabolism of quazepam.

Herb/Nutraceutical: Avoid St John's wort (may increase the metabolism of quazepam).

Monitoring ParametersRespiratory and cardiovascular status; mental status

Nursing: Physical Assessment/MonitoringFor inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions (see Adverse Reactions) at beginning of therapy and periodically with long-term use.

Patient EducationAvoid alcohol and other CNS depressants; avoid activities needing good psychomotor coordination until CNS effects are known; drug may cause physical or psychological dependence; avoid abrupt discontinuation after prolonged use

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Doral®: 15 mg

Generic AvailableNo

ManufacturerQuestcor Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Doral)

7.5 mg (30): $100.99

15 mg (30): $127.99

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Absorption: Rapid

Protein binding: >95%

Metabolism: Hepatic; forms metabolites (active)- 2-oxoquasepam and N-desalkyl-2-oxoquazepam

Half-life elimination, serum: Quazepam, 2-oxoquasepam: 39 hours; N-desalkyl-2-oxoquazepam: 73 hours

Time to peak, plasma: ~2 hours

Excretion: Urine (31%, only trace amounts as unchanged drug); feces (23%)

Related Information

- Benzodiazepines
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy Pearls More likely than short-acting benzodiazepine to cause daytime sedation and fatigue. Classified as a long-acting benzodiazepine hypnotic (eg, flurazepam), this long duration of action may prevent withdrawal symptoms when therapy is discontinued. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and abnormal taste perception.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health Comment In 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Quazepam is a long half-life benzodiazepine. Duration of action after a single dose is determined by redistribution rather than metabolism. Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include personal or family history of substance abuse and personality disorder.

Anesthesia and Critical Care Concerns/Other Considerations Quazepam is more likely than short-acting benzodiazepine to cause daytime sedation and fatigue. It is classified as a long-acting benzodiazepine hypnotic (like flurazepam - Dalmane®); this long duration of action may prevent withdrawal symptoms when therapy is discontinued. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

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Martinez HT and Serna CT, “Short-Term Treatment With Quazepam of Insomnia in Geriatric Patients,” *Clin Ther*, 1982, 5(2):174-8. [PubMed 6130842]

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International Brand Names Dorme (ZA); Prosedar (PT); Quazium (IT); Quiedorm (ES)

QUEtiapine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

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Medication Safety Issues

Sound-alike/look-alike issues:

QUEtiapine may be confused with OLANZapine

Seroquel® may be confused with Serentil®, Serzone®, Sinequan®

Pronunciation(kwe TYE a peen)

U.S. Brand NamesSeroquel®; Seroquel® XR

Canadian Brand NamesApo-Quetiapine; CO-Quetiapine; Gen-Quetiapine; Novo-Quetiapine; PMS-Quetiapine; ratio-Quetiapine; Riva-Quetiapine; Sandoz-Quetiapine; Seroquel®; Seroquel® XR

Pharmacologic Category[Antipsychotic Agent, Atypical](Antipsychotic Agent, Atypical)

Use: Labeled IndicationsTreatment of schizophrenia; treatment of acute manic episodes associated with bipolar I disorder (as monotherapy or in combination with lithium or divalproex); maintenance treatment of bipolar I disorder (in combination with lithium or divalproex); treatment of depressive episodes associated with bipolar disorder

Use: Unlabeled/InvestigationalAutism, psychosis (children); psychosis/agitation related to Alzheimer’s dementia

Dosing: Adults

Bipolar disorder:

Depression: Oral:

Immediate release tablet: Initial: 50 mg/day the first day; increase to 100 mg/day on day 2, further increasing by 100 mg/day each day until a target dose of 300 mg/day is reached by day 4. Further increases up to 600 mg/day by day 8 have been evaluated in clinical trials, but no additional antidepressant efficacy was noted.

Extended release tablet: Initial: 50 mg/day the first day; increase to 100 mg on day 2, further increasing by 100 mg/day each day until a target dose of 300 mg/day is reached by day 4.

Mania: Oral:

Immediate release tablet: Initial: 50 mg twice daily on day 1, increase dose in increments of 100 mg/day to 200 mg twice daily on day 4; may increase to a target dose of 800 mg/day by day 6 at increments ≤200 mg/day. Usual dosage range: 400-800 mg/day.

Extended release tablet: Initial: 300 mg on day 1; increase to 600 mg on day 2 and adjust dose to 400-800 mg once daily on day 3, depending on response and tolerance.

Maintenance therapy: Immediate release tablet: 200-400 mg twice daily with lithium or divalproex; **Note:** Average time of stabilization was 15 weeks in clinical trials.

Schizophrenia/psychoses: Oral:

Immediate release tablet: Initial: 25 mg twice daily; increase in increments of 25-50 mg 2-3 times/day on the second and third day, if tolerated, to a target dose of 300-400 mg/day in 2-3 divided doses by day 4. Make further adjustments as needed at intervals of at least 2 days in adjustments of 25-50 mg twice daily. Usual maintenance range: 300-800 mg/day.

Extended-release tablet: Initial: 300 mg once daily; increase in increments of up to 300 mg/day (in intervals of ≥1 day). For dosage requirements <200 mg during initial titration, the immediate release formulation should be used. Usual maintenance range: 400-800 mg/day.

Note: Dose reductions should be attempted periodically to establish lowest effective dose in patients with psychosis. Patients being restarted after 1 week of no drug need to be titrated as above.

Dosing: ElderlyAdults >65 years: 40% lower mean oral clearance of quetiapine in adults >65 years of age; higher plasma levels expected and, therefore, dosage adjustment may be needed; elderly patients usually require 50-200 mg/day of immediate release tablets or 50 mg/day of extended release tablets with a slower titration schedule. Increase immediate release dose by 25-50 mg/day or extended release dose by 50 mg/day to effective dose, based on clinical response and tolerability. If initiated with immediate release tablets, patient may transition to extended release formulation (at equivalent total daily dose) when effective dose has been reached. See “Note” in adult dosing.

Psychosis/agitation related to Alzheimer’s dementia (unlabeled use): Initial: 12.5-50 mg/day; if necessary, gradually increase as tolerated not to exceed 200-300 mg/day

Dosing: PediatricChildren and Adolescents:

Autism (unlabeled use): Oral: 100-350 mg/day (1.6-5.2 mg/kg/day)

Psychosis and mania (unlabeled use): Oral: Initial: 25 mg twice daily; titrate as necessary to 450 mg/day

Dosing: Renal ImpairmentNo dosage adjustment required: 25% lower mean oral clearance of quetiapine than normal subjects; however, plasma concentrations similar to normal subjects receiving the same dose.

Dosing: Hepatic ImpairmentLower clearance in hepatic impairment (30%), may result in higher concentrations. Dosage adjustment may be required.

Immediate release tablet: Oral: Initial: 25 mg/day, increase dose by 25-50 mg/day to effective dose, based on clinical response and tolerability to patient. If initiated with immediate-release formulation, patient may transition to extended-release formulation (at equivalent total daily dose) when effective dose has been reached.

Extended release tablet Oral: Initial: 50 mg/day; increase dose by 50 mg/day to effective dose, based on clinical response and tolerability to patient.

Administration: Oral

Immediate release tablet: May be administered with or without food.

Extended release tablet: Administer without food or with a light meal (≤300 calories), preferably in the evening. Swallow tablet whole; do not break, crush, or chew.

Dietary Considerations

Immediate-release tablet: May be taken with or without food.

Extended release tablet: Take without food or with a light meal (≤300 calories).

StorageStore at controlled room temperature of 25°C (77°F).

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/drug/antidepressants/MG_template.pdf. Dispense to parents or guardians of children and adolescents receiving this medication.

Contraindications

U.S. labeling: There are no contraindications listed in manufacturers labeling.

Canadian labeling: Hypersensitivity to quetiapine or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Dementia: See “Disease-related concerns” below.

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor all patients for clinical worsening, suicidality, or unusual changes in behavior; particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increased or decreases); the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Quetiapine is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants (for any indication) should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. **Quetiapine is FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics.

- Anticholinergic effects: May cause anticholinergic effects (confusion, agitation, constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, urinary retention, BPH, xerostomia, or visual problems. Relative to other antipsychotics, quetiapine has a moderate potency of cholinergic blockade.

- Blood dyscrasias: Leukopenia, neutropenia, and agranulocytosis (sometimes fatal) have been reported in clinical trials and postmarketing reports; presence of risk factors (eg, pre-existing low WBC or history of drug-induced leuko/neutropenia) should prompt periodic blood count assessment and discontinuation at first signs of blood dyscrasias.

- Cataracts: Use has been noted to cause cataracts in animals; lens examination on initiation of therapy and every 6 months is recommended.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is generally much lower relative to typical/conventional antipsychotics). Risk of dystonia (and probably other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Hyperglycemia: Atypical antipsychotics have been associated with development of hyperglycemia; in some cases, may be extreme and associated with ketoacidosis, hyperosmolar coma, or death. Use with caution in patients with diabetes or other disorders of glucose regulation; monitor for worsening of glucose control.

- Hyperlipidemia: Increases in cholesterol and triglycerides have been noted. Use with caution in patients with pre-existing abnormal lipid profile.

- Neuroleptic malignant syndrome (NMS): Use may be associated with neuroleptic malignant syndrome (NMS); monitor for mental status changes, fever, muscle rigidity and/or autonomic instability. This risk in association with quetiapine is very low relative to other antipsychotics.

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May be sedating; use with caution in disorders where CNS depression is a feature. Patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Suicidal ideation: The possibility of a suicide attempt is inherent in psychotic illness or bipolar disorder; use with caution in high-risk patients during initiation of therapy. Prescriptions should be written for the smallest quantity consistent with good patient care.

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

- Weight gain: Significant weight gain has been observed with antipsychotic therapy; incidence varies with product. Monitor waist circumference and BMI.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiac disease, hemodynamic instability, prior myocardial infarction, ischemic heart disease, or hypercholesterolemia.

- Dementia: **[U.S. Boxed Warning]: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo.** An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Quetiapine is not approved for this indication.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with hepatic disease or impairment; may increase transaminases (primarily ALT). Substantial hepatic metabolism via CYP3A4; may require dose adjustment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with Parkinson's disease.

- Renal impairment: Use with caution in patients with renal disease.

- Seizures: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold. Elderly patients may be at increased risk of seizures due to an increased prevalence of predisposing factors.

- Thyroid disease: Use with caution in patients with thyroid disease.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs due to antiemetic effects.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Patients using immediate release tablets may be switched to extended release tablets at the same total daily dose taken once daily. Dosage adjustments may be necessary based on response and tolerability.

Other warnings/precautions:

- Withdrawal syndrome: Use caution when withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Abrupt cessation may cause (rarely) acute withdrawal symptoms (eg, nausea, vomiting, or insomnia).

Geriatric ConsiderationsAny changes in disease status in any organ system can result in behavior changes.

Extrapyramidal syndrome symptoms occur less often than with traditional antipsychotics from the phenothiazine and butyrophenone classes. Many elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior. Before initiating antipsychotic medication, the clinician should investigate any possible reversible cause; any stress or stress from any disease can cause acute “confusion” or worsening of baseline nonpsychotic behavior. Most commonly acute changes in behavior are due to increases in drug dose or addition of new drug to regimen; fluid electrolyte loss; infections; and changes in environment.

In the treatment of agitated, demented elderly patients, authors of meta-analyses of controlled trials of the response to the traditional antipsychotics (eg, phenothiazines, butyrophenones) in controlling agitation, have concluded that the use of neuroleptics results in a response rate of 18%. Clearly neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control. In light of significant risks and adverse effects in elderly population compared with limited data demonstrating efficacy in the treatment of dementia related psychosis, aggression, and agitation, an extensive risk:benefit analysis should be performed prior to use.

Pregnancy Risk FactorC
Pregnancy ConsiderationsHealthcare providers are encouraged to enroll women 18-45 years of age exposed to quetiapine during pregnancy in the Atypical Antipsychotics Pregnancy Registry (1-866-961-2388).
LactationEnters breast milk/use caution
Adverse ReactionsActual frequency may be dependant upon dose and/or indication. Unless otherwise noted, frequency of adverse effects is reported for the immediate release oral formulation in adults.

>10%:

Central nervous system: Somnolence (18% to 34%; extended release ≤52%), sedation (30%), headache (17% to 21%), agitation (6% to 20%), dizziness (9% to 18%), extrapyramidal symptoms (8% to 12%)

Endocrine & metabolic: Triglycerides increased (14% to 23%), cholesterol increased (9% to 16%)

Gastrointestinal: Xerostomia (9% to 44%), weight gain (dose-related; 5% to 23%), appetite increased (5%; extended release <5% to 12%)

1% to 10%:

Cardiovascular: Orthostatic hypotension (4% to 7%), tachycardia (6%), syncope (extended release <5%), palpitation (≥1%), peripheral edema (≥1%)

Central nervous system: Fatigue (10%), pain (7%), lethargy (5%), akathisia (extended release <5%), dystonia (extended release <5%), tardive dyskinesia (extended release <5%), anxiety (4%), fever (2%)

Dermatologic: Rash (4%)

Endocrine & metabolic: Hyperglycemia (≥200 mg/dL post glucose challenge or fasting glucose ≥126 mg/dL, 4%)

Gastrointestinal: Constipation (8% to 10%), dyspepsia (dose-related; 5% to 7%), abdominal pain (dose-related; 4% to 7%), vomiting (5% to 6%), drooling (extended release <5%), dysphagia (extended release <5%), gastroenteritis (2%), anorexia (≥1%)

Hematologic: Leukopenia (≥1%)

Hepatic: Transaminases increased (1% to 6%), GGT increased (1%)

Neuromuscular & skeletal: Weakness (5% to 10%), tremor (8%), back pain (3% to 5%), dysarthria (≥1%), hypertonia (≥1%)

Ocular: Blurred vision (extended release <5%), amblyopia (2%)

Respiratory: Pharyngitis (4% to 6%), nasal congestion (5%), rhinitis (3%), cough (≥1%), dyspnea (≥1%)

Miscellaneous: Diaphoresis (≥1%), flu-like syndrome (≥1%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Abnormal dreams, acute renal failure, agranulocytosis, alkaline phosphatase increased, amnesia, anaphylactic reaction, anaphylaxis, anemia, angina, asthma, bradycardia, bundle branch block, cardiomyopathy, cataract formation, cerebral ischemia, cerebrovascular accident, CHF, confusion, creatinine increased, dehydration, diabetes mellitus, dysuria, eosinophilia, epistaxis, exfoliative dermatitis, hallucinations, hypoglycemia, hyper-/hypothyroidism, hypersensitivity, hypokalemia, hyponatremia, involuntary movements, leukocytosis, lymphadenopathy, myocarditis, neuroleptic malignant syndrome, neutropenia, pancreatitis, pneumonia, priapism, QRS duration increased, QT prolongation, rectal bleeding, restless leg syndrome, rhabdomyolysis, seizure, SIADH, Stevens-Johnson syndrome, ST segment elevation, suicide attempt, thrombocytopenia, tinnitus, T-wave abnormal, T-wave inversion, urinary retention, vertigo

⇧ Metabolism/Transport Effects **Substrate** of CYP2D6 (minor), 3A4 (major)

⇧ Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Atypical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Phenytoin: May increase the metabolism of QUEtiapine. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause excessive impairment in cognition/motor function).

Food: In healthy volunteers, administration of quetiapine (immediate release) with food resulted in an increase in the peak serum concentration and AUC (each by ~15%) compared to the fasting state. Administration of the extended release with a high-fat meal (~800-1000 calories) resulted in an increase in peak serum concentration by 44% to 52% and AUC by 20% to 22% for the 50 mg and 300 mg tablets; administration with a light meal had no significant effect on the C_{max} or AUC.

Herb/Nutraceutical: St John's wort may decrease quetiapine levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersVital signs; fasting lipid profile and fasting blood glucose/Hgb A_{1c} (prior to treatment, at 3 months, then annually); CBC frequently during first few months of therapy in patients with pre-existing low WBC or a history of drug-induced leukopenia/neutropenia; BMI, personal/family history of obesity, waist circumference; blood pressure; mental status, abnormal involuntary movement scale (AIMS). Weight should be assessed prior to treatment, at 4 weeks, 8 weeks, 12 weeks, and then at quarterly intervals. Consider titrating to a different antipsychotic agent for a weight gain ≥5% of the initial weight. Patients should have eyes checked for cataracts every 6 months while on this medication. Observe for new or worsening depression, anxiety, irritability, aggression, or other symptoms of unusual behavior, mood, or suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased).

Nursing: Physical Assessment/MonitoringAssess other medications patient is taking for effectiveness and interactions (especially drugs affected by P450 enzymes). Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. Assess mental status for depression and suicidal ideation. Evaluate for cataracts before initiating treatment and every 6 months during chronic treatment. Monitor weight prior to initiating therapy and at least monthly. Consider titrating to a different antipsychotic agent for weight gain ≥5% of initial weight. Initiate at lower doses and taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsFasting lipid profile and fasting blood glucose/Hgb A_{1c} (prior to treatment, at 3 months, then annually); CBC frequently during first few months of therapy in patients with pre-existing low WBC or a history of drug-induced leukopenia/neutropenia

Patient EducationUse exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results; do not discontinue without consulting prescriber. Avoid alcohol or caffeine and other prescriptions or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, you may experience increased blood sugars. Monitor blood glucose closely. Avoid overeating and/or dehydration. You may experience excess drowsiness, restlessness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); mouth sores or GI upset (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); weight gain; constipation (increased exercise, fluids, fruit, or fiber may help); or postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing). Report persistent CNS effects (eg, somnolence, agitation, insomnia); suicidal ideation; severe dizziness; vision changes; respiratory difficulty; muscle stiffness; high fever; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Seroquel®: 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg

Tablet, extended release:

Seroquel® XR: 50 mg, 200 mg, 300 mg, 400 mg

Generic AvailableNo

ManufacturerAstraZeneca Pharmaceuticals LP

Pricing: U.S. (www.drugstore.com)

Tablets (Seroquel)

25 mg (60): $139.82

50 mg (100): $372.86

100 mg (60): $233.03

200 mg (60): $437.22

300 mg (60): $605.88

400 mg (30): $370.52

Mechanism of ActionQuetiapine is a dibenzothiazepine atypical antipsychotic. It has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 (5-HT_2) antagonism. It is an antagonist at multiple neurotransmitter receptors in the brain: serotonin 5-HT_{1A} and 5-HT_2, dopamine D_1 and D_2, histamine H_1, and adrenergic alpha$_1$- and alpha$_2$-receptors; but appears to have no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors.

Antagonism at receptors other than dopamine and 5-HT_2 with similar receptor affinities may explain some of the other effects of quetiapine. The drug's antagonism of histamine H_1-receptors may explain the somnolence observed with it. The drug's antagonism of adrenergic alpha$_1$-receptors may explain the orthostatic hypotension observed with it.

Pharmacodynamics/Kinetics

Absorption: Rapidly absorbed following oral administration

Distribution: V_d: 6-14 L/kg; V_{dss}: ~2 days

Protein binding, plasma: 83%

Metabolism: Primarily hepatic; via CYP3A4; forms the metabolite N-desalkyl quetiapine (active) and two inactive metabolites

Bioavailability: 9% ± 4%; tablet is 100% bioavailable relative to solution

Half-life elimination:

Mean: Terminal: Quetiapine: ~6 hours; Extended release: ~7 hours

Metabolite: N-desalkyl quetiapine: 9-12 hours

Time to peak, plasma: Immediate release: 1.5 hours; Extended release: 6 hours

Excretion: Urine (73% as metabolites, <1% as unchanged drug); feces (20%)

Related Information

- Agents Approved for Bipolar Disorder
- Antipsychotic Agents
- Antipsychotic Receptor Profile
- Atypical Antipsychotics
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsQuetiapine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Child/Adolescent ConsiderationsSix children with autistic disorder (mean age: 10.9 years) received 100-350 mg/day (1.6-5.2 mg/kg/day; Martin, 1999). Ten patients with DSM-IV chronic or intermittent psychotic disorders (12.3-15.9 years of age) received quetiapine twice daily starting at 25 mg and reaching 400 mg by day 20. The trial ended on day 23 (McConville, 2000). Thirty manic or mixed bipolar I adolescents (12-18 years of age) received quetiapine 25 mg twice daily with titration to 450 mg/day by day 7 (DelBello, 2001).

DelBello MP, Schwiers ML, Rosenberg HL, et al, “Quetiapine as Adjunctive Treatment for Adolescent Mania,” Poster presented at Fourth International Conference on Bipolar Disorder, Pittsburgh, PA: Jun 14.

Martin A, Koenig K, Scahill L, et al, “Open-Label Quetiapine in the Treatment of Children and Adolescents With Autistic Disorder,” *J Child Adolesc Psychopharmacol*, 1999, 9(2):99-107.

McConville BJ, Arvanitis LA, Thyrum PT, et al, “Pharmacokinetics, Tolerability, and Clinical Effectiveness of Quetiapine Fumarate: An Open-Label Trial in Adolescents With Psychotic Disorders,” *J Clin Psychiatry*, 2000, 61(4):252-60.

Mental Health CommentQuetiapine is an antipsychotic agent of a class often referred to as atypical. It should be noted that the definition of the term “atypical” is not universally agreed upon. Some prefer to describe antipsychotics based on their pharmacological properties. A common feature of all definitions used to describe “atypical” antipsychotics is the lack of significant acute or subacute EPS, at dosages generally associated with antipsychotic actions. Other experts have included definitions of atypicality that include a) failure to increase serum prolactin levels; b) superior efficacy for positive, negative, and cognitive symptoms; and c) lack of evidence of tardive dyskinesia or dystonia following chronic administration.

Clinically, the dosage range for quetiapine is large and depends on what is being targeted. The general dose range for GAD and depression is low (50-300 mg/day), bipolar mania and depression is 300-600 mg/day, while dosages for schizophrenia can range from 300-1200 mg/day.

Tardive dyskinesia (TD) secondary to **typical** antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. The incidence of TD associated with the atypical antipsychotics is estimated to be 0.5% to 1%. It is not clear if this estimate represents a risk associated with mental illness or to what extent drug therapy can be implicated. Atypical antipsychotics appear less likely to cause tardive dyskinesia than typical antipsychotics (fluphenazine, haloperidol).

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Anesthesia and Critical Care Concerns/Other ConsiderationsQuetiapine has a very low incidence of extrapyramidal symptoms such as restlessness and abnormal movement, and is at least as effective as conventional antipsychotics. For patients who have been off quetiapine for more than 1 week, dose titration is necessary when restarting the medication.

Index TermsQuetiapine Fumarate

References

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Rabins PV, Blacker D, Rovner BW, et al, “Practice Guidelines for the Treatment of Patients With Alzheimer’s Disease and Other Dementias,” October, 2007. Available at http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm.

Schneider LS, Tariot PN, Dagerman KS, et al, “Effectiveness of Atypical Antipsychotic Drugs in Patients With Alzheimer's Disease,” *N Engl J Med*, 2006, 355(15):1525-38.[PubMed 17035647]

Shaw JA, Lewis JE, Pascal S, et al, “An Open Trial of Quetiapine in Adolescents With a Diagnosis of a Psychotic Disorder,” Poster presented at NCDEU 41st Annual Meeting, Phoenix, AZ: May 28.

International Brand NamesQuetapel (NZ); Quetapin (KP); Seroquel (AR, AU, BB, BE, BG, BM, BO, BR, BS, BZ, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, EE, ES, FI, GB, GT, GY, HK, HN, ID, IE, IL, IT, JM, KP, MX, MY, NI, NL, NO, PA, PE, PH, PK, PL, PR, PT, PY, SE, SG, SR, SV, TH, TT, TW, UY, VE); Socalm (IN); Utapine (TW)

Quinagolide

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English

Jump To Field (Select Field Name)

Pronunciation(kwin AG o lide)
Canadian Brand NamesNorprolac®
Pharmacologic CategoryHyperprolactinemia Agent, Dopamine (D2) Agonist
Use: Labeled IndicationsTreatment of hyperprolactinemia due to prolactin-secreting pituitary tumors (microadenoma or macroadenoma) or idiopathic in nature
Dosing: Adults**Hyperprolactinemia:** Oral:

Initial: 0.025 mg/day for 3 days followed by 0.05 mg/day for 3 days (starter pack)

Maintenance (beginning on day 7): 0.075 mg/day; if needed, a further stepwise titration of dose may occur with intervals of at least 1 week minimum; usual maintenance range: 0.075-0.15 mg/day

Maximum dose: Titrate by increasing dose by 0.075-0.15 mg/day no more frequently than every 4 weeks, up to 0.9 mg/day

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentUse in contraindicated.
Dosing: Hepatic ImpairmentUse in contraindicated.
Administration: OralAdminister with snack at bedtime. Nausea and vomiting may be alleviated by premedicating with a peripheral dopamine antagonist.
StorageStore at 5°C to 30°C (59°F to 86°F). Protect from light and humidity.
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to quinagolide or any component of the formulation; hepatic or renal impairment
Warnings/Precautions

Concerns related to adverse effects:

- Fertility changes: Use caution in women of childbearing age; restoration of fertility may occur; patients not wanting to conceive should implement a reliable method of birth control.

- G.I. distress: Use may be associated with frequent (but transient) nausea and vomiting early in therapy; during initial therapy, premedication with a peripheral dopamine antagonist may alleviate these effects and improve tolerance.

- Hypotension: Hypotensive episodes along with syncope may occur with the onset of therapy; monitor blood pressure early in therapy.

- Sedation: Use may be associated with sudden sleep onset and somnolence (especially in patients with Parkinson's disease); patients should be cautioned about performing dangerous tasks such as operating heavy machinery or driving. Use with other agents known to induce somnolence or sleep may be expected to potentiate these risks.

Disease-related concerns:

- Psychosis: Use with caution in patients with prior psychotic disorders; the onset of acute psychosis has rarely been observed with use of quinagolide (reversible upon discontinuation).

Special populations:

- Pediatrics: Safety and efficacy have not been established in patients <18 years of age.

- Pregnancy: Use caution when discontinuing therapy in patients who become pregnant. Monitor for headache or visual field deterioration which may indicate tumor enlargement and a need to resume therapy. Treatment may not exclude the need for radiation and/or surgical intervention if appropriate.

Pregnancy ConsiderationsAnimal studies revealed no embryotoxic or teratogenic effects. Fertility may be restored with treatment. Discontinue use with confirmed pregnancy unless medically necessary to continue. No increase in the incidence of abortion has been seen with a discontinuation of the drug during pregnancy. The reinstitution of therapy may be necessary in patients who display symptoms of tumor enlargement (headaches, visual field changes).
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsBy inhibiting prolactin secretion, quinagolide suppresses lactation.
Adverse Reactions

>10%:

Central nervous system: Dizziness, fatigue, headache

Gastrointestinal: Nausea, vomiting

1% to 10%:

Cardiovascular: Edema (2%), flushing (1%), hypotension (1%), palpitation (1%), syncope (1%)

Central nervous system: Sedation (3%), insomnia (2%), concentration decreased (1%), malaise (1%), mood lability (1%)

Gastrointestinal: Abdominal pain/discomfort (3%), constipation (3%), anorexia (2%), dyspepsia (2%), diarrhea (1%), weight gain (1%)

Endocrine & metabolic: Breast pain (1%)

Neuromuscular & skeletal: Weakness (3%), extremity pain (1%)

Respiratory: Nasal congestion (2%)

<1%: Acute psychosis, bilirubin increased, creatine phosphokinase increased, hematocrit decreased, hemoglobin decreased, neutropenia, potassium increased, somnolence, transaminases increased, triglycerides increased

Metabolism/Transport EffectsAgents with dopamine antagonist activity may be expected to decrease the effects of quinagolide.

Drug InteractionsNo drug interactions have been reported with quinagolide. However, the following may be anticipated based on the mechanism of action.

Antihypertensives: May potentiate the hypotensive effects of quinagolide.

Dopamine antagonists (eg, phenothiazines, haloperidol, pimozide, metoclopramide, prochlorperazine):.Effects of quinagolide may be decreased.

Peripheral dopamine-2 antagonists (eg, domperidone): May improve tolerance during initial therapy.

Ethanol/Nutrition/Herb InteractionsEthanol: May reduce tolerability of quinagolide.

Monitoring ParametersCBC, basic metabolic panel, transaminases, triglycerides, prolactin levels; blood pressure; sedation, mental changes

Monitoring: Lab TestsCBC, basic metabolic panel, transaminases, triglycerides, prolactin levels

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Combination package [not available in the U.S.]:

Norprolac® [CAN] [starter pack]:

Tablet, as hydrochloride: 0.025 mg (3s)

Tablet, as hydrochloride: 0.05 mg (3s)

Tablet, as hydrochloride: 0.075 mg (3s)

Tablet, as hydrochloride:

Norprolac® [CAN]: 0.075 mg, 0.15 mg [not available in the U.S.]

Generic AvailableNo

Manufacturer

Ferring Pharmaceuticals

Mechanism of ActionSelective dopamine D$_2$ receptor agonist that exerts a direct inhibitory effect on cells (lactotrophs) in the anterior pituitary gland which synthesize and secrete prolactin; not an ergot alkaloid

Pharmacodynamics/Kinetics

Onset of action: 2 hours; maximum effect: 4-6 hours

Duration: >24 hours

Absorption: Rapid

Distribution: V$_d$: 100 L

Protein binding: 90%

Metabolism: Hepatic; via conjugation (glucuronide and sulfate)

Bioavailability: 4%

Half-life elimination: 11.5 hours; steady state: 17 hours

Time to peak, serum: 30-60 minutes

Excretion: Urine (50%); feces (40%); >95% as metabolites

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and fatigue are common; may cause psychosis, sedation, insomnia, decreased concentration, and mood lability.

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concurrent use with lithium, carbamazepine, valproic acid, and SSRIs may produce additive effects. Effects of quinagolide may be decreased by antipsychotics (dopamine antagonists).

Index Terms Quinagolide Hydrochloride

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Schultz PN, Ginsberg L, McCutcheon IE, et al, “Quinagolide in the Management of Prolactinoma,” *Pituitary*, 2000, 3(4):239-49.[PubMed 11788012]

International Brand Names Norprolac (AT, CA, CH, DE, ES, FI, FR, GB, GR, HK, IL, MX, NL, NO, SE, ZA)

Quinapril and Hydrochlorothiazide

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(KWIN a pril & hye droe klor oh THYE a zide)

U.S. Brand NamesAccuretic®; Quinaretic

Canadian Brand NamesAccuretic®

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension (not for initial therapy)

Dosing: Adults

Hypertension: Oral:

Patients with inadequate response to quinapril monotherapy: Quinapril 10 mg/hydrochlorothiazide 12.5 mg **or** quinapril 20 mg/hydrochlorothiazide 12.5 mg once daily

Patients with adequate blood pressure control on hydrochlorothiazide 25 mg/day, but significant potassium loss: Quinapril 10 mg/hydrochlorothiazide 12.5 mg **or** quinapril 20 mg/hydrochlorothiazide 12.5 mg once daily

Note: Clinical trials of quinapril/hydrochlorothiazide combinations used quinapril doses of 2.5-40 mg/day and hydrochlorothiazide doses of 6.25-25 mg/day.

Dosing: ElderlyIf previous response to individual components is unknown, initial dose selection should be cautious, at the low end of adult dosage range; titration should occur at 1- to 2-week intervals.

Dosing: PediatricSafety and efficacy have not been established.

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute/1.73 m^2 or serum creatinine ≤3 mg/dL: Use is not recommended.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsMay be taken without regard to meals.

StorageStore at 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to quinapril, hydrochlorothiazide, sulfonamide-derived drugs, or any other component of the formulation; angioedema related to previous treatment with an ACE inhibitor; anuria

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Electrolyte disturbances: Hyperkalemia may occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.
- Neutropenia/agranulocytosis: Another ACE Inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.
- Photosensitivity: Photosensitization may occur.
- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.
- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.
- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.
- Collagen vascular disease: Use quinapril with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity. Hydrochlorothiazide can cause systemic lupus erythematosus (SLE) exacerbation or activation.
- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.
- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.
- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.
- Renal artery stenosis: Use quinapril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.
- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment. Avoid hydrochlorothiazide in severe renal disease (ineffective). Contraindicated in anuric patients.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss, or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsCombination products are not recommended for first-line treatment. Hydrochlorothiazide is not effective in patients with a Cl_{cr} <30 mL/minute, therefore, it may not be a useful agent in many elderly patients. Due to frequent decreases in glomerular filtration (also creatinine clearance) with aging, elderly patients may have exaggerated responses to ACE inhibitors; differences in clinical response due to hepatic changes are not observed. ACE inhibitors may be preferred agents in elderly patients with CHF and diabetes mellitus. Diabetic proteinuria is reduced and insulin sensitivity is enhanced. In general, the side effect profile is favorable in the elderly and causes little or no CNS confusion; use lowest dose recommendations initially. Adjust for renal function. Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.

Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)

Pregnancy Considerations See individual agents.

LactationEnters breast milk/use caution

Adverse Reactions

1% to 10%:

Central nervous system: Dizziness (5%), somnolence (1%)

Neuromuscular & skeletal: Weakness (1%)

Renal: Serum creatinine increased (3%), blood urea nitrogen increased (4%)

Respiratory: Cough (3%), bronchitis (1%)

<1%: Acute renal failure, agranulocytosis, alopecia, anaphylactoid reaction, angina pectoris, angioedema, arrhythmia, arthralgia, calcium increased (serum), cerebrovascular accident, cholesterol increased (serum), diaphoresis increased, dyspnea, erythema multiforme, exfoliative dermatitis, gastrointestinal hemorrhage, glucose increased (serum), heart failure, hypercalcemia, hyperkalemia, hypertensive crisis, impotence, liver function test abnormalities, magnesium increased (serum), malaise, MI, nervousness, orthostatic hypotension, palpitation, pancreatitis, paresthesia, pemphigus, photosensitivity, pruritus, sinusitis, tachycardia, uric acid increased (serum), thrombocytopenia, triglyceride increased (serum), vertigo, xerostomia

Postmarketing and/or case reports: Abnormal gait, abnormal vision, albuminuria, amnesia, anemia, arthritis, ascites, asthma, bradycardia, cellulitis, cholestatic jaundice, cor pulmonale, deep thrombosis, diarrhea, esophagitis, generalized edema, hematuria, hemiplegia, hepatitis, kidney function abnormality, macropapular rash, meningism, myopathy, myositis, nephrosis, paralysis, petechiae, pneumonia, pyuria, shock, urticaria, vasculitis, weight loss

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Quinolone Antibiotics: Quinapril may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Tetracycline Derivatives: Quinapril may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure; BUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsBUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

10/12.5: Quinapril 10 mg and hydrochlorothiazide 12.5 mg

20/12.5: Quinapril 20 mg and hydrochlorothiazide 12.5 mg

20/25: Quinapril 20 mg and hydrochlorothiazide 25 mg

Accuretic® 10/12.5, Quinaretic 10/12.5: Quinapril 10 mg and hydrochlorothiazide 12.5 mg

Accuretic® 20/12.5, Quinaretic 20/12.5: Quinapril 20 mg and hydrochlorothiazide 12.5 mg

Accuretic® 20/25, Quinaretic 20/25: Quinapril 20 mg and hydrochlorothiazide 25 mg

Generic AvailableYes

ManufacturerPfizer

Pricing: U.S. (www.drugstore.com)

Tablets (Accuretic)

10-12.5 mg (30): $51.07

20-12.5 mg (30): $55.99

20-25 mg (30): $51.07

Tablets (Quinapril-Hydrochlorothiazide)

20-12.5 mg (90): $86.99

20-25 mg (90): $86.99

Tablets (Quinaretic)

10-12.5 mg (30): $35.99

20-12.5 mg (30): $25.99

20-25 mg (30): $33.99

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Hydrochlorothiazide
- Quinapril

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness; may rarely cause insomnia or depression

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine. May decrease lithium clearance, resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels.

Index TermsHydrochlorothiazide and Quinapril

References

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International Brand NamesAccupro Comp (FI, SE); Accuretic (AR, AU, BE, CH, CN, CO, CR, DO, GB, GR, GT, HN, IE, NI, PA, PE, SV, TZ, UG, VE, ZA, ZM, ZW); Accuzide (AE, BG, BH, CY, CZ, DE, EE, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PH, QA, SA, SY, YE); Acuilix (FR, MU); Acuretic (PT); Koretic (FR)

Quinapril

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Accupril® may be confused with Accolate®, Accutane®, AcipHex®, Monopril®

International issues:

Accupril® may be confused with Acepril® which is a brand name for lisinopril in Denmark, a brand name for enalapril in Hungary and Switzerland, and a brand name for captopril in Great Britain

Pronunciation(KWIN a pril)

U.S. Brand NamesAccupril®

Canadian Brand NamesAccupril®; GD-Quinapril

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor

Use: Labeled IndicationsTreatment of hypertension; treatment of heart failure

Use: Unlabeled/InvestigationalTreatment of left ventricular dysfunction after myocardial infarction; pediatric hypertension; to delay the progression of nephropathy and reduce risks of cardiovascular events in hypertensive patients with type 1 or 2 diabetes mellitus

Dosing: Adults

Hypertension: Oral: Initial: 10-20 mg once daily, adjust according to blood pressure response at peak and trough blood levels; initial dose may be reduced to 5 mg in patients receiving diuretic therapy if the diuretic is continued.

Usual dose range (JNC 7): 10-40 mg once daily

Heart failure: Oral: Initial: 5 mg once or twice daily, titrated at weekly intervals to 20-40 mg daily in 2 divided doses; target dose (heart failure): 20 mg twice daily (ACC/AHA 2005 Heart Failure Guidelines)

Dosing: ElderlyOral: Initial: 2.5-5 mg/day; increase dosage at increments of 2.5-5 mg at 1- to 2-week intervals; adjust for renal impairment.

Dosing: Pediatric**Hypertension (unlabeled use):** Oral: Initial 5-10 mg once daily; maximum: 80 mg/day

Dosing: Renal ImpairmentLower initial doses should be used; after initial dose (if tolerated), administer initial dose twice daily; may be increased at weekly intervals to optimal response:

Hypertension: Oral: Initial:

Cl_{cr} >60 mL/minute: Administer 10 mg/day

Cl_{cr} 30-60 mL/minute: Administer 5 mg/day

Cl_{cr} 10-30 mL/minute: Administer 2.5 mg/day

Heart failure: Oral: Initial:

Cl_{cr} >30 mL/minute: Administer 5 mg/day

Cl_{cr} 10-30 mL/minute: Administer 2.5 mg/day

Dosing: Hepatic ImpairmentIn patients with alcoholic cirrhosis, hydrolysis of quinapril to quinaprilat is impaired; however, the subsequent elimination of quinaprilat is unaltered.

Calculations

- Creatinine Clearance: Adults

StorageStore at room temperature.

ReconstitutionTo prepare solution for oral administration, mix prior to administration and use within 10 minutes.

Compatibility**Incompatible** with aqueous solutions.

ContraindicationsHypersensitivity to quinapril or any component of the formulation; angioedema related to previous treatment with an ACE inhibitor

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See special populations.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE Inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss, or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsDue to frequent decreases in glomerular filtration (also creatinine clearance) with aging, elderly patients may have exaggerated responses to ACE inhibitors; differences in clinical response due to hepatic changes are not observed. ACE inhibitors may be preferred agents in elderly patients with CHF and diabetes mellitus. Diabetic proteinuria is reduced and insulin sensitivity is enhanced. In general, the side effect profile is favorable in elderly and causes little or no CNS confusion; use lowest dose recommendations initially. Adjust for renal function. Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.

Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)

Pregnancy ConsiderationsDue to adverse events observed in some animal studies, quinapril is considered pregnancy category C during the first trimester. Based on human data, quinapril is considered pregnancy category D if used during the second and third trimesters (per the manufacturer; however, one study suggests that fetal injury may occur at anytime during pregnancy). Quinapril crosses the placenta. First trimester exposure to ACE inhibitors may cause major congenital malformations. An increased risk of cardiovascular and/or central nervous system malformations was observed in one study; however, an increased risk of teratogenic events was not observed in other studies. Second and third trimester use of an ACE inhibitor is associated with oligohydramnios. Oligohydramnios due to decreased fetal renal function may lead to fetal limb contractures, craniofacial deformation, and hypoplastic lung development. The use of ACE inhibitors during the second and third trimesters is also associated with anuria, hypotension, renal failure (reversible or irreversible), skull hypoplasia, and death in the fetus/neonate. Chronic maternal hypertension itself is also associated with adverse events in the fetus/infant. ACE inhibitors are not recommended during pregnancy to treat maternal hypertension or heart failure. Those who are planning a pregnancy should be considered for other medication options if an ACE inhibitor is currently prescribed or the ACE inhibitor should be discontinued as soon as possible once pregnancy is detected. The exposed fetus should be monitored for fetal growth, amniotic fluid volume, and organ formation. Infants exposed to an ACE inhibitor *in utero*, especially during the second and third trimester, should be monitored for hyperkalemia, hypotension, and oliguria.

[U.S. Boxed Warning]: Based on human data, ACE inhibitors can cause injury and death to the developing fetus when used in the second and third trimesters. ACE inhibitors should be discontinued as soon as possible once pregnancy is detected.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsQuinapril is excreted in breast milk. The manufacturer recommends that caution be exercised when administering quinapril to nursing women.

Pregnancy & Lactation, In-Depth

- Quinapril in Pregnancy & Lactation

Adverse Reactions**Note:** Frequency ranges include data from hypertension and heart failure trials. Higher rates of adverse reactions have generally been noted in patients with CHF. However, the frequency of adverse effects associated with placebo is also increased in this population.

1% to 10%:

Cardiovascular: Hypotension (3%), chest pain (2%), first-dose hypotension (up to 3%)

Central nervous system: Dizziness (4% to 8%), headache (2% to 6%), fatigue (3%)

Dermatologic: Rash (1%)

Endocrine & metabolic: Hyperkalemia (2%)

Gastrointestinal: Vomiting/nausea (1% to 2%), diarrhea (2%)

Neuromuscular & skeletal: Myalgias (2% to 5%), back pain (1%)

Renal: BUN/serum creatinine increased (2%, transient elevations may occur with a higher frequency), worsening of renal function (in patients with bilateral renal artery stenosis or hypovolemia)

Respiratory: Upper respiratory symptoms, cough (2% to 4%; up to 13% in some studies), dyspnea (2%)

<1% (Limited to important or life-threatening): Anaphylactoid reaction, angioedema, arthralgia, edema, back pain, malaise, viral infection, palpitation, vasodilation, tachycardia, heart failure, hyperkalemia, MI, cerebrovascular accident, hypertensive crisis, angina, orthostatic hypotension, arrhythmia, shock, hemolytic anemia, xerostomia, constipation, gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests, somnolence, vertigo, syncope, nervousness, depression, insomnia, paresthesia, alopecia, increased diaphoresis, pemphigus, pruritus, exfoliative dermatitis, photosensitivity, dermatopolymyositis, impotence, acute renal failure, eosinophilic pneumonitis, amblyopia, pharyngitis, agranulocytosis, hepatitis, thrombocytopenia

A syndrome which may include fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash, eosinophilia and positive ANA, and elevated ESR has been reported with ACE inhibitors. In addition, pancreatitis, hepatic necrosis, neutropenia, and/or agranulocytosis (particularly in patients with collagen-vascular disease or renal impairment) have been associated with many ACE inhibitors.

Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Quinolone Antibiotics: Quinapril may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Tetracycline Derivatives: Quinapril may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure; serum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringUse caution in presence of renal impairment, hypovolemia, collagen vascular diseases, valvular stenosis, hyperkalemia, or before, during, or immediately after anesthesia. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (especially anything that may impact fluid balance or cardiac status). It is advisable to administer first dose in prescriber's office with careful blood pressure monitoring (hypotension or angioedema can occur at any time during treatment, especially following first dose). Evaluate results of laboratory tests, therapeutic effectiveness (blood pressure and cardiac status), and adverse reactions (eg, hypovolemia, angioedema, postural hypotension) on a regular basis during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed; do not alter dose or discontinue without consulting prescriber. Take first dose at bedtime or when sitting down (hypotension may occur). This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause increased cough (if persistent or bothersome, contact prescriber); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); headache (consult prescriber for approved analgesic); dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or muscle or back pain (consult prescriber for approved analgesic). Immediately report swelling of face, mouth, lips, tongue, or throat; chest pain or respiratory difficulty; persistent cough; persistent pain in muscles, joints, or back; skin rash; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 5 mg, 10 mg, 20 mg, 40 mg

Accupril®: 5 mg, 10 mg, 20 mg, 40 mg

Generic AvailableYes
ManufacturerPfizer
Pricing: U.S. (www.drugstore.com)

Tablets (Accupril)

5 mg (30): $56.99

10 mg (30): $55.97

20 mg (30): $54.99

40 mg (30): $55.99

Tablets (Quinapril HCl)

5 mg (30): $21.99

10 mg (30): $19.99

20 mg (30): $26.97

40 mg (30): $21.99

Mechanism of ActionCompetitive inhibitor of angiotensin-converting enzyme (ACE); prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor; results in lower levels of angiotensin II which causes an increase in plasma renin activity and a reduction in aldosterone secretion; a CNS mechanism may also be involved in hypotensive effect as angiotensin II increases adrenergic outflow from CNS; vasoactive kallikreins may be decreased in conversion to active hormones by ACE inhibitors, thus reducing blood pressure
Pharmacodynamics/Kinetics

Onset of action: 1 hour

Duration: 24 hours

Absorption: Quinapril: ≥60%

Protein binding: Quinapril: 97%; Quinaprilat: 97%

Metabolism: Rapidly hydrolyzed to quinaprilat, the active metabolite

Half-life elimination: Quinapril: 0.8 hours; Quinaprilat: 3 hours; increases as Cl_{cr} decreases

Time to peak, serum: Quinapril: 1 hour; Quinaprilat: ~2 hours

Excretion: Urine (50% to 60% primarily as quinaprilat)

Related Information

- Angiotensin Agents
- Heart Failure (Systolic)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness; may rarely cause insomnia or depression
Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels
Cardiovascular Considerations

Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines recommend that ACE inhibitors be used in patients with a reduced EF (with or without heart failure symptoms) unless contraindicated. ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. In this situation, they decrease hospitalizations for, and retard progression to, congestive heart failure. When used in patients with heart failure, the target dose should be achieved, if possible. Lower daily doses of ACE inhibitors have demonstrated the same mortality effects as high doses, but have not decreased hospitalizations to the extent that high-dose ACE inhibitors have, as demonstrated in the ATLAS study (Packer M, 1999).

Hypertension: The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) can be beneficial in patients with hypertension and LVH without symptoms of heart failure. JNC 7 suggests that patients can benefit from treatment with an ACE inhibitor if they have hypertension **and** heart failure, acute myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, a history of stroke.

Vascular Disease: The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors can be useful in preventing heart failure in patients who have a history of atherosclerotic vascular disease, diabetes, or hypertension with associated cardiovascular risk factors. The HOPE trial (Heart Outcomes Prevention Evaluation Study Investigators, 2000) investigated the value of an ACE inhibitor (ramipril 5-10 mg daily) versus placebo in patients who had evidence of vascular disease or diabetes (one other cardiovascular risk factor) and were at least 55 years of age. Patients were excluded if they had a low ejection fraction, heart failure, or were on an ACE inhibitor. The primary outcome was a composite of death from cardiovascular cause, myocardial infarction, or stroke; 9297 patients were enrolled and randomized. Ramipril significantly reduced the risk of death from CV causes, MI, or stroke over placebo. New cases of diabetes were also reduced in the ramipril group. In the EUROPA trial, patients with stable coronary artery disease (at low risk for cardiovascular events) received perindopril or placebo and were evaluated for incidence of cardiovascular events after four years of treatment. In this randomized, placebo-controlled, prospective study, 12,218 patients received either perindopril (8 mg/day, n=6110) or placebo (n=6108) and were assessed for the primary endpoint of a cardiovascular event, defined as cardiovascular death, myocardial infarction, or cardiac arrest. The study population was well balanced with respect to baseline demographics and concomitant medication use (including beta-blockers, platelet inhibitors, antihyperlipidemics, calcium channel blockers, nitrates, and diuretics). Intent-to-treat analysis revealed that 603 (10%) of placebo patients experienced the primary endpoint of a cardiovascular event compared to 488 (8%) of perindopril-receiving patients, for a 20% relative risk reduction (p=0.0003). This result was not influenced by presence of other comorbidities (eg, diabetes, hypertension) or concomitant beta-blocker, calcium channel blocker, or lipid-lowering therapies. Withdrawal from the study (postrandomization) due to adverse reactions was similar between treatment groups. Number needed to treat analysis suggests that treatment of 50 patients over a 4-year period will prevent one major cardiovascular event.

Acute Coronary Syndromes: In the treatment of unstable angina/non-ST-segment elevation MI, ACE inhibitors are recommended when hypertension persists despite treatment with nitroglycerin and a beta-blocker in patients with LV systolic dysfunction or CHF and in ischemic patients with diabetes (Class I). ACE inhibitors are also recommended for all post-ACS individuals (Class IIa). According to 2004 ACC/AHA STEMI guidelines, an ACE inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF <0.4, in the absence of hypotension or known contraindications to this class of medicines. In the emergency management of complicated STEMI, a short-acting ACEI (eg, captopril 1-6.25 mg) may be added once the patient's systolic blood pressure is >100 mm Hg and not <30 mm Hg below baseline. The VALIANT trial evaluated the effects of valsartan (target dose: 160 mg twice daily), captopril (target dose: 50 mg twice daily), and the combination (target doses: valsartan 80 mg twice daily and captopril 150 mg once daily) in a randomized, double-blind trial of patients with acute MI (0.5-10 days post-MI) complicated by left ventricular systolic dysfunction, heart failure, or both. Enrollment in the study numbered 14,703 patients and followed for a median of 24.7 months. There was no difference in the primary endpoint (all cause mortality) among the 3 groups. There was no difference in incidence of CV death, recurrent MI, or hospitalization for heart failure either. Hypotension and renal dysfunction occurred significantly more often in the valsartan group than captopril alone. Cough, rash, and taste disturbances occurred more often in the captopril group. The authors (Pfeffer MA, 2003) concluded that valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after MI. Combining valsartan with captopril increased the rate of adverse events without improving survival.

Potential Adverse Events: ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. In those patients experiencing cough on an ACE inhibitor, the ACE inhibitor may be discontinued and, if necessary, ARB therapy instituted. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Drug Interactions: Concomitant indomethacin therapy may blunt the reduction in sitting and 24-hour ambulatory diastolic blood pressure. Use of NSAIDs should be avoided or limited, with monitoring of blood pressure control in this setting. In patients with heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

Anesthesia and Critical Care Concerns/Other ConsiderationsACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. ACE inhibitors are also indicated in patients postmyocardial infarction in whom left ventricular ejection fraction is <40%.

ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. To prevent this, discontinue diuretics 2-3 days prior to initiating quinapril; may restart diuretics if blood pressure is not controlled by quinapril alone. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Index TermsQuinapril Hydrochloride

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International Brand NamesAccupril (AR, AU, BE, BO, BR, BZ, CN, CO, CR, DO, EC, GT, HK, HN, ID, KP, LU, MX, NI, PA, PE, PH, PK, PR, PY, SV, TH, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Accuprin (IT); Accupro (AT, BG, CH, CZ, DE, DK, EE, FI, GB, HN, HU, IE, PL, SE); Accupron (GR); Acequin (IT); Acquin (AU); Acuitel (AE, BH, CY, EG, FR, IL, IQ, IR, JO, KW, LB, LY, MU, OM, QA, SA, SY, YE); Acupril (MX, NL, PT); Asig (AU); Ectren (ES); Filpril (AU); Korec (FR); Lidaltrin (ES); Qpril (AU); Quinapro (IE); Quinaril (TH); Quinaspen (ZA); Quinaten (CO); Quinazil (IT); Quinsil (TH)

QuiNIDine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

QuiNIDine may be confused with cloNIDine, quiNINE, Quinora®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V. formulation) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(KWIN i deen)

Canadian Brand NamesApo-Quinidine®; BioQuin® Durules™; Novo-Quinidin; Quinate®

Pharmacologic CategoryAntiarrhythmic Agent, Class Ia

Use: Labeled IndicationsProphylaxis after cardioversion of atrial fibrillation and/or flutter to maintain normal sinus rhythm; prevent recurrence of paroxysmal supraventricular tachycardia, paroxysmal AV junctional rhythm, paroxysmal ventricular tachycardia, paroxysmal atrial fibrillation, and atrial or ventricular premature contractions; has activity against *Plasmodium falciparum* malaria

Dosing: Adults

Note: Dosage expressed in terms of the salt: 267 mg of quinidine gluconate = 275 mg of quinidine polygalacturonate = 200 mg of quinidine sulfate.

Test dose for idiosyncratic reaction: Oral, I.M.: 200 mg administered several hours before full dosage (to determine possibility of idiosyncratic reaction)

Antiarrhythmic:

Oral:

Sulfate: 100-600 mg/dose every 4-6 hours; begin at 200 mg/dose and titrate to desired effect (maximum daily dose: 3-4 g)

Gluconate: 324-972 mg every 8-12 hours

I.M.: 400 mg/dose every 4-6 hours

I.V.: 200-400 mg/dose diluted and given at a rate ≤10 mg/minute

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Note: Dosage expressed in terms of the salt: 267 mg of quinidine gluconate = 200 mg of quinidine sulfate.

Test dose for idiosyncratic reaction (sulfate, oral or gluconate, I.M.): Children: 2 mg/kg or 60 mg/m^2

Antiarrhythmic: Oral (quinidine sulfate): Children: 15-60 mg/kg/day in 4-5 divided doses or 6 mg/kg every 4-6 hours; usual 30 mg/kg/day or 900 mg/m^2/day given in 5 daily doses

I.V. **not** recommended (quinidine gluconate): Children: 2-10 mg/kg/dose given at a rate ≤10 mg/minute every 3-6 hours as needed

Dosing: Renal Impairment

Cl_{cr} <10 mL/minute: Administer 75% of normal dose.

Hemodialysis effects: Slightly hemodialyzable (5% to 20%); 200 mg supplemental dose posthemodialysis is recommended; not dialyzable (0% to 5%) by peritoneal dialysis.

Dosing: Hepatic ImpairmentLarger loading dose may be indicated; reduce maintenance doses by 50% and monitor serum levels closely.

Calculations

- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Give around-the-clock to promote less variation in peak and trough serum levels. Maximum I.V. infusion rate: 10 mg/minute. Minimize use of PVC tubing to enhance bioavailability.

Administration: I.V. DetailpH: 5.5-7.0 (injection)
Administration: OralDo not crush, chew, or break sustained release dosage forms. Give around-the-clock to promote less variation in peak and trough serum levels.
Dietary ConsiderationsAdminister with food or milk to decrease gastrointestinal irritation. Avoid changes in dietary salt intake.
StorageDo not use discolored parenteral solution.
CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Diazepam, milrinone. **Incompatible:** Furosemide. **Variable (consult detailed reference):** Heparin.

Compatibility when admixed: Compatible: Bretylium, cimetidine, milrinone, ranitidine, verapamil. **Incompatible:** Atracurium. **Variable (consult detailed reference):** Amiodarone.

Extemporaneously PreparedA 10 mg/mL oral liquid preparation made from tablets and three different vehicles (cherry syrup, a 1:1 mixture of Ora-Sweet® and Ora-Plus®, or a 1:1 mixture of Ora-Sweet® SF and Ora-Plus®) was stable for 60 days when stored in amber plastic prescription bottles in the dark at room temperature (25°C) or under refrigeration (5°C). Grind six 200 mg tablets in a mortar into a fine powder; add 15 mL of the vehicle and mix well to form a uniform paste; mix while adding the vehicle in geometric proportions to **almost** 120 mL; transfer to a calibrated bottle and qsad to 120 mL; label “shake well” and “protect from light” (Allen 1998).

Allen LV and Erickson MA, “Stability of Bethanechol Chloride, Pyrazinamide, Quinidine Sulfate, Rifampin, and Tetracycline in Extemporaneously Compounded Oral Liquids,” *Am J Health Syst Pharm*, 1998, 55(17):1804-9.

ContraindicationsHypersensitivity to quinidine or any component of the formulation; thrombocytopenia; thrombocytopenic purpura; myasthenia gravis; heart block greater than first degree; idioventricular conduction delays (except in patients with a functioning artificial pacemaker); those adversely affected by anticholinergic activity; concurrent use of quinolone antibiotics which prolong QT interval, cisapride, amprenavir, or ritonavir
Allergy Considerations

- QuiNIDine/QuiNINE Derivative Allergy

Warnings/Precautions

Boxed warnings:

- Arrhythmias: Appropriate use: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Hepatotoxicity: Has been associated with severe hepatotoxic reactions, including granulomatous hepatitis.
- Hypersensitivity reactions: With use, hypersensitivity reactions may occur.
- Proarrhythmic effects: Watch for proarrhythmic effects; monitor and adjust dose to prevent QT_c prolongation.

Disease-related concerns:

- Arrhythmias: Appropriate use: **[U.S. Boxed Warning]: Antiarrhythmic drugs have not been shown to enhance survival in non-life-threatening ventricular arrhythmias and may increase mortality; the risk is greatest with structural heart disease. Quinidine may increase mortality in treatment of atrial fibrillation/flutter.**
- Atrial fibrillation/flutter: May increase ventricular response rate in patients with atrial fibrillation or flutter; control AV conduction before initiating.
- Conduction disturbances: Use with caution in patients at risk for heart block; can unmask sick sinus syndrome (causes bradycardia).
- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.
- G6PD deficiency: Hemolysis may occur in patients with G6PD (glucose-6-phosphate dehydrogenase) deficiency.
- Heart failure (HF): Use with caution in patients with HF; may precipitate or exacerbate condition.
- Hepatic impairment: Use with caution in patients with hepatic impairment; reduced dosage recommended.

Concurrent drug therapy issues:

- Antiarrhythmics: Use with caution with concurrent use of other antiarrhythmics.
- Digoxin: Use may cause digoxin-induced toxicity; adjust digoxin's dose.

Dosage form specific issues:

- Different salts: Do not interchange the different salt products.

Other warnings/precautions:

- CAST trial: In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, non-life-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide. An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. Antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Geriatric ConsiderationsClearance may be decreased with a resultant increased half-life. Must individualize dose. Bioavailability and half-life are increased in the elderly due to decreases in both renal and hepatic function with age.

Pregnancy Risk FactorC

LactationEnters breast milk/compatible

Adverse Reactions

Frequency not defined: Hypotension, syncope

>10%:

Cardiovascular: QT_c prolongation (modest prolongation is common, however, excessive prolongation is rare and indicates toxicity)

Central nervous system: Lightheadedness (15%)

Gastrointestinal: Diarrhea (35%), upper GI distress, bitter taste, anorexia, nausea, vomiting, stomach cramping (22%)

1% to 10%:

Cardiovascular: Angina (6%), palpitation (7%), new or worsened arrhythmia (proarrhythmic effect)

Central nervous system: Syncope (1% to 8%), headache (7%), fatigue (7%), sleep disturbance (3%), tremor (2%), nervousness (2%), incoordination (1%)

Dermatologic: Rash (5%)

Neuromuscular & skeletal: Weakness (5%)

Ocular: Blurred vision

Otic: Tinnitus

Respiratory: Wheezing

<1% (Limited to important or life-threatening): Tachycardia, QT_c prolongation (excessive), torsade de pointes, heart block, ventricular fibrillation, ventricular tachycardia, paradoxical increase in ventricular rate during atrial fibrillation/flutter, exacerbated bradycardia (in sick sinus syndrome), vascular collapse, confusion, delirium, vertigo, hearing impaired, respiratory depression, pneumonitis, bronchospasm, fever, urticaria, flushing, exfoliative rash, psoriaform rash, pruritus, lymphadenopathy, hemolytic anemia, vasculitis, thrombocytopenic purpura, thrombocytopenia, pancytopenia, uveitis, angioedema, agranulocytosis, sicca syndrome, arthralgia, myalgia, CPK increased, drug-induced lupus-like syndrome, cerebral hypoperfusion (possibly resulting in ataxia, apprehension, and seizure), acute psychotic reactions, depression, hallucinations, mydriasis, disturbed color perception, night blindness, scotoma, optic neuritis, visual field loss, photosensitivity, abnormal pigmentation, granulomatous hepatitis, hepatotoxic reaction (rare), eczematous dermatitis, livedo reticularis

Postmarketing and/or case reports: Melanin pigmentation of the hard palate, esophagitis, nephropathy, cholestasis, pneumonitis, lichen planus

Note: Cinchonism, a syndrome which may include tinnitus, high-frequency hearing loss, deafness, vertigo, blurred vision, diplopia, photophobia, headache, confusion, and delirium has been associated with quinidine use. Usually associated with chronic toxicity, this syndrome has also been described after brief exposure to a moderate dose in sensitive patients. Vomiting and diarrhea may also occur as isolated reactions to therapeutic quinidine levels.

Metabolism/Transport Effects**Substrate** of CYP2C9 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP2C9 (weak), 2D6 (strong), 3A4 (strong)

Drug Interactions

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amiodarone: Antiarrhythmic Agents (Class Ia) may enhance the QTc-prolonging effect of Amiodarone. Amiodarone may increase the metabolism of Antiarrhythmic Agents (Class Ia). *Risk D: Consider therapy modification*

Antacids: May decrease the excretion of QuiNIDine. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of QuiNIDine. Management: Itraconazole, voriconazole, and posaconazole are specifically contraindicated with quinidine. Use of quinidine with any azole antifungal may require quinidine dose adjustment and should be done with caution and close monitoring. *Risk X: Avoid combination*

Barbiturates: May increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Beta-Blockers: QuiNIDine may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Carteolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Dihydropyridine): May decrease the serum concentration of QuiNIDine. **Exceptions:** Felodipine; Nisoldipine. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May increase the serum concentration of QuiNIDine. *Risk D: Consider therapy modification*

Carbonic Anhydrase Inhibitors: May decrease the excretion of QuiNIDine. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Cardiac Glycosides: QuiNIDine may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Strong) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: QuiNIDine may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dextromethorphan: QuiNIDine may decrease the metabolism of Dextromethorphan. *Risk D: Consider therapy modification*

Dihydrocodeine: QuiNIDine may diminish the analgesic effect of Dihydrocodeine. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of QuiNIDine. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Haloperidol: QuiNIDine may increase the serum concentration of Haloperidol. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Hydrocodone: QuiNIDine may diminish the analgesic effect of Hydrocodone. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Kaolin: May decrease the absorption of QuiNIDine. *Risk D: Consider therapy modification*

Macrolide Antibiotics: May decrease the metabolism of QuiNIDine. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mefloquine: QuiNIDine may enhance the adverse/toxic effect of Mefloquine. Specifically, the risk for QTc-prolongation and the risk for convulsions may be increased. Management: Avoid concurrent use, and delay administration of mefloquine until at least 12 hours after the last dose of quinidine when possible. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents: QuiNIDine may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May diminish the therapeutic effect of QuiNIDine. *Risk C: Monitor therapy*

Primidone: May increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of QuiNIDine. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of QuiNIDine. Fluvoxamine appears to be the only SSRI of concern. **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk D: Consider therapy modification*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Strong) may decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Tetrabenazine: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Tetrabenazine. Specifically, concentrations of the active alpha- and beta-dihydrotetrabenazine metabolites may be increased. Management: Tetrabenazine dose should be reduced by 50% when starting a strong CYP2D6 inhibitor. Maximum tetrabenazine dose is 50mg/day when used with a strong CYP2D6 inhibitor. *Risk D: Consider therapy modification*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the QTc-prolonging effect of QuiNIDine. QuiNIDine may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): QuiNIDine may enhance the anticoagulant effect of Vitamin K Antagonists. Note that the prothrombin time might be unchanged in the face of increased bleeding. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Dietary salt intake may alter the rate and extent of quinidine absorption. A decrease in dietary salt may lead to an increase in quinidine serum concentrations. Avoid changes in dietary salt intake. Quinidine serum levels may be increased if taken with food. Food has a variable effect on absorption of sustained release formulation. The rate of absorption of quinidine may be decreased following the ingestion of grapefruit juice. In addition, CYP3A4 metabolism of quinidine may be reduced by grapefruit juice. Grapefruit juice should be avoided. Excessive intake of fruit juices or vitamin C may decrease urine pH and result in increased clearance of quinidine with decreased serum concentration. Alkaline foods may result in increased quinidine serum concentrations.

Herb/Nutraceutical: St John's wort may decrease quinidine levels. Avoid ephedra (may worsen arrhythmia).

Monitoring ParametersCardiac monitor required during I.V. administration; CBC, liver and renal function tests, should be routinely performed during long-term administration

Reference RangeTherapeutic: 2-5 mcg/mL (SI: 6.2-15.4 μmol/L). Patient-dependent therapeutic response occurs at levels of 3-6 mcg/mL (SI: 9.2-18.5 μmol/L). Optimal therapeutic level is method dependent; >6 mcg/mL (SI: >18 μmol/L).

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. I.V. requires use of infusion pump and continuous cardiac and hemodynamic monitoring. Assess results of laboratory tests, therapeutic effectiveness (monitor cardiac functioning closely), and adverse reactions at beginning of therapy, when titrating dosage, and on a regular basis with long-term therapy. **Note:** Quinidine has a low TI and overdose may easily produce severe and life-threatening reactions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsRoutine CBC, liver and renal function during long-term administration

Patient EducationTake exactly as directed, around-the-clock; do not take additional doses or discontinue without consulting prescriber. Do not crush, chew, or break sustained release dosage forms. Do not take with grapefruit juice. You will need regular cardiac checkups and blood tests while taking this medication. You may experience dizziness, drowsiness, or visual changes (use caution when driving or engaging in tasks requiring alertness until response to drug is known); abnormal taste, nausea or vomiting, or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); headaches (prescriber may recommend mild analgesic); or diarrhea (yogurt or boiled milk may help; if persistent consult prescriber). Report chest pain, palpitation, or erratic heartbeat; respiratory difficulty or wheezing; CNS changes (confusion, delirium, fever, consistent dizziness); skin rash; sense of fullness or ringing in ears; or vision changes. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as gluconate: 80 mg/mL (10 mL) [equivalent to quinidine base 50 mg/mL]

Tablet, as sulfate: 200 mg, 300 mg

Tablet, extended release, as gluconate: 324 mg [equivalent to quinidine base 202 mg]

Tablet, extended release, as sulfate: 300 mg [equivalent to quinidine base 249 mg]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, controlled release (Quinidine Gluconate CR)

324 mg (90): $60.08

Tablet, controlled release (Quinidine Sulfate CR)

300 mg (90): $46.99

Tablets (Quinidine Sulfate)

200 mg (90): $19.99

300 mg (90): $36.99

Mechanism of ActionClass Ia antiarrhythmic agent; depresses phase O of the action potential; decreases myocardial excitability and conduction velocity, and myocardial contractility by decreasing sodium influx during depolarization and potassium efflux in repolarization; also reduces calcium transport across cell membrane

Pharmacodynamics/Kinetics

Distribution: V_d: Adults: 2-3.5 L/kg, decreased with congestive heart failure, malaria; increased with cirrhosis; crosses placenta; enters breast milk

Protein binding:

Newborns: 60% to 70%; decreased protein binding with cyanotic congenital heart disease, cirrhosis, or acute myocardial infarction

Adults: 80% to 90%

Metabolism: Extensively hepatic (50% to 90%) to inactive compounds

Bioavailability: Sulfate: 80%; Gluconate: 70%

Half-life elimination, plasma: Children: 2.5-6.7 hours; Adults: 6-8 hours; prolonged with elderly, cirrhosis, and congestive heart failure

Excretion: Urine (15% to 25% as unchanged drug)

Related Information

- Antacid Drug Interactions
- Antiarrhythmic Drugs
- Malaria Treatment

Dental Health: Effects on Dental TreatmentWhen taken over a long period of time, the anticholinergic side effects from quinidine can cause a reduction of saliva production or secretion contributing to discomfort and dental disease (ie, caries, oral candidiasis, and periodontal disease).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsQuinidine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay cause dizziness; may rarely cause confusion or delirium

Mental Health: Effects on Psychiatric TreatmentContraindicated with ziprasidone. May cause anemia; use caution with clozapine and carbamazepine. Concurrent use with TCAs may raise serum levels or produce AV block; avoid combination. Concurrent use with beta-blockers may increase bradycardia.

Cardiovascular ConsiderationsAs with other Class Ia agents, it is prudent to avoid quinidine use in patients with cardiovascular disease, particularly recent myocardial infarction and heart failure, due to a possible increase in proarrhythmia and mortality. Quinidine may be used to pharmacologically convert atrial fibrillation to normal sinus rhythm. Patients should be monitored (ECG) in a controlled setting when initiating therapy. Therapy should be discontinued or the dose reduced if the QT interval increases ≥25% from baseline. Proarrhythmia (torsade de pointes) may occur early or after months of therapy. It is important to note (see Drug Interactions) that quinidine may increase digoxin levels by twofold, often necessitating a reduction of the digoxin dosage by 50% when quinidine therapy is initiated.

Index Terms Quinidine Gluconate; Quinidine Polygalacturonate; Quinidine Sulfate

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International Brand Names Cardioquina (UY); Cardioquinol (EC); Chinidin (BG); Chinidin Retard (HN); Chinidinum prolongatum (PL); Chinidinum sulfuricum (PL); Kiditard (NL); Kinidin (AE, BH, CY, CZ, EG, FI, GR, IE, IL, IQ, IR, JO, KW, LB, LY, NO, OM, PH, QA, SA, SE, SY, YE); Kinidin Durules (AU); Kinidin durules (PL); Kinidine (NL); Kinilentin (PL); Kinitard (PL); Naticardina (IT); Quinaglute Dura-tabs (ZA); Quinicardine (PE); Quiniduran (IL); Ritmocor (IT); Sulfas-Chinidin (ID); Wanidine (TW)

QuiNINE

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Medication Safety Issues

Sound-alike/look-alike issues:

QuiNINE may be confused with quiNIDine

Pronunciation(KWYE nine)

U.S. Brand NamesQualaquin™

Canadian Brand NamesApo-Quinine®; Novo-Quinine; Quinine-Odan™

Pharmacologic CategoryAntimalarial Agent

Use: Labeled IndicationsIn conjunction with other antimalarial agents, treatment of uncomplicated chloroquine-resistant *P. falciparum* malaria

Use: Unlabeled/InvestigationalTreatment of *Babesia microti* infection in conjunction with clindamycin

Note: Prevention/treatment of nocturnal leg cramps (unapproved) removed following FDA-issued warning regarding severe adverse events (eg, cardiac arrhythmias, thrombocytopenia, and severe hypersensitivity reactions) and potentially serious drug interactions associated with quinine; use not justified in this condition.

Dosing: Adults

Treatment of chloroquine-resistant malaria: 648 mg every 8 hours for 7 days with tetracycline, doxycycline, or clindamycin

> **Note:** Actual duration of treatment for malaria may be dependent upon the geographic region or pathogen.

Babesiosis (unlabeled use): 650 mg every 8 hours for 7 days with clindamycin

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Treatment of chloroquine-resistant malaria (CDC guidelines): 30 mg/kg/day in divided doses every 8 hours for 3-7 days with tetracycline, doxycycline, or clindamycin (consider risk versus benefit of using tetracycline or doxycycline in children <8 years of age).

> **Note:** Actual duration of treatment for malaria may be dependent upon the geographic region or pathogen.

Babesiosis (unlabeled use): 25 mg/kg/day divided every 8 hours for 7 days with clindamycin.

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer every 8-12 hours

Cl_{cr} <10 mL/minute: Administer every 24 hours

Severe chronic renal failure not on dialysis: Initial dose: 648 mg followed by 324 mg every 12 hours

Dialysis: Administer dose after dialysis

Not removed by hemo- or peritoneal dialysis; dose as for Cl_{cr} <10 mL/minute.

Continuous arteriovenous or hemodialysis: Dose as for Cl_{cr} 10-50 mL/minute.

Dosing: Hepatic Impairment

Child-Pugh Class B: No dosing adjustment required; monitor closely

Child-Pugh Class C: Data not available

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAvoid use of aluminum- or magnesium-containing antacids because of drug absorption problems. Swallow dose whole to avoid bitter taste. May be administered with food.

Dietary ConsiderationsTake with food to decrease incidence of gastric upset.

StorageStore at 25°C to 30°C (77°F to 86°F); do not refrigerate or freeze.

ContraindicationsHypersensitivity to quinine or any component of the formulation; hypersensitivity to mefloquine or quinidine (cross sensitivity reported); prolonged QT interval; myasthenia gravis; optic neuritis; G6PD deficiency; history of black water fever; thrombotic thrombocytopenia purpura, hemolytic uremic syndrome, thrombocytopenia

Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Severe hypersensitivity reactions (eg, Stevens-Johnson syndrome, anaphylactic shock) have occurred; discontinue following any signs of sensitivity. Other events, including thrombocytopenia and hemolytic uremic syndrome, may also be attributed to hypersensitivity reactions.
- Hypoglycemia: Use may cause significant hypoglycemia.

Disease-related concerns:

- Altered cardiac conduction: Use with caution in patients with atrial fibrillation or flutter. Use with caution in patients with clinical conditions which may prolong the QT interval or cause cardiac arrhythmias; use contraindicated in patients with QT prolongation.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.
- QT prolonging agents: Use caution with medications which may prolong the QT interval or cause cardiac arrhythmias.

Other warnings/precautions:

- Nocturnal leg cramps: Because of the potential for severe and/or life-threatening side effects (eg, cardiac arrhythmias, thrombocytopenia, and severe hypersensitivity reactions) and serious drug interactions, as well as the absence of clinical effectiveness, quinine is no longer recommended for the treatment of nocturnal leg cramps. In addition, an FDA warning issued (December 2006) stated that due to these potential serious events, the risks associated with quinine use do not justify its use in the unapproved/unlabeled prevention and treatment of leg cramps.

Geriatric ConsiderationsQuinine's efficacy as a treatment for nocturnal leg cramps is not well supported in the medical and pharmacy literature. The FDA's decision to remove all quinine products (except one that is indicated for the treatment of malaria) indicates that quinine's benefits for nocturnal leg cramps do not out weigh its risks.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects have been reported in some animal studies. Quinine crosses the human placenta. Cord plasma to maternal plasma quinine ratios have been reported as 0.18-0.46 and should not be considered therapeutic to the infant. Teratogenic effects, optic nerve hypoplasia, and deafness have been reported in the infant following maternal use of very high doses; however, therapeutic doses used for malaria are generally considered safe. Quinine may also cause significant hypoglycemia when used during pregnancy. Malaria infection in pregnant women may be more severe than in nonpregnant women. The CDC recommends the use of quinine sulfate for the treatment of chloroquine-resistant *P. falciparum* malaria during pregnancy. Pregnant women should be advised not to travel to areas of *P. falciparum* resistance to chloroquine.

LactationEnters breast milk/use caution (AAP rate "compatible")

Breast-Feeding ConsiderationsBased on limited data, it is estimated that nursing infants would receive <0.4% of the maternal dose from breast-feeding.

Adverse Reactions

Frequency not defined.

Cardiovascular: Atrial fibrillation, atrioventricular block, bradycardia, cardiac arrest, chest pain, hypotension, irregular rhythm, nodal escape beats, palpitation, postural hypotension, QT prolongation, syncope, tachycardia, torsade de pointes, unifocal premature ventricular contractions, U waves, vasodilation, ventricular fibrillation, ventricular tachycardia

Central nervous system: Aphasia, ataxia, chills, coma, confusion, disorientation, dizziness, dystonic reaction, fever, flushing, headache, mental status altered, restlessness, seizure, suicide, vertigo

Dermatologic: Acral necrosis, allergic contact dermatitis, bullous dermatitis, bruising, cutaneous rash (urticaria, papular, scarlatinal), cutaneous vasculitis, diaphoresis, exfoliative dermatitis, erythema multiforme, petechiae, photosensitivity, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis

Endocrine & metabolic: Hypoglycemia

Gastrointestinal: Abdominal pain, anorexia, diarrhea, esophagitis, gastric irritation, nausea, vomiting

Hematologic: Agranulocytosis, aplastic anemia, coagulopathy, disseminated intravascular coagulation, hemolytic anemia, hemolytic uremic syndrome, hemorrhage, hypoprothrombinemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, thrombotic thrombocytopenic purpura

Hepatic: Granulomatous hepatitis, hepatitis, jaundice, liver function test abnormalities

Neuromuscular & skeletal: Myalgia, tremor, weakness

Ocular: Blindness, blurred vision (with or without scotomata), color vision disturbance, diminished visual fields, diplopia, night blindness, optic neuritis, photophobia, pupillary dilation, vision loss (sudden)

Otic: Deafness, hearing impaired, tinnitus

Respiratory: Asthma, dyspnea, pulmonary edema

Renal: Acute interstitial nephritis, hemoglobinuria, renal failure, renal impairment

Miscellaneous: Black water fever, hypersensitivity syndrome, lupus anticoagulant, lupus-like syndrome

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2C19 (minor), 3A4 (major); **Inhibits** CYP2C8 (moderate), 2C9 (moderate), 2D6 (moderate), 3A4 (weak)

Drug Interactions

Antihypertensives: Herbs (Hypotensive Properties) may enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): Antimalarial Agents may increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Cardiac Glycosides: QuiNINE may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the adverse/toxic effect of other Herbs (Hypotensive Properties). Excessive blood pressure lowering may manifest. *Risk C: Monitor therapy*

Mefloquine: QuiNINE may enhance the adverse/toxic effect of Mefloquine. Specifically, the risk for QTc-prolongation and the risk for convulsions may be increased. Mefloquine may increase the serum concentration of QuiNINE. Management: Avoid concurrent use, and delay administration of mefloquine until at least 12 hours after the last dose of quinine when possible. *Risk X: Avoid combination*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease quinine levels. Black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, and shepherd's purse may cause excessive decreases in blood pressure.

Test InteractionsPositive Coombs' [direct]; false elevation of urinary steroids (when assayed by Zimmerman method) and catecholamines

Monitoring ParametersMonitor CBC with platelet count, liver function tests, blood glucose, ophthalmologic examination

Reference RangeToxic: >10 mcg/mL

Nursing: Physical Assessment/MonitoringAssess allergy history prior to beginning therapy. Use caution in presence of cardiac arrhythmias (quinine has quinidine-like activity) and myasthenia gravis. Assess potential for interactions with other pharmacological agents patient may be taking (eg, increased or decreased level/effects and toxicity [digoxin, beta-blockers, warfarin, oxycodone, lidocaine, etc]). Evaluate therapeutic effectiveness (according to purpose for therapy) and adverse reactions (monitor for cinchonism with larger doses or long-term therapy). Teach patient appropriate use, possible side effects/interventions, and adverse symptoms to report.

Monitoring: Lab TestsMonitor CBC with platelet count, liver function tests, blood glucose, ophthalmologic examination

Patient EducationDo not take any new medication during therapy unless approved by prescriber (avoid use of any aluminum-containing antacids). Take on schedule as directed, with full 8 oz of water with or without food. Do not increase dose without consulting prescriber; overdose can cause severe systemic effects. You will need to return for follow-up blood tests. May cause severe headache (consult prescriber for approved analgesic); nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report any vision changes (blurring, night-blindness, double vision, etc); ringing in ears; or other persistent side effects. Seek emergency help for chest pain, respiratory difficulty, or seizures. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule, as sulfate: 325 mg [DSC]

Qualaquin™: 324 mg

Tablet, as sulfate: 260 mg [DSC]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Qualaquin)

324 mg (30): $143.29

Mechanism of ActionDepresses oxygen uptake and carbohydrate metabolism; intercalates into DNA, disrupting the parasite's replication and transcription; cardiovascular effects similar to quinidine

Pharmacodynamics/Kinetics

Absorption: Readily, mainly from upper small intestine

Distribution: 2.5-7.1 L/kg; varies with severity of infection

Intraerythrocytic levels are ~30% to 50% of the plasma concentration; distributes poorly to the CSF (~2% to 7% of plasma concentration)

Protein binding: 69% to 92% in healthy subjects; 78% to 95% with malaria

Metabolism: Primarily hepatic via CYP450 enzymes, including CYP3A4 and 2C19; forms metabolites; major metabolite, 3-hydroxyquinine, is less active than parent

Bioavailability: 76% to 88% in healthy subjects; increased with malaria

Half-life elimination:

Children: ~3 hours in healthy subjects; ~12 hours with malaria

Healthy adults: 10-13 hours

Time to peak, serum:

Children: 2 hours in healthy subjects; 4 hours with malaria

Adults: 1-3 hours in healthy subjects; 1.2-11 hours with malaria

Excretion: Urine (<20% as unchanged drug)

Related Information

- Malaria Treatment

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may decrease serum concentrations of quinine; CYP2D6 inhibitor; may interact with TCAs or beta-blockers; monitor

Cardiovascular ConsiderationsIt is very important that the physician's orders be clear when prescribing quinine so as to avoid possible confusion and cardiac toxicity of inadvertent quinidine therapy.

Index TermsQuinine Sulfate

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International Brand NamesAethylcarbonis Chinin (ID); Circonyl (AR); Genin (TH); Kinin (DK, SE); Q200 (HK, NZ); Q300 (HK, NZ); Quinate (AU); Quinbisu (AU); Quinimax (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Quininga (IN); Quinsul (AU)

Quinupristin and Dalfopristin

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Pronunciation(kwi NYOO pris tin & dal FOE pris tin)

U.S. Brand NamesSynercid®

Canadian Brand NamesSynercid®

Pharmacologic CategoryAntibiotic, Streptogramin

Use: Labeled IndicationsTreatment of serious or life-threatening infections associated with vancomycin-resistant *Enterococcus faecium* bacteremia; treatment of complicated skin and skin structure infections caused by methcillin-susceptible *Staphylococcus aureus* or *Streptococcus pyogenes*

Has been studied in the treatment of a variety of infections caused by *Enterococcus faecium* (not *E. fecalis*) including vancomycin-resistant strains. May also be effective in the treatment of serious infections caused by *Staphylococcus* species including those resistant to methicillin.

Dosing: Adults

Vancomycin-resistant*Enterococcus faecium*: I.V.: 7.5 mg/kg every 8 hours

Complicated skin and skin structure infection: I.V.: 7.5 mg/kg every 12 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricLimited information: Dosages similar to adult dosing have been used in the treatment of complicated skin/soft tissue infections and infections caused by vancomycin-resistant *Enterococcus faecium*

CNS shunt infection due to vancomycin-resistant*Enterococcus faecium*: I.V.: 7.5 mg/kg/dose every 8 hours. Concurrent intrathecal doses of 1-2 mg/day have been administered for up to 68 days.

Dosing: Renal ImpairmentNo adjustment is necessary in renal failure, hemodialysis, or peritoneal dialysis.

Dosing: Hepatic ImpairmentPharmacokinetic data suggest dosage adjustment may be necessary; however, specific recommendations have not been proposed.

Administration: I.V.Line should be flushed with 5% dextrose in water prior to and following administration. Infusion should be completed over 60 minutes (toxicity may be increased with shorter infusion). If severe venous irritation occurs following peripheral administration of quinupristin/dalfopristin diluted in 250 mL 5% dextrose in water, consideration should be given to increasing the infusion volume to 500 mL or 750 mL, changing the infusion site, or infusing by a peripherally-inserted central catheter (PICC) or a central venous catheter.

StorageStore unopened vials under refrigeration (2°C to 8°C/36°F to 46°F).

ReconstitutionReconstitute single dose vial with 5 mL of 5% dextrose in water or sterile water for injection. Swirl gentle to dissolve; do not shake (to limit foam formation). The reconstituted solution should be diluted within 30 minutes. Stability of the diluted solution prior to the infusion is established as 5 hours at room temperature or 54 hours if refrigerated at 2°C to 8°C. Reconstituted solution should be added to at least 250 mL of 5% dextrose in water for peripheral administration (increase to 500 mL or 750 mL if necessary to limit venous irritation). An infusion volume of 100 mL may be used for central line infusions. Do not freeze solution.

Compatibility Stable in D_5W. **Incompatible** with saline.

ContraindicationsHypersensitivity to quinupristin, dalfopristin, pristinamycin, or virginiamycin, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Arthralgias/myalgias: May cause arthralgias and/or myalgias with use; reduction of dosing frequency may improve.
- Hyperbilirubinemia: May cause hyperbilirubinemia (>5 times ULN) possibly through competition for excretory pathways.
- Phlebitis: May cause pain and phlebitis when infused through a peripheral line (not relieved by hydrocortisone or diphenhydramine).
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Concurrent drug therapy issues:

- Cisapride: Concurrent therapy with cisapride (which may prolong QT_c interval and lead to arrhythmias) should be avoided.
- Drugs metabolized by CYP3A4: May inhibit the metabolism of many drugs metabolized by CYP3A4.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <16 years of age.

Geriatric ConsiderationsNo pharmacokinetic changes in the elderly in one study. No dose adjustment necessary.

Pregnancy Risk FactorB

Pregnancy ConsiderationsBecause adverse effects were not observed in animal reproduction studies, quinupristin/dalfopristin is classified pregnancy category B. There are no adequate and well-controlled studies of quinupristin/dalfopristin in pregnant women.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if quinupristin/dalfopristin is excreted in human milk. The manufacturer recommends caution if administering quinupristin/dalfopristin to a nursing woman. The increased molecular weight of quinupristin/dalfopristin may minimize excretion into human milk. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Quinupristin and Dalfopristin in Pregnancy & Lactation

Adverse Reactions

>10%:

Hepatic: Hyperbilirubinemia (3% to 35%)

Local: Inflammation at infusion site (38% to 42%), local pain (40% to 44%), local edema (17% to 18%), infusion site reaction (12% to 13%)

Neuromuscular & skeletal: Arthralgia (up to 47%), myalgia (up to 47%)

1% to 10%:

Central nervous system: Pain (2% to 3%), headache (2%)

Dermatologic: Pruritus (2%), rash (3%)

Endocrine & metabolic: Hyperglycemia (1%)

Gastrointestinal: Nausea (3% to 5%), diarrhea (3%), vomiting (3% to 4%)

Hematologic: Anemia (3%)

Hepatic: GGT increased (2%), LDH increased (3%)

Local: Thrombophlebitis (2%)

Neuromuscular & skeletal: CPK increased (2%)

<1%: Abdominal pain, allergic reaction, anaphylactoid reaction, anxiety, apnea, arrhythmia, bone pain, BUN increased, cardiac arrest, chest pain, coagulation disorder, confusion, constipation, creatinine increased, diaphoresis, dizziness, dysautonomia, dyspepsia, dyspnea, encephalopathy, fever, gastrointestinal hemorrhage, gout, hematuria, hemolysis, hemolytic anemia, hepatitis, hyperkalemia, hypertonia, hypoglycemia, hyponatremia, hypotension, hypoventilation, hypovolemia, infection, insomnia, leg cramps, maculopapular rash, mesenteric artery occlusion, myasthenia, neck rigidity, neuropathy, oral candidiasis, palpitation, pancreatitis, pancytopenia, paraplegia, paresthesia, pericarditis, peripheral edema, phlebitis, pleural effusion, pseudomembranous colitis, respiratory distress, seizure, shock, skin ulcer, stomatitis, syncope, thrombocytopenia, tremor, transaminases increased, urticaria, vaginitis, vasodilation

Metabolism/Transport EffectsQuinupristin: **Inhibits** CYP3A4 (weak)

Drug Interactions

Calcium Channel Blockers: Quinupristin may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk C: Monitor therapy*

CycloSPORINE: Quinupristin may decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringAssess allergy history prior to starting treatment. Use caution in presence of hepatic or renal impairment. Assess effectiveness and interactions of other pharmacological agents (eg, cisapride). See Administration prior to starting infusion for exact infusion protocols. Infusion site must be closely monitored (may cause venous irritation). Assess effectiveness (reduction of infection) and adverse reactions (eg, arthralgia, headache, rash, hyperglycemia, opportunistic infection [fever, chills, sore throat, burning urination, fatigue], pseudomembranous colitis, hyperbilirubinemia, dyspnea, ataxia). Teach patient possible side effects/interventions, and adverse symptoms to report.

Monitoring: Lab TestsCulture and sensitivity

Patient EducationThis drug can only be administered by intravenous infusion. Report immediately any pain, irritation, redness, burning, or swelling at infusion site. You may experience other side effects. Report headache; rash; nausea; vomiting; diarrhea; pain; heat or swelling in muscle areas, especially in lower extremities; respiratory difficulty, tremors; or difficulty speaking. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Synercid®: 500 mg: Quinupristin 150 mg and dalfopristin 350 mg

Generic AvailableNo

Mechanism of ActionQuinupristin/dalfopristin inhibits bacterial protein synthesis by binding to different sites on the 50S bacterial ribosomal subunit thereby inhibiting protein synthesis

Pharmacodynamics/Kinetics

Distribution: Quinupristin: 0.45 L/kg; Dalfopristin: 0.24 L/kg

Protein binding: Moderate

Metabolism: To active metabolites via nonenzymatic reactions

Half-life elimination: Quinupristin: 0.85 hour; Dalfopristin: 0.7 hour (mean elimination half-lives, including metabolites: 3 and 1 hours, respectively)

Excretion: Feces (75% to 77% as unchanged drug and metabolites); urine (15% to 19%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay rarely cause anxiety, confusion, or insomnia
Mental Health: Effects on Psychiatric TreatmentMay rarely produce pancytopenia; caution with clozapine and carbamazepine
Index TermsPristinamycin; RP-59500
References

Bryson HM and Spencer CM, “Quinupristin/Dalfopristin,” *Drugs*, 1996, 52(3):406-15. [PubMed 8875130]

Chant C and Rybak MH, “Quinupristin/Dalfopristin (RP 59500): A New Streptogramin Antibiotic,” *Ann Pharmacother*, 1995, 29(10):1022-7. [PubMed 8845540]

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International Brand NamesPyostacine (BE, FR, LU, PL); Synercid (AU, IT, KP)

R-CVP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen UseLymphoma, non-Hodgkin's

Index TermsCVP-R; Rituximab-CVP; Rituximab-Cyclophosphamide-Vincristine-Prednisone

Regimen

Rituximab: I.V.: 375 mg/m^2 day 1

[total dose/cycle = 375 mg/m^2]

Cyclophosphamide: I.V.: 750 mg/m^2 day 1

[total dose/cycle = 750 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 day 1

[total dose/cycle = 1.4 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 5

[total dose/cycle = 200 mg/m^2]

Repeat cycle every 21 days

References

Marcus R, Imrie K, Belch A, et al, âCVP Chemotherapy Plus Rituximab Compared With CVP as First-Line Treatment for Advanced Follicular Lymphoma,â *Blood*, 2005, 105(4):1417-23.[PubMed 15494430]

Rabeprazole

Lexi-Drugs Online

English English

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Special Alerts

Clopidogrel (Plavix®) and Proton Pump Inhibitors (PPIs): Ongoing Safety Review - January 2009

The U.S. Food and Drug Administration (FDA) is communicating important information regarding an ongoing safety review of clopidogrel and its effectiveness when used with proton pump inhibitors (PPIs).

Clopidogrel is a prodrug requiring hepatic conversion via CYP3A4 and/or CYP2C19 to its active metabolite. Impaired clopidogrel conversion to its active metabolite may be due to either CYP450 polymorphisms or drug-drug interactions resulting in suboptimal antiplatelet activity.

A PPI is often prescribed with the combination of aspirin and clopidogrel to prevent gastrointestinal bleeding. A number of PPIs are available and include esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. Several studies have reported greater clinical event rates (eg, myocardial infarction, death) or greater platelet reactivity associated with concurrent use of clopidogrel and a PPI (Ho, 2008; Pezella, 2008; Gilard, 2006). Similarly, a prospective, randomized, double-blind trial demonstrated a reduction in antiplatelet activity when omeprazole and clopidogrel are used concurrently (Gilard, 2008). Another controlled trial with the PPI lansoprazole also found evidence of a possible interaction resulting in less antiplatelet activity (Small, 2008). This interaction is thought to result from competitive inhibition of the CYP2C19-mediated activation of clopidogrel by omeprazole and other PPIs, which are all metabolized to at least some degree by CYP2C19. In contrast, one study with esomeprazole and pantoprazole did not find evidence of reduced antiplatelet activity when administered with clopidogrel (Siller-Matula, 2009), highlighting the need for additional studies to determine the degree to which individual PPIs may differ in their potential for interacting with clopidogrel.

The manufacturer of Plavix® has agreed to conduct further studies to better understand the effect of other drugs (including PPIs) and genetic factors on the effectiveness of clopidogrel. The FDA is recommending that healthcare providers continue to prescribe clopidogrel while reevaluating the need for prescription or over-the-counter (OTC) PPIs in patients taking clopidogrel. Patients should continue taking clopidogrel as directed. If taking a PPI with clopidogrel, patients should consult with their healthcare provider.

For more information, healthcare professionals may refer to the following FDA website:
http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm

References:

Ho PM, Maddox TM, Wang L, et al, “Proton Pump Inhibitors May Attenuate the Benefits of Clopidogrel Among ACS Patients: Using Registry Data to Address Medication Effectiveness,” United States Department of Veterans Affairs, 2008 QUERI National Meeting Abstract. Available at http://www.hsrd.research.va.gov/meetings/QUERI08/display_abstract.cfm?RecordID=118; accessed October 30, 2008).

Pezalla E, Day D, and Pulliadath I, “Initial Assessment of Clinical Impact of a Drug Interaction Between Clopidogrel and Proton Pump Inhibitors,” *J Am Coll Cardiol*, 2008, 52(12): 1038-9.

Gilard M, Arnaud B, Le Gal G, et al, “Influence of Omeprazol on the Antiplatelet Action of Clopidogrel Associated to Aspirin,” *J Thromb Haemost*, 2006, 4(11):2508-9.

Gilard M, Arnaud B, Cornily JC, et al, “Influence of Omeprazole on the Antiplatelet Action of Clopidogrel Associated With Aspirin: The Randomized, Double-Blind Ocla (Omeprazole Clopidogrel Aspirin) Study,” *J Am Coll Cardiol*, 2008, 51(3):256-60.

Siller-Matula JM, Spiel AO, Lang IM, et al, “Effects of Pantoprazole and Esomeprazole on Platelet Inhibition by Clopidogrel,” *Am Heart J*, 2009, 157(1): 148.e1-5.

Small DS, Farid NA, Payne CD, et al, “Effects of the Proton Pump Inhibitor Lansoprazole on the Pharmacokinetics and Pharmacodynamics of Prasugrel and Clopidogrel,” *J Clin Pharmacol*, 2008, 48(4):475-84.

Medication Safety Issues

Sound-alike/look-alike issues:

AcipHex® may be confused with Acephen®, Accupril®, Aricept®, pHisoHex®

Rabeprazole may be confused with aripiprazole,donepezil, lansoprazole, omeprazole, raloxifene

Pronunciation(ra BEP ra zole)

U.S. Brand NamesAcipHex®

Canadian Brand NamesAcipHex®; Novo-Rabeprazole EC; Pariet®; PMS-Rabeprazole; Ran-Rabeprazole; Sandoz-Rabeprazole

Pharmacologic CategoryProton Pump Inhibitor; Substituted Benzimidazole

Use: Labeled IndicationsShort-term (4-8 weeks) treatment and maintenance of erosive or ulcerative gastroesophageal reflux disease (GERD); symptomatic GERD; short-term (up to 4 weeks) treatment of duodenal ulcers; long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome; *H. pylori* eradication (in combination with amoxicillin and clarithromycin)

Canadian labeling: Additional uses (not in U.S. labeling): Treatment of nonerosive reflux disease (NERD); treatment of gastric ulcers

Use: Unlabeled/InvestigationalMaintenance of duodenal ulcer

Dosing: Adults

GERD, erosive/ulcerative: Oral: Treatment: 20 mg once daily for 4-8 weeks; if inadequate response, may repeat up to an additional 8 weeks; maintenance: 20 mg once daily

Canadian labeling: Oral: 20 mg once daily for 4 weeks; if inadequate response, may repeat for an additional 4 weeks (lack of symptom control after 4 weeks warrants further evaluation); maintenance: 10 mg once daily (maximum: 20 mg once daily)

GERD, symptomatic: Oral: Treatment: 20 mg once daily for 4 weeks; if inadequate response, may repeat for an additional 4 weeks

Canadian labeling: 10 mg once daily (maximum: 20 mg once daily) for 4 weeks; lack of symptom control after 4 weeks warrants further evaluation

Duodenal ulcer: Oral: 20 mg/day before breakfast for 4 weeks; additional therapy may be required for some patients

Gastric ulcers (*Canadian labeling*): Oral: 20 mg once daily up to 6 weeks; additional therapy may be required for some patients

***H. pylori*eradication:** Oral: 20 mg twice daily for 7 days; to be administered with amoxicillin 1000 mg and clarithromycin 500 mg, also given twice daily for 7 days.

Hypersecretory conditions: Oral: 60 mg once daily; dose may need to be adjusted as necessary. Doses as high as 100 mg once daily and 60 mg twice daily have been used, and continued as long as necessary (up to 1 year in some patients).

NERD (*Canadian labeling*): Oral: Treatment: 10 mg (maximum: 20 mg once daily) for 4 weeks; lack of symptom control after 4 weeks warrants further evaluation

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Short-term treatment of GERD:***U.S. labeling:* Children ≥12 years: 20 mg once daily for ≤8 weeks

Dosing: Renal ImpairmentNo dosage adjustment required.

Dosing: Hepatic Impairment

Mild to moderate: Elimination decreased; no dosage adjustment required.

Severe: Use caution.

Administration: OralMay be administered with or without food; best if taken before breakfast. Do not crush, split, or chew tablet. May be administered with an antacid.

Dietary ConsiderationsMay be taken with or without food; best if taken before breakfast.

StorageStore at 25°C (77°F). Protect from moisture.

ContraindicationsHypersensitivity to rabeprazole, substituted benzimidazoles (ie, esomeprazole, lansoprazole, omeprazole, pantoprazole), or any component of the formulation

Allergy Considerations

- Proton Pump Inhibitor, Benzimidazole Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Atrophic gastritis: Long-term omeprazole therapy has caused atrophic gastritis (by biopsy); this may also occur with rabeprazole.
- Carcinoma: No reports of enterochromaffin-like (ECL) cell carcinoids, dysplasia, or neoplasia has occurred.

Disease-related concerns:

- Gastric malignancy: Relief of symptoms does not preclude the presence of a gastric malignancy.
- Gastrointestinal infection (eg, *Salmonella, Campylobacter*): Use of proton pump inhibitors may increase risk of these infections.
- Hepatic impairment: Use caution in patients with severe hepatic impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Geriatric ConsiderationsNo difference in efficacy or safety was noted in elderly subjects as compared to younger subjects. No dosage adjustment is necessary in the elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsNot shown to be teratogenic in animal studies, however, adequate and well-controlled studies have not been done in humans; use during pregnancy only if clearly needed

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

1% to 10%:

Central nervous system: Pain (3%), headache (2% to 5%)

Gastrointestinal: Diarrhea (3%), flatulence (3%), constipation (2%), nausea (2%)

Respiratory: Pharyngitis (3%)

Miscellaneous: Infection (2%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Abdomen enlarged, abdominal pain, abnormal stools, abnormal vision, agitation, agranulocytosis, albuminuria, allergic reaction, alopecia, amblyopia, anaphylaxis, anemia, angina pectoris, angioedema, anorexia, apnea, arrhythmia, arthralgia, arthritis, ascites, asthma, bloody diarrhea, bone pain, bradycardia, breast enlargement, bullous and other drug eruptions of skin, bundle branch block, bursitis, cataract, cellulitis, cerebral hemorrhage, chest pain substernal, cholangitis, cholecystitis, cholelithiasis, colitis, coma, contact dermatitis, convulsions, corneal opacity, CPK increased, cystitis, deafness, delirium, depression, diaphoresis, diabetes mellitus, diplopia, disorientation, dizziness, duodenitis, dysmenorrhea, dyspepsia, dysphagia, dyspnea, dysuria, edema, electrocardiogram abnormal, embolus, epistaxis, erythema multiforme, esophageal stenosis, esophagitis, extrapyramidal syndrome, eye hemorrhage, facial edema, fever, fungal dermatitis, gastritis, gastroenteritis, gastrointestinal hemorrhage, gingivitis, glaucoma, glossitis, gout, gynecomastia, hematuria, hemolytic anemia, hepatic encephalopathy, hepatic cirrhosis, hepatic enzymes increased, hepatitis, hepatoma, hernia, hyperammonemia, hypercholesteremia, hyperglycemia, hyperkinesia, hyperlipemia, hypertension, hyper-/hypothyroidism, hypertonia, hypokalemia, hyponatremia, hypoxia, impotence, injection site hemorrhage/pain/reaction, insomnia, interstitial nephritis, interstitial pneumonia, jaundice, kidney calculus, leukocytosis, leukopenia, leukorrhea, liver fatty deposit, lymphadenopathy, malaise, melena, menorrhagia, metrorrhagia, MI, migraine, myalgia, neck rigidity, nervousness, neuralgia, neuropathy, neutropenia, orchitis, palpitation, pancreatitis, pancytopenia, paresthesia, peripheral edema, photosensitivity, polycystic kidney, polyuria, proctitis, pruritus, PSA increased, psoriasis, pulmonary embolus, QT_c prolongation, rash, rectal hemorrhage, retinal degeneration, rhabdomyolysis, salivary gland enlargement, sinus bradycardia, skin discoloration, somnolence, Stevens-Johnson syndrome, stomatitis, strabismus, sudden death, supraventricular tachycardia, syncope, tachycardia, taste abnormal, thrombocytopenia, thrombophlebitis, thrombosis, thirst (rare) tinnitus, toxic epidermal necrolysis, tremor, TSH increased, ulcerative colitis, urinary incontinence, urticaria, vasodilation, ventricular arrhythmias, vertigo, vomiting, weakness, weight gain/loss, xerostomia

Metabolism/Transport Effects **Substrate** (major) of CYP2C19, 3A4; **Inhibits** CYP2C8 (moderate), 2C19 (moderate), 2DC (weak), 3A4 (weak)
Drug Interactions

Atazanavir: Proton Pump Inhibitors may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Clopidogrel: Proton Pump Inhibitors may diminish the therapeutic effect of Clopidogrel. This appears to be due to reduced formation of the active clopidogrel metabolite. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: Proton Pump Inhibitors may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Proton Pump Inhibitors may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Erlotinib: Proton Pump Inhibitors may decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Fluconazole: May increase the serum concentration of Proton Pump Inhibitors. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Indinavir: Proton Pump Inhibitors may decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Iron Salts: Proton Pump Inhibitors may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk C: Monitor therapy*

Itraconazole: Proton Pump Inhibitors may decrease the serum concentration of Itraconazole. *Risk D: Consider therapy modification*

Ketoconazole: Proton Pump Inhibitors may decrease the serum concentration of Ketoconazole. Ketoconazole may increase the serum concentration of Proton Pump Inhibitors. *Risk D: Consider therapy modification*

Mesalamine: Proton Pump Inhibitors may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids; proton pump inhibitors would be expected to interact in a similar manner. *Risk X: Avoid combination*

Methotrexate: Proton Pump Inhibitors may decrease the excretion of Methotrexate. Antirheumatic doses of methotrexate probably hold minimal risk. *Risk C: Monitor therapy*

Mycophenolate: Proton Pump Inhibitors may decrease the serum concentration of Mycophenolate. Specifically, concentrations of the active mycophenolic acid may be reduced. *Risk C: Monitor therapy*

Nelfinavir: Proton Pump Inhibitors may decrease serum concentrations of the active metabolite(s) of Nelfinavir. Proton Pump Inhibitors may decrease the serum concentration of Nelfinavir. *Risk X: Avoid combination*

Saquinavir: Proton Pump Inhibitors may increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

Tipranavir: May decrease the serum concentration of Proton Pump Inhibitors. These data are derived from studies with Ritonavir-boosted Tipranavir. *Risk C: Monitor therapy*

Voriconazole: Proton Pump Inhibitors may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause gastric mucosal irritation).

Food: High-fat meals may delay absorption, but C_{max} and AUC are not altered.

Herb/Nutraceutical: St John's wort may increase the metabolism and thus decrease the levels/effects of rabeprazole.

Nursing: Physical Assessment/MonitoringAssess other medications, especially those dependent on cytochrome P450 metabolism (eg, digoxin) and those requiring acid environment for absorption (eg, ketoconazole, ampicillin). Monitor therapeutic effectiveness (reduction in symptoms) and adverse reactions and toxicity. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse reactions to report.

Patient EducationTake as directed. Swallow whole, do not crush, split, or chew. Follow recommended diet and activity instructions. Avoid alcohol. You may experience headache (use of mild analgesic may help) or other side effects. Report these to prescriber if they persist. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet, delayed release, enteric coated, as sodium:

AcipHex®: 20 mg

Pariet® [CAN]: 10 mg, 20 mg

Generic AvailableNo

ManufacturerEisai Inc

Pricing: U.S. (www.drugstore.com)

Tablet, EC (Aciphex)

20 mg (30): $159.99

Mechanism of ActionPotent proton pump inhibitor; suppresses gastric acid secretion by inhibiting the parietal cell H+/K+ ATP pump

Pharmacodynamics/Kinetics

Onset of action: Within 1 hour

Duration: 24 hours

Absorption: Oral: Well absorbed within 1 hour

Protein binding, serum: ~96%

Metabolism: Hepatic via CYP3A and 2C19 to inactive metabolites

Bioavailability: Oral: ~52%

Half-life elimination (dose dependent): 1-2 hours

Time to peak, plasma: 2-5 hours

Excretion: Urine (90% primarily as thioether carboxylic acid metabolites); remainder in feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia, anxiety, dizziness, depression, nervousness, somnolence, vertigo, convulsions, abnormal dreams; may rarely cause agitation, amnesia, confusion, extrapyramidal syndrome

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPariprazole

References

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Wolfe MM and Sachs G, "Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome," *Gastroenterology*, 2000,118(2 Suppl 1):9-31.

International Brand NamesAciprazol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Gastrodine (CN); Pariet (AE, AR, AT, AU, BE, BG, BH, BO, BR, CH, CL, CN, CO, CR, CY, DE, DK, DO, EC, EG, ES, FI, FR, GB, GR, GT, HN, ID, IE, IL, IQ, IR, IT, JO, JP, KP, KW, LB, LY, MX, MY, NI, NL, OM, PA, PE, PH, PL, PR, PT, PY, QA, SA, SE, SG, SV, SY, TH, TW, UY, VE, YE, ZA); Rabec (AR); Rabecid (PK); Rabeloc (IN)

Rabies Immune Globulin (Human)

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Pronunciation(RAY beez i MYUN GLOB yoo lin, HYU man)
U.S. Brand NamesHyperRAB™ S/D; Imogam® Rabies-HT
Canadian Brand NamesHyperRAB™ S/D; Imogam® Rabies Pasteurized
Pharmacologic CategoryImmune Globulin
Use: Labeled IndicationsPart of postexposure prophylaxis of persons with rabies exposure who lack a history of pre-exposure or postexposure prophylaxis with rabies vaccine or a recently documented neutralizing antibody response to previous rabies vaccination
Dosing: Adults**Postexposure prophylaxis:** Local wound infiltration: 20 units/kg in a single dose, RIG should always be administered as part of rabies vaccine regimen. If anatomically feasible, the full rabies immune globulin dose should be infiltrated around and into the wound(s); remaining volume should be administered I.M. at a site distant from the vaccine administration site. If rabies vaccine was initiated without rabies immune globulin, rabies immune globulin may be administered through the seventh day after the administration of the first dose of the vaccine. Administration of RIG is not recommended after the seventh day post vaccine since an antibody response to the vaccine is expected during this time period.

Note: Persons known to have an adequate titer or who have previously received postexposure prophylaxis with rabies vaccine should not receive RIG.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Administration: I.M.Postexposure wound infiltration: If anatomically feasible, the full rabies immune globulin dose should be infiltrated around and into the wound(s); remaining volume should be administered I.M. in the deltoid muscle of the upper arm or lateral thigh muscle. The gluteal area should be avoided to reduce the risk of sciatic nerve damage. Do not administer rabies vaccine in the same syringe or at the same administration site as RIG.
Administration: I.V.Do not administer I.V.
StorageStore between 2°C to 8°C (36°F to 46°F); do not freeze. Discard product exposed to freezing.
ContraindicationsThere are no contraindications listed within the FDA-approved manufacturer's labeling.
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1:1000) should be available. Use with caution in patients with isolated immunoglobulin A deficiency or a history of systemic hypersensitivity to human immunoglobulins.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with thrombocytopenia or coagulation disorders; I.M. injections may be contraindicated.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

Other warnings/precautions:

- Administration: Not for intravenous administration.

Geriatric ConsiderationsNo special considerations are needed for initiating therapy. No specific data relevant to the elderly to date.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not be conducted. Pregnancy is not a contraindication to postexposure prophylaxis.
Adverse ReactionsFrequency not defined.

Central nervous system: Fever (mild), headache, malaise

Dermatologic: Angioedema, rash, urticaria

Local: Soreness at injection site, tenderness, stiffness

Renal: Nephrotic syndrome

Miscellaneous: Anaphylaxis

Drug Interactions

Vaccines (Live): Immune Globulins may diminish the therapeutic effect of Vaccines (Live). **Exceptions:** Influenza Virus Vaccine; Yellow Fever

Vaccine. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

HyperRAB™ S/D: 150 int. units/mL (2 mL, 10 mL) [solvent/detergent treated]

Imogam® Rabies-HT: 150 int. units/mL (2 mL, 10 mL) [heat treated]

Generic AvailableNo

Mechanism of ActionRabies immune globulin is a solution of globulins dried from the plasma or serum of selected adult human donors who have been immunized with rabies vaccine and have developed high titers of rabies antibody. It generally contains 10% to 18% of protein of which not less than 80% is monomeric immunoglobulin G.

Related Information

- Immunization Recommendations

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsRIG

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International Brand NamesBayer Bayrab Rabies Immune Globulin (PH); Bayrab (PK); Hyperrab S D (IL); Imogam (AU); Imogam Rabia (AR, PY); Imogam Rabies (BF, BG, BJ, CI, EE, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, PH, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); PARS (IN); Rabigam (ZA); Rabuman Berna (PH, TH)

Rabies Vaccine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(RAY beez vak SEEN)
U.S. Brand NamesImovax® Rabies; RabAvert®
Canadian Brand NamesImovax® Rabies; RabAvert®
Pharmacologic CategoryVaccine, Inactivated (Viral)
Use: Labeled IndicationsPre-exposure and postexposure vaccination against rabies

The Advisory Committee on Immunization Practices (ACIP) recommends a primary course of prophylactic immunization (pre-exposure vaccination) for the following:

- Persons with continuous risk of infection including rabies research laboratory and biologics production workers
- Persons with frequent risk of infection in areas where rabies is enzootic, including rabies diagnostic laboratory workers, cavers, veterinarians and their staff, animal control and wildlife workers; persons who frequently handle bats
- Persons with infrequent risk of infection, including veterinarians and animal control staff with terrestrial animals in areas where rabies infection is rare, veterinary students, travelers visiting areas where rabies is enzootic and immediate access to medical care and biologicals is limited

The ACIP recommends the use of postexposure vaccination for a particular person be assessed by the severity and likelihood versus the actual risk of acquiring rabies. Consideration should include the type of exposure, epidemiology of rabies in the area, species of the animal, circumstances of the incident, and the availability of the exposing animal for observation or rabies testing. Postexposure vaccination is used in both previously vaccinated and previously unvaccinated individuals.

Dosing: Adults

Pre-exposure vaccination: I.M.: 1 mL on days 0, 7, and 21 to 28.

Note: Prolonging the interval between doses does not interfere with immunity achieved after the concluding dose of the basic series.

Postexposure vaccination: All postexposure treatment should begin with immediate cleansing of the wound with soap and water

Persons not previously immunized as above: I.M.: 5 doses (1 mL each) on days 0, 3, 7, 14, 28. In addition, patients should receive rabies immune globulin with the first dose (day 0)

Persons who have previously received postexposure prophylaxis with rabies vaccine, received a recommended I.M. pre-exposure series of rabies vaccine or have a previously documented rabies antibody titer considered adequate: I.M.: Two doses (1 mL each) on days 0 and 3; do not administer rabies immune globulin

Booster (for persons with continuous or frequent risk of infection): I.M.: 1 mL based on antibody titers

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Administration: I.M.For I.M. administration only; this rabies vaccine product must not be administered intradermally; in adults and children, administer I.M. injections in the deltoid muscle, not the gluteal; for younger children, use the outer aspect of the thigh.

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

Administration with other vaccines:

Rabies vaccine with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Rabies vaccine with live vaccines: May be given simultaneously or at any interval between doses.

Vaccine administration with antibody-containing products: Rabies vaccine may be given simultaneously at different sites or at any interval between doses. Examples of antibody containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StoragePrior to reconstitution, store under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light.
ReconstitutionReconstitute with provided diluent; gently swirl to dissolve. Use immediately after reconstitution.

Imovax®: Suspension will appear pink to red

RabAvert®: Suspension will appear clear to slightly opaque

Contraindications

Pre-exposure prophylaxis: Hypersensitivity to rabies vaccine or any component of the formulation

Postexposure prophylaxis: There are no contraindications listed within the FDA-approved manufacturer's labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use. Once postexposure prophylaxis has begun, administration should generally not be interrupted or discontinued due to local or mild adverse events. Continuation of vaccination following severe systemic reactions should consider the persons risk of developing rabies. Report serious reactions to the State Health Department or the manufacturer/distributor.

- Immune complex-like reactions: An immune complex reaction is possible 2-21 days following booster doses of HDCV. Symptoms may include arthralgia, arthritis, angioedema, fever, generalized urticaria, malaise, nausea, and vomiting.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination.

Dosage form specific issues:

- Imovax® Rabies: Contains albumin and neomycin.

- RabAvert®: Contains amphotericin B, bovine gelatin, chicken protein, chlortetracycline, and neomycin.

Other warnings/precautions:

- Appropriate use: Rabies: Rabies vaccine should not be used in persons with a confirmed diagnosis of rabies; use after the onset of symptoms may be detrimental. Postexposure vaccination may begin regardless of the length of time from documented or likely exposure, as long as clinical signs of rabies are not present.

Geriatric ConsiderationsNo specific data for use in the elderly. Use as recommended in elderly patients for whom this vaccine would be indicated.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Pregnancy is not a contraindication to postexposure prophylaxis. Pre-exposure prophylaxis during pregnancy may also be considered if risk of rabies is great.

LactationExcretion in breast milk unknown

Breast-Feeding ConsiderationsBreast-feeding mothers may be vaccinated.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

>10%:

Central nervous system: Dizziness, headache, malaise

Gastrointestinal: Abdominal pain, nausea

Local: Erythema, itching, pain, swelling

Neuromuscular & skeletal: Myalgia

Miscellaneous: Lymphadenopathy

Uncommon, frequency not defined, postmarketing, and/or case reports:

Cardiovascular: Circulatory reactions, edema, palpitation

Central nervous system: Chills, fatigue, fever >38°C (100°F), Guillain-Barré syndrome, encephalitis, meningitis, multiple sclerosis, myelitis, neuroparalysis, vertigo

Dermatologic: Pruritus, urticaria, urticaria pigmentosa

Endocrine & metabolic: Hot flashes

Local: Limb swelling (extensive)

Neuromuscular & skeletal: Limb pain, monoarthritis, paralysis (transient), paresthesias (transient)

Otic: Retrobulbar neuritis, visual disturbances

Respiratory: Bronchospasm

Miscellaneous: Allergic reactions, anaphylaxis, hypersensitivity reactions, swollen lymph nodes

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Monitoring Parameters Monitor for syncope for ≥15 minutes following vaccination.

Antibody response to vaccination is not recommended for otherwise healthy persons who complete the pre-exposure or Postexposure regimen. Serologic testing to determine if the antibody titer is at an acceptable level is required for the following persons (booster vaccination recommended if titer is below the acceptable level):

Persons with continuous risk of infection: Serologic testing every 6 months

Persons with frequent risk of infection: Serologic testing every 2 years

Monitoring of antibody response to vaccination is not recommended for otherwise healthy persons who complete the pre-exposure or Postexposure regimen.

Reference Range Adequate adaptive immune response: antibody titers of 0.5 int. units/mL [WHO] or complete virus neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test (RFFIT) [ACIP]

Dosage Forms Injection, powder for reconstitution [preservative free]:

Imovax® Rabies: ≥2.5 int. units [HDCV; grown in human diploid cell culture; contains albumin (human), neomycin (may have trace amounts)]

RabAvert®: ≥2.5 int. units [contains albumin (human), amphotericin B (may have trace amounts), bovine gelatin, chicken egg protein, chlortetracycline (may have trace amounts), neomycin (may have trace amounts); PCEC; grown in chicken fibroblast culture]

Generic Available No

Pricing: U.S. (www.drugstore.com)

Suspension (reconstituted) (RabAvert)

(1): $250.99

Mechanism of Action Rabies vaccine is an inactivated virus vaccine which promotes immunity by inducing an active immune response. The production of specific antibodies requires about 7-10 days to develop. Rabies immune globulin or antirabies serum, equine (ARS) is given in conjunction with rabies vaccine to provide immune protection until an antibody response can occur.

Pharmacodynamics/Kinetics

Onset of action: I.M.: Rabies antibody: ~7-10 days

Peak effect: ~30-60 days

Duration: ≥1 year

Related Information

- Immunization Recommendations

Pharmacotherapy Pearls Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness and malaise

Mental Health: Effects on Psychiatric Treatment None reported

Mental Health Comment May cause neuroparalytic reactions and encephalomyelitis

Index Terms HDCV; Human Diploid Cell Cultures Rabies Vaccine; PCEC; Purified Chick Embryo Cell

References

“A New Rabies Vaccine,” *Med Lett Drugs Ther*, 1998, 40(1029):64-5. [PubMed 9653425]

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Lang J and Plotkin SA, “Rabies Risk and Immunoprophylaxis in Children,” *Adv Pediatr Infect Dis*, 1997, 13:219-55. [PubMed 9544314]

Strady A, Lang J, Lienard M, et al, “Antibody Persistence Following Pre-exposure Regimens of Cell-Culture Rabies Vaccines: 10-Year Follow-up and Proposal for a New Booster Policy,” *J Infect Dis*, 1998, 177(5):1290-5.[PubMed 9593014]

International Brand Names Berirab P (PH); Imovax Rabbia (IT); Imovax Rabia (UY); Lyssavac N Berna (HK, MY, PH, TH); Rabies MIRV Vaccine (NZ); Rabies-Imovax (FI, NO, SE); Rabipur (AT, AU, BG, CZ, DE, FR, GB, HN, IE, IN, SE); Rasilvax (IT); Verorab (CL, MY)

Raloxifene

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English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Evista® may be confused with Avinza™

Pronunciation(ral OKS i feen)

U.S. Brand NamesEvista®

Canadian Brand NamesEvista®

Pharmacologic CategorySelective Estrogen Receptor Modulator (SERM)

Use: Labeled IndicationsPrevention and treatment of osteoporosis in postmenopausal women; risk reduction for invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women with high risk for invasive breast cancer

Dosing: Adults

Osteoporosis: Females: Oral: 60 mg/day

Invasive breast cancer risk reduction: Female: Oral: 60 mg/day for 5 years

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic ImpairmentChild-Pugh class A: Plasma concentrations were higher and correlated with total bilirubin. Safety and efficacy in hepatic insufficiency have not been established

Administration: OralMay be administered any time of the day without regard to meals.

Dietary ConsiderationsSupplemental calcium or vitamin D may be required if dietary intake is not adequate.

StorageStore between 15°C to 30°C (59°F to 86°F).

ContraindicationsHistory of or current venous thromboembolic disorders (including DVT, PE, and retinal vein thrombosis); pregnancy; breast-feeding

Warnings/Precautions

Boxed warnings:

- Cardiovascular disease: See “Disease-related concerns” below.
- Thromboembolic disease: See “Disease-related concerns” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: The risk of death due to stroke may be increased in women with coronary heart disease or in women at risk for coronary events;** use with caution in patients with cardiovascular disease. Do not use for the prevention of cardiovascular disease.
- Cervical/uterine carcinoma: Use with caution in patients with a history of cervical/uterine carcinoma.
- Hepatic impairment: Use with caution in patients with hepatic impairment; safety and efficacy have not been established.
- Lipid effects: Women with a history of elevated triglycerides in response to treatment with oral estrogens (or estrogen/progestin) may develop elevated triglycerides when treated with raloxifene; monitor.
- Renal impairment: Use with caution in patients with moderate-to-severe renal impairment; safety and efficacy have not been established.
- Thromboembolic disease: **[U.S. Boxed Warning]: May increase the risk for DVT or PE;** use with caution in patients at high risk for venous thromboembolism. Use contraindicated in patients with history of or current venous thromboembolic disorders. The risk for DVT and PE are higher in the first 4 months of treatment.
- Uterine bleeding: Use with caution in patients with unexplained uterine bleeding.

Concurrent drug therapy issues:

- Estrogens: Use with systemic estrogen therapy is not recommended; safety has not been established.

Special populations:

- Males: Safety and efficacy have not been established in men.

- Premenopausal women: Safety and efficacy have not been established in premenopausal women

Other warnings/precautions:

- Appropriate use: Not indicated for treatment of invasive breast cancer, to reduce the risk of recurrence of invasive breast cancer, or to reduce the risk of noninvasive breast cancer. The efficacy (for breast cancer risk reduction) in women with inherited BRCA1 and BRCA1 mutations has not been established.

- Prolonged immobilization: Discontinue at least 72 hours prior to and during prolonged immobilization (postoperative recovery or prolonged bedrest).

Geriatric ConsiderationsNo need to cycle with progesterone.

Pregnancy Risk FactorX

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenicity and fetal loss. There are no adequate and well-controlled studies in pregnant women. Raloxifene should not be used by pregnant women or by women planning to become pregnant in the immediate future.

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions**Note:** Raloxifene has been associated with increased risk of thromboembolism (DVT, PE) and superficial thrombophlebitis; risk is similar to reported risk of HRT

>10%:

Cardiovascular: Peripheral edema (3% to 14%)

Endocrine & metabolic: Hot flashes (8% to 29%)

Neuromuscular & skeletal: Arthralgia (11% to 16%), leg cramps/muscle spasm (6% to 12%)

Miscellaneous: Flu syndrome (14% to 15%), infection (11% to 15%)

1% to 10%:

Cardiovascular: Chest pain (3% to 4%), syncope (2%), varicose vein (2%), venous thromboembolism (1% to 2%)

Central nervous system: Headache (9%), depression (6%), insomnia (6%), vertigo (4%), fever (3% to 4%), migraine (2%), hypoesthesia (≤2%)

Dermatologic: Rash (6%)

Endocrine & metabolic: Breast pain (4%)

Gastrointestinal: Nausea (8% to 9%), weight gain (9%), abdominal pain (7%), diarrhea (7%), dyspepsia (6%), vomiting (3% to 5%), flatulence (2% to 3%), cholelithiasis (≤3%), gastroenteritis (≤3%)

Genitourinary: Vaginal bleeding (6%), cystitis (3% to 5%), urinary tract infection (4%), vaginitis (4%), leukorrhea (3%), urinary tract disorder (3%), uterine disorder (3%), vaginal hemorrhage (3%), endometrial disorder (≤3%)

Neuromuscular & skeletal: Myalgia (8%), arthritis (4%), tendon disorder (4%), neuralgia (≤2%)

Ocular: Conjunctivitis (2%)

Respiratory: Bronchitis (10%), rhinitis (10%), sinusitis (8% to 10%), cough (6% to 9%), pharyngitis (5% to 8%), pneumonia (3%), laryngitis (≤2%)

Miscellaneous: Diaphoresis (3%)

<1%, postmarketing, and/or case reports: Apolipoprotein A1 increased, apolipoprotein B decreased, death related to VTE, fibrinogen decreased, hypertriglyceridemia (in women with a history of increased triglycerides in response to oral estrogens), intermittent claudication, LDL cholesterol decreased, lipoprotein decreased, muscle spasm, retinal vein occlusion, stroke related to VTE, superficial thrombophlebitis, total serum cholesterol decreased

Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Raloxifene. *Risk D: Consider therapy modification*

Levothyroxine: Raloxifene may decrease the absorption of Levothyroxine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase risk of osteoporosis).

Monitoring ParametersBone mineral density (BMD), CBC, lipid profile; adequate diagnostic measures, including endometrial sampling, if indicated, should be performed to rule out malignancy in all cases of undiagnosed abnormal vaginal bleeding

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions. Evaluate results of laboratory test (lipid profile, BMD, CBC), effectiveness, and adverse response (eg, DVT, PE, chest pain, migraine, rash, hot flashes, vaginitis, UTI, myalgia, cough) on a regular basis during therapy. Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report (eg, thromboembolism). **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. For use in postmenopausal women only.

Monitoring: Lab TestsMonitor lipid profile, bone mineral density (BMD), CBC

Patient EducationDo not take any new prescription, OTC medications, or herbal products during therapy without consulting prescriber. Avoid excessive use of alcohol (ethanol may increase risk of osteoporosis). May be taken at any time of day without regard to meals. Additional vitamin supplements may be recommended by your prescriber. May cause flu-like symptoms at beginning of therapy (these should resolve with use); GI disturbances (eg, nausea, vomiting, dyspepsia; small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or joint pain (consult prescriber for approved analgesic). Report immediately any pain, redness, warmth, or cramping in leg muscles; sudden chest pain; unusual cough or respiratory difficulty; or sudeen loss of consciousness or unusual weakness. Report persistent fever, acute migraine, insomnia or emotional depression, weight gain (>5 lb/week), unresolved gastric distress, urinary infection, or vaginal burning or itching. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. For use in postmenopausal women only. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride:

Evista®: 60 mg

Generic AvailableNo

ManufacturerEli Lilly and Co

Pricing: U.S. (www.drugstore.com)

Tablets (Evista)

60 mg (30): $107.89

Mechanism of ActionA selective estrogen receptor modulator (SERM), meaning that it affects some of the same receptors that estrogen does, but not all, and in some instances, it antagonizes or blocks estrogen; it acts like estrogen to prevent bone loss and has the potential to block some estrogen effects in the breast and uterine tissues. Raloxifene decreases bone resorption, increasing bone mineral density and decreasing fracture incidence.

Pharmacodynamics/Kinetics

Onset of action: 8 weeks

Absorption: Rapid; ~60%

Distribution: 2348 L/kg

Protein binding: >95% to albumin and α-glycoprotein; does not bind to sex-hormone-binding globulin

Metabolism: Hepatic, extensive first-pass effect; metabolized to glucuronide conjugates

Bioavailability: ~2%

Half-life elimination: 28-33 hours

Excretion: Primarily feces; urine (<0.2% as unchanged drug; <6% as glucuronide conjugates)

Pharmacotherapy PearlsThe decrease in estrogen-related adverse effects with the selective estrogen-receptor modulators in general and raloxifene in particular should improve compliance and decrease the incidence of cardiovascular events and fractures while not increasing breast cancer.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia or depression

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsKeoxifene Hydrochloride; NSC-706725; Raloxifene Hydrochloride

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Disease Outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial," *JAMA*, 2006, 295(23):2727-41.[PubMed 16754727]

International Brand NamesBonmax (IN); Celvista (TH); Evista (AR, AT, AU, BE, BF, BG, BJ, BR, CH, CI, CL, CN, CO, CZ, DE, DK, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, ID, IE, IL, IT, KE, KP, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, PE, PH, PK, PL, PT, PY, RU, SC, SD, SE, SG, SL, SN, TN, TR, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Loxar (UY); Loxifen (PY); Optruma (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Raxeto (AR)

Raltegravir

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(ral TEG ra vir)
U.S. Brand NamesIsentress™
Canadian Brand NamesIsentress™
Pharmacologic CategoryAntiretroviral Agent, Integrase Inhibitor
Use: Labeled IndicationsTreatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced patients with virus that shows multidrug resistance and active replication
Dosing: Adults**HIV treatment:** Oral: 400 mg twice daily
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**HIV treatment:** Adolescents ≥16 years: Refer to adult dosing.
Dosing: Renal Impairment No dosage adjustment required in severe impairment.
Dosing: Hepatic ImpairmentNo dosage adjustment required with mild-to-moderate impairment. No data available in severe impairment.
Dietary ConsiderationsMay be taken with or without food.
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).
Contraindications

U.S. labeling: There are no contraindications listed in the manufacturer's labeling.

Canadian labeling: Hypersensitivity to raltegravir or any other component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.

- Myopathy: Grade 2-4 creatine kinase (CK) increases have been observed and myopathy and rhabdomyolysis have been reported; use caution in patients with risk factors for CK elevations and/or skeletal muscle abnormalities.

Concurrent drug therapy issues:

- Potential for interactions: Use caution with medications known to induce (eg, rifampin) or inhibit (eg, atazanavir) UGT1A1 glucuronidation, as serum levels/therapeutic effects may be reduced or increased, respectively.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <16 years of age.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies revealed treatment-related increases in rib formation at 3-4 times human doses; no other embryo-/fetotoxic or teratogenic effects noted. There are no adequate and well-controlled studies in pregnant women and available data is insufficient to recommend use in pregnancy. An antiretroviral registry has been established to monitor maternal and fetal outcomes in women receiving antiretroviral drugs. Physicians are encouraged to register patients at 1-800-258-4263 or www.APRegistry.com.
LactationExcretion in breast milk unknown/contraindicated
Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.
Adverse Reactions

>10%: Endocrine & metabolic: Total cholesterol increased (grade 2: 16%; grade 3: 6%)

2% to 10%:

Cardiovascular: Hypertension (3%)

Central nervous system: Fatigue (8%), dizziness (4%), insomnia (4%)

Dermatologic: Rash (5%), pruritus (3% to 4%), folliculitis (2%)

Endocrine & metabolic: Glucose increased (≤250 mg/dL: 9%), LDL-cholesterol increased (grade 2: 9%; grade 3: 4%), hypertriglyceridemia (grade 3: 4%)

Gastrointestinal: Abdominal pain (5%), vomiting (4%), amylase increased (2.1-5 x ULN: 4%), gastroenteritis (3%), lipase increased (1.6-3 x ULN: 3%), anorexia (2%), constipation (2%)

Hepatic: Hyperbilirubinemia (9%; 2.6-5 x ULN: 3%), AST increased (2.6-5 x ULN: 9%), ALT increased (5.1-10 x ULN: 3%), alkaline phosphatase increased (2.6-5 x ULN: 2%)

Neuromuscular & skeletal: Arthralgia (3%), extremity pain (3%), creatine kinase increased (all grades: 2%)

Renal: Creatinine increased (1.4-1.8 x ULN: 3%)

Respiratory: Nasopharyngitis (6%), cough (5%), influenza (3%), sinusitis (3%)

Miscellaneous: Herpes zoster (4%), lymphadenopathy (3%), anogenital warts (2%)

Frequency <2% or not defined: Acneiform dermatitis, allodynia, anemia, anxiety, appetite increased, asthenia, back pain, cellulitis, central obesity, chest discomfort, chills, depression, diabetes mellitus, dreams abnormal, drug hypersensitivity, dry skin, dyspepsia, dyslipidemia, epistaxis, erectile dysfunction, erythema, facial wasting, flatulence, neutropenia, fever, gastritis, GERD, glossitis, gynecomastia, headache, hepatitis, hepatomegaly, herpes simplex, hyperhidrosis, hyperlactacidemia, irritability, lipodystrophy, macrocytic anemia, maculopapular rash, MI, muscle atrophy, muscle spasms, myalgia, myositis, nephropathy, nephrotic syndrome, neuropathy, night sweats, nocturia, palpitation, paresthesia, pollakiuria, prurigo, renal failure, renal tubular necrosis, skin infection, somnolence, vertigo, ventricular extrasystoles, visual disturbance, weight changes

Postmarketing and/or case reports: Stevens-Johnson syndrome

Drug Interactions

Efavirenz: May decrease the serum concentration of Raltegravir. *Risk C: Monitor therapy*

Rifampin: May decrease the serum concentration of Raltegravir. *Risk C: Monitor therapy*

Tipranavir: May decrease the serum concentration of Raltegravir. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: High-fat meal increased AUC by 19%, but raltegravir was administered without regard to meals in clinical trials.

Herb/Nutraceutical: St John's wort may decrease the levels/effects of raltegravir.

Monitoring ParametersViral load, CD4 count, lipid profile

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological or herbal agents patient may be taking (eg, risk of toxicity, decreased effects). Evaluate results of laboratory tests at baseline and periodically (CD4 count and viral load). Evaluate therapeutic effectiveness (clinical and laboratory indicators) and adverse reactions during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsViral load, CD4 count, lipid profile

Patient EducationDo not take any new prescription, OTC medications, or herbal products during therapy unless approved by prescriber. This drug will not cure HIV, nor has it been found to reduce the transmission of HIV; use appropriate precautions to prevent spread of the disease. This drug may be prescribed as one part of a multidrug combination: Take exactly as directed for full course of therapy. If you miss a dose, take it as soon as you remember; do not double doses. You may be more susceptible to infection; avoid crowds and exposure to known infection. May cause dizziness, headache, or fatigue (use caution to avoid falls, when driving or when engaging in tasks that require alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, or yogurt may reduce diarrhea); or itchy skin (if persistent, consult prescriber). Report signs of infection (unusual fever or chills, white plaques in mouth, vaginal itching or foul-smelling vaginal discharge, unusual cough, congestion, or unhealed wounds); muscle pain, tenderness, or weakness; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Isentress™: 400 mg

Generic AvailableNo

Manufacturer

Merck & Co, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Isentress)

400 mg (60): $953.01

Mechanism of ActionIncorporation of viral DNA into the host cell’s genome is required to produce a self-replicating provirus and propagation of infectious virion particles. The viral cDNA strand produced by reverse transcriptase is subsequently processed and inserted into the human genome by the enzyme HIV-1 integrase (encoded by the pol gene of HIV). Raltegravir inhibits the catalytic activity of integrase, thus preventing integration of the proviral gene into human DNA.

Pharmacodynamics/Kinetics

Absorption: AUC increased 19% with high-fat meal

Protein binding: ~83%

Metabolism: Primarily hepatic glucuronidation mediated by UGT1A1

Half-life elimination: ~9 hours

Time to peak, plasma: ~3 hours

Excretion: Feces (51%, as unchanged drug); urine (32%; 9% as unchanged drug)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Perinatal HIV Guidelines

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue, dizziness, or insomnia. Rarely associated with anxiety, depression, abnormal dreams, irritability, and somnolence.

Mental Health: Effects on Psychiatric TreatmentMay cause elevation in lipid panel; concomitant use with atypical antipsychotics may produce additive effects. St John's wort may decrease the serum levels/effects of raltegravir.

Index TermsMK-0518

References

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Kassahun K, McIntosh I, Cui D, et al, “Metabolism and Disposition in Humans of Raltegravir (MK-0518), an Anti-AIDS Drug Targeting the Human Immunodeficiency Virus 1 Integrase Enzyme,” *Drug Metab Dispos*, 2007, 35(9):1657-63.[PubMed 17591678]

Nair V and Chi G, “HIV Integrase Inhibitors as Therapeutic Agents in AIDS,” *Rev Med Virol*, 2007, 17(4):277-95.[PubMed 17503547]

“Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,” July 8, 2008. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” July 29, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesIsentress (CH, CZ, DE, DK, EE, GB, IE, NO, SE)

Raltitrexed

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ral ti TREX ed)
Canadian Brand NamesTomudex®
Pharmacologic CategoryAntineoplastic Agent, Antimetabolite
Use: Labeled IndicationsTreatment of advanced colorectal neoplasms
Use: Unlabeled/InvestigationalUndergoing clinical trials for a variety of neoplasms, including breast, colorectal nonsmall cell lung, ovarian and pancreatic cancers
Dosing: AdultsRefer to individual protocols.

Colorectal cancer: I.V.: 3 mg/m^2 every 3 weeks

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal Impairment

Cl_{cr} 55-65 mL/minute: Administer 75% of dose every 4 weeks

Cl_{cr} 25-54 mL/minute: Administer % of dose equivalent to Cl_{cr} every 4 weeks (ie, 25% of dose for Cl_{cr} of 25 mL/minute)

Cl_{cr} <25 mL/minute: Do not administer

Dosing: Hepatic ImpairmentNo adjustment required for mild-moderate hepatic insufficiency. Patients who develop hepatic toxicity should have treatment held until returns to grade 2.
Dosing: Adjustment for Toxicity

Grade 4 gastrointestinal toxicity or grade 3 gastrointestinal toxicity in combination with grade 4 hematologic toxicity: Discontinue therapy

Grade 3 hematologic toxicity or grade 2 gastrointestinal toxicity: Reduce dose by 25%

Grade 4 hematologic toxicity or grade 3 gastrointestinal toxicity: Reduce dose by 50%

Calculations

- Body Surface Area: Adults
- Creatinine Clearance: Adults

Administration: I.V.Infuse over 15 minutes.
Dietary ConsiderationsAvoid folic acid, folinic acid, and multivitamins with folic acid close to and during administration.
StorageIntact vials should be refrigerated at 2°C to 25°C. Protect from light. Solutions reconstituted with saline or dextrose to a concentrate of 0.5 mg/mL are stable for up to 24 hours under refrigeration at 2°C to 8°C.
ReconstitutionReconstitute 2 mg vial with 4 mL SWFI; add to 50-250 mL NS or D_5W.
CompatibilityStable in D_5W, NS. Do not mix with other medications.
RestrictionsNot available in U.S./Investigational
ContraindicationsHypersensitivity to raltitrexed or any component of the formulation; uncontrolled diarrhea; severe renal or hepatic impairment; pregnancy or breast-feeding
Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Malaise/weakness: Use with caution in patients with malaise/weakness; caution patients concerning operation of machinery/driving.

Disease-related concerns:

- Gastrointestinal disease: Use with caution in patients with a history of gastrointestinal problems (particularly diarrhea).

- Hepatic impairment: Use with caution in patients with mild-to-moderate hepatic impairment. Therapy interruption is required in patients with hepatotoxicity.

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Chemotherapy: Use with caution in patients heavily pretreated with chemotherapy, especially if myelosuppression, stomatitis, hepatic or renal toxicities persist.

- Folic acid/folate-containing medications: Folinic acid, folic acid, or folate-containing medications (eg, multivitamins) may interfere with raltitrexed; do not administer immediately prior to or concurrently with raltitrexed.

Special populations:

- Elderly: Use with caution in the elderly.

- Pediatrics: Safety and efficacy have not been established in children.

- Radiation therapy recipients: Use with caution in patients heavily pretreated with radiation, especially if myelosuppression, stomatitis, hepatic or renal toxicities persist.

Pregnancy Risk FactorX

Pregnancy ConsiderationsExclude pregnancy prior to treatment with raltitrexed. Avoid pregnancy during treatment and for 6 months following treatment. Pregnant women should not handle this medication.

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions

>10%:

Central nervous system: Fever (2% to 23%), may be delayed until several days after administration

Dermatologic: Rashes (14%), usually pruritic papular lesions on head and thorax

Gastrointestinal: Nausea (58%; grade 3 or 4 in 12%), mucositis/stomatitis (12% to 48%; grade 3 or 4 in 2%), diarrhea (38%; grade 3 or 4 in 11%), vomiting (37%), anorexia (27%), abdominal pain (18%), constipation (13% to 15%; grade 3 or 4 in 2%)

Hematologic: Myelosuppression; leukopenia occurs in about 21% of patients (grade 3 or 4 in 12%), nadirs occur in ~8 days, but may be delayed to day 21, with recovery in ~10 days; thrombocytopenia (5% to 6%; grade 3 or 4 in 4%), anemia (15% to 18%; grade 3 or 4 in 7%)

Hepatic: Transaminases increased (14% to 18%; grade 3 or 4 in 10%)

Neuromuscular & skeletal: Weakness (46% to 48%; grade 3 or 4 in 9%)

1% to 10%:

Cardiovascular: Arrhythmias (3%), edema (9% to 10%), CHF (2%)

Central nervous system: Malaise, headache, pain, chills, insomnia, depression, paresthesia

Dermatologic: Alopecia, cellulitis, exfoliative eruptions

Endocrine & metabolic: Dehydration, hypokalemia

Gastrointestinal: Dyspepsia, flatulence, xerostomia, weight loss, taste perversion

Genitourinary: Urinary tract infection

Hepatic: Alkaline phosphatase increased, bilirubin increased

Neuromuscular & skeletal: Arthralgia, myalgia, hypotonia

Ocular: Conjunctivitis

Renal: Serum creatinine increased

Respiratory: Cough (increased), dyspnea, pharyngitis

Miscellaneous: Flu-like syndrome (6% to 8%), diaphoresis, infection, sepsis

<1%: Hypersensitivity/allergic reaction (including stridor and wheezing following the first dose), desquamation

Oncology: VesicantNo

Oncology: Emetic PotentialMild to moderate (30% to 60%)

Drug Interactions

Folic Acid: May diminish the therapeutic effect of Raltitrexed. *Risk X: Avoid combination*

Leucovorin-Levoleucovorin: May diminish the therapeutic effect of Raltitrexed. *Risk X: Avoid combination*

Methylfolate: May diminish the therapeutic effect of Raltitrexed. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid folic acid and multivitamins with folic acid close to and during administration.

Monitoring ParametersCBC with differential, hepatic function tests, serum lipids, serum creatinine

Monitoring: Lab TestsCBC with differential, hepatic function tests, serum lipids, serum creatinine

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as disodium: 2 mg

Generic AvailableNo
ManufacturerAstraZeneca (Canada)
Mechanism of ActionRaltitrexed is a folate analogue that inhibits thymidylate synthase, blocking purine synthesis. This results in an overall inhibition of DNA synthesis.
Pharmacodynamics/Kinetics

Distribution: V_{ss}: 548 L

Protein binding: 93%

Metabolism: Undergoes extensive intracellular metabolism to active polyglutamate forms; appears to be little or no systemic metabolism of the drug

Half-life elimination: Triphasic; Beta: 2 hours; Terminal: Up to 198 hours

Excretion: Urine (50% as unchanged drug); feces (15%)

Pharmacotherapy PearlsNot available in U.S.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause depression, insomnia, and malaise
Mental Health: Effects on Psychiatric TreatmentGI side effects are common; additive effects may be seen with SSRIs, lithium, and valproic acid derivatives. Myelosuppression is common; use caution with clozapine, carbamazepine, and valproic acid derivatives.
Mental Health Comment Flu-like syndrome may occur in up to 8% of individuals receiving this agent. Consider SSRI withdrawal syndrome in physician differential diagnosis.
Index TermsICI-D1694; NSC-639186; Raltitrexed Disodium; ZD1694
References

Clarke SJ, Beale PJ, and Rivory LP, "Clinical and Preclinical Pharmacokinetics of Raltitrexed," *Clin Pharmacokinet*, 2000, 39(6):429-43. [PubMed 11192475]

Taylor SC, "Raltitrexed for Advanced Colorectal Cancer. The Story So Far," *Cancer Pract*, 2000, 8(1):51-4. [PubMed 10732541]

Van Cutsem E, Cunningham D, Maroun J, et al, "Raltitrexed: Current Clinical Status and Future Directions," *Ann Oncol*, 2002, 13(4):513-22.[PubMed 12056700]

International Brand NamesTomudex (AR, AT, AU, BE, BG, BR, CH, CZ, EE, ES, FR, GB, HN, HU, IE, IT, LU, MX, NL, NO, PL, SG, UY, VE)

Ramelteon

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Ramelteon may be confused with Remeron®

Rozerem® may be confused with Razadyne™, Remeron®

Pronunciation(ra MEL tee on)

U.S. Brand NamesRozerem®

Pharmacologic CategoryHypnotic, Nonbenzodiazepine

Use: Labeled IndicationsTreatment of insomnia characterized by difficulty with sleep onset

Dosing: Adults**Insomnia:** Oral: One 8 mg tablet within 30 minutes of bedtime

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment required

Dosing: Hepatic Impairment No adjustment required for mild-to-moderate impairment; use caution. Not recommended with severe impairment.

Administration: OralDo not administer with a high-fat meal. Swallow tablet whole; do not break.

Dietary ConsiderationsTaking with high-fat meal delays T_{max} and increases AUC (~31%); do not take with high-fat meal.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture.

RestrictionsAn FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHistory of angioedema with previous ramelteon therapy (do not rechallenge); concurrent use with fluvoxamine

Warnings/Precautions

Concerns related to adverse effects:

- Abnormal thinking/behavioral changes: Hypnotics/sedatives have been associated with abnormal thinking and behavior changes including decreased inhibition, aggression, bizarre behavior, agitation, hallucinations, and depersonalization. These changes may occur unpredictably and may indicate previously unrecognized psychiatric disorders; evaluate appropriately.

- CNS depression: May cause CNS depression impairing physical and mental capabilities; patients must be cautioned about performing tasks, which require mental alertness (operating machinery or driving).

- Hypersensitivity reactions: Postmarketing studies have indicated that the use of hypnotic/sedative agents (including ramelteon) for sleep has been associated with hypersensitivity reactions including anaphylaxis as well as angioedema. Do not rechallenge patients who have developed angioedema with ramelteon therapy.

- Reproductive hormonal regulation disturbances: May cause disturbances of reproductive hormonal regulation (eg, disruption of menses or decreased libido).

- Sleep-related activities: An increased risk for hazardous sleep-related activities such as sleep-driving; cooking and eating food, and making phone calls while asleep have also been noted.

Disease-related concerns:

- Depression: Use with caution in patients with depression; worsening of depression, including suicidal ideation has been reported with the use of hypnotics.

- Hepatic impairment: Use with caution in patients with hepatic impairment; use not recommended with severe impairment.

- Respiratory disease: Use with caution in patients with respiratory compromise, COPD or sleep apnea.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

- CYP1A2 inhibitors: Use with caution when administered concomitantly with strong CYP1A2 inhibitors.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Symptomatic treatment of insomnia should be initiated only after careful evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after a reasonable period of treatment may indicate psychiatric and/or medical illness.

- Rapid onset: Because of the rapid onset of action, administer immediately prior to bedtime or after the patient has gone to bed and is having difficulty falling asleep.

Geriatric ConsiderationsAlthough the C_{max} and AUC of ramelteon were increased in elderly patients, in clinical trials there were no significant differences in safety or efficacy between elderly and younger adult subjects.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies have demonstrated teratogenic effects. May cause disturbances of reproductive hormonal regulation (eg, disruption of menses or decreased libido). There are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions 1% to 10%:

Central nervous system: Dizziness (4% to 5%), somnolence (3% to 5%), fatigue (3% to 4%), insomnia worsened (3%), depression (2%)

Endocrine & metabolic: Serum cortisol decreased (1%)

Gastrointestinal: Nausea (3%), taste perversion (2%)

Neuromuscular & skeletal: Myalgia (2%), arthralgia (2%)

Respiratory: Upper respiratory infection (3%)

Miscellaneous: Influenza (1%)

Postmarketing and/or case reports: Anaphylaxis, angioedema, complex sleep-related behavior (sleep-driving, cooking or eating food, making phone calls), prolactin levels increased, testosterone levels decreased

Metabolism/Transport Effects**Substrate** of CYP1A2 (major), CYP3A4 (minor), CYP2C family (minor)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Ramelteon. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Fluconazole: May decrease the metabolism of Ramelteon. *Risk C: Monitor therapy*

Fluvoxamine: May decrease the metabolism of Ramelteon. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Taking with high-fat meal delays T_{max} and increases AUC (~31%); do not take with high-fat meal.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Nursing: Physical Assessment/MonitoringMonitor therapeutic response and adverse reactions. Be alert to possibility of anaphylaxis any time during therapy. Monitor for CNS changes, abnormal thinking, and behavior changes. Assess effectiveness and interactions of other medications patient may be taking. Assess knowledge/teach patient appropriate use, possible side effects/interventions, and adverse symptoms to report.
Patient EducationTake approximately 30 minutes before desiring to go to sleep. Avoid alcohol and other CNS depressants. You may experience dizziness or lightheadedness (use caution when driving or engaging in activities requiring alertness until response to drug is known), or headache. Avoid meal high in fat prior to taking this medication. Report abnormal thinking or behavior; unusual swelling, especially on face or neck; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Rozerem®: 8 mg

Generic AvailableNo
ManufacturerTakeda Pharmaceuticals Co, Ltd
Pricing: U.S. (www.drugstore.com)

Tablets (Rozerem)

8 mg (30): $120.89

Mechanism of ActionPotent, selective agonist of melatonin receptors MT_1 and MT_2 (with little affinity for MT_3) within the suprachiasmic nucleus of the hypothalamus, an area responsible for determination of circadian rhythms and synchronization of the sleep-wake cycle. Agonism of MT_1 is thought to preferentially induce sleepiness, while MT_2 receptor activation preferentially influences regulation of circadian rhythms. Ramelteon is eightfold more selective for MT_1 than MT_2 and exhibits nearly sixfold higher affinity for MT_1 than melatonin, presumably allowing for enhanced effects on sleep induction.

Pharmacodynamics/Kinetics

Onset of action: 30 minutes

Absorption: Rapid; high-fat meal delays T_{max} and increases AUC (~31%)

Distribution: 74 L

Protein binding: ~82%

Metabolism: Extensive first-pass effect; oxidative metabolism primarily through CYP1A2 and to a lesser extent through CYP2C and CYP3A4; forms active metabolite (M-II)

Bioavailability: Absolute: 1.8%

Half-life elimination: Ramelteon: 1-2.6 hours; M-II: 2-5 hours

Time to peak, plasma: Median: 0.5-1.5 hours

Excretion: Primarily as metabolites: Urine (84%); feces (4%)

Related Information

- CMS: Long-Term Care Facility Thresholds
- Nonbenzodiazepine Anxiolytics and Hypnotics

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

Index TermsTAK-375

References

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Nguyen NN, Uy SS, and Song JC, "Ramelteon: A Novel Melatonin Receptor Agonist for the Treatment of Insomnia," *Formulary*, 2005, 40:146-55.

Ramipril and Felodipine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(RA mi pril & fe LOE di peen)

Canadian Brand NamesAltace® Plus Felodipine

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Calcium Channel Blocker

Use: Labeled IndicationsTreatment of hypertension when combination therapy is appropriate (not for initial therapy)

Dosing: Adults**Note:** Not for initial therapy; titration of individual agents to an appropriate clinical response is required before patient is converted over to an equivalent dose of the combination product.

Hypertension (dose is individualized): Oral: Ramipril 2.5-10 mg and felodipine ER 2.5-10 mg once daily; adjust dose no more frequently than every 2 weeks

Dosing: ElderlyInitial: 2.5 mg daily based on felodipine ER component

Dosing: Renal ImpairmentDose reduction required. See individual agents. Maximum dosage: 5 mg/day based on ramipril component.

Dosing: Hepatic ImpairmentDose reduction required. See individual agents. Maximum dosage: 10 mg/day based on felodipine ER component.

Administration: OralSwallow tablet whole; tablet should not be divided, crushed, or chewed

Dietary ConsiderationsMay be taken with or without food.

StorageStore at 15°C to 30°C (59°F to 86°F). Protect from moisture.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to felodipine or other dihydropyridines, ramipril or other ACE inhibitors, or any other component of the formulation; history of angioedema; pregnancy; breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

- Angina/MI: With initiation or dosage titration of dihydropyridine calcium channel blockers, reflex tachycardia may occur resulting in angina and/or MI in patients with obstructive coronary disease especially in the absence of concurrent beta-blockade.

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors. It may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with idiopathic or hereditary angioedema or previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Gingival hyperplasia: Gingival hyperplasia may be induced by felodipine in patients with gingivitis and periodontitis. Effects may be reversed with good oral hygiene and mechanical debridement of teeth.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial ding and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE Inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Peripheral edema: The most common side effect of felodipine (dose dependent) is peripheral edema; occurs within 2-3 weeks of starting therapy.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation of therapy; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with extreme caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.
- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.
- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.
- Heart failure: Use with caution. Safety and efficacy has not been established in patients with heart failure.
- Hepatic impairment: Use with caution in patients with hepatic impairment; ACEI therapy has been associated with hepatitis, and elevated hepatic enzymes and bilirubin; lower starting dose may be necessary; evaluate hepatic function at baseline before initiating therapy and closely monitor thereafter.
- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.
- Renal artery stenosis: Use with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.
- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment.

Special populations:

- Elderly: Initiate therapy at a lower dose in the elderly.
- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: Use is contraindicated in pregnancy. Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. Women of child bearing potential should employ a reliable means of contraception. ACEIs should be discontinued as soon as possible once pregnancy is detected.

Other warnings/precautions:

- Appropriate use: Used as a replacement for separate dosing of components or combination therapy when response to single agent is suboptimal; the fixed combination is not indicated for initial treatment of hypertension.
- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous rennin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Pregnancy ConsiderationsUse is contraindicated in pregnancy. See individual agents.
LactationExcretion of felodipine and ramipril into breast milk unknown/contraindicated
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsIncidence observed with combination product. Also see individual agents.

1% to 10%:

Cardiovascular: Vasodilation (3%), peripheral edema (2%), palpitation (1%)

Central nervous system: Headache (8%), dizziness (3%), vertigo (2%)

Gastrointestinal: Nausea (2%), abdominal pain (1%), diarrhea (1%)

Neuromuscular & skeletal: Back pain (2%), weakness (2%)

Respiratory: Cough (6%), bronchitis (3%), upper respiratory infection (1%)

Miscellaneous: Flu-like syndrome (2%)

<1%: Angina pectoris, anorexia, anxiety, arrhythmia, arthralgia, arthritis, arthrosis, bilirubin increased, blurred vision, bronchospasm, cerebrovascular accident, colitis, constipation, cystitis, depression, diabetes mellitus, diaphoresis, dyspepsia, dyspnea, dysuria, ECG abnormal, edema, enteritis, epistaxis, extrasystoles, facial edema, fever, flatulence, gastritis, gastroenteritis, gout, heaviness in extremities, hemiplegia, hemoglobin decreased, hepatic enzymes increased, hydronephrosis, hypesthesia, insomnia, joint disorder, laryngitis, libido decreased, liver fatty deposit, MI, migraine, pain, muscle cramps, myalgia, nervousness, paresthesia, peripheral vascular disorder, pharyngitis, polyuria, postural hypotension, pruritus, pulmonary embolism, pyelonephritis, rash, retinal disorder, rhinitis, shock, sinus bradycardia, sinusitis, somnolence, tachycardia, tinnitus, T-wave inverted, urinary tract infection, urticaria, vomiting, xerostomia

Metabolism/Transport EffectsSee individual agents.
Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

CycloSPORINE: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). Nicardipine may likewise inhibit the metabolism of cyclosporine. Cyclosporine dosage adjustments might be needed. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). *Risk D: Consider therapy modification*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Tacrolimus: Calcium Channel Blockers (Dihydropyridine) may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring Parameters Blood pressure; serum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/Monitoring See individual agents.

Monitoring: Lab Tests Serum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient Education See individual agents.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet, variable release:

Altace® Plus Felodipine 2.5/2.5 [CAN]: Ramipril 2.5 mg [immediate release] and felodipine 2.5 mg [extended release] [not available in the U.S.]

Altace® Plus Felodipine 5/5 [CAN]: Ramipril 5 mg [immediate release] and felodipine 5 mg [extended release] [not available in the U.S.]

Generic Available No

Manufacturer Sanofi-Aventis Canada Inc

Mechanism of Action

Ramipril is an ACE inhibitor which first undergoes enzymatic saponification by esterases in the liver, to its active metabolite ramiprilat. The pharmacodynamic effects of ramipril result from the high-affinity, competitive, reversible binding of ramiprilat to angiotensin-converting enzyme thus preventing the formation of the potent vasoconstrictor angiotensin II from angiotensin I. This isomerized enzyme-inhibitor complex has a slow rate of dissociation, which results in high potency and a long duration of action; a CNS mechanism may also be involved in the hypotensive effect as angiotensin II increases adrenergic outflow from CNS; vasoactive kallikreins may be decreased in conversion to active hormones by ACE inhibitors, thus reducing blood pressure

Felodipine inhibits calcium ions from entering the “slow channels” or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization, producing a relaxation of coronary vascular smooth muscle and coronary vasodilation, increases myocardial oxygen delivery in patients with vasospastic angina.

Pharmacodynamics/Kinetics See individual agents.

Related Information

- Felodipine
- Ramipril

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Index Terms Felodipine and Ramipril; Ramipril and Felodipine ER

References

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Cvetkovic R and Plosker G, "Ramipril/Felodipine Extended-Release Fixed-Dose Combination: A Review of Its Use in the Management of Essential Hypertension," *Drugs*, 2005, 65(13):1851-68.[PubMed 16114982]

Mastrobattista JM, "Angiotensin Converting Enzyme Inhibitors in Pregnancy," *Semin Perinatol*, 1997, 21(2):124-34.[PubMed 9201818]

Ramipril and Hydrochlorothiazide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Altace® HCT may be confused with alteplase, Artane®, Altace®

Pronunciation(RA mi pril & hye droe klor oh THYE a zide)

Canadian Brand NamesAltace® HCT

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of essential hypertension (not for initial therapy)

Dosing: Adults**Hypertension:** Oral: **Note:** Not for initial therapy; titration of individual agents to an appropriate clinical response is required before patient is converted over to an equivalent dose of the combination product.

Usual dosage: Ramipril 2.5 mg/hydrochlorothiazide 12.5 mg once daily; titrate to maximum ramipril 10 mg/hydrochlorothiazide 50 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 30-60 mL/minute: Use caution; maximum dose: Ramipril 5 mg/hydrochlorothiazide 25 mg once daily

Cl_{cr} <30 mL/minute: Hydrochlorothiazide is usually ineffective

Dosing: Hepatic ImpairmentNo specific dosing available.

Calculations

- Creatinine Clearance: Adults

Administration: OralAdminister without regard to meals.

Dietary ConsiderationsMay be taken without regard to meals.

StorageStore at 15°C to 30°C (59°F to 86°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to ramipril, hydrochlorothiazide, other ACE inhibitors or thiazides, sulfonamide-derived drugs, or any other component of the formulation; angioedema related to previous treatment with an ACE inhibitor; patients with idiopathic or hereditary angioedema; anuria; pregnancy; breast-feeding

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with idiopathic or hereditary angioedema or previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs. Consider discontinuing therapy if symptoms of hepatic dysfunction (eg, fever, malaise, muscle pain, rash) present within the first weeks to months of therapy.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Electrolyte disturbances: Hyperkalemia may occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE Inhibitor, captopril, has been associated with bone marrow suppression including rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hyperplasia. Patients with collagen vascular disease (eg, systemic lupus erythematosus) and/or renal disease are at a higher risk of developing bone marrow suppression. Monitor CBC with differential in these patients.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Collagen vascular disease: Use ACE inhibitors with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity. Hydrochlorothiazide may cause systemic lupus erythematosus (SLE) exacerbation or activation.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use with caution in patients with severe hepatic dysfunction. In cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use ramipril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use ACE inhibitors with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment. Patients with renal impairment may be at increased risk for hematologic toxicity. Avoid hydrochlorothiazide in severe renal disease (ineffective). Contraindicated in patients with anuria.

Special populations:

- Pediatrics: Safety and efficacy of ramipril/hydrochlorothiazide have not been established in children.

- Pregnancy: **[Canadian Boxed Warning]: ACEIs can cause injury and death to the developing fetus when used in pregnancy. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsSee individual agents.
Pregnancy ConsiderationsUse is contraindicated. See individual agents.
LactationEnters breast milk/contraindicated
Breast-Feeding ConsiderationsSee individual agents.
Adverse Reactions**Note:** Observed with ramipril/hydrochlorothiazide. Also see individual agents.

1% to 10%:

Central nervous system: Headache (4%), dizziness (2%)

Neuromuscular & skeletal: Neuralgia (2%), back pain (1%), weakness (1%)

Respiratory: Bronchitis (2%), cough increased (1%), upper respiratory infection (1%)

Miscellaneous: Infection (2%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Acute liver failure, acute renal failure, agranulocytosis, allergic reactions, alopecia, anaphylactoid reaction, angina, angioedema, anxiety, apathy, arrhythmia, arthralgia, auditory disturbance, bilirubin increased, bone marrow depression, bronchospasm, BUN increased, confusion, constipation, conjunctivitis, creatinine (serum) increased, depression, diaphoresis, diarrhea, drowsiness, dry (nonproductive) cough, dyspnea, enanthema, eosinophilia, erythema multiforme, exanthema, exfoliative dermatitis, fever, gastroenteritis, gastrointestinal pain, glossitis, gout, hemolytic anemia, hot flushes, hypercalcemia, hypercholesterolemia hyperglycemia, hyper-/hypokalemia, hypertriglyceridemia, hyperuricemia, hypochloremia, hypomagnesemia, hyponatremia, hypotension, impotence, interstitial nephritis, ischemic stroke, jaundice, leukopenia, libido decreased, liver function test abnormalities, maculopapular rash, magnesium increased (serum), metabolic alkalosis, MI, muscle cramps, myalgia, nausea, nervousness, orthostatic hypotension, palpitation, pancreatitis, pancytopenia, paresthesia, pemphigus, peripheral edema, photosensitivity, polydipsia, postural hypotension, pruritus, psoriasis, rash, renal failure, restlessness, shock, sinusitis, sleep disorder, smell disturbance, somnolence, Stevens-Johnson syndrome, syncope, tachycardia, taste disturbance, thrombocytopenia, toxic epidermal necrolysis, tinnitus, tremor, transaminases increased, urticaria, vasculitis, visual disturbances, vomiting, xerostomia

Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions See individual agents.
Monitoring Parameters Blood pressure; BUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential
Nursing: Physical Assessment/Monitoring See individual agents.
Monitoring: Lab Tests BUN, serum creatinine, and electrolytes; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential
Patient Education See individual agents.
Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet:

Altace® HCT 2.5/12.5 [CAN]: Ramipril 2.5 mg and hydrochlorothiazide 12.5 mg [not available in the U.S.]

Altace® HCT 5/12.5 [CAN]: Ramipril 5 mg and hydrochlorothiazide 12.5 mg [not available in the U.S.]

Altace® HCT 5/25 [CAN]: Ramipril 5 mg and hydrochlorothiazide 25 mg [not available in the U.S.]

Altace® HCT 10/12.5 [CAN]: Ramipril 10 mg and hydrochlorothiazide 12.5 mg [not available in the U.S.]

Altace® HCT 10/25 [CAN]: Ramipril 10 mg and hydrochlorothiazide 25 mg [not available in the U.S.]

Generic Available No
Manufacturer Sanofi-Aventis Canada Inc
Pharmacodynamics/Kinetics See individual agents.
Related Information

- Hydrochlorothiazide
- Ramipril

Index Terms Hydrochlorothiazide and Ramipril
References

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International Brand Names Altace Plus (VE); Ampril HL (EE); Cardace-H (IN); Co-ramipril (BE); Cotriatec (FR); Ramace H (IN); Ramicard (DE);

Ramipril Comp (EE); Ramipril Plus (IL); Triatec Comp (CH, DK, PT, SE); Triatec D (BR); Triatec Plus (GR); Tritace Comp (IL, TH); Tritace Comp LS (TH); Tritace Plus (BG, KP); Tritace-HCT (AR, CR, DO, GT, HN, NI, PA, PY, SV); Tritazide (BE, CZ, MX)

Ramipril

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Ramipril may be confused with enalapril, Monopril®

Altace® may be confused with alteplase, Amaryl®, Amerge®, Artane®

International issues:

Altace® may be confused with Altace® HCT which is a brand name for ramipril/hydrochlorothiazide combination product in Canada

Pronunciation(RA mi pril)

U.S. Brand NamesAltace®

Canadian Brand NamesAltace®; Apo-Ramipril®; CO Ramipril; GEN-Ramipril; Novo-Ramipril; RAN-Ramipril; ratio-Ramipril; Sandoz-Ramipril

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor

Use: Labeled IndicationsTreatment of hypertension, alone or in combination with thiazide diuretics; treatment of left ventricular dysfunction after MI; to reduce risk of MI, stroke, and death in patients at increased risk for these events

Use: Unlabeled/InvestigationalTreatment of heart failure; to delay the progression of nephropathy and reduce risks of cardiovascular events in hypertensive patients with type 1 or 2 diabetes mellitus

Dosing: Adults

Hypertension: Oral: 2.5-5 mg once daily, maximum: 20 mg/day

To reduce the risk of MI, stroke, and death from cardiovascular causes: Oral: Initial: 2.5 mg once daily for 1 week, then 5 mg once daily for the next 3 weeks, then increase as tolerated to 10 mg once daily (may be given as divided dose)

Left ventricular dysfunction postmyocardial infarction: Oral: Initial: 2.5 mg twice daily titrated upward, if possible, to 5 mg twice daily.

Heart failure (unlabeled use): Initial: 1.25-2.5 mg once daily; target dose: 10 mg once daily (ACC/AHA 2005 Heart Failure Guidelines)

Note: The dose of any concomitant diuretic should be reduced. If the diuretic cannot be discontinued, initiate therapy with 1.25 mg. After the initial dose, the patient should be monitored carefully until blood pressure has stabilized.

Dosing: ElderlyRefer to adult dosing (see Geriatric Considerations). Adjust for renal function for elderly since glomerular filtration rates are decreased; may see exaggerated hypotensive effects if renal clearance is not considered.

Dosing: Renal Impairment

Cl_{cr} <40 mL/minute: Administer 25% of normal dose.

Renal failure and hypertension: Administer 1.25 mg once daily, titrated upward as possible.

Renal failure and heart failure: Administer 1.25 mg once daily, increasing to 1.25 mg twice daily up to 2.5 mg twice daily as tolerated.

Calculations

- Creatinine Clearance: Adults

Administration: OralCapsule is usually swallowed whole, but may be may be mixed in water, apple juice, or applesauce.

StorageStore at controlled room temperature.

ContraindicationsHypersensitivity to ramipril or any component of the formulation; prior hypersensitivity (including angioedema) to ACE inhibitors

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.
- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.
- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.
- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.
- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.
- Neutropenia/agranulocytosis: Another ACE Inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.
- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.
- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.
- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.
- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.
- Renal artery stenosis: Use ramipril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.
- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment may be needed. Avoid rapid dosage escalation which may lead to further renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsDue to frequent decreases in glomerular filtration (also creatinine clearance) with aging, elderly patients may have exaggerated responses to ACE inhibitors; differences in clinical response due to hepatic changes are not observed. ACE inhibitors may be preferred agents in elderly patients with CHF and diabetes mellitus. Diabetic proteinuria is reduced and insulin sensitivity is enhanced. In general, the side effect profile is favorable in the elderly and causes little or no CNS confusion; use lowest dose recommendations initially. Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.

Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)

Pregnancy ConsiderationsDue to adverse events observed in some animal studies, ramipril is considered pregnancy category C during the first trimester. Based on human data, ramipril is considered pregnancy category D if used during the second and third trimesters (per the manufacturer; however, one study suggests that fetal injury may occur at anytime during pregnancy). Ramipril crosses the placenta. First trimester exposure to ACE inhibitors may cause major congenital malformations. An increased risk of cardiovascular and/or central nervous system malformations was observed in one study; however, an increased risk of teratogenic events was not observed in other studies. Second and third trimester use of an ACE inhibitor is associated with oligohydramnios. Oligohydramnios due to decreased fetal renal function may lead to fetal limb contractures, craniofacial deformation, and hypoplastic lung development. The use of ACE inhibitors during the second and third trimesters is also associated with anuria, hypotension, renal failure (reversible or irreversible), skull hypoplasia, and death in the fetus/neonate. Chronic maternal hypertension itself is also associated with adverse events in the fetus/infant. ACE inhibitors are not recommended during pregnancy to treat maternal hypertension or heart failure. Those who are planning a pregnancy should be considered for other medication options if an ACE inhibitor is currently prescribed or the ACE inhibitor should be discontinued as soon as possible once pregnancy is detected. The exposed fetus should be monitored for fetal growth, amniotic fluid volume, and organ formation. Infants exposed to an ACE inhibitor *in utero*, especially during the second and third trimester, should be monitored for hyperkalemia, hypotension, and oliguria.

[U.S. Boxed Warning]: Based on human data, ACE inhibitors can cause injury and death to the developing fetus when used in the second and third trimesters. ACE inhibitors should be discontinued as soon as possible once pregnancy is detected.

Lactation Excretion in breast milk unknown/not recommended

Breast-Feeding Considerations Ramipril and its metabolites were not detected in breast milk following a single oral dose of 10 mg. It is not known if multiple doses will produce detectable levels. Breast-feeding is not recommended by the manufacturer.

Pregnancy & Lactation, In-Depth

- Ramipril in Pregnancy & Lactation

Adverse Reactions **Note:** Frequency ranges include data from hypertension and heart failure trials. Higher rates of adverse reactions have generally been noted in patients with CHF. However, the frequency of adverse effects associated with placebo is also increased in this population.

>10%: Respiratory: Cough (increased) (7% to 12%)

1% to 10%:

Cardiovascular: Hypotension (11%), angina (up to 3%), postural hypotension (2%), syncope (up to 2%)

Central nervous system: Headache (1% to 5%), dizziness (2% to 4%), fatigue (2%), vertigo (up to 2%)

Endocrine & metabolic: Hyperkalemia (1% to 10%)

Gastrointestinal: Nausea/vomiting (1% to 2%)

Neuromuscular & skeletal: Chest pain (noncardiac) (1%)

Renal: Renal dysfunction (1%), serum creatinine increased (1% to 2%), BUN increased (<1% to 3%); transient increases of creatinine and/or BUN may occur more frequently

Respiratory: Cough (estimated 1% to 10%)

<1%: Agranulocytosis, abdominal pain, amnesia, anaphylactoid reaction, angioedema, anorexia, anxiety, arrhythmia, arthralgia, arthritis, bone marrow depression, cerebrovascular events, constipation, convulsions, decreased hematocrit, decreased hemoglobin, depression, diarrhea, dyspepsia, dysphagia, dyspnea, edema, eosinophilia, epistaxis, erythema multiforme, gastroenteritis, hearing loss, hemolytic anemia, hepatitis, hypersensitivity reactions (fever, rash, urticaria), hyponatremia, impotence, increased diaphoresis, increased salivation, insomnia, malaise, myalgia, MI, nervousness, neuralgia, neuropathy, onycholysis, palpitation, pancreatitis, pancytopenia, paresthesia, pemphigoid, pemphigus, photosensitivity, proteinuria, purpura, somnolence, Stevens-Johnson syndrome, symptomatic hypotension, taste disturbance, thrombocytopenia, tinnitus, toxic epidermal necrolysis, transaminases increased, tremor, vision disturbances, weight gain, xerostomia

Postmarketing and/or case reports: Agitation

Worsening of renal function may occur in patients with bilateral renal artery stenosis or in hypovolemia. In addition, a syndrome which may include fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash, eosinophilia and positive ANA, and elevated ESR has been reported with ACE inhibitors. Risk of pancreatitis and agranulocytosis may be increased in patients with collagen vascular disease or renal impairment.

Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Test InteractionsIncreases BUN, creatinine, potassium, positive Coombs' [direct]; decreases cholesterol (S); may cause false-positive results in urine acetone determinations using sodium nitroprusside reagent

Monitoring ParametersBlood pressure; serum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringEvaluate carefully for necessary use cautions. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (especially anything that may impact fluid balance or cardiac status). May be advisable to administer first dose in prescriber's office with careful blood pressure monitoring (hypotension or angioedema can occur at any time during treatment, especially following first dose). Assess results of laboratory tests, therapeutic effectiveness (blood pressure and cardiac status), and adverse response (eg, cough, renal dysfunction, nausea/vomiting, hypovolemia, angioedema, postural hypotension) on a regular basis during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take as directed; do not alter dose or discontinue without consulting prescriber. Take first dose at bedtime or when sitting down (hypotension may occur). This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause increased cough (if persistent or bothersome, contact prescriber); headache (consult prescriber for approved analgesic); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); dizziness (use caution when driving or engaging in tasks that require alertness until response to drug is known); or nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Immediately report swelling of face, mouth, lips, tongue or throat; chest pain or irregular heartbeat. Report respiratory difficulty or persistent cough; persistent pain in muscles, joints, or back; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 1.25 mg, 2.5 mg, 5 mg, 10 mg

Altace®: 1.25 mg, 2.5 mg, 5 mg, 10 mg

Tablet:

Altace®: 1.25 mg, 2.5 mg, 5 mg, 10 mg

Generic AvailableYes: Capsule

ManufacturerMonarch Pharmaceuticals
Pricing: U.S. (www.drugstore.com)

Capsules (Altace)

- 1.25 mg (30): $57.11
- 2.5 mg (30): $64.99
- 5 mg (30): $65.99
- 10 mg (30): $76.99

Capsules (Ramipril)

- 1.25 mg (100): $139.99
- 2.5 mg (30): $49.99
- 5 mg (30): $55.99
- 10 mg (30): $61.99

Mechanism of ActionRamipril is an ACE inhibitor which prevents the formation of angiotensin II from angiotensin I and exhibits pharmacologic effects that are similar to captopril. Ramipril must undergo enzymatic saponification by esterases in the liver to its biologically active metabolite, ramiprilat. The pharmacodynamic effects of ramipril result from the high-affinity, competitive, reversible binding of ramiprilat to angiotensin-converting enzyme, thus preventing the formation of the potent vasoconstrictor angiotensin II. This isomerized enzyme-inhibitor complex has a slow rate of dissociation, which results in high potency and a long duration of action; a CNS mechanism may also be involved in the hypotensive effect as angiotensin II increases adrenergic outflow from CNS; vasoactive kallikreins may be decreased in conversion to active hormones by ACE inhibitors, thus reducing blood pressure

Pharmacodynamics/Kinetics

Onset of action: 1-2 hours

Duration: 24 hours

Absorption: Well absorbed (50% to 60%)

Distribution: Plasma levels decline in a triphasic fashion; rapid decline is a distribution phase to peripheral compartment, plasma protein and tissue ACE (half-life: 2-4 hours); second phase is an apparent elimination phase representing the clearance of free ramiprilat (half-life: 9-18 hours); and final phase is the terminal elimination phase representing the equilibrium phase between tissue binding and dissociation

Protein binding:

- Ramipril: 73%
- Ramiprilat: 56%

Metabolism: Hepatic to the active form, ramiprilat

Bioavailability:

- Ramipril: 28%
- Ramiprilat: 44%

Half-life elimination: Ramiprilat: Effective: 13-17 hours; Terminal: >50 hours

Time to peak, serum:

- Ramipril: ~1 hour
- Ramiprilat: 2-4 hours

Excretion: Urine (60%) and feces (40%) as parent drug and metabolites

Related Information

- Angiotensin Agents
- Heart Failure (Systolic)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness; may rarely cause nervousness, amnesia, insomnia, or depression
Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels
Cardiovascular Considerations

Congestive Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines recommend that ACE inhibitors be used in patients with a reduced EF (with or without heart failure symptoms) unless contraindicated. ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. In this situation, they decrease hospitalizations for, and retard progression to, congestive heart failure. When used in patients with heart failure, the target dose should be achieved, if possible. Lower daily doses of ACE inhibitors have demonstrated the same mortality effects as high doses, but have not decreased hospitalizations to the extent that high-dose ACE inhibitors have, as demonstrated in the ATLAS study (Packer M, 1999).

Hypertension: The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) can be beneficial in patients with hypertension and LVH without symptoms of heart failure. JNC 7 suggests that patients can benefit from treatment with an ACE inhibitor if they have hypertension **and** heart failure, acute myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, or history of stroke.

Vascular Disease: The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors can be useful in preventing heart failure in patients who have a history of atherosclerotic vascular disease, diabetes, or hypertension with associated cardiovascular risk factors. The HOPE trial (Heart Outcomes Prevention Evaluation Study Investigators, 2000) investigated the value of an ACE inhibitor (ramipril 5-10 mg daily) versus placebo in patients who had evidence of vascular disease or diabetes (one other cardiovascular risk factor) and were at least 55 years of age. Patients were excluded if they had a low ejection fraction, heart failure, or were on an ACE inhibitor. The primary outcome was a composite of death from cardiovascular cause, myocardial infarction, or stroke; 9297 patients were enrolled and randomized. Ramipril significantly reduced the risk of death from CV causes, MI, or stroke over placebo. New cases of diabetes were also reduced in the ramipril group. In the EUROPA trial, patients with stable coronary artery disease (at low risk for cardiovascular events) received perindopril or placebo and were evaluated for incidence of cardiovascular events after four years of treatment. In this randomized, placebo-controlled, prospective study, 12,218 patients received either perindopril (8 mg/day, n=6110) or placebo (n=6108) and were assessed for the primary endpoint of a cardiovascular event, defined as cardiovascular death, myocardial infarction, or cardiac arrest. The study population was well balanced with respect to baseline demographics and concomitant medication use (including beta-blockers, platelet inhibitors, antihyperlipidemics, calcium channel blockers, nitrates, and diuretics). Intent-to-treat analysis revealed that 603 (10%) of placebo patients experienced the primary endpoint of a cardiovascular event compared to 488 (8%) of perindopril-receiving patients, for a 20% relative risk reduction (p=0.0003). This result was not influenced by presence of other comorbidities (eg, diabetes, hypertension) or concomitant beta-blocker, calcium channel blocker, or lipid-lowering therapies. Withdrawal from the study (postrandomization) due to adverse reactions was similar between treatment groups. Number needed to treat analysis suggests that treatment of 50 patients over a 4-year period will prevent one major cardiovascular event.

Acute Coronary Syndromes: In the treatment of unstable angina/non-ST-segment elevation MI, ACE inhibitors are recommended when hypertension persists despite treatment with nitroglycerin and a beta-blocker in patients with LV systolic dysfunction or CHF and in ischemic patients with diabetes (Class I). ACE inhibitors are also recommended for all post-ACS individuals (Class IIa). According to 2004 ACC/AHA STEMI guidelines, an ACE inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF <0.4, in the absence of hypotension or known contraindications to this class of medicines. In the emergency management of complicated STEMI, a short-acting ACEI (eg, captopril 1-6.25 mg) may be added once the patient's systolic blood pressure is >100 mm Hg and not <30 mm Hg below baseline. The VALIANT trial evaluated the effects of valsartan (target dose: 160 mg twice daily), captopril (target dose: 50 mg twice daily), and the combination (target doses: valsartan 80 mg twice daily and captopril 150 mg once daily) in a randomized, double-blind trial of patients with acute MI (0.5-10 days post-MI) complicated by left ventricular systolic dysfunction, heart failure, or both. Enrollment in the study numbered 14,703 patients and followed for a median of 24.7 months. There was no difference in the primary endpoint (all cause mortality) among the 3 groups. There was no difference in incidence of CV death, recurrent MI, or hospitalization for heart failure either. Hypotension and renal dysfunction occurred significantly more often in the valsartan group than captopril alone. Cough, rash, and taste disturbances occurred more often in the captopril group. The authors (Pfeffer MA, 2003) concluded that valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after MI. Combining valsartan with captopril increased the rate of adverse events without improving survival.

Potential Adverse Events: ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. In those patients experiencing cough on an ACE inhibitor, the ACE inhibitor may be discontinued and, if necessary, ARB therapy instituted. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Drug Interactions: Concomitant indomethacin therapy may blunt the reduction in sitting and 24-hour ambulatory diastolic blood pressure. Use of NSAIDs should be avoided or limited, with monitoring of blood pressure control in this setting. In patients with heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

Anesthesia and Critical Care Concerns/Other ConsiderationsA recently completed trial (HOPE), examining the use of ramipril (at a dose of between 2.5-10 mg daily) in patients at high risk for cardiovascular events but who did not have heart failure, documented a significant improvement in cardiovascular outcome in the treated group.

ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. ACE inhibitors are also indicated in patients postmyocardial infarction in whom left ventricular ejection fraction is <40%.

ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

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International Brand NamesAcovil (ES); Altace (VE); Cardace (ID, IN); Corpril (TH); Delix (DE); Heartprilprotect (KP); Hyperil (ID); Hypren (AT); Lostapres (AR); Naprix (BR); Piramil (EE, TH); Pramace (SE); Quark (IT); Ramace (AU, BE, DK, FI, LU, MY, NL, PH, SG, TH); Rameril (KP); Ramicor (PL); Ramipil (KP); Ramipres (CN); Ramiprin (KP); Ramipro (PH); Ramiril (TH); Ramitace (TW); Ramixal (ID); Rampil (ZA); Ramtace (TH); Ruisutan (CL); Triatec (BR, CH, CN, DK, GR, ID, IL, IT, NO, PT, SE); Triateckit (FR); Tritace (AR, AT, AU, BB, BE, BF, BJ, BM, BS, BZ, CI, CR, CZ, DK, DO, EC, ET, GB, GH, GM, GN, GT, GY, HK, HN, HR, HU, IE, JM, KE, KP, LR, LU, MA, ML, MR, MU, MW, MX, NE, NG, NI, NL, PA, PH, PK, PL, PR, PY, SC, SD, SL, SN, SR, SV, TN, TT, TW, TZ, UG, UY, ZA, ZM, ZW); Tritace Protect (KP); Unipril (IT); Vesdil (DE)

Ranibizumab

Lexi-Drugs Online

English

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Pronunciation(ra ni BIZ oo mab)
U.S. Brand NamesLucentis®
Canadian Brand NamesLucentis®
Pharmacologic CategoryAngiogenesis Inhibitor; Monoclonal Antibody; Ophthalmic Agent; Vascular Endothelial Growth Factor (VEGF) Inhibitor
Use: Labeled IndicationsTreatment of neovascular (wet) age-related macular degeneration (AMD)
Dosing: Adults

Age-related macular degeneration (AMD): Intravitreal injection: 0.5 mg (0.05 mL) once a month. **Note:** Frequency may be reduced after the first 4 injections to once every 3 months if monthly injections are not feasible; however, this regimen has reportedly resulted in a ~5 letter (1 line) loss of visual acuity over 9 months, as compared to monthly dosing. Dosing every 3 months will lead to an ~5 letter (1 line) loss of visual acuity over 9 months, as compared to monthly dosing.

Canadian labeling: AMD: Intravitreal injection: 0.5 mg (0.05 mL) once a month. Frequency may be reduced after the first 3 injections to once every 3 months if monthly injections are not feasible.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentDose adjustment not expected.
Dosing: Hepatic ImpairmentDose adjustment not expected.
Administration: OtherFor ophthalmic intravitreal injection only. Remove contents from vial using a 5 micron 19-gauge filter needle attached to a tuberculin syringe. Discard filter needle and replace with a sterile 30 gauge $^{1}/_{2}$ inch needle for injection. Adequate anesthesia and a broad-spectrum antimicrobial agent should be administered prior to the procedure.
StorageStore in original carton under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light. Do not freeze.
ContraindicationsHypersensitivity to ranibizumab or any component of the formulation; ocular or periocular infection

Canadian labeling: Additional contraindications: Active intraocular inflammation

Warnings/Precautions

Concerns related to adverse effects:

- Endophthalmitis/retinal detachment: Intravitreous injections may be associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques should be used and patients should be instructed to report any signs of infection immediately.

- Hypersensitivity reactions: Hypersensitivity may present as severe intraocular inflammation. Rare hypersensitivity reactions (including anaphylaxis) have been associated with another VEGF inhibitor, pegaptanib, occurring within several hours of use; monitor closely. Equipment and appropriate personnel should be available for monitoring and treatment of anaphylaxis.

- Increased intraocular pressure: Following intravitreal injection, intraocular pressure may increase. Onset is seen within 60 minutes.

- Thromboembolic events: Risk of thromboembolic events, particularly stroke, may be increased following intravitreal administration of VEGF inhibitors.

- Visual disturbances: Intravitreal injections of ranibizumab may induce temporary visual disturbances that impair the ability to drive or operate machinery. Affected patients should be advised to abstain from driving or using machinery until resolution of visual disturbances.

Special populations:

- Pediatrics: Safety and efficacy have not been established in patients <18 years of age.

Other warnings/precautions:

- Concurrent therapy (Canadian labeling): Safety and efficacy of ranibizumab administered concurrently to both eyes or in recipients of previous intravitreal injections has not been established.

- Duration of therapy: Use for >24 months has not been evaluated.

Geriatric ConsiderationsIn clinical trials, ~94% of the patients were >65 years and 68% were >75 years of age. No differences were seen in efficacy with increasing age. After correcting for creatinine clearance, age did not affect systemic exposure of ranibizumab.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted. Use during pregnancy only if clearly needed.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions**Note:** Rates of ocular adverse reactions reported for control group when percentages overlapped with treatment group.

>10%:

Central nervous system: Headache (2% to 15%)

Neuromuscular & skeletal: Arthralgia (3% to 11%)

Ocular: Conjunctival hemorrhage (43% to 77%; control: 29% to 66%), eye pain (17% to 37%; control 11% to 33%), vitreous floaters (3% to 32%), intraocular pressure increased (8% to 24%), vitreous detachment (7% to 22%; control 13% to 18%), intraocular inflammation (5% to 18%; control 3% to 11%), eye irritation (4% to 19%; control 6% to 20%), visual disturbance (up to 14%), blepharitis (3% to 13%), retinal disorder (≤13%), retinal degeneration (1% to 11%)

Note: Cataract, foreign body sensation, lacrimation increased, pruritus, and subretinal fibrosis occurred in >10% of patients, but also occurred in similar percentages to the control; visual acuity blurred/decreased occurred more often in the control.

Respiratory: Nasopharyngitis (5% to 16%), upper respiratory tract infection (2% to 15%)

1% to 10%:

Cardiovascular: Arterial thromboembolic events (≤5%; stroke ≤3%), atrial fibrillation (≤5%)

Endocrine & metabolic: Hypercholesterolemia (1% to 8%), diabetes mellitus (≤5%)

Gastrointestinal: Nausea (2% to 9%), viral gastroenteritis ≤5%)

Hematologic: Anemia (3% to 8%; control up to 8%)

Ocular: Conjunctival hyperemia (≤9%), posterior capsule opacification (≤8%), injection site hemorrhage (≤5%), vitreous hemorrhage (≤4%)

Note: Ocular hyperemia, maculopathy, dry eye, and ocular discomfort occurred in 1% to 10% of patients, but also occurred in similar percentages to the control; retinal exudates occurred more often in the control.

Respiratory: Bronchitis (3% to 10%), cough (3% to 10%), sinusitis (2% to 8%), chronic obstructive pulmonary disease (COPD) (≤5%), dyspnea (≤5%)

Miscellaneous: Influenza (2% to 10%), ranibizumab antibodies (1% to 6%), herpes zoster (≤5%)

<1%: Endophthalmitis, iatrogenic traumatic cataracts, retinal tear, rhegmatogenous retinal detachments

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersIntraocular pressure (within 30 minutes and between 2-7 days following administration); retinal perfusion, endophthalmitis

Nursing: Physical Assessment/MonitoringFor ophthalmic intravitreal injection only under controlled aseptic conditions with adequate anesthesia and broad-spectrum antimicrobial agent administered before hand. Patient should be monitored closely at time of injection and for several hours after injections for hypersensitivity reaction (treatment for anaphylactic reaction should be immediately available), for elevation in intraocular pressure and for endophthalmitis. Assess therapeutic effectiveness, and adverse reactions (eg. thromboembolic events, endophthalmitis) on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis medication can only be administered by injection. You will be monitored closely during and following injection procedure. Report immediately any acute eye pain, difficulty breathing or swallowing, chest pain, heart palpitations, or other acute reactions. In the days following injection, you may experience headache (consult prescriber for approved analgesic); mild cough; flu symptoms (consult prescriber if persistent); foreign body sensation; and increased tearing or visual blurring (use caution when driving or engaged in potentially hazardous tasks). Report immediately if your eye becomes red, painful, swollen, sensitive to light, or if there is a change in your vision; report any other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian product availability

Injection, solution [preservative free]:

Lucentis®: 10 mg/mL (0.2 mL)

Lucentis® [CAN]: 10 mg/mL (0.3 mL)

Generic AvailableNo

ManufacturerGenentech, Inc

Mechanism of ActionRanibizumab is a recombinant humanized monoclonal antibody fragment which binds to and inhibits human vascular endothelial growth factor A (VEGF-A). Ranibizumab inhibits VEGF from binding to its receptors and thereby suppressing neovascularization and slowing vision loss.

Pharmacodynamics/Kinetics

Absorption: Low levels are detected in the serum following intravitreal injection

Half-life elimination: Vitreous: ~9 days

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsrhuFabV2

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International Brand Names Lucentis (AR, BE, CH, CZ, DE, DK, EE, ES, FR, GB, HK, ID, IE, IL, KP, MY, NO, NZ, PE, SE, TH)

Ranitidine

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Ranitidine may be confused with amantadine, rimantadine

Zantac® may be confused with Xanax®, Zarontin®, Zofran®, Zyrtec®

International issues:

Antagon®: Brand name for astemizole in Mexico; brand name for ganirelix in the U.S.

Pronunciation(ra NI ti deen)

U.S. Brand NamesZantac 150™ [OTC]; Zantac 75® [OTC]; Zantac®; Zantac® EFFERdose®

Canadian Brand NamesAcid Reducer; Acid Reducer Maximum Strength Non Prescription; Alti-Ranitidine; Apo-Ranitidine®; BCI-Ranitidine; CO Ranitidine; Dom-Ranitidine; Gen-Ranidine; Novo-Ranidine; Nu-Ranit; PMS-Ranitidine; Ranitidine Injection, USP; Ratio-Ranitidine; Rhoxal-Ranitidine; Riva-Ranitidine; Sandoz-Ranitidine; ScheinPharm Ranitidine; Zantac 75®; Zantac Maximum Strength Non-Prescription; Zantac®

Pharmacologic CategoryHistamine H_2 Antagonist

Use: Labeled Indications

Zantac®: Short-term and maintenance therapy of duodenal ulcer, gastric ulcer, gastroesophageal reflux, active benign ulcer, erosive esophagitis, and pathological hypersecretory conditions; as part of a multidrug regimen for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence

Zantac 75® [OTC]: Relief of heartburn, acid indigestion, and sour stomach

Use: Unlabeled/InvestigationalRecurrent postoperative ulcer, upper GI bleeding, prevention of acid-aspiration pneumonitis during surgery, and prevention of stress-induced ulcers

Dosing: Adults

Duodenal ulcer: Oral: Treatment: 150 mg twice daily, or 300 mg once daily after the evening meal or at bedtime; maintenance: 150 mg once daily at bedtime

Eradication of*Helicobacter pylori*: Oral: 150 mg twice daily; requires combination therapy

Pathological hypersecretory conditions:

Oral: 150 mg twice daily; adjust dose or frequency as clinically indicated; doses of up to 6 g/day have been used

I.V.: Continuous infusion for Zollinger-Ellison: 1 mg/kg/hour; measure gastric acid output at 4 hours, if >10 mEq or if patient is symptomatic, increase dose in increments of 0.5 mg/kg/hour; doses of up to 2.5 mg/kg/hour have been used

Gastric ulcer, benign:*Oral:* 150 mg twice daily; maintenance: 150 mg once daily at bedtime

Erosive esophagitis: *Oral:* Treatment: 150 mg 4 times/day; maintenance: 150 mg twice daily

Prevention of heartburn:*Oral:* Zantac 75® [OTC]: 75 mg 30-60 minutes before eating food or drinking beverages which cause heartburn; maximum: 150 mg in 24 hours; do not use for more than 14 days

Patients not able to take oral medication:

I.M.: 50 mg every 6-8 hours

I.V.: Intermittent bolus or infusion: 50 mg every 6-8 hours

Continuous I.V. infusion: 6.25 mg/hour

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Duodenal and gastric ulcer:

Oral: Children 1 month to 16 years:

Treatment: 2-4 mg/kg/day divided twice daily; maximum treatment dose: 300 mg/day

Maintenance: 2-4 mg/kg once daily; maximum maintenance dose: 150 mg/day

I.V.: 2-4 mg/kg/day divided every 6-8 hours; maximum: 200 mg/day

GERD and erosive esophagitis: Children 1 month to 16 years:

Oral: 5-10 mg/kg/day divided twice daily; maximum: GERD: 300 mg/day, erosive esophagitis: 600 mg/day

I.V. (unlabeled): 2-4 mg/kg/day divided every 6-8 hours; maximum: 200 mg/day **or as an alternative**

Continuous infusion: Initial: 1 mg/kg/dose for one dose followed by infusion of 0.08-0.17 mg/kg/hour or 2-4 mg/kg/day

Prevention of heartburn:*Oral:* Children ≥12 years: Zantac 75® [OTC]: 75 mg 30-60 minutes before eating food or drinking beverages which cause heartburn; maximum: 150 mg/24 hours; do not use for more than 14 days

Dosing: Renal ImpairmentAdults: Cl_{cr} <50 mL/minute:

Oral: 150 mg every 24 hours; adjust dose cautiously if needed

I.V.: 50 mg every 18-24 hours; adjust dose cautiously if needed

Hemodialysis: Adjust dosing schedule so that dose coincides with the end of hemodialysis.

Dosing: Hepatic ImpairmentPatients with hepatic impairment may have minor changes in ranitidine half-life, distribution, clearance, and bioavailability; dosing adjustments are not necessary; monitor patient.

Calculations

- Creatinine Clearance: Adults

Administration: I.M.No dilution is needed

Administration: I.V.

Intermittent bolus: Dilute vials to 2.5 mg/mL; infuse at 4 mL/minute (5 minutes)

Intermittent infusion: Dilute vials to 0.5 mg/mL; infuse at 5-7 mL/minute (15-20 minutes)

Continuous I.V. infusion: Administer at 6.25 mg/hour and titrate dosage based on gastric pH by continuous infusion over 24 hours

Administration: I.V. DetailI.V. must be diluted and may be administered IVP or IVPB or continuous I.V. infusion.

pH: 6.7-7.3

Administration: OralEFFERdose®: Should not be chewed, swallowed whole, or dissolved on tongue: 25 mg tablet: Dissolve in at least 5 mL (1 teaspoonful) of water; wait until completely dissolved before administering

Dietary ConsiderationsOral dosage forms may be taken with or without food.

Zantac® EFFERdose®: Effervescent tablet 25 mg contains sodium 1.33 mEq/tablet and phenylalanine 2.81 mg/tablet

Storage

Injection: Vials: Store between 4°C to 30°C (39°F to 86°F). Protect from light. Solution is a clear, colorless to yellow solution; slight darkening does not affect potency. Vials mixed with NS or D_5W are stable for 48 hours at room temperature.

Premixed bag: Store between 2°C to 25°C (36°F to 77°F). Protect from light.

EFFERdose® formulations: Store between 2°C to 30°C (36°F to 86°F).

Syrup: Store between 4°C to 25°C (39°F to 77°F). Protect from light.

Tablets: Store in dry place, between 15°C to 30°C (59°F to 86°F). Protect from light.

ReconstitutionVials can be mixed with NS or D_5W.

Intermittent bolus injection: Dilute to maximum of 2.5 mg/mL.

Intermittent infusion: Dilute to maximum of 0.5 mg/mL.

Compatibility

Stable in $D_5{}^1/_2NS$, D_5W, $D_{10}W$, fat emulsion 10%, LR, NS, sodium bicarbonate 5%; for injection, do not add other medications to premixed bag; **variable compatibility (consult detailed reference)** in D_5LR, TPN.

Y-site administration: Compatible: Acyclovir, aldesleukin, allopurinol, amifostine, aminophylline, amsacrine, atracurium, aztreonam, bretylium, cefazolin, cefepime, cefoperazone, cefoxitin, ceftazidime, ceftizoxime, ciprofloxacin, cisatracurium, cisplatin, cladribine, clarithromycin, cyclophosphamide, cytarabine, diltiazem, dobutamine, docetaxel, dopamine, doxorubicin, doxorubicin liposome, enalaprilat, epinephrine, esmolol, etoposide, fentanyl, filgrastim, fluconazole, fludarabine, foscarnet, furosemide, gatifloxacin, gemcitabine, granisetron, heparin, hydromorphone, idarubicin, labetalol, linezolid, lorazepam, melphalan, meperidine, methotrexate, midazolam, milrinone, morphine, nicardipine, nitroglycerin, norepinephrine, ondansetron, ondansetron with paclitaxel, paclitaxel, pancuronium, piperacillin, piperacillin/tazobactam, procainamide, propofol, remifentanil, sargramostim, tacrolimus, teniposide, theophylline, thiopental, thiotepa, vecuronium, vinorelbine, warfarin, zidovudine. **Incompatible:** Amphotericin B cholesteryl sulfate complex, hetastarch, insulin (regular). **Variable (consult detailed reference):** TPN.

Compatibility in syringe: Compatible: Atropine, cyclizine, dexamethasone sodium phosphate, dimenhydrinate, diphenhydramine, dobutamine, dopamine, fentanyl, glycopyrrolate, hydromorphone, isoproterenol, meperidine, metoclopramide, morphine, nalbuphine, oxymorphone, pentazocine, perphenazine, prochlorperazine edisylate, promethazine, scopolamine, thiethylperazine. **Incompatible:** Hydroxyzine, methotrimeprazine, midazolam, pentobarbital, phenobarbital. **Variable (consult detailed reference):** Chlorpromazine, diazepam, lorazepam.

Compatibility when admixed: Compatible: Acetazolamide, amikacin, aminophylline, ampicillin, chloramphenicol, chlorothiazide, ciprofloxacin, colistimethate, dexamethasone sodium phosphate, digoxin, dobutamine, dopamine, doxycycline, epinephrine, erythromycin lactobionate, floxacillin, fluconazole with ondansetron, flumazenil, furosemide, gentamicin, heparin, isoproterenol, lidocaine, lincomycin, meropenem, methylprednisolone sodium succinate, penicillin G potassium, penicillin G sodium, polymyxin B sulfate, potassium chloride, protamine, quinidine gluconate, sodium nitroprusside, ticarcillin, tobramycin, vancomycin. **Incompatible:** Amphotericin B, atracurium, cefamandole, cefazolin, cefoxitin, ceftazidime, cefuroxime, ethacrynate, metaraminol, phytonadione. **Variable (consult detailed reference):** Clindamycin, insulin (regular), norepinephrine.

ContraindicationsHypersensitivity to ranitidine or any component of the formulation

Allergy Considerations

- Histamine H_2 Antagonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- B_{12} deficiency: Long-term therapy may be associated with vitamin B_{12} deficiency.
- Confusion: Reversible confusional states (rare), usually clearing within 3-4 days after discontinuation, have been linked to use. Increased age (>50 years) and renal or hepatic impairment are thought to be associated.

Disease-related concerns:

- Gastric malignancy: Relief of symptoms does not preclude the presence of a gastric malignancy.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Porphyria: Avoid use in patients with a history of acute porphyria; may precipitate attacks.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Special populations:

- Pediatrics: Safety and efficacy have not been established in infants <1 month of age.

Dosage form specific issues:

- Phenylalanine: EFFERdose® formulation contains phenylalanine.

Geriatric ConsiderationsUlcer healing rates and incidence of adverse effects are similar in the elderly, when compared to younger patients; dosing adjustments not necessary based on age alone. Always adjust dose based upon creatinine clearance. Serum half-life is increased to 3-4 hours in elderly patients. H_2 blockers are the preferred drugs for treating PUD in the elderly due to cost and ease of administration. These agents are no less or more effective than any other therapy. The preferred agents, due to side effects and drug interaction profile and pharmacokinetics are ranitidine, famotidine, and nizatidine. Treatment for PUD in the elderly is recommended for 12 weeks since their lesions are larger; therefore, take longer to heal. This drug is substantially cleared renally, and elderly, having decreased renal function in general, should be monitored closely for adverse effects, especially CNS.

Pregnancy Risk FactorB

Pregnancy ConsiderationsRanitidine crosses the placenta, teratogenic effects to the fetus have not been reported in animal studies. Use with caution during pregnancy.

LactationEnters breast milk/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Atrioventricular block, bradycardia, premature ventricular beats, tachycardia, vasculitis

Central nervous system: Agitation, dizziness, depression, hallucinations, headache, insomnia, malaise, mental confusion, somnolence, vertigo

Dermatologic: Alopecia, erythema multiforme, rash

Endocrine & metabolic: Increased prolactin levels

Gastrointestinal: Abdominal discomfort/pain, constipation, diarrhea, nausea, pancreatitis, vomiting

Hematologic: Acquired hemolytic anemia, agranulocytosis, aplastic anemia, granulocytopenia, leukopenia, pancytopenia, thrombocytopenia

Hepatic: Hepatic failure, hepatitis

Local: Transient pain, burning or itching at the injection site

Neuromuscular & skeletal: Arthralgia, involuntary motor disturbance, myalgia

Ocular: Blurred vision

Renal: Serum creatinine increased

Respiratory: Pneumonia (causal relationship not established)

Miscellaneous: Anaphylaxis, angioneurotic edema, hypersensitivity reactions

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 2C19, 2D6; **Inhibits** CYP1A2 (weak), 2D6 (weak)
Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): H2-Antagonists may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole; Voriconazole. *Risk D: Consider therapy modification*

Atazanavir: H2-Antagonists may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Cefpodoxime: H2-Antagonists may decrease the absorption of Cefpodoxime. Separate oral doses by at least 2 hours. *Risk C: Monitor therapy*

Cefuroxime: H2-Antagonists may decrease the absorption of Cefuroxime. Separate oral doses by at least 2 hours. *Risk C: Monitor therapy*

Dasatinib: H2-Antagonists may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Erlotinib: H2-Antagonists may decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Fosamprenavir: H2-Antagonists may decrease the serum concentration of Fosamprenavir. Cimetidine may also inhibit the metabolism of the active metabolite amprenavir, making its effects on fosamprenavir/amprenavir concentrations difficult to predict. *Risk C: Monitor therapy*

Indinavir: H2-Antagonists may decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Iron Salts: H2-Antagonists may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk C: Monitor therapy*

Mesalamine: H2-Antagonists may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids; H2-antagonists would be expected to interact in a similar manner. *Risk X: Avoid combination*

Nelfinavir: H2-Antagonists may decrease the serum concentration of Nelfinavir. Concentrations of the active M8 metabolite may also be reduced. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Saquinavir: H2-Antagonists may increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause gastric mucosal irritation).

Food: Does not interfere with absorption of ranitidine.

Test InteractionsFalse-positive urine protein using Multistix®, gastric acid secretion test, skin test allergen extracts, serum creatinine, urine protein test
Monitoring ParametersAST, ALT, serum creatinine; when used to prevent stress-related GI bleeding, measure the intragastric pH and try to maintain pH >4; signs and symptoms of peptic ulcer disease, occult blood with GI bleeding, monitor renal function to correct dose; monitor for side effects
Nursing: Physical Assessment/MonitoringUse caution in presence of renal or hepatic impairment. Assess potential for interactions with other pharmacological agents patient may be taking (eg, increased or decreased levels/effects and toxicity). Evaluate results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, bradycardia, PVCs, tachycardia, CNS changes [depression, hallucinations, confusion, malaise], rash, gynecomastia, GI disturbance, hepatic failure). Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsAST, ALT, serum creatinine; when used to prevent stress-related GI bleeding, measure the intragastric pH and try to maintain pH >4; occult blood with GI bleeding; monitor renal function and adjust dosage as indicated.
Patient EducationDo not take any new medication during therapy without consulting prescriber. Take exactly as directed; do not increase dose - may take several days before you notice relief. Allow 1 hour between any other antacids (if approved by prescriber) and ranitidine. Avoid excessive alcohol. Follow diet as prescriber recommends. May cause drowsiness, dizziness, or fatigue (use caution when driving or engaging in tasks requiring alertness until response to drug is known). Report chest pain or irregular heartbeat; skin rash; CNS changes (mental confusion, hallucinations, somnolence); unusual persistent weakness or lethargy; yellowing of skin or eyes; or change in color of urine or stool. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule 150 mg, 300 mg

Infusion [premixed in NaCl 0.45%; preservative free]:

Zantac®: 50 mg (50 mL)

Injection, solution: 25 mg/mL (2 mL, 6 mL)

Zantac®: 25 mg/mL (2 mL, 6 mL, 40 mL) [contains phenol 0.5% as preservative]

Syrup: 15 mg/mL (5 mL, 10 mL, 473 mL)

Zantac®: 15 mg/mL (473 mL) [contains alcohol 7.5%; peppermint flavor]

Tablet: 75 mg [OTC], 150 mg, 300 mg

Zantac®: 150 mg, 300 mg

Zantac 75®: 75 mg

Zantac 150™: 150 mg

Tablet, for solution, oral [effervescent]:

Zantac® EFFERdose®: 25 mg [contains phenylalanine 2.81 mg/tablet, sodium 1.33 mEq/tablet, sodium benzoate]

Generic AvailableYes: Excludes effervescent tablet

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Capsules (Ranitidine HCl)

150 mg (60): $35.99

300 mg (30): $30.99

Syrup (Zantac)

15 mg/mL (300): $224.88

Tablet, effervescent (Zantac EFFERdose)

25 mg (60): $207.92

Tablets (Ranitidine HCl)

150 mg (90): $17.99

300 mg (30): $14.99

Tablets (Zantac)

150 mg (60): $225.43

300 mg (30): $207.93

Tablets (Zantac 75)

75 mg (4): $8.99

75 mg (10): $7.99

75 mg (20): $7.99

75 mg (30): $17.99

75 mg (60): $20.99

Mechanism of ActionCompetitive inhibition of histamine at H_2-receptors of the gastric parietal cells, which inhibits gastric acid secretion, gastric volume, and hydrogen ion concentration are reduced. Does not affect pepsin secretion, pentagastrin-stimulated intrinsic factor secretion, or serum gastrin.

Pharmacodynamics/Kinetics

Absorption: Oral: 50%

Distribution: Normal renal function: V_d: 1.7 L/kg; Cl_{cr} 25-35 mL/minute: 1.76 L/kg minimally penetrates the blood-brain barrier; enters breast milk

Protein binding: 15%

Metabolism: Hepatic to N-oxide, S-oxide, and N-desmethyl metabolites

Bioavailability: Oral: 48%

Half-life elimination:

Oral: Normal renal function: 2.5-3 hours; Cl_{cr} 25-35 mL/minute: 4.8 hours

I.V.: Normal renal function: 2-2.5 hours

Time to peak, serum: Oral: 2-3 hours; I.M.: ≤15 minutes

Excretion: Urine: Oral: 30%, I.V.: 70% (as unchanged drug); feces (as metabolites)

Related Information

- Antacid Drug Interactions

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; concurrent use with diazepam may reduce diazepam's effectiveness

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Ranitidine causes fewer CNS adverse reactions and drug interactions compared to cimetidine.

Evidence-Based Information: The 2008 Surviving Sepsis Campaign guidelines recommend that stress ulcer prophylaxis using an H_2 blocker (Grade 1A) or proton pump inhibitor (Grade 1B) be given to patients with severe sepsis to prevent upper GI bleed. Benefit of prevention of upper GI bleed must be weighed against potential effect of increased stomach pH on development of ventilator-associated pneumonia.

Index TermsRanitidine Hydrochloride

References

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Todd P, Norris P, Hawk JL, et al, “Ranitidine-Induced Photosensitivity,” *Clin Exp Dermatol*, 1995, 20(2):146-8.[PubMed 8565251]

International Brand NamesAceptin (PH); Acidex (AR); Aciflux (CN); Aciloc (BF, BJ, CI, CZ, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Acloral (MX); Aldin (ID, IN); Antagonin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Antak (BR); Apo-Ranitidine (NZ, PL); Arnetin (MY); Artonil (SE); Atural (PE); Ausran (AU); Azantac (FR, MX); Consec (IN); Cudin (KP); Danitin (PH); Eltidine (KP); Eu-Ran (PH); Ezopta (GR); Galidrin (MX); Gastoren (PL); Gastrial (AR); Gastridin (ID); Gastrone (PH); Gastrosedol (AR); Hexal Ranitic (AU); Hexal Ranitic Forte (AU); Hexer (ID); Histac (BF, BJ, CI, ET, GH, GM, GN, HU, IN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, PL, SC, SD, SG, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Histac EVT (MY); Histak (ZA); Huma-Ranidine (HU); Hyzan (HK, SG); Iqfadina (MX); Junizac (DE); Locid (KP); Lydin (IN); Nadine (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Neoceptin-R (SG); Novo-Ranidine (PL); Peptoran (HR); Ponaltin (KP); Ptinolin (GR); Pylorid (HR, HU, LU, PL); R-Loc (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Radinat (EC); Radine (PH); Ragastin (PL); Randin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Rani 2

(AU); Ranial (IN); Raniben (IT); Raniberl (CZ, PL); Ranibeta (AU); Ranic (PL); Ranicux (DE); Ranidil (IT); Ranidin (ES); Ranidine (TH); Raniflux (AU); Ranigasan (PL); Ranigast (PL); Ranihexal (AU); Ranilex (ID); Ranimax (PL); Ranimex (FI); Ranin (ID); Raniplex (FR); Raniratio (PL); Ranisan (AE, BH, CY, CZ, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE); Ranisen (MX); Ranitab (PH); Ranital (CZ, HR, PL); Ranitic (LU); Ranitidin-B (HU); Ranitidine (PL); Ranitin (PL); Ranitine (PL); Ranitydyna (PL); Ranoxyl Heartburn Relief (AU); Rantac (AE, BH, CY, EG, IL, IN, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Rantacid (FI); Rantagon (PL); Rantin (ID); Ratic (TH); Ratinal (ID); Raxide (PH); Ribotine (KP); Riflux (PL); RND (TW); Rolan (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Solvertyl (PL); Sostril (DE); Tanidina (ES); Taural (AR); Tricker-150 (ID); Ulcaid (ZA); Ulceran (HU, PE); Ulceranin (ID); Ulcerit (BR); Ulcex (IT); Ulcin (PH); Ulcodin (HR); Ulcosan (CZ); Ulran (PL); Ulsal (AT); Ulticer (HK); Ultran (PH, PL); Umaren (HU); Utac (TH); Verlost (GR); Vizerul (AR); Weichilin (TW); Weidos (TW); X'Tac (MY); Xanidine (SG, TH); Xanomel (HU); Zantac (AE, AU, BB, BE, BF, BG, BH, BJ, BM, BS, BZ, CI, CL, CO, CR, CY, CZ, DK, DO, EE, EG, ET, FI, GB, GH, GM, GN, GR, GT, GY, HK, HN, HU, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PK, PL, PT, PY, QA, SA, SC, SD, SE, SL, SN, SR, SV, SY, TH, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Zantadin (ID); Zantic (CH, DE); Zendhin (HK, MY); Zerdin (PH); Zinetac (IN)

Ranolazine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Ranexa™ may be confused with Celexa®

Pronunciation(ra NOE la zeen)
U.S. Brand NamesRanexa®
Pharmacologic CategoryCardiovascular Agent, Miscellaneous
Use: Labeled IndicationsTreatment of chronic angina
Dosing: Adults

Chronic angina: Oral: Initial: 500 mg twice daily; maximum recommended dose: 1000 mg twice daily

Dosage adjustment for ranolazine with concomitant medications:

Diltiazem, verapamil, and other moderate CYP3A inhibitors: Dose should not exceed 500 mg twice daily

P-glycoprotein inhibitors (eg, cyclosporine): Down-titrate ranolazine based on clinical response

Dosing: ElderlyRefer to adult dosing. Select dose cautiously, starting at the lower end of the dosing range.
Dosing: Renal ImpairmentDosage adjustment recommendations have not been established. However, plasma ranolazine levels increased ~50% in patients with varying degrees of renal dysfunction. Patients with severe renal dysfunction had an increase in mean diastolic blood pressure of 10-15 mm Hg. Monitor blood pressure closely in these patients. Ranolazine has not been evaluated in patients requiring dialysis.
Dosing: Hepatic ImpairmentUse with caution in patients with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment. Use is contraindicated with clinically significant hepatic impairment.
Administration: OralMay be taken with or without meals. Swallow tablet whole; do not crush, break, or chew.
Dietary ConsiderationsMay be taken with or without food.
StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
ContraindicationsClinically significant hepatic impairment; concurrent strong CYP3A inhibitors; concurrent inducers of CYP3A
Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: Has been shown to prolong QT interval in a dose/plasma concentration-related manner. Hepatically-impaired patients may have a more significant increase in QT interval. The incidence of symptomatic arrhythmias was similar to placebo in one trial (Morrow, 2007).

Disease-related concerns:

- Acute angina: Ranolazine does not relieve acute angina attacks.

- Hepatic impairment: Ranolazine plasma levels increase by 30% in patients with mild (Child-Pugh class A) and by 60% in patients with moderate (Child-Pugh class B) hepatic impairment. Use is contraindicated with clinically significant hepatic impairment.

- Renal impairment: Use with caution in patients with renal dysfunction; plasma levels may increase by 50%. With severe impairment, an elevation in diastolic blood pressure (15 mm Hg) may be observed. Monitor blood pressure in patients with renal dysfunction. Ranolazine has not been evaluated in patients requiring dialysis.

Concurrent drug therapy issues:

- High potential for interactions: Ranolazine is primarily metabolized by CYP3A; use is contraindicated with inducers and strong inhibitors of CYP3A.

- P-glycoprotein inhibitors/substrates: Ranolazine is a substrate for and a moderate inhibitor of P-glycoprotein. Inhibitors of P-glycoprotein may increase serum concentrations of ranolazine. Ranolazine may increase serum concentrations of substrates for P-glycoprotein (eg, digoxin).

- QT-prolonging drugs: Ranolazine has potential to prolong the QT interval; use caution when administered concomitantly with QT-prolonging drugs.

Special populations:

- Elderly: Use with caution in patients ≥75 years of age; they may experience more adverse events (eg, constipation, dizziness, nausea) than younger patients.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Tumorigenesis: In APC$^{(Min/+)}$ mice, an established model of spontaneous intestinal tumorigenesis, ranolazine was shown to have a dose-dependent increase in the number of intestinal tumors. Clinical significance of this effect in humans is unknown. However, use caution when administering ranolazine to patients with a history of malignant neoplasms or adenomatous polyps.

Geriatric ConsiderationsElderly comprised 48% of study group participants. For those elderly, no overall difference in efficacy was observed between younger and older adults. There was, however, a higher incidence of adverse effects for those ≥75 years of age, resulting in drug discontinuations. The most common adverse effects were constipation (19%), nausea (6%), and dizziness (6%). Therefore, start dosing at lower end of dosing range recommended.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse effects were observed in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

>10%:

Central nervous system: Dizziness (5% to 13%; dose related)

Gastrointestinal: Constipation (5% to 8%; 19% in the elderly)

>0.5% to 10%:

Cardiovascular: Syncope (≤3%), bradycardia (≤2%), hypotension (≤2%), orthostatic hypotension (≤2%), palpitation (≤2%), peripheral edema (≤2%), QT$_c$ prolongation (>500 msec: ≤1%)

Central nervous system: Headache (3% to 6%), vertigo (≤2%)

Gastrointestinal: Nausea (4% to 9%), abdominal pain (≤2%), vomiting (≤2%), xerostomia (≤2%)

Hematologic: Hematocrit decreased (1%)

Otic: Tinnitus (≤2%)

Respiratory: Dyspnea (≤2%)

≤0.5%: Angioedema, blood pressure increased, blurred vision, confusion, eosinophilia, hemoglobin A$_{1c}$ decreased, hematuria, hypoesthesia, leukopenia, pancytopenia, paresthesia, pulmonary fibrosis, renal failure, serum creatinine increased, thrombocytopenia, T-wave amplitude decreased, T-wave changes (notched), torsade de pointes (case report [Morrow, 2007]), tremor, weakness

Metabolism/Transport Effects**Substrate** of CYP3A4 (major), 2D6 (minor), P-glycoprotein; **Inhibits** CYP3A4 (weak), 2D6 (moderate), P-glycoprotein

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Ranolazine. *Risk X: Avoid combination*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Ranolazine. *Risk X: Avoid combination*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

CYP3A4 Inhibitors (Moderate): May increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Digoxin: Ranolazine may increase the serum concentration of Digoxin. *Risk C: Monitor therapy*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Rifampin: May decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Simvastatin: Ranolazine may increase the serum concentration of Simvastatin. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: Limit the use of grapefruit, grapefruit juice, or grapefruit-containing products; if use is significant and consistent, the dose of ranolazine should be limited to 500 mg twice daily.

Monitoring ParametersBaseline and follow up ECG to evaluate QT interval; blood pressure in patients with renal dysfunction; correct and maintain serum potassium in normal limits

Nursing: Physical Assessment/MonitoringAssess other prescription and OTC medications patient may be taking to avoid duplications and interactions. Stress that this medication is not intended to treat an acute angina episode. Instruct them in appropriate measures to take if an acute episode occurs. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Monitoring: Lab TestsBaseline and follow up ECG to evaluate QT interval; correct and maintain serum potassium in normal limits

Patient EducationThis medication is not intended to be used to treat an acute angina episode. Follow instructions provided by prescriber for acute management. Swallow tablets whole; do not crush, break, or chew the tablets. Avoid grapefruit juice or grapefruit products while taking this medication. You may experience dizziness, lightheadedness (use caution when driving or engaging in activities requiring alertness until response to drug is known), or constipation (increasing exercise, fluids, fruit/fiber may help). Report palpitations, fainting spells, or chest pain that does not respond to recommended interventions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, extended release:

Ranexa®: 500 mg, 1000 mg

Generic AvailableNo

ManufacturerCV Therapeutics

Pricing: U.S. (www.drugstore.com)

Tablet, 12-hour (Ranexa)

500 mg (60): $211.49

1000 mg (60): $325.54

Mechanism of ActionRanolazine exerts antianginal and anti-ischemic effects without changing hemodynamic parameters (heart rate or blood pressure). At therapeutic levels, ranolazine inhibits the late phase of the inward sodium channel (late I_{Na}) in ischemic cardiac myocytes during cardiac repolarization reducing intracellular sodium concentrations and thereby reducing calcium influx via Na^+-Ca^{2+} exchange. Decreased intracellular calcium reduces ventricular tension and myocardial oxygen consumption. It is thought that ranolazine produces myocardial relaxation and reduces anginal symptoms through this mechanism although this is uncertain. At higher concentrations, ranolazine inhibits the rapid delayed rectifier potassium current (I_{Kr}) thus prolonging the ventricular action potential duration and subsequent prolongation of the QT interval.

Pharmacodynamics/Kinetics

Absorption: Highly variable; ranolazine is a substrate of P-glycoprotein; concurrent use of P-glycoprotein inhibitors may increase absorption

Protein binding: ~62%

Metabolism: Hepatic via CYP3A (major) and 2D6 (minor); gut

Bioavailability: 35% to 55%

Half-life elimination: Terminal: 7 hours

Time to peak, plasma: 2-5 hours

Excretion: Primarily urine (75% mostly as metabolites); feces (25% mostly as metabolites); in feces and urine, <5% to 7% excreted unchanged

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsRanolazine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentContraindicated with QT_c-prolonging agents including amitriptyline, chlorpromazine, domperidone, droperidol, fluoxetine, flupenthixol, haloperidol, imipramine, loxapine, mesoridazine, pimozide, quetiapine, thioridazine, thiothixene, ziprasidone, and zuclopenthixol. Also contraindicated with strong or moderate CYP3A4 inhibitors such as nefazodone. Carbamazepine may reduce the levels and/or effects of ranolazine.

Cardiovascular Considerations

The relationship between the change in corrected QT and ranolazine plasma concentration is linear with a slope of ~2.6 msec per 1000 ng/mL ranolazine. At T_{max} following repeat dosing at 1000 mg twice daily, the mean change in QT_c is ~6 msec, but 5% of the population (with the highest plasma concentrations) has at least a 15 msec increase. Avoid concurrent use of drugs with QT_c-prolonging potential and drugs that inhibit ranolazine metabolism (CYP3A4 inhibitors).

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Rasagiline

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Azilect® may be confused with Aricept®

Pronunciation(ra SA ji leen)

U.S. Brand NamesAzilect®

Pharmacologic CategoryAnti-Parkinson's Agent, MAO Type B Inhibitor

Use: Labeled IndicationsInitial monotherapy or as adjunct to levodopa in the treatment of idiopathic Parkinson's disease

Dosing: Adults**Parkinson's disease:** Oral:

Monotherapy: 1 mg once daily

Adjunctive therapy with levodopa: Initial: 0.5 mg once daily; may increase to 1 mg once daily based on response and tolerability

Note: When added to existing levodopa therapy, a dose reduction of levodopa may be required to avoid exacerbation of dyskinesias; typical dose reductions of ~9% to 13% were employed in clinical trials.

Dose reduction with concomitant ciprofloxacin or other CYP1A2 inhibitors: 0.5 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Mild impairment: No adjustment necessary.

Moderate-to-severe impairment: No data available.

Dosing: Hepatic Impairment

Mild impairment (Child-Pugh ≤6): 0.5 mg once daily

Moderate-to-severe impairment: Not recommended.

Dietary ConsiderationsAvoid tyramine-containing foods/beverages. Some examples include aged or matured cheese, air-dried or cured meats (including sausages and salamis), fava or broad bean pods, tap/draft beers, Marmite concentrate, sauerkraut, soy sauce and other soybean condiments.

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to rasagiline or any component of the formulation; concomitant use of amphetamine, tramadol, propoxyphene, methadone, dextromethorphan, St John's wort, mirtazapine, cyclobenzaprine, or sympathomimetic amines (eg, pseudoephedrine, ephedrine); use of meperidine or other MAO inhibitor within 14 days of rasagiline; elective surgery requiring general anesthesia, local anesthesia containing sympathomimetic vasoconstrictors; patients with pheochromocytoma

Allergy Considerations

- Rasagiline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause hallucinations; signs of severe CNS toxicity (some fatal), including hyperpyrexia, hyperthermia, rigidity, altered mental status, seizure and coma have been reported in combination with antidepressants.
- Melanoma: Risk of melanoma may be increased with rasagiline, although increased risk has been associated with Parkinson's disease itself; patients should have regular and frequent skin examinations.
- Orthostatic hypotension: May cause orthostatic hypotension, particularly in combination with levodopa; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with mild hepatic impairment; dose reduction recommended. Avoid with moderate to severe impairment.

Concurrent drug therapy issues:

- Antidepressants: Use of rasagiline with tricyclic antidepressants and SSRIs has also been associated with rare reactions and should generally be avoided. Do not use within 5 weeks of fluoxetine discontinuation; do not initiate tricyclic, SSRI or SNRI therapy within 2 weeks of discontinuing rasagiline.

- Levodopa: Addition of oral selegiline to levodopa therapy may result in exacerbation of levodopa adverse effects, requiring a reduction in levodopa dosage.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Elective surgery: Due to the potential for hemodynamic instability, patients should not undergo elective surgery requiring general anesthesia and should avoid local anesthesia containing sympathomimetic vasoconstrictors within 14 days of discontinuing rasagiline. If surgery is required, benzodiazepines, mivacurium, fentanyl, morphine or codeine may be used cautiously.

- Tyramine-containing products: Use caution with foods high in tyramine content, supplements containing tyrosine, phenylalanine, tryptophan, or caffeine; hypertensive crisis may occur; avoid for at least 2 weeks following discontinuation of rasagiline.

Geriatric ConsiderationsIn clinical trials, no significant differences in the safety profile were seen between elderly and younger adults.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies have documented decreased offspring survival and birth weight. An increased incidence of teratogenic effects, embryo-fetal deaths, and cardiovascular abnormalities were also noted with rasagiline in combination with levodopa/carbidopa. There are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsAnimal studies have shown rasagiline is capable of inhibiting prolactin secretion.
Adverse ReactionsUnless otherwise noted, the following adverse reactions are as reported for monotherapy. Spectrum of adverse events was generally similar with adjunctive (levodopa) therapy, though the incidence tended to be higher.

>10%:

Central nervous system: Dyskinesia (18% adjunct therapy), headache (14%)

Gastrointestinal: Nausea (10% to 12% adjunct therapy)

1% to 10%:

Cardiovascular: Postural hypotension (6% to 9% adjunct therapy; dose dependent), bundle branch block angina, chest pain, syncope

Central nervous system: Depression (5%), hallucinations (4% to 5% adjunct therapy), fever (3%), malaise (2%), vertigo (2%), anxiety, dizziness

Dermatologic: Bruising (2%), alopecia, skin carcinoma, vesiculobullous rash

Endocrine & metabolic: Impotence, libido decreased

Gastrointestinal: Constipation (4% to 9% adjunct therapy), weight loss (2% to 9% adjunct therapy; dose dependent), dyspepsia (7%), xerostomia (2% to 6% adjunct therapy; dose dependent), gastroenteritis (3%), anorexia, diarrhea, gastrointestinal hemorrhage, vomiting

Genitourinary: Hematuria, urinary incontinence

Hematologic: Leukopenia

Hepatic: Liver function tests increased

Neuromuscular & skeletal: Arthralgia (7%), neck pain (2%), arthritis (2%), paresthesia (2%), abnormal gait, hyperkinesias, hypertonia, neuropathy, tremor, weakness

Ocular: Conjunctivitis (3%)

Renal: Albuminuria

Respiratory: Rhinitis (3%), asthma, cough increased

Miscellaneous: Fall (5%), flu-like syndrome (5%), allergic reaction

<1% (Limited to important or life-threatening): Acute kidney failure, aphasia, apnea, atrial arrhythmia, bigeminy, blepharitis, blindness, bone necrosis, cerebral hemorrhage, cerebral ischemia, circumoral paresthesia, deafness, deep thrombophlebitis, delirium, diplopia, dysautonomia, dysesthesia, emphysema, esophageal ulcer, exfoliative dermatitis, facial paralysis, glaucoma, gynecomastia, heart failure, hematemesis, hemiplegia, hemorrhage (various locations), hostility, hypocalcemia, incoordination, interstitial pneumonia, intestinal obstruction, intestinal perforation, intestinal stenosis, jaundice, keratitis, kidney calculus, large intestine perforation, laryngismus, larynx edema, leukoderma, leukorrhea, lung fibrosis, macrocytic anemia, manic depressive reaction, mania, megacolon, menstrual abnormalities, MI, muscle atrophy, myelitis, neuralgia, neuritis, neurosis, nocturia, paranoid reaction, parosmia, personality disorder, pleural effusion, pneumothorax, polyuria, psychosis, psychotic depression, ptosis, purpura, retinal degeneration, retinal detachment, seizure, stomach ulcer, strabismus, stupor, thrombocythemia, thrombosis, tongue edema, urinary disorders, vaginal moniliasis, ventricular fibrillation, ventricular tachycardia, vestibular disorder, visual field defect

Metabolism/Transport Effects**Substrate** of CYP1A2 (major)
Drug Interactions

Alpha-/Beta-Agonists (Direct-Acting): MAO Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists (Indirect-Acting): MAO Inhibitors may enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Alpha1-Agonists: MAO Inhibitors may enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Alpha2-Agonists (Ophthalmic): MAO Inhibitors may enhance the hypertensive effect of Alpha2-Agonists (Ophthalmic). *Risk X: Avoid combination*

Altretamine: May enhance the orthostatic effect of MAO Inhibitors. *Risk C: Monitor therapy*

Amphetamines: MAO Inhibitors may enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Anilidopiperidine Opioids: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. *Risk D: Consider therapy modification*

Atomoxetine: MAO Inhibitors may enhance the neurotoxic (central) effect of Atomoxetine. *Risk X: Avoid combination*

Beta2-Agonists: MAO Inhibitors may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: MAO Inhibitors may enhance the neurotoxic (central) effect of BuPROPion. *Risk X: Avoid combination*

BusPIRone: May enhance the adverse/toxic effect of MAO Inhibitors. Elevated blood pressure has been reported. *Risk X: Avoid combination*

COMT Inhibitors: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Cyclobenzaprine: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Dexmethylphenidate: MAO Inhibitors may enhance the hypertensive effect of Dexmethylphenidate. *Risk X: Avoid combination*

Dextromethorphan: MAO Inhibitors may enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

Levodopa: May enhance the adverse/toxic effect of MAO Inhibitors. Of particular concern is the development of hypertensive reactions when levodopa is used with nonselective MAOI. *Risk D: Consider therapy modification*

Linezolid: MAO Inhibitors may enhance the adverse/toxic effect of Linezolid. *Risk X: Avoid combination*

Lithium: MAO Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Maprotiline: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

Meperidine: MAO Inhibitors may enhance the serotonergic effect of Meperidine. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methyldopa: MAO Inhibitors may enhance the adverse/toxic effect of Methyldopa. *Risk X: Avoid combination*

Methylphenidate: MAO Inhibitors may enhance the hypertensive effect of Methylphenidate. *Risk X: Avoid combination*

Mirtazapine: MAO Inhibitors may enhance the neurotoxic (central) effect of Mirtazapine. *Risk X: Avoid combination*

Propoxyphene: May enhance the adverse/toxic effect of MAO Inhibitors. Specifically, the risk of serotonin syndrome or other serotonergic adverse events may be increased. *Risk X: Avoid combination*

Rauwolfia Alkaloids: MAO Inhibitors may enhance the adverse/toxic effect of Rauwolfia Alkaloids. Existing MAOI therapy can result in paradoxical effects of added rauwolfia alkaloids (eg, excitation, hypertension). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: MAO Inhibitors may decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. **Exceptions:** Eletriptan; Frovatriptan; Naratriptan. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tetrabenazine: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

TraMADol: May enhance the neuroexcitatory and/or seizure-potentiating effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: MAO Inhibitors may enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol. Avoid beverages containing tyramine (hearty red wine and beer).

Food: Concurrent ingestion of foods rich in tyramine may cause sudden and severe high blood pressure (hypertensive crisis). Avoid tyramine-containing foods with MAO-Is. Food's freshness is also an important concern; improperly stored or spoiled food can create an environment where tyramine concentrations may increase.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava (may increase risk of serotonin syndrome and/or excessive sedation); Avoid supplements containing caffeine, tyrosine, tryptophan, or phenylalanine. Ingestion of large quantities may increase the risk of severe side effects (eg, hypertensive reactions, serotonin syndrome).

Monitoring ParametersBlood pressure; symptoms of parkinsonism; general mood and behavior (increased anxiety, or presence of mania or agitation); skin examination for presence of melanoma (higher incidence in Parkinson's patients- drug causation not established)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness according to rationale for therapy and adverse reactions at beginning of therapy and periodically throughout therapy. Monitor blood pressure. Be alert to thoughts of suicide. Patient should be cautioned against eating foods high in tyramine (see Tyramine Contents of Foods list). Increased risk for melanoma exists. Do skin exam periodically. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed (may be prescribed in conjunction with levodopa/carbidopa); do not change dosage or discontinue without consulting prescriber. Therapeutic effects may take several weeks or months to achieve and you may need frequent monitoring during first weeks of therapy. Take with meals if GI upset occurs, before meals if dry mouth occurs, or after eating if drooling or if nausea occurs. Take at the same time each day. Avoid tyramine-containing foods and for two weeks once the medication had been stopped. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol and prescription or OTC sedatives or CNS depressants without consulting prescriber. You may experience drowsiness, dizziness, confusion, or vision changes (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); orthostatic hypotension (use caution when changing position - rising to standing from sitting or lying); constipation (increased exercise, fluids, fruit, or fiber may help); runny nose or flu-like symptoms (consult prescriber for appropriate relief); or nausea, vomiting, loss of appetite, or stomach discomfort (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). You are at an increased risk of melanoma. Have skin monitored by a qualified professional. Report any skin changes or suspicious areas. Report unresolved constipation or vomiting; chest pain, palpitations, irregular heartbeat; CNS changes (hallucination, loss of memory, seizures, acute headache, nervousness, thoughts of suicide, etc); painful or difficult urination; increased muscle spasticity, rigidity, or involuntary movements; skin rash; or significant worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Azilect®: 0.5 mg, 1 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Azilect)

0.5 mg (30): $297.81

1 mg (30): $284.66

Mechanism of ActionPotent, irreversible and selective inhibitor of brain monoamine oxidase (MAO) type B, which plays a major role in the catabolism of dopamine. Inhibition of dopamine depletion in the striatal region of the brain reduces the symptomatic motor deficits of Parkinson's disease. There is also experimental evidence of rasagiline conferring neuroprotective effects (antioxidant, antiapoptotic), which may delay onset of symptoms and progression of neuronal deterioration.

Pharmacodynamics/Kinetics

Onset of action: Therapeutic: Within 1 hour

Duration: ~1 week (irreversible inhibition); may require ~14-40 days for complete restoration of (brain) MAO-B activity

Absorption: Rapid

Protein binding: 88% to 94%

Metabolism: Hepatic N-dealkylation and/or hydroxylation via CYP1A2 to multiple inactive metabolites (nonamphetamine derivatives)

Distribution: V_{dss}: 87 L

Bioavailability: 36%

Half-life elimination: ~1.3-3 hours (no correlation with biologic effect due to irreversible inhibition)

Time to peak, plasma: 30 minutes to 1 hour

Excretion: Urine (62%, >99% as metabolites); feces (7%)

Related Information

- Antiparkinsonian Agents
- Tyramine Content of Foods

Pharmacotherapy PearlsWhen adding rasagiline to levodopa/carbidopa, the dose of the latter can usually be decreased. Studies are investigating the use of rasagiline in early Parkinson's disease to slow the progression of the disease.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation). Anticholinergic side effects can cause a reduction of saliva production or secretion, contributing to discomfort and dental disease (ie, caries, oral candidiasis, and periodontal disease). May cause orthostatic hypotension particularly during the first 2 months of therapy.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsRasagiline in approved doses of 0.5-1 mg daily should not inhibit type-A MAO; however, the possibility exists of nonselective MAO inhibition at higher doses and/or in certain sensitive individuals. Therefore, attempts should be made to avoid use of vasoconstrictors due to possibility of hypertensive episodes.

Mental Health Comment

Adverse effects: Rasagiline is a second generation MAO type B selective inhibitor derived from the propargylamine class of compounds from which selegiline originates. However, unlike selegiline, the parent structure of rasagiline is not an amphetamine derivative, nor is it metabolized to an amphetamine-like structure. This structural difference may differentiate rasagiline from selegiline in terms of an overall lower incidence of psychiatric and vasoactive side effects (eg, hallucinations, orthostasis).

Selective MAO inhibition: Comparable to selegiline, rasagiline has been shown in both *in vitro* and *in vivo* animal model investigations to inhibit MAO-B (by 50%) approximately 17- to 65-fold more selectively than MAO-A. However, >80% inhibition of MAO-B is regarded as necessary for therapeutic benefit. As selectivity is lost in a dose-dependent manner, higher dosages needed to achieve this target may compromise selectivity. *In vivo* animal data show that ≥80% inhibition of MAO-B was achieved by rasagiline doses in rats which were 10-fold higher than the therapeutic human dose (on a mg/kg basis). At this dose level, rasagiline retained nearly fourfold selectivity for MAO-B. The extent of selectivity for MAO-B given higher doses and/or extended durations of exposure in humans is not known. Given the lack of clinical data fully characterizing the effects of rasagiline on gut MAO-A activity at therapeutically effective doses, there remains a warning on the dietary consumption of tyramine-containing foods.

Anesthesia and Critical Care Concerns/Other ConsiderationsWhen adding rasagiline to levodopa/carbidopa, the dose of the latter can usually be decreased. Studies are investigating the use of rasagiline in early Parkinson's disease to slow the progression of the disease.

Index TermsAGN 1135; Rasagiline Mesylate; TVP-1012

References

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International Brand NamesAzilect (AR, AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IL, IT, NL, NO, PT, RU, SE, TR)

Rasburicase

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ras BYOOR i kayse)

U.S. Brand NamesElitek™

Canadian Brand NamesFasturtec®

Pharmacologic CategoryEnzyme; Enzyme, Urate-Oxidase (Recombinant)

Use: Labeled IndicationsInitial management of uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies receiving anticancer therapy expected to result in tumor lysis and elevation of plasma uric acid

Use: Unlabeled/InvestigationalPrevention and treatment of malignancy-associated hyperuricemia in adults

Dosing: Adults**Management of malignancy-associated hyperuricemia** (unlabeled use): 0.2 mg/kg/day for 3-7 days, beginning the day before or day of chemotherapy **or** 0.15-0.2 mg/kg as a single dose, repeated if needed based on uric acid levels **or** 3-6 mg as a single dose, repeated (1.5-6 mg) if needed based on uric acid levels

Dosing: ElderlyRefer to adult dosing. Insufficient data collected in geriatric patients to determine response to treatment.

Dosing: Pediatric

Management of uric acid levels: I.V.: Children: 0.15 mg/kg or 0.2 mg/kg once daily for 5 days (manufacturer-recommended duration); begin chemotherapy 4-24 hours after the first dose

Note: Limited data suggest that a single prechemotherapy dose (versus multiple-day administration) may be sufficiently efficacious. Monitoring electrolytes, hydration status, and uric acid concentrations are necessary to identify the need for additional doses. Other clinical manifestations of tumor lysis syndrome (eg, hyperphosphatemia, hypocalcemia, and hyperkalemia) may occur.

Administration: I.V.I.V. infusion over 30 minutes; do **not** administer as a bolus infusion. Do **not** filter during infusion. If not possible to administer through a separate line, I.V. line should be flushed with at least 15 mL saline prior to and following rasburicase infusion.

StoragePrior to reconstitution, store with diluent at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Reconstituted and final solution may be stored up to 24 hours at 2°C to 8°C (36°F to 46°F). Discard unused product.

ReconstitutionReconstitute each vial with 1 mL of the provided diluent. Mix by gently swirling; do **not** shake or vortex. Discard if discolored or containing particulate matter. Total dose should be further diluted in NS to a final volume of 50 mL.

ContraindicationsHypersensitivity, hemolytic or methemoglobinemia reactions to rasburicase or any component of the formulation; glucose-6-phosphatase dehydrogenase (G6PD) deficiency

Warnings/Precautions

Boxed warnings:

- Anaphylaxis/hypersensitivity reactions: See “Concerns related to adverse effects” below.
- Hemolysis: See “Concerns related to adverse effects” below.
- Methemoglobinemia: See “Concerns related to adverse effects” below.
- Uric acid degradation: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: **[U.S. Boxed Warning]: Hypersensitivity reactions (including anaphylaxis) have been reported;** reactions may occur at any time during treatment (including the initial dose); discontinue **immediately and permanently** in patients developing any of these reactions.
- Hemolysis: **[U.S. Boxed Warning]: Hemolysis may be associated with G6PD deficiency; patients at higher risk for G6PD deficiency should be screened prior to therapy.** Use is contraindicated in patients with G6PD deficiency.
- Methemoglobinemia: **[U.S. Boxed Warning]: Discontinue immediately and permanently in any patient developing methemoglobinemia.**

Other warnings/precautions:

- Multiple courses: Rasburicase is immunogenic and can elicit an antibody response; administration of more than one course is not recommended.
- Uric acid degradation: **[U.S. Boxed Warning]: Enzymatic degradation of uric acid in blood samples will occur if left at room temperature;** specific guidelines for the collection of plasma uric acid samples must be followed.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsAs reported in patients receiving rasburicase with antitumor therapy versus active-control:

>10%:

- Central nervous system: Fever (5% to 46%), headache (26%)
- Dermatologic: Rash (13%)
- Gastrointestinal: Vomiting (50%), nausea (27%), abdominal pain (20%), constipation (20%), diarrhea (≤1% to 20%), mucositis (2% to 15%)

1% to 10%:

- Hematologic: Neutropenia with fever (4%), neutropenia (2%)
- Respiratory: Respiratory distress (3%)
- Miscellaneous: Sepsis (3%)

<1%: Acute renal failure, anaphylaxis, arrhythmia, cardiac arrest, cardiac failure, cellulitis, cerebrovascular disorder, chest pain, convulsions, cyanosis, dehydration, hemolysis, hemorrhage, hot flashes, ileus, infection, intestinal obstruction, methemoglobinemia, MI, pancytopenia, paresthesia, pneumonia, pulmonary edema, pulmonary hypertension, retinal hemorrhage, rigors, thrombosis, thrombophlebitis

Drug InteractionsThere are no known significant interactions.

Test InteractionsSpecific handling procedures must be followed to prevent the degradation of uric acid in plasma samples. Blood must be collected in prechilled tubes containing heparin anticoagulant. Samples must then be **immediately** immersed in an ice water bath. Prepare samples by centrifugation in a precooled centrifuge (4°C). Samples must be kept in ice water bath and analyzed within 4 hours of collection.

Monitoring ParametersPlasma uric acid levels, CBC

Nursing: Physical Assessment/MonitoringSee I.V. Administration for specifics. Patient must be observed closely for hypersensitivity reaction (which can occur within minutes of administration). Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions prior to initiating therapy and on a regular basis throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Patient EducationThis medication can only be administered by infusion; you will be monitored closely during and following infusion. Report immediately any pain, burning, swelling at infusion site, or any signs of allergic reaction (eg, respiratory difficulty or swallowing, back pain, chest tightness, rash, hives, swelling of lips or mouth). Report headache, nausea, or respiratory difficulty.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

- Elitek™: 1.5 mg [packaged with three 1 mL ampuls of diluent]; 7.5 mg [packaged with 5 mL of diluent]

Generic AvailableNo

ManufacturerSanofi-Synthelabo, Inc

Mechanism of ActionRasburicase is a recombinant urate-oxidase enzyme, which converts uric acid to allantoin (an inactive and soluble metabolite of uric acid); it does not inhibit the formation of uric acid.

Pharmacodynamics/Kinetics

Distribution: Pediatric patients: 110-127 mL/kg

Half-life elimination: Pediatric patients: 18 hours

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; use caution with SSRIs. May cause neutropenia; use caution with clozapine.

Index TermsNSC-721631; Recombinant Urate Oxidase

References

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International Brand NamesFasturtec (AT, AU, BE, BG, BR, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IT, KP, NL, NO, PL, PT, RU, SE, SG, TR, TW, VE)

Regadenoson

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(re ga DEN of son)

U.S. Brand NamesLexiscan™

Pharmacologic CategoryDiagnostic Agent

Use: Labeled IndicationsRadionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress testing

Dosing: Adults**Myocardial perfusion imaging:** I.V.: 0.4 mg (5 mL) over ~10 seconds, followed immediately by a 5 mL saline flush. Wait 10-20 seconds, then administer the radionuclide myocardial perfusion imaging agent.

Dosing: ElderlyRefer to adult dosing.

Administration: I.V.Administer over approximately 10 seconds into a peripheral vein using a 22-gauge or larger catheter or needle, followed immediately by a 5 mL saline flush. Wait 10-20 seconds, then administer the radionuclide myocardial perfusion imaging agent. The radionuclide may be injected directly into the same catheter as regadenoson.

Dietary ConsiderationsAvoid dietary caffeine for at least 12 hours prior to pharmacologic stress testing.

StorageStore at controlled room temperature of 25°C (77°F).

Warnings/Precautions

Concerns related to adverse events:

- Myocardial ischemia: Pharmacological stress agents may produce myocardial ischemia resulting in life threatening ventricular arrhythmias, MI, and cardiac arrest. Equipment for resuscitation and trained personnel experienced in handling cardiac emergencies should always be immediately available prior to administration. If serious reactions occur, consider the use of aminophylline, an adenosine antagonist.

- Conduction disturbances: Regadenoson depresses SA and AV node conduction and may produce first-, second-, third-degree heart block, or sinus bradycardia. Use caution in patients with first-degree AV block or bundle branch block. Functional pacemaker must be in place to use in patients with second- or third-degree AV block or sinus node dysfunction.

- Hypotension: May produce profound vasodilation with subsequent hypotension especially in the elderly. Use with caution in patients with autonomic dysfunction, carotid stenosis (with cerebrovascular insufficiency), uncorrected hypovolemia, left main coronary artery stenosis, pericarditis, pericardial effusion and/or stenotic valvular heart disease.

Disease-related concerns:

- Respiratory disease: Regadenoson may cause bronchoconstriction in patients with asthma; should be used cautiously in patients with obstructive lung disease not associated with bronchoconstriction (eg, COPD/emphysema, bronchitis). Equipment for resuscitation and appropriate bronchodilator (eg, albuterol) therapy should always be immediately available prior to administration.

Concurrent drug therapy issues:

- Dipyridamole: When possible, dipyridamole should be withheld for at least 2 days prior to regadenoson administration; concurrent use of dipyridamole increases the risk of adverse effects of regadenoson.

- Theophylline derivatives: Patients should avoid consumption of any products containing theophylline derivatives (eg, aminophylline, caffeine) for at least 12 hours prior to regadenoson administration. Aminophylline may be used to reverse any severe or persistent adverse reactions to regadenoson.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

Geriatric ConsiderationsIn initial studies, elderly had a higher incidence of hypotension (2% vs <1%).

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have demonstrated embryo-fetal toxicity and maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Use only if potential benefit outweighs risk to fetus.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse effects in the nursing infant, the manufacturer recommends interrupting nursing for 10 hours after administration.

Adverse Reactions

>10%:

Cardiovascular: Tachycardia (22%), flushing (16%), premature ventricular contractions (14%), chest discomfort (13%), angina or ST segment depression (12%)

Central nervous system: Headache (26%)

Respiratory: Dyspnea (28%)

1% to 10%:

Cardiovascular: Chest pain (7%), premature atrial contractions (7%), systolic blood pressure decreased >35 mm Hg (7%), ventricular conduction abnormalities (6%) diastolic blood pressure decreased >25 mm Hg (4%), first-degree AV block (PR prolongation >220 msec; 3%)

Central nervous system: Dizziness (8%)

Gastrointestinal: Nausea (6%), abdominal discomfort (5%), dysgeusia (5%)

Miscellaneous: Feeling hot (5%)

<1%: Second-degree AV block, AV conduction abnormalities (other than AV blocks)

Drug Interactions

Aminophylline: May diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Caffeine: May diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Dipyridamole: May enhance the therapeutic effect of Regadenoson. *Risk D: Consider therapy modification*

Theophylline: May diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Avoid food or drugs with caffeine. Regadenoson's diagnostic effect may be decreased if used concurrently with caffeine. Avoid dietary caffeine for at least 12 hours prior to pharmacologic stress testing.

Monitoring ParametersHeart rate, blood pressure, continuous cardiac monitoring, oxygen saturation

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions or toxicity (eg, hold theophylline derivatives [12 hours] and dipyridamole [2 days]). See Administration for I.V. specifics. Patient must be monitored closely. Cardiopulmonary resuscitation equipment and experienced staff should be available during administration. Teach patient purpose for use and procedure, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis drug can only be administered by intravenous infusion. You will be monitored closely during and following infusion. Report immediately any dizziness, nausea, headache, difficulty breathing, or chest pain or tightness. Following infusion, you may experience a headache (consult prescriber for appropriate analgesic), abdominal discomfort (consult prescriber if this persists), or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Lexiscan™ 0.08 mg/mL (5 mL) [contains edetate disodium and propylene glycol 150 mg/mL]

Generic AvailableNo

ManufacturerBaxter Pharmaceutical Solutions LLC

Mechanism of ActionRegadenoson, a low affinity agonist of the A2A adenosine receptor, increases coronary blood flow (CBF) and mimics the increase in CBF caused by exercise. Myocardial uptake of the radiopharmaceutical is proportional to CBF creating the contrast required to identify stenotic coronary arteries.

Pharmacodynamics/Kinetics

Distribution: 11.5 L

Metabolism: Unknown

Half-life elimination: Intermediate phase: 30 minutes; Terminal phase: 2 hours

Time to peak: 1-4 minutes

Excretion: Urine (57% as unchanged drug)

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCVT-3146

References

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Regimen A1

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Neuroblastoma

Regimen UseNeuroblastoma

Regimen

Cyclophosphamide: I.V.: 1.2 g/m^2 day 1

[total dose/cycle = 1.2 g/m^2]

Vincristine: I.V.: 1.5 mg/m^2 day 1

[total dose/cycle = 1.5 mg/m^2]

Doxorubicin: I.V.: 40 mg/m^2 day 3

[total dose/cycle = 40 mg/m^2]

Cisplatin: I.V.: 90 mg/m^2 day 5

[total dose/cycle = 90 mg/m^2]

Repeat cycle every 28 days

References

Kaneko M, Nishihira H, Mugishima H, et al, âStratification of Treatment of Stage 4 Neuroblastoma Patients Based on N-myc Amplification Status. Study Group of Japan for Treatment of Advanced Neuroblastoma, Tokyo, Japan,â *Med Pediatr Oncol*, 1998, 31(1):1-7.[PubMed 9607422]

Regimen A2

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Neuroblastoma
Regimen UseNeuroblastoma
Index TermsRegimen new A1
Regimen

Cyclophosphamide: I.V.: 1.2 g/m^2 day 1

[total dose/cycle = 1.2 g/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Doxorubicin: I.V.: 40 mg/m^2 day 3

[total dose/cycle = 40 mg/m^2]

Cisplatin: I.V.: 90 mg/m^2 day 5

[total dose/cycle = 90 mg/m^2]

Repeat cycle every 28 days

References

Kaneko M, Nishihira H, Mugishima H, et al, âStratification of Treatment of Stage 4 Neuroblastoma Patients Based on N-myc Amplification Status. Study Group of Japan for Treatment of Advanced Neuroblastoma, Tokyo, Japan,â *Med Pediatr Oncol*, 1998, 31(1):1-7.[PubMed 9607422]

Remifentanil

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Remifentanil may be confused with alfentanil

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(rem i FEN ta nil)
U.S. Brand NamesUltiva®
Canadian Brand NamesUltiva®
Pharmacologic CategoryAnalgesic, Opioid; Anilidopiperidine Opioid
Use: Labeled IndicationsAnalgesic for use during the induction and maintenance of general anesthesia; for continued analgesia into the immediate postoperative period; analgesic component of monitored anesthesia
Use: Unlabeled/InvestigationalManagement of pain in mechanically-ventilated patients
Dosing: AdultsAnesthesia: I.V. continuous infusion: **Note:**Dose should be based on ideal body weight (IBW) in obese patients (>30% over IBW).

Induction of anesthesia: 0.5-1 mcg/kg/minute; if endotracheal intubation is to occur in <8 minutes, an initial dose of 1 mcg/kg may be given over 30-60 seconds

Coronary bypass surgery: 1 mcg/kg/minute

Maintenance of anesthesia: Supplemental bolus dose of 1 mcg/kg may be administered every 2-5 minutes. Consider increasing concomitant anesthetics with infusion rate >1 mcg/kg/minute. Infusion rate can be titrated upward in increments of 25% to 100% or downward in decrements of 25% to 50%. May titrate every 2-5 minutes.

With nitrous oxide (66%): 0.4 mcg/kg/minute (range: 0.1-2 mcg/kg/minute)

With isoflurane: 0.25 mcg/kg/minute (range: 0.05-2 mcg/kg/minute)

With propofol: 0.25 mcg/kg/minute (range: 0.05-2 mcg/kg/minute)

Coronary bypass surgery: 1 mcg/kg/minute (range: 0.125-4 mcg/kg/minute); supplemental dose: 0.5-1 mcg/kg

Continuation as an analgesic in immediate postoperative period: 0.1 mcg/kg/minute (range: 0.025-0.2 mcg/kg/minute). Infusion rate may be adjusted every 5 minutes in increments of 0.025 mcg/kg/minute. Bolus doses are not recommended. Infusion rates >0.2 mcg/kg/minute are associated with respiratory depression.

Coronary bypass surgery, continuation as an analgesic into the ICU: 1 mcg/kg/minute (range: 0.05-1 mcg/kg/minute)

Analgesic component of monitored anesthesia care:

Note: Supplemental oxygen is recommended:

Single I.V. dose given 90 seconds prior to local anesthetic:

Remifentanil alone: 1 mcg/kg over 30-60 seconds

With midazolam: 0.5 mcg/kg over 30-60 seconds

Continuous infusion beginning 5 minutes prior to local anesthetic:

Remifentanil alone: 0.1 mcg/kg minute

With midazolam: 0.05 mcg/kg/minute

Continuous infusion given after local anesthetic:

Remifentanil alone: 0.05 mcg/kg/minute (range: 0.025-0.2 mcg/kg/minute)

With midazolam: 0.025 mcg/kg/minute (range: 0.025-0.2 mcg/kg/minute)

Note: Following local or anesthetic block, infusion rate should be decreased to 0.05 mcg/kg/minute; rate adjustments of 0.025 mcg/kg/minute may be done at 5-minute intervals

Critically-ill patients (unlabeled dose): Continuous infusion: 42-1050 mcg/hour (based on 70 kg patient) **or** 0.6-15 mcg/kg/hour

Dosing: ElderlyElderly patients have an increased sensitivity to effect of remifentanil. Doses should be decreased by $^1/_2$ and titrated.

Dosing: Pediatric**Note:** Dose should be based on ideal body weight (IBW) in obese patients (>30% over IBW).

Maintenance of anesthesia with nitrous oxide (70%): Children Birth to 2 months: Continuous I.V. infusion: 0.4 mcg/kg/minute (range: 0.4-1 mcg/kg/minute); supplemental bolus dose of 1 mcg/kg may be administered, smaller bolus dose may be required with potent inhalation agents, potent neuraxial anesthesia, significant comorbidities, significant fluid shifts, or without atropine pretreatment. Clearance in neonates is highly variable; dose should be carefully titrated.

Maintenance of anesthesia with halothane, sevoflurane, or isoflurane: Continuous I.V. infusion: Children 1-12 years: 0.25 mcg/kg/minute (range: 0.05-1.3 mcg/kg/minute); supplemental bolus dose of 1 mcg/kg may be administered every 2-5 minutes. Consider increasing concomitant anesthetics with infusion rate >1 mcg/kg/minute. Infusion rate can be titrated upward in increments up to 50% or titrated downward in decrements of 25% to 50%. May titrate every 2-5 minutes.

Calculations

- Ideal Body Weight: Adults
- Ideal Body Weight: Pediatrics

Administration: I.V.An infusion device should be used to administer continuous infusions. During the maintenance of general anesthesia, I.V. boluses may be administered over 30-60 seconds. Injections should be given into I.V. tubing close to the venous cannula; tubing should be cleared after treatment to prevent residual effects when other fluids are administered through the same I.V. line.

StoragePrior to reconstitution, store at 2°C to 25°C (36°F to 77°F). Stable for 24 hours at room temperature after reconstitution and further dilution to concentrations of 20-250 mcg/mL (4 hours if diluted with LR).

ReconstitutionPrepare solution by adding 1 mL of diluent per 1 mg of remifentanil. Shake well. Further dilute to a final concentration of 20, 25, 50, or 250 mcg/mL.

CompatibilityStable in D$_5$LR, D$_5$NS, D$_5$W, $^1/_2$NS, NS, sterile water for injection; **variable stability (consult detailed reference)** in LR.

Incompatible with blood products.

Y-site administration: Compatible: Acyclovir, alfentanil, amikacin, aminophylline, ampicillin, ampicillin/sulbactam, aztreonam, bretylium, bumetanide, buprenorphine, butorphanol, calcium gluconate, cefazolin, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, cimetidine, ciprofloxacin, cisatracurium, clindamycin, dexamethasone sodium phosphate, digoxin, diphenhydramine, dobutamine, dopamine, doxycycline, droperidol, enalaprilat, epinephrine, esmolol, famotidine, fentanyl, fluconazole, furosemide, ganciclovir gatifloxacin, gentamicin, haloperidol, heparin, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, imipenem/cilastatin, inamrinone, isoproterenol, ketorolac, lidocaine, linezolid, lorazepam, magnesium sulfate, mannitol, meperidine, methylprednisolone sodium succinate, metoclopramide, metronidazole, midazolam, minocycline, morphine, nalbuphine, netilmicin, nitroglycerin, norepinephrine, ofloxacin, ondansetron, phenylephrine, piperacillin, piperacillin/tazobactam, potassium chloride, procainamide, prochlorperazine edisylate, promethazine, ranitidine, sodium bicarbonate, sufentanil, theophylline, thiopental, ticarcillin, ticarcillin/clavulanate potassium, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, zidovudine. **Incompatible:** Amphotericin B cholesteryl sulfate complex. **Variable (consult detailed reference):** Amphotericin B, cefoperazone, chlorpromazine, diazepam.

Compatibility when admixed: Compatible: Propofol.

RestrictionsC-II

ContraindicationsNot for intrathecal or epidural administration, due to the presence of glycine in the formulation; hypersensitivity to remifentanil, fentanyl, or fentanyl analogs, or any component of the formulation

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Hypotension: May cause hypotension; use with caution in patients with hypovolemia, cardiovascular disease (including acute MI), or drugs which may exaggerate hypotensive effects (including phenothiazines or general anesthetics).
- Intraoperative awareness: In patients <55 years of age, intraoperative awareness has been reported when used with propofol rates of ≤75 mcg/kg/minute.
- Opioid agonist toxicities: Shares the toxic potentials of opiate agonists, and precautions of opiate agonist therapy should be observed.

Disease-related concerns:

- Bradycardia: Use with caution when administering to patients with bradycardia.
- Obesity: Use with caution in patients who are morbidly obese.

Special populations:

- Pediatrics: Safety and efficacy for postoperative analgesic or monitored anesthesia care have not been established in children.

Other warnings/precautions:

- Discontinuation of therapy: Interruption of an infusion will result in offset of effects within 5-10 minutes; the discontinuation of infusion should be preceded by the establishment of adequate postoperative analgesia orders, especially for patients in whom postoperative pain is anticipated.
- General anesthesia use: Not recommended as the sole agent in general anesthesia, because the loss of consciousness cannot be assured.

- Rapid infusion: Inject slowly over 3-5 minutes; rapid I.V. infusion may result in skeletal muscle and chest wall rigidity, impaired ventilation, or respiratory distress/arrest; nondepolarizing skeletal muscle relaxant may be required.

- Trained individuals: Due to the high incidence of apnea, hypotension, tachycardia and muscle rigidity; it should be administered by individuals specifically trained in the use of anesthetic agents and should not be used in diagnostic or therapeutic procedures outside the monitored anesthesia setting; resuscitative and intubation equipment should be readily available.

Geriatric ConsiderationsElderly patients have an increased sensitivity to effect of remifentanil, therefore, doses should be decreased by $^{1}/_{2}$ and titrated.
Pregnancy Risk FactorC
Pregnancy ConsiderationsRemifentanil has been shown to cross the placenta. Neonatal respiratory depression and sedation may occur.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%: Gastrointestinal: Nausea, vomiting

1% to 10%:

Cardiovascular: Bradycardia (dose dependent), hypertension, hypotension (dose dependent), tachycardia

Central nervous system: Agitation, dizziness, fever, headache

Dermatologic: Pruritus

Neuromuscular & skeletal: Muscle rigidity (dose dependent)

Ocular: Visual disturbances

Respiratory: Apnea, hypoxia, respiratory depression

Miscellaneous: Postoperative pain, shivering

<1% (Limited to important or life-threatening): Anemia, anxiety, arrhythmia, bronchospasm, confusion, constipation, CPK-MB increased, diarrhea, dysphagia, electrolyte disorders, hallucination, heart block, pleural effusion, prolonged emergence from anesthesia, pulmonary edema, syncope, thrombocytopenia, xerostomia

Postmarketing and/or case reports: Anaphylactic/anaphylactoid reactions, asystole

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Beta-Blockers: Anilidopiperidine Opioids may enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): Anilidopiperidine Opioids may enhance the bradycardic effect of Calcium Channel Blockers (Nondihydropyridine). Anilidopiperidine Opioids may enhance the hypotensive effect of Calcium Channel Blockers (Nondihydropyridine). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

MAO Inhibitors: Anilidopiperidine Opioids may enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. *Risk D: Consider therapy modification*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Monitoring ParametersRespiratory and cardiovascular status, blood pressure, heart rate
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 1 mg, 2 mg, 5 mg [contains glycine 15 mg]

Generic AvailableNo
ManufacturerGlaxoSmithKline

Mechanism of ActionBinds with stereospecific mu-opioid receptors at many sites within the CNS, increases pain threshold, alters pain reception, inhibits ascending pain pathways

Pharmacodynamics/Kinetics

Onset of action: I.V.: 1-3 minutes

Distribution: V_d: 100 mL/kg; increased in children

Protein binding: ~70% (primarily alpha$_1$ acid glycoprotein)

Metabolism: Rapid via blood and tissue esterases

Half-life elimination (dose dependent): Terminal: 10-20 minutes; effective: 3-10 minutes

Excretion: Urine

Related Information

- Narcotic / Opioid Analgesics

Pharmacotherapy PearlsUltra short-acting narcotic that is unique compared to other short-acting narcotics. This agent is not considered suitable as the sole agent for induction; remifentanil should be used in combination with other induction agents. Bolus doses are not recommended for sedation cases and in treatment of postoperative pain due to risk of respiratory depression and muscle rigidity. Due to remifentanil's short duration of action, when postoperative pain is anticipated, discontinuation of an infusion of remifentanil should be preceded by an adequate postoperative analgesic (ie, fentanyl, morphine).

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or agitation

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other ConsiderationsUltra short-acting narcotic that is unique compared to other short-acting narcotics. This agent is not considered suitable as the sole agent for induction; remifentanil should be used in combination with other induction agents; bolus doses are not recommended for sedation cases and in treatment of postoperative pain due to risk of respiratory depression and muscle rigidity; due to remifentanil's short duration of action, when postoperative pain is anticipated, discontinuation of an infusion of remifentanil should be preceded by an adequate postoperative analgesic (ie, fentanyl, morphine).

Elderly patients have an increased sensitivity to effect of remifentanil, doses should be decreased by $^1/_2$ and titrated.

Index TermsGI87084B

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International Brand NamesRestinil (UY); Ultiva (AE, AR, AT, AU, BB, BE, BG, BH, BM, BR, BS, BZ, CH, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, FI, FR, GB, GR, GT, GY, HK, HN, IE, IL, IQ, IR, IT, JM, JO, KP, KW, LB, LY, MX, NI, NL, NO, OM, PA, PE, PL, PT, QA, SA, SE, SG, SR, SV, SY, TT, VE, YE)

Repaglinide and Metformin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

PrandiMet™ may be confused with Avandamet®, Prandin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(re PAG li nide & met FOR min)

U.S. Brand NamesPrandiMet™

Pharmacologic CategoryAntidiabetic Agent, Biguanide; Antidiabetic Agent, Meglitinide Derivative; Hypoglycemic Agent, Oral

Use: Labeled IndicationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM), as an adjunct to diet and exercise, in patients currently receiving or not adequately controlled on metformin and/or a meglitinide

Dosing: Adults**Type 2 diabetes mellitus:** Oral:

Patients currently taking repaglinide and metformin: Initial doses should be based on (but not exceeding) the patient's current doses of repaglinide and metformin; daily doses should be divided and given 2-3 times daily with meals (maximum single dose: 4 mg/dose [repaglinide], 1000 mg/dose [metformin]; maximum daily dose: 10 mg/day [repaglinide], 2500 mg/day [metformin])

Patients inadequately controlled on metformin alone: Initial dose: repaglinide 1 mg/ metformin 500 mg twice daily with meals. Titrate slowly to reduce the risk of repaglinide-induced hypoglycemia.

Patients inadequately controlled on a meglitinide alone: Initial dose: metformin 500 mg twice daily plus repaglinide at a dose similar to (but not exceeding) the patient's current dose. Titrate slowly to reduce the risk of metformin-induced gastrointestinal adverse effects.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentDo not use in renal impairment; metformin use is contraindicated in patients with renal impairment (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females).

Dosing: Hepatic ImpairmentAvoid use in patients with impaired liver function.

Calculations

- Creatinine Clearance: Adults

Administration: OralAdminister 15-30 minutes before meals to avoid risk of hypoglycemia/GI upset; if a meal skipped or patient is NPO, do not administer dose.

Dietary ConsiderationsShould be taken 15-30 minutes before meals to prevent hypoglycemia and decrease the risk of GI upset; if the patient misses a meal or is NPO, the fixed-dose repaglinide/metformin combination agent should not be administered. Dietary modifications based on ADA recommendations are a part of therapy. Treatment may cause hypoglycemia; the patient should be able to recognize the signs and symptoms of hypoglycemia (palpitations, tachycardia, sweaty palms, diaphoresis, lightheadedness, etc). Monitor for signs and symptoms of vitamin B_{12} and/or folic acid deficiency; supplementation may be required.

StorageDo not store above 25°C (77°F). Protect from moisture.

ContraindicationsHypersensitivity to repaglinide, metformin, or any component of the formulation; renal impairment (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females); acute or chronic metabolic acidosis (including diabetic ketoacidosis); concomitant administration of gemfibrozil and/or itraconazole

Warnings/Precautions

Boxed warnings:

- Lactic acidosis: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Cardiovascular mortality: Some studies suggest that sulfonylureas may be associated with increased cardiovascular events. Theoretically, repaglinide may also increase cardiovascular events, but there are no long-term studies assessing this concern; metformin does not appear to share this risk.

- Hypoglycemia: May cause hypoglycemia; appropriate patient selection, dosage, and patient education are important to avoid hypoglycemic episodes.

- Lactic acidosis: **[U.S. Boxed Warning]: Lactic acidosis is a rare, but potentially severe consequence of therapy with metformin.** Lactic acidosis should be suspected in any patient with diabetes receiving metformin with evidence of acidosis but without evidence of ketoacidosis. Discontinue metformin in clinical situations predisposing to hypoxemia, including conditions such as cardiovascular collapse, respiratory failure, acute myocardial infarction, acute congestive heart failure, and septicemia. The risk of accumulation and lactic acidosis increases with the degree of impairment of renal function.

Disease-related concerns:

- Adrenal/pituitary impairment: Use with caution in patients with adrenal and/or pituitary impairment; may be more susceptible to glucose-lowering effects.

- Diabetes mellitus (type 1): Not indicated for use in patients with insulin-dependent diabetes mellitus (IDDM; type 1).

- Heart failure: Use caution in patients with congestive heart failure requiring pharmacologic management, particularly in patients with unstable or acute heart failure; risk of lactic acidosis may be increased secondary to hypoperfusion.

- Hepatic impairment: Avoid use in patients with impaired liver function due to potential for lactic acidosis.

- Renal impairment: The combination product is not recommended for use in patients with renal impairment. Metformin is substantially excreted by the kidney; patients with renal function below the limit of normal for their age should not receive therapy. Use of concomitant medications that may affect renal function (ie, affect tubular secretion) may also affect metformin disposition. Metformin should be withheld in patients with dehydration and/or prerenal azotemia.

- Stress-related states: It may be necessary to discontinue therapy and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Concurrent drug therapy issues:

- Gemfibrozil: Concomitant use has been reported to result in prolonged, severe hypoglycemia; the addition of itraconazole may augment the effect of gemfibrozil on repaglinide. Concurrent use of gemfibrozil and/or itraconazole is contraindicated with the repaglinide/metformin fixed-dose combination product.

- NPH insulin: Repaglinide is not indicated for use in combination with NPH insulin; in two studies, reports of myocardial ischemia (6 events) in patients using repaglinide plus insulin have caused concern. Further evaluation is required to assess the safety of this combination.

Special populations:

- Elderly: Use with caution in the elderly; may be more susceptible to glucose-lowering effects. Metformin should not be initiated in patients ≥80 years of age unless normal renal function is confirmed.

- Malnourished patients: Use with caution in malnourished patients; may be more susceptible to glucose-lowering effects.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism.

- Iodinated contrast: Metformin therapy should be temporarily discontinued prior to or at the time of intravascular administration of iodinated contrast media (potential for acute alteration in renal function). Metformin should be withheld for 48 hours after the radiologic study and restarted only after renal function has been confirmed as normal.

- Surgical procedures: Therapy should be suspended for any surgical procedures (resume only after normal intake resumed and normal renal function is verified).

Geriatric ConsiderationsIntensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted with this combination; therefore, repaglinide/metformin is classified as pregnancy category C. See individual agents.

Lactation

Metformin: Enters breast milk/not recommended

Repaglinide: Excretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsSee individual agents.

Pregnancy & Lactation, In-Depth

- MetFORMIN in Pregnancy & Lactation
- Repaglinide in Pregnancy & Lactation

Adverse Reactions**Note:** The following information reflects the frequency of adverse effects experienced by patients who received the repaglinide/metformin fixed-dose combination product. Also see individual agents.

>10%:

Central nervous system: Headache (22%)

Endocrine & metabolic: Hypoglycemia (33%)

Gastrointestinal: Diarrhea (19%), nausea (15%)

Respiratory: Upper respiratory tract infection (11%)

Metabolism/Transport Effects Repaglinide: **Substrate** of CYP2C8 (major), 3A4 (major)

Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Repaglinide. Management: Concurrent use of an azole antifungal with both repaglinide and gemfibrozil should be avoided. *Risk C: Monitor therapy*

Cephalexin: May increase the serum concentration of MetFORMIN. *Risk C: Monitor therapy*

Cimetidine: May decrease the excretion of MetFORMIN. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

CycloSPORINE: May increase the serum concentration of Repaglinide. *Risk C: Monitor therapy*

CYP2C8 Inducers (Highly Effective): May increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Moderate): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Strong): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Gemfibrozil: May increase the serum concentration of Repaglinide. The addition of itraconazole may augment the effect of gemfibrozil on repaglinide. Management: Consider alternative therapy combinations to avoid this potentially significant interaction. Avoid concurrent use when also used with a CYP3A4 inhibitor. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Iodinated Contrast Agents: May enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Macrolide Antibiotics: May increase the serum concentration of Repaglinide. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Repaglinide. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Trimethoprim: May decrease the metabolism of Repaglinide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol (incidence of lactic acidosis may be increased; may cause hypoglycemia).

Food: Food may delay and decrease the extent of absorption of metformin; the AUC of repaglinide may also be decreased. Metformin may decrease the absorption of vitamin B_{12} and/or folic acid.

Herb/Nutraceutical: St John's wort may increase the metabolism of repaglinide. The following herbs exhibit hypoglycemic activity; concomitant use may increase the risk of hypoglycemia: Alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, stinging nettle.

Monitoring Parameters Regular assessment of fasting blood glucose, postprandial blood glucose, and hemoglobin A_{1c}; initial and periodic monitoring of hematologic parameters (eg, hemoglobin/hematocrit, red blood cell indices) and renal function should be performed at least annually. Evaluation of vitamin B_{12} and folate should be performed if anemia is present.

Reference Range Recommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsRegular assessment of fasting blood glucose, postprandial blood glucose, and hemoglobin A_{1c}; initial and periodic monitoring of hematologic parameters (eg, hemoglobin/hematocrit, red blood cell indices) and renal function should be performed at least annually. Evaluation of vitamin B_{12} and folate should be performed if anemia is present.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

- PrandiMet™:
  - 1/500: Repaglinide 1 mg and metformin hydrochloride 500 mg
  - 2/500: Repaglinide 2 mg and metformin hydrochloride 500 mg

Generic AvailableNo

ManufacturerNovo Nordisk Inc

Mechanism of ActionCombination therapy; repaglinide and metformin act to improve glycemic control via two different mechanisms of action:

Repaglinide is a nonsulfonylurea hypoglycemic agent which stimulates insulin release by blocking ATP-dependent potassium channels, depolarizing the membrane and facilitating calcium entry through calcium channels; increased intracellular calcium stimulates insulin release from the pancreatic beta cells.

Metformin prevents hyperglycemia by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity via increased peripheral glucose uptake and utilization.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Diabetes Mellitus Management, Adults
- MetFORMIN
- Repaglinide

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Patients with diabetes (noninsulin dependent, type 2) taking repaglinide and metformin combination should schedule dental treatment in morning in order to minimize stress-induced hypoglycemia

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentRepaglinide is a CYP3A4 substrate; monitor glucose when used with an enzyme inducer (carbamazepine, barbiturates) or an inhibitor (nefazodone, fluvoxamine). St John's wort may decrease repaglinide levels.

Index TermsMetformin and Repaglinide; Repaglinide and Metformin Hydrochloride

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Repaglinide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Prandin® may be confused with Avandia®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(re PAG li nide)
U.S. Brand NamesPrandin®
Canadian Brand NamesGlucoNorm®; Prandin®
Pharmacologic CategoryAntidiabetic Agent, Meglitinide Derivative
Use: Labeled IndicationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as an adjunct to diet and exercise; may be used in combination with metformin or thiazolidinediones
Dosing: Adults

Type 2 diabetes: Oral:

Note: Doses should be taken within 15 minutes of the meal, but time may vary from immediately preceding the meal to as long as 30 minutes before the meal

Patients not previously treated or whose Hb A_{1c} is <8%: Initial: 0.5 mg before each meal

Patients previously treated with blood glucose-lowering agents whose Hb A_{1c} is ≥8%: Initial: 1 or 2 mg before each meal.

Dose adjustment: Determine dosing adjustments by blood glucose response, usually fasting blood glucose. Double the preprandial dose up to 4 mg until satisfactory blood glucose response is achieved. At least 1 week should elapse to assess response after each dose adjustment.

Dose range: 0.5-4 mg taken with meals. Repaglinide may be dosed preprandial 2, 3, or 4 times/day in response to changes in the patient's meal pattern. Maximum recommended daily dose: 16 mg.

Patients receiving other oral hypoglycemic agents: When repaglinide is used to replace therapy with other oral hypoglycemic agents, it may be started the day after the final dose is given. Observe patients carefully for hypoglycemia because of potential overlapping of drug effects. When transferred from longer half-life sulfonylureas (eg, chlorpropamide), close monitoring may be indicated for up to ≥1 week.

Note: Combination therapy: If repaglinide monotherapy does not result in adequate glycemic control, metformin or a thiazolidinedione may be added. Or, if metformin or thiazolidinedione therapy does not provide adequate control, repaglinide may be added. The starting dose and dose adjustments for combination therapy are the same as repaglinide monotherapy. Carefully adjust the dose of each drug to determine the minimal dose required to achieve the desired pharmacologic effect. Failure to do so could result in an increase in the incidence of hypoglycemic episodes. Use appropriate monitoring of FPG and Hb A_{1c} measurements to ensure that the patient is not subjected to excessive drug exposure or increased probability of secondary drug failure. If glucose is not achieved after a suitable trial of combination therapy, consider discontinuing these drugs and using insulin.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal Impairment

Cl_{cr} 40-80 mL/minute (mild to moderate renal dysfunction): Initial dosage adjustment does not appear to be necessary.

Cl_{cr} 20-40 mL/minute: Initiate 0.5 mg with meals; titrate carefully.

Cl_{cr} <20 mL/minute: Not studied.

Dosing: Hepatic ImpairmentUse conservative initial and maintenance doses. Use longer intervals between dosage adjustments.
Calculations

- Creatinine Clearance: Adults

Administration: OralAdminister repaglinide 15-30 minutes before meals. Patients who are anorexic or NPO, may need to have their dose held to avoid hypoglycemia. Patients consuming extra meals should be instructed to add a dose for the extra meal.
Dietary ConsiderationsAdminister repaglinide 15-30 minutes before meals. Dietary modification based on ADA recommendations is a part of therapy. May cause hypoglycemia. Must be able to recognize symptoms of hypoglycemia (palpitations, tachycardia, sweaty palms, diaphoresis, lightheadedness).
StorageDo not store above 25°C (77°F). Protect from moisture.

ContraindicationsHypersensitivity to repaglinide or any component of the formulation; diabetic ketoacidosis, with or without coma (treat with insulin); type 1 diabetes (insulin dependent, IDDM)

Warnings/Precautions

Concerns related to adverse effects:

- Hypoglycemia: May cause hypoglycemia; appropriate patient selection, dosage, and patient education are important to avoid hypoglycemic episodes.

Disease-related concerns:

- Adrenal/pituitary impairment: Use with caution in patients with adrenal and/or pituitary impairment; may be more susceptible to glucose-lowering effects.
- Cardiovascular mortality: Some studies suggest that sulfonylureas may be associated with increased cardiovascular events. Theoretically, repaglinide may also increase cardiovascular events, but there are no long-term studies assessing this concern.
- Hepatic impairment: Use with caution in patients with moderate-to-severe hepatic impairment.
- Renal impairment: Use with caution in patients with severe renal impairment; may be more susceptible to glucose-lowering effects.
- Stress-related states: It may be necessary to discontinue repaglinide and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Concurrent drug therapy issues:

- NPH insulin: Not indicated for use in combination with NPH insulin; in two studies, reports of myocardial ischemia (6 events) in patients using repaglinide plus insulin have caused concern. Further evaluation is required to assess the safety of this combination.

Special populations:

- Elderly: Use with caution in the elderly; may be more susceptible to glucose-lowering effects.
- Malnourished patients: Use with caution in malnourished patients; may be more susceptible to glucose-lowering effects.
- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsRepaglinide has not been studied exclusively in the elderly; information from the manufacturer states that no differences in its effectiveness or adverse effects had been identified between persons younger than and older than 65 years of age. How “tightly” a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood glucose <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional status, how well he/she recognizes hypoglycemic or hyperglycemic symptoms, and how to respond to them and their other disease states. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in some animal studies; therefore, repaglinide is classified as pregnancy category C. Information describing the effects of repaglinide on pregnancy outcomes is limited. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if repaglinide is excreted in breast milk. Breast-feeding is not recommended by the manufacturer.

Pregnancy & Lactation, In-Depth

- Repaglinide in Pregnancy & Lactation

Adverse Reactions

>10%:

Central nervous system: Headache (9% to 11%)

Endocrine & metabolic: Hypoglycemia (16% to 31%)

Respiratory: Upper respiratory tract infection (10% to 16%)

1% to 10%:

Cardiovascular: Ischemia (4%), chest pain (2% to 3%)

Gastrointestinal: Diarrhea (4% to 5%), constipation (2% to 3%), tooth disorder (≤2%)

Genitourinary: Urinary tract infection (2% to 3%)

Neuromuscular & skeletal: Arthralgia (3% to 6%), back pain (5% to 6%)

Respiratory: Sinusitis (3% to 6%), bronchitis (2% to 6%)

Miscellaneous: Allergy (1% to 2%)

<1%: Anaphylactoid reaction, arrhythmia, ECG abnormal, hepatitis, hypertension, jaundice, leukopenia, liver function tests increased, MI, palpitation, thrombocytopenia

Postmarketing and/or case reports: Alopecia, hemolytic anemia, hepatic dysfunction (severe), pancreatitis, Stevens-Johnson syndrome

Metabolism/Transport Effects**Substrate** of CYP2C8 (major), 3A4 (major)

Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Repaglinide. Management: Concurrent use of an azole antifungal with both repaglinide and gemfibrozil should be avoided. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

CycloSPORINE: May increase the serum concentration of Repaglinide. *Risk C: Monitor therapy*

CYP2C8 Inducers (Highly Effective): May increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Moderate): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Strong): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Gemfibrozil: May increase the serum concentration of Repaglinide. The addition of itraconazole may augment the effect of gemfibrozil on repaglinide. Management: Consider alternative therapy combinations to avoid this potentially significant interaction. Avoid concurrent use when also used with a CYP3A4 inhibitor. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Macrolide Antibiotics: May increase the serum concentration of Repaglinide. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Repaglinide. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Trimethoprim: May decrease the metabolism of Repaglinide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause hypoglycemia).

Food: When given with food, the AUC of repaglinide is decreased.

Herb/Nutraceutical: St John's wort may decrease repaglinide levels. Avoid gymnema, garlic (may cause hypoglycemia).

Monitoring ParametersMonitor fasting blood glucose (periodically) and glycosylated hemoglobin (Hb A_{1c}) levels (every 3 months) with a goal of decreasing these levels towards the normal range. During dose adjustment, fasting glucose can be used to determine response.

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (especially anything that is metabolized via the cytochrome P450 isoenzyme 3A4 route). Assess results of laboratory tests and patient response on a regular basis throughout therapy. Teach patient proper use (or refer patient to diabetic educator), possible side effects/appropriate interventions, and adverse symptoms to report (eg, signs of hypoglycemia).

Monitoring: Lab TestsFasting blood glucose (periodically) and glycosylated hemoglobin (Hb A_{1c}) levels (every 3 months)

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take this medication exactly as directed (3-4 times a day) 15-30 minutes prior to a meal. If you skip a meal (or add an extra meal), skip (or add) a dose for that meal. Do not change dosage or discontinue without consulting prescriber. Follow dietary and lifestyle directions of prescriber or diabetic educator. Avoid alcohol. You will be instructed in signs of hypo- or hyperglycemia by prescriber or diabetic educator; be alert for adverse hypoglycemia (lightheadedness, tachycardia or palpitations, sweaty palms or profuse perspiration, yawning, tingling of lips and tongue, seizures, or change in sensorium) and follow prescriber's instructions for intervention. May cause headache or mild GI effects during first weeks of therapy (nausea, vomiting, diarrhea, constipation, heartburn), if these do not diminish, consult prescriber for approved medication. Report chest pain; respiratory difficulty or symptoms of upper respiratory infection; urinary tract infection (burning or itching on urination); muscle pain or back pain; or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Prandin®: 0.5 mg, 1 mg, 2 mg

Generic AvailableNo

ManufacturerNovo Nordisk Pharm, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Prandin)

0.5 mg (30): $65.69

1 mg (90): $175.19

2 mg (90): $175.19

Mechanism of ActionNonsulfonylurea hypoglycemic agent of the meglitinide class (the nonsulfonylurea moiety of glyburide) used in the management of type 2 diabetes mellitus; stimulates insulin release from the pancreatic beta cells

Pharmacodynamics/Kinetics

Onset of action: Single dose: Increased insulin levels: ~15-60 minutes

Duration: 4-6 hours

Absorption: Rapid and complete

Distribution: V_d: 31 L

Protein binding, plasma: >98% to albumin

Metabolism: Hepatic via CYP3A4 and CYP2C8 isoenzymes and glucuronidation to inactive metabolites

Bioavailability: Mean absolute: ~56%

Half-life elimination: ~1 hour

Time to peak, plasma: ~1 hour

Excretion: Within 96 hours: Feces (~90%, <2% as parent drug); Urine (~8%)

Related Information

- Diabetes Mellitus Management, Adults

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tooth disorder.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentRepaglinide is a CYP3A4 substrate; monitor glucose when used with an enzyme inducer (carbamazepine, barbiturates) or an inhibitor (nefazodone, fluvoxamine)

References

American Diabetes Association, “Standards of Medical Care in Diabetes Mellitus -- 2009,” *Diabetes Care*, 2009, 32(Suppl 1):13-61.[PubMed 19118286]

Furlong NJ, Hulme SA, O'Brien SV, et al, “Comparison of Repaglinide vs Gliclazide in Combination With Bedtime NPH Insulin in Patients With Type 2 Diabetes Inadequately Controlled With Oral Hypoglycaemic Agents,” *Diabet Med*, 2003, 20(11):935-41. [PubMed 14632720]

Furlong NJ, Hulme SA, O'Brien SV, et al, “Repaglinide Versus Metformin in Combination With Bedtime NPH Insulin in Patients With Type 2 Diabetes Established on Insulin/Metformin Combination Therapy,” *Diabetes Care*, 2002, 25(10):1685-90. [PubMed 12351462]

Nathan DM, Buse JB, Davidson MB, et al, “Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A Consensus Statement of the American Diabetes Association and the European Association for the Study of Diabetes," *Diabetes Care*, 2009, 32(1):193-203.[PubMed 18945920]

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Quast U, Stephan D, Bieger S, et al, "The Impact of ATP-Sensitive K+ Channel Subtype Selectivity of Insulin Secretagogues for the Coronary Vasculature and the Myocardium," *Diabetes*, 2004, 53(Suppl 3):156-64.

International Brand NamesHipover (PE); NovoNorm (AE, AR, AT, AU, BE, BF, BG, BH, BJ, BR, CH, CI, CL, CN, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, IE, IL, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PH, PK, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SY, TH, TN, TR, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Novonorm (PL); Prandin (AT, BE, BG, BR, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Rapilin (IN); Repanorm (TW); Sestrine (AR); Supernide (TW)

Reserpine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Reserpine may be confused with Risperdal®, risperidone

Pronunciation(re SER peen)

Pharmacologic CategoryCentral Monoamine-Depleting Agent; Rauwolfia Alkaloid

Use: Labeled IndicationsManagement of mild-to-moderate hypertension; treatment of agitated psychotic states (schizophrenia)

Use: Unlabeled/InvestigationalManagement of tardive dyskinesia

Dosing: Adults

Hypertension:

Manufacturer's labeling: Initial: 0.5 mg/day for 1-2 weeks; maintenance: 0.1-0.25 mg/day

Note: Clinically, the need for a “loading” period (as recommended by the manufacturer) is not well supported, and alternative dosing is preferred.

Alternative dosing (unlabeled): Initial: 0.1 mg once daily; adjust as necessary based on response.

Usual dose range (JNC 7): 0.05-0.25 mg once daily; 0.1 mg every other day may be given to achieve 0.05 mg once daily

Schizophrenia (labeled use) or tardive dyskinesia (unlabeled use): Dosing recommendations vary; initial dose recommendations generally range from 0.05-0.25 mg (although manufacturer recommends 0.5 mg once daily initially in schizophrenia). May be increased in increments of 0.1-0.25 mg; maximum dose in tardive dyskinesia: 5 mg/day.

Dosing: ElderlyOral: Initial: 0.05 mg once daily increasing by 0.05 mg every week as necessary (full antihypertensive effects may take as long as 3 weeks).

Dosing: PediatricChildren: Hypertension: 0.01-0.02 mg/kg/24 hours divided every 12 hours; maximum dose: 0.25 mg/day (not recommended in children)

Dosing: Renal Impairment

Cl_{cr} <10 mL/minute: Avoid use.

Not removed by hemo- or peritoneal dialysis; supplemental dose is not necessary.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

StorageProtect oral dosage forms from light.

ContraindicationsHypersensitivity to reserpine or any component of the formulation; active peptic ulcer disease, ulcerative colitis; history of mental depression (especially with suicidal tendencies); patients receiving electroconvulsive therapy (ECT)

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: At high doses, significant mental depression, anxiety, or psychosis may occur (uncommon at dosages <0.25 mg/day).
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of hypotension or in patients where transient hypotensive episodes would be poorly tolerated (cardiovascular disease or cerebrovascular disease).

Disease-related concerns:

- Asthma: Use with caution in patients with asthma.
- Gallstones: Use with caution in patients with gallstones.
- Gastrointestinal disease: Use with caution in patients with inflammatory bowel disease or history of peptic ulcer disease.
- Parkinson's disease: Use with caution in patients with Parkinson’s disease.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- MAO inhibitors: Avoid concurrent use of MAO inhibitors and/or drugs with MAO-inhibiting properties.

Special populations:

- Elderly: Use with caution in the elderly.

Dosage form specific issues:

- Tartrazine: Some products may contain tartrazine.

Other warnings/precautions:

- Electroshock therapy: Discontinue reserpine 7 days before electroshock therapy.

Geriatric ConsiderationsSome studies advocate the use of reserpine because of its low cost, long half-life, and efficacy, but it is generally not considered a first-line drug.
Pregnancy Risk FactorC
LactationEnters breast milk/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, bradycardia, chest pain, hypotension, peripheral edema, PVC, syncope

Central nervous system: Dizziness, drowsiness, dull sensorium, fatigue, headache, mental depression, nightmares, nervousness, parkinsonism, paradoxical anxiety

Dermatologic: Flushing of skin, pruritus, purpura, rash

Endocrine & metabolic: Gynecomastia, weight gain

Gastrointestinal: Anorexia, diarrhea, dry mouth, gastric acid secretion increased, nausea, salivation increased, vomiting

Genitourinary: Impotence, libido decreased

Hematologic: Thrombocytopenia purpura

Neuromuscular & skeletal: Muscle ache

Ocular: Blurred vision, optic atrophy

Respiratory: Dyspnea, epistaxis, nasal congstion

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amphetamines: Gastrointestinal Acidifying Agents may decrease the serum concentration of Amphetamines. *Risk C: Monitor therapy*

Beta-Blockers: Reserpine may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Iobenguane I 123: Reserpine may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the adverse/toxic effect of Rauwolfia Alkaloids. Existing MAOI therapy can result in paradoxical effects of added rauwolfia alkaloids (eg, excitation, hypertension). *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Tetrabenazine: Reserpine may enhance the adverse/toxic effect of Tetrabenazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe (may worsen hypertension). Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression). Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure, standing and sitting/supine

Nursing: Physical Assessment/MonitoringUse caution and monitor closely with a history of depression, PUD, or gallstones. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, increase hypotensive effect (TCAs), hypertensive reaction (MAO-Is, ephedra, yohimbe), increased effects of toxicity (CNS depressants). Assess blood pressure and cardiac status prior to starting therapy, during first doses, when changing dose, and regularly thereafter (eg, arrhythmia, hypotension, CNS changes [nervousness, depression], Parkinsonism, rash, diarrhea, nausea, vomiting). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy without consulting prescriber (especially any sleep remedies or stimulants). Take as directed; do not alter dose or discontinue without consulting prescriber. May take up to 2 weeks to see effects of therapy. Avoid alcohol and maintain recommended diet. May cause mild nervousness, dizziness, or fatigue (use caution when driving or engaging in hazardous activities until response to drug is known); orthostatic hypotension (use caution when rising from sitting or lying position or when climbing stairs until response to therapy is known): nausea or loss of appetite (small frequent meals or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); nasal stuffiness (avoid OTC medications and consult prescriber for approved medication); or impotence (will resolve when medication is discontinued). Report chest pain, rapid heartbeat, or palpitations; respiratory difficulty; sudden increase in weight; swelling in ankles or hands; black tarry stools; or unusual feelings of depression, alteration in gait or balance, or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 0.1 mg, 0.25 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Reserpine)

0.25 mg (30): $39.56

Mechanism of ActionReduces blood pressure via depletion of sympathetic biogenic amines (norepinephrine and dopamine); this also commonly results in sedative effects

Pharmacodynamics/Kinetics

Onset of action: Antihypertensive: 3-6 days

Duration: 2-6 weeks

Absorption: ~40%

Distribution: Crosses placenta; enters breast milk

Protein binding: 96%

Metabolism: Extensively hepatic (>90%)

Half-life elimination: 50-100 hours

Excretion: Feces (30% to 60%); urine (10%)

Related Information

- Depression
- Hypertension

Pharmacotherapy PearlsAdverse effects are usually dose related, mild, and infrequent when administered for the management of hypertension.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, nightmares, and drowsiness; high dose may cause depression, anxiety, or psychosis

Mental Health: Effects on Psychiatric TreatmentContraindicated in depression and with MAO inhibitors. Discontinue reserpine 7 days before ECT. Combined use with CNS depressants may produce additive effects. TCAs may diminish reserpine's antihypertensive effects.

Cardiovascular ConsiderationsCurrently, reserpine is used only infrequently for treatment of hypertension. An important side effect is drowsiness. It is important that reserpine be discontinued at least 1 week before elective electroshock therapy.

Anesthesia and Critical Care Concerns/Other ConsiderationsCurrently, reserpine is used only infrequently for treatment of hypertension. Nasal congestion, sedation, depression, and activation of peptic ulcer are important adverse effects.

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Treatment of High Blood Pressure: The JNC 7 Report," *JAMA*, 2003, 289(19):2560-71.[PubMed 12748199]

International Brand NamesRaupasil (BG, PL); Rauserpine (TW); Rauverid (PH); Resapin (ID); Respine (MY); Serpasil (ID, IN)

Retapamulin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(re te PAM ue lin)
U.S. Brand NamesAltabax™
Pharmacologic CategoryAntibiotic, Pleuromutilin; Antibiotic, Topical
Use: Labeled IndicationsTreatment of impetigo caused by susceptible strains of *S. pyogenes* or methicillin-susceptible *S. aureus*
Dosing: Adults**Impetigo:** Topical: Apply to affected area twice daily for 5 days. Total treatment area should not exceed 100 cm^2 total body surface area.
Dosing: Pediatric**Impetigo:** Children ≥9 months: Topical: Apply to affected area twice daily for 5 days. Total treatment area should not exceed 2% of total body surface area.
Administration: TopicalMay cover treatment area with sterile bandage or gauze dressing if needed. Concomitant use with other topical products to the same treatment area has not been evaluated.
StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to retapamulin or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Irritation: If skin irritation occurs, discontinue use.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <9 months of age.

Other warnings/precautions:

- Appropriate use: For external use only; not for intranasal, intravaginal, ophthalmic, oral, or mucosal application. For treatment of impetigo covering up to 100 cm^2 total area in adults, or 2% of total body surface area in children. Concomitant use with other topical products to the same treatment area has not been evaluated.

Geriatric ConsiderationsNo specific recommendations for elderly patients.
Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

1% to 10%:

Central nervous system: Headache (1% to 2%), pyrexia (1%)

Dermatologic: Pruritus (2%), eczema (1%)

Gastrointestinal: Diarrhea (1% to 2%), nausea (1%)

Local: Application site irritation (2%), application site pruritus (2%)

Respiratory: Nasopharyngitis (1% to 2%)

<1%: Application site erythema, contact dermatitis, creatinine phosphokinase increased

Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringFor external use only to treat or prevent infections proven or suspected to be caused by susceptible bacteria. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Patient EducationThis medication is for external use only; do not swallow, and do not use in the eyes, on the mouth or lips, inside the nose, or inside the female genital area. Do not take any other prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. Use for the full time recommended by prescriber, even if symptoms have improved. Apply to affected area as directed; may cover treatment area with sterile bandage or gauze dressing. Wash hands thoroughly after applying (if hands are not the area for treatment). Report immediately if the application area worsens with increased irritation, redness, itching, burning, swelling, blistering, or oozing. Notify prescriber if there is no improvement in symptoms within 3-4 days after starting use.
Dosage Forms

Ointment, topical:

Altabax™: 1% (5 g, 10 g, 15 g)

Generic AvailableNo
ManufacturerGlaxoSmithKline
Pricing: U.S. (www.drugstore.com)

Ointment (Altabax)

1% (5): $46.99

1% (10): $71.01

1% (15): $86.69

Mechanism of ActionPrimarily bacteriostatic. Inhibits normal bacterial protein biosynthesis by binding at a unique site (protein L3) on the ribosomal 50S subunit; prevents formation of active 50S ribosomal subunits by inhibiting peptidyl transfer and blocking P-site interactions at this site

Pharmacodynamics/Kinetics

Absorption: Topical: Low; increased when applied to abraded skin

Protein binding: 94%

Metabolism: Hepatic via CYP 3A4; extensively metabolized by mono-oxygenation and di-oxygenation to multiple metabolites

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
References

Parish LC, Jorizzo JL, Breton JJ, et al, "Topical Retapamulin Ointment (1%, wt/wt) Twice Daily for 5 Days Versus Oral Cephalexin Twice Daily for 10 Days in the Treatment of Secondarily Infected Dermatitis: Results of a Randomized Controlled Trial," *J Am Acad Dermatol*, 2006, 55(6):1003-13.[PubMed 17097398]

International Brand NamesAltargo (BE, CZ, DE, DK, EE, GB, IE, NO, SE)

Reteplase

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English

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V.) among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(RE ta plase)
U.S. Brand NamesRetavase®
Canadian Brand NamesRetavase®
Pharmacologic Category[Thrombolytic Agent]
Use: Labeled IndicationsManagement of ST-elevation myocardial infarction (STEMI); improvement of ventricular function; reduction of the incidence of CHF and the reduction of mortality following AMI

Recommended criteria for treatment: STEMI: Chest pain ≥20 minutes duration, onset of chest pain within 12 hours of treatment (or within prior 12-24 hours in patients with continuing ischemic symptoms), and ST-segment elevation >0.1 mV in at least two contiguous precordial leads or two adjacent limb leads on ECG or new or presumably new left bundle branch block (LBBB)

Dosing: Adults

STEMI: I.V.: 10 units I.V. over 2 minutes, followed by a second dose 30 minutes later of 10 units I.V. over 2 minutes; withhold second dose if serious bleeding or anaphylaxis occurs.

Note: All patients should receive 162-325 mg of chewable nonenteric coated aspirin as soon as possible and then daily. Administer concurrently with heparin 60 units/kg bolus (maximum: 4000 units) followed by continuous infusion of 12 units/kg/hour (maximum: 1000 units/hour) and adjust to aPTT target of 50-70 seconds (or 1.5-2 times the upper limit of control).

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricNot recommended
Administration: I.V.Infuse over 2 minutes.
Administration: I.V. DetailNo other medications should be added to the injection solution.
StorageDosage kits should be stored at 2°C to 25°C (36°F to 77°F) and remain sealed until use in order to protect from light.
ReconstitutionReteplase should be reconstituted using the diluent, syringe, needle, and dispensing pin provided with each kit.
ContraindicationsHypersensitivity to reteplase or any component of the formulation; active internal bleeding; history of cerebrovascular accident; recent intracranial or intraspinal surgery or trauma; intracranial neoplasm, arteriovenous malformations, or aneurysm; known bleeding diathesis; severe uncontrolled hypertension
Allergy Considerations

- Thrombolytic Agent, Fibrin-Specific Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis: Rare anaphylactic reactions can occur.
- Arrhythmias: Coronary thrombolysis may result in reperfusion arrhythmias.
- Bleeding: Monitor all potential bleeding sites. If serious bleeding occurs, the infusion of reteplase and heparin should be stopped.
- Cholesterol embolism: Has rarely been reported.

Disease-related concerns:

- Conditions that increase bleeding risk: For the following conditions the risk of bleeding is higher with use of reteplase and should be weighed against the benefits of therapy: recent (within 10 days) major surgery (eg, CABG, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels), cerebrovascular disease, recent gastrointestinal or genitourinary bleeding, recent trauma including CPR, hypertension (systolic BP >180 mm Hg and/or diastolic BP >110 mm Hg), high likelihood of left heart thrombus (eg, mitral stenosis with atrial fibrillation), acute pericarditis, subacute bacterial endocarditis, hemostatic defects including ones caused by severe renal or hepatic dysfunction, significant hepatic dysfunction, diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions, septic thrombophlebitis or occluded AV cannula at seriously infected site, or any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of location.
- Myocardial infarct (MI): Appropriate use: Follow standard management for MI while infusing reteplase.

Concurrent drug therapy issues:

- Anticoagulants: Use with caution in patients receiving oral anticoagulants; increased risk of bleeding.

- Heparin: Concurrent heparin anticoagulation may contribute to bleeding.

Special populations:

- Elderly: Use with caution in patients with advanced age (eg, >75 years); increased risk of bleeding.
- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: Use with caution in pregnancy; increased risk of bleeding.

Other warnings/precautions:

- Administration: Intramuscular injections and nonessential handling of the patient should be avoided. Venipunctures should be performed carefully and only when necessary. If arterial puncture is necessary, use an upper extremity vessel that can be manually compressed.

Geriatric ConsiderationsNo specific changes in use in the elderly are necessary.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsBleeding is the most frequent adverse effect associated with reteplase. Heparin and aspirin have been administered concurrently with reteplase in clinical trials. The incidence of adverse events is a reflection of these combined therapies, and are comparable with comparison thrombolytics.

>10%: Local: Injection site bleeding (4.6% to 48.6%)

1% to 10%:

Gastrointestinal: Bleeding (1.8% to 9.0%)

Genitourinary: Bleeding (0.9% to 9.5%)

Hematologic: Anemia (0.9% to 2.6%)

<1% (Limited to important or life-threatening): Intracranial hemorrhage (0.8%), allergic/anaphylactoid reactions, cholesterol embolization

Other adverse effects noted are frequently associated with MI (and therefore may or may not be attributable to Retavase®) and include arrhythmia, hypotension, cardiogenic shock, pulmonary edema, cardiac arrest, reinfarction, pericarditis, tamponade, thrombosis, and embolism.

Drug Interactions

Anticoagulants: Thrombolytic Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Aprotinin: May diminish the therapeutic effect of Thrombolytic Agents. *Risk D: Consider therapy modification*

Drotrecogin Alfa: Thrombolytic Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Thrombolytic Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Monitoring ParametersMonitor for signs of bleeding (hematuria, GI bleeding, gingival bleeding)
Nursing: Physical Assessment/MonitoringUse caution when there is significant risk of bleeding (see Warnings/Precautions for specific use cautions). Assess potential risk interactions with other pharmacological and herbal products patient may be taking (especially those medications that may affect coagulation or platelet function). See Administration for infusion specifics. Patient should be closely monitored for bleeding during and following treatment: infusion site, neurological status (eg, intracranial hemorrhage), vital signs, and ECG. Bleeding precautions should be maintained; avoid I.M. injections, venipunctures (unless absolutely necessary), and nonessential handling of the patient. If arterial puncture is necessary, use an upper extremity vessel that can be manually compressed. Patient instructions determined by patient condition.
Monitoring: Lab TestsCBC, PTT, signs and symptoms of bleeding, ECG monitoring
Patient EducationThis medication can only be administered by infusion; you will be monitored closely during and after treatment. You will have a tendency to bleed easily; use caution to prevent injury (use electric razor, soft toothbrush, and caution with knives, needles, or anything sharp). Follow instructions for strict bedrest to reduce the risk of injury. If bleeding occurs, report immediately and apply pressure to bleeding spot until bleeding stops completely. Report unusual pain (acute headache, joint pain, chest pain); unusual bruising or bleeding; blood in urine, stool, or vomitus; bleeding gums; vision changes; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Retavase®: 10.4 units [equivalent to reteplase 18.1 mg; contains sucrose and polysorbate 80; packaged with sterile water for injection]

Generic AvailableNo

ManufacturerCentocor, Inc

Mechanism of ActionReteplase is a nonglycosylated form of tPA produced by recombinant DNA technology using *E. coli*; it initiates local fibrinolysis by binding to fibrin in a thrombus (clot) and converts entrapped plasminogen to plasmin

Pharmacodynamics/Kinetics

Onset of action: Thrombolysis: 30-90 minutes

Half-life elimination: 13-16 minutes

Excretion: Feces and urine

Clearance: Plasma: 250-450 mL/minute

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular Considerations

ST-Elevation Myocardial Infarction: The 2004 ACC/AHA guidelines for the management of patients with acute myocardial infarction recommend prehospital thrombolysis in special circumstances (eg, transport time >30 minutes). Efforts to quickly identify and safely treat appropriate candidates for therapy continue. Reducing treatment delays is very important to improve mortality. Thrombolytic therapy is indicated in patients with ST-segment elevation of >1 mm in two or more contiguous leads or at least 2 adjacent limb leads in patients with chest discomfort >30 minutes but ≤12 hours. Patients with chest discomfort suggestive of ischemia and new-onset left bundle branch block (LBBB) are also candidates for thrombolysis. Generally there is only a small trend for benefit of therapy after a delay of more than 12-24 hours, but thrombolysis may be considered for selected patients with ongoing ischemic pain and extensive ST elevation. Additional absolute contraindications for fibrinolysis use in ST-elevation myocardial infarction from the 2004 ACC/AHA guidelines: Any prior intracranial hemorrhage, ischemic stroke within 3 months (except one within 3 hours), significant closed head or facial trauma within 3 months. Additional relative contraindications include history of chronic severe, poorly-controlled hypertension, severe uncontrolled hypertension on presentation (systolic BP >180 mm Hg or diastolic >110 mm Hg; could be an absolute contraindication in low-risk patients), history of prior ischemic stroke > 3 months, dementia, or known intracranial pathology, traumatic or prolonged (>10 minutes) CPR or major surgery (<3 weeks), recent (within 2-4 weeks) internal bleeding, noncompressible vascular punctures, pregnancy, active peptic ulcer, current use of anticoagulants.

Thrombolytic and GP IIb/IIIa Inhibitor: In the GUSTO V trial, patients with acute MI were randomized to standard-dose reteplase or half-dose reteplase (two boluses of 5 units each, 30 minutes apart) and full dose abciximab. Thirty-day mortality (primary endpoint) was similar in both groups. The combination treatment group had fewer deaths or nonfatal reinfarctions, less need for urgent revascularization, fewer major ischemic complications. More bleeding occurred in the combination treatment group, but intracranial hemorrhage and nonfatal disabling stroke were similar in both groups. All cause mortality at one year was similar in both groups. In TIMI 14, the combination of full-dose abciximab (0.25 mg/kg bolus followed by a 12-hour infusion of 0.125 mcg/kg/minute, maximum 10 mcg/minute) and half-dose alteplase (15 mg bolus followed by 35 mg infusion over 60 minutes) resulted in 74% of patients achieving TIMI grade 3 flow at 90 minutes. The 2004 ACC/AHA guidelines for the management of patients with acute myocardial infarction suggests that abciximab and half-dose reteplase or tenecteplase may be considered for prevention of reinfarction in patients with an anterior MI, who <75 years of age and have no risk factors for bleeding.

However, more recently, the 2008 American College of Chest Physicians guidelines recommends against the combination of half-dose reteplase or tenecteplase and standard-dose abciximab (with low dose unfractionated heparin) in any patient with STEMI due to the lack of mortality benefit and the risk of major bleeding (Goodman, 2008).

Anesthesia and Critical Care Concerns/Other Considerations

Evidence-Based Information:

Management of Intracerebral Hemorrhage (ICH) Due to Thrombolysis: Overall management of ICH is similar regardless of cause; however, iatrogenic spontaneous ICH may have specific treatments. According to the 2007 ACC/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage, fibrinolytic-related ICH should be treated with infusion of platelets (6-8 units) and cryoprecipitate which contains factor VIII (Class IIb recommendation).

Index Termsr-PA; Recombinant Plasminogen Activator

References

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Antman EM, Anbe SC, Alpert JS, et al, "ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction - Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction)," *Circulation*, 2004, 110(5):588-636. Available at: http://www.circulationaha.org/cgi/content/full/110/5/588. Last accessed October 26, 2004. [PubMed 15289388]

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5. [PubMed 12413372]

Ryan TJ, Anderson JK, Antman EM, et al, “ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction),” *J Am Coll Cardiol*, 1996, 28:1328-428. [PubMed 8890834]

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Topol EJ, GUSTO V Investigators, “Reperfusion Therapy for Acute Myocardial Infarction With Fibrinolytic Therapy or Combination Reduced Fibrinolytic Therapy and Platelet Glycoprotein IIb/IIIa Inhibition: The GUSTO V Randomized Trial,” *Lancet*, 2001, 357:1905-14.[PubMed 11425410]

International Brand Names Rapilysin (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

$_o$(D) Immune Globulin'; return;">

Rh$_o$(D) Immune Globulin

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English English

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Pronunciation(ar aych oh (dee) i MYUN GLOB yoo lin)

U.S. Brand NamesHyperRHO™ S/D Full Dose; HyperRHO™ S/D Mini Dose; MICRhoGAM®; RhoGAM®; Rhophylac®; WinRho® SDF

Canadian Brand NamesWinRho® SDF

Pharmacologic CategoryImmune Globulin

Use: Labeled Indications

Suppression of Rh isoimmunization: Use in the following situations when an Rh$_o$(D)-negative individual is exposed to Rh$_o$(D)-positive blood: During delivery of an Rh$_o$(D)-positive infant; abortion; amniocentesis; chorionic villus sampling; ruptured tubal pregnancy; abdominal trauma; hydatidiform mole; transplacental hemorrhage. Used when the mother is Rh$_o$(D) negative, the father of the child is either Rh$_o$(D) positive or Rh$_o$(D) unknown, the baby is either Rh$_o$(D) positive or Rh$_o$(D) unknown.

Transfusion: Suppression of Rh isoimmunization in Rh$_o$(D)-negative individuals transfused with Rh$_o$(D) antigen-positive RBCs or blood components containing Rh$_o$(D) antigen-positive RBCs

Treatment of idiopathic thrombocytopenic purpura (ITP): Used in the following nonsplenectomized Rh$_o$(D) positive individuals: Children with acute or chronic ITP, adults with chronic ITP, children and adults with ITP secondary to HIV infection

Dosing: Adults

ITP:

Rhophylac®: I.V.: 50 mcg/kg

WinRho® SDF: I.V.:

Initial: 50 mcg/kg as a single injection, or can be given as a divided dose on separate days. If hemoglobin is <10 g/dL: Dose should be reduced to 25-40 mcg/kg

Subsequent dosing: 25-60 mcg/kg can be used if required to elevate platelet count

Maintenance dosing if patient **did respond** to initial dosing: 25-60 mcg/kg based on platelet and hemoglobin levels

Maintenance dosing if patient **did not respond** to initial dosing:

Hemoglobin 8-10 g/dL: Redose between 25-40 mcg/kg

Hemoglobin >10 g/dL: Redose between 50-60 mcg/kg

Hemoglobin <8 g/dL: Use with caution

Rh$_o$(D) suppression:Note: One “full dose” (300 mcg) provides enough antibody to prevent Rh sensitization if the volume of RBC entering the circulation is ≤15 mL. When >15 mL is suspected, a fetal red cell count should be performed to determine the appropriate dose.

Pregnancy:

Antepartum prophylaxis: In general, dose is given at 28 weeks. If given early in pregnancy, administer every 12 weeks to ensure adequate levels of passively acquired anti-Rh

HyperRHO™ S/D Full Dose, RhoGAM®: I.M.: 300 mcg

Rhophylac®, WinRho® SDF: I.M., I.V.: 300 mcg

Postpartum prophylaxis: In general, dose is administered as soon as possible after delivery, preferably within 72 hours. Can be given up to 28 days following delivery

HyperRHO™ S/D Full Dose, RhoGAM®: I.M.: 300 mcg

Rhophylac®: I.M., I.V.: 300 mcg

WinRho® SDF: I.M., I.V.: 120 mcg

Threatened abortion, any time during pregnancy (with continuation of pregnancy):

HyperRHO™ S/D Full Dose, RhoGAM®: I.M.: 300 mcg; administer as soon as possible

Rhophylac®, WinRho® SDF: I.M./I.V.: 300 mcg; administer as soon as possible

Abortion, miscarriage, termination of ectopic pregnancy:

RhoGAM®: I.M.: ≥13 weeks gestation: 300 mcg.

HyperRHO™ S/D Mini Dose, MICRhoGAM®: <13 weeks gestation: I.M.: 50 mcg

Rhophylac®: I.M., I.V.: 300 mcg

WinRho® SDF: I.M., I.V.: After 34 weeks gestation: 120 mcg; administer immediately or within 72 hours

Amniocentesis, chorionic villus sampling:

HyperRHO™ S/D Full Dose, RhoGAM®: I.M.: At 15-18 weeks gestation or during the 3rd trimester: 300 mcg. If dose is given between 13-18 weeks, repeat at 26-28 weeks and within 72 hours of delivery.

Rhophylac®: I.M., I.V.: 300 mcg

WinRho® SDF: I.M., I.V.:

Before 34 weeks gestation: 300 mcg; administer immediately, repeat dose every 12 weeks during pregnancy

After 34 weeks gestation: 120 mcg, administered immediately or within 72 hours

Excessive fetomaternal hemorrhage (>15 mL): Rhophylac®: I.M., I.V.: 300 mcg within 72 hours plus 20 mcg/mL fetal RBCs in excess of 15 mL if excess transplacental bleeding is quantified **or** 300 mcg/dose if bleeding cannot be quantified

Abdominal trauma, manipulation:

HyperRHO™ S/D Full Dose, RhoGAM®: I.M.: 2nd or 3rd trimester: 300 mcg. If dose is given between 13-18 weeks, repeat at 26-28 weeks and within 72 hours of delivery.

Rhophylac®: I.M., I.V.: 300 mcg within 72 hours

WinRho® SDF: I.M., I.V.: After 34 weeks gestation: 120 mcg; administer immediately or within 72 hours

Transfusion:

HyperRHO™ S/D Full Dose, RhoGAM®: I.M.: Multiply the volume of Rh positive whole blood administered by the hematocrit of the donor unit to equal the volume of RBCs transfused. The volume of RBCs is then divided by 15 mL, providing the number of 300 mcg doses (vials/syringes) to administer. If the dose calculated results in a fraction, round up to the next higher whole 300 mcg dose (vial/syringe).

WinRho® SDF: Administer within 72 hours after exposure of incompatible blood transfusions or massive fetal hemorrhage.

I.V.: Calculate dose as follows; administer 600 mcg every 8 hours until the total dose is administered:

Exposure to Rh$_o$(D) positive whole blood: 9 mcg/mL blood

Exposure to Rh$_o$(D) positive red blood cells: 18 mcg/mL cells

I.M.: Calculate dose as follows; administer 1200 mcg every 12 hours until the total dose is administered:

Exposure to Rh$_o$(D) positive whole blood: 12 mcg/mL blood

Exposure to Rh$_o$(D) positive red blood cells: 24 mcg/mL cells

Rhophylac®: I.M., I.V.:20 mcg per 2 mL transfused blood or 1 mL erythrocyte concentrate

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**ITP, transfusion:** Rhophylac®, WinRho® SDF: Refer to adult dosing.
Dosing: Renal Impairment I.V. infusion: Use caution; may require infusion rate reduction or discontinuation.
Administration: I.MAdminister into the deltoid muscle of the upper arm or anterolateral aspect of the upper thigh. Avoid gluteal region due to risk of sciatic nerve injury. If large doses (>5 mL) are needed, administration in divided doses at different sites is recommended. **Note:** Do not administer I.M. Rho(D) immune globulin for ITP.
Administration: I.V.

WinRho® SDF: Infuse over at least 3-5 minutes; do not administer with other medications

Rhophylac®: ITP: Infuse at 2 mL per 15-60 seconds

Administration: I.V. Detail**Note:** If preparing dose using liquid formulation, withdraw the entire contents of the vial to ensure accurate calculation of the dosage requirement.
StorageStore at 2°C to 8°C (35°F to 46°F); do not freeze.

Rhophylac®: Protect from light.

ContraindicationsHypersensitivity to immune globulins or any component of the formulation; prior sensitization to Rh$_o$(D)
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis: Use with caution in patients with IgA deficiency, may contain trace amounts of IgA; patients who are IgA deficient may have the potential for developing IgA antibodies, anaphylactic reactions may occur.

- Intravascular hemolysis (IVH): Rare but serious signs and symptoms (eg, back pain, shaking, chills, fever, discolored urine; onset within 4 hours of infusion) of IVH have been reported in postmarketing experience in patients treated for ITP. Clinically-compromising anemia, acute renal insufficiency and disseminated intravascular coagulation (DIC) have also been reported. ITP patients should be advised of the signs and symptoms of IVH and instructed to report them immediately.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with thrombocytopenia or coagulation disorders; bleeding/hematoma may occur from I.M. administration.

- Immune globulin deficiency syndromes: Not for replacement therapy in immune globulin deficiency syndromes.

- ITP: Appropriate use: Safety and efficacy not established in Rh_o(D) negative, non-ITP thrombocytopenia, or splenectomized patients. Decrease dose with hemoglobin <10 g/dL; use with extreme caution if hemoglobin <8 g/dL. Do not administer I.M. or SubQ; administer dose I.V. only.

- Renal impairment: Use with caution in patients with renal impairment; may require an infusion rate reduction or discontinuation.

- Rh_o(D) suppression: For use in the mother; do not administer to the neonate.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

- Maltose: Some products may contain maltose, which may result in falsely-elevated blood glucose readings.

- Rhophylac®: Safety and efficacy have not been established for Rhophylac® in patients with anemia.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have not been conducted. Available evidence suggests that Rh_o(D) immune globulin administration during pregnancy does not harm the fetus or affect future pregnancies.

LactationDoes not enter breast milk

Adverse ReactionsFrequency not defined.

Cardiovascular: Hyper-/hypotension, pallor, tachycardia, vasodilation

Central nervous system: Chills, dizziness, fever, headache, malaise, somnolence

Dermatologic: Pruritus, rash

Gastrointestinal: Abdominal pain, diarrhea, nausea, vomiting

Hematologic: Haptoglobin decreased, hemoglobin decreased (patients with ITP), intravascular hemolysis (patients with ITP)

Hepatic: Bilirubin increased, LDH increased

Local: Injection site reaction: Discomfort, induration, mild pain, redness, swelling

Neuromuscular & skeletal: Arthralgia, back pain, hyperkinesia, myalgia, weakness

Renal: Acute renal insufficiency

Miscellaneous: Anaphylaxis, diaphoresis, infusion-related reactions, positive anti-C antibody test (transient), shivering

Postmarketing and/or case reports: Anemia (clinically-compromising), DIC, dyspnea, erythema, hemoglobinuria (transient in patients with ITP), injection site irritation, vertigo

Drug Interactions

Vaccines (Live): Immune Globulins may diminish the therapeutic effect of Vaccines (Live). **Exceptions:** Influenza Virus Vaccine; Yellow Fever Vaccine. *Risk D: Consider therapy modification*

Test InteractionsSome infants born to women given Rh_o(D) antepartum have a weakly positive Coombs' test at birth. Fetal-maternal hemorrhage may cause false blood-typing result in the mother; when there is any doubt to the patients' Rh type, Rh_o(D) immune globulin should be administered. WinRho® SDF liquid contains maltose; may result in falsely elevated blood glucose levels with dehydrogenase pyrroloquinolinequinone or glucose-dye-oxidoreductase testing methods. WinRho® SDF contains trace amounts of anti-A, B, C and E; may alter Coombs' tests following administration.

Monitoring ParametersSigns and symptoms of intravascular hemolysis (IVH), anemia, and renal insufficiency; observe patient for side effects for at least 20 minutes following administration; patients with suspected IVH should have CBC, haptoglobin, plasma hemoglobin, urine dipstick, BUN, serum creatinine, liver function tests, DIC-specific tests (D-dimer, fibrin degradation products [FDP] or fibrin split products [FSP]) for differential diagnosis. Clinical response may be determined by monitoring platelets, red blood cell (RBC) counts, hemoglobin, and reticulocyte levels.

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests, therapeutic effectiveness, and adverse reactions. Monitor blood pressure; may cause hyper- or hypotension. Teach patient possible side effects, interventions to reduce side effects, and adverse reactions to report.

Monitoring: Lab TestsPatients with suspected IVH should have CBC, haptoglobin, plasma hemoglobin, urine dipstick, BUN, serum creatinine, liver function tests, DIC-specific tests (D-dimer, fibrin degradation products [FDP] or fibrin split products [FSP]) for differential diagnosis.

Clinical response may be determined by monitoring platelets, red blood cell (RBC) counts, hemoglobin, and reticulocyte levels.

Patient EducationDo not have live virus vaccinations within 3 months of receiving this medication. This medication can only be administered by injection or infusion; report immediately any difficulty breathing, chills, rapid heart beat, back rash, pain, or redness, swelling, pain at injection site, discolored urine, decreased urine output, sudden weight gain, or swelling of extremities. You may experience headache or mild headache (consult prescriber for appropriate analgesic); or sleepiness or dizziness (avoid driving or engaging in activities requiring alertness until response to medication is known). Report any acute or persistent adverse effects. **Pregnancy precautions:** Inform prescriber if you are pregnant or plan to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution [preservative free]:

HyperRHO™ S/D Full Dose: 300 mcg [for I.M. use only]

HyperRHO™ S/D Mini Dose: 50 mcg [for I.M. use only]

MICRhoGAM®: 50 mcg [for I.M. use only; contains polysorbate 80]

RhoGAM®: 300 mcg [for I.M. use only; contains polysorbate 80]

Rhophylac®: 300 mcg/2 mL (2 mL) [1500 int. units; for I.M. or I.V. use; contains human albumin]

WinRho® SDF:

120 mcg/~0.5 mL (~0.5 mL) [600 int. units; contains maltose and polysorbate 80; for I.M. or I.V. use] [DSC]

300 mcg/~1.3 mL (~1.3 mL) [1500 int. units; contains maltose and polysorbate 80; for I.M. or I.V. use]

500 mcg/~2.2 mL (~2.2 mL) [2500 int. units; contains maltose and polysorbate 80; for I.M. or I.V. use]

1000 mcg/~4.4 mL (~4.4 mL) [5000 int. units; contains maltose and polysorbate 80; for I.M. or I.V. use]

3000 mcg/~13 mL (~13 mL) [15,000 int. units; contains maltose and polysorbate 80; for I.M. or I.V. use]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Injection (RhoGAM (Human))

300 mcg (5): $662.50

Mechanism of Action

Rh suppression: Prevents isoimmunization by suppressing the immune response and antibody formation by Rh_o(D) negative individuals to Rh_o(D) positive red blood cells.

ITP: Not completely characterized; Rh_o(D) immune globulin is thought to form anti-D-coated red blood cell complexes which bind to macrophage Fc receptors within the spleen; blocking or saturating the spleens ability to clear antibody-coated cells, including platelets. In this manner, platelets are spared from destruction.

Pharmacodynamics/Kinetics

Onset of platelet increase: ITP: Platelets should rise within 1-2 days

Peak effect: In 7-14 days

Duration: Suppression of Rh isoimmunization: ~12 weeks; Treatment of ITP: 30 days (variable)

Distribution: V_d: I.M.: 8.59 L

Bioavailability: I.M.: Rhophylac®: 69%

Half-life elimination: 12-30 days

Time to peak, plasma: I.M.: 5-10 days; I.V. (WinRho® SDF): ≤2 hours

Pharmacotherapy PearlsA “full dose” of Rh_o(D) immune globulin has previously been referred to as a 300 mcg dose. It is not the actual anti-D content. Although dosing has traditionally been expressed in mcg, potency is listed in int. units (1 mcg = 5 int. units). ITP patients requiring transfusions should be transfused with Rho-negative blood cells to avoid exacerbating hemolysis; platelet products may contain red blood cells; caution should be exercised if platelets are from Rh_o-positive donors.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness and sedation

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsRhIG; Rho(D) Immune Globulin (Human); RhoIGIV; RhoIVIM

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Ware RE and Zimmerman SA, “Anti-D: Mechanisms of Action,” *Semin Hematol*, 1998, 35(1 Suppl 1):14-22.

International Brand Names Bay Rho-D (IL); BayRHo-D (ID); Hyperrho-D (TW); IGRHO (IL); KamRho-D IM (IL); KamRho-D IV (IL); Natead (FR); Partobulin (CZ, GB, HK, IT, TR); Partogamma (IT); Partogloman (AT); Probi RHO (D) (MX); Rhesogam (DE); Rhesogamma (SE); Rhesogamma P (AR); Rhesonativ (AE, BH, CY, DE, DK, EE, EG, IL, IQ, IR, JO, KW, LB, LY, NO, OM, QA, SA, SE, SY, YE); Rhesugam (ZA); Rhesuman (CH, ES, GR, IN, IT, PK, TR); Rhesuman Berna (CO, HK, IL, MY, TH); Rhogam (BE, HK); Rhophylac (FR, GB, IL); WinRho SDF (AU, IL, PH)

Ribavirin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Ribavirin may be confused with riboflavin, rifampin, Robaxin®

Pronunciation(rye ba VYE rin)

U.S. Brand NamesCopegus®; Rebetol®; RibaPak™; Ribasphere®; Virazole®

Canadian Brand NamesVirazole®

Pharmacologic CategoryAntiviral Agent

Use: Labeled Indications

Inhalation: Treatment of patients with respiratory syncytial virus (RSV) infections; specially indicated for treatment of severe lower respiratory tract RSV infections in patients with an underlying compromising condition (prematurity, bronchopulmonary dysplasia and other chronic lung conditions, congenital heart disease, immunodeficiency, immunosuppression), and recent transplant recipients

Oral capsule:

In combination with interferon alfa-2b (Intron® A) injection for the treatment of chronic hepatitis C in patients with compensated liver disease who have relapsed after alpha interferon therapy or were previously untreated with alpha interferons

In combination with peginterferon alfa-2b (PEG-Intron®) injection for the treatment of chronic hepatitis C in patients with compensated liver disease who were previously untreated with alpha interferons

Oral solution: In combination with interferon alfa 2b (Intron® A) injection for the treatment of chronic hepatitis C in patients with compensated liver disease who were previously untreated with alpha interferons or patients who have relapsed after alpha interferon therapy

Oral tablet: In combination with peginterferon alfa-2a (Pegasys®) injection for the treatment of chronic hepatitis C in patients with compensated liver disease who were previously untreated with alpha interferons (includes patients with histological evidence of cirrhosis [Child-Pugh class A] and patients with clinically-stable HIV disease)

Use: Unlabeled/InvestigationalUsed in other viral infections including influenza A and B and adenovirus

Dosing: Adults

Chronic hepatitis C (in combination with peginterferon alfa-2a): Oral tablet (Copegus®):

Monoinfection, genotype 1,4:

<75 kg: 1000 mg/day, in 2 divided doses

≥75 kg: 1200 mg/day, in 2 divided doses

Monoinfection, genotype 2,3: 800 mg/day, in 2 divided doses

Coinfection with HIV: 800 mg/day in 2 divided doses

Note: Treatment duration may vary. Consult current guidelines and literature. Pretreatment platelets should be ≥90,000/mm^3 (75,000/mm^3 for cirrhosis or 70,000/mm^3 for coinfection with HIV), ANC ≥1500/mm^3, hemoglobin ≥12 g/dL for women and ≥13 g/dL for men (11 g/dL for HIV coinfected women and 12 g/dL for coinfected men), and TSH and T_4 within normal limits or controlled adequately. CD4+ cell count should be ≥200 cells/microL (or CD4+ count 100-200 cells/microL and HIV-1 RNA <5000 copies/mL) for coinfection with HIV.

Chronic hepatitis C (in combination with interferon alfa-2b): Oral capsule (Rebetol®, Ribasphere®):

≤75 kg: 400 mg in the morning, then 600 mg in the evening

>75 kg: 600 mg in the morning, then 600 mg in the evening

Note: Treatment duration may vary. Consult current guidelines and literature.

Chronic hepatitis C (in combination with peginterferon alfa-2b): Oral capsule (Rebetol®, Ribasphere®): 400 mg twice daily

Note: Treatment duration may vary. Consult current guidelines and literature.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

RSV infection: Infants and Children: Aerosol inhalation: Use with Viratek® small particle aerosol generator (SPAG-2): A concentration of 20 mg/mL (6 g reconstituted with 300 mL of sterile water without preservatives) administered for 12-18 hours/day for 3 days, up to 7 days in length.

Chronic hepatitis C (in combination with interferon alfa-2b): Oral solution should be used in children 3-5 years of age, children ≤25 kg, or those unable to swallow capsules.

Capsule/oral solution: Children ≥3 years: 15 mg/kg/day in 2 divided doses.

Capsule dosing recommendations:

25-36 kg: 400 mg/day (200 mg morning and evening)

37-49 kg: 600 mg/day (200 mg in the morning and 400 mg in the evening)

50-61 kg: 800 mg/day (400 mg in the morning and evening)

>61 kg: Refer to adult dosing.

Note: Treatment duration may vary. Consult current guidelines and literature.

Dosing: Renal ImpairmentCl_{cr} <50 mL/minute: Oral route is not recommended.

Dosing: Hepatic ImpairmentHepatic decompensation (Child-Pugh class B and C): Use of ribavirin tablets is contraindicated.

Dosing: Adjustment for ToxicityOral: Capsule, solution, tablet:

Patient **without** cardiac history:

Hemoglobin <10 g/dL:

Children: Decrease dose to 7.5 mg/kg/day

Adults: Decrease dose to 600 mg/day

Hemoglobin <8.5 g/dL: Children and Adults: Permanently discontinue treatment

Patient **with** cardiac history:

Hemoglobin has decreased ≥2 g/dL during any 4-week period of treatment:

Children: Decrease dose to 7.5 mg/kg/day

Adults: Decrease dose to 600 mg/day

Hemoglobin <12 g/dL after 4 weeks of reduced dose: Children and Adults: Permanently discontinue treatment

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister concurrently with interferon alfa injection. Capsule should not be opened, crushed, chewed, or broken. Capsules are not for use in children <5 years of age. Use oral solution for children 3-5 years, those ≤25 kg, or those who cannot swallow capsules.

Capsule, in combination with interferon alfa-2b: May be administered with or without food, but always in a consistent manner in regard to food intake.

Capsule, in combination with peginterferon alfa 2b: Administer with food.

Solution, in combination with interferon alfa-2b: May be administered with or without food, but always in a consistent manner in regard to food intake.

Tablet: Should be administered with food.

Administration: InhalationRibavirin should be administered in well-ventilated rooms (at least 6 air changes/hour). In mechanically-ventilated patients, ribavirin can potentially be deposited in the ventilator delivery system depending on temperature, humidity, and electrostatic forces; this deposition can lead to malfunction or obstruction of the expiratory valve, resulting in inadvertently high positive end-expiratory pressures. The use of one-way valves in the inspiratory lines, a breathing circuit filter in the expiratory line, and frequent monitoring and filter replacement have been effective in preventing these problems. Solutions in SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution. Should not be mixed with other aerosolized medication.

Dietary ConsiderationsWhen used in combination with interferon alfa-2b, capsules and solution may be taken with or without food, but always in a consistent manner in regard to food intake (ie, always take with food or always take on an empty stomach). When used in combination with peginterferon alfa 2b, capsules should be taken with food. Tablets should be taken with food.

Storage

Inhalation: Store vials in a dry place at 15°C to 30°C (59°F to 86°F).

Oral: Store at controlled room temperature of 25°C (77°F). Solution may also be refrigerated at 2°C to 8°C (36°F to 46°F).

ReconstitutionInhalation: Do not use any water containing an antimicrobial agent to reconstitute drug. Reconstituted solution is stable for 24 hours at room temperature.

CompatibilityInhalation: Should not be mixed with other aerosolized medication.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) for treatment of hepatitis C where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to ribavirin or any component of the formulation; women of childbearing age who will not use contraception reliably; pregnancy

Additional contraindications for oral formulation: Male partners of pregnant women; hemoglobinopathies (eg, thalassemia major, sickle cell anemia); patients with autoimmune hepatitis; ribavirin tablets are contraindicated in patients with hepatic decompensation (Child-Pugh class B and C)

Refer to individual monographs for Interferon Alfa-2b (Intron® A) and Peginterferon Alfa-2a (Pegasys®) for additional contraindication information.

Warnings/Precautions

Boxed warnings:

- Hemolytic anemia: See "Concerns related to adverse effects" below.
- Hepatitis C: See "Disease-related concerns" below.
- Inhalation: Ventilator patients: See "Dosage form specific issues" below.
- Pregnancy: See "Special populations" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Hemolytic anemia: **[U.S. Boxed Warning]: Hemolytic anemia is the primary toxicity of oral therapy; usually occurring within 1-2 weeks of therapy initiation;** observed in ~10% to 13% of patients when alfa interferons were combined with ribavirin. Assess cardiac function before initiation of therapy. Anemia associated with ribavirin may worsen underlying cardiac disease. Avoid use in patients with significant/unstable cardiac disease. If any deterioration in cardiovascular status occurs, discontinue therapy. Patients with renal dysfunction and/or those >50 years of age should be carefully assessed for development of anemia.

Disease-related concerns:

- Hepatic impairment: Discontinue therapy if evidence of hepatic decompensation (Child-Pugh score ≥6) is observed.
- Hepatitis C: Appropriate use: **[U.S. Boxed Warning]: Ribavirin monotherapy is not effective for chronic hepatitis C infection.**
- Renal impairment: Use with caution in patients with renal impairment; avoid use in patients with Cl_{cr} <50 mL/minute.

Concurrent drug therapy issues:

Combination therapy with alfa interferons:

- Autoimmune/infectious disorders: Have occurred with combination therapy; use with caution in patients with autoimmune disease or severe infection.
- Bone marrow suppression: Has occurred with combination therapy; discontinue if occurs.
- Dental and periodontal disorders: Have been reported with combination therapy; patients should be instructed to brush teeth twice daily and have regular dental exams. Xerostomia may contribute to and/or exacerbate dental disorders.
- Dermatologic reactions: Severe cutaneous reactions, including Stevens-Johnson syndrome and exfoliative dermatitis have been reported (rarely) with combination therapy; discontinue with signs or symptoms of severe skin reactions.
- Diabetes: Has occurred with combination therapy; monitor blood sugars closely.
- Hypersensitivity reactions: Acute hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchoconstriction, and urticaria) have been observed (rarely) with combination therapy.
- Pancreatitis: Has occurred with combination therapy; discontinue therapy in suspected/confirmed pancreatitis.
- Psychiatric disorders: Severe psychiatric events have occurred including depression and suicidal behavior during combination therapy. Avoid use in patients with a psychiatric history; discontinue if severe psychiatric symptoms occur.
- Pulmonary events: Pulmonary symptoms (eg, dyspnea, pulmonary infiltrates, pneumonitis, pneumonia [rarely fatal]) have been associated with combination therapy; use with caution in patients with pulmonary disease, including sarcoidosis (exacerbation reported).

Special populations:

- Elderly: Use with caution in the elderly; may be more susceptible to adverse effects
- Pediatrics: Safety and efficacy of the oral products have not been established in children <3 years of age.

- Pregnancy: **[U.S. Boxed Warning]: Significant teratogenic effects have been observed in all animal studies.** A negative pregnancy test is required before initiation and monthly thereafter. Avoid pregnancy in female patients and female partners of male patients, during therapy, and for at least 6 months after treatment; two forms of contraception should be used.

Dosage form specific issues:

- Inhalation: **[U.S. Boxed Warning]: Use with caution in patients requiring assisted ventilation because precipitation of the drug in the respiratory equipment may interfere with safe and effective patient ventilation; sudden deterioration of respiratory function has been observed;** monitor carefully in patients with COPD and asthma for deterioration of respiratory function. Ribavirin is potentially mutagenic, tumor-promoting, and gonadotoxic. Although anemia has not been reported with inhalation therapy, consider monitoring for anemia 1-2 weeks post-treatment. Pregnant healthcare workers may consider unnecessary occupational exposure; ribavirin has been detected in healthcare workers' urine. Healthcare professionals or family members who are pregnant (or may become pregnant) should be counseled about potential risks of exposure and counseled about risk reduction strategies.

Other warnings/precautions:

- Appropriate use: Safety and efficacy have not been established in patients who have failed other alpha interferon therapy, received organ transplants, or been coinfected with hepatitis B or HIV (Copegus® may be used in HIV coinfected patients unless CD4+ cell count is <100 cells/microL). Oral products should not be used for HIV infection, adenovirus, RSV, or influenza infections.

Geriatric ConsiderationsNo specific recommendations are necessary in the elderly.
Pregnancy Risk FactorX
Pregnancy Considerations**[U.S. Boxed Warning]: Significant teratogenic effects have been observed in all animal studies** at ~0.01 times the maximum recommended daily human dose. Use is contraindicated in pregnancy. Negative pregnancy test is required before initiation and monthly thereafter. Avoid pregnancy in female patients and female partners of male patients during therapy by using two effective forms of contraception; continue contraceptive measures for at least 6 months after completion of therapy. If patient or female partner becomes pregnant during treatment, she should be counseled about potential risks of exposure. If pregnancy occurs during use or within 6 months after treatment, report to the ribavirin pregnancy registry (800-593-2214).
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

Inhalation:

1% to 10%:

Central nervous system: Fatigue, headache, insomnia

Gastrointestinal: Nausea, anorexia

Hematologic: Anemia

<1%: Hypotension, cardiac arrest, digitalis toxicity, conjunctivitis, mild bronchospasm, worsening of respiratory function, apnea

Note: Incidence of adverse effects (approximate) in healthcare workers: Headache (51%); conjunctivitis (32%); rhinitis, nausea, rash, dizziness, pharyngitis, and lacrimation (10% to 20%); bronchospasm and/or chest pain (case reports in individuals with underlying airway disease)

Oral (all adverse reactions are documented while receiving combination therapy with alfa interferons; percentages as reported in adults); asterisked (*) percentages are those similar to interferon therapy alone:

>10%:

Central nervous system: Fatigue (60% to 70%)*, headache (43% to 66%)*, fever (32% to 46%)*, insomnia (26% to 41%), depression (20% to 36%)*, irritability (23% to 33%), dizziness (14% to 26%), impaired concentration (10% to 21%)*, emotional lability (7% to 12%)*

Dermatologic: Alopecia (27% to 36%), pruritus (13% to 29%), rash (5% to 28%), dry skin (10% to 24%), dermatitis (≤16%)

Endocrine and metabolic: Hyperuricemia (33% to 38%)

Gastrointestinal: Nausea (25% to 47%), anorexia (21% to 32%), weight decrease (10% to 29%), vomiting (9% to 25%)*, diarrhea (10% to 22%), dyspepsia (6% to 16%), abdominal pain (8% to 13%), xerostomia (≤12%), RUQ pain (≤12%)

Hematologic: Leukopenia (6% to 45%), neutropenia (8% to 42%; grade 4: 2% to 11%; 40% with HIV coinfection), hemoglobin decreased (21% to 36%), anemia (11% to 17%), thrombocytopenia (<1% to 15%), lymphopenia (12% to 14%), hemolytic anemia (10% to 13%)

Hepatic: Bilirubin increase (10% to 32%)

Neuromuscular & skeletal: Myalgia (40% to 64%)*, rigors (25% to 48%), arthralgia (22% to 34%)*, musculoskeletal pain (19% to 28%)

Respiratory: Dyspnea (13% to 26%), cough (7% to 23%), pharyngitis (≤13%), sinusitis (≤12%)*

Miscellaneous: Flu-like syndrome (13% to 18%)*, viral infection (≤12%), diaphoresis (≤11%)

1% to 10%:

Cardiovascular: Chest pain (5% to 9%)*, flushing (≤4%)

Central nervous system: Pain (≤10%), mood alteration (≤6%; 9% with HIV coinfection), agitation (5% to 8%), nervousness (6%)*, memory impairment (≤6%), malaise (≤6%), suicidal ideation (adolescents: 2%; adults: 1%)

Dermatologic: Eczema (4% to 5%)

Endocrine & metabolic: Menstrual disorder (≤7%), hypothyroidism (≤5%)

Gastrointestinal: Taste perversion (4% to 9%), constipation (≤5%)

Hepatic: Hepatomegaly (≤4%), transaminases increased (1% to 3%), hepatic decompensation (2% with HIV coinfection)

Neuromuscular & skeletal: Weakness (9% to 10%), back pain (5%)

Ocular: Blurred vision (≤6%), conjunctivitis (≤5%)

Respiratory: Rhinitis (≤8%), exertional dyspnea (≤7%)

Miscellaneous: Fungal infection (≤6%), bacterial infection (3% to 5%)

<1%: Aggression, angina, anxiety, aplastic anemia, arrhythmia; autoimmune disorders (systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis); cerebral hemorrhage, cholangitis, colitis, coma, corneal ulcer, diabetes mellitus, drug abuse relapse/overdose, fatty liver, gastrointestinal bleeding, gout, hallucination, hepatic dysfunction, hyper-/hypothyroidism, myositis, pancreatitis, peptic ulcer, peripheral neuropathy, psychosis, psychotic disorder, pulmonary dysfunction, pulmonary embolism, suicide, thrombotic thrombocytopenic purpura, thyroid function test abnormalities

Postmarketing and/or case reports: Dehydration, dental disorders, exfoliative dermatitis, hearing impairment/ loss, hypersensitivity (including anaphylaxis, angioedema, bronchoconstriction, and urticaria), periodontal disorders, pneumonitis, pulmonary infiltrates, pure red cell aplasia; skin reactions (erythema multiforme, exfoliative dermatitis, urticaria, vesiculobullous eruptions); sarcoidosis exacerbation, Stevens-Johnson syndrome, vertigo

Note: Incidence of anorexia, headache, fever, suicidal ideation, and vomiting are higher in children.

Drug Interactions

Influenza Virus Vaccine: Antiviral Agents (Influenza A and B) may diminish the therapeutic effect of Influenza Virus Vaccine. This only pertains to live, attentuated influenza virus vaccine. *Risk D: Consider therapy modification*

Interferons (Alfa): May enhance the adverse/toxic effect of Ribavirin. Hemolytic anemia has been observed. *Risk C: Monitor therapy*

Reverse Transcriptase Inhibitors (Nucleoside): Ribavirin may enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Oral: High-fat meal increases the AUC and C_{max}.

Monitoring Parameters

Inhalation: Respiratory function, hemoglobin, reticulocyte count, CBC with differential, I & O

Oral: Hemoglobin and hematocrit (pretreatment, 2- and 4 weeks after initiation), CBC with differential; pretreatment and monthly pregnancy test for women of childbearing age; LFTs, renal function, TSH, serum HCV RNA ; pretreatment ECG in patients with pre-existing cardiac disease; dental exams

Reference Range

Early viral response (EVR): >2 log decrease in HCV RNA after 12 weeks of treatment

End of treatment response (ETR): Absence of detectable HCV RNA at end of the recommended treatment period

Sustained treatment response (STR): Absence of HCV RNA in the serum 6 months following completion of full treatment course

Nursing: Physical Assessment/MonitoringNote specific cautions for healthcare professionals' exposure risks with inhalation formulation. Evaluate patient health status and history for contraindications and use cautions prior to beginning therapy. Evaluate results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, CNS effects [headache, fatigue, irritability, impaired concentration], GI disturbance [nausea, vomiting, anorexia], hematologic [anemia], deterioration of hepatic, respiratory, or cardiac status) on a regular basis with long-term therapy. Teach patient proper use (according to formulation), possible side effects/appropriate interventions, and adverse symptoms to report. Instruct patient to carefully read the FDA-approved medication guide distributed to each patient to whom this medication is dispensed for the treatment of hepatitis C. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Do not give to women of childbearing age or males who may have intercourse with pregnant or childbearing women unless both male and female are capable of complying with using two effective forms of contraception during therapy and 6 months following therapy.

Monitoring: Lab Tests

Inhalation: Respiratory function, CBC with differential

Oral: Hemoglobin and hematocrit (pretreatment, 2- and 4 weeks after initiation), CBC with differential; pretreatment and monthly pregnancy test for women of childbearing age; LFTs, renal function, TSH, serum HCV RNA; pretreatment ECG in patients with pre-existing cardiac disease

Patient EducationFor oral administration, take as directed (capsules, with food; solution, with or without food, but always in a consistent manner in regard to food intake). For aerosol use, follow exact directions for use of aerosol device. Do not allow pregnant women or women of childbearing age to come in any contact with this medication. If prescribed in conjunction with other medications (injections), maintain schedule as directed. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will need regular blood tests while taking this drug. You may experience increased susceptibility to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause dental or periodontal disorders (brush teeth at least twice daily and have regular dental exams). May cause confusion, insomnia, impaired concentration, emotional lability or headache (use cautions when driving or engaging in potentially hazardous tasks until response to drug is known); nausea, vomiting, or anorexia (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea (buttermilk, boiled milk, or yogurt may relieve diarrhea); or loss of hair (reversible). Report chest pain or palpitations; unusual cough or difficulty breathing; rash; signs of infection (fever, chills, unusual bleeding or bruising, infection, or unhealed sores or white plaques in mouth); tingling, weakness, or pain in extremities; CNS changes (suicidal ideation, fatigue, insomnia, irritability, depression, impaired concentration); or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Both males and females should use appropriate barrier contraceptive measures during and for 6 months following end of therapy. Do not allow family members or friends who are pregnant or may become pregnant to handle inhalation powder. This drug may cause serious fetal defects. Consult prescriber for appropriate barrier contraceptive measures if necessary or if you suspect you might be pregnant. Do not donate blood during or for 6 months following therapy. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 200 mg

- Rebetol®, Ribasphere®: 200 mg

Combination package [dose pack]:

- RibaPak™ 400/600 [each package contains]:
  - Tablet: 400 mg (7s)
  - Tablet: 600 mg (2s)

Powder for solution, for nebulization:

- Virazole®: 6 g (1s) [reconstituted product contains ribavirin 20 mg/mL]

Solution, oral:

- Rebetol®: 40 mg/mL (100 mL) [contains propylene glycol and sodium benzoate; bubble-gum flavor]

Tablet: 200 mg

- Copegus®: 200 mg
- Ribasphere®: 200 mg, 400 mg, 600 mg

Tablet [dose pack]:

- RibaPak™: 400 mg (14s); 600 mg (14s)

Generic AvailableYes: Capsule, tablet

Pricing: U.S. (www.drugstore.com)

Capsules (Rebetol)

- 200 mg (60): $553.99

Capsules (Ribasphere)

- 200 mg (30): $280.00

Capsules (Ribavirin)

- 200 mg (56): $260.02

Solution (Rebetol)

- 40 mg/mL (100): $223.97

Mechanism of ActionInhibits replication of RNA and DNA viruses; inhibits influenza virus RNA polymerase activity and inhibits the initiation and elongation of RNA fragments resulting in inhibition of viral protein synthesis

Pharmacodynamics/Kinetics

Absorption: Inhalation: Systemic; dependent upon respiratory factors and method of drug delivery; maximal absorption occurs with the use of aerosol generator via endotracheal tube; highest concentrations in respiratory tract and erythrocytes

Distribution: Oral capsule: Single dose: V_d 2825 L; distribution significantly prolonged in the erythrocyte (16-40 days), which can be used as a marker for intracellular metabolism

Protein binding: Oral: None

Metabolism: Hepatically and intracellularly (forms active metabolites); may be necessary for drug action

Bioavailability: Oral: 64%

Half-life elimination, plasma:

- Children: Inhalation: 6.5-11 hours
- Adults: Oral:
  - Capsule, single dose (Rebetol®, Ribasphere®): 24 hours in healthy adults, 44 hours with chronic hepatitis C infection (increases to ~298 hours at steady state)

Tablet, single dose (Copegus®): ~120-170 hours

Time to peak, serum: Inhalation: At end of inhalation period; Oral capsule: Multiple doses: 3 hours; Tablet: 2 hours

Excretion: Inhalation: Urine (40% as unchanged drug and metabolites); Oral capsule: Urine (61%), feces (12%)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusWhen used in combination with interferon alfa-2A or alfa-2b: Dizziness and drowsiness are common; may rarely cause delirium. Severe psychiatric disorders, including depression and suicidal behavior, have been associated with the use of some interferons. Careful neuropsychiatric monitoring is recommended.

Mental Health: Effects on Psychiatric TreatmentWhen used in combination with interferon alfa-2A or alfa-2b: May cause leukopenia; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce additive sedation and dry mouth

Index TermsRTCA; Tribavirin

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International Brand NamesCopegus (BE, CH, CO, CZ, DE, DK, EC, EE, FI, FR, GB, HK, IE, IL, IT, MX, NL, NO, NZ, PL, SE, SG, TH, UY); Desiken (MX); Probirina (MX); Rebetol (AT, BE, BG, CH, CN, CR, CZ, DE, DK, DO, ES, FI, FR, GB, GR, GT, HK, HN, IE, IL, IT, MY, NI, NL, NO, NZ, PA, PL, PT, RU, SE, SG, SV, TH, TR, VE); Ribavin (IN); Ribazole (PH); Robatrol (TW); Robavin (KP); Trivorin (MX); Vibuzol (AR); Vilona (MX); Viramid (IT, KP); Virazide (AU, ID, MX, PK); Virazole (AE, BE, BH, BR, CR, CY, EG, GB, GT, HK, HN, IL, IQ, IR, JO, KW, LB, LY, NI, OM, QA, SA, SE, SG, SV, SY, YE); Xinweilin (CL)

Riboflavin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Riboflavin may be confused with ribavirin

Pronunciation(RYE boe flay vin)
U.S. Brand NamesRibo-100
Pharmacologic Category[Vitamin, Water Soluble]
Use: Labeled IndicationsPrevention of riboflavin deficiency and treatment of ariboflavinosis
Dosing: Adults

Riboflavin deficiency: Oral: 5-30 mg/day in divided doses

Recommended daily allowance: Oral: 1.2-1.7 mg

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Riboflavin deficiency: Oral: Children: 2.5-10 mg/day in divided doses

Recommended daily allowance: Oral: Children: 0.4-1.8 mg

Warnings/Precautions

Other warnings/precautions:

â˘ Vitamin deficiency: Single vitamin deficiency is rare; evaluate for other deficiencies.

Pregnancy Risk FactorA/C (dose exceeding RDA recommendation)
LactationEnters breast milk/compatible
Adverse ReactionsFrequency not defined: Genitourinary: Discoloration of urine (yellow-orange)
Drug InteractionsThere are no known significant interactions.
Test InteractionsLarge doses may interfere with urinalysis based on spectrometry; may cause false elevations in fluorometric determinations of catecholamines and urobilinogen
Monitoring ParametersCBC and reticulocyte counts (if anemic when treating deficiency)
Nursing: Physical Assessment/MonitoringAssess knowledge/teach patient appropriate use, dietary instruction, possible side effects, and adverse symptoms to report.
Patient EducationTake with food. Large doses may cause bright yellow or orange urine.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 25 mg, 50 mg, 100 mg

Ribo-100: 100 mg

Generic AvailableYes
Mechanism of ActionComponent of flavoprotein enzymes that work together, which are necessary for normal tissue respiration; also needed for activation of pyridoxine and conversion of tryptophan to niacin
Pharmacodynamics/Kinetics

Absorption: Readily via GI tract, however, food increases extent; decreased with hepatitis, cirrhosis, or biliary obstruction

Metabolism: None

Half-life elimination: Biologic: 66-84 minutes

Excretion: Urine (9%) as unchanged drug

Pharmacotherapy PearlsDietary sources of riboflavin include liver, kidney, dairy products, green vegetables, eggs, whole grain cereals, yeast, and mushroom.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsLactoflavin; Vitamin B_2; Vitamin G

International Brand NamesArcavit-B!2 (AT); B2-ASmedic (DE); Beflavine (FR); Berivine (BE, LU); Bi-Love-G (JP); Bisanorin (JP); Bisulase (JP); Bituvitan (JP); Bonabon B!2 (JP); Butirid (JP); Dalivit (BR); Eyekas (JP); Flavitol (AT); Hibon (JP); Lacflavin (JP); Liperox (AR); Multiscleran (DE); Ribobis (JP); Ribobutin (JP); Ribon (BE, LU); Riboract (JP); Vita-B2 (FI, PL); Vitamin B!2 Jenapharm (DE); Vitamin B!2 Jenapharm[inj.] (DE); Vitamin B!2 Streuli[Ampullen] (CH); Vitamin B!2 Streuli[Tab.] (CH); Vitamin B!2-Injektopas (DE); Vitaminum B2 (PL); Wakaflavin-L (JP); Werdo (DE)

RICE

Lexi-Drugs Online

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Pharmacologic Category Chemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen Use Lymphoma, non-Hodgkin's

Index Terms R-ICE; Rituximab-ICE

Regimen

Rituximab: I.V.: 375 mg/m^2/day days -2 and 1 (cycle 1)

[total dose/cycle = 750 mg/m^2]

Rituximab: I.V.: 375 mg/m^2 day 1 (cycles 2 and 3)

[total dose/cycle = 375 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 3, 4, and 5

[total dose/cycle = 300 mg/m^2]

Carboplatin: I.V.: AUC = 5 (maximum 800 mg) day 4

[total dose/cycle = AUC = 5]

Ifosfamide: I.V.: 5000 mg/m^2 continuous infusion day 4

[total dose/cycle = 5000 mg/m^2]

Mesna: I.V.: 5000 mg/m^2 continuous infusion day 4

[total dose/cycle = 5000 mg/m^2]

Filgrastim: SubQ: 5 mcg/kg/day days 7 to 14 (cycles 1 and 2)

[total dose/cycle = 40 mcg/kg]

Filgrastim: SubQ: 10 mcg/kg/day days 7 to 14 (cycle 3)

[total dose/cycle = 80 mcg/kg]

Repeat cycle every 2 weeks

References

Kewalramani T, Zelenetz AD, Nimer SD, et al, âRituximab and ICE as Second-Line Therapy before Autologous Stem Cell Transplantation for Relapsed or Primary Refractory Diffuse Large B-Cell Lymphoma,â *Blood*, 2004, 103(10):3684-8. [PubMed 14739217]

Rifabutin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Rifabutin may be confused with rifampin

Pronunciation(rif a BYOO tin)

U.S. Brand NamesMycobutin®

Canadian Brand NamesMycobutin®

Pharmacologic CategoryAntibiotic, Miscellaneous; Antitubercular Agent

Use: Labeled IndicationsPrevention of disseminated *Mycobacterium avium* complex (MAC) in patients with advanced HIV infection

Use: Unlabeled/InvestigationalUtilized in multidrug regimens for treatment of MAC

Dosing: Adults

Disseminated MAC in advanced HIV infection:

Prophylaxis: Oral: 300 mg once daily (alone or in combination with azithromycin)

Treatment (unlabeled use): Oral:

Patients not receiving NNRTIs or protease inhibitors:

Initial phase: 5 mg/kg daily (maximum: 300 mg)

Second phase: 5 mg/kg daily or twice weekly

Dosage adjustment for concurrent nelfinavir, amprenavir, indinavir: Reduce rifabutin dose to 150 mg/day; no change in dose if administered twice weekly

Dosage adjustment for concurrent efavirenz (no concomitant protease inhibitor): Increase rifabutin dose to 450-600 mg daily, or 600 mg 3 times/week

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Disseminated MAC in advanced HIV infection: Children >1 year:

Prophylaxis: Oral: 5 mg/kg daily; higher dosages have been used in limited trials

Treatment (unlabeled use): Oral: Patients not receiving NNRTIs or protease inhibitors:

Initial phase (2 weeks to 2 months): 10-20 mg/kg daily (maximum: 300 mg).

Second phase: 10-20 mg/kg daily (maximum: 300 mg) or twice weekly

Dosing: Renal ImpairmentCl$_{cr}$ <30 mL/minute: Reduce dose by 50%

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralShould be administered on an empty stomach, but may be taken with meals to minimize nausea or vomiting.

Dietary ConsiderationsMay be taken with meals or without food or mix with applesauce.

ContraindicationsHypersensitivity to rifabutin, any other rifamycins, or any component of the formulation; rifabutin is contraindicated in patients with a WBC <1000/mm^3 or a platelet count <50,000/mm^3

Allergy Considerations

- Rifamycin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with liver impairment; discontinue in patients with AST >500 units/L or if total bilirubin is >3 mg/dL.

- Renal impairment: Use with caution in patients with renal impairment; modification of dosage should be considered.
- Tuberculosis: Appropriate use: As a single agent must not be administered to patients with active tuberculosis since its use may lead to the development of tuberculosis that is resistant to both rifabutin and rifampin.

Geriatric ConsiderationsNo specific recommendations for the elderly.
Pregnancy Risk FactorB
LactationExcretion in breast milk unknown
Adverse Reactions

>10%:

Dermatologic: Rash (11%)

Genitourinary: Discoloration of urine (30%)

Hematologic: Neutropenia (25%), leukopenia (17%)

1% to 10%:

Central nervous system: Headache (3%)

Gastrointestinal: Abdominal pain (4%), vomiting/nausea (3%), diarrhea (3%), eructation (3%), anorexia (2%), flatulence (2%)

Hematologic: Anemia, thrombocytopenia (5%)

Hepatic: ALT increased (7% to 9%), AST increased (7% to 9%)

Neuromuscular & skeletal: Myalgia

<1%: Chest pain, dyspepsia, dyspnea, fever, insomnia, taste perversion, uveitis

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Induces** CYP3A4 (strong)
Drug Interactions

Alfentanil: Rifamycin Derivatives may increase the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Amiodarone: Rifamycin Derivatives may increase the metabolism of Amiodarone. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Rifamycin Derivatives may increase the metabolism of Angiotensin II Receptor Blockers. **Exceptions:** Candesartan; Eprosartan; Olmesartan; Telmisartan; Valsartan. *Risk C: Monitor therapy*

Antiemetics (5HT3 Antagonists): Rifamycin Derivatives may increase the metabolism of Antiemetics (5HT3 Antagonists). **Exceptions:** Dolasetron; Granisetron; Palonosetron. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Rifamycin Derivatives. Only rifabutin appears to be affected. Rifamycin Derivatives may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Aprepitant: Rifamycin Derivatives may increase the metabolism of Aprepitant. *Risk C: Monitor therapy*

Atovaquone: Rifamycin Derivatives may decrease the serum concentration of Atovaquone. *Risk D: Consider therapy modification*

Barbiturates: Rifamycin Derivatives may increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Rifamycin Derivatives may increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

BusPIRone: Rifamycin Derivatives may increase the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Rifamycin Derivatives may increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Clopidogrel: Rifamycin Derivatives may enhance the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Contraceptive (Progestins): Rifamycin Derivatives may decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Rifamycin Derivatives may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Rifamycin Derivatives may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dapsone: Rifamycin Derivatives may increase the metabolism of Dapsone. *Risk D: Consider therapy modification*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Delavirdine: May decrease the metabolism of Rifamycin Derivatives. Rifamycin Derivatives may increase the metabolism of Delavirdine. *Risk D:*

Consider therapy modification

Disopyramide: Rifamycin Derivatives may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Efavirenz: May decrease the serum concentration of Rifabutin. Rifabutin may decrease the serum concentration of Efavirenz. Management: If efavirenz is to be used with daily rifabutin, increase the planned rifabutin dose by 50%. If used with regimens where rifabutin is administered 2-3 times per week, consider doubling the rifabutin dose. *Risk D: Consider therapy modification*

Etravirine: Rifabutin may decrease the serum concentration of Etravirine. Management: Avoid concomitant use with rifabutin if a protease inhibitor/ritonavir combination is also used. *Risk C: Monitor therapy*

FentaNYL: Rifamycin Derivatives may decrease the serum concentration of FentaNYL. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Rifamycin Derivatives. This appears only affect rifabutin. Rifamycin Derivatives may increase the metabolism of Fluconazole. *Risk C: Monitor therapy*

Gefitinib: Rifamycin Derivatives may increase the metabolism of Gefitinib. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Rifamycin Derivatives may increase the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Rosuvastatin. *Risk D: Consider therapy modification*

Imatinib: Rifamycin Derivatives may increase the metabolism of Imatinib. *Risk D: Consider therapy modification*

Isoniazid: Rifamycin Derivatives may enhance the hepatotoxic effect of Isoniazid. Even so, this is a frequently employed combination regimen. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Rifamycin Derivatives. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Morphine Sulfate: Rifamycin Derivatives may decrease the serum concentration of Morphine Sulfate. *Risk C: Monitor therapy*

Mycophenolate: Rifamycin Derivatives may decrease the serum concentration of Mycophenolate. Specifically, rifamycin derivatives may decrease the concentration of the active metabolite mycophenolic acid. *Risk X: Avoid combination*

Nevirapine: Rifabutin may decrease the serum concentration of Nevirapine. Nevirapine may decrease the serum concentration of Rifabutin. Nevirapine may increase the serum concentration of Rifabutin. *Risk C: Monitor therapy*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Rifamycin Derivatives may decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: Rifamycin Derivatives may increase the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Propafenone: Rifamycin Derivatives may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

QuiNIDine: Rifamycin Derivatives may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ramelteon: Rifamycin Derivatives may increase the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Rifamycin Derivatives may increase the metabolism of Repaglinide. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Sunitinib: Rifamycin Derivatives may increase the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Tacrolimus: Rifamycin Derivatives may increase the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Tamoxifen: Rifamycin Derivatives may increase the metabolism of Tamoxifen. *Risk C: Monitor therapy*

Temsirolimus: Rifamycin Derivatives may decrease the serum concentration of Temsirolimus. Rifamycins will likely cause an even greater decrease in the concentration of the active metabolite sirolimus. Management: Temsirolimus prescribing information recommends against coadministration with strong CYP3A4 inducers such as rifampin; however, if concurrent therapy is necessary, an increase in temsirolimus dose to 50 mg/week should be considered. *Risk D: Consider therapy modification*

Terbinafine: Rifamycin Derivatives may increase the metabolism of Terbinafine. *Risk D: Consider therapy modification*

Tocainide: Rifamycin Derivatives may increase the metabolism of Tocainide. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Rifamycin Derivatives may increase the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Voriconazole: May increase the serum concentration of Rifamycin Derivatives. Rifamycin Derivatives may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Zaleplon: Rifamycin Derivatives may increase the metabolism of Zaleplon. *Risk C: Monitor therapy*

Zolpidem: Rifamycin Derivatives may increase the metabolism of Zolpidem. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: High-fat meal may decrease the rate but not the extent of absorption.
Monitoring ParametersPeriodic liver function tests, CBC with differential, platelet count
Nursing: Physical Assessment/MonitoringNot for use in patients with active tuberculosis. Assess potential for interactions with other pharmacological agents patient may be taking (eg, decreased levels/effects of multiple other agents). Caution females using hormone contraceptive about potential for decreased contraceptive effects. Evaluate results of laboratory tests, therapeutic effectiveness (prevention of MAC in patients with HIV), and adverse response (eg, anemia, neutropenia, GI disturbance). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsPeriodic liver function, CBC with differential, platelet count
Patient EducationDo not take any new medication during therapy without consulting prescriber. Take as directed, with or without food. Complete full course of therapy; do not skip doses. Will discolor urine, stool, saliva, tears, sweat, and other body fluid a red-brown color. Stains on clothing or contact lenses are permanent. Report skin rash; persistent vomiting or diarrhea; fever, chills, or flu-like symptoms; dark urine or pale stools; unusual bleeding or bruising; or unusual confusion, depression, or fatigue. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 150 mg

Generic AvailableNo
ManufacturerPharmacia & Upjohn
Pricing: U.S. (www.drugstore.com)

Capsules (Mycobutin)

150 mg (100): $971.61

Mechanism of ActionInhibits DNA-dependent RNA polymerase at the beta subunit which prevents chain initiation
Pharmacodynamics/Kinetics

Absorption: Readily, 53%

Distribution: V_d: 9.32 L/kg; distributes to body tissues including the lungs, liver, spleen, eyes, and kidneys

Protein binding: 85%

Metabolism: To active and inactive metabolites

Bioavailability: Absolute: HIV: 20%

Half-life elimination: Terminal: 45 hours (range: 16-69 hours)

Time to peak, serum: 2-4 hours

Excretion: Urine (10% as unchanged drug, 53% as metabolites); feces (10% as unchanged drug, 30% as metabolites)

Related Information

- Antimicrobial Drugs of Choice
- Tuberculosis
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Saliva (reddish orange).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay rarely cause insomnia
Mental Health: Effects on Psychiatric TreatmentNeutropenia is common; avoid clozapine and carbamazepine; rifabutin is a hepatic enzyme inducer; monitor for altered clinical effects when used concurrently with psychotropics
Index TermsAnsamycin
References

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International Brand NamesAlfacid (DE); Ansamycin (CZ); Ansatipin (ES, FI, SE); Ansatipine (FR); Mycobutin (AR, AT, AU, BE, BG, CH, DE, GB, HK, HN, HU, IE, IL, IT, LU, NL, TW); Rifabutin "Pharmacia" (DK)

Rifampin and Isoniazid

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Rifamate® may be confused with rifampin

Pronunciation(rif AM pin & eye soe NYE a zid)
U.S. Brand NamesIsonaRif™; Rifamate®
Canadian Brand NamesRifamate®
Pharmacologic CategoryAntibiotic, Miscellaneous
Use: Labeled IndicationsManagement of active tuberculosis; see individual agents for additional information
Dosing: Adults**Tuberculosis:** Oral: 2 capsules/day
Dosing: ElderlyRefer to dosing in individual monographs.
Allergy Considerations

- Isoniazid Allergy
- Rifamycin Allergy

Warnings/PrecautionsSee individual agents.
Pregnancy Risk FactorC
Pregnancy ConsiderationsRefer to Rifampin monograph.
LactationEnters breast milk/compatible
Metabolism/Transport Effects

Rifampin: **Induces** CYP1A2 (strong), 2A6 (strong), 2B6 (strong), 2C8 (strong), 2C9 (strong), 2C19 (strong), 3A4 (strong)

Isoniazid: **Substrate** of CYP2E1 (major); **Inhibits** CYP1A2 (weak), 2A6 (moderate), 2C9 (weak), 2C19 (strong), 2D6 (moderate), 2E1 (moderate), 3A4 (strong); **Induces** CYP2E1 (after discontinuation) (weak)

Drug Interactions

Acetaminophen: Isoniazid may enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Alfentanil: Rifamycin Derivatives may increase the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Amiodarone: Rifamycin Derivatives may increase the metabolism of Amiodarone. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Rifamycin Derivatives may increase the metabolism of Angiotensin II Receptor Blockers. **Exceptions:** Candesartan; Eprosartan; Olmesartan; Telmisartan; Valsartan. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Antidiabetic Agents (Thiazolidinedione): Rifampin may increase the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Antiemetics (5HT3 Antagonists): Rifamycin Derivatives may increase the metabolism of Antiemetics (5HT3 Antagonists). **Exceptions:** Dolasetron; Granisetron; Palonosetron. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Rifamycin Derivatives. Only rifabutin appears to be affected. Rifamycin Derivatives may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Aprepitant: Rifamycin Derivatives may increase the metabolism of Aprepitant. *Risk C: Monitor therapy*

Atazanavir: Rifampin may decrease the serum concentration of Atazanavir. *Risk X: Avoid combination*

Atovaquone: Rifamycin Derivatives may decrease the serum concentration of Atovaquone. *Risk D: Consider therapy modification*

Barbiturates: Rifamycin Derivatives may increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inducers (Strong) may decrease the serum concentration of Bendamustine. Concentrations of active metabolites may be increased. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Rifamycin Derivatives may increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Isoniazid may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Beta-Blockers: Rifamycin Derivatives may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Carteolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

BusPIRone: Rifamycin Derivatives may increase the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Rifamycin Derivatives may increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: Isoniazid may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Caspofungin: Rifampin may decrease the serum concentration of Caspofungin. Management: Caspofungin prescribing information recommends using a dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) who are also receiving rifampin. *Risk D: Consider therapy modification*

Caspofungin: Inducers of Drug Clearance may decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) when coadministered with known inducers of drug clearance. *Risk D: Consider therapy modification*

Chloramphenicol: Rifampin may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

Chlorzoxazone: Isoniazid may decrease the metabolism of Chlorzoxazone. *Risk C: Monitor therapy*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Clopidogrel: Rifamycin Derivatives may enhance the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

Contraceptive (Progestins): Rifamycin Derivatives may decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Rifamycin Derivatives may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticosteroids (Systemic): May decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

CycloSERINE: May enhance the CNS depressant effect of Isoniazid. *Risk D: Consider therapy modification*

CycloSPORINE: Rifamycin Derivatives may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inducers (Strong) may increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2A6 Substrates: CYP2A6 Inducers (Strong) may increase the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2A6 Substrates: CYP2A6 Inhibitors (Moderate) may decrease the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inducers (Strong) may increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C19 Substrates: CYP2C19 Inducers (Strong) may increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inducers (Highly Effective) may increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inducers (Highly Effective) may increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP2E1 Substrates: CYP2E1 Inhibitors (Moderate) may decrease the metabolism of CYP2E1 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dapsone: Rifamycin Derivatives may increase the metabolism of Dapsone. *Risk D: Consider therapy modification*

Delavirdine: May decrease the metabolism of Rifamycin Derivatives. Rifamycin Derivatives may increase the metabolism of Delavirdine. *Risk D: Consider therapy modification*

Disopyramide: Rifamycin Derivatives may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Efavirenz: Rifampin may decrease the serum concentration of Efavirenz. Management: Efavirenz dose adjustment (to 800mg daily) may be required, particularly for patients weighing more than 60kg. *Risk C: Monitor therapy*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

Erlotinib: Rifampin may increase the metabolism of Erlotinib. *Risk D: Consider therapy modification*

Etravirine: Rifamycin Derivatives may decrease the serum concentration of Etravirine. *Risk X: Avoid combination*

Exemestane: Rifampin may increase the metabolism of Exemestane. *Risk D: Consider therapy modification*

FentaNYL: Rifamycin Derivatives may decrease the serum concentration of FentaNYL. *Risk C: Monitor therapy*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Fexofenadine: Rifampin may decrease the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Rifamycin Derivatives. This appears only affect rifabutin. Rifamycin Derivatives may increase the metabolism of Fluconazole. *Risk C: Monitor therapy*

Fosaprepitant: Rifampin may decrease the serum concentration of Fosaprepitant. More specifically, rifampin may decrease concentrations of the active metabolite aprepitant. *Risk C: Monitor therapy*

Gefitinib: Rifamycin Derivatives may increase the metabolism of Gefitinib. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: Rifamycin Derivatives may increase the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Rosuvastatin. *Risk D: Consider therapy modification*

Imatinib: Rifamycin Derivatives may increase the metabolism of Imatinib. *Risk D: Consider therapy modification*

Isoniazid: Rifamycin Derivatives may enhance the hepatotoxic effect of Isoniazid. Even so, this is a frequently employed combination regimen. *Risk C: Monitor therapy*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

LamoTRIgine: Rifampin may increase the metabolism of LamoTRIgine. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Rifamycin Derivatives. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Rifamycin Derivatives may increase the metabolism of Methadone. *Risk C: Monitor therapy*

Morphine Sulfate: Rifamycin Derivatives may decrease the serum concentration of Morphine Sulfate. *Risk C: Monitor therapy*

Mycophenolate: Rifamycin Derivatives may decrease the serum concentration of Mycophenolate. Specifically, rifamycin derivatives may decrease the concentration of the active metabolite mycophenolic acid. *Risk X: Avoid combination*

Nevirapine: Rifampin may decrease the serum concentration of Nevirapine. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Rifamycin Derivatives may decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Isoniazid may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Phenytoin: Rifamycin Derivatives may increase the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Praziquantel: Rifampin may decrease the serum concentration of Praziquantel. *Risk X: Avoid combination*

Propafenone: Rifamycin Derivatives may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

Pyrazinamide: May enhance the hepatotoxic effect of Rifampin. Severe (even fatal) liver injury has been reported in patients receiving these 2 drugs as a 2-month treatment regimen for latent TB infection. *Risk D: Consider therapy modification*

QuiNIDine: Rifamycin Derivatives may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Raltegravir: Rifampin may decrease the serum concentration of Raltegravir. *Risk C: Monitor therapy*

Ramelteon: Rifamycin Derivatives may increase the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ranolazine: Rifampin may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Rifamycin Derivatives may increase the metabolism of Repaglinide. *Risk C: Monitor therapy*

Rifamycin Derivatives: May enhance the hepatotoxic effect of Isoniazid. Even so, this is a frequently employed combination regimen. *Risk C: Monitor therapy*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Rifampin may increase the metabolism of Sirolimus. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Sulfonylureas: Rifampin may increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Sunitinib: Rifamycin Derivatives may increase the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Tacrolimus: Rifamycin Derivatives may increase the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Tamoxifen: Rifamycin Derivatives may increase the metabolism of Tamoxifen. *Risk C: Monitor therapy*

Temsirolimus: Rifamycin Derivatives may decrease the serum concentration of Temsirolimus. Rifamycins will likely cause an even greater decrease in the concentration of the active metabolite sirolimus. Management: Temsirolimus prescribing information recommends against coadministration with strong CYP3A4 inducers such as rifampin; however, if concurrent therapy is necessary, an increase in temsirolimus dose to 50 mg/week should be considered. *Risk D: Consider therapy modification*

Terbinafine: Rifamycin Derivatives may increase the metabolism of Terbinafine. *Risk D: Consider therapy modification*

Theophylline Derivatives: Isoniazid may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Thyroid Products: Rifampin may decrease the serum concentration of Thyroid Products. *Risk C: Monitor therapy*

Tocainide: Rifamycin Derivatives may increase the metabolism of Tocainide. *Risk C: Monitor therapy*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Valproic Acid: Rifampin may decrease the serum concentration of Valproic Acid. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Rifamycin Derivatives may increase the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Voriconazole: May increase the serum concentration of Rifamycin Derivatives. Rifamycin Derivatives may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Zaleplon: Rifamycin Derivatives may increase the metabolism of Zaleplon. *Risk C: Monitor therapy*

Zidovudine: Rifamycin Derivatives may increase the metabolism of Zidovudine. *Risk D: Consider therapy modification*

Zolpidem: Rifamycin Derivatives may increase the metabolism of Zolpidem. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

IsonaRif™, Rifamate®: 300/150: Rifampin 300 mg and isoniazid 150 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Rifamate)

150-300 mg (60): $207.13

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Isoniazid
- Rifampin
- Tuberculosis

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusRifampin may cause drowsiness, dizziness, confusion, behavioral changes, or ataxia; report of cognitive disturbances, delusions, and hallucinations; isoniazid may cause drowsiness or dizziness; may rarely cause depression or psychosis; reports of insomnia, restlessness, disorientation, hallucinations, delusions, obsessive-compulsive symptoms, and exacerbation of schizophrenia

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; rifampin is a potent hepatic enzyme inducer; monitor for altered clinical effects when used concurrently with psychotropics; isoniazid may impair the metabolism of carbamazepine and oxidatively metabolized benzodiazepines; monitor for adverse effects

Index TermsIsoniazid and Rifampin

International Brand NamesBifix (PH); Dipicin-INH (PH); R-Cinex 600 (IN); Ramicin-ISO (ID, PH); Refinah 300 (MY, PH, TH); Rifaina (TW); Rifazida (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Rifinah (AE, AR, BF, BH, BJ, CI, CY, DE, EG, ET, FR, GB, GH, GM, GN, GR, HK, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NZ, OM, PK, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Rifinah 300 (MY, TW); Rifoldin 300MG + INH (AT); Rifzin (PH); Rimactazid (BB, BF, BJ, BM, BS, BZ, CH, CI, ET, GH, GM, GN, GR, GY, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, PE, PR, SC, SD, SE, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Rimactazid 300 (PH); Rimpazid 450 (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Rina (TW)

Rifampin, Isoniazid, and Pyrazinamide

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Rifater® may be confused with Rifadin®

Pronunciation(rif AM pin, eye soe NYE a zid, & peer a ZIN a mide)

U.S. Brand NamesRifater®

Canadian Brand NamesRifater®

Pharmacologic CategoryAntibiotic, Miscellaneous

Use: Labeled IndicationsInitial phase, short-course treatment of pulmonary tuberculosis; see individual agents for additional information

Dosing: Adults**Tuberculosis:** Oral: Patients weighing:

≤44 kg: 4 tablets

45-54 kg: 5 tablets

≥55 kg: 6 tablets

Doses should be administered in a single daily dose.

Dosing: ElderlyRefer to dosing in individual monographs.

Dietary ConsiderationsAdminister dose either 1 hour before or 2 hours after a meal with a full glass of water.

Contraindications

Hypersensitivity to rifampin, isoniazid, pyrazinamide, or any component of the formulation; acute or chronic liver disease; gout; concurrent use with amprenavir or saquinavir/ritonavir (and possibly other protease inhibitors); severe fever, chills, or arthritis

Allergy Considerations

- Isoniazid Allergy
- Rifamycin Allergy

Warnings/Precautions

Boxed warnings:

- Hepatitis: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Flu-like syndrome: Regimens of rifampin >600 mg once or twice weekly have been associated with a high incidence of adverse reactions including a flu-like syndrome.

- Hepatitis: **[U.S. Boxed Warning]: Severe and sometimes fatal hepatitis may occur or develop even after many months of treatment with isoniazid.** Patients must report any prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea, or vomiting. Baseline serum uric acid and LFTs are recommended; monitor for hyperbilirubinemia and discontinue therapy if this occurs in conjunction with clinical symptoms or any signs of significant hepatocellular damage.

- Hypersensitivity: Hypersensitivity reactions have occurred in patients taking >600 mg of rifampin once or twice weekly.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

- Thrombocytopenia: May cause thrombocytopenia; monitor closely.

Disease-related concerns:

- Alcoholism: Use with caution in patients with a history of alcoholism (even if ethanol consumption is discontinued during therapy).

- Diabetes: Use with caution in patients with diabetes mellitus.

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage reduction may be necessary. Rifampin, isoniazid, and pyrazinamide can each cause liver impairment.

- Meningococcal disease: Do not use for meningococcal disease, only for short-term treatment of asymptomatic carrier states.

- Porphyria: Use with caution in patients with porphyria; exacerbations have been reported.

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Medications associated with hepatotoxicity: Use with caution in patients receiving concurrent medications associated with hepatotoxicity.

- Pyridoxine: Malnourished patients or individuals likely to develop peripheral neuropathies should receive concomitant pyridoxine therapy (10-50 mg/day).

Special populations:

- Pediatrics: Fixed combination product should not be used in children <15 years of age.

Other warnings/precautions:

- Compliance: Monitor for compliance.

- Ophthalmic examinations: Periodic ophthalmic examinations are recommended even when usual symptoms do not occur.

- Red/orange discoloration: Urine, feces, saliva, sweat, tears, and CSF may be discolored to red/orange.

Pregnancy Risk FactorC
Pregnancy ConsiderationsSee individual agents.
LactationEnters breast milk/use caution
Adverse ReactionsNote: During clinical trial evaluation, the frequency of cardiorespiratory events (eg, chest pain, hemoptysis, palpitation, chest tightness, and pneumothorax) was higher with the combination product (7%) that that reported with individual agents (2%). Also see individual agents.
Metabolism/Transport Effects

Rifampin: **Induces** CYP1A2 (strong), 2A6 (strong), 2B6 (strong), 2C8 (strong), 2C9 (strong), 2C19 (strong), 3A4 (strong)

Isoniazid: **Substrate** of CYP2E1 (major); **Inhibits** CYP1A2 (weak), 2A6 (moderate), 2C9 (weak), 2C19 (strong), 2D6 (moderate), 2E1 (moderate), 3A4 (strong); CYP2E1 (after discontinuation) (weak)

Drug Interactions

Acetaminophen: Isoniazid may enhance the adverse/toxic effect of Acetaminophen. *Risk C: Monitor therapy*

Alfentanil: Rifamycin Derivatives may increase the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Amiodarone: Rifamycin Derivatives may increase the metabolism of Amiodarone. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Rifamycin Derivatives may increase the metabolism of Angiotensin II Receptor Blockers. **Exceptions:** Candesartan; Eprosartan; Olmesartan; Telmisartan; Valsartan. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Antidiabetic Agents (Thiazolidinedione): Rifampin may increase the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Antiemetics (5HT3 Antagonists): Rifamycin Derivatives may increase the metabolism of Antiemetics (5HT3 Antagonists). **Exceptions:** Dolasetron; Granisetron; Palonosetron. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Rifamycin Derivatives. Only rifabutin appears to be affected. Rifamycin Derivatives may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Aprepitant: Rifamycin Derivatives may increase the metabolism of Aprepitant. *Risk C: Monitor therapy*

Atazanavir: Rifampin may decrease the serum concentration of Atazanavir. *Risk X: Avoid combination*

Atovaquone: Rifamycin Derivatives may decrease the serum concentration of Atovaquone. *Risk D: Consider therapy modification*

Barbiturates: Rifamycin Derivatives may increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inducers (Strong) may decrease the serum concentration of Bendamustine. Concentrations of active metabolites may be increased. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Rifamycin Derivatives may increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Isoniazid may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Beta-Blockers: Rifamycin Derivatives may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Carteolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

BusPIRone: Rifamycin Derivatives may increase the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Rifamycin Derivatives may increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: Isoniazid may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Caspofungin: Rifampin may decrease the serum concentration of Caspofungin. Management: Caspofungin prescribing information recommends using a dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) who are also receiving rifampin. *Risk D: Consider therapy modification*

Caspofungin: Inducers of Drug Clearance may decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) when coadministered with known inducers of drug clearance. *Risk D: Consider therapy modification*

Chloramphenicol: Rifampin may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

Chlorzoxazone: Isoniazid may decrease the metabolism of Chlorzoxazone. *Risk C: Monitor therapy*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Clopidogrel: Rifamycin Derivatives may enhance the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

Contraceptive (Progestins): Rifamycin Derivatives may decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Rifamycin Derivatives may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticosteroids (Systemic): May decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

CycloSERINE: May enhance the CNS depressant effect of Isoniazid. *Risk D: Consider therapy modification*

CycloSPORINE: Rifamycin Derivatives may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CycloSPORINE: Pyrazinamide may decrease the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inducers (Strong) may increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2A6 Substrates: CYP2A6 Inducers (Strong) may increase the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2A6 Substrates: CYP2A6 Inhibitors (Moderate) may decrease the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inducers (Strong) may increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C19 Substrates: CYP2C19 Inducers (Strong) may increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inducers (Highly Effective) may increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inducers (Highly Effective) may increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP2E1 Substrates: CYP2E1 Inhibitors (Moderate) may decrease the metabolism of CYP2E1 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dapsone: Rifamycin Derivatives may increase the metabolism of Dapsone. *Risk D: Consider therapy modification*

Delavirdine: May decrease the metabolism of Rifamycin Derivatives. Rifamycin Derivatives may increase the metabolism of Delavirdine. *Risk D: Consider therapy modification*

Disopyramide: Rifamycin Derivatives may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Efavirenz: Rifampin may decrease the serum concentration of Efavirenz. Management: Efavirenz dose adjustment (to 800mg daily) may be required, particularly for patients weighing more than 60kg. *Risk C: Monitor therapy*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

Erlotinib: Rifampin may increase the metabolism of Erlotinib. *Risk D: Consider therapy modification*

Etravirine: Rifamycin Derivatives may decrease the serum concentration of Etravirine. *Risk X: Avoid combination*

Exemestane: Rifampin may increase the metabolism of Exemestane. *Risk D: Consider therapy modification*

FentaNYL: Rifamycin Derivatives may decrease the serum concentration of FentaNYL. *Risk C: Monitor therapy*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Fexofenadine: Rifampin may decrease the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Rifamycin Derivatives. This appears only affect rifabutin. Rifamycin Derivatives may increase the metabolism of Fluconazole. *Risk C: Monitor therapy*

Fosaprepitant: Rifampin may decrease the serum concentration of Fosaprepitant. More specifically, rifampin may decrease concentrations of the active metabolite aprepitant. *Risk C: Monitor therapy*

Gefitinib: Rifamycin Derivatives may increase the metabolism of Gefitinib. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: Rifamycin Derivatives may increase the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Rosuvastatin. *Risk D: Consider therapy modification*

Imatinib: Rifamycin Derivatives may increase the metabolism of Imatinib. *Risk D: Consider therapy modification*

Isoniazid: Rifamycin Derivatives may enhance the hepatotoxic effect of Isoniazid. Even so, this is a frequently employed combination regimen. *Risk C: Monitor therapy*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

LamoTRIgine: Rifampin may increase the metabolism of LamoTRIgine. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Rifamycin Derivatives. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Rifamycin Derivatives may increase the metabolism of Methadone. *Risk C: Monitor therapy*

Morphine Sulfate: Rifamycin Derivatives may decrease the serum concentration of Morphine Sulfate. *Risk C: Monitor therapy*

Mycophenolate: Rifamycin Derivatives may decrease the serum concentration of Mycophenolate. Specifically, rifamycin derivatives may decrease the concentration of the active metabolite mycophenolic acid. *Risk X: Avoid combination*

Nevirapine: Rifampin may decrease the serum concentration of Nevirapine. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Rifamycin Derivatives may decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Isoniazid may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Phenytoin: Rifamycin Derivatives may increase the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Praziquantel: Rifampin may decrease the serum concentration of Praziquantel. *Risk X: Avoid combination*

Propafenone: Rifamycin Derivatives may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

Pyrazinamide: May enhance the hepatotoxic effect of Rifampin. Severe (even fatal) liver injury has been reported in patients receiving these 2 drugs as a 2-month treatment regimen for latent TB infection. *Risk D: Consider therapy modification*

QuiNIDine: Rifamycin Derivatives may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Raltegravir: Rifampin may decrease the serum concentration of Raltegravir. *Risk C: Monitor therapy*

Ramelteon: Rifamycin Derivatives may increase the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ranolazine: Rifampin may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Rifamycin Derivatives may increase the metabolism of Repaglinide. *Risk C: Monitor therapy*

Rifampin: Pyrazinamide may enhance the hepatotoxic effect of Rifampin. Severe (even fatal) liver injury has been reported in patients receiving these 2 drugs as a 2-month treatment regimen for latent TB infection. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May enhance the hepatotoxic effect of Isoniazid. Even so, this is a frequently employed combination regimen. *Risk C: Monitor therapy*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Rifampin may increase the metabolism of Sirolimus. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Sulfonylureas: Rifampin may increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Sunitinib: Rifamycin Derivatives may increase the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Tacrolimus: Rifamycin Derivatives may increase the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Tamoxifen: Rifamycin Derivatives may increase the metabolism of Tamoxifen. *Risk C: Monitor therapy*

Temsirolimus: Rifamycin Derivatives may decrease the serum concentration of Temsirolimus. Rifamycins will likely cause an even greater decrease in the concentration of the active metabolite sirolimus. Management: Temsirolimus prescribing information recommends against coadministration with strong CYP3A4 inducers such as rifampin; however, if concurrent therapy is necessary, an increase in temsirolimus dose to 50 mg/week should be considered. *Risk D: Consider therapy modification*

Terbinafine: Rifamycin Derivatives may increase the metabolism of Terbinafine. *Risk D: Consider therapy modification*

Theophylline Derivatives: Isoniazid may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Thyroid Products: Rifampin may decrease the serum concentration of Thyroid Products. *Risk C: Monitor therapy*

Tocainide: Rifamycin Derivatives may increase the metabolism of Tocainide. *Risk C: Monitor therapy*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Valproic Acid: Rifampin may decrease the serum concentration of Valproic Acid. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Rifamycin Derivatives may increase the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Voriconazole: May increase the serum concentration of Rifamycin Derivatives. Rifamycin Derivatives may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Zaleplon: Rifamycin Derivatives may increase the metabolism of Zaleplon. *Risk C: Monitor therapy*

Zidovudine: Rifamycin Derivatives may increase the metabolism of Zidovudine. *Risk D: Consider therapy modification*

Zolpidem: Rifamycin Derivatives may increase the metabolism of Zolpidem. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

See individual agents.

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Rifampin 120 mg, isoniazid 50 mg, and pyrazinamide 300 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tables (Rifater)

50-120-300 mg (60): $166.00

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Isoniazid
- Pyrazinamide
- Rifampin

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusRifampin may cause drowsiness, dizziness, confusion, behavioral changes, or ataxia; report of cognitive disturbances, delusions, and hallucinations; isoniazid may cause drowsiness or dizziness; may rarely cause depression or psychosis; reports of insomnia, restlessness, disorientation, hallucinations, delusions, obsessive-compulsive symptoms, and exacerbation of schizophrenia

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; rifampin is a potent hepatic enzyme inducer; monitor for altered clinical effects when used concurrently with psychotropics; isoniazid may impair the metabolism of carbamazepine and oxidatively metabolized benzodiazepines; monitor for adverse effects

Index TermsIsoniazid, Rifampin, and Pyrazinamide; Pyrazinamide, Rifampin, and Isoniazid

References

Centers for Disease Control and Prevention, "Treatment of Tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America," *MMWR Morb Mortal Wkly Rep*, 2003, 52(RR-11):1-77.

International Brand NamesRifater (AT, BF, BJ, CH, CI, DE, ES, ET, FR, GB, GH, GM, GN, GR, HK, IE, IN, IT, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, PH, PK, PT, SC, SD, SL, SN, TH, TN, TW, TZ, UG, ZA, ZM, ZW); Rimcure 3-FDC (MY); Yu Yu Rifater (KP)

Rifampin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Rifadin® may be confused with Rifater®, Ritalin®

Rifampin may be confused with ribavirin, rifabutin, Rifamate®, rifapentine, rifaximin

Pronunciation(rif AM pin)

U.S. Brand NamesRifadin®

Canadian Brand NamesRifadin®; Rofact™

Pharmacologic CategoryAntibiotic, Miscellaneous; Antitubercular Agent

Use: Labeled IndicationsManagement of active tuberculosis in combination with other agents; elimination of meningococci from the nasopharynx in asymptomatic carriers

Use: Unlabeled/InvestigationalProphylaxis of *Haemophilus influenzae* type b infection; *Legionella* pneumonia; used in combination with other anti-infectives in the treatment of staphylococcal infections; treatment of *M. leprae* infections

Dosing: Adults

Tuberculosis, active: Oral, I.V.: **Note:** A four-drug regimen (isoniazid, rifampin, pyrazinamide, and ethambutol) is preferred for the initial, empiric treatment of TB. When the drug susceptibility results are available, the regimen should be altered as appropriate.

Daily therapy: 10 mg/kg/day (maximum: 600 mg/day)

Twice weekly directly observed therapy (DOT): 10 mg/kg (maximum: 600 mg); 3 times/week: 10 mg/kg (maximum: 600 mg)

Tuberculosis, latent infection (LTBI): As an alternative to isoniazid: Oral, I.V.: 10 mg/kg/day (maximum: 600 mg/day) for 4 months. **Note:** Combination with pyrazinamide should not generally be offered (*MMWR*, Aug 8, 2003).

***H. influenzae*prophylaxis (unlabeled use):** Oral, I.V.: 600 mg every 24 hours for 4 days

Leprosy (unlabeled use): Oral, I.V.:

Multibacillary: 600 mg once monthly for 24 months in combination with ofloxacin and minocycline

Paucibacillary: 600 mg once monthly for 6 months in combination with dapsone

Single lesion: 600 mg as a single dose in combination with ofloxacin 400 mg and minocycline 100 mg

Meningococcal meningitis prophylaxis (unlabeled use): Oral, I.V.: 600 mg every 12 hours for 2 days

Meningitis*(Pneumococcus*or*Staphylococcus)*(unlabeled use): Oral, I.V.: 600 mg once daily

Nasal carriers of*Staphylococcus aureus*(unlabeled use): Oral, I.V.: 600 mg/day for 5-10 days in combination with other antibiotics

Nontuberculous mycobacterium (*M. kansasii*) (unlabeled use): Oral, I.V.: 10 mg/kg/day (maximum: 600 mg/day) for duration to include 12 months of culture-negative sputum; typically used in combination with ethambutol and isoniazid

Synergy for*Staphylococcus aureus*infections (unlabeled use): Oral, I.V.: 300-600 mg twice daily with other antibiotics

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Tuberculosis, active: Oral, I.V.:

Infants and Children <12 years:

Daily therapy: 10-20 mg/kg/day usually as a single dose (maximum: 600 mg/day)

Twice weekly directly observed therapy (DOT): 10-20 mg/kg (maximum: 600 mg)

See "Note" in adult dosing.

Tuberculosis, latent infection (LTBI): As an alternative to isoniazid: Children: 10-20 mg/kg/day (maximum: 600 mg/day) for 6 months

***H. influenzae*prophylaxis (unlabeled use):** Oral, I.V.: Infants and Children: 20 mg/kg/day every 24 hours for 4 days, not to exceed 600 mg/dose

Meningitis*(Pneumococcus*or*Staphylococcus)* (unlabeled use):Oral, I.V.: Infants and Children: 20 mg/kg/day as a single dose or in 2 divided doses; maximum: 600 mg/day

Note: Recommended only for organisms known to be rifampin-susceptible and highly penicillin- or cephalosporin-resistant. May be used in place of or in addition to vancomycin when dexamethasone therapy employed.

Meningococcal prophylaxis (unlabeled use): Oral:

<1 month: 10 mg/kg/day in divided doses every 12 hours for 2 days

Infants and Children: 20 mg/kg/day in divided doses every 12 hours for 2 days (maximum: 600 mg/dose)

Nasal carriers of *Staphylococcus aureus* (unlabeled use): Oral, I.V.: 15 mg/kg/day divided every 12 hours for 5-10 days in combination with other antibiotics

Dosing: Renal ImpairmentPlasma rifampin concentrations are not significantly affected by hemodialysis or peritoneal dialysis.
Dosing: Hepatic ImpairmentDose reductions are necessary to reduce hepatotoxicity.
Administration: I.M.Do not administer I.M. or SubQ
Administration: I.V.Administer I.V. preparation once daily by slow I.V. infusion over 30 minutes to 3 hours at a final concentration not to exceed 6 mg/mL.
Administration: I.V. DetailAvoid extravasation.

pH: 7.8-8.8

Administration: OralAdminister on an empty stomach with a glass of water (ie, 1 hour prior to, or 2 hours after meals or antacids) to increase total absorption (food may delay and reduce the amount of rifampin absorbed). The compounded oral suspension must be shaken well before using. May mix contents of capsule with applesauce or jelly.
Dietary ConsiderationsRifampin should be taken on an empty stomach.
StorageRifampin powder is reddish brown. Intact vials should be stored at room temperature and protected from excessive heat and light. Reconstituted vials are stable for 24 hours at room temperature.

Stability of parenteral admixture at room temperature (25°C) is 4 hours for D_5W and 24 hours for NS.

ReconstitutionReconstitute powder for injection with SWFI. Prior to injection, dilute in appropriate volume of compatible diluent (eg, 100 mL D_5W).
Compatibility**Variable stability (consult detailed reference)** in D_5W, NS.

Y-site administration: Incompatible: Diltiazem.

Compatibility when admixed: Incompatible: Minocycline.

Extemporaneously PreparedFor pediatric and adult patients with difficulty swallowing or where lower doses are needed, the package insert lists an extemporaneous liquid suspension as follows:

Rifampin 1% w/v suspension (10 mg/mL) can be compounded using one of four syrups (Syrup NF, simple syrup, Syrpalta® syrup, or raspberry syrup)

Empty contents of four 300 mg capsules or eight 150 mg capsules onto a piece of weighing paper

If necessary, crush contents to produce a fine powder

Transfer powder blend to a 4 oz amber glass or plastic prescription bottle

Rinse paper and spatula with 20 mL of syrup and add the rinse to bottle; shake vigorously

Add 100 mL of syrup to the bottle and shake vigorously

This compounding procedure results in a 1% w/v suspension containing 10 mg rifampin/mL; stability studies indicate suspension is stable at room temperature (25°C ± 3°C) or in refrigerator (2°C to 8°C) for 4 weeks; shake well prior to administration

ContraindicationsHypersensitivity to rifampin, any rifamycins, or any component of the formulation; concurrent use of amprenavir, saquinavir/ritonavir (possibly other protease inhibitors)
Allergy Considerations

- Rifamycin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Flu-like syndrome: Regimens of >600 mg once or twice weekly have been associated with a high incidence of adverse reactions including a flu-like syndrome.

- Hematologic effects: May cause thrombocytopenia, leukopenia, or anemia with regimens >600 mg once or twice weekly.

- Hyperbilirubinemia: Discontinue therapy if this occurs in conjunction with clinical symptoms or any signs of significant hepatocellular damage develop.

- Hypersensitivity: Hypersensitivity reactions have occurred in patients taking >600 mg once or twice weekly.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Alcoholism: Use with caution in patients with a history of alcoholism (even if ethanol consumption is discontinued during therapy).
- Hepatic impairment: Use with caution in patients with liver impairment; dosage modification recommended.
- Meningococcal disease: Do not use for meningococcal disease, only for short-term treatment of asymptomatic carrier states.
- Porphyria: Use with caution in patients with porphyria; exacerbations have been reported due to enzyme-inducing properties.

Concurrent drug therapy issues:

- Medications associated with hepatotoxicity: Use with caution in patients receiving concurrent medications associated with hepatotoxicity.

Other warnings/precautions:

- Appropriate administration: Do not administer I.V. form via I.M. or SubQ routes; restart infusion at another site if extravasation occurs.
- Compliance: Monitor for compliance in patients on intermittent therapy.
- Contact lenses: Remove soft contact lenses during therapy since permanent staining may occur.
- Red/orange discoloration: Urine, feces, saliva, sweat, tears, and CSF may be discolored to red/orange.

Geriatric ConsiderationsRifampin, in combination with isoniazid, is the foundation of tuberculosis treatment. Since most older patients acquired their *Mycobacterium tuberculosis* infection before effective chemotherapy was available, either a 9-month regimen of isoniazid and rifampin or a 6-month regimen of isoniazid and rifampin with pyrazinamide (the first 2 months) should be effective.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects have bee reported in animal studies. Rifampin crosses the human placenta. Due to the risk of tuberculosis to the fetus, treatment is recommended when the probability of maternal disease is moderate to high. Postnatal hemorrhages have been reported in the infant and mother with isoniazid administration during the last few weeks of pregnancy.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Adverse Reactions

Frequency not defined:

Cardiovascular: Edema, flushing

Central nervous system: Ataxia, behavioral changes, concentration impaired, confusion, dizziness, drowsiness, fatigue, fever, headache, numbness, psychosis

Dermatologic: Pemphigoid reaction, pruritus, urticaria

Endocrine & metabolic: Adrenal insufficiency, menstrual disorders

Hematologic: Agranulocytosis (rare), DIC, eosinophilia, hemoglobin decreased, hemolysis, hemolytic anemia, leukopenia, thrombocytopenia (especially with high-dose therapy)

Hepatic: Hepatitis (rare), jaundice

Neuromuscular & skeletal: Myalgia, osteomalacia, weakness

Ocular: Exudative conjunctivitis, visual changes

Renal: Acute renal failure, BUN increased, hemoglobinuria, hematuria, interstitial nephritis, uric acid increased

Miscellaneous: Flu-like syndrome

1% to 10%:

Dermatologic: Rash (1% to 5%)

Gastrointestinal (1% to 2%): Anorexia, cramps, diarrhea, epigastric distress, flatulence, heartburn, nausea, pseudomembranous colitis, pancreatitis vomiting

Hepatic: LFTs increased (up to 14%)

Metabolism/Transport Effects**Induces** CYP1A2 (strong), 2A6 (strong), 2B6 (strong), 2C8 (strong), 2C9 (strong), 2C19 (strong), 3A4 (strong)

Drug Interactions

Alfentanil: Rifamycin Derivatives may increase the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Amiodarone: Rifamycin Derivatives may increase the metabolism of Amiodarone. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Rifamycin Derivatives may increase the metabolism of Angiotensin II Receptor Blockers. **Exceptions:** Candesartan; Eprosartan; Olmesartan; Telmisartan; Valsartan. *Risk C: Monitor therapy*

Antidiabetic Agents (Thiazolidinedione): Rifampin may increase the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Antiemetics (5HT3 Antagonists): Rifamycin Derivatives may increase the metabolism of Antiemetics (5HT3 Antagonists). **Exceptions:** Dolasetron; Granisetron; Palonosetron. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Rifamycin Derivatives. Only rifabutin appears to be affected. Rifamycin Derivatives may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Aprepitant: Rifamycin Derivatives may increase the metabolism of Aprepitant. *Risk C: Monitor therapy*

Atazanavir: Rifampin may decrease the serum concentration of Atazanavir. *Risk X: Avoid combination*

Atovaquone: Rifamycin Derivatives may decrease the serum concentration of Atovaquone. *Risk D: Consider therapy modification*

Barbiturates: Rifamycin Derivatives may increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inducers (Strong) may decrease the serum concentration of Bendamustine. Concentrations of active metabolites may be increased. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Rifamycin Derivatives may increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Beta-Blockers: Rifamycin Derivatives may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Carteolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

BusPIRone: Rifamycin Derivatives may increase the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Rifamycin Derivatives may increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Caspofungin: Rifampin may decrease the serum concentration of Caspofungin. Management: Caspofungin prescribing information recommends using a dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) who are also receiving rifampin. *Risk D: Consider therapy modification*

Caspofungin: Inducers of Drug Clearance may decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) when coadministered with known inducers of drug clearance. *Risk D: Consider therapy modification*

Chloramphenicol: Rifampin may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

Clopidogrel: Rifamycin Derivatives may enhance the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Contraceptive (Progestins): Rifamycin Derivatives may decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Rifamycin Derivatives may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Rifamycin Derivatives may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP1A2 Substrates: CYP1A2 Inducers (Strong) may increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2A6 Substrates: CYP2A6 Inducers (Strong) may increase the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inducers (Strong) may increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inducers (Strong) may increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inducers (Highly Effective) may increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inducers (Highly Effective) may increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dapsone: Rifamycin Derivatives may increase the metabolism of Dapsone. *Risk D: Consider therapy modification*

Delavirdine: May decrease the metabolism of Rifamycin Derivatives. Rifamycin Derivatives may increase the metabolism of Delavirdine. *Risk D: Consider therapy modification*

Disopyramide: Rifamycin Derivatives may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Efavirenz: Rifampin may decrease the serum concentration of Efavirenz. Management: Efavirenz dose adjustment (to 800mg daily) may be required, particularly for patients weighing more than 60kg. *Risk C: Monitor therapy*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Erlotinib: Rifampin may increase the metabolism of Erlotinib. *Risk D: Consider therapy modification*

Etravirine: Rifamycin Derivatives may decrease the serum concentration of Etravirine. *Risk X: Avoid combination*

Exemestane: Rifampin may increase the metabolism of Exemestane. *Risk D: Consider therapy modification*

FentaNYL: Rifamycin Derivatives may decrease the serum concentration of FentaNYL. *Risk C: Monitor therapy*

Fexofenadine: Rifampin may decrease the serum concentration of Fexofenadine. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Rifamycin Derivatives. This appears only affect rifabutin. Rifamycin Derivatives may increase the metabolism of Fluconazole. *Risk C: Monitor therapy*

Fosaprepitant: Rifampin may decrease the serum concentration of Fosaprepitant. More specifically, rifampin may decrease concentrations of the active metabolite aprepitant. *Risk C: Monitor therapy*

Gefitinib: Rifamycin Derivatives may increase the metabolism of Gefitinib. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: Rifamycin Derivatives may increase the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Rosuvastatin. *Risk D: Consider therapy modification*

Imatinib: Rifamycin Derivatives may increase the metabolism of Imatinib. *Risk D: Consider therapy modification*

Isoniazid: Rifamycin Derivatives may enhance the hepatotoxic effect of Isoniazid. Even so, this is a frequently employed combination regimen. *Risk C: Monitor therapy*

LamoTRIgine: Rifampin may increase the metabolism of LamoTRIgine. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Rifamycin Derivatives. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Rifamycin Derivatives may increase the metabolism of Methadone. *Risk C: Monitor therapy*

Morphine Sulfate: Rifamycin Derivatives may decrease the serum concentration of Morphine Sulfate. *Risk C: Monitor therapy*

Mycophenolate: Rifamycin Derivatives may decrease the serum concentration of Mycophenolate. Specifically, rifamycin derivatives may decrease the concentration of the active metabolite mycophenolic acid. *Risk X: Avoid combination*

Nevirapine: Rifampin may decrease the serum concentration of Nevirapine. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Rifamycin Derivatives may decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Rifamycin Derivatives may increase the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Praziquantel: Rifampin may decrease the serum concentration of Praziquantel. *Risk X: Avoid combination*

Propafenone: Rifamycin Derivatives may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

Pyrazinamide: May enhance the hepatotoxic effect of Rifampin. Severe (even fatal) liver injury has been reported in patients receiving these 2 drugs as a 2-month treatment regimen for latent TB infection. *Risk D: Consider therapy modification*

QuiNIDine: Rifamycin Derivatives may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Raltegravir: Rifampin may decrease the serum concentration of Raltegravir. *Risk C: Monitor therapy*

Ramelteon: Rifamycin Derivatives may increase the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ranolazine: Rifampin may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Rifamycin Derivatives may increase the metabolism of Repaglinide. *Risk C: Monitor therapy*

Sirolimus: Rifampin may increase the metabolism of Sirolimus. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Sulfonylureas: Rifampin may increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Sunitinib: Rifamycin Derivatives may increase the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Tacrolimus: Rifamycin Derivatives may increase the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Tamoxifen: Rifamycin Derivatives may increase the metabolism of Tamoxifen. *Risk C: Monitor therapy*

Temsirolimus: Rifamycin Derivatives may decrease the serum concentration of Temsirolimus. Rifamycins will likely cause an even greater decrease in the concentration of the active metabolite sirolimus. Management: Temsirolimus prescribing information recommends against coadministration with strong CYP3A4 inducers such as rifampin; however, if concurrent therapy is necessary, an increase in temsirolimus dose to 50 mg/week should be considered. *Risk D: Consider therapy modification*

Terbinafine: Rifamycin Derivatives may increase the metabolism of Terbinafine. *Risk D: Consider therapy modification*

Thyroid Products: Rifampin may decrease the serum concentration of Thyroid Products. *Risk C: Monitor therapy*

Tocainide: Rifamycin Derivatives may increase the metabolism of Tocainide. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Valproic Acid: Rifampin may decrease the serum concentration of Valproic Acid. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Rifamycin Derivatives may increase the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Voriconazole: May increase the serum concentration of Rifamycin Derivatives. Rifamycin Derivatives may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Zaleplon: Rifamycin Derivatives may increase the metabolism of Zaleplon. *Risk C: Monitor therapy*

Zidovudine: Rifamycin Derivatives may increase the metabolism of Zidovudine. *Risk D: Consider therapy modification*

Zolpidem: Rifamycin Derivatives may increase the metabolism of Zolpidem. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase risk of hepatotoxicity).

Food: Food decreases the extent of absorption; rifampin concentrations may be decreased if taken with food.

Herb/Nutraceutical: St John's wort may decrease rifampin levels.

Test InteractionsPositive Coombs' reaction [direct], rifampin inhibits standard assay's ability to measure serum folate and B_{12}; transient increase in LFTs and decreased biliary excretion of contrast media

Monitoring ParametersPeriodic (baseline and every 2-4 weeks during therapy) monitoring of liver function (AST, ALT, bilirubin), CBC; hepatic status and mental status, sputum culture, chest x-ray 2-3 months into treatment

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking (eg, concurrent use with rifampin may decrease levels/effects of multiple other drugs, including some oral contraceptives, anticoagulants, hypoglycemics, and beta-blockers). See Administration for infusion specifics; infusion site must be monitored to prevent extravasation. Assess results of periodic laboratory tests and chest x-ray, therapeutic effectiveness, and adverse reactions (eg, hypersensitivity reactions, hepatotoxicity, CNS changes, hematologic changes, visual disturbances, and gastrointestinal upset) on a regular basis during therapy. Monitor patient compliance with treatment regimen. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPeriodic monitoring of liver function (AST, ALT), CBC; sputum culture, chest x-ray 2-3 months into treatment

Patient EducationDo not take any new medication during therapy without consulting prescriber. Rifampin may be prescribed in conjunction with another medication; maintain dosing schedule of both drugs as directed. Take rifampin on an empty stomach, 1 hour before or 2 hours after meals. It is extremely important that you complete full course of therapy and do not skip doses. Keep appointments for scheduled laboratory tests and chest x-rays. This medication will discolor urine, stool, saliva, tears, sweat, and other body fluid a red-brown color. Stains on contact lenses and clothing are permanent. Report persistent vomiting or diarrhea; rash; fever, chills, or flu-like symptoms; unusual bruising or bleeding; or other persistent adverse effects. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant. This drug may interfere with effectiveness of oral/systemic contraceptives; consult prescriber for alternative contraceptive measures.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 150 mg, 300 mg

Injection, powder for reconstitution: 600 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Rifadin)

150 mg (60): $136.70

Mechanism of ActionInhibits bacterial RNA synthesis by binding to the beta subunit of DNA-dependent RNA polymerase, blocking RNA transcription

Pharmacodynamics/Kinetics

Duration: ≤24 hours

Absorption: Oral: Well absorbed; food may delay or slightly reduce peak

Distribution: Highly lipophilic; crosses blood-brain barrier well

Relative diffusion from blood into CSF: Adequate with or without inflammation (exceeds usual MICs)

CSF:blood level ratio: Inflamed meninges: 25%

Protein binding: 80%

Metabolism: Hepatic; undergoes enterohepatic recirculation

Half-life elimination: 3-4 hours; prolonged with hepatic impairment; End-stage renal disease: 1.8-11 hours

Time to peak, serum: Oral: 2-4 hours

Excretion: Feces (60% to 65%) and urine (~30%) as unchanged drug

Related Information

- Antibiotic Treatment of Adults With Infective Endocarditis
- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Desensitization Protocols
- Prophylaxis for Patients Exposed to Common Communicable Diseases
- Tuberculosis
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, confusion, behavioral changes, or ataxia; report of cognitive disturbances, delusions, and hallucinations

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; rifampin is a potent hepatic enzyme inducer; monitor for altered clinical effects when used concurrently with psychotropics

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Rifampin causes body secretions to turn orange and may stain contact lenses.

Index TermsRifampicin

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International Brand NamesArficin (HR); Diabacil (ES); Dinoldin (ES); Eremfat (DE); Fenampicin (ES); Fimizina (ES); Manorifcin (TH); Medifam (PH); Oxitrin (PY); Prolung (ID); Ramicin (ID); Rifabiotic (ID); Rifacilin (IN); Rifadex (EC); Rifadin (AE, AR, AU, BF, BH, BJ, CI, CY, CZ, EG, ET, GB, GH, GM, GN, GR, HK, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, OM, PH, PK, PT, QA, SA, SC, SD, SE, SL, SN, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Rifadine (BE, FR, LU); Rifagen (ES); Rifaldin (BR, CN, ES); Rifaldin[inj.] (ES); Rifamax (PH); Rifamcin (TH); Rifamed (HU); Rifampicin Labatec (CH); Rifampicyna (PL); Rifampin (KP); Rifapiam (IT); Rifapin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Rifaprodin (ES); Rifarad (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Rifarm (FI); Rifasynt (HK, MY); Rifodex (KP); Rifoldin (AT); Rifoldine (CH); Rifonilo (ES); Riforal (ES); Rimactan (AT, BG, CH, CO, DK, ES, FR, HR, IT, LU, MX, NL, NO, PE, SE, UY, VE); Rimactane (BB, BF, BJ, BM, BS, BZ, CI, ET, GB, GH, GM, GN, GY, HK, ID, IL, IN, JM, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SL, SN, SR, TH, TN, TT, TZ, UG, ZA, ZM, ZW); Rimactan[inj.] (CH); Rimafed (PH); Rimapen (FI); Rimecin (TH); Rimpacin (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Rimpin (IN); Rimycin (AU); Ripin (TW); Tubocin (HU); Tugaldin (ES)

Rifapentine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Rifapentine may be confused with rifampin

Pronunciation(rif a PEN teen)

U.S. Brand NamesPriftin®

Canadian Brand NamesPriftin®

Pharmacologic CategoryAntitubercular Agent

Use: Labeled IndicationsTreatment of pulmonary tuberculosis; rifapentine must always be used in conjunction with at least one other antituberculosis drug to which the isolate is susceptible; it may also be necessary to add a third agent (either streptomycin or ethambutol) until susceptibility is known.

Dosing: Adults**Note: Rifapentine should not be used alone**; initial phase should include a 3- to 4-drug regimen.

Tuberculosis, intensive phase (initial 2 months) of short-term therapy: 600 mg (four 150 mg tablets) given twice weekly (with an interval of not less than 72 hours between doses); following the intensive phase, treatment should continue with rifapentine 600 mg once weekly for 4 months in combination with INH or appropriate agent for susceptible organisms.

Dosing: ElderlyRefer to adult dosing.

StorageStore at room temperature (15°C to 30°C; 59°F to 86°F). Protect from excessive heat and humidity.

ContraindicationsHypersensitivity to rifapentine, rifampin, rifabutin, any rifamycin analog, or any component of the formulation

Allergy Considerations

- Rifamycin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hepatic impairment: Patients with abnormal liver tests and/or liver disease should only be given rifapentine when absolutely necessary and under strict medical supervision. Monitoring of liver function tests should be carried out prior to therapy and then every 2-4 weeks during therapy if signs of liver disease occur or worsen, rifapentine should be discontinued.

- Porphyria: Use with caution in patients with porphyria; exacerbation is possible.

Special populations:

- HIV-infected patients: Experience in treating TB in HIV-infected patients is limited.

Other warnings/precautions:

- Compliance: Compliance with dosing regimen is absolutely necessary for successful drug therapy.

- Contact lenses: Remove soft contact lenses during therapy since permanent staining may occur.

- Monitoring: All patients treated with rifapentine should have baseline measurements of liver function tests and enzymes, bilirubin, and a complete blood count. Patients should be seen monthly and specifically questioned regarding symptoms associated with adverse reactions. Routine laboratory monitoring in people with normal baseline measurements is generally not necessary.

- Red/orange discoloration: Urine, feces, saliva, sweat, tears, skin, teeth, tongue, and CSF may be discolored to red/orange.

Pregnancy Risk FactorC

Pregnancy ConsiderationsHas been shown to be teratogenic in rats and rabbits. Rat offspring showed cleft palates, right aortic arch, and delayed ossification and increased number of ribs. Rabbits displayed ovarian agenesis, pes varus, arhinia, microphthalmia, and irregularities of the ossified facial tissues. Rat studies also show decreased fetal weight, increased number of stillborns, and decreased gestational survival. There are no adequate and well-controlled studies in pregnant women. Rifapentine should be used during pregnancy only if the potential benefits justifies the potential risk to the fetus.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsMay discolor breast milk

Adverse Reactions

>10%: Endocrine & metabolic: Hyperuricemia (most likely due to pyrazinamide from initiation phase combination therapy)

1% to 10%:

Cardiovascular: Hypertension

Central nervous system: Dizziness, headache

Dermatologic: Acne, pruritus, rash

Gastrointestinal: Anorexia, diarrhea, dyspepsia, nausea, vomiting

Hematologic: Anemia, leukopenia, lymphopenia, neutropenia, thrombocytosis

Hepatic: ALT increased, AST increased

Neuromuscular & skeletal: Arthralgia, pain

Renal: Hematuria, proteinuria, pyuria, urinary casts

Respiratory: Hemoptysis

<1%: Aggressive reaction, alkaline phosphatase increased, arthrosis, bilirubinemia, constipation, esophagitis, fatigue, gastritis, gout, hematoma, hepatitis, hyperkalemia, hypovolemia, LDH increased, leukocytosis, neutrophilia, pancreatitis, peripheral edema, purpura, skin discoloration, thrombocytopenia, urticaria

Postmarketing and/or case reports: Rifampin has been associated with exacerbation of porphyria. Rifapentine is assumed to share this potential.

Metabolism/Transport Effects **Induces** CYP2C8 (strong), 2C9 (strong), 3A4 (strong)

Drug Interactions

Alfentanil: Rifamycin Derivatives may increase the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Amiodarone: Rifamycin Derivatives may increase the metabolism of Amiodarone. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Rifamycin Derivatives may increase the metabolism of Angiotensin II Receptor Blockers. **Exceptions:** Candesartan; Eprosartan; Olmesartan; Telmisartan; Valsartan. *Risk C: Monitor therapy*

Antiemetics (5HT3 Antagonists): Rifamycin Derivatives may increase the metabolism of Antiemetics (5HT3 Antagonists). **Exceptions:** Dolasetron; Granisetron; Palonosetron. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Rifamycin Derivatives. Only rifabutin appears to be affected. Rifamycin Derivatives may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Aprepitant: Rifamycin Derivatives may increase the metabolism of Aprepitant. *Risk C: Monitor therapy*

Atovaquone: Rifamycin Derivatives may decrease the serum concentration of Atovaquone. *Risk D: Consider therapy modification*

Barbiturates: Rifamycin Derivatives may increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Rifamycin Derivatives may increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Beta-Blockers: Rifamycin Derivatives may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Carteolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

BusPIRone: Rifamycin Derivatives may increase the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Rifamycin Derivatives may increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Clopidogrel: Rifamycin Derivatives may enhance the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Contraceptive (Progestins): Rifamycin Derivatives may decrease the serum concentration of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Rifamycin Derivatives may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Rifamycin Derivatives may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inducers (Highly Effective) may increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inducers (Highly Effective) may increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dapsone: Rifamycin Derivatives may increase the metabolism of Dapsone. *Risk D: Consider therapy modification*

Delavirdine: May decrease the metabolism of Rifamycin Derivatives. Rifamycin Derivatives may increase the metabolism of Delavirdine. *Risk D:*

Consider therapy modification

Disopyramide: Rifamycin Derivatives may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Etravirine: Rifamycin Derivatives may decrease the serum concentration of Etravirine. *Risk X: Avoid combination*

FentaNYL: Rifamycin Derivatives may decrease the serum concentration of FentaNYL. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Rifamycin Derivatives. This appears only affect rifabutin. Rifamycin Derivatives may increase the metabolism of Fluconazole. *Risk C: Monitor therapy*

Gefitinib: Rifamycin Derivatives may increase the metabolism of Gefitinib. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: Rifamycin Derivatives may increase the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Rosuvastatin. *Risk D: Consider therapy modification*

Imatinib: Rifamycin Derivatives may increase the metabolism of Imatinib. *Risk D: Consider therapy modification*

Isoniazid: Rifamycin Derivatives may enhance the hepatotoxic effect of Isoniazid. Even so, this is a frequently employed combination regimen. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Rifamycin Derivatives may increase the metabolism of Methadone. *Risk C: Monitor therapy*

Morphine Sulfate: Rifamycin Derivatives may decrease the serum concentration of Morphine Sulfate. *Risk C: Monitor therapy*

Mycophenolate: Rifamycin Derivatives may decrease the serum concentration of Mycophenolate. Specifically, rifamycin derivatives may decrease the concentration of the active metabolite mycophenolic acid. *Risk X: Avoid combination*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Rifamycin Derivatives may decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: Rifamycin Derivatives may increase the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Propafenone: Rifamycin Derivatives may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

QuiNIDine: Rifamycin Derivatives may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ramelteon: Rifamycin Derivatives may increase the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Rifamycin Derivatives may increase the metabolism of Repaglinide. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Sunitinib: Rifamycin Derivatives may increase the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Tacrolimus: Rifamycin Derivatives may increase the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Tamoxifen: Rifamycin Derivatives may increase the metabolism of Tamoxifen. *Risk C: Monitor therapy*

Temsirolimus: Rifamycin Derivatives may decrease the serum concentration of Temsirolimus. Rifamycins will likely cause an even greater decrease in the concentration of the active metabolite sirolimus. Management: Temsirolimus prescribing information recommends against coadministration with strong CYP3A4 inducers such as rifampin; however, if concurrent therapy is necessary, an increase in temsirolimus dose to 50 mg/week should be considered. *Risk D: Consider therapy modification*

Terbinafine: Rifamycin Derivatives may increase the metabolism of Terbinafine. *Risk D: Consider therapy modification*

Tocainide: Rifamycin Derivatives may increase the metabolism of Tocainide. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Rifamycin Derivatives may increase the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Voriconazole: May increase the serum concentration of Rifamycin Derivatives. Rifamycin Derivatives may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Zaleplon: Rifamycin Derivatives may increase the metabolism of Zaleplon. *Risk C: Monitor therapy*

Zidovudine: Rifamycin Derivatives may increase the metabolism of Zidovudine. *Risk D: Consider therapy modification*

Zolpidem: Rifamycin Derivatives may increase the metabolism of Zolpidem. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Food increases AUC and maximum serum concentration by 43% and 44% respectively as compared to fasting conditions.

Test InteractionsRifampin has been shown to inhibit standard microbiological assays for serum folate and vitamin B_{12}; this should be considered for rifapentine; therefore, alternative assay methods should be considered.

Monitoring ParametersPatients with pre-existing hepatic problems should have liver function tests monitored every 2-4 weeks during therapy

Nursing: Physical Assessment/MonitoringFor use in combination with other antitubercular medications. Use caution in presence of liver disease. Assess potential for interactions with other pharmacological agents patient may be taking (eg, concurrent use with rifapentine may decrease levels/effects of multiple other drugs, including some oral contraceptives, anticoagulants, hypoglycemics, and beta-blockers). Evaluate results of baseline and periodic laboratory tests and chest x-ray, therapeutic effectiveness, and adverse reactions (eg, hepatotoxicity, CNS changes, hematologic changes, visual disturbances, and gastrointestinal upset) on a regular basis during therapy. Monitor patient compliance with treatment regimen. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPerform baseline liver function tests at beginning of therapy. Patients with pre-existing hepatic problems should have liver function tests monitored every 2-4 weeks during therapy. Perform CBC monthly.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Rifapentine will be prescribed in conjunction with other medications; maintain dosing schedule as directed. It is extremely important that you complete full course of therapy and do not skip doses. Keep appointments for scheduled laboratory tests and chest x-rays. This medication will discolor urine, stool, saliva, tears, sweat, breast milk, and other body fluids a red-brown color. Stains on contact lenses and clothing are permanent. Report persistent vomiting or diarrhea; rash; fever, chills, or flu-like symptoms; unusual bruising or bleeding; yellowing of skin or sclera, pale stool, or other persistent adverse effects. **Pregnancy precaution:** Inform prescriber is you are or intend to become pregnant. This drug may interfere with effectiveness of oral/systemic contraceptives; consult prescriber for alternative contraceptive measures.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 150 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Priftin)

150 mg (32): $120.98

Mechanism of ActionInhibits DNA-dependent RNA polymerase in susceptible strains of *Mycobacterium tuberculosis* (but not in mammalian cells). Rifapentine is bactericidal against both intracellular and extracellular MTB organisms. MTB resistant to other rifamycins including rifampin are likely to be resistant to rifapentine. Cross-resistance does not appear between rifapentine and other nonrifamycin antimycobacterial agents.

Pharmacodynamics/Kinetics

Absorption: Food increases AUC and C_{max} by 43% and 44% respectively.

Distribution: V_d: ~70.2 L; rifapentine and metabolite accumulate in human monocyte-derived macrophages with intracellular/extracellular ratios of 24:1 and 7:1 respectively

Protein binding: Rifapentine and 25-desacetyl metabolite: 97.7% and 93.2%, primarily to albumin

Metabolism: Hepatic; hydrolyzed by an esterase and esterase enzyme to form the active metabolite 25-desacetyl rifapentine

Bioavailability: ~70%

Half-life elimination: Rifapentine: 14-17 hours; 25-desacetyl rifapentine: 13 hours

Time to peak, serum: 5-6 hours

Excretion: Urine (17% primarily as metabolites)

Pharmacotherapy PearlsRifapentine has only been studied in patients with tuberculosis receiving a 6-month short-course intensive regimen approval. Outcomes have been based on 6-month follow-up treatment observed in clinical trial 008 as a surrogate for the 2-year follow-up generally accepted as evidence for efficacy in the treatment of pulmonary tuberculosis.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness; has rarely been associated with aggression

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine; rifapentine is an inducer of CYP3A4; monitor of altered clinical effects with barbiturates, benzodiazepines, phenytoin, beta-blockers, haloperidol and TCAs.

References

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Keung AC, Eller MG, and Weir SJ, “Pharmacokinetics of Rifapentine in Patients With Varying Degrees of Hepatic Dysfunction,” *J Clin Pharmacol*, 1998, 38(6):517-24. [PubMed 9650541]

Moghazeh SI, Pan X, Arain T, et al, “Comparative Antimycobacterial Activities of Rifampin, Rifapentine, and KRM-1648 Against a Collection of Rifampin-Resistant *Mycobacterium* Tuberculosis Isolates With Known rpoβ Mutations,” *Antimicrob Agents Chemother*, 1996, 40:265-7.

Tam CM, Chan SL, Lam CW, et al, “Rifapentine and Isoniazid in the Continuation Phase of Treating Pulmonary Tuberculosis, Initial Report,” *Am J Respir Crit Care Med*, 1998, 157(6 Pt 1):1726-33.[PubMed 9620898]

International Brand NamesPriftin (CA)

Rifaximin

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Rifaximin may be confused with rifampin

Pronunciation(rif AX i min)
U.S. Brand NamesXifaxan™
Pharmacologic CategoryAntibiotic, Miscellaneous
Use: Labeled IndicationsTreatment of travelers' diarrhea caused by noninvasive strains of *E. coli*
Dosing: Adults**Travelers' diarrhea:** Oral: 200 mg 3 times/day for 3 days
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Travelers' diarrhea:** Oral: Children ≥12 years: Refer to adult dosing.
Administration: OralMay be administered with or without food.
Dietary ConsiderationsMay be taken with or without food.
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).
ContraindicationsHypersensitivity to rifaximin, other rifamycin antibiotics, or any component of the formulation; diarrhea with fever or blood in the stool
Allergy Considerations

- Rifamycin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Diarrhea: Appropriate use: Efficacy has not been established for the treatment of diarrhea due to pathogens other than *E. coli*, including *C. jejuni*, *Shigella*, and *Salmonella*; consider alternative therapy if symptoms persist or worsen after 24-48 hours of treatment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Appropriate use: Not for treatment of systemic infections; <1% is absorbed orally.

Geriatric ConsiderationsRifaximin has not been studied in the elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAdverse events have been observed in animal reproduction studies; therefore, the manufacturer classifies rifaximin as pregnancy category C. Due to the limited oral absorption of rifaximin (<0.4%), exposure to the fetus is expected to be extremely low.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsIt is not known if rifaximin is excreted in human milk. Due to the limited oral absorption of rifaximin (<0.4%), exposure to the nursing infant is expected to be extremely low. Use of rifaximin during breast-feeding is not recommended by the manufacturer.
Pregnancy & Lactation, In-Depth

- Rifaximin in Pregnancy & Lactation

Adverse ReactionsIncidence of adverse effects reported as ≥2% occurred more in the placebo group than the rifaximin group except for headache.

2% to 10%: Central nervous system: Headache (10%; placebo 9%)

<2%, postmarketing, and/or case reports (limited to important or life-threatening): Abnormal dreams, allergic dermatitis, angioneurotic edema (includine tongue and facial edema with dysphagia), exfoliative dermatitis, fatigue, flushing, hypersensitivity reactions, insomnia, motion sickness, pruritus, rash, sunburn, tinnitus, urticaria

Metabolism/Transport Effects**Induces** CYP3A4 (minor)
Drug Interactions

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Monitoring ParametersTemperature, blood in stool, change in symptoms

Nursing: Physical Assessment/MonitoringSee Contraindications and Warnings/Precautions for use cautions. Cause of diarrhea should be ascertained prior to administering. Teach patient proper use, possible side effects/interventions, and adverse symptoms to report (see Patient Education). **Pregnancy risk factor C** - benefits of use should outweigh possible risks. Note breast-feeding caution.

Patient EducationInform prescriber of any allergies you may have. Take exactly as directed. May cause headache (consult prescriber if headache acute). Report skin rash, swelling of lips or mouth, abnormal dreams or inability to sleep, or unusual ringing in ears. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 200 mg

Generic AvailableNo

ManufacturerSalix Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Xifaxan)

200 mg (30): $160.99

Mechanism of ActionRifaximin inhibits bacterial RNA synthesis by binding to bacterial DNA-dependent RNA polymerase.

Pharmacodynamics/Kinetics

Absorption: Oral: <0.4%

Distribution: 80% to 90% in the gut

Half-life elimination: ~6 hours

Excretion: Feces (~97% as unchanged drug); urine (<1%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause abnormal dreams, insomnia, or fatigue

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesColoximina (AR); Flonorm (CO, MX); Lormyx (CL); Normix (BG, CZ, HN, IT, KP); Spiraxin (ES); Zaxine (ES)

Rilonacept

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English

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Pronunciation(ri LON a sept)

U.S. Brand NamesArcalyst™

Pharmacologic CategoryInterleukin-1 Inhibitor

Use: Labeled Indications**Orphan drug:** Treatment of cryopyrin-associated periodic syndromes (CAPS) including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS)

Dosing: Adults**Cryopyrin-associated periodic syndromes:** SubQ: Loading dose 320 mg given as 2 separate injections (160 mg each) on the same day at 2 different sites, followed a week later by 160 mg, then once weekly. **Note:** Do not administer more frequently than once weekly.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Cryopyrin-associated periodic syndromes:** Children ≥12 years: SubQ: Loading dose 4.4 mg/kg (maximum dose: 320 mg) given as 1-2 separate injections (maximum: 2 mL/injection) on the same day, followed by 2.2 mg/kg (maximum dose: 160 mg) once weekly. **Note:** Do not administer more frequently than once weekly.

Administration: OtherSubQ: Rotate injection sites (thigh, abdomen, upper arm); injections should never be made at sites that are bruised, red, tender, or hard

StorageStore powder in refrigerator at 2°C to 8°C (36°F to 46°F); do not freeze. Do not shake. Protect from light. After reconstitution, may be stored at controlled room temperature. Protect from light. Use within 3 hours of reconstitution.

ReconstitutionReconstitute rilonacept 220 mg powder for injection with SWFI 2.3 mL; do not use bacteriostatic water containing benzyl alcohol or parabens. After reconstituting with SWFI, gently shake the vial for 1 minute, then allow solution to sit for 1 minute. Each reconstituted vial allows for withdrawal of 2 mL (160 mg) for SubQ administration.

ContraindicationsThere are no contraindications listed in the manufacturer's labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: May cause rare hypersensitivity, anaphylaxis, or anaphylactoid reactions; medications for the treatment of hypersensitivity reactions should be available for immediate use.
- Infections: Caution should be exercised when considering use in patients with a history of new/recurrent infections, with conditions that predispose them to infections, or with latent or localized infections. Patients who develop a new infection while undergoing treatment should be monitored closely. If a patient develops a serious infection, therapy should be discontinued. Therapy should not be initiated in patients with active or chronic infections.
- Malignancy: Use may impair defenses against malignancies; impact on the development and course of malignancies is not fully defined.

Disease-related concerns:

- Hyperlipidemia: Use may increase total cholesterol, HDL, LDL, and triglycerides. Periodic assessment of lipid profile should occur. Initiation of lipid-lowering therapy may be necessary.

Concurrent drug therapy issues:

- Tumor necrosis factor (TNF)-blocking agents: Should not be used in combination with TNF-antagonists (eg, etanercept). There is an increased risk of serious infection.

Special populations:

- Elderly: Use caution due to the potential higher risk for infections.
- Pediatrics: Safety and efficacy has not been established in patients <12 years of age.

Other warnings/precautions:

- Immunizations: Patients should be brought up to date with all immunizations including pneumococcal and influenza vaccines before initiating therapy. Live vaccines should not be given concurrently; there is no data available concerning secondary transmission of live vaccines in patients receiving therapy. Administration of inactivated (killed) vaccines while on therapy may not be effective.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenic effects and fetal loss. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if potential benefit to the mother outweighs potential risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is unknown whether or not rilonacept is excreted in human breast milk. Use with caution in breast-feeding.

Adverse Reactions

>10%:

Local: Injection site reactions (48%; majority mild-moderate; typically lasting 1-2 days; characterized by erythema, bruising, dermatitis, inflammation, pain, pruritus, swelling, urticaria, vesicles, warmth, and hemorrhage)

Respiratory: Upper respiratory tract infection (26%)

Miscellaneous: Infection (48% during winter months; 18% during summer months), antibody formation to rilonacept (35%)

1% to 10%:

Central nervous system: Hypoesthesia (9%)

Respiratory: Cough (9%), sinusitis (9%)

<1%, postmarketing, and/or case reports: HDL cholesterol increased, LDL cholesterol increased, neutropenia (transient), triglycerides increased, total cholesterol increased

Drug Interactions

Anti-TNF Agents: May enhance the adverse/toxic effect of Rilonacept. *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersCBC with differential, lipid profile, C-reactive protein (CRP), serum amyloid A; signs of infection

Nursing: Physical Assessment/MonitoringMonitor therapeutic response and adverse reactions at the beginning and periodically throughout therapy. Evaluate for signs and symptoms of infection. This drug should not be used when active or chronic infections are present. Immunization should be given prior to initiating therapy. Teach patient proper use, including appropriate injection techniques and syringe/needle disposal, possible side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, lipid profile, C-reactive protein (CRP), serum amyloid A

Patient EducationInform prescriber of all prescription or OTC medications or herbal products you are taking. You may experience a reaction (redness, swelling, pain, itching, or swelling) at the site of injection. This typically lasts 1-2 days. Do not receive any immunizations unless approved by prescriber. You may be susceptible to infections; avoid crowds and exposure to infections. Report signs of infection immediately. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Arcalyst™: 220 mg

Generic AvailableNo

ManufacturerRegeneron Pharmaceuticals, Inc

Mechanism of ActionCryopyrin-associated periodic syndromes (CAPS) refers to rare genetic syndromes caused by mutations in the nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3 (NLRP-3) gene or the cold-induced autoinflammatory syndrome-1 (CIAS1) gene. Cryopyrin, a protein encoded by this gene, regulates interleukin-1 beta (IL-1β) activation. Deficiency of cryopyrin results in excessive inflammation. Rilonacept reduces inflammation by binding to IL-1β (some binding of IL-1α and IL-1 receptor antagonist) and preventing interaction with cell surface receptors.

Pharmacodynamics/KineticsOnset of action: Steady state reached by 6 weeks

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause changes in lipid profile; combined use with antipsychotic agents may produce additve effects; monitor

Riluzole

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English

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Pronunciation(RIL yoo zole)
U.S. Brand NamesRilutek®
Canadian Brand NamesRilutek®
Pharmacologic CategoryGlutamate Inhibitor
Use: Labeled IndicationsTreatment of amyotrophic lateral sclerosis (ALS); riluzole can extend survival or time to tracheostomy
Dosing: Adults

ALS treatment: Oral: 50 mg every 12 hours; no increased benefit can be expected from higher daily doses, but adverse events are increased.

Dosage adjustment in smoking: Cigarette smoking is known to induce CYP1A2; patients who smoke cigarettes would be expected to eliminate riluzole faster. There is no information, however, on the effect of, or need for, dosage adjustment in these patients.

Dosage adjustment in special populations: Females and Japanese patients may possess a lower metabolic capacity to eliminate riluzole compared with male and Caucasian subjects, respectively.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentUse with caution in patients with concomitant renal insufficiency.
Dosing: Hepatic ImpairmentUse with caution in patients with current evidence or history of abnormal liver function indicated by significant abnormalities in serum transaminase, bilirubin or GGT levels. Baseline elevations of several LFTs (especially elevated bilirubin) should preclude use of riluzole.
Administration: OralAdminister at the same time each day, 1 hour before or 2 hours after a meal.
Dietary ConsiderationsTake at least 1 hour before, or 2 hours after, a meal.
StorageStore at 20°C to 25°C (68°F to 77°F). Protect from bright light.
ContraindicationsSevere hypersensitivity reactions to riluzole or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause dizziness or somnolence; caution should be used performing tasks which require alertness (operating machinery or driving).
- Neutropenia: Among 4000 patients given riluzole for ALS, there were 3 cases of marked neutropenia (ANC <500/mm^3), all seen within the first 2 months of treatment.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; do not administer if baseline liver function tests are elevated. May cause elevations in transaminases (usually transient); discontinue if jaundice develops.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Elderly: Use with caution in the elderly; clearance decreased.
- Females: Use with caution in females; clearance decreased.
- Japanese patients: Use with caution in Japanese patients; clearance decreased.
- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsIn clinical trials, no difference was demonstrated between elderly and younger adults. However, renal and hepatic changes with age can be expected to result in higher serum concentrations of the parent drug and its metabolites.
Pregnancy Risk FactorC
Pregnancy ConsiderationsImpaired fertility, decreased implantation, increased intrauterine death, and adverse effects on offspring growth and viability were observed in animal studies. There are no adequate or well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%:

Gastrointestinal: Nausea (12% to 21%)

Neuromuscular & skeletal: Weakness (15% to 20%)

Respiratory: Lung function decreased (10% to 16%)

1% to 10%:

Cardiovascular: Edema, hypertension, tachycardia

Central nervous system: Agitation, circumoral paresthesia, depression, dizziness, headache, insomnia, malaise, somnolence, tremor, vertigo

Dermatologic: Alopecia, eczema, pruritus

Gastrointestinal: Abdominal pain, anorexia, diarrhea, dyspepsia, flatulence, oral moniliasis, stomatitis, vomiting

Hepatic: Liver function tests increased

Neuromuscular & skeletal: Arthralgia, back pain

Respiratory: Cough increased, rhinitis, sinusitis

Miscellaneous: Aggravation reaction

<1% (Limited to important or life-threatening): Exfoliative dermatitis, neutropenia, postural hypertension, seizure

Metabolism/Transport Effects**Substrate** of CYP1A2 (major)
Drug Interactions

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (due to CNS depression and possible risk of liver toxicity).

Food: A high-fat meal decreases absorption of riluzole (decreasing AUC by 20% and peak blood levels by 45%). Charbroiled food may increase riluzole elimination.

Monitoring ParametersMonitor serum aminotransferases including ALT levels before and during therapy. Evaluate serum ALT levels every month during the first 3 months of therapy, every 3 months during the remainder of the first year and periodically thereafter. Evaluate ALT levels more frequently in patients who develop elevations. Maximum increases in serum ALT usually occurred within 3 months after the start of therapy and were usually transient when <5 times ULN (upper limits of normal).

In trials, if ALT levels were <5 times ULN, treatment continued and ALT levels usually returned to below 2 times ULN within 2-6 months. There is no experience with continued treatment of ALS patients once ALT values exceed 5 times ULN.

If a decision is made to continue treatment in patients when the ALT exceeds 5 times ULN, frequent monitoring (at least weekly) of complete liver function is recommended. Discontinue treatment if ALT exceeds 10 times ULN or if clinical jaundice develops. Monitor temperature, especially during first 2 months of therapy.

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (decreased liver function) at beginning of therapy and periodically throughout therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Monitoring: Lab TestsMonitor serum aminotransferases (including ALT levels) before and during therapy. Evaluate serum ALT levels every month during the first 3 months of therapy, every 3 months during the remainder of the first year, and periodically thereafter. Evaluate ALT levels more frequently in patients who develop elevations. Maximum increases in serum ALT usually occurred within 3 months after the start of therapy and were usually transient when <5 times ULN.

In trials, if ALT levels were <5 times ULN, treatment continued and ALT levels usually returned to below 2 times ULN within 2-6 months. Treatment in studies was discontinued, however, if ALT levels exceed 5 times ULN, so that there is no experience with continued treatment of ALS patients once ALT values exceed 5 times ULN.

If a decision is made to continue treatment in patients when the ALT exceeds 5 times ULN, frequent monitoring (at least weekly) of complete liver function is recommended. Discontinue treatment if ALT exceeds 10 times ULN or if clinical jaundice develops.

Patient EducationThis drug will not cure or stop disease but it may slow progression. Take as directed, at the same time each day, preferably on an empty stomach, 1 hour before or 2 hours after meals. Avoid alcohol. You may experience increased spasticity, dizziness or sleepiness; use caution when driving or engaging in tasks requiring alertness until response to drug is known. Small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may reduce nausea, vomiting, or anorexia. Report fever; severe vomiting, diarrhea, or constipation; change in color of urine or stool; yellowing of skin or eyes; acute back pain or muscle pain; or worsening of condition.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 50 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Rilutek)

50 mg (60): $882.92

Mechanism of ActionMechanism of action is not known. Pharmacologic properties include inhibitory effect on glutamate release, inactivation of voltage-dependent sodium channels; and ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors

Pharmacodynamics/Kinetics

Absorption: 90%; high-fat meal decreases AUC by 20% and peak blood levels by 45%

Protein binding, plasma: 96%, primarily to albumin and lipoproteins

Metabolism: Extensively hepatic to six major and a number of minor metabolites via CYP1A2 dependent hydroxylation and glucuronidation

Bioavailability: Oral: Absolute: 60%

Half-life elimination: 12 hours

Excretion: Urine (90%; 85% as metabolites, 2% as unchanged drug) and feces (5%) within 7 days

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral moniliasis and stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause agitation, depression, dizziness, insomnia, malaise, or somnolence

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine. GI side effects are common; concomitant use with SSRIs, carbamazepine, valproic acid, and lithium may produce additive effects. Riluzole is a CYP1A2 substrate; cigarette smoking may increase metabolism of riluzole.

Anesthesia and Critical Care Concerns/Other ConsiderationsRiluzole may be more effective for amyotrophic lateral sclerosis of bulbar onset.

Index Terms2-Amino-6-Trifluoromethoxy-benzothiazole; RP-54274

References

Bensimon G, Lacomblez L, Meininger V, et al, “A Controlled Trial of Riluzole in Amyotrophic Lateral Sclerosis. ALS/Riluzole Study Group,” *N Engl J Med*, 1994, 330(9):585-91 [PubMed 8302340]

Wokke J, “Riluzole,” *Lancet*, 1996, 348(9030):795-9.[PubMed 8813989]

International Brand NamesRilutek (AR, AT, AU, BE, BG, BO, BR, CH, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, HK, HN, IE, IL, IT, KP, LU, MX, NI, NL, NO, PA, PE, PH, PL, PR, PT, PY, RU, SE, SV, TH, TR, TW, UY, VE); Ritek (TW)

Rimantadine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

CDC Interim Recommendations Concerning Use of Antivirals During 2008-09 Influenza Season - December 2008

The Centers for Disease Control (CDC) has issued a Health Advisory with interim recommendations for chemoprophylaxis or influenza treatment with the following antiviral agents: Oseltamivir (Tamiflu®), zanamivir (Relenza®), rimantadine (Flumadine®), amantadine (Symmetrel®).

The recommendations were prompted by preliminary data in a limited number of states indicating a high prevalence of the oseltamivir-resistant influenza A (H1N1) strain. Influenza activity remains low at the present time, but of the 50 H1N1 isolates from 12 states tested between October 1 and December 19, 2008, 49 (98%) were resistant to oseltamivir. The CDC is unable to make any accurate predictions of which influenza virus types (A or B) or subtypes of influenza A (H1N1 or H3N2) will predominate during the 2008-09 season, but based on the current findings, the following recommendations have been made:

- Patients testing positive for influenza type B: If treatment is indicated, patients may receive either oseltamivir or zanamivir (no preference).

- Patients testing positive for influenza type A (or patients testing negative for influenza, but likelihood of influenza infection is high): If treatment is indicated, patient may receive zanamivir. If zanamivir therapy is inappropriate (eg, patients with chronic respiratory disease, patients <7 years of age) or zanamivir is unavailable, combination treatment with oseltamivir and rimantadine is acceptable (if rimantadine is unavailable, amantadine may be substituted). Oseltamivir monotherapy should only be used if local surveillance indicates that influenza A (H3N2) or influenza type B viruses are likely.

- If confirmatory diagnostic testing to distinguish between subtypes of influenza A (H1N1 or H3N2) is available, and treatment is indicated:

  Patients testing positive for influenza A (H3N2): Use oseltamivir or zanamivir (no preference)

  Patients testing positive for influenza A (H1N1): Use zanamivir (or combination treatment with oseltamivir and rimantadine as an alternative)

Patients requiring chemoprophylaxis due to potential exposure with laboratory-confirmed influenza A (H3N2) or influenza B should receive oseltamivir or zanamivir. Patients requiring chemoprophylaxis due to influenza A (H1N1) virus should receive zanamivir (or rimantadine, if zanamivir use contraindicated).

The CDC is reminding clinicians to continue to vaccinate patients using the influenza vaccine, which is expected to be effective against all circulating influenza vaccines, including the oseltamivir-resistant strain.

For additional information, including the CDC Health Advisory, please refer to http://www2a.cdc.gov/HAN/ArchiveSys/ViewMsgV.asp?AlertNum=00279

Rimantadine ACIP 2008-2009 Influenza Guidelines (July 2008)

The Advisory Committee on Immunization Practices (ACIP), as part of their recommendations for the Prevention and Control of Influenza, do not recommend the use of amantadine or rimantadine for the treatment or chemoprophylaxis of influenza A infection. This recommendation is for the 2008-2009 season for residents of the United States and is based on current patterns of resistance to these medications. Oseltamivir or zanamivir are the recommended antiviral agents. In some areas, resistance is developing against oseltamivir. If resistance is suspected, amantadine or rimantadine may be used in combination with oseltamivir for the treatment or prophylaxis of influenza A infection when zanamivir therapy is not indicated (such as in children of certain ages).

For additional information, refer to the ACIP guidelines on the following CDC website:
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e717a1.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Rimantadine may be confused with amantadine, ranitidine, Rimactane®

Flumadine® may be confused with fludarabine, flunisolide, flutamide

Pronunciation(ri MAN ta deen)

U.S. Brand NamesFlumadine®

Canadian Brand NamesFlumadine®

Pharmacologic CategoryAntiviral Agent, Adamantane

Use: Labeled IndicationsProphylaxis (adults and children >1 year of age) and treatment (adults) of influenza A viral infection (per manufacturer labeling; also refer to current ACIP guidelines for recommendations during current flu season)

Note: In certain circumstances, the ACIP recommends use of rimantadine in combination with oseltamivir for the treatment or prophylaxis of influenza A infection when resistance to oseltamivir is suspected.

Dosing: Adults

Prophylaxis of influenza A: Oral: 100 mg twice daily

Treatment of influenza A: Oral: 100 mg twice daily

Dosing: Elderly

Prophylaxis of influenza A: Oral: 100 mg/day in nursing home patients or all elderly patients who may experience adverse effects using the adult dose

Treatment of influenza A: Oral: 100 mg once daily in patients ≥65 years

Dosing: Pediatric**Prophylaxis of influenza A:** Oral:

Children 1-10 years: 5 mg/kg once daily; maximum: 150 mg

Children >10 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} >10 mL/minute: Dose adjustment not required

Cl_{cr} ≤10 mL/minute: 100 mg/day

Dosing: Hepatic Impairment Severe dysfunction: 100 mg/day

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralInitiation of rimantadine within 48 hours of the onset of influenza A illness halves the duration of illness and significantly reduces the duration of viral shedding and increased peripheral airways resistance. Continue therapy for 5-7 days after symptoms begin.

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to drugs of the adamantine class, including rimantadine and amantadine, or any component of the formulation

Allergy Considerations

- Adamantane Derivative Allergy

Warnings/Precautions

Disease-related concerns:

- Eczema: Avoid use, if possible, in patients with recurrent and eczematoid dermatitis.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Influenza A: Appropriate use: Consult current guidelines. Due to increased resistance, the ACIP has recommended that rimantadine and amantadine no longer be used for the treatment or prophylaxis of influenza A in the United States until susceptibility has been re-established.

- Psychosis: Avoid use, if possible, in patients with uncontrolled psychosis or severe psychoneurosis.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizures: Use with caution in patients with a history of seizure disorder; an increase in seizure incidence may occur. Discontinue if seizures occur.

Other warnings/precautions:

- Resistance: May develop during treatment; viruses exhibit cross-resistance between amantadine and rimantadine.

Geriatric ConsiderationsAdverse CNS and GI effects occur frequently if dosage is not adjusted. Monitor GI effects in the elderly or patients with renal or hepatic impairment. Dosing must be individualized (100 mg 1-2 times/day). It is recommended that nursing home patients receive 100 mg/day.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal data suggest embryotoxicity, maternal toxicity, and offspring mortality at doses 7-11 times the recommended human dose. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/ not recommended

Breast-Feeding ConsiderationsDo not use in nursing mothers due to potential adverse effect in infants.

Adverse Reactions

1% to 10%:

Central nervous system: Dizziness (1% to 2%), insomnia (2% to 3%), concentration impaired (2%), anxiety (1%), fatigue (1%), headache (1%), nervousness (1% to 2%)

Gastrointestinal: Nausea (3%), anorexia (2%), vomiting (2%), xerostomia (2%), abdominal pain (1%)

Neuromuscular & skeletal: Weakness (1%)

<1%: Agitation, ataxia, bronchospasm, cardiac failure, concentration impaired, confusion, convulsions, cough, depression, diarrhea, dyspepsia, dyspnea, euphoria, gait abnormality, hallucinations, heart block, hyperkinesias, hypertension, lactation, palpitation, pallor, parosmia, pedal edema, rash, somnolence, syncope, tachycardia, taste alteration, tinnitus, tremor

Drug Interactions

Influenza Virus Vaccine: Antiviral Agents (Influenza A and B) may diminish the therapeutic effect of Influenza Virus Vaccine. This only pertains to live, attentuated influenza virus vaccine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Food does not affect rate or extent of absorption

Monitoring ParametersMonitor for CNS or GI effects in elderly or patients with renal or hepatic impairment

Nursing: Physical Assessment/MonitoringUse caution with hepatic or renal impairment, seizure disorders, uncontrolled psychoses, or severe psychoneurosis. Assess effectiveness (resolution of infection) and adverse reactions (eg, hypotension, CNS changes [confusion, anxiety, agitation], gastrointestinal upset, anticholinergic effects [dry mouth, urinary retention, mydriases]). Teach patient appropriate use, possible side effects/interventions (eg, postural hypotension), and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed. Complete full course of therapy even if feeling better. Take a missed dose as soon as possible. If almost time for next dose, skip the missed dose and return to your regular schedule. Do not take a double dose. May cause dizziness, insomnia, fatigue, nervousness (use caution when driving or engaged in potentially hazardous tasks until response to medication is known); gastrointestinal upset (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report rash, palpitations; severe nausea or vomiting; persistent CNS changes (eg, confusion, insomnia, anxiety, restlessness, irritability, hallucinations) or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Syrup, as hydrochloride:

Flumadine®: 50 mg/5 mL (240 mL) [raspberry flavor] [DSC]

Tablet, as hydrochloride: 100 mg

Flumadine®: 100 mg

Generic AvailableYes: Tablet

ManufacturerForest Pharmaceuticals, Inc

Pricing: U.S. (www.drugstore.com)

Syrup (Flumadine)

50 mg/5 mL (240): $55.99

Tablets (Flumadine)

100 mg (14): $43.99

Mechanism of ActionExerts its inhibitory effect on three antigenic subtypes of influenza A virus (H1N1, H2N2, H3N2) early in the viral replicative cycle, possibly inhibiting the uncoating process; it has no activity against influenza B virus and is two- to eightfold more active than amantadine

Pharmacodynamics/Kinetics

Onset of action: Antiviral activity: No data exist establishing a correlation between plasma concentration and antiviral effect

Absorption: Tablet and syrup formulations are equally absorbed

Metabolism: Extensively hepatic

Half-life elimination: 25.4 hours; prolonged in elderly

Time to peak: 6 hours

Excretion: Urine (<25% as unchanged drug)

Clearance: Hemodialysis does not contribute to clearance

Related Information

- Community-Acquired Pneumonia in Adults

- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, anxiety, confusion, insomnia, restlessness, irritability, or hallucinations

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsRimantadine Hydrochloride

References

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“Drugs for Non-HIV Viral Infections,” *Med Lett Drugs Ther*, 1994, 36(919):27. [PubMed 8127252]

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Keating MR, “Antiviral Agents,” *Mayo Clin Proc*, 1992, 67(2):160-78. [PubMed 1347578]

Patriarca PA, Kater NA, Kendal AP, et al, “Safety of Prolonged Administration of Rimantadine Hydrochloride in the Prophylaxis of Influenza A Virus Infections in Nursing Homes,” *Antimicrob Agents Chemother*, 1984, 26(1):101-3. [PubMed 6476812]

Wintermeyer SM and Nahata MC, “Rimantadine: A Clinical Perspective,” *Ann Pharmacother*, 1995, 29(3):299-310.[PubMed 7606077]

International Brand NamesGabirol (CR, DO, MX, NI, SV); Jin Di Na (CL); Oclovir (AR); Remantadin (BG); Roflual (FR)

Rimexolone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Vexol® may be confused with VoSol®

Pronunciation(ri MEKS oh lone)
U.S. Brand NamesVexol®
Canadian Brand NamesVexol®
Pharmacologic CategoryCorticosteroid, Ophthalmic
Use: Labeled IndicationsTreatment of inflammation after ocular surgery and the treatment of anterior uveitis
Dosing: Adults**Anti-inflammatory:** Ophthalmic: Instill 1 drop in conjunctival sac 2-4 times/day up to every 4 hours; may use every 1-2 hours during first 1-2 days
Dosing: ElderlyRefer to adult dosing.
ContraindicationsHypersensitivity to rimexolone or any component of the formulation; fungal, viral, or untreated pus-forming bacterial ocular infections
Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Infection: Steroids may mask infection or enhance existing ocular infection; prolonged use may result in secondary infections due to immunosuppression.

- Ocular effects: Prolonged use may result in glaucoma and injury to the optic nerve. Visual defects in acuity and field of vision may occur. Posterior subcapsular cataracts may form after long-term use. Use with caution in presence of glaucoma (steroids increase intraocular pressure). Perforation may occur with topical steroids in diseases which thin the cornea or sclera. Steroid use may delay healing after cataract surgery. Intraocular pressure should be monitored if this product is used >10 days.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo special considerations; must limit the time steroids are used to prevent adverse effects.
Pregnancy Risk FactorC
Adverse Reactions

1% to 10%: Ocular: Temporary mild blurred vision

<1%: Stinging, burning eyes, corneal thinning, increased intraocular pressure, glaucoma, damage to the optic nerve, defects in visual activity, cataracts, secondary ocular infection

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Monitoring ParametersIntraocular pressure and periodic examination of lens (with prolonged use)
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, ophthalmic: 1% (5 mL, 10 mL) [contains benzalkonium chloride]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Suspension (Vexol)

1% (5): $39.99

1% (10): $67.17

Mechanism of ActionDecreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability
Pharmacodynamics/Kinetics

Absorption: Through aqueous humor

Metabolism: Hepatic for any amount of drug absorbed

Excretion: Urine and feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesBaxol (KP); Rimexel (LU); Vexol (AR, AT, BR, CH, DE, DK, ES, FI, FR, GB, GR, HK, IE, IT, KP, MX, NL, NO, PT, SE); Vexolon (BE)

Risedronate and Calcium

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Bisphosphonates: Safety Update Regarding Possible Association With Atrial Fibrillation - November 2008

The Food and Drug Administration (FDA) has been reviewing placebo-controlled trials of the 7 bisphosphonates currently marketed in the US. This review is in response to study results associating an increased incidence of atrial fibrillation (AF) with alendronate or zoledronic acid use in women (65-89 years of age) with osteoporosis.

The FDA reviewed all the submitted data (19,687 bisphosphonate-treated patients and 18,358 placebo-treated patients) from these studies. Overall, the occurrence of AF was rare in each study with an absolute difference in event rates between each of the bisphosphonate and placebo arms of 0-3 per 1000. A zoledronic acid study showed a statistically significant increase in the rate of AF in the active treatment arm. However, no clear association between bisphosphonate use and AF could be established. In this study, AF events were diagnosed more than 30 days after receiving zoledronic acid in 47 of the 50 patients diagnosed with AF. According to the FDA, healthcare providers should not alter their prescribing patterns for bisphosphonates and patients should not stop taking their medication.

The FDA will continue monitoring the safety of bisphosphonates through postmarketing reports and is assessing the need for additional epidemiologic studies.

Further information is available at http://www.fda.gov/cder/drug/early_comm/bisphosphonates_update_200811.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Actonel® may be confused with Actos®

Pronunciation(ris ED roe nate & KAL see um)
U.S. Brand NamesActonel® and Calcium
Pharmacologic CategoryBisphosphonate Derivative; Calcium Salt
Use: Labeled IndicationsTreatment and prevention of osteoporosis in postmenopausal women
Dosing: Adults**Osteoporosis in postmenopausal females:** Oral:

Risedronate: 35 mg once weekly on day 1 of 7-day treatment cycle

Calcium carbonate: 1250 mg (elemental calcium 500 mg) once daily on days 2 through 7 of 7-day treatment cycle

Dosing: Elderly

Refer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <30 mL/minute: Not recommended for use.
Calculations

- Creatinine Clearance: Adults

Administration: OralRisedronate should be administered ≥30 minutes before the first food or drink of the day other than water. Risedronate should be taken in an upright position with a full glass (6-8 oz) of plain water and the patient should avoid lying down for 30 minutes to minimize the possibility of GI side effects. Calcium should be taken with food. If additional calcium is needed (other than what is provided in blister package), it should be taken at a separate time of the day.
Dietary ConsiderationsTake risedronate ≥30 minutes before the first food or drink of the day other than water. Calcium should be taken with food. Vitamin D supplementation may be needed.
StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to risedronate, bisphosphonates, or any component of the formulation; hypocalcemia, hypercalcemia; abnormalities of the esophagus which delay esophageal emptying (eg, stricture or achalasia); inability to stand or sit upright for at least 30 minutes; severe renal impairment (Cl_{cr} <30 mL/minute)
Warnings/Precautions

Concerns related to adverse effects:

- Bone/joint/muscle pain: Infrequently, severe (and occasionally debilitating) bone, joint, and/or muscle pain have been reported during bisphosphonate treatment. The onset of pain ranged from a single day to several months. Symptoms usually resolve upon discontinuation. Some patients experienced recurrence when rechallenged with same drug or another bisphosphonate; avoid use in patients with a history of these symptoms in association with bisphosphonate therapy.

- Gastrointestinal mucosa irritation: May cause irritation to upper gastrointestinal mucosa. Esophagitis, esophageal ulcers, esophageal erosions, and esophageal stricture (rare) have been reported with oral bisphosphonates; risk increases in patients unable to comply with dosing instructions. Use with caution in patients with dysphagia, esophageal disease, gastritis, duodenitis, or ulcers (may worsen underlying condition).

- Osteonecrosis of the jaw: Bisphosphonate therapy has been associated with osteonecrosis, primarily of the jaw; this has been observed mostly in cancer patients, but also in patients with postmenopausal osteoporosis and other diagnoses. Risk factors include a diagnosis of cancer, with concomitant chemotherapy, radiotherapy, or corticosteroids; anemia, coagulopathy, infection, or pre-existing dental disease. Symptoms included nonhealing extraction socket or an exposed jawbone. There are no data addressing whether discontinuation of therapy reduces the risk of developing osteonecrosis; however, as a precautionary measure, dental exams and preventative dentistry should be performed prior to placing patients with risk factors on chronic bisphosphonate therapy. Invasive dental procedures should be avoided during treatment.

Disease-related concerns:

- Hypocalcemia: Before therapy initiation hypocalcemia must be corrected; ensure adequate vitamin D intake.

- Renal impairment: Use with caution in patients with renal impairment (not recommended in patients with a Cl_{cr} <30 mL/minute). Calcium should be used with caution in patients with a history of kidney stones or hypercalciuria.

Special populations:

- Males: Safety and efficacy of using the combination for the treatment of primary osteoporosis as packaged have not been established in men.

- Pediatrics: Safety and efficacy of using the combination as packaged have not been established in children.

Other warnings/precautions:

- Absorption: Calcium carbonate absorption is impaired in achlorhydria (common in elderly); administer calcium component with food.

Geriatric ConsiderationsSee individual agents.
Pregnancy Risk FactorC
Pregnancy ConsiderationsSee individual agents.
LactationExcretion of risedronate in breast milk is unknown/not recommended
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsSee individual agents.
Drug Interactions

Aminoglycosides: May enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Magaldrate; Sodium Bicarbonate. *Risk D: Consider therapy modification*

Calcium Salts: May decrease the absorption of Bisphosphonate Derivatives. *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral iron salts are of concern. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Phosphate Supplements: Bisphosphonate Derivatives may enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase risk of osteoporosis).

Food:

Risedronate: Food may reduce absorption (similar to other bisphosphonates); mean oral bioavailability is decreased when given with food.

Calcium: Food increases absorption. Calcium may decrease iron absorption. Bran, foods high in oxalates, or whole grain cereals may decrease calcium absorption

Test InteractionsBisphosphonates may interfere with diagnostic imaging agents such as technetium-99m-diphosphonate in bone scans.
Monitoring ParametersPain and fracture rate, bone mineral density, height
Reference RangeCalcium (total): Adults: 9.0-11.0 mg/dL (2.05-2.54 mmol/L), may slightly decrease with aging; phosphorus: 2.5-4.5 mg/dL (0.81-1.45 mmol/L)
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Combination package [each package contains]:

Tablet (Actonel®): Risedronate 35 mg (4s)

Tablet: Calcium carbonate 1250 mg (24s) [equivalent to elemental calcium 500 mg]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Actonel With Calcium)

35-1250 mg (28): $105.11

Mechanism of Action

Risedronate inhibits bone resorption via actions on osteoclasts or on osteoclast precursors; decreases the rate of bone resorption, leading to an indirect increase in bone mineral density.

Calcium helps to prevent or decrease the rate of bone loss.

Pharmacodynamics/KineticsSee individual agents.

Dental Health Professional ConsiderationsSee Risedronate monograph.

Dental Health: Effects on Dental TreatmentOsteonecrosis of the jaw (ONJ), generally associated with local infection and/or tooth extraction and often with delayed healing, has been reported in patients taking bisphosphonates. Symptoms included nonhealing extraction socket or an exposed jawbone. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates. However, some have occurred in patients with postmenopausal osteoporosis taking oral bisphosphonates. Dental surgery may exacerbate ONJ. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Patients who develop ONJ while on bisphosphonate therapy should receive care by an oral surgeon. See Dental Comment in Risedronate monograph.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression, insomnia, anxiety, and dizziness

Mental Health: Effects on Psychiatric TreatmentNausea and diarrhea are common; concomitant use with SSRIs, lithium, valproic acid, or carbamazepine may produce additive effects

Index TermsCalcium and Risedronate; Risedronate Sodium and Calcium Carbonate

References

Author Unknown, "Safety Update: Bone-Building Drugs: Risks Explained," *Consum Rep Health*, 2006, 18(5):3.

Marx RE, Sawatari Y, Fortin M, et al, "Bisphosphonate-Induced Exposed Bone (Osteonecrosis/Osteopetrosis) of the Jaws: Risk Factors, Recognition, Prevention, and Treatment," *J Oral Maxillofac Surg*, 2005, 63(11):1567-75.[PubMed 16243172]

International Brand NamesActonel Combi (AU, EE, IE); Dronacal Pack (UY); Optinate Combi (SE); Ridron Pack (AR)

Risedronate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Bisphosphonates: Safety Update Regarding Possible Association With Atrial Fibrillation - November 2008

The Food and Drug Administration (FDA) has been reviewing placebo-controlled trials of the 7 bisphosphonates currently marketed in the US. This review is in response to study results associating an increased incidence of atrial fibrillation (AF) with alendronate or zoledronic acid use in women (65-89 years of age) with osteoporosis.

The FDA reviewed all the submitted data (19,687 bisphosphonate-treated patients and 18,358 placebo-treated patients) from these studies. Overall, the occurrence of AF was rare in each study with an absolute difference in event rates between each of the bisphosphonate and placebo arms of 0-3 per 1000. A zoledronic acid study showed a statistically significant increase in the rate of AF in the active treatment arm. However, no clear association between bisphosphonate use and AF could be established. In this study, AF events were diagnosed more than 30 days after receiving zoledronic acid in 47 of the 50 patients diagnosed with AF. According to the FDA, healthcare providers should not alter their prescribing patterns for bisphosphonates and patients should not stop taking their medication.

The FDA will continue monitoring the safety of bisphosphonates through postmarketing reports and is assessing the need for additional epidemiologic studies.

Further information is available at http://www.fda.gov/cder/drug/early_comm/bisphosphonates_update_200811.htm

Medication Safety Issues

Sound-alike/look-alike issues:

> Actonel® may be confused with Actos®

Pronunciation(ris ED roe nate)

U.S. Brand NamesActonel®

Canadian Brand NamesActonel®

Pharmacologic CategoryBisphosphonate Derivative

Use: Labeled IndicationsTreatment of Paget's disease of the bone; treatment and prevention of glucocorticoid-induced osteoporosis; treatment and prevention of osteoporosis in postmenopausal women; treatment of osteoporosis in men

Dosing: Adults

Paget's disease of bone: Oral: 30 mg once daily for 2 months

> **Note:** Retreatment may be considered (following post-treatment observation of at least 2 months) if relapse occurs, or if treatment fails to normalize serum alkaline phosphatase. For retreatment, the dose and duration of therapy are the same as for initial treatment. No data are available on more than one course of retreatment.

Osteoporosis (postmenopausal) prevention and treatment: Oral: 5 mg once daily **or** 35 mg once weekly **or** one 75 mg tablet taken on 2 consecutive days once a month (total of 2 tablets/month) **or** 150 mg once a month

Osteoporosis (male) treatment: 35 mg once weekly

Osteoporosis (glucocorticoid-induced) prevention and treatment: Oral: 5 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} ≥30 mL/minute: No adjustment required

Cl_{cr} <30 mL/minute: Use is not recommended

Calculations

- Creatinine Clearance: Adults

Administration: OralRisedronate should be administered at least 30 or more minutes before the first food or drink of the day other than water. Risedronate should be taken in an upright position with a full glass (6-8 oz) of plain water and the patient should avoid lying down for 30 minutes to minimize the possibility of GI side effects. Tablet should be swallowed whole; do not crush or chew.

Dietary ConsiderationsTake ≥30 minutes before the first food or drink of the day other than water. Supplemental calcium and/or vitamin D may be required if dietary intake is not adequate.

StorageStore at room temperature of 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to risedronate, bisphosphonates, or any component of the formulation; hypocalcemia; inability to stand or sit upright for at least 30 minutes

Allergy Considerations

- Bisphosphonate Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bone/joint/muscle pain: Infrequently, severe (and occasionally debilitating) bone, joint, and/or muscle pain have been reported during bisphosphonate treatment. The onset of pain ranged from a single day to several months. Symptoms usually resolve upon discontinuation. Some patients experienced recurrence when rechallenged with same drug or another bisphosphonate; avoid use in patients with a history of these symptoms in association with bisphosphonate therapy.

- Gastrointestinal mucosa irritation: May cause irritation to upper gastrointestinal mucosa. Dysphagia, esophagitis, esophageal or gastric ulcers, esophageal erosions, and esophageal stricture (rare) have been reported with oral bisphosphonates; risk increases in patients unable to comply with dosing instructions. Use with caution in patients with dysphagia, esophageal disease, gastritis, duodenitis, or ulcers (may worsen underlying condition). Discontinue if new or worsening symptoms occur.

- Osteonecrosis of the jaw: Bisphosphonate therapy has been associated with osteonecrosis, primarily of the jaw; this has been observed mostly in cancer patients, but also in patients with postmenopausal osteoporosis and other diagnoses. Risk factors include a diagnosis of cancer, with concomitant chemotherapy, radiotherapy, or corticosteroids; anemia, coagulopathy, infection, or pre-existing dental disease. Symptoms included nonhealing extraction socket or an exposed jawbone. There are no data addressing whether discontinuation of therapy reduces the risk of developing osteonecrosis; however, as a precautionary measure, dental exams and preventative dentistry should be performed prior to placing patients with risk factors on chronic bisphosphonate therapy. Invasive dental procedures should be avoided during treatment.

Disease-related concerns:

- Glucocorticoid-induced osteoporosis: Evaluate sex steroid hormonal status prior to treatment initiation; consider appropriate hormone replacement if necessary.

- Hypocalcemia: Before initiation of therapy hypocalcemia must be corrected; ensure adequate calcium and vitamin D intake, especially for patients with Paget's disease in whom the pretreatment rate of bone turnover may be greatly elevated.

- Renal impairment: Use with caution in patients with renal impairment (not recommended in patients with a Cl_{cr} <30 mL/minute).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo dosage adjustment required if Cl_{cr} ≥30 mL/minute. Since elderly often receive diuretics, evaluate electrolyte status periodically due to the drug class (bisphosphonates). Should assure that immobile patients are sitting up for at least 30 minutes after swallowing tablets.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic and nonteratogenic embryo/fetal effects have been reported in animal studies. There are no adequate and well-controlled studies in pregnant women. Bisphosphonates are incorporated into the bone matrix and gradually released over time. Theoretically, there may be a risk of fetal harm when pregnancy follows the completion of therapy. Based on limited case reports with pamidronate, serum calcium levels in the newborn may be altered if administered during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsThe manufacturer recommends discontinuing nursing or discontinuing risedronate.

Adverse ReactionsFrequency may vary with dose and indication.

>10%:

Cardiovascular: Hypertension (11%)

Central nervous system: Headache (10% to 18%)

Dermatologic: Rash (8% to 12%)

Endocrine & metabolic: Serum PTH levels decreased (<30%)

Gastrointestinal: Diarrhea (5% to 20%), constipation (7% to 13%), nausea (7% to 13%), abdominal pain (7% to 12%), dyspepsia (7% to 11%)

Genitourinary: Urinary tract infection (11%)

Neuromuscular & skeletal: Arthralgia (12% to 33%), back pain (18% to 28%)

Miscellaneous: Infection (≤31%)

1% to 10%:

Cardiovascular: Peripheral edema (8%), chest pain (5% to 7%), arrhythmia (2%)

Central nervous system: Depression (7%), dizziness (7%), insomnia (5%)

Endocrine & metabolic: Hypocalcemia (≤5%), hypophosphatemia (<3%)

Gastrointestinal: Gastritis (3%), duodenitis (≤1%), glossitis (≤1%)

Genitourinary: Prostatic hyperplasia (5%; benign), nephrolithiasis (3%)

Neuromuscular & skeletal: Joint disorder (7%), myalgia (5% to 7%), neck pain (5%), weakness (5%), neuralgia (4%)

Ocular: Cataract (7%), dry eyes (3%)

Respiratory: Bronchitis (3% to 10%), pharyngitis (6%), rhinitis (6%), dyspnea (4%)

Miscellaneous: Flu-like syndrome (10%), acute phase reaction (≤8%; includes fever, influenza-like illness)

<1%, postmarketing, and/or case reports: Allergic reaction, angioedema, arthritis, bullous skin reaction, cough, dysphagia, esophagitis, esophageal ulcer, gastric ulcer, hypersensitivity reaction, iritis, joint pain, liver function test abnormality, musculoskeletal pain (rarely severe or incapacitating), osteonecrosis (primarily of the jaw), sinusitis, uveitis

Drug Interactions

Aminoglycosides: May enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Magaldrate; Sodium Bicarbonate. *Risk D: Consider therapy modification*

Calcium Salts: May decrease the absorption of Bisphosphonate Derivatives. *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral iron salts are of concern. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Phosphate Supplements: Bisphosphonate Derivatives may enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase risk of osteoporosis).

Food: Food reduces absorption (similar to other bisphosphonates); mean oral bioavailability is decreased when given with food.

Test InteractionsBisphosphonates may interfere with diagnostic imaging agents such as technetium-99m-diphosphonate in bone scans.
Monitoring ParametersAlkaline phosphatase should be periodically measured; serum calcium, phosphorus; monitor pain and fracture rate; bone mineral density

Evaluate sex steroid hormonal status prior to treatment initiation (when treating glucocorticoid-induced osteoporosis).

Reference RangeCalcium (total): Adults: 9.0-11.0 mg/dL (2.05-2.54 mmol/L), may slightly decrease with aging; phosphorus: 2.5-4.5 mg/dL (0.81-1.45 mmol/L)
Nursing: Physical Assessment/MonitoringAssess history for any previous adverse response to bisphosphonates and ability to comply with administration instructions. Use caution with renal impairment. Correct any hypocalcemia prior to beginning treatment. Patients at risk for osteonecrosis (eg, chemotherapy, corticosteroids, poor oral hygiene) should have dental exams and necessary preventive dentistry should be done before beginning bisphosphonate therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions or toxicity. Assess results of periodic laboratory tests, therapeutic effectiveness (eg, pain, fracture rate, bone density), and adverse reactions (eg, immediate or long-term musculoskeletal pain). Teach appropriate use and specific administration directions, lifestyle and dietary changes according to purpose for use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsAlkaline phosphatase should be periodically measured; serum calcium, phosphorus
Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take with a full glass of water on an empty stomach at least 30 minutes before eating or taking anything else. Stay in sitting or standing position for 30 minutes following administration and until after the first food of the day to reduce potential for esophageal irritation. Consult prescriber to determine necessity of dietary supplements of calcium or increased dietary vitamin D. Certain dental procedures should be avoided if possible while you are taking this medication; consult prescriber. You may experience temporary nausea or vomiting (small frequent meals may help); diarrhea (boiled milk or yogurt may help); or bone pain (consult prescriber for analgesic). Report persistent muscle or bone pain; leg cramps; muscle twitching; unusual fever; convulsions; difficulty breathing; rash; bloody stool; pain in mouth, jaws, or teeth; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or if you are breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as sodium:

Actonel®: 5 mg, 30 mg, 35 mg, 75 mg, 150 mg

Generic AvailableNo
ManufacturerProcter & Gamble Pharmaceuticals
Pricing: U.S. (www.drugstore.com)

Tablets (Actonel)

5 mg (30): $109.52

30 mg (10): $240.85

35 mg (4): $105.11

75 mg (2): $110.58

150 mg (1): $110.58

Mechanism of ActionA bisphosphonate which inhibits bone resorption via actions on osteoclasts or on osteoclast precursors; decreases the rate of bone resorption, leading to an indirect increase in bone mineral density. In Paget's disease, characterized by disordered resorption and formation of bone, inhibition of resorption leads to an indirect decrease in bone formation; but the newly-formed bone has a more normal architecture.

Pharmacodynamics/Kinetics

Onset of action: May require weeks

Absorption: Rapid

Distribution: V_d: 13.8 L/kg

Protein binding: ~24%

Metabolism: None

Bioavailability: Poor, ~0.54% to 0.75%

Half-life elimination: Initial: 1.5 hours; Terminal: 480-561 hours

Time to peak, serum: 1 hour

Excretion: Urine (up to 85%); feces (as unabsorbed drug)

Dental Health Professional ConsiderationsCases of oral bisphosphonate-associated ONJ have been reported. A report by the Council of Scientific Affairs of the American Dental Association (accessed at: http://www.ada.org/prof/resources/topics/osteonecrosis.asp) as of July 2006 gave an estimated incidence of 0.7 cases for every 100,000 person-years of exposure to alendronate (Fosamax®). This translates to one case for every 142,857 person-years exposure. This figure from the ADA report was based on information received from Merck & Co citing 170 worldwide cases for alendronate (Fosamax®). In addition, Procter & Gamble Pharmaceuticals has cited 20 cases for risedronate (Actonel®) and Roche Laboratories has cited one case for ibandronate (Boniva®).

Consumer Reports On Health stated that the risk of jaw bone osteoporosis due to alendronate (Fosamax®), risedronate (Actonel®), or ibandronate (Boniva®) taken to prevent osteoporosis is very low and is estimated to be one out of every 20,000 users. That report mentioned that tooth extraction or implants increase the risk of developing osteonecrosis in patients taking any of these drugs for osteoporosis. The report also recommended that patients should stop taking any of these oral drugs 1-2 months before and after such dental treatment. No evidence was presented to support this statement.

In terms of length of exposure to oral bisphosphonates prior to onset of ONJ, data from large population studies or controlled studies is lacking. A report by Marx et al, observed that of three cases of ONJ associated with Fosamax® exposure, one patient had been taking 10 mg/day by mouth for 6 years and the other two patients 10 mg/day by mouth for 3 and 2 years respectively. In contrast, they observed that in cancer patients receiving intravenous bisphosphonates, the time period between the first doses of the bisphosphonate to first recognition of exposed bone either by the patients or by the clinician, was 9.4 months for zoledronate (Zometa®), 14.3 months for pamidronate (Aredia®), and 12.1 months for pamidronate then to zoledronate.

Dental Health: Effects on Dental TreatmentOsteonecrosis of the jaw (ONJ), generally associated with local infection and/or tooth extraction and often with delayed healing, has been reported in patients taking bisphosphonates. Symptoms included nonhealing extraction socket or an exposed jawbone. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates. However, some have occurred in patients with postmenopausal osteoporosis taking oral bisphosphonates. Dental surgery may exacerbate ONJ. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Patients who develop ONJ while on bisphosphonate therapy should receive care by an oral surgeon. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression, insomnia, anxiety, and dizziness

Mental Health: Effects on Psychiatric TreatmentNausea and diarrhea are common; concomitant use with SSRIs, lithium, valproic acid, or carbamazepine may produce additive effects

Index TermsRisedronate Sodium

References

Author Unknown, "Safety Update: Bone-Building Drugs: Risks Explained," *Consum Rep Health*, 2006, 18(5):3.

French AE, Kaplan N, Lishner M, et al, “Taking Bisphosphonates During Pregnancy,” *Can Fam Physician*, 2003, 49:1281-2. [PubMed 14594094]

Marx RE, Sawatari Y, Fortin M, et al, "Bisphosphonate-Induced Exposed Bone (Osteonecrosis/Osteopetrosis) of the Jaws: Risk Factors, Recognition, Prevention, and Treatment," *J Oral Maxillofac Surg*, 2005, 63(11):1567-75.[PubMed 16243172]

International Brand NamesActonel (AR, AU, BB, BE, BM, BO, BR, BS, BZ, CH, CN, CO, CR, CZ, DE, DO, EC, EE, ES, FR, GB, GT, GY, HK, HN, ID, IE, IL, JM, JP, KP, MX, MY, NI, NL, PA, PE, PH, PL, PR, PT, PY, SG, SR, SV, TH, TT, TW, UY, VE); Actonel Once A Week (IL, ZA); Avestra (SE); Norsed (SE); Optinate (DK, NO); Osteoclax (CO); Osteonate (ID); Ribastamin (AR); Risofos (IN)

Risperidone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

Gill SS, Bronskill SE, Normand SL, et al, “Antipsychotic Drug Use and Mortality in Older Adults With Dementia,” *Ann Intern Med*, 2007, 146(11):775-86.[PubMed 17548409]

Schneeweiss S, Setoguchi S, Brookhart A, et al, “Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients,” *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Medication Safety Issues

Sound-alike/look-alike issues:

Risperidone may be confused with reserpine

Risperdal® may be confused with lisinopril, reserpine

Pronunciation(ris PER i done)

U.S. Brand NamesRisperdal®; Risperdal® Consta®; Risperdal® M-Tab®

Canadian Brand NamesApo-Risperidone®; CO Risperidone; Dom-Risperidone; Gen-Risperidone; Novo-Risperidone; PHL-Risperidone; PMS-Risperidone ODT; PRO-Risperidone; Ran-Risperidone; Ratio-Risperidone; Risperdal®; Risperdal® Consta®; Risperdal® M-Tab®; Riva-Risperidone; Sandoz Risperidone

Pharmacologic CategoryAntimanic Agent; Antipsychotic Agent, Atypical

Use: Labeled IndicationsTreatment of schizophrenia; treatment of acute mania or mixed episodes associated with bipolar I disorder (as monotherapy in children or adults, or in combination with lithium or valproate in adults); treatment of irritability/aggression associated with autistic disorder

Use: Unlabeled/InvestigationalTreatment of Tourette's disorder; treatment of pervasive developmental disorder; psychosis/agitation related to Alzheimer’s dementia

Dosing: Adults

Bipolar mania: Oral: Recommended starting dose: 2-3 mg once daily; if needed, adjust dose by 1 mg/day in intervals ≥24 hours; dosing range: 1-6 mg/day.

Schizophrenia:

Oral: Initial: 1 mg twice daily; may be increased by 1-2 mg/day at intervals ≥24 hours to a recommended dosage range of 4-8 mg/day; may be given as a single daily dose once maintenance dose is achieved; daily dosages >6 mg do not appear to confer any additional benefit, and the incidence of extrapyramidal symptoms is higher than with lower doses. Further dose adjustments should be made in increments/decrements of 1-2 mg/day on a weekly basis. Dose range studied in clinical trials: 4-16 mg/day. Maintenance: Recommended dosage range: 2-8 mg/day

I.M. (Risperdal® Consta®): 25 mg every 2 weeks; some patients may benefit from larger doses; maximum dose not to exceed 50 mg every 2 weeks. Dosage adjustments should not be made more frequently than every 4 weeks. A lower initial dose of 12.5 mg may be appropriate in some patients.

Note: Oral risperidone (or other antipsychotic) should be administered with the initial injection of Risperdal® Consta® and continued for 3 weeks (then discontinued) to maintain adequate therapeutic plasma concentrations prior to main release phase of risperidone from injection site.

Tourette's disorder (unlabeled use): Oral: Initial: 0.5 mg; titrate to 2-4 mg/day

Dosing: Elderly

Oral: A starting dose of 0.5 mg twice daily, and titration should progress slowly in increments of no more than 0.5 mg twice daily; increases to dosages >1.5 mg twice daily should occur at intervals of ≥1 week.

Psychosis/agitation related to Alzheimer’s dementia (unlabeled use): Initial: 0.25-1 mg/day; if necessary, gradually increase as tolerated not to exceed 1.5-2 mg/day

I.M. (Risperdal® Consta®): A lower initial dose of 12.5 mg may be appropriate.

Additional monitoring of renal function and orthostatic blood pressure may be warranted. If once-a-day dosing in the elderly or debilitated patient is considered, a twice daily regimen should be used to titrate to the target dose, and this dose should be maintained for 2-3 days prior to attempts to switch to a once-daily regimen.

Dosing: PediatricChildren and Adolescents:

Autism: Children ≥5 years and Adolescents: Oral:

<15 kg: Use with caution; specific dosing recommendations not available

<20 kg: Initial: 0.25 mg/day; may increase dose to 0.5 mg/day after ≥4 days, maintain dose for ≥14 days. In patients not achieving sufficient clinical response, may increase dose by 0.25 mg/day in ≥2-week intervals. Therapeutic effect reached plateau at 1 mg/day in clinical trials. Following clinical response, consider gradually lowering dose. May be administered once daily or in divided doses twice daily.

≥20 kg: Initial: 0.5 mg/day; may increase dose to 1 mg/day after ≥4 days, maintain dose for ≥14 days. In patients not achieving sufficient clinical response, may increase dose by 0.5 mg/day in ≥2-week intervals. Therapeutic effect reached plateau at 2.5 mg/day (3 mg/day in children >45 kg) in clinical trials. Following clinical response, consider gradually lowering dose. May be administered once daily or in divided doses twice daily.

Bipolar disorder: Children and Adolescents 10-17 years: Oral: Initial: 0.5 mg once daily; dose may be adjusted in increments of 0.5-1 mg/day at intervals ≥24 hours to a dose of 2.5 mg/day. Doses ranging from 0.5-6 mg/day have been evaluated, however doses >2.5 mg/day do not confer additional benefit and are associated with increased adverse events.

Pervasive developmental disorder (unlabeled use): Oral: Initial: 0.25 mg twice daily; titrate up 0.25 mg/day every 5-7 days; optimal dose range: 0.75-3 mg/day

Schizophrenia: Adolescents 13-17 years: Oral: Initial: 0.5 mg once daily; dose may be adjusted in increments of 0.5-1 mg/day at intervals ≥24 hours to a dose of 3 mg/day. Doses ranging from 1-6 mg/day have been evaluated, however, doses >3 mg/day do not confer additional benefit and are associated with increased adverse events.

Tourette's disorder (unlabeled use): Refer to adult dosing.

Dosing: Renal Impairment

Oral: Starting dose of 0.5 mg twice daily; titration should progress slowly in increments of no more than 0.5 mg twice daily; increases to dosages >1.5 mg twice daily should occur at intervals of ≥1 week. Clearance of the active moiety is decreased by 60% in patients with moderate-to-severe renal disease compared to healthy subjects.

I.M.: An initial dose of 12.5 mg may be considered

Dosing: Hepatic Impairment

Oral: Starting dose of 0.5 mg twice daily; titration should progress slowly in increments of no more than 0.5 mg twice daily; increases to dosages >1.5 mg twice daily should occur at intervals of ≥1 week. The mean free fraction of risperidone in plasma was increased by 35% in patients with hepatic impairment compared to healthy subjects.

I.M.: An initial dose of 12.5 mg may be considered

Administration: I.M.Risperdal® Consta® should be administered I.M. into either the deltoid muscle or the upper outer quadrant of the gluteal area. Avoid inadvertent injection into vasculature. Injection should alternate between the two arms or buttocks. Do not combine two different dosage strengths into one single administration. Do not substitute any components of the dose-pack; administer with needle provided (1-inch needle for deltoid administration or 2-inch needle for gluteal administration).

Administration: OralOral solution can be mixed with water, coffee, orange juice, or low-fat milk, but is **not compatible** with cola or tea. May be administered with or without food.

In children or adolescents experiencing somnolence, half the daily dose may be administered twice daily **or** the once-daily dose may be administered at bedtime.

When reinitiating treatment after discontinuation, the initial titration schedule should be followed.

Risperdal® M-Tabs® should not be removed from blister pack until administered. Using dry hands, place immediately on tongue. Tablet will dissolve within seconds, and may be swallowed with or without liquid. Do not split or chew.

Dietary ConsiderationsMay be taken with or without food. Risperdal® M-Tabs® contain phenylalanine.

Storage

Injection: Risperdal® Consta®: Store in refrigerator at 2°C to 8°C (36°F to 46°F) and protect from light. May be stored at room temperature of 25°C (77°F) for up to 7 days prior to administration. Following reconstitution, store at room temperature and use within 6 hours. Suspension settles in ~2 minutes; shake vigorously to resuspend prior to administration.

Oral solution, tablet: Store at 15°C to 25°C (59°F to 77°F). Protect from light and moisture. Keep orally-disintegrating tablets sealed in foil pouch until ready to use. Do not freeze solution.

ReconstitutionRisperdal® Consta®: Bring to room temperature prior to reconstitution. Reconstitute with provided diluent only. Shake vigorously to mix; will form thick, milky suspension. Following reconstitution, store at room temperature and use within 6 hours. Suspension settles in ~2 minutes; shake vigorously to resuspend prior to administration.

ContraindicationsHypersensitivity to risperidone or any component of the formulation

Allergy Considerations

- Risperidone Allergy

Warnings/Precautions

Boxed warnings:

- Dementia: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics. Use caution with history of conduction abnormalities. Relative to other neuroleptics, risperidone has a low risk of arrhythmias.
- Anticholinergic effects: May cause anticholinergic effects (confusion, agitation, constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, urinary retention, BPH, xerostomia, or visual problems. Relative to other neuroleptics, risperidone has a low potency of cholinergic blockade.
- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (eg, Alzheimer's disease).
- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is generally much lower relative to typical/conventional antipsychotics). Risk of dystonia (and probably other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.
- Hyperglycemia: Atypical antipsychotics have been associated with development of hyperglycemia; in some cases, may be extreme and associated with ketoacidosis, hyperosmolar coma, or death. Use with caution in patients with diabetes or other disorders of glucose regulation; monitor for worsening of glucose control.
- Neuroleptic malignant syndrome (NMS): Use may be associated with neuroleptic malignant syndrome (NMS); monitor for mental status changes, fever, muscle rigidity and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect (eg, concurrent medication use which may predispose to hypotension/bradycardia or presence of hypovolemia) or in those who would not tolerate transient hypotensive episodes. Use caution with history of cerebrovascular or cardiovascular disease (MI, heart failure, or ischemic disease).
- Priapism: Rare cases of priapism have been reported.
- Sedation: May be low to moderately sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Suicidal ideation: The possibility of a suicide attempt is inherent in psychotic illness or bipolar disorder; use with caution in high-risk patients during initiation of therapy. Prescriptions should be written for the smallest quantity consistent with good patient care.
- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.
- Weight gain: Significant weight gain has been observed with antipsychotic therapy; incidence varies with product. Monitor waist circumference and BMI.

Disease-related concerns:

- Dementia: **[U.S. Boxed Warning]: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo.** An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Risperidone is not approved for the treatment of dementia-related psychosis.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with hepatic disease or impairment; dosage reduction is recommended.

- Hyperprolactinemia: Elevates prolactin levels; effects seen in adults and children. Use with caution in breast cancer or other prolactin-dependent tumors.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with Parkinson's disease.

- Renal impairment: Use with caution in patients with renal disease; dosage reduction is recommended.

- Seizures: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold. Elderly patients may be at increased risk of seizures due to an increased prevalence of predisposing factors.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reyes syndrome, brain tumor) due to antiemetic effects.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <5 years of age (<18 years of age for I.M. injection). Long-term effects on growth or sexual maturation have not been evaluated.

Dosage form specific issues:

- Vehicle used in injectable (polylactide-co-glycolide microspheres): Has rarely been associated with retinal artery occlusion in patients with abnormal arteriovenous anastomosis (eg, patent foramen ovale).

Geriatric ConsiderationsAny changes in disease status in any organ system can result in behavior changes.

Extrapyramidal syndrome symptoms occur less with this agent when total daily dose remains <6 mg as compared with phenothiazines and butyrophenone classes of antipsychotics. Many elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior. Before initiating antipsychotic medication, the clinician should investigate any possible reversible cause; any stress or stress from any disease can cause acute “confusion” or worsening of baseline nonpsychotic behavior. Most commonly acute changes in behavior are due to increases in drug dose or addition of new drug to regimen; fluid electrolyte loss; infections; and changes in environment.

In the treatment of agitated, demented, elderly patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control. In light of significant risks and adverse effects in elderly population compared with limited data demonstrating efficacy in the treatment of dementia related psychosis, aggression, and agitation, an extensive risk:benefit analysis should be performed prior to use.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies indicate an increase in fetal mortality. Reversible EPS symptoms were noted in neonates following use of risperidone during the last trimester. Agenesis of the corpus callosum has also been noted in one case report. There are no adequate and well-controlled studies in pregnant women. When using Risperdal® Consta®, patients should notify healthcare provider if they become or intend to become pregnant during therapy or within 12 weeks of last injection. Risperidone may cause hyperprolactinemia, which may decrease reproductive function in both males and females. Healthcare providers are encouraged to enroll women 18-45 years of age exposed to risperidone during pregnancy in the Atypical Antipsychotics Pregnancy Registry (1-866-961-2388).

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsRisperidone and its metabolite are excreted in breast milk; it is recommended that women not breast-feed during therapy or for 12 weeks after the last injection if using Risperdal® Consta®.

Adverse ReactionsThe frequency of adverse effects is reported as absolute percentages and is not based upon net frequencies as compared to placebo. Actual frequency may be dependant upon dose and/or indication. Events are reported from placebo-controlled studies and not with combination therapy. Unless otherwise noted, frequency of adverse effects is reported for the oral formulation in adults.

>10%:

Central nervous system: Somnolence (children 12% to 67%; adults 5% to 14%; I.M. injection 5% to 6%), fatigue (children 18% to 42%; adults 1% to 3%), headache (I.M. injection 15% to 21%), fever (children 20%; adults 1% to 2%), dystonia (children 9% to 18%; adults 5% to 11%), anxiety (children ≤16%; adults 2% to 16%), dizziness (children 7% to 16%; adults 4% to 10%), Parkinsonism (children 2% to 16%; adults 12% to 20%)

Dermatologic: Rash (children ≤11%; adults 2% to 4%)

Gastrointestinal: Appetite increased (children 4% to 49%), vomiting (children 10% to 25%), salivation increased (children ≤22%; adults 1% to 3%), constipation (children 21%; adults 8% to 9%), abdominal pain (children 15% to 18%; adults 3% to 4%), nausea (children 8% to 16%; adults 4% to 9%), dyspepsia (children 5% to 16%; adults 4% to 10%), xerostomia (children 13%; adults ≤4%)

Genitourinary: Urinary incontinence (children 5% to 22%; adults <2%)

Neuromuscular & skeletal: Tremor (adults 6%; children 10% to 12%)

Respiratory: Rhinitis (children 13% to 36%; adults 7% to 11%), upper respiratory infection (children 34%; adults 2% to 3%), cough (children 34%; adults 3%)

1% to 10%:

Cardiovascular: Tachycardia (children ≤7%; adults 1% to 5%), chest pain (1% to 3%), creatine phosphokinase increased (≤2%), postural hypotension (≤2%), arrhythmia (≤1%), edema (≤1%), hypotension (≤1%), syncope (≤1%)

Central nervous system: Akathisia (children ≤10%; adults 5% to 9%), automatism (children 7%), confusion (children 5%)

Dermatologic: Seborrhea (up to 2%), acne (1%)

Endocrine & metabolic: Lactation nonpuerperal (children 2% to 5%; adults 1%), ejaculation failure (≤1%)

Gastrointestinal: Diarrhea (children 7% to 8%; adults ≤3%), anorexia (children 8%; adults ≤2%;), weight gain (children 5%; adults ≤1%), toothache (I.M. injection 1% to 3%)

Genitourinary: Urinary tract infection (≤3%)

Hematologic: Anemia (I.M. injection <2%; oral ≤1%)

Hepatic: Transaminases increased (I.M. injection ≥1%; oral 1%)

Neuromuscular & skeletal: Dyskinesia (children 7%; adults 1%), arthralgia (2% to 3%), back pain (2% to 3%), myalgia (≤2%), weakness (1%)

Ocular: Abnormal vision (children 4% to 7%; adults 1% to 3%), blurred vision (I.M. injection 2% to 3%)

Otic: Earache (1%)

Respiratory: Dyspnea (children 2% to 5%; adults 2%), epistaxis (≤2%)

≤1%, postmarketing, and/or case reports (limited to important or life-threatening): Agranulocytosis, allergic reaction, amenorrhea, amnesia, anaphylactic reaction, angina pectoris, angioedema, antidiuretic hormone disorder, aphasia, apnea, ascites, aspiration, asthma, atrial fibrillation, AV block, bronchospasm, cachexia, catatonic reaction, cerebrovascular accident, cerebrovascular disorder, cholecystitis, cholelithiasis, cholestatic hepatitis, cholinergic syndrome, coma, dehydration, delirium, depression, diabetes mellitus, diabetic ketoacidosis, diverticulitis, dysphagia, esophagitis, esophageal dysmotility, fecal incontinence, flu-like syndrome, gastroenteritis, hematemesis, hematuria, hemorrhage, hepatic failure, hepatocellular damage, hyper-/hypoglycemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypokalemia, hyponatremia, hypoproteinemia, intestinal obstruction, jaundice, leukocytosis, leukopenia, leukorrhea, lymphadenopathy, mastitis, menstrual irregularities, migraine, myocardial infarction, myocarditis, palpitation, pancreatitis, Pelger-Huët anomaly, pituitary adenomas, pneumonia, precocious puberty, premature atrial contractions, priapism, pulmonary embolism, purpura, QT_c prolongation, RBC disorders, renal insufficiency, retinal artery occlusion (I.M. formulation), rigors, sarcoidosis, skin exfoliation, skin ulceration, ST depression, stomatitis, stridor, stroke, superficial phlebitis, synostosis, T wave inversions, thrombocytopenia, thrombophlebitis, thrombotic thrombocytopenic purpura, tinnitus, tongue discoloration, tongue edema, tongue paralysis, torticollis, transient ischemic attack, urinary retention, urticaria, ventricular extrasystoles, ventricular tachycardia, water intoxication, withdrawal syndrome, xerophthalmia

Metabolism/Transport Effects **Substrate** of CYP2D6 (major), 3A4 (minor); **Inhibits** CYP2D6 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Atypical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

CarBAMazepine: May decrease the serum concentration of Risperidone. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Risperidone. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Valproic Acid: May enhance the adverse/toxic effect of Risperidone. Generalized edema has developed. *Risk C: Monitor therapy*

Verapamil: May increase the serum concentration of Risperidone. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Monitoring ParametersVital signs; fasting lipid profile and fasting blood glucose/Hgb A_{1c} (prior to treatment, at 3 months, then annually); BMI, personal/family history of obesity, waist circumference; blood pressure; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms; orthostatic blood pressure changes for 3-5 days after starting or increasing dose. Weight should be assessed prior to treatment, at 4 weeks, 8 weeks, 12 weeks, and then at quarterly intervals. Consider titrating to a different antipsychotic agent for a weight gain ≥5% of the initial weight.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Monitor results of periodic ophthalmic exams. Assess therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Monitor weight prior to initiating therapy and at least monthly. Be alert to the potential for orthostatic hypotension, especially during the titration phase. Initiate at lower doses and titrate to target dose. Taper dosage slowly when discontinuing. Teach patient appropriate use, possible side effects, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsFasting lipid profile and fasting blood glucose/Hgb A_{1c} (prior to treatment, at 3 months, then annually)

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Use exactly as directed; do not increase dose or frequency. It may take several weeks to achieve desired results; do not discontinue without consulting prescriber. Dilute solution with water, milk, or orange juice; do not dilute with beverages containing tannin or pectinate (eg, colas, tea). Avoid alcohol or caffeine unless approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, you may experience increased blood sugars. Monitor blood sugars closely. You may experience excess sedation, drowsiness, restlessness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); dry mouth, nausea, or GI upset (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); or urinary retention (void before taking medication). Report persistent CNS effects (eg, trembling fingers, altered gait or balance, excessive sedation, seizures, unusual muscle or skeletal movements, anxiety, abnormal thoughts [especially thoughts of suicide], confusion, personality changes); chest pain, palpitations, rapid heartbeat, severe dizziness; swelling or pain in breasts (male and female), altered menstrual pattern, sexual dysfunction; pain or difficulty on urination; vision changes; skin rash or yellowing of skin; respiratory difficulty; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, microspheres for reconstitution, extended release:

Risperdal® Consta®: 12.5 mg, 25 mg, 37.5 mg, 50 mg [contains polylactide-co-glycolide; supplied in a dose-pack containing vial with active ingredient in microsphere formulation, prefilled syringe with diluent, needle-free vial access device, and 2 safety needles (1- and 2-inch)]

Solution, oral: 1 mg/mL (30 mL)

Risperdal®: 1 mg/mL (30 mL) [contains benzoic acid]

Tablet: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg

Risperdal®: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg

Tablet, orally disintegrating: 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg

Risperdal® M-Tabs®: 0.5 mg [contains phenylalanine 0.14 mg]; 1 mg [contains phenylalanine 0.28 mg]; 2 mg [contains phenylalanine 0.42 mg]; 3 mg [contains phenylalanine 0.63 mg]; 4 mg [contains phenylalanine 0.84 mg]

Generic AvailableYes: Excludes injection

ManufacturerJanssen Pharmaceutica Products, LP

Pricing: U.S. (www.drugstore.com)

Solution (Risperdal)

1 mg/mL (60): $282.27

Tablet, orally-disintegrating (Risperdal M-TAB)

0.5 mg (28): $131.41

1 mg (28): $148.55

Tablets (Risperdal)

0.25 mg (30): $113.30

0.5 mg (30): $122.92

1 mg (30): $145.38

2 mg (30): $224.48

3 mg (30): $289.99

4 mg (30): $331.37

Tablets (Risperidone)

0.25 mg (60): $145.99

0.5 mg (60): $179.98

1 mg (60): $195.98

2 mg (60): $289.96

3 mg (60): $299.99

4 mg (60): $399.98

Mechanism of ActionRisperidone is a benzisoxazole atypical antipsychotic with mixed serotonin-dopamine antagonist activity that binds to 5-HT$_2$-receptors in the CNS and in the periphery with a very high affinity; binds to dopamine-D$_2$ receptors with less affinity. The binding affinity to the dopamine-D$_2$ receptor is 20 times lower than the 5-HT$_2$ affinity. The addition of serotonin antagonism to dopamine antagonism (classic neuroleptic mechanism) is thought to improve negative symptoms of psychoses and reduce the incidence of extrapyramidal side effects. Alpha$_1$, alpha$_2$ adrenergic, and histaminergic receptors are also antagonized with high affinity. Risperidone has low to moderate affinity for 5-HT$_{1C}$, 5-HT$_{1D}$, and 5-HT$_{1A}$ receptors, weak affinity for D$_1$ and no affinity for muscarinics or beta$_1$ and beta$_2$ receptors

Pharmacodynamics/Kinetics

Absorption:

Oral: Rapid and well absorbed; food does not affect rate or extent

Injection: <1% absorbed initially; main release occurs at ~3 weeks and is maintained from 4-6 weeks

Distribution: V$_d$: 1-2 L/kg

Protein binding, plasma: Risperidone 90%; 9-hydroxyrisperidone: 77%

Metabolism: Extensively hepatic via CYP2D6 to 9-hydroxyrisperidone (similar pharmacological activity as risperidone); *N*-dealkylation is a second minor pathway

Bioavailability: Oral: 70%; Tablet (relative to solution): 94%; orally-disintegrating tablets and oral solution are bioequivalent to tablets

Half-life elimination: Active moiety (risperidone and its active metabolite 9-hydroxyrisperidone)

Oral: 20 hours (mean)

Extensive metabolizers: Risperidone: 3 hours; 9-hydroxyrisperidone: 21 hours

Poor metabolizers: Risperidone: 20 hours; 9-hydroxyrisperidone: 30 hours

Injection: 3-6 days; related to microsphere erosion and subsequent absorption of risperidone

Time to peak, plasma: Oral: Risperidone: Within 1 hour; 9-hydroxyrisperidone: Extensive metabolizers: 3 hours; Poor metabolizers: 17 hours

Excretion: Urine (70%); feces (14%)

Related Information

- Agents Approved for Bipolar Disorder
- Antipsychotic Agents
- Antipsychotic Receptor Profile
- Atypical Antipsychotics
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Liquid Compatibility
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsRisperdal® Consta® is an injectable formulation of risperidone using the extended release Medisorb® drug-delivery system; small polymeric microspheres degrade slowly, releasing the medication at a controlled rate.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation) and toothache.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Child/Adolescent Considerations

Aggression: In a randomized, double-blind, placebo-controlled study, 10 children and adolescents 6-14 years of age (mean: 9.2 ± 2.9 years) with conduct disorder and prominent aggressive behavior received risperidone in the following doses: Patients <50 kg: Initial: 0.25 mg once daily; doses were increased as needed by 0.25 mg/day increments each week to a maximum of 1.5 mg/day; patients ≥50 kg: Initial: 0.5 mg once daily; doses were increased as needed by 0.5 mg/day increments each week to a maximum of 3 mg/day; final dose: 0.75-1.5 mg/day; mean: 0.028 ± 0.004 mg/kg/day (Findling, 2000). In another randomized, double-blind, placebo-controlled study, 19 adolescents (mean age: 14 ± 1.5 years; 7 with borderline IQ and 6 with mild mental retardation) received initial risperidone doses of 0.5 mg twice daily; doses were increased as needed by 1 mg/day increments up to a planned maximum of 5 mg twice daily; final doses: Range: 1.5-4 mg/day (0.019-0.08 mg/kg/day); mean: 2.9 mg/day (0.044 mg/kg/day); the authors recommend the following initial doses for clinical practice: Patients <25 kg: 0.25 mg/day; patients ≥25 kg: 0.5 mg/day (Buitelaar, 2001).

In an open trial, 26 children and adolescents 10-18 years of age (mean: 15 ± 1.9 years) with a borderline IQ (n=19) or mild mental retardation (n=5) received initial risperidone doses of 0.5 mg/day; doses were increased by 0.5-1 mg/day increments every 3 days up to a planned maximum of 6 mg/day and given in twice daily doses; final dose: 0.5-4 mg/day; mean: 2.1 ± 1 mg/day (Buitelaar, 2000). Eleven children and adolescents 5.5-16 years of age (mean: 9.8 years) with mood disorders and aggressive behavior received risperidone in titrated doses in an open trial; final dose: 0.75-2.5 mg/day given in 2-3 divided doses (Schreier, 1998).

Autism: A multicenter double-blind, placebo-controlled trial of risperidone in children and adolescents 5-17 years of age (mean: 8.8 ± 2.7 years) with autism and serious behavioral problems demonstrated the short-term efficacy of risperidone for the treatment of aggression, tantrums, or self-injurious behavior. The following doses were used: Children 15-20 kg: Initial: 0.25 mg/day. Children 20-45 kg: Initial: 0.5 mg at bedtime on days 1-3 and 0.5 mg twice daily on day 4; dose was gradually increased in 0.5 mg increments to a maximum dose of 2.5 mg/day. Children >45 kg: Maximum dose: 3.5 mg/day; mean effective dose: 1.8 ± 0.7 mg/day (range: 0.5-3.5 mg/day) (McCracken, 2002).

In an open-labeled prospective study, 10 boys 4.5-10.8 years of age (mean: 7.2 ± 2.2 years) with autistic disorder were started on risperidone 0.5 mg/day; final dose: range: 1-2.5 mg/day (0.03-0.08 mg/kg/day); mean: 1.3 ± 0.5 mg/day (0.05 ± 0.2 mg/kg/day) (Nicolson, 1998). In an open clinical trial, 6 children 5-9 years of age (mean: 7.33 years) with autistic disorder were started on risperidone monotherapy 0.25 mg at bedtime; final dose: range: 0.75-1.5 mg/day (0.03-0.06 mg/kg/day); mean: 1.1 mg (0.04 mg/kg/day) (Findling, 1997).

Bipolar disorder: In a retrospective chart review, 28 children and adolescents 4-17 years of age (mean: 10.4 ± 3.8 years) were treated for bipolar disorder; optimal mean dose: 1.7 ± 1.3 mg/day (Frazier 1999).

Pervasive developmental disorders (PDDs): In a prospective open-labeled study, children and adolescents 5-18 years of age (mean 10.2 ± 3.7 years) were treated for PDDs (11 with autistic disorder) with initial doses of 0.5 mg at night; optimal dose: 1-4 mg/day (mean: 1.8 ± 1 mg/day) (McDougle, 1997). Fourteen children and adolescents 9-17 years of age (mean: 12.7 ± 4 years) were treated in an open case series, for PDDs (4 with autistic disorder) with initial doses of 0.25 mg twice daily; optimal dose: 0.75-1.5 mg/day given in divided doses (Fisman, 1996). In an open trial, 6 children and adolescents 7-14 years of age (mean: 10.7 ± 3.3 years) were treated for PDDs (5 with autistic disorder; all 6 with severe behavioral problems) with initial doses of 0.5 mg once or twice daily; optimal dose: 1-6 mg/day (mean 2.7 ± 2.2 mg/day) (Perry, 1997). Twenty children and adolescents (age: 8-17 years) with developmental disorders refractory to previous psychotropic agents were treated in an open clinical trial with risperidone; final doses: 1.5-10 mg/day; responders: 1-4 mg/day; nonresponders: 4.5-10 mg/day (Hardan, 1996).

Schizophrenia: In a prospective, open-labeled pilot study, 10 children and adolescents 11-18 years of age (mean: 15.1 years) were treated for schizophrenia with initial doses of 1 mg twice daily; final dose: Range: 4-10 mg/day (0.05-0.17 mg/kg/day); mean: 6.6 mg/day (0.095 mg/kg/day) (Armenteros, 1997). In a retrospective study, 16 children and adolescents 9-20 years of age (mean 14.9 ± 2.73 years) were treated for psychotic disorders with initial doses of 1 mg twice daily; optimal dose: 2-10 mg/day (mean: 5.9 ± 2.8 mg/day) divided and given in 2-3 doses/day (Grcevich, 1996).

Tourette's syndrome: In a multicenter, double-blind, parallel-group comparative study, 50 patients 11-50 years of age were treated for Tourette's syndrome with risperidone versus pimozide; final dose: 0.5-6 mg/day (mean: 3.8 mg/day) (Bruggeman, 2001).

Seven children and adolescents 11-16 years of age (mean: 12.9 ± 1.9 years) were treated in a prospective open-labeled trial for chronic tic disorders (5 with Tourette's syndrome) with initial doses of 0.5 mg at bedtime; final dose: 1-2.5 mg/day (Lombroso, 1995). In a retrospective review, 28 children and adolescents 5-18 years of age (mean 11.1 ± 3.6 years) with Tourette's syndrome and aggressive behavior were treated with risperidone; final dose: 0.5-9 mg/day (mean: 2 mg/day) (Sandor, 2000).

Armenteros JL, Whitaker AH, Welikson M, et al, “Risperidone in Adolescents With Schizophrenia: An Open Pilot Study,” *J Am Acad Child Adolesc Psychiatry*, 1997, 36(5):694-700.

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Mental Health Comment

Risperidone is an antipsychotic agent of a class often referred to as atypical. It should be noted that the definition of the term “atypical” is not universally agreed upon. Some prefer to describe antipsychotics based on their pharmacological properties. A common feature of all definitions used to describe “atypical” antipsychotics is the lack of significant acute or subacute EPS, at dosages generally associated with antipsychotic actions. Other experts have included definitions of atypicality that include a) failure to increase serum prolactin levels; b) superior efficacy for positive, negative, and cognitive symptoms; and c) lack of evidence of tardive dyskinesia or dystonia following chronic administration.

Risperidone is associated with a dose dependent increase in EPS. Optimal dosage for most patients is ~4 mg/day. EPS is low when dosed ≤6 mg/day. Dosages >6 mg/day give a clinical picture similar to haloperidol.

Tardive dyskinesia (TD) secondary to **typical** antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. The incidence of TD associated with the atypical antipsychotics is estimated to be 0.5% to 1%. It is not clear if this estimate represents a risk associated with mental illness or to what extent drug therapy can be implicated. Atypical antipsychotics appear less likely to cause tardive dyskinesia than typical antipsychotics (fluphenazine, haloperidol).

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

The long acting dosage form of risperidone is formed by cross-linking polylactide and glycolide molecules into a polymer, then exposing that polymer to risperidone to create microspheres that are 25-150 microns in diameter. The microspheres must be suspended in the water-based diluent (provided in the kit) prior to injection. Since the microspheres may not be uniformly distributed in the diluent, the entire contents of the vial must be injected to ensure accurate dosing (dividing a dose is not accurately possible). Further, the bore of the needle (included in the kit) is Teflon® coated to prevent destruction of the microspheres and loss of drug due to sticking to the interior surface during injection.

Approximately 1% of the drug is released for the first 3 weeks after an injection. Therefore, one must overlap with oral therapy for at least 3 weeks and often 4-6 weeks or longer. This dosage form is not amenable to loading dose strategies. However, it is water-based (as opposed to oil) and is associated with less pain after injection than haloperidol decanoate or fluphenazine decanoate. The vials can be stored at room temperature for ≤7 days total prior to reconstitution and should be stored in a refrigerator until the day of injection.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Cardiovascular Considerations

Risperidone may cause orthostatic hypotension and tachycardia but to a degree which may be less than is seen with other agents (eg, phenothiazines: chlorpromazine, thioridazine). Risperidone may also prolong the QT interval. For these reasons, patient's with cardiovascular disease should be monitored closely while on therapy.

Anesthesia and Critical Care Concerns/Other Considerations

Risperidone may cause orthostatic hypotension and tachycardia but to a degree which may be less than is seen with other agents (eg, phenothiazines: chlorpromazine, thioridazine).

Index Terms

Risperdal M-Tab

References

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International Brand NamesAspidon (PH); Ispidon (PE); Riper (TW); Riperidon (KP); Risdol (TW); Risdon (TW); Risfree (KP); Rispen (KP); Risperatio (PL); Risperdal (AE, AR, AT, AU, BD, BE, BF, BG, BH, BJ, BO, BR, CH, CI, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, HK, HN, ID, IE, IL, IN, IQ, IR, IT, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PK, PR, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SV, SY, TH, TN, TR, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Risperdal Const (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Risperdal Consta (AU, CH, DE, GB, HK, ID, IE, IL, KP, MY, PH, SE, SG, TH, TW); Risperdal Quicklet (BB, BM, BS, BZ, DE, GB, GY, HK, IE, IL, JM, KP, NL, NZ, PH, SG, SR, TH, TT); Risperdalconsta LP (FR); Risperidex (IL); Rispid (IN); Rispolept (PL); Rispolet (EE); Rispolux (CR, GT, HN, NI, PA, SV); Rispond (IL, PH); Risset (PL); Rizodal (ID); Sequinan (AR); Zargus (BR); Zofredal (ID); Ñorispez (MX)

Ritonavir

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Ritonavir may be confused with Retrovir®

Norvir® may be confused with Norvasc®

Pronunciation(ri TOE na veer)

U.S. Brand NamesNorvir®

Canadian Brand NamesNorvir®; Norvir® SEC

Pharmacologic CategoryAntiretroviral Agent, Protease Inhibitor

Use: Labeled IndicationsTreatment of HIV infection; should always be used as part of a multidrug regimen (at least three antiretroviral agents); may be used as a pharmacokinetic "booster" for other protease inhibitors

Dosing: Adults

Treatment of HIV infection: Oral: 600 mg twice daily; dose escalation tends to avoid nausea that many patients experience upon initiation of full dosing. Escalate the dose as follows: 300 mg twice daily for 1 day, 400 mg twice daily for 2 days, 500 mg twice daily for 1 day, then 600 mg twice daily. Ritonavir may be better tolerated when used in combination with other antiretrovirals by initiating the drug alone and subsequently adding the second agent within 2 weeks.

Pharmacokinetic “booster” in combination with other protease inhibitors: 100-400 mg/day

Refer to individual monographs; specific dosage recommendations often require adjustment of both agents.

Dosage adjustments for ritonavir when administered in combination therapy:

Amprenavir: Adjustments necessary for each agent:

Amprenavir 1200 mg with ritonavir 200 mg once daily **or**

Amprenavir 600 mg with ritonavir 100 mg twice daily

Amprenavir plus efavirenz (3-drug regimen): Amprenavir 1200 mg twice daily plus ritonavir 200 mg twice daily plus efavirenz at standard dose

Indinavir: Adjustments necessary for agent:

Indinavir 800 mg twice daily plus ritonavir 100-200 mg twice daily **or**

Indinavir 400 mg twice daily plus ritonavir 400 mg twice daily

Nelfinavir: Ritonavir 400 mg twice daily

Rifabutin: Decrease rifabutin dose to 150 mg every other day

Saquinavir: Ritonavir 400 mg twice daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

HIV infection: Oral: Children >1 month: 350-400 mg/m^2 twice daily (maximum dose: 600 mg twice daily). Initiate dose at 250 mg/m^2 twice daily; titrate dose upward every 2-3 days by 50 mg/m^2 twice daily.

Dosing: Hepatic ImpairmentNo adjustment required in mild or moderate impairment; however, careful monitoring is required in moderate hepatic impairment (levels may be decreased); caution advised with severe impairment (no data available).

Calculations

- Body Surface Area: Pediatrics

Administration: OralAdminister with food. Liquid formulations usually have an unpleasant taste. Consider mixing it with chocolate milk or a liquid nutritional supplement. Whenever possible, administer oral solution with calibrated dosing syringe. Shake liquid well before use.

Dietary ConsiderationsShould be taken with food. Oral solution contains 43% ethanol by volume.

Storage

Capsule: Store under refrigeration at 2°C to 8°C (36°F to 46°F); may be left out at room temperature of <25°C (<77°F) if used within 30 days. Protect from light. Avoid exposure to excessive heat.

Solution: Store at room temperature at 20°C to 25°C (68°F to 77°F); do not refrigerate. Avoid exposure to excessive heat.

ContraindicationsHypersensitivity to ritonavir or any component of the formulation; concurrent alfuzosin, amiodarone, cisapride, dihydroergotamine, ergonovine, ergotamine, flecainide, methylergonovine, midazolam, pimozide, propafenone, quinidine, triazolam, and voriconazole (when ritonavir ≥800 mg/day)

Allergy Considerations

- Ritonavir Allergy

Warnings/Precautions

Boxed warnings:

- High potential for interactions: See "Concurrent drug therapy issues" below.

Concerns related to adverse effects:

- Hypersensitivity reactions: Protease inhibitors have been associated with a variety of hypersensitivity events (some severe), including rash, anaphylaxis (rare), angioedema, bronchospasm, erythema multiforme, and/or Stevens-Johnson syndrome (rare). It is generally recommended to discontinue treatment if severe rash or moderate symptoms accompanied by other systemic symptoms occur.

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).

- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.

- Increased cholesterol: Increases in total cholesterol and triglycerides have been reported; screening should be done prior to therapy and periodically throughout treatment.

- PR interval prolongation: Ritonavir has been associated with AV block due to prolongation of PR interval; use caution with drugs that prolong the PR interval.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiomyopathy, ischemic heart disease, pre-existing conduction abnormalities, or structural heart disease; may be at increased risk of conduction abnormalities (eg, second- or third-degree AV block).

- Diabetes: Changes in glucose tolerance, hyperglycemia, exacerbation of diabetes, DKA, and new-onset diabetes mellitus have been reported in patients receiving protease inhibitors.

- Hemophilia A or B: Use with caution in patients with hemophilia A or B; increased bleeding events, including spontaneous skin hematoma and hemarthrosis, during protease inhibitor therapy have been reported.

- Hepatic impairment: May cause hepatitis, jaundice, and/or exacerbation of pre-existing hepatic dysfunction; use with caution in patients with underlying hepatic disease, such as hepatitis B or C or cirrhosis; monitor transaminases.

- Pancreatitis: Use with caution in patients with increased triglycerides; pancreatitis has been observed. Monitor serum lipase and amylase, and for symptoms of nausea, vomiting, and/or abdominal pain.

Concurrent drug therapy issues:

- High potential for interactions: **[U.S. Boxed Warning]: Ritonavir may interact with many medications, resulting in potentially serious and/or life-threatening adverse events.** Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see drug interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

- Not recommended for use with alfuzosin, amiodarone, cisapride, ergot derivatives, flecainide, lovastatin, midazolam, pimozide, propafenone quinidine, simvastatin, St John's wort, triazolam, or voriconazole.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <1 month of age.

Pregnancy Risk FactorB

Pregnancy ConsiderationsNo increased risk of overall birth defects has been observed following 1st trimester exposure according to data collected by the antiretroviral pregnancy registry. Early studies have shown lower plasma levels during pregnancy compared to postpartum. If needed during pregnancy, use in combination with another PI to boost levels of second PI. Pregnancy and protease inhibitors are both associated with an increased risk of hyperglycemia. Glucose levels should be closely monitored. The Perinatal HIV Guidelines Working Group considers ritonavir to be an alternative PI for use during pregnancy. Healthcare professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse ReactionsPercentages as reported for combined experiences in both treatment-naive and experienced adults:

>10%:

Endocrine & metabolic: Hypercholesterolemia (>240 mg/dL: 37% to 45%), triglycerides increased (>800 mg/dL: 17% to 34%; >1500 mg/dL: 1%

to 13%)

Gastrointestinal: Nausea (26% to 30%), diarrhea (15% to 23%), vomiting (14% to 17%), taste perversion (7% to 11%)

Hepatic: GGT increased (5% to 20%)

Neuromuscular & skeletal: Weakness (10% to 15%), creatine phosphokinase increased (9% to 12%)

2% to 10%:

Cardiovascular: Vasodilation (2%)

Central nervous system: Fever (1% to 5%), dizziness (3% to 4%), insomnia (2% to 3%), somnolence (2% to 3%), depression (2%), anxiety (up to 2%)

Dermatologic: Rash (up to 4%)

Endocrine & metabolic: Uric acid increased (up to 4%)

Gastrointestinal: Abdominal pain (6% to 8%), anorexia (2% to 8%), dyspepsia (up to 6%), local throat irritation (2% to 3%)

Hepatic: Transaminases increased (6% to 10%)

Neuromuscular & skeletal: Paresthesia (3% to 7%), arthralgia (up to 2%), myalgia (2%)

Respiratory: Pharyngitis (≤1% to 3%)

Miscellaneous: Diaphoresis (2% to 3%)

<2% (Limited to important or life-threatening): Abnormal vision, acute myeloblastic leukemia, adrenal cortex insufficiency, allergic reaction, amnesia, anemia, angioedema, aphasia, asthma, bronchospasm, cachexia, cerebral ischemia, cerebral venous thrombosis, chest pain, cholestatic jaundice, coma, dehydration, dementia, depersonalization, diabetes mellitus, dyspnea, edema, esophageal ulcer, gastroenteritis, gastrointestinal hemorrhage, hallucinations, hepatic coma, hepatitis, hepatomegaly, hepatosplenomegaly, hypercholesteremia, hyper-/hypotension, hypothermia, hypoventilation, ileus, interstitial pneumonia, kidney failure, larynx edema, leukopenia, lymphadenopathy, lymphocytosis, manic reaction, MI, myeloproliferative disorder, neuropathy, palpitation, pancreatitis, paralysis, postural hypotension, pseudomembranous colitis, rectal hemorrhage, seizure, skin melanoma, subdural hematoma, syncope, tachycardia, thrombocytopenia, tongue edema, ulcerative colitis, urticaria, vasospasm

Postmarketing and/or case reports: Adrenal suppression. anaphylaxis, atrioventricular block (first, second or third degree), bleeding increased (in patients with hemophilia A or B), Cushing's syndrome, orthostatic hypotension, redistribution of body fat, right bundle branch block, Stevens-Johnson syndrome

Metabolism/Transport Effects **Substrate** of CYP1A2 (minor), 2B6 (minor), 2D6 (major), 3A4 (major); **Inhibits** CYP2C8 (strong), 2C9 (weak), 2C19 (weak), 2D6 (strong), 2E1 (weak), 3A4 (strong); **Induces** CYP1A2 (weak), 2C8 (weak), 2C9 (weak), 3A4 (weak)

Drug Interactions

Abacavir: Protease Inhibitors may decrease the serum concentration of Abacavir. *Risk C: Monitor therapy*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amiodarone: Protease Inhibitors may decrease the metabolism of Amiodarone. *Risk X: Avoid combination*

Antacids: May decrease the absorption of Protease Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Atovaquone: Ritonavir may decrease the serum concentration of Atovaquone. *Risk C: Monitor therapy*

Benzodiazepines (metabolized by oxidation): Protease Inhibitors may decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

BuPROPion: Ritonavir may decrease the serum concentration of BuPROPion. *Risk C: Monitor therapy*

Calcium Channel Blockers (Dihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Protease Inhibitors. Protease Inhibitors may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cisapride: Protease Inhibitors may decrease the metabolism of Cisapride. The resultant increase in serum cisapride concentrations may result in QTc prolongation and malignant cardiac arrhythmias. *Risk X: Avoid combination*

Clarithromycin: Protease Inhibitors may diminish the therapeutic effect of Clarithromycin. Specifically, certain protease inhibitors may decrease formation of the active 14-hydroxy-clarithromycin metabolite, which may negatively impact clarithromycin effectiveness vs. H. influenzae and other non-MAC infections. Protease Inhibitors may increase the serum concentration of Clarithromycin. Clarithromycin dose adjustment in renally impaired patients may be needed. Clarithromycin may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Codeine: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): Protease Inhibitors may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk D: Consider therapy modification*

CycloSPORINE: Protease Inhibitors may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Strong) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Strong) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Delavirdine: Protease Inhibitors may decrease the serum concentration of Delavirdine. Delavirdine may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Digoxin: Protease Inhibitors may increase the serum concentration of Digoxin. Increased serum concentrations of digoxin may increase risk of AV nodal blockade. *Risk C: Monitor therapy*

Disulfiram: May enhance the adverse/toxic effect of Ritonavir. This is specific for the lopinavir/ritonavir (Kaletra) oral solution due to its alcohol content (42%). Management: Concomitant use of Kaletra (lopinavir/ritonavir) oral solution and disulfiram should be avoided. Kaletra contains 42% alcohol. *Risk X: Avoid combination*

Dronabinol: Ritonavir may increase the serum concentration of Dronabinol. *Risk C: Monitor therapy*

Efavirenz: May increase the metabolism of Protease Inhibitors. This specifically includes amprenavir, indinavir, and saquinavir. Efavirenz may increase the serum concentration of Protease Inhibitors. This specifically includes nelfinavir and ritonavir. *Risk D: Consider therapy modification*

Enfuvirtide: Protease Inhibitors may increase the serum concentration of Enfuvirtide. Enfuvirtide may increase the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

Eplerenone: Protease Inhibitors may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Protease Inhibitors may decrease the metabolism of Ergot Derivatives. **Exceptions:** Cabergoline. *Risk X: Avoid combination*

Etravirine: Ritonavir may decrease the serum concentration of Etravirine. *Risk X: Avoid combination*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

FentaNYL: Protease Inhibitors may decrease the metabolism of FentaNYL. *Risk C: Monitor therapy*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Flecainide: Ritonavir may decrease the metabolism of Flecainide. *Risk X: Avoid combination*

Fusidic Acid: Protease Inhibitors may decrease the metabolism of Fusidic Acid. Fusidic Acid may decrease the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Garlic: May decrease the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Protease Inhibitors may increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. **Exceptions:** Fluvastatin. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

LamoTRIgine: Ritonavir may decrease the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Meperidine: Protease Inhibitors may enhance the adverse/toxic effect of Meperidine. Protease Inhibitors may decrease the serum concentration of Meperidine. Concentrations of the toxic Normeperidine metabolite may be increased. *Risk D: Consider therapy modification*

Methadone: Protease Inhibitors may decrease the metabolism of Methadone. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nefazodone: Protease Inhibitors may decrease the metabolism of Nefazodone. *Risk C: Monitor therapy*

Nevirapine: May increase the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): May diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May decrease the serum concentration of Ritonavir. Ritonavir may decrease the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Phosphodiesterase 5 Inhibitors: Protease Inhibitors may decrease the metabolism of Phosphodiesterase 5 Inhibitors. Management: Dose restrictions for tadalafil, and/or sildenafil and vardenafil are recommended in combination with ritonavir, atazanavir, indinavir, darunavir and saquinavir. Consult specific prescribing information for detailed recommendations. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Protease Inhibitors may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Propafenone: Ritonavir may decrease the metabolism of Propafenone. *Risk X: Avoid combination*

Protease Inhibitors: May increase the serum concentration of other Protease Inhibitors. Management: Atazanavir--indinavir combination contraindicated. Amprenavir oral solution not recommended with ritonavir oral solution; tipranavir/ritonavir or atazanavir/ritonavir not recommended with other protease inhibitors. Other combos may require dose changes. *Risk D: Consider therapy modification*

QuiNIDine: Protease Inhibitors may decrease the metabolism of QuiNIDine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: Protease Inhibitors may decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Protease Inhibitors may increase the serum concentration of Sirolimus. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Protease Inhibitors. *Risk X: Avoid combination*

Tacrolimus: Protease Inhibitors may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Strong) may decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

Temsirolimus: Protease Inhibitors may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tenofovir: May decrease the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Tenofovir. *Risk C: Monitor therapy*

Tetrabenazine: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Tetrabenazine. Specifically, concentrations of the active alpha- and beta-dihydrotetrabenazine metabolites may be increased. Management: Tetrabenazine dose should be reduced by 50% when starting a strong CYP2D6 inhibitor. Maximum tetrabenazine dose is 50mg/day when used with a strong CYP2D6 inhibitor. *Risk D: Consider therapy modification*

Theophylline Derivatives: Protease Inhibitors may decrease the serum concentration of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

TraZODone: Protease Inhibitors may increase the serum concentration of TraZODone. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Protease Inhibitors may increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Valproic Acid: Protease Inhibitors may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Voriconazole: Ritonavir may increase the metabolism of Voriconazole. High-dose ritonavir (400 mg every 12 hours) is contraindicated. Use caution with lower doses. *Risk X: Avoid combination*

Warfarin: Ritonavir may decrease the serum concentration of Warfarin. *Risk C: Monitor therapy*

Zidovudine: Protease Inhibitors may decrease the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Food enhances absorption.

Herb/Nutraceutical: St John's wort may decrease ritonavir serum levels. Avoid use.

Monitoring ParametersTriglycerides, cholesterol, CBC, LFTs, CPK, uric acid, basic HIV monitoring, viral load, CD4 count, glucose, serum amylase and lipase

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions or toxicity; (multiple liver enzyme interactions may increase or decrease levels/effects drugs and increase potential for severe toxicity or loss of effectiveness) dosing adjustments may be necessary. A list of medications that should not be used is available in each bottle and patients should be provided with this information. Assess therapeutic response (eg, CD4 count, hepatic function) and adverse reactions at regular intervals during therapy (eg, gastrointestinal disturbance [nausea, vomiting, diarrhea] that can lead to dehydration and weight loss, hyperlipidemia and redistribution of body fat, rash, CNS effects [malaise, insomnia, abnormal thinking], electrolyte imbalance). Caution patients to monitor glucose levels closely; protease inhibitors may cause hyperglycemia or new-onset diabetes. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions (eg, glucose testing [protease inhibitors may cause hyperglycemia; exacerbation or new-onset diabetes], use of barrier contraceptives [protease inhibitors may decrease effectiveness of oral contraceptives]), and adverse symptoms to report.

Monitoring: Lab TestsTriglycerides, cholesterol, LFTs, CBC, CPK, uric acid, viral load, CD4 count, glucose, serum amylase and lipase

Patient EducationYou will be provided with a list of specific medications that should not be used during therapy; do not take any new prescription or over-the-counter medications, or herbal products during therapy (even if they are not on the list) without consulting prescriber. This is not a cure for HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. Take exactly as directed with meals. Mix liquid formulation with chocolate milk or liquid nutritional supplement. Capsules may be stored in refrigerator (do not freeze or expose to excessive heat) or stored at room temperature if used within 30 days. Protect from light. Solution should be stored at room temperature. Do not refrigerate. Maintain adequate hydration (2-3 L/day of fluids), unless instructed to restrict fluid intake. If you miss a dose, take as soon as possible and return to your regular schedule (never take a double dose). Frequent blood tests may be required with prolonged therapy. You may be advised to check your glucose levels (this drug can cause exacerbation or new-onset diabetes). May cause body changes due to redistribution of body fat, facial atrophy, or breast enlargement (normal effects of drug). May cause dizziness, insomnia, abnormal thinking (use caution when driving or engaging in potentially hazardous tasks until response to drug is known); nausea, vomiting, or taste perversion (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); muscle weakness (consult prescriber for approved analgesic); or headache (consult prescriber for medication). Inform prescriber if you experience muscle numbness or tingling; unresolved persistent vomiting, diarrhea, or abdominal pain; respiratory difficulty or chest pain; unusual skin rash; or change in color of stool or urine. or any persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Effectiveness of oral contraceptives may be decreased, use of alternative (nonhormonal) forms of contraception is recommended, consult prescriber for appropriate measures.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, soft gelatin:

Norvir®: 100 mg [contains ethanol and polyoxyl 35 castor oil]

Solution:

Norvir®: 80 mg/mL (240 mL) [contains ethanol, polyoxyl 35 castor oil, and propylene glycol; peppermint and caramel flavor]

Generic AvailableNo

ManufacturerAbbott Laboratories (Pharmaceutical Product Division)

Pricing: U.S. (www.drugstore.com)

Capsules (Norvir)

100 mg (30): $289.99

Solution (Norvir)

80 mg/mL (240): $1507.54

Mechanism of ActionRitonavir inhibits HIV protease and renders the enzyme incapable of processing the gag-pol polyprotein precursor which leads to production of noninfectious immature HIV particles

Pharmacodynamics/Kinetics

Absorption: Variable; increased with food

Distribution: High concentrations in serum and lymph nodes; V_d: 0.16-0.66 L/kg

Protein binding: 98% to 99%

Metabolism: Hepatic via CYP3A4 and 2D6; five metabolites, low concentration of an active metabolite (M-2) achieved in plasma (oxidative)

Half-life elimination: 3-5 hours

Time to peak, plasma: Oral solution: 2 hours (fasted); 4 hours (nonfasted)

Excretion: Urine (~11%; ~4% as unchanged drug); feces (~86%; ~34% as unchanged drug)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV
- Perinatal HIV Guidelines

Pharmacotherapy PearlsPotential compliance problems, frequency of administration and adverse effects should be discussed with patients before initiating therapy to help prevent the emergence of resistance.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause abnormal dreams, agitation, amnesia, aphasia, confusion, depersonalization, emotional lability, euphoria, hallucinations, mania, nervousness, and sleep disturbances

Mental Health: Effects on Psychiatric TreatmentContraindicated with pimozide, midazolam, and triazolam (may use temazepam or lorazepam). Concomitant use of ritonavir and St John's wort is not recommended. Coadministration of protease inhibitors (ritonavir) with St John's wort is expected to substantially decrease protease inhibitor serum concentrations leading to a loss of virologic response and possible resistance to ritonavir or to the class of protease inhibitors. Ritonavir may increase the levels of many antidepressants, including TCAs, SSRIs, bupropion, and trazodone. Use cautiously and monitor closely for adverse effects.

Ritonavir oral solution contains alcohol and can produce a disulfiram-like reaction when coadministered with disulfiram. Ritonavir affects anticonvulsants in opposite directions depending on the anticonvulsants. Ritonavir may increase levels of carbamazepine, clonazepam, and ethosuximide with concomitant use while combined use with divalproex, lamotrigine and phenytoin may result in lower serum concentrations. Be mindful of the anticonvulsant used. A dose increase or decrease may be needed. Check serum levels, and monitor for adverse reactions.

A dose decrease may be needed when coadministered with antipsychotics (includes perphenazine, risperidone, thioridazine); sedative/hypnotics (includes buspirone, clorazepate, diazepam, estazolam, flurazepam, and zolpidem); and stimulants (includes methamphetamine). Monitor for dose-dependent adverse reactions.

References

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“Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,” July 8, 2008. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

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Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” July 29, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesKaletra (MX); Kaletra [+ Lopinavir] (PL); Norvir (AE, AT, AU, BE, BG, BH, BR, CH, CN, CO, CY, CZ, DE, DK, EC, EG, ES, FI, FR, GB, GR, HK, HN, HU, ID, IE, IL, IQ, IR, IT, JO, KW, LB, LU, LY, MY, NL, NO, OM, PE, PL, PT, QA, RU, SA, SE, SY, TH, TR, TW, VE, YE); Rifaxi (AR); Ritovir (IN, UY)

Rituximab-CHOP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lymphoma, non-Hodgkin's

Regimen Use Lymphoma, non-Hodgkin's

Index Terms CHOP-Rituximab; R-CHOP

Regimen

Rituximab: I.V.: 375 mg/m^2 day 1

[total dose/cycle = 375 mg/m^2]

Cyclophosphamide: I.V.: 750 mg/m^2 day 1

[total dose/cycle = 750 mg/m^2]

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2 (maximum 2 mg) day 1

[total dose/cycle = 1.4 mg/m^2; maximum 2 mg]

Prednisone: Oral: 40 mg/m^2/day days 1 to 5

[total dose/cycle = 200 mg/m^2]

Repeat cycle every 21 days

References

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RiTUXimab

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Rituximab: Additional Report of Progressive Multifocal Leukoencephalopathy (PML) - September 2008

In conjunction with the U.S. Food and Drug Administration (FDA), Genentech, Inc has issued a “Dear Healthcare Professional” letter informing of an additional case of fatal PML, reported in a patient who had received rituximab for the treatment of rheumatoid arthritis (RA). In this case, PML was diagnosed 18 months after the last rituximab dose; confounding factors include a long history of immunosuppressant therapy and treatment with a tumor necrosis factor (TNF) antagonist for RA, plus development of oropharyngeal cancer (subsequently treated with chemotherapy and radiation therapy [after rituximab therapy, but 9 months prior to the diagnosis of PML]).

PML has previously been associated with rituximab use, although previous reports were confined to patients treated for hematologic malignancies and an unapproved use, systemic lupus erythematosus (SLE). The product labeling, which previously contained warnings regarding PML, has been updated to reflect this new report. Any new-onset neurological changes should be evaluated promptly; consider neurology consultation, brain MRI, and lumbar puncture for suspected PML. Discontinue rituximab in patients who develop PML; consider reduction/discontinuation of concurrent chemotherapy or immunosuppressants.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Rituxan

Medication Safety Issues

Sound-alike/look-alike issues:

Rituxan® may be confused with Remicade®

RiTUXimab may be confused with inFLIXimab

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

The rituximab dose for rheumatoid arthritis is a flat dose (1000 mg) and is not based on body surface area (BSA).

Pronunciation(ri TUK si mab)

U.S. Brand NamesRituxan®

Canadian Brand NamesRituxan®

Pharmacologic CategoryAntineoplastic Agent, Monoclonal Antibody; Antirheumatic, Miscellaneous; Monoclonal Antibody

Use: Labeled IndicationsTreatment of low-grade or follicular CD20-positive, B-cell non-Hodgkin's lymphoma (NHL); treatment of diffuse large B-cell CD20-positive NHL; treatment of moderately- to severely-active rheumatoid arthritis (RA) in combination with methotrexate

Use: Unlabeled/InvestigationalTreatment of autoimmune hemolytic anemia (AIHA) in children; chronic immune thrombocytopenic purpura (ITP); chronic lymphocytic leukemia (CLL); small lymphocytic lymphoma (SLL); pemphigus vulgaris, Waldenström’s macroglobulinemia (WM); treatment of systemic autoimmune diseases (other than rheumatoid arthritis); treatment of refractory chronic graft-versus-host disease (GVHD)

Dosing: AdultsRefer to individual protocols: **Note:** Pretreatment with acetaminophen and an antihistamine is recommended.

NHL (relapsed/refractory, low-grade or follicular CD20-positive, B-cell): 375 mg/m^2 once weekly for 4 or 8 doses

Retreatment following disease progression: 375 mg/m^2 once weekly for 4 doses

NHL (diffuse large B-cell): 375 mg/m^2 given on day 1 of each chemotherapy cycle for up to 8 doses

NHL (follicular, CD20-positive, B-cell, previously untreated): 375 mg/m^2 given on day 1 of each chemotherapy cycle for up to 8 doses

NHL (nonprogressing, low-grade, CD20-positive, B-cell, after first line CVP): 375 mg/m^2 once weekly for 4 doses every 6 months for up to 4 cycles (initiate after 6-8 cycles of chemotherapy are completed)

Rheumatoid arthritis: 1000 mg on days 1 and 15 in combination with methotrexate

Note: Premedication with a corticosteroid (eg, methylprednisolone 100 mg I.V.) 30 minutes prior to each rituximab dose is recommended. In clinical trials, patients received oral corticosteroids on a tapering schedule from baseline through day 16.

CLL/SLL (unlabeled use): 100 mg day 1, then 375 mg/m^2 3 times/week for 11 doses

Refractory pemphigus vulgaris (unlabeled use): 375 mg/m^2 once weekly of weeks 1, 2, and 3 of a 4-week cycle, repeat for 1 additional cycle, then 1 dose per month for 4 months (total of 10 doses in 6 months)

Refractory chronic GVHD, Waldenström's macroglobulinemia (unlabeled uses): 375 mg/m^2 once weekly for 4 weeks

Combination therapy with ibritumomab: 250 mg/m^2 I.V. day 1; repeat in 7-9 days with ibritumomab (also see Ibritumomab monograph):

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Note:** Pretreatment with acetaminophen and an antihistamine is recommended.

AIHA, chronic ITP (unlabeled uses): I.V.: 375 mg/m^2 once weekly for 2-4 doses

Dosing: Combination Regimens

Leukemia, chronic lymphocytic:

Fludarabine-Cyclophosphamide-Rituximab (CLL)

Fludarabine-Rituximab (CLL)

PCR

Lymphoma, non-Hodgkin's:

Bendamustine-Rituximab

Fludarabine-Cyclophosphamide-Mitoxantrone-Rituximab

Fludarabine-Cyclophosphamide-Rituximab (NHL-Follicular)

Fludarabine-Mitoxantrone-Dexamethasone-Rituximab

Fludarabine-Mitoxantrone-Rituximab

Rituximab-CHOP

R-CVP

RICE

Lymphoma, non-Hodgkin's: (Mantle Cell):

Bendamustine-Rituximab

Hyper-CVAD + Rituximab

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Do **not** administer I.V. push or bolus.

Initial infusion: Start rate of 50 mg/hour; if there is no reaction, increase the rate by 50 mg/hour increments every 30 minutes, to a maximum rate of 400 mg/hour.

Subsequent infusions: If patient did not tolerate initial infusion follow initial infusion guidelines. If patient tolerated initial infusion, start at 100 mg/hour; if there is no reaction, increase the rate by 100 mg/hour increments every 30 minutes, to a maximum rate of 400 mg/hour.

Note: If a reaction occurs, slow or stop the infusion. If the reaction abates, restart infusion at 50% of the previous rate.

In patients with NHL who are receiving a corticosteroid as part of their combination chemotherapy regimen and after tolerance has been established at the recommended infusion rate in cycle 1, a rapid infusion rate has been used beginning with cycle 2. The daily corticosteroid, acetaminophen, and diphenhydramine are administered prior to treatment, then the rituximab dose is administered over 90 minutes, with 20% of the dose administered in the first 30 minutes and the remaining 80% is given over 60 minutes (Sehn, 2007).

Administration: I.V. DetailDiscontinue infusions in the event of serious or life-threatening cardiac arrhythmias.

pH: 6.5

StorageStore vials under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Do not shake. Protect vials from direct sunlight. Solutions for infusion are stable at 2°C to 8°C (36°F to 46°F) for 24 hours and at room temperature for an additional 24 hours.
ReconstitutionWithdraw necessary amount of rituximab and dilute to a final concentration of 1-4 mg/mL with 0.9% sodium chloride or 5% dextrose in water. Gently invert the bag to mix the solution. Do not shake.
RestrictionsAn FDA-approved medication guide is available; distribute to each patient to whom this medication is dispensed.
ContraindicationsThere are no contraindications listed in the manufacturer's labeling.
Warnings/Precautions

Boxed warnings:

- Infusion reactions: See "Concerns related to adverse effects" below.

- Mucocutaneous reactions: See "Concerns related to adverse effects" below.

- Progressive multifocal leukoencephalopathy: See "Concerns related to adverse effects" below.

- Tumor lysis syndrome: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Bowel obstruction/perforation: Have been reported, with an average onset of symptoms of ~6 days; complaints of abdominal pain should be evaluated, especially if early in the treatment course.

- Infusion reactions: **[U.S. Boxed Warning]: Severe (occasionally fatal) infusion-related reactions have been reported, usually with the first infusion; fatalities have been reported within 24 hours of infusion; monitor closely and discontinue with grades 3 or 4 infusion reactions.** Reactions usually occur within 30-120 minutes and may include hypotension, angioedema, bronchospasm, hypoxia, urticaria, and in more severe cases pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and/or anaphylaxis. Risk factors associated with fatal outcomes include chronic lymphocytic leukemia, female gender, mantle cell lymphoma, or pulmonary infiltrates. Closely monitor patients with a history of prior cardiopulmonary reactions or with pre-existing cardiac or pulmonary conditions and patients with high numbers of circulating malignant cells (>25,000/mm^3). Discontinue infusion for severe reactions and serious or life-threatening cardiac arrhythmias; subsequent doses should include cardiac monitoring during and after the infusion. Medications for the treatment of hypersensitivity reactions (eg, bronchodilators, epinephrine, antihistamines, corticosteroids) should be available for immediate use; treatment is symptomatic. Mild-to-moderate infusion-related reactions (eg, chills, fever, rigors) occur frequently and are typically managed through slowing or interrupting the infusion. Infusion may be resumed at a 50% infusion rate reduction upon resolution of symptoms. Due to the potential for hypotension, consider withholding antihypertensives 12 hours prior to treatment.

- Mucocutaneous reactions: **[U.S. Boxed Warning]: Severe and sometimes fatal mucocutaneous reactions (lichenoid dermatitis, paraneoplastic pemphigus, Stevens-Johnson syndrome, toxic epidermal necrolysis and vesiculobullous dermatitis) have been reported,** occurring from 1-13 weeks following exposure. Discontinue in patients experiencing severe mucocutaneous skin reactions; the safety of re-exposure following mucocutaneous reactions has not been evaluated.

- Progressive multifocal leukoencephalopathy: **[U.S. Boxed Warning]: Progressive multifocal leukoencephalopathy (PML) due to JC virus infection has been reported with rituximab use.** Cases were reported in patients with hematologic malignancies receiving rituximab either with combination chemotherapy, or with hematopoietic stem cell transplant. Cases were also reported in patients receiving rituximab for autoimmune diseases who had received concurrent or prior immunosuppressant therapy. Onset may be delayed, although most cases were diagnosed within 12 months of the last rituximab dose. Evaluate any neurological change promptly; consider neurology consultation, brain MRI and lumbar puncture for suspected PML. Discontinue rituximab in patients who develop PML; consider reduction/discontinuation of concurrent chemotherapy or immunosuppressants.

- Renal toxicity: May cause renal toxicity in patients with hematologic malignancies; consider discontinuation with increasing serum creatinine or oliguria.

- Tumor lysis syndrome: **[U.S. Boxed Warning]: Tumor lysis syndrome leading to acute renal failure requiring dialysis may occur 12-24 hours following the first dose.** Hyperkalemia, hypocalcemia, hyperuricemia, and/or hyperphosphatemia may occur. Consider prophylaxis (allopurinol, hydration) in patients at high risk (high numbers of circulating malignant cells ≥25,000/mm^3 or high tumor burden).

- Viral infections: Rarely, reactivation of hepatitis B (with fulminant hepatitis and hepatic failure) has been reported in association with use; screen high-risk patients prior to therapy initiation. Other serious and potentially fatal viral infections, either new or reactivated, associated with use include cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. Viral infections may be delayed; occurring up to 1 year after discontinuation of therapy.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with pre-existing cardiovascular disease or prior cardiopulmonary events.

- Respiratory disease: Use with caution in patients with pre-existing pulmonary disease, or prior cardiopulmonary events.

Concurrent drug therapy issues:

- Biologic agents: Safety and efficacy of rituximab in combination with biologic agents have not been established.

- Disease-modifying antirheumatic drugs (DMARD): Safety and efficacy of rituximab in combination DMARD other than methotrexate have not been established.

- Immunizations: Live vaccines should not be given concurrently with rituximab; there is no data available concerning secondary transmission of live vaccines with or following rituximab treatment. RA patients should be brought up to date with nonlive immunizations (following current guidelines) before initiating therapy; evaluate risks of therapy delay versus benefit (of nonlive vaccines) for NHL patients.

Special populations:

- Elderly: Use with caution in the elderly; higher risk of cardiac (supraventricular arrhythmia) and pulmonary adverse events (pneumonia, pneumonitis).

- Pediatrics: Not approved for use in children.

- Rheumatoid arthritis (RA) patients: Monitor closely RA patients during and after each infusion; increased risk of cardiovascular events. Safety and efficacy of retreatment for RA have not been established.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have demonstrated adverse effects including decreased (reversible) B-cells and immunosuppression. There are no adequate and well-controlled studies in pregnant women. IgG molecules are known to cross the placenta (rituximab is an engineered IgG molecule) and rituximab has been detected in the serum of infants exposed *in utero*. B-Cell lymphocytopenia lasting <6 months may occur in exposed infants. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if rituximab is excreted in human milk. However, human IgG is excreted in breast milk, and therefore, rituximab may also be excreted in milk. The manufacturer recommends discontinuing breast-feeding until circulating levels of rituximab are no longer detectable.

Adverse Reactions**Note:** Patients treated with rituximab for rheumatoid arthritis (RA) may experience fewer adverse reactions.

>10%:

Central nervous system: Fever (5% to 53%), chills (3% to 33%), headache (19%), pain (12%)

Dermatologic: Rash (15%; grades 3/4: 1%), pruritus (5% to 14%), angioedema (11%; grades 3/4: 1%)

Gastrointestinal: Nausea (8% to 23%), abdominal pain (2% to 14%)

Hematologic: Cytopenias (grades 3/4: ≤48%; may be prolonged), lymphopenia (48%; grades 3/4: 40%; median duration 14 days), leukopenia (14%; grades 3/4: 4%), neutropenia (14%; grades 3/4: 6%; median duration 13 days), thrombocytopenia (12%; grades 3/4: 2%)

Neuromuscular & skeletal: Weakness (2% to 26%)

Respiratory: Cough (13%), rhinitis (3% to 12%)

Miscellaneous: Infusion-related reactions (lymphoma: first dose 77%; decreases with subsequent infusions; may include angioedema, bronchospasm, chills, dizziness, fever, headache, hyper-/hypotension, myalgia, nausea, pruritus, rash, rigors, urticaria, and vomiting; reactions reported are lower [first infusion: 32%] in RA); infection (31%; grades 3/4: 4%; bacterial: 19%; viral 10%; fungal: 1%), night sweats (15%)

1% to 10%:

Cardiovascular: Hypotension (10%), peripheral edema (8%), hypertension (6% to 8%), flushing (5%), edema (<5%)

Central nervous system: Dizziness (10%), anxiety (2% to 5%), agitation (<5%), depression (<5%), hypoesthesia (<5%), insomnia (<5%), malaise (<5%), nervousness (<5%), neuritis (<5%), somnolence (<5%), vertigo (<5%), migraine (RA: 2%)

Dermatologic: Urticaria (2% to 8%)

Endocrine & metabolic: Hyperglycemia (9%), hypoglycemia (<5%), hypercholesterolemia (2%)

Gastrointestinal: Diarrhea (10%), vomiting (10%), dyspepsia (3%), anorexia (<5%), weight loss (<5%)

Hematologic: Anemia (8%; grades 3/4: 3%)

Local: Pain at the injection site (<5%)

Neuromuscular & skeletal: Back pain (10%), myalgia (10%), arthralgia (6% to 10%), paresthesia (2%), arthritis (<5%), hyperkinesia (<5%), hypertonia (<5%), neuropathy (<5%)

Ocular: Conjunctivitis (<5%), lacrimation disorder (<5%)

Respiratory: Throat irritation (2% to 9%), bronchospasm (8%), dyspnea (7%), upper respiratory tract infection (RA: 7%), sinusitis (6%)

Miscellaneous: LDH increased (7%)

Postmarketing and/or case reports: Acute renal failure, anaphylactoid reaction/anaphylaxis, angina, aplastic anemia, ARDS, arrhythmia, bowel obstruction, bronchiolitis obliterans, cardiac failure, cardiogenic shock, disease progression (Kaposi's sarcoma), fatal infusion-related reactions, fulminant hepatitis, gastrointestinal perforation, hemolytic anemia, hepatic failure, hepatitis, hepatitis B reactivation, hyperviscosity syndrome (in Waldenström's macroglobulinemia), hypogammaglobulinemia, hypoxia, interstitial pneumonitis, lichenoid dermatitis, lupus-like syndrome, marrow hypoplasia, MI, neutropenia (late-onset occurring >40 days after last dose), optic neuritis, pancytopenia (prolonged), paraneoplastic pemphigus (uncommon), pleuritis, pneumonia, pneumonitis, polyarticular arthritis, progressive multifocal leukoencephalopathy (PML), pure red cell aplasia, renal toxicity, serum sickness, Stevens-Johnson syndrome, supraventricular arrhythmia, systemic vasculitis, toxic epidermal necrolysis, tumor lysis syndrome, urticaria, uveitis, vasculitis with rash, ventricular fibrillation, ventricular tachycardia, vesiculobullous dermatitis, viral reactivation (includes JC virus, cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C)

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Abciximab: May enhance the potential for allergic or hypersensitivity reactions to Monoclonal Antibodies. Also may cause thrombocytopenia or diminished therapeutic effects. *Risk C: Monitor therapy*

Antihypertensives: May enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid echinacea (may diminish the therapeutic effect of immunosuppressants). Avoid hypoglycemic herbs, including alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, and stinging nettle (may enhance the hypoglycemic effect of rituximab).

Monitoring ParametersCBC with differential and platelets, peripheral $CD20^+$ cells; HAMA/HACA titers (high levels may increase the risk of allergic reactions); renal function, fluid balance; vital signs; monitor for infusion reactions, cardiac monitoring during and after infusion in rheumatoid arthritis patients and in patients with pre-existing cardiac disease or if arrhythmias develop during or after subsequent infusions

Screen for hepatitis B in high-risk patients prior to initiation of rituximab therapy (the NCCN NHL guidelines recommend screening **all** NHL patients prior to therapy). In addition, carriers and patients with evidence of recovery from prior hepatitis B infection should be monitored closely for clinical and laboratory signs of HBV infection during therapy and for up to a year following completion of treatment. High-risk patients should be screened for hepatitis C (per NCCN guidelines).

Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment. Signs or symptoms of progressive multifocal leukoencephalopathy (focal neurologic deficits, which may present as hemiparesis, visual field deficits, cognitive impairment, aphasia, ataxia, and/or cranial nerve deficits). If PML is suspected, obtain brain MRI scan and lumbar puncture.

Nursing: Physical Assessment/MonitoringAssess patient history with mouse antibodies prior to beginning therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, anything that may increase hypotensive effects of this drug). Evaluate results of laboratory tests prior to, during, and following therapy. Patient must be monitored closely during and following each infusion; severe infusion reactions can occur. Pretreatment with acetaminophen and diphenhydramine is recommended (corticosteroid when used to treat RA). Emergency equipment and medications (epinephrine, antihistamines, corticosteroids) should be immediately available during infusion. In the event of severe infusion reaction, infusion should be stopped and prescriber notified immediately. Evaluate patient response closely after each dose and following discontinuation of therapy (eg, abdominal pain [bowel obstruction and perforation], hyper-/hypertension, CNS changes, hyper-/hypoglycemia, rash); bowel obstruction and perforation can occur early in therapy; acute tumor lysis syndrome leading to acute renal failure can occur 12-24 hours after first dose; severe mucocutaneous reactions can occur from 1-13 weeks following treatment; and new or reactivated serious viral infection may occur up to one year following discontinuation of therapy. Teach patient possible side effects/appropriate interventions and importance of reporting adverse reactions.

Monitoring: Lab TestsCBC with differential and platelets, peripheral CD20+ cells. Patients with elevated HAMA/HACA titers may have an allergic reaction when treated with rituximab or other antibodies from a mouse genetic source.

Patient EducationThis medication is only administered by infusion. You may experience a reaction during the infusion of this medication, including high fever, chills, respiratory difficulty, or congestion. You will be closely monitored and comfort measures provided. Maintain adequate hydration (2-3 L/day of fluids during entire course of therapy) unless instructed to restrict fluid intake. You will be susceptible to infection and people may wear masks and gloves while caring for you to protect you as much as possible (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). If you have diabetes, monitor glucose levels closely; this medication may impact glucose control. May cause dizziness or trembling (use caution until response to medication is known); nausea, vomiting, or loss of appetite (small, frequent meals and frequent mouth care may help); diarrhea (increase dietary fiber, buttermilk, or yogurt); bone or muscle pain (ask prescriber for appropriate analgesic). Report immediately any unusual abdominal pain; skin rash or redness, persistent dizziness, swelling of extremities, unusual weight gain, respiratory difficulty, chest pain or tightness; symptoms of respiratory infection (wheezing, bronchospasms, or difficulty breathing); unresolved GI disturbance (nausea, vomiting); opportunistic infection (sore or irritated throat; unusual and persistent fatigue, chills, fever, unhealed sores, white plaques in mouth or genital area; unusual bruising or bleeding); CNS changes (confusion, agitation, insomnia); pain, tingling, loss of sensation in extremities, or loss of coordination); or other unusual effects related to this medication. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

Rituxan®: 10 mg/mL (10 mL, 50 mL) [contains polysorbate 80]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Concentrate (Rituxan)

10 mg/mL (10): $616.44

Mechanism of ActionRituximab is a monoclonal antibody directed against the CD20 antigen on B-lymphocytes. CD20 regulates cell cycle initiation; and, possibly, functions as a calcium channel. Rituximab binds to the antigen on the cell surface, activating complement-dependent B-cell cytotoxicity; and to human Fc receptors, mediating cell killing through an antibody-dependent cellular toxicity. B-cells are believed to play a role in the development and progression of rheumatoid arthritis. Signs and symptoms of RA are reduced by targeting B-cells and the progression of structural damage is delayed.

Pharmacodynamics/Kinetics

Duration: Detectable in serum 3-6 months after completion of treatment; B-cell recovery begins ~6 months following completion of treatment; median B-cell levels return to normal by 12 months following completion of treatment

Absorption: I.V.: Immediate and results in a rapid and sustained depletion of circulating and tissue-based B cells

Distribution: 4.3 L (following two 1000 mg doses for rheumatoid arthritis)

Half-life elimination:

Cancer: Proportional to dose; wide ranges reflect variable tumor burden and changes in CD20 positive B-cell populations with repeated doses:

>100 mg/m^2: 4.4 days (range 1.6-10.5 days)

375 mg/m^2:

Following first dose: Mean half-life: 3.2 days (range 1.3-6.4 days)

Following fourth dose: Mean half-life: 8.6 days (range 3.5-17 days)

RA: Mean terminal half-life: 19 days

Excretion: Uncertain; may undergo phagocytosis and catabolism in the reticuloendothelial system (RES)

Related Information

- Common Toxicity Criteria
- Ibritumomab
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or depression

Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; avoid concurrent use with clozapine or carbamazepine

Index TermsAnti-CD20 Monoclonal Antibody; C2B8 Monoclonal Antibody; IDEC-C2B8; NSC-687451

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International Brand NamesMabthera (AR, AT, AU, BB, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CZ, DE, DK, EC, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, ID, IE, IL, IT, JM, KE, KP, LR, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, PE, PH, PK, PL, PT, PY, RU, SC, SD, SE, SG, SL, SN, SR, TN, TR, TT, TZ, UG, UY, VE, ZA, ZM, ZW)

Rivaroxaban

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(riv a ROX a ban)
Canadian Brand NamesXarelto®
Pharmacologic CategoryFactor Xa Inhibitor
Use: Labeled IndicationsPostoperative thromboprophylaxis in patients who have undergone total hip or knee replacement procedures
Dosing: Adults **Note:** Therapy should not be initiated until hemostasis has been established.

Postoperative thromboprophylaxis: Oral:

Knee replacement: 10 mg once daily; initial dose should be administered within 6-10 hours after completion of surgery and establishment of hemostasis (total duration of therapy: 14 days)

Hip replacement: 10 mg once daily; initial dose should be administered within 6-10 hours after completion of surgery and establishment of hemostasis (total duration of therapy: 35 days)

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal Impairment
Moderate renal impairment (Cl_{cr} 30-49 mL/minute): Use with caution; no specific dosage adjustments are specified in approved labeling.

Severe renal impairment (Cl_{cr} <30 mL/minute): Use not recommended.

Dosing: Hepatic Impairment
Mild hepatic impairment: Manufacturer provides no specific dosing recommendations in approved labeling. Limited data indicates pharmacokinetics and pharmacodynamic response were similar to healthy subjects.

Significant hepatic impairment (including Child-Pugh classes B and C): Use is contraindicated.

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered without regard to meals.
Dietary ConsiderationsMay be taken without regard to meals.
StorageStore at 15°C to 30°C (59°F to 86°F).
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to rivaroxaban or any component of the formulation; hepatic disease (including Child-Pugh classes B and C) associated with coagulopathy and clinically relevant bleeding risk; clinically significant active bleeding, including hemorrhagic manifestations and bleeding diathesis; lesions at increased risk of clinically significant bleeding (eg, hemorrhagic or ischemic cerebral infarction) within previous 6 months; spontaneous hemostasis impairment; concomitant systemic treatment with strong CYP3A4 and P-glycoprotein (P-gp) inhibitors; pregnancy; lactation
Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: The most common complication is bleeding. Certain patients are at increased risk of bleeding; risk factors include bacterial endocarditis, congenital or acquired bleeding disorders, vascular retinopathy, thrombocytopenia, recent puncture of large vessels or organ biopsy, stroke, intracerebral surgery, or other neuraxial procedure, severe uncontrolled hypertension, renal impairment, recent major surgery, recent major bleeding (intracranial, GI, intraocular, or pulmonary). Monitor for signs and symptoms of bleeding (weakness, dizziness, unexplained edema). Prompt clinical evaluation is warranted with any unexplained decrease in hemoglobin or blood pressure.

Disease-related concerns:

- Hepatic impairment: Use in significant hepatic dysfunction was not evaluated during clinical trials. Use is contraindicated in hepatic dysfunction (including Child-Pugh classes B and C) associated with coagulopathy and clinically significant risk of bleeding. Limited data in patients with mild hepatic dysfunction without coagulopathy suggests use may be appropriate.

- Renal impairment: Use caution in patients with moderate renal impairment (Cl_{cr} 30-49 mL/minute) including patients receiving concomitant drug therapy that may increase rivaroxaban systemic exposure and those with deteriorating renal function. Use in severe renal impairment (Cl_{cr} <30 mL/minute) has not been studied and is not recommended. Discontinue use with onset of acute renal failure.

Concurrent drug therapy issues:

- Anticoagulants and antiplatelet agents: Due to an increased risk of bleeding, avoid use with direct thrombin inhibitors (eg, bivalirudin), unfractionated heparin or heparin derivatives, low molecular weight heparins (eg, enoxaparin), aspirin, coumarin derivatives, and sulfinpyrazone. NSAIDs and other platelet aggregation inhibitors (eg, clopidogrel) should be used cautiously.

- CYP3A4 inducers: Use with strong CYP3A4 inducers with caution; monitor for decreased levels/effects of rivaroxaban.

- CYP3A4/P-gp inhibitors: Concomitant use with strong inhibitors of both CYP3A4 and P-gp is contraindicated.

Special populations:

- Patients <50 kg: Use with caution; rivaroxaban maximum concentration (C_{max}) increased by 24% and PT prolongation effect increased by ~20% in this patient population.

- Pediatrics: Safety and efficacy have not been established in patients <18 years of age.

Dosage form specific issues:

- Lactose intolerance: Formulation contains lactose; use is not recommended in patients with lactose or galactose intolerance (eg, Lapp lactase deficiency, glucose-galactose malabsorption).

Other warnings/precautions:

- Neuraxial anesthesia: If possible, avoid use in patients undergoing anesthesia with postoperative indwelling epidural catheters. Hematomas (spinal or epidural) resulting in extended or permanent paralysis may occur. Avoid removal of epidural catheter for at least 18 hours following last rivaroxaban dose. Avoid rivaroxaban administration for at least 6 hours following epidural catheter removal. Monitor for signs of neurologic impairment (eg, numbness/weakness of legs, bowel/bladder dysfunction); prompt diagnosis and treatment are necessary.

Pregnancy ConsiderationsUse is contraindicated in pregnancy.

LactationUse is contraindicated.

Adverse Reactions

1% to 10%:

Gastrointestinal: Nausea (1%)

Hematologic: Bleeding: Major: (<1% to 2%, includes surgical site bleeding events with decreased hemoglobin or transfusion); Nonmajor: (4% to 7%), anemia (1%)

Hepatic: Transaminases increased (2%; ALT >3 X upper limit of normal [ULN] 2% to 6%), GGT increased (1%)

<1%, postmarketing, and/or case reports: Abdominal pain, alkaline phosphatase increased, allergic dermatitis, amylase increased, bilirubin increased, BUN increased, constipation, creatinine increased, diarrhea, dizziness, dyspepsia, ecchymosis, fatigue, fever, headache, hematuria, hypersensitivity, hypotension, jaundice, LDH increased, lipase increased, pain, peripheral edema, pruritus, rash, syncope, tachycardia, thrombocythemia, urticaria, vomiting, weakness, xerostomia

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Erythromycin: May increase the serum concentration of Rivaroxaban. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of Rivaroxaban. **Exceptions:** Erythromycin. *Risk X: Avoid combination*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Grapefruit juice may increase levels/effects of rivaroxaban; use caution.

Herb/Nutraceutical: Avoid St John's wort (may decrease levels/effects of rivaroxaban; avoid concomitant use if possible; use with caution if concomitant use can not be avoided).

Test InteractionsProlongs activated partial thromboplastin time (aPTT), HepTest®, and Russell viper venom time

Monitoring ParametersProthrombin time (PT), CBC with differential, renal function, hepatic function; **Note:** In clinical trials, monitoring of aPTT, PT/INR, or antifactor Xa levels did not occur. However, certain patient populations (eg, renal insufficiency, hepatic impairment, low body weight, extreme obesity) may require monitoring of the PT time).

Nursing: Physical Assessment/MonitoringMonitor for unusual bleeding. Invasive procedures should be avoided if possible. Assess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Monitoring: Lab TestsProthrombin time (PT), CBC with differential, renal function, hepatic function

Patient EducationLimit intake of grapefruit juice. Do not take any new medications without consulting prescriber. You may be prone to bleeding while taking this medication. Brush teeth with a soft brush, use waxed dental floss and an electric razor, and use extra care when using scissors or sharp knives and utensils. Report unusual bleeding or bruising; blood in stool, vomitus, or urine; nosebleeds; bleeding gums; or unusual pain, especially in joints or back. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Use during pregnancy is not recommended. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet:

Xarelto® [CAN]: 10 mg [contains lactose] [not available in U.S.]

Generic AvailableNo

ManufacturerBayer Inc, Canada

Mechanism of ActionInhibits platelet activation and fibrin clot formation via direct, selective and reversible inhibition of factor Xa (FXa) in both the intrinsic and extrinsic coagulation pathways. FXa, as part of the prothrombinase complex consisting also of factor Va, calcium ions, factor II and phospholipid, catalyzes the conversion of prothrombin to thrombin. Thrombin both activates platelets and catalyzes the conversion of fibrinogen to fibrin.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: V_{dss}: ~50 L

Protein binding: 92% to 95% (primarily to albumin)

Metabolism: Hepatic via CYP3A4, CYP3A5, and CYP2J2

Bioavailability: Absolute bioavailability: ~100%

Half-life elimination: Young individual: 5-9 hours; Elderly: 11-13 hours

Time to peak, plasma: 2-4 hours

Excretion: Urine (33% as unchanged drug; 33% as inactive metabolites); feces (33% as inactive metabolites)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Surgical site bleeding may occur.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index TermsBAY 59-7939

References

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Rivastigmine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(ri va STIG meen)

U.S. Brand NamesExelon®

Canadian Brand NamesExelon®

Pharmacologic CategoryAcetylcholinesterase Inhibitor (Central)

Use: Labeled IndicationsTreatment of mild-to-moderate dementia associated with Alzheimer's disease or Parkinson's disease

Use: Unlabeled/InvestigationalSevere dementia associated with Alzheimer's disease; Lewy body dementia

Dosing: Adults**Note:** Exelon® oral solution and capsules are bioequivalent.

Mild-to-moderate Alzheimer's dementia:

Oral: Initial: 1.5 mg twice daily; may increase by 3 mg/day (1.5 mg/dose) every 2 weeks based on tolerability (maximum recommended dose: 6 mg twice daily)

Note: If GI adverse events occur, discontinue treatment for several doses then restart at the same or next lower dosage level; antiemetics have been used to control GI symptoms. If treatment is interrupted for longer than several days, restart the treatment at the lowest dose and titrate as previously described.

Transdermal patch: Initial: 4.6 mg/24 hours; if well tolerated, may be increased (after at least 4 weeks) to 9.5 mg/24 hours (recommended effective dose). Maintenance: 9.5 mg/24 hours (maximum dose: 9.5 mg/24 hours).

Note: If intolerance is noted (nausea, vomiting), patch should be removed and treatment interrupted for several days and restarted at the same or lower dosage. If interrupted for more than several days, reinitiate at lowest dosage and increase to maintenance dose after 4 weeks.

Conversion from oral therapy: If oral daily dose <6 mg, switch to 4.6 mg/24 hours patch; if oral daily dose 6-12 mg, switch to 9.5 mg/24 hours patch. Apply patch on the next day following last oral dose.

Mild-to-moderate Parkinson's-related dementia:

Oral: Initial: 1.5 mg twice daily; may increase by 3 mg/day (1.5 mg/dose) every 4 weeks based on tolerability (maximum recommended dose: 6 mg twice daily)

Transdermal patch: See transdermal dosing for Alzheimer's dementia.

Dosing: ElderlyFollowing oral administration, clearance is significantly lower in patients >60 years of age, but dosage adjustments are not recommended. Age was not associated with exposure in patients treated transdermally. Titrate dose to individual's tolerance. Refer to adult dosing.

Dosing: Renal ImpairmentDosage adjustments are not recommended, however, titrate the dose to the individual's tolerance.

Dosing: Hepatic ImpairmentClearance is significantly reduced in mild to moderately impaired patients. Although dosage adjustments are not recommended, use lowest possible dose and titrate according to individual's tolerance. Consider intervals of >2 weeks between dosage adjustments.

Administration: OralShould be administered with meals (breakfast or dinner). Capsule should be swallowed whole. Liquid form is available for patients who cannot swallow capsules (can be swallowed directly from syringe or mixed with water, soda, or cold fruit juice). Stir well and drink within 4 hours of mixing.

Administration: TopicalTransdermal patch: Apply transdermal patch to upper or lower back (alternatively, may apply to upper arm or chest). Avoid reapplication to same spot of skin for 14 days (may rotate sections of back, for example). Do not apply to red, irritated, or broken skin. Avoid areas of recent application of lotion or powder. After removal, fold patch to press adhesive surfaces together, and discard. Avoid eye contact; wash hands after handling patch. Replace patch every 24 hours. Avoid exposing the patch to external sources of heat (eg, sauna, excessive light) for prolonged periods of time.

Dietary ConsiderationsCapsules should be taken with meals.

Storage

Oral: Store at 15°C to 30°C (59°F to 86°F); do not freeze. Store solution in an upright position.

Transdermal patch: Store at 15°C to 30°C (59°F to 86°F). Patches should be kept in sealed pouch until use.

ContraindicationsHypersensitivity to rivastigmine, other carbamate derivatives (eg, neostigmine, pyridostigmine, physostigmine), or any component of the formulation

Allergy Considerations

- Cholinesterase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anorexia/weight loss: Significant anorexia and weight loss are associated with use; occurs more frequently in women and during the titration phase. Monitor weight during therapy.

- Nausea/vomiting: Significant nausea and/or vomiting have been associated with use; occurs more frequently in women and during the titration phase. May be severe, particularly at doses higher than recommended.

- Vagotonic effects: Cholinesterase inhibitors may have vagotonic effects which may cause bradycardia and/or heart block with or without a history of cardiac disease.

Disease-related concerns:

- Cardiac conduction abnormalities: Use with caution in patients with sick-sinus syndrome, bradycardia, or conduction abnormalities. Alzheimer's treatment guidelines consider bradycardia to be a relative contraindication for use of centrally-active cholinesterase inhibitors.

- Peptic ulcer disease: Use with caution in patients at risk of ulcer disease (eg, previous history or NSAID use); may increase gastric acid secretion. Monitor for symptoms of bleeding.

- Respiratory disease: Use with caution in patients with COPD and/or asthma.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

- Urinary tract obstruction: Use with caution in patients with bladder outlet obstruction or prostatic hyperplasia; cholinomimetics may cause or worsen outflow obstructions, including possible exacerbation of BPH symptoms.

Concurrent drug therapy issues:

- Depolarizing neuromuscular-blocking agents: May exaggerate neuromuscular blockade effects of depolarizing neuromuscular-blocking agents (eg, succinylcholine).

Special populations:

- Low body weight (<50 kg): Use caution due to increased risk of adverse reactions.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Initiation/interruption of therapy: Should be started at lowest dose and titrated; if treatment is interrupted for more than several days, reinstate at the lowest daily dose.

Geriatric ConsiderationsTitrate dose to tolerance.
Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Should be used only if the benefit outweighs the potential risk to the fetus.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions**Note:** Many concentration-related effects are reported at a lower frequency by transdermal route.

>10%:

Central nervous system: Dizziness (2% to 21%), headache (3% to 17%)

Gastrointestinal: Nausea (7% to 47%), vomiting (6% to 31%), diarrhea (5% to 19%), anorexia (3% to 17%), abdominal pain (1% to 13%)

1% to 10%:

Cardiovascular: Syncope (3%), hypertension (3%)

Central nervous system: Fatigue (2% to 9%), insomnia (1% to 9%), confusion (8%), depression (4% to 6%), anxiety (2% to 5%), malaise (5%), somnolence (4% to 5%), hallucinations (4%), aggressiveness (3%), parkinsonism symptoms worsening (2% to 3%), vertigo (≤2%)

Gastrointestinal: Dyspepsia (9%), constipation (5%), flatulence (4%), weight loss (3% to 8%), eructation (2%), dehydration (2%)

Genitourinary: Urinary tract infection (1% to 7%)

Neuromuscular & skeletal: Weakness (2% to 6%), tremor (1%; up to 10% in Parkinson’s patients)

Respiratory: Rhinitis (4%)

Miscellaneous: Diaphoresis (4%), flu-like syndrome (3%)

<1% (Limited to important or life-threatening symptoms; reactions may be at a similar frequency to placebo): Abnormal hepatic function, acute renal failure, albuminuria, allergy, anemia, angina, aphasia, apnea, apraxia, ataxia, atrial fibrillation, AV block, bradycardia, bronchospasm, bundle branch block, cachexia, cardiac arrest, cardiac failure, chest pain, cholecystitis, diplopia, diverticulitis, dysphagia, dyspnea, dysphonia, edema, esophagitis, extrasystoles, fecal incontinence, gastritis, gastroesophageal reflux, GGT increased, glaucoma, hematuria, hot flashes, hyper-/hypoglycemia, hypercholesterolemia, hyper-/hypokinesia, hypertonia, hypokalemia, hyponatremia, hypotension (including postural), hypothermia, hypothyroidism, intestinal obstruction, intracranial hemorrhage, mastitis, MI, migraine, neuralgia, palpitation, pancreatitis, paresthesia, periorbital or facial edema, peripheral ischemia, peripheral neuropathy, pneumonia, pruritus, psychiatric disorders (eg, delirium, depersonalization, psychosis, emotional lability, suicidal ideation or tendencies), rash, retinopathy, rigors, seizure, sick-sinus syndrome, sudden cardiac death, supraventricular tachycardia, thrombocytopenia, thrombophlebitis, thrombosis, transient ischemic attack, ulcerative stomatitis, urinary incontinence, urticaria, vasovagal syncope

Postmarketing and/or case reports: Stevens-Johnson syndrome, severe vomiting with esophageal rupture (following inappropriate reinitiation of dose)

Drug Interactions

Anticholinergics: May diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotics: Acetylcholinesterase Inhibitors (Central) may enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Beta-Blockers: Acetylcholinesterase Inhibitors may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Cholinergic Agonists: Acetylcholinesterase Inhibitors may enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Ginkgo Biloba: May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): Acetylcholinesterase Inhibitors may diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Succinylcholine: Acetylcholinesterase Inhibitors may enhance the neuromuscular-blocking effect of Succinylcholine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Smoking: Nicotine increases the clearance of rivastigmine by 23%.

Ethanol: Avoid ethanol (due to risk of sedation; may increase GI irritation).

Food: Food delays absorption by 90 minutes, lowers C_{max} by 30% and increases AUC by 30%.

Herb/Nutraceutical: Avoid ginkgo biloba (may increase cholinergic effects).

Monitoring ParametersCognitive function at periodic intervals (MMSE), symptoms of GI intolerance, weight

Nursing: Physical Assessment/MonitoringAssess bladder and sphincter adequacy prior to administering medication. Assess other medications for effectiveness and interactions. Monitor weight, therapeutic effectiveness, and adverse reactions at beginning of therapy and regularly with long-term use. Assess cognitive function at periodic intervals. Assess knowledge/teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis drug is not a cure for Alzheimer's disease, but it may reduce the symptoms. Use as directed; do not increase dose or discontinue without consulting prescriber. Swallow capsule whole with meals (do not crush or chew). Liquid can be swallowed directly from syringe or mixed with water, soda, or cold fruit juice; stir well and drink within 4 hours of mixing. Apply transdermal patch to skin free from redness or irritation. Rotate sites; do not apply to same site within 14 days. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid alcohol. May cause dizziness, drowsiness, or postural hypotension (rise slowly from sitting or lying position and use caution when driving or climbing stairs); vomiting or loss of appetite (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or constipation (increased exercise, fluids, fruit, or fiber may help); or urinary frequency. Report persistent abdominal discomfort, diarrhea, or constipation; significantly increased salivation, sweating, tearing, or urination; chest pain, palpitations, acute headache; CNS changes (eg, excessive fatigue, agitation, insomnia, dizziness, confusion, aggressiveness, depression); increased muscle, joint, or body pain; vision changes or blurred vision; shortness of breath, coughing, or wheezing; skin rash; or other persistent adverse reactions. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Exelon®: 1.5 mg, 3 mg, 4.5 mg, 6 mg

Solution, oral:

Exelon®: 2 mg/mL (120 mL) [contains sodium benzoate]

Transdermal system [once-daily patch]:

Exelon®: 4.6 mg/24 hours (30s) [5 cm^2; contains rivastigmine 9 mg]; 9.5 mg/24 hours (30s) [10 cm^2; contains rivastigmine 18 mg]

Generic AvailableNo

ManufacturerNovartis Pharmaceuticals Corp

Pricing: U.S. (www.drugstore.com)

Capsules (Exelon)

1.5 mg (60): $202.18

3 mg (60): $202.07

4.5 mg (60): $203.29

6 mg (60): $202.18

Patch, 24-hour (Exelon)

4.6 mg/24 hrs (30): $199.99

9.5 mg/24 hrs (30): $202.65

Mechanism of ActionA deficiency of cortical acetylcholine is thought to account for some of the symptoms of Alzheimer's disease and the dementia of Parkinson's disease; rivastigmine increases acetylcholine in the central nervous system through reversible inhibition of its hydrolysis by cholinesterase

Pharmacodynamics/Kinetics

Duration: Anticholinesterase activity (CSF): ~10 hours (6 mg oral dose)

Absorption: Oral: Fasting: Rapid and complete within 1 hour

Distribution: V_d: 1.8-2.7 L/kg; penetrates blood-brain barrier (CSF levels are ~40% of plasma levels following oral administration)

Protein binding: 40%

Metabolism: Extensively via cholinesterase-mediated hydrolysis in the brain; metabolite undergoes N-demethylation and/or sulfate conjugation hepatically; CYP minimally involved; linear kinetics at 3 mg twice daily, but nonlinear at higher doses

Bioavailability: Oral: 36% to 40%

Half-life elimination: Oral: 1.5 hours; Transdermal patch: 3 hours (after removal)

Time to peak: Oral: 1 hour; Transdermal patch: 10-16 hours following first dose

Excretion: Urine (97% as metabolites); feces (0.4%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Cardiovascular ConsiderationsBecause of the cholinergic activity due to inhibition of acetylcholinesterase, rivastigmine may induce significant bradycardia. Caution is especially indicated in patients with sick sinus syndrome and pre-existing cardiac conduction abnormalities. Interactions with beta-blockers, calcium channel blockers, and digoxin may potentiate bradycardia and may predispose to significant hypotension.

Index TermsENA 713; Rivastigmine Tartrate; SDZ ENA 713

References

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International Brand NamesExelon (AR, AT, AU, BE, BG, BO, BR, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, FI, FR, GB, GR, GT, HK, HN, HU, ID, IE, IL, IT, MX, MY, NI, NL, NO, PA, PE, PH, PK, PL, PR, PT, PY, RU, SE, SG, SV, TH, TR, TW, UY, VE); Exelon Patch (TH); Prometax (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Rivadem (IN)

Rizatriptan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(rye za TRIP tan)

U.S. Brand NamesMaxalt-MLT®; Maxalt®

Canadian Brand NamesMaxalt RPD™; Maxalt™

Pharmacologic CategoryAntimigraine Agent; Serotonin 5-HT$_{1B, 1D}$ Receptor Agonist

Use: Labeled IndicationsAcute treatment of migraine with or without aura

Dosing: Adults **Note:** In patients with risk factors for coronary artery disease, following adequate evaluation to establish the absence of coronary artery disease, the initial dose should be administered in a setting where response may be evaluated (physician's office or similarly staffed setting). ECG monitoring may be considered.

Migraine: Oral: 5-10 mg, repeat after 2 hours if significant relief is not attained; maximum: 30 mg in a 24-hour period (use 5 mg dose in patients receiving propranolol with a maximum of 15 mg in 24 hours)

Note: For orally-disintegrating tablets (Maxalt-MLT®): Patient should be instructed to place tablet on tongue and allow to dissolve. Dissolved tablet will be swallowed with saliva.

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsOrally-disintegrating tablet contains phenylalanine (1.05 mg per 5 mg tablet, 2.10 mg per 10 mg tablet).

StorageStore in blister pack until administration.

ContraindicationsHypersensitivity to rizatriptan or any component of the formulation; documented ischemic heart disease or Prinzmetal's angina; uncontrolled hypertension; basilar or hemiplegic migraine; during or within 2 weeks of MAO inhibitors; during or within 24 hours of treatment with another 5-HT$_1$ agonist, or an ergot-containing or ergot-type medication (eg, methysergide, dihydroergotamine)

Allergy Considerations

- Serotonin 5-HT$_{1B,1D}$ Receptor Agonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac events: Coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia/fibrillation, cardiac arrest, and death have been reported with 5-HT$_1$ agonist administration. Patients who experience sensations of chest pain/pressure/tightness or symptoms suggestive of angina following dosing should be evaluated for coronary artery disease or Prinzmetal's angina before receiving additional doses.
- Cerebrovascular events: Cerebral/subarachnoid hemorrhage and stroke have been reported with 5-HT$_1$ agonist administration.
- Elevated blood pressure: Significant elevation in blood pressure, including hypertensive crisis, has also been reported on rare occasions in patients with and without a history of hypertension.
- Vasospasm-related events: Peripheral vascular ischemia and colonic ischemia have been reported with 5-HT$_1$ agonist.

Disease-related concerns:

- Coronary artery disease: Should not be given to patients who have risk factors for CAD (eg, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, menopause, male >40 years of age) without adequate cardiac evaluation. Patients with suspected CAD should have cardiovascular evaluation to rule out CAD before considering use; if cardiovascular evaluation "is satisfactory", first dose should be given in the healthcare provider's office. Periodic evaluation of cardiovascular status should be done in all patients.
- Hepatic impairment: Use with caution in patients with hepatic impairment; drug clearance may be reduced leading to increased plasma concentrations.
- Renal impairment: Use with caution in dialysis patients.

Concurrent drug therapy issues:

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce rizatriptan's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

Dosage form specific issues:

- Phenylalanine: Maxalt-MLT® tablets contain phenylalanine.

Other warnings/precautions:

- Appropriate use: Only indicated for treatment of acute migraine; if a patient does not respond to the first dose, the diagnosis of migraine should be reconsidered.

Geriatric ConsiderationsSince the elderly often have cardiovascular disease, careful evaluation of the use of 5-HT agonists is needed to avoid complications with the use of these agents. The pharmacokinetic disposition of these agents is similar to that seen in younger adults.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies using rizatriptan in pregnant women. Use only if potential benefit to the mother outweighs the potential risk to the fetus. A pregnancy registry has been established to monitor outcomes of women exposed to rizatriptan during pregnancy (800-986-8999). In some animal studies, administration was associated with decreased weight gain, developmental toxicity and increased mortality in the offspring. Teratogenic effects were not observed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Cardiovascular: Systolic/diastolic blood pressure increases (5-10 mm Hg), chest pain (5%), palpitation

Central nervous system: Dizziness, drowsiness, fatigue (13% to 30%, dose related)

Dermatologic: Skin flushing

Endocrine & metabolic: Mild increase in growth hormone, hot flashes

Gastrointestinal: Abdominal pain, dry mouth (<5%), nausea

Respiratory: Dyspnea

<1%: Akinesia, angina, arrhythmia, arthralgia, blurred vision, bradykinesia, decreased mental activity, diaphoresis, diarrhea, dry eyes, eye pain, facial edema, bradycardia, chills, hangover, heat sensitivity muscle weakness, myalgia, nasopharyngeal irritation, neck pain/stiffness, neurological/psychiatric abnormalities, pharyngitis, polyuria, pruritus, syncope, tachycardia, tinnitus

Postmarketing and/or case reports: Angioedema, dysgeusia, myocardial ischemia, MI, stroke, toxic epidermal necrolysis, wheezing

Drug Interactions

Ergot Derivatives: May enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

MAO Inhibitors: May decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. *Risk X: Avoid combination*

Propranolol: May increase the serum concentration of Serotonin 5-HT1D Receptor Agonists. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: Food delays absorption.

Monitoring ParametersHeadache severity, signs/symptoms suggestive of angina; consider monitoring blood pressure, heart rate, and/or ECG with first dose in patients with likelihood of unrecognized coronary disease, such as patients with significant hypertension, hypercholesterolemia, obese patients, patients with diabetes, smokers with other risk factors or strong family history of coronary artery disease

Nursing: Physical Assessment/MonitoringFor use only with clear diagnosis of migraine. Evaluate presence of or at risk for coronary disease. Initial dose should be administered in a setting where response may be evaluated and ECG monitoring may be considered. Assess potential for interactions with other pharmacological agents patient may be taking (eg, ergot containing drugs, SSRIs). Assess effectiveness (relief of migraine) and adverse response (eg, drowsiness, nausea/vomiting, chest pain, palpitations). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsConsider monitoring vital signs and ECG with first dose in patients with unrecognized coronary disease, such as patients with significant hypertension, hypercholesterolemia, obese patients, patients with diabetes, smokers with other risk factors or strong family history of coronary artery disease

Patient EducationThis drug is to be used to reduce your migraine, not to prevent or reduce the number of attacks. Follow exact instructions for use. For orally-disintegrating tablets (Maxalt-MLT®), do not open blister pack before using. Open with dry hands, place on tongue, and allow to dissolve (dissolved tablet will be swallowed with saliva). Do not crush, break, or chew. Do not take within 24 hours of any other migraine medication without first consulting prescriber. If first dose brings relief, second dose may be taken anytime after 2 hours if migraine returns. Do not take more than two doses without consulting prescriber. May cause dizziness or drowsiness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); dry mouth (frequent mouth care and sucking on lozenges may help); skin flushing or hot flashes (cool clothes or a cool environment may help); or mild abdominal discomfort or nausea or vomiting. Report immediately any chest pain, palpitations, or irregular heartbeat; severe dizziness, acute headache, stiff or painful neck or facial swelling; muscle weakness or pain; changes in mental acuity; blurred vision or eye pain; or excessive perspiration or urination. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Maxalt®: 5 mg, 10 mg

Tablet, orally disintegrating:

Maxalt-MLT®: 5 mg [contains phenylalanine 1.05 mg/tablet; peppermint flavor]; 10 mg [contains phenylalanine 2.1 mg/tablet; peppermint flavor]

Generic AvailableNo
ManufacturerMerck & Co
Pricing: U.S. (www.drugstore.com)

Tablet, orally-disintegrating (Maxalt-MLT)

5 mg (3): $58.29

10 mg (6): $125.99

Tablets (Maxalt)

5 mg (6): $107.44

5 mg (12): $265.99

10 mg (12): $255.51

Mechanism of ActionSelective agonist for serotonin (5-HT$_{1D}$ receptor) in cranial arteries to cause vasoconstriction and reduce sterile inflammation associated with antidromic neuronal transmission correlating with relief of migraine
Pharmacodynamics/Kinetics

Onset of action: ~30 minutes

Duration: 14-16 hours

Protein binding: 14%

Metabolism: Via monoamine oxidase-A; first-pass effect

Bioavailability: 40% to 50%

Half-life elimination: 2-3 hours

Time to peak: 1-1.5 hours

Excretion: Urine (82%, 8% to 16% as unchanged drug); feces (12%)

Related Information

- Antimigraine Drugs: 5-HT1 Receptor Agonists

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDrowsiness and dizziness are common
Mental Health: Effects on Psychiatric TreatmentContraindicated with other serotonin agonists (SSRIs) and MAO inhibitors
Cardiovascular ConsiderationsCoronary vasospasm has been associated with 5-HT$_{1B/1D}$ agonists. These agents are contraindicated in patients with documented ischemic of vasospastic coronary artery disease. Patients with risk factors for CAD may receive these agents, provided a cardiovascular evaluation yields satisfactory evidence that the patient is free of cardiovascular disease. In patients with risk factors for CAD, administration of the initial dose in a medically staffed/equipped facility (ie, physician's office) is recommended. In addition, ECG monitoring after the initial dose should be considered. Patients who acquire risk factors for CAD, or long-term users of agents from this class of medications, should undergo periodic cardiovascular evaluation.
Anesthesia and Critical Care Concerns/Other ConsiderationsRizatriptan should not be used in patients with a history of vasospastic disease, Prinzmetal's angina, or any critical vascular disease.
Index TermsMK462
References

Boyer EW and Shannon M, “The Serotonin Syndrome,” *N Engl J Med*, 2005, 352:1112-20.[PubMed 15784664]

International Brand NamesMaxalt (AR, AT, BE, BG, BR, CH, CN, CR, DE, DK, EE, ES, FI, GB, GR, GT, HN, HU, IT, MX, NL, NO, NZ, PA, PE, PL, SE, SV); Maxalt RPD (CN, PE, VE); Rizact (IN); Rizalt (IL)

Rocuronium

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Zemuron® may be confused with Remeron®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(roe kyoor OH nee um)
U.S. Brand NamesZemuron®
Canadian Brand NamesZemuron®
Pharmacologic CategoryNeuromuscular Blocker Agent, Nondepolarizing
Use: Labeled IndicationsAdjunct to general anesthesia to facilitate both rapid sequence and routine endotracheal intubation and to relax skeletal muscles during surgery; to facilitate mechanical ventilation in ICU patients
Dosing: AdultsAdminister I.V.; dose to effect; doses will vary due to interpatient variability; use ideal body weight for obese patients

Tracheal intubation: I.V.:

Initial: 0.6 mg/kg is expected to provide approximately 31 minutes of clinical relaxation under opioid/nitrous oxide/oxygen anesthesia with neuromuscular block sufficient for intubation attained in 1-2 minutes; lower doses (0.45 mg/kg) may be used to provide 22 minutes of clinical relaxation with median time to neuromuscular block of 1-3 minutes; maximum blockade is achieved in <4 minutes

Maximum: 0.9-1.2 mg/kg may be given during surgery under opioid/nitrous oxide/oxygen anesthesia without adverse cardiovascular effects and is expected to provide 58-67 minutes of clinical relaxation; neuromuscular blockade sufficient for intubation is achieved in <2 minutes with maximum blockade in <3 minutes

Maintenance: 0.1, 0.15, and 0.2 mg/kg administered at 25% recovery of control T_1 (defined as 3 twitches of train-of-four) provides a median of 12, 17, and 24 minutes of clinical duration under anesthesia

Rapid sequence intubation: 0.6-1.2 mg/kg in appropriately premedicated and anesthetized patients with excellent or good intubating conditions within 2 minutes

Continuous infusion: Initial: 0.01-0.012 mg/kg/minute only after early evidence of spontaneous recovery of neuromuscular function is evident; infusion rates have ranged from 0.004-0.016 mg/kg/minute.

ICU neuromuscular blockade: 10 mcg/kg/minute; adjust dose to maintain appropriate degree of neuromuscular blockade (eg, 1 or 2 twitches on train-of-four)

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricAdminister I.V.; dose to effect; doses will vary due to interpatient variability; use ideal body weight for obese patients

Tracheal intubation: I.V.: Children ≥3 months:

Initial: 0.6 mg/kg under halothane anesthesia produce excellent to good intubating conditions within 1 minute and will provide a median time of 41 minutes of clinical relaxation in children 3 months to 1 year of age, and 27 minutes in children 1-12 years

Maintenance: 0.075-0.125 mg/kg administered upon return of T_1 to 25% of control provides clinical relaxation for 7-10 minutes

Administration: I.V.Administer I.V. only; may be given undiluted as a bolus injection or via a continuous infusion using an infusion pump
StorageStore under refrigeration (2°C to 8°C), do not freeze. When stored at room temperature, it is stable for 60 days; once opened, use within 30 days. Dilutions up to 5 mg/mL in 0.9% sodium chloride, dextrose 5% in water, 5% dextrose in sodium chloride 0.9%, or lactated Ringer's are stable for up to 24 hours at room temperature.
ContraindicationsHypersensitivity to rocuronium or any component of the formulation
Allergy Considerations

- Neuromuscular-Blocking Agent Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during use.

- Neuromuscular cross-sensitivity: Cross-sensitivity with other neuromuscular-blocking agents may occur; use extreme caution in patients with previous anaphylactic reactions.

Disease-related concerns:

- Burn injury: Resistance may occur in burn patients (>30% of body) for period of 5-70 days postinjury.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease; onset of action may be delayed and duration of action may be prolonged.
- Conditions which may *antagonize* neuromuscular blockade: Alkalosis, hypercalcemia, demyelinating lesions, peripheral neuropathies, denervation, infection, muscle trauma, and diabetes mellitus may result in antagonism of neuromuscular blockade.
- Conditions which may *potentiate* neuromuscular blockade: Electrolyte abnormalities, severe hyponatremia, severe hypocalcemia, severe hypokalemia, hypermagnesemia, neuromuscular diseases, acidosis, acute intermittent porphyria, Eaton-Lambert syndrome, myasthenia gravis, renal failure, and hepatic failure may result in potentiation of neuromuscular blockade.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Special populations:

- Elderly: Use with caution in the elderly, effects and duration are more variable.
- Immobilized patients: Resistance may occur in patients who are immobilized.
- Pediatrics: Safety and efficacy have not been established in children <3 months of age

Other warnings/precautions:

- Appropriate use: Maintenance of an adequate airway and respiratory support is critical. Rocuronium does not relieve pain or produce sedation; use should include appropriate anesthesia, pain control, and sedation.
- Experienced personnel: Should be administered by adequately trained individuals familiar with its use.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Rocuronium crosses the placenta; umbilical venous plasma levels are ~18% of the maternal concentration. The manufacturer does not recommend use for rapid sequence induction during cesarean section.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>1%: Cardiovascular: Transient hypotension (<1% to 2%) and hypertension (<1% to 2%)

<1%: Abnormal ECG, anaphylactoid reaction, anaphylaxis, arrhythmia, bronchospasm, edema, hiccups, injection site pruritus, nausea, rash, rhonchi, shock, tachycardia, vomiting, wheezing

Postmarketing and/or case reports: Acute quadriplegic myopathy syndrome (prolonged use), myositis ossificans (prolonged use)

Drug Interactions

Acetylcholinesterase Inhibitors: May diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Aminoglycosides: May enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Neuromuscular-Blocking Agents may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Neuromuscular-Blocking Agents may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Calcium Channel Blockers: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Cardiac Glycosides: Neuromuscular-Blocking Agents may enhance the arrhythmogenic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Colistimethate: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Neuromuscular-Blocking Agents (Nondepolarizing) may enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

Inhalational Anesthetics: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Neuromuscular-Blocking Agents (Nondepolarizing). Specifically, episodes of apnea have been reported in patients using this combination. *Risk C: Monitor therapy*

Lincosamide Antibiotics: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Lithium: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Loop Diuretics: May diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Loop Diuretics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Magnesium Salts: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Polymyxin B: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Procainamide: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

QuiNIDine: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Tetracycline Derivatives: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Vancomycin: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Monitoring ParametersPeripheral nerve stimulator measuring twitch response, heart rate, blood pressure, assisted ventilation status

Nursing: Physical Assessment/MonitoringOnly clinicians experienced in the use of neuromuscular blocking agents should administer and/or manage the use of rocuronium. Assess potential for interactions with other prescription or OTC medications or herbal products patient may be taking (eg, other drugs that affect neuromuscular activity may increase/decrease neuromuscular block induced by rocuronium). Dosage and rate of administration should be individualized and titrated to the desired effect, according to relevant clinical factors, premedication, concomitant medication, age, and general condition of the patient. Ventilatory support must be instituted and maintained until adequate respiratory muscle function and/or airway protection are assured. This drug does not cause anesthesia or analgesia; pain must be treated with appropriate agents. Continuous monitoring of vital signs, cardiac and respiratory status, and neuromuscular block (objective assessment with peripheral external nerve stimulator) are mandatory until full muscle tone has returned. Safety precautions must be maintained until full muscle tone has returned. Muscle tone returns in a predictable pattern; starting with diaphragm, abdomen, chest, limbs, and finally muscles of the neck, face, and eyes. **Note:** It may take longer for return of muscle tone in obese or elderly persons or patients with renal or hepatic disease, myasthenia gravis, myopathy, other neuromuscular diseases, dehydration, electrolyte imbalance, or severe acid/base imbalance. Provide appropriate teaching/support prior to, during, and following administration.

Long-term use: Monitor level of neuromuscular blockade, skeletal muscle movement, and respiratory effort. Every 2- to 3-hour repositioning, and skin, mouth, and eye care is necessary while patient is sedated. Emotional and sensory support (auditory and environmental) should be provided.

Patient EducationPatient education should be appropriate for patient condition. Reassurance of constant monitoring and emotional support should precede and follow administration. Patients should be reminded as muscle tone returns not to attempt to change position or rise from bed without assistance and to report and skin rash, hives, pounding heartbeat, respiratory difficulty, or muscle tremors. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as bromide: 10 mg/mL (5 mL, 10 mL)

Zemuron®: 10 mg/mL (5 mL, 10 mL)

Generic AvailableYes

Mechanism of ActionBlocks acetylcholine from binding to receptors on motor endplate inhibiting depolarization

Pharmacodynamics/Kinetics

Onset of action: Good intubation conditions in 1-2 minutes; maximum neuromuscular blockade within 4 minutes

Duration: ~30 minutes (with standard doses, increases with higher doses)

Distribution: V_d: ~0.25 L/kg

Protein binding: ~30%

Metabolism: Minimally hepatic; 17-desacetylrocuronium (5% to 10% activity of parent drug)

Half-life elimination: 60-70 minutes

Excretion: Feces (50%); urine (30%)

Related Information

- Neuromuscular-Blocking Agents

Pharmacotherapy PearlsRocuronium is classified as an intermediate-duration neuromuscular-blocking agent. Do not mix in the same syringe with barbiturates. Rocuronium does not relieve pain or produce sedation.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentPatients maintained on carbamazepine or phenytoin may have a decreased effect of rocuronium.

Mental Health CommentPatients with myasthenia gravis display an increased sensitivity to this neuromuscular-blocking agent.

Anesthesia and Critical Care Concerns/Other ConsiderationsClassified as an intermediate duration neuromuscular-blocking agent; do not mix in same syringe with barbiturates.

Critically-Ill Adult Patients:

The 2008 Surviving Sepsis Campaign guidelines recommend avoiding use of neuromuscular blockers if at all possible in the septic patient due to the risk of prolonged neuromuscular blockade following discontinuation. If one is required, monitor the depth of blockade (Grade 1B).

The 2002 ACCM/SCCM/ASHP clinical practice guidelines for sustained neuromuscular blockade in the adult critically-ill patient recommend:

Optimize sedatives and analgesics prior to initiation and monitor and adjust accordingly during course. Neuromuscular blockers do not relieve pain or produce sedation.

Protect patient's eyes from development of keratitis and corneal abrasion by administering ophthalmic ointment and taping eyelids closed or using eye patches. Reposition patient routinely to protect pressure points from breakdown. Address DVT prophylaxis.

Concurrent use of a neuromuscular blocker and corticosteroids appear to increase the risk of certain ICU myopathies; avoid or administer the corticosteroid at the lowest dose possible. Reassess need for neuromuscular blocker daily.

Using daily drug holidays (stopping neuromuscular-blocking agent until patient requires it again) may decrease the incidence of acute quadriplegic myopathy syndrome.

Tachyphylaxis can develop; switch to another neuromuscular blocker (taking into consideration the patient's organ function) if paralysis is still necessary.

Atracurium or cisatracurium is recommended for patients with significant hepatic or renal disease, due to organ-independent Hofmann elimination.

Monitor patients clinically and via “Train of Four” (TOF) testing with a goal of adjusting the degree of blockade to 1-2 twitches on based upon the patient's clinical condition.

Index TermsORG 946; Rocuronium Bromide

References

Bartkowski RR, Witkowski TA, Azad S, et al, “Rocuronium Onset of Action: A Comparison With Atracurium and Vecuronium,” *Anesth Analg*, 1993, 77(3):574-8. [PubMed 8103649]

Dellinger RP, Levy MM, Carlet JM, et al, “Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008,” *Intensive Care Med*, 2008, 34(1): 17-60. Available at http://www.survivingsepsis.org/system/files/images/2008_20International_20SSC_20Guidelines_1_.pdf[PubMed 18058085]

Khuenl-Brady KS, Sparr H, Puhringer F, et al, “Rocuronium Bromide in the ICU: Dose Finding and Pharmacokinetics,” *Eur J Anaesthesiol Suppl*, 1995, 11:79-80. [PubMed 8557012]

Murray MJ, Cowen J, DeBlock H, et al, “Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient. Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists, American College of Chest Physicians,” *Crit Care Med*, 2002, 30(1):142-56. Available at: http://www.sccm.org/pdf/NeuromuscularBlockade.pdf. Accessed August 6, 2003. [PubMed 11902255]

Puhringer FK, Khuenl-Brady KS, and Mitterschiffthaler G, “Rocuronium Bromide: Time-Course of Action in Underweight, Normal Weight, Overweight and Obese Patients,” *Eur J Anaesthesiol Suppl*, 1995, 11:107-10.[PubMed 8556996]

International Brand NamesEsmero-N (MX); Esmeron (AE, AT, AU, BE, BG, BH, BR, CH, CL, CN, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JO, KW, LB, LY, MY, NL, NO, OM, PE, PH, PK, PL, PT, QA, RU, SA, SE, SG, SY, TH, TR, TW, VE, YE); Roculax (ID); Rocur (UY); Rocuron (PH); Rocuronio (CO); Zemuron (AR)

Romiplostim

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(roe mi PLOE stim)

U.S. Brand NamesNplate™

Pharmacologic Category[Colony Stimulating Factor]; [Thrombopoietic Agent]

Use: Labeled IndicationsTreatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia purpura (ITP) who have had insufficient response to corticosteroids, immune globulin, or splenectomy

Dosing: Adults**Note:** Initial dose is based on actual body weight. Discontinue if platelet count does not respond to a level that avoids clinically important bleeding after 4 weeks at the maximum recommended dose.

ITP: SubQ: Initial: 1 mcg/kg once weekly; adjust dose by 1 mcg/kg/week to achieve platelet count ≥50,000/mm^3 and to reduce the risk of bleeding; Maximum: 10 mcg/kg (median dose needed to achieve response in clinical trials: 2 mcg/kg)

Dosage adjustment recommendations:

Platelet count <50,000/mm^3: Increase dose by 1 mcg/kg

Platelet count >200,000/mm^3 for 2 consecutive weeks: Reduce dose by 1 mcg/kg

Platelet count >400,000/mm^3: Withhold dose; assess platelet count weekly; when platelet count <200,000/mm^3, resume with the dose reduced by 1 mcg/kg

Dosing: ElderlyRefer to adult dosing.

Administration: OtherAdminister SubQ. Administration volume may be small; use appropriate syringe (with graduations to 0.01 mL) for administration.

Dietary ConsiderationsNplate™ 250 mcg vial contains sucrose 15 mg and 500 mcg vial contains sucrose 25 mg.

StorageStore intact vials refrigerated at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Reconstituted solution may be stored at room temperature of 25°C (77°F) or refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours. Protect reconstituted solution from light.

ReconstitutionReconstitute with preservative free SWFI to a final concentration of 500 mcg/mL. Gently invert vial and swirl; do not shake.

RestrictionsApproved for use only under a risk management and restricted distribution program, Nplate™ NEXUS (Network of Experts Understanding and Supporting Nplate™ and Patients) program (1-877-675-2831 or www.nplate.com). Prescribers and patients must be registered with the program.

An FDA-approved medication guide is available; distribute to each patient to whom this medication is dispensed.

ContraindicationsThere are no contraindications listed within the manufacturer's labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Bone marrow reticulin: May increase the risk for bone marrow reticulin formation or progression. Collagen fibrosis with cytopenias was not observed in clinical trials, although patients receiving romiplostim may be at risk for marrow fibrosis with cytopenias. Onset of new or worsening cellular abnormalities or cytopenias may warrant therapy discontinuation and subsequent bone marrow biopsy.

- Malignancy/tumorigenicity: Stimulation of cell surface thrombopoietin (TPO) receptors may increase the risk for hematologic malignancies. May increase the risk for progression of underlying myelodysplastic syndrome (MDS).

- Rebound thrombocytopenia: Upon discontinuation of therapy, thrombocytopenia may worsen. Severity may be greater than pretreatment level. Risk of bleeding is increased, particularly in patients receiving anticoagulants or antiplatelet agents; monitor closely. Rebound thrombocytopenia generally resolves within 14 days.

- Thromboembolism: Thromboembolism may occur with treatment. Use with caution in patients with a history of cerebrovascular disease.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; not studied in this population.

- Renal impairment: Use with caution in patients with renal impairment; not studied in this population.

Concurrent drug therapy issues:

- Concomitant ITP medications: May be used in combination with other therapies for ITP, including corticosteroids, danazol, azathioprine, immune globulin, or Rho(D) immune globulin. Reduce dose of or discontinue ITP medications when platelet count ≥50,000/mm^3.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Inadequate platelet response may be due to neutralizing antibodies (to romiplostim or TPO) or bone marrow fibrosis. Indicated only when the degree of thrombocytopenia and clinical conditions increase the risk for bleeding; use the lowest dose necessary to achieve and maintain platelet count platelet count ≥50,000/mm^3. Do not use to normalize platelet counts. Discontinue if platelet count does not respond to a level to avoid clinically important bleeding after 4 weeks at the maximum recommended dose.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAdverse effects were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus. The Nplate™ pregnancy registry has been established to monitor outcomes of women exposed to romiplostim during pregnancy (1-877-675-2831).
LactationExcretion in breast milk unknown/ not recommended.
Adverse Reactions

>10%:

Central nervous system: Headache (35%), fatigue (33%), dizziness (17%), insomnia (16%)

Gastrointestinal: Diarrhea (17%), nausea (13%), abdominal pain (11%)

Neuromuscular & skeletal: Arthralgia (26%), myalgia (14%), back pain (13%), limb pain (13%)

Respiratory: Epistaxis (32%), upper respiratory tract infection (17%)

1% to 10%:

Gastrointestinal: Dyspepsia (7%)

Hematologic: Rebound thrombocytopenia (7%), bone marrow reticulin formation/deposition (4%)

Neuromuscular & skeletal: Shoulder pain (8%), paresthesia (6%)

Miscellaneous: Antibody formation (romiplostim 10%; TPO 5%)

<1%, postmarketing, and/or case reports: Thromboembolism

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersCBC with differential and platelets (baseline, during treatment [weekly until platelet response stable for 4 weeks then monthly] and weekly for at least 2 weeks following completion of treatment)

Evaluate for neutralizing antibodies in patients with inadequate response (blood samples may be submitted to Amgen for assay [1-800-772-6436]).

Reference RangeTarget platelet count of 50,000-200,000/mm^3; platelet life span: 8-11 days
Nursing: Physical Assessment/MonitoringPatient and provider must be registered with the Network of Experts Understanding and Supporting Nplate and Patients program (NEXUS™). Evaluate history of cerebrovascular disease prior to beginning treatment. Evaluate results of laboratory tests prior to, on a regular scheduled basis during therapy, and following discontinuation of therapy (rebound thrombocytopenia may be severe). Assess adverse response on a frequent basis during therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.
Monitoring: Lab TestsCBC with differential and platelets (baseline, during treatment [weekly until platelet response stable for 4 weeks then monthly] and weekly for at least 2 weeks following completion of treatment)

Evaluate for neutralizing antibodies in patients with inadequate response (blood samples may be submitted to Amgen for assay [1-800-772-6436]).

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy unless approved by prescriber. This medication can only be administered by injection. You will require frequent blood tests to determine appropriate dosage and to reduce potential for severe adverse effects; maintaining laboratory testing schedule is vital. May cause nausea, vomiting, or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); dizziness, lightheadedness, fatigue, or insomnia (use caution when driving or engaging in tasks that require alertness until response to drug is known); or muscle, joint, back, or limb pain (consult prescriber for appropriate analgesic; do not self-medicate for pain). Report difficulty breathing, signs of a respiratory infection, or other unusual or persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Nplate™: 250 mcg [contains sucrose 15 mg/vial]; 500 mcg [contains sucrose 25 mg/vial]

Generic AvailableNo
ManufacturerAmgen, Inc
Mechanism of ActionThrombopoietin (TPO) peptide mimetic which increases platelet counts in ITP by binding to and activating the human TPO receptor.
Pharmacodynamics/Kinetics

Onset of action: Platelet count increase: SubQ: 4-9 days; Peak platelet count increase: Days 12-16

Duration: Platelet counts return to baseline by day 28

Absorption: SubQ: Slow

Half-life elimination: Median: 3.5 days (range: 1-34 days)

Time to peak, plasma: SubQ: Median: 14 hours (range: 7-50 hours)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDizziness, fatigue, and insomnia are common
Mental Health: Effects on Psychiatric TreatmentGI side effects are common; combined use with SSRIs, lithium, valproic acid, and carbamazepine may produce additive effects
Index TermsAMG 531
References

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Kuter DJ, “New Thrombopoietic Growth Factors,” *Blood*, 2007, 109(11):4607-16.[PubMed 17289815]

Kuter DJ, Bussel JB, Lyons RM, et al, “Efficacy of Romiplostim in Patients With Chronic Immune Thrombocytopenic Purpura: A Double-Blind Randomised Controlled Trial,” *Lancet*, 2008, 371(9610):395-403.[PubMed 18242413]

Wang B, Nichol JL, and Sullivan JT, “Pharmacodynamics and Pharmacokinetics of AMG 531, a Novel Thrombopoietin Receptor Ligand,” *Clin Pharmacol Ther*, 2004, 76(6):628-38.[PubMed 15592334]

Ropinirole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Requip® may be confused with Reglan®

Ropinirole may be confused with ropivacaine

Pronunciation(roe PIN i role)

U.S. Brand NamesRequip®; Requip® XL™

Canadian Brand NamesRequip®

Pharmacologic CategoryAnti-Parkinson's Agent, Dopamine Agonist

Use: Labeled IndicationsTreatment of idiopathic Parkinson's disease; in patients with early Parkinson's disease who were not receiving concomitant levodopa therapy as well as in patients with advanced disease on concomitant levodopa; treatment of moderate-to-severe primary Restless Legs Syndrome (RLS)

Dosing: Adults

Parkinson's disease: Oral:

Immediate release tablet: The dosage should be increased to achieve a maximum therapeutic effect, balanced against the principal side effects of nausea, dizziness, somnolence and dyskinesia. Recommended starting dose is 0.25 mg 3 times/day; based on individual patient response, the dosage should be titrated with weekly increments as described below:

- Week 1: 0.25 mg 3 times/day; total daily dose: 0.75 mg
- Week 2: 0.5 mg 3 times/day; total daily dose: 1.5 mg
- Week 3: 0.75 mg 3 times/day; total daily dose: 2.25 mg
- Week 4: 1 mg 3 times/day; total daily dose: 3 mg

Note: After week 4, if necessary, daily dosage may be increased by 1.5 mg/day on a weekly basis up to a dose of 9 mg/day, and then by up to 3 mg/day weekly to a total of 24 mg/day

Parkinson's disease discontinuation taper: Ropinirole should be gradually tapered over 7 days as follows: reduce frequency of administration from 3 times daily to twice daily for 4 days, then reduce to once daily for remaining 3 days.

Extended release tablet: Initial: 2 mg once daily for 1-2 weeks, followed by increases of 2 mg/day at weekly or longer intervals based on therapeutic response and tolerability (maximum: 24 mg/day); **Note:** When discontinuing gradually taper over 7 days.

Restless legs syndrome: Oral: Immediate release tablets: Initial: 0.25 mg once daily 1-3 hours before bedtime. Dose may be increased after 2 days to 0.5 mg daily, and after 7 days to 1 mg daily. Dose may be further titrated upward in 0.5 mg increments every week until reaching a daily dose of 3 mg during week 6. If symptoms persist or reappear, the daily dose may be increased to a maximum of 4 mg beginning week 7.

Note: Doses up to 4 mg per day may be discontinued without tapering.

Converting from ropinirole immediate release tablets to ropinirole extended-release tablets: Choose a once daily extended-release dose that most closely matches current immediate-release daily dose.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

No adjustment needed in patients with moderate renal impairment (Cl_{cr} 30-50 mL/minute); has not been studied in patients with severe impairment.

Removal by hemodialysis is unlikely.

Dosing: Hepatic ImpairmentTitrate with caution; has not been studied.

Administration: OralMay be administered with or without food; taking with food may reduce nausea. Swallow extended-release tablet whole; do not crush, split, or chew.

Dietary ConsiderationsMay be taken with or without food; taking with food may reduce nausea.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light.

ContraindicationsHypersensitivity to ropinirole or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Hallucinations: May cause hallucinations; risk may be increased in the elderly.

- Impulsive control disorders: Dopamine agonists used for Parkinson’s disease or restless legs syndrome have been associated with compulsive behaviors and/or loss of impulse control, which has manifested as pathological gambling, libido increases (hypersexuality), and/or binge eating. Causality has not been established, and controversy exists as to whether this phenomenon is related to the underlying disease, prior behaviors/addictions and/or drug therapy. Dose reduction or discontinuation of therapy has been reported to reverse these behaviors in some, but not all cases.

- Melanoma: Risk of melanoma has been reported in patients receiving ropinirole; drug causation has not been established.

- Orthostatic hypotension: May cause orthostatic hypotension; Parkinson's disease patients appear to have an impaired capacity to respond to a postural challenge. Use with caution in patients at risk of hypotension (such as those receiving antihypertensive drugs) or where transient hypotensive episodes would be poorly tolerated (cardiovascular disease or cerebrovascular disease). Parkinson's patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation, and should be informed of this risk. Syncope, sometimes associated with bradycardia, was observed in association with ropinirole in both early Parkinson's disease (without levodopa) patients and advanced Parkinson's disease (with levodopa) patients.

- Pleural/retroperitoneal fibrosis: Risk of fibrotic complications (eg, pleural effusion/fibrosis, interstitial lung disease) has been reported in patients receiving ropinirole; drug causation has not been established.

- Retinal changes: Pathologic degenerative changes were observed in the retinas of albino rats during studies with this agent, but were not observed in the retinas of albino mice or in other species. The significance of these data for humans remains uncertain.

- Somnolence: Patients have reported falling asleep while engaging in activities of daily living; this has been reported to occur without significant warning signs. Monitor for daytime somnolence or pre-existing sleep disorder; caution with concomitant sedating medication; discontinue if significant daytime sleepiness or episodes of falling asleep occur. Patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). Use with caution in patients receiving other CNS depressants or psychoactive agents. Effects with other sedative drugs or ethanol may be potentiated.

Disease-related concerns:

- Dyskinesias: Use with caution in patients with pre-existing dyskinesias; may be exacerbated.

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Psychotic disorders: Avoid use in patients with a major psychotic disorder; may exacerbate psychosis.

- Renal impairment: Use with caution in patients with severe renal impairment.

- Restless legs syndrome (RLS): Augmentation (earlier onset of symptoms in the evening/afternoon, increase and/or spread of symptoms to other extremities) or rebound (shifting of symptoms to early morning hours) may occur in some RLS patients.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Discontinuation of therapy: Dopaminergic agents have been associated with a syndrome resembling neuroleptic malignant syndrome on abrupt withdrawal or significant dosage reduction after long-term use.

Geriatric ConsiderationsSince the dose is titrated to clinical response, no specific dosage adjustment is necessary in the elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects have been observed in animal studies. There are no adequate and well-controlled studies in pregnant women; use only if potential benefit outweighs the risk to the fetus.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsRopinirole inhibits prolactin secretion in humans and may potentially inhibit lactation. Ropinirole has been detected in the milk of lactating rats, however, transfer of ropinirole in human milk has not been demonstrated. Due to the potential for serious adverse reactions, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Adverse Reactions

Data inclusive of trials in early Parkinson's disease (without levodopa) and Restless Legs Syndrome:

>10%:

Cardiovascular: Syncope (1% to 12%)

Central nervous system: Somnolence (11% to 40%), dizziness (6% to 40%), fatigue (8% to 11%)

Gastrointestinal: Nausea (immediate release: 40% to 60%; extended release: 19%), vomiting (11% to 12%)

Miscellaneous: Viral infection (11%)

1% to 10%:

Cardiovascular: Dependent/leg edema (2% to 7%), orthostasis (1% to 6%), hypertension (5%), chest pain (4%), flushing (3%), palpitation (3%), peripheral ischemia (2% to 3%), atrial fibrillation (2%), extrasystoles (2%), hypotension (2%), tachycardia (2%)

Central nervous system: Pain (3% to 8%), headache (extended release: 6%), confusion (5%), hallucinations (up to 5%; dose related), hypoesthesia (4%), amnesia (3%), malaise (3%), yawning (3%), concentration impaired (2%), vertigo (2%)

Dermatologic: Hyperhidrosis (3%)

Gastrointestinal: Constipation (≥5%), dyspepsia (4% to 10%), abdominal pain (3% to 7%), xerostomia (3% to 5%), diarrhea (5%), anorexia (4%), flatulence (3%)

Genitourinary: Urinary tract infection (5%), impotence (3%)

Hepatic: Alkaline phosphatase increased (3%)

Neuromuscular & skeletal: Weakness (6%), arthralgia (4%), muscle cramps (3%), paresthesia (3%), hyperkinesia (2%)

Ocular: Abnormal vision (6%), xerophthalmia (2%)

Respiratory: Pharyngitis (6% to 9%), rhinitis (4%), sinusitis (4%), bronchitis (3%), dyspnea (3%), influenza (3%), cough (3%), nasal congestion (2%)

Miscellaneous: Diaphoresis increased (3% to 6%)

Advanced Parkinson's disease (with levodopa):

>10%:

Central nervous system: Dizziness (immediate release: 26%; extended-release: 8%), somnolence (immediate release: 20%, extended release: 7%), headache (17%)

Gastrointestinal: Nausea (immediate release: 30%; extended-release: 11%)

Neuromuscular & skeletal: Dyskinesias (immediate release: 34%; extended-release: 13%; dose related)

1% to 10%:

Cardiovascular: Hypotension (2% to 5%; including orthostatic), peripheral edema (4%), syncope (3%), hypertension (3%; dose related)

Central nervous system: Hallucinations (7% to 10%; dose related), confusion (9%), anxiety (2% to 6%), amnesia (5%), nervousness (5%), pain (5%), vertigo (4%), abnormal dreaming (3%), paresis (3%), aggravated parkinsonism, insomnia

Gastrointestinal: Abdominal pain (6% to 9%), vomiting (7%), constipation (4% to 6%), diarrhea (3% to 5%), xerostomia (2% to 5%), dysphagia (2%), flatulence (2%), salivation increased (2%), weight loss (2%)

Genitourinary: Urinary tract infection (6%), pyuria (2%), urinary incontinence (2%)

Hematologic: Anemia (2%)

Neuromuscular & skeletal: Falls (2% to 10%; dose related), arthralgia (7%), tremor (6%), hypokinesia (5%), paresthesia (5%), arthritis (3%), back pain (3%)

Ocular: Diplopia (2%)

Respiratory: Upper respiratory tract infection (9%), dyspnea (3%)

Miscellaneous: Injury, diaphoresis increased (7%), viral infection, increased drug level (7%)

Other adverse effects (all phase 2/3 trials for Parkinson's disease and Restless Leg Syndrome):

≥1%: Asthma, BUN increased, depression, gastroenteritis, gastrointestinal reflux, irritability, migraine, muscle spasm, myalgia, neck pain, neuralgia, osteoarthritis, pharyngolaryngeal pain, rash, rigors, sleep disorder, tendonitis

<1% (Limited to important or life-threatening): Abnormal coordination, acidosis, agitation, aneurysm, angina, aphasia, behavioral disorders, bradycardia, bundle branch block, cardiac arrest, cardiac failure, cardiomegaly, cellulitis, cholecystitis, cholelithiasis, choreoathetosis, colitis, coma, conjunctival hemorrhage, dehydration, diabetes mellitus, diverticulitis, Dupuytren's contracture, dysphonia, electrolyte disturbances, eosinophilia, extrapyramidal symptoms, gangrene, gastrointestinal hemorrhage, gastrointestinal ulceration, glaucoma, goiter, gynecomastia, hematuria, hemiparesis, hemiplegia, hepatitis (ischemic), hyperbilirubinemia, hypercholesterolemia, hyper-/hypothyroidism, hyper-/hypotonia, hypoglycemia, hyponatremia, hyperphosphatemia, hyperuricemia; infections (bacterial, viral or fungal); intestinal obstruction, leukocytosis, leukopenia, limb embolism, liver enzymes increased, lymphadenopathy, lymphedema, lymphocytosis, lymphopenia, menstrual abnormalities, mitral insufficiency, MI, neoplasms (various), pancreatitis, paralysis, peripheral neuropathy, photosensitivity, pleural effusion, proteinuria, psychiatric disorders, pulmonary edema, pulmonary embolism, renal calculus, renal failure (acute), seizure, sepsis, SIADH, skin disorders, stomatitis, stupor, subarachnoid hemorrhage, suicide attempt, SVT, thrombocytopenia, thrombosis, tinnitus, tongue edema, torticollis, urticaria, vagina/uterine hemorrhage, ventricular tachycardia, visual disturbances

Postmarketing and/or case reports: Cardiac valvulopathy; impulsive/compulsive behaviors (eg, pathological gambling, hypersexuality, binge eating); interstitial lung disease, pleural fibrosis

Metabolism/Transport Effects **Substrate** of CYP1A2 (major), 3A4 (minor); **Inhibits** CYP1A2 (weak)
Drug Interactions

Antipsychotics (Atypical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Antipsychotics (Typical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Ciprofloxacin: May decrease the metabolism of Ropinirole. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Ropinirole. *Risk C: Monitor therapy*

Metoclopramide: May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Monitoring Parameters

Blood pressure (orthostatic); daytime alertness

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Monitor blood pressure periodically. Assess therapeutic effectiveness and adverse responses on a regular basis during therapy. Monitor for CNS depression/somnolence. Teach patient proper use, side effects/appropriate interventions, and adverse reactions to report.

Patient EducationTake exactly as directed, without regard to food. Avoid alcohol use and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. May cause dizziness; sudden, overwhelming sleepiness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution and avoid quick moves when rising from sitting or lying position, when climbing stairs, or engaging in activities that require quick movements); loss of impulse control (possibly manifested as pathological gambling, libido increases, and/or binge eating); or nausea, vomiting, lack of appetite, or mouth sores (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report unusual and persistent sleepiness; chest pain or palpitations; CNS changes (confusion, hallucinations, amnesia, abnormal dreaming, insomnia); suicide ideation; skeletal weakness or increased random tremors or movements, gait changes, or difficulty walking; signs of urinary tract or respiratory infection (pain or burning on urination, pus or blood in urine, or unusual cough and chest tightness); or unusual persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Combination package:

Requip® [starter kit; contents per each administration card]: Tablet: 0.25 mg (2s), 0.5 mg (5s), 1 mg (7s) [DSC]

Tablet: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg

Requip®: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg

Tablet, extended-release:

Requip® XL™: 2 mg, 4 mg, 8 mg

Generic AvailableYes: Excludes combination package, extended-release tablets

ManufacturerSmithKline Beecham Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Requip XL)

4 mg (90): $409.98

Tablets (Requip)

0.25 mg (90): $251.69

0.5 mg (90): $251.69

1 mg (90): $251.69

2 mg (90): $251.69

3 mg (90): $260.43

4 mg (90): $260.43

5 mg (90): $260.43

Tablets (Ropinirole HCl)

0.25 mg (100): $89.90

0.5 mg (100): $89.90

1 mg (100): $89.90

2 mg (100): $89.90

3 mg (100): $89.90

4 mg (100): $89.90

5 mg (100): $65.98

Mechanism of ActionRopinirole has a high relative *in vitro* specificity and full intrinsic activity at the D_2 and D_3 dopamine receptor subtypes, binding with higher affinity to D_3 than to D_2 or D_4 receptor subtypes; relevance of D_3 receptor binding in Parkinson's disease is unknown. Ropinirole has moderate *in vitro* affinity for opioid receptors. Ropinirole and its metabolites have negligible *in vitro* affinity for dopamine D_1, 5-HT_1, 5-HT_2, benzodiazepine, GABA, muscarinic, alpha$_1$-, alpha$_2$-, and beta-adrenoreceptors. Although precise mechanism of action of ropinirole is unknown, it is believed to be due to stimulation of postsynaptic dopamine D_2-type receptors within the caudate putamen in the brain. Ropinirole caused decreases in systolic and diastolic blood pressure at doses >0.25 mg. The mechanism of ropinirole-induced postural hypotension is believed to be due to D_2-mediated blunting of the noradrenergic response to standing and subsequent decrease in peripheral vascular resistance.

Pharmacodynamics/Kinetics

Absorption: Not affected by food

Distribution: V_d: 525 L

Protein binding: 40%

Metabolism: Extensively hepatic via CYP1A2 to inactive metabolites; first-pass effect

Bioavailability: Absolute: 45% to 55%

Half-life elimination: ~6 hours

Time to peak: Immediate release: ~1-2 hours; Extended release: 6-10 hours; T_{max} increased by 2.5-3 hours when drug taken with food

Excretion: Urine (<10% as unchanged drug, 60% as metabolites)

Clearance: Reduced by 15% to 30% in patients >65 years of age

Related Information

- Antiparkinsonian Agents

Pharmacotherapy PearlsIf therapy with a drug known to be a potent inhibitor of CYP1A2 is stopped or started during treatment with ropinirole, adjustment of ropinirole dose may be required. Ropinirole binds to melanin-containing tissues (ie, eyes, skin) in pigmented rats. After a single dose, long-term retention of drug was demonstrated, with a half-life in the eye of 20 days; not known if ropinirole accumulates in these tissues over time.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and increased salivation (normal salivary flow resumes upon discontinuation) and dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Anesthesia and Critical Care Concerns/Other ConsiderationsIf therapy with a drug known to be a potent inhibitor of CYP1A2 is stopped or started during treatment with ropinirole, adjustment of ropinirole dose may be required.

Index TermsRopinirole Hydrochloride

References

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International Brand NamesAdartrel (CH, FR, GB, IE, NO, SE); Parkirop (IN); Repreve (AU); Requip (AR, AT, BE, BG, CH, CN, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HK, HN, HR, HU, IE, IL, IT, KP, MY, NL, NO, NZ, PL, PT, SE, SG)

Ropivacaine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Ropivacaine may be confused with bupivacaine, ropinirole

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (epidural administration) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(roe PIV a kane)

U.S. Brand NamesNaropin®

Canadian Brand NamesNaropin®

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsLocal anesthetic for use in surgery, postoperative pain management, and obstetrical procedures when local or regional anesthesia is needed

Dosing: AdultsDose varies with procedure, onset and depth of anesthesia desired, vascularity of tissues, duration of anesthesia, and condition of patient

Surgical anesthesia:

Lumbar epidural: 15-30 mL of 0.5% to 1% solution

Lumbar epidural block for cesarean section:

20-30 mL dose of 0.5% solution

15-20 mL dose of 0.75% solution

Thoracic epidural block: 5-15 mL dose of 0.5% to 0.75% solution

Major nerve block:

35-50 mL dose of 0.5% solution (175-250 mg)

10-40 mL dose of 0.75% solution (75-300 mg)

Field block: 1-40 mL dose of 0.5% solution (5-200 mg)

Labor pain management: Lumbar epidural: Initial: 10-20 mL 0.2% solution; continuous infusion dose: 6-14 mL/hour of 0.2% solution with incremental injections of 10-15 mL/hour of 0.2% solution

Postoperative pain management:

Lumbar or thoracic epidural: Continuous infusion dose: 6-14 mL/hour of 0.2% solution

Infiltration/minor nerve block:

1-100 mL dose of 0.2% solution

1-40 mL dose of 0.5% solution

Dosing: ElderlyRefer to adult dosing.

Administration: OtherAdministered via local infiltration, epidural block and epidural infusion, or intermittent bolus

StorageStore at 20°C to 25°C (68°F to 77°F). Infusions should be discarded after 24 hours.

ContraindicationsHypersensitivity to ropivacaine, amide-type local anesthetics (eg, bupivacaine, mepivacaine, lidocaine), or any component of the formulation

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS toxicity: Careful and constant monitoring of the patient's state of consciousness should be done following each local anesthetic injection; at such times, restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression, or drowsiness may be early warning signs of CNS toxicity. Treatment is primarily symptomatic and supportive.

- Respiratory arrest: Local anesthetics have been associated with rare occurrences of sudden respiratory arrest.

- Seizures: Convulsions due to systemic toxicity leading to cardiac arrest have also been reported, presumably following unintentional intravascular injection.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with hypotension, hypovolemia, heart block, or cardiovascular disease; may be at greater risk for toxicity.

- Hepatic impairment: Use with caution in patients with hepatic impairment; may be at greater risk for toxicity.

- Neurological disorders: Use with caution in patients with neurological disorders; may be at greater risk for toxicity.

- Psychiatric disorders: Use with caution in patients with psychiatric disorders; may be at greater risk for toxicity.

Concurrent drug therapy issues:

- Type III antiarrhythmics: Use with caution in patients on type III antiarrhythmics (eg, amiodarone); consider ECG monitoring since cardiac effects may be additive.

Special populations:

- Acutely ill patients: Use with caution in acutely ill; may be at greater risk for toxicity.

- Debilitated patients: Use with caution in debilitated patient; may be at greater risk for toxicity.

- Elderly: Use with caution in the elderly: may be at greater risk for toxicity. Cardiovascular adverse events (bradycardia, hypotension) may be age-related (more common in patients >61 years of age).

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Administration: Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided.

- Rapid administration: Ropivacaine is not recommended for use in emergency situations where rapid administration is necessary.

- Trained personnel: Clinicians using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

⇧ Pregnancy Risk FactorB

⇧ Pregnancy ConsiderationsTeratogenic events were not observed in animal studies. When used for epidural block during labor and delivery, systemically absorbed ropivacaine may cross the placenta, resulting in varying degrees of fetal or neonatal effects (eg, CNS or cardiovascular depression). Fetal or neonatal adverse events include fetal bradycardia (12%), neonatal jaundice (8%), low Apgar scores (3%), fetal distress (2%), neonatal respiratory disorder (3%). Maternal hypotension may also result from systemic absorption. In cases of hypotension, position pregnant woman in left lateral decubitus position to prevent aortocaval compression by the gravid uterus. Epidural anesthesia may prolong the second stage of labor.

⇧ LactationExcretion in breast milk unknown/use caution

⇧ Adverse Reactions

>10%:

Cardiovascular: Hypotension (dose-related and age-related: 32% to 69%), bradycardia (6% to 20%)

Gastrointestinal: Nausea (11% to 29%), vomiting (7% to 14%)

Neuromuscular & skeletal: Back pain (7% to 16%)

1% to 10%:

Cardiovascular: Hypertension, tachycardia, chest pain (1% to 5%)

Central nervous system: Fever (3% to 9%), headache (5% to 8%), dizziness (3%), chills (2% to 3%), anxiety (1%), lightheadedness

Dermatologic: Pruritus (1% to 5%)

Endocrine & metabolic: Hypokalemia

Genitourinary: Urinary retention (1% to 5%), urinary tract infection (1% to 5%)

Hematologic: Anemia (6%)

Neuromuscular & skeletal: Paresthesia (2% to 6%), hypoesthesia, rigors, circumoral paresthesia

Renal: Oliguria

Respiratory: Dyspnea

Miscellaneous: Shivering

<1% (Limited to important or life-threatening): Accidental I.V. injection (0.2%), angioedema, allergic reaction, apnea (usually associated with epidural block in head/neck region), bronchospasm, cardiac arrest, cardiovascular collapse, dyskinesia, hallucination, hyperthermia, laryngeal edema, myocardial depression, MI, rash, seizure, syncope, tinnitus, urticaria, ventricular arrhythmia

Metabolism/Transport Effects**Substrate** of CYP1A2 (major), 2B6 (minor), 2D6 (minor), 3A4 (minor; may be major in cases of 1A2 inhibition/deficiency)

Drug Interactions

Ciprofloxacin: May decrease the metabolism of Ropivacaine. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Fluvoxamine: May decrease the metabolism of Ropivacaine. *Risk C: Monitor therapy*

Fospropofol: May increase the serum concentration of Ropivacaine. Specifically, propofol (the active metabolite of fospropofol) is the entity with the potential to interact with ropivacaine. *Risk C: Monitor therapy*

Propofol: May increase the serum concentration of Ropivacaine. *Risk C: Monitor therapy*

Monitoring ParametersHeart rate, blood pressure, ECG monitoring (if used with antiarrhythmics)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion, as hydrochloride:

Naropin®: 2 mg/mL (100 mL, 200 mL)

Injection, solution, as hydrochloride [preservative free]:

Naropin®: 2 mg/mL (10 mL, 20 mL); 5 mg/mL (20 mL, 30 mL); 7.5 mg/mL (20 mL); 10 mg/mL (10 mL, 20 mL)

Generic AvailableNo

ManufacturerAstraZeneca Pharmaceuticals LP

Mechanism of ActionBlocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction

Pharmacodynamics/Kinetics

Onset of action: Anesthesia (route dependent): 3-15 minutes

Duration (dose and route dependent): 3-15 hours

Metabolism: Hepatic, via CYP1A2 to metabolites

Half-life elimination: Epidural: 5-7 hours

Excretion: Urine (86% as metabolites)

Dental Health Professional ConsiderationsNot available with vasoconstrictor (epinephrine) and not available in dental (1.8 mL) carpules

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions (see Dental Comment)

Mental Health: Effects on Mental StatusMay cause anxiety or dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Mental Health CommentConcomitant use with fluvoxamine may produce increased effects of ropivacaine

Anesthesia and Critical Care Concerns/Other ConsiderationsOnly preservative-free solutions should be used for epidural and spinal administration. Although ropivacaine is chemically related to bupivacaine, it is not a racemic mixture (made up of the S-form enantiomer only) and, is less toxic than bupivacaine.

Local anesthetic toxicity: Cardiac arrest: Lipid infusion has been used in animal studies and several human cases (Bupivacaine: Rosenblatt, 2006; Levobupivacaine: Foxall, 2007; Ropivacaine: Litz, 2006) where cardiovascular toxicity, unresponsive to conventional resuscitation, resulted. Additional information is available at http://www.lipidrescue.org. The protocol from the website is: **20% Fat Emulsion:** 1.5 mL/kg administered over 1 minute, followed immediately by an infusion of 0.25 mL/kg/minute. Continue chest compressions (lipid must circulate). Repeat bolus every 3-5 minutes up to 3 mL/kg total dose until circulation restored. Continue infusion until hemodynamic stability is restored. Increase the infusion rate to 0.5 mL/kg/minute if BP declines. A maximum total dose of 8 mL/kg is recommended.

Index TermsRopivacaine Hydrochloride

References

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International Brand NamesNarop (IL, SE); Naropeine (FR, GR, PT); Naropin (AE, AR, AT, AU, BB, BE, BH, BM, BR, BS, BZ, CH, CL, CN, CO, CY, CZ, DE, DK, EG, ES, FI, GB, GY, HK, HN, ID, IE, IL, IQ, IR, JM, JO, KW, LB, LU, LY, MX, NL, NO, OM, PH, PL, QA, SA, SG, SR, SY, TH, TT, VE, YE); Naropina (IT)

Rosiglitazone and Glimepiride

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(roh si GLI ta zone & GLYE me pye ride)

U.S. Brand NamesAvandaryl®

Pharmacologic CategoryAntidiabetic Agent, Sulfonylurea; Antidiabetic Agent, Thiazolidinedione

Use: Labeled IndicationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as an adjunct to diet and exercise

Dosing: Adults**Type 2 diabetes mellitus:** Oral: Initial: Rosiglitazone 4 mg and glimepiride 1 mg once daily **or** rosiglitazone 4 mg and glimepiride 2 mg once daily (for patients previously treated with sulfonylurea or thiazolidinedione monotherapy)

Patients switching from combination rosiglitazone and glimepiride as separate tablets: Use current dose.

Titration:

Dose adjustment in patients previously on sulfonylurea monotherapy: May take 2 weeks to observe decreased blood glucose and 2-3 months to see full effects of rosiglitazone component. If not adequately controlled after 8-12 weeks, increase daily dose of rosiglitazone component.

Dose adjustment in patients previously on thiazolidinedione monotherapy: If not adequately controlled after 1-2 weeks, increase daily dose of glimepiride component in ≤2 mg increments in 1-2 week intervals.

Maximum dose:

U.S. labeling: Rosiglitazone 8 mg and glimepiride 4 mg once daily

Canadian labeling: Rosiglitazone 4 mg and glimepiride 4 mg once daily

Dosing: Elderly Rosiglitazone 4 mg and glimepiride 1 mg once daily. Carefully titrate dose.

Dosing: Renal ImpairmentRosiglitazone 4 mg and glimepiride 1 mg once daily. Carefully titrate dose.

Dosing: Hepatic ImpairmentRosiglitazone 4 mg and glimepiride 1 mg once daily. Carefully titrate dose.

ALT ≤2.5 times ULN: Use with caution.

ALT >2.5 times ULN: Do not initiate therapy.

ALT >3 times ULN or jaundice: Discontinue.

Administration: OralShould be administered with the first meal of the day.

Dietary ConsiderationsAdminister with the first main meal of the day. Dietary modification based on ADA recommendations is a part of therapy. Decreases blood glucose concentration. Hypoglycemia may occur. Must be able to recognize symptoms of hypoglycemia (palpitations, sweaty palms, lightheadedness).

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsNYHA Class III/IV heart failure (initiation of therapy)

Canadian labeling: Additional contraindications (not in U.S. labeling): Hypersensitivity to rosiglitazone, glimepiride, other sulfonamides, or any component of the formulation; any stage of heart failure (eg, NYHA Class I, II, III, IV); serious hepatic impairment; diabetic ketoacidosis (with or without coma); pregnancy

Warnings/Precautions

Boxed warnings:

- Heart failure/cardiac effects: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS) have not supported an association.

- Fractures: Increased incidence of bone fractures in females treated with rosiglitazone observed during analysis of long-term trial;

majority of fractures occurred in the upper arm, hand and foot (differing from the hip or spine fractures usually associated with postmenopausal osteoporosis). Consider risk of fracture prior to initiation and during use.

- Heart failure/cardiac effects: **[U.S. Boxed Warning]: Thiazolidinediones, including rosiglitazone, may cause or exacerbate congestive heart failure;** closely monitor for signs and symptoms of congestive heart failure (eg, rapid weight gain, dyspnea, edema), particularly after initiation or dose increases. Not recommended for use in any patient with symptomatic heart failure. In the U.S., initiation of therapy is contraindicated in patients with NYHA class III or IV heart failure; in Canada, use is contraindicated in patients with any stage of heart failure (NYHA I, II, III, IV). Use with caution in patients with edema; may increase plasma volume and/or cause fluid retention. A higher frequency of cardiovascular events has been noted in patients with NYHA class I or II heart failure treated with rosiglitazone. Use may also be associated with an increased risk of angina and MI. Use with caution in patients at risk for cardiovascular events and monitor closely. Discontinue if any deterioration in cardiac status occurs.

- Hematologic effects: Rosiglitazone may decrease hemoglobin, hematocrit, and/or WBC count (slight); effects may be related to increased plasma volume and/or dose-related. Use with caution in patients with anemia; may reduce hemoglobin and hematocrit.

- Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when ethanol is ingested, or when more than one glucose-lowering drug is used. It is also more likely in elderly patients, malnourished patients and in patients with impaired renal or hepatic function; use with caution.

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). A risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Use in patients with sulfonamide allergy is specifically contraindicated in Canadian labeling.

- Weight gain: Dose-related weight gain observed with rosiglitazone use; mechanism unknown but likely associated with fluid retention and fat accumulation.

Disease-related concerns:

- Diabetes, type 1: Mechanism of rosiglitazone requires the presence of insulin; therefore, use in type 1 diabetes (insulin dependent, IDDM) or diabetic ketoacidosis is not recommended.

- Hepatic impairment: Use rosiglitazone with caution in patients with elevated transaminases (AST or ALT); do not initiate in patients with active liver disease of ALT >2.5 times the upper limit of normal (ULN) at baseline; evaluate patients with ALT ≤2.5 times ULN at baseline or during therapy for cause of enzyme elevation. During therapy, if ALT >3 times ULN, reevaluate levels promptly and discontinue if elevation persists or if jaundice occurs at any time during use. Idiosyncratic hepatotoxicity has been reported with another thiazolidinedione agent (troglitazone); avoid use in patients who previously experienced jaundice during troglitazone therapy.

- Macular edema/diabetic retinopathy: Use rosiglitazone with caution in patients with pre-existing macular edema or diabetic retinopathy; postmarketing reports of new-onset or worsening diabetic macular edema with decreased visual acuity has been reported.

- Stress-related states: It may be necessary to discontinue therapy and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Concurrent drug therapy issues:

- Hypoglycemic agents: Combination therapy with other hypoglycemic agents may increase risk for hypoglycemic events; dose reduction with the concomitant agent may be warranted.

- Insulin: Avoid use of rosiglitazone with insulin due to an increased risk of edema, congestive heart failure, and myocardial ischemic events.

- Nitrates: Concomitant use of rosiglitazone with nitrates is not recommended. An increased risk of myocardial ischemia has been observed in nitrate users versus non-nitrate users in clinical studies.

- Metformin/sulfonylureas (Canadian labeling; not in U.S. labeling): Rosiglitazone may be added to metformin or a sulfonylurea (if metformin is contraindicated or not tolerated) if glycemic control is inadequate. The use of triple therapy (rosiglitazone in combination with metformin and a sulfonylurea) is not indicated due to increased risks of congestive heart failure and fluid retention.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Premenopausal/anovulatory females: Use rosiglitazone with caution in premenopausal, anovulatory women; may result in a resumption of ovulation, increasing the risk of pregnancy.

Geriatric ConsiderationsRapid and prolonged hypoglycemia (>12 hours) despite hypertonic glucose injections have been reported; age, hepatic, and renal impairment are independent risk factors for hypoglycemia; dosage titration should be made at weekly intervals. How "tightly" a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar of <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well they recognize hypoglycemic or hyperglycemic symptoms, and how to respond to them and their other disease states. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with this combination; therefore, rosiglitazone/glimepiride is classified as pregnancy category C. See individual agents.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsSee individual agents.

Pregnancy & Lactation, In-Depth

- Glimepiride in Pregnancy & Lactation
- Rosiglitazone in Pregnancy & Lactation

Adverse ReactionsPercentages below refer to combination Avandaryl®. Also see individual agents.

1% to 10%:

Cardiovascular: Edema (3%), hypertension (2% to 3%)

Central nervous system: Headache (3% to 6%)

Endocrine & metabolic: Hypoglycemia (4% to 6%)

Respiratory: Nasopharyngitis (4% to 5%)

<1%, postmarketing, and/or case reports: CHF, weight gain

Metabolism/Transport Effects

Rosiglitazone: **Substrate** of CYP2C8 (major), 2C9 (minor); **Inhibits** CYP2C8 (moderate), 2C9 (weak), 2C19 (weak), 2D6 (weak)

Glimepiride: **Substrate** of CYP2C9 (major)

Drug Interactions

Alcohol (Ethyl): Sulfonylureas may enhance the adverse/toxic effect of Alcohol (Ethyl). A flushing reaction may occur. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Antidiabetic Agents (Thiazolidinedione). *Risk D: Consider therapy modification*

Chloramphenicol: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Cyclic Antidepressants: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonylureas may increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP2C8 Inducers (Highly Effective): May increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Moderate): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Strong): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Fibric Acid Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Fluconazole: May increase the serum concentration of Sulfonylureas. *Risk C: Monitor therapy*

Gemfibrozil: May decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Insulin: May enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pregabalin: May enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Salicylates: May enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. **Exceptions:** Sulfacetamide. *Risk C: Monitor therapy*

Trimethoprim: May decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Vasodilators (Organic Nitrates): May enhance the adverse/toxic effect of Rosiglitazone. Specifically, a greater risk of myocardial ischemia was reported for users of this combination in a meta-analysis. Management: Consider alternatives to this combination when possible. Rosiglitazone prescribing information states that the combination of rosiglitazone and a nitrate is not recommended. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Caution with ethanol (may cause hypoglycemia).

Herb/Nutraceutical: Caution with alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, stinging nettle (may cause hypoglycemia).

Monitoring ParametersHemoglobin A_{1c}, fasting serum glucose; signs and symptoms of fluid retention or heart failure, blood pressure; liver enzymes (prior to initiation of therapy, then periodically thereafter); ophthalmic exams. Evaluate patients with ALT ≤2.5 times ULN at baseline or during therapy for cause of enzyme elevation. Patients with an elevation in ALT >3 times ULN should be rechecked as soon as possible. If the ALT levels remain >3 times ULN, therapy should be discontinued. Signs and symptoms of hypoglycemia (fatigue, excessive hunger, profuse sweating, numbness of extremities).

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Nursing: Physical Assessment/Monitoring

See individual agents.

Monitoring: Lab TestsHemoglobin A_{1c}, fasting serum glucose; liver enzymes (prior to initiation of therapy, then periodically thereafter). Evaluate patients with ALT ≤2.5 times ULN at baseline or during therapy for cause of enzyme elevation. Patients with an elevation in ALT >3 times ULN should be rechecked as soon as possible. If the ALT levels remain >3 times ULN, therapy should be discontinued.

Patient Education

See individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Avandaryl® 4 mg/1 mg: Rosiglitazone maleate 4 mg and glimepiride 1 mg

Avandaryl® 4 mg/2 mg: Rosiglitazone maleate 4 mg and glimepiride 2 mg

Avandaryl® 4 mg/4 mg: Rosiglitazone maleate 4 mg and glimepiride 4 mg

Avandaryl® 8 mg/2 mg: Rosiglitazone maleate 8 mg and glimepiride 2 mg

Avandaryl® 8 mg/4 mg: Rosiglitazone maleate 8 mg and glimepiride 4 mg

Generic AvailableNo

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Tablets (Avandaryl)

4-1 mg (30): $130.43

4-2 mg (30): $131.59

4-4 mg (30): $130.43

Mechanism of Action

Rosiglitazone is a thiazolidinedione antidiabetic agent that lowers blood glucose by improving target cell response to insulin, without increasing pancreatic insulin secretion. It has a mechanism of action that is dependent on the presence of insulin for activity.

Glimepiride stimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites.

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Glimepiride
- Rosiglitazone

Dental Health: Effects on Dental TreatmentDependent patients with diabetes (noninsulin dependent, type 2) should be appointed for dental treatment in the morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause headache and fatigue

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine. Phenothiazines, atypical antipsychotics, and TCAs may antagonize glimepiride hypoglycemic effects; MAO inhibitors and TCAs may enhance hypoglycemic effects. Weight gain is common; caution with atypical antipsychotics, valproic acid, and lithium.

Index TermsGlimepiride and Rosiglitazone Maleate

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Singh S, Loke YK, and Furberg CD, “Long-Term Risk of Cardiovascular Events With Rosiglitazone,” *JAMA*, 2007, 298(10):1189-95.[PubMed 17848653]

International Brand NamesAvaglim (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Avandaryl (ID, PH); Enselin-2G (IN); Grexa Plus (PE)

Rosiglitazone and Metformin

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Avandamet® may be confused with Anzemet®

Pronunciation(roh si GLI ta zone & met FOR min)

U.S. Brand NamesAvandamet®

Canadian Brand NamesAvandamet®

Pharmacologic CategoryAntidiabetic Agent, Biguanide; Antidiabetic Agent, Thiazolidinedione

Use: Labeled IndicationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as an adjunct to diet and exercise in patients where dual rosiglitazone and metformin therapy is appropriate

Dosing: Adults**Type 2 diabetes mellitus:** Oral:

First-line therapy (drug-naive patients): Initial: Rosiglitazone 2 mg and metformin 500 mg once or twice daily; may increase by 2 mg/500 mg per day after 4 weeks to a maximum of 8 mg/2000 mg per day.

Second-line therapy:

Patients inadequately controlled on metformin alone: Initial dose: Rosiglitazone 4 mg/day plus current dose of metformin

Patients inadequately controlled on rosiglitazone alone: Initial dose: Metformin 1000 mg/day plus current dose of rosiglitazone

Note: When switching from combination rosiglitazone and metformin as separate tablets: Use current dose

Dose adjustment: Doses may be increased as increments of rosiglitazone 4 mg and/or metformin 500 mg, up to the maximum dose; doses should be titrated gradually.

After a change in the metformin dosage, titration can be done after 1-2 weeks

After a change in the rosiglitazone dosage, titration can be done after 8-12 weeks

Maximum dose: Rosiglitazone 8 mg/metformin 2000 mg daily

Dosing: ElderlyThe initial and maintenance dosing should be conservative, due to the potential for decreased renal function (monitor). Generally, elderly patients should not be titrated to the maximum. Do not use in patients ≥80 years unless normal renal function has been established.

Dosing: Renal ImpairmentDo not use with renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females or abnormal clearance).

Dosing: Hepatic ImpairmentDo not initiate therapy with active liver disease or ALT >2.5 times the upper limit of normal.

Administration: OralAdminister with meals. Patients who are NPO may need to have their dose held to avoid hypoglycemia.

Dietary ConsiderationsShould be taken with meals. Avoid ethanol. Dietary modification based on ADA recommendations is a part of therapy. Monitor for signs and symptoms of vitamin B_{12} and/or folic acid deficiency; supplementation may be required.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsNYHA Class III/IV heart failure (initiation of therapy); renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females, or abnormal creatinine clearance which may also result from conditions such as cardiovascular collapse, acute myocardial infarction, and septicemia); acute or chronic metabolic acidosis, including diabetic ketoacidosis (with or without coma); concurrent iodinated radiocontrast adminstration (manufacturer recommends temporary discontinuation of metformin)

Canadian labeling: Additional contraindications (not in U.S. labeling): Hypersensitivity to rosiglitazone, metformin, or any component of the formulation; any stage of heart failure (eg, NYHA Class I, II, III, or IV); history of lactic acidosis, regardless of precipitating factors; serious hepatic impairment; pregnancy

Allergy Considerations

- Biguanide Allergy
- Thiazolidinedione Allergy

Warnings/Precautions

Boxed warnings:

- Heart failure: See "Concerns related to adverse effects" below.

- Lactic acidosis: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Fractures: Increased incidence of bone fractures in females treated with rosiglitazone observed during analysis of long-term trial; majority of fractures occurred in the upper arm, hand and foot (differing from the hip or spine fractures usually associated with postmenopausal osteoporosis). Consider risk of fracture prior to initiation and during use.

- Heart failure/cardiac effects: **[U.S. Boxed Warning]: Thiazolidinediones, including rosiglitazone, may cause or exacerbate congestive heart failure;** closely monitor for signs and symptoms of congestive heart failure (eg, rapid weight gain, dyspnea, edema), particularly after initiation or dose increases. Not recommended for use in any patient with symptomatic heart failure. In the U.S., initiation of therapy is contraindicated in patients with NYHA class III or IV heart failure; in Canada use is contraindicated in patients with any stage of heart failure (NYHA I, II, III, IV). Use with caution in patients with edema; may increase plasma volume and/or cause fluid retention. A higher frequency of cardiovascular events has been noted in patients with NYHA class I or II heart failure treated with rosiglitazone. In addition, metformin should be used with caution in patients with heart failure requiring pharmacologic management, particularly in unstable or acute heart failure due to risk of lactic acidosis secondary to hypoperfusion. Rosiglitazone may also be associated with an increased risk of angina and MI. Use with caution in patients at risk for cardiovascular events and monitor closely. Discontinue if any deterioration in cardiac status occurs.

- Hematologic effects: Rosiglitazone may decrease hemoglobin, hematocrit, and/or WBC count (slight); effects may be related to increased plasma volume and/or dose-related. Use rosiglitazone with caution in patients with anemia or depressed leukocyte counts (may reduce hemoglobin, hematocrit, and/or WBC). Metformin may impair vitamin B_{12} absorption; monitor for anemia.

- Lactic acidosis: **[U.S. Boxed Warning]: Lactic acidosis is a rare, but potentially severe consequence of therapy with metformin.** Lactic acidosis should be suspected in any patient with diabetes receiving metformin with evidence of acidosis but without evidence of ketoacidosis. Discontinue metformin in clinical situations predisposing to hypoxemia, including conditions such as cardiovascular collapse, respiratory failure, acute myocardial infarction, acute congestive heart failure, and septicemia. The risk of accumulation and lactic acidosis increases with the degree of impairment of renal function.

- Weight gain: Dose-related weight gain observed with use; mechanism unknown but likely associated with fluid retention and fat accumulation.

Disease-related concerns:

- Diabetes, type 1: Mechanism of rosiglitazone requires the presence of insulin; therefore, use in type 1 diabetes (insulin dependent, IDDM) or diabetic ketoacidosis is not recommended.

- Hepatic impairment: Avoid rosiglitazone and metformin use in patients with impaired liver function due to potential for lactic acidosis with metformin. Use rosiglitazone with caution in patients with elevated transaminases (AST or ALT); do not initiate in patients with active liver disease of ALT >2.5 times the upper limit of normal (ULN) at baseline; evaluate patients with ALT ≤2.5 times ULN at baseline or during therapy for cause of enzyme elevation. During therapy, if ALT >3 times ULN, reevaluate levels promptly and discontinue rosiglitazone if elevation persists or if jaundice occurs at any time during use. Idiosyncratic hepatotoxicity has been reported with another thiazolidinedione agent (troglitazone); avoid use in patients who previously experienced jaundice during troglitazone therapy.

- Macular edema/diabetic retinopathy: Use rosiglitazone with caution in patients with pre-existing macular edema or diabetic retinopathy; postmarketing reports of new-onset or worsening diabetic macular edema with decreased visual acuity has been reported.

- Renal impairment: Metformin is substantially excreted by the kidney; patients with renal function below the limit of normal for their age should not receive therapy. Use of concomitant medications that may affect renal function (ie, affect tubular secretion) may also affect metformin disposition. Metformin should be withheld in patients with dehydration and/or prerenal azotemia.

- Stress-related states: It may be necessary to discontinue metformin and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Concurrent drug therapy issues:

- Hypoglycemic agents: Combination therapy with other hypoglycemic agents may increase risk for hypoglycemic events; dose reduction with the concomitant agent may be warranted.

- Insulin: Avoid use of rosiglitazone with insulin due to an increased risk of edema, congestive heart failure, and myocardial ischemic events.

- Nitrates: Concomitant use of rosiglitazone with nitrates is not recommended. An increased risk of myocardial ischemia has been observed in nitrate users versus non-nitrate users in clinical studies.

- Metformin/sulfonylureas (Canadian labeling; not in U.S. labeling): Rosiglitazone may be added to metformin or a sulfonylurea (if metformin is contraindicated or not tolerated) if glycemic control is inadequate. The use of triple therapy (rosiglitazone in combination with metformin and a sulfonylurea) is not indicated due to increased risks of congestive heart failure and fluid retention.

Special populations:

- Elderly: Metformin should not be initiated in patients ≥80 years of age unless normal renal function is confirmed.

- Pediatrics: Safety and efficacy have not been established in children.

- Premenopausal/anovulatory females: Use rosiglitazone with caution in premenopausal, anovulatory women; may result in a resumption of ovulation, increasing the risk of pregnancy.

Other warnings/precautions:

- Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism.
- Iodinated contrast: Metformin therapy should be temporarily discontinued prior to or at the time of intravascular administration of iodinated contrast media (potential for acute alteration in renal function). Metformin should be withheld for 48 hours after the radiologic study and restarted only after renal function has been confirmed as normal.
- Surgical procedures: Metformin therapy should be suspended 2 days prior to any surgical procedures (resume only after normal intake resumed and normal renal function is verified).

Geriatric ConsiderationsIntensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies were not conducted with this combination; therefore, rosiglitazone/metformin is classified as pregnancy category C. Refer to individual agents.

Lactation

Rosiglitazone: Excretion in breast milk unknown/not recommended

Metformin: Enters breast milk/not recommended

Breast-Feeding ConsiderationsRefer to individual agents.

Pregnancy & Lactation, In-Depth

- MetFORMIN in Pregnancy & Lactation
- Rosiglitazone in Pregnancy & Lactation

Adverse ReactionsAlso see individual agents. Percentages of adverse effects as reported with the combination product.

>10%:

Central nervous system: Headache (7% to 11%)

Gastrointestinal: Nausea/vomiting (16%), diarrhea (13% to 14%)

Respiratory: Upper respiratory tract infection (9% to 16%)

1% to 10%:

Cardiovascular: Edema (6%)

Central nervous system: Dizziness (8%), fatigue (6%)

Endocrine & metabolic: Hypoglycemia (3%)

Gastrointestinal: Dyspepsia (10%), abdominal pain (5%), loose stools (5%), constipation (5%)

Hematologic: Anemia (4% to 7%)

Neuromuscular & skeletal: Arthralgia (5%), back pain (5%)

Respiratory: Sinusitis (6%), nasopharyngitis (6%)

Miscellaneous: Injury (8%), viral infection (5%), flu-like syndrome (1%)

Metabolism/Transport EffectsRosiglitazone: **Substrate** of CYP2C8 (major), 2C9 (minor); **Inhibits** CYP2C8 (moderate), 2C9 (weak), 2C19 (weak), 2D6 (weak)

Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Antidiabetic Agents (Thiazolidinedione). *Risk D: Consider therapy modification*

Cephalexin: May increase the serum concentration of MetFORMIN. *Risk C: Monitor therapy*

Cimetidine: May decrease the excretion of MetFORMIN. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

CYP2C8 Inducers (Highly Effective): May increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Moderate): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Strong): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

Gemfibrozil: May decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Insulin: May enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Iodinated Contrast Agents: May enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pregabalin: May enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Trimethoprim: May decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Vasodilators (Organic Nitrates): May enhance the adverse/toxic effect of Rosiglitazone. Specifically, a greater risk of myocardial ischemia was reported for users of this combination in a meta-analysis. Management: Consider alternatives to this combination when possible. Rosiglitazone prescribing information states that the combination of rosiglitazone and a nitrate is not recommended. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsSee individual agents.

Monitoring ParametersHemoglobin A_{1c}; signs and symptoms of fluid retention or heart failure; renal function (baseline and every 6 months); blood pressure; liver enzymes (prior to initiation of therapy, then periodically thereafter). Evaluate patients with ALT ≤2.5 times ULN at baseline or during therapy for cause of enzyme elevation. Patients with an elevation in ALT >3 times ULN should be rechecked as soon as possible. If the ALT levels remain >3 times ULN, therapy with rosiglitazone should be discontinued. Serum glucose, CBC; vitamin B_{12} and folate if anemia is present. Regular ophthalmic examinations

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsSee individual components listed in Related Information.

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Avandamet®: 2/500: Rosiglitazone 2 mg and metformin hydrochloride 500 mg

Avandamet®: 4/500: Rosiglitazone 4 mg and metformin hydrochloride 500 mg

Avandamet®: 2/1000: Rosiglitazone 2 mg and metformin hydrochloride 1000 mg

Avandamet®: 4/1000: Rosiglitazone 4 mg and metformin hydrochloride 1000 mg

Generic AvailableNo

ManufacturerGlaxoSmithKline Laboratories

Pricing: U.S. (www.drugstore.com)

Tablets (Avandamet)

1-500 mg (60): $67.85

2-500 mg (60): $146.21

2-1000 mg (60): $135.76

4-500 mg (60): $236.02

4-1000 mg (60): $236.02

Mechanism of ActionRosiglitazone is a thiazolidinedione antidiabetic agent that lowers blood glucose by improving target cell response to insulin, without increasing pancreatic insulin secretion. It has a mechanism of action that is dependent on the presence of insulin for activity. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity (increases peripheral glucose uptake and utilization).

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentDependent diabetics (noninsulin dependent, type 2) should be appointed for dental treatment in the morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue

Mental Health: Effects on Psychiatric TreatmentMay cause weight gain; concurrent use with psychotropics may produce additive weight gain

Index TermsMetformin and Rosiglitazone; Metformin Hydrochloride and Rosiglitazone Maleate; Rosiglitazone Maleate and Metformin Hydrochloride

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Singh S, Loke YK, and Furberg CD, “Long-Term Risk of Cardiovascular Events With Rosiglitazone,” *JAMA*, 2007, 298(10):1189-95.[PubMed 17848653]

International Brand NamesAvandamet (AR, AT, AU, BB, BE, BG, BM, BR, BS, BZ, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, FI, FR, GB, GR, GT, GY, HK, HN, ID, IE, IL, IT, JM, KP, MY, NI, NL, NO, PA, PE, PH, PT, RU, SE, SG, SR, SV, TH, TR, TT, TW, UY, VE); Enselin 2M (IN); Interac (PY)

Rosiglitazone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Avandia® may be confused with Avalide®, Coumadin®, Prandin®

International issues:

Avandia® may be confused with Avanza® which is a brand name for mirtazapine in Australia

Pronunciation(roh si GLI ta zone)

U.S. Brand NamesAvandia®

Canadian Brand NamesAvandia®

Pharmacologic CategoryAntidiabetic Agent, Thiazolidinedione

Use: Labeled IndicationsType 2 diabetes mellitus (noninsulin dependent, NIDDM):

Monotherapy: Improve glycemic control as an adjunct to diet and exercise

Note: Canadian labeling approves use as monotherapy only when metformin is contraindicated or not tolerated.

Combination therapy: **Note:** Use when diet, exercise, and a single agent do not result in adequate glycemic control.

U.S. labeling: In combination with a sulfonylurea, metformin, or sulfonylurea plus metformin

Canadian labeling: In combination with metformin; in combination with a sulfonylurea only when metformin use is contraindicated or not tolerated

Use: Unlabeled/InvestigationalPolycystic ovary syndrome (PCOS)

Dosing: Adults**Type 2 diabetes:** Oral: **Note:** All patients should be initiated at the lowest recommended dose.

Monotherapy: Initial: 4 mg daily as a single daily dose or in divided doses twice daily. If response is inadequate after 8-12 weeks of treatment, the dosage may be increased to 8 mg daily as a single daily dose or in divided doses twice daily. In clinical trials, the 4 mg twice-daily regimen resulted in the greatest reduction in fasting plasma glucose and Hb A_{1c}.

Combination therapy: When adding rosiglitazone to existing therapy, continue current dose(s) of previous agents:

U.S. labeling: With sulfonylureas or metformin (or sulfonylurea plus metformin): Initial: 4 mg daily as a single daily dose or in divided doses twice daily. If response is inadequate after 8-12 weeks of treatment, the dosage may be increased to 8 mg daily as a single daily dose or in divided doses twice daily. Reduce dose of sulfonylurea if hypoglycemia occurs. It is unlikely that the dose of metformin will need to be reduced due to hypoglycemia.

Canadian labeling:

With metformin: Initial: 4 mg daily as a single daily dose or in divided doses twice daily. If response is inadequate after 8-12 weeks of treatment, the dosage may be increased to 8 mg daily as a single daily dose or in divided doses twice daily.

With a sulfonylurea: 4 mg daily as a single daily dose or in divided doses twice daily. Dose should not exceed 4 mg daily when using in combination with a sulfonylurea. Reduce dose of sulfonylurea if hypoglycemia occurs.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentClearance is significantly lower in hepatic impairment. Therapy should not be initiated if the patient exhibits active liver disease or increased transaminases (ALT >2.5 times the upper limit of normal) at baseline.

Dietary ConsiderationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM) should include diet control. May be taken without regard to meals.

StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

Contraindications

U.S. labeling: NYHA Class III/IV heart failure (initiation of therapy)

Canadian labeling: Hypersensitivity to rosiglitazone or any component of the formulation; any stage of heart failure (eg, NYHA Class I, II, III, IV); serious hepatic impairment; pregnancy

Allergy Considerations

- Thiazolidinedione Allergy

Warnings/Precautions

Boxed warnings:

- Heart failure/cardiac effects: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Fractures: Increased incidence of bone fractures in females treated with rosiglitazone observed during analysis of long-term trial; majority of fractures occurred in the upper arm, hand and foot (differing from the hip or spine fractures usually associated with postmenopausal osteoporosis). Consider risk of fracture prior to initiation and during use.

- Heart failure/cardiac effects: **[U.S. Boxed Warning]: Thiazolidinediones, including rosiglitazone, may cause or exacerbate congestive heart failure;** closely monitor for signs and symptoms of congestive heart failure (eg, rapid weight gain, dyspnea, edema), particularly after initiation or dose increases. Not recommended for use in any patient with symptomatic heart failure. In the U.S., initiation of therapy is contraindicated in patients with NYHA class III or IV heart failure; in Canada, use is contraindicated in patients with any stage of heart failure (NYHA I, II, III, IV). Use with caution in patients with edema; may increase plasma volume and/or cause fluid retention. A higher frequency of cardiovascular events has been noted in patients with NYHA class I or II heart failure treated with rosiglitazone. Use may also be associated with an increased risk of angina and MI. Use with caution in patients at risk for cardiovascular events and monitor closely. Discontinue if any deterioration in cardiac status occurs.

- Hematologic effects: May decrease hemoglobin, hematocrit, and/or WBC count (slight); effects may be related to increased plasma volume and/or dose-related.

- Weight gain: Dose-related weight gain observed with use; mechanism unknown but likely associated with fluid retention and fat accumulation.

Disease-related concerns:

- Anemia: Use with caution in patients with anemia; may reduce hemoglobin and hematocrit.

- Diabetes, type 1: Mechanism requires the presence of insulin; therefore, use in type 1 diabetes (insulin dependent, IDDM) or diabetic ketoacidosis is not recommended.

- Hepatic impairment: Use with caution in patients with elevated transaminases (AST or ALT); do not initiate in patients with active liver disease or ALT >2.5 times the upper limit of normal (ULN) at baseline; evaluate patients with ALT ≤2.5 times ULN at baseline or during therapy for cause of enzyme elevation; during therapy, if ALT >3 times ULN, reevaluate levels promptly and discontinue if elevation persists or if jaundice occurs at any time during use. Idiosyncratic hepatotoxicity has been reported with another thiazolidinedione agent (troglitazone); avoid use in patients who previously experienced jaundice during troglitazone therapy.

- Macular edema/diabetic retinopathy: Use with caution in patients with pre-existing macular edema or diabetic retinopathy; postmarketing events of new-onset or worsening diabetic macular edema with decreased visual acuity have been reported.

Concurrent drug therapy issues:

- Hypoglycemic agents: Combination therapy with other hypoglycemic agents may increase risk for hypoglycemic events; dose reduction with the concomitant agent may be warranted.

- Insulin: Avoid use of rosiglitazone with insulin due to an increased risk of edema, congestive heart failure, and myocardial ischemic events.

- Nitrates: Concomitant use of rosiglitazone with nitrates is not recommended. An increased risk of myocardial ischemia has been observed in nitrate users versus non-nitrate users in clinical studies.

- Metformin/sulfonylureas (Canadian labeling; not in U.S. labeling): Rosiglitazone may be added to metformin or a sulfonylurea (if metformin is contraindicated or not tolerated) if glycemic control is inadequate. The use of triple therapy (rosiglitazone in combination with metformin and a sulfonylurea) is not indicated due to increased risks of congestive heart failure and fluid retention.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Premenopausal/anovulatory females: Use with caution in premenopausal, anovulatory women; may result in a resumption of ovulation, increasing the risk of pregnancy.

Geriatric ConsiderationsNo dosage adjustment required. Due to the increased incidence of fractures in the hand, upper arm, and foot, rosiglitazone's benefits should be weighed against its risks in patients with a history of fractures, low bone mineral density, or falling. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsRosiglitazone is classified as pregnancy category C due to adverse effects observed in initial animal studies. Rosiglitazone has been found to cross the placenta during the first trimester of pregnancy. Inadvertent use early in pregnancy has not shown adverse fetal effects although in the majority of cases, the medication was stopped as soon as pregnancy was detected. Thiazolidinediones may cause ovulation in anovulatory premenopausal women, increasing the risk of pregnancy; adequate contraception in premenopausal women is recommended. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if rosiglitazone is excreted in breast milk. Breast-feeding is not recommended by the manufacturer.

Pregnancy & Lactation, In-Depth

- Rosiglitazone in Pregnancy & Lactation

Adverse Reactions**Note:** The rate of certain adverse reactions (eg, anemia, edema, hypoglycemia) may be higher with some combination therapies.

>10%: Endocrine & metabolic: HDL-cholesterol increased, LDL-cholesterol increased, total cholesterol increased, weight gain

1% to 10%:

Cardiovascular: Edema (5%), hypertension (4%); heart failure/CHF (up to 2% to 3% in patients receiving insulin; incidence likely higher in patients with pre-existing HF; myocardial ischemia (3%; incidence likely higher in patients with preexisting CAD)

Central nervous system: Headache (6%)

Endocrine & metabolic: Hypoglycemia (1% to 3%; combination therapy with insulin: 12% to 14%)

Gastrointestinal: Diarrhea (3%)

Hematologic: Anemia (2%)

Neuromuscular & skeletal: Fractures (up to 9%; incidence greater in females; usually upper arm, hand, or foot), arthralgia (5%), back pain (4% to 5%)

Respiratory: Upper respiratory tract infection (4% to 10%), nasopharyngitis (6%)

Miscellaneous: Injury (8%)

<1%, postmarketing, and/or case reports: Anaphylaxis, angina, angioedema, bilirubin increased, blurred vision, cardiac arrest, dyspnea, coronary artery disease, coronary thrombosis, hematocrit decreased, hemoglobin decreased, hepatic failure, hepatitis, HDL-cholesterol decreased, jaundice (reversible), macular edema, MI, pleural effusion, pruritus, pulmonary edema, rash, Stevens-Johnson syndrome, thrombocytopenia, transaminases increased, urticaria, visual acuity decreased, weight gain (rapid, excessive; usually due to fluid accumulation), WBC count decreased

Note: Rare cases of hepatocellular injury have been reported in men in their 60s within 2-3 weeks after initiation of rosiglitazone therapy. LFTs in these patients revealed severe hepatocellular injury which responded with rapid improvement of liver function and resolution of symptoms upon discontinuation of rosiglitazone. Patients were also receiving other potentially hepatotoxic medications (Al-Salman, 2000; Freid, 2000).

Metabolism/Transport Effects**Substrate** of CYP2C8 (major), 2C9 (minor); **Inhibits** CYP2C8 (moderate), 2C9 (weak), 2C19 (weak), 2D6 (weak)

Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Antidiabetic Agents (Thiazolidinedione). *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

CYP2C8 Inducers (Highly Effective): May increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Moderate): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Strong): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

Gemfibrozil: May decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Insulin: May enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pregabalin: May enhance the fluid-retaining effect of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Trimethoprim: May decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

Vasodilators (Organic Nitrates): May enhance the adverse/toxic effect of Rosiglitazone. Specifically, a greater risk of myocardial ischemia was reported for users of this combination in a meta-analysis. Management: Consider alternatives to this combination when possible. Rosiglitazone prescribing information states that the combination of rosiglitazone and a nitrate is not recommended. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may cause hypoglycemia).

Food: Peak concentrations are lower by 28% and delayed when administered with food, but these effects are not believed to be clinically significant.

Herb/Nutraceutical: Avoid alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, stinging nettle (may cause hypoglycemia).

Monitoring ParametersHemoglobin A_{1c}, fasting serum glucose; signs and symptoms of fluid retention or heart failure; liver enzymes (prior to initiation of therapy, then periodically thereafter); ophthalmic exams. Evaluate patients with ALT ≤2.5 times ULN at baseline or during therapy for cause of enzyme elevation. Patients with an elevation in ALT >3 times ULN should be rechecked as soon as possible. If the ALT levels remain >3 times ULN, therapy with rosiglitazone should be discontinued.

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Nursing: Physical Assessment/MonitoringMonitor laboratory results closely. Assess other prescriptions, OTC medications, or herbal products patient may be taking. Assess for signs of fluid retention and congestive heart failure. Monitor weight. Monitor response to therapy closely until response is stable. Advise women using oral contraceptives about need for alternative method of contraception. Assess knowledge/teach risks of hyper-/hypoglycemia, its symptoms, treatment, and predisposing conditions. Refer patient to a diabetic educator, if possible. Teach appropriate use of medication, interventions to reduce side effects, and adverse reactions to report.

Monitoring: Lab TestsHemoglobin A_{1c}, serum glucose; liver enzymes (prior to initiation of therapy, then periodically thereafter). Evaluate patients with ALT ≤2.5 times ULN at baseline or during therapy for cause of enzyme elevation. Patients with an elevation in ALT >3 times ULN should be rechecked as soon as possible. If the ALT levels remain >3 times ULN, therapy with rosiglitazone should be discontinued.

Patient EducationMay be taken without regard to meals. Follow directions of prescriber. If dose is missed at the usual meal, take it with next meal. Do not double dose if daily dose is missed completely. Monitor urine or serum glucose as recommended by prescriber. More frequent monitoring is required during periods of stress, trauma, surgery, pregnancy, increased activity or exercise. Avoid alcohol. Report chest pain, rapid heartbeat or palpitations, abdominal pain, fever, rash, hypoglycemia reactions, yellowing of skin or eyes, dark urine or light stool, or unusual fatigue or nausea/vomiting. Report unusually rapid weight gain; swelling of ankles, legs, or abdomen; or weakness or shortness of breath. **Pregnancy/breast-feeding precautions:** In anovulatory, premenopausal women, ovulation may occur, increasing the risk of pregnancy. Adequate contraception is recommended. Use alternate means of contraception if using oral contraceptives. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Avandia®: 2 mg, 4 mg, 8 mg

Generic AvailableNo

ManufacturerSmithKline Beecham Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Avandia)

2 mg (60): $152.47

4 mg (30): $120.10

8 mg (30): $223.49

Mechanism of ActionThiazolidinedione antidiabetic agent that lowers blood glucose by improving target cell response to insulin, without increasing pancreatic insulin secretion. It has a mechanism of action that is dependent on the presence of insulin for activity. Rosiglitazone is an agonist for peroxisome proliferator-activated receptor-gamma (PPARgamma). Activation of nuclear PPARgamma receptors influences the production of a number of gene products involved in glucose and lipid metabolism. Thiazolidinedione antidiabetic agent that lowers blood glucose by improving target cell response to insulin, without increasing pancreatic insulin secretion. It has a mechanism of action that is dependent on the presence of insulin for activity. PPARgamma is abundant in the cells within the renal collecting tubules; fluid retention results from stimulation by thiazolidinediones which increases sodium reabsorption.

Pharmacodynamics/Kinetics

Onset of action: Delayed; Maximum effect: Up to 12 weeks

Distribution: V_{dss} (apparent): 17.6 L

Protein binding: 99.8%; primarily albumin

Metabolism: Hepatic (99%) via CYP2C8; minor metabolism via CYP2C9

Bioavailability: 99%

Half-life elimination: 3-4 hours

Time to peak, plasma: 1 hour; delayed with food

Excretion: Urine (64%) and feces (23%) as metabolites

Dental Health: Effects on Dental TreatmentRosiglitazone-dependent patients with diabetes should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause headache and fatigue

Mental Health: Effects on Psychiatric TreatmentWeight gain is common; caution with atypical antipsychotics

Cardiovascular ConsiderationsThe glitazones are peroxisome proliferator-activated receptor gamma (PPAR gamma) agonists used to treat type 2 diabetes. Recently, there has been interest in this group's effects on cardiovascular risk. Pioglitazone has shown some promise (PROACTIVE study) in reducing a variety of cardiovascular endpoints (nonfatal MI, stroke, ACS). Rosiglitazone, however, may not be cardioprotective; Nissen and Wolski showed an association with MI and rosiglitazone use through a meta-analysis. Since that time, RECORD's interim findings (Home PD, 2007) have been published and Singh and colleagues (2007) have performed a more recent meta-analysis analyzing rosiglitazone's cardiovascular safety.

Rosiglitazone: Nissen and Wolski reviewed 42 randomized controlled studies (each > 6 months duration) in patients with type 2 diabetes or impaired glucose tolerance comparing rosiglitazone (as monotherapy or in combination regimens that may include a sulfonylurea, metformin, or insulin) to a control group (another diabetic agent or placebo). The meta-analysis tabulated the number of myocardial infarctions and cardiovascular deaths from each trial. Of the 42 studies, 38 reported at least one MI and 22 reported at least one CV related death. The meta analysis evaluated 15,560 patients who received regimens that included rosiglitazone and 12,283 patients in the comparative group without rosiglitazone. In comparing the rosiglitazone group to the control group, the odds ratio for myocardial infarction was 1.43 (95% CI 1.03 to 1.98; p=0.03). The odds ratio for death from cardiovascular disease was 1.64 (95% CI, 0.98 to 2.74; p=0.06). Rosiglitazone was associated with a significant increase risk of myocardial infarction in this pooled analysis. The clinical significance of these initial results is unclear. The study has limitations but raises safety questions that require further research to answer.

The RECORD interim evaluation was inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes. Rosiglitazone was associated with an increased risk of HF. Singh's meta-analysis includes the DREAM and ADOPT data from Nissen's analysis, RECORD's interim analysis, and another small trial in patients with NYHA class I and II heart failure. All were randomized, controlled studies (each >1 year duration) in type 2 diabetics or in patients with impaired glucose tolerance. The DREAM, ADOPT, and RECORD studies excluded patients with cardiovascular disease or heart failure. All had an independent cardiology team reviewing the cardiovascular events. The numbers of cardiovascular events were small but the conclusion was that rosiglitazone was associated with a significant increased risk of MI and heart failure (HF), without a significant risk of cardiovascular mortality.

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International Brand NamesAvandia (AR, AT, AU, BB, BE, BG, BM, BO, BR, BS, BZ, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, GY, HK, HN, ID, IE, IL, IT, JM, MX, MY, NI, NL, NO, PA, PE, PH, PK, PL, PR, PT, PY, RU, SE, SG, SR, SV, TH, TR, TT, TW, UY, VE); Rezult (IN); Rosizone (TW); Rossini (IL)

Rosuvastatin

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Special Alerts

HMG-CoA Reductase Inhibitors: Evidence Does Not Suggest Increased Incidence of Amyotrophic Lateral Sclerosis (ALS) - Results of FDA Analysis - September 30, 2008

The U.S. Food and Drug Administration's (FDA) review of 41 long-term controlled clinical trials of HMG-CoA reductase inhibitors finds no evidence of an increased incidence of ALS (also known as Lou Gehrig's disease) related to these medications. This analysis occurred after the FDA had received notice of numerous adverse events of which 109 of these reports mentioned ALS, Lou Gehrig's disease, or motor neurone disease. The clinical trials included in the analysis had a median duration of treatment of 3.3 years (range of duration: 6 months to 5 years) and involved 120,964 patients. The analysis identified a total of 19 cases of ALS – 9 cases per 64,602 patients (0.014%) with statin therapy and 10 cases per 56,362 patients (0.017%) with placebo. The incidence rates, based on approximately 400,000 person-years, were 4.2 per 100,000 person-years in the statin-treated group and 5 per 100,000 person-years in the placebo-treated group.

The FDA recommends that health care providers continue to prescribe, and patients continue to use these products as described within their labeling.

For more information, healthcare professionals may refer to the following:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Statin

Colman E, Szarfman A, Wyeth J, et al, "An Evaluation of a Data Mining Signal for Amyotrophic Lateral Sclerosis and Statins Detected in FDA's Spontaneous Adverse Event Reporting System," *Pharmacoepidemiol Drug Saf*, 2008 (epub ahead of print)

Pronunciation(roe soo va STAT in)

U.S. Brand NamesCrestor®

Canadian Brand NamesCrestor®

Pharmacologic CategoryAntilipemic Agent, HMG-CoA Reductase Inhibitor

Use: Labeled IndicationsUsed with dietary therapy for hyperlipidemias to reduce elevations in total cholesterol (TC), LDL-C, apolipoprotein B, nonHDL-C, and triglycerides (TG) in patients with primary hypercholesterolemia (elevations of 1 or more components are present in Fredrickson type IIa, IIb, and IV hyperlipidemias); treatment of primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia); treatment of homozygous familial hypercholesterolemia (FH); to slow progression of atherosclerosis as an adjunct to diet to lower TC and LDL-C

Dosing: Adults

Hyperlipidemia, mixed dyslipidemia, hypertriglyceridemia, primary dysbetalipoproteinemia, slowing progression of atherosclerosis: Oral:

Initial dose:

General dosing: 10 mg once daily; 20 mg once daily may be used in patients with severe hyperlipidemia (LDL >190 mg/dL) and aggressive lipid targets

Conservative dosing: Patients requiring less aggressive treatment or predisposed to myopathy (including patients of Asian descent): 5 mg once daily

Titration: After 2 weeks, may be increased by 5-10 mg once daily; dosing range: 5-40 mg/day (maximum dose: 40 mg once daily)

Note: The 40 mg dose should be reserved for patients who have not achieved goal cholesterol levels on a dose of 20 mg/day, including patients switched from another HMG-CoA reductase inhibitor.

Homozygous familial hypercholesterolemia (FH): Oral: Initial: 20 mg once daily (maximum dose: 40 mg/day)

Dosage adjustment with concomitant medications: Oral:

Cyclosporine: Rosuvastatin dose should not exceed 5 mg/day

Gemfibrozil or lopinavir/ritonavir: Rosuvastatin dose should not exceed 10 mg/day

Dosage adjustment for hematuria and/or persistent, unexplained proteinuria while on 40 mg/day: Reduce dose and evaluate causes.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Mild-to-moderate impairment: No dosage adjustment required.

Cl_{cr} <30 mL/minute/1.73 m^2: Initial: 5 mg/day; do not exceed 10 mg once daily

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken with or without food. Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.

StorageStore between 20°C and 25°C (68°F to 77°F). Protect from moisture.

ContraindicationsHypersensitivity to rosuvastatin or any component of the formulation; active liver disease; unexplained persistent elevations of serum transaminases (>3 times ULN); pregnancy; breast-feeding

Allergy Considerations

- HMG-CoA Reductase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Myopathy/rhabdomyolysis: Patients receiving HMG-CoA reductase inhibitors have developed rhabdomyolysis with acute renal failure and/or myopathy; patients should be monitored closely. This risk is dose-related and is increased with concurrent use of other lipid lowering medications. Temporarily discontinue for elective major surgery, acute medical or surgical conditions, or in any patient experiencing an acute or serious condition predisposing to renal failure (eg, sepsis, hypotension, trauma, uncontrolled seizures). Based upon current evidence, HMG-CoA reductase inhibitor therapy should be continued in the perioperative period unless risk outweighs cardioprotective benefit. Use caution in patients with renal impairment, inadequately treated hypothyroidism, and those taking other drugs associated with myopathy (eg, colchicine); these patients are predisposed to myopathy. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine.

Disease-related concerns:

- Hepatic impairment and/or ethanol use: Use with caution in patients who consume large amounts of ethanol or have a history of liver disease.

- Renal impairment: Dosage adjustment required in patients with a Cl_{cr} <30 mL/minute/1.73 m^2

Concurrent drug therapy issues:

- Cyclosporine: Cyclosporine significantly increases levels of rosuvastatin. Dose of rosuvastatin should be limited to 5 mg/day.

- Gemfibrozil: Gemfibrozil significantly increases levels of rosuvastatin. Concomitant use of gemfibrozil is not recommended. If use of gemfibrozil is warranted, dose of rosuvastatin should be limited to 10 mg/day.

- Lopinavir/ritonavir: Lopinavir/ritonavir significantly increases levels of rosuvastatin. Dose of rosuvastatin should be limited to 10 mg/day.

- Niacin: Use of niacin may increase the risk of myopathy when used with rosuvastatin. A reduction in rosuvastatin dose should be considered.

- Warfarin: Rosuvastatin significantly increases INR in patients on warfarin. INR should be monitored before starting rosuvastatin and frequently during therapy.

Special Populations:

- Asian population: Increased risk of rosuvastatin-associated myopathy in certain subgroups.

- Elderly: Use with caution in patients with advanced age, these patients are predisposed to myopathy.

- Pediatrics: Safety and efficacy have not been established. Limited experience in pediatric patients >8 years of age with homozygous FH. In patients 10-17 years of age, C_{max} and AUC were similar to that observed in adult patients receiving the same dosage.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

Geriatric ConsiderationsEffective and well tolerated in the elderly. The definition of and, therefore, when to treat hyperlipidemia in geriatrics is a controversial issue. The National Cholesterol Education Program recommends that all adults maintain a plasma cholesterol <160 mg/dL. Elderly with one additional risk factor, goal LDL would be <130 mg/dL. It is the authors' belief that pharmacologic treatment be reserved for those who are unable to obtain a desirable plasma cholesterol concentration by diet alone and for whom the benefits of treatment are believed to outweigh the potential adverse effects, drug interactions, and cost of treatment.

Pregnancy Risk FactorX

Pregnancy ConsiderationsCholesterol biosynthesis may be important in fetal development. Contraindicated in pregnancy. Administer to women of childbearing potential only when conception is highly unlikely and patients have been informed of potential hazards.

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions

>10%: Neuromuscular & skeletal: Myalgia (3% to 13%)

2% to 10%:

Central nervous system: Headache (6%), dizziness (4%)

Gastrointestinal: Nausea (3%), abdominal pain (2%), constipation (2%)

Hepatic: ALT increased (2%; >3 times ULN)

Neuromuscular & skeletal: Arthralgia (10%), CPK increased (3%), weakness (3%)

<2%, postmarketing, and/or case reports: Alkaline phosphatase increased, AST increased, bilirubin increased, GGT increased, hematuria (microscopic), hepatitis, hyperglycemia; hypersensitivity reactions (including angioedema, pruritis, rash, urticaria); memory deficits, myoglobinuria, myositis, myopathy, pancreatitis, proteinuria (dose related), renal failure, rhabdomyolysis, thyroid function test abnormalities

Adverse reactions reported with other HMG-CoA reductase inhibitors include a hypersensitivity syndrome (symptoms may include anaphylaxis, angioedema, arthralgia, erythema multiforme, eosinophilia, hemolytic anemia, lupus syndrome, photosensitivity, polymyalgia rheumatica, positive ANA, purpura, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, vasculitis)

Metabolism/Transport Effects**Substrate** (minor) of CYP2C9, 3A4

Drug Interactions

Amiodarone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. Management: Dose of HMG-CoA reductase inhibitor may need to be reduced (e.g., simvastatin prescribing information recommends not exceeding 20 mg/day during concurrent therapy). *Risk D: Consider therapy modification*

Colchicine: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CycloSPORINE: May increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

DAPTOmycin: HMG-CoA Reductase Inhibitors may enhance the adverse/toxic effect of DAPTOmycin. Specifically, the risk of skeletal muscle toxicity may be increased. Management: Consider temporarily stopping HMG-CoA reductase inhibitor therapy prior to daptomycin. If used together, regular (i.e., at least weekly) monitoring of CPK concentrations is recommended. *Risk D: Consider therapy modification*

Eltrombopag: May increase the serum concentration of Rosuvastatin. Management: According to eltrombopag prescribing information, consideration should be given to a preventative 50% reduction in rosuvastatin dose when starting this combination. *Risk D: Consider therapy modification*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Fenofibrate: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fenofibric Acid: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Gemfibrozil: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Gemfibrozil may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Niacin: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Niacinamide: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): HMG-CoA Reductase Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid excessive ethanol consumption (due to potential hepatic effects).

Food: Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.

Monitoring ParametersTotal cholesterol, LDL, and HDL cholesterol within 2-4 weeks of treatment initiation or dose change; liver function tests should be determined at baseline (prior to initiation), 3 months following initiation, 3 months after any increase in dose, and periodically thereafter (eg, semiannually); baseline CPK (recheck CPK in any patient with symptoms suggestive of myopathy)

Nursing: Physical Assessment/MonitoringUse caution with history of hepatic or renal disease. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, other lipid lowering drugs may increase risk of myopathy or rhabdomyolysis). Assess results of laboratory tests (eg, LFTS, cholesterol profile) prior to treatment and periodically thereafter. Evaluate therapeutic effectiveness and adverse reactions (eg, myalgia, CNS changes, gastrointestinal effects) on a regular basis throughout therapy. Teach patient proper use (as adjunct to diet and exercise program), possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to women of childbearing age unless they are capable of complying with effective contraceptive use. Instruct patient in appropriate contraceptive measures.

Monitoring: Lab TestsTotal cholesterol, LDL, and HDL cholesterol within 2-4 weeks of treatment initiation or dose change; liver function tests should be determined at baseline (prior to initiation), 3 months following initiation, 3 months after any increase in dose, and periodically thereafter (eg, semiannually); baseline CPK (recheck CPK in any patient with symptoms suggestive of myopathy)

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take at same time each day with or without food. Follow cholesterol-lowering diet and exercise regimen as prescribed. Avoid excess alcohol. You will have periodic blood tests to assess effectiveness. You may experience mild nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea (buttermilk, boiled milk, or yogurt may help); constipation (increased exercise, fruit, fluids, or fiber may help); or headache, dizziness, insomnia (use caution when driving or engaged in potentially hazardous tasks until response to drug in known). Contact prescriber immediately with persistent muscle pain or cramping, skeletal or joint pain, or numbness. Report other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during and for 1 month following therapy. Consult prescriber for appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Crestor®: 5 mg, 10 mg, 20 mg, 40 mg

Generic AvailableNo

ManufacturerAstraZeneca (Canada)

Pricing: U.S. (www.drugstore.com)

Tablets (Crestor)

5 mg (30): $114.99

10 mg (30): $111.29

20 mg (30): $115.49

40 mg (30): $115.49

Mechanism of ActionInhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis (reduces the production of mevalonic acid from HMG-CoA); this then results in a compensatory increase in the expression of LDL receptors on hepatocyte membranes and a stimulation of LDL catabolism

Pharmacodynamics/Kinetics

Onset of action: Within 1 week; maximal at 4 weeks

Distribution: V_d: 134 L

Protein binding: 88%

Metabolism: Hepatic (10%), via CYP2C9 (1 active metabolite identified)

Bioavailability: 20% (high first-pass extraction by liver)

Asian patients have been noted to have increased bioavailability.

Half-life elimination: 19 hours

Time to peak, plasma: 3-5 hours

Excretion: Feces (90%), primarily as unchanged drug

Related Information

- Lipid-Lowering Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentUse caution in patients who drink large amounts of alcohol; hepatotoxic effects may be enhanced

Cardiovascular Considerations

Primary Prevention: HMG-CoA reductase inhibitors are effective in primary and secondary prevention of cardiovascular events in patients with hyperlipidemia. For primary prevention, a patient's major risk factors (cigarette smoking, hypertension or currently taking antihypertensives, low HDL-C, family history, age, gender) should be evaluated. Patients with multiple risk factors (≥2) require more intensive therapy guided by the calculation of a 10-year absolute CHD risk (eg, the percent probability of having a CHD event in next 10 years). An individual's 10-year absolute CHD risk can be calculated at www.med-decisions.com/cvtool/phys/phys.html. LDL cholesterol goals, therapeutic lifestyle changes, and drug therapy are determined based upon a patient's risk factor profile.

Primary prevention trials show that cholesterol-lowering drugs reduce the risk of major coronary events, coronary death, and cerebrovascular events even in the first 6-12 months of use. The WOSCOP trial suggested a trend towards enhanced survival using pravastatin in their patients (mean LDL-cholesterol of 192 mg/dL and no history of MI). In a recent trial (Sever, 2003), patients with HTN and at least three other risk factors were randomized to 10 mg daily of atorvastatin or placebo. These patients had a total nonfasting cholesterol <250 mg/dL before treatment. LDL-C levels were 132 mg/dL before treatment and fell to an average of 90 mg/dL in the atorvastatin-treated group. There was a significant reduction in stroke, cardiovascular events, and coronary events in the atorvastatin-treated group as compared to the placebo group. There was no difference in mortality between the groups.

HMG-CoA reductase inhibitors decrease C-reactive protein (CRP), an inflammatory marker and an acute phase reactant. Elevated levels of high sensitive CRP (hsCRP), which detects CRP levels as low as 0.175 mg/L, have been shown to be associated with an increased risk of cardiovascular events. Recently, the JUPITER trial demonstrated that the use of rosuvastatin in healthy patients (men ≥50 years and women ≥60 years) without a history of cardiovascular disease with LDL <130 mg/dL and a hsCRP level ≥2 mg/L reduced the risk of major cardiovascular events (eg, nonfatal MI, stroke, death from cardiovascular causes), The number needed to treat over 5 years to prevent 1 cardiovascular event is 25. Current guidelines do not recommend drug treatment for patients with an LDL <130 mg/dL. However, identification of the patient at higher risk of cardiovascular events within this subgroup using hsCRP is now important given that statins may prevent the occurrence of these serious cardiovascular events (Ridker, 2008).

Secondary Prevention: Secondary prevention trials indicate that "statin" therapy reduces mortality, major coronary events, coronary artery procedures, and stroke. The Heart Protection Study proved that lowering serum cholesterol levels reduces the rate of major vascular events among high-risk individuals with documented vascular disease (CHD, cerebrovascular, peripheral vascular) or diabetes regardless of initial cholesterol concentrations. PROVE IT is a randomized, double-blind trial evaluating hospitalized patients with acute coronary syndrome to determine the effects of intense LDL-C lowering therapy. Four thousand patients with an LDL-C levels of 106 mg/dL were randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily. After 2 years, the combined cardiovascular endpoint (death, MI, unstable angina requiring hospitalization, revascularization and stroke) was ~26% in the pravastatin patients (median LDL-C 95 mg/dL) and ~22% in the atorvastatin treated patients (median LDL-C 62 mg/dL).

LaRosa and colleagues assessed the efficacy and safety of lowering LDL cholesterol <100 mg/dL in patients with stable coronary heart disease (LaRosa, 2005). Ten thousand and one patients with baseline LDL levels <130 mg/dL were randomized to atorvastatin 10 mg or 80 mg daily and followed for a median of 4.9 years. The primary endpoint was the occurrence of the first major cardiovascular event (death from CVD, MI, resuscitation after cardiac arrest, or stroke). A primary event occurred in 434 patients (8.7%) receiving 80 mg daily (mean LDL 77 mg/dL) and 548 patients (10.9%) receiving 10 mg dose (mean LDL 101 mg/dL) (95% CI, 0.69-0.89; p <0.001). There was no mortality difference between the two treatment groups.

In addition to the ability of HMG-CoA reductase inhibitors to decrease levels of high-sensitivity C-reactive protein (hs-CRP), they also possess pleiotropic properties including improved endothelial function, reduced inflammation at the site of the coronary plaque, inhibition of platelet aggregation, and anticoagulant effects. These nonlipid effects may be beneficial when HMG-CoA reductase inhibitors are introduced early in the management of acute coronary syndromes (de Denus, 2002).

Myopathy: Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years of age), women more frequently than men, small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, drug interactions (use with caution or avoid). The combination of a HMG-CoA reductase inhibitor plus nicotinic acid seems to carry a lower risk of myopathy than does a HMG-CoA reductase inhibitor plus a fibrate. Other medications, when used concurrently, may enhance the risk of myopathy associated with statins; these include drugs that inhibit CYP3A4 isoenzymes (lovastatin, simvastatin, atorvastatin) or CYP2C9 isoenzymes (fluvastatin). HMG-CoA reductase inhibitors may exacerbate exercise-induced skeletal muscle injury. Many experts favor getting a baseline creatine kinase (CK) measurement before initiating therapy (asymptomatic CK elevations are common). Obtain a CK measurement if patient complains of muscle soreness, tenderness, or pain.

Anesthesia and Critical Care Concerns/Other ConsiderationsBased on the atorvastatin component: **Myopathy:** Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years), gender (occurs in women more frequently than men), small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, and drug interactions (use with caution or avoid).

Based on current research, HMG-CoA reductase inhibitors should be continued in the perioperative period. Postoperative discontinuation of statin therapy is associated with an increased risk of cardiac morbidity and mortality.

Index TermsRosuvastatin Calcium

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International Brand Names Crestor (AR, AU, BB, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CZ, DK, DO, EC, EE, ET, FI, FR, GB, GH, GM, GN, GT, GY, HK, HN, ID, IE, IL, IT, JM, KE, KP, LR, MA, ML, MR, MU, MW, MX, NE, NG, NI, NL, NO, PA, PE, PH, PT, SC, SD, SE, SG, SL, SN, SR, SV, TH, TN, TT, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Fortius (IN); Rovartal (PY)

Rotavirus Vaccine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(ROE ta vye rus vak SEEN)
U.S. Brand NamesRotarix®; RotaTeq®
Pharmacologic Category[Vaccine, Live (Viral)]
Use: Labeled IndicationsPrevention of rotavirus gastroenteritis in infants and children

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of all infants.

Dosing: Pediatric**Prevention of rotavirus gastroenteritis:** Oral:**Manufacturer's labeling:**

Infants 6-24 weeks of age: Rotarix®: A total of two 1mL doses, the first dose given at 6-14 weeks of age. The first and second dose should be separated by ≥4 weeks. The 2-dose series should be completed by 24 weeks of age.

Infants 6-32 weeks: RotaTeq®: A total of three 2 mL doses given at 2-, 4-, and 6 months of age; the first given at 6-14 weeks of age, followed by subsequent doses at 4- to 10-week intervals. Routine administration of the first dose at >12 weeks of age is not recommended (insufficient data). Administer all doses by 32 weeks of age. Infants who have had rotavirus gastroenteritis before getting the full course of vaccine should still initiate or complete the 3-dose schedule; initial infection provides only partial immunity.

ACIP recommendations: The first dose can be given at 6-14 weeks of age. The series should not be started in infants ≥15 weeks. The final dose in the series should be administered by 8 months 0 days of age. A total of three doses, administered at 2-, 4-, and 6 months of age, however, if Rotarix® is used at ages 2- and 4 months, a dose at 6 months is not indicated. The ACIP Provisional Recommendations for vaccination recommend completing the vaccine series with the same product whenever possible. If continuing with same product will cause vaccination to be deferred, or if product used previously is unknown, vaccination should be completed with the product available. If RotaTeq® was used in any previous doses, or if the specific product used was unknown, a total of three doses should be given

Administration: Oral

Rotarix®: Using oral applicator, administer contents into infant’s inner cheek. If most of dose is spit out or regurgitated, may administer a replacement dose at the same visit. Dispose of applicator and vaccine vial in biologic waste container.

RotaTeq®: Gently squeeze dose from ready-to-use dosing tube into infant’s inner cheek. If infant spits or regurgitates vaccine, a replacement dose is not recommended. In general, vaccine administration should be deferred for 42 days following an antibody-containing product. However, if deferral causes first dose of vaccine to be scheduled at ≥13 weeks of age, a shorter deferral interval should be used. After use, dispose of the empty tube and cap in a biologic waste container.

Administration with other vaccines:

Rotavirus vaccine with inactivated vaccines: May be given simultaneously or at any interval between doses

Rotavirus vaccine with other live vaccines:

Intranasal: If not given simultaneously, wait at least 4 weeks between administration

Injectable: May be given simultaneously or at any interval between doses of live injectable vaccines

Vaccine administration with antibody-containing products: Do not give rotavirus vaccine simultaneously. Defer rotavirus vaccine for 6 weeks after receipt of antibody containing product unless deferral will cause first dose of rotavirus vaccine to be given ≥13 weeks of age. Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

Dietary ConsiderationsDo not mix or dilute vaccine. May be administered before or after food, milk, or breast milk.
Storage

Rotarix®: Prior to reconstitution, store powder under refrigeration at 2°C to 8°C (36°F to 46°F); diluent may be stored at room temperature 20°C to 25°C (68°F to 77°F). Protect from light; discard if frozen. Following reconstitution, may be refrigerated or stored at room temperature for up to 24 hours. Discard if frozen.

RotaTeq®: Store and transport under refrigeration at 2°C to 8°C (36°F to 46°F). Use as soon as possible once removed from refrigerator. Protect from light.

ReconstitutionRotarix®: Reconstitute only with provided diluent and transfer adapter. Shake vigorously to form suspension.
ContraindicationsHypersensitivity to rotavirus vaccine or any component of the formulation

In addition, Rotarix® is contraindicated with a history of an uncorrected congenital malformation of the GI tract.

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine administration.

- Intussusception: Was observed with a previous licensed rotavirus vaccine; an increased risk in intussusception was not observed in clinical trials with current vaccines, however, cases have been noted in postmarketing reports. Use caution with a history of intussusception.

Disease-related concerns:

- Acute illness: May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever).

- Gastrointestinal disease: Use with caution in infants with history of GI disorders, acute GI illness, chronic diarrhea, failure to thrive, congenital abdominal disorders, abdominal surgery, and intussusception; vaccine may be used with controlled gastroesophageal reflux disease. Consider delaying administration to infants with acute diarrhea or vomiting. Rotarix® is contraindicated with a history of an uncorrected congenital malformation of the GI tract.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Adults: Not intended for use in adults.

- Immunocompromised family members: Virus from live virus vaccines may be transmitted to nonvaccinated contacts; use with caution in the presence of immunocompromised family members.

- Immunocompromised infants: Safety and efficacy have not been established for use in immunocompromised infants (including blood dyscrasias, leukemia, lymphoma, malignant neoplasms affecting bone marrow or lymphatic system), infants on immunosuppressants (including high-dose corticosteroids; may be administered with topical corticosteroids or inhaled steroids), primary and acquired immunodeficiencies (including HIV), or infants receiving blood products or immunoglobulins within 42 days.

- Pediatrics: Safety and efficacy of RotaTeq® have not been established in infants <6 weeks or >32 weeks of age. Safety and efficacy of Rotarix® have not been established in infants <6 weeks or >24 weeks of age.

Other warnings/precautions:

- Postexposure prophylaxis: Information is not available for use in postexposure prophylaxis.

Dosage form specific issues:

- Latex: Some packaging may contain natural latex/natural rubber

Pregnancy Risk FactorC

Pregnancy Considerations

Reproduction studies have not been conducted. Not indicated for use in women of reproductive age. Infants living in households with pregnant women may be vaccinated.

Breast-Feeding ConsiderationsInfants receiving vaccine may be breast fed.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967 or www.vaers.hhs.gov.**

Note: Ranges reported; actual percentage may vary between products.

>10%:

Central nervous system: Fever ≥38.1°C (17% to 20%; equal to placebo), irritability (3% to 11%)

Gastrointestinal: Diarrhea (4% to 24%), vomiting (3% to 15%)

Otic: Otitis media (15%)

1% to 10%:

Gastrointestinal: Flatulence (2%)

Respiratory: Nasopharyngitis (7%), bronchospasm (1%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Hematochezia, idiopathic thrombocytopenic purpura, intussusception, Kawasaki disease, seizure, urticaria

Drug Interactions

Immune Globulins: May diminish the therapeutic effect of Vaccines (Live). *Risk D: Consider therapy modification*

Immunosuppressants: May enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Tuberculin Tests: Vaccines (Live) may diminish the diagnostic effect of Tuberculin Tests. *Risk D: Consider therapy modification*

Test Interactions Tuberculin tests: Rotavirus vaccine may diminish the diagnostic effect of tuberculin tests.
Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder, for suspension, oral [preservative free; human derived]:

Rotarix®: G1P[8] $\geq 10^6$ infectious units per 1 mL [oral applicator contains natural latex/natural rubber]

Suspension, oral [preservative free; bovine and human derived]:

RotaTeq®: G1 ≥2.2 10^6 infectious units, G2 ≥2.8 10^6 infectious units, G3 ≥2.2 10^6 infectious units, G4 ≥2 10^6 infectious units, and P1 [8] ≥2.3 10^6 infectious units per 2 mL (2 mL)

Generic Available No
Mechanism of Action A live vaccine; replicates in the small intestine and promotes active immunity to rotavirus gastroenteritis. Rotarix® is specifically indicated for prevention of rotavirus gastroenteritis caused by serotypes G1, G3, G4 and G9 and RotaTeq® is specifically indicated for prevention of rotavirus gastroenteritis caused by serotypes G1, G2, G3, and G4. However, vaccines may provide immunity to other serotypes.
Pharmacodynamics/Kinetics **Note:** There is no established relationship between antibody response and protection against gastroenteritis.

Seroconversion:

Rotarix®: Antirotavirus IgA antibodies were noted 1-2 months following competition of the 2-dose series in 77% to 87% of infants.

RotaTeq®: A threefold increase in antirotavirus IgA was noted following completion of the 3-dose regimen in 93% to 100% of infants.

Duration: Following administration of rotavirus vaccine, efficacy of protecting against any grade of rotavirus gastroenteritis through two seasons was 70% to 79%

Related Information

- Immunization Recommendations

Pharmacotherapy Pearls Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title and address be entered into the patient's permanent medical record.
Dental Health: Effects on Dental Treatment No significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions
Mental Health: Effects on Mental Status None reported
Mental Health: Effects on Psychiatric Treatment None reported
Index Terms Human Rotavirus Vaccine, Attenuated (HRV); Pentavalent Human-Bovine Reassortant Rotavirus Vaccine (PRV); Rotavirus Vaccine, Pentavalent; RV1 (Rotarix®); RV5 (RotaTeq®)
References

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International Brand Names Rotarix (AR, AT, AU, BE, BG, CH, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, HK, HN, IE, IT, JM, MX, MY, NI, NL, NO, PA, PE, PT, RU, SE, SV, TH, TR, TT, VE); RotaTeq (HK, IL, KP, MY, NZ, PH, SG)

Rotigotine

Lexi-Drugs Online

English

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Special Alerts

Rotigotine (Neupro®): Recall and Downward-Titration Recommendation - March 2008

Schwarz Pharma (a company of the UCB group) has issued a "Dear Healthcare Provider" letter describing steps that must be performed as a result of the nationwide recall of Neupro®. Beginning in the latter part of April 2008, Neupro® will not be available in the U.S.; therefore, patients currently receiving therapy must begin downward titration with the patches currently available. Gradual downward titration per product labeling should be done by decreasing the dose by 2 mg/24 hours every other day. Abrupt discontinuation of therapy without downward titration is **not** recommended and may result in akinetic crises or a syndrome resembling neuroleptic malignant syndrome.

The patches are being recalled secondary to the formation of rotigotine crystals (resembling snowflakes). This crystallization results in decreased drug available for absorption and altered efficacy. Patches without crystallization or minimal crystallization may be used for down-titration. Refer to the manufacturer's website for example pictures as a guide in determining if amount of crystallization is appropriate for use or not.

Additional information and example pictures of crystallization may be found at http://www.neupro.com/Home/Home.asp

Medication Safety Issues

Sound-alike/look-alike issues:

Neupro® may be confused with Neupogen®

Transdermal patch contains metal (eg, aluminum); remove patch prior to MRI.

Pronunciation(roe TIG oh teen)

U.S. Brand NamesNeupro® [DSC]

Pharmacologic CategoryAnti-Parkinson's Agent, Dopamine Agonist

Use: Labeled IndicationsTreatment of the signs and symptoms of early-stage idiopathic Parkinson's disease

Dosing: Adults**Parkinson's disease:** Topical: Transdermal: Initial: Apply 2 mg/24 hours patch once daily; may increase by 2 mg/24 hours weekly, based on clinical response and tolerability (maximum: 6 mg/24 hours)

Dosage reductions or discontinuation: Decrease by 2 mg/24 hours every other day

Note: In clinical trials, the lowest effective dose was 4 mg/24 hours and doses >6 mg/24 hours did not provide any additional therapeutic benefit and increased incidence of adverse effects

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentSevere impairment (Cl_{cr} 15-29 mL/minute): No dosage adjustment required

Dosing: Hepatic Impairment
Moderate hepatic impairment (Child-Pugh class B): No dosage adjustment required

Severe hepatic impairment: Not studied

Administration: TopicalInspect patches for formation of crystals. Do not use if crystallization is present. Apply to clean, dry, hairless area of skin on the front of the abdomen, thigh, hip, flank, shoulder, or upper arm at approximately the same time daily. Remove from pouch immediately before use and press patch firmly in place on skin for 20-30 seconds. Application sites should be rotated on a daily basis. Do not apply to same application site for more than once every 14 days or apply patch to oily, irritated or damaged skin. Avoid exposing patch to external heat sources (eg, heating pad, electric blanket, heat lamp, hot tub). If applied to hairy area, shave ≥3 days prior to applying patch. If patch detaches, immediately apply a new one to a new site.

StorageStore at 15°C to 30°C (59°F to 86°F). Store in original pouch until application.

ContraindicationsHypersensitivity to rotigotine or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Fibrosis: Rare cases of pleural, retroperitoneal fibrosis and/or cardiac valvulopathy have been reported in patients treated with ergot-derived dopamine agonists, generally with prolonged use. The potential of rotigotine, a nonergot derived dopamine agonist, to cause similar fibrotic complications is unknown.

- Hallucinations: May cause hallucinations.

- Impulsive control disorders: Dopamine agonists used for Parkinson's disease or restless legs syndrome have been associated with compulsive behaviors and/or loss of impulse control, which has manifested as pathological gambling, libido increases (hypersexuality), and/or binge eating. Causality has not been established, and controversy exists as to whether this phenomenon is related to the underlying disease, prior behaviors/addictions and/or drug therapy. Dose reduction or discontinuation of therapy has been reported to reverse these behaviors in some, but not all cases.

- Melanoma: Risk for melanoma development is increased in Parkinson's disease patients; drug causation or factors contributing to risk have not been established.

- Orthostatic hypotension: Dopamine agonists may cause orthostatic hypotension and syncope; Parkinson's disease patients appear to have an impaired capacity to respond to a postural challenge. Use with caution in patients at risk of hypotension (such as those receiving antihypertensive drugs) or where transient hypotensive episodes would be poorly tolerated (cardiovascular disease or cerebrovascular disease). Parkinson's patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation, and should be informed of this risk.

- Somnolence: Use commonly associated with somnolence. In addition, patients falling asleep during activities of daily living, including driving, have also been reported and may occur without significant warning signs. Monitor for daytime somnolence or pre-existing sleep disorder. Patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). Use with caution in patients receiving other CNS depressants or psychoactive agents; discontinue if significant daytime sleepiness or episodes of falling asleep occur. Effects with other sedative drugs or ethanol may be potentiated.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with pre-existing cardiovascular disease; therapy has been associated with inconsistent increases in blood pressure (as well as orthostatic hypotension), increased heart rate (average increase of 2-4 bpm), and fluid retention.

- Dyskinesia: Use with caution in patients with pre-existing dyskinesia; therapy may exacerbate.

Special populations:

- Pediatrics: Safety and effectiveness have not been established in children <18 years of age.

Dosage form specific issues:

- Aluminum: Patch contains aluminum; remove patch prior to magnetic resonance imaging or cardioversion to avoid skin burns

- Sulfites: Patch contains sodium metabisulfite which may cause allergic reaction in susceptible individuals.

Other warnings/precautions:

- Appropriate use: Patients should rotate application sites to reduce incidence of application site reactions. Reactions increasing in severity, spreading outside of application site or persistent reactions (lasting longer than several days) prompt assessment and any generalized skin reaction require discontinuation of therapy. Patients should be instructed to avoid patch exposure to heat sources; heat application may result in several fold increases in drug absorption.

- Discontinuation of therapy: Taper treatment when discontinuing therapy; do not stop abruptly. Other dopaminergic agents have been associated with a syndrome resembling neuroleptic malignant syndrome on withdrawal and/or significant dosage reduction.

Geriatric ConsiderationsIn clinical trials, no differences in efficacy or safety were seen in younger and older patients. Plasma concentrations of rotigotine in patients 65-80 years of age were similar to younger patients. Plasma concentrations were not measured in patients >80 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsFetal death and adverse effects on embryo-fetal development were observed in some, but not all animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsProlactin secretion may be inhibited.

Adverse Reactions

>10%:

Central nervous system: Somnolence (13% to 25%), dizziness (18%), headache (14%), insomnia (6% to 14%)

Gastrointestinal: Nausea (34% to 48%), vomiting (10% to 20%)

Local: Application site reactions (21% to 37%)

1% to 10%:

Cardiovascular: Sinus tachycardia (9%), peripheral edema (7%), orthostatic hypotension (5% to 7%), hypertension (3%), syncope

Central nervous system: Fatigue (8%), abnormal dreams (2% to 5%), hallucination (≤3%), vertigo (3%), ataxia, confusion, fever, hypoesthesia, malaise

Dermatologic: Erythematous rash (2% to 6%), contact dermatitis, pruritus, purpura

Endocrine & metabolic: Hypoglycemia (7%)

Gastrointestinal: Constipation (dose related; 5%), dyspepsia (4%), anorexia (dose related; 3%), xerostomia (3%), weight gain (3%), weight loss (≤2%)

Genitourinary: Urinary tract infection (3%), urinary incontinence

Hematologic: Hemoglobin decreased

Hepatic: Albumin decreased, GGT increased

Neuromuscular & skeletal: Back pain (6%), arthralgia (4%), myalgia (≤2%), abnormal gait, hypertonia, leg pain, neuralgia, paresthesia

Ocular: Vision changes (dose related; 3%)

Respiratory: Sinusitis (3%)

Miscellaneous: Accident (5%), diaphoresis increased (4%)

<1%, postmarketing, and/or case reports: Allergic reaction, appetite increased, atrial fibrillation, AV block, BUN increased, bundle branch block, flushing, heart failure, hot flashes, hyperesthesia, impotence, paranoia, psychosis, photopsia, rigors, saliva increased, seizure, sexual urgency, thrombocytopenia, tinnitus, ventricular arrhythmia, ventricular tachycardia

Reported with dopamine agonists: Impulsive/compulsive behaviors (eg, pathological gambling, hypersexuality, binge eating)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antipsychotics (Atypical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Antipsychotics (Typical): May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Metoclopramide: May diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersBlood pressure (orthostatic); daytime alertness; periodic skin evaluations (melanoma development)

Nursing: Physical Assessment/MonitoringAssess other prescription and OTC medications patient may be taking to avoid duplications and interactions. Monitor therapeutic response and adverse reactions at the beginning and periodically throughout therapy. Taper dosage slowly when discontinuing. Do not discontinue abruptly. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report.

Patient EducationInform prescriber of all prescription medications, OTC medications, or herbal products you are taking. Avoid alcohol; may increase drowsiness. Patch contains aluminum. Remove patch prior to magnetic resonance imaging or cardioversion to avoid skin burns. Avoid exposure of patch to heat sources. You may experience drowsiness or dizziness, even when performing activities of daily living (do not drive or engage in tasks requiring alertness until response to drug is known); loss of impulse control (possibly manifested as pathological gambling, libido increases, and/or binge eating); nausea (small, frequent meals, frequent oral care, sucking lozenges, or chewing gum may help); orthostatic hypotension (use caution when changing position from lying or sitting to standing); headache; or insomnia. Report rapid heart beat, unexplained weight gain (>3-5 pounds/week), swelling of extremities, shortness of breath, suicide ideation, compulsive behavior and trouble controlling strong urges, generalized skin reaction, or hallucinations. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Transdermal system [once-daily patch]:

Neupro®:

2 mg/24 hours (7s, 30s) [10 cm^2, total rotigotine 4.5 mg; contains sodium metabisulfite] [DSC]

4 mg/24 hours (7s, 30s) [20 cm^2, total rotigotine 9 mg; contains sodium metabisulfite] [DSC]

6 mg/24 hours (7s, 30s) [30 cm^2, total rotigotine 13.5 mg; contains sodium metabisulfite] [DSC]

Generic AvailableNo

ManufacturerSchwarz Pharma

Pricing: U.S. (www.drugstore.com)

Patch, 24-hour (Neupro)

6 mg/24 hrs (30): $264.99

Mechanism of ActionRotigotine is a nonergot dopamine agonist with specificity for D_3-, D_2-, and D_1-dopamine receptors. Although the precise mechanism of action of rotigotine is unknown, it is believed to be due to stimulation of postsynaptic dopamine D_2-type auto receptors within the substantia nigra in the brain, leading to improved dopaminergic transmission in the motor areas of the basal ganglia, notably the caudate nucleus/putamen regions.

Pharmacodynamics/Kinetics

Distribution: V_d: 84 L/kg

Protein binding: ~90%

Metabolism: Extensive conjugation and N-dealkylation

Half-life elimination: After removal of patch: ~5-7 hours

Time to peak, plasma: 15-18 hours; can occur 4-27 hours post application

Excretion: Urine (~71% as metabolites, <1% as unchanged drug); feces (~11%)

Related Information

- Antiparkinsonian Agents

Dental Health: Effects on Dental Treatment

Key adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation). Dopamine agonists may cause orthostatic hypotension and syncope. Parkinson's disease patients should be carefully assisted from the chair and observed for signs of orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions

No information available to require special precautions

Index Terms

N-0923

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International Brand Names

Neupro (CH, CZ, DE, DK, EE, ES, GB, IE, NO, SE)

Rubella Virus Vaccine (Live)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Meruvax® II may be confused with Attenuvax®

Pronunciation(rue BEL a VYE rus vak SEEN, live)
U.S. Brand NamesMeruvax® II
Pharmacologic CategoryVaccine
Use: Labeled IndicationsSelective active immunization against rubella

Note: Trivalent measles - mumps - rubella (MMR) vaccine is the preferred immunizing agent for most children and many adults.

Dosing: Adults**Immunization:** SubQ: 0.5 mL

Adults without documentation of immunity: Vaccination is recommended for students entering colleges and other institutions of higher education, for military personal, for healthcare workers, for international travelers who visit endemic areas, and to women of childbearing potential. Do not administer to women who may become pregnant within 4 weeks of receiving vaccine; administer following completion or termination of pregnancy

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Immunization:** SubQ: Children ≥12 months: Primary immunization is recommended at 12-15 months; revaccination with MMR-II at 4-6 years of age is recommended prior to elementary school. Previously unvaccinated children of susceptible pregnant women should be vaccinated.
Administration: I.V.Not for I.V. administration.
Administration: OtherSubQ injection only in outer aspect of upper arm; avoid injection into blood vessel. **Not for I.V. administration.**
StorageVaccine is to be shipped at 10°C (50°F). May use dry ice. Protect from light at all times. Prior to reconstitution, store at 2°C to 8°C (36°F to 46°F) or colder. Discard reconstituted vaccine after 8 hours.
ContraindicationsHypersensitivity to rubella vaccine or any component of the vaccine; history of anaphylactic reactions to neomycin; individuals with blood dyscrasias, leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic systems; concurrent immunosuppressive therapy (not including steroid replacement); primary and acquired immunodeficiency states; family history of congenital or hereditary immunodeficiency; active/untreated tuberculosis; current febrile illness; pregnancy
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use. Use extreme caution in patients with immediate-type hypersensitivity reactions to eggs.

- Neomycin sensitivity: Contact dermatitis to neomycin is not a contraindication to the vaccine.

Disease-related concerns:

- Acute illness: The manufacturer contraindicates use with febrile infections; however, the ACIP notes that patients with minor illnesses with or without fever (diarrhea, mild upper respiratory tract infection, otitis media) may receive vaccines.

- Thrombocytopenia: Use with caution in patients with thrombocytopenia and those who develop thrombocytopenia after first dose; thrombocytopenia may worsen.

- Tuberculosis: Therapy to treat tuberculosis should be started prior to administering vaccine to patients with untreated, active tuberculosis.

Concurrent drug therapy issues:

- Immune globulins: Recent administration of immune globulins may interfere with immune response.

Special populations:

- Altered immunocompetence: Use is contraindicated in severely immunocompromised patients (eg, patients receiving chemo-/radiation therapy or other immunosuppressive therapy (including high-dose corticosteroids)); may have a reduced response to vaccination. Patients with HIV infection, who are asymptomatic and not severely immunosuppressed may be vaccinated. Patients with leukemia who are in remission and who have not received chemotherapy for at least 3 months may be vaccinated.

- Healthcare workers: Acceptable evidence of immunity is recommended healthcare workers at time of employment.

- Pediatrics: Safety and efficacy have not been established in children <12 months of age.

- Students: Acceptable evidence of immunity is recommended for students entering institutions of higher learning.

- Travelers to endemic areas: Acceptable evidence of immunity is recommended for travelers to endemic areas.

Dosage form specific issues:

- Albumin: Products may contain albumin.

- Gelatin: Products may contain gelatin.

- Neomycin: Products may contain neomycin.

Other warnings/precautions:

- Blood products: Recent administration of blood or blood products may interfere with immune response.

Geriatric ConsiderationsNot a vaccine necessary for most adults and elderly; however, necessary to protect persons without immunity traveling into endemic or epidemic countries. May need to test for rubella immunity if no record of disease of vaccination is available.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Women who are pregnant when vaccinated or who become pregnant within 28 days of vaccination should be counseled on the theoretical risks to the fetus. The risk of rubella-associated malformations in these women is so small as to be negligible. MMR is the vaccine of choice if recipients are likely to be susceptible to measles or mumps as well as to rubella. Evidence of rubella immunity should be determined in women of childbearing potential.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsFollowing vaccination in the mother, rubella virus may be transmitted to the nursing infant via breast milk. Infants may show serologic evidence of infection, however, severe disease is not expected.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Frequency not defined.

Cardiovascular: Syncope, vasculitis

Central nervous system: Dizziness, encephalitis, fever, Guillain-Barré syndrome, headache, irritability, malaise, polyneuritis, polyneuropathy

Dermatologic: Angioneurotic edema, erythema multiforme, pruritus, purpura, rash, Stevens-Johnson syndrome, urticaria

Gastrointestinal: Diarrhea, nausea, sore throat, vomiting

Hematologic: Leukocytosis, thrombocytopenia

Local: Injection site reactions which include burning, induration, pain, redness, stinging, wheal and flare

Neuromuscular & skeletal: Arthralgia/arthritis (variable; highest rates in women, 12% to 26% versus children, up to 3%), myalgia, paresthesia

Ocular: Conjunctivitis, optic neuritis, papillitis, retrobulbar neuritis

Otic: Nerve deafness, otitis media

Respiratory: Bronchial spasm, cough, rhinitis

Miscellaneous: Anaphylactoid reactions, anaphylaxis, regional lymphadenopathy

Drug Interactions

Immune Globulins: May diminish the therapeutic effect of Vaccines (Live). *Risk D: Consider therapy modification*

Immunosuppressants: May enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Tuberculin Tests: Vaccines (Live) may diminish the diagnostic effect of Tuberculin Tests. *Risk D: Consider therapy modification*

Test InteractionsMay depress tuberculin skin test sensitivity

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]:

Meruvax® II: ≥1000 TCID_{50} (Wistar RA 27/3 Strain) [contains gelatin, human albumin, sorbitol, sucrose, and neomycin]

Generic AvailableNo

ManufacturerMerck & Co

Mechanism of ActionRubella vaccine is a live attenuated vaccine that contains the Wistar Institute RA 27/3 strain, which is adapted to and propagated in human diploid cell culture. Promotes active immunity by inducing rubella hemagglutination-inhibiting antibodies.

Pharmacodynamics/KineticsOnset of action: Antibodies to vaccine: 2-4 weeks

Related Information

- Immunization Recommendations

Pharmacotherapy PearlsLive virus vaccine. Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent record.

Acceptable presumptive evidence of immunity includes one of the following:

1. Documentation of adequate vaccination
2. Laboratory evidence of immunity
3. Documentation of physician-diagnosed disease

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness, irritability, or malaise
Mental Health: Effects on Psychiatric TreatmentNone reported
Mental Health CommentMay cause encephalitis, Guillain-Barré syndrome, polyneuritis, and polyneuropathy.
Index TermsGerman Measles Vaccine
References

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Centers for Disease Control, “Notice to Readers: Revised ACIP Recommendation for Avoiding Pregnancy After Receiving a Rubella-Containing Vaccine,” *MMWR*, 2001, 50(49):1117. [PubMed 11794623]

Centers for Disease Control, “Simultaneous Administration of Varicella Vaccine and Other Recommended Childhood Vaccine,” *MMWR*, 2001, 50(47):1058-61. [PubMed 11808928]

Gardner P and Schaffner W, “Immunization of Adults,” *N Engl J Med*, 1993, 328(17):1252-8.[PubMed 8464436]

International Brand NamesCendevax (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Ervevax (AT, AU, BG, CH, CZ, DE, GB, IE, IT, MY, NL, NZ, PH, PK, TH, TW); Gunevax (PH, TH); Meruvax II (AU, HK, IT, TW); R-Vac (IN); Rubavax (GB); Rubeaten (AT, CH, CZ, GR, IT); Rubeaten Berna (MY, PH, TH, TW); Rudivax (IL, MY, TW)

Rufinamide

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Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Pronunciation(roo FIN a mide)
U.S. Brand NamesBanzel™
Pharmacologic CategoryAnticonvulsant, Triazole Derivative
Use: Labeled IndicationsAdjunctive therapy in the treatment of generalized seizures of Lennox-Gastaut syndrome
Dosing: Adults**Lennox-Gastaut (adjunctive):** Oral: Initial: 400-800 mg/day in 2 equally divided doses; increase dose by 400-800 mg/day every 2 days until maximum daily dose: 3200 mg/day in 2 equally divided doses
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Lennox-Gastaut (adjunctive):** Children ≥4 years: Oral: Initial: 10 mg/kg/day in 2 equally divided doses; increase dose by ~10 mg/kg/day every other day to a target dose of 45 mg/kg/day **or** 3200 mg/day (whichever is lower) in 2 equally divided doses
Dosing: Renal Impairment

Cl_{cr} <30 mL/minute: No dosage adjustment needed.

Hemodialysis: No specific guidelines available; consider dosage adjustment for loss of drug.

Dosing: Hepatic Impairment
Mild-to-moderate impairment: Use caution.

Severe impairment: Use in severe impairment has not been studied and is not recommended.

Administration: OralAdminister with food. Tablets may be split in half or crushed.
Dietary ConsiderationsTake with food.
StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture.
RestrictionsAn FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.
ContraindicationsPatients with familial short QT syndrome
Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: Has been associated with shortening of the QT interval. Use caution in patients receiving concurrent medications that shorten the QT interval. Contraindicated in patients with familial short-QT syndrome.

- CNS effects: Use has been associated with CNS-related adverse events, most significant of these were cognitive symptoms (including somnolence or fatigue) and coordination abnormalities (including ataxia, dizziness, and gait disturbances). Caution patients about performing tasks which require mental alertness (eg, operating machinery or driving).

- Multiorgan hypersensitivity reactions: Potentially serious, sometimes fatal, multiorgan hypersensitivity reactions have been reported with some antiepileptic drugs, including rufinamide; monitor for signs and symptoms of possible disparate manifestations associated with lymphatic, hepatic, renal, and/or hematologic organ systems; gradual discontinuation and conversion to alternate therapy may be required.

- Rash: Closely monitor any patient who develops a rash; instruct patients to report any rash associated with fever.

- Suicidal ideation: Antiepileptics may increase the risk of suicidal ideation. Monitor patients closely for unusual changes in mood or behavior, worsening depression, or suicidal behavior or thoughts. Caregivers and families should also be educated to watch for these signs and symptoms and notify healthcare provider if signs/symptoms develop.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with mild to moderate impairment; use in not recommended in patients with severe impairment.

Concurrent drug therapy issues:

- Contraceptive failure: Concurrent use with hormonal contraceptives may lead to contraceptive failure.

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Other warnings/precautions:

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal. Reducing dose by ~25% every two days was effective in trials.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse effects were seen in animal studies. There are no adequate and well-controlled studies in pregnant women; use during pregnancy only if clearly needed. Hormonal contraceptives may be less effective with concurrent rufinamide use; additional forms of nonhormonal contraceptives should be used.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsExcretion into breast milk is unknown, but may be expected. Breast-feeding is not recommended by the manufacturer due to the potential for adverse effects in the nursing infant.

Adverse Reactions

>10%:

Cardiovascular: QT shortening (46% to 65%; dose related)

Central nervous system: Headache (16% to 27%), somnolence (11% to 24%), dizziness (3% to 19%), fatigue (9% to 16%)

Gastrointestinal: Vomiting (5% to 17%), nausea (7% to 12%)

1% to 10%:

Central nervous system: Ataxia (4 % to 5%), seizure (children 5%), status epilepticus (up to 4%), aggression (children 3%), anxiety (adults 3%), attention disturbance (children 3%), hyperactivity (children 3%), vertigo (adults 3%)

Dermatologic: Rash (children 4%), pruritus (children 3%)

Gastrointestinal: Appetite decreased (≥1% to 5%), abdominal pain (3%), constipation (adults 3%), dyspepsia (adults 3%), appetite increased (≥1%)

Hematologic: Leukopenia (≤4%), anemia (≥1%)

Neuromuscular & skeletal: Tremor (adults 6%), back pain (adults 3%), gait disturbance (1% to 3%)

Ocular: Diplopia (4% to 9%), blurred vision (adults 6%), nystagmus (adults 6%)

Otic: Otitis media (children 3%)

Renal: Pollakiuria (≥1%)

Respiratory: Nasopharyngitis (≥5%), bronchitis (children 3%), sinusitis (children 3%)

Miscellaneous: Influenza (children 5%)

<1%, postmarketing, and/or case reports: Atrioventricular block (first degree), bundle branch block (right), dysuria, enuresis, hematuria, incontinence, iron-deficiency anemia, lymphadenopathy, nephrolithiasis, neutropenia, nocturia, polyuria, thrombocytopenia, urinary incontinence

In addition, multiorgan hypersensitivity (including rash, urticaria, facial edema, fever, eosinophilia, stuporous state, severe hepatitis, LFTs increased) has been reported.

Drug Interactions

CarBAMazepine: Rufinamide may decrease the serum concentration of CarBAMazepine. CarBAMazepine may decrease the serum concentration of Rufinamide. *Risk C: Monitor therapy*

Ethinyl Estradiol: Rufinamide may decrease the serum concentration of Ethinyl Estradiol. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Norethindrone: Rufinamide may decrease the serum concentration of Norethindrone. *Risk D: Consider therapy modification*

PHENobarbital: Rufinamide may increase the serum concentration of PHENobarbital. PHENobarbital may decrease the serum concentration of Rufinamide. *Risk C: Monitor therapy*

Phenytoin: Rufinamide may increase the serum concentration of Phenytoin. Phenytoin may decrease the serum concentration of Rufinamide. *Risk C: Monitor therapy*

Primidone: May decrease the serum concentration of Rufinamide. *Risk C: Monitor therapy*

Valproic Acid: May increase the serum concentration of Rufinamide. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Food increases the absorption of rufinamide.

Herb/Nutraceutical: Avoid evening primrose (seizure threshold decreased).

Monitoring ParametersSeizure (frequency and duration); serum levels of concurrent anticonvulsants

Monitoring: Lab TestsSerum levels of concurrent anticonvulsants

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Banzel™: 200 mg, 400 mg

Generic AvailableNo

ManufacturerEisai Co, Ltd

Mechanism of ActionA triazole-derivative antiepileptic whose exact mechanism is unknown. *In vitro*, it prolongs the inactive state of the sodium channels, thereby limiting repetitive firing of sodium-dependent action potentials mediating anticonvulsant effects.

Pharmacodynamics/Kinetics

Absorption: Slow; extensive ≥85%; increased with food

Distribution: V_d: ~50 L

Protein binding: 34%, primarily to albumin

Metabolism: Extensively via carboxylesterase-mediated hydrolysis of the carboxylamide group to CGP 47292 (inactive metabolite); weak inhibitor of CYP2E1 and weak inducer of CYP3A4

Bioavailability: Extent decreased with increased dose

Half-life elimination: ~6-10 hours

Time to peak, plasma: 4-6 hours

Excretion: Urine (85%, ~66% as CGP 47292, <2% as unchanged drug)

Dental Health Professional ConsiderationsRufinamide is known to prolong the QT interval. The QT interval is measured as the time and distance between the Q point of the QRS complex and the end of the T wave in the ECG tracing. After adjustment for heart rate, the QT interval is defined as prolonged if it is more than 450 msec in men and 460 msec in women. A long QT syndrome was first described in the 1950s and 60s as a congenital syndrome involving QT interval prolongation and syncope and sudden death. Some of the congenital long QT syndromes were characterized by a peculiar electrocardiographic appearance of the QRS complex involving a premature atria beat followed by a pause, then a subsequent sinus beat showing marked QT prolongation and deformity. This type of cardiac arrhythmia was originally termed “torsade de pointes” (translated from the French as “twisting of the points”).

Prolongation of the QT interval is thought to result from delayed ventricular repolarization. The repolarization process within the myocardial cell is due to the efflux of intracellular potassium. The channels associated with this current can be blocked by many drugs and predispose the electrical propagation cycle to torsade de pointes.

Rufinamide is considered as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. It is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsRufinamde may prolong QT interval resulting in cardiac conduction problems; it is not known what effect vasoconstrictors will have in patients taking medications that could prolong QT interval. It is suggested that the clinician consult with the physician prior to use of vasoconstrictor in suspected patients; use vasoconstrictor with caution.

Index TermsCGP 33101; E 2080; RUF 331; Xilep

References

Deeks ED and Scott LJ, “Rufinamide,” *CNS Drugs*, 2006, 20(9):751-60.[PubMed 16953653]

Glauser T, Kluger G, Sachdeo R, et al, “Rufinamide for Generalized Seizures Associated With Lennox-Gastaut Syndrome,” *Neurology*, 2008, 70(21):1950-8.[PubMed 18401024]

Perucca E, Cloyd J, Critchley D, et al, “Rufinamide: Clinical Pharmacokinetics and Concentration-Response Relationships in Patients With Epilepsy,” *Epilepsia*, 2008, 49(7):1123-41.[PubMed 18503564]

Saccharomyces boulardii'; return;">

Saccharomyces boulardii

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(sak roe MYE sees boo LAR dee)

U.S. Brand NamesFlorastor® Kids [OTC]; Florastor® [OTC]

Pharmacologic CategoryDietary Supplement; Probiotic

Use: Labeled IndicationsPromote maintenance of normal microflora in the gastrointestinal tract; used in management of bloating, gas, and diarrhea, particularly to decrease the incidence of diarrhea associated with antibiotic use

Dosing: Adults**Dietary supplement:** Oral: Dosing varies by manufacturer; consult product labeling.

Florastor®: 250 mg twice daily

Dosing: ElderlyRefer to adult dosing. Use caution in debilitated patients.

Dosing: Pediatric**Dietary supplement:** Oral: Dosing varies by manufacturer; consult product labeling.

Florastor® Kids: 250 mg twice daily

Dietary ConsiderationsFlorastor® and Florastor® Kids: Contain lactose; may be given with or without food.

StorageSome preparations may need to be refrigerated or stored in freezer; consult individual product labeling.

Florastor®, Florastor® Kids: Store at ≤25°C (≤77°F); refrigeration not necessary.

ContraindicationsHypersensitivity to *Saccharomyces boulardii* or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Yeast allergy: Use with caution in patients allergic to yeast; *S. boulardii* is a live yeast preparation and a subtype of the species, *S. cervasiae*, which is also referred to as “baker’s yeast” or “brewer’s yeast.”

Concurrent drug therapy issues:

- Antifungals: Avoid use in patients with concurrent systemic antifungals; *S. boulardii* may be susceptible.

Special populations:

- Immunocompromised patients: Use with caution or avoid use in immunocompromised, debilitated, or critically ill patients, particularly those with a central venous catheter and/or previous or current antibiotic therapy; *S. boulardii*, although a nonpathogenic yeast, use has been associated with case reports of fungemia in this population.

Dosage form specific issues:

- Lactose: Some products may contain lactose; use with caution in patients with lactose intolerance.
- Various preparations: Significant differences may exist from one preparation of *S. boulardii* compared to another with respect to biologic activity and composition.

Other warnings/precautions:

- Dietary supplement: Probiotics are classified as dietary supplements; therefore, there are no safety reviews or approved therapeutic indications by the FDA. There is no conclusive evidence to support widespread use in the treatment of diarrhea.

Geriatric ConsiderationsUse caution in debilitated patients.

Adverse ReactionsFrequency not defined.

Gastrointestinal: Constipation, flatulence

Miscellaneous: Thirst

Postmarketing and/or case reports: Fungemias

Drug Interactions

Antifungal Agents: May diminish the therapeutic effect of Saccharomyces boulardii. **Exceptions:** Butenafine; Butoconazole; Ciclopirox; Econazole; Gentian Violet; Iodoquinol; Naftifine; Natamycin; Oxiconazole; Povidone-Iodine; Sertaconazole; Sulconazole; Sulfanilamide; Terconazole; Tioconazole; Tolnaftate; Triacetin; Undecylenic Acid. *Risk D: Consider therapy modification*

Patient EducationMay cause constipation, bloating, or excessive gas. Consult prescriber if unable to manage independently.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, oral:

Florastor®: *S. boulardii lyo* 250 mg [provides 5 billion live cells; contains lactose 32.5 mg and magnesium 2.85 mg per capsule]

Powder, oral:

Florastor® Kids: *S. boulardii lyo* 250 mg/packet (10s) [provides 5 billion live cells; contains lactose 32.5 mg and magnesium 2.85 mg per packet; tutti frutti flavor]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Pack (Florastor Kids)

250 mg (10): $17.99

Mechanism of Action*S. boulardii*, a nonpathogenic live yeast probiotic, acts as temporary flora to help re-establish the normal gastrointestinal microflora. May also modulate the immune system by inducing cytokines and suppress pathogenic bacteria growth.

Pharmacodynamics/Kinetics

Onset of action: Yeast cell release from capsules/powder: 30 minutes

Duration: Yeast cells cleared in 5-7 days

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms*S. boulardii*; *Saccharomyces boulardii lyo*

References

Enache-Angoulvant A and Hennequin C, “Invasive Saccharomyces Infection: A Comprehensive Review,” *Clin Infect Dis*, 2005, 41(11):1559-68.[PubMed 16267727]

International Brand NamesCodex (IT); Econorm (IN); Enflor (PK); Enterol (BE, BG, CZ, EE); Floratil (AR, CO, EC, MX, PE); Florestor (VE); Inteflora (ZA); Perenterol (CH, CR, DO, GT, HN, NI, PA, PY, SV); Perenteryl (CN); Perocur (CN); Precosa (FI, NO, SE); UL-250 (PT); Ultra-Levora (ES)

Sacrosidase

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English English

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Special Alerts

Sacrosidase (Sucraid®): Manufacturing Change May Lead to an Increase in Papain-Induced Hypersensitivity Reactions - December 2008

To prevent any shortages of sacrosidase (Sucraid®) oral solution, the Food and Drug Administration (FDA) has allowed for a manufacturing change which permits QOL Medical, the sole manufacturer of Sucraid®, to obtain the active ingredient, sacrosidase, from a different manufacturer. However, the newly manufactured product may contain increased levels of papain, which may be introduced during the manufacturing process performed to obtain sacrosidase. Steps are taken to remove any papain contamination, but there is no assurance that papain has been completely eliminated from the final product. Papain exposure has been associated with severe hypersensitivity reactions, including anaphylaxis. Tachycardia and hypotension have also been observed in association with some papain-induced hypersensitivity reactions. In addition, some data also suggest a possible cross-sensitivity may exist between patients with natural rubber latex hypersensitivity and papaya, the source of papain.

For additional information, refer to:

> http://www.fda.gov/bbs/topics/NEWS/2008/NEW01915.html
>
> http://www.fda.gov/cder/news/papain/qa.htm

Pronunciation(sak ROE si dase)
U.S. Brand NamesSucraid®
Canadian Brand NamesSucraid®
Pharmacologic CategoryEnzyme, Gastrointestinal
Use: Labeled Indications**Orphan drug:** Oral replacement therapy in sucrase deficiency, as seen in congenital sucrase-isomaltase deficiency (CSID)
Dosing: Adults**Sucrase deficiency:** Oral: 17,000 int. units (2 mL) per meal or snack. Doses should be diluted with 2-4 ounces of water, milk or formula with each meal or snack. Approximately one-half of the dose may be taken before, and the remainder of a dose taken at the completion of each meal or snack.
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Infants ≥5 months and Children <15 kg: Oral: 8500 int. units (1 mL) per meal or snack

Children >15 kg: Refer to adult dosing.

Administration: OralDo not administer with fruit juices, warm or hot liquids; the solution is fully soluble with water, milk, or formula
StorageStore under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from heat or light. After initial opening, discard any unused product after 4 weeks.
RestrictionsSucraid® is not available in retail pharmacies or via mail-order pharmacies. To obtain the product, please refer to http://www.sucraid.net/ or call 1-866-740-2743.
ContraindicationsHypersensitivity to yeast, yeast products, or glycerin
Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Hypersensitivity reactions to sacrosidase, including bronchospasm, have been reported. Administer initial doses in a setting where acute hypersensitivity reactions may be treated within a few minutes. Skin testing for hypersensitivity may be performed prior to administration to identify patients at risk.

Dosage form specific issues

- Papain: Product may contain papain. Severe hypersensitivity reactions, including anaphylaxis, have been observed with papain exposure. Tachycardia and hypotension, in association with some papain-induced hypersensitivity reactions, has also been observed. In addition, inconclusive data suggests a possible cross-sensitivity may exist between patients with natural rubber latex hypersensitivity and papaya, the source of papain.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies have not been conducted. Should be administered to a pregnant woman only when indicated.
LactationEnters breast milk/compatible
Adverse Reactions

1% to 10%: Gastrointestinal: Abdominal pain, constipation, diarrhea, nausea, vomiting

<1%: Bronchospasm, dehydration, headache, hypersensitivity reaction, insomnia, nervousness

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsFood: May be inactivated or denatured if administered with fruit juice, warm or hot food or liquids. Since isomaltase deficiency is not addressed by supplementation of sacrosidase, adherence to a low-starch diet may be required.

Nursing: Physical Assessment/MonitoringHypersensitivity reactions can occur (including bronchospasm), administer initial dose where adverse reactions can be treated immediately; skin testing for hypersensitivity may be performed prior to administering first dose to identify patients at risk. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationUse exactly as directed. Dilute dose in 2-4 oz of water, milk, or formula; do not dilute with fruit juice or warm or cold liquids. Take half the dose at beginning of meal and half the dose at end of meal. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Follow prescribers recommended diet exactly. You may experience headache or nervousness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea, vomiting, or GI disturbance (frequent mouth care, chewing gum, or sucking hard candy may help). Report immediately skin rash or respiratory difficulty; persistent vomiting, abdominal pain, or blood in stools; change in CNS status (depression, agitation, lethargy); or other adverse response. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral:

Sucraid®: 8500 int. units per mL (118 mL)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Sucraid)

8500 units/mL (118): $347.32

Mechanism of ActionSacrosidase is a naturally-occurring gastrointestinal enzyme which breaks down the disaccharide sucrose to its monosaccharide components. Hydrolysis is necessary to allow absorption of these nutrients.

Pharmacodynamics/Kinetics

Absorption: Amino acids

Metabolism: GI tract to individual amino acids

Pharmacotherapy PearlsOral solution contains 50% glycerol. Oral solution may contain papain, an enzyme used during the manufacturing process to obtain sacrosidase.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

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International Brand NamesSucraid (TW)

Salicylic Acid

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Occlusal®-HP may be confused with Ocuflox®

Transdermal patch may contain conducting metal (eg, aluminum); remove patch prior to MRI.

Pronunciation(sal i SIL ik AS id)

U.S. Brand NamesAkurza; Aliclen™; Beta Sal® [OTC]; Compound W® One-Step Wart Remover for Feet [OTC]; Compound W® One-Step Wart Remover for Kids [OTC]; Compound W® One-Step Wart Remover [OTC]; Compound W® [OTC]; Dermarest® Psoriasis Medicated Moisturizer [OTC]; Dermarest® Psoriasis Medicated Scalp Treatment [OTC]; Dermarest® Psoriasis Medicated Shampoo/Conditioner [OTC]; Dermarest® Psoriasis Medicated Skin Treatment [OTC]; Dermarest® Psoriasis Overnight Treatment [OTC]; Dermarest® Psoriasis Scalp Treatment Mousse [OTC] [DSC]; DHS™ Sal [OTC]; Freezone® [OTC]; Fung-O® [OTC]; Gordofilm® [OTC]; Hydrisalic™ [OTC]; Ionil Plus® [OTC]; Ionil® [OTC]; Keralyt® [OTC]; LupiCare® Dandruff [OTC]; LupiCare® Psoriasis Scalp [OTC] [DSC]; LupiCare® Psoriasis [OTC]; Mosco® Callus & Corn Remover [OTC]; Neutrogena® Advanced Solutions™ [OTC]; Neutrogena® Blackhead Eliminating™ 2-in-1 Foaming Pads [OTC]; Neutrogena® Blackhead Eliminating™ Astringent [OTC] [DSC]; Neutrogena® Blackhead Eliminating™ Daily Scrub [OTC]; Neutrogena® Blackhead Eliminating™ Treatment Mask [OTC] [DSC]; Neutrogena® Body Clear® [OTC]; Neutrogena® Clear Pore™ Oil-Controlling Astringent [OTC]; Neutrogena® Oil-Free Acne Wash 60 Second Mask Scrub [OTC]; Neutrogena® Oil-Free Acne Wash Cream Cleanser [OTC]; Neutrogena® Oil-Free Acne Wash Foam Cleanser [OTC]; Neutrogena® Oil-Free Acne Wash [OTC]; Neutrogena® Rapid Clear® Acne Defense [OTC]; Neutrogena® Rapid Clear® Acne Eliminating [OTC]; Occlusal®-HP [OTC]; Off-Ezy® Wart Remover [OTC] [DSC]; P&S® [OTC]; Palmer's® Skin Success Acne Cleanser [OTC]; Sal-Acid® [OTC]; Sal-Plant® [OTC]; Salactic® [OTC]; SalAc® [OTC]; Salex®; Salex™ [DSC]; Salitop™; Stridex® Essential Care® [OTC]; Stridex® Facewipes To Go® [OTC]; Stridex® Maximum Strength [OTC]; Stridex® Sensitive Skin [OTC]; Tinamed® Corn and Callus Remover [OTC]; Tinamed® Wart Remover [OTC]; Trans-Ver-Sal® [OTC]; Wart-Off® Maximum Strength [OTC]

Canadian Brand NamesDuofilm®; Duoforte® 27; Occlusal™-HP; Sebcur®; Soluver®; Soluver® Plus; Trans-Plantar®; Trans-Ver-Sal®

Pharmacologic CategoryAcne Products; Keratolytic Agent; Topical Skin Product, Acne

Use: Labeled IndicationsTopically for its keratolytic effect in controlling seborrheic dermatitis or psoriasis of body and scalp, dandruff, and other scaling dermatoses; also used to remove warts, corns, and calluses; acne

Dosing: Adults

Acne:

Cream, cloth, foam, or liquid cleansers (2%): Use to cleanse skin once or twice daily. Massage gently into skin, work into lather and rinse thoroughly. Cloths should be wet with water prior to using and disposed of (not flushed) after use.

Gel (0.5% or 2%): Apply small amount to face in the morning or evening; if peeling occurs, may be used every other day. Some products may be labeled for OTC use up to 3 or 4 times per day. Apply to clean, dry skin

Pads (0.5% or 2%): Use pad to cover affected area with thin layer of salicylic acid one to three times a day. Apply to clean, dry skin. Do not leave pad on skin.

Patch (2%): At bedtime, after washing face, allow skin to dry at least 5 minutes. Apply patch directly over pimple being treated. Remove in the morning.

Shower/bath gels or soap (2%): Use once daily in shower or bath to massage over skin prone to acne. Rinse well.

Callus, corns, or warts:

Gel or liquid (17%): Apply to each wart and allow to dry. May repeat once or twice daily, up to 12 weeks. Apply to clean dry area.

Gel (6%): Apply to affected area once daily, generally used at night and rinsed off in the morning.

Plaster or transdermal patch (40%): Apply directly over affected area, leave in place for 48 hours. Some products may be cut to fit area or secured with adhesive strips. May repeat procedure for up to 12 weeks. Apply to clean, dry skin

Transdermal patch (15%): Apply directly over affected area at bedtime, leave in place overnight and remove in the morning. Patch should be trimmed to cover affected area. May repeat daily for up to 12 weeks.

Dandruff, psoriasis, or seborrheic dermatitis:

Cream (2.5%): Apply to affected area 3-4 times daily. Apply to clean, dry skin. Some products may be left in place overnight.

Ointment (3%): Apply to scales or plaques on skin up to 4 times per day (not for scalp or face)

Shampoo (1.8% to 3%): Massage into wet hair or affected area; leave in place for several minutes; rinse thoroughly. Labeled for OTC use 2-3 times a week, or as directed by healthcare provider. Some products may be left in place overnight.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren: Refer to adult dosing.

Consult specific product labeling for use in children <12 years.

ContraindicationsHypersensitivity to salicylic acid or any component of the formulation
Allergy Considerations

- Salicylate Allergy/Sensitivity

Warnings/Precautions

Disease-related concerns:

- Diabetes: Prior to OTC use, consult with healthcare provider if you have diabetes.

- Poor circulation: Prior to OTC use, consult with healthcare provider if have poor circulation.

Other warnings/precautions:

- Appropriate use: For external use only; not for application to areas that are irritated, infected, reddened, birthmarks, genital or facial warts, eyes or mucous membranes.

Geriatric ConsiderationsNo specific considerations are needed if used according to recommended doses and duration of use. Many elderly may have diabetes or impaired circulation and avoidance of topical salicylic acid would be advised.
Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined.

Central nervous system: Dizziness, mental confusion, headache

Local: Burning and irritation at site of exposure on normal tissue, peeling, scaling

Otic: Tinnitus

Respiratory: Hyperventilation

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol, topical [foam]:

Dermarest® Psoriasis Scalp Treatment Mousse: 3% (90 mL) [DSC]

Bar, topical [soap]: 2%

Cloth, topical:

Neutrogena® Oil-Free Acne Wash: 2% (30s)

Cream, topical: 6% (400 g)

Akurza: 6% (340 g)

LupiCare® Psoriasis Scalp: 2% (113 g, 227 g) [DSC]

LupiCare™ Psoriasis: 2% (56 g [DSC]; 227 g)

Neutrogena® Oil-Free Acne Wash Cream Cleanser: 2% (200 mL) [contains ethanol]

Salex®: 6% (400 g [DSC]; 454 g)

Salex™: 6% (400 g) [DSC]

Salitop™: 6% (400 g) [contains ethanol]

Gel, topical:

Compound W®: 17.6% (7 g) [contains ethanol 67.5%]

Dermarest® Psoriasis Medicated Scalp Treatment: 3% (118 mL)

Dermarest® Psoriasis Medicated Skin Treatment: 3% (118 mL)

Dermarest® Psoriasis Overnight Treatment: 3% (56.7 g)

Hydrisalic®: 6% (28 g) [contains ethanol]

Keralyt®: 3% (30 g); 6% (40 g) [contains ethanol 21%]

Neutrogena® Oil-Free Acne Wash: 2% (177 mL) [contains tartrazine]

Neutrogena® Rapid Clear® Acne Eliminating: 2% (15 mL) [contains ethanol 38%]

Sal-Plant®: 17% (14 g) [contains isopropyl alcohol]

Gel, topical [mask]:

Neutrogena® Blackhead Eliminating™ Treatment Mask: 0.5% (56 g) [DSC]

Gel, topical [peel]:

Neutrogena® Advanced Solutions™: 2% (40 g)

Liquid, topical: 17% (14.8 mL)

Compound W®: 17.6% (9 mL) [contains ethanol 21.2%]

Freezone®: 17.6% (9.3 mL) [contains ethanol]

Fung-O®: 17% (15 mL) [contains ethanol 2%]

Gordofilm: 16.7% (15 mL)

Mosco® Callus & Corn Remover: 17.6% (9 mL) [contains ethanol 27%]

Neutrogena® Blackhead Eliminating™ Astringent: 0.5% (250 mL) [contains ethanol 35%] [DSC]

Neutrogena® Blackhead Eliminating™ Daily Scrub: 2% (125 mL)

Neutrogena® Clear Pore™ Oil-Controlling Astringent: 2% (236 mL) [contains ethanol 45%]

Occlusal®-HP: 17% (10 mL)

Off-Ezy® Wart Remover: 17% (13.3 mL) [DSC]

Palmer's® Skin Success Acne Cleanser: 0.5% (240 mL) [contains aloe, vitamin E]

Salactic®: 17% (15 mL) [contains isopropyl alcohol]

Tinamed® Corn and Callus Remover: 17% (15 mL)

Tinamed® Wart Remover: 17% (15 mL)

Wart-Off® Maximum Strength: 17% (13 mL) [contains ethanol]

Liquid, topical [body scrub with microbeads]:

Neutrogena® Body Clear®: 2% (250 mL) [contains tartrazine]

Liquid, topical [body wash]:

Neutrogena® Body Clear®: 2% (250 mL) [contains tartrazine]

Liquid, topical [cleanser]:

SalAc®: 2% (177 mL) [contains benzyl alcohol]

Liquid, topical [foam]:

Neutrogena® Oil-Free Acne Wash Foam Cleanser: 2% (150 mL)

Liquid, topical [mask/wash]:

Neutrogena® Oil-Free Acne Wash 60 Second Mask Scrub: 1% (170 g) [ethanol free]

Lotion, topical: 6% (414 mL, 420 mL)

Akurza: 6% (355 mL)

Dermarest® Psoriasis Medicated Moisturizer: 2% (118 mL)

Neutrogena® Rapid Clear® Acne Defense: 2% (50 mL) [contains ethanol]

Salex®: 6% (237 mL; 414 mL [DSC])

Salex™: 6% (414 mL) [DSC]

Salitop™: 6% (414 mL) [contains ethanol]

Pad, topical:

Neutrogena® Blackhead Eliminating™ 2-in-1 Foaming Pads: 0.5% (28s)

Stridex® Essential Care®: 1% (55s) [ethanol free; contains vitamin A, vitamin E]

Stridex® Facewipes To Go™: 0.5% (32s) [contains aloe, ethanol 28%]

Stridex® Maximum Strength: 2% (55s, 90s) [ethanol free]

Stridex® Sensitive Skin: 0.5% (55s, 90s) [ethanol free]

Patch, topical:

Compound W® One-Step Wart Remover for Feet: 40% (20s)

Compound W® One-Step Wart Remover: 40% (14s)

Compound W® One-Step Wart Remover for Kids: 40% (12s)

Trans-Ver-Sal®: 15% (10s, 25s) [20 mm PlantarPatch]

Trans-Ver-Sal®: 15% (15s, 40s) [contains propylene glycol]

Trans-Ver-Sal®: 15% (12s, 40s) [contains propylene glycol; 12 mm AdultPatch]

Plaster, topical:

Sal-Acid®: 40% (14s) [applied as plaster-impregnated bandages]

Shampoo, topical: 6% (177 mL)

Aliclen™, Salex®: 6% (177 mL)

Beta Sal®: 3% (480 mL)

DHS™ Sal: 3% (120 mL)

Ionil Plus®: 2% (240 mL) [conditioning shampoo]

Ionil®: 2% (120 mL; 240 mL, 480 mL, 960 mL [DSC])

LupiCare® Dandruff: 2% (237 mL)

LupiCare® Psoriasis: 2% (118 mL [DSC]; 237 mL)

P&S®: 2% (118 mL, 236 mL)

Shampoo/conditioner, topical:

Dermarest® Psoriasis Medicated Shampoo/Conditioner: 3% (236 mL)

Generic AvailableYes: Cream, gel, lotion, soap

Pricing: U.S. (www.drugstore.com)

Gel (Keralyt)

3% (28.4): $11.35

6% (40): $42.99

Kit (Salex)

6% (cream) (1): $175.34

6% (lotion) (597): $98.68

Liquid (Occlusal-HP)

17% (10): $23.99

Lotion (Salex)

6% (414): $102.55

Shampoo (Salex)

6% (177): $84.70

Mechanism of ActionProduces desquamation of hyperkeratotic epithelium via dissolution of the intercellular cement which causes the cornified tissue to swell, soften, macerate, and desquamate. Salicylic acid is keratolytic at concentrations of 3% to 6%; it becomes destructive to tissue at concentrations >6%. Concentrations of 6% to 60% are used to remove corns and warts and in the treatment of psoriasis and other hyperkeratotic disorders.

Pharmacodynamics/Kinetics

Absorption: Percutaneous; systemic toxicity unlikely with normal use

Time to peak, serum: Within 5 hours of application with occlusion

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause confusion

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesAcido Salicilico (IT); Acnisal (GB); Acrisal (IE); Anticors Lefebvre (BE); Antiphlogistine (CH); Callicida Globodermis (ES); Callicida Gras (ES); Callicida Salve (ES); Callofin (ES); Clearasil Spot Control 3 in 1 Exfoliating Cleanser (MY, SG); Clearasil Spot Control Ice Wash Gel Cleanser (MY, SG); Clearasil Ultra Deep Pore Cleansing Gel Wash (SG); Clearasil Ultra Deep Pore Cleansing Toner (SG); Clearasil Ultra Deep Pore Treatment Wash (SG); Contrheuma (LU); Coricide le diable (FR); Corn (PL); Corn and Callous (PL); Cornina (ES); Cross Brand (ZA); Disques coricides (FR); Duofilm (NL, PL); Duoplant Gel (CO, CR, DO, GT, HN, NI, PA, SV); Entreik (PL); Feuille de saule (FR); Formule W (NL); Ionil Plus (BR, CN, PE); Isocorn (CH); Lygal (LU); Mediklin (CN); Methazil (IN); Miniderm (PL); Occlusal (GB); Pansements coricides (FR); Plaster na odciski (PL); Pommade Mo Cochon (FR); Psorimed (DE); Saldiam (PL); Salicilico (IT); Salicyl (DK); Salicylol (PL); Salicylzuur Collodium FNA (NL); Salicylzuur Hydrogel FNA (NL); Salicylzuur Zalf FNA (NL); Salicylzuuroplossing FNA (NL); Saliderm Gel (PL); Salikaren (IL); Salisol-2 (IL); Salpad (AR); Salsyvase (SE); Scholl Corn/Callous Removers (IL); Seal and Heal (PL); Septisol (FR); Sicombyl (BE, LU); Soft Corn (PL); Sophtal (FR); Spiritus salicylatus (PL); Squamasol (AT); Sunspot Cream (AU); Trans-Ver-Sal (IT); Transvercid (FR); Unguento Morryth (ES); Unguentum acidi salicylici (PL); Urgo Cor Dressing (PL); Urgocall (ES); Verrugon (GB); Verrutrix (AR); Wart-Off (PH)

Saliva Substitute

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(sa LYE va SUB stee tute)

U.S. Brand NamesAquoral™; Caphosol®; Entertainer's Secret® [OTC]; Moi-Stir® [OTC]; Mouthkote® [OTC]; Numoisyn™; Oasis®; Oral Balance® [OTC]; Saliva Substitute® [OTC] [DSC]; Salivart® [OTC]; SalivaSure™ [OTC]

Pharmacologic CategoryGastrointestinal Agent, Miscellaneous

Use: Labeled IndicationsRelief of dry mouth and throat in xerostomia or hyposalivation; adjunct to standard oral care in relief of symptoms associated with chemotherapy or radiation therapy-induced mucositis

Use: DentalRelief of dry mouth and throat in xerostomia

Dosing: Adults

Mucositis (due to high-dose chemotherapy or radiation therapy): Caphosol®: Swish and spit 4-10 doses per day beginning at onset of chemo- or radiation therapy

Xerostomia: Oral: Use as needed, or product-specific dosing:

Caphosol®: Swish and spit 2-10 doses per day

Numoisyn™ liquid: Use 2 mL as needed

Numoisyn™ lozenges: Dissolve 1 lozenge in mouth as needed; maximum 16 lozenges/day

Oasis® mouthwash: Rinse mouth with ~30 mL twice daily or as needed; do not swallow

Oasis® spray: 1-2 sprays as needed; maximum 60 sprays/day

Oral Balance®: Use after meals, at bedtime, and as needed

Dosing: ElderlyRefer to adult dosing.

Administration: Oral

Caphosol®: Mix contents of 1 blue (A) and 1 clear (B) ampul in clean container, swish thoroughly with $^{1}/_{2}$ of mixture (15 mL) for 1 minute and spit; repeat. Avoid eating or drinking for at least 15 minutes after use.

Numoisyn™ liquid: Rinse in mouth before swallowing.

Numoisyn™ lozenges: Dissolve slowly in mouth.

Oasis® mouthwash: Rinse for 30 seconds.

Oasis® spray: Spray into mouth holding bottle upright; do not rinse.

Dietary ConsiderationsCaphosol®: Contains sodium 75 mg/30 mL dose

Storage

Caphosol®: Store at room temperature; do not refrigerate.

Numoisyn™ liquid: Store at room temperature; do not refrigerate. Use within 3 months after opening.

Numoisyn™ lozenges: Store at room temperature.

ReconstitutionCaphosol®: Mix contents of 1 blue (A) and 1 clear (B) ampul in clean container; use immediately after mixing.

Geriatric ConsiderationsSaliva production has not been shown to change with aging, however, many drugs used by elderly can cause dry mouth. These patients may benefit from a saliva substitute.

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Liquid:

Numoisyn™: Water, sorbitol, linseed extract, *Chondrus crispus*, methylparaben, sodium benzoate, potassium sorbate, dipotassium phosphate, propylparaben (300 mL)

Oral Balance®: Water, starch, sunflower oil, propylene glycol, xylitol, glycerine, purified milk extract (45 mL) [sugar-free]

Lozenge:

Numoisyn™: Sorbitol 0.3 g/lozenge, polyethylene glycol, malic acid, sodium citrate, calcium phosphate dibasic, hydrogenated cottonseed oil, citric acid, magnesium stearate, silicon dioxide (100s)

SalivaSure™: Xylitol, citric acid, apple acid, sodium citrate dihydrate, sodium carboxymethylcellulose, dibasic calcium phosphate, silica colloidal, magnesium stearate, stearic acid (90s)

Solution, oral:

Caphosol®: Dibasic sodium phosphate 0.032%, monobasic sodium phosphate 0.009%, calcium chloride 0.052%, sodium chloride 0.569%, purified water (30 mL) [packaged in two 15 mL ampuls when mixed together provide one 30 mL dose]

Entertainer's Secret®: Sodium carboxymethylcellulose, aloe vera gel, glycerin (60 mL) [alcohol-free; honey-apple flavor]

Saliva Substitute®: Sorbitol, sodium carboxymethylcellulose, methylparaben (120 mL) [alcohol free, dye free, sugar free; mild mint flavor] [DSC]

Solution, oral [mouthwash/gargle]:

Oasis®: Water, glycerin, sorbitol, poloxamer 338, PEG-60, hydrogenated castor oil, copovidone, sodium benzoate, carboxymethycellulose (473 mL) [alcohol free, sugar free; mild mint flavor]

Solution, oral [preservative free; spray]:

Salivart®: Water, sodium carboxymethylcellulose, sorbitol, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, potassium phosphate (74 mL) [alcohol free]

Solution, oral [spray]:

Aquoral™: Oxidized glycerol triesters and silicon dioxide (40 mL) [contains aspartame; delivers 400 sprays, citrus flavor]

Moi-Stir®: Water, sorbitol, sodium carboxymethylcellulose, methylparaben, propylparaben, potassium chloride, dibasic sodium phosphate, calcium chloride, magnesium chloride, sodium chloride (120 mL)

Mouthkote®: Water, xylitol, sorbitol, yerba santa, citric acid, ascorbic acid, sodium saccharin, sodium benzoate (5 mL, 60 mL, 240 mL) [alcohol free, sugar free; lemon-lime flavor]

Oasis®: Glycerin, cetylpyridinium, copovidone (30 mL) [alcohol free, sugar free; contains sodium benzoate; delivers ~150 sprays, mild mint flavor]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Aerosol solution (Aquoral)

(40): $82.99

Mechanism of ActionProtein or electrolyte mixtures which restore/replace saliva, lubricate, moisten, and provide a coating on oral mucosa

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsArtificial Saliva

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Salmeterol

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Salmeterol may be confused with Salbutamol, Solu-Medrol®

Serevent® may be confused with Atrovent®, Combivent®, Serentil®, sertraline, Sinemet®, Spiriva®, Zoloft®

Pronunciation(sal ME te role)

U.S. Brand NamesSerevent® Diskus®

Canadian Brand NamesSerevent® Diskhaler® Disk; Serevent® Diskus®

Pharmacologic CategoryBeta$_2$ Agonist; Beta$_2$-Adrenergic Agonist, Long-Acting

Use: Labeled IndicationsMaintenance treatment of asthma; prevention of bronchospasm with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma; prevention of exercise-induced bronchospasm; maintenance treatment of bronchospasm associated with COPD

Dosing: Adults

Asthma, maintenance and prevention: Inhalation, powder (50 mcg/inhalation): One inhalation twice daily (~12 hours apart); maximum: 1 inhalation twice daily. **Note:** For long-term asthma control, long acting beta$_2$-agonists (LABAs) should be used in combination with inhaled corticosteroids and not as monotherapy.

Exercise-induced asthma, prevention: Inhalation, powder (50 mcg/inhalation): One inhalation at least 30 minutes prior to exercise; additional doses should not be used for 12 hours; should not be used in individuals already receiving salmeterol twice daily. **Note:** Because LABAs may disguise poorly controlled persistent asthma, frequent or chronic use of LABAs for exercise-induced bronchospasm is discouraged by the NIH Asthma Guidelines (NIH, 2007).

COPD maintenance: Inhalation, powder (50 mcg/inhalation): One inhalation twice daily (~12 hours apart); maximum: 1 inhalation twice daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Asthma (maintenance/prevention) and exercise-induced asthma (prevention):** Inhalation, powder (50 mcg/inhalation): Children ≥4 years: Refer to adult dosing.

Dosing: Hepatic ImpairmentNo dosage adjustment required; manufacturer suggests close monitoring of patients with hepatic impairment.

Administration: Inhalation**Not** to be used for the relief of acute attacks. Not for use with a spacer device. Administer with Diskus® in a level, horizontal position. Do not wash mouthpiece; Diskus® should be kept dry.

Dietary ConsiderationsPowder for oral inhalation contains lactose; very rare anaphylactic reactions have been reported in patients with severe milk protein allergy.

StorageInhalation powder (Serevent® Diskus®): Store at controlled room temperature 20°C to 25°C (68°F to 77°F) in a dry place away from direct heat or sunlight. Stable for 6 weeks after removal from foil pouch.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to salmeterol or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Asthma-related deaths: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Asthma-related deaths: **[U.S. Boxed Warning]: Long-acting beta$_2$-agonists (LABAs) may increase the risk of asthma-related deaths. Salmeterol should only be used as adjuvant therapy in patients not adequately controlled on inhaled corticosteroids or whose disease requires two maintenance therapies.** In a large, randomized clinical trial (SMART, 2006), salmeterol was associated with a small, but statistically significant increase in asthma-related deaths (when added to usual asthma therapy); risk may be greater in African-American patients versus Caucasians.

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.

- Hypersensitivity reactions: Immediate hypersensitivity reactions (urticaria, angioedema, rash, bronchospasm) have been reported.

- Serious effects/fatalities: Do not exceed recommended dose; serious adverse events, including fatalities, have been associated with excessive use of inhaled sympathomimetics.

- Upper airway symptoms: There have been reports of laryngeal spasm, irritation, swelling (stridor, choking) with use.

Disease-related concerns:

- Asthma: Appropriate use: Do **not** use for acute asthmatic symptoms. Short-acting beta$_2$-agonist (eg, albuterol) should be used for acute symptoms and symptoms occurring between treatments. Do **not** initiate in patients with significantly worsening or acutely deteriorating asthma; reports of severe (sometimes fatal) respiratory events have been reported when salmeterol has been initiated in this situation. Salmeterol should only be used as adjuvant therapy in patients not adequately controlled on inhaled corticosteroids or whose disease requires two maintenance therapies. Corticosteroids should not be stopped or reduced when salmeterol is initiated. Salmeterol is not a substitute for inhaled or systemic corticosteroids and should not be used as monotherapy. During the initiation of salmeterol watch for signs of worsening asthma.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease (arrhythmia, hypertension or HF); beta-agonists may cause elevation in blood pressure, heart rate and result in CNS stimulation/excitation. Beta$_2$-agonists may also increase risk of arrhythmias.

- Diabetes: Use with caution in patients with diabetes mellitus; beta$_2$-agonists may increase serum glucose.

- Exercise-induced bronchospasm: Because LABAs may disguise poorly controlled persistent asthma, frequent or chronic use of LABAs for exercise-induced bronchospasm is discouraged by the NIH Asthma Guidelines (NIH, 2007).

- Glaucoma: Use with caution in patients with glaucoma; may elevate intraocular pressure.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Hyperthyroidism: Use with caution in hyperthyroidism; may stimulate thyroid activity.

- Hypokalemia: Use with caution in patients with hypokalemia; beta$_2$-agonists may decrease serum potassium.

- Seizures: Use with caution in patients with seizure disorders; beta-agonists may result in CNS stimulation/excitation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <4 years of age.

Dosage form specific issues:

- Lactose: Powder for oral inhalation contains lactose; very rare anaphylactic reactions have been reported in patients with severe milk protein allergy.

Other warnings/precautions:

- Patient information: Patients must be instructed to use inhaled short-acting beta$_2$-agonists (eg, albuterol) for acute asthmatic or COPD symptoms and to seek medical attention in cases where acute symptoms are not relieved or a previous level of response is diminished. The need to increase frequency of use of inhaled short-acting beta$_2$-agonist may indicate deterioration of asthma, and treatment must not be delayed. Salmeterol should not be used more than twice daily; do not use with other long-acting beta$_2$-agonists.

Geriatric ConsiderationsGeriatric patients were included in four clinical studies of salmeterol; no apparent differences in efficacy and safety were noted in geriatric patients compared to younger adults. Because salmeterol is only to be used for prevention of bronchospasm, patients also need a short-acting beta-agonist to treat acute attacks. Elderly patients should be carefully counseled about which inhaler to use and the proper scheduling of doses.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have demonstrated (dose-dependent) teratogenicity. There are no adequate and well-controlled studies in pregnant women. Beta-agonists may interfere with uterine contractility if administered during labor. Use only if clearly needed.

LactationEnters breast milk/use caution

Adverse Reactions

>10%:

Central nervous system: Headache (13% to 17%)

Neuromuscular & skeletal: Pain (1% to 12%)

1% to 10%:

Cardiovascular: Hypertension (4%), edema (1% to 3%), pallor

Central nervous system: Dizziness (4%), sleep disturbance (1% to 3%), fever (1% to 3%), anxiety (1% to 3%), migraine (1% to 3%)

Dermatologic: Rash (1% to 4%), contact dermatitis (1% to 3%), eczema (1% to 3%), urticaria (3%), photodermatitis (1% to 2%)

Endocrine & metabolic: Hyperglycemia (1% to 3%)

Gastrointestinal: Throat irritation (7%), nausea (1% to 3%), dyspepsia (1% to 3%), dental pain (1% to 3%), gastrointestinal infection (1% to 3%), oropharyngeal candidiasis (1% to 3%), xerostomia (1% to 3%)

Neuromuscular & skeletal: Muscular cramps/spasm (3%), articular rheumatism (1% to 3%), arthralgia (1% to 3%), joint pain (1% to 3%), muscular stiffness (1% to 3%), paresthesia (1% to 3%), rigidity (1% to 3%)

Ocular: Keratitis/conjunctivitis (1% to 3%)

Respiratory: Nasal congestion (4% to 9%), tracheitis/bronchitis (7%), pharyngitis (≤6%), cough (5%), influenza (5%), viral respiratory tract infection (5%), sinusitis (4% to 5%), rhinitis (4% to 5%), asthma (3% to 4%)

<1%, postmarketing, and/or case reports: Abdominal pain, agitation, aggression, anaphylactic reaction (Diskus®: severe milk allergy), angioedema, aphonia, arrhythmia, atrial fibrillation, bronchospasm and immediate bronchospasm, cataracts, chest congestion, chest tightness, choking, contusions, Cushing syndrome, Cushingoid features, depression, dysmenorrhea, dyspnea, earache, ecchymoses, edema (facial, oropharyngeal), eosinophilic conditions, glaucoma, growth velocity reduction in children/adolescents, hypercorticism, hypersensitivity reaction (immediate and delayed), hypokalemia, hypothyroidism, intraocular pressure increased, laryngeal spasm/irritation, irregular menstruation, myositis, osteoporosis, pallor, paradoxical tracheitis, paranasal sinus pain, PID, restlessness, stridor, supraventricular tachycardia, syncope, tremor, vaginal candidiasis, vaginitis, vulvovaginitis, rare cases of vasculitis (Churg-Strauss syndrome), ventricular tachycardia, weight gain

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)
Drug Interactions

Alpha-/Beta-Blockers: May diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Atomoxetine: May enhance the tachycardic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Betahistine: May diminish the therapeutic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Monitoring ParametersFEV_1, peak flow, and/or other pulmonary function tests; blood pressure, heart rate; CNS stimulation. Monitor for increased use of short-acting beta$_2$-agonist inhalers; may be marker of a deteriorating asthma condition.
Nursing: Physical Assessment/MonitoringNot for use to relieve acute asthmatic attacks. Use caution in presence of cardiovascular disease, seizures disorder, diabetes, glaucoma, hyperthyroidism, hepatic impairment, or hypokalemia. Assess other pharmacological or herbal products patient may be taking for potential interactions or toxicity. Assess effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Evaluate for increased use of short-acting beta$_2$-agonist inhalers; may be marker of a deteriorating asthma condition. For inpatient care, monitor vital signs and lung sounds prior to and periodically during therapy. An FDA medication guide must be distributed when new or refill prescription is dispensed. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Monitoring: Lab TestsFEV_1, peak flow, and/or other pulmonary function tests
Patient EducationThis medication is not to be used as a rescue treatment for acute asthmatic symptoms. You will be provided with a medication guide; read this guide carefully. Do not take any new prescription or over-the-counter medications, or herbal products during therapy without consulting prescriber. Use exactly as directed; do not alter dose or decrease without consulting prescriber. Do not use more often than recommended (excessive use may result in tolerance, overdose may result in serious adverse effects) and do not discontinue without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, check blood sugar regularly; blood glucose level may be affected. You may experience headache, nervousness, dizziness, or fatigue (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or dry mouth, stomach upset (small frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help). Report immediately any swelling of face, tongue, or throat, rash, difficulty swallowing or choking. Report unresolved GI upset; dizziness or fatigue; vision changes; chest pain, rapid heartbeat, or palpitations; insomnia; nervousness or hyperactivity; muscle cramping, tremors, or pain; unusual cough; or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Powder for oral inhalation:

Serevent® Diskus®: Salmeterol xinafoate 50 mcg (28s, 60s) [delivers 50 mcg/inhalation; contains lactose]

Serevent® Diskhaler® Disk [CAN]: Salmeterol xinafoate 50 mcg (60s) [delivers 50 mcg/inhalation; contains lactose] [not available in U.S]

Generic AvailableNo
ManufacturerGlaxoSmithKline
Pricing: U.S. (www.drugstore.com)

Aerosol powder (Serevent Diskus)

50 mcg/dose (60): $153.62

Mechanism of ActionRelaxes bronchial smooth muscle by selective action on beta$_2$-receptors with little effect on heart rate; salmeterol acts locally in the lung.

Pharmacodynamics/Kinetics

Onset of action: Asthma: 30-48 minutes, COPD: 2 hours

Peak effect: Asthma: 3 hours, COPD: 2-5 hours

Duration: 12 hours

Absorption: Systemic: Inhalation: Undetectable to poor

Protein binding: 96%

Metabolism: Hepatic; hydroxylated via CYP3A4

Half-life elimination: 5.5 hours

Time to peak, serum: ~20 minutes

Excretion: Feces (60%), urine (25%)

Related Information

- Bronchodilators
- Inhalant Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), dental pain, and oropharyngeal candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness, dizziness, hyperactivity, or insomnia

Mental Health: Effects on Psychiatric TreatmentSalmeterol is a sympathomimetic; use MAO inhibitors and TCAs with caution

Cardiovascular ConsiderationsInhaled beta-agonists may increase heart rate. This should be considered in patients with disease states that may require heart rate control (eg, atrial fibrillation) since frequent use may counteract pharmacologic interventions directed at rate control.

Because of the frequent coexistence of chronic obstructive lung disease and coronary artery disease, many patients may require concurrent therapy with beta-agonists and beta-blockade. Selectivity for the beta-1 receptor varies among the available beta blockers. Cardioselective beta blockade (eg, atenolol, esmolol, metoprolol) with careful titration is preferred when this situation exists (Anderson, 2007). When an inhaled beta-agonist becomes necessary, monitor heart rate closely.

Index TermsSalmeterol Xinafoate

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International Brand NamesAeromax (DE); Seretide (PH); Seretide [+ Fluticason propionate] (PL); Serevent (AE, AR, AT, BB, BE, BF, BG, BH, BJ, BM, BO, BR, BS, BZ, CH, CI, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, NZ, OM, PA, PE, PK, PL, PR, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SR, SV, SY, TH, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Serevent Dysk (PL); Serevent Inhaler and Disks (AU); Serevent Rotadisk (PL); Serevent Rotadisks (HU); Serobid (IN)

Salsalate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Salsalate may be confused with sucralfate, sulfasalazine

Pronunciation(SAL sa late)

U.S. Brand NamesAmigesic® [DSC]

Canadian Brand NamesAmigesic®; Salflex®

Pharmacologic CategorySalicylate

Use: Labeled IndicationsTreatment of minor pain or fever; arthritis

Dosing: Adults**Pain, inflammation (arthritis):** Oral: 3 g/day in 2-3 divided doses

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentPatients with end-stage renal disease undergoing hemodialysis: Administer 750 mg twice daily with an additional 500 mg after dialysis.

Dietary ConsiderationsMay be taken with food to decrease GI distress.

ContraindicationsHypersensitivity to salsalate or any component of the formulation; GI ulcer or bleeding; pregnancy (3rd trimester)

Allergy Considerations

- Salicylate Allergy/Sensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Salicylate sensitivity: Patients with sensitivity to tartrazine dyes, nasal polyps, and asthma may have an increased risk of salicylate sensitivity. Previous nonreaction does not guarantee future safe taking of medication.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with platelet and bleeding disorders.
- Dehydration: Use with caution in patients with dehydration.
- Gastrointestinal disease: Use with caution in patients with erosive gastritis or peptic ulcer.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Pediatrics: Children and teenagers who have or are recovering from chickenpox or flu-like symptoms should not use this product. Changes in behavior (along with nausea and vomiting) may be an early sign of Reye's syndrome; patients should be instructed to contact their healthcare provider if these occur.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of the elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucinations are generally seen in overdose or high dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (3rd trimester)

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsSalsalate is metabolized to salicylate which is contraindicated while breast-feeding.

Adverse Reactions

>10%: Gastrointestinal: Nausea, heartburn, stomach pain, dyspepsia

1% to 10%:

Central nervous system: Fatigue

Dermatologic: Rash

Gastrointestinal: Gastrointestinal ulceration

Hematologic: Hemolytic anemia

Neuromuscular & skeletal: Weakness

Respiratory: Dyspnea

Miscellaneous: Anaphylactic shock

<1%: Bronchospasm, hepatotoxicity, impaired renal function, insomnia, iron-deficiency anemia, jitters, leukopenia, nervousness, occult bleeding, thrombocytopenia; does not appear to inhibit platelet aggregation

Drug Interactions

ACE Inhibitors: Salicylates may diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Anticoagulants: Salicylates may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: Salicylates may enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Salicylates may enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Drotrecogin Alfa: Salicylates may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the antiplatelet effect of Salicylates. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk D: Consider therapy modification*

Methotrexate: Salicylates may increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

NSAID (Nonselective): May enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Diclofenac. *Risk D: Consider therapy modification*

Salicylates: May enhance the anticoagulant effect of other Salicylates. *Risk C: Monitor therapy*

Sulfonylureas: Salicylates may enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Thrombolytic Agents: Salicylates may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Uricosuric Agents: Salicylates may diminish the therapeutic effect of Uricosuric Agents. Specifically, uricosuria. *Risk C: Monitor therapy*

Valproic Acid: Salicylates may increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: Salicylates may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Salicylates may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Salsalate peak serum levels may be delayed if taken with food.

Herb/Nutraceutical: Avoid cat's claw, dong quai, evening primrose, feverfew, garlic, ginger, ginkgo, red clover, horse chestnut, green tea, ginseng (all have additional antiplatelet activity).

Test InteractionsFalse-negative results for glucose oxidase urinary glucose tests (Clinistix®); false-positives using the cupric sulfate method (Clinitest®); also, interferes with Gerhardt test, VMA determination; 5-HIAA, xylose tolerance test and T_3 and T_4

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess effectiveness and interactions of other medications patient may be taking. Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, GI effects, unusual bleeding, hepatotoxicity) at beginning of therapy and periodically throughout therapy. Schedule ophthalmic evaluations for patients who are on long-term NSAID therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake this medication exactly as directed; do not increase dose without consulting prescriber. Do not crush tablets. Take with food or milk to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol, aspirin or aspirin-containing medication, or any other anti-inflammatory medications without consulting prescriber. You may experience drowsiness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). GI bleeding, ulceration, or perforation can occur with or without pain; discontinue medication and contact prescriber if persistent abdominal pain or cramping, or blood in stool occurs. Report breathlessness or respiratory difficulty; chest pain; unusual bruising or bleeding; blood in urine, stool, mouth, or vomitus; unusual fatigue; skin rash or itching; change in urinary pattern; or change in hearing or ringing in ears. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: 500 mg, 750 mg

Amigesic®: 500 mg [DSC], 750 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Salsalate)

500 mg (100): $15.99

750 mg (60): $13.99

Mechanism of ActionWeakly inhibits cyclooxygenase enzymes, which result in decreased formation of prostaglandin precursors; antipyretic, analgesic, and anti-inflammatory properties.

Pharmacodynamics/Kinetics

Onset of action: Therapeutic: 3-4 days of continuous dosing

Absorption: Complete from small intestine

Metabolism: Hepatically hydrolyzed to two moles of salicylic acid (active)

Half-life elimination: 7-8 hours

Excretion: Primarily urine

Pharmacotherapy PearlsDoes not appear to inhibit platelet aggregation; salsalate causes less GI and renal toxicity than aspirin and other NSAIDs

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness; may rarely cause nervousness or insomnia

Mental Health: Effects on Psychiatric TreatmentMay rarely cause leukopenia; use caution with clozapine and carbamazepine

Anesthesia and Critical Care Concerns/Other ConsiderationsSalsalate does not appear to inhibit platelet aggregation.

Index TermsDisalicylic Acid; Salicylsalicylic Acid

References

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International Brand NamesDisal (TW); Disalcid (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Mono-Getic (TW)

Sapropterin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Sapropterin may be confused with cyproterone

Pronunciation(sap roe TER in)

U.S. Brand NamesKuvan™

Pharmacologic CategoryEnzyme Cofactor

Use: Labeled IndicationsAdjunct to dietary management in the treatment of tetrahydrobiopterin (BH4) responsive phenylketonuria (PKU)

Dosing: Adults**PKU:** Oral: Initial: 10 mg/kg once daily; adjust after 1 month based on blood phenylalanine levels (if phenylalanine levels do not decrease from baseline, increase dose to 20 mg/kg once daily); discontinue if phenylalanine levels do not decrease after 1 month of treatment at 20 mg/kg/day (nonresponder). Maintenance range: 5-20 mg/kg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**PKU:** Children ≥4 years: Refer to adult dosing.

Administration: OralAdminister with food, preferably at the same time each day. Dissolve tablets in 120-240 mL (4-8 oz) water or apple juice. May crush or stir to aid in dissolution. Take within 15 minutes of dissolution. Tablets may not dissolve completely; rinse remaining tablet residue (with more water or apple juice) and drink.

Dietary ConsiderationsPatients should maintain adherence to a phenylalanine-restricted diet. Take with food to increase absorption.

StorageStore at 20°C to 25°C (68°F to 77°F); excursions to 15°C to 30°C (59°F to 86°F) permitted. Protect from moisture.

ContraindicationsThere are no contraindications listed in the manufacturer's labeling

Warnings/Precautions

Concerns related to adverse effects:

- Allergic reaction: Although severe allergic reactions were not observed in clinical trials, do not administer to patients with allergy to any component of the formulation. Patients with mild-to-moderate allergy (eg, rash) should be evaluated for risk versus benefit prior to continuing therapy.

Disease-related concerns:

- Hepatic impairment: Has not been studied in patients with hepatic impairment. Monitor carefully; hepatic damage has been associated with impaired phenylalanine metabolism.

- Phenylketonuria: Phenylalanine levels should be monitored and maintained within the target range during sapropterin treatment. Low levels of phenylalanine are associated with catabolism and protein breakdown. Dietary management of phenylalanine intake is required to ensure nutritional balance and adequate phenylalanine control.

- Renal impairment: Has not been studied in patients with renal impairment; use with caution.

Concurrent drug therapy issues:

- Folic acid antagonists: Folic acid antagonists (eg, methotrexate) may decrease tetrahydrobiopterin (BH4) levels via dihydropteridine reductase enzyme inhibition.

- Levodopa: In sapropterin clinical studies for a non-PKU use, seizure, over stimulation, and irritability were reported in patients also receiving levodopa; use caution.

- PDE-5 inhibitors: Use with caution with medications that affect nitric oxide-mediated vasorelaxation, including PDE-5 inhibitors (eg, sildenafil, tadalafil, vardenafil); additive effect may lead to hypotension. Sapropterin use has not been evaluated in combination with PDE-5 inhibitors.

Special populations:

- Nonresponders: Response to sapropterin treatment is established through treatment (cannot be predetermined by lab testing). Patients whose phenylalanine levels do not decrease after treatment at 20 mg/kg/day for 1 month are considered nonresponders.

- Pediatrics: Safety and efficacy have not been established in children <4 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsStatistically significant teratogenic effects were not observed in animal studies; however, there are no adequate and well-controlled studies in pregnant women. High levels of maternal phenylalanine are associated with congenital heart disease, developmental delay, facial dysmorphism, learning difficulties, and microcephaly. Phenylalanine concentrations should be normalized prior to conception and dietary control with proper supplementation are recommended during pregnancy. Some clinicians recommend that dietary control be achieved for at least 4 weeks prior to conception; however, studies suggest that as long as control is achieved by 10 weeks of pregnancy, teratogenic effects of untreated maternal phenylketonuria can be decreased. The effects of sapropterin on pregnancy have not been determined. Pregnant women exposed to sapropterin are encouraged to enroll in the Kuvan™ pregnancy registry.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if sapropterin is found in breast milk. Phenylalanine and tyrosine are natural components of human milk and are amino acids required for normal development. The effects of sapropterin have not been determined.

Adverse Reactions

>10%:

Central nervous system: Headache (15%)

Respiratory: Rhinorrhea (11%)

1% to 10%:

Gastrointestinal: Diarrhea (8%), vomiting (8%), nausea

Dermatologic: Bruising (5%)

Hematologic: Neutropenia (4%)

Respiratory: Pharyngolaryngeal pain (10%), cough (7%), nasal congestion (4%)

<1%, postmarketing, and/or case reports: Abdominal pain, agitation, appetite decreased, arthralgia, bleeding (postprocedural), dizziness, fatigue, fever, flatulence, gastritis, gastrointestinal bleeding, GGT increased, hyperreflexia, irritability, MI, over stimulation, peripheral edema, polyuria, rash, respiratory failure, seizure, seizure exacerbation, thrombocytopenia, tremor, upper respiratory tract infection

Drug Interactions

Levodopa: Sapropterin may enhance the adverse/toxic effect of Levodopa. *Risk C: Monitor therapy*

Methotrexate: May decrease the serum concentration of Sapropterin. Specifically, methotrexate may decrease tissue concentrations of tetrahydrobiopterin. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: Sapropterin may enhance the hypotensive effect of Phosphodiesterase 5 Inhibitors. *Risk C: Monitor therapy*

Monitoring ParametersBlood phenylalanine levels (baseline, after 1 week of treatment, periodically for first month, regularly thereafter); children may require more frequent monitoring

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking. Assess results of laboratory tests at baseline and periodically thereafter. Teach patient or caregiver proper use (requirements for phenylalanine-restricted diet), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsBlood phenylalanine levels (baseline, after 1 week of treatment, periodically for first month, regularly thereafter); children may require more frequent monitoring

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take at same time each day with food. Follow prescribed diet closely. You may experience headache; diarrhea, nausea, or vomiting; or nasal congestion or cough (consult prescriber if persistent or severe). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as dihydrochloride:

Kuvan™: 100 mg

Generic AvailableNo

ManufacturerBioMarin Pharmaceutical, Inc

Mechanism of ActionSapropterin is a synthetic form of the cofactor BH4 (tetrahydrobiopterin) for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates phenylalanine to form tyrosine. BH4 activates residual PAH enzyme, improving normal phenylalanine metabolism and decreasing phenylalanine levels in sapropterin responders.

Pharmacodynamics/Kinetics

Onset of action: Within 24 hours; maximum effect: 1-2 months

Duration: 24 hours

Absorption: Absorption is enhanced when administered with food (high fat/high calorie)

Half-life elimination: ~7 hours (range: 4-17 hours)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusHeadaches are common; rare reports of agitation, dizziness, fatigue, and irritability

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with lithium, SSRIs, valproic acid, and carbamazepine may produce additive effects. May cause neutropenia; use caution with clozapine and carbamazepine. Concomitant use with levodopa may increase the risk for seizures, over stimulation, and irritability.

Index Terms6R-BH4; Phenoptin; Sapropterin Dihydrochloride

References

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Maillot F, Cook P, Lilburn M, et al, “A Practical Approach to Maternal Phenylketonuria Management,” *J Inherit Metab Dis*, 2007, 30(2):198-201.

Saquinavir

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Saquinavir may be confused with Sinequan®

Pronunciation(sa KWIN a veer)

U.S. Brand NamesInvirase®

Canadian Brand NamesInvirase®

Pharmacologic CategoryAntiretroviral Agent, Protease Inhibitor

Use: Labeled IndicationsTreatment of HIV infection; used in combination with at least two other antiretroviral agents

Dosing: Adults**HIV infection:** Oral: Invirase®: 1000 mg (five 200 mg capsules or two 500 mg tablets) twice daily given in combination with ritonavir 100 mg twice daily. This combination should be given together and within 2 hours after a full meal in combination with a nucleoside analog. **Note:** Saquinavir (Invirase®) should not be used in "unboosted regimens."

Dosage adjustments when administered in combination therapy: Lopinavir and ritonavir (Kaletra™): Invirase® 1000 mg twice daily

Dosing: ElderlyClinical studies did not include sufficient numbers of patients ≥65 years of age. Use caution due to increased frequency of organ dysfunction.

Dosing: Pediatric

HIV infection: Oral: Children >16 years: Refer to adult dosing.

Administration: OralTake saquinavir within 2 hours after a full meal. When used with ritonavir, saquinavir and ritonavir should be administered at the same time.

Dietary ConsiderationsAdminister within 2 hours of a meal. Invirase® capsules contain lactose 63.3 mg/capsule (not expected to induce symptoms of intolerance).

StorageInvirase®: Store at room temperature.

ContraindicationsHypersensitivity to saquinavir or any component of the formulation; severe hepatic impairment; coadministration with amiodarone, cisapride, flecainide, midazolam, pimozide, propafenone, quinidine, rifampin, triazolam, or ergot derivatives

Warnings/Precautions

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Increased cholesterol: Increases in total cholesterol and triglycerides have been reported; screening should be done prior to therapy and periodically throughout treatment.

Disease-related concerns:

- Diabetes: Changes in glucose tolerance, hyperglycemia, exacerbation of diabetes, DKA, and new-onset diabetes mellitus have been reported in patients receiving protease inhibitors.
- Hemophilia A or B: Use with caution in patients with hemophilia A or B; increased bleeding during protease inhibitor therapy has been reported.
- Hepatic impairment: May cause hepatitis and/or exacerbate pre-existing hepatic dysfunction; use with caution in patients with underlying hepatic disease, such as hepatitis B or C or cirrhosis.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.
- Invirase®: May be used only if combined with ritonavir.
- Not recommended: St. John's Wort, lovastatin, and simvastatin should not be used concurrently with saquinavir/ritonavir. A listing of medications that should not be used is available with each bottle and patients should be provided with this information.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children ≤16 years of age.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events were not observed in animal studies and saquinavir crosses the human placenta in minimal amounts. Based on limited data, Invirase® 1000 mg (capsules and tablets) administered twice daily with ritonavir 100 mg twice daily provide adequate levels in pregnant women. The Perinatal HIV Guidelines Working Group considers Invirase® capsules and ritonavir to be an alternative combination for use during pregnancy. Pregnancy and protease inhibitors are both associated with an increased risk of hyperglycemia. Glucose levels should be closely monitored. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease postnatal transmission of HIV.

Adverse Reactions

Incidence data shown for saquinavir soft gel capsule formulation (no longer available) in combination with ritonavir.

10%: Gastrointestinal: Nausea (11%)

1% to 10%:

Cardiovascular: Chest pain

Central nervous system: Fatigue (6%), fever (3%), anxiety, depression, headache, insomnia, pain

Dermatologic: Pruritus (3%), rash (3%), dry lips/skin (2%), eczema (2%), verruca

Endocrine & metabolic: Lipodystrophy (5%), hyperglycemia (3%), hypoglycemia, hyperkalemia, libido disorder, serum amylase increased

Gastrointestinal: Diarrhea (8%), vomiting (7%), abdominal pain (6%), constipation (2%), abdominal discomfort, appetite decreased, buccal mucosa ulceration, dyspepsia, flatulence, taste alteration

Hepatic: AST increased, ALT increased, bilirubin increased

Neuromuscular & skeletal: Back pain (2%), CPK increased, paresthesia, weakness

Renal: Creatinine kinase increased

Respiratory: Pneumonia (5%), bronchitis (3%), sinusitis (3%)

Miscellaneous: Influenza (3%)

Incidence not currently defined (limited to significant reactions; reported for hard or soft gel capsule with/without ritonavir)

Cardiovascular: Cyanosis, heart valve disorder (including murmur), hyper-/hypotension, peripheral vasoconstriction, syncope, thrombophlebitis

Central nervous system: Agitation, amnesia, ataxia, confusion, hallucination, hyper-/hyporeflexia, myelopolyradiculoneuritis, neuropathies, poliomyelitis, progressive multifocal encephalopathy, psychosis, seizures, somnolence, speech disorder, suicide attempt

Dermatologic: Alopecia, bullous eruption, dermatitis, erythema, maculopapular rash, photosensitivity, Stevens-Johnson syndrome, skin ulceration, urticaria

Endocrine & metabolic: Dehydration, diabetes, electrolyte changes, TSH increased

Gastrointestinal: Ascites, colic, dysphagia, esophagitis, bloody stools, gastritis, intestinal obstruction, hemorrhage (rectal), pancreatitis, stomatitis

Genitourinary: impotence, prostate enlarged, hematuria, UTI

Hematologic; Acute myeloblastic leukemia, anemia (including hemolytic), leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia

Hepatic: Alkaline phosphatase increased, GGT increased, hepatitis, hepatomegaly, hepatosplenomegaly, jaundice, liver disease exacerbation

Neuromuscular & skeletal: Arthritis, LDH increased

Ocular: Blepharitis, visual disturbance

Otic: Otitis, hearing decreased, tinnitus

Renal: Nephrolithiasis, renal calculus

Respiratory: Dyspnea, hemoptysis, pharyngitis, upper respiratory tract infection

Miscellaneous: Infections (bacterial, fungal, viral)

Metabolism/Transport Effects**Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2C9 (weak), 2C19 (weak), 2D6 (weak), 3A4 (moderate)

Drug Interactions

Abacavir: Protease Inhibitors may decrease the serum concentration of Abacavir. *Risk C: Monitor therapy*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amiodarone: Protease Inhibitors may decrease the metabolism of Amiodarone. *Risk X: Avoid combination*

Antacids: May decrease the absorption of Protease Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Protease Inhibitors may decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Dihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Protease Inhibitors. Protease Inhibitors may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cisapride: Protease Inhibitors may decrease the metabolism of Cisapride. The resultant increase in serum cisapride concentrations may result in QTc prolongation and malignant cardiac arrhythmias. *Risk X: Avoid combination*

Clarithromycin: Protease Inhibitors may diminish the therapeutic effect of Clarithromycin. Specifically, certain protease inhibitors may decrease formation of the active 14-hydroxy-clarithromycin metabolite, which may negatively impact clarithromycin effectiveness vs. H. influenzae and other non-MAC infections. Protease Inhibitors may increase the serum concentration of Clarithromycin. Clarithromycin dose adjustment in renally impaired patients may be needed. Clarithromycin may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): Protease Inhibitors may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk D: Consider therapy modification*

CycloSPORINE: Protease Inhibitors may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Darunavir: Saquinavir may decrease the serum concentration of Darunavir. *Risk X: Avoid combination*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Delavirdine: Protease Inhibitors may decrease the serum concentration of Delavirdine. Delavirdine may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Digoxin: Protease Inhibitors may increase the serum concentration of Digoxin. Increased serum concentrations of digoxin may increase risk of AV nodal blockade. *Risk C: Monitor therapy*

Efavirenz: May increase the metabolism of Protease Inhibitors. This specifically includes amprenavir, indinavir, and saquinavir. Efavirenz may increase the serum concentration of Protease Inhibitors. This specifically includes nelfinavir and ritonavir. *Risk D: Consider therapy modification*

Enfuvirtide: Protease Inhibitors may increase the serum concentration of Enfuvirtide. Enfuvirtide may increase the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Eplerenone. *Risk X: Avoid combination*

Eplerenone: Protease Inhibitors may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Protease Inhibitors may decrease the metabolism of Ergot Derivatives. **Exceptions:** Cabergoline. *Risk X: Avoid combination*

Etravirine: Protease Inhibitors may decrease the serum concentration of Etravirine. This effect is anticipated with darunavir & saquinavir (with low-dose ritonavir). Etravirine may increase the serum concentration of Protease Inhibitors. This effect is anticipated with nelfinavir. Protease Inhibitors may increase the serum concentration of Etravirine. This is expected with lopinavir/ritonavir. Management: Low-dose ritonavir boosting MUST be used when these protease inhibitors are used with etravirine. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

FentaNYL: Protease Inhibitors may decrease the metabolism of FentaNYL. *Risk C: Monitor therapy*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fusidic Acid: Protease Inhibitors may decrease the metabolism of Fusidic Acid. Fusidic Acid may decrease the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Garlic: May decrease the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

H2-Antagonists: May increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Protease Inhibitors may increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. **Exceptions:** Fluvastatin. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Meperidine: Protease Inhibitors may enhance the adverse/toxic effect of Meperidine. Protease Inhibitors may decrease the serum concentration of Meperidine. Concentrations of the toxic Normeperidine metabolite may be increased. *Risk D: Consider therapy modification*

Methadone: Protease Inhibitors may decrease the metabolism of Methadone. *Risk C: Monitor therapy*

Nefazodone: Protease Inhibitors may decrease the metabolism of Nefazodone. *Risk C: Monitor therapy*

Nevirapine: May increase the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nisoldipine. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): May diminish the therapeutic effect of Protease Inhibitors. Protease Inhibitors may decrease the serum concentration of Oral Contraceptive (Estrogens). *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: Protease Inhibitors may decrease the metabolism of Phosphodiesterase 5 Inhibitors. Management: Dose restrictions for tadalafil, and/or sildenafil and vardenafil are recommended in combination with ritonavir, atazanavir, indinavir, darunavir and saquinavir. Consult specific prescribing information for detailed recommendations. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Protease Inhibitors may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Protease Inhibitors: May increase the serum concentration of other Protease Inhibitors. Management: Atazanavir--indinavir combination contraindicated. Amprenavir oral solution not recommended with ritonavir oral solution; tipranavir/ritonavir or atazanavir/ritonavir not recommended with other protease inhibitors. Other combos may require dose changes. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Saquinavir. *Risk C: Monitor therapy*

QuiNIDine: Protease Inhibitors may decrease the metabolism of QuiNIDine. *Risk X: Avoid combination*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: Protease Inhibitors may decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Protease Inhibitors may increase the serum concentration of Sirolimus. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Protease Inhibitors. *Risk X: Avoid combination*

Tacrolimus: Protease Inhibitors may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Temsirolimus: Protease Inhibitors may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Theophylline Derivatives: Protease Inhibitors may decrease the serum concentration of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

TraZODone: Protease Inhibitors may increase the serum concentration of TraZODone. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Protease Inhibitors may increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Valproic Acid: Protease Inhibitors may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Zidovudine: Protease Inhibitors may decrease the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: A high-fat meal maximizes bioavailability. Saquinavir levels may increase if taken with grapefruit juice.

Herb/Nutraceutical: Saquinavir serum concentrations may be decreased by St John's wort; avoid concurrent use. Garlic capsules may decrease saquinavir serum concentrations; avoid use if saquinavir is the only protease inhibitor.

Monitoring ParametersMonitor viral load, CD4 count, triglycerides, cholesterol, glucose

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential interactions or toxicity (multiple liver enzyme interactions may increase or decrease levels/effects of drugs and increase potential for severe toxicity or loss of effectiveness); dosing adjustments may be necessary. A list of medications that should not be used is available in each bottle and patients should be provided with this information. Assess therapeutic response (CD4 count, hepatic function) and adverse reactions (gastrointestinal disturbance, nausea, vomiting, diarrhea that can lead to dehydration and weight loss; hyperlipidemia and redistribution of body fat; rash; CNS effects, malaise, insomnia, abnormal thinking, electrolyte imbalance) at regular intervals during therapy. Caution patients to monitor glucose levels closely; protease inhibitors may cause hyperglycemia or new-onset diabetes. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions (eg, use of barrier contraceptives; protease inhibitors may decrease effectiveness of oral contraceptives), and adverse symptoms to report.

Monitoring: Lab TestsCBC, renal and liver function, electrolytes, triglycerides, cholesterol, glucose, CD4 cell count, plasma levels of HIV RNA

Patient EducationYou will be provided with a list of specific medications that should not be used during therapy; do not take any new prescriptions, over-the-counter medications, or herbal products (even if they are not on the list) without consulting prescriber. This is not a cure for HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. Take exactly as directed. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you miss a dose, take as soon as possible and return to your regular schedule (never take a double dose). Frequent blood tests may be required with prolonged therapy. You may be advised to check your glucose levels (this drug can cause exacerbation or new-onset diabetes). May cause body changes due to redistribution of body fat, facial atrophy, or breast enlargement (normal effects of drug). May cause dizziness, insomnia, abnormal thinking (use caution when driving or engaging in potentially hazardous tasks until response to drug is known); nausea, vomiting, or taste perversion (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); muscle weakness (consult prescriber for approved analgesic); or headache or insomnia (consult prescriber for medication). Inform prescriber if you experience muscle numbness or tingling; unresolved persistent vomiting, diarrhea, or abdominal pain; respiratory difficulty or chest pain; unusual skin rash; change in color of stool or urine; or any persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Effectiveness of oral contraceptives may be decreased, use of alternative (nonhormonal) forms of contraception is recommended; consult prescriber for appropriate contraceptives. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Invirase®: 200 mg [contains lactose 63.3 mg/capsule]

Tablet:

Invirase®: 500 mg

Generic AvailableNo

ManufacturerRoche Laboratories Inc

Pricing: U.S. (www.drugstore.com)

Capsules (Fortovase)

200 mg (180): $229.12

Capsules (Invirase)

200 mg (270): $797.93

Tablets (Invirase)

500 mg (120): $890.75

Mechanism of ActionAs an inhibitor of HIV protease, saquinavir prevents the cleavage of viral polyprotein precursors which are needed to generate functional viral proteins required for the maturation of an infectious HIV virion.

Pharmacodynamics/Kinetics

Absorption: Poor; increased with high fat meal; Fortovase® has improved absorption over Invirase®

Distribution: V_d: 700 L; does not distribute into CSF

Protein binding, plasma: ~98%

Metabolism: Extensively hepatic via CYP3A4; extensive first-pass effect

Bioavailability: Invirase®: ~4%

Excretion: Feces (81% to 88%), urine (1% to 3%) within 5 days

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV
- Perinatal HIV Guidelines

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Buccal mucosa ulceration and taste alteration.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay rarely cause confusion or ataxia; report of acute paranoia reaction to saquinavir
Mental Health: Effects on Psychiatric TreatmentContraindicated with triazolam and midazolam; barbiturates and carbamazepine may increase the metabolism of saquinavir. Concomitant use of saquinavir and St John's wort is not recommended. Coadministration of protease inhibitors (saquinavir) with St John's wort is expected to substantially decrease protease inhibitor serum concentrations leading to a loss of virologic response and possible resistance to saquinavir or to the class of protease inhibitors.
Anesthesia and Critical Care Concerns/Other ConsiderationsPotential compliance problems, frequency of administration, and adverse effects should be discussed with patients before initiating therapy to help prevent the emergence of resistance.
Index TermsSaquinavir Mesylate
References

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International Brand NamesFortovase (AR, AU, BG, BR, CN, EC, IN, MX, PE, PL, SE, TH, UY, VE); Invirase (AT, BB, BE, BF, BJ, BM, BS, BZ, CH, CI, CO, CZ, DE, DK, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, IE, IL, IT, JM, KE, LR, LU, MA, ML, MR, MU, MW, NE, NG, NL, NO, PH, PL, PT, RU, SC, SD, SL, SN, SR, TN, TR, TT, TW, TZ, UG, ZA, ZM, ZW)

Sargramostim

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Special Alerts

Sargramostim: Liquid Reformulated - June 2008

Bayer Healthcare has reformulated liquid sargramostim (Leukine®). The new formulation, which does not contain edetate disodium (EDTA), is now available.

Medication Safety Issues

Sound-alike/look-alike issues:

Leukine® may be confused with Leukeran®, leucovorin

Pronunciation(sar GRAM oh stim)

U.S. Brand NamesLeukine®

Canadian Brand NamesLeukine®

Pharmacologic CategoryColony Stimulating Factor

Use: Labeled Indications

Acute myelogenous leukemia (AML) following induction chemotherapy in older adults (≥55 years of age) to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death

Bone marrow transplant (allogeneic or autologous) failure or engraftment delay

Myeloid reconstitution after allogeneic bone marrow transplantation

Myeloid reconstitution after autologous bone marrow transplantation: Non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL), Hodgkin's lymphoma

Peripheral stem cell transplantation: Mobilization and myeloid reconstitution following autologous peripheral stem cell transplantation

Dosing: Adults

I.V. infusion over ≥2 hours or SubQ: **Rounding the dose to the nearest vial size enhances patient convenience and reduces costs without clinical detrement.**

Myeloid reconstitution after allogeneic or autologous bone marrow transplant: I.V.: 250 mcg/m^2/day (over 2 hours), begin 2-4 hours after the marrow infusion and ≥24 hours after chemotherapy or radiotherapy, when the post marrow infusion ANC is <500 cells/mm^3, and continue until ANC >1500 cells/mm^3 for 3 consecutive days

If a severe adverse reaction occurs, reduce the dose by 50% or temporarily discontinue until the reaction abates

If blast cells appear or progression of the underlying disease occurs, discontinue treatment

If ANC >20,000 cells/mm^3, interrupt treatment or reduce the dose by 50%

Neutrophil recovery following chemotherapy in AML: I.V.: 250 mcg/m^2/day (over 4 hours) starting approximately on day 11 or 4 days following the completion of induction chemotherapy, if day 10 bone marrow is hypoplastic with <5% blasts

If a second cycle of chemotherapy is necessary, administer ~4 days after the completion of chemotherapy if the bone marrow is hypoplastic with <5% blasts

Continue sargramostim until ANC is >1500 cells/mm^3 for 3 consecutive days or a maximum of 42 days

Discontinue sargramostim immediately if leukemic regrowth occurs

If a severe adverse reaction occurs, reduce the dose by 50% or temporarily discontinue the dose until the reaction abates

If ANC >20,000 cells/mm^3, interrupt treatment or reduce the dose by 50%

Mobilization of peripheral blood progenitor cells: I.V., SubQ: 250 mcg/m^2/day I.V. over 24 hours or SubQ once daily

Continue the same dose through the period of PBPC collection

The optimal schedule for PBPC collection has not been established (usually begun by day 5 and performed daily until protocol specified targets are achieved)

If WBC >50,000 cells/mm^3, reduce the dose by 50%

If adequate numbers of progenitor cells are not collected, consider other mobilization therapy

Postperipheral blood progenitor cell transplantation: I.V., SubQ: 250 mcg/m^2/day I.V. over 24 hours or SubQ once daily beginning immediately following infusion of progenitor cells and continuing until ANC is >1500 cells/mm^3 for 3 consecutive days is attained

BMT failure or engraftment delay: I.V.: 250 mcg/m^2/day over 2 hours for 14 days

May be repeated after 7 days off therapy if engraftment has not occurred

If engraftment still has not occurred, a third course of 500 mcg/m^2/day for 14 days may be tried after another 7 days off therapy; if there is still no improvement, it is unlikely that further dose escalation will be beneficial

If a severe adverse reaction occurs, reduce the dose by 50% or temporarily discontinue the dose until the reaction abates

If blast cells appear or disease progression occurs, discontinue treatment

If ANC >20,000 cells/mm^3, interrupt treatment or reduce the dose by 50%

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDosage not established in children (unlabeled use). Refer to adult dosing.

Dosing: Combination Regimens

Lymphoma, non-Hodgkin's: CODOX-M

Calculations

- ANC: Absolute Neutrophil Count
- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Can premedicate with analgesics and antipyretics (eg, acetaminophen) to control adverse events (eg, fever, chills, myalgia, etc); control bone pain with non-narcotic analgesics I.V. infusion should be over 2-24 hours; incompatible with dextrose-containing solutions. An in-line membrane filter should **NOT** be used for intravenous administration.

Administration: I.V. DetailpH: 7.1-7.7

Administration: OtherAdminister by SubQ (undiluted). Do not shake solution. When administering GM-CSF subcutaneously, rotate injection sites.

Storage Store at 2°C to 8°C (36°F to 46°F); do not freeze. Do not shake.

Solution for injection: May be stored for up to 20 days at 2°C to 8°C (36°F to 46°F) once the vial has been entered. Discard remaining solution after 20 days.

Powder for injection: Preparations made with SWFI should be administered as soon as possible, and discarded within 6 hours of reconstitution. Preparations made with bacteriostatic water may be stored for up to 20 days at 2°C to 8°C (36°F to 46°F).

I.V. infusion administration: Preparations diluted with NS are stable for 48 hours at room temperature and refrigeration.

Reconstitution

Powder for injection: May be reconstituted with preservative free SWFI or bacteriostatic water for injection (with benzyl alcohol 0.9%). Gently swirl to reconstitute; do not shake.

Sargramostim may also be further diluted in 25-50 mL NS to a concentration ≥10 mcg/mL for I.V. infusion administration.

If the final concentration of sargramostim is <10 mcg/mL, 1 mg of human albumin/1 mL of NS (eg, 1 mL of 5% human albumin/50 mL of NS) should be added.

CompatibilityStable in NS, sterile water for injection, bacteriostatic water; **incompatible** with dextrose-containing solutions.

Y-site administration: Compatible: Amikacin, aminophylline, aztreonam, bleomycin, butorphanol, calcium gluconate, carboplatin, carmustine, cefazolin, cefepime, cefotaxime, cefotetan, ceftizoxime, ceftriaxone, cefuroxime, cimetidine, cisplatin, clindamycin, co-trimoxazole, cyclophosphamide, cyclosporine, cytarabine, dacarbazine, dactinomycin, dexamethasone sodium phosphate, diphenhydramine, dopamine, doxorubicin, doxycycline, droperidol, etoposide, famotidine, fentanyl, floxuridine, fluconazole, fluorouracil, furosemide, gentamicin, granisetron, heparin, idarubicin, ifosfamide, immune globulin, magnesium sulfate, mannitol, mechlorethamine, meperidine, mesna, methotrexate, metoclopramide, metronidazole, minocycline, mitoxantrone, netilmicin, pentostatin, piperacillin/tazobactam, potassium chloride, prochlorperazine edisylate, promethazine, ranitidine, teniposide, ticarcillin, ticarcillin/clavulanate, vinblastine, vincristine, zidovudine. **Incompatible:** Acyclovir, ampicillin, ampicillin/sulbactam, cefoperazone, chlorpromazine, ganciclovir, haloperidol, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, imipenem/cilastatin, lorazepam, methylprednisolone sodium succinate, mitomycin, morphine, nalbuphine, ondansetron, piperacillin, sodium bicarbonate, tobramycin. **Variable (consult detailed reference):** Amphotericin B, amsacrine, ceftazidime, vancomycin.

ContraindicationsHypersensitivity to sargramostim, yeast-derived products, or any component of the formulation; concurrent (24 hours preceding/following) myelosuppressive chemotherapy or radiation therapy; patients with excessive (≥10%) leukemic myeloid blasts in bone marrow or peripheral blood

Warnings/Precautions

Concerns related to adverse effects:

- Allergic reactions: Anaphylaxis or other serious allergic reactions have been reported; discontinue immediately if occur.

Disease-related concerns:

- Cardiac disease: Use with caution in patients with pre-existing cardiac problems or HF. Transient supraventricular arrhythmias have been reported in patients with history of arrhythmias.

- Fluid retention: Edema, capillary leak syndrome, pleural and/or pericardial effusion have been reported. Use with caution in patients with pre-existing fluid retention; may worsen.

- Hepatic impairment: Use with caution in patients with hepatic impairment; monitor hepatic function in patients with history of hepatic dysfunction. Bilirubin and transaminase elevations have been observed with use.

- Renal impairment: Use with caution in patients with renal impairment; monitor renal function in patients with history of renal dysfunction. Serum creatinine elevations have been observed with use.

- Respiratory problems: Dyspnea may occur; monitor respiratory symptoms during and following infusion. Decrease infusion rate by 50% if dyspnea occurs; discontinue with persistent dyspnea. Use with caution in patients with hypoxia, pulmonary infiltrates, or pre-existing lung disease.

Concurrent drug therapy issues:

- Cytotoxic chemotherapy/radiotherapy: Simultaneous administration, or administration 24 hours preceding/following cytotoxic chemotherapy or radiotherapy is not recommended.

Other warnings/precautions:

- Benzyl alcohol: Solution contains benzyl alcohol which has been associated with "gasping syndrome" in neonates.

- Blood counts: If there is a rapid increase in blood counts (ANC >20,000/mm^3, WBC >50,000/mm^3, or platelets >500,000/mm^3), decrease dose by 50% or discontinue drug (counts will fall to normal within 3-7 days after discontinuing drug).

- First dose effect: There is a “first-dose effect” (refer to Adverse Reactions for details) which is seen (rarely) with the first dose of a cycle and does not usually occur with subsequent doses within that cycle.

- Tumor growth factor: May potentially act as a growth factor for any tumor type, particularly myeloid malignancies; caution should be exercised when using in any malignancy with myeloid characteristics. Tumors of nonhematopoietic origin may have surface receptors for sargramostim. Discontinue use if disease progression occurs during treatment.

Pregnancy Risk FactorC

Pregnancy ConsiderationsClinical effects to the fetus: Animal reproduction studies have not been conducted. It is not known whether sargramostim can cause fetal harm when administered to a pregnant woman or can affect reproductive capability. Sargramostim should be given to a pregnant woman only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Cardiovascular: Hypertension (34%), pericardial effusion (4% to 25%), edema (13% to 25%), chest pain (15%), peripheral edema (11%), tachycardia (11%)

Central nervous system: Fever (81%), malaise (57%), headache (26%), chills (25%), anxiety (11%), insomnia (11%)

Dermatologic: Rash (44%), pruritus (23%)

Endocrine & metabolic: Hyperglycemia (25%), hypercholesterolemia (17%), hypomagnesemia (15%)

Gastrointestinal: Diarrhea (≤89%), nausea (58% to 70%), vomiting (46% to 70%), abdominal pain (38%), weight loss (37%), anorexia (13%), hematemesis (13%), dysphagia (11%), gastrointestinal hemorrhage (11%)

Genitourinary: Urinary tract disorder (14%)

Hepatic: Hyperbilirubinemia (30%)

Neuromuscular & skeletal: Weakness (66%), bone pain (21%), arthralgia (11% to 21%) myalgia (18%)

Ocular: Eye hemorrhage (11%)

Renal: BUN increased (23%), serum creatinine increased (15%)

Respiratory: Pharyngitis (23%), epistaxis (17%), dyspnea (15%)

Miscellaneous: Antibody formation (2%)

1% to 10%: Respiratory: Pleural effusion (1%)

<1%, postmarketing, and/or case reports: Allergic reaction, anaphylaxis, arrhythmia, capillary leak syndrome, constipation, dizziness, eosinophilia; first-dose effect (syndrome with respiratory distress, hypoxia, flushing, hypotension, syncope, and/or tachycardia occurring with the first dose of a treatment cycle); injection site reaction, lethargy, leukocytosis, liver function abnormalities (transient), pain, pericarditis, prothrombin time prolonged, rigors, sore throat, supraventricular arrhythmia (transient), thrombocytosis, thrombophlebitis, thrombosis

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug InteractionsThere are no known significant interactions.

Test InteractionsMay interfere with bone imaging studies; increased hematopoietic activity of the bone marrow may appear as transient positive bone imaging changes

Monitoring ParametersVital signs, hydration status, weight, CBC with differential twice weekly during therapy, renal/liver function tests at least biweekly during therapy (in patients displaying renal or hepatic dysfunction prior to initiation of treatment), pulmonary function

Reference RangeExcessive leukocytosis: ANC >20,000/mm^3 or WBC >50,000 cells/mm^3

Nursing: Physical Assessment/MonitoringUse with caution in presence of pre-existing cardiac problems or hepatic, renal, or pulmonary impairment. See Administration, Reconstitution, and Compatibility for specific infusion directions. Patient must be monitored closely during and following infusion for respiratory symptoms and "first-dose effect" (hypotension, tachycardia, flushing, and syncope with the first dose of a cycle). Assess results of laboratory tests closely. Premedication may be used to control adverse events. Evaluate therapeutic response and adverse reactions frequently throughout therapy (eg, respiratory symptoms, fluid balance [I and O], rash, hypotension, tachycardia, GI disturbance [diarrhea, stomatitis, mucositis], myalgia, bone pain). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential twice weekly during therapy, renal/liver function tests at least biweekly during therapy (in patients displaying renal or hepatic dysfunction prior to initiation of treatment)

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. This medication can only be administered by infusion or injection. Report immediately any redness, swelling, pain, or burning at infusion/injection site; difficulty breathing; or chest pain. You will require frequent blood tests during treatment. You may experience bone, joint, or muscle pain (consult prescriber for analgesic); nausea, vomiting, or loss of appetite (small, frequent meals, chewing gum, or sucking lozenges may help); hair loss (reversible); diarrhea (buttermilk, boiled milk, or yogurt may help); or headache, dizziness, or insomnia (use caution when driving or engaging in potentially hazardous tasks until response to drug is known). At any time during treatment, report chest pain or palpitations, signs or symptoms of edema (eg, swollen extremities, difficulty breathing, rapid weight gain), onset of severe headache, acute back or chest pain, muscular tremors or seizure activity, or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Leukine®: 250 mcg [contains sucrose 10 mg/mL]

Injection, solution:

Leukine®: 500 mcg/mL (1 mL) [contains benzyl alcohol and sucrose 10 mg/mL]

Generic AvailableNo

ManufacturerBayer

Mechanism of ActionStimulates proliferation, differentiation and functional activity of neutrophils, eosinophils, monocytes, and macrophages, as indicated.

Pharmacodynamics/Kinetics

Onset of action: Increase in WBC: 7-14 days

Duration: WBCs return to baseline within 1 week of discontinuing drug

Half-life elimination: I.V.: 60 minutes; SubQ: 2.7 hours

Time to peak, serum: SubQ: 1-3 hours

Related Information

- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsReimbursement Hotline (Leukine®): 1-800-321-4669

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentMay be used to treat clozapine-induced agranulocytosis; lithium may potentiate the release of neutrophils; use with caution

Index TermsGM-CSF; Granulocyte-Macrophage Colony Stimulating Factor; NSC-613795; rhuGM-CSF

References

Lieschke GJ and Burgess AW, “Granulocyte Colony-Stimulating Factor and Granulocyte-Macrophage Colony-Stimulating Factor,” (1) *N Engl J Med*, 1992, 327(1):28-35. [PubMed 1375975]

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International Brand NamesInterberin (AT)

Scopolamine Derivatives

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues
Transdermal patch may contain conducting metal (eg, aluminum); remove patch prior to MRI.

Pronunciation(skoe POL a meen dah RIV ah tives)
U.S. Brand NamesIsopto® Hyoscine; Scopace™; Transderm Scōp®
Canadian Brand NamesBuscopan®; Transderm-V®
Pharmacologic CategoryAnticholinergic Agent
Use: Labeled Indications

Scopolamine base:

Transdermal: Prevention of nausea/vomiting associated with motion sickness and recovery from anesthesia and surgery

Scopolamine hydrobromide:

Injection: Preoperative medication to produce amnesia, sedation, tranquilization, antiemetic effects, and decrease salivary and respiratory secretions

Ophthalmic: Produce cycloplegia and mydriasis; treatment of iridocyclitis

Oral: Symptomatic treatment of postencephalitic parkinsonism and paralysis agitans; in spastic states; inhibits excessive motility and hypertonus of the gastrointestinal tract in such conditions as the irritable colon syndrome, mild dysentery, diverticulitis, pylorospasm, and cardiospasm

Scopolamine butylbromide [not available in the U.S.]:

Oral/injection: Treatment of smooth muscle spasm of the genitourinary or gastrointestinal tract; injection may also be used to prior to radiological/diagnostic procedures to prevent spasm

Dosing: Adults**Note:** Scopolamine (hyoscine) hydrobromide should not be interchanged with scopolamine butylbromide formulations. Dosages are not equivalent.
Scopolamine base:

Preoperative: Transdermal patch: Apply 1 patch to hairless area behind ear the night before surgery or 1 hour prior to cesarean section (apply no sooner than 1 hour before surgery to minimize newborn exposure); remove 24 hours after surgery

Motion sickness: Transdermal patch: Apply 1 patch behind the ear at least 4 hours prior to exposure and every 3 days as needed; effective if applied as soon as 2-3 hours before anticipated need, best if 12 hours before

Scopolamine hydrobromide:

Antiemetic: SubQ: 0.6-1 mg

Preoperative: I.M., I.V., SubQ: 0.3-0.65 mg

Sedation, tranquilization: I.M., I.V., SubQ: 0.6 mg 3-4 times/day

Refraction: Ophthalmic: Instill 1-2 drops of 0.25% to eye(s) 1 hour before procedure

Iridocyclitis: Ophthalmic: Instill 1-2 drops of 0.25% to eye(s) up to 4 times/day

Parkinsonism, spasticity, motion sickness: Oral: 0.4-0.8 mg. May repeat every 8-12 hours as needed; the dosage may be cautiously increased in parkinsonism and spastic states. For motion sickness, administration at least 1 hour before exposure is recommended.

Scopolamine butylbromide:

Gastrointestinal/genitourinary spasm (Buscopan® [CAN]; not available in the U.S.):

Oral: 10-20 mg daily (1-2 tablets); maximum: 6 tablets/day

I.M., I.V., SubQ: 10-20 mg; maximum: 100 mg/day. Intramuscular injections should be administered 10-15 minutes prior to radiological/diagnostic procedures

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Scopolamine hydrobromide:**

Antiemetic: SubQ: 0.006 mg/kg

Preoperative: I.M., I.V., SubQ:

Children 6 months to 3 years: 0.1-0.15 mg

Children 3-6 years: 0.2-0.3 mg

Refraction: Ophthalmic: Instill 1 drop of 0.25% to eye(s) twice daily for 2 days before procedure

Iridocyclitis: Ophthalmic: Instill 1 drop of 0.25% to eye(s) up to 3 times/day

Administration: I.V.

Hydrobromide: Inject over 2-3 minutes

Butylbromide: Inject at a rate of 1 mL/minute

Administration: I.V. Detail

Hydrobromide: Dilute with an equal volume of sterile water and administer by direct I.V.

pH: 3.5-6.5

Butylbromide: No dilution is necessary prior to injection

Administration: Topical

Ophthalmic: Remove contact lenses prior to administration; wait 15 minutes before reinserting if using products containing benzalkonium chloride. Wash hands following administration.

Transdermal: Topical patch is programmed to deliver 1 mg over 3 days. Once applied, do not remove the patch for 3 full days. Apply to hairless area of skin behind the ear. Wash hands before and after applying the disc to avoid drug contact with eyes.

Storage

Injection: Store at room temperature of 15°C to 30°C (58°F to 86°F). Protect from light.

Hydrobromide injection: Avoid acid solutions, hydrolysis occurs at pH <3.

Butylbromide injection: Stable in D_5W, NS, $D_{10}W$, and LR for up to 8 hours.

Ophthalmic solution: Store at 8°C to 27°C (46°F to 80°F). Protect from light.

Tablet: Store at room temperature of 15°C to 30°C (58°F to 86°F).

Transdermal system: Store at 20°C to 25°C (68°F to 77°F).

Compatibility

Y-site administration: Hydrobromide: Compatible: Heparin, hydrocortisone sodium succinate, potassium chloride, propofol, sufentanil, vitamin B complex with C.

Compatibility in syringe:

Hydrobromide: Compatible: Atropine, butorphanol, chlorpromazine, cimetidine, diamorphine, dimenhydrinate, diphenhydramine, droperidol, fentanyl, glycopyrrolate, hydromorphone, hydroxyzine, meperidine, metoclopramide, midazolam, morphine, nalbuphine, pentazocine, pentobarbital, perphenazine, prochlorperazine edisylate, promazine, promethazine, ranitidine, sufentanil, thiopental.

Butylbromide: Compatible: Dimenhydrinate, fentanyl, midazolam, morphine.

Compatibility when admixed: Hydrobromide: Compatible: Floxacillin, furosemide, meperidine, succinylcholine.

ContraindicationsHypersensitivity to scopolamine, other belladonna alkaloids, or any component of the formulation; narrow-angle glaucoma; acute hemorrhage; paralytic ileus; tachycardia secondary to cardiac insufficiency; myasthenia gravis

Tablet formulations are contraindicated in patients with prostatic hyperplasia, pyloric obstruction, or patients with an idiosyncrasy to anticholinergic drugs.

Injectable formulations are contraindicated in patients with chronic lung disease (repeated administration).

Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause drowsiness and/or blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Idiosyncratic reaction: Patients with idiosyncratic reaction to anticholinergics, including scopolamine, may experience disorientation, delirium and/or marked somnolence; may be accompanied by dilated pupils, rapid pulse and xerostomia.

- Visual disturbances: Discontinue if patient reports unusual visual disturbances or pain within the eye.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with coronary artery disease, tachyarrhythmias, heart failure, or hypertension; evaluate tachycardia prior to administration.

- Gastrointestinal obstruction: Use with caution in patients with GI obstruction.

- Hepatic impairment: Use with caution in patients with hepatic impairment; adverse CNS effects occur more often in these patients.

- Hiatal hernia: Use with caution in patients with hiatal hernia with reflux esophagitis.

- Prostatic hyperplasia/urinary retention: Use injectable, ophthalmic, and transdermal products with caution in patients with prostatic hyperplasia (nonobstructive) or urinary retention; oral products are contraindicated.

- Psychosis: Use with caution in patients with a history of psychosis; may exacerbate condition.

- Renal impairment: Use with caution in patients with renal impairment; adverse CNS effects occur more often in these patients.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; may exacerbate condition.

- Ulcerative colitis: Use with caution in patients with ulcerative colitis; may precipitate/aggravate toxic megacolon.

Special populations:

- Pediatrics: Use with caution in infants and children since they may be more susceptible to adverse effects; safety and efficacy have not been established for the use of transdermal and oral scopolamine in children.

Dosage form specific issues:

- Ophthalmic products: May contain benzalkonium chloride which may be absorbed by contact lenses; remove contacts prior to administration and wait 15 minutes before reinserting.

- Product interchangeability: Scopolamine (hyoscine) hydrobromide should not be interchanged with scopolamine butylbromide formulations; dosages are not equivalent.

- Transdermal patch: May contain conducting metal (eg, aluminum); remove patch prior to MRI.

Geriatric ConsiderationsBecause of its long duration of action as a mydriatic agent, it should be avoided in elderly patients. Anticholinergic agents are not well tolerated in the elderly and their use should be avoided when possible.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; embryotoxic events were observed in some studies. Scopolamine crosses the placenta; may cause respiratory depression and/or neonatal hemorrhage when used during pregnancy. Transdermal scopolamine has been used as an adjunct to epidural anesthesia for cesarean delivery without adverse CNS effects on the newborn. Except when used prior to cesarean section, use during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Adverse ReactionsFrequency not defined.

Ophthalmic:Note: Systemic adverse effects have been reported following ophthalmic administration.

Central nervous system: Drowsiness, somnolence, visual hallucination

Dermatologic: Eczematoid dermatitis

Ocular: Blurred vision, edema, exudate, follicular conjunctivitis, increased intraocular pressure, local irritation, photophobia, vascular congestion

Respiratory: Congestion

Systemic:

Cardiovascular: Flushing, orthostatic hypotension, palpitation, tachycardia, ventricular fibrillation

Central nervous system: Acute toxic psychosis (rare), agitation (rare), ataxia, confusion, delusion (rare), disorientation, dizziness, drowsiness, fatigue, hallucination (rare), headache, loss of memory, paranoid behavior (rare), restlessness

Dermatologic: Dry skin, erythema, increased sensitivity to light, rash

Endocrine & metabolic: Decreased flow of breast milk, thirst

Gastrointestinal: Bloated feeling, constipation, dry throat, dysphagia, nausea, vomiting, xerostomia

Genitourinary: Dysuria, urinary retention

Local: Irritation at injection site

Neuromuscular & skeletal: Tremor, weakness

Ocular: Accommodation impaired, blurred vision, cycloplegia, dryness, glaucoma (narrow-angle), increased intraocular pain, itching, photophobia, pupil dilation

Respiratory: Dry nose

Miscellaneous: Diaphoresis (decreased), heat intolerance

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Test InteractionsInterferes with gastric secretion test

Monitoring ParametersBody temperature, heart rate, urinary output, intraocular pressure

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, ergot-containing drugs). When used preoperatively, safety precautions should be observed and patient should be advised about blurred vision. For all uses, assess therapeutic effectiveness and adverse reactions. Teach patient appropriate use (according to formulation and purpose), interventions to reduce side effects, and adverse symptoms to report. Systemic effects have been reported following ophthalmic administration.

Patient EducationUse as directed. May cause drowsiness, confusion, impaired judgment, or vision changes (use caution when driving or engaging in tasks requiring alertness until response to drug is known); dry mouth, nausea, or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); orthostatic hypotension (use caution when climbing stairs and when rising from lying or sitting position); constipation (increased exercise, fluids, fruit, or fiber may help; if not effective consult prescriber); increased sensitivity to heat and decreased perspiration (avoid extremes of heat, reduce exercise in hot weather); or decreased milk if breast-feeding. Report hot, dry, flushed skin; blurred vision or vision changes; difficulty swallowing; chest pain, palpitations, or rapid heartbeat; painful or difficult urination; increased confusion, depression, or loss of memory; rapid or difficult respirations; muscle weakness or tremors; or eye pain. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Transdermal: Apply patch behind ear the day before traveling. Wash hands before and after applying, and avoid contact with the eyes. Do not remove for 3 days. Patch may contain metal; remove prior to MRI.

Ophthalmic: Instill as often as recommended. Wash hands before using. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Sit or lie down, open eye, look at ceiling, and instill prescribed amount of solution. Do not blink for 30 seconds, close eye and roll eye in all directions, and apply gentle pressure to inner corner of eye for 1-2 minutes. Temporary stinging or blurred vision may occur.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, solution, as hydrobromide: 0.4 mg/mL (1 mL)

Injection, solution, as hyoscine-N-butylbromide:

Buscopan® [CAN]: 20 mg/mL [not available in U.S.]

Solution, ophthalmic, as hydrobromide:

Isopto® Hyoscine: 0.25% (5 mL) [contains benzalkonium chloride]

Tablet, as hyoscine-N-butylbromide:

Buscopan® [CAN]: 10 mg [not available in U.S.]

Tablet, soluble, as hydrobromide:

Scopace™: 0.4 mg

Transdermal system:

Transderm Scōp®: 1.5 mg (4s, 10s, 24s) [releases ~1 mg over 72 hours]

Generic AvailableYes: Injection

Pricing: U.S. (www.drugstore.com)

Patch, 72-hour (Transderm-Scop)

1.5 mg (4): $39.95

1.5 mg (10): $97.95

Solution (Isopto Hyoscine)

0.25% (5): $30.99

Tablets (Scopace)

0.4 mg (30): $21.10

Mechanism of ActionBlocks the action of acetylcholine at parasympathetic sites in smooth muscle, secretory glands and the CNS; increases cardiac output, dries secretions, antagonizes histamine and serotonin; dilates pupils

Pharmacodynamics/Kinetics

Onset of action: Oral, I.M.: 0.5-1 hour; I.V.: 10 minutes

Peak effect: 20-60 minutes; may take 3-7 days for full recovery; transdermal: 24 hours

Duration: Oral, I.M.: 4-6 hours; I.V.: 2 hours

Absorption: Tertiary salts (hydrobromide) are well absorbed; quaternary salts (butylbromide) are poorly absorbed (local concentrations in the GI tract following oral dosing may be high)

Metabolism: Hepatic

Half-life elimination: 4.8 hours

Excretion: Urine (<10%, as parent drug and metabolites)

Related Information

- Cycloplegic Mydriatics

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation), dry throat (transdermal), and dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness; may rarely cause confusion or amnesia

Mental Health: Effects on Psychiatric TreatmentMay decrease the effects of levodopa; concurrent use with psychotropics may produce additive sedation of anticholinergic side effects (dry mouth)

Cardiovascular ConsiderationsScopolamine, at usual recommended cardiovascular doses, causes blockade of muscarinic receptors at the cardiac SA-node and is parasympatholytic (ie, blocks vagal activity increasing heart rate). In administering scopolamine, it is important to recognize that lower doses (0.1 mg) may have vagal mimetic effects (ie, increase vagal tone causing paradoxical bradycardia). It is likely that the vagal tonic effects of scopolamine are mediated by blockade of muscarinic receptors at the level of the brain.

Anesthesia and Critical Care Concerns/Other ConsiderationsIn administering scopolamine, it is important to recognize that lower doses (0.1 mg) may have vagal mimetic effects (ie, increase vagal tone causing paradoxical bradycardia). It is likely that the vagal tonic effects of scopolamine are mediated by blockade of muscarinic receptors at the level of the brain. Disc is programmed to deliver *in vivo* 1 mg over 3 days.

Index TermsHyoscine Butylbromide; Hyoscine Hydrobromide; Scopolamine Base; Scopolamine Butylbromide; Scopolamine Hydrobromide

References

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Tavorath R and Hesketh PJ, “Drug Treatment of Chemotherapy-Induced Delayed Emesis,” *Drugs*, 1996, 52(5):639-48. [PubMed 9118814]

Tortorice PV and O'Connell MB, “Management of Chemotherapy-Induced Nausea and Vomiting,” *Pharmacotherapy*, 1990, 10(2):129-45.[PubMed 2190193]

International Brand NamesAriel TDDS (HK); Belloid (IN); Boro-Scopol (DE); Bupasmol (UY); Buscapina (AR, CN, CO, PE, PY, UY, VE); Buscolysin (PL); Buscopalamin (HK); Buscopan (AU, BR, CZ, DK, FI, GB, GR, HK, HN, IE, IN, IT, KP, MY, PH, PK, PL, SE, SG, TH, TW); Cifespasma (AR); Copan (HK); Escapin (PE); Gastride (PH); Hyospasmol (ZA); Labinpina (CO); Modul (PE); Scoburen (FR); Scobutrin (ID); Scolmin (PH); Scopamin (ID); Scopma (ID); Scopoderm (DK, FI, GB, IE, NO, SE); Scopoderm TTS (AT, CH, DE, FR, NL); Scopolamine Dispersa (CH); Scopolamine-POS (DE); Scopolaminum hydrobromicum ”Eifelfango” (DE); Scopolan (PL); Setacol (AU); Soonway (TW); Spasmolit (ID); Vacopan (MY, SG, TH); Vorigeno (ES)

Secobarbital

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Seconal® may be confused with Sectral®

Pronunciation(see koe BAR bi tal)

U.S. Brand NamesSeconal®

Pharmacologic CategoryBarbiturate

Use: Labeled IndicationsPreanesthetic agent; short-term treatment of insomnia

Dosing: Adults**Insomnia (hypnotic):** Oral: 100 mg/dose at bedtime; range: 100-200 mg/dose

Dosing: ElderlyNot recommended for use in the elderly (see Geriatric Considerations).

Dosing: Pediatric

Preoperative sedation: Oral: Children: 2-6 mg/kg (maximum dose: 100 mg/dose) 1-2 hours before procedure

Sedation: Oral: Children: 6 mg/kg/day divided every 8 hours

Dosing: Renal ImpairmentSlightly dialyzable (5% to 20%)

RestrictionsC-II

ContraindicationsHypersensitivity to barbiturates or any component of the formulation; marked hepatic impairment; dyspnea or airway obstruction; porphyria; pregnancy

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypersensitivity reactions: Postmarketing studies have indicated that the use of hypnotic/sedative agents for sleep has been associated with hypersensitivity reactions including anaphylaxis as well as angioedema.
- Paradoxical responses: May cause paradoxical responses, including agitation and hyperactivity, particularly in acute pain, chronic pain and pediatric patients.
- Sleep-related activities: An increased risk for hazardous sleep-related activities such as sleep-driving; cooking and eating food, and making phone calls while asleep have also been noted. Discontinue treatment in patients who report a sleep-driving episode.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; may cause hypotension.
- Depression: Use with caution in patients with depression or suicidal tendencies.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease; may cause respiratory depression.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; closely monitor elderly or debilitated patients for impaired cognitive or motor performance.
- Pediatrics: Use with caution in children.

Other warnings/precautions:

- Appropriate use: Symptomatic treatment of insomnia should be initiated only after careful evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric and/or medical illness.

- Withdrawal: Abrupt cessation may precipitate withdrawal, including status epilepticus in epileptic patients.

Geriatric ConsiderationsUse of this agent in the elderly is not recommended due to its long half-life and addiction potential.
Pregnancy Risk FactorD
LactationEnters breast milk/use caution (AAP rates "compatible")
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension

Central nervous system: Dizziness, lightheadedness, "hangover" effect, drowsiness, CNS depression, fever, confusion, mental depression, unusual excitement, nervousness, faint feeling, headache, insomnia, nightmares, hallucinations

Dermatologic: Exfoliative dermatitis, rash, Stevens-Johnson syndrome

Gastrointestinal: Nausea, vomiting, constipation

Hematologic: Agranulocytosis, megaloblastic anemia, thrombocytopenia, thrombophlebitis, urticaria

Local: Pain at injection site

Respiratory: Apnea, laryngospasm, respiratory depression

Postmarketing and/or case reports: Anaphylaxis, angioedema, complex sleep-related behavior (sleep-driving, cooking or eating food, making phone calls)

Metabolism/Transport Effects**Induces** CYP2A6 (strong), 2C8 (strong), 2C9 (strong)
Drug Interactions

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2A6 Substrates: CYP2A6 Inducers (Strong) may increase the metabolism of CYP2A6 Substrates. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inducers (Highly Effective) may increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inducers (Highly Effective) may increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

Griseofulvin: Barbiturates may decrease the absorption of Griseofulvin. *Risk D: Consider therapy modification*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersBlood pressure, heart rate, respiratory rate, CNS status

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess patient for history of addiction; long-term use can result in dependence, abuse, or tolerance and evaluate periodically for need for continued use. Be alert to possibility of anaphylaxis any time during therapy. Assess for CNS depression, abnormal thinking, and behavior changes. Monitor vital signs and respiratory status. After long-term use, taper dosage slowly when discontinuing. **Oral:** For inpatient use, institute safety measures. For outpatient use, monitor effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationUse exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol or other prescription or OTC medications (especially, pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help). Report skin rash or irritation; CNS changes (confusion, depression, increased sedation, excitation, headache, insomnia, or nightmares); respiratory difficulty or shortness of breath; difficulty swallowing or feeling of tightness in throat; unusual weakness or unusual bleeding in mouth, urine, or stool; unusual swelling, especially on face or neck; or other unanticipated adverse effects. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Use appropriate contraceptive measures. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as sodium: 100 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Seconal)

100 mg (20): $25.99

Mechanism of ActionDepresses CNS activity by binding to barbiturate site at GABA-receptor complex enhancing GABA activity, depressing reticular activity system; higher doses may be gabamimetic

Pharmacodynamics/Kinetics

Onset of hypnosis: 15-30 minutes

Duration: 3-4 hours with 100 mg dose

Distribution: 1.5 L/kg; crosses the placenta; appears in breast milk

Protein binding: 45% to 60%

Metabolism: Hepatic, by microsomal enzyme system

Half-life elimination: 15-40 hours, mean: 28 hours

Time to peak, serum: Within 2-4 hours

Excretion: Urine (as inactive metabolites, small amounts as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

Index Terms Quinalbarbitone Sodium; Secobarbital Sodium

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Nahata MC, Starling S, and Edwards RC, “Prolonged Sedation Associated With Secobarbital in Newborn Infants Receiving Ventilatory Support,” *Am J Perinatol*, 1991, 8(1):35-6. [PubMed 1987965]

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Wolfert RR and Cox RM, “Room Temperature Stability of Drug Products Labeled for Refrigerated Storage,” *Am J Hosp Pharm*, 1975, 32(6):585-7.[PubMed 1155470]

International Brand Names Dormatylan (AT); Seconal Sodium (GB)

Secretin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(SEE kr tin)
U.S. Brand NamesChiRhoStim®; SecreFlo™ [DSC]
Pharmacologic CategoryDiagnostic Agent
Use: Labeled IndicationsSecretin-stimulation testing to aid in diagnosis of pancreatic exocrine dysfunction; diagnosis of gastrinoma (Zollinger-Ellison syndrome); facilitation of endoscopic retrograde cholangiopancreatography (ERCP) visualization
Dosing: Adults**Note:** A test dose of 0.1 mL (0.2-0.4 mcg) is injected to test for possible allergy. Dosing may be completed if no reaction occurs after 1 minute.

Diagnosis of pancreatic dysfunction, facilitation of ERCP: I.V.: 0.2 mcg/kg over 1 minute

Diagnosis of gastrinoma: I.V.: 0.4 mcg/kg over 1 minute

Dosing: ElderlyRefer to adult dosing.
Administration: I.V.Administer by direct I.V. injection slowly over 1 minute
Administration: I.V. DetailpH: 3-6.5
Dietary ConsiderationsSecreFlo™: Patients should be in a fasting state (12- to 15-hour fast) prior to testing for gastrinoma.
StoragePrior to reconstitution, store frozen at -20°C. Protect from light. Human product may also be stored under refrigeration for up to 1 year or at room temperature for up to 6 months.
ReconstitutionAdd 8 mL NS to the 16 mcg vial to yield concentration of 2 mcg/mL; add 10 mL NS to the 40 mcg vial to yield a concentration of 4 mcg/mL; shake vigorously.
ContraindicationsHypersensitivity to secretin or any component of the formulation; acute pancreatitis
Warnings/Precautions

Concerns related to adverse effects:

- Allergic reaction: Potential for allergic reactions exists; test dose is recommended. Medications for the treatment of hypersensitivity should be available for immediate use. Patients with a history of asthma or atopy are at higher risk for reaction.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment (including ethanol-induced disease); volume response to secretin may be exaggerated.

- Inflammatory bowel disease: Response may be blunted in the presence of inflammatory bowel disease; blunted response is not indicative of pancreatic disease.

Concurrent drug therapy issues:

- Anticholinergics: Response may be blunted in the presence of anticholinergic agents; blunted response is not indicative of pancreatic disease.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Vagotomy: Response may be blunted following vagotomy; blunted response is not indicative of pancreatic disease.

Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

1% to 10%:

Cardiovascular: Flushing (1%)

Gastrointestinal: Nausea (1% to 2%), abdominal discomfort (≤1%), abdominal pain (≤1%), vomiting (≤1%)

Miscellaneous: Bleeding (sphincterectomy, ≤1%)

<1%: Abdominal cramps, anxiety, bloating, bradycardia (mild), diaphoresis, diarrhea, dyspepsia, faintness, fatigue, fever, headache, heart rate increased, hypotension, leukocytoplastic vasculitis, lightheadedness, numbness/tingling in the extremities, oral secretions increased, oxygen saturation decreased, pallor, pancreatitis (mild), rash (abdominal), respiratory distress (transient), sedation, seizure, warm sensation (abdomen/face)

Drug Interactions

Anticholinergic Agents: May diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Monitoring ParametersRefer to protocols for collection of pancreatic secretion and/or serum gastrin.
Monitoring: Lab TestsRefer to protocols for collection of pancreatic secretion and/or serum gastrin.
Patient EducationTake nothing by mouth for 12-15 hours prior to testing. May cause nausea, abdominal pain, and/or flushing.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution [human derived]:

ChiRhoStim®: 16 mcg

Injection, powder for reconstitution [porcine derived]:

SecreFlo™: 16 mcg [DSC]

Generic AvailableNo
Mechanism of ActionHuman and porcine secretin are both synthetically derived products and are equally potent on an osmolar basis. Secretin is a hormone which is normally secreted by duodenal mucosa and upper jejunal mucosa. It increases the volume and bicarbonate content of pancreatic juice; stimulates the flow of hepatic bile with a high bicarbonate concentration; stimulates gastrin release in patients with Zollinger-Ellison syndrome.
Pharmacodynamics/Kinetics

Onset of action: Peak output of pancreatic secretions: ~30 minutes

Duration: Human: 1.5-2 hours; Porcine: 1-1.5 hours

Distribution: V_d: Human: 2.7 L; Porcine: 2 L

Half-life elimination: Human: 45 minutes; Porcine: 27 minutes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentConcomitant use with psychotropics may blunt the response to secretin stimulation.
Mental Health CommentUse caution in patients with ethanol-induced hepatic disease.
Index TermsSecretin, Human; Secretin, Porcine
References

Metz DC, Buchanan M, Purich E, et al, "A Randomized Controlled Crossover Study Comparing Synthetic Porcine and Human Secretins With Biologically Derived Porcine Secretin to Diagnose Zollinger-Ellison Syndrome," *Aliment Pharmacol Ther*, 2001, 15(5):669-76.[PubMed 11328261]

International Brand NamesSecrepan (JP); Secretin Ferring (FI); Sekretolin (CZ)

Selegiline

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Selegiline may be confused with Salagen®, Serentil®, sertraline, Serzone®, Stelazine®

Eldepryl® may be confused with Elavil®, enalapril

Zelapar™ may be confused with zaleplon, Zemplar®

Pronunciation(se LE ji leen)

U.S. Brand NamesEldepryl®; Emsam®; Zelapar™

Canadian Brand NamesApo-Selegiline®; Gen-Selegiline; Novo-Selegiline; Nu-Selegiline

Pharmacologic CategoryAnti-Parkinson's Agent, MAO Type B Inhibitor; Antidepressant, Monoamine Oxidase Inhibitor

Use: Labeled IndicationsAdjunct in the management of parkinsonian patients in which levodopa/carbidopa therapy is deteriorating (oral products); treatment of major depressive disorder (transdermal product)

Use: Unlabeled/InvestigationalEarly Parkinson's disease; attention-deficit/hyperactivity disorder (ADHD); negative symptoms of schizophrenia; extrapyramidal symptoms

Dosing: Adults

Parkinson’s disease:

Capsule/tablet: 5 mg twice daily with breakfast and lunch or 10 mg in the morning

Orally disintegrating tablet (Zelapar™): Initial 1.25 mg daily for at least 6 weeks; may increase to 2.5 mg daily based on clinical response (maximum: 2.5 mg daily)

Depression: Transdermal (Emsam®): Initial: 6 mg/24 hours once daily; may titrate based on clinical response in increments of 3 mg/day every 2 weeks up to a maximum of 12 mg/24 hours

Dosing: Elderly

Parkinson's disease:

Capsule/tablet: Initial: 5 mg in the morning; may increase to a total of 10 mg/day.

Orally disintegrating tablet (Zelapar™): Initial 1.25 mg daily for at least 6 weeks; may increase to 2.5 mg daily based on clinical response (maximum: 2.5 mg daily)

Depression: Transdermal (Emsam®): 6 mg/24 hours

Dosing: Pediatric**ADHD** (unlabeled use): Children and Adolescents: Oral: 5-15 mg/day

Dosing: Renal ImpairmentNo adjustment necessary.

Dosing: Hepatic ImpairmentNo adjustment necessary in mild-moderate hepatic impairment.

Administration: OralOrally disintegrating tablet (Zelapar™): Take in morning before breakfast; place on top of tongue and allow to dissolve. Avoid food or liquid 5 minutes before and after administration.

Administration: TopicalTransdermal (Emsam®): Apply to clean, dry, intact skin to the upper torso (below the neck and above the waist), upper thigh, or outer surface of the upper arm. Avoid exposure of application site to external heat source, which may increase the amount of drug absorbed. Apply at the same time each day and rotate application sites. Wash hands with soap and water after handling. Avoid touching the sticky side of the patch.

Dietary ConsiderationsAvoid tyramine-containing foods/beverages. Some examples include aged or matured cheese, air-dried or cured meats (including sausages and salamis), fava or broad bean pods, tap/draft beers, Marmite concentrate, sauerkraut, soy sauce and other soybean condiments.

Emsam® 9 mg/24 hours or 12 mg/24 hours: Avoid tyramine-rich foods or beverages beginning the first day of treatment or for 2 weeks after discontinuation or dose reduction to 6 mg/24 hours.

Zelapar™: Phenylalanine 1.25 mg per 1.25 mg tablet; do not take with food or liquid

Storage

Capsule, tablet: Store at controlled room temperature 15°C to 30°C (59°F to 86°F).

Orally-disintegrating tablet: Store at controlled room temperature 15°C to 30°C (59°F to 86°F). Use within 3 months of opening pouch and immediately after opening individual blister.

Transdermal: Store at 20°C to 25°C (68°F to 77°F).

Restrictions An FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing a transdermal selegiline outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

Contraindications Hypersensitivity to selegiline or any component of the formulation; concomitant use of meperidine

Orally disintegrating tablet: Additional contraindications: Concomitant use of dextromethorphan, methadone, propoxyphene, tramadol, oral selegiline, other MAO inhibitors

Transdermal: Additional contraindications: Pheochromocytoma; concomitant use of bupropion, selective or dual serotonin reuptake inhibitors (including SSRIs and SNRIs), tricyclic antidepressants, buspirone, tramadol, propoxyphene, methadone, dextromethorphan, St. John’s wort, mirtazapine, cyclobenzaprine, oral selegiline and other MAO inhibitors; carbamazepine, and oxcarbazepine; elective surgery requiring general anesthesia, local anesthesia containing sympathomimetic vasoconstrictors; sympathomimetics (and related compounds); foods high in tyramine content; supplements containing tyrosine, phenylalanine, tryptophan, or caffeine

Allergy Considerations

- Amphetamine Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings (transdermal product):

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription.**Transdermal selegiline is not FDA approved for use in children <12 years of age.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Selegiline is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Orthostatic hypotension: Transdermal product may cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

Disease-related concerns:

- Hepatic impairment: Use transdermal product with caution in patients with hepatic impairment.

- Renal impairment: Use transdermal product with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Antidepressants: Use of oral selegiline with tricyclic antidepressants and SSRIs has also been associated with rare reactions and should generally be avoided. Transdermal selegiline should not be used in combination with other antidepressants. Do not use within 5 weeks of fluoxetine discontinuation or 1 week of other antidepressant discontinuation. Wait 2 weeks after discontinuing transdermal selegiline before initiating therapy with buspirone or any other contraindicated drug.

- Levodopa: Addition of oral selegiline to levodopa therapy may result in exacerbation of levodopa adverse effects, requiring a reduction in levodopa dosage.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age (transdermal patch) or <16 years of age (orally-disintegrating formulation); there is no FDA-approved labeling for use of the oral capsule/tablet in children.

Other warnings/precautions:

- Discontinuation of therapy: Medication should not be stopped abruptly; taper off as rapidly as possible.

- Elective surgery: Discontinue transdermal product at least 10 days prior to elective surgery.

- Tyramine-containing products: Nonselective MAO inhibition occurs with transdermal delivery and is necessary for antidepressant efficacy. Hypertensive crisis as a result of ingesting tyramine-rich foods is always a concern with nonselective MAO inhibition. Although transdermal delivery minimizes inhibition of MAO-A in the gut, there is limited data with higher transdermal doses; dietary restrictions are recommended with doses >6 mg/24 hours. With the oral product, MAO-B selective inhibition should not pose a problem with tyramine-containing products as long as the typical oral doses are employed, however, rare reactions have been reported. Increased risk of nonselective MAO inhibition occurs with oral capsule/tablet doses >10 mg/day or orally disintegrating tablet doses >2.5 mg/day.

Geriatric ConsiderationsDo not use capsule/tablet at doses >10 mg/day or orally disintegrating tablet at doses >2.5 mg/day because of the risks associated with nonselective inhibition of MAO.

Orally-disintegrating tablets: In clinical trials, adverse effects were seen more frequently in the elderly compared to younger adults. This is particularly of concern for hypertension, orthostatic hypotension, dizziness, and somnolence. If using the orally disintegrating tablets, administer at the lowest dose and monitor for side effects.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic and adverse behavioral events were noted in animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsUnless otherwise noted, the percentage of adverse events is reported for the transdermal patch (**Note:** ODT = orally disintegrating tablet, Oral = capsule/tablet)

>10%:

Central nervous system: Headache (18%; ODT 7%; oral 2%), insomnia (12%; ODT 7%), dizziness (ODT 11%; oral 7%)

Gastrointestinal: Nausea (ODT 11%; oral 10%)

Local: Application site reaction (24%)

1% to 10%:

Cardiovascular: Hypotension (including postural 3% to 10%), chest pain (≥1%; ODT 2%), hypertension (≥1%), peripheral edema (≥1%)

Central nervous system: Pain (ODT 8%), hallucinations (ODT 4%; oral 3%), confusion (ODT 4%; oral 3%), ataxia (ODT 3%), somnolence (ODT 3%), agitation (≥1%), amnesia (≥1%), paresthesia (≥1%), thinking abnormal (≥1%), depression (<1%; ODT 2%)

Dermatologic: Rash (4%), ecchymosis (ODT 2%), bruising (≥1%), pruritus (≥1%), acne (≥1%)

Endocrine & metabolic: Weight loss (5%), hypokalemia (ODT 2%), sexual side effects (≤1%)

Gastrointestinal: Diarrhea (9%; ODT 2%), xerostomia (8%; ODT 4%), stomatitis (ODT 5%), abdominal pain (oral 4%), dyspepsia (4%; ODT 5%), constipation (≥1%; ODT 4%), flatulence (≥1%; ODT 2%), anorexia (≥1%), gastroenteritis (≥1%), taste perversion (≥1%; ODT 2%), vomiting (≥1%; ODT 3%), tooth disorder (ODT 2%), dysphagia (ODT 2%)

Genitourinary: Dysmenorrhea (≥1%), metrorrhagia (≥1%), UTI (≥1%), urinary frequency (≥1%)

Neuromuscular & skeletal: Dyskinesia (ODT 6%), back pain (ODT 5%), ataxia (<1%; ODT 3%), leg cramps (ODT 3%), myalgia (≥1%; ODT 3%), neck pain (≥1%), tremor (<1%; ODT 3%)

Otic: Tinnitus (≥1%)

Respiratory: Rhinitis (ODT 7%), pharyngitis (3%; ODT 4%), sinusitis (3%), cough (≥1%), bronchitis (≥1%), dyspnea (<1%; ODT 3%)

Miscellaneous: Diaphoresis (≥1%)

Oral and/or transdermal patch: <1% or frequency not defined (limited to important or life-threatening): Abnormal liver function tests, alkaline phosphatase increased, appetite increased, arrhythmia, asthma, ataxia, atrial fibrillation, bacterial infection, behavior/mood changes, bilirubinemia, bradycardia, bradykinesia, breast neoplasm (female), breast pain, chorea, circumoral paresthesia, colitis, dehydration, delusions, dental caries, depersonalization, depression, emotional lability, epistaxis, eructation, euphoria, face edema, fever, fungal infection, gastritis, generalized spasm, glossitis, heat stroke, hematuria (female), hernia, hostility, hypercholesterolemia, hyperesthesia, hyperglycemia, hyperkinesias, hypertonia, hypoglycemic reaction, hyponatremia, kidney calculus (female), lactate dehydrogenase increased, laryngismus, leukocytosis, leukopenia, libido increased, loss of balance, lymphadenopathy, maculopapular rash, manic reaction, melena, migraine, moniliasis, myasthenia, myocardial infarct, myoclonus, neoplasia, neurosis, osteoporosis, otitis external, palpitation, paranoid reaction, parasitic infection, parosmia, pelvic pain, periodontal abscess, peripheral vascular disorder, pneumonia, polyuria (female), prostatic hyperplasia, rectal hemorrhage, salivation increased, skin hypertrophy, skin benign neoplasm, suicide attempt, syncope, tachycardia, tenosynovitis, tongue edema, twitching, urinary retention, urinary urgency (male and female), urination impaired (male), urticaria, vaginal hemorrhage, vaginal moniliasis, vaginitis, vasodilatation, vertigo, vesiculobullous rash, viral infection, visual field defect

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2A6 (minor), 2B6 (major), 2C8 (minor), 2C19 (minor), 2D6 (minor), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2A6 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak), 3A4 (weak)

Drug Interactions

Alpha-/Beta-Agonists (Direct-Acting): MAO Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists (Indirect-Acting): MAO Inhibitors may enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Alpha1-Agonists: MAO Inhibitors may enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Alpha2-Agonists (Ophthalmic): MAO Inhibitors may enhance the hypertensive effect of Alpha2-Agonists (Ophthalmic). *Risk X: Avoid combination*

Altretamine: May enhance the orthostatic effect of MAO Inhibitors. *Risk C: Monitor therapy*

Amphetamines: MAO Inhibitors may enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Anilidopiperidine Opioids: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. *Risk D: Consider therapy modification*

Atomoxetine: MAO Inhibitors may enhance the neurotoxic (central) effect of Atomoxetine. *Risk X: Avoid combination*

Beta2-Agonists: MAO Inhibitors may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: MAO Inhibitors may enhance the neurotoxic (central) effect of BuPROPion. *Risk X: Avoid combination*

BusPIRone: May enhance the adverse/toxic effect of MAO Inhibitors. Elevated blood pressure has been reported. *Risk X: Avoid combination*

COMT Inhibitors: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Cyclobenzaprine: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

CYP2B6 Inducers (Strong): May increase the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Moderate): May decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2B6 Inhibitors (Strong): May decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

Dexmethylphenidate: MAO Inhibitors may enhance the hypertensive effect of Dexmethylphenidate. *Risk X: Avoid combination*

Dextromethorphan: MAO Inhibitors may enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

Levodopa: May enhance the adverse/toxic effect of MAO Inhibitors. Of particular concern is the development of hypertensive reactions when levodopa is used with nonselective MAOI. *Risk D: Consider therapy modification*

Linezolid: MAO Inhibitors may enhance the adverse/toxic effect of Linezolid. *Risk X: Avoid combination*

Lithium: MAO Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Maprotiline: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

Meperidine: MAO Inhibitors may enhance the serotonergic effect of Meperidine. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methyldopa: MAO Inhibitors may enhance the adverse/toxic effect of Methyldopa. *Risk X: Avoid combination*

Methylphenidate: MAO Inhibitors may enhance the hypertensive effect of Methylphenidate. *Risk X: Avoid combination*

Mirtazapine: MAO Inhibitors may enhance the neurotoxic (central) effect of Mirtazapine. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): May increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Oral Contraceptive (Progestins): May increase the serum concentration of Selegiline. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the adverse/toxic effect of MAO Inhibitors. Specifically, the risk of serotonin syndrome or other serotonergic adverse events may be increased. *Risk X: Avoid combination*

Rauwolfia Alkaloids: MAO Inhibitors may enhance the adverse/toxic effect of Rauwolfia Alkaloids. Existing MAOI therapy can result in paradoxical effects of added rauwolfia alkaloids (eg, excitation, hypertension). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: MAO Inhibitors may decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. **Exceptions:** Eletriptan; Frovatriptan; Naratriptan. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tetrabenazine: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

TraMADol: May enhance the neuroexcitatory and/or seizure-potentiating effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: MAO Inhibitors may enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (based on CNS depressant effects and potential tyramine content)

Food: Concurrent ingestion of foods rich in tyramine may cause sudden and severe high blood pressure (hypertensive crisis). Avoid tyramine-containing foods with MAO-Is. Food's freshness is also an important concern; improperly stored or spoiled food can create an environment where tyramine concentrations may increase.

Herb/Nutraceuticals: Avoid valerian, St John's wort, SAMe, kava kava. Avoid supplements containing caffeine, tryptophan, or phenylalanine. Ingestion of large quantities may increase the risk of severe side effects (eg, hypertensive reactions, serotonin syndrome).

Monitoring ParametersBlood pressure; symptoms of parkinsonism; general mood and behavior (increased anxiety, presence of mania or agitation); suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness according to rationale for therapy and adverse reactions at beginning of therapy and periodically throughout therapy. Monitor blood pressure. Be alert to thoughts of suicide. Patient should be cautioned against eating foods high in tyramine (see Tyramine Contents of Foods list). Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. Discontinue at least 10 days prior to elective surgery. Taper dose when discontinuing.

Patient EducationTake exactly as directed (may be prescribed in conjunction with levodopa/carbidopa); do not change dosage or discontinue without consulting prescriber. Therapeutic effects may take several weeks or months to achieve and you may need frequent monitoring during first weeks of therapy. Take oral capsule/tablet with meals if GI upset occurs, before meals if dry mouth occurs, or after eating if drooling or if nausea occurs. Do not take food or liquid for 5 five minutes before or after administering orally disintegrating tablets. Do not swallow orally disintegrating tablet; allow to dissolve on tongue. Take at the same time each day. Avoid tyramine-containing foods (low potential for reaction) with oral products. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol, prescription or OTC sedatives, or CNS depressants without consulting prescriber. You may experience drowsiness, dizziness, confusion, or vision changes (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); orthostatic hypotension (use caution when changing position - rising to standing from sitting or lying); constipation (increased exercise, fluids, fruit, or fiber may help); runny nose or flu-like symptoms (consult prescriber for appropriate relief); or nausea, vomiting, loss of appetite, or stomach discomfort (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report unresolved constipation or vomiting; chest pain, palpitations, irregular heartbeat; CNS changes (hallucination, loss of memory, seizures, acute headache, nervousness, thoughts of suicide, etc); painful or difficult urination; stiff neck; increased muscle spasticity, rigidity, or involuntary movements; skin rash; or significant worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, oral, as hydrochloride: 5 mg

Eldepryl®: 5 mg

Tablet, oral, as hydrochloride: 5 mg

Tablet, orally-disintegrating:

Zelapar™: 1.25 mg [contains phenylalanine 1.25 mg/tablet]

Transdermal system, topical [once-daily patch]:

Emsam®: 6 mg/24 hours (30s) [20 cm^2, total selegiline 20 mg]; 9 mg/24 hours (30s) [30 cm^2, total selegiline 30 mg]; 12 mg/24 hours (30s) [40 cm^2, total selegiline 40 mg]

Generic AvailableYes: Capsule, tablet

Pricing: U.S. (www.drugstore.com)

Capsules (Eldepryl)

5 mg (60): $170.00

Capsules (Selegiline HCl)

5 mg (60): $28.96

Patch, 24-hour (Emsam)

6 mg/24 hrs (30): $518.92

9 mg/24 hrs (30): $528.66

Tablet, orally-disintegrating (Zelapar)

1.25 mg (30): $160.49

Tablets (Selegiline HCl)

5 mg (60): $35.98

Mechanism of ActionPotent, irreversible inhibitor of monoamine oxidase (MAO). Plasma concentrations achieved via administration of oral dosage forms in recommended doses confer selective inhibition of MAO type B, which plays a major role in the metabolism of dopamine; selegiline may also increase dopaminergic activity by interfering with dopamine reuptake at the synapse. When administered transdermally in recommended doses, selegiline achieves higher blood levels and effectively inhibits both MAO-A and MAO-B, which blocks catabolism of other centrally-active biogenic amine neurotransmitters.

Pharmacodynamics/Kinetics

Onset of action: Therapeutic: Oral: Within 1 hour

Duration: Oral: 24-72 hours

Absorption:

Orally disintegrating tablet: Rapid; greater bioavailability than capsule/tablet

Transdermal: 25% to 30% (of total selegiline content) over 24 hours

Protein binding: ~90%

Metabolism: Hepatic, primarily via CYP2B6 to active (N-desmethylselegiline, amphetamine, methamphetamine) and inactive metabolites

Half-life elimination: Oral: 10 hours; Transdermal: 18-25 hours

Excretion: Urine (primarily metabolites); feces

Related Information

- Antidepressant Agents
- Antiparkinsonian Agents
- Teratogenic Risks of Psychotropic Medications
- Tyramine Content of Foods

Pharmacotherapy Pearls When adding selegiline to levodopa/carbidopa, the dose of the latter can usually be decreased.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation). Anticholinergic side effects can cause a reduction of saliva production or secretion, contributing to discomfort and dental disease (ie, caries, oral candidiasis, and periodontal disease).

Orally disintegrating tablet: Dysphagia, tooth disorder, stomatitis, and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Selegiline in doses of 10 mg a day or less does not inhibit type-A MAO. Therefore, there are no precautions with the use of vasoconstrictors.

Mental Health: Child/Adolescent Considerations Twenty-nine children 6-18 years of age (mean: 11.2 years) with ADHD refractory to conventional treatments received an average daily dose of 8.1 mg (5-15 mg/day) for an average of 6.7 months (Jankovic, 1993).

Two randomized, double-blind, placebo-controlled trials have shown selegiline to be as effective, and possibly better tolerated, than methylphenidate in the treatment of children (n=68, range: 4-15 years of age) with ADHD (Akhondzadeh, 2003; Mohammadi, 2004).

Akhondzadeh S, Tavakolian R, Davari-Ashtiani R, et al, “Selegiline in the Treatment of Attention Deficit Hyperactivity Disorder in Children: A Double Blind and Randomized Trial,” *Prog Neuropsychopharmacol Biol Psychiatry*, 2003, 27(5):841-5.

Jankovic J, “Deprenyl in Attention Deficit Associated With Tourette's Syndrome,” *Arch Neurol*, 1993, 50(3):286-8.

Mohammadi MR, Ghanizadeh A, Alaghband-Rad J, et al, “Selegiline in Comparison With Methylphenidate in Attention Deficit Hyperactivity Disorder Children and Adolescents in a Double-Blind, Randomized Clinical Trial,” *J Child Adolesc Psychopharmacol*, 2004, 14(3):418-25.

Mental Health Comment Selegiline is a selective MAO-B inhibitor when used in low oral doses (≤10 mg/day). The patch formulation inhibits both MAO-A and MAO-B inhibitors. When using the 6 mg/day patch, no special diet is required; however, when using the 9 mg/day or 12 mg/day patch a tyramine-restricted diet should be utilized.

Anesthesia and Critical Care Concerns/Other Considerations When adding selegiline to levodopa/carbidopa, the dose of the latter can usually be decreased. Studies are investigating the use of selegiline in early Parkinson's disease to slow the progression of the disease. With doses >10 mg/day, selegiline loses MAO type “B” specificity.

Index Terms Deprenyl; L-Deprenyl; Selegiline Hydrochloride

References

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International Brand NamesAntiparkin (LU); Apo-Selegiline (NZ); Apo-selin (PL); Brintenal (AR); Comenter (EC); Deprenyl (FR); Eldepryl (AU, BE, DK, FI, GB, IE, NL, NO, SE); Endopryl (CY); Julab (TH); Jumex (AR, AT, BG, CR, CZ, DO, HK, HN, HR, HU, ID, IL, IT, KP, MY, NI, PH, PL, PT, PY, TH, UY, VE); Jumexal (CH, TW); MAO-B (KP); MAOtil (DE); Movergan (DE, HR); Niar (BR, MX, PL); Parkilyne (ZA); Parkinil (PL); Plurimen (ES); Procythol (GR); Sedicel (CO); Sefmex (HK, MY); Segan (PL); Selegil (CO, PE); Selegos (HK, SG); Selenor (PL); Selerin (PL); Selgene (AU, TH); Selgin (IN, PK, PL); Selgina (CN); Selgres (PL); Seliratio (PL); Si Ji Ning (CL); Xilopar (DE)

Selenium Sulfide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(se LEE nee um SUL fide)

U.S. Brand NamesDandrex [OTC]; Head & Shoulders® Intensive Treatment [OTC]; Selseb®; Selsun blue® 2-in-1 Treatment [OTC]; Selsun blue® Daily Treatment [OTC]; Selsun blue® Medicated Treatment [OTC]; Selsun blue® Moisturizing Treatment [OTC]; Tersi

Canadian Brand NamesVersel®

Pharmacologic CategoryTopical Skin Product

Use: Labeled IndicationsTreatment of itching and flaking of the scalp associated with dandruff, to control scalp seborrheic dermatitis; treatment of tinea versicolor

Dosing: Adults

Dandruff, seborrhea: Topical: Massage 5-10 mL of shampoo into wet scalp, leave on scalp 2-3 minutes, rinse thoroughly; rub foam into affected skin twice daily

Tinea versicolor: Topical: Apply the 2.5% lotion to affected area and lather with small amounts of water; leave on skin for 10 minutes, then rinse thoroughly; apply every day for 7 days; rub foam into affected skin twice daily

Dosing: ElderlyRefer to adult dosing.

Administration: TopicalShake well before using. May damage jewelry; remove before treatment. For external use only; do not apply to broken or inflamed skin.

Foam: Invert canister to administer.

Storage

Foam, shampoo: Store at controlled room temperature of 15°C to 25°C (59°F to 77°F).

Lotion: Store below 30°C (86°F)

ContraindicationsHypersensitivity to selenium or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue use if irritation occurs.

Special populations:

- Pediatrics: Avoid topical use in very young children; safety of topical in infants has not been established.

Other warnings/precautions:

- Appropriate use: For external use only; avoid contact with eyes and genital areas. Due to the risk of systemic toxicity, do not use on damaged skin or mucous membranes

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have not been conducted. Avoid use in pregnant women unless the potential benefit justifies the potential risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Central nervous system: Lethargy

Dermatologic: Alopecia or hair discoloration, unusual dryness or oiliness of scalp

Gastrointestinal: Vomiting following long-term use on damaged skin, abdominal pain, garlic breath

Local: Burning, itching, irritation, stinging (transient)

Neuromuscular & skeletal: Tremor

Miscellaneous: Diaphoresis

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol, topical [foam]:

Tersi: 2.25% (70 g)

Lotion, topical: 2.5% (120 mL)

Shampoo, topical: 1% (210 mL)

Dandrex: 1% (240 mL)

Head & Shoulders® Intensive Treatment: 1% (420 mL)

Selseb®: 2.25% (180 mL)

Selsun blue® Daily Treatment: 1% (207 mL, 325 mL)

Selsun blue® Medicated Treatment: 1% (120 mL, 207 mL, 325 mL) [contains menthol]

Selsun blue® Moisturizing Treatment: 1% (207 mL, 325 mL) [contains aloe and moisturizers]

Selsun blue® 2-in-1 Treatment: 1% (207 mL, 325 mL) [contains conditioner]

Generic AvailableYes: Excludes foam

Pricing: U.S. (www.drugstore.com)

Lotion (Selenium Sulfide)

2.5% (118): $19.99

Shampoo (Selseb)

2.25% (180): $96.84

Mechanism of ActionMay block the enzymes involved in growth of epithelial tissue

Pharmacodynamics/KineticsAbsorption: Topical: None through intact skin, but can be absorbed through damaged skin

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

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International Brand NamesAbbottselsun (ES); Bioselenium (CR, DO, GT, HN, MY, NI, PA, SV); Sebo-Lenium (CH); Sebosel (IL, TH); Selenix (PT); Selfide (TH); Sellon (HK, TH); Selson (KP); Selsun (AE, AR, AT, AU, BB, BE, BH, BM, BR, BS, BZ, CH, CY, DK, EG, FI, FR, GB, GR, GY, ID, IE, IL, IN, IQ, IR, JM, JO, KW, LB, LU, LY, MY, NL, NO, OM, PK, PL, QA, SA, SE, SR, SY, TT, YE); Selsun Amarillo (CO, PE); Selsun Blue (AE, AU, BH, CN, CY, EG, FI, ID, IL, IQ, IR, JO, KW, LB, LY, NO, OM, QA, SA, SE, SY, YE); Selsun Blue (PL); Selsun R (NL); Selukos (AT, DE, FI, NO, SE)

Selenium

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(se LEE nee um)
U.S. Brand NamesSelenicaps [OTC]; Selenimin [OTC]
Pharmacologic CategoryTrace Element, Parenteral
Use: Labeled IndicationsTrace metal supplement
Dosing: Adults**Nutritional supplement:** I.V. in TPN solutions:

Metabolically stable: 20-40 mcg/day

Deficiency from prolonged TPN support: 100 mcg/day for 24 and 31 days

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Nutritional supplement:** I.V. in TPN solutions: Children: 3 mcg/kg/day
ContraindicationsHypersensitivity to selenium or any component of the formulation
Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined.

Central nervous system: Lethargy

Dermatologic: Alopecia or hair discoloration

Gastrointestinal: Vomiting following long-term use on damaged skin; abdominal pain, garlic breath

Local: Irritation

Neuromuscular & skeletal: Tremor

Miscellaneous: Diaphoresis

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 200 mcg

Selenicaps: 200 mcg [sugar, gluten free]

Injection, solution: 40 mcg/mL (10 mL)

Tablet: 50 mcg, 100 mcg, 200 mcg

Selenimin: 50 mcg, 125 mcg, 200 mcg

Tablet, timed release: 200 mcg

Generic AvailableYes
Mechanism of ActionPart of glutathione peroxidase which protects cell components from oxidative damage due to peroxidases produced in cellular metabolism
Pharmacodynamics/KineticsExcretion: Urine, feces, lungs, skin
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesCerosel (PL); Selenium Microsol (FR)

Senna

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Perdiem® may be confused with Pyridium®

Senexon® may be confused with Cenestin®

Senokot® may be confused with Depakote®

Pronunciation(SEN na)

U.S. Brand NamesBlack-Draught Tablets [OTC]; Evac-U-Gen [OTC]; ex-lax® Maximum Strength [OTC]; ex-lax® [OTC]; Fletcher's® [OTC]; Little Tummys® Laxative [OTC]; Perdiem® Overnight Relief [OTC]; Senexon [OTC]; Senna-Gen® [OTC]; SenokotXTRA® [OTC]; Senokot® [OTC]; SenoSol™ [OTC] [DSC]; SenoSol™-X [OTC] [DSC]; Uni-Cenna [OTC] [DSC]

Pharmacologic CategoryLaxative, Stimulant

Use: Labeled IndicationsShort-term treatment of constipation; evacuate the colon for bowel or rectal examinations

Dosing: Adults

Bowel evacuation: Oral: OTC labeling: Usual dose: Sennosides 130 mg (X-Prep® 75 mL) between 2-4 PM the afternoon of the day prior to procedure

Constipation: Oral: OTC ranges: Sennosides 15 mg once daily (maximum: 70-100 mg/day, divided twice daily)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Bowel evacuation: OTC labeling: Children ≥12 years: Refer to adult dosing.

Constipation: OTC ranges: Children:

2-6 years:

Sennosides: Initial: 3.75 mg once daily (maximum: 15 mg/day, divided twice daily)

Senna concentrate: 33.3 mg/mL: 5-10 mL up to twice daily

6-12 years:

Sennosides: Initial: 8.6 mg once daily (maximum: 50 mg/day, divided twice daily)

Senna concentrate: 33.3 mg/mL: 10-30 mL up to twice daily

≥12 years: Refer to adult dosing.

Administration: OralOnce daily doses should be taken at bedtime. Granules may be eaten plain, sprinkled on food, or mixed in liquids

Dietary ConsiderationsLiquid may be administered with fruit juice or milk to mask taste. X-Prep® liquid contains sugar 50 g/75 mL.

ContraindicationsPer Commission E: Intestinal obstruction, acute intestinal inflammation (eg, Crohn's disease), colitis ulcerosa, appendicitis, abdominal pain of unknown origin; pregnancy

Allergy Considerations

- Anthraquinone Allergy

Warnings/Precautions

Other warnings/precautions:

- Self-medication (OTC use): Not recommended for use in patients experiencing stomach pain, nausea, vomiting, or a sudden change in bowel movements which lasts >2 weeks. Not recommended for OTC use in children <2 years of age.

Geriatric ConsiderationsElderly are often predisposed to constipation due to disease, immobility, drugs, and a decreased “thirst reflex” with age enhancing the possibility of dehydration. Avoid stimulant cathartic use on a chronic basis if possible. Use osmotic, lubricant, stool softeners, and bulk agents as prophylaxis. Patients should be instructed for proper dietary fiber and fluid intake as well as regular exercise. Monitor closely for fluid/electrolyte imbalance, CNS signs of fluid/electrolyte loss, and hypotension.

Adverse ReactionsFrequency not defined: Gastrointestinal: Nausea, vomiting, diarrhea, abdominal cramps

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringDetermine cause of constipation before treating. Teach patient proper use, side effects/interventions, and symptoms to report.

Patient EducationTake exactly as directed. DO NOT exceed recommended dosage; may cause dependence with prolonged or excessive use. Your urine may be discolored (red-brown) this is normal. Stop use and contact prescriber if you develop nausea, vomiting, persistent diarrhea, or abdominal cramps. If constipation worsens or you experience no relief contact prescriber. **Note:** Increased fluids, fruits, fiber, and exercise may help relieve constipation. OTC labeling does not recommend for use longer than 1 week in children <2 years of age or in women who are pregnant or nursing.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Liquid:

Senexon: Sennosides 8.8 mg/5 mL (240 mL) [contains propylene glycol]

Liquid [concentrate]:

Fletcher's®: Senna concentrate 33.3 mg/mL (75 mL) [alcohol free; contains sodium benzoate; root beer flavor]

Liquid [concentrate; drops]:

Little Tummys® Laxative: Sennosides 8.8 mg/1 mL (30 mL) [alcohol free, dye free; contains propylene glycol and soya lecithin; chocolate flavor]

Syrup: Sennosides 8.8 mg/5 mL (240 mL)

Tablet: Sennosides 8.6 mg

ex-lax®: Sennosides USP 15 mg

ex-lax® Maximum Strength: Sennosides USP 25 mg

Perdiem® Overnight Relief: Sennosides USP 15 mg

Senokot®, Senexon®, Senna-Gen®, SenoSol™ [DSC], Uni-Cenna [DSC]: Sennosides 8.6 mg

SenokotXTRA®, SenoSol™-X [DSC]: Sennosides 17 mg

Tablet, chewable:

Black-Draught™: Sennosides 10 mg

ex-lax®: Sennosides USP 15 mg [chocolate flavor]

Evac-U-Gen: Sennosides 10 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Senna-Gen)

8.6 mg (100): $11.99

Pharmacotherapy PearlsSome products that may have previously been labeled as standardized senna concentrate are now labeled as sennosides. For example, Senokot® tablets, previously labeled as standardized senna concentrate 187 mg, are now labeled as sennosides 8.6 mg. The actual content of senna in this product did not change. Individual product labeling should be consulted prior to dosing.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesAgiolax (MX); Bekunis (GR); Bekunis Krauter (DE); Bekunis Senna (AU); Sennalax (ZA); Senokot (GB, HK, IE, PH, SG)

Sermorelin Acetate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(ser moe REL in AS e tate)
U.S. Brand NamesGeref® Diagnostic [DSC]
Pharmacologic CategoryDiagnostic Agent
Use: Labeled Indications Geref® Diagnostic: For evaluation of the ability of the pituitary gland to secrete growth hormone (GH)
Dosing: Adults**Diagnostic aid:** I.V.: 1 mcg/kg as a single dose in the morning following an overnight fast
Dosing: ElderlyResponse to diagnostic test may be decreased in patients >40 years.
Dosing: Pediatric

Diagnostic: Children: Refer to adult dosing.

Administration: I.V.Diagnostic: Venous blood samples for growth hormone determinations should be drawn 15 minutes before and immediately prior to sermorelin administration. Administer a bolus of 1 mcg/kg/body weight sermorelin I.V. over 1-3 minutes at a final concentration not to exceed 100 mcg/mL followed by a 3 mL normal saline flush. Draw venous blood samples for growth hormone determinations at 15, 30, 45, and 60 minutes after sermorelin administration.
StorageLyophilized preparation must be stored in the refrigerator. Use immediately after reconstitution.
ReconstitutionEach ampul should be reconstituted with a minimum of 0.5 mL of the accompanying sterile diluent.
ContraindicationsHypersensitivity to sermorelin acetate, mannitol, or any component of the formulation
Allergy Considerations

- GH-RH Analog Allergy

Warnings/Precautions

Disease-related concerns:

- Acromegaly: Not used for the diagnosis of acromegaly.

Other warnings/precautions:

- Appropriate use: Thyroid status should be evaluated prior to treatment.

Pregnancy Risk FactorC
Pregnancy ConsiderationsSermorelin has been shown to produce minor variations in fetuses of rats and rabbits. There are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Cardiovascular: Tightness in the chest

Central nervous system: Headache, dizziness, hyperactivity, somnolence

Dermatologic: Transient flushing of the face, urticaria

Gastrointestinal: Dysphagia, nausea, vomiting

Local: Pain, redness, and/or swelling at the injection site

Drug InteractionsThere are no known significant interactions.
Test InteractionsSee Drug Interactions
Reference RangePeak growth hormone levels of >7-10 mcg/L are rarely achieved upon provocation in patients with classic growth hormone deficiency; a marked growth hormone response in these patients (>10-12 mcg/L) is strongly suggestive of hypothalamic dysfunction, as opposed to pituitary dysfunction
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution, as acetate: 50 mcg [packaged with diluent] [DSC]

Generic AvailableNo
ManufacturerSerono
Pharmacodynamics/KineticsOnset of action: Peak response: Diagnostic: Children 30 ± 27 minutes; Adults: 35 ± 29 minutes
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dysphagia.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness, sedation, or hyperactivity
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesGeref (AT, BG, CH, DE, DK, ES, FI, GB, GR, IE, IT, MY, NO, PT, SE); Gerel (FR)

Sertaconazole

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(ser ta KOE na zole)
U.S. Brand NamesErtaczo®
Pharmacologic CategoryAntifungal Agent, Topical
Use: Labeled IndicationsTopical treatment of tinea pedis (athlete's foot)
Dosing: Adults**Tinea pedis:** Topical: Apply between toes and to surrounding healthy skin twice daily for 4 weeks
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Tinea pedis:** Topical: Children ≥12 years: Refer to adult dosing.
Administration: TopicalFor external use only. Apply to affected area between toes and to surrounding healthy skin. Make sure skin is dry before applying. Avoid use of occlusive dressing. Avoid contact with eyes, nose, mouth, and other mucous membranes.
StorageStore at 25°C (77°F).
ContraindicationsHypersensitivity to sertaconazole, other imidazoles (manufacturer-based contraindication), or any component of the formulation
Allergy Considerations

- Azole Antifungal Allergy

Warnings/Precautions

Concerns related to adverse effects:

• Irritation: Discontinue drug if sensitivity or irritation occurs.

Special populations:

• Immunocompromised patients: Has not been studied in immunocompromised patients.

• Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

• Appropriate use: For topical use only; avoid contact with eyes or vagina.

Pregnancy Risk FactorC
Pregnancy ConsiderationsThere are no adequate or well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

1% to 10%: Dermatologic: Burning, contact dermatitis, dry skin, tenderness

Postmarketing and/or case reports: Desquamation, erythema, hyperpigmentation, pruritus, vesiculation

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersReassess diagnosis if no clinical improvement after 2 weeks.
Nursing: Physical Assessment/MonitoringFor external use only; not for ophthalmic or intravaginal use. Teach patient proper use, appropriate interventions to reduce side effects, and adverse symptoms to report.
Patient EducationThis medication is for topical use only. Avoid contact with eyes, nose, mouth, and other mucous membranes. Use exactly as directed. Wash feet and dry thoroughly. Apply to affected area between toes and to surrounding healthy skin. Avoid use of occlusive dressing. Wash hands thoroughly after application; infection can be spread to other parts of your body or to other persons. Wear socks that keep your feet dry, and change them frequently if you perspire heavily. Do not share foot wear with others. May cause dry skin, mild tenderness, or slight discomfort (burning) after application. Stop using and contact prescriber if burning or tenderness persists or if other adverse skin reactions occur. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical, as nitrate:

Ertaczo®: 2% (30 g, 60 g)

Generic AvailableNo
ManufacturerDPT Laboratories
Pricing: U.S. (www.drugstore.com)

Cream (Ertaczo)

2% (30): $72.99

Mechanism of ActionAlters fungal cell wall membrane permeability; inhibits the CYP450-dependent synthesis of ergosterol

Pharmacodynamics/Kinetics

Absorption: Topical: Minimal

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsSertaconazole Nitrate

International Brand NamesDermofix (BE, ES, ID, KP, PT); Gyno-Zalain (PE); Monazol (FR); Zalain (AR, BO, BR, CN, CO, CR, CZ, DE, DO, EC, GT, HK, HN, MX, NI, PA, PE, PH, PL, PR, PY, SV, TH, TW, UY, VE)

Sertraline

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Sertraline may be confused with selegiline, Serentil®, Serevent®

Zoloft® may be confused with Zocor®

Pronunciation(SER tra leen)

U.S. Brand NamesZoloft®

Canadian Brand NamesApo-Sertraline®; CO Sertraline; Dom-Sertraline; Gen-Sertraline; GMD-Sertraline; Novo-Sertraline; Nu-Sertraline; PHL-Sertraline; PMS-Sertraline; ratio-Sertraline; Rhoxal-sertraline; Riva-Sertraline; Sandoz-Sertraline; Zoloft®

Pharmacologic CategoryAntidepressant, Selective Serotonin Reuptake Inhibitor

Use: Labeled IndicationsTreatment of major depression; obsessive-compulsive disorder (OCD); panic disorder; post-traumatic stress disorder (PTSD); premenstrual dysphoric disorder (PMDD); social anxiety disorder

Use: Unlabeled/InvestigationalEating disorders; generalized anxiety disorder (GAD); impulse control disorders; treatment of mild dementia-associated agitation in nonpsychotic patients

Dosing: Adults

Depression/obsessive-compulsive disorder: Oral: Initial: 50 mg/day

Note: May increase daily dose, at intervals of not less than 1 week, to a maximum of 200 mg/day. If somnolence is noted, give at bedtime.

Panic disorder, post-traumatic stress disorder, social anxiety disorder: Oral: Initial: 25 mg once daily; increased after 1 week to 50 mg once daily (see “Note” above)

Premenstrual dysphoric disorder: 50 mg/day either daily throughout menstrual cycle **or** limited to the luteal phase of menstrual cycle, depending on physician assessment. Patients not responding to 50 mg/day may benefit from dose increases (50 mg increments per menstrual cycle) up to 150 mg/day when dosing throughout menstrual cycle **or** up to 100 mg day when dosing during luteal phase only. If a 100 mg/day dose has been established with luteal phase dosing, a 50 mg/day titration step for 3 days should be utilized at the beginning of each luteal phase dosing period.

Dosing: ElderlyOral: Initial: 25 mg/day in the morning; increase by 25 mg/day increments every 2-3 days if tolerated to 50-100 mg/day; additional increases may be necessary; maximum: 200 mg/day. **Note:** Patients with Alzheimer’s dementia-related depression may require a lower starting dosage of 12.5 mg/day, with titration intervals of 1-2 weeks, up to 150-200 mg/day maximum.

Dosing: Pediatric

Obsessive-compulsive disorder: Oral: Children:

6-12 years: Initial: 25 mg once daily

13-17 years: Initial: 50 mg once daily

May increase daily dose, at intervals of not less than 1 week, to a maximum: 200 mg/day. If somnolence is noted, give at bedtime.

Dosing: Renal ImpairmentMultiple-dose pharmacokinetics are unaffected by renal impairment.

Hemodialysis effect: Not removed by hemodialysis

Dosing: Hepatic ImpairmentSertraline is extensively metabolized by the liver. Caution should be used in patients with hepatic impairment. A lower dose or less frequent dosing should be used.

Administration: OralOral concentrate: Must be diluted before use. Immediately before administration, use the dropper provided to measure the required amount of concentrate; mix with 4 ounces ($^{1}/_{2}$ cup) of water, ginger ale, lemon/lime soda, lemonade, or orange juice **only**. Do not mix with any other liquids than these. The dose should be taken immediately after mixing; do not mix in advance. A slight haze may appear after mixing; this is normal. **Note:** Use with caution in patients with latex sensitivity; dropper dispenser contains dry natural rubber.

StorageTablets and oral solution should be stored at controlled room temperature of 15°C to 30°C (59°F to 86°F).

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to sertraline or any component of the formulation; use of MAO inhibitors within 14 days; concurrent use of pimozide; concurrent use of sertraline oral concentrate with disulfiram

Allergy Considerations

- Selective Serotonin Reuptake Inhibitor (SSRI) Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Sertraline is not FDA approved for use in children with major depressive disorder (MDD). However, it is approved for the treatment of obsessive-compulsive disorder (OCD) in children ≥6 years of age.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Sertraline is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: Relatively devoid of these side effects

- Bleeding risk: May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin, NSAIDs, warfarin or other anticoagulants. Bleeding related to SSRI use has been reported to range from relatively minor bruising and epistaxis to life-threatening hemorrhage.

- CNS depression: Has a low potential to impair cognitive or motor performance; caution operating hazardous machinery or driving.

- Sexual dysfunction: May cause or exacerbate sexual dysfunction.

- SIADH and hyponatremia: SSRIs and SNRIs have been associated with the development of SIADH; hyponatremia has been reported rarely (including severe cases with serum sodium <110 mmol/L), predominately in the elderly. Volume depletion and/or concurrent use of diuretics likely increases risk.

- Weight loss: May cause weight loss; use caution in patients where weight loss is undesirable.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; clearance is decreased and plasma concentrations are increased; a lower dosage may be needed.

- Other concurrent illness: Use caution in patients with certain concomitant systemic illness; due to limited experience.

- Renal impairment: Use with caution in patients with renal impairment; clearance is decreased and plasma concentrations are increased; a lower dosage may be needed.

- Seizure disorder: Use with caution in patients with a previous seizure disorder or condition predisposing to seizures such as brain damage or alcoholism.

- Uric acid nephropathy: Use with caution in patients at risk of uric acid nephropathy; sertraline acts as a mild uricosuric.

Concurrent drug therapy issues:

- Agents which lower seizure threshold: Concurrent therapy with other drugs which lower the seizure threshold.

- Anticoagulants/Antiplatelets: Use caution with concomitant use of NSAIDs, ASA, or other drugs that affect coagulation; the risk of bleeding may be potentiated.

- CNS depressants: Use caution with concomitant therapy.

- MAO inhibitors: Potential for severe reaction when used with MAO inhibitors; autonomic instability, coma, death, delirium, diaphoresis, hyperthermia, mental status changes/agitation, muscular rigidity, myoclonus, neuroleptic malignant syndrome features, and seizures may occur. Concomitant use is contraindicated.

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce sertraline's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

Special populations:

- Elderly: Use caution in elderly patients; risk of hyponatremia and other adverse events may be increased.
- Pediatrics: Monitor growth in pediatric patients.

Dosage form specific issues:

- Latex sensitivity: Use oral concentrate formulation with caution in patients with latex sensitivity; dropper dispenser contains dry, natural rubber.

Other warnings/precautions:

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.
- Withdrawal syndrome: May cause dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Upon discontinuation of sertraline therapy, gradually taper dose. If intolerable symptoms occur following a decrease in dosage or upon discontinuation of therapy, then resuming the previous dose with a more gradual taper should be considered.

Geriatric ConsiderationsSertraline's favorable side effect profile makes it a useful alternative to the traditional tricyclic antidepressants; its potential stimulation effect and anorexia may be bothersome. Has the shortest half-life of the currently marketed serotonin-reuptake inhibitors. Data from a clinical trial comparing fluoxetine to tricyclics suggest that fluoxetine is significantly less effective than nortriptyline in hospitalized elderly patients with unipolar major affective disorder, especially those with melancholia and concurrent cardiovascular diseases. The elderly are more prone to SSRI/SNRI-induced hyponatremia.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDue to adverse effects observed in animal studies, sertraline is classified as pregnancy category C. Sertraline crosses the human placenta. Nonteratogenic effects in the newborn following SSRI exposure late in the third trimester include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypo- or hypertonia, hyper-reflexia, jitteriness, irritability, constant crying, and tremor. An increased risk of low birth weight, lower APGAR scores, and blunted behavioral response to pain for a prolonged period after delivery has also been reported. Exposure to SSRIs after the twentieth week of gestation has been associated with persistent pulmonary hypertension of the newborn (PPHN). Adverse effects may be due to toxic effects of the SSRI or drug discontinuation. The long-term effects of *in utero* SSRI exposure on infant development and behavior are not known.

Due to pregnancy-induced physiologic changes, women who are pregnant may require increased doses of sertraline to achieve euthymia. Women treated for major depression and who are euthymic prior to pregnancy are more likely to experience a relapse when medication is discontinued as compared to pregnant women who continue taking antidepressant medications. The ACOG recommends that therapy with SSRIs or SNRIs during pregnancy be individualized; treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary healthcare provider, and pediatrician (ACOG, 2007). If treatment during pregnancy is required, consider tapering therapy during the third trimester in order to prevent withdrawal symptoms in the infant. If this is done and the woman is considered to be at risk from her major depressive disorder, the medication can be restarted following delivery, although the dose should be readjusted to that required before pregnancy.

LactationEnters breast milk/use caution (AAP rates “of concern”)

Breast-Feeding ConsiderationsSertraline and desmethylsertraline are excreted in breast milk. Infants exposed to sertraline while breast-feeding generally receive a low relative dose and serum concentrations are not detectable in most infants. Adverse reactions have not been reported in nursing infants. Sertraline concentrations in the hindmilk are higher than in foremilk. If the benefits of the mother receiving the sertraline and breast-feeding outweigh the risks, the mother may consider pumping and discarding breast milk with the feeding 7-9 hours after the daily dose to decrease sertraline exposure to the infant. The long-term effects on development and behavior have not been studied. The manufacturer recommends that caution be exercised when administering sertraline to nursing women. The AAP recommends sertraline be considered “a drug for which the effect on nursing infants is unknown but may be of concern."

Adverse Reactions

>10%:

Central nervous system: Dizziness, fatigue, headache, insomnia, somnolence

Endocrine & metabolic: Libido decreased

Gastrointestinal: Anorexia, diarrhea, nausea, xerostomia

Genitourinary: Ejaculatory disturbances

Neuromuscular & skeletal: Tremors

Miscellaneous: Diaphoresis

1% to 10%:

Cardiovascular: Chest pain, palpitation

Central nervous system: Agitation, anxiety, hypoesthesia, malaise, nervousness, pain

Dermatologic: Rash

Endocrine & metabolic: Impotence

Gastrointestinal: Appetite increased, constipation, dyspepsia, flatulence, vomiting, weight gain

Neuromuscular & skeletal: Back pain, hypertonia, myalgia, paresthesia, weakness

Ocular: Visual difficulty, abnormal vision

Otic: Tinnitus

Respiratory: Rhinitis

Miscellaneous: Yawning

<1% (Limited to important or life-threatening), postmarketing, and/or case reports: Abdominal pain, acute renal failure, agranulocytosis, allergic reaction, anaphylactoid reaction, angioedema, aplastic anemia, atrial arrhythmia, AV block, bilirubin increased, blindness, bradycardia, cataract, dystonia, extrapyramidal symptoms, galactorrhea, gum hyperplasia, gynecomastia, hallucinations, hepatic failure, hepatitis, hepatomegaly, hyperglycemia, hyperprolactinemia, hypothyroidism, jaundice, leukopenia, lupus-like syndrome, micturition disorders, neuroleptic malignant syndrome, oculogyric crisis, serotonin syndrome, SIADH, Stevens-Johnson syndrome (and other severe dermatologic reactions), optic neuritis, pancreatitis (rare), photosensitivity, priapism, psychosis, PT/INR increased, pulmonary hypertension, QT_c prolongation, serum sickness, thrombocytopenia, torsade de pointes, transaminases increased, vasculitis, ventricular tachycardia

Additional adverse reactions reported in pediatric patients (frequency >2%): Aggressiveness, epistaxis, hyperkinesia, purpura, sinusitis, urinary incontinence

Metabolism/Transport Effects **Substrate** of CYP2B6 (minor), 2C9 (minor), 2C19 (major), 2D6 (major), 3A4 (minor); **Inhibits** CYP1A2 (weak), 2B6 (moderate), 2C8 (weak), 2C9 (weak), 2C19 (moderate), 2D6 (moderate), 3A4 (moderate)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha-/Beta-Blockers: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Alpha-/Beta-Blockers. *Risk C: Monitor therapy*

Analgesics (Opioid): May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Serotonin Reuptake Inhibitor/Antagonist): Selective Serotonin Reuptake Inhibitors may enhance the serotonergic effect of Antidepressants (Serotonin Reuptake Inhibitor/Antagonist). This may cause serotonin syndrome. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Aspirin: Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Beta-Blockers: Selective Serotonin Reuptake Inhibitors may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Acebutolol; Atenolol; Carteolol; Esmolol; Levobunolol; Metipranolol; Nadolol; Penbutolol. *Risk C: Monitor therapy*

BusPIRone: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. Selective Serotonin Reuptake Inhibitors may decrease the metabolism of BusPIRone. *Risk C: Monitor therapy*

CarBAMazepine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of CarBAMazepine. Specifically those SSRIs that inhibit CYP3A4 isoenzymes. CarBAMazepine may increase the metabolism of Selective Serotonin Reuptake Inhibitors. Specifically those agents metabolized via CYP1A2, 2C, and/or 3A4 isoenzymes. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Selective Serotonin Reuptake Inhibitors. *Risk D: Consider therapy modification*

Clozapine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inhibitors (Moderate) may decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Cyproheptadine: May diminish the therapeutic effect of Selective Serotonin Reuptake Inhibitors. *Risk C: Monitor therapy*

Darunavir: May decrease the serum concentration of Sertraline. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Desmopressin: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dextromethorphan: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Dextromethorphan. *Risk D: Consider therapy modification*

Disulfiram: May enhance the adverse/toxic effect of Sertraline. This is specifically related to sertraline oral concentrate due to its alcohol content (12%). Management: Sertraline Oral Concentrate contains 12% alcohol, and its use should be avoided with disulfiram. *Risk X: Avoid* *combination*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Efavirenz: May decrease the serum concentration of Sertraline. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Galantamine: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Galantamine. *Risk C: Monitor therapy*

Haloperidol: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Haloperidol. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Iobenguane I 123: Selective Serotonin Reuptake Inhibitors may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Selective Serotonin Reuptake Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Methadone. Fluvoxamine appears to be the only interacting SSRI. *Risk D: Consider therapy modification*

Metoclopramide: May enhance the adverse/toxic effect of Sertraline. Specifically, the risk of serotonin syndrome may be increased. *Risk C: Monitor therapy*

NSAID (COX-2 Inhibitor): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk D: Consider therapy modification*

NSAID (Nonselective): Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Phenytoin: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Selective Serotonin Reuptake Inhibitors may enhance the adverse/toxic effect of Pimozide. *Risk X: Avoid combination*

Propafenone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Propafenone. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Risperidone: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Risperidone. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

TraMADol: Selective Serotonin Reuptake Inhibitors may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. TraMADol may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Selective Serotonin Reuptake Inhibitors may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tryptophan: May enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Selective Serotonin Reuptake Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Sertraline average peak serum levels may be increased if taken with food.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersMonitor nutritional intake and weight; mental status for depression, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased), anxiety, social functioning, mania, panic attacks; akathisia; growth in pediatric patients

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess mental status for worsening of depression, suicidal ideation, anxiety, social functioning, mania, or panic attack (especially during initiation of therapy and when dosage is changed). Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. Pediatric patients: Monitor growth pattern.

Patient EducationTake exactly as directed; do not increase dose or frequency; or discontinue use abruptly. It may take 2-3 weeks to achieve desired results. Take in the morning to reduce the incidence of insomnia. Avoid alcohol, caffeine, and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or lightheadedness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, anorexia, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); postural hypotension (use caution when climbing stairs or changing position from sitting or lying to standing); urinary pattern changes (void before taking medication); or male sexual dysfunction (reversible). Report persistent insomnia or daytime sedation, agitation, nervousness, fatigue; muscle cramping, tremors, weakness, or change in gait; chest pain, palpitations, or swelling of extremities; vision changes or eye pain; hearing changes (ringing in ears); respiratory difficulty or breathlessness; skin rash or irritation; suicidal ideation; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral [concentrate]: 20 mg/mL (60 mL)

Zoloft®: 20 mg/mL (60 mL) [contains ethanol 12%; natural rubber/natural latex in packaging]

Tablet: 25 mg, 50 mg, 100 mg

Zoloft®: 25 mg, 50 mg, 100 mg

Generic AvailableYes

ManufacturerMerck & Co

Pricing: U.S. (www.drugstore.com)

Concentrate (Zoloft)

20 mg/mL (60): $87.71

Tablets (Sertraline HCl)

25 mg (30): $19.99

50 mg (30): $14.99

100 mg (30): $15.99

Tablets (Zoloft)

25 mg (30): $101.33

50 mg (30): $99.99

100 mg (30): $104.84

Mechanism of ActionAntidepressant with selective inhibitory effects on presynaptic serotonin (5-HT) reuptake and only very weak effects on norepinephrine and dopamine neuronal uptake. *In vitro* studies demonstrate no significant affinity for adrenergic, cholinergic, GABA, dopaminergic, histaminergic, serotonergic, or benzodiazepine receptors.

Pharmacodynamics/Kinetics

Onset of action: Depression: The onset of action is within a week, however, individual response varies greatly and full response may not be seen until 8-12 weeks after initiation of treatment.

Absorption: Slow

Protein binding: 98%

Metabolism: Hepatic; may involve CYP2C19 and CYP2D6; extensive first pass metabolism; forms metabolite N-desmethylsertraline

Bioavailability: Bioavailability of tablets and solution are equivalent

Half-life elimination: Sertraline: 26 hours; N-desmethylsertraline: 66 hours (range: 62-104 hours)

Time to peak, plasma: Sertraline: 4.5-8.4 hours

Excretion: Urine and feces

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Selective Serotonin Reuptake Inhibitors (SSRIs) CYP Profile
- Selective Serotonin Reuptake Inhibitors (SSRIs) FDA-Approved Indications
- Selective Serotonin Reuptake Inhibitors (SSRIs) Pharmacokinetics
- Selective Serotonin Reuptake Inhibitors (SSRIs) Receptor Profile
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsBuspirone (15-60 mg/day) may be useful in treatment of sexual dysfunction during treatment with a selective serotonin reuptake inhibitor. May exacerbate tics in Tourette's syndrome.

Dental Health Professional ConsiderationsProblems with SSRI-induced bruxism have been reported and may preclude their use; clinicians attempting to evaluate any patient with bruxism or involuntary muscle movement, who is simultaneously being treated with an SSRI drug, should be aware of the potential association.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) (see Dental Comment).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAlthough caution should be used in patients taking tricyclic antidepressants, no interactions have been reported with vasoconstrictor and sertraline, a nontricyclic antidepressant which acts to increase serotonin; no precautions appear to be needed

Mental Health: Child/Adolescent ConsiderationsTwenty-nine children (6-12 years of age) and 32 adolescents (13-17 years of age) with major depression, obsessive-compulsive disorder, or both, received 25-200 mg/day (Alderman, 1998). Fifty-three children (6-12 years of age) and 39 adolescents (13-17 years of age) with obsessive-compulsive disorder (OCD) received up to 200 mg/day (March, 1998).

The efficacy of sertraline in the treatment of OCD was demonstrated in a 12-week, multicenter, placebo-controlled study with 187 outpatients 6-17 years of age. The safety of sertraline use in children and adolescents (6-18 years of age) was evaluated in a 12-week, multicenter, placebo-controlled study with 187 outpatients (6-17 years of age), and in a flexible dose, 52-week open extension study of 137 patients (6-18 years of age), who had completed the initial 12-week, double-blind, placebo-controlled study. Sertraline was administered at doses of either 25 mg/day (children 6-12 years of age) or 50 mg/day (adolescents 13-18 years of age). The dose was then titrated in weekly 25 mg/day or 50 mg/day increments, respectively, to a maximum dose of 200 mg/day based upon clinical response. The mean dose for completers was 157 mg/day. In the acute 12-week pediatric study and in the 52 week study, sertraline had an adverse event profile generally similar to that observed in adults (Zoloft® package insert, Pfizer, November, 2001).

A recent report describes 5 children (8-15 years of age) who developed epistaxis (n=4) or bruising (n=1) while receiving sertraline (Lake, 2000). Another recent report describes the SSRI discontinuation syndrome in 6 children; the syndrome was similar to that reported in adults (Diler, 2002).

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Mental Health CommentThe SSRIs as a class are generally considered to be safe and equally effective. Allow sufficient dose-response time (6-12 weeks). Differences lie in approved indications, receptor profiles, pharmacokinetics, and cytochrome P450 activity profile. Subtle differences exist in adverse effect profiles. All SSRIs have the potential to cause sexual dysfunction. Among the SSRIs, sertraline is felt to be associated with the most GI side effects.

Anesthesia and Critical Care Concerns/Other ConsiderationsBuspirone (15-60 mg/day) may be useful in treatment of sexual dysfunction during treatment with a selective serotonin reuptake inhibitor; may exacerbate tics in Tourette's syndrome.

Index TermsSertraline Hydrochloride

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International Brand NamesAleval (MX); Altruline (MX); Aluprex (MX); Antipres (ID); Aremis (ES); Asentra (PL); Atruline (CR, DO, GT, HN, NI, PA, SV); Concorz (AU); Deprax (CN); Deptral (ID); Doxime (PY); Eleva (AU); Emergen (PE); Fatral (ID); Fridep (ID); Gladem (AT, DE); Iglodep (ID); Lesefer (CO); Lustral (GB, IE, IL); Lustraline (TW); Nudep (ID); Prosertin (MX); Seltra (KP); Sercerin (BR); Serdep (HK); Serenada (IL); Serenata (PH); Serlain (BE); Serlife (ZA); Serlift (MY, TH); Sernade (ID); Serolux (MX); Sertex (MX); Sertra (AU); Sertranex (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Setrona (AU); Sosser (CO); Stimuloton (BB, BM, BS, BZ, GY, HK, JM, PL, SR, TT); Traline (KP); Xydep (AU); You-Jet (TW); Zerlin (ID); Zoloft (AE, AR, AU, BB, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CY, CZ, DE, DK, EC, EE, EG, ET, FI, FR, GH, GM, GN, GY, HK, HN, ID, IL, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PE, PH, PK, PL, PT, QA, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Zosert (IN)

Medication Safety Issues

Sound-alike/look-alike issues:

Renagel® may be confused with Reglan®, Regonol®, Renal Caps, Renvela®

Renvela® may be confused with Reglan®, Regonol®, Renagel®, Renal Caps

Sevelamer may be confused with Savella™

International issues:

Renagel® may be confused with Remegel® which is a brand name for calcium carbonate in Ireland, Italy, and Great Britain

Pronunciation(se VEL a mer)

U.S. Brand NamesRenagel®; Renvela®

Canadian Brand NamesRenagel®

Pharmacologic CategoryPhosphate Binder

Use: Labeled IndicationsReduction or control of serum phosphorous in patients with chronic kidney disease on hemodialysis

Dosing: Adults **Note:** The dosing of sevelamer carbonate and sevelamer hydrochloride are expected to be similar, when switching from one product to another, the same dose (on a mg per mg basis) should be utilized.

Control of serum phosphorous: Oral:

Patients not taking a phosphate binder: 800-1600 mg 3 times/day with meals; the initial dose may be based on serum phosphorous levels:

>5.5 mg/dL to <7.5 mg/dL: 800 mg 3 times/day

≥7.5 mg/dL to <9.0 mg/dL: 1200-1600 mg 3 times/day

≥9.0 mg/dL: 1600 mg 3 times/day

Maintenance dose adjustment based on serum phosphorous concentration (goal range of 3.5-5.5 mg/dL; maximum dose studied was equivalent to 13 g/day [sevelamer hydrochloride] or 14 g/day [sevelamer carbonate]):

>5.5 mg/dL: Increase by 1 tablet per meal at 2-week intervals

3.5-5.5 mg/dL: Maintain current dose

<3.5 mg/dL: Decrease by 1 tablet per meal

Dosage adjustment when switching between phosphate binder products: 667 mg of calcium acetate is equivalent to 800 mg sevelamer (carbonate or hydrochloride)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Control of serum phosphorous (unlabeled use):** Oral: Sevelamer hydrochloride: Doses of 121-163 mg/kg/day divided 3 times/day given with meals have been used in small studies. Doses should be rounded to nearest tablet size.

Maintenance dose adjustment based on serum phosphorous concentration (based on age).

Administration: OralMust be administered with meals. Tablets should be swallowed whole; do not crush, chew, or break.

Dietary ConsiderationsTake with meals. Reduced levels of folic acid, and vitamins D, E, and K may occur; most hemodialysis patients in clinical trials received vitamin supplementation.

StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture.

ContraindicationsHypophosphatemia; bowel obstruction

Warnings/Precautions

Disease-related concerns:

- Gastrointestinal disease: Use with caution in patients with gastrointestinal disorders including dysphagia, swallowing disorders, severe gastrointestinal motility disorders (including constipation), or major gastrointestinal surgery.

Concurrent drug therapy issues:

- Gastrointestinal binding: Sevelamer may bind to some drugs in the gastrointestinal tract and decrease their absorption. When changes in absorption of oral medications may have significant clinical consequences (such as antiarrhythmic and antiseizure medications), these medications should be taken at least 1 hour before or 3 hours after a dose of sevelamer.

- Vitamins: May cause reductions in vitamin D, E, K, and folic acid absorption.

Dosage form specific issues:

- Tablets: Should not be taken apart or chewed; broken or crushed tablets will rapidly expand in water/saliva and may be a choking hazard.

Geriatric ConsiderationsNo specific dose changes needed for the elderly. Since electrolyte changes (ie, phosphorus, calcium) can have dramatic effects in the elderly, monitor closely.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal studies have shown reduced or irregular ossification of fetal bones. Because sevelamer may cause a reduction in the absorption of some vitamins, it should be used with caution in pregnant women.
LactationExcretion in breast milk unknown/use caution (not absorbed systemically but may alter maternal nutrition)
Breast-Feeding ConsiderationsIt is not known whether sevelamer is excreted in human milk. Because sevelamer may cause a reduction in the absorption of some vitamins, it should be used with caution in nursing women.
Adverse Reactions**Note:** A decreased incidence of gastrointestinal adverse events was observed in a clinical trial of sevelamer carbonate compared to sevelamer hydrochloride.

>10%:

Dermatologic: Pruritus (13%)

Gastrointestinal: Vomiting (22%), nausea (7% to 20%), diarrhea (4% to 19%), dyspepsia (5% to 16%)

Neuromuscular & skeletal: Limb pain (13%), arthralgia (12%)

Respiratory: Nasopharyngitis (14%), bronchitis (11%)

1% to 10%:

Cardiovascular: Hypertension (10%)

Central nervous system: Headache (9%), pyrexia (5%)

Endocrine & metabolic: Hypercalcemia (5% to 7%)

Gastrointestinal: Abdominal pain (9%), flatulence (4% to 8%), constipation (2% to 8%)

Neuromuscular & skeletal: Back pain (4%)

Respiratory: Dyspnea (10%), cough (7%), upper respiratory tract infection (5%)

Miscellaneous: Peritonitis (peritoneal dialysis: 8%)

Postmarketing and/or case reports: Fecal impaction, ileus (rare), intestinal obstruction (rare), intestinal perforation (rare), rash

Drug Interactions

Mycophenolate: Sevelamer may decrease the serum concentration of Mycophenolate. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Sevelamer may decrease the absorption of Quinolone Antibiotics. *Risk D: Consider therapy modification*

Monitoring ParametersSerum chemistries, including phosphorus, calcium, bicarbonate, chloride
Nursing: Physical Assessment/MonitoringAssess knowledge/teach patient appropriate use, possible side effects/interventions, and adverse symptoms to report. Monitor blood pressure.
Monitoring: Lab TestsSerum chemistries, including phosphorus, calcium, bicarbonate, chloride
Patient EducationTake as directed, with meals. Do not break or chew tablets (contents will expand in water). You may experience headache or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or heartburn (small frequent meals, frequent mouth care, or sucking hard candy may help); diarrhea (yogurt or buttermilk may help); itching; or mild neuromuscular pain or stiffness (mild analgesic may help). Report persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as carbonate:

Renvela®: 800 mg

Tablet, as hydrochloride:

Renagel®: 400 mg, 800 mg

Generic AvailableNo
ManufacturerGenzyme Corp
Pricing: U.S. (www.drugstore.com)

Tablets (Renagel)

400 mg (180): $248.74

800 mg (30): $93.74

Mechanism of ActionSevelamer (a polymeric compound) binds phosphate within the intestinal lumen, limiting absorption and decreasing serum phosphate concentrations without altering calcium, aluminum, or bicarbonate concentrations. Increased serum bicarbonate levels have been observed with the use of sevelamer carbonate, compared to sevelamer hydrochloride.

Pharmacodynamics/Kinetics

Absorption: Not systemically absorbed

Excretion: Feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsSevelamer Carbonate; Sevelamer Hydrochloride

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Storms LE, Chicella MF, and Dice JE, “Sevelamer Therapy for Pediatric End-Stage Renal Disease,” *Pharmacotherapy*, 2006, 26(3):410-13.[PubMed 16503722]

International Brand NamesGenzyme-Renagel (CN); Renagel (AU, BE, CH, CZ, DK, EE, ES, FI, FR, GB, HK, IL, IT, KP, NL, NO, PL, SE, TW, UY); RenaGel (DE)

Sevoflurane

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Ultane® may be confused with Ultram®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(see voe FLOO rane)
U.S. Brand NamesSojourn™; Ultane®
Canadian Brand NamesSevorane® AF
Pharmacologic CategoryGeneral Anesthetic, Inhalation
Use: Labeled IndicationsInduction and maintenance of general anesthesia
Dosing: Adults**Anesthesia:** Inhalation: Minimum alveolar concentration (MAC), the concentration that abolishes movement in response to a noxious stimulus (surgical incision) in 50% of patients, is 2.6% (25 years of age) for sevoflurane. Surgical levels of anesthesia are generally achieved with concentrations from 0.5% to 3%; the concentration at which amnesia and loss of awareness occur is 0.6%.

Minimum alveolar concentrations (MAC) values for surgical levels of anesthesia:

25 years:

Sevoflurane in oxygen: 2.6%

Sevoflurane in 65% N_20/35% oxygen: 1.4%

40 years:

Sevoflurane in oxygen: 2.1%

Sevoflurane in 65% N_20/35% oxygen: 1.1%

60 years:

Sevoflurane in oxygen: 1.7%

Sevoflurane in 65% N_20/35% oxygen: 0.9%

80 years:

Sevoflurane in oxygen: 1.4%

Sevoflurane in 65% N_20/35% oxygen: 0.7%

Dosing: ElderlyRefer to adult dosing. MAC is reduced in the elderly (50% reduction by age 80).
Dosing: Pediatric**Anesthesia:** Inhalation: Minimum alveolar concentration (MAC), the concentration that abolishes movement in response to a noxious stimulus (surgical incision) in 50% of patients, is 2.6% (25 years of age) for sevoflurane. Surgical levels of anesthesia are generally achieved with concentrations from 0.5% to 3%; the concentration at which amnesia and loss of awareness occur is 0.6%.

Minimum alveolar concentrations (MAC) values for surgical levels of anesthesia:

0 to 1 month old full-term neonates: Sevoflurane in oxygen: 3.3%

1 to <6 months: Sevoflurane in oxygen: 3%

6 months to <3 years:

Sevoflurane in oxygen: 2.8%

Sevoflurane in 60% N_20/40% oxygen: 2%

3-12 years: Sevoflurane in oxygen: 2.5%

Dosing: Renal ImpairmentUse with caution in renal insufficiency.
Dosing: Hepatic ImpairmentUse with caution in patients with underlying hepatic conditions.
Administration: InhalationVia sevoflurane-specific calibrated vaporizers; use cautiously in low-flow or closed-circuit systems since sevoflurane is unstable and potentially toxic breakdown products have been liberated.

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsPrevious hypersensitivity to sevoflurane, other halogenated anesthetics, or any component of the formulation; known or suspected susceptibility to malignant hyperthermia

Warnings/Precautions

Concerns related to adverse effects:

- Agitation/delirium: Monitor for emergence agitation or delirium.
- Hepatitis: Postoperative hepatitis or hepatic dysfunction with or without jaundice has rarely been reported.
- Hyperkalemia: Use of other inhaled anesthetics has been associated with rare cases of perioperative hyperkalemia; concomitant use of succinylcholine was associated with many of the reported cases, but not all. Risk of hyperkalemia is increased in pediatric patients with underlying neuromuscular disease (eg, Duchenne muscular dystrophy). Other abnormalities may include elevation in CPK and myoglobinuria. Monitor closely for arrhythmias. Aggressively identify and treat hyperkalemia.
- Increased intracranial pressure: May dilate the cerebral vasculature and may, in certain conditions, increase intracranial pressure.
- Malignant hyperthermia: May trigger malignant hyperthermia; avoid use in patients susceptible to malignant hyperthermia.
- Respiratory depression: Causes dose-dependent respiratory depression and blunted ventilatory response to hypoxia and hypercapnia. Hypoxic pulmonary vasoconstriction is blunted which may lead to increased pulmonary shunt.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; safety with severe impairment has not been established.
- Renal impairment: Use with caution in patients with renal impairment; safety with severe impairment has not been established.
- Seizure disorder: Use with caution in patients at risk for seizures; seizures have been reported in children and young adults.

Other warnings/precautions:

- Desiccated absorbents: Reaction of sevoflurane with CO_2 absorbents that become desiccated within circle breathing equipment can lead to formation of formaldehyde (causing respiratory irritation) and carbon monoxide; maintain fresh absorbent as per manufacturer guidelines regardless of state of colorimetric indicator. An exothermic reaction of sevoflurane with desiccated CO_2 absorbents has been reported to generate extreme heat, smoke and/or fire within breathing circuit. This reaction also leads to formation of a fluorinated byproduct, compound A, which has been reported to cause nephrotoxicity (eg, proteinuria, glycosuria) in animal studies. Compound A-induced renal toxicity is dose- and exposure time-dependent; minimize exposure risk by not exceeding 2 MAC hours and fresh flow rates <2 L/minute (low fresh gas flow rates maximize rebreathing of the anesthetic).

Pregnancy Risk FactorB

Breast-Feeding ConsiderationsConcentrations in breast milk are of no clinical importance 24 hours after anesthesia.

Adverse Reactions

>10%:

Cardiovascular: Hypotension (4% to 11% dose dependent)

Central nervous system: Agitation (7% to 15%)

Gastrointestinal: Nausea (25%), vomiting (18%)

Respiratory: Cough increased (5% to 11%)

1% to 10%:

Cardiovascular: Bradycardia (5%), tachycardia (2% to 6%), hypertension (2%)

Central nervous system: Somnolence (8%), dizziness (4%), hypothermia (1%), headache (1%), fever (1%), emergence delirium

Gastrointestinal: Salivation (2% to 4%)

Respiratory: Laryngospasm (2% to 8%), airway obstruction (8%), breath-holding (2% to 5%), apnea (2%)

Miscellaneous: Shivering (6%)

<1%, postmarketing, and/or case reports: Acidosis, albuminuria, alkaline phosphatase increased, allergic reactions, ALT increased, AST increased, amblyopia, anaphylactic/anaphylactoid reaction, arrhythmia, asthenia, atrial arrhythmia, atrial fibrillation, bigeminy, bilirubinemia, bronchospasm, BUN increased, complete AV block, confusion, conjunctivitis, creatinine increased, creatinine phosphokinase increased, crying, dry mouth, dyspnea, fluorosis, glycosuria, hemorrhage, hepatic dysfunction, hepatic failure, hepatic necrosis, hepatitis, hiccup, hyperglycemia, hyperkalemia (pediatric patients, postoperative), hypertonia, hyper-/hypoventilation, hypophosphatemia, hypoxia, insomnia, inverted T wave, jaundice, leukocytosis, LDH increased, liver enzymes increased, malignant hyperthermia, myoglobinuria, nervousness, oliguria, pain, pharyngitis, pruritus, rash, second-degree AV block, seizure, sputum, ST depression, stridor, supraventricular extrasystoles, syncope, taste perversion, thrombocytopenia, urinary retention, ventricular extrasystoles, wheezing

Metabolism/Transport Effects**Substrate** of CYP2A6 (minor), 2B6 (minor), 2E1 (major), 3A4 (minor)

Drug Interactions

CYP2E1 Inhibitors (Moderate): May decrease the metabolism of CYP2E1 Substrates. *Risk C: Monitor therapy*

CYP2E1 Inhibitors (Strong): May decrease the metabolism of CYP2E1 Substrates. *Risk D: Consider therapy modification*

EPINEPHrine: Inhalational Anesthetics may enhance the arrhythmogenic effect of EPINEPHrine. *Risk D: Consider therapy modification*

Methylphenidate: May enhance the hypertensive effect of Inhalational Anesthetics. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): Inhalational Anesthetics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Monitoring Parameters Blood pressure, temperature, heart rate and rhythm, oxygen saturation, end-tidal CO_2 and end-tidal sevoflurane concentrations should be monitored prior to and throughout anesthesia; temperature of CO_2 absorbent canister

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid for inhalation: 100% (250 mL)

Sojourn™, Ultane®: 100% (250 mL)

Generic Available Yes

Mechanism of Action Inhaled anesthetics alter activity of neuronal ion channels particularly the fast synaptic neurotransmitter receptors (nicotinic acetylcholine, GABA, and glutamate receptors). Limited effects on sympathetic stimulation including cardiovascular system. Seroflurane does not cause respiratory irritation or circulatory stimulation. May depress myocardial contractility, decrease blood pressure through a decrease in systemic vascular resistance and decrease sympathetic nervous activity.

Pharmacodynamics/Kinetics Sevoflurane has a low blood/gas partition coefficient and therefore is associated with a rapid onset of anesthesia and recovery

Onset of action: Time to induction: Within 2 minutes

Duration: Emergence time: Depends on blood concentration when sevoflurane is discontinued. The rate of change of anesthetic concentration in the lung is rapid with sevoflurane because of its low blood gas solubility (0.63). The 90% decrement time (time required for anesthetic concentration in vessel-rich tissues to decrease by 90%) for sevoflurane is short when the duration of anesthesia is <2 hours but increases dramatically as the duration of administration is lengthened.

Metabolism: 3% to 5% hepatic via CYP2E1

Excretion: Exhaled gases

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause agitation, somnolence, or dizziness

Mental Health: Effects on Psychiatric Treatment None reported

Anesthesia and Critical Care Concerns/Other Considerations When sevoflurane is used in conjunction with desiccated CO_2, isolated reports of fire or extreme heat in the respiratory circuit of anesthesia machines have been reported. Steps that might reduce the risk of these events include: Replace CO_2 absorbent if it has not been used for an extended period of time, shut off anesthesia machine at the end of clinical use or after any case when a subsequent extended period of nonuse is expected, turn off all vaporizers when not in use, verify the integrity of new CO_2 absorbents prior to use, monitor the temperature of the CO_2 absorbent canisters, and monitor the correlation between sevoflurane vaporizer setting and the inspired concentration.

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International Brand NamesSevofran (KP); Sevofrane (CL, JP); Sevorane (AR, AT, AU, BG, BO, BR, CH, CN, CO, CR, CZ, DE, DK, DO, EC, EE, ES, FI, FR, GR, GT, HK, HN, HU, ID, IE, IL, IT, KP, LU, MX, MY, NI, NL, NO, PA, PE, PH, PL, PR, PY, SE, SG, SV, TH, UY, VE)

Sibutramine

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Meridia® may be confused with Aredia®

Pronunciation(si BYOO tra meen)
U.S. Brand NamesMeridia®
Canadian Brand NamesMeridia®
Pharmacologic CategoryAnorexiant; Sympathomimetic
Use: Labeled IndicationsManagement of obesity
Dosing: Adults**Obesity:** Oral:

Initial: 10 mg once daily; after 4 weeks may titrate up to 15 mg once daily as needed and tolerated (may be used for up to 2 years, per manufacturer labeling)

Maintenance: 5-15 mg once daily

Dosing: ElderlyUse with caution; adjust dose based on renal or hepatic function.
Dosing: PediatricChildren ≥16 years: Refer to adult dosing.
Dosing: Renal ImpairmentShould not be used in patients with severe renal impairment.
Dosing: Hepatic ImpairmentNo adjustment necessary for mild-to-moderate liver failure. Sibutramine should not be used in patients with severe liver failure.
Calculations

- Body Mass Index

Administration: OralMay take with or without food.
Dietary ConsiderationsSibutramine, as an appetite suppressant, is the most effective when combined with a low calorie diet and behavior modification counseling.
StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).
RestrictionsC-IV

Pharmacotherapy for weight loss is recommended only for obese patients with a body mass index ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of other risk factors such as hypertension, diabetes, and/or dyslipidemia or a high waist circumference; therapy should be used in conjunction with a comprehensive weight management program. Rule out organic causes of obesity (eg, untreated hypothyroidism) prior to use.

ContraindicationsHypersensitivity to sibutramine or any component of the formulation; during or within 2 weeks of MAO inhibitors or concomitant centrally-acting appetite suppressants; anorexia nervosa, bulimia nervosa; poorly-controlled or uncontrolled hypertension, coronary artery disease, CHF arrhythmia; stroke
Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May impair the ability to engage in potentially hazardous activities.
- Hypertension: May cause increase in blood pressure; monitor baseline and on-therapy blood pressure. For patients experiencing a sustained increase in blood pressure dose reduction or discontinuation should be considered. Caution should be used in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases in blood pressure. Should not be used in patients with coronary artery disease, HF, arrhythmia, or stroke.
- Primary pulmonary hypertension (PPH): A rare and frequently fatal pulmonary disease (PPH), has been reported to occur in patients receiving other agents with serotonergic activity which have been used as anorexiants. Although not reported in clinical trials, it is possible that sibutramine may share this potential; patients should be monitored closely.
- Tachycardia: May cause increased heart rate; monitor baseline and on-therapy pulse. For patients experiencing a sustained increase in pulse, dose reduction or discontinuation should be considered. Caution should be used in patients with hypertension and other cardiovascular conditions that might be exacerbated by increases heart rate. Should not be used in patients with coronary artery disease, CHF, arrhythmia. or stroke.
- Valvular heart disease: The use of some anorexigens has been associated with the development of valvular heart disease. Avoid stimulants in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that could increase the risk of sudden death that these conditions alone carry.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with bleeding disorders; rare cases of bleeding have occurred.
- Diabetes: Use with caution in patients with diabetes mellitus; antidiabetic agent requirements may be altered with anorexigens and concomitant dietary restrictions.
- Gallstones: Use with caution in patients with a history of gallstones; weight loss may precipitate or exacerbate gallstone formation.
- Glaucoma: Use with caution in patients with narrow-angle glaucoma; mydriasis has been reported.
- Hepatic impairment: Use with caution in patients with mild-moderate hepatic impairment; avoid use in severe impairment.
- Renal impairment: Use with caution in patients with mild-moderate renal impairment; avoid use in severe impairment.
- Psychiatric disorders: Use with caution and monitor closely in patients with a history of psychiatric symptoms; rare reports of depression, suicide and suicidal ideation have been documented in patients on sibutramine.
- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with use.
- Tourette's syndrome: Use with caution in patients with Tourette's syndrome; stimulants may unmask tics.

Concurrent drug therapy issues:

- Serotonergic agents: As sibutramine blocks neuronal serotonin uptake, there is a potential for development of serotonin syndrome if used with other serotonergic agents; concurrent use of serotonergic agents (eg, SSRIs, sumatriptan, dihydroergotamine, dextromethorphan, meperidine, pentazocine, fentanyl, lithium) should be avoided.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <16 years of age.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies except at doses also causing maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Use in pregnancy is not recommended.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Central nervous system: Headache (30%), insomnia (11%)

Gastrointestinal: Xerostomia (17%), anorexia (13%), constipation (12%)

1% to 10%:

Cardiovascular: Tachycardia (3%), vasodilation (2%), hypertension (2%), palpitation (2%), chest pain (2%)

Central nervous system: Dizziness (7%), nervousness (5%), anxiety (5%), depression (4%), somnolence (2%), CNS stimulation (2%), emotional lability (1%)

Dermatologic: Rash (4%)

Endocrine & metabolic: Dysmenorrhea (4%)

Gastrointestinal: Appetite increased (9%), nausea (6%), abdominal pain (5%), dyspepsia (5%), gastritis (2%), taste perversion (2%)

Genitourinary: Vaginal *Monilia* (1%)

Hepatic: Abnormal LFTs (2%)

Neuromuscular & skeletal: Back pain (8%), weakness (6%), arthralgia (6%), neck pain (2%), myalgia (2%), paresthesia (2%), tenosynovitis (1%), joint disorder (1%)

Otic: Ear disorder (2%)

Respiratory: Pharyngitis (10%), rhinitis (10%), sinusitis (5%), cough (4%)

Miscellaneous: Flu-like syndrome (8%), diaphoresis (3%), allergic reactions (2), thirst (2%)

<1%: Bruising

Frequency not defined:

Cardiovascular: Peripheral edema

Central nervous system: Thinking abnormal, agitation, fever

Dermatologic: Pruritus

Endocrine & metabolic: Menstrual disorders/irregularities

Gastrointestinal: Diarrhea, flatulence, gastroenteritis, tooth disorder

Neuromuscular & skeletal: Arthritis, hypertonia, leg cramps

Ocular: Amblyopia

Respiratory: Bronchitis, dyspnea

Postmarketing and/or case reports (frequency not defined; limited to important or life-threatening): Amnesia, anaphylactic shock, anaphylactoid reaction, anemia, angina, angioedema, arrhythmia, arthrosis, atrial fibrillation, blurred vision, cardiac arrest, cerebrovascular accident, CHF, cholecystitis, cholelithiasis, GI hemorrhage, goiter, hematuria, hyper-/hypoglycemia, hyper-/hypothyroidism, hypersensitivity reaction, impotence, interstitial nephritis, intestinal obstruction, intraocular pressure increased, leukopenia, lymphadenopathy, mania, mouth/stomach ulcer, mydriasis, photosensitivity, seizure, serotonin syndrome, stroke, suicidal ideation, syncope, thrombocytopenia, tongue edema, torsade de pointes, Tourette's syndrome, urinary retention, urticaria, transient ischemic attack, vascular headache, ventricular arrhythmia, vertigo

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ergot Derivatives: Sibutramine may enhance the serotonergic effect of Ergot Derivatives. This may cause serotonin syndrome. *Risk X: Avoid combination*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Serotonin Modulators: Sibutramine may enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid excess ethanol ingestion.

Herb/Nutraceutical: St John's wort and SAMe may decrease sibutramine levels.

Monitoring ParametersWeight, waist circumference, blood pressure, heart rate. Do initial blood pressure and heart rate evaluation and then monitor regularly during therapy. If patient has sustained increases in either blood pressure or pulse rate, consider discontinuing or reducing the dose of the drug.

Reference Range

Adult classification of weight by BMI (kg/m^2):

Underweight: <18.5

Normal: 18.5-24.9

Overweight: 25-29.9

Obese, class I: 30-34.9

Obese, class II: 35-39.9

Extreme obesity (class III): ≥40

Waist circumference: In adults with a BMI of 25-34.9 kg/m^2, high-risk waist circumference is defined as:

Men >102 cm (>40 in)

Women >88 cm (>35 in)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic response and periodically evaluate the need for continued use. Monitor vital signs, weight, and adverse reactions at start of therapy, when changing dosage, and at regular intervals during therapy. Assess knowledge/teach patient appropriate use, possible side effects, and symptoms to report.

Patient EducationTake exactly as directed; do not increase dose or frequency without consulting prescriber. May be taken with meals (do not take at bedtime). Avoid alcohol, caffeine, or OTC medications that act as stimulants. You may experience restlessness, dizziness, sleepiness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); insomnia (taking medication early in morning may help, warm milk, and quiet environment at bedtime may help); increased appetite, nausea or vomiting (small frequent meals, frequent mouth care may help); constipation (increased exercise, fluids, fruit, or fiber may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or altered menstrual periods (reversible when drug is discontinued). Report chest pain, palpitations, or irregular heartbeat; excessive nervousness, excitation, or sleepiness; back pain, muscle weakness, or tremors; CNS changes (acute headache, aggressiveness, restlessness, excitation, sleep disturbances); menstrual pattern changes; rash; blurred vision; runny nose, sinusitis, cough, or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride:

Meridia®: 5 mg, 10 mg, 15 mg

Generic AvailableNo

ManufacturerKnoll Pharmaceutical Company

Pricing: U.S. (www.drugstore.com)

Capsules (Meridia)

5 mg (30): $104.47

10 mg (30): $109.99

15 mg (30): $133.89

Mechanism of ActionSibutramine and its two primary metabolites block the neuronal uptake of norepinephrine, serotonin, and (to a lesser extent) dopamine. There is no monoamine-releasing (or depleting) activity.

Pharmacodynamics/Kinetics

Absorption: 77%; rapid

Protein binding, plasma: Parent drug and metabolites: >94%

Metabolism: Hepatic; undergoes first-pass metabolism via CYP3A4; forms two primary metabolites (M_1 and M_2; active)

Half-life elimination: Sibutramine: 1 hour; Metabolites: M_1: 14 hours; M_2: 16 hours

Time to peak: Sibutramine: 1.2 hours; Metabolites (M_1 and M_2): 3-4 hours

Excretion: Primarily urine (77% as inactive metabolites); feces

Related Information

- Obesity Treatment Guidelines for Adults

Pharmacotherapy PearlsPhysicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (eg, development of tolerance, excessive increases of doses, drug seeking behavior).

Dental Health Professional ConsiderationsThe mechanism of action is thought to be different from the “fen” drugs. Sibutramine works to suppress the appetite by inhibiting the reuptake of norepinephrine and serotonin. Unlike dexfenfluramine and fenfluramine, it is not a serotonin releaser. Sibutramine is closer chemically to the widely used antidepressants such as fluoxetine (Prozac®). The FDA approved sibutramine over the objections of its own advisory panel, who called the drug too risky. FDA reported that the drug causes blood pressure to increase, generally by a small amount, though in some patients the increases were higher. It is now recommended that patients taking sibutramine have their blood pressure evaluated regularly.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and taste perversion (see Dental Comment).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Cardiovascular ConsiderationsSibutramine may induce a significant blood pressure increase and should be avoided in patients with cardiovascular disease. The hypertensive effect of sibutramine may theoretically potentiate the nocturnal hypertension in patients with sleep apnea. Because this drug is used in the management of obesity, it is likely that many of the patients receiving it will have coexisting obstructive sleep apnea.

Unlike dexfenfluramine and fenfluramine, the medication does not cause the release of serotonin from neurons. Tests done on humans show no evidence of valvular heart disease and experiments done on animals show no evidence of the neurotoxicity which was found in similar testing using animals treated with fenfluramine and dexfenfluramine; has minimal potential for abuse.

Index TermsSibutramine Hydrochloride Monohydrate

References

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King DJ and Devaney N, “Clinical Pharmacology of Sibutramine Hydrochloride (BTS 54524), A New Antidepressant, in Healthy Volunteers,” *Br J Clin Pharmacol*, 1988, 26(5):607-11.[PubMed 3207566]

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“U.S. Preventative Services Task Force. Screening for Obesity in Adults: Recommendations and Rationale,” *Ann Intern Med*, 2003, 139(11):933-49[PubMed 14644896]

International Brand NamesAdisar (PE); Atenix (CN); Cetonil (CR, DO, NI, SV); Controlex (DO, GT, HN, NI, SV); Diatramine (KP); Ectiva (MX); Lostil (KP); Maleni (KP); Meridia (CZ, PL); Plenty (BR, CO); Raductil (AR, BB, BM, BS, BZ, CR, DO, GT, GY, HN, JM, MX, NI, NL, PA, SR, SV, TT); Reductil (AE, AT, AU, BE, BG, BH, BR, CH, CL, CO, CY, DE, DK, EE, EG, ES, FI, GB, HK, HN, HU, ID, IE, IL, IQ, IR, IT, JO, KP, KW, LB, LY, MX, MY, NL, NO, OM, PE, PH, PK, PT, PY, QA, SA, SE, SG, SY, UY, VE, YE); Reductmine (KP); Redumin (EC); Reduten (CN); Reslim (KP); Sacietyl (AR); Sibutral (FR); Sibutrex (IN); Zytrim (PH)

Sildenafil

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Revatio® may be confused with ReVia®

Sildenafil may be confused with silodosin, tadalafil, vardenafil

Viagra® may be confused with Allegra®, Vaniqa™

Pronunciation(sil DEN a fil)
U.S. Brand NamesRevatio®; Viagra®
Canadian Brand NamesViagra®
Pharmacologic CategoryPhosphodiesterase-5 Enzyme Inhibitor
Use: Labeled Indications

Revatio®: Treatment of pulmonary arterial hypertension (WHO Group I)

Viagra®: Treatment of erectile dysfunction (ED)

Use: Unlabeled/InvestigationalPulmonary arterial hypertension in children
Dosing: Adults

Erectile dysfunction (Viagra®): Oral: Usual dose: 50 mg once daily 1 hour (range: 30 minutes to 4 hours) before sexual activity; dosing range: 25-100 mg once daily.

Pulmonary arterial hypertension (Revatio®): Oral: 20 mg 3 times/day, taken 4-6 hours apart

Dosage considerations for patients stable on alpha-blockers: Viagra®: Initial: 25 mg

Dosage adjustment for concomitant use of potent CYP34A inhibitors:

Revatio®:

Erythromycin, saquinavir: No dosage adjustment

Itraconazole, ketoconazole, ritonavir: Not recommended

Viagra®:

Erythromycin, itraconazole, ketoconazole, saquinavir: Starting dose of 25 mg should be considered

Ritonavir: Maximum: 25 mg every 48 hours

Dosing: ElderlyElderly >65 years: Use with caution.

Revatio®: Refer to adult dosing.

Viagra®: Starting dose of 25 mg should be considered.

Dosing: Pediatric**Pulmonary arterial hypertension (unlabeled use):** Oral: Children ≥1 month: 0.25-2 mg/kg/dose every 4-6 hours. Most reports used 0.5 mg/kg/dose and titrated up to 2 mg/kg/dose
Dosing: Renal Impairment
Revatio®: Dose adjustment not necessary

Viagra®: Cl_{cr} <30 mL/minute: Starting dose of 25 mg should be considered.

Dosing: Hepatic Impairment

Revatio®: Child-Pugh class A and B: Dose adjustment not necessary.

Viagra®: Child-Pugh class A and B: Starting dose of 25 mg should be considered; not studied in severe impairment (Child-Pugh class C).

Administration: Oral
Revatio®: Administer tablets at least 4-6 hours apart

Viagra®: Administer orally 30 minutes to 4 hours before sexual activity

Storage Store tablets at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Extemporaneously Prepared A stable suspension of sildenafil citrate (2.5 mg/mL) may be prepared as follows: Triturate thirty (30) sildenafil 25 mg tablets (Viagra®) to a fine powder in a mortar and pestle. Create a uniform paste by stirring in a small volume of suspending agent (1:1 mixture of methylcellulose 1% and simple syrup NF or a 1:1 mixture of Ora-Sweet® and Ora-Plus®). Continue adding vehicle to the paste in a geometric manner, with mixing, until near the desired volume. Transfer suspension to a graduated cylinder and QS to 300 mL with vehicle. Final suspension should be transferred to amber plastic bottles, labeled with “shake well” and dated for 90-day expiration at room temperature (25°C) or under refrigeration (4°C).

Nahata MC, Morosco RS, and Brady MT, “Extemporaneous Sildenafil Citrate Oral Suspensions for the Treatment of Pulmonary Hypertension in Children,” *Am J Health-Syst Pharm*, 2006, 63:254-7.

Contraindications Hypersensitivity to sildenafil or any component of the formulation; concurrent use (regularly/intermittently) of organic nitrates in any form (eg, nitroglycerin, isosorbide dinitrate)

Warnings/Precautions

Concerns related to adverse effects:

- Color discrimination: May cause dose-related impairment of color discrimination. Use caution in patients with retinitis pigmentosa; a minority have genetic disorders of retinal phosphodiesterases (no safety information available).

- Hearing loss: Sudden decrease or loss of hearing has been reported rarely; hearing changes may be accompanied by tinnitus and dizziness. A direct relationship between therapy and hearing loss has not been determined.

- Hypotension: Decreases in blood pressure may occur due to vasodilator effects; use with caution in patients with left ventricular outflow obstruction (aortic stenosis or hypertrophic obstructive cardiomyopathy); may be more sensitive to hypotensive actions. Concurrent use with alpha-adrenergic antagonist therapy or substantial alcohol consumption may cause symptomatic hypotension; patients should be hemodynamically stable prior to initiating therapy at the lowest possible dose.

- Vision loss: Vision loss may occur rarely and be a sign of nonarteritic anterior ischemic optic neuropathy (NAION). Risk may be increased with history of vision loss. Other risk factors for NAION include low cup-to-disc ratio (“crowded disc”), coronary artery disease, diabetes, hypertension, hyperlipidemia, smoking, and >50 years of age. Safety and efficacy were not studied in patients with known degenerative retinal disorders (eg, retinitis pigmentosa); use is not recommended. A direct relationship between therapy and vision loss has not been determined.

- Priapism: Painful erection >6 hours in duration; rare. Educate patient to seek medical assistance for erection lasting >4 hours.

Disease-related concerns:

- Anatomical penis deformation: Use with caution in patients with anatomical deformation of the penis (angulation, cavernosal fibrosis, or Peyronie's disease).

- Bleeding disorders: Use with caution in patients with bleeding disorders; safety and efficacy have not been established. *In vitro* studies have suggested a decreased effect on platelet aggregation.

- Cardiovascular disease: Use with caution in patients with hypotension (<90/50 mm Hg); uncontrolled hypertension (>170/110 mm Hg); life-threatening arrhythmias, stroke or MI within the last 6 months; cardiac failure or coronary artery disease causing unstable angina; safety and efficacy have not been studied in these patients. Use caution in patients with left ventricular outflow obstruction (eg, aortic stenosis). There is a degree of cardiac risk associated with sexual activity; therefore, physicians should consider the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction.

- Cardiovascular disease: Use is not recommended in patients with hypotension (<90/50 mm Hg); uncontrolled hypertension (>170/100 mm Hg); unstable angina or angina during intercourse; life-threatening arrhythmias, stroke or MI within the last 6 months; cardiac failure or coronary artery disease causing unstable angina. Safety and efficacy have not been studied in these patients. Use caution in patients with left ventricular outflow obstruction (eg, aortic stenosis). There is a degree of cardiac risk associated with sexual activity; therefore, physicians may wish to consider the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction.

- Conditions predisposing to priapism: Use with caution in patients who have conditions which may predispose them to priapism (sickle cell anemia, multiple myeloma, leukemia). All patients should be instructed to seek immediate medical attention if erection persists >4 hours.

- Hepatic impairment: Use with caution in patients with hepatic impairment; use lowest starting dose (25 mg).

- Peptic ulcer disease: Use with caution in patients with active peptic ulcer disease; safety and efficacy have not been established.

- Renal impairment: Use with caution in patients with renal impairment; dose adjustment may be needed; use lowest starting dose (25 mg) in severe dysfunction (Cl_{cr} <30 mL/minute).

Concurrent drug therapy issues:

- Alpha-blockers: Use with caution in patients taking alpha-blockers; may cause symptomatic hypotension. Safety of this combination may be affected by other antihypertensives and intravascular volume depletion. Patients should be hemodynamically stable prior to initiating therapy. Initiate sildenafil at the lowest recommended dose. Alpha-blockers should be initiated at the lowest recommended dose in patients currently receiving sildenafil.

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors (eg, ritonavir can increase sildenafil levels, initiate sildenafil at decreased dose; see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

- Nitrates: Concomitant (regularly/intermittently) use with all forms of nitrates is contraindicated. If nitrate administration is medically necessary, it is not known when nitrates can be safely administered following the use of sildenafil (per manufacturer); the ACC/AHA 2007 guidelines supports administration of nitrates only if 24 hours have elapsed.

- Other treatments for erectile dysfunction: Safety and efficacy with other treatments for erectile dysfunction have not been established; use is not recommended.

- Pulmonary arterial hypertension: Efficacy with concurrent bosentan therapy has not been evaluated; use with caution.

Special populations:

- Elderly: Use with caution; dose adjustment may be required.

Other warnings/precautions:

- Appropriate use: Potential underlying causes of erectile dysfunction should be evaluated prior to treatment.

Geriatric ConsiderationsSince the elderly often have concomitant diseases, many of which may contraindicate the use of sildenafil, a thorough knowledge of diseases and medications used must be assessed. Adjust dose for renal/hepatic function.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Less than 0.001% appears in the semen.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsBased upon normal doses for either indication. (Adverse effects such as flushing, diarrhea, myalgia, and visual disturbances may be increased with doses >100 mg/24 hours.)

>10%:

Central nervous system: Headache (16% to 46%)

Gastrointestinal: Dyspepsia (7% to 17%; dose related)

2% to 10%:

Cardiovascular: Flushing (10%)

Central nervous system: Insomnia (≤7%), pyrexia (6%), dizziness (2%)

Dermatologic: Erythema (6%), rash (2%)

Gastrointestinal: Diarrhea (3% to 9%), gastritis (≤3%)

Genitourinary: Urinary tract infection (3%)

Hepatic: LFTs increased

Neuromuscular & skeletal: Myalgia (≤7%), paresthesia (≤3%)

Ocular: Abnormal vision (color changes, blurred vision, or increased sensitivity to light 3% to 11%; dose related)

Respiratory: Epistaxis (9% to 13%), dyspnea exacerbated (≤7%), nasal congestion (4%), rhinitis (4%), sinusitis (3%)

<2%, postmarketing, and/or case reports (limited to important or life-threatening): Allergic reaction, amnesia (transient global), anemia, angina pectoris, anorgasmia, asthma, AV block, cardiac arrest, cardiomyopathy, cataract, cerebral thrombosis, cerebrovascular hemorrhage, colitis, cystitis, depression, dysphagia, edema, exfoliative dermatitis, eye hemorrhage, gout, hearing decreased, hearing loss, heart failure, hematuria, hemorrhage, hyper-/hypoglycemia, hypernatremia, hyper-/hypotension, hyperuricemia, intracerebral hemorrhage, intraocular pressure increased, leukopenia, migraine, myocardial ischemia, MI, myasthenia, mydriasis, neuralgia, nonarteritic ischemic optic neuropathy (NAION), palpitation, postural hypotension, priapism, pulmonary hemorrhage, rectal hemorrhage, retinal vascular disease or bleeding, seizure, shock, stomatitis, subarachnoid hemorrhage, syncope, tachycardia, tendon rupture, TIA, urinary incontinence, ventricular arrhythmia, vertigo, visual field loss, vitreous detachment/traction, vomiting

Metabolism/Transport Effects**Substrate** of CYP2C9 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak), 3A4 (weak)

Drug Interactions

Alpha1-Blockers: Phosphodiesterase 5 Inhibitors may enhance the hypotensive effect of Alpha1-Blockers. **Exceptions:** Dapiprazole [Off Market]. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Bosentan: May increase the metabolism of Sildenafil. Sildenafil may increase the serum concentration of Bosentan. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Etravirine: May decrease the serum concentration of Phosphodiesterase 5 Inhibitors. Management: No empiric dosage adjustments are recommended with concomitant therapy; however, dose of the phosphodiesterase inhibitor may need to be altered based on clinical response. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Sildenafil may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Pravastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Macrolide Antibiotics: May decrease the metabolism of Phosphodiesterase 5 Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Phosphodiesterase 5 Inhibitors. Management: Dose restrictions for tadalafil, and/or sildenafil and vardenafil are recommended in combination with ritonavir, atazanavir, indinavir, darunavir and saquinavir. Consult specific prescribing information for detailed recommendations. *Risk D: Consider therapy modification*

Sapropterin: May enhance the hypotensive effect of Phosphodiesterase 5 Inhibitors. *Risk C: Monitor therapy*

Vasodilators (Organic Nitrates): Phosphodiesterase 5 Inhibitors may enhance the vasodilatory effect of Vasodilators (Organic Nitrates). *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Amount and rate of absorption of sildenafil is reduced when taken with a high-fat meal. Serum concentrations/toxicity may be increased with grapefruit juice; avoid concurrent use.

Herb/Nutraceutical: St John's wort may decrease sildenafil levels.

Nursing: Physical Assessment/MonitoringMonitor other medications patient may be taking for effectiveness and interactions. Instruct patient on appropriate use and cautions, possible side effects, and symptoms to report

Patient EducationInform prescriber of all other medications you are taking; serious side effects can result when sildenafil is used with nitrates and some other medications. Avoid grapefruit juice. Do not combine sildenafil with other approaches to treating erectile dysfunction without consulting prescriber. **Note:** Sildenafil provides no protection against sexually-transmitted diseases, including HIV. You may experience headache, flushing, or abnormal vision (color changes, blurred or increased sensitivity to light); use caution when driving at night or in poorly lit environments. Report immediately acute allergic reactions; chest pain or palpitations; persistent dizziness; sign of urinary tract infection; skin rash; respiratory difficulty; change in vision; change in hearing or ringing in the ears; genital swelling; or other adverse reactions. If erection lasts longer than 4 hours, contact prescriber immediately; permanent damage to the penis can occur.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Revatio®: 20 mg

Viagra®: 25 mg, 50 mg, 100 mg

Generic AvailableNo

ManufacturerPfizer U.S. Pharmaceuticals Group

Pricing: U.S. (www.drugstore.com)

Tablets (Revatio)

20 mg (30): $448.07

Tablets (Viagra)

25 mg (10): $133.99

50 mg (10): $133.99

100 mg (10): $133.99

Mechanism of Action

Erectile dysfunction: Does not directly cause penile erections, but affects the response to sexual stimulation. The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE-5), which is responsible for degradation of cGMP in the corpus cavernosum; when sexual stimulation causes local release of NO, inhibition of PDE-5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum; at recommended doses, it has no effect in the absence of sexual stimulation.

Pulmonary arterial hypertension (PAH): Inhibits phosphodiesterase type 5 (PDE-5) in smooth muscle of pulmonary vasculature where PDE-5 is responsible for the degradation of cyclic guanosine monophosphate (cGMP). Increased cGMP concentration results in pulmonary vasculature relaxation; vasodilation in the pulmonary bed and the systemic circulation (to a lesser degree) may occur.

Pharmacodynamics/Kinetics

Onset of action: ~60 minutes

Duration: 2-4 hours

Absorption: Rapid; slower with a high-fat meal

Distribution: V_{dss}: 105 L

Protein binding, plasma: ~96%

Metabolism: Hepatic via CYP3A4 (major) and CYP2C9 (minor route); forms metabolite (active)

Bioavailability: 40%

Half-life elimination: 4 hours

Time to peak: 30-120 minutes; delayed by 60 minutes with a high-fat meal

Excretion: Feces (80%); urine (13%)

Pharmacotherapy PearlsSildenafil is ~10 times more selective for PDE-5 as compared to PDE6. This enzyme is found in the retina and is involved in phototransduction. At higher plasma levels, interference with PDE6 is believed to be the basis for changes in color vision noted in some patients.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentUseful for psychotropic-induced sexual dysfunction

Cardiovascular ConsiderationsSildenafil, when used in conjunction with nitrates, may be associated with severe hypotension, myocardial infarction, and possibly death. While there are no clear significant increased cardiovascular events with PDE-5 inhibitors alone, this drug should be absolutely avoided in conjunction with nitrates and may also induce significant and possibly fatal hypotension in patients with heart failure. Hemodynamic effects of PDE-5 inhibitors alone include a very slight drop in blood pressure without significant changes in heart rate. The most recent guidelines on the use of sildenafil in patients with cardiovascular disease are outlined in detail (Cheitlin, 1999). The general clinical recommendations are as follows.

> Use of sildenafil is contraindicated in patients currently taking nitrate preparations.
>
> Cardiovascular effects of sildenafil may be potentially hazardous in patients with:
>
> - active coronary ischemia (not on nitrates)
> - heart failure and with borderline low blood pressure and borderline low volume status
> - complicated, multidrug antihypertensive regimens
> - potential for drug-drug interactions that may prolong sildenafil half-life (eg, drugs that predominantly inhibit cytochrome P450 3A4 - HMG-CoA reductase inhibitors, calcium channel blockers, ketoconazole, erythromycin etc)

Additional guidelines for the treatment of ED in patients with cardiovascular disease have also been published (Jackson, 2006). These guidelines, referred to as the Princeton II Guidelines, support the use of PDE-5 inhibition only in patients with asymptomatic coronary disease and <3 of the following risk factors: Controlled hypertension, mild stable angina, successful coronary revascularization, previous uncomplicated MI (>6-8 weeks), mild valvular disease, and left ventricular dysfunction (with or without NYHA Class I limitations).

When nitrate administration becomes medically necessary, the ACC/AHA 2004 guidelines on treatment of ST-segment elevation MI and the ACC/AHA 2007 guidelines on treatment of unstable angina/non ST-segment elevation MI supports administration of nitrates only if 24 hours have elapsed after use of sildenafil and 48 hours after use of tadalafil. The appropriate delay for the use of nitrates after vardenafil has not been determined.

Sildenafil is selective for PDE-5 and has limited effect on PDE-3, which controls cardiac contractility.

Anesthesia and Critical Care Concerns/Other Considerations

Use of sildenafil is contraindicated in patients currently taking nitrate preparations.

Cardiovascular effects of sildenafil may be potentially hazardous in patients with:

- active coronary ischemia (not on nitrates)
- congestive heart failure and with low blood pressure and low volume status
- complicated, multidrug antihypertensive regimens
- potential for drug-drug interactions that may prolong sildenafil half-life (eg, drugs that predominantly inhibit CYP3A4, such as HMG-CoA reductase inhibitors, protease inhibitors, certain macrolide antibiotics, imidazole antibiotics)

Index TermsUK92480

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International Brand Names Andros (PH); Aphrodil (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Edegra (IN); Ejertol (CO); Elonza (TH); Erasmo (CR, GT, HN, NI, PA, SV); Erectol (AR); Erilin (CO); Eroxim (CO); Maxigra (PL); Patrex (SE); Penegra (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Revatio (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, NL, NO, NZ, PT, RU, SE, TR); Rigix (PY); Ripol (CN); Sildefil (AR); Supra (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Viagra (AE, AT, AU, BE, BF, BG, BH, BJ, BR, CH, CI, CL, CN, CR, CY, CZ, DE, DK, DO, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, HK, HN, HU, ID, IE, IL, IQ, IR, IT, JO, JP, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PL, PT, QA, RU, SA, SC, SD, SE, SG, SL, SN, SV, SY, TH, TN, TR, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Vimax (ID); Zwagra (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE)

Silodosin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Rapaflo® may be confused with Rapamune®, Raptiva®

Silodosin may be confused with sildenafil

Pronunciation(SI lo doe sin)

U.S. Brand NamesRapaflo®

Pharmacologic CategoryAlpha $_1$ Blocker

Use: Labeled IndicationsTreatment of signs and symptoms of benign prostatic hyperplasia (BPH)

Dosing: Adults**BPH:** Oral: 8 mg once daily with a meal

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} >50 mL/minute: No adjustment needed.

Cl_{cr} 30-50 mL/minute: 4 mg once daily.

Cl_{cr} <30 mL/minute: Use is contraindicated.

Dosing: Hepatic Impairment

Mild-to-moderate impairment (Child-Pugh classes A and B): No adjustment needed.

Severe impairment (Child-Pugh class C): Use is contraindicated.

Administration: OralAdminister once daily with a meal.

Dietary ConsiderationsTake with a meal.

StorageStore at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light. Protect from moisture.

ContraindicationsConcurrent use with strong CYP3A4 inhibitors (eg, clarithromycin, itraconazole, ketoconazole, ritonavir); severe renal impairment (Cl_{cr} <30 mL/minute); severe hepatic impairment (Child-Pugh class C)

Warnings/Precautions

Concerns related to adverse effects:

- Floppy iris syndrome: Intraoperative floppy iris syndrome has been observed in cataract surgery patients who were on or were previously treated with alpha$_1$-blockers; causality has not been established and there appears to be no benefit in discontinuing alpha-blocker therapy prior to surgery.

- Orthostatic hypotension/syncope: May cause significant orthostatic hypotension and syncope, especially with first dose; anticipate a similar effect if therapy is interrupted for a few days, if dosage is rapidly increased, or if another antihypertensive drug (particularly vasodilators) or a PDE-5 inhibitor (eg, sildenafil, tadalafil, vardenafil) is introduced. “First-dose” orthostatic hypotension may occur 4-8 hours after dosing; may be dose related. Patients should be cautioned about performing hazardous tasks when starting new therapy or adjusting dosage upward.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with mild-to-moderate hepatic impairment; contraindicated with severe impairment; not studied.

- Prostate cancer: It is recommended to rule out prostatic carcinoma before beginning therapy.

- Renal impairment: Use with caution in patients with moderate renal impairment; dosage adjustment recommended. Contraindicated in patients with severe impairment (Cl_{cr} <30 mL/minute).

Concurrent drug therapy issues:

- High potential for interactions: Contraindicated in patients on strong CYP3A4 inhibitors.

Special populations:

- Females: Not indicated for use in women.

- Pediatrics: Not indicated for use in children.

Other warnings/precautions:

- Antihypertensive use: Not intended for use as an antihypertensive drug.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; however, silodosin is not approved for use in women.

Adverse Reactions

>10%: Miscellaneous: Retrograde ejaculation (28%)

1% to 10%:

Cardiovascular: Orthostatic hypotension (3%)

Central nervous system: Dizziness (3%), headache (2%), insomnia (1% to 2%)

Gastrointestinal: Diarrhea (3%), abdominal pain (1% to 2%)

Genitourinary: PSA increased (1% to 2%)

Neuromuscular & skeletal: Weakness (1% to 2%)

Respiratory: Nasal congestion (2%), nasopharyngitis (2%), rhinorrhea (1% to 2%), sinusitis (1% to 2%)

<1%, postmarketing, and/or case reports: Hepatic impairment, intraoperative floppy iris syndrome (IFIS), jaundice, priapism, purpura, syncope, toxic skin eruption, transaminases increased

Drug Interactions

Alfuzosin: Alpha1-Blockers may enhance the antihypertensive effect of Alfuzosin. Risk of orthostatic hypotension or syncope may be increased. Alfuzosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Alpha1-Blockers: May enhance the adverse/toxic effect of Silodosin. Of particular concern are the risk of postural hypotension, syncope, and/or hypotension. Silodosin may enhance the hypotensive effect of Alpha1-Blockers. Of particular concern are the risk of postural hypotension, syncope, and/or hypotension. *Risk X: Avoid combination*

Beta-Blockers: May enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Alpha1-Blockers may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Phosphodiesterase 5 Inhibitors: May enhance the hypotensive effect of Alpha1-Blockers. *Risk D: Consider therapy modification*

Tamsulosin: Alpha1-Blockers may enhance the antihypertensive effect of Tamsulosin. Risk of orthostatic hypotension or syncope may be increased. Tamsulosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: AUC decrease by 4% to 49% and C_{max} decreased by ~18% to 43% with moderate calorie/fat meal.

Herb/Nutraceutical: Avoid St. John's wort (may decrease the levels/effects of silodosin). Avoid herbs with hypotensive properties (black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, Shepherd's purse); may enhance the hypotensive effect of silodosin. Avoid saw palmetto (due to limited experience with this combination).

Monitoring ParametersBlood pressure; urinary symptoms

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Rapaflo®: 4 mg, 8 mg

Generic AvailableNo

ManufacturerWatson Laboratories, Inc

Mechanism of ActionSilodosin is a selective antagonist of alpha$_{1A}$-adrenoreceptors in the prostate and bladder. Smooth muscle tone in the prostate is mediated by alpha$_{1A}$-adrenoreceptors; blocking them leads to relaxation of smooth muscle in the bladder neck and prostate causing an improvement of urine flow and decreased symptoms of BPH. Approximately 75% of the alpha1-receptors in the prostate are of the alpha$_{1A}$ subtype.

Pharmacodynamics/Kinetics

Distribution: V_d: 49.5 L

Protein binding: ~97%

Metabolism: Extensive, via CYP3A4, glucuronidation, and alcohol and aldehyde dehydrogenase pathways; KMD-3213G (active *in vitro*) and KMD-3293 (not significant) metabolites formed

Bioavailability: ~32%

Half-life elimination: Healthy volunteers: Silodosin: 5-21 hours; KMD-3213G: ~24 hours

Time to peak, plasma: ~3 hours

Excretion: Feces (55%); urine (34%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Postural hypotension, particularly with initial dosing; dizziness; nasal congestion or rhinitis

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or insomnia

Mental Health: Effects on Psychiatric TreatmentContraindicated with potent CYP3A4 inhibitors (eg, nefazodone). May cause orthostatic hypotension; concomitant use with psychotropics may produce additive effects. Avoid use with St John's wort; levels of silodosin may be decreased.

Index TermsKMD 3213

References

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Silver Nitrate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(SIL ver NYE trate)

Pharmacologic Category[Antibiotic, Topical](); [Cauterizing Agent, Topical](); [Topical Skin Product, Antibacterial]()

Use: Labeled IndicationsCauterization of wounds and sluggish ulcers, removal of granulation tissue and warts; aseptic prophylaxis of burns

Dosing: Adults**Antiseptic:** Topical:

Sticks: Apply to mucous membranes and other moist skin surfaces only on area to be treated 2-3 times/week for 2-3 weeks.

Topical solution: Apply a cotton applicator dipped in solution on the affected area 2-3 times/week for 2-3 weeks.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Antiseptic:** Topical: Refer to adult dosing.

Administration: OtherApplicators are **not** for ophthalmic use.

StorageMust be stored in a dry place. Store in a tight, light-resistant container. Exposure to light causes silver to oxidize and turn brown. Dipping in water causes oxidized film to readily dissolve.

ContraindicationsHypersensitivity to silver nitrate or any component of the formulation; not for use on broken skin, cuts, or wounds

Warnings/Precautions

Concerns related to adverse effects:

- Skin discoloration: Prolonged use may result in skin discoloration.

Other warnings/precautions:

- Appropriate use: Do not use applicator sticks on the eyes.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Dermatologic: Burning and skin irritation, staining of the skin

Endocrine & metabolic: Hyponatremia

Hematologic: Methemoglobinemia

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersWith prolonged use, monitor methemoglobin levels

Nursing: Physical Assessment/MonitoringAssess knowledge/teach appropriate technique for topical application. Monitor for overuse symptoms.

Monitoring: Lab TestsWith prolonged use, monitor methemoglobin levels.

Patient EducationUse as directed; do not use more often than instructed. Store container in dry, dark place. Handle with care; silver nitrate stains skin, clothing and utensils. Discontinue and contact prescriber if treated areas worsen or if redness, or irritation develops in surrounding area. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Sticks: Apply to mucous membranes and other moist skin surfaces to be treated 2-3 times each week for 2-3 weeks. Not for ophthalmic use.

Solution: Apply to affected area with cotton applicator dipped in solution 2-3 times each week for 2-3 weeks.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Applicator sticks, topical: Silver nitrate 75% and potassium nitrate 25% (6”, 12”, 18”)

Solution, topical: 0.5% (960 mL); 10% (30 mL); 25% (30 mL); 50% (30 mL)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Misc (Arzol Silver Nit Applicators)

75-25% (100): $49.27

Mechanism of ActionFree silver ions precipitate bacterial proteins by combining with chloride in tissue forming silver chloride; coagulates cellular protein to form an eschar; silver ions or salts or colloidal silver preparations can inhibit the growth of both gram-positive and gram-negative bacteria. This germicidal action is attributed to the precipitation of bacterial proteins by liberated silver ions. Silver nitrate coagulates cellular protein to form an eschar, and this mode of action is the postulated mechanism for control of benign hematuria, rhinitis, and recurrent pneumothorax.

Pharmacodynamics/Kinetics

Absorption: Because silver ions readily combine with protein, there is minimal GI and cutaneous absorption of the 0.5% and 1% preparations

Excretion: Highest amounts of silver noted on autopsy have been in kidneys, excretion in urine is minimal

Pharmacotherapy PearlsSilver nitrate solutions stain skin and utensils.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAgNO$_3$

References

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U.S. Department of Health and Human Services, “1993 Sexually Transmitted Diseases Treatment Guidelines,” *MMWR Recomm Rep*, 1993, 42(RR-14).

International Brand NamesMova Nitrat Pipette (PL)

Silver Sulfadiazine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(SIL ver sul fa DYE a zeen)

U.S. Brand NamesSilvadene®; SSD®; SSD® AF; Thermazene®

Canadian Brand NamesFlamazine®

Pharmacologic CategoryAntibiotic, Topical

Use: Labeled IndicationsPrevention and treatment of infection in second and third degree burns

Dosing: Adults**Antiseptic, burns:** Topical: Apply once or twice daily

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: TopicalApply with a sterile-gloved hand. Apply to a thickness $^{1}/_{16}$". Burned area should be covered with cream at all times.

StorageDiscard if cream is darkened (reacts with heavy metals resulting in release of silver).

ContraindicationsHypersensitivity to silver sulfadiazine or any component of the formulation; premature infants or neonates <2 months of age (sulfonamides may displace bilirubin and cause kernicterus); pregnancy (approaching or at term)

Allergy Considerations

- Sulfonamide Antibiotic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

- Systemic effects: Systemic absorption may be significant and adverse reactions may occur.

DIsease-related concerns:

- G6PD deficiency: Use with caution in patients with G6PD deficiency; hemolysis may occur.

- Hepatic impairment: Use with caution in patients with hepatic impairment; sulfadiazine may accumulate.

- Renal impairment: Use with caution in patients with renal impairment; sulfadiazine may accumulate.

Concurrent drug therapy issues:

- Analgesics: Use of an analgesic might be needed before application.

Geriatric ConsiderationsNo specific recommendations for use in the elderly.

Pregnancy Risk FactorB

LactationFor external use

Adverse ReactionsFrequency not defined.

Dermatologic: Itching, rash, erythema multiforme, discoloration of skin, photosensitivity

Hematologic: Hemolytic anemia, leukopenia, agranulocytosis, aplastic anemia

Hepatic: Hepatitis

Renal: Interstitial nephritis

Miscellaneous: Allergic reactions may be related to sulfa component

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersSerum electrolytes, urinalysis, renal function tests, CBC in patients with extensive burns on long-term treatment

Nursing: Physical Assessment/MonitoringAssess allergy history before treatment (sulfonamides). Assess results of laboratory tests, therapeutic effectiveness (development of granulation), adverse response (eg, rash, irritation, burning, itching of unburned areas). Monitor for hepatic, renal, or hematological response effects with long-term use or use over large areas.

Monitoring: Lab TestsSerum electrolytes, urinalysis, renal function, CBC in patients with extensive burns on long-term treatment

Patient EducationUsually applied by professional in burn care setting. Patient instruction should be appropriate to extent of burn, patient understanding, etc. Report persistent diarrhea.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical: 1% (25 g, 50 g, 85 g, 400 g)

Silvadene®, Thermazene®: 1% (20 g, 50 g, 85 g, 400 g, 1000 g)

SSD®: 1% (25 g, 50 g, 85 g, 400 g)

SSD® AF: 1% (50 g, 400 g)

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Cream (Silvadene)

1% (20): $23.94

1% (85): $25.05

1% (400): $60.00

Cream (Silver Sulfadiazine)

1% (50): $20.99

1% (85): $19.99

1% (400): $30.00

Mechanism of ActionActs upon the bacterial cell wall and cell membrane. Bactericidal for many gram-negative and gram-positive bacteria and is effective against yeast. Active against *Pseudomonas aeruginosa*, *Pseudomonas maltophilia*, *Enterobacter* species, *Klebsiella* species, *Serratia* species, *Escherichia coli*, *Proteus mirabilis*, *Morganella morganii*, *Providencia rettgeri*, *Proteus vulgaris*, *Providencia* species, *Citrobacter* species, *Acinetobacter calcoaceticus*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus* species, *Candida albicans*, *Corynebacterium diphtheriae*, and *Clostridium perfringens*
Pharmacodynamics/Kinetics

Absorption: Significant percutaneous absorption of silver sulfadiazine can occur especially when applied to extensive burns

Half-life elimination: 10 hours; prolonged with renal impairment

Time to peak, serum: 3-11 days of continuous therapy

Excretion: Urine (~50% as unchanged drug)

Related Information

- Sulfonamide Derivatives

Pharmacotherapy PearlsContains methylparaben and propylene glycol
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine
References

Kulick MI, Wong R, Okarma TB, et al, “Prospective Study of Side Effects Associated With the Use of Silver Sulfadiazine in Severely Burned Patients,” *Ann Plast Surg*, 1985, 14(5):407-18. [PubMed 4083697]

Lockhart SP, Rushworth A, Azmy AA, et al, “Topical Silver Sulfadiazine: Side Effects and Urinary Excretion,” *Burns Incl Therm Inj*, 1983, 10(1):9-12.[PubMed 6640389]

International Brand NamesAldo-Silvederma (HK); Argenzil (UY); Dermazin (HK, ID, PL); Dermazine (BR); Flamazine (AE, BH, CY, DK, EG, FI, GB, IL, IQ, IR, JO, KW, LB, LY, NO, OM, PK, QA, SA, SY, TH, TW, YE, ZA); Flammazine (AT, BE, BG, CH, DE, ES, FR, HN, NL, PH, PL, PT); Flugen (TW); Platsul-A (AR, CN); Silvadene (MX, TW); Silvadyn (EC); Silvederma (ES, VE); Silverdiazina (PE); Silverol (IL); Silvirin (IN); Sofargen (IT); Sterizol (PH); Sulfadiacina de Plata (PY); Sulfadin (PH); Sulfaplata (CO); Sulfargin (EE); Uburn (TW); Ustionil (IT)

Simethicone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Infants' Mylicon® Gas Relief Dye Free Drops: Recall Due to Possible Metal Fragments - November 2008

Johnson & Johnson Merck Consumer Pharmaceuticals Company (JJMCP) is voluntarily recalling Infants' Mylicon® Gas Relief Dye Free Drops distributed after October 5, 2008 due to concern that metal fragments may have been generated during the manufacturing process.

For more information, including lots involved, please refer to the FDA MedWatch alert: http://www.fda.gov/medwatch/safety/2008/safety08.htm#mylicon

Medication Safety Issues

Sound-alike/look-alike issues:

Simethicone may be confused with cimetidine

Mylanta® may be confused with Mynatal®

Mylicon® may be confused with Modicon®, Myleran®

Phazyme® may be confused with Pherazine®

Pronunciation(sye METH i kone)

U.S. Brand NamesEqualizer Gas Relief [OTC]; Gas-X® Extra Strength [OTC]; Gas-X® Infant [OTC]; Gas-X® Maximum Strength [OTC]; Gas-X® Thin Strips™ [OTC]; Gas-X® [OTC]; Gas-X®, Children's Tongue Twisters™ [OTC]; Genasyme® [OTC]; Infantaire Gas Drops [OTC]; Little Tummys® Gas Relief [OTC]; Mylanta® Gas Maximum Strength [OTC]; Mylicon® Infants [OTC]; Phazyme® Ultra Strength [OTC]

Canadian Brand NamesOvol®; Phazyme™

Pharmacologic CategoryAntiflatulent

Use: Labeled IndicationsPostoperative gas pain or for use in endoscopic examination; relief of bloating, pressure, and discomfort of gas

Dosing: Adults**Flatulence/bloating:** Oral: 40-360 mg after meals and at bedtime, as needed

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Flatulence/bloating:** Oral:

Infants and Children <2 years or <11 kg: 20 mg 4 times/day, as needed

Children >2 years or >11 kg: 40 mg 4 times/day, as needed

Children >12 years: Refer to adult dosing.

Administration: OralShake oral suspension (drops) before using; mix with water, infant formula, or other liquids.

Dietary ConsiderationsShould be taken after meals.

StorageStore at room temperature. Avoid high humidity and excessive heat.

ContraindicationsHypersensitivity to simethicone or any component of the formulation

Geriatric ConsiderationsBefore treating excess gas or pain due to gas accumulation, a thorough evaluation must be made to determine cause since many bowel diseases may present with flatulence and bloating.

Adverse ReactionsNo data reported

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsFood: Avoid carbonated beverages and gas-forming foods.

Patient EducationSome tablets may be chewed thoroughly before swallowing, follow with a glass of water

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Softgels: 125 mg

Gas-X® Extra Strength, Mylanta® Gas Maximum Strength: 125 mg

Gas-X® Maximum Strength: 166 mg

Phazyme® Ultra Strength: 180 mg

Strips, oral:

Gas-X®, Children's Tongue Twisters™: 40 mg (16s) [sweet cinnamon flavor]

Gas-X® Thin Strips™: 62.5 mg (18s, 32s) [peppermint flavor]; 62.5 mg (18s) [cinnamon flavor]

Suspension, oral [drops]: 40 mg/0.6 mL (30 mL)

Equalizer Gas Relief, Genasyme®, Infantaire Gas: 40 mg/0.6 mL (30 mL)

Gas-X® Infant: 40 mg/0.6 mL (30 mL) [alcohol free; contains sodium benzoate]

Little Tummys® Gas Relief: 40 mg/0.6 mL (30 mL, 45 mL) [contains sodium benzoate; strawberry flavor]

Mylicon® Infants: 40 mg/0.6 mL (15 mL, 30 mL) [alcohol free; contains sodium benzoate; available in a nonstaining formula]

Tablet, chewable: 80 mg, 125 mg

Gas-X®: 80 mg [sodium free; contains calcium 30 mg/tablet; peppermint creme or cherry creme flavor]

Gas-X® Extra Strength: 125 mg [contains calcium 45 mg/tablet; peppermint creme or cherry creme flavor]

Genasyme®: 80 mg

Mylanta® Gas Maximum Strength: 125 mg [cherry and mint flavors]

Generic AvailableYes

Mechanism of ActionDecreases the surface tension of gas bubbles thereby disperses and prevents gas pockets in the GI system

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsActivated Dimethicone; Activated Methylpolysiloxane

International Brand NamesAero-Om (EC); Aero-Red (ES); Aerox (PE); AF adult (GT); AF infantil (GT); De-Gas (AU); Disflatyl (AT, CH, FI); Espumisan (BG, CL, CZ, DE, EE); Flapex (CN); Gastyl (MY); Gazim X (IL); Hedrin (IL); Infacol (IE); Lefaxin (AT); Liberan (MX); Minifom (FI, NO, SE); Mylicon (KP); Mylom (TH); Neogasol (CN); Ovol (MY); Phazyme 125 (AU); Siligas (CO); Simethicone (PL)

Simvastatin

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Ezetimibe (Zetia®), Ezetimibe/Simvastatin (Vytorin®), and Simvastatin (Zocor®): Completed Review of the ENHANCE Trial - January 2009

On January 25, 2008, the U.S. Food and Drug Administration (FDA) communicated that they would be reviewing the data from the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial (Kastelein, 2008).

The FDA has completed its review of the ENHANCE trial which evaluated the effects of simvastatin (Zocor®) and ezetimibe/simvastatin (Vytorin®) on carotid-artery intima-media thickness (CIMT) in patients with familial hypercholesterolemia. CIMT is a surrogate endpoint believed to translate in a reduction of future cardiovascular events. It is important to note that this was an imaging trial and was not powered for clinical outcomes (eg, MI, stroke). Following two years of treatment, CIMT was increased by 0.011 mm in the ezetimibe and simvastatin combination group and by 0.006 mm in the simvastatin alone group. This difference was not statistically significant even though the combination group demonstrated statistically significant greater reductions in LDL.

Possible explanations for this observation include: 1) Issues with enrolled patient population (eg, prior exposure to lipid-lowering therapy; baseline CIMT), 2) duration of trial, and 3) other unknown properties of ezetimibe that may negate the beneficial effects of statin therapy on LDL reduction.

Based on this information, the FDA has not changed its position that an elevated LDL level is a risk factor for cardiovascular disease and that lowering LDL reduces this risk. Three large clinical outcome trials evaluating the use of ezetimibe/simvastatin will be presented over the next 2-3 years.

Patients should not stop taking their ezetimibe/simvastatin (Vytorin®), ezetimibe (Zetia®), or simvastatin (Zocor®). Instead, patients should talk with their healthcare provider if they have questions about the ENHANCE trial.

For more information, U.S. healthcare professionals may refer to the following:

FDA: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Ezetimibe

American College of Cardiology (ACC) Statement on ENHANCE Trial: http://www.acc.org/enhance.htm

HMG-CoA Reductase Inhibitors: Evidence Does Not Suggest Increased Incidence of Amyotrophic Lateral Sclerosis (ALS) - Results of FDA Analysis - September 30, 2008

The U.S. Food and Drug Administration's (FDA) review of 41 long-term controlled clinical trials of HMG-CoA reductase inhibitors finds no evidence of an increased incidence of ALS (also known as Lou Gehrig's disease) related to these medications. This analysis occurred after the FDA had received notice of numerous adverse events of which 109 of these reports mentioned ALS, Lou Gehrig's disease, or motor neurone disease. The clinical trials included in the analysis had a median duration of treatment of 3.3 years (range of duration: 6 months to 5 years) and involved 120,964 patients. The analysis identified a total of 19 cases of ALS – 9 cases per 64,602 patients (0.014%) with statin therapy and 10 cases per 56,362 patients (0.017%) with placebo. The incidence rates, based on approximately 400,000 person-years, were 4.2 per 100,000 person-years in the statin-treated group and 5 per 100,000 person-years in the placebo-treated group.

The FDA recommends that health care providers continue to prescribe, and patients continue to use these products as described within their labeling.

For more information, healthcare professionals may refer to the following:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#Statin

Colman E, Szarfman A, Wyeth J, et al, "An Evaluation of a Data Mining Signal for Amyotrophic Lateral Sclerosis and Statins Detected in FDA's Spontaneous Adverse Event Reporting System," *Pharmacoepidemiol Drug Saf*, 2008 (epub ahead of print)

Ezetimibe (Zetia®), Simvastatin (Zocor®), and Ezetimibe/Simvastatin (Vytorin®): Preliminary Results From the SEAS Trial - Updated September 2008

The U.S. Food and Drug Administration (FDA) has communicated important information regarding an ongoing safety review of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial. The SEAS trial (Rossebo, 2008), recently available online, evaluated the effects of the combination ezetimibe/simvastatin (Vytorin®) on clinical outcomes in patients with mild-to-moderate asymptomatic aortic stenosis. The 5-year trial demonstrated that ezetimibe/simvastatin was no better than placebo in reducing the primary composite outcomes – major cardiovascular events (eg, death from cardiovascular causes, aortic-valve replacement, heart failure) or the composite outcome of aortic-valve-related clinical events and ischemia. Additionally, a higher incidence of newly diagnosed cancer of any type (105 patients taking ezetimibe/simvastatin vs 70 patients taking placebo, p=0.01) and cancer-related death (39 patients taking ezetimibe/simvastatin vs 23 patients taking placebo, p=0.05) was observed in the patients receiving ezetimibe/simvastatin compared to those receiving placebo. Of note, 8 patients diagnosed with cancer prior to randomization experienced recurrence (3 in the ezetimibe/simvastatin group vs 5 in the placebo group).

Subsequently, an interim analysis of the ongoing Study of Heart and Renal Protection (SHARP) trial and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) with a total of 20,617 randomized patients demonstrated no overall excess of cancer (313 active-treatment vs 326 control, p=0.61) (Peto, 2008). The SHARP trial randomized patients with chronic kidney disease to either ezetimibe/simvastatin or placebo. The IMPROVE-IT trial randomized patients with acute coronary syndrome to either ezetimibe/simvastatin or simvastatin alone. When the SEAS trial data is included in this analysis, there still is no significant excess of cancer (414 active-treatment vs 391 control, p=0.46). However, cancer-associated deaths were significantly higher when compared to controls (134 vs 92, respectively; p=0.007). Previous trials and meta-analyses involving the use of ezetimibe, simvastatin, or ezetimibe/simvastatin also have not shown an increased risk of cancer.

The FDA estimates that it will take approximately 6 months to fully evaluate the clinical trial data after receipt of the final SEAS trial report. At this time, the FDA recommends that patients continue taking their cholesterol-lowering medications.

For more information, U.S. healthcare professionals may refer to the following:

FDA: http://www.fda.gov/medwatch/safety/2008/safety08.htm#ezetimibe2

Peto R, Emberson J, Landray M, et al, “Analysis of Cancer Data From Three Ezetimibe Trials,” *N Engl J Med*, 2008, http://content.nejm.org/cgi/content/full/NEJMsa0806603

Rossebo AB, Pederson TR, Boman K, et al, “Intensive Lipid Lowering With Simvastatin and Ezetimibe in Aortic Stenosis,” *N Engl J Med*, 2008, http://content.nejm.org/cgi/content/full/NEJMoa0804602

Simvastatin and Amiodarone Concurrent Therapy: Dose-Related Increased Risk of Rhabdomyolysis - August 2008

The U.S. Food and Drug Administration (FDA) has issued an alert to remind practitioners of a dose-related increased risk of rhabdomyolysis when amiodarone is used concurrently with simvastatin at doses >20 mg. If patients require simvastatin >20 mg, an alternative HMG-CoA reductase inhibitor (statin) should be used. This information has previously been incorporated into the Lexi-Comp monograph.

Additional information may be found at http://www.fda.gov/cder/drug/InfoSheets/HCP/simvastatin_amiodaroneHCP.htm

Ezetimibe/Simvastatin (Vytorin®), Ezetimibe (Zetia®), and Simvastatin (Zocor®): ENHANCE Results - January, 2008

The U.S. Food and Drug Administration (FDA) is communicating important information regarding the preliminary results of the Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) trial, originally released on January 14, 2008, by Merck/Schering Plough. This multinational, randomized, double-blind trial was conducted in 720 patients with heterozygous familial hypercholesterolemia (HeFH) over a two-year period. Patients were randomized to either ezetimibe 10 mg/simvastatin 80 mg (Vytorin®) or simvastatin 80 mg alone (Zocor®). The primary endpoint of the trial was mean change in carotid intima-media thickness (CIMT) which is a surrogate endpoint believed to translate in a reduction of future cardiovascular events. It is important to note that this was an imaging trial and was not powered for clinical outcomes (eg, MI, stroke). Although ezetimibe/simvastatin lowered LDL cholesterol more effectively as compared to simvastatin alone, there was no difference seen in mean change in CIMT. Adverse events were similar between both groups.

Upon completion of full data analysis, the manufacturer will submit a final report to the FDA. Once the report is received, the FDA estimates it will take about 6 months to fully evaluate the data and decide whether or not further regulatory action is necessary. Three large clinical outcome trials evaluating the use of ezetimibe/simvastatin will be presented over the next 2-3 years.

At this point in time, patients should not stop taking their ezetimibe/simvastatin (Vytorin®), ezetimibe (Zetia®), or simvastatin (Zocor®). Instead patients should talk with their healthcare provider if they have questions about the ENHANCE trial.

For more information, U.S. healthcare professionals may refer to the following:

FDA: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Ezetimibe

American College of Cardiology (ACC) Statement on ENHANCE Trial: http://www.acc.org/enhance.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Zocor® may be confused with Cozaar®, Yocon®, Zoloft®

International issues:

Cardin® [Poland] may be confused with Cardene® which is a brand name for nicardipine in the U.S.

Cardin® [Poland] may be confused with Cardem® which is a brand name for celiprolol in Spain

Pronunciation(sim va STAT in)
U.S. Brand NamesZocor®
Canadian Brand NamesApo-Simvastatin®; CO Simvastatin; Dom-Simvastatin; Gen-Simvastatin; Novo-Simvastatin; Nu-Simvastatin; PHL-Simvastatin; PMS-Simvastatin; ratio-Simvastatin; Riva-Simvastatin; Sandoz-Simvastatin; Taro-Simvastatin; Zocor®
Pharmacologic CategoryAntilipemic Agent, HMG-CoA Reductase Inhibitor
Use: Labeled IndicationsUsed with dietary therapy for the following:

Secondary prevention of cardiovascular events in hypercholesterolemic patients with established coronary heart disease (CHD) or at high risk for CHD: To reduce cardiovascular morbidity (myocardial infarction, coronary revascularization procedures) and mortality; to reduce the risk of stroke and transient ischemic attacks

Hyperlipidemias: To reduce elevations in total cholesterol, LDL-C, apolipoprotein B, and triglycerides, and increase HDL-C in patients with primary hypercholesterolemia (elevations of 1 or more components are present in Fredrickson type IIa, IIb, III, and IV hyperlipidemias); treatment of homozygous familial hypercholesterolemia

Heterozygous familial hypercholesterolemia (HeFH): In adolescent patients (10-17 years of age, females >1 year postmenarche) with HeFH having LDL-C ≥190 mg/dL **or** LDL ≥160 mg/dL with positive family history of premature cardiovascular disease (CVD), or 2 or more CVD risk factors in the adolescent patient

Dosing: Adults**Note:** Doses should be individualized according to the baseline LDL-cholesterol levels, the recommended goal of therapy, and the patient's response; adjustments should be made at intervals of 4 weeks or more; doses may need adjusted based on concomitant medications

Homozygous familial hypercholesterolemia: Oral: 40 mg once daily in the evening **or** 80 mg/day (given as 20 mg, 20 mg, and 40 mg evening dose)

Prevention of cardiovascular events, hyperlipidemias: Oral: 20-40 mg once daily in the evening; range: 5-80 mg/day

Patients requiring only moderate reduction of LDL-cholesterol: May be started at 10 mg once daily

Patients requiring reduction of >45% in low-density lipoprotein (LDL) cholesterol: May be started at 40 mg once daily in the evening

Patients with CHD or at high risk for CHD: Dosing should be started at 40 mg once daily in the evening; simvastatin should be started simultaneously with diet therapy.

Dosage adjustment for simvastatin with concomitant medications:

Cyclosporine or danazol: Initial: 5 mg, should **not** exceed 10 mg/day

Gemfibrozil: Dose should **not** exceed 10 mg/day

Amiodarone or verapamil: Dose should **not** exceed 20 mg/day

Dosing: ElderlyOral: Initial: Maximum reductions in LDL-cholesterol may be achieved with daily dose ≤20 mg.
Dosing: PediatricHeFH: Oral: Children 10-17 years (females >1 year postmenarche): 10 mg once daily in the evening; range: 10-40 mg/day (maximum: 40 mg/day)

Dosage adjustment with concomitant medications: With concomitant amiodarone, cyclosporine, danazol, gemfibrozil, or verapamil: Refer to adult dosing.

Note: Doses should be individualized according to the baseline LDL-cholesterol levels, the recommended goal of therapy, and the patient's response; adjustments should be made at intervals of 4 weeks or more; doses may need adjusted based on concomitant medications

Dosing: Renal ImpairmentBecause simvastatin does not undergo significant renal excretion, modification of dose should not be necessary in patients with mild to moderate renal insufficiency.

Severe renal impairment: Cl_{cr} <10 mL/minute: Initial: 5 mg/day with close monitoring.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralMay be taken without regard to meals. Administer in the evening for maximal efficacy.
Dietary Considerations Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.
StorageTablets should be stored in tightly-closed containers at temperatures between 5°C to 30°C (41°F to 86°F).
ContraindicationsHypersensitivity to simvastatin or any component of the formulation; active liver disease; unexplained persistent elevations of serum transaminases; pregnancy; breast-feeding
Allergy Considerations

- HMG-CoA Reductase Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Myopathy/rhabdomyolysis: Patients receiving HMG-CoA reductase inhibitors have developed rhabdomyolysis with acute renal failure and/or myopathy; patients should be monitored closely. This risk is dose-related and is increased with concurrent use of other lipid lowering medications. Temporarily discontinue for elective major surgery, acute medical or surgical conditions, or in any patient experiencing an acute or serious condition predisposing to renal failure (eg, sepsis, hypotension, trauma, uncontrolled seizures). Based upon current evidence, HMG-CoA reductase inhibitor therapy should be continued in the perioperative period unless risk outweighs cardioprotective benefit. Use caution in patients with renal impairment, inadequately treated hypothyroidism, and those taking other drugs associated with myopathy (eg, colchicine); these patients are predisposed to myopathy. Patients should be instructed to report unexplained muscle pain, tenderness, weakness, or brown urine.

Disease-related concerns:

- Hepatic impairment and/or ethanol use: Use with caution in patients who consume large amounts of ethanol or have a history of liver disease. Use is contraindicated with active liver disease and with unexplained transaminase elevations.

Concurrent drug therapy issues:

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors (see drug interactions); consider alternative agents that avoid or lessen potential for CYP-mediated interactions.

Special Populations:

- Elderly: Use with caution in patients with advanced age, these patients are predisposed to myopathy.

- Pediatrics: Safety and efficacy have not been established in patients <10 years of age or premenarcheal girls.

Other warnings/precautions:

- Hyperlipidemia: Secondary causes of hyperlipidemia should be ruled out prior to therapy.

- Liver function tests: Must be monitored by periodic laboratory assessment.

Geriatric ConsiderationsEffective and well tolerated in the elderly. The definition of and, therefore, when to treat hyperlipidemia in the elderly is a controversial issue. The National Cholesterol Education Program recommends that all adults maintain a plasma cholesterol <160 mg/dL. In elderly with one additional risk factor, goal LDL would be <130 mg/dL. It is the authors' belief that pharmacologic treatment be reserved for those who are unable to obtain a desirable plasma cholesterol concentration by diet alone and for whom the benefits of treatment are believed to outweigh the potential adverse effects, drug interactions, and cost of treatment.

Pregnancy Risk FactorX

Pregnancy ConsiderationsCholesterol biosynthesis may be important in fetal development. Contraindicated in pregnancy. Administer to women of childbearing potential only when conception is highly unlikely and patients have been informed of potential hazards. If pregnancy occurs during treatment, discontinue simvastatin immediately.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsExcretion in breast milk is unknown, but would be expected; other medications in this class are excreted in human milk. Breast-feeding is contraindicated.

Adverse Reactions

1% to 10%:

Gastrointestinal: Constipation (2%), flatulence (1% to 2%), dyspepsia (1%)

Hepatic: Transaminases increased (>3x ULN; 1%)

Neuromuscular & skeletal: CPK elevation (>3x normal on one or more occasions; 5%)

Respiratory: Upper respiratory infection (2%)

<1%: Abdominal pain, diarrhea, dizziness, fatigue, headache, insomnia, nausea, pruritus, thrombocytopenia, vertigo, weakness

Postmarketing and/or case reports: Depression, dermatomyositis, hypotension, lichen planus, muscle pain, muscle tenderness, muscle weakness, myopathy, photosensitivity

Additional class-related events or case reports (not necessarily reported with simvastatin therapy): Alopecia, alkaline phosphatase increased, alteration in taste, alopecia, anaphylaxis, angioedema, anorexia, anxiety, arthralgia, arthritis, bilirubin increased, cataracts, chills, cholestatic jaundice, cirrhosis, decreased libido, depression, dermatomyositis, dryness of skin/mucous membranes, dyspnea, eosinophilia, erectile dysfunction/impotence, erythema multiforme, facial paresis, fatty liver, fever, flushing, fulminant hepatic necrosis, gynecomastia, hemolytic anemia, hepatic failure, hepatitis, hepatoma, hyperbilirubinemia, hypersensitivity reaction, impaired extraocular muscle movement, increased alkaline phosphatase, increased CPK (>10x normal), increased ESR, increased GGT, leukopenia, malaise, memory loss, myopathy, nail changes, nodules, ophthalmoplegia, pancreatitis, paresthesia, peripheral nerve palsy, peripheral neuropathy, photosensitivity, polymyalgia rheumatica, positive ANA, pruritus, psychic disturbance, purpura, rash, renal failure (secondary to rhabdomyolysis), rhabdomyolysis, skin discoloration, Stevens-Johnson syndrome, systemic lupus erythematosus-like syndrome, thrombocytopenia, thyroid dysfunction, toxic epidermal necrolysis, transaminases increased, tremor, urticaria, vasculitis, vertigo, vomiting

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP2C8 (weak), 2C9 (weak), 2D6 (weak)

Drug Interactions

Amiodarone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. Management: Dose of HMG-CoA reductase inhibitor may need to be reduced (e.g., simvastatin prescribing information recommends not exceeding 20 mg/day during concurrent therapy). *Risk D: Consider*

therapy modification

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Bosentan: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Colchicine: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CycloSPORINE: May increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Danazol: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

DAPTOmycin: HMG-CoA Reductase Inhibitors may enhance the adverse/toxic effect of DAPTOmycin. Specifically, the risk of skeletal muscle toxicity may be increased. Management: Consider temporarily stopping HMG-CoA reductase inhibitor therapy prior to daptomycin. If used together, regular (i.e., at least weekly) monitoring of CPK concentrations is recommended. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Etravirine: May decrease the serum concentration of HMG-CoA Reductase Inhibitors. This applies to atorvastatin, lovastatin and simvastatin. Conversely, levels of fluvastatin may be increased. Management: Dose adjustment of the HMG-CoA reductase inhibitor may be warranted. No interaction is expected with rosuvastatin or pravastatin. *Risk C: Monitor therapy*

Fenofibrate: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fenofibric Acid: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Gemfibrozil: May enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors. Gemfibrozil may increase the serum concentration of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Grapefruit Juice: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Imatinib: May decrease the metabolism of Simvastatin. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Niacin: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Niacinamide: May enhance the adverse/toxic effect of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Protease Inhibitors: May increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. *Risk D: Consider therapy modification*

Ranolazine: May increase the serum concentration of Simvastatin. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

Sildenafil: May decrease the metabolism of HMG-CoA Reductase Inhibitors. *Risk D: Consider therapy modification*

St Johns Wort: May increase the metabolism of HMG-CoA Reductase Inhibitors. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): HMG-CoA Reductase Inhibitors may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid excessive ethanol consumption (due to potential hepatic effects).

Food: Simvastatin serum concentration may be increased when taken with grapefruit juice; avoid concurrent intake of large quantities (>1 quart/day). Red yeast rice contains an estimated 2.4 mg lovastatin per 600 mg rice.

Herb/Nutraceutical: St John's wort may decrease simvastatin levels.

Monitoring ParametersCreatine phosphokinase levels due to possibility of myopathy; serum cholesterol (total and fractionated)

Obtain liver function tests prior to initiation, dose, and thereafter when clinically indicated. Patients titrated to the 80 mg dose should be tested prior to initiation and 3 months after initiating the 80 mg dose. Thereafter, periodic monitoring (ie, semiannually) is recommended for the first year of treatment. Patients with elevated transaminase levels should have a second (confirmatory) test and frequent monitoring until values normalize. Discontinue if increase in ALT/AST is persistently >3 times ULN.

Nursing: Physical Assessment/MonitoringUse with caution and monitor closely in presence of impaired liver function. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, other lipid-lowering drugs may increase risk of myopathy or rhabdomyolysis). Assess results of laboratory tests (LFTs, cholesterol profile) prior to treatment and periodically thereafter. Evaluate therapeutic response (reduction in lipid levels) and adverse reactions on a regular basis throughout therapy. Teach patient proper use (as adjunct to diet and exercise program), possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to women of childbearing age unless they are capable of complying with effective contraceptive use. Instruct patient in appropriate contraceptive measures.

Monitoring: Lab TestsCreatine phosphokinase levels due to possibility of myopathy; serum cholesterol (total and fractionated)

Obtain liver function tests prior to initiation, dose, and thereafter when clinically indicated. Patients titrated to the 80 mg dose should be tested prior to initiation and 3 months after initiating the 80 mg dose. Thereafter, periodic monitoring (ie, semiannually) is recommended for the first year of treatment. Patients with elevated transaminase levels should have a second (confirmatory) test and frequent monitoring until values normalize. Discontinue if increase in ALT/AST is persistently >3 times ULN.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Take at same time each day, in the evening with or without food. Follow cholesterol-lowering diet and exercise regimen as prescribed. Avoid excessive grapefruit juice (>1 quart/day) and excessive alcohol while taking this medication. You will have periodic blood tests to assess effectiveness. You may experience mild GI upset (should diminish with use); constipation (increased exercise, fluids, fiber, and fruit may help); or headache, dizziness, insomnia (use caution when driving or engaged in potentially hazardous tasks until response to drug in known). Contact prescriber immediately with persistent muscle or skeletal pain, joint pain, or numbness. Report other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during and for 1 month following therapy. Consult prescriber for appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 5 mg, 10 mg, 20 mg, 40 mg, 80 mg

  Zocor®: 5 mg, 10 mg, 20 mg, 40 mg, 80 mg

Generic AvailableYes

ManufacturerMerck & Co

Pricing: U.S. (www.drugstore.com)

Tablets (Simvastatin)

  5 mg (30): $17.99

  10 mg (30): $19.99

  20 mg (30): $27.99

  40 mg (30): $27.99

  80 mg (30): $32.99

Tablets (Zocor)

  5 mg (30): $66.99

  10 mg (90): $240.98

  20 mg (30): $139.99

  40 mg (90): $405.99

  80 mg (30): $146.99

Mechanism of ActionSimvastatin is a methylated derivative of lovastatin that acts by competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis

Pharmacodynamics/Kinetics

Onset of action: >3 days

  Peak effect: 2 weeks

Absorption: 85%

Protein binding:~95%

Metabolism: Hepatic via CYP3A4; extensive first-pass effect

Bioavailability: <5%

Half-life elimination: Unknown

Time to peak: 1.3-2.4 hours

Excretion: Feces (60%); urine (13%)

Related Information

- Hyperlipidemia Management
- Lipid-Lowering Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness
Mental Health: Effects on Psychiatric TreatmentRhabdomyolysis with acute renal failure has occurred; risk is increased with concurrent use of fluvoxamine nefazodone and verapamil
Cardiovascular Considerations

Primary Prevention: HMG-CoA reductase inhibitors are effective in primary and secondary prevention of cardiovascular events in patients with hyperlipidemia. For primary prevention, a patient's major risk factors (cigarette smoking, hypertension or currently taking antihypertensives, low HDL-C, family history, age, gender) should be evaluated. Patients with multiple risk factors (≥2) require more intensive therapy guided by the calculation of a 10-year absolute CHD risk (eg, the percent probability of having a CHD event in next 10 years). An individual's 10-year absolute CHD risk can be calculated at www.med-decisions.com/cvtool/phys/phys.html. LDL cholesterol goals, therapeutic lifestyle changes, and drug therapy are determined based upon a patient's risk factor profile.

Primary prevention trials show that cholesterol-lowering drugs reduce the risk of major coronary events, coronary death, and cerebrovascular events even in the first 6-12 months of use. The WOSCOP trial suggested a trend towards enhanced survival using pravastatin in their patients (mean LDL-cholesterol of 192 mg/dL and no history of MI). In a recent trial (Sever, 2003), patients with HTN and at least three other risk factors were randomized to 10 mg daily of atorvastatin or placebo. These patients had a total nonfasting cholesterol <250 mg/dL before treatment. LDL-C levels were 132 mg/dL before treatment and fell to an average of 90 mg/dL in the atorvastatin-treated group. There was a significant reduction in stroke, cardiovascular events, and coronary events in the atorvastatin-treated group as compared to the placebo group. There was no difference in mortality between the groups.

HMG-CoA reductase inhibitors decrease C-reactive protein (CRP), an inflammatory marker and an acute phase reactant. Elevated levels of high sensitive CRP (hsCRP), which detects CRP levels as low as 0.175 mg/L, have been shown to be associated with an increased risk of cardiovascular events. Recently, the JUPITER trial demonstrated that the use of rosuvastatin in healthy patients (men ≥50 years and women ≥60 years) without a history of cardiovascular disease with LDL <130 mg/dL and a hsCRP level ≥2 mg/L reduced the risk of major cardiovascular events (eg, nonfatal MI, stroke, death from cardiovascular causes), The number needed to treat over 5 years to prevent 1 cardiovascular event is 25. Current guidelines do not recommend drug treatment for patients with an LDL <130 mg/dL. However, identification of the patient at higher risk of cardiovascular events within this subgroup using hsCRP is now important given that statins may prevent the occurrence of these serious cardiovascular events (Ridker, 2008).

Secondary prevention: Secondary prevention trials indicate that “statin” therapy reduces mortality, major coronary events, coronary artery procedures, and stroke. The Heart Protection Study proved that lowering serum cholesterol levels reduces the rate of major vascular events among high-risk individuals with documented vascular disease (CHD, cerebrovascular, peripheral vascular) or diabetes regardless of initial cholesterol concentrations. PROVE IT is a randomized, double-blind trial evaluating hospitalized patients with acute coronary syndrome to determine the effects of intense LDL-C lowering therapy. Four thousand patients with an LDL-C levels of 106 mg/dL were randomized to pravastatin 40 mg daily or atorvastatin 80 mg daily. After 2 years, the combined cardiovascular endpoint (death, MI, unstable angina requiring hospitalization, revascularization and stroke) was ~26% in the pravastatin patients (median LDL-C 95 mg/dL) and ~22% in the atorvastatin treated patients (median LDL-C 62 mg/dL).

LaRosa and colleagues assessed the efficacy and safety of lowering LDL cholesterol <100 mg/dL in patients with stable coronary heart disease (LaRosa, 2005). Ten thousand and one patients with baseline LDL levels <130 mg/dL were randomized to atorvastatin 10 mg or 80 mg daily and followed for a median of 4.9 years. The primary endpoint was the occurrence of the first major cardiovascular event (death from CVD, MI, resuscitation after cardiac arrest, or stroke). A primary event occurred in 434 patients (8.7%) receiving 80 mg daily (mean LDL 77 mg/dL) and 548 patients (10.9%) receiving 10 mg dose (mean LDL 101 mg/dL) (95% CI, 0.69-0.89; p <0.001). There was no mortality difference between the two treatment groups.

In addition to the ability of HMG-CoA reductase inhibitors to decrease levels of high-sensitivity C-reactive protein (hs-CRP), they also possess pleiotropic properties including improved endothelial function, reduced inflammation at the site of the coronary plaque, inhibition of platelet aggregation, and anticoagulant effects. These nonlipid effects may be beneficial when HMG-CoA reductase inhibitors are introduced early in the management of acute coronary syndromes (de Denus, 2002).

Myopathy: Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years of age), women more frequently than men, small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, drug interactions (use with caution or avoid). The combination of a HMG-CoA reductase inhibitor plus nicotinic acid seems to carry a lower risk of myopathy than does a HMG-CoA reductase inhibitor plus a fibrate. Other medications, when used concurrently, may enhance the risk of myopathy associated with statins; these include drugs that inhibit CYP3A4 isoenzymes (lovastatin, simvastatin, atorvastatin) or CYP2C9 isoenzymes (fluvastatin). HMG-CoA reductase inhibitors may exacerbate exercise-induced skeletal muscle injury. Many experts favor getting a baseline creatine kinase (CK) measurement before initiating therapy (asymptomatic CK elevations are common). Obtain a CK measurement if patient complains of muscle soreness, tenderness, or pain.

Anesthesia and Critical Care Concerns/Other Considerations**Myopathy:** Currently-marketed HMG-CoA reductase inhibitors appear to have a similar potential for causing myopathy. Incidence of severe myopathy is about 0.08% to 0.09%. The factors that increase risk include advanced age (especially >80 years), gender (occurs in women more frequently than men), small body frame, frailty, multisystem disease (eg, chronic renal insufficiency especially due to diabetes), multiple medications, and drug interactions (use with caution or avoid).

Based on current research, HMG-CoA reductase inhibitors should be continued in the perioperative period. Postoperative discontinuation of statin therapy is associated with an increased risk of cardiac morbidity and mortality.

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International Brand NamesAvastinee (HK); Bestatin (TH); Biosim (IN); Cardin (PL); Cholestat (ID); Clinfar (BR); Colesken (MX); Corstat (HK); Covastin (HK, SG); Decrelip (PY); Ecuvas (EC); Esvat (ID); Eucor (TH); Euvasten (PH); Forcad (PH); Ifistatin (SG); Invast (AU); Klonastin (AR); Kolestevan (CR); Lesvatin (ID); Lipart (PL); Lipecor (KP); Lipex (AU, HR); Lipinorm (ID); Liponorm (IT); Lipovas (JP); Lochol (TH); Lodales (FR); Mersivas (ID); Nimicor (CN); Nor-Vastina (SV); Normofat (ID); Orovas (PH); Pusarat (MX); Resista (AU); Roco (KP); Rowestin (CR, DO, HN, NI, PA, SV); Simaspen (ZA); Simbado (ID); Simcard (HK); Simchol (ID); Simcor (ID); Simgal (PL); Simlo (MX); Simovil (IL); Simplaqor (MX); Simratio (PL); Simredin (PL); SimStatin (NZ); Simtin (HK, MY, PH, SG); Simvabell (AU); Simvacard (PL); Simvachol (PL); Simvacor (IL, MY, PL, SG); Simvahex (PH); Simvahexal (AU, PL, TW); Simvalord (KP); Simvar (AU); Simvastan (KP); Simvasterol (PL); Simvata (KP); Simvatin (AE, BH, CY, EG, IL, IQ, IR, JO, KP, KW, LB, LY, OM, QA, SA, SY, YE, ZA); Simvaxon (IL); Simvor (PL, SG, TH); Sinty (TW); Sinvacor (IT); Sivas (KP); Sivastin (IT); Statin (CO); Stavid (MY); Torio (TH); Tulip (MX); Vascor (MY, SG, TH); Vasilip (HK, PL); Vasotenal (PE); Vazz (PH); Vidastat (PH); Zeid (MX); Zimcol (AU); Zimmex (TH); Zimstat (AU); Zocor (AR, AU, BB, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CZ, DE, DK, EC, EE, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HR, HU, ID, IE, IT, JM, KE, KP, LR, LU, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, PE, PH, PK, PL, PT, SC, SD, SL, SN, SR, TH, TN, TT, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Zocor HP (PH); Zocord (AT, SE); Zorced (MX); Zovast (ID, PH)

Sincalide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(SIN ka lide)
U.S. Brand NamesKinevac®
Pharmacologic CategoryDiagnostic Agent
Use: Labeled IndicationsPostevacuation cholecystography; gallbladder bile sampling; stimulate pancreatic secretion for analysis; accelerate the transit of barium through the small bowel
Dosing: Adults

Contraction of gallbladder:

I.V.: 0.02 mcg/kg over 30-60 seconds; may repeat in 15 minutes with a 0.04 mcg/kg dose

Infusion: 0.12 mcg/kg in 100 mL of NS; administer over 50 minutes

I.M.: 0.1 mcg/kg

Pancreatic function: I.V.: 0.02 mcg/kg over 30 minutes

Accelerate barium transit through small bowel:

I.V.: 0.04 mcg/kg over 30-60 seconds; if movement of barium has not occurred in 30 minutes, may repeat dose

Infusion: 0.12 mcg/kg in 30 mL of NS; administer over 30 minutes

Dosing: ElderlyRefer to adult dosing.
Administration: I.V.Administration via infusion may help manage some adverse events or increase GI tolerance.
Administration: I.V. Detail

I.V. push: Administer over 30-60 seconds

I.V. infusion: Administer over 30-50 minutes. For pancreatic testing, administer over 30 minutes beginning after secretin infusion is started.

pH: 6-8

StorageStore unopened vial at 15°C to 30°C (59°F to 86°F). Once reconstituted, store at room temperature for up to 8 hours. Discard any unused portion. If further diluted for infusion, may be kept at room temperature; use within 1 hour.
ReconstitutionAdd 5 mL SWFI to vial. For I.V. infusion, put dose in 30-100 mL NS.
ContraindicationsHypersensitivity to sincalide or any component of the formulation; intestinal obstruction
Warnings/Precautions

Concerns related to adverse effects:

- Obstruction: Some risk of evacuating small gallstones into cystic duct or common bile duct and obstructing flow.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: Use with caution in pregnancy; may induce premature labor (especially if near term) or spontaneous abortion.

Dosage form specific issues:

- Sodium metabisulfite: Solution for injection contains sodium metabisulfite which may cause allergic reactions in some individuals.

Pregnancy Risk FactorB
Pregnancy ConsiderationsFetal harm was not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Because of its effect on smooth muscle, use during pregnancy should be avoided (may cause spontaneous abortion or premature labor). Use during pregnancy only if clearly needed. Should not be administered near term; may induce labor.
LactationExcretion in breast milk unknow/use caution
Adverse Reactions

>10%: Gastrointestional: Abdominal pain (20%), cramps, nausea (20%)

1% to 10%: Central nervous system: Dizziness (2%)

<1%: Diaphoresis, diarrhea, dyspnea, fecal urgency, flushing, headache, hyper-/hypotension, numbness, rash, sneezing, vomiting

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersFor cholecystography, xrays are taken at 5-minute intervals after the injection. For visualization of the cystic duct,

xrays may be required at 1-minute intervals for the first 5 minutes after injection.

Reference RangeGallbladder size: ≥40% reduction considered a satisfactory contraction.

Monitoring: Lab TestsFor cholecystography, xrays are taken at 5-minute intervals after the injection. For visualization of the cystic duct, xrays may be required at 1-minute intervals for the first 5 minutes after injection.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 5 mcg [contains sodium metabisulfitel]

Generic AvailableNo

Mechanism of ActionStimulates contraction of the gallbladder; inhibits gastric emptying by causing pyloric contraction, and increases intestinal motility; stimulates pancreatic secretion; causes smooth muscle contraction

Pharmacodynamics/Kinetics

Onset of action: Contraction of the gallbladder: ~5-15 minutes

Duration: ~1 hour

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsC8-CCK; OP-CCK

Sinecatechins

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(sin e KAT e kins)

U.S. Brand NamesVeregen®

Pharmacologic CategoryImmunomodulator, Topical; Topical Skin Product

Use: Labeled IndicationsTreatment of external genital and perianal warts secondary to *Condylomata acuminata*

Dosing: Adults*Condylomata acuminata:* Topical: Apply a thin layer (~0.5 cm strand) 3 times/day to all external genital and perianal warts until all warts have been cleared (maximum duration: 16 weeks)

Dosing: Renal ImpairmentNo adjustment required.

Dosing: Hepatic ImpairmentNo adjustment required.

Administration: TopicalWash hands before and after application; apply with fingers, leaving a thin layer of ointment; do not wash ointment off affected area after application. Discontinue treatment if the severity of local skin reactions becomes unacceptable. Do not apply internally; do not apply to open wounds; do not apply occlusive dressing. Sexual contact should be avoided while ointment is on skin. For females requiring tampon use during treatment, tampon should be inserted prior to application of ointment to prevent accidental application of ointment into the vagina. May stain clothing or bedding.

StorageStore at 2°C to 8°C (36°F to 46°F) until dispensed; after dispensing, patient may store under refrigeration or up to 25°C (77°F). Do not freeze.

ContraindicationsThere are no contraindications listed in the manufacturer’s labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Skin irritation: Local skin reactions are common, if possible, continue treatment; severe reactions may require treatment interruption or discontinuation.

Disease-related concerns:

- HPV infection: Not intended for the treatment of urethral, intravaginal, cervical, rectal, or intra-anal human papilloma viral disease. Women should continue to undergo regular gynecological examination, including monitoring and screening for cervical dysplasia.

Special populations:

- Immunosuppressed patients: Safety and efficacy have not been established in immunosuppressed patients.

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

- Women: Severe reactions were reported more commonly in women; it is possible that women are at a higher risk of serious local events (eg, erosion/ulceration, burning, itching, pain).

Other warnings/precautions:

- Appropriate use: For topical use only; ointment is **not** intended for internal use; avoid topical application to open wounds; has been shown to increase the risk of adverse reactions. Avoid exposure of treated area to sun and/or UV-light.

- Duration of therapy: Continue treatment until all warts have been cleared (maximum duration: 16 weeks); the safety and efficacy of treatment lasting >16 weeks have not been established.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women; use only if possible benefit outweighs potential risk to the fetus. Sinecatechins ointment may weaken condoms and diaphragms.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Dermatologic: Erythema (70%), pruritus (69%), edema (45%), vesicular rash (20%)

Local: Burning (67%), pain/discomfort (56%), erosion/ulceration (49%), induration (35%)

1% to 10%:

Dermatologic: Desquamation (5%), rash (1%), scar formation (1%)

Local: Discharge (3%), lymphadenitis (3%), bleeding (2%), reaction (2%), irritation (1%)

Miscellaneous: Phimosis (uncircumcised males; 3%), hypersensitivity (2%)

<1%: Discoloration, dryness, eczema, facial rash, hyperesthesia, necrosis, papules, pelvic pain, perianal infection, pigmentation changes,

staphylococcemia, urethritis, vulvitis

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersRoutine gynecological exams (females)
Nursing: Physical Assessment/MonitoringMonitor therapeutic response and adverse reactions at the beginning and periodically throughout therapy. Assess knowledge/teach appropriate application of this medication.
Patient EducationUse on affected areas as prescribed. Apply thin layer of medication; do not wash off. Wash your hands immediately after application. Avoid contact with eyes, nostrils, or mouth. Women using tampons should insert the tampon prior to application so as not to introduce the ointment into the vagina. Avoid exposure to sunlight. Do not apply to open wounds, vagina, or anal area. Avoid sexual contact. Genital warts are sexually transmitted; you may infect your partner. If you choose to have sexual contact, wash off the ointment carefully before protected contact as the ointment may weaken condoms and vaginal diaphragms. Avoid use of occlusive dressing. You may experience redness, swelling, or itching at the site of application. Report development of open sores or severe reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Ointment, topical:

Veregen®: 15% (15 g)

Generic AvailableNo
Manufacturer

Bradley Pharmaceuticals, Inc

Mechanism of ActionThe mechanism by which sinecatechins ointment aids in the clearance of genital and perianal warts is unknown. Antioxidant properties have been demonstrated *in vitro*; however, the significance of this finding is not known.
Pharmacodynamics/KineticsAbsorption: Topical: Not sufficiently studied; based on limited data, minimal systemic absorption is expected.
Pharmacotherapy PearlsSinecatechins ointment represents the first botanical drug product to be approved by the FDA. The product contains an extract of dried green tea leaves. The active ingredient(s) are not known; however, sinecatechins is a mixture of catechins (85% to 95% by weight) with the major component being (-)-Epigallocatechin gallate (EGCg). Approximately 2.5% of the mixture contains gallic acid, caffeine, and theobromine.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsCatechins; Green Tea Extract; Kunecatechins; Polyphenols; Polyphenon E

Sirolimus

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Rapamune® may be confused with Rapaflo®

Sirolimus may be confused with tacrolimus, temsirolimus

Pronunciation(sir OH li mus)

U.S. Brand NamesRapamune®

Canadian Brand NamesRapamune®

Pharmacologic CategoryImmunosuppressant Agent; mTOR Kinase Inhibitor

Use: Labeled IndicationsProphylaxis of organ rejection in patients receiving renal transplants, in combination with corticosteroids and cyclosporine (cyclosporine may be withdrawn in low-to-moderate immunological risk patients after 2-4 months, in conjunction with an increase in sirolimus dosage; in high-risk patients, use in combination with cyclosporine and corticosteroids is recommended for the first year)

Use: Unlabeled/InvestigationalProphylaxis of organ rejection in heart transplant recipients; immunosuppression in peripheral stem cell/bone marrow transplantation

Dosing: Adults

Low-to-moderate risk renal transplant patients: Oral:

<40 kg: Loading dose: 3 mg/m^2 on day 1, followed by maintenance dosing of 1 mg/m^2 once daily

≥40 kg: Loading dose: 6 mg on day 1; maintenance: 2 mg once daily

High-risk renal transplant patients: Oral: Loading dose: Up to 15 mg on day 1; maintenance: 5 mg/day; obtain trough concentration between days 5-7 and adjust accordingly. Continue concurrent cyclosporine/sirolimus therapy for 1 year following transplantation. Further adjustment of the regimen must be based on clinical status.

Dosage adjustment: Sirolimus dosages should be adjusted to maintain trough concentrations within desired range based on risk and concomitant therapy. Maximum daily dose: 40 mg. Dosage should be adjusted at intervals of 7-14 days to account for the long half-life of sirolimus. In general, dose proportionality may be assumed. New sirolimus dose **equals** current dose **multiplied by** (target concentration/current concentration). **Note:** If large dose increase is required, consider loading dose calculated as:

Loading dose **equals** (new maintenance dose **minus** current maintenance dose) **multiplied by** 3

Maximum dose in 1 day: 40 mg; if required dose is >40 mg (due to loading dose), divide over 2 days. Serum concentrations should not be used as the sole basis for dosage adjustment (monitor clinical signs/symptoms, tissue biopsy, and laboratory parameters).

Maintenance therapy after withdrawal of cyclosporine: Cyclosporine withdrawal is not recommended in high immunological risk patients. Following 2-4 months of combined therapy, withdrawal of cyclosporine may be considered in low-to-moderate risk patients. Cyclosporine should be discontinued over 4-8 weeks, and a necessary increase in the dosage of sirolimus (up to fourfold) should be anticipated due to removal of metabolic inhibition by cyclosporine and to maintain adequate immunosuppressive effects. Dose-adjusted trough target concentrations are typically 16-24 ng/mL for the first year post-transplant and 12-20 ng/mL thereafter (measured by chromatographic methodology).

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Immunosuppression: Children ≥13 years: Oral: Refer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment (in loading or maintenance dose) is necessary in renal impairment. However, adjustment of regimen (including discontinuation of therapy) should be considered when used concurrently with cyclosporine and elevated or increasing serum creatinine is noted.

Dosing: Hepatic Impairment

Loading dose : No adjustment required

Maintenance dose:

Mild-to-moderate hepatic impairment: reduce maintenance dose by ~33%.

Severe hepatic impairment: reduce maintenance dose by ~50%.

Calculations

- Body Mass Index
- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: OralInitial dose should be administered as soon as possible after transplant. Sirolimus should be taken 4 hours after oral cyclosporine (Neoral® or Gengraf®).

Solution: Mix with at least 2 ounces of water or orange juice. No other liquids should be used for dilution. Patient should drink diluted solution immediately. The cup should then be refilled with an additional 4 ounces of water or orange juice, stirred vigorously, and the patient should drink the contents at once.

Tablet: Do not crush, split. or chew.

Dietary ConsiderationsTake consistently, with or without food, to minimize variability of absorption.

Storage

Oral solution: Store under refrigeration, 2°C to 8°C (36°F to 46°F). Protect from light. A slight haze may develop in refrigerated solutions, but the quality of the product is not affected. After opening, solution should be used in 1 month. If necessary, may be stored at temperatures up to 25°C (77°F) for ≤15 days after opening. Product may be stored in amber syringe for a maximum of 24 hours (at room temperature or refrigerated). Solution should be used immediately following dilution.

Tablet: Store at room temperature of 20°C to 25°C (68°F to 77°F). Protect from light.

ContraindicationsHypersensitivity to sirolimus or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Infection: See “Concerns related to adverse effects” below.
- Liver transplants: See “Special populations” below.
- Lung transplants: See “Special populations” below.
- Malignancy: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactic/hypersensitivity reactions: Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis have been reported.
- Angioedema: Has been reported; concurrent use with other drugs known to cause angioedema (eg, ACE inhibitors) may increase risk.
- Infection: **[U.S. Boxed Warning]: Immunosuppressive agents, including sirolimus, increase the risk of infection.** Immune suppression may also increase the risk of opportunistic infections and sepsis. Prophylactic treatment for *Pneumocystis jirovec* pneumonia (PCP) should be administered for 1 year post-transplant; prophylaxis for cytomegalovirus (CMV) should be taken for 3 months in patients at risk for CMV.
- Interstitial lung disease: Cases of interstitial lung disease (eg, pneumonitis, bronchiolitis obliterans organizing pneumonia, pulmonary fibrosis) have been observed (some fatal); risk may be increased with higher trough levels.
- Lymphocele/fluid accumulation: Use has been associated with an increased risk of fluid accumulation and lymphocele. Peripheral edema, lymphedema, and pleural and pericardial effusions (including significant effusions and tamponade) were reported; use with caution in patients in whom fluid accumulation may be poorly tolerated, such as in cardiovascular disease (heart failure or hypertension) and pulmonary disease.
- Malignancy: **[U.S. Boxed Warning]: Immunosuppressive agents, including sirolimus, may be associated with the development of lymphoma.** Immunosuppressant therapy is associated with an increased risk of skin cancer; limit sun and ultraviolet light exposure; use appropriate sun protection.
- Proteinuria: Increased urinary protein excretion has been observed when converting renal transplant patients from calcineurin inhibitors to sirolimus during maintenance therapy. A higher level of proteinuria prior to sirolimus conversion correlates with a higher degree of proteinuria after conversion. In some patients, proteinuria may reach nephrotic levels.
- Renal effects: May increase serum creatinine and decrease GFR.
- Wound dehiscence/healing: May be associated with wound dehiscence and impaired healing; use caution in the perioperative period. Patients with a body mass index (BMI) >30 kg/m^2 are at increased risk for abnormal wound healing.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; a reduction in the maintenance dose is recommended.
- Hyperlipidemia: Use with caution in patients with hyperlipidemia; may increase serum lipids (cholesterol and triglycerides).

Concurrent drug therapy issues:

- Calcineurin inhibitors: Concurrent use with a calcineurin inhibitor (cyclosporine, tacrolimus) may increase the risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA).
- Cyclosporine: Monitor renal function closely when combined with cyclosporine; consider dosage adjustment or discontinue in patients

with increasing serum creatinine. Safety and efficacy of combination therapy with cyclosporine in high-risk patients has not been studied beyond 12 months of treatment; adjustment of immunosuppressive therapy beyond 12 months should be considered based on clinical judgement.

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors and moderate or strong CYP3A4 inducers (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

- Nephrotoxic drugs: Use with caution in patients concurrently taking medications which may alter renal function.

Special populations:

- Liver transplants: **[U.S. Boxed Warning]: Sirolimus is not recommended for use in *de novo* liver transplant patients;** studies indicate an association with an increase risk of hepatic artery thrombosis, graft failure, and increased mortality in these patients when sirolimus is used in combination with cyclosporine and/or tacrolimus.

- Lung transplants: **[U.S. Boxed Warning]: Sirolimus is not recommended for use in *de novo* lung transplant patients.** Cases of bronchial anastomotic dehiscence have been reported in lung transplant patients when sirolimus was used as part of an immunosuppressive regimen; most of these reactions were fatal.

- Pediatrics: Not labeled for use in children <13 years of age, or in adolescent patients <18 years of age considered at high immunological risk.

- Renal transplant: In renal transplant patients, *de novo* use without cyclosporine has been associated with higher rates of acute rejection. Sirolimus may delay recovery of renal function in patients with delayed allograft function.

Pregnancy Risk FactorC

Pregnancy ConsiderationsEmbryotoxicity and fetotoxicity may occur, as evidenced by increased mortality, reduced fetal weights and delayed ossification in animal studies. There are no adequate and well-controlled studies in pregnant women. Effective contraception must be initiated before therapy with sirolimus and continued for 12 weeks after discontinuation.

The National Transplantation Pregnancy Registry (NTPR, Temple University) is a registry for pregnant women taking immunosuppressants following any solid organ transplant. The NTPR encourages reporting of all immunosuppressant exposures during pregnancy in transplant recipients at 877-955-6877.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for adverse reactions in the breast-fed infant, including possible immunosuppression, breast-feeding is not recommended.

Adverse ReactionsIncidence of many adverse effects is dose related.

>20%:

Cardiovascular: Peripheral edema (54% to 64%), hypertension (39% to 49%), edema (16% to 24%), chest pain (16% to 24%)

Central nervous system: Fever (23% to 34%), headache (23% to 34%), pain (24% to 33%), insomnia (13% to 22%)

Dermatologic: Acne (20% to 31%), rash (10% to 20%)

Endocrine & metabolic: Hypertriglyceridemia (38% to 57%), hypercholesterolemia (38% to 46%), hypophosphatemia (15% to 23%), hypokalemia (11% to 21%)

Gastrointestinal: Diarrhea (25% to 42%), constipation (28% to 38%), abdominal pain (28% to 36%), nausea (25% to 36%), vomiting (19% to 25%), dyspepsia (17% to 25%), weight gain (8% to 21%)

Genitourinary: Urinary tract infection (20% to 33%)

Hematologic: Anemia (23% to 37%), thrombocytopenia (13% to 30%)

Neuromuscular & skeletal: Weakness (22% to 40%), arthralgia (25% to 31%), tremor (21% to 31%), back pain (16% to 26%)

Renal: Serum creatinine increased (35% to 40%)

Respiratory: Dyspnea (22% to 30%), upper respiratory infection (20% to 26%), pharyngitis (16% to 21%)

3% to 20%:

Cardiovascular: Atrial fibrillation, CHF, DVT, facial edema, hypervolemia, hypotension, palpitation, peripheral vascular disorder, postural hypotension, syncope, tachycardia, thrombosis, vasodilation, venous thromboembolism

Central nervous system: Chills, malaise, anxiety, confusion, depression, dizziness, emotional lability, hypoesthesia, hypotonia, neuropathy, somnolence

Dermatologic: Dermatitis (fungal), hirsutism, pruritus, skin hypertrophy, dermal ulcer, ecchymosis, cellulitis, skin carcinoma (up to 3%; includes basal cell carcinoma, squamous cell carcinoma, melanoma), wound healing abnormal

Endocrine & metabolic: Cushing's syndrome, diabetes mellitus, glycosuria, acidosis, dehydration, hypercalcemia, hyperglycemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypomagnesemia, hyponatremia, hyperkalemia (12% to 17%)

Gastrointestinal: Enlarged abdomen, anorexia, dysphagia, eructation, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, gingival hyperplasia, ileus, mouth ulceration, oral moniliasis, stomatitis, weight loss

Genitourinary: Pelvic pain, scrotal edema, testis disorder, impotence

Hematologic: Leukocytosis, polycythemia, TTP, hemolytic-uremic syndrome, hemorrhage, leukopenia (9% to 15%)

Hepatic: Abnormal liver function tests, alkaline phosphatase increased, ascites, LDH increased, transaminases increased

Local: Thrombophlebitis

Neuromuscular & skeletal: Arthrosis, bone necrosis, CPK increased, leg cramps, myalgia, osteoporosis, tetany, hypertonia, paresthesia

Ocular: Abnormal vision, cataract, conjunctivitis

Otic: Ear pain, deafness, otitis media, tinnitus

Renal: Albuminuria, bladder pain, BUN increased, dysuria, hematuria, hydronephrosis, kidney pain, tubular necrosis, nocturia, oliguria, pyelonephritis, pyuria, nephropathy (toxic), urinary frequency, urinary incontinence, urinary retention

Respiratory: Asthma, atelectasis, bronchitis, cough, epistaxis, hypoxia, lung edema, pleural effusion, pneumonia, pulmonary embolism, rhinitis, sinusitis

Miscellaneous: Abscess, diaphoresis, flu-like syndrome, herpesvirus infection, hernia, infection (including opportunistic), lymphadenopathy, lymphocele, lymphoproliferative disease/lymphoma (1% to 3%), peritonitis, sepsis

Infrequent, postmarketing, and/or case reports: Anaphylactoid reaction, anaphylaxis, anastomotic disruption, angioedema, azoospermia, cytomegalovirus, Epstein-Barr virus, exfoliative dermatitis, fascial dehiscence, hepatic necrosis, hepatotoxicity, hypersensitivity reaction, hypersensitivity vasculitis; interstitial lung disease (dose–related; includes pneumonitis, pulmonary fibrosis, and bronchiolitis obliterans organizing pneumonia [BOOP] with no identified infectious etiology); joint disorders, lymphedema, nephrotic syndrome, neutropenia, pancreatitis, pancytopenia, pericardial effusion, *Pneumocystis* pneumonia, proteinuria, pulmonary hemorrhage, tamponade, tuberculosis, wound dehiscence

Note: Hepatic artery thrombosis and graft failure have been reported in liver transplant patients (not an approved use); bronchial anastomotic dehiscence has been reported in lung transplant patients (not an approved use); and calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA) has been reported with concurrent cyclosporine and/or tacrolimus.

Metabolism/Transport Effects **Substrate** of CYP3A4 (major), P-glycoprotein; **Inhibits** CYP3A4 (weak)

Drug Interactions

ACE Inhibitors: Sirolimus may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Sirolimus. Management: Sirolimus dose reductions of up to 50-90% may be necessary when starting an azole antifungal. Use of sirolimus with the azole antifungals voriconazole and posaconazole is contraindicated. *Risk D: Consider therapy modification*

CycloSPORINE: Sirolimus may enhance the adverse/toxic effect of CycloSPORINE. An increased risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA) has been described. CycloSPORINE may increase the serum concentration of Sirolimus. This is of specific concern with cyclosporine [MODIFIED]. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Sirolimus. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Sirolimus. *Risk D: Consider therapy modification*

Protease Inhibitors: May increase the serum concentration of Sirolimus. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Sirolimus. *Risk D: Consider therapy modification*

Tacrolimus: Sirolimus may enhance the adverse/toxic effect of Tacrolimus. An increased risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA) has been described. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Avoid grapefruit juice; may decrease clearance of sirolimus. Ingestion with high-fat meals decreases peak concentrations but increases AUC by 23% to 35%. Sirolimus should be taken consistently either with or without food to minimize variability.

Herb/Nutraceutical: St John's wort may decrease sirolimus levels; avoid concurrent use. Avoid cat's claw, echinacea (have immunostimulant properties; consider therapy modifications). Herbs with hypoglycemic properties may increase the risk of sirolimus-induced hypoglycemia; includes alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, stinging nettle.

Monitoring ParametersMonitor LFTs and CBC during treatment. Monitor sirolimus levels in all patients (especially in pediatric patients, patients ≥13 years of age weighing <40 kg, patients with hepatic impairment, or on concurrent potent inhibitors or inducers of CYP3A4, and/or if cyclosporine dosing is markedly reduced or discontinued), and when changing dosage forms of sirolimus. Also monitor serum cholesterol and triglycerides, blood pressure, serum creatinine, and urinary protein. Serum drug concentrations should be determined 3-4 days after loading doses and 7-14 days after dosage adjustments; however, these concentrations should not be used as the sole basis for dosage adjustment, especially during withdrawal of cyclosporine (monitor clinical signs/symptoms, tissue biopsy, and laboratory parameters). **Note:** Specific ranges will vary with assay methodology (chromatographic or immunoassay) and are not interchangeable.

Reference Range**Note:** Differences in sensitivity and specificity exist between methods of detection (eg, immunoassay vs HPLC); on average, chromatographic methods yield values ~20% lower than (whole blood) immunoassay determinations. Target range may vary based on assay conditions.

Serum trough concentrations (based on HPLC methods):

Concomitant cyclosporine: 4-12 ng/mL

After cyclosporine withdrawal: 16-24 ng/mL for the first year after transplant; after 1 year: 12-20 ng/mL

Note: Trough concentrations vary based on clinical context and use of additional immunosuppressants. The following represents typical ranges.

When combined with tacrolimus and mycophenolate mofetil (MMF) without steroids: 6-8 ng/mL

As a substitute for tacrolimus (starting 4-8 weeks post-transplant), in combination with MMF and steroids: 8-12 ng/mL

Following conversion from tacrolimus to sirolimus >6 months post-transplant due to chronic allograft nephropathy: 4-6 ng/mL

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications. Assess results of laboratory tests at beginning and periodically during therapy, therapeutic effectiveness, and adverse reactions and toxicity. Assess lipid profiles; evaluate the need for medication intervention. Monitor blood pressure, weight, and renal function. Assess for signs of fluid retention and infection. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse reactions to report.

Monitoring: Lab TestsMonitor LFTs and CBC during treatment. Monitor sirolimus levels in all patients (especially in pediatric patients, patients ≥13 years of age weighing <40 kg, patients with hepatic impairment, or on concurrent potent inhibitors or inducers of CYP3A4, and/or if cyclosporine dosing is markedly reduced or discontinued), and when changing dosage forms of sirolimus. Also monitor serum cholesterol and triglycerides, blood pressure, serum creatinine, and urinary protein. Serum drug concentrations should be determined 3-4 days after loading doses and 7-14 days after dosage adjustments; however, these concentrations should not be used as the sole basis for dosage adjustment, especially during withdrawal of cyclosporine (monitor clinical signs/symptoms, tissue biopsy, and laboratory parameters). **Note:** Specific ranges will vary with assay methodology (chromatographic or immunoassay) and are not interchangeable.

Patient EducationDo not alter dose or discontinue without consulting prescriber. Do not ever mix sirolimus solution with anything other than water or orange juice. Do not crush, split, or chew tablets. May be taken with or without food, but should be taken consistently with regard to food (always on an empty stomach or always with food). Avoid grapefruit juice. Consult prescriber about timing of any other prescribed or OTC medications. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will be susceptible to infection (avoid crowds and exposure to infection). If you have diabetes, monitor glucose levels closely (drug may alter glucose levels). Limit exposure to sunlight by wearing protective clothing or sunscreen. You may experience nausea, vomiting, loss of appetite (small frequent meals, good mouth care, chewing gum, or sucking hard candy may help); constipation (increase exercise, fluids, fruit, or fiber may help); or diarrhea (yogurt or buttermilk); or muscle or back pain (mild analgesic). Inform prescriber of any adverse effects including, but not limited to, unresolved GI problems; respiratory difficulty, cough, infection; persistent fever; skin rash or irritation; headache, insomnia, anxiety, confusion, emotional lability; unusual bleeding; changes in voiding pattern, burning, itching, or pain on urination; persistent bone, joint, or muscle cramping, pain or weakness; chest pain, palpitations, swelling of extremities; weight gain of 3-5 lbs per week; vision changes or hearing; or any other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral:

Rapamune®: 1 mg/mL (60 mL) [contains ethanol 1.5% to 2.5%; packaged with oral syringes and a carrying case]

Tablet:

Rapamune®: 1 mg, 2 mg

Generic AvailableNo

ManufacturerWyeth-Ayerst Laboratories

Pricing: U.S. (www.drugstore.com)

Solution (Rapamune)

1 mg/mL (60): $534.04

Tablets (Rapamune)

1 mg (30): $277.58

2 mg (100): $1812.11

Mechanism of ActionSirolimus inhibits T-lymphocyte activation and proliferation in response to antigenic and cytokine stimulation and inhibits antibody production. Its mechanism differs from other immunosuppressants. Sirolimus binds to FKBP-12, an intracellular protein, to form an immunosuppressive complex which inhibits the regulatory kinase, mTOR (mammalian target of rapamycin). This inhibition suppresses cytokine mediated T-cell proliferation, halting progression from the G1 to the S phase of the cell cycle. It inhibits acute rejection of allografts and prolongs graft survival.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: 12 L/kg (range: 4-20 L/kg)

Protein binding: 92%, primarily to albumin

Metabolism: Extensively hepatic via CYP3A4; to 7 major metabolites

Bioavailability: Oral solution: 14%; Oral tablet: 18%

Half-life elimination: Mean: 62 hours (range: 46-78 hours); extended in hepatic impairment (Child-Pugh class A or B) to 113 hours

Time to peak: 1-2 hours

Excretion: Feces (91% due to P-glycoprotein-mediated efflux into gut lumen); urine (2%)

Pharmacotherapy Pearls

Sirolimus tablets and oral solution are not bioequivalent, due to differences in absorption. Clinical equivalence was seen using 2 mg tablet and 2 mg solution. It is not known if higher doses are also clinically equivalent. Monitor sirolimus levels if cages in dosage forms are made.

Sirolimus solution may cause irritation if administered undiluted.

High-risk renal transplant patients are defined (per the manufacturer's labeling) as African-American transplant recipients and/or repeat renal transplant recipients who lost a previous allograft based on an immunologic process and/or patients with high PRA (panel-reactive antibodies; peak PRA level >80%). Individual transplant centers may have differences in their definitions. For example, some centers would consider a PRA >50% to be at higher risk of rejection.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mouth ulceration, oral moniliasis, stomatitis, gingival hyperplasia, gingivitis, and dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia is common; may cause anxiety, confusion, depression, emotional lability, and somnolence

Mental Health: Effects on Psychiatric TreatmentLeukopenia is common; use caution with clozapine and carbamazepine; nefazodone may increase serum levels of sirolimus

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International Brand Names Limus (IN); Rapamune (AR, AT, AU, BE, BG, BR, CH, CL, CN, CO, CR, CZ, DE, DK, ES, FI, FR, GB, GR, GT, HK, HN, IE, IL, IT, KP, MX, MY, NI, NL, NO, PA, PE, PH, PL, PT, RU, SE, SG, SV, TH, TR, TW, VE)

Sitagliptin and Metformin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Janumet™ may be confused with Jantoven™

Pronunciation(sit a GLIP tin & met FOR min)

U.S. Brand NamesJanumet™

Pharmacologic CategoryAntidiabetic Agent, Biguanide; Antidiabetic Agent, Dipeptidyl Peptidase IV (DPP-IV) Inhibitor; Hypoglycemic Agent, Oral

Use: Labeled IndicationsManagement of type 2 diabetes mellitus (noninsulin dependent, NIDDM) in patients not adequately controlled on metformin or sitagliptin monotherapy and as an adjunct to diet and exercise

Dosing: Adults**Type 2 diabetes mellitus:** Oral: Initial doses should be based on current dose of sitagliptin and metformin; daily doses should be divided and given twice daily with meals. Maximum: Sitagliptin 100 mg/metformin 2000 mg daily

Patients inadequately controlled on metformin alone: Initial dose: Sitagliptin 100 mg/day plus current dose of metformin. **Note:** Per manufacturer labeling, patients currently receiving metformin 850 mg twice daily should receive an initial dose of sitagliptin 50 mg and metformin 1000 mg twice daily

Patients inadequately controlled on sitagliptin alone: Initial dose: Metformin 1000 mg/day plus sitagliptin 100 mg/day. **Note:** Patients currently receiving a renally adjusted dose of sitagliptin should not be switched to combination product.

Dosing adjustment: Metformin component may be gradually increased up to the maximum dose. Maximum dose: Sitagliptin 100 mg/metformin 2000 mg daily

Dosing: ElderlyRefer to adult dosing. The initial and maintenance dosing should be conservative, due to the potential for decreased renal function (monitor). Do not use in patients ≥80 years of age unless normal renal function has been established.

Dosing: Renal ImpairmentDo not use with renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females or abnormal clearance).

Dosing: Hepatic ImpairmentAvoid metformin; liver disease is a risk factor for the development of lactic acidosis during metformin therapy.

Administration: OralAdminister with meals.

Dietary ConsiderationsShould be taken with meals (to decrease GI upset). Take at the same time each day. Dietary modification based on ADA recommendations is a part of therapy. Monitor for signs and symptoms of vitamin B_{12} and/or folic acid deficiency; supplementation may be required.

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to sitagliptin, metformin, or any component of the formulation; renal disease or renal dysfunction (serum creatinine ≥1.5 mg/dL in males or ≥1.4 mg/dL in females, or abnormal creatinine clearance which may also result from conditions such as cardiovascular collapse, acute myocardial infarction, and septicemia); acute or chronic metabolic acidosis including diabetic ketoacidosis (with or without coma).

Warnings/Precautions

Boxed warnings:

- Lactic acidosis: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Hypersensitivity reactions: Rare hypersensitivity reactions (including anaphylaxis, angioedema and/or severe dermatologic reactions, such as Stevens-Johnson syndrome) have been reported in postmarketing surveillance; discontinue if signs/symptoms of hypersensitivity reactions occur. Events have generally been noted within the first 3 months of therapy, and may occur with the initial dose.

- Lactic acidosis: **[U.S. Boxed Warning]: Lactic acidosis is a rare, but potentially severe consequence of therapy with metformin.** Lactic acidosis should be suspected in any patient with diabetes receiving metformin with evidence of acidosis but without evidence of ketoacidosis. Discontinue metformin in clinical situations predisposing to hypoxemia, including conditions such as cardiovascular collapse, respiratory failure, acute myocardial infarction, acute congestive heart failure, and septicemia. The risk of accumulation and lactic acidosis increases with the degree of impairment of renal function.

Disease-related concerns:

- Diabetes mellitus (type 1): Not indicated for use in patients with insulin-dependent diabetes mellitus (IDDM) (type 1)

- Heart failure: Use with caution in patients with congestive heart failure requiring pharmacologic management, particularly in patients with unstable acute heart failure; risk of lactic acidosis may be increased secondary to hypoperfusion.

- Hepatic impairment: Avoid metformin use in patients with impaired liver function due to potential for lactic acidosis.

- Renal impairment: Metformin is substantially excreted by the kidney; patients with renal function below the limit of normal for their age should not receive therapy. Use of concomitant medications that may affect renal function (ie, affect tubular secretion) may also affect metformin disposition. Metformin should be withheld in patients with dehydration and/or prerenal azotemia.

- Stress-related states: It may be necessary to discontinue metformin and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Special populations:

- Elderly: Metformin should not be initiated in patients ≥80 years of age unless normal renal function is confirmed.

- Pediatrics: Safety and efficacy of this combination have not been established in children.

Other warnings/precautions:

- Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism.

- Iodinated contrast: Metformin therapy should be temporarily discontinued prior to or at the time of intravascular administration of iodinated contrast media (potential for acute alteration in renal function). Metformin should be withheld for 48 hours after the radiologic study and restarted only after renal function has been confirmed as normal.

- Surgical procedures: Therapy should be suspended for any surgical procedures (resume only after normal intake resumed and normal renal function is verified).

Geriatric Considerations Sitagliptin has not been studied exclusively in the elderly. The manufacturer reports that 725 out of 3884 patients in clinical trials were >65 years of age (only 61 were ≥75 years), with no difference in safety or efficacy compared to younger patients. Limited data suggest that metformin's total body clearance may be decreased and AUC and half-life increased in elderly patients; presumably due to decreased renal clearance. Metformin has been well tolerated by the elderly but lower doses and frequent monitoring are recommended. In one study of elderly subjects, its effects could not be distinguished from tolbutamide, except for weight loss. The initial and maintenance dosing should be conservative, due to the potential for decreased renal function. Generally, elderly patients should not be titrated to the maximum dose of metformin. Do not use in patients ≥80 years of age unless normal renal function has been established. How “tightly” an elderly patient's blood glucose should be controlled is controversial; however, a fasting blood sugar of <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well they recognize hypoglycemic or hyperglycemic symptoms, and how to respond to them and their other disease states. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk Factor B

Pregnancy Considerations

Reproduction studies have not been conducted with this combination. Adverse events were not observed in animal studies of the individual agents; therefore, sitagliptin/metformin is classified as pregnancy category B. See individual agents. Health professionals are encouraged to report any prenatal exposure to Janumet™ by contacting Merck’s pregnancy registry (1-800-986-8999).

Lactation

Sitagliptin: Execretion in breast milk unknown/use caution

Metformin: Enters breast milk

Breast-Feeding Considerations See individual agents.

Pregnancy & Lactation, In-Depth

- MetFORMIN in Pregnancy & Lactation
- SitaGLIPtin in Pregnancy & Lactation

Adverse Reactions See individual agents.

Drug Interactions

Cephalexin: May increase the serum concentration of MetFORMIN. *Risk C: Monitor therapy*

Cimetidine: May decrease the excretion of MetFORMIN. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Iodinated Contrast Agents: May enhance the adverse/toxic effect of MetFORMIN. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis. *Risk D: Consider therapy modification*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsSee individual agents.
Monitoring ParametersHgb A_{1c} and serum glucose, hematologic parameters (eg, hemoglobin/hematocrit, red blood cell indices); hepatic function, renal function; vitamin B_{12} and folate (if megaloblastic anemia is suspected)
Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringSee individual agents.
Monitoring: Lab TestsHgb A_{1c} and serum glucose, hematologic parameters (eg, hemoglobin/hematocrit, red blood cell indices); hepatic function, renal function; vitamin B_{12} and folate (if megaloblastic anemia is suspected)
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Janumet™:

50/500: Sitagliptin 50 mg and metformin hydrochloride 500 mg

50/1000: Sitagliptin 50 mg and metformin hydrochloride 1000 mg

Generic AvailableNo
ManufacturerMerck
Pricing: U.S. (www.drugstore.com)

Tablets (Janumet)

50-500 mg (60): $184.25

50-1000 mg (60): $183.19

Mechanism of ActionSitagliptin inhibits dipeptidyl peptidase IV (DPP-IV) enzymes resulting in prolonged active incretin levels. Incretin hormones [eg, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)] regulate glucose homeostasis by increasing insulin synthesis and release from pancreatic beta cells and decreasing glucagon secretion from pancreatic alpha cells. Decreased glucagon secretion results in decreased hepatic glucose production. Under normal physiologic circumstances, incretin hormones are released by the intestine throughout the day and levels are increased in response to a meal; incretin hormones are rapidly inactivated by DPP-IV enzymes.

Metformin decreases hepatic glucose production, decreasing intestinal absorption of glucose, and improves insulin sensitivity (increases peripheral glucose uptake and utilization).

Pharmacodynamics/KineticsSee individual agents.
Related Information

- Diabetes Mellitus Management, Adults

Dental Health: Effects on Dental TreatmentSitagliptin- and metformin-dependent patients with diabetes (noninsulin dependent, Type 2) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness
Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concurrent use with lithium, carbamazepine, valproic acid, and SSRIs may produce additive effects.
Index TermsMetformin and Sitagliptin; Sitagliptin Phosphate and Metformin Hydrochloride
References

American Diabetes Association, “Standards of Medical Care in Diabetes Mellitus -- 2009,” *Diabetes Care*, 2009, 32(Suppl 1):13-61.[PubMed 19118286]

SitaGLIPtin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Januvia™ may be confused with Jantoven™

SitaGLIPtin may be confused with SUMAtriptan

Pronunciation(sit a GLIP tin)
U.S. Brand NamesJanuvia™
Pharmacologic CategoryAntidiabetic Agent, Dipeptidyl Peptidase IV (DPP-IV) Inhibitor
Use: Labeled Indications

U.S. labeling: Management of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as an adjunct to diet and exercise as monotherapy or in combination therapy with other antidiabetic agents

Canadian labeling: Management of NIDDM in combination with metformin therapy, diet, and exercise. **Note:** Use as monotherapy is not approved in Canadian labeling.

Dosing: Adults **Type 2 diabetes:** Oral: 100 mg once daily

Concomitant use with sulfonylureas: Reduced dose of sulfonylurea may be needed.

Dosing: Renal Impairment

Cl_{cr} ≥50 mL/minute: No adjustment required

Cl_{cr} ≥30 to <50 mL/minute: 50 mg once daily

S_{cr}: Males: >1.7 to ≤3.0 mg/dL; Females: >1.5 to ≤2.5 mg/dL: 50 mg once daily

Cl_{cr}<30 mL/minute: 25 mg once daily

S_{cr}: Males: >3.0 mg/dL; Females: >2.5 mg/dL: 25 mg once daily

ESRD requiring hemodialysis or peritoneal dialysis: 25 mg once daily; administered without regard to timing of hemodialysis

Dosing: Hepatic Impairment

Mild-to-moderate impairment (Child-Pugh score 7-9): No dosage adjustment required

Severe impairment (Child-Pugh score >9): Not studied

Calculations

- Creatinine Clearance: Adults

Administration: Oral May be administered with or without food.
Dietary Considerations May be taken with or without food.
Storage Store at 20°C to 25°C (68°F to 77°F).
Contraindications Serious hypersensitivity (eg, anaphylaxis, angioedema) or any component of the formulation; type 1 diabetes mellitus (insulin dependent, IDDM), diabetic ketoacidosis
Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Rare hypersensitivity reactions, including anaphylaxis, angioedema, and/or severe dermatologic reactions such as Stevens-Johnson syndrome, have been reported in postmarketing surveillance; discontinue if signs/symptoms of hypersensitivity reactions occur. Events have generally been noted within the first 3 months of therapy, and may occur with the initial dose.

Disease-related concerns:

- Renal impairment: Use with caution in patients with moderate-to-severe renal dysfunction and end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis; dosing adjustment required.

Concurrent drug therapy issues:

- Sulfonylureas: Use caution when used in conjunction with sulfonylureas; risk of hypoglycemia is increased. Monitor blood glucose closely; dosage adjustments of the sulfonylurea may be necessary.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

Geriatric ConsiderationsSitagliptin has not been studied exclusively in the elderly. The manufacturer reports that 725 out of 3884 patients in clinical trials were >65 years (only 61 were age 75 years and older), with no difference in safety or efficacy compared to younger patients. How “tightly” a geriatric patient's blood glucose should be controlled is controversial; however, a fasting blood sugar of <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well they recognize hypoglycemic or hyperglycemic symptoms, and how to respond to them and their other disease states. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events have not been observed in animal reproduction studies; therefore, sitagliptan is classified as pregnancy category B. There are no adequate and well controlled studies in pregnant women. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy. Health professionals are encouraged to report any prenatal exposure to sitagliptin by contacting Merck’s pregnancy registry (1-800-986-8999).

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if sitagliptin is excreted in breast milk. The manufacturer recommends that caution be used if administered to breast-feeding women.

Pregnancy & Lactation, In-Depth

- SitaGLIPtin in Pregnancy & Lactation

Adverse Reactions

1% to 10%:

Gastrointestinal: Diarrhea (3%), abdominal pain (2%), nausea (1%)

Respiratory: Nasopharyngitis (5%)

Postmarketing and/or case reports: Anaphylaxis, angioedema, exfoliative dermatitis, hypoglycemia (risk increased in conjunction with sulfonylureas), hypersensitivity, liver enzymes increased, rash, serum creatinine increased, Stevens-Johnson syndrome, urticaria, white blood cells increased

Metabolism/Transport Effects**Substrate** (minor) of CYP2C8, 3A4

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersHgb A_{1C} and serum glucose; renal function prior to initiation and periodically during treatment.

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringUse with caution in presence of moderate-to-severe renal disease. Assess for potential adverse interactions with any other prescriptions, OTC medications, or herbal products patient may be taking (eg, sulfonylureas or anything else that may affect glucose levels). Evaluate results of laboratory tests and renal function prior to beginning treatment and regularly thereafter. Refer patient to diabetic educator for diabetic education if necessary. Teach patient correct use, possible side effects/appropriate interventions, and adverse symptoms to report (rare hypersensitivity reactions have been reported).

Monitoring: Lab TestsHgb A_{1C} and serum glucose; renal function prior to initiation and periodically during treatment.

Patient EducationThis medication will not cure diabetes and may be prescribed in conjunction with another antidiabetic medication. Do not take any new prescriptions, OTC medications, or herbal products during therapy unless approved by prescriber. Take as directed; may be taken with or without food. It is important to follow dietary and lifestyle recommendations and glucose monitoring instructions of prescriber or diabetic educator. You will be instructed in signs of hyper- or hypoglycemia; always carry a source of glucose with you in event of hypoglycemia. You may experience mild headache, upper respiratory infection, stuffy or runny nose, sore throat, or diarrhea when beginning treatment. Notify prescriber immediately of any hypersensitivity reaction (difficulty breathing, chest pain, difficulty swallowing, swelling of mouth, blistering or erosion of skin, or oral membranes); or other persistent and unresolved adverse effects. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Januvia™: 25 mg, 50 mg, 100 mg

Generic AvailableNo

ManufacturerMerck

Pricing: U.S. (www.drugstore.com)

Tablets (Januvia)

100 mg (30): $181.09

Mechanism of ActionSitagliptin inhibits dipeptidyl peptidase IV (DPP-IV) enzyme resulting in prolonged active incretin levels. Incretin hormones (eg, glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]) regulate glucose homeostasis by increasing insulin synthesis and release from pancreatic beta cells and decreasing glucagon secretion from pancreatic alpha cells. Decreased glucagon secretion results in decreased hepatic glucose production. Under normal physiologic circumstances, incretin hormones are released by the intestine throughout the day and levels are increased in response to a meal; incretin hormones are rapidly inactivated by the DPP-IV enzyme.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: ~198 L

Protein binding: 38%

Metabolism: Not extensively metabolized; minor metabolism via CYP3A4 and 2C8 to metabolites (inactive) suggested by *in vitro* studies

Bioavailability: ~87%

Half-life elimination: 12 hours

Time to peak, plasma: 1-4 hours

Excretion: Urine 87% (79% as unchanged drug, 16% as metabolites); feces 13%

Related Information

- Diabetes Mellitus Management, Adults

Dental Health: Effects on Dental TreatmentSitagliptin-dependent patients with diabetes should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay produce GI side effects; concomitant use with SSRIs, carbamazepine, valproic acid, and lithium may produce additive effects

Index TermsMK-0431; Sitagliptin Phosphate

References

American Diabetes Association, “Standards of Medical Care in Diabetes Mellitus -- 2009,” *Diabetes Care*, 2009, 32(Suppl 1):13-61.[PubMed 19118286]

International Brand NamesJanuvia (AR, BB, BE, BM, BS, BZ, CH, CN, CO, CZ, DE, DK, EE, GB, GY, HK, IE, IL, JM, KP, MX, MY, NL, NO, NZ, PE, PH, SE, SG, SR, TH, TT, TW)

Sitaxsentan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(sye TACKS en tan)
Canadian Brand NamesThelin™
Pharmacologic CategoryEndothelin Antagonist; Vasodilator
Use: Labeled IndicationsTreatment of primary pulmonary arterial hypertension (PAH) or pulmonary hypertension secondary to connective tissue disease, in World Health Organization (WHO) class III patients unresponsive to conventional therapy; treatment of PAH in WHO class II patients who are unresponsive to conventional therapy and have no alternative treatment options
Dosing: Adults **Pulmonary arterial hypertension:** Oral: 100 mg once daily. (**Note:** Doses above 100 mg/day are not recommended; higher doses have not been shown to provide additional benefit and may increase risk of hepatic toxicity).
Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo adjustment required.
Dosing: Adjustment for ToxicityDosage modifications based on transaminase elevation:

AST/ALT >3 but ≤8 times ULN: Confirm with additional test; if confirmed, interrupt treatment. Monitor transaminase levels at least every 2 weeks until levels are <3 times ULN. Reinitiate treatment as appropriate with return to pretreatment values and with more frequent checks of transaminase levels (3 days after restarting therapy and every 2 weeks thereafter).

AST/ALT >8 times ULN: Stop treatment and do not reintroduce.

Note: If any elevation, regardless of degree, is accompanied by clinical symptoms of hepatic injury (unusual fatigue, nausea, vomiting, abdominal pain, fever, or jaundice) or a serum bilirubin >2 times ULN, treatment should be stopped and not reintroduced.

Administration: OralAdminister with or without food.
Dietary ConsiderationsMay be taken without regard to meals.
StorageStore at 15°C to 25°C (59°F to 77°F). Protect from moisture.
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to sitaxsentan or any component of the formulation; concurrent use with cyclosporine; prior hepatic impairment (mild-to-severe, Child-Pugh class A-C); elevated AST/ALT >3 times upper limit of normal (ULN); breast-feeding; pregnancy
Warnings/Precautions

Boxed warnings:

- Cyclosporine: See “Concurrent drug therapy issues” below.
- Hepatic toxicity: See “Concerns related to adverse effects” below.
- Warfarin: See “Concurrent drug therapy issues” below.

Concerns related to adverse effects:

- Hematologic changes: A reduction in hematocrit (Hct)/hemoglobin (Hgb) may be observed within the first few weeks of therapy with subsequent stabilization of levels observed by week four of therapy. Hgb reductions >15% have been observed in some patients. Obtain baseline Hgb level. After initiating therapy, measure Hgb at 1 month, 3 months, and every 3 months thereafter. Patients with significant decreases in Hgb require evaluation for the cause and appropriate treatment.
- Hepatic toxicity: **[Canadian Boxed Warning]: Use has been associated with reversible, dose-dependent transaminase (ALT or AST) elevations (observe with doses ≥300 mg/day while incidence less than placebo with 100 mg/day). Increased bilirubin levels may be observed as well. Mild-to-severe hepatitis (including one fatality) has been reported with use.** Obtain transaminase levels prior to starting therapy and monthly thereafter for the duration of treatment. Interrupt therapy if transaminases >3 times ULN. Permanently discontinue therapy with transaminase levels >8 times ULN; elevated transaminases accompanied by symptoms of hepatic injury (unusual fatigue, jaundice, nausea, vomiting, abdominal pain, and/or fever); or elevated serum bilirubin >2 times ULN.

Disease-related concerns:

- Cardiovascular disease: Initiate therapy with caution in patients with systemic systolic blood pressure (SBP) <85 mm Hg.

Concurrent drug therapy issues:

- Cyclosporine: **[Canadian Boxed Warning]: Concurrent use of sitaxsentan with cyclosporine is contraindicated.**
- Warfarin: **[Canadian Boxed Warning]: A reduction in warfarin dosing may be necessary when used concurrently with sitaxsentan due to increased risk of prolonged PT/INR.**

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

Geriatric ConsiderationsNo specific data for use in elderly to date. Follow adult dosing and monitor LFTs (see Montoring Parameters).

Pregnancy ConsiderationsThe use of sitaxsentan is contraindicated in pregnancy. Based on animal studies, sitaxsentan is likely to produce major birth defects if used by pregnant women. Pregnancy must be excluded prior to initiation of therapy and follow-up pregnancy tests should be obtained monthly. Reliable contraceptive methods should be utilized during therapy.

LactationExcretion into breast milk unknown/contraindicated

Adverse Reactions

>10%: Central nervous system: Headache (15%)

1% to 10%:

Cardiovascular: Peripheral edema (9%), flushing (4%)

Central nervous system: Fatigue (3%), insomnia (2%)

Endocrine & metabolic: Menorrhagia (1%)

Gastrointestinal: Nausea (7%), constipation (3%), vomiting (3%), dyspepsia (2%), upper abdominal pain (2%), bleeding gums (1%)

Genitourinary: Vaginal hemorrhage (1%)

Hematologic: Hemoglobin decreased by >15% (dose related; 7%), INR increased (6%), PT prolonged (5%), hematoma (1%), hematocrit decreased (dose related)

Hepatic: ALT increased (2% to 3%, occurrence less then placebo), AST increased (2% to 3%, occurrence less then placebo)

Neuromuscular & skeletal: Muscle cramping (2%)

Renal: Hematuria (1%)

Respiratory: Nasal congestion (9%), epistaxis (up to 8%), hemoptysis (2%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Abortifacient, agitation, angina pectoris, anorexia, aPTT prolonged, ascites, ataxia, atrial flutter, AV block (first degree), bicarbonate decreased, bradycardia, cardiac murmur, CHF, cholelithiasis, cholecystitis, cholestasis, colitis, conjunctival hemorrhage, conjunctivitis, creatine phosphokinase increased, creatinine increased, deafness, ear pain, ECG QT prolonged, eosinophilia, eye edema, gastrointestinal hemorrhage, gingivitis, goiter, hepatic failure, hepatitis, hepatomegaly, hyperbilirubinemia, hypercholesterolemia, hyperglycemia, hyper-/hypokalemia, hyper-/hypotension, hypernatremia, hypersensitivity, hypocalcemia, hypoxia, ischemic stroke, jaundice, lacrimation increased, lactate dehydrogenase increased, lactic acidosis, leukopenia, lymphoma, MI, migraine, multiorgan failure, myeloproliferative disorder, orthostatic hypotension, pancreatitis acute, pancytopenia, pericardial effusion, peptic ulcer, phosphorous increased, photophobia, polydipsia, pulmonary embolism, rash, respiratory failure, seizure, stomatitis, supraventricular tachycardia, systemic lupus erythematosus, tachycardia, tongue discoloration, ventricular tachycardia, thrombocytopenia, tinnitus, tremor, ventricular premature contraction, vertigo, visual disturbance, xerostomia

Metabolism/Transport Effects**Substrate** of CYP3A4/5 (minor), 2C9 (minor); **Inhibits** CYP2C9 (strong), 2C19 (strong), 3A4/5 (moderate)

Drug Interactions

CycloSPORINE: May increase the serum concentration of Sitaxsentan. *Risk X: Avoid combination*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Warfarin: Sitaxsentan may increase the serum concentration of Warfarin. *Risk D: Consider therapy modification*

Monitoring ParametersSerum transaminase (AST and ALT) and bilirubin should be determined prior to the initiation of therapy and at monthly intervals thereafter. Monitor for clinical signs and symptoms of liver injury (eg, abdominal pain, fatigue, fever, jaundice, nausea, vomiting). Interrupt therapy if transaminases >3 times ULN and ≤8 times ULN. Monitor levels every 2 weeks until they are <3 times ULN. Therapy may be resumed with more frequent monitoring of levels. Discontinue therapy with transaminase levels >8 times ULN and in patients with elevated transaminases with accompanying symptoms of hepatic injury, or bilirubin >2 times ULN.

Hemoglobin and hematocrit should be measured at baseline, 1 month, 3 months, and every 3 months thereafter (levels generally stabilize within 4 weeks from the initiation of therapy). Obtain baseline blood pressure and initiate therapy with caution with SBP <85 mm Hg. A woman of childbearing potential must have a negative pregnancy test prior to the initiation of therapy and monthly thereafter.

Nursing: Physical Assessment/MonitoringMonitor blood pressure at the beginning of therapy and periodically thereafter. Monitor laboratory tests, adverse reactions, and therapeutic response. Assess other prescription and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use, side effects, the need for careful contraception, and symptoms to report.

Monitoring: Lab TestsSerum transaminase (AST and ALT) and bilirubin should be determined prior to the initiation of therapy and at monthly intervals thereafter. Monitor for clinical signs and symptoms of liver injury (eg, abdominal pain, fatigue, fever, jaundice, nausea, vomiting). Interrupt therapy if transaminases >3 times ULN and ≤8 times ULN. Monitor levels every 2 weeks until they are <3 times ULN. Therapy may be resumed with more frequent monitoring of levels. Discontinue therapy with transaminase levels >8 times ULN and in patients with elevated transaminases with accompanying symptoms of hepatic injury, or bilirubin >2 times ULN.

Hemoglobin and hematocrit should be measured at baseline, 1 month, 3 months, and every 3 months thereafter (levels generally stabilize within 4 weeks from the initiation of therapy). Obtain baseline blood pressure and initiate therapy with caution with SBP <85 mm Hg. A woman of childbearing potential must have a negative pregnancy test prior to the initiation of therapy and monthly thereafter.

Patient EducationMay cause headache, nausea, nasal congestion, nose bleeds, or peripheral edema. Report increase in shortness of breath, unexplained weight gain >3 pounds per week, unusual fatigue, jaundice, nausea, vomiting, abdominal pain, or fever. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. If menses is missed, contact prescriber immediately. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. CAN = Canadian brand name

Tablet:

Thelin™ [CAN]: 100 mg [contains lactose; not available in U.S.]

Generic AvailableNo

ManufacturerEncysive Canada Inc

Mechanism of ActionSitaxsentan is a selective antagonist of the A subtype of endothelin-1 receptors (ETA) located in pulmonary smooth muscle. Stimulation of these receptors by endogenous endothelin-1 causes vasoconstriction, thus worsening symptoms of PAH. Sitaxsentan exhibits 6500-fold greater selectivity for the ET_A over the ET_B subtype, the latter of which predominates on vascular endothelial cells. Thus, preferential antagonism of ET_A reduces vasoconstriction, without compromising the vasodilatory/antiproliferative actions mediated through endothelin-1 binding to the ET_B subtype.

Pharmacodynamics/Kinetics

Absorption: Rapid

Protein binding: >99% (primarily albumin)

Metabolism: Hepatic via CYP2C9 and 3A4 into 1,3 keto and 1-keto-2-hydroxy metabolites (metabolites have minimal activity on ET_A receptor, not active on ET_B receptor)

Bioavailability: >90%

Half-life elimination: 10 hours

Time to peak, plasma: 1-4 hours

Excretion: Urine (50% to 60%, 1% as unchanged drug); feces

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Bleeding gums has been reported.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index TermsSitaxsentan Sodium

References

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International Brand NamesThelin (BE, CZ, DK, EE, FR, GB, NO, SE)

Smallpox Vaccine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(SMAL poks vak SEEN)

U.S. Brand NamesACAM2000™

Pharmacologic CategoryVaccine

Use: Labeled IndicationsActive immunization against vaccinia virus, the causative agent of smallpox in persons determined to be at risk for smallpox infection. The ACIP recommends vaccination of laboratory workers at risk of exposure from cultures or contaminated animals which may be a source of vaccinia or related Orthopoxviruses capable of causing infections in humans (monkeypox, cowpox, or variola). The ACIP also recommends that consideration be given for vaccination in healthcare workers having contact with clinical specimens, contaminated material, or patients receiving vaccinia or recombinant vaccinia viruses. ACIP recommends revaccination every 10 years. The Armed Forces recommend vaccination of certain personnel categories. Recommendations for use in response to bioterrorism are regularly updated by the CDC, and may be found at www.cdc.gov.

Dosing: AdultsNot for I.M., I.V., or SubQ injection: Vaccination by scarification (multiple-puncture technique) only: **Note:** A trace of blood should appear at vaccination site after 15-20 seconds; if no trace of blood is visible, an additional 3 insertions should be made using the same needle, without reinserting the needle into the vaccine bottle.

ACAM2000™:

Primary vaccination and revaccination: Use a single drop of vaccine suspension and 15 needle punctures (using the same bifurcated needle) into the superficial skin

Note: According to the manufacturer, revaccination is recommended every 3 years for patients at a continued high risk for smallpox infection. This recommendation differs from the current ACIP recommendations for routine nonemergency smallpox revaccination. Additional information can be obtained from the Department of Defense and the CDC.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥12 months in emergency conditions only: Refer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment required.

Administration: OtherVaccination should only be performed by healthcare providers trained in the safe and efficacious administration of the smallpox vaccine via the percutaneous route. Using a bifurcated needle, 1 drop of vaccine is introduced into the superficial layers of the skin using a multiple-puncture technique. The skin over the insertion of the deltoid muscle or the posterior aspect of the arm over the triceps are the preferred sites for vaccination.

A single-use bifurcated needle should be dipped carefully into the reconstituted vaccine (following removal of rubber stopper). Visually confirm that the needle picks up a drop of vaccine solution. Deposit the drop of vaccine onto clean, dry skin at the vaccination site. If alcohol is used to clean the skin, allow site to dry completely prior to administration to prevent the inactivation of the vaccine by the alcohol. Holding the bifurcated needle perpendicular to the skin, punctures are to be made rapidly within a diameter of about 5 mm into the superficial skin of the vaccination site. The puncture strokes should be vigorous enough to allow a trace of blood to appear after approximately 15-20 seconds. Wipe off any remaining vaccine with dry sterile gauze. Dispose of all materials in a biohazard waste container. All materials must be burned, boiled, or autoclaved. If no evidence of vaccine take is apparent after 7 days, the individual may be vaccinated again.

To prevent transmission of the virus, avoid scratching the vaccination site and cover with gauze; cover gauze with a semipermeable barrier or clothing. Ointment or salves should not be applied to the vaccination site. Good handwashing prevents inadvertent inoculation. Vaccinees should change bandages away from others and launder their own linens separately to prevent transmission.

StorageStore at -15°C to -25°C (5°F to -13°F); prior to reconstitution, may be stored at 2°C to 8°C (36°F to 46°F) for up to 18 months. Following reconstitution, stable for 6 to 8 hours at room temperature of 20°C to 25°C (68°F to 77°F) or for up to 30 days when refrigerated at 2°C to 8°C (36°F to 46°F). The provided diluent should be stored at room temperature of 15°C to 30°C (59°F to 86°F).

ReconstitutionBring to room temperature prior to reconstitution. Using the syringe provided, inject 0.3 mL of provided diluent into the vaccine vial. Swirl gently until the solution becomes a slightly hazy, colorless to straw-colored liquid free from particulate matter; avoid contact between the solution and the rubber stopper.

RestrictionsThe smallpox vaccine is not available for general public use. All supplies are currently owned by the federal government for inclusion in the Strategic National Stockpile. In October 2002, the FDA approved the licensing of the stockpile of smallpox vaccine. This approval allows the vaccine to be distributed and administered in the event of a smallpox attack. The bulk of current supplies have been designated for use by the U.S. military. Additionally, laboratory workers who may be at risk of exposure may require vaccination. Bioterrorism experts have proposed immunization of first responders (including police, fire, and emergency workers), but these plans may not be implemented until additional stocks of vaccine are licensed.

ACAM2000™ is subject to a Risk Minimization Action Plan (RiskMAP) which includes mandatory adverse event reporting, risk management evaluation, and education for both healthcare providers administering the vaccine and patients. Patients who receive the vaccine must be given an FDA-approved medication guide which is available at http://www.fda.gov/cber/label/acam2000pi.pdf.

ContraindicationsThere are no absolute contraindications regarding vaccination of individuals with a high-risk exposure to smallpox. The decision to vaccinate in an emergency situation must be based on a careful analysis of potential benefits and possible risks.

For non-emergent use: Hypersensitivity to the vaccine or any component of the formulation; patients with a history of eczema or patients whose household contacts have acute or chronic exfoliative skin conditions (atopic dermatitis, eczema, burns, impetigo, Varicella zoster, or wounds); history of Darier disease (or if household contact has active disease); immunosuppressed patients and their household contacts, including patients with congenital or acquired immune deficiencies (including HIV, agammaglobulinemia, leukemia, lymphoma, neoplastic disease of the bone marrow or lymphatic system), patients receiving radiation, immunosuppressive drugs, or systemic corticosteroids ≥20 mg/day or ≥2 mg/kg body weight of prednisone for >2 weeks; patients using ocular steroid medications; moderate to severe intercurrent illness; cardiac disease, including previous MI, angina, CHF, cardiomyopathy, chest pain, or shortness of breath requiring medical therapy; pregnancy or suspected pregnancy (including household contacts of pregnant women); breast-feeding.

Warnings/Precautions

Boxed warnings:

- Altered immunocompetence: See “Special populations” below.
- Cardiovascular disease: See “Disease-related concerns” below.
- Eczema: See “Disease-related concerns” below.
- Encephalitis: See “Concerns related to adverse effects” below.
- Myopericarditis: See “Concerns related to adverse effects” below.
- Ocular complications: See “Concerns related to adverse effects” below.
- Pediatrics: See “Special populations” below.
- Pregnancy: See “Special populations” below.
- Skin and systemic reactions: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Encephalitis: **[U.S. Boxed Warning]: Following vaccination, encephalitis, encephalomyelitis, and encephalopathy have been observed.**
- Myopericarditis: **[U.S. Boxed Warning]: Following vaccination, acute myopericarditis and/or pericarditis have been observed.**
- Ocular complications: [**U.S. Boxed Warning]: Following vaccination, accidental infection of the eye may occur resulting in keratitis, corneal scarring, and blindness. Patients using topical steroids may be at an increased risk for ocular vaccinia.**
- Skin and systemic reactions: **[U.S. Boxed Warning]: Following vaccination, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, and erythema multiforme major (including Stevens-Johnson syndrome) have been observed.**

Disease-related concerns:

- Cardiovascular disease: **[U.S. Boxed Warning]: Patients with cardiovascular disease and patients at risk for cardiovascular disease (eg, hypertension, hyperlipidemia, diabetes, and family history) may be at an increased risk for severe adverse reactions;** these patients should not be vaccinated in nonemergency situations.
- Eczema: **[U.S. Boxed Warning]: Patients with eczema of any type/severity may be at an increased risk for severe skin infections;** these patients should not be vaccinated in nonemergency situations.

Special populations:

- Altered immunocompetence: **[U.S. Boxed Warning]: Immunocompromised patients may be at an increased risk for progressive vaccinia;** these patients should not be vaccinated in nonemergency situations.
- Elderly: Safety and efficacy have not been established in patients ≥65 years of age.
- Pediatrics: **[U.S. Boxed Warning]: Infants <12 months of age may be at increased risk for severe adverse reactions;** vaccine is not recommended for use in infants <12 months of age (emergency situations) or in pediatric patients <18 years of age (nonemergency situations).
- Pregnancy: **[U.S. Boxed Warning]: Pregnant women should not be vaccinated in nonemergency situations.***In utero* transmission of virus has been observed. Pregnant women should be warned about the possibility of inadvertent transmission of vaccinia virus from others who have recently been vaccinated.

Dosage form specific issues:

- Antibiotics: Some dosage forms may contain chlortetracycline, dihydrostreptomycin, neomycin, or polymyxin B.
- Albumin: Some dosage forms may contain human albumin.

Other warnings/precautions:

- Administration: For vaccination by scarification (multiple punctures into superficial layers of the skin) only. **Not for I.M., I.V., or SubQ injection.**

- Appropriate use: The Advisory Committee on Immunization Practices (ACIP) recommends smallpox vaccination of laboratory or healthcare workers at risk of exposure. Recommendations for use in response to bioterrorism are regularly updated by the CDC, and may be found at www.cdc.gov.

- Blood and organ donation: Patients should be advised not to donate blood or organs for 21-30 days following vaccination; contacts who have inadvertently contracted vaccinia should avoid donating blood for 14 days.

- Transmission of virus: Virus may be cultured from vaccination sites until scab separates from lesion. Individuals should be instructed to avoid contact with patients at high risk of transmission/adverse effects, including patients with eczema or immunodeficiency during this time.

Pregnancy Risk FactorD

Pregnancy Considerations**[U.S. Boxed Warning]: Pregnant women should not be vaccinated in nonemergency situations.** Animal reproduction studies have not been conducted. Vaccinia vaccine has not been associated with the development of congenital malformations. On rare occasions, vaccination has been reported to cause fetal infection. Fetal vaccina infection is associated with stillbirth or neonatal mortality. Pregnancy should be avoided for at least 28 days following vaccination. Healthcare providers may enroll pregnant women who were inadvertently vaccinated during pregnancy (or within 42 days prior to conception) in the CDC pregnancy registry by calling 404-639-8253 or 877-554-4625. Military cases should be reported to the Department of Defense.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsNot recommended for use in a breast-feeding woman in a nonemergency situation. Breast-feeding should be interrupted if the vaccine is administered in an emergency situation. Breast-feeding women should take precautions to avoid inadvertent contact with a vaccinee. One case of tertiary transfer to an infant has been reported following secondary transfer to a breast-feeding woman.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967. In addition, clinicians may enroll patients with adverse reactions in the CDC Registry at 877-554-4625. Serious adverse reactions to ACAM2000™ may also be reported to the manufacturer, Acambis Inc, at 866-440-9440.**

>10%:

Central nervous system: Fever (up to 70%; may be ≥102°F in up to 20% of children; frequency in adults may be lower), fatigue (48% to 56%), headache (35% to 51%), malaise (28% to 37%)

Dermatologic: Erythema (22% to 24%); rash (6% to 11% erythematous, folliculitis, papulovesicular, urticarial, nonspecific)

Gastrointestinal: Nausea (10% to 19%), diarrhea (12% to 16%)

Local: Injection site: Pruritus (82% to 92%), erythema (61% to 74%), pain (37% to 67%), edema (28% to 48%)

Neuromuscular & skeletal: Myalgia (27% to 46%), rigors (21% to 23%)

Miscellaneous: Lymph node pain (19% to 57%), feeling hot (20% to 32%), exercise tolerance decreased (8% to 11%), lymphadenopathy (6% to 8%)

1% to 10%:

Gastrointestinal: Constipation (6%), vomiting (3% to 5%)

Neuromuscular & skeletal: Arthralgia, back pain

Respiratory: Dyspnea (3% to 4%)

Frequency not defined: Abdominal pain, blindness, Bell's palsy, cardiomyopathy (nonischemic/dilated), contact dermatitis, corneal scarring, death, dizziness, eczema vaccinatum, encephalitis, encephalomyelitis, encephalopathy, erythema multiforme, generalized vaccinia, Guillain-Barré syndrome, hypersensitivity reactions; inadvertent inoculation at other sites (including autoinoculation to eyelid, face, genitalia, lips, mouth, nose, rectum); ischemic heart disease, keratitis, meningitis, myocarditis, myopericarditis (asymptomatic or symptomatic), ocular vaccinia, paresthesia, pericarditis, photophobia, progressive vaccinia, secondary pyogenic infection, seizure, Stevens-Johnson syndrome, vaccinial skin infection, vertigo

Drug Interactions

Immune Globulins: May diminish the therapeutic effect of Vaccines (Live). *Risk D: Consider therapy modification*

Immunosuppressants: May enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Tuberculin Tests: Vaccines (Live) may diminish the diagnostic effect of Tuberculin Tests. *Risk D: Consider therapy modification*

Varicella Virus Vaccine: Smallpox Vaccine may enhance the adverse/toxic effect of Varicella Virus Vaccine. It may be difficult to determine which vaccine caused skin lesions or other adverse effects. *Risk D: Consider therapy modification*

Test InteractionsRapid plasma regain (RPR) test: Smallpox vaccine may induce false-positive RPR test for syphilis; confirm positive RPR test using a more specific test (eg, FTA assay).

Tuberculin skin (PPD) and blood tests: Smallpox vaccine may diminish the diagnostic utility of tuberculin skin (PPD) and blood tests; avoid skin test for ≥1 month after vaccine to prevent false-negative results.

Monitoring ParametersMonitor vaccination site; inspect after 6-8 days. Evidence of a major reaction (vesicular or pustular lesion or an area of palpable induration surrounding a central lesion) confirms success of vaccination. An equivocal reaction (all responses other than a major reaction) requires revaccination in patients undergoing primary vaccination only (preferably with another vial or vaccine lot, if available). Consult CDC or state or local health department if response to a second vaccination from a different vial or lot is equivocal.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution [purified monkey cell source]:

ACAM2000™: 1-5 x 10^8 plaque-forming units per mL [contains polymyxin B, neomycin (trace amounts) and human albumin; packed with diluent, tuberculin syringes for reconstitution, and 100 bifurcated needles for administration]

Generic AvailableNo

Mechanism of ActionVaccinia virus is similar to the variola (smallpox) virus. By inducing a localized infection with vaccinia virus, immunity to both vaccinia and smallpox is achieved. Vaccination results in viral replication, production of neutralizing antibodies, immunity, and cellular hypersensitivity.

Pharmacodynamics/KineticsOnset of action: Neutralizing antibodies appear 10-13 days after vaccination.

Pharmacotherapy PearlsInitial reaction of the vaccine includes formation of a papule (2-5 days following vaccination). The papule forms a vesicle on day 5 or day 6, which becomes pustular, with surrounding erythema and induration. The maximal area of erythema usually occurs between day 8 and day 10, and crusting of the lesion normally occurs between day 14 and day 21. Formation of a major cutaneous reaction in patients undergoing primary vaccination by day 6-8 is indicative of successful acquisition of protective immunity. In patients previously vaccinated, the major cutaneous reaction typically seen by day 6-8 may be modified and/or reduced; a lack of cutaneous response does not indicate vaccination failure and revaccination is not required in these patients. At the peak of the reaction, systemic symptoms (fever, malaise) and lymphadenopathy may occur. All materials used in vaccination must be burned, boiled, or autoclaved. Vaccination can decrease the rate of severe or fatal smallpox if administered during the first 4 days of exposure.

If vaccination failure occurs, revaccination should be attempted using a different vial or vaccine lot. If the second vaccination (from a different vial or lot) also fails, contact the Centers for Disease Control and Prevention (CDC) at 404-639-3670 and/or the state or local health department prior to administering any additional vaccine.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusFatigue is common; may rarely cause encephalitis and encephalopathy

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsDried Smallpox Vaccine; Live Smallpox Vaccine; Vaccinia Vaccine

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Sodium Acetate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(SOW dee um AS e tate)

Pharmacologic CategoryElectrolyte Supplement, Parenteral

Use: Labeled IndicationsSodium source in large volume I.V. fluids to prevent or correct hyponatremia in patients with restricted intake; used to counter acidosis through conversion to bicarbonate

Dosing: Adults

Note: Sodium acetate is metabolized to bicarbonate on an equimolar basis outside the liver; administer in large volume I.V. fluids as a sodium source. Refer to Sodium Bicarbonate monograph.

Maintenance electrolyte requirements of sodium in parenteral nutrition solutions:

Daily requirements: 3-4 mEq/kg/24 hours or 25-40 mEq/1000 kcal/24 hours

Maximum: 100-150 mEq/24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Maintenance electrolyte requirements of sodium in parenteral nutrition solutions:** I.V.: 3-4 mEq/kg/24 hours

Administration: I.V.Must be diluted prior to I.V. administration; infusion hypertonic solutions (>154 mEq/L) via a central line; maximum rate of administration: 1 mEq/kg/hour

Dietary ConsiderationsSodium and acetate content of 1 g: 7.3 mEq

StorageProtect from light, heat, and freezing.

Compatibility**Incompatible** with acids, acidic salts, alkaloid salts, calcium salts, catecholamines, atropine.

Y-site administration: Compatible: Enalaprilat, esmolol, labetalol, ondansetron.

Compatibility in syringe: Compatible: Cimetidine.

ContraindicationsAlkalosis, hypocalcemia, low sodium diets, edema, cirrhosis

Warnings/Precautions

Concerns related to adverse effects:

- Hypernatremia: Close monitoring of serum sodium concentrations is needed to avoid hypernatremia.

Disease-related concerns:

- Acid/base disorders: Use with caution in patients with acid/base alterations; contains acetate, monitor closely during acid/base correction.
- Edema: Use with caution in edematous patients.
- Heart failure (HF): Use extreme caution in patients with HF; monitor closely for edema.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment; monitor serum sodium concentrations closely.

Dosage form specific issues:

- Aluminum: Solution for injection contains aluminum; use with caution in patients with impaired renal function and in premature infants.

Other warnings/precautions:

- Extravasation: Avoid extravasation.

Pregnancy Risk FactorC

Adverse Reactions1% to 10%:

Cardiovascular: Thrombosis, hypervolemia

Dermatologic: Chemical cellulitis at injection site (extravasation)

Endocrine & metabolic: Hypernatremia, dilution of serum electrolytes, overhydration, hypokalemia, metabolic alkalosis, hypocalcemia

Gastrointestinal: Gastric distension, flatulence

Local: Phlebitis

Respiratory: Pulmonary edema

Miscellaneous: Congestive conditions

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution [concentrate]: 2 mEq/mL (20 mL, 50 mL, 100 mL; 250 mL [DSC]); 4 mEq/mL (50 mL, 100 mL)

Generic AvailableYes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Sodium Bicarbonate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(SOW dee um bye KAR bun ate)

U.S. Brand NamesBrioschi® [OTC]; Neut®

Pharmacologic CategoryAlkalinizing Agent; Antacid; Electrolyte Supplement, Oral; Electrolyte Supplement, Parenteral

Use: Labeled IndicationsManagement of metabolic acidosis; gastric hyperacidity; as an alkalinization agent for the urine; treatment of hyperkalemia; management of overdose of certain drugs, including tricyclic antidepressants and aspirin

Use: Unlabeled/InvestigationalPrevention of contrast-induced nephropathy (CIN)

Dosing: Adults

Cardiac arrest: I.V.: Initial: 1 mEq/kg/dose one time; maintenance: 0.5 mEq/kg/dose every 10 minutes or as indicated by arterial blood gases

Routine use of NaHCO$_3$is not recommended. May be considered in the setting of prolonged cardiac arrest only after adequate alveolar ventilation has been established and effective cardiac compressions. **Note:** In some cardiac arrest situations (eg, metabolic acidosis, hyperkalemia, or tricyclic antidepressant overdose), sodium bicarbonate may be beneficial.

Metabolic acidosis: I.V.: Dosage should be based on the following formula if blood gases and pH measurements are available:

HCO_3^-(mEq) = 0.2 x weight (kg) x base deficit (mEq/L)

Administer $^1/_2$ dose initially, then remaining $^1/_2$ dose over the next 24 hours; monitor pH, serum HCO_3^-, and clinical status

Note: If acid-base status is not available: 2-5 mEq/kg I.V. infusion over 4-8 hours; subsequent doses should be based on patient's acid-base status

Hyperkalemia: I.V.: 50 mEq over 5 minutes (as appropriate, consider methods of enhancing potassium removal/excretion)

Chronic renal failure: Oral: Initiate when plasma HCO_3^- <15 mEq/L Start with 20-36 mEq/day in divided doses, titrate to bicarbonate level of 18-20 mEq/L

Renal tubular acidosis: Oral:

Distal: 0.5-2 mEq/kg/day in 4-5 divided doses

Proximal: Initial: 5-10 mEq/kg/day; maintenance: Increase as required to maintain serum bicarbonate in the normal range

Urine alkalinization: Oral: Initial: 48 mEq (4 g), then 12-24 mEq (1-2 g) every 4 hours; dose should be titrated to desired urinary pH; doses up to 16 g/day (200 mEq) in patients <60 years and 8 g (100 mEq) in patients >60 years

Antacid: Oral: 325 mg to 2 g 1-4 times/day

Prevention of contrast-induced nephropathy (unlabeled use): I.V. infusion: 154 mEq/L sodium bicarbonate in D_5W solution: 3 mL/kg/hour for 1 hour immediately before contrast injection, then 1mL/kg/hour during contrast exposure and for 6 hours after procedure

To prepare solution, remove 154 mL from 1000 mL bag of D_5W; replace with 154 mL of 8.4% sodium bicarbonate; resultant concentration is 154 mEq/L (Merten, 2004); more practically, institutions may remove 150 mL from 1000 mL bag of D_5W and replace with 150 mL of 8.4% sodium bicarbonate; resultant concentration is 150 mEq/L

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Cardiac arrest: I.V.: Infants and Children: 0.5-1 mEq/kg/dose repeated every 10 minutes or as indicated by arterial blood gases; rate of infusion should not exceed 10 mEq/minute; neonates and children <2 years of age should receive 4.2% (0.5 mEq/mL) solution.

Routine use of NaHCO$_3$is not recommended. May be considered in the setting of prolonged cardiac arrest only after adequate alveolar ventilation has been established and effective cardiac compressions. **Note:** In some cardiac arrest situations (eg, metabolic acidosis, hyperkalemia, or tricyclic antidepressant overdose), sodium bicarbonate may be beneficial.

Metabolic acidosis: I.V.: Infants and Children: Dosage should be based on the following formula if blood gases and pH measurements are available:

HCO_3^- (mEq) = 0.3 x weight (kg) x base deficit (mEq/L)

Administer $^1/_2$ dose initially, then remaining $^1/_2$ dose over the next 24 hours; monitor pH, serum HCO_3^-, and clinical status

Note: If acid-base status is not available: Dose for older Children: 2-5 mEq/kg I.V. infusion over 4-8 hours; subsequent doses should be based on patient's acid-base status.

Chronic renal failure: Oral: Children: Initiate when plasma HCO_3^- <15 mEq/L: 1-3 mEq/kg/day

Renal tubular acidosis, distal: Oral: Children: 2-3 mEq/kg/day

Renal tubular acidosis, proximal: Children: Initial: 5-10 mEq/kg/day; maintenance: Increase as required to maintain serum bicarbonate in the normal range

Urine alkalinization: Oral: Children: 1-10 mEq (84-840 mg)/kg/day in divided doses every 4-6 hours; dose should be titrated to desired urinary pH.

Administration: I.V. DetailObserve for extravasation when giving I.V.

pH: 7.0-8.5

Dietary ConsiderationsOral product should be administered 1-3 hours after meals.

Sodium content:

Injection: 50 mL, 8.4% = 1150 mg = 50 mEq; each mL of 8.4% $NaHCO_3$ contains 23 mg sodium; 1 mEq $NaHCO_3$ = 84 mg

Granules: 2.69 g packet or capful = 770 mg sodium

Powder: 30 mEq sodium per $^1/_2$ teaspoon

StorageStore injection at room temperature. Protect from heat and from freezing. Use only clear solutions.

ReconstitutionPrevention of contrast-induced nephropathy (unlabeled use): Remove 154 mL from 1000 mL bag of D_5W; replace with 154 mL of 8.4% sodium bicarbonate; resultant concentration is 154 mEq/L (Merten, 2004); more practically, institutions may remove 150 mL from 1000 mL bag of D_5W and replace with 150 mL of 8.4% sodium bicarbonate; resultant concentration is 150 mEq/L

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, $D_5{}^1/_4$NS, $D_5{}^1/_2$NS, D_5NS, D_5W, $D_{10}W$, $^1/_2$NS, NS; **incompatible** with acids, acidic salts, alkaloid salts, calcium salts, catecholamines, and atropine; **variable stability (consult detailed reference)** in D_5LR, LR, fat emulsion 10%, TPN.

Y-site administration: Compatible: Acyclovir, alatrofloxacin, amifostine, asparaginase, aztreonam, cefepime, ceftriaxone, cladribine, cyclophosphamide, cytarabine, daunorubicin, dexamethasone sodium phosphate, dexchlorpheniramine, docetaxel, doxorubicin, etoposide, famotidine, filgrastim, fludarabine, gatifloxacin, gemcitabine, granisetron, heparin, heparin with hydrocortisone sodium succinate, ifosfamide, indomethacin, insulin (regular), levofloxacin, linezolid, melphalan, mesna, methylprednisolone sodium succinate, milrinone, morphine, paclitaxel, piperacillin/tazobactam, potassium chloride, propofol, remifentanil, tacrolimus, teniposide, thiotepa, tolazoline, vancomycin, vitamin B complex with C. **Incompatible:** Allopurinol, amiodarone, amphotericin B cholesteryl sulfate complex, calcium chloride, doxorubicin liposome, idarubicin, imipenem/cilastatin inamrinone, leucovorin, midazolam, nalbuphine, ondansetron, oxacillin, sargramostim, verapamil, vincristine, vindesine, vinorelbine. **Variable (consult detailed reference):** Ciprofloxacin, cisatracurium, diltiazem, TPN.

Compatibility in syringe: Compatible: Milrinone, pentobarbital. **Incompatible:** Etidocaine, glycopyrrolate, mepivacaine, metoclopramide, thiopental. **Variable (consult detailed reference):** Bupivacaine, chloroprocaine, lidocaine.

Compatibility when admixed: Compatible: Amikacin, aminophylline, amobarbital, amphotericin B, ampicillin, atropine, bretylium, calcium chloride, cefoxitin, ceftazidime, chloramphenicol, chlorothiazide, cimetidine, clindamycin, cytarabine, ergonovine, erythromycin lactobionate, esmolol, fentanyl and droperidol, floxacillin, furosemide, heparin, hyaluronidase, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, kanamycin, lidocaine, mannitol, metaraminol, methotrexate, methyldopate, multivitamins, nafcillin, nalmefene, netilmicin, nizatidine, ofloxacin, oxacillin, oxytocin, phenobarbital, phenylephrine, phenytoin, phytonadione, potassium chloride, prochlorperazine edisylate, thiopental, verapamil. **Incompatible:** Amiodarone, ascorbic acid injection, carboplatin, carmustine, cefotaxime, ciprofloxacin, cisplatin, dobutamine, dopamine, epinephrine, hydromorphone, imipenem/cilastatin, isoproterenol, labetalol, levorphanol, magnesium sulfate, meropenem, morphine, norepinephrine, pentazocine, procaine, streptomycin, succinylcholine, ticarcillin/clavulanate potassium, vitamin B complex with C. **Variable (consult detailed reference):** Calcium chloride, calcium gluconate, corticotropin, meperidine, methylprednisolone sodium succinate, penicillin G potassium, pentobarbital, promazine, vancomycin.

ContraindicationsAlkalosis, hypernatremia, severe pulmonary edema, hypocalcemia, unknown abdominal pain

Warnings/Precautions

Disease-related concerns:

- Cirrhosis: Use with caution in patients with cirrhosis.
- Edema: Use with caution in patients with edema.
- Heart failure: Use with caution in patients with heart failure.
- Peptic ulcer disease: Not to be used in treatment of peptic ulcer disease.
- Renal impairment: Use with caution in patients with renal impairment; may cause sodium retention.

Special populations:

- Elderly: Not the antacid of choice for the elderly because of sodium content and potential for systemic alkalosis.
- Pediatrics: Rapid administration in neonates and children <2 years of age has led to hypernatremia, decreased CSF pressure and intracranial hemorrhage.

Dosage form specific issues:

- Injection: **Use of I.V. $NaHCO_3$should be reserved for documented metabolic acidosis and for hyperkalemia-induced cardiac arrest.** Routine use in cardiac arrest is not recommended. Avoid extravasation, tissue necrosis can occur due to the hypertonicity of $NaHCO_3$.

Geriatric ConsiderationsNot the antacid of choice for the elderly because of sodium content and potential for systemic alkalosis (see maximum daily dose under Dosage).
Pregnancy Risk FactorC
LactationEnters breast milk/compatible
Adverse ReactionsFrequency not defined.

Cardiovascular: Cerebral hemorrhage, CHF (aggravated), edema

Central nervous system: Tetany

Gastrointestinal: Belching, flatulence (with oral), gastric distension

Endocrine & metabolic: Hypernatremia, hyperosmolality, hypocalcemia, hypokalemia, increased affinity of hemoglobin for oxygen-reduced pH in myocardial tissue necrosis when extravasated, intracranial acidosis, metabolic alkalosis, milk-alkali syndrome (especially with renal dysfunction)

Respiratory: Pulmonary edema

Drug Interactions

ACE Inhibitors: Antacids may decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists: Antacids may decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Dipivefrin. *Risk C: Monitor therapy*

Amphetamines: Alkalinizing Agents may decrease the excretion of Amphetamines. *Risk D: Consider therapy modification*

Amphetamines: Antacids may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticonvulsants (Hydantoin): Antacids may decrease the serum concentration of Anticonvulsants (Hydantoin). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Antacids may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Antipsychotic Agents (Phenothiazines): Antacids may decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Atazanavir: Antacids may decrease the absorption of Atazanavir. *Risk D: Consider therapy modification*

Bisacodyl: Antacids may diminish the therapeutic effect of Bisacodyl. Antacids may cause the delayed-release bisacodyl tablets to release drug prior to reaching the large intestine. Gastric irritation and/or cramps may occur. *Risk D: Consider therapy modification*

Cefpodoxime: Antacids may decrease the serum concentration of Cefpodoxime. *Risk C: Monitor therapy*

Cefuroxime: Antacids may decrease the serum concentration of Cefuroxime. *Risk C: Monitor therapy*

Corticosteroids (Oral): Antacids may decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

CycloSPORINE: Antacids may decrease the serum concentration of CycloSPORINE. Specifically when cyclosporine is administered orally. *Risk C: Monitor therapy*

Dabigatran Etexilate: Antacids may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: Antacids may decrease the absorption of Dasatinib. *Risk D: Consider therapy modification*

Delavirdine: Antacids may decrease the absorption of Delavirdine. *Risk D: Consider therapy modification*

Erlotinib: Antacids may decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Iron Salts: Antacids may decrease the absorption of Iron Salts. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Isoniazid: Antacids may decrease the absorption of Isoniazid. *Risk D: Consider therapy modification*

Lithium: Sodium Bicarbonate may increase the excretion of Lithium. *Risk C: Monitor therapy*

Memantine: Sodium Bicarbonate may decrease the excretion of Memantine. *Risk C: Monitor therapy*

Mesalamine: Antacids may diminish the therapeutic effect of Mesalamine. This appears to be formulation-related and specific to the Apriso brand of mesalamine. Management: One specific formulation of mesalamine (i.e., Apriso-brand capsules containing coated granules) should not be administered with antacids. *Risk X: Avoid combination*

Methenamine: Antacids may diminish the therapeutic effect of Methenamine. *Risk D: Consider therapy modification*

Penicillamine: Antacids may decrease the serum concentration of Penicillamine. *Risk D: Consider therapy modification*

Phosphate Supplements: Antacids may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Protease Inhibitors: Antacids may decrease the absorption of Protease Inhibitors. **Exceptions:** Darunavir. *Risk C: Monitor therapy*

QuiNIDine: Antacids may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

Tetracycline Derivatives: Antacids may decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Tocainide: Antacids may increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Trientine: Antacids may decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Concurrent doses with iron may decrease iron absorption.

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. **I.V.:** Monitor therapeutic effectiveness, adverse reactions, and infusion site (if extravasation occurs, elevate extravasation site and apply warm compresses). Monitor for signs of fluid retention. Teach patient adverse symptoms to report. **Oral:** Monitor effectiveness of treatment and adverse response. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationDo not use for chronic gastric acidity. Take as directed. Chew tablets thoroughly and follow with a full glass of water, preferably on an empty stomach (2 hours before or after food). Report CNS effects (eg, irritability, confusion); muscle rigidity or tremors; swelling of feet or ankles; respiratory difficulty; chest pain or palpitations; respiratory changes; or tarry stools. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Granules, for solution, oral [effervescent]:

Brioschi®: 2.69 g/packet (12s) [contains sodium 770 mg/packet; lemon flavor]; 2.69 g/capful (120 g, 240 g) [contains sodium 770 mg/capful; lemon flavor]

Infusion [premixed in water for injection]: 5% (500 mL) [5.95 mEq/10 mL]

Injection, solution:

4.2% (10 mL) [5 mEq/10 mL]

7.5% (50 mL) [8.92 mEq/10 mL]

8.4% (10 mL, 50 mL, 250 mL, 500 mL) [10 mEq/10 mL]

Neut®: 4% (5 mL) [2.4 mEq/5 mL; contains edetate disodium]

Powder: Sodium bicarbonate USP (120 g, 480 g) [contains sodium 30 mEq per $^1/_2$ teaspoon]

Tablet: 325 mg [3.8 mEq]; 650 mg [7.6 mEq]

Generic AvailableYes: Excludes granules

Pricing: U.S. (www.drugstore.com)

Tablets (Sodium Bicarbonate)

650 mg (1000): $20.00

Mechanism of ActionDissociates to provide bicarbonate ion which neutralizes hydrogen ion concentration and raises blood and urinary pH

Pharmacodynamics/Kinetics

Onset of action: Oral: Rapid; I.V.: 15 minutes

Duration: Oral: 8-10 minutes; I.V.: 1-2 hours

Absorption: Oral: Well absorbed

Excretion: Urine (<1%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay decrease serum lithium levels due to increased clearance but overall effect is minimal; does not offer much benefit in lithium overdose; if lithium toxicity is severe, dialysis is the treatment of choice

Cardiovascular Considerations**Prevention of Contrast-Induced Nephropathy:** A prospective, single-center, randomized trial (Merten, 2004) evaluating the efficacy of sodium bicarbonate (154 mEq/L sodium bicarbonate in D_5W) infusion (3 mL/kg/hour for 1 hour before iopamidol contrast and 1 mL/kg/hour for 6 hours after procedure) versus sodium chloride infusion (3 mL/kg/hour for 1 hour before iopamidol contrast and 1 mL/kg/hour for 6 hours after procedure). Both solutions contained 154 mEq/L of sodium. Patients needed a baseline creatinine of >1.1 mg/dL. Contrast-induced nephropathy was defined as an increase in serum creatinine levels of >25% within 2 days of contrast. One hundred and thirty-seven patients were randomized, but 119 patients completed the study. Contrast-induced nephropathy occurred in 8 patients (13.6%) infused with sodium chloride and 1 patient (1.7%) infused with sodium bicarbonate (CI 2.6-21.2%; p = 0.02). No patients developed clinical heart failure or respiratory distress with treatment. All patients had a moderate (11-14 mm Hg) increase in mean arterial pressure after the initial bolus. One patient in the sodium bicarbonate group developed a significant blood pressure increase with the bolus of sodium bicarbonate and required discontinuation of it and diuresis.

Briguori and collegues evaluated three prophylactic regimens (normal saline and acetylcysteine [NAC]; sodium bicarbonate and NAC; normal saline, ascorbic acid, and NAC) in 326 patients with chronic kidney disease (serum creatinine ≥2mg/dL) undergoing coronary and/or peripheral procedures with iodixanol. Saline was given I.V. at 1 mL/kg/hour (0.5 mL/kg/hour for LVEF <40%) for 12 hours before and 12 hours after contrast administration. Sodium bicarbonate administration was similar to that in the Merten trial. The oral NAC dose was 1200 mg twice daily given the day before and the day of contrast administration (4 doses total). The ascorbic acid dose was given I.V. as 3 g 2 hours before the procedure followed by 2 g the night of and the morning after the procedure. The amount of contrast administered and the contrast nephropathy risk scores were similar in each group. Contrast-induced nephropathy (CIN) occurred in 9.9% (11/111 of patients) of saline/NAC group, 2% (2/108 of patients) of bicarbonate/NAC group, and 10.3 %(11/107 of patients) in saline/NAC/ascorbic acid group. The bicarbonate/NAC group had significantly fewer episodes of CIN when compared to saline/NAC group in this patient population. Patients in the bicarbonate group were the only ones to achieve urinary alkalinization.

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: The use of bicarbonate for the treatment of lactic acidosis has not been proven useful. Increased pCO_2 after bicarbonate administration may result in an acute decrease in intracellular pH. Bicarbonate does not improve any hemodynamic parameters resulting in improved cardiovascular function. Many clinicians do not use bicarbonate in the treatment of lactic acidosis regardless of the patient's pH level.

Evidence-Based Information: The 2008 Surviving Sepsis Campaign guidelines recommend avoiding use of sodium bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic academia with pH ≥7.15 (Grade 1B).

Index Terms

Baking Soda; $NaHCO_3$; Sodium Acid Carbonate; Sodium Hydrogen Carbonate

References

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International Brand Names

Betsol "Z" (MX); Natrium bicarbonicum (PL)

Sodium Chloride

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Per JCAHO recommendations, concentrated electrolyte solutions (eg, NaCl >0.9%) should not be available in patient care areas.

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V. formulation >0.9% concentration) among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(SOW dee um KLOR ide)

U.S. Brand Names4-Way® Saline Moisturizing Mist [OTC]; Altachlore [OTC]; Altamist [OTC]; Ayr® Allergy Sinus [OTC]; Ayr® Baby Saline [OTC]; Ayr® Saline No-Drip [OTC]; Ayr® Saline [OTC]; Breathe Free® [OTC]; Deep Sea [OTC]; Entsol® [OTC]; Humist® for Kids [OTC]; Humist® [OTC]; Hyper-Sal™; Little Noses® Saline [OTC]; Little Noses® Stuffy Nose Kit [OTC] ; Muro 128® [OTC]; Mycinaire™ [OTC] [DSC]; Na-Zone® [OTC]; Nasal Moist® Saline [OTC]; Nasal Spray [OTC]; NāSal™ [OTC]; Ocean® for Kids [OTC]; Ocean® [OTC]; Pretz® [OTC]; Saline Mist [OTC]; SalineX® [OTC] [DSC]; Simply Saline® Baby [OTC]; Simply Saline® Nasal Moist® [OTC] ; Simply Saline® [OTC]; Syrex; Wound Wash Saline™ [OTC]

Pharmacologic CategoryElectrolyte Supplement, Parenteral; Genitourinary Irrigant; Irrigant; Lubricant, Ocular; Sodium Salt

Use: Labeled Indications

Parenteral: Restores sodium ion in patients with restricted oral intake (especially hyponatremia states or low salt syndrome). In general, parenteral saline uses:

Bacteriostatic sodium chloride: Dilution or dissolving drugs for I.M., I.V., or SubQ injections

Concentrated sodium chloride: Additive for parenteral fluid therapy

Hypertonic sodium chloride: For severe hyponatremia and hypochloremia

Hypotonic sodium chloride: Hydrating solution

Normal saline: Restores water/sodium losses

Pharmaceutical aid/diluent for infusion of compatible drug additives

Ophthalmic: Reduces corneal edema

Inhalation: Restores moisture to pulmonary system; loosens and thins congestion caused by colds or allergies; diluent for bronchodilator solutions that require dilution before inhalation

Intranasal: Restores moisture to nasal membranes

Irrigation: Wound cleansing, irrigation, and flushing

Use: Unlabeled/InvestigationalTraumatic brain injury (hypertonic sodium chloride)

Dosing: Adults

GU irrigant: Irrigation: 1-3 L/day by intermittent irrigation

Replacement: I.V.: Determined by laboratory determinations mEq

Hyponatremia: Sodium deficiency (mEq/kg) = [% dehydration (L/kg)/100 x 70 (mEq/L)] + [0.6 (L/kg) x (140 - serum sodium) (mEq/L)]

To correct acute, serious hyponatremia: mEq sodium = [desired sodium (mEq/L) - actual sodium (mEq/L)] x [0.6 x wt (kg)]; for acute correction use 125 mEq/L as the desired serum sodium; acutely correct serum sodium in 5 mEq/L/dose increments; more gradual correction in increments of 10 mEq/L/day is indicated in the asymptomatic patient

Traumatic brain injury (unlabeled use): I.V.: Hypertonic saline: **Note:** Dosing may vary among institutions. Some protocols include: 7.5%: 250 mL; 23.5%: 30 mL administered over 30 minutes; 2% to 3% as a continuous infusion (some clinicians may mix with sodium acetate to decrease hyperchloremic acidosis). Adjust according to intracranial pressure, serum sodium and chloride, and acid-base status.

Chloride maintenance electrolyte requirement in parenteral nutrition: 2-4 mEq/kg/24 hours or 25-40 mEq/1000 kcals/24 hours; maximum: 100-150 mEq/24 hours

Sodium maintenance electrolyte requirement in parenteral nutrition: 3-4 mEq/kg/24 hours or 25-40 mEq/1000 kcals/24 hours; maximum: 100-150 mEq/24 hours.

Approximate Deficits of Water and Electrolytes in Moderately Severe Dehydration[1]

Condition	**Water**	**Sodium**

	(mL/kg)	(mEq/kg)
Fasting and thirsting	100-120	5-7
Diarrhea		
isonatremic	100-120	8-10
hypernatremic	100-120	2-4
hyponatremic	100-120	10-12
Pyloric stenosis	100-120	8-10
Diabetic acidosis	100-120	9-10
[1] A **negative** deficit indicates total body **excess** prior to treatment.		
Adapted from Behrman RE, Kleigman RM, Nelson WE, et al, eds, *Nelson Textbook of Pediatrics*, 14th ed, WB Saunders Co, 1992.		

Ophthalmic:

Ointment: Apply once daily or more often

Solution: Instill 1-2 drops into affected eye(s) every 3-4 hours

Bronchodilator diluent: Inhalation: 1-3 sprays (1-3 mL) to dilute bronchodilator solution in nebulizer before administration

Nasal congestion: Intranasal: 2-3 sprays in each nostril as needed

Irrigation: Spray affected area

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Hyponatremia: I.V.: Children: Hypertonic solutions (>0.9%) should only be used for the initial treatment of acute serious symptomatic hyponatremia; maintenance: 3-4 mEq/kg/day; maximum: 100-150 mEq/day; dosage varies widely depending on clinical condition

Replacement: Determined by laboratory determinations mEq

Sodium deficiency (mEq/kg) = [% dehydration (L/kg)/100 x 70 (mEq/L)] + [0.6 (L/kg) x (140 - serum sodium) (mEq/L)]

Children ≥2 years:

Intranasal: Refer to adult dosing.

Irrigation: Refer to adult dosing.

Inhalation: Refer to adult dosing.

Administration: TopicalIrrigation solution: Do not warm >66°C (150°F); not for I.V. use. Wound Wash Saline™: Before use, expel a short stream into air to clear nozzle.
StorageStore injection at room temperature; do not freeze. Protect from heat. Use only clear solutions.
CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4$NS, $D_5{}^1/_2$NS, D_5NS, D_5W, D_{10}W, LR, ${}^1/_2$NS, NS; **variable stability (consult detailed reference)** in fat emulsion 10%, mannitol 20%, mannitol 25%.

Y-site administration: Compatible: Ciprofloxacin.

Compatibility in syringe: Compatible: Cimetidine.

ContraindicationsHypersensitivity to sodium chloride or any component of the formulation; hypertonic uterus, hypernatremia, fluid retention
Warnings/Precautions

Concerns related to adverse effects:

- Sodium toxicity: Is almost exclusively related to how fast a sodium deficit is corrected; both rate and magnitude are extremely important.

Disease-related concerns:

- Cirrhosis: Use with caution in patients with cirrhosis.

- Edema: Use with caution in patients with edema.
- Heart failure: Use with caution in patients with heart failure.
- Hypertension: Use with caution in patients with hypertension.
- Renal impairment: Use with caution in patients with renal impairment; may cause sodium retention.

Dosage form specific issues:

- Bacteriostatic sodium chloride: Do not use bacteriostatic sodium chloride in newborns since benzyl alcohol preservatives have been associated with toxicity.
- Irrigants: For external use only; not for parenteral use. Do not use during electrosurgical procedures. Irrigating fluids may be absorbed into systemic circulation; monitor for fluid or solute overload.
- Wound Wash Saline™: For single-patient use only.

Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined.

Cardiovascular: Congestive conditions

Endocrine & metabolic: Extravasation, hypervolemia, hypernatremia, dilution of serum electrolytes, overhydration, hypokalemia

Local: Thrombosis, phlebitis, extravasation

Respiratory: Pulmonary edema

Drug Interactions

Lithium: Sodium Chloride may increase the excretion of Lithium. *Risk C: Monitor therapy*

Monitoring ParametersSerum sodium, potassium, chloride, and bicarbonate levels; I & O, weight
Reference RangeSerum/plasma sodium levels:

Neonates:

Full-term: 133-142 mEq/L

Premature: 132-140 mEq/L

Children ≥2 months to Adults: 135-145 mEq/L

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol, intranasal [spray; preservative free]:

Entsol®: 3% (100 mL) [chlorofluorocarbon free]

Gel, intranasal:

Ayr® Saline: <0.5% (14 g) [contains soybean oil and aloe]

Entsol®: 3% (20 g) [contains benzalkonium chloride; with aloe and vitamin E]

Simply Saline® Nasal Moist®: 0.65% (30 g) [contains aloe]

Gel, intranasal [spray]:

Ayr® Saline No-Drip: <0.5% (22 mL) [contains benzalkonium chloride, benzyl alcohol, and soybean oil]

Injection, solution: 0.45% (25 mL, 50 mL, 100 mL, 250 mL, 500 mL, 1000 mL); 0.9% (25 mL, 50 mL, 100 mL, 150 mL, 250 mL, 500 mL, 1000 mL, 1 g); 3% (500 mL); 5% (500 mL)

Injection, solution [preservative free]: 0.9% (2 mL, 3 mL, 5 mL, 10 mL, 20 mL, 50 mL, 100 mL)

Injection, solution [I.V. flush]: 0.9% (10 mL)

Injection, solution [I.V. flush; preservative free]: 0.9% (1 mL, 2 mL, 2.5 mL, 3 mL, 5 mL, 10 mL)

Syrex: 0.9% (2.5 mL, 3 mL, 5 mL, 10 mL)

Injection, solution [bacteriostatic]: 0.9% (10 mL, 20 mL, 30 mL)

Injection, solution [concentrate]: 14.6% (40 mL); 23.4% (100 mL, 250 mL)

Injection, solution [concentrate; preservative free]: 14.6% (20 mL, 40 mL); 23.4% (30 mL, 100 mL, 200 mL)

Ointment, ophthalmic: 5% (3.5 g)

Altachlore: 5% (3.5 g)

Ointment, ophthalmic [preservative free]:

Muro 128®: 5% (3.5 g)

Powder for solution, intranasal [preservative free]:

Entsol®: 3% (10.5 g)

Solution for blood processing [not for injection]: 0.9% (3000 mL)

Solution for inhalation [preservative free]: 0.9% (3 mL, 5 mL, 15 mL); 3% (15 mL)

Solution for inhalation [hypertonic; preservative free]: 10% (15 mL)

Solution for inhalation [hypotonic; preservative free]: 0.45% (5 mL)

Solution for injection [I.V. flush; preservative free]: 0.9% (2.5 mL, 5 mL, 10 mL)

Solution for irrigation: 0.45% (2000 mL); 0.9% (250 mL, 500 mL, 1000 mL, 1500 mL, 2000 mL, 3000 mL, 4000 mL, 5000 mL)

Solution for irrigation [preservative free]: 0.45% (1500 mL [DSC]; 2000 mL); 0.9% (250 mL, 500 mL, 1000 mL, 1500 mL, 2000 mL, 3000 mL)

Solution for irrigation [slush solution]: 0.9% (1000 mL)

Solution for nebulization [preservative free]:

Hyper-Sal™: 7% (4 mL)

Solution, intranasal [preservative free]:

Simply Saline®: 3% (44 mL)

Solution, intranasal [drops]:

Ayr® Saline: 0.65% (50 mL) [alcohol free; contains benzalkonium chloride]

NāSal™: 0.65% (15 mL) [alcohol free; contains benzalkonium chloride]

SalineX®: 0.4% (15 mL) [contains benzalkonium chloride] [DSC]

Solution, intranasal [drops, mist, spray]

Humist®: 0.65% (45 mL) [ethanol free]

Humist® for Kids: 0.65% (30 mL) [ethanol free; bubblegum flavor]

Ocean®: 0.65% (45 mL, 473 mL) [gluten free; contains benzalkonium chloride and benzyl alcohol]

Ocean® for Kids: 0.65% (37.5 mL) [alcohol free; contains benzalkonium chloride]

Solution, intranasal [drops, spray]:

Ayr® Baby Saline: 0.65% (30 mL) [ethanol free; contains benzalkonium chloride]

Little Noses® Saline: 0.65% (30 mL) [contains benzalkonium chloride]

Little Noses® Stuffy Nose Kit: 0.65% (15 mL) [contains benzalkonium chloride]

Solution, intranasal [drops, spray, stream]:

Saline Mist: 0.65% (45 mL) [contains benzalkonium chloride] [DSC]

Solution, intranasal [irrigation]:

Pretz®: 0.75% (237 mL, 960 mL) [contains benzalkonium chloride and sodium benzoate; with yerba santa]

Solution, intranasal [mist]:

Ayr® Allergy Sinus: 2.65% (50 mL)

Ayr® Saline: 0.65% (50 mL) [ethanol free; contains benzalkonium chloride]

Entsol®: 3% (30 mL) [contains benzalkonium chloride]

Mycinaire™: 0.65% (30 mL) [contains benzalkonium chloride] [DSC]

Saline Mist: 0.65% (45 mL) [contains benzalkonium chloride]

SalineX®: 0.4% (50 mL) [contains benzalkonium chloride] [DSC]

4-Way® Moisturizing Mist: 0.74% (29.6 mL) [ethanol free; contains benzalkonium chloride and menthol]

Solution, intranasal [mist, preservative free]:

Simply Saline®: 0.9% (44 mL, 90 mL)

Simply Saline® Baby: 0.9% (45 mL)

Solution, intranasal [nasal wash; preservative free]:

Entsol®: 3% (240 mL)

Solution, intranasal [spray]:

Altamist: 0.65% (60 mL) [contains benzalkonium chloride]

Breathe Free®: 0.65% (44.3 mL) [contains benzalkonium chloride]

Deep Sea: 0.65% (45 mL) [contains benzalkonium chloride and benzyl alcohol]

Na-Zone®: 0.65% (60 mL) [contains benzalkonium chloride]

Nasal Moist® Saline: 0.65% (45 mL)

Nasal Spray: 0.65% (45 mL) [contains benzalkonium chloride and benzyl alcohol]

NāSal™: 0.65% (30 mL) [ethanol free; contains benzalkonium chloride and thimerosal]

Solution, intranasal [spray, isotonic, buffered]:

Pretz®: 0.75% (50 mL) [contains benzalkonium chloride and sodium benzoate; with yerba santa]

Solution, ophthalmic: 5% (15 mL)

Solution, ophthalmic [drops]: 5% (15 mL)

Altachlore: 5% (15 mL, 30 mL)

Muro 128®: 2% (15 mL); 5% (15 mL, 30 mL)

Solution, topical [preservative free]:

Wound Wash Saline™: 0.9% (90 mL, 210 mL)

Swab, intranasal:

Ayr® Saline: <0.5% (20) [contains aloe and soybean oil]

Tablet for solution, topical: 1000 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Nebulization (Sodium Chloride)

0.9% (300): $36.99

Ointment (Muro 128)

5% (3.5): $18.34

Solution (Muro 128)

5% (15): $18.34

Solution (Saline Flush)

0.9% (500): $61.55

0.9% (1000): $68.80

Solution (Sodium Chloride)

0.9% (10): $10.99

0.9% (1000): $14.90

Solution (Sodium Chloride (Hypertonic))

5% (15): $13.99

Solution (Sodium Chloride Bacteriostatic)

0.9% (25): $17.99

Mechanism of ActionPrincipal extracellular cation; functions in fluid and electrolyte balance, osmotic pressure control, and water distribution
Pharmacodynamics/Kinetics

Absorption: Oral, I.V.: Rapid

Distribution: Widely distributed

Excretion: Primarily urine; also sweat, tears, saliva

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentSodium chloride intake may decrease serum lithium levels; monitor
Mental Health CommentHyponatremia is associated with neuropsychiatric symptoms; rule out psychogenic polydipsia.
Anesthesia and Critical Care Concerns/Other ConsiderationsAn Australian/New Zealand group recently published results from their evaluation of resuscitation fluid (4% albumin versus normal saline) in a heterogeneous intensive care population (Finfer, 2004). They conducted this multicenter, randomized, double-blind trial to compare the effects of resuscitation fluid on mortality from any cause during the 28-day period after randomization. Patients were eligible for inclusion if the treating clinician judged that fluid resuscitation was required for intravascular fluid depletion as supported by one of the following criteria:

Heart rate >90 bpm

Systolic BP <100 mm Hg

Mean arterial BP <75 mm Hg

Decrease of 40 mm Hg in systolic or mean arterial BP (as compared with baseline)

CVP <10 mm Hg

PCWP <12 mm Hg

Respiratory variation in systolic or mean BP >5 mm Hg

Capillary refill time >1 second

Urine output <0.5 mL/kg for 1 hour

Patients were excluded for a variety of reasons, including ICU transfer following cardiac or liver transplantation surgery, or burn treatment. Almost 7000 patients were randomized; 3497 to albumin and 3500 to saline. Baseline characteristics were similar between the groups, except CVP pressure was slightly higher in the albumin group (9.0 in albumin versus 8.6 in saline). There was no significant mortality difference between groups (726 deaths in albumin group; 729 deaths in saline group). There were no significant differences in secondary endpoints (length of stay in the ICU or hospital, days of mechanical ventilation, and days of renal replacement therapy). Similar outcomes resulted from use of either fluid for resuscitation in this patient population.

The 2008 Surviving Sepsis Campaign guidelines suggest that during the first 6 hours of resuscitation, the goals of sepsis-induced hypoperfusion should include central venous pressure 8-12 mm Hg, mean arterial pressure ≥65 mm Hg, urine output >0.5 mL/kg/hour, central venous (superior vena cava) oxygen saturation ≥70% or mixed venous oxygen saturation ≥65% (Grade 2C).

Management of Intracerebral Hemorrhage (ICH): Rapid identification of patients experiencing ICH is essential and should be considered a medical emergency due to the progressive deterioration, severe clinical deficits, and high mortality and morbidity. Treatment for ICH has evolved rapidly in recent years. According to the 2007 ACC/AHA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults, patients with ICH should be treated in a balanced and graded approach with therapies that reduce intracranial pressure (ICP) (eg, mannitol, hypertonic saline solutions, barbiturate coma, head of bed elevation) (Class IIa recommendation). Direct monitoring of ICP and central perfusion pressure (CPP) may be necessary if patient is treated more aggressively. Treatment of ICH with recombinant factor VIIa (rFVIIa) within the first 3-4 hours after onset to slow progression of bleeding has shown promise; however, at this time it cannot be routinely recommended in all patients experiencing ICH (Class IIb recommendation).

Blood pressure (BP) management in patients who are hypertensive is also of paramount importance in treating ICH. The primary rationale for lowering BP is to prevent further progression of the bleed. This can be accomplished using a number of different pharmacologic treatments (eg, nicardipine, labetalol, nitroprusside). Nitroprusside may increase ICP due to the pronounced vasodilatory actions and as a result may be less preferable. Specific BP targets are not supported by available evidence. The 2007 ACC/AHA Guidelines recommend initiating antihypertensive therapy if the SBP >180 mm Hg or if MAP >130 mm Hg.

Index TermsNaCl; Normal Saline; Salt
References

Barer J, Hill LL, Hill RM, et al, “Fatal Poisoning From Salt Used as an Emetic,” *Am J Dis Child*, 1973, 125:889-90. [PubMed 4708280]

Broderick J, Connolly S, Feldmann E, et al, "Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults: 2007 Update: A Guideline From the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group," *Stroke*, 2007, 38(6):2001-23. Available at http://stroke.ahajournals.org/cgi/content/short/STROKEAHA.107.183689.[PubMed 17478736]

Dellinger RP, Levy MM, Carlet JM, et al, “Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008,” *Intensive Care Med*, 2008, 34(1): 17-60. Available at http://www.survivingsepsis.org/system/files/images/2008_20International_20SSC_20Guidelines_1_.pdf[PubMed 18058085]

Finfer S, Bellomo R, Boyce N, et al, “A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. SAFE Study Investigators,” *N Engl J Med*, 2004, 350(22):2247-56.[PubMed 15163774]

Gresham GS and Mashru MK, “Fatal Poisoning With Sodium Chloride,” *Forensic Sci Int*, 1982, 20:87-8. [PubMed 7095681]

Joint Commission on Accreditation of Healthcare Organizations, “2005 National Patient Safety Goals,” available at http://www.jcaho.org/accredited+organizations/patient+safety/05_npsg_guidelines Last accessed October 15, 2004.

Meadow R, “Nonaccidental Salt Poisoning,” *Arch Dis Child*, 1993, 68(4):448-52. [PubMed 8503665]

Moder KG and Hurley DL, “Fatal Hypernatremia From Exogenous Salt Intake: Report of a Case and Review of the Literature,” *Mayo Clin Proc*, 1990, 65(12):1587-94. [PubMed 2255221]

Smith EJ, and Palevsky S, “Salt Poisoning in a Two-Year-Old Child,” *Am J Emerg Med*, 1990, 8:571-2.[PubMed 2222612]

International Brand NamesChlorek Sodowy 24Na (PL); Hiperton (MX); Inj. natrii chlorati isotonica (PL); Miwana (PL); Natrii chloridum 0,9% solutio pro irrigatione (PL); Natrium chloratum (PL); Oftarinol (PL); Physiodose (PL); Sensitive Eyes Saline Solution (PL); Sodium Chloride (PL); Solnasin (PL)

Sodium Chondroitin Sulfate and Sodium Hyaluronate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(SOW de um kon DROY tin SUL fate & SOW de um hye al yoor ON ate)
U.S. Brand NamesDisCoVisc®; Viscoat®
Pharmacologic CategoryOphthalmic Agent, Viscoelastic
Use: Labeled IndicationsOphthalmic surgical aid in the anterior segment during cataract extraction and intraocular lens implantation
Dosing: Adults**Surgical aid:** Ophthalmic: Carefully introduce (using a 27-gauge cannula) into anterior chamber during surgery
Dosing: ElderlyRefer to adult dosing.
Administration: OtherConsult specific product instructions on preparing ophthalmic device for use and administration by physician during surgery. May inject in the anterior segment of the eye prior to or following delivery of the crystalline lens. Instillation prior to lens delivery provides additional protection to corneal endothelium, protecting it from possible damage arising from surgical instrumentation. May also be used to coat intraocular lens and tips of surgical instruments prior to implantation surgery. May inject additional solution during anterior segment surgery to fully maintain the solution lost during surgery. At the end of surgery, remove solution by thoroughly irrigating and aspirating with a sterile irrigating solution (eg, balanced salt solution).
Storage

Viscoat®: Store at 2°C to 8°C (36°F to 46°F); do not freeze.

DisCoVisc™: Store at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Prior to use, allow product to warm to room temperature (~20-40 minutes).

ContraindicationsHypersensitivity to chondroitin, hyaluronate, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Elevated intraocular pressure: Intraocular pressure may be elevated as a result of pre-existing glaucoma, compromised outflow, and by operative procedures and sequelae.

- Hypersensitivity: Potential risk of hypersensitivity may exist to the use of any biological material.

Dosage form specific issues:

- Latex: Some dosage forms may contain latex.

Other warnings/precautions:

- Appropriate use: Do not overfill the anterior chamber; carefully monitor IOP, especially during the immediate postoperative period. For intraocular use only; serious eye injury may occur if proper assembly using cannula and cannula locking ring are not followed or alternate cannula is used.

Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined: Ocular: Intraocular pressure increased
Drug InteractionsThere are no known significant interactions.
Test InteractionsFalse-negative results for Clinistix® urine test; false-positive results with Clinitest®
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, intraocular:

DisCoVisc®: Sodium chondroitin sulfate ≤4% and sodium hyaluronate ≤1.7% (0.5 mL, 1 mL) [provided in a kit which also contains 27-gauge cannula and cannula locking ring]

Viscoat®: Sodium chondroitin sulfate ≤4% and sodium hyaluronate ≤3% (0.5 mL, 0.75 mL) [packaging contains latex; packaged with 27-gauge cannula and cannula locking ring]

Generic AvailableNo
Mechanism of ActionOphthalmic viscosurgical device which modulates the interactions between adjacent tissues by space creation, tissue stabilization, balancing pressure, and providing protection of the corneal endothelial cells during surgery.
Pharmacodynamics/Kinetics

Absorption: Intravitreous injection: Diffusion occurs slowly

Excretion: By Canal of Schlemm

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms Chondroitin Sulfate and Sodium Hyaluronate; Sodium Hyaluronate and Chondroitin Sulfate

References

Arshinoff SA and Jafari M, “Laboratory Science: New Classification of Ophthalmic Viscosurgical Devices-2005” *J Cataract Refract Surg*, 2005, 31(11):2167-71.[PubMed 16412934]

Sodium Citrate and Citric Acid

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(SOW dee um SIT rate & SI trik AS id)
U.S. Brand NamesBicitra®; Cytra-2; Oracit®; Shohl's Solution (Modified)
Canadian Brand NamesPMS-Dicitrate
Pharmacologic CategoryAlkalinizing Agent, Oral
Use: Labeled IndicationsTreatment of metabolic acidosis; alkalinizing agent in conditions where long-term maintenance of an alkaline urine is desirable
Dosing: Adults**Systemic alkalization:** Oral: 10-30 mL with water after meals and at bedtime
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Systemic alkalization:** Oral: Infants and Children: 2-3 mEq/kg/day in divided doses 3-4 times/day **or** 5-15 mL with water after meals and at bedtime
Administration: OralAdminister after meals. Dilute with 30-90 mL of water to enhance taste. Chilling solution prior to dosing helps to enhance palatability.
Dietary ConsiderationsShould be taken after meals to avoid laxative effect.
StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F); do not freeze. Protect from excessive heat.
ContraindicationsHypersensitivity to sodium citrate, citric acid, or any component of the formulation; severe renal insufficiency; sodium-restricted diet
Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with heart failure or hypertension; contains sodium.
- Edema: Use with caution in patients with peripheral or pulmonary edema; contains sodium.
- Hepatic impairment: Use with caution in patients with hepatic failure; conversion to bicarbonate may be impaired.
- Renal impairment: Use with caution in patients with renal impairment; contains sodium. Contraindicated in patients with severe impairment.
- Severely ill: Use with caution in patients who are severely ill; conversion to bicarbonate may be impaired.
- Shock: Use with caution in patients who are in shock; conversion to bicarbonate may be impaired.

Pregnancy Risk FactorNot established
Pregnancy ConsiderationsUse caution with toxemia of pregnancy.
LactationExcretion in breast milk unknown/compatible
Adverse ReactionsFrequency not defined. Generally well tolerated with normal renal function.

Central nervous system: Tetany

Endocrine & metabolic: Metabolic alkalosis, hyperkalemia

Gastrointestinal: Diarrhea, nausea, vomiting

Drug Interactions

Aluminum Hydroxide: Citric Acid Derivatives may increase the absorption of Aluminum Hydroxide. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringAssess kidney function prior to starting therapy. Monitor cardiac status and serum potassium at beginning of therapy and at regular intervals with long-term therapy. Assess knowledge/teach patient appropriate use, possible side effects, and adverse symptoms to report.
Patient EducationTake as often as directed, after meals, and at least 2 hours before or after any other medications. Dilute with 1-3 oz of water and follow with additional water; chilling solution prior to taking will help to improve taste. You may experience diarrhea or nausea and vomiting; if severe, contact prescriber. Report CNS changes status (eg, irritability, tremors, confusion); swelling of feet or ankles; respiratory difficulty or palpitations; abdominal pain or tarry stools.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. **Note:** Contains sodium 1 mEq/mL and is equivalent to bicarbonate 1 mEq/mL

Solution, oral: Sodium citrate 500 mg and citric acid 334 mg per 5 mL (480 mL)

Bicitra®: Sodium citrate 500 mg and citric acid 334 mg per 5 mL (480 mL) [sugar free; grape flavor]

Cytra-2: Sodium citrate 500 mg and citric acid 334 mg per 5 mL (480 mL) [alcohol free, dye free, sugar free; contains propylene glycol and sodium benzoate; grape flavor]

Oracit®: Sodium citrate 490 mg and citric acid 640 mg per 5 mL (15 mL, 30 mL, 500 mL, 3840 mL)

Shohl's Solution (Modified): Sodium citrate 500 mg and citric acid 300 mg per 5 mL (480 mL) [contains alcohol]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Bicitra)

500-334 mg/5 mL (473): $31.98

Solution (Cytra-2)

500-334 mg/5 mL (473): $14.00

Pharmacodynamics/Kinetics

Metabolism: Oxidized to sodium bicarbonate

Excretion: Urine (<5% as sodium citrate)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentSodium chloride intake may decrease serum lithium levels; monitor

Mental Health CommentAlkalization of the urine may increase toxicity of amphetamine, ephedrine, and pseudoephedrine.

Index TermsModified Shohl's Solution

Sodium Hypochlorite Solution

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(SOW dee um hye poe KLOR ite soe LOO shun)
U.S. Brand NamesDakin's Solution; Di-Dak-Sol
Pharmacologic CategoryDisinfectant, Antibacterial, Topical
Use: Labeled IndicationsTreatment of athlete's foot (0.5%); wound irrigation (0.5%); disinfection of utensils and equipment (5%)
Dosing: Adults**Disinfectant:** Topical: Via irrigation
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricTopical irrigation
Administration: TopicalFor external use only; do **not** ingest.
StorageUse prepared solution within 7 days.
ContraindicationsHypersensitivity to any component of the formulation
Warnings/Precautions

Other warnings/precautions:

â˘ Appropriate use: For external use only; avoid eye or mucous membrane contact; do not use on open wounds.

Pregnancy Risk FactorC
LactationFor external use
Adverse ReactionsFrequency not defined.

Dermatologic: Irritating to skin

Hematologic: Dissolves blood clots, delays clotting

Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringAssess knowledge/teach patient appropriate application and use and adverse symptoms to report.
Patient EducationUse exactly as directed; do not overuse. Avoid contact with eyes. Report worsening of condition or lack of healing. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, topical:

Dakin's: 0.125% (480 mL); 0.25% (480 mL); 0.5% (480 mL, 3840 mL)

Di-Dak-Sol: 0.0125% (480 mL)

Generic AvailableNo
Pharmacotherapy PearlsDakin's solution may hinder wound healing.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsModified Dakin's Solution

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^{131}'; return;">

Sodium Iodide I^{131}

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(SOW dee um EYE oh dide)

U.S. Brand NamesHicon™; Iodotope®

Pharmacologic CategoryAntithyroid Agent; Radiopharmaceutical

Use: Labeled IndicationsFor diagnostic use with the radioactive iodide (RAI) uptake test to evaluate thyroid function; treatment of hyperthyroidism and select cases of thyroid cancer

Dosing: Adults**Note:** Consult manufacturer potency tables when applicable. All doses should be individualized; general ranges are listed here:

Diagnostic procedures: Oral (based on a 70 kg patient):

Thyroid uptake: 0.185–0.555 megabecquerels (5-15 microcuries)

Scintiscanning: 1.85-3.7 megabecquerels (50-100 microcuries)

Localization of extrathyroid metastases: 37 megabecquerels (1000 microcuries)

Treatment: Oral:

Hyperthyroidism: 148-370 megabecquerels (4-10 millicuries)

Thyroid cancer:

Iodotope®: Ablation of normal thyroid tissue: Initial: 1850 megabecquerels (50 millicuries)

Subsequent therapeutic doses: 3700-5550 megabecquerels (100-150 millicuries)

Hicon™: Ablation of normal thyroid tissue: Initial: 1100-3700 megabecquerels (1.1-3.7 gigabecquerels or 30-100 millicuries)

Subsequent metastases ablation: 3700-7400 megabecquerels (3.7-7.4 gigabecquerels or 100-200 millicuries)

Dosing: ElderlyRefer to adult dosing.

Administration: Oral

Hicon™ must be diluted prior to administration. Ensure adequate hydration before and after treatment. Waterproof gloves should be worn while handling and administering sodium iodide I^{131}.

Dietary ConsiderationsSome dietary sources of iodine include cow's milk and dairy products, fish, seaweed, eggs, chocolate, and iodized salt.

StorageStore at controlled room temperature. Products should be adequately shielded.

Hicon™: Prior to use, store solution at 2°C to 25°C (36°F to 77°F). Prepared capsule should be stored in suitable polypropylene container inside a lead pot; use within 7 days of preparation.

ReconstitutionHicon™: Wear waterproof gloves for preparation and handling. Using a shielded syringe, transfer appropriate amount to shielded empty vial. Dilute with purified water containing sodium thiosulfate 0.2% (as reducing agent). Place unopened small capsule (contains dibasic sodium phosphate as absorbing buffer) into bottom half of opened large (empty) capsule; inject appropriate volume of diluted sodium iodide I^{131} into the center of the unopened small capsule, cover and seal with upper half of large capsule. Refer to manufacturer's labeling for additional details.

ContraindicationsHypersensitivity to iodine or any component of the formulation; pre-existing vomiting and diarrhea (treatment); concurrent antithyroid medication (Hicon™); pregnancy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Disease-related concerns:

- Hyperthyroidism/thyrotoxic cardiac disease: May be aggravated by radiation thyroiditis; consider pre- and post-treatment with antithyroid agents and/or beta-blockers.
- Hypochloremia: May increase thyroid uptake of sodium iodide I^{131}.
- Renal impairment: Use with caution in patients with renal impairment; risk of adverse reactions may be increased. Nephrosis may increase thyroid uptake of sodium iodide I^{131}.

Concurrent drug therapy issues:

- Iodine/thyroid medications: Concomitant use of iodine, thyroid, or antithyroid medications may interfere with the uptake of radioiodide; medications should be discontinued for an appropriate time prior to dosing.

Special populations:

- Patients <30 years of age: Use is not generally recommended for treatment of hyperthyroidism in patients <30 years of age.

Dosage form specific issues:

- Sodium bisulfite: Some dosage forms may contain sodium bisulfite which may cause allergic reactions in some individuals.

Other warnings/precautions:

- Appropriate use: Patients should be adequately hydrated prior to dosing.

- Experienced staff: Should only be used by nuclear physicians and/or radiopharmacists qualified and experienced in use and handling of radionuclides.

- Patient information: Patients must be instructed in measures to minimize exposure of others.

Pregnancy Risk FactorX

Pregnancy ConsiderationsIodine-131 crosses the placenta and may cause severe and irreversible hypothyroidism in neonates. Pregnancy should be ruled out prior to therapy. Effective contraception is recommended for 12 months following treatment for cancer, 6-12 months following treatment for hyperthyroidism.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsBreast milk concentrations may be equal to or greater than maternal plasma levels. The American Academy of Pediatrics considers radioactive iodine a compound which requires temporary cessation of breast-feeding. They suggest the breast-feeding mother pump prior to the study and store milk in the freezer for feeding the infant. Following the study, pumping should continue to maintain milk production, but milk should be discarded until radioactivity is no longer detected in the milk. The Society of Nuclear Medicine guidelines suggest breast-feeding for that child be discontinued permanently.

Adverse ReactionsFrequency not defined, dose dependent.

Cardiovascular: Chest pain, tachycardia

Dermatologic: Alopecia, hives, itching, rash

Endocrine & metabolic: Acute thyroid crisis

Gastrointestinal: Nausea, sialoadenitis, sore throat, swallowing pain, vomiting

Hematologic: Acute leukemia, anemia, blood dyscrasia, leukopenia, thrombocytopenia

Neuromuscular & skeletal: Neck tenderness/swelling

Respiratory: Bronchospasm, cough

Miscellaneous: Allergic reactions, anaphylaxis, chromosomal abnormalities, hypersensitivity, immunosuppression

Drug Interactions

Amiodarone: May diminish the therapeutic effect of Sodium Iodide I131. *Risk D: Consider therapy modification*

Antithyroid Agents: May diminish the therapeutic effect of Sodium Iodide I131. Management: Discontinue antithyroid therapy 3-4 days prior to sodium iodide I-131 administration. *Risk X: Avoid combination*

Thyroid Products: May diminish the therapeutic effect of Sodium Iodide I131. *Risk X: Avoid combination*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule [diagnostic]: 0.555 megabecquerels [15 microcuries]; 0.925 megabecquerels [25 microcuries]; 1.85 megabecquerels [50 microcuries]; 3.7 megabecquerels [100 microcuries]

Capsule [therapeutic]: 28-3700 megabecquerels [0.75-100 millicuries]

    Iodotope®: 37-4810 megabecquerels [1-130 millicuries]

Kit [therapeutic]:

- Hicon™ 9.25 gigabecquerels (250 millicuries):
    - Capsule: Dibasic sodium phosphate 300 mg (10s)
    - Capsule: Empty large gelatin capsule (10s)
    - Solution: Sodium iodide I^{131} 9.25 gigabecquerels (250 millicuries) per 0.25 mL (0.25 mL) [contains edetate disodium, sodium thiosulphate and dibasic sodium phosphate]
- Hicon™ 18.5 gigabecquerels (250 millicuries):
    - Capsule: Dibasic sodium phosphate 300 mg (10s)

Capsule: Empty large gelatin capsule (10s)

Solution: Sodium iodide I^{131} 18.5 gigabecquerels (500 millicuries) per 0.5 mL (0.5 mL) [contains edetate disodium, sodium thiosulphate and dibasic sodium phosphate]

Hicon™ 37 gigabecquerels (1000 millicuries):

Capsule: Dibasic sodium phosphate 300 mg (10s)

Capsule: Empty large gelatin capsule (10s)

Solution: Sodium iodide I^{131} 37 gigabecquerels (1000 millicuries) per 1 mL (1 mL) [contains edetate disodium, sodium thiosulphate and dibasic sodium phosphate]

Solution [therapeutic]: 129.5-5550 megabecquerels per vial [3.5-150 millicuries per vial; contains sodium bisulfite and edetate disodium]

Generic AvailableYes

Pharmacodynamics/Kinetics

Absorption: Readily absorbed following oral administration

Distribution: Extracellular fluid; primarily trapped by the thyroid

Protein binding: None

Metabolism: Iodide is rapidly oxidized to iodine in the thyroid

Excretion: Urine (37% to 75%)

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsI ^{131}; Iodine ^{131}

References

American Academy of Pediatrics Committee on Drugs, “The Transfer of Drugs and Other Chemicals Into Human Milk,” *Pediatrics*, 2001, 108(3):776-89.[PubMed 11533352]

Meier DA, Brill DR, Becker DV, et al, “Procedure Guideline for Therapy of Thyroid Disease With (131)Iodine,” *J Nucl Med*, 2002, 43(6):856-61.[PubMed 12050333]

Sodium Lactate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(SOW dee um LAK tate)
Pharmacologic CategoryAlkalinizing Agent, Parenteral
Use: Labeled IndicationsSource of bicarbonate for prevention and treatment of mild to moderate metabolic acidosis
Dosing: Adults**Bicarbonate precursor:** I.V.: Dosage depends on degree of acidosis
Dosing: ElderlyRefer to adult dosing.
Administration: I.V.The rate of I.V. infusion should not exceed 300 mL/hour of the $^1/_6$ molar injection.
Administration: I.V. DetailpH: 6.0-7.3
CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4$NS, $D_5{}^1/_2$NS, D_5NS, D_5W, D_{10}W, LR, $^1/_2$NS, NS.

Compatibility in syringe: Compatible: Cimetidine.

Compatibility when admixed: Compatible: Lidocaine, nafcillin. **Incompatible:** Sodium bicarbonate.

Pregnancy Risk FactorA
LactationExcretion in breast milk unknown/compatible
Drug Interactions

Amphetamines: Alkalinizing Agents may decrease the excretion of Amphetamines. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringMonitor laboratory results. Support/instruct patient according to purpose for use.
Patient EducationThis medication can only be administered by intravenous infusion. You will be closely monitored during infusion. Inform prescriber of any herbal, OTC, or prescription medications you are taking. Report immediately any sudden chest pain, respiratory difficulty, muscle twitching, or confusion.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion: 18.7 g (1000 mL) [contains sodium 167 mEq and lactate 167 mEq per liter]

Injection, solution [concentrate; preservative free]: 560 mg/mL (10 mL) [contains sodium 5 mEq and lactate 5 mEq per 1 mL]

Generic AvailableYes
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported

Sodium Nitrite, Sodium Thiosulfate, and Amyl Nitrite

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(SOW dee um NYE trite, SOW dee um thye oh SUL fate, & AM il NYE trite)

U.S. Brand NamesCyanide Antidote Package

Pharmacologic CategoryAntidote

Use: Labeled IndicationsTreatment of cyanide poisoning

Dosing: Adults**Cyanide poisoning:** 0.3 mL ampul of amyl nitrite is crushed every minute and vapor is inhaled for 15-30 seconds until an I.V. sodium nitrite infusion is available. Following administration of 300 mg or 10 mg/kg I.V. sodium nitrite, inject 12.5 g sodium thiosulfate I.V. (over ~10 minutes), if needed; injection of both may be repeated at $^{1}/_{2}$ the original dose.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Cyanide poisoning:** 0.3 mL ampul of amyl nitrite is crushed every minute and vapor is inhaled for 15-30 seconds until an I.V. sodium nitrite infusion is available. Following administration of sodium nitrite I.V. 10 mg/kg (0.33 mL/kg or 6-8 mL/m^2 of a 3% solution; maximum: 10 mL), inject sodium thiosulfate I.V. 7 g/m^2 (maximum: 12.5 g) over ~10 minutes, if needed; injection of both may be repeated at $^{1}/_{2}$ the original dose.

Calculations

- Body Surface Area: Pediatrics

Administration: I.V.

Sodium nitrite: Administer at a rate of 2.5-5 mL/minute.

Sodium thiosulfate: Administer over 10 minutes.

Storage

Amyl nitrite is stable at room temperature. Protect from light. Highly flammable.

Sodium nitrite is stable at room temperature.

Compatibility Do not mix with other medications.

ContraindicationsHypersensitivity to amyl nitrite, sodium nitrite, nitrates, sodium thiosulfate, or any component of the formulation; severe anemia, pregnancy (amyl nitrite)

Warnings/Precautions

Concerns related to adverse effects:

- Methemoglobinemia: Both amyl nitrite and sodium nitrite may induce methemoglobinemia.

Disease-related concerns:

- Cardiovascular disease: Use amyl nitrite with caution in patients with coronary artery disease and patients with hypotension.
- Increased intracranial pressure: Use amyl nitrite with caution in patients with increased intracranial pressure.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Pediatrics: Methemoglobin reductase, which is responsible for converting methemoglobin back to hemoglobin, has reduced activity in pediatric patients. In addition, infants and young children have some proportion of fetal hemoglobin which forms methemoglobin more readily than adult hemoglobin. Therefore, pediatric patients are more susceptible to excessive nitrite-induced methemoglobinemia.

Other warnings/precautions:

- Initiation of treatment: Collection of pretreatment blood cyanide concentrations does not preclude administration and should not delay administration in the emergency management of highly suspected or confirmed cyanide toxicity.
- Return of symptoms: Patients receiving treatment for acute cyanide toxicity must be monitored for return of symptoms for 24-48 hours.
- Smoke inhalation: Use nitrites cautiously in patients with cyanide poisoning related to smoke inhalation because methemoglobinemia and carboxyhemoglobinemia may worsen oxygen-carrying capacity.

Pregnancy Risk FactorC (sodium thiosulfate and sodium nitrite); C (amyl nitrite)

Adverse ReactionsFrequency not defined.

Amyl nitrite:

Cardiovascular: Postural hypotension; cutaneous flushing of head, neck, and clavicular area; tachycardia; palpitation; vasodilation; syncope

Central nervous system: Headache, dizziness, restlessness

Dermatologic: Skin rash (contact dermatitis)

Gastrointestinal: Nausea, vomiting

Hematologic: Hemolytic anemia

Ocular: Increased intraocular pressure

Sodium nitrite:

Cardiovascular: Tachycardia, syncope, cyanosis, hypotension (associated with rapid infusion), flushing

Central nervous system: Dizziness, headache

Gastrointestinal: Nausea, vomiting

Miscellaneous: Methemoglobin formation

Sodium thiosulfate:

Cardiovascular: Hypotension

Central nervous system: Coma, CNS depression secondary to thiocyanate intoxication, psychosis, confusion

Dermatologic: Contact dermatitis

Local: Local irritation

Neuromuscular & skeletal: Weakness

Otic: Tinnitus

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Kit [each kit contains] (Cyanide Antidote Package):

Injection, solution:

Sodium nitrite 300 mg/10 mL (2)

Sodium thiosulfate 12.5 g/50 mL (2)

Inhalant: Amyl nitrite 0.3 mL (12)

[kit also includes disposable syringes, stomach tube, tourniquet, and instructions]

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, restlessness, confusion, psychosis, and CNS depression

Mental Health: Effects on Psychiatric TreatmentMay cause hypotension and anticholinergic effects; concomitant use with psychotropic agents may produce additive effects; monitor

Index TermsAmyl Nitrite,Sodium Thiosulfate, and Sodium Nitrite; Cyanide Antidote Kit; Sodium Thiosulfate, Sodium Nitrite, and Amyl Nitrite

References

Geller RJ, Barthold C, Saiers JA, et al, "Pediatric Cyanide Poisoning: Causes, Manifestations, Management, and Unmet Needs," *Pediatrics*, 2006, 118(5):2146-58.[PubMed 17079589]

Gracia R and Shepherd G, "Cyanide Poisoning and Its Treatment," *Pharmacotherapy*, 2004, 24(10):1358-65.[PubMed 15628833]

Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922.[PubMed 12628894]

Sodium Oxybate

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(SOW dee um ox i BATE)

U.S. Brand NamesXyrem®

Canadian Brand NamesXyrem®

Pharmacologic CategoryCentral Nervous System Depressant

Use: Labeled IndicationsTreatment of cataplexy and daytime sleepiness in patients with narcolepsy

Dosing: Adults**Narcolepsy:** Oral: Initial: 4.5 g/day, in 2 equal doses; first dose to be given at bedtime after the patient is in bed, and second dose to be given 2.5-4 hours later. Dose may be increased or adjusted in 2-week intervals; average dose: 6-9 g/day (maximum: 9 g/day)

Dosing: ElderlySafety and efficacy have not been studied in patients >65 years.

Dosing: Pediatric**Narcolepsy:** Oral: Children ≥16 years: Refer to adult dosing.

Dosing: Renal ImpairmentAdjustment not necessary; consider sodium content.

Dosing: Hepatic ImpairmentDecrease starting dose to half and titrate doses carefully in patients with liver dysfunction. Elimination half-life significantly longer in patients with Child's Class C liver dysfunction.

Administration: OralTake on an empty stomach; separate last meal (or food) and first dose by several hours; try to take at similar time each day. Doses should be administered while patient is sitting up in bed. Both doses should be prepared prior to bedtime. The first dose is taken at bedtime and the second dose is taken 2.5-4 hours later; an alarm clock may need to be set for the second dose. After taking the dose, patient is to lie down and remain in bed.

Dietary ConsiderationsTake on an empty stomach; separate last meal (or food) and first dose by several hours; try to take at similar time each day.

Xyrem® 500 mg/mL contains sodium 91 mg/mL.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F) in the original bottle and in a safe and secure place (may need to be locked up).

ReconstitutionPrepare both doses prior to bedtime and place safely near bed, out of reach of pets and children. Each dose should be diluted with 2 ounces of water in the child-resistant dosing cups. Once diluted, solutions should be used within 24 hours.

RestrictionsC-I (illicit use); C-III (medical use)

Sodium oxybate oral solution will be available only to prescribers enrolled in the Xyrem® Patient Success Program® and dispensed to the patient through the designated centralized pharmacy (1-866-997-3688). Prior to dispensing the first prescription, prescribers will be sent educational materials to be reviewed with the patient and enrollment forms for the postmarketing surveillance program. Patients must be seen at least every 3 months; prescriptions can be written for a maximum of 3 months (the first prescription may only be written for a 1-month supply).

An FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to sodium oxybate or any component of the formulation; ethanol and other CNS depressants; semialdehyde dehydrogenase deficiency

Warnings/Precautions

Boxed warnings:

- Abuse potential: See “Other warnings/precautions” below.
- Xyrem® Patient Success Program®: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- CNS depression: Patients should be instructed not to engage in hazardous activities requiring mental alertness for at least 6 hours after taking this medication and that CNS effects may carryover to the next day.
- CNS effects: May cause confusion, psychosis, paranoia, hallucinations, agitation, depression and sleepwalking; use caution with history of depression or suicide attempt.
- Incontinence: May cause urinary and/or fecal incontinence.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with heart failure or hypertension; contains significant amounts of sodium.
- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment; contains significant amounts of sodium.

- Respiratory disease: Use with caution with compromised respiratory function; may impair respiratory drive.

Concurrent drug therapy issues:

- Stimulant use: Most patients (~80%) in clinical trials were also treated with stimulants; therefore, an independent assessment of the effects of sodium oxybate is lacking.

Special populations:

- Pediatrics: Safety and efficacy have not been established in patients <16 years of age.

Other warnings/precautions:

- Abuse potential: **[U.S. Boxed Warning]: Sodium oxybate is a CNS depressant with abuse potential; it should not be used with ethanol or other CNS depressants.** Seizures, respiratory depression, decreases in level of consciousness, coma, and death have been reported when used for nonprescription purposes.

- Administration: Due to the rapid onset of CNS depressant effects, doses should be administered only at bedtime and while the patient is sitting up in bed.

- Tolerance/withdrawal: Tolerance to sodium oxybate, or withdrawal following its discontinuation, have not been clearly defined in controlled clinical trials, but have been reported at larger doses used for illicit purposes.

- Xyrem® Patient Success Program®: **[U.S. Boxed Warning]: Sodium oxybate oral solution will be available only to prescribers enrolled in the Xyrem® Patient Success Program® and dispensed to the patient through the designated centralized pharmacy (1-866-997-3688).**

Pregnancy Risk FactorB

Pregnancy ConsiderationsReproduction studies in animals have not shown teratogenic effects. However, there are no well-controlled studies in pregnant women. Use during pregnancy only if clearly needed. Past use during labor and delivery as an anesthetic has shown a slight decrease in Apgar scores due to sleepiness in the neonate.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Dizziness (8% to 37%), headache (9% to 37%), pain (9% to 20%), somnolence (1% to 14%), confusion (3% to 17%), sleep disorder (6% to 14%)

Gastrointestinal: Nausea (8% to 40%), vomiting (2% to 23%), abdominal pain (3% to 11%)

Genitourinary: Urinary incontinence (<1% to 14%, usually nocturnal), enuresis (3% to 17%), cystitis, metrorrhagia, urinary frequency

Miscellaneous: Diaphoresis (3% to 11%)

1% to 10%:

Cardiovascular: Hypertension (6%), chest pain, edema

Central nervous system: Disorientation (up to 9%), inebriation (up to 9%), concentration decreased (3% to 9%), dream abnormality (3% to 9%), sleepwalking (4% to 7%), depression (3% to 6%), amnesia (3% to 6%), anxiety (3% to 6%), thinking abnormality (3% to 6%), lethargy (up to 6%), insomnia (5%), agitation, ataxia, chills, fatigue, malaise, memory impairment, nervousness, pyrexia, seizure, stupor, tremor, vertigo

Dermatologic: Hyperhidrosis (3% to 6%), pruritus, rash

Endocrine & metabolic: Dysmenorrhea (3% to 6%)

Gastrointestinal: Dyspepsia (6% to 9%), diarrhea (6% to 8%), abdominal pain (6%), nausea and vomiting (6%), anorexia, constipation, tooth ache, weight gain

Hepatic: Alkaline phosphatase increased, hypercholesteremia, hypocalcemia

Neuromuscular & skeletal: Hypoesthesia (6%), weakness (6% to 8%), myasthenia (3% to 6%), pain (3% to 6%), arthritis, leg cramps, myalgia

Ocular: Amblyopia (6%), blurred vision (6%)

Otic: Tinnitus (6%), ear pain

Renal: Albuminuria, hematuria

Respiratory: Pharyngitis (6% to 8%), rhinitis (8%), nasopharyngitis (3% to 8%), infection (3% to 6%), bronchitis, cough, dyspnea

Miscellaneous: Infection (3% to 6%), viral infection (3% to 9%), allergic reaction, flu-like syndrome

<1%: Abdominal distension, accident, acne, affect lability, akathisia, ALT increased, allergic reaction, alopecia, anemia, apathy, apnea, arthritis, asthma, AST increased, bilirubinemia, bronchitis, bruising, coma, conjunctivitis, contusion, contact dermatitis, creatinine increased, dehydration, depersonalization, dysgeusia, dysphagia, edema, epistaxis, eructation, euphoria, eye irritation, eye pain, eye redness, eye swelling, fall, fecal incontinence, flatulence, fracture, gastroinesophageal reflux disease, gait abnormal, hangover, hematuria, hiccups, hypersensitivity, hyperuricemia, hyperglycemia, hypernatremia, hypertonia, hypotension, infection, injury, keratoconjunctivitis sicca, laceration, leukocytosis, leukopenia, libido decreased, lymphadenopathy, mental impairment, migraine, miosis, mouth ulceration, myoclonus, neck rigidity, neuralgia, night sweats, paralysis, paranoia, polyarthritis, polycythemia, positive ANA

test, proteinuria, psychomotor activity, restless leg syndrome, rosacea, salivary hypersecretion, sinusitis, snoring, stomatitis, suicidal behavior/thoughts, suicidal attempts, syncope, tachycardia, taste loss, tendonitis, thirst, urinary urgency, urticaria

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (increases CNS depression).

Food: High-fat meal decreases bioavailability, delays absorption, and decreases peak serum level.

Herb/Nutraceutical: Avoid any products that may cause CNS depression (eg, kava kava or valerian).

Monitoring ParametersSigns and symptoms of depression, drug abuse

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, CNS depressants). Assess therapeutic effectiveness and adverse response when beginning therapy and at regular intervals during treatment. Instruct patient (and caregiver) specifics about appropriate preparation and use, side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Avoid alcohol use. **This medication should only be used by the person it was prescribed for; it is illegal to share with others. Keep in a safe place and prevent access by anyone else.** This medication will cause sleep immediately. It must be taken at bedtime and only after getting in bed. Do not engage in any hazardous activity or one requiring alertness for at least 6 hours after taking. Do not take with food. Both doses should be mixed prior to getting into bed and stored in the containers provided (you may need to set an alarm clock for the second dose). In addition to sleepiness, may cause dizziness or confusion, which carry over into daytime (use extreme caution when driving or engaging in tasks requiring alertness until response to drug is known). May cause nausea, vomiting, loss of appetite, urinary frequency or bedwetting; increased sweating; or acne. Report respiratory difficulty (awake or asleep); CNS changes (abnormal thoughts, loss of consciousness, sleepwalking, amnesia, agitation, or depression, suicidal thoughts, or seizures); skin rash; alternation in menstrual cycle; persistent GI problems; unusual muscle weakness, cramps, or tremor; or other persistent adverse effects. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral:

Xyrem®: 500 mg/mL (180 mL) [contains sodium 91 mg/mL; supplied in a kit containing bottle adapter, two dosing cups, and oral syringe (as measuring device)]

Generic AvailableNo

ManufacturerOrphan Medical, Inc

Mechanism of ActionSodium oxybate is derived from gamma aminobutyric acid (GABA) and acts as an inhibitory chemical transmitter in the brain. May function through specific receptors for gamma hydroxybutyrate (GHB) and GABA (B).

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: 190-384 mL/kg

Protein binding: <1%

Metabolism: Primarily via the Krebs cycle to form water and carbon dioxide; secondarily via beta oxidation; significant first-pass effect; no active metabolites; metabolic pathways are saturable

Bioavailability: 25%

Half-life elimination: 30-60 minutes

Time to peak: 30-75 minutes

Excretion: Primarily pulmonary (as carbon dioxide); urine (<5% unchanged drug)

Pharmacotherapy PearlsSodium oxybate is a known substance of abuse. When used illegally, it has been referred to as a “date-rape drug”. Street names include Liquid Ecstasy, Liquid X, Liquid E, Georgia Home Boy, Grievous Bodily Harm, G-Riffick, Soap, Scoop, Salty Water, Somatomax, and Organic Quaalude. As part of the FDA approval for prescription use, all patients and prescribers must be enrolled in a program designed to restrict its distribution and to provide postmarketing evaluations. Detailed instructions for the use of sodium oxybate will be provided to the patient and healthcare provider prior dispensing the first dose.

Dental Health Professional ConsiderationsSodium oxybate is a known substance of abuse. When used illegally, it has been referred to as a “date-rape drug”. The dentist should be aware of patients showing signs of CNS depression, as with all other drugs in this class.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tooth ache (see Dental Comment).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index Terms4-Hydroxybutyrate; Gamma Hydroxybutyric Acid; GHB; Sodium 4-Hydroxybutyrate

References

Teter CJ and Guthrie SK, “A Comprehensive Review of MDMA and GHB: Two Common Club Drugs,” *Pharmacotherapy*, 2001, 21(12):1486-513.[PubMed 11765302]

Tunnicliff G, "Sites of Action of Gamma-hydroxybutyrate (GHB) -- A Neuroactive Drug With Abuse Potential," *J Toxicol Clin Toxicol*, 1997, 35(6):581-90.[PubMed 9365423]

Wong CG, Chan KF, Gibson KM, "Gamma-hydroxybutyric Acid: Neurobiology and Toxicology of a Recreational Drug," *Toxicol Rev*, 2004, 23(1):3-20.[PubMed 15298489]

International Brand NamesAlcover (HN, HU); Anetamin (JP); Xyrem (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Special Alerts

Sodium Phenylacetate and Sodium Benzoate: FDA Issues Alert on Particulate Matter Found in Admixture - September 2008

The U.S. Food and Drug Administration (FDA) is alerting healthcare professionals of possible particulate matter detected by Ucyclyd Pharma in their Ammonul® injection. The company is advising, to ensure patient safety, that a Millex® Durapore GV 33 mm Sterile Syringe Filter (0.22 micron) be used when injecting Ammonul® into the $D_{10}W$ bag during admixture. This filter should be used regardless of visible particulate matter in the vial. Testing of the filter has confirmed that the filter will remove the particulate matter. Ucyclyd Pharma will be packaging filters with all shipments until further notice. Healthcare providers may contact Ucyclyd Pharma at 1-888-829-2593 or 1-800-900-6389 24 hours/day, 7 days/week with questions or concerns.

Further information may be obtained at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Ammonul

Pronunciation(SOW dee um fen il AS e tate & SOW dee um BENZ oh ate)

U.S. Brand NamesAmmonul®

Pharmacologic CategoryAntidote; Urea Cycle Disorder (UCD) Treatment Agent

Use: Labeled IndicationsAdjunct to treatment of acute hyperammonemia and encephalopathy in patients with urea cycle disorders involving partial or complete deficiencies of carbamyl-phosphate synthetase (CPS), ornithine transcarbamoylase (OTC), argininosuccinate lysase (ASL), or argininosuccinate synthetase (ASS); for use with hemodialysis in acute neonatal hyperammonemic coma, moderate-to-severe hyperammonemic encephalopathy and hyperammonemia which fails to respond to initial therapy

Dosing: AdultsAdminister as a loading dose over 90-120 minutes, followed by an equivalent maintenance infusion given over 24 hours. Dosage based on weight and specific enzyme deficiency; therapy should continue until ammonia levels are in normal range. Repeat loading doses are not recommended due to the prolonged plasma levels.

>20 kg:

CPS and OTC deficiency: Ammonul® 55 mL/m^2 and arginine 10% 2 mL/kg (provides sodium phenylacetate 5.5 g/m^2, sodium benzoate 5.5 g/m^2, and arginine hydrochloride 200 mg/kg)

ASS and ASL deficiency: Ammonul® 55 mL/m^2 and arginine 10% 6 mL/kg (provides sodium phenylacetate 5.5 g/m^2, sodium benzoate 5.5 g/m^2, and arginine hydrochloride 600 mg/kg)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAdminister as a loading dose over 90-120 minutes, followed by an equivalent maintenance infusion given over 24 hours. Dosage based on weight and specific enzyme deficiency; therapy should continue until ammonia levels are in normal range. Repeat loading doses are not recommended due to the prolonged plasma levels.

≤20 kg:

CPS and OTC deficiency: Ammonul® 2.5 mL/kg and arginine 10% 2 mL/kg (provides sodium phenylacetate 250 mg/kg, sodium benzoate 250 mg/kg, and arginine hydrochloride 200 mg/kg).

ASS and ASL deficiency: Ammonul® 2.5 mL/kg and arginine 10% 6 mL/kg (provides sodium phenylacetate 250 mg/kg, sodium benzoate 250 mg/kg, and arginine hydrochloride 600 mg/kg)

Note: Pending a specific diagnosis in infants, the bolus and maintenance dose of arginine should be 6 mL/kg. If ASS or ASL are excluded as diagnostic possibilities, reduce dose of arginine to 2 mL/kg/day.

>20 kg: Refer to adult dosing.

Dosing: Renal ImpairmentUse with caution; monitor closely.

Dialysis: Ammonia clearance is ~10 times greater with hemodialysis than by peritoneal dialysis or hemofiltration. Exchange transfusion is ineffective.

Dosing: Hepatic ImpairmentUse with caution.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Must be administered via central line; administration via peripheral line may cause burns. Must be diluted prior to administration. In case of extravasation, discontinue infusion and resume at new injection site. Antiemetics may be needed to decrease nausea during infusion. Infuse loading dose over 90-120 minutes; maintenance dose is a continuous infusion.

Administration: I.V. DetailExtravasation may cause skin necrosis. Treatment of extravasation may include aspiration of residual mediation from catheter, limb elevation, intermittent cooling with cold packs.

Dietary ConsiderationsCaloric supplementation and dietary protein restriction should be part of treatment. Caloric intake of >80 cal/kg/day should be attempted.

StoragePrior to dilution, store at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Following dilution, solution for infusion may be stored at room temperature for up to 24 hours.

ReconstitutionDilute in $D_{10}W$ at ≥25 mL/kg. Per manufacturer, it is now a requirement to use a 0.22 micron filter when injecting the solution into the $D_{10}W$ bag during preparation. The manufacturer recommends a Millex® Durapore GV 33 mm syringe filter (provided).

Compatibility**Compatible** with arginine 10%.

ContraindicationsHypersensitivity to sodium phenylacetate, sodium benzoate, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Nausea/vomiting: May occur; premedication with antiemetics may be required.

Disease-related concerns:

- Edema: Use with caution in patients with sodium retention associated with edema.
- Heart failure: Use with caution in patients with heart failure.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment and/or severe renal insufficiency.

Other warnings/precautions:

- Appropriate use: Administer through a central line; peripheral administration may result in burning. Must be diluted prior to administration; avoid extravasation (may cause necrosis).
- Nonpharmacologic support: Severity of hyperammonemia may require hemodialysis, as well as nutritional management and medical support.

Pregnancy Risk FactorC

Pregnancy ConsiderationsIn animal studies, phenylacetate was shown to cause neurological toxicity. Reproduction studies have not been conducted with this combination.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsNonspecific adverse reactions include: Nervous system disorders (22%); metabolism and nutrition disorders (21%); respiratory, thoracic, and mediastinal disorders (15%); general disorders and injection site reactions (14%); gastrointestinal disorders (13%); blood and lymphatic system disorders (11%); cardiac disorders (9%); skin and subcutaneous tissue disorders (6%); vascular disorders (6%); psychiatric disorders (5%); injury, poisoning, and procedural complications (4%); renal and urinary disorders (4%)

More blood and lymphatic system, and vascular disorders were reported for patients ≤30 days of age; more gastrointestinal disorders were reported for patients >30 days.

>10%: Miscellaneous: Infections (12%)

3% to 10%:

Cardiovascular: Hypotension (4%)

Central nervous system: Mental impairment (6%), seizure (6%), brain edema (5%), fever (5%), agitation (3%), coma (3%)

Endocrine & metabolic: Hyperglycemia (7%), hypokalemia (7%), hyperammonemia (5%), metabolic acidosis (4%), acidosis (3%), hypocalcemia (3%)

Gastrointestinal: Vomiting (9%), diarrhea (3%), nausea (3%)

Genitourinary: Urinary tract infection (3%)

Hematologic: Anemia (4%), disseminated intravascular coagulation (DIC) (3%)

Local: Injection site reaction (3%)

Respiratory: Respiratory distress (3%)

<3%, postmarketing, and/or case reports: Abdominal distention, acute psychosis, acute respiratory distress syndrome, aggression, alkalosis, alopecia, anuria, areflexia, ataxia, atrial rupture, blindness, blood carbon dioxide changes, blood glucose changes, blood pH increased, bradycardia, brain death, brain hemorrhage, brain herniation, brain infarction, cardiac arrest/failure, cardiac output decreased, cardiogenic shock, cardiomyopathy, cardiopulmonary arrest/failure, cerebral atrophy, chest pain, cholestasis, clonus, coagulopathy, confusion, consciousness depressed, dehydration, dyspnea, edema, encephalopathy, fluid overload/retention, flushing, gastrointestinal hemorrhage, hallucinations, hemangioma, hemorrhage, hepatic artery stenosis, hepatic failure, hepatotoxicity, hypercapnia, hyperkalemia, hypernatremia, hypertension, hyperventilation, injection site reaction (blistering, extravasation, hemorrhage), intracranial pressure increased, jaundice, Kussmaul respiration, maculopapular rash, multiorgan failure, nerve paralysis, pancytopenia, pCO2 changes, pericardial effusion, phlebothrombosis, pneumonia aspiration, pneumothorax, pruritus, pulmonary edema, pulmonary hemorrhage, rash, renal failure, respiratory alkalosis/acidosis, respiratory arrest/failure, respiratory rate increased, sepsis, septic shock, subdural hematoma, tetany, thrombocytopenia, thrombosis, tremor, urinary retention, urticaria, weakness

Drug Interactions

Probenecid: May increase the serum concentration of Sodium Phenylacetate. Specifically, probenecid may inhibit the renal transport of the phenylacetylglutamine metabolite of sodium phenylacetate. *Risk C: Monitor therapy*

Probenecid: May increase the serum concentration of Sodium Benzoate. Specifically, probenecid may inhibit the renal transport of the hippuric acid metabolite of sodium benzoate. *Risk C: Monitor therapy*

Monitoring ParametersNeurologic status, plasma ammonia, plasma glutamine, clinical response, serum electrolytes (potassium or bicarbonate supplementation may be required), acid-base balance, infusion site

Reference RangeLong-term target levels (may not be appropriate for every patient):

Plasma ammonia: <40 µmol/L

Plasma glutamine: <1000 µmol/L

Normal plasma levels of alanine, glycine, lysine, arginine (except in arginase deficiency); normal urinary orotate excretion; normal plasma protein concentration

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [concentrate]:

Ammonul®: Sodium phenylacetate 100 mg and sodium benzoate 100 mg per 1 mL (50 mL)

Generic AvailableNo

Mechanism of ActionSodium phenylacetate and sodium benzoate provide alternate pathways for the removal of ammonia through the formation of their metabolites. One mole of sodium phenylacetate removes two moles of nitrogen; one mole of sodium benzoate removes one mole of nitrogen.

Pharmacodynamics/Kinetics

Metabolism: Hepatic and renal; sodium phenylacetate conjugates with glutamine, forming the active metabolite, phenylacetylglutamine (PAG); sodium benzoate combines with glycine to form the active metabolite hippuric acid (HIP)

Excretion: Urine

Pharmacotherapy PearlsUcephan® (sodium phenylacetate and sodium benzoate), was previously available as an oral liquid for chronic treatment of urea cycle disorders. Although no longer commercially available, this combination may be compounded for patients not responsive to or tolerant of other treatments.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSeveral nervous system disorders have been reported. May cause agitation, aggression, confusion, hallucinations, and psychosis.

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsNAPA and NABZ; Sodium Benzoate and Sodium Phenylacetate

References

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Gutteridge C and Kuhn RJ, "Compatibility of 10% Sodium Benzoate Plus 10% Sodium Phenylacetate With Various Flavored Vehicles," *Am J Hosp Pharm*, 1994, 51(19):2508, 2510. [PubMed 7847413]

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Sodium Phenylbutyrate

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(SOW dee um fen il BYOO ti rate)

U.S. Brand NamesBuphenyl®

Pharmacologic CategoryUrea Cycle Disorder (UCD) Treatment Agent

Use: Labeled IndicationsAdjunctive therapy in the chronic management of patients with urea cycle disorder involving deficiencies of carbamoylphosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase

Dosing: Adults**Management of urea cycle disorders:** Powder or tablet: Oral: 9.9-13 g/m^2/day, administered in equally divided amounts with each meal or feeding, 3-6 times daily (maximum dose: 20 g/day)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricOral: **Management of urea cycle disorders:**

Children <20 kg: Powder: 450-600 mg/kg/day, administered in equally divided amounts with each meal or feeding, 3-6 times daily (maximum dose: 20 g/day)

Children ≥20 kg: Powder or tablet: Refer to adult dosing.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: OralPowder should be mixed with food (solid or liquid). When mixed with a liquid, shake lightly prior to use. Excipients may not dissolve. Powder may be given orally or via nasogastric and gastrostomy tube.

Dietary ConsiderationsMust be used in conjunction with a protein-restricted diet and, if indicated, essential amino acid supplementation. Patients requiring calorie supplementation should receive protein-free caloric supplements.

Infants with neonatal-onset ornithine transcarbamylase and carbamoylphosphate synthetase deficiency: Initially limit to a protein intake of approximately 1.6 g/kg/day. May increase (after the first 4 months) to 1.9 g/kg/day if tolerated. Protein tolerance will decrease with decreasing growth rate. Infants from 4 months to 1 year should receive at least 1.4 g/kg/day protein, although 1.7 g/kg/day is advisable. From 1-3 years, protein intake should be at least 1.2 g/kg/day although 1.4 g/kg/day is advisable. Citruline supplementation is recommended at 0.17 g/kg/day or 3.8 g/m^2/day; free-base arginine may be used for mild disease.

Late-onset or infants with neonatal-onset argininosuccinic acid synthetase deficiency: May initially receive age-determined minimal protein allowance; increase as tolerated based on blood glutamine and other amino acid levels.

Argininosuccinic acid synthetase deficiency: Arginine (free base) supplementation is recommended at 0.4-0.7 g/kg/day or 8.8-15.4 g/m^2/day

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). After opening, containers should be kept tightly closed.

ContraindicationsShould not be used in the treatment of acute hyperammonemia

Warnings/Precautions

Concerns related to adverse effects:

- Fluid retention: May cause sodium and fluid retention; use with caution in patients where fluid accumulation may be poorly tolerated, such as in HF, hypertension or renal insufficiency.
- Hyperammonemia: Hyperammonemia and hyperammonemic encephalopathy may still occur while on therapy; hyperammonemia should be managed as a medical emergency.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Restricted sodium intake: Contains sodium 125 mg per gram of sodium phenylbutyrate; use with caution, if at all, in patients who must maintain a low sodium intake.

Dosage form specific issues:

- Tablet formulation: The use of sodium phenylbutyrate tablets in children weighing <20 kg is not recommended.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

>10%: Endocrine & metabolic: Amenorrhea/menstrual dysfunction (23%), acidosis (14%), hypoalbuminemia (11%)

3% to 10%:

Endocrine & metabolic: Alkalosis (7%), hyperchloremia (7%), hypophosphatemia (6%), total protein decreased (3%)

Gastrointestinal: Anorexia/appetite decreased (4%), abnormal taste (3%)

Hematologic: Anemia (9%), leukocytosis (4%), leukopenia (4%), thrombocytopenia (3%)

Hepatic: Alkaline phosphatase increased (6%), transaminases increased (4%)

Miscellaneous: Offensive body odor (3%)

≤2%: Abdominal pain, aplastic anemia, arrhythmia, bruising, constipation, depression, edema, gastritis, headache, hyperbilirubinemia, hypernatremia, hyperphosphatemia, hyperuricemia, hypokalemia, nausea, pancreatitis, peptic ulcer disease, rash, rectal bleeding, renal tubular acidosis, syncope, thrombocytosis, vomiting, weight gain

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersBlood ammonia, arginine, amino acid (branch chain), serum proteins and glutamine concentration; serum electrolytes, CBC with differential, hepatic and renal function tests; urinalysis; monitor for physical signs/symptoms of hyperammonemia (eg, lethargy, ataxia, confusion, vomiting, seizures, and memory impairment)
Reference RangePlasma glutamine <1,000 micro mol/L
Nursing: Physical Assessment/Monitoring**Pregnancy risk factor C** - benefits of use should outweigh possible risks. Note breast-feeding caution.
Monitoring: Lab TestsBlood ammonia, arginine, amino acid (branch chain), serum proteins and glutamine concentration; serum electrolytes, CBC with differential, hepatic and renal function tests; urinalysis
Patient EducationIt is important that patients understand and follow the dietary restrictions required when treating this disorder, the medication must be taken in strict accordance with the prescribed regimen and the patient should avoid altering the dosage without the prescriber's knowledge. The powder formulation has a very salty taste. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder, for oral solution:

Buphenyl®: 3 g/level teaspoon (250 g) [contains sodium 125 mg/g; packaged with measuring devices]

Tablet:

Buphenyl®: 500 mg [contains sodium 124 mg/g]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Buphenyl)

500 mg (100): $662.18

Mechanism of ActionSodium phenylbutyrate is a prodrug that, when given orally, is rapidly converted to phenylacetate, which is in turn conjugated with glutamine to form the active compound phenylacetylglutamine; phenylacetylglutamine serves as a substitute for urea and is excreted in the urine whereby it carries with it 2 moles of nitrogen per mole of phenylacetylglutamine and can thereby assist in the clearance of nitrogenous waste in patients with urea cycle disorders
Pharmacodynamics/Kinetics

Metabolism: Hepatic and renal: Metabolized to phenylacetate and then to phenylacetylglutamine

Half-life elimination: Phenylbutyrate: 0.8 hours; phenylacetate: 1.3 hours

Time to peak, plasma: Within 1 hour

Excretion: Urine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Abnormal taste.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsAmmonapse
References

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International Brand NamesAmmonaps (DE, ES, FR, GB, SE); Buphenyl (TW)

Sodium Phosphates

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Acute Phosphate Nephropathy Associated with Prescription and Over-the-Counter [OTC] Oral Sodium Phosphate (OSP) Bowel Cleansing Products - December 12, 2008

The U.S. Food and Drug Administration (FDA) has issued an alert notifying healthcare practitioners and consumers of reports of acute phosphate nephropathy associated with OSP products (eg, over-the-counter products Fleet® Phospho-soda® and prescription products Visicol® and OsmoPrep®) when used as bowel cleansing preparations prior to colonoscopy and other procedures. Acute phosphate nephropathy is associated with calcium-phosphate crystal deposits in the renal tubules and may result in permanent renal dysfunction. Risk factors for acute phosphate nephropathy include age >55 years, hypovolemia, patients with pre-existing renal impairment, bowel obstruction, or active colitis; and patients taking medications that may affect renal perfusion or function (eg, diuretics, ACE Inhibitors, angiotensin receptor blockers, and possibly NSAIDs). Some cases have been reported in patients without apparent risk factors.

The FDA is requiring the manufacturers of the prescription OSP products, Visicol® and OsmoPrep®, to add boxed warnings regarding acute phosphate nephropathy to the product labeling. Additionally, the FDA is requiring the manufacturers to develop and implement a risk management program which will include a Medication Guide and conducting a postmarketing clinical trial to further evaluate the risk of acute kidney injury with these agents. Over-the-counter OSP products should not be used for bowel cleansing, and consumers should only use OSPs for bowel cleansing when prescribed by a healthcare provider. The FDA will also remove bowel cleansing from the professional labeling for all over-the-counter OSPs.

Additional information can be found at: http://www.fda.gov/medwatch/safety/2008/safety08.htm#OSP

Medication Safety Issues

Sound-alike/look-alike issues:

Visicol® may be confused with VESIcare®

Enemas and oral solution are available in pediatric and adult sizes; prescribe by “volume” not by “bottle.”

Pronunciation(SOW dee um FOS fates)

U.S. Brand NamesFleet® Enema Extra® [OTC]; Fleet® Enema for Children [OTC]; Fleet® Enema [OTC]; Fleet® Phospho-soda® EZ-Prep™ [OTC]; Fleet® Phospho-soda® [OTC]; LaCrosse Complete [OTC]; OsmoPrep®; Visicol®

Canadian Brand NamesFleet Enema®; Fleet® Phospho-Soda® Oral Laxative

Pharmacologic CategoryCathartic; Electrolyte Supplement, Oral; Electrolyte Supplement, Parenteral; Laxative, Bowel Evacuant

Use: Labeled Indications

Oral, rectal: Short-term treatment of constipation and to evacuate the colon for rectal and bowel exams

I.V.: Source of phosphate in large volume I.V. fluids and parenteral nutrition; treatment and prevention of hypophosphatemia

Dosing: Adults

Normal requirements elemental phosphorus: Oral:

≥19 years: RDA: 700 mg

Hypophosphatemia: It is difficult to provide concrete guidelines for the treatment of severe hypophosphatemia because the extent of total body deficits and response to therapy are difficult to predict. Aggressive doses of phosphate may result in a transient serum elevation followed by redistribution into intracellular compartments or bone tissue. Intermittent I.V. infusion should be reserved for severe depletion situations (<1 mg/dL in adults); large doses of oral phosphate may cause diarrhea and intestinal absorption may be unreliable. I.V. solutions should be infused slowly. Use caution when mixing with calcium and magnesium, precipitate may form. The following dosages are empiric guidelines. **Note:** 1 mmol phosphate = 31 mg phosphorus; 1 mg phosphorus = 0.032 mmol phosphate

Hypophosphatemia treatment: Doses listed as mmol of phosphate:

Intermittent I.V. infusion: Acute repletion or replacement:

Varying dosages: 0.15-0.3 mmol/kg/dose over 12 hours; may repeat as needed to achieve desired serum level **or**

15 mmol/dose over 2 hours; use if serum phosphorus <2 mg/dL **or**

Low dose: 0.16 mmol/kg over 4-6 hours; use if serum phosphorus level 2.3-3 mg/dL

Intermediate dose: 0.32 mmol/kg over 4-6 hours; use if serum phosphorus level 1.6-2.2 mg/dL

High dose: 0.64 mmol/kg over 8-12 hours; use if serum phosphorus <1.5 mg/dL

Oral: 0.5-1 g elemental phosphorus 2-3 times/day may be used when serum phosphorus level is 1-2.5 mg/dL

Maintenance: Doses listed as mmol of phosphate:

Oral: 50-150 mmol/day in divided doses

I.V.: 50-70 mmol/day

Laxative (Fleet®): Rectal: Contents of one 4.5-ounce enema as a single dose, may repeat

Laxative (Fleet® Phospho-soda®): Oral: Take on an empty stomach; dilute dose with 8 ounces cool water, then follow dose with 8 ounces water; **do not repeat dose within 24 hours**

15-45 mL as a single dose; maximum daily dose: 45 mL

Bowel cleansing prior to colonoscopy:Note: Each dose should be taken with a minimum of 8 ounces of clear liquids. Do not repeat treatment within 7 days. Do not use additional agents, especially sodium phosphate products.

Fleet® Phospho-Soda®: Oral: Prior to procedure (timing of doses determined by prescriber): One dose is equal to 45 mL (2 doses are recommended): Each dose is diluted as follows:

Mix 45 mL with 120 mL clear liquid; drink, then follow with at least 240 mL of clear liquid; **or**

Mix 15 mL with 240 mL clear liquid; drink, then follow with 240 mL clear liquid; repeat every 10 minutes for a total of 45 mL

Visicol®: Oral: Adults: A total of 40 tablets divided as follows:

Evening before colonoscopy: 3 tablets every 15 minutes for 6 doses, then 2 additional tablets in 15 minutes (total of 20 tablets)

3-5 hours prior to colonoscopy: 3 tablets every 15 minutes for 6 doses, then 2 additional tablets in 15 minutes (total of 20 tablets)

OsmoPrep®: A total of 32 tablets divided as follows:

Evening before colonoscopy: 4 tablets every 15 minutes for 5 doses (total of 20 tablets)

3-5 hours prior to colonoscopy: 4 tablets every 15 minutes for 3 doses (total of 12 tablets)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Normal requirements elemental phosphorus: Oral:

0-6 months: Adequate intake: 100 mg/day

6-12 months: Adequate intake: 275 mg/day

1-3 years: RDA: 460 mg

4-8 years: RDA: 500 mg

9-18 years: RDA: 1250 mg

Note: 1 mmol phosphate = 31 mg phosphorus; 1 mg phosphorus = 0.032 mmol phosphate

Hypophosphatemia treatment: Doses listed as mmol of phosphate:

Acute repletion; Intermittent I.V. infusion:

Low dose: 0.08 mmol/kg over 6 hours; use if losses are recent and uncomplicated

Intermediate dose: 0.16-0.24 mmol/kg over 4-6 hours; use if serum phosphorus level 0.5-1 mg/dL

High dose: 0.36 mmol/kg over 6 hours; use if serum phosphorus <0.5 mg/dL

Maintenance: Doses listed as mmol of phosphate:

Oral: 2-3 mmol/kg/day in divided doses

I.V.: 0.5-1.5 mmol/kg/day

Laxative (Fleet®): Rectal:

Children 2-<5 years: One-half contents of one 2.25 oz pediatric enema

Children 5-12 years: Contents of one 2.25 oz pediatric enema, may repeat

Children ≥12 years: Refer to adult dosing.

Laxative (Fleet® Phospho-soda®): Oral: Take on an empty stomach; dilute dose with 8 ounces cool water, then follow dose with 8 ounces water; **do not repeat dose within 24 hours**

Children 5-9 years: 7.5 mL as a single dose; maximum daily dose: 7.5 mL

Children 10-12 years: 15 mL as a single dose; maximum daily dose: 15 mL

Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentUse with caution; ionized inorganic phosphate is excreted by the kidneys. Oral solution is contraindicated in patients with kidney disease.

Administration: I.V. DetailFor intermittent I.V. infusion, dilute at a maximum concentration of 0.12 mmol/mL and infuse over 4-6 hours; maximum rate of infusion: 0.06 mmol/kg/hour

Administration: OralBowel cleansing: Have patient drink ~8 ounces of water with each dose of sodium phosphate (total of 2 quarts/64 ounces); have patient rehydrate before and after colonoscopy

Dietary ConsiderationsShould be taken on an empty stomach with water; a clear liquid diet should be used for 12 hours prior to tablet administration.

Oral solution contains 556 mg (24.17 mEq) sodium/ 5 mL; 20.6 mmol phosphate/5 mL

Oral tablet contains 312 mg (13.6 mEq) sodium/tablet; 336 mg (10.8 mmol phosphate) elemental phosphorus/tablet

Whole cow's milk: 0.29 mmol/mL phosphate; 0.025 mEq/mL sodium; 0.035 mEq/mL potassium

StorageStore at 15°C to 30°C (59°F to 86°F).

Compatibility

Y-site administration: Compatible: Gatifloxacin. **Incompatible:** Ciprofloxacin. **Variable (consult detailed reference):** TPN.

Compatibility when admixed: Variable (consult detailed reference): Calcium chloride, calcium gluconate, ciprofloxacin.

ContraindicationsHypersensitivity to sodium phosphate salts or any component of the formulation; congestive heart failure, hyperparathyroidism, ascites

Enema: Imperforate anus

Intravenous preparation: Diseases with hyperphosphatemia, hypocalcemia, or hypernatremia

Oral preparation: Acute colitis, acute phosphate nephropathy (biopsy proven), bowel obstruction, bowel perforation, congenital megacolon, gastric retention, hypomotility syndromes, ileus, pseudo-obstruction, severe chronic constipation, toxic megacolon, unstable angina

Warnings/Precautions

Concerns related to adverse effects:

- Acute phosphate nephropathy: Acute phosphate nephropathy has been reported (rarely) with use as a colon cleanser prior to colonoscopy. Some cases have resulted in permanent renal impairment (some requiring dialysis). Risk factors for acute phosphate nephropathy may include increased age (>55 years of age), pre-existing renal dysfunction, bowel obstruction, active colitis, or dehydration, and the use of medicines that affect renal perfusion or function (eg, ACE inhibitors, angiotensin receptor blockers, diuretics, and possibly NSAIDs). Other preventive measures may include avoid exceeding maximum recommended doses and concurrent use of other laxatives containing sodium phosphate; encourage patients to drink sufficient quantities of clear fluids during bowel cleansing (eg, electrolyte rehydration solution); obtain baseline and postprocedure labs in patients at risk; consider hospitalization and intravenous hydration during bowel cleansing for patients unable to hydrate themselves (eg, frail patients).

- QT prolongation: Prolongation of the QT interval has been reported (associated with hypokalemia, hypocalcemia); use caution in patients with or at risk for arrhythmias (eg, cardiomyopathy, prolonged QT interval, history of uncontrolled arrhythmias, recent MI) or with concurrent use of other QT prolonging medications.

Disease-related concerns:

- Electrolyte disturbances: Use with caution in patients with pre-existing electrolyte imbalances, dehydration, or risk of electrolyte disturbance (hypocalcemia, hyperphosphatemia, hypernatremia). Correct dehydration prior to using for bowel preparations.

- Inflammatory bowel disease: Use with caution in patients with chronic inflammatory bowel disease; may induce colonic aphthous ulceration. Colitis has been associated with acute phosphate nephropathy.

- Renal impairment: Use with caution in patients with renal impairment; may increase risk for acute phosphate nephropathy.

- Seizure disorder: Use with caution in patients with a history of seizures, those at higher risk of seizures or on medication that lowers seizure threshold.

Special populations:

- Bulimia nervosa patients: Laxatives and purgatives have the potential for abuse by bulimia nervosa patients.

- Debilitated patients: Use with caution in debilitated patients; consider each patient’s ability to hydrate properly.

- Elderly: Use with caution in the elderly; ensure they are able to hydrate themselves if using for bowel preparation.
- Gastric bypass/stapling surgery: Use with caution in patients with gastric bypass or stapling surgery.
- Pediatrics: Safety and efficacy of tablets have not been established in children.

Dosage form specific issues:

- Enemas/oral solutions: Available in pediatric and adult sizes; prescribe by “volume” not by “bottle.”
- Visicol®: Use caution with history of swallowing difficulties or esophageal narrowing. Tablet particles may be seen in the stool.

Other warnings/precautions:

- Bowel evacuation: Appropriate use: If using as a bowel evacuant, correct electrolyte abnormalities before administration. Inadequate fluid intake may lead to excessive fluid loss and hypovolemia. Other oral medications may not be well absorbed when given during bowel evacuation because of rapid intestinal peristalsis.

Geriatric ConsiderationsThe use of laxatives should be limited in the elderly since abuse could lead to fluid/electrolyte deficiencies. Since elderly often have reduced renal function, or disease that could predispose them to adverse effects, caution must be used with parenteral sodium phosphate.
Pregnancy Risk FactorC
Pregnancy ConsiderationsReproduction studies have not been conducted. Use with caution in pregnant women.
LactationUse caution in nursing women.
Adverse ReactionsFrequency not defined.

Cardiovascular: Edema, hypotension

Central nervous system: Dizziness, headache

Endocrine & metabolic: Hypocalcemia, hypernatremia, hyperphosphatemia, calcium phosphate precipitation

Gastrointestinal: Nausea, vomiting, diarrhea, abdominal bloating, abdominal pain, mucosal bleeding, superficial mucosal ulcerations

Renal: Acute renal failure

Postmarketing and/or case reports: Acute phosphate nephropathy, atrial fibrillation following severe vomiting (tablet formulation); nephrocalcinosis (oral solution)

Drug Interactions

Antacids: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: May enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Calcium Salts: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Iron Salts: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Sucralfate: May decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Monitoring Parameters

I.V.: Serum calcium and phosphate levels; renal function

Oral: Bowel cleansing: Baseline and post-procedure labs (electrolytes, calcium, phosphate, BUN, creatinine) in patients at risk for acute renal nephropathy, seizure, or who have a history of electrolyte abnormality; ECG in patients with risks for prolonged QT or arrhythmias. Ensure euvolemia before initiating bowel preparation.

Monitoring: Lab TestsI.V.: Serum calcium and phosphate levels; renal function
Patient EducationMay cause diarrhea with the oral preparation; excessive or prolonged use as a laxative may cause dependence. Do not use over-the-counter laxatives when you are nauseated, vomiting, or have abdominal pain, unless directed to by prescriber. Do not use recommended dose more than once in 24 hours. In general, laxative products should not be used for longer than 1 week, unless under guidance of prescriber. Do not use with other laxative products, especially those containing phosphate. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Enemas: Not for oral use. Insert bottle gently into rectum with tip of bottle pointed towards naval; do not force. Squeeze bottle to expel liquid, stop if resistance is felt. Contact prescriber immediately if no liquid is returned following administration, or if rectal bleeding occurs.

Tablets: Undigested or partially-digested tablets of this or other medications may be seen in stool. Take each dose with 8 oz of clear liquids.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Kit [packaged as a two-dose kit which contains]:

Fleet® Phospho-soda® EZ-Prep™:

Solution, oral: Monobasic sodium phosphate monohydrate 2.4 g and dibasic sodium phosphate heptahydrate 0.9 g per 5 mL (30 mL)

[sugar-free; contains sodium 556 mg/5 mL and phosphate 62.25 mEq/5 mL; packaged with lemonade flavor packets which contain phenylalanine]

Solution, oral: Monobasic sodium phosphate monohydrate 2.4 g and dibasic sodium phosphate heptahydrate 0.9 g per 5 mL (45 mL) [sugar-free; contains sodium 556 mg/5 mL and phosphate 62.25 mEq/5 mL; packaged with lemonade flavor packets which contain phenylalanine]

Injection, solution [concentrate; preservative free]: Phosphorus 3 mmol and sodium 4 mEq per 1 mL (5 mL, 15 mL, 50 mL) [equivalent to phosphorus 93 mg and sodium 92 mg per 1 mL; source of electrolytes; monobasic and dibasic sodium phosphate]

Solution, oral: Monobasic sodium phosphate monohydrate 2.4 g and dibasic sodium phosphate heptahydrate 0.9 g per 5 mL (45 mL)

Fleet® Phospho-soda®: Monobasic sodium phosphate monohydrate 2.4 g and dibasic sodium phosphate heptahydrate 0.9 g per 5 mL (45 mL) [sugar free; contains sodium 556 mg/5 mL, sodium benzoate, and phosphate 62.25 mEq/5 mL; unflavored or ginger-lemon flavor]

Solution, rectal [enema]: Monobasic sodium phosphate monohydrate 19 g and dibasic sodium phosphate heptahydrate 7 g per 118 mL delivered dose (133 mL)

Fleet® Enema: Monobasic sodium phosphate monohydrate 19 g and dibasic sodium phosphate heptahydrate 7 g per 118 mL delivered dose (133 mL) [contains sodium 4.4 g/118 mL]

Fleet® Enema Extra®: Monobasic sodium phosphate monohydrate 19 g and dibasic sodium phosphate heptahydrate 7 g per 197 mL delivered dose (230 mL) [contains sodium 4.4 g/197 mL]

Fleet® Enema for Children: Monobasic sodium phosphate monohydrate 9.5 g and dibasic sodium phosphate heptahydrate 3.5 g per 59 mL delivered dose (66 mL) [contains sodium 2.2 g/59 mL]

LaCrosse Complete: Monobasic sodium phosphate monohydrate 19 g and dibasic sodium phosphate heptahydrate 7 g per 118 mL delivered dose (133 mL) [contains sodium 4.4 g/118 mL]

Tablet, oral [scored]:

OsmoPrep®, Visicol®: Monobasic sodium phosphate monohydrate 1.102 g and dibasic sodium phosphate anhydrous 0.398 g [sodium phosphate 1.5 g per tablet; gluten free]

Generic AvailableYes: Enema, injection, oral solution
Pricing: U.S. (www.drugstore.com)

Tablets (OsmoPrep)

1.102-0.398 g (100): $188.30

Tablets (Visicol)

1.102-0.398 g (40): $151.28

Mechanism of ActionAs a laxative, exerts osmotic effect in the small intestine by drawing water into the lumen of the gut, producing distention and promoting peristalsis and evacuation of the bowel; phosphorous participates in bone deposition, calcium metabolism, utilization of B complex vitamins, and as a buffer in acid-base equilibrium
Pharmacodynamics/Kinetics

Onset of action: Cathartic: 3-6 hours; Rectal: 2-5 minutes

Absorption: Oral: ~1% to 20%

Related Information

- Laxatives, Classification and Properties

Pharmacotherapy PearlsPhosphate salts may precipitate when mixed with calcium salts; solubility is improved in amino acid parenteral nutrition solutions; check with a pharmacist to determine compatibility.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsPhosphates, Sodium
References

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Sodium Polystyrene Sulfonate

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Kayexalate® may be confused with Kaopectate®

Always prescribe either one-time doses or as a specific number of doses (eg, 15 g q6h x 2 doses). Scheduled doses with no dosage limit could be given for days leading to dangerous hypokalemia.

International issues:

Kionex™ may be confused with Kinex® which is a brand name for biperiden in Mexico

Pronunciation(SOW dee um pol ee STYE reen SUL fon ate)
U.S. Brand NamesKayexalate®; Kionex®; SPS®
Canadian Brand NamesKayexalate®; PMS-Sodium Polystyrene Sulfonate
Pharmacologic CategoryAntidote
Use: Labeled IndicationsTreatment of hyperkalemia
Dosing: Adults**Hyperkalemia:**

Oral: 15 g 1-4 times/day

Rectal: 30-50 g every 6 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Hyperkalemia:**

Oral: Children: 1 g/kg/dose every 6 hours

Rectal: Children: 1 g/kg/dose every 2-6 hours (in small children and infants, employ lower doses by using the practical exchange ratio of 1 mEq K^+/g of resin as the basis for calculation)

Administration: OralAdminister orally (or NG) as a suspension using the commercially available suspension or the powder for suspension. **Do not mix in orange juice.** Chilling the oral mixture will increase palatability. Shake suspension well prior to administration.

Powder for suspension: For each 1 g of the powdered resin, add 3–4 mL of water or syrup (amount of fluid usually ranges from 20–100 mL)

Administration: OtherRectal: Enema route is less effective than oral administration. Administer cleansing enema first. Retain enema in colon for at least 30-60 minutes and for several hours, if possible. Enema should be followed by irrigation with normal saline to prevent necrosis.
Dietary ConsiderationsDo **not** mix in orange juice. Powder for suspension contains sodium 100 mg/g (4.1 mEq/g). SPS® suspension contains sodium 1500 mg/60 mL (65 mEq/60 mL).
StorageStore prepared suspensions at 15°C to 30°C (59°F to 86°F). Store repackaged product in refrigerator and use within 14 days. Freshly prepared suspensions should be used within 24 hours. Do not heat resin suspension.
ContraindicationsHypersensitivity to sodium polystyrene sulfonate or any component of the formulation; hypernatremia, hypokalemia, obstructive bowel disease
Warnings/Precautions

Concerns related to adverse effects:

- Fecal impaction: Large oral doses may cause fecal impaction (especially in elderly).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe heart failure and/or hypertension.
- Edema: Use with caution in patients with edema.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Neonates: Avoid using the commercially available liquid product in neonates due to the preservative content.

Other warnings/precautions:

- Enema vs. oral administration: Enema will reduce the serum potassium faster than oral administration, but the oral route will result in a greater reduction over several hours.

Geriatric ConsiderationsLarge doses in the elderly may cause fecal impaction and intestinal obstruction. Best to administer using sorbitol 70% as vehicle.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Endocrine & metabolic: Hypernatremia, hypokalemia, hypocalcemia, hypomagnesemia

Gastrointestinal: Anorexia, colonic necrosis (rare), constipation, fecal impaction, intestinal obstruction (due to concretions in association with aluminum hydroxide), nausea, vomiting

Drug Interactions

Antacids: Sodium Polystyrene Sulfonate may enhance the adverse/toxic effect of Antacids. The combined use of these two agents may result in metabolic alkalosis. **Exceptions:** Sodium Bicarbonate. *Risk D: Consider therapy modification*

Monitoring ParametersExchange capacity is 1 mEq/g *in vivo*, and *in vitro* capacity is 3.1 mEq/g, therefore, a wide range of exchange capacity exists such that close monitoring of serum electrolytes (potassium, sodium, calcium, magnesium) is necessary; ECG
Reference RangeSerum potassium: Adults: 3.5-5.2 mEq/L
Nursing: Physical Assessment/MonitoringAssess results of laboratory tests. Monitor ECG until potassium levels are normal. Monitor for adverse reactions and teach patient interventions and importance of reporting adverse symptoms promptly.
Monitoring: Lab TestsSerum electrolytes, calcium, magnesium
Patient EducationEmergency instructions depend on patient's condition. You will be monitored for effects of this medication and frequent blood tests may be necessary. Oral: Take as directed. Mix well with a full glass of liquid (not orange juice). You may experience nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or constipation or fecal impaction (increased dietary fluids and exercise may help). Report persistent constipation or GI distress; chest pain or rapid heartbeat; or mental confusion or muscle weakness. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for suspension, oral/rectal:

Kayexalate®: 15 g/4 level teaspoons (480 g) [contains sodium 100 mg (4.1 mEq)/g]

Kionex®: 15 g/4 level teaspoons (454 g) [contains sodium 100 mg (4.1 mEq)/g]

Suspension, oral/rectal: 15 g/60 mL (60 mL, 120 mL, 200 mL, 500 mL)

SPS®: 15 g/60 mL (60 mL, 120 mL, 480 mL) [contains alcohol 0.3%, sodium 1500 mg (65 mEq)/60 mL, propylene glycol, and sorbitol; cherry flavor]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Powder (Kayexalate)

(453.6): $317.11

Powder (Kionex)

(454): $148.59

Powder (Sodium Polystyrene Sulfonate)

(454): $132.75

Suspension (Sodium Polystyrene Sulfonate)

15 g/60 mL (60): $14.99

Mechanism of ActionRemoves potassium by exchanging sodium ions for potassium ions in the intestine before the resin is passed from the body
Pharmacodynamics/Kinetics

Onset of action: 2-24 hours

Absorption: None

Excretion: Completely feces (primarily as potassium polystyrene sulfonate)

Related Information

- Antacid Drug Interactions

Pharmacotherapy Pearls1 g of resin binds approximately 1 mEq of potassium
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsWhile Kayexalate® can be used in the treatment of hyperkalemia, if hyperkalemia is associated with ECG changes, more emergent therapy needs to be used (ie, glucose-insulin or calcium). ECG signs of hyperkalemia that require acute interventional measures include peaked T waves, QRS prolongation, and cardiac conduction abnormalities including heart block. Kayexalate® can be used as an additional measure for maintaining control of potassium levels. Note that the mechanism of action consists of an exchange of potassium for sodium, therefore, Kayexalate® should be used with caution in patients with severe heart failure, hypertension, or renal failure. While rectal administration of Kayexalate® achieves a more rapid action, oral administration results in a more sustained potassium reduction.

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: While sodium polystyrene sulfonate can be used in the treatment of hyperkalemia, if hyperkalemia is associated with ECG changes, more emergent therapy needs to be used (ie, glucose-insulin or calcium). Sodium polystyrene sulfonate should be used with caution in patients with severe heart failure, hypertension, or renal failure. While rectal administration of sodium polystyrene sulfonate achieves a more rapid action, oral administration results in a more sustained potassium reduction.

Colonic necrosis is a rare but deadly complication of sodium polystyrene sulfonate-sorbitol when used orally or as an enema in the critically ill patient with hyperkalemia. The clinician should be keenly aware of this devastating side effect and its management. After administration, patients should be closely monitored for abdominal pain, fever, and hypotension. If possible, critically ill patients should receive alternative therapies for potassium removal (eg, hemodialysis).

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International Brand NamesKayexalate (BB, BE, BM, BS, BZ, FR, GY, IL, IT, JM, NL, SR, TH, TT); Kexelate (ZA); Resinsodio (SG); Resonium (DK, FI, PT, SE); Resonium A (AT, AU, GB, HK, HN, MY, NL, TW)

Sodium Tetradecyl

Lexi-Drugs Online

English

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Pronunciation(SOW dee um tetra DEK il)

U.S. Brand NamesSotradecol®

Canadian Brand NamesTrombovar®

Pharmacologic CategorySclerosing Agent

Use: Labeled IndicationsTreatment of small, uncomplicated varicose veins of the lower extremities

Dosing: Adults**Sclerosing agent:** I.V.: Test dose: 0.5 mL given several hours prior to administration of larger dose; 0.5-2 mL (preferred maximum: 1 mL) in each vein, maximum: 10 mL per treatment session; 3% solution reserved for large varices

Dosing: ElderlyRefer to adult dosing.

Administration: I.V.Inject slowly.

Administration: I.V. DetailpH 7.9

StorageStore at controlled room temperature.

CompatibilityChemically **incompatible** with heparin.

ContraindicationsHypersensitivity to sodium tetradecyl or any component of the formulation; arterial disease, acute thrombophlebitis; valvular or deep vein incompetence, phlebitis migrans, cellulitis, acute infections; bedridden patients; patients with uncontrolled systemic disease such as diabetes, toxic hyperthyroidism, tuberculosis, asthma, neoplasm, sepsis, blood dyscrasias, and acute respiratory or skin diseases; huge superficial veins with wide open communications to deeper veins; allergic conditions; varicosities caused by abdominal and pelvic tumors (unless tumor has been removed)

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis: Observe for hypersensitivity/anaphylactic reaction; emergency resuscitation equipment should be available.

- Thromboembolism: Deep vein thrombosis (DVT) and pulmonary embolism (PE) have occurred following treatment.

Disease-related concerns:

- Arteriosclerosis: Use with caution in patients with peripheral arteriosclerosis.

- Thromboangiitis obliterans: Use with caution in patients with thromboangiitis obliterans.

Other warnings/precautions:

- Appropriate use: Valvular and venous competency should be evaluated prior to use.

- Extravasation: Avoid extravasation.

Geriatric ConsiderationsDue to possible contraindications with disease states that may be “out of control,” the elderly patient's medical condition must be thoroughly evaluated before use. No specific geriatric data available.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Central nervous system: Headache

Dermatologic: Discoloration at site of injection, sloughing and tissue necrosis following extravasation

Gastrointestinal: Nausea, vomiting

Local: Pain, itching, or ulceration at injection site

Miscellaneous: Allergic reaction (including hives, asthma, hay fever); anaphylactic shock

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersMonitor for DVT or PE (up to 4 weeks after injection)

Nursing: Physical Assessment/MonitoringMonitor for allergic reaction/anaphylaxis. Have resuscitation equipment available. Monitor injection site for extravasation. Can cause sloughing and necrosis of tissue. **Pregnancy risk factor C:** Benefits of use should outweigh possible risks. Note breast-feeding caution.

Patient EducationA permanent discoloration may remain along the site of the injections. You may experience headache, nausea, and vomiting. Report chest pain or shortness of breath immediately. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber before breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, as sulfate:

Sotradecol®: 1% (2 mL) [contains benzyl alcohol]; 3% (2 mL) [contains benzyl alcohol]

Generic AvailableNo

ManufacturerBioniche

Mechanism of ActionActs by irritation of the vein intimal endothelium and causes thrombosis formation leading to occlusion of the injected vein

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsSodium Tetradecyl Sulfate

International Brand NamesFibro Vein (PL); Fibro-Vein (AU, AU, GB, IE, IT, IT, NZ); S.T.D. (ZA); Setrol (IN); Sotradecol (KP); STD (AU); Trombovar (FR, FR, IT, IT, NL, NL)

Sodium Thiosulfate

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English English

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Pronunciation(SOW dee um thye oh SUL fate)
U.S. Brand NamesVersiclear™
Pharmacologic CategoryAntidote
Use: Labeled Indications

Parenteral: Used alone or with sodium nitrite or amyl nitrite in cyanide poisoning; reduce the risk of nephrotoxicity associated with cisplatin therapy; treatment of cyanide poisoning due to nitroprusside

Topical: Treatment of tinea versicolor

Use: Unlabeled/InvestigationalManagement of I.V. extravasation
Dosing: Adults

Cyanide poisoning: I.V.: 12.5 g given over 10 minutes; may repeat at $^1/_2$ the original dose if symptoms return.

Cisplatin rescue (should be given before or during cisplatin administration): I.V. infusion (in sterile water): 12 g/m^2 over 6 hours or 9 g/m^2 I.V. push followed by 1.2 g/m^2 continuous infusion for 6 hours

Tinea versicolor: Topical: 20% to 25% solution: Apply a thin layer to affected areas twice daily

Drug extravasation (unlabeled use): SubQ: 1/6 M (~4%) solution: Inject into the affected area; various volumes have also been suggested for direct injection into existing I.V. line; however, the optimal volume and efficacy of such practices have not been thoroughly evaluated. **Note:** Use only for large cisplatin infiltrates (>20 mL) and cisplatin concentrations >0.5 mg/mL.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Cyanide poisoning: I.V.: 7 g/m^2 (maximum dose: 12.5 g) given over 10 minutes; may repeat at $^1/_2$ the original dose if symptoms return.

Cisplatin rescue (should be given before or during cisplatin administration): I.V. infusion (in sterile water): 12 g/m^2 over 6 hours or 9 g/m^2 I.V. push followed by 1.2 g/m^2 continuous infusion for 6 hours.

Tinea versicolor: Topical: Refer to adult dosing.

Drug extravasation (unlabeled use): Refer to adult dosing.

Administration: I.V.Inject slowly, over at least 10 minutes; rapid administration may cause hypotension
Administration: TopicalDo not apply to or near eyes.
ContraindicationsHypersensitivity to sodium thiosulfate or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Infusion reactions: Rapid I.V. infusion has caused transient hypotension and ECG changes in dogs.

- Thiocyanate intoxication: Can increase risk of thiocyanate intoxication.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; thiocyanate is eliminated by the kidneys.

Special populations:

- Fire victims: Fire victims may present with both cyanide and carbon monoxide poisoning. In this scenario, sodium thiosulfate may be used alone to promote the clearance of cyanide. Sodium thiosulfate does, however, have a slow onset of action.

- Pregnancy: Safety in pregnancy has not been established.

Dosage form specific issues:

- Topical: Discontinue topical use if irritation or sensitivity occurs.

Other warnings/precautions:

- Initiation of treatment: Collection of pretreatment blood cyanide concentrations does not preclude administration and should not delay administration in the emergency management of highly suspected or confirmed cyanide toxicity.

- Return of symptoms: Patients receiving treatment for acute cyanide toxicity must be monitored for return of symptoms for 24-48 hours.

Pregnancy Risk FactorC
Pregnancy ConsiderationsSafety has not been established in pregnant women. Use only when potential benefit to the mother outweighs the possible risk to the fetus.
Adverse ReactionsFrequency not defined

Cardiovascular: Hypotension (infusion rate-dependent)

Dermatologic: Contact dermatitis, local irritation

Gastrointestinal: Nausea, vomiting

Miscellaneous: Hypersensitivity reactions

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Drug InteractionsThere are no known significant interactions.
Monitoring ParametersMonitor for signs of thiocyanate toxicity; monitor for hypotension and hypersensitivity reactions
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 100 mg/mL (10 mL); 250 mg/mL (50 mL)

Lotion: Sodium thiosulfate 25% and salicylic acid 1% (120 mL) [contains isopropyl alcohol 10%]

Generic AvailableYes: Injection
Pricing: U.S. (www.drugstore.com)

Lotion (Versiclear)

25-1% (120): $19.99

Mechanism of Action

Cyanide toxicity: Accelerates the clearance of cyanide via the rhodanase-catalyzed detoxification of cyanide to thiocyanate (much less toxic than cyanide). The accelerated action of rhodanase is a result of the exogenous sulfur provided by sodium thiosulfate.

Cisplatin toxicity: Complexes with cisplatin to form a compound that is nontoxic to either normal or cancerous cells

Pharmacodynamics/Kinetics

Absorption: Oral: Poor

Distribution: Extracellular fluid

Half-life elimination: 0.65 hour

Excretion: Urine (28.5% as unchanged drug)

Related Information

- Management of Drug Extravasations

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause coma, CNS depression secondary to thiocyanate intoxication, psychosis, or confusion
Mental Health: Effects on Psychiatric TreatmentCNS depressant effect of psychotropics may be potentiated; monitor
Index TermsDisodium Thiosulfate Pentahydrate; Pentahydrate; Sodium Hyposulfate; Sodium Thiosulphate; Thiosulfuric Acid Disodium Salt
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International Brand NamesKrem Ochronny z Tiosiarczanem Sodu A (PL); Soft Mate Consept 2 (PL)

Solifenacin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

VESIcare® may be confused with Visicol®

Pronunciation(sol i FEN a sin)

U.S. Brand NamesVESIcare®

Pharmacologic CategoryAnticholinergic Agent

Use: Labeled IndicationsTreatment of overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence

Dosing: Adults**Overactive bladder:** Oral: 5 mg/day; if tolerated, may increase to 10 mg/day.

Dosage adjustment with concomitant CYP3A4 inhibitors: Maximum solifenacin dose: 5 mg/day

Dosing: ElderlyBase dosing on renal/hepatic function.

Dosing: Renal ImpairmentUse with caution in reduced renal function; Cl_{cr} <30 mL/minute: Maximum dose: 5 mg/day

Dosing: Hepatic ImpairmentUse with caution in reduced hepatic function:

Moderate (Child-Pugh class B): Maximum dose: 5 mg/day

Severe (Child-Pugh class C): Use is not recommended

Calculations

- Creatinine Clearance: Adults

Administration: OralSwallow tablet whole; administer with liquids; may be taken without regard to food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to solifenacin or any component of the formulation; urinary retention; gastric retention; uncontrolled narrow-angle glaucoma.

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause drowsiness and/or blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Heat prostration: May occur in the presence of increased environmental temperature; use caution in hot weather and/or exercise.

Disease-related concerns:

- Bladder outflow obstruction: Use with caution in patients with bladder outflow obstruction; increased risk of urinary retention.
- Gastrointestinal disease: Use with caution in patients with gastrointestinal obstructive disorders or decreased gastrointestinal motility.
- Glaucoma: Use with caution in patients with controlled (treated) narrow-angle glaucoma; use is contraindicated in uncontrolled narrow-angle glaucoma.
- Hepatic impairment: Use with caution in patients with moderate hepatic impairment (Child-Pugh class B); dosage adjustment is required; use is not recommended in patients with severe hepatic impairment (Child-Pugh class C).
- QT prolongation: Use with caution in patients with a known history of QT prolongation or other risk factors for QT prolongation (eg, concomitant use of medications known to prolong QT interval and/or electrolyte abnormalities).The risk for QT prolongation is dose-related.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment is required for severe renal impairment (Cl_{cr} <30 mL/minute).

Concurrent drug therapy issues:

- High potential for interactions: Patients on potent CYP3A4 inhibitors require the lower dose of solifenacin.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsIn patients with Cl_{cr} <30 mL/minute, doses >5 mg/day are not recommended. Similar safety and effectiveness were observed in elderly and younger patients.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDecreased fetal weight, increased incidence of cleft palate, and delayed physical development were observed in some animal studies. There are no adequate or well-controlled studies in pregnant women. Use during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%: Gastrointestinal: Xerostomia (11% to 28%; dose-related), constipation (5% to 13%; dose-related)

1% to 10%:

Cardiovascular: Edema (≤1%), hypertension (≤1%)

Central nervous system: Headache (3% to 6%), fatigue (1% to 2%), depression (≤1%)

Gastrointestinal: Dyspepsia (1% to 4%), nausea (2% to 3%), upper abdominal pain (1% to 2%)

Genitourinary: Urinary tract infection (3% to 5%), urinary retention (≤1%)

Ocular: Blurred vision (4% to 5%), dry eyes (≤2%)

Respiratory: Cough (≤1%)

Miscellaneous: Influenza (≤2%)

<1%, postmarketing, and/or case reports: Angioneurotic edema, confusion, fecal impaction, gastrointestinal obstruction, hallucination, hypersensitivity, pruritus, QT_c prolongation, rash, torsade de pointes, urticaria

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Solifenacin. *Risk D: Consider therapy modification*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Grapefruit juice may increase the serum level effects of solifenacin.

Herb/Nutraceutical: St John's wort (*Hypericum*) may decrease the levels/effects of solifenacin.

Monitoring ParametersAnticholinergic effects (eg, fixed and dilated pupils, blurred vision, tremors or dry skin); creatinine clearance (prior to treatment for dosing adjustment); liver function

Nursing: Physical Assessment/MonitoringAssess other prescriptions and OTC medications the patient may be taking to avoid duplications and interactions. Assess knowledge/teach patient appropriate use, side effects, and symptoms to report. Monitor therapeutic response to medication; urination pattern.

Monitoring: Lab TestsCreatinine clearance (prior to treatment for dosing adjustment); liver function tests

Patient EducationMaintain adequate hydration (2-3 L/day) unless instructed to restrict fluid intake by prescriber. This medication may cause dry mouth (sucking on lozenges or hard candy may help). You may be more susceptible to heat prostration due to decreased ability to sweat. Use caution in hot weather (maintain adequate fluids, reduce exercise activity, rest frequently). You may experience constipation (increased exercise, fluids, fruit/fiber may help), nausea, vomiting, blurred vision and dry eyes. Report difficulty, pain, or burning on urination. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber before breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as succinate:

VESIcare®: 5 mg, 10 mg

Generic AvailableNo
ManufacturerAstellas Pharma Technologies Inc
Pricing: U.S. (www.drugstore.com)

Tablets (VESIcare)

5 mg (30): $136.38

10 mg (30): $136.38

Mechanism of ActionInhibits muscarinic receptors resulting in decreased urinary bladder contraction, increased residual urine volume, and decreased detrusor muscle pressure.
Pharmacodynamics/Kinetics

Distribution: V_d: 600 L

Protein binding: ~98% bound primarily to alpha$_1$-acid glycoprotein

Metabolism: Extensively hepatic; via N-oxidation and 4 R-hydroxylation, forms one active and three inactive metabolites; primary pathway for elimination is via CYP3A4

Bioavailability: ~90%

Half-life elimination: 45-68 hours following chronic dosing

Time to peak, plasma: 3-8 hours

Excretion: Urine 69% (<15% as unchanged drug); feces 23%

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation). Prolonged xerostomia may contribute to discomfort and dental disease (eg, caries, periodontal disease, and oral candidiasis).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause depression, sedation, or dizziness
Mental Health: Effects on Psychiatric TreatmentDry mouth and constipation are common; concomitant use with psychotropic agents may produce additive effects; monitor. Carbamazepine, phenobarbital, phenytoin, and St John's wort may decrease levels of solifenacin while nefazodone may increase the levels of solifenacin; monitor.
Index TermsSolifenacin Succinate; YM905
References

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Chapple CR, Arano P, Bosch JL, et al, “Solifenacin Appears Effective and Well Tolerated in Patients With Symptomatic Idiopathic Detrusor Overactivity in a Placebo- and Tolterodine-Controlled Phase 2 Dose-Finding Study,” *BJU Int*, 2004, 93(1):71-7.[PubMed 14678372]

Garely AD, Kaufman JM, Sand PK, et al, “Symptom Bother and Health-Related Quality of Life Outcomes Following Solifenacin Treatment for Overactive Bladder: The VESIcare Open-Label Trial (VOLT),” *Clin Ther*, 2006, 28(11):1935-46.[PubMed 17213014]

International Brand NamesVesicare (AR, AU, BE, BG, CH, CZ, DK, EE, ES, FI, FR, GB, HK, HN, ID, IL, NL, NO, NZ, PH, PT, SE, TH, TW); Vesikur (DE); Vesitrim (IE)

Somatropin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Somatrem may be confused with somatropin

Somatropin may be confused with somatrem, sumatriptan

International issues:

Genotropin® may be confused with Genatropine® which is a brand name for atropine in France

Pronunciation(soe ma TROE pin)

U.S. Brand NamesGenotropin Miniquick®; Genotropin®; Humatrope®; Norditropin®; Norditropin® NordiFlex®; Nutropin AQ®; Nutropin®; Omnitrope™; Saizen®; Serostim®; Tev-Tropin®; Zorbtive®

Canadian Brand NamesHumatrope®; Nutropine®; Nutropin® AQ; Saizen®; Serostim®

Pharmacologic CategoryGrowth Hormone

Use: Labeled Indications

Children:

Treatment of growth failure due to inadequate endogenous growth hormone secretion (Genotropin®, Humatrope®, Norditropin®, Nutropin®, Nutropin AQ®, Omnitrope™, Saizen®, Tev-Tropin®)

Treatment of short stature associated with Turner syndrome (Genotropin®, Humatrope®, Norditropin®, Nutropin®, Nutropin AQ®)

Treatment of Prader-Willi syndrome (Genotropin®)

Treatment of growth failure associated with chronic renal insufficiency (CRI) up until the time of renal transplantation (Nutropin®, Nutropin AQ®)

Treatment of growth failure in children born small for gestational age who fail to manifest catch-up growth by 2 years of age (Genotropin®) or by 2-4 years of age (Norditropin®)

Treatment of idiopathic short stature (nongrowth hormone-deficient short stature) defined by height standard deviation score (SDS) less than or equal to -2.25 and growth rate not likely to attain normal adult height (Genotropin®, Humatrope®, Nutropin®, Nutropin AQ®)

Treatment of short stature or growth failure associated with short stature homeobox gene (SHOX) deficiency (Humatrope®)

Treatment of short stature associated with Noonan syndrome (Norditropin®)

Adults:

HIV patients with wasting or cachexia with concomitant antiviral therapy (Serostim®)

Replacement of endogenous growth hormone in patients with adult growth hormone deficiency who meet both of the following criteria (Genotropin®, Humatrope®, Norditropin®, Nutropin®, Nutropin AQ®, Omnitrope™, Saizen®):

Biochemical diagnosis of adult growth hormone deficiency by means of a subnormal response to a standard growth hormone stimulation test (peak growth hormone ≤5 mcg/L). Confirmatory testing may not be required in patients with congenital/genetic growth hormone deficiency or multiple pituitary hormone deficiencies due to organic diseases.

and

Adult-onset: Patients who have adult growth hormone deficiency whether alone or with multiple hormone deficiencies (hypopituitarism) as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma

or

Childhood-onset: Patients who were growth hormone deficient during childhood, confirmed as an adult before replacement therapy is initiated

Treatment of short-bowel syndrome (Zorbtive®)

Use: Unlabeled/InvestigationalInvestigational: Congestive heart failure; pediatric HIV patients with wasting/cachexia (Serostim®); HIV-associated adipose redistribution syndrome (HARS) (Serostim®)

Dosing: Adults

Growth hormone deficiency: Adjust dose based on individual requirements: To minimize adverse events in older or overweight patients, reduced dosages may be necessary. During therapy, dosage should be decreased if required by the occurrence of side effects or excessive IGF-I levels.

Norditropin®: SubQ: Initial dose ≤0.004 mg/kg/day; after 6 weeks of therapy, may increase dose up to 0.016 mg/kg/day

Nutropin®, Nutropin® AQ: SubQ: ≤0.006 mg/kg/day; dose may be increased up to a maximum of 0.025 mg/kg/day in patients <35 years of age, or up to a maximum of 0.0125 mg/kg/day in patients ≥35 years of age

Humatrope®: SubQ: ≤0.006 mg/kg/day; dose may be increased up to a maximum of 0.0125 mg/kg/day

Genotropin®, Omnitrope™: SubQ: Weekly dosage: ≤0.04 mg/kg divided into 6-7 daily doses; dose may be increased at 4- to 8-week intervals to a maximum of 0.08 mg/kg/week

Saizen®: SubQ: ≤0.005 mg/kg/day; dose may be increased to not more than 0.01 mg/kg/day after 4 weeks

Alternate dosing (growth hormone deficiency): SubQ: Initial: 0.2 mg/day (range: 0.15-0.3 mg/day); may increase every 1-2 months by 0.1-0.2 mg/day

Dosage adjustment with estrogen supplementation (growth hormone deficiency): Larger doses of somatropin may be needed for women taking oral estrogen replacement products; dosing not affected by topical products

HARS (unlabeled use): Serostim®: SubQ: Induction: 4 mg once daily at bedtime for 12 weeks; Maintenance: 2 mg or 4 mg every other day at bedtime for 12-24 weeks. **Note:** Every-other-day dosing during induction has also been studied. Although a greater response was seen with daily dosing, it was associated with an increased incidence of adverse events.

HIV patients with wasting or cachexia:

Serostim®: SubQ: 0.1 mg/kg once daily at bedtime (maximum: 6 mg/day). Alternately, patients at risk for side effects may be started at 0.1 mg/kg every other day. Patients who continue to lose weight after 12 weeks should be re-evaluated for opportunistic infections or other clinical events; rotate injection sites to avoid lipodystrophy Adjust dose if needed to manage side effects.

Daily dose based on body weight:

<35 kg: 0.1 mg/kg

35-45 kg: 4 mg

45-55 kg: 5 mg

>55 kg: 6 mg

Short-bowel syndrome:*Zorbtive®:* SubQ: 0.1 mg/kg once daily for 4 weeks (maximum: 8 mg/day)

Fluid retention (moderate) or arthralgias: Treat symptomatically or reduce dose by 50%

Severe toxicity: Discontinue therapy for up to 5 days; when symptoms resolve, restart at 50% of dose. If severe toxicity recurs or does not disappear within 5 days after discontinuation, permanently discontinue treatment.

Dosing: ElderlyPatients ≥65 years of age may be more sensitive to the action of growth hormone and more prone to adverse effects; in general, dosing should be cautious, beginning at low end of dosing range.

Dosing: Pediatric

Growth hormone deficiency:

Genotropin®, Omnitrope™: SubQ: Weekly dosage: 0.16-0.24 mg/kg divided into 6-7 daily doses

Humatrope®: I.M., SubQ: Weekly dosage: 0.18 mg/kg; maximum replacement dose: 0.3 mg/kg/week; dosing should be divided into equal doses given 3 times/week on alternating days, 6 times/week, or daily

Norditropin®: SubQ: 0.024-0.034 mg/kg/day, 6-7 times/week

Nutropin®, Nutropin® AQ: SubQ: Weekly dosage: 0.3 mg/kg divided into daily doses; pubertal patients: ≤0.7 mg/kg/week divided daily

Tev-Tropin®: SubQ: Up to 0.1 mg/kg administered 3 times/week

Saizen®: I.M., SubQ: 0.18 mg/kg/week in divided doses administered daily **or** as 0.06 mg/kg/dose administered 3 times/week **or** as 0.03 mg/kg/dose administered 6 times/week

Note: Therapy should be discontinued when patient has reached satisfactory adult height, when epiphyses have fused, or when the patient ceases to respond. Growth of 5 cm/year or more is expected, if growth rate does not exceed 2.5 cm in a 6-month period, double the dose for the next 6 months; if there is still no satisfactory response, discontinue therapy

Chronic renal insufficiency (CRI):*Nutropin®, Nutropin® AQ:* SubQ: Weekly dosage: 0.35 mg/kg divided into daily injections; continue until the time of renal transplantation

Dosage recommendations in patients treated for CRI who require dialysis:

Hemodialysis: Administer dose at night prior to bedtime or at least 3-4 hours after hemodialysis to prevent hematoma formation from heparin

CCPD: Administer dose in the morning following dialysis

CAPD: Administer dose in the evening at the time of overnight exchange

Turner syndrome:

Genotropin®: SubQ: Weekly dosage: 0.33 mg/kg divided into 6-7 doses

Humatrope®, Nutropin®, Nutropin® AQ: SubQ: Weekly dosage: ≤0.375 mg/kg divided into equal doses 3-7 times per week

Norditropin®: Up to 0.067 mg/kg/day

Prader-Willi syndrome:*Genotropin®:* SubQ: Weekly dosage: 0.24 mg/kg divided into 6-7 doses

Small for gestational age:

Genotropin®: SubQ: Weekly dosage: 0.48 mg/kg divided into 6-7 doses

Norditropin®: SubQ: Up to 0.067 mg/kg/day

Alternate dosing (small for gestational age): In older/early pubertal children or children with very short stature, consider initiating therapy at higher doses (0.067 mg/kg/day) and then consider reducing the dose (0.033 mg/kg/day) if substantial catch-up growth observed. In younger children (<4 years) with less severe short stature, consider initiating therapy with lower doses (0.033 mg/kg/day) and then titrating the dose upwards as needed.

Idiopathic short stature:

Gentropin®: SubQ: Weekly dosage: 0.47 mg/kg divided into equal doses 6-7 times per week

Humatrope®: SubQ: Weekly dosage: 0.37 mg/kg divided into equal doses 6-7 times per week

Nutropin®, Nutropin AQ®: SubQ: Weekly dosage: Up to 0.3 mg/kg divided into daily doses

SHOX deficiency:*Humatrope®:* SubQ: 0.35 mg/kg/week divided into equal daily doses

HIV patients with wasting or cachexia (unlabeled use):*Serostim®:* SubQ: Limited data; doses of 0.04 mg/kg/day were reported in five children, 6-17 years of age; doses of 0.07 mg/kg/day were reported in six children, 8-14 years of age

Noonan syndrome:*Norditropin®:* SubQ: Up to 0.066 mg/kg/day

Dosing: Renal ImpairmentReports indicate patients with chronic renal failure tend to have decreased clearance; specific dosing suggestions not available

Dosing: Hepatic ImpairmentClearance may be reduced in patients with severe hepatic dysfunction; specific dosing suggestions are not available.

Administration: I.M.Not all products are approved for I.M. administration. Rotate administration sites to avoid tissue atrophy. When administering Humatrope® for growth hormone deficiency, SubQ route is preferred

Administration: OtherDo not shake; administer SubQ or I.M. (not all products are approved for I.M. administration). Rotate administration sites to avoid tissue atrophy. When administering to newborns, reconstitute with sterile water for injection. Norditropin® cartridge must be administered using the corresponding color-coded NordiPen® injection pen. Solution in the Omnitrope™ cartridges must be administered using the Omnitrope™ pen; when installing a new cartridge, prime pen prior to first use. When administering Humatrope® for growth hormone deficiency, SubQ route is preferred. When administering Tev-Tropin®, SubQ injections of solutions >1 mL not recommended.

Dietary Considerations

Prader-Willi syndrome: All patients should have effective weight control (use is contraindicated in severely-obese patients).

Short-bowel syndrome: Intravenous parenteral nutrition requirements may need reassessment as gastrointestinal absorption improves.

Storage

Genotropin®: Store at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Following reconstitution of 5.8 mg and 13.8 mg cartridge, store under refrigeration and use within 21 days.

Genotropin® Miniquick®: Store in refrigerator prior to dispensing, but may be stored ≤25°C (77°F) for up to 3 months after dispensing. Once reconstituted, solution must be refrigerated and used within 24 hours. Discard unused portion.

Humatrope®:

Vial: Before and after reconstitution, store at 2°C to 8°C (36°F to 46°F); do not freeze. When reconstituted with provided diluent or bacteriostatic water for injection, use within 14 days. When reconstituted with sterile water for injection, use within 24 hours and discard unused portion.

Cartridge: Before and after reconstitution, store at 2°C to 8°C (36°F to 46°F); do not freeze. Following reconstitution with provided diluent, stable for 28 days under refrigeration.

Norditropin®: Store at 2°C to 8°C (36°F to 46°F); do not freeze. Avoid direct light.

Cartridge: When refrigerated, must be used within 4 weeks once inserted into pen. Orange cartridges (5 mg/1.5 mL) may also be stored up to 3 weeks at ≤25°C (77°F).

Prefilled pen: When refrigerated, must be used within 4 weeks after initial injection. Orange and blue prefilled pens may also be stored up to 3 weeks at ≤25°C (77°F).

Nutropin®: Before and after reconstitution, store at 2°C to 8°C (36°F to 46°F); do not freeze.

Vial: Use reconstituted vials within 14 days. When reconstituted with sterile water for injection, use immediately and discard unused portion.

AQ formulation: Use within 28 days following initial use.

Omnitrope™:

Powder for injection: Prior to reconstitution, store under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Reconstitute with provided diluent. Swirl gently; do not shake. Following reconstitution with the provided diluents, the 5.8 mg vial may be stored under refrigeration for up to 3 weeks. Store vial in carton to protect from light.

Solution: Prior to use, store under refrigeration at 2°C to 8°C (36°F to 46°F). Once the cartridge is loaded into the pen delivery system, store under refrigeration for up to 21 days after first use.

Saizen®: Prior to reconstitution, store at room temperature 15°C to 30°C (59°F to 86°F). Following reconstitution with bacteriostatic water for injection, reconstituted solution should be refrigerated and used within 14 days. When reconstituted with sterile water for injection, use immediately and discard unused portion. The Saizen® easy click cartridge, when reconstituted with the provided bacteriostatic water, should be stored under refrigeration and used within 21 days.

Serostim®: Prior to reconstitution, store at room temperature 15°C to 30°C (59°F to 86°F). When reconstituted with sterile water for injection, use immediately and discard unused portion.

Tev-Tropin®: Prior to reconstitution, store at 2°C to 8°C (36°F to 46°F). Following reconstitution with bacteriostatic NS, solution should be refrigerated and used within 14 days. Some cloudiness may occur; do not use if cloudiness persists after warming to room temperature.

Zorbtive®: Store unopened vials and diluent at room temperature of 15°C to 30°C (59°F to 86°F). Store reconstituted vial under refrigeration at 2°C to 8°C (36°F to 46°F) for up to 14 days; do not freeze.

Reconstitution

Genotropin®: Reconstitute with diluent provided.

Genotropin MiniQuick®: Reconstitute with diluent provided. Consult the instructions provided with the reconstitution device.

Humatrope®:

Cartridge: Consult HumatroPen™ User Guide for complete instructions for reconstitution. **Do not use diluent provided with vials.**

Vial: 5 mg: Reconstitute with 1.5-5 mL diluent provided. Swirl gently, do not shake.

Nutropin®: Vial:

5 mg: Reconstitute with 1-5 mL bacteriostatic water for injection. Swirl gently, do not shake.

10 mg: Reconstitute with 1-10 mL bacteriostatic water for injection. Swirl gently, do not shake.

Omnitrope™ powder: Reconstitute with provided diluent. Swirl gently; do not shake.

Saizen®: Vial:

5 mg: Reconstitute with 1-3 mL bacteriostatic water for injection or sterile water for injection. Gently swirl; do not shake.

8.8 mg: Reconstitute with 2-3 mL bacteriostatic water for injection or sterile water for injection. Gently swirl; do not shake.

Serostim®: Vial: Reconstitute with 0.5-1 mL sterile water for injection.

Tev-Tropin®: Reconstitute with 1-5 mL of diluent provided. Gently swirl; do not shake. May use preservative-free NS for use in newborns.

Zorbtive®: 8.8 mg vial: Reconstitute with 1-2 mL bacteriostatic water for injection. Swirl gently.

Contraindications

Hypersensitivity to growth hormone or any component of the formulation; growth promotion in pediatric patients with closed epiphyses; progression of any underlying intracranial lesion or actively growing intracranial tumor; acute critical illness due to complications following open heart or abdominal surgery; multiple accidental trauma or acute respiratory failure; evidence of active malignancy; active proliferative or severe nonproliferative diabetic retinopathy; use in patients with Prader-Willi syndrome **without** growth hormone deficiency (except Genotropin®) or in patients with Prader-Willi syndrome **with** growth hormone deficiency who are severely obese or have severe respiratory impairment

Warnings/Precautions

Concerns related to adverse effects:

- Fluid retention: May occur frequently in adults during use; manifestations of fluid retention (eg, edema, arthralgia, myalgia, nerve compression syndromes/paresthesias) are generally transient and dose dependent.

- Intracranial hypertension (IH): With headache, nausea, papilledema, visual changes, and/or vomiting has been reported with growth hormone product, funduscopic examinations are recommended. Patients with Turner syndrome, chronic renal failure and Prader-Willi syndrome may be at increased risk for IH.

- Neoplasm: Use in contraindicated with active malignancy. Monitor patients with preexisting tumors or growth failure secondary to an intracranial lesion for recurrence or progression of underlying disease.

- Progression of scoliosis: May occur in children experiencing rapid growth.

- Slipped capital epiphyses: Patients with growth hormone deficiency may develop slipped capital epiphyses more frequently; evaluate any child with new onset of a limp or with complaints of hip or knee pain.

Disease-related concerns:

- Acute critical illness: Initiation of somatropin is contraindicated with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or acute respiratory failure; mortality may be increased. The safety of continuing somatropin in patients who develop these illnesses during therapy has not been established; use with caution

- Diabetes: Use with caution in patients with diabetes or with risk factors for impaired glucose tolerance; may decrease insulin sensitivity.

- Hypothyroidism: Untreated/undiagnosed hypothyroidism may decrease response to therapy.

- Noonan syndrome: Safety and efficacy have not been established for the treatment of Noonan syndrome in children with significant cardiac disease.

- Prader-Willi syndrome: Fatalities have been reported in pediatric patients with Prader-Willi syndrome following the use of growth hormone. The reported fatalities occurred in patients with one or more risk factors, including severe obesity, sleep apnea, respiratory impairment, or unidentified respiratory infection; male patients with one or more of these factors may be at greater risk. Treatment interruption is recommended in patients who show signs of upper airway obstruction, including the onset of, or increased, snoring. In addition, evaluation of and/or monitoring for sleep apnea and respiratory infections are recommended.

- Turner syndrome: Patients with Turner syndrome are at increased risk for otitis media and other ear/hearing disorders, cardiovascular disorders (including stroke, aortic aneurysm, hypertension), and thyroid disease, monitor carefully

Concurrent therapy issues:

- Glucocorticoids: Concurrent glucocorticoid therapy may inhibit growth promotion effects; may require dosage adjustment or replacement glucocorticoid therapy in patients with ACTH deficiency.

Special populations:

- HIV patients: Patients with HIV infection should be maintained on antiretroviral therapy to prevent the potential increase in viral replication.

Dosage form specific issues:

- Benzyl alcohol: Products may contain benzyl alcohol which has been associated with "gasping syndrome" in neonates; when administering to newborns, reconstitute with sterile water or saline for injection.

- M-cresol: Some products may contain m-cresol as a preservative.

Other warnings/precautions:

- Administration: Not for I.V. injection.

Pregnancy Risk FactorB/C (depending upon manufacturer)
Pregnancy ConsiderationsReproduction studies have not been conducted with all agents. Teratogenic effects were not observed in animal studies. During normal pregnancy, maternal production of endogenous growth hormone decreases as placental growth hormone production increases. Data with somatropin use during pregnancy is limited.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

Growth hormone deficiency: Adverse reactions reported with growth hormone deficiency vary greatly by age. Generally, percentages are less in pediatric patients than adults, and many of the reactions reported in adults are dose related. Percentages reported also vary by product. Below is a listing by age group; events reported more commonly overall are noted with an asterisk (*).

Children: Antibodies development, arthralgia, edema, eosinophilia, glycosuria, Hb A_{1c} increased, headache, hematoma, hematuria, hyperglycemia (mild), hypertriglyceridemia, hypoglycemia, hypothyroidism, injection site reaction, leg pain, lipoatrophy, muscle pain, psoriasis exacerbation, rash, seizure, weakness

Adults: Arthralgia*, back pain, bronchitis, carpal tunnel syndrome, chest pain, depression, diaphoresis, dizziness, edema*, fatigue, flu-like syndrome*, glucose intolerance, glucosuria, headache*, hyperglycemia (mild), hypertension, hypoesthesia, hypothyroidism, infection, insomnia, leg edema, muscle pain, myalgia*, nausea, pain in extremities, paresthesia*, peripheral edema*, rhinitis, skeletal pain*, stiffness in extremities, upper respiratory tract infection, weakness

Additional/postmarketing reactions observed with growth hormone deficiency: Gynecomastia, increased growth of pre-existing nevi, pancreatitis

HARS: Serostim®: Limited to >10%: Edema (peripheral) (19% to 45%), arthralgia (28% to 37%), pain (extremity) (5% to 19%), hypoesthesia (9% to 15%), headache (4% to 14%), blood glucose increased (4% to 14%), paresthesia (11% to 13%), myalgia (3% to 13%)

Idiopathic short stature: Percentages reported using Humatrope® versus placebo: Myalgia (24%), scoliosis (19%), otitis media (16%), arthralgia (11%), arthrosis (11 %), hyperlipidemia (8%), gynecomastia (5%), hip pain (3%), hypertension (3%). Additional adverse reactions listed as reported using other products from ISS NCGS Cohort (frequencies <1%): Aggressiveness, benign intracranial hypertension, diabetes, edema, hair loss, headache, injection site reaction

Prader-Willi syndrome: Genotropin® (frequency not defined): Aggressiveness, arthralgia, edema, hair loss, headache, benign intracranial hypertension, myalgia; fatalities associated with use in this population have been reported

Turner syndrome: Percentages reported using Humatrope® compared to untreated patients. Additional adverse reactions reported from other products, frequency not specified: Surgical procedures (45%), otitis media (43%), ear disorders (18%), hypothyroidism (14%), nevi increased (11%), peripheral edema (7%), joint pain, respiratory illness, urinary tract infection

HIV patients with wasting or cachexia: Serostim® (limited to ≥5%): Musculoskeletal disorders (arthralgia, arthrosis, myalgia: 78%), peripheral edema (26%), headache (13%), nausea (9%), paresthesia (8%), edema (6%), gynecomastia (6%), hypoesthesia (5%)

Short-bowel syndrome: Zorbtive® (limited to >10%): Peripheral edema (69% to 81%), facial edema (44% to 50%), arthralgia (31% to 44%), nausea (13% to 31%), injection site pain (up to 31%), flatulence (25%), injection site reaction (19% to 25%), abdominal pain (13% to 25%), vomiting (19%), pain (6% to 19%), chest pain (up to 19%), dehydration (up to 19%), infection (up to 19%), rhinitis (up to 19%), hearing symptoms (13%), dizziness (6% to 13%), rash (6% to 13%), diaphoresis (up to 13%), generalized edema (up to 13%), malaise (up to 13%), moniliasis (up to 13%), myalgia (up to 13%)

SHOX deficiency: Humatrope®: Arthralgia (11%), gynecomastia (8%), excessive cutaneous nevi (7%), scoliosis (4%)

Small for gestational age: Genotropin® (frequency not defined): Mild, transient hyperglycemia; benign intracranial hypertension (rare); central precocious puberty; jaw prominence (rare); aggravation of pre-existing scoliosis (rare); injection site reactions; progression of pigmented nevi

Drug Interactions

Antidiabetic Agents: Somatropin may diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Cortisone: Somatropin may diminish the therapeutic effect of Cortisone. Growth hormone may reduce the conversion of cortisone to the active cortisol metabolite. *Risk D: Consider therapy modification*

Estrogen Derivatives: May diminish the therapeutic effect of Somatropin. Shown to be a concern with oral hormone replacement therapy in postmenopausal women. **Exceptions:** Ethinyl Estradiol; Mestranol. *Risk D: Consider therapy modification*

PredniSONE: Somatropin may diminish the therapeutic effect of PredniSONE. Growth hormone may reduce the conversion of prednisone to the active prednisolone metabolite. *Risk D: Consider therapy modification*

Monitoring ParametersGrowth curve, periodic thyroid function tests, bone age (annually), periodical urine testing for glucose, somatomedin C (IGF-I) levels; funduscopic examinations at initiation of therapy and periodically during treatment; serum phosphorus, alkaline phosphatase and parathyroid hormone. If growth deceleration is observed in children treated for growth hormone deficiency, and not due to other causes, evaluate for presence of antibody formation. Strict blood glucose monitoring in patients with diabetes. Progression or recurrence of pre-existing tumors or malignant transformation of skin lesions.

CRI: Progression of renal osteodystrophy

Prader-Willi syndrome: Monitor for sleep apnea, respiratory infections, snoring (onset of or increased)

Turner syndrome: Ear disorders including otitis media; cardiovascular disorders

Noonan syndrome: Prior to use, verify short stature syndrome.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness (according to purpose for use), and adverse reactions Perform funduscopic examinations at initiation of therapy and periodically during treatment; Instruct patients with diabetes to monitor glucose levels closely (may induce insulin intolerance). Instruct patient in proper use if self-administered (storage, reconstitution, injection techniques, and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report. Pediatrics: Monitor growth curve: annually determine bone age.

Monitoring: Lab TestsPeriodic thyroid function tests, periodical urine testing for glucose, somatomedin C (IGF-I) levels; serum phosphorus, alkaline phosphatase and parathyroid hormone. If growth deceleration is observed in children treated for growth hormone deficiency, and not due to other causes, evaluate for presence of antibody formation. Strict blood glucose monitoring in patients with diabetes.

Patient EducationThis drug can only be administered by injection. If self-administered, you will be instructed by prescriber on proper storage, reconstitution, injection technique, and syringe/needle disposal. Do not shake. Rotate injection sites. Use exactly as prescribed; do not discontinue or alter dose without consulting prescriber. Report immediately any pain, redness, burning, drainage, or swelling at injection site. If you have diabetes, monitor glucose levels closely; this medication may cause an alteration in your insulin levels. May cause side effects which are particular to purpose for use and formulation prescribed; your prescriber will instruct you in particular side effects for your medication. Report immediately unusual or persistent bleeding, excessive fatigue or swelling (edema) of extremities, joint or muscle pain or headache, nausea or vomiting, personality changes, or other persistent adverse effects. **Pregnancy/breast-feeding precaution:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [rDNA origin]:

Genotropin®: 5.8 mg [~15 int. units/mL; delivers 5 mg/mL; contains m-cresol]; 13.8 mg [~36 int. units/mL; delivers 12 mg/mL; contains m-cresol]

Genotropin Miniquick® [preservative free]: 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, 2 mg [each strength delivers 0.25 mL]

Humatrope®: 5 mg [15 int. units], 6 mg [18 int. units], 12 mg [36 int. units], 24 mg [72 int. units]

Nutropin®: 5 mg [~15 int. units; packaged with diluent containing benzyl alcohol]; 10 mg [~30 int. units; packaged with diluent containing benzyl alcohol]

Omnitrope™: 5.8 mg [~17.4 int. units; packaged with diluent containing benzyl alcohol]

Saizen®: 5 mg [~15 int. units; contains sucrose 34.2 mg; packaged with diluent containing benzyl alcohol]; 8.8 mg [~26.4 int. units; contains sucrose 60.2 mg; packaged with diluent containing benzyl alcohol]

Serostim®: 4 mg [~12 int. units; contains sucrose 27.3 mg; packaged with diluent containing benzyl alcohol; 5 mg [~15 int. units; contains sucrose 34.2 mg]; 6 mg [~18 int. units; contains sucrose 41 mg]; 8.8 mg [~26.4 int. units; contains sucrose 60.19 mg; packaged with diluent containing benzyl alcohol]

Tev-Tropin®: 5 mg [15 int. units/mL; packaged with diluent containing benzyl alcohol]

Zorbtive®: 8.8 mg [~26.4 int. units; contains sucrose 60.19 mg; packaged with diluent containing benzyl alcohol]

Injection, solution [rDNA origin]:

Norditropin®: 5 mg/1.5 mL (1.5 mL); 15 mg/1.5 mL (1.5 mL)

Norditropin® NordiFlex®: 5 mg/1.5 mL (1.5 mL); 10 mg/1.5 mL (1.5 mL); 15 mg/1.5 mL (1.5 mL)

Nutropin AQ®: 5 mg/mL (2 mL) [~15 int. units/mL]

Omnitrope™: 5 mg/1.5 mL (1.5 mL); 10 mg/1.5 mL (1.5 mL)

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Solution (Norditropin)

5 mg/1.5 mL (1.5): $313.96

15 mg/1.5 mL (1.5): $943.73

Solution (Norditropin NordiFlex Pen)

5 mg/1.5 mL (1.5): $323.27

10 mg/1.5 mL (1.5): $674.13

15 mg/1.5 mL (1.5): $951.79

Solution (reconstituted) (Genotropin)

0.2 mg (7): $94.94

0.4 mg (7): $196.23

0.6 mg (7): $280.59

0.8 mg (7): $372.39

1 mg (7): $465.16

1.2 mg (7): $558.19

1.4 mg (7): $654.05

1.6 mg (7): $744.25

2 mg (7): $930.32

5.8 mg (1): $310.16

13.8 mg (1): $797.45

Solution (reconstituted) (Saizen)

5 mg (1): $328.58

8.8 mg (1): $490.73

Solution (reconstituted) (Saizen Click.Easy)

8.8 mg (1): $490.73

Solution (reconstituted) (Tev-Tropin)

5 mg (1): $211.84

Mechanism of ActionSomatropin is a purified polypeptide hormones of recombinant DNA origin; somatropin contains the identical sequence of amino acids found in human growth hormone; human growth hormone stimulates growth of linear bone, skeletal muscle, and organs; stimulates erythropoietin which increases red blood cell mass; exerts both insulin-like and diabetogenic effects; enhances the transmucosal transport of water, electrolytes, and nutrients across the gut

Pharmacodynamics/Kinetics

Duration: Maintains supraphysiologic levels for 18-20 hours

Absorption: I.M., SubQ: Well absorbed

Distribution: ~1 L/kg

Metabolism: Hepatic and renal (~90%)

Bioavailability: SubQ: ~70% to 90%

Half-life elimination: Preparation and route of administration dependent; SubQ: ~2-4 hours

Excretion: Urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause aggression (in pediatric patients with Prader-Willi syndrome)

Mental Health: Effects on Psychiatric TreatmentContraindicated in pediatric patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment; fatalities have been reported.

Index TermshGH; Human Growth Hormone; Somatrem

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International Brand NamesDeclage (KP); Genheal (PH); Genotonorm (FR); Genotonorm Miniquick (FR); Genotropin (AE, AU, BH, CH, CR, CY, DE, DO, EG, GT, HN, ID, IL, IN, IQ, IR, JO, KW, LB, LY, NI, OM, PA, PK, PL, QA, SA, SV, SY, UY, VE, YE); Grorm (PL); Growject BC (JP); Growtropin-Aq (CO); Humatrope (AR, BF, BJ, BR, CI, CN, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, PE, PH, PL, SC, SD, SL, SN, TN, TW, TZ, UG, ZA, ZM, ZW); Maxomat (FR); Nordilet (KP); Norditropin (AR, BR, CL, CO, JP, KP, PL); Norditropin Nordilet (SG, TH); Norditropin S (JP); Norditropin Simplex (KP); Norditropin Simplexx (DE, ES, NZ, TH); Novell-Eutropin (ID); Nutropin AQ (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Nutropinaq (FR); Omnitrope (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Saizen (AR, AU, BR, CH, CL, DE, EC, FR, HK, IL, MX, MY, PE, PH, PL, TW); Scitropin (AU, HK, KP, PH); Serostim (MX); Somatonorm (HR); Valtropin (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Zomacton (PL)

Sorafenib

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Nexavar® may be confused with Nexium®

Sorafenib may be confused with sunitinib

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(sor AF e nib)
U.S. Brand NamesNexavar®
Canadian Brand NamesNexavar®
Pharmacologic CategoryAntineoplastic Agent, Tyrosine Kinase Inhibitor; Vascular Endothelial Growth Factor (VEGF) Inhibitor
Use: Labeled IndicationsTreatment of advanced renal cell cancer (RCC), unresectable hepatocellular cancer (HCC)
Use: Unlabeled/InvestigationalTreatment of advanced thyroid cancer
Dosing: Adults

Advanced renal cell carcinoma: Oral: 400 mg twice daily

Hepatocellular cancer: Oral: 400 mg twice daily

Thyroid cancer (unlabeled use): 400 mg twice daily (Gupta-Abramson, 2008)

Dosage adjustment for concomitant CYP3A4 inducers: Avoid the concomitant use of a strong CYP3A4 inducer (eg, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, St. John's wort) with sorafenib. If a strong CYP3A4 inducer is required, the sorafenib dose may need to be increased, with careful monitoring. When the strong CYP3A4 inducer is discontinued, reduce sorafenib to the indicated dose.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo adjustment is required for mild, moderate, or severe renal impairment (not dependant on dialysis); has not been studied in dialysis patients.
Dosing: Hepatic ImpairmentNo adjustment required for mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment; not studied in severe hepatic impairment (Child-Pugh class C). Use with extreme caution in patients with HCC with elevated bilirubin levels.
Dosing: Adjustment for ToxicityTemporary interruption and/or dosage reduction may be necessary for management of adverse drug reactions. The dose may be reduced to 400 mg once daily and then further reduced to 400 mg every other day.

Dose modification for severe/persistent hypertension (despite antihypertensive therapy) or cardiac ischemia/infarction: Consider temporarily or permanently discontinuing treatment.

Dose modification for hemorrhage requiring medical intervention or gastrointestinal perforation: Consider permanently discontinuing treatment.

Dose modification for skin toxicity:

Grade 1 (numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which do not disrupt normal activities): Continue sorafenib and consider symptomatic treatment with topical therapy.

Grade 2 (painful erythema and swelling of the hands or feet and/or discomfort affecting normal activities):

1st occurrence: Continue sorafenib and consider symptomatic treatment with topical therapy. **Note:** If no improvement within 7 days, see dosing for 2nd or 3rd occurrence.

2nd or 3rd occurrence: Hold treatment until resolves to grade 0-1; resume treatment with dose reduced by one dose level (400 mg daily or 400 mg every other day)

4th occurrence: Discontinue treatment

Grade 3 (moist desquamation, ulceration, blistering, or severe pain of the hands or feet or severe discomfort that prevents working or performing daily activities):

1st or 2nd occurrence: Hold treatment until resolves to grade 0-1; resume treatment with dose reduced by one dose level (400 mg daily or 400 mg every other day)

3rd occurrence: Discontinue treatment

Administration: OralAdminister with water on an empty stomach (1 hour before or 2 hours after eating). Swallow tablet whole.
Dietary ConsiderationsTake without food (1 hour before or 2 hours after eating).

StorageStore at room temperature of 25°C (77°F); excursions permitted to 15°C and 30°C (59°F and 86°F). Protect from moisture.
ContraindicationsHypersensitivity to sorafenib or any component of the formulation
Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bleeding: Increased risk of bleeding may occur; consider discontinuing with serious bleeding events.
- Cardiac ischemia/infarction: May cause cardiac ischemia or infarction; discontinuation (temporary or permanent) in patients who develop these should be considered. Use in patients with unstable coronary artery disease or recent myocardial infarction has not been studied. Use with caution in patients with cardiovascular disease.
- Dermatologic reactions: Hand-foot skin reaction and rash are the most common adverse events; usually managed with topical treatment, treatment delays, and/or dose reductions.
- Gastrointestinal perforation: Gastrointestinal perforation has been reported (rare); monitor patients for signs/symptoms (abdominal pain, constipation, or vomiting); discontinue treatment if gastrointestinal perforation occurs.
- Hypertension: May cause hypertension, especially in the first 6 weeks of treatment; monitor. Use caution in patients with underlying or poorly-controlled hypertension.
- Wound healing complications: May complicate wound healing; temporarily withhold treatment for patients undergoing major surgical procedures.

Disease-related concerns:

- Hepatic impairment: Sorafenib levels may be lower in HCC patients with mild-to-moderate hepatic impairment (Child-Pugh classes A and B). Use with extreme caution in patients with HCC with elevated bilirubin levels. Not studied in patients with severe hepatic impairment (Child-Pugh class C). The optimal dose in non-HCC patients with hepatic impairment has not been established.
- Renal impairment: Not studied in dialysis patients.

Concurrent drug therapy issues:

- CYP3A4 inducers: Avoid concurrent use (if possible) with strong CYP3A4 inducers (eg, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, St. John's wort); may decrease sorafenib levels/effects.
- UGT1A1 substrates: Use caution when administering sorafenib with compounds that are metabolized predominantly via UGT1A1 (eg, irinotecan).
- Warfarin: Monitor PT/INR in patients on warfarin therapy; due to potential for bleeding events to occur.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo difference in efficacy or safety was observed between older and younger patients, but only 4% of patients studied were >75 years of age.
Pregnancy Risk FactorD
Pregnancy ConsiderationsAnimal studies have demonstrated teratogenicity and fetal loss. There are no adequate and well-controlled studies in pregnant women. Because sorafenib inhibits angiogenesis, a critical component of fetal development, adverse effects on pregnancy would be expected. Women of childbearing potential should be advised to avoid pregnancy. Men and women should use effective birth control during treatment and for at least 2 weeks after treatment is discontinued.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsDue to the potential for serious adverse effects in the nursing infant, breast-feeding is not recommended.
Adverse Reactions

>10%:

Cardiovascular: Hypertension (9% to 17%; grade 3: 3% to 4%; grade 4: <1%; onset: ~3 weeks)

Central nervous system: Fatigue (37% to 46%), sensory neuropathy (≤13%), pain (11%)

Dermatologic: Rash/desquamation (19% to 40%; grade 3: ≤1%), hand-foot syndrome (21% to 30%; grade 3: 6% to 8%), alopecia (14% to 27%), pruritus (14% to 19%), dry skin (10% to 11%), erythema

Endocrine & metabolic: Hypoalbuminemia (≤59%), hypophosphatemia (35% to 45%; grade 3: 11% to 13%; grade 4: <1%)

Gastrointestinal: Diarrhea (43% to 55%; grade 3: 2% to 10%; grade 4: <1%), lipase increased (40% to 41% [usually transient]), amylase increased (30% to 34% [usually transient]), abdominal pain (11% to 31%), weight loss (10% to 30%), anorexia (16% to 29%), nausea (23% to 24%), vomiting (15% to 16%), constipation (14% to 15%)

Hematologic: Lymphopenia (23% to 47%; grades 3/4: ≤13%), thrombocytopenia (12% to 46%; grades 3/4: 1% to 4%), INR increased (≤42%), neutropenia (≤18%; grades 3/4: ≤5%), hemorrhage (15% to 18%; grade 3: 2% to 3%; grade 4: ≤2%), leukopenia

Hepatic: Liver dysfunction (≤11%; grade 3: 2%; grade 4: 1%)

Neuromuscular & skeletal: Muscle pain, weakness

Respiratory: Dyspnea (≤14%), cough (≤13%)

1% to 10%:

Cardiovascular: Cardiac ischemia/infarction (≤3%), flushing

Central nervous system: Headache (≤10%), depression, fever

Dermatologic: Acne, exfoliative dermatitis

Gastrointestinal: Appetite decreased, dyspepsia, dysphagia, esophageal varices bleeding (2%), glossodynia, mucositis, stomatitis, xerostomia

Genitourinary: Erectile dysfunction

Hematologic: Anemia

Hepatic: Transaminases increased (transient)

Neuromuscular & skeletal: Joint pain (≤10%), arthralgia, myalgia

Respiratory: Hoarseness

Miscellaneous: Influenza-like symptoms

<1%, postmarketing, and/or case reports: Acute renal failure, alkaline phosphatase increased, arrhythmia, bilirubin increased, bone pain, cardiac failure, cerebral hemorrhage, CHF, dehydration, eczema, epistaxis, erythema multiforme, folliculitis, gastritis, gastrointestinal hemorrhage, gastrointestinal perforation, gastrointestinal reflux, gynecomastia, hypersensitivity (skin reaction, urticaria), hypertensive crisis, hyponatremia, hypothyroidism, infection, jaundice, MI, mouth pain, myocardial ischemia, pancreatitis, pleural effusion, preeclampsia-like syndrome (reversible hypertension and proteinuria), renal failure, respiratory hemorrhage, reversible posterior leukoencephalopathy syndrome (RPLS), rhinorrhea, skin cancer (squamous cell/keratoacanthomas), thromboembolism, tinnitus, transient ischemic attack, tumor pain, voice alteration

Oncology: Emetic PotentialLow (10% to 30%)

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor); **Inhibits** CYP2B6 (moderate), 2C8 (strong), 2C9 (moderate)

Drug Interactions

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

CYP2B6 Substrates: CYP2B6 Inhibitors (Moderate) may decrease the metabolism of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Strong) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Dacarbazine: Sorafenib may decrease the serum concentration of Dacarbazine. Sorafenib may also increase the concentration of dacarbazine's active metabolite. *Risk C: Monitor therapy*

DOXOrubicin: Sorafenib may increase the serum concentration of DOXOrubicin. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fluorouracil: Sorafenib may decrease the serum concentration of Fluorouracil. Sorafenib may increase the serum concentration of Fluorouracil. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Irinotecan: Sorafenib may increase the serum concentration of Irinotecan. Sorafenib may also increase the concentration of the active metabolite of irinotecan, SN-38. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Warfarin: Sorafenib may enhance the anticoagulant effect of Warfarin. Sorafenib may increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Bioavailability is decreased 29% with a high-fat meal (bioavailability is similar to fasting state when administered with a moderate-fat meal).

Herb/Nutraceutical: Avoid St John's wort (may decrease the levels/effects of sorafenib).

Monitoring ParametersCBC with differential, electrolytes, phosphorus, lipase and amylase levels; blood pressure (baseline, weekly for the first 6 weeks, then periodic)

Nursing: Physical Assessment/MonitoringUse caution in presence of hypertension, cardiac artery disease or recent MI. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg. warfarin, digoxin). Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions or toxicity on a regular basis (gastrointestinal perforation [abdominal pain, constipation, vomiting], diarrhea, fatigue, rash, or hand-foot syndrome); dosing adjustments may be necessary. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential, electrolytes, phosphorus, lipase and amylase levels

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take exactly as directed 1 hour before or 2 hours after eating. You may need periodic laboratory tests while taking this medication. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience loss of appetite; nausea and vomiting (small, frequent meals and frequent mouth care may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or hair loss (may grow back when treatment is discontinued). Report immediately persistent or acute headache, dizziness, or vision changes (monitor blood pressure if recommended by prescriber); chest pain or palpitations; or unusual bleeding. Report unusual skin rash; hand and foot syndrome (redness, tenderness, dryness, peeling, numbness, or tingling of the palms and soles); persistent gastrointestinal upset (diarrhea, constipation, abdominal pain); unusual or persistent cough; bone, joint, or muscle weakness or pain or loss of sensation; flu-like symptoms; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber is you are pregnant. Do not get pregnant while taking this drug or for two weeks after discontinuing. May cause fetal defects or fetal loss. Males and females should consult prescriber for appropriate contraceptive measures while on this medication. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as tosylate:

Nexavar®: 200 mg

Generic AvailableNo

ManufacturerBayer HealthCare

Mechanism of ActionMultikinase inhibitor; inhibits tumor growth and angiogenesis by inhibiting intracellular Raf kinases (CRAF, BRAF, and mutant BRAF), and cell surface kinase receptors (VEGFR-2, VEGFR-3, PDGFR-beta, cKIT, and FLT-3)

Pharmacodynamics/Kinetics

Protein binding: 99.5%

Metabolism: Hepatic, via CYP3A4 (primarily oxidated to the pyridine N-oxide; active, minor) and UGT1A9 (glucuronidation)

Bioavailability: 38% to 49%; reduced when administered with a high-fat meal

Half-life elimination: 25-48 hours

Time to peak, plasma: ~3 hours

Excretion: Feces (77%, 51% as unchanged drug); urine (19%, as metabolites)

Related Information

- Common Toxicity Criteria
- Management of Nausea and Vomiting
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mouth pain, mucositis, stomatitis, xerostomia (normal salivary flow resumes upon discontinuation), and dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsSorafenib may cause hypertension; monitor blood pressure prior to vasoconstrictor use

Mental Health: Effects on Mental StatusSedation is common; may cause depression

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with SSRIs, lithium, valproic acid may produce additive effects. Sedative effects may be additive if used in combination with psychotropics. May cause neutropenia, thrombocytopenia, or leukopenia; use caution with clozapine, carbamazepine, and valproic acid. Avoid concurrent use with St John's wort.

Index TermsBAY 43-9006; NSC-724772; Sorafenib Tosylate

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International Brand NamesNexavar (AR, AT, AU, BE, BG, BR, CH, CL, CN, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IT, KP, MX, MY, NL, NO, NZ, PE, PH, PT, RU, SE, SG, TH, TR, UY)

Sorbitol

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Pronunciation(SOR bi tole)

Pharmacologic CategoryGenitourinary Irrigant; Laxative, Osmotic

Use: Labeled IndicationsGenitourinary irrigant in transurethral prostatic resection or other transurethral resection or other transurethral surgical procedures; diuretic; humectant; sweetening agent; hyperosmotic laxative; facilitate the passage of sodium polystyrene sulfonate through the intestinal tract

Dosing: Adults

Hyperosmotic laxative (as single dose, at infrequent intervals):

Oral: 30-150 mL (as 70% solution)

Rectal enema: 120 mL as 25% to 30% solution

Adjunct to sodium polystyrene sulfonate: 15 mL as 70% solution orally until diarrhea occurs (10-20 mL/2 hours) or 20-100 mL as an oral vehicle for the sodium polystyrene sulfonate resin

When administered with charcoal:

Oral: 4.3 mL/kg of 70% sorbitol with 1 g/kg of activated charcoal every 4 hours until first stool containing charcoal is passed

Transurethral surgical procedures: Irrigation: Topical: 3% to 3.3% as transurethral surgical procedure irrigation

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Hyperosmotic laxative (as single dose, at infrequent intervals):

Children 2-11 years:

Oral: 2 mL/kg (as 70% solution)

Rectal enema: 30-60 mL as 25% to 30% solution

Children >12 years: Oral, Rectal enema: Refer to adult dosing.

When administered with charcoal: Oral: Children: 4.3 mL/kg of 35% sorbitol with 1 g/kg of activated charcoal

StorageAvoid storage in temperatures >150°F; do not freeze.

ContraindicationsAnuria

Warnings/Precautions

Concerns related to adverse effects:

- Fluid/electrolyte imbalance: Large volumes may result in fluid overload and/or electrolyte changes.

Disease-related concerns:

- Cardiopulmonary disease: Use with caution in patients with severe cardiopulmonary disease.
- Renal impairment: Use with caution in patients with renal impairment.
- Unable to metabolize sorbitol: Use with caution in patients unable to metabolize sorbitol.

Geriatric ConsiderationsCauses for constipation must be evaluated prior to initiating treatment. Nonpharmacological dietary treatment should be initiated before laxative use. Sorbitol is as effective as lactulose but is much less expensive.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined.

Cardiovascular: Edema

Endocrine & metabolic: Fluid and electrolyte losses, hyperglycemia, lactic acidosis

Gastrointestinal: Diarrhea, nausea, vomiting, abdominal discomfort, xerostomia

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersMonitor for fluid overload and/or electrolyte disturbances following large volumes; changes may be delayed due to slow absorption

Nursing: Physical Assessment/MonitoringWhen used as cathartic, determine cause of constipation before use. Assess knowledge/teach patient about use of nonpharmacological interventions to prevent constipation.

Monitoring: Lab TestsElectrolytes

Patient EducationCathartic: Use of cathartics on a regular basis will have adverse effects. Increased exercise, increased fluid intake, or increased dietary fruit and fiber may be effective in preventing and resolving constipation. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, genitourinary irrigation: 3% (3000 mL, 5000 mL); 3.3% (2000 mL, 4000 mL)

Solution, oral: 70% (30 mL, 480 mL, 3840 mL)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Sorbitol)

70% (473): $17.99

Mechanism of ActionA polyalcoholic sugar with osmotic cathartic actions

Pharmacodynamics/Kinetics

Onset of action: 0.25-1 hour

Absorption: Oral, rectal: Poor

Metabolism: Primarily hepatic to fructose

Related Information

- Laxatives, Classification and Properties

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

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International Brand NamesAgarol (CH); Ardeanutrisol SO (CZ); Cystosol (SE); klysma Sorbit (DE); Medevac (AU); Progras (AR); Resulax (SE); Sladial (HR); Sorbilande (IT); Sorbilax (AU); Sorbit Fresenius (AT); Sorbit Leopold (AT); Sorbit Mayrhofer (AT); Sorbitol Aguettant (FR); Sorbitol Baxter (LU); Sorbitol Delalande (BE, FR); Sorbitol-Infusionslosung (DE); Syn M.D. (BE, CH, LU)

Sotalol

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English

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Sotalol may be confused with Stadol®

Betapace® may be confused with Betapace AF®

Betapace AF® may be confused with Betapace®

Pronunciation(SOE ta lole)

U.S. Brand NamesBetapace AF®; Betapace®; Sorine®

Canadian Brand NamesApo-Sotalol®; Betapace AF®; CO Sotalol; DOM-Sotalol; Gen-Sotalol; Lin-Sotalol; MED-Sotalol; Novo-Sotalol; Nu-Sotalol; PHL-Sotalol; PMS-Sotalol; PRO-Sotalol; RATIO-Sotalol; RHOXAL-Sotalol; Riva-Sotalol; Rylosol; SANDOZ-Sotalol

Pharmacologic CategoryAntiarrhythmic Agent, Class II; Antiarrhythmic Agent, Class III; Beta Blocker, Nonselective

Use: Labeled IndicationsTreatment of documented ventricular arrhythmias (ie, sustained ventricular tachycardia), that in the judgment of the physician are life-threatening; maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation and atrial flutter who are currently in sinus rhythm. Manufacturer states substitutions should not be made for Betapace AF® since Betapace AF® is distributed with a patient package insert specific for atrial fibrillation/flutter.

Dosing: AdultsSotalol should be initiated and doses increased in a hospital with facilities for cardiac rhythm monitoring and assessment. Proarrhythmic events can occur after initiation of therapy and with each upward dosage adjustment.

Ventricular arrhythmias (Betapace®, Sorine®): Oral:

Initial: 80 mg twice daily; dose may be increased gradually to 240-320 mg/day; allow 3 days between dosing increments (to attain steady-state plasma concentrations and to allow monitoring of QT intervals).

Usual range: Most patients respond to 160-320 mg/day in 2-3 divided doses.

Maximum: Some patients, with life-threatening refractory ventricular arrhythmias, may require doses as high as 480-640 mg/day; prescribed ONLY when the potential benefit outweighs the increased of adverse events.

Atrial fibrillation or atrial flutter (Betapace AF®): Oral: Initial: 80 mg twice daily

Note: If the initial dose does not reduce the frequency of relapses of atrial fibrillation/flutter and is tolerated without excessive QT prolongation (not >520 msec) after 3 days, the dose may be increased to 120 mg twice daily. This may be further increased to 160 mg twice daily if response is inadequate and QT prolongation is not excessive.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricSotalol should be initiated and doses increased in a hospital with facilities for cardiac rhythm monitoring and assessment. Proarrhythmic events can occur after initiation of therapy and with each upward dosage adjustment.

Note: The safety and efficacy of sotalol in children have not been established

Supraventricular arrhythmias: Oral: **Note:** Dosing per manufacturer, based on pediatric pharmacokinetic data; wait at least 36 hours between dosage adjustments to allow monitoring of QT intervals

Children ≤2 years: Dosage should be adjusted (decreased) by plotting of the child's age on a logarithmic scale; see graph or refer to manufacturer's package labeling.

Children >2 years: Initial: 90 mg/m^2/day in 3 divided doses; may be incrementally increased to a maximum of 180 mg/m^2/day

Dosing: Renal ImpairmentAdults: Impaired renal function can increase the terminal half-life, resulting in increased drug accumulation. Sotalol (Betapace AF®) is contraindicated per the manufacturer for treatment of atrial fibrillation/flutter in patients with a Cl_{cr} <40 mL/minute.

Ventricular arrhythmias (Betapace®, Sorine®):

Cl_{cr} >60 mL/minute: Administer every 12 hours.

Cl_{cr} 30-60 mL/minute: Administer every 24 hours.

Cl_{cr} 10-30 mL/minute: Administer every 36-48 hours.

Cl_{cr} <10 mL/minute: Individualize dose.

Atrial fibrillation/flutter (Betapace AF®):

Cl_{cr} >60 mL/minute: Administer every 12 hours.

Cl_{cr} 40-60 mL/minute: Administer every 24 hours.

Cl_{cr} <40 mL/minute: Use is contraindicated.

Dialysis: Hemodialysis would be expected to reduce sotalol plasma concentrations because sotalol is not bound to plasma proteins and does not undergo extensive metabolism. Administer dose postdialysis or administer supplemental 80 mg dose. Peritoneal dialysis does not remove sotalol; supplemental dose is not necessary.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsAdminister on an empty stomach.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Extemporaneously PreparedTo make a 5 mg/mL oral solution, using a 6-ounce amber plastic prescription bottle, add five sotalol 120 mg tablets to 120 mL of simple syrup containing 0.1% sodium benzoate (tablets do not need to be crushed). Shake well. Allow tablets to hydrate for ~2 hours; shake intermittently until tablets completely disintegrate. Store at room temperature; shake well before use. Stable for 3 months. (Refer to manufacturer's current labeling.)

ContraindicationsHypersensitivity to sotalol or any component of the formulation; bronchial asthma; sinus bradycardia; second- and third-degree AV block (unless a functioning pacemaker is present); congenital or acquired long QT syndromes; cardiogenic shock; uncontrolled congestive heart failure. Betapace AF® is contraindicated in patients with significantly reduced renal filtration (Cl_{cr} <40 mL/minute).

Allergy Considerations

- Beta-Blocker Allergy

Warnings/Precautions

Boxed warnings:

- Dose initiation/increases: See “Other warnings/precautions” below.
- Product substitution: See “Dosage form specific issues” below.

Concerns related to adverse effects:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.
- Proarrhythmic effects: Watch for proarrhythmic effects; monitor and adjust dose to prevent QT_c prolongation.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.
- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.
- Electrolyte imbalances: Correct electrolyte imbalances before initiating (especially hypokalemia and hypomagnesemia).
- Heart failure (HF): Use with caution in patients with compensated heart failure and monitor for a worsening of the condition.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; may worsen disease.
- Myocardial infarction: Use with caution within the first 2 weeks post-MI (experience limited).
- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).
- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.
- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required. Creatinine clearance must be calculated with dose initiation and dose increases.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents which decrease myocardial function.
- Calcium channel blockers: Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur.
- QT_c-prolonging drugs: Concurrent use with other QT_c-prolonging drugs (including Class I and Class III antiarrhythmics) is generally not recommended; withhold for 3 half-lives.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Product substitution: **[U.S. Boxed Warning]: Betapace® should not be substituted for Betapace® AF; Betapace® AF is distributed with an educational insert specifically for patients with atrial fibrillation/flutter.**

Other warnings/precautions:

- Abrupt withdrawal: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.

- Dose initiation/increases: **[U.S. Boxed Warning]: Manufacturer recommends initiation (or reinitiation) and dose increases be done in a hospital setting with continuous monitoring and staff familiar with the recognition and treatment of life-threatening arrhythmias.** Some experts will initiate therapy on an outpatient basis in a patient without heart disease or bradycardia, who has a baseline uncorrected QT interval <450 msec, and normal serum potassium and magnesium levels; close EKG monitoring during this time is necessary. ACC/AHA guidelines for management of atrial fibrillation also recommend that for outpatient initiation the patient not have risk factors predisposing to drug-induced ventricular proarrhythmia (Fuster, 2001). Dosage should be adjusted gradually with 3 days between dosing increments to achieve steady-state concentrations, and to allow time to monitor QT intervals.

Geriatric ConsiderationsSince elderly frequently have Cl_{cr} <60 mL/minute, attention to dose, creatinine clearance, and monitoring is important. Make dosage adjustments at 3-day intervals or after 5-6 doses at any dosage.

Pregnancy Risk FactorB

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Beta-blockers have been associated with bradycardia, hypotension, and IUGR; IUGR is probably related to maternal hypertension. Sotalol has been shown to cross the placenta, and is found in amniotic fluid; therefore, sotalol should be used during pregnancy only if the potential benefit outweighs the potential risk. Cases of neonatal hypoglycemia have been reported following maternal use of beta-blockers at parturition or during breast-feeding. Monitor breast-fed infant for symptoms of beta-blockade.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsSotalol is considered compatible by the AAP. It is recommended that the infant be monitored for signs or symptoms of beta-blockade (hypotension, bradycardia, etc) with long-term use.

Adverse Reactions

>10%:

Cardiovascular: Bradycardia (16%), chest pain (16%), palpitation (14%)

Central nervous system: Fatigue (20%), dizziness (20%), lightheadedness (12%)

Neuromuscular & skeletal: Weakness (13%)

Respiratory: Dyspnea (21%)

1% to 10%:

Cardiovascular: Edema (8%), abnormal ECG (7%), hypotension (6%), proarrhythmia (5%), syncope (5%), CHF (5%), peripheral vascular disorders (3%)

Central nervous system: Headache (8%), sleep problems (8%), mental confusion (6%), anxiety (4%), depression (4%)

Dermatologic: Itching/rash (5%)

Endocrine & metabolic: Sexual ability decreased (3%)

Gastrointestinal: Nausea/vomiting (10%), diarrhea (7%),stomach discomfort (3% to 6%), flatulence (2%)

Genitourinary: Impotence (2%)

Hematologic: Bleeding (2%)

Neuromuscular & skeletal: Extremity pain (7%), paresthesia (4%), back pain (3%)

Ocular: Visual problems (5%)

Respiratory: Upper respiratory problems (5% to 8%), asthma (2%)

<1% (Limited to important or life-threatening): Alopecia, clouded sensorium, cold extremities, diaphoresis, emotional lability, eosinophilia, fever, hyperlipidemia, incoordination, leukopenia, myalgia, paralysis, phlebitis, photosensitivity reaction, pruritus, pulmonary edema, Raynaud's phenomenon, red crusted skin, serum transaminases increased, skin necrosis after extravasation, thrombocytopenia, vertigo, xerostomia

Postmarketing and/or case reports: Bronchiolitis obliterans with organized pneumonia, leukocytoclastic vasculitis, retroperitoneal fibrosis

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Sotalol peak serum concentrations may be decreased if taken with food.

Herb/Nutraceutical: Avoid ephedra (may worsen arrhythmia).

Monitoring ParametersSerum magnesium, potassium, ECG

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess blood pressure and heart rate prior to and following first dose and with any change in dosage. Assess results of laboratory tests, therapeutic effectiveness, and adverse effects (eg, cardiac and pulmonary status). Advise patients with diabetes to monitor glucose levels closely (beta-blockers may alter glucose tolerance). Do not discontinue abruptly; dose should be tapered gradually. Teach patient appropriate use, possible side effects/interventions (hypotension precautions), and adverse symptoms to report.

Monitoring: Lab TestsSerum magnesium, potassium

Patient EducationDo not take any new medications without consulting prescriber. Take exactly as directed; do not adjust dosage or discontinue without consulting prescriber. Take pulse daily (prior to medication) and follow prescriber's instruction about holding of medication. If you have diabetes, monitor serum sugar closely (drug may alter glucose tolerance or mask signs of hypoglycemia). May cause fatigue, dizziness, lightheadedness (use caution when driving or engaging in activities requiring alertness until response to drug is known), or postural hypotension (use caution when changing position from lying or sitting to standing, when driving, or climbing stairs until response to medication is known); alteration in sexual performance (reversible); nausea or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (boiled milk, buttermilk, or yogurt may help). Report immediately any chest pain, palpitations, irregular heartbeat; swelling of extremities, respiratory difficulty, new cough, or unusual fatigue; persistent nausea, vomiting, or diarrhea; or unusual muscle weakness. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 80 mg, 80 mg [artrial fibrillation], 120 mg, 120 mg [artrial fibrillation], 160 mg, 160 mg [artrial fibrillation], 240 mg

Betapace®: 80 mg, 120 mg, 160 mg, 240 mg

Betapace AF®: 80 mg, 120 mg, 160 mg [artrial fibrillation]

Sorine®: 80 mg, 120 mg, 160 mg, 240 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Betapace)

80 mg (60): $216.46

120 mg (60): $289.44

160 mg (30): $180.58

240 mg (30): $234.98

Tablets (Betapace AF)

120 mg (60): $254.00

160 mg (100): $484.79

Tablets (Sotalol HCl)

80 mg (90): $15.99

120 mg (60): $110.98

160 mg (30): $68.99

240 mg (30): $71.99

Tablets (Sotalol HCl (AF))

80 mg (100): $85.98

120 mg (30): $96.99

160 mg (30): $123.99

Mechanism of Action

Beta-blocker which contains both beta-adrenoreceptor-blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) properties

Class II effects: Increased sinus cycle length, slowed heart rate, decreased AV nodal conduction, and increased AV nodal refractoriness

Class III effects: Prolongation of the atrial and ventricular monophasic action potentials, and effective refractory prolongation of atrial muscle, ventricular muscle, and atrioventricular accessory pathways in both the antegrade and retrograde directions

Sotalol is a racemic mixture of *d*- and *l*-sotalol; both isomers have similar Class III antiarrhythmic effects while the *l*-isomer is responsible for virtually all of the beta-blocking activity

Sotalol has both beta$_1$- and beta$_2$-receptor blocking activity

The beta-blocking effect of sotalol is a noncardioselective [half maximal at about 80 mg/day and maximal at doses of 320-640 mg/day]. Significant beta-blockade occurs at oral doses as low as 25 mg/day.

The Class III effects are seen only at oral doses ≥160 mg/day

Pharmacodynamics/Kinetics

Onset of action: Rapid, 1-2 hours

Peak effect: 2.5-4 hours

Duration: 8-16 hours

Absorption: Decreased 20% to 30% by meals compared to fasting

Distribution: Low lipid solubility; enters milk of laboratory animals and is reported to be present in human milk

Protein binding: None

Metabolism: None

Bioavailability: 90% to 100%

Half-life elimination: 12 hours; Children: 9.5 hours; terminal half-life decreases with age <2 years (may by ≥1 week in neonates)

Excretion: Urine (as unchanged drug)

Pharmacotherapy PearlsPharmacokinetics in children are more relevant for BSA than age.

Dental Health: Effects on Dental TreatmentSotalol is a nonselective beta-blocker and may enhance the pressor response to epinephrine, resulting in hypertension and bradycardia. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution; epinephrine has interacted with nonselective beta-blockers to result in initial hypertensive episode followed by bradycardia. Sotalol is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusDizziness and drowsiness are common; may cause confusion, anxiety, or depression

Mental Health: Effects on Psychiatric TreatmentContraindicated with ziprasidone. May rarely cause leukopenia; use caution with clozapine and carbamazepine. Barbiturates may decrease the effects of beta-blockers; beta-blockers may alter the effects antipsychotics; monitor for altered response.

Cardiovascular ConsiderationsAs with other antiarrhythmics, sotalol is proarrhythmic (eg, torsade de pointes) and therapy with the d-isomer (d-sotalol) increased mortality, presumably due to arrhythmias, in patients with heart failure and myocardial infarction. It is therefore prudent to carefully select and monitor patients on sotalol and avoid its use in patients with a history of heart failure or myocardial infarction.

Anesthesia and Critical Care Concerns/Other Considerations**Withdrawal:** Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia and hypertension.

Index TermsSotalol Hydrochloride

References

"A Comparison of Antiarrhythmic-Drug Therapy With Implantable Defibrillators in Patients Resuscitated From Near-Fatal Ventricular Arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators," *N Engl J Med*, 1997, 337(22):1576-83. [PubMed 9411221]

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Kuhlkamp V, Mewis C, Mermi J, et al, "Suppression of Sustained Ventricular Tachyarrhythmias: A Comparison of d,1-Sotalol With No Antiarrhythmic Drug Treatment," *J Am Coll Cardiol*, 1999, 33(1):46-52. [PubMed 9935007]

Lang DM, "Anaphylactoid and Anaphylactic Reactions. Hazards of Beta-Blockers," *Drug Saf*, 1995, 12(5):299-304.[PubMed 7669259]

Mason JW, "A Comparison of Seven Antiarrhythmic Drugs in Patients With Ventricular Tachyarrhythmias. Electrophysiologic Study versus Electrocardiographic Monitoring Investigators," *N Engl J Med*, 1993, 329(7):452-8. [PubMed 8332150]

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Pacifico A, Hohnloser SH, Williams JH, et al, “Prevention of Implantable-Defibrillator Shocks by Treatment With Sotalol. d,1-Sotalol Implantable Cardioverter-Defibrillator Study Group,” *N Engl J Med*, 1999, 340(24):1855-62. [PubMed 10369848]

Waldo AL, Camm AJ, deRuyter H, et al, “Effect of d-sotalol on Mortality in Patients With Left Ventricular Dysfunction After Recent and Remote Myocardial Infarction. The SWORD Investigators. Survival With Oral d-Sotalol,” *Lancet*, 1996, 348(9019):7-12.[PubMed 8691967]

International Brand NamesAlosot (UY); Beta-Cardone (GB, IE); Betacor (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Betades (IT); Biosotal (PL); Cardol (AU, TW); Darob (AT, HR, PL); Gilucor (HR, HU, PL); Hipecor (CN); Jutalex (DE); Rentibloc (KP); Solavert (AU); Sotacor (AR, AT, AU, BF, BJ, BR, CI, CL, CO, DK, ET, FI, GB, GH, GM, GN, HK, ID, IE, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, SC, SD, SE, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Sotagard (IN); Sotahexal (AU, DE, HU, PL, ZA); Sotalex (BE, BG, CH, CZ, DE, FR, GR, HN, HU, IT, LU, PH, PL, PT, SG); Sotalex Mite (EE); Sotalol Knoll (HU); Sotapor (ES)

Spectinomycin

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Trobicin® may be confused with tobramycin

Pronunciation(spek ti noe MYE sin)
U.S. Brand NamesTrobicin® [DSC]
Pharmacologic CategoryAntibiotic, Miscellaneous
Use: Labeled IndicationsTreatment of uncomplicated gonorrhea
Dosing: Adults

Uncomplicated gonorrhea (urethral, cervical, pharyngeal, or rectal): I.M.: 2 g deep I.M. or 4 g where antibiotic resistance is prevalent 1 time; 4 g (10 mL) dose should be given as two 5 mL injections, followed by adequate chlamydial treatment (doxycycline 100 mg twice daily for 7 days)

Disseminated gonococcal infection: I.M.: 2 g every 12 hours

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Gonorrhea:** I.M.: Children:

<45 kg: 40 mg/kg/dose 1 time (ceftriaxone preferred)

≥45 kg: Refer to adult dosing.

Children >8 years who are allergic to PCNS/cephalosporins may be treated with oral tetracycline.

Dosing: Renal ImpairmentHemodialysis effects: 50% removed by hemodialysis
Administration: I.M.For I.M. use only.
StorageUse reconstituted solutions within 24 hours.
ReconstitutionReconstitute with supplied diluent only.
ContraindicationsHypersensitivity to spectinomycin or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Syphilis: Since spectinomycin is ineffective in the treatment of syphilis and may mask symptoms, all patients should be tested for syphilis at the time of gonorrheal diagnosis and 3 months later.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorB
LactationEnters breast milk/effect on infant unknown
Adverse Reactions<1%: Chills, dizziness, headache, nausea, pain at injection site, pruritus, rash, urticaria, vomiting
Drug Interactions

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringAssess knowledge/teach patient sexually transmitted diseases precautions. Monitor effectiveness and evaluate laboratory results.
Monitoring: Lab TestsTest for syphilis before treatment and 3 months later (see Warnings/Precautions).
Patient EducationThis medication can only be administered I.M. You will need to return for follow-up blood tests. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as hydrochloride:

Trobicin®: 2 g [diluent contains benzyl alcohol] [DSC]

Generic AvailableNo

Mechanism of ActionA bacteriostatic antibiotic that selectively binds to the 30s subunits of ribosomes, and thereby inhibiting bacterial protein synthesis

Pharmacodynamics/Kinetics

Duration: Up to 8 hours

Absorption: I.M.: Rapid and almost complete

Distribution: Concentrates in urine; does not distribute well into the saliva

Half-life elimination: 1.7 hours

Time to peak: ~1 hour

Excretion: Urine (70% to 100% as unchanged drug)

Related Information

- Antimicrobial Drugs of Choice
- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsSpectinomycin Hydrochloride

References

U.S. Department of Health and Human Services, “1993 Sexually Transmitted Diseases Treatment Guidelines,” *MMWR Recomm Rep*, 1993, 42(RR-14).

International Brand NamesKirin (BG, HK, MY); Specin (TW); Togamycin (AE, AR, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Trobicin (AT, AU, BE, BG, BR, CH, CL, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, HR, HU, ID, IE, IN, IT, KP, LU, NL, NO, PK, PL, PT, RU, SE, TH, TR, ZA); Trobicine (FR); Vabicin (TH)

Spiramycin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(speer a MYE sin)
Canadian Brand NamesRovamycine®
Pharmacologic CategoryAntibiotic, Macrolide
Use: Labeled IndicationsTreatment of infections of the respiratory tract, buccal cavity, skin and soft tissues due to susceptible organisms. *N. gonorrhoeae*: as an alternate choice of treatment for gonorrhea in patients allergic to the penicillins. Before treatment of gonorrhea, the possibility of concomitant infection due to *T. pallidum* should be excluded.
Use: Unlabeled/InvestigationalTreatment of *Toxoplasma gondii* to prevent transmission from mother to fetus
Dosing: Adults

Mild-moderate infections: Oral: 6,000,000 to 9,000,000 int. units (4-6 capsules of Rovamycine® "500" per day) in 2 divided doses

Severe infections: Oral: 12,000,000 to 15,000,000 int. units (8-10 capsules of Rovamycine® "500" per day) in 2 divided doses

Gonorrhea: Oral: 12,000,000 to 13,500,000 int. units (8-9 capsules of Rovamycine® "500") as a single dose

Dosing: ElderlyRefer to adult dosage.
Dosing: PediatricSusceptible infections: Oral: Dosage by body weight; usual dosage 150,000 int units/kg; expressed as the number of 750,000 int. unit (Rovamycine "250") capsules per day. Daily dose should be administered in 2-3 divided doses.

15 kg = 3 capsules per day

20 kg = 4 capsules per day

30 kg = 6 capsules per day

Note: In severe infections, dosage may be increased by 50%.

Dosing: Renal ImpairmentNo dosage adjustment required.
Dietary ConsiderationsMay be taken with or without food. Food may improve gastrointestinal tolerance.
StorageStore at 20°C to 25°C (68°F to 77°F).
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to spiramycin, other macrolides (eg, erythromycin) or any component of the formulation
Allergy Considerations

- Macrolide Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: Macrolides have been associated with rare QT_c prolongation and ventricular arrhythmias, including torsade de pointes; use with caution in patients at risk of prolonged cardiac repolarization.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with pre-existing liver disease; hepatic impairment, including hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been observed. Discontinue if symptoms of malaise, nausea, vomiting, abdominal colic, and fever.

Pregnancy Risk FactorNot assigned (other macrolides rated B); C per expert analysis
Pregnancy ConsiderationsCrosses placenta. Specific safety information is not available. However, spiramycin has been used to treat *Toxoplasma gondii* to prevent transmission from mother to fetus.
LactationEnters breast milk/compatible (based on other macrolides)
Breast-Feeding ConsiderationsExcreted in breast milk in bacteriostatic concentrations.
Adverse ReactionsFrequency not defined.

Dermatologic: Rash, urticaria, pruritus, angioedema (rare)

Gastrointestinal: Nausea, vomiting, diarrhea, pseudomembranous colitis (rare)

Hepatic: Transaminases increased

Neuromuscular & skeletal: Paresthesia (rare)

Miscellaneous: Anaphylactic shock (rare)

Note: Rare adverse reactions associated with other macrolide antibiotics include life-threatening ventricular arrhythmia, prolongation of QT_c, and neuromuscular blockade.

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)
Drug Interactions

Cardiac Glycosides: Macrolide Antibiotics may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Etravirine: May decrease the serum concentration of Macrolide Antibiotics. Clarithromycin AUC is reduced and levels of the active metabolite (14-hydroxy-clarithromycin) are modestly increased. Management: For the treatment of *Mycobacterium avium* complex, consider changing to alternative agent, such as azithromycin. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Patient Education

Report persistent diarrhea.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Rovamycine® “250”: 750,000 int. units

Rovamycine® “500”: 1,500,000 int. units

Generic AvailableNo
ManufacturerAventis Pharma (Canada)
Mechanism of ActionInhibits growth of susceptible organisms; mechanism not established.
Pharmacotherapy PearlsNot available in U.S.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentCarbamazepine, phenobarbital, and phenytoin may decrease the effects of spiramycin, while nefazodone may increase its effects. Effects of levodopa/carbidopa may be decreased.
Mental Health CommentMacrolides have been associated with QT_c prolongation; avoid ziprasidone.
References

Rovamycine® product monograph, Aventis Pharma Inc, Quebec, October 2000.

International Brand NamesAcetylspiramycin (JP); Dicorvin (ES); Osmycin (ID); Rovamicina (BR, IT); Rovamycin (AT, IL, NO, TH); Rovamycin Forte (IN); Rovamycine (AR, BE, BG, CH, CZ, DE, EE, ES, FR, GR, HK, HN, HU, ID, KP, LU, MY, NL, PK, PL, PT, SG); Rovamycin[inj.] (CH); Selectomycin (DE); Spirabiotic (ID)

Spironolactone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Aldactone® may be confused with Aldactazide®

International issues:

Aldactone®: Brand name for potassium canrenoate in Austria, Czech Republic, Germany, and Hungary

Pronunciation(speer on oh LAK tone)

U.S. Brand NamesAldactone®

Canadian Brand NamesAldactone®; Novo-Spiroton

Pharmacologic CategoryDiuretic, Potassium Sparing; Selective Aldosterone Blocker

Use: Labeled IndicationsManagement of edema associated with excessive aldosterone excretion; hypertension; congestive heart failure; primary hyperaldosteronism; hypokalemia; cirrhosis of liver accompanied by edema or ascites

Use: Unlabeled/InvestigationalFemale acne (adjunctive therapy); hirsutism; hypertension (pediatric); diuretic (pediatric)

Dosing: AdultsTo reduce delay in onset of effect, a loading dose of 2 or 3 times the daily dose may be administered on the first day of therapy. Oral:

Edema, hypokalemia: 25-200 mg/day in 1-2 divided doses

Hypertension (JNC 7): 25-50 mg/day in 1-2 divided doses

Diagnosis of primary aldosteronism: 100-400 mg/day in 1-2 divided doses

Acne in women (unlabeled use): 25-200 mg once daily

Hirsutism in women (unlabeled use): 50-200 mg/day in 1-2 divided doses

CHF, severe (with ACE inhibitor and a loop diuretic ± digoxin): 12.5-25 mg/day; maximum daily dose: 50 mg (higher doses may occasionallly be used). In the RALES trial, 25 mg every other day was the lowest maintenance dose possible.

Note: If potassium >5.4 mEq/L, consider dosage reduction.

Dosing: ElderlyOral: Initial: 25-50 mg/day in 1-2 divided doses; increase by 25-50 mg every 5 days as needed. Adjust for renal impairment.

Dosing: PediatricAdministration with food increases absorption. To reduce delay in onset of effect, a loading dose of 2 or 3 times the daily dose may be administered on the first day of therapy.

Edema, hypertension (unlabeled use): Oral: Children 1-17 years: Initial: 1 mg/kg/day divided every 12-24 hours (maximum dose: 3.3 mg/kg/day, up to 100 mg/day)

Diagnosis of primary aldosteronism (unlabeled use): Oral: 125-375 mg/m^2/day in divided doses

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer every 12-24 hours.

Cl_{cr} <10 mL/minute: Avoid use.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Dietary ConsiderationsShould be taken with food to decrease gastrointestinal irritation and to increase absorption. Excessive potassium intake (eg, salt substitutes, low-salt foods, bananas, nuts) should be avoided.

StorageProtect from light.

Extemporaneously PreparedA 25 mg/mL oral suspension can be prepared by crushing one hundred twenty (120) 25 mg tablets in a mortar (reducing to a fine powder), and then mixing in 20 mL of vehicle (a 1:1 combination of Ora-Sweet® or Ora-Sweet® SF and Ora-Plus®) to create a uniform paste. Continue to add vehicle in geometric amounts (while mixing) until near-final volume is achieved. Transfer to a graduate and add sufficient quantity to make 120 mL. Label “shake well” and “refrigerate.” Refrigerated stability is 60 days.

Allen LV Jr and Erickson MA III, “Stability of Ketoconazole, Metolazone, Metronidazole, Procainamide Hydrochloride, and Spironolactone in Extemporaneously Compounded Oral Liquids,” *Am J Health Syst Pharm*, 1996, 53:2073-8.

Nahata MC, Morosco RS, and Hipple TF, 4th ed, *Pediatric Drug Formulations*, Cincinnati, OH: Harvey Whitney Books Co, 2000.

Contraindications Hypersensitivity to spironolactone or any component of the formulation; anuria; acute renal insufficiency; significant impairment of renal excretory function; hyperkalemia; pregnancy (pregnancy-induced hypertension - per expert analysis)

Warnings/Precautions

Boxed warnings:

- Tumorigenic: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Fluid/electrolyte loss: Excess amounts can lead to profound diuresis with fluid and electrolyte loss; close medical supervision and dose evaluation are required. Watch for and correct electrolyte disturbances; adjust dose to avoid dehydration.

- Gynecomastia: Related to dose and duration of therapy.

- Tumorigenic: **[U.S. Boxed Warning]: Shown to be a tumorigen in chronic toxicity animal studies. Avoid unnecessary use.**

Disease-related concerns:

- Adrenal vein catheterization: Discontinue use prior to adrenal vein catheterization.

- Cirrhosis: In cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Heart failure: When evaluating a heart failure patient for spironolactone treatment, creatinine should be ≤2.5 mg/dL in men or ≤2 mg/dL in women and potassium <5 mEq/L.

Concurrent drug therapy issues:

- Potassium supplements: Avoid potassium supplements, potassium-containing salt substitutes, a diet rich in potassium, or other drugs that can cause hyperkalemia.

Geriatric Considerations When used in combination with ACE inhibitors, monitor patient for hyperkalemia.

Pregnancy Risk Factor C/D in pregnancy-induced hypertension (per expert analysis)

Pregnancy Considerations Teratogenic effects were not observed in animal studies; however, doses used were less than or equal to equivalent doses in humans. The antiandrogen effects of spironolactone have been shown to cause feminization of the male fetus in animal studies. Two case reports did not demonstrate this effect in humans however, the authors caution that adequate data is lacking. Diuretics are generally avoided in pregnancy due to the theoretical risk that decreased plasma volume may cause placental insufficiency. Diuretics should not be used during pregnancy in the presence of reduced placental perfusion (eg, pre-eclampsia, intrauterine growth restriction).

Lactation Enters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding Considerations The active metabolite of spironolactone has been found in breast milk. Effects to humans are not known; however, this metabolite was found to be carcinogenic in rats. The manufacturer recommends discontinuing spironolactone or using an alternative method of feeding.

Adverse Reactions Incidence of adverse events is not always reported. (Mean daily dose: 26 mg)

Cardiovascular: Edema (2%, placebo 2%)

Central nervous system: Disorders (23%, placebo 21%) which may include drowsiness, lethargy, headache, mental confusion, drug fever, ataxia, fatigue

Dermatologic: Maculopapular, erythematous cutaneous eruptions, urticaria, hirsutism, eosinophilia

Endocrine & metabolic: Gynecomastia (men 9%; placebo 1%), breast pain (men 2%; placebo 0.1%), serious hyperkalemia (2%, placebo 1%), hyponatremia, dehydration, hyperchloremic metabolic acidosis in decompensated hepatic cirrhosis, inability to achieve or maintain an erection, irregular menses, amenorrhea, postmenopausal bleeding

Gastrointestinal: Disorders (29%, placebo 29%) which may include anorexia, nausea, cramping, diarrhea, gastric bleeding, ulceration, gastritis, vomiting

Genitourinary: Disorders (12%, placebo 11%)

Hematologic: Agranulocytosis

Hepatic: Cholestatic/hepatocellular toxicity

Renal: Increased BUN concentration

Respiratory: Disorders (32%, placebo 34%)

Miscellaneous: Deepening of the voice, anaphylactic reaction, breast cancer

Drug Interactions

ACE Inhibitors: Potassium-Sparing Diuretics may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can

not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Ammonium Chloride: Potassium-Sparing Diuretics may enhance the adverse/toxic effect of Ammonium Chloride. Specifically the risk of systemic acidosis. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Cardiac Glycosides: Potassium-Sparing Diuretics may diminish the therapeutic effect of Cardiac Glycosides. Specifically, the inotropic effects. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Drospirenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Mitotane: Potassium-Sparing Diuretics may diminish the therapeutic effect of Mitotane. High dose diuretics (eg, Cushings syndrome) may present significantly higher risk than low doses (eg, CHF). *Risk D: Consider therapy modification*

Potassium Salts: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: Potassium-Sparing Diuretics may diminish the therapeutic effect of QuiNIDine. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Food increases absorption.

Herb/Nutraceutical: Avoid natural licorice (due to mineralocorticoid activity)

Test InteractionsMay cause false elevation in serum digoxin concentrations measured by RIA

Monitoring ParametersBlood pressure, serum electrolytes (potassium, sodium), renal function, I & O ratios and daily weight throughout therapy

CHF: Potassium levels and renal function should be checked in 3 days and 1 week after initiation, then every 2-4 weeks for 3-12 months, then every 3-6 months.

Nursing: Physical Assessment/MonitoringDiuretic effect may be delayed 2-3 days and antihypertensive effect may be delayed 2-3 weeks (see Dosing for loading dose recommendations). Assess potential for interactions with other pharmacological agents patient may be taking (eg, anything that will increase risk of hyperkalemia). Assess serum electrolytes and hepatic function on a regular basis during therapy. Monitor effectiveness (fluid status) and adverse reactions periodically (eg, CNS changes [drowsiness, headache, confusion], rash, gynecomastia, dehydration, hyperkalemia, jaundice). Teach patient appropriate use, possible side effects/appropriate interventions and symptoms to report.

Monitoring: Lab TestsSerum electrolytes (potassium, sodium), renal function

Patient EducationTake as directed, with meals. Avoid any potassium supplements (vitamin/mineral products), potassium-containing salt substitutes, natural licorice, or extra dietary intake of potassium. Weigh yourself weekly at the same time, in the same clothes, and report weight loss >5 lb/week. May cause dizziness, drowsiness, confusion, or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or dry mouth (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or decreased sexual ability, gynecomastia, impotence, menstrual irregularities (reversible with discontinuing of medication). Report mental confusion; clumsiness; persistent fatigue, chills, numbness, or muscle weakness in hands, feet, or face; acute persistent diarrhea; chest pain, rapid heartbeat, or palpitations; excessive thirst; or respiratory difficulty; breast tenderness or increased body hair in females; breast enlargement or inability to achieve erection in males. **Pregnancy precaution:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 25 mg, 50 mg, 100 mg

Aldactone®: 25 mg

Aldactone®: 50 mg, 100 mg [scored]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Aldactone)

25 mg (30): $33.99

50 mg (30): $51.99

100 mg (30): $79.99

Tablets (Spironolactone)

25 mg (30): $15.99

50 mg (30): $21.99

Mechanism of ActionCompetes with aldosterone for receptor sites in the distal renal tubules, increasing sodium chloride and water excretion while conserving potassium and hydrogen ions; may block the effect of aldosterone on arteriolar smooth muscle as well

Pharmacodynamics/Kinetics

Duration: 2-3 days

Protein binding: 91% to 98%

Metabolism: Hepatic to multiple metabolites, including canrenone (active)

Half-life elimination: 78-84 minutes

Time to peak, serum: 1-3 hours (primarily as the active metabolite)

Excretion: Urine and feces

Related Information

- Heart Failure (Systolic)

Pharmacotherapy PearlsMaximum diuretic effect may be delayed 2-3 days and maximum hypertensive effects may be delayed 2-3 weeks.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, nervousness, or confusion

Mental Health: Effects on Psychiatric TreatmentHas been used to treat lithium-related edema

Cardiovascular Considerations

Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines suggest that the addition of an aldosterone antagonist is reasonable in selected patients with moderately severe to severe symptoms of heart failure (HF) and reduced LVEF who can be carefully monitored (renal function and serum potassium). When evaluating a heart failure patient for aldosterone antagonist treatment, creatinine should be ≤2.5 mg/dL in men or ≤2 mg/dL in women and potassium <5 mEq/L. Patients are not candidates for such therapy if they are unable to comply with the monitoring required. In addition, the routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended in patients with current or prior symptoms of HF and reduced LVEF. In severe heart failure, spironolactone (25 mg/day), when combined with maximal standard therapy, resulted in a striking improvement in cardiovascular outcome (Pitt B, 1999). In the RALES trial, potassium supplementation was stopped with the initiation of spironolactone unless the patient was hypokalemic.

Monitoring Issues: Recently, a group of investigators published an observational study evaluating the effect of the RALES study on hospitalization for hyperkalemia in an older (>66 years of age) heart failure population on ACE inhibitors. This study was a population-based, timed-series analysis of healthcare databases in Ontario, Canada from January 1994 through December 2001(Juurlink DN, 2004). Computerized prescription records were reviewed to identify prescriptions for spironolactone, ACE inhibitors, angiotensin receptor antagonists, beta-blockers, loop diuretics, nonsteroidal anti-inflammatory agents, potassium supplements, thiazide diuretics, or other potassium-sparing diuretics. Hospitalization records were reviewed to identify hospitalizations for hyperkalemia or heart failure. Among patients treated with ACE inhibitors who had recently been hospitalized for heart failure, the spironolactone prescription rate significantly increased after RALES publication (34 per 1000 patients in 1994 and 149 per 1000 patients in 2001). The rate of hospitalizations for hyperkalemia significantly rose from 2.4 per 1000 patients (1994) to 11 per 1000 patients (2001). The associated mortality significantly rose from 0.2 per 1000 (1994) to 2 per 1000 (2001). The authors concluded that closer laboratory monitoring may be necessary, in addition to proper prescribing of spironolactone. The ACC/AHA 2005 Heart Failure Guidelines emphasize factors to consider in minimizing the risk of hyperkalemia such as initial dosages to use, avoidance of NSAIDs, discontinuing or reducing potassium supplements, and following monitoring guidelines. They suggest that potassium levels and renal function be checked in 3 days and at 1 week after initiation of therapy and at least monthly for the first 3 months. If serum potassium increases to a level of >5.4 mEq/L while on spironolactone, dose reduction is suggested. The RALES trial used 25 mg every other day as the lowest maintenance dose possible.

Hypertension: Aldosterone antagonists may add additional antihypertensive benefits in patients who have severe LV dysfunction (NYHA class III and IV), but only after ACE inhibitors and beta-blockers have been instituted (if no contraindications or intolerances exist).

Anesthesia and Critical Care Concerns/Other ConsiderationsIn severe heart failure, spironolactone (25 mg/day), when combined with maximal standard therapy, resulted in a striking improvement in cardiovascular outcome (*N Engl J Med*, 1999, 341:709-17).

Potassium levels should be monitored in patients on an aldosterone blocker, particularly in those who have underlying renal impairment or concurrent ACE inhibitor therapy.

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Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy,” *Am J Obstet Gynecol*, 2000, 183(1):S1-22.

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Thiboutot D and Chen W, “Update and Future of Hormonal Therapy in Acne,” *Dermatology*, 2003, 206(1):57-67.[PubMed 12566806]

International Brand NamesAldactin (TW); Aldactone (AE, AT, AU, BE, BF, BG, BH, BJ, BR, CH, CI, CO, CR, CY, CZ, DE, DK, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, OM, PA, PE, PH, PK, PT, QA, RU, SA, SC, SD, SE, SG, SL, SN, SV, SY, TH, TN, TR, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Aldactone A (AR, BB, BM, BS, BZ, EC, ES, GY, JM, SR, TT, UY); Aldospirone (IL); Aldoxol (PY); Alizar (CN); Almatol (TW); Altone (TH); Flumach (FR); Huma-Spiroton (HU); Hyles (TH); Osiren (AT); Osyrol (DE, JP); Polspiron (PL); Pondactone (TH); Spiractin (AU, ZA); Spirix (DK, FI, NO); Spiroctan (FR, LU); Spirola (ID); Spirolacton (ID); Spirolon (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Spiron (DK, HU); Spirone (PE); Spirono-Isis (DE); Spironol (IL, PL); Spironolacton (PL); Spironolacton Stada (PL); Spironolacton-ratiopharm (LU); Spironolactone-Eurogenerics (LU); Spironolactone-Searle (LU); Spirotone (NZ); Unilactone (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Uractone (LU); Uractonum (SG); Verospiron (BG, CZ, EE, HN, HU, PL); Vivitar (MX); Xenalon Lactabs (DO)

Stanford V Regimen

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Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lymphoma, Hodgkin's Disease

Regimen Use Lymphoma, Hodgkin's disease

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Mechlorethamine: I.V.: 6 mg/m^2 day 1

[total dose/cycle = 6 mg/m^2]

Doxorubicin: I.V.: 25 mg/m^2/day days 1 and 15

[total dose/cycle = 50 mg/m^2]

Vinblastine: I.V.: 6 mg/m^2/day days 1 and 15

[total dose/cycle = 12 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/day (maximum 2 mg) days 8 and 22

[total dose/cycle = 2.8 mg/m^2; maximum 4 mg]

Bleomycin: I.V.: 5 units/m^2/day days 8 and 22

[total dose/cycle = 10 units/m^2]

Etoposide: I.V.: 60 mg/m^2/day days 15 and 16

[total dose/cycle = 120 mg/m^2]

Prednisone: Oral: 40 mg/m^2 every other day for 9 weeks

followed by tapering of dose by 10 mg every other day, beginning at week 10

Repeat cycle every 28 days for 3 cycles; **Note:** In cycle 3, for patients ≥50 years of age, decrease vinblastine dose to 4 mg/m^2/dose and decrease vincristine dose to 1 mg/m^2/dose

Variation 2:

Mechlorethamine: I.V.: 6 mg/m^2/dose weeks 1, 5, and 9

[total dose/cycle = 18 mg/m^2]

Doxorubicin: I.V.: 25 mg/m^2/dose weeks 1, 3, 5, 7, 9, and 11

[total dose/cycle = 150 mg/m^2]

Vinblastine: I.V.: 6 mg/m^2/dose weeks 1, 3, 5, 7, 9, and 11

[total dose/cycle = 36 mg/m^2]

Vincristine: I.V.: 1.4 mg/m^2/dose (maximum 2 mg) weeks 2, 4, 6, 8, 10, and 12

[total dose/cycle = 8.4 mg/m^2; maximum 12 mg]

Bleomycin: I.V.: 5 units/m^2/dose weeks 2, 4, 6, 8, 10, and 12

[total dose/cycle = 30 units/m^2]

Etoposide: I.V.: 60 mg/m^2/day for 2 consecutive days, weeks 3, 7, and 11

[total dose/cycle = 360 mg/m^2]

Prednisone: Oral: 40 mg/m^2 every other day for 10 weeks

[total dose prior to taper = 1400 mg/m^2]

followed by tapering of prednisone dose during weeks 11 and 12

Treatment cycle is 12 weeks

References

Variation 1:

Bartlett NL, Rosenberg SA, Hoppe RT, et al, “Brief Chemotherapy, Stanford V, and Adjuvant Radiotherapy for Bulky or Advanced-Stage Hodgkin's Disease: A Preliminary Report,” *J Clin Oncol*, 1995, 13(5):1080-8.[PubMed 7537796]

Variation 2:

Horning SJ, Hoppe RT, Breslin S, et al, "Stanford V and Radiotherapy for Locally Extensive and Advanced Hodgkin's Disease: Mature Results of a Prospective Clinical Trial," *J Clin Oncol*, 2002, 20(3):630-7.[PubMed 11821442]

Stavudine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Zerit® may be confused with Ziac®

Pronunciation(STAV yoo deen)

U.S. Brand NamesZerit®

Canadian Brand NamesZerit®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)

Use: Labeled IndicationsTreatment of HIV infection in combination with other antiretroviral agents

Dosing: Adults**HIV infection (in combination with other antiretrovirals):** Oral:

≥60 kg: 40 mg every 12 hours

<60 kg: 30 mg every 12 hours

Dosing: ElderlyOlder patients should be closely monitored for signs and symptoms of peripheral neuropathy. Dosage should be carefully adjusted to renal function.

Dosing: Pediatric**HIV infection:** Oral:

Newborns (Birth to 13 days): 0.5 mg/kg every 12 hours

Children:

- >14 days and <30 kg: 1 mg/kg every 12 hours
- ≥30 kg: 30 mg every 12 hours

Dosing: Renal Impairment

Children: Specific recommendations not available. Reduction in dose or increase in dosing interval should be considered.

Adults:

- Cl_{cr} >50 mL/minute:
  - ≥60 kg: 40 mg every 12 hours
  - <60 kg: 30 mg every 12 hours
- Cl_{cr} 26-50 mL/minute:
  - ≥60 kg: 20 mg every 12 hours
  - <60 kg: 15 mg every 12 hours
- Cl_{cr} 10-25 mL/minute, hemodialysis (administer dose after hemodialysis on day of dialysis):
  - ≥60 kg: 20 mg every 24 hours
  - <60 kg: 15 mg every 24 hours

Dosing: Adjustment for ToxicityIf symptoms of peripheral neuropathy occur, discontinue until symptoms resolve. Treatment may then be resumed at 50% the recommended dose. If symptoms recur at lower dose, permanent discontinuation should be considered.

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered without regard to meals. Oral solution should be shaken vigorously prior to use.

Dietary ConsiderationsMay be taken without regard to meals. Oral solution contains sucrose 50 mg/mL.

StorageCapsules and powder for reconstitution may be stored at controlled room temerature of 25°C (77°F). Reconstituted oral solution should be stored in refrigerator at 2°C to 8°C (36°F to 46°F) and is stable for 30 days.

ReconstitutionReconstitute powder for oral suspension with 202 mL of purified water as specified on the bottle. Shake vigorously until suspended. Final suspension will be 1 mg/mL (200 mL).

ContraindicationsHypersensitivity to stavudine or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Lactic acidosis/hepatomegaly: See "Concerns related to adverse effects" below.
- Pancreatitis: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** combination therapy with didanosine may increase risk; use with caution in patients with risk factors for liver disease (although acidosis has occurred in patients without known risk factors, risk may be increased with female gender, obesity, pregnancy, or prolonged exposure). Suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).
- Motor weakness: Severe motor weakness (resembling Guillain-Barré syndrome) has been reported (including fatal cases, usually in association with lactic acidosis); manufacturer recommends discontinuation if motor weakness develops (with or without lactic acidosis).
- Pancreatitis: **[U.S. Boxed Warning]: Pancreatitis (including some fatal cases) has occurred during combination therapy with didanosine (with or without hydroxyurea).** Suspend therapy with agents toxic to the pancreas (including stavudine, didanosine, or hydroxyurea) in patients with suspected pancreatitis.
- Peripheral neuropathy: The dose-limiting side effect, may be peripheral neuropathy; use with caution in patients with pre-existing peripheral neuropathy. If neuropathy recurs after interruption and reinitiation of therapy (at a reduced dose), consider permanent discontinuation.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with pre-existing bone marrow suppression.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Concurrent drug therapy issues:

- Combination with didanosine (with or without hydroxyurea): May increase risk of hepatotoxicity/pancreatitis; avoid this combination.
- Interferon alfa: Use with caution in combination with interferon alfa with or without ribavirin in HIV/HBV coinfected patients; monitor closely for hepatic decompensation, anemia, or neutropenia; dose reduction or discontinuation of interferon and/or ribavirin may be required if toxicity evident.
- Zidovudine: Should not use zidovudine in combination with stavudine.

Pregnancy Risk FactorC

Pregnancy ConsiderationsNo increased risk of overall birth defects has been observed following 1st trimester exposure according to data collected by the antiretroviral pregnancy registry. Cases of fatal and nonfatal lactic acidosis, with or without pancreatitis, have been reported in pregnant women. It is not known if pregnancy itself potentiates this known side effect; however, pregnant women may be at increased risk of lactic acidosis and liver damage. Combination treatment with didanosine may also contribute to the risk of lactic acidosis, and should be considered only if benefit outweighs risk. Hepatic enzymes and electrolytes should be monitored frequently during the 3rd trimester of pregnancy. Pharmacokinetics of stavudine are not significantly altered during pregnancy; dose adjustments are not needed. There are no adequate and well-controlled studies in pregnant women; however, the Perinatal HIV Guidelines Working Group considers stavudine to be an alternative NRTI in dual nucleoside combination regimens; use with didanosine only if no alternatives are available, do not use with zidovudine. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse ReactionsAdverse reactions reported below represent experience with combination therapy with other nucleoside analogues and protease inhibitors.

>10%:

Central nervous system: Headache (25% to 46%)

Dermatologic: Rash (18% to 30%)

Gastrointestinal: Nausea (43% to 53%; less than comparator group), vomiting (18% to 30%; less than comparator group), diarrhea (34% to 45%)

Hepatic: Hyperbilirubinemia (65% to 68%; grade 3/4: 7% to 16%), AST increased (42% to 53%; grade 3/4: 5% to 7%), ALT increased (40% to 50%; grade 3/4: 6% to 8%), GGT increased (15% to 28%; grade 3/4: 2% to 5%)

Neuromuscular & skeletal: Peripheral neuropathy (8% to 21%)

Miscellaneous: Amylase increased (21% to 31%; grade 3/4: 4% to 8%), lipase increased (~27%; grade 3/4: 5% to 6%)

Postmarketing and/or case reports: Abdominal pain, allergic reaction, anemia, anorexia, chills, diabetes mellitus, fever, hepatic failure, hepatitis, hepatomegaly (with steatosis; some fatal), hyperglycemia, hyperlactatemia (symptomatic), immune reconstitution syndrome, insomnia, lactic acidosis (some fatal), leukopenia, macrocytosis, motor weakness (severe), myalgia, pancreatitis, redistribution/accumulation of body fat, thrombocytopenia

Drug Interactions

Didanosine: Stavudine may enhance the adverse/toxic effect of Didanosine. Lactic acidosis (possibly fatal) is of particular concern. *Risk D: Consider therapy modification*

DOXOrubicin: May diminish the therapeutic effect of Stavudine. *Risk D: Consider therapy modification*

DOXOrubicin (Liposomal): May diminish the therapeutic effect of Stavudine. *Risk D: Consider therapy modification*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Zidovudine: May diminish the therapeutic effect of Stavudine. *Risk D: Consider therapy modification*

Monitoring ParametersMonitor liver function tests and renal function tests; signs and symptoms of peripheral neuropathy; monitor viral load and CD4 count

Nursing: Physical Assessment/MonitoringAssess closely for any previous allergy history prior to beginning treatment. Assess other pharmacological or herbal products patient may be taking for potential interactions or toxicity; dosing adjustments may be necessary. **Note:** Patient must be monitored frequently during therapy for any sign of adverse response (eg, peripheral neuropathy, lactic acidosis, hepatomegaly, motor weakness) that may require suspension of therapy. Assess effectiveness of therapy (decrease in infections and progress of disease, viral load) periodically during therapy. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsLiver function, renal function tests, viral load

Patient EducationDo not take any new prescription, over-the-counter medications, or herbal products without consulting prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. This drug is prescribed as one part of a multidrug combination; take exactly as directed, for full course of therapy. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. You may be susceptible to infection (avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber). Frequent blood tests may be required with prolonged therapy. May cause dizziness or weakness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report immediately any tingling, pain, or loss of sensation in toes, feet, muscles or joints; swollen glands; alterations in urinary pattern; swelling of extremities, weight gain, or other persistent adverse effects. If you are instructed to stop the medication, do not restart without specific instruction by your prescriber. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 15 mg, 20 mg, 30 mg, 40 mg

Zerit®: 15 mg, 20 mg, 30 mg, 40 mg

Powder for solution, oral:

Zerit®: 1 mg/mL (200 mL) [dye free; contains sucrose 50 mg/mL; fruit flavor]

Generic AvailableYes: Capsule

ManufacturerBristol-Myers Squibb Company (Pharmaceutical Division)

Pricing: U.S. (www.drugstore.com)

Capsules (Zerit)

15 mg (60): $349.97

20 mg (60): $359.96

30 mg (60): $385.97

40 mg (60): $395.99

Solution (reconstituted) (Zerit)

1 mg/mL (200): $79.98

Mechanism of ActionStavudine is a thymidine analog which interferes with HIV viral DNA dependent DNA polymerase resulting in inhibition of viral replication; nucleoside reverse transcriptase inhibitor

Pharmacodynamics/Kinetics

Distribution: V_d: 46 L

Bioavailability: 86.4%

Metabolism: Undergoes intracellular phosphorylation to an active metabolite

Half-life elimination: 1.2-1.6 hours

Time to peak, serum: 1 hour

Excretion: Urine (42% as unchanged drug)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV
- Perinatal HIV Guidelines

Pharmacotherapy PearlsPotential compliance problems, frequency of administration and adverse effects should be discussed with patients before initiating therapy to help prevent the emergence of resistance.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, insomnia, anxiety, or depression

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine; concurrent use with lithium may increase the risk of peripheral neuropathy

Index Termsd4T

References

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“Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,” July 8, 2008. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

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Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” July 29, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesLandstav (MX); Ranstar (MX); Stavir (IN); Tonavir (PY, UY); Virostav (MY); Zerit (AR, AT, AU, BE, BG, CH, CL, CN, CO, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, HU, ID, IE, IT, KP, LU, MX, NL, NO, PE, PL, PT, RU, SE, SG, TH, TR, VE, ZA); Zeritavir (BR)

Streptomycin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Streptomycin may be confused with streptozocin

Pronunciation(strep toe MYE sin)

Pharmacologic CategoryAntibiotic, Aminoglycoside; Antitubercular Agent

Use: Labeled IndicationsPart of combination therapy of active tuberculosis; used in combination with other agents for treatment of streptococcal or enterococcal endocarditis, mycobacterial infections, plague, tularemia, and brucellosis

Dosing: Adults

Brucellosis: I.M.: 1 g/day for 14-21 days (with doxycycline, 100 mg twice daily for 6 weeks)

Endocarditis: I.M.:

Enterococcal: 1 g every 12 hours for 2 weeks, 500 mg every 12 hours for 4 weeks in combination with penicillin

Streptococcal: 1 g every 12 hours for 1 week

***Mycobacterium avium*complex:** I.M.: Adjunct therapy (with macrolide, rifamycin, and ethambutol): 15 mg/kg 3 times/week for first 2-3 months for severe disease

Plague: I.M.: 15 mg/kg (or 1 g) every 12 hours until the patient is afebrile for at least 3 days

Tuberculosis: I.M.:

Daily therapy: 15 mg/kg/day (maximum: 1 g)

Directly observed therapy (DOT), twice weekly: 25-30 mg/kg (maximum: 1.5 g)

Directly observed therapy (DOT), 3 times/week: 25-30 mg/kg (maximum: 1.5 g)

Tularemia: I.M.: 10-15 mg/kg every 12 hours (maximum: 2 g/day) for 7-10 days or until patient is afebrile for 5-7 days

Dosing: ElderlyI.M.: 10 mg/kg/day, not to exceed 750 mg/day; dosing interval should be adjusted for renal function. Some authors suggest not to give more than 5 days/week or give as 20-25 mg/kg/dose twice weekly.

Dosing: Pediatric

Tuberculosis: I.M.:

Daily therapy: 20-40 mg/kg/day (maximum: 1 g/day)

Directly observed therapy (DOT), twice weekly: 25-30 mg/kg (maximum: 1.5 g)

Directly observed therapy DOT, 3 times/week: 25-30 mg/kg (maximum: 1.5 g)

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minute: Administer every 24-72 hours.

Cl_{cr} <10 mL/minute: Administer every 72-96 hours.

Removed by hemo- and peritoneal dialysis: Administer dose postdialysis.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Inject deep I.M. into large muscle mass.

Administration: I.V.I.V. administration is not recommended. Has been administered intravenously over 30-60 minutes.

Administration: I.V. DetailpH: 5-8 (injection)

StorageDepending upon manufacturer, reconstituted solution remains stable for 2-4 weeks when refrigerated and 24 hours at room temperature. Exposure to light causes darkening of solution without apparent loss of potency.

Compatibility

Y-site administration: Compatible: Esmolol.

Compatibility in syringe: Compatible: Penicillin G sodium. **Incompatible:** Heparin. **Variable (consult detailed reference):** Ampicillin.

Compatibility when admixed: Compatible: Bleomycin. **Incompatible:** Amobarbital, amphotericin B, chlorothiazide, heparin, methohexital, norepinephrine, pentobarbital, phenobarbital, phenytoin, sodium bicarbonate.

ContraindicationsHypersensitivity to streptomycin or any component of the formulation; pregnancy

Warnings/Precautions

Boxed warnings:

- Nephrotoxicity: See "Concerns related to adverse effects" below.
- Neuromuscular blockade and respiratory paralysis: See "Concerns related to adverse effects" below.
- Neurotoxicity: See "Concerns related to adverse effects" below.
- Parenteral formulation: See "Dosage form specific issues" below.

Concerns related to adverse effects:

- Nephrotoxicity: **[U.S. Boxed Warning]: May cause nephrotoxicity;** usual risk factors include pre-existing renal impairment, concomitant nephrotoxic medications, advanced age and dehydration. Discontinue treatment if signs of nephrotoxicity occur; renal damage is usually reversible.
- Neuromuscular blockade and respiratory paralysis: **[U.S. Boxed Warning]: May cause neuromuscular blockade and respiratory paralysis;** especially when given soon after anesthesia or muscle relaxants.
- Neurotoxicity: **[U.S. Boxed Warning]: May cause neurotoxicity;** usual risk factors include pre-existing renal impairment, concomitant neuro-/nephrotoxic medications, advanced age and dehydration. Ototoxicity is proportional to the amount of drug given and the duration of treatment. Tinnitus or vertigo may be indications of vestibular injury and impending bilateral irreversible damage. Discontinue treatment if signs of ototoxicity occur.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hearing impairment: Use with caution in patients with pre-existing vertigo, tinnitus, or hearing loss.
- Neuromuscular disorders: Use with caution in patients with neuromuscular disorders, including myasthenia gravis.
- Renal impairment: Use with caution in patients with pre-existing renal insufficiency; dosage modification required.

Dosage form specific issues:

- Parenteral formulation: **[U.S. Boxed Warning]: Parenteral form should be used only where appropriate audiometric and laboratory testing facilities are available.**

Geriatric ConsiderationsStreptomycin is indicated for persons from endemic areas of drug-resistant *Mycobacterium tuberculosis* or who are HIV infected. Since most older patients acquired the *M. tuberculosis* infection prior to the availability of effective chemotherapy, isoniazid and rifampin are usually effective unless resistant organisms are suspected or the patient is HIV infected. Adjust dose interval for renal function.

Pregnancy Risk FactorD

Pregnancy ConsiderationsStreptomycin crosses the placenta. Many case reports of hearing impairment in children exposed *in utero* have been published. Impairment has ranged from mild hearing loss to bilateral deafness. Because of several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy, the manufacturer classifies streptomycin as pregnancy risk factor D.

LactationEnters breast milk/not recommended (AAP rates "compatible")

Breast-Feeding ConsiderationsStreptomycin is excreted into breast milk; however, it is not well absorbed when taken orally. This limited oral absorption may minimize exposure to the nursing infant. Nondose-related effects could include modification of bowel flora. The AAP considers streptomycin to be "usually compatible with breast-feeding."

Pregnancy & Lactation, In-Depth

- Streptomycin in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension

Central nervous system: Neurotoxicity, drowsiness, headache, drug fever, paresthesia

Dermatologic: Skin rash

Gastrointestinal: Nausea, vomiting

Hematologic: Eosinophilia, anemia

Neuromuscular & skeletal: Arthralgia, weakness, tremor

Otic: Ototoxicity (auditory), ototoxicity (vestibular)

Renal: Nephrotoxicity

Respiratory: Difficulty in breathing

Drug Interactions

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Test InteractionsFalse-positive urine glucose with Benedict's solution or Clinitest®; penicillin may decrease aminoglycoside serum concentrations *in vitro*

Monitoring ParametersHearing (audiogram), BUN, creatinine; serum concentration of the drug should be monitored in all patients; eighth cranial nerve damage is usually preceded by high-pitched tinnitus, roaring noises, sense of fullness in ears, or impaired hearing and may persist for weeks after drug is discontinued

Reference RangeTherapeutic: Peak: 20-30 mcg/mL; Trough: <5 mcg/mL; Toxic: Peak: >50 mcg/mL; Trough: >10 mcg/mL

Nursing: Physical Assessment/MonitoringAssess for allergy history prior to starting therapy. Assess potential for interactions with other pharmacological agents patient may be taking (eg, increased risk of toxicity with other nephrotoxic or ototoxic drugs). Assess results of laboratory tests, effectiveness (resolution of infection), and adverse effects (eg, ototoxicity [auditory or vestibular], neurotoxicity [drowsiness, paresthesia], nephrotoxicity [I & O, hematuria, edema]) on a regular basis during therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsHearing (audiogram), BUN, creatinine; serum concentration of the drug should be monitored. Perform culture and sensitivity prior to initiating therapy.

Patient EducationDo not take any new medication during therapy without consulting prescriber. This medication can only be given by intramuscular injection. Therapy for TB may last several months. Do not discontinue even if you are feeling better. Maintain adequate hydration (2-3 L/day of fluids unless instructed to restrict fluid intake). May cause headache or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea, vomiting, or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report immediately change in hearing or sense of fullness in ears; pain, weakness, tremors, or numbness in muscles; unusual clumsiness or change in strength or altered gait; change in urinary pattern or back pain; persistent diarrhea; or respiratory difficulty or chest pain. **Pregnancy precaution:** Do not get pregnant while taking this medication. Consult prescriber for appropriate barrier contraceptive measures.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 1 g

Generic AvailableYes

Mechanism of ActionInhibits bacterial protein synthesis by binding directly to the 30S ribosomal subunits causing faulty peptide sequence to form in the protein chain

Pharmacodynamics/Kinetics

Absorption:

Oral: Poorly absorbed

I.M.: Well absorbed

Distribution: To extracellular fluid including serum, abscesses, ascitic, pericardial, pleural, synovial, lymphatic, and peritoneal fluids; poorly distributed into CSF

Protein binding: 34%

Half-life elimination: Newborns: 4-10 hours; Adults: 2-4.7 hours, prolonged with renal impairment

Time to peak: I.M.: Within 1 hour

Excretion: Urine (90% as unchanged drug); feces, saliva, sweat, and tears (<1%)

Related Information

- Antimicrobial Drugs of Choice
- Tuberculosis

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsStreptomycin Sulfate

References

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International Brand NamesAmbistryn-S (IN); Estrepto-Monaxin (MX); Estreptomicina (AR); Strepto (TH); Strepto-Hefa (DE); Streptocin (MY); Streptomycinum (PL)

Streptozocin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Streptozocin may be confused with streptomycin

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(strep toe ZOE sin)

U.S. Brand NamesZanosar®

Canadian Brand NamesZanosar®

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent

Use: Labeled IndicationsTreatment of metastatic islet cell carcinoma of the pancreas, carcinoid tumor and syndrome, Hodgkin's disease, palliative treatment of colorectal cancer

Dosing: Adults**Antineoplastic:** Refer to individual protocols.

Single agent therapy: I.V.: 1-1.5 g/m^2 weekly for 6 weeks followed by a 4-week rest period

Combination therapy: I.V.: 0.5-1 g/m^2 for 5 consecutive days followed by a 4- to 6-week rest period

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Dosing: Renal ImpairmentThe FDA-approved labeling does not contain dosing adjustments; however, it is recommended to use clinical judgment weighing benefit vs risk of renal toxicity in patients with pre-existing renal impairment. The following dosing adjustments have been used by some clinicians (Aronoff, 2007): Adults:

Cl_{cr} 10-50 mL/minute: Administer 75% of dose

Cl_{cr} <10 mL/minute: Administer 50% of dose

Dosing: Hepatic ImpairmentThere are no specific guidelines on dosage adjustment in patients with hepatic impairment. Streptozocin is rapidly hepatically metabolized; dose should be decreased in patients with severe liver disease.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Administer as short (30-60 minutes) or 6-hour infusion; may be given by rapid I.V. push

Administration: I.V. DetailpH: 3.5-4.5

StorageStore intact vials under refrigeration. Vials are stable for 1 year at room temperature. Solution reconstituted with SWFI or NS is stable for 48 hours at room temperature and 96 hours under refrigeration. Further dilution in D_5W or NS is stable for 48 hours at room temperature and 96 hours under refrigeration when protected from light.

ReconstitutionDilute powder with 9.5 mL SWFI or NS to a concentration of 100 mg/mL.

CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Amifostine, etoposide phosphate, filgrastim, gemcitabine, granisetron, melphalan, ondansetron, teniposide, thiotepa, vinorelbine. **Incompatible:** Allopurinol, aztreonam, cefepime, piperacillin/tazobactam.

ContraindicationsPregnancy

Allergy Considerations

- Nitrosourea Allergy

Warnings/Precautions

Boxed warnings:

- Dose-related toxicities: See “Concerns related to adverse effects” below.

- Experienced physician: See “Other warnings/precautions” below.
- Renal toxicity: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Dose-related toxicities: **[U.S. Boxed Warning]: Other major toxicities include liver dysfunction, diarrhea, nausea, and vomiting.**
- Insulin release: There may be an acute release of insulin during treatment; keep syringe of $D_{50}W$ at bedside during administration.
- Renal toxicity: **[U.S. Boxed Warning]: Renal toxicity is dose-related and cumulative and may be severe or fatal.**

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**
- Extravasation/tissue irritation: Local tissue irritation may occur; extravasation may cause local tissue lesions and necrosis.

Pregnancy Risk FactorD

LactationEnters breast milk/contraindicated

Adverse Reactions

>10%:

Gastrointestinal: Nausea and vomiting (100%)

Hepatic: Increased LFTs

Miscellaneous: Hypoalbuminemia

Renal: BUN increased, Cl_{cr} decreased, hypophosphatemia, nephrotoxicity (25% to 75%), proteinuria, renal dysfunction (65%), renal tubular acidosis

1% to 10%:

Endocrine & metabolic: Hypoglycemia (6%)

Gastrointestinal: Diarrhea (10%)

Local: Pain at injection site

<1%: Confusion, lethargy, depression, leukopenia, thrombocytopenia, liver dysfunction, secondary malignancy

Myelosuppressive:

WBC: Mild

Platelets: Mild

Onset: 7 days

Nadir: 14 days

Recovery: 21 days

Oncology: VesicantPossibly; see Management of Drug Extravasations.

Oncology: Emetic PotentialVery high (>90%)

Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersMonitor renal function closely

Nursing: Physical Assessment/MonitoringAntiemetic should be administered prior to therapy (emetic potential 100%). Assess potential for interactions with other pharmacological agents. See Administration for infusion specifics. Infusion site should be monitored closely to prevent extravasation. Assess results of laboratory tests at baseline and weekly during therapy. Evaluate therapeutic response and adverse reactions (eg, nephrotoxicity/renal dysfunction [I & O, hematuria, edema, BUN], hepatotoxicity [jaundice, fatigue, LFTs], hypoglycemia, diarrhea [dehydration]) on a regular basis. Caution patients with diabetes to monitor glucose levels closely (may precipitate hypoglycemia). Teach patient (or caregiver) possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsLiver function tests, CBC, renal function tests (BUN, serum creatinine) at baseline and weekly during therapy

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug can only be given I.V.; report immediately any redness, swelling, pain, or burning at infusion site. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You will be more sensitive to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). If you have diabetes, monitor glucose levels closely; may cause hypoglycemia. May cause nausea and vomiting (consult prescriber for antiemetic); nervousness, dizziness, confusion, or lethargy (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or loss of body hair (reversible when treatment is finished). Report unusual back pain, change in urinary pattern; persistent fever, chills, or sore throat; unusual bleeding; blood in urine, vomitus, or stool; chest pain, palpitations, or respiratory difficulty; or swelling of feet or lower legs. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Male: Do not cause a female to become pregnant. Male/female: Consult prescriber for instruction on appropriate barrier contraceptive measures. This drug may cause severe fetal damage. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 1 g

Generic AvailableNo

Mechanism of ActionInterferes with the normal function of DNA by alkylation and cross-linking the strands of DNA, and by possible protein modification

Pharmacodynamics/Kinetics

Duration: Disappears from serum in 4 hours

Distribution: Concentrates in liver, intestine, pancreas, and kidney

Metabolism: Rapidly hepatic

Half-life elimination: 35-40 minutes

Excretion: Urine (60% to 70% as metabolites); exhaled gases (5%); feces (1%)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause lethargy, confusion, or depression

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; renal dysfunction occurs commonly with streptozocin; will need to monitor and adjust lithium and gabapentin doses

Index TermsNSC-85998

References

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International Brand NamesZanosar (CH, FR, IL, NL, NO)

Strontium-89

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(STRON shee um atey nine)
U.S. Brand NamesMetastron®
Canadian Brand NamesMetastron®
Pharmacologic CategoryRadiopharmaceutical
Use: Labeled IndicationsRelief of bone pain in patients with skeletal metastases
Dosing: Adults**Bone pain:** I.V.: 148 megabecquerel (4 millicurie) administered by slow I.V. injection over 1-2 minutes or 1.5-2.2 megabecquerel (40-60 microcurie)/kg; repeated doses are generally not recommended at intervals <90 days; measure the patient dose by a suitable radioactivity calibration system immediately prior to administration
Dosing: ElderlyRefer to adult dosing.
StorageStore vial and its contents inside its transportation container at room temperature.
ContraindicationsHypersensitivity to any strontium-containing compounds or any other component of the formulation; pregnancy; breast-feeding
Warnings/Precautions

Special handling:

- Radioactive: Handle with caution, in a similar manner to other radioactive drugs; appropriate safety measures to minimize radiation to personnel should be instituted. Body fluids may remain radioactive up to one week after injection.

Concerns related to adverse effects:

- Bone pain: A small number of patients have experienced a transient increase in bone pain at 36-72 hours postdose; this reaction is generally mild and self-limiting.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with bone marrow suppression. Use with caution in patients whose platelet counts fall <60,000/mm^3 or whose white blood cell counts fall <2400/mm^3.

- Incontinence: Incontinent patients may require urinary catheterization.

- Renal impairment: Use with caution in patients with renal impairment; renally eliminated.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Not indicated for use in patients with cancer not involving bone.

Pregnancy Risk FactorD
Adverse ReactionsMost severe reactions of marrow toxicity can be managed by conventional means

Frequency not defined:

Cardiovascular: Flushing (most common after rapid injection)

Central nervous system: Fever and chills (rare)

Hematologic: Thrombocytopenia, leukopenia

Neuromuscular & skeletal: Increase in bone pain may occur (10% to 20% of patients)

Oncology: VesicantNo
Oncology: Emetic PotentialLow (<10%)
Drug InteractionsThere are no known significant interactions.
Monitoring ParametersRoutine blood tests
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as chloride [preservative free]:

Metastron®: 10.9-22.6 mg/mL (4 mL) [148 megabecquerel, 4 millicurie per vial]

Generic AvailableNo
Pharmacotherapy PearlsDuring the first week after injection, strontium-89 will be present in the blood and urine, therefore, the following common sense precautions should be instituted:

1. Where a normal toilet is available, use in preference to a urinal, flush the toilet twice

2. Wipe away any spilled urine with a tissue and flush it away

3. Have patient wash hands after using the toilet

4. Immediately wash any linen or clothes that become stained with blood or urine

5. Wash away any spilled blood if a cut occurs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsStrontium-89 Chloride
References

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International Brand NamesMetastron (CA)

Succimer

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(SUKS si mer)
U.S. Brand NamesChemet®
Canadian Brand NamesChemet®
Pharmacologic CategoryAntidote
Use: Labeled Indications Treatment of lead poisoning in children with serum lead levels >45 mcg/dL
Use: Unlabeled/Investigational

Treatment of lead poisoning in symptomatic adults

Dosing: AdultsFor the treatment of high blood lead levels in adults, the CDC guidelines recommend chelation therapy with blood lead levels >50 mcg/dL and significant symptoms; chelation therapy may also be indicated with blood lead levels ≥100 mcg/dL and/or symptoms. (Kosnett, 2007).

Mild symptoms or blood lead levels 70-100 mg/dL; unlabeled use: 10 mg/kg/dose (or 350 mg/m^2/dose) every 8 hours for 5 days, followed by 10 mg/kg/dose (or 350 mg/m^2/dose) every 12 hours for 14 days; Maximum: 500 mg/dose

Note: Treatment courses may be repeated, but 2-week intervals between courses is generally recommended.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricFor the treatment of high blood lead levels in children, the CDC recommends chelation treatment when blood lead levels are >45 mcg/dL (CDC, 2002). Children with blood lead levels >70 mcg/dL or symptomatic lead poisoning should be treated with parenteral agents (AAP, 2005).

Oral: 10 mg/kg/dose (or 350 mg/m^2/dose) every 8 hours for 5 days followed by 10 mg/kg/dose (or 350 mg/m^2/dose) every 12 hours for 14 days. Maximum: 500 mg/dose. For children <5 years of age, dose should be based on mg/m^2; dosing by mg/kg may be suboptimal.

Note: Treatment courses may be repeated, but 2-week intervals between courses is generally recommended.

Dosing: Renal ImpairmentAdminister with caution and monitor closely.
Dosing: Hepatic ImpairmentAdminister with caution and monitor closely
Administration: OralCapsule can be separated and contents sprinkled on a small amount of soft food, or the contents placed on a spoon and administered followed by fruit drink.
StorageStore between 15°C to 25°C (59°F to 77°F); avoid excessive heat.
ContraindicationsHypersensitivity to succimer or any component of the formulation
Warnings/Precautions

Disease-related concerns:

- Lead poisoning: Investigate, identify, and remove sources of lead exposure prior to treatment. Succimer is not used to prevent lead poisoning. Primary care providers should consult experts in chemotherapy of lead toxicity before using chelation drug therapy.
- Encephalopathy: Succimer does not cross blood brain barrier and should not be used to treat encephalopathy associated with lead toxicity.
- Hepatic impairment: Use with caution in patients with hepatic impairment; monitor serum transaminase levels closely.
- Renal impairment: Use with caution in patients with renal impairment. Succimer is dialyzable, however, the lead chelates are not.

Other warnings/precautions:

- Hydration: Adequate hydration should be maintained during therapy.
- Rebounding serum lead levels: May occur after treatment as lead is released from storage sites into blood. Severity of rebound may guide intensity of future monitoring.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAdverse events were observed in animal reproduction studies. Following maternal occupational exposure, lead crosses the placenta in amounts related to maternal plasma levels. Possible outcomes of maternal lead exposure >10 mcg/dL includes spontaneous abortion, postnatal developmental delay, and reduced birth weight. Chelation therapy during pregnancy is for maternal benefit only and should be limited to the treatment of severe, symptomatic lead poisoning.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsIt is not known if succimer is found in breast milk. The amount of lead in breast milk may range from 0.6% to 3% of the maternal serum concentration. Calcium supplementation may reduce the amount of lead in breast milk.
Adverse Reactions**Note:** Percentages as reported in pediatric patients unless otherwise noted.

>10%: Gastrointestinal: Appetite decreased, diarrhea, hemorrhoid symptoms, metallic taste, loose stools, nausea, vomiting

1% to 10%:

Cardiovascular: Arrhythmia (adults 2%)

Central nervous system: Chills, dizziness, drowsiness, fatigue, fever, headache, sleepiness

Dermatologic: Rash (including papular rash, herpetic rash and mucocutaneous eruptions); pruritus

Endocrine & metabolic: Cholesterol increased

Gastrointestinal: Abdominal cramps, mucosal irritation, sore throat

Genitourinary: Proteinuria (adults), urine output decreased (adults), voiding difficulty (adults)

Hepatic: Alkaline phosphatase increased, ALT increased, AST increased

Neuromuscular & skeletal: Back pain, flank pain, leg pain (adults), neuropathy, paresthesia, rib pain

Ocular: Cloudy film in eye, watery eyes

Otic: Otitis media, plugged ears

Respiratory: Cough, nasal congestion, rhinorrhea

Miscellaneous: Flu-like syndrome, moniliasis

<1%, postmarketing, and/or case reports: Allergic reactions (especially with retreatment), eosinophilia, neutropenia (causal relationship not established)

Drug Interactions There are no known significant interactions.

Test Interactions False-positive ketones (U) using nitroprusside methods, falsely decreased serum CPK; falsely decreased uric acid measurement

Monitoring Parameters Blood lead levels (baseline and 7-21 days after completing chelation therapy); serum aminotransferase, CBC with differential, platelets (baseline, and weekly during treatment); hemoglobin or hematocrit, iron status, free erythrocyte protoporphyrin or zinc protoporphyrin; neurodevelopmental changes

Monitoring: Lab Tests Blood lead levels (baseline and 7-21 days after completing chelation therapy); serum aminotransferase, CBC with differential, platelets (baseline, and weekly during treatment); hemoglobin or hematocrit, iron status, free erythrocyte protoporphyrin or zinc protoporphyrin

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Chemet®:100 mg

Generic Available No

Mechanism of Action Succimer is an analog of dimercaprol. It forms water soluble chelates with heavy metals which are subsequently excreted renally. Succimer binds heavy metals; however, the chemical form of these chelates is not known.

Pharmacodynamics/Kinetics

Absorption: Rapid but incomplete

Protein binding: Highly bound to albumin

Metabolism: Rapidly and extensively to mixed succimer cysteine disulfides

Half-life elimination: 2 days

Time to peak, serum: ~1-2 hours

Excretion: Urine (~25%) with peak urinary excretion between 2-4 hours (90% as mixed succimer-cysteine disulfide conjugates, 10% as unchanged drug); feces (as unabsorbed drug)

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause drowsiness or dizziness

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms DMSA

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International Brand NamesChemet (AT); Succicaptal (FR)

Succinylcholine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(suks in il KOE leen)

U.S. Brand NamesAnectine®; Quelicin®

Canadian Brand NamesQuelicin®

Pharmacologic CategoryNeuromuscular Blocker Agent, Depolarizing

Use: Labeled IndicationsAdjunct to general anesthesia to facilitate both rapid sequence and routine endotracheal intubation and to relax skeletal muscles during surgery; to reduce the intensity of muscle contractions of pharmacologically- or electrically-induced convulsions; does not relieve pain or produce sedation

Dosing: Adults**Neuromuscular blockade:** I.M., I.V.: Dose to effect; doses will vary due to interpatient variability; use ideal body weight for obese patients

I.M.: Up to 3-4 mg/kg, total dose should not exceed 150 mg

I.V.: Initial:

Short surgical procedures: 0.6 mg/kg (range 0.3-1.1 mg/kg)

Long surgical procedures:

Continuous infusion: 2.5-4.3 mg/minute; adjust dose based on response

Intermittent: Initial: 0.3-1.1 mg/kg; maintenance: 0.04-0.07 mg/kg/dose as required

Note: Initial dose of succinylcholine must be increased when nondepolarizing agent pretreatment used because of the antagonism between succinylcholine and nondepolarizing neuromuscular-blocking agents.

Dose adjustment with reduced plasma cholinesterase activity: Administer a test dose of 5-10 mg to evaluate sensitivity, or cautiously administer 1 mg/mL by slow I.V. infusion to produce neuromuscular blockade

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Neuromuscular blockade:** I.M., I.V.: Dose to effect; doses will vary due to interpatient variability; use ideal body weight for obese patients

I.M.: Children: Refer to adult dosing.

I.V.: Children: **Note:** Because of the risk of malignant hyperthermia, use of continuous infusions is not recommended in infants and children

Smaller Children: Intermittent: Initial: 2 mg/kg/dose one time; maintenance: 0.3-0.6 mg/kg/ dose every 5-10 minutes as needed

Older Children and Adolescents: Intermittent: Initial: 1 mg/kg/dose one time; maintenance: 0.3-0.6 mg/kg every 5-10 minutes as needed

Note: Initial dose of succinylcholine must be increased when nondepolarizing agent pretreatment used because of the antagonism between succinylcholine and nondepolarizing neuromuscular-blocking agents.

Dosing: Hepatic ImpairmentDose should be reduced in patients with severe liver disease.

Calculations

- Succinylcholine

Administration: I.M.I.M. injections should be made deeply, preferably high into deltoid muscle. Use only when I.V. access is not available.

Administration: I.V.May be given by rapid I.V. injection without further dilution.

Administration: I.V. DetailpH: 3.0-4.5

StorageRefrigerate at 2°C to 8°C (36°F to 46°F); however, stable for ≤3 months unrefrigerated (25°C). Stability of parenteral admixture (1-2 mg/mL) at refrigeration temperature (4°C) is 24 hours in D_5W or NS.

ReconstitutionMay dilute to a final concentration of 1-2 mg/mL. Do not mix with alkaline solutions (pH >8.5).

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, LR, ${}^1/_2NS$, NS.

Y-site administration: Compatible: Etomidate, heparin with hydrocortisone sodium succinate, potassium chloride, propofol, vitamin B complex with C. **Incompatible:** Thiopental.

Compatibility in syringe: Compatible: Heparin.

Compatibility when admixed: Compatible: Amikacin, isoproterenol, meperidine, methyldopate, morphine, norepinephrine, scopolamine. **Incompatible:** Methohexital, nafcillin, sodium bicarbonate, thiopental. **Variable (consult detailed reference):** Pentobarbital.

ContraindicationsHypersensitivity to succinylcholine or any component of the formulation; personal or familial history of malignant hyperthermia; myopathies associated with elevated serum creatine phosphokinase (CPK) values; acute phase of injury following major burns, multiple trauma, extensive denervation of skeletal muscle or upper motor neuron injury

Allergy Considerations

- Neuromuscular-Blocking Agent Allergy

Warnings/Precautions

Boxed warnings:

- Pediatrics: See "Special populations" below.

Concerns related to adverse effects:

- Bradycardia: Risk of bradycardia may be increased with second dose and may occur more in children. Occurrence may be reduced by pretreating with atropine

- Increased intraocular pressure (IOP): May increase IOP; use caution with narrow-angle glaucoma or penetrating eye injuries

- Malignant hyperthermia: Use may be associated with acute onset of malignant hyperthermia; risk may be increased with concomitant administration of volatile anesthetics.

- Vagal tone: May increase vagal tone.

Disease-related concerns:

- Burn injury: Use with caution in patients with extensive or severe burns; risk of hyperkalemia is increased following injury. Onset of time and duration of risk are variable, but risk is generally greatest 7-10 days after injury.

- Conditions which may antagonize neuromuscular blockade: Alkalosis, hypercalcemia, demyelinating lesions, peripheral neuropathies, denervation, infection, muscle trauma, and diabetes mellitus may result in antagonism of neuromuscular blockade.

- Conditions which may potentiate neuromuscular blockade: Electrolyte abnormalities, severe hyponatremia, severe hypocalcemia, severe hypokalemia, hypermagnesemia, neuromuscular diseases, acidosis, acute intermittent porphyria, Eaton-Lambert syndrome, myasthenia gravis, renal failure, and hepatic failure may result in potentiation of neuromuscular blockade.

- Hyperkalemia: Use with caution in patients with pre-existing hyperkalemia. Severe hyperkalemia may develop in patients with chronic abdominal infections, burn injuries, children with skeletal muscle myopathy, subarachnoid hemorrhage, or conditions which cause degeneration of the nervous system.

- Plasma pseudocholinesterase disorders: Metabolized by plasma cholinesterase; use with caution (if at all) in patients suspected of being homozygous for the atypical plasma cholinesterase gene. Plasma cholinesterase activity may also be reduced by burns, decompensated heart disease, infections, malignant tumors, myxedema, pregnancy, severe hepatic or renal dysfunction, ulcer, and certain medications and chemicals

Special populations:

- Elderly: Use with caution in the elderly, effects and duration are more variable.

- Pediatrics: **[U.S. Boxed Warning]: Use caution in children and adolescents. Acute rhabdomyolysis with hyperkalemia, ventricular arrhythmias and cardiac arrest have been reported (rarely) in children with undiagnosed skeletal muscle myopathy; occurs soon after administration and requires immediate treatment of hyperkalemia.** Prolonged resuscitation may be required. Use in children should be reserved for emergency intubation or where immediate airway control is necessary.

Other warnings/precautions:

- Appropriate use: Maintenance of an adequate airway and respiratory support is critical.

- Experienced personnel: Should be administered by adequately trained individuals familiar with its use.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. Small amounts cross the placenta. Sensitivity to succinylcholine may be increased due to a ~24% decrease in plasma cholinesterase activity during pregnancy and several days postpartum.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

Frequency not defined.

Cardiovascular: Arrhythmias, bradycardia (higher with 2nd dose, more frequent in children), cardiac arrest, hyper-/hypotension, tachycardia

Dermatologic: Rash

Endocrine & metabolic: Hyperkalemia

Gastrointestinal: Salivation (excessive)

Neuromuscular & skeletal: Jaw rigidity, muscle fasciculation, postoperative muscle pain, rhabdomyolysis (with possible myoglobinuric acute renal failure)

Ocular: Intraocular pressure increased

Renal: Acute renal failure (secondary to rhabdomyolysis)

Respiratory: Apnea, respiratory depression (prolonged)

Miscellaneous: Anaphylaxis, malignant hyperthermia

Postmarketing and/or case reports: Acute quadriplegic myopathy syndrome (prolonged use), myositis ossificans (prolonged use)

Causes of prolonged neuromuscular blockade: Excessive drug administration; cumulative drug effect, decreased metabolism/excretion (hepatic and/or renal impairment); accumulation of active metabolites; electrolyte imbalance (hypokalemia, hypocalcemia, hypermagnesemia, hypernatremia); hypothermia; drug interactions; increased sensitivity to muscle relaxants (eg, neuromuscular disorders such as myasthenia gravis or polymyositis)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the neuromuscular-blocking effect of Succinylcholine. *Risk C: Monitor therapy*

Aminoglycosides: May enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Analgesics (Opioid): Succinylcholine may enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Botulinum Toxin Type A: Neuromuscular-Blocking Agents may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Neuromuscular-Blocking Agents may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Cardiac Glycosides: Neuromuscular-Blocking Agents may enhance the arrhythmogenic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Colistimethate: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Cyclophosphamide: May decrease the metabolism of Succinylcholine. *Risk D: Consider therapy modification*

Echothiophate Iodide: May decrease the metabolism of Succinylcholine. *Risk D: Consider therapy modification*

Lincosamide Antibiotics: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Lithium: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Loop Diuretics: May diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Loop Diuretics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Magnesium Salts: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Phenelzine: May enhance the neuromuscular-blocking effect of Succinylcholine. *Risk D: Consider therapy modification*

Polymyxin B: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Procainamide: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

QuiNIDine: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Tetracycline Derivatives: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Vancomycin: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Monitoring Parameters

Monitor cardiac, blood pressure, and oxygenation during administration; temperature, serum potassium and calcium, assisted ventilator status; neuromuscular function with a peripheral nerve stimulator

Nursing: Physical Assessment/Monitoring

Only clinicians experienced in the use of neuromuscular-blocking drugs should administer and/or manage the use of succinylcholine. Dosage and rate of administration should be individualized and titrated to the desired effect, according to relevant clinical factors, premedication, concomitant medications, age, and general condition of patient. Ventilatory support must be instituted and maintained until adequate respiratory muscle function and/or airway protection are assured. Assess other medications for effectiveness and safety. Other drugs that affect neuromuscular activity may increase/decrease neuromuscular block induced by succinylcholine. This drug does not cause anesthesia or analgesia; pain must be treated with appropriate analgesic agents. Continuous monitoring of vital signs, cardiac status, respiratory status, and degree of neuromuscular block (objective assessment with external nerve stimulator) is mandatory during infusion and until full muscle tone has returned. Muscle tone returns in a predictable pattern, starting with limbs, abdomen, chest diaphragm, intercostals, and finally muscles of the neck, face, and eyes. Safety precautions must be maintained until full muscle tone has returned. Provide appropriate patient teaching/support prior to and following administration.

Monitoring: Lab Tests

Serum potassium and calcium

Patient Education

Patient will usually be unconscious prior to administration. Education should be appropriate to individual situation. Reassurance of constant monitoring and emotional support to reduce fear and anxiety should precede and follow administration. Following return of muscle tone, do not attempt to change position or rise from bed without assistance. Report immediately any skin rash or hives, pounding heartbeat, respiratory difficulty, or muscle tremors. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as chloride:

Anectine®: 20 mg/mL (10 mL)

Quelicin®: 20 mg/mL (10 mL)

Injection, solution, as chloride [preservative free]:

Quelicin®: 100 mg/mL (10 mL)

Generic AvailableNo

Mechanism of ActionActs similar to acetylcholine, produces depolarization of the motor endplate at the myoneural junction which causes sustained flaccid skeletal muscle paralysis produced by state of accommodation that developes in adjacent excitable muscle membranes

Pharmacodynamics/Kinetics

Onset of action: I.M.: 2-3 minutes; I.V.: Complete muscular relaxation: 30-60 seconds

Duration: I.M.: 10-30 minutes; I.V.: 4-6 minutes with single administration

Metabolism: Rapidly hydrolyzed by plasma pseudocholinesterase

Excretion: Urine

Related Information

- Neuromuscular-Blocking Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMAO inhibitors may prolong the effects of succinylcholine

Anesthesia and Critical Care Concerns/Other ConsiderationsClassified as an ultra-short duration neuromuscular-blocking agent; some formulations may contain benzyl alcohol.

Critically-Ill Adult Patients: The 2002 ACCM/SCCM/ASHP clinical practice guidelines for sustained neuromuscular blockade in the adult critically-ill patient recommend:

Optimize sedatives and analgesics prior to initiation and monitor and adjust accordingly during course. Neuromuscular blockers do not relieve pain or produce sedation.

Protect patient's eyes from development of keratitis and corneal abrasion by administering ophthalmic ointment and taping eyelids closed or using eye patches. Reposition patient routinely to protect pressure points from breakdown. Address DVT prophylaxis.

Concurrent use of a neuromuscular blocker and corticosteroids appear to increase the risk of certain ICU myopathies; avoid or administer the corticosteroid at the lowest dose possible. Reassess need for neuromuscular blocker daily.

Using daily drug holidays (stopping neuromuscular-blocking agent until patient requires it again) may decrease the incidence of acute quadriplegic myopathy syndrome.

Tachyphylaxis can develop; switch to another neuromuscular blocker (taking into consideration the patient's organ function) if paralysis is still necessary.

Atracurium or cisatracurium is recommended for patients with significant hepatic or renal disease, due to organ-independent Hofmann elimination.

Monitor patients clinically and via “Train of Four” (TOF) testing with a goal of adjusting the degree of blockade to 1-2 twitches or based upon the patient's clinical condition.

Index TermsSuccinylcholine Chloride; Suxamethonium Chloride

References

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International Brand NamesAnectine (AE, BB, BH, BM, BS, BZ, CY, EG, ES, GB, GY, IE, IL, IQ, IR, JM, JO, KW, LB, LY, MX, OM, QA, SA, SR, SY, TT, YE); Celocurin (SE); Celocurine (FR); Chlorsuccillin (PL); Curacit (NO); Curalest (NL); Ethicholine (MY); Fosfitone (AR, UY); Leptosuccin (HR); Lysthenon (AT, CH, DE, EE); Midarine (IN); Mioflex (ES); Myo-Relaxin (DE); Myoplegine (BE, LU); Myotenlis (IT); Pantolax (DE); Quelicin Chloride (BR, PH); Relaxin (TW); Scoline (AU, IN); Succi (AR); Succicholine (KP); Succicuran (DE); Succinyl Asta (HU, LU); Succinyl Forte (IL); Succinylcholin curasan (DE); Sukolin (FI, HN); Sumeth (PK); Suxamethonium (NZ); Suxamethonium Chloride (AU); Suxameton (DK); Suxametonio Cloruro (CN, PY)

Sucralfate

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Sucralfate may be confused with salsalate

Carafate® may be confused with Cafergot®

Pronunciation(soo KRAL fate)

U.S. Brand NamesCarafate®

Canadian Brand NamesNovo-Sucralate; Nu-Sucralate; PMS-Sucralate; Sulcrate®; Sulcrate® Suspension Plus

Pharmacologic CategoryGastrointestinal Agent, Miscellaneous

Use: Labeled IndicationsShort-term (≤8 weeks) management of duodenal ulcers; maintenance therapy for duodenal ulcers

Use: Unlabeled/InvestigationalGastric ulcers; suspension may be used topically for treatment of stomatitis due to cancer chemotherapy and other causes of esophageal and gastric erosions; GERD, esophagitis; treatment of NSAID mucosal damage; prevention of stress ulcers; postsclerotherapy for esophageal variceal bleeding

Dosing: Adults

Stress ulcer prophylaxis (unlabeled use): Oral: 1 g 4 times/day

Stress ulcer treatment (unlabeled use): Oral: 1 g every 4 hours

Treatment of duodenal ulcer: Oral:

Initial treatment: 1 g 4 times/day, 1 hour before meals or food and at bedtime for 4-8 weeks, or alternatively 2 g twice daily; treatment is recommended for 4-8 weeks in adults

Maintenance/prophylaxis of duodenal ulcer: 1 g twice daily

Stomatitis (unlabeled use): Oral: 10 mL (1 g/10 mL suspension); swish and spit or swish and swallow 4 times/day.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDoses of 40-80 mg/kg/day divided every 6 hours have been used

Stomatitis (unlabeled use): Oral: Children: 5-10 mL (1 g/10 mL suspension), swish and spit or swish and swallow 4 times/day

Dosing: Renal ImpairmentAluminum salt is minimally absorbed (<5%), however, may accumulate in renal failure.

Administration: OralTablet may be broken or dissolved in water before ingestion. Administer with water on an empty stomach.

Dietary ConsiderationsAdminister with water on an empty stomach.

StorageSuspension: Shake well. Store at 20°C to 25°C (68°F to 77°F); do **not** freeze.

ContraindicationsHypersensitivity to sucralfate or any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Duodenal ulceration: Because sucralfate acts locally at the ulcer, successful therapy with sucralfate should not be expected to alter the posthealing frequency of recurrence or the severity of duodenal ulceration.
- Renal impairment: Use with caution in patients with chronic renal failure; sucralfate is an aluminum complex, small amounts of aluminum are absorbed following oral administration. Excretion of aluminum may be decreased in patients with chronic renal failure.

Concurrent drug therapy issues:

- Altered absorption: Because of the potential for sucralfate to alter the absorption of some drugs, separate administration (take other medication 2 hours before sucralfate) should be considered when alterations in bioavailability are believed to be critical.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsCaution should be used in the elderly due to reduced renal function. Patients with Cl_{cr} <30 mL/minute may be at risk for aluminum intoxication. Due to low side effect profile, this may be an agent of choice in the elderly with PUD.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Sucralfate is only minimally absorbed following oral administration.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%: Gastrointestinal: Constipation (2%)

<1%, postmarketing, and/or case reports: Back pain, bezoar formation, diarrhea, dizziness, flatulence, headache, gastric discomfort; hypersensitivity (urticaria, angioedema, facial swelling, laryngospasm, respiratory difficulty, rhinitis); indigestion, insomnia, nausea, pruritus, rash, sleepiness, vertigo, vomiting, xerostomia

Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): Sucralfate may decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). **Exceptions:** Miconazole. *Risk C: Monitor therapy*

Eltrombopag: Sucralfate may decrease the serum concentration of Eltrombopag. Management: Separate administration of eltrombopag and any polyvalent cation (e.g., aluminum-containing products such as sucralfate) by at least 4 hours. *Risk D: Consider therapy modification*

Levothyroxine: Sucralfate may decrease the serum concentration of Levothyroxine. *Risk C: Monitor therapy*

Phosphate Supplements: Sucralfate may decrease the absorption of Phosphate Supplements. *Risk D: Consider therapy modification*

Quinolone Antibiotics: Sucralfate may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of quinolones. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Sucralfate may interfere with absorption of vitamin A, vitamin D, vitamin E, and vitamin K.

Nursing: Physical Assessment/MonitoringUse caution is presence of renal failure. Assess potential for interactions with other pharmacological agents patient may be taking (eg, will affect absorption of concurrently administered drugs). Assess therapeutic effectiveness (reduction in clinical symptoms) and adverse reactions. Teach patient proper use (eg, timing of other medications), possible side effects (eg, constipation) and interventions, and adverse symptoms to report.

Patient EducationTake recommended dose with water on an empty stomach, 1 hour before or 2 hours after meals. Take any other medications at least 2 hours before taking sucralfate. Do not take antacids (if prescribed) within 30 minutes of taking sucralfate. May cause constipation (increased exercise, fluids, fruit, or fiber may help). If constipation persists, consult prescriber for approved stool softener.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, oral: 1 g/10 mL (10 mL)

Carafate®: 1 g/10 mL (420 mL)

Tablet: 1 g

Carafate®: 1 g

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Suspension (Carafate)

1 g/10 mL (420): $59.01

Tablets (Carafate)

1 g (30): $44.99

Tablets (Sucralfate)

1 g (90): $32.99

Mechanism of ActionForms a complex by binding with positively charged proteins in exudates, forming a viscous paste-like, adhesive substance. This selectively forms a protective coating that acts locally to protect the gastric lining against peptic acid, pepsin, and bile salts.

Pharmacodynamics/Kinetics

Onset of action: Paste formation and ulcer adhesion: 1-2 hours

Duration: Up to 6 hours

Absorption: Oral: <5%

Distribution: Acts locally at ulcer sites; unbound in GI tract to aluminum and sucrose octasulfate

Metabolism: None

Excretion: Urine (small amounts as unchanged compounds)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, or insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAluminum Sucrose Sulfate, Basic

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International Brand NamesAlsucral (FI, MY, PL, SG); Alusac (UY); Alusulin (HU); Ancrusal (PL); Andapsin (SE); Antepsin (AR, BR, DK, FI, GB, IE, IT, NO); Calfate (PT); Carafate (AU); Dip (CO, EC); Dolisec (GR); Exinol (VE); Gastrem (PL); Inpepsa (ID); Iselpin (PH); Keal (FR, LU, TW); Musin (ID); Neciblok (ID); Peptonorm (GR); Sucrabest (LU); Sucral (PY); Sucralan (PL); Sucralbene (HN); Sucralfate (PL); Sucralfin (IT); Sucramal (CR, DO, GT, HN, IT, NI, PA, SV); Sucrate (CL); Sude (CL); Sulcran (CN); Sulcrate (JP); Suratio (PL); Treceptan (CN); Ulcafate (PK); Ulcar (AE, BH, CY, EG, FR, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ulcerfate (IN); Ulcerlmin (JP, KP); Ulcermin (PT); Ulcertec (MY, SG); Ulcetab (ZA); Ulcogant (AT, BE, CH, CZ, DE, HN, HU, LU, NL, PE, PL); Ulcyte (AU); Ulgastran (PL); Ulsaheal (AE, BH, IQ, JO, SA); Ulsanic (HK, ID, IL, JP, TH, ZA); Ulsicral (ID); Ulsidex Forte (ID); Unival (MX); Urbal (ES); Venter (EE, HR, HU, PL)

SUFentanil

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

SUFentanil may be confused with alfentanil, fentaNYL

Sufenta® may be confused with Alfenta®, Sudafed®, Survanta®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(soo FEN ta nil)

U.S. Brand NamesSufenta®

Canadian Brand NamesSufentanil Citrate Injection, USP; Sufenta®

Pharmacologic CategoryAnalgesic, Opioid; Anilidopiperidine Opioid; General Anesthetic

Use: Labeled IndicationsAnalgesic supplement in maintenance of balanced general anesthesia; primary anesthetic for induction and maintenance of anesthesia in patients undergoing major surgical procedures; epidural anesthetic in conjunction with bupivacaine in labor and delivery

Dosing: Adults**Note:** Dose should be based on body weight. In obese patients (ie, >20% above ideal body weight), use lean body weight to determine dosage.

Surgical analgesia (surgery duration: 1-2 hours): I.V.: 1-2 mcg/kg with N_2O/O_2; maintenance: 5-20 mcg as needed

Analgesia: Epidural: 10-15 mcg with 10 mL bupivacaine 0.125% with/without epinephrine. May repeat at ≥1-hour interval for 2 additional doses.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Anesthesia: I.V.: Children 2-12 years: Induction: 10-25 mcg/kg (10-15 mcg/kg most common dose) with 100% O_2; maintenance: up to 1-2 mcg/kg total dose

Calculations

- Ideal Body Weight: Adults

Administration: I.V. Detail

pH: 3.5-6

Administration: OtherEpidural: Sufentanil and bupivacaine should be mixed together before administration. Ensure proper needle/catheter placement in epidural space. Administer by slow injection.

CompatibilityStable in D_5W; **variable stability (consult detailed reference)** in NS.

Y-site administration: Compatible: Amphotericin B cholesteryl sulfate complex, atropine, cisatracurium, dexamethasone sodium phosphate, diazepam, diphenhydramine, etomidate, gatifloxacin, haloperidol, hydroxyzine, ketorolac, linezolid, methotrimeprazine, metoclopramide, midazolam, palonosetron, phenobarbital, prochlorperazine edisylate, propofol, remifentanil, scopolamine. **Incompatible:** Lorazepam, phenytoin, thiopental.

Compatibility in syringe: Compatible: Atracurium, atropine, dexamethasone sodium phosphate, diphenhydramine, haloperidol, hydroxyzine, ketorolac, methotrimeprazine, metoclopramide, midazolam, prochlorperazine edisylate, scopolamine. **Incompatible:** Diazepam, lorazepam, phenobarbital, phenytoin.

Compatibility when admixed: Compatible: Bupivacaine.

RestrictionsC-II

ContraindicationsHypersensitivity to sufentanil or any component of the formulation

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Opioid agonist toxicities: Shares the toxic potentials of opiate agonists, and precautions of opiate agonist therapy should be observed.

Disease-related concerns:

- Bradycardia: Use with caution when administering to patients with bradycardia.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Obesity: Use with caution in patients who are morbidly obese. Consider use of lean body weight for dosing in patients >20% over ideal body weight.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with pre-existing respiratory compromise (hypoxia and/or hypercapnia), COPD or other obstructive pulmonary disease, and kyphoscoliosis or other skeletal disorder which may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.

Other warnings/precautions:

- Rapid infusion: Inject slowly over 3-5 minutes; rapid I.V. infusion may result in skeletal muscle and chest wall rigidity, impaired ventilation, or respiratory distress/arrest; nondepolarizing skeletal muscle relaxant may be required.
- Trained individuals: Due to the high incidence of apnea, hypotension, tachycardia and muscle rigidity; it should be administered by individuals specifically trained in the use of anesthetic agents and should not be used in diagnostic or therapeutic procedures outside the monitored anesthesia setting; resuscitative and intubation equipment should be readily available.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects. Decrease initial dose.
- Pediatric use: Use caution in neonates as clearance of sufentanil is much slower than adults; neonates with cardiovascular disease have an even slower clearance.

Pregnancy Risk FactorC/D (prolonged use or high doses at term)
Pregnancy Considerations

Animal studies suggest embryocidal effects when given I.V. for a period of 10 days to >30 days. No evidence of teratogenic effects observed in animals. Administration of epidural sufenanil with bupivacaine with or without epinephrine is indicated in labor and delivery. Intravenous use or larger epidural doses are not recommended in pregnant women.

Adverse Reactions

>10%: Dermatologic: Pruritus (epidural: 25%)

1% to 10%:

Cardiovascular: Bradycardia (dose related; 3% to 9%), hyper-/hypotension (3% to 9%; more common with I.V. administration)

Central nervous system: Somnolence (3% to 9%), CNS depression, confusion

Gastrointestinal: Nausea (3% to 9%), vomiting (3% to 9%)

Neuromuscular & skeletal: Chest wall rigidity (dose related; 3% to 9%)

Ocular: Blurred vision

<1%: Anaphylaxis, apnea, arrhythmia, biliary spasm, bronchospasm, cardiac arrest, chills, circulatory depression; cold, clammy skin; dizziness, dysesthesia, erythema, itching, laryngospasm, mental depression, paradoxical CNS excitation or delirium, physical and psychological dependence with prolonged use, respiratory depression (dose related), seizure, skeletal muscle rigidity, skin rash, tachycardia, urinary tract spasm, urinary retention, urticaria

Metabolism/Transport Effects**Substrate** of CYP3A4 (major)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Beta-Blockers: Anilidopiperidine Opioids may enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): Anilidopiperidine Opioids may enhance the bradycardic effect of Calcium Channel Blockers (Nondihydropyridine). Anilidopiperidine Opioids may enhance the hypotensive effect of Calcium Channel Blockers (Nondihydropyridine). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

MAO Inhibitors: Anilidopiperidine Opioids may enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. *Risk D: Consider therapy modification*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Monitoring ParametersPain relief, respiratory and mental status, blood pressure

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 50 mcg/mL (1 mL, 2 mL, 5 mL)

Sufenta®: 50 mcg/mL (1 mL, 2 mL, 5 mL)

Generic AvailableYes

Mechanism of ActionBinds to opioid receptors throughout the CNS. Once receptor binding occurs, effects are exerted by opening K+ channels and inhibiting Ca++ channels. These mechanisms increase pain threshold, alter pain perception, inhibit ascending pain pathways; short-acting narcotic; dose-related inhibition of catecholamine release (up to 30 mcg/kg) controls sympathetic response to surgical stress.

Pharmacodynamics/Kinetics

Onset of action: Analgesia: I.V.: 1-3 minutes; epidural: 10 minutes

Duration: Dose dependent; Epidural:10-15 mcg with bupivacaine: 1.7 hours

Protein binding: Neonates: 79%; Adults: 91% to 93%

Metabolism: Primarily hepatic and small intestine

Half-life elimination: Neonates: 5-10 hours; Infants & Children: 55-139 minutes; Adults: 164 minutes

Excretion: Primarily urine as metabolites (2% excreted as unchanged drug)

Related Information

- Narcotic / Opioid Analgesics

Pharmacotherapy PearlsShort-acting narcotic; sufentanil is 5-10 times more potent than fentanyl. Sufentanil is packaged in the same concentration as fentanyl, 50 mcg/mL. Keep in mind the differences in potency to prevent overdose with sufentanil. May choose to dilute sufentanil to decrease concentration; this will decrease the potential for administering excessive doses.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause confusion; may rarely cause delirium or depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation

Anesthesia and Critical Care Concerns/Other ConsiderationsSufentanil is a short-acting narcotic, 5-10 times more potent than fentanyl; it is packaged in the same concentration as fentanyl (50 mcg/mL); keep in mind the differences in potency to prevent overdose with sufentanil. Sufentanil may be diluted to decrease concentration; this will decrease the potential for administering excessive doses.

Index TermsSufentanil Citrate

References

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International Brand NamesFentafienil (IT); Sufenta (AR, AT, BE, BR, CH, CN, CZ, DE, DK, FI, FR, HR, ID, LU, NL, NO, PL, PT, SE, TW, UY, ZA); Sufenta Forte (ZA); Sufentanil curasan (DE); Sufentanil epidural Curamed (DE); Sufentanil Torrex (PL); Sufentanil-hameln (DE); Sufentil (IN)

Sulconazole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(sul KON a zole)
U.S. Brand NamesExelderm®
Canadian Brand NamesExelderm®
Pharmacologic Category[Antifungal Agent, Topical]
Use: Labeled IndicationsTreatment of superficial fungal infections of the skin, including tinea cruris (jock itch), tinea corporis (ringworm), tinea versicolor, and possibly tinea pedis (athlete's foot, cream only)
Dosing: Adults**Tinea infection**: Topical: Apply a small amount to the affected area and gently massage once or twice daily for 3 weeks (tinea cruris, tinea corporis, tinea versicolor) to 4 weeks (tinea pedis).
Dosing: ElderlyRefer to adult dosing.
ContraindicationsHypersensitivity to sulconazole or any component of the formulation
Allergy Considerations

- [Azole Antifungal Allergy]

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue if sensitivity or irritation occurs.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: For topical use only; avoid contact with eyes.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse Reactions1% to 10%:

Dermatologic: Itching

Local: Burning, stinging, redness

Metabolism/Transport Effects**Inhibits** CYP1A2 (weak), 2A6 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak), 3A4 (weak)
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, as nitrate:

Exelderm®: 1% (15 g, 30 g, 60 g)

Solution, topical, as nitrate:

Exelderm®: 1% (30 mL)

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Cream (Exelderm)

1% (15): $17.59

1% (30): $32.99

1% (60): $52.79

Solution (Exelderm)

1% (30): $37.39

Mechanism of ActionSubstituted imidazole derivative which inhibits metabolic reactions necessary for the synthesis of ergosterol, an essential membrane component. The end result is usually fungistatic; however, sulconazole may act as a fungicide in *Candida albicans* and *Candida parapsilosis* during certain growth phases.
Pharmacodynamics/Kinetics

Absorption: Topical: ~8.7% percutaneously

Excretion: Primarily urine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsSulconazole Nitrate
International Brand NamesExelderm (GB, IE, IT, KP, TW); Genfuxen (TW); Minot (AR); Myk (FR); Myk 1 (BE, LU, NL); Suldisyn (GR); Zynoc (TW)

Sulfabenzamide, Sulfacetamide, and Sulfathiazole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(sul fa BENZ a mide, sul fa SEE ta mide, & sul fa THYE a zole)

U.S. Brand NamesV.V.S.®

Pharmacologic CategoryAntibiotic, Vaginal

Use: Labeled IndicationsTreatment of *Haemophilus vaginalis* vaginitis

Dosing: Adults***Haemophilus vaginalis* vaginitis:** Intravaginal: Cream: Insert 1 applicatorful in vagina twice daily for 4-6 days. Dosage may then be decreased to $^1/_2$ to $^1/_4$ of an applicatorful twice daily.

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to sulfabenzamide, sulfacetamide, sulfathiazole, or any component of the formulation; renal dysfunction; pregnancy (if near term)

Allergy Considerations

- Sulfonamide Antibiotic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Blood dyscrasias: Severe reactions including agranulocytosis, aplastic anemia and other blood dyscrasias have occurred with sulfonamides (regardless of route).
- Dermatologic reactions: Severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred with sulfonamides (regardless of route).
- Hepatic necrosis: Fatalities associated with fulminant hepatic necrosis have occurred with sulfonamides (regardless of route).
- Hypersensitivity reactions: Rarely, systemic hypersensitivity reactions may occur; use caution if applying to denuded or abraded skin.
- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Pregnancy Risk FactorC (avoid if near term)

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined.

Dermatologic: Pruritus, urticaria, Stevens-Johnson syndrome

Local: Local irritation

Miscellaneous: Allergic reactions

Drug Interactions

Methotrexate: Sulfonamide Derivatives may enhance the adverse/toxic effect of Methotrexate. *Risk D: Consider therapy modification*

Phenytoin: Sulfonamide Derivatives may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Procaine: May diminish the therapeutic effect of Sulfonamide Derivatives. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Sulfonamide Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringSee Contraindications, Warnings/Precautions, and Dosing for use cautions. Assess other medications patient may be taking for effectiveness and interactions (see Warnings/Precautions and Drug Interactions). Teach appropriate administration and adverse symptoms to report (see Patient Education). **Pregnancy risk factor C** - note breast-feeding caution.

Patient EducationInform prescriber of all prescriptions, OTC medications, or herbal products you are taking, and any allergies you have. This medication is only to be inserted into vagina. Use exactly as directed and complete full course of therapy. Follow exact directions for filling applicator with cream. Wash hands before inserting applicator gently into vagina and releasing cream. Wash hands and applicator with soap and water following each application. Discontinue and notify prescriber immediately if burning, irritation, or allergic reaction occurs. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant before use. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, vaginal: Sulfabenzamide 3.7%, sulfacetamide 2.86%, and sulfathiazole 3.42% (78 g with applicator)

Generic Available Yes

Mechanism of Action Interferes with microbial folic acid synthesis and growth via inhibition of para-aminobenzoic acid metabolism

Pharmacodynamics/Kinetics

Absorption: Absorption from vagina is variable and unreliable

Metabolism: Primarily via acetylation

Excretion: Urine

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Triple Sulfa

International Brand Names Sultrin (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, GR, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PH, PT, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW)

Sulfacetamide and Prednisolone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Blephamide® may be confused with Bleph®-10

Pronunciation(sul fa SEE ta mide & pred NIS oh lone)
U.S. Brand NamesBlephamide®
Canadian Brand NamesBlephamide®; Dioptimyd®
Pharmacologic CategoryAntibiotic/Corticosteroid, Ophthalmic
Use: Labeled IndicationsSteroid-responsive inflammatory ocular conditions in which a corticosteroid is indicated and where infection is present or there is a risk of infection
Dosing: Adults **Conjunctivitis:** Ophthalmic:

Ointment: Apply ~$^{1}/_{2}$ inch ribbon to lower conjunctival sac 3-4 times/day and 1-2 times at night

Solution: Instill 2 drops every 4 hours

Suspension: Instill 2 drops every 4 hours during the day and at bedtime

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric **Conjunctivitis:** Ophthalmic: Children ≥6 years: Refer to adult dosing.
Administration: OtherDo not apply with silver preparations. Discontinue if symptoms do not improve after 2 days. No more than 20 mL or 8 g should be prescribed without proper re-evaluation of the patient.

Suspension: Shake well before use.

Storage

Ointment: Store at 15°C to 25˚C (59°F to 77°F).

Solution, suspension: Do not freeze; protect from light. May darken on prolonged standing or exposure to heat and light. Do not use if darkened; yellowing does not affect activity.

Solution: Store at 15°C to 25˚C (59°F to 77°F).

Suspension: Store at 8°C to 24˚C (46°F to 75°F) in upright position.

ContraindicationsHypersensitivity to sulfacetamide, prednisolone, other sulfonamides or corticosteroids; active viral (including herpes simplex keratitis, vaccinia, varicella) infections of the cornea or conjunctiva, fungal infection of ocular structures, or mycobacterial ocular infections
Allergy Considerations

- Corticosteroid Allergy
- Sulfonamide Antibiotic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Blood dyscrasias: Severe reactions including agranulocytosis, aplastic anemia and other blood dyscrasias have occurred with sulfonamides (regardless of route).
- Dermatologic reactions: Severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred with sulfonamides (regardless of route).
- Hepatic necrosis: Fatalities associated with fulminant hepatic necrosis have occurred with sulfonamides (regardless of route).
- Hypersensitivity reactions: Rarely, systemic hypersensitivity reactions may occur.
- Infection: Steroids may mask infection or enhance existing ocular infection; prolonged use may result in secondary infections due to immunosuppression.
- Ocular effects: Prolonged use of steroids may result in glaucoma and injury to the optic nerve. Visual defects in acuity and field of vision may occur. Use with caution in presence of glaucoma (steroids increase intraocular pressure). Perforation may occur with topical steroids in diseases which thin the cornea or sclera. Steroid use may delay healing after cataract surgery. Intraocular pressure should be monitored if this product is used >10 days.

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Disease-related concerns:

- Dry eye: Use with caution in patients with severe dry eye

Special populations:

- Contact lens wearers: Products may contain benzalkonium chloride which may be adsorbed by contact lenses; remove contacts prior to administration.

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Other warnings/precautions:

- Appropriate use: Re-evaluate if signs and symptoms do not improve after 2 days. Use of >20 mL (solution/suspension) or 8 g (ointment) should only be done following proper re-examination of the patient (eg, slit-lamp biomicroscopy, fluorescein staining).

- P-aminobenzoic acid: May be present in purulent exudates and may reduce the effectiveness of sulfonamides.

- Topical: Not for injection into the eye.

Geriatric ConsiderationsAssess whether patient can adequately instill drops or ointment.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted with sulfacetamide. See individual agents.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsFrequency not defined. Also refer to individual agents.

Dermatologic: Stevens-Johnson syndrome, toxic epidermal necrolysis, wound healing delayed

Hematologic: Agranulocytosis, aplastic anemia

Hepatic: Hepatic necrosis (fulminant)

Local: Irritation

Ocular: Accommodation loss, anterior uveitis (acute), intraocular pressure elevation, glaucoma, globe perforation, mydriasis, optic nerve damage (infrequent), posterior subcapsular cataract formation, ptosis

Miscellaneous: Allergic reactions, hypercorticoidism (systemic; rare), secondary infections (bacterial, fungal)

Metabolism/Transport EffectsPrednisolone: **Substrate** of CYP3A4 (minor); **Inhibits** CYP3A4 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Methotrexate: Sulfonamide Derivatives may enhance the adverse/toxic effect of Methotrexate. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Phenytoin: Sulfonamide Derivatives may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Procaine: May diminish the therapeutic effect of Sulfonamide Derivatives. *Risk X: Avoid combination*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Sulfonamide Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Monitoring Parameters

Signs and symptoms of improvement after 2 days of therapy; signs and symptoms of secondary infection; intraocular pressure in patients with glaucoma or with prolonged use; periodic exam of lens with prolonged use

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient Education

See individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Ointment, ophthalmic:

Blephamide®: Sulfacetamide sodium 10% and prednisolone acetate 0.2% (3.5 g)

Solution, ophthalmic [drops]: Sulfacetamide sodium 10% and prednisolone sodium phosphate 0.25% (5 mL, 10 mL)

Suspension, ophthalmic [drops]:

Blephamide®: Sulfacetamide sodium 10% and prednisolone acetate 0.2% (5 mL, 10 mL) [contains benzalkonium chloride]

Generic AvailableYes: Solution

Pricing: U.S. (www.drugstore.com)

Ointment (Blephamide S.O.P.)

10-0.2% (3.5): $58.79

Solution (Sulfacetamide-Prednisolone)

10-0.23% (5): $18.99

10-0.23% (10): $24.99

Suspension (Blephamide)

10-0.2% (5): $55.71

10-0.2% (10): $81.37

Mechanism of ActionInterferes with bacterial growth by inhibiting bacterial folic acid synthesis through competitive antagonism of PABA; decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability; suppresses the immune system by reducing activity and volume of the lymphatic system

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause dizziness or psychosis

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPrednisolone and Sulfacetamide

International Brand NamesBlefamide (CO); Blefamide SF (MX); Blefamide SOP (MX); Blephamide (AT, AU, BG, CH, DE, TW); Lonace (PH); Metimyd (MX); Sterilid-V (PH)

Sulfacetamide

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Bleph®-10 may be confused with Blephamide®

Klaron® may be confused with Klor-Con®

Pronunciation(sul fa SEE ta mide)
U.S. Brand NamesBleph®-10; Carmol® Scalp Treatment; Klaron®; Mexar™ [DSC]; Ovace®; Ovace® Plus; Rosula® NS; Seb-Prev™
Canadian Brand NamesCetamide™; Diosulf™
Pharmacologic CategoryAcne Products; Antibiotic, Ophthalmic; Antibiotic, Sulfonamide Derivative; Topical Skin Product, Acne
Use: Labeled Indications

Ophthalmic: Treatment and prophylaxis of conjunctivitis due to susceptible organisms; corneal ulcers; adjunctive treatment with systemic sulfonamides for therapy of trachoma

Dermatologic: Scaling dermatosis (seborrheic); bacterial infections of the skin; acne vulgaris

Dosing: Adults

Conjunctivitis: Ophthalmic:

Ointment: Apply to lower conjunctival sac 1-4 times/day and at bedtime

Solution: Instill 1-2 drops several times daily up to every 2-3 hours in lower conjunctival sac during waking hours and less frequently at night; increase dosing interval as condition responds. Usual duration of treatment: 7-10 days

Trachoma: Instill 2 drops into the conjunctival sac every 2 hours; must be used in conjunction with systemic therapy

Acne: Topical: Apply thin film to affected area twice daily

Seborrheic dermatitis: Topical: Apply at bedtime and allow to remain overnight; in severe cases, may apply twice daily. Duration of therapy is usually 8-10 applications; dosing interval may be increased as eruption subsides. Applications once or twice weekly, or every other week may be used to prevent eruptions.

Secondary cutaneous bacterial infections: Topical: Apply 2-4 times/day until infection clears

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Conjunctivitis: Ophthalmic: Children >2 months: Refer to adult dosing.

Dermatologic: Topical: Children >12 years: Refer to adult dosing.

Administration: Topical

Scalp lotion: Shampoo hair with a nonirritating shampoo prior to application. Part hair in sections and apply small quantities of lotion to scalp; rub in gently. Brush hair for 2-3 minutes. May discolor white fabric.

Acne lotion: Shake well before using.

StorageStore at controlled room temperature.

Ophthalmic solution: Solution may be used if yellow; do not use if darkened.

Carmol® Scalp treatment: Do not freeze. May be used if slightly discolored.

Compatibility**Incompatible** with silver and zinc sulfate.

Incompatible with blood or purulent exudates.

ContraindicationsHypersensitivity to sulfacetamide, sulfonamides, or any component of the formulation
Allergy Considerations

- Sulfonamide Antibiotic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Blood dyscrasias: Severe reactions including agranulocytosis, aplastic anemia and other blood dyscrasias have occurred with sulfonamides (regardless of route).

- Dermatologic reactions: Severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred with sulfonamides (regardless of route).

- Hepatic necrosis: Fatalities associated with fulminant hepatic necrosis have occurred with sulfonamides (regardless of route).

- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Dosage form specific issues:

- Ophthalmic: Inactivated by purulent exudates containing PABA; use with caution in severe dry eye; ointment may retard corneal epithelial healing. For topical application to the eye only; not for injection. Safety and efficacy have not been established in children <2 months of age.

- Topical: Use caution if applied to denuded or abraded skin. Some products contain sodium metabisulfite which may cause allergic reactions in certain individuals. For external use only; avoid contact with eyes. Safety and efficacy have not been established in children <12 years of age.

Geriatric ConsiderationsAssess whether patient can adequately instill drops or ointment.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted and there are no adequate and well-controlled studies in pregnant women. Use of systemic sulfonamides during pregnancy may cause kernicterus in the newborn; the amount of systemic absorption following topical administration is not known. Use during pregnancy only if clearly needed.
LactationExcretion in breast milk unknown/use caution
Breast-Feeding ConsiderationsThe amount of systemic absorption following topical administration is not known. When used orally, small amounts of sulfonamides are excreted in breast milk.
Adverse ReactionsFrequency not defined.

Cardiovascular: Edema

Dermatologic: Burning, erythema, irritation, itching, stinging, Stevens-Johnson syndrome

Ocular (following ophthalmic application): Burning, conjunctivitis, conjunctival hyperemia, corneal ulcers, irritation, stinging

Miscellaneous: Allergic reactions, systemic lupus erythematosus

Drug Interactions

Methotrexate: Sulfonamide Derivatives may enhance the adverse/toxic effect of Methotrexate. *Risk D: Consider therapy modification*

Phenytoin: Sulfonamide Derivatives may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Procaine: May diminish the therapeutic effect of Sulfonamide Derivatives. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Sulfonamide Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Monitoring ParametersResponse to therapy
Nursing: Physical Assessment/MonitoringAssess for previous sulfonamide allergy. Assess effectiveness (resolution of infection). Teach patient appropriate use (ophthalmic/topical), interventions to reduce side effects, and adverse symptoms to report.
Patient EducationUse as directed. Complete full course of therapy even if condition appears improved. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.

Ophthalmic: Do not use other eye preparations at this time without consulting prescriber. Store at room temperature. Shake solution before using. Apply prescribed amount as often as directed. Wash hands before using. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). When using solution, tilt head back and look upward. Gently pull down lower lid and put drop(s) in inner corner of eye. When using ointment, place medicine inside the lower lid, close eye, and roll eyeball in all directions. Do not blink for ${}^{1}/_{2}$ minute. Apply gentle pressure to inner corner of eye for 30 seconds. Wipe away excess from skin around eye. Do not use any other eye preparation for at least 10 minutes. Do not share medication with anyone else. May cause sensitivity to bright light (dark glasses may help); temporary stinging or blurred vision may occur. Inform prescriber if you experience eye pain, redness, burning, watering, dryness, double vision, puffiness around eye, vision changes, or other adverse eye response; worsening of condition or lack of improvement within 3-4 days.

Topical: For external use only. Apply a thin film to affected area as often as directed. Do not cover with occlusive dressing; do not apply other lotions, creams, or medications to the area while using this medication. Report increased skin redness, irritation, or development of open sores; or if condition worsens or does not improve.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] =

Discontinued product

Aerosal, topical, as sodium [foam]:

Ovace®: 10% (50 g [DSC], 100 g)

Cream, topical, as sodium:

Ovace®: 10% (30 g, 60 g) [DSC]

Seb-Prev™: 10% (30 g, 60 g)

Gel, topical, as sodium:

Ovace® [DSC], Seb-Prev™: 10% (30 g, 60 g)

Lotion, topical, as sodium: 10% (120 mL)

Carmol® Scalp Treatment: 10% (85 g) [contains urea 10%]

Klaron®: 10% (120 mL) [contains sodium metabisulfite]

Lotion, topical, as sodium [wash]:

Ovace®: 10% (180 mL, 360 mL)

Lotion, topical, as sodium [emulsion-based wash]:

Ovace® Plus: 10% (180 mL, 360 mL)

Ointment, ophthalmic, as sodium: 10% (3.5 g) [DSC]

Pad, topical, as sodium:

Rosula® NS: 10% (30s) [contains urea 10%]

Soap, topical, as sodium [wash]:

Mexar™: 10% (170 mL) [DSC]

Seb-Prev™: 10% (170 mL, 340 mL)

Solution, ophthalmic, as sodium [drops]: 10% (15 mL)

Bleph®-10: 10% (5 mL) [contains benzalkonium chloride]

Suspension, topical, as sodium: 10% (118 mL)

Generic AvailableYes: Ointment, solution, suspension
Pricing: U.S. (www.drugstore.com)

Cream (Ovace)

10% (60): $109.99

Foam (Ovace)

10% (50): $68.72

10% (100): $130.28

Gel (Ovace)

10% (30): $65.99

Liquid (Ovace Wash)

10% (170): $84.32

10% (360): $154.80

Liquid (Ovace Wash Plus)

10% (180): $102.22

Lotion (Carmol Scalp Treatment)

10-10% (85): $95.35

Lotion (Klaron)

10% (118): $130.79

Lotion (Sulfacetamide Sodium (Acne))

10% (118): $97.00

Pads (Rosula NS)

10-10% (30): $112.19

Solution (Bleph-10)

10% (5): $20.99

Solution (Sulfacetamide Sodium)

10% (15): $12.99

Mechanism of ActionInterferes with bacterial growth by inhibiting bacterial folic acid synthesis through competitive antagonism of PABA

Pharmacodynamics/Kinetics

Half-life elimination: 7-13 hours

Excretion: When absorbed, primarily urine (as unchanged drug)

Related Information

- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsSodium Sulfacetamide; Sulfacetamide Sodium

References

Lohr JA, Austin RD, Grossman M, et al, “Comparison of Three Topical Antimicrobials for Acute Bacterial Conjunctivitis,” *Pediatr Infect Dis J*, 1988, 7(9):626-9.[PubMed 2845348]

International Brand NamesAcetopt (NZ, PH); Albucid (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, DE, EG, ET, GH, GM, GN, GY, ID, IL, IN, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Alesten (CZ); Antebor (BE, FR, LU); Beocid (AT); Blef-10 (CO, EC); Bleph-10 (AE, AU, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, MY, OM, QA, SA, SY, YE); Bleph-30 (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Cetazin (AT); Cushing (AR); Examida (MX); Isopto Cetamide (AE, BE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LU, LY, OM, QA, SA, SY, YE); Langal[ophthalm.] (ES); Optamid (IT); Prontamid (IT); Spersacet (CH); Sulfa 10 (BE); Sulfacet Sodium (VE); Sulfacetamid Ofteno (CR, DO, HN, NI, PA); Sulfacetamidum (PL); SulfacidE (IL); Sulfacidin (GB); Sulfanil (BR); Sulfex (HK); Sulop (PE); Vitaseptine (FR); Vitasul F (PH)

SulfADIAZINE

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Medication Safety Issues

Sound-alike/look-alike issues:

SulfaDIAZINE may be confused with sulfasalazine, sulfiSOXAZOLE

Pronunciation(sul fa DYE a zeen)

Pharmacologic CategoryAntibiotic, Sulfonamide Derivative

Use: Labeled IndicationsTreatment of urinary tract infections and nocardiosis; adjunctive treatment in toxoplasmosis; uncomplicated attack of malaria

Use: Unlabeled/InvestigationalRheumatic fever prophylaxis

Dosing: Adults

Toxoplasmosis: Oral: 2-6 g/day divided every 6 hours in conjunction with pyrimethamine 50-75 mg/day and with supplemental folinic acid

Asymptomatic meningococcal carriers: 1 g twice daily for 2 days

Nocardiosis: 4-8 g/day for a minimum of 6 weeks

Prevention of recurrent attacks of rheumatic fever (unlabeled use): 1 g/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Asymptomatic meningococcal carriers: Oral:

Infants 1-12 months: 500 mg once daily for 2 days

Children 1-12 years: 500 mg twice daily for 2 days

Congenital toxoplasmosis: Oral:

Newborns and Children <2 months: 100 mg/kg/day divided every 6 hours in conjunction with pyrimethamine 1 mg/kg/day once daily and supplemental folinic acid 5 mg every 3 days for 6 months

Children >2 months: 25-50 mg/kg/dose 4 times/day

Toxoplasmosis: Oral:

Children >2 months: Loading dose: 75 mg/kg; maintenance dose: 120-150 mg/kg/day, maximum dose: 6 g/day; divided every 4-6 hours in conjunction with pyrimethamine 2 mg/kg/day divided every 12 hours for 3 days followed by 1 mg/kg/day once daily with supplemental folinic acid

Prevention of recurrent attacks of rheumatic fever (unlabeled use): Oral: >30 kg: 1 g/day; <30 kg: 0.5 g/day

Administration: OralTablets may be crushed to prepare oral suspension of the drug in water or with a sucrose-containing solution. Aqueous suspension with concentrations of 100 mg/mL should be stored in the refrigerator and used within 7 days. Administer around-the-clock to promote less variation in peak and trough serum levels.

Dietary ConsiderationsSupplemental folinic acid should be administered to reverse symptoms or prevent problems due to folic acid deficiency.

StorageTablets may be crushed to prepare oral suspension of the drug in water or with a sucrose-containing solution. Aqueous suspension with concentrations of 100 mg/mL should be stored in the refrigerator and used within 7 days.

ContraindicationsHypersensitivity to any sulfa drug or any component of the formulation; porphyria; children <2 months of age unless indicated for the treatment of congenital toxoplasmosis; sunscreens containing PABA; pregnancy (at term)

Allergy Considerations

- Sulfonamide Antibiotic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Blood dyscrasias: Fatalities associated with severe reactions including agranulocytosis, aplastic anemia and other blood dyscrasias have occurred; discontinue use at first sign of rash.

- Dermatologic reactions: Fatalities associated with severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred; discontinue use at first sign of rash.

- Hepatic necrosis: Fatalities associated with hepatic necrosis have occurred; discontinue use at first sign of rash.
- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- G6PD deficiency: Use with caution in patients with G6PD deficiency; hemolysis may occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment; dosage modification required.

Other warnings/precautions:

- Appropriate use: Fluid intake should be maintained ≥1500 mL/day or administer sodium bicarbonate to keep urine alkaline; more likely to cause crystalluria because it is less soluble than other sulfonamides.

Pregnancy Risk FactorB/D (at term)
LactationEnters breast milk/contraindicated
Adverse ReactionsFrequency not defined.

Central nervous system: Dizziness, fever, headache

Dermatologic: Lyell's syndrome, Stevens-Johnson syndrome, itching, rash, photosensitivity

Endocrine & metabolic: Thyroid function disturbance

Gastrointestinal: Anorexia, diarrhea, nausea, vomiting

Genitourinary: Crystalluria

Hematologic: Aplastic anemia, granulocytopenia, hemolytic anemia, leukopenia, thrombocytopenia

Hepatic: Hepatitis, jaundice

Renal: Hematuria, acute nephropathy, interstitial nephritis

Miscellaneous: Serum sickness-like reactions

Metabolism/Transport Effects**Substrate** of CYP2C9 (major), 2E1 (minor), 3A4 (minor); **Inhibits** CYP2C9 (strong)
Drug Interactions

CycloSPORINE: Sulfonamide Derivatives may enhance the nephrotoxic effect of CycloSPORINE. Sulfonamide Derivatives may decrease the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Methotrexate: Sulfonamide Derivatives may enhance the adverse/toxic effect of Methotrexate. *Risk D: Consider therapy modification*

Phenytoin: Sulfonamide Derivatives may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Procaine: May diminish the therapeutic effect of Sulfonamide Derivatives. *Risk X: Avoid combination*

Sulfonylureas: Sulfonamide Derivatives may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Sulfonamide Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Avoid large quantities of vitamin C or acidifying agents (cranberry juice) to prevent crystalluria.

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization).

Nursing: Physical Assessment/MonitoringAssess for allergy history prior to starting therapy (sulfonamides). Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, increased or decreased levels/effects of concurrently administered drugs. Evaluate effectiveness (reduced clinical symptoms) and adverse reactions (eg, rash, photosensitivity, gastrointestinal disturbance [nausea, vomiting, anorexia], anemia, jaundice, hematuria). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity prior to initiating therapy.

Patient EducationInform prescriber of any allergies you have. Do not take any new medication during therapy without consulting prescriber. Take as directed, at regular intervals around-the-clock. Take on an empty stomach, 1 hour before or 2 hours after meals with full glass of water. Complete full course of therapy even if you are feeling better. Take a missed dose as soon as possible. If almost time for next dose, skip the missed dose and return to your regular schedule. Do not take a double dose. Avoid large quantities of vitamin C. Maintain adequate hydration to prevent kidney damage (2-3 L/day of fluids unless instructed to restrict fluid intake). May cause dizziness or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); photosensitivity (use sunblock, wear protective clothing and eyewear, and avoid direct sunlight); nausea, vomiting, or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report skin rash, persistent nausea, vomiting, or diarrhea; opportunistic infection (sore throat, fever, vaginal itching or discharge, unusual bruising or bleeding, fatigue); blood in urine or change in urinary pattern; persistent headache; abdominal pain; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (SulfADIAZINE)

500 mg (30): $46.32

Mechanism of ActionInterferes with bacterial growth by inhibiting bacterial folic acid synthesis through competitive antagonism of PABA

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: Throughout body tissues and fluids including pleural, peritoneal, synovial, and ocular fluids; throughout total body water; readily diffused into CSF; enters breast milk

Metabolism: Via N-acetylation

Half-life elimination: 10 hours

Time to peak: Within 3-6 hours

Excretion: Urine (43% to 60% as unchanged drug, 15% to 40% as metabolites)

Related Information

- Sulfonamide Derivatives
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; sulfonamides reported to cause restlessness, irritability, depression, euphoria, disorientation, panic, hallucinations, and delusions

Mental Health: Effects on Psychiatric TreatmentPhotosensitivity is common; use caution with concurrent psychotropics; may cause granulocytopenia; caution with clozapine and carbamazepine

References

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Katlama C, De Wit S, O'Doherty E, et al, “Pyrimethamine-Clindamycin vs Pyrimethamine-Sulfadiazine as Acute and Long-Term Therapy for Toxoplasmic Encephalitis in Patients With AIDS,” *Clin Infect Dis*, 1996, 22(2):268-75. [PubMed 8838183]

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International Brand NamesAdiazin (FI); Adiazine (FR); Labdiazina (PT); Sulfadiazin Streuli (CH); Sulfadiazin-Heyl (DE); Sulfadiazina (IT); Sulfadiazina Reig Jofre (ES); Sulfadiazine (GB); Sulfadiazine Suspensie FNA (NL)

Sulfadoxine and Pyrimethamine

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(sul fa DOKS een & peer i METH a meen)

U.S. Brand NamesFansidar®

Pharmacologic CategoryAntimalarial Agent

Use: Labeled IndicationsTreatment of *Plasmodium falciparum* malaria in patients in whom chloroquine resistance is suspected; malaria prophylaxis for travelers to areas where chloroquine-resistant malaria is endemic

Dosing: Adults

Treatment of acute malaria attacks: Oral: A single dose of the following number of Fansidar® tablets is used in sequence with quinine or alone: 3 tablets

Malaria prophylaxis: A single dose should be carried for self-treatment in the event of febrile illness when medical attention is not immediately available: Oral: 3 tablets

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Treatment of acute malaria attacks: Oral: A single dose of the following number of Fansidar® tablets is used in sequence with quinine or alone:

2-11 months: $^1/_4$ tablet

1-3 years: $^1/_2$ tablet

4-8 years: 1 tablet

9-14 years: 2 tablets

>14 years: Refer to adult dosing.

Malaria prophylaxis: A single dose should be carried for self-treatment in the event of febrile illness when medical attention is not immediately available: Oral:

2-11 months: $^1/_4$ tablet

1-3 years: $^1/_2$ tablet

4-8 years: 1 tablet

9-14 years: 2 tablets

>14 years: Refer to adult dosing.

StorageProtect from light.

ContraindicationsHypersensitivity to any sulfa drug, pyrimethamine, or any component of the formulation; porphyria, megaloblastic anemia; repeated prophylactic use is contraindicated in patients with renal failure, hepatic failure, or blood dyscrasias; children <2 months of age due to competition with bilirubin for protein binding sites; pregnancy (at term)

Allergy Considerations

- Sulfonamide Antibiotic Allergy

Warnings/Precautions

Boxed warnings:

- Dermatologic reactions: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Blood dyscrasias: Fatalities associated with severe reactions including agranulocytosis, aplastic anemia and other blood dyscrasias have occurred.
- Dermatologic reactions: **[U.S. Boxed Warning]: Fatalities associated with severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred; discontinue use at first sign of rash, myelosuppression or active bacterial/fungal infection.**
- Hepatic necrosis: Fatalities associated with hepatic necrosis have occurred.

- Photosensitivity: May cause photosensitivity.
- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Disease-related concerns:

- Folate deficiency: Use caution in patients with possible folate deficiency (eg, malabsorption syndrome, pregnancy, alcoholism).
- G6PD deficiency: Use with caution in patients with possible G6PD deficiency; hemolysis occurs.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment.
- Seizure disorders: Use with caution in patients with a history of seizure disorders.

Concurrent drug therapy issues:

- Chloroquine: Increased adverse reactions are seen in patients also receiving chloroquine.
- Leucovorin: Should be administered to reverse signs and symptoms of folic acid deficiency.

Special populations:

- Pediatrics: Do not give to infants <2 months of age.

Pregnancy Risk FactorC/D (at term)
Adverse ReactionsFrequency not defined.

Cardiovascular: Myocarditis (allergic), pericarditis (allergic), periorbital edema

Central nervous system: Ataxia, hallucinations, headache, polyneuritis, seizure

Dermatologic: Photosensitivity, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, rash

Endocrine & metabolic: Thyroid function dysfunction

Gastrointestinal: Anorexia, atrophic glossitis, gastritis, pancreatitis, vomiting

Genitourinary: Crystalluria

Hematologic: Megaloblastic anemia, leukopenia, thrombocytopenia, pancytopenia

Hepatic: Hepatic necrosis, hepatitis

Neuromuscular & skeletal: Tremors

Renal: BUN increased, interstitial nephritis, renal failure, serum creatinine increased

Respiratory: Respiratory failure, alveolitis (resembling eosinophilic or allergic)

Miscellaneous: Anaphylactoid reaction, drug fever, hypersensitivity, Lupus-like syndrome, periarteritis nodosum

Metabolism/Transport EffectsPyrimethamine: **Inhibits** CYP2C8/9 (moderate), 2D6 (moderate)
Drug Interactions

Antipsychotic Agents (Phenothiazines): Antimalarial Agents may increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonamide Derivatives may enhance the nephrotoxic effect of CycloSPORINE. Sulfonamide Derivatives may decrease the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Methotrexate: Sulfonamide Derivatives may enhance the adverse/toxic effect of Methotrexate. *Risk D: Consider therapy modification*

Methylfolate: May diminish the therapeutic effect of Pyrimethamine. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Phenytoin: Sulfonamide Derivatives may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Procaine: May diminish the therapeutic effect of Sulfonamide Derivatives. *Risk X: Avoid combination*

Sulfonylureas: Sulfonamide Derivatives may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Sulfonamide Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Monitoring ParametersCBC, including platelet counts, and urinalysis should be performed periodically

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: Sulfadoxine 500 mg and pyrimethamine 25 mg

Generic AvailableNo

Mechanism of ActionSulfadoxine interferes with bacterial folic acid synthesis and growth via competitive inhibition of para-aminiobenzoic acid; pyrimethamine inhibits microbial dihydrofolate reductase, resulting in inhibition of tetrahydrofolic acid synthesis

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: Sulfadoxine: Well distributed like other sulfonamides; Pyrimethamine: Widely distributed, mainly in blood cells, kidneys, lungs, liver, and spleen

Metabolism: Pyrimethamine: Hepatic; Sulfadoxine: None

Half-life elimination: Pyrimethamine: 80-95 hours; Sulfadoxine: 5-8 days

Time to peak, serum: 2-8 hours

Excretion: Urine (as unchanged drug and several unidentified metabolites)

Related Information

- Immunization Recommendations
- Malaria Treatment

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Atrophic glossitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSulfonamides reported to cause restlessness, irritability, depression, euphoria, disorientation, panic, hallucinations, and delusions

Mental Health: Effects on Psychiatric TreatmentPhotosensitivity is common; use caution with concurrent psychotropics; may cause leukopenia; caution with clozapine and carbamazepine

Index TermsPyrimethamine and Sulfadoxine

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International Brand NamesCroydoxin-FM (IN); Fansidar (AE, AT, AU, BH, BR, CH, CY, EG, FR, GB, GH, ID, IE, IL, IQ, IR, JO, KW, LB, LY, MY, OM, PE, PH, PK, QA, SA, SY, TZ, UG, YE, ZM); Fansitab (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Laridox (IN); Madomine (MY); Malerim (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Malocide (IN); Plasmodin (ID); Pyralfin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Rimodar (IN); Suldox (ID)

Sulfamethoxazole and Trimethoprim

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Medication Safety Issues

Sound-alike/look-alike issues:

Bactrim™ may be confused with bacitracin, Bactine®, Bactroban®

Co-trimoxazole may be confused with clotrimazole

Septra® may be confused with Ceptaz®, Sectral®

Septra® DS may be confused with Semprex®-D

Pronunciation(sul fa meth OKS a zole & trye METH oh prim)

U.S. Brand NamesBactrim™; Bactrim™ DS; Septra®; Septra® DS; Sulfatrim®

Canadian Brand NamesApo-Sulfatrim®; Apo-Sulfatrim® DS; Apo-Sulfatrim® Pediatric; Novo-Trimel; Novo-Trimel D.S.; Nu-Cotrimox; Septra® Injection

Pharmacologic CategoryAntibiotic, Miscellaneous; Antibiotic, Sulfonamide Derivative

Use: Labeled Indications

Oral treatment of urinary tract infections due to *E. coli*, *Klebsiella* and *Enterobacter* sp, *M. morganii*, *P. mirabilis* and *P. vulgaris*; acute otitis media in children; acute exacerbations of chronic bronchitis in adults due to susceptible strains of *H. influenzae* or *S. pneumoniae*; treatment and prophylaxis of *Pneumocystis jiroveci* pneumonitis (PCP); traveler's diarrhea due to enterotoxigenic *E. coli*; treatment of enteritis caused by *Shigella flexneri* or *Shigella sonnei*

I.V. treatment or severe or complicated infections when oral therapy is not feasible, for documented PCP, empiric treatment of PCP in immune compromised patients; treatment of documented or suspected shigellosis, typhoid fever, *Nocardia asteroides* infection, or other infections caused by susceptible bacteria

Use: Unlabeled/InvestigationalCholera and *Salmonella*-type infections and nocardiosis; chronic prostatitis; as prophylaxis in neutropenic patients with *P. jiroveci* infections, in leukemia patients, and in patients following renal transplantation, to decrease incidence of PCP; treatment of *Cyclospora* infection, typhoid fever, *Nocardia asteroides* infection; prophylaxis against urinary tract infection

Dosing: AdultsDosage recommendations are based on the trimethoprim component. Double-strength tablets are equivalent to sulfamethoxazole 800 mg and trimethoprim 160 mg.

Urinary tract infection:

Oral: One double-strength tablet every 12 hours for 10-14 days

Duration of therapy: Uncomplicated: 3-5 days; Complicated: 7-10 days

Pyelonephritis: 14 days

Prostatitis: Acute: 2 weeks; Chronic: 2-3 months

I.V.: 8-10 mg TMP/kg/day in divided doses every 6, 8, or 12 hours for up to 14 days with severe infections

Chronic bronchitis (acute): Oral: One double-strength tablet every 12 hours for 10-14 days

Meningitis (bacterial): I.V.: 10-20 mg TMP/kg/day in divided doses every 6-12 hours

Shigellosis:

Oral: One double strength tablet every 12 hours for 5 days

I.V.: 8-10 mg TMP/kg/day in divided doses every 6, 8, or 12 hours for up to 5 days

Travelers' diarrhea: Oral: One double strength tablet every 12 hours for 5 days

Sepsis: I.V.: 20 TMP/kg/day divided every 6 hours

Pneumocystis jiroveci:

Prophylaxis: Oral: 1 double strength tablet daily or 3 times/week

Treatment: Oral, I.V.: 15-20 mg TMP/kg/day in 3-4 divided doses

Cyclospora (unlabeled use): Oral, I.V.: 160 mg TMP twice daily for 7-10 days. **Note:** AIDS patients: Oral: 1 double strength tablet 2-4 times/day for 10 days, then 1 double strength tablet 3 times/week for 10 weeks (Verdier, 2000 and Pape, 1994).

Nocardia (unlabeled use): Oral, I.V.:

Cutaneous infections: 5-10 mg TMP/kg/day in 2-4 divided doses

Severe infections (pulmonary/cerebral): 15 mg TMP/kg/day in 2-4 divided doses for 3-4 weeks, then 10 mg TMP/kg/day in 2-4 divided doses. Treatment duration is controversial; an average of 7 months has been reported.

Note: Therapy for severe infection may be initiated I.V. and converted to oral therapy (frequently converted to approximate dosages of oral solid dosage forms: 2 DS tablets every 8-12 hours). Although not widely available, sulfonamide levels should be considered in patients with questionable absorption, at risk for dose-related toxicity, or those with poor therapeutic response.

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRecommendations are based on the trimethoprim component.

General dosing guidelines: Children >2 months:

Mild-to-moderate infections: Oral: 8-12 mg TMP/kg/day in divided doses every 12 hours

Serious infection:

Oral: 20 mg TMP/kg/day in divided doses every 6 hours

I.V.: 8-12 mg TMP/kg/day in divided doses every 6 hours

Acute otitis media: Oral: 8 mg TMP/kg/day in divided doses every 12 hours for 10 days. **Note:** Recommended by the American Academy of Pediatrics as an alternative agent in penicillin allergic patients at a dose of 6-10mg TMP/kg/day (AOM guidelines, 2004).

Urinary tract infection:

Treatment:

Oral: 6-12 mg TMP/kg/day in divided doses every 12 hours

I.V.: 8-10 mg TMP/kg/day in divided doses every 6, 8, or 12 hours for up to 14 days with serious infections

Prophylaxis: Oral: 2 mg TMP/kg/dose daily or 5 mg TMP/kg/dose twice weekly

Pneumocystis:

Treatment: Oral, I.V.: 15-20 mg TMP/kg/day in divided doses every 6-8 hours

Prophylaxis: Oral, 150 mg TMP/m^2/day in divided doses every 12 hours for 3 days/week; dose should not exceed trimethoprim 320 mg and sulfamethoxazole 1600 mg daily

Alternative prophylaxis dosing schedules include:

150 mg TMP/m^2/day as a single daily dose 3 times/week on consecutive days

or

150 mg TMP/m^2/day in divided doses every 12 hours administered 7 days/week

or

150 mg TMP/m^2/day in divided doses every 12 hours administered 3 times/week on alternate days

Shigellosis:

Oral: 8 mg TMP/kg/day in divided doses every 12 hours for 5 days

I.V.: 8-10 mg TMP/kg/day in divided doses every 6, 8, or 12 hours for up to 5 days

Cyclospora (unlabeled use): Oral, I.V.: 5 mg TMP/kg twice daily for 7-10 days

Dosing: Renal Impairment

Cl_{cr} 15-30 mL/minute: Administer 50% of recommended dose.

Cl_{cr} <15 mL/minute: Not recommended

Calculations

- Body Surface Area: Pediatrics
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Infuse over 60-90 minutes, must dilute well before giving.
Administration: I.V. DetailMay be given less diluted in a central line. Not for I.M. injection. Administer around-the-clock every 6-12 hours.

pH: 10

Administration: OralMay be taken with or without food. Administer with at least 8 ounces of water.

Dietary ConsiderationsShould be taken with 8 oz of water.

Storage

Injection: Store at room temperature; do not refrigerate. Less soluble in more alkaline pH. Protect from light. Solution must be diluted prior to administration. Following dilution, store at room temperature; do not refrigerate. Manufacturer recommended dilutions and stability of parenteral admixture at room temperature (25°C):

5 mL/125 mL D_5W; stable for 6 hours.

5 mL/100 mL D_5W; stable for 4 hours.

5 mL/75 mL D_5W; stable for 2 hours.

Studies have also confirmed limited stability in NS; detailed references should be consulted.

Suspension, tablet: Store at controlled room temperature of 15°C to 25°C (59°F to 77°F). Protect from light.

CompatibilityStable in $D_5{}^1/_2$NS, LR, $^1/_2$NS; **variable stability (consult detailed reference)** in D_5W, NS.

Y-site administration: Compatible: Acyclovir, aldesleukin, allopurinol, amifostine, amphotericin B cholesteryl sulfate complex, atracurium, aztreonam, bivalirudin, cefepime, cyclophosphamide, dexmedetomidine, diltiazem, docetaxel, doxorubicin liposome, enalaprilat, esmolol, etoposide phosphate, fenoldopam, filgrastim, fludarabine, gallium nitrate, gatifloxacin, gemcitabine, granisetron, hydromorphone, labetalol, linezolid, lorazepam, magnesium sulfate, melphalan, meperidine, morphine, nicardipine, pancuronium, pemetrexed, perphenazine, piperacillin/tazobactam, remifentanil, sargramostim, tacrolimus, teniposide, thiotepa, vecuronium, zidovudine. **Incompatible:** Fluconazole, midazolam, vinorelbine. **Variable (consult detailed reference):** Cisatracurium, foscarnet.

Compatibility in syringe: Compatible: Dimenhydramine, heparin. **Incompatible:** Pantoprazole.

Compatibility when admixed: Incompatible: Fluconazole, linezolid, verapamil.

ContraindicationsHypersensitivity to any sulfa drug, trimethoprim, or any component of the formulation; megaloblastic anemia due to folate deficiency; infants <2 months of age; marked hepatic damage or severe renal disease (if patient not monitored); pregnancy (at term); breast-feeding

Allergy Considerations

- Sulfonamide Antibiotic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Blood dyscrasias: Fatalities associated with severe reactions including agranulocytosis, aplastic anemia and other blood dyscrasias have occurred; discontinue use at first sign of rash or signs of serious adverse reactions.
- Dermatologic reactions: Fatalities associated with severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred; discontinue use at first sign of rash.
- Hepatic necrosis: Fatalities associated with hepatic necrosis have occurred; discontinue use at first sign of rash or signs of serious adverse reactions.
- Hyperkalemia: May cause hyperkalemia (associated with high doses of trimethoprim).
- Hypoglycemia: May cause hypoglycemia, particularly in malnourished, or patients with renal or hepatic impairment.
- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Asthma/allergies: Use with caution in patients with allergies or asthma.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended. Maintain adequate hydration to prevent crystalluria.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Special populations:

- AIDS patients: Incidence of adverse effects appears to be increased in patients with AIDS.
- Elderly: Use with caution in the elderly; greater risk for more severe adverse reactions.
- G6PD deficiency: Use with caution in patients with G6PD deficiency; hemolysis may occur (dose-related).
- Patients with potential for folate deficiency: Use with caution in patients with potential folate deficiency (malnourished, chronic

anticonvulsant therapy, or elderly).

- Slow acetylators: May be more prone to adverse reactions.

Dosage form specific issues:

- Injection vehicle: May contain benzyl alcohol which has been associated with "gasping syndrome" in neonates and sodium metabisulfite.

Geriatric ConsiderationsElderly patients appear at greater risk for more severe adverse reactions.

Pregnancy Risk FactorC/D (at term - expert analysis)

Pregnancy ConsiderationsDo not use at term to avoid kernicterus in the newborn; use during pregnancy only if risks outweigh the benefits since folic acid metabolism may be affected.

LactationEnters breast milk/contraindicated (AAP rates “compatible with restrictions”)

Breast-Feeding ConsiderationsSulfonamides are excreted in low concentrations in breast milk. Use during breast feeding in infants <2 months of age is contraindicated according to the manufacturer. The AAP considers use during breast-feeding “compatible” in full term neonates; however, breast-feeding is not recommended if the infant is ill, stressed, or premature **or** if the infant has glucose-6-phosphate dehydrogenase deficiency or hyperbilirubinemia.

Adverse ReactionsThe most common adverse reactions include gastrointestinal upset (nausea, vomiting, anorexia) and dermatologic reactions (rash or urticaria). Rare, life-threatening reactions have been associated with co-trimoxazole, including severe dermatologic reactions, blood dyscrasias, and hepatotoxic reactions. Most other reactions listed are rare, however, frequency cannot be accurately estimated.

Cardiovascular: Allergic myocarditis

Central nervous system: Apathy, aseptic meningitis, ataxia, chills, depression, fatigue, fever, hallucinations, headache, insomnia, kernicterus (in neonates), nervousness, peripheral neuritis, seizure, vertigo

Dermatologic: Photosensitivity, pruritus, rash, skin eruptions, urticaria; rare reactions include erythema multiforme, exfoliative dermatitis, Henoch-Schönlein purpura, Stevens-Johnson syndrome, and toxic epidermal necrolysis

Endocrine & metabolic: Hyperkalemia (generally at high dosages), hypoglycemia (rare), hyponatremia

Gastrointestinal: Abdominal pain, anorexia, diarrhea, glottis, nausea, pancreatitis, pseudomembranous colitis, stomatitis, vomiting

Hematologic: Agranulocytosis, aplastic anemia, eosinophilia, hemolysis (with G6PD deficiency), hemolytic anemia, hypoprothrombinemia, leukopenia, megaloblastic anemia, methemoglobinemia, neutropenia, thrombocytopenia

Hepatic: Hepatotoxicity (including hepatitis, cholestasis, and hepatic necrosis), hyperbilirubinemia, transaminases increased

Neuromuscular & skeletal: Arthralgia, myalgia, rhabdomyolysis, weakness

Otic: Tinnitus

Renal: BUN increased, crystalluria, diuresis (rare), interstitial nephritis, nephrotoxicity (in association with cyclosporine), renal failure, serum creatinine increased, toxic nephrosis (with anuria and oliguria)

Respiratory: Cough, dyspnea, pulmonary infiltrates

Miscellaneous: Allergic reaction, anaphylaxis, angioedema, periarteritis nodosa (rare), serum sickness, systemic lupus erythematosus (rare)

Oncology: VesicantNo

Metabolism/Transport Effects

Sulfamethoxazole: **Substrate** of CYP2C9 (major), 3A4 (minor); **Inhibits** CYP2C9 (moderate)

Trimethoprim: **Substrate** (major) of CYP2C9, 3A4; **Inhibits** CYP2C8 (moderate), 2C9 (moderate)

Drug Interactions

ACE Inhibitors: Trimethoprim may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amantadine: Trimethoprim may enhance the adverse/toxic effect of Amantadine. Specifically, the risk of myoclonus and/or delerium may be increased. Amantadine may increase the serum concentration of Trimethoprim. Trimethoprim may increase the serum concentration of Amantadine. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Trimethoprim may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Antidiabetic Agents (Thiazolidinedione): Trimethoprim may decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

AzaTHIOprine: Sulfamethoxazole may enhance the myelosuppressive effect of AzaTHIOprine. *Risk C: Monitor therapy*

AzaTHIOprine: Trimethoprim may enhance the myelosuppressive effect of AzaTHIOprine. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonamide Derivatives may enhance the nephrotoxic effect of CycloSPORINE. Sulfonamide Derivatives may decrease the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dapsone: Trimethoprim may increase the serum concentration of Dapsone. Dapsone may increase the serum concentration of Trimethoprim. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dofetilide: Trimethoprim may decrease the excretion of Dofetilide. *Risk X: Avoid combination*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

LamiVUDine: Trimethoprim may decrease the excretion of LamiVUDine. *Risk C: Monitor therapy*

Leucovorin-Levoleucovorin: May diminish the therapeutic effect of Trimethoprim. *Risk D: Consider therapy modification*

Memantine: Trimethoprim may enhance the adverse/toxic effect of Memantine. Specifically, the risk of myoclonus and/or delerium may be increased. Trimethoprim may increase the serum concentration of Memantine. Memantine may increase the serum concentration of Trimethoprim. *Risk C: Monitor therapy*

Methotrexate: Sulfonamide Derivatives may enhance the adverse/toxic effect of Methotrexate. *Risk D: Consider therapy modification*

Methotrexate: Trimethoprim may enhance the adverse/toxic effect of Methotrexate. *Risk D: Consider therapy modification*

Phenytoin: Sulfonamide Derivatives may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Phenytoin: Trimethoprim may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Procainamide: Trimethoprim may decrease the excretion of Procainamide. *Risk D: Consider therapy modification*

Procaine: May diminish the therapeutic effect of Sulfonamide Derivatives. *Risk X: Avoid combination*

Repaglinide: Trimethoprim may decrease the metabolism of Repaglinide. *Risk C: Monitor therapy*

Sulfonylureas: Sulfonamide Derivatives may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Sulfonamide Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai; St John's wort (may diminish effects and also cause photosensitization).
Test InteractionsIncreased creatinine (Jaffé alkaline picrate reaction); increased serum methotrexate by dihydrofolate reductase method
Monitoring ParametersPerform culture and sensitivity testing prior to initiating therapy; CBC, serum potassium, creatinine, BUN
Nursing: Physical Assessment/MonitoringSee individual agent for Trimethoprim.
Monitoring: Lab TestsPerform culture and sensitivity testing prior to initiating therapy; CBC, serum potassium, creatinine, BUN
Patient EducationSee individual agent for Trimethoprim.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. **Note:** The 5:1 ratio (SMX:TMP) remains constant in all dosage forms.

Injection, solution: Sulfamethoxazole 80 mg and trimethoprim 16 mg per mL (5 mL, 10 mL, 30 mL)

Suspension, oral: Sulfamethoxazole 200 mg and trimethoprim 40 mg per 5 mL (480 mL)

Sulfatrim®: Sulfamethoxazole 200 mg and trimethoprim 40 mg per 5 mL (100 mL, 480 mL) [contains alcohol ≤0.5% propylene glycol; cherry flavor]

Tablet: Sulfamethoxazole 400 mg and trimethoprim 80 mg

Bactrim™: Sulfamethoxazole 400 mg and trimethoprim 80 mg

Septra®: Sulfamethoxazole 400 mg and trimethoprim 80 mg

Tablet, double strength: Sulfamethoxazole 800 mg and trimethoprim 160 mg

Bactrim™ DS: Sulfamethoxazole 800 mg and trimethoprim 160 mg

Septra® DS: Sulfamethoxazole 800 mg and trimethoprim 160 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Suspension (Sulfamethoxazole-Trimethoprim)

200-40 mg/5 mL (200): $18.98

Suspension (Sulfatrim)

200-40 mg/5 mL (480): $33.98

Tablets (Bactrim)

400-80 mg (30): $37.54

Tablets (Septra DS)

800-160 mg (30): $69.99

Tablets (Sulfamethoxazole-TMP DS)

800-160 mg (30): $19.99

Tablets (Sulfamethoxazole-Trimethoprim)

400-80 mg (30): $15.99

Mechanism of ActionSulfamethoxazole interferes with bacterial folic acid synthesis and growth via inhibition of dihydrofolic acid formation from para-aminobenzoic acid; trimethoprim inhibits dihydrofolic acid reduction to tetrahydrofolate resulting in sequential inhibition of enzymes of the folic acid pathway

Pharmacodynamics/Kinetics

Absorption: Oral: Almost completely, 90% to 100%

Protein binding: SMX: 68%, TMP: 45%

Metabolism: SMX: N-acetylated and glucuronidated; TMP: Metabolized to oxide and hydroxylated metabolites

Half-life elimination: SMX: 9 hours, TMP: 6-17 hours; both are prolonged in renal failure

Time to peak, serum: Within 1-4 hours

Excretion: Both are excreted in urine as metabolites and unchanged drug

Effects of aging on the pharmacokinetics of both agents has been variable; increase in half-life and decreases in clearance have been associated with reduced creatinine clearance

Related Information

- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Desensitization Protocols
- Treatment of Sexually-Transmitted Infections
- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusRarely may cause depression, hallucination, or confusion; sulfonamides may cause euphoria, restlessness, irritability, disorientation, panic, and delusions

Mental Health: Effects on Psychiatric TreatmentMay rarely cause granulocytopenia; use caution with clozapine and carbamazepine

Index TermsCo-Trimoxazole; SMZ-TMP; Sulfatrim; TMP-SMZ; Trimethoprim and Sulfamethoxazole

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International Brand NamesAbacin (IT); Acuco (ZA); Alcorim-F (IN); Anitrim (MX); Bacidal (PH); Bacin (MY, TH); Bactelan (MX); Bacteric (MX); Bacterol (CN); Bacterol Forte (CN); Bacticel (AR, CR, DO, GT, HN, NI, PA, SV); Bactiver (MX); Bactoprim (ID); Bactramin (JP); Bactrim (AE, AR, AT, AU, BE, BG, BH, CH, CY, CZ, DE, DK, EC, EG, ES, FI, FR, GB, GR, HN, ID, IE, IL, IN, IQ, IR, IT, JO, KW, LB, LY, MX, MY, NL, NO, OM, PK, PT, QA, RU, SA, SE, SY, TH, TR, YE); Bactrim DS (AU); Bactrim F (CO); Bactrim Forte (AT, BG, FI, FR, PT, SE); Bactrimel (GR, NL, VE); Bactropin (MX); Brogamax (MX); Colizole (IN); Colizole DS (IN); Conprim (TH); Costazole (PH); Cotrim (BF, BJ, CI, ET, GH, GM, GN, HK, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SL, SN, TN, TW, TZ, UG, ZA, ZM, ZW); Cotrim DS (MY); Cotrimel (HK, HN); Cotrimel Forte (HN); Cotrix (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Cozole (PH); Dibaprim (MX); Diseptyl (IL); Dotrim (ID); Dotrim Forte (ID); Duocide (TW); Duratrimet (DE); Ectaprim (MX); Epitrim (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Escoprim (CH); Espectrin (BR); Eusaprim (AT, BE, FI, IT, NL, NO, SE); Fectrim (GB); Fedimed (PH); Fermagex (PH); Gantaprim (IT); Gantrim (IT); Ikaprim (ID); Infectrim (PE); Introcin (CN); Isotrim (IT); Kepinol (DE); Ladar Child (TH); Lagatrim (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Lagatrim Forte (BB, BF, BJ, BM, BS, BZ, CI, ET, GH, GM, GN, GY, JM, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, PR, SC, SD, SL, SN, SR, TN, TT, TZ, UG, ZA, ZM, ZW); Lastrim (TH); Leprim (PH); M-Trim (TH); Mano-Trim (TH); Mano-Trim Forte (TH); Medixin (IT); Metoxiprim (MX); Microtrim (DE); Nopil (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Nufaprim Forte (ID); Octex (MX); Omsat (BF, BJ, CI, DE, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Oriprim DS (KE, TZ, UG, ZW); Oxaprim (IT); Purbal (ZA); Resprim (AU, IL, MY); Resprim Forte (AU); Rotrace (PH); Sanprima (ID); Sanprima Forte (ID); Septran (IN, PY); Septran Forte (CR, DO, GT, HN, NI, PA, SV); Septrin (AE, AU, BF, BH, BJ, CI, CO, CY, EG, ES, ET, GB, GH, GM, GN, ID, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, OM, PE, PH, QA, SA, SC, SD, SL, SN, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW); Septrin DS (HK); Septrin Forte (AU); Servitrim (MX); Sigaprim (DE); Soltrim (MX); Suftrex (EC); Sulfacet (DE); Sulfaprim (MY); Sulfoid Trimetho (MX); Sulfotrimin (DE); Sultrimmix (ID); Sultrimmix DS (ID); Sultrimmix P (ID); Sumetropin (PE); Suntrim (TH); Suntrim Forte (TH); Suprim (PE); Suprin (IT); Synermed (PH); Timexole (MX); Timizol (PH); Timizol Forte (PH); TMS (DE); Trim (IT, ZA); Trimaxazole (SG); Trimel (NZ); Trimephar (PH); Trimetoger (MX); Trimexazol (MX); Trimezole (ID); Trimoxis (PH); Trisul (NZ); Trisulcom (PH); Trizole (ID, PH); TS

Tab (KP); Ulfaprim (ID); Unitrizole (PH); Zoltrim (EC); Zultrop (ID); Zultrop Forte (ID)

Sulfasalazine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Sulfasalazine may be confused with salsalate, sulfaDIAZINE, sulfiSOXAZOLE

Azulfidine® may be confused with Augmentin®, azaTHIOprine

Pronunciation(sul fa SAL a zeen)

U.S. Brand NamesAzulfidine®; Azulfidine® EN-tabs®; Sulfazine; Sulfazine EC

Canadian Brand NamesAlti-Sulfasalazine; Salazopyrin En-Tabs®; Salazopyrin®

Pharmacologic Category5-Aminosalicylic Acid Derivative

Use: Labeled IndicationsManagement of ulcerative colitis; enteric coated tablets are also used for rheumatoid arthritis (including juvenile rheumatoid arthritis) in patients who inadequately respond to analgesics and NSAIDs

Use: Unlabeled/InvestigationalAnkylosing spondylitis, collagenous colitis, Crohn's disease, psoriasis, psoriatic arthritis, juvenile chronic arthritis

Dosing: Adults

Ulcerative colitis: Oral: Initial: 1 g 3-4 times/day, 2 g/day maintenance in divided doses; may initiate therapy with 0.5-1 g/day

Rheumatoid arthritis: Oral (enteric coated tablet): Initial: 0.5-1 g/day; increase weekly to maintenance dose of 2 g/day in 2 divided doses; maximum: 3 g/day (if response to 2 g/day is inadequate after 12 weeks of treatment)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Ulcerative colitis: Oral: Children ≥2 years: Initial: 40-60 mg/kg/day in 3-6 divided doses; maintenance dose: 20-30 mg/kg/day in 4 divided doses

Juvenile rheumatoid arthritis: Oral (enteric coated tablet): Children ≥6 years: 30-50 mg/kg/day in 2 divided doses; Initial: Begin with $^1/_4$ to $^1/_3$ of expected maintenance dose; increase weekly; maximum: 2 g/day typically

Dosing: Renal Impairment

Cl_{cr} 10-30 mL/minute: Administer twice daily.

Cl_{cr} <10 mL/minute: Administer once daily.

Dosing: Hepatic ImpairmentAvoid use.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralGI intolerance is common during the first few days of therapy (give with meals).

Dietary ConsiderationsSince sulfasalazine impairs folate absorption, consider providing 1 mg/day folate supplement.

StorageProtect from light.

ContraindicationsHypersensitivity to sulfasalazine, sulfa drugs, salicylates, or any component of the formulation; porphyria; GI or GU obstruction; pregnancy (at term)

Allergy Considerations

- 5-Aminosalicylic Acid Derivative Allergy
- Sulfonamide Antibiotic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Deaths from irreversible neuromuscular and central nervous system have been reported.
- Fibrosing alveolitis: Deaths from fibrosing alveolitis have been reported.
- Folate deficiency: May cause folate deficiency; consider providing 1 mg/day folate supplement.
- Oligospermia: In males, oligospermia (rare) has been reported.
- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product

labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Disease-related concerns:

- Allergies/asthma: Use with caution in patients with severe allergies or asthma.
- Blood dyscrasias: Use with caution in patients with blood dyscrasias; deaths from agranulocytosis, aplastic anemia, and other blood dyscrasias have been reported.
- G6PD deficiency: Use with caution in patients with G6PD deficiency.
- Hepatic impairment: Use with caution in patients with impaired hepatic function.
- Renal impairment: Use with caution in patients with renal impairment.
- Urinary obstruction: Use with caution in patients with urinary obstruction.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Geriatric ConsiderationsAdjust dose for renal function.

Pregnancy Risk FactorB/D (at term)

LactationEnters breast milk/use caution (AAP recommends use “with caution”)

Breast-Feeding ConsiderationsSulfonamides are excreted in human breast milk and may cause kernicterus in the newborn. Although sulfapyridine has poor bilirubin-displacing ability, use with caution in women who are breast-feeding. The AAP classifies this agent to be used with caution since adverse effects have been reported in nursing infants.

Adverse Reactions

>10%:

Central nervous system: Headache (33%)

Dermatologic: Photosensitivity

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea (33%), gastric distress

Genitourinary: Reversible oligospermia (33%)

<3%:

Dermatologic: Urticaria/pruritus (<3%)

Hematologic: Hemolytic anemia (<3%), Heinz body anemia (<3%)

<0.1%: Alopecia, anaphylaxis, aplastic anemia, ataxia, convulsions, crystalluria, depression, drowsiness, epidermal necrolysis, exfoliative dermatitis, granulocytopenia, hallucinations, hearing loss, hematuria, hepatitis, insomnia, interstitial nephritis, jaundice, leukopenia, Lyell's syndrome, myelodysplastic syndrome, nephropathy (acute), neutropenic enterocolitis, pancreatitis, peripheral neuropathy, photosensitization, rhabdomyolysis, serum sickness-like reactions, skin discoloration, Stevens-Johnson syndrome, thrombocytopenia, thyroid function disturbance, tinnitus, urine discoloration, vasculitis, vertigo

Additional events reported with sulfonamides and/or 5-ASA derivatives: Cholestatic jaundice, eosinophilia pneumonitis, erythema multiforme, fibrosing alveolitis, hepatic necrosis, Kawasaki-like syndrome, SLE-like syndrome, pericarditis, seizure, transverse myelitis

Drug Interactions

Cardiac Glycosides: 5-ASA Derivatives may decrease the absorption of Cardiac Glycosides. *Risk C: Monitor therapy*

Methylfolate: Sulfasalazine may decrease the serum concentration of Methylfolate. *Risk C: Monitor therapy*

Thiopurine Analogs: 5-ASA Derivatives may decrease the metabolism of Thiopurine Analogs. *Risk C: Monitor therapy*

Varicella Virus-Containing Vaccines: 5-ASA Derivatives may enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. The primary concern is the potential development of Reye's Syndrome, a condition that has been associated with the use of salicylates in children with varicella infections. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: May impair folate absorption.

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization)

Nursing: Physical Assessment/MonitoringAssess for allergy history prior to starting therapy (sulfa drugs, salicylates). Assess potential for interactions with other pharmacological agents patient may be taking (eg, increased or decreased levels/effects of concurrently administered drugs). Evaluate therapeutic effectiveness (reduced clinical symptoms) and adverse reactions (eg, photosensitivity, gastrointestinal disturbance [nausea, vomiting, anorexia], anemia, jaundice, hematuria). Caution patients with diabetes to monitor glucose levels closely (may cause altered effect of oral hypoglycemic agents). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationInform prescriber of any allergies you have. Do not take any new medication during therapy without consulting prescriber. Take as directed, at regular intervals around-the-clock with food. Do not crush, chew, or dissolve coated tablets. Complete full course of therapy even if you are feeling better. Take a missed dose as soon as possible. If almost time for next dose, skip the missed dose and return

to your regular schedule. Do not take a double dose. Maintain adequate hydration to prevent kidney damage (2-3 L/day of fluids unless instructed to restrict fluid intake). If you have diabetes, monitor glucose levels closely (may cause decreased effect of oral hypoglycemic agents). May cause dizziness or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); photosensitivity (use sunblock, wear protective clothing and eyewear, and avoid direct sunlight); or nausea, vomiting, or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report rash; persistent nausea, vomiting, or diarrhea; opportunistic infection (sore throat, fever, vaginal itching or discharge, unusual bruising or bleeding, fatigue); blood in urine or change in urinary pattern; swelling of face, lips, or tongue, tightness in chest, bad cough, blue skin color, or other persistent adverse effects.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 500 mg

Azulfidine®, Sulfazine: 500 mg

Tablet, delayed release, enteric coated: 500 mg

Azulfidine® EN-tabs®, Sulfazine EC: 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablet, EC (Azulfidine EN-tabs)

500 mg (100): $65.99

Tablet, EC (Sulfazine EC)

500 mg (60): $24.99

Tablets (Azulfidine)

500 mg (100): $54.99

Tablets (Sulfasalazine)

500 mg (100): $18.99

Mechanism of ActionActs locally in the colon to decrease the inflammatory response and systemically interferes with secretion by inhibiting prostaglandin synthesis

Pharmacodynamics/Kinetics

Absorption: 10% to 15% as unchanged drug from small intestine

Distribution: Small amounts enter feces and breast milk

Metabolism: Via colonic intestinal flora to sulfapyridine and 5-aminosalicylic acid (5-ASA); following absorption, sulfapyridine undergoes N-acetylation and ring hydroxylation while 5-ASA undergoes N-acetylation

Half-life elimination: 5.7-10 hours

Excretion: Primarily urine (as unchanged drug, components, and acetylated metabolites)

Related Information

- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; sulfonamides reported to cause restlessness, irritability, depression, euphoria, disorientation, panic, hallucinations, and delusions

Mental Health: Effects on Psychiatric TreatmentPhotosensitivity is common; use caution with concurrent psychotropics; may cause leukopenia; caution with clozapine and carbamazepine

Index TermsSalicylazosulfapyridine

References

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International Brand NamesAzulfidina (MX); Azulfidine (CN, DE, GR, VE); Azulfidine EN-tabs (AR, CN); Azulfin (BR); Bomecon (TW); Colo-Pleon (DE); Disalazin (PE); Falazine (EC); Gastropyrin (FI, PL); Lazafin (ID); Pyralin EN (AU); Rosulfant (CO); SAAZ (IN); Salazine (TW); Salazodin (UY); Salazopirina (PT); Salazopyrin (AE, AT, AU, BH, CH, CY, DK, EG, ES, FI, GB, HN, HU, IE, IL, IQ, IR, IT, JO, KW, LB, LY, NO, NZ, OM, PK, PL, QA, SA, SE, SY, YE, ZA); Salazopyrin Entabs (AE, BH, CY, DK, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Salazopyrin-EN (AU, BG, CH, CO, CZ, EE, FI, GB, HK, IL, IT, KP, MY, NO, SE, TH, TW, ZA); Salazopyrina (ES); Salazopyrine (BE, FR, LU, NL); Salazopyrine EC (BE); Salopyr (FI); Saridine-E (TH); Sulcolon (ID); Sulfasalazin (HR, PL); Ulcol (AU); Zopyrin (KP)

SulfiSOXAZOLE

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English English

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Medication Safety Issues

Sound-alike/look-alike issues:

SulfiSOXAZOLE may be confused with sulfaDIAZINE, sulfamethoxazole, sulfasalazine

Gantrisin® may be confused with Gastrosed™

Pronunciation(sul fi SOKS a zole)
U.S. Brand NamesGantrisin®
Canadian Brand NamesNovo-Soxazole; Sulfizole®
Pharmacologic Category[Antibiotic, Sulfonamide Derivative]
Use: Labeled IndicationsTreatment of urinary tract infections, otitis media, *Chlamydia*; nocardiosis
Dosing: Adults**Susceptible infections:** Oral: 2-4 g stat, 4-8 g/day in divided doses every 4-6 hours
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricNot for use in patients <2 months of age:

Children >2 months: Oral: Initial: 75 mg/kg, followed by 120-150 mg/kg/day in divided doses every 4-6 hours; not to exceed 6 g/day

Dosing: Renal Impairment

Cl_{cr} 10-50 mL/minutes: Administer every 8-12 hours.

Cl_{cr} <10 mL/minute: Administer every 12-24 hours.

Hemodialysis effects: >50% is removed by hemodialysis.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels.
Dietary ConsiderationsShould be taken with a glass of water on an empty stomach.
StorageProtect from light.
ContraindicationsHypersensitivity to sulfisoxazole, any sulfa drug, or any component of the formulation; porphyria; infants <2 months of age (sulfas compete with bilirubin for protein binding sites); patients with urinary obstruction; sunscreens containing PABA; pregnancy (at term)
Allergy Considerations

- Sulfonamide Antibiotic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Blood dyscrasias: Fatalities associated with severe reactions including agranulocytosis, aplastic anemia and other blood dyscrasias have occurred; discontinue use at first sign of rash.
- Dermatologic reactions: Fatalities associated with severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred; discontinue use at first sign of rash.
- Hepatic necrosis: Fatalities associated with hepatic necrosis have occurred; discontinue use at first sign of rash.
- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- G6PD deficiency: Use with caution in patients with G6PD deficiency; hemolysis may occur.
- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment; dosage modification required. Risk of crystalluria should be considered.

Geriatric ConsiderationsSulfisoxazole is an effective anti-infective agent. Most prescribers prefer the combination of sulfamethoxazole and trimethoprim for its dual mechanism of action. Trimethoprim penetrates the prostate. Adjust dose for renal function.
Pregnancy Risk FactorB/D (near term)
LactationEnters breast milk/compatible
Adverse ReactionsFrequency not defined.

Cardiovascular: Vasculitis

Central nervous system: Dizziness, fever, headache

Dermatologic: Itching, Lyell's syndrome, rash, photosensitivity, Stevens-Johnson syndrome

Endocrine & metabolic: Thyroid function disturbance

Gastrointestinal: Anorexia, diarrhea, nausea, vomiting

Genitourinary: Crystalluria, hematuria

Hematologic: Aplastic anemia, granulocytopenia, hemolytic anemia, leukopenia, thrombocytopenia

Hepatic: Hepatitis, jaundice

Renal: Interstitial nephritis

Miscellaneous: Serum sickness-like reactions

Metabolism/Transport Effects**Substrate** of CYP2C9 (major); **Inhibits** CYP2C9 (strong)
Drug Interactions

CycloSPORINE: Sulfonamide Derivatives may enhance the nephrotoxic effect of CycloSPORINE. Sulfonamide Derivatives may decrease the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Methotrexate: Sulfonamide Derivatives may enhance the adverse/toxic effect of Methotrexate. *Risk D: Consider therapy modification*

Phenytoin: Sulfonamide Derivatives may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Procaine: May diminish the therapeutic effect of Sulfonamide Derivatives. *Risk X: Avoid combination*

Sulfonylureas: Sulfonamide Derivatives may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Sulfonamide Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Interferes with folate absorption.

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization).

Test InteractionsFalse-positive protein in urine; false-positive urine glucose with Clinitest®
Monitoring ParametersCBC, urinalysis, renal function tests, temperature
Nursing: Physical Assessment/MonitoringAssess for allergy history prior to starting therapy (sulfa drugs). Assess potential for interactions with other pharmacological agents patient may be taking (eg, increased or decreased levels/effects of concurrently administered drugs). Assess effectiveness (reduced clinical symptoms) and adverse reactions (eg, photosensitivity, gastrointestinal disturbance [nausea, vomiting, anorexia], anemia, jaundice, hematuria). Caution patients with diabetes to monitor glucose levels closely (may cause altered response to oral hypoglycemics and may cause false-positive urine glucose with Clinitest®). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsCBC, urinalysis, renal function. Obtain specimen for culture prior to first dose.
Patient EducationTake as directed with a full glass of water, at regular intervals around-the-clock, on an empty stomach (1 hour before or 2 hours after a meal). Complete full course of therapy even if you are feeling better. Take a missed dose as soon as possible. If almost time for next dose, skip the missed dose and return to your regular schedule. Do not take a double dose. Maintain adequate hydration (2-3 L/day of fluids) to prevent kidney damage unless instructed to restrict fluid intake. If you have diabetes, this medication may cause increased effect of oral hypoglycemics - monitor glucose levels closely; may alter Clinitest® response; use of alternative method of glucose monitoring is preferable. May cause dizziness or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); photosensitivity (use sunblock, wear protective clothing and eyewear, and avoid direct sunlight); or nausea, vomiting, or loss of appetite (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report persistent nausea, vomiting, or

diarrhea; opportunistic infection (sore throat, fever, vaginal itching or discharge, unusual bruising or bleeding, fatigue); blood in urine or change in urinary pattern; swelling of face, lips, or tongue; tightness in chest; bad cough; or other persistent adverse effects. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Suspension, oral [pediatric]

Gantrisin®: 500 mg/5 mL (480 mL) [contains alcohol 0.3%; raspberry flavor]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Suspension (Gantrisin Pediatric)

500 mg/5 mL (200): $28.00

Mechanism of ActionInterferes with bacterial growth by inhibiting bacterial folic acid synthesis through competitive antagonism of PABA

Pharmacodynamics/Kinetics

Absorption: Sulfisoxazole acetyl is hydrolyzed in GI tract to sulfisoxazole which is readily absorbed

Distribution: Crosses placenta; enters breast milk

CSF:blood level ratio: Normal meninges: 50% to 80%; Inflamed meninges: 80+%

Protein binding: 85% to 88%

Metabolism: Hepatic via acetylation and glucuronide conjugation to inactive compounds

Half-life elimination: 4-7 hours; prolonged with renal impairment

Time to peak, serum: 2-3 hours

Excretion: Urine (95%, 40% to 60% as unchanged drug) within 24 hours

Related Information

- Antimicrobial Drugs of Choice
- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; sulfonamides reported to cause restlessness, irritability, depression, euphoria, disorientation, panic, hallucinations, and delusions

Mental Health: Effects on Psychiatric TreatmentPhotosensitivity is common; use caution with concurrent psychotropics; may cause leukopenia; caution with clozapine and carbamazepine

Index TermsSulfisoxazole Acetyl; Sulphafurazole

References

Boisvert A, Barbeau G, and Belanger PM, “Pharmacokinetics of Sulfisoxazole in Young and Elderly Subjects,” *Gerontology*, 1984, 30(2):125-31. [PubMed 6706125]

Kaplan SA, Weinfold RE, Abruzzo CW, et al, “Pharmacokinetic Profile of Sulfisoxazole Following IM, IV, and PO Administration to Man,” *J Pharm Sci*, 1972, 61:773. [PubMed 5035788]

Liston TE and Harbison R, “Sulfisoxazole Chemoprophylaxis for Frequent Otitis Media,” *Pediatrics*, 1983, 71:524-30. [PubMed 6601256]

Thoene DE and Johnson CE, “Pharmacotherapy of Otitis Media,” *Pharmacotherapy*, 1991, 11(3):212-21.[PubMed 1862012]

Sulfonated Phenolics and Sulfuric Acid

Lexi-Drugs Online

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Pronunciation

(SUL fo NATE ed fe NOL iks in AYE kwee us so LU shun)

U.S. Brand NamesDebacterol®
Pharmacologic CategoryAphthous Ulcer Treatment Agent
Use: DentalTherapeutic cauterization in the treatment of oral mucosal lesions (aphthous stomatitis, gingivitis, moderate to severe periodontitis)
ContraindicationsHypersensitivity to sulfur; for external use only
Warnings/Precautions

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Accidental ingestion: If ingested, do not induce vomiting; immediately dilute with milk or water and get medical help or contact a Poison Control Center.
- Appropriate use: For topical use only. Debacterol® is not intended for the treatment of cold sores and fever blisters. Prolonged use of Debacterol® on normal tissue should be avoided.
- Eye exposure: If eye exposure occurs, immediately remove contact lenses, irrigate eyes for at least 15 minutes with lukewarm water, and contact a physician.

Pregnancy Risk FactorC
Breast-Feeding ConsiderationsUnknown if excreted in breast milk; use with caution
Adverse ReactionsLocal: Irritation upon administration
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, topical:

Debacterol®: Sulfonated phenolics 50% and sulfuric acid 30% (1.5 mL) [for professional use only]

Swab, topical [for oral mucosa]:

Debacterol®: Sulfonated phenolics 50% and sulfuric acid 30% (0.2 mL) [for professional use only]

Generic AvailableNo
Mechanism of ActionSemiviscous, chemical cautery agent which provides controlled, focal debridement and sterilization of necrotic tissues; relieving pain, sealing damaged tissue, and providing local antiseptic action
Dental Health Professional ConsiderationsPrior to application/treatment, the ulcerated mucosal area should be thoroughly dried using the drying swab. After drying lesion, hold applicator "swab" with the colored ring end up. Bend the colored ring tip gently to the side until it snaps to release liquid inside. Liquid flows down into the white tip applicator. Apply the Debacterol® coated applicator tip to the dried ulcer area for at least 5 seconds, but no more than 10 seconds. Use rolling motion to completely cover the entire ulcer bed and ulcer rim. A "stinging" sensation is experienced immediately upon application. Debacterol® will not harm normal mucosa when used as directed. Thoroughly rinse out the mouth with water and spit out the rinse water. If the ulcer pain returns shortly after rinsing with water, it is an indication that some part of the ulcer was not covered. Repeat application one more time following directions above. One application per ulcer is usually sufficient. If excess irritation occurs during use, a rinse with sodium bicarbonate (baking soda) solution will neutralize the reaction (use 0.5 teaspoon in 120 mL water). It is not recommended that more than one Debacterol® treatment session be performed on an individual ulcer.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
References

Rhodus NL and Bereuter J, "An Evaluation of a Chemical Cautery Agent and an Anti-inflammatory Ointment for the Treatment of Recurrent Aphthous Stomatitis: A Pilot Study," *Quintessence Int*, 1998, 29(12):769-73.[PubMed 10196853]

Sulfur and Sulfacetamide

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English

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Pronunciation(SUL fur & sul fa SEE ta mide)

U.S. Brand NamesAVAR™ [DSC]; AVAR™-e; AVAR™-e Green [DSC]; Clarifoam™ EF; Clenia™; Plexion SCT®; Plexion TS® [DSC]; Plexion®; Prascion®; Prascion® AV [DSC]; Prascion® FC; Prascion® RA; Prascion® TS; Rosac®; Rosanil®; Rosula®; Rosula® Clarifying; Sulfacet-R®; Sulfatol®; Sulfatol®-M; Suphera™

Canadian Brand NamesSulfacet-R®

Pharmacologic CategoryAcne Products; Antibiotic, Sulfonamide Derivative; Antiseborrheic Agent, Topical; Topical Skin Product, Acne

Use: Labeled IndicationsAid in the treatment of acne vulgaris, acne rosacea, and seborrheic dermatitis

Dosing: Adults**Acne vulgaris, acne rosacea, seborrheic dermatitis:** Topical: Apply in a thin film 1-3 times/day. Cleansing products should be used 1-2 times/day.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentUse is contraindicated.

Administration: TopicalAvoid contact with eyes, lips, and mucous membranes.

Cleanser: Apply to wet skin and massage gently into skin working into full lather; rinse thoroughly and pat dry.

StorageStore at room temperature 15°C to 25C°C (59°F to 77°F); do not freeze. Avoid excessive heat.

Sulfacet-R®: Once mixed, use within 4 months.

ReconstitutionSulfacet-R®: Prior to dispensing, mix sulfacetamide into bottle containing sulfur. Shake well or stir with glass rod.

ContraindicationsHypersensitivity to sulfur, sulfonamides, or any component of the formulation; kidney disease

Allergy Considerations

- Sulfonamide Antibiotic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Blood dyscrasias: Severe reactions including agranulocytosis, aplastic anemia and other blood dyscrasias have occurred with sulfonamides (regardless of route).
- Dermatologic reactions: Severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred with sulfonamides (regardless of route).
- Hepatic necrosis: Fatalities associated with fulminant hepatic necrosis have occurred with sulfonamides (regardless of route).
- Hypersensitivity reactions: Rarely, systemic hypersensitivity reactions may occur; use caution if applying to denuded or abraded skin.
- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Dosage form specific issues:

- Sodium metabisulfite: Some products may contain sodium metabisulfite.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies with this combination have not been conducted.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not define, but are reported to be rare.

Central nervous system: Drug fever

Dermatologic: Contact dermatitis, dryness, erythema, exfoliative dermatitis, itching, Stevens-Johnson syndrome

Hematologic: Agranulocytosis, hemolytic anemia (acute), purpura hemorrhagica

Hepatic: Jaundice

Local: Irritation

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol, topical [foam]:

Clarifoam™ EF: Sulfur 5% and sulfacetamide sodium 10% (60 g)

Cleanser, topical:

AVAR™: Sulfur 5% and sulfacetamide sodium 10% (228 g)

Plexion®: Sulfur 5% and sulfacetamide sodium 10% (170 g, 340 g)

Prascion®: Sulfur 5% and sulfacetamide sodium 10% (170 g, 340 g)

Prascion® AV: Sulfur 5% and sulfacetamide sodium 10% (227 g) [DSC]

Rosanil®: Sulfur 5% and sulfacetamide sodium 10% (170 g, 390 g)

Rosula®: Sulfur 5% and sulfacetamide sodium 10% (355 mL) [contains urea 10%]

Cleanser, topoical [emulsion-based]:

Sulfatol®: Sulfur 5% and sulfacetamide sodium 10% (355 mL) [contains urea 10%]

Cream, topical:

AVAR™-e: Sulfur 5% and sulfacetamide sodium 10% (45 g) [contains benzyl alcohol]

AVAR™-e Green: Sulfur 5% and sulfacetamide sodium 10% (45 g) [contains benzyl alcohol; color corrective cream]

Clenia™: Sulfur 5% and sulfacetamide sodium 10% (28 g)

Plexion SCT®: Sulfur 5% and sulfacetamide sodium 10% (120 g) [contains benzyl alcohol]

Prascion® RA: Sulfur 5% and sulfacetamide sodium 10% (45 g) [contains benzyl alcohol and sunscreen]

Rosac®: Sulfur 5% and sulfacetamide sodium 10% (45 g) [contains benzyl alcohol and sunscreen]

Suphera™: Sulfur 5% and sulfacetamide sodium 10% (113 g)

Gel, topical:

AVAR™: Sulfur 5% and sulfacetamide sodium 10% (45 g) [contains benzyl alcohol]

Rosula®: Sulfur 5% and sulfacetamide sodium 10% (45 mL) [contains urea 10% and benzyl alcohol]

Gel, topical [emulsion-based]:

Sulfatol®: Sulfur 5% and sulfacetamide sodium 10% (45 mL) [contains urea 10%]

Lotion, topical: Sulfur 5% and sulfacetamide sodium 10% (25 g, 30 g, 45 g, 60 g)

Sulfacet-R®: Sulfur 5% and sulfacetamide sodium 10% (25 g) [contains sodium metabisulfite; tint formulation]

Sulfatol-M®: Sulfur 5% and sulfacetamide sodium 10% (25 g) [contains sodium metabisulfite; tint formulation]

Sulfatol-M®: Sulfur 5% and sulfacetamide sodium 10% (25 g) [contains sodium metabisulfite; tint-free formulation]

Pad, topical [cleansing cloth]:

Plexion®: Sulfur 5% and sulfacetamide sodium 10% (30s, 60s) [contains aloe vera]

Prascion® FC: Sulfur 5% and sulfacetamide sodium 10% (30s, 60s)

Suspension, topical: Sulfur 5% and sulfacetamide sodium 10% (30 g)

Plexion® TS: Sulfur 5% and sulfacetamide sodium 10% (30 g) [contains benzyl alcohol] [DSC]

Prascion® TS: Sulfur 5% and sulfacetamide sodium 10% (30 g)

Wash, topical: Sulfur 5% and sulfacetamide sodium 10% (170 g, 340 g)

Clenia™: Sulfur 5% and sulfacetamide sodium 10% (170 g, 340 g)

Rosac®: Sulfur 1% and sulfacetamide sodium 10% (170 g)

Wash, topical [emulsion-based]:

Rosula® Clarifying: Sulfur 4% and sulfacetamide sodium 10% (473 mL) [contains urea 10%]

Generic Available Yes: Lotion, wash

Pricing: U.S. (www.drugstore.com)

Cream (AVAR-e Emollient)

10-5% (45): $61.52

Cream (Clenia)

10-5% (28): $56.99

Cream (Plexion SCT)

10-5% (113.4): $113.54

Cream (Prascion RA)

10-5% (45): $65.99

Cream (Rosac)

10-5% (45): $111.16

Emulsion (Avar Cleanser)

10-5% (226.8): $122.20

Emulsion (Clenia Foaming Wash)

10-5% (170): $46.99

10-5% (340): $102.99

Emulsion (Plexion Cleanser)

10-5% (170.3): $104.63

10-5% (340.2): $189.80

Emulsion (Prascion)

10-5% (170.3): $42.44

10-5% (340.2): $54.98

Emulsion (Rosac Wash)

10-1% (170.1): $83.98

Emulsion (Rosula Clarifying Wash)

10-4% (473): $161.67

Emulsion (Rosula Cleanser)

10-5% (355): $166.35

Emulsion (Sulfacetamide Sod-Sulfur Wash)

10-5% (170.1): $39.99

Foam (Clarifoam EF)

10-5% (60): $104.52

Gel (Avar)

10-5% (45): $106.66

Gel (Rosula)

10-5% (45): $148.58

Gel (Sulfatol)

10-5% (45): $64.99

Kit (Rosanil)

10-5% (1): $110.98

Lotion (Sulfacetamide Sodium-Sulfur)

10-5% (25): $70.99

10-5% (30): $28.58

Misc (Plexion Cleansing Cloth)

10-5% (30): $158.13

Pads (Prascion FC)

10-5% (30): $79.99

10-5% (60): $179.99

Suspension (Plexion TS)

10-5% (30): $95.99

Suspension (Sulfacetamide Sodium-Sulfur)

10-5% (30): $47.63

Mechanism of ActionSulfacetamide, an antibacterial agent that competitively antagonizes para-aminobenzoic acid, a component essential for bacterial growth. Sulfur is a keratolytic. Used in combination to inhibit the growth of *P. acnes*.

Pharmacodynamics/KineticsAbsorption: Sulfur, topical: ~1%

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsSodium Sulfacetamide and Sulfur; Sulfacetamide and Sulfur; Sulfur and Sulfacetamide Sodium

International Brand NamesSulfacet-R (CA)

Sulindac

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Clinoril® may be confused with Cleocin®, Clozaril®, Oruvail®

Pronunciation(SUL in dak)

U.S. Brand NamesClinoril®

Canadian Brand NamesApo-Sulin®; Novo-Sundac; Nu-Sundac

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsManagement of inflammatory diseases including osteoarthritis, rheumatoid arthritis, acute gouty arthritis, ankylosing spondylitis, acute painful shoulder (bursitis/tendonitis)

Dosing: Adults**Note:** Maximum daily dose: 400 mg

Osteoarthritis, rheumatoid arthritis, ankylosing spondylitis: 150 mg twice daily

Acute painful shoulder (bursitis/tendonitis): 200 mg twice daily; usual treatment: 7-14 days

Acute gouty arthritis: 200 mg twice daily; usual treatment: 7 days

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDose not established

Dosing: Renal ImpairmentNot recommended with advanced renal impairment; if required, decrease dose and monitor closely.

Dosing: Hepatic ImpairmentDose reduction is necessary; discontinue if abnormal liver function tests occur.

Administration: OralShould be administered with food or milk.

Dietary ConsiderationsDrug may cause GI upset, bleeding, ulceration, perforation; take with food or milk to minimize GI upset.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).

Extemporaneously PreparedA suspension of sulindac can be prepared by triturating 1000 mg sulindac (5 x 200 mg tablets) with 50 mg of kelco and 400 mg of Veegum® until a powder mixture is formed; then add 30 mL of sorbitol 35% (prepared from 70% sorbitol) to form a slurry; finally add a sufficient quantity of 35% sorbitol to make a final volume of 100 mL; the final suspension is 10 mg/mL and is stable for 7 days

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity or allergic-type reactions to sulindac, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy
- Sulindac Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Coronary artery bypass graft surgery: See “Disease-related concerns” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure to NSAIDs, anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Aseptic meningitis: May increase the risk of aseptic meningitis, especially in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including**

MI, stroke, and new onset or worsening of pre-existing hypertension. Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin's cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.

- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Pancreatitis: Has been reported; discontinue with suspected pancreatitis.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur. May require dosage adjustment in hepatic dysfunction; sulfide and sulfone metabolites may accumulate.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis. Use caution in patients with renal lithiasis; sulindac metabolites have been reported as components of renal stones; use hydration in patients with a history of renal stones.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of the elderly who develop GI complications can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high-dose situations, but the elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorC/D (3rd trimester)

Pregnancy ConsiderationsAnimal studies have not documented teratogenic effects. However, known effects of NSAIDs suggest the potential for premature ductus arteriosus closure, particularly in late pregnancy.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

1% to 10%:

Cardiovascular: Edema (1% to 3%)

Central nervous system: Dizziness (3% to 9%), headache (3% to 9%), nervousness (1% to 3%)

Dermatologic: Rash (3% to 9%), pruritus (1% to 3%)

Gastrointestinal: GI pain (10%), constipation (3% to 9%), diarrhea (3% to 9%), dyspepsia (3% to 9%), nausea (3% to 9%), abdominal cramps (1% to 3%), anorexia (1% to 3%), flatulence (1% to 3%), vomiting (1% to 3%)

Otic: Tinnitus (1% to 3%)

<1% (Limited to important or life-threatening): Agranulocytosis, ageusia, alopecia, anaphylaxis, angioneurotic edema, aplastic anemia, arrhythmia, aseptic meningitis, bitter taste, blurred vision, bone marrow depression, bronchial spasm, bruising, CHF, cholestasis, colitis, conjunctivitis, crystalluria, depression, dry mucous membranes, dyspnea, dysuria, epistaxis, erythema multiforme, exfoliative dermatitis, fever, gastritis, GI bleeding, GI perforation, glossitis, gynecomastia, hearing decreased, hematuria, hemolytic anemia, hepatitis, hepatic failure, hyperglycemia, hyperkalemia, hypersensitivity reaction, hypersensitivity syndrome (includes chills, diaphoresis, fever, flushing), hypersensitivity vasculitis, hypertension, insomnia, intestinal stricture, interstitial nephritis, jaundice, leukopenia, liver function abnormal, metallic taste, necrotizing fascitis, nephrotic syndrome, neuritis, neutropenia, palpitation, pancreatitis, paresthesia, peptic ulcer, photosensitivity, proteinuria, psychosis, purpura, renal calculi, renal failure, renal impairment, retinal disturbances, seizure,

somnolence, Stevens-Johnson syndrome, stomatitis, syncope, thrombocytopenia, toxic epidermal necrolysis, urine discoloration, vaginal bleeding, vertigo, visual disturbance, weakness

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dimethyl Sulfoxide: May decrease the metabolism of Sulindac. Specifically, the concentrations of the active sulfide metabolite are decreased. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Test InteractionsIncreased chloride (S), increased sodium (S), increased bleeding time

Monitoring ParametersLiver enzymes, BUN, serum creatinine, CBC, blood pressure; signs and symptoms of GI bleeding; ophthalmic exam (if ocular complaints develop during treatment)

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess effectiveness and interactions of other medications patient may be taking. Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests, therapeutic effectiveness according to purpose for therapy, and adverse reactions (eg, GI bleeding, hepatotoxicity, ototoxicity) at beginning of therapy and periodically throughout therapy. Schedule ophthalmic evaluations for patients who are taking NSAIDs for long periods of time. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsLiver enzymes, BUN, serum creatinine, CBC, platelets

Patient EducationTake this medication exactly as directed; do not increase dose without consulting prescriber. Take with food or milk to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol, aspirin or aspirin-containing medication, or any other anti-inflammatory medications without consulting prescriber. Regularly scheduled ophthalmic exams are advised with long-term use of NSAIDs. You may experience dizziness, nervousness, or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or constipation (increased exercise, fluids, fruit, or fiber may help). GI bleeding, ulceration, or perforation can occur with or without pain; discontinue medication and contact prescriber if persistent abdominal pain, cramping, or blood in stool occurs. Report breathlessness or respiratory difficulty; chest pain; unusual bruising or bleeding; blood in urine, stool, mouth, or vomitus; unusual fatigue; skin rash or itching; change in urinary pattern; or change in hearing or ringing in ears. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 150 mg, 200 mg

Clinoril®: 200 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Clinoril)

200 mg (60): $84.98

Tablets (Sulindac)

150 mg (60): $18.99

200 mg (100): $33.91

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Absorption: 90%

Protein binding: Sulindac, sulfone, and sulfide metabolites: 93% to 98% primarily to albumin

Distribution: Crosses blood-brain barrier (brain concentrations <4% of plasma concentrations) and placental barriers

Metabolism: Hepatic; prodrug metabolized to sulfide metabolite (active) for therapeutic effects and to sulfone metabolites (inactive); parent and inactive sulfone metabolite undergo extensive enterohepatic recirculation

Half-life elimination: Parent drug: ~8 hours; Active metabolite: ~16 hours

Excretion: Urine (~50%, primarily as inactive metabolites, <1% as active metabolite); feces (~25%, primarily as metabolites)

Related Information

- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentNSAID formulations are known to reversibly decrease platelet aggregation via mechanisms different than observed with aspirin. The dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness; may rarely cause drowsiness, confusion, insomnia, hallucinations, or depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance (evidence suggest that this effect may be less than with other NSAIDs) resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A recent meta-analysis (see References) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be conducted and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 chronic heart failure guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin's inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

Sulindac is associated with the highest incidence of upper GI bleeds among NSAIDs. It may be less likely to inhibit renal prostaglandin synthesis and adversely affect renal function than most other NSAIDs. Maximum therapeutic response may not be realized for up to 3 weeks.

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International Brand NamesAclin (AU, HK); Adco-Sulindac (ZA); Algocetil (IT); Antribid (PT); Arthrocine (FR); Brurem (MX); Cenlidac (TH); Clinoril (AE, AT, BE, BF, BH, BJ, CH, CI, CY, EG, ET, GB, GH, GM, GN, HN, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, OM, PL, QA, SA, SC, SD, SE, SL, SN, SY, TH, TN, TZ, UG, VE, YE, ZA, ZM, ZW); Clison (MX); Daclin (NZ); Dometon (TW); Imbaron (KP); Renidac (MX); Saldac (NZ); Sudaclin (PL); Sulindal (ES); Sulindec (TW); Suloril (TW); Vindacin (MX); Weisu (TW)

Sumatriptan and Naproxen

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Naproxen may be confused with Natacyn®, Nebcin®, neomycin, niacin

SUMAtriptan may be confused with somatropin, zolmitriptan

Treximet™ may be confused with Trexall™

Pronunciation(soo ma TRIP tan & na PROKS en)

U.S. Brand NamesTreximet™

Pharmacologic CategoryAntimigraine Agent; Nonsteroidal Anti-inflammatory Drug (NSAID), Oral; Serotonin 5-HT$_{1B, 1D}$ Receptor Agonist

Use: Labeled IndicationsAcute treatment of migraine with or without aura

Dosing: Adults**Migraine:** Oral: 1 tablet (sumatriptan 85 mg and naproxen 500 mg). If a satisfactory response has not been obtained at 2 hours, a second dose may be administered (maximum: 2 tablets/24 hours). **Note:** The safety of treating an average of >5 migraine headaches in a 30-day period has not been established.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl$_{cr}$ ≥30 mL/minute Dosage adjustment not necessary.

Cl$_{cr}$ <30 mL/minute: Use not recommended.

Dosing: Hepatic ImpairmentMild-to-severe impairment: Use is contraindicated by the manufacturer.

Administration: OralMay be administered with or without food. Swallow tablet whole; tablet should not be divided, crushed, or chewed.

Dietary ConsiderationsMay be taken with or without food. Tablet contains sodium 61.2 mg (2.7 mEq/naproxen sodium 500 mg)

StorageStore at controlled room temperature of 25°C (77°F).

Restrictions

An FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to sumatriptan, naproxen, aspirin, other NSAIDs, or any component of the formulation; patients with a history of ischemic heart disease or signs or symptoms of ischemic heart disease (including Prinzmetal's angina, angina pectoris, myocardial infarction, silent myocardial ischemia); patients with a history of or signs/symptoms of cerebrovascular syndromes (including strokes, transient ischemic attacks); patients with a history of or signs/symptoms of peripheral vascular syndromes (including ischemic bowel disease); patients who have had coronary artery bypass (CABG) surgery; uncontrolled hypertension; use within 24 hours of ergotamine derivatives; use within 24 hours of another 5-HT$_1$ agonist; concurrent administration or within 2 weeks of discontinuing an MAO inhibitor, specifically MAO type A inhibitors; management of hemiplegic or basilar migraine; prophylactic treatment of migraine; hepatic impairment

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See “Concerns related to adverse effects” below.
- Gastrointestinal events: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: Associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Should not be given to patients with documented CAD, history of CABG (contraindicated), or who have risk factors for CAD (eg, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, menopause, male >40 years of age) without adequate cardiac evaluation. Patients with suspected CAD should have cardiovascular evaluation to rule out CAD before considering use; if cardiovascular evaluation “is satisfactory,” first dose should be given in the healthcare provider's office.

Periodic evaluation of cardiovascular status should be done in all patients. Coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia/fibrillation, cardiac arrest, and death have been reported with 5-HT_1 agonist administration. Patients who experience sensations of chest pain/pressure/tightness or symptoms suggestive of angina following dosing should be evaluated for coronary artery disease or Prinzmetal's angina before receiving additional doses.

- Cerebrovascular events: Cerebral/subarachnoid hemorrhage and stroke have been reported with 5-HT_1 agonist administration.

- Elevated blood pressure: Significant elevation in blood pressure, including hypertensive crisis, has also been reported on rare occasions in patients with and without a history of hypertension; contraindicated in patients with uncontrolled hypertension.

- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.

- Hepatic impairment: Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; use is contraindicated in patients with existing hepatic impairment. Closely monitor patients with any abnormal LFT; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

- Vasospasm-related events: Peripheral vascular ischemia and colonic ischemia have been reported with 5-HT_1 agonist.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Heart failure/edema: Use with caution in patients with heart failure or fluid retention; edema has occurred in patients receiving NSAIDs.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease (Cl_{cr} <30 mL/minute). Long-term NSAID use may result in renal papillary necrosis.

- Seizure disorders: Use with caution in patients with history of seizure disorder or in patients with a lowered seizure threshold; seizures have been reported in patients receiving sumatriptan.

Concurrent drug therapy issues:

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce sumatriptan's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Only indicated for treatment of acute migraine; if a patient does not respond to the first dose, the diagnosis of migraine should be reconsidered.

Geriatric ConsiderationsSee individual agents.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events were observed in animal studies. There are no well-controlled studies in pregnant women. Women exposed to this combination during pregnant are encouraged to contact the Treximet™ Pregnancy Registry (800-336-2176). Also refer to individual agents.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsSumatriptan and naproxen are excreted in breast milk. Breast-feeding is not recommended. Also refer to individual agents.

Adverse Reactions

>1% to 10%:

Cardiovascular: Chest pain/discomfort (3%), palpitations (>1%)

Central nervous system: Dizziness (4%), somnolence (3%), fatigue (≥1%)

Gastrointestinal: Nausea (3%), dyspepsia (2%), xerostomia (2%), abdominal pain (≥1%)

Neuromuscular & skeletal: Neck, throat, and jaw pain/tightness/pressure (3%), paresthesia (2%), weakness (≥1%), muscle tightness (>1%)

Miscellaneous: Feeling hot (>1%)

≤1%: Abdominal distention, acute coronary syndrome, ambulation difficulties, anemia, anxiety, aphasia, arthralgia, asthma, attention disturbances, back pain, biliary colic, bruising, burning, cardiac flutter, cataract, CHF, colitis, conjunctival hemorrhage, conjunctivitis, constipation, cough, depression, diabetes mellitus, diarrhea, disorientation, diverticulitis, dysgeusia, dysphagia, dyspnea, ear pain, epistaxis, facial edema, facial palsy, fever, flatulence, flushing, gastric ulcer, gastritis, gastroesophageal reflux, goiter, heaviness sensation, hyperhidrosis, hypertension, hypoglycemia, hypothyroidism, infection (various), insomnia, irritability, irritable bowel syndrome, jittery, lethargy, leukopenia, lymphadenopathy, malaise, mental impairment, motion sickness, myalgia, nephrolithiasis, nervousness, oral mucosal blistering, oropharyngeal edema, panic attacks, peripheral coldness, peripheral edema, pleurisy, pruritus, psychomotor impairment, rash, renal insufficiency, right ventricular failure, sedation, systemic lupus erythematosus, tachycardia, temperature intolerance, thirst, tinnitus, tongue edema, tremor, urticaria, ventricular extrasystoles, vertigo, viral myocarditis, visual disturbance, vomiting

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: May enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

MAO Inhibitors: May decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. *Risk X: Avoid combination*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Test InteractionsNaproxen may interfere with 5-HIAA urinary assays; due to an interaction with m-dinitrobenzene, naproxen should be discontinued 72 hours before adrenal function testing if the Porter-Silber test is used.

Monitoring ParametersOccult blood loss; periodic liver function test, CBC, BUN, serum creatinine; urine output; blood pressure; periodic cardiovascular evaluation (long-term use)

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsOccult blood loss; periodic liver function test, CBC, BUN, serum creatinine

Patient EducationSee individual agents. **Pregnancy/breast-feeding:** Inform prescriber if you are pregnant or intend to become pregnant or breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Treximet™ 85/500: Sumatriptan 85 mg and naproxen sodium 500 mg [contains sodium 61.2 mg/tablet (~2.7 mEq/tablet)]

Generic AvailableNo

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Tablets (Treximet)

85-500 mg (9): $199.98

Mechanism of Action

Sumatriptan: Selective agonist for serotonin (5-HT$_{1B}$, 5-HT$_{1D}$ receptors) in cranial arteries to cause vasoconstriction and reduces sterile inflammation associated with antidromic neuronal transmission correlating with relief of migraine

Naproxen: Reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentSee individual agents.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness. May rarely cause drowsiness, confusion, insomnia, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentContraindicated with other serotonin agonists (SSRIs/SNRIs) and MAO inhibitors. Naproxen may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels. SSRIs may enhance the antiplatelet effects of naproxen.

Index TermsNaproxen and Sumatriptan; Naproxen Sodium and Sumatriptan; Naproxen Sodium and Sumatriptan Succinate; Sumatriptan Succinate and Naproxen; Sumatriptan Succinate and Naproxen Sodium

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SUMAtriptan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

SUMAtriptan may be confused with sitaGLIPtin, somatropin, zolmitriptan

International issues:

Imitrex® may be confused with Nitrex® which is a brand name for isosorbide mononitrate in Italy

Pronunciation(soo ma TRIP tan)

U.S. Brand NamesImitrex®

Canadian Brand NamesApo-Sumatriptan®; CO Sumatriptan; Dom-Sumatriptan; Gen-Sumatriptan; Imitrex®; Imitrex® DF; Imitrex® Nasal Spray; Novo-Sumatriptan; PHL-Sumatriptan; PMS-Sumatriptan; ratio-Sumatriptan; Rhoxal-sumatriptan; Riva-Sumatriptan; Sandoz-Sumatriptan; Sumatryx

Pharmacologic CategoryAntimigraine Agent; Serotonin 5-HT$_{1B, 1D}$ Receptor Agonist

Use: Labeled Indications

Oral, SubQ: Acute treatment of migraine with or without aura

SubQ: Acute treatment of cluster headache episodes

Dosing: Adults

Migraine:

Oral: A single dose of 25 mg, 50 mg, or 100 mg (taken with fluids). If a satisfactory response has not been obtained at 2 hours, a second dose may be administered. Results from clinical trials show that initial doses of 50 mg and 100 mg are more effective than doses of 25 mg, and that 100 mg doses do not provide a greater effect than 50 mg and may have increased incidence of side effects. Although doses of up to 300 mg/day have been studied, the total daily dose should not exceed 200 mg. The safety of treating an average of >4 headaches in a 30-day period have not been established.

Intranasal: Single dose of 5, 10, or 20 mg administered in one nostril; a 10 mg dose may be achieved by administration of a single 5 mg dose in each nostril; if headache returns, the dose may be repeated once after 2 hours, not to exceed a total daily dose of 40 mg. The safety of treating an average of >4 headaches in a 30-day period has not been established.

SubQ: Up to 6 mg; if side effects are dose-limiting, lower doses may be used. A second injection may be administered at least 1 hour after the initial dose, but not more than 2 injections in a 24-hour period.

Cluster headache: Refer to dosing under "Migraine, SubQ"

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentDosage adjustment is not necessary.

Dosing: Hepatic ImpairmentBioavailability of oral sumatriptan is increased with liver disease. If treatment is needed, do not exceed single doses of 50 mg. The nasal spray has not been studied in patients with hepatic impairment, however, because the spray does not undergo first-pass metabolism, levels would not be expected to alter. Use of all dosage forms is contraindicated with severe hepatic impairment.

Administration: I.V.Do **not** administer I.V.; may cause coronary vasospasm.

Administration: OralOral: Should be taken with fluids as soon as symptoms appear.

Administration: OtherAdminister injection formulation subcutaneously. An autoinjection device (STATdose System®) is available for use with the 4 mg and 6 mg cartridges.

StorageStore at 2°C to 20°C (36°F to 86°F). Protect from light.

ContraindicationsHypersensitivity to sumatriptan or any component of the formulation; patients with ischemic heart disease or signs or symptoms of ischemic heart disease (including Prinzmetal's angina, angina pectoris, myocardial infarction, silent myocardial ischemia); cerebrovascular syndromes (including strokes, transient ischemic attacks); peripheral vascular syndromes (including ischemic bowel disease); uncontrolled hypertension; use within 24 hours of ergotamine derivatives; use within 24 hours of another 5-HT$_1$ agonist; concurrent administration or within 2 weeks of discontinuing an MAO inhibitor, specifically MAO type A inhibitors; management of hemiplegic or basilar migraine; prophylactic treatment of migraine; severe hepatic impairment; not for I.V. administration

Allergy Considerations

- Serotonin 5-HT$_{1B,1D}$ Receptor Agonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac events: Coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia/fibrillation, cardiac arrest, and death have been reported with 5-HT$_1$ agonist administration. Patients who experience sensations of chest pain/pressure/tightness or symptoms suggestive of angina following dosing should be evaluated for coronary artery disease or Prinzmetal's angina before receiving additional doses.

- Cerebrovascular events: Cerebral/subarachnoid hemorrhage and stroke have been reported with 5-HT$_1$ agonist administration.

- Elevated blood pressure: Significant elevation in blood pressure, including hypertensive crisis, has also been reported on rare occasions in patients with and without a history of hypertension.

- Vasospasm-related events: Peripheral vascular ischemia and colonic ischemia have been reported with 5-HT$_1$ agonist.

Disease-related concerns:

- Coronary artery disease: Should not be given to patients who have risk factors for CAD (eg, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, menopause, male >40 years of age) without adequate cardiac evaluation. Patients with suspected CAD should have cardiovascular evaluation to rule out CAD before considering use; if cardiovascular evaluation "is satisfactory", first dose should be given in the healthcare provider's office. Periodic evaluation of cardiovascular status should be done in all patients.

- Hepatic impairment: Use with caution in patients with hepatic impairment. Drug clearance may be reduced leading to increased plasma concentrations; dosage reduction of the oral product is recommended.

- Seizure disorders: Use with caution in patients with history of seizure disorder or in patients with a lowered seizure threshold.

Concurrent drug therapy issues:

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce sumatriptan's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

Other warnings/precautions:

- Appropriate use: Only indicated for the treatment of migraine or cluster headache.

Geriatric ConsiderationsUse cautiously in the elderly, particularly since many elderly have cardiovascular disease which would put them at risk for cardiovascular adverse effects. Safety and efficacy in the elderly (>65 years) have not been established. Pharmacokinetic disposition is, however, similar to that in young adults.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies using sumatriptan in pregnant women. Use only if potential benefit to the mother outweighs the potential risk to the fetus. A pregnancy registry has been established to monitor outcomes of women exposed to sumatriptan during pregnancy (800-336-2176). Preliminary data from the registry do not suggest a greater risk of birth defects than the general population and so far a specific pattern of malformations has not been identified. However, sample sizes are small and studies are ongoing. In some (but not all) animal studies, administration was associated with embryolethality, fetal malformations and pup mortality.

LactationEnters breast milk/use caution (AAP rates "compatible")

Breast-Feeding ConsiderationsThe amount of sumatriptan an infant would be exposed to following breast-feeding is considered to be small (although the mean milk-to-plasma ratio is ~4.9, weight adjusted doses estimates suggest breast-fed infants receive 3.5% of a maternal dose). Expressing and discarding the milk for 8-12 hours after a single dose is suggested to reduce the amount present even further. The half-life of sumatriptan in breast milk is 2.22 hours.

Adverse Reactions

Injection:

>10%:

Central nervous system: Dizziness (12%), warm/hot sensation (11%)

Local: Pain at injection site (59%)

Neuromuscular & skeletal: Paresthesia (14%)

1% to 10%:

Cardiovascular: Chest pain/tightness/heaviness/pressure (2% to 3%), hyper-/hypotension (1%)

Central nervous system: Burning (7%), feeling of heaviness (7%), flushing (7%), pressure sensation (7%), feeling of tightness (5%), drowsiness (3%), malaise/fatigue (1%), feeling strange (2%), headache (2%), tight feeling in head (2%), cold sensation (1%), anxiety (1%)

Gastrointestinal: Abdominal discomfort (1%), dysphagia (1%)

Neuromuscular & skeletal: Neck, throat, and jaw pain/tightness/pressure (2% to 5%), mouth/tongue discomfort (5%), weakness (5%), myalgia (2%); muscle cramps (1%), numbness (5%)

Ocular: Vision alterations (1%)

Respiratory: Throat discomfort (3%), nasal disorder/discomfort (2%)

Miscellaneous: Diaphoresis (2%)

Nasal spray:

>10%: Gastrointestinal: Bad taste (13% to 24%), nausea (11% to 13%), vomiting (11% to 13%)

1% to 10%:

Central nervous system: Dizziness (1% to 2%)

Respiratory: Nasal disorder/discomfort (2% to 4%), throat discomfort (1% to 2%)

Tablet:

1% to 10%:

Cardiovascular: Chest pain/tightness/heaviness/pressure (1% to 2%), hyper-/hypotension (1%), palpitation (1%), syncope (1%)

Central nervous system: Burning (1%), dizziness (>1%), drowsiness (>1%), malaise/fatigue (2% to 3%), headache (>1%), nonspecified pain (1% to 2%, placebo 1%), vertigo (<1% to 2%), migraine (>1%), sleepiness (>1%)

Gastrointestinal: Diarrhea (1%), nausea (>1%), vomiting (>1%), hyposalivation (>1%)

Genitourinary: Hematuria (1%)

Hematologic: Hemolytic anemia (1%)

Neuromuscular & skeletal: Neck, throat, and jaw pain/tightness/pressure (2% to 3%), paresthesia (3% to 5%), myalgia (1%), numbness (1%)

Otic: Ear hemorrhage (1%), hearing loss (1%), sensitivity to noise (1%), tinnitus (1%)

Respiratory: Allergic rhinitis (1%), dyspnea (1%), nasal inflammation (1%), nose/throat hemorrhage (1%), sinusitis (1%), upper respiratory inflammation (1%)

Miscellaneous: Hypersensitivity reactions (1%), nonspecified pressure/tightness/heaviness (1% to 3%, placebo 2%); warm/cold sensation (2% to 3%, placebo 2%)

Route unspecified: <1%: Postmarketing and uncontrolled studies (limited to important or life-threatening): Abdominal aortic aneurysm, abdominal discomfort, abnormal menstrual cycle, abnormal/elevated liver function tests, accommodation disorders, acute renal failure, agitation, anaphylactoid reaction, anaphylaxis, anemia, angioneurotic edema, arrhythmia, atrial fibrillation, bronchospasm, cerebral ischemia, cerebrovascular accident, convulsions, deafness, death, decreased appetite, dental pain, diarrhea, dyspeptic symptoms, dysphagia, dystonic reaction, ECG changes, fluid disturbances (including retention), flushing, gastrointestinal pain, hallucinations, heart block, hematuria, hemolytic anemia, hiccups, hypersensitivity reactions, intestinal obstruction, intracranial pressure increased, ischemic colitis, joint ache, muscle stiffness, nose/throat hemorrhage, numbness of tongue, optic neuropathy (ischemic), pancytopenia, paresthesia, phlebitis, photosensitivity, Prinzmetal's angina, pruritus, psychomotor disorders, pulmonary embolism, rash, Raynaud syndrome, sensation changes, shock, subarachnoid hemorrhage, swallowing disorders, syncope, thrombocytopenia, thrombophlebitis, thrombosis, transient myocardial ischemia, TSH increased, vasculitis, vision loss, xerostomia

Drug Interactions

Ergot Derivatives: May enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

MAO Inhibitors: May decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Nursing: Physical Assessment/MonitoringFor use only with a clear diagnosis of migraine or cluster headaches. Use caution with CAD or history of seizure disorder. Assess potential for interactions with other pharmacological agents patient may be taking (eg, ergot-containing drugs, MAO inhibitors, SSRIs). See Administration for specifics of SubQ, intranasal, oral formulation use. Assess therapeutic effectiveness (relief of headaches) and adverse response (eg, dizziness, tingling, drowsiness, myalgia, vision alternation, nausea, vomiting; reactions differ according to formulation). Teach patient proper use according to formulation (eg, with SubQ, appropriate injection technique and syringe/needle disposal), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationTake at first sign of migraine attack. This drug is to be used to reduce your migraine, not to prevent or reduce the number of attacks. Follow exact instructions for use.

Nasal spray: Administer dose into one nostril. If headache returns or is not fully resolved after the first dose, the dose may be repeated after 2 hours. **Do not exceed 40 mg in 24 hours.**

Oral: If headache returns or is not fully resolved after first dose, the dose may be repeated after 2 hours. **Do not exceed 200 mg in 24 hours.** Take whole with fluids.

SubQ: If headache returns or is not fully resolved after first dose, the dose may be repeated after 1 hour. **Do not exceed two injections in 24 hours.**

All forms: Do not take any form of this drug within 24 hours of any other migraine medication without consulting prescriber. May cause dizziness, fatigue, or drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known); or nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking on lozenges may help). Report chest tightness or pain; excessive drowsiness; acute abdominal pain; skin rash or burning sensation; muscle weakness, soreness, or numbness; respiratory difficulty; or any other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. **Note:** Strength expressed as sumatriptan base

Injection, solution, as succinate: 8 mg/mL (0.5 mL); 12 mg/mL (0.5 mL)

Imitrex®: 8 mg/mL (0.5 mL); 12 mg/mL (0.5 mL)

Solution, intranasal [spray]: 5 mg/0.1 mL (6s); 20 mg/0.1 mL (6s)

Imitrex®: 5 mg/0.1 mL (6s); 20 mg/0.1 mL (6s)

Tablet, as succinate: 25 mg, 50 mg, 100 mg

Imitrex®: 25 mg, 50 mg, 100 mg

Generic AvailableYes

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Kit (Imitrex STATdose Refill)

6 mg/0.5 mL (1): $196.98

Kit (Imitrex STATdose System)

6 mg/0.5 mL (1): $196.97

Solution (Imitrex)

5 mg/ACT (1): $50.33

6 mg/0.5 mL (2.5): $448.66

20 mg/ACT (6): $236.38

Tablets (Imitrex)

25 mg (9): $247.31

50 mg (9): $229.78

100 mg (9): $215.98

Mechanism of ActionSelective agonist for serotonin (5-HT$_{1D}$ receptor) in cranial arteries to cause vasoconstriction and reduces sterile inflammation associated with antidromic neuronal transmission correlating with relief of migraine

Pharmacodynamics/Kinetics

Onset of action: ~30 minutes

Distribution: V$_d$: 2.4 L/kg

Protein binding: 14% to 21%

Metabolism: Hepatic, primarily via MAO-A isoenzyme

Bioavailability: SubQ: 97% ± 16% of that following I.V. injection; Oral: 15%

Half-life elimination: Injection, tablet: 2.5 hours; Nasal spray: 2 hours

Time to peak, serum: 5-20 minutes

Excretion:

Injection: Urine (38% as indole acetic acid metabolite, 22% as unchanged drug)

Nasal spray: Urine (42% as indole acetic acid metabolite, 3% as unchanged drug)

Tablet: Urine (60% as indole acetic acid metabolite, 3% as unchanged drug); feces (40%)

Related Information

- Antimigraine Drugs: 5-HT1 Receptor Agonists

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Bad taste, dysphagia, hyposalivation (tablet), mouth/tongue discomfort (injection).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause drowsiness

Mental Health: Effects on Psychiatric TreatmentContraindicated with other serotonin agonists (SSRIs) and MAO inhibitors

Cardiovascular ConsiderationsCoronary vasospasm has been associated with 5-HT$_{1B/1D}$ agonists. These agents are contraindicated in patients with documented ischemic of vasospastic coronary artery disease. Patients with risk factors for CAD may receive these agents, provided a cardiovascular evaluation yields satisfactory evidence that the patient is free of cardiovascular disease. In patients with risk factors for CAD, administration of the initial dose in a medically staffed/equipped facility (ie, physician's office) is recommended. In addition, ECG monitoring after the initial dose should be considered. Patients who acquire risk factors for CAD, or long-term users of agents from this class of medications, should undergo periodic cardiovascular evaluation.

Anesthesia and Critical Care Concerns/Other ConsiderationsSumatriptan should not be used in patients with a history of vasospastic disease, Prinzmetal's angina, or any critical vascular disease.

Index TermsSumatriptan Succinate

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International Brand NamesFermig (MX); Imigran (AT, AU, BB, BG, BM, BR, BS, BZ, CH, CN, CO, CY, CZ, DE, DK, EE, ES, FI, GB, GR, GY, HK, HN, HR, HU, IE, IT, JM, KP, MX, MY, NL, NO, PE, PH, PL, PT, PY, SE, SR, TH, TT, UY, VE); Imigran Radis (GB, IE); Imiject (FR); Imitrex (AR, BE, IL, LU); Iptam (AU); Migragesin (CO); Migrastat (IE); Nograine (MX); Sumagran (NZ); Sumamigren (PL); Sumatridex (IL); Sumigran (PH); Sumitrex (IN); Suvalan (AU); Tebegran (MX); Triptagic (ID)

Sunitinib

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Special Alerts

Sunitinib: Reports of Microangiopathic Hemolytic Anemia (MAHA) in Association With Concomitant Bevacizumab Therapy - July 2008

Genentech Inc (in conjunction with the U.S. Food and Drug Administration [FDA]) and Hoffmann-La Roche Limited (in conjunction with Health Canada) have issued warnings to their respective healthcare professionals regarding the risk for MAHA in association with the concomitant use of bevacizumab (Avastin®) and sunitinib (Sutent®). Upcoming changes to the Canadian labeling for bevacizumab are based on observations made in 2 recent investigational U.S. studies involving combination therapy with a fixed dose of bevacizumab (10 mg/kg every 2 weeks) and variable doses of sunitinib (25 mg, 37.5 mg, or 50 mg/day) in patients with metastatic renal cell carcinoma (mRCC).

Although not reported in patients receiving bevacizumab with sunitinib at lower doses, laboratory findings (schistocytes on microscopy, LDH increased, serum haptoglobin decreased) consistent with MAHA were observed in 37% (n=19) of patients receiving bevacizumab and sunitinib 50 mg/day. Symptoms of MAHA include darkened urine, jaundice, confusion, fever, and splenomegaly or hepatomegaly. Grades 3 or 4 hypertension and reversible posterior leukoencephalopathy syndrome (RPLS), were observed in some patients who developed MAHA. Resolution of these adverse findings was observed within 3 weeks of discontinuing both bevacizumab and sunitinib. In the U.S. and in Canada bevacizumab is **not** approved for use in combination with sunitinib or in the treatment of mRCC.

Further information may be found at:

U.S.: http://www.fda.gov/medwatch/safety/2008/safety08.htm#Avastin

Canada:

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/avastin_nth-aah-eng.ph

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2008/avastin_pc-cp-eng.php

Medication Safety Issues

Sound-alike/look-alike issues:

Sunitinib may be confused with sorafenib

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(su NIT e nib)

U.S. Brand NamesSutent®

Canadian Brand NamesSutent®

Pharmacologic CategoryAntineoplastic Agent, Tyrosine Kinase Inhibitor; Vascular Endothelial Growth Factor (VEGF) Inhibitor

Use: Labeled IndicationsTreatment of gastrointestinal stromal tumor (GIST) intolerance to or disease progression on imatinib; treatment of advanced renal cell cancer (RCC)

Dosing: Adults**Gastrointestinal stromal tumor, renal cell cancer:** Oral: 50 mg once daily for 4 weeks of a 6-week treatment cycle (4 weeks on, 2 weeks off). **Note:** Dosage modifications should be done in increments of 12.5 mg; individualize based on safety and tolerability.

Dosage adjustment with concurrent CYP3A4 inhibitor: Dose reductions are more likely to be needed when sunitinib is administered concomitantly with strong CYP3A4 inhibitors (eg, clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, protease inhibitors, telithromycin, voriconazole); dose reductions to a minimum of 37.5 mg/day should be considered with strong CYP3A4 inhibitors.

Dosage adjustment with concurrent CYP3A4 inducer: May require increased doses; dosage increases to a maximum of 87.5 mg/day with careful monitoring should be considered with strong CYP3A4 inducers (eg, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, St. John's wort).

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot studied in patients with serum creatinine >2 x ULN; pharmacokinetics were unaltered in patients with Cl_{cr} ≥42 mL/minute.

Dosing: Hepatic ImpairmentNo adjustment is necessary with mild-to-moderate (Child-Pugh Class A or B) hepatic impairment; not studied in patients with severe (Child-Pugh Class C) hepatic impairment. Studies excluded patients with ALT/AST >2.5 x ULN, or if due to liver metastases, ALT/AST >5 x ULN.

Dosing: Adjustment for Toxicity

Cardiac toxicity:

Ejection fraction <50% and >20% below baseline without evidence of CHF: Interrupt treatment and/or reduce dose

LV dysfunction with CHF clinical manifestations: Discontinue treatment

Severe hypertension: Temporarily interrupt treatment until hypertension is controlled

Hepatic failure, nephrotic syndrome, or pancreatitis: Discontinue treatment

RPLS or thrombotic microangiopathy: Temporarily withhold treatment; after resolution, may resume with discretion.

Administration: OralMay be taken with or without food.
Dietary ConsiderationsMay be taken with or without food. Avoid grapefruit juice.
StorageStore at room temperature of 25°C (77°F); excursions permitted to 15°C and 30°C (59°F and 86°F).
Extemporaneously Prepared

Sunitinib 10 mg/mL oral suspension: In a mortar, mix the contents of three 50-mg sunitinib capsules with a 1:1 mixture of Ora-Sweet® and Ora-Plus® to a final volume of 15 mL, yielding a final sunitinib concentration of 10 mg/mL; transfer to amber plastic bottle. This suspension maintains an average concentration of 96% to 106% (of the original concentration) at room temperature or refrigerated for up to 60 days in plastic amber prescription bottles. Note: Shake well before use.

Navid F, Christensen R, Minkin P, et al, “Stability of Sunitinib in Oral Suspension,” *Ann Pharmacother*, 2008, 42(7):962-6.

ContraindicationsThere are no contraindications listed within the FDA-approved manufacturer’s labeling.

Canadian labeling: Hypersensitivity to sunitinib or any component of the formulation; pregnancy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal toxicity: Has been reported; monitor for adrenal insufficiency for patients with trauma, severe infection, or undergoing surgery.
- Bleeding: Hemorrhagic events have been reported including epistaxis, rectal, gingival, upper GI, genital, wound bleeding, tumor-related, and hemoptysis/pulmonary hemorrhage.
- Depigmentation: May cause skin and/or hair depigmentation or discoloration.
- Gastrointestinal complications: Serious and fatal gastrointestinal complications, including gastrointestinal perforation, have occurred (rarely).
- Hypertension: May cause hypertension; monitor and control with antihypertensives if needed; interrupt therapy until hypertension is controlled for severe hypertension. Use caution and closely monitor in patients with underlying or poorly-controlled hypertension.
- Left ventricular dysfunction/heart failure: May cause a decrease in left ventricular ejection fraction (LVEF), including grade 3 reductions; monitor with baseline and periodic LVEF evaluations. Mean onset of symptomatic HF is 22 days from treatment initiation. Interrupt therapy and/or decrease dose with LVEF <50% or >20% reduction from baseline. Discontinue with clinical signs and symptoms of heart failure (HF). Use caution with cardiac dysfunction; patients with MI, bypass grafts, HF, vascular diseases (including CVA and TIA), and PE were excluded from clinical trials.
- QT_c prolongation: QT_c prolongation and torsade de pointes have been observed; use caution in patients with a history of QT_c prolongation, with medications known to increase sunitinib levels or prolong the QT interval, or patients with pre-existing (relevant) cardiac disease, bradycardia, or electrolyte imbalance. A baseline and periodic 12-lead ECG should be obtained; correct electrolyte abnormalities prior to treatment and monitor and correct potassium, calcium, and magnesium levels during therapy.
- Reversible posterior leukoencephalopathy syndrome (RPLS): Has been reported (rarely). Symptoms of RPLS include confusion, headache, hypertension, lethargy, seizure, blindness and/or other vision, or neurologic disturbances; interrupt treatment and begin management of hypertension.
- Thyroid disorders: Hypothyroidism may occur; the risk for hypothyroidism appears to increase with therapy duration. Hyperthyroidism, sometimes followed by hypothyroidism, has also been reported. Monitor thyroid function at baseline and if symptomatic

Disease-related concerns:

- Hepatic impairment: Has not been studied in patients with severe hepatic impairment (Child-Pugh class C); patients with ALT or AST >2.5 times ULN (or >5 times ULN if due to liver metastases) were excluded from clinical trials.

Concurrent drug therapy issues:

- Bevacizumab: Microangiopathic hemolytic anemia (MAHA) has been reported when sunitinib has been used in combination with bevacizumab.
- CYP3A4 inhibitors/inducers: Use with caution in patients concurrently taking strong CYP3A4 inhibitors (may increase sunitinib levels; eg, clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, protease inhibitors, telithromycin, voriconazole) or inducers (may decrease sunitinib levels; eg, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, St. John’s wort); dosage adjustments of sunitinib may be required.
- QT_c-prolonging agents: Concurrent use with other drugs which may prolong QT_c interval may increase the risk of potentially-fatal arrhythmias.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric Considerations Of the 450 patients studied, 115 (25.6%) were ≥65 years of age. No overall differences in safety or effectiveness were noted between younger adults and geriatric patients. Note, however, warning of left ventricular changes in ejection fraction as many elderly have systolic failure.

Pregnancy Risk Factor D

Pregnancy Considerations Animal studies have demonstrated teratogenicity and fetal loss. There are no adequate and well-controlled studies in pregnant women. Because sunitinib inhibits angiogenesis, a critical component of fetal development, adverse effects on pregnancy would be expected. Women of childbearing potential should be advised to avoid pregnancy.

Lactation Excretion in breast milk unknown/not recommended

Breast-Feeding Considerations Due to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

>10%:

Cardiovascular: Hypertension (15% to 30%; grades 3/4: 4% to 10%), LVEF decreased (11% to 21%; grades 3/4: 1%), heart failure (≤15%), peripheral edema (11%)

Central nervous system: Fatigue (42% to 58%), fever (17% to 18%), headache (13% to 18%), chills (11%), insomnia (11%)

Dermatologic: Hyperpigmentation (19% to 33%), skin discoloration (19% to 30%), rash (14% to 27%), hand-foot syndrome (12% to 21%), dry skin (17% to 18%), hair color changes (7% to 16%)

Endocrine & metabolic: Hyperuricemia (15% to 41%), hypophosphatemia (9% to 36%), hypocalcemia (35%), hypoglycemia (19%), hypoalbuminemia (18%), hyperglycemia (15%), hyponatremia (6% to 14%), hypokalemia (12%), hyperkalemia (6% to 11%), hypernatremia (10% to 11%)

Gastrointestinal: Diarrhea (40% to 58%), lipase increased (25% to 52%), nausea (31% to 49%), taste perversion (21% to 44%), mucositis/stomatitis (29% to 43%), anorexia (31% to 38%), constipation (16% to 34%), abdominal pain (22% to 33%), dyspepsia (28%), vomiting (24% to 28%), amylase increased (5% to 17%), weight loss (12%), xerostomia (12%), GERD/reflux (11%)

Hematologic: Leukopenia (up to 78%; grades 3/4: 5%), neutropenia (53% to 72%; grades 3/4: 10% to 12%), anemia (26% to 72%; grades 3/4: 3% to 7%), thrombocytopenia (38% to 65%; grades 3/4: 5% to 8%), lymphopenia (38% to 59%; grades 3/4: up to 59%), hemorrhage/bleeding (18% to 30%)

Hepatic: AST increased (39% to 52%), ALT increased (39% to 46%), alkaline phosphatase increased (24% to 42%), hyperbilirubinemia (10% to 19%)

Neuromuscular & skeletal: Creatine kinase increased (41%), weakness (21% to 22%), back pain (11% to 19%), arthralgia (12% to 18%), limb pain (14% to 17%), myalgia (14%)

Renal: Creatinine increased (12% to 66%)

Respiratory: Dyspnea (10% to 28%), cough (8% to 17%)

1% to 10%:

Cardiovascular: Venous thrombotic events (2% to 3%), DVT (1% to 3%), myocardial ischemia (1%)

Central nervous system: Depression (8%), dizziness (7%)

Dermatologic: Skin blistering (7%), alopecia (5%)

Endocrine & metabolic: Dehydration (8%), hypothyroidism (3% to 7%)

Gastrointestinal: Flatulence (10%), glossodynia (10%), oral pain (6% to 10%), appetite disturbance (9%), pancreatitis (1%)

Neuromuscular & skeletal: Peripheral neuropathy (10%)

Ocular: Periorbital edema (7%), lacrimation increased (6%)

Respiratory: Pulmonary embolism (1%)

<1%, postmarketing, and/or case reports: Acute renal failure, adrenal dysfunction, atrial flutter, febrile neutropenia, gastrointestinal perforation, hepatic failure, hyperthyroidism, infection, microangiopathic hemolytic anemia (when used in combination with bevacizumab), MI, myopathy, nephrotic syndrome, neutropenic infection, preeclampsia-like syndrome (proteinuria and reversible hypertension), proteinuria, pulmonary hemorrhage, QT_c prolongation, reversible posterior leukoencephalopathy syndrome (RPLS), rhabdomyolysis, seizure, thrombotic microangiopathy, torsade de pointes, ventricular arrhythmia

Oncology: Emetic Potential Low (10% to 30%)

Metabolism/Transport Effects **Substrate** of CYP3A4 (major)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Bevacizumab: Sunitinib may enhance the adverse/toxic effect of Bevacizumab. Specifically, the risk of a specific form of anemia, microangiopathic hemolytic anemia (MAHA), may be increased. *Risk X: Avoid combination*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Grapefruit juice may increase the levels/effects of sunitinib. Food has no effect on the bioavailability of sunitinib.

Herb/Nutraceutical: Avoid St John's wort (may increase metabolism and decrease sunitinib concentrations).

Monitoring ParametersLVEF, baseline (and periodic with cardiac risk factors), ECG (12-lead; baseline and periodic), blood pressure, adrenal function, CBC with differential and platelets (prior to each treatment cycle), serum chemistries including magnesium, phosphate, and potassium (prior to each treatment cycle), thyroid function (baseline; then if symptomatic), urinalysis (for proteinuria development or worsening)

Monitoring: Lab TestsLVEF, baseline (and periodic with cardiac risk factors), blood pressure, adrenal function, CBC with differential and platelets (prior to each treatment cycle), serum chemistries including magnesium, phosphate, and potassium (prior to each treatment cycle), thyroid function (baseline; then if symptomatic), urinalysis (for proteinuria development or worsening)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Sutent®: 12.5 mg, 25 mg, 50 mg

Generic AvailableNo

ManufacturerPfizer, Inc

Pricing: U.S. (www.drugstore.com)

Capsules (Sutent)

12.5 mg (28): $2056.00

25 mg (28): $4224.25

50 mg (28): $7612.23

Mechanism of ActionExhibits antitumor and antiangiogenic properties by inhibiting multiple receptor tyrosine kinases, including platelet-derived growth factors (PDGFRα and PDGFRβ), vascular endothelial growth factors (VEGFR1, VEGFR2, and VEGFR3), FMS-like tyrosine kinase-3 (FLT3), colony-stimulating factor type 1 (CSF-1R), and glial cell-line-derived neurotrophic factor receptor (RET).

Pharmacodynamics/Kinetics

Distribution: V_d/F: 2230 L

Protein binding: Sunitinib: 95%; SU12662: 90%

Metabolism: Hepatic; primarily metabolized by CYP3A4 to the N-desethyl metabolite SU12662 (active)

Half-life elimination: Sunitinib: 40-60 hours; SU12662: 80-110 hours

Time to peak, plasma: 6-12 hours

Excretion: Feces (61%); urine (16%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), mucositis/stomatitis, taste perversion, and oral pain.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsSunitinib is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusFatigue and dizziness are common

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; combined use with lithium, valproic acid, carbamazepine, and SSRIs may produce an additive risk. Neutropenia and thrombocytopenia are common; concomitant use with clozapine, carbamazepine, and valproic acid may produce additive risks. Carbamazepine and St John's wort may reduce the effectiveness of sunitinib.

Index TermsNSC-736511; SU11248; Sunitinib Malate

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International Brand NamesSutene (KP); Sutent (AR, AT, AU, BE, BG, BR, CH, CL, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, MY, NL, NO, NZ, PE, PH, PT, RU, SE, SG, TH, TR, UY)

Suramin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(SUR a min)

Pharmacologic CategoryAntineoplastic Agent

Use: Unlabeled/InvestigationalInvestigational: Treatment of prostate cancer; chemosensitizing agent in treatment of various solid tumors

Dosing: AdultsRefer to individual protocols.

Prostate cancer: I.V.: 350 mg/m^2/day continuous I.V. infusion for 7 days, then titrated to a plasma level of 250-300 mcg/mL for 7 days, repeated after an 8-week interval.

Titrate to a plasma level of 300 mcg/mL for 14 days, repeat after an 8-week interval.

Chemosensitizing agent: I.V.: Doses are not yet established; anticipated to be significantly lower than cancer treatment doses.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentDosage reductions have been suggested for “severe” renal dysfunction; however, specific guidelines have not been published.

Dosing: Hepatic ImpairmentDosage reductions of 50% to 75% have been suggested for “severe” hepatic dysfunction; however, specific guidelines have not been published.

Calculations

- Body Surface Area: Adults

Administration: I.V.Usually administered as a carefully titrated continuous infusion

StorageSolutions of 10 mg/mL in saline or dextrose solutions are stable for up to 2 weeks at room temperature of 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to suramin or any component of the formulation

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with significant hepatic impairment.
- Hypoalbuminemia: Use with caution in patients with decreased serum albumin levels.
- Malnourishment: Use with caution in patients who are malnourished.

Adverse Reactions

>10%:

Central nervous system: Fever (78%), headache; palmar and plantar hyperesthesia occur at levels >350 mcg/mL

Dermatologic: Rash (48%)

Endocrine & metabolic: Adrenal insufficiency (23%), patients usually require adrenocorticoid therapy; transaminases increased (transient 14%)

Gastrointestinal: Nausea (20%), vomiting (35%), metallic taste

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia (12% to 26%), usually not dose limiting

Hepatic: Transient increases in bilirubin levels (14%)

Neuromuscular & skeletal: Paresthesia, peripheral neuropathy (33%), may be dose limiting; areflexia and paralysis may occur at levels >375 mcg/mL

Ocular: Keratopathy (11%), possibly related to dose and/or rate of infusion

Renal: Mild, nondose-limiting, proteinuria (33%); decrease in creatinine clearance

1% to 10%:

Gastrointestinal: Stomatitis (5%)

Neuromuscular & skeletal: Myalgia (3%)

<1%: Abdominal pain, atrial fibrillation, diarrhea; coagulopathy (dose limiting, inhibits factors V, VIII, IX, X, XI, and XII)

Immediate hypersensitivity reactions, including nausea, vomiting, shock, and loss of consciousness (0.1% to 0.3%); a 100-200 mg (10-20 mg in children) test dose prior to the first treatment cycle is occasionally given

Oncology: VesicantNo; may be an irritant

Oncology: Emetic PotentialModerate (30% to 60%)

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 600 mg

Generic AvailableNo

Mechanism of ActionSuramin inhibits a number of growth factors and enzymes essential to cell proliferation including platelet-derived growth factor (PDGF), fibroblast growth factor, DNA polymerase, glycerol phosphate oxidase, reverse transcriptase, and various lysosomal enzymes. Suramin may also have some angiogenic inhibitory activity.

Pharmacodynamics/Kinetics

Absorption: Not absorbed orally

Distribution: V_d: 31-46 L; does not penetrate the CNS

Protein binding: >99%

Half-life elimination: Triphasic, terminal half-life: 50 days

Excretion: Urine (as unchanged drug); bile (small amounts)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with SSRIs, lithium, or valproic acid may produce additive effects. Hematologic effects are common; use caution with clozapine, carbamazepine, and valproic acid derivatives.

Index Terms309F; Antrypol; Bayer 205; Forneau-309; Naphuride Sodium; NSC-34936; Suramin Sodium

References

Eisenberger MA and Reyno LM, "Suramin," *Cancer Treat Rev*, 1994, 20(3):259-73. [PubMed 8020006]

Larsen AK, "Suramin: An Anticancer Drug With Unique Biological Effects," *Cancer Chemother Pharmacol*, 1993, 32(2):96-8. [PubMed 8387401]

Stein CA, "Suramin: A Novel Antineoplastic Agent With Multiple Potential Mechanisms of Action," *Cancer Res*, 1993, 53(10 Suppl):2239-48. [PubMed 8485709]

Voogd TE, Vansterkenburg EL, Wilting J, et al, "Recent Research on the Biological Activity of Suramin," *Pharmacol Rev*, 1993, 45(2):177-203.[PubMed 8396782]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

Index TermsATC

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Cyclophosphamide: I.V.: 500 mg/m^2 day 1

[total dose/cycle = 500 mg/m^2]

Repeat cycle every 3 weeks

Variation 2:

Docetaxel: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Doxorubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat cycle every 3 weeks

References

Variation 1:

Martin M, Pienkowski T, Mackey J, et al, “Adjuvant Docetaxel for Node-Positive Breast Cancer,” *N Engl J Med*, 2005, 352(22):2302-13.[PubMed 15930421]

Nabholtz JM, Smylie M, Mackey JR, et al, “Docetaxel/Doxorubicin/Cyclophosphamide in the Treatment of Metastatic Breast Cancer,” *Oncology (Williston Park)*, 1997, 11(6 Suppl 6):25-7.[PubMed 9213324]

Variation 2:

Smith RE, Anderson SJ, Brown A, et al,“Phase II Trial of Doxorubicin/Docetaxel/Cyclophosphamide for Locally Advanced and Metastatic Breast Cancer: Results From NSABP Trial BP-58,” *Clin Breast Cancer*, 2002, 3(5):333-40.[PubMed 12533263]

Tacrine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Cognex® may be confused with Corgard®

International issues:

Cognex® may be confused with Codex® which is a brand name for *Saccharomyces boulardii* in Italy

Pronunciation(TAK reen)

U.S. Brand NamesCognex®

Pharmacologic CategoryAcetylcholinesterase Inhibitor (Central)

Use: Labeled IndicationsTreatment of mild-to-moderate dementia of the Alzheimer's type

Use: Unlabeled/InvestigationalLewy body dementia

Dosing: Adults

Alzheimer's disease: Oral: Initial: 10 mg 4 times/day; may increase by 40 mg/day adjusted every 6 weeks; maximum: 160 mg/day; best administered separate from meal times.

Dose adjustment based upon transaminase elevations:

ALT ≤3 times ULN:* Continue titration

ALT >3 to ≤5 times ULN:* Decrease dose by 40 mg/day, resume when ALT returns to normal

ALT >5 times ULN:* Stop treatment, may rechallenge upon return of ALT to normal

*ULN = upper limit of normal

Note: Patients with clinical jaundice confirmed by elevated total bilirubin (>3 mg/dL) should not be rechallenged with tacrine

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic ImpairmentPatients with clinical jaundice confirmed by elevated total bilirubin (>3 mg/dL) should not be rechallenged with tacrine.

Dietary ConsiderationsGive with food if GI side effects are intolerable.

ContraindicationsHypersensitivity to tacrine, acridine derivatives, or any component of the formulation; patients previously treated with tacrine who developed jaundice

Warnings/Precautions

Concerns related to adverse effects:

- Abnormal liver function tests: The use of tacrine has been associated with elevations in serum transaminases; serum transaminases (specifically ALT) must be monitored throughout therapy; use extreme caution in patients with current evidence of a history of abnormal liver function tests.
- Diarrhea: May cause loose stools.
- Nausea/vomiting: May cause nausea and/or vomiting.
- Neutropenia: May be associated with neutropenia.
- Vagotonic effects: Cholinesterase inhibitors may have vagotonic effects which may cause bradycardia and/or heart block with or without a history of cardiac disease.

Disease-related concerns:

- Cardiac conduction abnormalities: Use with caution in patients with sick-sinus syndrome, bradycardia, or conduction abnormalities; tacrine may cause bradycardia and/or heart block. Alzheimer's treatment guidelines consider bradycardia to be a relative contraindication for use of centrally-active cholinesterase inhibitors.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Peptic ulcer disease: Use with caution in patients at risk of ulcer disease (eg, previous history or NSAID use); may increase gastric acid secretion. Monitor for symptoms of bleeding.
- Respiratory disease: Use with caution in patients with COPD and/or asthma.

- Seizure disorder: Use with caution in patients with a history of seizure disorder.

- Urinary tract obstruction: Use with caution in patients with bladder outlet obstruction or prostatic hyperplasia; cholinomimetics may cause or worsen outflow obstructions, including possible exacerbation of BPH symptoms.

Concurrent drug therapy issues:

- Depolarizing neuromuscular-blocking agents: May exaggerate neuromuscular blockade effects of depolarizing neuromuscular-blocking agents like succinylcholine.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Discontinuation of therapy: Abrupt discontinuation or dosage decrease may worsen cognitive function.

Geriatric ConsiderationsTacrine is not a cure for Alzheimer's disease. At least 25% of patients may not tolerate the drug and only 50% of patients demonstrate some improvement in symptoms or a slowing of deterioration. While worth a trial in mild-to-moderate dementia of the Alzheimer's type, patients and their families must be counseled about the limitations of the drug and the importance of regular monitoring of liver function tests. No specific dosage adjustments are necessary due to age.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%:

Central nervous system: Dizziness, headache

Gastrointestinal: Diarrhea, nausea, vomiting

Miscellaneous: Transaminases increased

1% to 10%:

Cardiovascular: Flushing

Central nervous system: Ataxia, confusion, depression, fatigue, insomnia, somnolence

Dermatologic: Rash

Gastrointestinal: Abdominal pain, anorexia, constipation, dyspepsia, flatulence, weight loss

Neuromuscular & skeletal: Myalgia, tremor

Respiratory: Rhinitis

Metabolism/Transport Effects**Substrate** of CYP1A2 (major); **Inhibits** CYP1A2 (weak)
Drug Interactions

Anticholinergics: May diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotics: Acetylcholinesterase Inhibitors (Central) may enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Beta-Blockers: Acetylcholinesterase Inhibitors may enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Cholinergic Agonists: Acetylcholinesterase Inhibitors may enhance the adverse/toxic effect of Cholinergic Agonists. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Fluvoxamine: May decrease the metabolism of Tacrine. *Risk D: Consider therapy modification*

Ginkgo Biloba: May enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): Acetylcholinesterase Inhibitors may diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Succinylcholine: Acetylcholinesterase Inhibitors may enhance the neuromuscular-blocking effect of Succinylcholine. *Risk C: Monitor therapy*

Theophylline Derivatives: Tacrine may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Food decreases bioavailability.

Monitoring ParametersALT levels and other liver enzymes weekly for at least the first 18 weeks, then monitor once every 3 months

Reference RangeIn clinical trials, serum concentrations >20 ng/mL were associated with a much higher risk of development of symptomatic adverse effects

Nursing: Physical Assessment/MonitoringAssess bladder and sphincter adequacy prior to administering medication. Assess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests throughout therapy, therapeutic effectiveness, and adverse reactions (eg, cholinergic crisis). Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsALT levels and other liver enzymes at least every other week from weeks 4-16, then monitor once every 3 months

Patient EducationThis medication will not cure the disease, but may help reduce symptoms. Use as directed; do not increase dose or discontinue without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause dizziness, sedation, or hypotension (rise slowly from sitting or lying position and use caution when driving or climbing stairs); vomiting or loss of appetite (small frequent meals, frequent mouth care, or chewing gum, or sucking lozenges may help); or diarrhea (boiled milk, yogurt, or buttermilk may help). Report persistent abdominal discomfort; significantly increased salivation, sweating, tearing, or urination; flushed skin; chest pain or palpitations; acute headache; unresolved diarrhea; excessive fatigue, insomnia, dizziness, or depression; increased muscle, joint, or body pain; vision changes or blurred vision; shortness of breath or wheezing; or signs of jaundice (yellowing of eyes or skin, dark colored urine or light colored stool, abdominal pain, or easy fatigue). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 10 mg, 20 mg, 30 mg, 40 mg

Generic AvailableNo

ManufacturerParke-Davis

Pricing: U.S. (www.drugstore.com)

Capsules (Cognex)

10 mg (120): $315.98

20 mg (120): $309.97

40 mg (120): $311.96

Mechanism of ActionCentrally-acting cholinesterase inhibitor. It elevates acetylcholine in cerebral cortex by slowing the degradation of acetylcholine.

Pharmacodynamics/Kinetics

Absorption: Oral: Rapid

Distribution: V_d: Mean: 349 L; reduced by food

Protein binding, plasma: 55%

Metabolism: Extensively by CYP450 to multiple metabolites; first pass effect

Bioavailability: Absolute: 17%

Half-life elimination, serum: 2-4 hours; Steady-state: 24-36 hours

Time to peak, plasma: 1-2 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index TermsTacrine Hydrochloride; Tetrahydroaminoacrine; THA

References

Byrne J and Arie T, “Tetrahydroaminoacridine (THA) in Alzheimer's Disease,” *BMJ*, 1989, 298(6677):845-6. [PubMed 2497817]

Crismon ML, “Tacrine: First Drug Approved for Alzheimer's Disease,” *Ann Pharmacother*, 1994, 28(6):744-51. [PubMed 7919566]

Davis KL and Powchik P, “Tacrine,” *Lancet*, 1995, 345(8950):625-30. [PubMed 7534856]

Davis KL, Thal LJ, Gamzu ER, et al, “A Double-Blind, Placebo-Controlled Multicenter Study of Tacrine for Alzheimer's Disease,” *N Engl J Med*, 1992, 327(18):1253-9. [PubMed 1406817]

Eagger SA, Levy R, Sahakian BJ, et al, “Tacrine in Alzheimer's Disease,” *Lancet*, 1991, 338(8758):50-1.

Farlow M, Gracon SI, Hershey LA, et al, “A Controlled Trial of Tacrine in Alzheimer's Disease,” *JAMA*, 1992, 268(18):2523-9. [PubMed 1404819]

Knapp MJ, Knopman DS, Solomon PR, et al, “A 30-Week Randomized Controlled Trial of High-Dose Tacrine in Patients With Alzheimer's Disease,” *JAMA*, 1994, 271(13):985-91. [PubMed 8139083]

Madden S, Spaldin V, and Park BK, “Clinical Pharmacokinetics of Tacrine,” *Clin Pharmacokinet*, 1995, 28(6):449-57. [PubMed 7656503]

Rabins PV, Blacker D, Rovner BW, et al, “Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias,” October, 2007. Available at http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm

Watkins PB, Zimmerman HJ, Knapp MJ, et al, “Hepatotoxic Effects of Tacrine Administration in Patients With Alzheimer's Disease,” *JAMA*, 1994, 271(13):992-8.[PubMed 8139084]

International Brand NamesCognex (AR, AT, AU, BE, CH, ES, FI, FR, LU, PT); Cognitiv (AR); Congnex (PK); Tacrinal (BR); THA (AU)

Tacrolimus

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Prograf® may be confused with Gengraf®, Prozac®

Tacrolimus may be confused with sirolimus, temsirolimus

Pronunciation(ta KROE li mus)

U.S. Brand NamesPrograf®; Protopic®

Canadian Brand NamesAdvagraf™; Prograf®; Protopic®

Pharmacologic CategoryImmunosuppressant Agent; Topical Skin Product

Use: Labeled Indications

Oral/injection: Potent immunosuppressive drug used in heart, kidney, or liver transplant recipients

Topical: Moderate-to-severe atopic dermatitis in patients not responsive to conventional therapy or when conventional therapy is not appropriate

Use: Unlabeled/InvestigationalPotent immunosuppressive drug used in lung, small bowel transplant recipients; immunosuppressive drug for peripheral stem cell/bone marrow transplantation

Use: DentalTopical: Treatment of severe ulcerative or vesicobullous lesions (usually in consult with patient's physician)

Dosing: Adults

Notes: If switching from I.V. to oral, the oral dose should be started 8-12 hours after stopping the infusion. Adjunctive therapy with corticosteroids is recommended early post-transplant. I.V. route should only be used in patients not able to take oral medications and continued only until oral medication can be tolerated; anaphylaxis has been reported. Begin no sooner than 6 hours post-transplant; adjunctive therapy with corticosteroids is recommended.

Liver transplant:

Oral: Initial dose: 0.1-0.15 mg/kg/day in 2 divided doses, given every 12 hours; begin oral dose no sooner than 6 hours post-transplant

I.V.: Initial dose: 0.03-0.05 mg/kg/day as a continuous infusion

Heart transplant:

Oral: Initial dose: 0.075 mg/kg/day in 2 divided doses, given every 12 hours; begin oral dose no sooner than 6 hours post-transplant

I.V.: Initial dose: 0.01 mg/kg/day as a continuous infusion

Kidney transplant:

Oral: Initial dose: 0.2 mg/kg/day in 2 divided doses, given every 12 hours; initial dose may be given within 24 hours of transplant, but should be delayed until renal function has recovered; African-American patients may require larger doses to maintain trough concentration

I.V.: Initial dose: 0.03-0.05 mg/kg/day as a continuous infusion

Prevention of graft-vs-host disease:*I.V.:* 0.03 mg/kg/day as continuous infusion

Atopic dermatitis (moderate-to-severe):*Topical:* Apply minimum amount of 0.03% or 0.1% ointment to affected area twice daily; rub in gently and completely. Discontinue use when symptoms have cleared. If no improvement within 6 weeks, patients should be re-examined to confirm diagnosis.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Liver transplant:

Oral: Initial dose: 0.15-0.20 mg/kg/day in 2 divided doses, given every 12 hours; begin oral dose no sooner than 6 hours post-transplant

I.V.: Refer to adult dosing.

Notes: Patients without pre-existing renal or hepatic dysfunction have required (and tolerated) higher doses than adults to achieve similar blood concentrations. It is recommended that therapy be initiated at high end of the recommended adult I.V. and oral dosing ranges; dosage adjustments may be required. If switching from I.V. to oral, the oral dose should be started 8-12 hours after stopping the infusion. Adjunctive therapy with corticosteroids is recommended early post-transplant.

Moderate-to-severe atopic dermatitis:*Topical:* Children ≥2 years: Refer to adult dosing.

Dosing: Renal ImpairmentEvidence suggests that lower doses should be used; patients should receive doses at the lowest value of the recommended I.V. and oral dosing ranges; further reductions in dose below these ranges may be required.

Tacrolimus therapy should usually be delayed up to 48 hours or longer in patients with postoperative oliguria.

Hemodialysis: Not removed by hemodialysis; supplemental dose is not necessary.

Peritoneal dialysis: Significant drug removal is unlikely based on physiochemical characteristics.

Dosing: Hepatic ImpairmentUse of tacrolimus in liver transplant recipients experiencing post-transplant hepatic impairment may be associated with increased risk of developing renal insufficiency related to high whole blood levels of tacrolimus. The presence of moderate-to-severe hepatic dysfunction (serum bilirubin >2 mg/dL; Child-Pugh score ≥10) appears to affect the metabolism of tacrolimus. The half-life of the drug was prolonged and the clearance reduced after I.V. administration. The bioavailability of tacrolimus was also increased after oral administration. The higher plasma concentrations as determined by ELISA, in patients with severe hepatic dysfunction are probably due to the accumulation of metabolites of lower activity. These patients should be monitored closely and dosage adjustments should be considered. Some evidence indicates that lower doses could be used in these patients.

Administration: I.V.Administer by I.V. continuous infusion only. Do not use PVC tubing when administering dilute solutions. Tacrolimus is dispensed in a 50 mL glass container with no overfill. It is usually intended to be administered as a continuous infusion over 24 hours.

Administration: I.V. DetailDo not mix with acyclovir or ganciclovir due to chemical degradation of tacrolimus (use different ports in multilumen lines). Do not alter dose with concurrent T-tube clamping. Adsorption of the drug to PVC tubing may become clinically significant with low concentrations.

Administration: OralIf dosed once daily (not common), administer in the morning. If dosed twice daily, doses should be 12 hours apart. If the morning and evening doses differ, the larger dose (differences are never >0.5-1 mg) should be given in the morning. If dosed 3 times/day, separate doses by 8 hours.

Administration: TopicalDo not use with occlusive dressings. Burning at the application site is most common in first few days; improves as atopic dermatitis improves. Limit application to involved areas. Continue as long as signs and symptoms persist; discontinue if resolution occurs; re-evaluate if symptoms persist >6 weeks.

Dietary ConsiderationsCapsule: Take on an empty stomach; be consistent with timing and composition of meals if GI intolerance occurs (per manufacturer).

Storage

Injection: Prior to dilution, store at 5°C to 25°C (41°F to 77°F). Following dilution, stable for 24 hours in D_5W or NS in glass or polyolefin containers.

Capsules and ointment: Store at room temperature of 15°C to 30°C (59°F to 86°F).

ReconstitutionDilute with 5% dextrose injection or 0.9% sodium chloride injection to a final concentration between 0.004 mg/mL and 0.02 mg/mL.

Compatibility**Variable stability (consult detailed reference)** in D_5W, NS (only in glass or polyolefin containers).

Y-site administration: Compatible: Acyclovir, aminophylline, amphotericin B, ampicillin, ampicillin/sulbactam, benztropine, calcium gluconate, cefazolin, cefotetan, ceftazidime, ceftriaxone, cefuroxime, chloramphenicol, cimetidine, ciprofloxacin, clindamycin, co-trimoxazole, dexamethasone sodium phosphate, digoxin, diphenhydramine, dobutamine, dopamine, doxycycline, erythromycin lactobionate, esmolol, fluconazole, furosemide, ganciclovir, gentamicin, haloperidol, heparin, hydrocortisone sodium succinate, hydromorphone, imipenem/cilastatin, insulin (regular), isoproterenol, leucovorin, lorazepam, methylprednisolone sodium succinate, metoclopramide, metronidazole, morphine, multivitamins, nitroglycerin, oxacillin, penicillin G potassium, perphenazine, phenytoin, piperacillin, potassium chloride, propranolol, ranitidine, sodium bicarbonate, sodium nitroprusside, sodium tetradecyl sulfate, tobramycin, vancomycin.

Compatibility when admixed: Compatible: Cimetidine.

Extemporaneously PreparedTacrolimus 0.5 mg/mL oral suspension: Mix the contents of six 5-mg tacrolimus capsules with equal amounts of Ora-Plus® and Simple Syrup, N.F., to make a final volume of 60 mL. The suspension is stable for 56 days at room temperature in glass or plastic amber prescription bottles.

Esquivel C, So S, McDiarmid S, Andrews W, and Colombani PM, “Suggested Guidelines for the Use of Tacrolimus in Pediatric Liver Transplant Patients,” *Transplantation*, 1996, 61(5):847-8.

Foster JA, Jacobson PA, Johnson CE, et al, “Stability of Tacrolimus in an Extemporaneously Compounded Oral Liquid (Abstract of Meeting Presentation),” *American Society of Health-System Pharmacists Annual Meeting*, 1996, 53:P-52(E).

Tacrolimus 1 mg/mL oral suspension: Mix the contents of six 5-mg capsules in approximately 5 mL of sterile water; add capsule contents to an empty amber bottle first, then add sterile water and agitate bottle until drug disperses and a slurry is formed. Add equal parts of Ora-Plus® (suspending agent) and Ora-Sweet® (sweetening agent) to a total volume of 30 mL. The suspension is stable for 4 months at room temperature in plastic amber prescription bottles.

Elefante A, Muindi J, West K, et al, “Long-Term Stability of a Patient-Convenient 1 mg/mL Suspension of Tacrolimus for Accurate Maintenance of Stable Therapeutic Levels,” *Bone Marrow Transplant*, 2006, 37(8):781-4.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing the outpatient prescription (new or refill) for tacrolimus ointment where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to tacrolimus or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Injection/oral: See “Dosage form specific issues” below.
- Topical: See “Dosage form specific issues” below.

Dosage form specific issues:

- Injection/oral: Insulin-dependent post-transplant diabetes mellitus (PTDM) has been reported (1% to 20%); risk increases in African-American and Hispanic kidney transplant patients. **[U.S. Boxed Warning]: Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression with tacrolimus.** Nephrotoxicity and neurotoxicity have been reported, especially with higher doses; to avoid excess nephrotoxicity do not administer simultaneously with cyclosporine; monitoring of serum concentrations (trough for oral therapy) is essential to prevent organ rejection and reduce drug-related toxicity. Tonic clonic seizures may have been triggered by tacrolimus. A period of 24 hours should elapse between discontinuation of cyclosporine and the initiation of tacrolimus. Use caution in renal or hepatic dysfunction, dosing adjustments may be required. Delay initiation if postoperative oliguria occurs. Use may be associated with the development of hypertension (common). Myocardial hypertrophy has been reported (rare). Each mL of injection contains polyoxyl 60 hydrogenated castor oil (HCO-60) (200 mg) and dehydrated alcohol USP 80% v/v. Anaphylaxis has been reported with the injection, use should be reserved for those patients not able to take oral medications. **[U.S. Boxed Warning]: Should be administered under the supervision of a physician experienced in immunosuppressive therapy in a facility appropriate for monitoring and managing therapy.**

- Topical: **[U.S. Boxed Warning]: Topical calcineurin inhibitors have been associated with rare cases of malignancy (including skin and lymphoma), therefore it should be limited to short-term and intermittent treatment using the minimum amount necessary for the control of symptoms and only on involved areas. Use in children <2 years of age is not recommended, children ages 2-15 should only use the 0.03% ointment.** Avoid use on malignant or premalignant skin conditions (eg cutaneous T-cell lymphoma). Should not be used in immunocompromised patients. Do not apply to areas of active bacterial or viral infection; infections at the treatment site should be cleared prior to therapy. Topical calcineurin agents are considered second-line therapies in the treatment of atopic dermatitis/eczema, and should be limited to use in patients who have failed treatment with other therapies. Patients with atopic dermatitis are predisposed to skin infections, and tacrolimus therapy has been associated with risk of developing eczema herpeticum, varicella zoster, and herpes simplex. If atopic dermatitis is not improved in <6 weeks, re-evaluate to confirm diagnosis. May be associated with development of lymphadenopathy; possible infectious causes should be investigated. Discontinue use in patients with unknown cause of lymphadenopathy or acute infectious mononucleosis. Acute renal failure has been observed (rarely) with topical use. Not recommended for use in patients with skin disease which may increase systemic absorption (eg, Netherton's syndrome). Minimize sunlight exposure during treatment. Safety not established in patients with generalized erythroderma. Safety of intermittent use for >1 year has not been established, particularly since the effect on immune system development is unknown.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTacrolimus crosses the placenta and reaches concentrations four times greater than maternal plasma concentrations. Neonatal hyperkalemia and renal dysfunction have been reported.

The National Transplantation Pregnancy Registry (NTPR, Temple University) is a registry for pregnant women taking immunosuppressants following any solid organ transplant. The NTPR encourages reporting of all immunosuppressant exposures during pregnancy in transplant recipients at 877-955-6877.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsConcentrations in breast milk are equivalent to plasma concentrations; breast-feeding is not advised.

Adverse Reactions

Oral, I.V.:

≥15%:

Cardiovascular: Chest pain, hypertension, pericardial effusion (heart transplant)

Central nervous system: Dizziness, headache, insomnia, tremor (headache and tremor are associated with high whole blood concentrations and may respond to decreased dosage)

Dermatologic: Pruritus, rash

Endocrine & metabolic: Diabetes mellitus, hyperglycemia, hyper-/hypokalemia, hyperlipemia, hypomagnesemia, hypophosphatemia

Gastrointestinal: Abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting

Genitourinary: Urinary tract infection

Hematologic: Anemia, leukocytosis, leukopenia, thrombocytopenia

Hepatic: Ascites

Neuromuscular & skeletal: Arthralgia, back pain, paresthesia, tremor, weakness

Renal: Abnormal kidney function, BUN increased, creatinine increased, oliguria, urinary tract infection

Respiratory: Atelectasis, bronchitis, dyspnea, increased cough, pleural effusion

Miscellaneous: CMV infection, infection

<15%:

Cardiovascular: Abnormal ECG (QRS or ST segment abnormal), angina pectoris, cardiopulmonary failure, deep thrombophlebitis, heart rate decreased, hemorrhage, hemorrhagic stroke, hypervolemia, hypotension, generalized edema, peripheral vascular disorder, phlebitis, postural hypotension, tachycardia, thrombosis, vasodilation

Central nervous system: Abnormal dreams, abnormal thinking, agitation, amnesia, anxiety, chills, confusion, depression, dizziness, elevated mood, emotional lability, encephalopathy, hallucinations, nervousness, paralysis, psychosis, quadriparesis, seizure, somnolence

Dermatologic: Acne, alopecia, cellulitis, exfoliative dermatitis, fungal dermatitis, hirsutism, increased diaphoresis, photosensitivity reaction, skin discoloration, skin disorder, skin ulcer

Endocrine & metabolic: Acidosis, alkalosis, Cushing's syndrome, decreased bicarbonate, decreased serum iron, diabetes mellitus, hypercalcemia, hypercholesterolemia, hyperphosphatemia, hypoproteinemia, increased alkaline phosphatase

Gastrointestinal: Anorexia, appetite increased, cramps, duodenitis, dysphagia, enlarged abdomen, esophagitis (including ulcerative), flatulence, gastritis, gastroesophagitis, GI perforation/hemorrhage, ileus, oral moniliasis, pancreatic pseudocyst, rectal disorder, stomatitis, weight gain

Genitourinary: Bladder spasm, cystitis, dysuria, nocturia, oliguria, urge incontinence, urinary frequency, urinary incontinence, urinary retention, vaginitis

Hematologic: Bruising, coagulation disorder, decreased prothrombin, hypochromic anemia, polycythemia

Hepatic: Abnormal liver function tests, ALT increased, AST increased, bilirubinemia, cholangitis, cholestatic jaundice, GGT increased, hepatitis (including granulomatous), jaundice, liver damage, increase LDH

Neuromuscular & skeletal: Hypertonia, incoordination, joint disorder, leg cramps, myalgia, myasthenia, myoclonus, nerve compression, neuropathy, osteoporosis

Ocular: Abnormal vision, amblyopia

Otic: Ear pain, otitis media, tinnitus

Renal: Albuminuria, renal tubular necrosis, toxic nephropathy

Respiratory: Asthma, lung disorder, pharyngitis, pneumonia, pneumothorax, pulmonary edema, respiratory disorder, rhinitis, sinusitis, voice alteration

Miscellaneous: Abscess, abnormal healing, allergic reaction, crying, flu-like syndrome, generalized spasm, hernia, herpes simplex, peritonitis, sepsis, writing impaired

Topical (as reported in children and adults, unless otherwise noted):

>10%:

Central nervous system: Headache (5% to 20%), fever (1% to 21%)

Dermatologic: Skin burning (43% to 58%; tends to improve as lesions resolve), pruritus (41% to 46%), erythema (12% to 28%)

Respiratory: Increased cough (18% children)

Miscellaneous: Flu-like syndrome (23% to 28%), allergic reaction (4% to 12%)

1% to 10%:

Cardiovascular: Peripheral edema (3% to 4% adults)

Central nervous system: Hyperesthesia (3% to 7% adults), pain (1% to 2%)

Dermatologic: Skin tingling (2% to 8%), acne (4% to 7% adults), localized flushing (following ethanol consumption 3% to 7% adults), folliculitis (2% to 6%), urticaria (1% to 6%), rash (2% to 5%), pustular rash (2% to 4%), vesiculobullous rash (4% children), contact dermatitis (3% to 4%), cyst (1% to 3% adults), eczema herpeticum (1% to 2%), fungal dermatitis (1% to 2% adults), sunburn (1% to 2% adults), dry skin (1% children)

Endocrine & metabolic: Dysmenorrhea (4% women)

Gastrointestinal: Diarrhea (3% to 5%), dyspepsia (1% to 4% adults), abdominal pain (3% children), vomiting (1% adults), gastroenteritis (adults 2%), nausea (1% children)

Neuromuscular & skeletal: Myalgia (2% to 3% adults), weakness (2% to 3% adults), back pain (2% adults)

Ocular: Conjunctivitis (2% adults)

Otic: Otitis media (12% children)

Respiratory: Rhinitis (6% children), sinusitis (2% to 4% adults), bronchitis (2% adults), pneumonia (1% adults)

Miscellaneous: Varicella/herpes zoster (1% to 5%), lymphadenopathy (3% children)

Oral, I.V., topical: Postmarketing and/or case reports (limited to important or life-threatening): Acute renal failure, alopecia, anaphylaxis, anaphylactoid reaction, angioedema, ARDS, arrhythmia, atrial fibrillation, atrial flutter, bile duct stenosis, blindness, cardiac arrest, cerebral infarction, cerebrovascular accident, deafness, delirium, depression, DIC, hemiparesis, hemolytic-uremic syndrome, hemorrhagic cystitis, hepatic necrosis, hepatotoxicity, hyperglycemia, leukoencephalopathy, lymphoproliferative disorder (related to EBV), myocardial hypertrophy (associated with ventricular dysfunction; reversible upon discontinuation), MI, neutropenia, pancreatitis (hemorrhagic and necrotizing), pancytopenia, paresthesia, photosensitivity reaction (topical), quadriplegia, QT_c prolongation, respiratory failure, seizure, skin discoloration (topical), Stevens-Johnson syndrome, syncope, toxic epidermal necrolysis, thrombocytopenic purpura, torsade de pointes, TTP, veno-occlusive hepatic disease, venous thrombosis, ventricular fibrillation

Note: Calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA) have been reported (with concurrent sirolimus).

Oncology: VesicantNo
Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (weak)
Drug Interactions

Alcohol (Ethyl): Tacrolimus may enhance the dermatologic adverse effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antidepressants (Serotonin Reuptake Inhibitor/Antagonist): May decrease the metabolism of Tacrolimus. **Exceptions:** TraZODone. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Tacrolimus. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Dihydropyridine): May increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Tacrolimus. *Risk C: Monitor therapy*

Caspofungin: May decrease the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Cinacalcet: May decrease the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fluconazole: May decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Grapefruit Juice: May decrease the metabolism of Tacrolimus. *Risk X: Avoid combination*

Macrolide Antibiotics: May increase the serum concentration of Tacrolimus. **Exceptions:** Dirithromycin [Off Market]; Spiramycin. *Risk C: Monitor therapy*

MetroNIDAZOLE: May decrease the metabolism of Calcineurin Inhibitors. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Tacrolimus. Tacrolimus may increase the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: May enhance the adverse/toxic effect of Tacrolimus. An increased risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA) has been described. *Risk D: Consider therapy modification*

St Johns Wort: May decrease the serum concentration of Tacrolimus. *Risk D: Consider therapy modification*

Temsirolimus: May enhance the adverse/toxic effect of Tacrolimus. An increased risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA) has been described with concomitant sirolimus and tacrolimus use. *Risk D: Consider therapy modification*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Localized flushing (redness, warm sensation) may occur at application site of topical tacrolimus following ethanol consumption.

Food: Decreases rate and extent of absorption. High-fat meals have most pronounced effect (35% decrease in AUC, 77% decrease in C_{max}). Grapefruit juice, CYP3A4 inhibitor, may increase serum level and/or toxicity of tacrolimus; avoid concurrent use.

Herb/Nutraceutical: St John's wort: May reduce tacrolimus serum concentrations (avoid concurrent use).

Monitoring ParametersRenal function, hepatic function, serum electrolytes (especially potassium), glucose and blood pressure, measure 3 times/week for first few weeks, then gradually decrease frequency as patient stabilizes. Whole blood concentrations should be used for monitoring (trough for oral therapy). Signs/symptoms of anaphylactic reactions during infusion should also be monitored. Patients should be monitored during the first 30 minutes of the infusion, and frequently thereafter.

Reference Range

Heart: Typical whole blood trough concentrations:

One week to 3 months: 8-20 ng/mL

Months 3-18: 6-18 ng/mL

Kidney transplant: Whole blood trough concentrations:

Months 1-3: 7-20 ng/mL

Months 4-12: 5-15 ng/mL

Liver transplant: Whole blood trough concentrations: Months 1-12: 5-20 ng/mL

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor blood pressure frequently. Assess results of laboratory tests prior to, during, and following therapy. Monitor response to therapy and adverse reactions. Patients with diabetes should be advised to monitor glucose levels closely (this medication may alter glucose levels). Monitor/instruct patient on appropriate use, interventions to reduce side effects, to monitor for signs of opportunistic infection, and adverse reactions to report.

Monitoring: Lab TestsRenal function, hepatic function, serum electrolytes (especially potassium), glucose. Since pharmacokinetics show great inter- and intrapatient variability over time, monitoring of serum concentrations (trough for oral therapy) has proven helpful to prevent organ rejection and reduce drug-related toxicity. Measure 3 times/week for first few weeks, then gradually decrease frequency as patient stabilizes.

Patient EducationTake as directed, on an empty stomach. Be consistent with timing and consistency of meals if GI intolerance occurs (per manufacturer). Do not take within 2 hours before or after antacids. Do not alter dose and do not discontinue without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) during entire course of therapy unless instructed to restrict fluid intake. You will be susceptible to infection (avoid crowds and exposure to infection). If you have diabetes, monitor glucose levels closely (drug may alter glucose levels). You may experience nausea, vomiting, loss of appetite (small frequent meals, frequent mouth care may help); diarrhea (boiled milk, yogurt, or buttermilk may help); constipation (increased exercise, fluids, fruit, fluid, or fiber may help; if unresolved, consult prescriber); or muscle or back pain (mild analgesics may be recommended). Report chest pain; acute headache or dizziness; symptoms of respiratory infection, cough, or respiratory difficulty; unresolved GI effects; fatigue, chills, fever, unhealed sores, white plaques in mouth, irritation in genital area; unusual bruising or bleeding; pain or irritation on urination or change in urinary patterns; rash or skin irritation; or other unusual effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Topical: Before applying, wash area gently and thoroughly. Apply in thin film to affected area. Do not cover skin with bandages. Wash hands only if not treating skin on the hands. Protect skin from sunlight or exposure to UV light.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule (Prograf®): 0.5 mg, 1 mg, 5 mg

Injection, solution (Prograf®): 5 mg/mL (1 mL) [contains dehydrated alcohol 80% and polyoxyl 60 hydrogenated castor oil]

Ointment, topical (Protopic®): 0.03% (30 g, 60 g, 100 g); 0.1% (30 g, 60 g, 100 g)

Generic AvailableNo

ManufacturerFujisawa Healthcare, Inc

Pricing: U.S. (www.drugstore.com)

Capsules (Prograf)

0.5 mg (120): $245.99

1 mg (100): $409.93

5 mg (60): $1404.00

Ointment (Protopic)

0.03% (30): $111.92

0.03% (60): $211.40

0.1% (30): $104.71

0.1% (60): $204.73

0.1% (100): $339.92

Mechanism of ActionSuppresses cellular immunity (inhibits T-lymphocyte activation), possibly by binding to an intracellular protein, FKBP-12

Pharmacodynamics/Kinetics

Absorption: Better in resected patients with a closed stoma; unlike cyclosporine, clamping of the T-tube in liver transplant patients does not alter trough concentrations or AUC

Oral: Incomplete and variable; food within 15 minutes of administration decreases absorption (27%)

Topical: Serum concentrations range from undetectable to 20 ng/mL (<5 ng/mL in majority of adult patients studied)

Protein binding: 99%

Metabolism: Extensively hepatic via CYP3A4 to eight possible metabolites (major metabolite, 31-demethyl tacrolimus, shows same activity as tacrolimus *in vitro*)

Bioavailability: Oral: Adults: 7% to 28%, Children: 10% to 52%; Topical: <0.5%; Absolute: Unknown

Half-life elimination: Variable, 21-61 hours in healthy volunteers

Time to peak: 0.5-4 hours

Excretion: Feces (~92%); feces/urine (<1% as unchanged drug)

Pharmacotherapy PearlsAdditional dosing considerations:

Switch from I.V. to oral therapy: Threefold increase in dose

Pediatric patients: About 2 times higher dose compared to adults

Liver dysfunction: Decrease I.V. dose; decrease oral dose

Renal dysfunction: Does not affect kinetics; decrease dose to decrease levels if renal dysfunction is related to the drug

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, oral moniliasis, dysphagia, and esophagitis (including ulcerative).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia is common

Mental Health: Effects on Psychiatric TreatmentContraindicated with ziprasidone; barbiturates and carbamazepine may decrease the effects of tacrolimus

Cardiovascular ConsiderationsTacrolimus administration has been associated with torsade de pointes. Use with caution in patients at higher risk for proarrhythmia. Correct any underlying conditions that may increase the risk of torsade de pointes prior to tacrolimus administration.

Anesthesia and Critical Care Concerns/Other Considerations

Additional dosing considerations:

Switch from I.V. to oral therapy: Threefold increase in dose

Pediatric patients: About 2 times higher dose compared to adults

Liver dysfunction: Decrease I.V. dose; decrease oral dose

Renal dysfunction: Does not affect kinetics; decrease dose to decrease levels if renal dysfunction is related to the drug

Tacrolimus is associated with more neurotoxicity, nephrotoxicity, and glucose intolerance but less hypertension, dyslipidemia, gingival hyperplasia, or hirsutism than cyclosporine.

Index TermsFK506

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International Brand Names Advagraf (GB, IE); Limustin (MX); Mustopic Oint (IN); Proalid (MX); Prograf (AE, AR, AU, BH, BR, CH, CL, CN, CO, CR, CY, DE, DK, DO, EG, FR, GB, GR, GT, HK, HN, IE, IL, IQ, IR, JO, JP, KP, KW, LB, LY, MX, MY, NI, OM, PA, PE, PH, PL, PY, QA, SA, SE, SG, SV, SY, TH, TW, UY, VE, YE); Protopic (AT, BE, BG, CH, CL, CZ, DE, DK, EC, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, MX, MY, NL, NO, PH, PT, RU, SE, SG, TR, TW); Protopy (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Tacrobell (KP); Tacrol (PK)

TAD

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid
Regimen UseLeukemia, acute myeloid
Regimen

Daunorubicin: I.V.: 60 mg/m^2/day days 3, 4, and 5

[total dose/cycle = 180 mg/m^2]

Cytarabine: I.V.: 100 mg/m^2/day continuous infusion days 1 and 2

[total dose/cycle = 200 mg/m^2]

followed by I.V.: 100 mg/m^2/day over 30 minutes every 12 hours days 3 to 8

[total dose/cycle = 1200 mg/m^2]

Thioguanine: Oral: 100 mg/m^2/day every 12 hours days 3 to 9

[total dose/cycle = 1400 mg/m^2]

Administer one cycle only

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Tadalafil

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Tadalafil may be confused with sildenafil, vardenafil

Pronunciation(tah DA la fil)

U.S. Brand NamesCialis®

Canadian Brand NamesCialis®

Pharmacologic CategoryPhosphodiesterase-5 Enzyme Inhibitor

Use: Labeled IndicationsTreatment of erectile dysfunction (ED)

Dosing: Adults**Erectile dysfunction:** Oral:

As-needed dosing: 10 mg at least 30 minutes prior to anticipated sexual activity (dosing range: 5-20 mg); to be given as one single dose and not given more than once daily. **Note:** Erectile function may be improved for up to 36 hours following a single dose; adjust dose.

Once-daily dosing: 2.5 mg once daily (dosing range: 2.5-5 mg/day) to be given at approximately the same time daily without regard to timing of sexual activity

Dosing adjustment with concomitant medications:

Alpha$_1$-blockers: If stabilized on either alpha-blockers or tadalafil therapy, initiate new therapy with the other agent at the lowest possible dose.

CYP3A4 inhibitors: Dose reduction of tadalafil is recommended with strong CYP3A4 inhibitors. When used on an as-needed basis, the dose of tadalafil should not exceed 10 mg, and tadalafil should not be taken more frequently than once every 72 hours. When used on a once-daily basis, the dose of tadalafil should not exceed 2.5 mg. Examples of such inhibitors include amprenavir, atazanavir, clarithromycin, conivaptan, delavirdine, diclofenac, fosamprenavir, imatinib, indinavir, isoniazid, itraconazole, ketoconazole, miconazole, nefazodone, nelfinavir, nicardipine, propofol, quinidine, ritonavir, and telithromycin.

Dosing: ElderlyRefer to adult dosing. No dose adjustment for patients >65 years of age; use with caution in patients with concomitant medications or renal/hepatic impairment.

Dosing: Renal Impairment

As-needed use:

Cl_{cr} 51-80 mL/minute: Dosage adjustment not required.

Cl_{cr} 31-50 mL/minute: Initial dose 5 mg once daily; maximum dose 10 mg not to be given more frequently than every 48 hours.

Cl_{cr} <30 mL/minute and on hemodialysis: Maximum dose 5 mg not to be given more frequently than every 72 hours.

Once-daily use:

Cl_{cr} 51-80 mL/minute: Dosage adjustment not required.

Cl_{cr} 31-50 mL/minute: Dose adjustment not needed.

Cl_{cr} <30 mL/minute and on hemodialysis: Use not recommended.

Dosing: Hepatic Impairment

As-needed use:

Mild-to-moderate hepatic impairment (Child-Pugh class A or B): Use with caution; dose should not exceed 10 mg once daily.

Severe hepatic impairment (Child-Pugh class C): Use is not recommended.

Once-daily use:

Mild-to-moderate hepatic impairment (Child-Pugh class A or B): Use with caution.

Severe hepatic impairment: Use is not recommended.

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered with or without food, prior to anticipated sexual activity. When used on an as-needed basis, should be taken at least 30 minutes prior to sexual activity. When used on a once-daily basis, should be taken at the same time each day, without regard to timing of sexual activity.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsConcurrent use (regularly/intermittently) of organic nitrates in any form (eg, nitroglycerin, isosorbide dinitrate)

Warnings/Precautions

Concerns related to adverse effects:

- Color discrimination: May cause dose-related impairment of color discrimination. Use caution in patients with retinitis pigmentosa; a minority have genetic disorders of retinal phosphodiesterases (no safety information available).

- Hearing loss: Sudden decrease or loss of hearing has been reported rarely; hearing changes may be accompanied by tinnitus and dizziness. A direct relationship between therapy and hearing loss has not been determined.

- Hypotension: Decreases in blood pressure may occur due to vasodilator effects; use with caution in patients with left ventricular outflow obstruction (aortic stenosis or hypertrophic obstructive cardiomyopathy); may be more sensitive to hypotensive actions. Concurrent use with alpha-adrenergic antagonist therapy or substantial alcohol consumption may cause symptomatic hypotension; patients should be hemodynamically stable prior to initiating therapy at the lowest possible dose.

- Priapism: Painful erection >6 hours in duration; rare. Educate patient to seek medical assistance for erection lasting >4 hours.

- Vision loss: Vision loss may occur rarely and be a sign of nonarteritic anterior ischemic optic neuropathy (NAION). Risk may be increased with history of vision loss. Other risk factors for NAION include low cup-to-disc ratio ("crowded disc"), coronary artery disease, diabetes, hypertension, hyperlipidemia, smoking, and >50 years of age. Safety and efficacy were not studied in patients with known degenerative retinal disorders (eg, retinitis pigmentosa); use is not recommended. A direct relationship between therapy and hearing loss has not been determined.

Disease-related concerns:

- Anatomical penis deformation: Use with caution in patients with anatomical deformation of the penis (angulation, cavernosal fibrosis, or Peyronie's disease).

- Bleeding disorders: Use with caution in patients with bleeding disorders; safety and efficacy have not been established. *In vitro* studies have suggested a decreased effect on platelet aggregation.

- Cardiovascular disease: Use with caution in patients with hypotension (<90/50 mm Hg), uncontrolled hypertension (>170/100 mm Hg), NYHA class II-IV heart failure within the last 6 months, uncontrolled arrhythmias, stroke within the last 6 months, MI within the last 3 months; safety and efficacy have not been studied in these patients. Use caution in patients with left ventricular outflow obstruction (eg, aortic stenosis). There is a degree of cardiac risk associated with sexual activity; therefore, physicians may wish to consider the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction.

- Conditions predisposing to priapism: Use with caution in patients who have conditions which may predispose them to priapism (sickle cell anemia, multiple myeloma, leukemia). All patients should be instructed to seek immediate medical attention if erection persists >4 hours.

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment/limitation is needed.

- Peptic ulcer disease: Use with caution in patients with active peptic ulcer disease; safety and efficacy have not been established.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment/limitation is needed.

Concurrent drug therapy issues:

- Alpha-blockers: Use with caution in patients taking alpha-blockers; may cause hypotension. Safety of this combination may be affected by other antihypertensives and intravascular volume depletion. Patients should be hemodynamically stable prior to initiating therapy. Initiate tadalafil at the lowest recommended dose. Alpha-blockers should be initiated at the lowest recommended dose in patients currently taking tadalafil.

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions. Once-daily tadalafil dosing results in continuous plasma levels; use caution when administered concurrently with medications.

- Nitrates: Concomitant use (regularly/intermittently) with all forms of nitrates is contraindicated. If nitrate administration is medically necessary following the use of tadalafil, at least 48 hours should elapse after the tadalafil dose and nitrate administration and should be given under close medical supervision with hemodynamic monitoring.

- Other treatments for erectile dysfunction: Safety and efficacy with other treatments for erectile dysfunction have not been established; use is not recommended.

Special populations:

- Elderly: Use with caution.

- Pediatrics: Safety and efficacy have not been established in children ≤18 years of age.

Other warnings/precautions:

- Appropriate use: Potential underlying causes of erectile dysfunction should be evaluated prior to treatment.

Geriatric ConsiderationsNo significant differences in pharmacokinetics were seen in elderly men versus younger men. Dosing should be adjusted for renal function. Since older adults often have concomitant diseases, many of which may be contraindicated with the use of tadalafil, prescriber should complete a thorough review of diseases and medications prior to prescribing tadalafil.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic events were not reported in animal reproduction studies. Postnatal development and pup survival was decreased at some doses. Tadalafil is not indicated for use in women. Less than 0.0005% is found in the semen of healthy males.

LactationExcretion in breast milk unknown

Breast-Feeding ConsiderationsTadalafil is not indicated for use in women

Adverse ReactionsSimilar adverse events are reported with once-daily dosing, but are generally lower than with doses used as needed.

>10%: Central nervous system: Headache (3% to 15%)

2% to 10%:

Cardiovascular: Flushing (1% to 3%), hypertension (1% to 3%)

Gastrointestinal: Dyspepsia (3% to 10%)

Neuromuscular & skeletal: Back pain (3% to 6%), CPK increased (2%), myalgia (1% to 4%), limb pain (1% to 3%)

Respiratory: Upper respiratory tract infection (3% to 4%), cough (2% to 4%), nasal congestion (2% to 4%)

<2%, postmarketing, and/or case reports: Abdominal pain (upper), amnesia (transient global), angina pectoris, arthralgia, blurred vision, chest pain, color perception change, color vision decreased, conjunctival hyperemia, conjunctivitis, diaphoresis, diarrhea, dizziness, dysphagia, dyspnea, epistaxis, esophagitis, exfoliative dermatitis, eye pain, eyelid swelling, facial edema, fatigue, gastritis, gastroesophageal reflux, hearing decreased, hearing loss, hepatic enzymes increased, hyper-/hypotension, hypoesthesia, GGTP increased, insomnia, lacrimation, migraine, MI, nausea, neck pain, nonarteritic ischemic optic neuropathy, pain, palpitation, paresthesia, pharyngitis, photophobia, postural hypotension, priapism (reported with drugs in this class), pruritus, rash, retinal artery occlusion, retinal vein occlusion, seizure, somnolence, Stevens-Johnson syndrome, stroke, sudden cardiac death, syncope, tachycardia, tinnitus, urinary tract infection, urticaria, vertigo, visual changes (color vision), visual field loss, vomiting, weakness, xerostomia

Metabolism/Transport Effects**Substrate of** CYP3A4 (major)

Drug Interactions

Alpha1-Blockers: Phosphodiesterase 5 Inhibitors may enhance the hypotensive effect of Alpha1-Blockers. **Exceptions:** Dapiprazole [Off Market]. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Etravirine: May decrease the serum concentration of Phosphodiesterase 5 Inhibitors. Management: No empiric dosage adjustments are recommended with concomitant therapy; however, dose of the phosphodiesterase inhibitor may need to be altered based on clinical response. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Phosphodiesterase 5 Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Phosphodiesterase 5 Inhibitors. Management: Dose restrictions for tadalafil, and/or sildenafil and vardenafil are recommended in combination with ritonavir, atazanavir, indinavir, darunavir and saquinavir. Consult specific prescribing information for detailed recommendations. *Risk D: Consider therapy modification*

Sapropterin: May enhance the hypotensive effect of Phosphodiesterase 5 Inhibitors. *Risk C: Monitor therapy*

Vasodilators (Organic Nitrates): Phosphodiesterase 5 Inhibitors may enhance the vasodilatory effect of Vasodilators (Organic Nitrates). *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Substantial consumption of ethanol may increase the risk of hypotension and orthostasis. Lower ethanol consumption has not been associated with significant changes in blood pressure or increase in orthostatic symptoms.

Food: Rate and extent of absorption are not affected by food. Grapefruit juice may increase serum levels/toxicity of tadalafil. When used on an as-needed basis, do not give more than a single 10 mg dose of tadalafil more frequently than every 72 hours in patients who regularly consume grapefruit juice. When used on a once-daily basis, the dose of tadalafil should not exceed 2.5 mg/day in patients who regularly consume grapefruit juice.

Herb/Nutraceutical: St John's wort: Use caution with concomitant use.

Monitoring ParametersMonitor for response and adverse effects.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescription, OTC medications, or herbal products patient may be using. Assess for therapeutic effectiveness and adverse reactions. Instruct patient on appropriate use and cautions, possible side effects, and symptoms to report.

Patient EducationInform prescriber of all other prescriptions, OTC medications, or herbal products you are taking and any allergies you have; serious side effects can result when tadalafil is used with some other medications. Avoid substantial consumption of alcohol. Do not combine tadalafil with other approaches to treating erectile dysfunction without consulting prescriber. **Note:** This drug provides no protection against sexually-transmitted diseases, including HIV. Take exactly as directed; do not take more often than prescribed. You may experience headache, fatigue, dizziness, or blurred vision (use caution when driving or engaging in hazardous tasks until response to drug is known); back or limb pain (consult prescriber for appropriate analgesic). Report immediately chest pain, palpitations; respiratory difficulty; unusual dizziness; change in vision; change in hearing or ringing in the ears; sign of urinary tract infection; skin rash; genital swelling or priapism, erection lasting >4 hours, or other persistent adverse reactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Cialis®: 2.5 mg, 5 mg, 10 mg, 20 mg

Generic AvailableNo

ManufacturerLilly

Pricing: U.S. (www.drugstore.com)

Tablets (Cialis)

2.5 mg (10): $49.99

5 mg (10): $49.99

10 mg (10): $149.99

20 mg (10): $149.97

Mechanism of ActionDoes not directly cause penile erections, but affects the response to sexual stimulation. The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation and inflow of blood to the corpus cavernosum. Tadalafil enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE-5), which is responsible for degradation of cGMP in the corpus cavernosum; when sexual stimulation causes local release of NO, inhibition of PDE-5 by tadalafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. At recommended doses, it has no effect in the absence of sexual stimulation.

Pharmacodynamics/Kinetics

Onset of action: Within 1 hour

Duration: Up to 36 hours

Distribution: V_d: 63 L

Protein binding: 94%

Metabolism: Hepatic, via CYP3A4 to metabolites (inactive)

Half-life elimination: 17.5 hours

Time to peak, plasma: ~2 hours (range: 30 minutes to 6 hours)

Excretion: Feces (61%, as metabolites); urine (36%, as metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, insomnia, or fatigue

Mental Health: Effects on Psychiatric TreatmentConcurrent use with antidepressants (eg, TCAs) and antipsychotics may produce significant hypotension secondary to alpha-receptor blockade; alpha-blockers contraindicated with tadalafil (except tamsulosin). Nefazodone may increase levels of tadalafil; dosage adjustment needed.

Cardiovascular ConsiderationsTadalafil, when used in conjunction with nitrates, may be associated with severe hypotension, myocardial infarction, and possibly death. While there are no clear significant increased cardiovascular events with PDE-5 inhibitors alone, these drugs should be absolutely avoided in conjunction with nitrates and may also induce significant and possibly fatal hypotension in patients with heart failure. Hemodynamic effects of PDE-5 inhibitors alone include a very slight drop in blood pressure without significant changes in heart rate. The most recent guidelines on the use of sildenafil (prototype PDE-5 inhibitor) in patients with cardiovascular disease are outlined in detail (Cheitlin, 1999). The general clinical recommendations are as follows.

Use of PDE-5 inhibitors is contraindicated in patients currently taking nitrate preparations.

Cardiovascular effects of PDE-5 inhibitors may be potentially hazardous in patients with:

- active coronary ischemia (not on nitrates)
- heart failure and with borderline low blood pressure and borderline low volume status
- complicated, multidrug antihypertensive regimens
- potential for drug-drug interactions that may prolong PDE-5 inhibitor half-life (eg, drugs that inhibit cytochrome P450 3A4)

Additional guidelines for the treatment of ED in patients with cardiovascular disease have also been published (Jackson, 2006). These guidelines, referred to as the Princeton II Guidelines, support the use of PDE-5 inhibition only in patients with asymptomatic coronary disease and <3 of the following risk factors: Controlled hypertension, mild stable angina, successful coronary revascularization, previous uncomplicated MI (>6-8 weeks), mild valvular disease, and left ventricular dysfunction (with or without NYHA Class I limitations).

When nitrate administration becomes medically necessary, the ACC/AHA 2004 guidelines on treatment of ST-segment elevation MI and the ACC/AHA 2007 guidelines on treatment of unstable angina/non ST-segment elevation MI supports administration of nitrates only if 24 hours have elapsed after use of sildenafil and 48 hours after use of tadalafil. The appropriate delay for the use of nitrates after vardenafil has not been determined.

Tadalafil is selective for PDE-5 and has limited effect on PDE-3, which controls cardiac contractility.

Index Terms GF196960

References

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McVary KT, “Clinical Practice. Erectile Dysfunction,” *N Engl J Med*, 2007, 357(24):2472-81.[PubMed 18077811]

Padma-Nathan H, “Efficacy and Tolerability of Tadalafil, A Novel Phosphodiesterase 5 Inhibitor, in Treatment of Erectile Dysfunction,” *Am J Cardiol*, 2003, 92(9A):19M-25M.[PubMed 14609620]

International Brand Names 36 Horas (PY); Cialis (AR, AT, AU, BE, BF, BG, BJ, BR, CH, CI, CL, CN, CO, CR, CZ, DE, DK, DO, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, HK, HN, ID, IE, IL, IT, KE, KP, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, PA, PE, PH, PL, PT, RU, SC, SD, SE, SG, SL, SN, SV, TH, TN, TR, TW, TZ, UG, VE, ZA, ZM, ZW); Forzest (IN); Zydalis (IN)

Talc (Sterile)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(talk STARE il)
U.S. Brand NamesSclerosol®; Sterile Talc Powder™
Pharmacologic CategorySclerosing Agent
Use: Labeled IndicationsPrevention of recurrence of malignant pleural effusion in symptomatic patients
Dosing: Adults**Pleural effusion:**

Intrapleural aerosol: 4-8 g (1-2 cans) as a single dose

Intrapleural instillation: 5 g

Administration: I.V.Not for I.V. administration.
Administration: OtherAdminister after adequate drainage of the effusion.

Sclerosol® Intrapleural Aerosol: Shake well and attach delivery tube. Insert delivery tube through pleural trocar, manually press on actuator button of canister to release; point in several different directions to distribute to all pleural surfaces. Keep canister in an upright position. Rate of delivery is 0.4 g per second.

Sterile Talc Powder™: Administer as a slurry. Shake well before instillation. Empty contents of each syringe into chest cavity through the chest tube by gently applying pressure to syringe plunger. After administration, flush with 10-25 mL of NS. Clamp chest tube and have patient rotate from supine to alternating decubitus positions at 20-30 minute intervals for 2 hours. For intrapleural use only; **not for I.V. administration.**

Storage

Sclerosol® Intrapleural Aerosol: Store at room temperature 15°C to 30°C (59°F to 86°F); do not freeze. Protect from heat and light.

Sterile Talc Powder™: Store at controlled room temperature of 18°C to 25°C (64°F to 77°F). Protect from light. Use within 12 hours of slurry preparation.

ReconstitutionSterile Talc Powder™: Vent bottle with needle; slowly add 50 mL of NS to bottle using aseptic technique. For doses >5 g, use a second bottle. Swirl the bottle to disperse talc and avoid settling. Divide the contents of each bottle into two 60 mL irrigation syringes (25 mL of talc slurry in each). Add an additional 25 mL of NS to each syringe for a total of 50 mL (2.5 g/50 mL). If not used immediately, label “For IntraPleural Use Only.”
ContraindicationsThere are no contraindications listed within the manufacturer’s labeling.
Warnings/Precautions

Concerns related to adverse effects:

- Pulmonary effects: Acute pneumonitis and acute respiratory distress syndrome (including one death) have rarely been reported with higher doses (10 g).

Dosage form specific issues:

- Sclerosol®: Contents under pressure and should be kept away from any heat source.

Other warnings/precautions:

- Appropriate use: Should not be used to treat malignancies; does not have antineoplastic activity. Clinicians should evaluate need for future diagnostic procedures before use; sclerosis of pleural space may preclude subsequent procedures (eg, pneumonectomy for transplantation).

Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women; use only if potential benefit outweighs possible risk to the fetus.
Adverse ReactionsFrequency not defined.

Cardiovascular: Asystolic arrest, chest pain, hypotension (transient), hypovolemia, MI, tachycardia

Central nervous system: Fever (generally lasting <24 hours)

Local: Bleeding (localized), infection at administration site, pain

Respiratory: ARDS, bronchopleural fistula, dyspnea, empyema, hemoptysis, hypoxemia, pneumonia, pulmonary edema, pulmonary embolism, subcutaneous emphysema

Nursing: Physical Assessment/MonitoringMonitor patient closely for pain or adverse response following administration.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol, intrapleural [powder]:

Sclerosol®: 4 g g [contains chlorofluorocarbon]

Powder, intrapleural:

Sterile Talc Powder™: Talc USP (5 g)

Mechanism of Action Induces an inflammatory reaction that promotes adherence of the visceral to the parietal pleura, therefore, preventing reaccumulation of pleural fluid.

Index Terms Intrapleural Talc; Sterile Talc; Talc; Talc for Pleurodesis

References

Dresler CM, Olak J, Herndon JE, et al, “Phase III Intergroup Study of Talc Poudrage vs Talc Slurry Sclerosis for Malignant Pleural Effusion,” *Chest*, 2005, 127(3):909-15.[PubMed 15764775]

Kvale PA, Seleecky PA, and Prakash UB, “Palliative Care in Lung Cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition),” *Chest*, 2007, 132(3 Suppl):368-403.[PubMed 17873181]

Tamoxifen-Epirubicin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer

Regimen Use Breast cancer

Regimen

Tamoxifen: Oral: 20 mg daily

[total dose/cycle = 560 mg]

Epirubicin: I.V.: 50 mg/m^2/day days 1 and 8

[total dose/cycle = 100 mg/m^2]

Repeat epirubicin cycle every 28 days for 6 cycles; continue tamoxifen for 4 years

References

Wils JA, Bliss JM, Marty M, et al, âEpirubicin Plus Tamoxifen Versus Tamoxifen Alone in Node-Positive Postmenopausal Patients With Breast Cancer: A Randomized Trial of the International Collaborative Cancer Group.â *J Clin Oncol*, 1999, 17(7):1988-98.[PubMed 10561249]

Tamoxifen

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English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Tamoxifen may be confused with pentoxifylline, Tambocor™

Pronunciation(ta MOKS i fen)

U.S. Brand NamesSoltamox™ [DSC]

Canadian Brand NamesApo-Tamox®; Gen-Tamoxifen; Nolvadex®; Nolvadex®-D; Novo-Tamoxifen; Tamofen®

Pharmacologic CategoryAntineoplastic Agent, Estrogen Receptor Antagonist; Selective Estrogen Receptor Modulator (SERM)

Use: Labeled IndicationsTreatment of metastatic (female and male) breast cancer; adjuvant treatment of breast cancer; reduce risk of invasive breast cancer in women with ductal carcinoma *in situ* (DCIS); reduce the incidence of breast cancer in women at high risk

Use: Unlabeled/InvestigationalTreatment of mastalgia, gynecomastia, melanoma and desmoid tumors; induction of ovulation; treatment of precocious puberty in females, secondary to McCune-Albright syndrome

Dosing: AdultsRefer to individual protocols.

Breast cancer treatment:

Metastatic (males and females) or adjuvant therapy (females): Oral: 20-40 mg/day; daily doses >20 mg should be given in 2 divided doses (morning and evening); doses greater than 20 mg/day are not more effective in adjuvant therapy

DCIS (females): Oral: 20 mg once daily for 5 years

Breast cancer risk reduction (pre- and postmenopausal high-risk females): Oral: 20 mg/day for 5 years

Induction of ovulation (unlabeled use): Oral: 5-40 mg twice daily for 4 days

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricFemale: Precocious puberty and McCune-Albright syndrome (unlabeled use): Oral: A dose of 20 mg/day has been reported in patients 2-10 years of age; safety and efficacy have not been established for treatment of longer than 1 year duration

Dosing: Combination Regimens

Breast cancer: Tamoxifen-Epirubicin

Melanoma:

CCDT (Melanoma)

Dartmouth Regimen

Administration: OralAdminister once or twice daily. Doses >20 mg/day should be given in divided doses.

Storage

Solution: Store at room temperature at or below 25°C (77°F); do not refrigerate or freeze. Protect from light. Use within 3 months of opening.

Tablet: Store at room temperature of 20°C to 25°C (68°F to 77°F). Protect from light.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing the outpatient prescription (new or refill) to females for breast cancer prevention or treatment of ductal carcinoma *in situ* where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to tamoxifen or any component of the formulation; concurrent warfarin therapy or history of deep vein thrombosis or pulmonary embolism (when tamoxifen is used for cancer risk reduction)

Warnings/Precautions

Boxed warnings:

- Serious and life-threatening events: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Thrombocytopenia and/or leukopenia may occur; neutropenia and pancytopenia have been reported rarely.

Although the relationship to tamoxifen therapy is uncertain, rare hemorrhagic episodes have occurred in patients with significant thrombocytopenia.

- Gynecologic effects/malignancies: Endometrial hyperplasia, polyps, endometriosis, uterine fibroids, and ovarian cysts have occurred. May increase risk of uterine or endometrial cancer; monitor. Amenorrhea and menstrual irregularities have been reported with tamoxifen use.

- Hepatotoxicity: Liver abnormalities such as cholestasis, fatty liver, hepatitis, and hepatic necrosis have occurred. Hepatocellular carcinomas have been reported in some studies; relationship to treatment is unclear.

- Ocular effects: Decreased visual acuity, retinal vein thrombosis, retinopathy, corneal changes, color perception changes and increased incidence of cataracts (and the need for cataract surgery) have been reported.

- Serious and life-threatening events: **[U.S. Boxed Warning]: Serious and life-threatening events (including stroke, pulmonary emboli, and uterine malignancy) have occurred at an incidence greater than placebo during use for cancer risk reduction;** these events are rare, but require consideration in risk:benefit evaluation. In patients already diagnosed with breast cancer, the benefits of tamoxifen use are greater than the risks.

- Thromboembolic events: An increased incidence of thromboembolic events, including DVT and pulmonary embolism, has been associated with use for breast cancer; risk is increased with concomitant chemotherapy; use with caution in individuals with a history of thromboembolic events.

Disease-related concerns:

- Bone mineral density: Tamoxifen use may be associated with changes in bone mineral density (BMD) and the effects may be dependant upon menstrual status. In postmenopausal women, tamoxifen use is associated with a protective effect on bone mineral density (BMD), preventing loss of BMD which lasts over the 5-year treatment period. In premenopausal women, a decline (from baseline) in BMD mineral density has been observed in women who continued to menstruate; may be associated with an increased risk of fractures.

- Hyperlipidemia: Use with caution in patients with hyperlipidemias; infrequent postmarketing cases of hyperlipemias have been reported.

- Metastatic breast cancer: Local disease flare and increased bone and tumor pain may occur; may be associated with (good) tumor response; onset is shortly after therapy initiation and usually resolves rapidly. In patients with bone metastasis, hypercalcemia has occurred usually within a few weeks of therapy initiation. Institute appropriate hypercalcemia management; discontinue if severe.

Geriatric ConsiderationsStudies have shown tamoxifen to be effective in the treatment of primary breast cancer in elderly women. Comparative studies with other antineoplastic agents in elderly women with breast cancer had more favorable survival rates with tamoxifen. Initiation of hormone therapy rather than chemotherapy is justified for elderly patients with metastatic breast cancer who are responsive. Reduction of mortality and recurrence was greater in those studies that used tamoxifen for ≥2 years than those that use it for <2 years.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated fetal adverse effects and fetal loss. There are no adequate and well-controlled studies in pregnant women. There have been reports of vaginal bleeding, birth defects and fetal loss in pregnant women. Tamoxifen use during pregnancy may have a potential long term risk to the fetus of a DES-like syndrome. For sexually-active women of childbearing age, initiate during menstruation (negative β-hCG immediately prior to initiation in women with irregular cycles). Tamoxifen may induce ovulation. Barrier or nonhormonal contraceptives are recommended. Pregnancy should be avoided during treatment and for 2 months after treatment has been discontinued.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if tamoxifen is excreted in breast milk, however, it has been shown to inhibit lactation. Reproductive tract defects were observed in neonatal rodents following exposure to tamoxifen. Due to the potential for adverse reactions, women taking tamoxifen should not breast-feed.

Adverse Reactions

>10%:

Cardiovascular: Flushing (33% to 41%), hypertension (11%), peripheral edema (11%)

Central nervous system: Pain (3% to 16%), mood changes (12% to 18%), depression (2% to 12%)

Dermatologic: Skin changes (6% to 19%), rash (13%)

Endocrine & metabolic: Hot flashes (3% to 80%), fluid retention (32%), altered menses (13% to 25%), amenorrhea (16%)

Gastrointestinal: Nausea (5% to 26%), weight loss (23%)

Genitourinary: Vaginal bleeding (2% to 23%), vaginal discharge (13% to 55%)

Neuromuscular & skeletal: Weakness (19%), arthritis (14%), arthralgia (11%)

Respiratory: Pharyngitis (14%)

1% to 10%:

Cardiovascular: Chest pain (5%), venous thrombotic events (5%), edema (4%), cardiovascular ischemia (3%), cerebrovascular ischemia (3%), angina (2%), deep venous thrombus (≤2%), MI (1%)

Central nervous system: Insomnia (9%), dizziness (8%), headache (8%), anxiety (6%), fatigue (4%)

Dermatologic: Alopecia (<1% to 5%)

Endocrine & metabolic: Oligomenorrhea (9%), breast pain (6%), menstrual disorder (6%), breast neoplasm (5%), hypercholesterolemia (4%)

Gastrointestinal: Abdominal pain (9%), weight gain (9%), constipation (4% to 8%), diarrhea (7%), dyspepsia (6%), throat irritation (oral solution 5%), abdominal cramps (1%), anorexia (1%)

Genitourinary: Urinary tract infection (10%), leukorrhea (9%), vaginal hemorrhage (6%), vaginitis (5%), ovarian cyst (3%)

Hematologic: Thrombocytopenia (≤10%), anemia (5%)

Hepatic: AST increased (5%), serum bilirubin increased (2%)

Neuromuscular & skeletal: Back pain (10%), bone pain (6% to 10%), osteoporosis (7%), fracture (7%), arthrosis (5%), myalgia (5%), paresthesia (5%), musculoskeletal pain (3%)

Ocular: Cataract (7%)

Renal: Serum creatinine increased (≤2%)

Respiratory: Cough (4% to 9%), dyspnea (8%), bronchitis (5%), sinusitis (5%)

Miscellaneous: Infection/sepsis (≤9%), diaphoresis (6%), flu-like syndrome (6%), allergic reaction (3%)

<1%, infrequent, or frequency not defined: Cholestasis, corneal changes, endometriosis, endometrial cancer, endometrial hyperplasia, endometrial polyps, fatty liver, hepatic necrosis, hepatitis, hypercalcemia, hyperlipidemia, lightheadedness, phlebitis, pruritus vulvae, pulmonary embolism, retinal vein thrombosis, retinopathy, second primary tumors, stroke, superficial phlebitis, taste disturbances, tumor pain and local disease flare (including increase in lesion size and erythema) during treatment of metastatic breast cancer (generally resolves with continuation), uterine fibroids, vaginal dryness

Postmarketing and/or case reports: Angioedema, bullous pemphigoid, erythema multiforme, hypersensitivity reactions, hypertriglyceridemia, impotence (males), interstitial pneumonitis, loss of libido (males), pancreatitis, Stevens-Johnson syndrome, visual color perception changes

⇧ Oncology: Emetic PotentialLow (10% to 30%)
⇧ Metabolism/Transport Effects**Substrate** of CYP2A6 (minor), 2B6 (minor), 2C9 (major), 2D6 (major), 2E1 (minor), 3A4 (major); **Inhibits** CYP2B6 (weak), 2C8 (moderate), 2C9 (weak), 3A4 (weak), p-glycoprotein
⇧ Drug Interactions

Aminoglutethimide: May increase the metabolism of Tamoxifen. *Risk D: Consider therapy modification*

Anastrozole: Tamoxifen may decrease the serum concentration of Anastrozole. *Risk D: Consider therapy modification*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Letrozole: Tamoxifen may decrease the serum concentration of Letrozole. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Tamoxifen. *Risk C: Monitor therapy*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Silodosin: P-Glycoprotein Inhibitors may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Tamoxifen may increase the serum concentration of Vitamin K Antagonists. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid black cohosh, dong quai in estrogen-dependent tumors. Avoid St John's wort (may decrease levels/effects of tamoxifen).

Test InteractionsT_4 elevations (which may be explained by increases in thyroid-binding globulin) have been reported; not accompanied by clinical hyperthyroidism

Monitoring ParametersCBC with platelets, serum calcium, LFTs; triglycerides and cholesterol (in patients with pre-existing hyperlipemias); abnormal vaginal bleeding; breast and gynecologic exams (baseline and routine), mammogram (baseline and routine)

Nursing: Physical Assessment/MonitoringUse caution in presence of leukopenia, thrombocytopenia, or hyperlipidemia or history of thrombolytic events. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (increased or decreased levels/effects of tamoxifen or other drugs administered concurrently). Assess results of CBC and platelet counts, therapeutic effectiveness (eg, complaints of bone pain may be an indication of a good therapeutic effectiveness in metastatic breast cancer patients and will usually subside as treatment continues), and adverse reactions (eg, flushing, fluid retention, hot flashes, vaginal bleeding or discharge, constipation, rash, mood changes). Teach patient proper use, possible side effects/appropriate interventions (eg, periodic ophthalmic evaluations and annual gynecological exams and mammogram with long-term use), and adverse symptoms to report.

Monitoring: Lab TestsCBC with platelets, serum calcium, LFTs; triglycerides and cholesterol (in patients with pre-existing hyperlipemias)

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take exactly as directed. It is important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake and adequate nutrition (small frequent meals may help). You should schedule an annual ophthalmic examination, gynecological exam, and mammogram if this medication is used long-term. You may experience hot flashes, hair loss, loss of libido (these will subside when treatment is completed). Bone pain may indicate a good therapeutic responses (consult prescriber for mild analgesics). May cause nausea, vomiting, loss of appetite (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); hot flashes (a cool room or cool compresses may help). Notify prescriber if menstrual irregularities, vaginal bleeding, or intolerable hot flashes occur. Report unusual bleeding or bruising; severe weakness or unusual fatigue; CNS changes (depression, mood changes); swelling or pain in calves; respiratory difficulty; vision changes; or other adverse effects. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication and for 2 months after treatment is discontinued; consult prescriber for appropriate barrier or nonhormonal contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, oral:

Soltamox™: 10 mg/5 mL (150 mL) [sugar free; licorice flavor] [DSC]

Tablet: 10 mg, 20 mg

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Tablets (Nolvadex)

10 mg (60): $114.79

20 mg (60): $220.37

Tablets (Tamoxifen Citrate)

20 mg (30): $21.99

Mechanism of ActionCompetitively binds to estrogen receptors on tumors and other tissue targets, producing a nuclear complex that decreases DNA synthesis and inhibits estrogen effects; nonsteroidal agent with potent antiestrogenic properties which compete with estrogen for binding sites in breast and other tissues; cells accumulate in the G_0 and G_1 phases; therefore, tamoxifen is cytostatic rather than cytocidal.

Pharmacodynamics/Kinetics

Absorption: Well absorbed; tablet and oral solution are bioequivalent

Distribution: High concentrations found in uterus, endometrial and breast tissue

Protein binding: 99%

Metabolism: Hepatic (via CYP3A4) to major metabolites, N-desmethyl tamoxifen (major) and 4-hydroxytamoxifen (minor), and a tamoxifen derivative (minor); undergoes enterohepatic recirculation

Half-life elimination: Distribution: 7-14 hours; Elimination: 5-7 days; Metabolites: 14 days

Time to peak, serum: 5 hours

Excretion: Feces (26% to 51%); urine (9% to 13%)

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsOral clonidine is being studied for the treatment of tamoxifen-induced “hot flashes.” The tumor flare reaction may indicate a good therapeutic response, and is often considered a good prognostic factor.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness, drowsiness, or confusion

Mental Health: Effects on Psychiatric Treatment May cause leukopenia; use caution with clozapine and carbamazepine

Index TermsICI-46474; Tamoxifen Citrate

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International Brand Names Bilem (TH); Canifen (PH); Canifen-DS (PH); Citofen (HR); Cytrolic (PH); Diemon (AR); Fenahex (PH); Genox (AU, MY); Ginarsan (PE); Ginarsan Forte (PE); Gynatam (PH, TH); Gynox (ID); Kessar (CN, FR, GR, IT, ZA); Mamofen (IN); Medtax (PH); Moxafen (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Neophedan (ZA); Nolvadex (AE, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CI, CN, CO, CR, CY, DE, DO, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HR, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, NE, NG, NI, NL, NO, OM, PA, PK, PL, PT, QA, SA, SC, SD, SE, SL, SN, SR, SV, SY, TN, TT, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Nolvadex-D (AU, EE, HK, IE, IL, MY, PY, UY); Novofen (HK, TH, TW); Novofen Forte (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Novofen-D (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Retaxim (HR); Soltamox (GB); Tadex (FI, TW); Tamec (CH); Tamifen (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Tamizam (BE, LU); Tamofen (CL, DK, FI, HK, ID, NO, NZ, PL, SG, TH, TW); Tamoplex (NL, PE, PH); Tamosin (AU); Tamoxi (IL); Tamoxifen (PL); Tamoxifen Hexal (PL); Tamoxifen-Ebewe (PL); Tamoxifen-Eurogenerics (LU); Tamoxifen-Hexal (LU); Tamoxifen-Knoll (PL); Tamoxifen-ratiopharm (LU); Tamoxifen-Teva (HU); Tamoxifen-Zeneca (LU); Taxus (PE); Tecnofen (MX); Zemide (PL); Zitazonium (CZ, HK, HN, HU, MY, PH, PL, TH)

Tamsulosin

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English

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Medication Safety Issues

Sound-alike/look-alike issues:

Flomax® may be confused with Flonase®, Flovent®, Foltx®, Fosamax®, Volmax®

Tamsulosin may be confused with tacrolimus, tamoxifen, terazosin

International issues:

Flomax®: Brand name for morniflumate in Italy

Flomax® may be confused with Flomox® which is a brand name for cefcapene in Japan

Pronunciation(tam SOO loe sin)

U.S. Brand NamesFlomax®

Canadian Brand NamesFlomax®; Flomax® CR; Gen-Tamsulosin; Novo-Tamsulosin; Ran-Tamsulosin; ratio-Tamsulosin; Sandoz-Tamsulosin

Pharmacologic CategoryAlpha$_1$ Blocker

Use: Labeled IndicationsTreatment of signs and symptoms of benign prostatic hyperplasia (BPH)

Use: Unlabeled/InvestigationalSymptomatic treatment of bladder outlet obstruction or dysfunction

Dosing: Adults

BPH: Oral: 0.4 mg once daily ~30 minutes after the same meal each day; dose may be increased after 2-4 weeks to 0.8 mg once daily in patients who fail to respond. If therapy is interrupted for several days, restart with 0.4 mg once daily.

Bladder outlet obstruction (unlabeled use): Oral: 0.4 mg once daily ~30 minutes after the same meal each day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} ≥10 mL/minute: No adjustment needed.

Cl_{cr} <10 mL/minute: Not studied.

Dosing: Hepatic Impairment

Mild-to-moderate impairment: No adjustment needed

Severe impairment: Not studied

Administration: OralAdminister 30 minutes after the same meal each day. Capsules should be swallowed whole; do not crush, chew, or open.

Dietary ConsiderationsTake once daily, 30 minutes after the same meal each day.

StorageStore at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to tamsulosin or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Angina: Discontinue if symptoms of angina occur or worsen.
- Floppy iris syndrome: Intraoperative floppy iris syndrome has been observed in cataract surgery patients who were on or were previously treated with alpha$_1$-blockers; causality has not been established and there appears to be no benefit in discontinuing alpha-blocker therapy prior to surgery.
- Orthostatic hypotension/syncope: May cause significant orthostatic hypotension and syncope, especially with first dose; anticipate a similar effect if therapy is interrupted for a few days, if dosage is rapidly increased, or if another antihypertensive drug (particularly vasodilators) or a PDE-5 inhibitor (eg, sildenafil, tadalafil, vardenafil) is introduced. "First-dose" orthostatic hypotension may occur 4-8 hours after dosing; may be dose related. Patients should be cautioned about performing hazardous tasks when starting new therapy or adjusting dosage upward.
- Priapism: Priapism has been associated with use (rarely).
- Sulfonamide allergy: Rarely, patients with a sulfa allergy have also developed an allergic reaction to tamsulosin; avoid use when previous reaction has been severe.

Disease-related concerns:

- Prostate cancer: It is recommended to rule out prostatic carcinoma before beginning therapy.

Special populations:

- Females: Not indicated for use in women.
- Pediatrics: Not indicated for use in children.

Other warnings/precautions:

- Antihypertensive use: Not intended for use as an antihypertensive drug.

Geriatric Considerations Metabolism of tamsulosin may be slower, and older patients may be more sensitive to the orthostatic hypotension caused by this medication. A 40% higher exposure (AUC) is anticipated in patients between 55 and 75 years of age as compared to younger subjects (20-32 years).

Pregnancy Risk Factor B

Pregnancy Considerations Teratogenic effects were not observed in animal studies, however, tamsulosin is not approved for use in women.

Adverse Reactions

>10%:

Cardiovascular: Orthostatic hypotension (6 % to 19%)

Central nervous system: Headache (19% to 21%), dizziness (15% to 17%)

Genitourinary: Abnormal ejaculation (8% to 18%)

Respiratory: Rhinitis (13% to 18%)

Miscellaneous: Infection (9% to 11%)

1% to 10%:

Cardiovascular: Chest pain (4%)

Central nervous system: Somnolence (3% to 4%), insomnia (1% to 2%), vertigo (≤1%)

Endocrine & metabolic: Libido decreased (1% to 2%)

Gastrointestinal: Diarrhea (4% to 6%), nausea (3% to 4%), tooth disorder (1% to 2%)

Neuromuscular & skeletal: Weakness (8% to 9%), back pain (7% to 8%)

Ocular: Blurred vision (≤2%)

Respiratory: Pharyngitis (5% to 6%), cough (3% to 5%), sinusitis (2% to 4%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Allergic reactions (angioedema, pruritus, rash, urticaria, respiratory symptoms); constipation, hypotension, intraoperative floppy iris syndrome, orthostasis (symptomatic), palpitation, priapism, skin desquamation, syncope, transaminases increased, vomiting

Metabolism/Transport Effects **Substrate** (major) of CYP2D6, 3A4

Drug Interactions

Alfuzosin: Alpha1-Blockers may enhance the antihypertensive effect of Alfuzosin. Risk of orthostatic hypotension or syncope may be increased. Alfuzosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Alpha1-Blockers: May enhance the antihypertensive effect of Tamsulosin. Risk of orthostatic hypotension or syncope may be increased. Tamsulosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Beta-Blockers: May enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Alpha1-Blockers may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: May enhance the hypotensive effect of Alpha1-Blockers. *Risk D: Consider therapy modification*

Silodosin: Alpha1-Blockers may enhance the adverse/toxic effect of Silodosin. Of particular concern are the risk of postural hypotension, syncope, and/or hypotension. Silodosin may enhance the hypotensive effect of Alpha1-Blockers. Of particular concern are the risk of postural hypotension, syncope, and/or hypotension. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Food: Fasting increases bioavailability by 30% and peak concentration 40% to 70%.

Herb/Nutraceutical: St John's wort: May decrease the levels/effects of tamsulosin. Avoid herbs with hypotensive properties (black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, Shepherd's purse); may enhance the hypotensive effect of tamsulosin. Avoid saw palmetto (due to limited experience with this combination).

Nursing: Physical Assessment/MonitoringNot for use as an antihypertensive. Assess potential for interactions with other pharmacological agents patient may be taking (eg, increased risk of hypotension). Assess results of periodic lipid panels, therapeutic effectiveness (improved urine flow), and adverse reactions (eg, "first dose" orthostatic hypotension, headache, gastrointestinal disturbance [nausea, vomiting], cough) at beginning of therapy and on a regular basis with long-term therapy. When discontinuing, dose should be tapered and blood pressure monitored closely. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPeriodic lipid panels

Patient EducationDo not take any new medication during therapy without consulting prescriber. Take as directed; do not skip dose or discontinue without consulting prescriber. May cause drowsiness, dizziness, or impaired judgment with first doses (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from sitting or lying position or when climbing stairs); nausea (frequent mouth care or sucking lozenges may help); urinary incontinence (void before taking medication); ejaculatory disturbance (reversible, may resolve with continued use of drug); diarrhea (buttermilk, boiled milk, or yogurt may help); palpitations or rapid heartbeat; respiratory difficulty, unusual cough, or sore throat; or other persistent side effects. Report palpitations or rapid heartbeat; respiratory difficulty; muscle weakness, fatigue, or pain; vision changes or hearing; rash; changes in urinary pattern; or other persistent side effects.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride:

Flomax®: 0.4 mg

Generic AvailableNo

ManufacturerBoehringer Ingelheim, Corp

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Flomax)

0.4 mg (30): $99.99

Mechanism of ActionTamsulosin is an antagonist of alpha$_{1A}$-adrenoreceptors in the prostate. Smooth muscle tone in the prostate is mediated by alpha$_{1A}$-adrenoreceptors; blocking them leads to relaxation of smooth muscle in the bladder neck and prostate causing an improvement of urine flow and decreased symptoms of BPH. Approximately 75% of the alpha$_1$-receptors in the prostate are of the alpha$_{1A}$ subtype.

Pharmacodynamics/Kinetics

Absorption: >90%

Protein binding: 94% to 99%, primarily to alpha$_1$ acid glycoprotein (AAG)

Metabolism: Hepatic via CYP3A4 and 2D6; metabolites undergo extensive conjugation to glucuronide or sulfate

Bioavailability: Fasting: 30% increase

Distribution: V$_d$: 16 L

Steady-state: By the fifth day of once-daily dosing

Half-life elimination: Healthy volunteers: 9-13 hours; Target population: 14-15 hours

Time to peak: Fasting: 4-5 hours; With food: 6-7 hours

Excretion: Urine (76%, <10% as unchanged drug); feces (21%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension and tooth disorder.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause drowsiness or insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular ConsiderationsTamsulosin should not be used as an antihypertensive agent despite its alpha-blocking properties. It may induce significant orthostatic hypotension with lightheadedness and possible loss of consciousness.

Anesthesia and Critical Care Concerns/Other ConsiderationsTamsulosin may induce significant orthostatic hypotension with lightheadedness and possible loss of consciousness.

Index TermsTamsulosin Hydrochloride

References

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International Brand NamesAlna (AT, DE); Comadex (EC); Flomax (NZ); Flomaxtra (AU); Flomaxtra XL (GB); Fokusin (BG); Harnal (CL, HK, ID, JP, PH, TH); Harnal OCAS (PH); Harnalidge D (TW); Harusin SR (KP); Josir (FR); Lutsnal (KP); Mecir LP (FR); Omexel LP (FR); Omic (BE, LU); Omix Ocas (CH); Omnexel (IE); Omnic (AR, CN, CO, CZ, DE, DK, EE, ES, FI, GR, HN, HU, IL, IT, NL, NO, PE, PL, PT, PY); Omnic OCAS (IL); Pradif (PT); Promnix (IL); Scarosin (KP); Secotex (AR, CN, CO, CR, DO, GT, HN, MX, NI, PA, PE, PY, SV, UY, VE); Sulosin (KP); Tabphyn MR (GB); Tamlosin (TW); Tamlosin SR (KP); Tamsnal SR (KP); Tamsulo (KP); Tamsulon (EC); Tamunal (KP); Urimax (IN); Zotan (TW)

Tazarotene

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(taz AR oh teen)

U.S. Brand NamesAvage™; Tazorac®

Canadian Brand NamesTazorac®

Pharmacologic CategoryAcne Products; Keratolytic Agent; Topical Skin Product, Acne

Use: Labeled IndicationsTopical treatment of facial acne vulgaris; topical treatment of stable plaque psoriasis of up to 20% body surface area involvement; mitigation (palliation) of facial skin wrinkling, facial mottled hyper-/hypopigmentation, and benign facial lentigines

Dosing: Adults**Note:** In patients experiencing excessive pruritus, burning, skin redness, or peeling, discontinue until integrity of the skin is restored, or reduce dosing to an interval the patient is able to tolerate.

Acne: Topical: Tazorac® cream/gel 0.1%: Cleanse the face gently. After the skin is dry, apply a thin film of tazarotene (2 mg/cm^2) once daily, in the evening, to the skin where the acne lesions appear; use enough to cover the entire affected area

Palliation of fine facial wrinkles, facial mottled hyper/hypopigmentation, benign facial lentigines: Topical: Avage™: Apply a pea-sized amount once daily to clean dry face at bedtime; lightly cover entire face including eyelids if desired. Emollients or moisturizers may be applied before or after; if applied before tazarotene, ensure cream or lotion has absorbed into the skin and has dried completely.

Psoriasis: Topical:

Tazorac® cream/gel 0.05% or 0.1%: Apply once daily, in the evening, to psoriatic lesions using enough (2 mg/cm^2) to cover only the lesion with a thin film to no more than 20% of body surface area. If a bath or shower is taken prior to application, dry the skin before applying. Unaffected skin may be more susceptible to irritation, avoid application to these areas. **Note:** In patients experiencing excessive pruritus, burning, skin redness, or peeling, discontinue until integrity of the skin is restored, or reduce dosing to an interval the patient is able to tolerate.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Note:** In patients experiencing excessive pruritus, burning, skin redness, or peeling, discontinue until integrity of the skin is restored, or reduce dosing to an interval the patient is able to tolerate.

Acne: Children ≥12 years: Topical: Tazorac® cream/gel 0.1%: Cleanse the face gently. After the skin is dry, apply a thin film of tazarotene (2 mg/cm^2) once daily, in the evening, to the skin where the acne lesions appear; use enough to cover the entire affected area

Psoriasis: Children ≥12 years: Topical: Tazorac® gel 0.05% or 0.1%: Apply once daily, in the evening, to psoriatic lesions using enough (2 mg/cm^2) to cover only the lesion with a thin film to no more than 20% of body surface area. If a bath or shower is taken prior to application, dry the skin before applying. Unaffected skin may be more susceptible to irritation, avoid application to these areas.

Palliation of fine facial wrinkles, facial mottled hyper/hypopigmentation, benign facial lentigines: Children ≥17 years: Topical: Avage™: Refer to adult dosing.

Administration: TopicalDo not apply to eczematous or sunburned skin; apply thin film to affected areas; avoid eyes and mouth

StorageStore at room temperature of 25°C (77°F), away from heat and direct light; do not freeze.

ContraindicationsHypersensitivity to tazarotene, other retinoids or vitamin A derivatives (isotretinoin, tretinoin, etretinate), or any component of the formulation; use in women of childbearing potential who are unable to comply with birth control requirements; pregnancy (negative pregnancy test required)

Allergy Considerations

- Retinoid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Photosensitivity: May cause photosensitivity; exposure to sunlight should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized (including use of sunscreens/protective clothing). Risk may be increased by concurrent therapy with known photosensitizers (thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides).

- Skin irritation: Treatment can increase skin sensitivity to weather extremes of wind or cold. Also, concomitant topical medications (eg, medicated or abrasive soaps, cleansers, or cosmetics with a strong drying effect) should be used with caution due to increased skin irritation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

- Women of childbearing potential: Must use adequate contraceptive measures because of potential teratogenicity.

Dosage form specific issues:

- Gel: Safety and efficacy of gel applied over >20% of BSA have not been established.

Other warnings/precautions:

- Appropriate use: For external use only; avoid contact with eyes, eyelids, and mouth. Not for use on eczematous, broken, or sunburned skin; not for treatment of lentigo maligna. Avoid application over extensive areas.

Geriatric ConsiderationsNo differences in safety or efficacy were seen when the cream formulation was administered to patients >65 years of age; may experience increased sensitivity. Increased incidence of adverse effects and lower treatment success rates were observed with the gel formulation in the treatment of psoriasis.

Pregnancy Risk FactorX

Pregnancy ConsiderationsMay cause fetal harm if administered to a pregnant woman. A negative pregnancy test should be obtained 2 weeks prior to treatment; treatment should begin during a normal menstrual period.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsPercentage of incidence varies with formulation and/or strength:

>10%: Dermatologic: Burning/stinging, desquamation, dry skin, erythema, pruritus, skin pain, worsening of psoriasis

1% to 10%: Dermatologic: Contact dermatitis, discoloration, fissuring, hypertriglyceridemia, inflammation, irritation, localized bleeding, rash

Frequency not defined:

Dermatologic: Photosensitization

Neuromuscular & skeletal: Peripheral neuropathy

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersDisease severity in plaque psoriasis during therapy (reduction in erythema, scaling, induration); routine blood chemistries (including transaminases) are suggested during long-term topical therapy; pregnancy test prior to treatment of female patients

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, accumulated photosensitivity). Assess therapeutic effectiveness and adverse response on a regular basis during therapy. Teach patient proper use, side effects/appropriate interventions, and adverse reactions to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Do not give to women of childbearing age unless they are capable of complying with contraceptive use. Instruct patients of childbearing age about appropriate contraceptive measures.

Patient EducationThis medication is for external use only; avoid using near eyes or mouth. Use exactly as directed; do not use more than recommended (severe skin reactions may occur). Avoid any other skin products (including cosmetics or personal products that may contain medications, spices, alcohols, or irritants) that are not approved by your prescriber. May cause photosensitivity, which will cause severe rash or burning (use sunblock SPF 15 or higher, wear protective clothing and eyewear, and avoid direct sunlight, sunlamps, or tanning beds). Report redness or discoloration, irritation, open sores, bleeding, burning, stinging, excessive dryness, or swelling of skin; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during treatment. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not allow anyone who may be or become pregnant to touch this medication. Consult prescriber if breast-feeding.

Application: Wash affected area gently and completely dry before applying medication. Apply a thin layer to cover affected area. Wash off any medication that gets on unaffected skin areas and wash hands thoroughly after application.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream:

Avage™: 0.1% (30 g) [contains benzyl alcohol]

Tazorac®: 0.05% (30 g, 60 g); 0.1% (30 g, 60 g) [contains benzyl alcohol]

Gel (Tazorac®): 0.05% (30 g, 100 g); 0.1% (30 g, 100 g) [contains benzyl alcohol]

Generic AvailableNo

ManufacturerAllergan, Inc

Pricing: U.S. (www.drugstore.com)

Cream (Avage)

0.1% (30): $121.78

Cream (Tazorac)

0.05% (30): $112.09

0.05% (60): $238.09

0.1% (30): $122.94

0.1% (60): $249.89

Gel (Tazorac)

0.05% (30): $116.72

0.05% (100): $361.01

0.1% (30): $122.94

0.1% (100): $382.80

Mechanism of Action Synthetic, acetylenic retinoid which modulates differentiation and proliferation of epithelial tissue and exerts some degree of anti-inflammatory and immunological activity

Pharmacodynamics/Kinetics

Duration: Therapeutic: Psoriasis: Effects have been observed for up to 3 months after a 3-month course of topical treatment

Absorption: Minimal following cutaneous application (≤6% of dose)

Distribution: Retained in skin for prolonged periods after topical application.

Protein binding: >99%

Metabolism: Prodrug, rapidly metabolized via esterases to an active metabolite (tazarotenic acid) following topical application and systemic absorption; tazarotenic acid undergoes further hepatic metabolism

Half-life elimination: 18 hours

Excretion: Urine and feces (as metabolites)

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment Use caution with drugs known to cause photosensitivity (psychotropics), effects may be augmented

International Brand Names Aguder (CN); Pzoret (CO); Sumaytene (TW); Suretin (CH, IT, MX); Tazoderm Forte (IN); Tezarac (TW); Zorac (AT, AU, BE, BG, BR, DE, ES, FR, GB, GR, IE, IL, IT, PL, SE); Zorac Gel (IL)

Tegaserod

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Tegaserod: Treatment Investigational New Drug (T-IND) Protocol Discontinued, Only Emergency Access Allowed - April 2008

Novartis, the manufacturer of tegaserod (Zelnorm®), announced the voluntary discontinuation of the T-IND protocol. In March 2007, tegaserod was discontinued from U.S. and Canadian markets, but in July 2007, the T-IND protocol was developed to allow limited availability of tegaserod for use only in the treatment of irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC) in women (<55 years of age) in which no other treatment alternatives exist. At present, Novartis has agreed to allow access to tegaserod only in emergency situations, defined as immediately life-threatening or situations which require hospitalization, under an emergency IND process. Requests for emergency use should be made to the FDA, who will either deny the request or authorize shipment of the medication by Novartis. Authorization will be denied if patients have any of the following conditions: Unstable angina, history of heart attack or stroke, hypertension, hyperlipidemia, diabetes, age ≥55 years, smoking, obesity, depression, anxiety, or suicidal ideation.

Physicians having patients who may qualify for emergency use of tegaserod may contact the FDA's Division of Drug Information via email (druginfo@fda.hhs.gov), by calling (301-796-3400), or at http://www.fda.gov/cder.

Additional information can be found at:

http://www.fda.gov/cder/drug/infopage/zelnorm/default.htm

http://www.zelnorm.com

Pronunciation(teg a SER od)

U.S. Brand NamesZelnorm®

Canadian Brand NamesZelnorm® [DSC]

Pharmacologic CategorySerotonin 5-HT$_4$ Receptor Agonist

Use: Labeled IndicationsEmergency treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in women (<55 years of age) in which no alternative therapy exists

Dosing: Adults

IBS with constipation: Females <55 years of age: Oral: 6 mg twice daily, before meals, for 4-6 weeks; may consider continuing treatment for an additional 4-6 weeks in patients who respond initially

Chronic idiopathic constipation: Females <55 years of age: Oral: 6 mg twice daily, before meals; the need for continued therapy should be reassessed periodically

Dosing: ElderlyUse in elderly women (≥55 years of age) is contraindicated.

Dosing: Renal ImpairmentC$_{max}$ and AUC of the inactive metabolite are increased with renal impairment.

Mild to moderate impairment: No dosage adjustment recommended

Severe impairment: Use is contraindicated

Dosing: Hepatic ImpairmentC$_{max}$ and AUC of tegaserod are increased with hepatic impairment.

Mild impairment: No dosage adjustment recommended; however, user caution

Moderate to severe impairment: Use is contraindicated

Administration: OralAdminister 30 minutes before meals.

Dietary ConsiderationsTake on an empty stomach, 30 minutes before meals.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from moisture.

RestrictionsAvailable in U.S. under an emergency investigational new drug (IND) process. Emergency situations are defined as immediately life-threatening or requiring hospitalization. Physicians with patients who may qualify can contact the FDA's Division of Drug Information via email (druginfo@fda.hhs.gov), by calling (301-796-3400), or at http://www.fda.gov/cder. The FDA may either deny the request or authorize shipment of Zelnorm® by Novartis. Additional information can be found at http://www.zelnorm.com or http://www.fda.gov/cder/drug/infopage/zelnorm/default.htm

ContraindicationsPer product labeling: Hypersensitivity to tegaserod or any component of the formulation; severe renal impairment; moderate or severe hepatic impairment; history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions. Treatment should not be started in patients with diarrhea or in those who experience diarrhea frequently.

Exclusion criteria under the emergency-IND process: Unstable angina, history of MI or stroke, hypertension, hyperlipidemia, diabetes, age ≥55 years, smoking, obesity, depression, anxiety, or suicidal ideation.

Warnings/Precautions

Concerns related to adverse reactions:

- Cardiovascular effects: Serious cardiovascular events (eg, MI, stroke, unstable angina) may occur; patients should seek emergency care following any sign and symptom suggestive of a serious cardiac event.
- Diarrhea: May occur after the start of treatment, most cases reported as a single episode within the first week of therapy, and may resolve with continued dosing. However, serious consequences of diarrhea (hypovolemia, syncope) have been reported; patients should be warned to contact healthcare provider immediately if they develop severe diarrhea, or diarrhea with severe cramping, abdominal pain, or dizziness.
- Intestinal ischemic events: Use has been associated with rare intestinal ischemic events; discontinue immediately with new or sudden worsening abdominal pain or rectal bleeding.

Disease-related concerns:

- Cardiovascular disease: Use will not be permitted in patients with unstable angina, a history of MI or stroke, hyperlipidemia, cigarette smoking, hypertension, or obesity.
- Depression: Use will not be permitted in patients with depression or anxiety, or with any signs of suicidal ideation or behavior.
- Diabetes: Use will not be permitted in patients with diabetes.
- Hepatic impairment: Use with caution in patients with mild hepatic impairment; not recommended with moderate or severe impairment.

Special populations:

- Elderly women: Contraindicated in women ≥55 years of age.
- Males: Safety and efficacy have not been established in males.
- Pediatrics: Safety and efficacy have not been established in children <18 years of age.

Other warnings/precautions:

- Risk vs benefit: Potential benefits should be weighed against potential risks in qualifying patients eligible for emergency-IND use.

Geriatric ConsiderationsNo dosing adjustment is required.

Pregnancy Risk FactorB

Pregnancy ConsiderationsSafety and efficacy have not been established in pregnant women. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Central nervous system: Headache (15%)

Gastrointestinal: Abdominal pain (12%)

1% to 10%:

Central nervous system: Dizziness (4%), migraine (2%)

Gastrointestinal: Diarrhea (9%; severe <1%), nausea (8%), flatulence (6%)

Neuromuscular & skeletal: Back pain (5%), arthropathy (2%), leg pain (1%)

<1%: Albuminuria, ALT increased, angina pectoris, appendicitis, appetite increased, arrhythmia, asthma, AST increased, breast carcinoma, bundle branch block, cholecystitis, concentration impaired, CPK increased, cramps, depression, diaphoresis, emotional lability, eructation, facial edema, fecal incontinence, flushing, hypotension, irritable colon, menorrhagia, micturition, miscarriage, ovarian cyst, pain, polyuria, pruritus, renal pain, serum bilirubin increased, sleep disorder, subileus, suicide attempt, supraventricular tachycardia, syncope, tenesmus, vertigo

Postmarketing and/or case reports: Alopecia, bile duct stone, cholecystitis (with increased transaminases), gangrenous bowel, hepatitis, hypersensitivity reaction, hypokalemia (secondary to diarrhea), ischemic colitis, mesenteric ischemia, MI, rectal bleeding, sphincter of Oddi spasm (suspected), severe diarrhea (complicated by hypovolemia, hypotension, syncope), stroke, unstable angina

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsFood: Bioavailability is decreased by 40% to 65% and C_{max} is decreased by 20% to 40% when taken with food. T_{max} is prolonged from 1 hour up to 2 hours when taken following a meal, but decreased to 0.7 hours when taken 30 minutes before a meal.

Nursing: Physical Assessment/Monitoring**For emergency use only under FDA emergency investigational new drug process.** Evaluate therapeutic effectiveness (improved bowel function) and adverse response (eg, cardiac event, clinically-significant diarrhea [hypovolemia, hypotension, syncope], ischemic colitis [rectal bleeding, bloody diarrhea, abdominal pain]) frequently when beginning therapy and at regular intervals during treatment. Teach patient appropriate use, side effects/appropriate interventions, and importance of reporting adverse reactions.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber.

Take exactly as directed, on an empty stomach, 30 minutes before meals. If you miss a dose, skip that dose and continue with regular schedule; do not double doses. Effectiveness of treatment will need to be evaluated by prescriber; maintain contact/appointment schedule as directed. May cause headache or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea or flatulence (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea. Stop taking Zelnorm® and contact prescriber immediately with any new or sudden worsening abdominal pain or rectal bleeding, or severe or bloody diarrhea. Seek emergency medical care immediately if you experience severe chest pain, shortness of breath, dizziness, sudden onset of weakness, or difficulty walking or talking. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Zelnorm®: 2 mg, 6 mg

Generic AvailableNo

ManufacturerNovartis Pharmaceuticals Corp

Pricing: U.S. (www.drugstore.com)

Tablets (Zelnorm)

2 mg (60): $198.24

6 mg (60): $198.24

Mechanism of ActionTegaserod is a partial neuronal 5-HT$_4$ receptor agonist. Its action at the receptor site leads to stimulation of the peristaltic reflex and intestinal secretion, and moderation of visceral sensitivity.

Pharmacodynamics/Kinetics

Distribution: V$_d$: 368 ± 223 L

Protein binding: 98% primarily to α_1-acid glycoprotein

Metabolism: GI: Hydrolysis in the stomach; Hepatic: Oxidation, conjugation, and glucuronidation; metabolite (negligible activity); significant first-pass effect

Bioavailability: Fasting: 10%

Half-life elimination: I.V.: 11 ± 5 hours

Time to peak: 1 hour

Excretion: Feces (~66% as unchanged drug); urine (~33% as metabolites)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness and headache; may rarely cause depression, mood lability, and insomnia

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; use caution with SSRIs

Index TermsHTF919; Tegaserod Maleate

International Brand NamesColonaid (CN, PY); Coloserod (UY); Gasprid (CO); Prozerada (DO, GT, HN, NI); Tegibs (IN); Zelmac (AR, AU, BR, CH, CL, CZ, EC, HK, ID, IL, KP, MX, MY, NZ, PE, PK, SG, TH, TW, VE); Zelnorm (PH)

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Telbivudine Use With Peginterferon Alfa-2a: Increased Risk of Peripheral Neuropathy - March 2008

Novartis Pharmaceuticals Canada Inc, in conjunction with Health Canada, has issued a “Dear Healthcare Professional” letter concerning an increased risk for peripheral neuropathy in chronic hepatitis B patients receiving telbivudine (Sebivo®) concomitantly with peginterferon alfa-2a (Pegasys®) versus telbivudine or peginterferon as monotherapy. In clinical trials, the incidence of peripheral neuropathy associated with telbivudine monotherapy was rare (0.3%). Conversely, the incidence associated with peginterferon alfa-2a monotherapy is more frequent (≥1% to <5%), and it appears the risk of peripheral neuropathy with the concomitant use of the two agents is further increased.

In a small ongoing clinical trial (n=48), peripheral neuropathy in association with the combination therapy occurred in 17% of patients and ~10% of these were described as severe. Symptoms included weakness, paresthesia, and leg pain (disabling in one patient), and were observed 1-6 months after initiation of therapy in those with severe reactions. Discontinuation of therapy may lead to symptom resolution; however, the outcomes for those patients discontinuing treatment in the described study are still either unknown or unresolved 1-6 months after discontinuing therapy. It is unknown if this increased risk applies to other pegylated or standard interferon agents. Patients receiving telbivudine concomitantly with an interferon product should be advised to consult their physician or healthcare professional.

Additional information can be found at

http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2008/sebivo_hpc-cps_e.html

Pronunciation(tel BI vyoo deen)

U.S. Brand NamesTyzeka™

Canadian Brand NamesSebivo®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)

Use: Labeled IndicationsTreatment of chronic hepatitis B with evidence of viral replication and either persistent transaminase elevations or histologically-active disease

Dosing: Adults**Chronic hepatitis B:** Oral: 600 mg once daily. **Note:** Usual treatment duration is at least 1 year and varies with HBeAg status, consult current guidelines and literature.

Dosing: Pediatric**Chronic hepatitis B:** Oral: Adolescents ≥16 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} 30-49 mL/minute: 600 mg every 48 hours

Cl_{cr} <30 mL/minute (not requiring dialysis): 600 mg every 72 hours

End-stage renal disease: 600 mg every 96 hours

Hemodialysis: Administer after dialysis session

Dosing: Hepatic Impairment No adjustment necessary.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralMay be administered without regard to food.

Dietary ConsiderationsMay be taken without regard to food.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to telbivudine or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Chronic hepatitis B: See “Disease-related concerns” below.

- Lactic acidosis/hepatomegaly: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).

- Myopathy: Use has been associated with myopathy (unexplained muscle aches and/or muscle weakness in conjunction with serum creatine kinase increases) several weeks to months after initiation of telbivudine; interrupt therapy if myopathy suspected and discontinue therapy if myopathy diagnosed.

Disease-related concerns:

- Chronic hepatitis B: **[U.S. Boxed Warning]: Severe, acute exacerbation of hepatitis B may occur upon discontinuation.** Monitor liver function several months after stopping treatment; reinitiation of antihepatitis B therapy may be required.

- Human immunodeficiency virus: Telbivudine does not exhibit any clinically-relevant activity against HIV type 1.

- Renal impairment: Use caution in patients with moderate to severe renal dysfunction and end stage renal disease (ESRD); dosing adjustment required (Cl_{cr} <50 mL/minute).

Concurrent drug therapy:

- Peginterferon alfa-2a: An increased risk of peripheral neuropathy (rarely observed with telbivudine monotherapy), has been associated with the concomitant use of telbivudine and peginterferon alfa-2a in a small study (n=48). Symptoms including weakness, paresthesia, and leg pain (disabling in one patient) have been observed 1-6 months after initiation of therapy. Symptoms may resolve with discontinuation of therapy; however, in the described study, outcomes for affected patients are either unresolved or not known 1-6 months after discontinuing therapy. It is unknown if this increased risk applies to other pegylated or standard interferon agents.

Special populations:

- Coinfections: Safety and efficacy have not been studied in patients coinfected with HIV, hepatitis C virus (HCV) or hepatitis D virus (HDV).

- Liver transplant recipients: Safety and efficacy in liver transplant patients have not been established; monitor renal function in patients receiving concurrent therapy of cyclosporine or tacrolimus.

- Pediatrics: Safety and efficacy have not been established in children <16 years of age.

Other warnings/precautions:

- Resistance: Cross-resistance among hepatitis B antivirals may develop; use caution in patients failing previous lamivudine therapy.

Geriatric ConsiderationsInsufficient clinical data in elderly to determine differences between aged patients and younger patients. Since elderly often have Cl_{cr} <50 mL/minute, dosage should be determined accordingly.
Pregnancy Risk FactorB
Pregnancy ConsiderationsTeratogenic effects have not been observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263).
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%:

Central nervous system: Fatigue (12%), malaise (12%), headache (11%)

Gastrointestinal: Abdominal pain (12%)

Neuromuscular & skeletal: CPK increased (72%; grades 3/4: 9%)

Respiratory: Upper respiratory tract infection (14%), nasopharyngitis (11%)

1% to 10%:

Central nervous system: Dizziness (4%), fever (4%), insomnia (3%)

Dermatologic: Rash (4%)

Endocrine & metabolic: Lipase increased (2%)

Gastrointestinal: Nausea (7%), vomiting (7%), diarrhea (7%), dyspepsia (3%)

Hematologic: Neutropenia (2%)

Hepatic: ALT increased (grades 3/4: 3% to 4%), AST increased (grades 3/4: 3%)

Neuromuscular & skeletal: Arthralgia (4%), back pain (4%), myalgia (3%)

Respiratory: Cough (7%), pharyngolaryngeal pain (5%)

Miscellaneous: Flu-like syndrome (7%), postprocedural pain (7%)

<1%: Amylase increased, bilirubin increased, gastritis, thrombocytopenia

Postmarketing and/or case reports: Peripheral neuropathy (increased incidence observed when used concomitantly with peginterferon alfa-2a)

Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb Interactions

Ethanol: Should be avoided in hepatitis B infection due to potential hepatic toxicity.

Food: Does not have a significant effect on telbivudine absorption.

Monitoring ParametersLFTs (eg, AST and ALT) periodically during therapy and for several months following discontinuation of therapy; renal function prior to initiation and periodically during treatment; signs and symptoms of peripheral neuropathy (eg, weakness, paresthesia, leg pain) or myopathy (eg, unexplained muscle pain, tenderness or weakness); serum creatine kinase)

Nursing: Physical Assessment/MonitoringUse caution in presence of impaired hepatic or renal function. Assess potential for interactions with other pharmacological agents patient may be taking. Assess results of laboratory tests (eg, LFTs, renal function, and serum creatinine kinase) prior to therapy, periodically during therapy, and for several months following discontinuation. Assess therapeutic effectiveness (suppression of HBV DNA) and adverse reactions on a regular basis throughout therapy (eg, peripheral neuropathy or myopathy [may be necessary to discontinue drug], gastrointestinal effects [pain or vomiting], upper respiratory infection). Patients should be assessed for several months following discontinuation of therapy for possible clinical exacerbations. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsLFTs (eg, AST and ALT) periodically during therapy and for several months following discontinuation of therapy; renal function prior to initiation and periodically during treatment; serum creatine kinase

Patient EducationDo not take any new prescription or OTC medications, or herbal products during therapy without consulting prescriber. This medication does not stop you from spreading HBV to others; consult prescriber about safe sex practices and do not share needles or personal items that may have blood or body fluids on them. Take as directed with or without food. Do not discontinue without consulting prescriber (symptoms may worsen and/or become very serious). Avoid alcohol (may increase potential for liver damage. Maintain adequate hydration (2-3 L/day of fluids, unless instructed to restrict fluid intake). This medication may be prescribed with a combination of other medications; time these medications as directed by prescriber. Frequent blood tests may be required with prolonged therapy. May cause nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); dizziness or fatigue (use caution when driving or engaging in tasks that require alertness until response to drug is known); headache, fever, or muscle pain (an analgesic may be recommended). Report immediately any signs of lactic acidosis (eg, persistent lethargy or fatigue, unusual muscle pain or weakness, feel cold [especially in arms and legs], rapid or irregular heart beat, or difficulty breathing) or liver toxicity (eg, yellowing of eyes or skin, pale stool and dark urine); upper respiratory infection or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Tyzeka™: 600 mg

Generic AvailableNo
ManufacturerNovartis Pharma
Pricing: U.S. (www.drugstore.com)

Tablets (Tyzeka)

600 mg (30): $633.22

Mechanism of ActionTelbivudine, a synthetic thymidine nucleoside analogue (L-enantiomer of thymidine), is intracellularly phosphorylated to the active triphosphate form, which competes with the natural substrate, thymidine 5'-triphosphate, to inhibit hepatitis B viral DNA polymerase; enzyme inhibition blocks reverse transcriptase activity thereby reducing viral DNA replication.

Pharmacodynamics/Kinetics

Distribution: V_d > total body water

Protein binding: 3%

Metabolism: No metabolites detected

Half-life elimination: Terminal: 40-49 hours

Time to peak, plasma: 1-4 hours

Excretion: Urine (as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusFatigue and malaise are common; may cause dizziness or insomnia
Mental Health: Effects on Psychiatric TreatmentMay cause myopathy with serum creatine kinase elevations, weeks to months after initiation; consider this when evaluating patients for neuroleptic malignant syndrome and malignant hyperthermia. May cause neutropenia; use caution with clozapine and carbamazepine.
Index TermsL-Deoxythymidine
References

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International Brand NamesSebivo (AR, CH, CL, CZ, DK, EE, GB, HK, ID, IL, MY, NO, NZ, PE, PH, SE, SG, TH, TW); Sevibo (KP)

Telithromycin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(tel ith roe MYE sin)

U.S. Brand NamesKetek®

Canadian Brand NamesKetek®

Pharmacologic CategoryAntibiotic, Ketolide

Use: Labeled IndicationsTreatment of community-acquired pneumonia (mild-to-moderate) caused by susceptible strains of *Streptococcus pneumoniae* (including multidrug-resistant isolates), *Haemophilus influenzae*, *Chlamydophila pneumoniae*, *Moraxella catarrhalis*, and *Mycoplasma pneumoniae*

Dosing: Adults

Community-acquired pneumonia: Oral: 800 mg once daily for 7-10 days

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricTonsillitis/pharyngitis (unlabeled use; Canadian indication): Children ≥13 years: Oral: Refer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} <30 mL/minute, including dialysis:

U.S. product labeling: 600 mg once daily; when renal impairment is accompanied by hepatic impairment, reduce dosage to 400 mg once daily

Canadian product labeling: Reduce dose to 400 mg once daily

Hemodialysis: Administer following dialysis

Dosing: Hepatic ImpairmentNo adjustment recommended, unless concurrent severe renal impairment is present.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at 15°C to 30°C (59°F to 86°F).

RestrictionsAn FDA-approved Medication Guide is available and must be dispensed with every prescription. Copies may be found at: http://www.fda.gov/cder/foi/label/2007/021144s012medg.pdf

ContraindicationsHypersensitivity to telithromycin, macrolide antibiotics, or any component of the formulation; myasthenia gravis; history of hepatitis and/or jaundice associated with telithromycin or other macrolide antibiotic use; concurrent use of cisapride or pimozide

Allergy Considerations

- Macrolide Allergy

Warnings/Precautions

Boxed warnings:

- Myasthenia gravis: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Altered cardiac conduction: May prolong QT_c interval, leading to a risk of ventricular arrhythmias; closely-related antibiotics have been associated with malignant ventricular arrhythmias and torsade de pointes. Avoid in patients with prolongation of QTc interval due to congenital causes, history of long QT syndrome, uncorrected electrolyte disturbances (hypokalemia or hypomagnesemia), significant bradycardia (<50 bpm), or concurrent therapy with QT_c-prolonging drugs (eg, class Ia and class III antiarrhythmics). Avoid use in patients with a prior history of confirmed cardiogenic syncope or ventricular arrhythmias while receiving macrolide antibiotics or other QT_c-prolonging drugs.

- Hepatic effects: Acute hepatic failure and severe liver injury, including hepatitis and hepatic necrosis (leading to some fatalities) have been reported, in some cases after only a few doses; if signs/symptoms of hepatitis or liver damage occur, discontinue therapy and initiate liver function tests.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea and pseudomembranous colitis.

- Syncope: May cause loss of consciousness (possibly vagal-related); caution patients that these events may interfere with ability to operate machinery or drive, and to use caution until effects are known.

- Visual disturbances: May cause severe visual disturbances (eg, changes in accommodation ability, diplopia, blurred vision).

Disease-related concerns:

- Myasthenia gravis: **[U.S. Boxed Warning]: Life-threatening (including fatal) respiratory failure has occurred in patients with myasthenia gravis;** use in these patients is contraindicated.

- Renal impairment: Use with caution in patients with renal impairment; severe impairment (Cl_{cr} <30 mL/minute) requires dosage adjustment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <13 years of age per Canadian approved labeling and <18 years of age per U.S. approved labeling.

Geriatric ConsiderationsBioavailability (57%) equivalent in persons ≥65 years compared to younger adults; although a 1.4- to 2-fold increase in AUC found in older adults. No dosage adjustment required.

Pregnancy Risk FactorC

Pregnancy ConsiderationsBecause adverse effects were observed in some animal studies, telithromycin is classified pregnancy category C. There are no adequate and well-controlled studies of telithromycin in pregnant women.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if telithromycin is excreted in breast milk. The manufacturer recommends caution if using telithromycin in a breast-feeding woman.

Pregnancy & Lactation, In-Depth

- Telithromycin in Pregnancy & Lactation

Adverse Reactions

>10%: Gastrointestinal: Diarrhea (10% to 11%)

2% to 10%:

Central nervous system: Headache (2% to 6%), dizziness (3% to 4%)

Gastrointestinal: Nausea (7% to 8%), vomiting (2% to 3%), loose stools (2%), dysgeusia (2%)

≥0.2% to <2%:

Central nervous system: Fatigue, insomnia, somnolence, vertigo

Dermatologic: Rash

Gastrointestinal: Abdominal distension, abdominal pain, anorexia, constipation, dyspepsia, flatulence, gastritis, gastroenteritis, GI upset, glossitis, stomatitis, watery stools, xerostomia

Genitourinary: Vaginal candidiasis, vaginitis

Hematologic: Platelets increased

Hepatic: Transaminases increased

Ocular: Blurred vision, accommodation delayed, diplopia

Miscellaneous: Candidiasis, diaphoresis increased

<0.2%: Alkaline phosphatase increased, anxiety, bilirubin increased, bradycardia, eczema, eosinophilia, erythema multiforme, flushing, hepatitis, hypotension, jaundice, paresthesia, pruritus, urticaria

Postmarketing and/or case reports: Acute repiratory failure, allergic reaction, anaphylaxis, angioedema, arrhythmia, edema (facial), hepatocellular injury (including necrosis), liver failure, loss of consciousness (may be vagal-related), muscle cramps, myasthenia gravis exacerbation (rare), pancreatitis, palpitation, pseudomembranous colitis, QT_c prolongation, syncope, torsade de pointes

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak), 3A4 (strong)

Drug Interactions

Alfentanil: Macrolide Antibiotics may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): Macrolide Antibiotics may decrease the metabolism of Antifungal Agents (Azole Derivatives, Systemic). Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Macrolide Antibiotics. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Macrolide Antibiotics may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

BusPIRone: Macrolide Antibiotics may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Macrolide Antibiotics may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: Macrolide Antibiotics may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Cardiac Glycosides: Macrolide Antibiotics may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cilostazol: Macrolide Antibiotics may decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Cisapride: Macrolide Antibiotics may decrease the metabolism of Cisapride. *Risk X: Avoid combination*

Clopidogrel: Macrolide Antibiotics may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Clozapine: Macrolide Antibiotics may decrease the metabolism of Clozapine. *Risk D: Consider therapy modification*

Colchicine: Macrolide Antibiotics may decrease the metabolism of Colchicine. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Macrolide Antibiotics may decrease the metabolism of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

CycloSPORINE: Macrolide Antibiotics may decrease the metabolism of CycloSPORINE. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disopyramide: Macrolide Antibiotics may enhance the QTc-prolonging effect of Disopyramide. Macrolide Antibiotics may decrease the metabolism of Disopyramide. *Risk X: Avoid combination*

Eletriptan: Macrolide Antibiotics may decrease the metabolism of Eletriptan. *Risk D: Consider therapy modification*

Eplerenone: Macrolide Antibiotics may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Macrolide Antibiotics may enhance the adverse/toxic effect of Ergot Derivatives. Specifically leading the development of ergotism. **Exceptions:** Cabergoline. *Risk D: Consider therapy modification*

Etravirine: May decrease the serum concentration of Macrolide Antibiotics. Clarithromycin AUC is reduced and levels of the active metabolite (14-hydroxy-clarithromycin) are modestly increased. Management: For the treatment of *Mycobacterium avium* complex, consider changing to alternative agent, such as azithromycin. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Macrolide Antibiotics may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Pravastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Phosphodiesterase 5 Inhibitors: Macrolide Antibiotics may decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Macrolide Antibiotics may decrease the metabolism of Pimozide. QTc prolongation is a risk. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Macrolide Antibiotics may decrease the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Macrolide Antibiotics may increase the serum concentration of Repaglinide. *Risk C: Monitor therapy*

Rifamycin Derivatives: Macrolide Antibiotics may decrease the metabolism of Rifamycin Derivatives. **Exceptions:** Rifapentine. *Risk D: Consider therapy modification*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Selective Serotonin Reuptake Inhibitors: Macrolide Antibiotics may decrease the metabolism of Selective Serotonin Reuptake Inhibitors. **Exceptions:** Fluvoxamine; PARoxetine. *Risk C: Monitor therapy*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Macrolide Antibiotics may decrease the metabolism of Sirolimus. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

Tacrolimus: Macrolide Antibiotics may increase the serum concentration of Tacrolimus. *Risk C: Monitor therapy*

Temsirolimus: Macrolide Antibiotics may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Macrolide Antibiotics may decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Zopiclone: Macrolide Antibiotics may increase the serum concentration of Zopiclone. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/nutraceutical: St John's wort: May decrease the levels/effects of telithromycin.

Monitoring ParametersLiver function tests; signs/symptoms of liver failure (eg, jaundice, fatigue, malaise, anorexia, nausea, bilirubinemia, acholic stools, liver tenderness, hepatomegaly); visual acuity

Nursing: Physical Assessment/MonitoringAssess culture and sensitivity report and previous experience with telithromycin or macrolide antibiotics prior to therapy. Assess patient for contraindications (history of hepatic dysfunction, myasthenia gravis, uncorrected electrolyte imbalance, history of prolonged QT interval). Assess for potential interactions with other pharmacologic agents patient may be using that may increase potential for adverse interactions. Assess results of laboratory tests (LFTs), therapeutic effectiveness (resolution of infection), and adverse reactions (eg, hepatic necrosis or failure, gastrointestinal disturbance [nausea, vomiting, diarrhea], CNS [vertigo, insomnia], rash, opportunistic infection, QT prolongation) during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report (especially any signs of jaundice or hepatic impairment).

Monitoring: Lab TestsCulture and sensitivity; liver function tests

Patient EducationYou will receive a medication guide with your prescription; read this information completely. Do not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. Take as directed, with or without food. Do not chew or crush tablets. Take complete prescription even if you are feeling better. May cause headache, dizziness, insomnia, blurred visions, or difficulty focusing (use caution when driving or engaging in tasks that require alertness until response to drug is known); nausea, vomiting, or loss of appetite (frequent small meals and frequent mouth care may help); diarrhea; or watery stools (boiled milk, buttermilk, or yogurt may help - consult prescriber if persistent). If you experience visual difficulties, loss of consciousness (fainting), dark urine, pale stool, or yellowing of skin or eyes, contact prescriber immediately before taking another dose. Report chest pain, palpitations, irregular heart beat; flushing or facial swelling; CNS disturbance (dizziness, headache, anxiety, abnormal dreams, tremor); unusual muscle weakness; skin rash; vaginal itching, burning, or discharge; or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Ketek®: 300 mg [not available in Canada], 400 mg

Generic AvailableNo

ManufacturerAventis Pharma (Canada)

Pricing: U.S. (www.drugstore.com)

Tablets (Ketek)

400 mg (60): $311.99

Tablets (Ketek Pak)

400 mg (10): $57.20

Mechanism of ActionInhibits bacterial protein synthesis by binding to two sites on the 50S ribosomal subunit. Telithromycin has also been demonstrated to alter secretion of IL-1alpha and TNF-alpha; the clinical significance of this immunomodulatory effect has not been evaluated.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: 2.9 L/kg

Protein binding: 60% to 70%; primarily to albumin

Metabolism: Hepatic, via CYP3A4 (50%) and non-CYP-mediated pathways

Bioavailability: 57% (significant first-pass metabolism)

Half-life elimination: 10 hours

Time to peak, plasma: 1 hour

Excretion: Urine (13% unchanged drug, remainder as metabolites); feces (7%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation), glossitis, stomatitis, and tooth discoloration.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsTelithromycin is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay cause dizziness, fatigue, somnolence, or insomnia; may rarely cause nervousness, tremor, and abnormal dreams

Mental Health: Effects on Psychiatric TreatmentMay prolong QT_c interval; use caution with thioridazine and ziprasidone. Gastrointestinal side effects are common; these effects may be additive with concomitant use of SSRIs, lithium, and valproic acid. Telithromycin may increase the effects of alprazolam, carbamazepine, ergot alkaloids, midazolam, mirtazapine, nefazodone, pimozide, triazolam, and venlafaxine. Concomitant use with ergots, midazolam, pimozide, or triazolam is generally contraindicated. Nefazodone may increase the effects of telithromycin. Carbamazepine, phenobarbital, and phenytoin may decrease the effects of telithromycin.

Index TermsHMR 3647

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International Brand NamesKetek (AR, AT, BE, BG, BR, CH, CN, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, HN, IE, IL, IT, KP, MX, NI, NL, NO, PA, PE, PL, PT, PY, RU, SE, SV, TH, TR, TW, UY, VE); Levviax (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Telmisartan and Hydrochlorothiazide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(tel mi SAR tan & hye droe klor oh THYE a zide)

U.S. Brand NamesMicardis® HCT

Canadian Brand NamesMicardis® Plus

Pharmacologic CategoryAngiotensin II Receptor Blocker; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension; combination product should not be used for initial therapy

Dosing: Adults**Hypertension:** Oral: Replacement therapy: Combination product can be substituted for individual titrated agents. Initiation of combination therapy when monotherapy has failed to achieve desired effects:

Patients currently on telmisartan: Initial dose if blood pressure is not currently controlled on monotherapy of 80 mg telmisartan: Telmisartan 80 mg/hydrochlorothiazide 12.5 mg once daily; may titrate up to telmisartan 160 mg/hydrochlorothiazide 25 mg if needed.

Patients currently on hydrochlorothiazide: Initial dose if blood pressure is not currently controlled on monotherapy of 25 mg once daily: Telmisartan 80 mg/hydrochlorothiazide 12.5 mg once daily or telmisartan 80 mg/hydrochlorothiazide 25 mg once daily; may titrate up to telmisartan 160 mg/hydrochlorothiazide 25 mg if blood pressure remains uncontrolled after 2-4 weeks of therapy. Patients who develop hypokalemia may be switched to telmisartan 80 mg/hydrochlorothiazide 12.5 mg.

Dosing: ElderlyRefer to adult dosing. Monitor renal function.

Dosing: Renal Impairment

Cl_{cr} >30 mL/minute: Usual recommended dose

Cl_{cr} ≤30 mL/minute: Not recommended

Dosing: Hepatic ImpairmentDosing should be started at telmisartan 40 mg/hydrochlorothiazide 12.5 mg. Do **not** use in patients with severe hepatic impairment.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsMay be given with or without food.

StorageStore at 20°C (77°C). Protect from moisture. Do not remove from blister pack until needed.

ContraindicationsHypersensitivity to telmisartan, hydrochlorothiazide, or any component of the formulation; sulfonamide-derived drugs; anuria

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Electrolyte disturbances: Hyperkalemia may occur with angiotensin II receptor antagonists; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration of renal function and/or increases in serum creatinine, particularly in patients dependent on renin-angiotensin-aldosterone system; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use with caution in patients who have biliary obstructive disorders or hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.

- Renal artery stenosis: Use telmisartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use telmisartan with caution with pre-existing renal insufficiency and severe renal impairment. Avoid hydrochlorothiazide in severe renal disease (ineffective); may precipitate azotemia; discontinue or consider withholding if renal impairment occurs.

- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Geriatric ConsiderationsNo dosing adjustment needed based on age. Monitor renal function.
Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)
Pregnancy Considerations

Telmisartan: C (1st trimester); D (2nd and 3rd trimesters): Discontinue as soon as possible when pregnancy is detected. Drugs that act directly on renin-angiotensin can cause fetal and neonatal morbidity and death. Adverse effects to the fetus appear to be limited to the 2nd and 3rd trimesters.

Hydrochlorothiazide: B (per manufacturer); D (based on expert analysis): Although there are no adequate and well-controlled studies using hydrochlorothiazide in pregnancy, thiazide diuretics may cause an increased risk of congenital defects. Hypoglycemia, hypokalemia, hyponatremia, jaundice, and thrombocytopenia are also reported as possible complications to the fetus or newborn.

LactationEnters breast milk/not recommended
Breast-Feeding ConsiderationsIt is not known if telmisartan is excreted in human breast milk, use during breast-feeding is not recommended. Thiazides are excreted in human breast milk; benefits to the mother should be weighed against possible risk to the newborn if used in a nursing woman.
Adverse ReactionsThe following reactions have been reported with the combination product; see individual agents for additional adverse reactions that may be expected from each agent.

2% to 10%:

Central nervous system: Dizziness (5%)

Gastrointestinal: Diarrhea (3%), nausea (2%)

Renal: BUN increased (3%)

Respiratory: Upper respiratory tract infection (8%), sinusitis (4%)

Miscellaneous: Flu-like syndrome (2%)

<2%: Abdominal pain, back pain, bilirubin increased, bronchitis, dyspepsia, hematocrit decreased, hemoglobin decreased, hypokalemia, liver enzymes increased, pharyngitis, postural hypotension, rash, serum creatinine increased, tachycardia, vomiting; rhabdomyolysis has been reported (rarely) with angiotensin-receptor antagonists

Postmarketing and/or case reprots: Angioneurotic edema, atrial fibrillation, chest pain, cough, diaphoresis increased, erectile dysfunction, erythema, fatigue, headache, hyperkalemia, hypersensitivity, hypotension, muscle cramps, myalgia, MI, syncope, urinary tract infection, urticaria

Metabolism/Transport EffectsTelmisartan: **Inhibits** CYP2C19 (weak)
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Cardiac Glycosides: Telmisartan may increase the serum concentration of Cardiac Glycosides. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may potentiate orthostatic hypotension).
Monitoring ParametersBlood pressure, serum electrolytes, BUN, creatinine, symptomatic hypotension, and tachycardia
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN]: Canadian brand name

Tablet:

Micardis® HCT [available in U.S.]:

40/12.5: Telmisartan 40 mg and hydrochlorothiazide 12.5 mg

80/12.5: Telmisartan 80 mg and hydrochlorothiazide 12.5 mg

80/25: Telmisartan 80 mg and hydrochlorothiazide 25 mg

Micardis® Plus [CAN]: 80/25: Telmisartan 80 mg and hydrochlorothiazide 25 mg [Not available in U.S.]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Micardis HCT)

40-12.5 mg (30): $79.70

80-12.5 mg (30): $87.35

80-25 mg (30): $93.89

Mechanism of Action

Telmisartan: Telmisartan is an angiotensin receptor antagonist. Angiotensin II acts as a vasoconstrictor. In addition to causing direct vasoconstriction, angiotensin II also stimulates the release of aldosterone. Once aldosterone is released, sodium as well as water are reabsorbed. The end result is an elevation in blood pressure. Telmisartan binds to the AT1 angiotensin II receptor. This binding prevents angiotensin II from binding to the receptor thereby blocking the vasoconstriction and the aldosterone secreting effects of angiotensin II.

Hydrochlorothiazide: Inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Hydrochlorothiazide
- Telmisartan

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or fatigue; may rarely cause insomnia, anxiety, nervousness, or depression

Mental Health: Effects on Psychiatric TreatmentMay decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels. May cause photosensitivity; concomitant use with psychotropics may further the risk. Use sunscreen, wear protective clothing and eyewear and avoid direct sunlight.

Cardiovascular Considerations

Hypertension: According to the 2003 JNC 7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Index TermsHydrochlorothiazide and Telmisartan

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International Brand Names Kinzalcomb (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Micardis HCT (BR); Micardis Plus (AR, AT, AU, BE, BG, CH, CN, CO, CR, CZ, DE, DK, DO, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IT, KP, MY, NI, NL, NO, PA, PE, PH, PT, PY, RU, SE, SG, SV, TH, TR, TW, UY, VE); Pritorplus (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, KP, NL, NO, PH, PT, RU, SE, TR); Telisid-H (IN)

Telmisartan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(tel mi SAR tan)

U.S. Brand NamesMicardis®

Canadian Brand NamesMicardis®

Pharmacologic CategoryAngiotensin II Receptor Blocker

Use: Labeled IndicationsTreatment of hypertension; may be used alone or in combination with other antihypertensive agents

Dosing: Adults**Hypertension:** Oral: Initial: 40 mg once daily; usual maintenance dose range: 20-80 mg/day. Patients with volume depletion should be initiated on the lower dosage with close supervision.

Dosing: ElderlyInitial: 20 mg/day; usual maintenance dose range: 20-80 mg/day

Dosing: Renal ImpairmentNo adjustment required; hemodialysis patients are more susceptible to orthostatic hypotension

Dosing: Hepatic ImpairmentSupervise patients closely.

Dietary ConsiderationsMay be taken without regard to food.

ContraindicationsHypersensitivity to telmisartan or any component of the formulation

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Hyperkalemia: May occur; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.
- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.
- Hepatic impairment: Use with caution in patients who have biliary obstructive disorders or hepatic dysfunction.
- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.
- Renal artery stenosis: Use telmisartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.
- Renal impairment: Use with caution with pre-existing renal insufficiency and severe renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Geriatric ConsiderationsNo initial dose adjustment is required. There appear to be no significant differences in response between the elderly and younger adults (limited data available). Monitor closely during initiation phase. Many elderly may be volume depleted due to diuretics and/or blunted thirst reflex resulting in inadequate fluid intake.

Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)

Pregnancy ConsiderationsMedications which act on the renin-angiotensin system are reported to have the following fetal/neonatal effects: Hypotension, neonatal skull hypoplasia, anuria, renal failure, and death; oligohydramnios is also reported. These effects are reported to occur with exposure during the second and third trimesters. There are no adequate and well-controlled studies in pregnant women. **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

LactationEnters breast milk/not recommended

Adverse ReactionsMay be associated with worsening of renal function in patients dependent on renin-angiotensin-aldosterone system.

1% to 10%:

Cardiovascular: Hypertension (1%), chest pain (1%), peripheral edema (1%)

Central nervous system: Headache (1%), dizziness (1%), pain (1%), fatigue (1%)

Gastrointestinal: Diarrhea (3%), dyspepsia (1%), nausea (1%), abdominal pain (1%)

Genitourinary: Urinary tract infection (1%)

Neuromuscular & skeletal: Back pain (3%), myalgia (1%)

Respiratory: Upper respiratory infection (7%), sinusitis (3%), pharyngitis (1%), cough (2%)

<1% (Limited to important or life-threatening): Abdominal pain, abnormal ECG, abnormal vision, abscess, allergic reaction, anemia, angina, angioedema, angioneurotic edema, anxiety, arthralgia, arthritis, asthma, atrial fibrillation, back pain, bradycardia, bronchitis, BUN increased, cerebrovascular disorder, CHF, conjunctivitis, constipation, cramps, creatinine kinase increased, cystitis, depression, dermatitis, diabetes mellitus, diaphoresis, dry mouth, dyspnea, earache, eczema, edema, enteritis, epistaxis, eosinophilia, erythema, erectile dysfunction, erythema, facial edema, fever, flatulence, flushing, frequent urination, fungal infection, gastroenteritis, gout, hemoglobin decreased, hemorrhoids, hepatic dysfunction, hypercholesterolemia, hyperkalemia, hypersensitivity, hypotension, impotence, insomnia, liver enzymes increased, malaise, MI, migraine, muscle cramps, nervousness, orthostatic hypotension (more frequent in dialysis patients), otitis media, palpitation, paresthesia, pruritus, renal dysfunction, renal failure, rhabdomyolysis, rash, reflux, rhinitis, serum creatinine increased, somnolence, syncope, tachycardia, thrombocytopenia, tinnitus, toothache, uric acid increased, urticaria, vertigo, weakness

Metabolism/Transport Effects**Inhibits** CYP2C19 (weak)

Drug Interactions

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Cardiac Glycosides: Telmisartan may increase the serum concentration of Cardiac Glycosides. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersSupine blood pressure, electrolytes, serum creatinine, BUN, urinalysis, symptomatic hypotension, and tachycardia

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, increased risk of hypercalcemia or increased hypotensive effects). Assess results of laboratory tests, therapeutic effectiveness (reduced hypertension), and adverse response (eg, hypotension, diarrhea, URI, cough) on a regular basis during therapy. Teach patient proper use, need for regular blood pressure monitoring, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsMonitor electrolytes, serum creatinine, BUN, urinalysis, symptomatic hypotension, and tachycardia

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed and do not alter dose or discontinue without consulting prescriber. Monitor blood pressure on a regular basis at same time of day, as advised by prescriber. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); or postural hypotension (use caution when rising from lying or sitting position or climbing stairs). Report unusual weight gain and swelling of ankles, hands, face, lips, throat, or tongue; persistent fatigue; dry cough or respiratory difficulty; palpitations or chest pain; CNS changes; GI disturbances; muscle or bone pain, cramping, or tremors; change in urinary pattern; changes in hearing or vision; or other adverse response. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 20 mg, 40 mg, 80 mg

Generic AvailableNo

ManufacturerBoehringer Ingelheim, Corp

Pricing: U.S. (www.drugstore.com)

Tablets (Micardis)

20 mg (28): $52.99

40 mg (30): $76.43

80 mg (30): $78.62

Mechanism of ActionAngiotensin II acts as a vasoconstrictor. In addition to causing direct vasoconstriction, angiotensin II also stimulates the release of aldosterone. Once aldosterone is released, sodium as well as water are reabsorbed. The end result is an elevation in blood pressure. Telmisartan is a nonpeptide AT1 angiotensin II receptor antagonist. This binding prevents angiotensin II from binding to the receptor thereby blocking the vasoconstriction and the aldosterone secreting effects of angiotensin II.

Pharmacodynamics/KineticsOrally active, not a prodrug

Onset of action: 1-2 hours

Peak effect: 0.5-1 hours

Duration: Up to 24 hours

Protein binding: >99.5%

Metabolism: Hepatic via conjugation to inactive metabolites; not metabolized via CYP

Bioavailability (dose dependent): 42% to 58%

Half-life elimination: Terminal: 24 hours

Excretion: Feces (97%)

Clearance: Total body: 800 mL/minute

Related Information

- Angiotensin Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or fatigue, may rarely cause insomnia, anxiety, nervousness, depression, or sedation

Mental Health: Effects on Psychiatric TreatmentMay decrease lithium clearance, resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Hypertension: According to the 2003 JNC 7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe angiotensin II receptor antagonists appear to have similar indications as the ACE inhibitors. In heart failure, the angiotensin II antagonists are especially useful in providing an alternative therapy in those patients who have intractable cough in response to ACE inhibitor therapy. Candesartan has been studied as an alternative therapy in chronic heart failure patients who cannot tolerate an ACE-I (CHARM-Alternative) and as an added therapy in heart failure patients who are maintained on an ACE-I (CHARM-Added). In both studies, the combined endpoint of cardiovascular death or heart failure hospitalizations was significantly improved over the placebo-treated group. Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

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McMurray JJ, Ostergren J, Swedberg K, et al, "Effects of Candesartan in Patients With Chronic Heart Failure and Reduced Left-Ventricular Systolic Function Taking Angiotensin-Converting-Enzyme Inhibitors: The CHARM-Added Trial," *Lancet*, 2003, 362(9386):767-71.[PubMed 13678869]

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International Brand NamesKinzalmono (AT, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Micardis (AE, AR, AT, AU, BE, BF, BG, BH, BJ, BR, CH, CI, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EG, ET, FI, FR, GB, GH, GM, GN, GR, GT, HK, HN, ID, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PH, PL, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SV, SY, TH, TN, TR, TZ, UG, UY, YE, ZA, ZM, ZW); Predxal (MX); Pritor (AR, KP, PE, PH, PL, VE); Pritoral (CN); Telma-20 (IN)

Temazepam

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Temazepam may be confused with flurazepam, LORazepam

Restoril® may be confused with Vistaril®, Zestril®

Pronunciation(te MAZ e pam)

U.S. Brand NamesRestoril®

Canadian Brand NamesApo-Temazepam®; CO Temazepam; Dom-Temazepam; Gen-Temazepam; Novo-Temazepam; Nu-Temazepam; PHL-Temazepam; PMS-Temazepam; ratio-Temazepam; Restoril®

Pharmacologic CategoryBenzodiazepine

Use: Labeled IndicationsShort-term treatment of insomnia

Use: Unlabeled/InvestigationalTreatment of anxiety; adjunct in the treatment of depression; management of panic attacks

Dosing: Adults **Insomnia:** Oral: 15-30 mg at bedtime

Dosing: Elderly15 mg in elderly or debilitated patients

RestrictionsC-IV

An FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to temazepam or any component of the formulation (cross-sensitivity with other benzodiazepines may exist); narrow-angle glaucoma (not in product labeling, however, benzodiazepines are contraindicated); pregnancy

Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypersensitivity reactions: Postmarketing studies have indicated that the use of hypnotic/sedative agents for sleep has been associated with hypersensitivity reactions including anaphylaxis as well as angioedema.
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.
- Sleep-related activities: An increased risk for hazardous sleep-related activities such as sleep-driving; cooking and eating food, and making phone calls while asleep have also been noted.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.
- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury.
- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.
- Hypnotic: Appropriate use: Should be used only after evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric or medical illness. A worsening of insomnia or the emergence of new abnormalities of thought or behavior may represent unrecognized psychiatric or medical illness and requires immediate and careful evaluation.
- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy.

Geriatric ConsiderationsBecause of its lack of active metabolites, temazepam is recommended in the elderly when a benzodiazepine hypnotic is indicated. Hypnotic use should be limited to 10-14 days. If insomnia persists, the patient should be evaluated for etiology.
Pregnancy Risk FactorX
LactationEnters breast milk/not recommended (AAP rates “of concern”)
Adverse Reactions

1% to 10%:

Central nervous system: Confusion, dizziness, drowsiness, fatigue, anxiety, headache, lethargy, hangover, euphoria, vertigo

Dermatologic: Rash

Endocrine & metabolic: Decreased libido

Gastrointestinal: Diarrhea

Neuromuscular & skeletal: Dysarthria, weakness

Ocular: Blurred vision

Miscellaneous: Diaphoresis

<1%: Amnesia, anorexia, ataxia, back pain, blood dyscrasias, drug dependence, increased dreaming, menstrual irregularities, palpitation, paradoxical reactions, reflex slowing, tremor, vomiting

Postmarketing and/or case reports: Anaphylaxis, angioedema, complex sleep-related behavior (sleep-driving, cooking or eating food, making phone calls)

Metabolism/Transport Effects**Substrate** (minor) of CYP2B6, 2C9, 2C19, 3A4
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Yohimbine: May diminish the therapeutic effect of Antianxiety Agents. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Serum levels may be increased by grapefruit juice.

Herb/Nutraceutical: St John's wort may decrease temazepam levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersRespiratory and cardiovascular status
Reference RangeTherapeutic: 26 ng/mL after 24 hours
Nursing: Physical Assessment/MonitoringFor short-term use. Assess effectiveness and interactions of other medications patient may be taking. Assess for history of addiction (long-term use can result in dependence, abuse, or tolerance) and periodically evaluate need for continued use. Be alert to possibility of anaphylaxis any time during therapy. After long-term use, taper dosage slowly when discontinuing. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions (eg, CNS depression) at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient

appropriate use, interventions to reduce side effects, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to sexually-active female patients unless capable of complying with contraceptive use.

Patient EducationUse exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. Drug may cause physical and/or psychological dependence. May take with food to decrease GI upset. While using this medication, do not use alcohol or other prescription or OTC medications (especially, pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, lightheadedness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or dry mouth or GI discomfort (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report CNS changes (confusion, depression, increased sedation, excitation, headache, abnormal thinking, insomnia, or nightmares, memory impairment, impaired coordination); muscle pain or weakness; respiratory difficulty; unusual swelling, especially on face or neck; persistent dizziness, chest pain, or palpitations; alterations in normal gait; vision changes; or ineffectiveness of medication. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 7.5 mg, 15 mg, 22.5 mg, 30 mg

Restoril®: 7.5 mg, 15 mg, 22.5 mg, 30 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Restoril)

7.5 mg (30): $267.50

15 mg (30): $291.02

22.5 mg (30): $270.95

30 mg (30): $262.60

Capsules (Temazepam)

15 mg (30): $12.99

30 mg (30): $13.99

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Distribution: V_d: 1.4 L/kg

Protein binding: 96%

Metabolism: Hepatic

Half-life elimination: 9.5-12.4 hours

Time to peak, serum: 2-3 hours

Excretion: Urine (80% to 90% as inactive metabolites)

Related Information

- Benzodiazepines
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsAbrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Temazepam is a short half-life benzodiazepine. Duration of action after a single dose is determined by redistribution rather than metabolism. Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include personal or family history of substance abuse and personality disorder. Temazepam is slowly absorbed; undergoes phase II metabolism and, therefore, is less likely to be effected in patients with hepatic dysfunction.

Cardiovascular Considerations Hypotension may result in orthostatic lightheadedness or syncope. Benzodiazepines, as a class, may depress respiration. These medications may often be prescribed for difficulty in sleeping but may exacerbate sleep-disordered breathing.

Anesthesia and Critical Care Concerns/Other Considerations Chronic use of this agent may increase perioperative benzodiazepine dose needed to achieve desired effect. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms. Benzodiazepines, as a class, may depress respiration; may exacerbate sleep-disordered breathing.

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Ho PC, Triggs EJ, Heazlewood V, et al, “Determination of Nitrazepam and Temazepam in Plasma by High Performance Liquid Chromatography,” *Ther Drug Monit*, 1983, 5(3):303-7. [PubMed 6138889]

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International Brand Names Dasuen (ES); Euhypnos (AU, BE, IE, LU, NL); Euipnos (IT); Levanxol (AT, BE, LU, NL); Mabertin (AR); Neodorm SP (DE); Nocturne (AU); Nomapam (AU); Norkotral Tema (DE); Normison (AU, BE, CH, FI, FR, GB, IE, IT, LU, NL, PT); Normitab (NL); Nortem (IE); Planum (CH, DE); Pronervon T (DE); Remestan (AT, DE); Signopam (HU, PL); Signopharm (HU); Temador (BE); Temaze (AU); temazep von ct (DE); Temazepam ”NM” (DK); Temtabs (AU); Tenox (FI, IE)

Temozolomide

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(te moe ZOE loe mide)

U.S. Brand NamesTemodar®

Canadian Brand NamesTemodal®; Temodar®

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent (Triazene)

Use: Labeled IndicationsTreatment of adult patients with refractory anaplastic astrocytoma; newly-diagnosed glioblastoma multiforme

Use: Unlabeled/InvestigationalMetastatic melanoma

Dosing: AdultsOral (refer to individual protocols):

Anaplastic astrocytoma (refractory): Initial dose: 150 mg/m^2/day for 5 days; repeat every 28 days. Subsequent doses of 100-200 mg/m^2/day for 5 days per treatment cycle; based upon hematologic tolerance.

ANC <1000/mm^3 or platelets <50,000/mm^3 on day 22 or day 29 (day 1 of next cycle): Postpone therapy until ANC >1500/mm^3 and platelets >100,000/mm^3; reduce dose by 50 mg/m^2/day for subsequent cycle

ANC 1000-1500/mm^3 or platelets 50,000-100,000/mm^3 on day 22 or day 29 (day 1 of next cycle): Postpone therapy until ANC >1500/mm^3 and platelets >100,000/mm^3; maintain initial dose

ANC >1500/mm^3 and platelets >100,000/mm^3 on day 22 or day 29 (day 1 of next cycle): Increase dose to or maintain dose at 200 mg/m^2/day for 5 days for subsequent cycle

Glioblastoma multiforme (high-grade glioma):

Concomitant phase: 75 mg/m^2/day for 42 days with radiotherapy (60Gy administered in 30 fractions). **Note:** PCP prophylaxis is required during concomitant phase and should continue in patients who develop lymphocytopenia until recovery (common toxicity criteria [CTC] ≤1). Obtain weekly CBC.

ANC ≥1500/mm^3, platelet count ≥100,000/mm^3, and nonhematologic CTC ≤grade 1 (excludes alopecia, nausea/vomiting): Temodar® 75 mg/m^2/day may be continued throughout the 42-day concomitant period up to 49 days

Dosage modification:

ANC ≥500/mm^3 but <1500/mm^3**or** platelet count ≥10,000/mm^3 but <100,000/mm^3**or** nonhematologic CTC grade 2 (excludes alopecia, nausea/vomiting): Interrupt therapy

ANC <500/mm^3**or** platelet count <10,000/mm^3**or** nonhematologic CTC grade 3/4 (excludes alopecia, nausea/vomiting): Discontinue therapy

Maintenance phase (consists of 6 treatment cycles): Begin 4 weeks after concomitant phase completion. **Note:** Each subsequent cycle is 28 days (consisting of 5 days of drug treatment followed by 23 days without treatment). Draw CBC within 48 hours of day 22; hold next cycle and do weekly CBC until ANC >1500/mm^3 and platelet count >100,000/mm^3; dosing modification should be based on lowest blood counts and worst nonhematologic toxicity during the previous cycle.

Cycle 1: 150 mg/m^2/day for 5 days; repeat every 28 days

Dosage modification for next cycle:

ANC <1000/mm^3, platelet count <50,000/mm^3, or nonhematologic CTC grade 3 (excludes for alopecia, nausea/vomiting) during previous cycle: Decrease dose by 50 mg/m^2/day for 5 days, unless dose has already been lowered to 100 mg/m^2/day, then discontinue therapy.

If dose reduction <100 mg/m^2/day is required or nonhematologic CTC grade 4 (excludes for alopecia, nausea/vomiting), or if the same grade 3 nonhematologic toxicity occurs after dose reduction: Discontinue therapy

Cycle 2: 200 mg/m^2/day for 5 days every 28 days, unless prior toxicity, then refer to Dosage Modifications under “Cycle 1” and give adjusted dose for 5 days

Cycles 3-6: Continue with previous cycle's dose for 5 days every 28 days unless toxicity has occurred then, refer to Dosage Modifications under “Cycle 1” and give adjusted dose for 5 days

Metastatic melanoma (unlabeled use): 200 mg/m^2/day for 5 days every 28 days (for up to 12 cycles). For subsequent cycles reduce dose to 75% of the original dose for grade 3/4 hematologic toxicity and reduce the dose to 50% of the original dose for grade 3/4 nonhematologic toxicity.

Dosing: ElderlyRefer to adult dosing. **Note:** Patients ≥70 years of age had a higher incidence of grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than patients <70 years of age.

Dosing: Renal ImpairmentCaution should be used when administered to patients with severe renal impairment (Cl_{cr} <36 mL/minute). Temozolomide has not been studied in dialysis patients.

Dosing: Hepatic ImpairmentCaution should be used when administering to patients with severe hepatic impairment.

Calculations

- ANC: Absolute Neutrophil Count
- Body Surface Area: Adults

Administration: OralCapsules should not be opened or chewed but swallowed whole with a glass of water. May be administered on an empty stomach to reduce nausea and vomiting. Bedtime administration may be advised.

Dietary ConsiderationsThe incidence of nausea/vomiting is decreased when the drug is taken on an empty stomach.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F).

Extemporaneously PreparedTemozolomide 10 mg/mL oral suspension: In a glass mortar, mix the contents of ten 100-mg capsules and 500 mg of povidine K-30 powder; add 25 mg anhydrous citric acid dissolved in 1.5 mL purified water; mix to form a paste; add 50 mL Ora-Plus® (add a small amount at first, mix, add balance); mix; transfer to amber plastic bottle; add enough Ora-Sweet® or Ora-Sweet® SF to bring a total volume of 100 mL by rinsing the mortar with small amounts of Ora-Sweet®; repeat rinsing 3 more times. The suspension is stable for 7 days at room temperature or 60 days refrigerated in plastic amber prescription bottles. **Note:** Use appropriate handling precautions during preparation.

Trissel LA, Yanping Z, and Koontz SE. "Temozolomide Stability in Extemporaneously Compounded Oral Suspension," *Int J Pharm Compounding*, 2006, 10(5):396-9.

ContraindicationsHypersensitivity to temozolomide or any component of the formulation; hypersensitivity to dacarbazine (since both drugs are metabolized to MTIC); pregnancy

Allergy Considerations

- Dacarbazine (DTIC)/Temozolomide Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Myelosuppression: May occur with use; an increased incidence has been reported in geriatric and female patients.
- Pneumonia: Pneumocystis *jiroveci* pneumonia (PCP) may occur; risk is increased in those receiving steroids or longer dosing regimens; PCP prophylaxis is required in patients receiving radiotherapy in combination with the 42-day temozolomide regimen.
- Secondary malignancies: Rare cases of myelodysplastic syndrome and secondary malignancies, including acute myeloid leukemia have been reported.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Renal impairment: Use with caution in patients with severe renal impairment.

Pregnancy Risk FactorD

Pregnancy ConsiderationsMay cause fetal harm when administered to pregnant women. Animal studies, at doses less than used in humans, resulted in numerous birth defects. Testicular toxicity was demonstrated in animal studies using smaller doses than recommended for cancer treatment. There are no adequate and well-controlled studies in pregnant women. Male and female patients should avoid pregnancy while receiving drug.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions**Note:** With CNS malignancies, it is difficult to distinguish between CNS adverse events caused by temozolomide versus the effects of progressive disease.

>10%:

Cardiovascular: Peripheral edema (11%)

Central nervous system: Fatigue (34% to 61%), headache (23% to 41%), seizure (6% to 23%), hemiparesis (18%), fever (13%), dizziness (5% to 12%), coordination abnormality (11%)

Dermatologic: Alopecia (55%), rash (8% to 13%)

Gastrointestinal: Nausea (49% to 53%; grades 3/4: 1% to 10%), vomiting (29% to 42%; grades 3/4: 2% to 6%), constipation (22% to 33%), anorexia (9% to 27%), diarrhea (10% to 16%)

Hematologic: Lymphopenia (grades 3/4: 55%), thrombocytopenia (grades 3/4: adults: 4% to 19%; children: 25%), neutropenia (grades 3/4: adults: 8% to 14%; children: 20%), leukopenia (grades 3/4: 11%)

Neuromuscular & skeletal: Weakness (7% to 13%)

Miscellaneous: Viral infection (11%)

1% to 10%:

Central nervous system: Amnesia (10%), insomnia (4% to 10%), somnolence (9%), ataxia (8%), paresis (8%), anxiety (7%), memory impairment (7%), depression (6%), confusion (5%)

Dermatologic: Pruritus (5% to 8%), dry skin (5%), radiation injury (2% maintenance phase after radiotherapy), erythema (1%)

Endocrine & metabolic: Hypercorticism (8%), breast pain (females 6%)

Gastrointestinal: Stomatitis (9%), abdominal pain (5% to 9%), dysphagia (7%), taste perversion (5%), weight gain (5%)

Genitourinary: Incontinence (8%), urinary tract infection (8%), urinary frequency (6%)

Hematologic: Anemia (grades 3/4: 4%)

Neuromuscular & skeletal: Paresthesia (9%), back pain (8%), abnormal gait (6%), arthralgia (6%), myalgia (5%)

Ocular: Blurred vision (5% to 8%), diplopia (5%), vision abnormality (visual deficit/vision changes 5%)

Respiratory: Pharyngitis (8%), upper respiratory tract infection (8%), cough (5% to 8%), sinusitis (6%), dyspnea (5%)

Miscellaneous: Allergic reaction (up to 3%)

Postmarketing and/or case reports: Anaphylaxis, aplastic anemia, erythema multiforme, myelodysplastic syndrome, opportunistic infection (eg, PCP), pancytopenia, secondary malignancies (including myeloid leukemia)

Oncology: Emetic PotentialModerate (30% to 60%)
Drug Interactions

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: Food reduces rate and extent of absorption.
Monitoring ParametersCBC with differential and platelets (prior to each cycle; weekly during glioma concomitant phase treatment; at or within 48 hours of day 22 and weekly until ANC >1500/mm^3 for glioma maintenance and astrocytoma treatment)
Nursing: Physical Assessment/MonitoringAssess results of laboratory tests (CBC) at recommended intervals. Evaluate effectiveness (reduction in symptoms) and adverse effects (eg, CNS effects [convulsions, fatigue, impaired coordination, ataxia], gastrointestinal disturbance [nausea, vomiting, constipation], myelosuppression, rash, opportunistic infection, vision disturbance, cough) on a regular basis throughout therapy. Teach patient proper use and timing, possible side effects, and appropriate interventions.
Monitoring: Lab TestsCBC with differential and platelets (prior to each cycle; weekly during glioma concomitant phase treatment; at or within 48 hours of day 22 and weekly until ANC >1500/mm^3 for glioma maintenance and astrocytoma treatment)
Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber. Take exactly as directed, on an empty stomach 1 hour before or 2 hours after meals or at bedtime. Do not open, crush, or chew capsules; swallow whole with full 8 oz of water. (If capsule is accidentally broken, do not inhale powder; wash hands thoroughly if powder gets skin). May cause headache, dizziness, confusion, fatigue, anxiety, insomnia, or impaired coordination (use caution when driving or engaging in tasks requiring alertness until response to medication is known); nausea, vomiting, or loss of appetite (small frequent meals, good mouth care, chewing gum, or sucking hard candy may help); or hot flashes (cool dark room or cold compresses may help). Report chest pain, palpitations, acute headache, unusual swelling of legs or feet; visual disturbances; unresolved GI problems (persistent nausea or vomiting); itching or burning on urination or vaginal discharge; acute joint, back, bone, or muscle pain or unusual weakness; difficulty breathing, cough, or signs of respiratory infection; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you pregnant. Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Temodar®: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Capsules (Temodar)

5 mg (5): $54.18

20 mg (5): $160.98

100 mg (5): $776.95

100 mg (14): $2449.57

180 mg (14): $4335.77

250 mg (5): $2009.84

Mechanism of ActionLike dacarbazine, temozolomide is converted to the active alkylating metabolite MTIC [(methyl-triazene-1-yl)-imidazole-4-carboxamide]. Unlike dacarbazine, however, this conversion is spontaneous, nonenzymatic, and occurs under physiologic conditions in all tissues to which the drug distributes.

Pharmacodynamics/Kinetics

Absorption: Rapid and complete

Distribution: V_d: Parent drug: 0.4 L/kg; penetrates blood brain barrier; CSF levels are ~35% to 39% of plasma levels

Protein binding: 15%

Metabolism: Prodrug, hydrolyzed to the active form, MTIC; MTIC is eventually eliminated as CO_2 and 5-aminoimidazole-4-carboxamide (AIC), a natural constituent in urine

Bioavailability: 100%

Half-life elimination: Mean: Parent drug: 1.8 hours

Time to peak: Empty stomach: 1 hour

Excretion: Urine (~38%; parent drug 6%); feces 0.8%

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, dysphagia, and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusFatigue, dizziness, amnesia, and insomnia are common; may cause somnolence, confusion, anxiety, depression

Mental Health: Effects on Psychiatric TreatmentMyelosuppression is common, use caution with clozapine and carbamazepine; nausea is very common, avoid use with SSRIs

Index TermsNSC-362856; TMZ

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International Brand NamesTemodal (AE, AR, AT, AU, BE, BG, BH, BO, BR, CH, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IL, IQ, IR, IT, JO, KP, KW, LB, LY, MX, NI, NL, NO, OM, PA, PE, PH, PL, PR, PT, PY, QA, RU, SA, SE, SG, SV, SY, TH, TR, TW, UY, VE, YE); Temozam (PH)

Temsirolimus

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Temsirolimus: Health Canada Issues Warning Concerning Hypersensitivity and Infusion Reactions - August 2008

Wyeth Canada, in conjunction with Health Canada, has issued a Dear Healthcare Professional letter concerning hypersensitivity and infusion related reactions associated with temsirolimus (Torisel™). To date there have been no serious postmarketing reports of this type in Canada, however, worldwide there have been 46 case reports including one fatality and six life-threatening reactions. Reported adverse events include loss of consciousness, hypotension, chest pain, dyspnea, apnea, and flushing. Although most reactions have occurred with initial dosing and frequently within minutes of starting the infusion, hypersensitivity reactions have also been reported with subsequent infusions.

Prior to temsirolimus infusion, it is recommended that patients be premedicated with a selective H_1-blocker (eg, diphenhydramine) and appropriate supportive care be readily available. Infusions should be interrupted immediately in any patient experiencing hypersensitivity or infusion related reactions and appropriate treatment administered accordingly. Patients in whom reinitiating therapy is considered beneficial, administration of an I.V. H_1-blocker and/or I.V. H_2-blocker (eg, famotidine) is recommended as well as reducing the infusion rate. Subsequent use of temsirolimus is contraindicated in any patient who has a history of or experiences an anaphylactic reaction associated with temsirolimus therapy, sirolimus therapy, or any component of the formulation.

Further information may be found at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/torisel_hpc-cps-eng.p

Medication Safety Issues

Sound-alike/look-alike issues:

Temsirolimus may be confused with sirolimus, tacrolimus

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Temsirolimus, for the treatment of advanced renal cell cancer, is a flat dose (25 mg) and is not based on body surface area (BSA).

Pronunciation(tem sir OH li mus)

U.S. Brand NamesTorisel®

Canadian Brand NamesTorisel®

Pharmacologic CategoryAntineoplastic Agent, mTOR Kinase Inhibitor

Use: Labeled IndicationsTreatment of advanced renal cell cancer (RCC)

Dosing: Adults**Note:** For infusion reaction prophylaxis, premedicate with an H_1 antagonist (eg, diphenhydramine 25-50 mg I.V.) 30 minutes prior to infusion.

RCC: I.V.: 25 mg weekly

Dosage adjustment for concomitant CYP3A4 inhibitors/inducers:

CYP3A4 inhibitors: Dose reductions are likely to be needed when temsirolimus is administered concomitantly with a strong CYP3A4 inhibitor (an alternate medication for CYP3A4 enzyme inhibitors should be investigated first); in the event that temsirolimus must be administered concomitantly with a potent enzyme inhibitor, consider reducing temsirolimus to 12.5 mg/week with careful monitoring. (When a strong CYP3A4 inhibitor is discontinued; allow ~1 week to elapse prior to adjusting the temsirolimus upward to the dose used prior to initiation of the CYP3A4 inhibitor.)

CYP3A4 inducers: Concomitant administration with CYP3A4 inducers may require increased temsirolimus doses (alternatives to the enzyme-inducing agent should be utilized first); consider adjusting temsirolimus dose to 50 mg/week, with careful monitoring. (If the strong CYP3A4 enzyme inducer is discontinued, reduce the temsirolimus to the dose used prior to initiation of the CYP3A4 inducer.)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNot studied in renal dysfunction, however, due to the minimal renal elimination (<5%), dosage adjustment for renal dysfunction is not recommended.

Hemodialysis: Has not been studied in hemodialysis patients.

Dosing: Hepatic ImpairmentThe FDA-approved labeling does not contain hepatic dosing adjustment guidelines. Patients with AST >3 times ULN (>5 times ULN in the presence of liver metastases) and total bilirubin >1.5 times ULN were excluded from clinical trials. Temsirolimus is primarily cleared hepatically.

Dosing: Adjustment for Toxicity

Hematologic toxicity: ANC <1000/mm^3 or platelets <75,000/mm^3: Withhold treatment until resolves and reinitiate treatment with a 5 mg/week dose reduction; minimum dose: 15 mg/week if adjustment for toxicity is needed.

Nonhematologic toxicity: Any toxicity ≥grade 3: Withhold treatment until resolves to ≤grade 2; reinitiate treatment with a 5 mg/week dose reduction; minimum dose: 15 mg/week if adjustment for toxicity is needed.

Administration: I.V.Infuse over 30-60 minute via an infusion pump (preferred). Use non-DEHP containing administration tubing. Administer through an inline polyethersulfone filter ≤5 micron. Premedicate with an H_1 antagonist (eg, diphenhydramine 25-50 mg I.V. 30 minutes prior to infusion. Monitor during infusion; interrupt infusion for hypersensitivity/infusion reaction; monitor for 30-60 minutes; may reinitiate at a reduced infusion rate (over 60 minutes) with discretion, 30 minutes after administration of a histamine H_1 antagonist and/or a histamine H_2 antagonist (eg, famotidine or ranitidine).

StorageStore intact vials under refrigeration at 2°C to 8°C (36°F to 46°F). Diluted solution in the vial (10 mg/mL) is stable for 24 hours at room temperature. Solutions diluted for infusion (in normal saline) must be infused within 6 hours of preparation. Protect from light during storage, preparation, and handling.

ReconstitutionVials should be diluted with 1.8 mL of provided diluent to a concentration of 10 mg/mL (vial contains overfill). Mix by inverting vial. After allowing air bubbles to subside, further dilute in 250 mL of NS in a non-DEHP/non-PVC container (glass, polyolefin or polypropylene). Avoid excessive shaking (may result in foaming). Use appropriate precautions for handling and disposal.

CompatibilityCompatible with normal saline; do not mix with other solutions or medications. Temsirolimus is degraded by acids and bases.

ContraindicationsThere are no contraindications listed within the FDA-approved manufacturer's labeling.

Canadian labeling: Additional contraindications (not in U.S. labeling): History of anaphylaxis after exposure to temsirolimus, sirolimus, or any component of the formulation

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Anaphylactic/hypersensitivity/infusion reactions: Hypersensitivity/infusion reactions (eg, anaphylaxis, apnea, dyspnea, flushing, loss of consciousness, hypotension, and/or chest pain) have been reported. Infusion reaction may occur with initial or subsequent infusions. Premedicate with an antihistamine (H_1 antagonist) prior to infusion; monitor during infusion; interrupt infusion for severe reaction. With discretion, treatment may be resumed at a slower infusion rate; administer an H_1 antagonist (if not given as premedication) and/or an H_2 antagonist 30 minutes prior to resuming infusion. Use with caution in patients with hypersensitivity to polysorbate 80.

- Angioedema: Has been reported; concurrent use with other drugs known to cause angioedema (eg, ACE inhibitors) may increase risk.

- Bowel perforation: Cases of bowel perforation (fatal) have occurred; promptly evaluate any new or worsening abdominal pain or bloody stools.

- Infection: Treatment may result in immunosuppression, may increase risk of opportunistic infections and/or sepsis.

- Interstitial lung disease (ILD): ILD, sometimes fatal, has been reported; symptoms include dyspnea, cough, hypoxia and/or fever, although asymptomatic cases may present; promptly evaluate worsening respiratory symptoms.

- Renal failure: Acute renal failure with rapid progression has been reported, including cases unresponsive to dialysis.

- Wound healing: May be associated with impaired wound healing; use caution in the perioperative period.

Disease-related concerns:

- CNS metastases/tumors: May be at increased risk for developing intracerebral bleeding.

- Diabetics: Increases in serum glucose are common; may alter insulin and/or oral hypoglycemic therapy requirements in patients with diabetes; monitor.

- Hepatic impairment: Has not been studied in patients with hepatic impairment; use caution. Temsirolimus is predominantly cleared by the liver.

- Hyperlipidemia: Use with caution in patients with hyperlipidemia; may increase serum lipids (cholesterol and triglycerides).

Concurrent drug therapy issues:

- Anticoagulants: Patients who are receiving anticoagulant therapy may be at increased risk for developing intracerebral bleeding.

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors and moderate or strong CYP3A4 inducers (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Immunizations: Patients should not be immunized with live viral vaccines during or shortly after treatment and should avoid close contact with recently vaccinated (live vaccine) individuals.

Pregnancy Risk FactorD

Pregnancy ConsiderationsEmbryotoxicity and fetotoxicity may occur, as evidenced by increased mortality, reduced fetal weights, and delayed ossification in animal studies. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should be advised to avoid pregnancy. Men and women should use effective birth control during temsirolimus treatment, and continue for 3 months after temsirolimus discontinuation.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.

Adverse Reactions

>10%:

Cardiovascular: Edema (35%), peripheral edema (27%), chest pain (16%)

Central nervous system: Pain (28%), fever (24%), headache (15%), insomnia (12%)

Dermatologic: Rash (47%), pruritus (19%), nail disorder/thinning (14%), dry skin (11%)

Endocrine & metabolic: Hyperglycemia (26% to 89%; grades 3/4: 16%), hypercholesterolemia (24% to 87%; grades 3/4: 2%), hyperlipidemia (27% to 83%; grades 3/4: 44%), hypophosphatemia (49%; grades 3/4: 18%), hypokalemia (21%; grades 3/4: 5%)

Gastrointestinal: Mucositis (41%), nausea (37%), anorexia (32%), diarrhea (27%), abdominal pain (21%), constipation (20%), stomatitis (20%), taste disturbance (20%), vomiting (19%), weight loss (19%)

Genitourinary: Urinary tract infection (15%)

Hematologic: Anemia (45% to 94%; grades 3/4: 20%), lymphopenia (53%; grades 3/4: 16%), thrombocytopenia (14% to 40%; grades 3/4: 1%; dose-limiting toxicity), leukopenia (6% to 32%; grades 3/4: 1%), neutropenia (7% to 19%; grades 3/4: 3% to 5%)

Hepatic: Alkaline phosphatase increased (68%; grades 3/4: 3%), AST increased (8% to 38%; grades 3/4: 1% to 2%)

Neuromuscular & skeletal: Weakness (51%), back pain (20%), arthralgia (18%)

Renal: Creatinine increased (14% to 57%; grades 3/4: 3%)

Respiratory: Dyspnea (28%), cough (26%), epistaxis (12%), pharyngitis (12%)

Miscellaneous: Infection (20% to 27%; includes abscess, bronchitis, cellulitis, herpes simplex, herpes zoster)

1% to 10%:

Cardiovascular: Hypertension (7%), venous thromboembolism (2%, includes DVT and PE), thrombophlebitis (1%)

Central nervous system: Chills (8%), depression (4%)

Dermatologic: Acne (10%), wound healing impaired (1%)

Gastrointestinal: Bowel perforation (fatal: 1%)

Hepatic: Hyperbilirubinemia (8%)

Neuromuscular & skeletal: Myalgia (8%)

Ocular: Conjunctivitis (7%)

Respiratory: Rhinitis (10%), pneumonia (8%), upper respiratory tract infection (7%), interstitial lung disease (2%)

Miscellaneous: Allergic/hypersensitivity/infusion reaction (9%; includes anaphylaxis, apnea, chest pain, dyspnea, flushing, hypotension, loss of consciousness)

<1%, postmarketing, and/or case reports: Acute renal failure, angioneurotic edema, pneumonitis

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (weak), 2D6 (weak)

Drug Interactions

ACE Inhibitors: Temsirolimus may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Temsirolimus. Concentrations of the active metabolite, sirolimus, are likely to be increased more substantially than those of the parent temsirolimus. *Risk D: Consider therapy modification*

CarBAMazepine: May decrease the serum concentration of Temsirolimus. Concentrations of the active metabolite, sirolimus, are also likely to be decreased (and maybe to an even greater degree). Management: Temsirolimus prescribing information recommends against coadministration with strong CYP3A4 inducers such as carbamazepine; however, if concurrent therapy is necessary, an increase in temsirolimus dose to 50 mg/week should be considered. *Risk D: Consider therapy modification*

CycloSPORINE: Temsirolimus may enhance the adverse/toxic effect of CycloSPORINE. An increased risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA) has been described with concomitant sirolimus use. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Macrolide Antibiotics: May enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May decrease the serum concentration of Temsirolimus. Concentrations of the active metabolite, sirolimus, are also likely to be decreased (and maybe to an even greater degree). Management: Temsirolimus prescribing information recommends against coadministration with strong CYP3A4 inducers such as phenytoin; however, if concurrent therapy is necessary, an increase in temsirolimus dose to 50 mg/week should be considered. *Risk D: Consider therapy modification*

Protease Inhibitors: May enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May decrease the serum concentration of Temsirolimus. Rifamycins will likely cause an even greater decrease in the concentration of the active metabolite sirolimus. Management: Temsirolimus prescribing information recommends against coadministration with strong CYP3A4 inducers such as rifampin; however, if concurrent therapy is necessary, an increase in temsirolimus dose to 50 mg/week should be considered. *Risk D: Consider therapy modification*

Tacrolimus: Temsirolimus may enhance the adverse/toxic effect of Tacrolimus. An increased risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA) has been described with concomitant sirolimus and tacrolimus use. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease sirolimus (the active metabolite of temsirolimus) levels; avoid concurrent use. Herbs with hypoglycemic properties may increase the risk of temsirolimus-induced hypoglycemia; includes alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, stinging nettle. Avoid grapefruit and grapefruit juice (may increase the levels/effects of sirolimus).

Monitoring ParametersCBC with differential and platelets (weekly), serum chemistries including glucose (baseline and every other week), serum cholesterol and triglycerides (baseline and periodic), liver and renal function tests

Monitor for infusion reactions; infection; symptoms of ILD (or radiographic changes)

Nursing: Physical Assessment/MonitoringAssess other pharmacological or herbal products patient may be taking for potential adverse interactions. Premedication with antihistamine prior to infusion. Patient must be monitored closely during and following each infusion for infusion reaction (eg, anaphylaxis, dyspnea, flushing, chest pain); medication/equipment for treating reactions should be readily available. Evaluate results of laboratory tests and adverse response (eg, altered glucose control, opportunistic infection, interstitial lung disease, bowel perforations, renal failure) at each infusion and throughout therapy; discontinuation may be necessary. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelets (weekly), serum chemistries including glucose (baseline and every other week), serum cholesterol and triglycerides (baseline and periodic), liver and renal function tests

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy unless approved by prescriber. This medication can only be administered by infusion; you will be closely monitored during infusion. Report immediately unusual back or abdominal pain; acute headache; difficulty breathing or chest pain; difficulty swallowing; itching or rash; or redness, swelling, or pain at infusion site. Between treatments maintain adequate hydration (2-3 L/day of fluids unless instructed to restrict fluid intake) and nutrition (small, frequent meals). You will be required to have regularly scheduled laboratory tests while on this medication. You will be more susceptible to infection (avoid crowds and exposure to infection and do not receive any vaccination unless approved by prescriber). If you have diabetes, you will be instructed to check your glucose levels closely and notify prescriber of significant changes, excessive thirst, or frequency of urination (this medication can affect glucose control and diabetic medications may need to be adjusted). You may experience headache or insomnia (use caution when driving or engaging in tasks that require alertness until response to drug is known); loss of appetite, nausea, dry mouth or taste changes (frequent oral care, sucking lozenges, or chewing gum may help); rash; thin nails; or dry skin. Report immediately changes in respiratory status (difficulty breathing, dyspnea, unusual cough, or fever); abdominal pain or blood in stool; signs or symptoms of any urinary tract infection (difficulty urinating, burning on urination, or perineal itching); unusual infection or delayed wound healing; or any other adverse reactions. **Pregnancy/breast-feeding precautions:** Do not get pregnant (females) or cause a pregnancy (males with partner of childbearing age) during this therapy or for 3 months after therapy has stopped. This drug can cause fetal harm. Consult prescriber for appropriate contraception. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [concentrate]:

Torisel®: 25 mg/mL [contains dehydrated ethanol, propylene glycol; diluent contains dehydrated ethanol, polyethylene glycol, polysorbate 80]

Generic AvailableNo

ManufacturerWyeth Pharmaceuticals, Inc

Mechanism of ActionTemsirolimus and its active metabolite, sirolimus, are targeted inhibitors of mTOR (mammalian target of rapamycin) kinase activity. Temsirolimus (and sirolimus) bind to FKBP-12, an intracellular protein, to form a complex which inhibits mTOR signaling, halting the cell cycle at the G1 phase in tumor cells. In renal cell carcinoma, mTOR inhibition also exhibits anti-angiogenesis activity by reducing levels of HIF-1 and HIF-2 alpha (hypoxia inducible factors) and vascular endothelial growth factor (VEGF).

Pharmacodynamics/Kinetics

Distribution: V_{dss}: 172 L

Metabolism: Hepatic; via CYP3A4 to sirolimus (primary active metabolite) and 4 minor metabolites

Half-life elimination: Temsirolimus: ~17 hours; Sirolimus: ~55 hours

Time to peak, plasma: Temsirolimus: At end of infusion; Sirolimus: 0.5-2 hours after temsirolimus infusion

Excretion: Feces (78%); urine (<5%)

Related Information

- Common Toxicity Criteria
- Management of Nausea and Vomiting
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Effects on oral cavity including mucositis, stomatitis, and taste disturbances.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia is common; may produce symptoms of mania or depression

Mental Health: Effects on Psychiatric TreatmentIncreases in serum glucose are common with temsirolimus and may alter insulin and/or oral hypoglycemic therapy requirements in diabetic patients. Hyperglycemia has also been associated with mental disorders as well as various psychotropic agents (especially atypical antipsychotics). Elevations in cholesterol and triglycerides may also be seen with psychotropics and temsirolimus. Concomitant use of these agents may produce additive effects; monitor metabolic profile. GI side effects are common; concurrent use with SSRIs, lithium, carbamazepine, or valproic acid may produce additive effects. Hematologic side effects are common; concurrent use with clozapine, carbamazepine, or valproic acid may produce additive effects. Temsirolimus is a CYP3A4 substrate; therefore, agents that inhibit its metabolism (nefazodone) may increase toxicity while inducers (eg, carbamazepine, barbiturates, phenytoin) may reduce its efficacy.

Index TermsCCI-779; NSC-683864

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International Brand NamesTorisel (CZ, DK, EE, IE, NO, SE)

Tenecteplase

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

TNKase® may be confused with t-PA

TNK (occasional abbreviation for TNKase®) is an error-prone abbreviation (mistaken as TPA)

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V.) among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ten EK te plase)

U.S. Brand NamesTNKase®

Canadian Brand NamesTNKase®

Pharmacologic CategoryThrombolytic Agent

Use: Labeled IndicationsThrombolytic agent used in the management of ST-elevation myocardial infarction (STEMI) for the lysis of thrombi in the coronary vasculature to restore perfusion and reduce mortality.

Recommended criteria for treatment: STEMI: Chest pain ≥20 minutes duration, onset of chest pain within 12 hours of treatment (or within prior 12-24 hours in patients with continuing ischemic symptoms), and S-T segment elevation >0.1 mV in at least two contiguous precordial leads or two adjacent limb leads on ECG or new or presumably new left bundle branch block (LBBB)

Use: Unlabeled/InvestigationalAcute MI - combination regimen of tenecteplase (unlabeled dose), abciximab, and heparin (unlabeled dose)

Dosing: Adults

STEMI: I.V.: The recommended total dose should not exceed 50 mg and is based on weight. Administer as a bolus over 5 seconds:

<60 kg: 30 mg dose

≥60 to <70 kg: 35 mg

≥70 to <80 kg: 40 mg

≥80 to <90 kg: 45 mg

≥90 kg: 50 mg

Note: All patients should receive 162-325 mg of chewable non-enteric coated aspirin as soon as possible and then daily. Administer concurrently with heparin 60 units/kg bolus (maximum: 4000 units) followed by continuous infusion of 12 units/kg/hour (maximum: 1000 units/hour) and adjust to aPTT target of 50-70 seconds (or 1.5-2 times the upper limit of control).

Combination regimen (unlabeled): Half-dose tenecteplase (15-25 mg based on weight) and abciximab 0.25 mg/kg bolus then 0.125 mcg/kg/minute (maximum 10 mcg/minute) for 12 hours with heparin dosing as follows: Concurrent bolus of 40 units/kg (maximum 3000 units), then 7 units/kg/hour (maximum 800 units/hour) as continuous infusion. Adjust to aPTT target of 50-70 seconds.

Note: The 2004 ACC/AHA guidelines for the management of patients with STEMI suggests that abciximab and half-dose reteplase or tenecteplase may be considered for prevention of reinfarction in patients with anterior MI, who are <75 years of age and have no risk factors for bleeding. However, more recently the American College of Chest Physicians recommends against the combination of half-dose reteplase or tenecteplase and standard-dose abciximab (with low dose unfractionated heparin) in any patient with STEMI due to the lack of mortality benefit and the risk of major bleeding (Goodman, 2008).

Dosing: ElderlyRefer to adult dosing. Although dosage adjustments are not recommended, the elderly have a higher incidence of morbidity and mortality with the use of tenecteplase. The 30-day mortality in the ASSENT-2 trial was 2.5% for patients younger than 65 years, 8.5% for patients between 65 and 74 years, and 16.2% for patients 75 years and older. The intracranial hemorrhage rate was 0.4% for patient younger than 65 years, 1.6% for patients between 65 and 74 years, and 1.7% for patients 75 years and older. The risks and benefits of use should be weighted carefully in the elderly.

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentSevere hepatic failure is a relative contraindication. Recommendations were not made for mild to moderate hepatic impairment.

Administration: I.V.Tenecteplase should be reconstituted using the supplied 10 mL syringe with TwinPak™ Dual Cannula Device and 10 mL SWFI. Do not shake when reconstituting. Slight foaming is normal; will dissipate if left standing for several minutes. Any unused solution should be discarded. The reconstituted solution is 5 mg/mL. Dextrose-containing lines must be flushed with a saline solution before and after administration. Check frequently for signs of bleeding. Avoid I.M. injections and nonessential handling of patient.

StorageStore at room temperature not to exceed 30°C (86°F) or under refrigeration 2°C to 8°C (36°F to 46°F). If reconstituted and not used immediately, store in refrigerator and use within 8 hours.

ReconstitutionTenecteplase should be reconstituted using the supplied 10 mL syringe with TwinPak™ Dual Cannula Device and 10 mL sterile water for injection.

Compatibility**Incompatible** with dextrose solutions.

ContraindicationsHypersensitivity to tenecteplase or any component of the formulation; active internal bleeding; history of stroke; intracranial/intraspinal surgery or trauma within 2 months; intracranial neoplasm; arteriovenous malformation or aneurysm; bleeding diathesis; severe uncontrolled hypertension

Allergy Considerations

- Thrombolytic Agent, Fibrin-Specific Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Arrhythmias: Coronary thrombolysis may result in reperfusion arrhythmias.
- Bleeding: Monitor all potential bleeding sites. If serious bleeding occurs, the infusion of tenecteplase and heparin should be stopped.
- Cholesterol embolism: Has rarely been reported.

Disease-related concerns:

- Conditions that increase bleeding risk: For the following conditions the risk of bleeding is higher with use of tenecteplase and should be weighed against the benefits of therapy: recent (within 10 days) major surgery (eg, CABG, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels), cerebrovascular disease, recent (within 10 days) gastrointestinal or genitourinary bleeding, recent trauma (within 10 days) including CPR, hypertension (systolic BP >180 mm Hg and/or diastolic BP >110 mm Hg), high likelihood of left heart thrombus (eg, mitral stenosis with atrial fibrillation), acute pericarditis, subacute bacterial endocarditis, hemostatic defects including ones caused by severe renal or hepatic dysfunction, significant hepatic dysfunction, diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions, septic thrombophlebitis or occluded AV cannula at seriously infected site, and/or any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of location.
- Myocardial infarct (MI): Appropriate use: Follow standard management for MI while infusing tenecteplase.

Concurrent drug therapy issues:

- Anticoagulants: Use with caution in patients receiving oral anticoagulants; increased risk of bleeding.
- GP IIb/IIIa inhibitors: Use with caution in patients who had recent administration of GP IIb/IIIa inhibitors.
- Heparin: Concurrent heparin anticoagulation may contribute to bleeding.

Special populations:

- Elderly: Use with caution in patients with advanced age (see Usual Dosing, Elderly); increased risk of bleeding.
- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: Use with caution in pregnancy; increased risk of bleeding.

Other warnings/precautions:

- Administration: Avoid intramuscular injections and nonessential handling of the patient for a few hours after administration. Venipunctures should be performed carefully and only when necessary. If arterial puncture is necessary, use an upper extremity vessel that can be manually compressed. Caution with readministration of tenecteplase.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdminister to pregnant women only if the potential benefits justify the risk to the fetus.

LactationUse caution

Adverse ReactionsAs with all drugs which may affect hemostasis, bleeding is the major adverse effect associated with tenecteplase. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the dosage administered, concurrent use of multiple agents which alter hemostasis, and patient predisposition. Rapid lysis of coronary artery thrombi by thrombolytic agents may be associated with reperfusion-related arterial and/or ventricular arrhythmia. The incidence of stroke and bleeding increase in patients >65 years.

>10%:

Hematologic: Bleeding (22% minor: ASSENT-2 trial)

Local: Hematoma (12% minor)

1% to 10%:

Central nervous system: Stroke (2%)

Gastrointestinal: GI hemorrhage (1% major, 2% minor), epistaxis (2% minor)

Genitourinary: GU bleeding (4% minor)

Hematologic: Bleeding (5% major: ASSENT-2 trial)

Local: Bleeding at catheter puncture site (4% minor), hematoma (2% major)

Respiratory: Pharyngeal bleeding (3% minor)

<1%: Intracranial hemorrhage (0.9%), retroperitoneal bleeding, respiratory tract bleeding, anaphylaxis, angioedema, laryngeal edema, rash, urticaria, cholesterol embolism (clinical features may include livedo reticularis, “purple toe” syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, MI, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, rhabdomyolysis), GU bleeding (<1% major), bleeding at catheter puncture site (<1% major)

Additional cardiovascular events associated with use in MI: Cardiogenic shock, arrhythmia, AV block, pulmonary edema, heart failure, cardiac arrest, recurrent myocardial ischemia, myocardial reinfarction, myocardial rupture, cardiac tamponade, pericarditis, pericardial effusion, mitral regurgitation, thrombosis, embolism, electromechanical dissociation, hypotension, fever, nausea, vomiting

Drug Interactions

Anticoagulants: Thrombolytic Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Aprotinin: May diminish the therapeutic effect of Thrombolytic Agents. *Risk D: Consider therapy modification*

Drotrecogin Alfa: Thrombolytic Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Thrombolytic Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Monitoring ParametersCBC, aPTT, signs and symptoms of bleeding, ECG monitoring

Nursing: Physical Assessment/MonitoringWeigh benefits against risks of use in conditions where bleeding constitutes a significant hazard or would be particularly difficult to manage because of location. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (especially those medications that may affect coagulation [warfarin] or platelet function [eg, NSAIDs, dipyridamole, ticlopidine, and clopidogrel]). See Administration for infusion specifics. Patient should be closely monitored for bleeding during and following treatment. Monitor infusion site, neurological status (eg, intracranial hemorrhage), vital signs, and ECG (reperfusion arrhythmias). Arrhythmias may occur; antiarrhythmic drugs should be immediately available. Bedrest and bleeding precautions should be maintained; avoid I.M. injections, venipuncture (unless absolutely necessary), and nonessential handling of the patient. If arterial puncture is necessary, an upper extremity vessel that can be manually compressed should be used. Patient instructions determined by patient condition.

Monitoring: Lab TestsCBC, PTT, signs and symptoms of bleeding, ECG monitoring

Patient EducationThis medication is only administered by infusion; you will be monitored closely during and after treatment. Immediately report burning, pain, redness, swelling, or oozing at infusion site. Following infusion you will have a tendency to bleed easily; use caution to prevent injury (use electric razor, soft toothbrush, and caution with knives, needles, or anything sharp) and follow instructions for strict bedrest to reduce the risk of injury. If bleeding does occur, report immediately and apply pressure to bleeding spot until bleeding stops completely. Report unusual pain (acute headache, joint pain, chest pain); unusual bruising or bleeding; blood in urine, stool, or vomitus; bleeding gums; vision changes; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [recombinant]:

TNKase®: 50 mg

Generic AvailableNo

Mechanism of ActionInitiates fibrinolysis by binding to fibrin and converting plasminogen to plasmin.

Pharmacodynamics/Kinetics

Distribution: V_d is weight related and approximates plasma volume

Metabolism: Primarily hepatic

Half-life elimination: 90-130 minutes

Excretion: Clearance: Plasma: 99-119 mL/minute

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause stroke

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular Considerations

ST-Elevation Myocardial Infarction: The 2004 ACC/AHA guidelines for the management of patients with acute myocardial infarction recommend prehospital thrombolysis in special circumstances (eg, transport time >30 minutes). Efforts to quickly identify and safely treat appropriate candidates for therapy continue. Reducing treatment delays is very important to improve mortality. Thrombolytic therapy is indicated in patients with ST-segment elevation of >1 mm in two or more contiguous leads or at least 2 adjacent limb leads in patients with chest discomfort >30 minutes but ≤12 hours. Patients with chest discomfort suggestive of ischemia and new-onset left bundle branch block (LBBB) are also candidates for thrombolysis. Generally there is only a small trend for benefit of therapy after a delay of more than 12-24 hours, but thrombolysis may be considered for selected patients with ongoing ischemic pain and extensive ST elevation. Additional absolute contraindications for fibrinolysis use in ST-elevation myocardial infarction from the 2004 ACC/AHA guidelines: Any prior intracranial hemorrhage, ischemic stroke within 3 months (except one within 3 hours), significant closed head or facial trauma within 3 months. Additional relative contraindications include history of chronic severe, poorly-controlled hypertension, severe uncontrolled hypertension on presentation (systolic BP >180 mm Hg or diastolic >110 mm Hg; could be an absolute contraindication in low-risk patients), history of prior ischemic stroke > 3 months, dementia, or known intracranial pathology, traumatic or prolonged (>10 minutes) CPR or major surgery (<3 weeks), recent (within 2-4 weeks) internal bleeding, noncompressible vascular punctures, pregnancy, active peptic ulcer, current use of anticoagulants.

Thrombolytic and GP IIb/IIIa Inhibitor: In the GUSTO V trial, patients with acute MI were randomized to standard-dose reteplase or half-dose reteplase (two boluses of 5 units each, 30 minutes apart) and full dose abciximab. Thirty-day mortality (primary endpoint) was similar in both groups. The combination treatment group had fewer deaths or nonfatal reinfarctions, less need for urgent revascularization, fewer major ischemic complications. More bleeding occurred in the combination treatment group, but intracranial hemorrhage and nonfatal disabling stroke were similar in both groups. All cause mortality at one year was similar in both groups. In TIMI 14, the combination of full-dose abciximab (0.25 mg/kg bolus followed by a 12-hour infusion of 0.125 mcg/kg/minute, maximum 10 mcg/minute) and half-dose alteplase (15 mg bolus followed by 35 mg infusion over 60 minutes) resulted in 74% of patients achieving TIMI grade 3 flow at 90 minutes. Patients with acute MI were randomized in an open-label study to full-dose tenecteplase and enoxaparin, half-dose tenecteplase with low-dose, weight-based heparin and a 12-hour infusion of abciximab or full-dose tenecteplase with weight-based heparin (ASSENT-3 Investigators, 2001). The primary endpoint (30 days) was mortality, in-house reinfarction, and in-house refractory ischemia. The abciximab arm and the enoxaparin arm had significantly less mortality, reinfarction, and refractory ischemia than in the unfractionated heparin/full-dose tenecteplase. One year mortality (secondary endpoint) was similar in all 3 treatment arms (Sinnaeve, 2004). However, 1 year outcome tended to be worse with abciximab in patients with diabetes. The 2004 ACC/AHA guidelines for the management of patients with acute myocardial infarction suggests that abciximab and half-dose reteplase or tenecteplase may be considered for prevention of reinfarction in patients with an anterior MI, who are <75 years of age and have no risk factors for bleeding.

However, more recently, the 2008 American College of Chest Physicians guidelines recommends against the combination of half-dose reteplase or tenecteplase and standard-dose abciximab (with low dose unfractionated heparin) in any patient with STEMI due to the lack of mortality benefit and the risk of major bleeding (Goodman, 2008).

Anesthesia and Critical Care Concerns/Other Considerations

Evidence-Based Information:

Management of Intracerebral Hemorrhage (ICH) Due to Thrombolysis: Overall management of ICH is similar regardless of cause; however, iatrogenic spontaneous ICH may have specific treatments. According to the 2007 ACC/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage, fibrinolytic-related ICH should be treated with infusion of platelets (6-8 units) and cryoprecipitate which contains factor VIII (Class IIb recommendation).

References

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International Brand Names

Metalyse (AE, AT, AU, BE, BF, BG, BH, BJ, BR, CH, CI, CN, CO, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, IE, IL, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, NO, OM, PE, PT, QA, RU, SA, SC, SD, SE, SG, SL, SN, SY, TH, TN, TR, TW, TZ, UG, YE, ZA, ZM, ZW)

Teniposide

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Teniposide may be confused with etoposide

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ten i POE side)

U.S. Brand NamesVumon®

Canadian Brand NamesVumon®

Pharmacologic CategoryAntineoplastic Agent, Miscellaneous

Use: Labeled IndicationsTreatment of acute lymphocytic leukemia, small cell lung cancer

Dosing: Adults

Antineoplastic: I.V. (refer to individual protocols): 50-180 mg/m^2 once or twice weekly for 4-6 weeks or 20-60 mg/m^2/day for 5 days

Small cell lung cancer: I.V.: 80-90 mg/m^2/day for 5 days every 4-6 weeks

Dosage adjustment in Down syndrome patient: Reduce initial dosing give the first course at half the usual dose. Patients with both Down syndrome and leukemia may be especially sensitive to myelosuppressive chemotherapy.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Antineoplastic: I.V. (refer to individual protocols): 130 mg/m^2/week, increasing to 150 mg/m^2 after 3 weeks and up to 180 mg/m^2 after 6 weeks

Acute lymphoblastic leukemia (ALL): I.V.: 165 mg/m^2 twice weekly for 8-9 doses **or** 250 mg/m^2 weekly for 4-8 weeks

Dosing: Renal ImpairmentData is insufficient, but dose adjustments may be necessary in patient with significant renal impairment.

Dosing: Hepatic ImpairmentData is insufficient, but dose adjustments may be necessary in patient with significant hepatic impairment.

Dosing: Combination Regimens

Leukemia, acute lymphocytic: Linker Protocol

Neuroblastoma:

CCDDT (Neuroblastoma)

CCT (Neuroblastoma)

OPEC

OPEC-D

PE-CAdO

Oncology: Bone Marrow - High DoseI.V.: 750-1000 mg/m^2

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Irritant. Slow I.V. infusion over ≥30 minutes.

Administration: I.V. DetailHypotension or increased nausea and vomiting can occur if infused rapidly. Flush thoroughly before and after administration. Incompatible with heparin. Do not use in-line filter during I.V. infusion.

Teniposide must be diluted with either D$_5$W or 0.9% sodium chloride solutions to a final concentration of 0.1, 0.2, 0.4, or 1 mg/mL. In order to prevent extraction of the plasticizer DEHP, solutions should be prepared in non-DEHP-containing containers such as glass or polyolefin containers. **The use of polyvinyl chloride (PVC) containers is not recommended.**

pH: 5

StorageStore ampuls in refrigerator at 2°C to 8°C (36°F to 46°F). Reconstituted solutions are stable at room temperature for up to 24 hours after preparation.

ReconstitutionTeniposide must be diluted with either D_5W or 0.9% sodium chloride solutions to a final concentration of 0.1, 0.2, 0.4, or 1 mg/mL. However, precipitation may occur at any concentration. **Solutions should be prepared in non-DEHP-containing containers such as glass or polyolefin containers.** The use of polyvinyl chloride (PVC) containers is not recommended. Administer 1 mg/mL solutions within 4 hours of preparation to reduce the potential for precipitation.

CompatibilityStable in D_5W, LR, NS.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, amikacin, aminophylline, amphotericin B, ampicillin, ampicillin/sulbactam, aztreonam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, carmustine, cefazolin, cefoperazone, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, chlorpromazine, cimetidine, ciprofloxacin, cisplatin, cladribine, clindamycin, co-trimoxazole, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, dexamethasone sodium phosphate, diphenhydramine, doxorubicin, doxycycline, droperidol, enalaprilat, etoposide, etoposide phosphate, famotidine, floxuridine, fluconazole, fludarabine, fluorouracil, furosemide, ganciclovir, gemcitabine, gentamicin, granisetron, haloperidol, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, ifosfamide, imipenem/cilastatin, leucovorin, lorazepam, mannitol, mechlorethamine, melphalan, meperidine, mesna, methotrexate, methylprednisolone sodium succinate, metoclopramide, metronidazole, minocycline, mitomycin, mitoxantrone, morphine, nalbuphine, netilmicin, ondansetron, piperacillin, plicamycin, potassium chloride, prochlorperazine edisylate, promethazine, ranitidine, sargramostim, sodium bicarbonate, streptozocin, thiotepa, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, vinblastine, vincristine, vinorelbine, zidovudine. **Incompatible:** Idarubicin, heparin.

ContraindicationsHypersensitivity to teniposide, Cremophor® EL (polyoxyethylated castor oil), or any component of the formulation; pregnancy

Allergy Considerations

- Epidophyllotoxin Allergy

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.
- Hypersensitivity reactions: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: Severe myelosuppression may occur;** monitor for infection and bleeding.
- Extravasation: For I.V. use only; may cause local tissue necrosis or thrombophlebitis if extravasation occurs.
- Hypersensitivity reactions: **[U.S. Boxed Warning]: Hypersensitivity reactions, including anaphylaxis-like reactions, have been reported;** monitor during infusion; immediate treatment for anaphylactic reaction should be available during administration.

Dosage form specific issues:

- Benzyl alcohol: Product contains benzyl alcohol which has been associated with "gasping syndrome" in neonates.
- Dehydrated alcohol: Product contains about 43% alcohol.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

LactationNot recommended

Adverse Reactions

>10%:

Gastrointestinal: Mucositis (75%); diarrhea, nausea, vomiting (20% to 30%); anorexia

Hematologic: Myelosuppression, leukopenia, neutropenia (95%), thrombocytopenia (65% to 80%), anemia

Onset: 5-7 days

Nadir: 7-10 days

Recovery: 21-28 days

1% to 10%:

Cardiovascular: Hypotension (2%), associated with rapid (<30 minutes) infusions

Dermatologic: Alopecia (9%), rash (3%)

Miscellaneous: Anaphylactoid reactions (5%) (fever, rash, hyper-/hypotension, dyspnea, bronchospasm), usually seen with rapid (<30 minutes) infusions

<1%: Lethargy, peripheral neuropathy, somnolence

Oncology: VesicantNo; may be an irritant
Oncology: Emetic PotentialModerate (30% to 60%)
Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP2C9 (weak), 3A4 (weak)
Drug Interactions

Barbiturates: May increase the metabolism of Teniposide. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease teniposide levels.
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, potential for increased or decreased levels/effects and risk of toxicity). Premedication with antiemetic may be beneficial. See Administration for infusion specifics. Infusion site should be closely monitored to prevent extravasation. Patient should be monitored closely during infusion for possible hypotension (may require discontinuing infusion and administering supportive therapy) or hypersensitivity reactions (chills, fever, tachycardia, dyspnea, hypotension). Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, mucositis, diarrhea, myelosuppression, leukopenia) prior to each infusion and throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.
Monitoring: Lab TestsCBC, platelet count
Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by infusion. Report immediately any swelling, pain, burning, or redness at infusion site. It is important to maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and adequate nutrition (small, frequent meals may help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or loss of hair (reversible). Report unusual bleeding or bruising, persistent fever or chills, sore throat, sores in mouth or vagina, or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate barrier contraceptive measures. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 10 mg/mL (5 mL) [contains benzyl alcohol, dehydrated ethanol 42.7%, and polyoxyethylated castor oil]

Generic AvailableNo
Mechanism of ActionTeniposide does not inhibit microtubular assembly; it has been shown to delay transit of cells through the S phase and arrest cells in late S or early G_2 phase. Teniposide is a topoisomerase II inhibitor, and appears to cause DNA strand breaks by inhibition of strand-passing and DNA ligase action.
Pharmacodynamics/Kinetics

Distribution: V_d: 0.28 L/kg; Adults: 8-44 L; Children: 3-11 L; mainly into liver, kidneys, small intestine, and adrenals; crosses blood-brain barrier to a limited extent

Protein binding: 99.4%

Metabolism: Extensively hepatic

Half-life elimination: 5 hours

Excretion: Urine (44%, 21% as unchanged drug); feces (≤10%)

Related Information

- Management of Drug Extravasations
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentMyelosuppression is common; avoid clozapine and carbamazepine
Index TermsEPT; VM-26
References

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International Brand NamesVM 26-Bristol (DE); Vumon (AR, AT, AU, BE, BG, BR, CH, CL, CN, CZ, ES, HN, HU, IT, LU, MX, NL, NO, PL, UY, ZA)

Tenofovir

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(te NOE fo veer)

U.S. Brand NamesViread®

Canadian Brand NamesViread®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleotide)

Use: Labeled IndicationsManagement of HIV infections in combination with at least two other antiretroviral agents; treatment of chronic hepatitis B virus (HBV)

Dosing: Adults**HIV infection, hepatitis B infection:** Oral: 300 mg once daily

Note: Concurrent use with adefovir and/or tenofovir combination products should be avoided.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} ≥50 mL/minute: No adjustment necessary.

Cl_{cr} 30-49 mL/minute: 300 mg every 48 hours

Cl_{cr} 10-29 mL/minute: 300 mg every 72-96 hours

Cl_{cr} <10 mL/minute without hemodialysis: No recommendation available.

Hemodialysis: 300 mg every 7 days or after a total of ~12 hours of dialysis (usually once weekly assuming 3 dialysis sessions lasting about 4 hours each)

Dosing: Hepatic ImpairmentNo dosage adjustment required.

Calculations

- Creatinine Clearance: Adults

Administration: OralMay be administered with or without food.

Dietary ConsiderationsMay be taken with or without food. Consider calcium and vitamin D supplementation in patients with history of bone fracture or osteopenia.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsThere are no contraindications listed within the FDA-approved labeling.

Warnings/Precautions

Boxed warnings:

- Chronic hepatitis B: See “Disease-related concerns” below.
- Lactic acidosis/hepatomegaly: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Decreased bone mineral density: Use has been associated with decreases in bone mineral density (~5% to 7%) and osteomalacia. Consider monitoring of bone density in patients at risk for osteopenia or with a history of pathologic fractures; consider calcium and vitamin D supplementation.
- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with tenofovir and other nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).
- Renal toxicity: May cause renal toxicity (acute renal failure and/or Fanconi syndrome); avoid use with concurrent or recent nephrotoxic therapy. Calculate creatinine clearance prior to initiation of therapy and monitor renal function (including recalculation of creatinine clearance and serum phosphorus) during therapy. Dosage adjustment required in patients with Cl_{cr} <50 mL/minute. Use with caution in patients with low body weight, or concurrent medications which increase tenofovir levels.

Disease-related concerns:

- Chronic hepatitis B: **[U.S. Boxed Warning]: Severe, acute exacerbation of hepatitis B may occur upon discontinuation.** Monitor liver function several months after discontinuing treatment; reinitiation of antihepatitis B therapy may be required. Treatment of HBV in patients with unrecognized/untreated HIV may lead to HIV resistance; patients should be tested for presence of HIV infection prior to initiating therapy

- Hepatic impairment: Use with caution in patients with hepatic impairment. No dosage adjustment is required; limited studies indicate the pharmacokinetics of tenofovir are not altered in hepatic dysfunction.

- HIV: Appropriate use: Do not use as monotherapy in treatment of HIV. Treatment of HIV in patients with unrecognized/untreated HBV may lead to rapid HBV resistance. Patients should be tested for presence of chronic hepatitis B infection prior to initiation of therapy.

- Renal impairment: Use with caution in patients with renal impairment (Cl_{cr} <50 mL/minute); dosage adjustment required.

Concurrent drug therapy issues:

- Adefovir: Do not use concurrently with adefovir for the treatment of chronic hepatitis B.

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

- Tenofovir combination products: Do not use concurrently with tenofovir combination products (Atripla™, Truvada®).

Special populations:

- Elderly: Due to a higher incidence of hepatic and/or renal impairment, use with caution in the elderly. Dosage adjustment based on renal function may be required.

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAnimal studies have shown decreased fetal growth and reduced fetal bone porosity. Clinical studies in children have shown bone demineralization with chronic use. Tenofovir crosses the human placenta; limited data indicate decreased maternal bioavailability during the 3rd trimester. Due to the potential for bone effects, use in pregnancy only if clearly needed. Cases of lactic acidosis/hepatic steatosis syndrome have been reported in pregnant women receiving nucleoside analogues. It is not known if pregnancy itself potentiates this known side effect; however, pregnant women may be at increased risk of lactic acidosis and liver damage. Hepatic enzymes and electrolytes should be monitored frequently during the 3rd trimester of pregnancy in women receiving nucleoside analogues. Health professionals are encouraged to contact the Antiretroviral Pregnancy Registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse ReactionsPercentages listed were from clinical trials with tenofovir addition to prior antiretroviral therapy. Only adverse events from treatment naïve patient studies which varied significantly were noted (eg, rash event). Frequencies listed are treatment-emergent adverse effects noted at higher frequency than in the placebo group. Patients treated for chronic hepatitis B had similar reactions and frequencies.

>10%:

Cardiovascular: Chest pain (3%)

Central nervous system: Pain (7% to 12%)

Gastrointestinal: Diarrhea (9% to 16%), nausea (8% to 11%)

Neuromuscular & skeletal: Weakness (7% to 11%)

1% to 10%:

Central nervous system: Depression (4% to 9%; treatment naïve 11%), fatigue (9%), headache (5% to 8%; treatment naïve 14%), fever (2% to 4%; treatment naïve 8%), dizziness (1% to 8%), anxiety (treatment naïve 6%), insomnia (3% to 5%)

Dermatologic: Rash event (maculopapular, pustular, or vesiculobullous rash, pruritus or urticaria 5% to 7%; treatment naïve 18%)

Endocrine & metabolic: Triglycerides increased (grades 3/4: 4% to 11%), hyperglycemia (grades 3/4: 2%)

Gastrointestinal: Vomiting (4% to 7%), abdominal pain (4% to 7%), serum amylase increased (grades 3/4: 4%; treatment naïve 9%), dyspepsia (3% to 4%), flatulence (3% to 4%), anorexia (3% to 4%), weight loss (2% to 4%)

Genitourinary: Hematuria (grades 3/4: 7%)

Hematologic: Neutropenia (1% to 2%; grade 3/4: 3%)

Hepatic: Transaminases increased (2% to 10%), alkaline phosphatase increased (grades 3/4: 1%)

Neuromuscular & skeletal: Creatine kinase (grade 3/4: 7% to 12%), back pain (3% to 4%; treatment naïve 9%), neuropathy (peripheral 3% to 5%), myalgia (3% to 4%)

Renal: Glycosuria (≤3%)

Respiratory: Respiratory tract infection (upper; 8%), sinusitis (8%), pharyngitis (5%), pneumonia (2% to 3%; treatment naïve 5%)

Miscellaneous: Diaphoresis (3%)

Postmarketing and/or case reports: Acute tubular necrosis, allergic reaction, bone mineral density decreased, dyspnea, Fanconi syndrome, hepatic steatosis, hepatitis, hypokalemia, hypophosphatemia, immune reconstitution syndrome, interstitial nephritis, lactic acidosis, muscle weakness, nephrogenic diabetes insipidus, nephrotoxicity, osteomalacia, pancreatitis, proteinuria, proximal renal tubulopathy, renal failure, renal myopathy, rhabdomyolysis, serum creatinine increased

Metabolism/Transport Effects **Inhibits** CYP1A2 (weak)

Drug Interactions

Acyclovir-Valacyclovir: May decrease the excretion of Tenofovir. *Risk C: Monitor therapy*

Adefovir: May diminish the therapeutic effect of Tenofovir. Specifically, adefovir-associated mutations in Hepatitis B viral reverse transcriptase may decrease viral susceptibility to tenofovir. Tenofovir may increase the serum concentration of Adefovir. Similarly, Adefovir may increase the concentration of Tenofovir. *Risk D: Consider therapy modification*

Atazanavir: Tenofovir may decrease the serum concentration of Atazanavir. Atazanavir may increase the serum concentration of Tenofovir. Management: When combined use required, tenofovir 300mg and atazanavir 300mg should be used together with ritonavir 100mg, all given as a single daily dose with food. Atazanavir without ritonavir should not be used with tenofovir. *Risk D: Consider therapy modification*

Didanosine: Tenofovir may diminish the therapeutic effect of Didanosine. Tenofovir may increase the serum concentration of Didanosine. *Risk D: Consider therapy modification*

Ganciclovir-Valganciclovir: May decrease the excretion of Tenofovir. *Risk C: Monitor therapy*

Lopinavir: May enhance the nephrotoxic effect of Tenofovir. Lopinavir may increase the serum concentration of Tenofovir. *Risk C: Monitor therapy*

Protease Inhibitors: Tenofovir may decrease the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Tenofovir. **Exceptions:** Saquinavir. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions Food: Fatty meals may increase the bioavailability of tenofovir. Tenofovir may be taken with or without food.

Monitoring Parameters

Patients with HIV: CBC with differential, reticulocyte count, serum creatine kinase, CD4 count, HIV RNA plasma levels, renal and hepatic function tests, bone density (long-term), serum phosphorus; testing for HBV is recommended prior to the initiation of antiretroviral therapy

Patients with HBV: HIV status (prior to initiation of therapy); bone density (long-term), serum phosphorus; serum creatinine (prior to initiation and during therapy; every 3 months in patients with medical conditions which predispose to renal insufficiency and in all patients treated for >1 year; more frequent monitoring required if preexisting renal insufficiency detected [Lok, 2007]); viral load; LFTs for several months following discontinuation of tenofovir.

Patients with HIV and HBV coinfection should be monitored for several months following tenofovir discontinuation.

Nursing: Physical Assessment/Monitoring Assess closely for any previous allergy history prior to beginning treatment. Evaluate other pharmacological or herbal products patient may be taking for potential interactions (eg, concurrent use with other antiretroviral nephrotoxic or hepatotoxic drugs may increase potential for severe toxicities). Assess results of all laboratory tests (specific to purpose for use). Evaluate therapeutic response and adverse reactions on a regular basis throughout therapy (eg, lactic acidosis osteomalacia, gastrointestinal disturbance, neutropenia, myalgia, peripheral neuropathy). Teach patient proper use (drugs that should not be used concurrently), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab Tests

Patients with HIV: CBC with differential, reticulocyte count, serum creatine kinase, CD4 count, HIV RNA plasma levels, renal and hepatic function tests, bone density (long-term), serum phosphorus; testing for HBV is recommended prior to the initiation of antiretroviral therapy

Patients with HBV: HIV status (prior to initiation of therapy); bone density (long-term), serum phosphorus; serum creatinine (prior to initiation and during therapy; every 3 months in patients with medical conditions which predispose to renal insufficiency and in all patients treated for >1 year; more frequent monitoring required if preexisting renal insufficiency detected [Lok, 2007]); viral load; LFTs for several months following discontinuation of tenofovir.

Patients with HIV and HBV coinfection should be monitored for several months following tenofovir discontinuation.

Patient Education Do not take any new prescription or OTC medications or herbal products without consulting prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other people. When used to treat HIV, this drug will be prescribed as one part of a multidrug combination; take exactly as directed for full course of therapy. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. You may be susceptible to infection (avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber). Frequent blood tests may be required with prolonged therapy. May cause dizziness or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known) or nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report immediately any tingling, pain, or loss of sensation in toes, feet, muscles, or joints; swollen glands; alterations in urinary pattern; swelling of extremities; weight gain or loss; unusual weakness; signs of opportunistic infection (burning on urination, perineal itching, white plaques in mouth, unhealed sores, persistent sore throat or cough); or other persistent adverse effects. If you are instructed to stop the medication; do not restart without specific instruction by your prescriber. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as disoproxil fumarate:

Viread®: 300 mg [equivalent to 245 mg tenofovir disoproxil]

Generic AvailableNo
ManufacturerGilead Sciences
Pricing: U.S. (www.drugstore.com)

Tablets (Viread)

300 mg (30): $621.49

Mechanism of ActionTenofovir disoproxil fumarate (TDF) is an analog of adenosine 5'-monophosphate; it interferes with the HIV viral RNA dependent DNA polymerase resulting in inhibition of viral replication. TDF is first converted intracellularly by hydrolysis to tenofovir and subsequently phosphorylated to the active tenofovir diphosphate; nucleotide reverse transcriptase inhibitor. Tenofovir inhibits replication of HBV by inhibiting HBV polymerase.
Pharmacodynamics/Kinetics

Distribution: 1.2-1.3 L/kg

Protein binding: ≤7% to serum proteins

Metabolism: Tenofovir disoproxil fumarate (TDF) is converted intracellularly by hydrolysis (by non-CYP enzymes) to tenofovir, then phosphorylated to the active tenofovir diphosphate

Bioavailability: ~25% (fasting); increases ~40% with high-fat meal

Half-life elimination: ~17 hours

Time to peak, serum: Fasting: 36-84 minutes; With food: 96-144 minutes

Excretion: Urine (70% to 80%) via filtration and active secretion, primarily as unchanged tenofovir

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV
- Perinatal HIV Guidelines

Pharmacotherapy PearlsApproval was based on two clinical trials involving patients who were previously treated with antiretrovirals with continued evidence of HIV replication despite therapy. The risk:benefit ratio for untreated patients has not been established (studies currently ongoing), however, patients who received tenofovir showed significant decreases in HIV replication as compared to continuation of standard therapy.

A high rate of early virologic nonresponse was observed when abacavir, lamivudine, and tenofovir were used as the initial regimen in treatment-naive patients. A high rate of early virologic nonresponse was also observed when didanosine, lamivudine, and tenofovir were used as the initial regimen in treatment-naive patients. Use of either of these combinations is not recommended; patients currently on either of these regimens should be closely monitored for modification of therapy. Early virologic failure was also observed with tenofovir and didanosine delayed release capsules, plus either efavirenz or nevirapine; use caution in treatment-naive patients with high baseline viral loads.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness and depression
Mental Health: Effects on Psychiatric TreatmentNausea and diarrhea are common; use caution with SSRIs, lithium, and valproic acid. May cause elevation of triglycerides; monitor in patients receiving antipsychotics especially clozapine, olanzapine, and quetiapine.
Index TermsPMPA; TDF; Tenofovir Disoproxil Fumarate
References

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Lok AS and McMahon BJ, “Chronic Hepatitis B,” *Hepatology*, 2007, 45(2):507-39.[PubMed 17256718]

“Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,” July 8, 2008. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” July 29, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesViread (AR, AT, AU, BE, BG, CH, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, MX, NL, NO, PT, RU, SE, TH, TR, UY)

Terazosin

Lexi-Drugs Online

English

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Pronunciation(ter AY zoe sin)

Canadian Brand NamesAlti-Terazosin; Apo-Terazosin®; Hytrin®; Novo-Terazosin; Nu-Terazosin; PMS-Terazosin

Pharmacologic CategoryAlpha $_1$ Blocker

Use: Labeled IndicationsManagement of mild to moderate hypertension; alone or in combination with other agents such as diuretics or beta-blockers; benign prostate hyperplasia (BPH)

Use: Unlabeled/InvestigationalPediatric hypertension

Dosing: Adults

Hypertension: Oral: Initial: 1 mg at bedtime; slowly increase dose to achieve desired blood pressure, up to 20 mg/day; usual dose range (JNC 7): 1-20 mg once daily

Dosage reduction may be needed when adding a diuretic or other antihypertensive agent; if drug is discontinued for greater than several days, consider beginning with initial dose and retitrate as needed; dosage may be given on a twice daily regimen if response is diminished at 24 hours and hypotensive is observed at 2-4 hours following a dose

Benign prostatic hyperplasia: Oral: Initial: 1 mg at bedtime, increasing as needed; most patients require 10 mg day. If no response after 4-6 weeks of 10 mg/day, may increase to 20 mg/day.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Hypertension (unlabeled use):** Oral: Initial: 1 mg once daily; gradually increase dose as necessary, up to maximum of 20 mg/day

Dietary ConsiderationsMay be taken without regard to meals at the same time each day.

ContraindicationsHypersensitivity to quinazolines (doxazosin, prazosin, terazosin) or any component of the formulation; concurrent use with phosphodiesterase-5 (PDE-5) inhibitors including sildenafil (>25 mg), tadalafil, or vardenafil

Allergy Considerations

- Alpha-Blocker, Piperazinyl Quinazoline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Angina: Discontinue if symptoms of angina occur or worsen.
- Floppy iris syndrome: Intraoperative floppy iris syndrome has been observed in cataract surgery patients who were on or were previously treated with alpha$_1$-blockers; causality has not been established and there appears to be no benefit in discontinuing alpha-blocker therapy prior to surgery.
- Orthostatic hypotension/syncope: May cause significant orthostatic hypotension and syncope, especially with first dose; anticipate a similar effect if therapy is interrupted for a few days, if dosage is rapidly increased, or if another antihypertensive drug (particularly vasodilators) or a PDE-5 inhibitor is introduced. Patients should be cautioned about performing hazardous tasks when starting new therapy or adjusting dosage upward.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Prostate cancer: It is recommended to rule out prostatic carcinoma before beginning therapy.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsAdverse reactions such as dry mouth and urinary problems can be particularly bothersome in the elderly.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown

Adverse ReactionsAsthenia, postural hypotension, dizziness, somnolence, nasal congestion/rhinitis, and impotence were the only events noted in clinical trials to occur at a frequency significantly greater than placebo ($p < 0.05$).

>10%:

Central nervous system: Dizziness, headache

Neuromuscular & skeletal: Muscle weakness

1% to 10%:

Cardiovascular: Edema, palpitation, chest pain, peripheral edema (3%), orthostatic hypotension (3% to 4%), tachycardia

Central nervous system: Fatigue, nervousness, drowsiness

Gastrointestinal: Dry mouth

Genitourinary: Urinary incontinence

Ocular: Blurred vision

Respiratory: Dyspnea, nasal congestion

<1% (Limited to important or life-threatening): Sexual dysfunction, syncope (0.8%)

Postmarketing and/or case reports: Allergic reactions, anaphylaxis, atrial fibrillation, priapism, thrombocytopenia

Drug Interactions

Alfuzosin: Alpha1-Blockers may enhance the antihypertensive effect of Alfuzosin. Risk of orthostatic hypotension or syncope may be increased. Alfuzosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

Calcium Channel Blockers: Alpha1-Blockers may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Phosphodiesterase 5 Inhibitors: May enhance the hypotensive effect of Alpha1-Blockers. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Silodosin: Alpha1-Blockers may enhance the adverse/toxic effect of Silodosin. Of particular concern are the risk of postural hypotension, syncope, and/or hypotension. Silodosin may enhance the hypotensive effect of Alpha1-Blockers. Of particular concern are the risk of postural hypotension, syncope, and/or hypotension. *Risk X: Avoid combination*

Tamsulosin: Alpha1-Blockers may enhance the antihypertensive effect of Tamsulosin. Risk of orthostatic hypotension or syncope may be increased. Tamsulosin may enhance the antihypertensive effect of Alpha1-Blockers. *Risk X: Avoid combination*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid saw palmetto. Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersStanding and sitting/supine blood pressure, especially following the initial dose at 2-4 hours following the dose and thereafter at the trough point to ensure adequate control throughout the dosing interval; urinary symptoms

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents and herbal products patient may be taking (especially anything that may decrease antihypertensive response [NSAIDS, ephedra, yohimbe, ginseng] or increase hypotensive effect [beta-blockers, diuretics, ACE inhibitors]). Assess therapeutic effectiveness (blood pressure) and adverse reactions (eg, hypotension, dizziness, somnolence, impotence) at beginning of therapy and on a regular basis with long-term therapy. When discontinuing, dose should be tapered and blood pressure monitored closely. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed; at bedtime. Do not skip dose or discontinue without consulting prescriber. Follow recommended diet and exercise program. May cause drowsiness, dizziness, or impaired judgment (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from sitting or lying position or when climbing stairs); dry mouth or nausea (frequent mouth care or sucking lozenges may help); urinary incontinence (void before taking medication); or sexual dysfunction (reversible, may resolve with continued use). Report altered CNS status (eg, fatigue, lethargy, confusion, nervousness); sudden weight gain (weigh yourself in the same clothes at the same time of day once a week); unusual or persistent swelling of ankles, feet, or extremities; palpitations or rapid heartbeat; respiratory difficulty; muscle weakness; or other persistent side effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 1 mg, 2 mg, 5 mg, 10 mg

Generic AvailableYes

ManufacturerAbbott Laboratories (Pharmaceutical Product Division)

Pricing: U.S. (www.drugstore.com)

Capsules (Terazosin HCl)

1 mg (30): $14.45

2 mg (30): $13.99

5 mg (30): $13.99

10 mg (30): $13.99

Mechanism of Action Alpha$_1$-specific blocking agent with minimal alpha$_2$ effects; this allows peripheral postsynaptic blockade, with the resultant decrease in arterial tone, while preserving the negative feedback loop which is mediated by the peripheral presynaptic alpha$_2$-receptors; terazosin relaxes the smooth muscle of the bladder neck, thus reducing bladder outlet obstruction

Pharmacodynamics/Kinetics

Onset of action: 1-2 hours

Absorption: Rapid

Protein binding: 90% to 95%

Metabolism: Extensively hepatic

Half-life elimination: 9.2-12 hours

Time to peak, serum: ~1 hour

Excretion: Feces (60%); urine (40%)

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Dizziness is common; may cause drowsiness or nervousness; may rarely cause insomnia or depression

Mental Health: Effects on Psychiatric Treatment None reported

Cardiovascular Considerations An alpha$_1$-blocker may be used in combination with other agents for the treatment of hypertension or alone in select patients who fail to respond or have contraindications to other agents. Patients with BPH may derive an extra benefit from therapy. Recently, the doxazosin treatment arm of ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) was prematurely stopped due to a significantly higher incidence (25%) of cardiovascular events (particularly heart failure events), compared to the diuretic (chlorthalidone) treatment arm. This unfavorable difference was also present when doxazosin was compared to the amlodipine and lisinopril treatment arms. This study does not address cardiovascular outcomes when doxazosin is combined with other antihypertensive medications. Consideration should be given to the ALLHAT results when considering the use of an alpha$_1$-blocker for treatment of hypertension.

References

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International Brand Names Adecur (CN, MX, PY); Adenex (PE); Benaprost (AR); Biphanti (KP); Centrax (EC); Conmy (PH, TW); Deflox (ES); Eglidon (AR); Flotrin (DE); Hitrin (CR, GT, HN, NI, PA, SV); Hykor (PH); Hyron (HU); Hytracin (JP); Hytrin (AU, BB, BE, BM, BR, BS, BZ, CL, CN, CO, CZ, GB, GR, GY, HK, HU, ID, IE, IL, IN, JM, LU, MX, MY, NL, PE, PH, PK, PL, PT, SR, TH, TT, TW, UY, VE); Hytrin BPH (CH); Hytrine (FR, KP); Hytrinex (SE); Itrin (IT); Kinzosin (TW); Kornam (PL); Lontencin (PH); Magnurol (ES); Olyster (IN); Setegis (HN, HU, PL); Sinalfa (DK, NO); Teralfa (IN); Terapam (KP); Terasin (MY); Terazoflo (DE); Tetrin (KP); Tracin (KP); Vasomet (JP); Vicard (AT); Zayasel (CR, GT, HN, NI, PA, SV); Zytrin (IN)

Terbinafine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Terbinafine may be confused with terbutaline

Lamisil® may be confused with Lamictal®, Lomotil®

International issues:

Lamisil® may be confused with Lemesil® which is a brand name for nimesulide in Greece and Romania

Pronunciation(TER bin a feen)

U.S. Brand NamesLamisil AT® [OTC]; Lamisil®

Canadian Brand NamesApo-Terbinafine®; CO Terbinafine; Gen-Terbinafine; Lamisil®; Novo-Terbinafine; PHL-Terbinafine; PMS-Terbinafine; RIVA-Terbinafine; SANDOZ-Terbinafine; Terbinafine-250

Pharmacologic CategoryAntifungal Agent, Oral; Antifungal Agent, Topical

Use: Labeled IndicationsActive against most strains of *Trichophyton mentagrophytes*, *Trichophyton rubrum*; may be effective for infections of *Microsporum gypseum* and *M. nanum*, *Trichophyton verrucosum*, *Epidermophyton floccosum*, *Candida albicans*, and *Scopulariopsis brevicaulis*

Oral: Onychomycosis of the toenail or fingernail due to susceptible dermatophytes; treatment of tinea capitis

Topical: Antifungal for the treatment of tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm) [OTC/prescription formulations]; tinea versicolor [prescription formulations]

Dosing: Adults

Superficial mycoses (onychomycosis): Oral:

Fingernail: 250 mg daily for up to 6 weeks; may be given in 2 divided doses

Toenail: 250 mg daily for 12 weeks; may be given in 2 divided doses

Systemic mycosis (unlabeled use): Oral: 250-500 mg/day for up to 16 months

Athlete's foot (tinea pedis): Topical:

Cream: Apply to affected area twice daily for at least 1 week, not to exceed 4 weeks [OTC/prescription formulations]

Gel: Apply to affected area twice daily for 7 days [OTC formulations]

Solution: Apply to affected area twice daily for 7 days [OTC/prescription formulations]

Ringworm and jock itch (tinea corporis, tinea cruris): Topical:

Cream: Apply to affected area once or twice daily for at least 1 week, not to exceed 4 weeks [OTC formulations]

Gel: Apply to affected area once daily for 7 days [OTC formulations]

Solution: Apply to affected area once daily for 7 days in tinea corporis and tinea cruris [OTC formulations]; apply to affected area twice daily for 7 days in tinea versicolor [prescription formulation]

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Tinea capitis: Oral: Granules: Children ≥4 years:

<25 kg: 125 mg once daily for 6 weeks

25-35 kg: 187.5 mg once daily for 6 weeks

>35 kg: 250 mg once daily for 6 weeks

Onychomycosis (unlabeled use): Oral: Tablet: Children:

10-20 kg: 62.5 mg once daily for 6 weeks (fingernails) **or** 12 weeks (toenails)

20-40 kg: 125 mg once daily for 6 weeks (fingernails) **or** 12 weeks (toenails)

>40 kg: 250 mg once daily for 6 weeks (fingernails) **or** 12 weeks (toenails)

Athlete's foot (tinea pedis), ringworm (tinea corporis), jock itch (tinea cruris): Topical cream, gel, solution: Children ≥12 years: Refer to adult dosing:

Dosing: Renal ImpairmentCl_{cr} <50 mL/minute: Oral administration is not recommended; clearance is decreased by ~50%.

Dosing: Hepatic ImpairmentHepatic cirrhosis: Oral administration is not recommended; clearance is decreased by ~50%.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralTablets may be administered without regard to meals. Granules should be sprinkled on a spoonful of nonacidic food (eg, mashed potatoes); swallow granules without chewing.

Storage

Cream: Store at 5°C to 30°C (41°F to 86°F).

Granules: Store at controlled room temperature if 15°C to 30°C (59°F to 86°F).

Solution: Store at 5°C to 25°C (41°F to 77°F); do not refrigerate.

Tablet: Store below 25°C (77°F). Protect from light.

ContraindicationsHistory of or allergic reaction to oral terbinafine

Warnings/Precautions

Concerns related to adverse effects:

- Allylamine antifungal hypersensitivity: Use caution in patients sensitive to allylamine antifungals (eg, naftifine, butenafine); cross sensitivity to terbinafine may exist

- Dermatologic effects: Although rare, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with oral use; discontinue therapy if progressive skin rash occurs.

- Hematologic effects: Although rare, pancytopenia and neutropenia have been reported with oral use; discontinuation of therapy may be required. Monitor CBCs in patients with pre-existing immunosuppression if use to continue >6 weeks.

- Hepatic failure: Rare cases of hepatic failure (including fatal cases) have been reported following oral treatment; not recommended for use in patients with active or chronic liver disease. Discontinue if symptoms or signs of hepatobiliary dysfunction or cholestatic hepatitis develop.

- Ocular effects: Although rare, changes in the ocular lens and retina have been reported with oral use; discontinuation of therapy may be required.

Disease-related concerns:

- Hepatic cirrhosis: Use of oral therapy not recommended in patients with hepatic cirrhosis; clearance is reduced by approximately 50%.

- Lupus: Precipitation or exacerbation of cutaneous or systemic lupus erythematosus has been observed with oral therapy; discontinue if signs and/or symptoms develop.

- Renal dysfunction: Use of oral therapy not recommended in patients with renal dysfunction (Cl_{cr} ≤50 mL/minute); clearance is reduced by approximately 50%.

Geriatric ConsiderationsNo specific information on the systemic use of terbinafine in the elderly is available; however, since many elderly will have creatinine clearances <50 mL/minute, this drug is not a drug of choice for elderly with onychomycosis.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Avoid use in pregnancy since treatment of onychomycosis is postponable.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsAlthough minimal concentrations of terbinafine cross into breast milk after topical use, oral or topical treatment during lactation should be avoided.

Adverse Reactions

Oral: Adverse events listed for tablets unless otherwise specified. Oral granules were studied in patients 4-12 years of age.

>10%: Central nervous system: Headache (13%; granules 7%)

1% to 10%:

Central nervous system: Fever (granules 7%)

Dermatologic: Rash (6%; granules 2%), pruritus (3%; granules 1%), urticaria (1%)

Gastrointestinal: Diarrhea (6%; granules 3%), vomiting (granules 5%), dyspepsia (4%), nausea (3%; granules 2%), taste disturbance (3%), abdominal pain (2%; granules 2% to 4%), toothache (granules 1%)

Hepatic: Liver enzyme abnormalities (3%)

Respiratory: Nasopharyngitis (granules 10%), cough (granules 6%), nasal congestion (granules 2%), pharyngeal pain (granules 2%), rhinorrhea (granules 2%)

<1%, postmarketing, and/or case reports: Acute pancreatitis, anemia, angioedema, agranulocytosis, allergic reactions, alopecia, anaphylaxis, appetite decreased, arthralgia, dizziness, fatigue, generalized exanthematous pustulosis (acute), hepatic failure, malaise, myalgia, neutropenia (severe), ocular lens and retina changes, precipitation/exacerbation of cutaneous and systemic lupus erythematosus, pancytopenia, psoriasiform eruption, psoriasis exacerbation, rhabdomyolysis, Stevens-Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis, visual field acuity decreased, visual field defects, vomiting

Topical: 1% to 10%:

Dermatologic: Burning, contact dermatitis, dryness, exfoliation, irritation, pruritus, rash

Local: Irritation, stinging

Metabolism/Transport Effects**Substrate** (minor) of 1A2, 2C9, 2C19, 3A4; **Inhibits** CYP2D6 (strong); **Induces** CYP3A4 (weak)

Drug Interactions

Codeine: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

CycloSPORINE: Terbinafine may decrease the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Strong) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Nebivolol: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Terbinafine. *Risk D: Consider therapy modification*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Tamoxifen: CYP2D6 Inhibitors (Strong) may decrease the metabolism of Tamoxifen. Specifically, strong CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk X: Avoid combination*

Tetrabenazine: CYP2D6 Inhibitors (Strong) may increase the serum concentration of Tetrabenazine. Specifically, concentrations of the active alpha- and beta-dihydrotetrabenazine metabolites may be increased. Management: Tetrabenazine dose should be reduced by 50% when starting a strong CYP2D6 inhibitor. Maximum tetrabenazine dose is 50mg/day when used with a strong CYP2D6 inhibitor. *Risk D: Consider therapy modification*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: CYP2D6 Inhibitors (Strong) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Terbinafine may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Monitoring ParametersAST/ALT prior to initiation, repeat if used >6 weeks; CBC

Nursing: Physical Assessment/MonitoringUse oral formulation with caution in presence of hepatic or renal impairment. Assess potential for interactions with other pharmacological or herbal agents patient may be taking (eg, risk of toxicity, decreased effects). Assess results of laboratory tests, therapeutic effectiveness (according to purpose for use), and adverse reactions at beginning of therapy and on a regular basis during therapy (adverse reactions may require discontinuing treatment). Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsAST/ALT prior to initiation, repeat if used >6 weeks; CBC

Patient EducationDo not take any new prescriptions, OTC medications, or herbal products during therapy unless approved by prescriber. Oral: Take exactly as directed at same time of day, with or without regard to meals. Granules may be sprinkled on a spoonful of nonacidic food (eg, mashed potatoes); swallow granules without chewing. It is important to take full prescription even if symptoms appear resolved; may take several months for full treatment (inadequate treatment may result in reinfection). May cause altered taste (normal); nausea, vomiting, or abdominal pain (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or diarrhea (buttermilk, boiled milk, or yogurt may reduce diarrhea). Report unusual fatigue; persistent gastrointestinal upset; nasal congestion, runny nose, sore throat, or unusual cough; skin rash or blistering; dark urine/pale stool; or other persistent adverse response. **Breast-feeding precaution:** Breast-feeding is not recommended.

Topical: Cream, gel, or spray for topical use only. Use exactly as directed (see package insert). Wash and dry area thoroughly before applying. Avoid contact with eyes, nose, or mouth. Do not use occlusive dressings. Report irritation, itching, or burning in treated area.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, topical, as hydrochloride: 1% (12 g, 24 g)

Lamisil AT®: 1% (12 g, 15 g, 24 g, 30 g, 36 g) [contains benzyl alcohol]

Gel, topical:

Lamisil AT®: 1% (6 g, 12 g) [contains benzyl alcohol]

Granules, oral:

Lamisil® 125 mg/packet (42s); 187.5 mg/packet (42s)

Solution, topical, as hydrochloride [spray]:

Lamisil AT®: 1% (30 mL) [contains ethanol]

Tablet, oral: 250 mg

Lamisil®: 250 mg

Generic AvailableYes: Excludes gel, granules, and solution
Pricing: U.S. (www.drugstore.com)

Solution (Lamisil)

1% (30): $77.03

Tablets (Lamisil)

250 mg (30): $392.99

Tablets (Terbinafine HCl)

250 mg (30): $48.98

Mechanism of ActionSynthetic allylamine derivative which inhibits squalene epoxidase, a key enzyme in sterol biosynthesis in fungi. This results in a deficiency in ergosterol within the fungal cell wall and results in fungal cell death.
Pharmacodynamics/Kinetics

Absorption: Topical: Limited (<5%); Oral: >70% (children and adults)

Distribution: V_d: 1000 L; distributed to sebum and skin predominantly

Protein binding: Plasma: >99% (children and adults)

Metabolism: Hepatic; no active metabolites; first-pass effect; little effect on CYP

Bioavailability: Oral: 40% (children 36% to 64%)

Half-life elimination:

Topical: 14-35 hours

Oral: Terminal half-life: 200-400 hours; very slow release of drug from skin and adipose tissues occurs; effective half-life: ~36 hours (children 27-31 hours)

Time to peak, plasma: 1-2 hours (children and adults)

Excretion: Urine (70% to 75%; children 70%)

Related Information

- Antifungal Agents

Pharmacotherapy PearlsDue to potential toxicity, the manufacturer recommends confirmation of diagnosis testing of nail specimens prior to treatment of onychomycosis. Patients should not be considered therapeutic failures until they have been symptom-free for 2-4 weeks off following a course of treatment; GI complaints usually subside with continued administration.

A meta-analysis of efficacy studies for toenail infections revealed that weighted average mycological cure rates for continuous therapy were 36.7% (griseofulvin), 54.7% (itraconazole), and 77% (terbinafine). Cure rate for 4-month pulse therapy for itraconazole and terbinafine were 73.3% and 80%. Additionally, the final outcome measure of final costs per cured infections for continuous therapy was significantly lower for terbinafine.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste disturbance.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentMay rarely cause pancytopenia and neutropenia; use caution with clozapine and carbamazepine. May cause GI side effects; concomitant use with SSRIs, carbamazepine, valproic acid, and lithium may produce additive effects. Terbinafine is a potent CYP2D6 inhibitor and may decrease the metabolism of thioridazine and tricyclic antidepressants; combined use with thioridazine should be avoided.
Index TermsTerbinafine Hydrochloride
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International Brand Names Binasil (KP); Dermafin (MY); Dermasil (IL); Exifine (MY); Fungitech (TW); Interbi (ID); Lamifen (PH); Lamisil (AE, AR, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BO, BR, BS, BZ, CH, CI, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IT, JM, JO, JP, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PK, PL, PR, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SV, SY, TH, TN, TR, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Lamisil AT (ID); Lamisil Dermgel (FR, IL); Lamisil Once (AU); Lamisilate (FR); Lamisilatt (PL); Lamonan (KP); Lisim (MY); Micoset (CN); Micosil (KP); Mozolasil (KP); Muzonal (KP); Namuzol (KP); Patir (IL); Sebifin (IN); SolvEasy Tinea Cream (AU); Sulmedin (TW); Tamsil (AU); Tenasil (PL); Terbafin (NZ); Terbifin (HK); Terbisil (PL, SG); Terekol (AR); Terfung (TW); Termisil (ID); Tinasil (AU)

Terbutaline

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English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Terbutaline may be confused with terbinafine, TOLBUTamide

Pronunciation(ter BYOO ta leen)

Canadian Brand NamesBricanyl®

Pharmacologic CategoryBeta$_2$ Agonist

Use: Labeled IndicationsBronchodilator in reversible airway obstruction and bronchial asthma

Use: Unlabeled/InvestigationalTocolytic agent (management of preterm labor)

Dosing: Adults

Asthma or bronchoconstriction:

Oral: 5 mg/dose every 6 hours 3 times/day; if side effects occur, reduce dose to 2.5 mg every 6 hours; not to exceed 15 mg in 24 hours.

SubQ: 0.25 mg/dose; may repeat in 15-30 minutes (maximum: 0.5 mg/4-hour period)

Bronchospasm (acute): *Inhalation* (Bricanyl® [CAN] MDI: 500 mcg/puff, *not labeled for use in the U.S.*): One puff as needed; may repeat with 1 inhalation (after 5 minutes); more than 6 inhalations should not be necessary in any 24 hour period. **Note:** If a previously effective dosage regimen fails to provide the usual relief, or the effects of a dose last for >3 hours, medical advice should be sought immediately; this is a sign of seriously worsening asthma that requires reassessment of therapy.

Premature labor (tocolysis; unlabeled use):

Acute: I.V. 2.5-10 mcg/minute; increased gradually every 10-20 minutes. Effective maximum dosages from 17.5-30 mcg/minute have been use with caution. Duration of infusion is at least 12 hours.

Maintenance: Oral: 2.5-10 mg every 4-6 hours for as long as necessary to prolong pregnancy depending on patient tolerance

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Asthma or bronchoconstriction:

Oral: Children:

<12 years: Initial: 0.05 mg/kg/dose 3 times/day, increased gradually as required; maximum: 0.15 mg/kg/dose 3-4 times/day or a total of 5 mg/24 hours

12-15 years: 2.5 mg every 6 hours 3 times/day; not to exceed 7.5 mg in 24 hours

>15 years: 5 mg/dose every 6 hours 3 times/day; if side effects occur, reduce dose to 2.5 mg every 6 hours; not to exceed 15 mg in 24 hours

SubQ: Children:

<12 years: 0.005-0.01 mg/kg/dose to a maximum of 0.3 mg/dose; may repeat in 15-20 minutes

≥12 years: Refer to adult dosing.

Bronchospasm (acute):*Inhalation:* Bricanyl® [CAN] MDI: 500 mcg/puff, *not labeled for use in the U.S.*): Children ≥6 years: Refer to adult dosing.

Dosing: Renal Impairment

Cl$_{cr}$ 10-50 mL/minute: Administer 50% of normal dose.

Cl$_{cr}$ <10 mL/minute: Avoid use.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Use infusion pump.

Administration: I.V. DetailpH: 3-5 (adjusted)

Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels.

StorageStore injection at room temperature; do not freeze. Protect from heat and light. Use only clear solutions. Store powder for inhalation

(Bricanyl® Turbuhaler [CAN]) at room temperature between 15°C and 30°C (58°F and 86°F).

CompatibilityStable in D_5W, $^1/_2$NS, NS.

Y-site administration: Compatible: Insulin (regular).

Compatibility in syringe: Compatible: Doxapram.

Compatibility when admixed: Compatible: Aminophylline. **Incompatible:** Bleomycin.

Extemporaneously PreparedA 1 mg/mL suspension made from terbutaline tablets in simple syrup NF is stable 30 days when refrigerated

Horner RK and Johnson CE, "Stability of An Extemporaneously Compounded Terbutaline Sulfate Oral Liquid," *Am J Hosp Pharm*, 1991, 48(2):293-5.

ContraindicationsHypersensitivity to terbutaline or any component of the formulation; cardiac arrhythmias associated with tachycardia; tachycardia caused by digitalis intoxication

Warnings/Precautions

Concerns related to adverse effects:

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.
- Hypersensitivity reactions: Immediate hypersensitivity reactions (urticaria, angioedema, rash, bronchospasm) have been reported.
- Serious effects/fatalities: Do not exceed recommended dose; serious adverse events, including fatalities, have been associated with excessive use of inhaled sympathomimetics.

Disease-related concerns:

- Asthma: Appropriate use: When used as a bronchodilator, optimize anti-inflammatory treatment before initiating maintenance treatment with terbutaline. Do not use as a component of chronic therapy without an anti-inflammatory agent. Only the mildest form of asthma (Step 1 and/or exercise-induced) would not require concurrent use based upon asthma guidelines.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (arrhythmia or hypertension or HF); beta-agonists may cause elevation in blood pressure, heart rate and result in CNS stimulation/excitation. Beta_2-agonists may also increase risk of arrhythmias.
- Diabetes: Use with caution in patients with diabetes mellitus; beta_2-agonists may increase serum glucose.
- Glaucoma: Use with caution in patients with glaucoma; may elevate intraocular pressure.
- Hyperthyroidism: Use with caution in hyperthyroidism; may stimulate thyroid activity.
- Hypokalemia: Use with caution in patients with hypokalemia; beta_2-agonists may decrease serum potassium.
- Seizures: Use with caution in patients with seizure disorders; beta-agonists may result in CNS stimulation/excitation.

Other warnings/precautions:

- Patient information: Patients must be instructed to seek medical attention in cases where acute symptoms are not relieved or a previous level of response is diminished. The need to increase frequency of use may indicate deterioration of asthma, and treatment must not be delayed.
- Tocolysis use: When used for tocolysis, there is some risk of maternal pulmonary edema, which has been associated with the following risk factors, excessive hydration, multiple gestation, occult sepsis and underlying cardiac disease. To reduce risk, limit fluid intake to 2.5-3 L/day, limit sodium intake, maintain maternal pulse to <130 beats/minute.

Geriatric ConsiderationsOral terbutaline should be avoided in the elderly due to the increased incidence of adverse effects as compared to the inhaled form.

Pregnancy Risk FactorB

LactationEnters breast milk/compatible

Adverse Reactions

>10%:

Central nervous system: Nervousness, restlessness

Endocrine & metabolic: Serum glucose increased, serum potassium decreased

Neuromuscular & skeletal: Trembling

1% to 10%:

Cardiovascular: Tachycardia, hypertension

Central nervous system: Dizziness, drowsiness, headache, insomnia

Gastrointestinal: Xerostomia, nausea, vomiting, bad taste in mouth

Neuromuscular & skeletal: Muscle cramps, weakness

Miscellaneous: Diaphoresis

<1%: Chest pain, arrhythmia, hypokalemia, paradoxical bronchospasm

Drug Interactions

Alpha-/Beta-Blockers: May diminish the therapeutic effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Atomoxetine: May enhance the tachycardic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Beta2-Agonists. Of particular concern with nonselective beta-blockers or higher doses of the beta1 selective beta-blockers. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Betahistine: May diminish the therapeutic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid ephedra, yohimbe (may cause CNS stimulation).

Monitoring ParametersSerum potassium, glucose; heart rate, blood pressure, respiratory rate; monitor for signs and symptoms of pulmonary edema (when used as a tocolytic); monitor FEV$_1$, peak flow, and/or other pulmonary function tests (when used as bronchodilator)

Nursing: Physical Assessment/Monitoring**Respiratory use:** Assess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. If you have diabetes, monitor blood glucose (may cause elevation in serum glucose). For inpatient care, monitor vital signs and lung sounds prior to and periodically during therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. **Preterm labor use: Inpatient:** Monitor maternal vital signs; respiratory, fluid status, cardiac, and electrolyte status; frequency, duration, and intensity of contractions; and fetal heart rate. **Outpatient:** Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsFEV$_1$, peak flow, and/or other pulmonary function tests; serum potassium, serum glucose (in selected patients)

Tocolysis: If patient receives therapy for more than 1 week, monitor serum glucose.

Patient EducationUse exactly as directed. Do not use more often than recommended (excessive use may result in tolerance, overdose may result in serious adverse effects) and do not discontinue without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, monitor blood sugar closely. Serum glucose may be elevated. You may experience nervousness, dizziness, or fatigue (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or dry mouth, stomach upset (small frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help). Report unresolved GI upset; dizziness or fatigue; vision changes; sudden weight gain; swelling of extremities; chest pain, rapid heartbeat, or palpitations; insomnia, nervousness, or hyperactivity; muscle cramping, tremors, or pain; unusual cough; or rash (hypersensitivity).

Preterm labor: Notify prescriber immediately if labor resumes or adverse side effects are noted

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, solution, as sulfate: 1 mg/mL (1 mL)

Powder for oral inhalation:

Bricanyl® Turbuhaler [CAN]: 500 mcg/actuation [50 or 200 metered actuations] [not available in U.S.]

Tablet, as sulfate: 2.5 mg, 5 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Brethine)

2.5 mg (90): $43.47

Tablets (Terbutaline Sulfate)

2.5 mg (90): $44.99

5 mg (90): $45.99

Mechanism of ActionRelaxes bronchial smooth muscle by action on beta$_2$-receptors with less effect on heart rate

Pharmacodynamics/Kinetics

Onset of action: Oral: 30-45 minutes; SubQ: 6-15 minutes

Protein binding: 25%

Metabolism: Hepatic to inactive sulfate conjugates

Bioavailability: SubQ doses are more bioavailable than oral

Half-life elimination: 11-16 hours

Excretion: Urine

Related Information

- Bronchodilators
- Inhalant Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and bad taste in mouth.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusRestlessness and nervousness are common; may cause dizziness, drowsiness, or insomnia

Mental Health: Effects on Psychiatric TreatmentConcurrent use with TCAs or MAO inhibitors may increase toxicity

Cardiovascular ConsiderationsBeta-agonists will induce increases in heart rate. This should be considered in patients with resting tachycardia. Because of the frequent coexistence of chronic obstructive lung disease and coronary artery disease, many patients are on simultaneous therapy with beta-agonists and beta-blockade.

Anesthesia and Critical Care Concerns/Other Considerations

Evidence-Based Information: Beta$_2$-selective agents lose much of their receptor selectivity when delivered parenterally or orally. Subcutaneous beta-agonist therapy has a deleterious therapeutic to toxicity ratio when compared with inhalation. There is no proven benefit of systemic therapy over aerosolized (Expert Report Panel 3, 2007).

Index TermsBrethaire [DSC]; Bricanyl [DSC]

References

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Lee DC, "Terbutaline Sulfate Overdose," *Ann Emerg Med*, 1995, 26(1):107-8. [PubMed 7793711]

Rachelefsky GS and Siegel SC, "Asthma in Infants and Children - Treatment of Childhood Asthma: Part II," *J Allergy Clin Immunol*, 1985, 76(3):409-25. [PubMed 2863296]

Tipton WR and Nelson HS, "Frequent Parenteral Terbutaline in the Treatment of Status Asthmaticus in Children," *Ann Allergy*, 1987, 58(4):252-6. [PubMed 3565860]

Zehner WJ Jr, Scott JM, Iannolo PM, et al, "Terbutaline vs Albuterol for Out-of-Hospital Respiratory Distress: Randomized Double-Blind Trial," *Acad Emerg Med*, 1995, 2(8):686-91.[PubMed 7584746]

International Brand NamesAlloxygen (PH); Asthmasian (TH); Ataline (HK, MY, SG, TH); Brasmatic (ID); Bricalin (IL); Bricanil (VE); Bricanyl (AE, AR, AT, AU, BB, BE, BF, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CY, CZ, DK, EG, ET, FI, FR, GB, GH, GM, GN, GY, HK, HN, HU, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PE, PH, PK, PT, QA, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Bricanyl retard (NL); Bricanyl Turbuhaler (HU, PL); Bricasma (ID); Bronchodam (PH); Bronconyl (TH); Brondyl (TW); Bucanil (MY); Bucaril (TH); Contimit (DE); Draconyl (GR); Glin (TW); Nairet (ID); Prosmalin (ID); Pulmonyl (PH); Pulmoxel (PH); Relivan (ID); Terasma (ID); Terbasmin (ES, IT); Terbul (LU); Terbulin (IL); Terburop (CO, EC); Terbuta (HK); Terbutalin AL (HU); Terbutalin Stada (PL); Tismalin (ID); Tolbin (MY); Vacanyl (TH); Yarisma (ID)

Terconazole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Terconazole may be confused with tioconazole

International issues:

Terazol® may be confused with Theradol® which is a brand name for tramadol in the Netherlands

Pronunciation(ter KONE a zole)
U.S. Brand NamesTerazol® 3; Terazol® 7; Zazole™
Canadian Brand NamesTerazol®
Pharmacologic CategoryAntifungal Agent, Vaginal
Use: Labeled IndicationsLocal treatment of vulvovaginal candidiasis
Dosing: Adults**Vulvovaginal candidiasis:** Intravaginal:

Terazol® 3, Zazole™ (0.8%) vaginal cream: Insert 1 applicatorful intravaginally at bedtime for 3 consecutive days.

Terazol® 7, Zazole™ (0.4%) vaginal cream: Insert 1 applicatorful intravaginally at bedtime for 7 consecutive days.

Terazol® 3 vaginal suppository: Insert 1 suppository intravaginally at bedtime for 3 consecutive days.

Dosing: ElderlyRefer to adult dosing.
StorageStore at room temperature of 13°C to 30°C (59°F to 86°F).
ContraindicationsHypersensitivity to terconazole or any component of the formulation
Allergy Considerations

- Azole Antifungal Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: If irritation or sensitization occurs, discontinue use.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Petrolatum-based: Petrolatum-based vaginal products may damage rubber or latex condoms or diaphragms; separate use by 3 days.

Other warnings/precautions:

- Lack of response: Microbiological studies (KOH smear and/or cultures) should be repeated in patients not responding to terconazole in order to confirm the diagnosis and rule out other pathogens.

Geriatric ConsiderationsAssess patient's ability to self-administer; may be difficult in patients with arthritis or limited range of motion.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

1% to 10%:

Central nervous system: Fever, chills

Gastrointestinal: Abdominal pain

Genitourinary: Vulvar/vaginal burning, dysmenorrhea

<1% (Limited to important or life-threatening): Vulvar itching, soreness, edema, or discharge; polyuria; burning or itching of penis of sexual partner; flu-like syndrome

Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/MonitoringAssess knowledge/teach patient appropriate administration, possible side effects/interventions,

and adverse symptoms to report.

Patient EducationComplete full course of therapy as directed. Insert vaginally as directed by prescriber or see package insert. Sexual partner may experience irritation of penis; best to refrain from intercourse during period of treatment. Suppositories may cause breakdown of rubber/latex products such as diaphragms; avoid concurrent use. Report persistent vaginal burning, itching, irritation, or discharge. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream, vaginal: 0.4% (45 g); 0.8% (20 g)

Terazol® 7: 0.4% (45 g) [packaged with measured-dose applicator]

Terazol® 3: 0.8% (20 g) [packaged with measured-dose applicator]

Zazole™: 0.4% (45 g) [packaged with measured-dose applicator]; 0.8% (20 g) [packaged with measured-dose applicator]

Suppository, vaginal:

Terazol® 3: 80 mg (3s) [may contain coconut and/or palm kernel oil]

Generic AvailableYes: Cream

Pricing: U.S. (www.drugstore.com)

Cream (Terazol 3)

0.8% (20): $55.99

Cream (Terazol 7)

0.4% (45): $51.99

Cream (Terconazole)

0.4% (45): $38.07

0.8% (20): $34.99

Suppository (Terazol 3)

80 mg (3): $51.99

Suppository (Terconazole)

80 mg (3): $45.99

Mechanism of ActionTriazole ketal antifungal agent; involves inhibition of fungal cytochrome P450. Specifically, terconazole inhibits cytochrome P450-dependent 14-alpha-demethylase which results in accumulation of membrane disturbing 14-alpha-demethylsterols and ergosterol depletion.

Pharmacodynamics/KineticsAbsorption: Extent of systemic absorption after vaginal administration may be dependent on presence of a uterus; 5% to 8% in women who had a hysterectomy versus 12% to 16% in nonhysterectomy women

Related Information

- Treatment of Sexually-Transmitted Infections

Pharmacotherapy PearlsWatch for local irritation; assist patient in administration, if necessary; assess patient's ability to self-administer, may be difficult in patients with arthritis or limited range of motion

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsTriaconazole

International Brand NamesFungistat (CO, MX, VE); Fungistat 3 (BB, BM, BS, BZ, GY, JM, PR, SR, TT); Gyno-Fungix (AR, BR); Gyno-Terazol (BE, CH, CZ, LU, NL, PL); Terazol (DK, FI); Terconal (IT); Terconer (TW)

Teriparatide

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ter i PAR a tide)

U.S. Brand NamesForteo®

Canadian Brand NamesForteo®

Pharmacologic CategoryParathyroid Hormone Analog

Use: Labeled IndicationsTreatment of osteoporosis in postmenopausal women at high risk of fracture; treatment of primary or hypogonadal osteoporosis in men at high risk of fracture

Dosing: Adults**Osteoporosis:** SubQ: 20 mcg once daily; **Note:** Initial administration should occur under circumstances in which the patient may sit or lie down, in the event of orthostasis.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo dosage adjustment required. Bioavailability and half-life increase with Cl_{cr} <30 mL/minute.

Administration: OtherAdminister by subcutaneous injection into the thigh or abdominal wall. Initial administration should occur under circumstances in which the patient may sit or lie down, in the event of orthostasis.

StorageStore at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Discard pen 28 days after first injection. Do not use if solution is cloudy, colored or contains solid particles.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to teriparatide or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Osteosarcoma: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia). Transient orthostatic hypotension usually occurs within 4 hours of dosing and within the first several doses.

- Osteosarcoma: **[U.S. Boxed Warning]: In animal studies, teriparatide has been associated with an increase in osteosarcoma;** risk was dependent on both dose and duration. Avoid use in patients with an increased risk of osteosarcoma (including Paget's disease, prior radiation, unexplained elevation of alkaline phosphatase, or in patients with open epiphyses). Do not use in patients with a history of skeletal metastases, hyperparathyroidism, or pre-existing hypercalcemia. Exclude metabolic bone disease other than osteoporosis prior to initiating therapy. Not for use in patients with metabolic bone disease other than osteoporosis.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; limited data available concerning safety and efficacy.

- Hepatic impairment: Use with caution in patients with hepatic impairment; limited data available concerning safety and efficacy.

- Renal impairment: Use with caution in patients with renal impairment; limited data available concerning safety and efficacy.

- Urolithiasis: Use with caution in patients with active or recent urolithiasis.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Use of teriparatide for longer than 2 years is not recommended.

Geriatric ConsiderationsNo age-related differences in pharmacokinetics have been seen. In studies, no significant difference was seen in either efficacy or adverse effects between older patients and younger patients. Teriparatide should be considered as a last resort in patents who cannot tolerate or have not responded to other treatments for osteoporosis.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events were observed in animal studies; the effect on human fetal development has not been studied. Teriparatide is not indicated for use in pregnant or premenopausal women.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIndicated for use in postmenopausal women. Studies have not been conducted to determine excretion in breast milk. Not recommended for use in breast-feeding women.

Adverse Reactions

>10%: Endocrine & metabolic: Hypercalcemia (transient increases noted 4-6 hours postdose [women 11%; men 6%])

1% to 10%:

- Cardiovascular: Chest pain (3%), syncope (3%)
- Central nervous system: Dizziness (8%), depression (4%), vertigo (4%)
- Dermatologic: Rash (5%)
- Endocrine & metabolic: Hyperuricemia (3%)
- Gastrointestinal: Nausea (9%), dyspepsia (5%), vomiting (3%), tooth disorder (2%)
- Neuromuscular & skeletal: Arthralgia (10%), weakness (9%), leg cramps (3%), muscle spasm
- Respiratory: Rhinitis (10%), pharyngitis (6%), dyspnea (4%), pneumonia (4%)
- Miscellaneous: Antibodies to teriparatide (3% of women in long-term treatment; hypersensitivity reactions or decreased efficacy were not associated in preclinical trials)

Postmarketing and/or case reports: Acute dyspnea, allergic reactions, edema (facial/oral), hypercalcemia >11 mg/dL; injection site reactions (bleeding, bruising, erythema, pain, pruritus, swelling); urticaria

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb Interactions

Ethanol: Excessive intake may increase risk of osteoporosis.

Herb/Nutraceutical: Ensure adequate calcium and vitamin D intake.

Test InteractionsTransiently increases serum calcium; maximal effect 4-6 hours postdose; generally returns to baseline ~16 hours postdose

Monitoring ParametersSerum calcium, serum phosphorus, uric acid; blood pressure; bone mineral density

Nursing: Physical Assessment/MonitoringInitial administration should occur where patient may sit or lie down, in the event of orthostasis. Assess results of laboratory tests (eg, calcium and phosphorus levels) prior to and periodically during therapy. Assess therapeutic effectiveness and adverse response (eg, chest pain, hypotension, nausea, vomiting, arthralgia, leg cramps, dyspnea) at beginning of and regular intervals during therapy. Teach patient proper use (administration with injector "pen" and disposal), possible side effects/appropriate interventions (diet with adequate calcium and vitamin D), and adverse symptoms to report.

Monitoring: Lab TestsSerum calcium, serum phosphorus

Patient EducationDo not take any new medication during therapy without consulting prescriber. Use injector pen and dispose of pen exactly as instructed (refer to Forteo® user manual dispensed with the medication); rotate injection sites in thigh or abdominal wall. Sit when administering to reduce possibility of falling or injury. Avoid excess alcohol (may increase risk of osteoporosis) and follow dietary instructions of prescriber. May cause dizziness (use caution when driving or engaged in potentially hazardous tasks until response to drug is known); nausea, vomiting, or upset stomach (small frequent meals or frequent mouth care may help); muscle or skeletal pain, weakness, or cramping (consult prescriber for approved analgesic). Report chest pain or palpitations; respiratory difficulty; or other persistent adverse effects.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Forteo®: 250 mcg/mL (3 mL) [prefilled syringe, delivers teriparatide 20 mcg/dose]

Generic AvailableNo

ManufacturerEli Lilly and Company

Pricing: U.S. (www.drugstore.com)

Solution (Forteo)

750 mcg/3 mL (3): $899.44

Mechanism of ActionTeriparatide is a recombinant formulation of endogenous parathyroid hormone (PTH), containing a 34-amino-acid sequence which is identical to the N-terminal portion of this hormone. The pharmacologic activity of teriparatide is similar to the physiologic activity of PTH, stimulating osteoblast function, increasing gastrointestinal calcium absorption, increasing renal tubular reabsorption of calcium. Treatment with teriparatide increases bone mineral density, bone mass, and strength. In postmenopausal women, it has been shown to decrease osteoporosis-related fractures.

Pharmacodynamics/Kinetics

Distribution: V_d: 0.12 L/kg

Metabolism: Hepatic (nonspecific proteolysis)

Bioavailability: 95%

Half-life elimination: Serum: I.V.: 5 minutes; SubQ: 1 hour

Time to peak, serum: 30 minutes

Excretion: Urine (as metabolites)

Pharmacotherapy Pearls Teriparatide was formerly marketed as a diagnostic agent (Perithar™); that agent was withdrawn from the market in 1997. Teriparatide (Forteo®) is manufactured through recombinant DNA technology using a strain of *E. coli*.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Tooth disorder.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness or depression

Mental Health: Effects on Psychiatric Treatment May cause orthostasis; use caution with psychotropics. May cause GI side effects; use caution with SSRIs.

Index Terms Parathyroid Hormone (1-34); Recombinant Human Parathyroid Hormone (1-34); rhPTH(1-34)

References

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Neer RM, Arnaud CD, Zanchetta JR, et al, “Effect of Parathyroid Hormone (1-34) on Fractures and Bone Mineral Density in Postmenopausal Women With Osteoporosis,” *N Engl J Med*, 2001, 344(19):1434-41. [PubMed 11346808]

Reeve, J, “Recombinant Human Parathyroid Hormone,” *BMJ*, 2002, 324(7335):435-6.[PubMed 11859030]

International Brand Names Forsteo (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, KP, NL, NO, PT, RU, SE, TR); Forteo (AR, AU, BR, CN, CO, CR, DO, GT, HK, HN, MX, MY, PA, PE, PH, SV, TH, VE); Human PTH (JP)

Testolactone

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Testolactone may be confused with testosterone

Pronunciation(tes toe LAK tone)
U.S. Brand NamesTeslac® [DSC]
Canadian Brand NamesTeslac®
Pharmacologic CategoryAndrogen
Use: Labeled IndicationsPalliative treatment of advanced or disseminated breast carcinoma
Dosing: Adults**Breast carcinoma (palliative):** Females: Oral: 250 mg 4 times/day for at least 3 months; desired response may take as long as 3 months.
Dosing: ElderlyRefer to adult dosing.
RestrictionsC-III
ContraindicationsHypersensitivity to testolactone or any component of the formulation; treatment of breast cancer in men
Allergy Considerations

- Androgen Allergy

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Diabetes: Use with caution in patients with diabetes mellitus; monitor carefully.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Porphyria: Use with caution in patients with a history of porphyria.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Women: For use in postmenopausal women or in premenopausal women without ovarian function only.

Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Testolactone should only be used in postmenopausal women; use during pregnancy is not recommended.
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Blood pressure increased, edema

Central nervous system: Malaise

Dermatologic: Alopecia (rare), maculopapular rash

Endocrine & metabolic: Hypercalcemia

Gastrointestinal: Anorexia, diarrhea, nausea, tongue edema

Neuromuscular & skeletal: Paresthesia, peripheral neuropathy

Miscellaneous: Nail growth disturbance (rare)

Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

CycloSPORINE: Androgens may enhance the hepatotoxic effect of CycloSPORINE. Androgens may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Androgens may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Test InteractionsPlasma estradiol concentrations by RIA

Monitoring ParametersPlasma calcium levels

Nursing: Physical Assessment/MonitoringFor use in postmenopausal women or in premenopausal women without ovarian function only. May increase effects of oral anticoagulants. Evaluate effectiveness of therapy, laboratory tests, and adverse reactions. Assess knowledge/teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPlasma calcium levels

Patient EducationTake as directed; do not discontinue without consulting prescriber. Effectiveness of therapy may take several months. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and diet and exercise program recommended by prescriber. You may experience nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report fluid retention (swelling of ankles, feet, or hands; respiratory difficulty or sudden weight gain); numbness, tingling, or swelling of fingers, toes, or face; skin rash, redness, or irritation; or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet:

Teslac®: 50 mg [DSC]

Generic AvailableNo

Mechanism of ActionTestolactone is a synthetic testosterone derivative without significant androgen activity. The drug inhibits steroid aromatase activity, thereby blocking the production of estradiol and estrone from androgen precursors such as testosterone and androstenedione. Unfortunately, the enzymatic block provided by testolactone is transient and is usually limited to a period of 3 months.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Metabolism: Hepatic (forms metabolites)

Excretion: Urine

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tongue edema.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesFludestrin (DE)

Testosterone

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Testosterone may be confused with testolactone

Testoderm® may be confused with Estraderm®

Transdermal patch may contain conducting metal (eg, aluminum); remove patch prior to MRI.

Pronunciation(tes TOS ter one)

U.S. Brand NamesAndroderm®; AndroGel®; Delatestryl®; Depo®-Testosterone; First®-Testosterone; First®-Testosterone MC; Striant®; Testim®; Testopel®

Canadian Brand NamesAndriol®; Androderm®; AndroGel®; Andropository; Delatestryl®; Depotest® 100; Everone® 200; Virilon® IM

Pharmacologic CategoryAndrogen

Use: Labeled Indications

Injection: Androgen replacement therapy in the treatment of delayed male puberty; male hypogonadism (primary or hypogonadotropic); inoperable metastatic female breast cancer (enanthate only)

Pellet: Androgen replacement therapy in the treatment of delayed male puberty; male hypogonadism (primary or hypogonadotropic)

Topical (buccal system, gel, transdermal system): Male hypogonadism (primary or hypogonadotropic)

Capsule (not available in U.S.): Androgen replacement therapy in the treatment of delayed male puberty; male hypogonadism (primary or hypogonadotropic); replacement therapy in impotence or for male climacteric symptoms due to androgen deficiency

Use: Unlabeled/InvestigationalAndrogen deficiency in men with AIDS wasting; postmenopausal women with decreased sexual desire (in combination with estrogen therapy)

Dosing: Adults

Inoperable metastatic breast cancer (females):*I.M. (testosterone enanthate):* 200-400 mg every 2-4 weeks

Hypogonadism:

I.M. (testosterone enanthate or testosterone cypionate): 50-400 mg every 2-4 weeks (FDA-approved dosing range); 75-100 mg/week or 150-200 mg every 2 weeks (per practice guidelines)

Pellet (for subcutaneous implantation): 150-450 mg every 3-6 months

Hypogonadism or hypogonadotropic hypogonadism (males):

Oral capsule (Andriol®; not available in U.S.): Initial: 120-160 mg/day in 2 divided doses for 2-3 weeks; adjust according to individual response; usual maintenance dose: 40-120 mg/day (in divided doses)

Topical:

Buccal: 30 mg twice daily (every 12 hours) applied to the gum region above the incisor tooth

Transdermal system: Androderm®: Initial: Apply 5 mg/day once nightly to clean, dry area on the back, abdomen, upper arms, or thighs (do **not** apply to scrotum); dosing range: 2.5-7.5 mg/day; in nonvirilized patients, dose may be initiated at 2.5 mg/day

Gel: AndroGel®, Testim®: 5 g (to deliver 50 mg of testosterone with 5 mg systemically absorbed) applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulder and upper arms. AndroGel® may also be applied to the abdomen. Dosage may be increased to a maximum of 10 g (100 mg). **Do not apply testosterone gel to the genitals.**

Dose adjustment based on testosterone levels:

Less than normal range: Increase dose from 5 g to 7.5 g to 10 g

Greater than normal range: Decrease dose. Discontinue if consistently above normal at 5 g/day

Delayed puberty (males):

I.M. (testosterone enanthate): 50-200 mg every 2-4 weeks for a limited duration

Oral capsule (Andriol®; not available in U.S.): Initial: 120-160 mg/day in 2 divided doses for 2-3 weeks; adjust according to individual response; usual maintenance dose: 40-120 mg/day (in divided doses)

Pellet (for subcutaneous implantation): 150-450 mg every 3-6 months

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Delayed puberty (males):

I.M. (testosterone enanthate): Refer to adult dosing.

Oral capsule (Andriol®; not available in U.S.): Refer to adult dosing.

Pellet (for subcutaneous implantation): Refer to adult dosing.

Hypogonadism:

I.M. (testosterone enanthate or testosterone cypionate): Refer to adult dosing.

Pellet (for subcutaneous implantation): Refer to adult dosing.

Hypogonadism or hypogonadotropic hypogonadism (males):*Oral capsule (Andriol®; not available in U.S.):* Refer to adult dosing.

Dosing: Hepatic ImpairmentReduce dose.

Administration: I.M.Warm injection to room temperature and shaking vial will help redissolve crystals that have formed after storage. Administer by deep I.M. injection into the upper outer quadrant of the gluteus maximus.

Administration: Oral

Oral, buccal application (Striant®): One mucoadhesive for buccal application (buccal system) should be applied to a comfortable area above the incisor tooth. Apply flat side of system to gum. Rotate to alternate sides of mouth with each application. Hold buccal system firmly in place for 30 seconds to ensure adhesion. The buccal system should adhere to gum for 12 hours. If the buccal system falls out, replace with a new system. If the system falls out within 4 hours of next dose, the new buccal system should remain in place until the time of the following scheduled dose. System will soften and mold to shape of gum as it absorbs moisture from mouth. Do not chew or swallow the buccal system. The buccal system will not dissolve; gently remove by sliding downwards from gum; avoid scratching gum.

Oral, capsule (Andriol®; not available in the U.S.): Should be administered with meals. Should be swallowed whole; do not crush or chew.

Administration: Topical

Transdermal patch: Androderm®: Apply patch to clean, dry area of skin on the arm, back, or upper buttocks. Following patch removal, mild skin irritation may be treated with OTC hydrocortisone cream. A small amount of triamcinolone acetonide 0.1% cream may be applied under the system to decrease irritation; do not use ointment. Patch should be applied nightly. Rotate administration sites, allowing 7 days between applying to the same site.

Gel: AndroGel®, Testim®: Apply (preferably in the morning) to clean, dry, intact skin of the shoulder and upper arms (AndroGel® may also be applied to the abdomen). Apply at the same time each day. Upon opening the packet(s), the entire contents should be squeezed into the palm of the hand and immediately applied to the application site(s). Alternatively, a portion may be squeezed onto palm of hand and applied, repeating the process until entire packet has been applied. Application sites should be allowed to dry for a few minutes prior to dressing. Hands should be washed with soap and water after application. **Do not apply testosterone gel to the genitals**. For optimal absorption, after application wait at least 5-6 hours prior to showering or swimming; however waiting at least 1 hour should have minimal affect on absorption if done infrequently. Alcohol-based gels are flammable; avoid fire or smoking until gel has dried. Testosterone may be transferred to another person following skin-to-skin contact with the application site. Thoroughly wash hands after application and cover application site with clothing (ie shirt) once gel has dried, or clean application site thoroughly with soap and water prior to contact in order to minimize transfer.

AndroGel® multidose pump: Prime pump 3 times (and discard this portion of product) prior to initial use.

Dietary ConsiderationsTestosterone USP may be synthesized from soy. Food and beverages have not been found to interfere with buccal system; ensure system is in place following eating, drinking, or brushing teeth.

Storage

Androderm®: Store at room temperature. Do not store outside of pouch. Excessive heat may cause system to burst.

AndroGel®, Delatestryl®, Striant®, Testim®: Store at room temperature.

Depo® Testosterone: Store at room temperature. Protect from light.

Testopel®: Store in a cool location.

RestrictionsC-III

ContraindicationsHypersensitivity to testosterone or any component of the formulation; males with carcinoma of the breast or prostate; pregnancy or women who may become pregnant; breast-feeding

Depo®-Testosterone: Also contraindicated in serious hepatic, renal, or cardiac disease

Andriol®: Also contraindicated in hepatic, renal, or cardiac disease; hypercalcemia; nephrosis or nephritic phase of nephritis; prepubertal males; patients who are easily sexually stimulated

Allergy Considerations

- Androgen Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Gynecomastia: May cause gynecomastia.
- Hepatic effects: Prolonged use of high doses of androgens has been associated with serious hepatic effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, jaundice).
- Hypercalcemia: May cause hypercalcemia in patients with prolonged immobilization or cancer.
- Hypercholesterolemia: May alter serum cholesterol; use caution with history of MI or coronary artery disease.
- Hypoglycemia: Has both androgenic and anabolic activity, the anabolic action may enhance hypoglycemia.
- Prostate cancer: May increase the risk of prostate cancer.
- Spermatogenesis: Large doses may suppress spermatogenesis.

Disease-related concerns:

- Benign prostatic hyperplasia (BPH): Urethral obstruction may develop in patients with BPH; treatment should be discontinued if this should occur (use lower dose if restarted). Withhold treatment pending urological evaluation if PSA >3 ng/mL.
- Edematous conditions: Use with caution in patients with conditions influenced by edema (eg, cardiovascular disease, migraine, seizure disorder, renal impairment); may cause fluid retention.
- Sleep apnea: May potentiate sleep apnea in some male patients (obesity or chronic lung disease).

Special populations:

- Elderly: Use with caution in elderly patients, they may be at greater risk for prostatic hyperplasia, prostate cancer, fluid retention, and transaminase elevations.
- Pediatrics: May accelerate bone maturation without producing compensatory gain in linear growth in children; in prepubertal children perform radiographic examination of the hand and wrist every 6 months to determine the rate of bone maturation and to assess the effect of treatment on the epiphyseal centers. Gels and buccal system have not been evaluated in males <18 years of age; safety and efficacy of injection have not been established in males <12 years of age.

Dosage form specific issues:

- Benzyl alcohol: Some dosage forms may contain benzyl alcohol which has been associated with "gasping syndrome" in neonates.
- Gel: Testosterone may be transferred to another person following skin-to-skin contact with the application site. Virilization of female sexual partners has been reported with male use of the topical gel.
- Soy: Some testosterone products may be chemically synthesized from soy.
- Transdermal patch: May contain conducting metal (eg, aluminum); remove patch prior to MRI.

Geriatric ConsiderationsElderly males treated with androgens may be at increased risk of developing prostatic hyperplasia and prostatic carcinoma. Increase in libido may occur.

Pregnancy Risk FactorX

Pregnancy ConsiderationsTestosterone may cause adverse effects, including masculinization of the female fetus, if used during pregnancy. Females who are or may become pregnant should also avoid skin-to-skin contact to areas where testosterone has been applied topically on another person.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsHigh levels of endogenous maternal testosterone, such as those caused by certain ovarian cysts, suppress milk production. Maternal serum testosterone levels generally fall following pregnancy and return to normal once breast-feeding is stopped. The amount of testosterone present in breast milk or the effect to the nursing infant following maternal supplementation is not known. Some products are contraindicated while breast-feeding.

Adverse ReactionsFrequency rarely defined.

Cardiovascular: Deep venous thrombosis, edema, hypertension, vasodilation

Central nervous system: Aggressive behavior, amnesia, anxiety, dizziness, emotional lability, excitation, headache, malaise, mental depression, nervousness, seizure, sleep apnea, sleeplessness

Dermatologic: Acne, alopecia, dry skin, hair discoloration, hirsutism (increase in pubic hair growth), pruritus, rash, seborrhea

Endocrine & metabolic: Breast soreness, gonadotropin secretion decreased, growth acceleration, gynecomastia, hot flashes, hypercalcemia, hyperchloremia, hypercholesterolemia, hyper-/hypokalemia, hyperlipidemia, hypernatremia, hypoglycemia, inorganic phosphate retention, libido changes, menstrual problems (including amenorrhea), virilism, water retention

Gastrointestinal: GI bleeding, GI irritation, nausea, taste disorder, vomiting, weight gain

Following buccal administration (most common): Bitter taste, gum edema, gum or mouth irritation, gum pain, gum tenderness, taste perversion

Genitourinary: Bladder irritability, epididymitis, impotence, oligospermia, priapism, prostatic carcinoma, prostatic hyperplasia, PSA increased, testicular atrophy, urination impaired

Hepatic: Bilirubin increased, cholestatic hepatitis, cholestatic jaundice, hepatic dysfunction, hepatic necrosis, hepatocellular neoplasms, liver function test changes, peliosis hepatis

Hematologic: Anemia, bleeding, hematocrit/hemoglobin increased, leukopenia, polycythemia, suppression of clotting factors

Local: Application site reaction (gel), injection site pain

Transdermal system: Pruritus at application site (37%), burn-like blisters under system (12%), erythema at application site (7%), vesicles at application site (6%), allergic contact dermatitis to system (4%), burning at application site (3%), induration at application site (3%)

Neuromuscular & skeletal: Paresthesia, weakness

Ocular: Lacrimation increased

Renal: Creatinine increased

Respiratory: Dyspnea

Miscellaneous: Anaphylactoid reactions, diaphoresis, hypersensitivity reactions, smell disorder

Postmarketing and/or case reports: Injection: Cough, coughing fits, respiratory distress

Metabolism/Transport Effects**Substrate** (minor) of CYP2B6, 2C9, 2C19, 3A4; **Inhibits** CYP3A4 (weak)
Drug Interactions

CycloSPORINE: Androgens may enhance the hepatotoxic effect of CycloSPORINE. Androgens may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Androgens may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease testosterone levels.
Test InteractionsMay cause a decrease in thyroid function tests
Monitoring ParametersPeriodic liver function tests, PSA and prostate exam (prior to therapy, at 3 months, then as based on current guidelines), cholesterol, hemoglobin and hematocrit (prior to therapy, at 3 months, then annually); radiologic examination of wrist and hand every 6 months (when using in prepubertal children). Withhold initial treatment with hematocrit >50%, hyperviscosity, untreated obstructive sleep apnea, or uncontrolled severe heart failure. Monitor urine and serum calcium and signs of virilization in women treated for breast cancer.

PSA: Withhold initial treatment if PSA >3 ng/mL, or with palpable prostate nodule or induration without further urological evaluation. Do not treat with severe untreated BPH with IPSS symptom score >19.

Serum testosterone: Monitor 3 months after initiating treatment, then annually.

Injection: Measure midway between injections

AndroGel®: Morning serum testosterone levels 14 days after start of therapy

Androderm®: Morning serum testosterone levels following application the previous evening

Striant®: Application area of gums; total serum testosterone 4-12 weeks after initiating treatment, prior to morning dose

Reference RangeTestosterone, urine: Male: 100-1500 ng/24 hours; Female: 100-500 ng/24 hours
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, effects of warfarin may be enhanced; may increase fluid retention with corticosteroids). Assess results of laboratory tests, therapeutic effectiveness (according to purpose for use), and adverse reactions regularly during therapy. Caution patients with diabetes, may cause hypoglycemic reaction. Teach patient proper use (according to formulation), possible side effects/appropriate interventions, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Instruct patients of childbearing age or males who may have intercourse with women of childbearing age on appropriate barrier contraceptive measures.
Monitoring: Lab TestsPeriodic liver function tests, PSA and prostate exam (prior to therapy, at 3 months, then as based on current guidelines), cholesterol, hemoglobin and hematocrit (prior to therapy, at 3 months, then annually). Withhold initial treatment with hematocrit >50%, hyperviscosity; monitor urine and serum calcium in women treated for breast cancer.

PSA: Withhold initial treatment if PSA >3 ng/mL, or with palpable prostate nodule or induration without further urological evaluation. Do not treat with severe untreated BPH with IPSS symptom score >19.

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Patient EducationUse exactly as directed according to formulation. For topical application (patch or gel) or buccal application, follow directions that accompany package. If using self-administered injections, follow prescriber's directions for injection procedure and disposal of syringes/needles. If you have diabetes, monitor serum glucose closely and notify prescriber of changes; this medication may alter hypoglycemic requirements. You may experience acne, growth of body hair, loss of libido, impotence, menstrual irregularity (usually reversible), nausea, taste disorder, or vomiting (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report changes in menstrual pattern; enlarged or painful breasts; deepening of voice; unusual growth of body hair; persistent penile erection; fluid retention (swelling of ankles, feet, or hands); respiratory difficulty or sudden weight gain); unresolved changes in CNS (nervousness, chills, insomnia, depression, aggressiveness); altered urinary patterns; change in color of urine or stool; yellowing of eyes or skin; unusual bruising or bleeding; blood in urine or stool; difficulty sleeping or sleep apnea; skin irritation, redness, burning, or swelling at application site or injection site; or other persistent adverse reactions.

Transdermal: Androderm®: Apply patch to clean, dry area of skin on the arm, back, or upper buttocks.

Topical gel: AndroGel®, Testim®: Apply gel to clean, dry, intact skin of the shoulder and upper arms (AndroGel® may also be applied to the abdomen). Apply at same time each day (preferably in the morning). Upon opening the packet(s), the entire contents should be squeezed into the palm of the hand and immediately applied to the application site(s). Alternatively, a portion may be squeezed onto palm of hand and applied, repeating the process until entire packet has been applied. Gel is flammable (avoid fire or smoking until gel has dried). Application sites should be allowed to dry for a few minutes prior to dressing. Wash hands thoroughly with soap and water after application. Do not apply testosterone gel to the genitals. Testosterone may be transferred to another person with skin-to-skin contact at application site; cover application site with clothing, or wash site thoroughly with soap and water prior to contact in order to minimize transfer.

Pregnancy/breast-feeding precautions: Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Male: Do not cause a female to become pregnant. Male/female: Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Capsule, gelatin, as undecanoate:

- Andriol™ [CAN]: 40 mg (10s) [not available in U.S.]

Gel, topical:

- AndroGel®:
  - 1.25 g/actuation (75 g) [1% metered-dose pump; delivers 5 g/4 actuations; provides sixty 1.25 g actuations; contains ethanol 67%; may be chemically synthesized from soy]
  - 2.5 g (30s) [1% unit dose packets; contains ethanol 67%; may be chemically synthesized from soy]
  - 5 g (30s) [1% unit dose packets; contains ethanol; may be chemically synthesized from soy]
- Testim®: 5 g (30s) [1% unit-dose tube; contains ethanol 74%; may be chemically synthesized from soy]

Implant, subcutaneous:

- Testopel®: 75 mg (10s, 100s)

Injection, in oil, as cypionate: 100 mg/mL (10 mL); 200 mg/mL (1 mL, 10 mL)

- Depo®-Testosterone: 100 mg/mL (10 mL); 200 mg/mL (1 mL, 10 mL) [contains benzyl alcohol, benzyl benzoate, and cottonseed oil]

Injection, in oil, as enanthate: 200 mg/mL (5 mL)

- Delatestryl®: 200 mg/mL (1 mL, 5 mL) [contains sesame oil]

Kit [for prescription compounding; testosterone 2%]:

- First®-Testosterone:
  - Injection, in oil: Testosterone propionate 100 mg/mL (12 mL) [contains sesame oil and benzyl alcohol]
  - Ointment: White petrolatum (48 g)
- First®-Testosterone MC:
  - Injection, in oil: Testosterone propionate 100 mg/mL (12 mL) [contains sesame oil and benzyl alcohol]
  - Cream: Moisturizing cream (48 g)

Mucoadhesive, for buccal application [buccal system]:

- Striant®: 30 mg (10s) [may be chemically synthesized from soy]

Transdermal system, topical:

- Androderm®: 2.5 mg/day (60s) [contains ethanol]; 5 mg/day (30s) [contains ethanol]

Generic AvailableYes: Injection

Pricing: U.S. (www.drugstore.com)

Cream (First-Testosterone MC)

- 2% (60): $49.03

Gel (AndroGel)

- 25 mg/2.5 g (75): $230.98

50 mg/5 g (150): $240.99

Gel (AndroGel Pump)

1% (150): $255.08

Gel (Testim)

1% (150): $267.48

Misc (Striant)

30 mg (60): $247.03

Oil (Delatestryl)

200 mg/mL (5): $91.99

Oil (Depo-Testosterone)

100 mg/mL (10): $74.99

200 mg/mL (1): $34.99

200 mg/mL (10): $125.98

Oil (Testosterone Cypionate)

100 mg/mL (10): $56.99

200 mg/mL (1): $24.99

200 mg/mL (10): $88.99

Oil (Testosterone Enanthate)

200 mg/mL (5): $79.99

Ointment (First-Testosterone)

2% (60): $47.81

Patch, 24-hour (Androderm)

2.5 mg/24 hrs (60): $225.31

5 mg/24 hrs (30): $232.04

Mechanism of ActionPrincipal endogenous androgen responsible for promoting the growth and development of the male sex organs and maintaining secondary sex characteristics in androgen-deficient males

Pharmacodynamics/Kinetics

Duration (route and ester dependent): I.M.: Cypionate and enanthate esters have longest duration, ≤2-4 weeks; gel: 24-48 hours

Absorption: Transdermal gel: ~10% of applied dose

Protein binding: 98%; bound to sex hormone-binding globulin (40%) and albumin

Metabolism: Hepatic; forms metabolites, including dihydrotestosterone (DHT) and estradiol (both active)

Half-life elimination: 10-100 minutes

Excretion: Urine (90%); feces (6%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Buccal administration: Bitter taste, gum edema, gum or mouth irritation, gum tenderness, and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, insomnia, aggressive behavior, or depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine

Index TermsTestosterone Cypionate; Testosterone Enanthate

References

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Cunningham GR, Cordero E, and Thornby JI, “Testosterone Replacement With Transdermal Therapeutic Systems. Physiological Serum Testosterone and Elevated Dihydrotestosterone Levels,” *JAMA*, 1989, 261(17):2525-30. [PubMed 2704112]

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NAMS Board of Trustees, "The Role of Testosterone Therapy in Postmenopausal Women: Position Statement of The North American Menopause Society," *Menopause*, 2005, 12(5):497-511.

Ruch W and Jenny P, “Priapism Following Testosterone Administration for Delayed Male Puberty,” *Am J Med*, 1989, 86(2):256.

International Brand NamesAndroderm (AU, NZ); Androgel (BE, CZ, EE, FR); Aquaviron (IN); Cypionax (TH); Depo-Testosterone (MY, ZA); Depot Hormon-M (TW); Intrinsa Patch (FR, GB, IE); Jenasteron (KP); Lowtiyel (MX); Omnadren (PL); Primoniat Depot (CN); Primoteston Depot (BF, BJ, CI, EC, ET, GH, GM, GN, KE, KP, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZM, ZW); Proviron Depot (VE); Striant SR Buccal (GB); Testex (ES); Testim (BE, GB, IE, NO); Testo Enant (IT); Testo Gel (IE); Testoderm (AT); Testopatch (FR); Testosteron Ferring (AT); Testosterone Implants (AU); Testosteronum propionicum (PL); Testotop (LU); Testoviron (GR); Testoviron Depot (IT); Testoviron-Depot (AR, CH, CO, DE, DK, IL, PE, PT, PY, SE, UY); Tostran (GB); Virormone (AE, BH, CY, EG, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE)

English English

Jump To Field (Select Field Name)

Pronunciation(TET a nus i MYUN GLOB yoo lin HYU man)
U.S. Brand NamesHyperTET™ S/D
Canadian Brand NamesHyperTET™ S/D
Pharmacologic CategoryImmune Globulin
Use: Labeled IndicationsProphylaxis against tetanus following injury in patients where immunization status is not known or uncertain

The Advisory Committee on Immunization Practices (ACIP) recommends passive immunization with TIG for the following:

- Persons with a wound that is not clean or minor and in whom contraindications to a tetanus-toxoid containing vaccine exist and they have not completed a primary series of tetanus toxoid immunization.
- Persons who are wounded in bombings or similar mass casualty events who have penetrating injuries or nonintact skin exposure and who cannot confirm receipt of a tetanus booster within the previous 5 years. In case of shortage, use should be reserved for persons ≥60 years of age.

Dosing: Adults

Prophylaxis of tetanus: I.M.: 250 units

Treatment of tetanus: I.M.: 500-6000 units. Infiltration of part of the dose around the wound is recommended.

Tetanus Prophylaxis in Wound Management

Number of Prior Tetanus Toxoid Doses	**Clean, Minor Wounds**		**All Other Wounds**	
	Td[1]	**TIG**[2]	**Td**[1]	**TIG**[2]
Unknown or <3	Yes	No	Yes	Yes
≥3[3]	No[4]	No	No[5]	No
[1]Adult tetanus and diphtheria toxoids; use pediatric preparations (DT or DTP) if the patient is <7 years old.				
[2]Tetanus immune globulin.				
[3]If only three doses of fluid tetanus toxoid have been received, a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.				
[4]Yes, if >10 years since last dose.				
[5]Yes, if >5 years since last dose.				
Adapted from Centers for Disease Control, “Diphtheria, Tetanus, and Pertussis: Recommendations for Vaccine Use and Other Preventive Measures: Recommendations of the Immunization Practices Advisory Committee (ACIP),” *MMWR* 1991:40(RR-10).				

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Prophylaxis of tetanus: I.M.:

Children <7 years: 4 units/kg; some recommend administering 250 units to small children

Children ≥7 years: Refer to adult dosing.

Treatment of tetanus: Refer to adult dosing.

Administration: I.M.Do not administer I.V.; I.M. use only. Administer in the anterolateral aspects of the upper thigh or the deltoid muscle of the upper arm. Avoid gluteal region due to risk of injury to sciatic nerve; if gluteal region is used, administer only in the upper outer quadrant. If tetanus vaccine and tetanus immune globulin are administered simultaneously, separate sites should be used for each injection. When used for the treatment of tetanus, infiltration of part of the dose around the wound is recommended.

Vaccine administration with antibody-containing products*:

Antibody-containing products and inactivated vaccines: May be given simultaneously at different sites or at any interval between doses.

Antibody-containing products and live vaccines: Do not give simultaneously.

*Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StorageStore at 2°C to 8°C (26°F to 46°F). Do not use if frozen.

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1:1000) should be available. Use with caution in patients with isolated immunoglobulin A deficiency or a history of systemic hypersensitivity to human immunoglobulins.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with thrombocytopenia or coagulation disorders; I.M. injections may be contraindicated.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

Other warnings/precautions:

- Administration: Not for intravenous administration.

- Skin testing: Skin testing should not be performed as local irritation can occur and be misinterpreted as a positive reaction.

Geriatric ConsiderationsTetanus is a rare disease in U.S. with <100 cases annually; 66% of cases occur in persons >50 years of age; protective tetanus and diphtheria antibodies decline with age; it is estimated that <50% of the elderly are protected.

Elderly are at risk because:

Many lack proper immunization maintenance

Higher case fatality ratio

Immunizations are not available from childhood

Indications for vaccination:

Primary series with combined tetanus-diphtheria (Td) should be given to all elderly lacking a clear history of vaccination

Boosters should be given at 10-year intervals; earlier for wounds

Elderly are more likely to require tetanus immune globulin with infection of tetanus due to lower antibody titer.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Tetanus immune globulin and a tetanus toxoid containing vaccine are recommended by the ACIP as part of the standard wound management to prevent tetanus in pregnant women.

Adverse ReactionsFrequency not defined.

Central nervous system: Temperature increased

Dermatologic: Angioneurotic edema (rare)

Local: Injection site: pain, soreness, tenderness

Renal: Nephritic syndrome (rare)

Miscellaneous: Anaphylactic shock (rare)

Drug Interactions

Vaccines (Live): Immune Globulins may diminish the therapeutic effect of Vaccines (Live). **Exceptions:** Influenza Virus Vaccine; Yellow Fever Vaccine. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]:

HyperTET™ S/D: 250 units/mL (1 mL) [prefilled syringe]

Generic AvailableNo
ManufacturerTalecris Biotherapeutics, Inc
Mechanism of ActionPassive immunity toward tetanus
Pharmacodynamics/KineticsAbsorption: Well absorbed
Related Information

- [Immunization Recommendations]

Pharmacotherapy PearlsTetanus immune globulin (TIG) must not contain <50 units/mL. Protein makes up 10% to 18% of TIG preparations. The great majority of this (≥90%) is IgG. TIG has almost no color or odor and it is a sterile, nonpyrogenic, concentrated preparation of immunoglobulins that has been derived from the plasma of adults hyperimmunized with tetanus toxoid. The pooled material from which the immunoglobulin is derived may be from fewer than 1000 donors. This plasma has been shown to be free of hepatitis B surface antigen.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsTIG
References

Centers for Disease Control, "Diphtheria, Tetanus, and Pertussis: Recommendations for Vaccine Use and Other Preventive Measures," *MMWR Recomm Rep*, 1991, 40(RR-10):1-28 [PubMed 1865873]

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Centers for Disease Control, "Recommendations for Postexposure Interventions to Prevent Infection With Hepatitis B Virus, Hepatitis C Virus, or Human Immunodeficiency Virus, and Tetanus in Persons Wounded During Bombings and Other Mass-Casualty Events -- United States, 2008: Recommendations of the Centers For Disease Control And Prevention (CDC)," *MMWR Recomm Rep*, 2008, 57(RR-6):1-21.[PubMed 18668022]

International Brand NamesBayTet (MX, PK); Clostet (PH); Hyper-Tet (KP); Hypertet (IL, TW); Sero-Tet (MY, PH); Tetabulin (AT, HK, IT); Tetabuline (BE); Tetagam (DE, ID, ZA); Tetagam N (CH); Tetagam-P (GR, ID); Tetagamma (IT); Tetaglobulin (DE, IN); Tetaglobuline (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Tetagloman (AT); Tetanobulin (TW); Tetanobulin S/D (DE); Tetanogamma (DO); Tetanogamma P (MX); Tetanosson (GR); Tetuman (NL); Tetuman berna (HK, MY, PE, TH, TW)

Tetanus Toxoid (Adsorbed)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Tetanus toxoid products may be confused with influenza virus vaccine and tuberculin products. Medication errors have occurred when tetanus toxoid products have been inadvertently administered instead of tuberculin skin tests (PPD) and influenza virus vaccine. These products are refrigerated and often stored in close proximity to each other.

Pronunciation(TET a nus TOKS oyd, ad SORBED)

Pharmacologic CategoryVaccine, Inactivated (Bacterial)

Use: Labeled IndicationsActive immunization against tetanus when combination antigen preparations are not indicated. **Note:** Tetanus and diphtheria toxoids for adult use (Td) is the preferred immunizing agent for most adults and for children after their seventh birthday. Young children should receive trivalent DTaP (diphtheria/tetanus/acellular pertussis), as part of their childhood immunization program, unless pertussis is contraindicated, then DT is warranted.

Dosing: Adults

Primary immunization: I.M.: 0.5 mL; repeat 0.5 mL at 4-8 weeks after first dose and at 6-12 months after second dose

Routine booster dose: Recommended every 10 years

Note: In most patients, Td is the recommended product for primary immunization, booster doses, and tetanus immunization in wound management.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥7 years: Refer to adult dosing.

Administration: I.M.Inject intramuscularly in the area of the vastus lateralis (midthigh laterally) or deltoid. Do not inject into gluteal area. Shake well prior to withdrawing dose; do not use if product does not form a suspension.

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

Administration with other vaccines:

Tetanus toxoid vaccine with other inactivated vaccines: May be given simultaneously or at any interval between doses.

Tetanus toxoid vaccine with live vaccines: May be given simultaneously or at any interval between doses

Vaccine administration with antibody-containing products: Tetanus toxoid vaccine may be be given simultaneously at different sites or at any interval between doses. Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products.

StorageStore at 2°C to 8°C (26°F to 46°F); do not freeze.

ContraindicationsHypersensitivity to tetanus toxoid or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during use.
- Arthus-type hypersensitivity: Tetanus containing vaccines and emergency doses of tetanus vaccine should not be given more frequently than every 10 years in patients who have experienced a serious Arthus-type hypersensitivity reaction following a prior use of tetanus toxoid.

Disease-related concerns:

- Acute illness: The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and the etiology of the disease. Immunization should be delayed during the course of an acute febrile illness.
- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.

- Guillain-Barré syndrome: Use with caution if Guillain-Barré syndrome occurred within 6 weeks of prior tetanus toxoid.

- Poliomyelitis: Defer elective immunization during outbreaks of poliomyelitis.

Concurrent drug therapy issues:

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Immunocompromised patients: Patients who are immunocompromised may have reduced response; may be used in patients with HIV infection.

- Pediatrics: Safety and efficacy have not been established in children <7 years of age.

Dosage form specific issues:

- Latex: Vial stopper may contain natural latex rubber.

- Thimerosal: Product may contain thimerosal.

Other warnings/precautions:

- Administration: Avoid injection into a blood vessel.

Geriatric ConsiderationsTetanus is a rare disease in U.S. with <100 cases annually; 66% of cases occur in persons >50 years of age; protective tetanus and diphtheria antibodies decline with age; it is estimated that <50% of elderly are protected.

Elderly are at risk because:

Many lack proper immunization maintenance

Higher case fatality ratio

Immunizations are not available from childhood

Indications for vaccination:

Primary series with combined tetanus-diphtheria (Td) should be given to all elderly lacking a clean history of vaccination

Boosters should be given at 10-year intervals; earlier for wounds

Elderly are more likely to require tetanus immune globulin with infection of tetanus due to lower antibody titer.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have not been conducted. The ACIP recommends vaccination in previously unvaccinated women or in women with an incomplete vaccination series, whose child may be born in unhygienic conditions. Tetanus immune globulin and a tetanus toxoid-containing vaccine are recommended by the ACIP as part of the standard wound management to prevent tetanus in pregnant women. Vaccination using Td is preferred.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions **All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Frequency not defined.

Cardiovascular: Hypotension

Central nervous system: Brachial neuritis, fever, malaise, pain

Gastrointestinal: Nausea

Local: Edema, induration (with or without tenderness), rash, redness, urticaria, warmth

Neuromuscular: Arthralgia, Guillain-Barré syndrome

Miscellaneous: Anaphylactic reaction, Arthus-type hypersensitivity reaction

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, suspension: Tetanus 5 Lf units per 0.5 mL (0.5 mL) [contains trace amounts of thimerosal]

Generic AvailableNo

ManufacturerSanofi Pasteur Inc

Mechanism of ActionTetanus toxoid preparations contain the toxin produced by virulent tetanus bacilli (detoxified growth products of *Clostridium tetani*). The toxin has been modified by treatment with formaldehyde so that it has lost toxicity but still retains ability to act as antigen and produce active immunity; the aluminum salt, a mineral adjuvant, delays the rate of absorption and prolongs and enhances its properties; duration ~10 years.

Pharmacodynamics/KineticsDuration: Primary immunization: ~10 years

Related Information

- Immunization Recommendations
- Skin Tests

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title and address be entered into the patient's permanent medical record.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

Bentley DW, “Vaccinations,” *Clin Geriatr Med*, 1992, 8(4):745-60. [PubMed 1423132]

Centers for Disease Control, “Prevention of Pertussis, Tetanus, and Diphtheria Among Pregnant and Postpartum Women and Their Infants, Recommendations of the Advisory Committee on Immunization Practices (ACIP),” *MMWR Recomm Rep*, 2008, 57(early release):1-47. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e0514a1.htm?s_cid=rr57e0514a1_e

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.[PubMed 17136024]

Gardner P and Schaffner W, “Immunization of Adults,” *N Engl J Med*, 1993, 328(17):1252-8.[PubMed 8464436]

Tetanus Toxoid (Fluid)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

> Tetanus toxoid products may be confused with influenza virus vaccine and tuberculin products. Medication errors have occurred when tetanus toxoid products have been inadvertently administered instead of tuberculin skin tests (PPD) and influenza virus vaccine. These products are refrigerated and often stored in close proximity to each other.

Pronunciation(TET a nus TOKS oyd FLOO id)

Pharmacologic CategoryToxoid

Use: Labeled IndicationsIndicated as booster dose in the active immunization against tetanus in the rare adult or child who is allergic to the aluminum adjuvant (a product containing adsorbed tetanus toxoid is preferred); not indicated for primary immunization

Use: Unlabeled/InvestigationalAnergy testing (no longer recommended)

Dosing: Adults

Primary immunization: Not indicated for this use.

Booster doses: I.M., SubQ: 0.5 mL every 10 years

Anergy testing (unlabeled use; no longer recommended for this indication): Intradermal: 0.1 mL; doses that have been used range from 0.1 mL of a 1:10 dilution to 0.1 mL of the undiluted product

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: I.M.Shake well prior to use. Administer I.M. in lateral aspect of midthigh or deltoid muscle of upper arm

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends “it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection.”

Administration: OtherSubQ: Shake well prior to use. Administer in area of the lateral aspect of midthigh or deltoid. SubQ route may be preferred in patients with thrombocytopenia or coagulation disorders.

StorageRefrigerate 2°C to 8°C (35°F to 46°F); do not freeze.

ContraindicationsHypersensitivity to tetanus toxoid or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during use. In patients with a history of severe local reaction (Arthus-type) or temperature of >39.4˚C (>103˚F) following previous dose, do not give further routine or emergency doses of tetanus and diphtheria toxoids for 10 years.

Disease-related concerns:

- Acute illness: The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and the etiology of the disease. Immunization should be delayed during the course of an acute febrile illness.

- Bleeding disorders: Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration. SubQ administration may be preferred.

- Poliomyelitis: Defer elective immunization during outbreaks of poliomyelitis.

Special populations:

- Immunocompromised patients: Patients who are immunocompromised may have reduced response; may be used in patients with HIV infection.

- Pediatrics: Safety and efficacy have not been established in children <6 weeks of age; this product is not indicated for use in children <7 years of age.

Dosage form specific issues:

- Latex: Vial stopper may contain natural latex rubber.

- Thimerosal: Product may contain thimerosal.

Geriatric ConsiderationsTetanus is a rare disease in U.S. with <100 cases annually; 66% of cases occur in persons >50 years of age; protective tetanus and diphtheria antibodies decline with age; it is estimated that <50% of elderly are protected.

Elderly are at risk because:

- Many lack proper immunization maintenance
- Higher case fatality ratio
- Immunizations are not available from childhood

Indications for vaccination:

- Primary series with combined tetanus-diphtheria (Td) should be given to all elderly lacking a clean history of vaccination
- Boosters should be given at 10-year intervals; earlier for wounds
- Elderly are more likely to require tetanus immune globulin with infection of tetanus due to lower antibody titer.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted and effects to the fetus are not known. Deferring immunization until the 2nd trimester may be considered.

Breast-Feeding ConsiderationsUse of tetanus toxoid has not been shown to affect the safety of breast-feeding mothers or their infants.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Frequency not defined.

Cardiovascular: Hypotension

Central nervous system: Brachial neuritis, fever, Guillain-Barré syndrome, malaise

Dermatologic: Rash, urticaria

Gastrointestinal: Nausea

Local: Edema, induration (with or without tenderness), redness, warmth

Neuromuscular & skeletal: Arthralgia

Miscellaneous: Anaphylaxis, Arthus-type hypersensitivity reactions (severe local reaction developing 2-8 hours following injection)

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution: Tetanus 4 Lf units per 0.5 mL (7.5 mL) [contains thimerosal; vial stopper contains dry natural latex rubber] [DSC]

Generic AvailableNo

Mechanism of ActionTetanus toxoid preparations contain the toxin produced by virulent tetanus bacilli (detoxified growth products of *Clostridium tetani*). The toxin has been modified by treatment with formaldehyde so that is has lost toxicity but still retains ability to act as antigen and produce active immunity.

Related Information

- Immunization Recommendations
- Skin Tests

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title and address be entered into the patient's permanent medical record.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause malaise

Mental Health: Effects on Psychiatric TreatmentNone reported

Mental Health CommentAssociated with Guillain-Barré syndrome

Index TermsTetanus Toxoid Plain

References

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 1994, 43(RR-1):23.

Gardner P and Schaffner W, “Immunization of Adults,” *N Engl J Med*, 1993, 328(17):1252-8.[PubMed 8464436]

International Brand NamesAnatetall (MY, PH, TH); Anatoxal TE (PE); TE Anatoxal (AT); TE Anatoxal Berna (CH); Tet-Tox (NZ); Tetanol (AE, AR, BH, CY, DE, EC, EG, GR, HN, IL, IQ, IR, JO, KW, LB, LY, MX, OM, QA, SA, SY, YE); Tetatox (IT); Tetavax (BG, DE, GB, HK, MY, NL, NO, PH, TH)

Tetrabenazine

Lexi-Drugs Online

English

Arabic

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(tet ra BEN a zeen)

U.S. Brand NamesXenazine®

Canadian Brand NamesNitoman™

Pharmacologic CategoryCentral Monoamine-Depleting Agent

Use: Labeled IndicationsTreatment of chorea associated with Huntington’s disease

Canadian labeling: Treatment of hyperkinetic movement disorders, including Huntington's chorea, hemiballismus, senile chorea, Tourette syndrome, and tardive dyskinesia

Dosing: AdultsDose should be individualized; titrate slowly

Chorea associated with Huntington’s disease: Oral:

Initial: 12.5 mg once daily, may increase to 12.5 mg twice daily after 1 week

Maintenance: May be increased by 12.5 mg/day at weekly intervals; doses >37.5 mg/day should be divided into 3 doses (maximum single dose 25 mg)

Patients requiring doses >50 mg/day: Genotype for CYP2D6:

Extensive/intermediate metabolizers: Maximum: 100 mg/day; 37.5 mg/dose

Poor metabolizers: Maximum: 50 mg/day; 25 mg/dose

Concomitant use with strong CYP2D6 inhibitors (eg, fluoxetine, paroxetine, quinidine): Dose of tetrabenazine should be reduced by 50% in patients receiving strong CYP2D6 inhibitors, follow dosing for poor CYP2D6 metabolizers. Use caution when adding a CYP2D6 inhibitor to patients already taking tetrabenazine.

Note: If treatment is interrupted for >5 days, retitration is recommended. If treatment is interrupted for <5 days resume at previous maintenance dose.

Canadian labeling: Hyperkinetic movement disorders: Initial: 12.5 mg twice daily (may be given 3 times/day); may be increased by 12.5 mg/day every 3-5 days; should be titrated slowly to maximal tolerated and effective dose (dose is individualized)

Usual maximum tolerated dosage: 25 mg 3 times/day; maximum recommended dose: 200 mg/day

Note: If there is no improvement at the maximum tolerated dose after 7 days, improvement is unlikely; discontinuation should be considered.

Dosing: ElderlyCanadian labeling: Elderly and/or debilitated patients: Consider initiation at lower doses; must be titrated slowly to individualize dosage.

Dosing: Hepatic ImpairmentUse is contraindicated.

Dosing: Adjustment for ToxicityFor toxicity/adverse reaction, including akathisia, restlessness, parkinsonism, insomnia, depression, suicidality, anxiety, sedation (intolerable): Suspend upward dosage titration and reduce dose; consider discontinuing if adverse reaction does not resolve (may be discontinued without tapering.

Administration: OralMay administer with or without food.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

RestrictionsAn FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider.

Contraindications

U.S. labeling: Patients who are actively suicidal or with untreated or inadequately treated depression; hepatic impairment; use with or within 14 days of MAO inhibitors; use with or within 20 days of reserpine

Canadian labeling: Hypersensitivity to tetrabenazine or any component of the formulation; history or current episode of clinical depression; use with or within 14 days of MAO inhibitors

Warnings/Precautions

Box warnings:

- Depression/suicidal ideation: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Akathisia: Use has been associated with akathisia; monitor for signs and symptoms of restlessness and agitation. Dosage reduction or discontinuation may be necessary.

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Depression/suicidal ideation: [**U.S. Boxed Warning]: May increase risk for depression and suicidal ideation; evaluate immediately if signs and/or symptoms of depression or suicidality are noted. Use with caution in patients with a history of depression; monitor patients closely for new or worsening signs or symptoms of depression.** Reduce dose if depression occurs; consider discontinuing if depression/suicidal ideation does not resolve.

- Esophageal dysmotility/aspiration: Use has been associated with esophageal dysmotility, dysphagia, and aspiration; use with caution in patients at risk of aspiration pneumonia.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity and/or autonomic instability. Discontinue with confirmed NMS; may reoccur with reintroduction of treatment; monitor carefully.

- Orthostatic hypotension: May cause orthostatic hypotension; monitor patients at risk closely.

- QT prolongation: Has been shown to prolong the QT interval alone (minimal) and with other drugs with comparable effects on the QT interval (additive). Avoid use in patients with congenital QT prolongation, a history of cardiac arrhythmias, or concomitant drugs known to cause QT prolongation.

Disease-related concerns:

- Parkinson's disease: Use with caution in patients with Parkinson's disease; may induce/exacerbate symptoms of parkinsonism (more common in elderly patients). Dose reduction or discontinuation of therapy may be necessary.

- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Psychiatric disease: Due to the possibility of comorbid psychiatric disorders and potential psychiatric adverse effects, patients should be carefully monitored for potential changes in psychiatric status during therapy.

Concurrent drug therapy issues:

- Neuroleptic drugs: Has not been studied with concomitant use of neuroleptic drugs (eg, haloperidol, olanzapine); adverse effects may be additive.

Special populations:

- CYP2D6 poor metabolizers: Patients should be tested for the CYP2D6 gene prior to initiating doses >50 mg/day; maximum dosage should not exceed 50 mg/day in poor metabolizers.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Should not be used to treat levodopa-induced dyskinesia.

Geriatric ConsiderationsNo specific geriatric information is available.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAdverse events were observed in some animal studies. There are no adequate and well-controlled studies in pregnant women. Avoid use in pregnant women unless the potential benefit justifies the potential risk to the fetus.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions**Note:** Many adverse effects are dose-related and may resolve at lower dosages. Adverse effects reported for adults with chorea associated with Huntington’s disease.

>10%:

Central nervous system: Extrapyramidal symptoms (15% to 33%), sedation (31%), somnolence (31%), fatigue (22%), insomnia (22%), akathisia (19%), depression (19%), anxiety (15%)

Gastrointestinal: Nausea (13%)

Neuromuscular & skeletal: Falls (15%)

Respiratory: Upper respiratory tract infection (11%)

1% to 10%:

Central nervous system: Parkinsonism (3% to 10%), irritability (9%), dizziness (4%), headache (4%), obsessive reaction (4%)

Dermatologic: Bruising (6%)

Gastrointestinal: Dysphagia (4% to 10%), vomiting (6%), appetite decreased (4%), diarrhea (2%)

Genitourinary: Dysuria (4%)

Neuromuscular & skeletal: Balance difficulty (9%), bradykinesia (9%), dysarthria (4%), gait disturbance (4%)

Respiratory: Bronchitis (4%), dyspnea (4%)

<1%, postmarketing, and/or case reports: Aspiration pneumonia, hyperprolactinemia, orthostatic hypotension, neuroleptic malignant syndrome, QT_c prolongation, restlessness, suicidal ideation, suicide, syncope, transaminases increased

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Antipsychotics: Tetrabenazine may enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May increase the serum concentration of Tetrabenazine. Specifically, concentrations of the active alpha- and beta-dihydrotetrabenazine metabolites may be increased. Management: Tetrabenazine dose should be reduced by 50% when starting a strong CYP2D6 inhibitor. Maximum tetrabenazine dose is 50mg/day when used with a strong CYP2D6 inhibitor. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

MAO Inhibitors: Tetrabenazine may enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Reserpine: May enhance the adverse/toxic effect of Tetrabenazine. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersImprovement in movement disorder; signs and/or symptoms of depression or suicidal ideation; signs and/or symptoms of NMS; orthostatic blood pressure. Due to the possibility of comorbid psychiatric disorders, and potential psychiatric adverse effects, patients should be carefully monitored for potential changes in psychiatric status during therapy. CYP2D6 genotyping for evaluation of metabolizer status.

Nursing: Physical Assessment/MonitoringEvaluate closely for presence or history of depression or other psychiatric disorders, hepatic impairment, cardiac abnormalities, or recent use of MAO inhibitors. Assess all other pharmacological or herbal products patient may be taking for potential interactions or toxicity; dosing adjustments may be necessary. Dosing should be individualized and titrated slowly. Evaluate therapeutic effectiveness (according to purpose for use) and adverse effects (especially psychiatric status or CNS changes) at beginning of therapy, with any dose change, and at frequent intervals during long-term therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy unless approved by prescriber. Take exactly as directed; do not alter dose or schedule without consulting prescriber. May cause dizziness, headache, or sedation (use caution when driving or engaging in tasks requiring alertness until response to drug is known) or nausea or vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report immediately any signs of CNS changes (mood changes, increased irritability or anxiety, cognition changes, depression, suicidal ideation, difficulty thinking or abnormal thoughts); neuromuscular changes (rigidity, unusual movement, gait disturbance, balance difficulty); difficulty swallowing; difficulty breathing or upper respiratory infection; or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian product

Tablet:

Nitoman™ [CAN]: 25 mg [not available in the U.S.]

Xenazine®: 12.5 mg, 25 mg

ManufacturerPrestwick Pharmaceuticals, Inc

Mechanism of ActionWithin basal ganglia, interferes with and depletes monoamine neurotransmitters (including dopamine, serotonin, and norepinephrine) in presynaptic vesicles (likely through actions on vesicle monoamine transporter). Tetrabenazine inhibits presynaptic dopamine release and also blocks CNS dopamine receptors. The effects resemble reserpine but with less peripheral activity and a shorter duration of action. Treatment results in symptomatic improvement of hyperkinetic movement disorders, including Huntington's chorea, hemiballismus, senile chorea, Tic and Hille's de la Tourette syndrome, and tardive dyskinesia.

Pharmacodynamics/Kinetics

Duration: 16-24 hours (at steady-state); chorea may recur within 12-18 hours after discontinuation

Protein binding: 82% to 85%; Metabolites: 59% to 68%

Metabolism: Hepatic (rapid and extensive), to alpha and beta hydroxytetrabenazine (HTBZ) via CYP2D6 (primary active moiety)

Bioavailability: Low and erratic (due to extensive first-pass effects); unaffected by food

Half-life elimination: Alpha-HTBZ: 4-8 hours; Beta-HTBZ: 2-4 hours (increased with hepatic impairment)

Time to peak, plasma: Within 1-1.5 hours

Excretion: Urine (75% as metabolites, <10% as alpha and beta HTBZ); feces (7% to 16%)

Dental Health: Effects on Dental Treatment

Key adverse event(s) related to dental treatment: Orthostatic hypotension has been reported; monitor patient during erect posture from dental chair and dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions

No information available to require special precautions

References

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International Brand Names

Nitoman (DE, DK, GB); Revocon (IN); Xenazine (FR, GB, IL, NZ)

Tetracaine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(TET ra kane)

U.S. Brand NamesPontocaine®; Pontocaine® Niphanoid®

Canadian Brand NamesAmetop™; Pontocaine®

Pharmacologic CategoryLocal Anesthetic

Use: Labeled IndicationsSpinal anesthesia; local anesthesia in the eye for various diagnostic and examination purposes; topically applied to nose and throat for various diagnostic procedures

Use: DentalEster-type local anesthetic; applied topically to throat for various diagnostic procedures and on cold sores and fever blisters for pain

Dosing: Adults

Short-term anesthesia of the eye: Ophthalmic 0.5% solution: Instill 1-2 drops; prolonged use (especially for at-home self-medication) is not recommended

Spinal anesthesia: Injection: **Note:** Dosage varies with the anesthetic procedure, the degree of anesthesia required, and the individual patient response; it is administered by subarachnoid injection for spinal anesthesia.

Perineal anesthesia: 5 mg

Perineal and lower extremities: 10 mg

Anesthesia extending up to costal margin: 15 mg; doses up to 20 mg may be given, but are reserved for exceptional cases

Low spinal anesthesia (saddle block): 2-5 mg

Topical mucous membranes (rhinolaryngology): Used as a 0.25% or 0.5% solution by direct application or nebulization; total dose should not exceed 20 mg

Dosing: ElderlyRefer to adult dosing.

Storage

Injection: Store solution under refrigeration. Protect from light.

Ophthalmic and topical solutions: Store under refrigeration at 2°C to 8°C.

Reconstitution

Solution for injection: Hyperbaric solution: May be made by mixing equal volumes of the 1% solution and $D_{10}W$.

Powder for injection:

Hyperbaric solution: Dissolve 10 mg of Pontocaine® Niphanoid® in 1 mL $D_{10}W$. Further dilute with equal volume of spinal fluid. Resulting solution is D_5W with tetracaine 5 mg/mL.

Hypobaric solution: Dissolve 1 mg of Pontocaine® Niphanoid® in 1 mL SWFI.

ContraindicationsHypersensitivity to tetracaine, ester-type anesthetics, aminobenzoic acid, or any component of the formulation; injection should not be used when spinal anesthesia is contraindicated

Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Decreased plasma esterase levels: Use with caution in patients with abnormal or decreased levels of plasma esterases.
- Hyperthyroidism: Use with caution in patients with hyperthyroidism.

Special populations:

- Acutely ill patients: Use with caution in acutely ill patients; dose reduction may be required.
- Debilitated patients: Use with caution in debilitated patients; dose reduction may be required.
- Elderly: Use with caution in the elderly; dose reduction may be required.
- Obstetric patients: Use with caution in obstetric patients; dose reduction may be required.
- Patients with increased intra-abdominal pressure: Use with caution in patients with increased intra-abdominal pressure; dose reduction may be required.

Dosage form specific issues:

- Ophthalmic: May delay wound healing. Prolonged use is not recommended. The anesthetized eye should be protected from irritation, foreign bodies, and rubbing to prevent inadvertent damage.

- Sodium bisulfite: Products may contain sodium bisulfite which may cause allergic reactions in some individuals.

- Trained personnel: Dental practitioners and/or clinicians using local anesthetic agents should be well trained in diagnosis and management of emergencies that may arise from the use of these agents. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use.

Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted.
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Injection: Note: Adverse effects listed are those characteristics of local anesthetics.

Cardiovascular: Cardiac arrest, hypotension

Central nervous system: Chills, convulsions, dizziness, drowsiness, nervousness, unconsciousness

Gastrointestinal: Nausea, vomiting

Neuromuscular & skeletal: Tremors

Ocular: Blurred vision, pupil constriction

Otic: Tinnitus

Respiratory: Respiratory arrest

Miscellaneous: Allergic reaction

Ophthalmic: Ocular: Chemosis, lacrimation, photophobia, transient stinging

With chronic use: Corneal erosions, corneal healing retardation, corneal opacification (permanent), corneal scarring, keratitis (severe)

Drug InteractionsThere are no known significant interactions.
Nursing: Physical Assessment/Monitoring**Note:** Tetracaine is 10 times as potent as procaine. Explain use, monitor vital signs, and monitor patient safety before, during, and following use according to formulation used and procedure being done. Caution patient that anesthetic effects of topical or ophthalmic preparation may last for some time after procedure (1-5 hours). Instruct in appropriate safety precautions.
Patient EducationTopical or ophthalmic anesthesia effects may last for some time following use; you will need to observe appropriate safety precautions to prevent injury. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Ophthalmic: Do not rub or touch your eye, scratch your nose, or attempt to apply eye make-up until all sensation returns. May cause temporary rash or stinging when used. Report any ringing in ears, feeling of weakness or faintness, chest pain or palpitation, or increased restlessness.

Topical: Do not eat or drink anything until full sensation returns to lips, mouth, and throat. Use caution with heat or cold; you will not have accurate hot or cold sensation until full effects of anesthesia have worn off.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as hydrochloride [preservative free]:

Pontocaine® Niphanoid®: 20 mg

Injection, solution, as hydrochloride [preservative free]: 1% [10 mg/mL] (2 mL)

Pontocaine®): 1% [10 mg/mL] (2 mL) [contains sodium bisulfite]

Solution, ophthalmic, as hydrochloride: 0.5% [5 mg/mL] (2 mL, 15 mL)

Solution, topical, as hydrochloride (Pontocaine®): 2% [20 mg/mL] (30 mL, 118 mL) [for rhinolaryngology]

Generic AvailableYes: Ophthalmic solution, solution for injection
Pricing: U.S. (www.drugstore.com)

Solution (Tetracaine HCl)

0.5% (15): $8.99

Mechanism of ActionEster local anesthetic blocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction
Pharmacodynamics/Kinetics
Onset of action: Anesthetic: Rhinolaryngology: 5-10 minutes

Duration: Rhinolaryngology: ~30 minutes

Metabolism: Hepatic; detoxified by plasma esterases to aminobenzoic acid

Excretion: Urine

Pharmacotherapy PearlsApproximately 10 times more potent than procaine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, or nervousness

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other ConsiderationsTetracaine is ~10 times more potent than procaine.

Local anesthetic toxicity: Cardiac arrest: Lipid infusion has been used in animal studies and several human cases (Bupivacaine: Rosenblatt, 2006; Levobupivacaine: Foxall, 2007; Ropivacaine: Litz, 2006) where cardiovascular toxicity, unresponsive to conventional resuscitation, resulted. Additional information is available at http://www.lipidrescue.org. The protocol from the website is: **20% Fat Emulsion:** 1.5 mL/kg administered over 1 minute, followed immediately by an infusion of 0.25 mL/kg/minute. Continue chest compressions (lipid must circulate). Repeat bolus every 3-5 minutes up to 3 mL/kg total dose until circulation restored. Continue infusion until hemodynamic stability is restored. Increase the infusion rate to 0.5 mL/kg/minute if BP declines. A maximum total dose of 8 mL/kg is recommended.

Index TermsAmethocaine Hydrochloride; Tetracaine Hydrochloride

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International Brand NamesAmetop (GB); Anestesia (ES); Chlorhydrate de tetracaine (LU); Gingicain D (DE); Hemonet (ES); Minims Amethocaine Hydrochloride (FI, GB, IE); Minims Ametocaina (IT); Minims Tetracaine (BE); Minims-Amethocain Hydrochlorid (AT); Oto-Flexiole N (DE); Tetracaine Faure (FR); Tetracaine Minims (NL); Tetracaine Ophtadose (BE); Tetracaine SDU Faure (CH); Tetrakain (HR, SE); Tetrakain Minims (NO)

Tetracycline Periodontal Fibers

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(tet ra SYE kleen per ee oh DON tal FYE bers)

U.S. Brand NamesActisite®

Pharmacologic CategoryAntibacterial, Dental

Use: Labeled IndicationsUsed exclusively in dental applications

Use: DentalTreatment of adult periodontitis; as an adjunct to scaling and root planing for the reduction of pocket depth and bleeding on probing in selected patients with adult periodontitis

Dosing: Adults

Periodontitis: Pocket insertion: Insert fiber to fill the periodontal pocket; each fiber contains 12.7 mg of tetracycline in 23 cm (9 inches) and provides continuous release of drug for 10 days; fibers are to be secured in pocket with cyanoacrylate adhesive and left in place for 10 days

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to tetracyclines or any component of the formulation

Allergy Considerations

- Tetracycline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Photosensitivity: May cause photosensitivity; discontinue if skin erythema occurs. Use skin protection and avoid prolonged exposure to sunlight; do not use tanning equipment.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Oral candidiasis: Safety and efficacy have not been established in the treatment of periodontitis in patients with oral candidiasis.

Special populations:

- Pregnancy: Do not use during pregnancy. In addition to affecting tooth development, tetracycline use has been associated with retardation of skeletal development and reduced bone growth.

Other warnings/precautions:

- Appropriate use: Fibers must be removed after 10 days. Pack fibers to allow for appropriate drainage. Do not use with acute periodontal abscess; not studied with chronic abscesses.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown

Adverse Reactions1% to 10%:

Dermatologic: Local erythema following removal

Miscellaneous: Discomfort from fiber placement

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Fibers: 23 cm (9”) in length [12.7 mg of tetracycline hydrochloride per fiber]

Generic AvailableNo

Mechanism of ActionTetracycline is an antibiotic which inhibits growth of susceptible microorganisms. Tetracycline binds primarily to the 30S subunits of bacterial ribosomes, and appears to prevent access of aminoacyl tRNA to the acceptor site on the mRNA-ribosome complex. The fiber releases tetracycline into the periodontal site at a rate of 2 mcg/cm/hour.

Pharmacodynamics/Kinetics

The fiber releases tetracycline at a rate of 2 mcg/cm/hour

Tissue fluid concentrations:

Gingival fluid: ~1590 mcg/mL of tetracycline per site over 10 days

Plasma: During fiber treatment of up to 11 teeth, the tetracycline plasma concentration was below any detectable levels (<0.1 mcg/mL)

Oral: 500 mg of tetracycline produces a peak plasma level of 3-4 mcg/mL

Saliva: ~50.7 mcg/mL of tetracycline immediately after fiber treatment of 9 teeth

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Gingival inflammation, mouth pain, glossitis, candidiasis, staining of tongue, local erythema following removal, and discomfort from fiber placement.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

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International Brand NamesActisite Fibra (ES)

Tetracycline

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Tetracycline may be confused with tetradecyl sulfate

Achromycin may be confused with actinomycin, Adriamycin PFS®

Pronunciation(tet ra SYE kleen)

Canadian Brand NamesApo-Tetra®; Nu-Tetra

Pharmacologic CategoryAntibiotic, Tetracycline Derivative

Use: Labeled IndicationsTreatment of susceptible bacterial infections of both gram-positive and gram-negative organisms; also infections due to *Mycoplasma*, *Chlamydia*, and *Rickettsia*; indicated for acne, exacerbations of chronic bronchitis, and treatment of gonorrhea and syphilis in patients who are allergic to penicillin; as part of a multidrug regimen for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence

Use: DentalTreatment of periodontitis associated with presence of *Actinobacillus actinomycetemcomitans* (AA); as adjunctive therapy in recurrent aphthous ulcers

Dosing: Adults

Usual dosage range: Oral: 250-500 mg every 6 hours

Acne: Oral: 250-500 twice daily

Chronic bronchitis, acute exacerbation: Oral: 500 mg 4 times/day

Erlichiosis: Oral: 500 mg 4 times/day for 7-14 days

Peptic ulcer disease: Eradication of *Helicobacter pylori*: Oral: 500 mg 2-4 times/day depending on regimen; requires combination therapy with at least one other antibiotic and an acid-suppressing agent (proton pump inhibitor or H_2 blocker)

Periodontitis: Oral: 250 mg every 6 hours until improvement (usually 10 days)

Vibrio cholerae: Oral: 500 mg 4 times/day for 3 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Usual dosage range:** Children >8 years: Oral: 25-50 mg/kg/day in divided doses every 6 hours

Dosing: Renal Impairment

Cl_{cr} 50-80 mL/minute: Administer every 8-12 hours.

Cl_{cr} 10-50 mL/minute: Administer every 12-24 hours.

Cl_{cr} <10 mL/minute: Administer every 24 hours.

Slightly dialyzable (5% to 20%) via hemo- and peritoneal dialysis or via continuous arteriovenous or venovenous hemofiltration; supplemental dose is not necessary.

Dosing: Hepatic ImpairmentUse caution; no dosing adjustment required

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralOral should be given on an empty stomach (ie, 1 hour prior to, or 2 hours after meals) to increase total absorption. Administer at least 1-2 hours prior to, or 4 hours after antacid because aluminum and magnesium cations may chelate with tetracycline and reduce its total absorption. Administer around-the-clock to promote less variation in peak and trough serum levels.

StorageOutdated tetracyclines have caused a Fanconi-like syndrome (nausea, vomiting, acidosis, proteinuria, glycosuria, aminoaciduria, polydipsia, polyuria, hypokalemia). Protect oral dosage forms from light.

ContraindicationsHypersensitivity to tetracycline or any component of the formulation; do not administer to children ≤8 years of age; pregnancy

Allergy Considerations

- Tetracycline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Increased BUN: May be associated with increases in BUN secondary to antianabolic effects; use caution in patients with renal impairment.

- Nephropathy: Outdated drug can cause nephropathy.

- Photosensitivity: May cause photosensitivity; discontinue if skin erythema occurs. Use skin protection and avoid prolonged exposure to sunlight; do not use tanning equipment.

- Pseudotumor cerebri: Has been (rarely) reported with tetracycline use; usually resolves with discontinuation.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hepatic impairment: Hepatotoxicity has been reported rarely; risk may be increased in patients with pre-existing hepatic or renal impairment.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Special populations:

- Pediatrics: May cause tissue hyperpigmentation, enamel hypoplasia, or permanent tooth discoloration; use of tetracyclines should be avoided during tooth development (children ≤8 years of age) unless other drugs are not likely to be effective or are contraindicated. However, recommended in treatment of anthrax exposure.

- Pregnancy: Do not use during pregnancy. In addition to affecting tooth development, tetracycline use has been associated with retardation of skeletal development and reduced bone growth.

Geriatric ConsiderationsThe role of tetracycline has decreased because of the emergence of resistant organisms. Doxycycline is the tetracycline of choice when one is indicated because of its better GI absorption, less interactions with divalent cations, longer half-life, and the fact that the majority is cleared by nonrenal mechanisms.

Pregnancy Risk FactorD

Pregnancy ConsiderationsTetracyclines cross the placenta, enter fetal circulation, and may cause permanent discoloration of teeth if used during the second or third trimester. Maternal hepatic toxicity has been associated with the use of tetracycline during pregnancy, especially in patients with azotemia or pyelonephritis. Because use during pregnancy may cause fetal harm, tetracycline is classified as pregnancy category D.

LactationEnters breast milk/not recommended (AAP rates “compatible”)

Breast-Feeding ConsiderationsTetracyclines are excreted in breast milk. Tetracycline binds to calcium. The calcium in the maternal milk will decrease the amount of tetracycline absorbed by the breast-feeding infant. Because of this “negligible absorption by the neonate,” the AAP considers tetracycline to be “usually compatible with breast-feeding.” Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Tetracycline in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Cardiovascular: Pericarditis

Central nervous system: Intracranial pressure increased, bulging fontanels in infants, pseudotumor cerebri, paresthesia

Dermatologic: Photosensitivity, pruritus, pigmentation of nails, exfoliative dermatitis

Endocrine & metabolic: Diabetes insipidus syndrome

Gastrointestinal: Discoloration of teeth and enamel hypoplasia (young children), nausea, diarrhea, vomiting, esophagitis, anorexia, abdominal cramps, antibiotic-associated pseudomembranous colitis, staphylococcal enterocolitis, pancreatitis

Hematologic: Thrombophlebitis

Hepatic: Hepatotoxicity

Renal: Acute renal failure, azotemia, renal damage

Miscellaneous: Superinfection, anaphylaxis, hypersensitivity reactions, candidal superinfection

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (moderate)

Drug Interactions

Antacids: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Atovaquone: Tetracycline may decrease the serum concentration of Atovaquone. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Bismuth: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Bismuth Subsalicylate: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Eplerenone: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Eplerenone. Management: A lower starting dose of eplerenone (25 mg once daily) is recommended in patients with hypertension who are also taking drugs that are moderate inhibitors of CYP3A4. *Risk D: Consider therapy modification*

FentaNYL: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Tetracycline Derivatives. Only a concern with orally administered products. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Tetracycline Derivatives. Only applicable to oral preparations of each agent. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Tetracycline Derivatives may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Penicillins: Tetracycline Derivatives may diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Quinapril: May decrease the absorption of Tetracycline Derivatives. *Risk D: Consider therapy modification*

Ranolazine: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Ranolazine. Management: Limit the ranolazine dose to a maximum of 500mg twice daily in patients concurrently receiving moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin, etc.). *Risk D: Consider therapy modification*

Retinoic Acid Derivatives: Tetracycline Derivatives may enhance the adverse/toxic effect of Retinoic Acid Derivatives. The development of pseudotumor cerebri is of particular concern. **Exceptions:** Adapalene; Alitretinoin; Tretinoin (Topical). *Risk X: Avoid combination*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Tetracycline Derivatives may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zinc Salts: May decrease the absorption of Tetracycline Derivatives. Only a concern when both products are administered orally. **Exceptions:** Zinc Chloride. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: Tetracycline serum concentrations may be decreased if taken with dairy products.

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization)

Test InteractionsFalse-negative urine glucose with Clinistix®

Monitoring ParametersRenal, hepatic, and hematologic function test, temperature, WBC, cultures and sensitivity, appetite, mental status

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient's allergy history prior to beginning therapy. Assess potential interactions with other pharmacological agents and herbal products patient may be using (eg, may decrease levels/effects of penicillins and CYP3A4 inducers, increase levels/effects of warfarin and CYP3A4 substrates). Assess results of laboratory tests, therapeutic effectiveness (resolution of infection), and adverse reactions (eg, nausea, diarrhea, pericarditis, photosensitivity, rash, opportunistic infection, hypersensitivity) at beginning of and periodically throughout therapy. Caution patients with diabetes to monitor glucose levels closely (may cause false-positive urine glucose with Clinitest®). Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsRenal, hepatic, and hematologic function; WBC. Perform culture and sensitivity studies prior to initiating therapy to determine the causative organism and its susceptibility to tetracycline.

Patient EducationDo not use more or more often than recommended. Preferable to take on an empty stomach, 1 hour before or 2 hours after meals. Take at regularly scheduled times, around-the-clock. Avoid antacids, iron, or dairy products within 2 hours of taking tetracycline. You may experience photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); dizziness or lightheadedness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea/vomiting (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report rash or intense itching, yellowing of skin or eyes, fever or chills, blackened stool, vaginal itching or discharge, foul-smelling stools, excessive thirst or urination, acute headache, unresolved or persistent diarrhea, respiratory difficulty, condition does not improve, or worsening of condition. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Use appropriate barrier contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 250 mg, 500 mg

Generic AvailableYes: Capsule

Pricing: U.S. (www.drugstore.com)

Capsules (Tetracycline HCl)

250 mg (100): $14.99

500 mg (100): $19.99

Mechanism of ActionInhibits bacterial protein synthesis by binding with the 30S and possibly the 50S ribosomal subunit(s) of susceptible bacteria; may also cause alterations in the cytoplasmic membrane

Pharmacodynamics/Kinetics

Absorption: Oral: 75%

Distribution: Small amount appears in bile

Relative diffusion from blood into CSF: Good only with inflammation (exceeds usual MICs)

CSF:blood level ratio: Inflamed meninges: 25%

Protein binding: ~65%

Half-life elimination: Normal renal function: 8-11 hours; End-stage renal disease: 57-108 hours

Time to peak, serum: Oral: 2-4 hours

Excretion: Urine (60% as unchanged drug); feces (as active form)

Related Information

- Antacid Drug Interactions
- Antimicrobial Drugs of Choice
- Malaria Treatment

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Esophagitis, superinfections, and candidal superinfection. Opportunistic “superinfection” with *Candida albicans*; tetracyclines are not recommended for use during pregnancy or in children ≤8 years of age since they have been reported to cause enamel hypoplasia and permanent teeth discoloration. The use of tetracyclines should only be used in these patients if other agents are contraindicated or alternative antimicrobials will not eradicate the organism. Long-term use associated with oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentTetracycline may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity although the clinical significance is likely minimal; monitor serum lithium levels

Index TermsAchromycin; TCN; Tetracycline Hydrochloride

References

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Smilack JD, Wilson WR, and Cockerill FR 3d, “Tetracyclines, Chloramphenicol, Erythromycin, Clindamycin, and Metronidazole,” *Mayo Clin Proc*, 1991, 66(12):1270-80. [PubMed 1749296]

Walters BN and Gubbay SS, “Tetracycline and Benign Intracranial Hypertension: Report of Five Cases,” *Br Med J (Clin Res Ed)*, 1981, 282(6257):19-20.

Wandstrat TL and Phillips J, “Pseudotumor Cerebri Responsive to Acetazolamide,” *Ann Pharmacother*, 1995, 29(3):318.

Yoshikawa TT, “Antimicrobial Therapy for the Elderly Patient,” *J Am Geriatr Soc*, 1990, 38(12):1353-72.[PubMed 2254575]

International Brand Names Achromycin (AE, AT, BH, CH, CY, EG, IL, IN, IQ, IR, JO, JP, KW, LB, LY, OM, PK, QA, SA, SY, TW, YE, ZA); Achromycin V (AE, BH, CY, EG, IL, IQ, IR, JO, JP, KW, LB, LY, OM, QA, SA, SY, YE); Acromicina (MX); Ambotetra (MX); Ambramicina (IT); Apocyclin (FI); Biotine (SG); Bocycline (TW); Bristaciclina (ES); Cadicycline (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Ciclobiotico (PT); Ciclotetryl (AR); Clincor (VE); Combicyclin (ID); Conmycin (ID); Cyclabid (ZA); Dhatracin (MY); Dicyclin Forte (IN); Economycin (GB); Enkacyclin (ID); Erifor (MX); Florocycline (FR); Hexacycline (FR); Hostacyclin (AT, GR); Hostacycline (IN, PH, ZA); Hostacycline-P (ZA); Ibicyn (TW); Imex (BG, DE, EE, KP, TW); Infex (BR); Latycin (AE, AU, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SG, SY, YE); Lenocin (TH); Medocycline (HK); Metrocycline (PH); Monocycline (PH); Optycin (AU); Oricyclin (FI); Panmycin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, MY, OM, QA, SA, SY, YE); Quemiciclina-S (PE); Quimocyclar (MX); Recycline (IL); Resteclin (IN); Rimatet (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PR, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Servitet (MY, TH); Steclin V (ZA); Subamycin (IN); Tc (PL); Tefilin (DE); Tetrabioptal (IT); Tetrabiotico (EC); Tetrachel (GB); Tetracyclinum (PL); Tetramig (FR); Tetrana (TH); Tetrano (TH); Tetrarco (ID, NL); Tetraseptin (CH); Tetrasuiss (AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PR, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW); Tetrecu (EC); Tetrex (AE, AU, BH, CY, EG, IL, IQ, IR, JO, JP, KW, LB, LY, MX, OM, QA, SA, SY, YE, ZA); Tevacycline (IL); Trinotrex (BR); Ttmycin (TW); Wintel (TW)

Tetrahydrocannabinol and Cannabidiol

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English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation

(TET ra hye droe can NAB e nol & can nab e DYE ol)

Canadian Brand NamesSativex®

Pharmacologic CategoryAnalgesic, Miscellaneous

Use: Labeled IndicationsAdjunctive treatment of neuropathic pain in multiple sclerosis; adjunctive treatment of moderate-to-severe pain in advanced cancer

Dosing: Adults**Neuropathic pain (MS), cancer pain:** Buccal spray: Initial: One spray every 4 hours to a maximum of 4 sprays on first day

Titration and individualization: Dosage is self-titrated by the patient. In the treatment of MS, the mean daily dosage after titration in clinical trials was 5 sprays per day. The usual maximum dose is 12 sprays per day although some patients may require and tolerate a higher number of sprays per day. In the treatment of cancer pain, the mean daily dosage after titration was 8 sprays per day. Dosage should be adjusted as necessary, based on effect and tolerance. Sprays should be evenly distributed over the course of the day during initial titration. If adverse reactions, including intoxication-type symptoms, are noted the dosage should be suspended until resolution of the symptoms; a dosage reduction or extension of the interval between doses may be used to avoid a recurrence of symptoms. Retitration may be required in the event of adverse reactions and/or worsening of symptoms.

Dosing: ElderlyRefer to adult dosing. Use with caution and monitor closely.

Dosing: Renal Impairment

Use with caution; has not been studied in patients with significant renal dysfunction.

Dosing: Hepatic Impairment

Use with caution; has not been studied in patients with significant hepatic dysfunction.

Administration: Oral**Note:** For buccal use only; spray should be directed below the tongue or on the inside of the cheeks (the site should be varied); avoid direction to the pharynx.

Shake vial before use and remove protective cap; replace protective cap following use. Do not apply spray to sore or inflamed mucosa.

Priming: Vial should be held in an upright position and primed prior to the initial use by depression of the actuator 2-3 times until a fine spray appears. Priming should not be required for subsequent uses. Do not spray near an open flame.

Normal use: Hold vial in upright position and spray into mouth; spray should be directed below the tongue or on the inside of the cheeks, avoiding direction to the pharynx. The site should be varied.

StoragePrior to first use, store unopened at 2°C to 8°C (36°F to 46°F); do not freeze. After opening, may be stored at room temperature of 15°C to 25°C (59°F to 77°F) for up to 28 days. Avoid heat and direct sunlight.

RestrictionsNot available in U.S.; CDSA-II

ContraindicationsHypersensitivity to cannabinoids or any component of the formulation; serious cardiovascular disease (including arrhythmias, severe heart failure, poorly controlled hypertension, and ischemic heart disease); history of psychotic disorders (including schizophrenia); women of childbearing potential who are not using a reliable form of contraception; males intending to start a family; children <18 years of age; pregnancy; breast-feeding

Warnings/Precautions

Boxed warnings:

- Ethanol/sedatives: See “Concurrent drug therapy issues” below.
- Cardiovascular effects: See “Concerns related to adverse effects” below.
- CNS effects: See “Concerns related to adverse effects” below.
- Physical/psychological dependence: See “Disease-related concerns” below.
- Prescribing restrictions: See “Other warnings/precautions” below.
- Seizures: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Buccal mucosa irritation: May be irritating to the buccal mucosa; avoid administration in an area of soreness or inflammation.

- Cardiovascular effects: **[Canadian Boxed Warning]: May be associated with adverse cardiovascular effects, including tachycardia and alterations in blood pressure (including orthostatic changes).** Dosage must be carefully titrated and monitored, with downward adjustment in patients with unacceptable adverse events. Use is contraindicated in ischemic heart disease, arrhythmias, poorly-controlled hypertension, and severe heart failure).

- CNS effects: **[Canadian Boxed Warning]: Use may be associated with dizziness, changes in mood, cognitive performance, memory, impulsivity, and coordination, as well as an altered perception of reality, particularly with respect to an awareness/sensation of time.** Adverse effects are dose-dependent and vary among patients. Dose reductions, greater intervals between doses, or interrupting therapy may resolve unwanted effects. Drug discontinuation is recommended, and a period of close observation should be instituted, in patients experiencing a psychotic reaction. May impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Genitourinary effects: Use caution in cancer patients. Increased risk for urinary retention and infection.

Disease-related concerns:

- Drug abuse: **[Canadian Boxed Warning]: Potential for drug dependency exists. Tolerance, psychological, and physical dependence may occur with prolonged use.** Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists.

- Hepatic dysfunction: Use in patients with significant hepatic dysfunction has not been studied. Use with caution.

- Renal dysfunction: Use in patients with significant renal dysfunction has not been studied. Use with caution.

- Seizure disorder: **[Canadian Boxed Warning]: Use with caution in patients with a history of seizure disorder.**

Concurrent drug therapy issues:

- Ethanol/sedatives: **[Canadian Boxed Warning]: Concurrent use with other sedatives, psychotropics, hypnotics, or ethanol may potentiate adverse CNS effects.**

Dosage form specific issues:

- Ethanol: Formulation contains ethanol; use with caution in alcoholism.

Other warnings/precautions:

- Prescribing restrictions: **[Canadian Boxed Warning]: Prescriptions should be written for the minimal amount needed between clinic visits.**

- Toxicology screen: Cannabinoids may be detectable in the urine and serum for several weeks following drug discontinuation.

Special populations:

- Elderly: Use with caution in the elderly. Close monitoring of this patient population is required.

Pregnancy ConsiderationsCannabinoids have been associated with reproductive toxicity. Animal studies indicate possible effects on fetal development and spermatogenesis. Use in pregnancy is contraindicated. Women of childbearing potential and males who are capable of causing pregnancy should use a reliable form of contraception for the duration of treatment and for 3 months following discontinuation.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsCannabinoids may concentrate in breast milk. Use is contraindicated.

Adverse Reactions

>10%:

Central nervous system: Dizziness (up to 32%), somnolence (9% to 15%), fatigue (14%)

Gastrointestinal: Oral application site events (≤20%), nausea (12%)

1% to 10%:

Cardiovascular: Hypotension (2% to 5%), hypertension (2%), flushing (1%), syncope (1%),

Central nervous system: Confusion (1% to 7%), disorientation (5%), vertigo (4% to 5%), attention disturbance (3% to 5%), impaired balance (3% to 5%), dissociation (3%), euphoria (3%), headache (3%), insomnia (3%), panic attack (3%), hallucination (up to 3%), amnesia (2%), anxiety (2%), lethargy (2%), malaise (2%), depression (1% to 2%), memory impairment (1%), paranoia (1%)

Endocrine & metabolic: Thirst (1%)

Gastrointestinal: Xerostomia (8%), vomiting (4% to 8%), oral discomfort/pain (up to 8%), diarrhea (5% to 7%), constipation (4% to 5%), abnormal taste (4%), tooth discoloration (4%), dysgeusia (3% to 5%), oral candidiasis (3%), anorexia (2%), appetite increased (2%), abdominal pain (1%), appetite decreased (1%)

Genitourinary: Urinary retention (5%)

Hepatic: ALT increased, AST increased (2.6%)

Neuromuscular & skeletal: Weakness (5% to 6%), muscle spasticity (3%), dysarthria (2%), fall (2%), paresthesia (2%)

Ocular: Vision blurred (2%)

Renal: Hematuria (3%)

Respiratory: Pharyngitis (2%), cough (1%), respiratory tract infection (1%), throat irritation (1%)

Miscellaneous: Drunken feeling (5%), sensation of heaviness (1%)

<1% and/or frequency not defined: Auditory hallucination, delusions, suicidal ideation, tachycardia, urinary infection

Metabolism/Transport Effects **Substrate** (minor) of CYP2C9, 2C19, 2D6, 3A4; **Inhibits** (weak) CYP1A2, 2C19, 2D6, 3A4

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Anticholinergic Agents: May enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Cocaine: May enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Sympathomimetics: Cannabinoids may enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Administration with high-lipid meals may increase absorption.

Monitoring Parameters Mental status, response to pain; mucosal integrity and inflammation

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Solution, buccal [spray]:

Sativex® [CAN]: Delta-9 tetrahydrocannabinol 27 mg/mL and cannabidiol 25 mg/mL (5.5 mL) [delivers 100 microliters/spray; 51 metered sprays; contains ethanol 50%, peppermint oil, and propylene glycol] [not available in U.S.]

Generic Available No

Manufacturer

Bayer Canada

Mechanism of Action Stimulates cannabinoid receptors CB1 and CB2 in the CNS and dorsal root ganglia as well as other sites in the body. Cannabinoid receptors in the pain pathways of the brain and spinal cord mediate cannabinoid-induced analgesia. Peripheral CB2 receptors modulate immune function through cytokine release.

Pharmacodynamics/Kinetics

Absorption: Rapidly absorbed from the buccal mucosa

Distribution: Widely distributed, particularly to fatty tissues

Protein binding: Extensive

Metabolism: Hepatic, via CYP isoenzymes (2C9, 2C19, 2D6 and 3A4) to THC metabolite 11-hydroxy-tetrahydrocannabinol (11-OH-THC, psycho-active) and CBD metabolite 7-hydroxy-cannabidiol.

Half-life elimination: Initial: 1-2 hours; terminal half-life may require 24-36 hours (or longer) due to redistribution from fatty tissue

Time to peak, plasma: 2-4 hours

Excretion: As metabolites, urine and feces

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), abnormal taste, oral pain, orthostatic hypotension; administered as buccal spray, associated with irritation to the buccal (oral) mucosa.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status Dizziness and fatigue are common; may cause mood changes (euphoria, depression), memory impairment, disorientation, dissociation, and impulsivity.

Mental Health: Effects on Psychiatric Treatment Contraindicated in patients with a history of psychotic disorders.

Index Terms Cannabidiol and Tetrahydrocannabinol; Delta-9-Tetrahydrocannabinol and Cannabinol; GW-1000-02; THC and CBD

References

Berman JS, Symonds C, and Birch R, "Efficacy of Two Cannabis Based Medicinal Extracts for Relief of Central Neuropathic Pain From Brachial Plexus Avulsion: Results of a Randomised Controlled Trial," *Pain*, 2004, 112(3):299-306.[PubMed 15561385]

Djulus J, Moretti M, and Koren G, "Marijuana Use and Breastfeeding," *Can Fam Physician*, 2005, 51:349-50.[PubMed 15794018]

Kozer E and Koren G, "Effects of Prenatal Exposure to Marijuana," *Can Fam Physician*, 2001, 47:263-4.[PubMed 11228023]

Smith, PF, "GW-1000. GW Pharmaceuticals," *Curr Opin Investig Drugs*, 2004, 5(7):748-54.[PubMed 15298072]

Wade DT, Makela P, Robson P, et al, "Do Cannabis-Cased Medicinal Extracts Have General or Specific Effects on Symptoms in Multiple Sclerosis? A Double-Blind, Randomized, Placebo-Controlled Study on 160 Patients," *Mult Scler*, 2004, 10(4):434-41.[PubMed 15327042]

International Brand Names Sativex (CA)

Tetrahydrozoline

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Visine® may be confused with Visken®

Pronunciation(tet ra hye DROZ a leen)

U.S. Brand NamesEye-Sine™ [OTC] [DSC]; Geneye [OTC]; Murine® Tears Plus [OTC]; Opti-Clear [OTC]; Optigene® 3 [OTC] [DSC]; Tyzine®; Tyzine® Pediatric; Visine® Advanced Relief [OTC]; Visine® Original [OTC]

Pharmacologic CategoryAdrenergic Agonist Agent; Imidazoline Derivative; Ophthalmic Agent, Vasoconstrictor

Use: Labeled IndicationsSymptomatic relief of nasal congestion and conjunctival congestion

Dosing: Adults

Nasal congestion: Intranasal: Instill 2-4 drops or 3-4 sprays of 0.1% solution every 3-4 hours as needed, no more frequent than every 3 hours

Conjunctival congestion: Ophthalmic: Instill 1-2 drops in each eye 2-4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricNasal congestion: Intranasal:

Children 2-6 years: Instill 2-3 drops of 0.05% solution every 4-6 hours as needed, no more frequent than every 3 hours.

Children >6 years: Refer to adult dosing.

StorageDo not use if solution changes color or becomes cloudy.

Geriatric ConsiderationsUse with caution in patients with cardiovascular disease.

Pregnancy Risk FactorC

Adverse Reactions

>10%:

Local: Transient stinging

Respiratory: Sneezing

1% to 10%:

Cardiovascular: Tachycardia, palpitation, hypertension, heart rate

Central nervous system: Headache

Neuromuscular & skeletal: Tremor

Ocular: Blurred vision

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, intranasal, as hydrochloride [drops]:

Tyzine®: 0.1% (30 mL) [contains benzalkonium chloride]

Tyzine® Pediatric: 0.05% (15 mL) [contains benzalkonium chloride]

Solution, intranasal, as hydrochloride [spray]:

Tyzine®: 0.1% (15 mL) [contains benzalkonium chloride]

Solution, ophthalmic, as hydrochloride: 0.05% (15 mL)

Eye-Sine™ [DSC], Geneye, Optigene® 3 [DSC]: 0.05% (15 mL) [may contain benzalkonium chloride]

Murine® Tears Plus: 0.05% (15 mL) [contains benzalkonium chloride]

Opti-Clear: 0.05% (15 mL)

Visine® Advanced Relief: 0.05% (30 mL) [contains benzalkonium chloride and polyethylene glycol]

Visine® Original: 0.05% (15 mL, 30 mL) [contains benzalkonium chloride; 15 mL size also available with dropper]

Generic AvailableYes: Ophthalmic solution
Pricing: U.S. (www.drugstore.com)

Solution (Tyzine)

0.05% (15): $43.70

0.1% (15): $49.99

Mechanism of ActionStimulates alpha-adrenergic receptors in the arterioles of the conjunctiva and the nasal mucosa to produce vasoconstriction
Pharmacodynamics/Kinetics

Onset of action: Decongestant: Intranasal: 4-8 hours

Duration: Ophthalmic vasoconstriction: 2-3 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentMAO inhibitors can cause an exaggerated adrenergic response if taken concurrently or within 21 days of discontinuing MAO inhibitor; beta-blockers can cause hypertensive episodes and increased risk of intracranial hemorrhage
Index TermsTetrahydrozoline Hydrochloride; Tetryzoline
International Brand NamesABC Spray (JP); Azoline (IL); Berberil (PL); Berberil N (DE, LU, TW); Eye Relief (IL); Insto (ID); Murine Plus (EC); Murine Sore Eyes (AU); Narbel (JP); Oftan-Starine (FI); Opsil-A (TH); Optizoline (HK, MY); Rhinopront (LU); Sinutab NS (PH); Starazolin (PL); Stilla drops (IL); Tyzine (DK, HR, HU, PL); Visimax (DO, HN, SV); Visina (CO); Visine (AE, BE, BF, BG, BH, BJ, CH, CI, CN, CY, CZ, EG, ET, FI, GH, GM, GN, GR, HN, HR, HU, IL, IN, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PE, PH, PL, PT, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Visine Classic (EE); Visine Ophthalmic Solution (AU); Visine Original Eye Drops (AU); Visolin (ID); Vispring (ES); Visto (ID); Visubril (AR)

TEX (Capecitabine + Docetaxel + Epirubicin)

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Pharmacologic Category Chemotherapy Regimen, Breast Cancer

Regimen Use Breast cancer

Regimen

Capecitabine: Oral: 1000 mg/m^2 twice daily days 1 to 14

[total dose/cycle = 28,000 mg/m^2]

Docetaxel: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Epirubicin: I.V.: 75 mg/m^2 day 1

[total dose/cycle = 75 mg/m^2]

Repeat cycle every 3 weeks

References

Venturini M, Durando A, Garrone O, et al, âCapecitabine in Combination With Docetaxel and Epirubicin in Patients With Previously Untreated, Advanced Breast Carcinoma,â *Cancer*, 2003, 97(5):1174-80. [PubMed 12599222]

Thalidomide-Dexamethasone

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Multiple Myeloma

Regimen Use Multiple myeloma

Index Terms Dexamethasone-Thalidomide

Regimen Note: Multiple variations are listed below.

Variation 1:

Thalidomide: Oral: 100 mg/day days 1 to 28

[total dose/cycle = 2800 mg]

Dexamethasone: Oral: 40 mg/day days 1 to 4

[total dose/cycle = 160 mg]

Repeat cycle every 28 days

Variation 2:

Thalidomide: Oral: 200 mg/day days 1 to 14 cycle 1

followed by Oral: 400 mg/day days 15 to 28 cycle 1

[total dose/cycle = 8400 mg]

Thalidomide: Oral: 400 mg/day days 1 to 28 (subsequent cycles)

[total dose/cycle = 11,200 mg]

Dexamethasone: Oral: 20 mg/m^2/day days 1 to 4, 9 to 12, and 17 to 20 cycle 1 (subsequent cycles)

[total dose/cycle = 240 mg/m^2]

Dexamethasone: Oral 20 mg/m^2/day days 1 to 4 (subsequent cycles)

[total dose/cycle = 80 mg/m^2]

Repeat cycle every 28 days

Variation 3:

Thalidomide: Oral: 100 mg/day days 1 to 7, 150 mg/day days 8 to 14, 200 mg/day days 15 to 21, 250 mg/day days 22 to 28, and 300 mg/day days 29 to 35 (cycle 1)

[total dose/cycle = 7000 mg]

Thalidomide: Oral: 300 mg/day days 1 to 35 (subsequent cycles)

[total dose/cycle = 10,500 mg]

Dexamethasone: Oral: 20 mg/m^2/day days 1 to 4, 9 to 12, and 17 to 20

[total dose/cycle = 240 mg/m^2]

Repeat cycle every 35 days

Variation 4:

Thalidomide: Oral: 200 mg/day days 1 to 28

[total dose/cycle = 5600 mg]

Dexamethasone: Oral: 40 mg/day days 1 to 4, 9 to 12, and 17 to 20 (odd cycles)

[total dose/cycle = 480 mg]

Dexamethasone: Oral: 40 mg/day days 1 to 4 (even cycles)

[total dose/cycle = 160 mg]

Repeat cycle every 28 days

References

Variation 1:

Palumbo A, Giaccone L, Bertola A, et al, “Low-Dose Thalidomide Plus Dexamethasone Is an Effective Salvage Therapy for Advanced Myeloma,” *Haematologica*, 2001, 86(4):399-403.[PubMed 11325646]

Variation 2:

Dimopoulos MA, Zervas K, Kouvatseas G, et al, “Thalidomide and Dexamethasone Combination for Refractory Multiple Myeloma,” *Ann Oncol*, 2001, 12(7):991-5.[PubMed 11521808]

Variation 3:

Alexanian R, Weber D, Giralt S, et al, “Consolidation Therapy of Multiple Myeloma With Thalidomide-Dexamethasone After Intensive Chemotherapy,” *Ann Oncol*, 2002, 13(7):1116-9.[PubMed 12176792]

Variation 4:

Rajkumar SV, Hayman S, Gertz MA, et al, “Combination Therapy With Thalidomide Plus Dexamethasone for Newly Diagnosed Myeloma,” *J Clin Oncol*, 2002, 20(21):4319-23.[PubMed 12409330]

Thalidomide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Thalidomide may be confused with flutamide

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

International issues:

Thalomid® may be confused with Thilomide® which is a brand name for lodoxamide in Greece and Turkey

Pronunciation(tha LI doe mide)

U.S. Brand NamesThalomid®

Canadian Brand NamesThalomid®

Pharmacologic CategoryAngiogenesis Inhibitor; Immunomodulator, Systemic; Tumor Necrosis Factor (TNF) Blocking Agent

Use: Labeled IndicationsTreatment of multiple myeloma; treatment and maintenance of cutaneous manifestations of erythema nodosum leprosum (ENL)

Use: Unlabeled/InvestigationalTreatment of Crohn's disease; graft-versus-host reactions after bone marrow transplantation; AIDS-related aphthous stomatitis; Behçet's syndrome; Waldenström's macroglobulinemia; Langerhans cell histiocytosis; may be effective in rheumatoid arthritis, discoid lupus erythematosus, and erythema multiforme

Dosing: Adults

Cutaneous ENL: Oral:

Initial: 100-300 mg/day taken once daily at bedtime with water (at least 1 hour after evening meal)

Adjustments to initial dose:

Patients weighing <50 kg: Initiate at lower end of the dosing range

Severe cutaneous reaction or patients previously requiring high dose: May be initiated at 400 mg/day; doses may be divided, but taken 1 hour after meals

Duration and tapering/maintenance:

Dosing should continue until active reaction subsides (usually at least 2 weeks), then tapered in 50 mg decrements every 2-4 weeks

Note: Patients who flare during tapering or with a history or requiring prolonged maintenance should be maintained on the minimum dosage necessary to control the reaction. Efforts to taper should be repeated every 3-6 months, in increments of 50 mg every 2-4 weeks.

Multiple myeloma: 200 mg once daily (with dexamethasone 40 mg daily on days 1-4, 9-12, and 17-20 of a 28-day treatment cycle)

Behçet's syndrome (unlabeled use): Oral: 100-400 mg/day

Graft-vs-host reactions (unlabeled use): Oral: 100-1600 mg/day; usual initial dose: 200 mg 4 times/day for use up to 700 days

AIDS-related aphthous stomatitis (unlabeled use): Oral: 200 mg twice daily for 5 days, then 200 mg/day for up to 8 weeks

Discoid lupus erythematosus (unlabeled use): Oral: 100-400 mg/day; maintenance dose: 25-50 mg

Dosing: ElderlyRefer to adult dosing.

Dosing: Combination Regimens

Multiple myeloma:

Bortezomib-Melphalan-Prednisone-Thalidomide

DTPACE

Melphalan-Prednisone-Thalidomide

Thalidomide-Dexamethasone

Prostate cancer: Docetaxel-Thalidomide

Administration: OralAdminister with water, preferably at bedtime once daily on an empty stomach, at least 1 hour after the evening meal. Doses >400 mg/day may be given in 2-3 divided doses. Avoid extensive handling of capsules; capsules should remain in blister pack until ingestion. If exposed to the powder content from broken capsules or body fluids from patients receiving thalidomide, the exposed area should be washed with soap and water.

Dietary ConsiderationsShould be taken at least 1 hour after the evening meal.

StorageStore at 15°C to 30°C (50°F to 86°F). Protect from light. Keep in original package.

RestrictionsThalidomide is approved for marketing only under a special distribution program. This program, called the "System for Thalidomide Education and Prescribing Safety" (STEPS® 1-888-423-5436), has been approved by the FDA. Prescribers and pharmacists must be registered with the program. No more than a 4-week supply should be dispensed. Blister packs should be dispensed intact (do not repackage capsules). Prescriptions must be filled within 7 days. Subsequent prescriptions may be filled only if fewer than 7 days of therapy remain on the previous prescription. A new prescription is required for further dispensing (a telephone prescription may not be accepted.)

ContraindicationsHypersensitivity to thalidomide or any component of the formulation; neuropathy (peripheral); patient unable to comply with STEPS® program (including males); women of childbearing potential unless alternative therapies are inappropriate and adequate precautions are taken to avoid pregnancy; pregnancy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.
- Thromboembolic events: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bradycardia: May cause bradycardia; use with caution in patients with cardiovascular disease.
- Hypersensitivity/skin reactions: Hypersensitivity, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported; withhold therapy and evaluate with skin rashes; permanently discontinue if rash is exfoliative, purpuric, bullous or if SJS or TEN is suspected.
- Neutropenia: May cause neutropenia; discontinue therapy if absolute neutrophil count decreases to <750/mm^3.
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients who would not tolerate transient hypotensive episodes.
- Peripheral neuropathy: Use has been associated with the development of peripheral neuropathy, which may be irreversible; use caution with other medications which may cause peripheral neuropathy. Consider immediate discontinuation (if clinically appropriate) in patients who develop neuropathy.
- Sedation: May cause sedation; patients must be warned to use caution when performing tasks which require alertness.
- Seizures: May cause seizures; use caution in patients with a history of seizures, concurrent therapy with drugs which alter seizure threshold, or conditions which predispose to seizures.
- Thromboembolic events: **[U.S. Boxed Warning]: Thrombotic events have been reported, generally in patients with other risk factors for thrombosis (neoplastic disease, inflammatory disease, or concurrent therapy with combination chemotherapy). Use in combination with dexamethasone is associated with increased risk for deep vein thrombosis (DVT) and pulmonary embolism (PE). Monitor for signs and symptoms of thromboembolism; patients at risk may benefit from prophylactic anticoagulation or aspirin.**

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Constipation: Use with caution in patients with constipation.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Neurological disorders: Use with caution in patients with neurological disorders, including seizure disorder.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Contraceptives: Use with caution with drugs which may decrease the efficacy of hormonal contraceptives.

Special populations:

- HIV infected patients: Use with caution in patients with HIV infection; has been associated with increased viral loads.
- Pediatrics: Safety and efficacy have not been established in children <12 years of age.
- Pregnancy: **[U.S. Boxed Warning]: Thalidomide is a known teratogen; effective contraception must be used for at least 4 weeks before initiating therapy, during therapy, and for 4 weeks following discontinuation of thalidomide for women of childbearing potential.**

Pregnancy Risk FactorX

Pregnancy Considerations**[U.S. Boxed Warning]: Thalidomide is a known teratogen; effective contraception must be used for at least 4 weeks before**

initiating therapy, during therapy, and for 4 weeks following discontinuation of thalidomide for women of childbearing potential. Embryotoxic with limb defects noted from the 27th to 40th gestational day of exposure; all cases of phocomelia occur from the 27th to 42nd gestational day; fetal cardiac, gastrointestinal, bone, external ear, eye, and genitourinary tract abnormalities have also been described. Mortality at or shortly after birth has also been reported. Either abstinence or two forms of effective contraception must be used for at least 4 weeks before initiating therapy, during therapy, and for 4 weeks following discontinuation of thalidomide. A negative pregnancy test (sensitivity of at least 50 mIU/mL) within 24 hours prior to beginning therapy, weekly during the first 4 weeks, and every 4 weeks (every 2 weeks for women with irregular menstrual cycles) thereafter is required for women of childbearing potential. Males (even those vasectomized) must use a latex condom during any sexual contact with women of childbearing age. Risk to the fetus from semen of male patients is unknown. Thalidomide must be immediately discontinued and the patient referred to a reproductive toxicity specialist if pregnancy occurs during treatment. Any suspected fetal exposure to thalidomide must be reported to the FDA via the MedWatch program (1-800-FDA-1088) and to Celgene Corporation (1-888-423-5436).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the infant, a decision should be made to discontinue nursing or discontinue treatment with thalidomide.

Adverse Reactions

>10%:

Cardiovascular: Edema (57%), thrombosis/embolism (23%; grade 3: 13%, grade 4: 9%), hypotension (16%)

Central nervous system: Fatigue (79%; grade 3: 3%, grade 4: 1%), somnolence (36% to 38%), dizziness (4% to 20%), sensory neuropathy (54%), confusion (28%), anxiety/agitation (9% to 26%), fever (19% to 23%), motor neuropathy (22%), headache (13% to 19%)

Dermatologic: Rash (21% to 31%), rash/desquamation (30%; grade 3: 4%), dry skin (21%), maculopapular rash (4% to 19%), acne (3% to 11%)

Endocrine & metabolic: Hypocalcemia (72%)

Gastrointestinal: Constipation (3% to 55%), anorexia (3% to 28%), nausea (4% to 24%), weight loss (23%), weight gain (22%), diarrhea (4% to 19%), oral moniliasis (4% to 11%)

Hematologic: Leukopenia (17% to 35%), neutropenia (31%), anemia (6% to 13%), lymphadenopathy (6% to 13%)

Hepatic: AST increased (3% to 25%), bilirubin increased (14%)

Neuromuscular & skeletal: Muscle weakness (40%), tremor (4% to 26%), weakness (6% to 22%), myalgia (17%), paresthesia (6% to 16%), arthralgia (13%)

Renal: Hematuria (11%)

Respiratory: Dyspnea (42%)

Miscellaneous: Diaphoresis (13%)

1% to 10%:

Cardiovascular: Facial edema (4%), peripheral edema (3% to 8%)

Central nervous system: Insomnia (9%), nervousness (3% to 9%), malaise (8%), vertigo (8%), pain (3% to 8%)

Dermatologic: Dermatitis (fungal 4% to 9%), pruritus (3% to 8%), nail disorder (3% to 4%)

Endocrine & metabolic: Hyperlipemia (6% to 9%)

Gastrointestinal: Xerostomia (8% to 9%), flatulence (8%), tooth pain (4%)

Genitourinary: Impotence (3% to 8%)

Hepatic: LFTs abnormal (9%)

Neuromuscular & skeletal: Neuropathy (8%), back pain (4% to 6%), neck pain (4%), neck rigidity (4%)

Renal: Albuminuria (3% to 8%)

Respiratory: Pharyngitis (4% to 8%), rhinitis (4%), sinusitis (4% to 8%)

Miscellaneous: Infection (6% to 8%)

Postmarketing and/or case reports (limited to important or life-threatening): Acute renal failure, alkaline phosphatase increased, ALT increased, amenorrhea, aphthous stomatitis, arrhythmia, atrial fibrillation, bile duct obstruction, bradycardia, BUN increased, carpal tunnel, CML, creatinine clearance decreased, creatinine increased, deafness, depression, diplopia, dysesthesia, ECG abnormalities, electrolyte imbalances, enuresis, eosinophilia, epistaxis, erythema multiforme, erythema nodosum, erythroleukemia, exfoliative dermatitis, febrile neutropenia, foot drop, galactorrhea, granulocytopenia, gynecomastia, hepatomegaly, Hodgkin's disease, hypercalcemia, hyper-/hypokalemia, hypersensitivity, hypertension, hyper-/hypothyroidism, hyperuricemia, hypomagnesemia, hyponatremia, hypoproteinemia, intestinal obstruction, intestinal perforation, interstitial pneumonitis, LDH increased, lethargy, leukocytosis, lymphedema, lymphopenia, mental status changes, metrorrhagia, migraine, myxedema, nystagmus, oliguria, orthostatic hypotension, pancytopenia, paresthesia, petechiae, peripheral neuritis, photosensitivity, pleural effusion, prothrombin time changes, psychosis, pulmonary embolus, pulmonary hypertension, purpura, Raynaud's syndrome, seizure, status epilepticus, Stevens-Johnson syndrome, stomach ulcer, stupor, suicide attempt, syncope, tachycardia, thrombocytopenia, toxic epidermal necrolysis, tumor lysis syndrome

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Abatacept: Anti-TNF Agents may enhance the adverse/toxic effect of Abatacept. An increased risk of serious infection during concomitant use has been reported. *Risk D: Consider therapy modification*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Anakinra: Anti-TNF Agents may enhance the adverse/toxic effect of Anakinra. An increased risk of serious infection during concomitant use has been reported. *Risk X: Avoid combination*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Dexamethasone: May enhance the dermatologic adverse effect of Thalidomide. Dexamethasone may enhance the thrombogenic effect of Thalidomide. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Pamidronate: Thalidomide may enhance the nephrotoxic effect of Pamidronate. *Risk C: Monitor therapy*

Rilonacept: Anti-TNF Agents may enhance the adverse/toxic effect of Rilonacept. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Zoledronic Acid: Thalidomide may enhance the adverse/toxic effect of Zoledronic Acid. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase sedation).

Herb/Nutraceutical: Avoid cat's claw and echinacea (have immunostimulant properties; consider therapy modifications).

Monitoring ParametersCBC with differential, platelets; signs of neuropathy monthly for the first 3 months, then periodically during treatment; consider monitoring of sensory nerve application potential amplitudes (at baseline and every 6 months) to detect asymptomatic neuropathy. In HIV-seropositive patients: viral load after 1 and 3 months, then every 3 months. Pregnancy testing (sensitivity of at least 50 mIU/mL) is required within 24 hours prior to initiation of therapy, weekly during the first 4 weeks, then every 4 weeks in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles.

Reference RangeTherapeutic plasma thalidomide levels in graft-vs-host reactions are 5-8 mcg/mL, although it has been suggested that lower plasma levels (0.5-1.5 mcg/mL) may be therapeutic; peak serum thalidomide level after a 200 mg dose: 1.2 mcg/mL

Nursing: Physical Assessment/MonitoringPatient must be capable of complying with STEPS® program. Instruct patient on risks of pregnancy, appropriate contraceptive measures, and necessity for frequent pregnancy testing (schedule pregnancy testing at time of dispensing and give patient schedule in writing). Assess other medications patient may be taking for possible interactions. Monitor for signs of fluid retention, weight gain, and blood pressure. Monitor closely for signs of neuropathy, neutropenia, and CNS depression. Instruct patient on signs and symptoms to report, and appropriate interventions for adverse reactions.

Pregnancy risk factor X: Pregnancy test is required within 24 hours prior to beginning therapy, weekly during first month of therapy, and monthly thereafter for all women of childbearing age. Effective contraception with at least two reliable forms of contraception must be used for 1 month prior to beginning therapy, during therapy, and for 1 month following discontinuance of therapy. Women who have undergone a hysterectomy or have been postmenopausal for at least 24 consecutive months are the only exception. Do not prescribe, administer, or dispense to women of childbearing age or males who may have intercourse with women of childbearing age unless both female and male are capable of complying with contraceptive measures. Even males who have undergone vasectomy must acknowledge these risks in writing, and must use a latex condom during any sexual contact with women of childbearing age. Oral and written warnings concerning contraception and the hazards of thalidomide must be conveyed to females and males and they must acknowledge their understanding in writing. Parents or guardians must consent and sign acknowledgment for patients between 12 and 18 years of age following therapy. Breast-feeding is contraindicated.

Monitoring: Lab Tests Pregnancy testing (sensitivity of at least 50 mIU/mL) is required within 24 hours prior to initiation of therapy, weekly during the first 4 weeks, then every 4 weeks in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. In HIV-seropositive patients; monitor viral load after 1 and 3 months, then every 3 months. CBC with differential, platelets. Consider monitoring of sensory nerve application potential amplitudes at baseline and every 6 months to detect asymptomatic neuropathy.

Patient EducationYou will be given oral and written instructions about the necessity of using two methods of contraception and the necessity of keeping return visits for pregnancy testing. Do not donate blood while taking this medicine. Male patients should not donate sperm. Avoid extensive handling of capsules; capsules should remain in blister pack until ingestion. If exposed to the powder content from broken capsules or body fluids from patients receiving thalidomide, the exposed area should be washed with soap and water. Avoid alcohol. You may experience postural hypotension (use caution when rising from lying or sitting position); sleepiness; dizziness; fatigue; fever; headaches; lack of concentration (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); nausea or vomiting or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation or diarrhea; oral thrush (frequent mouth care is necessary); or sexual dysfunction (reversible). Report any of the above if persistent or severe. Report chest pain or palpitations or swelling of extremities; respiratory difficulty; back, neck, muscle pain, muscle weakness, or stiffness; numbness or pain in extremities; significant weight loss or gain; skin rash or eruptions; increased nervousness, anxiety, confusion, or insomnia; or any other symptom of adverse reactions. **Pregnancy/breast-feeding precautions:** Do not get pregnant (females) or cause pregnancy (males) during treatment. The use of two forms of contraception are required for 1 month prior to therapy, during therapy, and for 1 month following discontinuation of therapy. Pregnancy tests will be routinely conducted during therapy. Consult prescriber if you suspect you might be pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Do not breast-feed while taking this medication or for 1 month following discontinuation.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Thalomid®: 50 mg, 100 mg, 200 mg

Generic AvailableNo

ManufacturerCelgene Corp

Mechanism of ActionHas immunomodulatory and antiangiogenic characteristics. Immunologic effects may vary based on conditions; may suppress excessive tumor necrosis factor-alpha production in patients with ENL, yet may increase plasma tumor necrosis factor-alpha levels in HIV-positive patients. In multiple myeloma, thalidomide is associated with an increase in natural killer cells and increased levels of interleukin-2 and interferon gamma. Other proposed mechanisms of action include suppression of angiogenesis, prevention of free-radical-mediated DNA damage, increased cell mediated cytotoxic effects, and altered expression of cellular.

Pharmacodynamics/Kinetics

Distribution: V_d: 120 L

Protein binding: 55% to 66%

Metabolism: Nonenzymatic hydrolysis in plasma; forms multiple metabolites

Half-life elimination: 5-7 hours

Time to peak, plasma: 3-6 hours

Excretion: Urine (<1% as unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral moniliasis (HIV-seropositive patients), toothache, xerostomia (normal salivary flow resumes upon discontinuation), and aphthous stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusSedation is common; may cause dizziness, nervousness, insomnia, agitation, abnormal thinking, amnesia, anxiety, confusion, depression, euphoria, and psychosis

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; concurrent use with other psychotropics may produce additive sedation

Index TermsNSC-66847

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International Brand NamesInmunoprin (CN, CO, UY); Thado (TW); Thalix (IN, PH)

Theophylline and Guaifenesin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(thee OFF i lin & gwye FEN e sin)
U.S. Brand NamesElixophyllin-GG速; Quibron速 [DSC]
Pharmacologic CategoryTheophylline Derivative
Use: Labeled IndicationsSymptomatic treatment of bronchospasm associated with bronchial asthma, chronic bronchitis, and pulmonary emphysema
Dosing: Adults**Bronchospasm:** Oral: 16 mg/kg/day or 400 mg theophylline/day in divided doses every 6-8 hours
Dosing: ElderlyRefer to dosing in individual monographs.
Dietary ConsiderationsShould be taken with water 1 hour before or 2 hours after meals.
Allergy Considerations

- GuaiFENesin Allergy

Pregnancy Risk FactorC
LactationEnters breast milk/compatible
Metabolism/Transport EffectsTheophylline: **Substrate** of CYP1A2 (major), 2C9 (minor), 2D6 (minor), 2E1 (major), 3A4 (major); **Inhibits** CYP1A2 (weak)
Drug Interactions

Adenosine: Theophylline Derivatives may diminish the therapeutic effect of Adenosine. *Risk D: Consider therapy modification*

Allopurinol: May increase the serum concentration of Theophylline Derivatives. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Benzodiazepines: Theophylline Derivatives may diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2E1 Inhibitors (Moderate): May decrease the metabolism of CYP2E1 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May increase the serum concentration of Theophylline Derivatives. *Risk C: Monitor therapy*

Fluvoxamine: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Interferons: May decrease the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

Lithium: Theophylline Derivatives may increase the excretion of Lithium. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Theophylline Derivatives. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin; Telithromycin. *Risk D: Consider therapy modification*

Mexiletine: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

Moricizine: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Pentoxifylline: May increase the serum concentration of Theophylline Derivatives. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Theophylline Derivatives. Theophylline Derivatives may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the serum concentration of Theophylline Derivatives. **Exceptions:** Amprenavir; Fosamprenavir. *Risk C: Monitor therapy*

Quinolone Antibiotics: May decrease the metabolism of Theophylline Derivatives. Ciprofloxacin and enoxacin are of greatest concern. Theophylline/quinolone therapy might augment the seizure-producing potential of each of the individual agents. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Sparfloxacin; Trovafloxacin. *Risk D: Consider therapy modification*

Regadenoson: Theophylline may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tacrine: May decrease the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Thiabendazole: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

Thyroid Products: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Ticlopidine: May decrease the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Zafirlukast: Theophylline Derivatives may decrease the serum concentration of Zafirlukast. *Risk C: Monitor therapy*

Zileuton: May increase the serum concentration of Theophylline. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringSee individual agents.

Patient EducationSee individual agents. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule:

Quibron速: Theophylline 150 mg and guaifenesin 90 mg [DSC]

Liquid:

Elixophyllin-GG速: Theophylline 100 mg and guaifenesin 100 mg per 15 mL (240 mL, 480 mL) [alcohol free, dye free, sugar free; cherry-berry flavor]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Quibron)

90-150 mg (30): $21.83

Solution (Elixophyllin GG)

100-100 mg/15 mL (480): $114.00

Pharmacodynamics/KineticsSee individual agents.

Related Information

- GuaiFENesin
- Theophylline

Dental Health: Effects on Dental TreatmentPrescribe erythromycin products with caution to patients taking theophylline products. Erythromycin will delay the normal metabolic inactivation of theophyllines leading to increased blood levels; this has resulted in nausea, vomiting, and CNS restlessness.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness, agitation, restlessness, insomnia, or dizziness

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may decrease serum levels while disulfiram, propranolol, and fluvoxamine may increase theophylline levels

Index TermsGuaifenesin and Theophylline

International Brand NamesBronchil (TH); Broncophylline (IL); Polyphed (TH)

Theophylline

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English

English

Jump To Field (Select Field Name)

Pronunciation(thee OFF i lin)

U.S. Brand NamesElixophyllin®; Theo-24®; TheoCap™; Theochron™; Uniphyl®

Canadian Brand NamesApo-Theo LA®; Novo-Theophyl SR; PMS-Theophylline; Pulmophylline; ratio-Theo-Bronc; Theochron® SR; Uniphyl® SRT

Pharmacologic CategoryTheophylline Derivative

Use: Labeled IndicationsTreatment of symptoms and reversible airway obstruction due to chronic asthma, or other chronic lung diseases; apnea of prematurity

Note: The National Heart, Lung, and Blood Institute Guidelines (2007) do not recommend oral theophylline as a long-term control medication for asthma in children ≤4years of age; use may be considered as an alternative (but not preferred) agent in older children and adults. The guidelines do not recommend theophylline I.V. for the treatment of exacerbations of asthma.

Dosing: Adults**Note:** Doses should be individualized based on peak serum concentrations and should be based on ideal body weight.
Acute symptoms: Loading dose: Oral, I.V.:

If no theophylline received within the previous 24 hours: 4.6 mg/kg loading dose (~5.8 mg/kg hydrous aminophylline) I.V. or 5 mg/kg orally. Loading dose intended to achieve a serum level of approximately 10 mcg/mL; loading doses should be given intravenously (preferred) or with a rapidly absorbed oral product (not an extended-release product). **Note:** On the average, for every 1 mg/kg theophylline given, blood levels will rise 2 mcg/mL.

If theophylline has been administered in the previous 24 hours: A loading dose is not recommended without obtaining a serum theophylline concentration. The loading dose should be calculated as follows:

Dose = (desired serum theophylline concentration - measured serum theophylline concentration) (V_d)

Acute symptoms: Maintenance dose: I.V.: **Note:** To achieve a target concentration of 10 mcg/mL unless otherwise noted. Lower initial doses may be required in patients with reduced theophylline clearance. Dosage should be adjusted according to serum level measurements during the first 12- to 24-hour period.

Adults 16-60 years (otherwise healthy, nonsmokers): 0.4 mg/kg/hour; maximum 900 mg/day unless serum levels indicate need for larger dose

Adults >60 years: 0.3 mg/kg/hour; maximum 400 mg/day unless serum levels indicate need for larger dose

Cardiac decompensation, cor pulmonale, hepatic dysfunction, sepsis with multiorgan failure, shock: 0.2 mg/kg/hour; maximum 400 mg/day unless serum levels indicate need for larger dose

Treatment of chronic conditions: Oral:

Adults 16-60 years **without** risk factors for impaired theophylline clearance: 300 mg/day in divided doses every 6-8 hours for 3 days, then increase to 400 mg/day in divided doses every 6-8 hours for 3 days; maintenance dose: 600 mg/day in divided doses every 6-8 hours

Increase dose only if tolerated. Consider lowering dose or using a slower titration if caffeine-like adverse events occur. Smaller doses given more frequently may be used in patients with a more rapid metabolism to prevent breakthrough symptoms which could occur due to low trough concentration prior to the next dose. Reliably absorbed slow release formulations can be used to decrease serum fluctuations and permit longer dosing intervals.

Dose adjustment in patients **with** risk factors for impaired theophylline clearance and patients in whom monitoring serum theophylline levels is not feasible: Do not exceed a dose of 400 mg/day

Dosage adjustment after serum theophylline measurement:

Within normal limits: 10-19.9 mcg/mL: Maintain dosage if tolerated. Recheck serum theophylline concentration at 24-hour intervals (for acute I.V. dosing) or at 6- to 12-month intervals (for oral dosing). Finer adjustments in dosage may be needed for some patients. If levels ≥15 mcg/mL, consider 10% dose reduction to improve safety margin.

Too high:

20-24.9 mcg/mL: Decrease doses by about 25%. Recheck serum theophylline concentrations (see "Note").

25-30 mcg/mL: Skip next dose (oral) or stop infusion for 12 hours (children) or 24 hours (adults) and decrease subsequent doses by about 25%. Recheck serum theophylline concentrations (see "Note").

>30 mcg/mL: Stop dosing and treat overdose; if resumed, decrease subsequent doses by 50%. Recheck serum theophylline concentrations (see "Note").

Too low: <9.9 mcg/mL: If tolerated, but symptoms remain, increase dose by about 25%. Recheck serum theophylline concentrations (see "Note").

Note: Recheck serum theophylline levels after 3 days when using oral dosing, or after 12 hours (children) or 24 hours (adults) when dosing intravenously. Patients maintained with oral therapy may be reassessed at 6- to 12-month intervals.

Dosing: Elderly

Acute symptoms: Adults >60 years:

Loading dose: Oral, I.V.: Refer to adult dosing.

Maintenance dose: I.V.: 0.3 mg/kg/hour; maximum 400 mg/day unless serum levels indicate need for larger dose

Chronic conditions: Oral: Adults >60 years: Do not exceed a dose of 400 mg/day

Cardiac decompensation, cor pulmonale, hepatic dysfunction, sepsis with multiorgan failure, shock: Refer to adult dosing.

Dosing: Pediatric**Note:** Doses should be individualized based on peak serum concentrations and should be based on ideal body weight.
Acute symptoms: Loading dose: Oral, I.V.:

If no theophylline received within the previous 24 hours: 4.6 mg/kg loading dose (~5.8 mg/kg hydrous aminophylline) I.V. or 5 mg/kg orally. Loading dose intended to achieve a serum level of approximately 10 mcg/mL; loading doses should be given intravenously (preferred) or with a rapidly absorbed oral product (not an extended-release product). **Note:** On the average, for every 1 mg/kg theophylline given, blood levels will rise 2 mcg/mL.

If theophylline has been administered in the previous 24 hours: A loading dose is not recommended without obtaining a serum theophylline concentration. The loading dose should be calculated as follows:

Dose = (desired serum theophylline concentration - measured serum theophylline concentration) (V_d)

Acute symptoms: Maintenance dose: I.V.: **Note:** To achieve a target concentration of 10 mcg/mL unless otherwise noted. Lower initial doses may be required in patients with reduced theophylline clearance. Dosage should be adjusted according to serum level measurements during the first 12- to 24-hour period.

Neonates ≤24 days: 1 mg/kg every 12 hours to achieve a target concentration of 7.5 mcg/mL for apnea of prematurity

Neonates >24 days: 1.5 mg/kg every 12 hours to achieve a target concentration of 7.5 mcg/mL for apnea of prematurity

Infants 6-52 weeks: mg/kg/hour = (0.008) (age in weeks) + 0.21

Children 1-9 years: 0.8 mg/kg/hour

Children 9-12 years: 0.7 mg/kg/hour

Adolescents >16 years: Refer to adult dosing.

Adolescents 12-16 years (cigarette or marijuana smokers): 0.7 mg/kg/hour

Adolescents 12-16 years (nonsmokers): 0.5 mg/kg/hour; maximum 900 mg/day unless serum levels indicate need for larger dose

Dosage adjustment for cardiac decompensation, cor pulmonale, hepatic dysfunction, sepsis with multiorgan failure, shock: 0.2 mg/kg/hour; maximum 400 mg/day unless serum levels indicate need for larger dose

Treatment of chronic conditions: Oral:

Infants <1 year: **Note:** Doses should be adjusted to maintain the peak steady state serum concentrations. The time to reach steady state will vary based on age and the presence of risk factors which may affect theophylline clearance. Theophylline serum levels obtained prior to reaching steady state should not be used to increase the maintenance dose even if the serum concentration is <10 mcg/mL. Peak steady state theophylline serum concentrations should be 5-10 mcg/mL in neonates and 10-15 mcg/mL in older infants.

Premature Neonates <24 days postnatal age: 1 mg/kg/dose every 12 hours

Premature Neonates ≥24 days postnatal age: 1.5 mg/kg/dose every 12 hours

Full-term Infants and Infants <26 weeks of age: Total daily dose (mg)= [(0.2 x age in weeks) +5] x (weight in kg); divide dose into 3 equal amounts and administer at 8-hour intervals

Full-term Infants and Infants ≥26 weeks and <52 weeks: Total daily dose (mg) = [(0.2 x age in weeks) +5] x (weight in kg); divide dose into 4 equal amounts and administer at 6-hour intervals

Children 1-15 years and <45 kg **without** risk factors for impaired theophylline clearance: 12-14 mg/kg/day in divided doses, every 4-6 hours for 3 days (maximum dose: 300 mg/day), then increase to 16 mg/kg/day in divided doses every 4-6 hours for 3 days (maximum dose: 400 mg/day); maintenance dose: 20 mg/kg/day in divided doses every 4-6 hours (maximum dose: 600 mg/day)

Increase dose only if tolerated. Consider lowering dose or using a slower titration if caffeine-like adverse events occur. Smaller doses given more frequently may be used in patients with a more rapid metabolism to prevent breakthrough symptoms which could occur due to low trough concentration prior to the next dose. Reliably absorbed slow release formulations can be used to decrease serum fluctuations and permit longer dosing intervals.

Children ≥16 years or >45 kg: Refer to adult dosing.

Dose adjustment in patients **with** risk factors for impaired theophylline clearance and patients in whom monitoring serum theophylline levels is not feasible:

Children 1-15 years: Do not exceed a dose of 16 mg/kg/day or 400 mg/day

Children ≥16: Do not exceed a dose of 400 mg/day

Dosage adjustment after serum theophylline measurement: Refer to adult dosing.

Calculations

- Ideal Body Weight: Adults
- Ideal Body Weight: Pediatrics

Administration: I.V. DetailpH: 4.3

Administration: OralLong-acting preparations should be taken with a full glass of water, swallowed whole, or cut in half if scored. Do **not** crush. Extended release capsule forms may be opened and the contents sprinkled on soft foods; do **not** chew beads.

Dietary ConsiderationsShould be taken with water 1 hour before or 2 hours after meals. Premixed injection may contain corn-derived dextrose and its use is contraindicated in patients with allergy to corn-related products.

StorageElixir, tablet, premixed infusion: Store at controlled room temperature of 25°C (77°F).

CompatibilityStable in D_5W.

Y-site administration: Compatible: Acyclovir, ampicillin, ampicillin/sulbactam, aztreonam, bivalirudin, cefazolin, cefotetan, ceftriaxone, cimetidine, cisatracurium, clindamycin, clonidine, dexamethasone sodium phosphate, dexmedetomidine, diltiazem, dobutamine, dopamine, doxycycline, erythromycin lactobionate, famotidine, fenoldopam, fluconazole, gentamicin, haloperidol, heparin, hydrocortisone sodium succinate, hetastarch in lactated electrolyte injection, lidocaine, linezolid, methyldopate, methylprednisolone sodium succinate, metronidazole, micafungin, midazolam, milrinone, nafcillin, nitroglycerin, oxaliplatin, penicillin G potassium, piperacillin, potassium chloride, ranitidine, remifentanil, sodium nitroprusside, ticarcillin, ticarcillin/clavulanate potassium, tigecycline, tobramycin, vancomycin. **Incompatible:** Cefepime, hetastarch in NS, phenytoin.

Compatibility when admixed: Compatible: Cefepime, chlorpromazine, fluconazole, furosemide, hydrocortisone hemisuccinate, lidocaine, methylprednisolone sodium succinate, papaverine, verapamil. **Incompatible:** Ascorbic acid injection, ceftriaxone.

ContraindicationsHypersensitivity to theophylline or any component of the formulation; premixed injection may contain corn-derived dextrose and its use is contraindicated in patients with allergy to corn-related products

Warnings/Precautions

Concerns related to adverse effects:

- Theophylline toxicity: If a patient develops signs and symptoms of theophylline toxicity (eg, persistent, repetitive vomiting), a serum level should be measured and subsequent doses held. Theophylline clearance may be decreased in patients with acute pulmonary edema, congestive heart failure, cor pulmonale, fever, hepatic disease, acute hepatitis, cirrhosis, hypothyroidism, sepsis with multiorgan failure, and shock; clearance may also be decreased in neonates, infants <3 months of age with decreased renal function, children <1 year of age, the elderly >60 years of age, and patients following cessation of smoking.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with tachyarrhythmias (eg, sinus tachycardia, atrial fibrillation) since use may exacerbate these arrhythmias.

- Hyperthyroidism: Use with caution in patients with hyperthyroidism; use may exacerbate this condition.

- Peptic ulcer disease: Use with caution in patient with peptic ulcer disease; use may exacerbate this condition.

- Seizure disorder: Use with caution in patients with a history of seizure disorder; use may exacerbate this condition.

Other warnings/precautions:

- Dosage adjustments: Due to potential saturation of theophylline clearance at serum levels within (or in some patients less than) the therapeutic range, dosage adjustment should be made in small increments (maximum: 25% reduction).

- Monitoring: Due to wide interpatient variability, theophylline serum level measurements must be used to optimize therapy and prevent serious toxicity.

Geriatric ConsiderationsAlthough there is a great intersubject variability for half-lives of methylxanthines (2-10 hours), elderly as a group have slower hepatic clearance. Therefore, use lower initial doses and monitor closely for response and adverse reactions. Additionally, elderly are at greater risk for toxicity due to concomitant disease (eg, CHF, arrhythmias), and drug use (eg, cimetidine, ciprofloxacin).

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events were observed in animal reproduction studies. Theophylline crosses the placenta; adverse effects may be seen in the newborn. Use is generally safe when used at the recommended doses (serum concentrations 5-12 mcg/mL) however maternal adverse events may be increased and efficacy may be decreased in pregnant women. Theophylline metabolism may change during pregnancy; the half-life is similar to that observed in otherwise healthy, nonsmoking adults with asthma during the first and second trimesters (~8.7 hours), but may increase to 13 hours (range 8-18 hours) during the third trimester. The volume of distribution is also increased during the third trimester. Monitor serum levels. The recommendations for the use of theophylline in pregnant women with asthma are similar to those used in nonpregnant adults (National Heart, Lung, and Blood Institute Guidelines, 2004).

LactationEnters breast milk/compatible (AAP rates “compatible”)

Breast-Feeding ConsiderationsThe concentration of theophylline in breast milk is similar to the maternal serum concentration. Irritability may be observed in the nursing infant. Serious adverse events in the infant are unlikely unless toxic serum levels are present in the mother.

Adverse ReactionsFrequency not defined. Adverse events observed at therapeutic serum levels:

Cardiovascular: Flutter, tachycardia

Central nervous system: Headache, hyperactivity (children), insomnia, restlessness, seizures

Endocrine & metabolic: Hypercalcemia (with concomitant hyperthyroid disease)

Gastrointestinal: Nausea, reflux or ulcer aggravation, vomiting

Genitourinary: Difficulty urinating (elderly males with prostatism)

Neuromuscular & skeletal: Tremor

Renal: Diuresis (transient)

Metabolism/Transport Effects **Substrate** of CYP1A2 (major), 2C9 (minor), 2D6 (minor), 2E1 (major), 3A4 (major); **Inhibits** CYP1A2 (weak)
Drug Interactions

Adenosine: Theophylline Derivatives may diminish the therapeutic effect of Adenosine. *Risk D: Consider therapy modification*

Allopurinol: May increase the serum concentration of Theophylline Derivatives. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Benzodiazepines: Theophylline Derivatives may diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Beta-Blockers (Beta1 Selective): May diminish the bronchodilatory effect of Theophylline Derivatives. This is true at higher beta-blockers doses where cardioselectivity is lost. *Risk C: Monitor therapy*

Beta-Blockers (Nonselective): May diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

CYP2E1 Inhibitors (Moderate): May decrease the metabolism of CYP2E1 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May increase the serum concentration of Theophylline Derivatives. *Risk C: Monitor therapy*

Fluvoxamine: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Interferons: May decrease the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Isoniazid: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

Lithium: Theophylline Derivatives may increase the excretion of Lithium. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Theophylline Derivatives. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin; Telithromycin. *Risk D: Consider therapy modification*

Mexiletine: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

Moricizine: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Pentoxifylline: May increase the serum concentration of Theophylline Derivatives. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Theophylline Derivatives. Theophylline Derivatives may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the serum concentration of Theophylline Derivatives. **Exceptions:** Amprenavir; Fosamprenavir. *Risk C: Monitor therapy*

Quinolone Antibiotics: May decrease the metabolism of Theophylline Derivatives. Ciprofloxacin and enoxacin are of greatest concern. Theophylline/quinolone therapy might augment the seizure-producing potential of each of the individual agents. **Exceptions:** Gatifloxacin; Gemifloxacin; Levofloxacin; Lomefloxacin; Moxifloxacin; Nalidixic Acid; Sparfloxacin; Trovafloxacin. *Risk D: Consider therapy modification*

Regadenoson: Theophylline may diminish the vasodilatory effect of Regadenoson. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tacrine: May decrease the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Thiabendazole: May decrease the metabolism of Theophylline Derivatives. *Risk D: Consider therapy modification*

Thyroid Products: May increase the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Ticlopidine: May decrease the metabolism of Theophylline Derivatives. *Risk C: Monitor therapy*

Zafirlukast: Theophylline Derivatives may decrease the serum concentration of Zafirlukast. *Risk C: Monitor therapy*

Zileuton: May increase the serum concentration of Theophylline. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Food does not appreciably affect the absorption of liquid, fast-release products, and most sustained release products; however, food may induce a sudden release (dose-dumping) of once-daily sustained release products resulting in an increase in serum drug levels and potential toxicity. Avoid excessive amounts of caffeine. Avoid extremes of dietary protein and carbohydrate intake. Changes in diet may affect the elimination of theophylline; charbroiled foods may increase elimination, reducing half-life by 50%.

Test InteractionsPlasma glucose, uric acid, free fatty acids, total cholesterol, HDL, HDL/LDL ratio, and urinary free cortisol excretion may be increased by theophylline. Theophylline may decrease triiodothyronine.

Monitoring ParametersMonitor heart rate, CNS effects (insomnia, irritability); respiratory rate (COPD patients often have resting controlled respiratory rates in low 20s); arterial or capillary blood gases (if applicable)

Theophylline levels: Serum theophylline levels should be monitored prior to making dose increases; in the presence of signs or symptoms of toxicity; or when a new illness, worsening of a present illness, or medication changes occur that may change theophylline clearance

I.V. loading dose: Measure serum concentrations 30 minutes after the end of an I.V. loading dose

I.V. infusion: Measure serum concentrations one half-life after starting a continuous infusion, then every 12-24 hours

Reference RangeTherapeutic levels:

Asthma: 5-15 mcg/mL (peak level)

Toxic concentration: >20 mcg/mL

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy (respiratory rate, lung sounds, characteristics of cough and sputum) and adverse reactions at beginning of therapy and periodically with long-term use. For inpatient care, monitor vital signs and lung sounds prior to and periodically during therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsArterial or capillary blood gases (if applicable)

Theophylline levels: Serum theophylline levels should be monitored prior to making dose increases; in the presence of signs or symptoms of toxicity; or when a new illness, worsening of a present illness, or medication changes occur that may change theophylline clearance

I.V. loading dose: Measure serum concentrations 30 minutes after the end of an I.V. loading dose

I.V. infusion: Measure serum concentrations one half-life after starting a continuous infusion, then every 12-24 hours

Patient EducationTake exactly as directed; do not exceed recommended dosage. Avoid smoking (smoking may interfere with drug absorption as well as exacerbate condition for which medication is prescribed). If you are smoking when dosage is prescribed; inform prescriber if you stop smoking (dosage may need to be adjusted to prevent toxicity). Preferable to take on empty stomach, 1 hour before or 2 hours after meals, with a full glass of water. Do not chew of crush sustained release forms; capsules may be opened and contents sprinkled on soft food (do not chew beads). Avoid dietary stimulants (eg, caffeine, tea, colas, or chocolate; may increase adverse side effects). Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience nausea, vomiting, or lose of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report acute insomnia or restlessness, chest pain or rapid heartbeat, emotional lability or agitation, muscle tremors or cramping, acute headache, abdominal pain and cramping, blackened stool, or worsening of respiratory condition. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release:

TheoCap™: 125 mg, 200 mg [12 hour]

Theo-24®: 100 mg, 200 mg, 300 mg, 400 mg [24 hours]

Elixir:

Elixophyllin®: 80 mg/15 mL (473 mL) [contains alcohol 20%; mixed fruit flavor]

Infusion [premixed in D_5W]: 200 mg (50 mL, 100 mL); 400 mg (250 mL, 500 mL); 800 mg (250 mL, 500 mL, 1000 mL)

Tablet, controlled release:

Uniphyl®: 400 mg, 600 mg [24 hours]

Tablet, extended release: 100 mg, 200 mg, 300 mg, 400 mg, 450 mg, 600 mg

Theochron™: 100 mg, 200 mg, 300 mg, 450 mg [12-24 hours]

Generic AvailableYes: Extended release capsule and tablet, infusion

Pricing: U.S. (www.drugstore.com)

Capsule, 12-hour (Theophylline CR)

125 mg (60): $43.57

200 mg (60): $29.99

300 mg (60): $49.99

Capsule, 24-hour (Theo-24)

100 mg (60): $34.97

200 mg (60): $55.99

300 mg (60): $69.95

400 mg (60): $89.99

Elixir (Elixophyllin)

80 mg/15 mL (480): $97.01

Tablet, 12-hour (Theophylline CR)

100 mg (60): $17.99

200 mg (60): $23.74

300 mg (60): $18.99

450 mg (60): $41.99

Tablet, 24-hour (Uniphyl)

400 mg (60): $80.99

600 mg (60): $114.80

Mechanism of ActionCauses bronchodilatation, diuresis, CNS and cardiac stimulation, and gastric acid secretion by blocking phosphodiesterase which increases tissue concentrations of cyclic adenine monophosphate (cAMP) which in turn promotes catecholamine stimulation of lipolysis, glycogenolysis, and gluconeogenesis and induces release of epinephrine from adrenal medulla cells

Pharmacodynamics/Kinetics

Absorption: Oral: Dosage form dependent

Distribution: 0.45 L/kg based on ideal body weight; distributes poorly into body fat; V_d may increase in premature neonates, patients with hepatic cirrhosis, acidemia (uncorrected), the elderly

Metabolism: Children >1 year and Adults: Hepatic; involves CYP1A2, 2E1 and 3A4; forms active metabolites (caffeine and 3-methylxanthine)

Protein binding: 40%, primarily to albumin

Half-life elimination: Highly variable and dependent upon age, liver function, cardiac function, lung disease, and smoking history

Premature infants, postnatal age 3-15 days: 30 hours (range: 17-43 hours)

Premature infants, postnatal age 25-57 days: 20 hours (range: 9.4-30.6 hours)

Children 6-17 years: 3.7 hours (range: 1.5-5.9 hours)

Adults 16-60 years with asthma, nonsmoking, otherwise healthy: 8.7 hours (range: 6.1-12.8 hours)

Time to peak, serum:

Oral: Liquid: 1 hour; Tablet, enteric-coated: 5 hours; Tablet, uncoated: 2 hours

I.V.: Within 30 minutes

Excretion: Urine

Neonates: 50% as unchanged theophylline

Children >3 months and Adults: ~10% as unchanged theophylline

Related Information

- Asthma

Dental Health: Effects on Dental TreatmentPrescribe erythromycin products with caution to patients taking theophylline products. Erythromycin will delay the normal metabolic inactivation of theophyllines leading to increased blood levels; this has resulted in nausea, vomiting, and CNS restlessness. Azithromycin does not cause these effects in combination with theophylline products.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause nervousness and restlessness; may rarely cause insomnia and irritability

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may decrease serum levels while disulfiram, propranolol, and fluvoxamine may increase theophylline levels

Cardiovascular ConsiderationsTheophylline results in significant tachycardia and, at higher doses, may impair ventricular rate control in patients with atrial fibrillation. This is particularly a concern since patients with underlying chronic obstructive lung disease often have coexisting atrial fibrillation. A theophylline derivative can be used to treat patients who have adverse hemodynamic responses to adenosine or dipyridamole during cardiovascular stress testing. Theophylline has been used for neurocardiogenic (vasovagal) syncope.

Index TermsTheophylline Anhydrous

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International Brand NamesAerobin (DE); Aerodyne Retard (AT); Afonilum (PL); Afonilum SR (PL); Asmasalon (PH); Austyn (KP); Bronchoretard (DE); Bronoday (TH); Bronsolvan (ID); Ditenaten (DE); Duralyn-CR (TH); Duraphyl (HN); Egifilin (HU); Elixine (CN); Elixofilina (PE); Etipramid (CL); Euphyllin (PL); Euphyllin Retard (ID, PL); Euphyllin Retard Mite (ID); Euphylong (AE, BH, CY, EG, HK, HU, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Euphylong Retardkaps (DE); Euphylong SR (PH); Lasma (AE, BH, CY, EG, GB, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Meridian AP (UY); Nefoben (AR); Neulin-SR (NZ, TW); Nosma (TW); Nuelin (AU, BB, BM, BS, BZ, DK, FI, GY, JM, NO, NZ, PH, PR, SG, SR, TT, VE); Nuelin SA (AE, BF, BH, BJ, CI, CR, CY, DO, EG, ET, GH, GM, GN, GT, HN, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NI, OM, PA, QA, SA, SC, SD, SL, SN, SV, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Nuelin SR (AE, AU, BH, CY, EG, HK, IL, IQ, IR, JO, KW, LB, LY, MY, OM, QA, SA, SG, SY, TH, YE); Pediaphyllin PL (LU); Pharmafil (MX); Pharphylline (NL); Phylobid (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Pulmidur (AT); Quibron T SR (ID); Quibron-T/SR (ID); Retafyllin (EE, HU); Slo-Phyllin (AE, BH, CY, EG, GB, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Slo-Theo (HK); Solosin (DE); Somofillina (IT); Talofilina (BR); Teoclear (KP); Teoclear LA (AR); Teofilina Retard (CO, EC); Teolin (HR); Teolong (BR, PY); Teosona (AR); Teotard (EE, HR, PL); Theo PA (IN); Theo-2 (BE, LU); Theo-24 (IT); Theo-Bros (GR); Theo-Caps (PL); Theo-Dur (AR, CZ, DK, FI, GR, IT, JP, LU, MY, NO, PK, PL, SE); Theoclear (KP); Theolair (CH, ES, IT, LU, NL); Theolair S (PE); Theolan (KP, TW); Theolin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Theolong (JP); Theophtard (HU); Theophyllin-ratiopharm (LU); Theophylline Bruneau (LU); Theophyllinum (PL); Theophyllinum prolongatum (PL); Theoplus (BG, PL); Theoplus Retard (AT, GR); Theori (TH); Theospirex (HU); Theospirex Retard (AT); Theospirex retard (PL); Theostat (LU); Theostat LP (FR); Theotard (IL); Theovent (PL); Theovent LA (HK); Tyrex (PE); Uni-Dur (HR, PL); Unicontin (PT); Unicontin-400 Continus (IN); Unifyl Retard (CH); Uniphyl CR (KP); Uniphyllin Continus (BF, BJ, CI, ET, GB, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Xanthium (LU)

Thiabendazole

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(thye a BEN da zole)

U.S. Brand NamesMintezol®

Pharmacologic CategoryAnthelmintic

Use: Labeled IndicationsTreatment of strongyloidiasis, cutaneous larva migrans, visceral larva migrans, dracunculiasis, trichinosis, and mixed helminthic infections

Use: Unlabeled/InvestigationalCutaneous larva migrans (topical application)

Dosing: Adults**Note:** Purgation is not required prior to use; drinking of fruit juice aids in expulsion of worms by removing the mucous to which the intestinal tapeworms attach themselves.

Parasitic infections: Oral: 50 mg/kg/day divided every 12 hours; maximum: 3 g/day

Treatment duration:

Strongyloidiasis: For 2 consecutive days

Cutaneous larva migrans: For 2 consecutive days; if active lesions are still present 2 days after completion, a second course of treatment is recommended.

Visceral larva migrans: For 7 consecutive days

Trichinosis: For 2-4 consecutive days; optimal dosage not established.

Dracunculosis: 50-75 mg/kg/day divided every 12 hours for 3 days

Cutaneous larva migrans: Topical (unlabeled): Apply directly to larval tracks 2-3 times/day for up to 2 weeks; application frequencies may range from 2-6 times/day. **Note:** Not available as a topical formulation; oral suspension (10% to 15%) has been used topically, as well as a number of extemporaneous formulations.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricParasitic infections: Children: Refer to adult dosing.

Dosing: Renal ImpairmentUse with caution.

Dosing: Hepatic ImpairmentUse with caution.

Extemporaneously PreparedTopical application of thiabendazole has been recommended for the treatment of cutaneous larva migrans (*Redbook*, 2003; *Med Letter*, 2002). In some cases, the commercially-available 10% oral suspension has been used for topical application. Alternatively, a number of extemporaneous preparations have used crushed tablets to prepare distinct formulations. These include a 10% ointment (in white petrolatum), a 15% topical lotion (suspended with compound tragacanth powder 250 mg/40 mL), a 15% cream (in either hydrophilic or fat-based creams), and topical solutions (2% to 4% in DMSO). The stability of these formulations has not been established, and there are no comparative studies evaluating different formulations. All preparations have been applied between 2-6 times daily for up to 2 weeks.

ContraindicationsHypersensitivity to thiabendazole or any component of the formulation; not for use as prophylactic treatment of enterobiasis (pinworm) infestation

Allergy Considerations

- Benzimidazole Anthelmintics Allergy

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypersensitivity reactions: Erythema multiforme and Stevens-Johnson syndrome have been reported (including fatalities); discontinue at first sign of reaction.
- Ocular effects: Ophthalmic changes may occur and persist >1 year.

Disease-related concerns:

- Anemia: Use with caution in patients with anemia.
- *Ascaris* infections: Not suitable treatment for mixed infections with *Ascaris*.
- Dehydration: Use with caution in patients with dehydration.
- Hepatic impairment: Use with caution in patients with hepatic impairment; jaundice, cholestasis and parenchymal liver damage have occurred.

- Malnutrition: Use with caution in patients with malnutrition.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Pediatrics: Safety and efficacy are limited in children <14 kg (30 lb).

Pregnancy Risk FactorC

Pregnancy ConsiderationsCleft palate and skeletal defects were observed in some animal studies. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Central nervous system: Chills, delirium, dizziness, drowsiness, hallucinations, headache, seizure

Dermatologic: Angioedema, pruritus, rash, Stevens-Johnson syndrome

Endocrine & metabolic: Hyperglycemia

Gastrointestinal: Abdominal pain, anorexia, diarrhea, drying of mucous membranes, nausea, vomiting

Genitourinary: Crystalluria, enuresis, hematuria, malodor of urine

Hematologic: Leukopenia

Hepatic: Cholestasis, hepatic failure, hepatotoxicity, jaundice

Neuromuscular & skeletal: Incoordination, numbness

Ocular: Abnormal sensation in eyes, blurred vision, dry eyes, Sicca syndrome, vision decreased, xanthopsia

Otic: Tinnitus

Renal: Nephrotoxicity

Miscellaneous: Anaphylaxis, hypersensitivity reactions, lymphadenopathy

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor); **Inhibits** CYP1A2 (strong)

Drug Interactions

Aminoquinolines (Antimalarial): May decrease the serum concentration of Anthelmintics. *Risk C: Monitor therapy*

Bendamustine: CYP1A2 Inhibitors (Strong) may increase the serum concentration of Bendamustine. Concentrations of the active metabolites of bendamustine may be decreased. *Risk C: Monitor therapy*

CYP1A2 Substrates: CYP1A2 Inhibitors (Strong) may decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Theophylline Derivatives: Thiabendazole may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk D: Consider therapy modification*

Monitoring ParametersPeriodic renal and hepatic function tests

Nursing: Physical Assessment/MonitoringWorm infestations are easily transmitted, all close family members should be treated. Instruct patient/caregiver on appropriate use, transmission prevention, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationTake exactly as directed for full course of medication. Tablets may be chewed, swallowed whole, or crushed and mixed with food. Increase dietary intake of fruit juices. All family members and close friends should also be treated. To reduce possibility of reinfection, wash hands and scrub nails carefully with soap and hot water before handling food, before eating, and before and after toileting. Keep hands out of mouth. Disinfect toilet daily and launder bed linens, undergarments, and nightclothes daily with hot water and soap. Do not go barefoot and do not sit directly on grass or ground. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or abdominal pain, nausea, dry mouth, or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report skin rash or itching, unresolved diarrhea or vomiting, CNS changes (hallucinations, delirium, acute headache), change in color of urine or stool, or easy bruising or unusual bleeding. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Suspension, oral: 500 mg/5 mL (120 mL) [DSC]

Tablet, chewable: 500 mg [orange flavor]

Generic AvailableNo

Mechanism of ActionInhibits helminth-specific mitochondrial fumarate reductase

Pharmacodynamics/Kinetics

Absorption: Rapid and well absorbed

Metabolism: Rapidly hepatic; metabolized to 5-hydroxy form

Half-life elimination: 1.2 hours

Time to peak, plasma: Oral suspension: Within 1-2 hours

Excretion: Urine (90%) and feces (5%) primarily as conjugated metabolites

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Drying of mucous membranes.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, hallucinations, or delirium
Mental Health: Effects on Psychiatric TreatmentMay rarely cause leukopenia; use caution with clozapine and carbamazepine
Index TermsTiabendazole
References

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“Drugs for Parasitic Infections,” *Med Lett Drugs Ther*, 2002. Available at: http://www.medicalletter.com/freedocs/parasitic.pdf. Accessed September 4, 2003. [PubMed 8544792]

Walden J, “Parasitic Diseases. Other Roundworms. *Trichuris*, Hookworm, and *Strongyloides*,” *Prim Care*, 1991, 18(1):53-74. [PubMed 2011642]

Zygmunt DJ, “*Strongyloides stercoralis*,” *Infect Control Hosp Epidemiol*, 1990, 11(9):495-7.[PubMed 2230053]

International Brand NamesFoldan (AR, BR); Folderm (BR); Lombristop (ES); Mintezol (AU, BF, BJ, CI, CZ, ET, FR, GB, GH, GM, GN, HU, IE, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Tiabenda (ES); Tiabendazole (CY); Tiabendazolo (IT); Triasox (ES)

Thiamine

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English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Thiamine may be confused with Tenormin®, Thorazine®

International issues:

Doxal® [Brazil] may be confused with Doxil® which is a brand name for doxorubicin in the U.S.

Doxal® [Brazil]: Brand name for doxycycline in Austria; brand name for pyridoxine in Brazil; brand name for doxepin in Finland

Pronunciation(THYE a min)

Canadian Brand NamesBetaxin®

Pharmacologic CategoryVitamin, Water Soluble

Use: Labeled IndicationsTreatment of thiamine deficiency including beriberi, Wernicke's encephalopathy, Korsakoff's syndrome, neuritis associated with pregnancy, or in alcoholic patients; dietary supplement

Dosing: Adults

Recommended daily intake:

≥19 years: Female: 1.1 mg; Male: 1.2 mg

Pregnancy, lactation: 1.4 mg

Parenteral nutrition supplementation: 6 mg/day; may be increased to 25-50 mg/day with history of alcohol abuse

Thiamine deficiency (beriberi): 5-30 mg/dose I.M. or I.V. 3 times/day (if critically ill); then orally 5-30 mg/day in single or divided doses 3 times/day for 1 month

Alcohol withdrawal syndrome: 100 mg/day I.M. or I.V. for several days, followed by 50-100 mg/day orally

Wernicke's encephalopathy: Treatment: Initial: 100 mg I.V., then 50-100 mg/day I.M. or I.V. until consuming a regular, balanced diet. Larger doses may be needed in patients with alcohol abuse.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Adequate Intake:

0-6 months: 0.2 mg/day

7-12 months: 0.3 mg/day

Recommended daily intake:

1-3 years: 0.5 mg

4-8 years: 0.6 mg

9-13 years: 0.9 mg

14-18 years: Female: 1 mg; Male: 1.2 mg

≥19 years: Refer to adult dosing.

Parenteral nutrition supplementation: Infants: 1.2 mg/day

Thiamine deficiency (beriberi): Children: 10-25 mg/dose I.M. or I.V. daily (if critically ill), or 10-50 mg/dose orally every day for 2 weeks, then 5-10 mg/dose orally daily for 1 month

Administration: I.M.Parenteral form may be administered I.M.

Administration: I.V.Parenteral form may be administered by I.V. injection. Various rates of administration have been reported. Local injection reactions may be minimized by slow administration (~30 minutes) into larger, more proximal veins. Thiamine should be administered prior to parenteral glucose solutions to prevent the precipitation of heart failure.

Administration: I.V. DetailpH: 2.5-4.5

Dietary ConsiderationsDietary sources include legumes, pork, beef, whole grains, yeast, and fresh vegetables. A deficiency state can occur in as little as 3 weeks following total dietary absence.

StorageInjection: Store at 15°C to 30°C (59°F to 86°F). Protect from light.
CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4NS$, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, fat emulsion 10%, LR, ${}^1/_2NS$, NS.

Y-site administration: Compatible: Famotidine.

Compatibility in syringe: Compatible: Doxapram.

ContraindicationsHypersensitivity to thiamine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Hypersensitivity reactions: Have been reported following repeated parenteral doses; consider skin test in individuals with history of allergic reactions.

Concurrent drug therapy issues:

- Dextrose: Administration of dextrose may precipitate acute symptoms of thiamine deficiency; use caution when thiamine status is marginal or suspect.

Dosage form specific issues:

- Aluminum: Some parenteral products contain aluminum; use caution in patients with impaired renal function and neonates.

Other warnings/precautions:

- Parenteral administration: Use with caution with parenteral route (especially I.V.) of administration.

- Vitamin deficiency: Single vitamin deficiency is rare; evaluate for other deficiencies.

Geriatric ConsiderationsNo special recommendations are necessary. Elderly are treated the same as younger adults.
Pregnancy Risk FactorA/C (dose exceeding RDA recommendation)
Pregnancy Considerations

Thiamine requirements are increased during pregnancy. Severe nausea and vomiting (hyperemesis gravidarum) may lead to thiamine deficiency manifested as Wernicke’s encephalopathy.

LactationEnters breast milk/use caution (AAP rates “compatible”)
Adverse ReactionsAdverse reactions reported with injection. Frequency not defined.

Cardiovascular: Cyanosis

Central nervous system: Restlessness

Dermatologic: Angioneurotic edema, pruritus, urticaria

Gastrointestinal: Hemorrharge into GI tract, nausea, tightness of the throat

Local: Induration and/or tenderness at the injection site (following I.M. administration)

Neuromuscular & skeletal: Weakness

Respiratory: Pulmonary edema

Miscellaneous: Anaphylactic/hypersensitivity reactions (following I.V. administration), diaphoresis, warmth

Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb Interactions

Ethanol: May decrease thiamine absorption.

Food: High carbohydrate diets may increase thiamine requirement.

Test InteractionsFalse-positive for uric acid using the phosphotungstate method and for urobilinogen using the Ehrlich's reagent; large doses may interfere with the spectrophotometric determination of serum theophylline concentration
Reference RangeNormal, serum: 1.1-1.6 mg/dL
Nursing: Physical Assessment/MonitoringAssess knowledge/teach patient appropriate administration (injection technique and needle disposal if I.M. self-administered) and dietary instruction.
Patient EducationTake exactly as directed; do not discontinue without consulting prescriber (deficiency state can occur in as little as 3 weeks). Follow dietary instructions (dietary sources include legumes, pork, beef, whole grains, yeast, fresh vegetables). **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride: 100 mg/mL (2 mL)

Tablet, as hydrochloride: 50 mg, 100 mg, 250 mg, 500 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Thiamine HCl)

100 mg (30): $5.41

Mechanism of ActionAn essential coenzyme in carbohydrate metabolism by combining with adenosine triphosphate to form thiamine pyrophosphate

Pharmacodynamics/Kinetics

Absorption: Oral: Adequate; I.M.: Rapid and complete

Distribution: Highest concentrations found in brain, heart, kidney, liver; crosses the placenta, enters breast milk

Excretion: Urine (as unchanged drug and as pyrimidine after body storage sites become saturated)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Tightness of the throat.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusWeakness and restlessness have been reported with injection

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsAneurine Hydrochloride; Thiamin; Thiamine Hydrochloride; Thiaminium Chloride Hydrochloride; Vitamin B_1

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Wrenn KD, Murphy F, and Slovis CM, "A Toxicity Study of Parenteral Thiamine Hydrochloride," *Ann Emerg Med*, 1989, 18(8):867-70.[PubMed 2757284]

International Brand NamesAberil (IT); Abery (JP); Actamin (JP); AFI-B (NO); Aliaron D 10 (JP); Anerex (MX); Aneurin-AS (DE); Aneurol (BE); Arcavit-B!1 (AT); B!1-Vicotrat (DE); B1-ASmedic (DE); Becaps (BR); Becozym (SE); Benerva (AE, AR, BB, BE, BH, BM, BS, BZ, CH, CO, CY, EG, ES, FR, GB, GH, GY, IL, IQ, IR, IT, JM, JO, KE, KW, LB, LU, LY, NL, OM, PE, QA, SA, SE, SR, SY, TT, TZ, UG, YE, ZM); Beneuran (AT); Beneurol (BE, LU); Beneuron (IN); Bermin B (JP); Beta-Sol (AU); Beta-Tabs (AU); Betabion (DE, ES, IT, SE); Betamin (AU); Betamine (BE, LU); Betar (IT); Bevitine (FR); Bevitol (AT); Biogen (JP); Bisolvit (IT); Dagravit B!1 (ES); Dagravit B1 (PT); Dexabion (MX); Dextamina B1 (ES); Dolo-Neurobion (MX); Dolo-Pangavit (MX); Dolo-Tiaminal (MX); Farmobion B1 (IT); Hiace (JP); Hithia (JP); Incremin con Hierro (MX); Juvabe <300> (CH); Juvabe <300>[inj.] (CH); Kirin B!1 (JP); Lifaton B1 (ES); Lophakomp-B1 (DE); Metabolin (JP); Mutsutamin (JP); Neo-Panlacticos (MX); Neuramin (FI); Neurobion (MX); Novo-Thiamina (IT); Optovite B1 (ES); Pagavit (MX); Pharmaton (MX); Plivit B1 (HR); Rivo B!1 (CH); Suma-B (MX); Thiamine Injection (AU); Tiamidexal (MX); Tiamin "Dak" (DK); Tiamina (CO); Tiaminal (MX); Tolima (DE); Tribedoce (MX); Trifosfaneurina (ES, PT); Vit. B1 Agepha (AT); Vita-B1 (FI); Vitabi1 (IT); Vitamin B 1 Kattwiga (DE); Vitamin B!1 (HU); Vitamin B!1 Jenapharm (DE); Vitamin B!1 Streuli (CH); Vitamin B!1-Hevert (DE); Vitamin B!1-Injektopas (DE); Vitamin B!1-ratiopharm (DE); Vitamina B1 Angelini (IT); Vitamina B1 Biol (AR); Vitamina B1 Salf (IT); Vitaminum B1 (PL); Vitanon[inj.] (JP); Vitantial (ES)

Thioguanine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

6-thioguanine and 6-TG are error-prone abbreviations (associated with six-fold overdoses of thioguanine)

Pronunciation(thye oh GWAH neen)
U.S. Brand NamesTabloid®
Canadian Brand NamesLanvis®
Pharmacologic CategoryAntineoplastic Agent, Antimetabolite (Purine Antagonist)
Use: Labeled IndicationsTreatment of acute myelogenous (nonlymphocytic) leukemia; treatment of chronic myelogenous leukemia and granulocytic leukemia
Dosing: AdultsTotal daily dose can be given at one time.

Antineoplastic: Oral: Refer to individual protocols: 2-3 mg/kg/day calculated to nearest 20 mg or 75-200 mg/m^2/day in 1-2 divided doses for 5-7 days or until remission is attained

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricTotal daily dose can be given at one time.

Antineoplastic: Oral (refer to individual protocols):

Infants and Children <3 years: Combination drug therapy for acute nonlymphocytic leukemia: 3.3 mg/kg/day in divided doses twice daily for 4 days

Children >3 years: Refer to adult dosing.

Dosing: Renal ImpairmentReduce dose.
Dosing: Hepatic ImpairmentReduce dose.
Dosing: Combination Regimens

Leukemia, acute myeloid:

DAT

TAD

V-TAD

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

StorageStore tablet at room temperature.
Reconstitution
Compatibility
Extemporaneously PreparedA 20 mg/mL oral suspension can be prepared by crushing fifteen 40 mg tablets in a mortar, and then adding 10 mL of methylcellulose 1% (in small amounts). Transfer to a graduate, then add a sufficient quantity of syrup to make 30 mL of suspension. Label “shake well.” Room temperature stability is 60 days.

Dressman JB and Poust RI, “Stability of Allopurinol and Five Antineoplastics in Suspension,” *Am J Hosp Pharm*, 1983, 40:616-8.

Nahata MC, Morosco RS, and Hipple TF, 4th ed, *Pediatric Drug Formulations*, Cincinnati, OH: Harvey Whitney Books Co, 2000.

RestrictionsThe I.V. formulation is not available in U.S.
ContraindicationsHypersensitivity to thioguanine or any component of the formulation; pregnancy
Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Myelosuppression is a common dose-related toxicity (may be delayed); patients with genetic deficiency of thiopurine methyltransferase (TPMT) or who are receiving drugs which inhibit this enzyme (mesalazine, olsalazine, sulfasalazine) may be highly sensitive to myelosuppressive effects.

- Hepatotoxicity: Not recommended for long-term continuous therapy due to potential for hepatotoxicity (hepatic veno-occlusive disease); discontinue in patients with evidence of hepatotoxicity.

- Secondary malignancies: Thioguanine is potentially carcinogenic.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment recommended.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

Special populations:

- Pregnancy: Thioguanine is potentially teratogenic.

Other warnings/precautions:

- Resistance: Caution with history of previous therapy resistance with either thioguanine or mercaptopurine (there is usually complete cross resistance between these two).

Pregnancy Risk FactorD
LactationExcretion in breast milk unknown
Adverse Reactions

>10%: Hematologic: Myelosuppressive:

WBC: Moderate

Platelets: Moderate

Onset: 7-10 days

Nadir: 14 days

Recovery: 21 days

1% to 10%:

Dermatologic: Skin rash

Endocrine & metabolic: Hyperuricemia

Gastrointestinal: Mild nausea or vomiting, anorexia, stomatitis, diarrhea

Neuromuscular & skeletal: Unsteady gait

<1%: Ascites, esophageal varices, hepatic necrosis, hepatitis, jaundice, LFTs increased, neurotoxicity, photosensitivity, portal hypertension, splenomegaly, thrombocytopenia, veno-occlusive hepatic disease

Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

5-ASA Derivatives: May decrease the metabolism of Thiopurine Analogs. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsFood: Enhanced absorption if administered between meals.
Monitoring ParametersCBC with differential and platelet count; liver function tests (weekly when beginning therapy then monthly, more frequently in patients with liver disease or concurrent hepatotoxic drugs); hemoglobin, hematocrit, serum uric acid; some laboratories offer testing for TPMT deficiency

Hepatotoxicity may present with signs of portal hypertension (splenomegaly, esophageal varices, thrombocytopenia) or veno-occlusive disease (fluid retention, ascites, hepatomegaly with tenderness, or hyperbilirubinemia)

Nursing: Physical Assessment/MonitoringUse caution with renal or hepatic impairment. Assess potential for interactions with other pharmacological agents patient may be taking. Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, myelosuppression, nausea, vomiting, malaise, rash, diarrhea) weekly when beginning therapy, then monthly. Teach patient appropriate use, possible side effects/appropriate interventions (eg, importance of adequate hydration), and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelet count; liver function tests (weekly when beginning therapy then monthly, more frequently in patients with liver disease or concurrent hepatotoxic drugs); serum uric acid, renal function; some laboratories offer testing for TPMT deficiency

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause nausea and vomiting, diarrhea, or loss of appetite (small, frequent meals may help/request medication); weakness or lethargy (use caution when driving or engaging in tasks requiring alertness until response to drug is known); mouth sores (use good oral care); or headache (request medication). You will be susceptible to infection (avoid crowds and exposure to infection). Report signs or symptoms of infection (eg, fever, chills, sore throat, burning urination, fatigue); bleeding (eg, tarry stools, easy bruising); vision changes; unresolved mouth sores, nausea, or vomiting; CNS changes (hallucinations); or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Do not get pregnant. Consult prescriber for appropriate contraceptive measures. The drug may cause permanent sterility and may cause birth defects. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet [scored]:

Tabloid®: 40 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Tablets (Tabloid)

40 mg (25): $196.97

Mechanism of ActionPurine analog that is incorporated into DNA and RNA resulting in the blockage of synthesis and metabolism of purine nucleotides

Pharmacodynamics/Kinetics

Absorption: 30% (highly variable)

Distribution: Crosses placenta

Metabolism: Hepatic; rapidly and extensively via TPMT to 2-amino-6-methylthioguanine (active) and inactive compounds

Half-life elimination: Terminal: 11 hours

Time to peak, serum: Within 8 hours

Excretion: Urine

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMyelosuppression is common; avoid clozapine and carbamazepine

Index Terms2-Amino-6-Mercaptopurine; 6-TG (error-prone abbreviation); 6-Thioguanine (error-prone abbreviation); NSC-752; TG; Tioguanine

References

Broxson EH, Dole M, Wong R, et al, “Portal Hypertension Develops in a Subset of Children With Standard Risk Acute Lymphoblastic Leukemia Treated With Oral 6-Thioguanine During Maintenance Therapy,” *Pediatr Blood Cancer*, 2005, 44(3):226-31

Elgemeie GH, "Thioguanine, Mercaptopurine: Their Analogs and Nucleosides as Antimetabolites," *Curr Pharm Des*, 2003, 9(31):2627-42.[PubMed 14529546]

Estlin EJ, “Continuing Therapy for Childhood Acute Lymphoblastic Leukaemia: Clinical and Cellular Pharmacology of Methotrexate, 6-Mercaptopurine and 6-Thioguanine,” *Cancer Treat Rev*, 2001, 27(6):351-63.[PubMed 11908928]

International Brand Names6-TG (IN); Lanvins (BR); Lanvis (AE, AR, AU, BB, BE, BF, BH, BJ, BM, BS, BZ, CH, CI, CN, CO, CY, CZ, EE, EG, ET, FR, GB, GH, GM, GN, GR, GY, HK, HN, HR, HU, IE, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PL, QA, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Tabloid (UY); Thioguanin Glaxo Wellcome (AT, DE); Thioguanine Wellcome (IT); Tioguanina (ES)

Thiopental

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(thye oh PEN tal)

U.S. Brand NamesPentothal®

Canadian Brand NamesPentothal®

Pharmacologic CategoryAnticonvulsant, Barbiturate; Barbiturate; General Anesthetic

Use: Labeled IndicationsInduction of anesthesia; adjunct for intubation in head injury patients; control of convulsive states; treatment of elevated intracranial pressure

Dosing: Adults

Anesthesia: I.V.:

Induction: 3-5 mg/kg

Maintenance: 25-100 mg as needed

Increased intracranial pressure: I.V.: Children and Adults: 1.5-5 mg/kg/dose; repeat as needed to control intracranial pressure

Seizures: I.V.: 75-250 mg/dose, repeat as needed

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Anesthesia: I.V.:

Induction:

Infants: 5-8 mg/kg

Children 1-12 years: 5-6 mg/kg

Maintenance: Children: 1 mg/kg as needed

Increased intracranial pressure: I.V.: Children: 1.5-5 mg/kg/dose; repeat as needed to control intracranial pressure

Seizures: I.V.: Children: 2-3 mg/kg/dose, repeat as needed

Dosing: Renal ImpairmentCl_{cr} <10 mL/minute: Administer 75% of normal dose.

Note: Accumulation may occur with chronic dosing due to lipid solubility. Prolonged recovery may result from redistribution of thiopental from fat stores.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Administer slowly over 20-30 seconds. Rapid I.V. injection may cause hypotension or decreased cardiac output; avoid extravasation, necrosis may occur. Check I.V. catheter placement prior to administration.

Dietary ConsiderationsSodium content of 1 g (injection): 86.8 mg (3.8 mEq)

StorageReconstituted solutions remain stable for 3 days at room temperature and 7 days when refrigerated.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, $D_5{}^1/_4$NS, $D_5{}^1/_2$NS, D_5W, $^1/_2$NS, NS; **incompatible** with D_5LR, D_{10}W, D_{10}NS, LR; **variable stability (consult detailed reference)** in D_5NS.

Y-site administration: Compatible: Doxacurium, fentanyl, heparin, milrinone, mivacurium, nitroglycerin, ranitidine, remifentanil. **Incompatible:** Alfentanil, ascorbic acid, atracurium, atropine, diltiazem, dobutamine, dopamine, ephedrine, epinephrine, furosemide, hydromorphone, labetalol, lidocaine, midazolam, nicardipine, norepinephrine, pancuronium, phenylephrine, succinylcholine, sufentanil, vecuronium. **Variable (consult detailed reference):** Cisatracurium, lorazepam, morphine.

Compatibility in syringe: Compatible: Aminophylline, hyaluronidase, hydrocortisone sodium succinate, neostigmine, pancuronium, pentobarbital, propofol, scopolamine, tubocurarine. **Incompatible:** Chlorpromazine, dimenhydrinate, diphenhydramine, doxapram, ephedrine, glycopyrrolate, meperidine, morphine, pentazocine, prochlorperazine edisylate, promethazine, sodium bicarbonate.

Compatibility when admixed: Compatible: Chloramphenicol, hydrocortisone sodium succinate, oxytocin, pentobarbital, phenobarbital, potassium chloride, sodium bicarbonate. **Incompatible:** Amikacin, cimetidine, clindamycin, dimenhydrinate, diphenhydramine, droperidol, fentanyl, fibrinolysin (human), hydromorphone, insulin (regular), levorphanol, meperidine, metaraminol, morphine, norepinephrine, penicillin G potassium, prochlorperazine edisylate, promazine, promethazine, succinylcholine. **Variable (consult detailed reference):** Atracurium, ephedrine, pancuronium.

RestrictionsC-III

ContraindicationsHypersensitivity to thiopental, barbiturates, or any component of the formulation; status asthmaticus; severe cardiovascular disease; porphyria (variegate or acute intermittent); should not be administered by intra-arterial injection

Allergy Considerations

- Aromatic Anticonvulsant Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Hypotension: May cause hypotension; use with caution in hemodynamically unstable patients (hypotension or shock).
- Laryngospasm/bronchospasms: May cause laryngospasm or bronchospasms; use with extreme caution in patients with reactive airway diseases (asthma or COPD).
- Paradoxical stimulatory response: May cause paradoxical responses, including agitation and hyperactivity, particularly in acute pain and pediatric patients.
- Respiratory depression: May cause respiratory depression; use with caution patients with respiratory disease.

Disease-related concerns:

- Addison's disease: Use with caution in patients with Addison's disease; may prolong or potentiate hypnotic effect.
- Anemia: Use with caution in patients with severe anemia; may prolong or potentiate hypnotic effect.
- Aneurysms: Use with caution in patients with unstable aneurysms.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Hepatic impairment: Use with caution in patients with hepatic impairment; may prolong or potentiate hypnotic effect.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; may prolong or potentiate hypnotic effect.
- Myxedema: Use with caution in patients with myxedema; may prolong or potentiate hypnotic effect.
- Renal impairment: Use with caution in patients with renal impairment; may prolong or potentiate hypnotic effect.
- Substance abuse: Use with caution in patients with a history of drug abuse; potential for drug dependency exists.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Debilitated patients: Use with caution in patients who are debilitated.
- Elderly: Use with caution in the elderly.
- Excessively premedicated patients: Use with caution in patients excessively premedicated; may prolong or potentiate hypnotic effect.
- Pediatrics: Use with caution in children.

Other warnings/precautions:

- Acute pain: Do not administer to patients in acute pain.
- Cumulative effect: Repeated dosing or continuous infusions may cause cumulative effects.
- Intravenous access: Ensure patient has intravenous access; extravasation or intra-arterial injection causes necrosis due to pH of 10.6.
- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Cardiovascular: Bradycardia, hypotension, syncope

Central nervous system: Drowsiness, lethargy, CNS excitation or depression, impaired judgment, “hangover” effect, confusion, somnolence, agitation, hyperkinesia, ataxia, nervousness, headache, insomnia, nightmares, hallucinations, anxiety, dizziness, shivering

Dermatologic: Rash, exfoliative dermatitis, Stevens-Johnson syndrome

Gastrointestinal: Nausea, vomiting, constipation

Hematologic: Agranulocytosis, thrombocytopenia, megaloblastic anemia, immune hemolytic anemia (rare)

Local: Pain at injection site, thrombophlebitis with I.V. use

Renal: Oliguria

Respiratory: Laryngospasm, respiratory depression, apnea (especially with rapid I.V. use), hypoventilation, sneezing, cough, bronchospasm

Miscellaneous: Gangrene with inadvertent intra-arterial injection, anaphylaxis, anaphylactic reactions

Drug Interactions

Acetaminophen: Barbiturates may increase the metabolism of Acetaminophen. This may 1) diminish the effect of acetaminophen; and 2) increase the risk of liver damage. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Beta-Blockers: Barbiturates may decrease the serum concentration of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Calcium Channel Blockers: Barbiturates may increase the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Carbonic Anhydrase Inhibitors: May enhance the adverse/toxic effect of Anticonvulsants (Barbiturate). Specifically, osteomalacia and rickets. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Barbiturates. Barbiturates may increase the metabolism of Chloramphenicol. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Contraceptive (Progestins): Barbiturates may diminish the therapeutic effect of Contraceptive (Progestins). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Barbiturates may increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Barbiturates may increase the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

Disopyramide: Barbiturates may increase the metabolism of Disopyramide. *Risk D: Consider therapy modification*

Doxycycline: Barbiturates may decrease the serum concentration of Doxycycline. *Risk D: Consider therapy modification*

Etoposide: Barbiturates may increase the metabolism of Etoposide. *Risk C: Monitor therapy*

Etoposide Phosphate: Barbiturates may decrease the serum concentration of Etoposide Phosphate. Barbiturates may increase the metabolism, via CYP isoenzymes, of etoposide phosphate. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Barbiturates. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

LamoTRIgine: Barbiturates may increase the metabolism of LamoTRIgine. *Risk D: Consider therapy modification*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Meperidine: Barbiturates may enhance the CNS depressant effect of Meperidine. *Risk C: Monitor therapy*

Methadone: Barbiturates may increase the metabolism of Methadone. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Barbiturates may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Primidone: May enhance the adverse/toxic effect of Barbiturates. Primidone is converted to phenobarbital, and thus becomes additive with existing barbiturate therapy. *Risk C: Monitor therapy*

Propafenone: Barbiturates may increase the metabolism of Propafenone. *Risk D: Consider therapy modification*

Pyridoxine: May increase the metabolism of Barbiturates. Apparent in high pyridoxine doses (eg, 200 mg/day) *Risk C: Monitor therapy*

QuiNIDine: Barbiturates may increase the metabolism of QuiNIDine. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Barbiturates. *Risk C: Monitor therapy*

Teniposide: Barbiturates may increase the metabolism of Teniposide. *Risk C: Monitor therapy*

Theophylline Derivatives: Barbiturates may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Barbiturates may increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Barbiturates may increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Monitoring ParametersRespiratory rate, heart rate, blood pressure

Reference RangeTherapeutic: Hypnotic: 1-5 mcg/mL (SI: 4.1-20.7 µmol/L); Coma: 30-100 mcg/mL (SI: 124-413 µmol/L); Anesthesia: 7-130 mcg/mL (SI: 29-536 µmol/L); Toxic: >10 mcg/mL (SI: >41 µmol/L)

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance. Periodically evaluate the need for continued use. I.V.: Keep patient under observation. Monitor cardio/respiratory status and institute patient safety precautions. Monitor effectiveness of therapy and adverse reactions. Respiratory status (for conscious sedation, includes pulse oximetry), cardiovascular status, CNS status (when used for procedures monitor sedation score); cardiac monitor and blood pressure monitor required. Infusion site should be monitored closely to prevent extravasation (see Administration).

Patient EducationResidual sedation following recovery is normal, due to slow release of the drug from lipid depots; patients should not drive or engage in similarly dangerous activities until at least the following day

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as sodium: 250 mg, 400 mg, 500 mg, 1 g

Generic AvailableNo

Mechanism of ActionShort-acting barbiturate with sedative, hypnotic, and anticonvulsant properties. Barbiturates depress the sensory cortex, decrease motor activity, alter cerebellar function, and produce drowsiness, sedation, and hypnosis. In high doses, barbiturates exhibit anticonvulsant activity; barbiturates produce dose-dependent respiratory depression.

Pharmacodynamics/Kinetics

Onset of action: Anesthetic: I.V.: 30-60 seconds

Duration: 5-30 minutes

Distribution: V_d: ~1.6 L/kg

Protein binding: 72% to 86%

Metabolism: Hepatic, primarily to inactive metabolites but pentobarbital is also formed

Half-life elimination: 3-11.5 hours; decreased in children

Pharmacotherapy PearlsThiopental switches from linear to nonlinear pharmacokinetics following prolonged continuous infusions.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Anesthesia and Critical Care Concerns/Other ConsiderationsThiopental switches from linear to nonlinear pharmacokinetics following prolonged continuous infusions.

Index TermsThiopental Sodium

References

Morgan DJ, Blackman GL, Paull JD, et al, “Pharmacokinetics and Plasma Binding of Thiopental. I: Studies in Surgical Patients,” *Anesthesiology*, 1981, 54(6):468-73.[PubMed 7235274]

Russo H and Bressolle F, “Pharmacodynamics and Pharmacokinetics of Thiopental,” *Clin Pharmacokinet*, 1998, 35(2):95-134.[PubMed 9739479]

International Brand NamesAnesthal (IN); Bensulf (AR); Hypnostan (FI); Intraval (AE, BB, BH, BM, BS, BZ, CY, EG, GB, GY, IL, IQ, IR, JM, JO, KW, LB, LY, NZ, OM, PR, QA, SA, SR, SY, TT, YE); Nesdonal (FR, HR, LU, NL); Penthotal (CN); Pentotex (MY); Pentothal (AU, BB, BE, BM, BS, BZ, CH, DK, FI, FR, GR, GY, HN, IL, IT, JM, LU, NO, PH, PT, PY, SE, SG, SR, TT, TW, UY, VE); Pentothal Sodico (ES, PE); Pentothal Sodium (ES, ID, PL); Thionembutal (BR); Thionyl (KP); Thiopen (PK); Thiopental (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE); Thiopental Biochemie (AT); Tiobarbital (ES); Tiopental (HR); Tiopental Sodico (AR, CO); Trapanal (DE, HU)

Thioridazine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

Gill SS, Bronskill SE, Normand SL, et al, “Antipsychotic Drug Use and Mortality in Older Adults With Dementia,” *Ann Intern Med*, 2007, 146(11):775-86.[PubMed 17548409]

Schneeweiss S, Setoguchi S, Brookhart A, et al, “Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients,” *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Medication Safety Issues

Sound-alike/look-alike issues:

Thioridazine may be confused with thiothixene, Thorazine®

Mellaril® may be confused with Elavil®, Mebaral®

Pronunciation(thye oh RID a zeen)

Canadian Brand NamesMellaril®

Pharmacologic CategoryAntipsychotic Agent, Typical, Phenothiazine

Use: Labeled IndicationsManagement of schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those medications

Use: Unlabeled/InvestigationalBehavior problems (children); severe psychoses (children); schizophrenia/psychoses (children); depressive disorders/dementia (children and adults); behavioral symptoms associated with dementia (elderly); psychosis/agitation related to Alzheimer's dementia

Dosing: Adults

Schizophrenia/psychosis: Oral: Initial: 50-100 mg 3 times/day with gradual increments as needed and tolerated; maximum: 800 mg/day in 2-4 divided doses

Depressive disorders, dementia (unlabeled use): Oral: Initial: 25 mg 3 times/day; maintenance dose: 20-200 mg/day

Dosing: ElderlyBehavioral symptoms associated with dementia (unlabeled use): Oral: Initial: 10-25 mg 1-2 times/day; increase at 4- to 7-day intervals by 10-25 mg/day; increase dose intervals (once daily, twice daily, etc) as necessary to control response or side effects. Maximum daily dose: 400 mg; gradual increases (titration) may prevent some side effects or decrease their severity.

Dosing: Pediatric

Schizophrenia/psychosis (unlabeled use): Oral:

Children >2-12 years: Range: 0.5-3 mg/kg/day in 2-3 divided doses; usual: 1 mg/kg/day; maximum: 3 mg/kg/day

Children >12 years: Refer to adult dosing.

Behavior problems (unlabeled use): Oral:

Children >2-12 years: Initial: 10 mg 2-3 times/day, increase gradually.

Children >12 years: Refer to adult dosing.

Severe psychoses (unlabeled use): Oral:

Children >2-12 years: Initial: 25 mg 2-3 times/day, increase gradually.

Children >12 years: Refer to adult dosing.

Dosing: Renal ImpairmentNot dialyzable (0% to 5%)

Administration: Oral Do not take antacid within 2 hours of taking drug.

StorageProtect from light.

ContraindicationsHypersensitivity to thioridazine or any component of the formulation (cross-reactivity between phenothiazines may occur); severe CNS depression; circulatory collapse; severe hypotension; bone marrow suppression; blood dyscrasias; coma; in combination with other drugs that are known to prolong the QT_c interval; in patients with congenital long QT syndrome or a history of cardiac arrhythmias; concurrent use with medications that inhibit the metabolism of thioridazine (fluoxetine, paroxetine, fluvoxamine, propranolol, pindolol); patients known to have genetic defect leading to reduced levels of activity of CYP2D6

Warnings/Precautions

Boxed warnings:

- Altered cardiac conduction: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Altered cardiac conduction: **[U.S. Boxed Warning]: Has dose-related effects on ventricular repolarization leading to QT_c prolongation, a potentially life-threatening effect.** Therefore, it should be reserved for patients with schizophrenia who have failed to respond to adequate levels of other antipsychotic drugs.

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to other neuroleptics, thioridazine has a high potency of cholinergic blockade.

- Blood dyscrasias: Check blood counts periodically and discontinue at first signs of blood dyscrasias; use is contraindicated in patients with bone marrow suppression.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is low relative to other neuroleptics). Risk of dystonia (and possibly other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Neuroleptic malignant syndrome (NMS): May be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Pigmentary retinopathy: May be associated with pigmentary retinopathy.

- Sedation: Highly sedating which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Dementia: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo. An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Thioridazine is not approved for this indication.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.
- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.
- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.
- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.
- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for developing tardive dyskinesia.

Geriatric ConsiderationsAny changes in disease status in any organ system can result in behavior changes.

Many elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior. Before initiating antipsychotic medication, the clinician should investigate any possible reversible cause; any stress or stress from any disease can cause acute “confusion” or worsening of baseline nonpsychotic behavior. Most commonly acute changes in behavior are due to increases in drug dose or addition of new drug to regimen; fluid electrolyte loss; infections; and changes in environment.

In the treatment of agitated, demented, older adult patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: ECG changes, hypotension, orthostatic hypotension, peripheral edema

Central nervous system: Akathisia, dizziness, drowsiness; EPS (pseudoparkinsonism, akathisia, dystonias, tardive dyskinesia); impairment of temperature regulation, lowering of seizure threshold, neuroleptic malignant syndrome (NMS), seizure

Dermatologic: Increased sensitivity to sun, rash, discoloration of skin (blue-gray)

Endocrine & metabolic: Amenorrhea, breast pain, galactorrhea, libido (changes in), menstrual cycle (changes in)

Gastrointestinal: Constipation, diarrhea, nausea, stomach pain, vomiting, weight gain, xerostomia

Genitourinary: Difficulty in urination, ejaculatory disturbances, urinary retention, priapism

Hematologic: Agranulocytosis, leukopenia

Hepatic: Cholestatic jaundice, hepatotoxicity

Neuromuscular & skeletal: Tremor

Ocular: Blurred vision, cornea and lens changes, pigmentary retinopathy

Respiratory: Nasal congestion

Metabolism/Transport Effects**Substrate** of CYP2C19 (minor), 2D6 (major); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2D6 (moderate), 2E1 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Analgesics (Opioid): Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antimalarial Agents: May increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Beta-Blockers: Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors: May decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Fluvoxamine: May increase the serum concentration of Thioridazine. *Risk X: Avoid combination*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid kava kava, valerian, St John's wort, gotu kola (may increase CNS depression). Avoid dong quai, St John's wort (may also cause photosensitization).

Test InteractionsFalse-positives for phenylketonuria, urinary amylase, uroporphyrins, urobilinogen

Monitoring ParametersBaseline and periodic ECG; vital signs; serum potassium, lipid profile, fasting blood glucose and Hgb A_{1c}; BMI; mental status, abnormal involuntary movement scale (AIMS); periodic eye exam; do not initiate if QT_c >450 msec

Reference RangeToxic: >1 mg/mL; lethal: 2-8 mg/dL

Nursing: Physical Assessment/MonitoringAssess other medications patient is taking for effectiveness and interactions. Review ophthalmic exam and monitor laboratory results, therapeutic effectiveness (mental status, mood, affect, gait), and adverse reactions at beginning of therapy and periodically with long-term use. Monitor for CNS depression/level of sedation. Avoid skin contact with liquid medication; may cause contact dermatitis (wash immediately with warm, soapy water). Initiate at lower doses and taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsBaseline ECG; serum potassium, lipid profile, fasting blood glucose and Hgb A_{1c}; BMI; do not initiate if QT_c >450 msec

Patient EducationUse exactly as directed; do not increase dose or frequency. Do not discontinue without consulting prescriber. Tablet may be taken with food. Mix oral solution with 2-4 oz of liquid (eg, juice, milk, water, pudding). Do not take within 2 hours of any antacid. Store away from light. Avoid alcohol or caffeine and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid skin contact with liquid medication; may cause contact dermatitis (wash immediately with warm, soapy water). May turn urine red-brown (normal). You may experience excess drowsiness, lightheadedness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); urinary retention (void before taking medication); ejaculatory dysfunction (reversible); decreased perspiration (avoid strenuous exercise in hot environments); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report persistent CNS effects (eg, trembling fingers, altered gait or balance, excessive sedation, seizures, unusual movements, anxiety, abnormal thoughts, confusion, personality changes); chest pain, palpitations, rapid heartbeat, severe dizziness; unresolved urinary retention or changes in urinary pattern; altered menstrual pattern, change in libido, swelling or pain in breasts (male or female); vision changes; skin rash, irritation, or changes in color of skin (gray-blue); or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, as hydrochloride: 10 mg, 15 mg [DSC], 25 mg, 50 mg, 100 mg, 150 mg [DSC], 200 mg [DSC]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Thioridazine HCl)

10 mg (90): $21.99

15 mg (90): $11.99

25 mg (90): $25.97

50 mg (90): $29.99

100 mg (90): $34.99

150 mg (90): $57.99

200 mg (90): $81.99

Mechanism of ActionThioridazine is a piperidine phenothiazine which blocks postsynaptic mesolimbic dopaminergic receptors in the brain; exhibits a strong alpha-adrenergic blocking effect and depresses the release of hypothalamic and hypophyseal hormones

Pharmacodynamics/Kinetics

Duration: 4-5 days

Half-life elimination: 21-25 hours

Time to peak, serum: ~1 hour

Related Information

- Antipsychotic Agents
- CMS: Long-Term Care Facility Thresholds
- Liquid Compatibility

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation). Significant hypotension may occur, especially when the drug is administered parenterally; orthostatic hypotension is due to alpha-receptor blockade, the elderly are at greater risk for orthostatic hypotension.

Tardive dyskinesia; Prevalence rate may be 40% in elderly; development of the syndrome and the irreversible nature are proportional to duration and total cumulative dose over time. Extrapyramidal reactions are more common in elderly with up to 50% developing these reactions after 60 years of age. Drug-induced Parkinson's syndrome occurs often; akathisia is the most common extrapyramidal reaction in elderly.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsMost pharmacology textbooks state that in presence of phenothiazines, systemic doses of epinephrine paradoxically decrease the blood pressure. This is the so called “epinephrine reversal” phenomenon. This has never been observed when epinephrine is given by infiltration as part of the anesthesia procedure. Thioridazine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health CommentThioridazine is a low-potency antipsychotic. Older antipsychotic medications (chlorpromazine, haloperidol), which do not meet specific criteria for “atypical” antipsychotics, are often referred to as typical antipsychotics. They are associated with the troubling side effect, EPS. However, it is commonly believed that in order for a drug to treat psychosis, it must block dopamine is some manner.

Common side effects include sedation and neuroleptic effect (reduced initiative, interest in the environment, and display of emotion or affect). All **typical** antipsychotics are considered to be equally effective if given in equipotent doses. An inverse relationship exists between intrinsic antimuscarinic activity and propensity to cause extrapyramidal side effects. If dystonia or pseudoparkinsonism occurs, antiparkinsonian agents should be considered. If akathisia occurs, beta-blockers (eg, propranolol), benzodiazepines, or antiparkinsonian agents should be considered. Tardive dyskinesia (TD) secondary to typical antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. After this time period, the incidence is estimated to be 2% to 3% per year. Prevalence rates are ~15% to 20%. Female gender and age constitute risk factors for TD. Indeed, prevalence rates have been reported to be as high as 70% in elderly females. No specific treatment exists for TD, however, patients are often initiated on/switched to an atypical antipsychotic because of their lower incidence to cause TD and hopes of suppression.

Typical antipsychotics are usually only indicated for schizophrenia, but are generally effective for mania and psychosis and/or behavioral syndromes secondary to other mental conditions. Nonpsychiatric uses include Tourette's syndrome, Huntington's disease, and occasionally, intractable hiccups, pruritus, nausea, and vomiting.

These drugs are thought to exert their antipsychotic activity by blocking dopamine D_2 receptors in the mesolimbic dopaminergic pathway. Side effects are often related to their ability to antagonize dopamine receptors in the nigrostriatal and tuberoinfundibular pathways.

Thioridazine has a black-box warning for prolongation of QT_c interval.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Index Terms Thioridazine Hydrochloride

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Seifert RD, “Therapeutic Drug Monitoring: Psychotropic Drugs,” *J Pharm Pract*, 1984, 6:403-16.

International Brand Names Aldazine (AU); Meleril (AR, CN, CO, PY, UY, VE); Mellerette (IT); Melleretten (AT, NL); Melleril (AE, AT, BE, BF, BG, BH, BJ, BR, CH, CI, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HN, ID, IE, IL, IN, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, NZ, OM, PE, PH, PK, PT, QA, RU, SA, SC, SD, SE, SL, SN, SY, TN, TR, TZ, UG, YE, ZA, ZM, ZW); Mellerzin (TW); Melzin (TW); Orsanil (FI); Ridazin (IL, IN); Ridazine (TH); Tensenol (CN); Thinin (TW); Thiomed (TH); Thioridazin (PL); Thioridazin prolongatum (PL); Thioril (IN); Thiosia (TH)

Thiotepa

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(thye oh TEP a)

Pharmacologic CategoryAntineoplastic Agent, Alkylating Agent

Use: Labeled IndicationsTreatment of superficial tumors of the bladder; palliative treatment of adenocarcinoma of breast or ovary; lymphomas and sarcomas; controlling intracavitary effusions caused by metastatic tumors; I.T. use: CNS leukemia/lymphoma, CNS metastases

Dosing: AdultsRefer to individual protocols.

Usual dose (range):

I.M., I.V., SubQ: 30-60 mg/m^2 once weekly

I.V.: 0.3-0.4 mg/kg by rapid I.V. administration every 1-4 weeks, **or** 0.2 mg/kg or 6-8 mg/m^2/day for 4-5 days every 2-4 weeks

I.M.: 15-30 mg in various schedules have been given

Intracavitary: 0.6-0.8 mg/kg or 30-60 mg weekly

Intrapericardial: 15-30 mg

Intrathecal: 10-15 mg or 5-11.5 mg/m^2

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols. Children: Sarcomas: I.V.: 25-65 mg/m^2 as a single dose every 21 days.

Dosing: Renal ImpairmentUse with extreme caution, reduced dose may be warranted.

Dosing: Combination Regimens

Breast cancer: VATH

Leukemia, acute lymphocytic: TVTG

Leukemia, acute myeloid: TVTG

Oncology: Bone Marrow - High DoseI.V.: 360-1125 mg/m^2 as a single dose or divided into 2 daily doses; generally combined with other high-dose chemotherapeutic drugs.

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Administer either as a short (10-60 minute) infusion or 1-2 minute push; a 1 mg/mL solution is considered isotonic; not a vesicant

Administration: I.V. DetailA 1 mg/mL solution is considered isotonic; not a vesicant.

pH: 5.5-7.5

Administration: OtherIntravesical lavage: Instill directly into the bladder and retain for at least 2 hours; patient should be repositioned every 15-30 minutes for maximal exposure

StorageStore intact vials under refrigeration (2°C to 8°C). Protect from light. Reconstituted solutions (10 mg/mL) are stable for up to 28 days under refrigeration (4°C to 8°C) or 7 days at room temperature (25°C).

Solutions for infusion in D$_5$W (≥5 mg/mL) are stable for 14 days under refrigeration (4°C) or 3 days at room temperature (23°C).

Solutions for infusion in NS (1, 3, or 5 mg/mL) are stable for 48 hours under refrigeration (4°C to 8°C) or 24 hours at room temperature (25°C). Solutions in NS at a concentration ≤0.5 mg/mL are stable for <1 hour.

ReconstitutionReconstitute each vial to 10 mg/mL. Solutions for infusion should be diluted to a concentration ≥5 mg/mL in 5% dextrose or 1, 3, or 5 mg/mL in 0.9% sodium chloride injection. Solutions for intravesicular administration should be diluted in 30-60 mL SWFI or NS. Solutions for intrathecal administration should be diluted in 1-5 mL NS or Elliott's B solution. Filter through a 0.22 micron filter prior to administration.

Compatibility**Variable stability (consult detailed reference)** in D$_5$W, NS.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, amikacin, aminophylline, amphotericin B, ampicillin, ampicillin/sulbactam, aztreonam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, carmustine, cefazolin, cefepime, cefoperazone, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, chlorpromazine, cimetidine, ciprofloxacin, clindamycin, co-trimoxazole, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, dexamethasone sodium phosphate, diphenhydramine,dobutamine, dopamine, doxorubicin, doxycycline, droperidol, enalaprilat, etoposide, etoposide phosphate, famotidine, floxuridine, fluconazole, fludarabine, fluorouracil, furosemide, ganciclovir, gemcitabine, gentamicin, granisetron, haloperidol, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, idarubicin, ifosfamide, imipenem/cilastatin, leucovorin, lorazepam, magnesium sulfate, mannitol, melphalan, meperidine, mesna, methotrexate, methylprednisolone sodium succinate, metoclopramide, metronidazole, , mitomycin, mitoxantrone, morphine, nalbuphine, netilmicin, ofloxacin, ondansetron, paclitaxel, piperacillin, piperacillin/tazobactam, plicamycin, potassium chloride, prochlorperazine edisylate, promethazine, ranitidine, sodium bicarbonate, streptozocin, teniposide, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, vinblastine, vincristine, zidovudine. **Incompatible:** Cisplatin, filgrastim, minocycline, vinorelbine. **Variable (consult detailed reference):** TPN.

Compatibility when admixed: Compatible: Epinephrine, lidocaine. **Incompatible:** Cisplatin.

ContraindicationsHypersensitivity to thiotepa or any component of the formulation; pregnancy

Allergy Considerations

- Nitrogen Mustard Allergy

Warnings/Precautions

Special handling:

• Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

• Fertility effects: May be mutagenic and teratogenic.

• Myelosuppression: Commonly with use, myelosuppression may occur; use with caution in patients with bone marrow damage, dosage reduction recommended.

• Secondary malignancies: Potentially carcinogenic; myelodysplastic syndromes and acute leukemias have been reported.

Disease-related concerns:

• Hepatic impairment: Use with caution in patients with hepatic impairment; dosage reduction recommended. Use should be limited to cases where benefit outweighs risk.

• Renal impairment: Use with caution in patients with renal impairment; dosage reduction recommended. Use should be limited to cases where benefit outweighs risk.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated teratogenicity and fetal loss. There are no adequate and well-controlled studies in pregnant women. May cause harm if administered during pregnancy. Effective contraception is recommended for men and women of childbearing potential.

LactationEnters breast milk/not recommended

Adverse Reactions

>10%:

Hematopoietic: Dose-limiting toxicity which is dose related and cumulative; moderate to severe leukopenia and severe thrombocytopenia have occurred. Anemia and pancytopenia may become fatal, so careful hematologic monitoring is required; intravesical administration may cause bone marrow suppression as well.

Hematologic: Myelosuppression (WBC: moderate; platelets: severe; onset: 7-10 days, nadir: 14 days, recovery: 28 days)

Local: Injection site pain

1% to 10%:

Central nervous system: Dizziness, fatigue, fever, headache

Dermatologic: Alopecia, depigmentation (with topical treatment), hyperpigmentation (with high-dose therapy), pruritus, rash, urticaria

Endocrine & metabolic: Amenorrhea, hyperuricemia

Gastrointestinal: Anorexia, nausea and vomiting rarely occur

Emetic potential: Low (<10%)

Genitourinary: Dysuria, hemorrhagic cystitis (intravesicular administration: rare), urinary retention

Neuromuscular & skeletal: Weakness

Ocular: Conjunctivitis

Renal: Hematuria

Miscellaneous: Tightness of the throat, allergic reactions

<1%: Stomatitis, anaphylaxis; like other alkylating agents, this drug is carcinogenic

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Oncology: Bone Marrow - Unique Toxicity

Central nervous system: Effect increased with doses >1000 mg/m^2: Confusion, inappropriate behavior, somnolence

Dermatologic: Hyperpigmentation (most common on occluded areas of skin)

Gastrointestinal: Mucositis, mild nausea and vomiting

Hepatic: Serum transaminitis, hyperbilirubinemia

Metabolism/Transport Effects**Inhibits** CYP2B6 (strong)
Drug Interactions

CYP2B6 Substrates: CYP2B6 Inhibitors (Strong) may decrease the metabolism of CYP2B6 Substrates. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (due to GI irritation).

Herb/Nutraceutical: Avoid black cohosh, dong quai in estrogen-dependent tumors.

Monitoring ParametersCBC with differential and platelet count (monitor for at least 3 weeks after treatment); uric acid, urinalysis
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological or herbal agents patient may be taking. See Administration for infusion specifics. Evaluate results of laboratory tests closely (eg, anemia and pancytopenia can become fatal). Assess therapeutic effectiveness and adverse response on a regular basis (eg, myelosuppression, leukopenia, dysuria, hematuria). Teach patient possible side effects/appropriate interventions (eg, importance of adequate hydration) and adverse symptoms to report.
Monitoring: Lab TestsCBC with differential and platelet count (monitor for at least 3 weeks after treatment); uric acid, urinalysis
Patient EducationDo not take any new prescription or over-the-counter medications or herbal products during therapy unless approved by prescriber (especially aspirin or aspirin-containing products). If administered by infusion, report immediately any redness, pain, swelling, or burning at infusion site. You will require regular blood tests to assess response to therapy. Maintain adequate hydration to prevent kidney damage (2-3 L/day of fluids unless instructed to restrict fluid intake). You may have increased sensitivity to infection (avoid crowds and exposure to infection and do not have any vaccinations unless approved by prescriber). May cause mild nausea, vomiting, or loss of appetite (small frequent meals, chewing gum, or sucking lozenges may help); rash; hair loss; or change in skin color (usually reversible after discontinuing treatment). Report any changes in urinary pattern or blood in your urine; unusual bleeding or bruising; persistent fever or chills; sore throat; sores in mouth or vagina; blackened stool; unusual or persistent weakness; difficulty swallowing; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant (females) or cause a pregnancy (males) during therapy and for 1 month following completion of therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Breast-feeding is not recommended.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 15 mg, 30 mg

Generic AvailableYes
Mechanism of ActionAlkylating agent that reacts with DNA phosphate groups to produce cross-linking of DNA strands leading to inhibition of DNA, RNA, and protein synthesis; mechanism of action has not been explored as thoroughly as the other alkylating agents, it is presumed that the aziridine rings open and react as nitrogen mustard; reactivity is enhanced at a lower pH
Pharmacodynamics/Kinetics

Absorption: Intracavitary instillation: Unreliable (10% to 100%) through bladder mucosa; I.M.: variable

Metabolism: Extensively hepatic; major metabolite (active): TEPA

Half-life elimination: Terminal (dose-dependent clearance): 109 minutes

Excretion: Urine (as metabolites and unchanged drug)

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsA 1 mg/mL solution is considered isotonic.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness
Mental Health: Effects on Psychiatric TreatmentMyelosuppression is common; avoid clozapine and carbamazepine; barbiturates may

increase clearance of thiotepa

Oncology: Bone Marrow CommentsAdministration of thiotepa over 30 minutes, 1 hour before infusion of cyclophosphamide over 60 minutes, reduced bioactivation of cyclophosphamide to 4-hydroxycyclophosphamide in 20 patients. This effect did not occur with administration of thiotepa 1 hour following infusion of cyclophosphamide.

Index TermsTESPA; Thiophosphoramide; Triethylenethiophosphoramide; TSPA

References

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International Brand NamesLedertepa (BE, LU, NL); Oncotiotepa (BE, ES, LU); Tespamin (JP, TW); Thio-Tepa (AR, CZ); Thiotepa Lederle (AT, CH, DE, FR)

Thiothixene

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

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Medication Safety Issues

Sound-alike/look-alike issues:

Thiothixene may be confused with thioridazine

Navane® may be confused with Norvasc®, Nubain®

Pronunciation(thye oh THIKS een)

U.S. Brand NamesNavane®

Canadian Brand NamesNavane®

Pharmacologic CategoryAntipsychotic Agent, Typical

Use: Labeled IndicationsManagement of schizophrenia

Use: Unlabeled/InvestigationalPsychotic disorders (children); rapid tranquilization of the agitated patient (children); nonpsychotic patient, dementia behavior (elderly); psychosis/agitation related to Alzheimer's dementia

Dosing: Adults

Mild to moderate psychosis: Oral: 2 mg 3 times/day, up to 20-30 mg/day; more severe psychosis: Initial: 5 mg 2 times/day, may increase gradually, if necessary; maximum: 60 mg/day

Rapid tranquilization of the agitated patient (administered every 30-60 minutes): Oral: 5-10 mg; average total dose for tranquilization: 15-30 mg

Dosing: ElderlyNonpsychotic patient, dementia behavior (unlabeled use): Initial: 1-2 mg 1-2 times/day; increase dose at 4- to 7-day intervals by 1-2 mg/day. Increase dosing intervals (bid, tid, etc) as necessary to control response or side effects; maximum daily dose: 30 mg. Gradual increases in dose may prevent some side effects or decrease their severity.

Dosing: Pediatric

Children <12 years (unlabeled use): Oral: 0.25 mg/kg/24 hours in divided doses (dose not well established; use not recommended)

Children >12 years (unlabeled use): Mild to moderate psychosis: Refer to adult dosing.

Dosing: Renal ImpairmentNot dialyzable (0% to 5%)

ContraindicationsHypersensitivity to thiothixene or any component of the formulation; severe CNS depression; circulatory collapse; blood dyscrasias; coma

Allergy Considerations

- Thioxanthene Allergy

Warnings/Precautions

Boxed warnings:

- Dementia: See "Disease-related concerns" below.

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics. Avoid use in patients with underlying QT prolongation, in those taking medicines that prolong the QT interval, or cause polymorphic ventricular tachycardia; monitor ECG closely for dose-related QT effects.

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to other neuroleptics, thiothixene has a low potency of cholinergic blockade.

- Blood dyscrasias: Myelosuppression (eg, leukopenia, agranulocytosis) has been observed with antipsychotic use; check blood counts periodically and discontinue at first signs of blood dyscrasias; use is contraindicated in patients with bone marrow suppression.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).

- Extrapyramidal symptoms: May cause extrapyramidal symptoms (EPS), including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is high relative to other neuroleptics). Risk of dystonia (and possibly other EPS) may be greater with increased doses, use of conventional antispychotics, males, and younger patients.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Pigmentary retinopathy: May be associated with pigmentary retinopathy.

- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Dementia: **[U.S. Boxed Warning]: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo.** An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Thiothixene is not approved for this indication.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Geriatric ConsiderationsAny changes in disease status in any organ system can result in behavior changes.

Many elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior. Before initiating antipsychotic medication, the clinician should investigate any possible reversible cause; any stress or stress from any disease can cause acute “confusion” or worsening of baseline nonpsychotic behavior. Most commonly acute changes in behavior are due to increases in drug dose or addition of new drug to regimen; fluid electrolyte loss; infections; and changes in environment.

In the treatment of agitated, demented, elderly patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension, nonspecific ECG changes, syncope, tachycardia

Central nervous system: Agitation, dizziness, drowsiness, extrapyramidal symptoms (akathisia, dystonias, lightheadedness, pseudoparkinsonism, tardive dyskinesia), insomnia restlessness

Dermatologic: Discoloration of skin (blue-gray), photosensitivity, pruritus, rash, urticaria

Endocrine & metabolic: Amenorrhea, breast pain, libido (changes in), changes in menstrual cycle, galactorrhea, gynecomastia, hyper-/hypoglycemia, hyperprolactinemia, lactation

Gastrointestinal: Constipation, nausea, salivation increased, stomach pain, vomiting, weight gain, xerostomia

Genitourinary: Difficulty in urination, ejaculatory disturbances, impotence

Hematologic: Leukocytes, leukopenia

Neuromuscular & skeletal: Tremors

Ocular: Blurred vision, pigmentary retinopathy

Respiratory: Nasal congestion

Miscellaneous: Diaphoresis

Metabolism/Transport Effects**Substrate** of CYP1A2 (major); **Inhibits** CYP2D6 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid kava kava, valerian, St John's wort, gotu kola (may increase CNS depression).

Test InteractionsMay cause false-positive pregnancy test

Monitoring ParametersVital signs; lipid profile, fasting blood glucose/Hgb A_{1c}; BMI; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms (EPS)

Nursing: Physical Assessment/MonitoringAssess other medications patient is taking for effectiveness and interactions. Review ophthalmic exam and monitor laboratory results, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. Avoid skin contact with liquid medication; may cause contact dermatitis (wash immediately with warm, soapy water). Initiate at lower doses and taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsLipid profile, fasting blood glucose/Hgb A_{1c}; BMI

Patient EducationUse exactly as directed; do not increase dose or frequency. Do not discontinue without consulting prescriber. Capsules may be taken with food. Do not take within 2 hours of any antacid. Avoid alcohol or caffeine and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May turn urine red-brown (normal). You may experience excess drowsiness, lightheadedness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); urinary retention (void before taking medication); ejaculatory dysfunction (reversible); decreased perspiration (avoid strenuous exercise in hot environments); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report persistent CNS effects (eg, trembling fingers, altered gait or balance, excessive sedation, seizures, unusual movements, anxiety, abnormal thoughts, confusion, personality changes); chest pain, palpitations, rapid heartbeat, severe dizziness; unresolved urinary retention or changes in urinary pattern; altered menstrual pattern, change in libido, swelling or pain in breasts (male or female); vision changes; skin rash, irritation, or changes in color of skin (gray-blue); or worsening of condition.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Capsule: 1 mg, 2 mg, 5 mg, 10 mg

Navane®: 1 mg [DSC], 2 mg, 5 mg, 10 mg, 20 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Navane)

2 mg (90): $84.10

5 mg (90): $131.30

10 mg (90): $175.61

20 mg (90): $243.49

Capsules (Thiothixene)

1 mg (90): $22.99

2 mg (90): $26.99

5 mg (90): $25.99

10 mg (90): $49.99

10 mg (100): $31.99

Mechanism of ActionThiothixene is a thioxanthene antipsychotic which elicits antipsychotic activity by postsynaptic blockade of CNS dopamine receptors resulting in inhibition of dopamine-mediated effects; also has alpha-adrenergic blocking activity

Pharmacodynamics/Kinetics

Metabolism: Extensively hepatic

Half-life elimination: >24 hours with chronic use

Related Information

- Antipsychotic Agents
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Liquid Compatibility
- Teratogenic Risks of Psychotropic Medications

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), significant hypotension may occur, especially when the drug is administered parenterally; orthostatic hypotension is due to alpha-receptor blockade, the elderly are at greater risk for orthostatic hypotension.

Tardive dyskinesia: Prevalence rate may be 40% in elderly; development of the syndrome and the irreversible nature are proportional to duration and total cumulative dose over time. Extrapyramidal reactions are more common in elderly with up to 50% developing these reactions after 60 years of age. Drug-induced Parkinson's syndrome occurs often; akathisia is the most common extrapyramidal reaction in elderly.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsMost pharmacology textbooks state that in presence of phenothiazines, systemic doses of epinephrine paradoxically decrease the blood pressure. This is the so called “epinephrine reversal” phenomenon. This has never been observed when epinephrine is given by infiltration as part of the anesthesia procedure. Thiothixene is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health: Child/Adolescent ConsiderationsThe use of thiothixene in children <12 years of age is not recommended; safety and efficacy have not been established for this age group.

Mental Health CommentThiothixene is a high-potency antipsychotic. Older antipsychotic medications (chlorpromazine, haloperidol), which do not meet specific criteria for “atypical” antipsychotics, are often referred to as typical antipsychotics. They are associated with the troubling side effect, EPS. However, it is commonly believed that in order for a drug to treat psychosis, it must block dopamine is some manner.

Common side effects include sedation and neuroleptic effect (reduced initiative, interest in the environment, and display of emotion or affect). All **typical** antipsychotics are considered to be equally effective if given in equipotent doses. An inverse relationship exists between intrinsic antimuscarinic activity and propensity to cause extrapyramidal side effects. If dystonia or pseudoparkinsonism occurs, antiparkinsonian agents should be considered. If akathisia occurs, beta-blockers (eg, propranolol), benzodiazepines, or antiparkinsonian agents should be considered. Tardive dyskinesia (TD) secondary to typical antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. After this time period, the incidence is estimated to be 2% to 3% per year. Prevalence rates are ~15% to 20%. Female gender and age constitute risk factors for TD. Indeed, prevalence rates have been reported to be as high as 70% in elderly females. No specific treatment exists for TD, however, patients are often initiated on/switched to an atypical antipsychotic because of their lower incidence to cause TD and hopes of suppression.

Typical antipsychotics are usually only indicated for schizophrenia, but are generally effective for mania and psychosis and/or behavioral syndromes secondary to other mental conditions. Nonpsychiatric uses include Tourette's syndrome, Huntington's disease, and occasionally, intractable hiccups, pruritus, nausea, and vomiting.

These drugs are thought to exert their antipsychotic activity by blocking dopamine D_2 receptors in the mesolimbic dopaminergic pathway. Side effects are often related to their ability to antagonize dopamine receptors in the nigrostriatal and tuberoinfundibular pathways.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Anesthesia and Critical Care Concerns/Other ConsiderationsCoadministration of two or more antipsychotics does not improve clinical response and may increase the potential for adverse effects.

Index TermsTiotixene

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International Brand NamesNavane (AU, BR, NL)

Thrombin (Topical)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Administration: For topical use only. Do not administer intravenously or intra-arterially.

To reduce the risk of intravascular administration, the Institute for Safe Medication Practices (ISMP) has the following recommendations:

- Prepare, label, and dispense topical thrombin from the pharmacy department (including doses used in the operating room).
- Do not leave vial or syringe at bedside.
- Add auxiliary label to all labels and syringes stating “For topical use only-do not inject”.
- When appropriate, use solutions which can be applied with an absorbable gelatin sponge or use a dry form on oozing surfaces.
- When appropriate, use spray kits to help differentiate between parenteral products.

Pronunciation(THROM bin, TOP i kal)

U.S. Brand NamesEvithrom™; Recothrom™; Thrombin-JMI®; Thrombin-JMI® Epistaxis Kit; Thrombin-JMI® Spray Kit; Thrombin-JMI® Syringe Spray Kit

Pharmacologic CategoryHemostatic Agent

Use: Labeled IndicationsHemostasis whenever minor bleeding from capillaries and small venules is accessible

Use: DentalHemostasis whenever minor bleeding from capillaries and small venules is accessible

Dosing: Adults**Bleeding:Note:** For topical use only; do not administer intravenously or intra-arterially.

Evithrom™: Dose depends on area to be treated; up to 10 mL was used with absorbable gelatin sponge in clinical studies

Recothrom™: Dose depends on area to be treated

Thrombin-JMI®:

Solution: Use 1000-2000 units/mL of solution where bleeding is profuse; use 100 units/mL for bleeding from skin or mucosal surfaces

Powder: May apply powder directly to the site of bleeding or on oozing surfaces

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: TopicalFor topical use only; do not administer intravenously or intra-arterially.

Evithrom™: Must be thawed prior to use. May thaw in refrigerator (1 day) or at room temperature (1 hour). The 2 mL and 5 mL vials may also be thawed at 37°C (98.6˚F) for up to 10 minutes.

Thrombin-JMI®: May be applied directly as a powder or as reconstituted solution; sponge surface free of blood prior to application, if possible.

Storage

Evithrom™: Store frozen at -18°C or colder; unopened vials may also be stored under refrigeration at 2°C to 8°C (36°F to 46°F) for up to 30 days. Stable for up to 24 hours at room temperature. Do not refreeze if thawed; do not refrigerate once at room temperature. Discard unused portion after 24 hours at room temperature.

Recothrom™: Store at 2°C to 25°C (36°F to 77°F). Following reconstitution, may store at this temperature for up to 24 hours.

Thrombin-JMI®: Store at 2°C to 25°C (36°F to 77°F). Solutions may be stored at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature for up to 8 hours

Reconstitution

Recothrom™: Reconstitute using diluent provided in prefilled syringe. Gently swirl to dissolve powder; avoid excessive agitation. Do not use diluent syringe to withdraw solution from vial.

Thrombin-JMI®: Reconstitute using sodium chloride 0.9%.

ContraindicationsHypersensitivity to thrombin or any component of the formulation; not for direct injection into the circulatory system (for topical use only); additionally,

Evithrom™ and Recothrom™ are also contraindicated for the treatment of severe or brisk arterial bleeding.

Evithrom™ is also contraindicated in patients with known anaphylactic or severe systemic reactions to blood products.

Recotrhom™ is also contraindicated in patients with hypersensitivity to hamster proteins.

Thrombin-JMI® is also contraindicated in patients with hypersensitivity to material of bovine origin.

Warnings/Precautions

Boxed warnings:

- Abnormal hemostasis: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Abnormal hemostasis: **[U.S. Boxed Warning]: Bovine-source topical thrombin (Thrombin-JMI®) may be associated with abnormal hemostasis, ranging from asymptomatic laboratory alterations to severe bleeding and/or thrombosis.** Abnormalities appear to be immunologically mediated; repeated applications increase risk. Consult expert in coagulation disorders if laboratory evidence and/or signs and symptoms of bleeding are noted. Re-exposure of patients who develop antibodies to bovine thrombin preparations should be avoided.

Dosage form specific issues:

- Evithrom™: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.

- Recothrom™: Use caution in patients with known hypersensitivity to snake proteins; the potential for allergic reaction exists.

Other warnings/precautions:

- Administration: For topical use only. Do not inject intravenously or intra-arterially. Intravascular clotting, possibly leading to death, may occur following injection. May be used in combination with absorbable gelatin sponges.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdequate reproduction studies have not been conducted. Reproduction studies conducted with the solvent/detergent used in processing the human-derived product showed adverse events in animals. Only residual levels of the solvent/detergent would be expected to remain in the finished product.

Adverse ReactionsFrequency not defined.

Dermatologic: Pruritus

Gastrointestinal: Nausea, vomiting

Hematologic: Bleeding, aPTT increased, INR increased, lymphocyte count decreased, neutrophil count increased, PT prolonged

Local: Incision site complication

Miscellaneous: Antibody development, hypersensitivity reactions

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for reconstitution, topical [bovine derived]:

Thrombin-JMI®: 5000 int. units, 20,000 int. units

Thrombin-JMI® Epistaxis kit: 5000 int. units

Thrombin-JMI® Spray Kit: 20,000 int. units

Thrombin-JMI® Syringe Spray Kit: 20,000 int. units

Powder for reconstitution, topical [preservative free; recombinant]:

Recothrom™: 5000 int. units; 20,000 int. units

Solution, topical [human derived]:

Evithrom™: 800-1200 int. units/mL (2 mL, 5 mL, 20 mL)

Generic AvailableNo

Mechanism of ActionActivates platelets and catalyzes the conversion of fibrinogen to fibrin to promote hemostasis.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesThrombostat (NZ); Trombine (NL)

Thyroid, Desiccated

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(THYE roid DES i kay tid)

U.S. Brand NamesArmour® Thyroid; Nature-Throid™; Westhroid™

Pharmacologic CategoryThyroid Product

Use: Labeled IndicationsReplacement or supplemental therapy in hypothyroidism; pituitary TSH suppressants (thyroid nodules, thyroiditis, multinodular goiter, thyroid cancer), thyrotoxicosis, diagnostic suppression tests

Dosing: Adults**Hypothyroidism:** Oral: Initial: 15-30 mg; increase with 15 mg increments every 2-4 weeks; use 15 mg in patients with cardiovascular disease or myxedema. Maintenance dose: Usually 60-120 mg/day; monitor TSH and clinical symptoms.

Note: Thyroid cancer requires larger amounts than replacement therapy.

Dosing: ElderlyNot recommended for use in the elderly (see Geriatric Considerations).

Dosing: PediatricHypothyroidism: Oral: See table.

Recommended Pediatric Dosage for Congenital Hypothyroidism

Age	**Daily Dose (mg)**	**Daily Dose/kg (mg)**
0-6 mo	15-30	4.8-6
6-12 mo	30-45	3.6-4.8
1-5 y	45-60	3-3.6
6-12 y	60-90	2.4-3
>12 y	>90	1.2-1.8

Dietary ConsiderationsShould be taken on an empty stomach.

ContraindicationsHypersensitivity to beef or pork or any component of the formulation; recent myocardial infarction; thyrotoxicosis uncomplicated by hypothyroidism; uncorrected adrenal insufficiency

Warnings/Precautions

Boxed warnings:

- Weight reduction: See “Other warnings/precautions” below.

Disease-related concerns:

- Adrenal insufficiency: Use with caution in patients with adrenal insufficiency; symptoms may be exaggerated or aggravated.
- Cardiovascular disease: Use with caution and reduce dosage in patients with angina pectoris or other cardiovascular disease; chronic hypothyroidism predisposes patients to coronary artery disease.
- Diabetes: Use with caution in patients with diabetes mellitus and insipidus; symptoms may be exaggerated or aggravated.
- Myxedema: Use with caution in patients with myxedema; symptoms may be exaggerated or aggravated.

Special populations:

- Elderly: Use with caution in the elderly; they may be more likely to have compromised cardiovascular function. Avoid use of desiccated thyroid; in the minds of many clinicians, drug of choice is levothyroxine.

Dosage form specific issues:

- Desiccated thyroid: Contains variable amounts of T_3, T_4, and other triiodothyronine compounds which are more likely to cause cardiac signs or symptoms due to fluctuating levels.

Other warnings/precautions:

- Weight reduction: **[U.S. Boxed Warning]: Thyroid supplements are ineffective and potentially toxic for weight reduction. High doses may produce serious or even life-threatening toxic effects particularly when used with some anorectic drugs.**

Geriatric ConsiderationsDesiccated thyroid contains variable amounts of T_3, T_4, and other triiodothyronine compounds which are more likely to cause cardiac signs or symptoms due to fluctuating levels. Should avoid use in the elderly for this reason. Many clinicians consider levothyroxine to be the drug of choice.

Pregnancy Risk FactorA

LactationEnters breast milk/compatible

Adverse Reactions<1%: Abdominal cramps, alopecia, ataxia, cardiac arrhythmia, changes in menstrual cycle, chest pain, constipation, diaphoresis, diarrhea, dyspnea, excessive bone loss with overtreatment (excess thyroid replacement), fever, hand tremor, headache, heat intolerance, increased appetite, insomnia, myalgia, nervousness, palpitation, tachycardia, tremor, vomiting, weight loss

Drug Interactions

Bile Acid Sequestrants: May decrease the absorption of Thyroid Products. *Risk C: Monitor therapy*

CarBAMazepine: May decrease the serum concentration of Thyroid Products. *Risk C: Monitor therapy*

Estrogen Derivatives: May diminish the therapeutic effect of Thyroid Products. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Thyroid Products. Phenytoin may also displace thyroid hormones from protein binding sites. *Risk C: Monitor therapy*

Rifampin: May decrease the serum concentration of Thyroid Products. *Risk C: Monitor therapy*

Sodium Iodide I131: Thyroid Products may diminish the therapeutic effect of Sodium Iodide I131. *Risk X: Avoid combination*

Theophylline Derivatives: Thyroid Products may increase the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Thyroid Products may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, may decrease level/effect of oral hypoglycemics, increase risk of toxicity with TCAs and some anorectics). Assess results of laboratory tests at baseline and regularly during therapy. **Note:** Many drugs may effect thyroid function tests. Monitor for hyperthyroidism (weight loss, nervousness, sweating, tachycardia, insomnia, heat intolerance, palpitations, vomiting, psychosis, fever, seizures, angina, arrhythmias). Caution patients with diabetes to monitor glucose levels closely (may increase need for oral hypoglycemics or insulin). Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsMonitor T_4 and TSH. TSH is the most reliable guide for evaluating adequacy of thyroid replacement dosage. TSH may be elevated during the first few months of thyroid replacement despite patients being clinically euthyroid. In cases where T_4 remains low and TSH is within normal limits, an evaluation of “free” (unbound) T_4 is needed to evaluate further increase in dosage.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Thyroid replacement therapy is generally for life. Take as directed, in the morning before breakfast. Do not take antacids or iron preparations within 8 hours of thyroid medication. Do not change brands and do not discontinue without consulting prescriber. If you have diabetes, monitor glucose levels closely (may increase need for oral hypoglycemics or insulin). Report chest pain, rapid heart rate, palpitations, heat intolerance, excessive sweating, increased nervousness, agitation, or lethargy.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 30 mg, 32.5 mg, 60 mg, 65 mg, 120 mg, 130 mg, 180 mg

Armour® Thyroid: 15 mg, 30 mg, 60 mg, 90 mg, 120 mg, 180 mg, 240 mg, 300 mg

Nature-Throid™: 16.25 mg, 32.5 mg, 65 mg, 130 mg, 195 mg

Westhroid™: 32.5 mg, 65 mg, 130 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Armour Thyroid)

15 mg (30): \$14.99

30 mg (30): \$14.99

60 mg (30): \$14.99

90 mg (30): \$17.99

120 mg (30): \$18.99

180 mg (30): \$23.99

240 mg (30): \$29.99

300 mg (30): \$32.99

Tablets (Nature-Throid)

130 mg (100): \$33.15

Mechanism of Action

The primary active compound is T_3 (triiodothyronine), which may be converted from T_4 (thyroxine) and then circulates throughout the body to influence growth and maturation of various tissues; exact mechanism of action is unknown; however, it is believed the thyroid hormone exerts its many metabolic effects through control of DNA transcription and protein synthesis; involved in normal metabolism, growth, and development; promotes gluconeogenesis, increases utilization and mobilization of glycogen stores and stimulates protein synthesis, increases basal metabolic rate

Pharmacodynamics/Kinetics

Absorption: T_4: 48% to 79%; T_3: 95%; desiccated thyroid contains thyroxine, liothyronine, and iodine (primarily bound)

Metabolism: Thyroxine: Largely converted to liothyronine

Half-life elimination, serum: Liothyronine: 1-2 days; Thyroxine: 6-7 days

Pharmacotherapy Pearls

Equivalent doses: The following statement on relative potency of thyroid products is included in a joint statement by American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE) and The Endocrine Society (TES): For purposes of conversion, levothyroxine sodium (T_4) 100 mcg is usually considered equivalent to desiccated thyroid 60 mg, thyroglobulin 60 mg, or liothyronine sodium (T_3) 25 mcg. However, these are rough guidelines only and do not obviate the careful re-evaluation of a patient when switching thyroid hormone preparations, including a change from one brand of levothyroxine to another. Joint position statement is available at http://www.thyroid.org/professionals/advocacy/04_12_08_thyroxine.html.

Dental Health: Effects on Dental Treatment

No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions

No precautions with vasoconstrictor are necessary if patient is well controlled with thyroid preparations

Mental Health: Effects on Mental Status

May cause nervousness or insomnia

Mental Health: Effects on Psychiatric Treatment

Use to augment antidepressants and treat lithium-induced hypothyroidism

Anesthesia and Critical Care Concerns/Other Considerations

Equivalent doses: The following statement on relative potency of thyroid products is included in a joint statement by American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE) and The Endocrine Society (TES): For purposes of conversion, levothyroxine sodium (T_4) 100 mcg is usually considered equivalent to desiccated thyroid 60 mg, thyroglobulin 60 mg, or liothyronine sodium (T_3) 25 mcg. However, these are rough guidelines only and do not obviate the careful re-evaluation of a patient when switching thyroid hormone preparations, including a change from one brand of levothyroxine to another. Joint position statement is available at http://www.thyroid.org/professionals/advocacy/04_12_08_thyroxine.html.

Index Terms

Desiccated Thyroid; Thyroid Extract; Thyroid USP

References

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Helfand M and Crapo LM, “Monitoring Therapy in Patients Taking Levothyroxine,” *Ann Intern Med*, 1990, 113(6):450-4. [PubMed 2143640]

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Thyrotropin Alfa

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Thyrogen® may be confused with Thyrolar®

Pronunciation(thye roe TROH pin AL fa)

U.S. Brand NamesThyrogen®

Canadian Brand NamesThyrogen®

Pharmacologic CategoryDiagnostic Agent

Use: Labeled IndicationsAs an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing; adjunctive treatment for radioiodine ablation of thyroid tissue remnants after total or near-total thyroidectomy in patients with well-differentiated thyroid cancer without evidence of metastatic disease

Potential clinical uses include: Patients with an undetectable Tg on thyroid hormone suppressive therapy to exclude the diagnosis of residual or recurrent thyroid cancer, patients requiring serum Tg testing and radioiodine imaging who are unwilling to undergo thyroid hormone withdrawal testing and whose treating physician believes that use of a less sensitive test is justified, patients who are either unable to mount an adequate endogenous TSH response to thyroid hormone withdrawal or in whom withdrawal is medically contraindicated, and patients without evidence of metastatic disease to ablate thyroid remnants (in combination with radioiodine [I^{131}]) following near-total thyroidectomy.

Dosing: Adults**Radioiodine imaging or ablation:** I.M.: 0.9 mg, followed 24 hours later by a second 0.9 mg dose

For radioiodine imaging or remnant ablation, radioiodine administration should be given 24 hours following the second thyrotropin injection. Diagnostic scanning should be performed 48 hours after radioiodine administration (72 hours after the second thyrotropin injection). Post-therapy scanning may be delayed (additional days) to allow decline of background activity.

For serum Tg testing, serum Tg should be obtained 72 hours after final injection of thyrotropin.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Diagnostic aid:** Children >16 years: Refer to adult dosing.

Administration: I.M.After reconstitution with 1.2 mL sterile water for injection, 1 mL of the resulting solution (0.9 mg/mL) should be administered into the buttock.

StorageStore intact vials at 2°C to 8°C (36°F to 46°F). If necessary, the reconstituted solution can be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F). Protect from light.

ReconstitutionReconstitute each vial with 1.2 mL of sterile water for injection to a final concentration of 0.9 mg/mL. Each vial should be reconstituted immediately prior to use with diluent provided.

ContraindicationsThere are no contraindications listed within the manufacturer's labeling.

Warnings/Precautions

Concerns related to adverse effects:

- Bovine TSH hypersensitivity: Caution should be exercised when administered to patients who have been previously treated with bovine TSH and, in particular, to those patients who have experienced hypersensitivity reactions to bovine TSH.

- Metastatic disease: Use with caution in patients with extensive metastatic disease. May cause edema and/or hemorrhage at metastatic sites, leading to impingement of vital anatomic structures. Pretreatment with corticosteroids may be considered.

- Renal impairment: Thyrotropin alfa elimination is significantly reduced in dialysis-dependent end-stage renal impairment, leading to prolonged elevation of thyroid-stimulating hormone (TSH) levels.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with known history of heart disease in the presence of significant residual thyroid tissue; thyrotropin-induced hyperthyroidism may lead to serious cardiovascular complications.

- Residual thyroid tissue: Use with caution in patients with significant residual thyroid tissue; will cause significant increases in thyroid hormone levels.

- Underlying illness: Use with caution in patients with serious underlying illness in the presence of significant residual thyroid tissue; thyrotropin-induced hyperthyroidism may lead to serious complications.

Special populations:

- Elderly: Thyrotropin use in elderly (with functioning thyroid tumors) may result in palpitations or cardiac rhythm disorders; arrhythmia has been reported in elderly patients with pre-existing cardiac disease; carefully evaluate risk versus benefit.

- Pediatrics: Safety and efficacy have not been established in children <16 years of age.

Other warnings/precautions:

- Administration: For I.M. use only.
- Considerations in the use of thyrotropin alfa:
  1. There remains a meaningful risk of missing the diagnosis of thyroid cancer or of underestimating the extent of disease when thyrotropin-stimulated Tg testing is performed even in combination with radioiodine imaging.
  2. Thyrotropin Tg levels are generally lower than, and do not correlate with, Tg levels after thyroid hormone withdrawal.
  3. Newly detectable Tg level or a Tg level rising over time after thyrotropin or a high index of suspicion of metastatic disease, even in the setting of a negative or low-stage thyrotropin radioiodine scan, should prompt further evaluation such as thyroid hormone withdrawal to definitively establish the location and extent of thyroid cancer.
  4. Decision to perform a thyrotropin radioiodine scan in conjunction with a thyrotropin serum Tg test and whether or when to withdraw a patient from thyroid hormones are complex. Pertinent factors in this decision include the sensitivity of the Tg assay used, the thyrotropin Tg level obtained, and the index of suspicion of recurrent or persistent local or metastatic disease.
  5. The signs and symptoms of hypothyroidism which accompany thyroid hormone withdrawal are avoided with thyrotropin use.
  6. Clinical experience in thyroid remnant ablation with thyrotropin is limited; long-term outcome data have not been established compared to withholding thyroid hormone.
  7. Thyrotropin studies for thyroid remnant ablation used I^{131} activity of 100 mCi ± 10%; activity of I^{131} used in clinical practice may vary; lower radioiodine doses may not be as effective.

Pregnancy Risk FactorC

Pregnancy Considerations

Animal studies have not been conducted. Effects on the fetus or pregnant woman are unknown.

Lactation

Excretion in breast milk unknown/use caution

Adverse Reactions

>10 %: Gastrointestinal: Nausea (3% to 12%)

1% to 10%:

Central nervous system: Headache (1% to 7%), dizziness (≤3%), fatigue (1% to 3%), insomnia (≤2%)

Endocrine & metabolic: Hypercholesterolemia (≤3%), cholesterol abnormal (≤1%)

Gastrointestinal: Vomiting (1% to 3%), diarrhea (≤1%)

Neuromuscular & skeletal: Paresthesia (≤2%), weakness (≤2%)

Respiratory: Nasopharyngitis (≤1%)

Adverse reactions which may be related to local edema or hemorrhage at metastatic sites: Acute visual loss, enlargement of locally-recurring papillary carcinoma (accompanied by dyspnea, stridor, or dysphonia), hemiplegia, hemiparesis, laryngeal edema with respiratory distress, pain

<1%, postmarketing, and/or case reports: Atrial arrhythmia, flu-like syndrome (arthralgia, chills, fever, myalgia, shivering); hypersensitivity reactions (eg, flushing, pruritus, rash, respiratory difficulty, urticaria); hyperthyroidism, MI, taste loss, thyrotropin alfa antibody formation

Drug InteractionsThere are no known significant interactions.

Test InteractionsThyroglobulin assay may be confounded by thyroglobulin antibodies, possibly leading to misinterpreted or difficult to interpret thyroglobulin levels.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Thyrogen®: 1.1 mg

Generic AvailableNo

Mechanism of ActionThyrotropin alfa, derived from a recombinant DNA source, has the identical amino acid sequence as endogenous human thyroid stimulating hormone (TSH). As a diagnostic tool in conjunction with serum thyroglobulin (Tg) testing, thyrotropin alfa stimulates the secretion of Tg from any remaining thyroid tissues (remnants). Under conditions of successful thyroidectomy and complete ablation, very little serum Tg should be detected under TSH stimulatory conditions; conversely, elevated Tg levels suggest the presence of remnant thyroid tissues. Since the source of TSH is exogenous, stimulation of Tg synthesis can be achieved in euthyroid patients, avoiding the need for thyroid hormone withdrawal.

As an adjunctive agent for radioiodine ablation treatment of thyroid cancer tissue remnants, thyrotropin alfa binds to TSH receptors on these tissues, stimulating the uptake and organification of iodine, including radiolabeled iodine (I^{131}). Cancerous tissue is destroyed via gamma emission from the radioiodine concentrated in these tissues.

Pharmacodynamics/Kinetics

Half-life elimination: 25 ± 10 hours

Time to peak: Median: 10 hours (range: 3-24 hours)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsHuman Thyroid Stimulating Hormone; Recombinant Human Thyrotropin; Rh-TSH; Thyrotropin Alpha; TSH

References

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International Brand NamesThyrogen (AT, DE, DK, NL, SE)

TiaGABine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

TiaGABine may be confused with tiZANidine

Pronunciation(tye AG a been)

U.S. Brand NamesGabitril®

Canadian Brand NamesGabitril®

Pharmacologic CategoryAnticonvulsant, Miscellaneous

Use: Labeled IndicationsAdjunctive therapy in adults and children ≥12 years of age in the treatment of partial seizures

Dosing: Adults**Partial seizures (adjunct):** Oral:

Patients receiving enzyme-inducing AED regimens: 4 mg once daily for 1 week; may increase by 4-8 mg weekly to response or up to 56 mg daily in 2-4 divided doses; usual maintenance: 32-56 mg/day

Patients **not** receiving enzyme-inducing AED regimens: The estimated plasma concentrations of tiagabine in patients not taking enzyme-inducing medications is twice that of patients receiving enzyme-inducing AEDs. Lower doses are required; slower titration may be necessary.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Partial seizures:** Oral:

Patients receiving enzyme-inducing AED regimens: Children 12-18 years: 4 mg once daily for 1 week; may increase to 8 mg daily in 2 divided doses for 1 week; then may increase by 4-8 mg weekly to response or up to 32 mg daily in 2-4 divided doses

Patients **not** receiving enzyme-inducing AED regimens: Refer to adult dosing.

Dietary ConsiderationsTake with food.

ContraindicationsHypersensitivity to tiagabine or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Dermatologic reactions: Severe reactions, including toxic epidermal necrolysis and Stevens-Johnson syndromes, although rarely reported, have resulted in fatalities; drug should be discontinued if there are any signs of hypersensitivity.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

Concurrent drug therapy issues:

- Enzyme-inducing drugs: Experience in patients not receiving enzyme-inducing drugs has been limited; caution should be used in treating any patient who is not receiving one of these medications (decreased dose and slower titration may be required).
- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Unlabeled use: New-onset seizures and status epilepticus have been associated with tiagabine use when taken for unlabeled indications; often these seizures have occurred shortly after the initiation of treatment or shortly after a dosage increase. Seizures have also occurred with very low doses or after several months of therapy. In most cases, patients were using concomitant medications (eg, antidepressants, antipsychotics, stimulants, narcotics). In these instances, the discontinuation of tiagabine, followed by an evaluation for an underlying seizure disorder, is suggested. Use for unapproved indications, however, has not been proven to be safe or effective and is not recommended.

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsNo special recommendations are made for the elderly; dose according to response.
Pregnancy Risk FactorC
LactationEnters breast milk/not recommended
Adverse Reactions

>10%:

Central nervous system: Concentration decreased, dizziness, nervousness, somnolence

Gastrointestinal: Nausea

Neuromuscular & skeletal: Tremor, weakness

1% to 10%:

Cardiovascular: Chest pain, edema, hypertension, palpitation, peripheral edema, syncope, tachycardia, vasodilation

Central nervous system: Agitation, ataxia, chills, confusion, depersonalization, depression, difficulty with memory, euphoria, hallucination, hostility, insomnia, malaise, migraine, paranoid reaction, personality disorder, speech disorder

Dermatologic: Alopecia, bruising, dry skin, pruritus, rash

Gastrointestinal: Abdominal pain, appetite increased, diarrhea, gingivitis, mouth ulceration, stomatitis, vomiting, weight gain/loss

Neuromuscular & skeletal: Abnormal gait, arthralgia, dysarthria, hyper-/hypokinesia, hyper-/hypotonia, myasthenia, myalgia, myoclonus, neck pain, paresthesia, reflexes decreased, stupor, twitching, vertigo

Ocular: Abnormal vision, amblyopia, nystagmus

Otic: Ear pain, hearing impairment, otitis media, tinnitus

Respiratory: Bronchitis, cough, dyspnea, epistaxis, pneumonia

Miscellaneous: Allergic reaction, cyst, diaphoresis, flu-like syndrome, lymphadenopathy

<1% (Limited to important or life-threatening): Abortion, abscess, amenorrhea, anemia, angina, apnea, arthrosis, asthma, blepharitis, blindness, cellulitis, cerebral ischemia, cholycystitis, cholelithiasis, CNS neoplasm, coma, deafness, dehydration, dysphagia, dystonia, electrocardiogram abnormal, encephalopathy, facial hemorrhage, erythrocytes abnormal, fecal incontinence, glossitis, goiter, herpes simplex/zoster, hirsutism, hematuria, hemiplegia, hemoptysis, hepatomegaly, hyperacusis, hypercholesteremia, hyper-/hypoglycemia, hyperlipemia, hyperventilation, hypokalemia, hyponatremia, hypotension, hypothyroidism, impotence, kidney failure, leukopenia, liver function tests abnormal, MI, neoplasm, peripheral vascular disorder, paralysis, photophobia, psychosis, petechia, photosensitivity, seizure (when used for unlabeled uses), sepsis, skin benign neoplasm, skin discoloration, spasm, suicide attempt, taste perversion, thrombocytopenia, thrombophlebitis, urinary retention, urinary urgency, urticaria, visual field defect

Metabolism/Transport Effects**Substrate** of 3A4 (major)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Food reduces the rate but not the extent of absorption.

Herb/Nutraceutical: St John's wort may decrease tiagabine levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersA reduction in seizure frequency is indicative of therapeutic response to tiagabine in patients with partial seizures; complete blood counts, renal function tests, liver function tests, and routine blood chemistry should be monitored periodically during therapy

Reference RangeMaximal plasma level after a 24 mg/dose: 552 ng/mL

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness (seizure activity, force, type, duration), laboratory values, and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, seizure safety precautions, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsA therapeutic range for tiagabine has not been established. Monitor complete blood counts, renal function tests, liver function tests, and routine blood chemistry.

Patient EducationTake exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, disturbed concentration, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea, vomiting, or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Wear identification of epileptic status and medications. Report behavioral or CNS changes, suicidal ideation, or depression; skin rash; muscle cramping, weakness, tremors, changes in gait; vision difficulties; persistent GI distress (cramping, pain, vomiting); chest pain, irregular heartbeat, or palpitations; cough or respiratory difficulty; or worsening of seizure activity or loss of seizure control. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride:

Gabitril®: 2 mg, 4 mg, 12 mg, 16 mg

Generic AvailableNo

ManufacturerCephalon

Pricing: U.S. (www.drugstore.com)

Tablets (Gabitril)

2 mg (30): $149.48

4 mg (30): $137.99

12 mg (30): $161.01

16 mg (30): $233.98

Mechanism of ActionThe exact mechanism by which tiagabine exerts antiseizure activity is not definitively known; however, *in vitro* experiments demonstrate that it enhances the activity of gamma aminobutyric acid (GABA), the major neuroinhibitory transmitter in the nervous system; it is thought that binding to the GABA uptake carrier inhibits the uptake of GABA into presynaptic neurons, allowing an increased amount of GABA to be available to postsynaptic neurons; based on *in vitro* studies, tiagabine does not inhibit the uptake of dopamine, norepinephrine, serotonin, glutamate, or choline

Pharmacodynamics/Kinetics

Absorption: Rapid (45 minutes); prolonged with food

Protein binding: 96%, primarily to albumin and α_1-acid glycoprotein

Metabolism: Hepatic via CYP (primarily 3A4)

Bioavailability: Oral: Absolute: 90%

Half-life elimination: 2-5 hours when administered with enzyme inducers; 7-9 hours when administered without enzyme inducers

Time to peak, plasma: 45 minutes

Excretion: Feces (63%); urine (25%); 2% as unchanged drug; primarily as metabolites

Pharmacotherapy PearlsAnimal studies suggest that tiagabine may bind to retina and uvea; however, no treatment-related ophthalmoscopic changes were seen long-term; periodic monitoring may be considered.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, gingivitis, and mouth ulceration.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index TermsTiagabine Hydrochloride

References

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Leach JP and Brodie MJ, “Tiagabine,” *Lancet*, 1998, 351(9097):203-7. [PubMed 9449883]

Patsalos PN and Sander JW, “Newer Antiepileptic Drugs: Towards an Improved Risk-Benefit Ratio,” *Drug Saf*, 1994, 11(1):37-67. [PubMed 7917080]

Samara EE, Gustavson LE, El-Shourbagy T, et al, “Population Analysis of the Pharmacokinetics of Tiagabine in Patients With Epilepsy,” *Epilepsia*, 1998, 39(8):868-73. [PubMed 9701378]

Uthman BM, Rowan AJ, Ahmann PA, et al, “Tiagabine for Complex Partial Seizures: A Randomized, Add-On, Dose-Response Trial,” *Arch Neurol*, 1998, 55(1):56-62.[PubMed 9443711]

International Brand Names Gabitril (AT, AU, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NO, PL, PT, TW)

Tiaprofenic Acid

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(tye ah PRO fen ik AS id)

Canadian Brand NamesApo-Tiaprofenic®; Dom-Tiaprofenic; Novo-Tiaprofenic; Nu-Tiaprofenic; PMS-Tiaprofenic; Surgam®; Tiaprofenic-200; Tiaprofenic-300

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsRelief of signs and symptoms of rheumatoid arthritis and osteoarthritis (degenerative joint disease)

Dosing: Adults

Rheumatoid arthritis: Oral:

Tablet: Usual initial and maintenance dose: 600 mg/day in 3 divided doses; some patients may do well on 300 mg twice daily; maximum daily dose: 600 mg

Sustained release capsule: Initial and maintenance dose: 2 sustained release capsules of 300 mg once daily

Osteoarthritis: Oral:

Tablet: Usual initial and maintenance dose: 600 mg/day in 2 or 3 divided doses; in rare instances patients may be maintained on 300 mg/day in divided doses; maximum daily dose: 600 mg

Sustained release capsule: Initial and maintenance dose: 2 sustained release capsules of 300 mg once daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo specific dosage adjustment recommended; note caution in renal impairment.

Administration: OralAdminister with food or milk. Capsule should be swallowed whole.

Dietary ConsiderationsShould be taken with food or milk.

StorageStore at 15°C to 30°C (59°F to 86°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to tiaprofenic acid, any component of the formulation, aspirin, or other nonsteroidal anti-inflammatory drugs (NSAIDs); asthma or nasal polyps; active hepatic disease; renal insufficiency (Cl_{cr} <30 mL/minute); active peptic ulcer or active inflammatory disease of gut (diverticulosis, ulcerative colitis, Crohn's disease); pregnancy (3rd trimester)

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid reactions: Fatal asthmatic and anaphylactoid reactions have occurred in patients with “aspirin triad.”
- Cardiovascular events: NSAIDs are associated with an increased risk of adverse cardiovascular events, including MI, stroke, and new onset or worsening of pre-existing hypertension. Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- Cystitis: Severe cases of cystitis (bladder pain, dysuria, urinary frequency, hematuria) have been reported. Avoid use in patients with prior history of urinary symptoms and discontinue at first sign of genitourinary problems.
- Gastrointestinal events: Gastrointestinal bleeding may occur without prior symptoms of gastrointestinal irritation. Use with caution in patients with a history of GI disease (bleeding, ulcers, or previous GI symptoms with NSAID use.

Disease-related concerns:

- Asthma: Do not administer to patients with asthma; severe bronchospasm may occur.
- Autoimmune disease: Patients with autoimmune disorders may be at greater risk of developing aseptic meningitis, as rare adverse reaction associated with some NSAIDs.
- Hepatic impairment: Use with caution in patients with decreased hepatic function.
- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Contraindicated in patients with deteriorating function or severe impairment (Cl_{cr} <30 mL/minute). Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Effective dose: Use lowest effective dose for shortest period possible; bleeding risk has been correlated to dose and duration of therapy.
- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are at a high risk for adverse effects from nonsteroidal anti-inflammatory agents. As much as 60% of elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers, omeprazole, and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol is the only prophylactic agent proven effective. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} 30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high-dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.

Pregnancy Risk FactorNot assigned; contraindicated (per manufacturer)

Pregnancy ConsiderationsAdequate and well-controlled studies have not been conducted in pregnant women. Fetal exposure to NSAIDs late in pregnancy is associated with premature closure of ductus arteriosus. First trimester miscarriages have been reported.

LactationEnters breast milk/not recommended (AAP rates other NSAIDs "compatible")

Adverse Reactions

1% to 10%:

Cardiovascular: Fluid retention, flushing

Central nervous system: Dizziness, headache, drowsiness, depression

Dermatologic: Rash, pruritus, erythema

Endocrine & metabolic: Hyperkalemia (2%)

Gastrointestinal: Dyspepsia (up to 14%), nausea, heartburn, epigastric distress, vomiting, abdominal pain, constipation, flatulence, diarrhea, stomatitis, xerostomia

Hematologic: Decreased hemoglobin/hematocrit (2.8%)

Renal: Increased BUN (up to 12% in elderly)

<1% (Limited to important or life-threatening): Anaphylaxis, angina, angioedema, asthma, bronchospasm, cystitis, disorientation, duodenal ulcer, dysuria, edema, enterocolitis, erythema multiforme, gastric ulcer, gastrointestinal hemorrhage, hepatotoxicity, hypertension, incontinence, increased serum creatinine, interstitial nephritis, intestinal perforation, melena, menstrual irregularities, paresthesia, photosensitivity, renal failure, Stevens-Johnson syndrome, thrombocytopenia, tinnitus, toxic epidermal necrolysis, urticaria, vaginal bleeding, vertigo. Aseptic meningitis, neutropenia, and leukopenia have been associated rarely with NSAIDs.

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Tiaprofenic acid peak serum levels may be decreased if taken with food.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Monitoring ParametersCBC; occult blood loss and periodic liver function tests; monitor response (pain, range of motion, grip strength, mobility, ADL function), inflammation; observe for weight gain, edema; monitor renal function (urine output, serum BUN, and creatinine); observe for bleeding, bruising; evaluate gastrointestinal effects (abdominal pain, bleeding, dyspepsia); mental confusion, disorientation; with long-term therapy, periodic ophthalmic exams

Nursing: Physical Assessment/MonitoringAssess patient for allergic reaction to salicylates or other NSAIDs (see Contraindications). Assess other medications patient may be taking for additive or adverse interactions (see Warnings/Precautions and Drug Interactions). Monitor therapeutic effectiveness, and signs of adverse reactions or overdose (see Adverse Reactions) at beginning of therapy and periodically during long-term therapy. Instruct patient to report dysuria or other urinary problems immediately. Assess knowledge/teach patient appropriate use. Teach patient to monitor for adverse reactions, adverse reactions to report, and appropriate interventions to reduce side effects. **Pregnancy risk factor not assigned** - see Pregnancy Risk Factor; benefits of use should outweigh possible risks. Breast-feeding is not recommended.

Monitoring: Lab TestsCBC, periodic liver function, renal function (serum BUN and creatinine)

Patient EducationIf self-administered, use exactly as directed; do not increase dose or frequency. Adverse reactions can occur with overuse. Consult your prescriber before use if you have hypertension or heart failure. Take with food or milk. While using this medication, do not use alcohol, other prescription or OTC medications containing aspirin or salicylate, or other NSAIDs without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience nausea, vomiting, gastric discomfort (frequent mouth care, small, frequent meals, chewing gum, sucking lozenges may help). GI bleeding, ulceration, or perforation can occur with or without pain. Stop taking medication and report urinary tract/bladder problems, ringing in ears; persistent cramping or stomach pain; unresolved nausea or vomiting; respiratory difficulty or shortness of breath; unusual bruising or bleeding (mouth, urine, stool); skin rash; unusual swelling of extremities; chest pain; or palpitations. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, sustained release: 300 mg

Tablet: 200 mg, 300 mg

Generic AvailableYes
ManufacturerAventis Pharma (Canada)
Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties
Pharmacodynamics/Kinetics

Absorption: Regular release tablet: Rapid

Protein binding: 98%

Metabolism: Minimal (10%) to inactive metabolites

Half-life elimination: 1.7 hours

Time to peak: 30-90 minutes

Excretion: Urine (primarily as unchanged drug)

Pharmacotherapy PearlsNot available in U.S.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause agitation, confusion, and hallucinations (especially in the elderly). May cause dizziness, drowsiness, or depression.
Mental Health: Effects on Psychiatric TreatmentMay decrease the clearance of lithium resulting in elevated serum levels; monitor.
References

Andreassen KH, Eldrup J, Hansen RI, et al, “Tiaprofenic Acid-Induced Cystitis: Three Cases and a Literature Review,” *Scand J Urol Nephrol*, 1999, 33(6):408-10. [PubMed 10636583]

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Catella-Lawson F, Reilly MP, Kapoor SC, et al, “Cyclooxygenase Inhibitors and the Antiplatelet Effects of Aspirin,” *N Engl J Med*, 2001, 345(25):1809-17.[PubMed 11752357]

Surgam® prescribing information, Aventis Pharma Inc, Quebec, Revised 1999.

International Brand NamesApo-Tiapro (PL); Artiflam (BE, LU); Derilate (ES); Doltaque (FR); Fengam (TH); Pain Will Pass (TW); Sufen (TW); Surgam (AU, BE, CH, CZ, DE, FR, GB, GR, HN, HR, HU, IE, LU, MX, NL, PK, PL, PT, SG, TW, ZA); Surgam SR (KP, NZ); Surgamic (ES); Surgamyl (DK, FI, IT); Torpas (VE)

Ticarcillin and Clavulanate Potassium

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(tye kar SIL in & klav yoo LAN ate poe TASS ee um)
U.S. Brand NamesTimentin®
Canadian Brand NamesTimentin®
Pharmacologic CategoryAntibiotic, Penicillin
Use: Labeled IndicationsTreatment of lower respiratory tract, urinary tract, skin and skin structures, bone and joint, gynecologic (endometritis) and intra-abdominal (peritonitis) infections, and septicemia caused by susceptible organisms. Clavulanate expands activity of ticarcillin to include beta-lactamase producing strains of *S. aureus*, *H. influenzae*, *Bacteroides* species, and some other gram-negative bacilli
Dosing: Adults**Note:** Timentin® (ticarcillin/clavulanate) is a combination product; each 3.1 g dosage form contains 3 g ticarcillin disodium and 0.1 g clavulanic acid.

Systemic infections: I.V.: 3.1 g (ticarcillin 3 g plus clavulanic acid 0.1 g) every 4-6 hours (maximum: 24 g of ticarcillin component/day)

Amnionitis, cholangitis, diverticulitis, endometritis, epididymo-orchitis, mastoiditis, orbital cellulitis, peritonitis, pneumonia (aspiration): I.V.: 3.1 g every 6 hours

Liver abscess, parafascial space infections, septic thrombophlebitis: I.V.: 3.1 g every 4 hours

***Pseudomonas*infections:** I.V.: 3.1 g every 4 hours

Urinary tract infections: I.V.: 3.1 g every 6-8 hours

Dosing: ElderlyI.V.: 3.1 g every 4-6 hours; adjust for renal function.
Dosing: Pediatric**Note:** Timentin® (ticarcillin/clavulanate) is a combination product; each 3.1 g dosage form contains 3 g ticarcillin disodium and 0.1 g clavulanic acid.

Systemic infections:

Children <60 kg: 200-300 mg of ticarcillin component/kg/day in divided doses every 4-6 hours

Children ≥60 kg: 3.1 g (ticarcillin 3 g plus clavulanic acid 0.1 g) every 4-6 hours; maximum: 24 g of ticarcillin component/day

Bite wounds (animal): 200 mg of ticarcillin component/kg/day in divided doses

Neutropenic fever: 75 mg of ticarcillin component/kg every 6 hours (maximum: 3.1 g/dose)

Pneumonia (nosocomial): 300 mg of ticarcillin component/kg/day in 4 divided doses (maximum: 18-24 g of ticarcillin component/day)

Dosing: Renal Impairment

Loading dose: I.V.: 3.1 g one dose, followed by maintenance dose based on creatinine clearance:

Cl_{cr} 30-60 mL/minute: Administer 2 g of ticarcillin component every 4 hours or 3.1 g every 8 hours

Cl_{cr} 10-30 mL/minute: Administer 2 g of ticarcillin component every 8 hours or 3.1 g every 12 hours

Cl_{cr} <10 mL/minute: Administer 2 g of ticarcillin component every 12 hours

Cl_{cr} <10 mL/minute with concomitant hepatic dysfunction: 2 g of ticarcillin component every 24 hours

Moderately dialyzable (20% to 50%)

Continuous ambulatory peritoneal dialysis: 3.1 g every 12 hours

Hemodialysis: 2 g of ticarcillin component every 12 hours; supplemented with 3.1 g after each dialysis

Continuous renal replacement therapy (CRRT): Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug levels in relation to target trough (if appropriate). The following are general recommendations only (based on dialysate flow/ultrafiltration rates of 1 L/hour) and should not supersede clinical judgment:

CVVH: 2 g every 6-8 hours

CVVHD/CVVHDF: 3.1 g every 6 hours

Note: Do not administer in intervals exceeding every 8 hours. Clavulanate component is hepatically eliminated; extending the dosing interval beyond 8 hours may result in loss of beta-lactamase inhibition.

Dosing: Hepatic ImpairmentWith concomitant renal dysfunction (Cl_{cr} <10 mL/minute): 2 g of ticarcillin component every 24 hours.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Infuse over 30 minutes.

Some penicillins (eg, carbenicillin, ticarcillin and piperacillin) have been shown to inactivate aminoglycosides *in vitro*. This has been observed to a greater extent with tobramycin and gentamicin, while amikacin has shown greater stability against inactivation. Concurrent use of these agents may pose a risk of reduced antibacterial efficacy *in vivo*, particularly in the setting of profound renal impairment. However, definitive clinical evidence is lacking. If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered.

Administration: I.V. DetailpH: 5.5-7.5

Dietary ConsiderationsSodium content of 1 g: 4.51 mEq; potassium content of 1 g: 0.15 mEq

Storage

Vials: Store intact vials at <24°C (<75°F). Reconstituted solution is stable for 6 hours at room temperature and 72 hours when refrigerated. I.V. infusion in NS or LR is stable for 24 hours at room temperature, 7 days when refrigerated, or 30 days when frozen. I.V. infusion in D_5W solution is stable for 24 hours at room temperature, 3 days when refrigerated, or 7 days when frozen. After freezing, thawed solution is stable for 8 hours at room temperature. Darkening of drug indicates loss of potency of clavulanate potassium.

Premixed solution: Store frozen at ≤-20°C (-4°F). Thawed solution is stable for 24 hours at room temperature or 7 days under refrigeration; do not refreeze.

CompatibilityStable in D_5W, LR, NS, sterile water for injection.

Y-site administration: Compatible: Allopurinol, amifostine, aztreonam, cefepime, clarithromycin, cyclophosphamide, diltiazem, docetaxel, doxorubicin liposome, etoposide, famotidine, filgrastim, fluconazole, fludarabine, foscarnet, gatifloxacin, gemcitabine, granisetron, heparin, insulin (regular), melphalan, meperidine, morphine, ondansetron, perphenazine, propofol, remifentanil, sargramostim, teniposide, theophylline, thiotepa, vinorelbine. **Incompatible:** Alatrofloxacin, amphotericin B cholesteryl sulfate complex. **Variable (consult detailed reference):** Cisatracurium, topotecan, vancomycin.

Compatibility when admixed: Incompatible: Sodium bicarbonate, aminoglycosides.

ContraindicationsHypersensitivity to ticarcillin, clavulanate, any penicillin, or any component of the formulation

Allergy Considerations

- Penicillin Allergy

Warnings/Precautions

Concern related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Serious and occasionally severe or fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy, especially with a history of beta-lactam hypersensitivity, history of sensitivity to multiple allergens, or previous IgE-mediated reactions (eg, anaphylaxis, angioedema, urticaria). Use with caution in asthmatic patients.

- Bleeding disorders: Particularly in patients with renal impairment, bleeding disorders have been observed; discontinue if thrombocytopenia or bleeding occurs.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Heart failure (HF): Use with caution in patients with HF, due to high sodium load.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment recommended.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; high levels, particularly in the presence of renal impairment, may increase risk of seizures.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <3 months of age.

Geriatric ConsiderationsWhen used as empiric therapy or for a documented pseudomonal pneumonia, it is best to combine with an aminoglycoside such as gentamicin or tobramycin. High sodium content may limit use in patients with congestive heart failure. Adjust dose for renal function.

Pregnancy Risk FactorB

Pregnancy ConsiderationsAdverse events were not observed in animal reproduction studies; therefore, ticarcillin/clavulanate is classified as pregnancy category B. Ticarcillin and clavulanate cross the placenta. Human experience with the penicillins during pregnancy has shown no evidence of adverse effects to the fetus. Ticarcillin/clavulanate is approved for the treatment of postpartum gynecologic infections, including endometritis, caused by susceptible organisms.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsSmall amounts of ticarcillin are found in breast milk; however, it is not orally-absorbed. The AAP considers ticarcillin alone to be “usually compatible with breast-feeding.”

Based on available data for ticacillin, ticarcillin/clavulanate is generally considered compatible (low risk to infant) while breast-feeding [human data].

Pregnancy & Lactation, In-Depth

- Ticarcillin and Clavulanate Potassium in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Confusion, drowsiness, fever, headache, Jarisch-Herxheimer reaction, seizure

Dermatologic: Erythema multiforme, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Endocrine & metabolic: Electrolyte imbalance

Gastrointestinal: *Clostridium difficile* colitis, diarrhea, nausea, vomiting

Hematologic: Bleeding, eosinophilia, hemolytic anemia, leukopenia, neutropenia, positive Coombs' reaction, prothrombin time prolonged, thrombocytopenia

Hepatic: Hepatotoxicity, jaundice

Local: Injection site reaction (pain, burning, induration); thrombophlebitis

Neuromuscular & skeletal: Myoclonus

Renal: BUN increased, interstitial nephritis (acute), serum creatinine increased

Miscellaneous: Anaphylaxis, hypersensitivity reactions

Oncology: VesicantNo
Oncology: Emetic PotentialVery low (<10%)
Drug Interactions

Aminoglycosides: Penicillins may decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. *Risk D: Consider therapy modification*

Fusidic Acid: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Methotrexate: Penicillins may decrease the excretion of Methotrexate. *Risk C: Monitor therapy*

Tetracycline Derivatives: May diminish the therapeutic effect of Penicillins. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Uricosuric Agents: May decrease the excretion of Penicillins. *Risk C: Monitor therapy*

Test InteractionsPositive Coombs' test, false-positive urinary proteins

Some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*, leading to a potential underestimation of aminoglycoside serum concentration.

Monitoring ParametersObserve for signs and symptoms of anaphylaxis during first dose.
Monitoring: Lab TestsSerum electrolytes, bleeding time, and periodic tests of renal, hepatic, and hematologic function; perform culture and sensitivity before administering first dose.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed, frozen]: Ticarcillin 3 g and clavulanic acid 0.1 g (100 mL) [contains sodium 4.51 mEq and potassium 0.15 mEq per g]

Injection, powder for reconstitution: Ticarcillin 3 g and clavulanic acid 0.1 g (3.1 g, 31 g) [contains sodium 4.51 mEq and potassium 0.15 mEq per g]

Generic AvailableNo
ManufacturerSmithKline Beecham Pharmaceuticals
Mechanism of ActionInhibits bacterial cell wall synthesis by binding to one or more of the penicillin binding proteins (PBPs); which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.
Pharmacodynamics/Kinetics

Absorption: Ticarcillin: Not absorbed orally

Protein binding: Ticarcillin: ~45%; Clavulanic acid: ~25%

Metabolism: Clavulanic acid: Hepatic

Half-life elimination: Ticarcillin: 1.1 hours;Clavulanic acid: 1.1 hours

Excretion: Ticarcillin: Urine (60% to 70%); Clavulanic acid: Urine (35% to 45% as unchanged drug)

Clearance: Clavulanic acid does not affect clearance of ticarcillin

Related Information

- Antimicrobial Drugs of Choice

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Prolonged use of penicillins may lead to development of oral candidiasis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness or confusion; penicillins reported to cause apprehension, illusions, hallucinations, depersonalization, agitation, insomnia, and encephalopathy

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsTicarcillin and Clavulanic Acid

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International Brand NamesBetabactyl (DE); Claventin (FR); Timenten (AT); Timentin (AE, AU, BE, BF, BH, BJ, BR, CI, CL, CY, CZ, EG, ET, GB, GH, GM, GN, GR, HK, ID, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, OM, PE, PH, QA, SA, SC, SD, SL, SN, SY, TN, TW, TZ, UG, YE, ZA, ZM, ZW)

Ticlopidine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(tye KLOE pi deen)

U.S. Brand NamesTiclid® [DSC]

Canadian Brand NamesAlti-Ticlopidine; Apo-Ticlopidine®; Gen-Ticlopidine; Novo-Ticlopidine; Nu-Ticlopidine; Rhoxal-ticlopidine; Sandoz-Ticlopidine; Ticlid®

Pharmacologic CategoryAntiplatelet Agent

Use: Labeled IndicationsPlatelet aggregation inhibitor that reduces the risk of thrombotic stroke in patients who have had a stroke or stroke precursors. **Note:** Due to its association with life-threatening hematologic disorders, ticlopidine should be reserved for patients who are intolerant to aspirin, or who have failed aspirin therapy. Adjunctive therapy (with aspirin) following successful coronary stent implantation to reduce the incidence of subacute stent thrombosis.

Use: Unlabeled/InvestigationalProtection of aortocoronary bypass grafts, diabetic microangiopathy, ischemic heart disease, prevention of postoperative DVT, reduction of graft loss following renal transplant

Dosing: Adults

Stroke prevention: Oral: 250 mg twice daily

Coronary artery stenting (initiate after successful implantation): Oral: 250 mg twice daily (in combination with antiplatelet doses of aspirin) for up to 30 days

Unstable angina, non-ST-segment elevation myocardial infarction (UA/NSTEMI) undergoing percutaneous coronary intervention (PCI) in patients unable to receive clopidogrel (unlabeled dosing): Initial: 500 mg loading dose given at least 6 hours prior to PCI, followed by 250 mg twice daily (in combination with aspirin 75-325 mg once daily). Duration of therapy dependent upon type of stent implanted during PCI.

Note:*Coronary artery stents:* Duration of ticlopidine (clopidogrel preferred) in combination with aspirin: According to the ACC/AHA/SCAI guidelines, ideally 12 months following drug-eluting stent (DES) placement in patients not at high risk for bleeding; at a minimum, 1, 3, and 6 months for bare metal (BMS), sirolimus-eluting, and paclitaxel-eluting stents, respectively, for uninterrupted therapy (Smith, 2005). The 2008 *Chest* guidelines recommend for patients who undergo PCI and receive a BMS (with ongoing ACS) or a DES (with or without ongoing ACS) that ticlopidine (clopidogrel preferred) be continued for at least 12 months. In patients receiving a BMS without ongoing ACS, ticlopidine (or clopidogrel) may be continued for at least 1 month. In patients receiving a DES, therapy with ticlopidine (or clopidogrel) beyond 12 months may be considered in patients without bleeding or tolerability issues (Becker, 2008). Premature interruption of therapy may result in stent thrombosis with subsequent fatal and nonfatal myocardial infarction.

Dosing: Elderly250 mg twice daily with food; dosage in older patients has not been determined; however, in two large clinical trials, the average age of subjects was 63 and 66 years. A dosage decrease may be necessary if bleeding develops.

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentNo specific guidelines for patients with hepatic impairment; use with caution. Use is contraindicated with severe renal impairment.

Administration: OralAdminister with food.

Dietary ConsiderationsShould be taken with food to reduce stomach upset.

ContraindicationsHypersensitivity to ticlopidine or any component of the formulation; active pathological bleeding such as peptic ulcer disease (PUD) or intracranial hemorrhage; severe liver dysfunction; hematopoietic disorders (neutropenia, thrombocytopenia, a past history of TTP or aplastic anemia)

Allergy Considerations

- Thienopyridine Allergy

Warnings/Precautions

Boxed warnings:

- Hematologic toxicity: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Hematologic toxicity: **[U.S. Boxed Warning]: May cause life-threatening hematologic reactions, including neutropenia, agranulocytosis, thrombotic thrombocytopenia purpura (TTP), and aplastic anemia.** Routine monitoring is required (see Monitoring Parameters). Monitor for signs and symptoms of neutropenia including WBC count. Discontinue if the absolute neutrophil count falls to $<1200/mm^3$ or if the platelet count falls to $<80,000/mm^3$.

Disease-related concerns:

- Bleeding disorders: Use with caution in patients with platelet disorders, bleeding disorders and/or at increased risk for bleeding (eg, PUD, trauma, or surgery).

- Hepatic impairment: Use with caution in patients with mild-to-moderate hepatic impairment. Use is contraindicated with severe hepatic impairment.

- Renal impairment: Use with caution in patients with moderate-to-severe renal impairment (experience is limited); bleeding times may be significantly prolonged and the risk of hematologic adverse events (eg, neutropenia) may be increased.

Concurrent drug therapy issues:

- Anticoagulants and platelet aggregation inhibitors: Use with caution in patients receiving either anticoagulants (eg, heparin, warfarin) or other platelet aggregation inhibitors; bleeding risk is increased.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Coronary artery stents: In patients who have received bare-metal or drug-eluting stents (sirolimus or paclitaxel), premature interruption of antiplatelet therapy may result in stent thrombosis with subsequent fatal and nonfatal myocardial infarction. Ideally, 12 months following drug-eluting stent placement in patients not at high risk for bleeding is preferred; minimum durations of therapy are 1 month, 3 months, and 6 months for bare metal stents, sirolimus-eluting stents (Cypher®), and paclitaxel-eluting stents (Taxus®), respectively.

- Elective surgery: Consider discontinuing 10-14 days before elective surgery (except in patients with cardiac stents that have not completed their full course of dual antiplatelet therapy; patient-specific situations need to be discussed with cardiologist; AHA/ACC/SCAI/ACS/ADA Science Advisory provides recommendations).

Geriatric ConsiderationsBecause of the risk of neutropenia and its relative expense as compared with aspirin, ticlopidine should only be used in patients with a documented intolerance to aspirin.

Pregnancy Risk FactorB

LactationExcretion in breast milk unknown

Adverse ReactionsAs with all drugs which may affect hemostasis, bleeding is associated with ticlopidine. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the use of multiple agents which alter hemostasis and patient susceptibility.

>10%:

Endocrine & metabolic: Total cholesterol increased (increases of ~8% to 10% within 1 month of therapy), triglycerides increased

Gastrointestinal: Diarrhea (13%)

1% to 10%:

Central nervous system: Dizziness (1%)

Dermatologic: Rash (5%), purpura (2%), pruritus (1%)

Gastrointestinal: Nausea (7%), dyspepsia (7%), gastrointestinal pain (4%), vomiting (2%), flatulence (2%), anorexia (1%)

Hematologic: Neutropenia (2%)

Hepatic: Alkaline phosphatase increased (>2 x upper limit of normal; 8%), abnormal liver function test (1%)

<1% (Limited to important or life-threatening): Agranulocytosis, anaphylaxis, angioedema, aplastic anemia, arthropathy, bilirubin increased, bone marrow suppression, conjunctival bleeding, ecchymosis, eosinophilia, epistaxis, erythema multiforme, erythema nodosum, exfoliative dermatitis, gastrointestinal bleeding, headache, hematuria, hemolytic anemia, hepatic necrosis, hepatitis, hyponatremia, intracranial bleeding (rare), jaundice, maculopapular rash, menorrhagia, myositis, nephrotic syndrome, pain, pancytopenia, peptic ulcer, peripheral neuropathy, pneumonitis (allergic), positive ANA, renal failure, sepsis, serum sickness, Stevens-Johnson syndrome, systemic lupus erythematosus, thrombocytopenia (immune), thrombocytosis, thrombotic thrombocytopenic purpura (TTP), tinnitus, urticaria, vasculitis, weakness

Postmarketing and/or case reports: Chronic diarrhea, increase in serum creatinine, bronchiolitis obliterans-organized pneumonia

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2C19 (strong), 2D6 (moderate), 2E1 (weak), 3A4 (weak)

Drug Interactions

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2C19 Substrates: CYP2C19 Inhibitors (Strong) may decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Phenytoin: Ticlopidine may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Theophylline Derivatives: Ticlopidine may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Ticlopidine bioavailability may be increased (20%) if taken with food. High-fat meals increase absorption, antacids decrease absorption.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, chamomile, coleus, cordyceps, dong quai, evening primrose oil, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American), ginseng (Panax), ginseng (Siberian), grape seed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Monitoring ParametersSigns of bleeding; CBC with differential every 2 weeks starting the second week through the third month of treatment; more frequent monitoring is recommended for patients whose absolute neutrophil counts have been consistently declining or are 30% less than baseline values. The peak incidence of TTP occurs between 3-4 weeks, the peak incidence of neutropenia occurs at approximately 4-6 weeks, and the incidence of aplastic anemia peaks after 4-8 weeks of therapy. Few cases have been reported after 3 months of treatment. Liver function tests (alkaline phosphatase and transaminases) should be performed in the first 4 months of therapy if liver dysfunction is suspected.

Nursing: Physical Assessment/MonitoringMonitor effectiveness of therapy (laboratory results) frequently at beginning of treatment and regularly thereafter. Monitor and teach patient bleeding precautions, possible side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelet counts every 2 weeks starting the second week through the third month of treatment; more frequent monitoring is recommended for patients whose absolute neutrophil counts have been consistently declining or are 30% less than baseline values. Liver function tests (alkaline phosphatase and transaminases) should be performed in the first 4 months of therapy if liver dysfunction is suspected.

Patient EducationTake exact dosage prescribed, with food. Do not use aspirin or aspirin-containing medications and OTC medications without consulting prescriber. You may experience easy bleeding or bruising (use soft toothbrush or cotton swabs and frequent mouth care, use electric razor, avoid sharp knives or scissors). Report unusual bleeding or bruising, persistent fever, sore throat, weakness, paleness, changes in neurological status; blood in urine, stool, or vomitus; delayed healing of any wounds; skin rash; yellowing of skin or eyes; changes in color of urine or stool; pain or burning on urination; respiratory difficulty; or skin rash. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, as hydrochloride: 250 mg

Ticlid®: 250 mg [DSC]

Generic AvailableYes
ManufacturerRoche Laboratories Inc
Pricing: U.S. (www.drugstore.com)

Tablets (Ticlid)

250 mg (30): $79.99

Tablets (Ticlopidine HCl)

250 mg (60): $100.99

250 mg (100): $225.98

Mechanism of ActionTiclopidine requires *in vivo* biotransformation to an unidentified active metabolite. This active metabolite irreversibly blocks the P2Y12 component of ADP receptors, which prevents activation of the GPIIb/IIIa receptor complex, thereby reducing platelet aggregation. Platelets blocked by ticlopidine are affected for the remainder of their lifespan.
Pharmacodynamics/Kinetics

Onset of action: ~6 hours

Peak effect: 3-5 days; serum levels do not correlate with clinical antiplatelet activity

Absorption: Well absorbed

Protein binding: Parent drug: 98%; <15% bound to alpha$_1$-acid glycoprotein

Metabolism: Extensively hepatic; has at least 1 active metabolite

Half-life elimination: 13 hours

Time to peak, serum: ~2 hours

Excretion: Urine (60%); feces (23%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported; if a patient is to undergo elective surgery and an antiplatelet effect is not desired, ticlopidine should be discontinued at least 7 days prior to surgery.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine
Cardiovascular ConsiderationsMay be used for secondary prevention with an efficacy at least similar to that of aspirin. Indicated in patients with unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI) who are unable to tolerate aspirin due to hypersensitivity or gastrointestinal disease. It takes time to achieve full antiplatelet effect. The adverse effect profile including neutropenia and thrombotic thrombocytopenia purpura (TTP), along with twice-daily dosing and GI upset, makes ticlopidine a less attractive option than clopidogrel. Neutropenia usually resolves within 1-3 weeks of discontinuation of therapy. TTP, although rare, is life-threatening and requires immediate plasma exchange.

Coronary Artery Stents: The 2005 ACC/AHA/SCAI guidelines for PCI recommends that along with aspirin, ticlopidine (clopidogrel preferred) be continued for at least 1 month after bare-metal stent implantation, for several months after drug-eluting stent implantation (3 months for sirolimus, 6 months for paclitaxel), and ideally for up to 12 months in patients who are not at high risk for bleeding. Clopidogrel is the preferred thienopyridine due to its lower incidence of serious side effects (eg, neutropenia) as compared to ticlopidine.

The 2008 *Chest* guidelines recommend for patients who undergo PCI and receive a BMS (with ongoing ACS) or a DES (with or without ongoing ACS) that clopidogrel (or ticlopidine) be continued for at least 12 months. In patients receiving a BMS without ongoing ACS, clopidogrel (or ticlopidine) may be continued for at least 1 month. In patients receiving a DES, therapy with clopidogrel (ticlopidine) beyond 12 months may be considered in patients without bleeding or tolerability issues (Becker, 2008).

The AHA/ACC/SCAI/ACS/ADA Science Advisory (2007) published recommendations (*Circulation*, February 13, 2007) to prevent premature discontinuation of dual antiplatelet therapy (clopidogrel [or ticlopidine] and aspirin) in patients with coronary artery stents. This advisory panel agreed with the 2004 ACC/AHA guidelines stressing the importance of 12 months of dual antiplatelet therapy after placement of a drug-eluting stent (DES) in patients who are not at high risk of bleeding. The advisory panel included these recommendations. Minor surgery, teeth cleaning, and tooth extraction can usually be performed without increased bleeding on the dual antiplatelet regimen. If increased bleeding is anticipated, then the procedure should be delayed until the antiplatelet regimen is completed. Elective procedures with a significant risk of bleeding should be postponed until the antiplatelet regimen is completed. The advisory panel recommends healthcare providers who perform invasive or surgical procedures contact the patient's cardiologist before discontinuing antiplatelet therapy. For patients with drug-eluting stents who must undergo a procedure that requires discontinuation of thienopyridine therapy, aspirin should be continued if possible and the thienopyridine restarted as soon as possible after the procedure. "Bridging" stent patients with warfarin, other antithrombins, or glycoprotein IIb/IIIa agents is not supported by the Advisory Committee.

For the complete review and additional recommendations available at http://www.acc.org/qualityandscience/clinical/pdfs/Final_Dual_Antiplatelet_Statement_010507.pdf.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe adverse effect profile including neutropenia and thrombotic thrombocytopenia purpura (TTP), along with twice-daily dosing and GI upset, makes ticlopidine a less attractive option than clopidogrel. Neutropenia usually resolves within 1-3 weeks of discontinuation of therapy. TTP, although rare, is life-threatening and requires immediate plasma exchange.

Perioperative Management of Ticlopidine: In patients with coronary stents the risk of stent thrombosis becomes elevated depending on the type of stent deployed (bare metal vs drug-eluting stent) and the time from implantation. According to the American College of Chest Physicians (Becker, 2008), the recommended length of therapy for ticlopidine (clopidogrel preferred) is at least 12 months in patients with ACS who undergo PCI with a bare metal stent (BMS) or drug-eluting stent (DES). In patients receiving a BMS without ongoing ACS, ticlopidine (clopidogrel preferred) may be continued for at least 1 month. Early discontinuation of ticlopidine (or clopidogrel) may result in stent thrombosis leading to nonfatal and fatal myocardial infarction. The perioperative recommendations for clopidogrel are below (Douketis, 2008):

Patients undergoing noncardiac surgery (low risk of cardiac event without coronary stent): Ticlopidine and other antiplatelet agents should be temporarily discontinued 5-10 days prior to surgery and resumed ~24 hours (or the next morning) after the procedure when adequate hemostasis is achieved.

Patients without coronary stent undergoing cardiac surgery (eg, CABG) or noncardiac surgery (high risk of cardiac event): Discontinue ticlopidine at least 5 days and, preferably, 10 days prior to surgery while continuing aspirin up to and beyond the time of surgery. If aspirin is interrupted, it should be reinitiated 6-48 hours after surgery; may resume ticlopidine ~24 hours (or the next morning) after the procedure when adequate hemostasis is achieved.

Patients undergoing cardiac surgery (eg, CABG) or noncardiac surgery (with coronary stent): Based on the risk of stent thrombosis, patients with a BMS who require surgery within 6 weeks of implantation or with a DES who require surgery within 12 months of implantation should continue on both aspirin and ticlopidine (clopidogrel preferred) during the perioperative period.

The AHA/ACC/SCAI/ACS/ADA Science Advisory (2007) published recommendations (*Circulation*, February 13, 2007) to prevent premature discontinuation of dual antiplatelet therapy (clopidogrel and aspirin) in patients with coronary artery stents. The advisory panel agreed with the 2004 ACC/AHA guidelines stressing the importance of 12 months of dual antiplatelet therapy after placement of a drug-eluting stent (DES) in patients who are not at high risk of bleeding. The advisory panel included these recommendations. Minor surgery, teeth cleaning, and tooth extraction can usually be performed without increased bleeding on the dual antiplatelet regimen. If increased bleeding is anticipated, then the procedure should be delayed until the antiplatelet regimen is completed. Elective procedures with a significant risk of bleeding should be postponed until the antiplatelet regimen is completed. The advisory panel recommends healthcare providers who perform invasive or surgical procedures contact the patient's cardiologist before discontinuing antiplatelet therapy. For patients with drug-eluting stents who must undergo a procedure that requires discontinuation of thienopyridine therapy, aspirin should be continued if possible and the thienopyridine restarted as soon as possible after the procedure. "Bridging" stent patients with warfarin, other antithrombins, or glycoprotein IIb/IIIa agents is not supported by the Advisory Committee.

For the complete review and additional recommendations available at
http://www.acc.org/qualityandscience/clinical/pdfs/Final_Dual_Antiplatelet_Statement_010507.pdf

Index TermsTiclopidine Hydrochloride
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International Brand NamesAclotin (PL); Agulan (ID); Anagregal (IT); Antigreg (MY, SG); Aplaket (MY, SG, TH); Apo-Clodin (PL); Cartrilet (ID); Cenpidine (TH); Cisen (CL); Clid (KP); Clotidone (PH); Declot (TW); Desitic (DE); Goclid (ID); Iclopid (PL); Ifapidin (PL); Ipaton (HU); Licodin (TW); Nichistate (TW); Nufaclapide (ID); Panaldine (JP); Piclodin (ID); Tagren (EE, HR, PL); Ticard (TH); Ticlid (AE, AR, AU, BB, BE, BH, BM, BO, BR, BS, BZ, CN, CO, CR, CY, CZ, DO, EC, EG, FR, GB, GR, GT, GY, HK, HN, HU, ID, IL, IQ, IR, JM, JO, KW, LB, LU, LY, MX, MY, NI, NL, NO, OM, PA, PE, PH, PK, PL, PR, PY, QA, SA, SE, SR, SV, SY, TH, TT, TW, UY, VE, YE); Ticlidil (IL); Ticlo (PL); Ticlodix (PT); Ticlodone (GR, IT); Ticlopid (BG); Ticlopidine Poli (PL); Ticlopine (MY); Ticloratio (PL); Ticuring (ID); Tikleen (IN); Tiklid (AT, ES, IT); Tiklyd (DE); Tikpid (PH); Tilodene (AU); Tipidin (HK, MY, SG); Tipidine (TH); Tyklid (IN); Viladil (TH)

Tigecycline

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Pronunciation(tye ge SYE kleen)

U.S. Brand NamesTygacil®

Pharmacologic CategoryAntibiotic, Glycylcycline

Use: Labeled IndicationsTreatment of complicated skin and skin structure infections caused by susceptible organisms, including methicillin-resistant *Staphylococcus aureus* and vancomycin-sensitive *Enterococcus faecalis*; treatment of complicated intra-abdominal infections

Dosing: Adults **Complicated skin/skin structure or intra-abdominal infections:** I.V.:
Initial: 100 mg as a single dose

Maintenance dose: 50 mg every 12 hours

Recommended duration of therapy: Intra-abdominal infections or complicated skin/skin structure infections: 5-14 days.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment No dosage adjustment required in renal impairment or after hemodialysis.

Dosing: Hepatic Impairment
Mild-to-moderate hepatic disease: No dosage adjustment required

Severe hepatic impairment (Child-Pugh class C): Initial dose of 100 mg should be followed with 25 mg every 12 hours

Administration: I.V.Infuse over 30-60 minutes through dedicated line or via Y-site

StorageStore at 15°C to 30°C (59°F to 86°F) prior to reconstitution. Once reconstituted, may be stored at room temperature for up to 24 hours (up to 6 hours in the vial and after further dilution, in the I.V. bag). Alternatively, may be refrigerated for up to 45 hours following immediate transfer of the reconstituted solution into the I.V. bag.

ReconstitutionAdd 5.3 mL NS or D5W to each 50 mg vial. Swirl gently to dissolve. Resulting solution is 10 mg/mL. Transfer immediately to 100 mL I.V. bag for infusion (final concentration should not exceed 1 mg/mL). Reconstituted solution is red-orange.

CompatibilityStable in NS or D_5W.

Y-site administration: Compatible: Amikacin, dobutamine, dopamine, gentamicin, haloperidol, LR, lidocaine, morphine, norephinephrine, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, theophylline, tobramycin. **Incompatible:** Amphotericin B, diazepam.

Contraindications Hypersensitivity to tigecycline or any component of the formulation

Allergy Considerations

- Tetracycline Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Antianabolic effects: May be associated with antianabolic effects observed with the tetracycline class (including increased BUN, azotemia, acidosis, and hyperphosphatemia).
- Pancreatitis: May be associated with pancreatitis due to structural similarities with tetracyclines.
- Photosensitivity: May be associated with photosensitivity due to structural similarities with tetracyclines.
- Pseudotumor cerebri: May be associated with pseudotumor cerebri due to structural similarities with tetracyclines.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.
- Tetracycline allergy: Due to structural similarity with tetracyclines, use with caution in patients with prior hypersensitivity and/or severe adverse reactions associated with tetracycline use.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment may be required with severe impairment.
- Intra-abdominal infections: Use with caution if using as monotherapy for patients with intestinal perforation (in the small sample of available cases, septic shock occurred more frequently than patients treated with imipenem/cilastatin comparator).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children. Permanent discoloration of the teeth may occur if used during tooth development (fetal stage through children up to 8 years of age).

Geriatric ConsiderationsThe manufacturer reports no significant differences in tigecycline's pharmacokinetics in small numbers of healthy older adults 65-75 years of age and >75 years compared to younger adults following a single 100 mg dose. No dosage adjustment is recommended.

Pregnancy Risk FactorD

Pregnancy ConsiderationsBecause adverse effects were observed in animals and because of the potential for permanent tooth discoloration, tigecycline is classified pregnancy category D. Tigecycline frequently causes nausea and vomiting and, therefore, may not be ideal for use in a patient with pregnancy-related nausea.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is not known if tigecycline is found in breast milk. The manufacturer recommends caution if giving tigecycline to a nursing woman. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Tigecycline in Pregnancy & Lactation

Adverse Reactions **Note:** Frequencies relative to placebo are not available; some frequencies are lower than those experienced with comparator drugs.

>10%: Gastrointestinal: Nausea (25% to 30%; severe in 1%), vomiting (20%; severe in 1%), diarrhea (13%)

2% to 10%:

Cardiovascular: Hypertension (5%), peripheral edema (3%), hypotension (2%), phlebitis (2%)

Central nervous system: Fever (7%), headache (6%), dizziness (4%), pain (4%), insomnia (2%)

Dermatologic: Pruritus (3%), rash (2%)

Endocrine & metabolic: Hypoproteinemia (5%), hyperglycemia (2%), hypokalemia (2%)

Gastrointestinal: Abdominal pain (7%), constipation (3%), dyspepsia (3%)

Hematologic: Thrombocythemia (6%), anemia (4%), leukocytosis (4%)

Hepatic: ALT increased (6%), AST increased (4%), alkaline phosphatase increased (4%), amylase increased (3%), bilirubin increased (2%), LDH increased (4%)

Local: Reaction to procedure (9%)

Neuromuscular & skeletal: Weakness (3%)

Renal: BUN increased (2%)

Respiratory: Cough increased (4%), dyspnea (3%), pulmonary physical finding (2%)

Miscellaneous: Abnormal healing (4%), infection (8%), abscess (3%), diaphoresis increased (2%)

<2%, postmarketing, and/or case reports: Abnormal stools, allergic reaction, anorexia, aPTT prolonged, back pain, bradycardia, chills, creatinine increased, dry mouth, eosinophilia, hypocalcemia, hypoglycemia, hyponatremia, injection site edema, injection site inflammation, injection site pain, injection site phlebitis, injection site reaction, INR increased, jaundice, leukorrhea, pancreatitis (acute), PT prolonged, septic shock, tachycardia, taste perversion, thrombocytopenia, thrombophlebitis, vaginal moniliasis, vaginitis, vasodilatation

Drug Interactions

Warfarin: Tigecycline may increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient’s allergy history prior to beginning therapy. Use caution in presence of hepatic impairment or intestinal perforation. Monitor INR when used concomitantly with warfarin. Assess results of therapeutic effectiveness (resolution of infection), and adverse reactions at beginning of and periodically throughout therapy (eg, nausea, vomiting, diarrhea, hypotention, peripheral edema, headache, rash, anemia, dyspnea, opportunistic infection [*C. difficile*], hypersensitivity). Teach patient purpose for use and adverse symptoms to report (refer to Patient Education).

Patient EducationThis medication is only administered intravenously. Report immediately any burning, pain, swelling at infusion site; difficulty breathing or swallowing, chest pain, or chills. Report an gastrointestinal upset (nausea, vomiting, diarrhea or constipation, stomach pain); headache, dizziness, difficulty breathing; increasing sweating, or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber in you are pregnant; this drug may cause fetal abnormalities.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Tygacil®: 50 mg [contains lactose 100 mg]

Generic Available No

Manufacturer

Wyeth

Mechanism of ActionBinds to the 30S ribosomal subunit of susceptible bacteria, inhibiting protein synthesis.

Pharmacodynamics/Kinetics **Note:** Systemic clearance is reduced by 55% and half-life increased by 43% in moderate hepatic impairment.

Distribution: V_d: 7-9 L/kg; extensive tissue distribution

Protein binding: 71% to 89%

Metabolism: Hepatic, via glucuronidation, N-acetylation, and epimerization to several metabolites, each <10% of the dose

Half-life elimination: Single dose: 27 hours; following multiple doses: 42 hours

Excretion: Urine (33%; with 22% as unchanged drug); feces (59%; primarily as unchanged drug)

Pharmacotherapy PearlsGenerally considered bacteriostatic. Tigecycline is a derivative of minocycline (9-t-butylglycylamido minocycline), but is not classified as a tetracycline. It has demonstrated activity against a variety of gram-positive and -negative bacterial pathogens.

Dental Health: Effects on Dental TreatmentKey adverse events(s) related to dental treatment: Tigecycline is structurally similar to tetracycline. Therefore, tigecycline is not recommended for use in pregnancy or in children ≤8 years of age. Permanent discoloration of the teeth may occur if used during tooth development.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or insomnia

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with lithium, SSRIs, or valproic acid may produce additive effects

Index TermsGAR-936

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Zhanel GG, Homenuik K, Nichol K, et al, "The Glycylcyclines: A Comparative Review With the Tetracyclines," *Drugs*, 2004, 64(1):63-88.[PubMed 14723559]

International Brand NamesTygacil (AR, AT, AU, BE, BG, BR, CH, CN, CO, CR, CZ, DE, DK, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IL, IT, MX, MY, NI, NL, NO, PA, PE, PH, PT, RU, SE, SG, SV, TH, TR, TW, VE)

Tiludronate

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Special Alerts

Bisphosphonates: Safety Update Regarding Possible Association With Atrial Fibrillation - November 2008

The Food and Drug Administration (FDA) has been reviewing placebo-controlled trials of the 7 bisphosphonates currently marketed in the US. This review is in response to study results associating an increased incidence of atrial fibrillation (AF) with alendronate or zoledronic acid use in women (65-89 years of age) with osteoporosis.

The FDA reviewed all the submitted data (19,687 bisphosphonate-treated patients and 18,358 placebo-treated patients) from these studies. Overall, the occurrence of AF was rare in each study with an absolute difference in event rates between each of the bisphosphonate and placebo arms of 0-3 per 1000. A zoledronic acid study showed a statistically significant increase in the rate of AF in the active treatment arm. However, no clear association between bisphosphonate use and AF could be established. In this study, AF events were diagnosed more than 30 days after receiving zoledronic acid in 47 of the 50 patients diagnosed with AF. According to the FDA, healthcare providers should not alter their prescribing patterns for bisphosphonates and patients should not stop taking their medication.

The FDA will continue monitoring the safety of bisphosphonates through postmarketing reports and is assessing the need for additional epidemiologic studies.

Further information is available at http://www.fda.gov/cder/drug/early_comm/bisphosphonates_update_200811.htm

Medication Safety Issues

International issues:

Skelid® may be confused with Skaelud® which is a brand name for pyrithione zinc in Denmark

Pronunciation(tye LOO droe nate)

U.S. Brand NamesSkelid®

Pharmacologic CategoryBisphosphonate Derivative

Use: Labeled IndicationsTreatment of Paget's disease of the bone (osteitis deformans) in patients who have a level of serum alkaline phosphatase (SAP) at least twice the upper limit of normal, or who are symptomatic, or who are at risk for future complications of their disease

Dosing: Adults**Paget's disease:** Oral: 400 mg (2 tablets of tiludronic acid) daily for a period of 3 months

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentTiludronate is excreted renally. It is not recommended for use in patients with severe renal impairment (Cl_{cr} <30 mL/minute) and is not removed by dialysis.

Calculations

- Creatinine Clearance: Adults

Administration: OralTake with 6-8 oz of plain water. Should not be taken with beverages containing minerals (eg, mineral water), food, or with other medications (may reduce absorption). Do not take within 2 hours of food, aspirin, indomethacin, or calcium-, magnesium-, or aluminum-containing medications.

Dietary ConsiderationsDo not take within 2 hours of food. Ensure adequate intake of vitamin D and calcium supplements during treatment.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Do not remove tablets from foil strips until they are to be used.

ContraindicationsHypersensitivity to tiludronate, bisphosphonates, or any component of the formulation

Allergy Considerations

- Bisphosphonate Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bone/joint/muscle pain: Infrequently, severe (and occasionally debilitating) bone, joint, and/or muscle pain have been reported during bisphosphonate treatment. The onset of pain ranged from a single day to several months. Symptoms usually resolve upon discontinuation. Some patients experienced recurrence when rechallenged with same drug or another bisphosphonate; avoid use in patients with a history of these symptoms in association with bisphosphonate therapy.

- Gastrointestinal mucosa irritation: May cause irritation to upper gastrointestinal mucosa. Esophagitis, esophageal ulcers, esophageal erosions, and esophageal stricture (rare) have been reported with oral bisphosphonates; risk increases in patients unable to comply with dosing instructions. Use with caution in patients with dysphagia, esophageal disease, gastritis, duodenitis, or ulcers (may worsen underlying condition).

- Osteonecrosis of the jaw: Bisphosphonate therapy has been associated with osteonecrosis, primarily of the jaw; this has been observed mostly in cancer patients, but also in patients with postmenopausal osteoporosis and other diagnoses. Risk factors include a diagnosis of cancer, with concomitant chemotherapy, radiotherapy, or corticosteroids; anemia, coagulopathy, infection, or pre-existing dental disease. Symptoms included nonhealing extraction socket or an exposed jawbone. There are no data addressing whether discontinuation of therapy reduces the risk of developing osteonecrosis; however, as a precautionary measure, dental exams and preventative dentistry should be performed prior to placing patients with risk factors on chronic bisphosphonate therapy. Invasive dental procedures should be avoided during treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with mild-to-moderate renal impairment (not recommended in patients with a Cl_{cr} <30 mL/minute).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo dose adjustment necessary.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic and nonteratogenic embryo/fetal effects have been reported in animal studies. There are no adequate and well-controlled studies in pregnant women. Bisphosphonates are incorporated into the bone matrix and gradually released over time. Theoretically, there may be a risk of fetal harm when pregnancy follows the completion of therapy. Based on limited case reports with pamidronate, serum calcium levels in the newborn may be altered if bisphosphonates are administered during pregnancy.
LactationExcretion in breast milk unknown/use caution
Adverse Reactions

1% to 10%:

Cardiovascular: Chest pain (3%), edema (3%), flushing, hypertension, syncope

Central nervous system: Anxiety, fatigue, insomnia, nervousness, somnolence, vertigo

Dermatologic: Rash (3%), skin disorder (3%), pruritus

Endocrine & metabolic: Hyperparathyroidism (3%)

Gastrointestinal: Nausea (9%), diarrhea (9%), dyspepsia (5%), vomiting (4%), flatulence (3%), tooth disorder (3%), abdominal pain, anorexia, constipation, gastritis, xerostomia

Genitourinary: Urinary tract infection

Neuromuscular & skeletal: Arthrosis (3%), paresthesia (4%), fractures, muscle spasm, weakness

Ocular: Cataract (3%), conjunctivitis (3%), glaucoma (3%)

Respiratory: Rhinitis (5%), sinusitis (5%), pharyngitis (3%), bronchitis

Miscellaneous: Accidental injury (4%), infection (3%), diaphoresis

<1%, postmarketing, and/or case reports: Musculoskeletal pain (sometimes severe and/or incapacitating), osteonecrosis (primarily of the jaw), Stevens-Johnson syndrome

Drug Interactions

Aminoglycosides: May enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Bisphosphonate Derivatives. Antacids containing aluminum, calcium, or magnesium are of specific concern. **Exceptions:** Magaldrate; Sodium Bicarbonate. *Risk D: Consider therapy modification*

Aspirin: May decrease the serum concentration of Tiludronate. *Risk C: Monitor therapy*

Calcium Salts: May decrease the absorption of Bisphosphonate Derivatives. *Risk D: Consider therapy modification*

Indomethacin: May increase the bioavailability of Tiludronate. *Risk C: Monitor therapy*

Iron Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral iron salts are of concern. **Exceptions:** Ferric Gluconate; Iron Dextran Complex; Iron Sucrose. *Risk D: Consider therapy modification*

Magnesium Salts: May decrease the absorption of Bisphosphonate Derivatives. Only oral magnesium salts are of concern. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Phosphate Supplements: Bisphosphonate Derivatives may enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: In single-dose studies, the bioavailability of tiludronate was reduced by 90% when an oral dose was administered with, or 2 hours after, a standard breakfast compared to the same dose administered after an overnight fast and 4 hours before a standard breakfast.
Test InteractionsBisphosphonates may interfere with diagnostic imaging agents such as technetium-99m-diphosphonate in bone scans.

Nursing: Physical Assessment/MonitoringAssess history for any previous adverse response to bisphosphonates. Use caution with renal impairment. Patients at risk for osteonecrosis (eg, chemotherapy, corticosteroids, poor oral hygiene) should have dental exams and necessary preventive dentistry should be done before beginning bisphosphonate therapy. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions. Teach patient appropriate use and administration of medication (eg, timing with food, supplements, and other medications), lifestyle and dietary changes that will have a beneficial impact on Paget's disease, possible side effects, interventions to reduce side effects, and adverse reactions to report.

Monitoring: Lab TestsSerum calcium, alkaline phosphatase

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy unless approved by prescriber. In order to be effective, this medication must be taken with a full glass of water (6-8 oz) at least 2 hours before or 2 hours after food. Do not take aspirin, antacids, or vitamin-mineral supplements containing calcium, magnesium, or aluminum within 2 hours of this medication. Do not remove medication from foil strip until ready to be used. Consult prescriber to determine recommended lifestyle changes (eg, decreased smoking, decreased alcohol intake, dietary supplements). Certain dental procedures should be avoided if possible while you are taking this medication; consult prescriber. Notify prescriber at once if experiencing any difficulty swallowing, pain when swallowing, or severe or persistent heartburn. You may experience mild/temporary skin rash, abdominal pain, or constipation (report if persistent). Report persistent muscle or bone pain; leg cramps; chest pain, palpitations, or swollen extremities; disturbed vision; ringing in the ears; unusual weakness; or significantly increased perspiration. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, tiludronic acid:

Skelid®: 200 mg [equivalent to 240 mg tiludronate disodium]

Generic AvailableNo

ManufacturerSanofi-Aventis Pharmaceuticals

Mechanism of ActionInhibition of normal and abnormal bone resorption. Inhibits osteoclasts through at least two mechanisms: disruption of the cytoskeletal ring structure, possibly by inhibition of protein-tyrosine-phosphatase, thus leading to the detachment of osteoclasts from the bone surface area and the inhibition of the osteoclast proton pump.

Pharmacodynamics/Kinetics

Onset of action: Delayed, may require several weeks

Absorption: Rapid

Distribution: Widely to bone and soft tissue

Protein binding: ~90%, primarily to albumin

Metabolism: Little, if any

Bioavailability: ~6% (range: 2% to 11%); reduced by 90% when given with food

Half-life elimination: Healthy volunteers: Single dose: 50 hours; Cl_{cr} 11-18 mL/minute: 205 hours; Pagetic patients: Repeated dosing: 150 hours

Time to peak, plasma: Within 2 hours

Excretion: Urine (~60%, as tiludronic acid within 13 days)

Dental Health Professional ConsiderationsThere is no data on the incidence of ONJ associated with use of tiludronate. A report by the Council of Scientific Affairs of the American Dental Association (accessed at: http://www.ada.org/prof/resources/topics/osteonecrosis.asp) as of July 2006 gave an estimated incidence of 0.7 cases for every 100,000 person-years of exposure to alendronate (Fosamax®). This translates to one case for every 142,857 person-years exposure. This figure from the ADA report was based on information received from Merck & Co citing 170 worldwide cases for alendronate (Fosamax®). In addition, Procter & Gamble Pharmaceuticals has cited 20 cases for risedronate (Actonel®) and Roche Laboratories has cited one case for ibandronate (Boniva®).

Consumer Reports On Health stated that the risk of jaw bone osteoporosis due to alendronate (Fosamax®), risedronate (Actonel®), or ibandronate (Boniva®) taken to prevent osteoporosis is very low and is estimated to be one out of every 20,000 users. That report mentioned that tooth extraction or implants increase the risk of developing osteonecrosis in patients taking any of these drugs for osteoporosis. The report also recommended that patients should stop taking any of these oral drugs 1-2 months before and after such dental treatment. No evidence was presented to support this statement.

In terms of length of exposure to oral bisphosphonates prior to onset of ONJ, data from large population studies or controlled studies is lacking. A report by Marx et al, observed that of three cases of ONJ associated with Fosamax® exposure, one patient had been taking 10 mg/day by mouth for 6 years and the other two patients 10 mg/day by mouth for 3 and 2 years respectively. In contrast, they observed that in cancer patients receiving intravenous bisphosphonates, the time period between the first doses of the bisphosphonate to first recognition of exposed bone either by the patients or by the clinician, was 9.4 months for zoledronate (Zometa®), 14.3 months for pamidronate (Aredia®), and 12.1 months for pamidronate then to zoledronate.

Dental Health: Effects on Dental TreatmentOsteonecrosis of the jaw (ONJ), generally associated with local infection and/or tooth extraction and often with delayed healing, has been reported in patients taking bisphosphonates. Symptoms included nonhealing extraction socket or an exposed jawbone. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates. However, some have occurred in patients with postmenopausal osteoporosis taking oral bisphosphonates. Dental surgery may exacerbate ONJ. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Patients who develop ONJ while on bisphosphonate therapy should receive care by an oral surgeon. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, anxiety, or nervousness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsTiludronate Disodium

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International Brand NamesSkelid (AT, AU, BE, CH, DE, ES, FI, FR, GB, HN, HU, LU, NL, SE)

Timolol

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Timolol may be confused with atenolol, Tylenol®

Timoptic® may be confused with Betoptic® S, Talacen®, Viroptic®

Bottle cap color change:

Timoptic®: Both the 0.25% and 0.5% strengths are now packaged in bottles with yellow caps; previously, the color of the cap on the product corresponded to different strengths.

International issues:

Betimol® may be confused with Betanol® which is a brand name for metipranolol in Monaco

Pronunciation(TIM oh lol)

U.S. Brand NamesBetimol®; Istalol®; Timolol GFS; Timoptic-XE®; Timoptic®; Timoptic® in OcuDose®

Canadian Brand NamesAlti-Timolol; Apo-Timol®; Apo-Timop®; Gen-Timolol; Nu-Timolol; Phoxal-timolol; PMS-Timolol; Sandoz-Timolol; Tim-AK; Timoptic-XE®; Timoptic®

Pharmacologic CategoryBeta Blocker, Nonselective; Ophthalmic Agent, Antiglaucoma

Use: Labeled Indications

Ophthalmic: Treatment of elevated intraocular pressure such as glaucoma or ocular hypertension

Oral: Treatment of hypertension and angina; to reduce mortality following myocardial infarction; prophylaxis of migraine

Dosing: Adults

Glaucoma: Ophthalmic:

Solution: Initial: 0.25% solution, instill 1 drop twice daily into affected eye(s); increase to 0.5% solution if response not adequate; decrease to 1 drop/day if controlled; do not exceed 1 drop twice daily of 0.5% solution.

Istalol®: Instill 1 drop (0.5% solution) once daily in the morning.

Gel-forming solution (Timolol GFS, Timoptic-XE®): Instill 1 drop (either 0.25% or 0.5%) once daily

Hypertension: Oral: Initial: 10 mg twice daily, increase gradually every 7 days, usual dosage: 20-40 mg/day in 2 divided doses; maximum: 60 mg/day.

Prevention of myocardial infarction: Oral: 10 mg twice daily initiated within 1-4 weeks after infarction.

Migraine prophylaxis: Oral: Initial: 10 mg twice daily, increase to maximum of 30 mg/day.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren: Ophthalmic: Refer to adult dosing.

Administration: OtherOphthalmic: Administer other topically-applied ophthalmic medications at least 10 minutes before Timoptic-XE®; wash hands before use; invert closed bottle and shake once before use; remove cap carefully so that tip does not touch anything; hold bottle between thumb and index finger; use index finger of other hand to pull down the lower eyelid to form a pocket for the eye drop and tilt head back; place the dispenser tip close to the eye and gently squeeze the bottle to administer 1 drop; remove pressure after a single drop has been released; **do not allow the dispenser tip to touch the eye**; replace cap and store bottle in an upright position in a clean area; do **not** enlarge hole of dispenser; do **not** wash tip with water, soap, or any other cleaner. Some ophthalmic solutions contain benzalkonium chloride; wait at least 10 minutes after instilling solution before inserting soft contact lenses.

Dietary ConsiderationsOral product should be administered with food at the same time each day.

StorageOphthalmic drops: Store at room temperature; do not freeze. Protect from light.

Timolol GFS: Store at 2°C to 25°C (36°F to 77°F). Protect from light.

Timoptic® in OcuDose®: Store in the protective foil wrap and use within 1 month after opening foil package.

ContraindicationsHypersensitivity to timolol or any component of the formulation; sinus bradycardia; sinus node dysfunction; heart block greater than first degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; uncompensated cardiac failure;

bronchospastic disease; pregnancy (2nd and 3rd trimesters)

Warnings/Precautions

Boxed warnings:

- Abrupt withdrawal: See “Other warnings/precautions” below.

Concerns related to adverse events:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.

Disease-related concerns:

- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.
- Conduction abnormality: Consider pre-existing conditions such as sick sinus syndrome before initiating.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.
- Heart failure: Use with caution in patients with compensated heart failure and monitor for a worsening of the condition.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; can worsen.
- Peripheral vascular disease (PVD): Use with caution in patients with PVD (including Raynaud's).
- Pheochromocytoma (untreated): Adequate alpha-blockade is required prior to use of any beta-blocker.
- Psychiatric disease: Use with caution in patients with a history of psychiatric illness; may cause or exacerbate CNS depression.
- Renal impairment: Use with caution in patients with severe renal impairment; marked hypotension can occur in patients maintained on hemodialysis.

Concurrent drug therapy issues:

- Anesthetic agents: Use with caution in patients receiving anesthetic agents which decrease myocardial function.
- Calcium channel blockers: Use with caution in patients on concurrent verapamil or diltiazem; bradycardia or heart block can occur.

Special populations:

- Contact lens wearers: Some product do contain benzalkonium chloride which may be absorbed by soft contact lenses; remove lens prior to administration and wait 15 minutes before reinserting.

Dosage form specific issues:

- Ophthalmic: Systemic absorption and adverse effects may occur, including bradycardia and/or hypotension. Should not be used alone in angle-closure glaucoma (has no effect on pupillary constriction). Multidose vials have been associated with development of bacterial keratitis; avoid contamination.

Other warnings/precautions:

- Abrupt withdrawal: **[U.S. Boxed Warning]: Beta-blocker therapy should not be withdrawn abruptly (particularly in patients with CAD), but gradually tapered to avoid acute tachycardia, hypertension, and/or ischemia.**

Geriatric ConsiderationsSince bioavailability increased in about twofold in elderly patients, geriatrics may require lower maintenance doses. Also, as serum and tissue concentrations increase beta$_1$ selectivity diminishes. Beta-adrenergic blockade may result in less hemodynamic response than seen in younger adults due to alterations in the beta-adrenergic autonomic system. Studies indicate that despite decreased sensitivity to the chronotropic effects of beta-blockade with age, there appears to be an increased myocardial sensitivity to the negative inotropic effect during stress (ie, exercise). Controlled trials have shown the overall response rate for propranolol to be only 20% to 50% in elderly populations. Therefore, all beta-adrenergic blocking drugs may result in a decreased response as compared to younger adults. Due to propranolol's CNS penetration and nonselective action, it may not be the beta-blocker of choice for use in elderly.

Pregnancy Risk FactorC (manufacturer); D (2nd and 3rd trimesters - expert analysis)

Pregnancy ConsiderationsTimolol was shown to cross the placenta in an *in vitro* perfusion study. Beta-blockers have been associated with bradycardia, hypotension, hypoglycemia, and intrauterine growth rate (IUGR); IUGR is probably related to maternal hypertension. Available evidence suggests beta-blockers are generally safe during pregnancy (JNC 7). Cases of neonatal hypoglycemia have been reported following maternal use of beta-blockers at parturition or during breast-feeding. Bradycardia and arrhythmia have been reported in an infant following ophthalmic administration of timolol during pregnancy.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Breast-Feeding ConsiderationsTimolol is excreted in breast milk following oral and ophthalmic administration, and is considered compatible by the AAP. It is recommended that the infant be monitored for signs or symptoms of beta-blockade (hypotension, bradycardia, etc) with long-term use.

Adverse Reactions

Ophthalmic:

>10%: Ocular: Burning, stinging

1% to 10%:

Cardiovascular: Hypertension

Central nervous system: Headache

Ocular: Blepharitis, blurred vision, cataract, conjunctival injection, conjunctivitis, foreign body sensation, hyperemia, itching, tearing, visual acuity decreased

Miscellaneous: Infection

Systemic:

1% to 10%:

Cardiovascular: Bradycardia

Central nervous system: Fatigue, dizziness

Respiratory: Dyspnea

Frequency not defined (reported with any dosage form):

Cardiovascular: Angina pectoris, arrhythmia, bradycardia, cardiac arrest, cardiac failure, cerebral ischemia, cerebral vascular accident, edema, heart block, hypotension, palpitation, Raynaud's phenomenon

Central nervous system: Anxiety, confusion, depression, disorientation, dizziness, hallucinations, insomnia, memory loss, nervousness, nightmares, somnolence

Dermatologic: Alopecia, angioedema, pseudopemphigoid, psoriasiform rash, psoriasis exacerbation, rash, urticaria

Endocrine & metabolic: Hypoglycemia masked, libido decreased

Gastrointestinal: Anorexia, diarrhea, dyspepsia, nausea, xerostomia

Genitourinary: Impotence, retoperitoneal fibrosis

Hematologic: Claudication

Neuromuscular & skeletal: Myasthenia gravis exacerbation, paresthesia

Ocular: Corneal sensitivity decreased, cystoid macular edema, diplopia, dry eyes, keratitis, ocular discharge, ocular pain, ptosis, refractive changes, visual disturbances

Otic: Tinnitus

Respiratory: Bronchospasm, cough, dyspnea, nasal congestion, pulmonary edema, respiratory failure

Miscellaneous: Allergic reactions, cold hands/feet, Peyronie's disease, systemic lupus erythematosus

Metabolism/Transport Effects **Substrate** of CYP2D6 (major); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure, apical and radial pulses, fluid I & O, daily weight, respirations, mental status, and circulation in extremities before and during therapy; monitor for systemic effect of beta-blockade even when administering ophthalmic product

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness (according to purpose of therapy) and adverse reactions at beginning of therapy and regularly with long-term therapy. Monitor blood pressure periodically. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationOral: Take exact dose prescribed; do not increase, decrease, or discontinue dosage without consulting prescriber. Take at the same time each day. If you have diabetes, monitor serum glucose closely. May cause postural hypotension (use caution when rising from sitting or lying position or climbing stairs); dizziness, drowsiness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); decreased sexual ability (reversible); or nausea or vomiting (small frequent meals or frequent mouth care may help). Report swelling of extremities, respiratory difficulty, or new cough; weight gain (>3 lb/week); unresolved diarrhea or vomiting; or cold blue extremities. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Ophthalmic: For ophthalmic use only. Apply prescribed amount as often as directed. Wash hands before using. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Tilt head back and look upward. Gently pull down lower lid and put drop(s) inside lower eyelid at inner corner. Close eye and roll eyeball in all directions. Do not blink for $^1/_2$ minute. Apply gentle pressure to inner corner of eye for 30 seconds. Wipe away excess from skin around eye. Do not use any other eye preparation for at least 10 minutes. Do not share medication with anyone else. Temporary stinging or blurred vision may occur. If using Istalol®, remove contact lenses prior to administration. Lenses may be reinserted 15 minutes following administration. Immediately report any adverse cardiac or CNS effects (usually signifies overdose). Report persistent eye pain, redness, burning, watering, dryness, double vision, puffiness around eye, vision changes, other adverse eye response, worsening of condition or lack of improvement.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Note: Unless otherwise specified, strength expressed as base.

Gel-forming solution, ophthalmic, as maleate:

Timolol GFS: 0.25% (2.5 mL, 5 mL); 0.5% (2.5 mL, 5 mL)

Timoptic-XE®: 0.25% (5 mL); 0.5% (5 mL)

Solution, ophthalmic, as hemihydrate:

Betimol®: 0.25% (5 mL, 10 mL [DSC], 15 mL [DSC]); 0.5% (5 mL, 10 mL, 15 mL) [contains benzalkonium chloride]

Solution, ophthalmic, as maleate: 0.25% (5 mL, 10 mL, 15 mL); 0.5% (5 mL, 10 mL, 15 mL)

Istalol®: 0.5% (10 mL) [contains benzalkonium chloride and potassium sorbate]

Timoptic®: 0.25% (5 mL); 0.5% (5 mL, 10 mL) [contains benzalkonium chloride]

Solution, ophthalmic, as maleate [preservative free]:

Timoptic® in OcuDose®: 0.25% (0.2 mL); 0.5% (0.2 mL)

Tablet, as maleate: 5 mg, 10 mg, 20 mg [strength expressed as salt]

Generic AvailableYes: Excludes hemihydrate ophthalmic solutions. gel-forming ophthalmic solutions, and preservative free maleate ophthalmic solutions

Pricing: U.S. (www.drugstore.com)

Solution (Betimol)

0.25% (5): $38.28

0.25% (15): $93.56

0.5% (5): $47.99

0.5% (10): $80.86

0.5% (15): $115.01

Solution (Istalol)

0.5% (5): $99.92

Solution (Timolol Maleate)

0.25% (5): $10.99

0.25% (10): $14.99

0.25% (15): $17.97

0.5% (5): $12.99

0.5% (10): $14.99

0.5% (15): $18.99

Solution (Timoptic)

0.5% (5): $28.99

0.5% (10): $44.99

Solution (Timoptic Ocudose)

0.25% (60): $96.99

0.5% (60): $116.99

Solution get-forming (Timolol Maleate)

0.25% (5): $32.99

0.5% (2.5): $25.99

0.5% (5): $33.99

Solution get-forming (Timoptic-XE)

0.25% (5): $34.99

0.5% (5): $37.99

Tablets (Timolol Maleate)

5 mg (60): $22.99

10 mg (60): $25.99

20 mg (60): $41.60

Mechanism of ActionBlocks both beta$_1$- and beta$_2$-adrenergic receptors, reduces intraocular pressure by reducing aqueous humor production or possibly outflow; reduces blood pressure by blocking adrenergic receptors and decreasing sympathetic outflow, produces a negative chronotropic and inotropic activity through an unknown mechanism

Pharmacodynamics/Kinetics

Onset of action:

Hypotensive: Oral: 15-45 minutes

Peak effect: 0.5-2.5 hours

Intraocular pressure reduction: Ophthalmic: 30 minutes

Peak effect: 1-2 hours

Duration: ~4 hours; Ophthalmic: Intraocular: 24 hours

Protein binding: 60%

Metabolism: Extensively hepatic; extensive first-pass effect

Half-life elimination: 2-2.7 hours; prolonged with renal impairment

Excretion: Urine (15% to 20% as unchanged drug)

Related Information

- Antiarrhythmic Drugs
- Beta-Blockers
- Glaucoma Drug Therapy

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Timolol is a nonselective beta-blocker and may enhance the pressor response to epinephrine, resulting in hypertension and bradycardia. Many nonsteroidal anti-inflammatory drugs, such as ibuprofen and indomethacin, can reduce the hypotensive effect of beta-blockers after 3 or more weeks of therapy with the NSAID. Short-term NSAID use (ie, 3 days) requires no special precautions in patients taking beta-blockers.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsEpinephrine has interacted with nonselective beta-blockers such as propranolol to result in initial hypertensive episode followed by bradycardia. Timolol is also a nonselective beta-blocker. Timolol is available as an eye drop and oral dose form. When administered as an eye drop, the significance of a potential systemic interaction with epinephrine is unknown. However, it is suggested that cautionary procedures be used, particularly if vasoconstrictor is used immediately following an ophthalmic dose of timolol taken by the patient. If patients are taking the oral form of timolol, then the significance of a potential systemic interaction is well known and cautionary use of epinephrine is advised.

Mental Health: Effects on Mental StatusMay cause dizziness or fatigue; may rarely cause anxiety, depression, or hallucinations

Mental Health: Effects on Psychiatric TreatmentBarbiturates and carbamazepine may decrease the effects of beta-blockers

Cardiovascular ConsiderationsIt is important to recognize that timolol eye drops may have systemic effects, particularly when patients are also on oral beta-blocker therapy or therapy with other negative chronotropic agents.

Atrial Fibrillation: Beta-blocker therapy provides effective rate control in patients with atrial fibrillation.

Chronic Stable Angina: Beta-blockers are effective in the treatment of chronic stable angina as monotherapy or when combined with nitrates and/or calcium channel blockers. In patients with severe intractable angina requiring negative cardiac chronotropic medications, pacemaker placement has been carried out to maintain heart rate in the setting of large doses of beta-blockers and/or calcium channel blockers. Beta-blockers are ineffective in the treatment of pure vasospastic (Prinzmetal) angina.

Hypertension: Beta-blocker therapy in the treatment of hypertension has been associated with improved cardiovascular outcomes. According to the 2003 JNC-VII guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Beta-blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for a beta-blocker include patients with heart failure, postmyocardial infarction, high coronary disease risk, or diabetes. In type 2 diabetic patients, a UK Prospective Diabetes Study Group (UKPDS) trial showed that beta-blocker therapy (atenolol) was as effective as an ACE inhibitor in reducing cardiovascular events and that the benefits of therapy were related more to the degree of antihypertensive efficacy rather than the class of drug used.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

ST-Segment Elevation Myocardial Infarction (STEMI): Beta-blockers, without intrinsic sympathomimetic activity (ISA), have been shown to decrease morbidity and mortality when initiated in the acute treatment of STEMI and continued long-term. Oral beta-blockade should be initiated promptly in patients without contraindications (eg, signs of heart failure, evidence of a low output state, risk of cardiogenic shock, or other beta-blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade may be considered and given promptly if the patient is experiencing concomitant hypertension or a tachyarrhythmia (Class IIa recommendation).

Unstable Angina/Non-ST-Segment Elevation MI (UA/NSTEMI): In the treatment of UA/NSTEMI, oral beta-blockade should be initiated within the first 24 hours in patients without contraindications (eg, signs of heart failure, evidence of a low output state, risk of cardiogenic shock, or other beta-blocker contraindications) (Class I recommendation). Use of intravenous beta-blockade should only be considered if the patient is experiencing concomitant hypertension upon presentation (Class IIa recommendation).

Withdrawal: Beta-blocker therapy should not be withdrawn abruptly, but gradually tapered to avoid acute tachycardia and hypertension.

Anesthesia and Critical Care Concerns/Other Considerations

Surgery: Based on available evidence, beta-blockers should be started days to weeks before elective surgery in selected patients when possible and titrated to a heart rate <65 beats per minute. Additional data suggest that long acting beta-blockers may be superior to short acting ones (Redelmeier, 2005). The ACC/AHA 2007 guidelines update on perioperative cardiovascular evaluation and care for noncardiac surgery recommend beta-blockers be continued in patients undergoing surgery who are receiving beta-blockers to treat angina, symptomatic arrhythmias, hypertension, or other ACC/AHA Class I guideline indications (Class I recommendation). The guidelines also recommend that beta-blockers be given to patients undergoing vascular surgery who have myocardial ischemia demonstrated during preoperative testing (Class I recommendation).

The guidelines also state that beta-blockers are probably recommended in patients undergoing intermediate risk (eg, carotid endarterectomy, prostate surgery) or vascular surgery in whom preoperative assessment identifies coronary heart disease or high cardiac risk (Class IIa recommendation). High cardiac risk is defined as having >1 of the following clinical risk factors: History of ischemic heart disease, compensated or prior heart failure, cerebrovascular disease, diabetes mellitus, or renal insufficiency. The use of beta-blockers is uncertain in patients undergoing intermediate risk or vascular surgery with ≤1 clinical risk factor (Class IIb recommendation).

The majority of published trials suggest a benefit of perioperative beta-blocker use during noncardiac surgery especially in high-risk patients; however, more recent clinical trials have not shown a benefit to perioperative beta-blockade for noncardiac surgery (Juul, 2006; Yang, 2006).

Index Terms

Timolol Hemihydrate; Timolol Maleate

References

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International Brand NamesApo-Timol (NZ, PL); Apo-Timop (NZ); Aquanil (DK, FI, NO, SE); Arutimol (DE); Betim (GB, GR, IE, NO); Blocadren (AE, AT, BE, BH, CY, EG, IL, IQ, IR, IT, JO, KW, LB, LY, MY, NL, NO, OM, QA, SA, SE, SY, YE); Blocanol (FI); Cardina (FI); Cusimolol (HN, MY, PL); Digaol (FR); Elevex (PH); Geltim LP (FR); Glafemak (GR); Glauco (TH); Glauco Oph (HK, TH); Glaucosan (ZA); Glautimol (BR); Globitan (MX); Glucomol (IN); Horex (MX); Hypermol (NZ); Imot Ofteno (MX); Imot Ofteno al (CR, DO, GT, HN, NI, PA, SV); Isotic Adretor (ID); Lolomit (CO); Noval (GR); Nyogel (FR, GB, IE); Nyogel LP (FR); Nyolol (CN, FR, HK, MX, PL, PY, SG, TW, UY, VE); Ocuper (PH); Ocupres (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Ocupres-E (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Ofal (AR); Oftan (PH); Oftan Timolol (HK, PL); Oftensin (PL); Opthil (ID); Optimol (DK, SE); Proflax (AR); Shemol (MX); Temserin (GR); Tenopt (AU); Tilmat (NZ); Tiloptic (IL); Timabak (HK); Timacar (DK); Timacor (FR); Timo-COMOD (KP); Timo-Comod (PL); Timoftol (ES); Timohexal (DE, HN, PL); Timol (TW); Timolast (TH, TW); Timolol-POS (PL); Timoptic (AT, BG, CH, CZ, HN, PL); Timoptic-XE (BB, BM, BS, BZ, EE, GY, JM, KP, SR, TT); Timoptol (AU, BF, BJ, CI, DE, EC, ET, FR, GB, GH, GM, GN, HK, IE, IT, KE, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, PH, PK, SC, SD, SL, SN, TH, TN, TW, TZ, UG, ZA, ZM, ZW); Timoptol-XE (AU, CN, EC, NZ, PE, PH, SG); Timozzard (MX); Ximex Opticom (ID); Yesan (GR)

Tinidazole

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(tye NI da zole)

U.S. Brand NamesTindamax®

Pharmacologic CategoryAmebicide; Antibiotic, Miscellaneous; Antiprotozoal, Nitroimidazole

Use: Labeled IndicationsTreatment of trichomoniasis caused by *T. vaginalis*; treatment of giardiasis caused by *G. duodenalis* (*G. lamblia*); treatment of intestinal amebiasis and amebic liver abscess caused by *E. histolytica*; treatment of bacterial vaginosis caused by *Bacteroides* spp, *Gardnerella vaginalis*, and *Prevotella* spp in nonpregnant females

Dosing: Adults

Amebiasis, intestinal: Oral: 2 g/day for 3 days

Amebiasis, liver abscess: Oral: 2 g/day for 3-5 days

Bacterial vaginosis: 2 g/day for 2 days or 1 g/day for 5 days

Giardiasis: Oral: 2 g as a single dose

Trichomoniasis: Oral: 2 g as a single dose; sexual partners should be treated at the same time

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Amebiasis, intestinal: Oral: Children >3 years: 50 mg/kg/day for 3 days (maximum dose: 2 g/day)

Amebiasis, liver abscess: Oral: Children >3 years: 50 mg/kg/day for 3-5 days (maximum dose: 2 g/day)

Giardiasis: Oral: Children >3 years: 50 mg/kg as a single dose (maximum dose: 2 g)

Dosing: Renal ImpairmentAdjustment not necessary. An additional dose equal to $^{1}/_{2}$ the usual dose, should be administered at the end of hemodialysis if tinidazole is administered on a day hemodialysis occurs.

Dosing: Hepatic ImpairmentSpecific recommendations are not available; use with caution.

Administration: OralAdminister with food.

Dietary ConsiderationsTake with food. The manufacturer recommends that ethanol be avoided during treatment and for 3 days after therapy is complete.

StorageStore at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from light.

Extemporaneously PreparedTo prepare an oral suspension: Grind four 500 mg tablets to a fine powder. Add cherry syrup 10 mL and mix until smooth. Transfer to a graduated container, rinsing mortar with a small amount of cherry syrup to remove any remaining medication. Add additional cherry syrup to q.s. to 30 mL. Suspension is stable for 7 days at room temperature. Shake well before using.

ContraindicationsHypersensitivity to tinidazole, nitroimidazole derivatives (including metronidazole), or any component of the formulation; pregnancy (1st trimester); breast-feeding

Allergy Considerations

- Nitroimidazole Allergy

Warnings/Precautions

Boxed warnings:

- Carcinogenicity: See “Concerns related to adverse effects” below

Concerns related to adverse effects:

- Carcinogenicity: [**U.S. Boxed Warning]: Carcinogenicity has been observed with another nitroimidazole derivative (metronidazole) in animal studies;** use should be reserved for approved indications only.

- CNS effects: Seizures and peripheral neuropathy have been reported with tinidazole and other nitroimidazole derivatives; use with caution in patients with CNS diseases.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD), pseudomembranous colitis, and/or vaginal candidiasis. CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Amebiasis: Appropriate use: When used for amebiasis, not indicated for the treatment of asymptomatic cyst passage.

- Blood dyscrasias: Use with caution in patients with current or a history of blood dyscrasias.

- Hepatic impairment: Use with caution in patients with current or a history of hepatic impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children ≤3 years of age.

Pregnancy Risk FactorC
Pregnancy ConsiderationsTinidazole crosses the placenta and enters the fetal circulation. Teratogenic effects have not been observed in animal studies. Should not be used during pregnancy for the treatment of bacterial vaginosis. Use during the first trimester is contraindicated; use during the 2nd and 3rd trimester only if clearly needed.
LactationEnters breast milk/contraindicated
Breast-Feeding ConsiderationsBreast-feeding should be discontinued during therapy and for 3 days after the last dose.
Adverse Reactions

1% to 10%:

Central nervous system: Fatigue/malaise (1% to 2%), dizziness (≤1%), headache (≤1%)

Endocrine & metabolic: Menorrhagia (>2%)

Gastrointestinal: Metallic/bitter taste (4% to 6%), nausea (3% to 5%), anorexia (2% to 3%), appetite decreased (>2%), flatulence (>2%), dyspepsia/cramps/epigastric discomfort (1% to 2%), vomiting (1% to 2%), constipation (≤1%)

Genitourinary: *Candida* vaginitis (5%), painful urination (>2%), pelvic pain (>2%), urine abnormality (>2%), vaginal odor (>2%), vulvovaginal discomfort (>2%)

Neuromuscular & skeletal: Weakness (1% to 2%)

Renal: Urinary tract infection (>2%)

Respiratory: Upper respiratory tract infection (>2%)

Frequency not defined.

Cardiovascular: Flushing, palpitation

Central nervous system: Ataxia, coma (rare), confusion (rare), depression (rare), drowsiness, fever, giddiness, insomnia, seizure, vertigo

Dermatologic: Angioedema, pruritus, rash, urticaria

Gastrointestinal: Abdominal pain, diarrhea, furry tongue (rare), oral candidiasis, salivation, stomatitis, thirst, tongue discoloration, xerostomia

Genitourinary: Urine darkened, vaginal discharge increased

Hematologic: Leukopenia (transient), neutropenia (transient), thrombocytopenia (reversible; rare)

Hepatic: Transaminases increased

Neuromuscular & skeletal: Arthralgia, arthritis, myalgia, peripheral neuropathy (transient, includes numbness and paresthesia)

Respiratory: Bronchospasm (rare), dyspnea (rare), pharyngitis (rare)

Miscellaneous: Burning sensation, *Candida* overgrowth, diaphoresis

Postmarketing and/or case reports: Acute hypersensitivity reaction (severe), erythema multiforme, Stevens-Johnson syndrome

Metabolism/Transport Effects**Substrate** of CYP3A4 (major), 2B6 (minor)
Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb Interactions

Ethanol: The manufacturer recommends to avoid all ethanol or any ethanol-containing drugs (may cause disulfiram-like reaction characterized by flushing, headache, nausea, vomiting, sweating or tachycardia) during and for at least 3 days after completion of treatment.

Food: Peak antibiotic serum concentration lowered and delayed, but total drug absorbed not affected.

Test InteractionsMay interfere with AST, ALT, triglycerides, glucose, and LDH testing
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess therapeutic effectiveness (symptoms and laboratory tests) and adverse response. Teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report
Patient EducationDo not take any new medications during therapy without consulting prescriber. Take exactly as directed. Avoid all alcohol while taking this medication and for 3 days following completion; may cause unpleasant reaction (flushing, nausea, vomiting, sweating, headache, rapid heart beat). Refrain from sexual intercourse or use contraceptive if being treated for trichomoniasis. May cause headache, drowsiness or dizziness (use caution when climbing stairs, driving, or engaged in potentially hazardous tasks until response to drug is known); mild gastrointestinal disturbance (nausea, vomiting, constipation, diarrhea, metallic/bitter taste, abdominal discomfort) small frequent meals, frequent mouth care, chewing gum or sucking lozenges may help. Report severe fatigue or weakness; chest pain or palpitations; swelling of lips or mouth, other persistent adverse reactions, lack of improvement or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is contraindicated.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet [scored]:

Tindamax®: 250 mg, 500 mg

Generic AvailableNo

ManufacturerMission Pharmacal Company

Pricing: U.S. (www.drugstore.com)

Tablets (Tindamax)

250 mg (40): $89.99

Mechanism of ActionAfter diffusing into the organism, it is proposed that tinidazole causes cytotoxicity by damaging DNA and preventing further DNA synthesis.

Pharmacodynamics/Kinetics

Absorption: Rapid and complete

Distribution: V_d: 50 L

Protein binding: 12%

Metabolism: Hepatic via CYP3A4 (primarily); undergoes oxidation, hydroxylation and conjugation; forms a metabolite

Half-life elimination: 13 hours

Time to peak, plasma: 1.6 hours

Excretion: Urine (20% to 25%); feces (12%)

Dental Health Professional ConsiderationsAlthough this drug is a member of the metronidazole family, there is no specific dental indication for its use. Just as with metronidazole, alcohol in any form is contraindicated while the patient is on this medication because of the danger of a disulfiram-type reaction.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), metallic/bitter taste, oral candidiasis, tongue discoloration, stomatitis, furry tongue. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue, malaise, ataxia, confusion, depression, giddiness, insomnia, and seizures

Mental Health: Effects on Psychiatric TreatmentBromocriptine, fluvoxamine, and nefazodone may increase levels of tinidazole; barbiturates, carbamazepine, oxcarbazepine, phenytoin, and fosphenytoin may decrease levels of tinidazole; monitor

References

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International Brand NamesAmibiol (CO); Asgin (TW); Dyzole (NZ); Estovit-T (MX); Fasigin (IT); Fasigyn (AR, BE, BG, BR, BZ, CH, CN, CR, EC, GR, GT, HN, IL, IN, MX, NI, NL, PA, PE, PK, PT, SE, SV, TH, UY, VE, ZA); Fasigyne (FR); Induken (MX); Su (TW); Tindol (MY); Tiniba (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Tinidazolum (PL); Tinigin (PL); Tricolam (ES); Tricor 500 (PY); Trinigyn (BB, BM, BS, GY, JM, SR, TT)

Tinzaparin

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English

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Special Alerts

Tinzaparin (Innohep®): Preliminary Results of Clinical Study Showing an Increase in All-Cause Mortality - December 2008; Updated December 31, 2008

The Food and Drug Administration (FDA) is communicating information to healthcare professionals regarding the clinical trial *Innohep® in Renal Insufficiency Study (IRIS)*. This multicenter European trial was prematurely halted in February 2008 after interim results showed an increase in all-cause mortality in patients receiving tinzaparin compared to patients receiving unfractionated heparin (UFH) in the treatment of deep vein thromboses (DVT) and/or pulmonary embolism (PE). Patients in the study were ≥70 years of age with impaired renal function and had a confirmed diagnosis of DVT and/or PE. Of the 350 patients completing 90 days of follow-up when the study was stopped, 23 of the 176 patients (13%) receiving tinzaparin died, compared to 9 of the 174 patients (5%) treated with UFH. According to the FDA, there is no clear pattern in the cause of death and it does not appear to be dose related (under- or overdosing). In addition, results do not appear to be attributed to a manufacturing issue with either agent.

In light of the IRIS preliminary data, the FDA is advising healthcare professionals to consider the use of alternative agents to tinzaparin in the treatment of DVT and/or PE in elderly patients >70 years of age with renal impairment. Of note, prescribing information for Innohep® was updated in July 2008, restricting its use in patients ≥90 years of age. The FDA is now requesting the manufacturer revise prescribing information to include the IRIS study results which suggest the risk of mortality may not be limited to only patients ≥90 years of age.

The FDA has issued an update (December 31, 2008) to the previous MedWatch alert informing practitioners that Celgene Pharmaceuticals has distributed a “Dear Healthcare Professional” letter concerning the issue and has also revised the prescribing information for Innohep®. The labeling now includes a warning that tinzaparin may increase the risk of death in elderly patients with renal insufficiency compared to UFH, and recommends considering alternatives when treating these patients for DVT and/or PE. The labeling also includes details of the IRIS study and defines the patient population involved (patients ≥70 years of age with Cl_{cr} ≤30 mL/minute or patients ≥75 years of age with Cl_{cr} ≤60 mL/minute).

The final IRIS study report is expected to be submitted in January 2009, and after the review is complete, the FDA will communicate its conclusions and any further recommendations.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Innohep

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

2009 National Patient Safety Goals: The Joint Commission on Accreditation of Healthcare Organizations requires healthcare organizations that provide anticoagulant therapy to have a process in place to reduce the risk of anticoagulant-associated patient harm. Patients receiving anticoagulants should receive individualized care through a defined process that includes standardized ordering, dispensing, administration, monitoring and education. This does not apply to routine short-term use of anticoagulants for prevention of venous thromboembolism when the expectation is that the patient’s laboratory values will remain within or close to normal values (NPSG.03.05.01).

Pronunciation(tin ZA pa rin)

U.S. Brand NamesInnohep®

Canadian Brand NamesInnohep®

Pharmacologic CategoryLow Molecular Weight Heparin

Use: Labeled IndicationsTreatment of acute symptomatic deep vein thrombosis, with or without pulmonary embolism, in conjunction with warfarin sodium

Dosing: Adults

DVT with or without pulmonary embolism (PE): SubQ: 175 anti-Xa int. units/kg of body weight once daily. The 2008 *Chest* guidelines recommend starting warfarin on the first treatment day and continuing tinzaparin until INR is between 2 and 3 (usually 5-7 days). Administer tinzaparin for at least 5 days and until INR ≥2 for at least 24 hours (Hirsh, 2008).

Note: To calculate the volume of solution to administer per dose: Volume to be administered (mL) = patient weight (kg) x 0.00875 mL/kg (may be rounded off to the nearest 0.05 mL)

Dosing adjustment in obesity: Weight based dosing (175 anti-Xa int. units/kg of body weight once daily) provided in product labeling for patients up to 162 kg. Limited clinical experience in patients with a BMI >40 kg/m^2.

Dosing: ElderlyRefer to adult dosing. Increased sensitivity to tinzaparin in elderly patients may be possible due to a decline in renal function. Increased all-cause mortality noted in patients ≥70 years of age with Cl_{cr} ≤30 mL/minute or ≥75 years of age and Cl_{cr} ≤60 mL/minute; consider alternative treatments in these patients.

Dosing: Renal Impairment

Cl_{cr} ≤50 mL/minute: Use with caution; clearance is decreased.

Cl_{cr} <30 mL/minute: Per manufacturer's labeling, use with caution. The 2008 *Chest* guidelines recommend avoiding use (in patients requiring therapeutic anticoagulation); if used, consider monitoring anti-Xa levels (Hirsh, 2008).

Dosing: Hepatic ImpairmentNo adjustment necessary.

Administration: OtherPatient should be lying down or sitting. Administer by deep SubQ injection, alternating between the left and right anterolateral and left and right posterolateral abdominal wall. Vary site daily. The entire needle should be introduced into the skin fold formed by the thumb and forefinger. Hold the skin fold until injection is complete. To minimize bruising, do not rub the injection site.

StorageStore at 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to tinzaparin sodium, heparin, or any component of the formulation; active major bleeding; heparin-induced thrombocytopenia (current or history of)

Allergy Considerations

- Low Molecular Weight Heparin Allergy

Warnings/Precautions

Boxed warnings:

- Neuraxial anesthesia: See "Other warnings/precautions" below.

Disease-related concerns:

- Renal impairment: Patients with severe renal impairment may show reduced elimination of tinzaparin. An increased risk of death has been observed in elderly patients with renal impairment.

Concerns related to adverse effects:

- Bleeding: Monitor patient closely for signs or symptoms of bleeding. Certain patients are at increased risk of bleeding. Risk factors include bacterial endocarditis; congenital or acquired bleeding disorders; active ulcerative or angiodysplastic GI diseases; severe uncontrolled hypertension; history of hemorrhagic stroke; or use shortly after brain, spinal, or ophthalmology surgery; in patient treated concomitantly with platelet inhibitors; recent GI bleeding; thrombocytopenia or platelet defects; severe liver disease; hypertensive or diabetic retinopathy; or in patients undergoing invasive procedures. Discontinue if bleeding occurs.

- Hyperkalemia: Monitor for hyperkalemia. Heparin can cause hyperkalemia by suppressing aldosterone production; similar reactions could occur with LMWHs. Most commonly occurs in patients with risk factors for the development of hyperkalemia (eg, renal dysfunction, concomitant use of potassium-sparing diuretics or potassium supplements, hematoma in body tissues).

- Thrombocytopenia: Rare cases of thrombocytopenia have occurred. Contraindicated in patients with history of heparin-induced thrombocytopenia; monitor platelet count closely. Manufacturer recommends discontinuation of therapy if platelets are <100,000/mm^3. Rare cases of thrombocytopenia with thrombosis have occurred. Use caution in patients with congenital or drug-induced thrombocytopenia or platelet defects.

- Renal impairment: Reduced tinzaparin clearance was observed in patients with moderate renal impairment (Cl_{cr} ≤50 mL/minute); patients with severe renal impairment (Cl_{cr} <30 mL/minute) had a 24% decrease in clearance. Use with caution in patients with renal insufficiency or avoid use, particularly in patients of advanced age with concomitant renal impairment. The 2008 *Chest* guidelines recommend that patients with Cl_{cr} <30 mL/minute be treated with unfractionated heparin instead of LMWH (Hirsh, 2008).

Special populations:

- Elderly: Use with caution in the elderly; delayed elimination may occur. Use in patients ≥70 years of age with renal insufficiency (Cl_{cr} ≤30 mL/minute or ≥75 years of age and Cl_{cr} ≤60 mL/minute) has been associated with an increased risk of death compared to use of unfractionated heparin; consider alternative treatments in these patients.

- Obese patients: Clinical experience is limited in patients with BMI >40 kg/m^2.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Benzyl alcohol: This product contains benzyl alcohol and should be used with caution in pregnant women. In neonates, large amounts of benzyl alcohol (>100 mg/kg/day) have been associated with fatal toxicity (gasping syndrome).

- Porcine intestinal mucosa: This product is derived from porcine intestinal mucosa and should not be used in patients allergic to pork products.

- Sodium metabisulfite: This product contains sodium metabisulfite which may cause allergic-type reactions, including anaphylactic symptoms and life-threatening asthmatic episodes in susceptible people; this is seen more frequently in asthmatics.

Other warnings/precautions:

- Administration: For subcutaneous use only; do not administer intramuscularly or intravenously.

- Conversion to other products: Not to be used interchangeably (unit for unit) with heparin or any other low molecular weight heparins.

- Neuraxial anesthesia: **[U.S. Boxed Warning]: Patients with recent or anticipated neuraxial anesthesia (epidural or spinal anesthesia) are at risk of spinal or epidural hematoma and subsequent paralysis.** Consider risk versus benefit prior to neuraxial anesthesia; risk is increased by concomitant agents which may alter hemostasis, as well as traumatic or repeated epidural or spinal puncture. Patient should be observed closely for bleeding and signs and symptoms of neurological impairment if therapy is administered during or immediately following diagnostic lumbar puncture, epidural anesthesia, or spinal anesthesia.

Geriatric ConsiderationsNo significant differences in safety or response were seen when used in patients ≥65 years of age. However, increased sensitivity to tinzaparin in elderly patients may be possible due to a decline in renal function. Results from the Innohep in Renal Insufficiency Study (IRIS) study showed an increased in all-cause mortality in elderly patients receiving tinzaparin compared to unfractionated heparin for treatment of DVT and/or PE. The at-risk population has defined as patients ≥70 years of age with $Cl_{cr} \le 30$ mL/minute or ≥75 years of age and $Cl_{cr} \le 60$ mL/minute.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic events were not observed in animal studies. Tinzaparin does not cross the human placenta. A pharmacokinetic study in pregnant women found no dose adjustment was needed during pregnancy. Pregnancy may increase the risk of thromboembolism; risk may be further increased with certain pre-existing conditions. As with all anticoagulants, bleeding is the major adverse effect of tinzaparin. Vaginal bleeding was reported in ~10% of pregnant patients during tinzaparin therapy. Contains benzyl alcohol; use with caution in pregnant women.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsAs with all anticoagulants, bleeding is the major adverse effect of tinzaparin. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables.

>10%:

Hepatic: ALT increased (13%)

Local: Injection site hematoma (16%)

1% to 10%:

Cardiovascular: Angina pectoris, chest pain (2%), hyper-/hypotension, tachycardia

Central nervous system: Confusion, dizziness, fever (2%), headache (2%), insomnia, pain (2%)

Dermatologic: Bullous eruption, pruritus, rash (1%), skin disorder

Gastrointestinal: Constipation (1%), dyspepsia, flatulence, nausea (2%), nonspecified gastrointestinal disorder, vomiting (1%)

Genitourinary: Dysuria, urinary retention, urinary tract infection (4%)

Hematologic: Anemia, hematoma, hemorrhage (2%), thrombocytopenia (1%)

Hepatic: AST increased (9%)

Local: Thrombophlebitis (deep)

Neuromuscular & skeletal: Back pain (2%)

Renal: Hematuria (1%)

Respiratory: Dyspnea (1%), epistaxis (2%), pneumonia, pulmonary embolism (2%), respiratory disorder

Miscellaneous: Impaired healing, infection, unclassified reactions

<1%: Abdominal pain, diarrhea, major bleeding

Additional serious adverse reactions reported in clinical trials and postmarketing experience: Abscess, acute febrile reaction, agranulocytosis, allergic purpura, allergic reaction, angioedema, anaphylactoid reaction, anorectal bleeding, cardiac arrhythmia, cellulitis, cerebral hemorrhage, cholestatic hepatitis, coronary thrombosis, dependent edema, epidermal necrolysis, erythematous gastrointestinal hemorrhage, granulocytopenia, hemarthrosis, hematemesis, hemoptysis, injection site bleeding, intracranial hemorrhage, ischemic necrosis, melena, MI, necrosis, neoplasm, ocular hemorrhage, pancytopenia, peripheral ischemia, priapism, purpura, rash, retroperitoneal/intra-abdominal bleeding, severe thrombocytopenia, skin necrosis, spinal epidural hematoma, Stevens-Johnson syndrome, thromboembolism, urticaria, vaginal hemorrhage, wound hematoma

Drug Interactions

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Drotrecogin Alfa: Heparin (Low Molecular Weight) may enhance the adverse/toxic effect of Drotrecogin Alfa. This is of most concern with therapeutic doses of LMW heparin. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Anticoagulants may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Anticoagulants may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Monitoring ParametersCBC including platelet count and hematocrit or hemoglobin, and stool for occult blood; the monitoring of PT and/or aPTT is not of clinical value. Patients receiving both warfarin and tinzaparin should have their INR drawn just prior to the next scheduled dose of tinzaparin.

According to 2008 *Chest* guidelines, routine monitoring of anti-Xa levels is generally not recommended; however, anti-Xa levels may be beneficial in certain patients (eg, obese patients, patients with severe renal insufficiency receiving therapeutic doses, and possibly pregnant women receiving therapeutic doses; Hirsh, 2008)

Nursing: Physical Assessment/MonitoringUse caution in the presence of increased risk of bleeding. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (especially anything that will impact coagulation or platelet aggregation). Assess results of laboratory tests on a regular basis. Monitor therapeutic effectiveness and adverse response (eg, bleeding at any source, rash, angina, confusion, urinary retention, dyspnea). Observe and teach bleeding precautions. Teach patient use if self-administered (appropriate injection technique and syringe/needle disposal), possible side effects/appropriate interventions (eg, bleeding precautions), and adverse symptoms to report.

Monitoring: Lab TestsCBC including platelet count and hematocrit or hemoglobin, and stool for occult blood; the monitoring of PT and/or PTT is not of clinical value. Patients receiving both warfarin and tinzaparin should have their INR drawn just prior to the next scheduled dose of tinzaparin.

According to 2008 *Chest* guidelines, routine monitoring of anti-Xa levels is generally not recommended; however, anti-Xa levels may be beneficial in certain patients (eg, obese patients, patients with severe renal insufficiency receiving therapeutic doses, and possibly pregnant women receiving therapeutic doses; Hirsh, 2008)

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This drug can only be administered by injection. If self-administered, use exactly as directed and follow instructions for syringe disposal. Do not alter dosage or discontinue without consulting prescriber. You may have a tendency to bleed easily while taking this drug (brush teeth with soft brush, use waxed dental floss, use electric razor, avoid scissors or sharp knives, and avoid potentially harmful activities). Report immediately any unusual bleeding or bruising (eg, mouth, nose, blood in urine or stool); chest pain or palpitations; confusion, dizziness, or headache; skin rash or itching; persistent GI upset (eg, nausea, vomiting, abdominal pain, acute constipation); warmth, swelling, pain, or redness in calves or other areas; back or muscle pain; respiratory difficulties; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sodium:

Innohep®: 20,000 anti-Xa int. units/mL (2 mL) [contains benzyl alcohol and sodium metabisulfite]

Generic AvailableNo

Mechanism of ActionStandard heparin consists of components with molecular weights ranging from 4000-30,000 daltons with a mean of 16,000 daltons. Heparin acts as an anticoagulant by enhancing the inhibition rate of clotting proteases by antithrombin III, impairing normal hemostasis and inhibition of factor Xa. Low molecular weight heparins have a small effect on the activated partial thromboplastin time and strongly inhibit factor Xa. The primary inhibitory activity of tinzaparin is through antithrombin. Tinzaparin is derived from porcine heparin that undergoes controlled enzymatic depolymerization. The average molecular weight of tinzaparin ranges between 5500 and 7500 daltons which is distributed as <2000 daltons (<10%), 2000-8000 daltons (60% to 72%), and >8000 daltons (22% to 36%). The anti-Xa activity is approximately 100 int. units/mg.

Pharmacodynamics/Kinetics

Onset of action: 2-3 hours

Distribution: 3-5 L

Half-life elimination: 3-4 hours

Metabolism: Partially metabolized by desulphation and depolymerization

Bioavailability: 87%

Time to peak: 4-5 hours

Excretion: Urine

Related Information

- Anticoagulants, Injectable

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia, confusion, or dizziness

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine

Cardiovascular ConsiderationsLow molecular weight heparins (LMWHs) compare favorably to unfractionated heparin (UFH) in the prevention and treatment of venous thromboembolism. LMWHs are associated with less thrombocytopenia, compared to heparin, and do not require routine therapeutic monitoring. The role of tinzaparin in the treatment of acute coronary syndromes is not established.

Obesity/Renal Dysfunction: The 2008 *Chest* guidelines recommends that dosing (prophylaxis or treatment) in patients with obesity should be weight-based and not a fixed-dose regimen (Grade 2C; Hirsh, 2008). Tinzaparin offers weight-based dosing (up to 162 kg) in its package insert. One study evaluated weight-based dosing (single doses of 75 and 175 units/kg) in patients between 100 and 165 kg and demonstrated achievement of similar anti-Xa activity levels compared to normal-weight individuals (Hainer, 2002). Monitoring anti-Xa activity 4 hours after an injection may be warranted.

Patients who have a reduction in calculated creatinine clearance are at risk of an accumulated anticoagulant effect when they are treated with certain LMWHs. All LMWHs may not behave the same in patients with renal dysfunction due to differences in molecular weight distribution. Monitoring anti-Xa activity for patients with Cl_{cr} <30 mL/minute may be necessary. Elderly patients with diminished renal function (Cl_{cr} ≤30 mL/minute) should not be treated with tinzaparin. Of note, the 2008 *Chest* guidelines recommends that patients with Cl_{cr} <30 mL/minute who require therapeutic anticoagulation be treated with unfractionated heparin instead of LMWH (Grade 2C; Hirsh, 2008).

Index TermsTinzaparin Sodium

References

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Simonneau G, Sors H, Charbonnier B, et al, “A Comparison of Low-Molecular-Weight Heparin With Unfractionated Heparin for Acute Pulmonary Embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire,” *N Engl J Med*, 1997, 337(10):663-9.[PubMed 9278462]

International Brand NamesInnohep (AR, BE, BG, CO, DE, DK, ES, FI, FR, GB, GR, HK, IE, IT, LU, MY, NL, NO, NZ, PH, PT, SE, SG, TH); innohep (CH); Logiparin (AT, CZ, IN)

Tioconazole

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Tioconazole may be confused with terconazole

Pronunciation(tye oh KONE a zole)

U.S. Brand Names1-Day™ [OTC]; Vagistat®-1 [OTC]

Pharmacologic CategoryAntifungal Agent, Vaginal

Use: Labeled IndicationsLocal treatment of vulvovaginal candidiasis

Dosing: Adults**Vulvovaginal candidiasis:** Vaginal: Insert 1 applicatorful in vagina, just prior to bedtime, as a single dose

Dosing: ElderlyRefer to adult dosing.

StorageStore at room temperature.

ContraindicationsHypersensitivity to tioconazole or any component of the formulation

Allergy Considerations

- Azole Antifungal Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: If irritation or sensitization occurs, discontinue use.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Petrolatum-based: Petrolatum-based vaginal products may damage rubber or latex condoms or diaphragms; separate use by 3 days.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsFrequency not defined.

Central nervous system: Headache

Gastrointestinal: Abdominal pain

Dermatologic: Burning, desquamation

Genitourinary: Discharge, dyspareunia, dysuria, irritation, itching, nocturia, vaginal pain, vaginitis, vulvar swelling

Metabolism/Transport Effects**Inhibits** CYP1A2 (weak), 2A6 (weak), 2C9 (weak), 2C19 (weak), 2D6 (weak), 2E1 (weak)

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringAssess knowledge/teach patient appropriate administration, possible side effects/interventions, and adverse symptoms to report.

Patient EducationConsult with prescriber if treating a vaginal yeast infection for the first time. Insert high into the vagina. Refrain from intercourse during treatment. May interact with condoms and vaginal contraceptive diaphragms (ie, weaken latex); do not rely on these products for 3 days following treatment. Do not use tampons, douches, spermicides, or other vaginal products during treatment. Although product is used for a single day, relief from symptoms usually takes longer than 1 day. Report persistent (>3 days) vaginal burning, irritation, or discharge. **Breast-feeding precaution:** Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Ointment, vaginal: 6.5% (4.6 g) [with applicator]

Generic AvailableNo

Mechanism of ActionA 1-substituted imidazole derivative with a broad antifungal spectrum against a wide variety of dermatophytes and yeasts, including *Trichophyton mentagrophytes*, *T. rubrum*, *T. erinacei*, *T. tonsurans*, *Microsporum canis*, *Microsporum gypseum*, and *Candida albicans*. Both agents appear to be similarly effective against *Epidermophyton floccosum*.

Pharmacodynamics/Kinetics

Onset of action: Some improvement: Within 24 hours; Complete relief: Within 7 days

Absorption: Intravaginal: Systemic (small amounts)

Distribution: Vaginal fluid: 24-72 hours

Excretion: Urine and feces

Related Information

- Treatment of Sexually-Transmitted Infections

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesDeocil Fem (AR); Fungibacid (DE); Gino Conazol (BR); Gino-Trosyd (CR, GT, HN, NI, PA, PT, SV); Ginotrosyd (IT); Gyno-Trosyd (AT, CH, FI, FR, HK, MY, PL, SG, ZA); Honguil (AR); Mykontral (DE); Tralen (BR); Trosid (ES); Trosil (GB); Trosyd (AR, AT, CH, FI, FR, HK, IT, MY, PE, PH, SG, TH); Trosyl (IE)

English

Jump To Field (Select Field Name)

Pronunciation(tye oh PROE nin)
U.S. Brand NamesThiola速
Canadian Brand NamesThiola速
Pharmacologic CategoryUrinary Tract Product
Use: Labeled IndicationsPrevention of kidney stone (cystine) formation in patients with severe homozygous cystinuric who have urinary cystine >500 mg/day who are resistant to treatment with high fluid intake, alkali, and diet modification, or who have had adverse reactions to penicillamine
Dosing: Adults**Prevention of nephrolithiasis (cystine):** Oral: Initial dose is 800 mg/day, average dose is 1000 mg/day
Dosing: ElderlyRefer to adult dosing.
Pregnancy Risk FactorC
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 100 mg

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Tablets (Thiola)

100 mg (30): $37.99

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
International Brand NamesAcadione (FR); Capen (AR); Captimer (DE); Epatiol (IT); Mucolysin[chart.] (CH, IT); Mucosyt (IT); Stargen (TW); Sutilan (ES); Thiokagen (TW); Thiola (BE, JP); Vincol (ES)

Tiotropium

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Tiotropium (Spiriva®): Ongoing Safety Evaluation of Stroke Risk - October 2008

The U.S. Food and Drug Administration (FDA) has received preliminary data from the UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium) trial. The UPLIFT trial is an international trial randomizing ~6,000 COPD patients to 4 years of tiotropium or placebo. The primary endpoint determines if tiotropium reduces the rate of decline in lung function over time (Tashkin, 2008). A secondary endpoint evaluates tiotropium's safety profile, with attention on the risk of stroke (mortality caused by stroke and adverse events reported as stroke).

Two recent analyses (Lee, 2008; Singh, 2008) showed an association with inhaled anticholinergics and an increase risk of cardiovascular events in COPD patients. Preliminary evaluation of the UPLIFT trial data did not support an association between the use of tiotropium and an increased risk of stroke.

Based upon these results, the FDA is going to independently examine the data from the UPLIFT trial. The FDA expects to receive the complete report for UPLIFT in November 2008 and review the final results.

Additional information may be found at http://www.fda.gov/cder/drug/early_comm/tiotropium.htm

Tiotropium (Spiriva®): Possible Increased Risk of Stroke - March 2008

Boehringer Ingelheim and the U.S. Food and Drug Administration (FDA) are informing practitioners of preliminary results of an analysis indicating a possible increased risk of stroke associated with the use of Spiriva®. The results are based on pooled analysis performed on safety data from 29 placebo-controlled clinical trials involving approximately 13,500 patients with chronic obstructive pulmonary disease (COPD). The results revealed an estimate of the risk of stroke in 8 patients per 1000 patients per year treated with Spiriva® compared to the risk of stroke in 6 patients per 1000 patients per year with placebo.

These results have not been confirmed by the FDA. The FDA will further evaluate this potential association and provide more information as it is made available. Boehringer Ingelheim has conducted a large 4-year study that will provide additional long-term safety data and is expected to be available in the summer of 2008. Patients should not discontinue Spiriva® and should discuss any concerns with their healthcare provider.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Tiotropium .

Medication Safety Issues

Sound-alike/look-alike issues:

Spiriva® may be confused with Inspra™, Serevent®

Spiriva® capsules for inhalation are for administration via HandiHaler® device and are **not** for oral use

Pronunciation(ty oh TRO pee um)

U.S. Brand NamesSpiriva® HandiHaler®

Canadian Brand NamesSpiriva®

Pharmacologic CategoryAnticholinergic Agent

Use: Labeled IndicationsMaintenance treatment of bronchospasm associated with COPD (bronchitis and emphysema)

Dosing: Adults**COPD:** Oral inhalation: Contents of 1 capsule (18 mcg) inhaled once daily using HandiHaler® device

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentPlasma concentrations increase in renal impairment. Use caution in moderate-severe impairment; no specific dosage adjustment recommended.

Administration: OralFor oral inhalation only. Capsule should not be swallowed.

Administration: InhalationAdminister once daily at the same time each day. Remove capsule from foil blister immediately before use. Capsule should not be swallowed. Place capsule in the capsule-chamber in the base of the HandiHaler® Inhaler. Must only use the HandiHaler® Inhaler. Close mouthpiece until a click is heard, leaving dustcap open. Exhale fully. Do not exhale into inhaler. Tilt head slightly back and inhale (rapidly, steadily and deeply); the capsule vibration may be heard within the device. Hold breath as long as possible. If any powder remains in capsule, exhale and inhale again. Repeat until capsule is empty. Throw away empty capsule; do not leave in inhaler. Do not use a spacer with the HandiHaler® Inhaler. Do not use HandiHaler® device for other medications. Always keep capsules and inhaler dry.

Delivery of dose: Instruct patient to place mouthpiece gently between teeth, closing lips around inhaler. Instruct patient to inhale deeply and hold breath held for 5-10 seconds. The amount of drug delivered is small, and the individual will not sense the medication as it is inhaled. Remove mouthpiece prior to exhalation. Patient should not breathe out through the mouthpiece.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Do not store capsules in HandiHaler® device. Capsules should be stored in the blister pack and only removed immediately before use. Once protective foil is peeled back and/or removed the capsule should be used immediately; if capsule is not used immediately it should be discarded.

ContraindicationsHypersensitivity to tiotropium, atropine or its derivatives, including ipratropium, or any component of the formulation (contains lactose)

Allergy Considerations

- Belladonna Alkaloid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bronchospasm: Rarely, paradoxical bronchospasm may occur with use of inhaled bronchodilating agents; this should be distinguished from inadequate response.
- Hypersensitivity reactions: Immediate hypersensitivity reactions (urticaria, angioedema, rash, bronchospasm) have been reported. Discontinue immediately if signs/symptoms occur.

Disease-related concerns:

- Asthma: Appropriate use: Not indicated for the initial (rescue) treatment of acute episodes of bronchospasm.
- Glaucoma: Use with caution in patients with narrow-angle glaucoma.
- Myasthenia gravis/bladder neck obstruction: Use with caution in patients with myasthenia gravis.
- Prostatic hyperplasia: Use with caution in patients with prostatic hyperplasia or bladder neck obstruction.
- Renal impairment: Use with caution in patients with moderate to severe renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: The contents of Spiriva® capsules are for inhalation only via the HandiHaler® device. Capsules should not be swallowed; there have been reports of incorrect administration (swallowing of the capsules).
- Avoid ocular contact: Avoid inadvertent instillation of powder into the eyes.

Geriatric ConsiderationsAssess patient's ability to use the HandiHaler®. In elderly patients, renal clearance of tiotropium was decreased and plasma concentrations were increased, due to decreased renal function. No significant difference in adverse effects were seen in young vs elderly patients. No dosage adjustments are recommended due to age or renal function. However, the manufacturer recommends monitoring patients with moderate-to-severe renal impairment.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events (fetal loss, decreased birth weights, delayed sexual maturation) were observed in some animal studies. There are no adequate and well-controlled studies in pregnant women. Use only when expected benefit to mother outweighs potential risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Gastrointestinal: Xerostomia (16%)

Respiratory: Upper respiratory tract infection (41% vs 37% with placebo), sinusitis (11% vs 9% with placebo)

1% to 10%:

Cardiovascular: Angina (1% to 7%), edema (dependent, 5%)

Central nervous system: Depression (1% to 3%), dysphonia (1% to 3%)

Dermatologic: Rash (4%)

Endocrine & metabolic: Hypercholesterolemia (1% to 3%), hyperglycemia (1% to 3%)

Gastrointestinal: Dyspepsia (6%), abdominal pain (5%), constipation (4%), vomiting (4%), gastroesophageal reflux (1% to 3%), ulcerative stomatitis (1% to 3%)

Genitourinary: Urinary tract infection (7%)

Neuromuscular & skeletal: Myalgia (4%), arthritis (≥3%), leg pain (1% to 3%), paresthesia (1% to 3%), skeletal pain (1% to 3%)

Ocular: Cataract (1% to 3%)

Respiratory: Pharyngitis (9%), rhinitis (6%), epistaxis (4%), cough (≥3%), laryngitis (1% to 3%)

Miscellaneous: Infection (4%), moniliasis (4%), flu-like syndrome (≥3%), allergic reaction (1% to 3%), herpes zoster (1% to 3%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Angioedema; application site irritation (glossitis, mouth ulceration, pharyngolaryngeal pain); atrial fibrillation, blurred vision, candidiasis (oral), dizziness, dysphagia, glaucoma, hoarseness, hypersensitivity reactions, ileus (paralytic), intestinal obstruction, intraocular pressure increased, palpitation, paradoxical bronchospasm, pruritus, pupil dilation (if powder comes in contact with eyes), stroke, supraventricular tachycardia, tachycardia, throat irritation, urinary difficulty, urinary retention, urticaria

Metabolism/Transport Effects**Substrate** (minor) of CYP2D6, 3A4

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Monitoring ParametersFEV$_1$, peak flow (or other pulmonary function studies)

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescription or OTC medications or herbal products patient may be taking. Assess results of pulmonary tests prior to and periodically during therapy. Assess therapeutic effectiveness and adverse response at beginning of therapy and at regular intervals during therapy. Teach patient proper use, appropriate interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsFEV$_1$, peak flow (or other pulmonary function studies)

Patient EducationUse inhaler and medication as instructed - once daily, at same time each day. Do not use more often than prescribed. Do not use as an acute "rescue" bronchodilator. Capsules are not to be swallowed. May cause nausea or vomiting (small frequent meals and frequent mouth care may help); dry mouth; hyperglycemia (if you have diabetes, monitor serum glucose closely); muscle or skeletal pain (consult prescriber for appropriate analgesic). Report swelling of face, mouth, or tongue; skin rash; chest pain or palpitations; persistent gastrointestinal effects; muscle or skeletal pain or weakness; change in vision; numbness or weakness of extremities; slurred speech; or respiratory changes, sore throat, or flu-like symptoms. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intent to be pregnant. Breast-feeding is not recommended.

Administration of HandiHaler® Inhaler: Remove capsule from blister pack immediately before using. Place capsule in capsule-chamber in the base of inhaler. Close mouthpiece until a click is heard, leaving dustcap open. Exhale fully (do not exhale into inhaler). Place mouthpiece gently between teeth, closing lips around inhaled, tilt head back slightly, and inhale once rapidly, steadily and deeply (the capsule vibration may be heard within the inhaler, but you will not sense the medication as it is inhaled.) Hold breath as long as possible. Remove inhaler from mouth before exhaling. If any powder remains in capsule, repeat inhalation again. Throw away empty capsule. Do not store capsule in inhaler and always keep inhaler and capsules dry.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for oral inhalation [capsule]:

Spiriva® HandiHaler®: 18 mcg/capsule (5s, 30s, 90s) [contains lactose]

Generic AvailableNo

ManufacturerBoehringer Ingelheim

Pricing: U.S. (www.drugstore.com)

Capsules (Spiriva HandiHaler)

18 mcg (6): $41.99

18 mcg (30): $159.98

Mechanism of ActionBlocks the action of acetylcholine at parasympathetic sites in bronchial smooth muscle causing bronchodilation

Pharmacodynamics/Kinetics

Absorption: Poorly absorbed from GI tract, systemic absorption may occur from lung

Distribution: V$_d$: 32 L/kg

Protein binding: 72%

Metabolism: Hepatic (minimal), via CYP2D6 and CYP3A4

Bioavailability: Following inhalation, 19.5%; oral solution: 2% to 3%

Half-life elimination: 5-6 days

Time to peak, plasma: 5 minutes (following inhalation)

Excretion: Urine (14% of an inhaled dose); feces (primarily nonabsorbed drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and ulcerative stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression

Mental Health: Effects on Psychiatric TreatmentNone reported

Mental Health CommentMany psychotropic agents possess intrinsic anticholinergic properties or produce anticholinergic side effects. Concomitant use with tiotropium may produce additive anticholinergic effects.

Index TermsTiotropium Bromide Monohydrate

References

Adams SG, Anzueto A, Briggs DD Jr, et al, “Tiotropium in COPD Patients Not Previously Receiving Maintenance Respiratory Medications,” *Respir Med*, 2006, 100(9):1495-503.[PubMed 16698259]

Gross NJ, “Tiotropium Bromide,” *Chest*, 2004, 126(6):1946-53.[PubMed 15596697]

Hvizdos KM and Goa KL, “Tiotropium Bromide,” *Drugs*, 2002 62(8):1195-203.[PubMed 12010082]

Maltais F, Hamilton A, Marciniuk D, et al, “Improvements in Symptom-Limited Exercise Performance Over 8 H With Once-Daily Tiotropium in Patients With COPD,” *Chest*, 2005, 128(3):1168-78.[PubMed 16162703]

Niewoehner DE, Rice K, Cote C, et al, “Prevention of Exacerbations of Chronic Obstructive Pulmonary Disease With Tiotropium, a Once-Daily Inhaled Anticholinergic Bronchodilator: A Randomized Trial,” *Ann Intern Med*, 2005, 143(5):317-26.[PubMed 16144890]

Rodrigo GJ and Nannini LJ, “Tiotropium for the Treatment of Stable Chronic Obstructive Pulmonary Disease: A Systematic Review With Meta-Analysis,” *Pulm Pharmacol Ther*, 2007, 20(5):495-502.[PubMed 16621638]

International Brand NamesSpiriva (AE, AR, AU, BE, BG, BH, BO, BR, CH, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EG, ES, FI, FR, GB, GT, HK, HN, ID, IE, IL, IQ, IR, IT, JO, KW, LB, LY, MX, MY, NI, NL, NO, OM, PA, PE, PH, PR, PT, PY, QA, SA, SE, SG, SV, SY, TH, TW, UY, VE, YE); Tiova Rotacaps (IN)

TIP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Esophageal Cancer; Chemotherapy Regimen, Head and Neck Cancer

Regimen UseEsophageal cancer; Head and neck cancer

Regimen

Paclitaxel: I.V.: 175 mg/m^2 day 1

[total dose/cycle = 175 mg/m^2]

Ifosfamide: I.V.: 1000 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 3000 mg/m^2]

Mesna: I.V.: 400 mg/m^2/day before ifosfamide days 1, 2, and 3

plus I.V.: 200 mg/m^2 4 hours after ifosfamide days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Cisplatin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 21-28 days

References

Shin DM, Glisson BS, Khuri FR, et al, âPhase II Trial of Paclitaxel, Ifosfamide, and Cisplatin in Patients With Recurrent Head and Neck Squamous Cell Carcinoma,â *J Clin Oncol*, 1998, 16(4):1325-30.[PubMed 9552033]

Tipranavir

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(tip RA na veer)

U.S. Brand NamesAptivus®

Canadian Brand NamesAptivus®

Pharmacologic CategoryAntiretroviral Agent, Protease Inhibitor

Use: Labeled IndicationsTreatment of HIV-1 infections in combination with ritonavir and other antiretroviral agents; limited to highly treatment-experienced or multiprotease inhibitor-resistant patients.

Dosing: Adults**HIV infection:** Oral: 500 mg twice daily with a high-fat meal. **Note:** Coadministration with ritonavir (200 mg twice daily) is required.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**HIV infection:** Children ≥2 years: Oral: 14 mg/kg or 375 mg/m^2 (maximum: 500 mg/dose) twice daily. **Note:** Coadministration with ritonavir (6 mg/kg or 150 mg/m^2 [maximum 200 mg/dose] twice daily) is required.

If intolerance or toxicity develops and virus is not resistant to multiple protease inhibitors: May decrease dose to 12 mg/kg or 290 mg/m^2 twice daily. **Note:** Coadministration with ritonavir (5 mg/kg or 115 mg/m^2 twice daily) is required.

Dosing: Renal ImpairmentNo adjustment required.

Dosing: Hepatic Impairment

Mild impairment (Child-Pugh class A): No adjustment required.

Moderate-to-severe impairment (Child-Pugh class B-C): Concurrent use is contraindicated.

Administration: Oral

Should be administered with a high-fat meal (bioavailability is increased); coadministration with ritonavir is required

Dietary ConsiderationsContains dehydrated ethanol 7% w/w (0.1 g per capsule). Oral solution formulation contains vitamin E; additional vitamin E supplements should be avoided.

Storage

Capsule: Prior to opening bottle, store under refrigeration at 2°C to 8°C (36°F to 46°F). After bottle is opened, may be stored at controlled room temperature of 25°C (77°F) for up to 60 days.

Oral solution: Store at 15°C to 30°C (59°F to 86°F). After bottle is open, use within 60 days. Do not refrigerator or freeze oral solution.

ContraindicationsConcurrent therapy of tipranavir/ritonavir with amiodarone, cisapride, ergot derivatives (eg, dihydroergotamine, ergonovine, ergotamine, methylergonovine), flecainide, lovastatin, midazolam, pimozide, propafenone, quinidine, rifampin, simvastatin, St John's wort, and triazolam; moderate-to-severe hepatic impairment (Child-Pugh class B and C)

Warnings/Precautions

Boxed warnings:

- Hepatotoxicity: See "Concerns related to adverse effects" below.
- Intracranial hemorrhage: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Hepatotoxicity: **[U.S. Boxed Warning]: In combination with ritonavir, may cause hepatitis (including fatalities) and/or exacerbate pre-existing hepatic dysfunction (causal relationship not established); patients with chronic hepatitis B or C are at increased risk.** Monitor patients closely; discontinue use if signs or symptoms of toxicity occur or if asymptomatic AST/ALT elevations >10 times upper limit of normal or AST/ALT elevations >5-10 times upper limit of normal concurrently with total bilirubin >2.5 times the upper limit of normal occur.
- Hypersensitivity reactions: Protease inhibitors have been associated with a variety of hypersensitivity events (some severe), including rash, anaphylaxis (rare), angioedema, bronchospasm, erythema multiforme, and/or Stevens-Johnson syndrome (rare). It is generally recommended to discontinue treatment if severe rash or moderate symptoms accompanied by other systemic symptoms occur.
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Increased cholesterol: Increases in total cholesterol and triglycerides have been reported; screening should be done prior to therapy and periodically throughout treatment.

- Intracranial hemorrhage: **[U.S. Boxed Warning]: Use in combination with ritonavir, has been associated with rare reports of fatal and nonfatal intracranial hemorrhage; causal relationship not established.** Events often occurred in patients with medical conditions (eg, CNS lesions, head trauma, recent neurosurgery, coagulopathy, alcohol abuse) or concurrent therapy which may have influenced these events.

- Sulfonamide allergy: Use with caution in patients with sulfonamide allergy.

Disease-related concerns:

- Diabetes: Changes in glucose tolerance, hyperglycemia, exacerbation of diabetes, DKA, and new-onset diabetes mellitus have been reported in patients receiving protease inhibitors.

- Hemophilia A or B: Use with caution in patients with hemophilia A or B; increased bleeding during protease inhibitor therapy has been reported.

- Hepatic impairment: Use with caution in patients with mild hepatic impairment; contraindicated in moderate-to-severe impairment.

- Platelet aggregation: May impair platelet aggregation, resulting in bleeding; use with caution in patients who may be at risk for increased bleeding (trauma, surgery or other medical conditions).

Concurrent drug therapy issues:

- Anticoagulants and antiplatelet agents: Coadministration may increase the risk of bleeding.

- Estrogens: Women receiving estrogen (as hormonal contraception or replacement therapy) have an increased incidence of rash. Alternative forms of contraception may be needed.

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors and moderate CYP3A4 inducers. Concomitant use with selected major CYP3A4 substrates and strong CYP3A4 inducers is contraindicated (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

- Ritonavir: Coadministration with ritonavir is required.

Concurrent drug therapy issues:

- Vitamin E: Oral solution formulation contains vitamin E; additional vitamin E supplements should be avoided.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Pregnancy Risk FactorC
Pregnancy ConsiderationsIt is not known if tipranavir crosses the human placenta. Pregnancy and protease inhibitors are both associated with an increased risk of hyperglycemia. Glucose levels should be closely monitored. Women receiving estrogen (as hormonal contraception or replacement therapy) have an increased incidence of rash. Alternative forms of contraception may be needed. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).
LactationExcretion in breast milk unknown/contraindicated
Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.
Adverse Reactions
>10%:

Dermatologic: Rash (children 21%; adults 3% to 10%)

Endocrine & metabolic: Hypercholesterolemia (>300 mg/dL: 22%), hypertriglyceridemia (>400 mg/dL: 61%)

Gastrointestinal: Diarrhea (15%)

Hepatic: Transaminases increased (>2.5 x ULN: 26% to 32%; grade 3/4: 10% to 20%)

Neuromuscular & skeletal: CPK increased (grade 3/4: children 11%)

2% to 10%:

Central nervous system: Fever (6% to 8%), fatigue (6%), headache (5%)

Endocrine & metabolic: Dehydration (2%)

Gastrointestinal: Nausea (5% to 9%), amylase increased (grade 3: 6% to 8%), vomiting (6%), abdominal pain (4%), diarrhea (children 4%), weight loss (3%)

Hematologic: Bleeding (children 8%), WBC decreased (grades 3: 5%), anemia (3%), neutropenia (2%)

Hepatic: ALT increased (2%, grades 3/4: 10%), AST increased (grades 3/4: 6%), GGT increased (2%)

Neuromuscular & skeletal: Myalgia (2%)

Respiratory: Cough (children 6%), dyspnea (2%), epistaxis (children 4%)

<2%: Abdominal distension, anorexia, appetite decreased, diabetes mellitus, dizziness, dyspepsia, exanthem, facial wasting, flatulence, flu-like syndrome, gastroesophageal reflux, hepatic failure, hepatic steatosis, hepatitis, hyperbilirubinemia, hyperglycemia, hypersensitivity, immune reconstitution syndrome, insomnia, intracranial hemorrhage, lipase increased, lipoatrophy, lipodystrophy (acquired), lipohypertrophy, malaise, mitochondrial toxicity, muscle cramp, neuropathy (peripheral), pancreatitis, pruritus, renal insufficiency, sleep

disorder, somnolence, thrombocytopenia

Metabolism/Transport Effects **Substrate** of CYP3A4 (major; minimal metabolism when coadministered with ritonavir)

Drug Interactions

Abacavir: Protease Inhibitors may decrease the serum concentration of Abacavir. *Risk C: Monitor therapy*

Amiodarone: Protease Inhibitors may decrease the metabolism of Amiodarone. *Risk X: Avoid combination*

Antacids: May decrease the absorption of Protease Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Protease Inhibitors may decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Dihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): Protease Inhibitors may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Protease Inhibitors. Protease Inhibitors may decrease the metabolism of CarBAMazepine. *Risk D: Consider therapy modification*

Cisapride: Protease Inhibitors may decrease the metabolism of Cisapride. The resultant increase in serum cisapride concentrations may result in QTc prolongation and malignant cardiac arrhythmias. *Risk X: Avoid combination*

Clarithromycin: Protease Inhibitors may diminish the therapeutic effect of Clarithromycin. Specifically, certain protease inhibitors may decrease formation of the active 14-hydroxy-clarithromycin metabolite, which may negatively impact clarithromycin effectiveness vs. H. influenzae and other non-MAC infections. Protease Inhibitors may increase the serum concentration of Clarithromycin. Clarithromycin dose adjustment in renally impaired patients may be needed. Clarithromycin may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): Protease Inhibitors may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk D: Consider therapy modification*

CycloSPORINE: Protease Inhibitors may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Delavirdine: Protease Inhibitors may decrease the serum concentration of Delavirdine. Delavirdine may increase the serum concentration of Protease Inhibitors. *Risk D: Consider therapy modification*

Didanosine: Tipranavir may decrease the serum concentration of Didanosine. *Risk C: Monitor therapy*

Digoxin: Protease Inhibitors may increase the serum concentration of Digoxin. Increased serum concentrations of digoxin may increase risk of AV nodal blockade. *Risk C: Monitor therapy*

Disulfiram: May enhance the adverse/toxic effect of Tipranavir. *Risk D: Consider therapy modification*

Efavirenz: May increase the metabolism of Protease Inhibitors. This specifically includes amprenavir, indinavir, and saquinavir. Efavirenz may increase the serum concentration of Protease Inhibitors. This specifically includes nelfinavir and ritonavir. *Risk D: Consider therapy modification*

Enfuvirtide: Protease Inhibitors may increase the serum concentration of Enfuvirtide. Enfuvirtide may increase the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

Eplerenone: Protease Inhibitors may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Ergot Derivatives: Protease Inhibitors may decrease the metabolism of Ergot Derivatives. **Exceptions:** Cabergoline. *Risk X: Avoid combination*

Estrogen Derivatives: May enhance the dermatologic adverse effect of Tipranavir. The combination of tipranavir/ritonavir and ethinyl estradiol/norethindrone was associated with a high incidence of skin rash. Tipranavir may decrease the serum concentration of Estrogen Derivatives. *Risk D: Consider therapy modification*

Etravirine: Tipranavir may decrease the serum concentration of Etravirine. *Risk X: Avoid combination*

FentaNYL: Protease Inhibitors may decrease the metabolism of FentaNYL. *Risk C: Monitor therapy*

Flecainide: Tipranavir may increase the serum concentration of Flecainide. *Risk X: Avoid combination*

Fusidic Acid: Protease Inhibitors may decrease the metabolism of Fusidic Acid. Fusidic Acid may decrease the metabolism of Protease

Inhibitors. *Risk D: Consider therapy modification*

Garlic: May decrease the serum concentration of Protease Inhibitors. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Protease Inhibitors may increase the serum concentration of HMG-CoA Reductase Inhibitors. Limited data suggest pravastatin may slightly decrease protease inhibitor concentrations. Management: Lovastatin and simvastatin are contraindicated with many protease inhibitors; use lowest possible HMG-CoA reductase inhibitor dose and monitor for signs and symptoms of rhabdomyolysis if these agents are used concomitantly. **Exceptions:** Fluvastatin. *Risk D: Consider therapy modification*

Meperidine: Protease Inhibitors may enhance the adverse/toxic effect of Meperidine. Protease Inhibitors may decrease the serum concentration of Meperidine. Concentrations of the toxic Normeperidine metabolite may be increased. *Risk D: Consider therapy modification*

Methadone: Protease Inhibitors may decrease the metabolism of Methadone. *Risk C: Monitor therapy*

MetroNIDAZOLE: May enhance the adverse/toxic effect of Tipranavir. *Risk C: Monitor therapy*

Nefazodone: Protease Inhibitors may decrease the metabolism of Nefazodone. *Risk C: Monitor therapy*

Nevirapine: May increase the metabolism of Protease Inhibitors. *Risk D: Consider therapy modification*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

PHENobarbital: May decrease the serum concentration of Tipranavir. Tipranavir may decrease the serum concentration of PHENobarbital. *Risk D: Consider therapy modification*

Phenytoin: May decrease the serum concentration of Tipranavir. Tipranavir may decrease the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Phosphodiesterase 5 Inhibitors: Protease Inhibitors may decrease the metabolism of Phosphodiesterase 5 Inhibitors. Management: Dose restrictions for tadalafil, and/or sildenafil and vardenafil are recommended in combination with ritonavir, atazanavir, indinavir, darunavir and saquinavir. Consult specific prescribing information for detailed recommendations. *Risk D: Consider therapy modification*

Pimozide: Protease Inhibitors may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Propafenone: Tipranavir may increase the serum concentration of Propafenone. *Risk X: Avoid combination*

Protease Inhibitors: May increase the serum concentration of other Protease Inhibitors. Management: Atazanavir--indinavir combination contraindicated. Amprenavir oral solution not recommended with ritonavir oral solution; tipranavir/ritonavir or atazanavir/ritonavir not recommended with other protease inhibitors. Other combos may require dose changes. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: Tipranavir may decrease the serum concentration of Proton Pump Inhibitors. These data are derived from studies with Ritonavir-boosted Tipranavir. *Risk C: Monitor therapy*

QuiNIDine: Protease Inhibitors may decrease the metabolism of QuiNIDine. *Risk X: Avoid combination*

Raltegravir: Tipranavir may decrease the serum concentration of Raltegravir. *Risk C: Monitor therapy*

Rifamycin Derivatives: Protease Inhibitors may decrease the metabolism of Rifamycin Derivatives. Specifically rifabutin. Rifamycin Derivatives may decrease the serum concentration of Protease Inhibitors. Rifampin administration should be avoided. Dosage adjustments with both rifabutin and the protease inhibitors are necessary if used together. Management: Avoid using rifampin with protease inhibitors. Rifabutin and protease inhibitor dose adjustments will likely be required when using rifabutin together with protease inhibitors; consult specific protease inhibitor(s) prescribing information. *Risk D: Consider therapy modification*

Sirolimus: Protease Inhibitors may increase the serum concentration of Sirolimus. *Risk C: Monitor therapy*

St Johns Wort: May decrease the serum concentration of Tipranavir. *Risk X: Avoid combination*

Tacrolimus: Protease Inhibitors may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Temsirolimus: Protease Inhibitors may enhance the adverse/toxic effect of Temsirolimus. Levels of sirolimus, the active metabolite, may be increased, likely due to inhibition of CYP-mediated metabolism. *Risk D: Consider therapy modification*

Tenofovir: May decrease the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Tenofovir. *Risk C: Monitor therapy*

Theophylline Derivatives: Protease Inhibitors may decrease the serum concentration of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

TraZODone: Protease Inhibitors may increase the serum concentration of TraZODone. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: Protease Inhibitors may increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Valproic Acid: Protease Inhibitors may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Zidovudine: Protease Inhibitors may decrease the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Capsules contain dehydrated alcohol 7% w/w (0.1g per capsule)

Food: Bioavailability is increased with a high-fat meal.

Herb/Nutraceutical: St Johns wort may decrease the levels/effects of tipranavir/ritonavir; concurrent use is contraindicated. Vitamin E (high dose) may increase the risk of bleeding.

Monitoring ParametersViral load, CD4, serum glucose, liver function tests, bilirubin

Nursing: Physical Assessment/MonitoringUse caution in presence of impaired hepatic function, sulfonamide allergy, and risk for bleeding. Assess other pharmacologic or herbal products patient may be taking for potential interactions or toxicity (multiple liver enzyme interactions may increase potential for severe toxicity or loss of effectiveness); dosing adjustments may be necessary. A list of medications that should not be used concurrently is available in each bottle and patients should be provided with this information. Assess therapeutic response (eg, CD4 count, hepatic function) and adverse reactions at regular intervals during therapy (eg, gastrointestinal disturbance [nausea, vomiting, diarrhea] that can lead to dehydration and weight loss, hyperlipidemia, redistribution of body fat, rash, electrolyte imbalance). Caution patients to monitor glucose levels closely; may alter effects of hypoglycemic agents or cause hyperglycemia. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsViral load, CD4, serum glucose, liver function tests, bilirubin

Patient EducationYou will be provided with a list of specific medications that should not be used during therapy; do not take any new prescriptions, over-the-counter medications, or herbal products during therapy (even if they are not on the list) without consulting prescriber. This is not a cure for HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. Take exactly as directed with a high-fat meal. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you miss a dose, take as soon as possible and return to your regular schedule (never take a double dose). Frequent blood tests may be required with prolonged therapy. You may be advised to check your glucose levels; this drug can cause exacerbation or new-onset diabetes. May cause body changes due to redistribution of body fat, facial atrophy, or breast enlargement (normal effects of drug). May cause dizziness, insomnia, abnormal thinking (use caution when driving or engaging in potentially hazardous tasks until response to drug is known); nausea, vomiting, or taste perversion (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); muscle weakness (consult prescriber for approved analgesic); or headache or insomnia (consult prescriber for medication). Inform prescriber if you experience muscle numbness or tingling; unresolved persistent vomiting, diarrhea, or abdominal pain; respiratory difficulty or chest pain; unusual skin rash; change in color of stool or urine; or any persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber for appropriate contraceptives. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, soft gelatin:

Aptivus®: 250 mg [contains dehydrated ethanol 7% per capsule]

Solution:

Aptivus®: 100 mg/mL (95 mL) [contains vitamin E, propylene glycol; buttermint-butter toffee flavor]

Generic AvailableNo

Manufacturer

Boehringer Ingelheim

Pricing: U.S. (www.drugstore.com)

Capsules (Aptivus)

250 mg (120): $1019.87

Mechanism of ActionTipranavir is a nonpeptide inhibitor of HIV-1 protease. It binds to the protease activity site and inhibits the activity of the enzyme. HIV protease is required for the cleavage of viral polyprotein precursors into individual functional proteins found in infectious HIV. Inhibition prevents cleavage of these polyproteins, resulting in the formation of immature, noninfectious viral particles.

Pharmacodynamics/Kinetics

Absorption: Incomplete (percentage not established)

Distribution: V_d: 7.7-10 L

Protein binding: >99% (albumin, alpha_1-acid glycoprotein)

Metabolism: Hepatic, via CYP3A4 (minimal when coadministered with ritonavir)

Bioavailability: Not established; increased with high-fat meal

Half-life elimination: Children 2-<6 years of age: ~8 hours, 6-<12 years of age: ~7 hours, 12-18 years: ~5 hours; Adults: 6 hours

Time to peak, plasma: 3 hours

Excretion: Feces (82%); urine (4%); primarily as unchanged drug (when coadministered with ritonavir)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Perinatal HIV Guidelines

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause fatigue and depression

Mental Health: Effects on Psychiatric TreatmentContraindicated with midazolam, pimozide, and triazolam. May cause hyperlipidemia and hyperglycemia; concurrent use with atypical antipsychotics, valproic acid, and carbamazepine may produce additive effects; monitor. Use caution with disulfiram (capsules contain dehydrated ethanol). Carbamazepine may decrease serum concentration of tipranavir. The effect of methadone may be reduced by tipranavir requiring a dosage adjustment.

Index Terms PNU-140690E; TPV

References

Graff J, von Hentig N, Kuczka, K, et al, “Significant Effects of Tipranavir on Platelet Aggregation and Thromboxane B_2 Formation *in vitro* and *in vivo*,” *J Antimicrob Chemother*, 2008, 61(2):394-9.[PubMed 18156609]

“Perinatal HIV Guidelines Working Group. Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,” July 8, 2008. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” July 29, 2008. Available at: http://www.aidsinfo.nih.gov.

International Brand Names Aptivus (AR, AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, MX, NL, NO, PT, RU, SE, TR)

Tirofiban

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Aggrastat® may be confused with Aggrenox®, argatroban

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(tye roe FYE ban)
U.S. Brand NamesAggrastat®
Canadian Brand NamesAggrastat®
Pharmacologic CategoryAntiplatelet Agent, Glycoprotein IIb/IIIa Inhibitor
Use: Labeled IndicationsIn combination with heparin, is indicated for the treatment of acute coronary syndrome, including patients who are to be managed medically and those undergoing PTCA or atherectomy. In this setting, it has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction or refractory ischemia/repeat cardiac procedure.
Dosing: Adults**Acute coronary syndromes:** I.V.: Initial rate of 0.4 mcg/kg/minute for 30 minutes and then continued at 0.1 mcg/kg/minute. Dosing should be continued through angiography and for 12-24 hours after angioplasty or atherectomy.
Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentCl_{cr} <30 mL/minute: Reduce dose to 50% of normal rate.
Calculations

- Creatinine Clearance: Adults

Administration: I.V.Infuse over 30 minutes. Tirofiban injection must be diluted to a concentration of 50 mcg/mL (premixed solution does not require dilution). Unused solution should be discarded. Do not administer via the same IV line as diazepam.
Administration: I.V. DetailIntended for intravenous delivery using sterile equipment and technique. Do not add other drugs or remove solution directly from the bag with a syringe. Do not use plastic containers in series connections. Such use can result in air embolism by drawing air from the first container if it is empty of solution. Discard any unused solution. May be administered through the same catheter as heparin, lidocaine, dopamine, potassium chloride, and famotidine.
StorageStore at 25°C (77°F); do not freeze. Protect from light during storage.
CompatibilityStable in $D_5{}^1/_2$NS, D_5W, NS.

Y-site administration: Compatible: Atropine, dobutamine, dopamine, epinephrine, famotidine, heparin, lidocaine, midazolam, morphine, nitroglycerin, potassium chloride, propranolol. **Incompatible:** Diazepam.

ContraindicationsHypersensitivity to tirofiban or any component of the formulation; active internal bleeding or a history of bleeding diathesis within the previous 30 days; history of intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, or aneurysm; history of thrombocytopenia following prior exposure; history of CVA within 30 days or any history of hemorrhagic stroke; major surgical procedure or severe physical trauma within the previous month; history, symptoms, or findings suggestive of aortic dissection; severe hypertension (systolic BP >180 mm Hg and/or diastolic BP >110 mm Hg); concomitant use of another parenteral GP IIb/IIIa inhibitor; acute pericarditis
Allergy Considerations

- Glycoprotein (GP) IIb/IIIa Inhibitor Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: The most common complication is bleeding, including retroperitoneal, pulmonary, and spontaneous GI and/or GU bleeding; watch closely for bleeding, especially the arterial access site for the cardiac catheterization. Use with extreme caution in patients with platelet counts <150,000/mm^3, patients with hemorrhagic retinopathy, previous history of GI disease, recent thrombolytic therapy and in chronic dialysis patients. Use caution with administration of other drugs affecting hemostasis. Minimize other procedures including arterial and venous punctures, I.M. injections, nasogastric tubes, etc.

Disease-related concerns:

- Renal impairment: Adjust the dose with severe renal dysfunction (Cl_{cr} <30 mL/minute).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Sheath removal: Prior to pulling the sheath, heparin should be discontinued for 3-4 hours and ACT <180 seconds or aPTT <45 seconds. Use standard compression techniques after sheath removal. Watch the site closely afterwards for further bleeding.

Geriatric ConsiderationsElderly patients receiving tirofiban with heparin or heparin alone had a higher incidence of bleeding in clinical trials. Caution must be used when using other drugs affecting hemostasis, which are commonly used in elderly.

Pregnancy Risk FactorB

LactationExcretion in breast milk unknown/contraindicated

Adverse ReactionsBleeding is the major drug-related adverse effect. Patients received background treatment with aspirin and heparin. Major bleeding was reported in 1.4% to 2.2%; minor bleeding in 10.5% to 12%; transfusion was required in 4% to 4.3%.

>1% (nonbleeding adverse events):

Cardiovascular: Bradycardia (4%), coronary artery dissection (5%), edema (2%)

Central nervous system: Dizziness (3%), fever (>1%), headache (>1%), vasovagal reaction (2%)

Gastrointestinal: Nausea (>1%)

Genitourinary: Pelvic pain (6%)

Hematologic: Thrombocytopenia: <90,000/mm^3 (1.5%), <50,000/mm^3 (0.3%)

Neuromuscular & skeletal: Leg pain (3%)

Miscellaneous: Diaphoresis (2%)

<1% (Limited to important or life-threatening): Intracranial bleeding (up to 0.1%), GI bleeding (0.1% to 0.2%), retroperitoneal bleeding (up to 0.6%), GU bleeding (up to 0.1%), hemopericardium, hives, pulmonary alveolar hemorrhage, rash, anaphylaxis (case reports), severe (<10,000/mm^3) thrombocytopenia (rare), spinal-epidural hematoma, urticaria

Drug Interactions

Anticoagulants: Antiplatelet Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of other Antiplatelet Agents. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Drotrecogin Alfa: Antiplatelet Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Antiplatelet Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Ibritumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Ibritumomab. Both agents may contribute to impaired platelet function and an increased risk of bleeding. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Omega-3-Acid Ethyl Esters: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the adverse/toxic effect of Antiplatelet Agents. Specifically, the risk of bleeding may be increased by concurrent use of these agents. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Salicylates: Antiplatelet Agents may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result. *Risk C: Monitor therapy*

Thrombolytic Agents: Antiplatelet Agents may enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Tositumomab and Iodine I 131 Tositumomab: Antiplatelet Agents may enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Monitoring ParametersPlatelet count. Hemoglobin and hematocrit should be monitored prior to treatment, within 6 hours following loading infusion, and at least daily thereafter during therapy. Platelet count may need to be monitored earlier in patients who received prior glycoprotein IIb/IIa antagonists. Persistent reductions of platelet counts <90,000/mm^3 may require interruption or discontinuation of infusion. Because tirofiban requires concurrent heparin therapy, aPTT levels should also be followed. Monitor vital signs and laboratory results prior to, during, and after therapy. Assess infusion insertion site during and after therapy (every 15 minutes or as institutional policy). Observe and teach patient bleeding precautions (avoid invasive procedures and activities that could result in injury). Monitor closely for signs of unusual or excessive bleeding (eg, CNS changes, blood in urine, stool, or vomitus, unusual bruising or bleeding). Breast-feeding is contraindicated.

Nursing: Physical Assessment/MonitoringMonitor vital signs and laboratory results prior to, during, and after therapy. Assess infusion insertion site during and after therapy. Monitor closely for bleeding and teach bleeding precautions.

Monitoring: Lab TestsPlatelet count, persistent reductions <90,000/mm^3 may require interruption or discontinuation of infusion. Hemoglobin and hematocrit should be monitored prior to treatment, within 6 hours following loading infusion, and at least daily thereafter during therapy. Platelet count may need to be monitored earlier in patients who received prior glycoprotein IIb/IIa antagonists. Because tirofiban requires concurrent heparin therapy, aPTT levels should also be followed.

Patient EducationEmergency use may dictate depth of patient education. This medication can only be administered I.V. You will have a tendency to bleed easily following this medication. Use caution to prevent injury (use electric razor, use soft toothbrush, use caution with sharps). If bleeding occurs, apply pressure to bleeding spot until bleeding stops completely. Report unusual bruising or bleeding (eg, blood in urine, stool, or vomitus, bleeding gums, vaginal bleeding, nosebleeds); unusual and persistent fever; dizziness or vision changes; back, leg, or pelvic pain; or persistent nausea or vomiting. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontuned product

Infusion [premixed in sodium chloride]:

Aggrastat®: 50 mcg/mL (100 mL, 250 mL)

Injection, solution:

Aggrastat®: 250 mcg/mL (50 mL) [DSC]

Generic AvailableNo

Mechanism of ActionA reversible antagonist of fibrinogen binding to the GP IIb/IIIa receptor, the major platelet surface receptor involved in platelet aggregation. When administered intravenously, it inhibits *ex vivo* platelet aggregation in a dose- and concentration-dependent manner. When given according to the recommended regimen, >90% inhibition is attained by the end of the 30-minute infusion. Platelet aggregation inhibition is reversible following cessation of the infusion.

Pharmacodynamics/Kinetics

Distribution: 35% unbound

Metabolism: Minimally hepatic

Half-life elimination: 2 hours

Excretion: Urine (65%) and feces (25%) primarily as unchanged drug

Clearance: Elderly: Reduced by 19% to 26%

Related Information

- Glycoprotein Antagonists

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentContraindicated in patients with a recent stroke (within 30 days)

Cardiovascular Considerations

Acute Coronary Syndromes (ACS): The 2004 ACC/AHA STEMI and the 2002 ACC/AHA unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) guidelines recommend administration of intravenous glycoprotein IIb/IIIa inhibitors in patients with non-ST-segment elevation ACS with high-risk features (eg, positive biochemical markers of infarction, ST-segment depression, or signs of LV dysfunction) or refractory ischemia. Eptifibatide or tirofiban (with ASA and LMWH or UFH) should be chosen in patients who have high-risk features where an invasive management strategy is not planned. In addition, a glycoprotein IIb/IIIa inhibitor is recommended for patients who will undergo percutaneous coronary intervention (PCI).

Adjunct to Thrombolysis: In the TARGET trial, abciximab (FDA-approved dose) and tirofiban (10 mcg/kg bolus; infusion of 0.15 mcg/kg/minute for 18-24 hours) were compared to each other in patients undergoing coronary stenting. The primary endpoint was death, nonfatal MI, or urgent target vessel revascularization at 30 days. Abciximab improved outcome to a greater extent than tirofiban, primarily by reducing nonfatal MI. Follow-up at one year revealed no significant difference in primary outcomes between treatments.

Platelet Effects: Tirofiban has a short duration of action and hemostasis is restored within ~4 hours after discontinuation in patients with normal renal function.

Anesthesia and Critical Care Concerns/Other Considerations**Platelet Effects:** Tirofiban has a short duration of action and hemostasis is restored within about 4 hours after discontinuation in patients with normal renal function.

Index TermsMK383; Tirofiban Hydrochloride

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International Brand NamesAggrastat (AT, BB, BE, BG, BM, BS, BZ, CH, CZ, DE, DK, EE, FI, GB, GY, HK, HN, HU, IE, IL, IT, JM, MY, NL, NO, NZ, PH, PK, PL, SE, SG, SR, TT, TW); Agrastat (AR, BR, CN, CO, CR, EC, ES, FR, GT, HN, KP, MX, NI, PA, PE, SV, UY, VE)

TiZANidine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

TiZANidine may be confused with tiaGABine

Zanaflex® capsules and Zanaflex® tablets (or generic tizanidine tablets) are not interchangeable

Pronunciation(tye ZAN i deen)

U.S. Brand NamesZanaflex Capsules™; Zanaflex®

Canadian Brand NamesApo-Tizanidine®; Gen-Tizanidine; Zanaflex®

Pharmacologic CategoryAlpha$_2$-Adrenergic Agonist

Use: Labeled IndicationsSkeletal muscle relaxant used for treatment of muscle spasticity

Use: Unlabeled/InvestigationalTension headaches, low back pain, and trigeminal neuralgia

Dosing: Adults**Spasticity:** Usual initial dose: 4 mg, may increase by 2-4 mg as needed for satisfactory reduction of muscle tone every 6-8 hours to a maximum of 3 doses in any 24 hour period

Range: 2-4 mg 3 times/day

Maximum: 36 mg/day

Dosing: ElderlyNo specific dosing guidelines exist; clearance is decreased; dose cautiously.

Dosing: Renal ImpairmentCl_{cr} <25 mL/minute: Use with caution; clearance reduced >50%. During initial dose titration, use reduced doses. If higher doses necessary, increase dose instead of increasing dosing frequency.

Dosing: Hepatic ImpairmentAvoid use in hepatic impairment; if used, lowest possible dose should be used initially with close monitoring for adverse effects (eg, hypotension).

Administration: OralCapsules may be opened and contents sprinkled on food; however, extent of absorption is increased up to 20% relative to administration of the capsule under fasted conditions.

Dietary ConsiderationsAdministration with food compared to administration in the fasting state results in clinically-significant differences in absorption and other pharmacokinetic parameters. Patients should be consistent and should not switch administration of the tablets or the capsules between the fasting and nonfasting state. In addition, switching between the capsules and the tablets in the fed state will also result in significant differences. Opening capsule contents to sprinkle on applesauce compared to swallowing intact capsules whole will also result in significant absorption differences. Patients should be consistent with regards to administration.

ContraindicationsHypersensitivity to tizanidine or any component of the formulation; concomitant therapy with ciprofloxacin or fluvoxamine (potent CYP1A2 inhibitors)

Warnings/Precautions

Concerns related to adverse effects:

- Hepatic effects: Potential for hepatotoxicity; AST/ALT elevations (≥2 times baseline) and rarely hepatic failure have occurred; monitor aminotransferases prior to and during use.
- Hypotension: Dose-related significant hypotension (possibly with bradycardia or orthostatic hypotension) may occur; use with caution in patients with cardiac disease or those at risk for severe hypotensive effects.
- Sedation: Dose-related sedation common with use; significant and severe sedation may also occur; use with caution in patients at risk for sedative effects.
- Visual hallucinations: Use has been associated with visual hallucinations or delusions, generally in first 6 weeks of therapy; use caution in patients with psychiatric disorders.

Disease-related concerns:

- Hepatic impairment: Avoid or use extreme caution in patients with hepatic impairment; potential for effects likely due to extensive hepatic metabolism of tizanidine.
- Renal impairment: Use with caution in patients with renal impairment; clearance decreased significantly in severe impairment (Cl_{cr} <25 mL/minute) and dose reductions recommended.

Concurrent drug therapy issues:

- Antihypertensives: Hypotensive effects may be potentiated when used with antihypertensives.
- CNS depressants: Sedative effects may be potentiated when used with other CNS depressants.
- High potential for interactions: In general, avoid use in patients taking other CYP1A2 inhibitors; if taken concomitantly, use with caution and monitor for increased hypotensive and sedative effects of tizanidine.

Special populations:

- Elderly: Use with caution; clearance decreased fourfold in the elderly; may increase risk of adverse effects and/or duration of effects. Elderly with severe renal impairment (Cl_{cr} <25 mL/minute) may have clearance reduced by >50% compared to healthy elderly subjects.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Abrupt withdrawal: Withdrawal resulting in rebound hypertension, tachycardia, and hypertonia may occur upon discontinuation; doses should be decreased slowly, particularly in patients receiving high doses for prolonged periods.

- Food: Food alters absorption profile relative to administration under fasting conditions. In addition, bioequivalence between capsules and tablets altered by food; capsules and tablets bioequivalent under fasting conditions, but not under nonfasting conditions.

- Long-term use: Limited data exists for chronic use of single doses >8 mg and multiple doses >24 mg/day.

Geriatric ConsiderationsSince elderly commonly have renal function of Cl_{cr}<30 mL/minute, creatinine clearance should be estimated before dosing this medication. Low doses should be started initially because of the possibility of CNS effects.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsFrequency percentages below reported during multiple-dose studies, unless specified otherwise.

>10%:

Cardiovascular: Hypotension (single-dose study with doses ≥8 mg: 16% to 33%)

Central nervous system: Somnolence (48%), dizziness (16%)

Gastrointestinal: Xerostomia (49%)

Neuromuscular & skeletal: Weakness (41%)

1% to 10%:

Cardiovascular: Bradycardia (single-dose study with doses ≥8 mg: 2% to 10%)

Central nervous system: Nervousness (3%), speech disorder (3%), visual hallucinations/delusions (3%; generally occurring in first 6 weeks of therapy), anxiety (1%), depression (1%), fever (1%)

Dermatologic: Rash (1%), skin ulcer (1%)

Gastrointestinal: Constipation (4%), vomiting (3%), abdominal pain (1%), diarrhea (1%), dyspepsia (1%)

Genitourinary: UTI (10%), urinary frequency (3%)

Hepatic: Liver enzymes increased (3% to 5%)

Neuromuscular & skeletal: Dyskinesia (3%), back pain (1%), myasthenia (1%), paresthesia (1%)

Ocular: Blurred vision (3%)

Respiratory: Pharyngitis (3%), rhinitis (3%)

Miscellaneous: Infection (6%), flu-like syndrome (3%), diaphoresis (1%)

<1%, frequency not defined, and postmarketing experience (limited to important or life-threatening): Adrenal insufficiency, allergic reaction, anemia, angina, arrhythmia, asthma, carcinoma, cellulitis, cholelithiasis, coronary artery disorder, deafness, dementia, dyslipidemias, fecal impaction, gastrointestinal hemorrhage, glaucoma, heart failure, hepatomegaly, hemiplegia, hepatic failure, hepatitis, hepatoma, hyperglycemia, hypokalemia, hyponatremia, hypoproteinemia, hypothyroidism, jaundice, leukopenia, leukocytosis, MI, optic neuritis, palpitation, personality disorder (various), pneumonia, postural hypotension, psychotic-like symptoms, pulmonary embolus, respiratory acidosis, retinal hemorrhage, sepsis, suicide attempt, syncope, thrombocythemia, thrombocytopenia, ventricular extrasystoles, ventricular tachycardia

Metabolism/Transport Effects**Substrate** of CYP1A2 (major)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Antidepressants (Alpha2-Antagonist): May diminish the hypotensive effect of Alpha2-Agonists. *Risk D: Consider therapy modification*

Beta-Blockers: May enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Levobunolol; Metipranolol. *Risk D: Consider therapy modification*

Ciprofloxacin: May decrease the metabolism of TiZANidine. *Risk X: Avoid combination*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Fluvoxamine: May decrease the metabolism of TiZANidine. *Risk X: Avoid combination*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Iobenguane I 123: Alpha2-Agonists may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Oral Contraceptive (Estrogens): May increase the serum concentration of TiZANidine. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May diminish the antihypertensive effect of Alpha2-Agonists. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May diminish the antihypertensive effect of Alpha2-Agonists. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: The tablet and capsule dosage forms are not bioequivalent when administered with food. Food increases both the time to peak concentration and the extent of absorption for both the tablet and capsule. However, maximal concentrations of tizanidine achieved when administered with food were increased by 30% for the tablet, but decreased by 20% for the capsule. Under fed conditions, the capsule is approximately 80% bioavailable relative to the tablet.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may increase hypotensive effects).

Monitoring ParametersMonitor liver function (aminotransferases) at baseline, 1, 3, 6 months and periodically thereafter; blood pressure; renal function

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. May cause hypotension; monitor blood pressure periodically. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions on a regular basis throughout therapy. Do not discontinue medication abruptly; can cause hypertension and tachycardia. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsMonitor liver function (aminotransferases) at baseline, 1, 3, 6 months and periodically thereafter; renal function

Patient EducationDo not take any new medications without approval from prescriber. Take exactly as directed; do not change dosage or discontinue without consulting prescriber. If you miss a dose, take the missed dose as soon as possible if it is within an hour or so of the regular time. If not within an hour or so, skip the missed dose and go back to your regular dosing schedule. Do not double doses. Avoid alcohol. May cause dizziness, nervousness, insomnia, or daytime drowsiness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution and avoid quick moves when rising from sitting or lying position, climbing stairs, or engaging in activities that require quick movements); or nausea, vomiting, dry mouth, mouth sores, or upset stomach (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report persistent dizziness or GI symptoms; chest pain or palpitations; CNS disturbances (delusions, confusion); muscle weakness or tremors; rash; respiratory difficulty; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Zanaflex Capsules™: 2 mg, 4 mg, 6 mg

Tablet: 2 mg, 4 mg

Zanaflex®: 2 mg [DSC], 4 mg [scored]

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Capsules (Zanaflex)

2 mg (150): $266.18

4 mg (150): $360.62

6 mg (150): $500.58

Tablets (Tizanidine HCl)

2 mg (90): $19.99

4 mg (90): $81.99

Tablets (Zanaflex)

4 mg (90): $173.98

Mechanism of ActionAn alpha$_2$-adrenergic agonist agent which decreases excitatory input to alpha motor neurons; an imidazole derivative chemically-related to clonidine, which acts as a centrally acting muscle relaxant with alpha$_2$-adrenergic agonist properties; acts on the level of the spinal cord

Pharmacodynamics/Kinetics

Duration: 3-6 hours

Absorption: Tablets and capsules are bioequivalent under fasting conditions, but not under nonfasting conditions.

Tablets administered with food: Peak plasma concentration is increased by ~30%; time to peak increased by 25 minutes; extent of absorption increased by ~30%.

Capsules administered with food: Peak plasma concentration decreased by 20%; time to peak increased by 2-3 hours; extent of absorption increased by ~10%.

Capsules opened and sprinkled on applesauce are not bioequivalent to administration of intact capsules under fasting conditions. Peak plasma concentration and AUC are increased by 15% to 20%.

Protein binding: ~30%

Metabolism: Extensively hepatic

Bioavailability: ~40% (extensive first-pass metabolism)

Half-life elimination: 2.5 hours

Time to peak, serum:

Fasting state: Capsule, tablet: 1 hour

Fed state: Capsule: 3-4 hours, Tablet: 1.5 hours

Excretion: Urine (60%); feces (20%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause dizziness, anxiety, nervousness, or insomnia; may rarely cause psychosis

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation and dry mouth

Index TermsSirdalud®

International Brand NamesMio-Relax (CO); Myores (ID); Myos-Nor (CO); Sirdalud (AE, AR, AT, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CN, CO, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HN, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, OM, PE, PH, PL, PR, PT, PY, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TR, TT, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Sirdalud MR (CH, NL, PL); Sirdalud Retard (DK, FI); Sirdalum (UY); Spaslax (TW); Stidine (TW); Ternelax (PH); Ternelin (JP); Tizalin (TW); Tizan (TH); Zanaflex (GB, IE); Zita (PK); Zitanid (ID)

Tobramycin and Dexamethasone

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English

English

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Medication Safety Issues

Sound-alike/look-alike issues:

TobraDex® may be confused with Tobrex®

Pronunciation(toe bra MYE sin & deks a METH a sone)

U.S. Brand NamesTobraDex®

Canadian Brand NamesTobradex®

Pharmacologic CategoryAntibiotic/Corticosteroid, Ophthalmic

Use: Labeled IndicationsTreatment of external ocular infection caused by susceptible gram-negative bacteria and steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, lid, cornea, and anterior segment of the globe

Dosing: Adults**Ocular infection/inflammation:** Ophthalmic: Instill 1-2 drops of solution every 4 hours; apply ointment 2-3 times/day; for severe infections apply ointment every 3-4 hours, or solution 2 drops every 30-60 minutes initially, then reduce to less frequent intervals

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Ocular infection/inflammation:** Children: Refer to adult dosing.

Administration: OtherContact lenses should not be worn during therapy.

Ointment: Do not touch tip of tube to eye. Instill ointment into pocket between eyeball and lower lid; patient should look downward before closing eye.

Suspension: Shake well before using; Tilt head back, instill suspension in conjunctival sac and close eye(s). Do not touch dropper to eye. Apply light finger pressure on lacrimal sac for 1 minute following instillation.

ContraindicationsHypersensitivity to tobramycin, dexamethasone, or any component of the formulation; viral, fungal, or tuberculosis diseases of the eye

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Infection: Steroids may mask infection or enhance existing ocular infection; prolonged use may result in secondary infections due to immunosuppression.
- Ocular effects: Prolonged use of corticosteroids may result in glaucoma; damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation may occur.
- Sensitivity reactions: Sensitivity to tobramycin may develop; discontinue if sensitivity reaction occurs.
- Superinfection: Prolonged use may result in fungal or bacterial superinfection.

Special populations:

- Cataract surgery patients: Use following cataract surgery may delay healing or increase the incidence of bleb formation.
- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Dosage form specific issues:

- Benzalkonium chloride: Suspension contains benzalkonium chloride which may be adsorbed by contact lenses; contact lenses should not be worn during treatment of ophthalmic infections.

Other warnings/precautions:

- Appropriate use: For ophthalmic use only. A maximum of 8 g of ointment or 20 mL of suspension should be prescribed initially; patients should be evaluated prior to additional refills.

Geriatric ConsiderationsAssess patient's ability to correctly self-administer eye drops.

Pregnancy Risk FactorC

Pregnancy ConsiderationsSee individual agents.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsIt is unknown if topical use results in sufficient absorption to produce detectable quantities in breast milk.

Adverse ReactionsUnless otherwise noted, frequency not defined.

Dermatologic: Allergic contact dermatitis, delayed wound healing

Ocular: Cataract formation, conjunctival erythema (<4%), glaucoma, intraocular pressure increased, keratitis, lacrimation, lid itching (<4%), lid swelling (<4%), optic nerve damage, secondary infection

Metabolism/Transport Effects

Dexamethasone: **Substrate** of CYP3A4 (minor); **Induces** CYP2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

Caspofungin: Inducers of Drug Clearance may decrease the serum concentration of Caspofungin. Management: Consider using an increased caspofungin dose of 70mg daily in adults (or 70mg/m^2, up to a maximum of 70mg, daily in pediatric patients) when coadministered with known inducers of drug clearance. *Risk D: Consider therapy modification*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inducers (Strong) may increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Lenalidomide: Dexamethasone may enhance the thrombogenic effect of Lenalidomide. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

Nilotinib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nilotinib. *Risk X: Avoid combination*

Nisoldipine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Nisoldipine. *Risk X: Avoid combination*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Ranolazine: CYP3A4 Inducers (Strong) may decrease the serum concentration of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Sorafenib: CYP3A4 Inducers (Strong) may decrease the serum concentration of Sorafenib. *Risk D: Consider therapy modification*

Thalidomide: Dexamethasone may enhance the dermatologic adverse effect of Thalidomide. Dexamethasone may enhance the thrombogenic effect of Thalidomide. *Risk D: Consider therapy modification*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Monitoring ParametersIntraocular pressure and secondary infection with prolonged use
Nursing: Physical Assessment/MonitoringSee individual agents.
Patient Education

See individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Ointment, ophthalmic: Tobramycin 0.3% and dexamethasone 0.1% (3.5 g)

Suspension, ophthalmic: Tobramycin 0.3% and dexamethasone 0.1% (2.5 mL, 5 mL, 10 mL) [contains benzalkonium chloride]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Ointment (TobraDex)

0.3-0.1% (3.5): $94.17

Suspension (TobraDex)

0.3-0.1% (2.5): $49.38

0.3-0.1% (5): $82.83

0.3-0.1% (10): $152.58

Mechanism of ActionRefer to individual monographs for Dexamethasone and Tobramycin
Pharmacodynamics/Kinetics

Absorption: Into aqueous humor

Time to peak, serum: 1-2 hours in the cornea and aqueous humor

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsDexamethasone and Tobramycin
International Brand NamesBralifex Plus (ID); Duocom (PH); Mydexin (PH); Mytodex (PH); Ramtrex (PH); Tobesyn Eye Drop (KP); Tobracort (CO, MX, PE); Tobradex (AE, AR, BE, BF, BG, BH, BJ, BR, CH, CI, CL, CN, CR, CY, DK, EE, EG, ES, ET, FR, GB, GH, GM, GN, GR, GT, HK, HN, IL, IN, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NI, OM, PA, PH, PK, PY, QA, SA, SC, SD, SL, SN, SV, SY, TN, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Tobragan D (CO, EC); Tobrasone (NO, SE)

Tobramycin

Lexi-Drugs Online

English

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Tobramycin may be confused with Trobicin®, vancomycin

AKTob® may be confused with AK-Trol®

Nebcin® may be confused with Inapsine®, Naprosyn®, Nubain®

Tobrex® may be confused with TobraDex®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (intrathecal administration) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(toe bra MYE sin)

U.S. Brand NamesAKTob®; TOBI®; Tobrex®

Canadian Brand NamesPMS-Tobramycin; Sandoz-Tobramycin; TOBI®; Tobramycin Injection, USP; Tobrex®

Pharmacologic Category[Antibiotic, Aminoglycoside](); [Antibiotic, Ophthalmic]()

Use: Labeled IndicationsTreatment of documented or suspected infections caused by susceptible gram-negative bacilli including *Pseudomonas aeruginosa*; topically used to treat superficial ophthalmic infections caused by susceptible bacteria. Tobramycin solution for inhalation is indicated for the management of cystic fibrosis patients (>6 years of age) with *Pseudomonas aeruginosa*.

Dosing: Adults**Note:** Individualization is **critical** because of the low therapeutic index.

Use of ideal body weight (IBW) for determining the mg/kg/dose appears to be more accurate than dosing on the basis of total body weight (TBW). In morbid obesity, dosage requirement may best be estimated using a dosing weight of IBW + 0.4 (TBW - IBW).

Initial and periodic plasma drug levels (eg, peak and trough with conventional dosing) should be determined, particularly in critically-ill patients with serious infections or in disease states known to significantly alter aminoglycoside pharmacokinetics (eg, cystic fibrosis, burns, or major surgery).

Severe life-threatening infections: I.M., I.V.:

Conventional: 1-2.5 mg/kg/dose every 8-12 hours; to ensure adequate peak concentrations early in therapy, higher initial dosage may be considered in selected patients when extracellular water is increased (edema, septic shock, postsurgical, and/or trauma)

Once-daily: 4-7 mg/kg/dose once daily; some clinicians recommend this approach for all patients with normal renal function; this dose is at least as efficacious with similar, if not less, toxicity than conventional dosing.

Brucellosis: I.M., I.V.: 240 mg (I.M.) daily or 5 mg/kg (I.V.) daily for 7 days; either regimen recommended in combination with doxycycline

Cholangitis: I.M., I.V.: 4-6 mg/kg once daily with ampicillin

Cystic fibrosis: Inhalation:

Aerosolized tobramycin injection (unlabeled use): 80 mg 2 times/day; **Note:** Injectable formulation may contain preservatives, which may increase risk of bronchospasm.

TOBI®: 300 mg every 12 hours (do not administer doses <6 hours apart); administer in repeated cycles of 28 days on drug followed by 28 days off drug.

Diverticulitis, complicated: I.M., I.V.: 1.5-2 mg/kg every 8 hours (with ampicillin and metronidazole)

Infective endocarditis or synergy (for gram-positive infections): I.M., I.V.: 1 mg/kg every 8 hours (with ampicillin)

Meningitis*(Enterococcus or Pseudomonas aeruginosa)*: I.V.: 5 mg/kg/day in divided doses every 8 hours (administered with another bacteriocidal drug)

Ocular infections: Ophthalmic:

Ointment: Apply 2-3 times/day; for severe infections, apply every 3-4 hours

Solution: Instill 1-2 drops every 4 hours; for severe infections, instill 2 drops every 30-60 minutes initially, then reduce to less frequent intervals

Pelvic inflammatory disease: I.M., I.V.: Loading dose: 2 mg/kg, then 1.5 mg/kg every 8 hours **or** 4.5 mg/kg once daily

Plague*(Yersinia pestis)*: I.M., I.V.: Treatment: 5 mg/kg/day, followed by postexposure prophylaxis with doxycycline

Pneumonia, hospital- or ventilator-associated: I.M., I.V.: 7 mg/kg/day (with antipseudomonal beta-lactam or carbapenem)

Prophylaxis against endocarditis (dental, oral, upper respiratory procedures, GI/GU procedures): I.M., I.V.: 1.5 mg/kg with ampicillin (50 mg/kg) 30 minutes prior to procedure. **Note:** AHA guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur. As of April 2007, routine prophylaxis no longer recommended by the AHA.

Tularemia: I.M., I.V.: 5 mg/kg/day divided every 8 hours for 1-2 weeks

Urinary tract infection: I.M., I.V.: 1.5 mg/kg/dose every 8 hours

Dosing: ElderlyDosage should be based on an estimate of ideal body weight.

I.M., I.V.: 1.5-5 mg/kg/day in 1-2 divided doses

I.V.: Once daily or extended interval: 5-7 mg/kg/dose given every 24, 36, or 48 hours based on Cl_{cr} (see Renal Impairment and Geriatric Considerations).

Dosing: PediatricIndividualization is **critical** because of the low therapeutic index

Use of ideal body weight (IBW) for determining the mg/kg/dose appears to be more accurate than dosing on the basis of total body weight (TBW). In morbid obesity, dosage requirement may best be estimated using a dosing weight of IBW + 0.4 (TBW - IBW).

Usual dosage range: I.M., I.V.:

Infants and Children <5 years: 2.5 mg/kg/dose every 8 hours

Children >5 years: 2-2.5 mg/kg/dose every 8 hours

Ocular infection: Ophthalmic: Children ≥2 months: Refer to adult dosing.

Cystic fibrosis:

I.M., I.V.: 2.5-3.3 mg/kg every 6-8 hours. **Note:** Some patients may require larger or more frequent doses if serum levels document the need (eg, cystic fibrosis or febrile granulocytopenic patients).

Inhalation:

Aerosolized tobramycin injection (unlabeled use): 80 mg 2 times/day. **Note:** Injectable formulation may contain preservatives, which may increase risk of bronchospasm.

TOBI®: Children ≥6 years: Refer to adult dosing.

Meningitis: Neonates: I.M., I.V.:

0-7 days: <2000 g: 2.5 mg/kg every 18-24 hours; >2000 g: 2.5 mg/kg every 12 hours

8-28 days: <2000 g: 2.5 mg/kg every 8-12 hours; >2000 g: 2.5 mg/kg every 8 hours

Dosing: Renal ImpairmentI.M., I.V.:

Conventional dosing:

Cl_{cr} ≥60 mL/minute: Administer every 8 hours.

Cl_{cr} 40-60 mL/minute: Administer every 12 hours.

Cl_{cr} 20-40 mL/minute: Administer every 24 hours.

Cl_{cr} 10-20 mL/minute: Administer every 48 hours.

Cl_{cr} <10 mL/minute: Administer every 72 hours.

High-dose therapy: Interval may be extended (eg, every 48 hours) in patients with moderate renal impairment (Cl_{cr} 30-59 mL/minute) and/or adjusted based on serum level determinations.

Dialyzable; 30% removal of aminoglycosides occurs during 4 hours of HD - administer dose after dialysis and follow levels.

Continuous arteriovenous or venovenous hemofiltration: Dose as for Cl_{cr} of 10-40 mL/minute and follow levels.

Administration via CAPD fluid:

Gram-negative infection: 4-8 mg/L (4-8 mcg/mL) of CAPD fluid

Gram-positive infection (ie, synergy): 3-4 mg/L (3-4 mcg/mL) of CAPD fluid

Administration IVPB/I.M.: Dose as for Cl_{cr} <10 mL/minute and follow levels.

Dosing: Hepatic ImpairmentMonitor plasma concentrations.

Calculations

- Adjusted Body Weight
- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics
- Ideal Body Weight: Adults
- Ideal Body Weight: Pediatrics

Administration: I.V.Infuse over 30-60 minutes.

Some penicillins (eg, carbenicillin, ticarcillin and piperacillin) have been shown to inactivate aminoglycosides *in vitro*. This has been observed to a greater extent with tobramycin and gentamicin, while amikacin has shown greater stability against inactivation. Concurrent use of these agents may pose a risk of reduced antibacterial efficacy *in vivo*, particularly in the setting of profound renal impairment. However, definitive clinical evidence is lacking. If combination penicillin/aminoglycoside therapy is desired in a patient with renal dysfunction, separation of doses (if feasible), and routine monitoring of aminoglycoside levels, CBC, and clinical response should be considered.

Administration: I.V. DetailFlush with saline before and after administration. **Incompatible** with heparin.

pH: 3.0-6.5 (injection, adjusted); 6-8 (reconstituted solution from powder)

Administration: InhalationTOBI®: To be inhaled over ~15 minutes using a handheld nebulizer (PARI-LC PLUS™). If multiple different nebulizer treatments are required, administer bronchodilator first, followed by chest physiotherapy, any other nebulized medications, and then TOBI® last. Do not mix with other nebulizer medications.

Administration: TopicalOphthalmic solution: Allow 5 minutes between application of "multiple-drop" therapy.

Administration: OtherOphthalmic: Contact lenses should not be worn during treatment of ophthalmic infections.

Ointment: Do not touch tip of tube to eye. Instill ointment into pocket between eyeball and lower lid; patient should look downward before closing eye.

Solution: Contact lenses should not be worn during treatment of ophthalmic infections. Allow 5 minutes between application of "multiple-drop" therapy.

Suspension: Shake well before using; tilt head back, instill suspension in conjunctival sac and close eye(s). Do not touch dropper to eye. Apply light finger pressure on lacrimal sac for 1 minute following instillation.

Dietary ConsiderationsMay require supplementation of calcium, magnesium, potassium.

Storage

Injection: Stable at room temperature both as the clear, colorless solution and as the dry powder. Reconstituted solutions remain stable for 24 hours at room temperature and 96 hours when refrigerated.

Ophthalmic solution: Store at 8°C to 27°C (46°F to 80°F).

Solution, for inhalation (TOBI®): Store under refrigeration at 2°C to 8°C (36°F to 46°F). May be stored in foil pouch at room temperature of 25°C (77°F) for up to 28 days. Avoid intense light. Solution may darken over time; however, do not use if cloudy or contains particles.

ReconstitutionDilute in 50-100 mL NS, D_5W for I.V. infusion.

CompatibilityStable in dextran 40 10% in dextrose, D_5NS, D_5W, $D_{10}W$, mannitol 20%, LR, NS; **variable stability (consult detailed reference)** in peritoneal dialysis solutions.

Y-site administration: Compatible: Acyclovir, alatrofloxacin, amifostine, amiodarone, amsacrine, aztreonam, ciprofloxacin, cisatracurium, cyclophosphamide, diltiazem, docetaxel, doxorubicin liposome, enalaprilat, esmolol, etoposide phosphate, filgrastim, fluconazole, fludarabine, foscarnet, furosemide, gatifloxacin, gemcitabine, granisetron, hydromorphone, IL-2, insulin (regular), labetalol, linezolid, magnesium sulfate, melphalan, meperidine, midazolam, morphine, perphenazine, remifentanil, tacrolimus, teniposide, theophylline, thiotepa, tolazoline, vinorelbine, zidovudine. **Incompatible:** Allopurinol, amphotericin B cholesteryl sulfate complex, cefoperazone, heparin, hetastarch, indomethacin, propofol, sargramostim.

Compatibility in syringe: Compatible: Doxapram. **Incompatible:** Cefamandole, clindamycin, heparin.

Compatibility when admixed: Compatible: Aztreonam, bleomycin, calcium gluconate, cefoxitin, ciprofloxacin, clindamycin, furosemide, metronidazole, metronidazole with sodium bicarbonate, ofloxacin, ranitidine, verapamil. **Incompatible:** Cefamandole, cefepime, cefotaxime, cefotetan, floxacillin, heparin.

ContraindicationsHypersensitivity to tobramycin, other aminoglycosides, or any component of the formulation; pregnancy (injection/inhalation)

Warnings/Precautions

Boxed warnings:

- Nephrotoxicity: See "Concerns related to adverse effects" below.
- Neurotoxicity: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Nephrotoxicity: **[U.S. Boxed Warning]: May cause nephrotoxicity;** usual risk factors include pre-existing renal impairment, concomitant nephrotoxic medications, advanced age and dehydration. Discontinue treatment if signs of nephrotoxicity occur; renal damage is usually reversible.

- Neuromuscular blockade and respiratory paralysis: May cause neuromuscular blockade and respiratory paralysis; especially when given soon after anesthesia or muscle relaxants.

- Neurotoxicity: **[U.S. Boxed Warning]: May cause neurotoxicity;** usual risk factors include pre-existing renal impairment, concomitant neuro-/nephrotoxic medications, advanced age and dehydration. Ototoxicity is proportional to the amount of drug given and the duration of treatment. Tinnitus or vertigo may be indications of vestibular injury and impending bilateral irreversible damage. Discontinue treatment if signs of ototoxicity occur.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hearing impairment: Use with caution in patients with pre-existing vertigo, tinnitus, or hearing loss.

- Hypocalcemia: Use with caution in patients with hypocalcemia.

- Neuromuscular disorders: Use with caution in patients with neuromuscular disorders, including myasthenia gravis.

- Renal impairment: Use with caution in patients with pre-existing renal insufficiency; dosage modification required.

Dosage form specific issues:

- Sulfite: Solution may contain sodium metabisulfate; use caution in patients with sulfite allergy.

Other warnings/precautions:

- Long-term use: Not intended for long-term therapy due to toxic hazards associated with extended administration.

Geriatric ConsiderationsThe aminoglycosides are an important therapeutic intervention for susceptible organisms and as empiric therapy in seriously ill patients. Their use is not without risk of toxicity; however, these risks can be minimized if initial dosing is adjusted for estimated renal function and appropriate monitoring is performed. High dose, once daily aminoglycosides have been advocated as an alternative to traditional dosing regimens. Once daily or extended interval dosing is as effective and may be safer than traditional dosing. Interval must be adjusted for renal function.

Pregnancy Risk FactorD (injection, inhalation); B (ophthalmic)

Pregnancy ConsiderationsTobramycin crosses the placenta and produces detectable serum levels in the fetus. Because of several reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy, the manufacturer classifies systemic tobramycin as pregnancy risk factor D. There have been no reports of fetal toxicity in humans from tobramycin. No adequate and well-controlled studies have been conducted in pregnant women and it is not known whether tobramycin can cause fetal harm. Although the manufacturer considers tobramycin pregnancy risk factor D, tobramycin-specific clinical data would suggest a pregnancy risk factor C.

Due to pregnancy induced physiologic changes, some pharmacokinetic parameters of tobramycin may be altered. Pregnant women have an average-to-larger volume of distribution which may result in lower serum peak levels than for the same dose in nonpregnant women. Serum half-life is also shorter.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsTobramycin is excreted into breast milk; however, it is not well absorbed when taken orally. This limited oral absorption may minimize exposure to the nursing infant. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Tobramycin in Pregnancy & Lactation

Adverse Reactions

Injection: Frequency not defined:

Central nervous system: Confusion, disorientation, dizziness, fever, headache, lethargy, vertigo

Dermatologic: Exfoliative dermatitis, itching, rash, urticaria

Endocrine & metabolic: Serum calcium, magnesium, potassium, and/or sodium decreased

Gastrointestinal: Diarrhea, nausea, vomiting

Hematologic: Anemia, eosinophilia, granulocytopenia, leukocytosis, leukopenia, thrombocytopenia

Hepatic: ALT increased, AST increased, bilirubin increased, LDH increased

Local: Pain at the injection site

Otic: Hearing loss, tinnitus, ototoxicity (auditory), ototoxicity (vestibular), roaring in the ears

Renal: BUN increased, cylindruria, serum creatinine increased, oliguria, proteinuria

Inhalation:

>10%:

Gastrointestinal: Sputum discoloration (21%)

Respiratory: Voice alteration (13%)

1% to 10%:

Central nervous system: Malaise (6%)

Otic: Tinnitus (3%)

Postmarketing and/or case reports: Hearing loss

Ophthalmic: <1%: Ocular: Conjunctival erythema, lid itching, lid swelling

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Amphotericin B: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Aminoglycosides may enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Aminoglycosides may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Aminoglycosides. *Risk C: Monitor therapy*

CARBOplatin: Aminoglycosides may enhance the ototoxic effect of CARBOplatin. Especially with higher doses of carboplatin. *Risk C: Monitor therapy*

CISplatin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Aminoglycosides may enhance the nephrotoxic effect of Colistimethate. Aminoglycosides may enhance the neuromuscular-blocking effect of Colistimethate. *Risk D: Consider therapy modification*

CycloSPORINE: Aminoglycosides may enhance the nephrotoxic effect of CycloSPORINE. *Risk C: Monitor therapy*

Gallium Nitrate: Aminoglycosides may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Loop Diuretics: May enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Aminoglycosides may enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Penicillins: May decrease the serum concentration of Aminoglycosides. Primarily associated with extended spectrum penicillins, and patients with renal dysfunction. **Exceptions:** Amoxicillin; Ampicillin; Cloxacillin; Dicloxacillin; Methicillin; Nafcillin; Oxacillin; Penicillin G (Parenteral/Aqueous); Penicillin G Benzathine; Penicillin G Procaine; Penicillin V Potassium. *Risk D: Consider therapy modification*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Vancomycin: May enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Test InteractionsSome penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*, leading to a potential underestimation of aminoglycoside serum concentration.

Monitoring ParametersUrinalysis, urine output, BUN, serum creatinine, peak and trough plasma tobramycin levels; be alert to ototoxicity; hearing should be tested before and during treatment

Some penicillin derivatives may accelerate the degradation of aminoglycosides *in vitro*. This may be clinically-significant for certain penicillin (ticarcillin, piperacillin, carbenicillin) and aminoglycoside (gentamicin, tobramycin) combination therapy in patients with significant renal impairment. Close monitoring of aminoglycoside levels is warranted.

Reference Range

Timing of serum samples: Draw peak 30 minutes after 30-minute infusion has been completed or 1 hour following I.M. injection or beginning of infusion; draw trough immediately before next dose

Therapeutic levels:

Peak:

Serious infections: 6-8 mcg/mL (SI: 12-17 µmol/L)

Life-threatening infections: 8-10 mcg/mL (SI: 17-21 µmol/L)

Urinary tract infections: 4-6 mcg/mL (SI: 7-12 µmol/L)

Synergy against gram-positive organisms: 3-5 mcg/mL

Trough:

Serious infections: 0.5-1 mcg/mL

Life-threatening infections: 1-2 mcg/mL

The American Thoracic Society (ATS) recommends trough levels of <1 mcg/mL for patients with hospital-acquired pneumonia.

Monitor serum creatinine and urine output; obtain drug levels after the third dose unless otherwise directed

Inhalation: Serum levels are ~1 mcg/mL one hour following a 300 mg dose in patients with normal renal function.

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess patient's hearing level before, during, and following therapy. Monitor therapeutic effectiveness, laboratory values, and adverse reactions (eg, ototoxicity and nephrotoxicity) at beginning of therapy and periodically throughout therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsUrinalysis, BUN, serum creatinine, plasma tobramycin levels (as appropriate to dosing method). Peak levels are drawn 30 minutes after the end of a 30-minute infusion or 1 hour after initiation of infusion or I.M. injection. The trough is drawn just before the next dose. Levels are typically obtained after the third dose in conventional dosing. Perform culture and sensitivity studies prior to initiating therapy to determine the causative organism and its susceptibility to tobramycin. Some penicillin derivatives may accelerate the degradation of aminoglycosides.

Patient EducationSystemic: Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Report decreased urine output, swelling of extremities, respiratory difficulty, vaginal itching or discharge, rash, diarrhea, oral thrush, unhealed wounds, dizziness, change in hearing acuity or ringing in ears, or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended.

Ophthalmic: Use as frequently as recommended; do not overuse. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Sit down, tilt head back, instill solution or drops inside lower eyelid, and roll eyeball in all directions. Close eye and apply gentle pressure to inner corner of eye for 30 seconds. May experience temporary stinging or blurred vision. Do not use any other eye preparation for 10 minutes. Inform prescriber if condition worsens or does not improve in 3-4 days.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Infusion [premixed in NS]: 60 mg (50 mL); 80 mg (100 mL)

Injection, powder for reconstitution: 1.2 g

Injection, solution: 10 mg/mL (2 mL, 8 mL); 40 mg/mL (2 mL, 30 mL, 50 mL) [may contain sodium metabisulfite]

Ointment, ophthalmic (Tobrex®): 0.3% (3.5 g)

Solution for nebulization [preservative free] (TOBI®): 60 mg/mL (5 mL)

Solution, ophthalmic (AKTob®, Tobrex®): 0.3% (5 mL) [contains benzalkonium chloride]

Generic AvailableYes: Excludes ophthalmic ointment, solution for nebulization

Pricing: U.S. (www.drugstore.com)

Nebulization (Tobi)

300 mg/5 mL (280): $3988.68

Ointment (Tobrex)

0.3% (3.5): $71.24

Solution (Tobramycin Sulfate)

0.3% (5): $15.99

40 mg/mL (8): $8.99

40 mg/mL (30): $35.99

Solution (Tobrex)

0.3% (5): $59.99

Mechanism of ActionInterferes with bacterial protein synthesis by binding to 30S and 50S ribosomal subunits resulting in a defective bacterial cell membrane

Pharmacodynamics/Kinetics

Absorption:

Oral: Poorly absorbed

I.M.: Rapid and complete

Inhalation: Peak serum concentrations are ~1 mcg/mL following a 300 mg dose

Distribution: V_d: 0.2-0.3 L/kg; Pediatrics: 0.2-0.7 L/kg; to extracellular fluid including serum, abscesses, ascitic, pericardial, pleural, synovial, lymphatic, and peritoneal fluids; poor penetration into CSF, eye, bone, prostate

Inhalation: Tobramycin remains concentrated primarily in the airways

Protein binding: <30%

Half-life elimination:

Neonates: ≤1200 g: 11 hours; >1200 g: 2-9 hours

Adults: 2-3 hours; directly dependent upon glomerular filtration rate

Adults with impaired renal function: 5-70 hours

Time to peak, serum: I.M.: 30-60 minutes; I.V.: ~30 minutes

Excretion: Normal renal function: Urine (~90% to 95%) within 24 hours

Related Information

- Antimicrobial Drugs of Choice

Pharmacotherapy PearlsOnce-daily dosing: Higher peak serum drug concentration to MIC ratios, demonstrated aminoglycoside postantibiotic effect, decreased renal cortex drug uptake, and improved cost-time efficiency are supportive reasons for the use of once daily dosing regimens for aminoglycosides. Current research indicates these regimens to be as effective for non-life-threatening infections, with no higher incidence of nephrotoxicity, than those requiring multiple daily doses. Doses are determined by calculating the entire day's dose via usual multiple dose calculation techniques and administering this quantity as a single dose. Doses are then adjusted to maintain mean serum concentrations above the MIC(s) of the causative organism(s). (Example: 2.5-5 mg/kg as a single dose; expected Cp_{max}: 10-20 mcg/mL and Cp_{min}: <1 mcg/mL). Further research is needed for universal recommendation in all patient populations and gram-negative disease; exceptions may include those with known high clearance (eg, children, patients with cystic fibrosis, or burns who may require shorter dosage intervals) and patients with renal function impairment for whom longer than conventional dosage intervals are usually required.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsTobramycin Sulfate

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International Brand NamesArtobin (PH); Bralifex (ID); Brulamycin (HU, PL); Cleo (TW); Consac (PH); Eyebrex (PH, TW); Gotabiotic (AR); Ikobel (GR); Isotic Tobryne (ID); Micitrex (MX); Nebcin (HR, PL); Nebcina (DK, NO); Obracin (LU, PL); Ocumicin (CO); Ocuracin (KP); Oftalbrax (AR); Ramitop (PH); Tirselon (GR); Tobacin (IN); Toberan (KP); Tobi (CH, FR, GB, IE, IL, MX, SE); Tobian (KP); Tobra-V (PH); Tobracin (JP); Tobragan (BR, CN); Tobral (IT); Tobramaxin (DE); Tobre (KP); Tobrex (AE, AT, AU, BB, BE, BF, BG, BH, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CY, CZ, EE, EG, ES, ET, FI, FR, GH, GM, GN, GR, GY, HK, HN, HR, HU, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, OM, PE, PH, PK, PL, PT, PY, QA, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Tobrimin (DO); Tobrin (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Tocin (TW); Toeyecin (KP); Trazil (CR, DO, GT, NI, PA, SV); Tronamycin (KP); Verbram (MX)

Tocainide

Lexi-Drugs Online

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Tonocard® may be confused with Torecan®

Pronunciation(TOE kay nide)

U.S. Brand NamesTonocard® [DSC]

Pharmacologic CategoryAntiarrhythmic Agent, Class Ib

Use: Labeled IndicationsSuppression and prevention of symptomatic life-threatening ventricular arrhythmias

Use: Unlabeled/InvestigationalTrigeminal neuralgia

Dosing: Adults**Ventricular arrhythmias:** Oral: 1200-1800 mg/day in 3 divided doses, up to 2400 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Cl_{cr} <30 mL/minute: Administer 50% of normal dose or 600 mg once daily.

Moderately dialyzable (20% to 50%)

Dosing: Hepatic ImpairmentMaximum daily dose: 1200 mg

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsShould be taken with food.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Keep container tightly closed.

ContraindicationsHypersensitivity to tocainide, any component of the formulation, or any local anesthetics of the amide type; second- or third-degree heart block (except in patients with a functioning artificial pacemaker)

Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Boxed warnings:

- Blood dyscrasias: See “Concerns related to adverse effects” below.
- CAST trial: See “Other warnings/precautions” below.
- Pulmonary fibrosis: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Blood dyscrasias: **[U.S. Boxed Warning]: During the first 3 months of therapy, blood dyscrasias (eg, agranulocytosis, leukopenia, neutropenia, aplastic/hypoplastic anemia, thrombocytopenia) can rarely occur.**
- Proarrhythmic effects: Watch for proarrhythmic effects; monitor and adjust dose to prevent QT_c prolongation.
- Pulmonary fibrosis: **[U.S. Boxed Warning]: Pulmonary fibrosis, interstitial pneumonitis, fibrosing alveolitis, pulmonary edema, and pneumonia have been reported with use (fatalities have occurred);** monitor for pulmonary symptoms.

Disease-related concerns:

- Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy.
- Heart failure (HF): Use with caution in patients with HF; may precipitate or exacerbate condition.
- Hepatic impairment: Use with caution in patients with significant hepatic impairment; dosage adjustment recommended.
- Renal impairment: Use with caution in patients with significant renal impairment; dosage adjustment recommended.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- CAST trial: **[U.S. Boxed Warning]: In the Cardiac Arrhythmia Suppression Trial (CAST), recent (>6 days but <2 years ago) myocardial infarction patients with asymptomatic, non-life-threatening ventricular arrhythmias did not benefit and may have been harmed by attempts to suppress the arrhythmia with flecainide or encainide.** An increased mortality or nonfatal cardiac arrest rate (7.7%) was seen in the active treatment group compared with patients in the placebo group (3%). The applicability of the CAST results to other populations is unknown. Antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias.

Geriatric ConsiderationsTocainide may cause confusion. Tremor indicates potential toxicity and should not be mistaken for age related changes. Renal and Phase I liver metabolism changes with age may affect clearance. Monitor closely since half-life may be prolonged.
Pregnancy Risk FactorC
LactationEnters breast milk/contraindicated
Breast-Feeding ConsiderationsTocainide is secreted in breast milk. The manufacturer recommends discontinuation of breast-feeding during treatment or discontinuation of tocainide, based upon risk:benefit to the mother.
Adverse Reactions

>10%:

Central nervous system: Dizziness (8% to 15%)

Gastrointestinal: Nausea (14% to 15%)

1% to 10%:

Cardiovascular: Tachycardia (3%), bradycardia/angina/palpitation (0.5% to 1.8%), hypotension (3%)

Central nervous system: Nervousness (0.5% to 1.5%), confusion (2% to 3%), headache (4.6%), anxiety, incoordination, giddiness, vertigo

Dermatologic: Rash (0.5% to 8.4%)

Gastrointestinal: Vomiting (4.5%), diarrhea (4% to 5%), anorexia (1% to 2%), loss of taste

Neuromuscular & skeletal: Paresthesia (3.5% to 9%), tremor (dose related: 2.9% to 8.4%), ataxia (dose related: 2.9% to 8.4%), hot and cold sensations

Ocular: Blurred vision (~1.5%), nystagmus (1%)

<1% (Limited to important or life-threatening): Abdominal pain, abnormal liver function tests, agitation, alopecia, angina, asthenia, AV block, cardiomegaly, chills, cinchonism, coma, constipation, convulsions, decreased mental acuity, delirium, depression, diaphoresis, diplopia, dysarthria, dyspepsia, dysphagia, dyspnea, earache, edema, erythema multiforme, exfoliative dermatitis, fever, fibrosing alveolitis, hallucinations, hepatitis, hiccup, hypersensitivity reactions, hypertension, impaired memory, increased ANA, increased QRS duration, insomnia, interstitial pneumonitis, jaundice, local anesthesia, malaise, muscle cramps, myasthenia gravis, neck pain, orthostatic hypotension, pallor, pancreatitis, pericarditis, pneumonia, polyuria, prolonged QT interval, pruritus, psychic disturbances, psychosis, pulmonary edema, pulmonary embolism, pulmonary fibrosis, respiratory arrest, right bundle branch block, sinoatrial block, sinus arrest, sleep disturbance, slurred speech, Stevens-Johnson syndrome, stomatitis, syncope, taste perversion, urinary retention, urticaria, vasculitis, vasovagal episodes, xerostomia, yawning

Postmarketing and/or case reports: Pericarditis, immune complex glomerulonephritis, granulomatous hepatitis

Note: Rare, potentially severe hematologic reactions, have occurred (generally within the first 12 weeks of therapy). These may include agranulocytosis, bone marrow depression, aplastic anemia, hypoplastic anemia, hemolytic anemia, anemia, leukopenia, neutropenia, thrombocytopenia, and eosinophilia.

Metabolism/Transport Effects**Inhibits** CYP1A2 (weak)
Drug Interactions

Antacids: May increase the serum concentration of Tocainide. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Tocainide. *Risk C: Monitor therapy*

Monitoring ParametersMonitor for tremor; titration of dosing and initiation of therapy require cardiac monitoring
Reference RangeTherapeutic: 5-12 mcg/mL (SI: 22-52 µmol/L)
Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions (see Drug Interactions). See Warnings/Precautions and Contraindications for use cautions. Monitor therapeutic effectiveness and adverse reactions (see Warnings/Precautions and Adverse Reactions) at beginning of therapy, when titrating dosage, and on a regular basis with long-term oral therapy. **Note:** Tocainide has a low TI and overdose may easily produce severe and life-threatening reactions (see Overdose/Toxicology). Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report (see Patient Education). **Pregnancy risk factor C** - benefits of use should outweigh possible risks. Breast-feeding is contraindicated.
Patient EducationTake exactly as directed with food. If dose is missed, take as soon as possible, do not double next dose. Do not discontinue without consulting prescriber. You will need regular cardiac checkups while taking this medication. You may experience dizziness, nervousness, or visual changes (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or loss of appetite (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or mild muscle discomfort (analgesics may be recommended). Report chest pain, palpitations, or erratic heartbeat; respiratory difficulty or unusual cough; mental confusion or depression; muscle tremor, weakness, or pain; or vision changes. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet, as hydrochloride [DSC]: 400 mg, 600 mg

Generic AvailableNo
ManufacturerAstraZeneca Pharmaceuticals LP
Mechanism of ActionClass 1B antiarrhythmic agent; suppresses automaticity of conduction tissue, by increasing electrical stimulation threshold of ventricle, His-Purkinje system, and spontaneous depolarization of the ventricles during diastole by a direct action on the tissues; blocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction
Pharmacodynamics/Kinetics

Absorption: Oral: 99% to 100%

Distribution: V_d: 1.62-3.2 L/kg

Protein binding: 10% to 20%

Metabolism: Hepatic to inactive metabolites; negligible first-pass effect

Half-life elimination: 11-14 hours; Renal and hepatic impairment: 23-27 hours

Time to peak, serum: 30-160 minutes

Excretion: Urine (40% to 50% as unchanged drug)

Related Information

- Antiarrhythmic Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Loss of taste.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness or confusion
Mental Health: Effects on Psychiatric TreatmentMay cause agranulocytosis; use caution with clozapine and carbamazepine; barbiturates may decrease the serum levels of tocainide
Cardiovascular ConsiderationsThe prophylactic use of tocainide in patients after myocardial infarction confers no benefit and in fact may be harmful. Great care is needed in administration of tocainide in the elderly and in patients with heart failure, shock, or hepatic disease, as toxic effects of tocainide may become evident earlier in these patients. This is especially problematic since tocainide-induced seizures may induce extension of underlying myocardial infarction. It is important to recognize that tocainide has a narrow therapeutic index. Severe toxicity may occur at doses slightly above the therapeutic range, particularly when tocainide is administered together with other antiarrhythmic drugs. While tocainide toxicity may elicit seizures, tocainide may also cause respiratory arrest and cardiac toxicity (AV block, asystole, and hypotension).
Index TermsTocainide Hydrochloride
References

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International Brand NamesTaquidil (AR); Tonocard (IE, NL); Xylotocan (DE)

TOLAZamide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

TOLAZamide may be confused with tolazoline, TOLBUTamide

Tolinase® may be confused with Orinase®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(tole AZ a mide)

Canadian Brand NamesTolinase®

Pharmacologic CategoryAntidiabetic Agent, Sulfonylurea

Use: Labeled IndicationsAdjunct to diet for the management of mild to moderately severe, stable, type 2 diabetes mellitus (noninsulin dependent, NIDDM)

Dosing: Adults

Type 2 diabetes: Oral (doses >500 mg/day should be given in 2 divided doses):

Initial: 100-250 mg/day with breakfast or the first main meal of the day

Fasting blood sugar <200 mg/dL: 100 mg/day

Fasting blood sugar >200 mg/dL: 250 mg/day

Patient is malnourished, underweight, elderly, or not eating properly: 100 mg/day

Adjustment/titration: Increase in increments of 100-250 mg/day at weekly intervals to response; maximum daily dose: 1 g (doses >1 g/day are not likely to improve control)

Conversion from insulin to tolazamide

<20 units day = 100 mg/day

21-<40 units/day = 250 mg/day

≥40 units/day = 250 mg/day and 50% of insulin dose

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentConservative initial and maintenance doses are recommended because tolazamide is metabolized to active metabolites, which are eliminated in the urine.

Dosing: Hepatic ImpairmentConservative initial and maintenance doses and careful monitoring of blood glucose are recommended.

ContraindicationsHypersensitivity to tolazamide, sulfonylureas, or any component of the formulation; type 1 diabetes mellitus (insulin dependent, IDDM) therapy; diabetic ketoacidosis

Allergy Considerations

- Sulfonylurea Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS) have not supported an association.
- Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when ethanol is ingested, or when more than one glucose-lowering drug is used. It is also more likely in elderly patients, malnourished patients and in patients with impaired renal or hepatic function; use with caution.
- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonylurea allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Disease-related concerns:

- Stress-related states: It may be necessary to discontinue therapy and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsHas not been studied in elderly patients, however, except for drug interactions it appears to have a safe profile and decline in renal function does not affect its pharmacokinetics. How “tightly” an elderly patient's blood glucose should be controlled is controversial; however, a fasting blood sugar of <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well they recognize hypoglycemic or hyperglycemic symptoms, and how to respond to them and their other disease states. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in animal studies; therefore, tolazamide is classified as pregnancy category C. Severe hypoglycemia lasting 4-10 days has been noted in infants born to mothers taking a sulfonylurea at the time of delivery. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. The manufacturer recommends if tolazamide is used during pregnancy, it should be discontinued at least 2 weeks before the expected delivery date. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if tolazamide is excreted in breast milk. Breast-feeding is not recommended by the manufacturer. Potentially, hypoglycemia may occur in a nursing infant exposed to a sulfonylurea via breast milk.

Pregnancy & Lactation, In-Depth

- TOLAZamide in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Dizziness, fatigue, headache, malaise, vertigo

Dermatologic: Maculopapular eruptions, morbilliform eruptions, photosensitivity, pruritus, rash, urticaria

Endocrine & metabolic: Disulfiram-like reaction, hypoglycemia, hyponatremia, SIADH

Gastrointestinal: Anorexia, constipation, diarrhea, epigastric fullness, heartburn, nausea, vomiting

Hematologic: Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, pancytopenia, porphyria cutanea tarda, thrombocytopenia

Hepatic: Cholestatic jaundice, hepatic porphyria

Neuromuscular & skeletal: Weakness

Renal: Diuretic effect

Drug Interactions

Alcohol (Ethyl): Sulfonylureas may enhance the adverse/toxic effect of Alcohol (Ethyl). A flushing reaction may occur. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Cyclic Antidepressants: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonylureas may increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

Fibric Acid Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Fluconazole: May increase the serum concentration of Sulfonylureas. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Salicylates: May enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. **Exceptions:** Sulfacetamide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (possible disulfiram-like reaction).

Herb/Nutraceutical: Herbs with hypoglycemic properties may enhance the hypoglycemic effect of tolazamide. This includes alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, stinging nettle.

Monitoring ParametersSigns and symptoms of hypoglycemia (fatigue, sweating, numbness of extremities); blood glucose; hemoglobin A_{1c}

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Monitoring: Lab TestsBlood glucose; hemoglobin A_{1c}

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 250 mg, 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (TOLAZamide)

100 mg (60): $23.99

250 mg (60): $35.24

500 mg (30): $34.99

Mechanism of ActionStimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites

Pharmacodynamics/Kinetics

Onset of hypoglycemic effect: 20 minutes

Peak hypoglycemic effect: 4-6 hours

Duration: 10-24 hours

Absorption: Rapid

Protein binding: 94%

Metabolism: Extensively hepatic to 5 metabolites (activity 0% to 70%)

Half-life elimination: 7 hours

Time to peak, serum: 3-4 hours

Excretion: Urine (85%); feces (7%)

Related Information

- Diabetes Mellitus Management, Adults
- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentUse salicylates with caution in patients taking tolazamide due to potential increased hypoglycemia; NSAIDs such as ibuprofen and naproxen may be safely used. Tolazamide-dependent patients with diabetes (noninsulin dependent, type 2) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common

Mental Health: Effects on Psychiatric TreatmentMay cause agranulocytosis; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce alterations in serum glucose concentrations; monitor glucose; clinical manifestation of hypoglycemia may be blocked by beta-blockers

Cardiovascular Considerations The possibility of higher doses of sulfonylureas eliciting an increase in cardiovascular events, because of their effects on blocking potassium sensitive ATP channels, has been raised. However, there are presently only limited data to support this premise, particularly with newer generation agents. An early study suggested poor cardiovascular outcomes in patients with diabetes treated with tolbutamide. Retrospective studies evaluating cardiovascular outcomes following angioplasty and acute myocardial infarction in patients with diabetes receiving newer sulfonylureas are inconsistent. Longer-term prospective trials of sulfonylurea therapy, such as the UKPDS, do not reveal any increased cardiovascular mortality.

References

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International Brand Names Desumide (TW); Diabewas (IT); Esulin (TW); Tolanase (GB); Tolinase (AE, BH, CY, EG, ES, IL, IQ, IR, JO, KW, LB, LY, NL, OM, QA, SA, SY, YE)

Tolazoline

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Tolazoline may be confused with TOLAZamide

Priscoline® may be confused with Apresoline®

Pronunciation(tole AZ oh leen)

U.S. Brand NamesPriscoline® [DSC]

Pharmacologic CategoryVasodilator

Use: Labeled IndicationsTreatment of persistent pulmonary vasoconstriction and hypertension of the newborn (persistent fetal circulation), peripheral vasospastic disorders

Dosing: Adults**Peripheral vasospastic disorder:** I.M., I.V., SubQ: 10-50 mg 4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Persistent pulmonary vasoconstriction and hypertension of the newborn (persistent fetal circulation):**

I.V.: Neonates: Initial: 1-2 mg/kg over 10-15 minutes via scalp vein or upper extremity; maintenance: 1-2 mg/kg/hour; use lower maintenance doses in patients with decreased renal function. Also used in neonates for acute vasospasm “cath toes” at 0.25 mg/kg/hour (no load); maximum dose: 6-8 mg/kg/hour.

Dosing interval in renal impairment in newborns: Urine output <0.9 mL/kg/hour: Decrease dose to 0.08 mg/kg/hour for every 1 mg/kg of loading dose

Dosing: Renal ImpairmentNewborns: Urine output <0.9 mL/kg/hour: Decrease dose to 0.08 mg/kg/hour for every 1 mg/kg of loading dose.

CompatibilityStable in dextran 6% in dextrose, dextran 6% in NS, D_5LR, $D_5{}^1/_4$NS, $D_5{}^1/_2$NS, D_5NS, D_5W, D_{10}W, LR, $^1/_2$NS, NS.

Y-site administration: Compatible: Aminophylline, ampicillin, calcium gluconate, cefotaxime, cimetidine, dobutamine, dopamine, furosemide, gentamicin, phytonadione, sodium bicarbonate, tobramycin, vancomycin. **Incompatible:** Indomethacin.

Compatibility when admixed: Compatible: Verapamil. **Incompatible:** Ethacrynate sodium.

ContraindicationsHypersensitivity to tolazoline or any component of the formulation; known or suspected coronary artery disease

Warnings/Precautions

Disease-related concerns:

- Gastrointestinal disease: Use with caution in patients with gastritis and/or peptic ulcer; stimulates gastric secretion and may activate stress ulcers.
- Mitral stenosis: Use with caution in patients with mitral stenosis.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, hyper-/hypotension, peripheral vasodilation, tachycardia

Endocrine & metabolic: Hypochloremic alkalosis

Gastrointestinal: Abdominal pain, diarrhea, GI bleeding, nausea

Hematologic: Agranulocytosis increased, pancytopenia, thrombocytopenia

Local: Burning at injection site

Neuromuscular & skeletal: Pilomotor activity increased

Ocular: Mydriasis

Renal: Acute renal failure, oliguria

Respiratory: Pulmonary hemorrhage

Miscellaneous: Increased secretions

Drug Interactions

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can

not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase vasodilation).

Monitoring ParametersVital signs, blood gases, cardiac monitor

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution, as hydrochloride [DSC]: 25 mg/mL (4 mL)

Generic AvailableNo

Mechanism of ActionCompetitively blocks alpha-adrenergic receptors to produce brief antagonism of circulating epinephrine and norepinephrine; reduces hypertension caused by catecholamines and causes vascular smooth muscle relaxation (direct action); results in peripheral vasodilation and decreased peripheral resistance

Pharmacodynamics/Kinetics

Half-life elimination: Neonates: 3-10 hours; prolonged with renal impairment

Time to peak, serum: Within 30 minutes

Excretion: Urine (primarily as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause agranulocytosis, caution with clozapine and carbamazepine; use with ethanol may produce “disulfiram reaction”

Anesthesia and Critical Care Concerns/Other ConsiderationsAcidosis may decrease tolazoline's effects.

Index TermsBenzazoline Hydrochloride; Tolazoline Hydrochloride

References

Ward RM, Daniel CH, Kendig JW, et al, “Oliguria and Tolazoline Pharmacokinetics in the Newborn,” *Pediatrics*, 1986, 77(3):307-15.[PubMed 3951911]

International Brand NamesDivascol (CZ); Priscol (CH, DE); Priscoline (AU); Vaso-Dilatan (AT)

TOLBUTamide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

TOLBUTamide may be confused with terbutaline, TOLAZamide

Orinase® may be confused with Orabase®, Ornex®, Tolinase®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(tole BYOO ta mide)

Canadian Brand NamesApo-Tolbutamide®

Pharmacologic CategoryAntidiabetic Agent, Sulfonylurea

Use: Labeled IndicationsAdjunct to diet for the management of type 2 diabetes mellitus (noninsulin dependent, NIDDM)

Dosing: Adults**Type 2 diabetes:** Oral: Initial: 1-2 g/day as a single dose in the morning or in divided doses throughout the day. Maintenance dose: 0.25-3 g/day; however, a maintenance dose >2 g/day is seldom required. **Note:** Divided doses may improve gastrointestinal tolerance

Dosing: ElderlyInitial: 250 mg 1-3 times/day; usual: 500-2000 mg; maximum: 3 g/day

Dosing: Renal ImpairmentAdjustment is not necessary.

Hemodialysis: Not dialyzable (0% to 5%)

Dosing: Hepatic ImpairmentReduced dose may be necessary.

Administration: OralOral: Entire dose can be administered in AM, divided doses may improve GI tolerance

ContraindicationsHypersensitivity to tolbutamide, sulfonylureas, or any component of the formulation; treatment of type 1 diabetes; diabetic ketoacidosis

Allergy Considerations

- Sulfonylurea Allergy

Warnings/Precautions

Concerns related to adverse reactions:

- Cardiovascular mortality: Product labeling states oral hypoglycemic drugs may be associated with an increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. Data to support this association are limited, and several studies, including a large prospective trial (UKPDS) have not supported an association.
- Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when ethanol is ingested, or when more than one glucose-lowering drug is used. It is also more likely in elderly patients, malnourished patients and in patients with impaired renal or hepatic function; use with caution.
- Sulfonamide allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonylurea allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Disease-related concerns:

- Stress-related states: It may be necessary to discontinue therapy and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsBecause of its low potency and short duration, it is a useful agent in elderly if drug interactions can be avoided. How “tightly” an elderly patient's blood glucose should be controlled is controversial; however, a fasting blood sugar <150 mg/dL is now an acceptable endpoint. Such a decision should be based on the patient's functional and cognitive status, how well they recognize hypoglycemic or hyperglycemic symptoms, and how to respond to them and their other disease states. Intensive glucose control (Hb A_{1c} <6.5) has been linked to increased all cause and cardiovascular mortality, hypoglycemia requiring assistance, and weight gain in adult type 2 diabetes. For elderly patients with diabetes who are relatively healthy, attaining target goals for aspirin use, blood pressure, lipids, smoking cessation, and diet and exercise may be more important than normalized glycemic control.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events have been observed in animal studies; therefore, tolbutamide is classified as pregnancy category

C. Tolbutamide crosses the placenta and levels can be measured in the serum of newborn infants following maternal use during pregnancy. Teratogenic effects have been noted in some case reports. Prolonged hyperinsulinemic hypoglycemia has been reported in an infant following maternal use of tolbutamide and severe hypoglycemia lasting 4-10 days has been noted in infants born to mothers taking a sulfonylurea at the time of delivery. Maternal hyperglycemia can be associated with adverse effects in the fetus, including macrosomia, neonatal hyperglycemia, and hyperbilirubinemia; the risk of congenital malformations is increased when the Hb A_{1c} is above the normal range. Diabetes can also be associated with adverse effects in the mother. Poorly-treated diabetes may cause end-organ damage that may in turn negatively affect obstetric outcomes. Physiologic glucose levels should be maintained prior to and during pregnancy to decrease the risk of adverse events in the mother and the fetus. Until additional safety and efficacy data are obtained, the use of oral agents is generally not recommended as routine management of GDM or type 2 diabetes mellitus during pregnancy. The manufacturer recommends if tolbutamide is used during pregnancy, it should be discontinued at least 2 weeks before the expected delivery date. Insulin is the drug of choice for the control of diabetes mellitus during pregnancy.

LactationEnters breast milk/compatible

Breast-Feeding ConsiderationsTolbutamide is excreted in breast milk. Breast-feeding is not recommended by the manufacturer. The AAP considers tolbutamide to be “usually compatible with breast-feeding.” Potentially, hypoglycemia may occur in a nursing infant exposed to a sulfonylurea via breast milk.

Pregnancy & Lactation, In-Depth

- TOLBUTamide in Pregnancy & Lactation

Adverse ReactionsFrequency not defined.

Central nervous system: Headache

Dermatologic: Erythema, maculopapular rash, morbilliform rash, pruritus, urticaria, photosensitivity

Endocrine & metabolic: Disulfiram-like reactions, hypoglycemia, hyponatremia, SIADH

Gastrointestinal: Epigastric fullness, heartburn, nausea, taste alteration

Hematologic: Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia

Hepatic: Cholestatic jaundice, hepatic porphyria, porphyria cutanea tarda

Miscellaneous: Hypersensitivity reaction

Metabolism/Transport Effects**Substrate** of CYP2C9 (major), 2C19 (minor); **Inhibits** CYP2C8 (weak), 2C9 (strong)

Drug Interactions

Alcohol (Ethyl): Sulfonylureas may enhance the adverse/toxic effect of Alcohol (Ethyl). A flushing reaction may occur. *Risk C: Monitor therapy*

Chloramphenicol: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Cyclic Antidepressants: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

CycloSPORINE: Sulfonylureas may increase the serum concentration of CycloSPORINE. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Fibric Acid Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Fluconazole: May increase the serum concentration of Sulfonylureas. *Risk C: Monitor therapy*

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

Luteinizing Hormone-Releasing Hormone Analogs: May diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Pegvisomant: May enhance the hypoglycemic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the hypoglycemic effect of Sulfonylureas. This appears to be particularly concerning early in the course of combination therapy. Quinolone Antibiotics may diminish the hypoglycemic effect of Sulfonylureas. With longer-term combination, there is a greater risk of hyperglycemia. *Risk C: Monitor therapy*

Rifampin: May increase the metabolism of Sulfonylureas. *Risk C: Monitor therapy*

Salicylates: May enhance the hypoglycemic effect of Sulfonylureas. Of concern with regular, higher doses of salicylates, not sporadic, low doses. *Risk C: Monitor therapy*

Somatropin: May diminish the hypoglycemic effect of Antidiabetic Agents. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May enhance the hypoglycemic effect of Sulfonylureas. **Exceptions:** Sulfacetamide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (possible disulfiram-like reaction).

Herb/Nutraceutical: Herbs with hypoglycemic properties may enhance the hypoglycemic effect of tolbutamide. This includes alfalfa, aloe, bilberry, bitter melon, burdock, celery, damiana, fenugreek, garcinia, garlic, ginger, ginseng (American), gymnema, marshmallow, stinging nettle.

Monitoring ParametersBlood glucose, hemoglobin A_{1c}; signs and symptoms of hypoglycemia

Reference RangeRecommendations for glycemic control in adults with diabetes:

Hb A_{1c}: <7%

Preprandial capillary plasma glucose: 70-130 mg/dL

Peak postprandial capillary blood glucose: <180 mg/dL

Blood pressure: <130/80 mm Hg

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess results of laboratory tests and therapeutic effectiveness, frequently during therapy. Monitor for adverse response (hypoglycemia). Assess knowledge/teach patient (or refer patient to diabetic educator for instruction) in appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsBlood glucose, hemoglobin A_{1c}

Patient EducationThis medication is used to control diabetes; it is not a cure. Inform prescriber of all other prescription or OTC medications you are taking; do not introduce new medication without consulting prescriber. Do not take other medication within 2 hours of this medication unless advised by prescriber. Other components of treatment plan are important: Follow prescribed diet, medication, and exercise regimen. Take exactly as directed; at the same time each day. Do not change dose or discontinue without consulting prescriber. Avoid alcohol while taking this medication; could cause severe reaction. If you experience hypoglycemic reaction, contact prescriber immediately. Maintain regular dietary intake and exercise routine and always carry quick source of sugar with you. You may be more sensitive to sunlight (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). You may experience side effects during first weeks of therapy (headache, nausea, diarrhea, constipation, anorexia); consult prescriber if these persist. Report severe or persistent side effects, extended vomiting or flu-like symptoms, skin rash, easy bruising or bleeding, or change in color of urine or stool. **Pregnancy precaution:** Do not get pregnant; use appropriate contraceptive measures to prevent possible harm to the fetus.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 500 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (TOLBUTamide)

500 mg (60): $26.25

Mechanism of ActionStimulates insulin release from the pancreatic beta cells; reduces glucose output from the liver; insulin sensitivity is increased at peripheral target sites, suppression of glucagon may also contribute

Pharmacodynamics/Kinetics

Onset of action: 1 hour

Duration: Oral: 6-24 hours

Absorption: Oral: Rapid

Distribution: V_d: 0.15 L/kg

Protein binding: ~95% (concentration dependent)

Metabolism: Hepatic via CYP2C9 to hydroxymethyltolbutamide (mildly active) and carboxytolbutamide (inactive); metabolism does not appear to be affected by age

Half-life elimination: 4.5-6.5 hours (range: 4-25 hours)

Time to peak, serum: 3-4 hours

Excretion: Urine (75% to 85% primarily as metabolites); feces

Related Information

- Diabetes Mellitus Management, Adults
- Sulfonamide Derivatives

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste alteration.

Use salicylates with caution in patients taking tolazamide due to potential increased hypoglycemia; NSAIDs such as ibuprofen and naproxen may be safely used. Tolbutamide-dependent patients with diabetes (noninsulin dependent, type 2) should be appointed for dental treatment in morning in order to minimize chance of stress-induced hypoglycemia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common

Mental Health: Effects on Psychiatric TreatmentMay cause agranulocytosis; use caution with clozapine and carbamazepine; concurrent use with psychotropics may produce alterations in serum glucose concentrations; monitor glucose; clinical manifestation of hypoglycemia may be blocked by beta-blockers

Cardiovascular ConsiderationsThe possibility of higher doses of sulfonylureas eliciting an increase in cardiovascular events, because of their effects on blocking potassium sensitive ATP channels, has been raised. However, there are presently only limited data to support this premise, particularly with newer generation agents. An early study suggested poor cardiovascular outcomes in patients with diabetes treated with tolbutamide. Retrospective studies evaluating cardiovascular outcomes following angioplasty and acute myocardial infarction in patients with diabetes receiving newer sulfonylureas are inconsistent. Longer-term prospective trials of sulfonylurea therapy, such as the UKPDS, do not reveal any increased cardiovascular mortality.

Index TermsTolbutamide Sodium

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International Brand NamesAglicem (ES); Aglycid (IT); Arcosal (DK); Artison (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Artosin (DE, JP, MX, NL); Asto (JP); Butamide (JP); Diaben (JP); Diabetol (PL); Diabeton Metilato (IT); Diabetose (JP); Diatol (HK, NZ); Dirastan (CZ); Dolipol (FR); Mellitos D (JP); Neobezeta (UY); Orabet (DE); Orsinon (IL); Rastinon (AE, AT, AU, BE, BH, CH, CY, EG, ES, GR, IE, IL, IN, IQ, IR, IT, JO, KW, LB, LU, LY, MX, OM, QA, SA, SY, YE); Tolbutamid R.A.N. (DE); Tolmide (SG); Tolsiran (JP); Tolumide (JP); Tydadex (ZA)

Tolcapone

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(TOLE ka pone)

U.S. Brand NamesTasmar®

Pharmacologic CategoryAnti-Parkinson's Agent, COMT Inhibitor

Use: Labeled IndicationsAdjunct to levodopa and carbidopa for the treatment of signs and symptoms of idiopathic Parkinson's disease in patients with motor fluctuations not responsive to other therapies

Dosing: Adults**Note:** If clinical improvement is not observed after 3 weeks of therapy (regardless of dose), tolcapone treatment should be discontinued.

Parkinson's Disease: Oral: Initial: 100 mg 3 times/day; may increase as tolerated to 200 mg 3 times/day. **Note:** Levodopa dose may need to be decreased upon initiation of tolcapone (average reduction in clinical trials was 30%). As many as 70% of patients receiving levodopa doses >600 mg daily required levodopa dosage reduction in clinical trials. Patients with moderate-to-severe dyskinesia prior to initiation are also more likely to require dosage reduction.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment necessary for mild-moderate impairment. Use caution with severe impairment; no safety information available in patients with Cl_{cr}<25 mL/minute.

Dosing: Hepatic ImpairmentDo not use. Discontinue immediately if signs/symptoms of hepatic impairment develop.

Administration: OralMay be administered with or without food. In clinical studies, the first dose of the day was administered with carbidopa/levodopa, and the subsequent doses were administered 6 hours and 12 hours later.

Dietary ConsiderationsMay be taken without regard to food.

StorageStore at 20°C to 25°C (68°F to 77°F).

RestrictionsA patient signed consent form acknowledging the risks of hepatic injury should be obtained by the treating physician.

ContraindicationsHypersensitivity to tolcapone or any component of the formulation; history of liver disease or tolcapone-induced hepatocellular injury; nontraumatic rhabdomyolysis or hyperpyrexia and confusion

Allergy Considerations

- COMT Inhibitor Allergy

Warnings/Precautions

Boxed warnings:

- Liver injury: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Diarrhea: Has been associated with delayed development of diarrhea (onset after 2-12 weeks); use with caution in patients with lower gastrointestinal disease or an increased risk of dehydration.

- Hallucinations: May cause hallucinations, which may improve with reduction in levodopa therapy.

- Liver injury: **[U.S. Boxed Warning]: Due to reports of fatal liver injury associated with use of this drug, the manufacturer is advising that tolcapone be reserved for patients who are experiencing inadequate symptom control or who are not appropriate candidates for other available treatments.** Patients must provide written consent acknowledging the risks of hepatic injury. Liver disease should be excluded prior to initiation; laboratory monitoring is recommended. Discontinue if signs and/or symptoms of hepatic injury are noted (eg, transaminases >2 times upper limit of normal) or if clinical improvement is not evident after 3 weeks of therapy.

- Neuroleptic malignant syndrome: Tolcapone, in conjunction with other drug therapy that alters brain biogenic amine concentrations (eg, MAO inhibitors, SSRIs), has been associated with a syndrome resembling neuroleptic malignant syndrome (hyperpyrexia and confusion - some fatal) on abrupt withdrawal or dosage reduction. Concomitant use of tolcapone and nonselective MAO inhibitors should be avoided.

- Orthostatic hypotension: May cause orthostatic hypotension and syncope; Parkinson's disease patients appear to have an impaired capacity to respond to a postural challenge; use with caution in patients at risk of hypotension (such as those receiving antihypertensive drugs) or where transient hypotensive episodes would be poorly tolerated (cardiovascular disease or cerebrovascular disease). Parkinson's patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation, and should be informed of this risk.

- Pleural/retroperitoneal fibrosis: Dopaminergic agents from the ergot class have been associated with fibrotic complications, such as retroperitoneal fibrosis, pulmonary infiltrates or effusion and pleural thickening. It is unknown whether non-ergot, pro-dopaminergic agents like tolcapone confer this risk.

- Rhabdomyolysis: Severe rhabdomyolysis has been reported with use.

Disease-related concerns:

- Dyskinesia: Use with caution in patients with pre-existing dyskinesias; exacerbation of pre-existing dyskinesia has been reported. Levodopa dosage reduction may be required, particularly in patients with levodopa dosages >600 mg daily or with moderate-to-severe dyskinesia prior to initiation.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with severe renal impairment.

Concurrent drug therapy issues:

- MAO inhibitors: Concomitant use of tolcapone and nonselective MAO inhibitors should be avoided. Selegiline is a selective MAO type B inhibitor (when given orally at ≤10 mg/day) and can be taken with tolcapone.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo specific data in elderly patients, but based on the pharmacokinetic profile, no dosage adjustment appears necessary.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTolcapone may be teratogenic based on animal studies. There are no adequate and well-controlled studies in pregnant women. Use only if benefit outweighs risk.
LactationExcretion in breast milk unknown/not recommended
Adverse Reactions

>10%:

Cardiovascular: Orthostatic hypotension (17%)

Central nervous system: Sleep disorder (24% to 25%), excessive dreaming (16% to 21%), somnolence (14% to 32%), hallucinations (8% to 24%) dizziness (6% to 13%), headache (10% to 11%), confusion (10% to 11%)

Gastrointestinal: Nausea (28% to 50%), anorexia (19% to 23%), diarrhea (16% to 34%; approximately 3% to 4% severe)

Neuromuscular & skeletal: Dyskinesia (42% to 51%), dystonia (19% to 22%), muscle cramps (17% to 18%)

1% to 10%:

Cardiovascular: Syncope (4% to 5%), chest pain (1% to 3%), hypotension (2%), palpitation

Central nervous system: Fatigue (3% to 7%), loss of balance (2% to 3%), agitation (1%), euphoria (1%), hyperactivity (1%), malaise (1%), panic reaction (1%), irritability (1%), mental deficiency (1%), fever (1%), depression, hypoesthesia, tremor, speech disorder, vertigo, emotional lability, hyperkinesia

Dermatologic: Alopecia (1%), bleeding (1%), tumor (1%), rash

Gastrointestinal: Vomiting (8% to 10%), constipation (6% to 8%), xerostomia (5% to 6%), abdominal pain (5% to 6%), dyspepsia (3% to 4%), flatulence (2% to 4%), tooth disorder

Genitourinary: UTI (5%), hematuria (4% to 5%), urine discoloration (2% to 3%), urination disorder (1% to 2%), uterine tumor (1%), incontinence, impotence

Hepatic: Transaminases increased (1% to 3%; 3 times ULN, usually with first 6 months of therapy)

Neuromuscular & skeletal: Paresthesia (1% to 3%), hyper-/hypokinesia (1% to 3%), arthritis (1% to 2%), neck pain (2%), stiffness (2%), myalgia, rhabdomyolysis

Ocular: Cataract (1%), eye inflammation (1%)

Otic: Tinnitus

Respiratory: Upper respiratory infection (5% to 7%), dyspnea (3%), sinus congestion (1% to 2%), bronchitis, pharyngitis

Miscellaneous: Diaphoresis (4% to 7%), influenza (3% to 4%), burning (1% to 2%), flank pain, injury, infection

<1%: Abnormal stools, abscess, allergic reaction, amnesia, anemia, antisocial reaction, apathy, apnea, arteriosclerosis, arthrosis, asthma, bladder calculus, breast neoplasm, carcinoma, cardiovascular disorder, cellulitis, cerebral ischemia, cerebrovascular accident, chills, cholecystitis, cholelithiasis, choreoathetosis, colitis, cough increased, death, dehydration, delirium, delusions, diabetes mellitus, diplopia, duodenal ulcer, dysphagia, dysuria, ear pain, eczema, edema, encephalopathy, epistaxis, erythema multiforme, esophagitis, extrapyramidal syndrome, eye hemorrhage, eye pain, facial edema, furunculosis, gastroenteritis, gastrointestinal carcinoma, gastrointestinal hemorrhage, glaucoma, hemiplegia, hernia, herpes simplex, herpes zoster, hiccup, hostility, hypercholesteremia, hyperventilation, hypoxia, infection (bacterial), infection (fungal), joint disorder, kidney calculus, lacrimation disorder, laryngitis, leukemia, libido changes, lung edema, manic reaction, meningitis, mouth ulceration, myoclonus, neoplasm, nervousness, neuralgia, neuropathy, nocturia, oliguria, otitis media, ovarian carcinoma, pain, paranoid reaction, parosmia, pericardial effusion, polyuria, prostatic carcinoma, prostatic disorder, pruritus, psychosis, rectal disorder, rhinitis, salivation increased, seborrhea, skin discoloration, skin disorder, stomach atony, surgical procedure, tenosynovitis, thinking abnormal, thirst, thrombocytopenia, thrombosis, tongue disorder, twitching, urinary retention, urinary tract disorder, urticaria, uterine atony, uterine disorder, uterine hemorrhage, vaginitis, viral infection

Metabolism/Transport Effects**Inhibits** CYP2C9 (weak)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

COMT Substrates: COMT Inhibitors may decrease the metabolism of COMT Substrates. *Risk C: Monitor therapy*

MAO Inhibitors: COMT Inhibitors may enhance the adverse/toxic effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Tolcapone, taken with food within 1 hour before or 2 hours after the dose, decreases bioavailability by 10% to 20%.

Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersBlood pressure, symptoms of Parkinson's disease, liver enzymes at baseline and then every 2-4 weeks for the first 6 months of therapy; thereafter, periodic monitoring should be conducted as deemed clinically relevant. If the dose is increased to 200 mg 3 times/day, reinitiate LFT monitoring every 2-4 weeks for 6 months, and then resume periodic monitoring. Discontinue therapy if the ALT or AST exceeds 2 times ULN or if the clinical signs and symptoms suggest the onset of liver failure.

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness (eg, mental status, involuntary movements) and adverse reactions at beginning of therapy and periodically throughout therapy. Monitor for CNS depression. Monitor blood pressure. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsLiver enzymes at baseline and then every 2-4 weeks for the first 6 months of therapy; thereafter, periodic monitoring should be conducted as deemed clinically relevant. If the dose is increased to 200 mg 3 times/day, reinitiate LFT monitoring every 2-4 weeks for 6 months, and then resume periodic monitoring. Discontinue therapy if the ALT or AST exceeds 2 times the upper limit of normal or if the clinical signs and symptoms suggest the onset of liver failure.

Patient EducationTake exactly as directed (may be prescribed in conjunction with levodopa/carbidopa); do not change dosage or discontinue without consulting prescriber. Therapeutic effects may take several weeks or months to achieve and you may need frequent monitoring during first weeks of therapy. Best to take 2 hours before or after a meal; however, may be taken with meals if GI upset occurs. Take at the same time each day. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Do not use alcohol and prescription or OTC sedatives or CNS depressants without consulting prescriber. Urine or perspiration may appear darker. You may experience drowsiness, dizziness, confusion, or vision changes (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); orthostatic hypotension (use caution when changing position - rising to standing from sitting or lying); increased susceptibility to heat stroke, decreased perspiration (use caution in hot weather; maintain adequate fluids and reduce exercise activity); constipation (increased exercise, fluids, or fruit, or fiber may help); dry skin or nasal passages (consult prescriber for appropriate relief); or nausea, vomiting, loss of appetite, or stomach discomfort (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report unresolved constipation or vomiting; chest pain or irregular heartbeat; respiratory difficulty; acute headache or dizziness; CNS changes (hallucination, loss of memory, nervousness, etc); painful or difficult urination; unusual muscle cramping or pain; yellowing of skin or eyes; easy bruising or bleeding; dry, colored stools; abdominal pain or blood in stool; increased muscle spasticity, rigidity, or involuntary movements; skin rash or persistent itching; or significant worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Tasmar®: 100 mg, 200 mg

Generic AvailableNo

ManufacturerRoche Laboratories Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Tasmar)

100 mg (90): $449.62

200 mg (90): $470.45

Mechanism of ActionTolcapone is a selective and reversible inhibitor of catechol-o-methyltransferase (COMT). In the presence of a decarboxylase inhibitor (eg, carbidopa), COMT is the major degradation pathway for levodopa. Inhibition of COMT leads to more sustained plasma levels of levodopa and enhanced central dopaminergic activity.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: 9 L

Protein binding: >99.0%

Metabolism: Hepatic, via glucuronidation, to inactive metabolite (>99%)

Bioavailability: 65%

Half-life elimination: 2-3 hours

Time to peak: ~2 hours

Excretion: Urine (60% as metabolites, 0.5% as unchanged drug); feces (40%)

Related Information

- Antiparkinsonian Agents

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation) and tooth disorder.

Dopaminergic therapy in Parkinson's disease (ie, treatment with levodopa) is associated with orthostatic hypotension. Tolcapone enhances levodopa bioavailability and may increase the occurrence of hypotension/syncope in the dental patient. The patient should be carefully assisted from the chair and observed for signs of orthostatic hypotension.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

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International Brand NamesTasmar (AR, AT, BB, BE, BG, BM, BR, BS, BZ, CH, CN, CR, CZ, DE, DK, DO, ES, FI, FR, GB, GR, GT, GY, HN, IE, IT, JM, MX, NI, NL, NO, NZ, PA, PE, PH, PL, PT, RU, SE, SR, SV, TR, TT, UY)

Tolmetin

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(TOLE met in)

Pharmacologic CategoryNonsteroidal Anti-inflammatory Drug (NSAID), Oral

Use: Labeled IndicationsTreatment of rheumatoid arthritis and osteoarthritis, juvenile rheumatoid arthritis

Dosing: Adults

Inflammation, arthritis: Oral: 400 mg 3 times/day; usual dose: 600 mg to 1.8 g/day; maximum: 1.8 g/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

JRA: Oral: Children ≥2 years: Initial: 20 mg/kg/day in 3-4 divided doses; Maintenance: 15-30 mg/kg/day in 3-4 divided doses (maximum 30 mg/kg/day)

Analgesic (unlabeled use): Oral: Children ≥2 years: 5-7 mg/kg/dose every 6-8 hours

Dietary ConsiderationsMay be taken with antacids to minimize stomach upset. Administration with food or milk decreases bioavailability by 16%. Sodium content: 200 mg: 0.8 mEq; 400 mg: 1.568 mEq; 600 mg: 2.35 mEq.

StorageStore at 15°C to 30°C (59°F to 86°F). Protect from light.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an oral outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to tolmetin, aspirin, other NSAIDs, or any component of the formulation; perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

Allergy Considerations

- Nonsteroidal Anti-inflammatory Drug (NSAID) Allergy

Warnings/Precautions

Boxed warnings:

- Cardiovascular events: See "Concerns related to adverse effects" below.
- Coronary artery bypass graft surgery: See "Disease-related concerns" below.
- Gastrointestinal events: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Anaphylactoid reactions: Even in patients without prior exposure anaphylactoid reactions may occur; patients with "aspirin triad" (bronchial asthma, aspirin intolerance, rhinitis) may be at increased risk. Do not use in patients who experience bronchospasm, asthma, rhinitis, or urticaria with NSAID or aspirin therapy.
- Bleeding/hemostasis: Platelet adhesion and aggregation may be decreased; may prolong bleeding time; patients with coagulation disorders or who are receiving anticoagulants should be monitored closely. Anemia may occur; patients on long-term NSAID therapy should be monitored for anemia.
- Cardiovascular events: **[U.S. Boxed Warning]: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including MI, stroke, and new onset or worsening of pre-existing hypertension.** Risk may be increased with duration of use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention, heart failure, or hypertension. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin's cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.
- Gastrointestinal events: **[U.S. Boxed Warning]: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation.** These events may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of alcohol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk.
- Skin reactions: NSAIDs may cause serious skin adverse events including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN); discontinue use at first sign of skin rash or hypersensitivity.

Disease-related concerns:

- Asthma: Do not administer to patients with aspirin-sensitive asthma; severe bronchospasm may occur. Use caution in patients with other forms of asthma.

- Coronary artery bypass graft surgery: **[U.S. Boxed Warning]: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.** Risk of MI and stroke may be increased with use following CABG surgery.

- Hepatic impairment: Use with caution in patients with decreased hepatic function. Closely monitor patients with any abnormal LFT. Severe hepatic reactions (eg, fulminant hepatitis, liver failure) have occurred with NSAID use, rarely; discontinue if signs or symptoms of liver disease develop, or if systemic manifestations occur.

- Renal impairment: NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.

Special populations:

- Elderly: The elderly are at increased risk for adverse effects (especially peptic ulceration, CNS effects, renal toxicity) from NSAIDs even at low doses.

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Other warnings/precautions:

- Surgical/dental procedures: Withhold for at least 4-6 half-lives prior to surgical or dental procedures.

Geriatric ConsiderationsElderly are a high-risk population for adverse effects from NSAIDs. As much as 60% of the elderly can develop peptic ulceration and/or hemorrhage asymptomatically. The concomitant use of H_2 blockers and sucralfate is not effective as prophylaxis with the exception of NSAID-induced duodenal ulcers which may be prevented by the use of ranitidine. Misoprostol and proton pump inhibitors are the only agents proven to help prevent the development of NSAID-induced ulcers. Also, concomitant disease and drug use contribute to the risk for GI adverse effects. Use lowest effective dose for shortest period possible. Consider renal function decline with age. Use of NSAIDs can compromise existing renal function especially when Cl_{cr} is ≤30 mL/minute. Tinnitus may be a difficult and unreliable indication of toxicity due to age-related hearing loss or eighth cranial nerve damage. CNS adverse effects such as confusion, agitation, and hallucination are generally seen in overdose or high dose situations, but elderly may demonstrate these adverse effects at lower doses than younger adults.
Pregnancy Risk FactorC/D (3rd trimester)
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Use of NSAIDs late in pregnancy may cause premature closure of the ductus arteriosus and may inhibit uterine contractions.
LactationEnters breast milk/not recommended (AAP rates “compatible”)
Adverse Reactions

>10%: Gastrointestinal: Nausea 11%

1% to 10%:

Cardiovascular: Edema (3% to 9%), hypertension (3% to 9%), chest pain (1% to 3%)

Central nervous system: Dizziness (3% to 9%), headache (3% to 9%), depression (1% to 3%), drowsiness (1% to 3%)

Dermatologic: Skin irritation (1% to 3%)

Endocrine & metabolic: Weight gain/loss (3% to 9%)

Gastrointestinal: Abdominal pain (3% to 9%), diarrhea (3% to 9%), dyspepsia (3% to 9%), flatulence (3% to 9%), gastrointestinal distress (3% to 9%), vomiting (3% to 9%), constipation (1% to 3%), gastritis (1% to 3%), peptic ulcer (1% to 3%)

Genitourinary: Urinary tract infection (1% to 3%)

Hematologic: Hemoglobin/hematocrit decreased (transient; 1% to 3%)

Neuromuscular & skeletal: Weakness (3% to 9%)

Ocular: Visual disturbances (1% to 3%)

Otic: Tinnitus (1% to 3%)

Renal: BUN increased (1% to 3%)

<1%, postmarketing, and/or case reports: Agranulocytosis, anaphylactoid reactions, CHF, dysuria, epistaxis, erythema multiforme, exfoliative dermatitis, fever, fluid retention, GI bleeding, GI perforation, glossitis, granulocytopenia, hematuria, hemolytic anemia, hepatic failure, hepatic necrosis, hepatitis, hepatitis (fulminant), interstitial nephritis, jaundice, liver function tests (abnormal), lymphadenopathy, macular changes, nephrotic syndrome, optic neuropathy, proteinuria, purpura, renal failure, retinal changes, serum sickness, stomatitis, Stevens-Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis, urticaria

Drug Interactions

ACE Inhibitors: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Aminoglycosides: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Aminoglycosides. Data only in premature infants. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Angiotensin II Receptor

Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Anticoagulants: Nonsteroidal Anti-Inflammatory Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antidepressants (Tricyclic, Tertiary Amine): May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Antiplatelet Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Antiplatelet Agents. An increased risk of bleeding may occur. Nonsteroidal Anti-Inflammatory Agents may diminish the cardioprotective effect of Antiplatelet Agents. This interaction is likely specific to aspirin, and not to other antiplatelet agents. *Risk C: Monitor therapy*

Beta-Blockers: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Nonsteroidal Anti-Inflammatory Agents. *Risk D: Consider therapy modification*

Bisphosphonate Derivatives: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

CycloSPORINE: Nonsteroidal Anti-Inflammatory Agents may enhance the nephrotoxic effect of CycloSPORINE. Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of CycloSPORINE. *Risk D: Consider therapy modification*

Desmopressin: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Eplerenone: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of Eplerenone. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk D: Consider therapy modification*

HydrALAZINE: Nonsteroidal Anti-Inflammatory Agents may diminish the antihypertensive effect of HydrALAZINE. *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. *Risk X: Avoid combination*

Lithium: Nonsteroidal Anti-Inflammatory Agents may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Methotrexate: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Methotrexate. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of other Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Pemetrexed: NSAID (Nonselective) may decrease the excretion of Pemetrexed. *Risk D: Consider therapy modification*

Probenecid: May increase the serum concentration of Nonsteroidal Anti-Inflammatory Agents. *Risk C: Monitor therapy*

Quinolone Antibiotics: Nonsteroidal Anti-Inflammatory Agents may enhance the neuroexcitatory and/or seizure-potentiating effect of Quinolone Antibiotics. *Risk C: Monitor therapy*

Salicylates: NSAID (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with use of this combination. NSAID (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of NSAID (Nonselective). **Exceptions:** Choline Magnesium Trisalicylate. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Thiazide Diuretics: Nonsteroidal Anti-Inflammatory Agents may diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thrombolytic Agents: Nonsteroidal Anti-Inflammatory Agents may enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Treprostinil: May enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Vancomycin: Nonsteroidal Anti-Inflammatory Agents may decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): NSAID (Nonselective) may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Tolmetin peak serum concentrations may be decreased if taken with food or milk.

Herb/Nutraceutical: Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, fenugreek, garlic, ginger, ginkgo biloba, ginseng (American, Panax, Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, prickly ash, red clover, reishi, SAMe (S-adenosylmethionine), sweet clover, turmeric, white willow (all have additional antiplatelet activity).

Monitoring ParametersMonitor CBC, liver enzymes, occult blood loss; monitor urine output and BUN/ serum creatinine in patients receiving diuretics and ACE inhibitors, monitor blood pressure in patients receiving antihypertensives

Nursing: Physical Assessment/MonitoringEvaluate cardiac risk and potential for GI bleeding prior to prescribing this medication. Assess effectiveness and interactions of other medications patient may be taking. Monitor blood pressure at the beginning of therapy and periodically during use. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions (eg, GI bleeding, hepatotoxicity, ototoxicity) at beginning of therapy and periodically throughout therapy. Patients who are on long-term NSAID therapy should have periodic ophthalmic evaluations. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCBC, liver enzymes, occult blood loss; monitor BUN/ serum creatinine in patients receiving diuretics and ACE inhibitors

Patient EducationTake this medication exactly as directed; do not increase dose without consulting prescriber. Do not crush tablets or break capsules. Take with food or milk to reduce GI distress. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You should have regular ophthalmic evaluations when using NSAIDs for long periods of time. Do not use alcohol, aspirin or aspirin-containing medication, or any other anti-inflammatory medications without consulting prescriber. You may experience dizziness, nervousness, or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea, vomiting, or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); or constipation (increased exercise, fluids, fruit, or fiber may help). GI bleeding, ulceration, or perforation can occur with or without pain. Discontinue medication and contact prescriber if persistent abdominal pain or cramping, or blood in stool occurs. Report chest pain or palpitations; breathlessness or respiratory difficulty; slurring of speech; unusual bruising/bleeding; blood in urine, stool, mouth, or vomitus; unusual fatigue; skin rash or itching; unusual weight gain or swelling of extremities; change in urinary pattern; or change in vision or hearing or ringing in ears. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 3rd trimester of pregnancy.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 400 mg

Tablet: 200 mg, 600 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Tolmetin Sodium)

400 mg (90): $89.99

Tablets (Tolectin)

600 mg (100): $195.75

Tablets (Tolmetin Sodium)

200 mg (100): $53.06

600 mg (100): $143.07

Mechanism of ActionReversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which result in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

Pharmacodynamics/Kinetics

Onset of action: Analgesic: 1-2 hours; Anti-inflammatory: Days to weeks

Absorption: Well absorbed, rapid

Bioavailability: Reduced 16% with food or milk

Half-life elimination: Biphasic: Rapid: 1-2 hours; Slow: 5 hours

Time to peak, serum: 30-60 minutes

Excretion: Urine (as inactive metabolites or conjugates) within 24 hours

Related Information

- Antacid Drug Interactions
- Nonsteroidal Anti-inflammatory Agents

Dental Health: Effects on Dental TreatmentThe dentist should be aware of the potential of abnormal coagulation. Caution should also be exercised in the use of NSAIDs in patients already on anticoagulant therapy with drugs such as warfarin (Coumadin®).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common; may cause nervousness; may rarely cause drowsiness, confusion, insomnia, hallucinations, or depression

Mental Health: Effects on Psychiatric TreatmentMay rarely cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Blood Pressure: In short-term use, NSAIDs vary considerably in their effect on blood pressure. A recent meta-analysis (see References) showed that indomethacin and naproxen had the largest effect on blood pressure. Other NSAIDs, including piroxicam, ibuprofen, and sulindac had less of an effect. Ibuprofen combined with captopril or losartan may attenuate the antihypertensive effects of ACE inhibition or receptor blockade on sitting or 24-hour ambulatory diastolic blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short.

Heart Failure: The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema. One study showed that NSAID use in elderly patients had an increased risk of hospitalization for heart failure. This study gives compelling reasons to avoid or limit the use of NSAIDs in patients with congestive heart failure, particularly in the elderly population. The ACC/AHA 2005 Heart Failure Guidelines suggest that NSAIDs be avoided or withdrawn whenever possible in patients with current or prior symptoms of heart failure and reduced LVEF.

Risk of Cardiovascular Events: Patients at increased risk of cardiovascular adverse events include patients immediately postoperative (10-14 days) from CABG surgery, and those with existing CAD, CVD, or history of TIA. Prescribers are encouraged to use the lowest effective dose for the shortest duration of time based on individual patient treatment goals. Available evidence reviewed by the FDA does not suggest an increased risk of serious CV events when NSAIDs are given short term and in the lower doses used OTC.

Drug Interactions: Nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen, may diminish the cardioprotective effect of aspirin (Catella-Lawson F, 2001; Capone ML, 2005). It is surmised that ibuprofen may exhibit greater affinity than aspirin for the COX-1 site or if dosed regularly (or prior to aspirin), it would gain access to the active site first. In either case, aspirin's inhibition of COX (irreversible) would be limited in favor of ibuprofen inhibition (reversible). Avoid regular use of NSAIDs (nonselective) if possible. If used occasionally, take after aspirin (immediate release) ingestion.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe 2002 ACCM/SCCM guidelines for analgesia (critically-ill adult) suggest that NSAIDs may be used in combination with opioids in select patients for pain management. Concern about adverse events (increased risk of renal dysfunction, altered platelet function and gastrointestinal irritation) limits its use in patients who have other underlying risks for these events.

In short-term use, NSAIDs vary considerably in their effect on blood pressure. When NSAIDs are used in patients with hypertension, appropriate monitoring of blood pressure responses should be completed and the duration of therapy, when possible, kept short. The use of NSAIDs in the treatment of patients with congestive heart failure may be associated with an increased risk for fluid accumulation and edema; may precipitate renal failure in dehydrated patients.

Index TermsTolectin; Tolmetin Sodium

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International Brand NamesArtrocaptin (ES); Tolectin (BF, BH, BJ, CI, CY, ET, GH, GM, GN, JO, KE, LB, LR, MA, ML, MR, MU, MW, NE, NG, OM, PL, SC, SD, SL, SN, SY, TN, TZ, UG, ZA, ZM, ZW); Tolectin-gel (PL); Tolectín (MX)

Tolnaftate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Tolnaftate may be confused with Tornalate®

Tinactin® may be confused with Talacen®

Pronunciation(tole NAF tate)

U.S. Brand NamesBlis-To-Sol® [OTC]; FungiGuard [OTC]; Mycocide® NS [OTC]; Podactin Powder [OTC]; Tinactin® Antifungal Deodorant [OTC]; Tinactin® Antifungal Jock Itch [OTC]; Tinactin® Antifungal [OTC]; Tinaderm [OTC]; Ting® Cream [OTC]; Ting® Spray Liquid [OTC]

Canadian Brand NamesPitrex

Pharmacologic CategoryAntifungal Agent, Topical

Use: Labeled IndicationsTreatment of tinea pedis, tinea cruris, tinea corporis

Dosing: Adults**Tinea infection:** Topical: Wash and dry affected area; spray aerosol or apply 1-3 drops of solution or a small amount of cream, or powder and rub into the affected areas 2 times/day

Note: May use for up to 4 weeks for tinea pedis or tinea corporis, and up to 2 weeks for tinea cruris.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren ≥2 years: Refer to adult dosing.

ContraindicationsHypersensitivity to tolnaftate or any component of the formulation; nail and scalp infections

Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue if sensitivity or irritation occurs.

Special populations:

- Pediatrics: Not for self-medication (OTC use) in children <2 years of age.

Other warnings/precautions:

- Appropriate use: For topical use only; avoid contact with eyes. Apply to clean, dry skin. When used for self-medication (OTC use), contact health care provider if condition does not improve within 4 weeks.

Geriatric ConsiderationsNo specific recommendations for use in the elderly.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Dermatologic: Pruritus, contact dermatitis

Local: Irritation, stinging

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol, topical [spray]:

Tinactin® Antifungal: 1% (150 g) [contains ethanol 29% v/v]

Ting®: 1% (128 g) [contains ethanol 41% v/v]

Aerosol, topical [powder, spray]:

Tinactin® Antifungal Deodorant: 1% (133 g) [contains ethanol 11% v/v, talc]

Tinactin® Antifungal: 1% (133 g) [contains ethanol 11% v/v, talc]

Tinactin® Antifungal Jock Itch: 1% (133 g) [contains ethanol 11%, talc]

Cream, topical: 1% (15 g, 30 g)

FungiGuard, Tinactin® Antifungal Jock Itch, Ting®: 1% (15 g)

Tinactin® Antifungal: 1% (15 g, 30 g)

Liquid, topical:

Blis-To-Sol®: 1% (30 mL, 55 mL)

FungiGuard: 1% (30 mL) [contains vitamin E and aloe]

Liquid, topical [spray]:

Tinactin® Antifungal: 1% (59 mL) [contains ethanol 70% v/v]

Powder, topical: 1% (45 g)

Podactin: 1% (45 g)

Tinactin® Antifungal: 1% (108 g)

Solution, topical: 1% (10 mL)

Mycocide® NS: 1% (30 mL)

Tinaderm: 1% (10 mL)

Generic AvailableYes: Cream, powder, solution

Mechanism of ActionDistorts the hyphae and stunts mycelial growth in susceptible fungi

Pharmacodynamics/KineticsOnset of action: 24-72 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesAthlete's Foot (AR, HU); Athletes Foot Powder (IL); Chinofungin (HU, PL); Chlorisept (DE); Ezon-T (JP); Focusan (AT, CH, CZ, NL); Hi-Alarzin (JP); Myco-Aid (MY); Pedimycose (FR); Pitrex (IL); Ringworm Ointment (AU); Separin (JP); Sorgoa (DE, LU); Sporiline (FR); Tinaderm (AR, AU, CN, EC, ES, IE, IN, IT, MX, PE, PY, SG, VE, ZA); Tinaderm M (CO); Tinaderme (PT); Tinatox (DE); Tineafax (AU); Tolnadem (IN); Tolnaderm (MY, PH); Tolnaftat Puder N (DE); Tolnaftat Spray (DE); Tolsol (IN); Tono (TH); Tonoftal (DE)

Tolterodine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Tolterodine may be confused with fesoterodine

Detrol® may be confused with Ditropan®

International issues:

Detrol® may be confused with Desurol® which is a brand name for oxolinic acid in the Czech Republic

Pronunciation(tole TER oh deen)

U.S. Brand NamesDetrol®; Detrol® LA

Canadian Brand NamesDetrol®; Detrol® LA; Unidet®

Pharmacologic CategoryAnticholinergic Agent

Use: Labeled IndicationsTreatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence

Dosing: Adults**Treatment of overactive bladder:** Oral:

Immediate release tablet: 2 mg twice daily; the dose may be lowered to 1 mg twice daily based on individual response and tolerability

Dosing adjustment in patients concurrently taking CYP3A4 inhibitors: 1 mg twice daily

Extended release capsule: 4 mg once a day; dose may be lowered to 2 mg daily based on individual response and tolerability

Dosing adjustment in patients concurrently taking CYP3A4 inhibitors: 2 mg daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentUse with caution (studies conducted in patients with Cl_{cr} 10-30 mL/minute):

Immediate release tablet: 1 mg twice daily

Extended release capsule: 2 mg daily

Dosing: Hepatic Impairment

Immediate release tablet: 1 mg twice daily

Extended release capsule: 2 mg daily

Calculations

- Creatinine Clearance: Adults

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light.

ContraindicationsHypersensitivity to tolterodine or any component of the formulation; urinary retention; gastric retention; uncontrolled narrow-angle glaucoma

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause drowsiness and/or blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- QT prolongation: Has been associated with QT_c prolongation at high (supratherapeutic) doses. The manufacturer recommends caution in patients with congenital prolonged QT or in patients receiving concurrent therapy with QT_c-prolonging drugs (class Ia or III antiarrhythmics). However, the extent of QT_c prolongation even at supratherapeutic dosages was less than 15 msec. Individuals who are CYP2D6 poor metabolizers or in the presence of inhibitors of CYP2D6 and CYP3A4 may be more likely to exhibit prolongation.

Disease-related concerns:

- Bladder flow obstruction: Use with caution in patients with bladder flow obstruction; may increase the risk of urinary retention.
- Gastrointestinal obstructive disorders: Use with caution in patients with decreased GI motility or gastrointestinal obstructive disorders (ie, pyloric stenosis); may increase the risk of gastric retention.

- Glaucoma: Use with caution in patients with controlled (treated) narrow-angle glaucoma.
- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment is required.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis.
- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment is required.

Concurrent drug therapy issues:

- CYP3A4 inhibitors: Dosage adjustment is recommended in patients receiving CYP3A4 inhibitors; a lower dose of tolterodine is recommended. Also see QT prolongation in “Concerns related to adverse effects” above.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo difference in safety has been noted between elderly and younger patients, therefore, no dosage adjustment is recommended.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were observed in some animal studies. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus.

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsAs reported with immediate release tablet, unless otherwise specified

>10%: Gastrointestinal: Dry mouth (35%; extended release capsules 23%)

1% to 10%:

Cardiovascular: Chest pain (2%)

Central nervous system: Headache (7%; extended release capsules 6%), somnolence (3%; extended release capsules 3%), fatigue (4%; extended release capsules 2%), dizziness (5%; extended release capsules 2%), anxiety (extended release capsules 1%)

Dermatologic: Dry skin (1%)

Gastrointestinal: Abdominal pain (5%; extended release capsules 4%), constipation (7%; extended release capsules 6%), dyspepsia (4%; extended release capsules 3%), diarrhea (4%), weight gain (1%)

Genitourinary: Dysuria (2%; extended release capsules 1%)

Neuromuscular & skeletal: Arthralgia (2%)

Ocular: Abnormal vision (2%; extended release capsules 1%), dry eyes (3%; extended release capsules 3%)

Respiratory: Bronchitis (2%), sinusitis (extended release capsules 2%)

Miscellaneous: Flu-like syndrome (3%), infection (1%)

Postmarketing and/or case reports: Anaphylactoid reactions, angioedema, confusion, dementia aggravated, disorientation, hallucinations, memory impairment, palpitation, peripheral edema, QT_c prolongation, tachycardia

Metabolism/Transport Effects**Substrate** of CYP2C9 (minor), 2C19 (minor), 2D6 (major), 3A4 (major)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Tolterodine. This is likely only of concern in CYP2D6-deficient patients (ie, "poor metabolizers") *Risk D: Consider therapy modification*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Tolterodine. This is likely only of concern in CYP2D6-deficient patients (ie, "poor metabolizers")

Risk C: Monitor therapy

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

VinBLAStine: May increase the serum concentration of Tolterodine. Management: Reduce tolterodine dosage to 1 mg twice daily (regular release formulation) or 2 mg daily (extended release formulation) and monitor for increased levels/effects of tolterodine with initiation of vinblastine therapy. *Risk D: Consider therapy modification*

Warfarin: Tolterodine may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Increases bioavailability (~53% increase) of tolterodine tablets (dose adjustment not necessary); does not affect the pharmacokinetics of tolterodine extended release capsules. As a CYP3A4 inhibitor, grapefruit juice may increase the serum level and/or toxicity of tolterodine, but unlikely secondary to high oral bioavailability.

Herb/Nutraceutical: St John's wort (*Hypericum*) appears to induce CYP3A enzymes.

Monitoring ParametersRenal function (BUN, creatinine); hepatic function

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking (eg, ergot-containing drugs). Assess therapeutic effectiveness and adverse reactions. Teach patient appropriate use (according to formulation and purpose), interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsRenal function (BUN, creatinine); hepatic function

Patient EducationTake as directed, preferably with food. Do not break, crush, or chew extended release medication. May cause headache (consult prescriber for a mild analgesic); dry mouth; dizziness, nervousness, or sleepiness (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); or abdominal discomfort, diarrhea, constipation, nausea, or vomiting (small frequent meals, increased exercise, adequate hydration may help). Report back pain, muscle spasms, alteration in gait, or numbness of extremities; unresolved or persistent constipation, diarrhea, or vomiting; or symptoms of upper respiratory infection or flu. Report immediately any chest pain or palpitations, difficulty urinating, or pain on urination. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release, as tartrate (Detrol® LA): 2 mg, 4 mg

Tablet, as tartrate (Detrol®): 1 mg, 2 mg

Generic AvailableNo

ManufacturerPharmacia & Upjohn

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Detrol LA)

2 mg (30): $119.99

4 mg (30): $126.98

Tablets (Detrol)

1 mg (60): $139.43

2 mg (60): $139.00

Mechanism of ActionTolterodine is a competitive antagonist of muscarinic receptors. In animal models, tolterodine demonstrates selectivity for urinary bladder receptors over salivary receptors. Urinary bladder contraction is mediated by muscarinic receptors. Tolterodine increases residual urine volume and decreases detrusor muscle pressure.

Pharmacodynamics/Kinetics

Absorption: Immediate release tablet: Rapid; ≥77%

Distribution: I.V.: V_d: 113 ± 27 L

Protein binding: >96% (primarily to alpha$_1$-acid glycoprotein)

Metabolism: Extensively hepatic, primarily via CYP2D6 (some metabolites share activity) and 3A4 usually (minor pathway). In patients with a genetic deficiency of CYP2D6, metabolism via 3A4 predominates.

Bioavailability: Immediate release tablet: Increased 53% with food

Half-life elimination:

Immediate release tablet: Extensive metabolizers: ~2 hours; Poor metabolizers: ~10 hours

Extended release capsule: Extensive metabolizers: ~7 hours; Poor metabolizers: ~18 hours

Time to peak: Immediate release tablet: 1-2 hours; Extended release tablet: 2-6 hours

Excretion: Urine (77%); feces (17%); primarily as metabolites (<1% unchanged drug) of which the active 5-hydroxymethyl metabolite accounts for 5% to 14% (<1% in poor metabolizers); as unchanged drug (<1%; <2.5% in poor metabolizers)

Dental Health: Effects on Dental Treatment The anticholinergic effects of tolterodine are selective for the urinary bladder rather than salivary glands; xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause drowsiness, dizziness, hallucinations, or nervousness

Mental Health: Effects on Psychiatric Treatment Fluoxetine and likely paroxetine increase the serum concentration of tolterodine; however, the magnitude of this increase is small (~25%, as reported for fluoxetine) and thus no dosage adjustment is required.

Index Terms Tolterodine Tartrate

International Brand Names Detrodin SR (KP); Detrol SR (KP); Detrusitol (AE, AR, AT, AU, BE, BG, BH, BR, CN, CO, CR, CY, CZ, DE, EC, EE, EG, ES, FI, FR, GB, GT, HK, HN, HU, ID, IE, IL, IN, IQ, IR, IT, JO, KW, LB, LY, MX, MY, NI, NL, NO, OM, PA, PE, PH, PK, PL, QA, SA, SE, SG, SV, SY, TW, VE, YE); Detrusitol Retard (DK, PT); Detrusitol SR (BG, CH, CZ, KP, MY, NO, SG, TH); Fluserin (UY); Sedatol SR (KP); Uretol SR (KP); Urginol (AR); Uridin (TW); Urositol (KP)

Topiramate

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Jump To Field (Select Field Name)

Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

Topamax® may be confused with Tegretol®, Tegretol®-XR, Toprol-XL®

Pronunciation(toe PYRE a mate)

U.S. Brand NamesTopamax®

Canadian Brand NamesApo-Topiramate; Co-Topiramate; Dom-Topiramate; Gen-Topiramate; Novo-Topiramate; PHL-Topiramate; PMS-Topiramate; ratio-Topiramate; Sandoz-Topiramate; Topamax®

Pharmacologic CategoryAnticonvulsant, Miscellaneous

Use: Labeled IndicationsMonotherapy or adjunctive therapy for partial onset seizures and primary generalized tonic-clonic seizures; adjunctive treatment of seizures associated with Lennox-Gastaut syndrome; prophylaxis of migraine headache

Use: Unlabeled/InvestigationalInfantile spasms, neuropathic pain, cluster headache

Dosing: Adults**Note:** Do not abruptly discontinue therapy; taper dosage gradually to prevent rebound effects. (In clinical trials, adult doses were withdrawn by decreasing in weekly intervals of 50-100 mg/day gradually over 2-8 weeks for seizure treatment, and by decreasing in weekly intervals by 25-50 mg/day for migraine prophylaxis.)

Partial onset seizure (monotherapy) and primary generalized tonic-clonic seizure (monotherapy): Oral: Initial: 25 mg twice daily; may increase weekly by 50 mg/day up to 100 mg twice daily (week 4 dose); thereafter, may further increase weekly by 100 mg/day up to the recommended maximum of 200 mg twice daily.

Migraine prophylaxis: Oral: Initial: 25 mg/day (in the evening), titrated at weekly intervals in 25 mg increments, up to the recommended total daily dose of 100 mg/day given in 2 divided doses

Partial onset seizures (adjunctive therapy): Oral: Initial: 25-50 mg/day (given in 2 divided doses) for 1 week; increase at weekly intervals by 25-50 mg/day until response; usual maintenance dose: 100-200 mg twice daily. Doses >1600 mg/day have not been studied.

Primary generalized tonic-clonic seizures (adjunctive therapy): Oral: Use initial dose as listed above for partial onset seizures, but use slower initial titration rate; titrate upwards to recommended dose by the end of 8 weeks; usual maintenance dose: 200 mg twice daily. Doses >1600 mg/day have not been studied.

Cluster headache (unlabeled use): Oral: Initial: 25 mg/day, titrated at weekly intervals in 25 mg increments, up to 200 mg/day

Neuropathic pain (unlabeled use): Oral: Initial: 25 mg/day, titrated at weekly intervals in 25-50 mg increments to target dose of 400 mg daily in 2 divided doses. Reported dosage range studied: 25-800 mg/day

Dosing: ElderlyMost older adults have creatinine clearances <70 mL/min; obtain a serum creatinine and calculate creatinine clearance prior to initiation of therapy. An initial dose of 25 mg/day may be recommended, followed by incremental increases of 25 mg at weekly intervals until an effective dose is reached; refer to adult dosing for titration schedule.

Dosing: Pediatric**Note:** Do not abruptly discontinue therapy; taper dosage gradually to prevent rebound effects.
*Monotherapy:***Partial onset seizure and primary generalized tonic-clonic seizure:** Children ≥10 years: Oral: Refer to adult dosing.

Adjunctive therapy:

Partial onset seizure or seizure associated with Lennox-Gastaut syndrome: Children 2-16 years: Oral: Initial dose titration should begin at 25 mg (or less, based on a range of 1-3 mg/kg/day) nightly for the first week; dosage may be increased in increments of 1-3 mg/kg/day (administered in 2 divided doses) at 1- or 2-week intervals to a total daily dose of 5-9 mg/kg/day

Adolescents ≥17 years: Refer to adult dosing.

Primary generalized tonic-clonic seizure: Children 2-16 years: Oral: Use initial dose listed above, but use slower initial titration rate; titrate to recommended maintenance dose by the end of 8 weeks

Adolescents ≥17 years: Refer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} <70 mL/minute: Administer 50% dose and titrate more slowly.

Hemodialysis: Supplemental dose may be needed during hemodialysis

Dialyzable: ~30%

Dosing: Hepatic ImpairmentClearance may be reduced.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralMay be administered without regard to meals

Capsule sprinkles: May be swallowed whole or opened to sprinkle the contents on soft food (drug/food mixture should not be chewed).

Tablet: Because of bitter taste, tablets should not be broken.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F). Protect from moisture.

ContraindicationsHypersensitivity to topiramate or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Cognitive dysfunction, psychiatric disturbances (mood disorders), and sedation (somnolence or fatigue) may occur with use; incidence may be related to rapid titration and higher doses. May also cause paresthesia, dizziness, and ataxia.

- Glaucoma: Has been associated with acute myopia and secondary angle-closure glaucoma in adults and children, typically within 1 month of initiation; discontinue in patients with acute onset of decreased visual acuity or ocular pain.

- Hyperthermia: May be associated (rarely) with severe oligohydrosis and hyperthermia, most frequently in children; use caution and monitor closely during strenuous exercise, during exposure to high environmental temperature, or in patients receiving drugs with anticholinergic activity.

- Metabolic acidosis (hyperchloremic, nonanion gap): May decrease serum bicarbonate concentrations, due to inhibition of carbonic anhydrase and increased renal bicarbonate loss. Decreases in serum bicarbonate are relatively common (7% to 67%) but usually mild to moderate (average decrease of 4 mEq/L at dose of 400 mg/day in adults and 6 mg/kg/day in children). Treatment-emergent metabolic acidosis is less common; however, risk may be increased in patients with a predisposing condition (renal, respiratory and/or hepatic impairment), ketogenic diet, or concurrent treatment with other drugs which may cause acidosis. Metabolic acidosis may occur at dosages as low as 50 mg/day. Serum bicarbonate should be monitored, as well as potential complications of chronic acidosis (nephrolithiasis, osteomalacia, and reduced growth rates in children). Dose reduction or discontinuation (by tapering dose) should be considered in patients with persistent or severe metabolic acidosis. If treatment is continued, alkali supplementation should be considered.

- Renal calculus: Topiramate exhibits carbonic anhydrase properties and the risk of kidney stones is about 2-4 times that of the untreated population. Kidney stones have been reported in children and adults. The risk of stones may be reduced by increasing fluid intake.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment may be required.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment may be required.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

- Valproate: Hyperammonemia with or without encephalopathy may occur and has been documented in patients who have tolerated each drug alone. Risk may be increased in patients with inborn errors of metabolism or decreased hepatic mitochondrial activity. Monitor for lethargy, vomiting, or unexplained changes in mental status.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <2 years of age for adjunctive treatment of seizures and <10 years of age for monotherapy treatment of seizures. Safety and efficacy have not been established in children for migraine prophylaxis.

Other warnings/precautions:

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal. Doses were also gradually withdrawn in migraine prophylaxis studies (decreased in weekly intervals by 25-50 mg/day).

Geriatric ConsiderationsThis drug may not be a drug of choice in the elderly until all other therapies for seizures have been exhausted. Follow the recommended titration schedule and adjust time intervals to meet patient's needs. Since most elderly will have a Cl_{cr} <70 mL/minute, it is important to either measure or estimate by calculation the Cl_{cr} prior to initiating therapy.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTopiramate was found to be teratogenic in animal studies; however, there is limited information in pregnant women; use only if benefit to the mother outweighs the risk to the fetus. Based on limited data, topiramate was found to cross the placenta. Postmarketing experience includes reports of hypospadias following *in vitro* exposure to topiramate.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsBased on limited data, topiramate was found in breast milk; low concentrations were detected in nursing infants.

Adverse ReactionsAdverse events are reported for placebo-controlled trials of adjunctive therapy in adult and pediatric patients. Unless otherwise noted, the percentages refer to incidence in epilepsy trials. Note: A wide range of dosages were studied; incidence of adverse events was frequently lower in the pediatric population studied.

>10%:

Central nervous system: Dizziness (4% to 32%), ataxia (6% to 16%), somnolence (15% to 29%), psychomotor slowing (3% to 21%), nervousness (9% to 19%), memory difficulties (2% to 14%), speech problems (2% to 13%), fatigue (9% to 30%), difficulty concentrating (5% to 14%), depression (9% to 13%), confusion (4% to 14%)

Endocrine & metabolic: Serum bicarbonate decreased (dose-related: 7% to 67%; marked reductions [to <17 mEq/L] 1% to 11%)

Gastrointestinal: Nausea (6% to 12%; migraine trial: 14%), weight loss (8% to 13%), anorexia (4% to 24%)

Neuromuscular & skeletal: Paresthesia (1% to 19%; migraine trial: 35% to 51%)

Ocular: Nystagmus (10% to 11%), abnormal vision (<1% to 13%)

Respiratory: Upper respiratory infection (migraine trial: 12% to 13%)

Miscellaneous: Injury (6% to 14%)

1% to 10%:

Cardiovascular: Chest pain (2% to 4%), edema (1% to 2%), bradycardia (1%), pallor (up to 1%), hypertension (1% to 2%)

Central nervous system: Abnormal coordination (4%), hypoesthesia (1% to 2%; migraine trial: 8%), convulsions (1%), depersonalization (1% to 2%), apathy (1% to 3%), cognitive problems (3%), emotional lability (3%), agitation (3%), aggressive reactions (2% to 9%), tremor (3% to 9%), stupor (1% to 2%), mood problems (4% to 9%), anxiety (2% to 10%), insomnia (4% to 8%), fever (migraine trial: 1% to 2%), vertigo (1% to 2%), neurosis (1%)

Dermatologic: Pruritus (migraine trial: 2% to 4%), skin disorder (1% to 3%), alopecia (2%), dermatitis (up to 2%), hypertrichosis (up to 2%), rash erythematous (up to 2%), eczema (up to 1%), seborrhea (up to 1%), skin discoloration (up to 1%)

Endocrine & metabolic: Hot flashes (1% to 2%); metabolic acidosis (hyperchloremia, nonanion gap), dehydration, breast pain (up to 4%), menstrual irregularities (1% to 2%), hypoglycemia (1%), libido decreased (<1% to 2%)

Gastrointestinal: Dyspepsia (2% to 7%), abdominal pain (5% to 7%), constipation (3% to 5%), xerostomia (2% to 4%), fecal incontinence (1%), gingivitis (1%), diarrhea (2%; migraine trial: 11%), vomiting (1% to 3%), gastroenteritis (1% to 3%), GI disorder (1%), dysgeusia (2% to 4%; migraine trial: 12% to 15%), appetite increased (1%), dysphagia (1%), flatulence (1%), GERD (1%), glossitis (1%), gum hyperplasia (1%), weight gain (1%)

Genitourinary: Impotence, dysuria/incontinence (<1% to 4%), prostatic disorder (2%), UTI (2% to 3%), premature ejaculation (migraine trial: 3%), cystitis (2%)

Hematologic: Leukopenia (1% to 2%), purpura (8%), hematoma (1%), prothrombin time increased (1%), thrombocytopenia (1%)

Neuromuscular & skeletal: Myalgia (2%), weakness (3% to 6%), back pain (1% to 5%), leg pain (2% to 4%), rigors (1%), hypertonia, arthralgia (1% to 7%), gait abnormal (2% to 8%), involuntary muscle contractions (2%; migraine trial: 4%), skeletal pain (1%), hyperkinesia (up to 5%), hyporeflexia (up to 2%)

Ocular: Conjunctivitis (1%), diplopia (2% to 10%), myopia (up to 1%)

Otic: Hearing decreased (1% to 2%), tinnitus (1% to 2%), otitis media (migraine trial: 1% to 2%)

Renal: Nephrolithiasis, renal calculus (1% to 2%), hematuria (<1% to 2%)

Respiratory: Pharyngitis (3% to 6%), sinusitis (4% to 6%; migraine trial: 8% to 10%), epistaxis (1% to 4%), rhinitis (4% to 7%), dyspnea (1% to 2%), pneumonia (5%), cough (migraine trial: 2% to 3%), bronchitis (migraine trial: 3%)

Miscellaneous: Flu-like syndrome (3% to 7%), allergy (2% to 3%), body odor (up to 1%), viral infection (migraine trial: 3% to 4%), infection (<1% to 2%), diaphoresis (≤1%), thirst (2%)

<1% (Limited to important or life-threatening): Anemia, angina, apraxia, AV block, bone marrow depression, deep vein thrombosis, dehydration, delirium, diabetes mellitus, dyskinesia, electrolyte imbalance, encephalopathy (with valproate therapy), eosinophilia, euphoria, granulocytopenia, hypokalemia, hypotension, liver enzymes increased, lymphadenopathy, lymphopenia, manic reaction, neuropathy, pancytopenia, paranoid reaction, photosensitivity, psychosis, pulmonary embolism, suicidal behavior, syncope, tongue edema

Postmarketing and/or case reports: Accommodation abnormality, erythema multiforme, eye pain, hepatic failure, hepatitis, hyperammonemia (with valproate therapy), hyperthermia (severe), migraine aggravated, oligohydrosis, pancreatitis, pemphigus, rash, renal tubular acidosis, Stevens-Johnson syndrome, syndrome of acute myopia/secondary angle-closure glaucoma, toxic epidermal necrolysis

Metabolism/Transport Effects**Inhibits** CYP2C19 (weak); **Induces** CYP3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CarBAMazepine: May decrease the serum concentration of Topiramate. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): Topiramate may decrease the serum concentration of Oral Contraceptive (Estrogens). Contraceptive failure is possible. *Risk D: Consider therapy modification*

Phenytoin: Topiramate may decrease the metabolism of Phenytoin. Phenytoin may increase the metabolism of Topiramate. *Risk C: Monitor therapy*

Valproic Acid: Topiramate may enhance the hepatotoxic effect of Valproic Acid. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Ketogenic diet may increase the possibility of acidosis and/or kidney stones.

Herb/Nutraceutical: Avoid evening primrose (seizure threshold decreased).

Monitoring ParametersSeizure frequency, hydration status; electrolytes (recommended monitoring includes serum bicarbonate at baseline and periodically during treatment), serum creatinine; monitor for symptoms of acute acidosis and complications of long-term acidosis (nephrolithiasis, osteomalacia, and reduced growth rates in children); ammonia level in patients with unexplained lethargy, vomiting, or mental status changes; intraocular pressure, symptoms of secondary angle closure glaucoma

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor therapeutic effectiveness (seizure activity, force, type, duration), laboratory values, and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. May cause weight loss; monitor weight periodically. Assess knowledge/teach patient appropriate use, seizure safety precautions, interventions to reduce side effects, and adverse symptoms to report..

Monitoring: Lab TestsRecommended monitoring includes serum bicarbonate (baseline and periodically during treatment) and serum creatinine. Ammonia level in patients with unexplained lethargy, vomiting, or mental status changes.

Patient EducationTake exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake; possibly to prevent the development of kidney stones and dehydration. You may be at risk for decreased sweating and increased body temperature, especially in hot weather. You may experience drowsiness, dizziness, disturbed concentration, memory changes, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or mouth sores, nausea, vomiting, or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Wear identification of epileptic status and medications. Report behavioral or CNS changes, suicidal ideation, or depression; skin rash; muscle cramping, numbness in extremities, weakness, tremors, changes in gait; chest pain, irregular heartbeat, or palpitations; hearing loss; cough or respiratory difficulty; or worsening of seizure activity or loss of seizure control. Seek immediate medical evaluation if you experience sudden vision changes, periorbital pain, flank pain, or blood in urine. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, sprinkle:

Topamax®: 15 mg, 25 mg

Tablet:

Topamax®: 25 mg, 50 mg, 100 mg, 200 mg

Generic AvailableNo

ManufacturerOrtho-McNeil Pharmaceutical, Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Topamax)

25 mg (60): $148.51

50 mg (60): $278.81

100 mg (60): $395.39

200 mg (60): $457.08

Mechanism of ActionAnticonvulsant activity may be due to a combination of potential mechanisms: Blocks neuronal voltage-dependent sodium channels, enhances GABA(A) activity, antagonizes AMPA/kainate glutamate receptors, and weakly inhibits carbonic anhydrase.

Pharmacodynamics/Kinetics

Absorption: Good, rapid; unaffected by food

Protein binding: 15% to 41% (inversely related to plasma concentrations)

Metabolism: Hepatic via P450 enzymes

Bioavailability: 80%

Half-life elimination: Mean: Adults: Normal renal function: 21 hours; shorter in pediatric patients; clearance is 50% higher in pediatric patients; Elderly: ~24 hours

Time to peak, serum: ~1-4 hours

Excretion: Urine (~70% to 80% as unchanged drug)

Dialyzable: ~30%

Related Information

- Anticonvulsants by Seizure Type

Pharmacotherapy Pearls May be associated with weight loss in some patients

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Gingivitis, dysphagia, glossitis, gum hyperplasia, and xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health Comment Large double-blind studies have failed to differentiate this drug from placebo when used for bipolar disorder.

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International Brand Names Epilramate (TW); Epitomax (FI, FR); Epitop (KP); Gabatopa (KP); Topamac (AR, CO, EC, IN, PE, PY, UY); Topamax (AE, AT, AU, BE, BG, BH, BR, CH, CL, CN, CY, CZ, DE, EE, EG, ES, FI, GB, HK, HN, IE, IL, IQ, IR, IT, JM, JO, KW, LB, LY, MX, MY, NI, NL, OM, PH, PK, PL, PT, QA, SA, SG, SY, TH, TW, VE, YE, ZA); Topamax Sprinkle (HK, IL, KP, NZ); Topimax (DK, NO, SE); Topinmate (TW); Topirid (KP); Topitrim (IL); Topomac (GR)

Topotecan (Oral Regimen)

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Nonsmall Cell); Chemotherapy Regimen, Lung Cancer (Small Cell); Chemotherapy Regimen, Ovarian Cancer

Regimen UseLung cancer, nonsmall cell; Lung cancer, small cell; Ovarian cancer

Regimen

Topotecan: Oral: 2.3 mg/m^2/day days 1 to 5

[total dose/cycle = 11.5 mg/m^2]

Repeat cycle every 21 days

References

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Topotecan (Oral)-Cisplatin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Small Cell)
Regimen UseLung cancer, small cell
Index TermsCisplatin-Topotecan (Oral)
Regimen

Topotecan: Oral: 1.7 mg/m^2/day days 1 to 5

[total dose/cycle = 8.5 mg/m^2]

Cisplatin: I.V.: 60 mg/m^2 day 5 only

[total dose/cycle = 60 mg/m^2]

Repeat cycle every 21 days for 4 cycles (or for 2 cycles beyond best response)

References

Eckardt JR, von Pawel J, Papai Z, et al, "Open-Label, Multicenter, Randomized, Phase III Study Comparing Oral Topotecan/Cisplatin Versus Etoposide/Cisplatin as Treatment for Chemotherapy-Naive Patients With Extensive-Disease Small-Cell Lung Cancer," *J Clin Oncol*, 2006, 24(13):2044-51.[PubMed 16648504]

Topotecan (Weekly)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lung Cancer (Small Cell); Chemotherapy Regimen, Ovarian Cancer

Regimen Use Lung cancer, small cell; Ovarian cancer

Regimen

Topotecan: I.V.: 4 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 12 mg/m^2]

Repeat cycle every 28 days

References

Homesley HD, Hall DJ, Martin DA, et al, "A Dose-Escalating Study of Weekly Bolus Topotecan in Previously Treated Ovarian Cancer Patients," *Gynecol Oncol*, 2001, 83(2):394-9.[PubMed 11606103]

Levy T, Inbar M, Menczer J, et al, "Phase II Study of Weekly Topotecan in Patients With Recurrent or Persistent Epithelial Ovarian Cancer," *Gynecol Oncol*, 2004, 95(3):686-90.[PubMed 15581982]

Shah C, Ready N, Perry M, et al, "A Multi-Center Phase II Study of Weekly Topotecan as Second-Line Therapy for Small Cell Lung Cancer," *Lung Cancer*, 2007, 57(1):84-8.[PubMed 17399850]

Topotecan-Cisplatin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Cervical Cancer

Regimen UseCervical cancer

Regimen**Note:** Body surface area capped at 2 m^2 maximum

Topotecan: I.V.: 0.75 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 2.25 mg/m^2]

Cisplatin: I.V.: 50 mg/m^2 day 1 only

[total dose/cycle = 50 mg/m^2]

Repeat cycle every 21 days

References

Long HJ 3rd, Bundy BN, Grendys EC Jr, et al, "Randomized Phase III Trial of Cisplatin With or Without Topotecan in Carcinoma of the Uterine Cervix: A Gynecologic Oncology Group Study," *J Clin Oncol*, 2005, 23(21):4626-33.[PubMed 15911865]

Topotecan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Hycamtin® may be confused with Hycomine®, Mycamine®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(toe poe TEE kan)

U.S. Brand NamesHycamtin®

Canadian Brand NamesHycamtin®

Pharmacologic CategoryAntineoplastic Agent, Camptothecin; Antineoplastic Agent, Natural Source (Plant) Derivative

Use: Labeled IndicationsTreatment of ovarian cancer and small cell lung cancer; cervical cancer (in combination with cisplatin)

Use: Unlabeled/InvestigationalInvestigational: Treatment of nonsmall cell lung cancer, myelodysplastic syndrome, sarcoma (pediatrics), neuroblastoma (pediatrics), refractory solid tumors (pediatrics)

Dosing: AdultsRefer to individual protocols: **Note:** Baseline neutrophil count should be >1500/mm^3; retreatment neutrophil count should be >1000/mm^3; baseline and retreatment platelet count should be >100,000/mm^3; (also, for oral topotecan, retreatment hemoglobin should be ≥9 g/dL):

Small cell lung cancer:

IVPB: 1.5 mg/m^2/day for 5 days; repeated every 21 days

Oral: 2.3 mg/m^2/day for 5 days; repeated every 21 days (round dose to the nearest 0.25 mg); if patient vomits after dose is administered, do not give a replacement dose.

Metastatic ovarian cancer:

IVPB: 1.5 mg/m^2/day for 5 days; repeated every 21 days

I.V. continuous infusion (unlabeled dose) 0.2-0.7 mg/m^2/day for 7-21 days

Cervical cancer: IVPB: 0.75 mg/m^2/day for 3 days (followed by cisplatin 50 mg/m^2 on day 1 only, [with hydration]); repeated every 21 days

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

The FDA-approved labeling recommends the following dosage adjustment:

I.V.:

Cl_{cr} 20-39 mL/minute: Reduce to 0.75 mg/m^2/dose

Cl_{cr} <20 mL/minute: Insufficient data available for dosing recommendation

Note: For topotecan in combination with cisplatin for cervical cancer, do not initiate treatment in patients with serum creatinine >1.5 mg/dL; consider discontinuing treatment in patients with serum creatinine >1.5 mg/dL in subsequent cycles.

Oral:

Cl_{cr} 30-49 mL/minute: Reduce dose to 1.8 mg/m^2/day

Cl_{cr} <30 mL/minute: Insufficient data available for dosing recommendation

The following guidelines have been used by some clinicians:

Aronoff, 2007: *I.V.:*

Children:

Cl_{cr} 30-50 mL/minute: Administer 75% of dose

Cl_{cr} 10-29 mL/minute: Administer 50% of dose or reduce by 0.75 mg/m^2/dose

Cl_{cr} <10 mL/minute: Administer 25% of dose

Hemodialysis: 0.75 mg/m^2

Continuous renal replacement therapy (CRRT): Administer 50% of dose or reduce by 0.75 mg/m^2/dose

Adults:

Cl_{cr} >50 mL/minute: Administer 75% of dose

Cl_{cr} 10-50 mL/minute: Administer 50% of dose

Cl_{cr} <10 mL/minute: Administer 25% of dose

Hemodialysis: Avoid use

Continuous ambulatory peritoneal dialysis (CAPD): Avoid use

Continuous renal replacement therapy (CRRT): 0.75 mg/m^2

Kintzel, 1995:

Cl_{cr} 46-60 mL/minute: Administer 80% of dose

Cl_{cr} 31-45 mL/minute: Administer 75% of dose

Cl_{cr} <30 mL/minute: Administer 70% of dose

Dosing: Hepatic ImpairmentThe FDA-approved labeling recommends the following:

I.V.: Bilirubin 1.5-10 mg/dL: No adjustment necessary.

Oral: Bilirubin >1.5 mg/dL: No adjustment necessary.

Dosing: Adjustment for Toxicity

I.V.:

Ovarian and small cell lung cancer: Dosage adjustment for hematological effects: Severe neutropenia or platelet count <25,000/mm^3: Reduce dose to 1.25 mg/m^2/day for subsequent cycles (may consider G-CSF support [beginning on day 6] prior to instituting dose reduction for neutropenia)

Cervical cancer: Severe febrile neutropenia (ANC <1000/mm^3 with temperature of 38°C) or platelet count <10,000/mm^3: Reduce topotecan to 0.6 mg/m^2/day for subsequent cycles (may consider C-CSF support [beginning on day 4] prior to instituting dose reduction for neutropenic fever.

For neutropenic fever despite G-CSF use, reduce dose to 0.45 mg/m^2/day for subsequent cycles). **Note:** Cisplatin may also require dose adjustment.

Oral:

Small cell lung cancer: Severe neutropenia (neutrophils <500/mm^3 associated with fever or infection or lasting >7 days) or prolonged neutropenia (neutrophils ≥500/mm^3 to ≤1000/mm^3 lasting beyond day 21) or platelets <25,000/mm^3 or grades 3/4 diarrhea: Reduce dose to 1.9 mg/m^2/day for subsequent cycles (may consider same dosage reduction for grade 2 diarrhea if clinically indicated).

Dosing: Combination Regimens

Cervical cancer: Topotecan-Cisplatin

Leukemia, acute lymphocytic: TVTG

Leukemia, acute myeloid: TVTG

Lung cancer, nonsmall cell: Topotecan (Oral Regimen)

Lung cancer, small cell:

Topotecan (Oral Regimen)

Topotecan (Oral)-Cisplatin

Topotecan (Weekly)

Ovarian cancer:

Topotecan (Oral Regimen)

Topotecan (Weekly)

Calculations

- Body Surface Area: Adults
- Creatinine Clearance: Adults

Administration: I.V.Administer IVPB over 30 minutes or by 24-hour continuous infusion. For combination chemotherapy with cisplatin, administer pretreatment hydration.

Administration: I.V. DetailpH: 2.5-3.5

Administration: OralAdminister with or without food. Swallow whole; do not crush, chew, or divide capsule. If vomiting occurs after dose, do not take replacement dose.

Dietary ConsiderationsMay be taken with or without food.

Storage

I.V.: Store intact vials of lyophilized powder for injection at room temperature of 20°C to 25°C (68°F to 77°F); protect from light. Reconstituted solution is stable for up to 28 days at room temperature of 20°C to 25°C (68°F to 77°F). When further diluted in 50-100 mL D_5W or NS, solution is stable for 24 hours at room temperature or up to 7 days under refrigeration.

Oral: Store at 15°C to 30°C (59°F to 86°F). Protect from light

ReconstitutionReconstitute vials with 4 mL SWFI. May be further diluted in 50-100 mL D_5W or NS for infusion.

CompatibilityStable in D_5W, NS.

Y-site administration: Compatible: Carboplatin, cimetidine, cisplatin, cyclophosphamide, doxorubicin, etoposide, gemcitabine, granisetron, ifosfamide, methylprednisolone sodium succinate, metoclopramide, ondansetron, paclitaxel, prochlorperazine edisylate, vincristine. **Incompatible:** Dexamethasone sodium phosphate, fluorouracil, mitomycin. **Variable (consult detailed reference):** Ticarcillin/clavulanate.

ContraindicationsHypersensitivity to topotecan or any component of the formulation; severe bone marrow depression; pregnancy; breast-feeding

Warnings/Precautions

Boxed warnings:

- Bone marrow suppression: See “Concerns related to adverse effects” below.
- Experienced physician: See “Other warnings/precautions” below.

Special handling:

- Hazardous agent - use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: The dose-limiting toxicity is bone marrow suppression (primarily neutropenia; may also cause thrombocytopenia and anemia); monitor bone marrow function. Neutropenia is not cumulative overtime. **[U.S. Boxed Warning]: Should only administer to patients with adequate bone marrow reserves, baseline neutrophils at least 1500 cells/mm^3** and platelet counts at least 100,000/mm^3. In a clinical study comparing I.V. to oral topotecan, G-CSF support was administered in a higher percentage of patients receiving oral topotecan.
- Diarrhea: Diarrhea has been reported with oral topotecan; may be severe; educate patients on proper management of diarrhea. The incidence of diarrhea may be higher in the elderly.
- Neutropenic colitis: Topotecan-induced neutropenia may lead to neutropenic colitis; should be considered in patients presenting with neutropenia, fever, and abdominal pain.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; may require dose adjustment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies found reduced fetal body weight, eye, brain, skull, and vertebrae malformations. May cause fetal harm in pregnant women. Use during pregnancy is contraindicated.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsBreast-feeding should be discontinued in women who are receiving topotecan.

Adverse Reactions

>10%:

Central nervous system: Fatigue (11% to 29%), fever (5% to 28%), pain (23%), headache (18%)

Dermatologic: Alopecia (10% to 49%), rash (16%)

Gastrointestinal: Nausea (27% to 64%), vomiting (19% to 45%), diarrhea (14% to 32%; Oral: grade 3: 4%; grade 4: ≤1%; onset: 9 days), constipation (29%), abdominal pain (22%), anorexia (7% to 19%), stomatitis (18%)

Hematologic: Neutropenia (83% to 97%; grade 4: 32% to 80%; nadir 8-11 days; duration: 7 days; recovery <21 days), leukopenia (86% to 97%; grade 4: 15% to 32%), anemia (89% to 98%; grade 4: 7% to 10%), thrombocytopenia (69% to 81%; grade 4: 6% to 29%; duration: 3 days), neutropenic fever/sepsis (2% to 28%)

Neuromuscular & skeletal: Weakness (3% to 25%)

Respiratory: Dyspnea (22%), cough (15%)

1% to 10%:

Hepatic: Transient increases in liver enzymes (8%)

Neuromuscular & skeletal: Paresthesia (7%)

Miscellaneous: Sepsis (grades 3/4: 5%)

<1%, postmarketing, and/or case reports: Abdominal pain, allergic reactions, anaphylactoid reactions, angioedema, bleeding (severe, associated with thrombocytopenia), dermatitis (severe), injection site reactions (mild erythema, bruising), neutropenic colitis, pancytopenia, pruritus (severe)

Oncology: VesicantI.V.: No; inadvertent extravasation may result in mild erythema and bruising
Oncology: Emetic PotentialLow (10% to 30%)
Drug Interactions

BCRP/ABCG2 Inhibitors: May increase the serum concentration of Topotecan. *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Filgrastim: May enhance the adverse/toxic effect of Topotecan. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inhibitors: May increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Platinum Derivatives: May enhance the adverse/toxic effect of Topotecan. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to GI irritation).
Test InteractionsNone known
Monitoring ParametersCBC with differential and platelet count, renal function tests, bilirubin
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking. I.V.: See administration specifics. Evaluate results of laboratory tests, therapeutic effectiveness, and adverse reactions prior to each infusion and on a regular basis with oral formulation (eg, signs of myelosuppression, renal function [I & O, edema], gastrointestinal disturbance [nausea, vomiting, diarrhea, pain], dyspnea). Teach patient appropriate use (oral), possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsCBC with differential and platelet count, renal function tests, bilirubin
Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. If this drug is administered by intravenous infusion, report immediately any burning, pain, redness, or swelling at infusion site; sudden chest pain; difficulty breathing or swallowing; or chills. Oral form may be taken with or without food. Swallow whole; do not crush, chew, or divide capsule. If vomiting occurs after dose, do not take replacement dose; take next dose at scheduled time. Maintain adequate hydration (3-4 L/day of fluids) unless instructed to restrict fluid intake during therapy. Maintain good oral hygiene (use soft toothbrush or cotton applicators several times a day and rinse mouth frequently). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations without consulting prescriber). May cause nausea or vomiting (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or hair loss (will regrow after treatment is completed). Report unresolved diarrhea, nausea, vomiting, or unusual abdominal pain; alterations in urinary pattern (increased or decreased); opportunistic infection (fever, chills, unusual bruising or bleeding, fatigue, purulent vaginal discharge, unhealed mouth sores); chest pain; respiratory difficulty; unexplained weakness or fatigue; or other persistent effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant or cause a pregnancy (males) while taking this medication. Consult prescriber for appropriate contraceptive measures (may cause severe fetal defects). Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Hycamtin®: 0.25 mg, 1 mg

Injection, powder for reconstitution:

Hycamtin®: 4 mg

Generic AvailableNo
Mechanism of ActionBinds to topoisomerase I and stabilizes the cleavable complex so that religation of the cleaved DNA strand cannot occur. This results in the accumulation of cleavable complexes and single-strand DNA breaks. Topotecan acts in S phase of the cell cycle.

Pharmacodynamics/Kinetics

Absorption: Oral: Rapid

Distribution: V_{dss} of the lactone is high (mean: 87.3 L/mm^2; range: 25.6-186 L/mm^2), suggesting wide distribution and/or tissue sequestering

Protein binding: ~35%

Metabolism: Undergoes a rapid, pH-dependent hydrolysis of the lactone ring to yield a relatively inactive hydroxy acid in plasma; metabolized in the liver to N-demethylated metabolite

Bioavailability: Oral: ~40%

Half-life elimination: I.V.: 2-3 hours; renal impairment: 5 hours; Oral: 3-6 hours

Time to peak, plasma: Oral 1-2 hours; delayed with high-fat meal (1.5-4 hours)

Excretion:

I.V.: Urine (51%; 3% as N-desmethyl topotecan); feces (18%; 2% as N-desmethyl topotecan)

Oral: Urine (20%; 2% as N-desmethyl topotecan); feces (33%; <2% as N-desmethyl topotecan)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine

Index TermsHycamptamine; NSC-609699; SKF 104864; SKF 104864-A; Topotecan Hydrochloride

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International Brand NamesHycamtin (AR, AT, AU, BE, BG, BR, CH, CL, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, HR, HU, IE, IL, IT, KP, NL, NO, PK, PL, PT, RU, SE, SG, TH, TR, TW, UY, VE); Oncotecam (PY); Oncotecan (EC, PE); Topokebir (AR); Topotel (IN, PH, TH)

Toremifene

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(tore EM i feen)

U.S. Brand NamesFareston®

Canadian Brand NamesFareston®

Pharmacologic CategoryAntineoplastic Agent, Estrogen Receptor Antagonist; Selective Estrogen Receptor Modulator (SERM)

Use: Labeled IndicationsTreatment of postmenopausal metastatic breast cancer (estrogen receptor positive or estrogen receptor status unknown)

Dosing: Adults **Metastatic breast carcinoma:** Oral: 60 mg once daily, generally continued until disease progression is observed

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentToremifene is extensively metabolized in the liver and dosage adjustments may be indicated in patients with liver disease; however, no specific guidelines have been developed.

Administration: OralAdminister as a single daily dose.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from heat and light.

ContraindicationsHypersensitivity to toremifene or any component of the formulation

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Bone marrow suppression: Leukopenia and thrombocytopenia have been reported rarely.
- Gynecologic effects: Endometrial hyperplasia has been reported; endometrial cancer has been reported, although the role of toremifene in endometrial cancer development has not been established.
- Hypercalcemia: May occur during the first weeks of treatment in breast cancer patients with bone metastases. Institute appropriate measures if hypercalcemia occurs; discontinue treatment if severe.
- Tumor flare: May occur during the first weeks of treatment in breast cancer patients with bone metastases. Tumor flare is a syndrome of diffuse musculoskeletal pain and erythema with increased size of tumor lesions which later regress. It is often accompanied by hypercalcemia and does not imply treatment failure or represent tumor progression.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Thromboembolic disease: Avoid use in patients with thromboembolic disease.

Concurrent drug therapy issues:

- Drugs that decrease renal calcium excretion: Use with caution drugs that decrease renal calcium excretion (eg, thiazide diuretics); they may increase the risk of hypercalcemia in patients receiving toremifene.

Geriatric ConsiderationsNo specific information concerning elderly patients.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated embryotoxicity and fetal adverse effects. There are no adequate and well-controlled studies in pregnant women. May cause fetal harm if administered during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Endocrine & metabolic: Hot flashes (35%)

Gastrointestinal: Nausea (14%)

Genitourinary: Vaginal discharge (13%)

Hepatic: Alkaline phosphatase increased (8% to 19%), AST increased (5% to 19%)

Miscellaneous: Diaphoresis (20%)

1% to 10%:

Cardiovascular: Edema (5%), arrhythmia (≤2%), CVA/TIA (≤2%), thrombosis (≤2%), cardiac failure (≤1%), MI (≤1%)

Central nervous system: Dizziness (9%)

Endocrine & metabolic: Hypercalcemia (≤3%)

Gastrointestinal: Vomiting (4%)

Genitourinary: Vaginal bleeding (2%)

Hepatic: Bilirubin increased (1% to 2%)

Local: Thrombophlebitis (≤2%)

Ocular: Cataracts (≤10%), xerophthalmia (≤9%), visual field abnormal (≤4%), corneal keratopathy (≤2%), glaucoma (≤2%), vision abnormal/diplopia (≤2%)

Respiratory: Pulmonary embolism (≤2%)

<1%, postmarketing, and/or case reports: Alopecia, angina, anorexia, arthritis, ataxia, constipation, corneal opacity (reversible), corneal verticulata, deep vein thrombosis, depression, dermatitis, dyspnea, endometrial cancer, endometrial hyperplasia, fatigue, hepatitis (toxic), incoordination, ischemic attack, jaundice, lethargy, leukopenia, paresis, pruritus, retinopathy, rigors, skin discoloration, thrombocytopenia, thrombophlebitis, tremor, tumor flare, vaginal dryness, vertigo, weakness

Oncology: Emetic PotentialModerate (10% to 30%)
Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 3A4 (major)
Drug Interactions

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid St John's wort (may decrease toremifene levels).
Monitoring ParametersObtain periodic complete blood counts, calcium levels, and liver function tests. Closely monitor patients with bone metastases for hypercalcemia during the first few weeks of treatment. Leukopenia and thrombocytopenia have been reported rarely; monitor leukocyte and platelet counts during treatment.
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents patient may be taking (drugs that decrease renal calcium excretion [eg, thiazide diuretics] may increase the risk of hypercalcemia, use with warfarin increases anticoagulant effect). Assess results of laboratory tests on a regular basis throughout therapy. Evaluate therapeutic effectiveness and adverse reactions regularly (eg, thromboembolism, MI, edema, hypercalcemia, endometriosis, nausea, vomiting, vision changes). Teach patient proper use, possible side effects/appropriate interventions and adverse symptoms to report.
Monitoring: Lab TestsObtain periodic complete blood counts, calcium levels, and liver function tests. Closely monitor patients with bone metastases for hypercalcemia during the first few weeks of treatment. Leukopenia and thrombocytopenia have been reported rarely; monitor leukocyte and platelet counts during treatment.
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, without regard to food. You may experience an initial “flare” of this disease (eg, increased bone pain and hot flashes), which will subside with continued use. May cause nausea, vomiting, or loss of appetite (frequent mouth care, small, frequent meals, chewing gum, or sucking lozenges may help); dizziness (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); or loss of hair (reversible). Report vomiting that occurs immediately after taking medication; chest pain, palpitations, or swollen extremities; vaginal bleeding, hot flashes, or excessive perspiration; chest pain, unusual coughing, or respiratory difficulty; or any vision changes or dry eyes. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate contraceptive measures. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Fareston®: 60 mg

Generic AvailableNo
ManufacturerGTx, Inc
Pricing: U.S. (www.drugstore.com)

Tablets (Fareston)

60 mg (30): $139.28

Mechanism of ActionNonsteroidal, triphenylethylene derivative with potent antiestrogenic properties (also has estrogenic effects). Competitively binds to estrogen receptors on tumors and other tissue targets, producing a nuclear complex that decreases DNA synthesis and inhibits estrogen effects. Competes with estrogen for binding sites in breast and other tissues; cells accumulate in the G_0 and G_1 phases; therefore, toremifene is cytostatic rather than cytocidal.
Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: V_d: 580 L (range: 457-958 L)

Protein binding, plasma: >99.5%, primarily to albumin

Metabolism: Extensively hepatic, principally by CYP3A4 to N-demethyltoremifene, which is also antiestrogenic but with weak *in vivo* antitumor potency

Half-life elimination: ~5 days

Time to peak, serum: ~3 hours (range: 2-6 hours)

Excretion: Primarily feces; urine (10%) during a 1-week period

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness, anxiety, irritability, insomnia, and depression are common

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFC1157a; Toremifene Citrate

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International Brand NamesFareston (AR, AT, AU, CH, DE, ES, FI, FR, GB, IT, LU, MX, PL, PT, SE)

Torsemide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Torsemide may be confused with furosemide

Demadex® may be confused with Denorex®

Pronunciation(TORE se mide)

U.S. Brand NamesDemadex®

Pharmacologic CategoryDiuretic, Loop

Use: Labeled IndicationsManagement of edema associated with congestive heart failure and hepatic or renal disease; used alone or in combination with antihypertensives in treatment of hypertension; I.V. form is indicated when rapid onset is desired

Dosing: Adults

Note: The oral form may be given regardless of meal times. Patients may be switched from the I.V. form to the oral and vice-versa with no change in dose.

Congestive heart failure: Oral, I.V.: 10-20 mg once daily; may increase gradually for chronic treatment by doubling dose until the diuretic response is apparent (for acute treatment. I.V. dose may be repeated every 2 hours with double the dose as needed). **Note:** ACC/AHA 2005 guidelines for chronic heart failure recommend a maximum daily oral dose of 200 mg; maximum single I.V. dose 100-200 mg

Continuous I.V. infusion: 20 mg I.V. load then 5-20 mg/hour

Chronic renal failure: Oral, I.V.: 20 mg once daily; increase as above.

Hepatic cirrhosis: Oral, I.V.: 5-10 mg once daily with an aldosterone antagonist or a potassium-sparing diuretic; increase as above.

Hypertension: Oral, I.V.: 2.5-5 mg once daily; increase to 10 mg after 4-6 weeks if an adequate hypotensive response is not apparent. If still not effective, an additional antihypertensive agent may be added.

Dosing: ElderlyUsual starting dose should be 5 mg; refer to adult dosing.

Administration: I.V.I.V. injections should be given over ≥2 minutes.

Administration: I.V. DetailOtotoxicity has occurred with too rapid of injection.

pH: >8.3

StorageIf torsemide is to be administered via continuous infusion, stability has been demonstrated through 24 hours at room temperature in plastic containers for the following fluids and concentrations:

200 mg torsemide (10 mg/mL) added to 250 mL D_5W, 250 mL NS or 500 mL 0.45% sodium chloride.

50 mg torsemide (10 mg/mL) added to 500 mL D_5W, 250 mL NS or 500 mL 0.45% sodium chloride.

CompatibilityStable in D_5W, NS, $^1/_2$NS.

Y-site administration: Compatible: Milrinone.

ContraindicationsHypersensitivity to torsemide, any component of the formulation, or any sulfonylureas; anuria

Allergy Considerations

- Loop Diuretic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Fluid/electrolyte loss: Loop diuretics are potent diuretics; excess amounts can lead to profound diuresis with fluid and electrolyte loss; close medical supervision and dose evaluation are required. Watch for and correct electrolyte disturbances; adjust dose to avoid dehydration.

- Nephrotoxicity: Monitor fluid status and renal function in an attempt to prevent oliguria, azotemia, and reversible increases in BUN and creatinine; close medical supervision of aggressive diuresis required.

- Ototoxicity: Rapid I.V. administration (associated with other loop diuretics), renal impairment, excessive doses, and concurrent use of other ototoxins is associated with ototoxicity; has been seen with oral torsemide.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonylurea allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Cirrhosis: In cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

Concurrent drug therapy issues:

- Antihypertensives: Coadministration of antihypertensives may increase the risk of hypotension.

Geriatric ConsiderationsLoop diuretics are potent diuretics, excess amounts can lead to profound diuresis with fluid and electrolyte loss. Close medical supervision and dose evaluation is required, particularly in elderly.

Pregnancy Risk FactorB

Pregnancy ConsiderationsA decrease in fetal weight, an increase in fetal resorption, and delayed fetal ossification has occurred in animal studies.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

1% to 10%:

Cardiovascular: Edema (1.1%), ECG abnormality (2%), chest pain (1.2%)

Central nervous system: Headache (7.3%), dizziness (3.2%), insomnia (1.2%), nervousness (1%)

Endocrine & metabolic: Hyperglycemia, hyperuricemia, hypokalemia

Gastrointestinal: Diarrhea (2%), constipation (1.8%), nausea (1.8%), dyspepsia (1.6%), sore throat (1.6%)

Genitourinary: Excessive urination (6.7%)

Neuromuscular & skeletal: Weakness (2%), arthralgia (1.8%), myalgia (1.6%)

Respiratory: Rhinitis (2.8%), cough increase (2%)

<1% (Limited to important or life-threatening): Syncope, atrial fibrillation, hypotension, ventricular tachycardia, shunt thrombosis, hypovolemia, GI hemorrhage, rash, rectal bleeding, angioedema, hypernatremia

Metabolism/Transport Effects**Substrate** of CYP2C8 (minor), 2C9 (major); **Inhibits** CYP2C19 (weak)

Drug Interactions

ACE Inhibitors: Loop Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Loop Diuretics may enhance the adverse/toxic effect of Allopurinol. Loop Diuretics may increase the serum concentration of Allopurinol. Specifically, Loop Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoglycosides: Loop Diuretics may enhance the adverse/toxic effect of Aminoglycosides. Specifically, nephrotoxicity and ototoxicity. *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Loop Diuretics. *Risk D: Consider therapy modification*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dofetilide: Loop Diuretics may enhance the QTc-prolonging effect of Dofetilide. *Risk C: Monitor therapy*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Neuromuscular-Blocking Agents: Loop Diuretics may diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Loop Diuretics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Phenytoin: May diminish the diuretic effect of Loop Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen hypertension). Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersRenal function, electrolytes, and fluid status (weight and I & O), blood pressure

Nursing: Physical Assessment/MonitoringAssess for allergy to sulfonylurea before beginning therapy. Assess potential for interactions with other pharmacological agents or herbal products the patient may be taking (especially anything that may impact fluid balance or increase potential for ototoxicity or hypotension). For intravenous use, see Administration specifics. Assess results of laboratory tests (electrolytes), therapeutic effectiveness, and adverse response (eg, dehydration, electrolyte imbalance, postural hypotension) on a regular basis during therapy. Caution patients with diabetes about closely monitoring glucose levels (glucose tolerance may be decreased). Teach patient appropriate use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsRenal function, electrolytes

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take as directed, with food or milk (to reduce GI distress), early in the day, or if twice daily, take last dose in late afternoon in order to avoid sleep disturbance and achieve maximum therapeutic effect. Include orange juice or bananas (or other potassium-rich foods) in daily diet. Do not take potassium supplements without consulting prescriber. Weigh yourself each day, at the same time, in the same clothes when beginning therapy, and weekly on long-term therapy; report unusual or unanticipated weight gain or loss. May cause postural hypotension (change position slowly when rising from sitting or lying); transient drowsiness, blurred vision, or dizziness (avoid driving or engaging in tasks that require alertness until response to drug is known); reduced tolerance to heat (avoid strenuous activity in hot weather or excessively hot showers); or constipation (increased exercise and increased dietary fiber, fruit, or fluids may help). Report unusual weight gain or loss (>5 lb/week), swelling of ankles and hands; persistent fatigue; unresolved constipation or diarrhea; weakness, fatigue, or dizziness; vomiting; cramps; change in hearing; or chest pain or palpitations. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution:

Demadex®: 10 mg/mL (2 mL [DSC], 5 mL [DSC])

Tablet: 5 mg, 10 mg, 20 mg, 100 mg

Demadex®: 5 mg, 10 mg, 20 mg, 100 mg [scored]

Generic AvailableYes: Tablet

ManufacturerRoche Laboratories Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Demadex)

5 mg (30): $41.39

10 mg (30): $43.69

20 mg (30): $49.44

100 mg (30): $160.98

Tablets (Torsemide)

5 mg (30): $18.99

10 mg (30): $19.99

20 mg (30): $22.99

100 mg (30): $75.98

Mechanism of ActionInhibits reabsorption of sodium and chloride in the ascending loop of Henle and distal renal tubule, interfering with the chloride-binding cotransport system, thus causing increased excretion of water, sodium, chloride, magnesium, and calcium; does not alter GFR, renal plasma flow, or acid-base balance

Pharmacodynamics/Kinetics

Onset of action: Diuresis: 30-60 minutes

Peak effect: 1-4 hours

Duration: ~6 hours

Absorption: Oral: Rapid

Protein binding, plasma: ~97% to 99%

Metabolism: Hepatic (80%) via CYP

Bioavailability: 80% to 90%

Half-life elimination: 2-4; Cirrhosis: 7-8 hours

Excretion: Urine (20% as unchanged drug)

Related Information

- Sulfonamide Derivatives

Pharmacotherapy Pearls10-20 mg torsemide is approximately equivalent to furosemide 40 mg or bumetanide 1 mg.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause dizziness

Mental Health: Effects on Psychiatric Treatment May cause agranulocytosis; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity, however, this is much more common and significant with the thiazide diuretics; monitor serum lithium levels; concurrent use with chloral hydrate may produce hot flashes and hypertension

Cardiovascular Considerations Torsemide may induce potent diuretic effects and, as with other potent diuretics, electrolytes and volume status needs to be closely monitored.

Anesthesia and Critical Care Concerns/Other Considerations If given the morning of surgery, it may render the patient volume depleted and blood pressure may be labile during general anesthesia. Torsemide may induce potent diuretic effects and, as with other potent diuretics, electrolytes and volume status needs to be closely monitored.

Dose equivalency (approximate): Bumetanide 1 mg = furosemide 40 mg = torsemide 20 mg

References

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International Brand Names Dytor (IN); Setoram (KP); Sutril (ES); Toral (ID); Torem (BG, CH, DE, EE, GB, KP, SE); Torrem (BE); Torsem (KP); Tuosai (CL); Unat (DE, HK, PT, TH)

Tositumomab and Iodine I 131 Tositumomab

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(toe si TYOO mo mab & EYE oh dyne eye one THUR tee one toe si TYOO mo mab)

U.S. Brand NamesBexxar®

Pharmacologic CategoryAntineoplastic Agent, Monoclonal Antibody; Radiopharmaceutical

Use: Labeled IndicationsTreatment of relapsed or refractory CD20 positive, low-grade, follicular, or transformed non-Hodgkin's lymphoma

Dosing: AdultsI.V.: Dosing consists of four components administered in 2 steps. Thyroid protective agents (SSKI, Lugol's solution or potassium iodide), acetaminophen and diphenhydramine should be given prior to or with treatment. Refer to Additional Information.

Step 1: Dosimetric step (Day 0):

Tositumomab 450 mg in NS 50 mL administered over 60 minutes

Iodine I 131 tositumomab (containing I-131 5.0 mCi and tositumomab 35mg) in NS 30 mL administered over 20 minutes

Note: Whole body dosimetry and biodistribution should be determined on Day 0; days 2, 3, or 4; and day 6 or 7 prior to administration of Step 2. If biodistribution is not acceptable, do not administer the therapeutic step. On day 6 or 7, calculate the patient specific activity of iodine I 131 tositumomab to deliver 75 cGy TBD or 65 cGy TBD (in mCi).

Step 2: Therapeutic step (Day 7):

Tositumomab 450 mg in NS 50 mL administered over 60 minutes

Iodine I 131 tositumomab:

Platelets ≥150,000/mm^3: Iodine I 131 calculated to deliver 75 cGy total body irradiation and tositumomab 35 mg over 20 minutes

Platelets ≥100,000/mm^3 and <150,000/mm^3: Iodine I 131 calculated to deliver 65 cGy total body irradiation and tositumomab 35 mg over 20 minutes

Dosing: ElderlyRefer to adult dosing.

Administration: I.V.

Tositumomab: Infuse over 60 minutes

Iodine I 131 tositumomab: Infuse over 20 minutes

Reduce the rate of tositumomab or iodine 131 tositumomab infusion by 50% for mild-to-moderate infusion-related toxicities; interrupt for severe toxicity. Once severe toxicity has resolved, infusion may be restarted at half the previous rate. Prior to infusion, patients should be premedicated and a thyroid-protective agent should be started.

Storage

Tositumomab: Store under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from strong light. Following dilution, tositumomab is stable for 24 hour when refrigerated or 8 hours at room temperature.

Iodine I 131 tositumomab: Store frozen at less than or equal to -20°C in the original lead pots. Allow 60 minutes for thawing at ambient temperature. Solutions for infusion are stable for up to 8 hours at 2°C to 8°C (36°F to 46°F) or room temperature.

Reconstitution

Tositumomab: Withdraw and discard 32 mL of saline from a 50 mL bag of NS. Add contents of both 225 mg vials of tositumomab (total 32 mL) to remaining NS to make a final volume of 50 mL. Gently mix by inverting bag; do not shake.

Iodine I 131 tositumomab: Calculate volume required for an iodine I 131 tositumomab activity of 5 mCi (specification sheet provided with product). If the amount of tositumomab contained in the iodine I 131 tositumomab solution contains <35 mg of tositumomab, use the 35 mg vial of tositumomab to prepare a final concentration of tositumomab 35 mg. Using NS, the final volume should equal 30 mL.

ContraindicationsHypersensitivity to murine proteins or any component of the formulation; pregnancy; breast-feeding

Warnings/Precautions

Boxed warnings:

- Anaphylactoid/hypersensitivity reactions: See “Concerns related to adverse effects” below.
- Cytopenias: See “Concerns related to adverse effects” below.
- Radioactive isotopes: See “Special handling” below.
- Women of childbearing potential: See “Special populations” below.

Special handling:

- Hazardous agent - use appropriate precautions for handling and disposal.
- Radioactive isotopes: **[U.S. Boxed Warning]: Treatment involves radioactive isotopes; appropriate precautions in handling and administration must be followed.** Patients must be instructed in measures to minimize exposure of others.

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: **[U.S. Boxed Warning]: Hypersensitivity reactions (including anaphylaxis) have been reported.** Patients should be screened for human antimouse antibodies (HAMA); may be at increased risk of allergic or serious hypersensitivity reactions.
- Cytopenias: **[U.S. Boxed Warning]: Severe or life-threatening cytopenias (NCI CTC grade 3 or 4) have been reported in a large number of patients;** may be prolonged and severe. Hematologic toxicity is reported to be the most common adverse effect with 27% patients requiring supportive care. Safety has not been established in patients with >25% lymphoma marrow involvement, platelet count <100,000 cells/mm^3 or neutrophil count <1500 cells/mm^3.
- Hypothyroidism: Treatment may lead to hypothyroidism; patients should receive thyroid-blocking medications prior to the start of therapy.
- Infusion reactions: Patients should be premedicated to prevent infusion-related reactions.
- Secondary malignancies: Myelodysplastic syndrome (MDS), acute leukemia and nonhematologic malignancy, including skin cancer have been reported following use.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment; safety and efficacy have not been established.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Women of childbearing potential: **[U.S. Boxed Warning]: Women of childbearing potential should be advised of potential fetal risk;** effective contraceptive measures should be used for 12 months following treatment (males and females).

Other warnings/precautions:

- Appropriate use: For a single course of therapy only; multiple courses or use in combination with other chemotherapy or irradiation have not been studied.
- Immunizations: The safety and efficacy of live vaccines in patients who have received therapy with tositumomab have not been established.

Pregnancy Risk FactorX

Pregnancy Considerations**[U.S. Boxed Warning]: Women of childbearing potential should be advised of potential fetal risk.** Iodine-131 crosses the placenta and may cause severe and irreversible hypothyroidism in neonates. Pregnancy should be ruled out prior to therapy. Males and females should be instructed to use effective contraception for 12 months following treatment.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsRadioiodine and immunoglobulins are excreted in breast milk. Quantity of radioiodine may be greater than maternal serum concentrations. Women should be advised to discontinue nursing prior to therapy. The AAP considers radioactive iodine a compound which requires temporary cessation of breast-feeding.

Adverse Reactions

>10%:

Central nervous system: Fever (37%), pain (19%), chills (18%), headache (16%)

Dermatologic: Rash (17%)

Endocrine & metabolic: Hypothyroidism (7% to 19%)

Gastrointestinal: Nausea (36%), abdominal pain (15%), vomiting (15%), anorexia (14%), diarrhea (12%)

Hematologic:

Neutropenia (grade 3 or 4, 63%); thrombocytopenia (grade 3 or 4, 53%)

Time to nadir: 4-7 weeks

Duration: 30 days (>90 days in 5% to 7% of patients)

Neuromuscular & skeletal: Weakness (46%), myalgia (13%)

Respiratory: Cough (21%), pharyngitis (12%), dyspnea (11%)

Miscellaneous: Infusion-related reactions (26%, occurred within 14 days of infusion, included bronchospasm, chills, dyspnea, fever, hypotension, nausea, rigors, diaphoresis), infection (21%), HAMA-positive seroconversion (11%; up to 21% at 1 year)

1% to 10%:

Cardiovascular: Hypotension (7% to 10%), peripheral edema (9%), chest pain (7%), vasodilation (5%)

Central nervous system: Dizziness (5%), somnolence (5%)

Dermatologic: Pruritus (10%)

Gastrointestinal: Constipation (6%), dyspepsia (6%), weight loss (6%)

Local: Injection site hypersensitivity

Neuromuscular & skeletal: Arthralgia (10%), back pain (8%), neck pain (6%)

Respiratory: Rhinitis (10%), pneumonia (6%), laryngismus

Miscellaneous: Diaphoresis (8%), hypersensitivity reaction (6%), secondary leukemia/myelodysplastic syndrome (3%; up to 6% at 5 years), anaphylactoid reaction, secondary malignancies, serum sickness

Drug Interactions

Anticoagulants: May enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse effects may be increased. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the adverse/toxic effect of Tositumomab and Iodine I 131 Tositumomab. Specifically, the risk of bleeding-related adverse events may be increased. *Risk C: Monitor therapy*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Test InteractionsMay interfere with tests using murine antibody technology.

Monitoring ParametersCBC with differential (prior to therapy and at least weekly for a minimum of 10 weeks); TSH (prior to therapy and yearly); serum creatinine (immediately prior to administration)

Following infusion of the iodine I 131 tositumomab dosimetric dose, the total body gamma camera counts and whole body images should be taken within 1 hour of the infusion and prior to urination, and 2-4 days after the infusion and following urination, and 6-7 days after the infusion and following urination.

Nursing: Physical Assessment/MonitoringPremedicate to reduce risk of infusion reactions. Assess results of laboratory tests prior to and immediately after therapy, and regularly thereafter, as recommended. Assess for signs of any adverse response (eg, infusion-related reactions have occurred up to 14 days of infusion). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential (prior to therapy and at least weekly); TSH (prior to therapy and yearly); serum creatinine (immediately prior to administration)

Following infusion of the iodine I 131 tositumomab dosimetric dose, the total body gamma camera counts and whole body images should be taken within 1 hour of the infusion and prior to urination, and 2-4 days after the infusion and following urination, and 6-7 days after the infusion and following urination.

Patient EducationDo not take any new medications during therapy without consulting prescriber. This medication can only be administered by intravenous infusion. You will be closely monitored prior to, during, and following infusion. Report immediately any chills, nausea, diaphoresis; difficulty swallowing or breathing; tightness in chest or chest pain. You will have frequent laboratory tests following therapy to assess effectiveness and response. Other medication will be prescribed related to this therapy. Take as directed; do not stop or alter dosage without consulting prescriber. You may experience nausea, vomiting, abdominal pain (if persistent, contact prescriber for medication); loss of appetite (small, frequent meals and frequent mouth care may help). Report immediately any chills, persistent or acute headache, fever, rash, swelling of extremities, chest pain, muscle or back pain, upper respiratory symptoms (sore throat, runny nose, persistent cough, pneumonia), signs of infection, or other adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Do not get pregnant (females) or cause a pregnancy (males) during therapy or for 12 months following therapy. Consult prescriber for appropriate contraceptives if necessary or if you suspect you might be pregnant. This medication will

cause severe fetal defects. Do not give blood during therapy of for 12 months following therapy. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Note: Not all components are shipped from the same facility. When ordering, ensure that all will arrive on the same day.

Kit [dosimetric package]: Tositumomab 225 mg/16.1 mL [2 vials], tositumomab 35 mg/2.5 mL [1 vial], and iodine I 131 tositumomab 0.1 mg/mL and 0.61mCi/mL (20 mL) [1 vial]

Kit [therapeutic package]: Tositumomab 225 mg/16.1 mL [2 vials], tositumomab 35 mg/2.5 mL [1 vial], and iodine I 131 tositumomab 1.1 mg/mL and 5.6 mCi/mL (20 mL) [1 or 2 vials]

Generic AvailableNo
ManufacturerCorixa Corp
Mechanism of ActionTositumomab is a murine IgG2a lambda monoclonal antibody which binds to the CD20 antigen, expressed on B-lymphocytes and on >90% of B-cell non-Hodgkin's lymphomas. Iodine I 131 tositumomab is a radio-iodinated derivative of tositumomab covalently linked to iodine 131. The possible actions of the regimen include apoptosis, complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and cell death. Administration results in depletion of CD20 positive cells.
Pharmacodynamics/Kinetics

Distribution: Tositumomab: V_d increased with high tumor burden, splenomegaly, or bone marrow involvement

Half-life elimination: Tositumomab:

Elimination: 36-48 hours

Terminal half-life decreased with high tumor burden, splenomegaly, or bone marrow involvement

Clearance: Blood: 68.2 mg/hour

Excretion: Iodine-131: Urine (98%) and decay

Pharmacotherapy PearlsThyroid protective agent: One of the following agents should be used starting at least 24 hours prior to the dosimetric dose and continued for 2 weeks after the therapeutic dose. Therapy should not begin without using one of the following agents:

SSKI: 4 drops 3 times/day

Lugol's solution: 20 drops 3 times/day

Potassium iodide: 130 mg once daily

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause sedation
Mental Health: Effects on Psychiatric TreatmentHematologic adverse reactions are common; use caution with clozapine, carbamazepine, valproic acid and derivatives, and mirtazapine. Rash is common; consider in differential in patients receiving lamotrigine. GI side effects are common; concurrent use with SSRIs may produce additive effects. May produce hypotension; concurrent use with psychotropic agents may produce additive blood pressure-lowering effects.
Index Terms131 I Anti-B1 Antibody; 131 I-Anti-B1 Monoclonal Antibody; Anti-CD20-Murine Monoclonal Antibody I-131; B1; B1 Antibody; Iodine I 131 Tositumomab and Tositumomab; Tositumomab I-131
References

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Total Parenteral Nutrition

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(TOE tal par EN ter al noo TRISH un)

Pharmacologic Category[Caloric Agent](); [Intravenous Nutritional Therapy]()

Use: Labeled IndicationsInfusion of nutrient solutions into the bloodstream to support nutritional needs during a time when patient is unable to absorb nutrients via the gastrointestinal tract, cannot take adequate nutrition orally or enterally, or have had (or are expected to have) inadequate oral intake for 7-14 days

Dosing: AdultsNutritional supplementation: I.V.:

Total calories: Calculate using Harris-Benedict equation or based on stress level as indicated below:

Harris-Benedict Equation (BEE):

Females: 655.1 + [(9.56 x W) + (1.85 x H) - (4.68 x A)]

Males: 66.47 + [(13.75 x W) + (5 x H) - (6.76 x A)]

Then multiply BEE x (activity factor) x (stress factor)

W = weight in kg; H = height in cm; A = age in years

Activity factor = 1.2 sedentary, 1.3 normal activity, 1.4 active, 1.5 very active

Stress factor = 1.5 for trauma, stressed, or surgical patients and underweight (to promote weight gain); 2.0 for severe burn patients

Stress level:

Normal/mild stress level: 20-25 kcal/kg/day

Moderate stress level: 25-30 kcal/kg/day

Severe stress level: 30-40 kcal/kg/day

Pregnant women in second or third trimester: Add an additional 300 kcal/day

Fluid: mL/day = 30-40 mL/kg

Carbohydrate (dextrose):

5 g/kg/day or 3.5 mg/kg/minute (maximum rate: 4-7 mg/kg/minute)

Minimum recommended amount: 400 calories/day or 100 g/day

Protein (amino acids):

Maintenance: 0.8-1 g/kg/day

Normal/mild stress level: 1-1.2 g/kg/day

Moderate stress level: 1.2-1.5 g/kg/day

Severe stress level: 1.5-2 g/kg/day

Burn patients (severe): Increase protein until significant wound healing achieved

Solid organ transplant: Perioperative: 1.5-2 g/kg/day

Renal failure:

Acute (severely malnourished or hypercatabolic): 1.5-1.8 g/kg/day

Chronic, with dialysis: 1.2-1.3 g/kg/day

Chronic, without dialysis: 0.6-0.8 g/kg/day

Continuous hemofiltration: ≥1 g/kg/day

Hepatic failure:

- Acute management when other treatments have failed:
  - With encephalopathy: 0.6-1 g/kg/day
  - Without encephalopathy: 1-1.5 g/kg/day
- Chronic encephalopathy: Use branch chain amino acid enriched diets only if unresponsive to pharmacotherapy

Pregnant women in second or third trimester: Add an additional 10-14 g/day

Fat:

Initial: 20% to 40 % of total calories (maximum: 60% of total calories or 2.5 g/kg/day); **Note:** Monitor triglycerides while receiving intralipids.

Safe for use in pregnancy

I.V. lipids are safe in adults with pancreatitis if triglyceride levels <400 mg/dL

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricNutritional supplementation:

Neonates: I.V.: **Note:** When indicated for premature neonates, start on day 1 of life if possible.

Total calories:

- Term: 85-105 kcal/kg/day
- Preterm (stable): 90-120 kcal/kg/day

Fluid:

- <1.5 kg: 130-150 mL/kg/day
- 1.5-2 kg: 110-130 mL/kg/day
- 2-10 kg: 100 mL/kg/day

Carbohydrate (dextrose):40% to 50 % of caloric intake; advance as tolerated

- Term: Initial: 6-8 mg/kg/minute; goal: 10-14 mg/kg/minute
- Premature: Initial: 6 mg/kg/minute; goal: 10-13 mg/kg/minute

Protein (amino acids):

- Term: Initial: 2.5 g/kg/day; goal: 3 g/kg/day
- Extremely (<1000 g) and very (<1500 g) low-birth-weight (stable): Initial: 1-1.5 g/kg/day; goal: 3.5-3.85 g/kg/day to promote utero growth rates.
- Sepsis, hypoxia: Initial: 1 g/kg/day; goal: 3-3.85 g/kg/day

Fat:

- Term: Initial: 0.5-1 g/kg/day (maximum: 3 g/kg/day); administer over 24 hours
- Preterm: Initial: 0.25-0.5 g/kg/day (maximum: 3 g/kg/day or 1 g/kg/day if on phototherapy); administer over 24 hours
- **Note:** Monitor triglycerides while receiving intralipids. If triglycerides >200 mg/dL, stop infusion and restart at 0.5-1g/kg/day

Heparin: 1 unit/mL of parenteral nutrition fluids should be added to enhance clearance of lipid emulsions

Children: I.V.: **Note:** Give within 5-7 days if unable to meet needs orally or with enteral nutrition:

Total calories:

- <6 months: 85-105 kcal/kg/day
- 6-12 months: 80-100 kcal/kg/day
- 1-7 years: 75-90 kcal/kg/day
- 7-12 years: 50-75 kcal/kg/day
- 12-18 years: 30-50 kcal/kg/day

Fluid:

- 2-10 kg: 100 mL/kg
- >10-20 kg: 1000 mL for 10 kg plus 50 mL/kg for each kg >10

>20 kg: 1500 mL for 10 kg plus 20 mL/kg for each kg >20

Carbohydrate (dextrose): 40% to 50% of caloric intake

<1 year: Initial: 6-8 mg/kg/minute; goal: 10-14 mg/kg/minute

1-10 years: Initial: 10% to 12.5%; daily increase: 5% increments (maximum: 15 mg/kg/minute)

>10 years: Initial: 10% to 15%; daily increase: 5% increments (maximum: 8.5 mg/kg/minute)

Protein (amino acids):

1-12 months: Initial: 2-3 g/kg/day; daily increase: 1 g/kg/day (maximum: 3 g/kg/day)

1-10 years: Initial: 1-2 g/kg/day; daily increase: 1 g/kg/day (maximum: 2-2.5 g/kg/day)

>10 years: Initial: 0.8-1.5 g/kg/day; daily increase: 1 g/kg/day (maximum: 1.5-2 g/kg/day)

Fat: Initial: 1 g/kg/day; daily increase: 1 g/kg/day (maximum: 3 g/kg/day); **Note:** Monitor triglycerides while receiving intralipids.

Calculations

- Adjusted Body Weight
- Ideal Body Weight: Adults
- Ideal Body Weight: Pediatrics

Administration: I.V.For I.V. administration only, usually via a central venous catheter; can be administered by continuous infusion over 24 hours or cyclic infusion over 12-14 hours. Cyclic infusion is used with a tapering-up period at the beginning and a tapering-down period at the end to avoid hyper-/hypoglycemia. For infants <2 years, taper over 1-2 hours.

Administration: I.V. DetailChange tubing after each infusion. Hang fat emulsion higher than other fluids (has low specific gravity and could run up into other lines). Infuse via pump using either peripheral or central venous line. Do not use in-line filter.

StorageUSP Chapter 797 Guidelines consider TPN a medium-risk preparation and state that (in the absence of passing a sterility test) storage period should not exceed 30 hours at room temperature, 7 days at cold temperature, and 45 days in a solid frozen state at -20°C or colder. For patients on home TPN, multiple vitamins should be added prior to TPN administration, due to limited stability of multiple vitamins.

CompatibilitySee detailed reference.

ContraindicationsVaries by composition:

Lipid-containing formulations are contraindicated in patients with hypersensitivity to fat emulsion or any component of the formulation; severe egg or legume (soybean) allergies; pathologic hyperlipidemia, lipoid nephrosis, pancreatitis with hyperlipemia

Dextrose is contraindicated in patients with hypersensitivity to corn or corn products; hypertonic solutions in patients with intracranial or intraspinal hemorrhage; glucose-galactose malabsorption syndrome

Amino acids are contraindicated in patients with hypersensitivity to one or more amino acids; severe liver disease or hepatic coma

Warnings/Precautions

Concerns related to adverse effects:

- Refeeding syndrome: Use with caution in patients at risk for refeeding syndrome. Refeeding syndrome is a medical emergency; it can consist of electrolyte disturbances (eg, potassium, phosphorus), respiratory distress, and cardiac arrhythmias, resulting in cardiopulmonary arrest. It is usually seen in patients with long-standing or severe malnutrition; initiate cautiously; approach goals slowly. Do not overfeed patients; caloric replacement should match as closely as possible to intake.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes or insulin resistance.

- Hepatic impairment: Use with caution and limit protein in patients with hepatic disease.

- Volume overload: Use with caution in patients who may be sensitive to volume overload (eg, HF, renal failure, hepatic failure).

Other warnings/precautions:

- Abrupt withdrawal: If TPN is discontinued abruptly, infuse 10% dextrose at same rate and monitor blood glucose for hypoglycemia.

- Monitoring: Monitor fluid and electrolyte status carefully.

Adverse ReactionsFrequency not defined (unless noted).

Endocrine & metabolic: Fluid overload, hypercapnia, hyperglycemia, hyper-/hypokalemia, hyper-/hypophosphatemia, metabolic bone disease, nonanion gap metabolic acidosis, refeeding syndrome

Hepatic: Cholestasis, cirrhosis (<1%), gallstones, liver function tests increased, pancreatitis, steatosis, triglycerides increased

Renal: Azotemia, BUN increased

Miscellaneous: Bacteremia, catheter-induced infection, exit-site infections

Monitoring Parameters

Electrolytes: Sodium, potassium, chloride, and bicarbonate should be monitored frequently upon initiation and until stable; phosphate should be monitored closely in patients with pulmonary disease.

Efficacy: Nutrition and outcome parameters should be measured serially.

Glucose: In patients with diabetes or patients with glucose intolerance risk factors, monitor closely. Monitor frequently upon initiation of therapy and with any changes in insulin dose or renal function.

Line site: Monitor for signs and symptoms of infection.

Liver function tests: Monitor periodically.

Triglycerides: Before initiation of lipid therapy and at least weekly during therapy.

Refeeding syndrome: Patients at risk should have phosphorus, magnesium, potassium, and glucose levels monitored closely at initiation.

Bone densitometry: Perform upon initiation of long-term therapy.

Vitamin A status: Should be carefully monitored in patients with chronic renal failure.

Neonates: Sodium, calcium and phosphate should be monitored closely. Frequent (some advise daily) platelet counts should be performed in neonatal patients receiving parenteral lipids.

Monitoring: Lab Tests

Electrolytes: Sodium, potassium, chloride, and bicarbonate should be monitored frequently upon initiation and until stable; phosphate should be monitored closely in patients with pulmonary disease.

Efficacy: Nutrition and outcome parameters should be measured serially.

Glucose: In patients with diabetes or patients with glucose intolerance risk factors, monitor closely. Monitor frequently upon initiation of therapy and with any changes in insulin dose or renal function.

Line site: Monitor for signs and symptoms of infection.

Liver function tests: Monitor periodically.

Triglycerides: Before initiation of lipid therapy and at least weekly during therapy.

Refeeding syndrome: Patients at risk should have phosphorus, magnesium, potassium, and glucose levels monitored closely at initiation.

Bone densitometry: Perform upon initiation of long-term therapy.

Vitamin A status: Should be carefully monitored in patients with chronic renal failure.

Neonates: Sodium, calcium and phosphate should be monitored closely. Frequent (some advise daily) platelet counts should be performed in neonatal patients receiving parenteral lipids.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling. TPN is usually compounded from optimal combinations of macronutrients (water, protein, dextrose, and lipids) and micronutrients (electrolytes, trace elements, and vitamins) to meet the specific nutritional requirements of a patient. Individual hospitals may have designated standard TPN formulas. There are a few commercially-available amino acids with electrolytes solutions; however, these products may not meet an individual's specific nutrition requirements.

See Dextrose and Fat Emulsion monographs for additional information.

Related Information

- Dextrose
- Fat Emulsion

Pharmacotherapy Pearls

Diabetes: Avoid excess calories.

Burns: Assess nutrition requirements with indirect calorimetry if possible.

Obesity: Assess nutrition requirements with indirect calorimetry if possible and give hypocaloric nutrition with supplemental protein.

Pulmonary disease: Use a fluid-restricted formula for ARDS. Energy (carbohydrate) intake should be kept at or below estimated needs in patients with pulmonary disease and hypercapnia.

1 g protein = 4 kcal

1 g dextrose = 3.4 kcal

1 g fat = 9 kcal

10% fat emulsion = 1.1 kcal

20% fat emulsion = 2 kcal

30% fat emulsion = 3 kcal

Adult standard daily electrolyte requirements:

- Acetate: As needed to maintain acid-base balance
- Calcium: 10-15 mEq
- Chloride: As needed to maintain acid-base balance
- Magnesium 8-20 mEq
- Phosphorus: 20-40 mmol
- Potassium: 1-2 mEq/kg
- Sodium: 1-2 mEq/kg

Adult daily requirements for parenteral vitamins:

- Ascorbic acid (C): 200 mg
- Biotin: 60 mcg
- Cyanocobalamin (B_{12}): 5 mcg
- Folic acid: 600 mcg
- Niacin (B_3): 40 mg
- Pantothenic acid: 15 mg
- Pyridoxine (B_6): 6 mg
- Riboflavin (B_2): 3.6 mg
- Thiamine (B_1): 6 mg
- Vitamin A: 3300 int. units
- Vitamin D: 200 int. units
- Vitamin E: 10 int. units
- Vitamin K: 150 mcg

Adult daily requirements for parenteral trace elements:

- Chromium: 10-15 mcg
- Copper: 0.3-0.5 mg
- Iron: Not routinely added
- Manganese: 60-100 mcg
- Selenium: 20-60 mcg
- Zinc: 2.5-5 mg

See Dextrose and Fat Emulsion monographs for additional information.

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsHyperal; Hyperalimentation; Parenteral Nutrition; PN; TPN

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Trace Metals

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English English

Jump To Field (Select Field Name)

Pronunciation(trase MET als)

U.S. Brand Names4 Trace Elements; Multitrace®-4; Multitrace®-4 Concentrate; Multitrace®-4 Neonatal; Multitrace®-4 Pediatric; Multitrace®-5; Multitrace®-5 Concentrate; Trace Elements 4 Pediatric

Pharmacologic CategoryTrace Element, Parenteral

Use: Labeled IndicationsPrevention and correction of trace metal deficiencies

Dosing: Adults**Recommended daily parenteral dosage:**

Chromium:[1] 10-15 mcg

Copper:[2] 0.5-1.5 mg

Manganese:[2,3] 150-800 mcg

Molybdenum:[1,4] 20-120 mcg

Selenium:[1,4] 20-40 mcg

Zinc: 2.5-4 mg

[1] Omit in patients with renal dysfunction.

[2] Omit in patients with obstructive jaundice.

[3] Current available commercial products are not in appropriate ratios to maintain this recommendation; doses of up to 10 mcg/kg have been used.

[4] Indicated for use in long-term parenteral nutrition patients.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Recommended daily parenteral dosage:**

Chromium:[1]

Infants: 0.2 mcg/kg

Children: 0.2 mcg/kg (maximum: 5 mcg)

Copper:[2]

Infants: 20 mcg/kg

Children: 20 mcg/kg (maximum: 300 mcg)

Manganese:[2,3]

Infants: 1 mcg/kg

Children: 1 mcg/kg (maximum: 50 mcg)

Molybdenum:[1,4]

Infants: 0.25 mcg/kg

Children: 0.25 mcg/kg (maximum: 5 mcg)

Selenium:[1,4]

Infants: 2 mcg/kg

Children: 2 mcg/kg (maximum: 30 mcg)

Zinc:

Infants, preterm: 400 mcg/kg

Infants, term <3 months: 250 mcg/kg

Infants, term >3 months: 100 mcg/kg

Children: 50 mcg/kg (maximum: 5 mg)

[1] Omit in patients with renal dysfunction.

[2] Omit in patients with obstructive jaundice.

[3] Current available commercial products are not in appropriate ratios to maintain this recommendation; doses of up to 10 mcg/kg have been used.

[4] Indicated for use in long-term parenteral nutrition patients.

Pregnancy Risk FactorC

Ethanol/Nutrition/Herb InteractionsFood: Decreased absorption of oral zinc when administered with bran products, protein, and phytates.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [combination products]:

Multitrace®-4: Chromium 4 mcg, copper 0.4 mg, manganese 0.1 mg, and zinc 1 mg per 1 mL (10 mL) [contains aluminum, benzyl alcohol]

Multitrace®-4 Concentrate: Chromium 10 mcg, copper 1 mg, manganese 0.5 mg, and zinc 5 mg per 1 mL (1 mL) [contains aluminum]; chromium 10 mcg, copper 1 mg, manganese 0.5 mg, and zinc 5 mg per 1 mL (10 mL) [contains benzyl alcohol]

Multitrace®-4 Neonatal: Chromium 0.85 mcg, copper 0.1 mg, manganese 0.025 mg, and zinc 1.5 mg per 1 mL (2 mL) [contains aluminum]

Multitrace®-5: Chromium 4 mcg, copper 0.4 mg, manganese 0.1 mg, selenium 20 mcg, and zinc 1 mg per 1 mL (10 mL) [contains aluminum, benzyl alcohol]

Multitrace®-5 Concentrate: Chromium 10 mcg, copper 1 mg, manganese 0.5 mg, selenium 60 mcg, and zinc 5 mg per 1 mL (1 mL) [contains aluminum]; chromium 10 mcg, copper 1 mg, manganese 0.5 mg, selenium 60 mcg, and zinc 5 mg per 1 mL (10 mL) [contains benzyl alcohol]

Trace Elements 4 Pediatric: Chromium 1 mcg, copper 0.1 mg, manganese 0.03 mg, and zinc 0.5 mg per 1 mL (10 mL) [contains aluminum, benzyl alcohol]

Injection, solution [combination products, preservative free]:

4 Trace Elements: Chromium 2 mcg, copper 0.2 mg, manganese 0.16 mg, and zinc 0.8 mg per 1 mL (5 mL, 50 mL) [contains aluminum]

Multitrace®-4 Pediatric: Chromium 1 mcg, copper 0.1 mg, manganese 0.025 mg, and zinc 1 mg per 1 mL (3 mL) [contains aluminum]

Generic AvailableYes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsChromium; Copper; Iodine; Manganese; Molybdenum; Neonatal Trace Metals; Selenium; Zinc

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TraMADol

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

TraMADol may be confused with Toradol®, Trandate®, traZODone, Voltaren®

Ultram® may be confused with Ultane®, Ultracet®, Voltaren®

International issues:

Theradol® [Netherlands] may be confused with Foradil® which is a brand name for formoterol in the U.S.

Theradol® [Netherlands] may be confused with Terazol® which is a brand name for terconazole in the U.S.

Theradol® [Netherlands] may be confused with Toradol® which is a brand name for ketorolac in the U.S.

Pronunciation(TRA ma dole)

U.S. Brand NamesUltram®; Ultram® ER

Canadian Brand NamesRalivia™ ER; Tridural™; Zytram® XL

Pharmacologic CategoryAnalgesic, Opioid

Use: Labeled IndicationsRelief of moderate to moderately-severe pain

Use: DentalRelief of moderate to moderately-severe dental pain

Dosing: Adults**Moderate-to-severe chronic pain:** Oral:

Immediate release formulation: 50-100 mg every 4-6 hours (not to exceed 400 mg/day)

For patients not requiring rapid onset of effect, tolerability may be improved by starting dose at 25 mg/day and titrating dose by 25 mg every 3 days, until reaching 25 mg 4 times/day. The total daily dose may then be increased by 50 mg every 3 days as tolerated, to reach dose of 50 mg 4 times/day. After titration, 50-100 mg may be given every 4-6 hours as needed up to a maximum 400 mg/day.

Extended release formulation:

Ultram® ER: Patients not currently on immediate-release: 100 mg once daily; titrate every 5 days (maximum: 300 mg/day); Patients currently on immediate-release: Calculate 24-hour immediate release total and initiate total daily dose (round dose to the next lowest 100 mg increment); titrate (maximum: 300 mg/day)

Ralivia™ ER (Canadian labeling, not available in U.S.): 100 mg once daily; titrate every 5 days as needed based on clinical response and severity of pain (maximum: 300 mg/day)

Tridural™ (Canadian labeling, not available in U.S.): 100 mg once daily; titrate by 100 mg/day every 2 days as needed based on clinical response and severity of pain (maximum: 300 mg/day)

Zytram® XL (Canadian labeling, not available in U.S.): 150 mg once daily; if pain relief is not achieved may titrate by increasing dosage incrementally, with sufficient time to evaluate effect of increased dosage; generally not more often than every 7 days (maximum: 400 mg/day)

Dosing: ElderlyOral: >75 years:

Immediate release: 50 mg every 6 hours (not to exceed 300 mg/day); see dosing adjustments for renal and hepatic impairment.

Extended release: Use with great caution. Refer to adult dosing.

Dosing: Renal Impairment

Immediate release: Cl_{cr} <30 mL/minute: Administer 50-100 mg dose every 12 hours (maximum: 200 mg/day).

Extended release: Should not be used in patients with Cl_{cr} <30 mL/minute.

Dosing: Hepatic Impairment

Immediate release: Cirrhosis: Recommended dose: 50 mg every 12 hours.

Extended release: Should not be used in patients with severe (Child-Pugh Class C) hepatic dysfunction.

Calculations

- Creatinine Clearance: Adults

Administration: OralExtended release tablet: Swallow whole; do not crush, chew, or split

Dietary ConsiderationsMay be taken with or without food. Extended release formulation: Be consistent; always give with food or always give on an empty stomach.

StorageStore at controlled room temperature of 25°C (77°F).

ContraindicationsHypersensitivity to tramadol, opioids, or any component of the formulation; opioid-dependent patients; acute intoxication with alcohol, hypnotics, centrally-acting analgesics, opioids, or psychotropic drugs

Note: Based on Canadian product labeling:

Tramadol is contraindicated during or within 14 days following MAO inhibitor therapy

Extended release formulations (Ralivia™ ER [CAN], Tridural™[CAN], and Zytram® XL [CAN]): Additional contraindications: Severe (Cl_{cr} <30 mL/minute) renal dysfunction, severe (Child-Pugh Class C) hepatic dysfunction

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid reactions: Rare but serious anaphylactoid reactions (including fatalities) often following initial dosing have been reported. Pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome also have been reported with use. Previous anaphylactoid reactions to opioids may increase risks for similar reactions to tramadol.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Seizures: Even when taken within the recommended dosage seizures may occur; risk is increased in patients receiving serotonin reuptake inhibitors (SSRIs or anorectics), other opioids, tricyclic antidepressants, other cyclic compounds (including cyclobenzaprine, promethazine), neuroleptics, MAO inhibitors, or drugs which may lower seizure threshold. Patients with a history of seizures, or with a risk of seizures (head trauma, metabolic disorders, CNS infection, malignancy, or during alcohol/drug withdrawal) are also at increased risk.

Disease-related concerns:

- Abdominal conditions: May obscure diagnosis or clinical course of patients with acute abdominal conditions.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists.
- Ethanol use: Use with caution in heavy alcohol users.
- Head trauma: Use with extreme caution in patients with head injury, intracranial lesions, or elevated intracranial pressure; exaggerated elevation of ICP may occur.
- Hepatic impairment: Use with caution and reduce dosage in patients with mild-to-moderate hepatic impairment; extended release formulations should not be used in severe hepatic impairment (Child-Pugh Class C)
- Renal impairment: Use with caution and reduce dosage in patients with mild-to-moderate renal impairment; extended release formulations should not be used in severe renal impairment Cl_{cr} <30 mL/minute.
- Respiratory disease: Patients with respiratory disorders (eg, significant chronic obstructive pulmonary disease (COPD), cor pulmonale, hypoxia, hypercapnia) may be at greater risk of respiratory depression.
- Suicide risk: Avoid use in patients who are suicidal.

Concurrent drug therapy issues:

- CNS depressants: Use with caution and reduce dosage when administering to patients receiving other CNS depressants; may cause CNS depression and/or respiratory depression.
- Serotonergic agents: Avoid use with serotonergic agents such as TCAs, MAO inhibitors (contraindicated in Canadian product labeling), triptans, venlafaxine, trazodone, lithium, sibutramine, meperidine, dextromethorphan, St John’s wort, SNRIs and SSRIs; concomitant use has been associated with the development of serotonin syndrome.

Special populations:

- Debilitated patients: Use with caution in debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages.
- Elderly: Extended-release formulation should be used with extreme caution in the elderly (particularly >75 years of age); may be more sensitive to adverse effects. Reduce initial dose.
- Pediatrics: Immediate release formulation: Safety and efficacy have not been established in children <16 years of age. Extended release formulation: Safety and efficacy have not been established in children <18 years of age.

Dosage form specific issues:

- Extended release tablets: Caution patients to swallow tablets whole. Rapid release absorption of tramadol from tablets that are broken, crushed, or chewed may lead to a potentially-lethal overdose.

Other warnings/precautions:

- Withdrawal: Tolerance or drug dependence may result from extended use (withdrawal symptoms have been reported); abrupt discontinuation should be avoided. Tapering of dose at the time of discontinuation limits the risk of withdrawal symptoms.

Geriatric ConsiderationsOne study in the elderly found that tramadol 50 mg was similar in efficacy as acetaminophen 300 mg with codeine 30 mg. In Ultram® ER trials, elderly patients experienced more adverse effects than younger adults, particularly constipation, fatigue, weakness, postural hypotension, and dyspepsia. For this reason, the extended release formulation should probably be avoided in the elderly, or only used with great caution.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events were observed in animal studies. Tramadol has been shown to cross the human placenta when administered during labor. Postmarketing reports following tramadol use during pregnancy include neonatal seizures, withdrawal syndrome, fetal death, and stillbirth. Not recommended for use during labor and delivery.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsSixteen hours following a single 100 mg I.V. dose, the amount of tramadol found in breast milk was 0.1% of the maternal dose. Use is not recommended by the manufacturer for postdelivery analgesia in nursing mothers.

Adverse Reactions

>10%:

  Cardiovascular: Flushing (8% to 16%)

  Central nervous system: Dizziness (16% to 33%), headache (12% to 32%), insomnia (7% to 11%), somnolence (7% to 25%)

  Dermatologic: Pruritus (6% to 12%)

  Gastrointestinal: Constipation (10% to 46%), nausea (15% to 40%), vomiting (5% to 17%), dyspepsia (1% to 13%)

  Neuromuscular & skeletal: Weakness (4% to 12%)

1% to 10%:

  Cardiovascular: Chest pain (1% to <5%), postural hypotension (2% to 5%), vasodilation (1% to <5%)

  Central nervous system: Anxiety (1% to <5%), confusion (1% to <5%), coordination impaired (1% to <5%), depression (1% to <5%), euphoria (1% to <5%), hypoesthesia (1% to <5%), lethargy (1% to <5%), nervousness (1% to <5%), pain (1% to <5%), pyrexia (1% to <5%), restlessness (1% to <5%), malaise (<1% to <5%)

  Dermatologic: Dermatitis (1% to <5%), rash (1% to <5%)

  Endocrine & metabolic: Hot flashes (2% to 9%), menopausal symptoms (1% to <5%)

  Gastrointestinal: Diarrhea (5% to 10%), xerostomia (5% to 10%), anorexia (1% to <6%), abdominal pain (1% to <5%), appetite decreased (1% to <5%), weight loss (1% to <5%), flatulence (<1% to <5%)

  Genitourinary: Urinary tract infection (1% to <5%), urinary frequency (<1% to <5%), urinary retention (<1% to <5%)

  Neuromuscular & skeletal: Arthralgia (1% to <5%), back pain (1% to <5%), hypertonia (1% to <5%), rigors (1% to <5%), paresthesia (1% to <5%), tremor (1% to <5%), creatinine phosphokinase increased (1% to <5%)

  Ocular: Blurred vision (1% to <5%), miosis (1% to <5%)

  Respiratory: Bronchitis (1% to <5%), congestion (nasal/sinus) (1% to <5%), cough (1% to <5%), dyspnea (1% to <5%), nasopharyngitis (1% to <5%), rhinorrhea (1% to <5%), sinusitis (1% to <5%), sneezing (1% to <5%), sore throat (1% to <5%), upper respiratory infection (1% to <5%)

  Miscellaneous: Diaphoresis (2% to 9%), flu-like syndrome (1% to < 5%), shivering (<1% to <5%)

<1% (Limited to important or life-threatening): Abnormal ECG, abnormal gait, agitation, allergic reaction, amnesia, anaphylactoid reactions, anaphylaxis, angioedema, appendicitis, ALT increased, AST increased, bronchospasm, cataracts, cellulitis, cholecystitis, cholelithiasis, clamminess, cognitive dysfunction, concentration difficulty, creatinine increased, deafness, disorientation, dreams abnormal, dysuria, ear infection, edema, gastroenteritis, gastrointestinal bleeding, hallucination, hematuria, hemoglobin decreased, hepatitis, hyperglycemia, hyper-/hypotension, irritability, joint stiffness, libido decreased, liver enzymes increased, liver failure, menstrual disorder, MI, migraine, muscle cramps, muscle spasms, muscle twitching, myalgia, myocardial ischemia, night sweats, palpitation, pancreatitis, peripheral edema, peripheral ischemia, pneumonia, proteinuria, pulmonary edema, pulmonary embolism, sedation, seizure, serotonin syndrome, sleep disorder, speech disorder, Stevens-Johnson syndrome, stomatitis, suicidal tendency, syncope, taste perversion, tachycardia, tinnitus, toxic epidermal necrolysis, urticaria, vertigo, vesicles

A withdrawal syndrome may occur with abrupt discontinuation; includes anxiety, diarrhea, hallucinations (rare), nausea, pain, piloerection, rigors, sweating, and tremor. Uncommon discontinuation symptoms may include severe anxiety, panic attacks, or paresthesia.

Metabolism/Transport Effects**Substrate** of CYP2D6 (major), 3A4 (major)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

MAO Inhibitors: TraMADol may enhance the neuroexcitatory and/or seizure-potentiating effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. TraMADol may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tricyclic Antidepressants: May enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food:

Immediate release: Does not affect the rate or extent of absorption.

Extended release: Reduced C_{max} and AUC and T_{max} occurred 3 hours earlier when taken with a high-fat meal.

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersPain relief, respiratory rate, blood pressure, and pulse; signs of tolerance or abuse

Reference Range100-300 ng/mL; however, serum level monitoring is not required

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for additive or adverse interactions. Monitor therapeutic effectiveness and adverse reactions or overdose at beginning of therapy and periodically during therapy. May cause physical and/or psychological dependence. Taper dose when discontinuing to avoid withdrawal symptoms. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationExtended release tablet must be swallowed whole; do not break, chew, or crush. If self-administered, use exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or cough preparations) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience headache, drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or constipation (increased exercise, fluids, fruit, or fiber may help). Report severe unresolved constipation, respiratory difficulty or shortness of breath, excessive sedation or increased insomnia and restlessness, rash or hives, changes in urinary pattern or menstrual pattern, seizures, muscle weakness or tremors, or chest pain or palpitations. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet, as hydrochloride: 50 mg

Ultram®: 50 mg

Tablet, extended release, as hydrochloride:

Ultram® ER: 100 mg, 200 mg, 300 mg

Ralivia™ ER [CAN]: 100 mg, 200 mg, 300 mg [not available in the U.S.]

Tridural™ [CAN]: 100 mg, 200 mg, 300 mg [not available in the U.S.]

Zytram® XL [CAN]: 150 mg, 200 mg, 300 mg, 400 mg [not available in the U.S.]

Generic AvailableYes: Excludes extended release tablet

Pricing: U.S. (www.drugstore.com)

Tablet, 24-hour (Ultram ER)

100 mg (30): $108.08

200 mg (30): $182.00

300 mg (30): $224.36

Tablets (Tramadol HCl)

50 mg (30): $16.99

Tablets (Ultram)

50 mg (30): $64.03

Mechanism of ActionTramadol and active metabolite (M1) binds to µ-opiate receptors in the CNS causing inhibition of ascending pain pathways, altering the perception of and response to pain; also inhibits the reuptake of norepinephrine and serotonin, which also modifies the ascending pain pathway

Pharmacodynamics/Kinetics

Onset of action: Immediate release: ~1 hour

Duration: 9 hours

Absorption: Immediate release formulation: Rapid and complete; Extended release formulation: Delayed

Distribution: V_d: 2.5-3 L/kg

Protein binding, plasma: 20%

Metabolism: Extensively hepatic via demethylation, glucuronidation, and sulfation; has pharmacologically active metabolite formed by CYP2D6 (M1; O-desmethyl tramadol)

Bioavailability: Immediate release: 75%; Extended release: Ultram® ER: 85% to 90% (as compared to immediate release), Zytram® XL, Tridural™: 70%

Half-life elimination: Tramadol: ~6-8 hours; Active metabolite: 7-9 hours; prolonged in elderly, hepatic or renal impairment; Zytram® XL: ~16 hours; Ralivia™ ER, Tridural™: ~5-9 hours

Time to peak: Immediate release: ~2 hours; Extended release: Ultram® ER: ~12 hours, Tridural™: ~4 hours

Excretion: Urine (30% as unchanged drug; 60% as metabolites)

Dental Health Professional ConsiderationsLiterature reports suggest that the efficacy of tramadol in oral surgery pain is equivalent to the combination of aspirin and codeine. One study (Olson et al 1990) showed acetaminophen and dextropropoxyphene combination to be superior to tramadol and another study showed tramadol to be superior to acetaminophen and dextropropoxyphene combination. Tramadol appears to be at least equal to if not better than codeine alone. Seizures have been reported with the use of tramadol.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation). See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, or restlessness

Mental Health: Effects on Psychiatric TreatmentContraindicated with opioid-dependent patients, MAO inhibitors, psychotropics; carbamazepine may decrease the effects of tramadol; concurrent use with MAO inhibitors and TCAs may produce seizures; tramadol has MAO inhibitor activity and should be used cautiously with other antidepressants

Anesthesia and Critical Care Concerns/Other ConsiderationsTramadol 50 mg is comparable to codeine 60 mg; tramadol 100 mg is comparable to aspirin 650 mg/codeine 60 mg. Tramadol is 5-10 times less potent than morphine and reported to cause less respiratory depression.

Index TermsTramadol Hydrochloride

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International Brand NamesAdamon (AR, DO, PL); Adamon SR (PL); Adolonta (ES); Amanda (TH); Analab (MY, TH); Andalpha (ID); Biodalgic (FR); Calmador (AR); Calmol (UY); Contramal (BE, FR, HN, HU, IN, IT); Contramal LP (FR); Crispin (JP); Dolana (ID); Dolmal (PH); Dolodol (ES); Dolotral (PH); Dolpaz (PH); Dolzam (LU); Dromadol (GB); Durodor Retard (MX); Eufindol (CN); Geadol (NO); Kontram XL SR (KP); Lumidol (HR); Mabron (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, MY, OM, QA, SA, SG, SY, YE); Mandolgin (DK); Monoalgic LP (FR); Monotramal LP (FR); Nobligan (NO, SE); Nonalges (ID); Paxilfar (PT); Pengesic (MY, PH, SG); Poltram (PL); Poltram Retard (PL); Rofy (TH); Sefmal (HK, SG); Sensitram (BR); Slovadol (PL); Takadol (FR); Tamolan (TH); Topalgic (FR); Trabilin (BB, BM, BS, BZ, CR, GT, GY, HN, JM, NI, PA, SR, SV, TT); Tradol-Puren (DE); Tradolan (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SE, SY, YE); Tradonal (PH); Tradorec XL (GB, IE); Tramada (MY); Tramadex (IL); Tramadol (PL); Tramadol Lannacher (PL); Tramadol Slovakofarma (HU); Tramadol Stada (PL); Tramadolor (CL); Tramagetic (DE); Tramagit (DE); Tramahexal (ZA); Tramahexal SR (AU); Tramake (IE); Tramal (AE, AT, AU, BF, BG, BH, BJ, CH, CI, CL, CO, CY, CZ, DE, EE, EG, ET, FI, GH, GM, GN, HK, HR, IL, IQ, IR, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, PE, PH, PK, PL, PT, QA, SA, SC, SD, SL, SN, SY, TH, TN, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Tramal Long (EC); Tramal retard (PL); Tramal SR (AU); Tramazac (BF, BJ, CI, ET, GH, GM, GN, IN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TH, TN, TZ, UG, ZA, ZM, ZW); Tramcontin (CL); Tramed (TW); Tramedo (AU); Tramundin (PL); TRD-Contin (IN); Trexol (MX); Tridol (KP); Trodon (PL); Unitral (PH); Zamadol (BR, GB); Zamudol (FR); Zodol (CN, PE, PY); Zumatran (ID); Zydol (AU, GB, IE); Zydol SR (AU); Zydol XL (GB); Zytram BD (NZ); Zytram XL SR (KP)

Trandolapril and Verapamil

Lexi-Drugs Online

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(tran DOE la pril & ver AP a mil)

U.S. Brand NamesTarka®

Canadian Brand NamesTarka®

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor; Calcium Channel Blocker

Use: Labeled IndicationsTreatment of hypertension; however, not indicated for initial treatment of hypertension

Dosing: Adults**Hypertension:** Oral: Individualize dose. Patients receiving trandolapril (up to 8 mg) and verapamil (up to 240 mg) in separate tablets may wish to receive Tarka® at equivalent dosages once daily.

Dosing: ElderlyRefer to dosing in individual monographs.

Dosing: Renal ImpairmentUsual regimen need not be adjusted unless patient's creatinine clearance is <30 mL/minute. Titration of individual components must be done prior to switching to combination product

Dosing: Hepatic ImpairmentHas not been evaluated in hepatic impairment. Verapamil is hepatically metabolized, adjustment of dosage in hepatic impairment is recommended.

ContraindicationsHypersensitivity to trandolapril, verapamil, or other ACE inhibitors, or any other component of the formulation; severe left ventricular dysfunction; hypotension (systolic blood pressure <90 mm Hg); cardiogenic shock; sick sinus syndrome (except in patients with a functioning pacemaker); second- or third-degree heart block (except in patients with a functioning pacemaker);atrial fibrillation or atrial flutter with an accessory bypass tract (eg, Wolff-Parkinson-White, Lown-Ganong-Levine syndromes); history of angioedema related to previous treatment with an ACE inhibitor

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity
- Verapamil Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising the airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Conduction abnormalities: Verapamil can cause first-degree AV block or sinus bradycardia; other conduction abnormalities are rare. Unless patients have a functioning pacemaker, contraindicated with sick sinus syndrome or second- or third-degree degree heart block.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE Inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia, or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Peripheral edema: The most common side effect of verapamil is peripheral edema; occurs within 2-3 weeks of starting therapy.
- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.
- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.
- Cirrhosis: Dosage adjustments of trandolapril are needed in patients with hepatic cirrhosis.
- Collagen vascular disease: Use trandolapril with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.
- Heart failure: Avoid verapamil in heart failure; can exacerbate condition. Contraindicated with severe left ventricular dysfunction or cardiogenic shock.
- Hepatic impairment: Use verapamil with caution in patients with hepatic impairment; may require lower starting dose.
- Hypertrophic obstructive cardiomyopathy (HOCM): Use with caution in patients with HOCM.
- Renal artery stenosis: Use trandolapril with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.
- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment is needed in severe renal dysfunction (Cl_{cr} <30 mL/minute). Avoid rapid dosage escalation which may lead to further renal impairment.

Concurrent drug therapy issues:

- Digoxin: Verapamil significantly increases digoxin serum concentrations; adjust digoxin dose.
- Neuromuscular-blocking agents: Verapamil may prolong recovery from nondepolarizing neuromuscular-blocking agents.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Pregnancy Risk FactorC/D (2nd and 3rd trimesters)
Pregnancy ConsiderationsSee individual monographs.
LactationEnters breast milk/contraindicated
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsVerapamil: **Substrate** of CYP1A2 (major), 2B6 (minor), 2C8/9 (minor), 2C19 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2C8/9 (weak), 2D6 (weak), 3A4 (moderate)
Drug Interactions

Alcohol (Ethyl): Verapamil may increase the serum concentration of Alcohol (Ethyl). *Risk C: Monitor therapy*

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amiodarone: Calcium Channel Blockers (Nondihydropyridine) may enhance the bradycardic effect of Amiodarone. Sinus arrest has been reported. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Calcium Channel Blockers (Nondihydropyridine). Anilidopiperidine Opioids may enhance the hypotensive effect of Calcium Channel Blockers (Nondihydropyridine). *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Beta-Blockers: Calcium Channel Blockers (Nondihydropyridine) may enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

BusPIRone: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Dihydropyridine): Calcium Channel Blockers (Nondihydropyridine) may enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of CarBAMazepine. CarBAMazepine may increase the metabolism of Calcium Channel Blockers (Nondihydropyridine). *Risk D: Consider therapy modification*

Cardiac Glycosides: Calcium Channel Blockers (Nondihydropyridine) may enhance the AV-blocking effect of Cardiac Glycosides. Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Cardiac Glycosides. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Colchicine: Verapamil may enhance the nephrotoxic effect of Colchicine. Colchicine may increase the serum concentration of Verapamil. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

CycloSPORINE: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of CycloSPORINE. CycloSPORINE may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dofetilide: Verapamil may increase the serum concentration of Dofetilide. *Risk X: Avoid combination*

Eletriptan: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Eletriptan. *Risk C: Monitor therapy*

Eplerenone: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Fexofenadine: Verapamil may increase the bioavailability of Fexofenadine. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Pravastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Lithium: Calcium Channel Blockers (Nondihydropyridine) may enhance the neurotoxic effect of Lithium. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Lithium. Decreased or unaltered lithium concentrations have also been reported with this combination. *Risk C: Monitor therapy*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Calcium Channel Blockers (Nondihydropyridine) may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. *Risk D: Consider therapy modification*

QuiNIDine: Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of QuiNIDine. *Risk D: Consider therapy modification*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Ranolazine: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

Risperidone: Verapamil may increase the serum concentration of Risperidone. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Salicylates: Calcium Channel Blockers (Nondihydropyridine) may enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Tacrolimus: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Tacrolimus. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure and heart rate; serum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringSee individual agents.

Monitoring: Lab TestsSerum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationSee individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, variable release:

1/240: Trandolapril 1 mg [immediate release] and verapamil hydrochloride 240 mg [sustained release]

2/180: Trandolapril 2 mg [immediate release] and verapamil hydrochloride 180 mg [sustained release]

2/240: Trandolapril 2 mg [immediate release] and verapamil hydrochloride 240 mg [sustained release]

4/240: Trandolapril 4 mg [immediate release] and verapamil hydrochloride 240 mg [sustained release]

Generic AvailableNo

ManufacturerKnoll Pharmaceutical Company

Pricing: U.S. (www.drugstore.com)

Tablet, controlled release (Tarka)

1-240 mg (30): $87.21

2-240 mg (30): $89.90

4-240 mg (30): $91.79

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Trandolapril
- Verapamil

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, nervousness, or insomnia

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels; concurrent use with low potency antipsychotics and TCAs may produce additive hypotensive effects; barbiturates may decrease verapamil serum concentrations; verapamil may increase carbamazepine serum concentrations

Cardiovascular ConsiderationsCombination therapy for the treatment of hypertension should be individualized for each patient. Potential advantages for trandolapril and verapamil combination therapy may include improved compliance and synergistic reductions in blood pressure with an accompanied reduction in side effects. See Cardiovascular Considerations for individual agents.

Index TermsVerapamil and Trandolapril

References

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Kaplan NM and Sever PS, “Combination Therapy: A Key to Comprehensive Patient Care,” *Am J Hypertens*, 1997, 10(7 Pt 2):127S. [PubMed 9231887]

Moser M and Black HR, “The Role of Combination Therapy in the Treatment of Hypertension,” *Am J Hypertens*, 1998, 11(6 Pt 2):73S-8S, 95S-100S.[PubMed 9655566]

International Brand NamesTarka (AR, AT, AU, CH, CO, CR, CZ, DE, DK, EE, ES, FI, FR, GB, GT, HK, HN, ID, IE, IT, NI, NL, PA, PE, PH, PK, SE, SV, VE, ZA); Tarka LP (FR); Udramil (DE); Ziaxel (NZ)

Trandolapril

Lexi-Drugs Online

English

English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(tran DOE la pril)

U.S. Brand NamesMavik®

Canadian Brand NamesMavik™

Pharmacologic CategoryAngiotensin-Converting Enzyme (ACE) Inhibitor

Use: Labeled IndicationsTreatment of hypertension alone or in combination with other antihypertensive agents; treatment of heart failure or left ventricular dysfunction after myocardial infarction

Use: Unlabeled/InvestigationalAs a class, ACE inhibitors are recommended in the treatment of heart failure; to delay the progression of nephropathy and reduce risks of cardiovascular events in hypertensive patients with type 1 or 2 diabetes mellitus

Dosing: Adults

Hypertension: Oral; Initial dose in patients not receiving a diuretic: 1 mg/day (2 mg/day in black patients). Adjust dosage according to the blood pressure response. Make dosage adjustments at intervals of ≥1 week. Most patients have required dosages of 2-4 mg/day. There is a little experience with doses >8 mg/day. Patients inadequately treated with once daily dosing at 4 mg may be treated with twice daily dosing. If blood pressure is not adequately controlled with trandolapril monotherapy, a diuretic may be added.

Usual dose range (JNC 7): 1-4 mg once daily

Heart failure postmyocardial infarction or left ventricular dysfunction postmyocardial infarction: Oral: Initial: 1 mg/day; titrate patients (as tolerated) towards the target dose of 4 mg/day. If a 4 mg dose is not tolerated, patients can continue therapy with the greatest tolerated dose.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentCl_{cr} ≤30 mL/minute: Administer lowest doses, starting at 0.5 mg/day.

Dosing: Hepatic ImpairmentPatients with hepatic cirrhosis: Start dose at 0.5 mg.

Calculations

- Creatinine Clearance: Adults

ContraindicationsHypersensitivity to trandolapril or any component of the formulation; history of angioedema related to previous treatment with an ACE inhibitor

Allergy Considerations

- ACE Inhibitor Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse reactions:

- Angioedema: At any time during treatment (especially following first dose) angioedema may occur rarely with ACE inhibitors; it may involve the head and neck (potentially compromising the airway) or the intestine (presenting with abdominal pain). African-Americans and patients with idiopathic or hereditary angioedema may be at an increased risk. Prolonged frequent monitoring may be required especially if tongue, glottis, or larynx are involved as they are associated with airway obstruction. Patients with a history of airway surgery may have a higher risk of airway obstruction. Aggressive early and appropriate management is critical. Use in patients with previous angioedema associated with ACE inhibitor therapy is contraindicated.

- Cholestatic jaundice: A rare toxicity associated with ACE inhibitors includes cholestatic jaundice, which may progress to fulminant hepatic necrosis; discontinue if marked elevation of hepatic transaminases or jaundice occurs.

- Cough: An ACE inhibitor cough is a dry, hacking, nonproductive one that usually occurs within the first few months of treatment and should generally resolve within 1-4 weeks after discontinuation of the ACE inhibitor. Other causes of cough should be considered (eg, pulmonary congestion in patients with heart failure) and excluded prior to discontinuation.

- Hyperkalemia: May occur with ACE inhibitors; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely.

- Hypersensitivity reactions: Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions can occur with ACE inhibitors. Severe anaphylactoid reactions may be seen during hemodialysis (eg, CVVHD) with high-flux dialysis membranes (eg, AN69), and rarely, during low density lipoprotein apheresis with dextran sulfate cellulose. Rare cases of anaphylactoid reactions have been reported in patients undergoing sensitization treatment with hymenoptera (bee, wasp) venom while receiving ACE inhibitors.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can occur with ACE inhibitors (usually with the first several doses); effects are most often observed in volume-depleted patients; correct volume depletion prior to initiation; close monitoring of patient is required especially with initial dosing and dosing increases; blood pressure must be lowered at a rate appropriate for the patient's clinical condition. Although dose reduction may be necessary, hypotension is not a reason for discontinuation of future ACE inhibitor use especially in patients with heart failure where a reduction in systolic blood pressure is a desirable observation.

- Neutropenia/agranulocytosis: Another ACE inhibitor, captopril, has been associated with rare cases of agranulocytosis, neutropenia or leukopenia with myeloid hypoplasia. Patients with renal impairment are at high risk of developing neutropenia. Patients with both renal impairment and collagen vascular disease (eg, systemic lupus erythematosus) are at an even higher risk of developing neutropenia. Periodically monitor CBC with differential in these patients.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic stenosis: Use with caution in patients with severe aortic stenosis; may reduce coronary perfusion resulting in ischemia.

- Cardiovascular disease: Initiation of therapy in patients with ischemic heart disease or cerebrovascular disease warrants close observation due to the potential consequences posed by falling blood pressure (eg, MI, stroke). Fluid replacement, if needed, may restore blood pressure; therapy may then be resumed. Discontinue therapy in patients whose hypotension recurs.

- Cirrhosis: Dosage adjustments are needed in patients with hepatic cirrhosis.

- Collagen vascular disease: Use with caution in patients with collagen vascular disease especially with concomitant renal impairment; may be at increased risk for hematologic toxicity.

- Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Use with caution in patients with HCM and outflow tract obstruction since reduction in afterload may worsen symptoms associated with this condition.

- Renal artery stenosis: Use with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution in pre-existing renal insufficiency; dosage adjustment is needed in severe renal dysfunction (Cl_{cr} <30 mL/minute). Avoid rapid dosage escalation which may lead to further renal impairment.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, ACEIs can cause injury and death to the developing fetus when used in the second and third trimesters. ACEIs should be discontinued as soon as possible once pregnancy is detected.**

Other warnings/precautions:

- Surgery: Use with caution before, during, or immediately after major surgery. Cardiopulmonary bypass, intraoperative blood loss, or vasodilating anesthesia increases endogenous renin release. Use of ACE inhibitors perioperatively will blunt angiotensin II formation and may result in hypotension.

Geriatric ConsiderationsDue to frequent decreases in glomerular filtration (also creatinine clearance) with aging, elderly patients may have exaggerated responses to ACE inhibitors; differences in clinical response due to hepatic changes are not observed. ACE inhibitors may be preferred agents in elderly patients with CHF and diabetes mellitus. Diabetic proteinuria is reduced and insulin sensitivity is enhanced. In general, the side effect profile is favorable in the elderly and causes little or no CNS confusion; use lowest dose recommendations initially. Adjust for renal function. Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.

Pregnancy Risk FactorC (1st trimester); D (2nd and 3rd trimesters)

Pregnancy ConsiderationsDue to adverse events observed in some animal studies, trandolapril is considered pregnancy category C during the first trimester. Based on human data, trandolapril is considered pregnancy category D if used during the second and third trimesters (per the manufacturer; however, one study suggests that fetal injury may occur at anytime during pregnancy). First trimester exposure to ACE inhibitors may cause major congenital malformations. An increased risk of cardiovascular and/or central nervous system malformations was observed in one study; however, an increased risk of teratogenic events was not observed in other studies. Second and third trimester use of an ACE inhibitor is associated with oligohydramnios. Oligohydramnios due to decreased fetal renal function may lead to fetal limb contractures, craniofacial deformation, and hypoplastic lung development. The use of ACE inhibitors during the second and third trimesters is also associated with anuria, hypotension, renal failure (reversible or irreversible), skull hypoplasia, and death in the fetus/neonate. Chronic maternal hypertension itself is also associated with adverse events in the fetus/infant. ACE inhibitors are not recommended during pregnancy to treat maternal hypertension or heart failure. Those who are planning a pregnancy should be considered for other medication options if an ACE inhibitor is currently prescribed or the ACE inhibitor should be discontinued as soon as possible once pregnancy is detected. The exposed fetus should be monitored for fetal growth, amniotic fluid volume, and organ formation. Infants exposed to an ACE inhibitor *in utero*, especially during the second and third trimester, should be monitored for hyperkalemia, hypotension, and oliguria.

[U.S. Boxed Warning]: Based on human data, ACE inhibitors can cause injury and death to the developing fetus when used in the second and third trimesters. ACE inhibitors should be discontinued as soon as possible once pregnancy is detected.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if trandolapril is excreted in breast milk. Breast-feeding is not recommended by the manufacturer.

Pregnancy & Lactation, In-Depth

- Trandolapril in Pregnancy & Lactation

Adverse Reactions **Note:** Frequency ranges include data from hypertension and heart failure trials. Higher rates of adverse reactions have generally been noted in patients with CHF. However, the frequency of adverse effects associated with placebo is also increased in this population.

>1%:

Cardiovascular: Hypotension (<1% to 11%), bradycardia (<1% to 4.7%), intermittent claudication (3.8%), stroke (3.3%), syncope (5.9%)

Central nervous system: Dizziness (1.3% to 23%), asthenia (3.3%)

Endocrine & metabolic: Uric acid increased (15%), hyperkalemia (5.3%), hypocalcemia (4.7%)

Gastrointestinal: Dyspepsia (6.4%), gastritis (4.2%)

Neuromuscular & skeletal: Myalgia (4.7%)

Renal: BUN increased (9%), serum creatinine increased (1.1% to 4.7%)

Respiratory: Cough (1.9% to 35%)

<1% (Limited to important or life-threatening): Chest pain, AV block (first-degree), edema, flushing, palpitation, drowsiness, insomnia, paresthesia, vertigo, pruritus, rash, pemphigus, epistaxis, pharyngitis, upper respiratory tract infection, anxiety, impotence, decreased libido, abdominal distension, abdominal pain, constipation, dyspepsia, diarrhea, vomiting, pancreatitis, leukopenia, neutropenia, thrombocytopenia, increased ALT, muscle pain, gout, dyspnea, angioedema, laryngeal edema, symptomatic hypotension, transaminases elevation, increased bilirubin. Worsening of renal function may occur in patients with bilateral renal artery stenosis or in hypovolemic patients. In addition, a syndrome which may include fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash, eosinophilia and positive ANA, and elevated ESR has been reported with ACE inhibitors.

Drug Interactions

Allopurinol: ACE Inhibitors may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Antacids: May decrease the serum concentration of ACE Inhibitors. *Risk C: Monitor therapy*

Aprotinin: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

AzaTHIOprine: ACE Inhibitors may enhance the neutropenic effect of AzaTHIOprine. *Risk C: Monitor therapy*

CycloSPORINE: ACE Inhibitors may enhance the nephrotoxic effect of CycloSPORINE. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Ferric Gluconate: ACE Inhibitors may enhance the adverse/toxic effect of Ferric Gluconate. *Risk C: Monitor therapy*

Gold Sodium Thiomalate: ACE Inhibitors may enhance the adverse/toxic effect of Gold Sodium Thiomalate. An increased risk of nitritoid reactions has been appreciated. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: ACE Inhibitors may increase the serum concentration of Lithium. *Risk D: Consider therapy modification*

Loop Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Loop Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Salicylates: May diminish the antihypertensive effect of ACE Inhibitors. They may also diminish other beneficial pharmacodynamic effects desired for the treatment of CHF. The effects are likely dose-related. 100 mg doses aspirin appear to cause no problems, whereas 300 mg doses appear to significantly affect ACE Inhibitor efficacy. *Risk C: Monitor therapy*

Sirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Temsirolimus: May enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Thiazide Diuretics: May enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Trimethoprim: May enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Monitoring ParametersBlood pressure; serum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents or herbal products patient may be taking (especially anything that may impact fluid balance or cardiac status). Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, hypovolemia, angioedema, postural hypotension) with first doses and on a regular basis during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsSerum creatinine and potassium; if patient has collagen vascular disease and/or renal impairment, periodically monitor CBC with differential

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed; do not discontinue without consulting prescriber. Do not take antacids within 2 hours of this medication. Take first dose at bedtime. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause dizziness, fainting, or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); or diarrhea (buttermilk, boiled milk, yogurt may help). Report immediately any swelling of face, mouth, lips, tongue or throat. Report chest pain or palpitations; swelling of extremities, mouth, or tongue; skin rash; respiratory difficulty or unusual cough; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 1 mg, 2 mg, 4 mg

Mavik®: 1 mg, 2 mg, 4 mg

Generic AvailableYes

ManufacturerKnoll Pharmaceutical Company

Pricing: U.S. (www.drugstore.com)

Tablets (Mavik)

1 mg (100): $124.62

2 mg (30): $44.28

4 mg (30): $43.99

Tablets (Trandolapril)

2 mg (100): $110.98

4 mg (100): $111.99

Mechanism of ActionTrandolapril is an ACE inhibitor which prevents the formation of angiotensin II from angiotensin I. Trandolapril must undergo enzymatic hydrolysis, mainly in liver, to its biologically active metabolite, trandolaprilat. A CNS mechanism may also be involved in the hypotensive effect as angiotensin II increases adrenergic outflow from the CNS. Vasoactive kallikrein's may be decreased in conversion to active hormones by ACE inhibitors, thus reducing blood pressure.

Pharmacodynamics/Kinetics

Onset of action: 1-2 hours

Peak effect: Reduction in blood pressure: 6 hours

Duration: Prolonged; 72 hours after single dose

Absorption: Rapid

Distribution:

Trandolapril: ~18L

Trandolaprilat (active metabolite) is very lipophilic in comparison to other ACE inhibitors

Protein binding: 80%

Metabolism: Hepatically hydrolyzed to active metabolite, trandolaprilat

Bioavailability:

Trandolapril: 10%

Trandolaprilat: 70%

Half-life elimination:

Trandolapril: 6 hours; Trandolaprilat: Effective: 10 hours, Terminal: 24 hours

Time to peak: Parent: 1 hour; Active metabolite trandolaprilat: 4-10 hours

Excretion: Urine (33%); feces (66%)

Clearance: Reduce dose in renal failure; creatinine clearances ≤30 mL/minute result in accumulation of active metabolite

Related Information

- Angiotensin Agents

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, nervousness, or insomnia

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels; concurrent use with low potency antipsychotics and TCAs may produce additive hypotensive effects

Cardiovascular Considerations

Heart Failure: The ACC/AHA 2005 Heart Failure Guidelines recommend that ACE inhibitors be used in patients with a reduced EF (with or without heart failure symptoms) unless contraindicated. ACE inhibitors decrease morbidity and mortality in patients with asymptomatic and symptomatic left ventricular dysfunction. In this situation, they decrease hospitalizations for, and retard progression to, congestive heart failure. When used in patients with heart failure, the target dose should be achieved, if possible. Lower daily doses of ACE inhibitors have demonstrated the same mortality effects as high doses, but have not decreased hospitalizations to the extent that high-dose ACE inhibitors have, as demonstrated in the ATLAS study (Packer M, 1999).

Hypertension: The ALLHAT study (ALLHAT Collaborative Group, 2002) compared CV outcomes of lisinopril, amlodipine, or chlorthalidone in hypertensive patients having at least one other risk factor for coronary heart disease. Investigators found no difference between the groups on the primary outcome of fatal coronary disease or nonfatal MI. The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors or angiotensin receptor blockers (ARBs) can be beneficial in patients with hypertension and LVH without symptoms of heart failure. JNC 7 suggests that patients can benefit from treatment with an ACE inhibitor if they have hypertension **and** heart failure, acute myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, or history of stroke.

Vascular Disease: The ACC/AHA 2005 Heart Failure Guidelines suggest that ACE inhibitors can be useful in preventing heart failure in patients who have a history of atherosclerotic vascular disease, diabetes, or hypertension with associated cardiovascular risk factors. The HOPE trial (Heart Outcomes Prevention Evaluation Study Investigators, 2000) investigated the value of an ACE inhibitor (ramipril 5-10 mg daily) versus placebo in patients who had evidence of vascular disease or diabetes (one other cardiovascular risk factor) and were at least 55 years of age. Patients were excluded if they had a low ejection fraction, heart failure, or were on an ACE inhibitor. The primary outcome was a composite of death from cardiovascular cause, myocardial infarction, or stroke; 9297 patients were enrolled and randomized. Ramipril significantly reduced the risk of death from CV causes, MI, or stroke over placebo. New cases of diabetes were also reduced in the ramipril group. In the EUROPA trial, patients with stable coronary artery disease (at low risk for cardiovascular events) received perindopril or placebo and were evaluated for incidence of cardiovascular events after four years of treatment. In this randomized, placebo-controlled, prospective study, 12,218 patients received either perindopril (8 mg/day, n=6110) or placebo (n=6108) and were assessed for the primary endpoint of a cardiovascular event, defined as cardiovascular death, myocardial infarction, or cardiac arrest. The study population was well balanced with respect to baseline demographics and concomitant medication use (including beta-blockers, platelet inhibitors, antihyperlipidemics, calcium channel blockers, nitrates, and diuretics). Intent-to-treat analysis revealed that 603 (10%) of placebo patients experienced the primary endpoint of a cardiovascular event compared to 488 (8%) of perindopril-receiving patients, for a 20% relative risk reduction (p=0.0003). This result was not influenced by presence of other comorbidities (eg, diabetes, hypertension) or concomitant beta-blocker, calcium channel blocker, or lipid-lowering therapies. Withdrawal from the study (postrandomization) due to adverse reactions was similar between treatment groups. Number needed to treat analysis suggests that treatment of 50 patients over a 4-year period will prevent one major cardiovascular event.

Acute Coronary Syndromes: In the treatment of unstable angina/non-ST-segment elevation MI, ACE inhibitors are recommended when hypertension persists despite treatment with nitroglycerin and a beta-blocker in patients with LV systolic dysfunction or CHF and in ischemic patients with diabetes (Class I). ACE inhibitors are also recommended for all post-ACS individuals (Class IIa). According to 2004 ACC/AHA STEMI guidelines, an ACE inhibitor should be administered orally within the first 24 hours of STEMI to patients with anterior infarction, pulmonary congestion, or LVEF <0.4, in the absence of hypotension or known contraindications to this class of medicines. In the emergency management of complicated STEMI, a short-acting ACEI (eg, captopril 1-6.25 mg) may be added once the patient's systolic blood pressure is >100 mm Hg and not <30 mm Hg below baseline. The VALIANT trial evaluated the effects of valsartan (target dose: 160 mg twice daily), captopril (target dose: 50 mg twice daily), and the combination (target doses: valsartan 80 mg twice daily and captopril 150 mg once daily) in a randomized, double-blind trial of patients with acute MI (0.5-10 days post-MI) complicated by left ventricular systolic dysfunction, heart failure, or both. Enrollment in the study numbered 14,703 patients and followed for a median of 24.7 months. There was no difference in the primary endpoint (all cause mortality) among the 3 groups. There was no difference in incidence of CV death, recurrent MI, or hospitalization for heart failure either. Hypotension and renal dysfunction occurred significantly more often in the valsartan group than captopril alone. Cough, rash, and taste disturbances occurred more often in the captopril group. The authors (Pfeffer MA, 2003) concluded that valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after MI. Combining valsartan with captopril increased the rate of adverse events without improving survival.

Potential Adverse Events: ACE inhibitor therapy may elicit rapid increases in potassium and creatinine, especially when used in patients with bilateral renal artery stenosis. When ACE inhibition is introduced in patients with pre-existing diuretic therapy who are hypovolemic, the ACE inhibitor may induce acute hypotension. In those patients experiencing cough on an ACE inhibitor, the ACE inhibitor may be discontinued and, if necessary, ARB therapy instituted. Because of the potent teratogenic effects of ACE inhibitors, these drugs should be avoided, if possible, when treating women of childbearing potential not on effective birth control measures.

Drug Interactions: Concomitant indomethacin therapy may blunt the reduction in sitting and 24-hour ambulatory diastolic blood pressure. Use of NSAIDs should be avoided or limited, with monitoring of blood pressure control in this setting. In patients with heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

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International Brand NamesGopten (AT, AU, BE, BG, BR, CH, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, HR, HU, ID, IE, IT, LU, MX, NL, NO, PK, PL, PT, RU, SE, TR, UY); Nortensin (AR); Odace (PH); Odrik (AU, DK, ES, FI, FR, GR, IE, LU, PE, PT); Udrik (DE); Zetpril (IN)

Tranexamic Acid

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

Cyklokapron® may be confused with cycloSPORINE

Pronunciation(tran eks AM ik AS id)
U.S. Brand NamesCyklokapron®
Canadian Brand NamesCyklokapron®; Tranexamic Acid Injection BP
Pharmacologic CategoryAntihemophilic Agent
Use: Labeled IndicationsShort-term use (2-8 days) in hemophilia patients during and following tooth extraction to reduce or prevent hemorrhage
Use: Unlabeled/InvestigationalHas been used as an alternative to aminocaproic acid for subarachnoid hemorrhage
Dosing: Adults**Hemophilia patients, during and following tooth extraction:** I.V.: 10 mg/kg immediately before surgery, then 25 mg/kg/dose orally 3-4 times/day for 2-8 days

Alternatively:

Oral: 25 mg/kg 3-4 times/day beginning 1 day prior to surgery

I.V.: 10 mg/kg 3-4 times/day in patients who are unable to take oral

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren: Refer to adult dosing (limited data in connection with tooth extraction).
Dosing: Renal Impairment

Cl_{cr} 50-80 mL/minute: Administer 50% of normal dose or 10 mg/kg twice daily I.V. or 15 mg/kg twice daily orally.

Cl_{cr} 10-50 mL/minute: Administer 25% of normal dose or 10 mg/kg/day I.V. or 15 mg/kg/day orally.

Cl_{cr} <10 mL/minute: Administer 10% of normal dose or 10 mg/kg/dose every 48 hours I.V. or 15 mg/kg/dose every 48 hours orally.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.May be given by direct I.V. injection at a maximum rate of 100 mg/minute; compatible with dextrose, saline, and electrolyte solutions; use plastic syringe only for I.V. push
CompatibilityStable in dextrose, saline, electrolyte solutions; **incompatible** with solutions containing penicillin.
ContraindicationsAcquired defective color vision; active intravascular clotting; subarachnoid hemorrhage; concurrent factor IX complex or anti-inhibitor coagulant concentrates
Warnings/Precautions

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease.
- Cerebrovascular disease: Use with caution in patients with cerebrovascular disease.
- Renal impairment: Use with caution in patients with renal impairment; dosage modification required.
- Subarachnoid hemorrhage: When used for subarachnoid hemorrhage, ischemic complications may occur.
- Thromboembolic disease: Use with caution in patients with thromboembolic disease; may increase risk of thrombosis.

Other warnings/precautions:

- Eye exams: Ophthalmic exam before and during therapy required if patient is treated beyond several days.

Pregnancy Risk FactorB
LactationEnters breast milk/use caution
Adverse Reactions

>10%: Gastrointestinal: Diarrhea, nausea, vomiting

1% to 10%:

Cardiovascular: Hypotension, thrombosis

Ocular: Blurred vision

<1%: Unusual menstrual discomfort

Postmarketing and/or case reports: Deep venous thrombosis (DVT), pulmonary embolus (PE), renal cortical necrosis, retinal artery obstruction, retinal vein obstruction, ureteral obstruction

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

Anti-inhibitor Coagulant Complex: Antifibrinolytic Agents may enhance the thrombogenic effect of Anti-inhibitor Coagulant Complex. *Risk D: Consider therapy modification*

Fibrinogen Concentrate (Human): Antifibrinolytic Agents may enhance the adverse/toxic effect of Fibrinogen Concentrate (Human). Specifically, the risk for thrombosis may be increased. Fibrinogen Concentrate (Human) may enhance the adverse/toxic effect of Antifibrinolytic Agents. Specifically, the risk for thrombosis may be increased. *Risk C: Monitor therapy*

Reference Range5-10 mcg/mL is required to decrease fibrinolysis

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 100 mg/mL (10 mL)

Tablet: 500 mg [Not marketed in U.S.; available from manufacturer for select cases]

Generic AvailableNo

Mechanism of ActionForms a reversible complex that displaces plasminogen from fibrin resulting in inhibition of fibrinolysis; it also inhibits the proteolytic activity of plasmin

Pharmacodynamics/Kinetics

Half-life elimination: 2-10 hours

Excretion: Urine (>90% as unchanged drug)

Dental Health Professional ConsiderationsAntifibrinolytic drugs are useful for the control of bleeding after dental extractions in patients with hemophilia because the oral mucosa and saliva are rich in plasminogen activators.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

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International Brand NamesAmchafibrin (ES); Caprilon (FI); Ciclokapron (VE); Clonex (ID); Cyklokapron (AE, AT, AU, BH, CH, CY, DE, DK, EE, EG, FI, GB, HK, IE, IL, IQ, IR, JO, KW, LB, LY, NL, NO, OM, QA, SA, SE, SY, YE, ZA); Dostan (PH); Espercil (CN); Exacyl (BE, CZ, FR, HN, LU, PL); Fibrinon (PH); Fimoplas (PH); Hemoclot (PH); Hemostan (PH); Hemotrex (PH); Hexakapron (IL); Kalnex (ID); Micranex (PH); Nexa (ID); Qualixamin (HK); Rikaparin (TW); Ronex (ID); Theranex (ID); Tiren (MY); Tramic (TH); Tranarest (IN); Tranex (IT); Tranexam (TW); Tranexic (TW); Tranexid (ID); Transamin (BR, CL, HK, ID, JP, KP, MY, PE, PK, TH, TW); Transamina (UY); Trenaxin (ID, PH)

Tranylcypromine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(tran il SIP roe meen)

U.S. Brand NamesParnate®

Canadian Brand NamesParnate®

Pharmacologic CategoryAntidepressant, Monoamine Oxidase Inhibitor

Use: Labeled IndicationsTreatment of major depressive episode without melancholia

Use: Unlabeled/InvestigationalPost-traumatic stress disorder

Dosing: Adults**Depression:** Oral: 10 mg twice daily, increase by 10 mg increments at 1- to 3-week intervals; maximum: 60 mg/day; usual effective dose: 30 mg/day

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsAvoid foods containing tryptophan and caffeine. Avoid tyramine-containing foods/beverages. Some examples include aged or matured cheese, air-dried or cured meats (including sausages and salamis), fava or broad bean pods, tap/draft beers, Marmite concentrate, sauerkraut, soy sauce and other soybean condiments.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to tranylcypromine, other MAO inhibitors, dibenzazepine derivatives, or any component of the formulation; cardiovascular disease; cerebrovascular defect; headache history; hepatic disease; hypertension; pheochromocytoma; renal disease; concurrent use of antihistamines, antiparkinson drugs, antihypertensives, bupropion, buspirone, CNS depressants, dexfenfluramine, dextromethorphan, diuretics, ethanol, meperidine, and SSRIs; general anesthesia (discontinue 10 days prior to elective surgery); local vasoconstrictors; spinal anesthesia (hypotension may be exaggerated); sympathomimetics (and related compounds); foods high in tyramine content; supplements containing tyrosine, phenylalanine, tryptophan, or caffeine

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription.**Tranylcypromine is not FDA approved for treatment of children and adolescents.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Tranylcypromine is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Hypertensive crisis: May occur with foods/supplements high in tyramine, tryptophan, phenylalanine, or tyrosine content; treatment with phentolamine is recommended for hypertensive crisis.

- Orthostatic hypotension: May cause orthostatic hypotension (especially at dosages >30 mg/day); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus; sensitization to the effects of insulin may occur, monitor blood glucose closely.

- Glaucoma: Use with caution in patients with glaucoma.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

- Thyroid dysfunction: Use with caution in patients with hyperthyroidism.

Concurrent drug therapy issues:

- High potential for interactions: Do not use with other MAO inhibitors or antidepressants. Avoid products containing sympathomimetic stimulants or dextromethorphan. Concurrent use with antihypertensive agents may lead to exaggeration of hypotensive effects.

Special populations:

- Elderly: The MAO inhibitors are effective and generally well tolerated by older patients. It is the potential interactions with tyramine or tryptophan-containing foods and other drugs, and their effects on blood pressure that have limited their use.

Other warnings/precautions:

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

- Myelography: Discontinue at least 48 hours prior to myelography.

Geriatric ConsiderationsMAO inhibitors are effective and generally well tolerated by older patients. Potential interactions with tyramine- or tryptophan-containing foods, other drugs, and adverse effects on blood pressure have limited use of MAO inhibitors. They are usually reserved for patients who do not tolerate or respond to traditional “cyclic” or “second generation” antidepressants. Tranylcypromine is the preferred MAO inhibitor because its enzymatic-blocking effects are more rapidly reversed. The brain activity of monoamine oxidase increases with age and even more so in patients with Alzheimer's disease. Therefore, MAO inhibitors may have an increased role in treating depressed patients with Alzheimer's disease.

Pregnancy Risk FactorC

LactationEnters breast milk/not recommended

Adverse ReactionsFrequency not defined.

Cardiovascular: Edema, orthostatic hypotension, palpitation, tachycardia

Central nervous system: Agitation, akinesia, anxiety, ataxia, chills, confusion, disorientation, dizziness, drowsiness, fatigue, headache, hyperreflexia, insomnia, mania, memory loss, restlessness, sleep disturbances, twitching

Dermatologic: Alopecia, cystic acne (flare), pruritus, rash, urticaria, scleroderma (localized)

Endocrine & metabolic: Hypernatremia, hypermetabolic syndrome; sexual dysfunction (anorgasmia, ejaculatory disturbances, impotence); SIADH

Gastrointestinal: Abdominal pain, anorexia, constipation, diarrhea, nausea, vomiting, weight gain, xerostomia

Genitourinary: Incontinence, urinary retention

Hematologic: Agranulocytosis, anemia, leukopenia, thrombocytopenia

Hepatic: Hepatitis

Neuromuscular & skeletal: Akinesis, muscle spasm, myoclonus, numbness, paresthesia, tremor, weakness

Ocular: Blurred vision, glaucoma

Otic: Tinnitus

Miscellaneous: Diaphoresis

Metabolism/Transport Effects**Inhibits** CYP1A2 (moderate), 2A6 (strong), 2C8 (weak), 2C9 (weak), 2C19 (moderate), 2D6 (moderate), 2E1 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): MAO Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Primarily with oral administration of phenylephrine. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha-/Beta-Agonists (Indirect-Acting): MAO Inhibitors may enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Alpha1-Agonists: MAO Inhibitors may enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Alpha2-Agonists (Ophthalmic): MAO Inhibitors may enhance the hypertensive effect of Alpha2-Agonists (Ophthalmic). *Risk X: Avoid combination*

Altretamine: May enhance the orthostatic effect of MAO Inhibitors. *Risk C: Monitor therapy*

Amphetamines: MAO Inhibitors may enhance the hypertensive effect of Amphetamines. *Risk X: Avoid combination*

Anilidopiperidine Opioids: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. Management: Avoid use of fentanyl (and other anilidopiperidine opioids when possible) in patients who have used a monoamine oxidase inhibitor within the past 14 days due to reports of unpredictable but severe adverse effects. *Risk D: Consider therapy modification*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Atomoxetine: MAO Inhibitors may enhance the neurotoxic (central) effect of Atomoxetine. *Risk X: Avoid combination*

Beta2-Agonists: MAO Inhibitors may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: MAO Inhibitors may enhance the neurotoxic (central) effect of BuPROPion. *Risk X: Avoid combination*

BusPIRone: May enhance the adverse/toxic effect of MAO Inhibitors. Elevated blood pressure has been reported. *Risk X: Avoid combination*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

COMT Inhibitors: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Cyclobenzaprine: May enhance the serotonergic effect of MAO Inhibitors. This could result in serotonin syndrome. *Risk X: Avoid combination*

CYP1A2 Substrates: CYP1A2 Inhibitors (Moderate) may decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP2A6 Substrates: CYP2A6 Inhibitors (Strong) may decrease the metabolism of CYP2A6 Substrates. *Risk D: Consider therapy modification*

CYP2C19 Substrates: CYP2C19 Inhibitors (Moderate) may decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

Dexmethylphenidate: MAO Inhibitors may enhance the hypertensive effect of Dexmethylphenidate. *Risk X: Avoid combination*

Dextromethorphan: MAO Inhibitors may enhance the serotonergic effect of Dextromethorphan. This may cause serotonin syndrome. *Risk X: Avoid combination*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Levodopa: May enhance the adverse/toxic effect of MAO Inhibitors. Of particular concern is the development of hypertensive reactions when levodopa is used with nonselective MAOI. *Risk D: Consider therapy modification*

Linezolid: MAO Inhibitors may enhance the adverse/toxic effect of Linezolid. *Risk X: Avoid combination*

Lithium: MAO Inhibitors may enhance the adverse/toxic effect of Lithium. *Risk C: Monitor therapy*

Maprotiline: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

Meperidine: MAO Inhibitors may enhance the serotonergic effect of Meperidine. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methyldopa: MAO Inhibitors may enhance the adverse/toxic effect of Methyldopa. *Risk X: Avoid combination*

Methylphenidate: MAO Inhibitors may enhance the hypertensive effect of Methylphenidate. *Risk X: Avoid combination*

Mirtazapine: MAO Inhibitors may enhance the neurotoxic (central) effect of Mirtazapine. *Risk X: Avoid combination*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the adverse/toxic effect of MAO Inhibitors. Specifically, the risk of serotonin syndrome or other serotonergic adverse events may be increased. *Risk X: Avoid combination*

Rauwolfia Alkaloids: MAO Inhibitors may enhance the adverse/toxic effect of Rauwolfia Alkaloids. Existing MAOI therapy can result in paradoxical effects of added rauwolfia alkaloids (eg, excitation, hypertension). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Serotonin 5-HT1D Receptor Agonists: MAO Inhibitors may decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. **Exceptions:** Eletriptan; Frovatriptan; Naratriptan. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: MAO Inhibitors may enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake

Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of MAO Inhibitors. *Risk X: Avoid combination*

Thioridazine: CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. *Risk X: Avoid combination*

TraMADol: May enhance the neuroexcitatory and/or seizure-potentiating effect of MAO Inhibitors. *Risk D: Consider therapy modification*

Tricyclic Antidepressants: MAO Inhibitors may enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (based on CNS depressant effects and potential tyramine content)

Food: Concurrent ingestion of foods rich in tyramine may cause sudden and severe high blood pressure (hypertensive crisis). Avoid tyramine-containing foods with MAO-Is. Food's freshness is also an important concern; improperly stored or spoiled food can create an environment where tyramine concentrations may increase.

Herb/Nutraceuticals: Avoid valerian, St John's wort, SAMe. Avoid supplements containing caffeine, gingko, yohimbime, ephedra, tyrosine, tryptophan or phenylalanine. Ingestion of large quantities may increase the risk of severe side effects (eg, hypertensive reactions, serotonin syndrome).

Monitoring ParametersBlood pressure, mental status, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased)

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Evaluate need for continued therapy on a regular basis. Assess results of laboratory tests, therapeutic effectiveness according to rationale for therapy, and adverse reactions at beginning of therapy and periodically with long-term use. Monitor blood pressure. Monitor for CNS depression. Observe for clinical worsening, suicidality, or unusual behavior changes, especially during the initial few months of therapy or during dosage changes. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsBlood glucose

Patient EducationTake exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results. Take in the morning to reduce the incidence of insomnia. Avoid alcohol, caffeine, and other prescription or OTC medications not approved by prescriber. Avoid tyramine-containing foods (eg, aged or matured cheese, air-dried or cured meats [including sausages and salamis], fava or broad bean pods, tap/draft beers, Marmite concentrate, sauerkraut, soy sauce and other soybean condiments); see prescriber for complete list of foods to be avoided. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, monitor blood glucose closely at the beginning of therapy. May cause hypoglycemia. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); anorexia or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); diarrhea (buttermilk, yogurt, or boiled milk may help); or orthostatic hypotension (use caution when climbing stairs or changing position from lying or sitting to standing); or altered sexual ability (reversible). Report persistent excessive sedation; muscle cramping, tremors, weakness, or change in gait; chest pain, palpitations, rapid heartbeat, or swelling of extremities; vision changes; suicidal ideation; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 10 mg

Generic AvailableNo

ManufacturerSmithKline Beecham Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Parnate)

10 mg (60): $86.45

Mechanism of ActionTranylcypromine is a nonhydrazine monoamine oxidase inhibitor. It increases endogenous concentrations of epinephrine, norepinephrine, dopamine, and serotonin through inhibition of the enzyme (monoamine oxidase) responsible for the breakdown of these neurotransmitters.

Pharmacodynamics/Kinetics

Onset of action: Therapeutic: 2 days to 3 weeks continued dosing

Half-life elimination: 90-190 minutes

Time to peak, serum: ~2 hours

Excretion: Urine

Related Information

- Antidepressant Agents
- Teratogenic Risks of Psychotropic Medications
- Tyramine Content of Foods

Pharmacotherapy PearlsTranylcypromine has a more rapid onset of therapeutic effect than other MAO inhibitors, but causes more severe hypertensive reactions.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Orthostatic hypotension. Avoid use as an analgesic due to toxic reactions with MAO inhibitors. Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAttempts should be made to avoid use of vasoconstrictor due to possibility of hypertensive episodes with monoamine oxidase inhibitors

Mental Health CommentNot commonly used due to a required low tyramine diet and drug-drug interactions. It is estimated that 20 mg of tranylcypromine = 40 mg of isocarboxazid = 45 mg phenelzine. Phenelzine and isocarboxazid are hydrazine MAO inhibitors and tranylcypromine is a nonhydrazine. These drugs produce irreversible inhibition of MAO inhibitors. The half-life for regeneration is 2-3 days. Therefore, a 2-week period is required when switching from an MAO inhibitor to another antidepressant.

While hypertension and hypertensive crisis are risks associated with MAO inhibitor therapy, orthostatic hypotension may also occur. Orthostasis associated with MAO inhibitor therapy is not related to alpha$_1$-adrenergic receptor blockade. The “false transmitter” concept is used to explain this side effect. This concept states that MAO inhibitors promote gradual accumulation in sympathetic nerve ending of amines lacking direct sympathomimetic activity (octopamine) at the expense of the normal synaptic transmitter, norepinephrine. Since octopamine has little ability to activate either alpha- or beta-adrenergic receptors, a functional impairment of sympathetic neurotransmission occurs.

The MAO inhibitors are usually reserved for patients who do not tolerate or respond to other antidepressants. The brain activity of monoamine oxidase increases with age and even more so in patients with Alzheimer's disease. Therefore, the MAO inhibitors may have an increased role in patients with Alzheimer's disease who are depressed. Phenelzine is less stimulating than tranylcypromine.

Index TermsTransamine Sulphate; Tranylcypromine Sulfate

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International Brand NamesJatrosom (DE); Parnate (AE, AR, AU, BF, BH, BJ, BR, CI, CY, DE, EG, ES, ET, GB, GH, GM, GN, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW)

Trastuzumab-Paclitaxel (Weekly)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer

Regimen Use Breast cancer

Index Terms Paclitaxel (Weekly)-Trastuzumab

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Week 1:

Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1

[total dose/week 1 = 4 mg/kg]

Paclitaxel: I.V.: 90 mg/m^2 day 2

[total dose/week 1 = 90 mg/m^2]

Subsequent weeks:

Paclitaxel: I.V.: 90 mg/m^2 day 1

[total dose/week = 90 mg/m^2]

Trastuzumab: I.V.: 2 mg/kg day 1

[total dose/week = 2 mg/kg]

Repeat weekly

Variation 2:

Week 1:

Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1

[total dose/week 1 = 4 mg/kg]

Paclitaxel: I.V.: 80 mg/m^2 day 1

[total dose/week 1 = 80 mg/m^2]

Subsequent weeks:

Trastuzumab: I.V.: 2 mg/kg day 1

[total dose/week = 2 mg/kg]

Paclitaxel: I.V.: 80 mg/m^2 day 1

[total dose/week = 80 mg/m^2]

Repeat weekly

References

Variation 1:

Seidman AD, Fornier MN, Esteva FJ, et al, "Weekly Trastuzumab and Paclitaxel Therapy for Metastatic Breast Cancer With Analysis of Efficacy by HER2 Immunophenotype and Gene Amplification," *J Clin Oncol*, 2001, 19(10):2587-95.[PubMed 11352950]

Variation 2:

Seidman AD, Berry D, Cirrincione C, et al, "Randomized Phase III Trial of Weekly Compared With Every-3-Weeks Paclitaxel for Metastatic Breast Cancer, With Trastuzumab for all HER-2 Overexpressors and Random Assignment to Trastuzumab or Not in HER-2 Nonoverexpressors: Final Results of Cancer and Leukemia Group B Protocol 9840," *J Clin Oncol*, 2008, 26(10):1642-9.[PubMed 18375893]

Trastuzumab-Paclitaxel-Carboplatin

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Breast Cancer]

Regimen UseBreast cancer

Index TermsPaclitaxel-Carboplatin-Trastuzumab

Regimen

Cycle 1:

- Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1
  - **followed by** I.V.: 2 mg/kg/day days 8 and 15
    - [total dose/cycle 1 = 8 mg/kg]
- Paclitaxel: I.V.: 175 mg/m^2 day 2
  - [total dose/cycle = 175 mg/m^2]
- Carboplatin: I.V.: AUC 6 day 2
  - [total dose/cycle = AUC = 6]
- Treatment cycle is 21 days

Subsequent cycles:

- Trastuzumab: I.V.: 2 mg/kg/day days 1, 8, and 15
  - [total dose/cycle = 6 mg/kg]
- Paclitaxel: I.V.: 175 mg/m^2 day 2
  - [total dose/cycle = 175 mg/m^2]
- Carboplatin: I.V.: AUC 6 day 2
  - [total dose/cycle = AUC = 6]
- Repeat cycle every 21 days for a total of at least 6 cycles (continue weekly trastuzumab after chemotherapy until disease progression or unacceptable toxicity)

References

Robert N, Leyland-Jones B, Asmar L, et al, "Randomized Phase III Study of Trastuzumab, Paclitaxel, and Carboplatin Compared With Trastuzumab and Paclitaxel in Women With HER-2-Overexpressing Metastatic Breast Cancer," *J Clin Oncol*, 2006, 24(18):2786-92.[PubMed 16782917]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

Index TermsPaclitaxel-Trastuzumab

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Cycle 1:

Paclitaxel: I.V.: 175 mg/m^2 day 1

[total dose/cycle = 175 mg/m^2]

Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1

followed by I.V.: 2 mg/kg/day days 8 and 15

[total dose/cycle 1 = 8 mg/kg]

Treatment cycle is 21 days

Subsequent cycles:

Paclitaxel: I.V.: 175 mg/m^2 day 1

[total dose/cycle = 175 mg/m^2]

Trastuzumab: I.V.: 2 mg/kg/day days 1, 8, and 15

[total dose/cycle = 6 mg/kg]

Repeat cycle every 21 days for a total of at least 6 cycles

Variation 2:

Cycle 1:

Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1

followed by I.V.: 2 mg/kg/day days 8 and 15

[total dose/cycle 1 = 8 mg/kg]

Paclitaxel: I.V.: 175 mg/m^2 day 2

[total dose/cycle = 175 mg/m^2]

Treatment cycle is 21 days

Subsequent cycles:

Trastuzumab: I.V.: 2 mg/kg/day days 1, 8, and 15

[total dose/cycle = 6 mg/kg]

Paclitaxel: I.V.: 175 mg/m^2 day 2

[total dose/cycle = 175 mg/m^2]

Repeat cycle every 21 days for a total of at least 6 cycles (continue weekly trastuzumab after chemotherapy until disease progression or unacceptable toxicity)

References

Variation 1:

Slamon DJ, Leyland-Jones B, Shak S, et al, “Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer That Overexpresses HER2,” *N Engl J Med*, 2001, 344(11):783-92.[PubMed 11248153]

Variation 2:

Robert N, Leyland-Jones B, Asmar L, et al, “Randomized Phase III Study of Trastuzumab, Paclitaxel, and Carboplatin Compared With Trastuzumab and Paclitaxel in Women With HER-2-Overexpressing Metastatic Breast Cancer,” *J Clin Oncol*, 2006, 24(18):2786-92.[PubMed 16782917]

Trastuzumab

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(tras TU zoo mab)

U.S. Brand NamesHerceptin®

Canadian Brand NamesHerceptin®

Pharmacologic CategoryAntineoplastic Agent, Monoclonal Antibody; Monoclonal Antibody

Use: Labeled IndicationsAdjuvant treatment of HER-2 overexpressing breast cancer; treatment of HER-2 overexpressing metastatic breast cancer

Dosing: AdultsDetails concerning dosing in combination regimens should also be consulted.

Adjuvant treatment of breast cancer: I.V. infusion:

With concurrent paclitaxel or docetaxel:

Initial loading dose: 4 mg/kg infused over 90 minutes

Maintenance dose: 2 mg/kg infused over 30 minutes weekly for total of 12 weeks, followed 1 week later (when concurrent chemotherapy completed) by 6 mg/kg infused over 30-60 minutes every 3 weeks for total therapy duration of 52 weeks

With concurrent docetaxel/carboplatin:

Initial loading dose: 4 mg/kg infused over 90 minutes

Maintenance dose: 2 mg/kg infused over 30 minutes weekly for total of 18 weeks, followed 1 week later (when concurrent chemotherapy completed) by 6 mg/kg infused over 30-60 minutes every 3 weeks for total therapy duration of 52 weeks

Following completion of anthracycline-based chemotherapy:

Initial loading dose: 8 mg/kg infused over 90 minutes

Maintenance dose: 6 mg/kg infused over 30 minutes every 3 weeks for total therapy duration of 52 weeks

Metastatic breast cancer (either as a single agent or in combination with paclitaxel): I.V. infusion:

Initial loading dose: 4 mg/kg infused over 90 minutes

Maintenance dose: 2 mg/kg infused over 30 minutes weekly until disease progression

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentNo adjustment necessary.

Dosing: Adjustment for Toxicity

Cardiotoxicity: LVEF ≥16% decrease from baseline within normal limits or LVEF below normal limits and ≥10% decrease from baseline: Withhold treatment for 4 weeks and repeat LVEF every 4 weeks. May resume trastuzumab treatment if LVEF returns to normal limits within 4-8 weeks and remains at ≤15% decrease from baseline value. Discontinue permanently for persistent (>8 weeks) LVEF decline or for >3 incidents of treatment interruptions for cardiomyopathy.

Infusion-related events:

Mild-moderate infusion reactions: Decrease infusion rate

Dyspnea, clinically significant hypotension: Interrupt infusion

Severe or life-threatening infusion reactions: Consider permanent discontinuation

Dosing: Combination Regimens

Breast cancer:

AC-Paclitaxel-Trastuzumab

Capecitabine-Trastuzumab

Docetaxel-Trastuzumab

Docetaxel-Trastuzumab-Carboplatin

Docetaxel-Trastuzumab-Cisplatin

Docetaxel-Trastuzumab-FEC

Docetaxel (Weekly)-Trastuzumab

Trastuzumab-Paclitaxel

Trastuzumab-Paclitaxel-Carboplatin

Trastuzumab-Paclitaxel (Weekly)

Vinorelbine-Trastuzumab

Vinorelbine-Trastuzumab-FEC

Administration: I.V.Administered by I.V. infusion; loading doses are infused over 90 minutes; maintenance doses may be infused over 30 minutes if tolerated. Do not administer I.V. push or by rapid bolus. Do not administer with D_5W.

Administration: I.V. DetailObserve patients closely during the infusion for fever, chills, or other infusion-related symptoms. Treatment with acetaminophen, diphenhydramine, and/or meperidine is usually effective for managing infusion-related events.

pH: 6

StoragePrior to reconstitution, store intact vials under refrigeration at 2°C to 8°C (36°F to 46°F). Following reconstitution with bacteriostatic SWFI, the solution in the vial is stable refrigerated for 28 days from the date of reconstitution; do not freeze. Solutions reconstituted with sterile water for injection without preservatives must be used immediately. The solution diluted in 250 mL NS for infusion is stable for 24 hours refrigerated; do not freeze.

ReconstitutionReconstitute each vial with 20 mL of bacteriostatic sterile water for injection to a concentration of 21 mg/mL. Swirl gently; do not shake. Allow vial to rest for ~5 minutes. If the patient has a known hypersensitivity to benzyl alcohol, trastuzumab may be reconstituted with sterile water for injection without preservatives, which must be used immediately. Determine the appropriate volume for the trastuzumab dose and further dilute in 250 mL NS prior to administration. Avoid rapid expulsion from syringe; gently invert bag to mix

Compatibility Stable in NS; **incompatible** with D_5W.

ContraindicationsThere are no contraindications listed within the manufacturer’s labeling.

Warnings/Precautions

Boxed warnings:

- Cardiac toxicity: See “Concerns related to adverse effects” below.
- Infusion reactions: See “Concerns related to adverse effects” below.
- Pulmonary toxicity: See “Concerns related to adverse effects” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Cardiomyopathy: **[U.S. Boxed Warning]: Trastuzumab is associated with symptomatic and asymptomatic reductions in left ventricular ejection fraction (LVEF) and severe heart failure (HF) and may result in mural thrombus formation and stroke, and even cardiac death; discontinue for cardiomyopathy.** Evaluate LVEF in all patients prior to and during treatments. Extreme caution should be used in patients with pre-existing cardiac disease or dysfunction. Concomitant administration of anthracyclines and prior exposure to anthracyclines or radiation therapy significantly increases the risk of cardiomyopathy; other potential risk factors include advanced age, high or low body mass index, smoking, diabetes, and hyper/hypothyroidism. Discontinuation should be strongly considered in patients who develop a clinically significant reduction in LVEF during therapy; treatment with HF medications (eg, ACE inhibitors, beta-blockers) should be initiated. Cardiomyopathy due to trastuzumab is generally reversible over a period of 1-3 months after discontinuation. (When LVEF returns to baseline, reinitiation may be considered if indicated.) Trastuzumab is also associated with arrhythmias and hypertension.

- Infusion reactions: **[U.S. Boxed Warning]: Infusion reactions (including fatalities) have been associated with use; discontinue for anaphylaxis or angioedema.** Most reactions occur during or within 24 hours of the first infusion; interrupt infusion for dyspnea or significant hypotension. Retreatment of patients who experienced severe hypersensitivity reactions has been attempted (with premedication). Some patients tolerated retreatment, while others experienced a second severe reaction.

- Pulmonary toxicity: **[U.S. Boxed Warning]: May cause serious pulmonary toxicity (dyspnea, hypoxia, interstitial pneumonitis, pulmonary infiltrates, pleural effusion, noncardiogenic pulmonary edema, pulmonary insufficiency, acute respiratory distress syndrome [ARDS], and/or pulmonary fibrosis); discontinue for ARDS or interstitial pneumonitis.** Use caution in patients with pre-existing pulmonary disease or patients with extensive pulmonary tumor involvement; these patient populations may have more severe toxicity. Pulmonary events may occur during or within 24 hours of administration; delayed reactions have occurred.

Concurrent drug therapy issues:

- Chemotherapy: When used in combination with myelosuppressive chemotherapy, trastuzumab may increase the incidence of neutropenia (moderate-to-severe) and febrile neutropenia.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorD

Pregnancy ConsiderationsReproductive studies in cynomolgus monkeys showed no evidence of impaired fertility or fetal harm. Trastuzumab inhibits HER2 protein, which has a role in embryonic development. Anhydramnios and oligohydramnios (reversible in some cases) have been reported with use during the second and third trimester of pregnancy. There are no adequate and well-controlled studies in pregnant women. Effective contraception is recommended during and for 6 months after treatment for women of childbearing potential. If used during pregnancy, monitor for oligohydramnios. Women exposed to trastuzumab during pregnancy are encouraged to enroll in the Cancer and Childbirth Registry (1-800-690-6720).

The National Comprehensive Cancer Network (NCCN) breast cancer guidelines (v2.2008) recommend administering trastuzumab in the postpartum period (if trastuzumab is indicated).

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known whether trastuzumab is secreted in human milk. Because many immunoglobulins are secreted in milk, and the potential for serious adverse reactions in the nursing infant exists, patients should discontinue nursing during treatment; the extended half-life should be considered for decisions regarding breast-feeding after therapy completion.

Adverse Reactions**Note:** Percentages reported with single-agent therapy.

>10%:

Cardiovascular: LVEF decreased (4% to 22%)

Central nervous system: Pain (47%), fever (6% to 36%), chills (5% to 32%), headache (10% to 26%), insomnia (14%), dizziness (4% to 13%)

Dermatologic: Rash (4% to 18%)

Gastrointestinal: Nausea (6% to 33%), diarrhea (7% to 25%), vomiting (4% to 23%), abdominal pain (2% to 22%), anorexia (14%)

Neuromuscular & skeletal: Weakness (4% to 42%), back pain (5% to 22%)

Respiratory: Cough (5% to 26%), dyspnea (3% to 22%), rhinitis (2% to 14%), pharyngitis (12%)

Miscellaneous: Infusion reaction (21% to 40%, chills and fever most common; severe: 1%), infection (20%)

1% to 10%:

Cardiovascular: Peripheral edema (5% to 10%), edema (8%), CHF (2% to 7%; severe: <1%), tachycardia (5%), hypertension (4%), arrhythmia (3%), palpitation (3%)

Central nervous system: Depression (6%)

Dermatologic: Acne (2%), nail disorder (2%), pruritus (2%)

Gastrointestinal: Constipation (2%), dyspepsia (2%)

Genitourinary: Urinary tract infection (3% to 5%)

Hematologic: Anemia (4%), leukopenia (3%)

Neuromuscular & skeletal: Paresthesia (2% to 9%), bone pain (3% to 7%), arthralgia (6% to 8%), myalgia (4%), muscle spasm (3%), peripheral neuritis (2%), neuropathy (1%)

Respiratory: Sinusitis (2% to 9%), nasopharyngitis (8%), upper respiratory infection (3%), epistaxis (2%), pharyngolaryngeal pain (2%)

Miscellaneous: Flu-like syndrome (2% to 10%), accidental injury (6%), influenza (4%), allergic reaction (3%), herpes simplex (2%)

<1%, postmarketing, and/or case reports: Acute respiratory distress syndrome (ARDS), amblyopia, anaphylaxis, anaphylactoid reaction, angioedema, apnea, ascites, asthma, ataxia, bone necrosis, bronchospasm, cardiac arrest, cardiomyopathy, cellulitis, coagulopathy, colitis, confusion, deafness, esophageal ulcer, gastroenteritis, glomerulonephritis (membraneous, focal and fibrillary), glomerulopathy, glomerulosclerosis, hematemesis, hemorrhage, hemorrhagic cystitis, hepatic failure, hepatitis, herpes zoster, hydrocephalus, hydronephrosis, hypercalcemia, hypersensitivity, hypotension, hypothyroidism, hypoxia, ileus, intestinal obstruction, interstitial pneumonitis, laryngitis, leukemia (acute), lymphangitis, mania, mural thrombosis, myopathy, nephrotic syndrome, neutropenia, pancreatitis, pancytopenia, paroxysmal nocturnal dyspnea, pathological fracture, pericardial effusion, pleural effusion, pneumonitis, pneumothorax, pulmonary edema (noncardiogenic), pulmonary fibrosis, pulmonary hypertension, pulmonary infiltrate, pyelonephritis, radiation injury, renal failure, respiratory distress, respiratory failure, seizure, sepsis, shock, skin ulcers, stroke, syncope, stomatitis, thyroiditis (autoimmune), vascular thrombosis, ventricular dysfunction, volume overload

Oncology: VesicantNo

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

Abciximab: May enhance the potential for allergic or hypersensitivity reactions to Monoclonal Antibodies. Also may cause thrombocytopenia or diminished therapeutic effects. *Risk C: Monitor therapy*

Antineoplastic Agents (Anthracycline): Trastuzumab may enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk D: Consider therapy modification*

Immunosuppressants: Trastuzumab may enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Paclitaxel: Trastuzumab may decrease the serum concentration of Paclitaxel. Paclitaxel may increase the serum concentration of Trastuzumab.
Risk C: Monitor therapy

Monitoring ParametersHER2 expression assessment (pretherapy); monitor vital signs during infusion; signs and symptoms of cardiac dysfunction; LVEF (baseline, every 3 months during treatment, upon therapy completion and every 6 months for at least 2 years; if treatment is withheld for significant LVEF dysfunction, monitor LVEF at 4-week intervals)

Nursing: Physical Assessment/MonitoringMonitor therapeutic effectiveness and adverse reactions. Monitor vital signs during infusion. Assess knowledge/teach patient interventions to reduce side effects and adverse symptoms to report.

Patient EducationThis medication can only be administered by infusion. Report immediately any adverse reactions during infusion (eg, respiratory difficulty, chills, fever, headache, backache, or nausea/vomiting) so appropriate medication can be administered. You will be susceptible to infection (avoid crowds and exposure to infection). You may experience dizziness or weakness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); diarrhea (boiled milk, yogurt, or buttermilk may help); or headache, back or joint pain (mild analgesics may offer relief). Report persistent GI effects; sore throat, runny nose, or respiratory difficulty; chest pain, irregular heartbeat, palpitations, swelling of extremities, or unusual weight gain; muscle or joint weakness, numbness, or pain; skin rash or irritation; itching or pain on urination; unhealed sores, white plaques in mouth or genital area, unusual bruising or bleeding; or other unusual adverse effects.
Pregnancy/breast-feeding precautions: Inform prescriber if you are or intend to be pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Herceptin®: 440 mg [packaged with bacteriostatic water for injection; diluent contains benzyl alcohol]

Generic AvailableNo

ManufacturerGenentech, Inc

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Herceptin)

440 mg (1): $2899.82

Mechanism of ActionTrastuzumab is a monoclonal antibody which binds to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER-2); it mediates antibody-dependent cellular cytotoxicity by inhibiting proliferation of cells which overexpress HER-2 protein.

Pharmacodynamics/Kinetics

Distribution: V_d: 44 mL/kg; not likely to cross the (intact) blood brain barrier (due to the large molecule size)

Half-life elimination: Weekly dosing: Mean: 6 days (range: 1-32 days); every 3 week regimen: Mean: 16 days (range: 11-23 days)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia and dizziness are common; may cause depression

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsNSC-688097

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Watson WJ, "Herceptin (Trastuzumab) Therapy During Pregnancy: Association With Reversible Anhydramnios," *Obstet Gynecol*, 2005, 105(3):642-3.[PubMed 15738038]

International Brand NamesHerceptin (AR, AT, AU, BB, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CO, CZ, DE, DK, EC, ES, ET, FI, FR, GB, GH, GM, GN, GR, GY, HK, HN, ID, IE, IL, IT, JM, KE, KP, LR, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, PE, PH, PL, PT, PY, RU, SC, SD, SE, SG, SL, SN, SR, TH, TN, TR, TT, TW, TZ, UG, UY, VE, ZA, ZM, ZW)

Travelers' Diarrhea and Cholera Vaccine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation

(TRAV uh lerz dahy uh REE uh & KOL er uh vak SEEN)

Canadian Brand NamesDukoral™
Pharmacologic CategoryVaccine
Use: Labeled IndicationsProtection against travelers' diarrhea and/or cholera in adults and children ≥2 years of age who will be visiting areas where there is a risk of contacting travelers' diarrhea caused by enterotoxigenic *E. coli* (ETEC) or cholera caused by *V. cholerae* O1 (classical and El Tor biotypes)
Dosing: Adults

Cholera: Oral:

Primary immunization: 2 doses given at intervals of ≥1 week and completed at least 1 week prior to trip to endemic/epidemic areas; restart treatment if interval between doses >6 weeks

Booster: 1 dose after 2 years have elapsed since vaccination

ETEC: Oral:

Primary immunization: 2 doses given at intervals of ≥1 week; restart treatment if interval between doses >6 weeks

Booster:

Continued risk: 1 dose every 3 months

Renewed protection: 1 dose may be given if last booster or original immunization was <5 years ago (if >5 years, revaccinate)

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Cholera: Oral:

Primary immunization:

Children 2-6 years: 3 doses given at intervals of ≥1 week and completed at least 1 week prior to trip to endemic/epidemic areas; restart treatment if interval between doses >6 weeks

Children ≥6 years: Refer to adult dosing.

Booster:

Children 2-6 years: 1 dose after 6 months have elapsed since vaccination

Children ≥6 years: Refer to adult dosing.

ETEC: Oral: Children ≥2 years: Refer to adult dosing.

Administration: OralFor oral use only; do no administer I.M., I.V., or SubQ. Food should be avoided 1 hour before and 1 hour following vaccine administration. Use reconstituted solution within 2 hours of mixing.
Dietary ConsiderationsFood may affect efficacy of vaccine; avoid 1 hour before and 1 hour following vaccine administration.
StorageReconstituted solution may be stored at room temperature (<27°C) for up to 2 hours. Vial should be stored between 2°C to 8°C (35°F to 46°F), and may be stored at room temperature up to 2 weeks on one occasion only. The sachet may be stored with the vial between 2°C to 8°C (35°F to 46°F) or separately at room temperature (<27°C).
ReconstitutionThe effervescent granules contained in the sachet, should be dissolved in a glass with 150 mL of water resulting in a buffer solution; do not use juice milk or other beverages. For children 2-6 years, half the amount of the buffer solution is poured away. The vial containing the vaccine should be shaken and the entire contents should be added to the buffer solution and mixed. Use reconstituted solution within 2 hours of mixing.
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to any component of the formulation; acute illness (excluding minor illnesses such as a mild upper respiratory tract infection)
Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Cholera infection: May not protect 100% of susceptible individuals; has not been shown to protect against cholera caused by 0139 Bengal strain in South Asia.

Special populations:

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination.

- Pediatrics: Safety and efficacy have not been established in children <2 years of age.

Dosage form specific issues:

- Formaldehyde: Product may contain trace amounts of formaldehyde.

- Latex: Packaging may contain natural latex rubber.

Pregnancy ConsiderationsSafety and efficacy in pregnant women have not been established; the vaccine is not recommended for use during pregnancy. However, since the vaccine is given orally in an inactivated form, acts locally in the gut, and does not replicate, it may not (in theory) cause a risk to the fetus. Use should only be considered if the potential benefit to the mother outweighs the potential risk to the fetus.

LactationExcretion in breast milk unknown

Breast-Feeding ConsiderationsThe manufacturer states that the vaccine may be given to lactating women.

Adverse ReactionsAll serious adverse reactions related to the administration of the product should be reported in accordance with local requirements and to the Senior Product Safety Officer, Pharmacovigilance Department, Aventis Pasteur Limited, 1755 Steeles Avenue West, Toronto, ON, M2R2T4, Canada. 1-888-621-1146 (phone) or 416-667-2435 (fax).

>10%: Gastrointestinal: Abdominal pain (16%), diarrhea (12%)

1% to 10%: Gastrointestinal: Vomiting (3%)

Postmarketing and/or case reports: Dizziness, dyspnea, headache

Drug Interactions

Immunosuppressants: May diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: May affect efficacy of vaccine. Avoid food 1 hour before and 1 hour following vaccine administration.

Nursing: Physical Assessment/MonitoringAssess any previous exposure to cholera vaccine prior to treatment. Instruct patient about safe eating and drinking practice. Teach patient proper use (how to prepare), possible side effects/appropriate interventions, instruct patient about anaphylactic treatment that should be available during use, and adverse symptoms to report.

Patient EducationEmergency treatment for anaphylactic reaction should be available during use (consult prescriber). Granules must be dissolved in a glass with 150 mL of water (do not use juice, milk, or other beverages). Shake small glass vial of vaccine and add vaccine from the vial to the solution in the glass, stir well and drink. Avoid food one hour before or one hour after taking vaccine. May cause mild transient abdominal pain or diarrhea (consult prescriber if necessary). Report immediately any serious adverse reactions.

Safe eating and drinking tips for travelers: Drink only bottled water, soft drinks, or fruit juices, alcoholic beverages without ice, and only pasteurized and properly refrigerated milk; only fruits and vegetables that are freshly peeled or freshly cooked, foods that are well cooked and served hot. Avoid tap water (even when brushing teeth) and ice cubes, fruits that don't need peeling, uncooked vegetables or salads, uncooked or undercooked meat, fish or shellfish, foods sold by street vendors.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Suspension [vial]:

Dukoral™ [CAN]: 2.5 x 10^{10} of each of the following *Vibrio cholerae* O1 strains: Inaba classic (heat inactived), Inaba El Tor (formalin inactivated), Ogawa classic (heat inactivated), Ogawa classic (formalin inactivated), and 1 mg recombinant cholera toxin B subunit (rCTB) (3 mL) [may contain trace amounts of formaldehyde; packaged with sachet containing 5.6 g sodium hydrogen carbonate (contains saccharin, raspberry flavor)] [not available in the U.S.]

ManufacturerSBL Vaccin AB

Pharmacodynamics/KineticsOnset of ETEC diarrhea and cholera immunity: 1 week after primary immunization is concluded

Pharmacotherapy PearlsDukoral™ may be administered to HIV-infected persons.

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms*Vibrio cholera* and Enterotoxigenic *Escherichia coli Vaccine* ; Cholera and Traveler's Diarrhea Vaccine; Enterotoxigenic *Escherichia coli* and *Vibrio cholera* Vaccine; Traveller's Diarrhea Vaccine and Cholera

International Brand NamesDukoral® (CA)

Travoprost and Timolol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

DuoTrav™ may be confused with DuoNeb®

Pronunciation(TRA voe prost & TIM oh lol)

Canadian Brand NamesDuoTrav™

Pharmacologic CategoryBeta Blocker, Nonselective; Ophthalmic Agent, Antiglaucoma; Prostaglandin, Ophthalmic

Use: Labeled IndicationsReduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers, prostaglandin analogues, or other IOP-reducing agents and in whom combination therapy is appropriate

Dosing: Adults**Control of intraocular pressure:** Ophthalmic: Instill 1 drop into affected eye(s) once daily in the morning

Dosing: ElderlyRefer to adult dosing.

Administration: OtherRemove contact lenses prior to administration; wait 15 minutes before reinserting if using products containing benzalkonium chloride. Separate administration of other ophthalmic agents by 5 minutes.

StorageStore between 2°C to 25°C (36°F to 77°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to travoprost, timolol, or any other component of the formulation; current or history of bronchial asthma, severe chronic obstructive pulmonary disease (COPD); sinus bradycardia, second- or third-degree atrioventricular block, overt cardiac failure, cardiogenic shock. Also see individual agents.

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactic reactions: Use caution with history of severe anaphylaxis to allergens; patients taking beta-blockers may become more sensitive to repeated challenges. Treatment of anaphylaxis (eg, epinephrine) in patients taking beta-blockers may be ineffective or promote undesirable effects.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Ocular effects: Use of agents that reduce/suppress aqueous humor production has been associated with choroidal detachment after filtration procedures. Discontinue use in patients with chronic or recurrent choroidal detachment. Macular edema, mainly in aphakic or pseudophakic patients with a torn posterior lens capsule, has been associated with use of prostaglandin analogues such as travoprost. May permanently change/increase brown pigmentation of the iris, the eyelid skin, and eyelashes. In addition, may increase the length and/or number of eyelashes (may vary between eyes); changes occur slowly and may not be noticeable for months or years. Long-term consequences and potential injury to eye are not known.

Disease-related concerns:

- Angle-closure glaucoma: Not for use alone to treat acute angle-closure glaucoma.
- Bronchospastic disease: In general, patients with bronchospastic disease should not receive beta-blockers; if used at all, should be used cautiously with close monitoring.
- Conduction abnormalities: Consider pre-existing conditions such as sick sinus syndrome before initiating.
- Diabetes: Use with caution in patients with diabetes mellitus; may potentiate hypoglycemia and/or mask signs and symptoms.
- Heart failure: Use with caution in patients with compensated heart failure and monitor for a worsening of the condition.
- Iritis/uveitis: Use caution in patients with active intraocular inflammation.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; may worsen disease or other myasthenic symptoms (diplopia, ptosis).
- Orthostatic hypotension: Use with caution in patients with orthostatic hypotension; signs and symptoms of hypotension may be enhanced.
- Renal Impairment: Safety and efficacy have not been established in renal impairment.
- Thyrotoxicosis: Signs of hyperthyroidism (eg, tachycardia) may be masked by beta-blockers. Avoid abrupt withdrawal if thyrotoxicosis is suspected (may precipitate thyroid storm).
- Vascular disease: Use caution in patients with cerebral/coronary vascular insufficiency.

Special populations:

- Contact lens wearers: Product contains benzalkonium chloride which may be absorbed by soft contact lenses; remove lens prior to administration and wait 15 minutes before reinserting.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Absorption: Systemic absorption and adverse effects may occur with ophthalmic use, including bradycardia and/or hypotension. Beta-blocker therapy should not be withdrawn abruptly in order to avoid acute tachycardia, hypertension, and/or ischemia. . Patients undergoing major surgery should be gradually tapered off therapy prior to procedure.

- Initial therapy: DuoTrav™ should not be used for initial therapy.

Also see individual agents.

Pregnancy ConsiderationsReproductive studies have not been conducted with this combination. See individual agents.
LactationEnters breast milk (timolol)/not recommended
Breast-Feeding ConsiderationsTimolol has been detected in human breast milk following ophthalmic administration. It is not known if travoprost is excreted in human milk. See individual agents.
Adverse ReactionsAlso see individual agents. Based on long-term studies:

>10%: Ocular: Hyperemia (14%)

1% to 10%: Ocular: Eye irritant (6%), eye pruritus (5%), dry eyes (3%), eyelash growth (2%), iris pigmentation changes (up to 2%), blurred vision (1%), eye pain (1%), photophobia (1%), punctuate keratitis (1%)

<1%: Allergic conjunctivitis, anterior chamber flare, arrhythmia, asthenopia, blepharitis, bradycardia, bronchospasm, chromaturia, conjunctival hemorrhage, contact dermatitis, cough, corneal staining, distichiasis, dizziness, dyspnea, extremity pain, eye allergy, eyelid dermatitis, eyelid edema, eyelid erythema, eyelid irritation, eyelid pain, eye swelling, headache, hyper-/hypotension, hypertrichosis, lacrimation increased, nervousness, ocular discomfort, periorbital disorder, postnasal drip, skin hyperpigmentation, thirst, throat irritation, urticaria, visual disturbance, xerophthalmia

Metabolism/Transport EffectsTimolol: **Substrate** of CYP2D6 (major); **Inhibits** CYP2D6 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Beta-Blockers may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Epinephrine used as a local anesthetic for dental procedures will not likely cause clinically relevant problems. **Exceptions:** Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Blockers: Beta-Blockers may enhance the orthostatic effect of Alpha1-Blockers. The risk associated with ophthalmic products is probably less than systemic products. *Risk D: Consider therapy modification*

Alpha2-Agonists: Beta-Blockers may enhance the rebound hypertensive effect of Alpha2-Agonists. This effect can occur when the alpha$_2$-agonist is abruptly withdrawn. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Aminoquinolines (Antimalarial): May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Amiodarone: May enhance the bradycardic effect of Beta-Blockers. Possibly to the point of cardiac arrest. Amiodarone may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Beta-Blockers. Anilidopiperidine Opioids may enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Beta2-Agonists: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Nondihydropyridine): May enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. *Risk C: Monitor therapy*

Cardiac Glycosides: Beta-Blockers may enhance the bradycardic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dipyridamole: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Disopyramide: May enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Insulin: Beta-Blockers may enhance the hypoglycemic effect of Insulin. *Risk C: Monitor therapy*

Lidocaine: Beta-Blockers may decrease the metabolism of Lidocaine. *Risk C: Monitor therapy*

Methacholine: Beta-Blockers may enhance the adverse/toxic effect of Methacholine. *Risk X: Avoid combination*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Beta-Blockers may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the antihypertensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Propafenone: May decrease the metabolism of Beta-Blockers. Propafenone possesses some independent beta blocking activity. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: May decrease the metabolism of Beta-Blockers. *Risk C: Monitor therapy*

Reserpine: May enhance the hypotensive effect of Beta-Blockers. *Risk C: Monitor therapy*

Rifamycin Derivatives: May decrease the serum concentration of Beta-Blockers. **Exceptions:** Rifabutin. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the bradycardic effect of Beta-Blockers. **Exceptions:** Fluvoxamine. *Risk C: Monitor therapy*

Theophylline Derivatives: Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Theophylline Derivatives. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Monitoring ParametersIOP, iris color changes, eyelash changes; systemic effects of beta blockade with ophthalmic administration

Nursing: Physical Assessment/Monitoring

See individual agents.

Patient Education

See individual agents.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Solution, ophthalmic:

DuoTrav™ [CAN]: Travoprost 0.004% and timolol 0.5%: (2.5 mL, 5 mL) [contains benzalkonium chloride] [not available in the U.S.]

Generic AvailableNo

ManufacturerAlcon Canada, Inc

Mechanism of Action

Travoprost: Selective FP prostanoid receptor agonist which lowers intraocular pressure by increasing trabecular meshwork and outflow

Timolol: Blocks both beta$_1$- and beta$_2$-adrenergic receptors, reduces intraocular pressure by reducing aqueous humor production or possibly outflow; reduces blood pressure by blocking adrenergic receptors and decreasing sympathetic outflow, produces a negative chronotropic and inotropic activity through an unknown mechanism

Pharmacodynamics/KineticsSee individual agents.

Mental Health: Effects on Mental StatusMay cause CNS depression; use with caution

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsTimolol Maleate and Travoprost

References

Barnebey HS, Orengo-Nania S, Flowers BE, et al, “The Safety and Efficacy of Travoprost 0.004%/Timolol 0.5% Fixed Combination Ophthalmic Solution,” *Am J of Ophthalmol*, 2005, 140(1):1-7.[PubMed 15990081]

Lang DM, “Anaphylactoid and Anaphylactic Reactions. Hazards of Beta-Blockers,” *Drug Saf*, 1995, 12(5):299-304.[PubMed 7669259]

Schuman JS, Katz GJ, Lewis RA, et al, “Efficacy and Safety of a Fixed Combination of Travoprost 0.004%/Timolol 0.5% Ophthalmic Solution Once Daily for Open-Angle Glaucoma or Ocular Hypertension,” *Am J of Ophthalmol*, 2005, 140(2): 242-50.[PubMed 16086946]

International Brand NamesDuoTrav (AR, AT, AU, BE, BG, CH, CZ, DE, DK, FI, FR, GB, GR, HK, HN, IE, IT, NL, NO, PH, PT, RU, SE, TR, TW)

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Travatan® may be confused with Xalatan®

Pronunciation(TRA voe prost)

U.S. Brand NamesTravatan®; Travatan® Z

Canadian Brand NamesTravatan®; Travatan® Z

Pharmacologic CategoryOphthalmic Agent, Antiglaucoma; Prostaglandin, Ophthalmic

Use: Labeled IndicationsReduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of the other IOP-lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another IOP-lowering medication

Dosing: Adults**Glaucoma (open angle) or ocular hypertension:** Ophthalmic: Instill 1 drop into affected eye(s) once daily in the evening; do not exceed once-daily dosing (may decrease IOP-lowering effect). If used with other topical ophthalmic agents, separate administration by at least 5 minutes.

Dosing: ElderlyRefer to adult dosing.

Administration: OtherMay be used with other eye drops to lower intraocular pressure. If using more than one ophthalmic product, wait at least 5 minutes in between application of each medication. Travatan®: Remove contact lenses prior to administration and wait 15 minutes before reinserting.

StorageStore between 2°C to 25°C (36°F to 77°F).

ContraindicationsHypersensitivity to travoprost or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Bacterial keratitis: Inadvertent contamination of multiple-dose ophthalmic solutions, has caused bacterial keratitis.
- Ocular effects: May permanently change/increase brown pigmentation of the iris, the eyelid skin, and eyelashes. In addition, may increase the length and/or number of eyelashes (may vary between eyes); changes occur slowly and may not be noticeable for months or years. Long-term consequences and potential injury to eye are not known.

Disease-related concerns:

- Ocular disease: Use with caution in patients with intraocular inflammation, aphakic patients, pseudophakic patients with a torn posterior lens capsule, or patients with risk factors for macular edema. Safety and efficacy have not been determined for use in patients with angle-closure-, inflammatory-, or neovascular glaucoma.

Special populations:

- Contact lens wearers: Travatan® contains benzalkonium chloride which may be adsorbed by contact lenses; remove lens prior to administration and wait 15 minutes before re-inserting.
- Pediatrics: Safety and efficacy have not been established in children.
- Pregnancy: Contact with contents of vial should be avoided in women who are pregnant or attempting to become pregnant; in case of accidental exposure to the skin, wash the exposed area with soap and water immediately.

Geriatric ConsiderationsEvaluate patient's ability to self-administer eye drops.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were observed in animal studies following systemic administration.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Ocular: Hyperemia (35% to 50%)

5% to 10%: Ocular: Decreased visual acuity, eye discomfort, foreign body sensation, pain, pruritus

1% to 5%:

Cardiovascular: Angina pectoris, bradycardia, hyper-/hypotension

Central nervous system: Depression, pain, anxiety, headache

Endocrine & metabolic: Hypercholesterolemia

Gastrointestinal: Dyspepsia

Genitourinary: Prostate disorder, urinary incontinence

Neuromuscular & skeletal: Arthritis, back pain, chest pain

Ocular (1% to 4%): Abnormal vision, blepharitis, blurred vision, conjunctivitis, dry eye, iris discoloration, keratitis, lid margin crusting, photophobia, subconjunctival hemorrhage, cataract, tearing, periorbital skin discoloration (darkening), eyelash darkening, eyelash growth increased

Respiratory: Bronchitis, sinusitis

Postmarketing and/or case reports: Bacterial keratitis (due to solution contamination)

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Monitor patient response and adverse effects. Teach patient proper use, side effects/appropriate interventions, and symptoms to report.

Patient EducationFor use in eyes only. Wash hands before instilling. Sit or lie down to instill. Open eye, look at ceiling, and instill prescribed amount of solution. Apply gentle pressure to inner corner of eye. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Contact prescriber concerning continued use of drops if eye infection develops, trauma occurs to the eye, and prior to eye surgery. Travatan® contains benzalkonium chloride which may be adsorbed by contact lenses; remove contacts prior to administration and wait 15 minutes before reinserting. May cause permanent changes in eye color (increases the amount of brown pigment in the iris), eyelid, and eyelashes. May also increase the length and/or number of eyelashes. Changes may occur slowly (months to years). May be used with other eye drops to lower intraocular pressure. If using more than one eye drop medicine, wait at least 5 minutes in between application of each medication. Notify prescriber if conjunctivitis or eyelid reactions occur with use of this product. In case of accidental contact with the solution, wash skin with soap and water immediately. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic:

Travatan®: 0.004% (2.5 mL, 5 mL) [contains benzalkonium chloride]

Travatan® Z: 0.004% (2.5 mL, 5 mL)

Generic AvailableNo

ManufacturerAlcon Laboratories, Inc

Pricing: U.S. (www.drugstore.com)

Solution (Travatan)

0.004% (2.5): $73.87

0.004% (5): $144.74

Solution (Travatan Z)

0.004% (2.5): $73.99

0.004% (5): $144.53

Mechanism of ActionA selective FP prostanoid receptor agonist which lowers intraocular pressure by increasing trabecular meshwork and outflow

Pharmacodynamics/Kinetics

Onset of action: ~2 hours

Peak effect: 12 hours

Duration: Plasma levels decrease to <10 pg/mL within 1 hour

Absorption: Absorbed via cornea

Metabolism: Hydrolyzed by esterases in the cornea to active free acid; systemically; the free acid is metabolized to inactive metabolites

Related Information

- Glaucoma Drug Therapy

Pharmacotherapy PearlsThe IOP-lowering effect was shown to be 7-8 mm Hg in clinical studies. The mean IOP reduction in African-American patients was up to 1.8 mm Hg greater than in non-African-American patients. The reason for this effect is unknown.

Dental Health: Effects on Dental TreatmentNo information available to require special precautions

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo significant effects or complications reported

Mental Health: Effects on Mental StatusMay cause anxiety and depression

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesTravatan (AR, AT, AU, BE, BG, BO, BR, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, HK, HN, IE, IL, IT, KP, MX, MY, NI, NL, NO, PA, PE, PH, PK, PL, PR, PT, PY, RU, SE, SG, SV, TH, TR, TW, UY, VE, ZA)

TraZODone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Desyrel® may be confused with Demerol®, Delsym®, Zestril®

TraZODone may be confused with traMADol

International issues:

Desyrel® may be confused with Deseril® which is a brand name for methysergide in multiple international markets

Pronunciation(TRAZ oh done)

Canadian Brand NamesAlti-Trazodone; Apo-Trazodone D®; Apo-Trazodone®; Desyrel®; Gen-Trazodone; Novo-Trazodone; Nu-Trazodone; PMS-Trazodone; ratio-Trazodone; Trazorel®

Pharmacologic CategoryAntidepressant, Serotonin Reuptake Inhibitor/Antagonist

Use: Labeled IndicationsTreatment of depression

Use: Unlabeled/InvestigationalPotential augmenting agent for antidepressants, hypnotic

Dosing: Adults

Depression: Oral: Initial: 150 mg/day in 3 divided doses (may increase by 50 mg/day every 3-7 days); maximum: 600 mg/day

Note: Therapeutic effects may take up to 6 weeks. Therapy is normally maintained for 6-12 months after optimum response is reached to prevent recurrence of depression.

Sedation/hypnotic (unlabeled use): Oral: 25-50 mg at bedtime (often in combination with daytime SSRIs). May increase up to 200 mg at bedtime.

Dosing: ElderlyOral: 25-50 mg at bedtime with 25-50 mg/day dose increase every 3 days for inpatients and weekly for outpatients, if tolerated; usual dose: 75-150 mg/day

Dosing: Pediatric

Depression (unlabeled use):

Children 6-12 years: Initial: 1.5-2 mg/kg/day in divided doses; increase gradually every 3-4 days as needed; maximum: 6 mg/kg/day in 3 divided doses

Adolescents: Initial: 25-50 mg/day; increase to 100-150 mg/day in divided doses

Administration: OralDosing after meals may decrease lightheadedness and postural hypotension.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to trazodone or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See “Major psychiatric warnings” below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient’s family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription.**Trazodone is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Trazodone is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Orthostatic hypotension: May cause orthostatic hypotension (risk is high relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is very high relative to other antidepressants.

- Sexual dysfunction: Priapism, including cases resulting in permanent dysfunction, has occurred with the use of trazodone.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk conduction abnormalities with this agent is low relative to other antidepressants. Not recommended for use in a patient during the acute recovery phase of MI.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- MAO inhibitors: Trazodone should be initiated with caution in patients who are receiving concurrent or recent therapy with a MAO inhibitor.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Discontinuation of therapy: Therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

Geriatric ConsiderationsVery sedating, but little anticholinergic effects.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTrazodone is classified as pregnancy category C due to adverse effects observed in animal studies. When trazodone is taken during pregnancy, an increased risk of major malformations has not been observed in the small number of pregnancies studied. The long-term effects on neurobehavior have not been evaluated.

Women treated for major depression and who are euthymic prior to pregnancy are more likely to experience a relapse when medication is discontinued as compared to pregnant women who continue taking antidepressant medications. Therapy during pregnancy should be individualized; treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary healthcare provider, and pediatrician. If treatment during pregnancy is required, consider tapering therapy during the third trimester to prevent potential withdrawal symptoms in the infant. If this is done and the woman is considered to be at risk of relapse from her major depressive disorder, the medication can be restarted following delivery.

LactationEnters breast milk/use caution (AAP rates “of concern”)
Breast-Feeding ConsiderationsTrazodone is excreted into breast milk; breast milk concentrations peak ~2 hours following administration. It is not known if the trazodone metabolite is found in breast milk. The long-term effects on neurobehavior have not been studied. The manufacturer recommends that caution be exercised when administering trazodone to nursing women. The AAP considers trazadone to be a “drug for which the effect on the nursing infant is unknown, but may be of concern."
Pregnancy & Lactation, In-Depth

- TraZODone in Pregnancy & Lactation

Adverse Reactions

>10%:

Central nervous system: Dizziness, headache, sedation

Gastrointestinal: Nausea, xerostomia

Ocular: Blurred vision

1% to 10%:

Cardiovascular: Syncope, hyper-/hypotension, edema

Central nervous system: Concentration decreased, confusion, fatigue, incoordination

Gastrointestinal: Diarrhea, constipation, weight gain/loss

Neuromuscular & skeletal: Tremor, myalgia

Respiratory: Nasal congestion

<1% (Limited to important and life-threatening): Agitation, allergic reactions, alopecia, anxiety, bradycardia, extrapyramidal symptoms, hepatitis, priapism, rash, seizure, speech impairment, tachycardia, urinary retention

Metabolism/Transport Effects **Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (moderate), 3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

BusPIRone: May enhance the serotonergic effect of Antidepressants (Serotonin Reuptake Inhibitor/Antagonist). This may cause serotonin syndrome. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Codeine: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Substrates: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fesoterodine: CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Nebivolol: CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of TraZODone. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the serotonergic effect of Antidepressants (Serotonin Reuptake Inhibitor/Antagonist). This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Tamoxifen: CYP2D6 Inhibitors (Moderate) may decrease the metabolism of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the formation of highly potent active metabolites. *Risk D: Consider therapy modification*

TraMADol: CYP2D6 Inhibitors (Moderate) may diminish the therapeutic effect of TraMADol. These CYP2D6 inhibitors may prevent the metabolic conversion of tramadol to its active metabolite that accounts for much of its opioid-like effects. *Risk C: Monitor therapy*

Venlafaxine: May enhance the serotonergic effect of TraZODone. This could result in serotonin syndrome. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Time to peak serum levels may be increased if trazodone is taken with food.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava (may increase risk of serotonin syndrome and/or excessive sedation).

Monitoring ParametersSuicidal ideation (especially at the beginning of therapy or when doses are increased or decreased)
Reference Range

Plasma levels do not always correlate with clinical effectiveness

Therapeutic: 0.5-2.5 mcg/mL

Potentially toxic: >2.5 mcg/mL

Toxic: >4 mcg/mL

Nursing: Physical Assessment/MonitoringAssess potential and monitor closely for interactions with other prescriptions, OTC medications, or herbal products patient may be taking. Assess results of laboratory tests, therapeutic effectiveness according to rationale for therapy, and adverse reactions at beginning of therapy and periodically with long-term use. Initiate at lower doses and taper dosage slowly when discontinuing (allow 3-4 weeks between discontinuing Desyrel® and starting another antidepressant). Teach patient appropriate use, side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsBaseline liver function prior to and periodically during therapy
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take exactly as directed; do not increase dose or frequency. It may take 2-4 weeks to achieve desired results. Take after meals. Avoid excessive alcohol and caffeine. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); postural hypotension (use caution when climbing stairs or changing position from lying or sitting to standing); nausea, dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); or diarrhea (buttermilk, yogurt, or boiled milk may help). Report persistent dizziness or headache; muscle cramping, tremors, or altered gait; blurred vision or eye pain; chest pain or irregular heartbeat; suicidal ideation; or worsening of condition. Report prolonged or inappropriate erections. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 50 mg, 100 mg, 150 mg, 300 mg

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Tablets (Desyrel)

100 mg (30): $103.98

Tablets (Trazodone HCl)

50 mg (30): $11.99

100 mg (30): $13.99

150 mg (30): $20.87

300 mg (100): $402.20

Mechanism of ActionInhibits reuptake of serotonin, causes adrenoreceptor subsensitivity, and induces significant changes in 5-HT presynaptic receptor adrenoreceptors. Trazodone also significantly blocks histamine (H_1) and alpha$_1$-adrenergic receptors.
Pharmacodynamics/Kinetics

Onset of action: Therapeutic (antidepressant): 1-3 weeks; sleep aid: 1-3 hours

Protein binding: 85% to 95%

Metabolism: Hepatic via CYP3A4 to an active metabolite (mCPP)

Half-life elimination: 7-8 hours, two compartment kinetics

Time to peak, serum: 30-100 minutes; delayed with food (up to 2.5 hours)

Excretion: Primarily urine; secondarily feces

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsTrazodone inhibits reuptake of both serotonin and norepinephrine and also blocks some serotonin receptors. No precautions with vasoconstrictors appear to be necessary.
Index TermsTrazodone Hydrochloride
References

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International Brand NamesAzonz (FI); Deprax (ES); Deprel (PK); Depresil (PH); Desirel (TH); Desyrel (JP); Devidon (HR); Donaren (BR); Mesyrel (CL); Molipaxin (GB, IE); Pragmarel (FR); Reslin (JP); Taxagon (AR); Taxagon AC (UY); Tazodac (IN); Thombran (DE); Trazo (TH); Trazodil (IL); Trazodone-Continental (LU); Trazolan (BE, IN, LU, NL); Trazone (PT, TW); Trazonil (IN); Trittico (AE, AT, BH, CH, CN, CO, CY, EG, GR, HK, IL, IQ, IR, IT, JO, KP, KW, LB, LY, OM, PE, PL, PY, QA, SA, SG, SY, VE, YE); Trittico AC (CN); Trittico CR (KP); Trittico Prolonged-Release (HK); Zodonrel (TH)

Treprostinil

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English

Jump To Field (Select Field Name)

Pronunciation(tre PROST in il)
U.S. Brand NamesRemodulin®
Canadian Brand NamesRemodulin®
Pharmacologic Category[Prostacyclin](); [Prostaglandin](); [Vasodilator]()
Use: Labeled IndicationsTreatment of pulmonary arterial hypertension (PAH) in patients with NYHA Class II-IV symptoms to decrease exercise-associated symptoms; to diminish clinical deterioration when transitioning from epoprostenol (I.V.)
Dosing: Adults**Note:** Prior to initiation, patients should be carefully evaluated for ability to administer treprostinil and care for the infusion system outside of inpatient setting. Immediate access to back up pump, infusion sets, and medication is essential to prevent treatment interruptions.

Pulmonary arterial hypertension (PAH): SubQ (preferred) or I.V. infusion:

Initial: New to prostacyclin therapy: 1.25 ng/kg/minute continuous; if dose cannot be tolerated due to systemic effects, reduce to 0.625 ng/kg/minute. Increase at rate not >1.25 ng/kg/minute per week for first 4 weeks, and not >2.5 ng/kg/minute per week for remainder of therapy. Limited experience with doses >40 ng/kg/minute. **Note:** Dose must be carefully and individually titrated (symptom improvement with minimal adverse effects). Avoid abrupt withdrawal. If infusion is restarted within a few hours of discontinuation, the same dose rate may be used. Interruptions for longer periods may require retitration.

Transitioning from epoprostenol (see table): SubQ (preferred) or I.V. infusion: **Note:** Transition should occur in a hospital setting to follow response (eg, walking distance, sign/symptoms of disease progression). May take 24-48 hours to transition. Transition is accomplished by initiating the infusion of treprostinil, and increasing it while simultaneously reducing the dose of intravenous epoprostenol. During transition, increases in PAH symptoms should be first treated with an increase in treprostinil dose. Occurrence of prostacyclin associated side effects should be treated by decreasing the dose of epoprostenol.

Transitioning From I.V. Epoprostenol to SubQ (preferred) or I.V. Treprostinil

Step	**Epoprostenol Dose**	**Treprostinil Dose**
1	Maintain current dose	Initiate at 10% initial epoprostenol dose
2	Decrease to 80% initial dose	Increase to 30% initial epoprostenol dose
3	Decrease to 60% initial dose	Increase to 50% initial epoprostenol dose
4	Decrease to 40% initial dose	Increase to 70% initial epoprostenol dose
5	Decrease to 20% initial dose	Increase to 90% initial epoprostenol dose
6	Decrease to 5% initial dose	Increase to 110% initial epoprostenol dose
7	Discontinue epoprostenol	Maintain current dose plus additional 5% to 10% as needed

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricLimited experience in patients <16 years of age.
Dosing: Renal ImpairmentNo specific dosage adjustment recommended; use with caution.
Dosing: Hepatic Impairment

Mild-to-moderate: Initial: 0.625 ng/kg/minute; increase with caution.

Severe: Has not been studied in patients with severe hepatic impairment.

Administration: I.V.I.V. infusion: I.V. use is recommended when SubQ infusion is not tolerated or when the benefit outweighs the potential risks of an indwelling central venous catheter. Prior to initiation, patients should be carefully evaluated for ability to administer treprostinil and care for the infusion system outside of inpatient setting. Solution must be diluted in SWFI or NS prior to use and administered by continuous infusion using a central indwelling catheter and infusion pump. Peripheral infusion may be used temporarily until central line is established. Avoid abrupt withdrawal (including interruptions in delivery) or rapid large dosage reductions. Immediate access to back up pump, infusion sets and medication is essential to prevent treatment interruptions.

Administration: I.V. DetailpH 6-7.2

Administration: OtherSubQ infusion (preferred): Administer undiluted via continuous SubQ infusion using an appropriately-designed infusion pump. Prior to initiation, patients should be carefully evaluated for ability to administer treprostinil and care for the infusion system outside of inpatient setting. Avoid abrupt withdrawal (including interruptions in delivery) or rapid large dosage reductions. Immediate access to back up pump, infusion sets and medication is essential to prevent treatment interruptions. Infusion site reactions may be helped by moving the infusion site every 3 days, local application of topical hot and cold packs, topical or oral analgesics. Injection site pain and erythema may improve after several months of therapy.

Dietary ConsiderationsSodium chloride content of solution for injection:

1 mg/mL, 2.5 mg/mL, and 5 mg/mL each contain sodium chloride 5.3 mg/mL

10 mg/mL contains sodium chloride 4 mg/mL

StorageStore vials at 15°C to 30°C (59°F to 86°F). Contents of a vial should not be used past 30 days after initial needle access into the vial. Stability for up to 48 hours has been shown for concentrations as low as 4000 ng/mL. Solutions diluted for infusion may be used for up to 48 hours at 37°C.

ReconstitutionFor SubQ infusion, **product should not be diluted prior to use**. For I.V. infusion, dilute in SWFI, NS, or Flolan® sterile diluent to a final volume of either 50 mL or 100 mL (dependent on system reservoir and calculated dose).

CompatibilityStable in SWFI, NS, or Flolan® sterile diluent.

ContraindicationsThere are no contraindications listed in the FDA-approved labeling.

Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dose reduction is recommended for the initial dose in patients with mild-to-moderate hepatic insufficiency; has not been studied in severe hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment

Special populations:

- Elderly: Use with caution in patients ≥65 years of age; clinical trial experience in this population is limited.

- Pediatrics: Safety and efficacy have not been established in children ≤16 years of age.

Other warnings/precautions:

- Discontinuation of therapy: Abrupt withdrawal/large dosage reductions may worsen symptoms of PAH. If infusion is restarted within a few hours of discontinuation, the same dose rate may be used. Interruptions for longer periods may require retitration.

- Infection: Chronic continuous I.V. infusion of treprostinil via a chronic indwelling central venous catheter has been associated with serious blood stream infections. This method of administration should be reserved for patients who are intolerant of the SubQ route or in whom the benefit outweighs the potential risks. Clinicians should routinely review with patient the importance of infection control practices for the management of a central venous catheter.

- Appropriate use: Treprostinil should only be used by clinicians experienced in the treatment of PAH. Prior to initiation, patients should be carefully evaluated for ability to administer treprostinil and care for the infusion system. Initiation must occur in a setting where adequate personnel and equipment necessary for hemodynamic monitoring and emergency treatment is available.

Pregnancy Risk FactorB

Pregnancy ConsiderationsSome skeletal malformations and maternal toxicity noted in animal studies. There are no adequate and well-controlled studies in pregnant women. Use with caution and only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Cardiovascular: Vasodilation (11%)

Central nervous system: Headache (27%)

Dermatologic: Rash (14%)

Gastrointestinal: Diarrhea (25%), nausea (22%)

Local: Infusion site pain (SubQ 85%, may improve after several months of therapy); infusion site reaction (SubQ 83%)

Neuromuscular & skeletal: Jaw pain (13%)

1% to 10%:

Cardiovascular: Edema (9%), hypotension (4%)

Central nervous system: Dizziness (9%)

Dermatologic: Pruritus (8%)

Postmarketing and/or case reports: Anxiety, arm swelling, bone pain, cellulitis, central venous catheter-related line infections, central venous catheter-related sepsis, hematoma, pain, paresthesia, restlessness, thrombocytopenia, thrombophlebitis

Drug Interactions

Anticoagulants: Prostacyclin Analogues may enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Antihypertensives: Prostacyclin Analogues may enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Antiplatelet Agents: Prostacyclin Analogues may enhance the antiplatelet effect of Antiplatelet Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: Treprostinil may enhance the adverse/toxic effect of Nonsteroidal Anti-Inflammatory Agents. Bleeding may occur. *Risk C: Monitor therapy*

Salicylates: Treprostinil may enhance the adverse/toxic effect of Salicylates. Bleeding may occur. *Risk C: Monitor therapy*

Monitoring ParametersBP, dyspnea, fatigue, activity tolerance, symptoms of excessive dose (eg, headache, nausea, vomiting)

Nursing: Physical Assessment/MonitoringTo be used only by clinicians experienced in the diagnosis and treatment of PAH. Initiation of therapy must be performed in a setting with necessary continuous pulmonary and hemodynamic arterial monitoring and emergency care. Therapy may be needed for prolonged periods, possibly years, patient's ability to prepare, administer, and care for continuous infusion per indwelling-central venous catheter via an infusion pump should be carefully assessed. Assess other pharmacological or herbal products patient may be taking for potential interactions (especially anything that may alter blood pressure or coagulation). Assess at beginning of therapy and regular intervals for effectiveness of therapy (improved pulmonary function and quality of life) and any adverse reactions. Teach patient/caregiver how to care for infusion pump and monitor for any pump malfunction, possible side effects/appropriate interventions (eg, monitoring vital signs on regular basis), and adverse or overdose symptoms to report (flushing, headache, hypotension, nausea, vomiting, diarrhea, and seizure activity).

Patient EducationThis drug can only be administered via a continuous infusion delivery system. Therapy will probably be prolonged, possibly for years. You will be taught how to prepare medication and care for and monitor the equipment; follow these directions completely. Notify contact person immediately with any problems or questions with equipment. You will be required to monitor your vital signs at regular intervals. You may experience mild headache, nervousness, or dizziness (use caution when driving or engaging in activities requiring alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, or sucking lozenges may help); diarrhea (buttermilk, boiled milk, or yogurt may help) or muscular pain (use of a mild analgesia may be recommended by your prescriber). Report immediately any signs or symptoms of flushing, increased dizziness or blurred vision, acute or severe headache; increased difficult breathing; fever or chills; any unusual bleeding or bruising; chest pain; palpitations; irregular, slow or fast pulse; seizure activity or any unresolved adverse effects. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 1 mg/mL (20 mL) [contains sodium chloride 5.3 mg/mL]; 2.5 mg/mL (20 mL) [contains sodium chloride 5.3 mg/mL]; 5 mg/mL (20 mL) [contains sodium chloride 5.3 mg/mL]; 10 mg/mL (20 mL) [contains sodium chloride 4 mg/mL]

Generic AvailableNo

ManufacturerBaxter Pharmaceuticals Solutions LLC; United Therapeutics Corporation (distributor)

Mechanism of ActionTreprostinil is a direct vasodilator of both pulmonary and systemic arterial vascular beds; also inhibits platelet aggregation.

Pharmacodynamics/Kinetics

Absorption: SubQ: Rapidly and completely

Distribution: 14 L/70 kg lean body weight

Protein binding: 91%

Metabolism: Hepatic (enzymes unknown); forms 5 metabolites (HU1-HU5)

Bioavailability: SubQ: 100%

Half-life elimination: Terminal: ~2-4 hours

Excretion: Urine (79%; 4% as unchanged drug, 64% as metabolites); feces (13%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported. Treprostinil may enhance the risk of bleeding associated with other antiplatelet agents (aspirin or NSAIDs).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause headache

Mental Health: Effects on Psychiatric TreatmentNausea and diarrhea are common, these effects may be additive with concurrent use of SSRIs, lithium, or valproate. Treprostinil inhibits platelet aggregation. Concomitant use with SSRIs which possess some antiplatelet activity may increase the risk of bleeding.

Index TermsTreprostinil Sodium

References

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International Brand NamesRemodulin (AR, AU, CH, CN, CZ, DK, EE, FR, IL, NO, SE, TW)

Tretinoin (Oral)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Tretinoin may be confused with isotretinoin, trientine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(TRET i noyn, oral)

U.S. Brand NamesVesanoid®

Canadian Brand NamesVesanoid®

Pharmacologic CategoryAntineoplastic Agent, Miscellaneous; Retinoic Acid Derivative

Use: Labeled IndicationsInduction of remission in patients with acute promyelocytic leukemia (APL), French American British (FAB) classification M3 (including the M3 variant)

Dosing: Adults

Acute promyelocytic leukemia (APL): Oral:

Remission induction: 45 mg/m^2/day in 2-3 divided doses for up to 30 days after complete remission (maximum duration of treatment: 90 days)

Remission maintenance: 45-200 mg/m^2/day in 2-3 divided doses for up to 12 months.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricAPL induction of remission, remission maintenance: Oral: Refer to adult dosing.

Dosing: Combination Regimens

Leukemia, acute promyelocytic: Tretinoin-Idarubicin

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: OralAdminister with meals; do not crush capsules

Dietary ConsiderationsTo enhance absorption, some clinicians recommend giving with a fatty meal. Capsule contains soybean oil.

StorageStore capsule at 15°C to 30°C (59°F to 86°F). Protect from light.

ContraindicationsSensitivity to parabens, vitamin A, other retinoids, or any component of the formulation; pregnancy

Allergy Considerations

- Retinoid Allergy

Warnings/Precautions

Boxed warnings:

- Acute promyelocytic leukemia (APL): See “Disease-related concerns” below.
- Experienced physician: See “Other warnings/precautions” below.
- Leukocytosis: See “Concerns related to adverse effects” below.
- Pregnancy: See “Special populations” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Leukocytosis: **[U.S. Boxed Warning]: During treatment, ~40% of patients will develop rapidly evolving leukocytosis;** may be associated with a higher risk of life-threatening complications. If signs and symptoms of the RA-APL syndrome are present together with leukocytosis, initiate treatment with high-dose steroids immediately. Consider adding full-dose chemotherapy (including an anthracycline, if not contraindicated) to the tretinoin therapy on day 1 or 2 for patients presenting with a WBC count of >5 x 10^9/L or immediately, for patients presenting with a WBC count of <5 x 10^9/L, if the WBC count reaches ≥6 x 10^9/L by day 5, or ≥10 x 10^9/L by day 10 or ≥15 x 10^9/L by day 28.

- Lipid effects: Up to 60% of patients experienced hypercholesterolemia or hypertriglyceridemia, which were reversible upon completion of treatment.

- Liver function test abnormalities: Elevated liver function test results occur in 50% to 60% of patients during treatment. Carefully monitor liver function test results during treatment and give consideration to a temporary withdrawal of tretinoin if test results reach >5 times the upper limit of normal.

- Pseudotumor cerebri: Retinoids have been associated with pseudotumor cerebri (benign intracranial hypertension), especially in children. Concurrent use of other drugs associated with this effect (eg, tetracyclines) may increase risk. Early signs and symptoms include papilledema, headache, nausea, vomiting and visual disturbances.

Disease-related concerns:

- Acute promyelocytic leukemia (APL): **[U.S. Boxed Warning]: Patients with APL are at high risk and can have severe adverse reactions to tretinoin. About 25% of patients with APL and treated with tretinoin, have experienced retinoic acid-APL (RA-APL) syndrome, characterized by fever, dyspnea, acute respiratory distress, weight gain, radiographic pulmonary infiltrates and pleural or pericardial effusions, edema, and hepatic, renal, and/or multiorgan failure.** This syndrome has occasionally been accompanied by impaired myocardial contractility and episodic hypotension. It has been observed with or without concomitant leukocytosis. Endotracheal intubation and mechanical ventilation have been required in some cases due to progressive hypoxemia, and several patients have expired with multiorgan failure. The syndrome usually occurs during the first month of treatment, with some cases reported following the first dose. Management of the syndrome has not been defined, but high-dose steroids given at the first suspicion of RA-APL syndrome appear to reduce morbidity and mortality. At the first signs suggestive of the syndrome, immediately initiate high-dose steroids (dexamethasone 10 mg I.V.) every 12 hours for 3 days or until resolution of symptoms, regardless of the leukocyte count. The majority of patients do not require termination of tretinoin therapy during treatment of the RA-APL syndrome.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <1 year of age.

- Pregnancy: **[U.S. Boxed Warning]: High risk of teratogenicity; not to be used in women of childbearing potential** unless the woman is capable of complying with effective contraceptive measures. Repeat pregnancy testing and contraception counseling monthly throughout the period of treatment.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**

Pregnancy Risk FactorD

Pregnancy Considerations**[U.S. Boxed Warning]: High risk of teratogenicity; not to be used in women of childbearing potential** unless the woman is capable of complying with effective contraceptive measures. Repeat pregnancy testing and contraception counseling monthly throughout the period of treatment. Major fetal abnormalities and spontaneous abortions have been reported with other retinoids. Effective contraception must be used during treatment and for 1 month following discontinuation of therapy.

LactationEnters breast milk/not recommended

Adverse ReactionsVirtually all patients experience some drug-related toxicity, especially headache, fever, weakness and fatigue. These adverse effects are seldom permanent or irreversible nor do they usually require therapy interruption.

>10%:

Cardiovascular: Peripheral edema (52%), chest discomfort (32%), edema (29%), arrhythmias (23%), flushing (23%), hypotension (14%), hypertension (11%)

Central nervous system: Headache (86%), fever (83%), malaise (66%), pain (37%), dizziness (20%), anxiety (17%), insomnia (14%), depression (14%), confusion (11%)

Dermatologic: Skin/mucous membrane dryness (77%), rash (54%), pruritus (20%), alopecia (14%)

Endocrine & metabolic: Hypercholesterolemia and/or hypertriglyceridemia (60%)

Gastrointestinal: Nausea/vomiting (57%), liver function tests increased (50% to 60%), GI hemorrhage (34%), abdominal pain (31%), mucositis (26%), diarrhea (23%), weight gain (23%), constipation (17%), dyspepsia (14%), abdominal distention (11%), weight loss (17%), xerostomia, anorexia (17%)

Hematologic: Hemorrhage (60%), leukocytosis (40%), disseminated intravascular coagulation (DIC) (26%)

Local: Phlebitis (11%), injection site reactions (17%)

Neuromuscular & skeletal: Bone pain (77%), paresthesia (17%), myalgia (14%)

Ocular: Visual disturbances (17%)

Otic: Earache/ear fullness (23%)

Renal: Renal insufficiency (11%)

Respiratory: Upper respiratory tract disorders (63%), dyspnea (60%), respiratory insufficiency (26%), pleural effusion (20%), pneumonia (14%), rales (14%), expiratory wheezing (14%), dry nose

Miscellaneous: Shivering (63%), infections (58%), retinoic acid-acute promyelocytic leukemia syndrome (25%), diaphoresis increased (20%)

1% to 10%:

Cardiovascular: Cerebral hemorrhage (9%), pallor (6%), cardiac failure (6%), cardiac arrest (3%), MI (3%), enlarged heart (3%), heart murmur (3%), stroke (3%), myocarditis (3%), pericarditis (3%), pulmonary hypertension (3%), secondary cardiomyopathy (3%), ischemia

Central nervous system: Intracranial hypertension (9%), agitation (9%), hallucination (6%), agnosia (3%), aphasia (3%), cerebellar edema (3%), cerebral hemorrhage (9%), seizure (3%), coma (3%), CNS depression (3%), dysarthria (3%), encephalopathy (3%), hypotaxia (3%), light reflex absent (3%), spinal cord disorder (3%), unconsciousness (3%), dementia (3%), forgetfulness (3%), somnolence (3%), slow speech (3%), hypothermia (3%)

Dermatologic: Cellulitis (8%), photosensitivity

Endocrine & metabolic: Acidosis (3%)

Gastrointestinal: Hepatosplenomegaly (9%), ulcer (3%)

Genitourinary: Dysuria (9%), acute renal failure (3%), micturition frequency (3%), renal tubular necrosis (3%), enlarged prostate (3%)

Hepatic: Ascites (3%), hepatitis (3%)

Neuromuscular & skeletal: Tremor (3%), leg weakness (3%), abnormal gait (3%), bone inflammation (3%), asterixis, dysarthria, facial paralysis, flank pain, hemiplegia, hyporeflexia

Ocular: Visual acuity change (6%), visual field deficit (3%), dry eyes

Otic: Hearing loss

Renal: Acute renal failure, renal tubular necrosis

Respiratory: Lower respiratory tract disorders (9%), pulmonary infiltration (6%), bronchial asthma (3%), pulmonary/larynx edema

Miscellaneous: Face edema

<1%: Arterial thrombosis, basophilia, cataracts, conjunctivitis, corneal opacities, erythema nodosum, erythrocyte sedimentation rate increased, gum bleeding, hematocrit decreased, hemoglobin decreased, hypercalcemia, hyperhistaminemia, hyperuricemia, inflammatory bowel syndrome, irreversible hearing loss, mood changes, myositis, optic neuritis, pancreatitis, pseudomotor cerebri, renal infarct, Sweet's syndrome, vasculitis, venous thrombosis

Oncology: Emetic PotentialModerate (30% to 60%)

Metabolism/Transport Effects**Substrate** (minor) of CYP2A6 (minor), 2B6 (minor), 2C8 (major), 2C9 (minor); **Inhibits** CYP2C9 (weak); **Induces** CYP2E1 (weak)

Drug Interactions

CYP2C8 Inducers (Highly Effective): May increase the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Moderate): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C8 Inhibitors (Strong): May decrease the metabolism of CYP2C8 Substrates (High risk). *Risk D: Consider therapy modification*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Retinoic Acid Derivatives may diminish the therapeutic effect of Oral Contraceptive (Estrogens). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): Retinoic Acid Derivatives may diminish the therapeutic effect of Oral Contraceptive (Progestins). Two forms of contraception are recommended in females of child-bearing potential during retinoic acid derivative therapy. *Risk C: Monitor therapy*

Tetracycline Derivatives: May enhance the adverse/toxic effect of Retinoic Acid Derivatives. The development of pseudotumor cerebri is of particular concern. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Absorption of retinoids has been shown to be enhanced when taken with food.

Herb/Nutraceutical: St John's wort may decrease tretinoin levels. Avoid dong quai, St John's wort (may also cause photosensitization). Avoid additional vitamin A supplementation. May lead to vitamin A toxicity.

Monitoring ParametersMonitor the patient's hematologic profile, coagulation profile, liver function test results and triglyceride and cholesterol levels frequently

Nursing: Physical Assessment/MonitoringTo be administered under the supervision of a physician who is experienced in the management of patients with acute leukemia. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking. Assess results of laboratory tests closely. Patient will require close monitoring (eg, cardiac, CNS, and respiratory status) on a frequent basis during therapy. Teach patient appropriate use, possible side effects/interventions, and adverse symptoms to report.

Monitoring: Lab TestsMonitor the patient's hematologic profile, coagulation profile, liver function results and triglyceride and cholesterol levels frequently. Consider temporary discontinuation if LFTs are >5 times the upper limit of normal.

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take with food. Do not crush, chew, or dissolve capsules. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid alcohol and foods containing vitamin A, and foods with high fat content. May cause lethargy, dizziness, visual changes, confusion, anxiety (avoid driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, loss of appetite, or dry mouth (small, frequent meals, chewing gum, or sucking lozenges may help); photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); dry, itchy skin; or dry or irritated eyes (avoid contact lenses). Report persistent vomiting or diarrhea, respiratory difficulty, unusual bleeding or bruising, acute GI pain, bone pain, swelling of extremities, unusual weight gain, or vision changes immediately. **Pregnancy/breast-feeding precautions:** Do not get pregnant (females) or cause a pregnancy (males) while taking this medication and for 1 month following completion of therapy. Consult prescriber for appropriate barrier contraceptive measures if necessary or if you suspect you might be pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 10 mg

Vesanoid®: 10 mg [contains soybean oil and parabens]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Vesanoid)

10 mg (30): $808.84

Mechanism of ActionTretinoin appears to bind one or more nuclear receptors and inhibits clonal proliferation and/or granulocyte differentiation

Pharmacodynamics/Kinetics

Protein binding: >95%

Metabolism: Hepatic via CYP; primary metabolite: 4-oxo-all-*trans*-retinoic acid

Half-life elimination: Terminal: Parent drug: 0.5-2 hours

Time to peak, serum: 1-2 hours

Excretion: Urine (63%); feces (30%)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness, anxiety, insomnia, depression, and confusion are common; may cause agitation, hallucinations, or cognitive impairment; may rarely cause mood changes

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms*trans*-Retinoic Acid; All-*trans*-Retinoic Acid; ATRA; NSC-122758; Ro 5488; tRA

References

Chen GQ, Shen ZX, Wu F, et al, “Pharmacokinetics and Efficacy of Low-Dose All-*trans* Retinoic Acid in the Treatment of Acute Promyelocytic Leukemia,” *Leukemia*, 1996, 10(5):825-8. [PubMed 8656678]

Kurzrock R, Estey E, and Talpaz M, “All-*trans* Retinoic Acid: Tolerance and Biologic Effects in Myelodysplastic Syndrome,” *J Clin Oncol*, 1993, 11(8):1489-95. [PubMed 8336187]

Lazzarino M, Regazzi MB, and Corso A, “Clinical Relevance of All-*trans* Retinoic Acid Pharmacokinetics and Its Modulation in Acute Promyelocytic Leukemia,” *Leuk Lymphoma*, 1996, 23(5-6):539-43. [PubMed 9031084]

Muindi JR, Frankel SR, Huselton C, et al, “Clinical Pharmacology of Oral All-*trans* Retinoic Acid in Patients With Acute Promyelocytic Leukemia,” *Cancer Res*, 1992, 52(8):2138-42. [PubMed 1559217]

Smith MA, Adamson PC, Balis FM, et al, “Phase I and Pharmacokinetic Evaluation of All-*trans*-Retinoic Acid in Pediatric Patients With Cancer,” *J Clin Oncol*, 1992, 10(11):1666-73.[PubMed 1403049]

International Brand NamesA-Acido (AR); Aberela (NO, SE); Acid A Vit (NL); Acne Free (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Airol (AR, CH, CZ, GR, IT, MY, TW); Alten (MY, SG); Avitcid (FI); Betarretin (PE); Derm A (PH); Effederm (FR); Eudyna (ID, MY, TW); Ilotycin-A (ZA); Locacid (IL); Optimal (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Renova (ZA); Retacnyl (CR, DO, GT, HN, MY, NI, PA, PE, PH, SG, SV, VE); Retavit (IL); Retin A (AT, BB, BM, BS, BZ, CZ, FR, GR, GY, HN, IL, JM, NL, PT, SR, TT); Retin-A (AU, BF, BH, BJ, BR, CH, CI, CN, CO, CY, ET, GB, GH, GM, GN, HK, ID, IE, IR, IT, JO, KE, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, PE, PH, SA, SC, SD, SL, SN, SY, TH, TN, TW, TZ, UG, ZA, ZM, ZW); Retin-a (PK); Retino-A (IN); Retinova (FR, NZ); Retirides (ES); Retrieve Cream (AU, HK); ReviDerm (ID); Stieva-A (AU, CO, KP, MY, PY, TH, UY); Stieva-A forte (MY); T3Actin (MY); Tracne (ID); Trentin (ID); Vesanoid (AR, AT, AU, BE, BR, CH, CN, CZ, FI, FR, GB, IE, IL, IT, JP, KP, MX, NL, NO, PE, PH, PK, PL, PY, TH, TW, VE)

Tretinoin (Topical)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Tretinoin may be confused with isotretinoin, trientine

International issues:

Renova® may be confused with Remov® which is a brand name for nimesulide in Italy

Pronunciation(TRET i noyn, TOP i kal)

U.S. Brand NamesAtralin™; Avita®; Renova®; Retin-A®; Retin-A® Micro; Tretin-X™

Canadian Brand NamesRejuva-A®; Retin-A®; Retin-A® Micro; Retinova®

Pharmacologic CategoryAcne Products; Retinoic Acid Derivative; Topical Skin Product, Acne

Use: Labeled IndicationsTreatment of acne vulgaris; photodamaged skin; palliation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin as part of a comprehensive skin care and sun avoidance program

Use: Unlabeled/InvestigationalSome skin cancers

Dosing: Adults

Acne vulgaris: Topical: Begin therapy with a weaker formulation of tretinoin (0.025% cream, 0.04% microsphere gel, or 0.01% gel) and increase the concentration as tolerated; apply once daily to acne lesions before retiring or on alternate days; if stinging or irritation develop, decrease frequency of application

Palliation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin: Topical: Pea-sized amount of the 0.02% or 0.05% cream applied to entire face once daily in the evening

Dosing: ElderlyUse of the 0.02% cream in patients 65-71 years of age showed similar improvement in fine wrinkles as seen in patients <65 years. Safety and efficacy of the 0.02% cream have not been established in patients >71 years of age. Safety and efficacy of the 0.05% cream have not been established in patients >50 years of age.

Dosing: PediatricChildren >12 years: Acne vulgaris: Topical: Refer to adult dosing.

Administration: TopicalPalliation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin: Cream: Prior to application, gently wash face with a mild soap. Pat dry. Wait 20-30 minutes to apply cream. Avoid eyes, ears, nostrils, and mouth.

StorageStore at 25°C (77°F). Gel is flammable; keep away from heat and flame.

ContraindicationsHypersensitivity to tretinoin or any component of the formulation; sunburn

Allergy Considerations

- Retinoid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Photosensitivity: Use is associated with increased susceptibility/sensitivity to UV light; avoid sunlamps or excessive sunlight exposure. Daily sunscreen use and other protective measures recommended.

- Skin irritation: Treatment can increase skin sensitivity to weather extremes of wind or cold. Also, concomitant topical medications (eg, medicated or abrasive soaps, cleansers, or cosmetics with a strong drying effect) should be used with caution due to increased skin irritation.

Disease-related concerns:

- Eczema: Use with caution in patients with eczema.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Dosage form specific issues:

- Cream 0.02% Do not use the 0.02% cream for longer than 52 weeks when using for palliation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin.

- Cream 0.05% Do not use the 0.05% cream for longer than 48 weeks when using for palliation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin.

- Gel: Flammable; do not expose to high temperatures or flame.

Other warnings/precautions:

- Appropriate use: For external use only; avoid contact with abraded skin, sunburned skin, mucous membranes, eyes, mouth, angles of the nose. Not for use on moderate- to heavily-pigmented skin.

Pregnancy Risk FactorC

Pregnancy ConsiderationsOral tretinoin is teratogenic and fetotoxic in rats at doses 1000 and 500 times the topical human dose, respectively. Tretinoin does not appear to be teratogenic when used topically since it is rapidly metabolized by the skin; however, there are rare reports of fetal defects. Use for acne only if benefit to mother outweighs potential risk to fetus. During pregnancy, do not use for palliation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin.

LactationEnters breast milk/compatible

Adverse Reactions

>10%: Dermatologic: Excessive dryness, erythema, scaling of the skin, pruritus

1% to 10%:

Dermatologic: Hyperpigmentation or hypopigmentation, photosensitivity, initial acne flare-up

Local: Edema, blistering, stinging

Metabolism/Transport Effects**Substrate** of CYP2A6 (minor), 2B6 (minor), 2C8 (major), 2C9 (minor); **Inhibits** CYP2C9 (weak); **Induces** CYP2E1 (weak)

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb Interactions

Food: Avoid excessive intake of vitamin A (cod liver oil, halibut fish oil).

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization). Avoid excessive amounts of vitamin A supplements.

Nursing: Physical Assessment/MonitoringAssess knowledge/instruct patient on appropriate application, possible adverse effects, and symptoms to report.

Patient EducationFor once-daily use, do not overuse. Avoid increased intake of vitamin A. Thoroughly wash hands before applying. Wash area to be treated at least 30 minutes before applying. Do not wash face more frequently than 2-3 times a day. Do not apply to areas near your mouth, eyes, corners of your nose, or open sores. Avoid using topical preparations that contain alcohol or harsh chemicals during treatment. It may take several weeks before the full benefit of the medication is seen. You may experience increased sensitivity to sunlight; protect skin with sunblock (minimum SPF 15), wear protective clothing, and avoid direct sunlight. Stop treatment and inform prescriber if rash, skin irritation, redness, scaling, or excessive dryness occurs. When used for hyperpigmentation and tactile redness of facial skin, wrinkles will not be eliminated. Must be used in combination with a comprehensive skin care program. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Gel: Flammable; do not expose to flame and do not smoke during use.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, topical: 0.025% (20 g, 45 g); 0.05% (20 g, 45 g); 0.1% (20 g, 45 g)

Avita®: 0.025% (20 g, 45 g)

Renova®: 0.02% (40 g, 60 g) [contains benzyl alcohol]

Retin-A®: 0.025% (20 g, 45 g); 0.05% (20 g, 45 g); 0.1% (20 g, 45 g)

Tretin-X™: 0.025% (35 g); 0.05% (35 g); 0.1% (35 g)

Gel, topical: 0.01% (15 g, 45 g); 0.025% (15 g, 45 g)

Atralin™: 0.05% (45 g) [contains benzyl alcohol and fish collagen]

Avita®: 0.025% (20 g, 45 g) [contains ethanol 83%]

Retin-A®: 0.01% (15 g, 45 g); 0.025% (15 g, 45 g) [contains ethanol 90%]

Tretin-X™: 0.025% (35 g); 0.01% (35 g) [contains ethanol 90%]

Gel, topical [microsphere gel]:

Retin-A® Micro: 0.04% (20 g, 45 g, 50 g); 0.1% (20 g, 45 g, 50 g) [contains benzyl alcohol]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Cream (Avita)

0.025% (20): $57.19

0.025% (45): $116.59

Cream (Renova)

0.02% (40): $169.08

Cream (Retin-A)

0.025% (20): $76.93

0.025% (45): $132.97

0.05% (20): $87.91

0.05% (45): $142.86

0.1% (20): $101.08

0.1% (45): $169.08

Gel (Atralin)

0.05% (45): $151.18

Gel (Avita)

0.025% (45): $116.59

Gel (Retin-A)

0.01% (15): $55.99

0.01% (45): $129.66

0.025% (15): $58.24

0.025% (45): $131.86

Gel (Retin-A Micro)

0.04% (20): $106.19

0.04% (45): $173.92

0.1% (20): $100.88

0.1% (45): $171.49

Gel (Retin-A Micro Pump)

0.04% (50): $199.10

0.1% (50): $200.47

Gel (Tretinoin)

0.01% (15): $35.99

Kit (Tretin-X)

0.01% gel (1): $132.98

0.025% cream (1): $138.30

0.025% gel (1): $139.99

0.05% cream (1): $167.56

0.1% cream (1): $171.57

Mechanism of ActionKeratinocytes in the sebaceous follicle become less adherent which allows for easy removal; inhibits microcomedone formation and eliminates lesions already present
Pharmacodynamics/Kinetics

Absorption: Minimal

Metabolism: Hepatic for the small amount absorbed

Excretion: Urine and feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index Terms*trans*-Retinoic Acid; Retinoic Acid; Vitamin A Acid
References

Winston MH, Shalita AR, “Acne Vulgaris, Pathogenesis and Treatment,” *Pediatr Clin North Am*, 1991, 38(4):889-903.[PubMed 1831256]

International Brand NamesAcfen-A (MX); Retacnyl (MX); Retin-A (MX); Stieva-A (MX)

Tretinoin-Idarubicin

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Myeloid M3 (Promyelocytic)

Regimen UseLeukemia, acute promyelocytic

RegimenNOTE: Multiple variations are listed below.

Induction:

Variation 1:

Tretinoin: Oral: 45 mg/m^2/day day 1 up to 90 days

[total dose/cycle = up to 4050 mg/m^2]

≤20 years: 25 mg/m^2/day day 1 up to 90 days

[total dose/cycle = up to 2250 mg/m^2]

Idarubicin: I.V.: 12 mg/m^2/day days 2, 4, 6, and 8

[total dose/cycle = 48 mg/m^2]

Consolidation:

Course 1:

Idarubicin: I.V.: 5 mg/m^2/day days 1 to 4

[total dose/cycle = 20 mg/m^2]

or

Idarubicin: I.V.: 7 mg/m^2/day days 1 to 4

[total dose/cycle = 28 mg/m^2]

Tretinoin: Oral: 45 mg/m^2/day days 1 to 15

[total dose/cycle = 675 mg/m^2]

Course 2:

Mitoxantrone: I.V.: 10 mg/m^2/day days 1 to 5

[total dose/cycle = 50 mg/m^2]

or

Mitoxantrone: I.V.: 10 mg/m^2/day days 1 to 5

[total dose/cycle = 50 mg/m^2]

Tretinoin: Oral: 45 mg/m^2/day days 1 to 15

[total dose/cycle = 675 mg/m^2]

Course 3:

Idarubicin: I.V.: 12 mg/m^2 day 1

[total dose/cycle = 12 mg/m^2]

or

Idarubicin: I.V.: 12 mg/m^2/day days 1 and 2

[total dose/cycle = 24 mg/m^2]

Tretinoin: Oral: 45 mg/m^2/day days 1 to 15

[total dose/cycle = 675 mg/m^2]

Administer courses sequentially at 1-month intervals for 3 months

Maintenance:

Mercaptopurine: Oral: 50 mg/m^2 daily

[total dose/cycle = 4500 mg/m^2 (90 days)]

Methotrexate: I.M.: 15 mg/m^2 weekly

[total dose/cycle = 180 mg/m^2]

Tretinoin: Oral: 45 mg/m^2/day days 1 to 15

[total dose/cycle = 675 mg/m^2]

Repeat cycle every 3 months for 2 years

Variation 2:

Induction:

Tretinoin: Oral: 45 mg/m^2/day day 1 up to 90 days

[total dose/cycle = up to 4050 mg/m^2]

<15 years: 25 mg/m^2/day day 1 up to 90 days

[total dose/cycle = up to 2250 mg/m^2]

Idarubicin: I.V.: 12 mg/m^2/day days 2, 4, 6, and 8

[total dose/cycle = 48 mg/m^2]

Consolidation:

Course 1:

Idarubicin: I.V.: 5 mg/m^2/day days 1 to 4

[total dose/cycle = 20 mg/m^2]

Course 2:

Mitoxantrone: I.V.: 10 mg/m^2/day days 1 to 5

[total dose/cycle = 50 mg/m^2]

Course 3:

Idarubicin: I.V.: 12 mg/m^2 day 1

[total dose/cycle = 12 mg/m^2]

Administer courses sequentially at 1-month intervals for 3 months

Maintenance:

Mercaptopurine: Oral: 90 mg/m^2 daily

[total dose/cycle = 8100 mg/m^2]

Methotrexate: I.M.: 15 mg/m^2 weekly

[total dose/cycle = 180 mg/m^2]

Tretinoin: Oral: 45 mg/m^2/day days 1 to 15

[total dose/cycle = 675 mg/m^2]

Repeat cycle every 3 months for 2 years

References

Variation 1: Sanz MA, Martin G, Gonzalez M, et al, “Risk-Adapted Treatment of Acute Promyelocytic Leukemia With All-Trans-Retinoic Acid and Anthracycline Monochemotherapy: A Multicenter Study by the PETHEMA Group,” *Blood*, 2004, 103(4):1237-43. [PubMed 14576047]

Variation 2: Sanz MA, Martin G, Rayon C, et al, “A Modified AIDA Protocol With Anthracycline-Based Consolidation Results in High Antileukemic Efficacy and Reduced Toxicity in Newly Diagnosed PML/RARalpha-Positive Acute Promyelocytic Leukemia,” *Blood* 1999, 94(9):3015-21.[PubMed 10556184]

Triacetin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Triacetin may be confused with Triacin速

Pronunciation(trye a SEE tin)

U.S. Brand NamesMyco-Nail [OTC]

Pharmacologic CategoryAntifungal Agent, Topical

Use: Labeled IndicationsFungistat for athlete's foot and other superficial fungal infections

Dosing: Adults**Superficial fungal infection:** Topical: Apply twice daily to affected areas; continue treatment for 7 days after symptoms have disappeared

Dosing: ElderlyRefer to adult dosing.

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, topical: 25% (30 mL)

Generic AvailableNo

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsGlycerol Triacetate

Triamcinolone Acetonide Paste

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Kenalog® may be confused with Ketalar®

Pronunciation(trye am SIN oh lone a SEE toe nide paste)

Canadian Brand NamesOracort®

Pharmacologic CategoryAnti-inflammatory Agent; Corticosteroid, Topical

Use: DentalFor adjunctive treatment and for the temporary relief of symptoms associated with oral inflammatory lesions and ulcerative lesions resulting from trauma

Dosing: Adults**Oral inflammatory lesions/ulcers:** Topical: Press a small dab (about $^1/_4$ inch) to the lesion until a thin film develops. A larger quantity may be required for coverage of some lesions. For optimal results use only enough to coat the lesion with a thin film.

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to triamcinolone or any component of the formulation; contraindicated in the presence of fungal, viral, or bacterial infections of the mouth or throat

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Impaired immune response: Normal immune responses of the oral tissues are depressed in patients receiving topical corticosteroid therapy; virulent strains of oral microorganisms may multiply without producing the usual warning symptoms of oral infections.

- Local irritation: If local irritation or sensitization should develop, the preparation should be discontinued.

Disease-related concerns:

- Diabetes: Use with caution in patients with diabetes mellitus.

- Peptic ulcer: Use with caution in patients with peptic ulcer.

- Tuberculosis: Use with caution in patients with tuberculosis.

Other warnings/precautions:

- Duration of therapy: If significant regeneration or repair of oral tissues has not occurred in seven days, re-evaluation of the etiology of the oral lesion is advised.

- Systemic effects: The small amount of steroid released from the topical preparation makes systemic effects very unlikely.

Pregnancy Risk FactorC

Adverse ReactionsNo data reported

Drug Interactions

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Paste, oral, topical, as acetonide: 0.1% (5 g)

Generic AvailableYes

Mechanism of ActionDecreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability; suppresses the immune system by reducing activity and volume of the lymphatic system; suppresses adrenal function at high doses

Pharmacodynamics/Kinetics

Absorption: Systemic

Half-life elimination, serum: Biological: 18-36 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesOracort (CA)

Triamcinolone

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Kenalog® may be confused with Ketalar®

Nasacort® may be confused with NasalCrom®

TAC (occasional abbreviation for triamcinolone) is an error-prone abbreviation (mistaken as tetracaine-adrenaline-cocaine)

Pronunciation(trye am SIN oh lone)

U.S. Brand NamesAristospan®; Azmacort®; Kenalog-10®; Kenalog-40®; Kenalog®; Nasacort® AQ; Tri-Nasal® [DSC]; Triderm®; Triesence™; Trivaris™; Zytopic™

Canadian Brand NamesAristospan®; Kenalog®; Kenalog® in Orabase; Nasacort® AQ; Oracort; Triaderm; Trinasal®

Pharmacologic CategoryCorticosteroid, Inhalant (Oral); Corticosteroid, Nasal; Corticosteroid, Ophthalmic; Corticosteroid, Systemic; Corticosteroid, Topical

Use: Labeled Indications

Intra-articular (soft tissue): Acute gouty arthritis, acute/subacute bursitis, acute tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis of osteoarthritis

Intralesional: Alopecia areata, discoid lupus erythematosus, keloids, granuloma annulare lesions (localized hypertrophic, infiltrated, or inflammatory), lichen planus plaques, lichen simplex chronicus plaques, psoriatic plaques, necrobiosis lipoidica diabeticorum, cystic tumors of aponeurosis or tendon (ganglia)

Nasal inhalation: Management of seasonal and perennial allergic rhinitis

Ophthalmic: Intravitreal: treatment of sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical corticosteroids

Triesence™: Visualization during vitrectomy

Oral inhalation: Control of bronchial asthma and related bronchospastic conditions

Oral topical: Adjunctive treatment and temporary relief of symptoms associated with oral inflammatory lesions and ulcerative lesions resulting from trauma

Systemic: Adrenocortical insufficiency, dermatologic diseases, endocrine disorders, gastrointestinal diseases, hematologic and neoplastic disorders, nervous system disorders, nephrotic syndrome, rheumatic disorders, allergic states, respiratory diseases, systemic lupus erythematosus (SLE), and other diseases requiring anti-inflammatory or immunosuppressive effects

Topical: Inflammatory dermatoses responsive to steroids

Use: DentalOral topical: Adjunctive treatment and temporary relief of symptoms associated with oral inflammatory lesions and ulcerative lesions resulting from trauma

Dosing: AdultsThe lowest possible dose should be used to control the condition; when dose reduction is possible, the dose should be reduced gradually. Parenteral dose is usually $^{1}/_{3}$ to $^{1}/_{2}$ the oral dose given every 12 hours. In life-threatening situations, parenteral doses larger than the oral dose may be needed.

Allergic rhinitis (perennial or seasonal):

Nasal spray: 220 mcg/day as 2 sprays in each nostril once daily; once symptoms controlled reduce to 110 mcg/day

Nasal inhaler: Initial: 220 mcg/day as 2 sprays in each nostril once daily; may increase dose to 440 mcg/day (given once daily or divided and given 2 or 4 times/day)

Asthma: Oral inhalation: 150 mcg 3-4 times/day **or** 300 mcg twice daily; maximum dose: 1200 mcg/day

NIH Asthma Guidelines (NIH, 2007) (administer in divided doses twice daily):

"Low" dose: 300-750 mcg/day

"Medium" dose: >750-1500 mcg/day

"High" dose: >1500 mcg/day

Carditis (acute rheumatic): Oral: Initial: 20-60 mg/day; reduce dose during maintenance therapy

Dermatoses (steroid-responsive, including contact/atopic dermatitis):

- Injection:
  - Acetonide: Intradermal: Initial: 1 mg
  - Hexacetonide: Intralesional, sublesional: up to 0.5 mg/square inch of affected skin
- Topical:
  - Cream, Ointment:
    - 0.025%: Apply thin film to affected areas 2-4 times/day
    - 0.1% or 0.5%: Apply thin film to affected areas 2-3 times/day
  - Spray: Apply to affected area 3-4 times/day

Hay fever/pollen asthma: I.M.: 40-100 mg as a single injection/season

Multiple sclerosis (acute exacerbation): I.M.: 160 mg daily for 1 week, followed by 64 mg every other day for 1 month

Ocular disease: Intravitreal: Initial: 4 mg as a single dose; additional doses may be given as needed

Oral inflammatory lesions/ulcers: Oral topical: Press a small dab (about $^1/_4$ inch) to the lesion until a thin film develops; a larger quantity may be required for coverage of some lesions. For optimal results, use only enough to coat the lesion with a thin film; do not rub in.

Rheumatic or arthritic disorders:

- Intra-articular (or similar injection as designated):
  - Acetonide: Intra-articular, intrabursal, tendon sheaths: Initial: Smaller joints: 2.5-5 mg, larger joints: 5-15 mg; may require up to 10 mg for small joints and up to 40 mg for large joints; maximum dose/treatment (several joints at one time): 20-80 mg
  - Hexacetonide: Intra-articular: Initial range: 2-20 mg/day
- I.M.:
  - Acetonide: Range: 2.5-100 mg/day; Initial: 60 mg

See table.

Triamcinolone Dosing

	Acetonide	**Hexacetonide**
Intrasynovial	5-40 mg	
Intralesional	1-30 mg (usually 1 mg per injection site); 10 mg/mL suspension usually used	Up to 0.5 mg/sq inch affected area
Sublesional	1-30 mg	
Systemic I.M.	2.5-60 mg/dose (usual adult dose: 60 mg; may repeat with 20-100 mg dose when symptoms recur)	
Intra-articular	2.5-40 mg	2-20 mg average
large joints	5-15 mg	10-20 mg
small joints	2.5-5 mg	2-6 mg
Tendon sheaths	2.5-10 mg	
Intradermal	1 mg/site	

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Allergic rhinitis (perennial or seasonal):

Nasal spray:

Children 2-5 years: 110 mcg/day as 1 spray in each nostril once daily (maximum: 110 mcg/day)

Children 6-11 years: Initial: 110 mcg/day as 1 spray in each nostril once daily; may increase to 220 mcg/day as 2 sprays in each nostril if response not adequate; once symptoms controlled may reduce to 110 mcg/day

Children ≥12 years: Refer to adult dosing.

Nasal inhaler:

Children 6-11 years: Initial: 220 mcg/day as 2 sprays in each nostril once daily

Children ≥12 years: Refer to adult dosing.

Asthma:*Oral inhalation:*

Children 6-12 years: 75-150 mcg 3-4 times/day **or** 150-300 mcg twice daily; maximum dose: 900 mcg/day

Children >12 years: Refer to adult dosing.

NIH Asthma Guidelines (NIH, 2007) (administer in divided doses twice daily):

Children: 5-11 years:

“Low” dose: 300-600 mcg/day

“Medium” dose: >600-900 mcg/day

“High” dose: >900 mcg/day

Children ≥12 years: Refer to adult dosing.

Ocular disease/visualization during vitrectomy: Refer to adult dosing.

Rheumatic conditions:*I.M. (acetonide):* Range: 2.5-100 mg/day

Children: Initial: 0.11-1.6 mg/kg/day in 3-4 divided doses

Children 6-12 years: Initial: 40 mg

Children ≥12 years: Refer to adult dosing.

Calculations

- Corticosteroid Conversion

Administration: I.M.Inject I.M. dose deep in large muscle mass, avoid deltoid.

Administration: Inhalation

Intranasal: Spray/inhaler: Shake well prior to use. Gently blow nose to clear nostrils.

Nasacort® AQ: Prime prior to first use, by shaking contents well and releasing 5 sprays into the air. If product is not used for more than 2 weeks, reprime with 1 spray.

Oral: Shake well prior to use. Rinse mouth and throat after using inhaler to prevent candidiasis. Use spacer device provided with Azmacort®. To prime inhaler prior to first use, shake inhaler, then press cannister to release 2 puffs. Inhaler will need to reprimed if not used for longer than 3 days.

Administration: Topical

Oral topical: Apply small dab to lesion until a thin film develops; do not rub in. Apply at bedtime or after meals if applications are needed throughout the day.

Topical:

Ointment: Apply a thin film sparingly. Do not use on open skin or wounds. Do not occlude area unless directed; if using occluding dressing, monitor for infection.

Spray: Avoid eyes and do not inhale if spraying near face. Occlusive dressing may be used if instructed; monitor for infection.

Administration: OtherAvoid subcutaneous administration.

Ophthalmic injection (intravitreal):

Triescence™: Not for I.V. use. Shake vial well prior to use. Administer under controlled aseptic conditions (eg, sterile gloves, sterile drape, sterile eyelid speculum). Adequate anesthesia and a broad-spectrum bactericidal agent should be administered prior to injection. Inject immediately after withdrawing from vial. If administration is required in the second eye, a new vial should be used. Do not use if agglomerated (clumpy or granular appearance).

Trivaris™: Can be administered intravitreal; **not for I.V use**. Bring to room temperature prior to administration. A 27 gauge $^{1}/_{2}$-inch needle is recommended for intravitreal administration.

Dietary Considerations

May be taken with food to decrease GI distress. Ensure adequate intake of calcium and vitamins (or consider supplementation) in patients on medium-to-high doses of systemic corticosteroids.

Storage

Injection, suspension:

Acetonide injectable suspension:

Kenalog®: Store at 20°C to 25°C (68°F to 77°F); avoid freezing. Protect from light.

Triesence™ : Store at 4°C to 25°C (39°F to 77°F); do not freeze. Protect from light.

Trivaris™: Store at 2°C to 8°C (36°F to 46°F); avoid freezing. Protect from light.

Hexacetonide injectable suspension: Diluted suspension stable up to 1 week.

Inhalation, oral: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F); avoid excessive heat. Do not puncture.

Intranasal: Store at controlled room temperature of 20°C to 25°C (68°F to 77°F); do not freeze.

Topical:

Ointment: Store at room temperature.

Spray: Store at room temperature; avoid excessive heat.

Reconstitution

Hexacetonide injectable suspension: Avoid diluents containing parabens, phenol, or other preservatives (may cause flocculation). Suspension for intralesional use may be diluted with D_5NS, $D_{10}NS$ or SWFI to a 1:1, 1:2, or 1:4 concentration. Solutions for intra-articular use, may be diluted with lidocaine 1% or 2%.

Contraindications

Hypersensitivity to triamcinolone or any component of the formulation; systemic fungal infections; primary treatment of status asthmaticus or other acute episodes of asthma; fungal, viral, or bacterial infections of the mouth or throat (oral topical formulation); cerebral malaria; idiopathic thrombocytopenic purpura (I.M. injection)

Allergy Considerations

- Corticosteroid Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Adrenal suppression: May cause hypercorticism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children or in patients receiving high doses for prolonged periods. HPA axis suppression may lead to adrenal crisis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully. Particular care is required when patients are transferred from systemic corticosteroids to inhaled products due to possible adrenal insufficiency or withdrawal from steroids, including an increase in allergic symptoms. Patients receiving >20 mg per day of prednisone (or equivalent) may be most susceptible. Fatalities have occurred due to adrenal insufficiency in asthmatic patients during and after transfer from systemic corticosteroids to aerosol steroids; aerosol steroids do **not** provide the systemic steroid needed to treat patients having trauma, surgery, or infections.

- Bronchospasm: May occur with wheezing after inhalation; if this occurs stop steroid and treat with a fast-acting bronchodilator (eg, albuterol).

- Delayed wound healing: Avoid nasal corticosteroid use in patients with recent nasal septal ulcers, nasal surgery or nasal trauma until healing has occurred.

- Immunosuppression: Prolonged use of corticosteroids may also increase the incidence of secondary infection, mask acute infection (including fungal infections), prolong or exacerbate viral infections, or limit response to vaccines. Exposure to chickenpox should be avoided; corticosteroids should not be used to treat ocular herpes simplex, cerebral malaria, or viral hepatitis. Close observation is required in patients with latent tuberculosis and/or TB reactivity; restrict use in active TB (only in conjunction with antituberculosis treatment). Use with caution in patients with threadworm infection; may cause serious hyperinfection.

- Kaposi's sarcoma: Prolonged treatment with corticosteroids has been associated with the development of Kaposi's sarcoma (case reports); if noted, discontinuation of therapy should be considered.

- Myopathy: Acute myopathy has been reported with high dose corticosteroids, usually in patients with neuromuscular transmission disorders; may involve ocular and/or respiratory muscles; monitor creatine kinase; recovery may be delayed.

- Psychiatric disturbances: Corticosteroid use may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes. Pre-existing psychiatric conditions may be exacerbated by corticosteroid use.

Disease-related concerns:

- Asthma: Supplemental steroids (oral or parenteral) may be needed during stress or severe asthma attacks. Not to be used in status asthmaticus or for the relief of acute bronchospasm.

- Cardiovascular disease: Use with caution in patients with HF or hypertension; long-term use has been associated with fluid retention and hypertension.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia.

- Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, peptic ulcer, ulcerative colitis) due to perforation risk.

- Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; long-term use has been associated with fluid retention.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids.

- Myocardial infarct (MI): Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

- Ocular disease: Use with caution in patients with cataracts and/or glaucoma; increased intraocular pressure, open-angle glaucoma, and cataracts have occurred with prolonged use. Risk is increased in patients receiving ophthalmic injection; monitor closely for increased intraocular pressure. Consider routine eye exams in chronic users. Do not use in patients with active ocular herpes simplex.

- Osteoporosis: Use with caution in patients with osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss and osteoporotic fractures.

- Renal impairment: Use with caution in patients with renal impairment; fluid retention and hypertension may occur.

- Seizure disorders: Use with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis.

- Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid ones.

- Tuberculosis: Restrict corticosteroid use to fulminating or disseminated tuberculosis; must be used in conjunction with appropriate tuberculosis regimen. Monitor closely in patients with latent tuberculosis.

Concurrent drug therapy issues:

- Immunizations: Patients should not be immunized with live, viral vaccines while receiving immunosuppressive doses of corticosteroids. The ability to respond to dead viral vaccines is unknown.

Special populations:

- Elderly: Because of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly in the smallest possible effective dose for the shortest duration. Azmacort® (metered dose inhaler) comes with its own spacer device attached and may be easier to use in older patients.

- Pediatrics: Orally-inhaled and intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients (~1 centimeter per year [range 0.3-1.8 cm per year] and related to dose and duration of exposure). To minimize the systemic effects of orally-inhaled and intranasal corticosteroids, each patient should be titrated to the lowest effective dose. Growth should be routinely monitored in pediatric patients.

Dosage form specific issues:

- High potency products: Avoid the use of high potency steroids on the face.

- Injection: Benzyl alcohol: Some injection suspension formulations contain benzyl alcohol; benzyl alcohol has been associated with the "gasping syndrome" in neonates and low-birth-weight infants.

- Injection: Ocular effects :Intravitreal (Triesence™, Trivaris™) injection has been associated with endophthalmitis and visual disturbances. Blindness has been reported following injection into nasal turbinates and intralesional injections into the head. Safety of intraturbinal, subconjunctival, subtenons, retrobulbar, or has not been demonstrated. Some formulations should not be administered intravitreally.

- Topical: Do not use occlusive dressings on weeping or exudative lesions and general caution with occlusive dressings should be observed; discontinue if skin irritation or contact dermatitis should occur; do not use in patients with decreased skin circulation.

- Topical (oral): Discontinue if local irritation or sensitization should develop. If significant regeneration or repair of oral tissues has not occurred in seven days, re-evaluation of the etiology of the oral lesion is advised.

Other warnings/precautions:

- Discontinuation of therapy: Withdraw systemic therapy with gradual tapering of dose. There have been reports of systemic corticosteroid withdrawal symptoms (eg, joint/muscle pain, lassitude, depression) when withdrawing oral inhalation therapy.

Geriatric ConsiderationsBecause of the risk of adverse effects, systemic corticosteroids should be used cautiously in the elderly, in the smallest possible dose, and for the shortest possible time. Azmacort® (metered dose inhaler) comes with its own spacer device attached and may be easier to use in older patients.

Pregnancy Risk FactorC/D (ophthalmic suspension)

Pregnancy ConsiderationsTriamcinolone was shown to be teratogenic following inhalation in animal studies and adverse events have been observed with corticosteroids in animal reproduction studies. Some studies have shown an association between first trimester corticosteroid use and oral clefts; adverse events in the fetus/neonate have been noted in case reports following large doses of systemic corticosteroids during pregnancy.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsCorticosteroids are excreted in human milk; information specific to triamcinolone has not been located.

Adverse Reactions

Inhalation (nasal, oral):

>10%:

Central nervous system: Headache (2% to 51%)

Respiratory: Pharyngitis (5% to 25%)

1% to 10%:

Cardiovascular: Facial edema (1% to 3%)

Central nervous system: Pain (1% to 3%)

Dermatologic: Photosensitivity (1% to 3%), rash (1% to 3%)

Endocrine & metabolic: Dysmenorrhea (≥2%)

Gastrointestinal: Taste perversion (5% to 8%), dyspepsia (3% to 5%), abdominal pain (1% to 5%), nausea (2% to 3%), diarrhea (1% to 3%), oral moniliasis (1% to 3%), toothache (1% to 3%), vomiting (1% to 3%), weight gain (1% to 3%), xerostomia (1% to 3%)

Genitourinary: Cystitis (1% to 3%), urinary tract infection (1% to 3%), vaginal moniliasis (1% to 3%)

Local: Nasal burning (≥2%; transient), nasal stinging (≥2%; transient)

Neuromuscular & skeletal: Back pain (2% to 8%), bursitis (1% to 3%), myalgia (1% to 3%), tenosynovitis (1% to 3%)

Ocular: Conjunctivitis (1% to 4%)

Otic: Otitis media (≥2%)

Respiratory: Sinusitis (2% to 9%), cough (≤8%), epistaxis (≤5%), bronchitis (children 3%), chest congestion (1% to 3%), asthma (≥2%), rhinitis (≥2%)

Miscellaneous: Flu-like syndrome (2% to 9%), voice alteration (1% to 3%), allergic reaction (≥2%), infection (≥2%)

<1%, postmarketing, and/or case reports: Anaphylaxis, blood cortisol decreased, bone mineral density loss (rare; prolonged use), cataracts, dizziness, dry throat, dyspnea, fatigue, glaucoma, growth suppression, hoarseness, hypersensitivity, insomnia, intraocular pressure increased, nasal septum perforation, oral candidiasis, osteoporosis (rare; prolonged use), pruritus, sneezing, throat irritation, urticaria (rare), wheezing, wound healing impaired

Injection:

Frequency not defined; reactions reported with corticosteroid therapy in general:

Cardiovascular: Arrhythmia, bradycardia, cardiac arrest, cardiac enlargement, CHF, circulatory collapse, edema, hypertension, hypertrophic cardiomyopathy (premature infants), myocardial rupture (following recent MI), syncope, tachycardia, thromboembolism, vasculitis

Central nervous system: Arachnoiditis (I.T.), depression, emotional instability, euphoria, headache, insomnia, intracranial pressure increased, malaise, meningitis (I.T.), mood changes, neuritis, neuropathy, personality change, pseudotumor cerebri (with discontinuation), seizure, vertigo

Dermatologic: Abscess (sterile), acne, allergic dermatitis, angioedema, atrophy (cutaneous/subcutaneous), bruising, dry skin, erythema, hair thinning, hirsutism, hyper-/hypopigmentation, hypertrichosis, impaired wound healing, lupus erythematosus-like lesions, petechiae, purpura, rash, skin test suppression, striae, thin skin

Endocrine & metabolic: Carbohydrate intolerance, Cushingoid state, diabetes mellitus, fluid retention, glucose intolerance, growth suppression (children), hypokalemia, hypokalemic alkalosis, menstrual irregularities, negative nitrogen balance, sodium retention, sperm motility altered

Gastrointestinal: Abdominal distention, appetite increased, GI hemorrhage, GI perforation, nausea, pancreatitis, peptic ulcer, ulcerative esophagitis, weight gain

Hepatic: Hepatomegaly, liver function tests increased

Local: Thrombophlebitis

Neuromuscular & skeletal: Aseptic necrosis of femoral and humeral heads, calcinosis, Charcot-like arthropathy, fractures, joint tissue damage, muscle mass loss, myopathy, osteoporosis, parasthesia, tendon rupture, vertebral compression fractures, weakness

Ocular: Cataracts, exophthalmos, glaucoma, ocular pressure increased, papilledema

Renal: Glycosuria

Respiratory: Pulmonary edema

Miscellaneous: Abnormal fat deposits, anaphylactoid reaction, anaphylaxis, diaphoresis, hiccups, infection, moon face

Ophthalmic:

>10%: Ocular: Cataract progression (20% to 60%), intraocular pressure increased (20% to 60%)

1% to 10%: Ocular: ≤2%: Blurred vision, conjunctival hemorrhage, discomfort (transient), endophthalmitis, glaucoma, hypopyon, inflammation, optic disc vascular disorder, retinal detachment, vitreous floaters, visual acuity decreased

<1%, postmarketing, and/or case reports: Exophthalmos

Topical:

Frequency not defined:

Dermatologic: Acneiform eruptions, allergic contact dermatitis, dryness, folliculitis,, hypertrichosis, hypopigmentation, itching, miliaria, perioral dermatitis, skin atrophy, skin infection (secondary), skin maceration, striae

Local: Burning, irritation

Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antidiabetic Agents: Corticosteroids (Orally Inhaled) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Orally Inhaled) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Triamcinolone interferes with calcium absorption.

Herb/Nutraceutical: Avoid cat's claw, echinacea (have immunostimulant properties).

Monitoring ParametersOphthalmic injection (intravitreal): Following injection monitor for increased intraocular pressure and endophthalmitis; check for perfusion of optic nerve head immediately after injection, tonometry within 30 minutes, biomicroscopy between 2-7 days after injection.

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess results of laboratory tests, therapeutic effectiveness, and adverse effects according to indications for therapy, dose, route (systemic or topical), and duration of therapy. With systemic administration, patients with diabetes should monitor glucose levels closely (corticosteroids may alter glucose levels). Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. When used for long-term therapy (>10-14 days), do not discontinue abruptly; decrease dosage incrementally.

Patient EducationThis drug is not intended for use during an acute asthma attack or for the relief of a bronchospasm. May take up to 2 weeks until the full effectiveness is seen. Use exactly as directed; do not increase dose or discontinue abruptly without consulting prescriber. Take oral medication with or after meals. Avoid alcohol. Limit intake of caffeine or stimulants. Prescriber may recommend increased dietary vitamins, minerals, or iron. If you have diabetes, monitor glucose levels closely (antidiabetic medication may need to be adjusted). Inform prescriber if you are experiencing greater than normal levels of stress (medication may need adjustment). Some forms of this medication may cause GI upset (oral medication may be taken with meals to reduce GI upset; or small frequent meals and frequent mouth care may reduce GI upset). You may be more susceptible to infection (avoid crowds and exposure to infection). Report promptly excessive nervousness or sleep disturbances; any signs of infection (sore throat, unhealed injuries); excessive growth of body hair or loss of skin color; vision changes; excessive or sudden weight gain (>3 lb/week); swelling of face or extremities; respiratory difficulty; muscle weakness; change in color of stools (black or tarry) or persistent abdominal pain; or worsening of condition or failure to improve. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Aerosol: Shake gently before use. Use at regular intervals, no more frequently than directed. Not for use during acute asthmatic attack. Follow directions that accompany product. Rinse mouth and throat after use to prevent candidiasis. Do not use intranasal product if you have a nasal infection, nasal injury, or recent nasal surgery. If using two products, consult prescriber in which order to use the two products. Report unusual cough or spasm; persistent nasal bleeding, burning, or irritation; or worsening of condition.

Inhalation: Sit when using. Take deep breaths for 3-5 minutes, and clear nasal passages before administration (use decongestant as needed). Hold breath for 5-10 seconds after use, and wait 1-3 minutes between inhalations. Follow package insert instructions for use. Do not exceed maximum dosage. If also using inhaled bronchodilator, use before triamcinolone. Rinse mouth and throat after use to reduce aftertaste and prevent candidiasis.

Topical: For external use only. Not for eyes or mucous membranes or open wounds. Apply in very thin layer to occlusive dressing. Apply dressing to area being treated. Avoid prolonged or excessive use around sensitive tissues, genital, or rectal areas. Inform prescriber if condition worsens (swelling, redness, irritation, pain, open sores) or fails to improve.

Product Availability Trivaris™: FDA approved June 2008; availability currently undetermined

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol for oral inhalation, as acetonide:

Azmacort®: 75 mcg per actuation (20 g) [contains chlorofluorocarbon; 240 actuations]

Aerosol, topical, as acetonide:

Kenalog®: 0.2 mg/2-second spray (63 g) [contains dehydrated ethanol 10.3%]

Cream, as acetonide: 0.025% (15 g, 80 g, 454 g); 0.1% (15 g, 80 g, 454 g, 2270 g); 0.5% (15 g)

Triderm®: 0.1% (30 g, 85 g)

Zytopic™: 0.1% (85 g)

Injection, suspension, as acetonide:

Kenalog-10®: 10 mg/mL (5 mL) [contains benzyl alcohol, polysorbate 80; not for I.V. or I.M. use]

Kenalog-40®: 40 mg/mL (1 mL, 5 mL, 10 mL) [contains benzyl alcohol, polysorbate 80; not for I.V. or intradermal use]

Triesence™: 40 mg/mL (1 mL) [contains polysorbate 80; not for I.V. use]

Trivaris™: 80 mg/mL (0.1 mL) [preservative free; not for I.V. use; (for intra-articular, intramuscular, intravitreal use)]

Injection, suspension, as hexacetonide:

Aristospan®: 5 mg/mL (5 mL); 20 mg/mL (1 mL, 5 mL) [contains benzyl alcohol, polysorbate 80; not for I.V. use]

Lotion, as acetonide: 0.025% (60 mL); 0.1% (60 mL)

Ointment, topical, as acetonide: 0.025% (15 g, 80 g, 454 g); 0.05% (430 g); 0.1% (15 g, 80 g, 454 g); 0.5% (15 g)

Paste, oral, topical, as acetonide: 0.1% (5 g)

Powder, for prescription compounding, as acetonide [micronized]: Triamcinolone acetonide USP (5 g)

Solution, intranasal, as acetonide [spray]:

Tri-Nasal®: 50 mcg/inhalation (15 mL) [120 actuations] [DSC]

Suspension, intranasal, as acetonide [spray]:

Nasacort® AQ: 55 mcg/inhalation (16.5 g) [120 actuations]

Generic AvailableYes: Cream, lotion, ointment, paste, powder
Pricing: U.S. (www.drugstore.com)

Aerosol solution (Azmacort)

75 mcg/ACT (20): $145.23

Aerosol solution (Kenalog)

(63): $65.99

Aerosol solution (Nasacort AQ)

55 mcg/ACT (16.5): $94.99

Cream (Kenalog)

0.1% (15): $18.99

0.5% (20): $54.99

Cream (Triamcinolone Acetonide)

0.025% (15): $11.99

0.025% (80): $12.99

0.1% (15): $11.99

0.1% (80): $12.99

0.1% (453.6): $29.99

0.5% (15): $12.99

Lotion (Kenalog)

0.1% (60): $51.99

Lotion (Triamcinolone Acetonide)

0.025% (60): $40.99

Ointment (Triamcinolone Acetonide)

0.025% (80): $9.99

0.1% (15): $8.99

0.1% (80): $25.99

0.5% (15): $14.99

Paste (Triamcinolone Acetonide)

0.1% (5): $42.99

Mechanism of ActionDecreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability; suppresses the immune system by reducing activity and volume of the lymphatic system; suppresses adrenal function at high doses

Pharmacodynamics/Kinetics

Duration: Oral: 8-12 hours

Absorption: Topical: Systemic

Distribution: V_d: 99.5 L

Protein binding: ~68%

Time to peak: I.M.: 8-10 hours

Half-life elimination: Biologic: 18-36 hours; Intravitreal: Nonvitrectomized patients: 13-24 days, Vitrectomized patients: ~3 days (based upon 1 patient)

Excretion: Urine (~40%); feces (~60%)

Related Information

- Asthma
- Corticosteroids
- Inhalant Agents

Pharmacotherapy Pearls16 mg triamcinolone is equivalent to 100 mg cortisone (no mineralocorticoid activity).

Effects of inhaled/intranasal steroids on growth have been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally-inhaled and intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Ulcerative esophagitis, perioral dermatitis, atrophy of oral mucosa, burning, irritation, and oral monilia (oral inhaler).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNervousness and insomnia are common; may cause drowsiness, delirium, euphoria, hallucinations, or mood swings

Mental Health: Effects on Psychiatric TreatmentBarbiturates may increase the metabolism of triamcinolone

Cardiovascular ConsiderationsInhaled steroid therapy, usually used for chronic obstructive lung disease, has the important advantage of having minimal systemic effects. The inhaled steroid, when administered appropriately, may be assumed to have pulmonary effects equivalent to about 10 mg of oral steroids but with minimal systemic consequences. Oral and intravenous steroid therapy in patients with heart failure should be administered cautiously with special attention given to signs and symptoms of fluid retention.

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Triamcinolone is a long-acting corticosteroid with minimal sodium-retaining potential.

Evidence-Based Information:

Neuromuscular Effects: ICU-acquired paresis was recently studied in five ICUs (three medical and two surgical ICUs) at four French hospitals. All ICU patients without pre-existing neuromuscular disease admitted from March 1999 through June 2000 were evaluated (de Jonghe, 2002). Each patient had to be mechanically ventilated for ≥7 days and was screened daily for awakening. The first day the patient was considered awake was Study Day 1. Patients with severe muscle weakness on Study Day 7 were considered to have ICU-acquired paresis. Among the 95 patients who were evaluated, about 25% developed ICU-acquired paresis. Independent predictors included female gender, the number of days with ≥2 organ dysfunction, and administration of corticosteroids. Further studies may be required to verify and characterize the association between the development of ICU-acquired paresis and use of corticosteroids. Concurrent use of a corticosteroid and muscle relaxant appears to increase the risk of certain ICU myopathies; avoid or administer the corticosteroid at the lowest dose possible.

Adrenal Insufficiency: Patients will often have steroid-induced adverse effects on glucose tolerance and lipid profiles. When discontinuing steroid therapy in patients on long-term steroid supplementation, it is important that the steroid therapy be discontinued gradually. Abrupt withdrawal may result in adrenal insufficiency with hypotension and hyperkalemia. Patients on long-term steroid supplementation will require higher corticosteroid doses when subject to stress (eg, trauma, surgery, severe infection). Guidelines for glucocorticoid replacement during various surgical procedures have been published (Coursin, 2002; Salem, 1994).

Index TermsTriamcinolone Acetonide, Aerosol; Triamcinolone Acetonide, Parenteral; Triamcinolone Diacetate, Oral; Triamcinolone Diacetate, Parenteral; Triamcinolone Hexacetonide; Triamcinolone, Oral

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International Brand NamesAdcortyl (GB, IE); Aristocort (BB, BM, BS, BZ, GY, JM, PR, SR, TT); Aristocort A (MY); Azmacort (BR, PK, PL); Delphicort (AT, DE); Dermacort (HK, MY); Ftorocort (BB, BM, BS, BZ, GY, JM, PR, SR, TT); Intralon (MX); Kanolone (MY); Kemzid (HK); Kenacort (AE, AR, BE, BH, CH, CY, EG, ET, FR, ID, IL, IN, IQ, IR, IT, JO, KE, KW, LB, LU, LY, NL, OM, PH, QA, SA, SE, SY, TW, TZ, UG, UY, VE, YE); Kenacort A (CL, CO); Kenacort E (PE); Kenacort IM (CO); Kenacort T (FI, NO); Kenacort T Munnsalve (NO); Kenacort-A (AU, CN, HK, MY, PE); Kenalog (DK, PK, PL); Kenalog in Orabase (AU, BF, BJ, CI, GH, GM, GN, LR, MA, ML, MR, MU, MW, MY, NE, NG, NZ, SC, SD, SL, SN, TN, ZA, ZM, ZW); Keno (SG); Ledercort (GB, IN, IT, LU, NL, PY, SE); Metoral (MY); Nasacort (BR, CN, ES, FI, GR, NO); Nasacort AQ (BF, BG, BJ, CI, CO, CR, CZ, DO, GH, GM, GN, GT, HK, HN, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, PA, PE, SC, SD, SL, SN, SV, TN, ZA, ZM, ZW); Nasocor AQ (BF, BJ, CI, GH, GM, GN, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, ZA, ZM, ZW); Nincort (CL); Oracort (NZ); Oramedy (HK, SG); Orrepaste (MY); Polcortolon [compr.] (PL); Polcortolone (HU); Shincort (HK, MY, SG); Simacort (TH); Sterocort (IL); Telnase (AU); Tracinone (KP); Triam-Denk (HK); Tricort (FI, TW); Tricortone (AU); Trigon (ES); Trinolon (ID); Volon (AT, DE)

Triamterene

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Triamterene may be confused with trimipramine

Dyrenium® may be confused with Pyridium®

Pronunciation(trye AM ter een)

U.S. Brand NamesDyrenium®

Pharmacologic CategoryDiuretic, Potassium Sparing

Use: Labeled IndicationsAlone or in combination with other diuretics in treatment of edema and hypertension; decreases potassium excretion caused by kaliuretic diuretics

Dosing: Adults**Edema, hypertension:** Oral: 100-300 mg/day in 1-2 divided doses; maximum dose: 300 mg/day; usual dosage range (JNC 7): 50-100 mg/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Hypertension (unlabeled use):** Oral: Initial: 1-2 mg/kg/day in 2 divided doses; maximum: 3-4 mg/kg/day, up to 300 mg/day

Dosing: Renal ImpairmentCl_{cr} <10 mL/minute: Avoid use.

Dosing: Hepatic ImpairmentDose reduction is recommended in patients with cirrhosis.

Calculations

- Creatinine Clearance: Adults

Dietary ConsiderationsMay be taken with food.

ContraindicationsHypersensitivity to triamterene or any component of the formulation; patients receiving other potassium-sparing diuretics; anuria; severe hepatic disease; hyperkalemia or history of hyperkalemia; severe or progressive renal disease; pregnancy (expert analysis)

Warnings/Precautions

Boxed warnings:

- Hyperkalemia: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Fluid/electrolyte loss: Excess amounts can lead to profound diuresis with fluid and electrolyte loss; close medical supervision and dose evaluation are required. Watch for and correct electrolyte disturbances; adjust dose to avoid dehydration.
- Hyperkalemia: **[U.S. Boxed Warning]: Hyperkalemia can occur; patients at risk include those with renal impairment, diabetes, the elderly, and the severely ill. Serum potassium levels must be monitored at frequent intervals especially when dosages are changed or with any illness that may cause renal dysfunction.**
- Photosensitivity: Can cause photosensitivity.

Disease-related concerns:

- Diabetes: Use with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.
- Hepatic impairment: Use with caution in patients with severe hepatic dysfunction; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.
- Kidney stones: Use with caution in patients with kidney stones.

Concurrent drug therapy issues:

- Potassium supplements: Avoid potassium supplements, potassium-containing salt substitutes, a diet rich in potassium, or other drugs that can cause hyperkalemia.

Geriatric ConsiderationsMonitor serum potassium.

Pregnancy Risk FactorB (manufacturer); D (expert analysis)

Pregnancy ConsiderationsNo data available. Generally, use of diuretics during pregnancy is avoided due to risk of decreased placental perfusion.

LactationExcretion in breast milk unknown

Breast-Feeding ConsiderationsNo data available.

Adverse Reactions

1% to 10%:

Cardiovascular: Hypotension, edema, CHF, bradycardia

Central nervous system: Dizziness, headache, fatigue

Gastrointestinal: Constipation, nausea

Respiratory: Dyspnea

<1% (Limited to important or life-threatening): Inability to achieve or maintain an erection, agranulocytosis, thrombocytopenia

Drug Interactions

ACE Inhibitors: Potassium-Sparing Diuretics may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Ammonium Chloride: Potassium-Sparing Diuretics may enhance the adverse/toxic effect of Ammonium Chloride. Specifically the risk of systemic acidosis. *Risk D: Consider therapy modification*

Angiotensin II Receptor Blockers: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Cardiac Glycosides: Potassium-Sparing Diuretics may diminish the therapeutic effect of Cardiac Glycosides. Specifically, the inotropic effects. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Drospirenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Eplerenone: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. Management: This combination is contraindicated in patients receiving eplerenone for treatment of hypertension. *Risk D: Consider therapy modification*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Indomethacin: May enhance the nephrotoxic effect of Triamterene. *Risk C: Monitor therapy*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Mitotane: Potassium-Sparing Diuretics may diminish the therapeutic effect of Mitotane. High dose diuretics (eg, Cushings syndrome) may present significantly higher risk than low doses (eg, CHF). *Risk D: Consider therapy modification*

Potassium Salts: May enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk D: Consider therapy modification*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

QuiNIDine: Potassium-Sparing Diuretics may diminish the therapeutic effect of QuiNIDine. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Test InteractionsInterferes with fluorometric assay of quinidine

Monitoring ParametersBlood pressure, serum electrolytes (especially potassium), renal function, weight, I & O

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 50 mg, 100 mg [contains benzyl alcohol]

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Dyrenium)

50 mg (30): $41.99

100 mg (30): $64.04

Mechanism of ActionInterferes with potassium/sodium exchange (active transport) in the distal tubule, cortical collecting tubule and collecting duct by inhibiting sodium, potassium-ATPase; decreases calcium excretion; increases magnesium loss

Pharmacodynamics/Kinetics

Onset of action: Diuresis: 2-4 hours

Duration: 7-9 hours

Absorption: Unreliable

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause drowsiness or dizziness

Mental Health: Effects on Psychiatric Treatment Triamterene may increase the side effects of amantadine (dizziness, nausea, dry mouth) necessitating a decrease in dosage; monitor

Cardiovascular Considerations Triamterene is usually combined with other antihypertensive agents for the treatment of hypertension. Triamterene may cause hyperkalemia, the ECG manifestations of which include peaked T waves, QRS prolongation, and cardiac conduction abnormalities.

Anesthesia and Critical Care Concerns/Other Considerations Abrupt discontinuation of therapy may result in rebound kaliuresis; taper off gradually. Triamterene may cause hyperkalemia particularly in diabetes mellitus and those patients with renal dysfunction.

References

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International Brand Names Diurene (ES); Dyrenium (CH); Dytac (BE, BF, BJ, CI, ET, GB, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Jatropur (DE); Triamteren (HU, PL); Triamthiazid (DE); Uretren (FI); Urinis (TW); Urocaudal (ES)

Triazolam

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Medication Safety Issues

Sound-alike/look-alike issues:

Triazolam may be confused with ALPRAZolam

Halcion® may be confused with halcinonide, Haldol®

Pronunciation(trye AY zoe lam)
U.S. Brand NamesHalcion®
Canadian Brand NamesApo-Triazo®; Gen-Triazolam; Halcion®
Pharmacologic CategoryBenzodiazepine
Use: Labeled IndicationsShort-term treatment of insomnia
Use: DentalOral premedication before dental procedures
Dosing: Adults**Note:** Onset of action is rapid, patient should be in bed when taking medication.

Insomnia (short-term): Oral: 0.125-0.25 mg at bedtime (maximum dose: 0.5 mg/day)

Dental (preprocedure): Oral: 0.25 mg taken the evening before oral surgery; or 0.25 mg 1 hour before procedure

Dosing: ElderlyOral: Insomnia (short-term use): Initial: 0.125 mg at bedtime; maximum dose: 0.25 mg/day
Dosing: Hepatic ImpairmentReduce dose or avoid use in cirrhosis.
Administration: OralMay take with food. Tablet may be crushed or swallowed whole. Onset of action is rapid, patient should be in bed when taking medication.
StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).
RestrictionsC-IV

An FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to triazolam or any component of the formulation (cross-sensitivity with other benzodiazepines may exist); concurrent therapy with itraconazole, ketoconazole, nefazodone, and other moderate/strong CYP3A4 inhibitors; pregnancy
Allergy Considerations

- Benzodiazepine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Anterograde amnesia: Benzodiazepines have been associated with anterograde amnesia.
- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hypersensitivity reactions: Postmarketing studies have indicated that the use of hypnotic/sedative agents for sleep has been associated with hypersensitivity reactions including anaphylaxis as well as angioedema.
- Paradoxical reactions: Paradoxical reactions, including hyperactive or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.
- Sleep-related activities: An increased risk for hazardous sleep-related activities such as sleep-driving; cooking and eating food, and making phone calls while asleep have also been noted.

Disease-related concerns:

- Depression: Use caution in patients with depression, particularly if suicidal risk may be present.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Impaired gag reflux: Use with caution in patients with an impaired gag reflux.
- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with respiratory compromise, COPD or sleep apnea.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers and major CYP3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

Special populations:

- Debilitated patients: Use with caution in debilitated patients.

- Elderly: Use with caution in the elderly; benzodiazepines have been associated with falls and traumatic injury.

- Fall risk: Use with extreme caution in patients who are at risk of falls; benzodiazepines have been associated with falls and traumatic injury.

Other warnings/precautions:

- Appropriate use: Does not have analgesic, antidepressant, or antipsychotic properties.

- Hypnotic: Appropriate use: Should be used only after evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric or medical illness. A worsening of insomnia or the emergence of new abnormalities of thought or behavior may represent unrecognized psychiatric or medical illness and requires immediate and careful evaluation. Prescription should be written for a maximum of 7-10 days and should not be prescribed in quantities exceeding a 1-month supply.

- Withdrawal: Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose. Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms. Flumazenil may cause withdrawal in patients receiving long-term benzodiazepine therapy. An increase in daytime anxiety may occur after as few as 10 days of continuous use, which may be related to withdrawal reaction in some patients.

Geriatric ConsiderationsDue to the higher incidence of CNS adverse reactions and its short half-life, this benzodiazepine is not a drug of first choice. For short-term only.

Pregnancy Risk FactorX

Pregnancy ConsiderationsOther benzodiazepines are known to cross the placenta and accumulate in the fetus. Teratogenic effects have been reported. Use of triazolam is contraindicated in pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if triazolam is excreted in breast milk; however, other benzodiazepines are known to be excreted in breast milk. The AAP rates use of related agents as “of concern” and breast-feeding is not recommended.

Adverse Reactions

>10%: Central nervous system: Drowsiness (14%)

1% to 10%:

Central nervous system: Headache (10%), dizziness (8%), nervousness (5%), lightheadedness (5%), ataxia (5%)

Gastrointestinal: Nausea (5%), vomiting (5%)

<1%, postmarketing, and/or case reports: Anaphylaxis, angioedema, anterograde amnesia; complex sleep-related behavior (sleep-driving, cooking or eating food, making phone calls); confusion, cramps, depression, dermatitis, dreaming/nightmares, dysesthesia, euphoria, fatigue, memory impairment, pain, paresthesia, tachycardia, visual disturbance, weakness, xerostomia

In addition, the following have been reported in association with triazolam and other benzodiazepines: Chest pain, dysarthria, libido changes; paradoxical reactions (eg, mania, sleep disturbances, hallucination, delusions, aggressiveness, falling, syncope); sedation, slurred speech

Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP2C8 (weak), 2C9 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Clozapine: Benzodiazepines may enhance the adverse/toxic effect of Clozapine. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Disulfiram: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Efavirenz: May increase the serum concentration of Triazolam. *Risk X: Avoid combination*

Fluconazole: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). Specifically, the active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Isoniazid: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Nefazodone: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Oral Contraceptive (Estrogens): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): May decrease the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Phenytoin: Benzodiazepines may increase the serum concentration of Phenytoin. Short-term exposure to benzodiazepines may not present as much risk as chronic therapy. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). Management: Amprenavir, atazanavir, darunavir, indinavir, nelfinavir, ritonavir, and tipranavir are contraindicated with midazolam and triazolam according to each protease inhibitor's prescribing information. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Benzodiazepines (metabolized by oxidation). **Exceptions:** Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Citalopram; Escitalopram; PARoxetine; Sertraline. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Benzodiazepines (metabolized by oxidation). *Risk C: Monitor therapy*

Theophylline Derivatives: May diminish the therapeutic effect of Benzodiazepines. *Risk D: Consider therapy modification*

Yohimbine: May diminish the therapeutic effect of Antianxiety Agents. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Food may decrease the rate of absorption. Benzodiazepine serum concentrations may be increased by grapefruit juice; monitor.

Herb/Nutraceutical: St John's wort may decrease levels/effects of benzodiazepines. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersRespiratory and cardiovascular status

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance; periodically evaluate need for continued use. Be alert to possibility of anaphylaxis any time during therapy. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Monitor for CNS depression. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before starting therapy. Do not give to sexually-active female patients unless capable of complying with contraceptive use.

Patient EducationTake exactly as directed; do not increase dose or frequency. Drug may cause physical and/or psychological dependence. Do not use alcohol or other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Avoid grapefruit juice. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, or dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); altered sexual drive or ability (reversible); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report persistent CNS effects (eg, memory impairment; confusion; depression; increased sedation; excitation; headache; agitation; insomnia or nightmares; dizziness; fatigue; impaired coordination; changes in personality, behavior, or cognition); changes in urinary pattern; muscle cramping, weakness, tremors, or rigidity; ringing in ears or visual disturbances; chest pain, palpitations, or rapid heartbeat; unusual swelling, especially on face or neck; excessive perspiration; excessive GI symptoms (cramping, constipation, vomiting, anorexia); or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant during or for 1 month following therapy. Consult prescriber for instruction on appropriate contraceptive measures. This drug may cause severe fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet: 0.125 mg, 0.25 mg

Halcion®: 0.125 mg [DSC], 0.25 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Halcion)

0.125 mg (30): $41.99

0.25 mg (30): $57.99

Tablets (Triazolam)

0.125 mg (30): $18.99

0.25 mg (30): $17.99

Mechanism of ActionBinds to stereospecific benzodiazepine receptors on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system, reticular formation. Enhancement of the inhibitory effect of GABA on neuronal excitability results by increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization.

Pharmacodynamics/Kinetics

Onset of action: Hypnotic: 15-30 minutes

Duration: 6-7 hours

Distribution: V_d: 0.8-1.8 L/kg

Protein binding: 89%

Metabolism: Extensively hepatic

Half-life elimination: 1.5-5.5 hours

Excretion: Urine as unchanged drug and metabolites

Related Information

- Benzodiazepines
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Dental Health Professional ConsiderationsTriazolam (0.25 mg) 1 hour prior to dental procedure has been used as an oral preop sedative.

Triazolam is a benzodiazepine and is being used in dentistry as a preprocedural oral sedative. There has been recent interest in its use as an orally titratable sedative to render anxious patients at ease during difficult dental procedures. This technique has been referred to as enteral conscious sedation (ECS) and oral conscious sedation (OCS).

Triazolam has the shortest half-life of all the orally administered benzodiazepines. Although midazolam is shorter, it is used parenterally, not orally. The relatively fast onset of action (15-30 minutes) of triazolam offers an advantage in its use as an oral sedative. The clinician is reminded that no kinetic data has been reported with multiple titration doses of triazolam, a technique often used in the ECS/OCS regimen.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep.

There are two subtypes of GABA receptors (GABA-A and GABA-B) and three different benzodiazepine receptors (Bz_1, Bz_2, and Bz_3). Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors. The role of GABA-B receptors is unclear. Benzodiazepines have no specificity for benzodiazepine receptor subtypes.

Triazolam is a short half-life benzodiazepine. Duration of action after a single dose is determined by redistribution rather than metabolism. Tolerance develops to the sedative, hypnotic, and anticonvulsant effects. It does not develop to the anxiolytic or skeletal muscle relaxing effects. Psychological and physical dependence may occur with prolonged use of benzodiazepines. The onset of withdrawal symptoms is usually seen on the first day without drug and lasts 5-7 days in patients receiving short half-life benzodiazepines, whereas, the onset occurs after 5 days with a duration of 10-14 days after abrupt discontinuance of long half-life benzodiazepines. Risk factors for abuse include personal or family history of substance abuse and personality disorder.

Anesthesia and Critical Care Concerns/Other Considerations Chronic use of this agent may increase the perioperative benzodiazepine dose needed to achieve desired effect. Abrupt discontinuation after sustained use (generally >10 days) may cause withdrawal symptoms.

References

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Varhe A, Olkkola KT, and Neuvonen PJ, “Oral Triazolam is Potentially Hazardous to Patients Receiving Systemic Antimycotics Ketoconazole or Itraconazole,” *Clin Pharmacol Ther*, 1994, 56(6 Pt 1):601-7. [PubMed 7995001]

Votey SR, Bosse GM, Bayer MJ, et al, “Flumazenil: A New Benzodiazepine Antagonist,” *Ann Emerg Med*, 1991, 20(2):181-8.[PubMed 1996802]

International Brand Names Arring (TW); Balidon (CN); Halcion (AT, AU, BB, BE, BF, BG, BJ, BM, BR, BS, BZ, CH, CI, CR, CZ, DE, DK, ES, ET, FI, FR, GB, GH, GM, GN, GR, GT, GY, HK, HN, HR, IE, IL, IT, JM, KE, KP, LR, LU, MA, ML, MR, MU, MW, MX, NE, NG, NI, NL, NO, PA, PK, PT, RU, SC, SD, SE, SL, SN, SR, SV, TH, TN, TR, TT, TW, TZ, UG, ZA, ZM, ZW); Hypam (NZ); Novidorm (AR); Nuctane (AR); Rilamir (DK, FI); Sleep (TW); Somese (CN, CO, EC, MY, PE, VE); Songar (IT); Trialam (TW); Triram (KP); Trycam (NZ); Zolmin (KP)

Trichloroacetic Acid

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(trye klor oh a SEE tik AS id)

U.S. Brand NamesTri-Chlor®; Trichlor Fresh Pac™

Pharmacologic CategoryKeratolytic Agent

Use: Labeled IndicationsChemical used in compounding agents for the treatment of warts, skin resurfacing (chemical peels)

Warnings/Precautions

Other warnings/precautions:

- Appropriate use: For prescription compounding and application by physician as part of a procedure. Serious injuries, including skin damage, burns, swelling, and pain may occur following improper application.

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid (Tri-Chlor®): 80% (15 mL)

Powder for reconstitution, topical (Trichlor Fresh Pac™): 10% (28 mL); 15% (28 mL); 20% (28 mL); 25% (28 mL); 30% (28 mL); 35% (28 mL); 40% (28 mL); 50% (28 mL) [supplied with diluent]

Generic AvailableYes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

References

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Levine PJ, "Chemical Facial Peel Formulations: An Overview," *International Journal of Pharmaceutical Compounding*, 1999, 3(5):375-7.

International Brand NamesAcido Tricloroacetico (IT); CL3 Bruciaporri (IT)

Trichophyton Skin Test'; return;">

Trichophyton Skin Test

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(trye koe FYE ton skin test)

Pharmacologic CategoryDiagnostic Agent

Use: Labeled IndicationsAssess cell-mediated immunity

Dosing: Adults**Diagnostic aid:** I.D.: 0.1 mL, examine reaction site in 24-48 hours; induration ≥5 mm in diameter is a positive reaction

Dosing: ElderlyRefer to adult dosing.

Administration: OtherAdminister by intradermal injection into flexor surface of forearm using a tuberculin syringe with a $^3/_8$" to $^1/_2$" 26- or 27-gauge needle; shallow SubQ injection is a less painful alternate method of administration; do not administer I.V.

StorageRefrigerate at 2°C to 8°C (36°F to 46°F).

Pregnancy Risk FactorC

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 1:200 (2 mL)

Generic AvailableYes

Related Information

- Skin Tests

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

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Triclosan and Fluoride

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Jump To Field (Select Field Name)

Pronunciation(trye KLOE san & FLOR ide)

U.S. Brand NamesColgate Total®

Pharmacologic Category[Antibacterial, Dental]; [Mineral, Oral, Topical]

Use: Labeled IndicationsUsed exclusively in dental applications

Use: DentalAnticavity, antigingivitis, antiplaque toothpaste

Dosing: Adults**Prevention of dental caries and gingivitis:** Oral: Brush teeth thoroughly after each meal or at least twice daily

Dosing: ElderlyRefer to adult dosing.

Warnings/Precautions

Special populations:

- Pediatrics: Antigingivitis and antiplaque effects have not been determined in children <6 years of age.

Other warnings/precautions:

- Accidental ingestion: If an amount greater than used for brushing is swallowed, seek professional assistance of contact a poison control center immediately.

Pregnancy Risk FactorNo data reported

Adverse ReactionsNo data reported

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Gel, oral [toothpaste]: Triclosan 0.30% and sodium fluoride 0.24% (119 g, 170 g, 221 g)

Paste, oral [toothpaste]: Triclosan 0.30% and sodium fluoride 0.24% (119 g, 170 g, 221 g)

Generic AvailableNo

Mechanism of ActionTriclosan is an antibacterial agent which helps to prevent gingivitis with regular use. Fluoride promotes remineralization of decalcified enamel, inhibits the cariogenic microbial process in dental plaque, and increases tooth resistance to acid dissolution

Dental Health Professional ConsiderationsIt has been shown that stannous fluoride and triclosan when formulated into a toothpaste vehicle provide plaque inhibitory effects. To provide a longer retention time of the triclosan in plaque, a polymer has been added to the toothpaste vehicle. The polymer is known as PVM/MA which stands for polyvinylmethyl ether/maleic acid copolymer, and is listed as an inactive ingredient (PVM/MA Copolymer) on the manufacturer's label. Studies have reported that the retention of triclosan in plaque (exceeding the minimal inhibitory concentration) after polymer application was 14 hours after brushing. Ongoing studies are evaluating the effects of triclosan/copolymer on alveolar bone loss. Rosling et al. have reported that the daily use of Colgate Total® reduced (1) the frequency of deep periodontal pockets and (2) the number of sites that exhibited additional probing attachment and bone loss.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported (see Dental Comment)

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFluoride and Triclosan (Dental)

References

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Trientine

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Trientine may be confused with Trental®, tretinoin

Pronunciation(TRYE en teen)
U.S. Brand NamesSyprine®
Canadian Brand NamesSyprine®
Pharmacologic CategoryChelating Agent
Use: Labeled IndicationsTreatment of Wilson's disease in patients intolerant to penicillamine
Dosing: Adults**Wilson's disease:** Oral (administer on an empty stomach): 750-1250 mg/day in divided doses 2-4 times/day; maximum dose: 2 g/day. The practice guideline suggests typical doses of 750-1500 mg/day in 2-3 divided doses with maintenance therapy of 750-1000 mg/day (Roberts, 2003)
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Wilson's disease:** Oral (administer on an empty stomach):

Children <12 years: 500-750 mg/day in divided doses 2-4 times/day; maximum: 1.5 g/day. The practice guideline suggests 20 mg/kg/day rounded off to the nearest 250 mg, given in 2-3 divided doses (Roberts, 2003).

Children ≥12 years: Refer to adult dosing.

Administration: OralDo not chew capsule, swallow whole followed by a full glass of water. Notify healthcare provider of any fever or skin changes. Any skin exposed to the contents of a capsule should be promptly washed with water.
Dietary ConsiderationsShould be taken 1 hour before or 2 hours after meals and at least 1 hour apart from any drug, food, or milk.
StorageStore at 2°C to 8°C (36°F to 46°F).
ContraindicationsHypersensitivity to trientine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Anemia: May cause iron-deficiency anemia; monitor closely.
- Copper deficiency: Induced by treatment; may lead to hepatic iron overload and/or sideroblastic anemia; reassess dose.
- Neurologic worsening: May occur with treatment initiation; less common than with penicillamine.

Other warnings/precautions:

- Hypersensitivity: Not reported with use; however, industrial workers exposed to trientine for prolonged periods have reported asthma, bronchitis, and dermatitis.

Pregnancy Risk FactorC
LactationExcretion in breast milk unknown/use caution
Adverse ReactionsFrequency not defined.

Central nervous system: Dystonia, malaise

Dermatologic: Rash, thickening and fissuring of skin

Endocrine & metabolic: Iron deficiency

Gastrointestinal: Abdominal pain, anorexia, aphthoid ulcer, colitis, epigastric pain, gastritis, heartburn, loss of taste

Hematologic: Aplastic anemia (rare), anemia, sideroblastic anemia (reversible)

Hepatic: Iron overload

Local: Tenderness

Neuromuscular & skeletal: Muscle cramps, muscle pain, muscular spasm, myasthenia gravis, rhabdomyolysis, weakness

Miscellaneous: Fixed drug eruption, lupus-like reactions

Drug Interactions

Antacids: May decrease the absorption of Trientine. *Risk D: Consider therapy modification*

Calcium Salts: May decrease the serum concentration of Trientine. Trientine may decrease the serum concentration of Calcium Salts. *Risk D: Consider therapy modification*

Carbonic Anhydrase Inhibitor Diuretics: May decrease the serum concentration of Trientine. *Risk C: Monitor therapy*

Iron Salts: Trientine may decrease the serum concentration of Iron Salts. Iron Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Magnesium Salts: Trientine may decrease the serum concentration of Magnesium Salts. Magnesium Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Zinc Salts: Trientine may decrease the serum concentration of Zinc Salts. Zinc Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Monitoring ParametersPeriodic 24-hour urinary copper assessment (every 6-12 months); free serum copper level

Reference RangeUrinary copper excretion: 200-500 mcg (3-8 micromoles)/day

Monitoring: Lab TestsPeriodic 24-hour urinary copper assessment (every 6-12 months); free serum copper level

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 250 mg

Generic AvailableNo

ManufacturerMerck & Co

Pricing: U.S. (www.drugstore.com)

Capsules (Syprine)

250 mg (100): $445.99

Mechanism of ActionTrientine hydrochloride is an oral chelating agent structurally dissimilar from penicillamine and other available chelating agents; an effective oral chelator of copper used to induce adequate cupriuresis

Pharmacodynamics/Kinetics

Absorption: Poor

Metabolism: To acetyltrien (chelating activity significantly less than parent)

Excretion: Urine (1% as parent; 8% as metabolite)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms2,2,2-tetramine; Trien; Trientine Hydrochloride; Triethylene Tetramine Dihydrochloride

References

Kodama H, Murata Y, Iitsuka T, et al, “Metabolism of Administrated Triethylene Tetramine Dihydrochloride In Humans,” *Life Sci*, 1997, 61(9):899-907.[PubMed 9284083]

Roberts EA and Schilsky ML, “A Practice Guideline on Wilson Disease,” *Hepatology*, 2003, 37(6):1475-92.[PubMed 12774027]

Walshe JM, “Treatment of Wilson's Disease With Trientine (Triethylene Tetramine) Dihydrochloride,” *Lancet*, 1982, 1(8273):643-7.[PubMed 6121964]

International Brand NamesSyprine (TW)

Triethanolamine Polypeptide Oleate-Condensate

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pronunciation(trye eth a NOLE a meen pol i PEP tide OH lee ate-KON den sate)
U.S. Brand NamesCerumenex® [DSC]
Canadian Brand NamesCerumenex®
Pharmacologic CategoryOtic Agent, Cerumenolytic
Use: Labeled IndicationsRemoval of ear wax (cerumen)
Dosing: Adults**Ear wax removal:** Otic: Fill ear canal, insert cotton plug; allow to remain 15-30 minutes; flush ear with lukewarm water as a single treatment; if a second application is needed for unusually hard impactions, repeat the procedure
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
ContraindicationsHypersensitivity to triethanolamine polypeptide oleate-condensate or any component of the formulation; perforated tympanic membrane or otitis media
Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue if sensitization or irritation occurs.

Other warnings/precautions:

- Administration: Avoid undue exposure to peridural skin during administration and the flushing out of ear canal.

Geriatric ConsiderationsAvoid contact with hearing aids.
Pregnancy Risk FactorC
Adverse Reactions<1%: Mild erythema and pruritus, severe eczematoid reactions, localized dermatitis
Drug InteractionsThere are no known significant interactions.
Monitoring ParametersEvaluate hearing before and after instillation of medication
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, otic: 10% (6 mL, 12 mL) [DSC]

Generic AvailableNo
Mechanism of ActionEmulsifies and disperses accumulated cerumen
Pharmacodynamics/KineticsOnset of action: Slight disintegration of very hard ear wax by 24 hours
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
References

Mehta AK, “An *In Vitro* Comparison of the Disintegration of Human Ear Wax by Five Cerumenolytics Commonly Used in General Practice,” *Br J Clin Pract*, 1985, 39(5):200-3.[PubMed 2416332]

Trifluoperazine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

Gill SS, Bronskill SE, Normand SL, et al, “Antipsychotic Drug Use and Mortality in Older Adults With Dementia,” *Ann Intern Med*, 2007, 146(11):775-86.[PubMed 17548409]

Schneeweiss S, Setoguchi S, Brookhart A, et al, “Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients,” *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Medication Safety Issues

Sound-alike/look-alike issues:

Trifluoperazine may be confused with triflupromazine, trihexyphenidyl

Stelazine® may be confused with selegiline

Pronunciation(trye floo oh PER a zeen)

Canadian Brand NamesApo-Trifluoperazine®; Novo-Trifluzine; PMS-Trifluoperazine; Terfluzine

Pharmacologic CategoryAntipsychotic Agent, Typical, Phenothiazine

Use: Labeled IndicationsTreatment of schizophrenia

Use: Unlabeled/InvestigationalManagement of psychotic disorders; behavioral symptoms associated with dementia behavior (elderly); psychosis/agitation related to Alzheimer's dementia

Dosing: Adults

Schizophrenia/psychoses: Oral:

Outpatients: 1-2 mg twice daily

Hospitalized or well supervised patient: Initial: 2-5 mg twice daily with optimum response in the 15-20 mg/day range; do not exceed 40 mg/day.

Nonpsychotic anxiety: Oral: 1-2 mg twice daily; maximum: 6 mg/day; therapy for anxiety should not exceed 12 weeks; do not exceed 6 mg/day for longer than 12 weeks when treating anxiety; agitation, jitteriness, or insomnia may be confused with original neurotic or psychotic symptoms.

Dosing: Elderly

Schizophrenia/psychoses: Oral: Refer to adult dosing. Dose selection should start at the low end of the dosage range and titration must be gradual.

Behavioral symptoms associated with dementia behavior (unlabeled use): Oral: Initial: 0.5-1 mg 1-2 times/day; increase dose at 4- to 7-day intervals by 0.5-1 mg/day; increase dosing intervals (bid, tid, etc) as necessary to control response or side effects. Maximum daily dose: 40 mg. Gradual increases (titration) may prevent some side effects or decrease their severity.

Dosing: Pediatric**Schizophrenia/psychoses:** Children 6-12 years: Oral: Hospitalized or well supervised patients: Initial: 1 mg 1-2 times/day, gradually increase until symptoms are controlled or adverse effects become troublesome; maximum: 15 mg/day.

Dosing: Renal ImpairmentNot dialyzable (0% to 5%)

Dietary ConsiderationsMay be taken with food to decrease GI distress.

ContraindicationsHypersensitivity to trifluoperazine or any component of the formulation (cross-reactivity between phenothiazines may occur); severe CNS depression; bone marrow suppression; blood dyscrasias; severe hepatic disease; coma

Allergy Considerations

- Phenothiazine Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction (life-threatening arrhythmias have occurred with therapeutic doses of phenothiazines).
- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to other antipsychotics, trifluoperazine has a low potency of cholinergic blockade.
- Blood dyscrasias: Check blood counts periodically and discontinue at first signs of blood dyscrasias; use is contraindicated in patients with bone marrow suppression.
- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).
- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is high relative to other neuroleptics). Risk of dystonia (and possibly other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.
- Neuroleptic malignant syndrome (NMS): May be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).
- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).
- Pigmentary retinopathy: May be associated with pigmentary retinopathy.
- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.
- Dementia: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo. An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Trifluoperazine is not approved for this indication.
- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.
- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.
- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.
- Renal impairment: Use with caution in patients with renal impairment.
- Respiratory disease: Use with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; increased risk for developing tardive dyskinesia.

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Geriatric ConsiderationsElderly are more susceptible to hypotension and neuromuscular reactions.

Many elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior. Before initiating antipsychotic medication, the clinician should investigate any possible reversible cause; any stress or stress from any disease can cause acute “confusion” or worsening of baseline nonpsychotic behavior. Most commonly acute changes in behavior are due to increases in drug dose or addition of new drug to regimen; fluid electrolyte loss; infections; and changes in environment.

Any changes in disease status in any organ system can result in behavior changes.

In the treatment of agitated, demented, elderly patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control.

Pregnancy Risk FactorC

LactationEnters breast milk/not recommended (AAP rates “of concern”)

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension, orthostatic hypotension, cardiac arrest

Central nervous system: Extrapyramidal symptoms (pseudoparkinsonism, akathisia, dystonias, tardive dyskinesia), dizziness, headache, neuroleptic malignant syndrome (NMS), impairment of temperature regulation, lowering of seizure threshold

Dermatologic: Increased sensitivity to sun, rash, discoloration of skin (blue-gray), photosensitivity

Endocrine & metabolic: Changes in menstrual cycle, libido (changes in), breast pain, hyperglycemia, hypoglycemia, gynecomastia, lactation, galactorrhea

Gastrointestinal: Constipation, weight gain, nausea, vomiting, stomach pain, xerostomia

Genitourinary: Difficulty in urination, ejaculatory disturbances, urinary retention, priapism

Hematologic: Agranulocytosis, leukopenia, pancytopenia, thrombocytopenic purpura, eosinophilia, hemolytic anemia, aplastic anemia

Hepatic: Cholestatic jaundice, hepatotoxicity

Neuromuscular & skeletal: Tremor

Ocular: Pigmentary retinopathy, cornea and lens changes

Respiratory: Nasal congestion

Metabolism/Transport Effects**Substrate** of CYP1A2 (major)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Analgesics (Opioid): Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antimalarial Agents: May increase the serum concentration of Antipsychotic Agents (Phenothiazines). *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Beta-Blockers: Antipsychotic Agents (Phenothiazines) may enhance the hypotensive effect of Beta-Blockers. Beta-Blockers may decrease the metabolism of Antipsychotic Agents (Phenothiazines). Antipsychotic Agents (Phenothiazines) may decrease the metabolism of Beta-Blockers. **Exceptions:** Atenolol; Levobunolol; Metipranolol; Nadolol. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP1A2 Inducers (Strong): May increase the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Moderate): May decrease the metabolism of CYP1A2 Substrates. *Risk C: Monitor therapy*

CYP1A2 Inhibitors (Strong): May decrease the metabolism of CYP1A2 Substrates. *Risk D: Consider therapy modification*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression). Avoid dong quai, St John's wort (may also cause photosensitization).

Test InteractionsFalse-positive for phenylketonuria

Monitoring ParametersVital signs; lipid profile, fasting blood glucose/Hgb A_{1c}; BMI; mental status, abnormal involuntary movement scale (AIMS)

Reference RangeTherapeutic response and blood levels have not been established

Nursing: Physical Assessment/MonitoringAssess other medications patient is taking for effectiveness and interactions. Review ophthalmic exam and monitor laboratory results, therapeutic effectiveness (according to rationale for therapy), and adverse reactions at beginning of therapy and periodically with long-term use. Initiate at lower doses and taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab Tests Lipid profile, fasting blood glucose, Hgb A_{1c}; BMI

Patient EducationUse exactly as directed; do not increase dose or frequency. Do not discontinue without consulting prescriber. Tablets may be taken with food. Do not take within 2 hours of any antacid. Avoid alcohol or caffeine and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience excess drowsiness, lightheadedness, dizziness, or blurred vision (use caution driving or when engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); postural hypotension (use caution climbing stairs or when changing position from lying or sitting to standing); urinary retention (void before taking medication); ejaculatory dysfunction (reversible); decreased perspiration (avoid strenuous exercise in hot environments); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report persistent CNS effects (eg, trembling fingers, altered gait or balance, excessive sedation, seizures, unusual movements, anxiety, abnormal thoughts, confusion, personality changes); chest pain, palpitations, rapid heartbeat, severe dizziness; unresolved urinary retention or changes in urinary pattern; altered menstrual pattern, changes in libido, swelling or pain in breasts (male or female); vision changes; skin rash, irritation, or changes in color of skin (gray-blue); or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 1 mg, 2 mg, 5 mg, 10 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Trifluoperazine HCl)

1 mg (60): $25.97

2 mg (60): $29.99

5 mg (60): $34.99

10 mg (60): $46.99

Mechanism of ActionTrifluoperazine is a piperazine phenothiazine antipsychotic which blocks postsynaptic mesolimbic dopaminergic receptors in the brain; exhibits alpha-adrenergic blocking effect and depresses the release of hypothalamic and hypophyseal hormones

Pharmacodynamics/Kinetics

Metabolism: Extensively hepatic

Half-life elimination: >24 hours with chronic use

Related Information

- Antipsychotic Agents
- CMS: Long-Term Care Facility Thresholds
- Liquid Compatibility

Pharmacotherapy PearlsDo not exceed 6 mg/day for longer than 12 weeks when treating anxiety. Agitation, jitteriness, or insomnia may be confused with original neurotic or psychotic symptoms.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant hypotension may occur, especially when the drug is administered parenterally; orthostatic hypotension is due to alpha-receptor blockade, the elderly are at greater risk for orthostatic hypotension. Xerostomia (normal salivary flow resumes upon discontinuation).

Tardive dyskinesia: Prevalence rate may be 40% in elderly; development of the syndrome and the irreversible nature are proportional to duration and total cumulative dose over time. Extrapyramidal reactions are more common in elderly with up to 50% developing these reactions after 60 years of age. Drug-induced Parkinson's syndrome occurs often; akathisia is the most common extrapyramidal reaction in elderly.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsMost pharmacology textbooks state that in presence of phenothiazines, systemic doses of epinephrine paradoxically decrease the blood pressure. This is the so called “epinephrine reversal” phenomenon. This has never been observed when epinephrine is given by infiltration as part of the anesthesia procedure.

Mental Health CommentOlder antipsychotic medications (chlorpromazine, haloperidol), which do not meet specific criteria for “atypical” antipsychotics, are often referred to as typical antipsychotics. They are associated with the troubling side effect, EPS. However, it is commonly believed that in order for a drug to treat psychosis, it must block dopamine is some manner.

Common side effects include sedation and neuroleptic effect (reduced initiative, interest in the environment, and display of emotion or affect). All **typical** antipsychotics are considered to be equally effective if given in equipotent doses. An inverse relationship exists between intrinsic antimuscarinic activity and propensity to cause extrapyramidal side effects. If dystonia or pseudoparkinsonism occurs, antiparkinsonian agents should be considered. If akathisia occurs, beta-blockers (eg, propranolol), benzodiazepines, or antiparkinsonian agents should be considered. Tardive dyskinesia (TD) secondary to typical antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. After this time period, the incidence is estimated to be 2% to 3% per year. Prevalence rates are ~15% to 20%. Female gender and age constitute risk factors for TD. Indeed, prevalence rates have been reported to be as high as 70% in elderly females. No specific treatment exists for TD, however, patients are often initiated on/switched to an atypical antipsychotic because of their lower incidence to cause TD and hopes of suppression.

Typical antipsychotics are usually only indicated for schizophrenia, but are generally effective for mania and psychosis and/or behavioral syndromes secondary to other mental conditions. Nonpsychiatric uses include Tourette's syndrome, Huntington's disease, and occasionally, intractable hiccups, pruritus, nausea, and vomiting.

These drugs are thought to exert their antipsychotic activity by blocking dopamine D_2 receptors in the mesolimbic dopaminergic pathway. Side effects are often related to their ability to antagonize dopamine receptors in the nigrostriatal and tuberoinfundibular pathways.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Anesthesia and Critical Care Concerns/Other ConsiderationsDo not exceed 6 mg/day for >12 weeks when treating anxiety; agitation, jitteriness or insomnia may be confused with original neurotic or psychotic symptoms.

Index TermsTrifluoperazine Hydrochloride

References

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FitzGerald MX and FitzGerald O, “Reaction to Trifluoperazine Abuse,” *Lancet*, 1969, 1(7605):1100.

Peabody CA, Warner MD, Whiteford HA, et al, “Neuroleptics and the Elderly,” *J Am Geriatr Soc*, 1987, 35(3):233-8. [PubMed 2880887]

Rabins PV, Blacker D, Rovner BW, et al, “Practice Guideline for the Treatment of Patients With Alzheimer's Disease and Other Dementias,” October, 2007. Available at http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm

Risse SC and Barnes R, “Pharmacologic Treatment of Agitation Associated With Dementia,” *J Am Geriatr Soc*, 1986, 34(5):368-76. [PubMed 2870097]

Saltz BL, Woerner MG, Kane JM, et al, “Prospective Study of Tardive Dyskinesia Incidence in the Elderly,” *JAMA*, 1991, 266(17):2402-6. [PubMed 1681122]

Seifert RD, “Therapeutic Drug Monitoring: Psychotropic Drugs,” *J Pharm Pract*, 1984, 6:403-16.

International Brand NamesApo-Trifluoperazine (PL); Eskazine (ES); Espazine (IN); Flupazine (MX); Flurazin (TW); Fuzine (TW); Jatroneural (DE); Jatroneural Retard (AT); Leptazine (VE); Modalina (IT); Modiur (CO); Psyrazine (TH); Stelazine (AE, AR, AU, BB, BF, BH, BJ, BM, BR, BS, BZ, CI, CO, CY, EG, ET, GB, GH, GM, GN, GR, GY, ID, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, NE, NG, NL, OM, PH, PK, PL, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TW, TZ, UG, YE, ZA, ZM, ZW); Stelazine Forte Solution (GB, IE); Terflurazine (ZA); Terfluzine (FR, HU, PL); Triflumed (TH); Trinicalm (IN); Triozine (TH)

Trifluridine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Viroptic® may be confused with Timoptic®

Pronunciation(trye FLURE i deen)
U.S. Brand NamesViroptic®
Canadian Brand NamesSAB-Trifluridine; Sandoz-Trifluridine; Viroptic®
Pharmacologic CategoryAntiviral Agent, Ophthalmic
Use: Labeled IndicationsTreatment of primary keratoconjunctivitis and recurrent epithelial keratitis caused by herpes simplex virus types I and II
Dosing: Adults**Herpes keratoconjunctivitis, keratitis:** Ophthalmic: Instill 1 drop into affected eye every 2 hours while awake, to a maximum of 9 drops/day, until re-epithelialization of corneal ulcer occurs. Then use 1 drop every 4 hours for another 7 days. Do **not** exceed 21 days of treatment. If improvement has not taken place in 7-14 days, consider another form of therapy.
Dosing: ElderlyRefer to adult dosing.
StorageRefrigerate at 2°C to 8°C (36°F to 46°F). Storage at room temperature may result in a solution altered pH which could result in ocular discomfort upon administration and/or decreased potency.
ContraindicationsHypersensitivity to trifluridine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Mild local irritation of conjunctival and cornea may occur when instilled but usually transient effects.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <6 years of age.

Geriatric ConsiderationsAssess ability to self-administer.
Pregnancy Risk FactorC
LactationExcretion in breast milk unknown
Adverse Reactions

1% to 10%: Local: Burning, stinging

<1%: Hyperemia, palpebral edema, epithelial keratopathy, keratitis, stromal edema, increased intraocular pressure, hypersensitivity reactions

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersOphthalmologic exam (test for corneal staining with fluorescein or rose bengal)
Nursing: Physical Assessment/MonitoringMonitor effectiveness of therapy, not for long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.
Patient EducationFor ophthalmic use only. Store in refrigerator; do not use discolored solution. Apply prescribed amount as often as directed. Wash hands before using. Do not let tip of applicator touch eye; do not contaminate tip of applicator (may cause eye infection, eye damage, or vision loss). Tilt head back and look upward. Gently pull down lower lid and put drop(s) in inner corner of eye. Close eye and roll eyeball in all directions. Do not blink for $^1/_2$ minute. Apply gentle pressure to inner corner of eye for 30 seconds. Wipe away excess from skin around eye. Do not use any other eye preparation for at least 10 minutes. Do not share medication with anyone else. May cause sensitivity to bright light (dark glasses may help); or temporary stinging or blurred vision may occur. Inform prescriber if you experience eye pain, redness, burning, watering, dryness, double vision, puffiness around eye, vision changes, or other adverse eye response; or worsening of condition or lack of improvement within 7-14 days. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic: 1% (7.5 mL)

Viroptic®: 1% (7.5 mL)

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Solution (Trifluridine)

1% (7.5): $117.75

Solution (Viroptic)

1% (7.5): $127.52

Mechanism of Action Interferes with viral replication by incorporating into viral DNA in place of thymidine, inhibiting thymidylate synthetase resulting in the formation of defective proteins

Pharmacodynamics/Kinetics Absorption: Ophthalmic: Systemic absorption negligible, corneal penetration adequate

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms F_3T; Trifluorothymidine

International Brand Names Bephen (HK, LU); Ocufridine (KP); TFT (BE, NL); TFT Ophtiole (PH, TW); Tri Fluoro Timidina Poen (AR); Triflumann (DE, LU); Trifluridin Thilo (AT); Triherpine (CH, HU, IT, PL); Trivirina (CO); Viridin (PT); Viromidin (ES); Virophta (FR)

Trihexyphenidyl

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Trihexyphenidyl may be confused with trifluoperazine

Artane may be confused with Altace®, Anturane®, Aramine®

Pronunciation(trye heks ee FEN i dil)

Canadian Brand NamesApo-Trihex®

Pharmacologic CategoryAnti-Parkinson's Agent, Anticholinergic; Anticholinergic Agent

Use: Labeled IndicationsAdjunctive treatment of Parkinson's disease; treatment of drug-induced extrapyramidal symptoms

Dosing: Adults**Parkinson's disease or drug-induced EPS:** Oral: Initial: 1-2 mg/day, increase by 2 mg increments at intervals of 3-5 days; usual dose: 5-15 mg/day in 3-4 divided doses

Dosing: ElderlyParkinsonism: Oral: 1 mg on first day, increase by 2 mg every 3-5 days as needed until a total of 6-10 mg/day (in 3-4 divided doses) is reached. If the patient is on concomitant levodopa therapy, the daily dose is reduced to 1-2 mg 3 times/day. Avoid use if possible (see Geriatric Considerations).

Administration: OralTolerated best if given in 3 daily doses and with food. High doses may be divided into 4 doses, at meal times and at bedtime. Patients may be switched to sustained-action capsules when stabilized on conventional dosage forms.

ContraindicationsHypersensitivity to trihexyphenidyl or any component of the formulation; narrow-angle glaucoma; pyloric or duodenal obstruction; stenosing peptic ulcers; bladder neck obstructions; achalasia; myasthenia gravis

Warnings/Precautions

Concerns related to adverse effects:

- Anhidrosis/hyperthermia: May cause anhidrosis and hyperthermia, which may be severe; use with caution in hot weather or during exercise, especially when administered concomitantly with other atropine-like drugs to chronically-ill patients, alcoholics, patients with CNS disease, or persons doing manual labor in a hot environment.
- Weakness: When given in large doses or to susceptible patients, may cause weakness and inability to move particular muscle groups.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with tachycardia, cardiac arrhythmias, hypertension, or hypotension.
- GI obstruction: Use with caution in patients with obstructive disease of the GI.
- Glaucoma: Use with caution in patients with glaucoma.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Mental illness: May exacerbate mental symptoms when used to treat extrapyramidal symptoms.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture or retention.
- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Elderly: Frequently develop increased sensitivity and require strict dosage regulation; side effects may be more severe in elderly patients with atherosclerotic changes.

Other warnings/precautions:

- Tardive dyskinesia: Does not relieve symptoms of tardive dyskinesia.

Geriatric ConsiderationsAnticholinergic agents are generally not well tolerated in the elderly (eg, confusion, constipation, urinary retention) and their use should be avoided when possible. In elderly, anticholinergic agents should not be used as prophylaxis against extrapyramidal symptoms.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsAnticholinergic agents may suppress lactation.

Adverse ReactionsFrequency not defined.

Cardiovascular: Tachycardia

Central nervous system: Confusion, agitation, euphoria, drowsiness, headache, dizziness, nervousness, delusions, hallucinations, paranoia

Dermatologic: Dry skin, increased sensitivity to light, rash

Gastrointestinal: Constipation, xerostomia, dry throat, ileus, nausea, vomiting, parotitis

Genitourinary: Urinary retention

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision, mydriasis, increase in intraocular pressure, glaucoma, blindness (long-term use in narrow-angle glaucoma)

Respiratory: Dry nose

Miscellaneous: Diaphoresis (decreased)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS depression).

Monitoring ParametersIOP monitoring and gonioscopic evaluations should be performed periodically

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Monitor renal function, therapeutic effectiveness, and adverse reactions (eg, anticholinergic syndrome) at beginning of therapy and periodically throughout therapy. Intraocular pressure monitoring and gonioscopic evaluations should be performed periodically. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed; with meals if GI upset occurs, before meals if dry mouth occurs, after eating if drooling or if nausea occurs. Take at the same time each day. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake; void before taking medication. Do not use alcohol and all prescription or OTC sedatives or CNS depressants without consulting prescriber. You may experience drowsiness, confusion, or vision changes (use caution when driving, climbing stairs, or engaging in tasks requiring alertness until response to drug is known); increased susceptibility to heat stroke, decreased perspiration (use caution in hot weather; maintain adequate fluids and reduce exercise activity); constipation (increased exercise, fluids, fruit, or fiber may help); or dry skin or nasal passages (consult prescriber for appropriate relief). Report unresolved constipation; chest pain or palpitations; respiratory difficulty; CNS changes (hallucination, loss of memory, nervousness, etc); painful or difficult urination; increased muscle spasticity or rigidity; skin rash; or significant worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Elixir, as hydrochloride: 2 mg/5 mL (480 mL)

Tablet, as hydrochloride: 2 mg, 5 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Trihexyphenidyl HCl)

2 mg (90): $22.99

5 mg (180): $65.99

Mechanism of ActionExerts a direct inhibitory effect on the parasympathetic nervous system. It also has a relaxing effect on smooth musculature; exerted both directly on the muscle itself and indirectly through parasympathetic nervous system (inhibitory effect)

Pharmacodynamics/Kinetics

Onset of action: Peak effect: ~1 hour

Half-life elimination: 3.3-4.1 hours

Time to peak, serum: 1-1.5 hours

Excretion: Primarily urine

Related Information

- Antiparkinsonian Agents
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsIncidence and severity of side effects are dose related. Patients may be switched to sustained-action capsules when stabilized on conventional dosage forms.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia, dry throat (normal salivary flow resumes upon discontinuation). Prolonged xerostomia may contribute to discomfort and dental disease (ie, caries, periodontal disease, and oral candidiasis).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentThis agent should not be used for an acute dystonic reaction. No injectable dosage form is available. However, oral dosage forms may be utilized to treat akathisia and pseudoparkinsonism. It is considered to be the least sedating antihistamine used to treat drug-induced EPS.

Index TermsArtane; Benzhexol Hydrochloride; Trihexyphenidyl Hydrochloride

References

Feinberg M, “The Problems of Anticholinergic Adverse Effects in Older Patients,” *Drugs Aging*, 1993, 3(4):335-48.[PubMed 8369593]

International Brand NamesACA (MY); Acamed (TH); Aparkan (HU); Apo-Trihex (MY); Arkine (ID); Artane (AE, AR, AT, AU, BE, BH, BR, CH, CN, CY, DE, EG, ES, FI, FR, GR, HR, IE, IL, IQ, IR, IT, JO, KW, LB, LU, LY, MY, NL, OM, PE, PT, QA, SA, SY, TW, YE, ZA); B-Hex (MY); Beahexol (SG); Benzhexol (CL, TH, TW, ZA); Broflex (GB); Desagit 5 (PY); Hexymer-2 (ID); Hipokinon (MX); Kinsol (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Pacitane (IN); Pargitan (SE); Parkan (HN, HU); Parkinane LP (FR); Parkopan (DE, EE, PL); Peragit (DK, NO); Pyramistin (JP); Sedrena (JP); Tridyl (TH); Trihexifenidilo (CO); Triphenidyl (CZ)

Trimebutine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(trye me BYOO teen)
Canadian Brand NamesApo-Trimebutine®; Modulon®
Pharmacologic Category5-HT_3 Receptor Antagonist
Use: Labeled IndicationsTreatment and relief of symptoms associated with irritable bowel syndrome (IBS) (spastic colon). In postoperative paralytic ileus in order to accelerate the resumption of the intestinal transit following abdominal surgery.
Dosing: Adults**Irritable bowel syndrome (IBS):** Oral: 200 mg 3 times/day before meals
Dosing: PediatricChildren ≥12 years: Refer to adult dosing.
Administration: OralAdminister before meals.
Dietary ConsiderationsShould be taken before meals.
StorageStore at room temperature of 15°C to 30°C.
RestrictionsNot available in U.S.
ContraindicationsHypersensitivity to trimebutine or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause drowsiness; use with caution in patients with CNS depression. Advise patient to avoid operating machinery/driving until response is known.

Concurrent drug therapy issues:

- Sedatives: May increase sedation from CNS depressants and/or ethanol.

Special populations:

- Safety and efficacy have not been established in children <12 years of age.

Pregnancy Risk FactorNot assigned; not recommended per manufacturer
Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use in pregnancy is not recommended per manufacturer.
LactationExcretion in breast milk unknown/not recommended
Adverse ReactionsMild to moderate effects in 7% of patients.

Central nervous system: Anxiety, drowsiness, dizziness, fatigue, headache

Dermatologic: Rash (0.4%)

Endocrine & metabolic: Gynecomastia, mastalgia, menstrual disorder

Gastrointestinal: Constipation, diarrhea, dyspepsia, epigastric discomfort, nausea, taste disorder, xerostomia

Genitourinary: Urinary retention

Otic: Hearing impairment

Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb InteractionsEthanol: Avoid use (may increase risk of sedation).
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as maleate: 100 mg, 200 mg

Generic AvailableNo
ManufacturerAxcan (Canada)
Mechanism of ActionSpasmolytic agent with antiserotonergic activity and moderate opiate receptor affinity. Reduces abnormal motility; does not alter normal GI motility.
Pharmacotherapy PearlsNot available in U.S.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness, anxiety, dizziness, or fatigue
Mental Health: Effects on Psychiatric TreatmentConcomitant use with psychotropic agents may produce additive sedative effects.
Index TermsTrimebutine Maleate
International Brand NamesAldar (UY); Biorgan (AR); Bumetin (CO); Cerekinon (CL, HK, JP, MY, SG, TH); Colobutine (BG, CZ); Debretin (PL); Debridat (AR, AT, CH, EC, FR, HU, IT, MX, PL, PT, VE); Debrum (IT); Depridat (PK); Digedrat (BR); Digerent (IT); Dolpic Forte (CN); Eumotil (UY); Fenatrop (AR); Garapepsin (GR); Ibutin (GR); Libertrim (MX); Modulon (FR); Mucarin (PY); Muvett (DO, EC, GT, PA, SV); Polibutin (ES); Recutin (KP); Tarabutine (KP); Tributin (CO); Tribux (PL); Trim (CN); Trima (MY); Trimet (PE)

Trimethobenzamide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Tigan® may be confused with Tiazac®, Ticar®, Ticlid®

Trimethobenzamide may be confused with metoclopramide, trimethoprim

Pronunciation(trye meth oh BEN za mide)
U.S. Brand NamesTigan®
Canadian Brand NamesTigan®
Pharmacologic CategoryAnticholinergic Agent; Antiemetic
Use: Labeled IndicationsTreatment of postoperative nausea and vomiting; treatment of nausea associated with gastroenteritis
Dosing: Adults

Nausea, vomiting:

Oral: 300 mg 3-4 times/day

I.M.: 200 mg 3-4 times/day

Postoperative nausea and vomiting (PONV): I.M.: 200 mg, followed 1 hour later by a second 200 mg dose

Dosing: ElderlyRefer to adult dosing. Consider dosage reduction or increasing dosing interval in elderly patients with renal impairment (specific adjustment guidelines are not provided in the manufacturer's labeling).
Dosing: Pediatric**Nausea, vomiting:** Children >40 kg: Oral: Refer to adult dosing. (Injection is contraindicated in children.)
Dosing: Renal ImpairmentCl_{cr} ≤70 mL/minute: Consider dosage reduction or increasing dosing interval (specific adjustment guidelines are not provided in the manufacturer's labeling)
Administration: I.M.Injection: Administer I.M. only. Inject deep into upper outer quadrant of gluteal muscle.
Administration: I.V.Injection: Not for I.V. administration.
Administration: I.V. DetailpH: 5
Administration: OralCapsule: Administer capsule orally without regard to meals.
StorageStore capsules and injection solution at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
Compatibility

Compatibility in syringe: Compatible: Glycopyrrolate, hydromorphone, midazolam, nalbuphine.

ContraindicationsHypersensitivity to trimethobenzamide or any component of the formulation; injection contraindicated in children
Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: The risk of CNS adverse effects (eg, coma, EPS, seizure) may be increased in patients with acute febrile illness, dehydration, electrolyte imbalance, encephalitis, and gastroenteritis; use with caution. May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Extrapyramidal symptoms: May cause extrapyramidal symptoms (EPS) which may be confused with CNS symptoms of primary disease responsible for emesis.

- Skin reactions: Allergic-type skin reactions have been reported with use; discontinue with signs of sensitization.

Disease-related concerns:

- Renal impairment: Trimethobenzamide clearance is predominantly renal; consider dosage reductions.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

Special populations:

- Pediatrics: Use capsule formulation with caution in children; antiemetics are not recommended for uncomplicated vomiting in children, limit antiemetic use to prolonged vomiting of known etiology. Use of injection is contraindicated in children.

Geriatric ConsiderationsNo specific data for use in the elderly have been established; as with any drug which has EPS adverse effects and possibility of confusion, caution should be used when administering to elderly.

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Safety and efficacy have not been established in pregnant patients. Trimethobenzamide has been used to treat nausea and vomiting of pregnancy.

LactationExcretion in breast milk unknown

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension (I.V. administration)

Central nervous system: Coma, depression, disorientation, dizziness, drowsiness, EPS, headache, Parkinson-like symptoms, seizure

Dermatologic: Allergic-type skin reactions

Gastrointestinal: Diarrhea

Hematologic: Blood dyscrasias

Hepatic: Jaundice

Local: Injection site burning, pain, redness, stinging, or swelling

Neuromuscular & skeletal: Muscle cramps, opisthotonos

Ocular: Blurred vision

Miscellaneous: Hypersensitivity reactions

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Concomitant use should be avoided (sedative effects may be additive).

Monitoring ParametersRenal function (at baseline)

Nursing: Physical Assessment/MonitoringAssess therapeutic effectiveness, and adverse reactions with first dose and on a regular basis during therapy (eg, hypovolemia, angioedema, postural hypotension). Teach patient appropriate use (if self-administered injection, teach injection technique and syringe disposal), possible side effects/interventions, and adverse symptoms to report.

Monitoring: Lab TestsRenal function (at baseline)

Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take capsule as directed before meals; do not increase dose and do not discontinue without consulting prescriber. If using injection formulation, follow directions for injection and disposal of syringe. May cause drowsiness or blurred vision (use caution when driving or engaging in tasks that require alertness until response to drug is known) or diarrhea (buttermilk or yogurt may help). Report chest pain or palpitations, persistent dizziness or blurred vision, or CNS changes (disorientation, depression, confusion). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 300 mg

Tigan®: 300 mg

Injection, solution, as hydrochloride: 100 mg/mL (2 mL)

Tigan®: 100 mg/mL (20 mL)

Injection, solution, as hydrochloride [preservative free]:

Tigan®: 100 mg/mL (2 mL)

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Tigan)

300 mg (30): $50.49

Capsules (Trimethobenzamide HCl)

300 mg (30): $39.99

Mechanism of ActionActs centrally to inhibit the medullary chemoreceptor trigger zone by blocking emetic impulses to the vomiting center

Pharmacodynamics/Kinetics

Onset of action: Antiemetic: Oral: 10-40 minutes; I.M.: 15-35 minutes

Duration: 3-4 hours

Metabolism: Via oxidation, forms metabolite trimethobenzamide N-oxide

Bioavailability: Oral: 60% to 100%

Half-life elimination: 7-9 hours

Time to peak: Oral: ~45 minutes; I.M.: ~30 minutes

Excretion: Urine (30% to 50%, as unchanged drug)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause dizziness; may rarely cause depression

Mental Health: Effects on Psychiatric TreatmentConcurrent use with psychotropics may produce additive sedation

Index TermsTrimethobenzamide Hydrochloride

References

ACOG (American College of Obstetrics and Gynecology) Practice Bulletin: "Nausea and Vomiting of Pregnancy," *Obstet Gynecol*, 2004, 103(4):803-14.[PubMed 15051578]

Ginsburg CM and Clahsen J, "Evaluation of Trimethobenzamide Hydrochloride (Tigan®) Suppositories for Treatment of Nausea and Vomiting in Children," *J Pediatr*, 1980, 96(4):767-9. [PubMed 7359291]

International Brand NamesAmetik (IT)

Trimethoprim and Polymyxin B

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(trye METH oh prim & pol i MIKS in bee)
U.S. Brand NamesPolytrimÂŽ
Canadian Brand NamesPMS-Polytrimethoprim; Polytrimâ˘
Pharmacologic CategoryAntibiotic, Ophthalmic
Use: Labeled IndicationsTreatment of surface ocular bacterial conjunctivitis and blepharoconjunctivitis
Dosing: Adults**Conjunctivitis, blepharoconjunctivitis:** Ophthalmic: Instill 1-2 drops in eye(s) every 4-6 hours
Dosing: ElderlyRefer to adult dosing.
Administration: OtherAvoid contamination of the applicator tip.
ContraindicationsHypersensitivity to trimethoprim, polymyxin B, or any component of the formulation
Warnings/PrecautionsSee individual agents.
Pregnancy Risk FactorC
Adverse Reactions1% to 10%: Local: Burning, stinging, itching, increased redness
Metabolism/Transport EffectsTrimethoprim: **Substrate** (major) of CYP2C9, 3A4; **Inhibits** CYP2C8 (moderate), 2C9 (moderate)
Drug Interactions

ACE Inhibitors: Trimethoprim may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amantadine: Trimethoprim may enhance the adverse/toxic effect of Amantadine. Specifically, the risk of myoclonus and/or delerium may be increased. Amantadine may increase the serum concentration of Trimethoprim. Trimethoprim may increase the serum concentration of Amantadine. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Trimethoprim may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Antidiabetic Agents (Thiazolidinedione): Trimethoprim may decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

AzaTHIOprine: Trimethoprim may enhance the myelosuppressive effect of AzaTHIOprine. *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Polymyxin B. *Risk C: Monitor therapy*

Colistimethate: Polymyxin B may enhance the neuromuscular-blocking effect of Colistimethate. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dapsone: Trimethoprim may increase the serum concentration of Dapsone. Dapsone may increase the serum concentration of Trimethoprim. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dofetilide: Trimethoprim may decrease the excretion of Dofetilide. *Risk X: Avoid combination*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

LamiVUDine: Trimethoprim may decrease the excretion of LamiVUDine. *Risk C: Monitor therapy*

Leucovorin-Levoleucovorin: May diminish the therapeutic effect of Trimethoprim. *Risk D: Consider therapy modification*

Memantine: Trimethoprim may enhance the adverse/toxic effect of Memantine. Specifically, the risk of myoclonus and/or delerium may be increased. Trimethoprim may increase the serum concentration of Memantine. Memantine may increase the serum concentration of Trimethoprim. *Risk C: Monitor therapy*

Methotrexate: Trimethoprim may enhance the adverse/toxic effect of Methotrexate. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents: Polymyxin B may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Phenytoin: Trimethoprim may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Procainamide: Trimethoprim may decrease the excretion of Procainamide. *Risk D: Consider therapy modification*

Repaglinide: Trimethoprim may decrease the metabolism of Repaglinide. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic: Trimethoprim 1 mg and polymyxin B sulfate 10,000 units per mL (10 mL) [contains benzalkonium chloride]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Solution (Polymyxin B-Trimethoprim)

10000-0.1 units/mg (10): $13.99

Solution (Polytrim)

10000-0.1 units/mg (10): $39.99

Pharmacodynamics/KineticsSee individual agents.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPolymyxin B and Trimethoprim

International Brand NamesDestrim (CO); Neoftalm (AR); Oftlamotrim (MY); Polytrim (AT, BE, NL, PT)

Trimethoprim

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Trimethoprim may be confused with trimethaphan

Proloprim® may be confused with Prolixin®, Protropin®

Pronunciation(trye METH oh prim)

U.S. Brand NamesPrimsol®

Canadian Brand NamesApo-Trimethoprim®

Pharmacologic CategoryAntibiotic, Miscellaneous

Use: Labeled IndicationsTreatment of urinary tract infections due to susceptible strains of *E. coli*, *P. mirabilis*, *K. pneumoniae*, *Enterobacter* sp and coagulase-negative *Staphylococcus* including *S. saprophyticus*; acute otitis media in children; acute exacerbations of chronic bronchitis in adults; in combination with other agents for treatment of toxoplasmosis, *Pneumocystis carinii*; treatment of superficial ocular infections involving the conjunctiva and cornea

Dosing: Adults**Susceptible infections:** Oral: 100 mg every 12 hours or 200 mg every 24 hours for 10 days; longer treatment periods may be necessary for prostatitis (ie, 4-16 weeks)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricOral: Children (>2 months or age): 4 mg/kg/day in divided doses every 12 hours

Dosing: Renal Impairment

Cl_{cr} 15-30 mL/minute: Administer 100 mg every 18 hours or 50 mg every 12 hours.

Cl_{cr} <15 mL/minute: Administer 100 mg every 24 hours or avoid use.

Moderately dialyzable (20% to 50%)

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister with milk or food.

Dietary ConsiderationsMay cause folic acid deficiency, supplements may be needed. Should be taken with milk or food.

StorageProtect the 200 mg tablet from light.

ContraindicationsHypersensitivity to trimethoprim or any component of the formulation; megaloblastic anemia due to folate deficiency

Warnings/Precautions

Concerns related to adverse effects:

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

Special populations:

- Patients with potential for folate deficiency: Use with caution in patients with potential folate deficiency (malnourished, chronic anticonvulsant therapy, or elderly).

Geriatric ConsiderationsTrimethoprim is often used in combination with sulfamethoxazole; it can be used alone in patients who are allergic to sulfonamides; adjust dose for renal function (see Pharmacokinetics and Dosage).

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no well-controlled studies on the use of trimethoprim during pregnancy. Because trimethoprim may interfere with folic acid metabolism, consider using only if the potential benefit to the mother outweighs the possible risk to the fetus.

LactationEnters breast milk/use caution (AAP rates “compatible”)

Adverse ReactionsFrequency not defined.

Central nervous system: Aseptic meningitis (rare), fever

Dermatologic: Maculopapular rash (3% to 7% at 200 mg/day; incidence higher with larger daily doses), erythema multiforme (rare), exfoliative dermatitis (rare), pruritus (common), phototoxic skin eruptions, Stevens-Johnson syndrome (rare), toxic epidermal necrolysis (rare)

Endocrine & metabolic: Hyperkalemia, hyponatremia

Gastrointestinal: Epigastric distress, glossitis, nausea, vomiting

Hematologic: Leukopenia, megaloblastic anemia, methemoglobinemia, neutropenia, thrombocytopenia

Hepatic: Liver enzyme elevation, cholestatic jaundice (rare)

Renal: BUN and creatinine increased

Miscellaneous: Anaphylaxis, hypersensitivity reactions

Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Substrate** (major) of CYP2C9, 3A4; **Inhibits** CYP2C8 (moderate), 2C9 (moderate)
Drug Interactions

ACE Inhibitors: Trimethoprim may enhance the hyperkalemic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amantadine: Trimethoprim may enhance the adverse/toxic effect of Amantadine. Specifically, the risk of myoclonus and/or delerium may be increased. Amantadine may increase the serum concentration of Trimethoprim. Trimethoprim may increase the serum concentration of Amantadine. *Risk C: Monitor therapy*

Angiotensin II Receptor Blockers: Trimethoprim may enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Antidiabetic Agents (Thiazolidinedione): Trimethoprim may decrease the metabolism of Antidiabetic Agents (Thiazolidinedione). *Risk C: Monitor therapy*

AzaTHIOprine: Trimethoprim may enhance the myelosuppressive effect of AzaTHIOprine. *Risk C: Monitor therapy*

CYP2C8 Substrates (High risk): CYP2C8 Inhibitors (Moderate) may decrease the metabolism of CYP2C8 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dapsone: Trimethoprim may increase the serum concentration of Dapsone. Dapsone may increase the serum concentration of Trimethoprim. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dofetilide: Trimethoprim may decrease the excretion of Dofetilide. *Risk X: Avoid combination*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

LamiVUDine: Trimethoprim may decrease the excretion of LamiVUDine. *Risk C: Monitor therapy*

Leucovorin-Levoleucovorin: May diminish the therapeutic effect of Trimethoprim. *Risk D: Consider therapy modification*

Memantine: Trimethoprim may enhance the adverse/toxic effect of Memantine. Specifically, the risk of myoclonus and/or delerium may be increased. Trimethoprim may increase the serum concentration of Memantine. Memantine may increase the serum concentration of Trimethoprim. *Risk C: Monitor therapy*

Methotrexate: Trimethoprim may enhance the adverse/toxic effect of Methotrexate. *Risk D: Consider therapy modification*

Phenytoin: Trimethoprim may decrease the metabolism of Phenytoin. *Risk C: Monitor therapy*

Procainamide: Trimethoprim may decrease the excretion of Procainamide. *Risk D: Consider therapy modification*

Repaglinide: Trimethoprim may decrease the metabolism of Repaglinide. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Reference RangeTherapeutic: Peak: 5-15 mg/L; Trough: 2-8 mg/L
Nursing: Physical Assessment/MonitoringPerform culture and sensitivity prior to initiating therapy. Assess potential for interactions with other pharmacological agents patient may be taking (eg, risk of increased or decreased levels/effects with other medications). Assess results of laboratory tests with long-term therapy. Evaluate therapeutic effectiveness (resolution of infection) and possible adverse reactions. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.
Monitoring: Lab TestsPeriodic CBC and serum potassium during long-term therapy. Perform culture and sensitivity prior to initiating therapy.
Patient EducationDo not take any new medication during therapy unless approved by prescriber. Take per recommended schedule. Complete full course of therapy even if feeling better; do not skip doses. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause nausea, vomiting, or GI upset (small, frequent meals, frequent mouth care, sucking lozenges, or chewing

gum may help). Report skin rash, redness, or irritation; feelings of acute fatigue or weakness; unusual bleeding or bruising; or other persistent adverse effects. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, oral:

Primsol®: 50 mg (base)/5 mL (473 mL) [dye free, ethanol free; contains propylene glycol, sodium benzoate; bubble gum flavor]

Tablet: 100 mg

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Tablets (Trimethoprim)

100 mg (30): $19.99

Mechanism of ActionInhibits folic acid reduction to tetrahydrofolate, and thereby inhibits microbial growth

Pharmacodynamics/Kinetics

Absorption: Readily and extensive

Distribution: Widely into body tissues and fluids (middle ear, prostate, bile, aqueous humor, CSF); crosses placenta; enters breast milk

Protein binding: 42% to 46%

Metabolism: Partially hepatic

Half-life elimination: 8-14 hours; prolonged with renal impairment

Time to peak, serum: 1-4 hours

Excretion: Urine (60% to 80%) as unchanged drug

Related Information

- Antimicrobial Drugs of Choice

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Glossitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine

Index TermsTMP

References

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International Brand NamesAbaprim (IT); Alprim (AU); Apo-Sulfatrim [+ Sulfamethoxazole] (PL); Bactrim [+ Sulfamethoxazole] (PL); Biseptol [+ Sulfamethoxazole] (PL); Catin (TW); Giprim (TW); Groseptol [+Sulfamethoxazole] (PL); Idotrim (SE); Infectotrimet (DE); l (IE); Monotrim (BF, BJ, CH, CI, DK, ET, GH, GM, GN, IE, KE, LR, MA, ML, MR, MU, MW, NE, NG, NL, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Motrim (AT); Primosept (CH); Septrin [+ Sulfamethoxazole] (PL); Sinersul (HR); Solotrim (AT, IL); Sulotrim (HR); Tediprima (ES); Tobyprim (ID); Trentina (ES); Trimcort (TW); Trimesan (PL); Trimetin (FI); Trimetop (EE); Trimetoprim (NO); Trimopan (DK, GB); Triprim (AU, CZ, TW); Two-Septol [+ Sulfamethoxazole] (PL); Urotrim (HR, PL); Utisept (TH); Wellcoprim (BE, FR, LU, NL)

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(tri me TREKS ate)

U.S. Brand NamesNeuTrexin® [DSC]

Pharmacologic CategoryAntineoplastic Agent, Miscellaneous

Use: Labeled IndicationsAlternative therapy for the treatment of moderate-to-severe *Pneumocystis jiroveci* pneumonia (PCP) in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS), who are intolerant of, or are refractory to, sulfamethoxazole/trimethoprim therapy or for whom sulfamethoxazole/trimethoprim and pentamidine are contraindicated

Use: Unlabeled/InvestigationalTreatment of nonsmall cell lung cancer, metastatic colorectal cancer, metastatic head and neck cancer, pancreatic adenocarcinoma, cutaneous T-cell lymphoma

Dosing: Adults**Note:** Concurrent leucovorin 20 mg/m^2 every 6 hours must be administered daily (oral or I.V.) during treatment and for 72 hours past the last dose of trimetrexate.

Pneumonia caused by*Pneumocystis jiroveci*(PCP): I.V.: 45 mg/m^2 once daily for 21 days; **alternative dosing based on weight:**

<50 kg: Trimetrexate 1.5 mg/kg/day; leucovorin 0.6 mg/kg 4 times/day

50-80 kg:Trimetrexate 1.2 mg/kg/day; leucovorin 0.5 mg/kg/4 times/day

>80 kg: Trimetrexate 1 mg/kg/day; leucovorin 0.5 mg/kg/4 times/day

Note: Oral doses of leucovorin should be rounded up to the next higher 25 mg increment.

Antineoplastic (unlabeled use): I.V.: 6-16 mg/m^2 once daily for 5 days every 21-28 days **or** 150-200 mg/m^2 every 2 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic ImpairmentAlthough it may be necessary to reduce the dose in patients with liver dysfunction, no specific dosage recommendations exist for treatment initiation with hepatic impairment.

Dosing: Adjustment for ToxicityLeucovorin therapy must be extended for 72 hours past the last dose of trimetrexate glucuronate.

Hematologic toxicity: See table.

Dosage Adjustment in Hematologic Toxicity

Toxicity Grade	**Neutrophils (Polys/Bands)**	**Platelets**	**Dosage Recommendations**	
			Trimetrexate	**Leucovorin**
1	>1000/mm^3	>75,000/mm^3	45 mg/m^2 once daily	20 mg/m^2 every 6 h
2	750-1000/mm^3	50,000-75,000/mm^3	45 mg/m^2 once daily	40 mg/m^2 every 6 h
3	500-749/mm^3	25,000-49,999/mm^3	22 mg/m^2 once daily	40 mg/m^2 every 6 h
4	<500/mm^3	<25,000/mm^3	Day 1-9: Discontinue Day 10-21: Interrupt up to 96 hours (see **Note**)	40 mg/m^2 every 6 h
Note:				

If Grade 4 hematologic toxicity occurs prior to day 10: Trimetrexate should be discontinued and leucovorin administered for an additional 72 hours.
If Grade 4 hematologic toxicity occurs at day 10 or later: Trimetrexate may be held up to 96 hours to allow counts to recover.
If counts recover to Grade 3 within 96 hours, trimetrexate should be administered at a dose of 22 mg/m^2 and leucovorin 40 mg/m^2 every 6 hours.
When counts recover to Grade 2 toxicity, trimetrexate may be increased to 45 mg/m^2. Continue leucovorin at 40 mg/m^2 for duration of treatment.
Discontinue trimetrexate if counts do not improve to less than or equal to Grade 3 toxicity within 96 hours. Continue leucovorin at 40 mg/m^2 every 6 hours for 72 hours following last dose.

Hepatic toxicity (during treatment): Hold drug therapy if transaminase levels or alkaline phosphatase levels increase to >5 times the upper limit of normal.

Renal toxicity (during treatment): Hold drug therapy if serum creatinine levels increase to >2.5 mg/dL and elevation is considered secondary to trimetrexate.

Other toxicities: Hold drug therapy in patients experiencing severe mucosal toxicity that interferes with oral intake. Treatment should be discontinued for fever that cannot be controlled with antipyretics (oral temperature ≥40.5°C/105°F).

In addition: If trimetrexate treatment is interrupted for toxicity, leucovorin therapy must continue for 72 hours past the last administered dose of trimetrexate.

Calculations

- Body Surface Area: Adults

Administration: I.V.Infuse over 60-90 minutes.
Administration: I.V. DetailMust be used with concurrent leucovorin; trimetrexate and leucovorin solutions **must** be administered separately. Intravenous lines should be flushed with at least 10 mL of D_5W before and after trimetrexate and between trimetrexate and leucovorin.

pH: 3.5-5.5

StoragePrior to reconstitution, vials should be stored at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light. Reconstituted solution is stable for 6 hours at room temperature and 24 hours under refrigeration. Diluted solutions for infusion are stable under refrigeration or at room temperature for 24 hours. Do not freeze. Precipitate occurs with leucovorin or any solution containing chloride ion.
ReconstitutionReconstitute with D_5W or SWFI to a concentration of 12.5 mg/mL. Do not use if cloudy or if precipitate forms. Prior to administration, solution should be further diluted with D_5W to a concentration of 0.25 mg/mL to 2 mg/mL.
CompatibilityStable in D_5W, sterile water for injection.

Y-site administration: Compatible: Amifostine, zidovudine. **Incompatible:** Foscarnet, indomethacin.

Compatibility when admixed: Incompatible: Chloride-containing solutions, leucovorin.

ContraindicationsHypersensitivity to trimetrexate, methotrexate, leucovorin, or any component of the formulation; severe existing myelosuppression; pregnancy
Allergy Considerations

- Methotrexate/Trimetrexate Allergy

Warnings/Precautions

Boxed warnings:

- Leucovorin: See “Concurrent drug therapy issues” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Hypersensitivity/allergic-type reactions have been reported, primarily when given as a bolus infusion, at higher than recommended doses for PCP, or in combination with fluorouracil or leucovorin. May cause anaphylactoid reactions (rarely) including acute hypotension and loss of consciousness. Epinephrine should be available for treatment of acute allergic symptoms.

Disease-related concerns:

- Bone marrow suppression: Use with caution in patients with mild myelosuppression.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hypoalbuminemia/hypoproteinemia: Use with caution in patients with hypoalbuminemia or hypoproteinemia.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Leucovorin: **[U.S. Boxed Warning]: Must be administered with concurrent leucovorin to avoid potentially serious or life-threatening toxicities.** Leucovorin therapy must extend for 72 hours past the last dose of trimetrexate.
- Myelosuppressive therapies: Use with caution in patients on previously extensive myelosuppressive therapies.
- Zidovudine: Withhold zidovudine during trimetrexate treatment.

Geriatric ConsiderationsNo specific recommendations are available for the elderly. Use with caution in patients with liver dysfunction (see Dosage).

Pregnancy Risk FactorD

Pregnancy ConsiderationsTeratogenic effects and fetal loss were observed in animal studies. May cause fetal harm when administered to pregnant women. Women of childbearing potential should avoid becoming pregnant while receiving treatment. If used in pregnancy, or if patient becomes pregnant during treatment, the patient should be apprised of potential hazard to the fetus.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is recommended to discontinue breast-feeding during trimetrexate therapy.

Adverse Reactions

>10%:

Hematologic: Neutropenia (30%)

Hepatic: ALT increased (11%), AST increased (14%)

1% to 10%:

Central nervous system: Fever (8%), confusion (3%), fatigue (2%)

Dermatologic: Rash/pruritus (6%)

Endocrine & metabolic: Hyponatremia (5%), hypocalcemia (2%)

Gastrointestinal: Nausea/vomiting (5%), stomatitis

Hematologic: Thrombocytopenia (10%), anemia (7%)

Hepatic: Alkaline phosphatase increased (5%), bilirubin increased (2%)

Neuromuscular & skeletal: Peripheral neuropathy

Miscellaneous: Flu-like illness; hypersensitivity/allergic reactions (chills, rigors); anaphylactoid reactions (acute hypotension, loss of consciousness)

<1%: Seizure, serum creatinine increased

Oncology: VesicantNo

Oncology: Emetic PotentialLow (<10%)

Drug Interactions

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Monitoring ParametersCheck and record patient's temperature daily; absolute neutrophil counts (ANC), platelet count, renal function tests (serum creatinine, BUN), and hepatic function tests (ALT, AST, alkaline phosphatase) twice weekly

Nursing: Physical Assessment/MonitoringTrimetrexate must be administered with concurrent leucovorin to avoid potentially serious or life-threatening toxicities. Leucovorin therapy must extend for 72 hours past the last dose of trimetrexate to reduce potential for life-threatening toxicities. Assess potential for interactions with other pharmacological agents patient may be taking. Patient must be monitored closely for anaphylactoid reactions; epinephrine should be available. Assess results of laboratory tests at baseline and periodically during therapy. Assess therapeutic effectiveness and adverse reactions (eg, rash, gastrointestinal upset, anemia, peripheral neuropathy, increased LFTs). Teach patient importance of maintaining prescribed schedule of leucovorin, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsAbsolute neutrophil counts (ANC), platelet count, renal function tests (serum creatinine, BUN), and hepatic function (ALT, AST, alkaline phosphatase) twice weekly

Patient EducationDo not take any new medication during therapy unless approved by prescriber (especially aspirin or aspirin-containing products). This medication is only administered by intravenous infusion. Report immediately any redness, swelling, or pain at infusion site. This medication is administered concurrently with an oral medication (leucovorin); maintain exact schedule as prescribed for oral medication in order to reduce potential for serious reaction. Maintain adequate hydration (2-3 L/day of fluids unless instructed to restrict fluid intake).

You may be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations unless approved by prescriber). Report unusual or persistent fever, chills, or joint pain; persistent gastrointestinal upset; changes in sensorium (eg, confusion, unusual or excessive fatigue); or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication or for 1 month after completing therapy. Consult prescriber for appropriate contraceptive measures. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, powder for reconstitution [preservative free]:

NeuTrexin®: 25 mg, 200 mg [DSC]

Generic AvailableNo

Mechanism of ActionTrimetrexate is a folate antimetabolite that inhibits DNA synthesis by inhibition of dihydrofolate reductase (DHFR); DHFR inhibition reduces the formation of reduced folates and thymidylate synthetase, resulting in inhibition of purine and thymidylic acid synthesis.

Pharmacodynamics/Kinetics

Distribution: V_d: 0.62 L/kg

Protein binding: 80% to 90% (concentration dependent)

Metabolism: Extensively hepatic: O-demethylation followed by conjugation to glucuronide or sulfate (major); N-demethylation and oxidation (minor)

Half-life elimination: 9-18 hours (11 hours with leucovorin)

Excretion: Urine (10% to 40% as unchanged drug); feces (<1% to 8%)

Related Information

- Safe Handling of Hazardous Drugs

Pharmacotherapy PearlsNot a vesicant; methotrexate derivative

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine

Index TermsNSC-352122; Trimetrexate Glucuronate

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International Brand NamesNeuTrexin (AR, DK, ES, FR, GB, IT, LU, NL, NO)

Trimipramine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Trimipramine may be confused with triamterene, trimeprazine

Pronunciation(trye MI pra meen)

U.S. Brand NamesSurmontil®

Canadian Brand NamesApo-Trimip®; Nu-Trimipramine; Rhotrimine®; Surmontil®

Pharmacologic CategoryAntidepressant, Tricyclic (Tertiary Amine)

Use: Labeled IndicationsTreatment of depression

Dosing: Adults**Depression:** Oral: 50-150 mg/day as a single bedtime dose up to a maximum of 200 mg/day for outpatients and 300 mg/day for inpatients

Dosing: ElderlyOral: Initial: 25 mg at bedtime; increase by 25 mg/day every 3 days for inpatients and weekly for outpatients, as tolerated, to a maximum of 100 mg/day (see Geriatric Considerations).

StorageSolutions stable at a pH of 4-5. Turns yellowish or reddish on exposure to light. Slight discoloration does not affect potency; marked discoloration is associated with loss of potency. Capsules stable for 3 years following date of manufacture.

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to trimipramine, any component of the formulation, or other dibenzodiazepines; use of MAO inhibitors within 14 days; use in a patient during the acute recovery phase of MI

Allergy Considerations

- Tricyclic Antidepressant and Related Compounds Allergy

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See "Major psychiatric warnings" below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor patients for clinical worsening, suicidality, or unusual changes in behavior, particularly during the initial 1-2 months of therapy or during periods of dosage adjustments (increases or decreases); the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants should be dispensed with each prescription. **Trimipramine is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Trimipramine is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. The degree of anticholinergic blockade produced by this agent is very high relative to other antidepressants.

- Orthostatic hypotension: May cause orthostatic hypotension (risk is high relative to other antidepressants); use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The degree of sedation is very high relative to other antidepressants.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with a history of cardiovascular disease (including previous MI, stroke, tachycardia, or conduction abnormalities); the risk conduction abnormalities with this agent is high relative to other antidepressants.

- Diabetes: Use with caution in patients with diabetes mellitus; may alter glucose regulation.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold.

- Thyroid dysfunction: Use with caution in patients with hyperthyroidism or those receiving thyroid supplementation.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Discontinuation of therapy: Therapy should not be abruptly discontinued in patients receiving high doses for prolonged periods.

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

Geriatric ConsiderationsSimilar to doxepin in its side effect profile; has not been well studied in the elderly; very anticholinergic and, therefore, not considered a drug of first choice in the elderly when selecting an antidepressant. Data from a clinical trial comparing fluoxetine to tricyclics suggest that fluoxetine is significantly less effective than nortriptyline in hospitalized elderly patients with unipolar major affective disorder, especially those with melancholia and concurrent cardiovascular diseases.
Pregnancy Risk FactorC
LactationEnters breast milk/contraindicated
Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmias, heart block, hyper-/hypotension, MI, palpitation, stroke, tachycardia

Central nervous system: Agitation, anxiety, confusion, delirium, delusions, drowsiness, exacerbation of psychosis, hallucinations, headache, insomnia, nervousness, nightmares, restlessness, seizure

Dermatologic: Itching, petechiae, photosensitivity, rash

Endocrine & metabolic: Breast enlargement, galactorrhea, sexual dysfunction, syndrome of inappropriate ADH secretion (SIADH)

Gastrointestinal: Anorexia, constipation, decreased lower esophageal sphincter tone may cause GE reflux, diarrhea, heartburn, increased appetite, nausea, trouble with gums, unpleasant taste, vomiting, weight gain, xerostomia

Genitourinary: Difficult urination, testicular edema, urinary retention

Hematologic: Agranulocytosis, eosinophilia, purpura, thrombocytopenia

Hepatic: Cholestatic jaundice, liver enzymes increased

Neuromuscular & skeletal: Ataxia, extrapyramidal symptoms, incoordination, numbness, paresthesia, peripheral neuropathy, tingling, tremor

Ocular: Blurred vision, disturbances in accommodation, eye pain, increased intraocular pressure, mydriasis

Otic: Tinnitus

Miscellaneous: Allergic reactions

Metabolism/Transport Effects**Substrate** (major) of CYP2C19, 2D6, 3A4
Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Direct-Acting): Tricyclic Antidepressants may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting).

Exceptions: Dipivefrin. *Risk D: Consider therapy modification*

Alpha1-Agonists: Tricyclic Antidepressants may enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Alpha2-Agonists: Tricyclic Antidepressants may diminish the antihypertensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk D: Consider therapy modification*

Altretamine: May enhance the orthostatic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Amphetamines: Tricyclic Antidepressants may enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Aspirin: Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Beta2-Agonists: Tricyclic Antidepressants may enhance the adverse/toxic effect of Beta2-Agonists. *Risk C: Monitor therapy*

BuPROPion: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Cinacalcet: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Moderate): May decrease the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C19 Inhibitors (Strong): May decrease the metabolism of CYP2C19 Substrates. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Desmopressin: Tricyclic Antidepressants may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Dexmethylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

DULoxetine: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Iobenguane I 123: Tricyclic Antidepressants may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

Lithium: May enhance the neurotoxic effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

MAO Inhibitors: May enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. *Risk X: Avoid combination*

Methylphenidate: May decrease the metabolism of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

NSAID (COX-2 Inhibitor): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Propoxyphene: May enhance the CNS depressant effect of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Protease Inhibitors: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Tricyclic Antidepressants may enhance the QTc-prolonging effect of QuiNIDine. QuiNIDine may decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

St Johns Wort: May increase the metabolism of Tricyclic Antidepressants. The risk of serotonin syndrome may theoretically be increased. *Risk D: Consider therapy modification*

Sulfonylureas: Cyclic Antidepressants may enhance the hypoglycemic effect of Sulfonylureas. *Risk C: Monitor therapy*

Terbinafine: May decrease the metabolism of Tricyclic Antidepressants. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

TraMADol: Tricyclic Antidepressants may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. *Risk C: Monitor therapy*

Valproic Acid: May increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Tricyclic Antidepressants may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Yohimbine: Tricyclic Antidepressants may increase the serum concentration of Yohimbine. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Grapefruit juice may inhibit the metabolism of some TCAs and clinical toxicity may result.

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava (may increase risk of serotonin syndrome and/or excessive sedation).

Monitoring ParametersBlood pressure and pulse rate prior to and during initial therapy; evaluate mental status, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased); monitor weight; ECG in older adults

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness (according to rationale for therapy), and adverse reactions at beginning of therapy and periodically with long-term use. Monitor for CNS depression, thoughts of suicide. Taper dosage slowly when discontinuing (allow 3-4 weeks between discontinuing Surmontil® and starting another antidepressant). Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationTake exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results. Take at bedtime. Avoid alcohol, caffeine, and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, lightheadedness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, altered taste, dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); diarrhea (buttermilk, yogurt, or boiled milk may help); increased appetite (monitor dietary intake to avoid excess weight gain); postural hypotension (use caution when climbing stairs or changing position from lying or sitting to standing); urinary retention (void before taking medication); or sexual dysfunction (reversible). Report persistent CNS effects (eg, insomnia, restlessness, fatigue, anxiety, impaired cognitive function, seizures, suicide ideation); muscle cramping or tremors; chest pain, palpitations, rapid heartbeat, swelling of extremities, or severe dizziness; unresolved urinary retention; vision changes or eye pain; yellowing of eyes or skin; pale stools/dark urine; suicidal ideation; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 25 mg, 50 mg, 100 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsules (Surmontil)

25 mg (100): $221.57

50 mg (100): $338.11

Capsules (Trimipramine Maleate)

50 mg (90): $282.84

Mechanism of ActionIncreases the synaptic concentration of serotonin and/or norepinephrine in the central nervous system by inhibition of their reuptake by the presynaptic neuronal membrane

Pharmacodynamics/Kinetics

Distribution: V_d: 17-48 L/kg

Protein binding: 95%; free drug: 3% to 7%

Metabolism: Hepatic; significant first-pass effect

Bioavailability: 18% to 63%

Half-life elimination: 16-40 hours

Excretion: Urine

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsMay cause alterations in bleeding time.
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and unpleasant taste. Long-term treatment with TCAs, such as trimipramine, increases the risk of caries by reducing salivation and salivary buffer capacity.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution; epinephrine and levonordefrin have been shown to have an increased pressor response in combination with TCAs. Trimipramine is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, mepivacaine and levonordefrin [Carbocaine® 2% with Neo-Cobefrin®]) be used with caution.
Mental Health CommentTricyclic antidepressants may be classified as tertiary (amitriptyline, doxepin, clomipramine, imipramine, trimipramine) or secondary amines (nortriptyline, desipramine, protriptyline). The tertiary amines are not recommended to treat depression in the elderly. If a TCA is used in the elderly, it should be a secondary amine. The tertiary amines are commonly used in low dosages for various conditions associated with pain. Toxicity is generally dose dependent. Relatively small overdoses (1-week supply) can be potentially fatal.
Index TermsTrimipramine Maleate
References

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Mokhlesi B, Leikin JB, Murray P, et al, “Adult Toxicology in Critical Care: Part II: Specific Poisonings,” *Chest*, 2003, 123(3):897-922. [PubMed 12628894]

Nebinger P and Koel M, “Specificity Data of the Tricyclic Antidepressants Assay by Fluorescent Polarization Immunoassay,” *J Anal Toxicol*, 1990, 14(4):219-21. [PubMed 2395342]

Pass SE and Simpson RW, “Discontinuation and Reinstitution of Medications During the Perioperative Period,” *Am J Health Syst Pharm*, 2004, 61(9):899-912. [PubMed 15156966]

Remy AJ, Larrey D, Pageaux GP, et al, “Cross Hepatotoxicity Between Tricyclic Antidepressants and Phenothiazines,” *Eur J Gastroenterol Hepatol*, 1995, 7(4):373-6. [PubMed 7600146]

Roose SP, Glassman AH, Attia E, et al, “Comparative Efficacy of Selective Serotonin Reuptake Inhibitors and Tricyclics in the Treatment of Melancholia,” *Am J Psychiatry*, 1994, 151(12):1735-9.[PubMed 7977878]

International Brand NamesApo-Trimip (MY); Sapilent (HN, HU); Stangyl (AT, DE); Sumontil (JP); Surmontil (AE, AR, AU, BB, BE, BH, BM, BS, BZ, CH, CY, DK, EG, ES, FI, FR, GB, GY, HK, IE, IN, IQ, IT, JM, KW, LU, NL, NO, OM, PH, PK, PT, QA, SE, SR, TT, YE); Trimin (CH); Tripress (NZ); Tydamine (ZA)

Triprolidine and Pseudoephedrine

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English

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Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Aprodine® may be confused with Aphrodyne®

Pronunciation(trye PROE li deen & soo doe e FED rin)

U.S. Brand NamesAllerfrim [OTC]; Aprodine® [OTC]; Genac® [OTC]; Silafed® [OTC]; Sudafed® Maximum Strength Sinus Nighttime [OTC] [DSC]; Tri-Sudo® [OTC] [DSC]; Zymine®-D

Canadian Brand NamesActifed®

Pharmacologic CategoryAlpha/Beta Agonist; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsTemporary relief of nasal congestion, decongest sinus openings, running nose, sneezing, itching of nose or throat and itchy, watery eyes due to common cold, hay fever, or other upper respiratory allergies

Dosing: Adults**Cold, allergy symptoms:** Oral:

Liquid (Zymine®-D): 5-10 mL every 4-6 hours (maximum pseudoephedrine: 240 mg/24 hours)

Syrup (Allerfrim, Aprodine®): 10 mL every 4-6 hours; do not exceed 4 doses in 24 hours

Tablet (Aprodine®): One tablet every 4-6 hours; do not exceed 4 doses in 24 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Cold, allergy symptoms:** Oral:

Liquid (Zymine®-D):

Children:

2-4 years: 1.25 mL every 4-6 hours (maximum pseudoephedrine: 60 mg/24 hours)

4-6 years: 2.5 mL every 4-6 hours (maximum pseudoephedrine: 60 mg/24 hours)

6-12 years: 2.5-5 mL every 4-6 hours (maximum pseudoephedrine: 120 mg/24 hours)

Children ≥12 years: Refer to adult dosing.

Syrup (Allerfrim, Aprodine®):

Children 6-12 years: 5 mL every 4-6 hours; do not exceed 4 doses in 24 hours

Children >12 years: Refer to adult dosing.

Tablet (Aprodine®):

Children 6-12 years:$^1/_2$ tablet every 4-6 hours; do not exceed 4 doses in 24 hours

Children >12 years: Refer to adult dosing.

ContraindicationsHypersensitivity to pseudoephedrine or any component of the formulation; MAO therapy, severe hypertension, severe coronary artery disease

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

Disease-related concerns:

- Asthma: Use with caution in patients with a history of asthma.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease (including hypertension and ischemic heart disease); contraindicated with severe disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Increased intraocular pressure/glaucoma: Use with caution in patients with increased intraocular pressure or glaucoma.
- Prostatic hyperplasia/urinary obstruction: Use with caution in patients with prostatic hyperplasia and/or GU obstruction.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in the elderly; may be more sensitive to adverse effects.
- Pediatrics: Not for OTC use in children <6 years of age.

Other warnings/precautions:

- Self-medication (OTC use): When used for self medication (OTC), notify healthcare provider if symptoms do not improve within 7 days or are accompanied by fever. Discontinue and contact healthcare provider if nervousness, dizziness or sleeplessness occur.

Geriatric ConsiderationsUse with caution in patients with cardiovascular disease; the anticholinergic action of triprolidine may cause confusion, constipation, or urinary retention in the elderly. Also refer to Pseudoephedrine.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Cardiovascular: Tachycardia

Central nervous system: Drowsiness, nervousness, insomnia, transient stimulation, headache, fatigue, dizziness

Respiratory: Thickening of bronchial secretions, pharyngitis

Gastrointestinal: Appetite increase, weight gain, nausea, diarrhea, abdominal pain, xerostomia

Genitourinary: Dysuria

Neuromuscular & skeletal: Arthralgia, weakness

Miscellaneous: Diaphoresis

Metabolism/Transport EffectsTriprolidine: **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Liquid:

Zymine®-D: Triprolidine hydrochloride 1.25 mg and pseudoephedrine hydrochloride 45 mg per 5 mL (480 mL)

Syrup: Triprolidine hydrochloride 1.25 mg and pseudoephedrine hydrochloride 30 mg per 5 mL (120 mL) [DSC]

Allerfrim: Triprolidine hydrochloride 1.25 mg and pseudoephedrine hydrochloride 30 mg per 5 mL (120 mL, 480 mL) [contains sodium benzoate]

Aprodine®: Triprolidine hydrochloride 1.25 mg and pseudoephedrine hydrochloride 30 mg per 5 mL (120 mL)

Silafed®: Triprolidine hydrochloride 1.25 mg and pseudoephedrine hydrochloride 30 mg per 5 mL (120 mL, 240 mL)

Tablet:

Allerfrim, Aprodine®, Genac®, Sudafed® Maximum Strength Sinus Nighttime, Tri-Sudo® [DSC]: Triprolidine hydrochloride 2.5 mg and pseudoephedrine hydrochloride 60 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Allerfrim)

2.5-60 mg (100): $12.99

Mechanism of ActionRefer to Pseudoephedrine monograph

Triprolidine is a member of the propylamine (alkylamine) chemical class of H_1-antagonist antihistamines. As such, it is considered to be relatively less sedating than traditional antihistamines of the ethanolamine, phenothiazine, and ethylenediamine classes of antihistamines. Triprolidine has a shorter half-life and duration of action than most of the other alkylamine antihistamines. Like all H_1-antagonist antihistamines, the mechanism of action of triprolidine is believed to involve competitive blockade of H_1-receptor sites resulting in the inability of histamine to combine with its receptor sites and exert its usual effects on target cells. Antihistamines do not interrupt any effects of histamine which have already occurred. Therefore, these agents are used more successfully in the prevention rather than the treatment of histamine-induced reactions.

Pharmacodynamics/KineticsSee Pseudoephedrine monograph.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation). Chronic use of antihistamines will inhibit salivary flow, particularly in elderly patients; this may contribute to periodontal disease and oral discomfort.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsUse with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental StatusDrowsiness, nervousness, and insomnia are common; may cause dizziness; may rarely cause depression, hallucinations, or paradoxical excitement

Mental Health: Effects on Psychiatric TreatmentContraindicated with MAO inhibitors; concurrent use with psychotropics may produce additive sedation

Index TermsPseudoephedrine and Triprolidine

International Brand NamesActifed (AE, AU, BB, BE, BF, BH, BJ, BM, BS, BZ, CI, CY, EE, EG, ET, GH, GM, GN, GY, HK, ID, IL, IQ, IR, JM, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, OM, PE, PY, QA, SA, SC, SD, SL, SN, SR, SY, TH, TN, TT, TZ, UG, VE, YE, ZA, ZM, ZW); Actifedrin (AR, BR, CN); Actiplex (TH); Beatafed (MY); Becanden (TW); Colfed (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Consudine (TH); Eugen (TW); Fedac (HK, MY); Hiscifed (TH); Histafed (IL); Histamine-Care (IL); Lapifed (ID); Mecofed (ID); Nasafed (ID); Nostel (ID); Peace (MY, TW); Policolo (TH); Pseudoephedrine T (MY); Tosumin (TW); Trifed (AE, BH, CY, EG, ID, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Triprodine (TH); Unifed (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Valved (ID)

Triprolidine, Pseudoephedrine, and Codeine

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Special Alerts

Health Canada: Labeling Changes for OTC Cough and Cold Preparations - December, 2008

Health Canada has issued an advisory to Canadian consumers regarding upcoming labeling changes for the use of over-the-counter (OTC) cough and cold medicines in children. Specific labeling changes as well as other important information may be found at http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_184-eng.php.

Manufacturers Voluntarily Change Pediatric OTC Product Labeling - October 7, 2008

Leading manufacturers of over-the-counter (OTC) pediatric cough and cold products, in consultation with the Food and Drug Administration (FDA), have announced that they are voluntarily transitioning product labeling as it relates to children <4 years of age. The decision to change the labeling followed a meeting on October 2, 2008, conducted by the FDA to gather additional information related to the use of these products in children. The safety of the ingredients in these products was not in question. It was found that dosing errors and accidental ingestions were the leading cause of rare adverse events in children. The new product labeling will state “Do not use in children under four years of age.” In addition, products with certain antihistamines will warn parents not to use these products to sedate or make a child sleepy. Labeling of adult products will not change. New product labels will be introduced during the 2008-2009 cough and cold season and some products will have the updated labeling by mid-October. Products with the old labeling will not be removed from the market. Prescription products are not affected.

It is important to note that these medications have not been shown to be unsafe when used correctly. Pharmacists may continue to see health care practitioners recommending these agents for use in pediatric patients, and should help to ensure that they are being used safely and at appropriate dosages. Parents should be advised that OTC cough and cold products are safe and effective when used as directed, but that they should not be used in children <4 years of age unless instructed to do so by their healthcare provider. Counseling tips from the Consumer Healthcare Products Association (CHPA) also include:

- Always follow dosing instructions exactly and use measuring devices provided with the medicine.
- Never give 2 medicines at the same time that contain the same active ingredient.
- Do not give a medicine intended for use in adults to a child.

Additional tips and information related to the labeling changes can be found on the following educational website of the CHPA: http://www.otcsafety.org.

The FDA had previously issued a Public Health Advisory reminding patients and caregivers that OTC cough and cold medications should not be used to treat infants and children <2 years of age. This is in response to the Centers for Disease Control and Prevention (CDC) report which noted that during 2004 and 2005, ~1519 children <2 years of age were seen in emergency departments for adverse effects, including overdose, associated with products containing nasal decongestants (eg, pseudoephedrine), antihistamines (eg, carbinoxamine), and cough suppressants (eg, dextromethorphan). In October of 2007, several manufacturers voluntarily removed these products in order to help reduce dosing errors and overdose in this age group.

Additional information available at the following FDA website: http://www.fda.gov/bbs/topics/NEWS/2008/NEW01899.html

For additional information on the advisory posted in January 2008, refer to the following websites:

http://www.fda.gov/medwatch/safety/2008/safety08.htm#cough

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm, Centers for Disease Control, “Infant Deaths Associated with Cough and Cold Medications - Two States, 2005,” *MMWR Morb Mortal Wkly Rep*, 2007, 56(01):1-4.

Medication Safety Issues

Sound-alike/look-alike issues:

Triacin-C® may be confused with triacetin

Pronunciation(trye PROE li deen, soo doe e FED rin, & KOE deen)

Canadian Brand NamesCoActifed®; Covan®; ratio-Cotridin

Pharmacologic CategoryAlpha/Beta Agonist; Analgesic, Opioid; Antitussive; Histamine H_1 Antagonist; Histamine H_1 Antagonist, First Generation

Use: Labeled IndicationsSymptomatic relief of upper respiratory symptoms and cough

Dosing: Adults**Cold, allergy symptoms:** Oral: 10 mL 4 times/day **or** 1 tablet 4 times/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Cold, allergy symptoms: Oral: Children:

2-6 years: 2.5 mL 4 times/day

7-12 years: 5 mL 4 times/day **or** $^1/_2$ tablet 4 times/day

Children ≥12 years: Refer to adult dosing.

RestrictionsC-V (CDSA-I)

ContraindicationsHypersensitivity to triprolidine, pseudoephedrine, opiates, or any component of the formulation (some formulations contain ethanol); acute respiratory depression; CNS depression or coma; increased intracranial pressure (ICP)/head trauma; convulsive disorder; acute abdomen/obstruction; use of MAO inhibitors within 14 days

Allergy Considerations

- Opioid Allergy/Hypersensitivity

Warnings/Precautions

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Overdosage: Hallucinations, seizures, CNS depression, and death may occur from overdosage.
- Phenanthrene hypersensitivity: Use with caution in patients with hypersensitivity reactions to other phenanthrene derivative opioid agonists (hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease including hypertension, tachycardia, and/or ischemic heart disease.
- Diabetes: Use with caution in patients with diabetes mellitus.
- Drug abuse: Use with caution in patients with a history of drug abuse or acute alcoholism; potential for drug dependency exists. Tolerance, psychological and physical dependence may occur with prolonged use.
- Glaucoma: Use with caution in patients with angle-closure glaucoma and/or increased intraocular pressure.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture.
- Pyloroduodenal obstruction: Use with caution in patients with pyloroduodenal obstruction (including stenotic peptic ulcer).
- Renal impairment: Use with caution in patients with severe renal impairment.
- Respiratory disease: Use with caution in patients with respiratory diseases including asthma, emphysema, and/or COPD.
- Thyroid dysfunction: Use with caution in patients with thyroid dysfunction.

Concurrent drug therapy issues:

- Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.

Special populations:

- Elderly: Use with caution in patients >60 years of age; may be more sensitive to adverse effects. Triprolidine may not be considered the antihistamine of choice for prolonged use in the elderly.
- Pediatrics: Not recommended as an antitussive for children <2 years of age. May cause paradoxical excitation in children.

Other warnings/precautions:

- Cough control: Codeine is not recommended for use for cough control in patients with a productive cough.
- Duration of therapy: Avoid prolonged use; generally limited to not more than 5 days.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypotension

Central nervous system: Sedation, dizziness, drowsiness, increased ICP, lightheadedness, dysphoria, euphoria, headache, agitation, hallucinations, seizure, respiratory depression

Dermatologic: Pruritus, rash

Gastrointestinal: Constipation, nausea, vomiting, anorexia, xerostomia, taste disturbance, biliary tract spasm

Genitourinary: Urinary retention, urinary tract spasm

Neuromuscular & skeletal: Muscle tremor, paresthesia, muscular rigidity (rare)

Ocular: Blurred vision, nystagmus

Miscellaneous: Diaphoresis, physical or psychological dependence with continued use, withdrawal syndrome

Metabolism/Transport Effects

Triprolidine: **Inhibits** CYP2D6 (weak)

Codeine: **Substrate** of CYP2D6 (major), 3A4 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alvimopan: Analgesics (Opioid) may enhance the adverse/toxic effect of Alvimopan. This is most notable for patients receiving long-term (i.e., more than 7 days) opiates prior to alvimopan initiation. Management: Alvimopan is contraindicated in patients receiving therapeutic doses of opioids for more than 7 consecutive days immediately prior to alvimopan initiation. *Risk D: Consider therapy modification*

Ammonium Chloride: May increase the excretion of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May enhance the analgesic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*

Antacids: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Aluminum Hydroxide. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Antipsychotic Agents (Phenothiazines): May enhance the hypotensive effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*

Bromocriptine: Alpha-/Beta-Agonists may enhance the adverse/toxic effect of Bromocriptine. Including increased blood pressure, ventricular arrhythmias, and seizure. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May decrease the excretion of Alpha-/Beta-Agonists. **Exceptions:** Brinzolamide; Dorzolamide. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May diminish the therapeutic effect of Codeine. These CYP2D6 inhibitors may prevent the metabolic conversion of codeine to its active metabolite morphine. *Risk D: Consider therapy modification*

Desmopressin: Analgesics (Opioid) may enhance the adverse/toxic effect of Desmopressin. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha-/Beta-Agonists (Indirect-Acting). *Risk X: Avoid combination*

Pegvisomant: Analgesics (Opioid) may diminish the therapeutic effect of Pegvisomant. *Risk C: Monitor therapy*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: Analgesics (Opioid) may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This may cause serotonin syndrome. *Risk C: Monitor therapy*

Serotonin/Norepinephrine Reuptake Inhibitors: May enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Somatostatin Analogs: May decrease the metabolism of Codeine. The formation of two major codeine metabolites (morphine and norcodeine) may be impaired by somatostatin analogs. *Risk C: Monitor therapy*

Succinylcholine: May enhance the bradycardic effect of Analgesics (Opioid). *Risk C: Monitor therapy*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Syrup:

- CoActifed® [CAN], ratio-Cotridin [CAN]: Triprolidine hydrochloride 2 mg, pseudoephedrine hydrochloride 30 mg, and codeine phosphate 10 mg per 5 mL (100 mL, 2000 mL) [not available in U.S.]
- CoVan® [CAN]: Triprolidine hydrochloride 2 mg, pseudoephedrine hydrochloride 30 mg, and codeine phosphate 10 mg per 5 mL (500 mL) [not available in U.S.]

Tablet:

- CoActifed® [CAN]: Triprolidine hydrochloride 4 mg, pseudoephedrine hydrochloride 60 mg, and codeine phosphate 20 mg (50s) [not available in U.S.]

Generic Available No

Pharmacodynamics/Kinetics See Pseudoephedrine and Codeine monographs.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Pseudoephedrine: Xerostomia (normal salivary flow resumes upon discontinuation) and taste disturbance.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions Use with caution since pseudoephedrine is a sympathomimetic amine which could interact with epinephrine to cause a pressor response

Mental Health: Effects on Mental Status Drowsiness, nervousness, and insomnia are common; may cause dizziness; may rarely cause depression, hallucinations, or paradoxical excitement

Mental Health: Effects on Psychiatric Treatment May see increased toxicity with MAO inhibitors (hypertensive crisis), sympathomimetics, CNS depressants, ethanol (sedation)

Index Terms Codeine, Pseudoephedrine, and Triprolidine; Codeine, Triprolidine, and Pseudoephedrine; Pseudoephedrine, Codeine, and Triprolidine; Pseudoephedrine, Triprolidine, and Codeine; Triprolidine, Codeine, and Pseudoephedrine

International Brand Names Actifed Antitusivo (PE); Actifed Compound (TH); Actifed Compound Linctus (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, HK, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TZ, UG, YE, ZA, ZM, ZW); CoActifed (CA); Covan (CA); Fedac Compound (HK, MY); ratio-Cotridin (CA)

Triptorelin

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(trip toe REL in)
U.S. Brand NamesTrelstar® Depot; Trelstar® LA
Canadian Brand NamesTrelstar® ; Trelstar® Depot; Trelstar® LA
Pharmacologic CategoryGonadotropin Releasing Hormone Agonist
Use: Labeled IndicationsPalliative treatment of advanced prostate cancer as an alternative to orchiectomy or estrogen administration
Use: Unlabeled/InvestigationalTreatment of endometriosis, growth hormone deficiency, hyperandrogenism, *in vitro* fertilization, ovarian carcinoma, pancreatic carcinoma, precocious puberty, uterine leiomyomata
Dosing: Adults**Advanced prostate carcinoma:**

Trelstar® Depot: 3.75 mg once every 28 days

Trelstar® LA: 11.25 mg once every 84 days

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentSpecific guidelines are not available.
Dosing: Hepatic ImpairmentSpecific guidelines are not available.
Administration: I.M.Administer by I.M. injection into the buttock; alternate injection sites.
Storage

Trelstar® Depot: Store at 15°C to 30°C (59°F to 86°F).

Trelstar® LA: Store at 20°C to 25°C (68°F to 77°F).

ReconstitutionReconstitute with 2 mL sterile water for injection. Shake well to obtain a uniform suspension.

Debioclip™: Follow manufacturer's instructions for mixing prior to use.

ContraindicationsHypersensitivity to triptorelin or any component of the formulation, other LHRH agonists or LHRH; pregnancy
Allergy Considerations

- GnRH Agonist Allergy

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Hypersensitivity reactions: Angioedema and anaphylaxis have rarely occurred.
- Pituitary apoplexy: Rare cases of pituitary apoplexy (frequently secondary to pituitary adenoma) have been observed with leuprolide administration (onset from 1 hour to usually <2 weeks); may present as sudden headache, vomiting, visual or mental status changes, and infrequently cardiovascular collapse; immediate medical attention required.
- Spinal cord compression: Cases of spinal cord compression have been reported with LHRH agonists; observe patients with metastatic vertebral lesions closely.
- Tumor flare: Transient increases in testosterone can lead to worsening symptoms (bone pain, hematuria, bladder outlet obstruction) of prostate cancer during the first few weeks of therapy.

Disease-related concerns:

- Urinary tract obstruction: Observe patients with urinary tract obstruction closely.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsSince many elderly men may have hypertension, blood pressure needs be monitored closely for the first 4-8 weeks.
Pregnancy Risk FactorX
Pregnancy ConsiderationsContraindicated in women who are or may become pregnant.
LactationExcretion in breast milk unknown/contraindicated
Adverse ReactionsAs reported with Trelstar® Depot and Trelstar® LA; frequency of effect may vary by product:

>10%:

Central nervous system: Headache (30% to 60%)

Endocrine & metabolic: Hot flashes (95% to 100%), glucose increased

Hematologic: Hemoglobin decreased, RBC count decreased

Hepatic: Alkaline phosphatase increased, ALT increased, AST increased

Neuromuscular & skeletal: Skeletal pain (12% to 13%)

Renal: BUN increased

1% to 10%:

Cardiovascular: Leg edema (6%), hypertension (4%), chest pain (2%), peripheral edema (1%)

Central nervous system: Dizziness (1% to 3%), pain (2% to 3%), emotional lability (1%), fatigue (2%), insomnia (2%)

Dermatologic: Rash (2%), pruritus (1%)

Endocrine & metabolic: Alkaline phosphatase increased (2%), breast pain (2%), gynecomastia (2%), libido decreased (2%), tumor flare (8%)

Gastrointestinal: Nausea (3%), anorexia (2%), constipation (2%), dyspepsia (2%), vomiting (2%), abdominal pain (1%), diarrhea (1%)

Genitourinary: Dysuria (5%), impotence (2% to 7%), urinary retention (1%), urinary tract infection (1%)

Hematologic: Anemia (1%)

Local: Injection site pain (4%)

Neuromuscular & skeletal: Leg pain (2% to 5%), back pain (3%), arthralgia (2%), leg cramps (2%), myalgia (1%), weakness (1%)

Ocular: Conjunctivitis (1%), eye pain (1%)

Respiratory: Cough (2%), dyspnea (1%), pharyngitis (1%)

Postmarketing and/or case reports: Anaphylaxis, angioedema, hypersensitivity reactions, pituitary apoplexy, spinal cord compression, renal dysfunction

Drug Interactions

Antidiabetic Agents: Luteinizing Hormone-Releasing Hormone Analogs may diminish the therapeutic effect of Antidiabetic Agents. *Risk C: Monitor therapy*

Test InteractionsPituitary-gonadal function may be suppressed with chronic administration and for up to 8 weeks after triptorelin therapy has been discontinued.

Monitoring ParametersSerum testosterone levels, prostate-specific antigen

Nursing: Physical Assessment/MonitoringAssess results of laboratory tests, therapeutic effectiveness, and adverse response. Teach patient possible side effects/appropriate interventions and adverse symptoms to report. **Pregnancy risk factor X.**

Monitoring: Lab TestsSerum testosterone levels, prostate-specific antigen

Patient EducationThis medication can only be administered by injection. If you have diabetes, may alter blood glucose levels; monitor blood sugar closely. Report swelling, pain, or burning at injection site. May cause disease flare (increased bone pain), blood in urine, or urinary retention during early treatment (usually resolves within 1 week); impotence; or hot flashes (cool cloth on forehead, cool environment, and light, layered clothing may help; contact prescriber if these become intolerable). Report any persistent adverse GI upset; chest pain, rapid heartbeat, or palpations; numbness in extremities; acute headache; alterations in urinary pattern; or other persistent adverse effects. Report immediately sudden headache, severe vomiting, visual or mental status change, and cardiovascular collapse. **Pregnancy/breast-feeding precautions:** This drug will cause severe fetal defects. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Trelstar® Depot: 3.75 mg [contains polylactide-co-glycolide; polysorbate 80]

Trelstar® LA: 11.25 mg [contains polylactide-co-glycolide; polysorbate 80]

Generic AvailableNo

ManufacturerPharmacia

Mechanism of ActionCauses suppression of ovarian and testicular steroidogenesis due to decreased levels of LH and FSH with subsequent decrease in testosterone (male) and estrogen (female) levels. After chronic and continuous administration, usually 2-4 weeks after initiation, a sustained decrease in LH and FSH secretion occurs.

Pharmacodynamics/Kinetics

Absorption: Oral: Not active

Distribution: V_d: 30-33 L

Protein binding: None

Metabolism: Unknown; unlikely to involve CYP; no known metabolites

Half-life elimination: 2.8 ± 1.2 hours

Moderate to severe renal impairment: 6.5-7.7 hours

Hepatic impairment: 7.6 hours

Time to peak: 1-3 hours

Excretion: Urine (42% as intact peptide); hepatic

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia, fatigue, emotional lability, or dizziness

Mental Health: Effects on Psychiatric TreatmentContraindicated with dopamine antagonists

Index TermsAY-25650; CL-118,532; D-Trp(6)-LHRH; Triptoraline; Triptorelin Pamoate; Tryptoreline

References

Anonymous, “Triptorelin Pamoate. Phase III Drug Profiles,” 1993, 3:1-8.

Filicor M, “Gonadotrophin-Releasing Hormone Agonists. A Guide to Use and Selection,” *Drugs*, 1994, 48(1):41-58. [PubMed 7525194]

Swanson LJ, Seely JH, and Garnick MB, “Gonadotropin-Releasing Hormone Analogs and Prostatic Cancer,” *Crit Rev Oncol Hematol*, 1988, 8(1):1-26.[PubMed 2964939]

International Brand NamesArvekap (GR); Decapeptyl (AE, AR, BE, BG, BH, CL, CN, CO, CY, CZ, DE, EC, EG, ES, FR, GB, HK, HN, HR, HU, IE, IL, IQ, IR, IT, JO, KW, LB, LU, LY, MY, NL, OM, PE, PL, PT, PY, QA, SA, SY, UY, VE, YE); Decapeptyl CR (AE, BH, CY, EG, IL, IQ, IR, JO, KP, KW, LB, LY, MY, OM, PH, QA, SA, SY, TH, TW, YE); Decapeptyl Depot (AT, CZ, DE, DK, EE, FI, KP, MY, SE); Decapeptyl LP (FR); Decapeptyl Retard (CH); Decapeptyl SR (PK); Diphereline (PL); Diphereline PR (HK, TW); Diphereline S.R. (PL); Gonapeptyl (FR, GB, IE); Gonapeptyl Depot (BR); Neo Decapeptyl (BR); Pamorelin (NO)

Trolamine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Myoflex® may be confused with Mycelex®

Pronunciation(TROLE a meen)

U.S. Brand NamesAspercreme® [OTC]; Flex-Power [OTC]; Mobisyl® [OTC]; Myoflex® [OTC]; Sportscreme® [OTC]

Canadian Brand NamesAntiphlogistine Rub A-535 No Odour; Myoflex®

Pharmacologic CategoryAnalgesic, Topical; Salicylate; Topical Skin Product

Use: Labeled IndicationsRelief of pain of muscular aches, rheumatism, neuralgia, sprains, arthritis on intact skin

Dosing: Adults**Pain:** Topical: Apply to area as needed

Dosing: ElderlyRefer to adult dosing.

Allergy Considerations

- Salicylate Allergy/Sensitivity

Adverse Reactions1% to 10%:

Central nervous system: Confusion, drowsiness

Gastrointestinal: Nausea, vomiting, diarrhea

Respiratory: Hyperventilation

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Cream, topical, as salicylate: 10% (90 g)

Aspercreme®: 10% (35 g, 85 g, 142 g) [odorless]

Flex-Power: 10% (57 g, 113 g)

Mobisyl®: 10% (100 g, 227 g) [contains sweet almond oil]

Myoflex®: 10% (57 g, 113 g)

Sportscreme®: 10% (35 g, 85 g) [contains tartrazine]

Lotion, topical, as salicylate:

Aspercreme®: 10% (180 mL)

Patch, topical, as salicylate:

Aspercreme®: 10% (5s) [DSC]

Generic AvailableYes: Cream

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsTEAS; Triethanolamine Salicylate; Trolamine Salicylate

International Brand NamesBiafine (CL, FR, IL, PE)

Tromethamine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Tromethamine may be confused with TrophAmine®

Pronunciation(troe METH a meen)

U.S. Brand NamesTHAM®

Pharmacologic CategoryAlkalinizing Agent, Parenteral

Use: Labeled IndicationsCorrection of metabolic acidosis associated with cardiac bypass surgery or cardiac arrest; to correct excess acidity of stored blood that is preserved with acid citrate dextrose (ACD); indicated in infants needing alkalinization after receiving maximum sodium bicarbonate (8-10 mEq/kg/24 hours)

Dosing: Adults

Note: Dose depends on buffer base deficit; when deficit is known: tromethamine (mL of 0.3 M solution) = body weight (kg) x base deficit (mEq/L) x 1.1

Metabolic acidosis with cardiac arrest:

I.V.: 3.6-10.8 g (111-333 mL); additional amounts may be required to control acidosis after arrest reversed

Open chest: Intraventricular: 2-6 g (62-185 mL). **Note:** Do not inject into cardiac muscle

Acidosis associated with cardiac bypass surgery: I.V.: Average dose: 9 mL/kg (2.7 mEq/kg); 500 mL is adequate for most adults; maximum dose: 500 mg/kg in ≤1 hour

Excess acidity of acid citrate dextrose (ACD) blood in coronary artery surgery: 15-77 mL of 0.3 molar solution added to each 500 mL of blood

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Metabolic acidosis associated with RDS: I.V.: Neonates and Infants: Initial: Approximately 1 mL/kg for each pH unit below 7.4; additional doses determined by changes in PaO_2, pH, and pCO_2; **Note:** Although THAM® solution does not raise pCO_2 when treating metabolic acidosis with concurrent respiratory acidosis, bicarbonate may be preferred because the osmotic effects of THAM® are greater.

Dosing: Renal ImpairmentUse with caution; monitor for toxicity.

Administration: I.V.Maximum concentration: 0.3 molar; infuse slowly over at least 1 hour; to avoid glucose or potassium changes, should not exceed 16.5 mL/kg in 1 hour

Administration: I.V. DetailOsmolality 389 mOsmol/L

pH 8.4-8.7

StorageStore at 20°C to 25°C (68°F to 77°F). Protect from freezing.

ContraindicationsHypersensitivity to tromethamine or any component of the formulation; uremia or anuria; chronic respiratory acidosis (neonates); salicylate intoxication (neonates)

Warnings/Precautions

Concerns related to adverse effects:

- Hypoglycemia: May cause hypoglycemia with extremely large doses.
- Respiratory depression: May cause respiratory depression; monitor closely especially if patient not intubated.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment; reduce dose and monitor pH carefully.

Other warnings/precautions:

- Duration of therapy: Drug should not be given for a period of longer than 24 hours unless for a life-threatening situation.
- Extravasation: Avoid extravasation; may cause tissue necrosis.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal studies have not been conducted. There are no adequate and well-controlled studies in pregnant women. Use only if potential benefit outweighs possible risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined.

Cardiovascular: Hypervolemia, venospasm

Endocrine & metabolic: Hyperkalemia, hypoglycemia (usually doses >500 mg/kg administered over <1 hour)

Hepatic: Hepatic necrosis (resulted during delivery via umbilical venous catheter)

Local: Necrosis with extravasation, phlebitis, tissue irritation

Respiratory: Apnea, pulmonary edema, respiratory depression

Drug Interactions

Amphetamines: Alkalinizing Agents may decrease the excretion of Amphetamines. *Risk D: Consider therapy modification*

Monitoring ParametersSerum electrolytes (especially potassium, blood glucose); renal function, arterial blood gases, ECG monitoring, fluid status, ventilation rate

Check infusion site frequently during administration.

Reference RangeBlood pH (physiologic): 7.38-7.42

Monitoring: Lab TestsSerum electrolytes (especially potassium, blood glucose); renal function; arterial blood gases

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

THAM®: 18 g [0.3 molar] (500 mL)

Generic AvailableNo

Mechanism of Action Acts as a proton acceptor, which combines with hydrogen ions, liberating bicarbonate buffer, to correct acidosis. It buffers both metabolic and respiratory acids, limiting carbon dioxide generation. Also an osmotic diuretic.

Pharmacodynamics/Kinetics

Distribution: Distributes quickly into extracellular space; at steady state distributes into a volume slightly greater than total body water; penetrates slowly intracellularly

Half-life elimination: 5.6 hours

Excretion: Urine (>75%) within 8 hours

Pharmacotherapy Pearls1 mM = 120 mg = 3.3 mL = 1 mEq of THAM®

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsTris Buffer; Tris(hydroxymethyl)aminomethane

References

Adrogue HJ and Madias NE, “Management of Life-Threatening Acid-Base Disorders: First of Two Parts,” *N Engl J Med*, 1998, 338(1):26-34.[PubMed 9414329]

Nahas GG, Sutin KM, Fermon C, et al, “Guidelines for the Treatment of Acidaemia With THAM,” *Drugs*, 1998, 55(2): 191-224.

English

Jump To Field (Select Field Name)

Pronunciation(troe PIK a mide)
U.S. Brand NamesMydral™; Mydriacyl®; Tropicacyl®
Canadian Brand NamesDiotrope®; Mydriacyl®
Pharmacologic CategoryOphthalmic Agent, Mydriatic
Use: Labeled IndicationsShort-acting mydriatic used in diagnostic procedures; as well as preoperatively and postoperatively; treatment of some cases of acute iritis, iridocyclitis, and keratitis
Dosing: Adults**Note:** Individuals with heavily pigmented eyes may require larger doses:

Cycloplegia: Ophthalmic: Instill 1-2 drops (1%); may repeat in 5 minutes

Exam must be performed within 30 minutes after the repeat dose; if the patient is not examined within 20-30 minutes, instill an additional drop

Mydriasis: Ophthalmic: Instill 1-2 drops (0.5%) 15-20 minutes before exam; may repeat every 30 minutes as needed

Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
StorageStore in tightly closed containers.
ContraindicationsHypersensitivity to tropicamide or any component of the formulation; glaucoma
Allergy Considerations

- Local Anesthetic Hypersensitivity/Allergy

Warnings/Precautions

Concerns related to adverse effects:

• Increased intraocular pressure: May cause an increase in intraocular pressure.

Special populations:

• Contact lens wearers: Remove contact lenses before using.

• Pediatrics: Use with caution in infants and children; may cause potentially dangerous CNS disturbances.

Other warnings/precautions:

• Appropriate use: For ophthalmic use only.

Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined.

Cardiovascular: Edema, tachycardia, vascular congestion

Central nervous system: Headache, parasympathetic stimulations, somnolence

Dermatologic: Eczematoid dermatitis

Gastrointestinal: Dryness of mouth

Local: Transient stinging

Ocular: Blurred vision, follicular conjunctivitis, increased intraocular pressure, photophobia with or without corneal staining

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersOphthalmic exam
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic [drops]: 0.5% (15 mL); 1% (2 mL, 3 mL, 15 mL)

Mydriacyl®: 1% (3 mL, 15 mL) [contains benzalkonium chloride]

Mydral™, Tropicacyl®: 0.5% (15 mL); 1% (15 mL) [contains benzalkonium chloride]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Solution (Mydriacyl)

1% (3): $14.99

1% (15): $52.99

Solution (Tropicamide)

0.5% (15): $12.99

1% (2): $7.99

1% (3): $13.99

1% (15): $13.99

Mechanism of ActionPrevents the sphincter muscle of the iris and the muscle of the ciliary body from responding to cholinergic stimulation

Pharmacodynamics/Kinetics

Onset of action: Mydriasis: ~20-40 minutes; Cycloplegia: ~30 minutes

Duration: Mydriasis: ~6-7 hours; Cycloplegia: <6 hours

Related Information

- Cycloplegic Mydriatics

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Dryness of mouth.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBistropamide

References

Caputo AR and Schnitzer RE, “Systemic Response to Mydriatic Eyedrops in Neonates: Mydriatics in Neonates,” *J Pediatr Ophthalmol Strabismus*, 1978, 15(2):109-22.[PubMed 368306]

International Brand NamesAlcon-Mydril (AR, PY, UY); Colircusi Tropicamida (ES); Losemin (TW); Midric (ID); Minims Tropicamide (GB, IE); Mydiacyl (CZ, HN); Mydramide (IL); Mydriacyl (AE, AU, BF, BH, BJ, BR, CI, CN, CY, DK, EE, EG, ET, GB, GH, GM, GN, HK, HU, IE, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, OM, PE, PH, PK, PL, QA, SA, SC, SD, SE, SL, SN, SY, TH, TN, TW, TZ, UG, VE, YE, ZA, ZM, ZW); Mydriaticum (AT, CH, DE, FR, HK, LU, NL); Mydrin-M (JP); Mydrum (HU); Oftan Mydrin (PL); Oftan-tropicamid (FI); Runzheng (CL); Sintropic (TW); Topimide (TW); Tropicamet (IN); Tropicamid (BG); Tropicamidum (PL); Tropicol (BE, LU, PT); Tropikamid (HR, NO, SE); Tropimil (IT); Visumidriatic (IT)

Trospium

Lexi-Drugs Online

English

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Pronunciation(TROSE pee um)

U.S. Brand NamesSanctura®; Sanctura® XR

Canadian Brand NamesTrosec

Pharmacologic CategoryAnticholinergic Agent

Use: Labeled IndicationsTreatment of overactive bladder with symptoms of urgency, incontinence, and urinary frequency

Dosing: AdultsOveractive bladder: Oral: Immediate release formulation: 20 mg twice daily; extended release formulation: 60 mg once daily

Dosing: Elderly≥75 years: Immediate release formulation: Consider initial dose of 20 mg once daily (based on tolerability) at bedtime

Dosing: Renal ImpairmentCl_{cr} ≤30 mL/minute: Immediate release formulation: 20 mg once daily at bedtime; Extended release formulation: Use not recommended

Calculations

- Creatinine Clearance: Adults

Administration: OralAdminister tablets at bedtime on an empty stomach. Administer extended release capsules in the morning with a full glass of water 1 hour before eating.

Dietary ConsiderationsGive 1 hour prior to meals or on an empty stomach.

StorageStore at 20°C to 25°C (68°F to 77°F).

ContraindicationsHypersensitivity to trospium or any component of the formulation; urinary retention; gastric retention; uncontrolled narrow-angle glaucoma

Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: May cause drowsiness and/or blurred vision, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Heat prostration: May occur in the presence of increased environmental temperature; use caution in hot weather and/or exercise.

Disease-related concerns:

- Alzheimer's disease: Use with caution in patients with Alzheimer's disease.
- Bladder flow obstruction: Use with caution in patients with bladder flow obstruction; may increase the risk of urinary retention.
- Gastrointestinal obstructive disorders: Use with caution in patients with gastrointestinal obstructive disorders (ie, pyloric stenosis); may increase the risk of gastric retention.
- Glaucoma: Use with caution in patients with controlled (treated) narrow-angle glaucoma.
- Hepatic impairment: Use with caution in patients with moderate-to-severe hepatic impairment.
- Myasthenia gravis: Use with caution in patients with myasthenia gravis due to decreased GI motility.
- Renal impairment: Avoid use of extended release formulation in severe renal impairment (Cl_{cr} <30 mL/minute). Use immediate release formulation with caution in patients with renal impairment; dosage adjustment is required.
- Ulcerative colitis: Use with caution in patients with ulcerative colitis due to decreased GI motility.

Concurrent drug therapy issues:

- Medications eliminated by active tubular secretion (ATS): ATS is a route of elimination; use caution with other medications that are eliminated by ATS (eg, procainamide, pancuronium, vancomycin, morphine).

Special populations:

- Elderly: Use with caution in the elderly ≥65 years of age; increased anticholinergic side effects are seen.
- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsIn studies, the incidence of anticholinergic side effects was higher in patients ≥65 years of age as compared to younger adults. The extended release formulation should be avoided in patients with Cl_{cr} <30 mL/minute. Not enough information to recommend its use in the elderly.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAdverse events were observed in animal studies. There are no adequate or well-controlled studies in pregnant women; use only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Gastrointestinal: Xerostomia (9% to 22%)

1% to 10%:

Cardiovascular: Tachycardia

Central nervous system: Headache (4% to 7%), fatigue (2%)

Dermatologic: Dry skin

Gastrointestinal: Constipation (9% to 10%), abdominal pain (1% to 3%), dyspepsia (1% to 2%), flatulence (1% to 2%), nausea (1%), abdominal distention (<2%), taste abnormal, vomiting

Genitourinary: Urinary retention (≤1%), urinary tract infection (1% to 7%)

Ocular: Dry eyes (1% to 2%), blurred vision (1%)

Respiratory: Nasopharyngitis (3%), nasal dryness (1%)

Miscellaneous: Influenza (2%)

<1%: Angioneurotic edema, back pain, feces hard, somnolence

Postmarketing and/or case reports: Anaphylaxis, chest pain, delirium, gastritis, hallucinations, hypertensive crisis, palpitation, rash, rhabdomyolysis, Stevens-Johnson syndrome, supraventricular tachycardia, syncope, T-wave inversion

Drug Interactions

Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Cannabinoids: Anticholinergic Agents may enhance the tachycardic effect of Cannabinoids. *Risk C: Monitor therapy*

Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. *Risk D: Consider therapy modification*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

Secretin: Anticholinergic Agents may diminish the stimulatory effect of Secretin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid use since ethanol may enhance the sedative effects of trospium. Ethanol should not be ingested within 2 hours of the administration of the trospium extended release formulation.

Food: Administration with a fatty meal reduces the absorption and bioavailability of trospium.

Nursing: Physical Assessment/MonitoringUse with caution in presence of narrow-angle glaucoma, bladder flow or gastrointestinal obstruction, renal or hepatic impairment, or Alzheimer's. Assess potential for interactions with other pharmacological agents or herbal products patient may be taking (eg, acetylcholinesterase inhibitors, other anticholinergics). Evaluate therapeutic effect (eg, voiding patterns) at baseline and periodically during therapy. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. Void before taking this medication. Take tablets at bedtime on an empty stomach. Take extended release capsules in the morning with a full glass of water 1 hour before eating. Avoid alcohol for 2 hours before or after taking extended release capsules. May cause dry or sore mouth (frequent mouth care, sucking lozenges or chewing gum may help); constipation (increased exercise, fluids, fruit, or fiber may help); headache or blurred vision (use caution when driving or engaged in potentially hazardous tasks until response to drug in known); or decreased sweating (avoid extreme exercise or activity in hot weather). Report rapid heart beat or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to be pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release, as chloride:

Sanctura® XR: 60 mg

Tablet, as chloride:

Sanctura®: 20 mg

Generic AvailableNo

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Sanctura XR)

60 mg (30): $105.98

Tablets (Sanctura)

20 mg (30): $66.98

Mechanism of ActionTrospium antagonizes the effects of acetylcholine on muscarinic receptors in cholinergically innervated organs. It reduces the smooth muscle tone of the bladder.

Pharmacodynamics/Kinetics

Absorption: <10%; decreased with food

Distribution: V_d: 395 - >600 L, primarily in plasma

Protein binding: 48% to 85% *in vitro*

Metabolism: Hypothesized to be via esterase hydrolysis and conjugation; forms metabolites

Bioavailability: Immediate release formulation: ~10% (range: 4% to 16%)

Half-life elimination: Immediate release formulation: 20 hours

Severe renal insufficiency (Cl_{cr} <30 mL/minute): ~33 hours; extended release formulation: ~35 hours

Time to peak, plasma: 5-6 hours

Excretion: Feces (85%); urine (~6%; mostly as unchanged drug) primarily via active tubular secretion

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause delirium and hallucinations

Mental Health: Effects on Psychiatric TreatmentDry mouth and other anticholinergic effects are common; concurrent use with psychotropics may produce additive effects; use caution in patients with Alzheimer's disease

Index TermsTrospium Chloride

References

Chancellor M and de Miguel F, “Treatment of Overactive Bladder Selective Use of Anticholinergic Agents With Low Drug-Drug Interaction Potential,” *Geriatrics*, 2007, 62(5):15-24.[PubMed 17489643]

Staskin D, Sand P, Zinner N, et al, “Once Daily Trospium Chloride is Effective and Well Tolerated for the Treatment of Overactive Bladder: Results From a Multicenter Phase III Trial,” *J Urol*, 2007, 178(3 Pt 1): 978-84.[PubMed 17632131]

Zinner N, Gittelman M, Harris R, et al, “Trospium Chloride Improves Overactive Bladder Symptoms: A Multicenter Phase III Trial,” *J Urol,* 2004, 171(6 Pt 1):2311-15.[PubMed 15126811]

International Brand NamesRegurin (GB, IE); Sancturos (KP); Spasmed (EE); Spasmex (AR, CN, IL, KP, TW); Spasmo-Lyt (AE, BG, BH, CY, CZ, DK, EG, FI, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Spasmo-Urgenin Neo (CH); Spasmolyt (DE); Spasmoplex (PT); Tospin (TW); Uraplex (ES, IT)

Trypan Blue

English

Jump To Field (Select Field Name)

Pronunciation(TRYE pan bloo)

U.S. Brand NamesVisionBlue®

Pharmacologic CategoryOphthalmic Agent

Use: Labeled IndicationsStaining of anterior capsule of the lens during cataract surgery

Dosing: Adults**Cataract surgery:** Topical: Apply onto anterior lens capsule using a blunt cannula. Irrigate with balanced salt solution to remove excess dye.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Cataract surgery:** Topical: Refer to adult dosing.

Administration: OtherOphthalmic: To minimize dilution, an air bubble should be injected into the anterior chamber of the eye prior to application of trypan blue. Irrigate with balanced salt solution to remove excess dye.

StorageStore at 15°C to 25°C (59°F to 77°F). Protect from direct sunlight.

ContraindicationsHypersensitivity to trypan blue or any component of the formulation; nonhydrated, hydrophilic acrylic intraocular lens (IOL) insertion

Warnings/Precautions

Other warnings/precautions:

- Appropriate use: Irrigate to remove excess solution following injection.
- Staining of dye: Dye may be absorbed by and stain a nonhydrated hydrophilic acrylic IOL.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects, increased fetal mortality, and decreased fetal weight were observed following systemic use in animal studies.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsOcular: Posterior lens staining, vitreous face staining; staining may last up to 1 week

Nursing: Physical Assessment/MonitoringThis medication is used during cataract surgery.

Patient EducationThis medication is used during cataract surgery. Teaching will be appropriate to situation. Posterior lens may become stained during procedure. May last for up to 1 week. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, ophthalmic: 0.06% (0.5 mL)

Generic AvailableNo

ManufacturerDORC International

Mechanism of ActionAn acid di-azo group dye which selectively stains connective tissue structures in the human eye

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Trypsin, Balsam Peru, and Castor Oil

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Granulex® may be confused with Regranex®

Pronunciation(TRIP sin, BAL sam pe RUE, & KAS tor oyl)

U.S. Brand NamesAllanderm-T™; Granulex®; Optase™; Xenaderm™

Pharmacologic CategoryProtectant, Topical

Use: Labeled IndicationsTreatment of decubitus ulcers, varicose ulcers, debridement of eschar, dehiscent wounds and sunburn; promote wound healing; reduce odor from necrotic wounds

Dosing: Adults**Dermatologic conditions:** Topical: Apply a minimum of twice daily or as often as necessary

Dosing: ElderlyRefer to adult dosing.

Administration: TopicalClean wound prior to application and at each redressing; shake can well before spraying; hold can upright ~12" from area to be treated. May be used with appropriate dressing if needed.

StorageStore at controlled room temperature; do not freeze. Do not expose spray to fire, open flame, or temperatures >120°F.

ContraindicationsHypersensitivity to trypsin, balsam peru, castor oil, or any component of the formulation

Warnings/Precautions

Disease-related concerns:

- Hemoglobin deficiency: Wound healing may be retarded in the presence of hemoglobin deficiency.
- Zinc deficiency: Wound healing may be retarded in the presence of zinc deficiency.

Other warnings/precautions:

- Appropriate use: For external use only; do not apply to fresh arterial clots.

Geriatric ConsiderationsPreventive skin care should be instituted in all elderly patients at high risk for decubitus ulcers. Practical experience with Granulex® has found that it is not as effective in debriding wounds as compared to other enzymatic products. Therefore, Granulex® may be more appropriately used on stage 1 and 2 decubiti.

Adverse ReactionsFrequency not defined: Local: Temporary stinging at application site

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Aerosol, topical: Trypsin 0.12 mg, balsam Peru 87 mg, and castor oil 788 mg per gram (120 g)

Granulex®: Trypsin 0.12 mg, balsam Peru 87 mg, and castor oil 788 mg per gram (60 g, 120 g)

Gel, topical:

Optase™: Trypsin 0.12 mg, balsam Peru 87 mg, and castor oil 788 mg per gram (95 g)

Ointment, topical:

Allanderm-T™, Xenaderm™: Trypsin 90 USP units, balsam Peru 87 mg, and castor oil 788 mg per gram (30 g, 60 g)

Generic AvailableYes: Aerosol

Pricing: U.S. (www.drugstore.com)

Ointment (Xenaderm)

(30): $59.99

(60): $68.80

Mechanism of ActionTrypsin is used to debride necrotic tissue; balsam peru stimulates circulation at the wound site and may be mildly bactericidal; castor oil improves epithelialization, acts as a protectant covering and helps reduce pain

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBalsam Peru, Trypsin, and Castor Oil; Castor Oil, Trypsin, and Balsam Peru

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Tuberculin Tests

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Aplisol® may be confused with Anusol®, A.P.L.®, Aplitest®, Atropisol®

Administration issues:

Tuberculin products may be confused with tetanus toxoid products and influenza virus vaccine. Medication errors have occurred when tuberculin skin tests (PPD) have been inadvertently administered instead of tetanus toxoid products and influenza virus vaccine. These products are refrigerated and often stored in close proximity to each other.

Pronunciation(too BER kyoo lin tests)

U.S. Brand NamesAplisol®; Tubersol®

Pharmacologic CategoryDiagnostic Agent

Use: Labeled IndicationsSkin test in diagnosis of tuberculosis

Dosing: Adults

Diagnosis of tuberculosis, cell-mediated immunodeficiencies: Intradermal: 0.1 mL

TST interpretation: Criteria for positive TST read at 48-72 hours (see Note below for healthcare workers):

Induration ≥5 mm: Persons with HIV infection (or risk factors for HIV infection, but unknown status), recent close contact to person with known active TB, persons with chest x-ray consistent with healed TB, persons who are immunosuppressed

Induration ≥10 mm: Persons with clinical conditions which increase risk of TB infection, recent immigrants, I.V. drug users, residents and employees of high-risk settings, children <4 years of age

Induration ≥15 mm: Persons who do not meet any of the above criteria (no risk factors for TB)

Note: A two-step test is recommended when testing will be performed at regular intervals (eg, for healthcare workers). If the first test is negative, a second TST should be administered 1-3 weeks after the first test was read.

TST interpretation (CDC guidelines) in a healthcare setting:

Baseline test: ≥10 mm is positive (either first or second step)

Serial testing without known exposure: Increase of ≥10 mm is positive

Known exposure:

≥5 mm is positive in patients with baseline of 0 mm

≥10 mm is positive in patients with negative baseline or previous screening result of ≥0mm

Read test at 48-72 hours following placement. Test results with 0 mm induration or measured induration less than the defined cutoff point are considered to signify absence of infection with *M. tuberculosis*. Test results should be documented in millimeters even if classified as negative. Erythema and redness of skin are not indicative of a positive test result.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Administration: OtherFor intradermal administration only. Administer to upper third of forearm (palm up) ≥2 inches from elbow, wrist, or other injection site. If neither arm can be used, may administer to back of shoulder. Administer using inch $^{1}/_{4}$ to $^{1}/_{2}$ inch 27-gauge needle or finer tuberculin syringe. Should form wheal (6-10 mm in diameter) as liquid is injected which will remain ~10 minutes. Avoid pressure or bandage at injection site. Document date and time of injection, person placing TST, location of injection site and lot number of solution.

StorageAplisol®, Tubersol®: Store under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Opened vials should be discarded after 30 days.

ContraindicationsHypersensitivity to tuberculin purified protein derivative (PPD) or any component of the formulation; previous severe reaction to tuberculin PPD skin test (TST)

Warnings/Precautions

Disease-related concerns:

- Burns: Do not administer to persons with extensive burns.

- Eczema: Do not administer to persons with eczema.

- Tuberculosis: Do not administer to persons with documented tuberculosis or a clear history of treatment for tuberculosis.

- Viral infections: Skin testing may be deferred with major viral infections.

Special populations:

- Pediatrics: Very young children (<6 weeks of age) may also have an absent or delayed response.

Other warnings/precautions:

- Administration: For intradermal administration only; do not administer I.V., I.M., or SubQ. Epinephrine (1:1000) should be available to treat possible allergic reactions.

- Appropriate use: Patients with a previous severe reaction to TST (vesiculation, ulceration, necrosis) at the injection site should not receive tuberculin PPD again.

- Conditions decreasing response: Tuberculous or other bacterial infections, viral infection, live virus vaccination, malignancy, immunosuppressive agents, and conditions which impair immune response may cause a decreased response to test.

- Vaccinations: Skin testing may be deferred with live-virus vaccination within 1 month.

Geriatric ConsiderationsDue to changes in the immune system with age, skin test response may be delayed or reduced in magnitude; therefore when testing, use a two-step test procedure; repeat test 2-4 weeks after reading first test dose; this elicits a “booster effect”.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. Pregnancy is not a contraindication to testing.

Breast-Feeding ConsiderationsBreast-feeding is not a contraindication to testing.

Adverse ReactionsSuspected adverse reactions should be reported to the Food and Drug Administration (FDA) MedWatch Program at 1-800-332-1088

Frequency not defined:

Dermatologic: Rash

Local: Injection site reactions: Bleeding, bruising, discomfort, erythematous reaction, hematoma, necrosis, pain, pruritus, redness, scarring, ulceration, vesiculation

Miscellaneous: Anaphylaxis

Drug Interactions

Vaccines (Live): May diminish the diagnostic effect of Tuberculin Tests. **Exceptions:** Poliovirus Vaccine (Live/Trivalent/Oral). *Risk D: Consider therapy modification*

Test InteractionsFalse-positive reactions may occur with BCG vaccination or previous mycobacteria (nonTB) infection (previous BCG vaccination is not a contraindication to testing). False-negative reactions may occur with impaired cell mediated immunity.

Monitoring ParametersMonitor for immediate hypersensitivity reactions for ~15 minutes following injection.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution:

Aplisol®, Tubersol®: 5 TU/0.1 mL (1 mL, 5 mL) [contains polysorbate 80]

Generic AvailableNo

Mechanism of ActionTuberculosis results in individuals becoming sensitized to certain antigenic components of the *M. tuberculosis* organism. Culture extracts called tuberculins are contained in tuberculin skin test preparations. Upon intracutaneous injection of these culture extracts, a classic delayed (cellular) hypersensitivity reaction occurs. This reaction is characteristic of a delayed course (peak occurs >24 hours after injection, induration of the skin secondary to cell infiltration, and occasional vesiculation and necrosis). Delayed hypersensitivity reactions to tuberculin may indicate infection with a variety of nontuberculosis mycobacteria, or vaccination with the live attenuated mycobacterial strain of *M. bovis* vaccine, BCG, in addition to previous natural infection with *M. tuberculosis*.

Pharmacodynamics/Kinetics

Onset of action: Delayed hypersensitivity reactions: 5-6 hours

Peak effect: 48-72 hours

Duration: Reactions subside over a few days

Related Information

- Prophylaxis for Patients Exposed to Common Communicable Diseases
- Skin Tests

Pharmacotherapy PearlsSituations where risk of tuberculosis infection may be increased are with contacts of recently-diagnosed persons with active disease, contact with immigrants from countries where tuberculosis is still common, or reactivation with impaired immunity (HIV infection, diabetes, renal failure, immunosuppressant use, pulmonary silicosis). Healthcare workers, staff of correctional facilities, and travelers at high risk of exposure should have routine testing. Patients with HIV infection should be tested as soon as possible following diagnosis.

The date of administration, the product manufacturer, and lot number of product must be entered into the patient's permanent medical record. Results should be recorded in millimeters (even if 0), not “negative” or “positive”.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms Mantoux; PPD; TB Skin Test; TST; Tuberculin Purified Protein Derivative; Tuberculin Skin Test

References

“Centers for Disease Control and Prevention, Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005,” *MMWR Recomm Rep*, 2005, 30;54(17):1-141.

Dutt AK and Stead WW, “Tuberculosis,” *Clin Geriatr Med*, 1992, 8(4):761-75.[PubMed 1423133]

Villarino ME, Burman W, Wang YC, et al, “Comparable Specificity of 2 Commercial Tuberculin Reagents in Persons at Low Risk for Tuberculous Infection,” *JAMA*, 1999, 281(2):169-71.[PubMed 9917121]

TVTG

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Leukemia, Acute Lymphocytic; Chemotherapy Regimen, Leukemia, Acute Myeloid

Regimen Use Leukemia, acute lymphocytic; Leukemia, acute myeloid

Regimen

Topotecan: I.V.: 1 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 5 mg/m^2]

Vinorelbine: I.V.: 20 mg/m^2/day days 0, 7, 14, and 21

[total dose/cycle = 80 mg/m^2]

Thiotepa: I.V.: 15 mg/m^2 day 2

Gemcitabine: I.V.: 3600 mg/m^2 day 7

Dexamethasone: Oral or I.V.: 45 mg/m^2/day days 7 to 14 (given in 3 divided doses)

[total dose/cycle = 315 mg/m^2]

Repeat cycle when ANC >500 cells/mm^3 and platelet count >75,000 cells/mm^3

References

Kolb EA and Steinherz PG, âA New Multidrug Reinduction Protocol With Topotecan, Vinorelbine, Thiotepa, Dexamethasone, and Gemcitabine for Relapsed or Refractory Acute Leukemia,â *Leukemia*, 2003, 17(10):1967-72.[PubMed 14513046]

Typhoid Vaccine

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Pronunciation(TYE foid vak SEEN)
U.S. Brand NamesTyphim Vi®; Vivotif®
Canadian Brand NamesTypherix®; Typhim Vi®; Vivotif®
Pharmacologic CategoryVaccine
Use: Labeled IndicationsActive immunization against typhoid fever caused by *Salmonella typhi*

Not for routine vaccination. In the United States and Canada, use should be limited to:

- Travelers to areas with a prolonged risk of exposure to *S. typhi*
- Persons with intimate exposure to a *S. typhi* carrier
- Laboratory technicians with exposure to *S. typhi*
- Travelers with achlorhydria or hypochlorhydria (Canadian recommendation)

Dosing: Adults**Immunization:**

Oral:

Primary immunization: One capsule on alternate days (day 1, 3, 5, and 7) for a total of 4 doses; all doses should be complete at least 1 week prior to potential exposure

Booster immunization: Repeat full course of primary immunization every 5 years

I.M.:

Initial: 0.5 mL given at least 2 weeks prior to expected exposure

Reimmunization:

Typhim Vi®: 0.5 mL; optimal schedule has not been established; a single dose every 2 years is currently recommended for repeated or continued exposure

Typherix®: 0.5 mL every 3 years

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Immunization:**

Children ≥6 years: Oral: Refer to adult dosing.

Children ≥2 years: I.M.: Refer to adult dosing.

Administration: I.M.Typhim Vi® and Typherix® may be given I.M. and are indicated for children ≥2 years of age; administer as a single 0.5 mL (25 mcg) injection in deltoid muscle. **Do not administer Typhim Vi® or Typherix® intravascularly.**

For patients at risk of hemorrhage following intramuscular injection, the ACIP recommends "it should be administered intramuscularly if, in the opinion of the physician familiar with the patients bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (23 gauge or smaller) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least 2 minutes. The patient should be instructed concerning the risk of hematoma from the injection."

Administration: OralCapsule: Swallow whole soon after placing into mouth; do not chew or open capsule. Capsule should be taken with a cold or lukewarm beverage (≤37˚C/98.6˚F). Take one hour prior to a meal. Avoid alcohol within 2 hours of administration.
Storage

Typherix®: Store between 2°C to 8°C (35°F to 46°F); do not freeze. Discard if vaccine has been frozen. Protect from light.

Typhim Vi®: Store between 2°C to 8°C (35°F to 46°F); do not freeze.

Vivotif®: Store between 2°C to 8°C (35°F to 46°F).

ContraindicationsHypersensitivity to any component of the vaccine. In addition, the oral vaccine is contraindicated with congenital or acquired immunodeficient state, acute febrile illness, acute GI illness
Warnings/Precautions

Disease-related concerns:

- Typhoid fever: Should not be used to treat typhoid fever. Not all recipients of typhoid vaccine will be fully protected against typhoid fever. Travelers should take all necessary precautions to avoid contact or ingestion of potentially contaminated food or water sources.

Special populations:

- Pediatrics: Safety and efficacy of the injection have not been established in children <2 years of age; safety and efficacy of oral form have not been established in children <6 years of age.

Dosage form specific issues:

- Injection: Administer at least 2 weeks prior to expected exposure. Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use. May consider deferring administration in patients with moderate or severe acute illness (with or without fever); may administer to patients with mild acute illness (with or without fever). Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy (including high dose corticosteroids)); may have a reduced response to vaccination. Use with caution in patients with a history of bleeding disorders (including thrombocytopenia) and/or patients on anticoagulant therapy; bleeding/hematoma may occur from I.M. administration.

- Oral: Full immunization schedule should be completed at least 1 week prior to expected exposure. The complete immunization schedule must be followed to achieve optimum immune response. Vaccination may be deferred with persistent diarrhea or vomiting.

Geriatric ConsiderationsVaccinating elderly is often overlooked; if no record of immunization can be recalled, repeat primary series.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted. The manufacturer of the Typhim Vi® injection suggests delaying vaccination until the 2nd or 3rd trimester if possible. Untreated typhoid fever may lead to miscarriage or vertical intrauterine transmission causing neonatal typhoid (rare).

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**In the U.S., all serious adverse reactions must be reported to the Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967. In Canada, adverse reactions are reported to the Canadian Adverse Events following Immunization Surveillance System (CAEFISS) via the Adverse Event Following Immunization Report Form available at http://www.phac-aspc.gc.ca/im/aefi-form_e.html.**

Oral:

1% to 10%:

Central nervous system: Headache (5%), fever (3%)

Dermatologic: Rash (1%)

Gastrointestinal: Abdominal pain (6%), diarrhea (3%), nausea (6%), vomiting (2%)

Postmarketing and/or case reports: Anaphylactic reaction, demyelinating disease, myalgia, pain, RA, urticaria, sepsis, weakness

Injection (incidence may vary based on age and/or product used):

>10%:

Central nervous system: Headache (16% to 20%), fever (undefined; 2% to 32%), malaise (4% to 24%)

Local: Injection site: Tenderness (97% to 98%), pain (27% to 41%), soreness (up to 16%), induration (5% to 15%)

Neuromuscular & skeletal: General aches (1% to 13%)

1% to 10%:

Central nervous system: Fever ≥100°F (2%), >102°F (2%)

Dermatologic: Pruritus (up to 8%)

Gastrointestinal: Nausea (up to 8%), vomiting (2%)

Local: Injection site: Erythema (up to 5%), swelling (up to 4%)

Neuromuscular & skeletal: Myalgia (3% to 7%)

Postmarketing and/or case reports: Abdominal pain, allergic reactions, anaphylaxis, arthralgia, cervical pain, diarrhea, dizziness, flu-like syndrome, Guillain-Barré syndrome, hypotension, injection site inflammation (including angioedema and urticaria), loss of consciousness, lymphadenopathy, malaise, perforated jejunum, rash, serum sickness, tremor, urticaria, vasodilation, weakness

Drug Interactions

Antibiotics: May diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. **Exceptions:** Acetic Acid; Aluminum Acetate; Bacitracin; Benzalkonium Chloride; Benzoin; Capreomycin; Gentian Violet; Hexachlorophene; Mafenide; Neomycin; Oxychlorosene; Polymyxin B; Povidone-Iodine; Silver Nitrate; Silver Sulfadiazine. *Risk D: Consider therapy modification*

Immune Globulins: May diminish the therapeutic effect of Vaccines (Live). *Risk D: Consider therapy modification*

Immunosuppressants: May enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Mefloquine: May enhance the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Tuberculin Tests: Vaccines (Live) may diminish the diagnostic effect of Tuberculin Tests. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid alcohol within 2 hours of taking the capsule; may disrupt the enteric coating
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Capsule, enteric coated:

Vivotif®: Viable *S. typhi* Ty21a 2-6.8 x 10^9 colony-forming units and nonviable *S. typhi* Ty21a 5-50 x 10^9 bacterial cells [contains lactose 100-180 mg/capsule and sucrose 26-130 mg/capsule]

Injection, solution:

Typherix® [CAN]: Vi capsular polysaccharide 25 mcg/0.5 mL (0.5 mL) [derived from *S. typhi* Ty2 strain] [not available in U.S.]

Typhim Vi®: Purified Vi capsular polysaccharide 25 mcg/0.5 mL (0.5 mL, 10 mL) [derived from *S. typhi* Ty2 strain]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Capsule, delayed release (Vivotif Berna Vaccine)

(4): $49.99

Mechanism of ActionVirulent strains of *Salmonella typhi* cause disease by penetrating the intestinal mucosa and entering the systemic circulation via the lymphatic vasculature. One possible mechanism of conferring immunity may be the provocation of a local immune response in the intestinal tract induced by oral ingesting of a live strain with subsequent aborted infection. The ability of *Salmonella typhi* to produce clinical disease (and to elicit an immune response) is dependent on the bacteria having a complete lipopolysaccharide. The live attenuate Ty21a strain lacks the enzyme UDP-4-galactose epimerase so that lipopolysaccharide is only synthesized under conditions that induce bacterial autolysis. Thus, the strain remains avirulent despite the production of sufficient lipopolysaccharide to evoke a protective immune response. Despite low levels of lipopolysaccharide synthesis, cells lyse before gaining a virulent phenotype due to the intracellular accumulation of metabolic intermediates.
Pharmacodynamics/Kinetics

Onset of action: Immunity to *Salmonella typhi*: Oral: ~1 week

Duration: Immunity: Oral: ~4-7 years; Parenteral: Typhim Vi®: >17-21 months, Typherix®: ~3 years

Related Information

- Immunization Recommendations

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause malaise
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsTy21a Vaccine; Typhoid Vaccine Live Oral Ty21a; Vi Vaccine
References

Begier EM, Burewn DR, Haber P, et al, “Postmarketing Safety Surveillance for Typhoid Fever Vaccines From the Vaccine Adverse Event Reporting System, July 1990 Through June 2002,” *Clin Infect Dis*, 2004, 38(6):771-9.[PubMed 14999618]

“Canadian Immunization Guide, Seventh Edition, 2006,” Ottawa, ONT: Minister of Public Works and Government Services Canada, Public Health Agency of Canada, National Advisory Committee on Immunization, 2006. Available at http://www.phac-aspc.gc.ca/publicat/cig-gci/index.html

Centers for Disease Control, “Recommendations of the Advisory Committee on Immunization Practices (ACIP): General Recommendations on Immunization,” *MMWR Recomm Rep*, 2006, 55(RR-15):1-48.

Gardner P and Schaffner W, “Immunization of Adults,” *N Engl J Med*, 1993, 328(17):1252-8.[PubMed 8464436]

Guzman CA, Borsutzky S, Griot-Wenk M, et al, “Vaccines Against Typhoid Fever,” *Vaccine*, 2006, 24(18):3804-11.[PubMed 16278037]

Parry CM, Hien TT, Dougan G, et al, “Typhoid Fever,” *N Engl J Med*, 2002, 347(22):1770-82.[PubMed 12456854]

International Brand NamesTyph-Vax (NZ); Typherix (HK, PH, SG); Typhim VI (AU, CO, CR, DO, EE, FI, GT, HK, ID, KP, MY, PH, PK, SG, SV, TH, TW); Typhoral (IN); Typhovax (KP); Tyrix Vi (KP); Vivotif (DE); Vivotif Berna (AT, CH, DK, ES, HK, IT, KP, MY, NL, PE, TH); Vivotif Berna Capsule (NO); Vivotif Oral (AU); Vivotif Oralt Vaccin (SE); Zerotyph (KP)

UFT

Jump To Field (Select Field Name)

U.S. Brand NamesOrzel® [DSC]

Pharmacologic CategoryAntineoplastic Agent, Antimetabolite (Pyrimidine Antagonist)

Use: Unlabeled/InvestigationalInvestigational: Treatment of unresectable or metastatic colorectal cancer

Dosing: AdultsRefer to individual protocols.

Oral: 300 mg/m^2/day (expressed as tegafur) in combination with oral leucovorin

Dosing: ElderlyRefer to adult dosing.

Calculations

- Body Surface Area: Adults

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Adverse ReactionsFrequency not defined.

Central nervous system: Fatigue, cerebellar toxicity (rare)

Dermatologic: Rash, skin pigmentation, photosensitivity, hand-foot syndrome (rare)

Gastrointestinal: Nausea, vomiting, anorexia, diarrhea (may be dose limiting)

Hematologic: Neutropenia (may be dose limiting)

Neuromuscular & skeletal: Neurotoxicity (peripheral neuropathy)

Ocular: Lacrimation

Oncology: VesicantNo

Oncology: Emetic PotentialModerate (30% to 60%)

Drug InteractionsNone reported

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC} = Discontinued product

Capsule:

Orzel® [DSC]: Tegafur 100 mg and uracil 224 mg

Generic AvailableNo

Mechanism of ActionTegafur is a prodrug of fluorouracil. It is converted *in vivo* to fluorouracil through hepatic microsomal cytochrome P450, and also via thymidine phosphorylase and spontaneous anabolic conversion. Uracil is a competitive inhibitor of dihydropyrimidine dehydrogenase (DPD), the enzyme responsible for catabolism of approximately 85% of fluorouracil to fluoro-β alanine.

Pharmacodynamics/Kinetics

Plasma levels: Tegafur > uracil > fluorouracil

Time to C_{pmax}: Tegafur: 0.6-2.1 hours; uracil: 0.6-4.1 hours; fluorouracil: 0.7-2.0 hours; the relationship between UFT dose and fluorouracil C_{pmax} is not linear

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause sedation

Mental Health: Effects on Psychiatric TreatmentGI side effects are common; concomitant use with SSRIs, lithium, and valproic acid may produce additive effects. Hematological side effects are common; use caution with clozapine, carbamazepine, and valproic acid.

Index TermsUracil and Ftorafur; Uracil and Tegafur; Uracil and Tetrahydrofuranyl-5-Fluorouracil

References

Ho DH, Covington WP, Pazdur R, et al, “Clinical Pharmacology of Combined Oral Uracil and Ftorafur,” *Drug Metab Disp*, 1992, 20(6):936-40.

Kohne CH and Peters GJ, “UFT: Mechanism of Drug Action,” *Oncology (Huntingt)*, 2000, 14(10 Suppl 9):13-8.

Sun W and Haller D, “UFT in the Treatment of Colorectal and Breast Cancer,” *Oncology (Huntingt)*, 2001, 15(1 Suppl 2):49-56.

International Brand NamesUFT (PL)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(un de sil EN ik AS id & dah RIV ah tivs)
U.S. Brand NamesFungi-Nail® [OTC]
Pharmacologic CategoryAntifungal Agent, Topical
Use: Labeled IndicationsTreatment of athlete's foot (tinea pedis); ringworm (except nails and scalp)
Dosing: Adults**Tinea and dermatophyte infections (superficial):** Topical: Apply twice daily to affected area for 4 weeks; apply to clean, dry area
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricChildren ≥2 years: Refer to adult dosing.
ContraindicationsHypersensitivity to undecylenic acid or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Irritation: Discontinue if sensitivity or irritation occurs.

Special populations:

- Pediatrics: Not for self-medication (OTC use) in children <2 years of age.

Other warnings/precautions:

- Appropriate use: For topical use only; avoid contact with eyes. Apply to clean, dry skin. When used for self-medication (OTC use), contact health care provider if condition does not improve within 4 weeks.

Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, topical:

Fungi-Nail®: Undecylenic acid 25% (29.57 mL)

Generic AvailableNo
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsZinc Undecylenate
International Brand NamesDerman (MX); Micotex (MX)

Unoprostone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(yoo noe PROS tone)

Canadian Brand NamesRescula®

Pharmacologic CategoryOphthalmic Agent, Antiglaucoma; Prostaglandin, Ophthalmic

Use: Labeled IndicationsTo lower intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension; should be used in patients who are not tolerant of, or failed treatment with other IOP-lowering medications

Dosing: Adults**Glaucoma or ocular hypertension:** Ophthalmic: Instill 1 drop into affected eye(s) twice daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentUse with caution, no dosing adjustment reported.

Dosing: Hepatic ImpairmentUse with caution, no dosing adjustment reported.

StorageStore between 2°C to 25°C (36°F to 77°F).

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to unoprostone, benzalkonium chloride, or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

- Ocular effects: May cause permanent change in eye color (increases the amount of brown pigment in the iris); long-term consequences and potential injury to eye are not known. Bacterial keratitis, caused by inadvertent contamination of multiple-dose ophthalmic solutions, has been reported.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; safety and efficacy have not been established.

- Ocular disease: Use with caution in patients with intraocular inflammation. Safety and efficacy have not been determined for use in patients angle closure, inflammatory or neovascular glaucoma.

- Renal impairment: Use with caution in patients with renal impairment; safety and efficacy have not been established.

Special populations:

- Contact lens wearers: Contains benzalkonium chloride which may be adsorbed by contact lenses; remove contacts prior to administration and wait 15 minutes before reinserting.

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsNo differences in safety and efficacy have been reported in the elderly. Assess patient's ability to self-administer eye drops.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%: Ocular: Burning/stinging (10% to 25%), dry eyes (10% to 25%), injection (10% to 25%), ophthalmic itching (10% to 25%), increased length of eyelashes (10% to 14%)

1% to 10%:

Cardiovascular: Hypertension

Central nervous system: Dizziness, headache, insomnia, pain

Endocrine & metabolic: Diabetes mellitus

Neuromuscular & skeletal: Back pain

Ocular: Abnormal vision (5% to 10%), eyelid disorder (5% to 10%), foreign body sensation (5% to 10%), lacrimation disorder (5% to 10%), decreased length of eyelashes (7%), blepharitis, cataract, conjunctivitis, corneal lesion, eye discharge, eye hemorrhage, eye pain, irritation, keratitis, photophobia, vitreous disorder

Respiratory: Bronchitis, increased cough, pharyngitis, rhinitis, sinusitis

Miscellaneous: Flu-like syndrome (6%), accidental injury, allergic reaction

<1%: Color blindness, corneal deposits, corneal edema, corneal opacity, diplopia, acute elevated intraocular pressure, hyperpigmentation of the eyelid, increase in number of eyelashes, iris hyperpigmentation, iritis, optic atrophy, ptosis, retinal hemorrhage, visual field defect

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, ophthalmic: 0.15% (5 mL) [contains benzalkonium chloride] [DSC]

Generic AvailableNo

Mechanism of ActionThe exact mechanism of action is unknown; however, unoprostone decreases IOP by increasing the outflow of aqueous humor. Cardiovascular and pulmonary function were not affected in clinical studies. IOP was decreased by 3-4 mm Hg in patients with a mean baseline IOP of 23 mm Hg.

Pharmacodynamics/Kinetics

Absorption: Through cornea and conjunctival epithelium

Metabolism: Hydrolyzed by esterases unoprostone-free acid

Half-life elimination: 14 minutes

Excretion: Urine (as metabolites)

Related Information

- Glaucoma Drug Therapy

Pharmacotherapy PearlsContains benzalkonium chloride 0.015% as a preservative

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or insomnia

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsUnoprostone Isopropyl

International Brand NamesRescula (AR, BR, CN, CO, CZ, ES, MX, PE, PH, PK, PL, SE, UY, VE)

Urea and Hydrocortisone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(yoor EE a & hye droe KOR ti sone)
U.S. Brand NamesCarmol-HC速
Canadian Brand NamesTi-U-Lac速 H; Uremol速 HC
Pharmacologic CategoryCorticosteroid, Topical
Use: Labeled IndicationsInflammation of corticosteroid-responsive dermatoses
Dosing: Adults**Steroid-responsive dermatoses:** Topical: Apply thin film and rub in well 1-4 times/day. Therapy should be discontinued when control is achieved; if no improvement is seen, reassessment of diagnosis may be necessary.
Dosing: ElderlyRefer to adult dosing.
Dosing: PediatricRefer to adult dosing.
Allergy Considerations

- Corticosteroid Allergy

Pregnancy Risk FactorC
Metabolism/Transport EffectsHydrocortisone: **Substrate** of CYP3A4 (minor); **Induces** CYP3A4 (weak)
Drug Interactions

Acetylcholinesterase Inhibitors: Corticosteroids (Systemic) may enhance the adverse/toxic effect of Acetylcholinesterase Inhibitors. Increased muscular weakness may occur. *Risk C: Monitor therapy*

Aminoglutethimide: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Amphotericin B: Corticosteroids (Systemic) may enhance the hypokalemic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the bioavailability of Corticosteroids (Oral). *Risk D: Consider therapy modification*

Antidiabetic Agents: Corticosteroids (Systemic) may diminish the hypoglycemic effect of Antidiabetic Agents. In some instances, corticosteroid-mediated HPA axis suppression has led to episodes of acute adrenal crisis, which may manifest as enhanced hypoglycemia, particularly in the setting of insulin or other antidiabetic agent use. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Aprepitant: May increase the serum concentration of Corticosteroids (Systemic). *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Bile Acid Sequestrants: May decrease the absorption of Corticosteroids (Oral). *Risk C: Monitor therapy*

Calcitriol: Corticosteroids (Systemic) may diminish the therapeutic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Corticorelin: Corticosteroids may diminish the therapeutic effect of Corticorelin. Specifically, the plasma ACTH response to corticorelin may be blunted by recent or current corticosteroid therapy. *Risk C: Monitor therapy*

CycloSPORINE: Corticosteroids (Systemic) may increase the serum concentration of CycloSPORINE. CycloSPORINE may increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Estrogen Derivatives: May increase the serum concentration of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of Corticosteroids (Systemic). The active metabolite aprepitant is likely responsible for this effect. *Risk D: Consider therapy modification*

Isoniazid: Corticosteroids (Systemic) may decrease the serum concentration of Isoniazid. *Risk C: Monitor therapy*

Loop Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Corticosteroids (Systemic). **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inducers may decrease the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents (Nondepolarizing): May enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (COX-2 Inhibitor). *Risk C: Monitor therapy*

NSAID (Nonselective): Corticosteroids (Systemic) may enhance the adverse/toxic effect of NSAID (Nonselective). *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Primidone: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the adverse/toxic effect of Corticosteroids (Systemic). Risk of tendon-related side effects, including tendonitis and rupture, may be enhanced. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Corticosteroids (Systemic). These specifically include gastrointestinal ulceration and bleeding. Corticosteroids (Systemic) may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity. *Risk C: Monitor therapy*

Thiazide Diuretics: Corticosteroids (Systemic) may enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Warfarin: Corticosteroids (Systemic) may enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream: Urea 10% and hydrocortisone acetate 1% (30 g) [in water soluble vanishing cream base]

Generic AvailableNo
Pricing: U.S. (www.drugstore.com)

Cream (Carmol-HC)

1-10% (28.35): $26.08

1-10% (85): $78.70

Pharmacodynamics/KineticsSee individual agents.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsHydrocortisone and Urea
International Brand NamesCalmurid (ZA); Ti-U-Lac H (CA); Uremol HC (CA)

Urea

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(yoor EE a)

U.S. Brand NamesAquacare® [OTC]; Aquaphilic® With Carbamide [OTC]; Carmol® 10 [OTC]; Carmol® 20 [OTC]; Carmol® 40; Carmol® Deep Cleaning; Cerovel™; DPM™ [OTC]; Gormel® [OTC]; Hydro 40™; Kerafoam™; Keralac™; Keralac™ Nailstik; Kerol™; Kerol™ Redi-Cloths; Kerol™ ZX; Lanaphilic® [OTC]; Nutraplus® [OTC]; Rea-Lo® [OTC]; Ultra Mide® [OTC]; Umecta® ; Ureacin® [OTC]; Vanamide™

Canadian Brand NamesUltraMide 25™; Uremol®; Urisec®

Pharmacologic CategoryDiuretic, Osmotic; Keratolytic Agent; Topical Skin Product

Use: Labeled IndicationsKeratolytic agent to soften nails or skin; OTC: Moisturizer for dry, rough skin

Dosing: Adults**Hyperkeratotic conditions, dry skin:** Topical: Apply 1-3 times/day.

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to urea or any component of the formulation; viral skin disease

Warnings/Precautions

Other warnings/precautions:

- Appropriate application: Urea should not be used near the eyes. Use with caution if applied to face or broken or inflamed skin.

Pregnancy Risk FactorC

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsFrequency not defined: Local: Transient stinging, local irritation

Drug InteractionsThere are no known significant interactions.

Nursing: Physical Assessment/MonitoringAssess knowledge/teach appropriate administration, possible side effects, and symptoms to report.

Patient EducationFor external use only. Best effect is obtained when applied to skin while still wet or moist after washing or bathing. Do not apply to broken, inflamed, or infected skin. Do not use near eyes. Report skin redness, irritation, or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Aerosol, topical [foam]:

Hydro 40™: 40% (70 g)

Kerafoam™: 30% (60 g)

Cloth, topical:

Kerol™ Redi-Cloths: 42% (30s) [contains lactic acid, vitamin E and zinc]

Cream, topical: 40% (30 g, 85 g, 199 g)

Aquacare®: 10% (75 g)

Carmol® 20: 20% (90 g)

Carmol® 40: 40% (30 g, 90 g, 210 g)

Cerovel™: 40% (133 g) [DSC]

DPM™: 20% (118 g) [contains menthol and peppermint oil]

Gormel®: 20% (75 g, 120 g, 454 g, 2270 g)

Keralac™: 50% (142 g, 255 g) [contains lactic acid, vitamin E, and zinc]

Nutraplus®: 10% (90 g, 454 g)

Rea-Lo®: 30% (60 g, 240 g)

Ureacin®-20: 20% (120 g)

Vanamide™: 40% (85 g, 199 g)

Emulsion, topical:

Kerol™: 50% (283.5 g) [contains lactic acid, vitamin E, and zinc]

Umecta®: 40% (120 mL, 480 mL)

Gel: 40% (15 mL)

Carmol® 40: 40% (15 mL)

Cerovel™: 40% (25 mL)

Keralac™: 50% (18 mL) [contains lactic acid and zinc]

Lotion, topical: 40% (240 mL)

Aquacare®: 10% (240 mL)

Carmol® 10: 10% (180 mL)

Carmol® 40: 40% (240 mL)

Cerovel™: 40% (325 mL)

Keralac™: 35% (207 mL, 325 mL) [contains lactic acid, vitamin E, and zinc]

Nutraplus®: 10% (240 mL, 480 mL)

Ultra Mide®: 25% (120 mL, 240 mL)

Ureacin®-10: 10% (240 mL)

Ointment, topical:

Aquaphilic® with Carbamide: 10% (180 g, 480 g); 20% (480 g)

Keralac™: 50% (90 g)

Lanaphilic®: 10% (454 g); 20% (454 g)

Shampoo, topical:

Carmol® Deep Cleaning: 10% (240 mL)

Solution, topical:

Keralac™ Nailstick: 50% (2.4 mL)

Kerol™ ZX: 50% (12 mL) [contains lactic acid, vitamin E, and zinc]

Suspension, topical: 50% (284 g)

Kerol™: 50% (284 g) [contains lactic acid, salicylic acid and vitamin E]

Umecta®: 40% (18 mL) [nail film with applicator], (300 mL)

Generic AvailableYes: Excludes ointment, shampoo

Pricing: U.S. (www.drugstore.com)

Cream (Carmol 20)

20% (85): $21.99

Cream (Carmol 40)

40% (28.35): $72.52

40% (85): $103.64

40% (198.6): $186.98

Cream (Keralac)

50% (142): $120.39

50% (255): $167.41

Cream (Urea)

40% (28.35): $24.99

40% (85.05): $34.99

40% (198.6): $66.23

Cream (Vanamide)

40% (85): $60.87

Emulsion (Umecta)

40% (120): $93.60

40% (227): $138.79

Foam (Hydro 40)

40% (70): $107.30

Gel (Carmol 40)

40% (15): $198.54

Gel (Keralac)

50% (18): $178.19

Lotion (Carmol 10)

10% (177): $23.99

Lotion (Carmol 40)

40% (236.6): $194.56

Lotion (Cerovel)

40% (325): $89.99

Lotion (Keralac)

35% (325): $204.82

Lotion (Urea)

40% (236.6): $74.98

Misc (Kerol Redi-Cloths)

42% (30): $149.60

Ointment (Keralac)

50% (45): $87.02

Shampoo (Carmol)

10% (240): $23.52

Solution (Keralac Nailstik)

50% (14.4): $152.89

Suspension (Kerol)

50% (284): $146.89

Suspension (Umecta)

40% (283.4): $160.97

Suspension (Umecta Nail Film)

40% (18): $162.54

Mechanism of ActionUrea softens hyperkeratotic areas by dissolving the intracellular matrix, resulting in loosening the horny layer of the skin, or softening and debridement of the nail plate

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCarbamide

International Brand NamesAlphadrate (NL); Aquacare HP (AU); Aquadrate (GB, IE); Aqurea (SG); Balisa (DE); Banjil (KP); Basodexan (AT, DE); Calmurid (BE, DE, LU, NL, PT); Calmuril (FI, SE); Carbaderm (NO); Carbaderme (PT); Carbamid (LU); Carbamid Widmer (DE); Carmed (ID); Carmol (HK); Caruderma (HK); Elacutan (DE); Elacutan F (PL); Eucerin (DE); Euderm (HK, SG); Fenuril (FI); Helicobacter Test Infai (IT); Hidrat 40 (EC); Hyanit (DE); Keratinamin (JP); Laceran (DE, PT); Linola Urea (DE); Nubral (DE); Nutraplus (CH, MX, MY, SG, TH, TW); Onychomal (DE, LU); Pastaron (JP); Penaderm (DE); Sebexol (DE); Soft U Derm (ID); Uramol (CN, PE); Ureadin (ES); Urecare (AU, HK); Urederm (AU); Uremol (AR); Ureotop (DE); Uricrim (VE); Uroderm (PL)

Urofollitropin

Lexi-Drugs Online

English

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Pronunciation(yoor oh fol li TROE pin)

U.S. Brand NamesBravelle®

Canadian Brand NamesBravelle®; Fertinorm® H.P.

Pharmacologic CategoryGonadotropin; Ovulation Stimulator

Use: Labeled IndicationsOvulation induction in patients who previously received pituitary suppression; development of multiple follicles with Assisted Reproductive Technologies (ART)

Dosing: Adults**Note:** Dose should be individualized. Use the lowest dose consistent with the expectation of good results. Over the course of treatment, doses may vary depending on individual patient response.

Females:

Ovulation induction: I.M., SubQ: Initial: 150 int. units daily for the first 5 days of treatment. Dose adjustments ≤75-150 int. units can be made every ≥2 days; maximum daily dose: 450 int. units; treatment >12 days is not recommended. If response to follitropin is appropriate, hCG is given 1 day following the last dose. Withhold hCG if serum estradiol is >2000 pg/mL, if the ovaries are abnormally enlarged, or if abdominal pain occurs.

ART: SubQ: 225 int. units daily for the first 5 days; dose may be adjusted based on patient response, but adjustments should not be made more frequently than once every 2 days; maximum adjustment: 75-150 int. units; maximum daily dose: 450 int. units; maximum duration of treatment: 12 days. When a sufficient number of follicles of adequate size are present, the final maturation of the follicles is induced by administering hCG. Withhold hCG in cases where the ovaries are abnormally enlarged on the last day of therapy.

Administration: I.M.Administer I.M. or SubQ; gently massage site after administration. For I.M. injection, administer in upper quadrant of buttock near hip.

Administration: OtherAdminister SubQ or I.M.; gently massage site after administration. For SubQ injection, administer on lower abdomen; thigh is not recommended unless abdomen cannot be used.

StorageLyophilized powder may be stored in the refrigerator or at room temperature of 3°C to 25°C (37°F to 77°F). Protect from light.

Reconstitution Dissolve contents of vial in sterile saline 1 mL; gently swirl (do not shake). Do not use if solution is not clear or contains particles. If more than 1 vial is required for a single dose, up to 6 vials can be reconstituted with sterile saline 1 mL and administered as a single injection. This is done by first reconstituting 1 vial with sterile saline as previously described, withdrawing the entire contents of the reconstituted vial, and (using this as the diluent for the second vial) injecting into the second vial, etc. Use immediately after reconstitution.

ContraindicationsHypersensitivity to follitropins or any component of the formulation; high levels of FSH indicating primary ovarian failure; uncontrolled thyroid or adrenal dysfunction; the presence of any cause of infertility other than anovulation; presence of an organic intracranial lesion (eg, pituitary tumor); abnormal vaginal bleeding of undetermined origin; ovarian cysts or enlargement not due to polycystic ovary syndrome; pregnancy

Warnings/Precautions

Concerns related to adverse effects:

- Ovarian enlargement: May be accompanied by abdominal distention or abdominal pain, occurs in ~20% of those treated with urofollitropin and hCG, and generally regresses without treatment within 2-3 weeks. If ovaries are abnormally enlarged on the last day of treatment, withhold hCG to reduce the risk of ovarian hyperstimulation syndrome (OHSS).

- Ovarian hyperstimulation syndrome (OHSS): OHSS is characterized by severe ovarian enlargement, abdominal pain/distention, nausea, vomiting, diarrhea, dyspnea, and oliguria, and may be accompanied by ascites, pleural effusion, hypovolemia, electrolyte imbalance, hemoperitoneum, and thromboembolic events. If hyperstimulation occurs, stop treatment and hospitalize patient. This syndrome develops rapidly within 24 hours to several days and generally occurs during the 7-10 days immediately following treatment. Hemoconcentration associated with fluid loss into the abdominal cavity has occurred and should be assessed by fluid intake and output, weight, hematocrit, serum and urinary electrolytes, urine specific gravity, BUN and creatinine, and abdominal girth. Determinations should be performed daily or more often if the need arises. Treatment is primarily symptomatic and consists of bedrest, fluid and electrolyte replacement, and analgesics. The ascitic, pleural, and pericardial fluids should not be removed unless needed to relieve symptoms of cardiopulmonary distress.

- Pulmonary effects: Serious pulmonary conditions (atelectasis, acute respiratory distress syndrome, and exacerbation of asthma) have been reported.

- Thromboembolic events: In association with and separate from ovarian hyperstimulation syndrome (OHSS), thromboembolic events have been reported.

Special populations:

- Elderly: Safety and efficacy have not been established in the elderly.

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Lactose: Products may contain lactose.

Other warnings/precautions:

- Appropriate use: To minimize risks, use only at the lowest effective dose. Monitor ovarian response with serum estradiol and vaginal ultrasound on a regular basis.
- Experienced physician: These medications should only be used by physicians who are thoroughly familiar with infertility problems and their management.
- Multiple births: May result from the use of these medications; advise patient of the potential risk of multiple births before starting the treatment.

Pregnancy Risk FactorX

Pregnancy ConsiderationsEctopic pregnancy, congenital abnormalities, spontaneous abortion, and multiple births have been reported. The incidence of congenital abnormality may be slightly higher after ART than with spontaneous conception; higher incidence may be related to parenteral characteristics (maternal age, sperm characteristics).

LactationExcretion in breast milk unknown/not recommended

Adverse ReactionsPercentage may vary by indication, route of administration.

>10%:

Central nervous system: Headache

Endocrine & metabolic: Ovarian enlargement, ovarian hyperstimulation syndrome

Gastrointestinal: Abdominal cramps

1% to 10%:

Cardiovascular: Hypertension

Central nervous system: Depression, emotional lability, fever, pain

Dermatologic: Acne, exfoliative dermatitis, rash

Endocrine & metabolic: Breast tenderness, hot flashes, ovarian disorder (pain, cyst)

Gastrointestinal: Abdomen enlarged, abdominal pain, constipation, diarrhea, dehydration, nausea, vomiting, weight gain

Genitourinary: Cervical disorder, urinary tract infection, pelvic pain/cramps, uterine spasms, vaginal discharge, vaginal hemorrhage, vaginal spotting

Local: Injection site reaction

Neuromuscular & skeletal: Neck pain

Respiratory: Respiratory disorder, sinusitis

Miscellaneous: Infection, postretrieval pain

Postmarketing, case reports, or events reported with gonadotropins: Acute respiratory distress syndrome, adnexal torsion, anaphylactic reactions, arterial occlusion, atelectasis, cerebral vascular occlusion, deep vein thrombosis, hemoperitoneum, hypersensitivity reactions, ovarian neoplasms, pulmonary embolism

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersMonitor sufficient follicular maturation. This may be directly estimated by sonographic visualization of the ovaries and endometrial lining or measuring serum estradiol levels. The combination of both ultrasonography and measurement of estradiol levels is useful for monitoring for the growth and development of follicles and timing hCG administration.

The clinical evaluation of estrogenic activity (changes in vaginal cytology and changes in appearance and volume of cervical mucus) provides an indirect estimate of the estrogenic effect upon the target organs and, therefore, it should only be used adjunctively with more direct estimates of follicular development (ultrasonography and serum estradiol determinations).

The clinical confirmation of ovulation is obtained by direct and indirect indices of progesterone production. The indices most generally used are: rise in basal body temperature, increase in serum progesterone, and menstruation following the shift in basal body temperature.

Monitor for signs and symptoms of OHSS for at least 2 weeks following hCG administration.

Nursing: Physical Assessment/MonitoringThis medication should only be prescribed by a fertility specialist. Assess results of laboratory tests and therapeutic effectiveness on a regular basis. Assess knowledge/teach patient appropriate use (injection technique and syringe disposal), interventions to reduce side effects, and adverse symptoms to report. **Pregnancy risk factor X:** Pregnancy must be excluded before starting medication.

Monitoring: Lab TestsMonitor sufficient follicular maturation. This may be directly estimated by sonographic visualization of the ovaries and endometrial lining or measuring serum estradiol levels. The combination of both ultrasonography and measurement of estradiol levels is useful for monitoring for the growth and development of follicles and timing hCG administration.

Patient EducationThis medication can only be administered by injection. If you are using this medication at home, follow exact instruction for administering injections and disposal of syringes. Administer exact amount as instructed; do not alter dosage or miss a dose. If dose is missed, notify prescriber. Frequent laboratory tests will be required while you are on this therapy; do not miss appointments for laboratory tests or ultrasound. You may experience headache, dizziness, or fever (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea or vomiting (small frequent meals, frequent oral care, sucking lozenges, or chewing gum may help). Report immediately abdominal pain/distension, bloating, persistent nausea, vomiting, diarrhea; dyspnea, respiratory difficulty, exacerbation of asthma; swelling, pain, or redness of extremities; itching or burning on urination; menstrual irregularity, acute backache; rash, pain, or inflammation at injection site; or other adverse response. **Pregnancy/breast-feeding precautions:** Pregnancy must be ruled out prior to initiating this medication. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [human origin]:

Bravelle®: 75 int. units [contains lactose; packaged with diluent]

Mechanism of ActionUrofollitropin is a preparation of highly purified follicle-stimulating hormone (FSH) extracted from the urine of postmenopausal women. Follitropins stimulate ovarian follicular growth in women who do not have primary ovarian failure. FSH is required for normal follicular growth, maturation, gonadal steroid production, and spermatogenesis.

Pharmacodynamics/Kinetics

Half-life elimination

I.M.: 37 hours, 15 hours following multiple doses

SubQ: 32 hours, 21 hours following multiple doses

Time to peak, plasma:

I.M.: 17 hours, 11 hours following multiple doses

SubQ: 21 hours, 10 hours following multiple doses

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsFollicle-Stimulating Hormone, Human; FSH; hFSH

References

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International Brand NamesBravelle (ES, IE, IL, NO, SE); Fertinorm (AT); Foligem (IN); Follegon (TW); Follimon (KP, TH); Follitrin (AR, CN, PY, UY); Fostimon (BG, CH, CZ, FR, GB, IL, MX); Fostipur (ES); Lishenbao (CL); Metrodin (GR, HK, MY, NL, PL); Metrodin HP (BR, PL)

Urokinase

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Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(ur oh KYE nase)

U.S. Brand NamesKinlytic™

Pharmacologic CategoryThrombolytic Agent

Use: Labeled IndicationsThrombolytic agent for the lysis of acute massive pulmonary emboli or pulmonary emboli with unstable hemodynamics

Use: Unlabeled/InvestigationalThrombolytic agent used in treatment of recent severe or massive deep vein thrombosis, and occluded I.V. or dialysis cannulas; peripheral arterial occlusive disease

Dosing: Adults

Acute pulmonary embolism: I.V.: Loading: 4400 int. units/kg over 10 minutes; maintenance: 4400 int. units/kg/hour for 12 hours. To prevent recurrent thrombosis, anticoagulation treatment is recommended after the completion of urokinase infusion; if heparin is used, do not administer heparin loading dose. Do not start anticoagulation until aPTT has decreased to less than twice the normal control value.

Acute peripheral arterial occlusion of leg (unlabeled use; Ouriel, 1998): I.V.: 4000 int. units/minute for 4 hours, followed by 2000 int. units/minute for up to a total duration of therapy of 48 hours. **Note:** Systemic heparinization should not be given concurrently.

Deep vein thrombosis (unlabeled use): I.V.: Loading: 4400 units/kg over 10 minutes, then 4400 units/kg/hour for 12 hours

Occluded I.V. catheters (unlabeled use):

5000 units in each lumen over 1-2 minutes, leave in lumen for 1-4 hours, then aspirate. May repeat with 10,000 units in each lumen if 5000 units fails to clear the catheter. **Do not infuse into the patient**. Volume to instill into catheter is equal to the volume of the catheter. Will not dissolve drug precipitate or anything other than blood products.

I.V. infusion: 200 units/kg/hour in each lumen for 12-48 hours at a rate of at least 20 mL/hour

Dialysis patient: 5000 units is administered in each lumen over 1-2 minutes; leave urokinase in lumen for 1-2 days, then aspirate.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricChildren: Deep vein thrombosis: I.V.: Refer to adult dosing.

Administration: I.V.Solution may be filtered with ≤0.45 micron filter during I.V. therapy. Administer using an infusion pump. When prepared to a total volume of 195 mL, the loading dose should be administered at 90 mL/hour over 10 minutes. The maintenance dose should be administered at 15 mL/hour over 12 hours. I.V. tubing should be flushed with NS or D_5W to ensure total dose is administered.

Administration: I.V. DetailpH: 6-7.5

StoragePrior to reconstitution, store in refrigerator at 2°C to 8°C (36°F to 46°F).

ReconstitutionReconstitute vial with 5 mL preservative free sterile water for injection by gently rolling and tilting; do not shake. Contains no preservatives; should not be reconstituted until immediately before using. Discard unused portion. Solution will look pale and straw colored. May filter through ≤0.45 micron filter. Prior to infusion, solution should be further diluted in D_5W or NS; the manufacturer recommends a total infusion volume of 195 mL.

CompatibilityStable in NS, D_5W.

Y-site administration: Variable (consult detailed reference): TPN.

ContraindicationsHypersensitivity to urokinase or any component of the formulation; active internal bleeding; recent (within 2 months) CVA, intracranial surgery or intraspinal surgery; recent trauma (including cardiopulmonary resuscitation); intracranial neoplasm, arteriovenous malformation, or aneurysm; known bleeding diathesis; severe uncontrolled arterial hypertension

Allergy Considerations

- Urokinase Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bleeding: Risk of bleeding is increased with use; fatal hemorrhage has been reported. Monitor all potential bleeding sites. If serious bleeding occurs, urokinase infusion should be stopped.
- Cholesterol embolization: Has been reported rarely with the use of thrombolytics, usually associated with invasive vascular procedures and/or anticoagulant therapy.
- Hypersensitivity: Hypersensitivity reactions, including fatal anaphylaxis (rare), bronchospasm, orolingual edema, and urticaria have been reported. Infusion reactions (eg, chills, rigor, hypoxia, hyper-/hypotension, tachycardia) may also occur. Reactions usually occur

within the first hour of infusion.

Disease-related concerns:

- Conditions that increase bleeding risk: For the following conditions the risk of bleeding is higher with use of thrombolytics and should be weighed against the benefits of therapy: Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, or previous puncture of noncompressible vessels; pregnancy, cerebrovascular disease, recent (within 10 days) gastrointestinal bleeding, high likelihood of left heart thrombus (in the setting of mitral stenosis with atrial fibrillation), subacute bacterial endocarditis, hemostatic defects including those caused by severe renal or hepatic dysfunction, diabetic hemorrhagic retinopathy, and/or any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of location. Use is contraindicated in recent trauma, including CPR.

Concurrent drug therapy issues:

- Anticoagulants: Use with caution in patients receiving oral anticoagulants or platelet inhibitors; increased risk of bleeding.

- Heparin: Concurrent heparin anticoagulation may contribute to bleeding.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Albumin: Formulated in human albumin; products made from human sources have a theoretical risk of transmitting infectious agents.

Other warnings/precautions:

- Administration: Intramuscular injections and nonessential handling of the patient should be avoided. Venipunctures should be performed carefully and only when necessary. If arterial puncture is necessary, use an upper extremity vessel that can be manually compressed.

Pregnancy Risk FactorB

Pregnancy ConsiderationsUrokinase was not found to be teratogenic in animal studies; it is not known if it crosses the human placenta. Placental separation and hemorrhage have been reported in one patient treated at 3 months gestation. Use during pregnancy only if clearly needed.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsAs with all drugs which may affect hemostasis, bleeding is the major adverse effect associated with urokinase. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the dosage administered, concurrent use of multiple agents which alter hemostasis, and patient predisposition.

>10%: Local: Injection site: Bleeding (5% decrease in hematocrit reported in 37% patients; most bleeding occurring at external incisions or injection sites, but also reported in other areas)

<1%, postmarketing, and/or case reports: Allergic reaction (includes anaphylaxis, bronchospasm, orolingual edema, urticaria, skin rash, pruritus), cardiac arrest, cerebral vascular accident, chest pain, cholesterol embolism, diaphoresis, hemiplegia, intracranial hemorrhage, retroperitoneal hemorrhage, MI, pulmonary edema, recurrent pulmonary embolism, reperfusion ventricular arrhythmia, stroke, substernal pain, thrombocytopenia, vascular embolization (cerebral and distal); infusion reactions (most occurring within 1 hour) including acidosis, back pain, chills, cyanosis, dyspnea, fever, hyper-/hypotension, hypoxia, nausea, rigors, tachycardia, vomiting

Drug Interactions

Anticoagulants: Thrombolytic Agents may enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Thrombolytic Agents. *Risk C: Monitor therapy*

Aprotinin: May diminish the therapeutic effect of Thrombolytic Agents. *Risk D: Consider therapy modification*

Drotrecogin Alfa: Thrombolytic Agents may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Thrombolytic Agents. Bleeding may occur. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Thrombolytic Agents. An increased risk of bleeding may occur. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure (avoid using lower extremities for BP), pulse; CBC, platelet count, aPTT, urinalysis

Nursing: Physical Assessment/MonitoringWeigh benefits against risks when bleeding/hemorrhage constitute a significant hazard. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (especially those medications that may affect coagulation or platelet function). See Administration for infusion specifics. Assess results of laboratory results. Patient should be closely monitored for bleeding during and following treatment (infusion site, neurological status [eg, intracranial hemorrhage], vital signs, ECG [reperfusion arrhythmias]). Bedrest and bleeding precautions should be maintained; avoid I.M. injections, venipuncture (unless absolutely necessary), and nonessential handling of the patient. If arterial puncture is necessary, use an upper extremity vessel that can be manually compressed. Patient instructions determined by patient condition.

Monitoring: Lab TestsCBC, platelet count, aPTT, urinalysis

Patient EducationInform prescriber of all medications or herbal products you are taking. This medication is only administered by infusion; you will be monitored closely during and after treatment. Immediately report burning, pain, redness, swelling, or oozing at infusion site;

sudden acute headache; joint pain; chest pain; or altered vision. Following infusion, you will have a tendency to bleed easily; use caution to prevent injury (use electric razor, soft toothbrush, and caution with knives, needles, or anything sharp). Follow instructions for strict bedrest to reduce the risk of injury. If bleeding occurs, report immediately and apply pressure to bleeding spot until bleeding stops completely. Report unusual bruising or bleeding; blood in urine, stool, or vomitus; bleeding gums; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Product Availability

Kinlytic™: ImaRx Therapeutics retired the trade name Abbokinase® for urokinase and is currently marketing urokinase under the trade name Kinlytic™

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution:

Kinlytic™: 250,000 int. units [contains albumin (human)]

Generic AvailableNo

ManufacturerIMARX Therapeutics

Mechanism of ActionPromotes thrombolysis by directly activating plasminogen to plasmin, which degrades fibrin, fibrinogen, and other procoagulant plasma proteins

Pharmacodynamics/Kinetics

Onset of action: I.V.: Fibrinolysis occurs rapidly

Duration: ≥4 hours

Distribution: 11.5 L

Half-life elimination: 6.4-18.8 minutes

Excretion: Urine and feces (small amounts)

Dental Health: Effects on Dental TreatmentNo effects or complications reported

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Cardiovascular Considerations

Acute Pulmonary Embolism (PE): The American College of Chest Physicians (Kearon, 2008) recommends the following:

All patients with PE: All patients with diagnosed PE should undergo rapid risk stratification based on risk of death from PE and bleeding. In general, the majority of patients with PE will not require treatment with thrombolytics; however, treatment with anticoagulation (eg, enoxaparin, heparin) will be necessary unless contraindicated.

Patients with PE without hemodynamic compromise: In general, patients without hemodynamic compromise should not receive thrombolytic therapy. However, patients without hemodynamic compromise but with poor prognostic indicators (elevated troponin, right ventricular dysfunction on echocardiogram, etc) are at high risk of an adverse outcome and may derive benefit from receiving systemic thrombolysis. Therefore, the most recent recommendation is to administer thrombolysis in these selected high-risk patients who have a low risk of bleeding. The use of regimens with short infusion times (eg, 2-hour infusion) is recommended over longer infusion times (eg, 12-hour infusions). The most widely used thrombolytic for this indication is alteplase which is administered as an infusion of 100 mg over 2 hours. Urokinase may also be used; however, the administration time for urokinase is 12 hours.

Patients with PE with hemodynamic compromise: Since thrombolytic therapy has been shown to accelerate thrombolysis resulting in more rapid resolution of perfusion scan abnormalities, decrement angiographic thrombus, reduction in elevated pulmonary artery pressures, and normalization of right ventricular dysfunction in patients with PE and hemodynamic compromise (usually defined as SBP <90 mm Hg requiring vasopressor therapy), the use of thrombolytic therapy via a peripheral vein is recommended unless major contraindications exist. The use of regimens with short infusion times (eg, 2-hour infusion) is recommended over longer infusion times (eg, 12-hour infusions). The most widely used thrombolytic for this indication is alteplase which is administered as an infusion of 100 mg over 2 hours. Urokinase may also be used; however, the administration time for urokinase is 12 hours.

Patients with PE experiencing cardiac arrest: According to the 2005 ACLS guidelines, when PE is responsible for cardiac arrest and the patient is unresponsive to cardiopulmonary resuscitation (CPR), it is reasonable to administer bolus thrombolytic therapy, specifically alteplase (Böttiger, 2001). However, routine use in cardiac arrest or undifferentiated pulseless electrical activity (PEA) is not recommended. Of note, ongoing CPR is not a contraindication in this setting.

Anesthesia and Critical Care Concerns/Other Considerations

Acute Pulmonary Embolism (PE): The American College of Chest Physicians (Kearon, 2008) recommends the following:

All patients with PE: All patients with diagnosed PE should undergo rapid risk stratification based on risk of death from PE and bleeding. In general, the majority of patients with PE will not require treatment with thrombolytics; however, treatment with anticoagulation (eg, enoxaparin, heparin) will be necessary unless contraindicated.

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Index TermsAbbokinase; UK

References

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Ouriel K, Gray B, Clair DG, et al, “Complications Associated With the Use of Urokinase and Recombinant Tissue Plasminogen Activator for Catheter-Directed Peripheral Arterial and Venous Thrombolysis,” *J Vasc Interv Radiol*, 2000, 11(3):295-8.[PubMed 10735422]

Ouriel K, Veith FJ, and Sasahara AA, “A Comparison of Recombinant Urokinase With Vascular Surgery as Initial Treatment for Acute Arterial Occlusion of the Legs,” *N Engl J Med*, 1998, 338(16):1105-11.[PubMed 9545358]

International Brand NamesAbbokinase (AT, LU, SE); Actosolv (AT, BE, DE, FR, IT, LU); Alphakinase (DE, LU); Corase (DE); Dukinase (IN); Medacinase (NL); Persolv (IT); Rheotromb (DE, HU, PL); Syner-Kinase (GB); Tecno-Uroquinasa (AR); Ukidan (AE, AR, AT, AU, BD, BH, CH, CL, CY, EG, GR, HK, HR, HU, ID, IL, IN, IQ, IR, IT, JO, JP, KP, KW, LB, LY, MY, OM, PE, PH, PK, PL, PT, QA, SA, SG, SY, TH, TW, YE); Urokinase Choay (LU); Urokinase HS medac (CH, DE); Urokinase Human (PL); Urokinaza (PL); Urokine (KP); Uroquidan (ES)

Ursodiol

Lexi-Drugs Online

English

English

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Pronunciation(ur soe DYE ol)

U.S. Brand NamesActigall®; Urso 250™; Urso Forte™

Canadian Brand NamesDOM-Ursodiol C; PHL-Ursodiol C; PMS-Ursodiol C; Urso®; Urso® DS

Pharmacologic CategoryGallstone Dissolution Agent

Use: Labeled IndicationsActigall®: Gallbladder stone dissolution; prevention of gallstones in obese patients experiencing rapid weight loss; Urso®: Primary biliary cirrhosis

Use: Unlabeled/InvestigationalLiver transplantation

Dosing: Adults

Gallstone dissolution: Oral: 8-10 mg/kg/day in 2-3 divided doses; use beyond 24 months is not established; obtain ultrasound images at 6-month intervals for the first year of therapy; 30% of patients have stone recurrence after dissolution

Gallstone prevention: Oral: 300 mg twice daily

Primary biliary cirrhosis: Oral: 13-15 mg/kg/day in 2-4 divided doses (with food)

Dosing: ElderlyRefer to adult dosing.

Administration: OralDo not administer with aluminum-based antacids. If aluminum-based antacids are needed, administer 2 hours after ursodiol. Urso® should be taken with food.

Dietary ConsiderationsUrso® should be taken with food.

StorageDo not store above 30°C (86°F).

Extemporaneously PreparedA 60 mg/mL ursodiol suspension may be made by opening twelve 300 mg capsules and wetting with sufficient glycerin and triturating to make a fine paste; gradually add 45 mL of simple syrup in three steps:

1. Add 15 mL to paste, triturate well, and transfer to 2 oz amber bottle
2. Rinse mortar with 10 mL simple syrup and add to amber bottle
3. Repeat step 2 with sufficient syrup to make 60 mL final volume; label “Shake Well and Store in Refrigerator”; 35-day stability

ContraindicationsHypersensitivity to ursodiol, bile acids, or any component of the formulation; not to be used with cholesterol, radiopaque, bile pigment stones, or stones >20 mm in diameter; allergy to bile acids

Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with chronic liver disease.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Duration of therapy: Gallbladder stone dissolution may take several months of therapy; complete dissolution may not occur and recurrence of stones within 5 years has been observed in 50% of patients.
- Nonvisualizing gallbladder: Use with caution in patients with a nonvisualizing gallbladder.

Geriatric ConsiderationsNo specific clinical studies in the elderly. Would recommend starting at lowest recommended dose with scheduled monitoring.

Pregnancy Risk FactorB

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Headache (up to 25%), dizziness (up to 17%)

Gastrointestinal: In treatment of primary biliary cirrhosis: Constipation (up to 26%)

1% to 10%:

Dermatologic: Rash (<1% to 3%), alopecia (<1% to 5%)

Gastrointestinal:

In gallstone dissolution: Most GI events (diarrhea, nausea, vomiting) are similar to placebo and attributable to gallstone disease.

In treatment of primary biliary cirrhosis: Diarrhea (1%)

Hematologic: Leukopenia (3%)

Miscellaneous: Allergy (5%)

<1%: Abdominal pain, biliary pain, fatigue, metallic taste, nausea, pruritus, vomiting

In treatment of primary biliary cirrhosis: Constipation, dyspepsia, headache

Drug InteractionsThere are no known significant interactions.
Monitoring ParametersALT, AST, sonogram
Nursing: Physical Assessment/MonitoringAssess results of laboratory tests, therapeutic effectiveness, and adverse reactions. Teach patient proper use and possible side effects signs to report.
Monitoring: Lab Tests

Gallstone disease: ALT, AST, ALP; sonogram may be required

Hepatic disease: Monitor hepatic function tests frequently

Patient EducationTake medication as directed with food. Drug will need to be taken for 1-3 months after stone is dissolved and stones may recur. Report any persistent nausea, vomiting, abdominal pain, or yellowing of skin or eyes. **Breast-feeding precaution:** Consult prescriber if breast-feeding.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule (Actigall®): 300 mg

Tablet:

Urso 250™: 250 mg

Urso Forte™: 500 mg

Generic AvailableYes: Capsule
Pricing: U.S. (www.drugstore.com)

Capsules (Actigall)

300 mg (30): $127.76

Capsules (Ursodiol)

300 mg (30): $71.99

Tablets (Urso 250)

250 mg (30): $85.85

Tablets (Urso Forte)

500 mg (30): $152.58

Mechanism of ActionDecreases the cholesterol content of bile and bile stones by reducing the secretion of cholesterol from the liver and the fractional reabsorption of cholesterol by the intestines. Mechanism of action in primary biliary cirrhosis is not clearly defined.
Pharmacodynamics/Kinetics

Metabolism: Undergoes extensive enterohepatic recycling; following hepatic conjugation and biliary secretion, the drug is hydrolyzed to active ursodiol, where it is recycled or transformed to lithocholic acid by colonic microbial flora

Half-life elimination: 100 hours

Excretion: Feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsUrsodeoxycholic Acid
References

Colombo C, Setchell KD, Podda M, et al, "Effect of Ursodeoxycholic Acid Therapy for Liver Disease Associated With Cystic Fibrosis," *J Pediatr*, 1990, 117(3):482-9. [PubMed 2391610]

Johnson CE and Nesbitt J, "Stability of Ursodiol in an Extemporaneously Compounded Oral Liquid," *Am J Health Syst Pharm*, 1995, 52(16):1798-800. [PubMed 8528836]

Lepage G, Paradis K, Lacaille F, et al, "Ursodeoxycholic Acid Improves the Hepatic Metabolism of Essential Fatty Acids and Retinol in Children With Cystic Fibrosis," *J Pediatr*, 1997, 130(1)52-8.

Spagnuolo MI, Iorio R, Vegnente A, et al, “Ursodeoxycholic Acid for Treatment of Cholestasis in Children on Long-Term Total Parenteral Nutrition - A Pilot Study,” *Gastroenterology*, 1996, 111(3):716-9. [PubMed 8780577]

Ullrich D, Rating D, Schroter W, et al, “Treatment With Ursodeoxycholic Acid Renders Children With Biliary Atresia Suitable for Liver Transplantation,” *Lancet*, 1987, 2(8571):1324.

International Brand NamesActigall (NZ); Adursal (FI); Biliepar (PL); Canlin (TW); Cholacid (DE); Destolit (GB); Deursil (IT); Dexo (PY); Estazor (ID); Litanin (ES); Pramur (ID); Taurolite (CL); Udihep (TH); Urdafalk (ID); Urdox (GB); Urosan (JP); Ursa (KP); Ursacol (BR, CO, IT); Urso (IN); Urso Vinas (ES); Ursobilane (ES); Ursocam (PL); Ursochol (BE, CH, ES, ID, LU, NL); Ursodamor (IT); Ursodeoxycholic Acid (GB); Ursofalk (AR, AT, AU, CL, CN, CR, DE, EC, EE, GB, GT, HK, HN, HU, IE, IL, LU, MX, MY, NI, NZ, PA, PE, PH, PK, PL, PT, SE, SV, TH, UY); Ursogal (GB); Ursolic (TW); Ursolin (TH); Ursolit (IL); Ursolite (ES); Ursolvan (FR); Ursopol (PL); Ursosan (CZ, JP); Usosan (PH)

Ustekinumab

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Stelara® may be confused with Aldara®

Ustekinumab may be confused with infliximab, rituximab

Pronunciation(yoo stek in YOO mab)

Canadian Brand NamesStelara®

Pharmacologic CategoryAntipsoriatic Agent; Interleukin-12 Inhibitor; Interleukin-23 Inhibitor; Monoclonal Antibody

Use: Labeled IndicationsTreatment of moderate-to-severe chronic plaque psoriasis

Dosing: Adults **Plaque psoriasis:** SubQ:

Initial and maintenance: **Note:** Following an interruption in therapy, retreatment may be initiated at the initial dosing interval. Consider therapy discontinuation in any patient failing to demonstrate a response after 12 weeks of therapy.

≤100 kg: 45 mg at 0- and 4 weeks, and then every 12 weeks thereafter (if inadequate response, may change to every 8 weeks)

>100 kg: 45 mg or 90 mg at 0- and 4 weeks, and then every 12 weeks thereafter (if inadequate response, may change to every 8 weeks)

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentUse has not been studied in renal dysfunction.

Dosing: Hepatic ImpairmentUse has not been studied in hepatic dysfunction.

Administration: OtherDo not use if cloudy or discolored. Administer by subcutaneous injection into the top of the thigh, abdomen, upper arms, or buttocks. Avoid areas of skin where psoriasis is present.

StorageStore vials refrigerated at 2°C to 8°C (36°F to 46°F); do not freeze. Do not shake . Protect from light; store in original container.

RestrictionsNot available in the U.S

ContraindicationsHypersensitivity to ustekinumab or any component of the formulation; severe infections such as sepsis, tuberculosis and opportunistic infections

Warnings/Precautions

Concerns related to adverse effects:

- Antibody formation: Antibody formation to ustekinumab has been observed with therapy and has been associated with decreased serum levels and therapeutic response in some patients.

- Hypersensitivity reactions: Discontinue immediately with signs/symptoms of hypersensitivity reaction and treat appropriately as indicated.

- Infections: Infrequent, but serious bacterial, fungal, and viral infections have been observed with use. Avoid use in patients with clinically important active infection. Exercise caution when considering use in patients with a history of new/recurrent infections, with conditions that predispose them to infections (eg, diabetes or residence/travel from areas of endemic mycoses), or with chronic, latent, or localized infections. Patients who develop a new infection while undergoing treatment should be monitored closely. If a patient develops a serious infection, therapy should be discontinued or withheld until successful resolution of infection.

- Malignancy: May increase the risk for malignancy although the impact on the development and course of malignancies is not fully defined. In clinical trials, the incidence of malignancy associated with ustekinumab therapy was comparable to that of the general population. Use with caution in patients with prior malignancy (use not studied in this population).

- Tuberculosis: Avoid use in patients with active tuberculosis (TB). Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test prior to starting therapy. Treatment of latent TB should be initiated before ustekinumab therapy is used. During and following treatment, monitor for signs/symptoms of active TB.

Disease-related concerns:

- Hepatic impairment: Use caution in patients with hepatic impairment. Use has not been studied in this patient population.

- Renal impairment: Use caution in patients with renal impairment. Use has not been studied in this patient population.

Concurrent drug therapy issues:

- Immunosuppressive therapy: Use in combination with other immunosuppressive drugs has not been studied; use caution.

Special populations:

- Patients >100 kg: May require higher dose to achieve adequate serum levels.

- Pediatrics: Use has not been studied in children <18 years of age.

Other warnings/precautions:

- Immunizations: Patients should be brought up to date with all immunizations before initiating therapy. **Live vaccines should not be given concurrently**; inactivated or nonlive vaccines may be given concurrently.

- Phototherapy: Use in combination with phototherapy has not been studied; use caution.

Pregnancy ConsiderationsReproduction studies have not been conducted in pregnant women. Use during pregnancy only if clearly needed.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsIt is not known whether ustekinumab is secreted in human milk. Because many immunoglobulins are secreted in milk and the potential for serious adverse reactions exists, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Adverse Reactions

1% to 10%:

Central nervous system: Headache (5%), fatigue (3%), dizziness (1% to 2%), depression (≤1%)

Dermatologic: Pruritus (1% to 2%), rash (<2%), urticaria (<2%)

Local: Injection site erythema (1% to 2%)

Neuromuscular & skeletal: Arthralgia (2% to 3%), back pain (1% to 2%), myalgia (1%)

Respiratory: Nasopharyngitis (7% to 8%), upper respiratory infection (4% to 5%), pharyngolaryngeal pain (1% to 2%)

Miscellaneous: Antibody formation (5%)

<1%, postmarketing, and/or case reports: Angina, bacterial infection, cellulitis, dactylitis, diverticulitis, fungal infection, gastroenteritis, herpes zoster, hypertension; injection site reactions (bruising, hemorrhage, induration, irritation, pain, pruritus, swelling); malignancy (breast, colon, head and neck, prostate, thyroid); MI, nephrolithiasis, osteomyelitis, pneumonia, stroke, urinary tract infection, viral infection

Drug Interactions

Abciximab: May enhance the potential for allergic or hypersensitivity reactions to Monoclonal Antibodies. Also may cause thrombocytopenia or diminished therapeutic effects. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersPlace and read PPD prior to initiating therapy; monitor for signs/symptoms of infection; CBC; Ustekinumab-antibody formation
Monitoring: Lab TestsPlace and read PPD prior to initiating therapy; CBC; Ustekinumab-antibody formation
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian product availability

Injection, solution [preservative free]:

Stelara® [CAN]: 45 mg/0.5 mL (0.5 mL); 90 mg/1 mL (1 mL) [not available in the U.S.]

Generic AvailableNo
ManufacturerJanssen-Ortho, Inc
Mechanism of ActionUstekinumab is a human monoclonal antibody that binds to and interferes with the proinflammatory cytokines, interleukin (IL)-12 and IL-23. Biological effects of IL-12 and IL-23 include natural killer (NK) cell activation, CD4+ T-cell differentiation and activation. Ustekinumab also interferes with the expression of monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor-alpha (TNF-α), interferon-inducible protein-10 (IP-10), and interleukin-8 (IL-8). Significant clinical improvement in psoriasis patients is seen in association with reduction of these proinflammatory signalers.
Pharmacodynamics/Kinetics

Distribution: V_d (terminal elimination phase): 0.076-0.161 L/kg

Bioavailability: Absolute bioavailability: SubQ: ~57%

Half-life elimination: 15-32 days

Time to peak, plasma: 8.5 days

Index TermsCNTO 1275
References

Leonardi CL, Kimball AB, Papp KA, et al, “Efficacy and Safety of Ustekinumab, a Human Interleukin-12/23 Monoclonal Antibody, in Patients With Psoriasis: 76-Week Results from a Randomised, Double-Blind, Placebo-Controlled Trial (PHOENIX 1),” *Lancet*, 2008, 371(9625): 1665-74.[PubMed 18486739]

Papp KA, Langley RG, Lebwohl M, et al, “Efficacy and Safety of Ustekinumab, a Human Interleukin-12/23 Monoclonal Antibody, in Patients With Psoriasis: 52-Week Results from a Randomised, Double-Blind, Placebo-Controlled Trial (PHOENIX 2),” *Lancet*, 2008, 371(9625): 1675-84.[PubMed 18486740]

Reddy M, Davis C, Wong J, et al, “Modulation of CLA, IL-12R, CD40L, and Il-2Rα Expression and Inhibition of IL-12- and IL-23-Induced Cytokine Secretion by CNTO 1275,” *Cell Immunol*, 2007, 247(1): 1-11.[PubMed 17761156]

V-TAD

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Leukemia, Acute Myeloid]

Regimen UseLeukemia, acute myeloid

RegimenInduction:

Etoposide: I.V.: 50 mg/m^2/day days 1, 2, and 3

[total dose/cycle = 150 mg/m^2]

Thioguanine: Oral: 75 mg/m^2/day every 12 hours days 1 to 5

[total dose/cycle = 750 mg/m^2]

Daunorubicin: I.V.: 20 mg/m^2/day days 1 and 2

[total dose/cycle = 40 mg/m^2]

Cytarabine: I.V.: 75 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 375 mg/m^2]

Up to 3 cycles may be given based on individual response; time between cycles not specified

References

Bigelow CL, Kopecky K, Files JC, et al, âTreatment of Acute Myelogenous Leukemia in Patients Over 50 Years of Age With V-TAD: A Southwest Oncology Group Study,â *Am J Hematol*, 1995, 48(4):228-32.[PubMed 7717369]

VAC (Retinoblastoma)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Retinoblastoma

Regimen Use Retinoblastoma

Regimen

Vincristine: I.V.: 1.5 mg/m^2 day 1

[total dose/cycle = 1.5 mg/m^2]

Dactinomycin: I.V.: 0.015 mg/kg/day days 1 to 5

[total dose/cycle = 0.075 mg/kg]

Cyclophosphamide: I.V.: 200 mg/m^2/day days 1 to 5

[total dose/cycle = 1000 mg/m^2]

References

Doz F, Khelfaoui F, Mosseri V, et al, âThe Role of Chemotherapy in Orbital Involvement of Retinoblastoma. The Experience of a Single Institution With 33 Patients,â *Cancer*, 1994, 74(2):722-32.[PubMed 8033054]

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Rhabdomyosarcoma

Regimen UseRhabdomyosarcoma

Regimen

Induction (weeks 1 to 17):

Vincristine: I.V. push: 1.5 mg/m^2 (maximum 2 mg) day 1 of weeks 1 to 13, then one dose at week 17

Dactinomycin: I.V. push: 0.015 mg/kg/day (maximum 0.5 mg) days 1 to 5 of weeks 1, 4, 7, and 17

Cyclophosphamide: I.V.: 2.2 g/m^2 day 1 of weeks 1, 4, 7, 10, 13, and 17

Continuation (weeks 21 to 44):

Vincristine: I.V. push: 1.5 mg/m^2 (maximum 2 mg) day 1 of weeks 21 to 26, 30 to 35, and 39 to 44

Dactinomycin: I.V. push: 0.015 mg/kg/day (maximum 0.5 mg) days 1 to 5 of weeks 21, 24, 30, 33, 39, and 42

Cyclophosphamide: I.V.: 2.2 g/m^2 day 1 of weeks 21, 24, 30, 33, 39, and 42

References

Baker KS, Anderson JR, Link MP, et al, âBenefit of Intensified Therapy for Patients With Local or Regional Embryonal Rhabdomyosarcoma: Results From the Intergroup Rhabdomyosarcoma Study IV,â *J Clin Oncol*, 2000, 18(12):2427-34.[PubMed 10856103]

VAC Alternating With IE (Ewing's Sarcoma)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Sarcoma

Regimen UseEwing's sarcoma

Regimen

Cycle A: (Odd numbered cycles)

Cyclophosphamide: I.V.: 1200 mg/m^2 day 1 (followed by mesna; dose not specified)

[total dose/cycle = 1200 mg/m^2]

Vincristine: I.V.: 2 mg/m^2 (maximum: 2 mg) day 1

[total dose/cycle = 2 mg/m^2; maximum 2 mg]

Doxorubicin: I.V.: 75 mg/m^2 day 1, for 5 cycles (maximum cumulative dose: 375 mg/m^2)

[total dose/cycle = 75 mg/m^2; maximum cumulative dose: 375 mg/m^2]

Dactinomycin: I.V.: 1.25 mg/m^2 day 1, begin cycle 11 (after reaching maximum cumulative doxorubicin dose)

[total dose/cycle = 1.25 mg/m^2]

Cycle B: (Even numbered cycles)

Ifosfamide: I.V.: 1800 mg/m^2/day days 1 to 5 (given with mesna)

[total dose/cycle = 9000 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Alternate Cycles A and B, administering a cycle every 3 weeks (alternating in the following sequence: ABABAB) for 17 cycles

References

Grier HE, Krailo MD, Tarbell NJ, et al, "Addition of Ifosfamide and Etoposide to Standard Chemotherapy for Ewing's Sarcoma and Primitive Neuroectodermal Tumor of Bone," *N Engl J Med*, 2003, 348(8):694-701.[PubMed 12594313]

VAC Pulse

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Rhabdomyosarcoma

Regimen UseRhabdomyosarcoma

Regimen

Vincristine: I.V.: 2 mg/m^2/dose (maximum 2 mg/dose) every 7 days, for 12 weeks

Dactinomycin: I.V.: 0.015 mg/kg/day (maximum 0.5 mg/day) days 1 to 5, every 3 months for 5 courses

Cyclophosphamide: Oral, I.V.: 10 mg/kg/day for 7 days, repeat every 6 weeks

References

Wilbur JR, Sutow WW, Sullivan MP, et al, âChemotherapy of Sarcomas,â *Cancer*, 1975, 36(2):765-9.[PubMed 1157036]

Vaccinia Immune Globulin (Intravenous)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(vax IN ee a i MYUN GLOB yoo lin IN tra VEE nus)

U.S. Brand NamesCNJ-016™

Pharmacologic CategoryImmune Globulin

Use: Labeled IndicationsTreatment of infectious complications of smallpox (vaccinia virus) vaccination, such as eczema vaccinatum, progressive vaccinia, and severe generalized vaccinia; treatment of vaccinia infections in individuals with concurrent skin conditions or accidental virus exposure to eyes (except vaccinia keratitis), mouth, or other areas where viral infection would pose significant risk

Dosing: Adults **Vaccinial infection:** I.V.:

CNJ-016™ (Cangene product): 6000 units/kg; 9000 units/kg may be considered if patient does not respond to initial dose.

DynPort product: Total dose: 2 mL/kg (100 mg/kg); higher doses (200-500 mg/kg) may be considered if patient does not respond to initial recommended dose (sucrose-related renal impairment is worsened at doses ≥400 mg/kg)

Dosing: ElderlySafety and efficacy have not been established.

Dosing: Renal ImpairmentUse caution. Doses ≥400 mg/kg of the DynPort product are not recommended.

Administration: I.V.Do not shake; avoid foaming. For intravenous use only. Predilution is not recommended. If dedicated line not available, flush with NS prior to administration of VIGIV. Do not exceed recommended rates of infusion.

CNJ-016™ (Cangene product): Patients ≥50 kg: Infuse at ≤2 mL/minute; Patients <50 kg: Infuse at 0.04 mL/kg/minute. Maximum assessed rate of infusion: 4 mL/minute. Decrease rate of infusion if minor adverse reactions develop in patients with risk factors for thrombosis/thromboembolism and/or renal insufficiency.

DynPort product: Infuse at 1 mL/kg/hour for 30 minutes, then 2 mL/kg/hour for 30 minutes, then 3 mL/kg/hour until complete. Administer through 0.22 micron filtered set; use of infusion pump is recommended.

Dietary ConsiderationsDynPort solution for injection contains sodium 0.02-0.03 mEq/mL.

StorageStore between 2°C and 8°C (35.6°F to 46.4°F).

CNJ-016™ (Cangene product): If frozen, use within 60 days of thawing at 2°C and 8°C. Infusion should begin within 4 hours after entering vial.

DynPort product: Use within 6 hours of piercing vial stopper; complete infusion within 12 hours of spiking vial.

Compatibility

Y-site administration:

CNJ-016™ (Cangene product): **Compatible** (in a dilution not to exceed 1:2, v/v) with NS.

DynPort product: **Compatible** (in a dilution not to exceed 1:2, v/v) with NS or 2.5% to 20% dextrose solutions with or without sodium chloride.

ContraindicationsHypersensitivity to immune globulin or any component of the formulation; isolated vaccinia keratitis; selective IgA deficiency

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1:1000) should be available. Contains trace amounts of IgA; use caution in IgA-deficient patients.
- Aseptic meningitis: Aseptic meningitis syndrome (AMS) has been reported with intravenous immune globulin administration (rare); may occur with high doses (≥2 g/kg).
- Hemolysis: Intravenous immune globulin has been associated with antiglobulin hemolysis; monitor for signs of hemolytic anemia.
- Pulmonary edema: Monitor for transfusion-related acute lung injury (TRALI); noncardiogenic pulmonary edema has been reported with intravenous immune globulin use.
- Renal impairment: Acute renal dysfunction (increased serum creatinine, oliguria, acute renal failure) can rarely occur; usually within 7 days of use (more likely with products stabilized with sucrose). Use with caution in the elderly, patients with renal disease, diabetes mellitus, volume depletion, sepsis, paraproteinemia, and nephrotoxic medications due to risk of renal dysfunction. In patients at risk of renal dysfunction, the rate of infusion and concentration of solution should be minimized. discontinue if renal function deteriorates.
- Thrombotic events: Thrombotic events have been reported with administration of intravenous immune globulin; use with caution in patients with cardiovascular risk factors.

Disease-related concerns:

- Hypovolemia: Patients should not be volume depleted prior to therapy.

- Postvaccinial encephalitis: Not effective for use in postvaccinial encephalitis.

Special populations:

- Elderly: Use with caution in the elderly; safety and efficacy have not been established.
- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Human plasma: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk. Infections thought to be transmitted by this product should be reported to the manufacturer.
- Maltose: Some products may contain maltose, which may result in falsely-elevated blood glucose readings.

Other warnings/precautions:

- Administration: For intravenous administration only.

Pregnancy Risk FactorC

Pregnancy ConsiderationsImmune globulins cross the placenta in increased amounts after 30 weeks gestation. There are no adequate and well-controlled studies in pregnant women; use only if benefits outweigh the risks.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**Note:** Actual frequency varies by dose, rate of infusion, and specific product used

Cardiovascular: Flushing

Central nervous system: Cold or hot feeling, dizziness, fatigue, headache, pain, pallor, pyrexia

Dermatologic: Erythema, urticaria

Gastrointestinal: Abdominal pain, appetite decreased, nausea, vomiting

Local: Injection site reaction

Neuromuscular & skeletal: Arthralgia, back pain, paraesthesia, muscle cramp, rigors, tremor, weakness

Miscellaneous: Diaphoresis

Postmarketing and/or case reports (as reported with other IVIG products): Apnea, acute respiratory distress syndrome, bronchospasm, bullous dermatitis, cardiac arrest, coma, Coombs' test positive, cyanosis, dyspnea, epidermolysis, erythema multiforme, hemolysis, hepatic dysfunction, hypoxemia, hypotension, leukopenia, loss of consciousness, lung injury (transfusion associated), pancytopenia, pulmonary edema, seizure, Stevens-Johnson syndrome, syncope, thromboembolism, vascular collapse

Drug Interactions

Vaccines (Live): Immune Globulins may diminish the therapeutic effect of Vaccines (Live). **Exceptions:** Influenza Virus Vaccine; Yellow Fever Vaccine. *Risk D: Consider therapy modification*

Test InteractionsCNJ-016™ contains maltose. Falsely-elevated blood glucose levels may occur when glucose monitoring devices and test strips utilizing the glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) based methods are used. Glucose monitoring devices and test strips which utilize the glucose-specific method are recommended.

Monitoring ParametersDuring infusion, monitor patient for signs of infusion-related reactions, including (but not limited to) flushing, fever, chills, respiratory distress, blood pressure or heart rate changes.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free; solvent-detergent treated]:

CNJ-016™ (Cangene product): ≥50,000 units/15 mL (15 mL) [contains maltose 10% and polysorbate 80 0.03%]

DynPort product: 50 mg/mL (50 mL) [contains sucrose 50 mg/mL, human albumin 10 mg/mL, sodium 0.02-0.03 mEq/mL]

Generic AvailableNo

Mechanism of ActionAntibodies obtained from pooled human plasma of individuals immunized with the smallpox vaccine provide passive immunity

Pharmacodynamics/Kinetics

Distribution: V_d: CNJ-016™ (Cangene product): 6630 L

Half-life elimination:

CNJ-016™ (Cangene product): 30 days (range 13-67 days)

DynPort product: 22 days

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsVIGIV

VAD/CVAD

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Leukemia, Acute Lymphocytic
Regimen UseLeukemia, acute lymphocytic
RegimenInduction cycle:

Vincristine: I.V.: 0.4 mg/day continuous infusion days 1 to 4 and 24 to 27

[total dose/cycle = 3.2 mg]

Doxorubicin: I.V.: 12 mg/m^2/day continuous infusion days 1 to 4 and 24 to 27

[total dose/cycle = 96 mg/m^2]

Dexamethasone: Oral: 40 mg/day days 1 to 4, 9 to 12, 17 to 20, 24 to 27, 32 to 35, and 40 to 43

[total dose/cycle = 960 mg]

Cyclophosphamide: I.V.: 1 g/m^2 day 24

[total dose/cycle = 1 g/m^2]

Administer one cycle only

References

Kantarjian H, Walters RS, Keating MJ, et al, âResults of the Vincristine, Doxorubicin, and Dexamethasone Regimen in Adults With Standard and High-Risk Acute Lymphocytic Leukemia,â *J Clin Oncol*, 1990, 8(6):994-1004.[PubMed 2189958]

VAD

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Multiple Myeloma

Regimen UseMultiple myeloma

Regimen

Vincristine: I.V.: 0.4 mg/day continuous infusion days 1 to 4

[total dose/cycle = 1.6 mg]

Doxorubicin: I.V.: 9 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 36 mg/m^2]

Dexamethasone: Oral: 40 mg/day days 1 to 4, 9 to 12, and 17 to 20

[total dose/cycle = 480 mg]

Repeat cycle every 28-35 days

References

Barlogie B, Smith L, and Alexanian R, âEffective Treatment of Advanced Multiple Myeloma Refractory to Alkylating Agents,â *N Engl J Med*, 1984, 310(21):1353-6.[PubMed 6546971]

Valacyclovir

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Valtrex® may be confused with Valcyte™

Valacyclovir may be confused with valganciclovir, vancomycin

Pronunciation(val ay SYE kloe veer)

U.S. Brand NamesValtrex®

Canadian Brand NamesAPO-Valacyclovir; PMS-Valacyclovir; RIVA-Valacyclovir; Valtrex®

Pharmacologic CategoryAntiviral Agent, Oral

Use: Labeled IndicationsTreatment of herpes zoster (shingles) in immunocompetent patients; treatment of first-episode and recurrent genital herpes; suppression of recurrent genital herpes and reduction of heterosexual transmission of genital herpes in immunocompetent patients; suppression of genital herpes in HIV-infected individuals; treatment of herpes labialis (cold sores); chickenpox in immunocompetent children

Use: Unlabeled/InvestigationalProphylaxis of cancer-related HSV, VZV, and CMV infections; treatment of cancer-related HSV, VZV infection

Use: DentalTreatment of herpes labialis (cold sores)

Dosing: Adults

CMV prophylaxis in allogeneic HSCT recipients (unlabeled use): 2 g 4 times/day

Herpes labialis (cold sores): Oral: 2 g twice daily for 1 day (separate doses by ~12 hours)

Herpes zoster (shingles): Oral: 1 g 3 times/day for 7 days

HSV, VZV in cancer patients (unlabeled use):

Prophylaxis: 500 mg 2-3 times/day

Treatment: 1 g 3 times/day

Genital herpes: Oral:

Initial episode: 1 g twice daily for 10 days

Recurrent episode: 500 mg twice daily for 3 days

Reduction of transmission: 500 mg once daily (source partner)

Suppressive therapy:

Immunocompetent patients: 1000 mg once daily (500 mg once daily in patients with <9 recurrences per year)

HIV-infected patients (CD4 ≥100 cells/mm^3): 500 mg twice daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Chickenpox: Children 2 to <18 years: 20 mg/kg/dose 3 times/day for 5 days (maximum: 1 g 3 times/day)

Herpes labialis (cold sores): Children ≥12 years: Refer to adult dosing.

Dosing: Renal Impairment

Herpes zoster: Adults:

Cl_{cr} 30-49 mL/minute: 1 g every 12 hours

Cl_{cr} 10-29 mL/minute: 1 g every 24 hours

Cl_{cr} <10 mL/minute: 500 mg every 24 hours

Genital herpes: Adults:

Initial episode:

Cl_{cr} 10-29 mL/minute: 1 g every 24 hours

Cl_{cr} <10 mL/minute: 500 mg every 24 hours

Recurrent episode: Cl_{cr} <29 mL/minute: 500 mg every 24 hours

Suppressive therapy: Cl_{cr} <29 mL/minute:

For usual dose of 1 g every 24 hours, decrease dose to 500 mg every 24 hours

For usual dose of 500 mg every 24 hours, decrease dose to 500 mg every 48 hours

HIV-infected patients: 500 mg every 24 hours

Herpes labialis: Adolescents and Adults:

Cl_{cr} 30-49 mL/minute: 1 g every 12 hours for 2 doses

Cl_{cr} 10-29 mL/minute: 500 mg every 12 hours for 2 doses

Cl_{cr} <10 mL/minute: 500 mg as a single dose

Hemodialysis: Dialyzable (~33% removed during 4-hour session); administer dose postdialysis

Chronic ambulatory peritoneal dialysis/continuous arteriovenous hemofiltration dialysis: Pharmacokinetic parameters are similar to those in patients with ESRD; supplemental dose not needed following dialysis

Dosing: Hepatic ImpairmentNo adjustment required.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralIf GI upset occurs, administer with meals.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at 15°C to 25°C (59°F to 77°F).

Extemporaneously Prepared

To prepare a valacyclovir 25 mg/mL oral suspension, crush five valacyclovir 500 mg caplets (10 caplets for 50 mg/mL suspension) into a fine powder in a mortar. Gradually add 5 mL aliquots of Suspension Structured Vehicle USP-NF (SSV) to powder and triturate until a paste is formed. Continue adding 5 mL aliquots of SSV to the mortar until a suspension is formed (minimum 20 mL SSV and maximum 40 mL SSV). Transfer to 100 mL bottle. Add the cherry flavor (amount recommended on package) to the mortar and dissolve in ~5 mL of SSV. Add to bottle once dissolved. Rinse the mortar at least 3 times with ~5 mL of SSV, transferring contents between additions of SSV. Continue to add the SSV to bring final volume to 100 mL. The preparation is stable for 28 days under refrigeration; shake well before using. (Refer to manufacturer's current labeling.)

ContraindicationsHypersensitivity to valacyclovir, acyclovir, or any component of the formulation

Allergy Considerations

- Antiviral Acyclic Guanine Derivative Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome: Has occurred in immunocompromised patients (at doses of 8 g/day).
- Urinary precipitation: Decreased precipitation in renal tubules may occur; adequately hydrate patient.

Disease-related concerns:

- Renal impairment: Use caution in patients with renal impairment, the elderly, and/or those receiving nephrotoxic agents. Acute renal failure and CNS effects have been observed in patients with renal dysfunction; dose adjustment may be required.

Special populations:

- Elderly: Use with caution in the elderly; CNS effects have been reported.
- Immunocompromised patients: Advanced HIV (CD4 <100 cells/mm^3): Safety and efficacy have not been established for treatment/suppression of recurrent genital herpes or disseminated herpes in patients with profound immunosuppression.
- Pediatrics: Safety and efficacy have not been established in patients <2 years of age.

Other warnings/precautions:

- Appropriate use: For cold sores, treatment should begin with earliest symptom (tingling, itching, burning). For genital herpes, treatment should begin as soon as possible after the first signs and symptoms (within 72 hours of onset of first diagnosis or within 24 hours of onset of recurrent episodes). For herpes zoster, treatment should begin within 72 hours of onset of rash. For chickenpox, treatment should begin with earliest sign or symptom.

Geriatric ConsiderationsMore convenient dosing and increased bioavailability, without increasing side effects, make valacyclovir a favorable choice compared to acyclovir. Has been shown to accelerate resolution of postherpetic pain. Adjust dose for renal impairment.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic events were not observed in animal studies. Data from a pregnancy registry has shown no increased rate of birth defects than that of the general population; however, the registry is small and use during pregnancy is only warranted if the potential benefit to the mother justifies the risk of the fetus.

LactationEnters breast milk/use caution

Breast-Feeding ConsiderationsPeak concentrations in breast milk range from 0.5-2.3 times the corresponding maternal acyclovir serum concentration. This is expected to provide a nursing infant with a dose of acyclovir equivalent to ~0.6 mg/kg/day following ingestion of valacyclovir 500 mg twice daily by the mother. Use with caution while breast-feeding.

Adverse Reactions

>10%:

Central nervous system: Headache (13% to 38%)

Gastrointestinal: Nausea (5% to 15%), abdominal pain (1% to 11%)

Hematologic: Neutropenia (≤18%)

Hepatic: ALT increased (≤14%), AST increased (2% to 16%)

Respiratory: Nasopharyngitis (≤16%)

1% to 10%:

Central nervous system: Fatigue (≤8%), depression (≤7%), fever (children 4%), dizziness (2% to 4%)

Dermatologic: Rash (≤8%)

Endocrine: Dysmenorrhea (≤1% to 8%), dehydration (children 2%)

Gastrointestinal: Vomiting (<1% to 6%), diarrhea (children 5%; adults <1%)

Hematologic: Thrombocytopenia (≤3%)

Hepatic: Alkaline phosphatase increased (≤4%)

Neuromuscular & skeletal: Arthralgia (<1 to 6%)

Respiratory: Rhinorrhea (children 2%)

Miscellaneous: Herpes simplex (children 2%)

<1%, postmarketing, and/or case reports: Acute hypersensitivity reactions (angioedema, anaphylaxis, dyspnea, pruritus, rash, urticaria); aggression, agitation, alopecia, anemia, aplastic anemia, ataxia, creatinine increased, coma, confusion, consciousness decreased, dysarthria, encephalopathy, erythema multiforme, facial edema, hallucinations (auditory and visual), hemolytic uremic syndrome (HUS), hepatitis, hypertension, leukocytoclastic vasculitis, leukopenia, mania, photosensitivity reaction, psychosis, renal failure, renal pain, seizure, tachycardia, thrombotic thrombocytopenic purpura (TTP), tremor, urinary precipitation, visual disturbances

Drug Interactions

Mycophenolate: Acyclovir-Valacyclovir may increase the serum concentration of Mycophenolate. Mycophenolate may increase the serum concentration of Acyclovir-Valacyclovir. *Risk C: Monitor therapy*

Tenofovir: Acyclovir-Valacyclovir may decrease the excretion of Tenofovir. *Risk C: Monitor therapy*

Zidovudine: Acyclovir-Valacyclovir may enhance the CNS depressant effect of Zidovudine. *Risk C: Monitor therapy*

Zoster Vaccine: Acyclovir-Valacyclovir may diminish the therapeutic effect of Zoster Vaccine. Management: When possible, discontinue antiviral agents with anti-zoster activity (i.e., acyclovir, valacyclovir, famciclovir) for at least 24 hours prior to and 14 days after receiving a live attenuated zoster vaccine. *Risk X: Avoid combination*

Monitoring ParametersUrinalysis, BUN, serum creatinine, liver enzymes, and CBC

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacologic agents or herbal products patient may be taking. Assess therapeutic effectiveness (resolution of clinical symptoms) and adverse responses (eg, CNS changes [dizziness, depression], nausea, vomiting, dysmenorrhea, arthralgia). Teach patient appropriate use (eg, timing of treatment according to purpose for use), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsUrinalysis, BUN, serum creatinine, liver enzymes, and CBC

Patient EducationThis medication is not a cure for genital herpes; it is not known if it will prevent transmission to others. Use appropriate precautions to prevent spread to other persons. Take as directed, with or without food. Begin use at first sign of herpes. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause headache, dizziness (use caution when driving or engaging in potentially hazardous tasks until response to drug is known); or nausea, vomiting, or abdominal pain (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Immediately report difficulty swallowing or breathing; rash or hives; changes in menses; or other persistent unresolved adverse effects. **Breast-feeding precaution:** Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet:

Valtrex®: 500 mg, 1000 mg

Generic AvailableNo

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Tablets (Valtrex)

1 g (30): $365.87

500 mg (30): $208.10

Mechanism of ActionValacyclovir is rapidly and nearly completely converted to acyclovir by intestinal and hepatic metabolism. Acyclovir is converted to acyclovir monophosphate by virus-specific thymidine kinase then further converted to acyclovir triphosphate by other cellular enzymes. Acyclovir triphosphate inhibits DNA synthesis and viral replication by competing with deoxyguanosine triphosphate for viral DNA polymerase and being incorporated into viral DNA.

Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: Acyclovir is widely distributed throughout the body including brain, kidney, lungs, liver, spleen, muscle, uterus, vagina, and CSF

Protein binding: ~14% to 18%

Metabolism: Hepatic; valacyclovir is rapidly and nearly completely converted to acyclovir and L-valine by first-pass effect; acyclovir is hepatically metabolized to a very small extent by aldehyde oxidase and by alcohol and aldehyde dehydrogenase (inactive metabolites)

Bioavailability: ~55% once converted to acyclovir

Half-life elimination: Normal renal function: Adults: Acyclovir: 2.5-3.3 hours, Valacyclovir: ~30 minutes; End-stage renal disease: Acyclovir: 14-20 hours; During hemodialysis: 4 hours

Excretion: Urine, primarily as acyclovir (89%); **Note:** Following oral administration of radiolabeled valacyclovir, 46% of the label is eliminated in the feces (corresponding to nonabsorbed drug), while 47% of the radiolabel is eliminated in the urine.

Related Information

- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause aggression, agitation, confusion, encephalopathy, hallucinations, mania, psychosis

Mental Health: Effects on Psychiatric TreatmentUse caution in patients with renal impairment; CNS symptoms have been reported in these patients

Index TermsValacyclovir Hydrochloride

References

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Grant DM, Mauskopf JA, Bell L, et al, “Comparison of Valaciclovir and Acyclovir for the Treatment of Herpes Zoster in Immunocompetent Patients Over 50 Years of Age: A Cost-Consequence Model,” *Pharmacotherapy*, 1997, 17(2):333-41. [PubMed 9085325]

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“Valacyclovir,” *Med Lett Drugs Ther*, 1996, 38(965):3-4. [PubMed 8551979]

Weller S, Blum MR, Doucette M, et al, “Pharmacokinetics of the Acyclovir Prodrug Valaciclovir After Escalating Single- and Multiple-Dose Administration to Normal Volunteers,” *Clin Pharmacol Ther*, 1993, 54(6):595-605.[PubMed 8275615]

International Brand NamesHerclov (ID); Lizhuwei (CL); Rapivir (MX, UY); Talavir (IT); Valcivir (IN); Valcyclor (CO); Valtrex (AE, AR, AT, AU, BB, BD, BG, BH, BM, BR, BS, BZ, CH, CL, CN, CO, CR, CY, CZ, DE, DO, EC, EE, EG, ES, FI, GB, GT, GY, HK, HN, ID, IE, IL, IN, IQ, IR, JM, JO, JP, KP, KW, LB, LY, MY, NI, NL, NO, OM, PA, PH, PK, PT, PY, QA, SA, SE, SG, SR, SV, SY, TH, TT, TW, VE, YE); Valvir (ID); Viranet (AR); Zelitrex (BE, DK, FR, NL); Zosvir (EC)

Valganciclovir

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Valcyte™ may be confused with Valium®, Valtrex®

Valganciclovir may be confused with valacyclovir

Pronunciation(val gan SYE kloh veer)

U.S. Brand NamesValcyte™

Canadian Brand NamesValcyte™

Pharmacologic CategoryAntiviral Agent

Use: Labeled IndicationsTreatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS); prevention of CMV disease in high-risk patients (donor CMV positive/recipient CMV negative) undergoing kidney, heart, or kidney/pancreas transplantation

Dosing: Adults

CMV retinitis: Oral:

Induction (active retinitis): 900 mg twice daily for 21 days (with food)

Maintenance: Following induction treatment, or for patients with inactive CMV retinitis who require maintenance therapy: Recommended dose: 900 mg once daily (with food)

Prevention of CMV disease following transplantation: Oral: 900 mg once daily (with food) beginning within 10 days of transplantation; continue therapy until 100 days post-transplantation.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Induction dose:

Cl_{cr} 40-59 mL/minute: 450 mg twice daily

Cl_{cr} 25-39 mL/minute: 450 mg once daily

Cl_{cr} 10-24 mL/minute: 450 mg every 2 days

Maintenance dose:

Cl_{cr} 40-59 mL/minute: 450 mg once daily

Cl_{cr} 25-39 mL/minute: 450 mg every 2 days

Cl_{cr} 10-24 mL/minute: 450 mg twice weekly

Note: Valganciclovir is not recommended in patients receiving hemodialysis. For patients on hemodialysis (Cl_{cr} <10 mL/minute), it is recommended that ganciclovir be used (dose adjusted as specified for ganciclovir).

Calculations

- Creatinine Clearance: Adults

Administration: OralAvoid direct contact with broken or crushed tablets. Consideration should be given to handling and disposal according to guidelines issued for antineoplastic drugs. However, there is no consensus on the need for these precautions.

Dietary ConsiderationsShould be taken with meals.

StorageStore at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

ContraindicationsHypersensitivity to valganciclovir, ganciclovir, acyclovir, or any component of the formulation; absolute neutrophil count <500/mm^3; platelet count <25,000/mm^3; hemoglobin <8 g/dL

Allergy Considerations

- Antiviral Acyclic Guanine Derivative Allergy

Warnings/Precautions

Boxed warnings:

- Blood dyscrasias: See "Concerns related to adverse effects" below.
- Carcinogenic/teratogenic/fertility effects: See "Concerns related to adverse effects" below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Blood dyscrasias: **[U.S. Boxed Warning]: May cause dose- or therapy-limiting granulocytopenia, anemia, and/or thrombocytopenia;** use with caution in patients with pre-existing bone marrow suppression, cytopenias, or in those receiving myelosuppressive drugs/irradiation.
- Carcinogenic/teratogenic/fertility effects: **[U.S. Boxed Warning]: Ganciclovir may adversely affect spermatogenesis and fertility;** due to its mutagenic potential, contraceptive precautions for female and male patients need to be followed during and for at least 90 days after therapy with the drug.

Disease-related concerns:

- Renal impairment: Use with caution in patients with impaired renal function; dosage adjustment required.

Special populations:

- Liver transplant recipients: Not indicated for use in liver transplant patients (higher incidence of tissue-invasive CMV relative to oral ganciclovir was observed in trials).
- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Product bioavailability variation: Due to differences in bioavailability, valganciclovir tablets cannot be substituted for ganciclovir capsules on a one-to-one basis.

Pregnancy Risk FactorC

Pregnancy ConsiderationsValganciclovir is converted to ganciclovir and shares its reproductive toxicity. **[U.S. Boxed Warning]: Ganciclovir may adversely affect spermatogenesis and fertility;** due to its mutagenic potential, contraceptive precautions for female and male patients need to be followed during and for at least 90 days after therapy with this drug.

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease the potential transmission of HIV.

Adverse Reactions

>10%:

Central nervous system: Fever (31%), headache (9% to 22%), insomnia (16%)

Gastrointestinal: Diarrhea (16% to 41%), nausea (8% to 30%), vomiting (21%), abdominal pain (15%)

Hematologic: Granulocytopenia (11% to 27%), anemia (8% to 26%)

Ocular: Retinal detachment (15%)

1% to 10%:

Central nervous system: Peripheral neuropathy (9%), paresthesia (8%), seizure (<5%), psychosis, hallucinations (<5%), confusion (<5%), agitation (<5%)

Hematologic: Thrombocytopenia (8%), pancytopenia (<5%), bone marrow depression (<5%), aplastic anemia (<5%), bleeding (potentially life-threatening due to thrombocytopenia <5%)

Renal: Renal function decreased (<5%)

Miscellaneous: Local and systemic infection, including sepsis (<5%); allergic reaction (<5%)

<1%: Valganciclovir is expected to share the toxicities which may occur at a low incidence or due to idiosyncratic reactions which have been associated with ganciclovir

Drug Interactions

Mycophenolate: May increase the serum concentration of Ganciclovir-Valganciclovir. Ganciclovir-Valganciclovir may increase the serum concentration of Mycophenolate. *Risk C: Monitor therapy*

Reverse Transcriptase Inhibitors (Nucleoside): Ganciclovir-Valganciclovir may enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. **Exceptions:** Stavudine; Zalcitabine. *Risk D: Consider therapy modification*

Tenofovir: Ganciclovir-Valganciclovir may decrease the excretion of Tenofovir. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Coadministration with a high-fat meal increased AUC by 30%.

Monitoring ParametersRetinal exam (at least every 4-6 weeks), CBC, platelet counts, serum creatinine

Nursing: Physical Assessment/MonitoringUse caution with renal impairment. Assess potential for interactions with other pharmacological agents patient may be taking (eg, increased risk of nephrotoxicity and hematologic toxicity). Assess results of laboratory tests, therapeutic effectiveness (reduction in clinical symptoms), and adverse response (eg, peripheral neuropathy, neutropenia, anemia, nephrotoxicity, retinal detachment, vomiting, bloody diarrhea) on a regular basis during therapy. Teach proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsRetinal exam (at least every 4-6 weeks), CBC, platelet counts, serum creatinine

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication is not a cure for CMV retinitis. Take exactly as directed; do not alter dosage or discontinue without consulting prescriber. You will need frequent and regular laboratory tests and ophthalmic exams while taking this medication. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may be more susceptible to infection (avoid crowds or exposure to infection and do not have any vaccinations unless approved by prescriber). May cause headache or insomnia (use caution when driving or engaging in hazardous tasks until response to drug is known); nausea or vomiting (small, frequent meals, good mouth care, sucking lozenges, or chewing gum may help); diarrhea (boiled milk, yogurt, or buttermilk may help); or photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight). Report fever; chills; unusual bleeding or bruising; infection or unhealed sores; white plaques in mouth or vaginal discharge; CNS disturbances (eg, hallucinations, confusion, nightmares); or weakness or loss of feeling in nerves or muscles. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Males and females should use appropriate barrier contraceptive measures during and for 90 days following end of therapy. Consult prescriber if you suspect you might be pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as hydrochloride: 450 mg [valganciclovir hydrochloride 496.3 mg equivalent to valganciclovir 450 mg]

Generic AvailableNo

ManufacturerRoche Laboratories Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Valcyte)

450 mg (60): $2189.19

Mechanism of ActionValganciclovir is rapidly converted to ganciclovir in the body. The bioavailability of ganciclovir from valganciclovir is increased 10-fold compared to oral ganciclovir. A dose of 900 mg achieved systemic exposure of ganciclovir comparable to that achieved with the recommended doses of intravenous ganciclovir of 5 mg/kg. Ganciclovir is phosphorylated to a substrate which competitively inhibits the binding of deoxyguanosine triphosphate to DNA polymerase resulting in inhibition of viral DNA synthesis.

Pharmacodynamics/Kinetics

Absorption: Well absorbed; high-fat meal increases AUC by 30%

Distribution: Ganciclovir: V_d: 15.26 L/1.73 m^2; widely to all tissue including CSF and ocular tissue

Protein binding: 1% to 2%

Metabolism: Converted to ganciclovir by intestinal mucosal cells and hepatocytes

Bioavailability: With food: 60%

Half-life elimination: Ganciclovir: 4.08 hours; prolonged with renal impairment; Severe renal impairment: Up to 68 hours

Excretion: Urine (primarily as ganciclovir)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia is common; may cause confusion and psychosis

Mental Health: Effects on Psychiatric TreatmentGastrointestinal side effects are common; use caution with SSRIs, lithium, and valproic acid. Granulocytopenia is common; use caution with clozapine, carbamazepine, and valproic acid.

Index TermsValganciclovir Hydrochloride

References

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International Brand NamesRovalcyte (FR); Valcyte (AU, BE, BG, BR, CH, CL, CZ, DE, DK, EE, ES, FI, GB, HK, HN, ID, IE, IL, IT, KP, MX, NL, NO, PH, PL, SE, SG, TH, TW); Valixa (AR, CN, CO, EC, PE, UY, VE)

Valproic Acid and Derivatives

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

Depakene® may be confused with Depakote®

Depakote® may be confused with Depakene®, Depakote® ER, Senokot®

Depakote® ER may be confused with Depakote®

Pronunciation(val PROE ik AS id & dah RIV ah tives)

U.S. Brand NamesDepacon®; Depakene®; Depakote®; Depakote® ER; Depakote® Sprinkle; Stavzor™

Canadian Brand NamesAlti-Divalproex; Apo-Divalproex®; Apo-Valproic®; Depakene®; Dom-Divalproex; Epival® I.V.; Gen-Divalproex; Novo-Divalproex; Nu-Divalproex; PHL-Divalproex; PHL-Valproic Acid; PHL-Valproic Acid E.C.; PMS-Valproic Acid; PMS-Valproic Acid E.C.; ratio-Valproic; ratio-Valproic ECC; Rhoxal-valproic; Sandoz-Valproic

Pharmacologic CategoryAnticonvulsant, Miscellaneous; Antimanic Agent; Histone Deacetylase Inhibitor

Use: Labeled Indications

Depacon®, Depakene®, Depakote®, Depakote® ER, Depakote® Sprinkle, Stavzor™: Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures; monotherapy and adjunctive therapy of simple and complex absence seizures; adjunctive therapy in patients with multiple seizure types that include absence seizures

Depakote®, Depakote® ER, Stavzor™: Mania associated with bipolar disorder; migraine prophylaxis

Use: Unlabeled/InvestigationalStatus epilepticus

Dosing: Adults

Seizures: Administer doses >250 mg/day in divided doses.

Oral:

Simple and complex absence seizure: Initial: 15 mg/kg/day; increase by 5-10 mg/kg/day at weekly intervals until therapeutic levels are achieved; maximum: 60 mg/kg/day.

Complex partial seizure: Initial: 10-15 mg/kg/day; increase by 5-10 mg/kg/day at weekly intervals until therapeutic levels are achieved; maximum: 60 mg/kg/day.

Note: Regular release and delayed release formulations are usually given in 2-4 divided doses/day; extended release formulation (Depakote® ER) is usually given once daily. Conversion to Depakote® ER from a stable dose of Depakote® may require an increase in the total daily dose between 8% and 20% to maintain similar serum concentrations.

I.V.: Administer as a 60-minute infusion (≤20 mg/minute) with the same frequency as oral products; switch patient to oral products as soon as possible. Rapid infusions ≤45 mg/kg over 5-10 minutes (1.5-6 mg/kg/minute) were generally well tolerated in clinical trials.

Rectal (unlabeled): Dilute syrup 1:1 with water for use as a retention enema; loading dose: 17-20 mg/kg one time; maintenance: 10-15 mg/kg/dose every 8 hours

Status epilepticus (unlabeled use):

Loading dose: I.V.: 15-45 mg/kg administered at ≤ 6 mg/kg/minute

Maintenance dose: I.V. infusion: 1-4 mg/kg/hour; titrate dose as needed based upon patient response and evaluation of drug-drug interactions

Mania:*Oral:*

Depakote® tablet, Stavzor™: Initial: 750 mg/day in divided doses; dose should be adjusted as rapidly as possible to desired clinical effect; maximum recommended dosage: 60 mg/kg/day

Depakote® ER: Initial: 25 mg/kg/day given once daily; dose should be adjusted as rapidly as possible to desired clinical effect; maximum recommended dose: 60 mg/kg/day.

Migraine prophylaxis: *Oral:*

Depakote® tablet, Stavzor™: 250 mg twice daily; adjust dose based on patient response, up to 1000 mg/day

Depakote® ER: 500 mg once daily for 7 days, then increase to 1000 mg once daily; adjust dose based on patient response; usual dosage range 500-1000 mg/day

Dosing: ElderlyInitiate at lower doses; dose escalation should be managed more slowly (in persons of advanced age). Refer to adult dosing.

Dosing: Pediatric

Seizures:

Oral, I.V.:

Simple and complex absence seizures: Refer to adult dosing. Larger maintenance doses may be required in younger children.

Complex partial seizures: Children ≥10 years: Refer to adult dosing. Larger maintenance doses may be required in younger children.

Note: Depakote® ER is not recommended for use in children <10 years of age.

Rectal (unlabeled): Refer to adult dosing.

Migraine prophylaxis: Oral: Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentA 27% reduction in clearance of unbound valproate is seen in patients with Cl_{cr} <10 mL/minute. Hemodialysis reduces valproate concentrations by 20%, therefore, no dose adjustment is needed in patients with renal failure. Protein binding is reduced, monitoring only total valproate concentrations may be misleading.

Dosing: Hepatic ImpairmentDosage reduction is required. Clearance is decreased with liver impairment. Hepatic disease is also associated with decreased albumin concentrations and 2- to 2.6-fold increase in the unbound fraction. Free concentrations of valproate may be elevated while total concentrations appear normal. Use is contraindicated in severe impairment.

Administration: I.V.Depacon®: Following dilution to final concentration, administer over 60 minutes at a rate ≤20 mg/minute. Alternatively, single doses up to 45 mg/kg have been administered as a rapid infusion over 5-10 minutes (1.5-6 mg/kg/minute).

Administration: Oral

Depakote® ER: Swallow whole; do not crush or chew. Patients who need dose adjustments smaller than 500 mg/day for migraine prophylaxis should be changed to Depakote® delayed release tablets.

Depakote® Sprinkle capsules may be swallowed whole or open capsule and sprinkle on small amount (1 teaspoonful) of soft food and use immediately (do not store or chew).

Depakene® capsule, Stavzor™: Swallow whole; do not chew.

Dietary ConsiderationsValproic acid may cause GI upset; take with large amount of water or food to decrease GI upset. May need to split doses to avoid GI upset.

Depakote® Sprinkle capsule contents may be mixed with semisolid food (eg, applesauce or pudding) in patients having difficulty swallowing; particles should be swallowed and not chewed.

Valproate sodium oral solution will generate valproic acid in carbonated beverages and may cause mouth and throat irritation; do not mix valproate sodium oral solution with carbonated beverages.

Storage

Depakote® tablet, Depakene® solution: Store below 30°C (86°F).

Depakote® Sprinkles: Store below 25°C (77°F).

Depakote® ER, Stavzor™: Store at controlled room temperature of 25°C (77°F).

Depakene® capsule: Store at controlled room temperature of 15˚C to 25°C (59°F to 77°F).

Depacon®: Store vial at room temperature of 15°C to 30°C (59°F to 86°F). Stable in D_5W, NS, and LR for at least 24 hours when stored in glass or PVC.

ReconstitutionDepacon®: Injection should be diluted in 50 mL of a compatible diluent.

CompatibilityStable in D_5W, NS, and LR.

Y-site administration: Compatible with cefepime, ceftazidime

ContraindicationsHypersensitivity to valproic acid, derivatives, or any component of the formulation; hepatic disease or significant impairment; urea cycle disorders

Allergy Considerations

- Valproic Acid Derivative Allergy

Warnings/Precautions

Boxed warnings:

- Hepatic failure: See "Concerns related to adverse effects" below.
- Pancreatitis: See "Concerns related to adverse effects" below.
- Pregnancy: See "Special populations" below.

Concerns related to adverse effects:

- CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).
- Hepatic failure: **[U.S. Boxed Warning]: Hepatic failure resulting in fatalities has occurred in patients; children <2 years of age are at considerable risk.** Other risk factors include organic brain disease, mental retardation with severe seizure disorders, congenital metabolic disorders, and patients on multiple anticonvulsants. Hepatotoxicity has usually been reported within 6 months of therapy initiation. Monitor patients closely for appearance of malaise, weakness, facial edema, anorexia, jaundice, and vomiting; discontinue immediately with signs/symptom of significant or suspected impairment. Liver function tests should be performed at baseline and at regular intervals after initiation of therapy, especially within the first 6 months. Hepatic dysfunction may progress despite discontinuing treatment. Should only be used as monotherapy in children <2 years of age and patients at high risk for hepatotoxicity.
- Hyperammonemia/encephalopathy: Hyperammonemia and/or encephalopathy, sometimes fatal, has been reported following the initiation of valproic acid therapy and may be present with normal transaminase levels. Ammonia levels should be measured in patients who develop unexplained lethargy and vomiting, or changes in mental status or in patients who present with hypothermia. Discontinue therapy if ammonia levels are increased and evaluate for possible urea cycle disorder (UCD). Contraindicated in patients with UCD. Evaluation of UCD should be considered for the following patients prior to the start of therapy: History of unexplained encephalopathy or coma; encephalopathy associated with protein load; pregnancy or postpartum encephalopathy; unexplained mental retardation; history of elevated plasma ammonia or glutamine; history of cyclical vomiting and lethargy; episodic extreme irritability, ataxia; low BUN or protein avoidance; family history of UCD or unexplained infant deaths (particularly male); or signs or symptoms of UCD (hyperammonemia, encephalopathy, respiratory alkalosis).
- Hypothermia: Hypothermia (unintentional drop in core body temperature to <35°C/95°F) has been reported with valproic acid therapy; may or may not be associated with hyperammonemia; may also occur with concomitant topiramate therapy.
- Multiorgan hypersensitivity reactions: Potentially serious, sometimes fatal multiorgan hypersensitivity reactions have rarely been reported with some antiepileptic drugs including valproic acid therapy in adults and children; monitor for signs and symptoms of possible disparate manifestations associated with lymphatic, hepatic, renal, and/or hematologic organ systems; discontinuation and conversion to alternate therapy may be required.
- Pancreatitis: **[U.S. Boxed Warning]: Cases of life-threatening pancreatitis, occurring at the start of therapy or following years of use, have been reported in adults and children.** Some cases have been hemorrhagic with rapid progression of initial symptoms to death. Promptly evaluate symptoms of abdominal pain, nausea, vomiting, and/or anorexia; should generally be discontinued if pancreatitis is diagnosed.
- Suicidal ideation: FDA reports demonstrate a statistically significant increased risk of suicidality; relative risk appears to be higher in patients with epilepsy compared to patients treated for psychiatric or other considerations. Monitor all patients for notable changes in behavior that might indicate suicidal thoughts or depression.
- Thrombocytopenia: May cause severe thrombocytopenia (may be dose-related), inhibition of platelet aggregation, and bleeding. In some cases, platelet counts may be normalized with continued treatment, however, reduce dose or discontinue drug if patient develops evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation. Evaluate platelet counts prior to initiating therapy and periodically thereafter.
- Tremors: May indicate overdosage.

Disease-related concerns:

- Hepatic impairment: Contraindicated with severe impairment.

Concurrent drug therapy issues:

- Carbapenem antibiotics: Concomitant use may reduce valproic acid levels to subtherapeutic levels; monitor levels frequently and consider alternate therapy if levels drop significantly or lack of seizure control occurs.
- Clonazepam: Concomitant use with clonazepam may induce absence status.
- Topiramate: Concomitant use with topiramate has been associated with hyperammonemia and hypothermia with or without encephalopathy.

Special populations:

- Elderly: Use with caution as elderly patients may be more sensitive to sedating effects; dose adjustment may be necessary.

- Pregnancy: **[U.S. Boxed Warning]: May cause teratogenic effects such as neural tube defects (eg, spina bifida).** Use in women of childbearing potential requires that benefits of use in mother be weighed against the potential risk to fetus, especially when used for conditions not associated with permanent injury or risk of death (eg, migraine).

Dosage form specific issues:

- Depacon® injection: Use of Depacon® injection is not recommended for post-traumatic seizure prophylaxis following acute head trauma.

Other warnings/precautions:

- Viral replication: *In vitro* studies have suggested valproic acid stimulates the replication of HIV and CMV viruses under experimental conditions. The clinical consequence of this is unknown, but should be considered when monitoring affected patients.

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsAlthough there is little data in elderly for the use of valproic acid in the treatment of seizures, there are a number of studies which demonstrate its benefit in the treatment of agitation and dementia and other psychiatric disorders. It is important that the clinician understand that serum concentrations do not correlate with behavior response; likewise, it is imperative to monitor LFTs and CBC during the first 6 months of therapy. See Warnings/Precautions, Monitoring Parameters, and Additional Information.

Elimination is decreased in elderly. Studies of older adults with dementia show a high incidence of somnolence (which is usually transient); cognitive side effects generally minimal. In some patients, this was associated with weight loss. Starting doses should be lower and increased slowly, with careful monitoring of nutritional intake and dehydration. Safety and efficacy for use in patients >65 years of age have not been studied for migraine prophylaxis.

Pregnancy Risk FactorD

Pregnancy Considerations**[U.S. Boxed Warning]: May cause teratogenic effects such as neural tube defects (eg, spina bifida).** Teratogenic effects have been reported in animals and humans. Valproic acid crosses the placenta. Neural tube, cardiac, facial (characteristic pattern of dysmorphic facial features), skeletal, multiple other defects reported. Epilepsy itself, number of medications, genetic factors, or a combination of these probably influence the teratogenicity of anticonvulsant therapy. Information from the North American Antiepileptic Drug Pregnancy Registry notes a fourfold increase in congenital malformations with exposure to valproic acid monotherapy during the 1st trimester of pregnancy when compared to monotherapy with other antiepileptic drugs (AED). The risk of neural tube defects is ~1% to 2% (general population risk estimated to be 0.14% to 0.2%). The effect of folic acid supplementation to decrease this risk is unknown, however, folic acid supplementation is recommended for all women contemplating pregnancy. An information sheet describing the teratogenic potential is available from the manufacturer.

Nonteratogenic effects have also been reported. Afibrinogenemia leading to fatal hemorrhage and hepatotoxicity have been noted in case reports of infants following *in utero* exposure to valproic acid. Use in women of childbearing potential requires that benefits of use in mother be weighed against the potential risk to fetus, especially when used for conditions not associated with permanent injury or risk of death (eg, migraine). Health professionals and patients are encouraged to contact the North American Antiepileptic Drug Pregnancy registry to monitor outcomes of pregnant women exposed to valproic acid and other AEDs (1-888-233-2334).

LactationEnters breast milk/not recommended (AAP considers “compatible”)

Breast-Feeding ConsiderationsBreast milk concentrations of valproic acid have been reported as 1% to 10% of maternal concentration. The weight-adjusted dose to the infant has been calculated to be ~4%.

Adverse Reactions

>10%:

Central nervous system: Headache (≤31%), somnolence (≤30%), dizziness (12% to 25%), insomnia (>1% to 15%), nervousness (>1% to 11%), pain (1% to 11%)

Dermatologic: Alopecia (>1% to 24%)

Gastrointestinal: Nausea (15% to 48%), vomiting (7% to 27%), diarrhea (7% to 23%), abdominal pain (7% to 23%), dyspepsia (7% to 23%), anorexia (>1% to 12%)

Hematologic: Thrombocytopenia (1% to 24%; dose related)

Neuromuscular & skeletal: Tremor (≤57%), weakness (6% to 27%)

Ocular: Diplopia (>1% to 16%), amblyopia/blurred vision (≤12%)

Miscellaneous: Infection (≤20%), flu-like syndrome (12%)

1% to 10%:

Cardiovascular: Peripheral edema (>1% to 8%), chest pain (>1% to <5%), edema (>1% to <5%), facial edema (>1% to <5%), hypertension (>1% to <5%), hypotension (>1% to <5%), palpitation (>1% to <5%), postural hypotension (>1% to <5%), tachycardia (>1% to <5%), vasodilation(>1% to <5%), arrhythmia

Central nervous system: Ataxia (>1% to 8%), amnesia (>1% to 7%), emotional lability (>1% to 6%), fever (>1% to 6%), abnormal thinking (≤6%), depression (>1% to 5%), abnormal dreams (>1% to <5%), agitation (>1% to <5%), anxiety (>1% to <5%), catatonia (>1% to <5%), chills (>1% to <5%), confusion (>1% to <5%), coordination abnormal (>1% to <5%), hallucination (>1% to <5%), malaise (>1% to <5%), personality disorder (>1% to <5%), speech disorder (>1% to <5%), tardive dyskinesia (>1% to <5%), vertigo (>1% to <5%), euphoria (1%), hypoesthesia (1%)

Dermatologic: Rash (>1% to 6%), bruising (>1% to 5%), discoid lupus erythematosus (>1% to <5%), dry skin (>1% to <5%), furunculosis (>1% to <5%), petechia (>1% to <5%), pruritus (>1% to <5), seborrhea (>1% to <5%)

Endocrine & metabolic: Amenorrhea (>1% to <5%), dysmenorrhea (>1% to <5%), metrorrhagia (>1% to <5%), hypoproteinemia

Gastrointestinal: Weight gain (4% to 9%), weight loss (6%), appetite increased (≤6%), constipation (>1% to 5%), xerostomia (>1% to 5%), eructation (>1% to <5%), fecal incontinence (>1% to <5%), flatulence (>1% to <5%), gastroenteritis (>1% to <5%), glossitis (>1% to <5%), hematemesis (>1% to <5%), pancreatitis (>1% to <5%), periodontal abscess (>1% to <5%), stomatitis (>1% to <5%), taste perversion (>1% to <5%), dysphagia, gum hemorrhage, mouth ulceration

Genitourinary: Cystitis (>1% to 5%), dysuria (>1% to 5%), urinary frequency (>1% to <5%), urinary incontinence (>1% to <5%), vaginal hemorrhage (>1% to 5%), vaginitis (>1% to <5%)

Hepatic: ALT increased (>1% to <5%), AST increased (>1% to <5%)

Local: Injection site pain (3%), injection site reaction (2%), injection site inflammation (1%)

Neuromuscular & skeletal: Back pain (≤8%), abnormal gait (>1% to <5%), arthralgia (>1% to <5%), arthrosis (>1% to <5%), dysarthria (>1% to <5%), hypertonia (>1% to <5%), hypokinesia (>1% to <5%), leg cramps (>1% to <5%), myalgia (>1% to <5%), myasthenia (>1% to <5%), neck pain (>1% to <5%), neck rigidity (>1% to <5%), paresthesia (>1% to <5%), reflex increased (>1% to <5%), twitching (>1% to <5%)

Ocular: Nystagmus (1% to 8%), dry eyes (>1% to 5%), eye pain (>1% to 5%), abnormal vision (>1% to <5%), conjunctivitis (>1% to <5%)

Otic: Tinnitus (1% to 7%), ear pain (>1% to 5%), deafness (>1% to <5%), otitis media (>1% to <5%)

Respiratory: Pharyngitis (2% to 8%), bronchitis (5%), rhinitis (>1% to 5%), dyspnea (1% to 5%), cough (>1% to <5%), epistaxis (>1% to <5%), pneumonia (>1% to <5%), sinusitis (>1% to <5%)

Miscellaneous: Diaphoresis (1%), hiccups

<1%, postmarketing, and/or case reports (limited to important and/or life-threatening): Aggression, agranulocytosis, allergic reaction, anaphylaxis, anemia, aplastic anemia, asterixis, behavioral deterioration, bilirubin increased, bleeding time altered, bone marrow suppression, bone pain, bradycardia, breast enlargement, cutaneous vasculitis, carnitine decreased, cerebral atrophy (reversible), coma (rare), dementia, encephalopathy (rare), enuresis, eosinophilia, erythema multiforme, Fanconi-like syndrome (rare, in children), galactorrhea, hematoma formation, hemorrhage, hepatic failure, hepatotoxicity, hostility, hyperactivity, hyperammonemia, hyperammonemic encephalopathy (in patients with UCD), hyperglycinemia, hypersensitivity reactions (severe, with multiorgan dysfunction), hypofibrinogenemia, hyponatremia, hypothermia, inappropriate ADH secretion, intermittent porphyria, LDH increased, leukopenia, lupus, lymphocytosis, macrocytosis, menstrual irregularities, pancytopenia parkinsonism, parotid gland swelling, photosensitivity, platelet aggregation inhibited, polycystic ovary disease (rare), psychosis, seeing "spots before the eyes," Stevens-Johnson syndrome, suicidal behavior/ideation, thyroid function tests abnormal, toxic epidermal necrolysis (rare), urinary tract infection

Metabolism/Transport EffectsFor valproic acid: **Substrate** (minor) of CYP2A6, 2B6, 2C9, 2C19, 2E1; **Inhibits** CYP2C9 (weak), 2C19 (weak), 2D6 (weak), 3A4 (weak); **Induces** CYP2A6 (weak)

Drug Interactions

Aminocamptothecin: Valproic Acid may decrease the serum concentration of Aminocamptothecin. *Risk C: Monitor therapy*

Barbiturates: Valproic Acid may decrease the metabolism of Barbiturates. Barbiturates may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

CarBAMazepine: May increase the metabolism of Valproic Acid. Valproic Acid may decrease the serum concentration of CarBAMazepine. Carbamazepine-Epoxide concentrations might increase, offsetting the decreases in the parent compound. *Risk C: Monitor therapy*

Carbapenems: May decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

ChlorproMAZINE: May increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Ethosuximide: May decrease the serum concentration of Valproic Acid. Valproic Acid may increase the serum concentration of Ethosuximide. *Risk C: Monitor therapy*

Felbamate: May increase the serum concentration of Valproic Acid. *Risk D: Consider therapy modification*

LamoTRIgine: Valproic Acid may enhance the adverse/toxic effect of LamoTRIgine. Valproic Acid may increase the serum concentration of LamoTRIgine. *Risk D: Consider therapy modification*

LORazepam: Valproic Acid may decrease the metabolism of LORazepam. *Risk D: Consider therapy modification*

Methylfolate: May decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

OXcarbazepine: Valproic Acid may decrease the serum concentration of OXcarbazepine. *Risk C: Monitor therapy*

Phenytoin: May increase the metabolism of Valproic Acid. A hepatotoxic metabolite of valproic acid may result. Valproic Acid may decrease the serum concentration of Phenytoin. Continued therapy usually yields a normalization (or slight increase) of serum phenytoin concentrations. Free phenytoin concentrations, however, tend to remain relatively stable (possibly increased with continued therapy). *Risk C: Monitor therapy*

Primidone: Valproic Acid may decrease the metabolism of Primidone. More specifically, the metabolism of phenobarbital, primidone's primary active metabolite, would be decreased. Primidone may decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Rifampin: May decrease the serum concentration of Valproic Acid. *Risk D: Consider therapy modification*

Risperidone: Valproic Acid may enhance the adverse/toxic effect of Risperidone. Generalized edema has developed. *Risk C: Monitor therapy*

Rufinamide: Valproic Acid may increase the serum concentration of Rufinamide. *Risk D: Consider therapy modification*

Salicylates: May increase the serum concentration of Valproic Acid. *Risk C: Monitor therapy*

Topiramate: May enhance the hepatotoxic effect of Valproic Acid. *Risk C: Monitor therapy*

Tricyclic Antidepressants: Valproic Acid may increase the serum concentration of Tricyclic Antidepressants. *Risk C: Monitor therapy*

Vorinostat: Valproic Acid may enhance the thrombocytopenic effect of Vorinostat. This may increase the risk of gastrointestinal bleeding. *Risk C: Monitor therapy*

Zidovudine: Valproic Acid may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Food may delay but does not affect the extent of absorption. Valproic acid serum concentrations may be decreased if taken with food. Milk has no effect on absorption.

Herb/Nutraceutical: Avoid evening primrose (seizure threshold decreased).

Test InteractionsFalse-positive result for urine ketones; accuracy of thyroid function tests

Monitoring ParametersLiver enzymes (at baseline and during therapy), CBC with platelets (baseline and periodic intervals), PT/PTT (especially prior to surgery), serum ammonia (with symptoms of lethargy, mental status change), serum valproate levels

Reference Range

Therapeutic:

Epilepsy: 50-100 mcg/mL (SI: 350-690 µmol/L)

Mania: 85-125 mcg/mL (SI: 350-860 µmol/L)

Toxic: Some laboratories may report >200 mcg/mL (SI: >1390 µmol/L) as a toxic threshold, although clinical toxicity can occur at lower concentrations. Probability of thrombocytopenia increases with total valproate levels ≥110 mcg/mL in females or ≥135 mcg/mL in males.

Seizure control: May improve at levels >100 mcg/mL (SI: 690 µmol/L), but toxicity may occur at levels of 100-150 mcg/mL (SI: 690-1040 µmol/L)

Mania: Clinical response seen with trough levels between 85-125 mcg/mL; risk of toxicity increases at levels >125 mcg/mL

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. **I.V.:** Keep patient under observation, observe safety/seizure precautions, and monitor therapeutic effectiveness (type of seizure activity, force, and duration). Monitor vital signs; neurological, cardiac, and respiratory status. Monitor for signs and symptoms of hepatic failure (malaise, weakness, facial edema, anorexia, jaundice, and vomiting), especially when used in children <2 years of age. Monitor for signs and symptoms of pancreatitis (abdominal pain, nausea, vomiting, and/or anorexia). For outpatients, monitor therapeutic effect, laboratory values, and adverse reactions at beginning of therapy and periodically with long-term use. Taper dosage slowly when discontinuing. Assess knowledge/teach patient seizure safety precautions, appropriate use, interventions to reduce side effects, and adverse symptoms to report. **Note:** Valproic acid will alter results of urine ketones (use serum glucose testing) and reduce effectiveness of oral contraceptives (use alternative form of contraception to prevent pregnancy). Some adverse reactions, including hepatic failure and thrombocytopenia, can occur 3 days to 6 months after beginning therapy.

Monitoring: Lab TestsLiver enzymes (at baseline and during therapy), CBC with platelets (baseline and periodic intervals), PT/PTT (especially prior to surgery), serum ammonia (with symptoms of lethargy, mental status change), serum valproate levels

Patient EducationWhen used to treat generalized seizures, patient instructions are determined by patient's condition and ability to understand. **Oral:** Take as directed; do not alter dose or timing of medication. Do not increase dose or take more than recommended. Do not crush or chew capsule or enteric-coated pill. While using this medication, do not use alcohol and other prescription or OTC medications (especially pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, monitor serum glucose closely (valproic acid will alter results of urine ketones). You may experience nervousness; decreased appetite; insomnia; headache; sleepiness or dizziness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); visual changes; and hair loss. Report suicidal ideation or depression; alterations in menstrual cycle; abdominal cramps, unresolved diarrhea, vomiting, or constipation; skin rash; tremors; unusual bruising or bleeding; blood in urine, stool, or vomitus; malaise; weakness; facial swelling; yellowing of skin or eyes; persistent abdominal pain; excessive sedation; change in mental status; extreme lethargy; or restlessness. **Pregnancy/breast-feeding precautions:** Do not get pregnant while taking this medication; use appropriate contraceptive measures if necessary or if you suspect you might be pregnant. This drug should not be used in the 2nd or 3rd trimester of pregnancy. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. **Note:** Strength expressed as valproic acid

Capsule, softgel, as valproic acid: 250 mg

Depakene®: 250 mg

Capsule, softgel, delayed release, as valproic acid:

Stavzor™: 125 mg, 250 mg, 500 mg

Capsule, sprinkles, as divalproex sodium:

Depakote® Sprinkle: 125 mg

Injection, solution, as valproate sodium: 100 mg/mL (5 mL)

Depacon®: 100 mg/mL (5 mL) [contains edetate disodium]

Syrup, as valproic acid: 250 mg/5 mL (5 mL, 10 mL, 480 mL)

Depakene®: 250 mg/5 mL (480 mL)

Tablet, delayed release, as divalproex sodium: 125 mg, 250 mg, 500 mg

Depakote®: 125 mg, 250 mg, 500 mg

Tablet, delayed release, enteric coated, as divalproex sodium: 125 mg, 250 mg, 500 mg

Tablet, extended release, as divalproex sodium:

Depakote® ER: 250 mg, 500 mg

Generic Available Yes: Capsule (excluding delayed release or sprinkle), injection, syrup

Pricing: U.S. (www.drugstore.com)

Capsule, sprinkles (Depakote Sprinkles)

125 mg (60): $56.59

Capsules (Depakene)

250 mg (30): $75.96

Capsules (Valproic Acid)

250 mg (30): $14.99

Syrup (Depakene)

250 mg/5 mL (150): $83.46

Syrup (Valproate Sodium)

250 mg/5 mL (150): $17.99

Tablet, 24-hour (Depakote ER)

250 mg (30): $54.01

500 mg (30): $90.75

Tablet, EC (Depakote)

125 mg (60): $59.67

250 mg (60): $105.69

500 mg (60): $195.98

Mechanism of ActionCauses increased availability of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, to brain neurons or may enhance the action of GABA or mimic its action at postsynaptic receptor sites

Pharmacodynamics/Kinetics

Distribution: Total valproate: 11 L/1.73 m^2; free valproate 92 L/1.73 m^2

Protein binding (dose dependent): 80% to 90%; decreased in the elderly and with hepatic or renal dysfunction

Metabolism: Extensively hepatic via glucuronide conjugation and mitochondrial beta-oxidation. The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear.

Bioavailability: Depakote® ER: ~90% relative to I.V. dose and ~89% relative to delayed release formulation

Half-life elimination (increased in neonates and with liver disease): Children >2 months: 7-13 hours; Adults: 9-16 hours

Time to peak, serum: Depakote® tablet: ~4 hours; Depakote® ER: 4-17 hours; Stavzor™: 2 hours

Excretion: Urine (30% to 50% as glucuronide conjugate, 3% as unchanged drug)

Related Information

- Adverse Effects of Approved Mood Stabilizers / Anticonvulsants
- Agents Approved for Bipolar Disorder
- Anticonvulsant Drugs of Choice
- Liquid Compatibility

- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsExtended release tablets have 10% to 20% less fluctuation in serum concentration than delayed release tablets. Extended release tablets are not bioequivalent to delayed release tablets.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Periodontal abscess and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentBoth valproic acid and lithium are considered first-line agents for the management of bipolar disorder. They are useful in patients with mixed and rapid-cycling bipolar disorder. Thrombocytopenia is dose dependent and may be more common in children (Koenig, 2008). Asymptomatic elevations of hepatic transaminases are also dose related and not necessarily associated with hepatic dysfunction. Severe hepatic dysfunction is a rare idiosyncratic reaction; it is not dose related. The majority of cases occur within the first 3 months. The cause is unknown but risk factors include young age (<2 years of age), multiple anticonvulsants, and the presence of a neurologic disease in addition to epilepsy. No hepatic fatalities have been reported in patients >10 years of age who received valproic acid monotherapy.

Valproic acid is one of only a few medications that displays saturation-dependent protein binding pharmacokinetics. Therefore, when large doses are taken, the protein binding sites become saturated. This leads to an increase in unbound drug, which in turn leads to an increase in total clearance with resulting steady-state concentrations less than what might be expected. The response threshold for bipolar disorder appears to be 50 mcg/mL. Serum concentration of the extended release dosage form taken 12 hours after the last dose will result in a 25% increase over the delayed release dosage form. Interpret the levels accordingly.

Use in dementia-related aggression: Valproic acid derivatives have been investigated for over 10 years in the setting of behavioral disturbances in dementia patients. Although a number of earlier investigations suggested that valproate was effective in reducing the severity of symptoms such as aggression and agitation, these studies were commonly limited by small numbers of patients, open-label design, and lack of statistical evaluation (see Pratt and Davis review). More recently, three randomized, controlled trials were reviewed by Sink et al. These studies evaluated the use of both long- and short-acting valproate formulations in a total of 270 nursing home patients presenting with dementia of the Alzheimer’s or vascular type. Although each study used a different rating scale for the assessment of neuropsychiatric symptoms, in none of the studies was the primary outcome variable significantly different ($p<0.05$) between valproate treatment and placebo.

In addition, a double-blind, randomized trial conducted by the Alzheimer’s Disease Cooperative Study group evaluated the use of divalproex in nursing home patients exhibiting dementia-associated agitation. Patients were randomized to receive divalproex (n=75) or placebo (n=78) for 6 weeks duration. The primary outcome variable was the Brief Psychiatry Rating Scale Agitation factor, with a secondary measure of the Clinical Global Impression of Change. Patients received an average dose of divalproex of 800 mg/day with approximately 88% compliance. There were no differences between treatment groups with respect to safety or tolerability. The results also showed no significant differences between groups in any of the outcome measures.

Taken together, data generated from several randomized, blinded studies do not support the use of valproic acid for the treatment of dementia-related aggression or agitation. Interestingly, there are experimental data both *in vitro* and *in vivo* which suggest a possible role for valproate in slowing the neuronal deterioration process resulting from Alzheimer’s pathology. Thus, there are studies ongoing to investigate the potential role that valproic acid may play in slowing disease progression and/or preserving cognitive function.

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Anesthesia and Critical Care Concerns/Other ConsiderationsValproic acid may be used in pharmacologic treatment of refractory status epilepticus (Limdi, 2005; Meierkord, 2006). Intravenous infusions are generally well tolerated (Limdi, 2006; Limdi, 2007).

Index Terms2-Propylpentanoic Acid; 2-Propylvaleric Acid; Dipropylacetic Acid; Divalproex Sodium; DPA; Valproate Semisodium; Valproate Sodium; Valproic Acid

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International Brand NamesAbsenor (FI, SE); Apilepsin (HR, PL); Convulex (DE, HU, LU, PL); Dapakan (PK); Depakene (AR, CR, DO, GT, HN, NI, PA, SV); Depakene-R (JP); Depakin (BG, IT, TR); Depakine (AE, AT, BE, BH, CH, CY, CZ, DK, EE, EG, ES, GR, HN, HU, IL, IQ, IR, JO, KW, LB, LU, LY, OM, PL, PT, QA, SA, SY, TH, YE); Depakine Chrono (BE, HN, LU, PT, TH, TW); Depakote (BB, BM, BR, BS, BZ, FR, GY, ID, JM, NL, SR, TT); Depakote ER (ID, KP, PH); Depakote Sprinkles (KP); Depalept (IL); Depalept Chrono (IL); Depamag (IT); Deprakine (FI, NO); Desorate (TH); Diproex ER (IN); Dipromal (PL); Epilex (TR); Epilim (AU, BF, BJ, CI, ET, GB, GH, GM, GN, HK, IE, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, PR, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Epilim Chrono (HK, MY); Episenta (GB, IE); Epival (AE, BH, CR, CY, DO, EG, GT, HN, IL, IQ, IR, JO, KP, KW, LB, LY, MX, NI, OM, PA, QA, SA, SV, SY, YE); Ergenyl (SE); Everiden (HU); Leptilan (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, PR, SC, SD, SL, SN, TN, TW, TZ, UG, ZA, ZM, ZW); Logical (AR); Logical Jarabe (AR); Orfiril (HK, HU, IL, PE, SE); Orfiril Retard (SG); Petilin (AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, PR, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW); Pragmaten (AR); Valcote (AR, CO, EC, PY, UY); Valpakine (CR, DO, GT, HN, NI, SV); Valparin (TH); Valporal (IL); Valprax (PE); Valpro (AU, HK); Vematina (MX); Vupral (PL)

Valrubicin

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Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Valstar® may be confused with valsartan

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(val ROO bi sin)

U.S. Brand NamesValstar® [DSC]

Canadian Brand NamesValstar®; Valtaxin®

Pharmacologic CategoryAntineoplastic Agent, Anthracycline

Use: Labeled IndicationsIntravesical therapy of BCG-refractory carcinoma *in situ* of the urinary bladder

Dosing: Adults**Urinary carcinoma *in situ*:** Intravesical: 800 mg once weekly for 6 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic ImpairmentNo adjustment necessary.

Administration: I.V.Intravesicular bladder lavage, usually in 75 mL of 0.9% sodium chloride injection. Retain in the bladder for 2 hours, then void. Due to the Cremophor® EL diluent, valrubicin should be administered through non-PVC tubing.

StorageStore unopened vials under refrigeration at 2°C to 8°C (36°F to 48°F). Stable for 12 hours when diluted in 0.9% sodium chloride.

ReconstitutionAllow vial to warm to room temperature without heating. Dilute 800 mg (20 mL) with 55 mL NS.

ContraindicationsHypersensitivity to anthracyclines, Cremophor® EL, or any component of the formulation; concurrent urinary tract infection or small bladder capacity (unable to tolerate a 75 mL instillation)

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Cremophor® EL hypersensitivity: Should be used cautiously (if at all) in patients having a history of hypersensitivity reactions to other medications prepared with Cremophor® EL.

- Red-tinged urine: May occur in first 24 hours after instillation.

Disease-related concerns:

- Bladder perforation: Do not administer if mucosal integrity of bladder has been compromised or bladder perforation is present.

- Irritable bladder symptoms: Use with caution in patients with severe irritable bladder symptoms; irritable bladder symptoms may occur during instillation and retention.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. All patients of reproductive age should use an effective method of contraception during the treatment period.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known whether valrubicin is secreted in human milk. Because many immunoglobulins are secreted in milk, and the potential for serious adverse reactions exists, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Adverse Reactions

>10%: Genitourinary: Frequency (61%), dysuria (56%), urgency (57%), bladder spasm (31%), hematuria (29%), bladder pain (28%), urinary incontinence (22%), cystitis (15%), urinary tract infection (15%)

1% to 10%:

Cardiovascular: Chest pain (2%), vasodilation (2%), peripheral edema (1%)

Central nervous system: Headache (4%), malaise (4%), dizziness (3%), fever (2%)

Dermatologic: Rash (3%)

Endocrine & metabolic: Hyperglycemia (1%)

Gastrointestinal: Abdominal pain (5%), nausea (5%), diarrhea (3%), vomiting (2%), flatulence (1%)

Genitourinary: Nocturia (7%), burning symptoms (5%), urinary retention (4%), urethral pain (3%), pelvic pain (1%), hematuria (microscopic) (3%)

Hematologic: Anemia (2%)

Neuromuscular & skeletal: Weakness (4%), back pain (3%), myalgia (1%)

Respiratory: Pneumonia (1%)

<1%: Tenesmus, pruritus, taste disturbance, skin irritation, urine flow decreased, urethritis

Drug Interactions

Bevacizumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk C: Monitor therapy*

Cardiac Glycosides: May diminish the cardiotoxic effect of Antineoplastic Agents (Anthracycline). Antineoplastic Agents (Anthracycline) may decrease the serum concentration of Cardiac Glycosides. The effects of liposomal formulations may be unique from those of the free drug, as liposomal formulation have unique drug disposition and toxicity profiles, and liposomes themselves may alter digoxin absorption/distribution. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Taxane Derivatives: May enhance the adverse/toxic effect of Antineoplastic Agents (Anthracycline). Taxane Derivatives may increase the serum concentration of Antineoplastic Agents (Anthracycline). Taxane Derivatives may also increase the formation of toxic anthracycline metabolites in heart tissue. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline). *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Monitoring ParametersCystoscopy, biopsy, and urine cytology every 3 months for recurrence or progression

Nursing: Physical Assessment/MonitoringThis medication is administered by a physician through a urinary bladder catheter, using aseptic technique. **Note:** Caution must be used to prevent exposure to this mediation. Assess patient response during and following instillation (genitourinary [frequency, urgency, incontinence or dysuria, bladder spasm or pain, hematuria, urinary tract infection], rash, nausea, vomiting, myalgia, hyperglycemia). Instruct patient on appropriate interventions to reduce side effects and adverse symptoms to report.

Monitoring: Lab TestsCystoscopy, biopsy, and urine cytology every 3 months for recurrence or progression

Patient EducationThis medication will be instilled into your bladder through a catheter to be retained for as long as possible. Your urine will be red tinged for the next 24 hours; report promptly if this continues for a longer period. May cause altered urination patterns (frequency, dysuria, or incontinence), some bladder pain, pain on urination, or pelvic pain; report if these persist. If you have diabetes, monitor glucose levels closely (may cause hyperglycemia). It is important that you maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause dizziness or fatigue (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea, vomiting, or taste disturbance (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report chest pain or palpitations; persistent dizziness; swelling of extremities; persistent nausea, vomiting, diarrhea, or abdominal pain; muscle weakness, pain, or tremors; unusual cough or respiratory difficulty; or other adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication and for 1 month following therapy; consult prescriber for appropriate barrier contraceptives. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Injection, solution [DSC]: 40 mg/mL (5 mL) [contains Cremophor® EL 50% (polyoxyethyleneglycol triricinoleate) and dehydrated alcohol 50%]

Generic AvailableNo

Mechanism of ActionBlocks function of DNA topoisomerase II; inhibits DNA synthesis, causes extensive chromosomal damage, and arrests cell development; unlike other anthracyclines, does not appear to intercalate DNA

Pharmacodynamics/Kinetics

Absorption: Well absorbed into bladder tissue, negligible systemic absorption. Trauma to mucosa may increase absorption, and perforation greatly increases absorption with significant systemic myelotoxicity.

Metabolism: Negligible after intravesical instillation and 2-hour retention

Excretion: Urine when expelled from urinary bladder (98.6% as intact drug; 0.4% as *N*-trifluoroacetyladriamycin)

Related Information

- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms*N*-trifluoroacetyladriamycin-14-valerate; AD3L

References

Greenberg RE, Bahnson RR, Wood D, et al, “Initial Report on Intravesical Administration of N-trifluoroacetyldoxorubicin-14-valerate (AD32) to Patients With Refractory Superficial Transitional Cell Carcinoma of the Urinary Bladder,” *Urology*, 1997, 49(3):471-5. [PubMed 9123721]

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Onrust SV and Lamb HM, “Valrubicin,” *Drugs Aging*, 1999, 15(1):69-75.[PubMed 10459733]

International Brand NamesValstar (CA, IL); Valtaxin (CA)

Valsartan and Hydrochlorothiazide

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English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Diovan® may be confused with Darvon®, Dioval®, Zyban®

Pronunciation(val SAR tan & hye droe klor oh THYE a zide)

U.S. Brand NamesDiovan HCT®

Canadian Brand NamesDiovan HCT®

Pharmacologic CategoryAngiotensin II Receptor Blocker; Diuretic, Thiazide

Use: Labeled IndicationsTreatment of hypertension

Dosing: Adults **Note:** Dose is individualized; combination product may be used as initial therapy or substituted for individual components in patients currently maintained on both agents separately or in patients not adequately controlled with monotherapy (using one of the agents or an agent within same antihypertensive class).

Hypertension: Oral:

Initial therapy: Valsartan 160 mg and hydrochlorothiazide 12.5 mg once daily; dose may be titrated after 1-2 weeks of therapy. Maximum recommended daily doses: Valsartan 320 mg; hydrochlorothiazide 25 mg.

Add-on/replacement therapy: Valsartan 80-160 mg and hydrochlorthiazide 12.5-25 mg once daily; dose may be titrated after 3-4 weeks of therapy. Maximum recommended daily dose: Valsartan 320 mg; hydrochlorothiazide 25 mg.

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

CL_{cr} >30 mL/minute: No adjustment needed

Cl_{cr} ≤30 mL/minute: Use of combination not recommended. Contraindicated in patients with anuria.

Dosing: Hepatic ImpairmentUse with caution; initiate at lower dose and titrate slowly.

Calculations

- Creatinine Clearance: Adults

Administration: OralAdminister with or without food.

Dietary ConsiderationsAvoid salt substitutes which contain potassium. May be taken with or without food.

StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture.

ContraindicationsHypersensitivity to valsartan, hydrochlorothiazide, sulfonamide-derived drugs, or any component of the formulation; anuria

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity
- Thiazide/Thiazide-Related Diuretic Allergy

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Electrolyte disturbances: Hyperkalemia may occur with angiotensin II receptor antagonists; risk factors include renal dysfunction, diabetes mellitus, and concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use cautiously, if at all, with these agents and monitor potassium closely. Thiazide diuretics may cause hypokalemia, hypochloremic alkalosis, hypomagnesemia, and hyponatremia.

- Photosensitivity: Photosensitization may occur.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

- Sulfa allergy: Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe. Discontinue if signs of hypersensitivity are noted.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.

- Diabetes: Use hydrochlorothiazide with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.

- Gout: In certain patients with a history of gout, a familial predisposition to gout, or chronic renal failure, gout can be precipitated by hydrochlorothiazide.

- Hepatic impairment: Use caution in patients with severe hepatic impairment; in cirrhosis, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy.

- Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported with thiazides.

- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.

- Renal artery stenosis: Use valsartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use valsartan with caution with pre-existing renal insufficiency, and severe renal impairment. Avoid hydrochlorothiazide in severe renal disease (ineffective); may precipitate azotemia; discontinue or consider withholding if renal impairment occurs. Contraindicated in patients with anuria.

- Systemic lupus erythematosus (SLE): Hydrochlorothiazide can cause SLE exacerbation or activation.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Pregnancy Risk FactorD
Pregnancy ConsiderationsMedications which act on the renin-angiotensin system are reported to have the following fetal/neonatal effects: Hypotension, neonatal skull hypoplasia, anuria, renal failure, and death; oligohydramnios is also reported. These effects are reported to occur with exposure during the 2nd and 3rd trimesters. Valsartan should be discontinued as soon as possible after pregnancy is detected. Hydrochlorothiazide crosses the placenta; adverse (but not teratogenic) effects have been reported in the fetus.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsExcretion of valsartan in breast milk is not known and use during nursing is not recommended; hydrochlorothiazide is excreted in breast milk
Adverse ReactionsPercentages reported with combination product; other reactions have been reported (see individual agents for additional information)

>10%: Renal: BUN increased (15%)

1% to 10%:

Cardiovascular: Hypotension (1%)

Central nervous system: Dizziness (6%; dose related)

Endocrine & metabolic: Hypokalemia (3%)

Renal: Creatinine increased (2%)

Respiratory: Nasopharyngitis (2%)

<1%, postmarketing, and/or case reports: Anaphylaxis, appetite increased, bronchospasm, constipation, dehydration, depression, dysuria, epistaxis, flushing, gout, hematocrit/hemoglobin decreased, hyperkalemia, libido decreased, orthostatic hypotension, photosensitivity, pruritus, syncope, transaminases increased

Rhabdomyolysis has been reported (rarely) with angiotensin-receptor antagonists.

Frequency not defined, but occurred at >0.2% incidence (limited to important or life-threatening): Arthralgia, chest pain, cough, diarrhea, dyspepsia, dyspnea, fatigue, infection, myalgia, palpitation, paresthesia, peripheral edema, pollakiuria, postural dizziness, rash, tachycardia, vomiting, weakness, xerostomia

Metabolism/Transport EffectsValsartan: **Inhibits** CYP2C9 (weak)
Drug Interactions

ACE Inhibitors: Thiazide Diuretics may enhance the hypotensive effect of ACE Inhibitors. Specifically, postural hypotension which can accompany ACE Inhibitor initiation. Thiazide Diuretics may enhance the nephrotoxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Allopurinol: Thiazide Diuretics may enhance the potential for allergic or hypersensitivity reactions to Allopurinol. Thiazide Diuretics may increase the serum concentration of Allopurinol. Specifically, Thiazide Diuretics may increase the concentration of Oxypurinolol, an active metabolite of Allopurinol. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Thiazide Diuretics. The diuretic response is likewise decreased. *Risk D: Consider therapy modification*

Calcitriol: Thiazide Diuretics may enhance the hypercalcemic effect of Calcitriol. *Risk C: Monitor therapy*

Calcium Salts: Thiazide Diuretics may decrease the excretion of Calcium Salts. Continued concomitant use can also result in metabolic alkalosis. *Risk C: Monitor therapy*

Corticosteroids (Orally Inhaled): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Corticosteroids (Systemic): May enhance the hypokalemic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Dofetilide: Thiazide Diuretics may enhance the QTc-prolonging effect of Dofetilide. Thiazide Diuretics may increase the serum concentration of Dofetilide. *Risk D: Consider therapy modification*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Thiazide Diuretics may decrease the excretion of Lithium. *Risk D: Consider therapy modification*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Thiazide Diuretics. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nursing: Physical Assessment/MonitoringSee individual agents.
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Diovan HCT® 80 mg/12.5 mg: Valsartan 80 mg and hydrochlorothiazide 12.5 mg

Diovan HCT® 160 mg/12.5 mg: Valsartan 160 mg and hydrochlorothiazide 12.5 mg

Diovan HCT® 160 mg/25 mg: Valsartan 160 mg and hydrochlorothiazide 25 mg

Diovan HCT® 320 mg/12.5 mg: Valsartan 320 mg and hydrochlorothiazide 12.5 mg

Diovan HCT® 320 mg/25 mg: Valsartan 320 mg and hydrochlorothiazide 25 mg

Generic AvailableNo
ManufacturerNovartis Pharmaceuticals Corp
Pricing: U.S. (www.drugstore.com)

Tablets (Diovan HCT)

80-12.5 mg (30): $73.43

160-12.5 mg (30): $77.51

160-25 mg (30): $91.79

320-12.5 mg (30): $95.87

320-25 mg (30): $117.29

Mechanism of ActionValsartan produces direct antagonism of the angiotensin II (AT2) receptors, unlike the ACE inhibitors. It displaces angiotensin II from the AT1 receptor and produces its blood pressure-lowering effects by antagonizing AT1-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic responses. This action results in more efficient blockade of the cardiovascular effects of angiotensin II and fewer side effects than the ACE inhibitors.

Hydrochlorothiazide inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions

Pharmacodynamics/KineticsSee individual agents.

Related Information

- Hydrochlorothiazide
- Valsartan

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine; barbiturates and carbamazepine may increase the metabolism of valsartan; may decrease lithium clearance resulting in an increase in serum lithium levels and potential lithium toxicity; monitor serum lithium levels

Cardiovascular Considerations

Congestive Heart Failure: Currently, the use of angiotensin II receptor blockers (ARBs) should not supersede angiotensin converting enzyme inhibitors (ACEIs) in the treatment of congestive heart failure. One may be considered, however, when an ACEI cannot be tolerated. Because they are angiotensin II blockers rather than inhibitors of ACE, ARBs do not cause increases in bradykinin levels. *ELITE II* (Pitt, 2000) compared losartan (50 mg/day) with captopril (150 mg/day) in a heart failure population (mean EF 31%). There were 280 deaths in the losartan group and 250 in the captopril group. Mortality was insignificantly higher for losartan (17.7% vs 16% for captopril). The secondary endpoint (sudden cardiac death or resuscitated cardiac arrest) favored captopril, but the improvement did not achieve statistical significance. The discontinuation rate for adverse events was significantly lower for losartan. In the doses used, losartan appears to be less effective or as effective as captopril.

CHARM-Alternative is a prospective, randomized trial (Granger, 2003) in ACE inhibitor-intolerant patients with CHF. Patients were randomized to candesartan (target dose: 32 mg/day; mean dose at 6 months: 23 mg/day) or placebo. Baseline characteristics included NYHA Class II or III (97% of patients), and mean LVEF 30%. Therapy included beta-blocker (55%), diuretic (86%), spironolactone (24%), and digitalis (46%). During a 33-month follow up, the combined primary endpoint (CV death or heart failure hospitalizations) was significantly reduced in the candesartan group mainly because of reduced hospitalization. Death due to cardiovascular disease was not significantly different. There were significantly more MIs (75) in the candesartan group than in the placebo group (48). Candesartan was discontinued because of hypotension, renal dysfunction, and hyperkalemia.

Congestive Heart Failure: Concomitant ACE-I Therapy: The *Val-HeFT study* (Cohn, 2001) randomized CHF patients maintained on standard therapy to valsartan (320 mg/day; mean dose 254 mg/day) or placebo. The primary outcome was mortality and a combined endpoint of morbidity and mortality (cardiac arrest, hospitalization for CHF, need for intravenous inotrope or vasodilator). Patients (5010 in number) with predominately NYHA class II or III heart failure (85% on diuretic; 67% on digoxin; 35% on beta-blocker; ~93% on ACEI; 5% on spironolactone) were randomized to valsartan or placebo. The mean duration of follow-up was 23 months. Overall mortality was similar in both groups. The incidence of combined endpoints was lower with valsartan than placebo (p=.009) primarily because of decreased heart failure hospitalizations in the valsartan group. In a post hoc analysis of the endpoints in subgroups defined by baseline treatments (ACEI or beta-blockers), valsartan had a positive effect on patients receiving neither or one of these drugs. A higher incidence of mortality was seen in patients receiving valsartan in combination with an ACEI and a beta-blocker.

CHARM-Added trial is a prospective, randomized trial (McMurray, 2003) evaluating the addition of candesartan therapy (target dose: 32 mg/day; mean dose at 6 months: 24 mg/day) to CHF patients maintained on an ACEI. Baseline characteristics: NYHA class II (24%), class III (73%), and mean LVEF 28%. Baseline therapy was similar to CHARM-Alternative except all patients were maintained on an ACEI and ~55% were on a beta-blocker. The median duration of follow-up was 41 months. The combined primary endpoint (CV death or heart failure hospitalizations) was significantly reduced in the candesartan group.

Hypertension: According to the 2003 JNC 7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Myocardial Infarction: The 2004 ACC/AHA STEMI guidelines suggest an angiotensin receptor blocker should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF <0.4. The *OPTIMAAL trial* evaluated whether losartan (50 mg/day) would be superior or noninferior to captopril (150 mg/day) in post-MI patients. They were randomized to one of two treatments and followed up for 2.7 years. There was no difference between the two treatment groups (499 deaths in losartan group; 447 deaths in the captopril-treated group). The VALIANT trial compared the effects of valsartan, captopril, and the combination in patients who had suffered a recent MI (0.5 to 10 days prior) complicated by left ventricular systolic dysfunction (Pfeffer, 2003). The primary endpoint was mortality from any cause. Mortality in the valsartan group and the valsartan-captopril group was similar to the captopril group alone. Valsartan was found to be noninferior to captopril in this patient population. Combining valsartan with captopril increased the rate of adverse events without improving survival. Hypotension and renal dysfunction were more common in the valsartan group. Cough, rash, and taste disturbances were more common in the captopril group.

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Index TermsHydrochlorothiazide and Valsartan

References

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Pitt B, Poole-Wilson PA, Segal R, et al, “Effect of Losartan Compared With Captopril on Mortality in Patients With Symptomatic Heart Failure: Randomised Trial - The Losartan Heart Failure Survival Study ELITE II,” *Lancet*, 2000, 355(9215):1582-7.[PubMed 10821361]

International Brand NamesCo-Diovan (BG, CH, CL, CZ, EE, GR, HK, ID, IL, MY, PH, PK, PT, SG, TH, TW); Co-Diovane (BE); CoDiovan (DE, GB, IE, KP, MX); Cotareg (FR, KP); Diovan Comp (DK, NO, SE); Diovan D (AR, PY, UY); Diovan HCT (BR, EC, HN, PE, VE); Nisisco (FR); Tareg D (CN); Valent-H (IN); Valsaprex-H (CO); Valtens H (GT)

Valsartan

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Valsartan may be confused with losartan, Valstar™

Diovan® may be confused with Darvon®, Dioval®, Zyban®

Pronunciation(val SAR tan)

U.S. Brand NamesDiovan®

Canadian Brand NamesDiovan®

Pharmacologic CategoryAngiotensin II Receptor Blocker

Use: Labeled IndicationsAlone or in combination with other antihypertensive agents in the treatment of essential hypertension; reduction of cardiovascular mortality in patients with left ventricular dysfunction postmyocardial infarction; treatment of heart failure (NYHA Class II-IV)

Dosing: Adults

Hypertension: Initial: 80 mg or 160 mg once daily (in patients who are not volume depleted); dose may be increased to achieve desired effect; maximum recommended dose: 320 mg/day

Heart failure: Initial: 40 mg twice daily; titrate dose to 80-160 mg twice daily, as tolerated; maximum daily dose: 320 mg

Left ventricular dysfunction after MI: Initial: 20 mg twice daily; titrate dose to target of 160 mg twice daily as tolerated; may initiate ≥12 hours following MI

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Hypertension:** Oral: Children 6-16 years: Initial: 1.3 mg/kg once daily (maximum: 40 mg/day); dose may be increased to achieve desired effect; doses >2.7 mg/kg (maximum: 160 mg) have not been studied.

Dosing: Renal Impairment

Children: Use is not recommended if Cl_{cr} <30 mL/minute.

Adults: No dosage adjustment necessary if Cl_{cr} >10 mL/minute.

Dialysis: Not significantly removed.

Dosing: Hepatic ImpairmentIn mild-to-moderate liver disease no adjustment is needed. Use caution in patients with liver disease. Patients with mild to moderate chronic disease have twice the exposure as healthy volunteers.

Administration: OralAdminister with or without food.

Dietary ConsiderationsAvoid salt substitutes which contain potassium. May be taken with or without food.

StorageStore at 25°C (77°F); excursions between 15°C to 30°C (59°F to 86°F) permitted. Protect from moisture.

Extemporaneously PreparedTo prepare valsartan suspension, add 80 mL of Ora-Plus® to an 8-ounce amber glass bottle containing eight (8) valsartan 80 mg tablets. Shake well ≥2 minutes. Allow the suspension to stand for a minimum of 1 hour then shake for 1 minute. Then add 80 mL of Ora-Sweet SF® to the bottle and shake for at least 10 seconds. Resulting 160 mL suspension will contain valsartan 4 mg/mL. Store for either up to 30 days at room temperature (below 30°C/86°F) or up to 75 days under refrigeration (2-8°C/35-46°F) in the glass bottle. Shake well before use.

Product information, December, 2007; Novartis Pharmaceuticals Corp.

Contraindications

U.S. labeling: There are no contraindications listed in manufacturer's labeling.

Canadian labeling: Hypersensitivity to valsartan or any component of the formulation

Allergy Considerations

- Angiotensin Receptor Antagonist Allergy/Hypersensitivity

Warnings/Precautions

Boxed warnings:

- Pregnancy: See “Special populations” below.

Concerns related to adverse effects:

- Hyperkalemia: May occur; risk factors include renal dysfunction, diabetes mellitus, concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salts. Use with caution with these agents; monitor potassium closely.

- Hypotension: During the initiation of therapy, hypotension may occur, particularly in patients with heart failure or post-MI patients.

- Renal function deterioration: May be associated with deterioration of renal function and/or increases in serum creatinine, particularly in patients with low renal blood flow (eg, renal artery stenosis, heart failure) whose glomerular filtration rate (GFR) is dependent on efferent arteriolar vasoconstriction by angiotensin II; deterioration may result in oliguria, acute renal failure, and progressive azotemia. Small increases in serum creatinine may occur following initiation; consider discontinuation only in patients with progressive and/or significant deterioration in renal function.

Disease-related concerns:

- Aortic/mitral stenosis: Use with caution in patients with significant aortic/mitral stenosis.

- Heart failure: Use caution when initiating in heart failure; may need to adjust dose, and/or concurrent diuretic therapy, because of valsartan-induced hypotension. Careful monitoring of BUN, serum creatinine, and potassium is necessary especially if preexisting renal disease exists.

- Hepatic impairment: Use caution in patients with significant hepatic impairment since clearance is significantly reduced.

- Hypovolemia: Avoid use or use a smaller dose in patients who are volume depleted; correct depletion first.

- Renal artery stenosis: Use valsartan with caution in patients with unstented unilateral/bilateral renal artery stenosis. When unstented bilateral renal artery stenosis is present, use is generally avoided due to the elevated risk of deterioration in renal function unless possible benefits outweigh risks.

- Renal impairment: Use with caution with pre-existing renal insufficiency and severe renal impairment.

Special populations:

- Pediatrics: Canadian labeling: Use is not approved in patients <18 years of age.

- Pregnancy: **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

Geriatric ConsiderationsNo dosage adjustment is necessary when initiating angiotensin II receptor antagonists in the elderly. In clinical studies, no differences between younger adults and elderly were demonstrated. Many elderly may be volume depleted due to diuretic use and/or blunted thirst reflex resulting in inadequate fluid intake.

Pregnancy Risk FactorD

Pregnancy ConsiderationsMedications which act on the renin-angiotensin system are reported to have the following fetal/neonatal effects: Hypotension, neonatal skull hypoplasia, anuria, renal failure, and death; oligohydramnios is also reported. These effects are reported to occur with exposure during the second and third trimesters. **[U.S. Boxed Warning]: Based on human data, drugs that act on the angiotensin system can cause injury and death to the developing fetus when used in the second and third trimesters. Angiotensin receptor blockers should be discontinued as soon as possible once pregnancy is detected.**

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsIt is not known if valsartan is found in breast milk; the manufacturer recommends discontinuing the drug or discontinuing nursing based on the importance of the drug to the mother.

Adverse Reactions

>10%:

Central nervous system: Dizziness (heart failure trials 17%)

Renal: BUN increased >50% (heart failure trials 17%)

1% to 10%:

Cardiovascular: Hypotension (heart failure trials 7%; MI trial 1%), postural hypotension (heart failure trials 2%), syncope (up to >1%)

Central nervous system: Dizziness (hypertension trial 2% to 8%), fatigue (heart failure trials 3%; hypertension trial 2%), postural dizziness (heart failure trials 2%), headache (heart failure trials >1%), vertigo (up to >1%)

Endocrine & metabolic: Serum potassium increased by >20% (4% to 10%), hyperkalemia (heart failure trials 2%)

Gastrointestinal: Diarrhea (heart failure trials 5%), abdominal pain (2%), nausea (heart failure trials >1%), upper abdominal pain (heart failure trials >1%)

Hematologic: Neutropenia (2%)

Neuromuscular & skeletal: Arthralgia (heart failure trials 3%), back pain (up to 3%)

Ocular: Blurred vision (heart failure trials >1%)

Renal: Creatinine doubled (MI trial 4%), creatinine increased >50% (heart failure trials 4%), renal dysfunction (up to >1%)

Respiratory: Cough (1% to 3%)

Miscellaneous: Viral infection (3%)

All indications: <1%, postmarketing, and/or case reports: Allergic reactions, alopecia, anaphylaxis, anemia, angioedema, anorexia, anxiety, chest pain, constipation, dyspepsia, dyspnea, flatulence, hematocrit/hemoglobin decreased, hepatitis, impotence, insomnia, liver function tests increased, microcytic anemia, muscle cramps, myalgia, palpitation, paresthesia, photosensitivity, pruritus, rash, rhabdomyolysis, somnolence, taste disorder, thrombocytopenia, vomiting, weakness, xerostomia

Metabolism/Transport Effects**Inhibits** CYP2C9 (weak)
Drug Interactions

ACE Inhibitors: Angiotensin II Receptor Blockers may enhance the adverse/toxic effect of ACE Inhibitors. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. Management: According to eltrombopag prescribing information, consideration of a preventative dose reduction may be warranted. *Risk D: Consider therapy modification*

Eplerenone: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Lithium: Angiotensin II Receptor Blockers may increase the serum concentration of Lithium. Management: Lithium dosage reductions will likely be needed following the addition of an angiotensin II receptor antagonist. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May diminish the therapeutic effect of Angiotensin II Receptor Blockers. The combination of these two agents may also significantly decrease glomerular filtration and renal function. *Risk C: Monitor therapy*

Potassium Salts: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Potassium-Sparing Diuretics: Angiotensin II Receptor Blockers may enhance the hyperkalemic effect of Potassium-Sparing Diuretics. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Trimethoprim: May enhance the hyperkalemic effect of Angiotensin II Receptor Blockers. *Risk C: Monitor therapy*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Food: Decreases rate and extent of absorption by 50% and 40%, respectively.

Herb/Nutraceutical: Avoid bayberry, blue cohosh, cayenne, ephedra, ginger, ginseng (American), kola, licorice (may worsen hypertension). Avoid black cohosh, California poppy, coleus, golden seal, hawthorn, mistletoe, periwinkle, quinine, shepherd's purse (may have increased antihypertensive effect).

Monitoring ParametersBaseline and periodic electrolyte panels, renal function, BP; in CHF, serum potassium during dose escalation and periodically thereafter
Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions with other pharmacological agents and herbal products patient may be taking (eg, concurrent use of potassium supplements, ACE inhibitors, potassium-sparing diuretics may increase risk of hyperkalemia). Assess results of laboratory tests at baseline and periodically during therapy. Assess therapeutic effectiveness (reduced hypertension) and adverse response on a regular basis during therapy (eg, changes in renal function, dizziness, bradycardia, cough, headache, nausea, hypotension, hyperkalemia). Teach patient appropriate use according to drug form and purpose of therapy, possible side effects/appropriate interventions, and adverse symptoms to report.
Monitoring: Lab TestsBaseline and periodic electrolyte panels, renal and liver function, urinalysis; in CHF, serum potassium during dose escalation and periodically thereafter
Patient EducationDo not take any new medication during therapy unless approved by prescriber (especially sleep remedies or antisleep products, cough or cold remedies, or weight-loss products). Take exactly as directed and do not discontinue without consulting prescriber. This drug does not eliminate need for diet or exercise regimen as recommended by prescriber. May cause dizziness or lightheadedness (use caution when driving or engaging in tasks that require alertness until response to drug is known); postural hypotension (use caution when rising from lying or sitting position or climbing stairs); or diarrhea (boiled milk, buttermilk, or yogurt may help). Report changes in urinary pattern; swelling of extremities; unusual back ache; chest pain or palpitations; unrelenting headache; muscle weakness or pain; unusual cough; or other persistent adverse reactions. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. This drug should not be used in pregnancy. Consult prescriber for appropriate contraceptive measures if necessary or if you suspect you might be pregnant. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Diovan®: 40 mg, 80 mg, 160 mg, 320 mg

Generic AvailableNo
ManufacturerNovartis Pharmaceuticals Corp
Pricing: U.S. (www.drugstore.com)

Tablets (Diovan)

40 mg (30): $59.15

80 mg (30): $73.43

160 mg (30): $74.45

320 mg (30): $113.21

Mechanism of ActionValsartan produces direct antagonism of the angiotensin II (AT2) receptors, unlike the ACE inhibitors. It displaces angiotensin II from the AT1 receptor and produces its blood pressure-lowering effects by antagonizing AT1-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic responses. This action results in more efficient blockade of the cardiovascular effects of angiotensin II and fewer side effects than the ACE inhibitors.

Pharmacodynamics/Kinetics

Onset of antihypertensive effect: 2 weeks (maximal: 4 weeks)

Distribution: V_d: 17 L (adults)

Protein binding: 95%, primarily albumin

Metabolism: To inactive metabolite

Bioavailability: Tablet: 25% (range 10% to 35%); suspension: ~40% (~1.6 times more than tablet)

Half-life elimination: ~6 hours

Time to peak, serum: 2-4 hours

Excretion: Feces (83%) and urine (13%) as unchanged drug

Related Information

- Angiotensin Agents
- Heart Failure (Systolic)

Pharmacotherapy PearlsValsartan may have an advantage over losartan due to minimal metabolism requirements and consequent use in mild-to-moderate hepatic impairment.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness or drowsiness

Mental Health: Effects on Psychiatric TreatmentMay rarely cause neutropenia; use caution with clozapine and carbamazepine; barbiturates and carbamazepine may increase the metabolism of valsartan

Cardiovascular Considerations

Congestive Heart Failure: Currently, the use of angiotensin II receptor blockers (ARBs) should not supersede angiotensin converting enzyme inhibitors (ACEIs) in the treatment of congestive heart failure. One may be considered, however, when an ACEI cannot be tolerated. Because they are angiotensin II blockers rather than inhibitors of ACE, ARBs do not cause increases in bradykinin levels. *ELITE II* (Pitt, 2000) compared losartan (50 mg/day) with captopril (150 mg/day) in a heart failure population (mean EF 31%). There were 280 deaths in the losartan group and 250 in the captopril group. Mortality was insignificantly higher for losartan (17.7% vs 16% for captopril). The secondary endpoint (sudden cardiac death or resuscitated cardiac arrest) favored captopril, but the improvement did not achieve statistical significance. The discontinuation rate for adverse events was significantly lower for losartan. In the doses used, losartan appears to be less effective or as effective as captopril.

CHARM-Alternative is a prospective, randomized trial (Granger, 2003) in ACE inhibitor-intolerant patients with CHF. Patients were randomized to candesartan (target dose: 32 mg/day; mean dose at 6 months: 23 mg/day) or placebo. Baseline characteristics included NYHA Class II or III (97% of patients), and mean LVEF 30%. Therapy included beta-blocker (55%), diuretic (86%), spironolactone (24%), and digitalis (46%). During a 33-month follow up, the combined primary endpoint (CV death or heart failure hospitalizations) was significantly reduced in the candesartan group mainly because of reduced hospitalization. Death due to cardiovascular disease was not significantly different. There were significantly more MIs (75) in the candesartan group than in the placebo group (48). Candesartan was discontinued because of hypotension, renal dysfunction, and hyperkalemia.

Congestive Heart Failure: Concomitant ACE-I Therapy: The *Val-HeFT study* (Cohn, 2001) randomized CHF patients maintained on standard therapy to valsartan (320 mg/day; mean dose 254 mg/day) or placebo. The primary outcome was mortality and a combined endpoint of morbidity and mortality (cardiac arrest, hospitalization for CHF, need for intravenous inotrope or vasodilator). Patients (5010 in number) with predominately NYHA class II or III heart failure (85% on diuretic; 67% on digoxin; 35% on beta-blocker; ~93% on ACEI; 5% on spironolactone) were randomized to valsartan or placebo. The mean duration of follow-up was 23 months. Overall mortality was similar in both groups. The incidence of combined endpoints was lower with valsartan than placebo (p=.009) primarily because of decreased heart failure hospitalizations in the valsartan group. In a post hoc analysis of the endpoints in subgroups defined by baseline treatments (ACEI or beta-blockers), valsartan had a positive effect on patients receiving neither or one of these drugs. A higher incidence of mortality was seen in patients receiving valsartan in combination with an ACEI and a beta-blocker.

CHARM-Added trial is a prospective, randomized trial (McMurray, 2003) evaluating the addition of candesartan therapy (target dose: 32 mg/day; mean dose at 6 months: 24 mg/day) to CHF patients maintained on an ACEI. Baseline characteristics: NYHA class II (24%), class III (73%), and mean LVEF 28%. Baseline therapy was similar to CHARM-Alternative except all patients were maintained on an ACEI and ~55% were on a beta-blocker. The median duration of follow-up was 41 months. The combined primary endpoint (CV death or heart failure hospitalizations) was significantly reduced in the candesartan group.

Hypertension: According to the 2003 JNC 7 guidelines for the treatment of hypertension, most patients with hypertension will require treatment with at least 2 antihypertensives. First-line therapy for hypertension is a diuretic (eg, hydrochlorothiazide or chlorthalidone). When a diuretic cannot be used or when a compelling indication exists for another drug, other types of antihypertensives may be used (eg, ACEIs, ARBs, beta-blockers, CCBs). Angiotensin II receptor blockers are among the multiple choices of agents that have shown benefit in a number of different patient subtypes. Compelling indications for an ARB include patients with heart failure, diabetes, or chronic kidney disease. The *LIFE trial* (Dahlof, 2002) confirmed that ARB (losartan 50-100 mg daily) was better tolerated than a beta-blocker (atenolol), and resulted in significant reduction in mortality, angina, or HF hospitalization (primary endpoint). Stroke and new-onset diabetes were significantly reduced in the losartan treatment group.

Treatment should be targeted to a goal blood pressure of <140/90 mm Hg. If diabetes or renal disease coexists, the blood pressure goal should be <130/80 mm Hg.

Myocardial Infarction: The 2004 ACC/AHA STEMI guidelines suggest an angiotensin receptor blocker should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF <0.4. The *OPTIMAAL trial* evaluated whether losartan (50 mg/day) would be superior or noninferior to captopril (150 mg/day) in post-MI patients. They were randomized to one of two treatments and followed up for 2.7 years. There was no difference between the two treatment groups (499 deaths in losartan group; 447 deaths in the captopril-treated group). The VALIANT trial compared the effects of valsartan, captopril, and the combination in patients who had suffered a recent MI (0.5 to 10 days prior) complicated by left ventricular systolic dysfunction (Pfeffer, 2003). The primary endpoint was mortality from any cause. Mortality in the valsartan group and the valsartan-captopril group was similar to the captopril group alone. Valsartan was found to be noninferior to captopril in this patient population. Combining valsartan with captopril increased the rate of adverse events without improving survival. Hypotension and renal dysfunction were more common in the valsartan group. Cough, rash, and taste disturbances were more common in the captopril group.

Cautions: Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema. Because of the lack of effect on the response to bradykinin, angiotensin receptor blockers are less likely to be associated with nonrenin-angiotensin effects such as cough and angioedema. The angiotensin II antagonists do not cause increases in levels of bradykinin as the ACEIs do.

Anesthesia and Critical Care Concerns/Other ConsiderationsThe angiotensin II receptor antagonists appear to have similar indications as the ACE inhibitors. In heart failure, the angiotensin II antagonists are especially useful in providing an alternative therapy in those patients who have intractable cough in response to ACE inhibitor therapy. Candesartan has been studied as an alternative therapy in chronic heart failure patients who cannot tolerate an ACE-I (CHARM-Alternative) and as an added therapy in heart failure patients who are maintained on an ACE-I (CHARM-Added). In both studies, the combined endpoint of cardiovascular death or heart failure hospitalizations was significantly improved over the placebo-treated group. Similar to ACE inhibitors, pre-existing volume depletion caused by diuretic therapy may potentiate hypotension in response to angiotensin II antagonists. Concomitant NSAID therapy may attenuate blood pressure control; use of NSAIDs should be avoided or limited, with monitoring of blood pressure control. In the setting of heart failure, NSAID use may be associated with an increased risk for fluid accumulation and edema.

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International Brand NamesDalzad (HN); Diovan (AE, AR, AT, BB, BD, BG, BH, BM, BO, BR, BS, BZ, CH, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EE, EG, ES, FI, GB, GR, GT, GY, HK, HN, ID, IE, IL, IN, IQ, IR, JM, JO, JP, KP, KW, LB, LY, MX, MY, NI, NL, NO, OM, PA, PE, PH, PK, PL, PR, PT, PY, QA, SA, SE, SG, SR, SV, SY, TH, TT, TW, UY, VE, YE); Diovane (BG); Disartan (TW); Nisis (FR); Provas (DE); Tareg (CN, FR, IT, KP); Valtensin (BG); Varcor (CO)

Vancomycin

Lexi-Drugs Online

English English

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Medication Safety Issues

Sound-alike/look-alike issues:

I.V. vancomycin may be confused with Invanz®

Vancomycin may be confused with clindamycin, gentamicin, tobramycin, valacyclovir, vecuronium, Vibramycin®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (intrathecal administration) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(van koe MYE sin)
U.S. Brand NamesVancocin®
Canadian Brand NamesVancocin®
Pharmacologic CategoryAntibiotic, Miscellaneous
Use: Labeled IndicationsTreatment of patients with infections caused by staphylococcal species and streptococcal species; used orally for staphylococcal enterocolitis or for antibiotic-associated pseudomembranous colitis produced by *C. difficile*
Use: Unlabeled/InvestigationalBacterial endophthalmitis
Dosing: Adults

Usual dosage range:

I.V.: 2-3 g/day (20-45 mg/kg/day) in divided doses every 6-12 hours; maximum 3 g/day; **Note:** Dose requires adjustment in renal impairment

Oral: 500-1000 mg/day in divided doses every 6 hours

Indication-specific dosing:

Catheter-related infections: Antibiotic lock technique: 2 mg/mL in SWFI/NS or D_5W; instill 3-5 mL into catheter port as a flush solution instead of heparin lock (**Note:** Do not mix with any other solutions.)

Colitis (*C. difficile*), enterocolitis*(S. aureus)*: Oral: 500-2000 mg/day in 3-4 divided doses for 7-10 days (usual dose: 125-250 mg every 6 hours)

Endophthalmitis (unlabeled use): Intravitreal: Usual dose: 1 mg/0.1 mL NS instilled into vitreum; may repeat administration if necessary in 3-4 days, usually in combination with ceftazidime or an aminoglycoside

Note: Some clinicians have recommended using a lower dose of 0.2 mg/0.1 mL, based on concerns for retinotoxicity.

Hospital-acquired pneumonia (HAP): I.V.: 15 mg/kg/dose every 12 hours (American Thoracic Society [ATS] 2005 guidelines)

Meningitis *(Pneumococcus* or*Staphylococcus)*:

I.V.: 30-45 mg/kg/day in divided doses every 8-12 hours **or** 500-750 mg every 6 hours (with third-generation cephalosporin for PCN-resistant *Streptococcus pneumoniae*); maximum dose: 2-3 g/day

Intrathecal: Up to 20 mg/day

Prophylaxis against infective endocarditis: I.V.:

Dental, oral, or upper respiratory tract surgery: 1 g 1 hour before surgery. **Note:** AHA guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur.

GI/GU procedure: 1 g plus 1.5 mg/kg gentamicin 1 hour prior to surgery. **Note:** As of April 2007, routine prophylaxis no longer recommended by the AHA.

Susceptible gram-positive infections: I.V.: 15-20 mg/kg/dose (usual: 750-1500 mg) every 12 hours

Dosing: ElderlyRefer to adult dosing. Elderly patients may require greater dosage reduction than expected. Best to individualize therapy; dose (mg/kg/24 hours) = (0.227 x Cl_{cr}) + 5.67.
Dosing: Pediatric

Usual dosage range: Infants >1 month and Children: I.V.: 10-15 mg/kg every 6 hours

Indication-specific dosing: Infants >1 month and Children:

Colitis (*C. difficile*), enterocolitis*(S. aureus)*: Oral: 40 mg/kg/day in 3-4 divided doses added to fluids for 7-10 days (maximum: 2000 mg/day)

Meningitis/CNS infection:

I.V.: 15 mg/kg every 6 hours

Intrathecal: 5-20 mg/day

Prophylaxis against infective endocarditis: I.V.:

Dental, oral, or upper respiratory tract surgery: 20 mg/kg 1 hour prior to the procedure. **Note:** American Heart Association (AHA) guidelines now recommend prophylaxis only in patients undergoing invasive procedures and in whom underlying cardiac conditions may predispose to a higher risk of adverse outcomes should infection occur.

GI/GU procedure: 20 mg/kg plus gentamicin 2 mg/kg 1 hour prior to surgery. **Note:** As of April 2007, routine prophylaxis no longer recommended by the AHA.

Susceptible gram-positive infections: I.V.: 10 mg/kg every 6 hours

Dosing: Renal ImpairmentVancomycin levels should be monitored in patients with any renal impairment:

Cl_{cr} >50 mL/minute: Start with 15-20 mg/kg/dose (usual: 750-1500 mg) every 12 hours

Cl_{cr} 20-49 mL/minute: Start with 15-20 mg/kg/dose (usual: 750-1500 mg) every 24 hours

Cl_{cr} <20 mL/minute: Will need longer intervals; determine by serum concentration monitoring

Dialysis: Variable, depending on method; poorly dialyzable by conventional hemodialysis (0% to 5%). Use of high-flux membranes and continuous renal replacement therapy (CRRT) increases vancomycin clearance, and generally requires replacement dosing.

Hemodialysis (HD): Following loading dose of 15-20 mg/kg, give 500 mg to 1 g after each dialysis session, depending on factors such as HD membrane type and flow rate; monitor levels closely.

Continuous ambulatory peritoneal dialysis (CAPD):

Administration via CAPD fluid: 15-30 mg/L (15-30 mcg/mL) of CAPD fluid

Systemic: 1 g loading dose, followed by 500 mg to 1 g every 48-72 hours with close monitoring of levels

Continuous renal replacement therapy (CRRT): Removal of vancomycin is highly dependent on the method of replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of levels in relation to target trough. The following are general recommendations only (based on Trotman, et al, 2005), and require consideration of the aforementioned parameters.

CVVH: Following loading dose of 15-20 mg/kg, give 1 g every 48 hours

CVVHD or CVVHDF: Following loading dose of 15-20 mg/kg, give 1 g every 24 hours

Trotman RL, Williamson JC, Shoemaker DM, et al, "Antibiotic Dosing in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy," *Clin Infect Dis*, 2005, 41:1159-66.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.M.Do not administer I.M.

Administration: I.V.Administer vancomycin by I.V. intermittent infusion over at least 60 minutes (recommended rate of ≥30 minutes for every 500 mg administered) at a final concentration not to exceed 5 mg/mL.

Red man syndrome may occur if the infusion is too rapid. It is not an allergic reaction, but may be characterized by hypotension and/or a maculopapular rash appearing on the face, neck, trunk, and/or upper extremities. If this should occur, slow the infusion rate to over $1^{1}/_{2}$ to 2 hours and increase the dilution volume. Reactions are often treated with antihistamines and steroids.

Extravasation treatment: Monitor I.V. site closely; extravasation will cause serious injury with possible necrosis and tissue sloughing. Rotate infusion site frequently.

Administration: I.V. Detail
pH: 3.9 (in distilled water or sodium chloride 0.9%); 2.5-4.5 (5% solution in water)

Administration: OralMay be administered with food. If patient cannot swallow capsules, the powder for injection may be reconstituted and diluted for oral administration.

Administration: OtherVancomycin is available as a powder for injection and may be diluted to 1-5 mg/mL concentration in preservative-free 0.9% sodium chloride for administration into the CSF
May be administered by intravitreal injection (unlabeled use).

Dietary ConsiderationsMay be taken with food.

StorageReconstituted 500 mg and 1 g vials are stable for at either room temperature or under refrigeration for 14 days. **Note:** Vials contain no bacteriostatic agent. Solutions diluted for administration in either D_5W or NS are stable under refrigeration for 14 days or at room temperature for 7 days.

ReconstitutionReconstitute vials with 20 mL of SWFI for each 1 g of vancomycin (10 mL/500 mg vial; 20 mL/1 g vial; 100 mL/5 g vial; 200 mL/10 g vial). The reconstituted solution must be further diluted with at least 100 mL of a compatible diluent per 500 mg of vancomycin prior to parenteral administration.

Intrathecal: Vancomycin is available as a powder for injection and may be diluted to 1-5 mg/mL concentration in preservative free 0.9% sodium chloride for administration into the CSF.

CompatibilityStable in dextran 6% in NS, D_5NS, D_5W, $D_{10}W$, LR, NS; **variable stability (consult detailed reference)** in peritoneal dialysis solutions, TPN.

Y-site administration: Compatible: Acyclovir, aldesleukin, allopurinol, amifostine, amiodarone, amsacrine, anidulafungin, atracurium, cisatracurium, clarithromycin, cyclophosphamide, dexmedetomidine, diltiazem, docetaxel, doxapram, doxorubicin liposome, enalaprilat, esmolol, etoposide phosphate, fenoldopam, filgrastim, fluconazole, fludarabine, gallium nitrate, gemcitabine, granisetron, hetastarch, hydromorphone, insulin (regular), labetalol, levofloxacin, linezolid, lorazepam, magnesium sulfate, melphalan, meperidine, meropenem, midazolam, milrinone, morphine, nicardipine, ondansetron, paclitaxel, pancuronium, pemetrexed, perphenazine, remifentanil, sodium bicarbonate, tacrolimus, teniposide, theophylline, thiotepa, tigecycline, tolazoline, vecuronium, vinorelbine, zidovudine. **Incompatible:** Albumin, amphotericin B cholesteryl sulfate complex, bivalirudin, drotrecogin alfa, idarubicin, omeprazole. **Variable (consult detailed reference):** Ampicillin, ampicillin/sulbactam, aztreonam, cefazolin, cefepime, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, foscarnet, heparin, methotrexate, nafcillin, piperacillin, piperacillin/tazobactam, propofol, sargramostim, ticarcillin/clavulanate, TPN, warfarin.

Compatibility in syringe: Compatible: Caffeine citrate, pantoprazole. **Incompatible:** Dimenhydrinate, heparin.

Compatibility when admixed: Compatible: Amikacin, atracurium, calcium gluconate, cefepime, cimetidine, corticotropin, dimenhydrinate, famotidine, fusidate sodium, hydrocortisone sodium succinate, meropenem, ofloxacin, potassium chloride, ranitidine, verapamil, vitamin B complex with C. **Incompatible:** Amobarbital, chloramphenicol, chlorothiazide, dexamethasone sodium phosphate, penicillin G potassium, pentobarbital, phenobarbital. **Variable (consult detailed reference):** Aminophylline, aztreonam, heparin, sodium bicarbonate.

ContraindicationsHypersensitivity to vancomycin or any component of the formulation; avoid in patients with previous severe hearing loss

Allergy Considerations

- Glycopeptide Antibiotic Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Nephrotoxicity: May cause nephrotoxicity; usual risk factors include pre-existing renal impairment, concomitant nephrotoxic medications, advanced age, and dehydration. Discontinue treatment if signs of nephrotoxicity occur; renal damage is usually reversible.

- Neurotoxicity: May cause neurotoxicity; usual risk factors include pre-existing renal impairment, concomitant neuro-/nephrotoxic medications, advanced age, and dehydration. Ototoxicity is proportional to the amount of drug given and the duration of treatment. Tinnitus or vertigo may be indications of vestibular injury and impending bilateral irreversible damage. Discontinue treatment if signs of ototoxicity occur.

- Neutropenia: Prolonged therapy (>1 week) or total doses exceeding 25 g may increase the risk of neutropenia; prompt reversal of neutropenia is expected after discontinuation of therapy.

- Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

Disease-related concerns:

- Renal impairment: Use with caution in patients with renal impairment or those receiving other nephrotoxic or ototoxic drugs; dosage modification required (especially elderly).

Other warnings/precautions:

- Appropriate use: Oral vancomycin is only indicated for the treatment of pseudomembranous colitis due to *C. difficile* and enterocolitis due to *S. aureus* and is not effective for systemic infections; parenteral vancomycin is not effective for the treatment of colitis due to *C. difficile* and enterocolitis due to *S. aureus*.

- Infusion reactions: Rapid I.V. administration may result in hypotension, flushing, erythema, urticaria, and/or pruritus; rate of infusion should be ≥60 minutes.

Geriatric ConsiderationsAs a result of age-related changes in renal function and volume of distribution, accumulation and toxicity are a risk in the elderly. Careful monitoring and dosing adjustment is necessary.

Pregnancy Risk FactorB (oral); C (injection)

Pregnancy ConsiderationsAdverse effects have not been observed in animal studies and there are no controlled studies in pregnant women; however, oral vancomycin is not systemically absorbed. Therefore, I.V. vancomycin has been classified pregnancy category C and oral vancomycin has been classified pregnancy category B. Vancomycin crosses the placenta. *In vivo* studies and human case reports have documented placental transfer of vancomycin in the second and third trimesters of pregnancy resulting in therapeutic fetal concentrations. Vancomycin has not caused adverse fetal effects, including hearing loss or nephrotoxicity, when administered during pregnancy. A case report has been published of a vancomycin dose rapidly administered over 3 minutes leading to maternal hypotension and fetal bradycardia.

The pharmacokinetics of vancomycin may be altered during pregnancy and pregnant patients may need a higher dose of vancomycin. Maternal half-life is unchanged, but the volume of distribution and the total plasma clearance are increased. Individualization of therapy through serum concentration monitoring may be warranted. Vancomycin is recommended for use in pregnant women for prevention of early-onset group B streptococcal (GBS) disease in newborns.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsSmall amounts of vancomycin are excreted in human milk and use during breast-feeding is not recommended by the manufacturer. If given orally to the mother, the minimal systemic absorption of the dose would limit the amount available to pass into the milk. If given intravenously, the small amount that distributes to the milk would not be expected to cause systemic toxicity due to the lack of GI absorption. Nondose-related effects could include modification of bowel flora.

Pregnancy & Lactation, In-Depth

- Vancomycin in Pregnancy & Lactation

Adverse Reactions

Oral:

>10%: Gastrointestinal: Bitter taste, nausea, vomiting

1% to 10%:

Central nervous system: Chills, drug fever

Hematologic: Eosinophilia

<1%: Interstitial nephritis, ototoxicity, renal failure, thrombocytopenia, vasculitis

Parenteral:

>10%:

Cardiovascular: Hypotension accompanied by flushing

Dermatologic: Erythematous rash on face and upper body (red neck or red man syndrome - infusion rate related)

1% to 10%:

Central nervous system: Chills, drug fever

Dermatologic: Rash

Hematologic: Eosinophilia, reversible neutropenia

<1%: Ototoxicity (especially with large doses), thrombocytopenia, renal failure (especially with renal dysfunction or pre-existing hearing loss), Stevens-Johnson syndrome, vasculitis

Oncology: VesicantNo

Drug Interactions

Aminoglycosides: Vancomycin may enhance the nephrotoxic effect of Aminoglycosides. *Risk C: Monitor therapy*

Colistimethate: Vancomycin may enhance the nephrotoxic effect of Colistimethate. *Risk D: Consider therapy modification*

Gallium Nitrate: Vancomycin may enhance the nephrotoxic effect of Gallium Nitrate. *Risk X: Avoid combination*

Neuromuscular-Blocking Agents: Vancomycin may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May decrease the excretion of Vancomycin. *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. *Risk D: Consider therapy modification*

Monitoring ParametersPeriodic renal function tests, urinalysis, serum vancomycin concentrations, WBC, audiogram

Reference Range

Timing of serum samples: Draw peak 1 hour after 1-hour infusion has completed; draw trough just before next dose

Therapeutic levels: Peak: 25-40 mcg/mL; Trough: 5-12 mcg/mL

Toxic: >80 mcg/mL (SI: >54 µmol/L)

The ATS guidelines recommend trough levels of 15-20 mcg/mL for hospital-acquired pneumonia. The Infectious Disease Society of America (ISDA) meningitis guidelines recommend trough levels of 15-20 mcg/mL.

Nursing: Physical Assessment/MonitoringAssess results of culture and sensitivity tests and patient’s allergy history prior to first dose. Use caution with renal impairment or previous hearing loss. Assess potential for interactions with other pharmacological agents patient may be taking (eg, concurrent use with anything that is ototoxic or nephrotoxic increases risk of toxicity). See Administration for infusion specifics (premedication with antihistamines may prevent or minimize "red man" reaction). Infusion site must be monitored closely to prevent extravasation. Assess results of laboratory tests, therapeutic effectiveness (resolution of infection), and adverse response (eg, hypotension, rash, neutropenia, nausea, vomiting, auditory changes) on a regular basis during therapy. Teach patient appropriate use (oral), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsPerform culture and sensitivity studies prior to first dose. Periodic renal function, urinalysis, serum vancomycin concentrations, WBC, audiogram with prolonged use. Obtain drug levels after the third dose unless otherwise directed. Peaks are drawn 1 hour after the completion of a 1- to 2-hour infusion. Troughs are obtained just before the next dose.

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy without consulting prescriber. If administered by infusion, report immediately any chills; pain, swelling, or redness at infusion site; or respiratory difficulty. Oral medication should be taken as directed. Take all of prescribed medication even if feeling better. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. May cause nausea, vomiting, or GI upset (small, frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report rash or hives; chills or fever; persistent GI disturbances; opportunistic infection (sore throat, chills, fever, burning, itching on urination, vaginal discharge, white plaques in mouth); respiratory difficulty; any change in urine output; chest pain or palpitations; changes in hearing or feeling of fullness in ears; other persistent adverse effects or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule (Vancocin®): 125 mg, 250 mg

Infusion [premixed in iso-osmotic dextrose] (Vancocin®): 500 mg (100 mL); 1 g (200 mL)

Injection, powder for reconstitution: 500 mg, 1 g, 5 g, 10 g

Generic AvailableYes: Injection

Pricing: U.S. (www.drugstore.com)

Capsules (Vancocin HCl)

125 mg (20): $221.72

250 mg (20): $638.61

Mechanism of ActionInhibits bacterial cell wall synthesis by blocking glycopeptide polymerization through binding tightly to D-alanyl-D-alanine portion of cell wall precursor

Pharmacodynamics/Kinetics

Absorption: Oral: Poor; I.M.: Erratic; Intraperitoneal: ~38%

Distribution: Widely in body tissue and fluids, except for CSF

Relative diffusion from blood into CSF: Good only with inflammation (exceeds usual MICs)

CSF:blood level ratio: Normal meninges: Nil; Inflamed meninges: 20% to 30%

Protein binding: 10% to 50%

Half-life elimination: Biphasic: Terminal:

Newborns: 6-10 hours

Infants and Children 3 months to 4 years: 4 hours

Children >3 years: 2.2-3 hours

Adults: 5-11 hours; significantly prolonged with renal impairment

End-stage renal disease: 200-250 hours

Time to peak, serum: I.V.: 45-65 minutes

Excretion: I.V.: Urine (80% to 90% as unchanged drug); Oral: Primarily feces

Related Information

- Antibiotic Treatment of Adults With Infective Endocarditis
- Antimicrobial Drugs of Choice
- Community-Acquired Pneumonia in Adults
- Desensitization Protocols
- Neutropenic Fever Guidelines
- Prevention of Infective Endocarditis
- Recommendations for Preventing the Spread of Vancomycin Resistance

Pharmacotherapy PearlsBecause of its long half-life, vancomycin should be dosed on an every 12-hour basis. Monitoring of peak and trough serum levels is advisable. “Red man syndrome”, characterized by skin rash and hypotension, is not an allergic reaction but rather is associated with too rapid infusion of the drug. To alleviate or prevent the reaction, infuse vancomycin at a rate of ≥30 minutes for each 500 mg of drug being administered (eg, 1 g over ≥60 minutes); 1.5 g over ≥90 minutes.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Bitter taste. “Red man syndrome”, characterized by skin rash and hypotension, is not an allergic reaction but rather is associated with too rapid infusion of the drug. To alleviate or prevent the reaction, infuse vancomycin at a rate of ≥30 minutes for each 500 mg of drug being administered (eg, 1 g over ≥60 minutes); 1.5 g over ≥90 minutes.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: "Red man syndrome" (characterized by skin rash and hypotension) is not an allergic reaction, but rather is associated with infusion administered too rapidly. To alleviate or prevent the reaction, infuse vancomycin at a rate of ≥30 minutes for each 500 mg of drug being administered (eg, 1 g over ≥60 minutes; 1.5 g over ≥90 minutes). CVVHD clears vancomycin from the circulation while conventional hemodialysis does not.

Limitations which may contribute to clinical failure include poor lung penetration, slow bactericidal activity against *S. aureus*, limited CNS penetration, high-level resistance to enterococci and *S. aureus*, and limited activity against bacteria that coat prosthetic devices.

Index TermsVancomycin Hydrochloride

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International Brand NamesAmplobac (BR); Diatracin (ES); Edicin (EE, PL, TH); Icoplax (AR); Liocovan (KP); Vagran (VE); Vancep (ID); Vancin (PH); Vancin-S (TH); Vanco (DE); Vanco-Teva (IL); Vancocid (BR); Vancocin (AT, PL); Vancocin CP (AU, BG, CL, CZ, HN, IN, MX, MY, PK, TH, TW); Vancocin HCl (AR, BE, BF, BJ, CH, CI, DK, ET, FI, GB, GH, GM, GN, HK, KE, LR, MA, ML, MR, MU, MW, NE, NG, NZ, PH, SC, SD, SE, SL, SN, TN, TW, TZ, UG, ZA, ZM, ZW); Vancocin HCl Pulvules (AU); Vancocina (IT); Vancocina CP (CN); Vancogen (TH); Vancoled (KP, MY, PL, TW); Vancomax (PY); Vancomicina (DO, GT, HN, PA); Vancomycin Hydrochloride (PL); Vancomycin-MIP (PL); Vancotex (MY); Vanmixan (PL); Vanosyn (PH); Varedet (UY); Voncon (GR)

Vardenafil

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Vardenafil may be confused with sildenafil, tadalafil

Levitra® may be confused with Kaletra®, Lexiva®

Pronunciation(var DEN a fil)

U.S. Brand NamesLevitra®

Canadian Brand NamesLevitra®

Pharmacologic CategoryPhosphodiesterase-5 Enzyme Inhibitor

Use: Labeled IndicationsTreatment of erectile dysfunction (ED)

Dosing: Adults

Erectile dysfunction: Oral: 10 mg 60 minutes prior to sexual activity; dosing range: 5-20 mg; to be given as one single dose and not given more than once daily

Dosing adjustment with concomitant medications:

Alpha-blocker (dose should be stable at time of vardenafil initiation): Initial vardenafil dose: 5 mg/24 hours; if an alpha-blocker is added to vardenafil therapy, it should be initiated at the smallest possible dose, and titrated carefully.

Atazanavir: Maximum vardenafil dose: 2.5 mg/24 hours

Clarithromycin: Maximum vardenafil dose: 2.5 mg/24 hours

Erythromycin: Maximum vardenafil dose: 5 mg/24 hours

Indinavir: Maximum vardenafil dose: 2.5 mg/24 hours

Itraconazole:

200 mg/day: Maximum vardenafil dose: 5 mg/24 hours

400 mg/day: Maximum vardenafil dose: 2.5 mg/24 hours

Ketoconazole:

200 mg/day: Maximum vardenafil dose: 5 mg/24 hours

400 mg/day: Maximum vardenafil dose: 2.5 mg/24 hours

Ritonavir: Maximum vardenafil dose: 2.5 mg/72 hours

Saquinavir: Maximum vardenafil dose: 2.5 mg/24 hours

Dosing: ElderlyErectile dysfunction: Elderly ≥65 years: Oral: Initial: 5 mg 60 minutes prior to sexual activity; to be given as one single dose and not given more than once daily.

Dosing: Renal ImpairmentDose adjustment not needed for mild, moderate, or severe impairment; use has not been studied in patients on renal dialysis.

Dosing: Hepatic Impairment

Child-Pugh class A: No adjustment required

Child-Pugh class B: Initial: 5 mg 60 minutes prior to sexual activity (maximum dose: 10 mg); to be given as one single dose and not given more than once daily

Child-Pugh class C: Has not been studied; use is not recommended by the manufacturer

Administration: OralMay be administered with or without food, 60 minutes prior to sexual activity.

Dietary ConsiderationsMay take with or without food.

StorageStore at controlled room temperature of 25°C (77°F); excursions permitted to 15°C to 25°C (59°F to 86°F).

ContraindicationsHypersensitivity to vardenafil or any component of the formulation; concurrent (regular or intermittent) use of organic nitrates in any form (eg, nitroglycerin, isosorbide dinitrate)

Warnings/Precautions

Concerns related to adverse effects:

- Color discrimination: May cause dose-related impairment of color discrimination. Use caution in patients with retinitis pigmentosa; a minority have genetic disorders of retinal phosphodiesterases (no safety information available).

- Hearing loss: Sudden decrease or loss of hearing has been reported rarely; hearing changes may be accompanied by tinnitus and dizziness. A direct relationship between therapy and hearing loss has not been determined.

- Hypotension: Decreases in blood pressure may occur due to vasodilator effects; use with caution in patients with left ventricular outflow obstruction (aortic stenosis or hypertrophic obstructive cardiomyopathy); may be more sensitive to hypotensive actions. Concurrent use with alpha-adrenergic antagonist therapy may cause symptomatic hypotension; patients should be hemodynamically stable prior to initiating therapy at the lowest possible dose.

- Priapism: Has been reported (rarely) with use. Instruct patients to seek immediate medical attention if erection persists >4 hours. Use with caution in patients who have conditions which may predispose them to priapism (sickle cell anemia, multiple myeloma, leukemia).

- Vision loss: Vision loss may occur rarely and be a sign of nonarteritic anterior ischemic optic neuropathy (NAION). Risk may be increased with history of vision loss. Other risk factors for NAION include low cup-to-disc ratio (“crowded disc”), coronary artery disease, diabetes, hypertension, hyperlipidemia, smoking, and >50 years of age. Safety and efficacy were not studied in patients with known degenerative retinal disorders (eg, retinitis pigmentosa); use is not recommended.

Disease-related concerns:

- Anatomical penis deformation: Use with caution in patients with anatomical deformation of the penis (angulation, cavernosal fibrosis, or Peyronie's disease).

- Bleeding disorders: Use with caution in patients with bleeding disorders; safety and efficacy have not been established.

- Cardiovascular disease: Use is not recommended in patients with hypotension (<90/50 mm Hg); uncontrolled hypertension (>170/100 mm Hg); unstable angina or angina during intercourse; life-threatening arrhythmias, stroke or MI within the last 6 months; cardiac failure or coronary artery disease causing unstable angina. Safety and efficacy have not been studied in these patients. Use caution in patients with left ventricular outflow obstruction (eg, aortic stenosis). There is a degree of cardiac risk associated with sexual activity; therefore, physicians may wish to consider the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction.

- Congenital QT prolongation: Not recommended for use in patients with congenital QT prolongation.

- Hepatic impairment: Use with caution in patients with hepatic impairment (Child-Pugh class B); dosage adjustment is needed. Safety and efficacy have not been studied in patients with severe hepatic impairment (Child-Pugh class C), therefore, use in these patients is not recommended.

- Peptic ulcer disease: Use with caution in patients with active peptic ulcer disease; safety and efficacy have not been established.

- Renal impairment: Safety and efficacy have not been studied in patients with end-stage renal disease requiring dialysis, therefore, use in these patients is not recommended.

Concurrent drug therapy issues:

- Alpha-blockers: Use with caution in patients taking alpha-blockers; may cause hypotension. Safety of this combination may be affected by other antihypertensives and intravascular volume depletion. Patients should be hemodynamically stable prior to initiating therapy. Initiate vardenafil at the lowest recommended dose.

- Drugs with QT prolongation potential: Use with caution in patients taking medications known to prolong the QT interval. Avoid use in patients taking Class Ia or III antiarrhythmics.

- High potential for interactions: Use with caution in patients taking strong CYP3A4 inhibitors (see Drug Interactions); dosage reductions may be necessary; consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

- Nitrates: Concomitant use with all forms of nitrates is contraindicated. If nitrate administration is medically necessary, it is not known when nitrates can be safely administered following the use of vardenafil; the ACC/AHA 2007 guidelines support administration of nitrates only if 24 hours have elapsed.

- Other treatments for erectile dysfunction: Safety and efficacy with other treatments for erectile dysfunction have not been established; concurrent use is not recommended.

Special populations:

- Elderly: Use with caution in the elderly.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Potential underlying causes of erectile dysfunction should be evaluated prior to treatment.

Geriatric ConsiderationsIn adults ≥65 years of age, vardenafil plasma concentrations were higher than younger males (mean C_{max} was 34% higher), therefore, initial dose should be lower than the usual adult dose. Since the elderly often have concomitant diseases, many of which may be contraindicated with the use of vardenafil, a thorough knowledge of disease and medications must be accessed.

Pregnancy Risk FactorB

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies; however, vardenafil is not indicated for use in women. No effects on sperm motility or morphology were observed in healthy males.

LactationExcretion in breast milk unknown/not indicated for use in women.

Adverse Reactions

>10%:

Cardiovascular: Flushing (11%)

Central nervous system: Headache (15%)

2% to 10%:

Central nervous system: Dizziness (2%)

Gastrointestinal: Dyspepsia (4%), nausea (2%)

Neuromuscular & skeletal: CPK increased (2%)

Respiratory: Rhinitis (9%), sinusitis (3%)

Miscellaneous: Flu-like syndrome (3%)

<2%, postmarketing, and/or case reports: Abdominal pain, abnormal ejaculation, amnesia (transient global), anaphylactic reaction, angina, arthralgia, back pain, blurred vision, chest pain, chromatopsia, color vision changes, conjunctivitis, diaphoresis, diarrhea, dim vision, dysphagia, dyspnea, epistaxis, esophagitis, eye pain, facial edema, gastritis, gastroesophageal reflux, GGT increased, glaucoma, hearing decreased, hearing loss, hypertension, hypertonia, hypoesthesia, hypotension, insomnia, laryngeal edema, liver function tests abnormal, MI, myalgia, myocardial ischemia, neck pain, nonarteritic ischemic optic neuropathy (NAION), pain, palpitation, paresthesia, pharyngitis, photophobia, photosensitivity reaction, postural hypotension, priapism, pruritus, rash, retinal vein occlusion, seizure, somnolence, syncope, tachycardia, tinnitus, vertigo, vision abnormal, vision loss (temporary or permanent), visual acuity reduced, visual field defects, vomiting, watery eyes, weakness, xerostomia

Metabolism/Transport Effects**Substrate** of CYP2C (minor), 3A5 (minor), 3A4 (major)

Drug Interactions

Alpha1-Blockers: Phosphodiesterase 5 Inhibitors may enhance the hypotensive effect of Alpha1-Blockers. **Exceptions:** Dapiprazole [Off Market]. *Risk D: Consider therapy modification*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Etravirine: May decrease the serum concentration of Phosphodiesterase 5 Inhibitors. Management: No empiric dosage adjustments are recommended with concomitant therapy; however, dose of the phosphodiesterase inhibitor may need to be altered based on clinical response. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Phosphodiesterase 5 Inhibitors. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Protease Inhibitors: May decrease the metabolism of Phosphodiesterase 5 Inhibitors. Management: Dose restrictions for tadalafil, and/or sildenafil and vardenafil are recommended in combination with ritonavir, atazanavir, indinavir, darunavir and saquinavir. Consult specific prescribing information for detailed recommendations. *Risk D: Consider therapy modification*

Sapropterin: May enhance the hypotensive effect of Phosphodiesterase 5 Inhibitors. *Risk C: Monitor therapy*

Vasodilators (Organic Nitrates): Phosphodiesterase 5 Inhibitors may enhance the vasodilatory effect of Vasodilators (Organic Nitrates). *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions Food: High-fat meals decrease maximum serum concentration 18% to 50%. Serum concentrations/toxicity may be increased with grapefruit juice; avoid concurrent use.

Monitoring ParametersMonitor for response and adverse reactions.

Nursing: Physical Assessment/MonitoringAssess potential for interactions with other prescriptions, OTC medications, and herbal products patient may be taking. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationDo not take any new medication during therapy without consulting prescriber. Use exactly as directed 60 minutes prior to sexual activity without regard to meals; avoid taking with high-fat meals or grapefruit juice. Do not combine with other approaches to treating erectile dysfunction without consulting prescriber. **Note:** This medication does not provide protection against sexually-transmitted diseases, including HIV. You may experience headache, flushing, or blurred vision (use caution when driving at night or in poorly lit environments until response is known). Report immediately chest pain; acute head pain; respiratory difficulty; change in vision (seeing a blue tinge to objects or having difficulty telling the difference between the colors blue and green); change in hearing or ringing in the ears; allergic response (chills, fever, respiratory difficulty, rash); genital swelling; erection lasting >4 hours; or other adverse reactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Levitra®: 2.5 mg, 5 mg, 10 mg, 20 mg

Generic AvailableNo

ManufacturerBayer Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Levitra)

5 mg (10): $135.99

10 mg (10): $137.99

20 mg (10): $136.99

Mechanism of ActionDoes not directly cause penile erections, but affects the response to sexual stimulation. The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation and inflow of blood to the corpus cavernosum. Vardenafil enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE-5), which is responsible for degradation of cGMP in the corpus cavernosum; when sexual stimulation causes local release of NO, inhibition of PDE-5 by vardenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum; at recommended doses, it has no effect in the absence of sexual stimulation.

Pharmacodynamics/Kinetics

Onset of action: ~60 minutes

Absorption: Rapid

Distribution: V_d: 208 L

Protein binding: ~95% (parent drug and metabolite)

Metabolism: Hepatic via CYP3A4 (major), CYP2C and 3A5 (minor); forms metabolite (active)

Bioavailability: ~15%; Elderly (≥65 years): AUC increased by 52%; Hepatic impairment (moderate, Child-Pugh class B): AUC increased by 160%

Half-life elimination: Terminal: Vardenafil and metabolite: 4-5 hours

Time to peak, plasma: 0.5-2 hours

Excretion: Feces (91% to 95% as metabolites); urine (2% to 6%)

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness; may rarely cause insomnia

Mental Health: Effects on Psychiatric TreatmentMay cause flu-like syndrome; consider this when evaluating for potential SSRI discontinuation syndrome; the symptoms are similar. Serum concentration of vardenafil may be increased with concurrent use of fluoxetine, fluvoxamine, and nefazodone; monitor.

Cardiovascular ConsiderationsVardenafil, when used in conjunction with nitrates, may be associated with severe hypotension, myocardial infarction, and possibly death. While there are no clear significant increased cardiovascular events with PDE-5 inhibitors alone, these drugs should be absolutely avoided in conjunction with nitrates and may also induce significant and possibly fatal hypotension in patients with heart failure. Hemodynamic effects of PDE-5 inhibitors alone include a very slight drop in blood pressure without significant changes in heart rate. The most recent guidelines on the use of sildenafil (prototype PDE-5 inhibitor) in patients with cardiovascular disease are outlined in detail (Cheitlin, 1999). The general clinical recommendations are as follows.

Use of PDE-5 inhibitors is contraindicated in patients currently taking nitrate preparations.

Cardiovascular effects of PDE-5 inhibitors may be potentially hazardous in patients with:

- active coronary ischemia (not on nitrates)
- heart failure and with borderline low blood pressure and borderline low volume status
- complicated, multidrug antihypertensive regimens
- potential for drug-drug interactions that may prolong PDE-5 inhibitor half-life (eg, drugs that inhibit cytochrome P450 3A4)

Additional guidelines for the treatment of ED in patients with cardiovascular disease have also been published (Jackson, 2006). These guidelines, referred to as the Princeton II Guidelines, support the use of PDE-5 inhibition only in patients with asymptomatic coronary disease and <3 of the following risk factors: Controlled hypertension, mild stable angina, successful coronary revascularization, previous uncomplicated MI (>6-8 weeks), mild valvular disease, and left ventricular dysfunction (with or without NYHA Class I limitations).

When nitrate administration becomes medically necessary, the ACC/AHA 2004 guidelines on treatment of ST-segment elevation MI and the ACC/AHA 2007 guidelines on treatment of unstable angina/non ST-segment elevation MI supports administration of nitrates only if 24 hours have elapsed after use of sildenafil and 48 hours after use of tadalafil. The appropriate delay for the use of nitrates after vardenafil has not been determined.

Vardenafil is selective for PDE-5 and has limited effect on PDE-3, which controls cardiac contractility.

Anesthesia and Critical Care Concerns/Other Considerations

Cardiovascular effects of PDE-5 inhibitors may be potentially hazardous in patients with:

- active coronary ischemia (not on nitrates)
- heart failure and with low blood pressure and low volume status
- complicated, multidrug antihypertensive regimens
- potential for drug-drug interactions that may prolong PDE-5 inhibitor half-life (eg, drugs that inhibit CYP3A4)

Vardenafil is selective for PDE-5 and has limited effect on PDE3, which controls cardiac contractility.

Index Terms Vardenafil Hydrochloride

References

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International Brand Names Levitra (AR, AT, AU, BB, BE, BG, BM, BR, BS, BZ, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, GY, HK, HN, ID, IE, IL, IT, JM, KP, MX, MY, NI, NL, NO, PA, PE, PH, PL, PT, PY, RU, SE, SG, SR, SV, TH, TR, TT, TW, VE); Vivanza (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR); Yaila (KP)

Varenicline

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Special Alerts

Varenicline: Psychiatric and Central Nervous System Adverse Events- Health Canada Issues Alert to Canadian Healthcare Professionals - June 2008

The Canadian Dear Healthcare Provider letter can be found at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2008/champix_hpc-cps-eng.php

Varenicline: Psychiatric and Central Nervous System Adverse Events - Updated May 16, 2008

These product labeling changes have previously been incorporated into the varenicline Lexi-Comp monograph.

The FDA MedWatch alert can be found at http://www.fda.gov/medwatch/safety/2007/safety07.htm#Chantix

Pronunciation(var e NI kleen)
U.S. Brand NamesChantix®
Canadian Brand NamesChampix®
Pharmacologic CategoryPartial Nicotine Agonist; Smoking Cessation Aid
Use: Labeled IndicationsTreatment to aid in smoking cessation
Dosing: Adults**Smoking cessation:** Oral:

Initial:

Days 1-3: 0.5 mg once daily

Days 4-7: 0.5 mg twice daily

Maintenance (≥ Day 8): 1 mg twice daily

Note: Start 1 week before target quit date. Patients who cannot tolerate adverse events may require temporary reduction in dose. If patient successfully quits smoking during the 12 weeks, may continue for another 12 weeks to help maintain success. If not successful in first 12 weeks, then stop medication and reassess factors contributing to failure.

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal Impairment

Cl_{cr} ≥30 mL/minute: No adjustment required

Cl_{cr} <30 mL/minute: Initiate: 0.5 mg once daily; maximum dose: 0.5 mg twice daily

Hemodialysis: Maximum dose: 0.5 mg once daily

Dosing: Hepatic ImpairmentDosage adjustment not required
Dosing: Adjustment for ToxicityLower dose for a period of time, then increase again.
Calculations

- Creatinine Clearance: Adults

Administration: OralAdminister with food and glass of water.
Dietary ConsiderationsShould be given with food and a full glass of water to decrease gastric upset.
StorageStore at controlled room temperature of 25°C (77°F).
RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.
ContraindicationsThere are no contraindications listed within the manufacturer's labeling.
Warnings/Precautions

Concerns related to adverse effects:

- Nausea: Dose-dependent nausea may occur; both transient and persistent nausea has been reported. Dosage reduction may be considered for intolerable nausea.

- Neuropsychiatric effects: Neuropsychiatric symptoms, including suicidal thoughts and erratic/aggressive behavior, have been reported with use as well as following withdrawal of varenicline. Smoking cessation (with or without treatment) is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness, however, some of the behavioral disturbances were reported in patients who continued to smoke. Monitor patients for behavioral changes and psychiatric symptoms (eg, agitation, depression, suicidal behavior, suicidal ideation); inform patients to discontinue treatment and contact their healthcare provider immediately if they experience any behavioral and/or mood changes.

- Sedation: May cause sedation, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). The FAA has banned varenicline for pilots and air traffic controllers, and the FMCSA, which governs the commercial trucking/busing industry, is advising against issuance of commercial operator licenses for individuals taking the drug.

Disease-related concerns:

- Psychiatric illness: Patients with pre-existing psychiatric illness (eg, bipolar disorder, major severe depression, schizophrenia) were not studied in clinical trials; safety and efficacy has not been established in these populations. Due to rare neuropsychiatric events, caution is warranted if treatment is initiated; worsening of psychiatric illness has been reported.

- Renal impairment: Use with caution in patients with renal impairment; dosage adjustment required with severe impairment.

Concurrent drug therapy issues:

- Nicotine: Safety and efficacy of varenicline with other smoking cessation therapies have not been established; increased adverse events when used concurrently with nicotine replacement therapy.

Special populations:

- Pediatrics: The manufacturer does not recommend use in patients <18 years of age.

Geriatric ConsiderationsDosage adjustment for renal function may be necessary. Although studies to date do not demonstrate any significant pharmacokinetic differences between elderly (65-75 years of age) and younger adults.

Pregnancy Risk FactorC

Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies, however, decreased fertility, decreased fetal weight, and increased auditory startle response were observed in the offspring. There are no adequate or well-controlled studies in pregnant women. Use only if benefit outweighs the potential risk to fetus.

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions

>10%:

Central nervous system: Insomnia (18% to 19%), headache (15% to 19%), abnormal dreams (9% to 13%)

Gastrointestinal: Nausea (16% to 40%; dose related)

1% to 10%:

Central nervous system: Sleep disorder (≤5%), somnolence (3%), nightmares (1% to 2%), lethargy (1% to 2%), malaise (≤7%)

Dermatologic: Rash (≤3%)

Gastrointestinal: Flatulence (6% to 9%), abdominal pain (≤7%), constipation (5% to 8%), abnormal taste (5% to 8%), xerostomia (≤6%), dyspepsia (5%), vomiting (1% to 5%), appetite increased (3% to 4%), anorexia (≤2%), gastroesophageal reflux (1%)

Respiratory: Dyspnea (≤2%), rhinorrhea (≤1%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Acute coronary syndrome, acute renal failure, aggression, agitation, amnesia, anemia, angina, anxiety, arrhythmia, asthma, atrial fibrillation, attention disturbance, behavioral changes, blindness (transient), blurred vision, bradycardia, bradyphrenia, cardiac flutter, cataract, cerebrovascular accident, chest pain, chills, conjunctivitis, coronary artery disease, cor pulmonale, deafness, depression, dermatitis, diabetes mellitus, diarrhea, disorientation, dissociation, dizziness, dysarthria, dysphagia, ECG abnormal, eczema, edema, emotional disorder, enterocolitis, epistaxis, erectile dysfunction, eructation, erythema, esophagitis, euphoria, facial palsy, fever, flu-like syndrome, flushing, gall bladder disorder, gastritis, gastric ulcer, gastrointestinal hemorrhage, gingivitis, hallucinations, hyperhidrosis, hyper-/hypokalemia, hyperlipidemia, hypersensitivity, hyper-/hypotension, hypoglycemia, intestinal obstruction, irritability, leukocytosis, libido decreased, liver function test abnormal, lymphadenopathy, mental impairment, MI, migraine, mood swings, mouth ulceration, muscle enzyme increased, musculoskeletal pain, multiple sclerosis, myositis, nephrolithiasis, night blindness, nocturia, nystagmus, ocular vascular disorder, osteoporosis, palpitation, pancreatitis, parosmia, peripheral ischemia, photophobia, photosensitivity, pleurisy, polyuria, psoriasis, psychomotor impairment, psychotic disorder, pulmonary embolism, restless leg syndrome, restlessness, seizure, sexual dysfunction, splenomegaly, suicidal behavior, suicidal ideation, suicide, syncope, tachycardia, thinking abnormal, thrombocytopenia, thrombosis, thyroid disorder, tinnitus, transient ischemic attack, tremor, urinary retention, urticaria, ventricular extrasystoles, vertigo, visual field defect, vitreous floaters, weight gain, xerophthalmia

Drug InteractionsThere are no known significant interactions.

Monitoring ParametersMonitor for behavioral changes and psychiatric symptoms (eg, agitation, depression, suicidal behavior, suicidal ideation)

Nursing: Physical Assessment/MonitoringProvide educational materials and counseling to support an attempt at quitting smoking. Carefully instruct patient in appropriate titration of doses. Monitor for behavioral and emotional changes and suicide ideation. Monitor other medications patient is taking for potential need for dose adjustment after quitting smoking.

Patient EducationInform prescriber of all prescription medications, OTC medications, or herbal products you are taking. Start medication 1 week prior to quit date designated. Take after eating with a full glass of water. You may experience nausea (small, frequent meals, frequent oral care, sucking lozenges, or chewing gum may help), vomiting, constipation (increasing exercise, fluids, fruit/fiber may help), headaches, problems sleeping, or unusual dreams. Use caution when driving or engaging in potentially hazardous tasks until response to drug is known.

Report persistent symptoms (depression, suicide ideation, or emotional/behavioral changes) to prescriber. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Chantix®: 0.5 mg, 1 mg

Combination package, oral [dose-pack]:

Chantix®:

Tablet, oral: 0.5 mg (11) [white tablets]

Tablet, oral: 1 mg (42) [light blue tablets]

Generic AvailableNo

ManufacturerPfizer, Inc

Pricing: U.S. (www.drugstore.com)

Misc (Chantix Starting Month Pak)

0.5 MG X 11 & 1 MG X 42 (53): $124.99

Tablets (Chantix)

0.5 mg (56): $120.98

1 mg (56): $119.99

Tablets (Chantix Continuing Month Pak)

1 mg (56): $124.99

Mechanism of ActionPartial neuronal alpha$_4$ β$_2$ nicotinic receptor agonist; prevents nicotine stimulation of mesolimbic dopamine system associated with nicotine addiction. Also binds to 5 HT$_3$ receptor (significance not determined) with moderate affinity. Varenicline stimulates dopamine activity but to a much smaller degree than nicotine does, resulting in decreased craving and withdrawal symptoms.

Pharmacodynamics/Kinetics

Absorption: Well absorbed; unaffected by food

Protein binding: ≤20%

Metabolism: Minimal (<10% of clearance is through metabolism)

Half-life elimination: ~24 hours

Time to peak, plasma: ~3-4 hours

Excretion: Primarily urine (92% as unchanged drug)

Related Information

- Addiction Treatments

Pharmacotherapy PearlsIn all studies, patients received an educational booklet on smoking cessation and received up to 10 minutes of counseling at each weekly visit. Dosing started 1 week before target quit date. Successful cessation of smoking may alter pharmacokinetic properties of other medications (eg, theophylline, warfarin, insulin).

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Index TermsVarenicline Tartrate

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International Brand NamesChampix (AR, AT, BE, BG, CH, CN, CR, CZ, DE, DK, ES, FI, FR, GB, GR, GT, HK, HN, IE, IL, IT, KP, MX, MY, NI, NL, NO, NZ, PA, PE, PH, PT, RU, SE, SG, SV, TR, TW, UY)

Varicella Virus Vaccine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Varicella virus vaccine has been given in error (instead of the indicated varicella immune globulin) to pregnant women exposed to varicella.

Both varicella vaccine and zoster vaccine are live, attenuated strains of varicella-zoster virus. Their indications, dosing, and composition are distinct. Varicella is indicated in children to prevent chickenpox, while zoster vaccine is indicated in older individuals to prevent reactivation of the virus which causes shingles. Zoster vaccine is **not** a substitute for varicella vaccine and should not be used in children.

Pronunciation(var i SEL a VYE rus vak SEEN)
U.S. Brand NamesVarivax®
Canadian Brand NamesVarilrix®; Varivax® III
Pharmacologic CategoryVaccine
Use: Labeled IndicationsImmunization against varicella in children ≥12 months of age and adults

The ACIP recommends vaccination for all children, adolescents, and adults who do not have evidence of immunity. Vaccination is especially important for:

- Persons with close contact to those at high risk for severe disease
- Persons living or working in environments where transmission is likely (teachers, child-care workers, residents and staff of institutional settings)
- Persons in environments where transmission has been reported
- Nonpregnant women of childbearing age
- Adolescents and adults in households with children
- International travelers

Postexposure prophylaxis: Vaccination within 3 days (possibly 5 days) after exposure to rash is effective in preventing illness or modifying severity of disease

Dosing: Adults**Varicella immunization:** SubQ: 2 doses of 0.5 mL separated by 4-8 weeks
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric

Children 12 months to 12 years: Varicella immunization: SubQ: 0.5 mL; a second dose may be administered ≥3 months later

Note: The ACIP recommends the routine childhood vaccination be 2 doses, with the first dose administered at 12-15 months of age. School age children should receive the second dose at 4-6 years of age, but it may be administered earlier provided ≥3 months have elapsed after the first dose. All children and adolescents who received only 1 dose of vaccine should receive a second dose.

Children ≥13 years: Varicella immunization: Refer to adult dosing.

Administration: I.M.SubQ administration is recommended; however, doses inadvertently given I.M. have resulted in similar seroconversion.
Administration: I.V.Do not administer I.V.
Administration: OtherInject immediately after reconstitution; inject SubQ into the outer aspect of the upper arm, if possible.
StorageStore powder in freezer at -15°C (5°F) or colder; protect from light. Store diluent separately at room temperature or in refrigerator. Powder may be stored under refrigeration for up to 72 continuous hours prior to reconstitution; if not used within 72 hours, vaccine should be discarded. Following reconstitution, discard reconstituted vaccine if not used within 30 minutes.

Canadian formulations: **Note:** Varicella vaccine has been reformulated to produce a refrigerator-stable preparation. Previously, the product required storage in a freezer prior to reconstitution. The new Canadian formulation may be stored in a freezer, but if transferred to a refrigerator, may not be refrozen. Individual product labeling should be consulted to confirm proper conditions.

ReconstitutionUse 0.7 mL of the provided diluent to reconstitute vaccine. Gently agitate to mix thoroughly. (Total volume of reconstituted vaccine will be ~0.5 mL.)
ContraindicationsHypersensitivity to any component of the vaccine; individuals with blood dyscrasias, leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic systems; those receiving immunosuppressive therapy; primary and acquired immunodeficiency states; family history of congenital or hereditary immunodeficiency; active, untreated tuberculosis; current febrile illness (per manufacturer labeling); pregnancy

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Acute illness: May administer to patients with mild acute illness (with or without low grade fever per CDC guidelines).
- HIV: Children with HIV infection with age-specific CD4+ T-lymphocyte percentages ≥15% may receive live attenuated varicella vaccine. Vaccination may be considered for adolescents and adults with CD4+ T-lymphocyte counts ≥200 cells/µL.

Concurrent drug therapy issues:

- Immune globulin: Defer vaccination for at least 5 months following immune globulin (IgG), or VZIG (avoid IgG or IVIG use for 2 months following vaccination).
- Salicylates: Avoid salicylates for 6 weeks after vaccination; varicella may increase the risk of Reye's syndrome.

Dosage form specific issues:

- Albumin: Products may contain albumin.
- Gelatin: Products may contain gelatin.
- Neomycin: Products may contain neomycin.

Other warnings/precautions:

- Blood products: Defer vaccination for at least 5 months following blood or plasma transfusions.
- Transmission of virus: Vaccinated individuals should not have close association with susceptible high-risk individuals (newborns, pregnant women, immunocompromised persons) for 6 weeks following vaccination.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Varivax® should not be administered to pregnant females and pregnancy should be avoided for 3 months (per manufacturer labeling; 1 month per ACIP) following vaccination. A pregnancy registry has been established for pregnant women exposed to varicella virus vaccine (800-986-8999). Varicella disease during the 1st or 2nd trimesters may result in congenital varicella syndrome. The onset of maternal varicella infection from 5 days prior to 2 days after delivery may cause varicella infection in the newborn. All women should be assessed for immunity during a prenatal visit; those without evidence of immunity should be vaccinated upon completion or termination of pregnancy.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

>10%:

Central nervous system: Fever (10% to 15%)

Local: Injection site reaction (19% to 33%)

1% to 10%:

Central nervous system: Chills, fatigue, headache, irritability, malaise, nervousness, sleep disturbance

Dermatologic: Generalized varicella-like rash (1% to 6%), contact rash, dermatitis, diaper rash, dry skin, eczema, heat rash, itching

Gastrointestinal: Abdominal pain, appetite decreased, cold/canker sore, constipation, diarrhea, nausea, vomiting

Hematologic: Lymphadenopathy

Local: Varicella-like rash at the injection site (1% to 3%)

Neuromuscular & skeletal: Arthralgia, myalgia, stiff neck

Otic: Otitis

Respiratory: Cough, lower/upper respiratory illness

Miscellaneous: Allergic reactions, teething

<1%: Febrile seizure, pneumonitis

Postmarketing/case reports: Anaphylaxis, aseptic meningitis, ataxia, Bell's palsy, cellulitis, cerebellar ataxia (acute), cerebrovascular accident, disseminated varicella infection, dizziness, encephalitis, erythema multiforme, Guillain-Barré syndrome, hemiparesis (acute), Henoch-Schönlein purpura, hepatitis, herpes zoster, impetigo, nonfebrile seizure, paresthesia, pharyngitis, pneumonia, secondary skin infection, Stevens-Johnson syndrome, thrombocytopenia, transverse myelitis, urticaria

Drug Interactions

5-ASA Derivatives: May enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. The primary concern is the potential development of Reye's Syndrome, a condition that has been associated with the use of salicylates in children with varicella infections. *Risk D: Consider therapy modification*

Immune Globulins: May diminish the therapeutic effect of Vaccines (Live). *Risk D: Consider therapy modification*

Immunosuppressants: May enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Salicylates: May enhance the adverse/toxic effect of Varicella Virus-Containing Vaccines. Reye's Syndrome may develop. *Risk D: Consider therapy modification*

Smallpox Vaccine: May enhance the adverse/toxic effect of Varicella Virus Vaccine. It may be difficult to determine which vaccine caused skin lesions or other adverse effects. *Risk D: Consider therapy modification*

Tuberculin Tests: Vaccines (Live) may diminish the diagnostic effect of Tuberculin Tests. *Risk D: Consider therapy modification*

Monitoring Parameters Rash, fever

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, powder for reconstitution [preservative free]:

Varivax®: 1350 plaque-forming units (PFU) [contains gelatin and trace amounts of neomycin; packaged with diluent]

Varivax® III [CAN]: 1350 plaque-forming units (PFU) [contains gelatin and trace amounts of neomycin; packaged with diluent; not available in U.S.]

Injection, powder for reconstitution (Valrilix® [CAN]): $10^{3.3}$ plaque-forming units (PFU) [contains albumin and gelatin; packaged with diluent; not available in U.S.]

Generic Available No

Manufacturer Merck & Co

Mechanism of Action As a live, attenuated vaccine, varicella virus vaccine offers active immunity to disease caused by the varicella-zoster virus

Pharmacodynamics/Kinetics

Onset of action: Seroconversion: ~4-6 weeks

Duration: Antibody titers detectable at 10 years postvaccination

Related Information

- Immunization Recommendations

Pharmacotherapy Pearls Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

Evidence of immunity to varicella includes any of the following:

Documentation of age appropriate vaccination with varicella vaccine.

Laboratory evidence of immunity or laboratory confirmation of disease.

Birth in the United States prior to 1980 (except for health care personnel, pregnant women and the immunocompromised).

Diagnosis or verification of varicella disease by healthcare provider.

Diagnosis or verification of herpes zoster by healthcare provider.

Persons who lack evidence of immunity should be vaccinated.

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Cold/canker sores.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status May cause fatigue, irritability, nervousness, or sleep disturbances

Mental Health: Effects on Psychiatric Treatment None reported

Mental Health Comment Case reports of Guillain-Barré syndrome

Index Terms Chickenpox Vaccine; Varicella-Zoster Virus (VZV) Vaccine (Varicella); VZV Vaccine (Varicella)

References

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International Brand NamesOkavax (HK, SG, TW); Suduvax (KP); V-Z Vax (PH); Vaccin Varilrix (FR); Varicela Biken (EC); Varilrix (AR, AU, BB, BE, BM, BR, BS, BZ, CH, CN, CO, CR, CZ, DK, DO, EE, ES, FI, GB, GT, GY, HK, HN, ID, IL, IN, JM, KP, MX, NI, NL, NO, PA, PE, PH, PY, SE, SR, SV, TH, TT, TW, UY); Varipox (IN); Varivax (DE, ES, FR, GB, HK, IE, PH)

Varicella-Zoster Immune Globulin (Human)

Lexi-Drugs Online

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Varicella virus vaccine has been given in error (instead of the indicated varicella immune globulin) to pregnant women exposed to varicella.

Pronunciation(var i SEL a- ZOS ter i MYUN GLOB yoo lin HYU man)

Canadian Brand NamesVariZIG™

Pharmacologic CategoryImmune Globulin

Use: Labeled IndicationsIn pregnant women, for the prevention or reduction in severity of maternal infection within 4 days of exposure to the varicella zoster virus.

Use: Unlabeled/InvestigationalIn the United States, the Centers for Disease Control and Prevention (CDC) recommends varicella-zoster immune globulin (VZIG) for the passive immunization of patients who are at a greater risk of complications following significant exposure to varicella and do not have evidence of immunity. Guidelines restrict administration to those patients meeting the following criteria:

- Immunocompromised patients without evidence of immunity, including those with neoplastic disease (eg, leukemia or lymphoma); primary or acquired immunodeficiency; immunosuppressive therapy (including steroid therapy equivalent to prednisone ≥2 mg/kg or 20 mg/day)
- Newborn of mother who had onset of varicella (chickenpox) within 5 days before delivery or within 48 hours after delivery
- Premature infants (≥28 weeks gestation) whose mother has no evidence of immunity
- Premature infants (<28 weeks gestation or ≤1000 g) regardless of maternal history
- Pregnant women without evidence of immunity

Significant exposure includes:

Continuous household contact

Face-to-face indoor contact (>5 minutes or >1 hour depending on reference)

Hospital contact (in same 2-4 bedroom or adjacent beds in a large ward or prolonged face-to-face contact with an infectious staff member or patient)

Dosing: Adults**Prevention or reduction of maternal infection (approved use), passive immunization (unlabeled use):** I.M., I.V.: 125 int. units/10 kg (minimum dose: 125 int. units; maximum dose: 625 int. units). Administer within 96 hours of exposure.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Passive immunization (unlabeled use):** I.M., I.V.: Refer to adult dosing.

Administration: I.M.For I.M. or I.V. administration. Bring to room temperature prior to use. Should be given as soon as possible following exposure; efficacy has not been established for use >96 hours following exposure. For I.M. injection, administer into deltoid muscle or anterolateral aspect of upper thigh; avoid gluteal region.

Administration: I.V.For I.M. or I.V. administration. Bring to room temperature prior to use. Should be given as soon as possible following exposure; efficacy has not been established for use >96 hours following exposure. For I.V. administration, inject over 3-5 minutes.

StoragePrior to reconstitution, store at 2°C to 8°C (36°F to 48°F); do not freeze. Following reconstitution, may store at 2°C to 8°C (36°F to 48°F) for up to 12 hours.

ReconstitutionReconstitute only with provided diluent. Inject diluent slowly and at an angle onto the inside glass wall of the vial. Gently invert vial and swirl to dissolve; do not shake. For I.V. administration, reconstitute with 2.5 mL/vial (provides 50 int. units/mL). For I.M. administration, reconstitute with 1.25 mL/vial (provides 100 int. units/mL).

RestrictionsVaricella-zoster immune globulin (VZIG) was discontinued in the United States in 2005. It is currently available as VariZIG™ under an Investigational New Drug Application Expanded Access protocol. Inventory for anticipated patients may be obtained by contacting FFF Enterprises at 800-843-7477 and faxing a release form. The release form can be accessed from the CDC (available at http://www.fda.gov/cber/infosheets/mphvzig020806.htm). VariZIG™ may also be prepositioned at qualified sites.

ContraindicationsSevere reaction associated with past human immune globulin administration; hypersensitivity to any component of the formulation; patients with evidence of immunity; IgA deficiency

Note: U.S. CDC guidelines: Healthy and immunocompromised patients (except bone marrow transplant recipients [BMT]) with positive history of varicella infection are considered immune. BMT patients who had varicella infection *prior to* transplant are **not** considered immune; however, the expanded access protocol does not include use for this indication. BMT patients who develop varicella infection *after* transplant **are** considered immune. Patients who are fully vaccinated, but later became immunocompromised should be monitored closely; treatment with VZIG is not indicated, but other therapy may be needed if disease occurs.

Warnings/Precautions

Boxed warnings:

- Anaphylaxis/hypersensitivity reactions: See “Concerns related to adverse effects” below.
- Human plasma: See “Dosage form specific issue” below.

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity reactions: **[Canadian Boxed Warning]: Hypersensitivity and anaphylactic reactions can occur; immediate treatment (including epinephrine 1:1000) should be available. Reactions can occur in patients with IgA deficiency or hypersensitivity reactions to human globulin.**
- Pulmonary edema: Monitor for transfusion-related acute lung injury (TRALI); noncardiogenic pulmonary edema has been reported with intravenous administration of immune globulin. Use caution with preexisting respiratory conditions. I.M. administration may be preferred in this patient population.
- Renal impairment: Acute renal dysfunction (increased serum creatinine, oliguria, acute renal failure) can rarely occur; usually within 7 days of use (more likely with products stabilized with sucrose). Use with caution in the elderly, patients with renal disease, diabetes mellitus, volume depletion, sepsis, paraproteinemia, and nephrotoxic medications due to risk of renal dysfunction.
- Thrombotic events: Thrombotic events have been reported with administration of intravenous immune globulin; use with caution in patients with cardiovascular risk factors. I.M. administration may be preferred in this patient population.

Special populations:

- Elderly: Safety and efficacy have not been established in patients >65 years of age.
- Pediatrics: Safety and efficacy have not been established in patients <18 years of age.

Dosage form specific issues:

- Human plasma: **[Canadian Boxed Warnings]: Product of human plasma; may potentially contain infectious agents which could transmit disease. Screening of donors, as well as testing and/or inactivation or removal of certain viruses, reduces the risk.** Infections thought to be transmitted by this product should be reported to the manufacturer (Cangene Corporation 800-768-2304)

Pregnancy Considerations

Animal reproduction studies have not been conducted. Clinical use of other immunoglobulins suggest that there are no adverse effects on the fetus. Pregnant women who do not have evidence of immunity to varicella may be at increased risk of infection following exposure. VZIG is used to prevent maternal complications, not fetal infection.

Lactation

Excretion in breast milk unknown/use caution

Adverse Reactions

>10%:

Central nervous system: Headache (7% to 11%)

Local: Injection site pain (17% to 47%)

1% to 10%:

Central nervous system: Dizziness (up to 5%), fever (up to 5%), pain (up to 5%), chills (up to 2%), fatigue (up to 2%), flushing (up to 2%), insomnia (up to 2%)

Dermatologic: Rash (up to 4%), dermatitis (up to 2%), erythematous rash (up to 2%)

Gastrointestinal: Nausea (2% to 5%), dysgeusia (up to 2%)

Local: Injection site bruising, itching, or tenderness (up to 2%)

Neuromuscular & skeletal: Neck pain (up to 5%), myalgia (up to 2%)

Drug Interactions

Vaccines (Live): Immune Globulins may diminish the therapeutic effect of Vaccines (Live). **Exceptions:** Influenza Virus Vaccine; Yellow Fever Vaccine. *Risk D: Consider therapy modification*

Test Interactions

May cause false-positive test for immunity to VZV for 3 months following administration. May cause a false-positive Coomb’s test.

Monitoring Parameters

Observe for adverse effects for 20 minutes following administration. The CDC also recommends monitoring for signs and symptoms of varicella infection for 28 days after VZIG administration.

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN = Canadian brand name]

Injection, powder for reconstitution [preservative free]:

VariZIG™ [CAN]: 125 int. units [package with diluent] [available in the U.S under expanded access protocol]

Generic Available

No

Manufacturer

Cangene Corporation

Mechanism of Action

Antibodies obtained from pooled human plasma of individuals with high titers of varicella-zoster provide passive immunity.

Pharmacodynamics/Kinetics

Duration: ≥6 weeks

Metabolism: Metabolized in the reticuloendothelial system

Bioavailability: 100%

Half-life elimination: I.V.: 18-24 days; I.M.: 24-30 days

Time to peak, plasma: I.V.: <3 hours; I.M.: 2-7 days

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause headaches, dizziness, fatigue, and insomnia
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsVZIG

References

Centers for Disease Control, “Prevention of Varicella, Recommendations of the Advisory Committee on Immunization Practices (ACIP),” *MMWR Recomm Rep*, 2007, 56(RR4);1-40. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5604a1.htm

International Brand NamesVaritect (HK, TH, TW); Vazigam (ZA)

Vasopressin

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Pitressin® may be confused with Pitocin®

Pronunciation(vay soe PRES in)

Canadian Brand NamesPressyn®; Pressyn® AR

Pharmacologic CategoryAntidiuretic Hormone Analog; Hormone, Posterior Pituitary

Use: Labeled IndicationsTreatment of diabetes insipidus; differential diagnosis of diabetes insipidus

Use: Unlabeled/InvestigationalAdjunct in the treatment of GI hemorrhage and esophageal varices; pulseless arrest (ventricular tachycardia [VT]/ventricular fibrillation [VF], asystole/pulseless electrical activity [PEA]); vasodilatory shock (septic shock)

Dosing: Adults

Diabetes insipidus:Note: Dosage is highly variable; titrated based on serum and urine sodium and osmolality in addition to fluid balance and urine output; vasopressin rarely used for this indication; other therapies are available.

I.M., SubQ: 5-10 units 2-3 times/day as needed

Continuous I.V. infusion (unlabeled route): 0.0005 unit/kg/hour; double dosage as needed every 30 minutes to a maximum of 0.01 unit/kg/hour

Variceal hemorrhage (unlabeled use):*Continuous I.V. infusion:* Dilute in NS or D_5W to 0.1-1 unit/mL. **Note:** Other therapies may be preferred.

[AASLD guidelines, 2007]: Continuous I.V. infusion: Initial: 0.2-0.4 units/minute, may titrate dose as needed to a maximum dose of 0.8 units/minute; maximum duration: 24 hours at highest effective dose continuously (to reduce incidence of adverse effects). Patient should also receive I.V. nitroglycerin concurrently to prevent myocardial ischemic complications. Monitor closely for signs/symptoms of ischemia (myocardial, peripheral, bowel).

Pulseless arrest (unlabeled use) [ACLS, 2005]:*I.V., I.O.:* 40 units; may give 1 dose to replace first or second dose of epinephrine. I.V./I.O. drug administration is preferred, but if no access, may give endotracheally. ACLS guidelines do not recommend a specific endotracheal dose; however, may be given endotracheally using the same I.V. dose (Wenzel, 1997). Mix with 5-10 mL of water or normal saline, and administer down the endotracheal tube.

Vasodilatory shock/septic shock (unlabeled use):*I.V.:* 0.01-0.04 units/minute for the treatment of septic shock. Doses >0.04 units/minute may have more cardiovascular side effects. Most case reports have used 0.04 units/minute continuous infusion as a fixed dose.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Diabetes insipidus:Note: Dosage is highly variable; titrated based on serum and urine sodium and osmolality in addition to fluid balance and urine output; vasopressin rarely used for this indication; other therapies are available.

I.M., SubQ: 2.5-10 units 2-4 times/day as needed

Continuous I.V. infusion (unlabeled route): 0.0005 unit/kg/hour; double dosage as needed every 30 minutes to a maximum of 0.01 unit/kg/hour

GI hemorrhage (unlabeled use): Continuous I.V. infusion: Dilute in NS or D_5W to 0.1-1 unit/mL. **Note:** Other therapies may be preferred.

Initial I.V. bolus: 0.3 units/kg (maximum: 20 units) may be given

Continuous I.V. infusion: 0.001-0.01 units/kg/minute; titrate dose as needed; maximum: 0.01 unit/kg/minute; if bleeding controlled for 12-24 hours, then taper off over 24-36 hours

Dosing: Hepatic ImpairmentSome patients respond to much lower doses with cirrhosis.

Administration: I.V.

GI hemorrhage: Administration requires the use of an infusion pump.

Infusion rates: 100 units in 500 mL D_5W rate

0.1 unit/minute: 30 mL/hour

0.2 unit/minute: 60 mL/hour

0.3 unit/minute: 90 mL/hour

0.4 unit/minute: 120 mL/hour

0.5 unit/minute: 150 mL/hour

0.6 unit/minute: 180 mL/hour

Vasodilatory shock: Administration through a central catheter is recommended.

Administration: I.V. DetailUse extreme caution to avoid extravasation because of risk of necrosis and gangrene. In treatment of varices, infusions are often supplemented with nitroglycerin infusions to minimize cardiac effects.
Administration: TopicalTopical administration on nasal mucosa: Administer injectable vasopressin on cotton plugs, as nasal spray, or by dropper. Should not be inhaled.
Administration: OtherIf no I.V./I.O. access may give endotracheally. ACLS guidelines do not recommend a specific endotracheal dose; however, may be given endotracheally using the same I.V. dose (Wenzel, 1997). Mix with 5-10 mL of water or normal saline, and administer down the endotracheal tube.
StorageStore injection at room temperature; do not freeze. Protect from heat. Use only clear solutions.
CompatibilityStable in D_5W, NS.

Compatibility when admixed: Compatible: Verapamil.

ContraindicationsHypersensitivity to vasopressin or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- I.V. infiltration: May lead to severe vasoconstriction and localized tissue necrosis; also, gangrene of extremities, tongue, and ischemic colitis.

- Water intoxication: May cause water toxication; early signs include drowsiness, listlessness, and headache, these should be recognized to prevent coma and seizures.

Disease-related concerns:

- Asthma: Use with caution in patients with asthma.

- Cardiovascular disease: Use with caution in patients with cardiovascular disease, including arteriosclerosis.

- Goiter: Use with caution in patients with a goiter with cardiac complications.

- Migraine: Use with caution in patients with a history of migraines.

- Renal impairment: Use with caution in patients with renal disease, including chronic nephritis with nitrogen retention (manufacturing labeling notes therapy contraindicated until nitrogen levels reduced).

- Seizures: Use with caution in patients with a history of seizure disorder.

- Vascular disease: Use with caution in patients with vascular disease.

Special populations:

- Elderly: Caution elderly patients not to increase their fluid intake beyond that sufficient to satisfy their thirst in order to avoid water intoxication and hyponatremia; under experimental conditions, the elderly have shown to have a decreased responsiveness to vasopressin with respect to its effects on water homeostasis.

Geriatric ConsiderationsElderly patients should be cautioned not to increase their fluid intake beyond that sufficient to satisfy their thirst in order to avoid water intoxication and hyponatremia. Under experimental conditions, the elderly have shown to have a decreased responsiveness to vasopressin with respect to its effects on water homeostasis.
Pregnancy Risk FactorC
Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Vasopressin and desmopressin have been used safely during pregnancy based on case reports.
LactationEnters breast milk/use caution
Breast-Feeding ConsiderationsBased on case reports, vasopressin and desmopressin have been used safely during nursing.
Adverse ReactionsFrequency not defined.

Cardiovascular: Arrhythmia, asystole (>0.04 units/minute), blood pressure increased, cardiac output decreased (>0.04 units/minute), chest pain, MI, vasoconstriction (with higher doses), venous thrombosis

Central nervous system: Pounding in head, fever, vertigo

Dermatologic: Ischemic skin lesions, circumoral pallor, urticaria

Gastrointestinal: Abdominal cramps, flatulence, mesenteric ischemia, nausea, vomiting

Genitourinary: Uterine contraction

Neuromuscular & skeletal: Tremor

Respiratory: Bronchial constriction

Miscellaneous: Diaphoresis

Drug InteractionsThere are no known significant interactions.
Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (due to effects on ADH).

Monitoring ParametersSerum and urine sodium, urine specific gravity, urine and serum osmolality; urine output, fluid input and output, blood pressure, heart rate

Reference RangePlasma: 0-2 pg/mL (SI: 0-2 ng/L) if osmolality <285 mOsm/L; 2-12 pg/mL (SI: 2-12 ng/L) if osmolality >290 mOsm/L

Nursing: Physical Assessment/MonitoringEvaluate patient history closely for use cautions. Assess potential for interactions with other pharmacological agents patient may be taking (eg, concurrent use that will block or enhance antidiuretic response). **Note:** Dosing and administration vary according to purpose for use. I.V. requires use of infusion pump and close monitoring to prevent extravasation (may cause severe necrosis and gangrene). Assess results of laboratory tests, therapeutic effectiveness, and adverse response (eg, cardiac status, blood pressure, CNS status, fluid balance, signs or symptoms of water intoxication, intranasal irritation) on a regular basis during therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsSerum and urine sodium, urine specific gravity, urine and serum osmolality

Patient EducationThis drug will usually be administered by infusion or injection and you will be closely monitored. Report immediately any chest pain or palpitations; difficulty breathing; abdominal cramping; redness, swelling, pain, or burning at infusion/injection site; or any other adverse effects. May cause dizziness or drowsiness (use caution when changing position or engaging in potentially hazardous tasks until response to drug is known). Report persistent nausea, vomiting, or abdominal cramps; tremor, acute headache, or dizziness; chest pain or irregular heartbeat; respiratory difficulty or excessive perspiration; CNS changes (confusion, drowsiness); or runny nose or painful nasal membranes (intranasal use). **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution: 20 units/mL (0.5 mL, 1 mL, 10 mL)

Generic AvailableYes

Mechanism of ActionIncreases cyclic adenosine monophosphate (cAMP) which increases water permeability at the renal tubule resulting in decreased urine volume and increased osmolality; causes peristalsis by directly stimulating the smooth muscle in the GI tract; direct vasoconstrictor without inotropic or chronotropic effects

Pharmacodynamics/Kinetics

Onset of action: Nasal: 1 hour

Duration: Nasal: 3-8 hours; I.M., SubQ: 2-8 hours

Metabolism: Nasal/Parenteral: Hepatic, renal

Half-life elimination: Nasal: 15 minutes; Parenteral: 10-20 minutes

Excretion: Nasal: Urine; SubQ: Urine (5% as unchanged drug) after 4 hours

Pharmacotherapy PearlsVasopressin increases factor VIII levels and may be useful in hemophiliacs.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay be somewhat useful as a treatment for lithium-induced diabetes insipidus; hydrochlorothiazide and amiloride are more effective, less expensive options

Anesthesia and Critical Care Concerns/Other Considerations

Shock: Low-dose vasopressin may be effective for the management of vasodilator shock. Vasopressin binds to different receptors than the catecholamine pressors. Vasoconstrictor effects are through the V_1 vascular receptors. In clinical studies and case reports, vasopressin increased blood pressure, systemic vascular resistance, and urine output. Vasopressin may decrease heart rate and cardiac output, especially at higher doses. Vasopressin has been used in doses of 0.01-0.1 units/minute. Doses >0.04 units/minute may have more cardiovascular effects (decreased cardiac output, asystole, cardiac ischemia). Use caution in patients with underlying cardiac dysfunction. Vasoconstriction appears to remain effective in severe acidosis. When possible, low-dose vasopressin should be infused via central catheter for the management of vasodilatory shock; peripheral administration has been associated with skin necrosis.

The 2008 Surviving Sepsis Campaign guidelines (Dellinger, 2007) suggest vasopressin should not be administered as the initial vasopressor in septic shock. Vasopressin 0.03 units/minute may be added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone (Grade 2C).

Pulseless Arrest: A multicenter, double-blind, randomized, controlled trial evaluated the efficacy of vasopressin or epinephrine when administered to adult patients who suffered an out-of-hospital cardiac arrest (Wenzel, 2004). For inclusions, patients presented with ventricular fibrillation, pulseless electrical activity, or asystole. They were excluded if they were successfully defibrillated without the administration of a vasopressor, had a terminal illness or a DNR order, a lack of intravenous access, hemorrhagic shock, pregnancy, cardiac arrest due to trauma, or were <18 years of age. Eligible patients were randomized to intravenous vasopressin (40 units) or epinephrine (1 mg). Each patient received an injection of the study drug. If spontaneous circulation was not restored in 3 minutes, they received a second dose (same amount) of the same study drug. If there was no response, the managing physician had the option of giving epinephrine. Patients with ventricular fibrillation were randomized if the first three attempts at defibrillation failed; all others were randomized immediately. The primary endpoint was survival to hospital admission; the secondary endpoint was survival to hospital discharge. Five hundred and eighty-nine patients were randomized to vasopressin and 597 patients were randomized to epinephrine. There was no significant difference in the rate of hospital admission between the vasopressin group and the epinephrine group if they had ventricular fibrillation (46.2% vs 43% respectively, p: 0.48) or pulseless electrical activity (33.7% vs 30.5% respectively, p: 0.65). Patients with asystole responded significantly better to vasopressin; having higher rates of hospital admission (29% vs 20.3% in the epinephrine group, p: 0.02) and hospital discharge (4.7% vs 1.5% in the epinephrine group, p: 0.04). Patients who failed vasopressin therapy and received additional epinephrine had significant improvement in survival to hospital admission (25.7% vs 16.4% in the epinephrine group, p: 0.002) and discharge (6.2% vs 1.7%, p: 0.002). Similar patients who were randomized to epinephrine and failed to respond did not improve with additional epinephrine. Cerebral performance among all patients who survived to discharge was similar in both groups. In this trial, vasopressin was superior to epinephrine in patients with asystole. Vasopressin followed by epinephrine may be more effective than epinephrine alone in refractory out-of-hospital cardiac arrest.

A small in-hospital cardiac arrest study evaluated the efficacy of vasopressin or epinephrine in 200 patients. These investigators did not find any differences between the two treatment groups with regard to survival, discharge, or cerebral performance (Stiell, 2001).

Index Terms8-Arginine Vasopressin; ADH; Antidiuretic Hormone

References

"2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care," *Circulation*, 2005, 112(24 Suppl):1-211.

Chojkier M, Groszmann RJ, Atterbury CE, et al, "A Controlled Comparison of Continuous Intraarterial and Intravenous Infusions of Vasopressin in Hemorrhage From Esophageal Varices," *Gastroenterology*, 1979, 77(3):540-6. [PubMed 313353]

Dellinger RP, Levy MM, Carlet JM, et al, "Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008," *Intensive Care Med*, 2008, 34(1): 17-60. Available at http://www.survivingsepsis.org/system/files/images/2008_20International_20SSC_20Guidelines_1_.pdf[PubMed 18058085]

Dunser MW, Mayr AJ, Ulmer H, et al, "The Effects of Vasopressin on Systemic Hemodynamics in Catecholamine-Resistant Septic and Postcardiotomy Shock: A Retrospective Analysis," *Anest Analg*, 2001, 93(1):7-13.

Garcia-Tsao G, Sanyal AJ, Grace ND, et al, "Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis," *Hepatology*, 2007, 46(3):922-38.[PubMed 17879356]

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Kahn JM, Kress JP, and Hall JB, "Skin Necrosis After Extravasation of Low-Dose Vasopressin Administered for Septic Shock," *Crit Care Med*, 2002, 30(8):1899-901. [PubMed 12163813]

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Miller JH and Shock NW, "Age Differences in the Renal Tubular Response to Antidiuretic Hormone," *J Gerontol*, 1953, 8(4):446-50. [PubMed 13130853]

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Rozenfeld V and Cheng JW, "The Role of Vasopressin in the Treatment of Vasodilation in Shock States," *Ann Pharmacother*, 2000, 34(2):250-4. [PubMed 10676834]

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Wenzel V, Krismer AC, Arntz HR, et al, "A Comparison of Vasopressin and Epinephrine for Out-of-Hospital Cardiopulmonary Resuscitation. European Resuscitation Council Vasopressor During Cardiopulmonary Resuscitation Study Group," *N Engl J Med*, 2004, 350(2):105-13.[PubMed 14711909]

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International Brand NamesHemopressin (PK); Pitressin (AU, CZ, DE, GB, HK, ID, IE, TW); Vasopin (IN); Vasosin (TW)

VATH

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

Regimen

Vinblastine: I.V.: 4.5 mg/m^2 day 1

[total dose/cycle = 4.5 mg/m^2]

Doxorubicin: I.V.: 45 mg/m^2 day 1

[total dose/cycle = 45 mg/m^2]

Thiotepa: I.V.: 12 mg/m^2 day 1

[total dose/cycle = 12 mg/m^2]

Fluoxymesterone: Oral: 10 mg 3 times/day days 1 to 21

[total dose/cycle = 630 mg]

Repeat cycle every 21 days

References

Hart RD, Perloff M, and Holland JF, “One-Day VATH (Vinblastine, Adriamycin®, Thiotepa, and Halotestin®) Therapy for Advanced Breast Cancer Refractory to Chemotherapy,” *Cancer*, 1981, 48(7):1522-7.[PubMed 6793224]

VBAP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Multiple Myeloma

Regimen UseMultiple myeloma

Regimen

Vincristine: I.V.: 1 mg day 1

[total dose/cycle = 1 mg]

Carmustine: I.V.: 30 mg/m^2 day 1

[total dose/cycle = 30 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 1

[total dose/cycle = 30 mg/m^2]

Prednisone: Oral: 100 mg/day days 1 to 4

[total dose/cycle = 400 mg]

Repeat cycle every 21 days

References

Bonnet J, Alexanian R, Salmon S, et al, âVincristine, BCNU, Doxorubicin, and Prednisone (VBAP) Combination in the Treatment of Relapsing or Resistant Multiple Myeloma: A Southwest Oncology Group Study,â *Cancer Treat Rep*, 1982, 66(6):1267-71.[PubMed 7044534]

VBMCP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Multiple Myeloma]

Regimen UseMultiple myeloma

Regimen

Vincristine: I.V.: 1.2 mg/m^2 (maximum 2 mg) day 1

[total dose/cycle = 1.2 mg/m^2; maximum 2 mg]

Carmustine: I.V.: 20 mg/m^2 day 1

[total dose/cycle = 20 mg/m^2]

Melphalan: Oral: 8 mg/m^2/day days 1 to 4

[total dose/cycle = 32 mg/m^2]

Cyclophosphamide: I.V.: 400 mg/m^2 day 1

[total dose/cycle = 400 mg/m^2]

Prednisone: Oral: 40 mg/m^2/day days 1 to 7 (all cycles)

[total dose/cycle = 280 mg/m^2]

followed by Oral: 20 mg/m^2/day days 8 to 14 (first 3 cycles only)

[total dose/cycle = 140 mg/m^2]

Repeat cycle every 35 days

References

Oken MM, Harrington DP, Abramson N, et al, âComparison of Melphalan and Prednisone With Vincristine, Carmustine, Melphalan, Cyclophosphamide, and Prednisone in the Treatment of Multiple Myeloma: Results of Eastern Cooperative Oncology Group Study E2479,â *Cancer*, 1997, 79(8):1561-7.[PubMed 9118039]

VBP

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Testicular Cancer

Regimen Use Testicular cancer

Index Terms PVB

Regimen

Vinblastine: I.V.: 0.15 mg/kg/day days 1 and 2

[total dose/cycle = 0.3 mg/kg]

Bleomycin: I.V.: 30 units/day days 2, 9, and 16

[total dose/cycle = 90 units]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 21 days for 4 cycles

References

Williams SD, Birch R, Einhorn LH, et al, âTreatment of Disseminated Germ-Cell Tumors With Cisplatin, Bleomycin, and Either Vinblastine or Etoposide,â *N Engl J Med*, 1987, 316(23):1435-40.[PubMed 2437455]

VCAP

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Multiple Myeloma

Regimen Use Multiple myeloma

Regimen

Vincristine: I.V.: 1 mg/m^2 (maximum 1.5 mg) day 1

[total dose/cycle = 1 mg/m^2]

Cyclophosphamide: Oral: 125 mg/m^2/day days 1 to 4

[total dose/cycle = 500 mg/m^2]

Doxorubicin: I.V.: 30 mg/m^2 day 1

[total dose/cycle = 30 mg/m^2]

Prednisone: Oral: 60 mg/m^2/day days 1 to 4

[total dose/cycle = 240 mg/m^2]

Repeat cycle every 21 days for 6-12 months

References

Salmon SE, Haut A, Bonnet JD, et al, âAlternating Combination Chemotherapy and Levamisole Improves Survival in Multiple Myeloma: A Southwest Oncology Group Study,â *J Clin Oncol*, 1983, 1(8):453-61.[PubMed 6366141]

VD

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer

Regimen UseBreast cancer

Regimen

Vinorelbine: I.V.: 25 mg/m^2/day days 1 and 8

[total dose/cycle = 50 mg/m^2]

Doxorubicin: I.V.: 50 mg/m^2 day 1

[total dose/cycle = 50 mg/m^2]

Repeat cycle every 3 weeks

References

Spielmann M, Dorval T, Turpin F, et al, “Phase II Trial of Vinorelbine/Doxorubicin as First-Line Therapy of Advanced Breast Cancer,” *J Clin Oncol*, 1994 12(9):1764-70.[PubMed 8083698]

Vecuronium

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Vecuronium may be confused with vancomycin

Norcuron® may be confused with Narcan®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(vek ue ROE nee um)

U.S. Brand NamesNorcuron® [DSC]

Canadian Brand NamesNorcuron®

Pharmacologic CategoryNeuromuscular Blocker Agent, Nondepolarizing

Use: Labeled IndicationsAdjunct to general anesthesia to facilitate endotracheal intubation and to relax skeletal muscles during surgery; to facilitate mechanical ventilation in ICU patients; does not relieve pain or produce sedation

Dosing: Adults

Neuromuscular blockade: I.V. (do not administer I.M.):

Initial: 0.08-0.1 mg/kg or 0.04-0.06 mg/kg after initial dose of succinylcholine for intubation

Maintenance: 0.01-0.015 mg/kg 25-40 minutes after initial dose, then 0.01-0.015 mg/kg every 12-15 minutes (higher doses will allow less frequent maintenance doses); may be administered as a continuous infusion at 0.8-2 mcg/kg/minute

Pretreatment/priming: Adults: 10% of intubating dose given 3-5 minutes before initial dose

Neuromuscular blockade in ICU patients: Adults: 0.05-0.1 mg/kg bolus followed by 0.8-1.7 mcg/kg/minute once initial recovery from bolus observed or 0.1-0.2 mg/kg/dose every 1 hour

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Neuromuscular blockade: I.V. (do not administer I.M.):

Infants >7 weeks to 1 year: Initial: 0.08-0.1 mg/kg/dose; maintenance: 0.05-0.1 mg/kg/every 60 minutes as needed

Children >1 year: Refer to adult dosing.

Dosing: Hepatic ImpairmentDose reductions are necessary in patients with liver disease.

Calculations

- Vecuronium

Administration: I.V.Concentration of 1 mg/mL may be administered by rapid I.V. injection. May further dilute reconstituted vial to 0.1-0.2 mg/mL in a compatible solution for I.V. infusion. Concentration of 1 mg/mL may be used for I.V. infusion in fluid-restricted patients.

Administration: I.V. DetailpH: 4

StorageStore intact vials of powder for injection at room temperature 15°C to 30°C (59°F to 86°F). Vials reconstituted with bacteriostatic water for injection (BWFI) may be stored for 5 days under refrigeration or at room temperature. Vials reconstituted with other compatible diluents (nonbacteriostatic) should be stored under refrigeration and used within 24 hours.

ReconstitutionReconstitute with compatible solution for injection to final concentration of 1 mg/mL.

CompatibilityStable in D_5W, D_5NS, LR, NS, SWI, BWFI; ; **incompatible** with alkaline solutions/medications.

Y-Site administration: Incompatible with thiopental.

Compatibility in syringe: Incompatible with thiopental.

ContraindicationsHypersensitivity to vecuronium or any component of the formulation

Allergy Considerations

- Neuromuscular-Blocking Agent Allergy

Warnings/Precautions

Boxed warnings:

- Experienced personnel: See “Other warnings/precautions” below.

Concerns related to adverse effects:

- Bradycardia: Does not counteract bradycardia produced by anesthetics/vagal stimulation.
- Neuromuscular cross-sensitivity: Cross-sensitivity with other neuromuscular-blocking agents may occur; use extreme caution in patients with previous anaphylactic reactions.

Disease-related concerns:

- Burn injury: Resistance may occur in burn patients (>30% of body) for period of 5-70 days postinjury.
- Conditions which may antagonize neuromuscular blockade: Alkalosis, hypercalcemia, demyelinating lesions, peripheral neuropathies, denervation, infection, muscle trauma, and diabetes mellitus may result in antagonism of neuromuscular blockade.
- Conditions which may potentiate neuromuscular blockade: Electrolyte abnormalities, severe hyponatremia, severe hypocalcemia, severe hypokalemia, hypermagnesemia, neuromuscular diseases, acidosis, acute intermittent porphyria, Eaton-Lambert syndrome, myasthenia gravis, renal failure, and hepatic failure may result in potentiation of neuromuscular blockade.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Renal impairment: Use with caution in patients with renal impairment

Special populations:

- Elderly: Use with caution in the elderly, effects and duration are more variable.
- Immobilized patients: Resistance may occur in patients who are immobilized.

Other warnings/precautions:

- Appropriate use: Maintenance of an adequate airway and respiratory support is critical.
- Experienced personnel: **[U.S. Boxed Warning]: Should be administered by adequately trained individuals familiar with its use.**

Pregnancy Risk FactorC

Pregnancy ConsiderationsUse in cesarean section has been reported. Umbilical venous concentrations were 11% of maternal.

LactationExcretion in breast milk unknown/use caution

Adverse Reactions

<1%: Tachycardia, flushing, edema, hypotension, circulatory collapse, bradycardia, rash, itching, hypersensitivity reaction

Postmarketing and/or case reports: Acute quadriplegic myopathy syndrome (prolonged use), myositis ossificans (prolonged use)

Drug Interactions

Acetylcholinesterase Inhibitors: May diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Aminoglycosides: May enhance the respiratory depressant effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Botulinum Toxin Type A: Neuromuscular-Blocking Agents may enhance the neuromuscular-blocking effect of Botulinum Toxin Type A. *Risk C: Monitor therapy*

Botulinum Toxin Type B: Neuromuscular-Blocking Agents may enhance the neuromuscular-blocking effect of Botulinum Toxin Type B. *Risk C: Monitor therapy*

Calcium Channel Blockers: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Capreomycin: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

CarBAMazepine: May decrease the serum concentration of Vecuronium. *Risk C: Monitor therapy*

Cardiac Glycosides: Neuromuscular-Blocking Agents may enhance the arrhythmogenic effect of Cardiac Glycosides. *Risk C: Monitor therapy*

Colistimethate: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): Neuromuscular-Blocking Agents (Nondepolarizing) may enhance the adverse neuromuscular effect of Corticosteroids (Systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur. *Risk D: Consider therapy modification*

Inhalational Anesthetics: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Ketorolac: May enhance the adverse/toxic effect of Neuromuscular-Blocking Agents (Nondepolarizing). Specifically, episodes of apnea have been reported in patients using this combination. *Risk C: Monitor therapy*

Lincosamide Antibiotics: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Lithium: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Loop Diuretics: May diminish the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Loop Diuretics may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Magnesium Salts: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. Only of concern in patients with increased serum magnesium concentrations. *Risk C: Monitor therapy*

Phenytoin: May decrease the serum concentration of Vecuronium. *Risk C: Monitor therapy*

Polymyxin B: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk D: Consider therapy modification*

Procainamide: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

QuiNIDine: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Tetracycline Derivatives: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Vancomycin: May enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents. *Risk C: Monitor therapy*

Monitoring ParametersBlood pressure, heart rate

Nursing: Physical Assessment/MonitoringOnly clinicians experienced in the use of neuromuscular-blocking drugs should administer and/or manage the use of vecuronium. Dosage and rate of administration should be individualized and titrated to the desired effect, according to relevant clinical factors, premedication, concomitant medications, age, and general condition of patient. Ventilatory support must be instituted and maintained until adequate respiratory muscle function and/or airway protection are assured. Assess other medications for effectiveness and safety. Other drugs that affect neuromuscular activity may increase/decrease neuromuscular block induced by vecuronium; monitor and adjust dosage as necessary. This drug does not cause anesthesia or analgesia; pain must be treated with appropriate analgesic agents. Continuous monitoring of vital signs, cardiac status, respiratory status, and degree of neuromuscular block (objective assessment with peripheral external nerve stimulator) is mandatory during infusion and until full muscle tone has returned. Muscle tone returns in a predictable pattern, starting with diaphragm, abdomen, chest, limbs, and finally muscles of the neck, face, and eyes. Safety precautions must be maintained until full muscle tone has returned. **Note:** It may take longer for return of muscle tone in obese or elderly patients or patients with renal or hepatic disease, myasthenia gravis, myopathy, other neuromuscular disease, dehydration, electrolyte imbalance, or severe acid/base imbalance. Provide appropriate patient teaching/support prior to and following administration.

Long-term use: Monitor level of neuromuscular blockade, skeletal muscle movement, and respiratory effort. Reposition patient and provide appropriate skin care, mouth care, and care of patient's eyes every 2-3 hours while sedated. Provide appropriate emotional and sensory support (auditory and environmental).

Patient EducationPatient will usually be unconscious prior to administration. Patient education should be appropriate to individual situation. Reassurance of constant monitoring and emotional support to reduce fear and anxiety should precede and follow administration. Following return of muscle tone, do not attempt to change position or rise from bed without assistance. Report immediately any skin rash or hives, pounding heartbeat, respiratory difficulty, or muscle tremors. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as bromide: 10 mg, 20 mg [may be supplied with diluent containing benzyl alcohol]

Generic AvailableYes

Mechanism of ActionBlocks acetylcholine from binding to receptors on motor endplate inhibiting depolarization

Pharmacodynamics/Kinetics

Onset of action:

Good intubation conditions: Within 2.5-3 minutes

Maximum neuromuscular blockade: Within 3-5 minutes

Duration: 20-40 minutes

Metabolism: Active metabolite: 3-desacetyl vecuronium ($^{1}/_{2}$ the activity of parent drug)

Half-life elimination: 51-80 minutes

Excretion: Primarily feces (40% to 75%); urine (30% as unchanged drug and metabolites)

Related Information

- Neuromuscular-Blocking Agents

Pharmacotherapy PearlsVecuronium is classified as an intermediate-duration neuromuscular-blocking agent. It produces minimal, if any, histamine release; does not relieve pain or produce sedation. It may produce cumulative effect on duration of blockade.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Mental Health CommentPatients with myasthenia gravis and Eaton-Lambert syndrome have an increased sensitivity to vecuronium.

Anesthesia and Critical Care Concerns/Other ConsiderationsClassified as an intermediate duration neuromuscular-blocking agent; produces minimal, if any, histamine release.

Critically-Ill Adult Patients:

The 2008 Surviving Sepsis Campaign guidelines recommend avoiding use of neuromuscular blockers if at all possible in the septic patient due to the risk of prolonged neuromuscular blockade following discontinuation. If one is required, monitor the depth of blockade (Grade 1B).

The 2002 ACCM/SCCM/ASHP clinical practice guidelines for sustained neuromuscular blockade in the adult critically-ill patient recommend:

Optimize sedatives and analgesics prior to initiation and monitor and adjust accordingly during course. Neuromuscular blockers do not relieve pain or produce sedation.

Protect patient's eyes from development of keratitis and corneal abrasion by administering ophthalmic ointment and taping eyelids closed or using eye patches. Reposition patient routinely to protect pressure points from breakdown. Address DVT prophylaxis.

Concurrent use of a neuromuscular blocker and corticosteroids appear to increase the risk of certain ICU myopathies; avoid or administer the corticosteroid at the lowest dose possible. Reassess need for neuromuscular blocker daily.

Using daily drug holidays (stopping neuromuscular-blocking agent until patient requires it again) may decrease the incidence of acute quadriplegic myopathy syndrome.

Tachyphylaxis can develop; switch to another neuromuscular blocker (taking into consideration the patient's organ function) if paralysis is still necessary.

Atracurium or cisatracurium is recommended for patients with significant hepatic or renal disease, due to organ-independent Hofmann elimination.

Monitor patients clinically and via “Train of Four” (TOF) testing with a goal of adjusting the degree of blockade to 1-2 twitches or based upon the patient's clinical condition.

Index Terms ORG NC 45

References

Dellinger RP, Levy MM, Carlet JM, et al, “Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2008,” *Intensive Care Med*, 2008, 34(1): 17-60. Available at http://www.survivingsepsis.org/system/files/images/2008_20International_20SSC_20Guidelines_1_.pdf[PubMed 18058085]

Murray MJ, Cowen J, DeBlock H, et al, “Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient. Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists, American College of Chest Physicians,” *Crit Care Med*, 2002, 30(1):142-56. Available at: http://www.sccm.org/pdf/NeuromuscularBlockade.pdf. Accessed August 6, 2003.[PubMed 11902255]

International Brand Names Nodescrón (MX); Norcuron (AE, AR, AT, AU, BE, BG, BH, BR, CH, CL, CN, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, HK, HN, HR, HU, ID, IE, IL, IN, IQ, IR, IT, JO, KP, KW, LB, LU, LY, MX, MY, NL, NO, OM, PH, PK, PL, PT, QA, RU, SA, SE, SY, TR, VE, YE); Vecaron (KP); Vecural (PE, PY, UY); Vecuron (PH, TH)

Venlafaxine

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English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(ven la FAX een)

U.S. Brand NamesEffexor XR®; Effexor®

Canadian Brand NamesCo-Venlafaxine XR; Effexor® XR; GEN-Venlafaxine XR; Novo-Venlafaxine XR; PMS-Venlafaxine XR; RATIO-Venlafaxine XR; RIVA-Venlafaxine XR; SANDOZ-Venlafaxine XR

Pharmacologic CategoryAntidepressant, Serotonin/Norepinephrine Reuptake Inhibitor

Use: Labeled IndicationsTreatment of major depressive disorder, generalized anxiety disorder (GAD), social anxiety disorder (social phobia), panic disorder

Use: Unlabeled/InvestigationalObsessive-compulsive disorder (OCD); hot flashes; neuropathic pain; attention-deficit/hyperactivity disorder (ADHD)

Dosing: Adults

Depression:

Immediate-release tablets: 75 mg/day, administered in 2 or 3 divided doses, taken with food; dose may be increased in 75 mg/day increments at intervals of at least 4 days, up to 225-375 mg/day

Extended-release capsules or tablets: 75 mg once daily taken with food; for some new patients, it may be desirable to start at 37.5 mg/day for 4-7 days before increasing to 75 mg once daily; dose may be increased by up to 75 mg/day increments every 4 days as tolerated, up to a recommended maximum of 225 mg/day

Generalized anxiety disorder: *Extended-release capsules:* 75 mg once daily taken with food; for some new patients, it may be desirable to start at 37.5 mg/day for 4-7 days before increasing to 75 mg once daily; dose may be increased by up to 75 mg/day increments every 4 days as tolerated, up to a maximum of 225 mg/day

Panic disorder:*Extended-release capsules:* 37.5 mg once daily for 1 week; may increase to 75 mg daily, with subsequent weekly increases of 75 mg/day up to a maximum of 225 mg/day.

Social anxiety disorder:

Extended-release capsules: 75 mg once daily taken with food; for some new patients, it may be desirable to start at 37.5 mg/day for 4-7 days before increasing to 75 mg once daily; dose may be increased by up to 75 mg/day increments every 4 days as tolerated, up to a maximum of 225 mg/day

Extended release tablets: 75 mg once daily taken with food (maximum: 75 mg/day); no evidence that doses >75 mg/day offer any additional benefit

Obsessive-compulsive disorder (unlabeled use): Titrate to usual dosage range of 150-300 mg/day; however, doses up to 375 mg daily have been used; response may be seen in 4 weeks

Neuropathic pain (unlabeled use): Dosages evaluated varied considerably based on etiology of chronic pain, but efficacy has been shown for many conditions in the range of 75-225 mg/day; onset of relief may occur in 1-2 weeks, or take up to 6 weeks for full benefit.

Hot flashes (unlabeled use): Doses of 37.5-75 mg/day have demonstrated significant improvement of vasomotor symptoms after 4-8 weeks of treatment; in one study, doses >75 mg/day offered no additional benefit; however, higher doses (225 mg/day) may be beneficial in patients with perimenopausal depression.

Attention-deficit disorder (unlabeled use): Initial: Doses vary between 18.75 to 75 mg/day; may increase after 4 weeks to 150 mg/day; if tolerated, doses up to 225 mg/day have been used

Note: When discontinuing this medication after more than 1 week of treatment, it is generally recommended that the dose be tapered. If venlafaxine is used for 6 weeks or longer, the dose should be tapered over 2 weeks when discontinuing its use.

Dosing: ElderlyRefer to adult dosing. No specific recommendations for elderly, but may be best to start lower at 25-50 mg twice daily and increase as tolerated by 25 mg/dose. Extended-release formulation: 37.5 mg once daily, increase by 37.5 mg every 4-7 days as tolerated

Alzheimer's dementia-related depression:

Immediate-release tablets: Initial: 25 mg/day; may increase at weekly intervals to maximum of 375 mg/day in divided doses

Extended-release capsules: Initial: 37.5 mg/day; may increase at weekly intervals to maximum of 225 mg/day

Dosing: Pediatric**Attention-deficit/hyperactivity disorder (unlabeled use):** Children and Adolescents: Oral: Initial: 12.5 mg/day

Children <40 kg: Increase by 12.5 mg/week to maximum of 50 mg/day in 2 divided doses

Children ≥40 kg: Increase by 25 mg/week to maximum of 75 mg/day in 3 divided doses.

Mean dose: 60 mg or 1.4 mg/kg administered in 2-3 divided doses

Dosing: Renal Impairment

Cl_{cr} 10-70 mL/minute: Decrease dose by 25%.

Hemodialysis: Decrease total daily dose by 50% given after completion of dialysis.

Dosing: Hepatic ImpairmentReduce total dosage by 50%.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralAdminister with food.

Extended release formulations: Swallow capsule or tablet whole; do not crush or chew. Contents of capsule may be sprinkled on a spoonful of applesauce and swallowed immediately without chewing; followed with a glass of water to ensure complete swallowing of the pellets.

Dietary ConsiderationsShould be taken with food.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F).

RestrictionsAn FDA-approved medication guide concerning the use of antidepressants in children, adolescents, and young adults must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm. Dispense to parents or guardians of children and adolescents receiving this medication.

ContraindicationsHypersensitivity to venlafaxine or any component of the formulation; use of MAO inhibitors within 14 days; should not initiate MAO inhibitor within 7 days of discontinuing venlafaxine

Warnings/Precautions

Boxed warnings:

- Suicidal thinking/behavior: See "Major psychiatric warnings" below.

Major psychiatric warnings:

- **[U.S. Boxed Warning]: Antidepressants increase the risk of suicidal thinking and behavior in children, adolescents, and young adults (18-24 years of age) with major depressive disorder (MDD) and other psychiatric disorders;** consider risk prior to prescribing. Short-term studies did not show an increased risk in patients >24 years of age and showed a decreased risk in patients ≥65 years. Closely monitor for clinical worsening, suicidality, or unusual changes in behavior; the patient's family or caregiver should be instructed to closely observe the patient and communicate condition with healthcare provider. A medication guide concerning the use of antidepressants in children and teenagers should be dispensed with each prescription. **Venlafaxine is not FDA approved for use in children.**

- The possibility of a suicide attempt is inherent in major depression and may persist until remission occurs. Patients treated with antidepressants should be observed for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Worsening depression and severe abrupt suicidality that are not part of the presenting symptoms may require discontinuation or modification of drug therapy. Use caution in high-risk patients during initiation of therapy.

- Prescriptions should be written for the smallest quantity consistent with good patient care. The patient's family or caregiver should be alerted to monitor patients for the emergence of suicidality and associated behaviors such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, and mania; patients should be instructed to notify their healthcare provider if any of these symptoms or worsening depression or psychosis occur.

- May worsen psychosis in some patients or precipitate a shift to mania or hypomania in patients with bipolar disorder. Monotherapy in patients with bipolar disorder should be avoided. Patients presenting with depressive symptoms should be screened for bipolar disorder. **Venlafaxine is not FDA approved for the treatment of bipolar depression.**

Concerns related to adverse effects:

- Anxiety/insomnia: May cause increase in anxiety, nervousness, and insomnia.

- Bleeding risk: May impair platelet aggregation resulting in increased risk of bleeding events, particularly if used concomitantly with aspirin or NSAIDs due to ulcerogenic potential. Data are inconclusive regarding extent of bleeding risk of SNRIs in combination with warfarin or other anticoagulants. Bleeding related to SNRI use has been reported to range from relatively minor bruising and epistaxis to life-threatening hemorrhage.

- CNS depression: Has a low potential to impair cognitive or motor performance; caution operating hazardous machinery or driving.

- Hypercholesterolemia: May cause significant increases in serum total cholesterol.

- Hypertension: Dose-related increases in systolic and diastolic blood pressure have been documented. Monitor blood pressure regularly, and if sustained increases noted, consider dose reduction or discontinuation.

- Pulmonary events: Interstitial lung disease and eosinophilic pneumonia have been rarely reported. May present as progressive dyspnea, cough, and/or chest pain. Prompt evaluation and possible discontinuation of therapy may be necessary.

- Sexual dysfunction: May cause or exacerbate sexual dysfunction.

- SIADH and hyponatremia: SSRIs and SNRIs have been associated with the development of SIADH; hyponatremia has been reported rarely (including severe cases with serum sodium <110 mmol/L), predominately in the elderly. Volume depletion and/or concurrent use of diuretics likely increases risk.

- Weight loss and anorectic effects: Dose-dependent weight loss has been observed in both pediatric and adult patients; weight loss was not limited to those experiencing reduced appetite.

Disease-related concerns:

- Cardiovascular disease: May cause sustained increase in blood pressure or tachycardia. Control pre-existing hypertension prior to initiation of venlafaxine. Use caution in patients with recent history of MI, unstable heart disease, or hyperthyroidism. Hypertensive effect is dose related and increases are generally modest (12-15 mm Hg diastolic).

- Hepatic impairment: Use caution; clearance is decreased and plasma concentrations are increased; dosage reduction recommended in patients with mild-to-moderate hepatic impairment.

- Narrow-angle glaucoma: May cause mydriasis; use caution in patients with increased intraocular pressure or at risk of acute narrow-angle glaucoma.

- Renal impairment: Use caution; clearance is decreased and plasma concentrations are increased; a lower dosage may be needed; dosage reduction recommended in patients with renal impairment.

- Seizure disorders: Use caution with a previous seizure disorder or condition predisposing to seizures such as brain damage or alcoholism.

Concurrent drug therapy issues:

- Agents which lower seizure threshold: Concurrent therapy with other drugs which lower the seizure threshold.

- Anticoagulants/antiplatelets: Use caution with concomitant use of NSAIDs, ASA, or other drugs that affect coagulation; the risk of bleeding may be potentiated.

- CNS depressants: Use caution with concomitant therapy.

- MAO inhibitors (MAO-Is): Potential for serotonin syndrome when used with MAO inhibitors; autonomic instability, coma, death, delirium, diaphoresis, hyperthermia, mental status changes/agitation, muscular rigidity, myoclonus, neuroleptic malignant syndrome features, and seizures may occur. Concurrent use with MAO inhibitors is contraindicated. Do not begin venlafaxine within 14 days of terminating MAO-I therapy; do not initiate MAO-I treatment within 7 days of discontinuing venlafaxine.

- Proserotonergic drugs: Serotonin syndrome (eg, symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia) may occur with concomitant proserotonergic drugs (ie, SSRIs/SNRIs or triptans) or agents which reduce venlafaxine's metabolism. Concurrent use of serotonin precursors (eg, tryptophan) is not recommended.

- Weight loss agents: Agents causing weight loss or anorectic effects should be avoided.

Special populations:

- Pediatrics: Small differences in height have been observed in pediatric patients receiving venlafaxine, particularly those <12 years of age, compared to placebo. Not FDA approved for use in children.

Other warnings/precautions:

- Electroconvulsive therapy: May increase the risks associated with electroconvulsive therapy; consider discontinuing, when possible, prior to ECT treatment.

- Withdrawal syndrome: Abrupt discontinuation or dosage reduction has been associated with a wide range of reactions, including (but not limited to) dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, impaired coordination/balance, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Upon discontinuation of venlafaxine therapy, gradually taper dose. If intolerable symptoms occur following a decrease in dosage or upon discontinuation of therapy, then resuming the previous dose with a more gradual taper should be considered.

Geriatric ConsiderationsVenlafaxine's low anticholinergic activity, minimal sedation, and hypotension properties makes this a valuable antidepressant in treating elderly with depression or anxiety disorders. No dose adjustment is necessary for age alone; adjust dose for renal function in the elderly. The elderly are more prone to SSRI/SNRI-induced hyponatremia.

Pregnancy Risk FactorC

Pregnancy ConsiderationsVenlafaxine is classified as pregnancy category C due to adverse effects observed in animal studies. Venlafaxine and its active metabolite ODV cross the human placenta. Neonatal seizures and neonatal abstinence syndrome have been noted in case reports following maternal use of venlafaxine during pregnancy. Nonteratogenic effects in the newborn following SSRI/SNRI exposure late in the third trimester include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hyper- or hypotonia, hyper-reflexia, jitteriness, irritability, constant crying, and tremor. The long-term effects on neurobehavior have not been studied.

Due to pregnancy-induced physiologic changes, some pharmacokinetic parameters of venlafaxine may be altered. Women should be monitored for decreased efficacy. Women treated for major depression and who are euthymic prior to pregnancy are more likely to experience a relapse when medication is discontinued as compared to pregnant women who continue taking antidepressant medications. The ACOG recommends that therapy with SSRIs or SNRIs during pregnancy be individualized; treatment of depression during pregnancy should incorporate the clinical expertise of the mental health clinician, obstetrician, primary healthcare provider, and pediatrician. If treatment during pregnancy is required, consider tapering therapy during the third trimester in order to prevent withdrawal symptoms in the infant. If this is done and the woman is considered to be at risk of relapse from her major depressive disorder, the medication can be restarted following delivery, although the dose should be readjusted to that required before pregnancy.

LactationEnters breast milk/not recommended

Breast-Feeding Considerations Venlafaxine and ODV are found in human milk. Low concentrations of ODV have been found in the serum of nursing infants whose mothers are taking venlafaxine; venlafaxine has also been detected in some infants. Adverse events have not been observed; however, it is recommended to monitor the infant for adverse events if the decision to breast-feed has been made. The long-term effects on neurobehavior have not been studied, thus one should prescribe venlafaxine to a mother who is breast-feeding only when the benefits outweigh the potential risks. The manufacturer does not recommend breast-feeding during therapy.

Pregnancy & Lactation, In-Depth

- Venlafaxine in Pregnancy & Lactation

Adverse Reactions

>10%:

Central nervous system: Headache (25% to 38%), insomnia (15% to 24%), somnolence (12% to 23%), nervousness (6% to 21%), dizziness (11% to 20%)

Gastrointestinal: Nausea (21% to 58%), xerostomia (12% to 22%), anorexia (8% to 20%), constipation (8% to 15%)

Genitourinary: Abnormal ejaculation/orgasm (2% to 19%)

Neuromuscular & skeletal: Weakness (8% to 19%)

Miscellaneous: Diaphoresis (10% to 14%)

1% to 10%:

Cardiovascular: Hypertension (dose related; 3% in patients receiving <100 mg/day, up to 13% in patients receiving >300 mg/day), vasodilation (3% to 4%), palpitation (3%), tachycardia (2%), chest pain (2%), postural hypotension (1%), edema

Central nervous system: Abnormal dreams (3% to 7%), anxiety (5% to 6%), yawning (3% to 5%), agitation (2% to 4%), chills (3%), confusion (2%), abnormal thinking (2%), depersonalization (1%), depression (1% to 3%), fever, migraine, amnesia, hypoesthesia, trismus, vertigo

Dermatologic: Rash (3%), pruritus (1%), bruising

Endocrine & metabolic: Libido decreased (3% to 9%), hypercholesterolemia (5%), triglycerides increased

Gastrointestinal: Diarrhea (6% to 8%), dyspepsia (7%), vomiting (3% to 6%), abdominal pain (6%), flatulence (3% to 4%), taste perversion (2%), weight loss (1% to 4%), appetite increased, weight gain

Genitourinary: Impotence (4% to 10%), urinary frequency (3%), urination impaired (2%), urinary retention (1%), prostatic disorder

Neuromuscular & skeletal: Tremor (4% to 10%), hypertonia (3%), paresthesia (2% to 3%), twitching (1% to 3%), neck pain, arthralgia

Ocular: Abnormal or blurred vision (4% to 6%), mydriasis (2%)

Otic: Tinnitus (2%)

Respiratory: Pharyngitis (7%), sinusitis (2%), cough increased, dyspnea

Miscellaneous: Infection (6%), flu-like syndrome (6%), trauma (2%)

<1%, postmarketing, and/or case reports (limited to important or life-threatening): Agranulocytosis, anaphylaxis, anemia, aplastic anemia, aneurysm, angina pectoris, anuria, appendicitis, arrhythmia (including atrial and ventricular tachycardia, fibrillation, and torsade de pointes), arteritis, asthma, ataxia, atelectasis, atrioventricular block, bacteremia, balance/coordination impaired, basophilia, bigeminy, biliary pain, bilirubinemia, bleeding time increased, bradycardia, bradykinesia, BUN increased, bundle branch block, carcinoma, cardiovascular disorder (mitral valve and circulatory disturbance), cataract, catatonia, cellulitis, cerebral ischemia, cholelithiasis, congestive heart failure, coronary artery disease, creatinine increased, crystalluria, cyanosis, deafness, DVT, dehydration, delusions, dementia, diabetes mellitus, dystonia, ECG abnormalities (including QT prolongation), embolus, eosinophilia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, extrasystoles, facial paralysis, fasciitis, fatty liver, gastrointestinal ulcer, glaucoma, glycosuria, granuloma, Guillain-Barré syndrome, heart arrest, hematemesis, hematoma, hemorrhage (eye, GI, mucocutaneous, rectal), hepatic necrosis, hepatic failure, hepatitis, homicidal ideation, hostility, hyperacusis, hypercalcinuria, hyperchlorhydria, hyper-/hypoglycemia, hyper-/hypokalemia, hyper-/hypophosphatemia, hyper-/hypothyroidism, hyperuricemia, hypocholesteremia, hyponatremia, hypoproteinemia, hypotension, interstitial lung disease (including eosinophilic pneumonia), intestinal obstruction, jaundice, kidney function abnormal, larynx edema, leukocytosis, leukoderma, leukopenia, liver enzymes increased, loss of consciousness, lymphadenopathy, lymphocytosis, maculopapular rash, menstrual abnormalities, miliaria, moniliasis, multiple myeloma, myasthenia, myocardial infarct, myoclonus, myopathy, neck rigidity, neuroleptic malignant-like syndrome, neuropathy, neutropenia, osteoporosis, pancreatitis, pancytopenia, peripheral vascular disorder, pleurisy, pneumonia, pyelonephritis, pyuria, renal failure, rhabdomyolysis, rheumatoid arthritis, seizure, serotonin syndrome, SIADH, skin atrophy, Stevens-Johnson syndrome, suicidal ideation (reported at a frequency up to 2% in children/adolescents with major depressive disorder), suicide attempt, syncope, tendon rupture, thrombocythemia, thrombocytopenia, tongue edema, toxic epidermal necrolysis, withdrawal syndrome

Metabolism/Transport Effects **Substrate** of CYP2C9 (minor), 2C19 (minor), 2D6 (major), 3A4 (major); **Inhibits** CYP2B6 (weak), 2D6 (weak), 3A4 (weak)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha-/Beta-Agonists: Serotonin/Norepinephrine Reuptake Inhibitors may enhance the tachycardic effect of Alpha-/Beta-Agonists. Serotonin/Norepinephrine Reuptake Inhibitors may enhance the vasopressor effect of Alpha-/Beta-Agonists. *Risk D: Consider therapy modification*

Alpha2-Agonists: Serotonin/Norepinephrine Reuptake Inhibitors may diminish the antihypertensive effect of Alpha2-Agonists. **Exceptions:** Apraclonidine; Brimonidine. *Risk C: Monitor therapy*

Aspirin: Serotonin/Norepinephrine Reuptake Inhibitors may enhance the antiplatelet effect of Aspirin. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Indinavir: Venlafaxine may decrease the serum concentration of Indinavir. *Risk C: Monitor therapy*

Iobenguane I 123: Serotonin/Norepinephrine Reuptake Inhibitors may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors. This may cause serotonin syndrome. *Risk X: Avoid combination*

Metoclopramide: May enhance the adverse/toxic effect of Venlafaxine. Specifically, the risk of serotonin syndrome may be increased. *Risk C: Monitor therapy*

NSAID (Nonselective): Serotonin/Norepinephrine Reuptake Inhibitors may enhance the antiplatelet effect of NSAID (Nonselective). *Risk C: Monitor therapy*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

TraZODone: Venlafaxine may enhance the serotonergic effect of TraZODone. This could result in serotonin syndrome. *Risk D: Consider therapy modification*

Voriconazole: May enhance the adverse/toxic effect of Venlafaxine. Voriconazole may increase the serum concentration of Venlafaxine. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS effects).

Herb/Nutraceutical: Avoid valerian, St John's wort, SAMe, kava kava, tryptophan (may increase risk of serotonin syndrome and/or excessive sedation).

Test InteractionsIncreased thyroid, uric acid, glucose, potassium, AST, cholesterol (S)

Monitoring ParametersBlood pressure should be regularly monitored, especially in patients with a high baseline blood pressure; may cause mean increase in heart rate of 4-9 beats/minute; cholesterol; mental status for depression, suicidal ideation (especially at the beginning of therapy or when doses are increased or decreased), anxiety, social functioning, mania, panic attacks; height and weight should be monitored in children

Reference RangePeak serum level of 163 ng/mL (325 ng/mL of ODV metabolite) obtained after a 150 mg oral dose

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. Monitor therapeutic effectiveness according to rationale for therapy and adverse reactions at beginning of therapy and periodically with long-term use. Observe for clinical worsening, suicidality, or unusual behavior changes; especially during the initial few months of therapy or during dosage changes. Taper dosage slowly when discontinuing. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCholesterol

Patient EducationTake exactly as directed; do not increase dose or frequency. It may take 2-3 weeks to achieve desired results. Take with food. Extended release capsules should be swallowed whole; do not crush or chew. Alternatively, contents may be emptied onto a spoonful of applesauce and swallowed without chewing. Avoid alcohol, caffeine, and other prescription or OTC medications not approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience excess drowsiness or insomnia, lightheadedness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); headache, nausea, vomiting, anorexia, altered taste, dry mouth (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); diarrhea (buttermilk, yogurt, or boiled milk may help); postural hypotension (use caution when climbing stairs or changing position from lying or sitting to standing); urinary retention (void before taking medication); or sexual dysfunction (reversible). Report persistent CNS effects (eg, insomnia, restlessness, fatigue, anxiety, abnormal thoughts, suicidal ideation, confusion, personality changes, impaired cognitive function); muscle cramping or tremors; chest pain, palpitations, rapid heartbeat, swelling of extremities, or severe dizziness; unresolved urinary retention; vision changes or eye pain; hearing changes or ringing in ears; skin rash or irritation; or worsening of condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, extended release:

Effexor XR®: 37.5 mg, 75 mg, 150 mg

Tablet: 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg

Effexor®: 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg

Tablet, extended release: 37.5 mg, 75 mg, 150 mg, 225 mg

Generic AvailableYes: Excludes extended release capsule

ManufacturerWyeth-Ayerst Laboratories

Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Effexor XR)

37.5 mg (30): $109.99

75 mg (90): $345.99

150 mg (30): $129.99

Tablets (Effexor)

25 mg (30): $69.99

37.5 mg (30): $75.99

50 mg (90): $197.86

75 mg (30): $79.99

100 mg (30): $80.99

Tablets (Venlafaxine HCl)

25 mg (30): $52.99

37.5 mg (30): $53.99

50 mg (100): $189.98

75 mg (30): $59.99

100 mg (100): $190.99

Mechanism of ActionVenlafaxine and its active metabolite, o-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant activity for muscarinic cholinergic, H_1-histaminergic, or alpha$_2$-adrenergic receptors. Venlafaxine and ODV do not possess MAO-inhibitory activity.

Pharmacodynamics/Kinetics

Absorption: Oral: 92% to 100%; food has no significant effect on the absorption of venlafaxine or formation of the active metabolite O-desmethylvenlafaxine (ODV)

Distribution: At steady state: Venlafaxine 7.5 ± 3.7 L/kg, ODV 5.7 ± 1.8 L/Kg

Protein binding: Bound to human plasma protein: Venlafaxine 27%, ODV 30%

Metabolism: Hepatic via CYP2D6 to active metabolite, O-desmethylvenlafaxine (ODV); other metabolites include N-desmethylvenlafaxine and N,O-didesmethylvenlafaxine

Bioavailability: Absolute: ~45%

Half-life elimination: Venlafaxine: 3-7 hours; ODV: 9-13 hours; Steady-state, plasma: Venlafaxine/ODV: Within 3 days of multiple-dose therapy; prolonged with cirrhosis (Adults: Venlafaxine: ~30%, ODV: ~60%) and with dialysis (Adults: Venlafaxine: ~180%, ODV: ~142%)

Time to peak:

Immediate release: Venlafaxine: 2 hours, ODV: 3 hours

Extended release: Venlafaxine: 5.5 hours, ODV: 9 hours

Excretion: Urine (~87%, 5% as unchanged drug, 29% as unconjugated ODV, 26% as conjugated ODV, 27% as minor inactive metabolites) within 48 hours

Clearance at steady state: Venlafaxine: 1.3 ± 0.6 L/hour/kg, ODV: 0.4 ± 0.2 L/hour/kg

Clearance decreased with:

Cirrhosis: Adults: Venlafaxine: ~50%, ODV: ~30%

Severe cirrhosis: Adults: Venlafaxine: ~90%

Renal impairment (Cl_{cr} 10-70 mL/minute): Adults: Venlafaxine: ~24%

Dialysis: Adults: Venlafaxine: ~57%, ODV: ~56%; due to large volume of distribution, a significant amount of drug is not likely to be removed.

Related Information

- Antidepressant Agents
- Antidepressant Receptor Profile

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Significant xerostomia (normal salivary flow resumes upon discontinuation); may contribute to oral discomfort, especially in the elderly; taste perversion

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsAlthough venlafaxine is not a tricyclic antidepressant, it does block norepinephrine reuptake within CNS synapses as part of its mechanisms. It has been suggested that vasoconstrictor be administered with caution and to monitor vital signs in dental patients taking antidepressants that affect norepinephrine in this way. This is particularly important in patients taking venlafaxine, which has been noted to produce a sustained increase in diastolic blood pressure and heart rate as a side effect.

Mental Health: Child/Adolescent ConsiderationsSixteen children and adolescents (mean age: 11.6 years) with attention-deficit/hyperactivity disorder (ADHD) received a mean daily dose of 60 mg (1.4 mg/kg) administered in 2-3 divided doses (Olvera, 1996). Thirty-three children 8-17 years of age with major depression participated in a 6-week trial. For children 8-12 years, doses were initiated at 12.5 mg once daily for 3 days, then increased to 12.5 mg twice daily for 3 days, then increased to 12.5 mg 3 times/day for the rest of the study. Both venlafaxine and placebo patients improved over time, however, no significant differences in symptoms were noted between groups (Mandoki, 1997). Higher initial doses of 37.5 mg/day for 1 week with increases to 75 mg/day for 2-8 weeks are currently being investigated (Weller, 2000). Ten children with autism spectrum disorder were initiated at 12.5 mg/day and adjusted on a flexible basis (mean: 24.4 mg/day; range 6.25-50 mg/day) (Hollander, 2000).

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Mental Health CommentVenlafaxine functions like an SSRI in low doses (75 mg/day), a dual mechanism agent in moderate doses (150-225 mg/day) and affects serotonin, norepinephrine, and dopamine in high doses (375 mg/day). May cause modest dose related increases in systolic blood pressure; monitor blood pressure.

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International Brand NamesCalmdown (TW); Dobupal (ES); Efectin (BG, CZ, HN, HU, PL); Efectin ER (PL); Efexor (AR, AT, BE, BR, CH, CO, CR, DK, DO, EE, FI, GB, GR, GT, HK, HN, IE, IT, LU, NI, NL, NO, NZ, PA, PE, PK, SE, SV, TH, ZA); Efexor Depot (FI, NO, SE); Efexor ER (CH); Efexor XL (ID); Efexor XR (AR, AU, BR, CN, CO, CR, EE, GT, HN, IL, MX, MY, NI, PA, PE, PH, PT, SG, SV, TH, VE); Efexor-XR SR (KP); Effexor (FR); Elafax (PY, UY); Elafax XR (PY, UY); Faxine (TW); Trevilor (DE); Trewilor (AT); Valax SR (EC); Valosine (TW); Vandral (ES); Veniz-XR (IN); Venla (IL); Venlax (CN); Venlax Retard (CN); Ventaxin OR (KP); Viepax (IL); Viepax XR (IL)

Verapamil

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Medication Safety Issues

Sound-alike/look-alike issues:

Calan® may be confused with Colace®

Covera-HS® may be confused with Provera®

Isoptin® may be confused with Isopto® Tears

Verelan® may be confused with Virilon®, Voltaren®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication (I.V. formulation) among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Significant differences exist between oral and I.V. dosing. Use caution when converting from one route of administration to another.

International issues:

Calan®: Brand name for vinpocetine in Japan

Pronunciation(ver AP a mil)

U.S. Brand NamesCalan®; Calan® SR; Covera-HS®; Isoptin® SR; Verelan®; Verelan® PM

Canadian Brand NamesApo-Verap®; Apo-Verap® SR; Calan®; Chronovera®; Covera-HS®; Covera®; Dom-Verapamil SR; Gen-Verapamil; Gen-Verapamil SR; Isoptin® SR; Med-Verapamil; Novo-Veramil SR; Nu-Verap; PHL-Verapamil; PMS-Verapamil SR; PRO-Verapamil SR; Riva-Verapamil SR; Verapamil Hydrochloride Injection, USP; Verelan SRC

Pharmacologic CategoryAntiarrhythmic Agent, Class IV; Calcium Channel Blocker

Use: Labeled IndicationsOrally for treatment of angina pectoris (vasospastic, chronic stable, unstable) and hypertension; I.V. for supraventricular tachyarrhythmias (PSVT, atrial fibrillation, atrial flutter)

Use: Unlabeled/InvestigationalMigraine; hypertrophic cardiomyopathy; bipolar disorder (manic manifestations)

Dosing: Adults

Angina: Oral: Initial: 80-120 mg twice daily (elderly or small stature: 40 mg twice daily); range: 240-480 mg/day in 3-4 divided doses

Hypertension: Oral:

Immediate release: 80 mg 3 times/day; usual dose range (JNC 7): 80-320 mg/day in 2 divided doses

Sustained release: 240 mg/day; usual dose range (JNC 7): 120-360 mg/day in 1-2 divided doses; 120 mg/day in the elderly or small patients (no evidence of additional benefit in doses >360 mg/day).

Extended release:

Covera-HS®: Usual dose range (JNC 7): 120-360 mg once daily (once-daily dosing is recommended at bedtime)

Verelan® PM: Usual dose range: 200-400 mg once daily at bedtime

Arrhythmia (SVT): I.V.: 2.5-5 mg (over 2 minutes); second dose of 5-10 mg (~0.15 mg/kg) may be given 15-30 minutes after the initial dose if patient tolerates, but does not respond to initial dose; maximum total dose: 20 mg

Dosing: Elderly

Immediate release: Oral: 120-480 mg/24 hours divided 3-4 times/day

Sustained release: Oral: 120 mg/day; adjust dose after 24 hours by increases of 120 mg/day. When switching from immediate release forms, total daily dose may remain the same. Controlled onset: initiate therapy with 180 mg in the evening; titrate upward as needed to obtain desired response and avoiding adverse effects.

Dosing: PediatricChildren: **SVT:**

I.V.:

<1 year: 0.1-0.2 mg/kg over 2 minutes; repeat every 30 minutes as needed

1-15 years: 0.1-0.3 mg/kg over 2 minutes; maximum: 5 mg/dose, may repeat dose in 15 minutes if adequate response not achieved; maximum for second dose: 10 mg/dose

Oral (dose not well established):

1-5 years: 4-8 mg/kg/day in 3 divided doses **or** 40-80 mg every 8 hours

>5 years: 80 mg every 6-8 hours

Dosing: Renal ImpairmentCl_{cr} <10 mL/minute: Administer 50% to 75% of normal dose.

Dosing: Hepatic ImpairmentIn cirrhosis, reduce dose to 20% to 50% of normal and monitor ECG.

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Rate of infusion: Over 2 minutes

Administration: I.V. DetailpH: 4.1-6.0

Administration: OralDo not crush or chew sustained or extended release products.

Calan® SR, Isoptin® SR: Administer with food.

Verelan®, Verelan® PM: Capsules may be opened and the contents sprinkled on 1 tablespoonful of applesauce, then swallowed without chewing.

Dietary ConsiderationsCalan® SR and Isoptin® SR products may be taken with food or milk, other formulations may be administered without regard to meals; sprinkling contents of Verelan® or Verelan® PM capsule onto applesauce does not affect oral absorption.

StorageStore injection at room temperature; do not freeze. Protect from heat. Use only clear solutions. Protect I.V. solution from light. Physically compatible in solutions of pH of 3-6, but may precipitate in solutions having a pH ≥6. Protect I.V. solution from light.

CompatibilityStable in dextran 40 10% in NS, dextran 75 6% in NS, D_5LR, $D_5{}^1/_2NS$, D_5NS, D_5W, LR, ${}^1/_2NS$, NS.

Y-site administration: Compatible: Ciprofloxacin, clarithromycin, dobutamine, dopamine, famotidine, gatifloxacin, hydralazine, inamrinone, linezolid, meperidine, milrinone, penicillin G potassium, piperacillin, ticarcillin. **Incompatible:** Albumin, amphotericin B cholesteryl sulfate complex, ampicillin, nafcillin, oxacillin, propofol, sodium bicarbonate.

Compatibility in syringe: Compatible: Heparin, inamrinone, milrinone.

Compatibility when admixed: Compatible: Amikacin, amiodarone, ascorbic acid, atropine, bretylium, calcium chloride, calcium gluconate, cefamandole, cefazolin, cefotaxime, cefoxitin, chloramphenicol, cimetidine, clindamycin, dexamethasone sodium phosphate, diazepam, digoxin, dopamine, epinephrine, erythromycin lactobionate, gentamicin, heparin, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, insulin (regular), isoproterenol, lidocaine, magnesium sulfate, mannitol, meperidine, metaraminol, methyldopate, methylprednisolone sodium succinate, metoclopramide, morphine, multivitamins, naloxone, nitroglycerin, norepinephrine, oxytocin, pancuronium, penicillin G potassium, penicillin G sodium, pentobarbital, phenobarbital, phentolamine, phenytoin, piperacillin, potassium chloride, potassium phosphates, procainamide, propranolol, protamine, quinidine gluconate, sodium bicarbonate, sodium nitroprusside, theophylline, ticarcillin, tobramycin, tolazoline, vancomycin, vasopressin, vitamin B complex with C. **Incompatible:** Albumin, amphotericin B, floxacillin, hydralazine, trimethoprim/sulfamethoxazole. **Variable (consult detailed reference):** Aminophylline, ampicillin, dobutamine, furosemide, nafcillin, oxacillin.

Extemporaneously PreparedTo prepare a verapamil 50 mg/mL liquid, crush 75 verapamil hydrochloride 80 mg tablets into a fine powder. Add ~40 mL of either Ora-Sweet® and Ora-Plus® (1:1 preparation), or Ora-Sweet® SF and Ora-Plus® (1:1 preparation), or cherry syrup. Mix to a uniform paste. Continue to add the vehicle to bring the final volume to 120 mL. The preparation is stable for 60 days; shake well before using and protect from light.

Allen LV and Erickson III MA, “Stability of Labetalol Hydrochloride, Metoprolol Tartrate, Verapamil Hydrochloride, and Spironolactone With Hydrochlorothiazide in Extemporaneously Compounded Oral Liquids,” *Am J Health Syst Pharm*, 1996, 53:304-9.

ContraindicationsHypersensitivity to verapamil or any component of the formulation; severe left ventricular dysfunction; hypotension (systolic pressure <90 mm Hg) or cardiogenic shock; sick sinus syndrome (except in patients with a functioning artificial pacemaker); second- or third-degree AV block (except in patients with a functioning artificial pacemaker); atrial flutter or fibrillation and an accessory bypass tract (WPW, Lown-Ganong-Levine syndrome)

Allergy Considerations

- Verapamil Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Angina/MI: Increased angina and/or MI has occurred with initiation or dosage titration of calcium channel blockers.

- Conduction abnormalities: Can cause first-degree AV block or sinus bradycardia; other conduction abnormalities are rare.

- Hypotension/syncope: Symptomatic hypotension with or without syncope can rarely occur; blood pressure must be lowered at a rate appropriate for the patient's clinical condition.

- Increased LFTs: Rare increases in liver function tests can be observed.

- Peripheral edema: The most common side effect is peripheral edema; occurs within 2-3 weeks of starting therapy.

Disease-related concerns:

- Attenuated neuromuscular transmission: Use I.V. with caution in patients with attenuated neuromuscular transmission (Duchenne's muscular dystrophy, myasthenia gravis).

- Heart failure: Avoid use in heart failure; can exacerbate condition.

- Hepatic impairment: Use with caution in patients with hepatic impairment; may require lower starting dose.

- Idiopathic hypertrophic subaortic stenosis (IHSS): Use with caution in patients with IHSS.

- Renal impairment: Adjust the dose in severe renal impairment.

Concurrent drug therapy issues:

- Beta-blockers: Use caution when using verapamil together with a beta-blocker; avoid concurrent use of I.V. verapamil with an I.V. beta-blocker; can result in asystole.

- Digoxin: Verapamil significantly increases digoxin serum concentrations; adjust digoxin's dose.

- Neuromuscular-blocking agents: May prolong recovery from nondepolarizing neuromuscular-blocking agents.

Geriatric ConsiderationsElderly may experience a greater hypotensive response. Constipation may be more of a problem in the elderly. Calcium channel blockers are no more effective in the elderly than other therapies; however, they do not cause significant CNS effects which is an advantage over some antihypertensive agents. Generic verapamil products which are bioequivalent in young adults may not be bioequivalent in the elderly; use generics cautiously.

Pregnancy Risk FactorC

Pregnancy ConsiderationsUse in pregnancy only when clearly needed and when the benefits outweigh the potential risk to the fetus. Crosses the placenta. One report of suspected heart block when used to control fetal supraventricular tachycardia. May exhibit tocolytic effects.

LactationEnters breast milk (small amounts)/not recommended

Breast-Feeding ConsiderationsCrosses into breast milk; manufacturer recommends to discontinue breast-feeding while taking verapamil. AAP considers **compatible** with breast-feeding.

Adverse Reactions

>10%: Gastrointestinal: Gingival hyperplasia (19%)

1% to 10%:

Cardiovascular: Bradycardia (1.4% oral, 1.2% I.V.); first-, second-, or third-degree AV block (1.2% oral, unknown I.V.); CHF (1.8% oral); hypotension (2.5% oral, 3% I.V.); peripheral edema (1.9% oral); symptomatic hypotension (1.5% I.V.); severe tachycardia (1% I.V.)

Central nervous system: Dizziness (3.3% oral, 1.2% I.V.), fatigue (1.7% oral), headache (2.2% oral, 1.2% I.V.)

Dermatologic: Rash (1.2% oral)

Gastrointestinal: Constipation (12% up to 42% in clinical trials), nausea (2.7% oral, 0.9% I.V.)

Respiratory: Dyspnea (1.4% oral)

Oral: <1% (Limited to important or life-threatening): Angina, atrioventricular dissociation, chest pain, claudication, MI, palpitation, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis, bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia, rash, exanthema, hair loss, hyperkeratosis, macules, diaphoresis, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, tinnitus, gynecomastia, galactorrhea/hyperprolactinemia, urination increased, spotty menstruation, impotence, flushing, abdominal discomfort

I.V.: <1% (Limited to important or life-threatening): Bronchi/laryngeal spasm, itching, urticaria, emotional depression, rotary nystagmus, sleepiness, vertigo, muscle fatigue, diaphoresis, respiratory failure, myoclonus

Postmarketing and/or case reports: Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis, EPS, gynecomastia, eosinophilia, ventricular fibrillation, asystole, electrical mechanical dissociation, shock, myoclonus, Parkinsonian syndrome, GI obstruction, pulmonary edema, respiratory failure, hair color change

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2B6 (minor), 2C9 (minor), 2C18 (minor), 2E1 (minor), 3A4 (major); **Inhibits** CYP1A2 (weak), 2C9 (weak), 2D6 (weak), 3A4 (moderate)

Drug Interactions

Alcohol (Ethyl): Verapamil may increase the serum concentration of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alpha1-Blockers: May enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Amifostine: Antihypertensives may enhance the hypotensive effect of Amifostine. Management: When amifostine is used at chemotherapy doses, antihypertensive medications should be withheld for 24 hours prior to amifostine administration. If antihypertensive therapy can not be withheld, amifostine should not be administered. *Risk D: Consider therapy modification*

Amiodarone: Calcium Channel Blockers (Nondihydropyridine) may enhance the bradycardic effect of Amiodarone. Sinus arrest has been reported. *Risk D: Consider therapy modification*

Anilidopiperidine Opioids: May enhance the bradycardic effect of Calcium Channel Blockers (Nondihydropyridine). Anilidopiperidine Opioids may enhance the hypotensive effect of Calcium Channel Blockers (Nondihydropyridine). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Barbiturates: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Benzodiazepines (metabolized by oxidation): Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of

Benzodiazepines (metabolized by oxidation). *Risk D: Consider therapy modification*

Beta-Blockers: Calcium Channel Blockers (Nondihydropyridine) may enhance the hypotensive effect of Beta-Blockers. Bradycardia and signs of heart failure have also been reported. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Beta-Blockers. **Exceptions:** Levobunolol; Metipranolol. *Risk C: Monitor therapy*

BusPIRone: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Calcium Channel Blockers (Dihydropyridine): Calcium Channel Blockers (Nondihydropyridine) may enhance the hypotensive effect of Calcium Channel Blockers (Dihydropyridine). Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Calcium Channel Blockers (Dihydropyridine). **Exceptions:** Clevidipine. *Risk C: Monitor therapy*

Calcium Salts: May diminish the therapeutic effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

CarBAMazepine: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of CarBAMazepine. CarBAMazepine may increase the metabolism of Calcium Channel Blockers (Nondihydropyridine). *Risk D: Consider therapy modification*

Cardiac Glycosides: Calcium Channel Blockers (Nondihydropyridine) may enhance the AV-blocking effect of Cardiac Glycosides. Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Cardiac Glycosides. *Risk D: Consider therapy modification*

Cimetidine: May decrease the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Clopidogrel: Calcium Channel Blockers may diminish the therapeutic effect of Clopidogrel. *Risk C: Monitor therapy*

Colchicine: Verapamil may enhance the nephrotoxic effect of Colchicine. Colchicine may increase the serum concentration of Verapamil. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of CycloSPORINE. CycloSPORINE may decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Dabigatran Etexilate: P-Glycoprotein Inhibitors may increase the serum concentration of Dabigatran Etexilate. *Risk X: Avoid combination*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Diazoxide: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Dofetilide: Verapamil may increase the serum concentration of Dofetilide. *Risk X: Avoid combination*

Eletriptan: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Eletriptan. *Risk C: Monitor therapy*

Eplerenone: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Eplerenone. *Risk C: Monitor therapy*

Fexofenadine: Verapamil may increase the bioavailability of Fexofenadine. *Risk C: Monitor therapy*

Fluconazole: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Grapefruit Juice: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (Hypertensive Properties): May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Herbs (Hypotensive Properties): May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

HMG-CoA Reductase Inhibitors: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Pravastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Lithium: Calcium Channel Blockers (Nondihydropyridine) may enhance the neurotoxic effect of Lithium. Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of Lithium. Decreased or unaltered lithium concentrations have also been reported with this combination. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Magnesium Salts: Calcium Channel Blockers may enhance the adverse/toxic effect of Magnesium Salts. Magnesium Salts may enhance the hypotensive effect of Calcium Channel Blockers. *Risk C: Monitor therapy*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methylphenidate: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Midodrine: Calcium Channel Blockers (Nondihydropyridine) may enhance the bradycardic effect of Midodrine. *Risk C: Monitor therapy*

Nafcillin: May increase the metabolism of Calcium Channel Blockers. *Risk D: Consider therapy modification*

Neuromuscular-Blocking Agents (Nondepolarizing): Calcium Channel Blockers may enhance the neuromuscular-blocking effect of Neuromuscular-Blocking Agents (Nondepolarizing). *Risk C: Monitor therapy*

Nitroprusside: Calcium Channel Blockers may enhance the hypotensive effect of Nitroprusside. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inhibitors may increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Phenytoin: Calcium Channel Blockers may decrease the metabolism of Phenytoin. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Moderate) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the hypotensive effect of Antihypertensives. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the metabolism of Calcium Channel Blockers (Nondihydropyridine). Increased serum concentrations of the calcium channel blocker may increase risk of AV nodal blockade. *Risk D: Consider therapy modification*

QuiNIDine: Calcium Channel Blockers (Nondihydropyridine) may increase the serum concentration of QuiNIDine. *Risk D: Consider therapy modification*

Quinupristin: May decrease the metabolism of Calcium Channel Blockers. *Risk C: Monitor therapy*

Ranolazine: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Ranolazine. *Risk X: Avoid combination*

Rifamycin Derivatives: May increase the metabolism of Calcium Channel Blockers. This primarily affects oral forms of calcium channel blockers. *Risk D: Consider therapy modification*

Risperidone: Verapamil may increase the serum concentration of Risperidone. *Risk C: Monitor therapy*

RiTUXimab: Antihypertensives may enhance the hypotensive effect of RiTUXimab. *Risk D: Consider therapy modification*

Rivaroxaban: P-Glycoprotein Inhibitors may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Salicylates: Calcium Channel Blockers (Nondihydropyridine) may enhance the anticoagulant effect of Salicylates. *Risk C: Monitor therapy*

Salmeterol: CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Salmeterol. *Risk C: Monitor therapy*

Tacrolimus: Calcium Channel Blockers (Nondihydropyridine) may decrease the metabolism of Tacrolimus. *Risk C: Monitor therapy*

Topotecan: P-Glycoprotein Inhibitors may increase the serum concentration of Topotecan. *Risk X: Avoid combination*

Yohimbine: May diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid or limit ethanol (may increase ethanol levels).

Food: Grapefruit juice may increase the serum concentration of verapamil; avoid concurrent use.

Herb/Nutraceutical: St John's wort may decrease levels. Avoid dong quai if using for hypertension (has estrogenic activity). Avoid ephedra, yohimbe, ginseng (may worsen arrhythmia or hypertension). Avoid garlic (may have increased antihypertensive effect).

Monitoring ParametersMonitor blood pressure closely

Reference RangeTherapeutic: 50-200 ng/mL (SI: 100-410 nmol/L) for parent; under normal conditions, norverapamil concentration is the same as parent drug. Toxic: >90 mcg/mL

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. I.V. requires use of infusion pump and continuous cardiac and hemodynamic monitoring. Assess results of laboratory tests, therapeutic effectiveness, and adverse reactions when beginning therapy, when titrating dosage, and periodically during long-term oral therapy. Assess knowledge/teach patient appropriate use (oral), interventions to reduce side effects, and adverse symptoms to report.

Patient Education**Oral:** Take as directed. Do not alter dosage or discontinue therapy without consulting prescriber. Do not crush or chew sustained or extended release forms. Avoid grapefruit juice; avoid (or limit) alcohol and caffeine. You may experience dizziness or lightheadedness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); or diarrhea (buttermilk, boiled milk, or yogurt may help). Report chest pain, palpitations, or irregular heartbeat; unusual cough, respiratory difficulty, or swelling of extremities (feet/ankles); muscle tremors or weakness; confusion or acute lethargy; or skin irritation or rash. **Pregnancy precaution:** Inform prescriber if you are or intend to become pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Caplet, sustained release, as hydrochloride: 120 mg, 180 mg, 240 mg

Calan® SR: 120 mg

Calan® SR: 180 mg, 240 mg [scored]

Capsule, extended release, oral, as hydrochloride: 120 mg, 180 mg, 240 mg

Capsule, extended release, controlled onset, as hydrochloride: 100 mg, 200 mg, 300 mg

Verelan® PM: 100 mg, 200 mg, 300 mg

Capsule, sustained release, as hydrochloride: 120 mg, 180 mg, 240 mg, 360 mg

Verelan®: 120 mg, 180 mg, 240 mg, 360 mg

Injection, solution, as hydrochloride: 2.5 mg/mL (2 mL, 4 mL)

Tablet, as hydrochloride: 40 mg, 80 mg, 120 mg

Calan®: 40 mg

Calan®: 80 mg, 120 mg [scored]

Tablet, extended release, as hydrochloride: 120 mg, 180 mg, 240 mg

Tablet, extended release, controlled onset, as hydrochloride:

Covera-HS®: 180 mg, 240 mg

Tablet, sustained release, as hydrochloride: 120 mg, 180 mg, 240 mg

Isoptin® SR: 120 mg

Isoptin® SR: 180 mg, 240 mg [scored]

Generic AvailableYes
Pricing: U.S. (www.drugstore.com)

Capsule, 24-hour (Verapamil HCl CR)

100 mg (100): $149.98

180 mg (30): $26.99

200 mg (30): $69.99

300 mg (30): $99.93

360 mg (30): $60.99

Capsule, 24-hour (Verelan)

180 mg (30): $83.17

240 mg (30): $100.11

360 mg (30): $159.33

Capsule, 24-hour (Verelan PM)

100 mg (30): $79.12

200 mg (30): $98.90

300 mg (30): $131.87

Tablet, 24-hour (Covera-HS)

180 mg (30): $59.99

240 mg (30): $75.59

Tablet, controlled release (Calan SR)

120 mg (30): $59.99

180 mg (30): $69.99

240 mg (30): $79.96

Tablet, controlled release (Isoptin SR)

120 mg (30): $62.38

180 mg (30): $68.99

240 mg (30): $79.69

Tablet, controlled release (Verapamil HCl CR)

120 mg (30): $21.99

180 mg (30): $13.99

240 mg (30): $18.99

Tablets (Calan)

40 mg (90): $66.00

80 mg (30): $35.99

120 mg (90): $106.61

Tablets (Verapamil HCl)

80 mg (90): $16.99

120 mg (90): $16.99

Mechanism of ActionInhibits calcium ion from entering the “slow channels” or select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization; produces a relaxation of coronary vascular smooth muscle and coronary vasodilation; increases myocardial oxygen delivery in patients with vasospastic angina; slows automaticity and conduction of AV node.

Pharmacodynamics/Kinetics

Onset of action: Peak effect: Oral: Immediate release: 1-2 hours; I.V.: 1-5 minutes

Duration: Oral: Immediate release tablets: 6-8 hours; I.V.: 10-20 minutes

Protein binding: 90%

Metabolism: Hepatic via multiple CYP isoenzymes; extensive first-pass effect

Bioavailability: Oral: 20% to 35%

Half-life elimination: Infants: 4.4-6.9 hours; Adults: Single dose: 2-8 hours, Multiple doses: 4.5-12 hours; prolonged with hepatic cirrhosis

Excretion: Urine (70%, 3% to 4% as unchanged drug); feces (16%)

Related Information

- Antiarrhythmic Drugs
- Calcium Channel Blockers
- Hypertension

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Gingival hyperplasia. Calcium channel blockers (CCB) have been reported to cause gingival hyperplasia (GH). Verapamil-induced GH has appeared 11 months or more after subjects took daily doses of 240-360 mg. The severity of hyperplastic syndrome does not seem to be dose dependent. Gingivectomy is only successful if CCB therapy is discontinued. GH regresses markedly 1 week after CCB discontinuance with all symptoms resolving in 2 months. If a patient must continue CCB therapy, begin a program of professional cleaning and patient plaque control to minimize severity and growth rate of gingival tissue.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness, dizziness, confusion, insomnia, psychotic symptoms, and extrapyramidal symptoms

Mental Health: Effects on Psychiatric TreatmentBarbiturates may decrease verapamil serum concentrations; verapamil may increase buspirone, carbamazepine, and midazolam serum concentrations; concurrent use with lithium may cause an increase or decrease in serum lithium concentrations; monitor; verapamil has been used to treat bipolar disorder, mania

Cardiovascular ConsiderationsVerapamil is an effective antihypertensive alone or in combination with other agents. Therapy should be individualized with consideration given to the patient's concomitant diseases and compelling indications for therapy. A verapamil preparation (Covera® HS, Verelan® PM) uses a chronotherapeutic approach to the treatment of hypertension and angina. This drug preparation provides peak drug effects in the early morning when the circadian distribution of cardiovascular events is also at a peak. The benefit of this theoretical approach to treatment has not been established. The CONVINCE trial is currently underway to address this issue.

There is some evidence that verapamil may reduce mortality in nonfatal cardiac events, primarily myocardial infarction, in patients with history of myocardial infarction (DAVIT-II). It is important to note that this benefit was observed in patients with coronary artery disease without heart failure.

In the treatment of acute myocardial infarction, verapamil may be used to treat hypertension or ongoing ischemia if beta-blocker therapy is ineffective or contraindicated and in the absence of left ventricular dysfunction, pulmonary congestion, or AV block. In this setting, verapamil may be beneficial. Verapamil should be avoided in patients with left ventricular dysfunction or pulmonary congestion.

Verapamil may be administered intravenously in the acute setting to attain ventricular rate control in patients with atrial fibrillation or flutter. Patients who respond, defined in general as at least a 20% decrease in ventricular response rate or attaining a rate <100 beats/minute, can be continued on oral therapy to maintain control. It is important to consider the potential drug interaction with digoxin, as these agents are both used in this setting.

In the treatment of unstable angina/non-ST-segment elevation MI, a nondihydropyridine calcium antagonist (diltiazem or verapamil) may be considered in patients with continuing or frequently recurring ischemia when beta-blockers are contraindicated (Class I). Oral long-acting calcium antagonists may also be considered in addition to beta-blockers and nitrates (Class IIa).

Anesthesia and Critical Care Concerns/Other ConsiderationsI.V. administration, hypertrophic cardiomyopathy, sick sinus syndrome, moderate-to-severe congestive heart failure, concomitant therapy with beta-blockers or digoxin can all increase incidence of adverse effects. Verapamil should be avoided in patients with left ventricular dysfunction, pulmonary congestion, or heart failure. Verapamil may be administered intravenously in the acute setting to attain ventricular rate control in patients with atrial fibrillation or flutter. Patients who respond, defined in general as at least a 20% decrease in ventricular response rate or attaining a rate <100 beats/minute, can be continued on oral therapy to maintain control. It is important to consider the potential drug interaction with digoxin, as these agents are both used in this setting.

Extemporaneously Prepared: To prepare a verapamil 50 mg/mL liquid, crush 75 verapamil hydrochloride 80 mg tablets into a fine powder. Add ~ 40 mL of either Ora-Sweet® and Ora-Plus® (1:1 preparation), or Ora-Sweet® SF and Ora-Plus® (1:1 preparation), or cherry syrup. Mix to a uniform paste. Continue to add the vehicle to bring the final volume to 120 mL. The preparation is stable for 60 days; shake well before using and protect from light.

Index TermsIproveratril Hydrochloride; Verapamil Hydrochloride

References

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International Brand NamesAnpec (AU, TW); Apo-Verap (PL); Calaptin (IN); Calaptin 240 SR (IN); Cardiolen (CN); Cardiover (ID); Caveril (AE, BB, BH, BM, BS, BZ, CY, EG, ET, GH, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LY, MU, NL, OM, PR, QA, SA, SR, SY, TT, TZ, YE); Cordilat (BR); Cordilox SR (AU); Cronovera (MX); Devincil (LU); Dilacoran (BR, MX); Fibrocard (LU); Flamon (BB, BM, BS, BZ, CH, GY, JM, MY, NL, PR, SR, TT); Geangin (NL); Hexasoptin (DK, FI); Ikacor (IL); Ikapress (IL); Isoptin (AT, AU, BG, CH, CO, CZ, DE, DK, EC, EE, FI, GR, HK, HR, HU, ID, IE, IT, KP, LU, MY, NL, NO, PE, PH, PK, PL, PT, SE, ZA); Isoptin Retard (AT, CH, CR, DE, DO, EE, FI, GR, GT, HN, IT, NI, PA, PT, SE, SV); Isoptin SR (PL); Isoptin SR (AU, CL, CZ, HK, HN, KP, NL, TW, ZA); Isoptine (BE, FR); Isoptino (AR, PY, UY); Lekoptin (HR, PL); Librapamil (EC); Manidon (ES, VE); Manidon Retard (ES); Novo-Veramil (PL); Quasar (IT); Securon (GB, IE); Staveran (PL); Staveran prolongatum (PL); Vasomil (ZA); Vasopten (IN, TH); Veracaps SR (AU); Veracor (IL); Verahexal (DE, LU); Veraloc (DK); Veramex (DE); Veramil (IN); Verapamil (PL); Verapamil Hydrochloride (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Verapamil Pharmavit (HU); Verapin (TH); Verapress 240 SR (IL); Verasal Retard (CR, DO, HN, NI, SV); Veratad (CO); Verelan (PH); Verisop (IE); Verpamil (AE, BH, CY, EG, HU, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Vetrimil (TW); Zolvera (GB, IE)

Verteporfin

Lexi-Drugs Online

English

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Pronunciation(ver te POR fin)
U.S. Brand NamesVisudyne®
Canadian Brand NamesVisudyne®
Pharmacologic CategoryOphthalmic Agent
Use: Labeled IndicationsTreatment of predominantly classic subfoveal choroidal neovascularization due to macular degeneration, presumed ocular histoplasmosis, or pathologic myopia
Use: Unlabeled/InvestigationalPredominantly **occult** subfoveal choroidal neovascularization
Dosing: AdultsTherapy is a two-step process; first the infusion of verteporfin, then the activation of verteporfin with a nonthermal diode laser (for light administration details, see Administration).

Subfoveal choroidal neovascularization: I.V.: 6 mg/m^2 body surface area

Note: Treatment in more than one eye: Patients who have lesions in both eyes should be evaluated and treatment should first be done to the more aggressive lesion. Following safe and acceptable treatment, the second eye can be treated one week later. Patients who have had previous verteporfin therapy, with an acceptable safety profile, may then have both eyes treated concurrently. Treat the more aggressive lesion followed immediately with the second eye. The light treatment to the second eye should begin no later than 20 minutes from the start of the infusion.

Dosing: ElderlyRefer to adult dosing. Patients ≥75 years were less likely to benefit from therapy in clinical trials.
Dosing: Hepatic ImpairmentHalf-life is increased by 20% with mild hepatic impairment. There are no clinical studies in patients with moderate-to-severe hepatic impairment.
Calculations

- Body Surface Area: Adults

Administration: I.V.A free-flowing I.V. line should be established prior to starting infusion. Use of the largest arm vein, especially in the elderly, is suggested; avoid small veins in the back of the hand. Reconstituted solution should be given at 3 mL/minute over 10 minutes using a syringe pump and an in-line filter. If extravasation occurs (see Extravasation management), protect the site from light. Use of rubber gloves and eye protection is recommended. Skin and eye contact should be avoided and all materials should be disposed of properly.

Light administration: Following intravenous infusion, verteporfin must be light activated using a nonthermal diode laser. The system must provide a stable power output at a wavelength of 689 ± 3 nm. Approved laser systems are listed in manufacturer's package insert. Light delivery should begin 15 minutes following the start of the 10-minute infusion. The light dose is J/cm^2 of neovascular lesion administered over 83 seconds at an intensity of 600 mW/cm^2. Instructions for determining lesion size and treatment spot size can also be found in the package insert.

Administration: I.V. DetailExtravasation management: Stop infusion. To decrease the chance of a severe burn, protect the area of extravasation from direct light until swelling and discoloration have faded. Apply cold compresses to the injection site.
StorageStore vial at 20°C to 25°C (68°F to 77°F).
ReconstitutionEach vial should be reconstituted with 7 mL of sterile water for injection, providing a total volume of 7.5 mL. Resulting solution will be 2 mg/mL. Solution should be protected from light and used within 4 hours. Once reconstituted, verteporfin will be an opaque dark green solution. The total volume of solution needed to administer the dose should be withdrawn from the vial and further diluted in D_5W to a total volume of 30 mL. Infuse at 3 mL/minute over 10 minutes, using syringe pump and in-line filter.
ContraindicationsHypersensitivity to verteporfin or any component of the formulation; porphyria
Warnings/Precautions

Concerns related to adverse effects:

- Infusion reactions: Chest pain, vasovagal and hypersensitivity reactions have occurred rarely; observation of patient during infusion is suggested.
- Photosensitivity: Avoid exposing skin or eyes to direct sunlight or bright indoor light for 5 days following treatment; in case of emergency surgery within 48 hours of treatment, protect as much of the internal tissue as possible from intense light.

Disease-related concerns:

- Biliary obstruction: Use with caution in patients with biliary obstruction; not studied.
- Hepatic impairment: Use with caution in patients with moderate-to-severe hepatic impairment; not studied.

Concurrent drug therapy issues:

- Anesthesia: Use with caution in patients under anesthesia; not studied.

Special populations:

- Elderly: Patients ≥75 years of age are less likely to benefit from therapy.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Do not retreat patients who experience a decrease of vision ≥4 lines within 1 week of treatment unless vision recovers and the potential benefits and risks are carefully considered. Use of incompatible lasers (which do not provide the required light for photoactivation) can result in incomplete treatment, overtreatment, or damage to normal tissue. Patients with dark irides, occult lesions, or <50% classic choroidal neovascularization are less likely to benefit from therapy.

- Concurrent administration in both eyes: Use in more than one eye has not been studied; however, it is recommended that if required, initial treatment should be applied to the more aggressive lesion first, followed by the second eye a week later (subsequent treatment may be concurrent).

- Extravasation: Standard precautions should be taken to avoid extravasation (eg free-flowing I.V. line, use of largest arm vein).

- Long-term use: Safety and efficacy have not been established of use for longer than 2 years.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Use only if the potential benefit to the mother outweighs the potential risk to the fetus.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsVerteporfin and its metabolite were in the breast milk of one woman; milk levels were 66% of plasma levels following infusion; the metabolite was still detected 48 hours later. The manufacturer recommends that nursing be discontinued or treatment be postponed.

Adverse Reactions

>10%:

Central nervous system: Headache

Local: Injection site reactions (including injection site extravasation, injection site rash)

Ocular: Blurred vision, visual acuity decreased, visual field defects, visual disturbances

1% to 10%:

Cardiovascular: Atrial fibrillation, hypertension, peripheral vascular disorder, varicose veins

Central nervous system: Fever, hypoesthesia, sleep disturbance, vertigo

Dermatologic: Eczema, photosensitivity

Gastrointestinal: Constipation, gastrointestinal cancers, nausea

Genitourinary: Prostatic disorder

Hematologic: Anemia, leukocytosis, leukopenia

Hepatic: Liver function tests increased

Neuromuscular & skeletal: Arthralgia, arthrosis, back pain (primarily during infusion), myasthenia, weakness

Ocular: Diplopia, lacrimation disorder

Treatment site: Blepharitis, cataracts, conjunctivitis/conjunctival injection, dry eyes, ocular itching, severe vision loss (1% to 4%, decrease in 4 lines or more within 7 days of treatment, partial recovery seen in many patients), subconjunctival, subretinal or vitreous hemorrhage.

Otic: Hearing loss

Renal: Albuminuria, creatinine increased

Respiratory: Cough, pharyngitis, pneumonia

Miscellaneous: Flu-like syndrome

Frequency not defined or <1%: Chest pain, hypersensitivity, musculoskeletal pain (during infusion), retinal detachment (nonrhegmatogenous), retinal or choroidal vessel nonperfusion, vasovagal reaction

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsEthanol: Ethanol may decrease efficacy of verteporfin.

Monitoring ParametersIntravenous site during infusion, to avoid extravasation; fluorescein angiography every 3 months to monitor choroidal neovascular leakage

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 15 mg [contains egg phosphatidylglycerol]

Generic AvailableNo

Mechanism of ActionFollowing intravenous administration, verteporfin is transported by lipoproteins to the neovascular endothelium in the affected eye(s), including choroidal neovasculature and the retina. Verteporfin then needs to be activated by nonthermal red light, which results in local damage to the endothelium, leading to temporary choroidal vessel occlusion.

Pharmacodynamics/Kinetics

Metabolism: Hepatic and by plasma esterases to diacid metabolite

Half-life elimination: Terminal: 5-6 hours, biexponential

Excretion: Feces

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Mental Health CommentMay cause photosensitivity; concomitant use with psychotropic agents may produce additive risk.

International Brand NamesVisudyne (AR, AT, AU, BE, BG, BR, CH, CL, CN, CO, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, ID, IE, IL, IT, KP, MY, NL, NO, PE, PH, PK, PL, PT, RU, SE, SG, TH, TR, TW, UY, VE)

Vigabatrin

Lexi-Drugs Online

English English

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Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Pronunciation(vye GA ba trin)

Canadian Brand NamesSabril®

Pharmacologic CategoryAnticonvulsant, Miscellaneous

Use: Labeled IndicationsActive management of partial or secondary generalized seizures not controlled by usual treatments; treatment of infantile spasms

Use: Unlabeled/InvestigationalSpasticity, tardive dyskinesias

Dosing: Adults**Adjunctive therapy of seizures:** Oral: Initial: 1 g/day (severe manifestations may require 2 g/day); dose may be given as a single daily dose or divided into 2 equal doses. Increase daily dose by 0.5 g based on response and tolerability. Optimal dose range: 2-3 g/day (maximum dose: 3 g/day).

Dosing: ElderlyRefer to adult dosing. Initiate at low end of dosage range. Monitor closely for sedation and confusion.

Dosing: Pediatric**Note:** Administer daily dose in 2 divided doses, especially in the higher dosage ranges:

Adjunctive therapy of seizures: Oral: Initial: 40 mg/kg/day; maintenance dosages based on patient weight:

10-15 kg: 0.5-1 g/day

16-30 kg: 1-1.5 g/day

31-50 kg: 1.5-3 g/day

>50 kg: 2-3 g/day

Infantile spasms: Oral: 50-100 mg/kg/day, depending on severity of symptoms. Higher doses (up to 150 mg/kg/day) have been used in some cases.

Dosing: Renal ImpairmentCl_{cr} <60 mL/minute: Initiate at lower dosage; monitor closely for sedation and confusion

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: OralMay be administered with or without food.

Sachet: Dissolve powder in 10 mL of water, juice, infant formula, or milk immediately before administration. The appropriate aliquot may be administered using an oral syringe.

Dietary ConsiderationsMay be taken with or without food.

StorageStore at controlled room temperature of 15°C to 30°C (68°F to 86°F). Protect from moisture.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to vigabatrin of any component of the formulation; pregnancy or breast-feeding

Allergy Considerations

- Vigabatrin Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Neurotoxicity: Patients must be closely monitored for potential neurotoxicity (observed in animal models but not established in humans).

- Visual disturbances: May be associated with ophthalmologic toxicities, which may be permanent; baseline and periodic monitoring is required. Patients must be instructed to report changes in vision.

Disease-related concerns:

- Psychiatric behavior: Use with caution in patients with a history of psychosis (psychotic/agitated reactions may occur more frequently), depression, or behavioral problems.

- Renal impairment: Use with caution in patients with renal impairment (Cl_{cr} <60 mL/minute).

- Seizures: May cause an increase in seizure frequency in some patients; use with particular caution in patients with myoclonic seizures, which may be more prone to this effect.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Pregnancy Risk FactorNot assigned; contraindicated per manufacturer

Pregnancy ConsiderationsThere are no adequate and well-controlled studies in pregnant women. Animal studies indicating fetal malformation and neurotoxicity are of concern.

LactationExcretion in breast milk unknown/contraindicated

Adverse Reactions

>10%:

Central nervous system: Fatigue (27%), headache (26%), drowsiness (22%), dizziness (19%), depression (13%), tremor (11%), agitation (11%). **Note:** In pediatric use, hyperactivity (hyperkinesia, agitation, excitation, or restlessness) was reported in 11% of patients.

Endocrine & metabolic: Weight gain (12%)

Ocular: Visual field defects (33%), abnormal vision (11%)

1% to 10%:

Cardiovascular: Chest pain, edema (dependent)

Central nervous system: Abnormal thinking, aggression, amnesia, anxiety, ataxia, concentration impaired, confusion, emotional lability, insomnia, nervousness, personality disorder, speech disorder, vertigo

Dermatologic: Rash (5%, similar to placebo), skin disorder

Endocrine & metabolic: Dysmenorrhea, menstrual disorder

Gastrointestinal: Abdominal pain, appetite increased, constipation, diarrhea, nausea, vomiting

Genitourinary: Urinary tract infection

Hematologic: Purpura

Neuromuscular & skeletal: Abnormal coordination, abnormal gait, arthralgia, arthrosis, back pain, hyporeflexia, paresthesia, weakness

Ocular: Diplopia, eye pain, nystagmus

Otic: Ear pain

Respiratory: Nasal congestion, sinusitis, throat irritation, upper respiratory tract infection

<1% (Limited to important or life-threatening): Bilateral optic disc pallor, optic/retinal atrophy, and rare optic neuritis have been reported (usually in first year of therapy). Additional rare reactions include hallucinations, hypomania, mania, psychosis, suicidal behavior, angioedema, hypersensitivity, urticaria, and stupor.

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Phenytoin: Vigabatrin may decrease the serum concentration of Phenytoin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid evening primrose (seizure threshold decreased). Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring Parameters Ophthalmologic examination at baseline and periodically during therapy (every 3 months); including mydriatic peripheral fundus examination and visual field perimetry. Observe patient for excessive sedation, especially when instituting or increasing therapy.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Powder for oral suspension [sachets]:

Sabril® [CAN]: 0.5 g [not available in the U.S.]

Tablet:

Sabril® [CAN]: 500 mg [not available in the U.S.]

Generic Available No

Manufacturer Aventis Pharma (Canada)

Mechanism of Action Irreversibly inhibits gamma-aminobutyric acid transaminase (GABA-T), increasing the levels of the inhibitory compound gamma amino butyric acid (GABA) within the brain. Duration of effect is dependent upon rate of GABA-T resynthesis.

Pharmacodynamics/Kinetics

Duration (rate of GABA-T resynthesis dependent): Variable (not strictly correlated to serum concentrations)

Absorption: Rapid

Metabolism: Minimal

Half-life elimination: 5-8 hours; Elderly: Up to 13 hours

Time to peak: 2 hours

Excretion: Urine (70%, as unchanged drug)

Pharmacotherapy Pearls Not available in U.S.

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

References

Bar-Oz B, Nulman I, Koren G, et al, “Anticonvulsants and Breast-Feeding: A Critical Review,” *Paediatr Drugs*, 2000, 2(2):113-26. [PubMed 10937463]

Challier JC, Rey E, Bintein T, et al, “Passage of S(+) and R(-) Gamma-vinyl-GABA Across the Human Isolated Perfused Placenta,” *Br J Clin Pharmacol*, 1992, 34(2):139-43. [PubMed 1419475]

Sabers A and Gram L, “Newer Anticonvulsants: Comparative Review of Drug Interactions and Adverse Effects,” *Drugs*, 2000, 60(1):23-33. [PubMed 10929928]

Sabril® product monograph, Aventis Pharma Inc, Quebec, April 2001.

Tran A, O'Mahoney T, Rey E, et al, “Vigabatrin: Placental Transfer *in vivo* and Excretion Into Breast Milk of the Enantiomers,” *Br J Clin Pharmacol*, 1998, 45(4):409-11.[PubMed 9578192]

International Brand Names Sabril (AR, AT, AU, BE, BR, CH, CN, CO, CZ, DE, FR, GB, GR, HK, HN, HR, HU, IE, IT, LU, NL, PL, PT, PY, TW, UY, ZA); Sabrilan (IL); Sabrilex (DK, ES, FI, NO, SE)

VinBLAStine

Lexi-Drugs Online

English English

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ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

VinBLAStine may be confused with vinCRIStine, vinorelbine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Note: Must be dispensed in overwrap which bears the statement **"Do not remove covering until the moment of injection. Fatal if given intrathecally. For I.V. use only."** Syringes should be labeled: **"Fatal if given intrathecally. For I.V. use only."**

Pronunciation(vin BLAS teen)

Pharmacologic CategoryAntineoplastic Agent, Natural Source (Plant) Derivative; Antineoplastic Agent, Vinca Alkaloid

Use: Labeled IndicationsTreatment of Hodgkin's and non-Hodgkin's lymphoma; testicular cancer; breast cancer; mycosis fungoides; Kaposi's sarcoma; histiocytosis (Letterer-Siwe disease); choriocarcinoma

Use: Unlabeled/InvestigationalTreatment of bladder cancer, melanoma, nonsmall cell lung cancer (NSCLC), ovarian cancer, prostate cancer, renal cancer, soft tissue sarcoma (desmoid tumors)

Dosing: AdultsDetails concerning dosing in combination regimens should also be consulted. **Note:** Frequency and duration of therapy may vary by indication, concomitant combination chemotherapy and hematologic response. **For I.V. use only.**

Antineoplastic (typical dosages): I.V.: Initial: 3.7 mg/m^2; adjust dose every 7 days (based on white blood cell response) up to 5.5 mg/m^2 (second dose); 7.4 mg/m^2 (third dose); 9.25 mg/m^2 (fourth dose); and 11.1 mg/m^2 (fifth dose); do not administer more frequently than every 7 days.

Usual range: 5.5-7.4 mg/m^2 every 7 days; Maximum dose: 18.5 mg/m^2; dosage adjustment goal is to reduce white blood cell count to ~3000/mm^3

Indication-specific dosing:

Hodgkin’s disease: Usual dose: 6 mg/m^2 every 2 weeks (as part of a combination chemotherapy regimen) (Horning, 2002; Bartlett, 1995)

Testicular cancer: Usual dose: 0.11 mg/kg daily for 2 days every 3 weeks (as part of a combination chemotherapy regimen) (Loehrer, 1998) **or** 6 mg/m^2/day for 2 days every 3-4 weeks (as part of a combination chemotherapy regimen) (Clemm, 1986)

Bladder cancer (unlabeled use): Usual dose: 3 mg/m^2 every 7 days for 3 out of 4 weeks (as part of combination chemotherapy) (Sternberg, 2001) **or** 3 mg/m^2 days 2, 15, and 22 of a 28-day treatment cycle (as part of a combination chemotherapy regimen) (von der Maase, 2000)

Melanoma (unlabeled used): 2 mg/m^2 days 1-4 and 22-25 of a 6-week treatment cycle (as part of a combination chemotherapy regimen) (Eton, 2002)

Nonsmall cell lung cancer (unlabeled use): 4 mg/m^2 days 1, 8, 15, 22, and 29, then every 2 weeks (as part of combination chemotherapy) (Arriagada, 2004)

Ovarian cancer (unlabeled use): 0.11 mg/kg daily for 2 days every 3 weeks (as part of a combination chemotherapy regimen) (Loehrer, 1998)

Prostate cancer (unlabeled use): 4 mg/m^2 every week for 6 weeks of an 8-week treatment cycle (as part of combination chemotherapy) (Hudes, 1999)

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricDetails concerning dosing in combination regimens should also be consulted. **Note:** Frequency and duration of therapy may vary by indication, concomitant combination chemotherapy and hematologic response. **For I.V. use only.**

Hodgkin’s disease: I.V.: Initial dose: 6 mg/m^2; do not administer more frequently than every 7 days

Letterer-Siwe disease: I.V.: Initial dose: 6.5 mg/m^2; do not administer more frequently than every 7 days

Testicular cancer: I.V.: Initial dose: 3 mg/m^2; do not administer more frequently than every 7 days

Dosing: Renal ImpairmentAccording to FDA-approved labeling, no adjustment is necessary in patients with renal impairment.

Dosing: Hepatic Impairment

The FDA-approved labeling recommends the following guidelines: Serum bilirubin >3 mg/dL: Administer 50% of dose

The following guidelines have been used by some clinicians:

Serum bilirubin >3.1 or ALT/AST >3 times ULN: Avoid use (Floyd, 2006) **or**

Serum bilirubin 1.5-3 mg/dL or AST 60-180 units: Administer 50% of dose

Serum bilirubin 3-5 mg/dL: Administer 25% of dose

Serum bilirubin >5 mg/dL or AST >180 units: Avoid use

Dosing: Combination Regimens

Bladder cancer:

CMV

M-VAC (Bladder Cancer)

Breast cancer:

M-VAC (Breast Cancer)

VATH

VM

Cervical cancer: M-VAC (Cervical Cancer)

Endometrial cancer: M-VAC (Endometrial Cancer)

Head and Neck cancer: M-VAC (Head and Neck Cancer)

Lung cancer (nonsmall cell): Cisplatin-Vinblastine (NSCLC)

Lymphoma, Hodgkin's:

ABVD

CAD/MOPP/ABV

ChIVPP

Etoposide-Vinblastine-Doxorubicin (Hodgkin's)

MOPP/ABV Hybrid

MOPP/ABVD

MVPP

Stanford V Regimen

Melanoma:

Cisplatin-Vinblastine-Dacarbazine (Melanoma)

CVD-Interleukin-Interferon (Melanoma)

Prostate cancer:

Doxorubicin + Ketoconazole/Estramustine + Vinblastine

Estramustine-Vinblastine

Soft tissue sarcoma: Methotrexate-Vinblastine (Desmoid Tumor)

Testicular cancer:

PVB

VBP

VIP (Vinblastine) (Testicular Cancer)

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Vesicant. **Fatal if given intrathecally.** For I.V. administration only, usually as a slow (2-3 minutes) push, or a bolus (5-15 minutes) infusion; the manufacturer recommends an undiluted 1-minute infusion to prevent venous irritation/extravasation. Prolonged administration times and/or increased administration volumes may the risk of vein irritation and extravasation. Assure proper needle or catheter placement prior to administration.

Administration: I.V. DetailpH: 3.5-5.0

Storage**Note: Must be dispensed in overwrap which bears the statement “Do not remove covering until the moment of injection. Fatal if given intrathecally. For I.V. use only.” Syringes should be labeled: “Fatal if given intrathecally. For I.V. use only.”**

Store intact vials under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light. Solutions reconstituted in bacteriostatic NS are stable for 28 days under refrigeration.

ReconstitutionReconstitute lyophilized powder to a concentration of 1 mg/mL with NS or bacteriostatic NS. For infusion, may dilute in 50 mL NS or D_5W; dilution in larger volumes (≥100 mL) of I.V. fluids is not recommended. Use appropriate precautions for handling and disposal.

CompatibilityStable in D_5W, LR, NS

Y-site administration: Compatible: Allopurinol, amifostine, amphotericin B cholesteryl sulfate complex, aztreonam, bleomycin, cisplatin, cyclophosphamide, doxorubicin, doxorubicin liposome, droperidol, etoposide phosphate, filgrastim, fludarabine, fluorouracil, gatifloxacin, gemcitabine, granisetron, heparin, leucovorin calcium, melphalan, methotrexate, metoclopramide, mitomycin, ondansetron, paclitaxel, piperacillin/tazobactam, sargramostim, teniposide, thiotepa, vincristine, vinorelbine. **Incompatible:** Cefepime, furosemide, lansoprazole.

Compatibility in syringe: Compatible: Bleomycin, cisplatin, cyclophosphamide, droperidol, fluorouracil, leucovorin calcium, methotrexate, metoclopramide, mitomycin, vincristine. **Incompatible:** Furosemide. **Variable (consult detailed reference):** Doxorubicin, heparin.

Compatibility when admixed: Compatible: Bleomycin, dacarbazine. **Variable (consult detailed reference):** Doxorubicin.

ContraindicationsSignificant granulocytopenia; presence of bacterial infection; I.T. administration is contraindicated (may result in death)

Allergy Considerations

- Vinca Alkaloid Allergy

Warnings/Precautions

Boxed warnings:

- Experienced physician: See “Other warnings/precautions” below.
- NOT for intrathecal use: See “Other warnings/precautions” below.
- Vesicant: See “Other warnings/precautions” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal. Avoid eye contamination (exposure may cause severe irritation).

Concerns related to adverse effects:

- Bone marrow suppression: Leukopenia is common; granulocytopenia may be severe with higher doses. Leukopenia may be more pronounced in cachectic patients and patients with skin ulceration. Thrombocytopenia and anemia may occur rarely.
- Neurotoxicity: May rarely cause disabling neurotoxicity; usually reversible.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; toxicity may be increased; may require dosage modification.
- Ischemic heart disease: Use with caution in patients with ischemic heart disease.

Concurrent drug therapy issues:

- Itraconazole: Itraconazole may decrease the metabolism of vinblastine via CYP3A4 inhibition and may increase the effects of vinblastine via P-glycoprotein effects. Severe myelosuppression and neurotoxicity may occur.
- Mitomycin C: Acute shortness of breath and severe bronchospasm have been reported, most often in association with concurrent administration of mitomycin; may occur within minutes to several hours following vinblastine administration or up to 14 days following mitomycin administration; use caution in patients with pre-existing pulmonary disease.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**
- NOT for intrathecal use: **[U.S. Boxed Warning]: For I.V. use only. Intrathecal administration may result in death.** Must be dispensed in overwrap which bears the statement **"Do not remove covering until the moment of injection. Fatal if given intrathecally. For I.V. use only."**
- Vesicant: **[U.S. Boxed Warning]: Vinblastine is a moderate vesicant; avoid extravasation. Individuals administering should be experienced in vinblastine administration.** Assure proper needle or catheter placement prior to administration.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies have demonstrated resorption and teratogenic effects. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should avoid becoming pregnant during vinblastine treatment. Aspermia has been reported in males who have received treatment with vinblastine.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.
Adverse ReactionsFrequency not defined.

Common:

Cardiovascular: Hypertension

Central nervous system: Malaise

Dermatologic: Alopecia

Gastrointestinal: Constipation

Hematologic: Myelosuppression, leukopenia/granulocytopenia (nadir: 5-10 days; recovery: 7-14 days; dose-limiting toxicity)

Neuromuscular & skeletal: Bone pain, jaw pain, tumor pain

Less common:

Cardiovascular: Angina, cerebrovascular accident, coronary ischemia, ECG abnormalities, MI, Raynaud's phenomenon

Central nervous system: Depression, dizziness, headache, neurotoxicity (duration: >24 hours), seizure, vertigo

Dermatologic: Dermatitis, photosensitivity (rare), rash, skin blistering

Endocrine & metabolic: Aspermia, hyperuricemia, SIADH

Gastrointestinal: Abdominal pain, anorexia, diarrhea, gastrointestinal bleeding, hemorrhagic enterocolitis, ileus, metallic taste, nausea (mild), paralytic ileus, rectal bleeding, stomatitis, vomiting (mild)

Genitourinary: Urinary retention

Hematologic: Anemia, thrombocytopenia (recovery within a few days)

Local: Cellulitis (with extravasation), irritation, phlebitis (with extravasation), radiation recall

Neuromuscular & skeletal: Deep tendon reflex loss, myalgia, paresthesia, peripheral neuritis, weakness

Ocular: Nystagmus

Otic: Auditory damage, deafness, vestibular damage

Respiratory: Bronchospasm, dyspnea, pharyngitis

Oncology: VesicantYes; see Management of Drug Extravasations.
Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak), 3A4 (weak)
Drug Interactions

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dabigatran Etexilate: P-Glycoprotein Inducers may decrease the serum concentration of Dabigatran Etexilate. *Risk C: Monitor therapy*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Itraconazole: May increase the serum concentration of VinBLAStine. *Risk C: Monitor therapy*

Lopinavir: May increase the serum concentration of VinBLAStine. Management: Monitor closely for signs and symptoms of vinblastine toxicity; consider temporary interruption of lopinavir/ritonavir antiviral therapy if patients develop significant toxicity with concurrent use. *Risk D: Consider therapy modification*

Mitomycin: Antineoplastic Agents (Vinca Alkaloids) may enhance the adverse/toxic effect of Mitomycin. Specifically, the risk of pulmonary toxicity may be increased. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Substrates: P-Glycoprotein Inducers may decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Tolterodine: VinBLAStine may increase the serum concentration of Tolterodine. Management: Reduce tolterodine dosage to 1 mg twice daily (regular release formulation) or 2 mg daily (extended release formulation) and monitor for increased levels/effects of tolterodine with initiation of vinblastine therapy. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid St John's wort (may decrease vinblastine levels). Avoid black cohosh, dong quai in estrogen-dependent tumors.

Monitoring ParametersCBC with differential and platelet count, serum uric acid, hepatic function tests

Nursing: Physical Assessment/MonitoringUse caution with impaired liver function. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, previous or concurrent use mitomycin-C can cause severe reaction). Premedication with antiemetic is advisable. Infusion site must be monitored closely to prevent extravasation (vesicant will cause tissue damage and necrosis). Assess results of laboratory tests, renal function, and adverse reactions (eg, SIADH, bone marrow suppression, leukopenia, hypertension, gastrointestinal disturbance, myalgia, depression, paresthesia) prior to each infusion and throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsCBC with differential and platelet count, serum uric acid, hepatic function

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by infusion; report immediately any redness, swelling, burning, or pain at infusion site; sudden difficulty breathing; swelling; chest pain; or chills. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition (small, frequent meals will help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations unless approved by prescriber). May cause hair loss (will grow back after therapy); nausea or vomiting (request antiemetic); photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); feelings of extreme weakness or lethargy (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or mouth sores (use soft toothbrush, waxed dental floss, and frequent oral care). Report persistent constipation or abdominal pain; numbness or tingling in fingers or toes (use care to prevent injury); weakness or pain in muscles or jaw; signs of infection (eg, fever, chills, sore throat, burning urination, fatigue); unusual bleeding (eg, tarry stools, easy bruising, blood in stool, urine, or mouth); unresolved mouth sores; skin rash or itching; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Do not get pregnant (females) or cause a pregnancy (males) during this therapy. Consult prescriber for appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as sulfate: 10 mg

Injection, solution, as sulfate: 1 mg/mL (10 mL) [contains benzyl alcohol]

Generic AvailableYes

Mechanism of ActionVinblastine binds to tubulin and inhibits microtubule formation, therefore, arresting the cell at metaphase by disrupting the formation of the mitotic spindle; it is specific for the M and S phases. Vinblastine may also interfere with nucleic acid and protein synthesis by blocking glutamic acid utilization.

Pharmacodynamics/Kinetics

Distribution: V_d: 27.3 L/kg; binds extensively to tissues; does not penetrate CNS or other fatty tissues; distributes to liver

Protein binding: 99%

Metabolism: Hepatic to active metabolite

Half-life elimination: Biphasic: Initial: 4 minutes; Terminal: 25 hours

Excretion: Feces (95%); urine (<1% as unchanged drug)

Related Information

- Management of Drug Extravasations
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Stomatitis, metallic taste, and jaw pain.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause depression

Mental Health: Effects on Psychiatric TreatmentBone marrow suppression is common; use caution with clozapine and carbamazepine

Index TermsNSC-49842; Velban; Vinblastine Sulfate; Vincaleukoblastine; VLB

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International Brand NamesBlastovin (IL, PY); Cytoblastin (IN); Lemblastine (MX); Oncostin (PH); Velban (BR); Velbe (AR, AT, AU, BE, BF, BG, BJ, CH, CI, CN, CZ, DE, DK, ES, ET, FI, FR, GB, GH, GM, GN, GR, HN, HR, IE, IT, KE, LR, LU, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, PE, PK, PL, PT, RU, SC, SD, SE, SL, SN, TN, TR, TZ, UG, ZA, ZM, ZW); Vinblastin (HU, PL); Vinblastine Sulfate Injection (AU); Xintoprost (AR)

VinCRIStine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

VinCRIStine may be confused with vinBLAStine

Oncovin® may be confused with Ancobon®

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

To prevent fatal inadvertent intrathecal injection, it is recommended that all doses be dispensed in a small minibag. If dispensing vincristine in a syringe, vincristine must be packaged in the manufacturer-provided overwrap which bears the statement **"Do not remove covering until the moment of injection. For intravenous use only. Fatal if given intrathecally."**

Pronunciation(vin KRIS teen)

U.S. Brand NamesVincasar PFS®

Canadian Brand NamesVincasar® PFS®

Pharmacologic CategoryAntineoplastic Agent, Natural Source (Plant) Derivative; Antineoplastic Agent, Vinca Alkaloid

Use: Labeled IndicationsTreatment of leukemias, Hodgkin's disease, non-Hodgkin's lymphomas, Wilms' tumor, neuroblastoma, rhabdomyosarcoma

Dosing: Adults**Note:** Doses are often capped at 2 mg; however, this may reduce the efficacy of the therapy and may not be advisable. Refer to individual protocols; orders for single doses >2.5 mg or >5 mg/treatment cycle should be verified with the specific treatment regimen and/or an experienced oncologist prior to dispensing.

Antineoplastic (typical dosages): I.V.: 0.4-1.4 mg/m^2, may repeat every week **or**

0.4-0.5 mg/day continuous infusion for 4 days every 4 weeks **or**

0.25-0.5 mg/m^2/day continuous infusion for 5 days every 4 weeks

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to individual protocols. **Note:** Doses are often capped at 2 mg; however, this may reduce the efficacy of the therapy and may not be advisable. Orders for single doses >2.5 mg or >5 mg/treatment cycle should be verified with the specific treatment regimen and/or an experienced oncologist prior to dispensing.

Antineoplastic (typical dosages): I.V.:

Children ≤10 kg or BSA <1 m^2: Initial therapy: 0.05 mg/kg once weekly then titrate dose

Children >10 kg or BSA ≥1 m^2: 1-2 mg/m^2, may repeat once weekly for 3-6 weeks; maximum single dose: 2 mg

Neuroblastoma: I.V. continuous infusion with doxorubicin: 1 mg/m^2/day for 72 hours

Dosing: Renal ImpairmentNo adjustment is necessary in patients with renal impairment.

Dosing: Hepatic Impairment

The FDA-approved labeling recommends the following guidelines: Serum bilirubin >3 mg/dL: Administer 50% of normal dose

The following guidelines have been used by some clinicians:

Serum bilirubin 1.5-3 mg/dL or AST 60-180 units: Administer 50% of dose

Serum bilirubin 3-5 mg/dL: Administer 25% of dose

Serum bilirubin >5 mg/dL or AST >180 units: Avoid use

Floyd, 2006: Serum bilirubin 1.5-3 mg/dL or ALT/AST 2-3 times ULN or alkaline phosphatase elevated: Administer 50% of dose

Dosing: Combination Regimens

Breast cancer: CMFVP (Cooper Regimen, VPCMF)

Brain tumors:

- 8 in 1 (Brain Tumors)
- COPE
- MOP
- MOPP (Medulloblastoma)
- PCV
- POC

Gestational trophoblastic tumor:

- CHAMOCA (Modified Bagshawe Regimen)
- CHAMOMA (Bagshawe Regimen)
- EMA/CO

Head and neck cancer: CABO

Leukemia, acute lymphocytic:

- DVP
- Hyper-CVAD + Imatinib
- Hyper-CVAD (Leukemia, Acute Lymphocytic)
- Larson Regimen
- Linker Protocol
- MTX/6-MP/VP (Maintenance)
- POMP
- PVA (POG 8602)
- PVDA
- VAD/CVAD

Leukemia, chronic lymphocytic: CVP (Leukemia)

Lung cancer (small cell): CAVE

Lymphoma, Hodgkin's:

- BEACOPP
- CAD/MOPP/ABV
- COMP
- LOPP
- MOPP (Lymphoma, Hodgkin's Disease)
- MOPP/ABV Hybrid
- MOPP/ABVD
- OPA
- OPPA
- Stanford V Regimen

Lymphoma, non-Hodgkin's:

- CHOP
- CNOP
- CODOX-M
- CODOX-M/IVAC
- COMLA
- COP-BLAM

- COPP
- CVP (Lymphoma, non-Hodgkin's)
- EPOCH
- Hyper-CVAD (Lymphoma, non-Hodgkin's)
- MACOP-B
- m-BACOD
- Pro-MACE-CytaBOM
- Rituximab-CHOP
- R-CVP

Lymphoma, non-Hodgkin's (Burkitt's): CODOX-M/IVAC

Lymphoma, non-Hodgkin's (Mantle cell): Hyper-CVAD + Rituximab

Melanoma:

- BOLD
- BOLD (Melanoma)
- BOLD + Interferon

Multiple myeloma:

- Doxorubicin (Liposomal)-Vincristine-Dexamethasone
- Hyper-CVAD (Multiple Myeloma)
- M-2
- VAD
- VBAP
- VBMCP
- VCAP

Neuroblastoma:

- CAV-P/VP
- CE-CAdO
- HIPE-IVAD
- N4SE Protocol
- N6 Protocol
- OPEC
- OPEC-D
- PE-CAdO
- Regimen A1

Prostate cancer: Cyclophosphamide + Vincristine + Dexamethasone

Retinoblastoma:

- 8 in 1 (Retinoblastoma)
- CO
- CV
- VAC (Retinoblastoma)

Rhabdomyosarcoma:

- CEV
- VAC Pulse
- VAC (Rhabdomyosarcoma)

Sarcoma:

CYVADIC

VAC Alternating With IE (Ewing's Sarcoma)

Wilms' tumor:

AAV (DD)

ACAV (J)

AV (EE)

AV (K)

AV (L)

AV (Wilms' Tumor)

AVD

EE

EE-4A

Calculations

- Body Surface Area: Adults
- Body Surface Area: Pediatrics

Administration: I.V.Vesicant. For I.V. use only. **Fatal if given intrathecally.** Usually administered as short (10-15 minutes) infusion (preferred) or slow (1-2 minutes) push; 24-hour continuous infusions are occasionally used

Administration: I.V. DetailFollow guidelines for handling cytotoxic agents. Drug should be administered by qualified personnel. Do not allow to come in contact with skin. If contact occurs, wash thoroughly with soap and water. Avoid extravasation; agent is a vesicant and will cause sloughing.

pH: 3.5-5.5

Administration: OtherIntralesional injection has been reported for Kaposi's sarcoma

Storage

Undiluted vials: Store under refrigeration. May be stable for up to 30 days at room temperature.

I.V. solution: Diluted in 20-50 mL NS or D$_5$W, stable for 7 days under refrigeration, or 2 days at room temperature. In ambulatory pumps, solution is stable for 7-10 days at room temperature.

Reconstitution Solutions for I.V. infusion may be mixed in NS or D$_5$W. **Note:** The World Health Organization (WHO) recommends dispensing vincristine in a minibag, rather than a syringe.

CompatibilityStable in D$_5$W, LR, NS.

Y-site administration: Compatible: Allopurinol, amifostine, amphotericin B cholesteryl sulfate complex, aztreonam, bleomycin, cisplatin, cladribine, cyclophosphamide, doxorubicin, doxorubicin liposome, droperidol, etoposide phosphate, filgrastim, fludarabine, fluorouracil, gatifloxacin, gemcitabine, granisetron, heparin, leucovorin, linezolid, melphalan, methotrexate, metoclopramide, mitomycin, ondansetron, paclitaxel, piperacillin/tazobactam, sargramostim, teniposide, thiotepa, topotecan, vinblastine, vinorelbine. **Incompatible:** Cefepime, furosemide, idarubicin, sodium bicarbonate.

Compatibility in syringe: Compatible: Bleomycin, cisplatin, cyclophosphamide, doxapram, doxorubicin, droperidol, fluorouracil, heparin, leucovorin, methotrexate, metoclopramide, mitomycin, vinblastine. **Incompatible:** Furosemide.

Compatibility when admixed: Compatible: Bleomycin, cytarabine, doxorubicin with ondansetron, fluorouracil, methotrexate. **Variable (consult detailed reference):** Doxorubicin with etoposide.

ContraindicationsHypersensitivity to vincristine or any component of the formulation; **for I.V. use only, fatal if given intrathecally**; patients with demyelinating form of Charcot-Marie-Tooth syndrome; pregnancy

Allergy Considerations

- Vinca Alkaloid Allergy

Warnings/Precautions

Boxed warnings:

- Not for intrathecal use: See “Other warnings/precautions” below.
- Vesicant: See “Other warnings/precautions” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal; avoid eye contamination.

Concerns related to adverse effects:

- Constipation: With use, constipation and/or paralytic ileus may occur; all patients should be on a prophylactic bowel management regimen.

- Neurotoxicity: Alterations in mental status such as depression, confusion, or insomnia may occur; neurologic effects may be additive with those of other neurotoxic agents and spinal cord irradiation.

- Respiratory effects: Observe closely for shortness of breath and bronchospasm.

- Urinary tract disturbances: With use, urinary tract disturbances may occur.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage modification required.

- Neuromuscular disease: Use with caution in patients with pre-existing neuromuscular disease; dosage modification required.

Concurrent drug therapy issues:

- Mitomycin C: Monitor closely for shortness of breath or bronchospasm in patients receiving in combination with mitomycin C.

Special populations:

- Elderly: Use with caution in the elderly.

Other warnings/precautions:

- Not for intrathecal use: **[U.S. Boxed Warning]: Intrathecal administration has uniformly caused severe neurologic damage and/or death; vincristine should never be administered by this route. For I.V. use only.**

- Vesicant: **[U.S. Boxed Warning]: Vincristine is a vesicant; avoid extravasation. (Individuals administering should be experienced in vincristine administration.)**

Pregnancy Risk FactorD
LactationEnters breast milk/not recommended
Adverse Reactions

>10%: Dermatologic: Alopecia (20% to 70%)

1% to 10%:

Cardiovascular: Orthostatic hypotension or hypertension, hyper-/hypotension

Central nervous system: CNS depression, confusion, cranial nerve paralysis, fever, headache, insomnia, motor difficulties, seizure

Intrathecal administration of vincristine has uniformly caused death; vincristine should never be administered by this route. Neurologic effects of vincristine may be additive with those of other neurotoxic agents and spinal cord irradiation.

Dermatologic: Rash

Endocrine & metabolic: Hyperuricemia

Gastrointestinal: Abdominal cramps, anorexia, bloating, constipation (and possible paralytic ileus secondary to neurologic toxicity), diarrhea, metallic taste, nausea (mild), oral ulceration, vomiting, weight loss

Genitourinary: Bladder atony (related to neurotoxicity), dysuria, polyuria, urinary retention

Hematologic: Leukopenia (mild), thrombocytopenia, myelosuppression (onset: 7 days; nadir: 10 days; recovery: 21 days)

Local: Phlebitis, tissue irritation and necrosis if infiltrated

Neuromuscular & skeletal: Cramping, jaw pain, leg pain, myalgia, numbness, weakness

Peripheral neuropathy: Frequently the dose-limiting toxicity of vincristine. Most frequent in patients >40 years of age; occurs usually after an average of 3 weekly doses, but may occur after just one dose. Manifested as loss of the deep tendon reflexes in the lower extremities, numbness, tingling, pain, paresthesia of the fingers and toes (stocking glove sensation), and “foot drop” or “wrist drop.”

Ocular: Optic atrophy, photophobia

<1%: SIADH (rare), stomatitis

Oncology: VesicantYes; moderate. See Management of Drug Extravasations.
Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Substrate** of CYP3A4 (major); **Inhibits** CYP3A4 (weak)
Drug Interactions

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of VinCRIStine. *Risk D: Consider therapy modification*

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. **Exceptions:** Digitoxin. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Lopinavir: May increase the serum concentration of VinCRIStine. Management: Monitor closely for signs and symptoms of vincristine toxicity; consider temporary interruption of lopinavir/ritonavir antiviral therapy if patients develop significant toxicity with concurrent use. *Risk D: Consider therapy modification*

Mitomycin: Antineoplastic Agents (Vinca Alkaloids) may enhance the adverse/toxic effect of Mitomycin. Specifically, the risk of pulmonary toxicity may be increased. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

NIFEdipine: May decrease the excretion of VinCRIStine. *Risk C: Monitor therapy*

P-Glycoprotein Inducers: May decrease the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

P-Glycoprotein Inhibitors: May increase the serum concentration of P-Glycoprotein Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: St John's wort may decrease vincristine levels.

Monitoring ParametersSerum electrolytes (sodium), hepatic function tests, neurologic examination, CBC, serum uric acid

Nursing: Physical Assessment/MonitoringUse caution with impaired liver function or pre-existing neuromuscular disease. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, previous or concurrent use with mitomycin-C can cause severe reaction). Premedication with antiemetic is advisable. Infusion site must be monitored closely to prevent extravasation (vesicant will cause tissue damage and necrosis). May cause severe constipation, paralytic ileus, intestinal obstruction, necrosis, and/or perforation; prophylactic bowel management regimen may be advisable. Assess results of laboratory tests, hepatic function, and adverse reactions prior to each infusion and throughout therapy (eg, CNS [motor difficulties, seizure, depression], neuromuscular [myalgia, cramping], peripheral neuropathy, photophobia). Teach patient possible side effects/appropriate interventions and adverse symptoms to report.

Monitoring: Lab TestsSerum electrolytes (sodium), hepatic function, CBC, serum uric acid

Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by infusion; report immediately any redness, swelling, burning, or pain at infusion site. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake and nutrition (small frequent meals will help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations unless approved by prescriber). May cause postural hypotension (use caution when rising from sitting or lying position or when climbing steps); hair loss (will grow back after therapy); nausea or vomiting (request antiemetic if persistent); photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); feelings of extreme weakness or lethargy (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or mouth sores (use soft toothbrush, waxed dental floss, and frequent oral care). Report persistent gastrointestinal changes (eg, constipation, abdominal cramps, bloating); numbness, tingling, or pain in legs, fingers, or toes (use care to prevent injury); signs of infection (eg, fever, chills, sore throat, burning urination, fatigue); unusual bleeding (eg, tarry stools, easy bruising, blood in stool, urine, or mouth); unresolved mouth sores; skin rash or itching; respiratory difficulty; or other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Do not get pregnant (females) or cause a pregnancy (males) during this therapy. Consult prescriber for appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as sulfate [preservative free]:

Vincasar PFS®: 1 mg/mL (1 mL, 2 mL)

Generic AvailableYes

Mechanism of ActionBinds to tubulin and inhibits microtubule formation, therefore, arresting the cell at metaphase by disrupting the formation of the mitotic spindle; it is specific for the M and S phases. Vincristine may also interfere with nucleic acid and protein synthesis by blocking glutamic acid utilization.

Pharmacodynamics/Kinetics

Absorption: Oral: Poor

Distribution: V_d: 163-165 L/m^2; poor penetration into CSF; rapidly removed from bloodstream and tightly bound to tissues; penetrates blood-brain barrier poorly

Protein binding: 75%

Metabolism: Extensively hepatic

Half-life elimination: Terminal: 24 hours

Excretion: Feces (~80%); urine (<1% as unchanged drug)

Related Information

- Management of Drug Extravasations
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral ulceration, metallic taste, orthostatic hypotension or hypertension.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause sedation, confusion, depression, or insomnia
Mental Health: Effects on Psychiatric TreatmentMay cause myelosuppression; use caution with clozapine and carbamazepine
Index TermsLeurocristine Sulfate; NSC-67574; Oncovin; Vincristine Sulfate
References

Ahn YS, Harrington WJ, Mylvaganam R, et al, “Slow Infusion of Vinca Alkaloids in the Treatment of Idiopathic Thrombocytopenic Purpura,” *Ann Intern Med*, 1984, 100(2):192-6. [PubMed 6537881]

Aronoff GR, Bennett WM, Berns JS, et al, *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*, 5th ed. Philadelphia, PA: American College of Physicians; 2007, p 102, 174.

Bermudez M, Fuster JL, Llinares E, et al, “Itraconazole-Related Increased Vincristine Neurotoxicity: Case Report and Review of Literature,” *J Pediatr Hematol Oncol*, 2005, 27(7):389-92.[PubMed 16012330]

Bohme A, Ganser A, and Hoelzer D, “Aggravation of Vincristine-Induced Neurotoxicity by Itraconazole in the Treatment of Adult ALL,” *Ann Hematol*, 1995, 71(6):311-2.[PubMed 8534764]

Camplejohn RS, “A Critical Review of the Use of Vincristine (VCR) as a Tumour Cell Synchronizing Agent in Cancer Therapy,” *Cell Tissue Kinet*, 1980, 13(3):327-35. [PubMed 6989508]

Floyd J, Mirza I, Sachs B, et al, "Hepatotoxicity of Chemotherapy," *Semin Oncol*, 2006, 33(1):50-67.[PubMed 16473644]

Joel S, “The Comparative Clinical Pharmacology of Vincristine and Vindesine: Does Vindesine Offer Any Advantage in Clinical Use?” *Cancer Treat Rev*, 1996, 21(6):513-25. [PubMed 8599802]

Legha SS, “Vincristine Neurotoxicity. Pathophysiology and Management,” *Med Toxicol*, 1986, 1(6):421-7. [PubMed 3540519]

McCune JS and Lindley C, “Appropriateness of Maximum-Dose Guidelines for Vincristine,” *Am J Health Syst Pharm*, 1997, 54(15):1755-8. [PubMed 9262750]

Tajti J, Somogyi I, and Szilard J, “Treatment of Chronic Pain Syndromes With Transcutaneous Iontophoresis of Vinca Alkaloids, With Special Regard to Postherpetic Neuralgia,” *Acta Med Hung*, 1989, 46(1):3-12.[PubMed 2549500]

International Brand NamesCitomid RU (MX, TH); Cristovin (IL); Cytocristin (IN); Farmistin CS (DE); Kyocristine (JP); Oncovin (AT, AU, BE, BF, BG, BJ, BR, CH, CI, CN, CZ, DE, DK, ES, ET, FI, FR, GB, GH, GM, GN, GR, HN, HR, IE, IT, KE, LR, LU, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, PE, PK, PL, PT, RU, SC, SD, SE, SL, SN, TN, TR, TZ, UG, ZA, ZM, ZW); Vinces (AR); Vincran (KP); Vincrina (PY); Vincristin (HU, PL); Vincristina (IT); Vincristine Delta West (HR); Vincristine Sulfate (PL); Vincristine Sulfate Injection (AU); Vincristine-David Bull (LU); Vincrisul (ES); Vinracine (MY); Vinsulgen (PH); Vintec (MX)

Vindesine

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Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

To prevent fatal inadvertent intrathecal injection, it is recommended by ISMP that all doses be dispensed in a small minibag. **Fatal if given intrathecally.**

Pronunciation(VIN de seen)

Pharmacologic CategoryAntineoplastic Agent, Vinca Alkaloid

Use: Unlabeled/InvestigationalInvestigational: Management of acute lymphocytic leukemia, chronic myelogenous leukemia; breast, head, neck, and lung cancers; lymphomas (Hodgkin's and non-Hodgkin's)

Dosing: AdultsRefer to individual protocols. I.V.:

3-4 mg/m^2 /week **or**

1-2 mg/m^2 days 1 and 2 every 2 weeks **or**

1-2 mg/m^2 days 1-5 (continuous infusion) every 2-4 weeks **or**

1-2 mg/m^2 days 1-5 every 3-4 weeks

Dosage adjustment in hepatic impairment: Dosage reductions of 50% to 75% have been suggested for “severe” hepatic dysfunction; however, specific guidelines have not been published.

Dosing: ElderlyRefer to adult dosing.

Dosing: Hepatic ImpairmentDosage reductions of 50% to 75% have been suggested for “severe” hepatic dysfunction; however, specific guidelines have not been published.

Dosing: Combination Regimens

Breast cancer: VM

Lymphoma, Hodgkin's disease: CAD/MOPP/ABV

Calculations

- Body Surface Area: Adults

Administration: I.V.Usually administered as a rapid I.V. push (2-3 minutes) or short (15-20 minutes) infusion; 24-hour continuous infusions are occasionally used.

StorageReconstituted solutions are stable for 30 days under refrigeration (2°C to 8°C/36°F to 46°F). Solutions diluted in dextrose or saline for I.V. infusion are stable for 24 hours at room temperature (15°C to 30°C/59°F to 86°F). **The drug will precipitate at pH >6.**

ReconstitutionThe powder is reconstituted to a concentration of 1 mg/mL.

RestrictionsNot available in U.S./Investigational

ContraindicationsHypersensitivity to vindesine, vinca alkaloids, or any component of the formulation

Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Disease-related concerns:

- Hepatic impairment: Use with caution (if at all) in patients with hepatic impairment.

- Neurologic impairment: Use with caution (if at all) in patients with neurologic problems.

Other warnings/precautions:

- Cross-resistance: Vindesine has been reported to be cross-resistance with vincristine.

- Not for intrathecal administration: **Intrathecal administration may be fatal.**

LactationBreast-feeding is not recommended.

Adverse Reactions

>10%:

Central nervous system: Pyrexia, malaise (up to 60%)

Dermatologic: Alopecia (6% to 92%)

Gastrointestinal: Mild nausea and vomiting (7% to 27%), constipation (10% to 17%) - related to the neurotoxicity

Hematologic: Leukopenia (50%) and thrombocytopenia (14% to 26%), may be dose limiting; thrombocytosis (20% to 28%)

Nadir: 6-12 days

Recovery: Days 14-18

Neuromuscular & skeletal: Paresthesia (40% to 70%); loss of deep tendon reflexes (35% to 60%, may be dose limiting); myalgia (up to 60%)

1% to 10%:

Dermatologic: Rashes

Gastrointestinal: Loss of taste

Hematologic: Anemia

Local: Phlebitis

Neuromuscular & skeletal: Facial paralysis

<1%: Acute chest pain, ECG changes, paralytic ileus, jaw pain, photophobia

Oncology: VesicantYes; see Management of Drug Extravasations.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 5 mg

Generic AvailableNo

Mechanism of ActionVindesine is a semisynthetic vinca alkaloid, having a mechanism of action similar to the other vinca derivatives. It arrests cell division in metaphase through inhibition of microtubular formation of the mitotic spindle. The drug is cell-cycle specific for the S phase.

Pharmacodynamics/Kinetics

Distribution: V_d: 8 L/kg; minimal distribution to adipose tissue or CNS

Metabolism: Hepatic

Half-life elimination:

Triphasic; Alpha: 2 minutes; Beta: 1 hour

Terminal: 24 hours

Excretion: Feces; urine (~3% to 25% of dose as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Loss of taste and facial paralysis.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMalaise is common

Mental Health: Effects on Psychiatric TreatmentHematological side effects are common; use caution with clozapine, carbamazepine, and valproic acid.

Mental Health CommentParesthesias are common.

Index TermsDAVA; Deacetyl Vinblastine Carboxamide; Desacetyl Vinblastine Amide Sulfate; DVA; Eldisine Lilly 99094; Lilly CT-3231; NSC-245467; Vindesine Sulfate

References

Dancey J and Steward WP, “The Role of Vindesine in Oncology - Recommendations After 10 Years' Experience,” *Anticancer Drugs*, 1995, 6(5):625-36. [PubMed 8845472]

Joel S, “The Comparative Clinical Pharmacology of Vincristine and Vindesine: Does Vindesine Offer Any Advantage in Clinical Use?” *Cancer Treat Rev*, 1996, 21(6):513-25. [PubMed 8599802]

Rhomberg W, Eiter H, Soltesz E, et al, “Long-Term Application of Vindesine: Toxicity and Tolerance,” *J Cancer Res Clin Oncol*, 1990, 116(6):651-3. [PubMed 2254384]

Sorenson JB and Hansen HH, “Is There a Role for Vindesine in the Treatment of Nonsmall Cell Lung Cancer?” *Invest New Drugs*, 1993, 11(2-3):103-33.[PubMed 8262725]

International Brand NamesEldisin (AT); Eldisine (AR, AU, BE, CH, DE, FI, FR, GB, IT, LU, NL, SE, ZA); Enisan (ES); Fildesin (JP); Gesidine (PT); XI AI KE (CL)

Vinorelbine-Cisplatin

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Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Lung Cancer (Nonsmall Cell)
Regimen Use Lung cancer, nonsmall cell
Index Terms Cisplatin-Vinorelbine; VC
Regimen NOTE: Multiple variations are listed below.

Variation 1:

Cisplatin: I.V.: 50 mg/m^2/day days 1 and 8

[total dose/cycle = 100 mg/m^2]

Vinorelbine: I.V.: 25 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 28 days for total of 4 cycles

Variation 2:

Vinorelbine: I.V.: 25 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 100 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 28 days

Variation 3:

Vinorelbine: I.V.: 30 mg/m^2 weekly

Cisplatin: I.V.: 120 mg/m^2/day days 1 and 29, then once every 6 weeks

Variation 4:

Vinorelbine: I.V.: 30 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 90 mg/m^2]

Cisplatin: I.V.: 80 mg/m^2 day 1

[total dose/cycle = 80 mg/m^2]

Repeat cycle every 21 days for total of 4 cycles

Note: Vinorelbine treatment is discontinued after day 1 of cycle 4

Variation 5:

Vinorelbine: I.V.: 30 mg/m^2/day days 1, 8, 15, and 22

[total dose/cycle = 120 mg/m^2]

Cisplatin: I.V.: 100 mg/m^2 day 1

[total dose/cycle = 100 mg/m^2]

Repeat cycle every 28 days for total of 3 or 4 cycles

Note: Vinorelbine treatment is discontinued after day 1 of last treatment cycle

References

Variation 1:

Winton T, Livingston R, Johnson D, et al, "Vinorelbine Plus Cisplatin Vs. Observation in Resected Non-Small-Cell Lung Cancer," *N Engl J Med*, 2005, 352(25):2589-97.[PubMed 15972865]

Variation 2:

Kelly K, Crowley J, Bunn PA Jr, et al, “Randomized Phase III Trial of Paclitaxel Plus Carboplatin Versus Vinorelbine Plus Cisplatin in the Treatment of Patients With Advanced Nonsmall-Cell Lung Cancer: A Southwest Oncology Group Trial,” *J Clin Oncol*, 2001, 19(13):3210-8. [PubMed 11432888]

Wozniak AJ, Crowley JJ, Balcerzak SP, et al, “Randomized Trial Comparing Cisplatin With Cisplatin Plus Vinorelbine in the Treatment of Advanced Nonsmall-Cell Lung Cancer: A Southwest Oncology Group Study,” *J Clin Oncol*, 1998, 16(7):2459-65. [PubMed 9667264]

Variation 3:

Le Chevalier T, Brisgand D, Douillard JY, et al, “Randomized Study of Vinorelbine and Cisplatin Versus Vindesine and Cisplatin Versus Vinorelbine Alone in Advanced Nonsmall-Cell Lung Cancer: Results of a European Multicenter Trial Including 612 Patients,” *J Clin Oncol*, 1994, 12(2):360-7.[PubMed 8113844]

Le Chevalier T, Pujol JL, Douillard JY, et al, “A Three-Arm Trial of Vinorelbine (Navelbine) Plus Cisplatin, Vindesine Plus Cisplatin, and Single-Agent Vinorelbine in the Treatment of Nonsmall Cell Lung Cancer: An Expanded Analysis,” *Semin Oncol*, 1994, 21(5 Suppl 10):28-33; discussion 33-4.[PubMed 7973766]

Variations 4 and 5:

Arriagada R, Bergman B, Dunant A, et al, "Cisplatin-Based Adjuvant Chemotherapy in Patients With Completely Resected Non-Small-Cell Lung Cancer," *N Engl J Med*, 2004, 350(4):351-60.[PubMed 14736927]

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer
Regimen Use Breast cancer
Index Terms FEC-Vinorelbine

Regimen

Cycles 1 and 2:

Vinorelbine: I.V.: 25 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 75 mg/m^2]

Treatment cycle is 21 days

Cycle 3:

Vinorelbine: I.V.: 25 mg/m^2/day days 1 and 8

[total dose/cycle 3 = 50 mg/m^2]

Treatment cycle is 21 days

Cycles 4, 5, and 6 (FEC):

Fluorouracil: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Epirubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat FEC cycle every 21 days for total of 3 cycles

References

Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al, "Adjuvant Docetaxel or Vinorelbine With or Without Trastuzumab for Breast Cancer," *N Engl J Med*, 2006, 354(8):809-20.[PubMed 16495393]

Vinorelbine-Gemcitabine

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Nonsmall Cell)

Regimen UseLung cancer, nonsmall cell

Regimen

Vinorelbine: I.V.: 20 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 60 mg/m^2]

Gemcitabine: I.V.: 800 mg/m^2/day days 1, 8, and 15

[total dose/cycle = 2400 mg/m^2]

Repeat cycle every 28 days

References

Chen YM, Perng RP, Yang KY, et al, âA Multicenter Phase II Trial of Vinorelbine Plus Gemcitabine in Previously Untreated Inoperable (Stage IIIB/IV) Nonsmall Cell Lung Cancer,â *Chest*, 2000, 117(6):1583-9.[PubMed 10858387]

Vinorelbine-Trastuzumab-FEC

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Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer
Regimen Use Breast cancer
Index Terms Vinorelbine-Trastuzumab-FEC
Regimen

Cycle 1:

Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1 cycle 1

followed by I.V.: 2 mg/kg/day days 8 and 15 cycle 1

[total dose/cycle 1 = 8 mg/kg]

Vinorelbine: I.V.: 25 mg/m^2/day days 1, 8, and 15

[total dose/cycle 1 = 75 mg/m^2]

Treatment cycle is 21 days

Cycle 2:

Trastuzumab: I.V.: 2 mg/kg/day days 1, 8, and 15

[total dose/cycle = 6 mg/kg]

Vinorelbine: I.V.: 25 mg/m^2/day days 1, 8, and 15

[total dose/cycle 2 = 75 mg/m^2]

Treatment cycle is 21 days

Cycle 3:

Trastuzumab: I.V.: 2 mg/kg/day days 1, 8, and 15

[total dose/cycle = 6 mg/kg]

Vinorelbine: I.V.: 25 mg/m^2/day days 1 and 8

[total dose/cycle 3 = 50 mg/m^2]

Treatment cycle is 21 days

Cycles 4, 5, and 6 (FEC):

Fluorouracil: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Epirubicin: I.V.: 60 mg/m^2 day 1

[total dose/cycle = 60 mg/m^2]

Cyclophosphamide: I.V.: 600 mg/m^2 day 1

[total dose/cycle = 600 mg/m^2]

Repeat FEC cycle every 21 days for total of 3 cycles

References

Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al, "Adjuvant Docetaxel or Vinorelbine With or Without Trastuzumab for Breast Cancer," *N Engl J Med*, 2006, 354(8):809-20.[PubMed 16495393]

Vinorelbine-Trastuzumab

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Breast Cancer

Regimen Use Breast cancer

Index Terms Trastuzumab-Vinorelbine

Regimen

Week 1:

Trastuzumab: I.V.: 4 mg/kg (loading dose) day 1 week 1

[total dose/week 1 = 4 mg/kg]

Vinorelbine: I.V.: 25 mg/m^2 day 1

[total dose/week 1 = 25 mg/m^2]

Subsequent weeks:

Trastuzumab: I.V.: 2 mg/kg (loading dose) day 1

[total dose/week = 2 mg/kg]

Vinorelbine: I.V.: 25 mg/m^2 day 1

[total dose/week = 25 mg/m^2]

Repeat weekly

References

Burstein HJ, Kuter I, Campos SM, et al, "Clinical Activity of Trastuzumab and Vinorelbine in Women With HER2-Overexpressing Metastatic Breast Cancer," *J Clin Oncol*, 2001, 19(10):2722-30.[PubMed 11352965]

Vinorelbine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Vinorelbine may be confused with vinBLAStine

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Vinorelbine is intended **for I. V. use only**: Inadvertent intrathecal administration of other vinca alkaloids has resulted in death. Syringes containing vinorelbine should be labeled **“For I.V. use only. Fatal if given intrathecally.”**

Pronunciation(vi NOR el been)

U.S. Brand NamesNavelbine®

Canadian Brand NamesNavelbine®; Vinorelbine Injection, USP; Vinorelbine Tartrate for Injection

Pharmacologic CategoryAntineoplastic Agent, Natural Source (Plant) Derivative; Antineoplastic Agent, Vinca Alkaloid

Use: Labeled IndicationsTreatment of nonsmall cell lung cancer (NSCLC)

Use: Unlabeled/InvestigationalTreatment of breast cancer, cervical cancer, and ovarian cancer

Dosing: AdultsDetails concerning dosing in combination regimens should also be consulted.

Nonsmall cell lung cancer: I.V.:

Single-agent therapy: 30 mg/m^2/dose every 7 days

Combination therapy with cisplatin: 25-30 mg/m^2/dose every 7 days (in combination with cisplatin)

Breast cancer (unlabeled use): I.V.: 25 mg/m^2/dose every 7 days

Cervical cancer (unlabeled use): I.V.: 30 mg/m^2/dose days 1 and 8 of a 21-day treatment cycle

Ovarian cancer (unlabeled use): I.V.: 25 mg/m^2/dose every 7 days **or** 30 mg/m^2/dose days 1 and 8 of a 21-day treatment cycle

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal ImpairmentNo adjustment is necessary.

Dosing: Hepatic Impairment

The FDA-approved labeling guidelines are as follows: Vinorelbine should be administered with caution in patients with hepatic insufficiency. In patients who develop hyperbilirubinemia during treatment with vinorelbine, the dose should be adjusted for total bilirubin as follows:

Serum bilirubin ≤2 mg/dL: Administer 100% of dose

Serum bilirubin 2.1-3 mg/dL: Administer 50% of dose

Serum bilirubin >3 mg/dL: Administer 25% of dose

In patients with concurrent hematologic toxicity and hepatic impairment, administer the lower of the doses determined from the adjustment recommendations under Adult Dosing.

Dosing: Adjustment for Toxicity

Dosage adjustment in hematological toxicity (based on granulocyte counts):

Granulocytes ≥1500 cells/mm^3 on day of treatment: Administer 100% of starting dose.

Granulocytes 1000-1499 cells/mm^3 on day of treatment: Administer 50% of starting dose.

Granulocytes <1000 cells/mm^3 on day of treatment: Do not administer. Repeat granulocyte count in 1 week. If 3 consecutive doses are held because granulocyte count is <1000 cells/mm^3, discontinue vinorelbine.

Adjustment: For patients who, during treatment, have experienced fever or sepsis while granulocytopenic or had 2 consecutive weekly doses held due to granulocytopenia, subsequent doses of vinorelbine should be:

75% of starting dose for granulocytes ≥1500 cells/mm^3

37.5% of starting dose for granulocytes 1000-1499 cells/mm^3

Dosage adjustment for neurotoxicity: Neurotoxicity ≥grade 2: Discontinue treatment

Dosing: Combination Regimens

Breast cancer:

Paclitaxel-Vinorelbine

VD

Vinorelbine-FEC

Vinorelbine-Trastuzumab

Vinorelbine-Trastuzumab-FEC

Cervical cancer: Cisplatin-Vinorelbine

Leukemia, acute lymphocytic: TVTG

Leukemia, acute myeloid: TVTG

Lung cancer (nonsmall cell):

Cetuximab-Cisplatin-Vinorelbine

Gemcitabine-Vinorelbine

Vinorelbine-Cisplatin

Vinorelbine-Gemcitabine

Lymphoma, Hodgkin's: Gemcitabine-Vinorelbine-Doxorubicin (Liposomal)

Prostate cancer: Estramustine + Vinorelbine

Calculations

- Body Surface Area: Adults

Administration: I.V.**FATAL IF GIVEN INTRATHECALLY.** Administer as a direct intravenous push or rapid bolus, over 6-10 minutes (up to 30 minutes). Longer infusions may increase the risk of pain and phlebitis. Intravenous doses should be followed by at least 75-125 mL of saline or D_5W to reduce the incidence of phlebitis and inflammation. Assure proper needle or catheter position prior to administration.

Administration: I.V. DetailDo not administer in an extremity with poor circulation or repeatedly into the same vein.

pH: 3.5 (injection)

StorageStore intact vials under refrigeration at 2°C to 8°C (36°F to 46°F); do not freeze. Protect from light. Intact vials are stable at room temperature of 25°C (77°F) for up to 72 hours. Dilutions in D_5W or NS are stable for 24 hours at room temperature.

ReconstitutionDilute in D_5W or NS to a final concentration of 1.5-3 mg/mL (for syringe) or 0.5-2 mg/mL (for I.V. bag).

CompatibilityStable in $D_5{}^1/_2$NS, D_5W, LR, NS, $^1/_2$NS.

Y-site administration: Compatible: Amikacin, aztreonam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, carmustine, cefotaxime, ceftazidime, ceftizoxime, chlorpromazine, cimetidine, cisplatin, clindamycin, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, dexamethasone sodium phosphate, diphenhydramine, doxorubicin, doxorubicin liposome, doxycycline, droperidol, enalaprilat, etoposide, famotidine, filgrastim, floxuridine, fluconazole, fludarabine, gatifloxacin, gemcitabine, gentamicin, granisetron, haloperidol, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, idarubicin, ifosfamide, imipenem/cilastatin, lorazepam, mannitol, mechlorethamine, melphalan, meperidine, mesna, methotrexate, metoclopramide, metronidazole, minocycline, mitoxantrone, morphine, nalbuphine, netilmicin, ondansetron, plicamycin, streptozocin, teniposide, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, vinblastine, vincristine, zidovudine. **Incompatible:** Acyclovir, allopurinol, aminophylline, amphotericin B, amphotericin B cholesteryl sulfate complex, ampicillin, cefazolin, cefoperazone, cefotetan, ceftriaxone, cefuroxime, co-trimoxazole, fluorouracil, furosemide, ganciclovir, methylprednisolone sodium succinate, mitomycin, piperacillin, sodium bicarbonate, thiotepa. **Variable (consult detailed reference):** Heparin.

ContraindicationsPretreatment granulocyte counts <1000/mm^3

Allergy Considerations

- Vinca Alkaloid Allergy

Warnings/Precautions

Boxed warnings:

• Bone marrow suppression: See “Concerns related to adverse effects” below.

• Experienced physician: See “Other warnings/precautions” below.

- Extravasation: See “Other warnings/precautions” below.
- NOT for intrathecal use: See “Other warnings/precautions” below.

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal; avoid eye contamination (exposure may cause severe irritation).

Concerns related to adverse effects:

- Bone marrow suppression: **[U.S. Boxed Warning]: Severe granulocytopenia may occur with treatment;** granulocytopenia is a dose-limiting toxicity; granulocyte counts should be ≥1000/mm^3 prior to treatment initiation; monitor closely for infections and/or fever; may require dosage adjustment. Use with caution in patients with compromised marrow reserve due to prior chemotherapy therapy or prior radiation therapy.
- Gastrointestinal effects: May cause severe constipation (grade 3-4), paralytic ileus, intestinal obstruction, necrosis, and/or perforation.
- Neuropathy: May cause new onset or worsening of pre-existing neuropathy; use with caution in patients with neuropathy.
- Pulmonary toxicity: Fatal cases of interstitial pulmonary changes and ARDS have been reported with single-agent therapy. Promptly evaluate changes in baseline pulmonary symptoms or any new-onset pulmonary symptoms.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage modification required.
- Neurotoxicity: Use with caution in patients with neurotoxicity; dosage modification required.
- Radiation therapy: May have radiosensitizing effects with prior or concurrent radiation therapy; radiation recall reactions may occur in patients who have received prior radiation therapy.

Concurrent drug therapy issues:

- Cisplatin: The incidence of granulocytopenia is significantly higher when given in combination with cisplatin when compared to single-agent vinorelbine.
- Mitomycin C: Acute shortness of breath and severe bronchospasm have been reported rarely; usually associated with concurrent administration of mitomycin.

Other warnings/precautions:

- Experienced physician: **[U.S. Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**
- Extravasation: **[U.S. Boxed Warning]: Avoid extravasation;** infiltration may cause irritation, thrombophlebitis and/or local tissue necrosis.
- NOT for intrathecal use: **[U.S. Boxed Warning]: Intrathecal administration may result in death.** For I.V. use only.

Pregnancy Risk FactorD
Pregnancy ConsiderationsAnimal studies have demonstrated embryotoxicity, fetotoxicity, decreased fetal weight, and delayed ossification. There are no adequate and well-controlled studies in pregnant women. Women of childbearing potential should avoid becoming pregnant during vinorelbine treatment.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.
Adverse Reactions**Note:** Reported with single-agent therapy.

>10%:

Central nervous system: Fatigue (27%)

Dermatologic: Alopecia (12% to 30%)

Gastrointestinal: Nausea (31% to 44%; grade 3: 1% to 2%), constipation (35%; grade 3: 3%), vomiting (20% to 31%; grade 3: 1% to 2%), diarrhea (12% to 17%)

Hematologic: Leukopenia (83% to 92%; grade 4: 6% to 15%), granulocytopenia (90%; grade 4: 36%; nadir: 7-10 days; recovery 14-21 days; dose-limiting), neutropenia (85%; grade 4: 28%), anemia (83%; grades 3/4: 9%)

Hepatic: AST increased (67%; grade 3: 5%; grade 4: 1%), total bilirubin increased (5% to 13%; grade 3: 4%; grade 4: 3%)

Local: Injection site reaction (22% to 28%; includes erythema, vein discoloration), injection site pain (16%)

Neuromuscular & skeletal: Weakness (36%), peripheral neuropathy (25%; grade 3: 1%; grade 4: <1%)

Renal: Creatinine increased (13%)

1% to 10%:

Cardiovascular: Chest pain (5%)

Dermatologic: Rash (<5%)

Gastrointestinal: Paralytic ileus (1%)

Hematologic: Neutropenic fever/sepsis (8%; grade 4: 4%), thrombocytopenia (3% to 5%; grades 3/4: 1%)

Local: Phlebitis (7% to 10%)

Neuromuscular & skeletal: Loss of deep tendon reflexes (<5%), myalgia (<5%), arthralgia (<5%), jaw pain (<5%)

Otic: Ototoxicity (≤1%)

Respiratory: Dyspnea (7%)

<1%, postmarketing, and/or case reports: Abdominal pain, allergic reactions, anaphylaxis, angioedema, back pain, DVT, dysphagia, esophagitis, flushing, gait instability, headache, hemorrhagic cystitis, hyper-/hypotension, hyponatremia, intestinal necrosis, intestinal obstruction, intestinal perforation, interstitial pulmonary changes, local rash, local urticaria, MI (rare), mucositis, muscle weakness, pancreatitis, paralytic ileus, pneumonia, pruritus, pulmonary edema, pulmonary embolus, radiation recall (dermatitis, esophagitis), skin blistering, syndrome of inappropriate ADH secretion, tachycardia, thromboembolic events, tumor pain, urticaria, vasodilation

Oncology: VesicantYes. See Management of Drug Extravasations.
Oncology: Emetic PotentialVery low (<10%)
Metabolism/Transport Effects**Substrate** of CYP2D6 (minor), 3A4 (major); **Inhibits** CYP2D6 (weak), 3A4 (weak)
Drug Interactions

CISplatin: May enhance the adverse/toxic effect of Vinorelbine. Specifically, the combination may be associated with a higher risk of granulocytopenia. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Mitomycin: Antineoplastic Agents (Vinca Alkaloids) may enhance the adverse/toxic effect of Mitomycin. Specifically, the risk of pulmonary toxicity may be increased. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Paclitaxel: May enhance the neurotoxic effect of Vinorelbine. *Risk C: Monitor therapy*

Paclitaxel (Protein Bound): May enhance the neurotoxic effect of Vinorelbine. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). *Risk C: Monitor therapy*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsHerb/Nutraceutical: Avoid St John's wort (may decrease vinorelbine levels).
Monitoring ParametersCBC with differential and platelet count, hepatic function tests; monitor for new-onset pulmonary symptoms (or worsening from baseline); monitor for neuropathy
Nursing: Physical Assessment/MonitoringAssess potential for interactions with other pharmacological agents and herbal products patient may be taking. Premedication with antiemetic is advisable. May cause severe constipation, paralytic ileus, intestinal obstruction, necrosis, and/or perforation; prophylactic bowel management regimen may be advisable. See Administration for infusion specifics. Infusion site must be monitored closely to prevent extravasation (may cause tissue damage and necrosis). Assess results of laboratory tests regularly. Evaluate therapeutic effectiveness and adverse reactions prior to each infusion and throughout therapy. Teach patient possible side effects/appropriate interventions and adverse symptoms to report.
Monitoring: Lab TestsCBC with differential and platelet count, hepatic function
Patient EducationDo not take any new medication during therapy unless approved by prescriber. This medication can only be administered by infusion; report immediately any redness, swelling, burning, or pain at infusion site. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake, and nutrition (small, frequent meals will help). You will be more susceptible to infection (avoid crowds and exposure to infection and do not have any vaccinations unless approved by prescriber). May cause hair loss (will grow back after therapy); nausea or vomiting (request antiemetic); photosensitivity (use sunscreen, wear protective clothing and eyewear, and avoid direct sunlight); feelings of weakness or lethargy (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or mouth sores (use soft toothbrush, waxed dental floss and frequent oral care). Report persistent constipation or abdominal pain; numbness or tingling in fingers or toes (use care to prevent injury); weakness, numbness, or pain in muscles or extremities; signs of infection (eg, fever, chills, sore throat, burning urination, fatigue); unusual bleeding (eg, tarry stools, easy bruising, blood in stool, urine, or mouth); unresolved mouth sores; skin rash or itching; or respiratory difficulty. **Pregnancy/breast-feeding precautions:** Do not get pregnant (females) or cause a pregnancy (males) during this therapy. Consult prescriber for appropriate contraceptive measures. Do not breast-feed.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 10 mg/mL (1 mL, 5 mL)

Navelbine®: 10 mg/mL (1 mL, 5 mL)

Generic AvailableYes

Mechanism of ActionSemisynthetic vinca alkaloid which binds to tubulin and inhibits microtubule formation, therefore, arresting the cell at metaphase by disrupting the formation of the mitotic spindle; it is specific for the M and S phases. Vinorelbine may also interfere with nucleic acid and protein synthesis by blocking glutamic acid utilization.

Pharmacodynamics/Kinetics

Absorption: Unreliable; must be given I.V.

Distribution: V_d: 25-40 L/kg; binds extensively to human platelets and lymphocytes (80% to 91%)

Protein binding: 80% to 91%

Metabolism: Extensively hepatic, via CYP3A4, to two metabolites, deacetylvinorelbine (active) and vinorelbine N-oxide

Bioavailability: Oral (not approved in the U. S.): 26% to 45%

Half-life elimination: Triphasic: Terminal: 28-44 hours

Excretion: Feces (46%); urine (18%, 10% to 12% as unchanged drug)

Clearance: Plasma: Mean: 0.97-1.26 L/hour/kg

Related Information

- Management of Drug Extravasations
- Safe Handling of Hazardous Drugs

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause drowsiness

Mental Health: Effects on Psychiatric TreatmentBone marrow suppression is common; avoid clozapine and carbamazepine

Index TermsDihydroxydeoxynorvinkaleukoblastine; Vinorelbine Tartrate

References

Bajetta E, Di Leo A, Biganzoli L, et al, “Phase II Study of Vinorelbine in Patients With Pretreated Advanced Ovarian Cancer: Activity in Platinum-Resistant Disease,” *J Clin Oncol*, 1996, 14(9):2546-51.[PubMed 8823334]

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Johnson SA, Harper P, Hortobagyi GN, et al, “Vinorelbine: An Overview,” *Cancer Treat Rev*, 1996, 22(2):127-42. [PubMed 8665565]

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LeVeque D and Jehl F, “Clinical Pharmacokinetics of Vinorelbine,” *Clin Pharmacokinet*, 1996, 31(3):184-97. [PubMed 8877249]

Muggia FM, Blessing JA, Method M, et al, “Evaluation of Vinorelbine in Persistent or Recurrent Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study,” *Gynecol Oncol*, 2004, 92(2):639-43.[PubMed 14766259]

Muggia FM, Blessing JA, Waggoner S, et al, “Evaluation of Vinorelbine in Persistent or Recurrent Nonsquamous Carcinoma of the Cervix: A Gynecologic Oncology Group Study,” *Gynecol Oncol*, 2005, 96(1):108-11.[PubMed 15589588]

Rothenberg ML, Liu PY, Wilczynski s, et al, “Phase II Trial of Vinorelbine for Relapsed Ovarian Cancer: A Southwest Oncology Group Study,” *Gynecol Oncol*, 2004, 95(3):506-12.[PubMed 15581954]

Toso C and Lindley C, “Vinorelbine: A Novel Vinca Alkaloid,” *Am J Health Syst Pharm*, 1995, 52(12):1287-304.[PubMed 7656116]

Zelek L, Barthier S, Riofrio M, et al, “Weekly Vinorelbine is an Effective Palliative Regimen After Failure With Anthracyclines and Taxanes in Metastatic Breast Carcinoma,” *Cancer*, 2001, 92(9):2267-72.[PubMed 11745280]

International Brand NamesFilcrin (UY); Navelbin (BG, HN); Navelbine (AE, AR, AT, AU, BB, BH, BM, BR, BS, BZ, CH, CL, CN, CY, CZ, DE, DK, EE, EG, ES, FI, FR, GB, GY, ID, IE, IL, IQ, IR, IT, JM, JO, KP, KW, LB, LU, LY, MX, MY, NL, NO, OM, PH, PK, QA, RU, SA, SE, SR, SY, TH, TT, TW, YE); Navelbine [tab] (PL); Viessia (TH); Vinbine (IN); Vinelbine (TH); Vinorgen (EC, PE, PY); Vinotel (PH); Zinavin (CO)

VIP (Etoposide) (Testicular Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Testicular Cancer

Regimen UseTesticular cancer

RegimenNOTE: Multiple variations are listed below.

Variation 1:

Etoposide: I.V.: 75 mg/m^2/day days 1 to 5

[total dose/cycle = 375 mg/m^2]

Ifosfamide: I.V.: 1200 mg/m^2/day days 1 to 5

[total dose/cycle = 6000 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Mesna: I.V.: 400 mg day 1 only

followed by I.V.: 1200 mg/day continuous infusion days 1 to 5

[total dose/cycle = 6400 mg]

Repeat cycle every 21 days for 4 cycles

Variation 2:

Etoposide: I.V.: 100 mg/m^2/day days 1 to 5

[total dose/cycle = 500 mg/m^2]

Ifosfamide: I.V.: 1200 mg/m^2/day days 1 to 5

[total dose/cycle = 6000 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Mesna: I.V.: 200 mg/m^2 every 4 hours, for 3 doses each day, days 1, 2, and 3

[total dose/cycle = 1800 mg/m^2]

Repeat cycle every 21 days

Variation 3:

Ifosfamide: I.V.: 2500 mg/m^2/day days 1 and 2

[total dose/cycle = 5000 mg/m^2]

Mesna: I.V.: 2400 mg/m^2/day days 1 and 2

[total dose/cycle = 4800 mg/m^2]

Etoposide: I.V.: 100 mg/m^2/day days 3, 4, and 5

[total dose/cycle = 300 mg/m^2]

Cisplatin: I.V.: 40 mg/m^2/day days 3, 4, and 5

[total dose/cycle = 120 mg/m^2]

Repeat cycle every 21 days

Variation 4:

Etoposide: I.V.: 75 mg/m^2/day days 1 to 5

[total dose/cycle = 375 mg/m^2]

Ifosfamide: I.V.: 1200 mg/m^2/day days 1 to 5

[total dose/cycle = 6000 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Mesna: I.V.: 120 mg/m^2 day 1 only

followed by I.V.: 1200 mg/m^2/day continuous infusion days 1 to 5

[total dose/cycle = 6120 mg/m^2]

Repeat cycle every 21 days for 4 cycles

References

Variation 1:

Loehrer PJ Sr, Lauer R, Roth BJ, et al, “Salvage Therapy in Recurrent Germ Cell Cancer: Ifosfamide and Cisplatin Plus Either Vinblastine or Etoposide,” *Ann Intern Med*, 1988, 109(7):540-6. [PubMed 2844110]

Variation 2:

Harstrick A, Schmoll HJ, Wilke H, et al, “Cisplatin, Etoposide, and Ifosfamide Salvage Therapy for Refractory or Relapsing Germ Cell Carcinoma,” *J Clin Oncol*, 1991, 9(9):1549-55. [PubMed 1651992]

Variation 3:

Pizzocaro G, Salvioni R, Piva L, et al, “Modified Cisplatin, Etoposide (or Vinblastine) and Ifosfamide Salvage Therapy for Male Germ-Cell Tumors. Long-Term Results,” *Ann Oncol*, 1992, 3(3):211-6. [PubMed 1316779]

Variation 4:

Nichols CR, Catalano PJ, Crawford ED, et al, “Randomized Comparison of Cisplatin and Etoposide and Either Bleomycin or Ifosfamide in Treatment of Advanced Disseminated Germ Cell Tumors: An Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study,” *J Clin Oncol*, 1998, 16(4):1287-93.[PubMed 9552027]

VIP (Small Cell Lung Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category[Chemotherapy Regimen, Lung Cancer (Small Cell)]
Regimen UseLung cancer, small cell
Regimen

Etoposide: I.V.: 75 mg/m^2/day days 1 to 4

[total dose/cycle = 300 mg/m^2]

Ifosfamide: I.V.: 1200 mg/m^2/day days 1 to 4

[total dose/cycle = 4800 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 4

[total dose/cycle = 80 mg/m^2]

Mesna: I.V.: 300 mg/m^2 day 1 only

followed by I.V.: 1200 mg/m^2/day continuous infusion days 1 to 4

[total dose/cycle = 5100 mg/m^2]

Repeat cycle every 21 days

References

Loehrer PJ Sr, Ansari R, Gonin R, et al, âCisplatin Plus Etoposide With and Without Ifosfamide in Extensive Small-Cell Lung Cancer: A Hoosier Oncology Group Study,â *J Clin Oncol*, 1995, 13(10):2594-9.[PubMed 7595712]

VIP (Vinblastine) (Testicular Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic Category Chemotherapy Regimen, Testicular Cancer

Regimen Use Testicular cancer

Regimen NOTE: Multiple variations are listed below.

Variation 1:

Vinblastine: I.V.: 0.11 mg/kg/day days 1 and 2

[total dose/cycle = 0.22 mg/kg]

Ifosfamide: I.V.: 1200 mg/m^2/day days 1 to 5

[total dose/cycle = 6000 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Mesna: I.V.: 400 mg day 1

followed by I.V.: 1200 mg/day continuous infusion days 1 to 5

[total dose/cycle = 6400 mg]

Repeat cycle every 21 days for 4 cycles

Variation 2:

Vinblastine: I.V.: 6 mg/m^2/day days 1 and 2

[total dose/cycle = 12 mg/m^2]

Ifosfamide: I.V.: 1500 mg/m^2/day days 1 to 5

[total dose/cycle = 7500 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 5

[total dose/cycle = 100 mg/m^2]

Mesna: I.V.: 300 mg/m^2 3 times/day days 1 to 5

[total dose/cycle = 4500 mg/m^2]

Repeat cycle every 21 days for 4 cycles

References

Variation 1:

Loehrer PJ Sr, Lauer R, Roth BJ, et al, “Salvage Therapy in Recurrent Germ Cell Cancer: Ifosfamide and Cisplatin Plus Either Vinblastine or Etoposide,” *Ann Intern Med*, 1988, 109(7):540-6. [PubMed 2844110]

Variation 2:

Clemm C, Hartenstein R, Willich N, et al, “Vinblastine-Ifosfamide-Cisplatin Treatment of Bulky Seminoma,” *Cancer*, 1986, 58(10):2203-7.[PubMed 3756768]

Vitamin A and Vitamin D

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(VYE ta min aye & VYE ta min dee)

U.S. Brand NamesA and D® Original [OTC]; Baza® Clear [OTC]; Sween Cream® [OTC]

Pharmacologic CategoryTopical Skin Product

Use: Labeled IndicationsTemporary relief of discomfort due to chapped skin, diaper rash, minor burns, abrasions, as well as irritations associated with ostomy skin care

Dosing: Adults**Superficial dermatologic irritation:** Topical: Apply locally with gentle massage as needed

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricRefer to adult dosing.

Pregnancy Risk FactorB

Adverse ReactionsFrequency not defined: Local: Irritation

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, softgel: Vitamin A 1250 int. units and vitamin D 135 int. units; vitamin A 1250 int. units and vitamin D 130 int. units; vitamin A 5,000 int. units and vitamin D 400 int. units; vitamin A 10,000 int. units and vitamin D 400 int. units; vitamin A 10,000 int. units and vitamin D 5000 int. units; vitamin A 25,000 int. units and vitamin D 1000 int. units

Cream:

Sween Cream®: 2 g, 85 g, 184 g, 339 g [original]

Sween Cream®: 57 g, 142 g [fresh scent]

Sween Cream®: 57 g [fragrance free]

Ointment: 0.9 g, 5 g, 60 g, 120 g, 454 g [in lanolin-petrolatum base]

A and D® Original: 45 g, 120 g, 454 g

Baza® Clear: 50 g, 150 g, 240 g

Tablet: Vitamin A 10,000 int. units and vitamin D 400 int. units

Generic AvailableYes: Capsule, ointment

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsCod Liver Oil

Vitamin A

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Aquasol® may be confused with Anusol®

Pronunciation(VYE ta min aye)

U.S. Brand NamesAquasol A®; Palmitate-A® [OTC]

Pharmacologic CategoryVitamin, Fat Soluble

Use: Labeled IndicationsTreatment and prevention of vitamin A deficiency; parenteral (I.M.) route is indicated when oral administration is not feasible or when absorption is insufficient (malabsorption syndrome)

Dosing: Adults

RDA:

Male: 1000 mcg

Female: 800 mcg

* mcg retinol equivalent (0.3 mcg retinol = 1 unit vitamin A)

Severe deficiency with xerophthalmia: Oral: 500,000 units/day for 3 days, then 50,000 units/day for 14 days, then 10,000-20,000 units/day for 2 months

Deficiency (without corneal changes): Oral: 100,000 units/day for 3 days then 50,000 units/day for 14 days

Parenteral treatment of deficiency: I.M.: **Note:** I.M. route is indicated when oral administration is not feasible or when absorption is insufficient (malabsorption syndrome): 10,000-20,000 units/day

Malabsorption syndrome (prophylaxis): Oral: 10,000-50,000 units/day of water miscible product

Dietary supplement: Oral: 4000-5000 units/day

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

RDA:

<1 year: 375 mcg

1-3 years: 400 mcg

4-6 years: 500 mcg*

7-10 years: 700 mcg*

>10 years: 800-1000 mcg*

* mcg retinol equivalent (0.3 mcg retinol = 1 unit vitamin A)

Vitamin A supplementation in measles (recommendation of the World Health Organization): Children: Oral: Administer as a single dose; repeat the next day and at 4 weeks for children with ophthalmologic evidence of vitamin A deficiency:

6 months to 1 year: 100,000 units

>1 year: 200,000 units

Note: Use of vitamin A in measles is recommended only for patients 6 months to 2 years of age hospitalized with measles and its complications **or** patients >6 months of age who have any of the following risk factors and who are not already receiving vitamin A: immunodeficiency, ophthalmologic evidence of vitamin A deficiency including night blindness, Bitot's spots or evidence of xerophthalmia, impaired intestinal absorption, moderate-to-severe malnutrition including that associated with eating disorders, or recent immigration from areas where high mortality rates from measles have been observed

Note: Monitor patients closely; dosages >25,000 units/kg have been associated with toxicity

Severe deficiency with xerophthalmia: Oral:

Children 1-8 years: 5000-10,000 units/kg/day for 5 days or until recovery occurs

Children >8 years: 500,000 units/day for 3 days, then 50,000 units/day for 14 days, then 10,000-20,000 units/day for 2 months

Deficiency (without corneal changes): Oral:

Infants <1 year: 100,000 units every 4-6 months

Children 1-8 years: 200,000 units every 4-6 months

Children >8 years: 100,000 units/day for 3 days then 50,000 units/day for 14 days

Parenteral treatment of deficiency: I.M.: **Note:** I.M. route is indicated when oral administration is not feasible or when absorption is insufficient (malabsorption syndrome):

Infants: 7500-15,000 units/day for 10 days

Children 1-8 years: 17,500-35,000 units/day for 10 days

Children >8 years: 100,000 units/day for 3 days, followed by 50,000 units/day for 2 weeks

Note: Follow-up therapy with an oral therapeutic multivitamin (containing additional vitamin A) is recommended:

Low Birth Weight Infants: Additional vitamin A is recommended, however, no dosage amount has been established

Children ≤8 years: 5000-10,000 units/day

Children >8 years: 10,000-20,000 units/day

Malabsorption syndrome (prophylaxis): Children >8 years and Adults: Oral: 10,000-50,000 units/day of water miscible product

Dietary supplement: Oral:

Infants up to 6 months: 1500 units/day

Children:

6 months to 3 years: 1500-2000 units/day

4-6 years: 2500 units/day

7-10 years: 3300-3500 units/day

Children >10 years: 4000-5000 units/day

Administration: I.V.**Do not give by I.V. push.**
Administration: I.V. DetailpH: 6.5-7.1
StorageProtect from light.
CompatibilityStable in fat emulsion 10%.
ContraindicationsHypersensitivity to vitamin A or any component of the formulation; hypervitaminosis A; pregnancy (dose exceeding RDA)
Warnings/Precautions

Dosage form specific issues:

- Parenteral vitamin A: In low birth weight infants, polysorbates have been associated with thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension, and metabolic acidosis (E-Ferol syndrome).

Other warnings/precautions:

- Appropriate use: Evaluate other sources of vitamin A while receiving this product; patients receiving >25,000 units/day should be closely monitored for toxicity.

Pregnancy Risk FactorA/X (dose exceeding RDA recommendation)
Pregnancy ConsiderationsExcessive use of vitamin A shortly before and during pregnancy could be harmful to babies.
LactationEnters breast milk/compatible at normal daily doses
Adverse Reactions1% to 10%:

Central nervous system: Fever, headache, irritability, lethargy, malaise, vertigo

Dermatologic: Drying or cracking of skin

Endocrine & metabolic: Hypercalcemia

Gastrointestinal: Weight loss

Ocular: Visual changes

Miscellaneous: Hypervitaminosis A

Drug Interactions

Retinoid-like Compounds: Vitamin A may enhance the adverse/toxic effect of Retinoid-like Compounds. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Vitamin A may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Reference Range1 RE = 1 retinol equivalent; 1 RE = 1 mcg retinol or 6 mcg beta-carotene; normal levels of vitamin A in serum = 80-300 units/mL

Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess knowledge/teach patient appropriate use and adverse symptoms to report. **Pregnancy risk factor A/X:** See Pregnancy Risk Factor for use cautions.

Patient EducationTake exactly as directed; do not take more than the recommended dose. Take with meals. Do not use mineral oil or other vitamin A supplements without consulting prescriber. Report persistent nausea, vomiting, or loss of appetite; excessively dry skin or lips; headache or CNS irritability; loss of hair; or vision changes. **Pregnancy precaution:** Inform prescriber if you are pregnant.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule [softgel]: 10,000 units; 25,000 units

Injection, solution (Aquasol A®): 50,000 units/mL (2 mL) [contains polysorbate 80]

Tablet (Palmitate-A®): 5000 units, 15,000 units

Generic AvailableYes: Capsule

Mechanism of ActionNeeded for bone development, growth, visual adaptation to darkness, testicular and ovarian function, and as a cofactor in many biochemical processes

Pharmacodynamics/Kinetics

Absorption: Vitamin A in dosages **not** exceeding physiologic replacement is well absorbed after oral administration; water miscible preparations are absorbed more rapidly than oil preparations; large oral doses, conditions of fat malabsorption, low protein intake, or hepatic or pancreatic disease reduces oral absorption

Distribution: Large amounts concentrate for storage in the liver; enters breast milk

Metabolism: Conjugated with glucuronide; undergoes enterohepatic recirculation

Excretion: Feces

Pharmacotherapy Pearls1 mg = 3333 units

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsOleovitamin A

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International Brand NamesA Grin (MX); A313 (FR); Arcavit A (AT); Arovit (AE, BE, BH, BR, CO, CY, EG, IL, IQ, IR, IT, JO, KW, LB, LY, OM, PE, QA, SA, SE, SY, YE); Avibon (FR); Avitan (GR); Avitina (IT); Avitol (AT); Davitamon A (AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE); Ro-A-Vit (GH, KE, TZ, UG, ZM); Vitamin A (AU)

Vitamin B Complex Combinations

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Nephrocaps® may be confused with Nephro-Calci®

Renal Caps may be confused with Renagel®, Renvela®

Surbex® may be confused with Sebex®, Suprax®, Surfak®

Pronunciation(VYE ta min bee KOM pleks kom bi NAY shuns)

U.S. Brand NamesAllbee® C-800 + Iron [OTC]; Allbee® C-800 [OTC]; Allbee® with C [OTC]; Apatate® [OTC]; DexFol™; Gevrabon® [OTC]; Kobee [OTC]; Metanx™; NephPlex® Rx; Nephro-Vite® Rx; Nephro-Vite® [OTC]; Nephrocaps®; Nephron FA®; Nephronex®; Quin B Strong with C and Zinc [OTC]; Quin B Strong [OTC]; Rena-Vite RX; Rena-Vite [OTC]; Renal Caps; Senilezol; Stresstabs® High Potency Advanced [OTC]; Stresstabs® High Potency Energy [OTC]; Stresstabs® High Potency Weight [OTC]; Strovite [DSC]; Super Dec B 100 [OTC]; Super Quints 50 [OTC]; Superplex-T™ [OTC]; Surbex-T® [OTC]; Vitafol; Z-Bec® [OTC]

Pharmacologic CategoryVitamin

Use: Labeled IndicationsSupplement for use in the wasting syndrome in chronic renal failure, uremia, impaired metabolic functions of the kidney, dialysis; labeled for OTC use as a dietary supplement

Dosing: Adults

Dietary supplement: Oral: One tablet daily

Apatate® liquid: One teaspoonful daily, 1 hour prior to mid-day meal

Gevrabon® liquid: Two tablespoonsful (30 mL) once daily; shake well before use

Renal patients: Oral: One tablet or capsule daily between meals; take after treatment if on dialysis

Nephron FA®: Two tablets once daily, between meals

Dosing: ElderlyRefer to adult dosing.

Dietary ConsiderationsMay be taken with food to decrease stomach upset.

StorageIron is a leading cause of fatal poisoning in children; store out of children's reach and in child-resistant containers.

ContraindicationsHypersensitivity to any component of the formulation

Warnings/Precautions

Boxed warnings:

- Iron toxicity: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Iron toxicity: **[U.S. Boxed Warning]: Severe iron toxicity may occur in overdose, particularly when ingested by children; iron is a leading cause of fatal poisoning in children; store out of children's reach and in child-resistant containers.** Adult preparations may contain amounts of iron which should not be used in children.

Pregnancy Risk FactorA (RDA recommended doses)

LactationEnters breast milk/compatible

Adverse ReactionsFrequency not defined.

Central nervous system: Somnolence

Dermatologic: Itching

Gastrointestinal: Bloating, constipation, diarrhea, flatulence, nausea, vomiting

Hematologic: Peripheral vascular thrombosis, polycythemia vera

Neuromuscular & skeletal: Paresthesia

Miscellaneous: Allergic reaction

Drug InteractionsThere are no known significant interactions.

Ethanol/Nutrition/Herb InteractionsFood: Iron absorption is inhibited by eggs and milk.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Content varies depending on product used. For more detailed information on ingredients in these and other multivitamins, please refer to Multivitamin Products.

Generic Available Yes

Related Information

- Multivitamin Products

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

Index Terms B Complex Combinations; B Vitamin Combinations

Vitamin E

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Aquasol E® may be confused with Anusol®

Pronunciation(VYE ta min ee)

U.S. Brand NamesAlph-E [OTC]; Alph-E-Mixed [OTC]; Aquasol E® [OTC]; Aquavit-E [OTC]; d-Alpha-Gems™ [OTC]; E-Gems Elite® [OTC]; E-Gems Plus® [OTC]; E-Gems® [OTC]; Ester-E™ [OTC]; Gamma E-Gems® [OTC]; Gamma-E Plus [OTC]; High Gamma Vitamin E Complete™ [OTC]; Key-E® Kaps [OTC]; Key-E® [OTC]

Pharmacologic CategoryVitamin, Fat Soluble

Use: Labeled IndicationsDietary supplement

Use: Unlabeled/InvestigationalTo reduce the risk of bronchopulmonary dysplasia or retrolental fibroplasia in infants exposed to high concentrations of oxygen; prevention and treatment of tardive dyskinesia; prevention and treatment of hemolytic anemia secondary to vitamin E deficiency

Dosing: AdultsVitamin E may be expressed as alpha-tocopherol equivalents (ATE), which refer to the biologically-active (R) stereoisomer content. Oral:

Recommended daily allowance (RDA): 15 mg; upper limit of intake should not exceed 1000 mg/day

Pregnant female:

- ≤18 years: 15 mg; upper level of intake should not exceed 800 mg/day
- 19-50 years: 15 mg; upper level of intake should not exceed 1000 mg/day

Lactating female:

- ≤18 years: 19 mg; upper level of intake should not exceed 800 mg/day
- 19-50 years: 19 mg; upper level of intake should not exceed 1000 mg/day

Vitamin E deficiency: 60-75 units/day

Prevention of vitamin E deficiency: Oral: 30 units/day

Cystic fibrosis: Oral: 100-400 units/day

Beta-thalassemia: Oral: 750 units/day

Sickle cell disease: Oral: 450 units/day

Tardive dyskinesia (unlabeled use): Oral: 1600 units/day

Superficial dermatologic irritation: Topical: Apply a thin layer over affected area.

Dosing: ElderlyRefer to adult dosing.

Dosing: PediatricVitamin E may be expressed as alpha-tocopherol equivalents (ATE), which refer to the biologically-active (R) stereoisomer content. Oral:

Recommended daily allowance (RDA):

Infants (adequate intake; RDA not established):

- ≤6 months: 4 mg
- 7-12 months: 6 mg

Children:

- 1-3 years: 6 mg; upper limit of intake should not exceed 200 mg/day
- 4-8 years: 7 mg; upper limit of intake should not exceed 300 mg/day
- 9-13 years: 11 mg; upper limit of intake should not exceed 600 mg/day
- 14-18 years: 15 mg; upper limit of intake should not exceed 800 mg/day

Vitamin E deficiency:

Children (with malabsorption syndrome): 1 unit/kg/day of water miscible vitamin E (to raise plasma tocopherol concentrations to the normal range within 2 months and to maintain normal plasma concentrations)

Cystic fibrosis, beta-thalassemia may require higher daily maintenance doses:

Cystic fibrosis: Oral: 100-400 units/day

Beta-thalassemia: Oral: 750 units/day

Administration: OralSwallow capsules whole; do not crush or chew.
StorageProtect from light.
ContraindicationsHypersensitivity to vitamin E or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Vitamin K deficiency: May induce vitamin K deficiency.

Special populations:

- Low birth weight infants: Necrotizing enterocolitis has been associated with oral administration of large dosages (eg, >200 units/day) of a hyperosmolar vitamin E preparation in low birth weight infants.

Geriatric ConsiderationsElderly may have vitamin E prescribed for those with cardiovascular disease. Elderly should be advised not to take more than prescribed.
Pregnancy Risk FactorA/C (dose exceeding RDA recommendation)
LactationEnters breast milk/compatible
Adverse ReactionsFrequency not defined.

Central nervous system: Fatigue, headache

Dermatologic: Contact dermatitis with topical preparation

Endocrine & metabolic: Gonadal dysfunction

Gastrointestinal: Diarrhea, intestinal cramps, nausea

Neuromuscular & skeletal: Weakness

Ocular: Blurred vision

Drug Interactions

Vitamin K Antagonists (eg, warfarin): Vitamin E may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Monitoring ParametersPlasma tocopherol concentrations (normal range: 6-14 mcg/mL)
Reference RangeTherapeutic: 0.8-1.5 mg/dL (SI: 19-35 µmol/L), some method variation
Nursing: Physical Assessment/MonitoringAssess effectiveness and interactions of other medications patient may be taking. Assess knowledge/teach patient appropriate use (according to formulation prescribed) and adverse symptoms to report.
Monitoring: Lab TestsPlasma tocopherol concentrations (normal range: 6-14 mcg/mL)
Patient EducationTake exactly as directed; do not take more than the recommended dose. Do not use mineral oil or other vitamin E supplements without consulting prescriber. Report persistent nausea, vomiting, or cramping; or gonadal dysfunction. **Pregnancy precaution:** Inform prescriber if you are pregnant.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 400 int. units, 1000 int. units

Key-E® Kaps: 200 int. units, 400 int. units

Capsule, softgel: 200 int. units, 400 int. units, 600 int. units, 1000 int. units

Alph-E: 200 int. units, 400 int. units

Alph-E-Mixed: 200 int. units [contains mixed tocopherols]; 400 int. units [contains mixed tocopherols], 1000 int. units [sugar free; contains mixed tocopherols]

Aqua Gem E®: 200 units, 400 units

d-Alpha-Gems™: 400 int. units [derived from soybean oil]

E-Gems®: 30 int. units, 100 int. units, 200 int. units, 400 int. units, 600 int. units, 800 int. units, 1000 int. units, 1200 int. units [derived from soybean oil]

E-Gems Plus®: 200 int. units, 400 int. units, 800 int. units [contains mixed tocopherols]

E-Gems Elite®: 400 int. units [contains mixed tocopherols]

Ester-E™: 400 int. units

Gamma E-Gems®: 90 int. units [also contains mixed tocopherols]

Gamma-E Plus: 200 int. units [contains soybean oil]

High Gamma Vitamin E Complete™: 200 int. units [contains soybean oil, mixed tocopherols]

Cream: 50 int. units/g (60 g), 100 int. units/g (60 g), 1000 int. units/120 g (120 g), 30,000 int. units/57 g (57 g)

Key-E®: 30 int. units/g (60 g, 120 g, 600 g)

Lip balm (E-Gem® Lip Care): 1000 int. units/tube [contains vitamin A and aloe]

Oil, oral/topical: 100 int. units/0.25 mL (60 mL, 75 mL); 1150 units/0.25 mL (30 mL, 60 mL, 120 mL); 28,000 int. units/30 mL (30 mL)

Alph-E: 28,000 int. units/30 mL (30 mL) [topical]

E-Gems®: 100 units/10 drops (15 mL, 60 mL)

Ointment, topical (Key-E®): 30 units/g (60 g, 120 g, 480 g)

Powder (Key-E®): 700 int. units per 1/4 teaspoon (15 g, 75 g, 1000 g) [derived from soybean oil]

Solution, oral drops: 15 int. units/0.3 mL (30 mL)

Aquasol E®: 15 int. units/0.3 mL (12 mL, 30 mL) [latex free]

Aquavit-E: 15 int. units/0.3 mL (30 mL) [butterscotch flavor]

Suppository, rectal/vaginal (Key-E®): 30 int. units (12s, 24s) [contains coconut oil]

Tablet: 100 int. units, 200 int. units, 400 int. units, 500 int. units

Key-E®: 200 int. units, 400 int. units

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Vitamin E)

1000 unit (30): $8.99

Mechanism of ActionPrevents oxidation of vitamin A and C; protects polyunsaturated fatty acids in membranes from attack by free radicals and protects red blood cells against hemolysis

Pharmacodynamics/Kinetics

Absorption: Oral: Depends on presence of bile; reduced in conditions of malabsorption, in low birth weight premature infants, and as dosage increases; water miscible preparations are better absorbed than oil preparations

Distribution: To all body tissues, especially adipose tissue, where it is stored

Metabolism: Hepatic to glucuronides

Excretion: Feces

Pharmacotherapy PearlsThe 2R-stereoisomeric forms of α-tocopherol are used to define vitamin E intake and RDA. While international units are no longer recognized, many fortified foods and supplements continue to use this term although USP units are now used by the pharmaceutical industry when labeling vitamin E supplements. Both IUs and USP units are based on the same equivalency. The following can be used to convert international units (IU) of vitamin E (and esters) to milligrams α-tocopherol in order to meet recommended daily intake:

Synthetic (eg, all-racemic α-tocopherol):

dl-α-tocopherol:

USP: 1.10 IU / mg; 0.91 mg / IU

Molar: 2.12 µmol / IU

α-tocopherol: 0.45 mg / IU

dl-α-tocopherol acetate:

USP: 1 IU / mg; 1 mg / IU

Molar: 2.12 µmol / IU

α-tocopherol: 0.45 mg / IU

dl-α-tocopherol succinate:

USP: 0.89 IU / mg; 1.12 mg / IU

Molar: 2.12 µmol / IU

α-tocopherol: 0.45 mg / IU

Natural (eg, RRR-α-tocopherol):

d-α-tocopherol:

USP: 1.49 IU / mg; 0.67 mg / IU

Molar: 1.56 µmol / IU

α-tocopherol: 0.67 mg / IU

d-α-tocopherol acetate:

USP: 1.36 IU / mg; 0.74mg / IU

Molar: 1.56 µmol / IU

α-tocopherol: 0.67 mg / IU

d-α-tocopherol succinate:

USP: 1.21 IU / mg; 0.83 mg / IU

Molar: 1.56 µmol / IU

α-tocopherol: 0.67 mg / IU

Historically, vitamin E supplements have been labeled (incorrectly) as *d*- or *dl*-α-tocopherol. Synthetic vitamin E compounds are racemic mixtures, and may be designated as all-racemic (all rac-α-tocopherol). The natural form contains the only RRR-α-tocopherol. All of these compounds may be present in fortified foods and multivitamins. Not all stereoisomers are capable of performing physiological functions in humans; therefore, cannot be considered to meet vitamin E requirements.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay rarely cause drowsiness

Mental Health: Effects on Psychiatric TreatmentUsed to prevent or treat tardive dyskinesia and Alzheimer's disease

Cardiovascular ConsiderationsThere is no compelling evidence that supplemental antioxidant therapy has a role in the primary or secondary prevention of cardiovascular disease. The ACC/AHA guidelines for the management of patients with chronic stable angina and the 2004 ACC/AHA STEMI guidelines do not recommend the use of vitamin E. The HOPE trial evaluated the use of vitamin E (400 int. units/day) in patients at high risk for cardiovascular events. There was no difference from placebo for the composite endpoint of cardiovascular death, MI, or stroke. In another trial (Brown, 2001), a daily antioxidant cocktail (vitamin E 800 int. units, vitamin C 1000 mg, beta carotene 25 mg, selenium 100 mcg) was evaluated in patients with coronary disease, low HDL, and normal LDL cholesterol. The protective increase in HDL2 with simvastatin plus niacin was attenuated by this concurrent antioxidant therapy. Progression of coronary stenosis occurred on average in patients taking niacin, simvastatin, and antioxidants compared to regression in those randomized to niacin and simvastatin alone. Patients should be encouraged to follow the Therapeutic Lifestyle Changes Diet (NCEP Expert Panel, 2001)

Index Terms*d*-Alpha Tocopherol; *dl*-Alpha Tocopherol

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International Brand NamesAquasol E (CO); Dermorelle (FR); E Perle (IT); Ephynal (AT, BE, CH, ES, GR, HN, IT, PT); Etec 1000 (EC); Eternal (MX); Evion (IN); Ixopolet (MX); Livingpherol (KP); Vita-E 400 (EC)

Vitamins (Multiple/Injectable)

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(VYE ta mins, MUL ti pul/in JEK ti bal)

U.S. Brand NamesInfuvite® Adult; Infuvite® Pediatric; M.V.I. Adult™; M.V.I.®-12 ; M.V.I® Pediatric

Pharmacologic CategoryVitamin

Use: Labeled IndicationsNutritional supplement in patients receiving parenteral nutrition or requiring intravenous administration

Dosing: Adults**Dietary supplement:** I.V. (not for direct infusion): Adult formulation: 10 mL/day added to TPN or ≥500 mL of appropriate solution

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Dietary supplement:** I.V. (not for direct infusion):

Children: ≥3 kg to 11 years: Pediatric formulation: 5 mL/day added to TPN or ≥100 mL of appropriate solution

Children >11 years and Adults: Refer to adult dosing.

Administration: I.V.Not for direct infusion; solution must be diluted prior to administration.

StorageStore injection at 2°C to 8°C (36°F to 46°F). Some components are light sensitive.

Powder for injection: Solution is stable for 4 hours prior to final dilution.

Solution: Once combined, solution should be immediately added to infusion solution.

Reconstitution

Powder for injection: M.V.I.® Pediatric: Add 5 mL SWFI, D_5W, or NS to vial; swirl gently to dissolve. Must be further diluted prior to administration.

Solution: Infuvite® Adult, Infuvite® Pediatric, M.V.I.®-12: Solution is provided as two separate vials which need combined to provide the usual daily dose following further dilution.

Compatibility**Incompatible** with alkaline solutions/medications (eg, acetazolamide, chlorothiazide, aminophylline, or bicarbonate), ampicillin, calcium salts, tetracyclines, or fat emulsions.

ContraindicationsHypersensitivity to any component of the formulation; pre-existing hypervitaminosis

Warnings/Precautions

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Megaloblastic anemia: Should not be used prior to testing for megaloblastic anemia.
- Renal impairment: Use with caution in patients with severe renal impairment.

Special populations:

- Pediatrics: Additional vitamin A may be required in pediatric patients.

Dosage form specific issues:

- Aluminum: Some formulations contain aluminum which may reach toxic levels with prolonged administration in renal impairment or immaturity.
- Polysorbates: Some formulations may contain polysorbates which have been associated with the E-Ferol syndrome in low birth weight infants.

Other warnings/precautions:

- RDA values: Are not requirements, but are recommended daily intakes of certain essential nutrients.

Pregnancy Risk FactorC

Pregnancy ConsiderationsReproduction studies have not been conducted.

Adverse ReactionsFrequency not defined.

Cardiovascular: Angioedema, edema

Central nervous system: Agitation, anxiety, dizziness, headache

Dermatologic: Erythema, pruritus, rash, urticaria

Ocular: Diplopia

Respiratory: Dyspnea, wheezing

Miscellaneous: Allergic reactions, anaphylaxis, hypervitaminosis

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Content varies depending on product used. For more detailed information on ingredients in these and other multivitamins, please refer to Multivitamin Products.

Generic AvailableNo

Related Information

- Multivitamin Products

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInjectable forms of multivitamins contain aluminum. Aluminum may reach toxic levels with prolonged administration if kidney function is impaired. Aluminum toxicity may manifest as impaired mental function.

Mental Health: Effects on Psychiatric TreatmentNone reported

Vitamins (Multiple/Oral)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Theragran® may be confused with Phenergan®

Pronunciation(VYE ta mins, MUL ti pul/OR al)

U.S. Brand NamesAndrovite® [OTC]; CalciFolic-D™; Centamin [OTC]; Centrum Cardio® [OTC]; Centrum Performance® [OTC]; Centrum® Silver® [OTC]; Centrum® [OTC]; Diatx®Zn; Drinkables® Fruits and Vegetables [OTC]; Drinkables® MultiVitamins [OTC]; Encora®; Foltrin®; Freedavite [OTC]; Geri-Freeda [OTC]; Geriation [OTC]; Geritol Complete® [OTC]; Geritol Extend® [OTC]; Geritol® Tonic [OTC]; Glutofac®-MX; Glutofac®-ZX; Gynovite® Plus [OTC]; Hemocyte Plus®; Hi-Kovite [OTC; Iberet®-500 [OTC]; Monocaps [OTC]; Myadec® [OTC]; Nutrimin-Plus [OTC]; Ocuvite® Adult 50+ [OTC]; Ocuvite® Extra® [OTC]; Ocuvite® Lutein [OTC]; Ocuvite® [OTC]; One A Day® Cholesterol Plus [OTC]; One A Day® Energy [OTC]; One A Day® Essential [OTC]; One A Day® Maximum [OTC]; One A Day® Men's 50+ Advantage [OTC]; One A Day® Men's Health Formula [OTC]; One A Day® Teen Advantage for Her [OTC]; One A Day® Teen Advantage for Him [OTC]; One A Day® Weight Smart® Advanced [OTC; One A Day® Women's 50+ Advantage [OTC]; One A Day® Women's Active Mind & Body [OTC]; One A Day® Women's [OTC]; Optivite® P.M.T. [OTC]; PreserVision® AREDS [OTC]; PreserVision® Lutein [OTC]; Quintabs [OTC]; Quintabs-M Iron-Free [OTC]; Quintabs-M [OTC]; Renax®; Renax® 5.5; Replace Without Iron [OTC]; Replace [OTC]; Repliva 21/7®; SourceCF®; Strovite®; Strovite® Advance; Strovite® Forte; Strovite® Plus; T-Vites [OTC]; Ultra Freeda A-Free [OTC]; Ultra Freeda Iron Free [OTC]; Ultra Freeda With Iron [OTC]; Viactiv® for Teens [OTC]; Viactiv® With Calcium [OTC]; Viactiv® [OTC]; Viactiv® Calcium Flavor Glides™ [OTC]; Viactiv® Flavor Glides [OTC]; Vitafol®; Xtramins [OTC]; Yelets [OTC]

Pharmacologic CategoryVitamin

Use: Labeled IndicationsPrevention/treatment of vitamin and mineral deficiencies; labeled for OTC use as a dietary supplement

Dosing: Adults**Dietary supplement:** Oral: Daily dose of adult preparations varies by product. Generally, 1 tablet or capsule or 5-15 mL of liquid per day. Consult package labeling. Prescription doses may be higher for burn or cystic fibrosis patients.

Dosing: ElderlyRefer to adult dosing.

Administration: OralMay administer with food to decrease stomach upset.

Dietary ConsiderationsMay be taken with food to decrease stomach upset.

StorageIron is a leading cause of fatal poisoning in children; store out of children's reach and in child-resistant containers.

ContraindicationsHypersensitivity to any component of the formulation; pre-existing hypervitaminosis

Warnings/Precautions

Boxed warnings:

- Iron toxicity: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Iron toxicity: **[U.S. Boxed Warning]: Severe iron toxicity may occur in overdose, particularly when ingested by children; iron is a leading cause of fatal poisoning in children; store out of children's reach and in child-resistant containers.** Adult preparations may contain amounts of iron which should not be used in children.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Renal impairment: Use with caution in patients with severe renal impairment.

Dosage form specific issues:

- Ethanol: Adult preparations may contain amounts of ethanol which should not be used in children.

Other warnings/precautions:

- RDA values: Are not requirements, but are recommended daily intakes of certain essential nutrients.

Pregnancy Risk FactorA (at RDA recommended dose)

LactationEnters breast milk/compatible

Adverse ReactionsRefer to individual vitamin monographs.

Ethanol/Nutrition/Herb InteractionsFood: Iron absorption is inhibited by eggs and milk.

Test InteractionsAscorbic acid in the urine can cause false-negative urine glucose determinations.

Reference RangeRecommended daily allowances are published by Food and Nutrition Board, National Research Council - National Academy of Sciences and are revised periodically. RDA quantities apply only to healthy persons and are not intended to cover therapeutic nutrition requirements in disease or other abnormal states (ie, metabolic disorders, weight reduction, chronic disease, drug therapy).

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Content varies depending on product used. For more detailed information on ingredients in these and other multivitamins, please refer to Multivitamin Products.

Generic AvailableYes

Related Information

- Multivitamin Products

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsMultiple Vitamins; Therapeutic Multivitamins; Vitamins, Multiple (Oral); Vitamins, Multiple (Therapeutic); Vitamins, Multiple With Iron

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Vitamins (Multiple/Pediatric)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(VYE ta mins, MUL ti pul/pe de AT rik)

U.S. Brand NamesADEKs® [OTC]; AquADEKs™ [OTC]; Centrum Kids® Complete Dora the Explorer™ [OTC]; Centrum Kids® Complete Rugrats™ [OTC]; Centrum Kids® Complete SpongeBob SquarePants™ [OTC]; Flintstones™ Complete [OTC]; Flintstones™ Gummies Vita-Packs [OTC]; Flintstones™ Gummies [OTC]; Flintstones™ Plus Bone Building Support [OTC]; Flintstones™ Plus Immunity Support [OTC]; Flintstones™ Plus Iron [OTC]; Flintstones™ Sour Gummies [OTC]; My First Flintstones™ [OTC]; MyKidz Iron FL™; MyKidz Iron™ [OTC]; One A Day® Kids Bugs Bunny and Friends Complete [OTC]; One A Day® Kids Scooby-Doo!™ Complete [OTC]; One A Day® Scooby-Doo!™ Gummies [OTC]; One A Day® Scooby-Doo!™ Plus Calcium [OTC]; Poly-Vi-Sol® With Iron [OTC]; Poly-Vi-Sol® [OTC]; SourceCF® [OTC]; Tri-Vi-Sol® With Iron [OTC]; Tri-Vi-Sol® [OTC]; Vitaball® Minis [OTC]; Vitaball® Wild 'N Fruity [OTC]; Vitaball® [OTC]; Vitalets [OTC]

Pharmacologic CategoryVitamin

Use: Labeled IndicationsPrevention/treatment of vitamin deficiency; products containing fluoride are used to prevent dental caries; labeled for OTC use as a dietary supplement

Dosing: PediatricDaily dose varies by product; refer to package insert for specific product labeling.

Administration: OralMay administer with food to decrease stomach upset. Chewable tablets may be crushed and mixed with food. Oral drops may be mixed with cereal, fruit juice, or food.

Dietary ConsiderationsMay take with food to decrease stomach upset. Flintstones® Complete contains phenylalanine 4.56 mg/chewable tablet. Flintstones® Plus Calcium contains phenylalanine <4 mg/chewable tablet. One-A-Day® Kids Bugs Bunny and Friends Plus Extra C chewable tablets contain phenylalanine.

StorageStore at 15°C to 30°C (59°F to 86°F). Iron is a leading cause of fatal poisoning in children; store out of children's reach and in child-resistant containers.

ContraindicationsHypersensitivity to any component of the formulation; pre-existing hypervitaminosis

Warnings/Precautions

Boxed warnings:

- Iron toxicity: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Iron toxicity: **[U.S. Boxed Warning]: Severe iron toxicity may occur in overdose, particularly when ingested by children; iron is a leading cause of fatal poisoning in children; store out of children's reach and in child-resistant containers.** Adult preparations may contain amounts of iron which should not be used in children.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with severe hepatic impairment.

- Renal impairment: Use with caution in patients with severe renal impairment.

Other warnings/precautions:

- Appropriate use: Not all products can be used in children of all age groups; consult specific product labeling prior to use. Do not exceed recommended doses.

Adverse ReactionsRefer to individual vitamin monographs.

Ethanol/Nutrition/Herb InteractionsFood: Iron absorption is inhibited by eggs and milk.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Content varies depending on product used. For more detailed information on ingredients in these and other multivitamins, please refer to Multivitamin Products.

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Chewable (Poly-Vi-Flor)

(30): $7.99

(30): $7.99

(30): $7.99

Solution (Poly-Vi-Flor)

(50): $15.99

(50): $15.99

Solution (Poly-Vi-Sol)

(50): $9.99

Solution (Tri-Vi-Sol)

(50): $7.99

Related Information

- Multivitamin Products

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsChildren's Vitamins; Multivitamins/Fluoride

Vitamins (Multiple/Prenatal)

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Niferex® may be confused with Nephrox®

PreCare® may be confused with Precose®

Pronunciation(VYE ta mins, MUL ti pul/pree NAY tal)

U.S. Brand NamesA-Free Prenatal; Advanced NatalCare®; Advanced-RF NatalCare®; Cal-Nate™; Calna [OTC]; CareNatal™ DHA; CitraNatal™ 90 DHA; CitraNatal™ DHA; CitraNatal™ Rx; ComBi Rx™; Duet®; Duet® DHA; Duet® DHA ^{ec}; KPN Prenatal [OTC]; Mini-Prenatal [OTC]; NataCaps™; NataChew® [OTC]; NataFort® [OTC]; NatalCare® GlossTabs™; NatalCare® PIC; NatalCare® PIC Forte; NatalCare® Plus; NatalCare® Rx; NatalCare® Three; NataTab™ CFe; NataTab™ FA; NataTab™ Rx; NutriNate®; NutriSpire™; One A Day® Women's Prenatal [OTC]; OptiNate®; PreCare Conceive®; PreCare Premier®; PreCare®; PremesisRx®; Prenatal 19 [OTC]; Prenatal AD [OTC]; Prenatal MR 90 Fe™; Prenatal MTR With Selenium; Prenatal One Daily [OTC]; Prenatal Rx 1; Prenatal U [OTC]; Prenatal Z Advanced Formula; Prenate DHA™; Prenate Elite®; PrimaCare®; PrimaCare® One; Select-OB™ [OTC]; Stuart Prenatal® [OTC]; Tandem® DHA; Tandem® OB; Trinate [OTC]; Ultra NatalCare®; Vitafol®-OB [OTC]; Vitafol®-OB+DHA [OTC]; Vitafol®-PN

Pharmacologic CategoryVitamin

Use: Labeled IndicationsNutritional supplement for use prior to conception, during pregnancy, and postnatal (in lactating and nonlactating women)

Dosing: Adults**Dietary supplement:** Oral:

Capsule, tablet: One daily

Powder: 4 teaspoonfuls/day; given once daily or in divided doses; mix 1 teaspoonful in 1 ounce of water

Dosing: ElderlyRefer to adult dosing.

Administration: OralMay administer with food to decrease stomach upset.

Dietary ConsiderationsMay be taken with food to decrease stomach upset. Obegyn® powder contains phenylalanine 84 mg/8.25 g. Duet® contains phenylalanine 15 mg/chewable tablet. StrongStart™ contains phenylalanine 6 mg/chewable tablet.

ContraindicationsHypersensitivity to any component of the formulation; pre-existing hypervitaminosis

Warnings/Precautions

Boxed warnings:

- Iron toxicity: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Iron toxicity: **[U.S. Boxed Warning]: Severe iron toxicity may occur in overdose, particularly when ingested by children; iron is a leading cause of fatal poisoning in children; store out of children's reach and in child-resistant containers.** Adult preparations may contain amounts of iron which should not be used in children.

Disease-related concerns:

- Hemochromatosis/hemosiderosis: Iron supplementation should not be used with hemochromatosis and hemosiderosis.
- Hepatic impairment: Use with caution in patients with severe hepatic impairment.
- Kidney stones: Use with caution in patients with kidney stones; due to calcium content.
- Renal impairment: Use with caution in patients with severe renal impairment.

Pregnancy Risk FactorA (in RDA recommended dose)

LactationEnters breast milk/compatible

Adverse ReactionsFrequency not defined.

Gastrointestinal: Abdominal pain, constipation, dark stools, diarrhea, nausea, vomiting

Miscellaneous: Allergic reaction

Ethanol/Nutrition/Herb InteractionsFood: Iron absorption is inhibited by eggs and milk.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Content varies depending on product used. For more detailed information on ingredients in these and other multivitamins, please refer to

Multivitamin Products.

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Chromagen FA)

70-150-2-0.01-1 mg (100): $98.99

Related Information

- Multivitamin Products

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsPrenatal Vitamins

VM

Lexi-Drugs Online

Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Breast Cancer
Regimen UseBreast cancer
Regimen

Variation 1:

Mitomycin: I.V.: 10 mg/m^2 days 1 and 28, for 2 cycles

[total dose/cycle = 20 mg/m^2]

followed by I.V.: 10 mg/m^2 day 1 only for subsequent cycles

[total dose/cycle = 10 mg/m^2]

Vinblastine: I.V.: 5 mg/m^2/day days 1, 14, 28, and 42, for 2 cycles

[total dose/cycle = 20 mg/m^2]

followed by I.V.: 5 mg/m^2/day days 1 and 21

[total dose/cycle = 10 mg/m^2]

Repeat cycle every 6-8 weeks

Variation 2:

Mitomycin: I.V.: 10 mg/m^2/day days 1 and 28, for 2 cycles

[total dose/cycle = 20 mg/m^2]

followed by I.V.: 10 mg/m^2 day 1 only for subsequent cycles

[total dose/cycle = 10 mg/m^2]

Vindesine: I.V.: 2 mg/m^2/day days 1, 14, 28, and 42, for 2 cycles

[total dose/cycle = 8 mg/m^2]

followed by I.V.: 2 mg/m^2/ day days 1 and 21 for subsequent cycles

[total dose/cycle = 4 mg/m^2]

Repeat cycle every 6-8 weeks

References

Garewal HS, Brooks RJ, Jones SE, et al, âTreatment of Advanced Breast Cancer With Mitomycin C Combined With Vinblastine or Vindesine,â *J Clin Oncol*, 1983, 1(12):772-5.[PubMed 6422004]

Voriconazole

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(vor i KOE na zole)

U.S. Brand NamesVFEND®

Canadian Brand NamesVFEND®

Pharmacologic CategoryAntifungal Agent, Oral; Antifungal Agent, Parenteral

Use: Labeled IndicationsTreatment of invasive aspergillosis; treatment of esophageal candidiasis; treatment of candidemia (in non-neutropenic patients); treatment of disseminated *Candida* infections of the skin and viscera; treatment of serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp (including *Fusarium solani*) in patients intolerant of, or refractory to, other therapy

Use: Unlabeled/Investigational

Fungal infection prophylaxis in intermediate or high risk neutropenic cancer patients with myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML), neutropenic allogeneic hematopoietic stem cell recipients, and patients with significant graft-versus-host disease; empiric antifungal therapy (second-line) for persistent neutropenic fever

Dosing: Adults

Aspergillosis, invasive, including disseminated and extrapulmonary infection: Duration of therapy should be a minimum of 6-12 weeks or throughout period of immunosuppression:

I.V.: Initial: Loading dose: 6 mg/kg every 12 hours for 2 doses; followed by maintenance dose of 4 mg/kg every 12 hours

Oral: May consider oral therapy in place of I.V. with dosing of 4 mg/kg (rounded up to convenient tablet dosage form) every 12 hours; however, I.V. administration is preferred in serious infections since comparative efficacy with the oral formulation has not been established.

Scedosporiosis, fusariosis: I.V.: Initial: Loading dose: 6 mg/kg every 12 hours for 2 doses; followed by maintenance dose of 4 mg/kg every 12 hours

Candidemia and other deep tissue *Candida*infections: I.V.: Initial: Loading dose 6 mg/kg every 12 hours for 2 doses; followed by maintenance dose of 3-4 mg/kg every 12 hours

Endophthalmitis, fungal: I.V.: 6 mg/kg every 12 hours for 2 doses, then 200 mg orally twice daily

Esophageal candidiasis: Oral:

Patients <40 kg: 100 mg every 12 hours; maximum: 300 mg/day

Patients ≥40 kg: 200 mg every 12 hours; maximum: 600 mg/day

Note: Treatment should continue for a minimum of 14 days, and for at least 7 days following resolution of symptoms.

Conversion to oral dosing:

Patients <40 kg: 100 mg every 12 hours; increase to 150 mg every 12 hours in patients who fail to respond adequately

Patients ≥40 kg: 200 mg every 12 hours; increase to 300 mg every 12 hours in patients who fail to respond adequately

Dosage adjustment in patients unable to tolerate treatment:

I.V.: Dose may be reduced to 3 mg/kg every 12 hours

Oral: Dose may be reduced in 50 mg decrements to a minimum dosage of 200 mg every 12 hours in patients weighing ≥40 kg (100 mg every 12 hours in patients <40 kg)

Dosage adjustment in patients receiving concomitant CYP450 enzyme inducers or substrates:

Cyclosporine: Reduce cyclosporine dose by $^1/_2$ and monitor closely.

Efavirenz: Oral: Increase maintenance dose of voriconazole to 400 mg every 12 hours and reduce efavirenz dose to 300 mg once daily

Phenytoin:

I.V.: Increase maintenance dosage to 5 mg/kg every 12 hours

Oral: Increase dose to 400 mg every 12 hours in patients ≥40 kg (200 mg every 12 hours in patients <40 kg)

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Children <12 years: No data available

Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentIn patients with Cl_{cr} <50 mL/minute, accumulation of the intravenous vehicle (SBECD) occurs. After initial I.V. loading dose, oral voriconazole should be administered to these patients, unless an assessment of the benefit:risk to the patient justifies the use of I.V. voriconazole. Monitor serum creatinine and change to oral voriconazole therapy when possible.

Hemodialysis: Oral dosage adjustment not required; I.V. dosing not recommended since SBECD vehicle is cleared at half the rate of voriconazole and may accumulate

Dosing: Hepatic Impairment

Mild-to-moderate hepatic dysfunction (Child-Pugh class A and B): Following standard loading dose, reduce maintenance dosage by 50%

Severe hepatic impairment: Should only be used if benefit outweighs risk; monitor closely for toxicity

Calculations

- Creatinine Clearance: Adults
- Creatinine Clearance: Pediatrics

Administration: I.V.Infuse over 1-2 hours (rate not to exceed 3 mg/kg/hour). Do not infuse concomitantly into same line or cannula with other drug infusions, including TPN.

Administration: OralAdminister 1 hour before or 1 hour after a meal.

Dietary ConsiderationsOral: Should be taken 1 hour before or 1 hour after a meal. Voriconazole tablets contain lactose; avoid administration in hereditary galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption. Suspension contains sucrose; use caution with fructose intolerance, sucrose-isomaltase deficiency, or glucose-galactose malabsorption.

Storage

Powder for injection: Store at 15°C to 30°C (59°F to 86°F). Reconstituted solutions are stable for up to 24 hours under refrigeration at 2°C to 8°C (36°F to 46°F).

Powder for oral suspension: Store at 2°C to 8°C (36°F to 46°F). Reconstituted oral suspension may be stored at 15°C to 30°C (59°F to 86°F).

Tablets: Store at 15°C to 30°C (59°F to 86°F).

Reconstitution

Powder for injection: Reconstitute 200 mg vial with 19 mL of sterile water for injection (use of automated syringe is not recommended). Resultant solution (20 mL) has a concentration of 10 mg/mL. Prior to infusion, must dilute to 0.5-5 mg/mL with NS, LR, D_5WLR, $D_5W^1/_2$NS, D_5W, D_5W with KCl 20 mEq, $^1/_2$NS, or D_5WNS. Do not dilute with 4.2% sodium bicarbonate infusion.

Powder for oral suspension: Add 46 mL of water to the bottle to make 40 mg/mL suspension. Discard unused portion after 14 days.

CompatibilityStable in NS, LR, D_5WLR, $D_5W^1/_2$NS, D_5W, D_5W with KCl 20 mEq, $^1/_2$NS, or D_5WNS. Do not infuse **concomitantly** into same line or cannula with other drug infusions, including TPN. May be infused simultaneously with TPN through a separate I.V. line.

Incompatible: Do not infuse simultaneously with blood products.

ContraindicationsHypersensitivity to voriconazole or any component of the formulation (cross-reaction with other azole antifungal agents may occur but has not been established, use caution); coadministration of CYP3A4 substrates which may lead to QT_c prolongation (cisapride, pimozide, or quinidine); coadministration with barbiturates (long acting), carbamazepine, efavirenz (with standard [eg, not adjusted] voriconazole and efavirenz doses), ergot derivatives, rifampin, rifabutin, ritonavir (≥800 mg/day), sirolimus, St John’s wort

Warnings/Precautions

Concerns related to adverse effects:

- Arrhythmias/QT prolongation: QT interval prolongation has been associated with voriconazole use; rare cases of arrhythmia (including torsade de pointes), cardiac arrest, and sudden death have been reported, usually in seriously ill patients with comorbidities and/or risk factors (eg, prior cardiotoxic chemotherapy, cardiomyopathy, electrolyte imbalance, or concomitant QT_c-prolonging drugs). Use with caution in these patient populations; correct electrolyte abnormalities (eg, hypokalemia, hypomagnesemia, hypocalcemia) prior to initiating therapy.

- Dermatologic reactions: Rarely, serious cutaneous reactions, including Stevens-Johnson syndrome have been reported with treatment. Consider discontinuing in patients developing a rash. Avoid strong, direct exposure to sunlight; may cause photosensitivity, especially with long-term use.

- Hallucinations: Visual and/or auditory hallucinations have been observed. Possibly dependent on serum concentrations and may be more common with the I.V. formulation.

- Ocular effects: Visual changes, including blurred vision, changes in visual acuity, color perception, and photophobia, are commonly associated with treatment. Patients should be warned to avoid tasks which depend on vision, including operating machinery or driving. Changes are reversible on discontinuation following brief exposure/treatment regimens (≤28 days); reversibility following long-term administration has not been evaluated.

Disease-related concerns:

- Hepatic impairment: Serious (and rarely fatal) hepatic toxicity (eg, hepatitis, cholestasis, fulminant failure) has been observed with azole therapy. Use with caution in patients with pre-existing hepatic impairment; monitor liver function closely and dosage adjustment or discontinuation may be warranted.

- Pancreatitis: Monitor pancreatic function in patients (children and adults) at risk for acute pancreatitis (eg, recent chemotherapy or hematopoietic stem cell transplantation). There have been postmarketing reports of pancreatitis in children.

- Renal impairment: Avoid the use of I.V. voriconazole in patients with renal impairment. See “Dosage forms specific issues: Injectable” below. Acute renal failure has been observed in severely ill patients; use with caution in patients receiving concomitant nephrotoxic medications.

Concurrent drug therapy issues:

- High potential for interactions: Use caution in patients taking strong cytochrome P450 inducers, CYP2C9 inhibitors, and major 3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Dosage form specific issues:

- Injectable: Avoid/limit use of intravenous formulation in patients with renal impairment; intravenous formulation contains excipient sulfobutyl ether beta-cyclodextrin (SBECD), which may accumulate in renal insufficiency. Anaphylactoid-type infusion-related reactions may occur with intravenous dosing. Consider discontinuation of infusion if reaction is severe. Do not infuse concomitantly with blood products or short-term concentrated electrolyte solutions, even if the two infusions are running in separate intravenous lines (or cannulas).

- Lactose: Tablets contain lactose; avoid administration in hereditary galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

- Sucrose: Suspension contains sucrose; use caution with fructose intolerance, sucrose-isomaltase deficiency, or glucose-galactose malabsorption.

Geriatric ConsiderationsThe manufacturer reports that median voriconazole plasma concentrations were increased in patients 65 years and older compared to those 65 years and younger. The recommendation that a dose adjustment is not needed for the elderly was based on a similar safety profile between young and older patients.

Pregnancy Risk FactorD

Pregnancy ConsiderationsVoriconazole can cause fetal harm when administered to a pregnant woman. Voriconazole was teratogenic and embryotoxic in animal studies, and lowered plasma estradiol in animal models. Women of childbearing potential should use effective contraception during treatment. Should be used in pregnant woman only if benefit to mother justifies potential risk to the fetus.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsExcretion in breast milk has not been investigated; avoid breast-feeding until additional data are available.

Adverse Reactions

>10%:

Central nervous system: Hallucinations (4% to 12%; auditory and/or visual and likely serum concentration-dependent)

Ocular: Visual changes (dose related; photophobia, color changes, increased or decreased visual acuity, or blurred vision occur in ~21%)

Renal: Creatinine increased (1% to 21%)

2% to 10%:

Cardiovascular: Tachycardia (≤2%)

Central nervous system: Fever (≤6%), chills (≤4%), headache (≤3%)

Dermatologic: Rash (≤7%)

Endocrine & metabolic: Hypokalemia (≤2%)

Gastrointestinal: Nausea (1% to 5%), vomiting (1% to 4%)

Hepatic: Alkaline phosphatase increased (4% to 5%), AST increased (2% to 4%), ALT increased (2% to 3%), cholestatic jaundice (1% to 2%)

Ocular: Photophobia (2% to 3%)

<2% (Limited to important or life-threatening): Acute tubular necrosis, adrenal cortical insufficiency, agranulocytosis, allergic reaction, alopecia, anaphylactoid reaction, anemia (aplastic, hemolytic, macrocytic, megaloblastic, or microcytic), angioedema, anuria, ascites, ataxia, atrial arrhythmia, atrial fibrillation, AV block, bigeminy, bleeding time increased, bone marrow depression, bone necrosis, bradycardia, brain edema, bundle branch block, BUN increased, cardiac arrest, cardiomegaly, cardiomyopathy, cerebral hemorrhage, cerebral ischemia, cerebrovascular accident, chest pain, CHF, cholecystitis, cholelithiasis, chromatopsia, color blindness, coma, confusion, cyanosis, delirium, dementia, depersonalization, depression, diabetes insipidus, diarrhea, DIC, discoid lupus erythematosus, duodenal ulcer perforation, DVT, dyspnea, edema, encephalopathy, endocarditis, eosinophilia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, fixed drug eruption, fulminant hepatic failure, gastrointestinal hemorrhage, GGT/LDH increased, glucose tolerance decreased, grand mal seizure, Guillain-Barré syndrome, hematemesis, hepatic coma, hepatic failure, hepatitis, hepatomegaly, hydronephrosis, hyperbilirubinemia, hypercholesterolemia, hyper-/hypocalcemia, hyper-/hypoglycemia, hyper-/hypomagnesemia, hyper-/hyponatremia, hyper-/hypotension, hyper-/hypothyroidism, hyperkalemia, hyperuricemia, hypophosphatemia, hypoxia, intestinal perforation, intracranial hypertension, jaundice, leukopenia, liver enlarged, lung edema, lymphadenopathy, lymphangitis, maculopapular rash, MI, multiorgan failure, myasthenia, myopathy, nephritis, nephrosis, neuropathy, night blindness, nodal arrhythmia, oculogyric crisis, optic atrophy, optic neuritis, osteomalacia, osteoporosis, palpitation, pancreatitis, pancytopenia, papilledema, paresthesia, peripheral edema, peritonitis, petechia, photosensitivity, pleural effusion, postural hypotension, pruritus, pseudomembraneous colitis, psychosis, pulmonary embolus, purpura, QT interval prolongation, renal dysfunction, renal failure (acute), respiratory distress syndrome, retinal hemorrhage, seizure, sepsis, somnolence, spleen enlarged, Stevens-Johnson syndrome, substernal chest pain, suicidal ideation,

supraventricular extrasystoles, supraventricular tachycardia, syncope, thrombocytopenia, thrombophlebitis, thrombotic thrombocytopenic purpura, tongue edema, torsade de pointes, toxic epidermal necrolysis, uremia, urinary retention, urticaria, uveitis, vasodilation, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, visual field defect

Metabolism/Transport Effects **Substrate** of CYP2C9 (major), 2C19 (major), 3A4 (minor); **Inhibits** CYP2C9 (weak), 2C19 (weak), 3A4 (moderate)

Drug Interactions

Alfentanil: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Alfentanil. *Risk D: Consider therapy modification*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Alosetron: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alosetron. *Risk C: Monitor therapy*

Amphotericin B: Antifungal Agents (Azole Derivatives, Systemic) may diminish the therapeutic effect of Amphotericin B. *Risk C: Monitor therapy*

Antacids: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Aprepitant: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Aprepitant. *Risk C: Monitor therapy*

Barbiturates: May decrease the serum concentration of Voriconazole. **Exceptions:** Methohexital; PENTobarbital; Secobarbital; Thiopental. *Risk X: Avoid combination*

Benzodiazepines (metabolized by oxidation): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Benzodiazepines (metabolized by oxidation). **Exceptions:** Quazepam. *Risk D: Consider therapy modification*

Bosentan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Bosentan. *Risk C: Monitor therapy*

BusPIRone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of BusPIRone. *Risk D: Consider therapy modification*

Busulfan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Busulfan. *Risk C: Monitor therapy*

Calcium Channel Blockers: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Calcium Channel Blockers. **Exceptions:** Clevidipine. *Risk D: Consider therapy modification*

CarBAMazepine: May decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

CarBAMazepine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CarBAMazepine. *Risk C: Monitor therapy*

Cardiac Glycosides: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Cardiac Glycosides. *Risk D: Consider therapy modification*

Ciclesonide: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ciclesonide. Specifically, concentrations of the active des-ciclesonide metabolite may be increased. *Risk C: Monitor therapy*

Cilostazol: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Cilostazol. *Risk D: Consider therapy modification*

Cinacalcet: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Cinacalcet. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Cisapride: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Cisapride. *Risk X: Avoid combination*

Conivaptan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Conivaptan. *Risk X: Avoid combination*

Corticosteroids (Orally Inhaled): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Orally Inhaled). **Exceptions:** Beclomethasone; Flunisolide; Triamcinolone. *Risk C: Monitor therapy*

Corticosteroids (Systemic): Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Corticosteroids (Systemic). *Risk C: Monitor therapy*

CycloSPORINE: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of CycloSPORINE. *Risk D: Consider therapy modification*

CYP2C19 Inducers (Strong): May increase the metabolism of CYP2C19 Substrates. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Substrates: CYP3A4 Inhibitors (Strong) may decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Darunavir: May decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Diclofenac: Voriconazole may increase the serum concentration of Diclofenac. *Risk D: Consider therapy modification*

Didanosine: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). Enteric coated didanosine capsules are not expected to affect these antifungals. *Risk D: Consider therapy modification*

Docetaxel: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Docetaxel. *Risk D: Consider therapy modification*

Dofetilide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Dofetilide. *Risk X: Avoid combination*

Eletriptan: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Eletriptan. *Risk D: Consider therapy modification*

Eplerenone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eplerenone. *Risk D: Consider therapy modification*

Ergot Derivatives: Voriconazole may increase the serum concentration of Ergot Derivatives. *Risk X: Avoid combination*

Erlotinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Erlotinib. *Risk C: Monitor therapy*

Eszopiclone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Eszopiclone. *Risk C: Monitor therapy*

FentaNYL: CYP3A4 Inhibitors (Strong) may increase the serum concentration of FentaNYL. *Risk D: Consider therapy modification*

Fesoterodine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Fesoterodine. Management: Avoid fesoterodine doses greater than 4mg daily in patients who are also receiving strong CYP3A4 inhibitors. *Risk D: Consider therapy modification*

Fosaprepitant: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Fosaprepitant. Specifically, concentrations of aprepitant are likely to be increased. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Gefitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Gefitinib. *Risk C: Monitor therapy*

Grapefruit Juice: May increase the metabolism of Antifungal Agents (Azole Derivatives, Systemic). This specifically applies to oral antifungal administration. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of HMG-CoA Reductase Inhibitors. **Exceptions:** Fluvastatin; Rosuvastatin. *Risk D: Consider therapy modification*

Imatinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Imatinib. *Risk C: Monitor therapy*

Irinotecan: Antifungal Agents (Azole Derivatives, Systemic) may enhance the adverse/toxic effect of Irinotecan. *Risk D: Consider therapy modification*

Ixabepilone: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Ixabepilone. *Risk D: Consider therapy modification*

Lopinavir: May decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Losartan: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Losartan. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Antifungal Agents (Azole Derivatives, Systemic). Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Macrolide Antibiotics. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Maraviroc: CYP3A4 Inhibitors may increase the serum concentration of Maraviroc. *Risk D: Consider therapy modification*

Methadone: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Methadone. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Nilotinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Nilotinib. *Risk X: Avoid combination*

Oral Contraceptive (Estrogens): Voriconazole may decrease the metabolism of Oral Contraceptive (Estrogens). Oral Contraceptive (Estrogens) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Oral Contraceptive (Progestins): Voriconazole may decrease the metabolism of Oral Contraceptive (Progestins). Oral Contraceptive (Progestins) may increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

Phenytoin: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Phenytoin. Phenytoin may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Phosphodiesterase 5 Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Phosphodiesterase 5 Inhibitors. *Risk D: Consider therapy modification*

Pimecrolimus: CYP3A4 Inhibitors (Strong) may decrease the metabolism of Pimecrolimus. *Risk C: Monitor therapy*

Pimozide: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Pimozide. *Risk X: Avoid combination*

Protease Inhibitors: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Protease Inhibitors. Protease Inhibitors may increase the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). Management: Limit indinavir to 600mg every 8 hours with itraconazole or ketoconazole. When used with ritonavir, limit ketoconazole to 200mg/day. Tipranavir labeling recommends limiting fluconazole, itraconazole, and ketoconazole to 200mg with tipranavir/ritonavir. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May increase the serum concentration of Voriconazole. *Risk C: Monitor therapy*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

QuiNIDine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of QuiNIDine. Management: Itraconazole, voriconazole, and posaconazole are specifically contraindicated with quinidine. Use of quinidine with any azole antifungal may require quinidine dose adjustment and should be done with caution and close monitoring. *Risk X: Avoid combination*

Ramelteon: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ramelteon. *Risk C: Monitor therapy*

Ranolazine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ranolazine. *Risk X: Avoid combination*

Repaglinide: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Repaglinide. Management: Concurrent use of an azole antifungal with both repaglinide and gemfibrozil should be avoided. *Risk C: Monitor therapy*

Reverse Transcriptase Inhibitors (Non-Nucleoside): May decrease the serum concentration of Voriconazole. Voriconazole may increase the serum concentration of Reverse Transcriptase Inhibitors (Non-Nucleoside). Management: Efavirenz and voriconazole should not be coadministered at standard doses. Concurrent therapy is acceptable if voriconazole is dosed at 400 mg every 12 hours and efavirenz is dosed at 300 mg daily throughout the course of therapy. **Exceptions:** Delavirdine; Etravirine. *Risk D: Consider therapy modification*

Rifamycin Derivatives: Voriconazole may increase the serum concentration of Rifamycin Derivatives. Rifamycin Derivatives may decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Rifamycin Derivatives: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Rifamycin Derivatives. Only rifabutin appears to be affected. Rifamycin Derivatives may decrease the serum concentration of Antifungal Agents (Azole Derivatives, Systemic). *Risk D: Consider therapy modification*

Ritonavir: May increase the metabolism of Voriconazole. High-dose ritonavir (400 mg every 12 hours) is contraindicated. Use caution with lower doses. *Risk X: Avoid combination*

Rivaroxaban: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Rivaroxaban. *Risk X: Avoid combination*

Saccharomyces boulardii: Antifungal Agents may diminish the therapeutic effect of Saccharomyces boulardii. *Risk D: Consider therapy modification*

Salmeterol: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Salmeterol. *Risk X: Avoid combination*

Silodosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Silodosin. *Risk X: Avoid combination*

Sirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Sirolimus. Management: Sirolimus dose reductions of up to 50-90% may be necessary when starting an azole antifungal. Use of sirolimus with the azole antifungals voriconazole and posaconazole is contraindicated. *Risk D: Consider therapy modification*

Solifenacin: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Solifenacin. *Risk D: Consider therapy modification*

Sorafenib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Sorafenib. *Risk C: Monitor therapy*

St Johns Wort: May decrease the serum concentration of Voriconazole. *Risk X: Avoid combination*

Sucralfate: May decrease the absorption of Antifungal Agents (Azole Derivatives, Systemic). *Risk C: Monitor therapy*

Sunitinib: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Sunitinib. *Risk D: Consider therapy modification*

Tacrolimus: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Tacrolimus. *Risk D: Consider therapy modification*

Temsirolimus: Antifungal Agents (Azole Derivatives, Systemic) may increase the serum concentration of Temsirolimus. Concentrations of the active metabolite, sirolimus, are likely to be increased more substantially than those of the parent temsirolimus. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Tolterodine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Tolterodine. This is likely only of concern in CYP2D6-deficient patients (ie, "poor metabolizers") *Risk D: Consider therapy modification*

Venlafaxine: Voriconazole may enhance the adverse/toxic effect of Venlafaxine. Voriconazole may increase the serum concentration of Venlafaxine. *Risk C: Monitor therapy*

VinCRIStine: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of VinCRIStine. *Risk D: Consider therapy modification*

Vitamin K Antagonists (eg, warfarin): Voriconazole may increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Ziprasidone. *Risk C: Monitor therapy*

Zolpidem: Antifungal Agents (Azole Derivatives, Systemic) may decrease the metabolism of Zolpidem. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Food: May decrease voriconazole absorption. Voriconazole should be taken 1 hour before or 1 hour after a meal. Avoid grapefruit juice (may decrease voriconazole levels).

Herb/Nutraceutical: St John's wort may decrease voriconazole levels; concurrent use with voriconazole is contraindicated.

Monitoring ParametersHepatic function at initiation and during course of treatment; renal function; serum electrolytes (particularly calcium, magnesium and potassium) prior to therapy initiation; visual function (visual acuity, visual field and color perception) if treatment course continues >28 days; may consider obtaining voriconazole trough level in patients failing therapy or exhibiting signs of toxicity; pancreatic function (in patients at risk for acute pancreatitis)

Nursing: Physical Assessment/MonitoringEvaluate hepatic function, renal function, and allergy history prior to beginning therapy. Assess all other pharmacological or herbal products patient may be taking for potential interactions or toxicity. Assess results of laboratory tests, therapeutic effectiveness (according to purpose for use), and adverse response (eg, vision changes [photophobia, changed visual acuity, blurred vision], hepatic toxicity [increased liver enzymes, jaundice], tachycardia, dermatologic reactions) on a regular basis. Teach patient proper use, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsHepatic function at initiation and during course of treatment; renal function; serum electrolytes (particularly calcium, magnesium and potassium) prior to therapy initiation; may consider obtaining voriconazole trough level in patients failing therapy or exhibiting signs of toxicity; pancreatic function (in patients at risk for acute pancreatitis)

Patient EducationDo not take any new medication during therapy unless approved by prescriber. **I.V.:** You will be monitored during intravenous administration; report immediately any pain, swelling, redness at infusion site, difficulty breathing or swallowing, back pain, itching, or other adverse effects. **Oral:** Take full course of medication as ordered. Preferable to take on empty stomach 1 hour before or 1 hour after a meal. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience headache, dizziness, blurred vision, photophobia, or changes in visual acuity (use caution when driving or engaging in tasks that require alertness until response to drug is known; vision changes are reversible shortly after treatment is completed or discontinued); nausea, vomiting, or abdominal pain (small frequent meals, frequent mouth care, sucking lozenges, chewing gum may help). Report immediately any change in vision. Report unusual tiredness, flu-like feelings, skin rash or itching, dark urine, light colored stool, yellowing of skin or eyes; fever; chest pain or rapid heartbeat; or any other persistent side effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this drug. Fetal harm can occur. Consult prescriber for appropriate contraceptive measures. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution: 200 mg [contains SBECD 3200 mg]

Powder for oral suspension: 200 mg/5 mL (70 mL) [contains sodium benzoate and sucrose; orange flavor]

Tablet: 50 mg, 200 mg [contains lactose]

Generic AvailableNo

ManufacturerPfizer Inc

Mechanism of ActionInterferes with fungal cytochrome P450 activity (selectively inhibits 14-alpha-lanosterol demethylation), decreasing ergosterol synthesis (principal sterol in fungal cell membrane) and inhibiting fungal cell membrane formation.

Pharmacodynamics/Kinetics

Absorption: Well absorbed after oral administration; administration of crushed tablets is considered bioequivalent to whole tablets

Distribution: V_d: 4.6 L/kg

Protein binding: 58%

Metabolism: Hepatic, via CYP2C19 (major pathway) and CYP2C9 and CYP3A4 (less significant); saturable (may demonstrate nonlinearity)

Bioavailability: 96%

Half-life elimination: Variable, dose-dependent

Time to peak: Oral: 1-2 hours; 0.5 hours (crushed tablet)

Excretion: Urine (as inactive metabolites; <2% as unchanged drug)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsVoriconazole is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health: Effects on Mental StatusMay cause abnormal dreams, agitation, amnesia, anxiety, confusion, delirium, dementia, depersonalization, depression, dizziness, encephalopathy, euphoria, insomnia, psychosis, somnolence, suicidal ideation

Mental Health: Effects on Psychiatric TreatmentContraindicated with CYP3A4 substrates which may lead to QT_c prolongation (pimozide); coadministration with barbiturates (long acting), carbamazepine, and ergot alkaloids. Blurred vision is common; use caution with anticholinergic agents. Concurrent use with benzodiazepines that are oxidatively metabolized (alprazolam, diazepam, temazepam, triazolam, and midazolam) may result in elevated benzodiazepine serum concentrations and potential risk for toxicity. Buspirone and zolpidem serum concentrations may be increased with concurrent use. St John's wort may decrease voriconazole levels; monitor.

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Based on high oral bioavailability, switching between I.V. and oral administration is appropriate when clinically indicated. Infusions of blood products and any electrolyte supplementation must not occur simultaneously with intravenous voriconazole. Voriconazole I.V. must not be infused into the same line or cannula concomitantly with other drug infusions.

Index TermsUK109496

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International Brand Names VFEND (AR, AT, AU, BE, BG, BR, BZ, CH, CL, CN, CO, CR, CZ, DE, DK, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IL, IT, MX, MY, NI, NL, NO, PA, PE, PT, RU, SE, SG, SV, TH, TR, TW, ZA); Vfend (PL); Vorcum (VE)

Vorinostat

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(vor IN oh stat)
U.S. Brand NamesZolinza™
Pharmacologic CategoryAntineoplastic Agent, Histone Deacetylase Inhibitor
Use: Labeled IndicationsTreatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL)
Dosing: Adults**Cutaneous T-cell lymphoma:** Oral: 400 mg once daily

In clinical trials, treatment was withheld for grade 4 anemia or thrombocytopenia or other grade 3 or 4 drug related toxicity, until resolved to ≤ grade 1. Therapy was reinitiated with dose modification (Olsen, 2007).

Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNot studied, however, based on the minimal renal elimination, adjustment may not be required.
Dosing: Hepatic ImpairmentNot studied; use caution based on predominant hepatic metabolism.
Dosing: Adjustment for ToxicityIntolerance: Reduce dose to 300 mg once daily; may further reduce to 300 mg daily for 5 consecutive days per week

In clinical trials, **dose reductions** were instituted for the following adverse events: Increased serum creatinine, decreased appetite, hypokalemia, leukopenia, nausea, neutropenia, thrombocytopenia, and vomiting. Vorinostat was **discontinued** for the following adverse events: Anemia, angioneurotic edema, weakness, chest pain, exfoliative dermatitis, DVT, ischemic stroke, lethargy, pulmonary embolism, and spinal cord injury.

Administration: OralAdminister with food. Do not open, crush, or chew capsules.
Dietary ConsiderationsTake with food.
StorageStore at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
ContraindicationsThere are no contraindications listed within the manufacturer’s labeling.
Warnings/Precautions

Special handling:

- Hazardous agent: Use appropriate precautions for handling and disposal.

Concerns related to adverse effects:

- Gastrointestinal toxicities: Nausea, vomiting, and diarrhea may occur; antiemetics and antidiarrheals may be required. Replace fluids and electrolytes to avoid dehydration.
- Hematologic toxicity: Dose-related anemia and thrombocytopenia may occur; may require dosage adjustments.
- Hyperglycemia: May cause hyperglycemia. Use with caution in patients with diabetes mellitus; monitor; may require diet and/or therapy modifications.
- QT_c prolongation: With use, QT_c prolongation has been observed; a baseline and periodic 12-lead ECG should be obtained. Correct electrolyte abnormalities prior to treatment and monitor and correct potassium, calcium, and magnesium levels during therapy. Use caution in patients with a history of QT_c prolongation or with medications known to prolong the QT interval.
- Thromboembolic events: Pulmonary embolism and deep vein thrombosis (DVT) have been reported; monitor. Use caution in patients with a history of thrombotic events.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorD
Pregnancy ConsiderationsAnimal studies have demonstrated adverse fetal effects, including fetal loss, decreased fetal weight, and skeletal malformation. There are no adequate and well-controlled studies in pregnant women. Inform patient of potential hazard if used during pregnancy or if pregnancy occurs during treatment.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsDue to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended.
Adverse Reactions

>10%:

Cardiovascular: Peripheral edema (13%)

Central nervous system: Fatigue (46% to 73%), chills (12% to 16%), dizziness (15%), headache (12%), fever (11%)

Dermatologic: Alopecia (18% to 19%), pruritus (12%)

Endocrine & metabolic: Hyperglycemia (8% to 69%; grade 3: 5%), dehydration (16%)

Gastrointestinal: Diarrhea (49% to 52%), nausea (41% to 49%), taste perversion (24% to 46%), xerostomia (11% to 35%), weight loss (20% to 27%), anorexia (22% to 24%), vomiting (12% to 24%), appetite decreased (14% to 22%), constipation (11% to 15%)

Hematologic: Thrombocytopenia (22% to 54%; grades 3/4: 5% to 19%), anemia (2% to 14%; grades 3/4: 1% to 3%)

Neuromuscular & skeletal: Muscle spasm (16% to 20%)

Renal: Proteinuria (51%), creatinine increased (15% to 47%)

Respiratory: Dyspnea (34%), cough (11%), upper respiratory infection (11%)

1% to 10%:

Cardiovascular: QT_c prolongation (3% to 6%)

Dermatologic: Squamous cell carcinoma (4%)

Respiratory: Pulmonary embolism (5%)

<1%, postmarketing, and/or case reports: Angioneurotic edema, blurred vision, chest pain, cholecystitis, creatine phosphokinase (CPK) increased, DVT, enterococcal infection, exfoliative dermatitis, gastrointestinal hemorrhage, hemoptysis, hypertension, hypocalcemia, hypokalemia, hyponatremia, hypophosphatemia, infection, lethargy, leukopenia, MI, neutropenia, pneumonia, renal failure, sepsis, spinal cord injury, streptococcal bacteremia, stroke (ischemic), syncope, T-cell lymphoma, transaminases increased, tumor hemorrhage, ureteric obstruction, ureteropelvic junction obstruction, urinary retention, vasculitis, weakness

Oncology: Emetic PotentialLow (10% to 30%)

Drug Interactions

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. *Risk X: Avoid combination*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Valproic Acid: May enhance the thrombocytopenic effect of Vorinostat. This may increase the risk of gastrointestinal bleeding. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Vorinostat may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Monitoring ParametersBaseline, then periodic 12-lead ECG; baseline, then every other week serum electrolytes (including calcium, magnesium and potassium), CBC with differential and platelets, serum creatinine and blood glucose for 2 months, then monthly

Nursing: Physical Assessment/MonitoringElectrolyte abnormalities should be corrected prior to treatment. Assess for potential adverse interactions with any other prescription, OTC, or herbal products patient may be taking (eg, anything that may prolong QT interval, increase risk of gastrointestinal bleeding, or increase risk of thrombocytopenia). Assess results of laboratory tests before beginning therapy and then regularly (eg, EKG, serum electrolytes, CBC, creatinine, and blood glucose). Evaluate therapeutic effectiveness and adverse reactions on a regular basis; dosing adjustment may be necessary. Caution patients with diabetes to monitor serum glucose closely. Teach patient correct use and proper handling of capsules, possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsBaseline, then periodic 12-lead ECG; baseline, then every other week serum electrolytes (including calcium, magnesium and potassium), CBC with differential and platelets, serum creatinine and blood glucose for 2 months, then monthly

Patient EducationDo not take any new prescription or OTC medications or herbal products during therapy unless approved by prescriber. Take exactly as directed, with food. Do not open, chew, or crush capsules. If capsule is accidentally opened or crushed, do not touch the capsules or powder. If powder gets on your skin, wash well with plain water and notify your prescriber. If you have diabetes, you should monitor your glucose levels closely and report immediately if your blood sugar is higher than normal. Maintain adequate hydration (2-3 L/day of fluids, unless instructed to restrict fluid intake) and nutrition (small, frequent meals). You may experience dry mouth, taste changes, nausea, or vomiting (frequent oral care, sucking lozenges, or chewing gum may help); loss of hair (will grow back after treatment is discontinued); or dizziness or headache (use care when driving or engaging in tasks that require alertness until response to drug is known). Report any chest pain or palpitations; upper respiratory infection or difficulty breathing; muscle pain, tremors, weakness or spasms; swelling in foot, ankle, or leg; rash or itching; or any other persistent or acute adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Do not get pregnant while taking this medication. This drug may cause fetal deformities or loss of pregnancy; see prescriber for appropriate contraceptives. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Zolinza™: 100 mg

Generic AvailableNo

Manufacturer

Merck & Co, Inc

Mechanism of ActionInhibition of histone deacetylase enzymes, HDAC1, HDAC2, HDAC3, and HDAC6, which catalyze acetyl group removal from protein lysine residues (including histones and transcription factors). Inhibition of histone deacetylase results in accumulation of acetyl groups, leading to alterations in chromatin structure and transcription factor activation causing termination of cell growth leading to cell death.

Pharmacodynamics/Kinetics

Protein binding: ~71%

Metabolism: Glucuronidated and hydrolyzed (followed by beta-oxidation) to inactive metabolites

Bioavailability: Fasting: ~43%

Half-life elimination: ~2 hours

Time to peak, plasma: With high-fat meal: ~4 hours (range: 2-10 hours)

Excretion: Urine: 52% (<1% as unchanged drug, ~52% as inactive metabolites)

Dental Health Professional ConsiderationsThis drug is known to prolong the QT interval. The QT interval is measured as the time and distance between the Q point of the QRS complex and the end of the T wave in the ECG tracing. After adjustment for heart rate, the QT interval is defined as prolonged if it is more than 450 msec in men and 460 msec in women. A long QT syndrome was first described in the 1950s and 60s as a congenital syndrome involving QT interval prolongation and syncope and sudden death. Some of the congenital long QT syndromes were characterized by a peculiar electrocardiographic appearance of the QRS complex involving a premature atria beat followed by a pause, then a subsequent sinus beat showing marked QT prolongation and deformity. This type of cardiac arrhythmia was originally termed “torsade de pointes” (translated from the French as “twisting of the points”).

Prolongation of the QT interval is thought to result from delayed ventricular repolarization. The repolarization process within the myocardial cell is due to the efflux of intracellular potassium. The channels associated with this current can be blocked by many drugs and predispose the electrical propagation cycle to torsade de pointes.

Vorinostat is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: High incidence of xerostomia (normal salivary flow resumes upon discontinuation) and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusFatigue is common; may cause dizziness

Mental Health: Effects on Psychiatric TreatmentVorinostat causes dose-related thrombocytopenia; use caution with valproic acid. GI side effects are common; concomitant use with lithium, valproic acid, carbamazepine, and SSRIs may produce additive effects. Hyperglycemia is common; psychotropics may further alter glucose regulation. Xerostomia is common; concomitant use with psychotropics may produce additive effects.

Index TermsNSC-701852; SAHA; Suberoylanilide Hydroxamic Acid

References

Duvic M, Talpur R, Ni X, et al, “Phase II Trial of Oral Vorinostat (Suberoylanilide Hydroxamic Acid, SAHA) for Refractory Cutaneous T-Cell Lymphoma (CTCL),” *Blood*, 2007, 109(1):31-9.[PubMed 16960145]

Kelly WK, O'Connor OA, Krug LM, et al, “Phase I Study of an Oral Histone Deacetylase Inhibitor, Suberoylanilide Hydroxamic Acid, in Patients With Advanced Cancer,” *J Clin Oncol*, 2005, 23(17):3923-31. [PubMed 15897550]

O'Connor OA, Heaney ML, Schwartz L, et al, “Clinical Experience With Intravenous and Oral Formulations of the Novel Histone Deacetylase Inhibitor Suberoylanilide Hydroxamic Acid in Patients With Advanced Hematologic Malignancies,” *J Clin Oncol*, 2006, 24(1):166-73. [PubMed 16330674]

Olsen EA, Kim YH, Kuzel TM, et al, “Phase IIb Multicenter Trial of Vorinostat in Patients With Persistent, Progressive, or Treatment Refractory Cutaneous T-Cell Lymphoma,” *J Clin Oncol*, 2007, 25(21):3109-15. [PubMed 17577020]

VP (Small Cell Lung Cancer)

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Jump To Field (Select Field Name)

Pharmacologic CategoryChemotherapy Regimen, Lung Cancer (Small Cell)
Regimen UseLung cancer, small cell
Regimen

Etoposide: I.V.: 100 mg/m^2/day days 1 to 4

[total dose/cycle = 400 mg/m^2]

Cisplatin: I.V.: 20 mg/m^2/day days 1 to 4

[total dose/cycle = 80 mg/m^2]

Repeat cycle every 21 days

References

Loehrer PJ Sr, Ansari R, Gonin R, et al, âCisplatin Plus Etoposide With and Without Ifosfamide in Extensive Small Cell Lung Cancer: A Hoosier Oncology Group Study,â *J Clin Oncol*, 1995, 13(10):2594-9.[PubMed 7595712]

Warfarin

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English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Coumadin® may be confused with Avandia®, Cardura®, Compazine®, Kemadrin®

Jantoven™ may be confused with Janumet™, Januvia™

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

2009 National Patient Safety Goals: The Joint Commission on Accreditation of Healthcare Organizations requires healthcare organizations that provide anticoagulant therapy to have a process in place to reduce the risk of anticoagulant-associated patient harm. Patients receiving anticoagulants should receive individualized care through a defined process that includes standardized ordering, dispensing, administration, monitoring and education. This does not apply to routine short-term use of anticoagulants for prevention of venous thromboembolism when the expectation is that the patient's laboratory values will remain within or close to normal values (NPSG.03.05.01).

Pronunciation(WAR far in)

U.S. Brand NamesCoumadin®; Jantoven®

Canadian Brand NamesApo-Warfarin®; Coumadin®; Gen-Warfarin; Novo-Warfarin; Taro-Warfarin

Pharmacologic CategoryAnticoagulant, Coumarin Derivative; Vitamin K Antagonist

Use: Labeled IndicationsProphylaxis and treatment of thromboembolic disorders (eg, venous, pulmonary) and embolic complications arising from atrial fibrillation or cardiac valve replacement; adjunct to reduce risk of systemic embolism (eg, recurrent MI, stroke) after myocardial infarction

Use: Unlabeled/InvestigationalPrevention of recurrent transient ischemic attacks

Dosing: Adults**Note:** New labeling identifies genetic factors which may increase patient sensitivity to warfarin. Specifically, genetic variations in the proteins CYP2C9 and VKORC1, responsible for warfarin's primary metabolism and pharmacodynamic activity, respectively, have been identified as predisposing factors associated with decreased dose requirement and increased bleeding risk. A genotyping test is available, and may provide important guidance on initiation of anticoagulant therapy.

Prevention/treatment of thrombosis/embolism:

I.V. (administer as a slow bolus injection): 2-5 mg/day

Oral: Initial dosing must be individualized. Consider the patient (hepatic function, cardiac function, age, nutritional status, concurrent therapy, risk of bleeding) in addition to prior dose response (if available) and the clinical situation. Start 2-5 mg daily for 2 days **or** 5-10 mg daily for 1-2 days (Ansell, 2008). Adjust dose according to INR results; usual maintenance dose ranges from 2-10 mg daily (individual patients may require loading and maintenance doses outside these general guidelines).

Note: Lower starting doses may be required for patients with hepatic impairment, poor nutrition, CHF, elderly, high risk of bleeding, or patients who are debilitated, or those with reduced function genomic variants of the catabolic enzymes CYP2C9 (*2 or *3 alleles) or VKORC1 (-1639 polymorphism). Higher initial doses may be reasonable in selected patients (ie, receiving enzyme-inducing agents and with low risk of bleeding).

Dosing: ElderlyOral: Initial dose ≤5 mg. Usual maintenance dose: 2-5 mg/day. The elderly tend to require lower dosages to produce a therapeutic level of anticoagulation (due to changes in the pattern of warfarin metabolism).

Dosing: Pediatric**Prevention/treatment of thrombosis:** Oral: Infants and Children (unlabeled use): Initial loading dose (if baseline INR is 1-1.3): 0.2 mg/kg (maximum: 10 mg/dose); adjust dose based on INR (reported ranges to maintain INR of 2-3: 0.09-0.33 mg/kg/day). Infants <12 months of age may require doses at or near the high end of this range; consistent anticoagulation may be difficult to maintain in children <5 years of age.

Dosing: Renal ImpairmentNo adjustment required, however, patients with renal failure have an increased risk of bleeding complications. Monitor closely.

Dosing: Hepatic ImpairmentMonitor effect at usual doses. The response to oral anticoagulants may be markedly enhanced in obstructive jaundice, hepatitis, and cirrhosis. INR should be closely monitored.

Administration: I.V.Administer as a slow bolus injection over 1-2 minutes. Avoid all I.M. injections.

Administration: I.V. DetailpH: 8.1-8.3

Administration: OralAdminister with or without food. Take at the same time each day.

Dietary ConsiderationsFoods high in vitamin K (eg, beef liver, pork liver, green tea, and leafy green vegetables) inhibit anticoagulant effect. Do not change dietary habits once stabilized on warfarin therapy. A balanced diet with a consistent intake of vitamin K is essential. Avoid large amounts of alfalfa, asparagus, broccoli, Brussels sprouts, cabbage, cauliflower, green teas, kale, lettuce, spinach, turnip greens, and watercress; decreased efficacy of warfarin. It is recommended that the diet contain a CONSISTENT vitamin K content of 70-140 mcg/day. Check with healthcare provider before changing diet.

Storage

Injection: Prior to reconstitution, store at 15°C to 30°C (59°F to 86°F). Following reconstitution with 2.7 mL of sterile water (yields 2 mg/mL solution), stable for 4 hours at 15°C to 30°C (59°F to 86°F). Protect from light.

Tablet: Store at 15°C to 30°C (59°F to 86°F). Protect from light.

ReconstitutionReconstitute with 2.7 mL of sterile water (yields 2 mg/mL solution).

CompatibilityStable in D_5LR, $D_5{}^1/_2NS$, D_5NS, D_5W, $D_{10}W$, **variable stability (consult detailed reference)** in LR, NS.

Y-site administration: Compatible: Amikacin, ascorbic acid injection, cefazolin, ceftriaxone, dopamine, epinephrine, heparin, lidocaine, metaraminol, morphine, nitroglycerin, oxytocin, potassium chloride, ranitidine. **Incompatible:** Aminophylline, bretylium, ceftazidime, cimetidine, ciprofloxacin, dobutamine, esmolol, gentamicin, labetalol, metronidazole, promazine, Ringer's injection. **Variable (consult detailed reference):** Ammonium chloride, vancomycin.

Compatibility in syringe: Incompatible: Heparin.

RestrictionsAn FDA-approved medication guide must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to warfarin or any component of the formulation; hemorrhagic tendencies (eg, patients bleeding from the GI, respiratory, or GU tract; aneurysm; cerebrovascular hemorrhage; following spinal puncture and other diagnostic or therapeutic procedures with potential for significant bleeding; history of bleeding diathesis); recent or potential surgery of the eye or CNS; major regional lumbar block anesthesia or surgery resulting in large, open surfaces; blood dyscrasias; severe uncontrolled or malignant hypertension; pericarditis or pericardial effusion; subacute bacterial endocarditis; history of warfarin-induced necrosis; an unreliable, noncompliant patient; alcoholism; patient who has a history of falls or is a significant fall risk; unsupervised senile or psychotic patient; eclampsia/pre-eclampsia, threatened abortion, pregnancy

Allergy Considerations

- Coumarin-Type Anticoagulant Allergy

Warnings/Precautions

Boxed warnings:

- Bleeding: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Anaphylaxis/hypersensitivity: May cause hypersensitivity reactions, including anaphylaxis; use with caution in patients with anaphylactic disorders.

- Bleeding: **[U.S. Boxed Warning]: May cause major or fatal bleeding.** Risk factors for bleeding include high intensity anticoagulation (INR >4), age (≥65 years), variable INRs, history of GI bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, severe diabetes, malignancy, trauma, renal insufficiency, polycythemia vera, vasculitis, open wound, history of PUD, indwelling catheters, menstruating and postpartum women, drug-drug interactions, long duration of therapy, or known genetic deficiency in CYP2C9 activity. Patient must be instructed to report bleeding, accidents, or falls as well as any new or discontinued medications, herbal or alternative products used, or significant changes in smoking or dietary habits. Unrecognized bleeding sites (eg, colon cancer) may be uncovered by anticoagulation.

- Skin necrosis/gangrene: Necrosis or gangrene of the skin and other tissue can occur (rarely, <0.1%) due to paradoxical local thrombosis; onset is usually within the first few days of therapy and is frequently localized to the limbs, breast, or penis. The risk of this effect is increased in patients with protein C or S deficiency.

- “Purple toe” syndrome, due to cholesterol microembolization, has been rarely described with coumarin-type anticoagulants. Typically, this occurs after several weeks of therapy, and may present as a dark, purplish, mottled discoloration of the plantar and lateral surfaces. Other manifestations of cholesterol microembolization may include rash; livedo reticularis; gangrene; abrupt and intense pain in lower extremities; abdominal, flank, or back pain; hematuria, renal insufficiency; hypertension; cerebral ischemia; spinal cord infarction; or other symptoms of vascular compromise.

Disease-related concerns:

- Dietary insufficiency: Use with caution in patients with prolonged dietary insufficiencies (vitamin K deficiency).

- Heparin-induced thrombocytopenia: Use with caution in patients with heparin-induced thrombocytopenia and DVT; limb ischemia, necrosis, and gangrene have occurred when warfarin was started or continued after heparin was stopped. Warfarin monotherapy is contraindicated in the initial treatment of active HIT; warfarin initially inhibits the synthesis of protein C, potentially accelerating the underlying active thrombotic process.

- Hepatic impairment: Reduced liver function, regardless of etiology, may impair synthesis of coagulation factors leading to increased warfarin sensitivity.

- Infection: Use with caution in patients with acute infection or active TB or any disruption of normal GI flora; antibiotics and fever may alter response to warfarin.

- Renal impairment: Use with caution in patients with moderate-to-severe renal impairment.

- Thyroid disease: Use with caution in patients with thyroid disease.

Special populations:

- Elderly: The elderly may be more sensitive to anticoagulant therapy.

- Ovulating women: May be at risk of developing ovarian hemorrhage at the time of ovulation.

- Patients with genomic variants in CYP2C9 and/or VKORC1: Presence of the CYP2C9*2 or *3 allele and/or polymorphism of the vitamin K oxidoreductase (VKORC1) gene may increase the risk of bleeding. The *2 allele is reported to occur with a frequency of 4% to 11% in African-Americans and Caucasians, respectively, while the *3 allele frequencies are 2% to 7% respectively. Other variant 2C9 alleles (eg, *5, *6, *9, and *11) are also associated with reduced metabolic activity and thus may increase risk of bleeding, but are much less common. Lower doses may be required in these patients; genetic testing may help determine appropriate dosing.

- Pediatrics: Safety and efficacy have not been established in children; monitor closely.

Other warnings/precautions:

- Patient selection: Use care in the selection of patients appropriate for this treatment; ensure patient cooperation especially from the alcoholic, illicit drug user, demented, or psychotic patient; ability to comply with routine laboratory monitoring is essential.

Geriatric ConsiderationsBefore committing an elderly patient to long-term anticoagulation therapy, the risk for bleeding complications secondary to falls, drug interactions, living situation, and cognitive status should be considered. A risk of bleeding complications has been associated with increased age.

Pregnancy Risk FactorX

Pregnancy ConsiderationsOral anticoagulants cross the placenta and produce fetal abnormalities. May also cause fatal fetal hemorrhage. Warfarin should not be used during pregnancy because of significant risks. Adjusted-dose heparin can be given safely throughout pregnancy in patients with venous thromboembolism.

LactationDoes not enter breast milk, only metabolites are excreted (AAP rates “compatible”)

Breast-Feeding ConsiderationsWarfarin does not pass into breast milk and can be given to nursing mothers (AAP rates “compatible”). However, limited data suggests prolonged PT may occur in some infants. Women who are breast-feeding should be carefully monitored to avoid excessive anticoagulation. Evaluation of coagulation tests and vitamin K status of breast-feeding infant is considered prudent.

Adverse ReactionsBleeding is the major adverse effect of warfarin. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the intensity of anticoagulation and patient susceptibility.

Cardiovascular: Angina, chest pain, edema, hemorrhagic shock, hypotension, pallor, syncope, vasculitis

Central nervous system: Coma, dizziness, fatigue, fever, headache, lethargy, malaise, pain, stroke

Dermatologic: Alopecia, bullous eruptions, dermatitis, rash, pruritus, urticaria

Gastrointestinal: Abdominal cramps, abdominal pain, anorexia, diarrhea, flatulence, gastrointestinal bleeding, mouth ulcers, nausea, taste disturbance, vomiting

Genitourinary: Hematuria, priapism

Hematologic: Agranulocytosis, anemia, leukopenia, retroperitoneal hematoma, unrecognized bleeding sites (eg, colon cancer) may be uncovered by anticoagulation

Hepatic: Cholestatic jaundice, hepatic injury, hepatitis, transaminases increased

Neuromuscular & skeletal: Joint pain, muscle pain, osteoporosis (potential association with long-term use), paralysis, paresthesia, weakness

Respiratory: Dyspnea, tracheobronchial calcification

Miscellaneous: Anaphylactic reaction, cold intolerance, hypersensitivity/allergic reactions, skin necrosis, gangrene, “purple toes” syndrome

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2C9 (major), 2C19 (minor), 3A4 (minor); **Inhibits** CYP2C9 (moderate), 2C19 (weak)

Drug Interactions

Acetaminophen: May enhance the anticoagulant effect of Vitamin K Antagonists. Most likely with daily acetaminophen doses >1.3 g for >1 week. *Risk C: Monitor therapy*

Allopurinol: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Aminoglutethimide: May increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Amiodarone: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Androgens: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Anticoagulants: May enhance the anticoagulant effect of other Anticoagulants. *Risk C: Monitor therapy*

Antineoplastic Agents: May enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. **Exceptions:** Alitretinoin; Altretamine; Aminoglutethimide; Anastrozole; Asparaginase; AzaCITIDine; Bleomycin; Capecitabine; CARBOplatin; Carmustine; Chlorambucil; CISplatin; Cladribine; Cytarabine; Cytarabine (Liposomal); Dacarbazine; DACTINomycin; DAUNOrubicin Citrate (Liposomal); DAUNOrubicin Hydrochloride; Denileukin Diftitox; Docetaxel; DOXOrubicin (Liposomal); Epirubicin; Estramustine; Etoposide Phosphate; Exemestane; Fludarabine; Goserelin; Hydroxyurea; IDArubicin; Irinotecan; Letrozole; Leuprolide; Lomustine; Mechlorethamine; Megestrol; Mitomycin; Mitoxantrone; Nilutamide; Paclitaxel; Pegaspargase; Pentostatin; Polyestradiol; Porfimer; RiTUXimab; Streptozocin; Tamoxifen; Temozolomide; Teniposide; Thioguanine; Thiotepa; Topotecan; Toremifene; Tretinoin (Oral); Valrubicin; VinBLAStine; Vinorelbine. *Risk C: Monitor therapy*

Antiplatelet Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Antithyroid Agents: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Aprepitant: May decrease the serum concentration of Warfarin. *Risk C: Monitor therapy*

Atazanavir: May increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

AzaTHIOprine: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Barbiturates: May increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Bile Acid Sequestrants: May decrease the absorption of Vitamin K Antagonists. *Risk C: Monitor therapy*

Bosentan: May increase the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Capecitabine: May increase the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

CarBAMazepine: May decrease the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Cephalosporins: May enhance the anticoagulant effect of Vitamin K Antagonists. **Exceptions:** Cefaclor; Cefadroxil; Cefdinir; Cefepime; Cefixime; Cefonicid; Cefotaxime; Cefpodoxime; Cefprozil; Ceftazidime; Ceftibuten; Ceftizoxime; Ceftobiprole; Cefuroxime; Cephalexin; Cephradine [Off Market]. *Risk C: Monitor therapy*

Cimetidine: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Clopidogrel: May enhance the anticoagulant effect of Warfarin. *Risk D: Consider therapy modification*

Coenzyme Q-10: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Contraceptive (Progestins): May diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Corticosteroids (Systemic): May enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Cranberry: May enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

Darunavir: May decrease the serum concentration of Warfarin. *Risk C: Monitor therapy*

Dasatinib: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Dicloxacillin: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Disulfiram: May increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Drotrecogin Alfa: Vitamin K Antagonists may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. *Risk D: Consider therapy modification*

Efavirenz: May increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Etoposide: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Fenofibrate: May enhance the anticoagulant effect of Warfarin. Fenofibrate may increase the serum concentration of Warfarin. *Risk D: Consider therapy modification*

Fenofibric Acid: May enhance the anticoagulant effect of Warfarin. Fenofibric Acid may increase the serum concentration of Warfarin. *Risk D: Consider therapy modification*

Fenugreek: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Fibric Acid Derivatives: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Fluconazole: May increase the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Fluorouracil: May increase the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Fosaprepitant: May decrease the serum concentration of Warfarin. The active metabolite aprepitant is likely responsible for this effect. *Risk C: Monitor therapy*

Gefitinib: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ginkgo Biloba: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Ginseng (American): May decrease the serum concentration of Warfarin. *Risk C: Monitor therapy*

Glucagon: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Glutethimide: May increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Griseofulvin: May increase the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Herbs (Anticoagulant/Antiplatelet Properties) (eg, Alfalfa, Anise, Bilberry): May enhance the adverse/toxic effect of Anticoagulants. Bleeding may occur. *Risk D: Consider therapy modification*

HMG-CoA Reductase Inhibitors: May enhance the anticoagulant effect of Vitamin K Antagonists. **Exceptions:** Atorvastatin. *Risk C: Monitor therapy*

Ifosfamide: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Imatinib: May enhance the anticoagulant effect of Warfarin. Imatinib may decrease the metabolism of Warfarin. *Risk D: Consider therapy modification*

Itraconazole: May increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ivermectin: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ketoconazole: May increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Leflunomide: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Lopinavir: May decrease the serum concentration of Warfarin. *Risk C: Monitor therapy*

Macrolide Antibiotics: May decrease the metabolism of Vitamin K Antagonists. **Exceptions:** Dirithromycin [Off Market]; Spiramycin. *Risk C: Monitor therapy*

Mercaptopurine: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

MetroNIDAZOLE: May decrease the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Miconazole: May increase the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Nafcillin: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

NSAID (COX-2 Inhibitor): May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

NSAID (Nonselective): May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Omega-3-Acid Ethyl Esters: May enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Oral Contraceptive (Estrogens): May diminish the anticoagulant effect of Vitamin K Antagonists. In contrast, enhanced anticoagulant effects have also been noted with some products. *Risk D: Consider therapy modification*

Orlistat: May enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Pentosan Polysulfate Sodium: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Phenytoin: May enhance the anticoagulant effect of Vitamin K Antagonists. Vitamin K Antagonists may increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Phytonadione: May diminish the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Posaconazole: May increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Propafenone: May increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Propoxyphene: May decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Prostacyclin Analogues: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the antiplatelet effects of these agents may lead to an increased risk of bleeding with the combination. *Risk C: Monitor therapy*

Proton Pump Inhibitors: May increase the serum concentration of Warfarin. **Exceptions:** Esomeprazole; Lansoprazole; Pantoprazole; Rabeprazole. *Risk C: Monitor therapy*

QuiNIDine: May enhance the anticoagulant effect of Vitamin K Antagonists. Note that the prothrombin time might be unchanged in the face of increased bleeding. *Risk C: Monitor therapy*

Quinolone Antibiotics: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ritonavir: May decrease the serum concentration of Warfarin. *Risk C: Monitor therapy*

Salicylates: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Selective Serotonin Reuptake Inhibitors: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Sitaxsentan: May increase the serum concentration of Warfarin. *Risk D: Consider therapy modification*

Sorafenib: May enhance the anticoagulant effect of Warfarin. Sorafenib may increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

St Johns Wort: May increase the metabolism of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Sulfinpyrazone [Off Market]: May decrease the metabolism of Vitamin K Antagonists. Sulfinpyrazone [Off Market] may decrease the protein binding of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Sulfonamide Derivatives: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Tamoxifen: May increase the serum concentration of Vitamin K Antagonists. *Risk X: Avoid combination*

Tetracycline Derivatives: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Thrombolytic Agents: May enhance the anticoagulant effect of Anticoagulants. *Risk C: Monitor therapy*

Thyroid Products: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk D: Consider therapy modification*

Tigecycline: May increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

Tolterodine: May enhance the anticoagulant effect of Warfarin. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Vitamin A: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Vitamin E: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Voriconazole: May increase the serum concentration of Vitamin K Antagonists. *Risk C: Monitor therapy*

Vorinostat: May enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zafirlukast: May decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Zileuton: May increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol. Acute ethanol ingestion (binge drinking) decreases the metabolism of warfarin and increases PT/INR. Chronic daily ethanol use increases the metabolism of warfarin and decreases PT/INR.

Food: The anticoagulant effects of warfarin may be decreased if taken with foods rich in vitamin K. Vitamin E may increase warfarin effect. Cranberry juice may increase warfarin effect.

Herb/Nutraceutical: Cranberry, fenugreek, ginkgo biloba, glucosamine, may enhance bleeding or increase warfarin's effect. Ginseng (American), coenzyme Q_{10}, and St John’s wort may decrease warfarin levels and effects. Avoid alfalfa, anise, bilberry, bladderwrack, bromelain, cat's claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose oil, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (American), ginseng (Panax), ginseng (Siberian), grapeseed, green tea, guggul, horse chestnut seed, horseradish, licorice, omega-3-acids, prickly ash, red clover, reishi, SAMe (s-adenosylmethionine), sweet clover, turmeric, and white willow (all have additional antiplatelet activity).

Monitoring ParametersProthrombin time, hematocrit, INR; consider genotyping of CYP2C9 and VKORC1 prior to initiation of therapy, if available

Reference Range

INR = patient prothrombin time/mean normal prothrombin time

ISI = international sensitivity index

INR should be increased by 2-3.5 times depending upon indication. An INR >4 does not generally add additional therapeutic benefit and is associated with increased risk of bleeding.

Adult INR ranges based upon indication: See table.

Adult Target INR Ranges Based Upon Indication

Indication	**Targeted INR**	**Targeted INR Range**
Cardiac		
Acute myocardial infarction (high risk)[1]	2.5	2-3[2,3]
Atrial fibrillation or atrial flutter	2.5	2-3
Valvular		
Bileaflet or Medtronic Hall tilting disk mechanical aortic valve in normal sinus rhythm and normal LA size	2.5	2-3
Bileaflet or tilting disk mechanical mitral valve	3	2.5-3.5

Caged ball or caged disk mechanical valve	3	2.5-3.5
Mechanical prosthetic valve with systemic embolism despite adequate anticoagulation	3 **or** 3.5[4]	2.5-3.5[4] **or** 3-4[4]
Mechanical valve and risk factors for thromboembolism (eg, AF, MI[5], LA enlargement, hypercoagulable state, low EF) or history of atherosclerotic vascular disease	3	2.5-3.5[6]
Bioprosthetic mitral valve	2.5	2-3[7]
Bioprosthetic mitral or aortic valve with prior history of systemic embolism	2.5	2-3[7]
Bioprosthetic mitral or aortic valve with evidence of LA thrombus at surgery	2.5	2-3[8]
Bioprosthetic mitral or aortic valve with risk factors for thromboembolism (eg, AF, hypercoagulable state or low EF)	2.5	2-3[9]
Prosthetic mitral valve thrombosis (resolved)	4	3.5-4.5[3]
Prosthetic aortic valve thrombosis (resolved)	3.5	3-4[3]
Rheumatic mitral valve disease and normal sinus rhythm (LA diameter >5.5 cm), AF, previous systemic embolism, or LA thrombus	2.5	2-3
Thromboembolism Treatment		
Venous thromboembolism	2.5	2-3[10,11]
Thromboprophylaxis		
Chronic thromboembolic pulmonary hypertension (CTPH)	2.5	2-3
Lupus inhibitor (no other risk factors)	2.5	2-3
Lupus inhibitor and recurrent thromboembolism	3	2.5-3.5
Major trauma patients with impaired mobility undergoing rehabilitation	2.5	2-3
Spinal cord injury (acute) undergoing rehabilitation	2.5	2-3
Total hip or knee replacement (elective) or hip fracture surgery	2.5	2-3[12]
Other Indications		
Cerebral venous sinus thrombosis	2.5	2-3[13]
Ischemic stroke due to AF	2.5	2-3

[1] High-risk includes large anterior MI, significant heart failure, intracardiac thrombus, atrial fibrillation, history of thromboembolism.

[2]Maintain anticoagulation for 3 months.
[3]Combine with aspirin 81 mg/day.
[4]Combine with aspirin 81 mg/day, if not previously receiving, **and/or** if previous target INR was 2.5, then new target INR should be 3 (2.5-3.5). If previous target INR was 3, then new target INR should be 3.5 (3-4).
[5]MI refers to anterior-apical ST-segment elevation myocardial infarction.
[6]Combine with aspirin 81 mg/day unless patient is at high risk of bleeding (eg, history of GI bleed, age >80 years).
[7]Maintain anticoagulation for 3 months after valve insertion then switch to aspirin 81 mg/day if no other indications for warfarin exist or clinically reassess need for warfarin in patients with prior history of systemic embolism.
[8]Maintain anticoagulation with warfarin until thrombus resolution.
[9]If patient has history of atherosclerotic vascular disease, combine with aspirin 81 mg/day unless patient is at high risk of bleeding (eg, history of GI bleed, age >80 years).
[10]Treat for 3 months in patients with VTE due to transient reversible risk factor. Treat for a minimum of 3 months in patients with unprovoked VTE and evaluate for long term therapy. Other risk groups (eg, cancer) may require >3 months of therapy.
[11]In patients with unprovoked VTE who prefer less frequent INR monitoring, low-intensity therapy (INR range: 1.5-1.9) with less frequent monitoring is recommended over stopping treatment.
[12]Continue for at least 10 days and up to 35 days after surgery.
[13]Continue for up to 12 months.

Warfarin levels are not used for monitoring degree of anticoagulation. They may be useful if a patient with unexplained coagulopathy is using the drug surreptitiously or if it is unclear whether clinical resistance is due to true drug resistance or lack of drug intake.

Normal prothrombin time (PT): 10.9-12.9 seconds. Healthy premature newborns have prolonged coagulation test screening results (eg, PT, aPTT, TT) which return to normal adult values at approximately 6 months of age. Healthy prematures, however, do not develop spontaneous hemorrhage or thrombotic complications because of a balance between procoagulants and inhibitors.

Nursing: Physical Assessment/MonitoringUse caution with any condition that increases risk of bleeding (eg, dietary vitamin K or C deficiency, hypertension, open wounds, TB, PUD, diabetes, thyroid or renal disease, recent surgery). Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (especially those medications that may affect coagulation or platelet aggregation). Assess results of laboratory tests closely. Patient should be monitored frequently for therapeutic effectiveness and adverse reactions (eg, bleeding from any site, rash, urticaria, gastrointestinal upset, abdominal pain, diarrhea, hypersensitivity reaction). Teach patient possible side effects/appropriate interventions (eg, safety precautions) and adverse symptoms to report. **Pregnancy risk factor X:** Determine that patient is not pregnant before beginning treatment. Teach patients of childbearing age appropriate use of contraceptives.
Monitoring: Lab TestsProthrombin time (desirable range usually 1.5-2 times the control), hematocrit, INR (desirable range usually 2-3 with standard therapy, 2.5-3.5 with high-dose therapy); consider genotyping of CYP2C9 and VKORC1 prior to initiation of therapy, if available
Patient EducationIt is imperative that you inform prescriber of all prescriptions, OTC medications, or herbal products you are taking. Do not take any new medication during therapy unless approved by prescriber. Take exactly as directed; if dose is missed, take as soon as possible. Do not double dose. Follow diet and activity as recommended by prescriber; check with prescriber before changing diet. Avoid alcohol. Do not make major changes in your dietary intake of vitamin K (green vegetables). You will have a tendency to bleed easily while taking this drug (use soft toothbrush, waxed dental floss, electric razor, and avoid scissors or sharp knives and potentially harmful activities). May cause nausea, vomiting, disturbed taste (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report any unusual bleeding or bruising (eg, bleeding gums, nosebleed, blood in urine, dark stool, bloody emesis, heavier than usual menses, or menstrual irregularities); skin rash or irritation; unusual fever; persistent nausea or GI upset; pain in joints or back; swelling or pain at injection site; or unhealed wounds. **Pregnancy precautions:** Do not get pregnant while taking this medication. Consult prescriber for appropriate barrier contraceptive measures.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution, as sodium:

Coumadin®: 5 mg

Tablet, as sodium: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg

Coumadin®: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg [scored]

Coumadin®: 10 mg [scored; dye free]

Jantoven®: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg [scored]

Jantoven®: 10 mg [scored; dye free]

Generic AvailableYes: Tablet

Pricing: U.S. (www.drugstore.com)

Tablets (Coumadin)

1 mg (30): $38.51

2 mg (30): $38.51

2.5 mg (30): $40.65

3 mg (30): $42.79

4 mg (30): $41.72

5 mg (30): $41.72

6 mg (30): $53.49

7.5 mg (30): $53.49

10 mg (30): $53.49

Tablets (Jantoven)

2 mg (30): $19.99

4 mg (30): $20.99

5 mg (30): $22.80

6 mg (30): $27.99

Tablets (Warfarin Sodium)

1 mg (30): $13.99

2 mg (30): $14.88

2.5 mg (30): $14.99

3 mg (30): $15.99

4 mg (30): $14.99

5 mg (30): $13.99

7.5 mg (30): $23.21

10 mg (30): $24.24

Mechanism of ActionHepatic synthesis of coagulation factors II, VII, IX, and X, as well as proteins C and S, requires the presence of vitamin K. These clotting factors are biologically activated by the addition of carboxyl groups to key glutamic acid residues within the proteins' structure. In the process, "active" vitamin K is oxidatively converted to an "inactive" form, which is then subsequently re-activated by vitamin K epoxide reductase complex 1 (VKORC1). Warfarin competitively inhibits the subunit 1 of the multi-unit VKOR complex, thus depleting functional vitamin K reserves and hence reduces synthesis of active clotting factors.

Pharmacodynamics/Kinetics

Onset of action: Anticoagulation: Oral: 24-72 hours

Peak effect: Full therapeutic effect: 5-7 days; INR may increase in 36-72 hours

Duration: 2-5 days

Absorption: Oral: Rapid, complete

Distribution: 0.14 L/kg

Protein binding: 99%

Metabolism: Hepatic, primarily via CYP2C9; minor pathways include CYP2C8, 2C18, 2C19, 1A2, and 3A4

Genomic variants: Approximately 37% reduced clearance of S-warfarin in patients heterozygous for 2C9 (*1/*2 or *1/*3), and ~70% reduced in patients homozygous for reduced function alleles (*2/*2, *2/*3, or *3/*3)

Half-life elimination: 20-60 hours; Mean: 40 hours; highly variable among individuals

Time to peak, plasma: Oral: ~4 hours

Excretion: Urine (92%, primarily as metabolites)

Related Information

- Target INR Ranges for Adult Patients With Prosthetic Heart Valves
- Treatment of Elevated INR Due to Warfarin

Pharmacotherapy PearlsProspective genotyping is available, and may provide important guidance on initiation of anticoagulant therapy. Commercial testing with PGxPredict™:WARFARIN is now available from PGxHealth™ (Division of Clinical Data, Inc, New Haven, CT). The test genotypes patients for presence of the CYP2C9*2 or *3 alleles and the VKORC1 -1639G>A polymorphism. The results of the test allow patients to be phenotyped as extensive, intermediate, or poor metabolizers (CYP2C9) and as low, intermediate, or high warfarin sensitivity (VKORC1). Ordering information is available at 888-592-7327 or warfarininfo@pgxhealth.com.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mouth ulcers and taste disturbance.

Signs of warfarin overdose may first appear as bleeding from gingival tissue.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentMay cause leukopenia; use caution with clozapine and carbamazepine; barbiturates and carbamazepine may decrease the anticoagulant effect of warfarin; chloral hydrate, alcohol, disulfiram, and SSRIs may enhance the anticoagulant effect

Cardiovascular Considerations

Factor VII half-life: 4-6 hours

Factor X half-life: 27-48 hours

Factor II half-life: 42-72 hours

Overlapping heparin and warfarin therapy by at least 5 days is necessary in treatment of DVT/PE even if the INR is therapeutic earlier. Although an elevation in INR (factor VII depletion) may be seen early (first 24-48 hours) in warfarin therapy, it does not represent adequate anticoagulation. Factors II and X must be depleted which takes considerably longer.

Vitamin K Rich Foods: Significant changes in vitamin K intake can upset warfarin stability. The list of usual foods with high vitamin K content are well known, however, unique ones continue to appear like green tea, chewing tobacco, a variety of oils (canola, corn, olive, peanut, safflower, sesame seed, soybean, and sunflower). Snack foods containing Olestra have 80 mcg of vitamin K added to each ounce. Some natural products may contain hidden sources of vitamin K.

Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombotic Thrombocytopenia Syndrome (HITTS): When a patient develops HIT/HITTS, warfarin monotherapy is contraindicated. Rather, a direct thrombin inhibitor should be initiated and continued until platelets return. When appropriate, initiating warfarin at low doses and overlapping with a direct thrombin inhibitor for at least 5 days and until the INR is therapeutic for at least 48 hours is suggested.

Anesthesia and Critical Care Concerns/Other Considerations

Clinical Pearls/Comments: Tube-feeding formulas are often a rich source of vitamin K.

Management of Oral Anticoagulation Prior to Surgery:

Patients with low risk of thromboembolism: Stop warfarin therapy approximately 4 days before surgery, allow the INR to return to a near normal level, briefly administer postoperative prophylaxis (if the intervention itself creates a higher risk of thrombosis) using low-dose heparin or LMWH, and simultaneously begin warfarin therapy after surgery.

Patients with intermediate risk of thromboembolism: Stop warfarin therapy approximately 4 days before surgery, allow the INR to fall. Initiate low-dose heparin or prophylactic dose of LMWH beginning 2 days before surgery. Then commence full-dose heparin or LMWH, and warfarin therapy after surgery.

Patients with high risk of thromboembolism (eg, a recent [<3 months] history of venous thromboembolism, a mechanical cardiac valve in the mitral position, or an old model of cardiac valve [ball/cage]): Stop warfarin therapy approximately 4 days before surgery, allow the INR to return to a normal level, begin therapy with full-dose heparin or full-dose LMWH as the INR falls (approximately 2 days before surgery). Heparin can be administered as a SubQ injection on an outpatient basis, can then be given as a continuous I.V. infusion after hospital admission in preparation for surgery, and can be discontinued 5 hours before surgery with the expectation that the anticoagulant effect will have worn off at the time of surgery. It is also possible to continue the administration of SubQ heparin or LMWH and to stop therapy 12-24 hours before surgery with the expectation that the anticoagulant effect will be very low or will have worn off by the time of surgery.

Patients with low risk of bleeding: Continue warfarin therapy at a lower dose and operate at an INR of 1.3-1.5, an intensity that has been shown to be safe in randomized trials of gynecologic and orthopedic surgical patients. The dose of warfarin can be lowered 4-5 days before surgery. Warfarin therapy then can be restarted after surgery and supplemented with low-dose heparin or LMWH if necessary.

Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombotic Thrombocytopenia Syndrome (HITTS): When a patient develops HIT/HITTS, warfarin monotherapy is contraindicated. Rather, a direct thrombin inhibitor should be initiated. Warfarin anticoagulation should be postponed in the patient with HIT until substantial recovery of the platelet count has occurred. When appropriate, initiating warfarin at low doses and overlapping with a direct thrombin inhibitor for at least 5 days and until the INR is therapeutic for at least 48 hours is suggested.

Evidence-Based Information:

Management of Intracerebral Hemorrhage (ICH) Due to Warfarin: Overall management of ICH is similar regardless of cause; however, iatrogenic spontaneous ICH may have specific treatments. According to the 2007 ACC/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage, warfarin-related ICH should be treated with I.V. vitamin K at a dose of 10 mg given slowly (not to exceed 1 mg/min) (Class I recommendation). It is important to also administer fresh frozen plasma (FFP) since vitamin K may take several hours to normalize INR. Other options besides FFP include prothrombin complex concentrate (PCC) which contains high levels of vitamin K-dependent factors (II, VII, and X) and factor IX complex which contains factors II, VII, IX, and X (Class IIb recommendation). Use of rFVIIa has shown promise for this indication. Advantages to rFVIIa include faster onset of action compared to FFP and vitamin K and a 50% lower volume is required compared to FFP. Disadvantages include a short half-life (~ 2.6 hours) requiring multiple doses to maintain a normalized INR and an increased risk of thromboembolic complications. Dosing of rFVIIa ranges between 15-90 mcg/kg. The use of factor-containing products has a risk of thromboembolism.

Index TermsWarfarin Sodium

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International Brand NamesAldocumar (ES); Befarin (TH); Circuvit (AR); Cofarin (TW); Coumadan (AR); Coumadin (AE, AU, BF, BH, BJ, CI, CN, CO, CY, DE, EG, ET, GH, GM, GN, IL, IQ, IR, IT, JO, KE, KP, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, OM, PE, PH, PK, PT, PY, QA, SA, SC, SD, SG, SL, SN, SY, TN, TZ, UG, VE, YE, ZA, ZM, ZW); Coumadine (FR); Dagonal (UY); Fargem (TH); Farin (TH); Lennon-Warfarin (ZA); Maforan (TH); Marevan (AU, BE, BR, DK, EE, FI, GB, IE, LU, NO, SG); Marivarin (HR); Orfarin (MY, TH, TW); Panwarfin (GR); Simarc-2 (ID); Tedicumar (ES); UniWarfin (IN); Waran (SE); Warfil 5 (DO)

Witch Hazel

Lexi-Drugs Online

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Pronunciation(witch HAY zel)
U.S. Brand NamesDickinson's® Witch Hazel [OTC]; Preparation H® Medicated Wipes [OTC]; T.N. Dickinson's® Hazelets [OTC]; Tucks® [OTC]
Canadian Brand NamesPreparation H® Cleansing Pads
Pharmacologic CategoryAstringent
Use: Labeled IndicationsAfter-stool wipe to remove most causes of local irritation; temporary management of vulvitis, pruritus ani and vulva; help relieve the discomfort of simple hemorrhoids, anorectal surgical wounds, and episiotomies
Dosing: Adults**Hemorrhoids:** Topical: Apply to anorectal area as needed
Dosing: ElderlyRefer to adult dosing.
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Liquid, topical: 100% (120 mL, 480 mL)

Dickinson's® Witch Hazel: 100% (60 mL, 240 mL, 480 mL)

Pads: 50% (100s)

Dickinson's® Witch Hazel: 50% (20s) [towelettes]; (50s) [contains aloe]; (100s) [hemorrhoidal]

Preparation H® Medicated Wipes: 50% (8s, 48s) [contains aloe]

T.N. Dickinson's® Hazelets: 50% (50s) [contains aloe]; (60s)

Tucks®: 50% (12s, 40s, 100s)

Generic AvailableYes
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsHamamelis Water
International Brand NamesPreparation H Cleansing Pads (CA)

XelOx (Colorectal Cancer)

Lexi-Drugs Online

Jump To Field (Select Field Name)

↑ Pharmacologic Category[Chemotherapy Regimen, Colorectal Cancer]
↑ Regimen UseColorectal cancer
↑ Index TermsCapecitabine-Oxaliplatin (Colorectal Cancer); Oxaliplatin-Capecitabine (Colorectal Cancer)
↑ RegimenNote: Multiple variations are listed below.

Variation 1:

Oxaliplatin: I.V.: 130 mg/m^2 day 1

[total dose/cycle = 130 mg/m^2]

Capecitabine: Oral: 2500 mg/m^2/day days 1 to 14

[total dose/cycle = 35,000 mg/m^2]

Repeat cycle every 21 days

Variation 2:

Oxaliplatin: I.V.: 85 mg/m^2 day 1

[total dose/cycle = 85 mg/m^2]

Capecitabine: Oral: 3500 mg/m^2/day days 1 to 7

[total dose/cycle = 24,500 mg/m^2]

Repeat cycle every 14 days

Variation 3:

Oxaliplatin: I.V.: 50-80 mg/m^2/day days 1, 8, 22, and 29

[total dose/cycle = 200-320 mg/m^2]

Capecitabine: Oral: 1650 mg/m^2/day days 1 to 14 and 22 to 35

[total dose/cycle = 46,200 mg/m^2]

Variation 4:

Oxaliplatin: I.V.: 70 mg/m^2/day days 1 and 8

[total dose/cycle = 140 mg/m^2]

Capecitabine: Oral: 2000 mg/m^2/day days 1 to 14

[total dose/cycle = 28,000 mg/m^2]

Repeat cycle every 21 days

Variation 5:

Oxaliplatin: I.V.: 120 mg/m^2 day 1

[total dose/cycle = 120 mg/m^2]

Capecitabine: Oral: 2500 mg/m^2/day days 1 to 14

[total dose/cycle = 35,000 mg/m^2]

Repeat cycle every 21 days

Variation 6:

Oxaliplatin: I.V.: 85 mg/m^2 day 1

[total dose/cycle = 85 mg/m^2]

Capecitabine: Oral: 2500 mg/m^2/day days 1 to 7

[total dose/cycle = 17,500 mg/m^2]

or Capecitabine: Oral: 3000 mg/m^2/day days 1 to 7

[total dose/cycle = 21,000 mg/m^2]

or Capecitabine: Oral: 3500 mg/m^2/day days 1 to 7

[total dose/cycle = 24,500 mg/m^2]

or Capecitabine: Oral: 4000 mg/m^2/day days 1 to 7

[total dose/cycle = 28,000 mg/m^2]

Repeat cycle every 14 days

Variation 7:

Oxaliplatin: I.V.: 130 mg/m^2 day 1

[total dose/cycle = 130 mg/m^2]

Capecitabine: Oral: 1000 mg/m^2 twice daily days 1 (beginning with evening dose) to 15 (ending with morning dose)

[total dose/cycle = 28,000 mg/m^2]

Repeat cycle every 21 days

References

Variation 1:

Borner MM, Dietrich D, Stupp R, et al, âPhase II Study of Capecitabine and Oxaliplatin in First- and Second-Line Treatment of Advanced or Metastatic Colorectal Cancer,â *J Clin Oncol*, 2002, 20(7):1759-66.[PubMed 11919232]

Variation 2:

Scheithauer W, Kornek GV, Raderer M, et al, "Randomized Multicenter Phase II Trial of Two Different Schedules of Capecitabine Plus Oxaliplatin as First-Line Treatment in Advanced Colorectal Cancer," *J Clin Oncol*, 2003, 21(7):1307-12.[PubMed 12663719]

Variation 3:

Rodel C, Grabenbauer GG, Papadopoulos T, et al, "Phase I/II Trial of Capecitabine, Oxaliplatin, and Radiation for Rectal Cancer," *J Clin Oncol*, 2003, 21(16):3098-104. [PubMed 12915600]

Variation 4:

Jordan K, Grothey A, Kellner O, et al, "Randomized Phase II Trial of Capecitabine Plus Irinotecan vs Capecitabine Plus Oxaliplatin as First-Line Therapy in Advanced Colorectal Cancer (ACRC): Results of an Interim Analysis," *Proc Annu Meet Am Soc Clin Oncol*, 2002, 21:2225.

Variation 5:

Zeuli M, Nardoni C, Pino MS, et al, "Phase II Study of Capecitabine and Oxaliplatin as First-Line Treatment in Advanced Colorectal Cancer," *Ann Oncol*, 2003, 14(9):1378-82.[PubMed 12954576]

Variation 6:

Scheithauer W, Kornek GV, Raderer M, et al, "Intermittent Weekly High-Dose Capecitabine in Combination With Oxaliplatin: A Phase I/II Study in First-Line Treatment of Patients With Advanced Colorectal Cancer," *Ann Oncol*, 2002, 13(10):1583-9.[PubMed 12377646]

Variation 7:

Cassidy J, Tabernero J, Twelves C, et al, "XELOX (Capecitabine Plus Oxaliplatin): Active First-Line Therapy for Patients With Metastatic Colorectal Cancer," *J Clin Oncol*, 2004, 22(11):2084-91.[PubMed 15169795]

Xylometazoline

Lexi-Drugs Online

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Otrivin® may be confused with Lotrimin®

Pronunciation(zye loe met AZ oh leen)
U.S. Brand NamesOtrivin® Pediatric [OTC] [DSC]; Otrivin® [OTC] [DSC]
Canadian Brand NamesBalminil
Pharmacologic CategoryImidazoline Derivative; Vasoconstrictor, Nasal
Use: Labeled IndicationsSymptomatic relief of nasal and nasopharyngeal mucosal congestion
Dosing: Adults**Nasal congestion:** Nasal: Instill 2-3 drops or sprays (0.1%) in each nostril every 8-10 hours
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Nasal congestion:** Nasal:

Children 2-12 years: Instill 2-3 drops (0.05%) in each nostril every 8-10 hours.

Children >12 years: Refer to adult dosing.

Geriatric ConsiderationsEvaluate the patient's ability to self-administer; use with caution in patients with cardiovascular disease.
Pregnancy Risk FactorC
Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation

Central nervous system: Dizziness, drowsiness, headache, seizure

Ocular: Blurred vision, ocular irritation, photophobia

Miscellaneous: Diaphoresis

Drug Interactions

Cannabinoids: May enhance the tachycardic effect of Sympathomimetics. *Risk C: Monitor therapy*

Iobenguane I 123: Sympathomimetics may diminish the therapeutic effect of Iobenguane I 123. *Risk X: Avoid combination*

MAO Inhibitors: May enhance the hypertensive effect of Alpha1-Agonists. *Risk X: Avoid combination*

Sympathomimetics: May enhance the adverse/toxic effect of other Sympathomimetics. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May enhance the vasopressor effect of Alpha1-Agonists. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, intranasal drops, as hydrochloride:

Otrivin® [DSC]: 0.1% (25 mL)

Otrivin® Pediatric [DSC]: 0.05% (25 mL)

Solution, intranasal spray, as hydrochloride (Otrivin® [DSC]): 0.1% (20 mL)

Generic AvailableNo
Mechanism of ActionStimulates alpha-adrenergic receptors in the arterioles of the conjunctiva and the nasal mucosa to produce vasoconstriction
Pharmacodynamics/Kinetics

Onset of action: Intranasal: Local vasoconstriction: 5-10 minutes

Duration: 5-6 hours

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause drowsiness or dizziness
Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms Xylometazoline Hydrochloride

International Brand Names Af-Care (IL); Amidrin (ES); Balkis (DE, LU); Colirio Azul Gotas Oftalmicas (CO); Donosan (PL); Gelonasal (DE); Hidropid (HR); Huma-Metazol (HU); Nasan (CZ, HN, HU, LU); NasenGel ratiopharm (LU); NasenGel-Ratiopharm (PL); NasenSpray K-Ratiopharm (PL); NasenSpray ratiopharm (LU); NasenTropfen ratiopharm (LU); Nasoferm (SE); Nasolin (FI); Neusdruppels (NL); Novorin (HU); Olynth (CH, EE); Otriven (DE); Otrivin (AT, AU, CH, DK, EE, ES, FI, GR, HK, HN, HU, ID, IL, IN, IT, KP, MY, NL, NO, PL, SE, TH, TW); Otrivina (AR, BR, PY, UY); Otrivine (BE, GB, IE, LU); Rhinidine (LU); Xoline (PK); Xylogel (PL); Xylometazolin (PL); Xylorhin (PL); Xylovit (IL); Xymelin (DK)

Yellow Fever Vaccine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(YEL oh FEE ver vak SEEN)

U.S. Brand NamesYF-VAX®

Canadian Brand NamesYF-VAX®

Pharmacologic CategoryVaccine, Live (Viral)

Use: Labeled IndicationsInduction of active immunity against yellow fever virus, primarily among persons traveling or living in areas where yellow fever infection exists and laboratory workers who may be exposed to the virus; vaccination may also be required for some international travelers

Dosing: Adults**Immunization:** SubQ: One dose (0.5 mL) ≥10 days before travel; Booster: Every 10 years for those at continued risk of exposure

Dosing: ElderlyRefer to adult dosing. Monitor closely.

Dosing: Pediatric**Immunization:** SubQ:

Children ≥6 months (unlabeled use [CDC guidelines]): One dose (0.5 mL) ≥10 days before travel; Booster: Every 10 years for those at continued risk of exposure

Children ≥9 months (per manufacturer): One dose (0.5 mL) ≥10 days before travel; Booster: Every 10 years for those at continued risk of exposure

Administration: OtherFor SubQ injection only. Do not administer I.M. or I.V.

StorageStore at 2°C to 8°C (35°F to 46°F); do not freeze.

ReconstitutionReconstitute only with diluent provided. Inject diluent slowly into vial and allow to stand for 1-2 minutes. Gently swirl until a uniform suspension forms; swirl well before withdrawing dose. Avoid vigorous shaking to prevent foaming of suspension. Vaccine must be used within 60 minutes of reconstitution. Keep suspension refrigerated until used.

ContraindicationsHypersensitivity to egg or chick embryo protein, or any component of the formulation; children <9 months of age (per manufacturer); children <6 months of age (CDC guidelines); acute or febrile disease; immunosuppressed patients; breast-feeding women

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use. Use is contraindicated in patients with immediate-type hypersensitivity reactions to eggs. Less severe or localized manifestations of allergy are not contraindications; in general, persons who are able to eat eggs or egg products may receive the vaccine.

Special populations:

- Acute illness: Immunization should be delayed during the course of an acute or febrile illness. The presence of a low-grade fever is generally not a reason to postpone vaccination.

- Altered immunocompetence: Use with caution in severely immunocompromised patients (eg, patients receiving chemo/radiation therapy or other immunosuppressive therapy [including high-dose corticosteroids and patients <24 months after hematopoietic stem cell transplant]); may have a reduced response to vaccination. Patients who are immunosuppressed have a theoretical risk of encephalitis with yellow fever vaccine administration; consider delaying travel or obtaining a waiver letter. Patients on low-dose or short-term corticosteroids, or with asymptomatic HIV infection are not considered immunosuppressed and may be offered the vaccine. If vaccination is only to satisfy an international requirement (as opposed to decreasing risk of infection), efforts should be made to obtain a waiver letter.

- Elderly: Use with caution in the elderly; the risk of adverse events is increased in patients ≥65 years of age

- Pediatrics: The manufacturer contraindicates use in infants <9 months of age due to risk of encephalitis. The CDC allows for use in infants 6-8 months of age when possible exposure with the yellow fever virus is unavoidable and the risk of infection exists. Infants <6 months of age should never be vaccinated.

- Pregnancy: Avoid use in pregnant women unless travel to high-risk areas is unavoidable.

Dosage form specific issues:

- Gelatin: Product may contain gelatin

- Latex: Packaging may contain natural latex rubber.

Geriatric ConsiderationsNo special considerations except in patients with immunodeficient diseases.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Adverse events were not observed in the mother or fetus following vaccination during the third trimester of pregnancy in Nigerian women; however maternal seroconversion was reduced. Inadvertent exposure early in the first trimester of pregnancy in Brazilian women did not show decreased maternal seroconversion; no major congenital abnormalities were noted. Vaccine should be administered if travel to an endemic area is unavoidable and the infant should be monitored after birth. Tests to verify maternal immune response may be considered. If a pregnant woman is to be vaccinated only to satisfy an international requirement (as opposed to decreasing risk of infection), efforts should be made to obtain a waiver letter.

Lactation Excretion in breast milk unknown/contraindicated

Breast-Feeding Considerations It is recommended to avoid nursing following vaccination due to a theoretical risk of 17D virus transmission to the infant. No adverse reactions or transmission of the 17D virus have been reported. Breast-feeding is contraindicated by the manufacturer, particularly in infants <9 months of age, due to the theoretical risk of encephalitis. Breast-feeding does not adversely affect immunization. In general, live vaccines have not been found in breast milk.

Adverse Reactions **All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

Frequency not defined (adverse reactions may be increased in patients <9 months or ≥65 years of age)

Central nervous system: Fever (incidence of these reactions have been reported to be as low as <5% and as high as 10% to 30% depending on the study), focal neurological defects, headache, seizure

Local: Injection site reactions (edema, hypersensitivity, mass, pain)

Neuromuscular & skeletal: Myalgia, weakness

Miscellaneous: Guillain-Barré syndrome, hypersensitivity (immediate), vaccine-associated neurotropic disease (rare), viscerotropic disease (rare; may be associated with multiorgan failure)

Drug Interactions

Immunosuppressants: May enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Tuberculin Tests: Vaccines (Live) may diminish the diagnostic effect of Tuberculin Tests. *Risk D: Consider therapy modification*

Monitoring Parameters Monitor for adverse effects 10-30 days after vaccination.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [17D-204 strain]:

YF-VAX®: ≥4.74 Log_{10} plaque-forming units (PFU) per 0.5 mL dose [single-dose or 5-dose vial; produced in chicken embryos; contains gelatin; packaged with diluent; vial stopper contains latex]

Generic Available No

Pharmacodynamics/Kinetics

Onset of action: Seroconversion: 10-14 days

Duration: ≥30 years

Related Information

- Immunization Recommendations

Pharmacotherapy Pearls Federal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record. A hypersensitivity screening test and desensitization procedure is available for persons with suspected or known severe egg sensitivity. Consult manufacturer's labeling for details. Some countries require a valid international Certification of Vaccination showing receipt of vaccine. The WHO requires revaccination every 10 years to maintain traveler's vaccination certificate.

The following CDC agencies may be contacted if serologic testing is needed or for advice when administering yellow fever vaccine to pregnant women, children <9 months, or patients with altered immune status:

Division of Vector-Borne Infectious Diseases: 970-221-6400

Division of Global Migration and Quarantine: 404-498-1600

Dental Health: Effects on Dental Treatment No significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

Mental Health: Effects on Mental Status None reported

Mental Health: Effects on Psychiatric Treatment None reported

References

Centers for Disease Control and Prevention, “General Recommendations on Immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP),” *MMMR Recomm Rep*, 2002, 51(R-2):1-35.

Centers for Disease Control and Prevention, “Yellow Fever Vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP),” *MMMR Recomm Rep*, 2002, 51(R-2):1-11.

Centers for Disease Control and Prevention, “Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients. Recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation,” *MMWR Recomm Rep*, 2004, 49(RR-10):89-90.

Suzano CE, Amaral E, Sato HK, et al, “The Effects of Yellow Fever Immunization (17DD) Inadvertently Used in Early Pregnancy During a Mass Campaign in Brazil. Campinas Group on Yellow Fever Immunization during Pregnancy,” *Vaccine*, 2006, 24(9):1421-6.[PubMed 16236402]

International Brand Names Arilvax (NL, ZA); Stamaril (AR, BE, BG, CH, CN, CZ, DK, EE, FI, GB, HN, IE, IL, IN, IT, NO, NZ, PE, PK, PY, SE, UY); Stamaril Pasteur (PL)

Yohimbine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Aphrodyne® may be confused with Aprodine®

Yocon® may be confused with Zocor®

Pronunciation(yo HIM bine)

U.S. Brand NamesAphrodyne® [DSC]; Yocon®

Canadian Brand NamesPMS-Yohimbine; Yocon®

Pharmacologic CategoryMiscellaneous Product

Use: Unlabeled/InvestigationalTreatment of SSRI-induced sexual dysfunction; weight loss; impotence; sympathicolytic and mydriatic; may have activity as an aphrodisiac

Dosing: Adults

Male erectile dysfunction: Oral: 5.4 mg tablet 3 times/day have been used. If side effects occur, reduce to $^1/_2$ tablet (2.7 mg) 3 times/day followed by gradual increases to 1 tablet 3 times/day. Results of therapy >10 weeks are not known.

Orthostatic hypotension: Oral: Doses of 12.5 mg/day have been utilized; however, more research is necessary

Dosing: ElderlyRefer to adult dosing.

ContraindicationsHypersensitivity to yohimbine or any component of the formulation; renal disease

Warnings/Precautions

Concerns related to adverse effects:

- Nausea/vomiting: Can cause nausea or vomiting.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease; may cause high blood pressure and tachycardia.
- Gastrointestinal disease: Should not be used in patients with a history of gastric or duodenal ulcer.
- Psychiatric disorders: Should not be used in patients with psychiatric disorders; may cause anxiety.

Special populations:

- Elderly: Do not use in the elderly.
- Females: Generally not for use in females.
- Pediatrics: Do not use in children.
- Pregnancy: Do not use in pregnancy.

Adverse ReactionsFrequency not defined.

Cardiovascular: Tachycardia, hypertension, hypotension (orthostatic), flushing

Central nervous system: Anxiety, mania, hallucinations, irritability, dizziness, psychosis, insomnia, headache, panic attacks

Gastrointestinal: Nausea, vomiting, anorexia, salivation

Neuromuscular & skeletal: Tremors

Miscellaneous: Antidiuretic action, diaphoresis

Metabolism/Transport Effects**Substrate** of CYP2D6 (minor); **Inhibits** CYP2D6 (weak)

Drug Interactions

Antianxiety Agents: Yohimbine may diminish the therapeutic effect of Antianxiety Agents. *Risk C: Monitor therapy*

Antihypertensives: Yohimbine may diminish the antihypertensive effect of Antihypertensives. *Risk C: Monitor therapy*

Tricyclic Antidepressants: May increase the serum concentration of Yohimbine. *Risk C: Monitor therapy*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Caplet, oral, as hydrochloride:

Aphrodyne®: 5.4 mg [DSC] [scored]

Tablet, as hydrochloride: 5.4 mg

Yocon®: 5.4 mg

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Tablets (Yocon)

5.4 mg (30): $25.39

Tablets (Yohimbine HCl)

5.4 mg (30): $15.99

Mechanism of ActionDerived from the bark of the yohimbe tree (*Corynanthe yohimbe*), this indole alkaloid produces a presynaptic alpha$_2$-adrenergic blockade. Peripheral autonomic effect is to increase cholinergic and decrease adrenergic activity; yohimbine exerts a stimulating effect on the mood and a mild antidiuretic effect.

Pharmacodynamics/Kinetics

Duration: Usually 3-4 hours, but may last 36 hours

Absorption: 33%

Distribution: V_d: 0.3-3 L/kg

Half-life elimination: 0.6 hour

Pharmacotherapy PearlsAlso a street drug of abuse that can be smoked; has a bitter taste. Dissociative state may resemble phencyclidine intoxication.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause anxiety, irritability, dizziness, insomnia, mania, panic attacks, and psychosis

Mental Health: Effects on Psychiatric TreatmentMay cause neutropenia; use caution with clozapine and carbamazepine; antidepressant should not be used with yohimbine; has been used to treat SSRI-induced sexual dysfunction

Index TermsYohimbine Hydrochloride

International Brand NamesPluriviron (DE); Virigen (DK); Yocon (DE); Yocoral (FR); Yohimbin Spiegel (DE, HU); Yohimbine Houde (FR, LU); Yohydrol (BR)

Zafirlukast

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Accolate® may be confused with Accupril®, Accutane®, Aclovate®

Pronunciation(za FIR loo kast)
U.S. Brand NamesAccolate®
Canadian Brand NamesAccolate®
Pharmacologic CategoryLeukotriene Receptor Antagonist
Use: Labeled IndicationsProphylaxis and chronic treatment of asthma in adults and children ≥5 years of age
Dosing: Adults**Asthma:** Oral: 20 mg twice daily
Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Asthma:** Oral:

Children 5-11 years: 10 mg twice daily. Safety and effectiveness have not been established in children <5 years of age.

Children ≥12 years: Refer to adult dosing.

Dosing: Renal Impairment

Dosage adjustment not required.

Dosing: Hepatic ImpairmentClearance of zafirlukast is reduced with a greater C_{max} and AUC of 50% to 60% in patients with alcoholic cirrhosis.
Administration: OralAdminister 1 hour before or 2 hours after meals.
Dietary ConsiderationsShould be taken on an empty stomach (1 hour before or 2 hours after meals).
StorageStore tablets at controlled room temperature (20°C to 25°C; 68°F to 77°F). Protect from light and moisture; dispense in original airtight container.
ContraindicationsHypersensitivity to zafirlukast or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Eosinophilia and vasculitis: In rare cases, patients may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. Healthcare providers should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between zafirlukast and these underlying conditions has not been established.

- Hepatotoxicity: There have been reports of hepatic adverse events (including hepatitis, hyperbilirubinemia, and hepatic failure); female patients may be at greater risk. Discontinue immediately if liver dysfunction is suspected; periodic testing of liver function may be considered (early detection is generally believed to improve the likelihood of recovery). If hepatic dysfunction is suspected (due to clinical signs/symptoms), liver function tests should be measured immediately. Do not resume or restart if hepatic function studies are consistent with dysfunction. Use caution in patients with alcoholic cirrhosis; clearance is reduced.

- Infections: An increased proportion of patients >55 years of age reported infections as compared to placebo-treated patients. These infections were mostly mild or moderate in intensity and predominantly affected the respiratory tract. Infections occurred equally in both sexes, were dose-proportional to total milligrams of zafirlukast exposure, and were associated with coadministration of inhaled corticosteroids.

Special populations:

- Pediatrics: Safety and efficacy have not been established in patients <5 years of age.

Other warnings/precautions:

- Reversal of bronchospasm: Not FDA approved for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus; therapy can be continued during acute exacerbations of asthma.

Geriatric ConsiderationsThe mean dose (mg/kg) normalized AUC and C_{max} increase and plasma clearance decreases with increasing age. In patients >65 years of age, there is a two- to threefold greater C_{max} and AUC compared to younger adults. Some studies have demonstrated slightly higher adverse effect reports in elderly compared to younger adults: Headache (4.7%), diarrhea and nausea (1.8%), and pharyngitis (1.3%). No changes in dose recommended for elderly.
Pregnancy Risk FactorB
Pregnancy ConsiderationsThere are no adequate and well-controlled trials in pregnant women. Teratogenic effects not observed in animal

studies; fetal defects were observed when administered in maternally toxic doses.

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsThe manufacturer does not recommend breast-feeding due to tumorigenicity observed in animal studies.

Adverse Reactions

>10%: Central nervous system: Headache (13%)

1% to 10%:

Central nervous system: Dizziness (2%), pain (2%), fever (2%)

Gastrointestinal: Nausea (3%), diarrhea (3%), abdominal pain (2%), vomiting (2%), dyspepsia (1%)

Hepatic: ALT increased (2%)

Neuromuscular & skeletal: Back pain (2%), myalgia (2%), weakness (2%)

Miscellaneous: Infection (4%)

<1%: Postmarketing and/or case reports: Agranulocytosis, angioedema, arthralgia, behavior/mood changes, bleeding, bruising, edema, eosinophilia (systemic), eosinophilic pneumonia, hepatic failure, hepatitis, hyperbilirubinemia, hypersensitivity reactions, insomnia, malaise, pruritus, rash, suicidality, suicide, urticaria, vasculitis with clinical features of Churg-Strauss syndrome (rare)

Metabolism/Transport Effects**Substrate** of CYP2C9 (major); **Inhibits** CYP1A2 (weak), 2C8 (weak), 2C9 (moderate), 2C19 (weak), 2D6 (weak), 3A4 (weak)

Drug Interactions

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP2C9 Substrates (High risk): CYP2C9 Inhibitors (Moderate) may decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

Erythromycin: May decrease the serum concentration of Zafirlukast. *Risk C: Monitor therapy*

Theophylline Derivatives: May decrease the serum concentration of Zafirlukast. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Zafirlukast may decrease the metabolism of Vitamin K Antagonists. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsFood: Decreases bioavailability of zafirlukast by 40%.

Monitoring ParametersMonitor for improvements in air flow; monitor closely for sign/symptoms of hepatic injury; periodic monitoring of LFTs may be considered (not proved to prevent serious injury, but early detection may enhance recovery)

Nursing: Physical Assessment/MonitoringNot for use in acute asthma attack. Assess effectiveness and interactions of other medications patient may be taking. Monitor effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Monitor for liver dysfunction. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsMonitor for improvements in air flow; periodic monitoring of LFTs may be considered (not proved to prevent serious injury, but early detection may enhance recovery)

Patient EducationDo not use during acute bronchospasm. Take regularly as prescribed, even during symptom-free periods. This medication should be taken on an empty stomach, 1 hour before or 2 hours after meals. Do not take more than recommended or discontinue use without consulting prescriber. Do not stop taking other antiasthmatic medications unless instructed by prescriber. Avoid aspirin or aspirin-containing medications unless approved by prescriber. You may experience headache, drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or gastric upset, nausea, or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report persistent CNS or GI symptoms; muscle or back pain; weakness, fever, chills; yellowing of skin or eyes; dark urine or pale stool; or skin rash. Contact prescriber immediately if experiencing right upper abdominal pain, nausea, fatigue, itching, flu-like symptoms; swelling of the eyes, face, neck, or throat; anorexia; or worsening of condition. **Breast-feeding precaution:** Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet: 10 mg, 20 mg

Generic AvailableNo

ManufacturerZeneca Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Tablets (Accolate)

10 mg (60): $94.09

20 mg (60): $95.99

Mechanism of ActionZafirlukast is a selectively and competitive leukotriene-receptor antagonist (LTRA) of leukotriene D4 and E4 (LTD4 and LTE4), components of slow-reacting substance of anaphylaxis (SRSA). Cysteinyl leukotriene production and receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, smooth muscle constriction, and altered cellular activity associated with the inflammatory process, which contribute to the signs and symptoms of asthma.

Pharmacodynamics/Kinetics

Protein binding: >99%, primarily to albumin

Metabolism: Extensively hepatic via CYP2C9

Bioavailability: Reduced 40% with food

Half-life elimination: 10 hours

Time to peak, serum: 3 hours

Excretion: Urine (10%); feces

Related Information

- Asthma

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause insomnia, malaise, or dizziness

Mental Health: Effects on Psychiatric TreatmentReports of agranulocytosis in association with zafirlukast; monitor CBC in patients receiving clozapine and carbamazepine

Index TermsICI-204,219

International Brand NamesAccolate (AR, AU, BB, BE, BF, BJ, BM, BR, BS, BZ, CH, CI, CL, CN, CZ, ES, ET, FI, GB, GH, GM, GN, GY, HK, HN, HU, ID, IE, IL, JM, KE, KP, LR, MA, ML, MR, MU, MW, MX, NE, NG, NL, NO, PE, PH, PK, PL, PT, SC, SD, SG, SL, SN, SR, TN, TT, TW, TZ, UG, UY, VE, ZA, ZM, ZW); Accoleit (IT); Zuvair (IN)

Zalcitabine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Pronunciation(zal SITE a been)

U.S. Brand NamesHivid® [DSC]

Canadian Brand NamesHivid®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)

Use: Labeled IndicationsIn combination with at least two other antiretrovirals in the treatment of patients with HIV infection; it is not recommended that zalcitabine be given in combination with didanosine, stavudine, or lamivudine due to overlapping toxicities, virologic interactions, or lack of clinical data

Dosing: Adults**HIV infection (component of combination therapy):** Oral: Daily dose: 0.75 mg every 8 hours

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**HIV infection:** Oral:

Children <13 years: Safety and efficacy have not been established; investigational dose: 0.01 mg/kg every 8 hours

Adolescents: Refer to adult dosing.

Dosing: Renal ImpairmentAdults:

Cl_{cr} 10-40 mL/minute: Administer 0.75 mg every 12 hours.

Cl_{cr} <10 mL/minute: Administer 0.75 mg every 24 hours.

Moderately dialyzable (20% to 50%)

Calculations

- Creatinine Clearance: Adults

Administration: OralFood decreases absorption; take on an empty stomach. Administer around-the-clock. Do not take at the same time with dapsone.

StorageTablets should be stored in tightly closed bottles at room temperature (59°F to 86°F).

ContraindicationsHypersensitivity to zalcitabine or any component of the formulation

Warnings/Precautions

Boxed warnings:

- Lactic acidosis/hepatomegaly: See "Concerns related to adverse effects" below.
- Pancreatitis: See "Concerns related to adverse effects" below.
- Peripheral neuropathy: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- Esophageal/oral ulcers: There have been reports of esophageal (rare) and/or oral ulcers with use.
- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases; some cases may possibly be related to underlying hepatitis B.** Use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).
- Pancreatitis: **[U.S. Boxed Warning]: Discontinue use immediately if pancreatitis is suspected;** careful monitoring of pancreatic enzymes and liver function tests in patients with a history of pancreatitis, increased amylase, those on parenteral nutrition, or with a history of ethanol abuse.
- Peripheral neuropathy: **[U.S. Boxed Warning]: Zalcitabine can cause severe peripheral neuropathy;** avoid use, if possible, in patients with pre-existing neuropathy or at risk of developing neuropathy. Risk factors include CD4 counts <50 cells/mm^3, diabetes mellitus, weight loss, other drugs known to cause peripheral neuropathy.

Disease-related concerns:

- Heart failure (HF): Use with caution in patients with HF; cardiomyopathy and HF have occurred.
- Hyperphosphatemia: Use with caution in patients with hyperphosphatemia.
- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Digitalis: Use with caution in patients on digitalis.

Pregnancy Risk FactorC

Pregnancy ConsiderationsIt is not known if zalcitabine crosses the human placenta. Animal studies have shown zalcitabine to be teratogenic, developmental toxicities were also observed. Cases of lactic acidosis/hepatic steatosis syndrome have been reported in pregnant women receiving nucleoside analogue drugs. It is not known if pregnancy itself potentiates this known side effect; however, pregnant women may be at increased risk of lactic acidosis and liver damage. Hepatic enzymes and electrolytes should be monitored frequently during the 3rd trimester of pregnancy in women receiving nucleoside analogues. Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationExcretion in breast milk unknown/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse Reactions

>10%:

Central nervous system: Fever (5% to 17%), malaise (2% to 13%)

Neuromuscular & skeletal: Peripheral neuropathy (28%)

1% to 10%:

Central nervous system: Headache (2%), fatigue (4%), seizure (1.3%), dizziness (1%)

Dermatologic: Rash (2% to 11%), pruritus (3% to 5%)

Endocrine & metabolic: Hypoglycemia (2% to 6%), hyperglycemia (1% to 6%), hyponatremia (4%)

Gastrointestinal: Diarrhea (<1% to 10%), abdominal pain (3% to 8%), amylase increased (3% to 8%), oral ulcers (3% to 7%), anorexia (4%), dysphagia (1% to 4%), vomiting (1% to 3%), nausea (3%), weight loss

Hematologic: Anemia (occurs as early as 2-4 weeks), granulocytopenia (usually after 6-8 weeks)

Hepatic: Abnormal hepatic function (9%), hyperbilirubinemia (2% to 5%)

Neuromuscular & skeletal: Myalgia (1% to 6%), foot pain

Respiratory: Nasal discharge (4%), cough (6%), pharyngitis (2%)

<1% (Limited to important or life-threatening): Atrial fibrillation, chest pain, constipation, edema, epistaxis, heart racing, hepatic failure, hepatitis, hepatomegaly, hypersensitivity (including anaphylaxis), hypertension, hypocalcemia, jaundice, lactic acidosis, myositis, night sweats, pain, palpitation, pancreatitis, redistribution/accumulation of body fat, syncope, tachycardia, weakness

Drug Interactions

Herbs (Hypoglycemic Properties): May enhance the hypoglycemic effect of Hypoglycemic Agents. *Risk C: Monitor therapy*

LamiVUDine: May diminish the therapeutic effect of Zalcitabine. *Risk D: Consider therapy modification*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Food decreases peak plasma concentrations by 39%. Extent and rate of absorption may be decreased with food.

Monitoring ParametersRenal function, viral load, liver function tests, CD4 counts, CBC, serum amylase, triglycerides, calcium

Nursing: Physical Assessment/MonitoringAssess closely for any previous allergy history prior to beginning treatment. Assess other pharmacological or herbal products patient may be taking (especially those that increase risk of peripheral neuropathy). Assess results of laboratory tests (CD4 count, renal function), therapeutic response, and adverse reactions (lactic acidosis [elevated transaminases]; gastrointestinal disturbance [nausea, vomiting, diarrhea]; myalgia; peripheral neuropathy) on a regular basis throughout therapy. Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab TestsCBC and serum chemistry (prior to initiation and appropriate intervals), renal function, CD4 counts, serum amylase, triglyceride, calcium, viral load

Patient EducationDo not take any new prescriptions, over-the-counter medications, or herbal products without consulting prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. This drug is prescribed as one part of a multidrug combination; take exactly as directed; preferably on an empty stomach, 1 hour before or 2 hours after meals. Do not take antacids or other medication within 1 hour of taking this medication. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. You may be susceptible to infection (avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber). Frequent blood tests may be required with prolonged therapy. May cause dizziness, fatigue, or headache (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea, vomiting, lack of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help). Report muscle weakness or pain; tingling, numbness, or pain in toes or fingers; weakness of extremities; chest pain, palpitations, or rapid heartbeat; swelling of extremities; weight gain or loss >5 lb/week; signs of infection (eg, fever, chills, sore throat, burning urination, fatigue); unusual bleeding (eg, tarry stools, easy bruising, or blood in stool, urine, or mouth); skin rash, irritation; or any other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet:

Hivid®: 0.375 mg, 0.75 mg [DSC]

Generic AvailableNo

ManufacturerRoche Laboratories Inc

Pricing: U.S. (www.drugstore.com)

Tablets (Hivid)

0.375 mg (90): $176.00

0.75 mg (90): $221.00

Mechanism of ActionPurine nucleoside (cytosine) analog, zalcitabine or 2′,3′-dideoxycytidine (ddC) is converted to active metabolite ddCTP; lack the presence of the 3′-hydroxyl group necessary for phosphodiester linkages during DNA replication. As a result, viral replication is prematurely terminated. ddCTP acts as a competitor for binding sites on the HIV-RNA dependent DNA polymerase (reverse transcriptase) to further contribute to inhibition of viral replication.

Pharmacodynamics/Kinetics

Absorption: Well, but variable; decreased 39% with food

Distribution: Minimal data available; variable CSF penetration

Protein binding: <4%

Metabolism: Intracellularly to active triphosphorylated agent

Bioavailability: >80%

Half-life elimination: 2.9 hours; Renal impairment: ≤8.5 hours

Excretion: Urine (>70% as unchanged drug)

Related Information

- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV
- Perinatal HIV Guidelines

Pharmacotherapy PearlsPotential compliance problems, frequency of administration, and adverse effects should be discussed with patients before initiating therapy to help prevent the emergence of resistance.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Oral ulcerations and dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDrowsiness is common; may cause dizziness

Mental Health: Effects on Psychiatric TreatmentMay cause granulocytopenia; use caution with clozapine; concurrent use with disulfiram can enhance peripheral neuropathy; avoid combination

Anesthesia and Critical Care Concerns/Other ConsiderationsPotential compliance problems, frequency of administration, and adverse effects should be discussed with patients before initiating therapy to help prevent the emergence of resistance.

Index TermsddC; Dideoxycytidine

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International Brand NamesHivid (AU, BB, BF, BJ, BM, BS, BZ, CI, ET, GH, GM, GN, GY, IL, JM, KE, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NL, PK, PL, SC, SD, SL, SN, SR, TN, TT, TW, TZ, UG, VE, ZA, ZM, ZW); Virorich (PY, UY)

Zaleplon

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(ZAL e plon)

U.S. Brand NamesSonata®

Pharmacologic CategoryHypnotic, Nonbenzodiazepine

Use: Labeled IndicationsShort-term (7-10 days) treatment of insomnia (has been demonstrated to be effective for up to 5 weeks in controlled trial)

Use: DentalHas not be established

Dosing: Adults**Insomnia (short-term use):** Oral: 10 mg at bedtime (range: 5-20 mg)

Dosing: ElderlyReduce dose to 5 mg at bedtime; recommended maximum: 10 mg/day

Dosing: Renal ImpairmentNo adjustment for mild-to-moderate renal impairment; use in severe renal impairment has not been adequately studied.

Dosing: Hepatic ImpairmentMild-to-moderate impairment: 5 mg; not recommended for use in patients with severe hepatic impairment.

Administration: OralAdminister immediately before bedtime or when the patient is in bed and cannot fall asleep.

Dietary ConsiderationsAvoid taking with or after a heavy, high-fat meal; reduces absorption.

StorageStore at controlled room temperature of 20°C to 25°C (68°F to 77°F). Protect from light.

RestrictionsC-IV

An FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. Medication guides are available at http://www.fda.gov/cder/Offices/ODS/medication_guides.htm.

ContraindicationsHypersensitivity to zaleplon or any component of the formulation

Allergy Considerations

- Zaleplon Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Abnormal thinking/behavioral changes: Hypnotics/sedatives have been associated with abnormal thinking and behavior changes including decreased inhibition, aggression, bizarre behavior, agitation, hallucinations, and depersonalization. These changes may occur unpredictably and may indicate previously unrecognized psychiatric disorders; evaluate appropriately.
- Amnesia: Can occur, do not take unless a full night's sleep and clearance of the drug from the body are possible.
- CNS depression: May cause CNS depression impairing physical and mental capabilities; patients must be cautioned about performing tasks which require mental alertness (operating machinery or driving).
- Hypersensitivity reactions: Postmarketing studies have indicated that the use of hypnotic/sedative agents for sleep has been associated with hypersensitivity reactions including anaphylaxis as well as angioedema.
- Sleep-related activities: An increased risk for hazardous sleep-related activities such as sleep-driving; cooking and eating food, and making phone calls while asleep have also been noted.

Disease-related concerns:

- Depression: Use with caution in patients with depression; worsening of depression, including suicidal ideation, has been reported with the use of hypnotics. Intentional overdose may be an issue in this population; prescribe least amount of medication needed.
- Drug abuse: Use with caution in patients with a history of drug dependence.
- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment recommended in mild-to-moderate impairment and avoid use in severe impairment.
- Respiratory disease: Use with caution in patients with respiratory compromise, COPD, or sleep apnea.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Elderly: Use with caution in the elderly; dosage adjustment recommended.
- Pediatrics: Safety and efficacy have not been established in children.

Dosage form specific issues:

- Tartrazine (FDC yellow #5): Capsules contain tartrazine; avoid in patients with sensitivity (caution in patients with asthma).

Other warnings/precautions:

- Appropriate use: Symptomatic treatment of insomnia should be initiated only after careful evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric and/or medical illness.

- Rapid onset: Because of the rapid onset of action, administer immediately prior to bedtime or after the patient has gone to bed and is having difficulty falling asleep.

- Withdrawal: Abrupt discontinuance may lead to withdrawal symptoms.

Geriatric ConsiderationsIn clinical trials, elderly responded to the 5 mg dose with decreased sleep latency. As with all hypnotics, assess underlying cause of insomnia.
Pregnancy Risk FactorC
Pregnancy ConsiderationsNot recommended for use during pregnancy
LactationEnters breast milk/not recommended
Adverse Reactions

>10 %: Central nervous system: Headache (30% to 42%)

1% to 10%:

Cardiovascular: Chest pain (≥1%), peripheral edema (≤1%)

Central nervous system: Dizziness (7% to 9%), somnolence (5% to 6%), amnesia (2% to 4%), depersonalization (<1% to 2%), hypoesthesia (<1% to 2%), malaise (<1% to 2%), abnormal thinking (≥1%), anxiety (≥1%), depression (≥1%), fever (≥1%), migraine (≥1%), nervousness (≥1%), confusion (≤1%), hallucination (≤1%), vertigo (≤1%)

Dermatologic: Pruritus (≥1%), rash (≥1%), photosensitivity reaction (≤1%)

Endocrine & metabolic: Dysmenorrhea (3% to 4%)

Gastrointestinal: Nausea (6% to 8%), abdominal pain (6%), anorexia (<1% to 2%), constipation (≥1%), dyspepsia (≥1%), taste perversion (≥1%), xerostomia (≥1%), colitis (up to 1%)

Neuromuscular & skeletal: Weakness (5% to 7%), paresthesia (3%), tremor (2%), arthralgia (≥1%), arthritis (≥1%), back pain (≥1%), myalgia (≥1%), hypertonia (1%)

Ocular: Eye pain (3% to 4%), abnormal vision (<1% to 2%), conjunctivitis (≥1%)

Otic: Hyperacusis (1% to 2%), ear pain (≤1%)

Respiratory: Bronchitis (≥1%), epistaxis (≤1%)

Miscellaneous: Parosmia (<1% to 2%)

<1% (Limited to important or life-threatening): Alopecia, ALT increased, anemia, angina, AST increased, ataxia, bigeminy, bilirubinemia, bleeding gums, bundle branch block, cardiospasm, cerebral ischemia, cholelithiasis, circumoral paresthesia, CNS stimulation, cyanosis, delusions, diabetes mellitus, duodenal ulcer, dysarthria, dystonia, dysuria, ecchymosis, eosinophilia, facial paralysis, gastroenteritis, glaucoma, goiter, hematuria, hyper-/hypoglycemia, hyper-/hypotension, hyperuricemia, hypothyroidism, impotence, incontinence, intestinal obstruction, ketosis, lactose intolerance, leukocytosis, lymphocytosis, liver function tests (abnormal), lymphadenopathy, myasthenia, myositis, osteoporosis, palpitation, peptic ulcer, pericardial effusion, photophobia, ptosis, pulmonary embolus, purpura, rash, rectal bleeding, sinus bradycardia, substernal chest pain, syncope, thrombophlebitis, tongue edema, ulcerative stomatitis, urinary retention, ventricular tachycardia, vasodilation, ventricular extrasystoles

Postmarketing and/or case reports: Anaphylaxis, angioedema, complex sleep-related behavior (sleep-driving, cooking or eating food, making phone calls)

Metabolism/Transport Effects**Substrate** of CYP3A4 (minor)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Cimetidine: May decrease the metabolism of Zaleplon. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Flumazenil: May diminish the sedative effect of Hypnotics (Nonbenzodiazepine). *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Zaleplon. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: High fat meal prolonged absorption; delayed t_{max} by 2 hours, and reduced C_{max} by 35%.

Herb/Nutraceutical: St John's wort may decrease zaleplon levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Nursing: Physical Assessment/MonitoringEvaluate etiology of insomnia; failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric and/or medical illness. Assess effectiveness and interactions of other medications. Evaluate risk for suicide and assess for history of addiction (long-term use may result in dependence, abuse, or tolerance). Prescription quantities should not exceed a 1 month supply; periodically evaluate need for continued use. Be alert to possibility of anaphylaxis any time during therapy. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse reactions to report.

Patient EducationTake exactly as directed; immediately before bedtime, or when you cannot fall asleep. Do not alter dosage or frequency, may be habit forming. Avoid alcohol and other prescription or OTC medications (especially medications to relieve pain, induce sleep, reduce anxiety, treat or prevent cold, coughs, or allergies) unless approved by prescriber. You may experience drowsiness, dizziness, somnolence, vertigo, lightheadedness, blurred vision (avoid driving or engaging in activities that require alertness until response to drug is known); photosensitivity (avoid exposure to direct sunlight, wear protective clothing, and sunscreen); nausea or GI discomfort (small frequent meals, good mouth care, chewing gum, or sucking hard candy may help); constipation (increase exercise, fluids, fruit, or fiber may help); or menstrual disturbances (reversible when drug is discontinued). Discontinue drug and report any severe CNS disturbances (hallucinations, acute nervousness or anxiety, persistent sleepiness or lethargy, impaired coordination, amnesia, or impaired thought processes); skin rash or irritation; eye pain or major vision changes; respiratory difficulty; unusual swelling, especially on face or neck; chest pain; ear pain; or muscle weakness or pain. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 5 mg, 10 mg

Sonata®: 5 mg, 10 mg [contains tartrazine]

Generic AvailableYes

ManufacturerWyeth-Ayerst Laboratories

Pricing: U.S. (www.drugstore.com)

Capsules (Sonata)

5 mg (30): $130.62

10 mg (30): $141.10

Capsules (Zaleplon)

5 mg (100): $39.99

10 mg (100): $39.99

Mechanism of ActionZaleplon is unrelated to benzodiazepines, barbiturates, or other hypnotics. However, it interacts with the benzodiazepine GABA receptor complex. Nonclinical studies have shown that it binds selectively to the brain omega-1 receptor situated on the alpha subunit of the GABA-A receptor complex.

Pharmacodynamics/Kinetics

Onset of action: Rapid

Duration: 6-8 hours

Absorption: Rapid and almost complete; high-fat meal delays absorption

Distribution: V_d: ~1.4 L/kg

Protein binding: ~45% to 75%

Metabolism: Extensive, primarily via aldehyde oxidase to form 5-oxo-zaleplon and, to a lesser extent, by CYP3A4 to desethylzaleplon; all metabolites are pharmacologically inactive

Bioavailability: ~30%

Half-life elimination: 1 hour

Time to peak, serum: 1 hour

Excretion: Urine (~70% primarily metabolites, <1% as unchanged drug); feces (~17%)

Clearance: Plasma: Oral: 3 L/hour/kg

Related Information

- CMS: Long-Term Care Facility Thresholds
- Nonbenzodiazepine Anxiolytics and Hypnotics

Pharmacotherapy PearlsPrescription quantities should not exceed a 1-month supply.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep. Zaleplon may be associated with a lower potential for abuse compared to benzodiazepines.

International Brand NamesHegon (AR); Hipnodem (AR); Noctiplon (CN); Plenidon (CN, PE); Prox (UY); Siweitan (CL); Sonata (AT, BE, BG, BR, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, MX, NL, NO, PL, PT, RU, SE, TR); Zaplon (IN); Zerene (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Zanamivir

Lexi-Drugs Online

English

English

Jump To Field (Select Field Name)

Special Alerts

CDC Interim Recommendations Concerning Use of Antivirals During 2008-09 Influenza Season - December 2008

The Centers for Disease Control (CDC) has issued a Health Advisory with interim recommendations for chemoprophylaxis or influenza treatment with the following antiviral agents: Oseltamivir (Tamiflu®), zanamivir (Relenza®), rimantadine (Flumadine®), amantadine (Symmetrel®).

The recommendations were prompted by preliminary data in a limited number of states indicating a high prevalence of the oseltamivir-resistant influenza A (H1N1) strain. Influenza activity remains low at the present time, but of the 50 H1N1 isolates from 12 states tested between October 1 and December 19, 2008, 49 (98%) were resistant to oseltamivir. The CDC is unable to make any accurate predictions of which influenza virus types (A or B) or subtypes of influenza A (H1N1 or H3N2) will predominate during the 2008-09 season, but based on the current findings, the following recommendations have been made:

- Patients testing positive for influenza type B: If treatment is indicated, patients may receive either oseltamivir or zanamivir (no preference).

- Patients testing positive for influenza type A (or patients testing negative for influenza, but likelihood of influenza infection is high): If treatment is indicated, patient may receive zanamivir. If zanamivir therapy is inappropriate (eg, patients with chronic respiratory disease, patients <7 years of age) or zanamivir is unavailable, combination treatment with oseltamivir and rimantadine is acceptable (if rimantadine is unavailable, amantadine may be substituted). Oseltamivir monotherapy should only be used if local surveillance indicates that influenza A (H3N2) or influenza type B viruses are likely.

- If confirmatory diagnostic testing to distinguish between subtypes of influenza A (H1N1 or H3N2) is available, and treatment is indicated:

    Patients testing positive for influenza A (H3N2): Use oseltamivir or zanamivir (no preference)

    Patients testing positive for influenza A (H1N1): Use zanamivir (or combination treatment with oseltamivir and rimantadine as an alternative)

Patients requiring chemoprophylaxis due to potential exposure with laboratory-confirmed influenza A (H3N2) or influenza B should receive oseltamivir or zanamivir. Patients requiring chemoprophylaxis due to influenza A (H1N1) virus should receive zanamivir (or rimantadine, if zanamivir use contraindicated).

The CDC is reminding clinicians to continue to vaccinate patients using the influenza vaccine, which is expected to be effective against all circulating influenza vaccines, including the oseltamivir-resistant strain.

For additional information, including the CDC Health Advisory, please refer to http://www2a.cdc.gov/HAN/ArchiveSys/ViewMsgV.asp?AlertNum=00279

Zanamivir (Relenza®) Associated With Neuropsychiatric Events - April 2, 2008

GlaxoSmithKline, in conjunction with the U.S. Food and Drug Administration (FDA), has issued a Dear Healthcare Professional letter concerning postmarketing reports of neuropsychiatric events in patients receiving neuraminidase inhibitors, including zanamivir (Relenza®). These events include hallucination, delirium, seizure, and abnormal behavior, which in some cases have led to injury (with fatalities). The reported events primarily occurred in pediatric patients from Japan and often had a sudden onset with rapid resolution. Although the role of zanamivir in the development of these events has not been established, the prescribing information has been revised to acknowledge their occurrence.

Patients with influenza (particularly pediatric patients) may be more susceptible to the development of adverse events (seizures, confusion, abnormal behavior) early in the course of their illness regardless of whether zanamivir therapy has been initiated. Additionally, adverse events may occur in the presence of encephalitis or encephalopathy, or in the absence of marked disease. Patients receiving zanamivir should be closely monitored for any unusual behavior and healthcare professionals should be notified immediately if such signs occur.

Additional information can be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Relenza

Pronunciation(za NA mi veer)

U.S. Brand NamesRelenza®
Canadian Brand NamesRelenza®
Pharmacologic CategoryAntiviral Agent; Neuraminidase Inhibitor
Use: Labeled IndicationsTreatment of uncomplicated acute illness due to influenza virus A and B in patients who have been symptomatic for no more than 2 days; prophylaxis against influenza virus A and B

The Advisory Committee on Immunization Practices (ACIP) recommends that **treatment** be considered for the following:

- Persons hospitalized with laboratory confirmed influenza (may also have benefit if started >48 hours after onset of illness).
- Persons with laboratory confirmed influenza pneumonia.
- Persons with laboratory confirmed influenza and bacterial infections.
- Persons with laboratory confirmed influenza and who are at higher risk for influenza complications.
- Persons presenting for care within 48 hours of laboratory confirmed influenza onset and who want to decrease duration and/or severity of their symptoms or decrease the risk of transmission to those at high risk for complications.

The ACIP recommends that **prophylaxis** be considered for the following:

- Persons at high risk for influenza infection during the first 2 weeks following vaccination (eg, children <9 years and not previously vaccinated) if the virus is circulating in the community.
- Persons at high risk for influenza infection, but the vaccination is contraindicated.
- Unvaccinated family members or healthcare providers with prolonged exposure to or close contact with high-risk persons, unvaccinated persons, or infants <6 months of age.
- Persons at high risk for influenza infection, their family members and close contacts, and healthcare workers when the circulating strain of influenza is not matched with the vaccine.
- Persons with immune deficiency or those who may not respond to vaccination.
- Unvaccinated staff and persons during response to an outbreak in a closed institutional setting that has patients at high risk for infection (eg, extended care facilities).

Dosing: Adults**Influenza virus A and B:**

Prophylaxis: Oral inhalation:

Household setting: Two inhalations (10 mg) once daily for 10 days. Begin within $1^{1}/_{2}$ days following onset of signs or symptoms of index case.

Community outbreak: Two inhalations (10 mg) once daily for 28 days. Begin within 5 days of outbreak.

Treatment: Oral inhalation: Two inhalations (10 mg total) twice daily for 5 days. Doses on first day should be separated by at least 2 hours; on subsequent days, doses should be spaced by ~12 hours. Begin within 2 days of signs or symptoms.

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Influenza virus A and B:**

Prophylaxis: Oral inhalation:

Household setting: Children ≥5 years: Refer to adult dosing.

Community outbreak: Adolescents: Refer to adult dosing.

Treatment: Oral inhalation: Children ≥7 years: Refer to adult dosing.

Administration: InhalationMust be used with Diskhaler® delivery device. Patients who are scheduled to use an inhaled bronchodilator should use their bronchodilator prior to zanamivir. With the exception of the initial dose when used for treatment, administer at the same time each day.
StorageStore at controlled room temperature (25°C) 77°F. Do not puncture blister until taking a dose using the Diskhaler®.
ContraindicationsHypersensitivity to zanamivir or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- Allergic reactions: Allergic-like reactions, including anaphylaxis, oropharyngeal edema, and serious skin rashes have been reported.
- Neuropsychiatric events: Rare occurrences of neuropsychiatric events (including confusion, delirium, hallucinations, and/or self-injury) have been reported from postmarketing surveillance; direct causation is difficult to establish (influenza infection may also be associated with behavioral and neurologic changes).
- Respiratory effects: Bronchospasm, decreased lung function, and other serious adverse reactions, including those with fatal outcomes, have been reported in patients with and without airway disease; discontinue with bronchospasm or signs of decreased lung function. For a patient with an underlying airway disease where a medical decision has been made to use zanamivir, a fast-acting bronchodilator should be made available, and used prior to each dose.

Disease-related concerns:

- Renal impairment: Safety and efficacy of use in patients with severe renal impairment have not been established.

- Respiratory disease: Not recommended for use in patients with underlying respiratory disease, such as asthma or COPD, due to lack of efficacy and risk of serious adverse effects.

Special populations:

- Nursing home patients: Effectiveness has not been established for prophylaxis of influenza in nursing home patients.

- Pediatrics: Indicated for children ≥5 years of age (for influenza prophylaxis) and children ≥7 years of age (for influenza treatment); children ages 5-6 years may have inadequate inhalation (via Diskhaler®) for the treatment of influenza.

Dosage form specific issues:

- Lactose: Powder for oral inhalation contains lactose.

Other warnings/precautions:

- Appropriate use: No data are available to support the use of this drug in patients who begin use for treatment after 48 hours of symptoms. Effectiveness has not been established in patients with significant underlying medical conditions. Not a substitute for annual flu vaccination; has not been shown to reduce risk of transmission of influenza to others. Patients must be instructed in the use of the delivery system. Consider primary or concomitant bacterial infections. Safety and efficacy of repeated courses have not been established.

Geriatric ConsiderationsA recent study demonstrated that most elderly were unable to use an inhaler device effectively.

Pregnancy Risk FactorC

Pregnancy ConsiderationsZanamivir has been shown to cross the placenta in animal models, however, no evidence of fetal malformations has been demonstrated. There are no adequate and well-controlled studies in pregnant women.

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsZanamivir has been shown to be excreted in the milk of animals, but its excretion in human milk is unknown. Caution should be used when zanamivir is administered to a nursing mother.

Adverse ReactionsMost adverse reactions occurred at a frequency which was less than or equal to the control (lactose vehicle).

>10%:

Central nervous system: Headache (prophylaxis 13% to 24%; treatment 2%)

Gastrointestinal: Throat/tonsil discomfort/pain (prophylaxis 8% to 19%)

Respiratory: Nasal signs and symptoms (prophylaxis 12% to 20%; treatment 2%), cough (prophylaxis 7% to 17%; treatment ≤2%)

Miscellaneous: Viral infection (prophylaxis 3% to 13%)

1% to 10%:

Central nervous system: Fever/chills (prophylaxis 5% to 9%; treatment <1.5%), fatigue (prophylaxis 5% to 8%; treatment <1.5%), malaise (prophylaxis 5% to 8%; treatment <1.5%), dizziness (treatment 1% to 2%)

Dermatologic: Urticaria (treatment <1.5%)

Gastrointestinal: Anorexia/appetite decreased (prophylaxis 2% to 4%), appetite increased (prophylaxis 2% to 4%), nausea (prophylaxis 1% to 2%; treatment ≤3%), diarrhea (prophylaxis 2%; treatment 2% to 3%), vomiting (prophylaxis 1% to 2%; treatment 1% to 2%), abdominal pain (treatment <1.5%)

Neuromuscular & skeletal: Muscle pain (prophylaxis 3% to 8%), musculoskeletal pain (prophylaxis 6%), arthralgia/articular rheumatism (prophylaxis 2%), arthralgia (treatment <1.5%), myalgia (treatment <1.5%)

Respiratory: Infection (ear/nose/throat; prophylaxis 2%; treatment 1% to 5%), sinusitis (treatment 3%), bronchitis (treatment 2%), nasal inflammation (prophylaxis 1%)

<1%: Asthma, hemorrhage (ear/nose/throat)

Postmarketing and/or case reports: Abnormal behavior, agitation, allergic or allergic-like reaction (including oropharyngeal edema), anxiety, arrhythmia, bronchospasm, confusion, consciousness altered, delirium, delusions, dyspnea, facial edema, hallucinations, nightmares, rash (including serious cutaneous reactions), seizure, syncope

Drug Interactions

Influenza Virus Vaccine: Antiviral Agents (Influenza A and B) may diminish the therapeutic effect of Influenza Virus Vaccine. This only pertains to live, attentuated influenza virus vaccine. *Risk D: Consider therapy modification*

Nursing: Physical Assessment/MonitoringTherapy for treatment must be started within 48 hours of first influenza symptoms. Monitor for change in behavior. Teach patient appropriate use (inhalation device), interventions to reduce side effects, and adverse reactions to report.

Patient EducationThis is **not** a substitute for the influenza vaccine. Use delivery device exactly as directed; complete full regimen, even if symptoms improve sooner. If you have asthma or COPD you may be at risk for bronchospasm; see prescriber for appropriate bronchodilator before using zanamivir. Stop using this medication and contact your prescriber if you experience shortness of breath, increased wheezing, or other signs of bronchospasm. You may experience dizziness or headache (use caution when driving or engaging in hazardous tasks until response to drug is known), sore throat, or nasal congestion. Report unresolved diarrhea, vomiting, or nausea; acute fever or muscle pain;

change in behavior, including hallucinations, confusion, delirium, or seizures; or other acute and persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Powder for oral inhalation: 5 mg/blister (20s) [4 blisters per Rotadisk® foil pack, 5 Rotadisk® per package; packaged with Diskhaler® inhalation device; contains lactose]

Generic AvailableNo

ManufacturerGlaxoSmithKline

Pricing: U.S. (www.drugstore.com)

Aerosol powder (Relenza Diskhaler)

5 mg/blister (20): $63.99

Mechanism of ActionZanamivir inhibits influenza virus neuraminidase enzymes, potentially altering virus particle aggregation and release.

Pharmacodynamics/Kinetics

Absorption: Inhalation: ~4% to 17%

Protein binding, plasma: <10%

Metabolism: None

Half-life elimination, serum: 2.5-5.1 hours

Excretion: Urine (as unchanged drug); feces (unabsorbed drug)

Related Information

- USPHS / IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected With HIV

Pharmacotherapy PearlsMajority of patients included in clinical trials were infected with influenza A, however, a number of patients with influenza B infections were also enrolled. Patients with lower temperature or less severe symptoms appeared to derive less benefit from therapy. No consistent treatment benefit was demonstrated in patients with chronic underlying medical conditions.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusMay cause dizziness; may rarely cause drowsiness

Mental Health: Effects on Psychiatric TreatmentNone reported

Anesthesia and Critical Care Concerns/Other ConsiderationsPatients with asthma or COPD should be informed of the risk of bronchospasm and should have a fast-acting bronchodilator available when treated with zanamivir. Majority of patients included in clinical trials were infected with influenza A, however, a number of patients with influenza B infections were also enrolled. Patients with lower temperature or less severe symptoms appeared to derive less benefit from therapy. No consistent treatment benefit was demonstrated in patients with chronic underlying medical conditions.

References

Centers for Disease Control, “Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP),” *MMWR Recomm Rep*, 2008, 56 (early release):1-60. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e717a1.htm

Dreitlein WB, Maratos J, and Brocavich J, “Zanamivir and Oseltamivir: Two New Options for the Treatment and Prevention of Influenza,” *Clin Ther*, 2001, 23(3):327-55.[PubMed 11318072]

International Brand NamesRelenza (AR, AT, AU, BE, BG, BR, CH, CZ, DE, DK, EE, ES, FI, FR, GB, HK, IE, IL, IT, KP, MX, MY, NL, NO, NZ, PL, PT, SE, SG, TW)

Ziconotide

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Pronunciation(zi KOE no tide)

U.S. Brand NamesPrialt®

Pharmacologic CategoryAnalgesic, Nonopioid; Calcium Channel Blocker, N-Type

Use: Labeled IndicationsManagement of severe chronic pain in patients requiring intrathecal (I.T.) therapy and who are intolerant or refractory to other therapies

Dosing: Adults**Chronic pain:** I.T.: Initial dose: ≤2.4 mcg/day (0.1 mcg/hour)

Dose may be titrated by ≤2.4 mcg/day (0.1 mcg/hour) at intervals ≤2-3 times/week to a maximum dose of 19.2 mcg/day (0.8 mcg/hour) by day 21; average dose at day 21: 6.9 mcg/day (0.29 mcg/hour). A faster titration should be used only if the urgent need for analgesia outweighs the possible risk to patient safety.

Dosing: ElderlyRefer to adult dosing. Use with caution.

Dosing: Adjustment for Toxicity

Cognitive impairment: Reduce dose or discontinue. Effects are generally reversible within 3-15 days of discontinuation.

Reduced level of consciousness: Discontinue until event resolves.

CK elevation with neuromuscular symptoms: Consider dose reduction or discontinuation.

Administration: I.V.**Not for I.V. administration**

Administration: OtherNot for I.V. administration. **For I.T. administration only** using Medtronic SynchroMed® EL, SynchroMed® II Infusion System, or CADD-Micro® ambulatory infusion pump.

Medtronic SynchroMed® EL or SynchroMed® II Infusion Systems:

Naive pump priming (first time use with ziconotide): Use 2 mL of undiluted ziconotide 25 mcg/mL solution to rinse the internal surfaces of the pump; repeat twice for a total of 3 rinses

Initial pump fill: Use only undiluted 25 mcg/mL solution and fill pump after priming. Following the initial fill only, adsorption on internal device surfaces will occur, requiring the use of the undiluted solution and refill within 14 days.

Pump refills: Contents should be emptied prior to refill. Subsequent pump refills should occur at least every 40 days if using diluted solution or at least every 84 days if using undiluted solution.

CADD-Micro® ambulatory infusion pump: Refer to manufacturers' manual for initial fill and refill instructions

pH: 4-5

StoragePrior to use, store vials at 2°C to 8°C (36°F to 46°F). Once diluted, may be stored at 2°C to 8°C (36°F to 46°F) for 24 hours; refrigerate during transit. Do not freeze. Protect from light.

When using the Medtronic SynchroMed® EL or SynchroMed® II Infusion System, solutions expire as follows:

25 mcg/mL: Undiluted:

Initial fill: Use within 14 days.

Refill: Use within 84 days.

100 mcg/mL:

Undiluted: Refill: Use within 84 days.

Diluted: Refill: Use within 40 days.

ReconstitutionPreservative free NS should be used when dilution is needed.

CADD-Micro® ambulatory infusion pump: Initial fill: Dilute to final concentration of 5 mcg/mL.

Medtronic SynchroMed® EL or SynchroMed® II infusion system: Prior to initial fill, rinse internal pump surfaces with 2 mL ziconotide (25 mcg/mL), repeat twice. Only the 25 mcg/mL concentration (undiluted) should be used for initial pump fill.

Contraindications Hypersensitivity to ziconotide or any component of the formulation; history of psychosis; I.V. administration

I.T. administration is contraindicated in patients with infection at the injection site, uncontrolled bleeding, or spinal canal obstruction that impairs CSF circulation

Warnings/Precautions

Boxed warnings:

- CNS toxicity: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

- CNS toxicity: **[U.S Boxed Warning]: Severe psychiatric symptoms and neurological impairment have been reported;** interrupt or discontinue therapy if cognitive impairment, hallucinations, mood changes, or changes in consciousness occur. May cause or worsen depression and/or risk of suicide. Cognitive impairment may appear gradually during treatment and is generally reversible after discontinuation (may take up to 2 weeks for cognitive effects to reverse). May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Elevated serum creatine kinase: With use, elevated serum creatine kinase can occur; particularly during the first 2 months of therapy. Consider dose reduction or discontinuing if combined with new neuromuscular symptoms (myalgias, myasthenia, muscle cramps, weakness) or reduction in physical activity.

- Meningitis: May occur with use of I.T. pumps; monitor for signs of meningitis; treatment of meningitis may require removal of system and discontinuation of intrathecal therapy.

Disease-related concerns:

- Hepatic impairment: Safety and efficacy have not been established in patients with hepatic impairment.

- Renal impairment: Safety and efficacy have not been established in patients with renal impairment.

Concurrent drug therapy issues:

- CNS depressants: May have additive effects with CNS-depressant medications.

- Opiates: May have additive CNS effects with opiates and may potentiate opioid-induced decreased GI motility; does not interact with opioid receptors or potentiate opiate-induced respiratory depression.

Special populations:

- Elderly: Use with caution in the elderly; may experience a higher incidence of confusion.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Withdrawal: Will not prevent or relieve symptoms associated with opiate withdrawal; unlike opioids, ziconotide therapy can be interrupted abruptly or discontinued without evidence of withdrawal.

Geriatric Considerations Manufacturer reports that in all trials there was a higher incidence of confusion in the elderly compared to younger adults.

Pregnancy Risk Factor C

Pregnancy Considerations Teratogenic effects were not observed in animal studies, but increased postimplantation pup loss was reported. Maternal toxicity was also noted. There are no adequate and well-controlled studies in pregnant women.

Lactation Excretion in breast milk unknown/not recommended

Breast-Feeding Considerations The manufacturer recommends discontinuing breast-feeding or discontinuing ziconotide.

Adverse Reactions

>10%:

Central nervous system: Dizziness (46%), confusion (15% to 33%), memory impairment (7% to 22%), somnolence (17%), ataxia (14%), speech disorder (14%), headache (13%), aphasia (12%), hallucination (12%; including auditory and visual)

Gastrointestinal: Nausea (40%), diarrhea (18%), vomiting (16%)

Neuromuscular & skeletal: Creatine kinase increased (40%; ≥3 times ULN: 11%), weakness (18%), gait disturbances (14%)

Ocular: Blurred vision (12%)

2% to 10%:

Cardiovascular: Hypotension, peripheral edema, postural hypotension

Central nervous system: Abnormal thinking (8%), amnesia (8%), anxiety (8%), vertigo (7%), insomnia (6%), fever (5%), paranoid reaction (3%), delirium (2%), hostility (2%), stupor (2%), agitation, attention disturbance, balance impaired, burning sensation, coordination abnormal, depression, disorientation, fatigue, fever, hypoesthesia, irritability, lethargy, mental impairment, mood disorder, nervousness, pain, sedation

Dermatologic: Pruritus (7%)

Gastrointestinal: Anorexia (6%), taste perversion (5%), abdominal pain, appetite decreased, constipation, xerostomia

Genitourinary: Urinary retention (9%), dysuria, urinary hesitance

Neuromuscular & skeletal: Dysarthria (7%), paresthesia (7%), rigors (7%), tremor (7%), muscle spasm (6%), limb pain (5%), areflexia, muscle cramp, muscle weakness, myalgia

Ocular: Nystagmus (8%), diplopia, visual disturbance

Respiratory: Sinusitis (5%)

Miscellaneous: Diaphoresis (5%)

<2%, postmarketing, and/or case reports: Acute renal failure, aspiration pneumonia (<1%), atrial fibrillation, cerebral vascular accident, ECG abnormalities, incoherence, loss of consciousness, mania, meningitis, myoclonus, psychosis (1%), psychotic disorder, respiratory distress, rhabdomyolysis, seizure (clonic and grand mal), sepsis, suicidal ideation, suicide attempt (<1%)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb InteractionsEthanol: Avoid ethanol (may increase CNS adverse effects).

Monitoring ParametersMonitor for psychiatric or neurological impairment; signs and symptoms of meningitis or other infection; serum CPK (every other week for first month then monthly); pain relief

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for effectiveness and interactions. This medication is given intrathecally via pump. Monitor for therapeutic response. Monitor for changes in behavior, cognitive impairment, hallucinations, or changes in mood or consciousness. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsCPK (every other week for first month, then monthly)

Patient EducationAvoid alcohol, other prescriptions, or OTC medications (especially sedatives, tranquilizers, antihistamines, and other pain medications) without consulting prescriber. You may experience dizziness, sleepiness, or lightheadedness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea or vomiting (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased exercise, fluids, fruit, or fiber may help); diarrhea (buttermilk, boiled milk, or yogurt may help); or loss of appetite. Report chest pain, swelling of extremities (feet/ankles); muscle weakness and poor coordination; hallucinations, confusion, or extreme weakness. **Pregnancy/breast-feeding precaution:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as acetate [preservative free]:

Prialt®: 25 mcg/mL (20 mL); 100 mcg/mL (1 mL, 5 mL)

Generic AvailableNo

ManufacturerElan Pharmaceuticals, Inc

Mechanism of ActionZiconotide selectively binds to N-type voltage-sensitive calcium channels located on the nociceptive afferent nerves of the dorsal horn in the spinal cord. This binding is thought to block N-type calcium channels, leading to a blockade of excitatory neurotransmitter release and reducing sensitivity to painful stimuli.

Pharmacodynamics/Kinetics

Distribution: I.T.: V_d: ~140 mL

Protein binding: ~50%

Metabolism: Metabolized via endopeptidases and exopeptidases present on multiple organs including kidney, liver, lung; degraded to peptide fragments and free amino acids

Half-life elimination: I.V.: 1-1.6 hours (plasma); I.T.: 2.9-6.5 hours (CSF)

Excretion: I.V.: Urine (<1%)

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and taste perversion.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness and sedation are common. May cause hallucinations, mood changes, cognitive impairment, changes in consciousness, anxiety, nervousness, agitation, abnormal dreams, insomnia, or hostility.

Mental Health: Effects on Psychiatric TreatmentContraindicated in individuals with a history of psychosis. Concomitant use with psychotropic agents may produce additive sedative effects; monitor. GI side effects are common; concomitant use with SSRIs, valproic acid, or lithium may produce additive effects; monitor.

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Wermeling D, Drass M, Ellis D, et al, “Pharmacokinetics and Pharmacodynamics of Intrathecal Ziconotide in Chronic Pain Patients,” *J Clin Pharmacol*, 2003, 43(6):624-36.[PubMed 12817525]

International Brand NamesPrialt (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PT, RU, SE, TR)

Zidovudine and Lamivudine

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Combivir® may be confused with Combivent®, Epivir®

AZT is an error-prone abbreviation (mistaken as azaTHIOprine, aztreonam)

Pronunciation(zye DOE vyoo deen & la MI vyoo deen)

U.S. Brand NamesCombivir®

Canadian Brand NamesCombivir®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)

Use: Labeled IndicationsTreatment of HIV infection when therapy is warranted based on clinical and/or immunological evidence of disease progression

Dosing: Adults**Treatment of HIV infection:** Oral: 1 tablet twice daily. Because this is a fixed-dose combination product, avoid use in patients requiring dosage reduction including children <12 years of age, renally-impaired patients with a creatinine clearance ≤50 mL/minute, hepatic impairment, or those patients experiencing dose-limiting adverse effects.

Dosing: ElderlySee Geriatric Considerations.

Dosing: PediatricChildren ≥12 years: Refer to adult dosing.

StorageStore between 2°C and 30°C (36°F and 86°F).

ContraindicationsHypersensitivity to lamivudine, zidovudine, or any component of the formulation

Allergy Considerations

- LamiVUDine Allergy
- Zidovudine Allergy

Warnings/Precautions

Boxed warnings:

- Chronic hepatitis B: See “Disease-related concerns” below.
- Hematologic toxicity: See “Concerns related to adverse effects” below.
- Lactic acidosis/hepatomegaly: See “Concerns related to adverse effects” below.
- Myopathy: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Hematologic toxicity: **[U.S. Boxed Warning]: Zidovudine is associated with hematologic toxicity including neutropenia and severe anemia.** Use with caution in patients with bone marrow compromise (granulocytes <1000 cells/mm^3 or hemoglobin <9.5 mg/dL).
- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.
- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).
- Myopathy: **[U.S. Boxed Warning]: Prolonged use of zidovudine has been associated with symptomatic myopathy and myositis.**

Disease-related concerns:

- Chronic hepatitis B: **[U.S. Boxed Warning]: Monitor closely for chronic hepatitis B for several months following discontinuation of therapy** in patients coinfected with HBV and HIV; clinical exacerbations may occur and may warrant antihepatitis B therapy.
- Hepatic impairment: Combivir® is not recommended for use in patients with hepatic impairment.
- Renal impairment: Combivir® is not recommended for use in patients with renal (Cl_{cr}<50 mL/minute).

Concurrent drug therapy issues:

- Interferon alfa: Use with caution in combination with interferon alfa with or without ribavirin in HIV/HBV coinfected patients; monitor closely for hepatic decompensation, anemia, or neutropenia; dose reduction or discontinuation of interferon and/or ribavirin may be required if toxicity evident.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Pregnancy Risk FactorC
Pregnancy ConsiderationsSee individual agents.
LactationSee individual agents.
Breast-Feeding ConsiderationsSee individual agents.
Adverse ReactionsSee individual agents.
Metabolism/Transport EffectsZidovudine: **Substrate** (minor) of CYP2A6, 2C9, 2C19, 3A4
Drug Interactions

Acyclovir-Valacyclovir: May enhance the CNS depressant effect of Zidovudine. *Risk C: Monitor therapy*

DOXOrubicin: May enhance the adverse/toxic effect of Zidovudine. DOXOrubicin may diminish the therapeutic effect of Zidovudine. *Risk D: Consider therapy modification*

DOXOrubicin (Liposomal): May enhance the adverse/toxic effect of Zidovudine. DOXOrubicin (Liposomal) may diminish the therapeutic effect of Zidovudine. *Risk D: Consider therapy modification*

Emtricitabine: LamiVUDine may enhance the adverse/toxic effect of Emtricitabine. *Risk X: Avoid combination*

Fluconazole: May decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Ganciclovir-Valganciclovir: May enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. *Risk D: Consider therapy modification*

Interferons: May enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Methadone: May increase the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Probenecid: May decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Zidovudine. **Exceptions:** Rifabutin. *Risk D: Consider therapy modification*

Stavudine: Zidovudine may diminish the therapeutic effect of Stavudine. *Risk D: Consider therapy modification*

Trimethoprim: May decrease the excretion of LamiVUDine. *Risk C: Monitor therapy*

Valproic Acid: May decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Zalcitabine: LamiVUDine may diminish the therapeutic effect of Zalcitabine. *Risk D: Consider therapy modification*

Monitoring ParametersAmylase, bilirubin, signs and symptoms of pancreatitis. Monitor CBC with differential and platelet count at least every 2 weeks, liver function tests (including signs/symptoms of hepatomegaly), MCV, serum creatinine kinase, viral load, and CD4 count; observe for appearance of opportunistic infections; signs of muscle weakness or pain; blood lactate levels and signs of acidosis
Nursing: Physical Assessment/MonitoringSee individual agents.
Monitoring: Lab TestsAmylase, bilirubin; monitor CBC with differential and platelet count at least every 2 weeks, liver function tests (including signs/symptoms of hepatomegaly), MCV, serum creatinine kinase, viral load, and CD4 count; blood lactate levels and signs of acidosis
Patient EducationSee individual agents.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet:

Combivir®: Zidovudine 300 mg and lamivudine 150 mg

Generic AvailableNo
ManufacturerGlaxoSmithKline
Pricing: U.S. (www.drugstore.com)

Tablets (Combivir)

150-300 mg (30): $411.19

Mechanism of ActionThe combination of zidovudine and lamivudine is believed to act synergistically to inhibit reverse transcriptase via DNA chain termination after incorporation of the nucleoside analogue as well as to delay the emergence of mutations conferring resistance
Pharmacodynamics/KineticsSee individual agents.

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- LamiVUDine
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV
- Zidovudine

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness, insomnia, sedation are common; may cause depression. May rarely cause confusion or mania.

Mental Health: Effects on Psychiatric TreatmentLeukopenia and granulocytopenia are common; caution with clozapine and carbamazepine. Increased toxicity may result if used concurrently with drugs that inhibit glucuronidation or excretion (lorazepam). Valproic acid increased zidovudine's AUC by 80% and decreased clearance by 38%.

Index TermsAZT + 3TC (error-prone abbreviation); Lamivudine and Zidovudine

References

“Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on Clinical Practices for Treatment of HIV Infection,” January 29, 2008. Available at http://www.aidsinfo.nih.gov

“Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States,” November 17, 2005. Available at: http://www.aidsinfo.nih.gov.

International Brand NamesBiovir (BR); Combid (TH); Combivir (AE, AT, AU, BE, BF, BG, BH, BJ, CH, CI, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EG, ET, FI, FR, GB, GH, GM, GN, GR, GT, HK, HN, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, NL, NO, OM, PA, PE, PH, PT, PY, QA, RU, SA, SC, SD, SE, SG, SL, SN, SV, SY, TN, TR, TW, TZ, UG, UY, VE, YE, ZA, ZM, ZW); Duovir (IN); Ganvirel Duo (AR); Lamuzid (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW); Virdual (CO)

Zidovudine

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Medication Safety Issues

Sound-alike/look-alike issues:

Azidothymidine may be confused with azaTHIOprine, aztreonam

Retrovir® may be confused with ritonavir

AZT is an error-prone abbreviation (mistaken as azathioprine, aztreonam)

Pronunciation(zye DOE vyoo deen)

U.S. Brand NamesRetrovir®

Canadian Brand NamesApo-Zidovudine®; AZT™; Retrovir®

Pharmacologic CategoryAntiretroviral Agent, Reverse Transcriptase Inhibitor (Nucleoside)

Use: Labeled IndicationsTreatment of HIV infection in combination with at least two other antiretroviral agents; prevention of maternal/fetal HIV transmission as monotherapy

Use: Unlabeled/InvestigationalPostexposure prophylaxis for HIV exposure as part of a multidrug regimen

Dosing: Adults

Prevention of maternal-fetal HIV transmission: Maternal (per AIDSinfo guidelines): 100 mg 5 times/day **or** 200 mg 3 times/day **or** 300 mg twice daily. Begin at 14-34 weeks gestation and continue until start of labor.

Note: Consider use of zidovudine in combination with nevirapine (and possibly lamivudine) in select situations (eg, infants born to mothers with suboptimal viral suppression at delivery, infants born to mothers with only intrapartum therapy or no therapy, or infants born to mothers with known antiretroviral drug-resistant virus) (AIDSinfo guidelines, July 2008).

During labor and delivery, administer zidovudine I.V. at 2 mg/kg as loading dose followed by a continuous I.V. infusion of 1 mg/kg/hour until the umbilical cord is clamped

HIV infection:

Oral: 300 mg twice daily or 200 mg 3 times/day

I.V.: 1 mg/kg/dose administered every 4 hours around-the-clock (5-6 doses/day)

Prevention of HIV following needlesticks (unlabeled use): Oral: 200 mg 3 times/day plus lamivudine 150 mg twice daily; a protease inhibitor (eg, indinavir) may be added for high risk exposures; begin therapy within 2 hours of exposure if possible

Note: Patients should receive I.V. therapy only until oral therapy can be administered

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Prevention of maternal-fetal HIV transmission (in neonates):Note: Consider use of zidovudine in combination with nevirapine (and possibly lamivudine) in select situations (eg, infants born to mothers with suboptimal viral suppression at delivery, infants born to mothers with only intrapartum therapy or no therapy, or infants born to mothers with known antiretroviral drug-resistant virus) (AIDSinfo guidelines, July 2008).

Note: Dosing should begin 6-12 hours after birth and continue for the first 6 weeks of life.

Oral:

Full-term infants: 2 mg/kg/dose every 6 hours

Infants ≥30 weeks and <35 weeks gestation at birth: 2 mg/kg/dose every 12 hours; at 2 weeks of age, advance to 2 mg/kg/dose every 8 hours

Infants <30 weeks gestation at birth: 2 mg/kg/dose every 12 hours; at 4 weeks of age, advance to 2 mg/kg/dose every 8 hours

I.V. (infants unable to receive oral dosing):

Full term: 1.5 mg/kg/dose every 6 hours

Infants ≥30 weeks and <35 weeks gestation at birth: 1.5 mg/kg/dose every 12 hours; at 2 weeks of age, advance to 1.5 mg/kg/dose every 8 hours

Infants <30 weeks gestation at birth: 1.5 mg/kg/dose every 12 hours; at 4 weeks of age, advance to 1.5 mg/kg/dose every 8 hours

Maternal: During labor and delivery, administer zidovudine I.V. at 2 mg/kg over 1 hour followed by a continuous I.V. infusion of 1 mg/kg/hour until the umbilical cord is clamped

Treatment of HIV infection: Children 6 weeks to 12 years:

Oral: Dose should be calculated by body weight (in kg) or body surface area and should not exceed the recommended adult dose. **Note:** Doses calculated by body weight may not be the same as those calculated by body surface area.

Dosing based on body surface area: 160 mg/m^2/dose every 8 hours **or** 240 mg/m^2 every 12 hours (maximum: 200 mg every 8 hours); some Working Group members use a dose of 180 mg/m^2 to 240 mg/m^2 every 12 hours when using in drug combinations with other antiretroviral compounds, but data on this dosing in children is limited.

Dosing based on weight:

4 to <9 kg: 12 mg/kg/dose twice daily **or** 8 mg/kg/dose 3 times a day

≥9 to <30 kg: 9 mg/kg/dose twice daily **or** 6 mg/kg/dose 3 times a day

≥30 kg: 300 mg twice daily **or** 200 mg 3 times a day

I.V. continuous infusion: 20 mg/m^2/hour

I.V. intermittent infusion: 120 mg/m^2/dose every 6 hours

Dosing: Renal Impairment

Cl_{cr} <15 mL/minute including hemo-/peritoneal dialysis: 100 mg (oral) or 1 mg/kg (I.V.) every 6-8 hours

Continuous arteriovenous or venovenous hemodiafiltration effects: Administer 100 mg every 8 hours

Dosing: Hepatic ImpairmentInsufficient data to make dosing recommendation.

Dosing: Adjustment for ToxicityConsider dose interruption for significant anemia (hemoglobin <7.5 g/dL or >25% reduction from baseline) and/or neutropenia (granulocyte count <750 $cells/mm^3$ or >50% reduction from baseline) until evidence of recovery. Anemia associated with chronic zidovudine may warrant dose reduction.

Calculations

- Body Surface Area: Pediatrics

Administration: I.M.Do not give I.M.

Administration: I.V.Avoid rapid infusion or bolus injection

Neonates: Infuse over 30 minutes

Adults: Infuse loading dose over 1 hour, followed by continuous infusion

Administration: I.V. DetailpH: 5.5

Administration: OralAdminister around-the-clock to promote less variation in peak and trough serum levels. Oral zidovudine may be administered without regard to food.

Dietary ConsiderationsMay be taken without regard to food.

StorageStore undiluted vials at 15°C to 25°C (59°F to 77°F). Protect from light. When diluted, solution is physically and chemically stable for 24 hours at room temperature and 48 hours if refrigerated.

ReconstitutionSolution for injection should be diluted with D_5W to a concentration ≤4 mg/mL. Attempt to administer diluted solution within 8 hours if stored at room temperature or 24 hours if refrigerated to minimize potential for microbially-contaminated solutions.

CompatibilityStable in D_5W, NS.

Incompatible with blood products and protein solutions.

Y-site administration: Compatible: Acyclovir, allopurinol, amifostine, amikacin, amphotericin B, amphotericin B cholesteryl sulfate complex, aztreonam, cefepime, ceftazidime, ceftriaxone, cimetidine, cisatracurium, clindamycin, dexamethasone sodium phosphate, dobutamine, docetaxel, dopamine, doxorubicin liposome, erythromycin lactobionate, etoposide, filgrastim, fluconazole, fludarabine, gatifloxacin, gemcitabine, gentamicin, granisetron, heparin, imipenem/cilastatin, linezolid, lorazepam, melphalan, metoclopramide, morphine, nafcillin, ondansetron, oxacillin, paclitaxel, pentamidine, phenylephrine, piperacillin, piperacillin/tazobactam, potassium chloride, ranitidine, remifentanil, sargramostim, teniposide, thiotepa, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, vinorelbine. **Variable (consult detailed reference):** Meropenem, TPN.

Compatibility when admixed: Variable (consult detailed reference): Meropenem.

ContraindicationsLife-threatening hypersensitivity to zidovudine or any component of the formulation

Allergy Considerations

- Zidovudine Allergy

Warnings/Precautions

Boxed warnings:

- Hematologic toxicity: See “Concerns related to adverse effects” below.

- Lactic acidosis/hepatomegaly: See “Concerns related to adverse effects” below.

- Myopathy: See “Concerns related to adverse effects” below.

Concerns related to adverse effects:

- Fat redistribution: May cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).

- Hematologic toxicity: **[U.S. Boxed Warning]: Often associated with hematologic toxicity including granulocytopenia, severe anemia requiring transfusions, or (rarely) pancytopenia.** Use with caution in patients with bone marrow compromise (granulocytes <1000 cells/mm^3 or hemoglobin <9.5 mg/dL); dosage adjustment may be required in patients who develop anemia or neutropenia.

- Immune reconstitution syndrome: Patients may develop immune reconstitution syndrome resulting in the occurrence of an inflammatory response to an indolent or residual opportunistic infection; further evaluation and treatment may be required.

- Lactic acidosis/hepatomegaly: **[U.S Boxed Warning]: Lactic acidosis and severe hepatomegaly with steatosis have been reported with nucleoside analogues, including fatal cases;** use with caution in patients with risk factors for liver disease (risk may be increased with female gender, obesity, pregnancy or prolonged exposure) and suspend treatment in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity (transaminase elevation may/may not accompany hepatomegaly and steatosis).

- Myopathy: **[U.S. Boxed Warning]: Prolonged use has been associated with symptomatic myopathy and myositis.**

Disease-related concerns:

- Renal impairment: Use with caution in patients with severe renal impairment; dosage adjustment recommended.

Concurrent drug therapy issues:

- Interferon alfa: Use with caution in combination with interferon alfa with or without ribavirin in HIV/HBV coinfected patients; monitor closely for hepatic decompensation, anemia, or neutropenia; dose reduction or discontinuation of interferon and/or ribavirin may be required if toxicity evident.

Pregnancy Risk FactorC

Pregnancy ConsiderationsZidovudine crosses the placenta. No increased risk of overall birth defects has been observed following 1st trimester exposure according to data collected by the antiretroviral pregnancy registry. The use of zidovudine reduces the maternal-fetal transmission of HIV by ~70% and should be considered for antenatal and intrapartum therapy whenever possible. The Perinatal HIV Guidelines Working Group considers zidovudine the preferred NRTI for use in combination regimens during pregnancy. In HIV-infected mothers not previously on antiretroviral therapy, treatment may be delayed until after 10-12 weeks gestation. Cases of lactic acidosis/hepatic steatosis syndrome have been reported in pregnant women receiving nucleoside analogues. It is not known if pregnancy itself potentiates this known side effect; however, pregnant women may be at increased risk of lactic acidosis and liver damage. Hepatic enzymes and electrolytes should be monitored frequently during the 3rd trimester of pregnancy in women receiving nucleoside analogues. Women in labor with an unknown HIV status should have a rapid HIV test. If the test is positive, begin I.V. zidovudine therapy. (If a postpartum confirmatory test is negative, zidovudine therapy in the infant can be stopped). Health professionals are encouraged to contact the antiretroviral pregnancy registry to monitor outcomes of pregnant women exposed to antiretroviral medications (1-800-258-4263 or www.APRegistry.com).

LactationEnters breast milk/contraindicated

Breast-Feeding ConsiderationsHIV-infected mothers are discouraged from breast-feeding to decrease potential transmission of HIV.

Adverse ReactionsAs reported in adult patients with asymptomatic HIV infection. Frequency and severity may increase with advanced disease.

>10%:

Central nervous system: Headache (63%), malaise (53%)

Gastrointestinal: Nausea (51%), anorexia (20%), vomiting (17%)

1% to 10%:

Gastrointestinal: Constipation (6%)

Hematologic: Granulocytopenia (2%; onset 6-8 weeks), anemia (1%; onset 2-4 weeks)

Hepatic: Transaminases increased (1% to 3%)

Neuromuscular & skeletal: Weakness (9%)

Frequency not defined:

Cardiovascular: Cardiomyopathy, chest pain, syncope, vasculitis

Central nervous system: Anxiety, chills, confusion, depression, dizziness, fatigue, insomnia, loss of mental acuity, mania, seizure, somnolence, vertigo

Dermatologic: Pruritus, rash, skin/nail pigmentation changes, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Endocrine & metabolic: Body fat redistribution, gynecomastia

Gastrointestinal: Abdominal cramps, abdominal pain, dyspepsia, dysphagia, flatulence, mouth ulcer, oral mucosa pigmentation, pancreatitis, taste perversion

Genitourinary: Urinary frequency, urinary hesitancy

Hematologic: Aplastic anemia, hemolytic anemia, leukopenia, lymphadenopathy, pancytopenia with marrow hypoplasia, pure red cell aplasia

Hepatic: Hepatitis, hepatomegaly with steatosis, hyperbilirubinemia, jaundice, lactic acidosis

Neuromuscular & skeletal: Arthralgia, back pain, CPK increased, LDH increased, musculoskeletal pain, myalgia, neuropathy, muscle spasm, myopathy, myositis, paresthesia, rhabdomyolysis, tremor

Ocular: Amblyopia, macular edema, photophobia

Otic: Hearing loss

Respiratory: Cough, dyspnea, rhinitis, sinusitis

Miscellaneous: Allergic reactions, anaphylaxis, angioedema, diaphoresis, flu-like syndrome, immune reconstitution syndrome

Metabolism/Transport Effects **Substrate** (minor) of CYP2A6, 2C9, 2C19, 3A4

Drug Interactions

Acyclovir-Valacyclovir: May enhance the CNS depressant effect of Zidovudine. *Risk C: Monitor therapy*

DOXOrubicin: May enhance the adverse/toxic effect of Zidovudine. DOXOrubicin may diminish the therapeutic effect of Zidovudine. *Risk D: Consider therapy modification*

DOXOrubicin (Liposomal): May enhance the adverse/toxic effect of Zidovudine. DOXOrubicin (Liposomal) may diminish the therapeutic effect of Zidovudine. *Risk D: Consider therapy modification*

Fluconazole: May decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Ganciclovir-Valganciclovir: May enhance the adverse/toxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Hematologic toxicity is of specific concern. *Risk D: Consider therapy modification*

Interferons: May enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Methadone: May increase the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Probenecid: May decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Protease Inhibitors: May decrease the serum concentration of Zidovudine. *Risk C: Monitor therapy*

Ribavirin: May enhance the hepatotoxic effect of Reverse Transcriptase Inhibitors (Nucleoside). Lactic acidosis may occur. *Risk D: Consider therapy modification*

Rifamycin Derivatives: May increase the metabolism of Zidovudine. **Exceptions:** Rifabutin. *Risk D: Consider therapy modification*

Stavudine: Zidovudine may diminish the therapeutic effect of Stavudine. *Risk D: Consider therapy modification*

Valproic Acid: May decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

Monitoring Parameters Monitor CBC and platelet count at least every 2 weeks, liver function tests, MCV, serum creatinine kinase, viral load, and CD4 count; observe for appearance of opportunistic infections

Nursing: Physical Assessment/Monitoring Assess closely for any previous allergy history prior to beginning treatment. Use caution in presence of bone marrow compromise, risk factors for liver disease, or renal impairment; dose reduction may be necessary. Assess other pharmacological or herbal products patient may be taking (eg, increased risk of nephrotoxicity, hepatotoxicity, lactic acidosis), especially those that increase risk of peripheral neuropathy. Assess results of laboratory tests (CD4 count and viral load, CBC and platelet count, LFTs), therapeutic response, and adverse reactions on a regular basis throughout therapy (eg, lactic acidosis [elevated transaminases], anemia, neutropenia, hepatic decompensation, gastrointestinal disturbance [nausea, vomiting, diarrhea], myalgia, peripheral neuropathy). Teach patient proper use (eg, timing of multiple medications and drugs that should not be used concurrently), possible side effects/appropriate interventions, and adverse symptoms to report.

Monitoring: Lab Tests Monitor CBC and platelet count at least every 2 weeks, liver function tests, MCV, serum creatinine kinase, CD4 cell count, viral load

Patient Education Do not take any new prescription or over-the-counter medications or herbal products during therapy without consulting prescriber. This drug will not cure HIV, nor has it been found to reduce transmission of HIV; use appropriate precautions to prevent spread to other persons. This drug is prescribed as one part of a multidrug combination; take exactly as directed for full course of therapy. Maintain adequate hydration (2-3 L/day of fluids) unless advised by prescriber to restrict fluids. Avoid alcohol to decrease risk of hypersensitivity reaction. You may be susceptible to infection (avoid crowds and exposure to known infections and do not have any vaccinations without consulting prescriber). Frequent blood tests may be required with prolonged therapy. May cause body changes due to redistribution of body fat, facial atrophy, or breast enlargement (normal effects of drug). May cause headache, dizziness, or weakness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea or vomiting; mouth sores (small, frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); constipation (increased dietary fluid and fibers may help); CNS changes (anxiety, chills, confusion, depression, loss of mental acuity, or seizures - contact prescriber); or back or muscle pain (if persistent contact prescriber for appropriate analgesic). Report excessive fatigue, easy bruising or bleeding, change in urinary pattern, dark urine or light stool, chest pain or palpitations, rash or skin sores, muscle or bone pain, or tremor. **Note:** Stop drug and report immediately symptoms of hypersensitivity/allergic reaction (eg, swelling of lips, face, mouth or throat; rash; difficulty breathing or chest tightness; excessive sweating; numbness or loss of sensation). Do not restart without specific instruction by your prescriber. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule:

Retrovir®: 100 mg

Injection, solution [preservative free]:

Retrovir®: 10 mg/mL (20 mL)

Syrup:

Retrovir®: 50 mg/5 mL (240 mL) [contains sodium benzoate; strawberry flavor]

Tablet: 300 mg

Retrovir®: 300 mg

Generic AvailableYes: Tablet
Pricing: U.S. (www.drugstore.com)

Capsules (Retrovir)

100 mg (180): $415.46

Syrup (Retrovir)

50 mg/5 mL (240): $59.14

Tablets (Retrovir)

300 mg (60): $418.15

Tablets (Zidovudine)

300 mg (60): $170.00

Mechanism of ActionZidovudine is a thymidine analog which interferes with the HIV viral RNA-dependent DNA polymerase resulting in inhibition of viral replication; nucleoside reverse transcriptase inhibitor
Pharmacodynamics/Kinetics

Distribution: Significant penetration into the CSF; crosses placenta

V_d: 1-2.2 L/kg

Relative diffusion from blood into CSF: Adequate with or without inflammation (exceeds usual MICs)

CSF:blood level ratio: Normal meninges: ~60%

Protein binding: 25% to 38%

Metabolism: Hepatic via glucuronidation to inactive metabolites; extensive first-pass effect

Bioavailability: 54% to 74%

Half-life elimination: Terminal: 0.5-3 hours

Time to peak, serum: 30-90 minutes

Excretion:

Oral: Urine (72% to 74% as metabolites, 14% to 18% as unchanged drug)

I.V.: Urine (45% to 60% as metabolites, 18% to 29% as unchanged drug)

Related Information

- Antiretroviral Agents
- Antiretroviral Therapy for HIV Infection: Adults and Adolescents
- Management of Healthcare Worker Exposures to HBV, HCV, and HIV
- Perinatal HIV Guidelines

Pharmacotherapy PearlsPotential compliance problems, frequency of administration, and adverse effects should be discussed with patients before initiating therapy to help prevent the emergence of resistance.
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Taste perversion, oral mucosa pigmentation, dysphagia, and mouth ulcer.
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause anxiety, confusion, depression, dizziness, drowsiness, insomnia, or mania
Mental Health: Effects on Psychiatric TreatmentGranulocytopenia is common; avoid clozapine and carbamazepine. Valproic acid may decrease the clearance of zidovudine. GI side effects are common; concurrent use with SSRIs may produce additive effects.
Anesthesia and Critical Care Concerns/Other ConsiderationsDoes not reduce risk of transmitting HIV infections. Potential compliance problems, frequency of administration, and adverse effects should be discussed with patients before initiating therapy to help prevent the emergence of resistance.
Index TermsAzidothymidine; AZT (error-prone abbreviation); Compound S; ZDV
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International Brand Names Adovi (ID); Antivir (TH); Aviral (CO); Avirzid (ID); Azovir (PL); Kedu (CL); Paravir (PL); Retrovir (AE, AR, AT, AU, BB, BE, BG, BH, BM, BS, BZ, CH, CY, CZ, DE, DK, EG, ES, FI, FR, GB, GR, GY, HK, HN, ID, IE, IL, IN, IQ, IR, IT, JM, JO, KW, LB, LY, MY, NL, NO, OM, PH, PL, PT, PY, QA, RU, SA, SE, SR, SY, TH, TR, TT, TW, UY, VE, YE); Retrovir-AZT (BR, CN, MX, PE); T-Za (TH); Timivudin (MX); Zidovir (IN, TW); Zydowin (BF, BJ, CI, ET, GH, GM, GN, KE, LR, MA, ML, MR, MU, MW, NE, NG, SC, SD, SL, SN, TN, TZ, UG, ZA, ZM, ZW)

Zileuton

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(zye LOO ton)
U.S. Brand NamesZyflo CR™; Zyflo® [DSC]
Pharmacologic Category5-Lipoxygenase Inhibitor
Use: Labeled IndicationsProphylaxis and chronic treatment of asthma in children ≥12 years of age and adults
Dosing: Adults**Asthma:** Oral:

Zyflo®: 600 mg 4 times/day

Zyflo CR™: 1200 mg twice daily

Dosing: ElderlyRefer to adult dosing.
Dosing: Pediatric**Asthma:** Oral:

Children <12 years: Safety and effectiveness have not been established.

Children ≥12 years: Refer to adult dosing.

Dosing: Renal ImpairmentAdjustment not necessary in renal failure or with hemodialysis.
Dosing: Hepatic ImpairmentContraindicated with hepatic dysfunction.
Administration: OralZyflo®: Administer without regard to meals (eg, with or without food). Zyflo CR™: Do not crush, cut, or chew tablet; administer with food.
Dietary ConsiderationsZyflo®: May be taken with or without food; Zyflo CR™: Take with food.
StorageStore tablets at 15°C to 30°C (59°F to 86°F). Protect from light.
ContraindicationsHypersensitivity to zileuton or any component of the formulation; active liver disease or transaminase elevations greater than or equal to three times the upper limit of normal (≥3 times ULN)
Warnings/Precautions

Concerns related to adverse effects:

- Hepatotoxicity: There have been reports of hepatic adverse effects (elevated transaminase levels); serum ALT should be monitored. Females >65 years and patients with pre-existing elevated transaminases may be at greater risk. Discontinue therapy and follow transaminases until normal if patients develop clinical signs/symptoms of liver dysfunction or with transaminase levels >5 times ULN; use caution with history of liver disease and/or in those patients who consume substantial quantities of ethanol.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <12 years of age.

Other warnings/precautions:

- Reversal of bronchospasm: Not FDA approved for the reversal of bronchospasm in acute asthma attacks, including status asthmaticus; therapy may be continued during acute asthma exacerbations.

Geriatric ConsiderationsNo differences in the pharmacokinetics found between younger adults and elderly; no dosage adjustments necessary. However, monitor liver effects closely as with any patient regardless of age.
Pregnancy Risk FactorC
Pregnancy ConsiderationsIn developmental studies, reduced body weight and increased skeletal variations were observed in rats. There are no adequate and well-controlled studies in pregnant women.
LactationExcretion in breast milk unknown/not recommended
Breast-Feeding ConsiderationsDue to the potential tumorigenicity of zileuton in animal studies, the manufacturer does not recommend breast-feeding.
Adverse Reactions

>10%: Central nervous system: Headache (23% to 25%)

1% to 10%:

Central nervous system: Pain (8%)

Dermatologic: Rash

Gastrointestinal: Dyspepsia (8%), nausea (6%), abdominal pain (5%), diarrhea, vomiting

Hematologic: Leukopenia (1% to 3%)

Hepatic: ALT increased (2% to 3%)

Neuromuscular & skeletal: Asthenia (4%), myalgia (3%)

Respiratory: Pharyngitis, sinusitis, upper respiratory tract infection

Miscellaneous: Hypersensitivity reactions

Frequency not defined:

Cardiovascular: Chest pain

Central nervous system: Dizziness, fever, insomnia, malaise, nervousness, somnolence

Dermatologic: Pruritus

Gastrointestinal: Constipation, flatulence

Genitourinary: Urinary tract infection, vaginitis

Neuromuscular & skeletal: Arthralgia, hypertonia, neck pain/rigidity

Ocular: Conjunctivitis

Miscellaneous: Lymphadenopathy

Postmarketing and/or case reports: Behavior/mood changes, hepatitis, hyperbilirubinemia, jaundice, liver failure, suicidality, suicide, urticaria

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 2C9, 3A4; **Inhibits** CYP1A2 (moderate)

Drug Interactions

Propranolol: Zileuton may increase the serum concentration of Propranolol. *Risk C: Monitor therapy*

Theophylline: Zileuton may increase the serum concentration of Theophylline. *Risk D: Consider therapy modification*

Warfarin: Zileuton may increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression; may increase risk of hepatic toxicity).

Food:

Zyflo CR™: Improved absorption when administered with food.

Zyflo®: Absorption not improved when taken with food.

Herb/Nutraceutical: St John's wort may decrease zileuton levels.

Monitoring ParametersEvaluate hepatic transaminases at initiation of, and during therapy. Monitor serum ALT before treatment begins, once-a-month for the first 3 months, every 2-3 months for the remainder of the first year, and periodically thereafter for patients receiving long-term zileuton therapy. If symptoms of liver dysfunction (right upper quadrant pain, nausea, fatigue, lethargy, pruritus, jaundice, or “flu-like” symptoms) develop or transaminase elevations >5 times ULN occur, discontinue therapy and follow transaminase levels until normal.

Nursing: Physical Assessment/MonitoringNot for use to relieve acute asthmatic attacks. Assess effectiveness and interactions of other medications patient may be taking. Monitor results of laboratory tests, therapeutic effectiveness, and adverse reactions at beginning of therapy and periodically with long-term use. For inpatient care, monitor vital signs and lung sounds prior to and periodically during therapy. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsLiver function tests

Patient EducationThis medication is not for an acute asthmatic attack; in acute attack, follow instructions of prescriber. Do not stop other asthma medication unless advised by prescriber. Do not discontinue, even if feeling better (this medication may help reduce incidence of acute attacks). Avoid alcohol and other medications unless approved by your prescriber. You may experience mild headache (mild analgesic may help); fatigue or dizziness (use caution when driving); or nausea or heartburn (small frequent meals, frequent mouth care, sucking lozenges, or chewing gum may help). Report persistent headache, chest pain, rapid heartbeat, or palpitations; skin rash or itching; unusual bleeding (eg, tarry stools, easy bruising, or blood in stool, urine, or mouth); skin rash or irritation; muscle weakness or tremors; redness, irritation, or infections of the eye; flu-like symptoms; itching; jaundice or dark urine; or worsening of asthmatic condition. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Tablet:

Zyflo®: 600 mg [DSC]

Tablet, extended release:

Zyflo CR™: 600 mg

Generic AvailableNo

ManufacturerCritical Therapeutics, Inc

Pricing: U.S. (www.drugstore.com)

Tablet, 12-hour (Zyflo CR)

600 mg (120): $276.00

Tablets (Zyflo)

600 mg (120): $280.00

Mechanism of Action Specific 5-lipoxygenase inhibitor which inhibits leukotriene formation. Leukotrienes augment neutrophil and eosinophil migration, neutrophil and monocyte aggregation, leukocyte adhesion, increased capillary permeability, and smooth muscle contraction (which contribute to inflammation, edema, mucous secretion, and bronchoconstriction in the airway of the asthmatic.)
Pharmacodynamics/Kinetics

Absorption: Rapid

Distribution: 1.2 L/kg

Protein binding: 93%

Metabolism: Hepatic and gastrointestinal; zileuton and N-dehydroxylated metabolite can be metabolized by CYP1A2, 2C9, and 3A4

Bioavailability: Unknown

Half-life elimination: ~3 hours

Time to peak, serum: 1.7 hours

Excretion: Urine (~95% primarily as metabolites); feces (~2%)

Related Information

- Asthma

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusMay cause dizziness, drowsiness, insomnia, or nervousness
Mental Health: Effects on Psychiatric TreatmentConcurrent use with propranolol may enhance beta-blocker activity

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Zinc Chloride

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(zink KLOR ide)

Pharmacologic CategoryTrace Element

Use: Labeled IndicationsCofactor for replacement therapy to different enzymes; helps maintain normal growth rates, normal skin hydration, and senses of taste and smell

Dosing: Adults

Nutritional supplement: I.V.:

> *Stable with fluid loss from small bowel:* 12.2 mg zinc/L TPN or 17.1 mg zinc/kg (added to 1000 mL I.V. fluids) of stool or ileostomy output
>
> *Metabolically stable:* 2.5-4 mg/day, add 2 mg/day for acute catabolic states

Note: Clinical response may not occur for up to 6-8 weeks.

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Nutritional supplement: I.V.: Added to I.V. solutions:

> Premature Infants <1500 g, up to 3 kg: 300 mcg/kg/day
>
> Infants (full term) and Children â¤5 years: 100 mcg/kg/day

Pregnancy Risk FactorC

Adverse Reactions<1%: Hypotension, indigestion, jaundice, leukopenia, nausea, neutropenia, pulmonary edema, vomiting

Drug Interactions

Quinolone Antibiotics: Zinc Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Zinc Salts. Zinc Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution [preservative free]: 1 mg/mL (10 mL, 50 mL)

Generic AvailableYes

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

International Brand NamesTracefusin (MX)

Jump To Field (Select Field Name)

Pronunciation(zink JEL ah tin)
U.S. Brand NamesGelucast®
Pharmacologic CategoryTopical Skin Product
Use: Labeled IndicationsAs a protectant and to support varicosities and similar lesions of the lower limbs
Dosing: Adults

Protectant: Topical: Apply externally as an occlusive boot

Dosing: ElderlyRefer to adult dosing.
ContraindicationsHypersensitivity to zinc gelatin or to any component of the formulation
Adverse Reactions1% to 10%: Local: Irritation
Drug InteractionsThere are no known significant interactions.
Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Bandage: 3” x 10 yards; 4” x 10 yards

Generic AvailableYes
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
Mental Health: Effects on Mental StatusNone reported
Mental Health: Effects on Psychiatric TreatmentNone reported
Index TermsDome Paste Bandage; Unna's Boot; Unna's Paste; Zinc Gelatin Boot

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Zinc Oxide

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Pronunciation(zink OKS ide)

U.S. Brand NamesAmmens® Medicated Deodorant [OTC]; Balmex® [OTC]; Boudreaux's® Butt Paste [OTC]; Critic-Aid Skin Care® [OTC]; Desitin® Creamy [OTC]; Desitin® [OTC]

Canadian Brand NamesZincofax®

Pharmacologic CategoryTopical Skin Product

Use: Labeled IndicationsProtective coating for mild skin irritations and abrasions; soothing and protective ointment to promote healing of chapped skin, diaper rash

Dosing: Adults

Protectant: Topical: Apply as required to affected areas several times daily

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric**Protectant:** Topical: Apply as required to affected areas several times daily

StorageAvoid prolonged storage at temperatures >30°C.

ContraindicationsHypersensitivity to zinc oxide or any component of the formulation

Adverse Reactions1% to 10%: Local: Skin sensitivity, irritation

Drug InteractionsThere are no known significant interactions.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Cream:

Balmex®: 11.3% (60 g, 120 g, 480 g) [contains aloe and vitamin E]

Ointment, topical: 20% (30 g, 60 g, 454 g); 40% (120 g)

Desitin®: 40% (30 g, 60 g, 90 g, 120 g, 270 g, 480 g) [contains cod liver oil and lanolin]

Desitin® Creamy: 10% (60 g, 120 g)

Paste, topical:

Boudreaux's® Butt Paste: 16% (30 g, 60 g, 120 g, 480 g) [contains castor oil, boric acid, mineral oil, and Peruvian balsam]

Critic-Aid Skin Care®: 20% (71 g, 170 g)

Powder, topical (Ammens® Medicated Deodorant): 9.1% (187.5 g, 330 g) [original and shower fresh scent]

Generic AvailableYes: Ointment

Pricing: U.S. (www.drugstore.com)

Ointment (Zinc Oxide)

20% (30): $8.99

Mechanism of ActionMild astringent with weak antiseptic properties

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsBase Ointment; Lassar's Zinc Paste

International Brand NamesDesitin (MX); Pasta de Lassar (MX); Pasta Zinci (PL); Unguentum Zinci Oxydati (PL)

Zinc Sulfate

Lexi-Drugs Online

English English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

$ZnSO_4$ is an error-prone abbreviation (mistaken as morphine sulfate)

Pronunciation(zink SUL fate)

U.S. Brand NamesOrazinc® [OTC]; Zincate®

Canadian Brand NamesAnuzinc; Rivasol

Pharmacologic CategoryTrace Element

Use: Labeled IndicationsZinc supplement (oral and parenteral); may improve wound healing in those who are deficient

Dosing: Adults

Recommended Daily Allowance (RDA): Oral: 15 mg elemental zinc/day

Zinc deficiency: Oral: 110-220 mg zinc sulfate (25-50 mg elemental zinc)/dose 3 times/day

Parenteral TPN: I.V.:

Acute metabolic states: 4.5-6 mg/day

Metabolically stable: 2.5-4 mg/day

Stable with fluid loss from the small bowel: 12.2 mg zinc/L of TPN solution, or an additional 17.1 mg zinc (added to 1000 mL I.V. fluids) per kg of stool or ileostomy output

Dosing: ElderlyRefer to adult dosing.

Dosing: Pediatric

Recommended daily allowance (RDA): Oral:

Birth to 6 months: 3 mg elemental zinc/day

6-12 months: 5 mg elemental zinc/day

1-10 years: 10 mg elemental zinc/day

≥11 years: 15 mg elemental zinc/day

Zinc deficiency: Oral: Infants and Children: 0.5-1 mg elemental zinc/kg/day divided 1-3 times/day; somewhat larger quantities may be needed if there is impaired intestinal absorption or an excessive loss of zinc

Parenteral TPN: I.V.:

Infants (premature, birth weight <1500 g up to 3 kg): 300 mcg/kg/day

Infants (full term) and Children ≤5 years: 100 mcg/kg/day

Dietary ConsiderationsMay be taken with food if GI upset occurs.

StorageStore oral liquid (injectable used orally) in refrigerator.

Geriatric ConsiderationsMay be useful to promote wound healing in patients with pressure sores.

Pregnancy Risk FactorC

Adverse ReactionsFrequency not defined.

Central nervous system: Dizziness, restlessness

Gastrointestinal: Diarrhea, gastric ulcers, nausea, vomiting

Drug Interactions

Quinolone Antibiotics: Zinc Salts may decrease the absorption of Quinolone Antibiotics. Of concern only with oral administration of both agents. *Risk D: Consider therapy modification*

Tetracycline Derivatives: Zinc Salts may decrease the absorption of Tetracycline Derivatives. Only a concern when both products are administered orally. **Exceptions:** Doxycycline. *Risk D: Consider therapy modification*

Trientine: May decrease the serum concentration of Zinc Salts. Zinc Salts may decrease the serum concentration of Trientine. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb InteractionsFood: Avoid foods high in calcium or phosphorus.

Patient EducationTake with food if GI upset occurs, but avoid foods high in calcium, phosphorus, or phytate. Do not exceed recommended dose. Notify prescriber if irritation persists or continues with ophthalmic use.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule (Orazinc®, Zincate®): 220 mg [elemental zinc 50 mg]

Injection, solution [preservative free]: 1 mg elemental zinc/mL (10 mL); 5 mg elemental zinc/mL (5 mL)

Tablet (Orazinc®): 110 mg [elemental zinc 25 mg]

Generic AvailableYes

Pricing: U.S. (www.drugstore.com)

Capsules (Zinc)

50 mg (100): $13.99

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index Terms$ZnSO_4$ (error-prone abbreviation)

International Brand NamesAfazol Z (MX); Dalidome (MX); Daribur (MX); Exastrin (MX); Vytral (MX); Zincteral (PL)

Ziprasidone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

ALERT: U.S. Boxed WarningThe FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Special Alerts

Antipsychotics (Conventional and Atypical): Association With an Increased Risk of Mortality in Elderly Patients Treated for Dementia-Related Psychosis - June 2008

The Food and Drug Administration (FDA) is notifying healthcare professionals that conventional antipsychotics (eg, haloperidol, fluphenazine) will now carry a similar boxed warning as atypical antipsychotics (eg, risperidone, aripiprazole) concerning an increased risk of mortality in elderly patients treated for dementia-related psychosis. Atypical antipsychotics received the boxed warning in April 2005 after study data from seven placebo-controlled trials indicated an increased risk of death in patients treated with certain atypicals for dementia-related behavioral disorders.

The FDA requirement to extend the warning to conventional antipsychotics was prompted by two recently published observational studies. Both studies revealed an increased risk of mortality in elderly patients treated with these medications. One of the two studies was a retrospective cohort study which examined 37,241 patients, ≥65 years of age, treated with antipsychotics. Of these patients, 12,882 received a conventional antipsychotic compared to 24,359 patients who received an atypical antipsychotic. All-cause mortality within the first 180 days of use was compared between the two groups. The results showed that the risk of death in patients who received a conventional-type antipsychotic was comparable to (and may be greater than) the risk of death in patients receiving an atypical. The second study was also a retrospective cohort study; it involved 27,259 matched pairs of patients, ≥66 years of age, diagnosed with dementia. Risk of death was compared in patients who received an atypical antipsychotic versus no antipsychotic, and in patients who received a conventional antipsychotic versus an atypical antipsychotic. An increased risk of death was observed in the groups receiving an atypical antipsychotic compared to no antipsychotic and also in patients receiving a conventional antipsychotic compared to patients receiving an atypical antipsychotic. This effect was seen at 30 days and persisted at 180 days, and was seen in both community-dwelling and long-term care facility patients.

The FDA believes that considering all the available evidence, conventional antipsychotics at least share a similar increased risk of death that has been observed with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. The FDA is reminding practitioners that antipsychotic medications are not approved for the treatment of dementia-related psychosis. Elderly patients treated with antipsychotics, conventional or atypical, are at an increased risk of death. Practitioners prescribing antipsychotics to elderly patients for this purpose should inform the patient and their caregivers of this risk prior to prescribing.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antipsychotics

References:

Gill SS, Bronskill SE, Normand SL, et al, “Antipsychotic Drug Use and Mortality in Older Adults With Dementia,” *Ann Intern Med*, 2007, 146(11):775-86.[PubMed 17548409]

Schneeweiss S, Setoguchi S, Brookhart A, et al, “Risk of Death Associated With the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients,” *CMAJ*, 2007, 176(5): 627-32.[PubMed 17325327]

Pronunciation(zi PRAS i done)

U.S. Brand NamesGeodon®

Canadian Brand NamesZeldox®

Pharmacologic CategoryAntipsychotic Agent, Atypical

Use: Labeled IndicationsTreatment of schizophrenia; treatment of acute manic or mixed episodes associated with bipolar disorder with or without psychosis; acute agitation in patients with schizophrenia

Use: Unlabeled/InvestigationalTourette's syndrome; psychosis/agitation related to Alzheimer's dementia

Dosing: Adults

Bipolar mania: Oral: Initial: 40 mg twice daily (with food)

Adjustment: May increase to 60 or 80 mg twice daily on second day of treatment; average dose 40-80 mg twice daily.

Schizophrenia: Oral: Initial: 20 mg twice daily (with food)

Adjustment: Increases (if indicated) should be made no more frequently than every 2 days; ordinarily patients should be observed for improvement over several weeks before adjusting the dose.

Maintenance: Range 20-100 mg twice daily; however, dosages >80 mg twice daily are generally not recommended.

Acute agitation (schizophrenia): I.M.: 10 mg every 2 hours **or** 20 mg every 4 hours (maximum: 40 mg/day). Oral therapy should replace I.M. administration as soon as possible.

Dosing: ElderlyNo dosage adjustment is recommended; consider initiating at a low end of the dosage range, with slower titration.
Dosing: Pediatric

Tourette's syndrome (unlabeled use): Children and adolescents: Oral: 5-40 mg/day

Dosing: Renal Impairment

Oral: No dosage adjustment is recommended

I.M.: Cyclodextrin, an excipient in the I.M. formulation, is cleared by renal filtration; use with caution.

Ziprasidone is not removed by hemodialysis.

Dosing: Hepatic ImpairmentNo adjustment necessary.
Administration: I.M.Injection: For I.M. administration only.
Administration: OralAdminister with food.
Storage

Capsule: Store at controlled room temperature of 15°C to 30°C (59°F to 86°F).

Vials for injection: Prior to reconstitution, store at controlled room temperature of 15°C to 30°C (59°F to 86°F). Protect from light. Following reconstitution, injection may be stored at room temperature up to 24 hours or up to 7 days if refrigerated. Protect from light.

ReconstitutionEach vial should be reconstituted with 1.2 mL SWI. Shake vigorously. Will form a pale, pink solution containing 20 mg/mL ziprasidone.
ContraindicationsHypersensitivity to ziprasidone or any component of the formulation; history (or current) prolonged QT; congenital long QT syndrome; recent myocardial infarction; history of arrhythmias; uncompensated heart failure; concurrent use of other QT_c-prolonging agents including amiodarone, arsenic trioxide, bretylium, chlorpromazine, cisapride, class Ia antiarrhythmics (quinidine, procainamide), dofetilide, dolasetron, droperidol, ibutilide, levomethadyl, mefloquine, mesoridazine, pentamidine, pimozide, probucol, some quinolone antibiotics (moxifloxacin), sotalol, tacrolimus, and thioridazine
Warnings/Precautions

Boxed warnings:

- Dementia: See “Disease-related concerns” below.

Concerns related to adverse effects:

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).

- Extrapyramidal symptoms (EPS): May cause extrapyramidal symptoms, including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is generally much lower relative to typical/conventional antipsychotics). Risk of dystonia (and probably other EPS) may be greater with increased doses, use of conventional antipsychotics, males, and younger patients.

- Hyperglycemia: Atypical antipsychotics have been associated with development of hyperglycemia; in some cases, may be extreme and associated with ketoacidosis, hyperosmolar coma, or death. Use with caution in patients with diabetes or other disorders of glucose regulation; monitor for worsening of glucose control. There is limited documentation with ziprasidone and specific risk associated with this agent is not known.

- Neuroleptic malignant syndrome (NMS): Use may be associated with neuroleptic malignant syndrome (NMS); monitor for mental status changes, fever, muscle rigidity and/or autonomic instability.

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- QT prolongation: May result in QT_c prolongation (dose related), which has been associated with the development of malignant ventricular arrhythmias (torsade de pointes) and sudden death. Observed prolongation was greater than with other atypical antipsychotic agents (risperidone, olanzapine, quetiapine), but less than with thioridazine. Avoid hypokalemia, hypomagnesemia. Use caution in patients with bradycardia. Discontinue in patients found to have persistent QT_c intervals >500 msec. Patients with symptoms of dizziness, palpitations, or syncope should receive further cardiac evaluation. Also see Contraindications.

- Rash: Use has been associated with a fairly high incidence of rash (5%); discontinue if alternative etiology is not identified.

- Sedation: Moderate to highly sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Suicidal ideation: The possibility of a suicide attempt is inherent in psychotic illness or bipolar disorder; use with caution in high-risk patients during initiation of therapy. Prescriptions should be written for the smallest quantity consistent with good patient care.

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects; not reported in premarketing trials of ziprasidone.

- Weight gain: Significant weight gain has been observed with antipsychotic therapy; incidence varies with product. Monitor waist circumference and BMI.

Disease-related concerns:

- Dementia: **[U.S. Boxed Warning]: Elderly patients with dementia-related behavioral disorders treated with atypical antipsychotics are at an increased risk of death compared to placebo.** An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Ziprasidone is not approved for this indication.

- Hepatic impairment: Use with caution in patients with hepatic disease or impairment.

- Parkinson's disease: Use with caution in patients with Parkinson's disease.

- Prolactin-dependent tumors: Use caution in breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Renal impairment: Use with caution in patients with renal impairment.

- Seizures: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage, alcoholism, or concurrent therapy with medications which may lower seizure threshold. Elderly patients may be at increased risk of seizures due to an increased prevalence of predisposing factors.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Geriatric ConsiderationsExtrapyramidal syndrome symptoms occur less with this agent than phenothiazine and butyrophenone classes of antipsychotics.

Many elderly patients receive antipsychotic medications for inappropriate nonpsychotic behavior. Before initiating antipsychotic medication, the clinician should investigate any possible reversible cause; any stress or stress from any disease can cause acute “confusion” or worsening of baseline nonpsychotic behavior. Most commonly, acute changes in behavior are due to increases in drug dose or addition of a new drug to regimen, fluid electrolyte loss, infection, and changes in environment. Any changes in disease status and any organ system can result in behavior changes.

In the treatment of agitated, demented, elderly patients, authors of meta-analysis of controlled trials of the response to the traditional antipsychotics (phenothiazines, butyrophenones) in controlling agitation have concluded that the use of neuroleptics results in a response rate of 18%. Clearly, neuroleptic therapy for behavior control should be limited with frequent attempts to withdraw the agent given for behavior control. In light of significant risks and adverse effects in elderly population compared with limited data demonstrating efficacy in the treatment of dementia related psychosis, aggression, and agitation, an extensive risk:benefit analysis should be performed prior to use.

Since diabetes is prevalent in elderly, monitor closely when using this agent in this population.

Pregnancy Risk FactorC

Pregnancy ConsiderationsDevelopmental toxicity demonstrated in animals. There are no adequate and well-controlled studies in pregnant women. Use only if potential benefit justifies risk to the fetus. Healthcare providers are encouraged to enroll women 18-45 years of age exposed to ziprasidone during pregnancy in the Atypical Antipsychotics Pregnancy Registry (1-866-961-2388).

LactationExcretion in breast milk unknown/not recommended

Adverse Reactions**Note:** Although minor QT_c prolongation (mean: 10 msec at 160 mg/day) may occur more frequently (incidence not specified), clinically-relevant prolongation (>500 msec) was rare (0.06%) and less than placebo (0.23%).

>10%:

Central nervous system: Extrapyramidal symptoms (2% to 31%), somnolence (8% to 31%), headache (3% to 18%), dizziness (3% to 16%)

Gastrointestinal: Nausea (4% to 12%)

1% to 10%:

Cardiovascular: Chest pain (5%), postural hypotension (5%), hypertension (2% to 3%), bradycardia (2%), tachycardia (2%), vasodilation (1%), facial edema, orthostatic hypotension

Central nervous system: Akathisia (2% to 10%), anxiety (2% to 5%), insomnia (3%), agitation (2%), speech disorder (2%), personality disorder (2%), psychosis (1%), akinesia, amnesia, ataxia, chills, confusion, coordination abnormal, delirium, dystonia, fever, hostility, hypothermia, oculogyric crisis, vertigo

Dermatologic: Rash (4%), fungal dermatitis (2%)

Endocrine & metabolic: Dysmenorrhea (2%)

Gastrointestinal: Weight gain (10%), constipation (2% to 9%), dyspepsia (1% to 8%), diarrhea (3% to 5%), vomiting (3% to 5%), salivation increased (4%), xerostomia (1% to 5%), tongue edema (3%), abdominal pain (2%), anorexia (2%), dysphagia (2%), rectal hemorrhage (2%), tooth disorder (1%), buccoglossal syndrome

Genitourinary: Priapism (1%)

Local: Injection site pain (7% to 9%)

Neuromuscular & skeletal: Weakness (2% to 6%), hypoesthesia (2%), myalgia (2%), paresthesia (2%), back pain (1%), cogwheel rigidity (1%), hypertonia (1%), abnormal gait, choreoathetosis, dysarthria, dyskinesia, hyper-/hypokinesia, hypotonia, neuropathy, tremor, twitching

Ocular: Vision abnormal (3% to 6%), diplopia

Respiratory: Infection (8%), rhinitis (1% to 4%), cough (3%), pharyngitis (3%), dyspnea (2%)

Miscellaneous: Diaphoresis (2%), furunculosis (2%), flu-like syndrome (1%), photosensitivity reaction, withdrawal syndrome

<1%, postmarketing, and/or case reports: Abnormal ejaculation, abnormal gait, accidental fall, akinesia, albuminuria, alkaline phosphatase increased, allergic reaction, alopecia, amenorrhea, amnesia, anemia, angina, anorgasmia, atrial fibrillation, ataxia, AV block (first degree), basophilia, blepharitis, BUN increased, bundle branch block, cardiomegaly, cataract, cerebral infarction, chills, cholestatic jaundice, choreoathetosis, circumoral paresthesia, confusion, conjunctivitis, contact dermatitis, CPK increased, creatinine (serum) increased, dehydration, delirium, dry eyes, dysphagia, ecchymosis, eczema, enuresis, eosinophilia, epistaxis, exfoliative dermatitis, facial droop, facial palsy/paresis, fatty liver, fecal impaction, fever, flank pain, galactorrhea, GGT increased, gingival bleeding, gout, gynecomastia, hematemesis, hemoptysis, hematuria, hepatitis, hepatomegaly, hostility, hypercholesterolemia, hyper-/hypoglycemia, hyper-/hypokalemia, hyperlipemia, hyper-/hypothyroidism, hyperuricemia, hypoesthesia, hypocalcemia, hypokinesia, hypomagnesemia, hyponatremia, hypoproteinemia, hypotonia, jaundice, keratitis, keratoconjunctivitis, ketosis, lactation (female), laryngismus, LDH increased, leukocytosis, leukoplakia (mouth), lymphadenopathy, lymphedema, lymphocytosis, maculopapular rash, mania/hypomania, melena, menorrhagia, metrorrhagia, monocytosis, motor vehicle accident, myocarditis, myoclonus, myopathy, neuroleptic malignant syndrome, neuropathy, nocturia, nystagmus, ocular hemorrhage, phlebitis, polycythemia, oliguria, opisthotonos, peripheral edema, photophobia, pneumonia, polyuria, pulmonary embolism, QT_c prolongation >500 msec (0.06%), respiratory alkalosis, seizure (0.4%), sexual dysfunction (male and female), stroke, syncope (0.6%), tardive dyskinesia, tenosynovitis, thirst, thrombocytopenia, thrombocythemia, thrombophlebitis, thyroiditis, tinnitus, torsade de pointes, torticollis, transaminases increased, tremor, trismus, urinary incontinence, urinary retention, urticaria, uterine hemorrhage, vaginal hemorrhage, vertigo, vesiculobullous rash, visual field defect

Metabolism/Transport Effects**Substrate** (minor) of CYP1A2, 3A4; **Inhibits** CYP2D6 (weak), 3A4 (weak)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Ziprasidone. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Atypical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

CarBAMazepine: May increase the metabolism of Ziprasidone. *Risk C: Monitor therapy*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents: May enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Administration with food increases serum levels twofold. Grapefruit juice may increase serum concentration of ziprasidone.

Herb/Nutraceutical: St John's wort may decrease serum levels of ziprasidone, due to a potential effect on CYP3A4. This has not been specifically studied. Avoid kava kava, chamomile (may increase CNS depression).

Test InteractionsIncreased cholesterol, triglycerides, eosinophils

Monitoring ParametersVital signs; serum potassium and magnesium; fasting lipid profile and fasting blood glucose/Hgb A_{1c} (prior to treatment, at 3 months, then annually); BMI, personal/family history of obesity, waist circumference; blood pressure; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms. Weight should be assessed prior to treatment, at 4 weeks, 8 weeks, 12 weeks, and then at quarterly intervals. Consider titrating to a different antipsychotic agent for a weight gain ≥5% of the initial weight. The value of routine ECG screening or monitoring has not been established.

Nursing: Physical Assessment/MonitoringAssess seizure risk (seizure history, ethanol use, head trauma, brain damage, or current therapy with medications that reduce seizure threshold) and cardiac status (bradycardia, QT prolongation) before starting therapy. Assess other medications patient may be taking for effectiveness and interactions (especially those dependent on cytochrome P450 metabolism). Monitor closely for therapeutic effectiveness and adverse reactions at beginning and at regular periods throughout therapy. Monitor weight prior to initiating therapy and at least monthly. Consider titrating to a different antipsychotic agent for a weight gain ≥5% of initial weight. Assess knowledge/teach appropriate use of this medication, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsSerum potassium and magnesium; fasting lipid profile and fasting blood glucose, Hgb A_{1c} (prior to treatment, at 3 months, then annually).

Patient EducationUse this mediation exactly as directed; do not alter dosage or discontinue without consulting prescriber; may take 2-3 weeks to achieve desired results. Do not share this medication with anyone else. Avoid alcohol, caffeine, other prescription or OTC medication unless approved by prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. If you have diabetes, you may experience increased blood sugars. Monitor blood sugars closely. You may experience drowsiness, lightheadedness, impaired coordination, dizziness, or blurred vision (use caution when driving or engaging in tasks hazardous tasks until response to drug is known); dry mouth, nausea, or GI upset (small frequent meals, good mouth care, sucking lozenges or chewing gum may help); postural hypotension (rise slowly when changing position from lying or sitting to standing or when climbing stairs); urinary retention (void before taking medication); or constipation (increased exercise, fluids, fruit, or fiber may help). Report immediately persistent CNS effects (eg, trembling, altered gait or balance, excessive sedation, seizures, unusual muscle or skeletal movements, excessive anxiety, hallucinations, nightmares, suicidal thoughts, or confusion); swelling or pain in breasts (male or female); altered menstrual pattern; sexual dysfunction; alteration in urinary pattern; vision changes; rash; respiratory difficulty; or chest pain or palpitations. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule, as hydrochloride: 20 mg, 40 mg, 60 mg, 80 mg

Injection, powder for reconstitution, as mesylate: 20 mg

Generic AvailableNo

ManufacturerPfizer U.S. Pharmaceuticals Group

Pricing: U.S. (www.drugstore.com)

Capsules (Geodon)

20 mg (60): $361.86

40 mg (60): $365.96

60 mg (60): $435.20

80 mg (60): $435.20

Mechanism of ActionZiprasidone is a benzylisothiazolylpiperazine antipsychotic. The exact mechanism of action is unknown. However, *in vitro* radioligand studies show that ziprasidone has high affinity for D_2, D_3, 5-HT_{2A}, 5-HT_{1A}, 5-HT_{2C}, 5-HT_{1D}, and alpha$_1$-adrenergic; moderate affinity for histamine H_1 receptors; and no appreciable affinity for alpha$_2$-adrenergic receptors, beta-adrenergic, 5-HT_3, 5-HT_4, cholinergic, mu, sigma, or benzodiazepine receptors. Ziprasidone functions as an antagonist at the D_2, 5-HT_{2A}, and 5-HT_{1D} receptors and as an agonist at the 5-HT_{1A} receptor. Ziprasidone moderately inhibits the reuptake of serotonin and norepinephrine.

Pharmacodynamics/Kinetics

Absorption: Well absorbed

Distribution: V_d: 1.5 L/kg

Protein binding: 99%, primarily to albumin and alpha$_1$-acid glycoprotein

Metabolism: Extensively hepatic, primarily via aldehyde oxidase; less than $^1/_3$ of total metabolism via CYP3A4 and CYP1A2 (minor)

Bioavailability: Oral (with food): 60% (up to twofold increase with food); I.M.: 100%

Half-life elimination: Oral: 7 hours; I.M.: 2-5 hours

Time to peak: Oral: 6-8 hours; I.M.: ≤60 minutes

Excretion: Feces (66%) and urine (20%) as metabolites; little as unchanged drug (1% urine, 4% feces)

Clearance: 7.5 mL/minute/kg

Related Information

- Agents Approved for Bipolar Disorder
- Antipsychotic Agents
- Antipsychotic Receptor Profile
- Atypical Antipsychotics
- CMS: Long-Term Care Facility Thresholds
- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsThe increased potential to prolong QT_c, as compared to other available antipsychotic agents, should be considered in the evaluation of available alternatives.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia and changes in salivation (normal salivary flow resumes upon discontinuation), orthostatic hypotension, tongue edema, dysphagia, and tooth disorder.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsZiprasidone is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.

Mental Health: Child/Adolescent Considerations Twenty-eight children 7-17 years of age with Tourette's syndrome and chronic tic disorder were randomly assigned to ziprasidone or placebo for 56 days. Ziprasidone was initiated at 5 mg/day and titrated to a maximum of 40 mg/day (Sallee, 2000).

An open-label trial of ziprasidone in 10 children and adolescents with pervasive developmental disorder showed 50% of patients as "much improved" at the end of the study (McDougle, 2002). Study duration averaged 14 weeks (range: 6-30 weeks) with an initial ziprasidone dosage of 20 mg twice daily, titrated up to an average maintenance of 30 mg twice daily (range: 20-120 mg/day). Sedation was the most common adverse reaction and no cardiovascular events (including QT prolongation) were noted.

McDougle CJ, Kem DL, and Posey DJ, “Case Series: Use of Ziprasidone for Maladaptive Symptoms in Youths With Autism,” *J Am Acad Child Adolesc Psychiatry*, 2002, 41(8):921-7.

Sallee FR, Kurlan R, Goetz CG, et al, “Ziprasidone Treatment of Children and Adolescents With Tourette's Syndrome: A Pilot Study,” *J Am Acad Child Adolesc Psychiatry*, 2000, 39(3):292-9.

Mental Health Comment Ziprasidone is an antipsychotic agent of a class often referred to as atypical. It should be noted that the definition of the term “atypical” is not universally agreed upon. Some prefer to describe antipsychotics based on their pharmacological properties. A common feature of all definitions used to describe “atypical” antipsychotics is the lack of significant acute or subacute EPS, at dosages generally associated with antipsychotic actions. Other experts have included definitions of atypicality that include a) failure to increase serum prolactin levels; b) superior efficacy for positive, negative, and cognitive symptoms; and c) lack of evidence of tardive dyskinesia or dystonia following chronic administration. Clinically, the dose range for ziprasidone appears to be higher than the approved range (40-160 mg/day); minimum effective dose for most patients is 120 mg/day. Therefore, appropriate dosing with this compound is important. It is also important that this medication be taken with a 500 calorie meal as the bioavailability is increased 100% in the presence of food.

The short-acting I.M. formulation appears to be as efficacious as other available agents for the management of acute agitation; however, comparative trials have not been conducted.

Tardive dyskinesia (TD) secondary to **typical** antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. The incidence of TD associated with the atypical antipsychotics is estimated to be 0.5% to 1%. It is not clear if this estimate represents a risk associated with mental illness or to what extent drug therapy can be implicated. Atypical antipsychotics appear less likely to cause tardive dyskinesia than typical antipsychotics (fluphenazine, haloperidol).

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Index Terms Zeldox; Ziprasidone Hydrochloride; Ziprasidone Mesylate

References

American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity, “Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes,” *Diabetes Care*, 2004, 27(2):596-601. [PubMed 14747245]

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Sallee FR, Kurlan R, Goetz CG, et al, “Ziprasidone Treatment of Children and Adolescents With Tourette's Syndrome: A Pilot Study,” *J Am Acad Child Adolesc Psychiatry*, 2000, 39(3):292-9.[PubMed 10714048]

International Brand Names Azona (IN); Geodon (BR, CO, CR, ES, GT, HN, IE, IL, MX, NI, PA, SV, TW, VE, ZA); Zeldox (AR, AU, BG, BR, CL, CN, CZ, DE, DK, EE, ES, FI, HK, HN, MY, NO, NZ, PE, PH, PL, PT, SE, SG, TH, UY)

Zoledronic Acid

Lexi-Drugs Online

English

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Special Alerts

Bisphosphonates: Safety Update Regarding Possible Association With Atrial Fibrillation - November 2008

The Food and Drug Administration (FDA) has been reviewing placebo-controlled trials of the 7 bisphosphonates currently marketed in the US. This review is in response to study results associating an increased incidence of atrial fibrillation (AF) with alendronate or zoledronic acid use in women (65-89 years of age) with osteoporosis.

The FDA reviewed all the submitted data (19,687 bisphosphonate-treated patients and 18,358 placebo-treated patients) from these studies. Overall, the occurrence of AF was rare in each study with an absolute difference in event rates between each of the bisphosphonate and placebo arms of 0-3 per 1000. A zoledronic acid study showed a statistically significant increase in the rate of AF in the active treatment arm. However, no clear association between bisphosphonate use and AF could be established. In this study, AF events were diagnosed more than 30 days after receiving zoledronic acid in 47 of the 50 patients diagnosed with AF. According to the FDA, healthcare providers should not alter their prescribing patterns for bisphosphonates and patients should not stop taking their medication.

The FDA will continue monitoring the safety of bisphosphonates through postmarketing reports and is assessing the need for additional epidemiologic studies.

Further information is available at http://www.fda.gov/cder/drug/early_comm/bisphosphonates_update_200811.htm

Medication Safety Issues

Sound-alike/look-alike issues:

Zometa® may be confused with Zofran®, Zoladex®

Pronunciation(zoe le DRON ik AS id)

U.S. Brand NamesReclast®; Zometa®

Canadian Brand NamesAclasta®; Zometa®

Pharmacologic CategoryAntidote; Bisphosphonate Derivative

Use: Labeled IndicationsTreatment of hypercalcemia of malignancy (albumin-corrected serum calcium ≥12 mg/dL), multiple myeloma, bone metastases of solid tumors, Paget's disease of bone; osteoporosis (to reduce the incidence of fractures in postmenopausal women with osteoporosis or to reduce the incidence of new clinical fractures in patients with low-trauma hip fracture)

Use: Unlabeled/InvestigationalPrevention of bone loss associated with aromatase inhibitor therapy in postmenopausal women with breast cancer; prevention of bone loss associated with androgen deprivation therapy in prostate cancer

Dosing: Adults**Note:** Patients treated for multiple myeloma, osteoporosis, and Paget's disease should receive a daily calcium supplement and multivitamin containing vitamin D (if dietary intake is inadequate)

Hypercalcemia of malignancy (albumin-corrected serum calcium ≥12 mg/dL): I.V. (Zometa®): 4 mg (maximum) given as a single dose. Wait at least 7 days before considering retreatment. Dosage adjustment may be needed in patients with decreased renal function following treatment.

Multiple myeloma or metastatic bone lesions from solid tumors: I.V. (Zometa®): 4 mg every 3-4 weeks

Osteoporosis (Reclast®, Aclasta® [CAN]): 5 mg infused over at least 15 minutes every 12 months

Paget's disease (Reclast®, Aclasta® [CAN]): 5 mg infused over at least 15 minutes. **Note:** Data concerning retreatment is not available.

Prevention of aromatase inhibitor-induced bone loss in breast cancer (unlabeled use): 4 mg every 6 months

Prevention of androgen deprivation-induced bone loss in nonmetastatic prostate cancer (unlabeled use): 4 mg every 3-12 months

Dosing: ElderlyRefer to adult dosing.

Dosing: Renal Impairment

Reclast®: Cl_{cr} <35 mL/minute: Not recommended

Zometa®: Multiple myeloma and bone metastases (at treatment initiation):

Cl_{cr} >60 mL/minute: 4 mg

Cl_{cr} 50-60 mL/minute: 3.5 mg

Cl_{cr} 40-49 mL/minute: 3.3 mg

Cl_{cr} 30-39 mL/minute: 3 mg

Cl_{cr} <30 mL/minute: Not recommended

Zometa®: Hypercalcemia of malignancy (at treatment initiation):

Mild-to-moderate impairment: No adjustment necessary

Severe impairment (serum creatinine >4.5 mg/dL): Evaluate risk versus benefit

Aclasta® [CAN]:

Cl_{cr} ≥30 mL/minute: No adjustment recommended

Cl_{cr} <30 mL/minute: Use is not recommended

Renal toxicity (during treatment):

Hypercalcemia of malignancy: Evidence of renal deterioration: Evaluate risk versus benefit.

Multiple myeloma and bone metastases: Evidence of renal deterioration: Withhold dose until renal function returns to within 10% of baseline: renal deterioration defined as follows:

Normal baseline creatinine: Increase of 0.5 mg/dL

Abnormal baseline creatinine: Increase of 1 mg/dL

Reinitiate dose at the same dose administered prior to treatment interruption.

Dosing: Hepatic ImpairmentSpecific guidelines are not available.

Calculations

- Calcium Correction
- Creatinine Clearance: Adults

Administration: I.V.Infuse over 15-30 minutes; do not infuse over <15 minutes.

Reclast®: If refrigerated, allow to reach room temperature prior to administration. Acetaminophen or ibuprofen after administration may reduce the incidence of acute reaction (eg, arthralgia, fever, flu-like symptoms, myalgia).

Administration: I.V. DetailInfuse in a line separate from other medications. Patients should be appropriately hydrated prior to treatment.

Zometa®: pH: 2

Reclast®, Aclasta® [CAN]: pH 6-7 (infusion)

Dietary Considerations

Multiple myeloma or metastatic bone lesions from solid tumors: Take daily calcium supplement (500 mg) and daily multivitamin (with 400 int. units vitamin D).

Osteoporosis: Ensure adequate calcium and vitamin D supplementation. Postmenopausal women generally require calcium 1200 mg/day and vitamin D 800-1000 int. units/day.

Paget's disease: Take calcium 1500 mg/day and vitamin D 800 units/day, particularly during the first 2 weeks after administration.

Storage

Aclasta® [CAN]: Store at room temperature of 15°C to 30°C (59°F to 86°F).

Reclast®: Store at room temperature of 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). After opening, stable for 24 hours at 2°C to 8°C (36°F to 46°F).

Zometa®: Store vials at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Solutions for infusion may be stored for 24 hours at 15°C to 30°C (59°F to 86°F). Infusion of solution must be completed within 24 hours.

ReconstitutionZometa®: Dilute solution for injection in 100 mL NS or D_5W prior to administration.

Compatibility**Incompatible** with calcium-containing solutions (eg, LR).

ContraindicationsHypersensitivity to zoledronic acid, other bisphosphonates, or any component of the formulation; hypocalcemia (Reclast®)

Note: In Canada, Aclasta® is also contraindicated with uncorrected hypocalcemia at the time of infusion and in pregnancy and breast-feeding.

Allergy Considerations

- Bisphosphonate Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Bone/joint/muscle pain: Infrequently, severe (and occasionally debilitating) bone, joint, and/or muscle pain have been reported during bisphosphonate treatment. The onset of pain ranged from a single day to several months. Symptoms usually resolve upon discontinuation. Some patients experienced recurrence when rechallenged with same drug or another bisphosphonate; avoid use in patients with a history of these symptoms in association with bisphosphonate therapy.

- Osteonecrosis of the jaw: Bisphosphonate therapy has been associated with osteonecrosis, primarily of the jaw; this has been observed mostly in cancer patients, but also in patients with postmenopausal osteoporosis and other diagnoses. Risk factors include a diagnosis of cancer, with concomitant chemotherapy, radiotherapy, or corticosteroids; anemia, coagulopathy, infection, or pre-existing dental disease. Symptoms included nonhealing extraction socket or an exposed jawbone. There are no data addressing whether discontinuation of therapy reduces the risk of developing osteonecrosis; however, as a precautionary measure, dental exams and preventative dentistry should be performed prior to placing patients with risk factors on chronic bisphosphonate therapy. Invasive dental procedures should be avoided during treatment.

- Renal deterioration: Single and multiple infusions have been associated with renal deterioration, resulting in renal failure and dialysis; has occurred in patients with normal and impaired renal function.

Disease-related concerns:

- Aspirin-sensitive asthma: Use with caution in patients with aspirin-sensitive asthma; may cause bronchoconstriction.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Hypocalcemia: May cause hypocalcemia in patients with Paget’s disease, in whom the pretreatment rate of bone turnover may be greatly elevated. Hypocalcemia must be corrected before initiation of therapy in patients with Paget's disease and osteoporosis. Ensure adequate calcium and vitamin D intake during therapy. Use caution in patients with disturbances of calcium and mineral metabolism (eg, hypoparathyroidism, thyroid surgery, malabsorption syndromes).

- Renal impairment: Use with caution in renal impairment. Dehydration and concurrent use of other nephrotoxic drugs may increase the risk for renal impairment. Adequate hydration is required during treatment (urine output ~2 L/day); avoid overhydration, especially in patients with heart failure.

  Reclast®: Use is not recommended in patients with severe renal impairment (Cl_{cr} <35 mL/minute).

  Zometa®: Dosage adjustment required with renal impairment. Use is not recommended in patients with severe renal impairment (serum creatinine >3 mg/dL) and bone metastases (limited data); use in patients with hypercalcemia of malignancy and severe renal impairment should only be done if the benefits outweigh the risks. In cancer patients, renal toxicity has been reported with doses >4 mg or infusions administered over 15 minutes. Risk factors for renal deterioration include pre-existing renal insufficiency and repeated doses and other bisphosphonates therapy. Dehydration and the use of other nephrotoxic drugs which may contribute to renal deterioration should be identified and managed. Diuretics should not be used before correcting hypovolemia. Renal function should be assessed prior to treatment; if decreased after treatment, additional treatments should be withheld until renal function returns to within 10% of baseline.

  Aclasta® [CAN; not available in U.S.]: Use is not recommended in patients with severe renal impairment (Cl_{cr} <30 mL/minute).

Special populations:

- Elderly: Use with caution in the elderly due to the possibility for decreased renal function; monitor.

- Pediatrics: Not approved for use in children.

- Women of childbearing age: Advise women of childbearing age against becoming pregnant.

Dosage form specific issues:

- Aclasta® [CAN], Reclast®: When used in the treatment of Paget's disease, significant renal deterioration has not been observed with the usual 5 mg dose administered over at least 15 minutes.

Geriatric ConsiderationsThis drug requires adequate hydration and adjustments for creatinine clearance for its use. Elderly are often volume depleted secondary to drugs and a blunted thirst reflex. See disease related concerns in Dosage: Renal Impairment.

Pregnancy Risk FactorD

Pregnancy ConsiderationsAnimal studies resulted in embryotoxicity and losses. Zoledronic acid should not be used during pregnancy; may cause fetal harm if administered to a pregnant woman. Bisphosphonates are incorporated into the bone matrix and gradually released over time. Theoretically, there may be a risk of fetal harm when pregnancy follows the completion of therapy. Based on limited case reports with pamidronate, serum calcium levels in the newborn may be altered if administered during pregnancy.

LactationExcretion in breast milk unknown/not recommended

Breast-Feeding ConsiderationsBecause it binds to bone long term, zoledronic acid use is not recommended in nursing women.

Adverse Reactions**Note:** An acute reaction (eg, arthralgia, fever, flu-like symptoms, myalgia) may occur within the first 3 days following infusion in up to 44% of patients; usually resolves within 3-4 days of onset, although may take up to 14 days to resolve. The incidence may be decreased with acetaminophen (prior to infusion and for 72 hours postinfusion).

Zometa®:

>10%:

Cardiovascular: Leg edema (5% to 21%), hypotension (11%)

Central nervous system: Fatigue (39%), fever (32% to 44%), headache (5% to 19%), dizziness (18%), insomnia (15% to 16%), anxiety (11% to 14%), depression (14%), agitation (13%), confusion (7% to 13%), hypoesthesia (12%)

Dermatologic: Alopecia (12%), dermatitis (11%)

Endocrine & metabolic: Dehydration (5% to 14%), hypophosphatemia (12% to 13%), hypokalemia (12%), hypomagnesemia (11%)

Gastrointestinal: Nausea (29% to 46%), constipation (27% to 31%), vomiting (14% to 32%), diarrhea (17% to 24%), anorexia (9% to 22%), abdominal pain (14% to 16%), weight loss (16%), appetite decreased (13%)

Genitourinary: Urinary tract infection (12% to 14%)

Hematologic: Anemia (22% to 33%), neutropenia (12%)

Neuromuscular & skeletal: Bone pain (55%), weakness (5% to 24%), myalgia (23%), arthralgia (5% to 21%), back pain (15%), paresthesia (15%), limb pain (14%), skeletal pain (12%), rigors (11%)

Renal: Renal deterioration (8% to 17%; up to 40% in patients with abnormal baseline creatinine)

Respiratory: Dyspnea (22% to 27%), cough (12% to 22%)

Miscellaneous: Cancer progression (16%), moniliasis (12%)

1% to 10%:

Cardiovascular: Chest pain (5% to 10%)

Central nervous system: Somnolence (5% to 10%)

Endocrine & metabolic: Hypocalcemia (5% to 10%; grades 3/4: ≤1%), hypermagnesemia (2%)

Gastrointestinal: Dysphagia (5% to 10%), dyspepsia (10%), mucositis (5% to 10%), stomatitis (8%), sore throat (8%)

Hematologic: Thrombocytopenia (5% to 10%), pancytopenia (5% to 10%), granulocytopenia (5% to 10%)

Renal: Serum creatinine increased (grades 3/4: 2%)

Respiratory: Pleural effusion, upper respiratory tract infection (10%)

Miscellaneous: Metastases (5% to 10%), nonspecific infection (5% to 10%)

Reclast®:

>10%:

Cardiovascular: Hypertension (7% to 13%)

Central nervous system: Fever (9% to 18%), headache (4% to 12%)

Neuromuscular & skeletal: Arthralgia (9% to 24%), myalgia (5% to 12%), limb pain (6% to 11%)

Miscellaneous: Flu-like syndrome (1% to 11%)

1% to 10%:

Cardiovascular: Peripheral edema (3% to 6%), atrial fibrillation (2% to 3%)

Central nervous system: Dizziness (2% to 9%), fatigue (2% to 8%), chills (2% to 5%), lethargy (5%), pain (2% to 5%), malaise (1% to 2%), hyperthermia (≤2%)

Dermatologic: Rash (3%)

Endocrine & metabolic: Hypocalcemia (≤3%)

Gastrointestinal: Nausea (5% to 9%), constipation (6%), diarrhea (5% to 6%), dyspepsia (2% to 5%), vomiting (2% to 5%), abdominal pain (1% to 5%), abdominal distension (2%), anorexia (1% to 2%)

Neuromuscular & skeletal: Bone pain (3% to 9%), rigors (8%), shoulder pain (≤7%), weakness (2% to 5%), back pain (4%), muscle spasm (2% to 4%), musculoskeletal pain (≤3%), muscle stiffness (2%), paresthesia (2%)

Renal: Serum creatinine increased (2%)

Respiratory: Dyspnea (5%)

Zometa® and/or Reclast®: <1%, postmarketing, and/or case reports: Allergic reaction, anaphylactic reaction/shock, angioneurotic edema, arrhythmia, blurred vision, bradycardia, bronchoconstriction, conjunctivitis, diaphoresis, episcleritis; flu-like syndrome (fever, chills, flushing, bone pain, arthralgia, myalgia); hematuria, hyperesthesia, hyperkalemia, hypernatremia, hypersensitivity, hypertension; injection site reaction (eg, itching, pain, redness); iritis, joint and/or muscle pain (sometimes severe and/or incapacitating), muscle cramps, osteonecrosis (primarily of the jaws), proteinuria, pruritus, rash, renal failure, renal impairment, taste perversion, tremor, urticaria, uveitis, weight gain, xerostomia

Oncology: VesicantNo

Oncology: Emetic PotentialVery low (<10%)

Drug Interactions

Aminoglycosides: May enhance the hypocalcemic effect of Bisphosphonate Derivatives. *Risk C: Monitor therapy*

Nonsteroidal Anti-Inflammatory Agents: May enhance the adverse/toxic effect of Bisphosphonate Derivatives. Both an increased risk of gastrointestinal ulceration and an increased risk of nephrotoxicity are of concern. *Risk C: Monitor therapy*

Phosphate Supplements: Bisphosphonate Derivatives may enhance the hypocalcemic effect of Phosphate Supplements. *Risk C: Monitor therapy*

Thalidomide: May enhance the adverse/toxic effect of Zoledronic Acid. *Risk C: Monitor therapy*

Test InteractionsBisphosphonates may interfere with diagnostic imaging agents such as technetium-99m-diphosphonate in bone scans.

Monitoring ParametersPrior to initiation of therapy, dental exam and preventative dentistry for patients at risk for osteonecrosis

Aclasta® [CAN]: Serum creatinine, calcium and vitamin D levels

Reclast®: Alkaline phosphatase, serum creatinine (prior to each dose and periodically thereafter in high risk patients), calcium and mineral (phosphorus and magnesium) levels

Zometa®: Serum creatinine prior to each dose; serum electrolytes, phosphate, magnesium, and hemoglobin/hematocrit should be evaluated regularly. Monitor serum calcium to assess response and avoid overtreatment.

Nursing: Physical Assessment/MonitoringRenal function and risk factors for osteonecrosis should be evaluated prior to beginning therapy. Patients at risk for osteonecrosis (eg, chemotherapy, corticosteroids, poor oral hygiene) should have dental exams and necessary preventive dentistry should be done before beginning bisphosphonate therapy. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, other nephrotoxic agents). Evaluate results of laboratory tests and patient response on a regular basis during therapy. Teach patient possible side effects/appropriate interventions (eg, need for adequate hydration) and adverse symptoms to report.

Monitoring: Lab Tests

Aclasta® [CAN]: Serum creatinine, calcium and vitamin D levels

Reclast®: Alkaline phosphatase, serum creatinine (prior to each dose and periodically thereafter in high risk patients), calcium and mineral (phosphorus and magnesium) levels

Zometa®: Serum creatinine prior to each dose; serum electrolytes, phosphate, magnesium, and hemoglobin/hematocrit should be evaluated regularly. Monitor serum calcium to assess response and avoid overtreatment.

Patient EducationThis medication is only administered by infusion or injection; report burning, redness, or pain at infusion/injection site immediately. Maintain adequate hydration (2-3 L/day of fluids unless instructed to restrict fluid intake). Certain dental procedures should be avoided if possible while you are taking this medication; consult prescriber. You may experience a brief reaction (3-14 days), including fever, flu-like symptoms, nausea, vomiting, or loss of appetite (small, frequent meals, good mouth care, sucking lozenges, or chewing gum may help); headache, dizziness, insomnia, confusion (use caution when driving or engaging in tasks that require alertness until response to drug is known); or muscle, joint, or recurrent bone pain (consult prescriber for appropriate analgesic). Report difficulty breathing; chest pain; persistent CNS changes (fatigue, depression, insomnia, agitation, dizziness); unusual muscle twitching or spasms; swollen legs; severe diarrhea/constipation; acute bone, joint, or muscle pain; changes in urinary pattern; skin rash; burning or itching on urination; or any other persistent adverse effects. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not get pregnant during therapy. Consult prescriber for instructions on appropriate contraceptive measures. This drug may cause fetal defects. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Infusion, solution [premixed]:

Aclasta® [CAN]: 5 mg (100 mL) [not available in U.S.]

Reclast®: 5 mg (100 mL)

Injection, solution:

Zometa®: 4 mg/5 mL (5 mL) [as monohydrate 4.264 mg]

Generic AvailableNo

ManufacturerNovartis Pharmaceuticals Corp

Pricing: U.S. (www.drugstore.com)

Concentrate (Zometa)

4 mg/5 mL (5): $984.99

Solution (Reclast)

5 mg/100 mL (30): $353.49

Mechanism of ActionA bisphosphonate which inhibits bone resorption via actions on osteoclasts or on osteoclast precursors; inhibits osteoclastic activity and skeletal calcium release induced by tumors. Decreases serum calcium and phosphorus, and increases their elimination. In osteoporosis, zoledronic acid inhibits osteoclast-mediated resorption, therefore reducing bone turnover.

Pharmacodynamics/Kinetics

Distribution: Binds to bone

Protein binding: 28% to 53%

Half-life elimination: Triphasic; Terminal: 146 hours

Excretion: Urine (39% ± 16% as unchanged drug) within 24 hours; feces (<3%)

Dental Health Professional ConsiderationsNovartis Pharmaceuticals Corporation has notified dental health professionals of the risk of **osteonecrosis of the jaw (ONJ)** and the use of the intravenous bisphosphonates, pamidronate (Zometa®) and zoledronic acid (Aredia®): *"Dear Dental Health Professional" Letter Issued for Intravenous Bisphosphonates, Pamidronate and Zoledronic Acid, Regarding the Risk of Osteonecrosis of the Jaw (ONJ) in Cancer Patients* – May 2005.

Often observed in patients receiving chemotherapy and corticosteroids, reports of ONJ (the majority being associated with dental procedures) have been documented in cancer patients. Dental exams and preventative dentistry should be performed prior to placing patients with risk factors (chemotherapy, corticosteroids, poor oral hygiene) on intravenous bisphosphonate therapy. Additionally, invasive dental procedures should be avoided during therapy; patients developing ONJ while on bisphosphonate therapy should not have invasive dental procedures because the condition may be exacerbated. It has not been determined whether the discontinuation of bisphosphonate therapy in patients requiring dental surgery decreases the risk of ONJ. The treating healthcare professional is encouraged to assess the benefits and risks.

Bisphosphonates are widely used in the management of metastatic bone disease to treat hypercalcemia associated with malignancies and to treat osteoporosis. It is suggested that because of the trend in the use of chronic bisphosphonate therapy, the observation of an associated risk of osteonecrosis of the jaw should alert practitioners to monitor for this previously unrecognized potential complication.

Additional information is available at http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#zometa2, or by contacting Novartis Oncology Medical Services at 1-888-669-6682.

Zoledronic acid (Reclast®) when used to prevent osteoporosis in postmenopause has not been shown to increase the risk of developing ONJ when given as a 15-minute I.V. infusion once annually.

Estimates of Percent Incidence of ONJ in Treated Cancer Patients

Two reports have attempted to assess the percent of cancer patients developing ONJ after bisphosphonate treatment. Maerevoet et al, reported that among 194 patients treated with Zometa® every 3-4 weeks, nine developed ONJ. Before receiving Zometa®, six had received Aredia® 90 mg every 3-4 weeks. The median duration of treatment with Aredia® was 39 months and for Zometa® 18 months. The incidence of ONJ in these patients was calculated to be 4.6%. Durie et al, described the results of a survey by the International Myeloma Foundation in 2004 to assess the risk factors of ONJ. Out of 1203 respondents, 904 had myeloma and 299 breast cancer. Of the myeloma patients, 62 developed ONJ and 54 had suspicious findings. Of the breast cancer patients, 13 had ONJ and 23 had suspicious findings. The total number of cases of either ONJ or suspicious findings was 152. ONJ developed in 10% of 211 patients receiving Zometa® compared to 4% of 413 receiving Aredia®. The mean time to onset of ONJ among patients taking Zometa® was 18 months; the mean time to onset after Aredia® was 6 years. It should be noted that an early report by authors from Novartis Pharmaceuticals Corporation (Tarassoff, 2003) stressed that Aredia® and Zometa® had been used in 2.5 million patients world wide and reports of ONJ during their extensive use had been rare. In addition, these authors stated that review of the reported cases revealed multiple risk factors for avascular necrosis. McMahon et al, followed up with a report that, along with other factors, bisphosphonates are additional stressors of bone health that can tip the balance to osteonecrosis. They suggested that the prevention of ONJ should be stressed such as the elimination of chronic dental infections prior to chemotherapy and bisphosphonate use in cancer patients.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Mucositis, dysphagia, stomatitis, and sore throat.

Osteonecrosis of the jaw (ONJ), generally associated with local infection and/or tooth extraction and often with delayed healing, has been reported in patients taking bisphosphonates. Most reported cases of bisphosphonate-associated osteonecrosis have been in cancer patients treated with intravenous bisphosphonates. However, some have occurred in patients with postmenopausal osteoporosis taking oral bisphosphonates. Dental surgery may exacerbate ONJ. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. See Dental Comment.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusInsomnia, anxiety, agitation, depression, and dizziness are common; may rarely cause confusion

Mental Health: Effects on Psychiatric TreatmentBisphosphonates have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. Use caution in patients receiving lithium. GI side effects are common; concomitant use with SSRIs may produce additive effects. May cause neutropenia; use caution with clozapine and carbamazepine.

Index TermsCGP-42446; NSC-721517; Zoledronate

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International Brand NamesAclasta (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HK, HN, IE, IL, IT, KP, NL, NO, NZ, PH, PT, RU, SE, TR); Blaztere (IN); Zomera (IL, TH); Zometa (AR, AT, AU, BE, BG, BO, BR, CH, CL, CN, CO, CR, CZ, DE, DK, DO, EC, ES, FI, FR, GB, GR, GT, HK, HN, ID, IE, IT, KP, MX, MY, NI, NL, NO, PA, PE, PH, PK, PL, PR, PT, PY, RU, SE, SG, SV, TR, TW, UY, VE)

Zolmitriptan

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Medication Safety Issues

Sound-alike/look-alike issues:

Zolmitriptan may be confused with SUMAtriptan

Pronunciation(zohl mi TRIP tan)

U.S. Brand NamesZomig-ZMT®; Zomig®

Canadian Brand NamesZomig®; Zomig® Nasal Spray; Zomig® Rapimelt

Pharmacologic CategoryAntimigraine Agent; Serotonin 5-HT$_{1B, 1D}$ Receptor Agonist

Use: Labeled IndicationsAcute treatment of migraine with or without aura

Dosing: Adults

Migraine headache:

Oral:

Tablet: Initial: ≤2.5 mg at the onset of migraine headache; may break 2.5 mg tablet in half

Orally-disintegrating tablet: Initial: 2.5 mg at the onset of migraine headache

Nasal spray: Initial: 1 spray (5 mg) at the onset of migraine headache

Note: Use the lowest possible dose to minimize adverse events. If the headache returns, the dose may be repeated after 2 hours; do not exceed 10 mg within a 24-hour period. Controlled trials have not established the effectiveness of a second dose if the initial one was ineffective.

Dosing: ElderlyRefer to adult dosing. No dosage adjustment needed, but elderly patients are more likely to have underlying cardiovascular disease and should have careful evaluation of cardiovascular system before prescribing.

Dosing: Renal ImpairmentNo dosage adjustment recommended. There is a 25% reduction in zolmitriptan's clearance in patients with severe renal impairment (Cl$_{cr}$ 5-25 mL/minute).

Dosing: Hepatic ImpairmentAdminister with caution in patients with liver disease, generally using doses <2.5 mg (doses <5 mg can only be achieved using oral tablets). Patients with moderate-to-severe hepatic impairment may have decreased clearance of zolmitriptan, and significant elevation in blood pressure was observed in some patients.

Administration: OralAdminister as soon as migraine headache starts. Tablets may be broken. Orally-disintegrating tablets: Must be taken whole; do not break, crush or chew. Place on tongue and allow to dissolve. Administration with liquid is not required

Administration: OtherNasal spray: Administer as soon as migraine headache starts. Blow nose gently prior to use. After removing protective cap, instill device into nostril. Block opposite nostril; breathe in gently through nose while pressing plunger of spray device. One dose (5 mg) is equal to 1 spray in 1 nostril.

StorageStore at 20°C to 25°C (68°F to 77°F). Protect from light and moisture.

ContraindicationsHypersensitivity to zolmitriptan or any component of the formulation; ischemic heart disease or vasospastic coronary artery disease, including Prinzmetal's angina; signs or symptoms of ischemic heart disease; uncontrolled hypertension; symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders; use with ergotamine derivatives (within 24 hours of); use within 24 hours of another 5-HT$_1$ agonist; concurrent administration or within 2 weeks of discontinuing an MAO inhibitor; management of hemiplegic or basilar migraine

Nasal spray: Additional contraindications with nasal spray: Cerebrovascular syndromes (eg, stroke, TIA); peripheral vascular disease (including ischemic bowel disease)

Allergy Considerations

- Serotonin 5-HT$_{1B,1D}$ Receptor Agonist Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Cardiac events: Coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia/fibrillation, cardiac arrest, and death have been reported with 5-HT$_1$ agonist administration. Patients who experience sensations of chest pain/pressure/tightness or symptoms suggestive of angina following dosing should be evaluated for coronary artery disease or Prinzmetal's angina before receiving additional doses.
- Cerebrovascular events: Cerebral/subarachnoid hemorrhage and stroke have been reported with 5-HT$_1$ agonist administration; nasal spray contraindicated in patients with cerebrovascular syndromes.

- Elevated blood pressure: Significant elevation in blood pressure, including hypertensive crisis, has also been reported on rare occasions in patients with and without a history of hypertension.

- Vasospasm-related events: Peripheral vascular ischemia and colonic ischemia have been reported with 5-HT$_1$ agonist.

- Visual effects: Rarely, partial vision loss and blindness (transient and permanent) have been reported with 5-HT$_1$ agonists.

Disease-related concerns:

- Coronary artery disease: Should not be given to patients who have risk factors for CAD (eg, hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, menopause, male >40 years of age) without adequate cardiac evaluation. Patients with suspected CAD should have cardiovascular evaluation to rule out CAD before considering use; if cardiovascular evaluation “is satisfactory,” first dose should be given in the healthcare provider's office. Periodic evaluation of cardiovascular status should be done in all patients.

- Hepatic impairment: Use with caution in patients with hepatic impairment. Drug clearance may be reduced leading to increased plasma concentrations; dosage reduction of the oral product is recommended.

Concurrent drug therapy issues:

- Serotonin syndrome: Symptoms of agitation, confusion, hallucinations, hyper-reflexia, myoclonus, shivering, and tachycardia may occur with concomitant proserotonergic drugs (eg, SSRIs/SNRIs or triptans) or agents which reduce zolmitriptan's metabolism. Concurrent use of serotonin precursors is not recommended (doses <5 mg can only be achieved using oral tablets).

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <18 years of age (oral) and <12 years of age (nasal).

Dosage form specific issues:

- Phenylalanine: Zomig-ZMT™ tablets contain phenylalanine.

Other warnings/precautions:

- Appropriate use: Only indicated for treatment of acute migraine; if a patient does not respond to the first dose, the diagnosis of migraine should be reconsidered.

Geriatric ConsiderationsNo dosage adjustment needed, but elderly patients are more likely to have underlying cardiovascular disease and should have careful evaluation of the cardiovascular system before prescribing.

Pregnancy Risk FactorC

Pregnancy ConsiderationsThere are no adequate and well-controlled studies using zolmitriptan in pregnant women. Use only if potential benefit to the mother outweighs the potential risk to the fetus. In animal studies, administration was associated with embryolethality, fetal abnormalities, and pup mortality.

LactationExcretion in breast milk unknown/use caution

Adverse ReactionsPercentages noted from oral preparations.

1% to 10%:

Cardiovascular: Chest pain (2% to 4%), palpitation (up to 2%)

Central nervous system: Dizziness (6% to 10%), somnolence (5% to 8%), pain (2% to 3%), vertigo (≤2%)

Gastrointestinal: Nausea (4% to 9%), xerostomia (3% to 5%), dyspepsia (1% to 3%), dysphagia (≤2%)

Neuromuscular & skeletal: Paresthesia (5% to 9%), weakness (3% to 9%), warm/cold sensation (5% to 7%), hypoesthesia (1% to 2%), myalgia (1% to 2%), myasthenia (up to 2%)

Miscellaneous: Neck/throat/jaw pain (4% to 10%), diaphoresis (up to 3%), allergic reaction (up to 1%)

<1%: Agitation, akathisia, alkaline phosphatase increased, amnesia, anorexia, anxiety, apathy, apnea, appetite increased, arrhythmia, arthritis, ataxia, back pain, bradycardia, bronchitis, bronchospasm, bruising, cerebral ischemia, chills, constipation, cyanosis, cystitis, depression, diplopia, dry eyes, dysmenorrhea, dystonia, ear pain, edema, emotional lability, eosinophilia, epistaxis, esophagitis, euphoria, extrasystole, eye pain, facial edema, fever, gastritis, gastroenteritis, hallucinations, hematemesis, hematuria, hiccups, hyperacusis, hyperesthesia, hyperglycemia, hyperkinesias, hypertension, hypertensive crisis, hyper-/hypotonia, insomnia, irritability, lacrimation, laryngitis, leg cramps, leukopenia, liver function abnormality, malaise, melena, miscarriage, pancreatitis, parosmia, photosensitivity, polyuria, postural hypotension, pruritus, QT prolongation, rash, syncope, tachycardia, tenosynovitis, tetany, thirst, thrombocytopenia, thrombophlebitis, tinnitus, tongue edema, twitching, ulcer, urinary frequency, urinary urgency, urticaria, voice alteration, yawning

Postmarketing and/or case reports: Anaphylactoid reaction, anaphylaxis, angina pectoris, coronary artery vasospasm, gastrointestinal infarction/necrosis, headache, ischemic colitis, MI, myocardial ischemia, serotonin syndrome, splenic infarction

Events related to other serotonin 5-HT$_{1D}$ receptor agonists: Cerebral hemorrhage, stroke, subarachnoid hemorrhage, peripheral vascular ischemia, ventricular fibrillation

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor)

Drug Interactions

Cimetidine: May increase the serum concentration of Zolmitriptan. *Risk C: Monitor therapy*

Ergot Derivatives: May enhance the vasoconstricting effect of Serotonin 5-HT1D Receptor Agonists. Serotonin 5-HT1D Receptor Agonists may enhance the vasoconstricting effect of Ergot Derivatives. *Risk X: Avoid combination*

MAO Inhibitors: May decrease the metabolism of Serotonin 5-HT1D Receptor Agonists. Management: If MAO inhibitor therapy is required, naratriptan, eletriptan or frovatriptan may be a suitable 5-HT1D agonist to employ. *Risk X: Avoid combination*

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. *Risk D: Consider therapy modification*

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb InteractionsEthanol: Limit use (may have additive CNS toxicity).

Nursing: Physical Assessment/MonitoringFor use only with a clear diagnosis of migraine headaches. Use caution in presence of cardiovascular risk factors and hepatic impairment. Assess potential for interactions with other pharmacological agents and herbal products patient may be taking (eg, ergot-containing drugs). Assess effectiveness and adverse response (eg, chest pain, nausea, dizziness, paresthesia, myalgia, pain). Teach patient proper use (according to formulation), possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis drug is to be used to reduce your migraine, not to prevent or reduce the number of attacks. Follow exact instructions for use. Remove orally-disintegrating tablet from blister package just before using, place on tongue, and allow to dissolve. Do not crush, break, or chew. Regular tablet may be broken in half for use. Do not remove protective cap from nasal spray until ready to use. Do not take within 24 hours of any other migraine medication without first consulting prescriber. If first dose brings relief, second dose may be taken anytime after 2 hours if migraine returns. If you have no relief with first dose, do not take a second dose without consulting prescriber. Do not exceed 10 mg in 24 hours. May cause dizziness or drowsiness (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or dry mouth (frequent mouth care and sucking on lozenges may help). Report immediately any chest pain, heart throbbing, or tightness in throat; swelling of eyelids, face, or lips; skin rash or hives; easy bruising; blood in urine, stool, or vomitus; pain or itching with urination; or pain, warmth, or numbness in extremities. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Consult prescriber if breast-feeding.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, intranasal [spray]:

Zomig®: 5 mg/0.1 mL (0.1 mL)

Tablet:

Zomig®: 2.5 mg, 5 mg

Tablet, orally disintegrating:

Zomig-ZMT®: 2.5 mg [contains phenylalanine 2.81 mg/tablet; orange flavor]; 5 mg [contains phenylalanine 5.62 mg/tablet; orange flavor]

Generic AvailableNo

ManufacturerAstraZeneca Pharmaceuticals LP

Pricing: U.S. (www.drugstore.com)

Solution (Zomig)

5 mg (6): $181.05

Tablet, orally-disintegrating (Zomig ZMT)

2.5 mg (6): $123.99

5 mg (3): $72.08

Tablets (Zomig)

2.5 mg (6): $125.99

5 mg (3): $70.99

Mechanism of ActionSelective agonist for serotonin (5-HT_{1B} and 5-HT_{1D} receptors) in cranial arteries to cause vasoconstriction and reduce sterile inflammation associated with antidromic neuronal transmission correlating with relief of migraine

Pharmacodynamics/Kinetics

Onset of action: 0.5-1 hour

Absorption: Well absorbed

Distribution: V_d: 7 L/kg

Protein binding: 25%

Metabolism: Converted to an active N-desmethyl metabolite (2-6 times more potent than zolmitriptan)

Bioavailability: 40%

Half-life elimination: 2.8-3.7 hours

Time to peak, serum: Tablet: 1.5 hours; Orally-disintegrating tablet and nasal spray: 3 hours

Excretion: Urine (~60% to 65% total dose); feces (30% to 40%)

Related Information

- Antimigraine Drugs: 5-HT1 Receptor Agonists

Pharmacotherapy PearlsNot recommended if the patient has risk factors for heart disease (high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, postmenopausal woman, or a male >40 years of age).

This agent is intended to relieve migraine, but not to prevent or reduce the number of attacks. Use only to treat an actual migraine attack.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and dysphagia.

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusDizziness is common, may cause drowsiness

Mental Health: Effects on Psychiatric TreatmentContraindicated with other serotonin agonists (SSRIs) and MAO inhibitors

Cardiovascular ConsiderationsCoronary vasospasm has been associated with $5\text{-HT}_{1B/1D}$ agonists. These agents are contraindicated in patients with documented ischemic of vasospastic coronary artery disease. Patients with risk factors for CAD may receive these agents, provided a cardiovascular evaluation yields satisfactory evidence that the patient is free of cardiovascular disease. In patients with risk factors for CAD, administration of the initial dose in a medically staffed/equipped facility (ie, physician's office) is recommended. In addition, ECG monitoring after the initial dose should be considered. Patients who acquire risk factors for CAD, or long-term users of agents from this class of medications, should undergo periodic cardiovascular evaluation.

Anesthesia and Critical Care Concerns/Other ConsiderationsZolmitriptan should not be used in patients with a history of vasospastic disease, Prinzmetal's angina, or any critical vascular disease.

Index Terms311C90

References

Boyer EW and Shannon M, “The Serotonin Syndrome,” *N Engl J Med*, 2005, 352(11):1112-20.[PubMed 15784664]

International Brand NamesAscotop (DE); Myslee (JP); Zomig (AT, AU, BB, BE, BF, BJ, BM, BR, BS, BZ, CH, CI, CR, CZ, DK, DO, ES, ET, FR, GB, GH, GM, GN, GT, GY, HK, HN, HU, IE, IL, IT, JM, KE, KP, LR, MA, ML, MR, MU, MW, MX, NE, NG, NI, NL, NO, PA, PE, PH, PK, PL, PT, SC, SD, SE, SG, SL, SN, SR, SV, TH, TN, TT, TZ, UG, VE, ZA, ZM, ZW); Zomig Rapimelt (EE, FI, HK, IL, SE); Zomigon (AR, UY); Zomigoro (FR)

Zolpidem

Lexi-Drugs Online

English

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Medication Safety Issues

Sound-alike/look-alike issues:

Ambien® may be confused with Ambi 10®

Pronunciation(zole PI dem)
U.S. Brand NamesAmbien CR®; Ambien®; Zolpimist®
Pharmacologic CategoryHypnotic, Nonbenzodiazepine
Use: Labeled Indications

Ambien®: Short-term treatment of insomnia (with difficulty of sleep onset)

Ambien CR®: Treatment of insomnia (with difficulty of sleep onset and/or sleep maintenance)

Use: DentalHas not been established
Dosing: Adults**Insomnia:** Oral:

Ambien®: 10 mg immediately before bedtime; maximum dose: 10 mg

Ambien CR®: 12.5 mg immediately before bedtime

Dosing: Elderly

Ambien®: 5 mg immediately before bedtime

Ambien CR®: 6.25 mg immediately before bedtime

Dosing: Renal ImpairmentDose adjustment not required; monitor closely.

Not dialyzable

Dosing: Hepatic Impairment

Ambien®: 5 mg

Ambien CR®: 6.25 mg

Administration: OralIngest immediately before bedtime due to rapid onset of action. Ambien CR® tablets should be swallowed whole; do not divide, crush, or chew.
Dietary ConsiderationsFor faster sleep onset, do not administer with (or immediately after) a meal.
StorageStore Ambien® at controlled room temperature of 20°C to 25°C (68°F to 77°F). Store Ambien CR® at controlled room temperature of 15°C to 25°C (59°F to 77°F).
RestrictionsC-IV

An FDA-approved patient medication guide is available and must be distributed when dispensing an outpatient prescription (new or refill) where this medication is to be used without direct supervision of a healthcare provider. The guide provides information about the appropriate use of zolpidem, and discusses concerns relating to "sleep-driving" and other activities of which the patient may have no recollection.

ContraindicationsHypersensitivity to zolpidem or any component of the formulation
Allergy Considerations

- Zolpidem Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Abnormal thinking/behavioral changes: Hypnotics/sedatives have been associated with abnormal thinking and behavior changes including decreased inhibition, aggression, bizarre behavior, agitation, hallucinations, and depersonalization. These changes may occur unpredictably and may indicate previously unrecognized psychiatric disorders; evaluate appropriately.

- CNS depression: May cause CNS depression impairing physical and mental capabilities; patients must be cautioned about performing tasks which require mental alertness (operating machinery or driving). Zolpidem should only be administered when the patient is able to stay in bed a full night (7-8 hours) before being active again.

- Hypersensitivity reactions: Postmarketing studies have indicated that the use of hypnotic/sedative agents for sleep has been associated with hypersensitivity reactions including anaphylaxis as well as angioedema.

- Sleep-related activities: An increased risk for hazardous sleep-related activities such as sleep-driving; cooking and eating food, and making phone calls while asleep have also been noted; amnesia may also occur. Discontinue treatment in patients who report a sleep-driving episode.

Disease-related concerns:

- Depression: Use with caution in patients with depression; worsening of depression, including suicide or suicidal ideation has been reported with the use of hypnotics. Intentional overdose may be an issue in this population. The minimum dose that will effectively treat the individual patient should be used. Prescriptions should be written for the smallest quantity consistent with good patient care.

- Drug abuse: Use with caution in patients with a history of drug dependence.

- Hepatic impairment: Use with caution in patients with hepatic impairment; dose adjustment recommended.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis.

- Respiratory disease: Use with caution in patients with respiratory compromise, COPD, or sleep apnea.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Elderly: Use with caution in the elderly; dose adjustment recommended. Closely monitor elderly or debilitated patients for impaired cognitive or motor performance.

- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Symptomatic treatment of insomnia should be initiated only after careful evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric and/or medical illness.

- Rapid onset: Because of the rapid onset of action, administer immediately prior to bedtime or after the patient has gone to bed and is having difficulty falling asleep.

- Withdrawal: Abrupt discontinuance may lead to withdrawal symptoms.

Geriatric ConsiderationsIn doses >5 mg, there was subjective evidence of impaired sleep on the first post-treatment night. There have been few reports of increased hypotension and/or falls in the elderly with this drug. Can be considered a drug of choice in the elderly when a hypnotic is indicated. With Ambien CR®, the adverse event profile of 6.25 mg in elderly patients was similar to the 12.5 mg dose in younger adults. Until there is more experience with this dosage form, use with caution in the elderly.
Pregnancy Risk FactorC
Pregnancy ConsiderationsTeratogenic effects were not observed in animal studies. Children born of mothers taking sedative/hypnotics may be at risk for withdrawal; neonatal flaccidity has been reported in infants following maternal use of sedative/hypnotics during pregnancy.
LactationEnters breast milk/not recommended (AAP rates “compatible”)
Breast-Feeding Considerations0.004% to 0.019% of the maternal dose is found in breast milk.
Adverse ReactionsActual frequency may be dosage form, dose, and/or age dependent

>10%: Central nervous system: Dizziness, headache, somnolence

1% to 10%:

Cardiovascular: Blood pressure increased, chest discomfort/pain, palpitation

Central nervous system: Abnormal dreams, anxiety, apathy, amnesia, ataxia, attention disturbance, body temperature increased, confusion, depersonalization, depression, disinhibition, disorientation, drowsiness, drugged feeling, euphoria, fatigue, fever, hallucinations, hypoesthesia, insomnia, memory disorder, lethargy, lightheadedness, mood swings, sleep disorder, stress

Dermatologic: Rash, urticaria, wrinkling

Endocrine & metabolic: Menorrhagia

Gastrointestinal: Abdominal discomfort, abdominal pain, abdominal tenderness, appetite disorder, constipation, diarrhea, dyspepsia, flatulence, gastroenteritis, gastroesophageal reflux, hiccup, nausea, vomiting, xerostomia

Genitourinary: Urinary tract infection

Neuromuscular & skeletal: Arthralgia, back pain, balance disorder, myalgia, neck pain, paresthesia, psychomotor retardation, tremor, weakness

Ocular: Asthenopia, blurred vision, depth perception altered, diplopia, visual disturbance, red eye

Otic: Labyrinthitis, tinnitus, vertigo

Renal: Dysuria

Respiratory: Pharyngitis, sinusitis, upper respiratory tract infection, throat irritation

Miscellaneous: Allergy, binge eating, flu-like syndrome

<1% (Limited to important or life-threatening): Agitation, anorexia, arthritis, bronchitis, cerebrovascular disorder, cognition decreased, concentrating difficulty, constipation, cough, cystitis, diaphoresis, dysarthria, dysphagia, dyspnea, edema, emotional lability, eye irritation, falling, hepatic function abnormalities, hyperglycemia, hyper-/hypotension, illusion, leg cramps, menstrual disorder, nervousness, pallor, postural hypotension, pruritus, rhinitis, scleritis, somnambulism (sleepwalking), speech disorder, stupor, syncope, tachycardia, taste perversion, thirst, urinary incontinence, vaginitis

Postmarketing and/or case reports: Anaphylaxis, angioedema, complex sleep-related behavior (sleep-driving, cooking or eating food, making phone calls)

Metabolism/Transport Effects**Substrate** of CYP1A2 (minor), 2C9 (minor), 2C19 (minor), 2D6 (minor), 3A4 (major)

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Zolpidem. **Exceptions:** Miconazole. *Risk D: Consider therapy modification*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Flumazenil: May diminish the sedative effect of Hypnotics (Nonbenzodiazepine). *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Rifamycin Derivatives: May increase the metabolism of Zolpidem. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: May enhance the adverse/toxic effects of zolpidem; avoid use.

Food: Maximum plasma concentration and bioavailability are decreased with food; time to peak plasma concentration is increased; half-life remains unchanged. Grapefruit juice may decrease the metabolism of zolpidem.

Herb/Nutraceutical: St John's wort may decrease the levels/effects of zolpidem; avoid concomitant use. In addition, concomitant use of valerian, kava kava, and gotu kola should be avoided due to the risk of increased CNS depression.

Monitoring ParametersDaytime alertness; respiratory rate; behavior profile

Reference Range80-150 ng/mL

Nursing: Physical Assessment/MonitoringFor short-term use. Assess effectiveness and interactions of other medications patient may be taking. Assess for history of addiction; long-term use can result in dependence, abuse, or tolerance; periodically evaluate need for continued use. After long-term use, taper dosage slowly when discontinuing. Be alert to possibility of anaphylaxis any time during therapy. Monitor for CNS depression. For inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor for effectiveness of therapy and adverse reactions at beginning of therapy and periodically with long-term use. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Patient EducationUse exactly as directed; do not increase dose or frequency or discontinue without consulting prescriber. Take immediately before going to bed. Only use this medication if you can get a full night's sleep (at least 7-8 hours). Drug may cause physical and/or psychological dependence. While using this medication, do not use alcohol or other prescription or OTC medications (especially, pain medications, sedatives, antihistamines, or hypnotics) without consulting prescriber. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); nausea (small frequent meals, frequent mouth care, chewing gum, or sucking lozenges may help); or diarrhea (buttermilk, boiled milk, yogurt may help). Report CNS changes (confusion, memory problems, depression, increased sedation, excitation, headache, abnormal thinking or behavior, insomnia, or nightmares); muscle pain or weakness; respiratory difficulty; unusual swelling, especially on face or neck; chest pain or palpitations; or ineffectiveness of medication. Report episodes of "sleep driving" or other complex behaviors such as driving a vehicle, preparing food, or other activities which you have no memory of performing.
Pregnancy/breast-feeding precaution: Inform prescriber if you are or intend to become pregnant. Breast-feeding is not recommended.

Product AvailabilityZolpimist® oral spray: FDA approved December, 2008; availability currently undetermined

Zolpimist® is an oral spray of zolpidem indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, as tartrate: 5 mg, 10 mg

Ambien®: 5 mg, 10 mg

Tablet, extended release, as tartrate:

Ambien CR®: 6.25 mg, 12.5 mg

Generic AvailableYes: Excludes extended release

ManufacturerSearle

Pricing: U.S. (www.drugstore.com)

Tablet, controlled release (Ambien CR)

6.25 mg (30): $136.99

12.5 mg (30): $135.99

Tablets (Ambien)

5 mg (30): $159.13

10 mg (30): $159.13

Tablets (Zolpidem Tartrate)

5 mg (30): $17.99

10 mg (30): $17.99

Mechanism of ActionZolpidem, an imidazopyridine hypnotic that is structurally dissimilar to benzodiazepines, enhances the activity of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), via selective agonism at the benzodiazepine-1 (BZ$_1$) receptor; the result is increased chloride conductance, neuronal hyperpolarization, inhibition of the action potential, and a decrease in neuronal excitability leading to sedative and hypotic effects. Because of its selectivity for the BZ$_1$ receptor site over the BZ$_2$ receptor site, zolpidem exhibits minimal anxiolytic, myorelaxant, and anticonvulsant properties (effects largely attributed to agonism at the BZ$_2$ receptor site).

Pharmacodynamics/Kinetics

Onset of action: 30 minutes

Duration: 6-8 hours

Absorption: Rapid

Distribution: V$_d$: 0.54 L/kg

Protein binding: ~93%

Metabolism: Hepatic methylation and hydroxylation via CYP3A4 (~60%), CYP2C9 (~22%), CYP1A2 (~14%), CYP2D6 (~3%), and CYP2C19 (~3%) to three inactive metabolites

Bioavailability: 70%

Half-life elimination: ~2.5 hours (range 1.4-4.5 hours); Cirrhosis: Up to 9.9 hours; Elderly: prolonged up to 32%

Time to peak, plasma: 1.6 hours; 2.2 hours with food

Excretion: Urine (48% to 67%, primarily as metabolites); feces (29% to 42%, primarily as metabolites)

Related Information

- CMS: Long-Term Care Facility Thresholds
- Nonbenzodiazepine Anxiolytics and Hypnotics

Pharmacotherapy PearlsCauses fewer disturbances in sleep stages as compared to benzodiazepines. Time spent in sleep stages 3 and 4 are maintained; zolpidem decreases sleep latency; should not be prescribed in quantities exceeding a 1-month supply.

Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation).

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health CommentIn 2007, the FDA requested that all manufacturers of sedative-hypnotic drug products revise labeling to include a greater emphasis on the risks of adverse effects. These risks include severe allergic reactions (anaphylaxis, angioedema) and complex sleep-related behaviors, which may include sleep-driving (driving while not fully awake and with no memory of the event), making phone calls, and preparing and eating food while asleep. Zolpidem may be associated with a lower potential for abuse compared to benzodiazepines.

Anesthesia and Critical Care Concerns/Other ConsiderationsCauses fewer disturbances in sleep stages as compared to benzodiazepines. Time spent in sleep stages 3 and 4 are maintained; zolpidem decreases sleep latency; should not be prescribed in quantities exceeding a 1-month supply.

Index TermsZolpidem Tartrate

References

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International Brand NamesAdormix (CN); Ambien (BB, BM, BS, BZ, GY, JM, NL, SR, TT); Amsic (DE); Conyx (KP); Dormeben (CO); Dormizol (AU); Durnit (AR); Flazinil (EC); Hypnogen (PL); Niotal (IT); Nitrest (IN); Sanval (PL); Sobrium (MY); Somidem (AU, MY); Somit (AR, PY, UY); Somnil (CO); Somno (PE); Stildem (AU); Stilnix (IL); Stilnoct (BE, BG, DK, FI, GB, IE, LU, NL, NO, SE); Stilnox (AT, AU, BF, BJ, BR, CH, CI, CL, CR, CZ, DE, DO, EC, EE, ES, ET, FR, GH, GM, GN, GR, GT, HK, HN, HU, ID, IT, KE, KP, LR, MA, ML, MR, MU, MW, MX, MY, NE, NG, NI, PA, PE, PH, PK, PL, PT, SC, SD, SL, SN, SV, TH, TN, TW, TZ, UG, VE, ZA, ZM, ZW); Stilnox CR (AU); Stilpidem (HK); Vicknox (HK); Ziohex (PH); Zodorm (IL); Zoldem (DE); Zoldox (TW); Zolmia (ID); Zolpic (PL); Zolpid (KP); Zolpinox (DE); Zopidem (TW); Zorimin (TW)

Zonisamide

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Special Alerts

Antiepileptics: Increased Risk of Suicidal Behavior or Ideation - Updated: December 2008

The U.S. Food and Drug Administration (FDA) has issued an update following the completion of its analysis concerning the risk of suicidality (suicidal behavior or ideation) observed during clinical trials of various antiepileptic drugs (compared to placebo) in the treatment of epilepsy, psychiatric disorders, and other conditions. The pooled analysis of 199 clinical trials involving 11 antiepileptic drugs (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy showed that patients receiving an antiepileptic had a 0.43% risk of suicidal behavior/ideation compared to 0.24% of patients receiving placebo. As a result of the findings, the FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality, and a medication guide be developed informing patients of this risk.

Additional information may be found at http://www.fda.gov/medwatch/safety/2008/safety08.htm#Antiepileptic

Medication Safety Issues

Sound-alike/look-alike issues:

Zonisamide may be confused with lacosamide

Pronunciation(zoe NIS a mide)
U.S. Brand NamesZonegran®
Canadian Brand NamesZonegran®
Pharmacologic CategoryAnticonvulsant, Miscellaneous
Use: Labeled IndicationsAdjunct treatment of partial seizures in children >16 years of age and adults with epilepsy
Use: Unlabeled/InvestigationalBipolar disorder
Dosing: Adults

Adjunctive treatment of partial seizures: Oral: Initial: 100 mg/day. Dose may be increased to 200 mg/day after 2 weeks. Further dosage increases to 300 mg and 400 mg/day can then be made with a minimum of 2 weeks between adjustments, in order to reach steady state at each dosage level. Doses of up to 600 mg/day have been studied, however, there is no evidence of increased response with doses >400 mg/day.

Mania (unlabeled use): Oral: Initial: 100-200 mg/day; maximum: 600 mg/day (Kanba, 1994)

Dosing: ElderlyData from clinical trials is insufficient for patients older than 65. Begin dosing at the low end of the dosing range.
Dosing: PediatricChildren >16 years: Refer to adult dosing.
Dosing: Renal ImpairmentSlower titration and frequent monitoring are indicated in patients with renal or hepatic disease. There is insufficient experience regarding dosing/toxicity in patients with estimated GFR <50 mL/minute. Marked renal impairment (Cl_{cr} <20 mL/minute) was associated with a 35% increase in AUC.
Dosing: Hepatic ImpairmentSlower titration and frequent monitoring are indicated.
Administration: OralCapsules should be swallowed whole. Dose may be administered once or twice daily. Doses of 300 mg/day and higher are associated with increased side effects. Steady-state levels are reached in 14 days.
Dietary ConsiderationsMay be taken with or without food.
StorageStore at controlled room temperature 25°C (77°F). Protect from moisture and light.
ContraindicationsHypersensitivity to zonisamide, sulfonamides, or any component of the formulation
Warnings/Precautions

Concerns related to adverse effects:

- CNS effects: Significant CNS effects include psychiatric symptoms, psychomotor slowing, and fatigue or somnolence; fatigue and somnolence occur within the first month of treatment, most commonly at doses of 300-500 mg/day.

- Renal calculus: Discontinue therapy in patients who develop acute renal failure or a significant sustained increase in creatinine/BUN concentration; kidney stones have been reported.

- Sulfonamide reactions: Rare, but potentially fatal sulfonamide reactions have occurred following use. These reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis, usually appearing within 2-16 weeks of drug initiation; discontinue if rash develops. Chemical similarities are present among sulfonamides, sulfonylureas, carbonic anhydrase inhibitors, thiazides, and loop diuretics (except ethacrynic acid). Use in patients with sulfonamide allergy is specifically contraindicated in product labeling, however, a risk of cross-reaction exists in patients with allergy to any of these compounds; avoid use when previous reaction has been severe.

Disease-related concerns:

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Renal impairment: Use with caution in patients with renal impairment.

Concurrent drug therapy issues:

- Sedatives: Effects with other sedative drugs or ethanol may be potentiated.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children <16 years of age. Decreased sweating (oligohydrosis) and hyperthermia requiring hospitalization have been reported in children.

Other warnings/precautions:

- Withdrawal: Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal.

Geriatric ConsiderationsConsider the CNS effects commonly experienced in the first month of therapy.
Pregnancy Risk FactorC
Pregnancy ConsiderationsFetal abnormalities and death have been reported in animals, however, there are no studies in pregnant women. Based on limited case reports, it appears zonisamide crosses the placenta. Use during pregnancy only if the potential benefits outweigh the potential risks.
LactationExcretion in breast milk unknown/contraindicated
Breast-Feeding ConsiderationsBased on limited case reports, it appears zonisamide is excreted in breast milk. Use during lactation only if the potential benefits outweigh the potential risks.
Adverse ReactionsAdjunctive therapy: Frequencies noted in patients receiving other anticonvulsants:
>10%:

Central nervous system: Somnolence (17%), dizziness (13%)

Gastrointestinal: Anorexia (13%)

1% to 10%:

Central nervous system: Headache (10%), agitation/irritability (9%), fatigue (8%), tiredness (7%), ataxia (6%), confusion (6%), concentration decreased (6%), memory impairment (6%), depression (6%), insomnia (6%), speech disorders (5%), mental slowing (4%), anxiety (3%), nervousness (2%), schizophrenic/schizophreniform behavior (2%), difficulty in verbal expression (2%), status epilepticus (1%), convulsion (1%), hyperesthesia (1%), incoordination (1%)

Dermatologic: Rash (3%), bruising (2%), pruritus (1%)

Gastrointestinal: Nausea (9%), abdominal pain (6%), diarrhea (5%), dyspepsia (3%), weight loss (3%), constipation (2%), dry mouth (2%), taste perversion (2%), vomiting (1%)

Neuromuscular & skeletal: Paresthesia (4%), abnormal gait (1%), tremor (1%), weakness (1%)

Ocular: Diplopia (6%), nystagmus (4%), amblyopia (1%)

Otic: Tinnitus (1%)

Respiratory: Rhinitis (2%), cough increased (1%), pharyngitis (1%)

Miscellaneous: Flu-like syndrome (4%), accidental injury (1%)

<1%: Abnormal dreams, acne, albuminuria, allergic reaction, alopecia, ALT increased, amenorrhea, anemia, apnea, arthralgia, arthritis, AST increased, atrial fibrillation, bladder calculus, bladder pain, bradycardia, cerebrovascular accident, chest pain, cholangitis, cholecystitis, cholelithiasis, cholestatic jaundice, circumoral paresthesia, colitis, conjunctivitis, deafness, dehydration, diaphoresis, dry skin, duodenitis, dysarthria, dyskinesia, dysphagia, dyspnea, dystonia, dysuria, eczema, edema, encephalopathy, enuresis, esophagitis, euphoria, facial edema, facial paralysis, fecal incontinence, flank pain, flatulence, gastritis, gastroduodenal ulcer, gastroenteritis, gingivitis, glaucoma, glossitis, gum hemorrhage, gum hyperplasia, gynecomastia, heart failure, hematemesis, hematuria, hemoptysis, hirsutism, hyper-/hypokinesia, hyper-/hypotension, hyper-/hypotonia, hypoglycemia, hyponatremia, immunodeficiency, impotence, iritis, lactic dehydrogenase increased, leg cramps, leukopenia, libido decreased, lupus erythematosus, lymphadenopathy, maculopapular rash, malaise, mastitis, melena, menorrhagia, microcytic anemia, mouth ulceration, movement disorder, myalgia, myasthenia, myoclonus, neck rigidity, neuropathy, nocturia, oculogyric crisis, palpitation, parosmia, peripheral edema, peripheral neuritis, petechia, photophobia, polyuria, pulmonary embolus, pustular rash, rectal hemorrhage, reflexes increased, stomatitis, syncope, tachycardia, thirst, thrombocytopenia, thrombophlebitis, twitching, ulcerative stomatitis, urinary frequency, urinary incontinence, urinary retention, urinary urgency, urticaria, vascular insufficiency, ventricular extrasystoles, vertigo, vesiculobullous rash, visual field defect, weight gain

Postmarketing and/or case reports: Agranulocytosis, aplastic anemia, BUN increased, hyperthermia, kidney stones, oligohydrosis, serum creatinine increased, serum alkaline phosphatase increased, Stevens-Johnson syndrome, suicidal behavior/ideation, toxic epidermal necrolysis

Metabolism/Transport Effects**Substrate** of CYP2C19 (minor), 3A4 (major)
Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ketorolac: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated in persons with a history of convulsions. If anticonvulsant is being used for another indication monitor response to treatment closely, as concurrent mefloquine may decrease response to treatment. *Risk D: Consider therapy modification*

Phenytoin: May increase the metabolism of Zonisamide. *Risk C: Monitor therapy*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Food delays time to maximum concentration, but does not affect bioavailability.

Monitoring ParametersMonitor BUN and serum creatinine

Nursing: Physical Assessment/MonitoringAssess other medications patient may be taking for increased risk of drug/drug interactions. Monitor therapeutic effectiveness, laboratory results, and adverse reactions at beginning of therapy and periodically with long-term use. Observe and teach seizure precautions. Assess knowledge/teach patient appropriate use, interventions to reduce side effects, and adverse symptoms to report.

Monitoring: Lab TestsMonitor BUN and serum creatinine

Patient EducationTake exactly as directed, as the same time each day, with or without food. Do not increase frequency, alter dose, or discontinue without consulting prescriber. If you miss a dose, take as soon as possible. If it is almost time for your next dose, skip the missed dose. Do not chew, crush, or open capsules; swallow whole. Maintain adequate hydration (2-3 L/day of fluids) unless instructed to restrict fluid intake. Avoid grapefruit juice while on this medication. While using this medication, avoid alcohol, herbal remedies, OTC or prescriptions drugs (especially pain medication, antihistamines, psychiatric medications, sedatives, or hypnotics) unless approved by your prescriber. Wear/carry identification of epileptic status and medications. You may experience drowsiness, dizziness, or blurred vision (use caution when driving or engaging in tasks requiring alertness until response to drug is known); or nausea, vomiting, constipation, dry mouth, or loss of appetite (small frequent meals, frequent mouth care, chewing gum, or sucking hard candy may help). Report CNS changes (changes in speech patterns, mentation changes, suicidal ideation, depression, changes in cognition or memory, unusual thought patterns, coordination difficulties, or excessive drowsiness); respiratory difficulty or tightening of the throat; swelling of mouth, lips, or tongue; muscle cramping, weakness, or pain; rash or skin irritations; unusual bruising or bleeding (mouth, urine, stool); fever, sore throat, sores in your mouth; swelling of extremities; sudden back pain, pain on urination, or dark/bloody urine (signs of kidney stones); or other adverse response including change in seizure type or frequency. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant. Do not breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule: 25 mg, 50 mg, 100 mg

Zonegran®: 25 mg, 100 mg

Generic AvailableYes

ManufacturerElan Pharmaceuticals

Pricing: U.S. (www.drugstore.com)

Capsules (Zonegran)

25 mg (30): $31.19

100 mg (30): $89.43

Capsules (Zonisamide)

25 mg (100): $49.99

50 mg (100): $91.99

100 mg (30): $59.99

Mechanism of ActionThe exact mechanism of action is not known. May stabilize neuronal membranes and suppress neuronal hypersynchronization through action at sodium and calcium channels. Does not affect GABA activity.

Pharmacodynamics/Kinetics

Distribution: V_d: 1.45 L/kg

Protein binding: 40%

Metabolism: Hepatic via CYP3A4; forms N-acetyl zonisamide and 2-sulfamoylacetyl phenol (SMAP)

Half-life elimination: 63 hours

Time to peak: 2-6 hours

Excretion: Urine (62%, 35% as unchanged drug, 65% as metabolites); feces (3%)

Related Information

- Anticonvulsants by Seizure Type

Dental Health: Effects on Dental Treatment Key adverse event(s) related to dental treatment: Xerostomia (normal salivary flow resumes upon discontinuation) and abnormal taste.

Dental Health: Vasoconstrictor/Local Anesthetic Precautions No information available to require special precautions

References

Kanba S, Yagi G, Kamijima K, et al, “The First Open Study of Zonisamide, A Novel Anticonvulsant, Shows Efficacy in Mania,” *Prog Neuropsychopharmacol Biol Psychiatry*, 1994, 18(4):707-15. [PubMed 7938561]

Kawada K, Itoh S, Kusaka T, et al, “Pharmacokinetics of Zonisamide in Perinatal Period,” *Brain Dev*, 2002, 24(2):95-7.[PubMed 11891100]

International Brand Names Excegran (JP, KP); Zonegran (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HN, IE, IT, NL, NO, PH, PT, RU, SE, TR)

Zopiclone

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(ZOE pi clone)

Canadian Brand NamesApo-Zopiclone®; CO Zopiclone; Dom-Zopiclone; Gen-Zopiclone; Imovane®; Novo-Zopiclone; Nu-Zopiclone; PMS-Zopiclone; RAN™-Zopiclone; ratio-Zopiclone; Rhovane®; Rhoxal-zopiclone; Riva-Zopiclone; Sandoz-Zopiclone

Pharmacologic CategoryHypnotic, Nonbenzodiazepine

Use: Labeled IndicationsSymptomatic relief of transient and short-term insomnia

Use: DentalHas not been established

Dosing: Adults

Hypnotic: Oral: 5-7.5 mg just before retiring for the night

Patients with chronic respiratory insufficiency: 3.75 mg; may increase up to 7.5 mg with caution in appropriate cases

Dosing: ElderlyInitial: 3.75 mg just before retiring for the night; may increase to 5-7.5 mg

Dosing: Hepatic Impairment3.75 mg; may increase up to 7.5 mg with caution in appropriate cases

Administration: OralAdminister just before bedtime.

StorageStore at room temperature of 15°C to 30°C (59°F to 86°F) in a dry place. Protect from light.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to zopiclone or any component of the formulation; patients with severe respiratory impairment (eg, sleep apnea); pregnancy (similar agents)

Warnings/Precautions

Concerns related to adverse effects:

- Abnormal thinking/behavioral changes: Hypnotics/sedatives have been associated with abnormal thinking and behavior changes including decreased inhibition, aggression, bizarre behavior, agitation, hallucinations, and depersonalization. These changes may occur unpredictably and may indicate previously unrecognized psychiatric disorders; evaluate appropriately.
- Amnesia: Can occur; do not take unless a full night's sleep and clearance of the drug from the body are possible.
- CNS depression: May cause CNS depression impairing physical and mental capabilities; patients must be cautioned about performing tasks which require mental alertness (operating machinery or driving).

Disease-related concerns:

- Depression: Use with caution in patients with depression; worsening of depression, including suicidal ideation, has been reported with the use of hypnotics. Intentional overdose may be an issue in this population; prescribe least amount of medication needed.
- Drug abuse: Use with caution in patients with a history of drug dependence.
- Hepatic impairment: Use with caution in patients with hepatic impairment; dosage adjustment recommended.
- Respiratory disease: Use with caution in patients with respiratory compromise, COPD, or sleep apnea.

Concurrent drug therapy issues:

- CNS depressants/psychoactive medications: Use with caution in patients receiving other CNS depressants or psychoactive medication; effects with other sedative drugs or ethanol may be potentiated.
- CYP3A4 inhibitors: Use with caution in patients taking strong CYP3A4 inhibitors.

Special populations:

- Elderly: Use with caution in the elderly; more susceptible to adverse reactions (confusion).
- Pediatrics: Safety and efficacy have not been established in children.

Other warnings/precautions:

- Appropriate use: Symptomatic treatment of insomnia should be initiated only after careful evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve after 7-10 days may indicate psychiatric and/or medical illness.
- Duration of therapy: Should not be administered for more than 7-10 days consecutively.
- Rapid onset: Because of the rapid onset of action, administer immediately prior to bedtime or after the patient has gone to bed and is having difficulty falling asleep.
- Withdrawal: Abrupt discontinuance may lead to withdrawal symptoms.

Pregnancy Risk FactorNot assigned; similar agents rated D

Pregnancy ConsiderationsThere is insufficient data on safety in pregnancy; however, benzodiazepines may cause congenital malformations during the 1st trimester and neonatal CNS depression during the last few weeks of pregnancy; it is expected zopiclone may do the same.

LactationEnters breast milk/not recommended

Breast-Feeding ConsiderationsZopiclone is excreted in human milk and its concentration may reach 50% of plasma levels; therefore, it is not recommended to use while breast-feeding.

Adverse ReactionsFrequency not defined.

Cardiovascular: Palpitation

Central nervous system: Agitation, anterograde amnesia, anxiety, asthenia, chills, confusion, depression, dizziness, drowsiness, euphoria, headache, hostility, memory impairment, nervousness, nightmares, somnolence, speech abnormalities

Dermatological: Rash, spots on skin

Endocrine & metabolic: Anorexia; libido decreased; alkaline phosphatase, ALT, and AST increased; appetite increased

Gastrointestinal: Constipation, coated tongue, diarrhea, dry mouth, dyspepsia, halitosis, nausea, taste alteration (bitter taste, common), vomiting

Neuromuscular & skeletal: Coordination impaired, hypotonia, limb heaviness, muscle spasms, paresthesia, tremor

Ocular: Amblyopia

Respiratory: Dyspnea

Miscellaneous: Diaphoresis

Metabolism/Transport Effects**Substrate** (major) of CYP2C9, 3A4

Drug Interactions

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2C9 Inducers (Highly Effective): May increase the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Moderate): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk C: Monitor therapy*

CYP2C9 Inhibitors (Strong): May decrease the metabolism of CYP2C9 Substrates (High risk). *Risk D: Consider therapy modification*

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Flumazenil: May diminish the sedative effect of Hypnotics (Nonbenzodiazepine). *Risk C: Monitor therapy*

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

Macrolide Antibiotics: May increase the serum concentration of Zopiclone. **Exceptions:** Azithromycin; Dirithromycin [Off Market]; Spiramycin. *Risk D: Consider therapy modification*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Food: Effect/toxicity may be increased by grapefruit juice; avoid concurrent use.

Herb/Nutraceutical: St John's wort may decrease levels. Avoid valerian, St John's wort, kava kava, gotu kola (may increase CNS depression).

Monitoring ParametersMonitor for confusion, excessive drowsiness (especially in elderly). Monitor patients with hepatic insufficiency closely.

Nursing: Physical Assessment/MonitoringFor inpatient use, institute safety measures and monitor effectiveness and adverse reactions. For outpatients, monitor therapeutic effectiveness and adverse reactions (see Adverse Reactions) at beginning of therapy and periodically with long-term use.

Patient EducationTake exactly as prescribed; do not change dose or take longer than prescribed without consulting prescriber. Do not take unless a full night's sleep is possible before you would need to be functional and active. Do not take with alcohol. Do not drive a car or operate dangerous machinery until you experience how the drug will affect you the next day. Zopiclone may cause drowsiness, dizziness, lightheadedness, and difficulty with coordination. If you experience unusual disturbing thoughts or behavior, notify your prescriber. You may experience an increase in sleep difficulties for 1-2 days after discontinuing. May cause dependence, especially when used regularly for more than a few weeks. You may experience withdrawal symptoms when discontinuing use. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are pregnant. Breast-feeding is not recommended.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Tablet: 5 mg, 7.5 mg [not available in the U.S.]

> Apo-Zopiclone® [CAN], Gen-Zopiclone [CAN], Imovane® [CAN], Novo-Zopiclone [CAN], Nu-Zopiclone [CAN], PMS-Zopiclone [CAN], Rhovane® [CAN], Rhoxal-zopiclone [CAN]: 5 mg, 7.5 mg

Generic AvailableYes
ManufacturerAventis Pharma (Canada)
Mechanism of ActionZopiclone is a cyclopyrrolone derivative and has a pharmacological profile similar to benzodiazepines. Zopiclone reduces sleep latency, increases duration of sleep, and decreases the number of nocturnal awakenings.
Pharmacodynamics/Kinetics

Absorption: Elderly: 75% to 94%

Distribution: Rapidly from vascular compartment

Protein binding: ~45%

Metabolism: Extensively hepatic

Half-life elimination: 5 hours; Elderly: 7 hours; Hepatic impairment: 11.9 hours

Time to peak, serum: <2 hours; Hepatic impairment: 3.5 hours

Excretion: Urine (75%); feces (16%)

Pharmacotherapy PearlsNot available in U.S.
Dental Health: Effects on Dental TreatmentKey adverse event(s) related to dental treatment: Coated tongue, dry mouth, halitosis, taste alteration (bitter taste, common).
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions
References

Imovane® product monograph, Aventis Pharma Inc, Quebec, October 2000.

International Brand NamesAmoban (JP); Datolan (ES); Docilen (PE, PY, UY); Dormex (PE); Ezolin (CO); Genclone (TW); Imovane (AR, AT, AU, BB, BE, BM, BR, BS, BZ, CH, CN, CZ, DK, EE, FI, FR, GR, GY, HN, HU, IL, IT, JM, KP, LU, MX, MY, NL, NO, PE, PL, SE, SG, SR, TT, TW, UY, VE); Imrest (AU); Nenia (IT); Nocturno (IL); Nuctane (PE); Optidorm (DE); Sedorm (CO); Siaten (ES); Somnal (AT); Somnol (HN); Somnols (EE); Somnosan (DE); Ximovan (DE); Z-Dorm (ZA); Zetix (CN, EC); Zimoclone (IE); Zimovane (GB); Zo-Tab (NZ); Zolinox (IN); Zolon (TW); Zometic (CN); Zopiclon (PL); Zopimed (ZA); Zopinox (FI); Zopiratio (PL); Zopitran (IN); Zopivane (ZA)

Zoster Vaccine

Lexi-Drugs Online

English

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Medication Safety Issues

Both varicella vaccine and zoster vaccine are live, attenuated strains of varicella-zoster virus. Their indications, dosing, and composition are distinct. Varicella vaccine is indicated for the prevention of chickenpox, while zoster vaccine is indicated in older individuals to prevent reactivation of the virus which causes shingles. Zoster vaccine is **not** a substitute for varicella vaccine and should not be used in children.

Pronunciation(ZOS ter vak SEEN)
U.S. Brand NamesZostavax®
Pharmacologic CategoryVaccine, Live (Viral)
Use: Labeled IndicationsPrevention of herpes zoster (shingles) in patients ≥60 years of age
The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of all patients ≥60 years of age, including:

- Patients who report a previous episode of zoster.
- Patients with chronic medical conditions (eg, chronic renal failure, diabetes mellitus, rheumatoid arthritis, chronic pulmonary disease) unless those conditions are contraindications.
- Residents of nursing homes and other long-term care facilities ≥60 years of age, without contraindications.

Dosing: Adults**Shingles:** Adults ≥60 years: SubQ: 0.65 mL administered as a single dose; there is no data to support readministration of the vaccine
Dosing: ElderlyRefer to adult dosing.
Dosing: Renal ImpairmentNo adjustment required.
Administration: I.V.Not for I.V. administration
Administration: OtherInject immediately after reconstitution. Inject SubQ into the deltoid region of the upper arm, if possible. In persons anticipating immunosuppression, give at least 14 days to 1 month prior to starting immunosuppressant.

Administration with chronic use of acyclovir, famciclovir, or valacyclovir: Discontinue ≥24 hours before administration of zoster vaccine. Do not use for ≥14 days after vaccination.

Administration with other vaccines:

Zoster vaccine with inactivated vaccines: May be given simultaneously or at any interval between doses

Zoster vaccine with other live vaccines:

Intranasal or injectable: If not given simultaneously, wait at least 4 weeks between administration

Oral: May be given simultaneously or at any interval between doses of live or inactivated injectable vaccines

Vaccine administration with antibody-containing products: Zoster vaccine may be given with blood or antibody-containing products. Examples of antibody-containing products include I.M. and I.V. immune globulin, hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, rabies immune globulin, whole blood, packed red cells, plasma, and platelet products

StorageDuring shipment, should be maintained at -15°C (5°F) or colder. Store powder in freezer at -15°C (5°F). Protect from light. Store diluent separately at room temperature or in refrigerator. Do not freeze reconstituted vaccine.
ReconstitutionWithdraw entire contents of the vial containing the provided diluent to reconstitute vaccine. Gently agitate to mix thoroughly. Withdraw entire contents of reconstituted vaccine vial for administration. Discard if reconstituted vaccine is not used within 30 minutes.
ContraindicationsHypersensitivity to any component of the vaccine; individuals with leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic systems; primary and acquired immunodeficiency states including AIDS or clinical manifestations of HIV; those receiving immunosuppressive therapy (including high-dose corticosteroids); pregnancy

In addition, ACIP recommends that the following immunocompromised patients should not receive zoster vaccine:

Patients undergoing hematopoietic stem cell transplant (limited data; assess risk/benefit, if needed, administer ≥24 months after transplantation);

Patients receiving recombinant human immune modulators, particularly antitumor necrosis factor agents (eg, adalimumab, infliximab, etanercept). Safety and efficacy of concurrent administration is unknown and not recommended. Defer vaccination for ≥1 month after discontinuation.

Patients with unspecified cellular immunodeficiency (exception, patients with impaired humoral immunity may receive vaccine).

Warnings/Precautions

Concerns related to adverse effects:

- Anaphylactoid/hypersensitivity reactions: Immediate treatment (including epinephrine 1:1000) for anaphylactoid and/or hypersensitivity reactions should be available during vaccine use.

Disease-related concerns:

- Acute illness: The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and the etiology of the disease. Immunization should be delayed during the course of an acute febrile illness; may administer to patients with mild acute illness (with or without fever).

- Postherpetic neuropathy (PHN): Not for use in the treatment of PHN.

- Tuberculosis: Defer treatment in patients with active untreated tuberculosis.

- Zoster infection: Not for use in the treatment of active zoster outbreak. May be used in patients with previous history of zoster.

Concurrent drug therapy issues:

- Antiviral drugs: Medications active against the herpesvirus family (eg, acyclovir, famciclovir, valacyclovir) may interfere with the zoster vaccine.

- Vaccines: In order to maximize vaccination rates, the ACIP recommends simultaneous administration of all age-appropriate vaccines (live or inactivated) for which a person is eligible at a single clinic visit, unless contraindications exist.

Special populations:

- Adults: Not for use in patients <60 years of age.

- Altered immunocompetence: In patients where immunosuppressant therapy is anticipated, zoster vaccine should be given at least 14 days to 1 month prior to beginning therapy when possible Use is contraindicated in severely immunocompromised patients (eg, patients receiving chemo-/radiation therapy or other immunosuppressive therapy [including high-dose corticosteroids]); may have a reduced response to vaccination. Patients receiving corticosteroids in low-to-moderate doses, topical (inhaled, nasal, skin), local injection (intra-articular, bursal, tendon) may receive vaccine.

- Pediatrics: Zoster vaccine is not a substitute for varicella vaccine and should not be used in children.

- Varicella vaccine recipients: The ACIP does not recommend zoster vaccination in patients of any age who have received the varicella vaccine.

Dosage form specific warnings:

- Gelatin: Contains gelatin; do not use in patients with a history of anaphylactic/anaphylactoid reaction to gelatin.

- Neomycin sensitivity: Contains neomycin; do not use in patients with a history of anaphylactic/anaphylactoid reaction to neomycin. Contact dermatitis to neomycin is not a contraindication to the vaccine.

Other warnings/precautions:

- Transmission of virus: Vaccinated individuals do not need to take precautions against spreading varicella following vaccination; transmission of virus is rare unless rash develops. In case of rash, standard contact precautions should be followed.

Geriatric ConsiderationsThis vaccine is intended for those >60 years of age. This live attenuated vaccine should be used with caution in patients with neoplastic disease or those who are immunosuppressed.

Pregnancy Risk FactorC

Pregnancy ConsiderationsAnimal reproduction studies have not been conducted. Use during pregnancy is contraindicated. Although women of childbearing potential are unlikely to receive the vaccine, women should avoid becoming pregnant for 4 weeks after vaccination. Risk to the fetus following exposure to wild-type varicella zoster virus is small and risk following exposure from the attenuated vaccine is probably even less. Inadvertent exposure to the vaccine during pregnancy should be reported to Merck's National Service Center (800-986-8999).

LactationExcretion in breast milk unknown/use caution

Breast-Feeding ConsiderationsMost live vaccines are not secreted into breast milk.

Adverse Reactions**All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS) 1-800-822-7967.**

>10%: Local: Injection site reaction (48%; includes erythema, tenderness, swelling, hematoma, pruritus, and/or warmth)

1% to 10% (**Note:** Rates similar to placebo):

Central nervous system: Fever (2%), headache (1%)

Dermatologic: Skin disorder (1%)

Gastrointestinal: Diarrhea (2%)

Neuromuscular & skeletal: Weakness (1%)

Respiratory: Respiratory tract infection (2%), rhinitis (1%)

Miscellaneous: Flu-like syndrome (2%)

<1%, postmarketing, and/or case reports following varicella vaccine have included (not reported specifically following zoster vaccine): Anaphylaxis, ataxia, Bell's palsy, cellulitis, cerebrovascular accident, dizziness, encephalitis, erythema multiforme, Guillain-Barré syndrome, Henoch-Schönlein purpura, herpes zoster, impetigo, nonfebrile seizure, paresthesia, pharyngitis, pyrexia, rash (noninjection site), secondary skin infection, Stevens-Johnson syndrome, thrombocytopenia, transverse myelitis

Drug Interactions

Acyclovir-Valacyclovir: May diminish the therapeutic effect of Zoster Vaccine. Management: When possible, discontinue antiviral agents with anti-zoster activity (i.e., acyclovir, valacyclovir, famciclovir) for at least 24 hours prior to and 14 days after receiving a live attenuated zoster vaccine. *Risk X: Avoid combination*

Famciclovir: May diminish the therapeutic effect of Zoster Vaccine. Management: When possible, discontinue antiviral agents with anti-zoster activity (i.e., acyclovir, valacyclovir, famciclovir) for at least 24 hours prior to and 14 days after receiving a live attenuated zoster vaccine. *Risk X: Avoid combination*

Immune Globulins: May diminish the therapeutic effect of Vaccines (Live). *Risk D: Consider therapy modification*

Immunosuppressants: May enhance the adverse/toxic effect of Vaccines (Live). Vaccinal infections may develop. Immunosuppressants may also decrease therapeutic response to vaccines. *Risk X: Avoid combination*

Tuberculin Tests: Vaccines (Live) may diminish the diagnostic effect of Tuberculin Tests. *Risk D: Consider therapy modification*

Monitoring ParametersFever, rash

Nursing: Physical Assessment/MonitoringThis is not a substitute for varicella vaccine; not for use in patients <60 years of age or in the treatment of active zoster outbreak. Assess patient history for contraindications prior to treatment. Deferring treatment should be considered in presence of acute illness or fever >101.3°F. Treatment for anaphylactic/anaphylactoid reaction should be immediately available during vaccine use. **Note:** All serious adverse reactions must be reported to the U.S. Department of Health and Human Services (DHHS). Date of administration, name of manufacturer, lot number, and administering person’s name, title, and address should be recorded in patient’s permanent medical record. Teach patient possible side effects/appropriate interventions, and adverse symptoms to report.

Patient EducationThis vaccine is not a treatment for shingles, but may help prevent the occurrence of shingles or reduce the pain if shingles develops despite the vaccination. Avoid other vaccinations for 2 months following this vaccine unless approved by prescriber. Avoid close and/or prolonged contact with highly susceptible individuals (newborns, pregnant women, immunocompromised persons) for six weeks following vaccination; there is a rare risk of transmitting the vaccine virus to those who have not had chickenpox. Notify prescriber immediately of any acute reaction to vaccination (eg, difficulty breathing, chest pain, acute headache, rash, or difficulty swallowing). May cause mild fever and some redness, pain, or swelling at injection site; consult prescriber if excessive or persisting. **Pregnancy/breast-feeding precautions:** Inform prescriber if you are or intend to become pregnant or breast-feed.

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, powder for reconstitution [preservative free]

Zostavax®: 19,400 plaque-forming units (PFU) [contains gelatin, sucrose, and trace amounts of neomycin]

Generic AvailableNo

ManufacturerMerck & Co, Inc

Pricing: U.S. (www.drugstore.com)

Solution (reconstituted) (Zostavax)

19400 units/0.65 mL (1): $192.99

Mechanism of ActionAs a live, attenuated vaccine (Oka/Merck strain of varicella-zoster virus), zoster virus vaccine stimulates active immunity to disease caused by the varicella-zoster virus. Administration has been demonstrated to protect against the development of herpes zoster, with the highest efficacy in patients 60-69 years of age. It may also reduce the severity of complications, including postherpetic neuralgia, in patients who develop zoster following vaccination.

Pharmacodynamics/Kinetics

Onset of action: Seroconversion: ~6 weeks

Duration: Not established; protection has been demonstrated for at least 4 years

Pharmacotherapy PearlsFederal law requires that the date of administration, the vaccine manufacturer, lot number of vaccine, and the administering person's name, title, and address be entered into the patient's permanent medical record.

The varicella-zoster virus (VZV) is capable of causing two distinct manifestations of infection. Primary infection results in chickenpox (varicella). These infections tend to occur in young children or younger adults. Reactivation of latent infection (painful vesicular cutaneous eruption usually in a dermatomal pattern) occurs in older patients or in immunosuppressed populations. This is commonly referred to as shingles (herpes zoster). Although the vaccines are directed against the same causative organism, healthcare workers should be aware of differences in indications, dosing, populations, and composition of the vaccine. Neither vaccine is intended for administration during active outbreaks.

Dental Health: Effects on Dental TreatmentNo significant effects or complications reported

Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsNo information available to require special precautions

Mental Health: Effects on Mental StatusNone reported

Mental Health: Effects on Psychiatric TreatmentNone reported

Index TermsShingles Vaccine; Varicella-Zoster (VZV) Vaccine (Zoster); VZV Vaccine (Zoster)

References

Centers for Disease Control and Prevention, “Prevention of Herpes Zoster: Recommendations of the Advisory Committee on Immunization Practices (ACIP),” *MMWR Recomm Rep*, 2008, 57(RR-5):1-30. Available at http://www.cdc.gov/mmwr/PDF/rr/rr5705.pdf[PubMed 18528318]

Oxman MN, Levin MJ, Johnson GR, et al, “A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults,” *N Engl J Med*, 2005, 352(22):2271-84.[PubMed 15930418]

International Brand Names Varilrix (PL)

Zuclopenthixol

Lexi-Drugs Online

English

Jump To Field (Select Field Name)

Pronunciation(zoo kloe pen THIX ol)

Canadian Brand NamesClopixol-Acuphase®; Clopixol®; Clopixol® Depot

Pharmacologic CategoryAntipsychotic Agent, Typical

Use: Labeled IndicationsManagement of schizophrenia; acetate injection is intended for short-term acute treatment; decanoate injection is for long-term management; dihydrochloride tablets may be used in either phase

Use: Unlabeled/InvestigationalBipolar disorder, psychoses; agitated states

Dosing: Adults

Management of schizophrenia/psychoses:

Oral (zuclopenthixol dihydrochloride): Initial: 20-30 mg/day in 2-3 divided doses; usual maintenance dose: 20-40 mg/day; maximum daily dose: 100 mg

I.M. (short-term: zuclopenthixol acetate): 50-150 mg; may be repeated in 2-3 days; no more than 4 injections should be given in the course of treatment; maximum dose during course of treatment: 400 mg (maximum treatment period: 2 weeks)

Transfer of patients from I.M. acetate (Acuphase®) to oral (tablets):

50 mg = 20 mg daily

100 mg = 40 mg daily

150 mg = 60 mg daily

Long-term management; depot injection (zuclopenthixol decanoate): I.M.: 100 mg by deep I.M. injection; additional I.M. doses of 100-200 mg may be given over the following 1-4 weeks; maximum weekly dose: 600 mg; usual maintenance dose: 150-300 mg every 2 weeks

Transfer of patients from oral (tablets) to I.M. decanoate (depot):

≤20 mg daily = 100 mg every 2 weeks

25-40 mg daily = 200 mg every 2 weeks

50-75 mg daily = 300 mg every 2 weeks

>75 mg/day = 400 mg every 2 weeks

Transfer of patients from I.M. acetate (Acuphase®) to I.M. decanoate (depot):

50 mg every 2-3 days = 100 mg every 2 weeks

100 mg every 2-3 days = 200 mg every 2 weeks

150 mg every 2-3 days = 300 mg every 2 weeks

Dosing: ElderlyRefer to adult dosing.

StorageStore at 20°C to 25°C (68°F to 77°F); do not freeze. Protect all dosage forms from light. Acuphase® and depot injections may be mixed together in the same syringe. Clear or slightly yellow solutions may be used. Dispense in amber or opaque vials/bottles.

RestrictionsNot available in U.S.

ContraindicationsHypersensitivity to zuclopenthixol, thioxanthenes, or any component of the formulation; acute intoxication (ethanol, barbiturate, or opioid); severe CNS depression; coma; suspected or established subcortical brain damage; circulatory collapse; blood dyscrasias; pheochromocytoma

Allergy Considerations

- Thioxanthene Allergy

Warnings/Precautions

Concerns related to adverse effects:

- Altered cardiac conduction: May alter cardiac conduction; life-threatening arrhythmias have occurred with therapeutic doses of antipsychotics. Avoid use in patients with underlying QT prolongation, in those taking medicines that prolong the QT interval, or cause polymorphic ventricular tachycardia; monitor ECG closely for dose-related QT effects. Adverse effects of decanoate may be prolonged.

- Anticholinergic effects: May cause anticholinergic effects (constipation, xerostomia, blurred vision, urinary retention); use with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention, BPH, xerostomia, or visual problems. Relative to other neuroleptics, zuclopenthixol has a low potency of cholinergic blockade.

- Blood dyscrasias: Myelosuppression (eg, leukopenia, agranulocytosis) has been observed with antipsychotic use; check blood counts periodically and discontinue at first signs of blood dyscrasias; use is contraindicated in patients with bone marrow suppression.

- Esophageal dysmotility/aspiration: Antipsychotic use has been associated with esophageal dysmotility and aspiration; use with caution in patients at risk of pneumonia (ie, Alzheimer's disease).

- Extrapyramidal symptoms: May cause extrapyramidal symptoms (EPS), including pseudoparkinsonism, acute dystonic reactions, akathisia, and tardive dyskinesia (risk of these reactions is high relative to other neuroleptics). Risk of dystonia (and possibly other EPS) may be greater with increased doses, use of conventional antispychotics, males, and younger patients.

- Neuroleptic malignant syndrome (NMS): Use may be associated with NMS; monitor for mental status changes, fever, muscle rigidity, and/or autonomic instability (risk may be increased in patients with Parkinson's disease or Lewy body dementia).

- Orthostatic hypotension: May cause orthostatic hypotension; use with caution in patients at risk of this effect or in those who would not tolerate transient hypotensive episodes (cerebrovascular disease, cardiovascular disease, hypovolemia, or concurrent medication use which may predispose to hypotension/bradycardia).

- Pigmentary retinopathy: May be associated with pigmentary retinopathy.

- Sedation: May be sedating, use with caution in disorders where CNS depression is a feature; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving).

- Temperature regulation: Impaired core body temperature regulation may occur; caution with strenuous exercise, heat exposure, dehydration, and concomitant medication possessing anticholinergic effects.

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with severe cardiovascular disease.

- Dementia: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo. An increased incidence of cerebrovascular adverse events (including fatalities) has been reported in elderly patients with dementia-related psychosis. Zuclopenthixol is not approved for this indication.

- Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended.

- Hepatic impairment: Use with caution in patients with hepatic impairment.

- Myasthenia gravis: Use with caution in patients with myasthenia gravis; condition may be exacerbated by cholinergic blockade.

- Parkinson's disease: Use with caution in patients with Parkinson's disease; they may be more sensitive to adverse effects.

- Prolactin-dependent tumors: Use with caution in patients with breast cancer or other prolactin-dependent tumors; elevates prolactin levels.

- Renal impairment: Use with caution in patients with renal impairment.

- Respiratory disease: Use with caution in patients with respiratory disease.

- Seizure disorder: Use with caution in patients at risk of seizures, including those with a history of seizures, head trauma, brain damage (subcortical-contraindicated), alcoholism, or concurrent therapy with medications which may lower seizure threshold.

Concurrent drug therapy issues:

- Antiemetic effects: May mask toxicity of other drugs or conditions (eg, intestinal obstruction, Reye's syndrome, brain tumor) due to antiemetic effects.

Special populations:

- Pediatrics: Safety and efficacy have not been established in children.

Pregnancy Risk FactorC
LactationEnters breast milk/not recommended
Adverse Reactions

>10%:

Central nervous system: Somnolence/drowsiness (32%), anxiety/nervousness (17%), insomnia (16%), akathisia (14%), extrapyramidal effects (13%), dizziness (11%)

Gastrointestinal: Xerostomia (15%)

Endocrine & metabolic: Libido decreased (3%), menstrual disorder (2%)

Neuromuscular & skeletal: Hypertonia (19%), tremor (19%), weakness (15%)

1% to 10%:

Central nervous system: Agitation (10%), depression (8%), concentration impaired (8%), headache (5%), vertigo (5%), dystonia (5%), tardive dyskinesia (3%), paresthesia (1%), hallucination (3%), apathy (3%), confusion (3%), amnesia (3%), abnormal dreams (2%)

Dermatologic: Seborrhea (2%), pruritus (up to 2%)

Gastrointestinal: Constipation (8%), salivation increased (8%), anorexia (4%), vomiting (3%), nausea (2%)

Genitourinary: Micturition disorder (3%)

Neuromuscular & skeletal: Hypokinesia (8%), abnormal gait (2%), myalgia (1%)

Ocular: Abnormal accommodation (6%), abnormal vision (4%)

Miscellaneous: Diaphoresis increased (3%)

<1% (Limited to important or life-threatening): Abdominal pain, agranulocytosis, allergic reaction, anorgasmia, apnea, ataxia, chest pain, corneal deposits, dysphagia, dyspnea, dyskinesia, erectile dysfunction, galactorrhea, glossitis, gynecomastia, hypotension, migraine, oculogyric crisis, neuroleptic malignant syndrome (NMS), paroniria, photosensitivity, purpura, rash, respiratory depression, seizure, speech disorder, tinnitus

Metabolism/Transport Effects**Substrate** of CYP2D6 (major)

Drug Interactions

Acetylcholinesterase Inhibitors (Central): May enhance the neurotoxic (central) effect of Antipsychotics. Severe extrapyramidal symptoms have occurred in some patients. *Risk C: Monitor therapy*

Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*

Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

Amphetamines: Antipsychotics may diminish the stimulatory effect of Amphetamines. *Risk C: Monitor therapy*

Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. **Exceptions:** Paliperidone. *Risk C: Monitor therapy*

Anti-Parkinson's Agents (Dopamine Agonist): Antipsychotics (Typical) may diminish the therapeutic effect of Anti-Parkinson's Agents (Dopamine Agonist). *Risk D: Consider therapy modification*

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

Darunavir: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk D: Consider therapy modification*

Lithium formulations: May enhance the neurotoxic effect of Antipsychotics. Lithium formulations may decrease the serum concentration of Antipsychotics. Specifically noted with chlorpromazine. *Risk C: Monitor therapy*

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. *Risk X: Avoid combination*

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. *Risk D: Consider therapy modification*

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. *Risk D: Consider therapy modification*

Tetrabenazine: May enhance the adverse/toxic effect of Antipsychotics. *Risk C: Monitor therapy*

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. *Risk X: Avoid combination*

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. *Risk X: Avoid combination*

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (may increase CNS depression).

Herb/Nutraceutical: Avoid dong quai, St John's wort (may also cause photosensitization). Avoid kava kava, gotu kola, valerian, St John's wort (may increase CNS depression).

Monitoring ParametersVital signs; lipid profile, fasting blood glucose/Hgb A_{1c}; BMI; mental status, abnormal involuntary movement scale (AIMS), extrapyramidal symptoms (EPS)

Reference RangeTherapeutic z-clopenthixol serum levels are 2-12 ng/mL; ingestion of 2.5 g resulted in a peak blood level of 900 ng/mL

Monitoring: Lab TestsLipid profile, fasting blood glucose/Hgb A_{1c}; BMI

Dosage FormsExcipient information presented when available (limited, particularly for generics); consult specific product labeling. [CAN] = Canadian brand name

Injection, as acetate:

Clopixol Acuphase® [CAN]: 50 mg/mL [zuclopenthixol 42.5 mg/mL] (1 mL, 2 mL) [not available in the U.S.]

Injection, as decanoate:

Clopixol® Depot [CAN]: 200 mg/mL [zuclopenthixol 144.4 mg/mL] (10 mL) [not available in the U.S.]

Tablet, as dihydrochloride:

Clopixol® [CAN]: 10 mg, 25 mg, 40 mg [not available in the U.S.]

Generic AvailableNo
ManufacturerLundbeck (Canada)
Mechanism of ActionZuclopenthixol is a thioxanthene antipsychotic with a piperazine side chain; related to fluphenazine, the cis(z)-clopenthixol is the active isomer of this neuroleptic; blocks postsynaptic dopaminergic brain receptors.
Pharmacodynamics/Kinetics

Onset of action: Acetate injection: Sedation within 2 hours

Duration: Acetate injection: 2-3 days; Decanoate injection: 2 weeks

Distribution: V_d: 15-20 L/kg

Metabolism: Hepatic via N-dealkylation

Half-life elimination: Terminal: Oral: 20 hours; Depot: 19 days

Time to peak: Acetate injection: 24-36 hours; Dihydrochloride tablet: 3 hours; Depot: 3-7 days

Related Information

- Discontinuation of Psychotropic Drugs
- Teratogenic Risks of Psychotropic Medications

Pharmacotherapy PearlsNot available in U.S.
Dental Health: Effects on Dental TreatmentNo significant effects or complications reported
Dental Health: Vasoconstrictor/Local Anesthetic PrecautionsZuclopenthixol is one of the drugs confirmed to prolong the QT interval and is accepted as having a risk of causing torsade de pointes. The risk of drug-induced torsade de pointes is extremely low when a single QT interval prolonging drug is prescribed. In terms of epinephrine, it is not known what effect vasoconstrictors in the local anesthetic regimen will have in patients with a known history of congenital prolonged QT interval or in patients taking any medication that prolongs the QT interval. Until more information is obtained, it is suggested that the clinician consult with the physician prior to the use of a vasoconstrictor in suspected patients, and that the vasoconstrictor (epinephrine, levonordefrin [Neo-Cobefrin®]) be used with caution.
Mental Health CommentOlder antipsychotic medications (chlorpromazine, haloperidol), which do not meet specific criteria for “atypical” antipsychotics, are often referred to as typical antipsychotics. They are associated with the troubling side effect, EPS. However, it is commonly believed that in order for a drug to treat psychosis, it must block dopamine is some manner.

Common side effects include sedation and neuroleptic effect (reduced initiative, interest in the environment, and display of emotion or affect). All **typical** antipsychotics are considered to be equally effective if given in equipotent doses. An inverse relationship exists between intrinsic antimuscarinic activity and propensity to cause extrapyramidal side effects. If dystonia or pseudoparkinsonism occurs, antiparkinsonian agents should be considered. If akathisia occurs, beta-blockers (eg, propranolol), benzodiazepines, or antiparkinsonian agents should be considered. Tardive dyskinesia (TD) secondary to typical antipsychotics has an estimated incidence of 3% to 5% per year for the first 5 years of treatment. After this time period, the incidence is estimated to be 2% to 3% per year. Prevalence rates are ~15% to 20%. Female gender and age constitute risk factors for TD. Indeed, prevalence rates have been reported to be as high as 70% in elderly females. No specific treatment exists for TD, however, patients are often initiated on/switched to an atypical antipsychotic because of their lower incidence to cause TD and hopes of suppression.

Typical antipsychotics are usually only indicated for schizophrenia, but are generally effective for mania and psychosis and/or behavioral syndromes secondary to other mental conditions. Nonpsychiatric uses include Tourette's syndrome, Huntington's disease, and occasionally, intractable hiccups, pruritus, nausea, and vomiting.

These drugs are thought to exert their antipsychotic activity by blocking dopamine D_2 receptors in the mesolimbic dopaminergic pathway. Side effects are often related to their ability to antagonize dopamine receptors in the nigrostriatal and tuberoinfundibular pathways.

Coadministration of two or more antipsychotics does not generally improve clinical response and may increase the potential for adverse effects.

In 2008, the FDA issued a warning regarding increased mortality risk with typical **and** atypical antipsychotic drugs when used in elderly patients with dementia-related psychosis.

Index TermsZ-chlopenthixol; Zuclopenthixol Acetate; Zuclopenthixol Decanoate; Zuclopenthixol Dihydrochloride
References

Li Wan Po A and Irwin WJ, “The Photochemical Stability of Cis- and Trans-Isomers of Tricyclic Neuroleptic Drugs,” *J Pharm Pharmacol*, 1980, 32:25-9. [PubMed 6102122]

Tracqui A, Kintz P, Cirimele V, et al, “HPLC-DAD and HPLC-MS Findings in a Fatality Involving (z)-Cis-Clopenthixol (Zuclopenthixol),” *J Anal Toxicol*, 1997, 21(4):314-8.[PubMed 9248952]

International Brand NamesCiatyl-Z (DE); Ciatyl-Z Acuphase (DE); Ciatyl-Z Depot (DE); Cisordinol (AT, CN, DK, EE, FI, HN, HU, NO, PE, PT, SE); Cisordinol Acutard (CN, EE, FI, PE, PT, SE); Cisordinol Depot (AT, CN, DK, EE, FI, HN, HU, NO, PE, PT, SE); Cisordinol-Acutard (NO); Cisordinol-Acutard[inj.] (HU); Clopixo (CZ); Clopixol (AR, AU, BE, BG, BR, CH, CL, ES, FR, GB, GR, HK, IE, IL, IT, LU, MX, MY, NL, PK, PL, SG, TH, TW, ZA); Clopixol

Acuphase (BR, HK, IL, IN, IT, MX, MY, PK, PL, TH, TW, ZA); Clopixol Acutard (CH); Clopixol Depot (BR, CH, CL, HK, IL, IN, IT, LU, MX, MY, NL, PK, PL, SG, TH, TW, ZA)
